# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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## Volume 1

## ADDITIONS TO C—X π-BONDS, PART 1

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C $\pi$-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N'*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| IpcBH$_2$ | isopinocampheylborane |
| Ipc$_2$BH | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Carbanions of Alkali and Alkaline Earth Cations: (i) Synthesis and Structural Characterization

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## 1.1.1 INTRODUCTION

In this chapter the focus is primarily on the recent structural work concerning carbanions of alkali and alkaline earth cations that are widely utilized in synthetic organic chemistry. In this context the year 1981 is significant because the first detailed X-ray diffraction analyses of two lithium enolates of simple ketones, *i.e.* 3,3-dimethyl-2-butanone and cyclopentanone, were published.[1] Since 1981 a number of detailed X-ray diffraction analyses of synthetically useful enolate anions of alkali and alkaline earth cations have been described. Within this chapter, many recent structural characterizations will be examined with the overall goal of collating this new information especially as it pertains to increasing our knowledge and control over the reactivity of these most useful and important synthetic reagents. The chapter is organized by functional group because this classification is quite natural to synthetic chemists. The examples chosen have come to my attention while thinking about the role of these species in synthetic reactions. It is neither practical nor feasible to include in this chapter an exhaustive review of all structural characterizations of carbanions of alkali and alkaline earth cations.[2] Should the complete list of all such structures be required, a comprehensive search of the Cambridge Structural Database (CSD) is recommended.[3] Throughout this chapter structural references are given to six letter CSD reference codes as follows, ⟨XXXXXX⟩. These refcodes will assist in obtaining crystallographic coordinates directly from the CSD.

At the outset it is especially useful to tabulate previous review articles containing a significant body of structural information about carbanions of alkali and alkaline earth cations, since these articles supplement the work reviewed herein. The first of these articles is an excellent review entitled 'Structure and Reactivity of Alkali Metal Enolates' by Jackman and Lange published in 1977.[4] It is significant that the fundamental details of the structure and the aggregation state of alkali metal ketone enolate anions in solution were outlined by Jackman mainly from NMR experiments and that this work predates the X-ray diffraction analyses. An earlier book by Schlosser entitled 'Struktur und Reaktivität polarer Organometalle' describes alkali and alkaline earth aggregates and their reactivities.[5] Some additional relevant structural information is reviewed in previous titles in this series, *i.e.* by Wakefield in Vol. 3 of 'Comprehensive Organic Chemistry'[6] and by the same author in Vol. 7 of 'Comprehensive Organometallic Chemistry'[7] and by O'Neill, Wade, Wardell, Bell and Lindsell in Vol. 1 of 'Comprehensive Organometallic Chemistry'.[8] A short review by Fraenkel *et al.* summarizes the solution structure and dynamic behavior of some aliphatic and alkynic lithium compounds by $^{13}$C, $^{6}$Li and $^{7}$Li NMR studies.[9] Additional comprehensive reviews regarding NMR spectroscopy of organometallic compounds contain information related to this topic.[10] A thorough listing and classification of the X-ray structural analyses of organo lithium, sodium, potassium, rubidium and cesium compounds sifted from the Cambridge Structural Database has been prepared by Schleyer and coworkers and covers published work until the latter 1980s.[11] Finally there are a few recent specialized reviews by Seebach, entitled 'Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective *C*-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures',[12] by Power, entitled 'Free Inorganic, Organic, and Organometallic Ions by Treatment of Their Lithium Salts with 12-Crown-4',[13] and by Boche, entitled 'Structure of Lithium Compounds of Sulfones, Sulfoximides, Sulfoxides, Thio Ethers and 1,3-Dithianes, Nitriles, Nitro Compounds and Hydrazones',[14] that mainly summarize the author's own recent contributions to the area. The reviews by Seebach and Boche are especially relevant to synthetic organic chemists and are highly recommended. Several additional articles may justifiably be included in this list; however, the reader is referred to the aforementioned publications, especially the Seebach, Boche and Schleyer reviews, for an exhaustive bibliography, since it will be unnecessary to repeat their bibliographic compilations.

Alkali and alkaline earth metal cations are associated with numerous carbanions in reactions found in nearly every contemporary total synthesis. The basis for our current mechanistic interpretation of the role of the these metal cations in synthetic reactions has been derived largely from correlating the stereochemistry of reaction products with the starting materials. These stereochemical correlations utilize as a foundation the conformational analysis of carbocyclic rings.[15] One simply notes how often chair-like or boat-like intermediates/transition states are employed to rationalize the stereochemical outcome of synthetic reactions incorporating alkali metal cations to verify the veracity of the previous statement. In almost all mechanistic pictures, one also notes that the metal cation occupies a prominent role in the purported intermediate and/or transition state. However, it has become increasingly clear that we still possess only an incomplete understanding of the aggregation state and of the structural features of many of the alkali or alkaline earth metal coordinated carbanions in solution. Presently the following conclusions about organic reactions in which carbanions of alkali and alkaline earth cations are involved will be made: (i) these carbanions are utilized almost routinely in nearly every organic synthetic endeavor; (ii) there exists a poignant lack of detailed structural information about the reactive species themselves; (iii) the development of new reactive intermediates especially those designed to enhance and to control stereoselectivity continues to grow; and (iv) the basic ideas for the design of new reagents emanates almost exclusively from detailed, but as yet largely speculative, structural postulates about these reactive organometallic species based nearly exclusively upon carbocyclic conformational analysis.

Perhaps the increasing number of intermediates and/or transition states[16,17] that have been proposed to explain the stereochemical outcome of enolate reactions can serve as a barometer of our attempts to analyze the situation. Currently we have set an all time high for the number of new mechanistic interpretations of enolate reactions. It is my feeling that this will not turn out to be as simple as an open and closed case that the present models suggest. On the contrary, there exists increasing evidence[18] for the role of highly organized, oligomeric species which play crucial roles in enolate reactions; especially in those reactions that are fast and reversible (*i.e.* thermodynamically controlled), such as the aldol reaction.

A precocious explanation of the complex role of alkali metal enolates was presented in a manuscript published in 1971.[19] A paragraph from this paper is reproduced below. It represents the manuscript's authors' explanation for the counterintuitive observation that more highly substituted (*i.e.* more sterically hindered) enolate anions undergo alkylation reactions faster than less highly substituted (*i.e.* less sterically hindered) enolates.

'The fact that less highly substituted alkali metal enolates may sometimes react more slowly with alkyl halides than their analogs having additional α-substituents has been noted in several studies.[20] These observations initially seem curious since adding α-substituents would be expected to increase the steric interference to forming a new bond at the α-carbon atom. However, there is considerable evidence that many of the metal enolates (and related metal alkoxides) exist in ethereal solvents either as tightly associated ion pairs or as aggregates (dimers, trimers, tetramers) of these ion pairs;[21] structures such as (**1**)–(**4**) (M = metal; *n* = 1, 2, oı 3; R = alkyl or the substituted vinyl portion of an enolate) have been suggested for such material with the smaller aggregates being favored as the steric bulk of the group R increases. Thus, the bromomagnesium enolate of isopropyl mesityl ketone is suggested to have structure (**1**) (M = MgBr), whereas the enolate of the analogous methyl ketone is believed to have structure (**2**) (M = MgBr).[22] The sodium enolates of several ketones are suggested to have the trimeric structures (**3**) in various ethereal solvents. Since the reactivities of metal enolates toward alkyl halides are very dependent on the degree of association and/or aggregation,[23] we suggest that the decreased reactivity observed for less highly substituted metal enolates both in this study and elsewhere may be attributable to a greater degree of aggregation of these enolates.' (Reproduced by permission of the American Chemical Society from *J. Org. Chem.*, 1971, **36**, 2361.)

$ROM(solvent)_n$

(**1**)

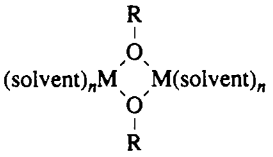

(**2**)

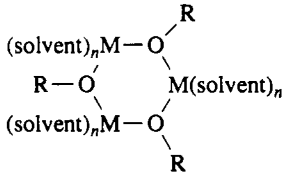

(**3**)

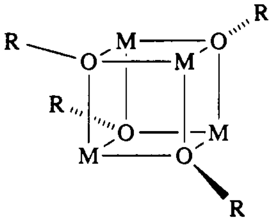

(**4**)

The above quotation aptly rationalizes a number of experimental observations having to do with alkylation reactions of enolate anions. It suggests that reactivity and, by logical extension, the stereochemical selectivity, of enolate reactions are related to the aggregation of the enolates. To me, this statement represents a general but very daring explanation. This quotation is now over 20 years old; however, the significance of the conclusions reflected here is only now becoming more widely acknowledged.[24]

Exactly 10 years after the previous statement appeared, the first lithium enolate crystal structures were published as (**5**) and (**6**).[1] Thus, structural information derived from X-ray diffraction analysis proved the tetrameric, cubic geometry for the THF-solvated, lithium enolates derived from *t*-butyl methyl ketone (pinacolone) and from cyclopentanone.[25] Hence, the tetrameric aggregate characterized previously by NMR[26] as (**7**) was now defined unambiguously. Moreover, the general tetrameric aggregate (**7**) now became embellished in (**5**) and (**6**) by the inclusion of coordinating solvent molecules, *i.e.* THF. A representative quotation from this 1981 crystal structure analysis is given below.

'There is increasing evidence that lithium enolates, the most widely used class of $d^2$-reagents in organic synthesis, form solvated, cubic, tetrameric aggregates of type (**8**). For the solid state this type of

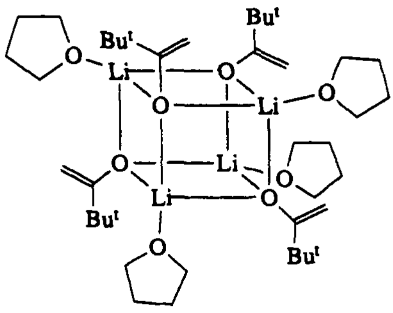

(5)

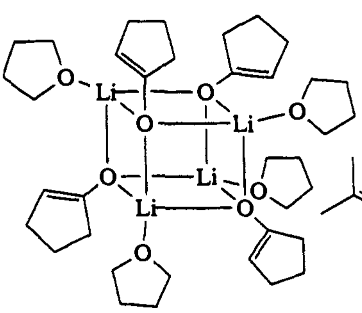

(6)

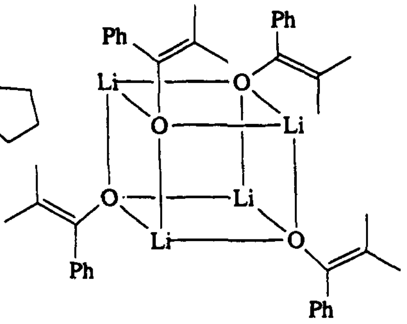

(7)

structure was definitely established for two crystalline lithium enolates and is strongly indicated for several others by their stoichiometry.... In aprotic solvents only aggregated species[27] are detected by NMR spectroscopy; even during reactions with electrophiles these aggregates are preserved and appear to be the actual reacting species, as indicated by reaction rates, which are first-order and not broken-order[28] in enolate concentration.' (Reproduced by permission of the Swiss Chemical Society from *Helv. Chim. Acta*, 1981, **64**, 2617.)

The authors of this quotation proceed to postulate the highly speculative but not unreasonable mechanism for the aldol reaction shown in Scheme 1. Justification for this mechanism appears to be based mainly upon characterization by X-ray diffraction analysis of the tetrameric cubic aggregates (**5**) and (**6**). Hence, X-ray diffraction analysis unambiguously provided the intimate structural details unobtainable by other methods.

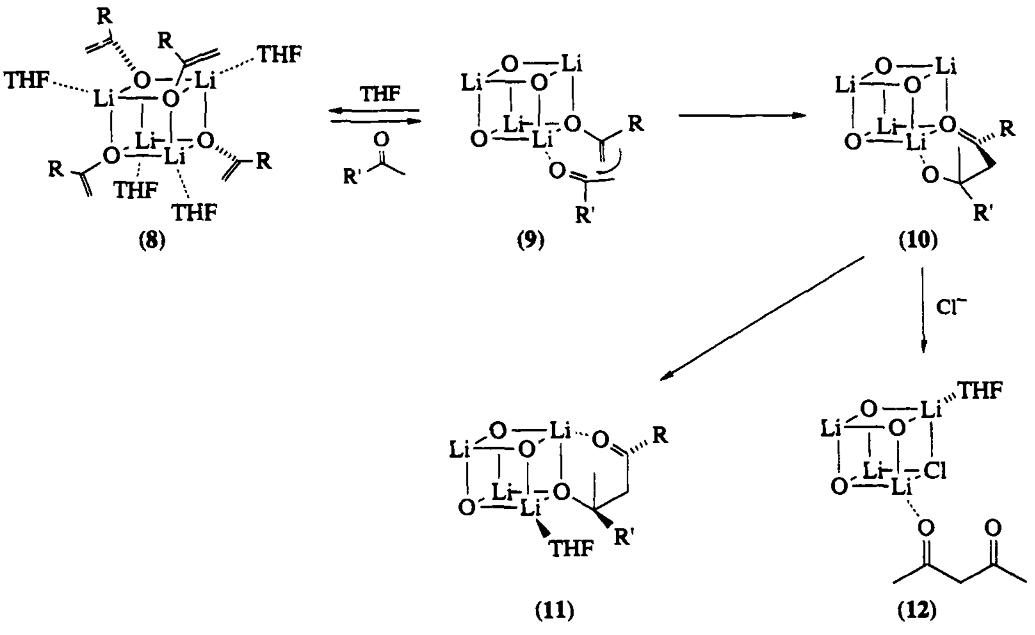

**Scheme 1**

Currently, the significance of the structural work in this area is aptly summarized by pointing out that it has been possible to obtain and to characterize the structure of aggregates corresponding to the intermediates (**8**) and (**9**) (M = Na), and (**11**) in the aldol reaction mechanism shown in Scheme 1.[29] At present we assume that ample evidence points to the existence of aggregated intermediates in several alkylation and aldol-like reactions.[30] Thus, the following sections of this chapter are classified roughly by functional group, and they contain structural results obtained by X-ray diffraction analysis. The examples were chosen with the thought of providing structural details about the reactive intermediates utilized in synthetic organic reactions, but it must be repeated that they do not represent a complete and comprehensive list of all such structures. As additional structural information is obtained, perhaps it will be possible to expand and to refine carbanion reaction mechanisms to include aggregated intermediates rather than simple monomers.

The results reviewed in the following pages of this chapter may provide fundamental information for the conduct, planning and strategy of organic synthesis. The origin of stereoselectivity in many organic reactions can be put on a more rational basis as more intimate structural details about the intermediates involved in these reactions are discovered. Of course, the long range goal and ultimate significance of this structural information is to provide a more thorough basis for accurate prediction and control of stereochemistry in organic reactions. Since enolate anions are universally utilized in all synthetic schemes, the successful obtention of additional structural results will have a great impact on the ability and the ease by which organic compounds will be prepared. I begin with a survey of known structural types.

## 1.1.2 STRUCTURAL FEATURES

### 1.1.2.1 Aggregation State

It is vital to recognize that metal cations impart a degree of order to the anions with which they are associated. Typically the first characteristic feature described is the stoichiometry. A simple chemical formula such as $M^+A^-$ requires additional clarification to denote a higher degree of association such as $(M^+A^-)_x$ where the subscript $x$ denotes the aggregation state of the species. The common descriptors of the aggregation state are monomer, dimer, trimer, tetramer, *etc.* Knowledge of the aggregation state is crucial since the reactivity of the anion is related to the aggregation state as well as to its structure.[31] The structures of the aggregates also depend critically upon the solvation of the cations. Fortunately, the majority of known structures can be built from a few simple structural patterns.

A motif found in the majority of alkali metal stabilized carbanion crystal structures is a nearly planar four-membered ring (**13**) with two metal atoms ($M^+$) and two anions ($A^-$), *i.e.* dimer. This simple pattern is rarely observed unadorned as in (**13**), yet almost every alkali metal and alkaline earth carbanion aggregate can be built up from this basic unit. The simplest possible embellishment to (**13**) is addition of two substituents (S) which produces a planar aggregate (**14**). Typically the substituents (S) in (**14**) are solvent molecules with heteroatoms that serve to donate a lone pair of electrons to the metal (M). Only slightly more complex than (**14**) is the four coordinate metal dimer (**15**). Often the substituents (S) in (**15**) are joined by a linear chain. The most common of these chains are tetramethylethylenediamine (TMEDA) or dimethoxyethane (DME) so that the spirocyclic structure (**16**) ensues. Alternatively the donors (S) in (**16**) have been observed as halide anions ($X^-$) when the metal ($M^{2+}$) is a divalent cation, *e.g.* (**17**) or (**18**). Obviously, the chelate rings found in (**16**) are entropically favorable relative to monodentate donors (S) in (**14**), (**15**), (**17**) or (**18**) (Scheme 2).

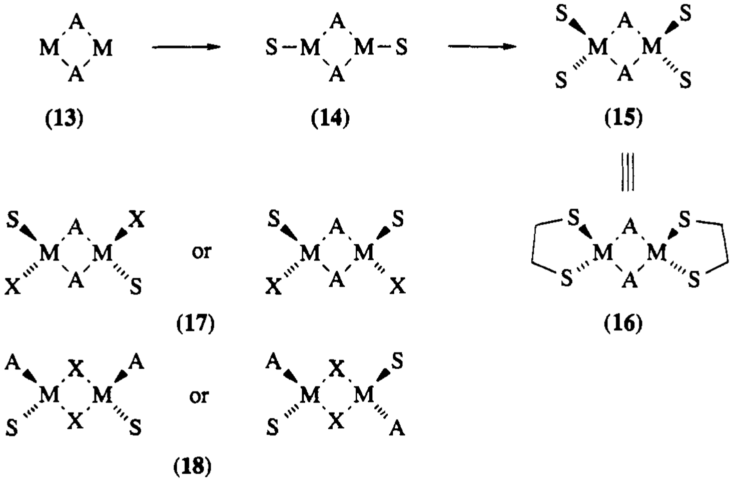

**Scheme 2**

Several structural types are based on the combination of two units of (**13**). The edge-to-edge combination of (**13**) yields a 'ladder'-type structure (**19**). Of course there are various combinations of solvent donor ligands and/or chelate donors possible in (**20**) and (**21**). The face-to-face combination of (**13**) can produce a relatively cubic infrastructure (**22**) as previously seen in the enolates (**5**) and (**6**). Distorted variations of the cube (**22**) are observed, such as (**23**), or alternatively as another variation (**24**), with opposite square faces offset from one another (by nearly 90° in **24**). Such variations may be described as a 'tetrahedron within a tetrahedron'. It is noteworthy that the cube (**22**) can be derived from the ladder (**21**) simply by decreasing the appropriate internal bond angles to about 90° as indicated by the sequence of formulae (**13**) → (**19**) → (**21**) → (**22**). An advantage of the closed cubic structure (**22**) over the ladder (**19**) is the additional coordination of the terminal metal cations (M) to a third anion. The cube (**22**) is most frequently observed with four-coordinate metal cations, as in (**25**) and not in its unsolvated form (**22**) (Scheme 3).

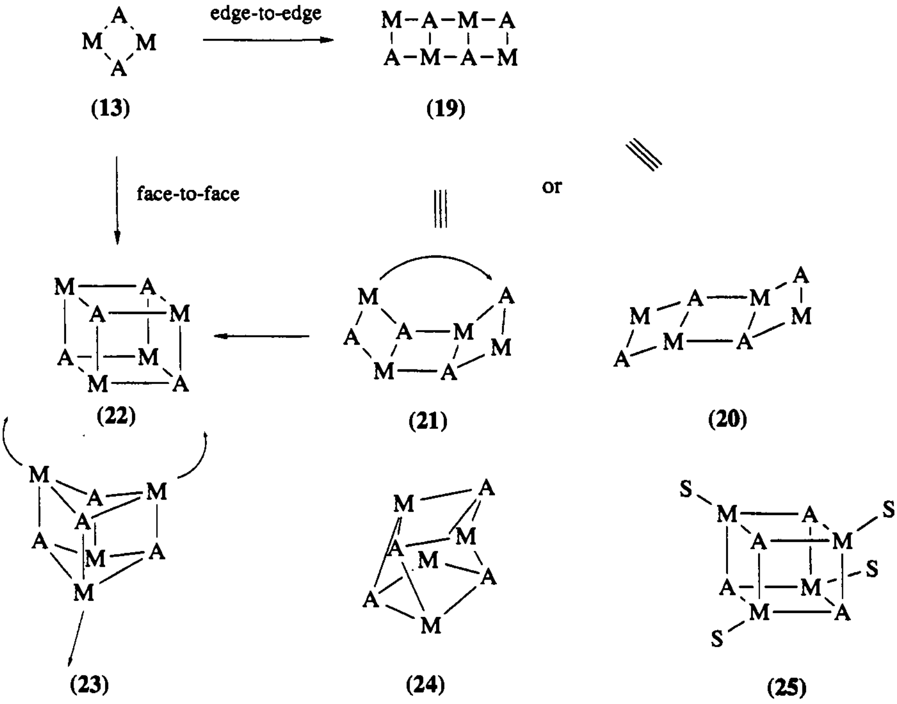

Scheme 3

Edge-to-edge combination of additional units of (**13**) leads to the longer ladders (**26**) or (**27**). We have already obtained one unusual lithium enolate crystal structure corresponding to (**26**) but with additional external chelate rings. Closure of (**27**), analogous to the closure of (**21**) to (**22**), produces a hexagonal prism (**28**). Examples of structural type (**28**) are observed in addition to the solvent-coordinated hexamer (**29**). Distortion of (**29**), shown as (**30**), will lead to a somewhat less sterically hindered structure allowing for solvation of the metal cations by solvent (Scheme 4).

An alternative dissection of the hexagonal prism (**28**) is given as (**31**) (Scheme 4). Hence the hexamer (**28**) could be built up from two units of a planar trimer (**31**). This is plausible, because an example of a planar trimeric structure corresponding to (**31**) is known, *i.e.* the trimeric, unsolvated lithium hexamethyldisilazide structure.[32]

Additional structural types are known for alkali carbanions in the solid state. Examples of these are the monocyclic tetramer (**32**) or the pentacyclic tetramer (**33**), the hexamer (**34**), the dodecamer (**35**) and the infinite polymer (**36**). Undoubtedly several new structural types will be observed as mixed aggregates containing different metal cations ($M^+$ and $M'^+$) and/or different anions ($A^-$ and $A'^-$) are characterized. Relatively long ladders, *i.e.* (**37**), corresponding to oligomeric chains of the dimer (**14**) combined edge-to-edge, are also likely to be characterized in the future. It is to be anticipated that the carbanions of limited solubility correspond to these extended ladders and that solubilization occurs by breaking these oligomers. A recent discussion of the propensity of lithiated amides to form either ladder structures or closed ring structures along with some *ab initio* calculations of these structural models has been presented by Snaith *et al.*[33]

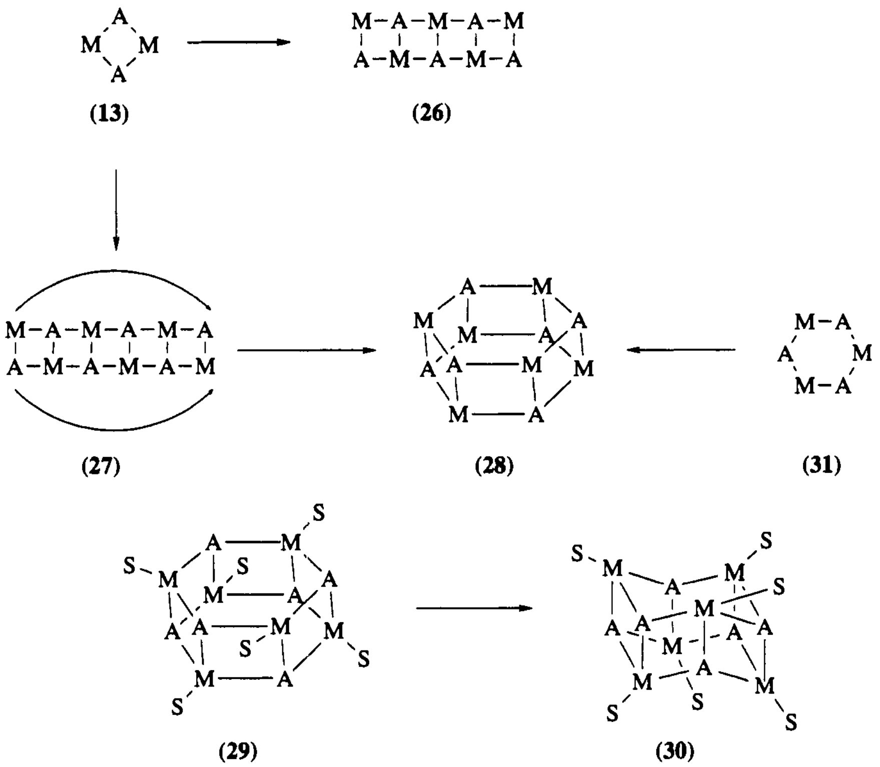

Scheme 4

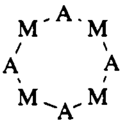

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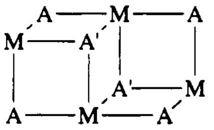

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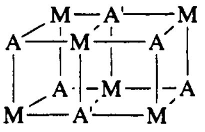

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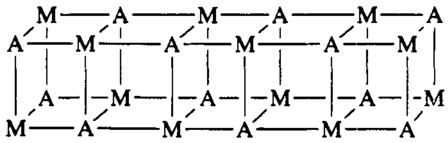

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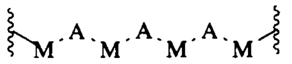

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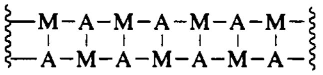

(37)

## 1.1.2.2 Coordination Geometry and Number

The directional preferences for coordination to the alkali metal and alkaline earth cations is obviously related to the number of substituents coordinated to the cation. As yet there is little predictability of the coordination number among these cations. For example, the first member of this series, the Li$^+$ cation, is the best characterized with well over 500 X-ray crystal structures containing this ion. Coordination numbers to Li$^+$ ranging from two through seven and all values in between can be found. The Li$^+$ cation is also found symmetrically π-complexed to the faces of aryl anions and to conjugated linear anions (see ref. 11). At present enough evidence exists to deduce only that the coordination number to the alkali metal and alkaline earth cations, and consequently the coordination geometry about these cations, is governed primarily by steric factors. Unfortunately the predictability of any individual unknown structure is relatively low.

In general the metal cation to substituent distances are found spanning a range of values. A working criterion for coordination to the metal cations is that the M—A distance not be greater than the sum of the van der Waals radii of M and A as listed by Pauling.[34] This criterion is particularly convenient when the anion is a typical heteroatom, such as O or N, or a halide, X. In such cases it is usually possible to derive accurate estimates of these distances from compiled sources.[35] However, the values of the M—A distance for cases where A is carbon and M is a Group Ia or IIa metal are not particularly well defined. Hence, Table 1 represents a recent search of the CSD for these values.[36]

**Table 1** Carbanion–Metal Bond Lengths

| *Bond* | *Mean* | *S.D.* | *Minimum (Å)* | *Maximum (Å)* | $N_{obs}$ |
|---|---|---|---|---|---|
| C—Li | 2.259 | 0.087 | 2.041 | 2.557 | 354 |
| C—Na | 2.646 | 0.060 | 2.566 | 2.756 | 12 |
| C—K | No examples found | | | | |
| C—Rb, C—Cs, C—Fr | No examples found | | | | |
| C—Be | 1.874 | 0.081 | 1.707 | 2.043 | 38 |
| C—Mg | 2.256 | 0.015 | 2.095 | 2.602 | 100 |
| C—Ca, C—Sr, C—Ba, C—Ra | No examples found | | | | |

This table includes all examples listed in the CSD (version 4.20, 1990) located by a fragment search (*i.e.* CONNSER) for C—M bonds where M = group Ia or IIa metals irrespective of the hybridization of carbon.

Related structural aspects of metal ion coordination geometry are covered in some recent publications and are worthy of note. The directional preferences of ether oxygen atoms towards alkali and alkaline earth cations are reported by Chakrabarti and Dunitz.[37] The conclusion of this work is that the larger cations show an apparent preference to approach the ether oxygen along a tetrahedral lone pair direction, whereas $Li^+$ cations tend to be found along the C—O—C bisector, *i.e.* along the trigonal lone pair direction. Metal cation coordination to the *syn* and *anti* lone pair of electrons of the oxygen atoms in a carboxylate group have been reviewed by Glusker *et al.*[38] Scatter plots of M—O distances *versus* C—O—M angles for a wide variety of cation types led to the conclusion that both the coordination geometry and the distances of coordination to carboxylate lone pairs are largely governed by steric influences. Recently, the geometry of carboxyl oxygen complexation to several Lewis acids has been summarized by Schreiber *et al.*[39] Although only a few alkali metal Lewis acid–carbonyl structures are known, the general conclusion is that alkali metal cations do not show a strong directional preference for binding to carbonyls and that coordination numbers and coordination geometries vary greatly in these complexes.

## 1.1.3 CARBANION CRYSTAL STRUCTURES

With the general background of structural types described as above, it is now appropriate to review a number of examples of X-ray crystal structures of alkali metal and alkaline earth cations. The choice of examples is biased in favor of those species that are relevant to synthetic organic chemists. Hence, I begin with a comparison of structures of aliphatic carbanions. This group of aliphatic carbanion structures is the most widely varied and surely the least predictable. Of particular significance will be the aggregation state, the coordination number and the relative geometry about the metal cation. The figures drawn in the following sections are not computer generated plots of the actual X-ray crystal structures but are approximations of the actual structures. It is not practical to enumerate all of the specific details such as all bond lengths, bond angles and torsion angles in these structures and the reader is referred to the original publications for this specific information.

### 1.1.3.1 Aliphatic Carbanions

#### *1.1.3.1.1 Unsubstituted aliphatic carbanions*

Among the earliest aliphatic carbanions to be structurally characterized by X-ray diffraction analysis are the simple unsubstituted alkyllithium reagents, *i.e.* methyl-,[40] ethyl-[41] and cyclohexyl-lithium.[42] Methyl- and ethyl-lithium have also been examined in detail by quantum mechanical calculations and by electrostatic calculations.[43] The structures of methyl- and ethyl-lithium are similar. Both of these compounds crystallize as tetrameric aggregates from hydrocarbon solvents. These tetramers are generally depicted as (**38**). The aggregate (**38**) is described as a tetrahedral arrangement of lithium atoms with a single alkyl group located on each of the four faces of the Li tetrahedron. The carbanionic carbons are not necessarily equidistant from the three closest lithium atoms. However, it is clear that the three covalently bound substituents on the carbon atoms (H or alkyl) are found at the locations expected for an $sp^3$-hybridized atom. The carbon–lithium interactions have been referred to as two-electron four-center bonds in these structures. A low temperature crystal structure of ethyllithium[44] reveals some small changes relative to the room temperature structure, but the basic tetramer remains intact.

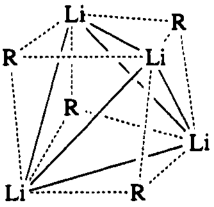

(**38**) R = Me, Et

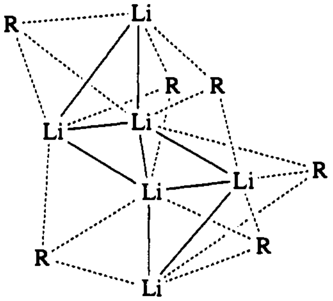

(**39**) R = cyclohexyl or
R = tetramethylcyclopropylmethyl

Cyclohexyllithium was prepared in hexane from cyclohexyl chloride and lithium sand and subsequently extracted and recrystallized from benzene solution to produce the hexameric aggregate (**39**).[42] The lithium atoms in this aggregate are nearly in an octahedral configuration, although the triangular faces of this octahedron have two short (~2.40 Å) and one long (~2.97 Å) Li—Li distance. A carbanionic carbon is found on six of the triangular faces and is most closely associated with the two lithium atoms which possess the longest Li—Li atom distance. The orientation of the cyclohexyl group is apparently determined by the interaction of α- and β-protons with the lithium atoms. The Li—C interactions in this hexamer are described as localized four-center bonds, as in the methyl- and ethyl-lithium tetramer (**38**). Two benzene molecules are occluded in the solid cyclohexyllithium hexamer, but these solvent molecules do not appear to interact with the hexamer.

Solvent-free (tetramethylcyclopropyl)methyllithium (**40**) also forms the hexameric aggregate (**39**), similar to hexameric cyclohexyllithium.[45] Both hexamers are characterized as a trigonal antiprism with triangular $Li^+$ faces. The (tetramethylcyclopropyl)methyllithium hexamer (**40**) was prepared in diethyl ether solution from both the Cl and the Hg compounds (**41**) as well as from the open chain compound (**42**). In contrast to the cyclohexyllithium hexamer, the hexamer (**40**) is obtained solvent free (Scheme 5).

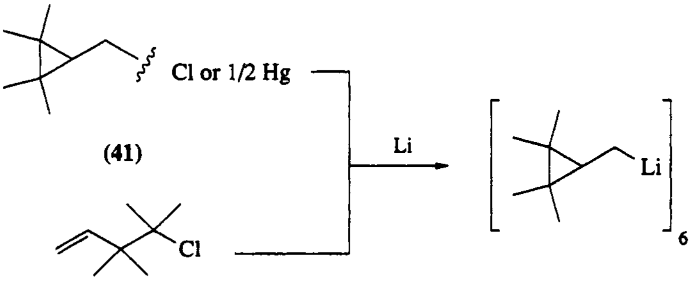

Scheme 5

An interesting cubic geometry is maintained in the mixed aggregate obtained from the reaction of cyclopropyl bromide (**43**) with lithium metal in diethyl ether solution.[46] The composition of the crystalline material is $(c\text{-}C_3H_5Li)_2\cdot(LiBr)_2\cdot 4Et_2O$. The aggregate was characterized as structure (**44**). Note the similarity of (**44**) with the cubic tetramers (**38**), except for the substitution of two carbanion residues by two bromides in (**44**). Note also that each of the lithium atoms in (**44**) is coordinated to an oxygen of a diethyl ether molecule. This solvation serves to increase the coordination number of the lithiums, but does not break up the overall tetrameric nature of the aggregate. This solid loses ether at room temperature and is transformed into an ether-insoluble, tetrahydrofuran-soluble, amorphous product. The mass spectrum of the ether-free substance shows only halide-free aggregates. It is likely that differing reactivity of the salt-containing and salt-free lithium alkyls is related to the direct incorporation of lithium halide into the carbanion aggregates.

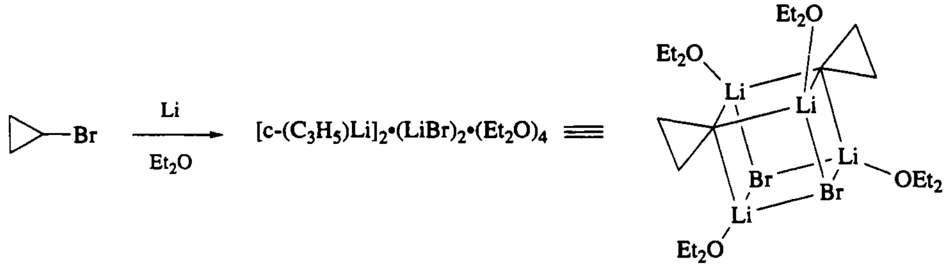

(**43**) (**44**)

Another mixed aggregate complex consisting of $Bu^nLi$ and *t*-butoxide was reported in 1990 as the tetramer (**45**).[47] This complex was first isolated by Lochmann[48] and has been shown to be tetrameric and dimeric in benzene and THF, respectively, by cryoscopic measurements,[49] and it has also been studied by rapid injection NMR techniques.[50] This species has received much attention because it is related to the synthetically useful 'superbasic' or 'LiKOR' reagents prepared by mixing alkali metal alkoxides with lithium alkyls or lithium amides.[51]

$[Bu^nLi\cdot LiOBu^t]_4$ ≡

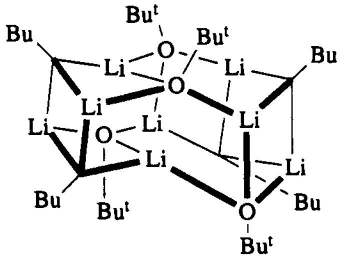

(**45**)

Another example of a solvated, cubic tetramer is methyllithium—TMEDA (**46**).[52] In this example an aggregate of composition $[(MeLi)_4\cdot 2TMEDA]_n$ with almost ideal $T_d$ symmetry crystallized from an ethereal solution of methyllithium and TMEDA at room temperature. This material consists of infinitely long chains of cubic tetramer linked by TMEDA molecules. Since TMEDA usually has a strong preference for formation of a chelate ring with a single lithium atom, it is somewhat unusual that such an intramolecular chelate is not observed here.

Deprotonation of bicyclobutane (**47**) by *n*-butyllithium in hexane containing a slight excess of TMEDA, followed by solvent evaporation, filtration and recrystallization from benzene yields the dimeric, bis-chelated aggregate (**48**).[53] This aggregate corresponds exactly to structural type (**16**). It is perhaps surprising that many more examples of aliphatic carbanions have not yet been characterized with this general bis-chelated dimeric structure.

Intramolecular solvated tetramers are observed for 3-lithio-1-methoxybutane (**49**)[54] and from 1-dimethylamino-3-lithiopropane (**50**)[55] in the solid state. These tetramers are shown in generalized form as (**51**) and (**52**), respectively. Note the significant difference between the aggregates (**51**) and (**52**). Variable temperature $^7Li$ NMR as well as $^1H$ NMR suggest that although the major form of 1-dimethylamino-3-lithiopropane (**50**) is the diastereomer (**51**), this structure is presumed to be in equilibrium with (**52**)

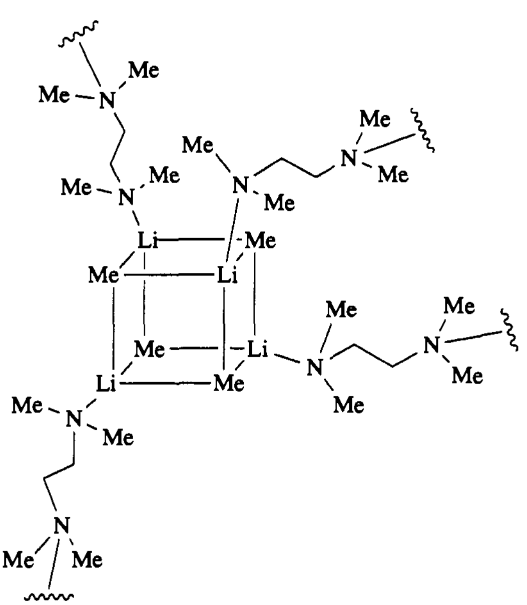

**(46)**

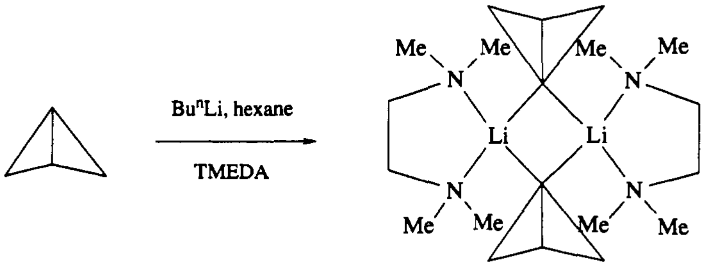

**(47)** **(48)**

in toluene (or cyclopentane) with activation parameters $\Delta H$‡ = 17 (16) ± 2 kcal mol$^{-1}$, $\Delta S$‡ = 13 (10) ± 3 cal (mol deg)$^{-1}$ (1 cal = 4.184 J).[55b]

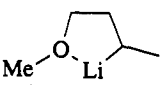

**(49)**

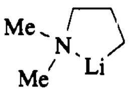

**(50)**

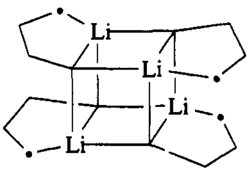

**(51)**

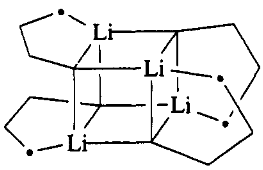

**(52)**

Benzyllithium crystallizes from hexane/toluene solution in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in infinite polymeric chains.[56] Inspection of the individual monomeric units of this structure reveals a unique interaction of the lithium atoms in an $\eta^3$-manner with the benzylic carbanion. This bonding is based upon the three relatively short Li—C contacts as indicated in structure (**53**). The two protons on the benzylic carbon center were located crystallographically; one of these lies in the plane of the aromatic ring and the other is significantly out of this plane. A similar $\eta^3$-Li—CCC interaction is observed in the diethyl ether solvate of triphenylmethyllithium (**54**).[57] This latter structure is depicted as (**55**).

When the lithium cation is unable to associate with the carbanion, as is the case for the Li$^+$ (12-crown-4) complexed lithium diphenylmethane carbanion (**56**) or Li$^+$ (12-crown-4) triphenylmethyl carbanion (**57**), the entire aromatic carbanions are relatively planar.[58] The planarity of (**56**) and (**57**) is indicative of

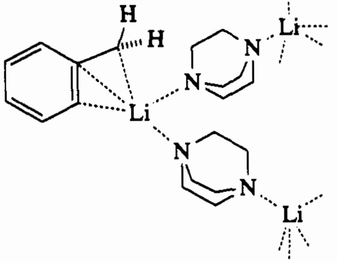

**(53)**

$Ph_3CLi{\bullet}(Et_2O)_2$

**(54)**

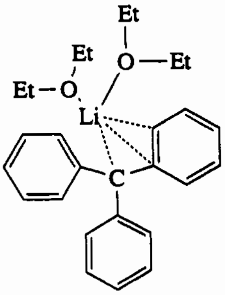

**(55)**

extensive delocalization in these structures. The triphenylmethyl carbanion in (**57**) can also be compared with this same species as it appears associated with $Li^+{\cdot}TMEDA$[59] and $Na^+{\cdot}TMEDA$[60] cations.

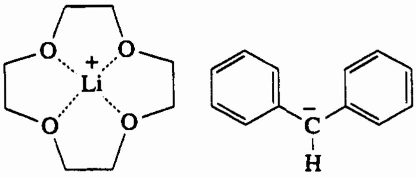

**(56)**

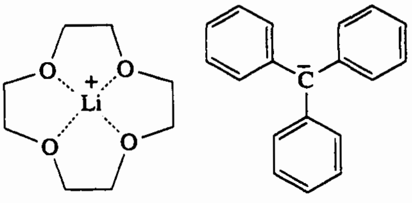

**(57)**

A dimer (**58**) of α-lithiated 2,6-dimethylpyridine crystallizes with TMEDA solvation.[61] This dimer is completely unlike the polymeric benzyllithium (**53**) in that no $\eta^3$-intramolecular bonding is observed. The central core of the dimer (**58**) consists of an eight-membered ring formed from two intermolecular chelated $Li^+$ atoms and nearly ideal perpendicular conformations of the $\alpha$-$CH_2Li^+$ groups. Dimer (**58**) is a relatively rare example of a lithiated π-system where $Li^+$ exhibits only one carbon contact.

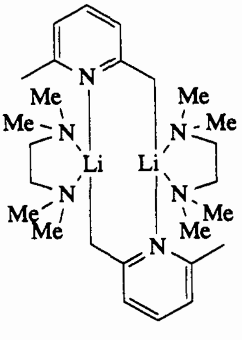

**(58)**

This discussion of aliphatic carbanion structures has included mainly organolithium compounds simply because the structures of most aliphatic carbanions incorporate lithium as the counterion and also because this alkali metal cation is the most widely used by synthetic organic chemists. For comparison the entire series of Group 1a methyl carbanion structures, *i.e.* MeNa, MeK, MeRb and MeCs, have been determined. Methylsodium was prepared by reaction of methyllithium with sodium *t*-butoxide.[62] Depending upon the reaction conditions, the products obtained by this procedure contain variable amounts of methyllithium and methylsodium (Na:Li atom ratios from 36:1 to 3:1). The crystal structure of these methylsodium preparations resembles the cubic tetramer (**38**) obtained for methyllithium with the Na—Na distances of 3.12 and 3.19 Å and Na—C distances of 2.58 and 2.64 Å.

Methylpotassium, prepared from MeHg and K/Na alloy or from methyllithium and potassium *t*-butoxide, has a hexagonal structure corresponding to the NiAs type (**59**).[63] Each methyl group is considered to be coordinated to six $K^+$ ions in a trigonal prismatic array. Methylrubidium and methylcesium, prepared from rubidium *t*-butoxide and cesium 2-methylpentanoate respectively, also possess hexagonal structures of the same type as methylpotassium.[64]

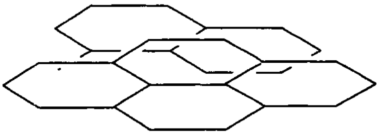

**(59)**

An extremely unusual pentacoordinate carbon with trigonal bipyramidal symmetry is observed in the crystalline, TMEDA solvate of benzylsodium.[65] This benzylsodium complex is best described as a tetramer with approximate $D_{2d}$ symmetry. The four sodium atoms define a square with a benzyl carbanion bisecting each edge. The resulting eight-membered ring is slightly puckered to alleviate crowding. This structure is depicted as (**60**).

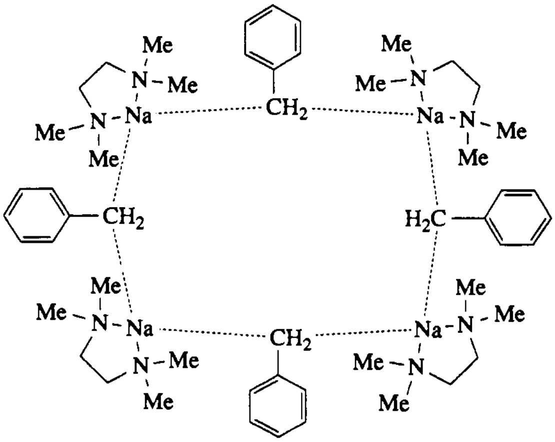

**(60)**

Other aliphatic carbanion structures associated with Group IIa cations are known. Some examples of these are dimethylberyllium[66] and lithium tri-*t*-butyl beryllate.[67] Since the beryllium alkyl carbanions have not yet been utilized as common synthetic reagents, these structures will not be discussed further.

Magnesium$^{2+}$ stands out among Group IIa metal cations that are commonly utilized in synthetic organic chemistry. Indeed there have been several structural investigations of aliphatic Grignard reagents and dialkylmagnesium reagents. The simplest Grignard reagents, *i.e.* RMgX, whose structures have been determined are MeMgBr·3THF (**61**),[68] (EtMgBr·OPr$^i_2$)$_2$ (**62**),[69] (EtMgBr·Et$_3$N)$_2$ (**63**),[70] EtMgBr·2Et$_2$O (**64**)[71] and the complex (EtMgCl·MgCl$_2$·3THF)$_2$ (**65**).[72] The crystal structures of these reagents exhibit a remarkable diversity for such seemingly similar species. As indicated in the aggregate molecular formulae above, both ethylmagnesium bromide diethyl ether solvate (**64**) and methylmagnesium bromide THF solvate (**61**) are monomeric. However, the magnesium in complex (**64**) is approximately tetrahedral and the magnesium in (**61**) is approximately trigonal bipyramidally coordinated. The general features of these latter two structures are depicted as (**66**) and (**67**). In the complex (**67**), the methyl groups and the bromine atom are disordered and the tetrahydrofuran rings are significantly distorted. The two dimeric complexes, (EtMgBr·OPr$^i_2$)$_2$ and (EtMgBr·Et$_3$N)$_2$ are similar. They both incorporate bridging bromine atoms and four-coordinate, tetrahedral Mg$^{2+}$ ions. The general structural type of both of these compounds is given as (**68**).

The ethylmagnesium chloride complex (**65**), depicted as (**69**), is extremely complex, but can be simplified if it is seen as a dimer of EtMgCl·MgCl$_2$ containing five four-membered bridging units of magnesium and chlorine atoms. Two different types of magnesium atoms are seen in this structure. These two types of metals exhibit five and six coordination. Additionally there are two three-coordinate bridging chlorine atoms and four two-coordinate chlorine atoms in this structure.

Treatment of hexamethyldisilazane (**70**) in hexane with a slight excess of a solution of the dialkylmagnesium reagent, Bu$^n$Bu$^s$Mg, initially yields the dimeric complex [Bu$^s$Mg·N(TMS)$_2$]$_2$.[73] This material is characterized as an unsolvated dimer (**71**).

Optically active diamines (–)-sparteine (**72**) and (–)-isosparteine (**73**) form complexes with ethylmagnesium bromide which crystallize in a form suitable for diffraction analysis. In both of these structures,

$EtMgBr\cdot 2Et_2O$ ≡

**(64)**

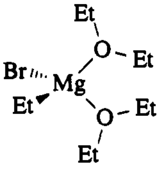

**(66)**

$MeMgBr\cdot 3THF$ ≡

**(61)**

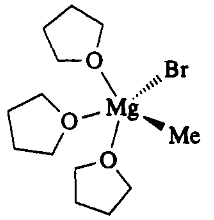

**(67)**

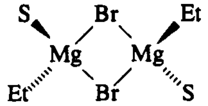

**(68)** $S = Pr^i_2O$ or $Et_3N$

$(EtMgCl\cdot MgCl_2\cdot STHF)_2$ ≡

**(65)**

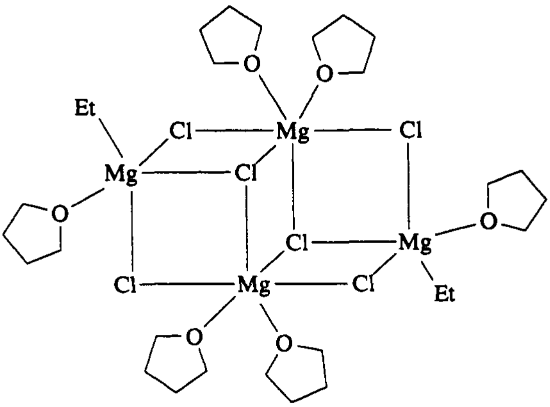

**(69)**

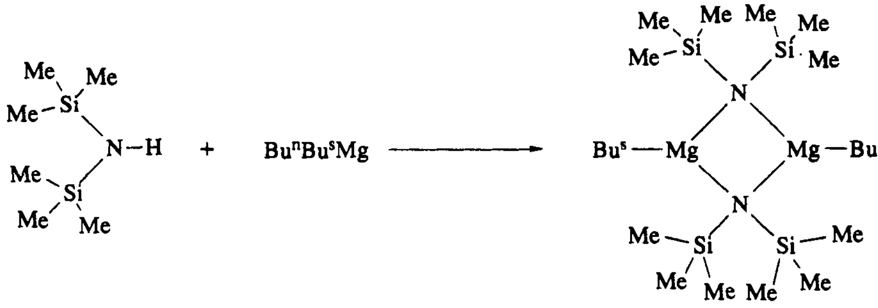

**(70)** **(71)**

depicted as (74) and (75), the $Mg^{2+}$ is tetrahedrally coordinated by the carbon atom of the ethyl group, the bromine atom and two nitrogens of the (iso)sparteine residue, respectively. The complex (74) of ethylmagnesium bromide with the chiral bidentate ligand (–)-sparteine is catalytically active in the asymmetric, selective polymerization of racemic methacrylates.[74] Similar structures are found for the complexes of *t*-butylmagnesium chloride with (–)-sparteine[75] and for ethylmagnesium bromide with (+)-6-benzylsparteine.[76]

Reaction of $MgH_2$, prepared by homogeneous catalysis, with 4-methoxy-1-butene in the presence of catalytic amounts of $ZrCl_4$ yielded the monomeric magnesium inner ion complex $Mg(C_4H_8OMe)_2$.[77] This complex crystallizes with the tetrahedrally four-coordinate magnesium as shown in (76). In a similar reaction, treatment of bis(dialkylamino)propylmagnesium inner complexes (77) or (78) with $MgEt_2$ yielded the crystalline dimer of ethyl-3-(*N*,*N*-dimethylamino)propylmagnesium (79) and ethyl-3-(*N*-cyclohexyl-*N*-methylamino)propylmagnesium (80).[78]

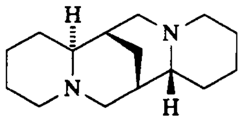

**(72)**

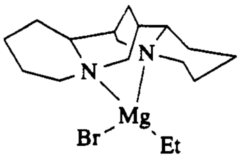

**(74)**

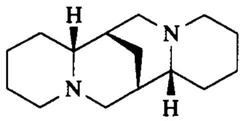

**(73)**

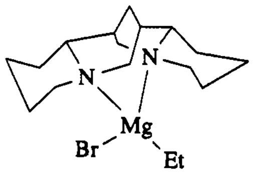

**(75)**

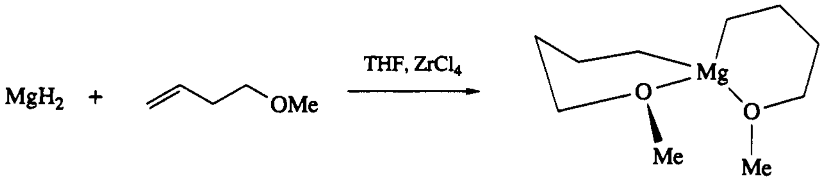

**(76)**

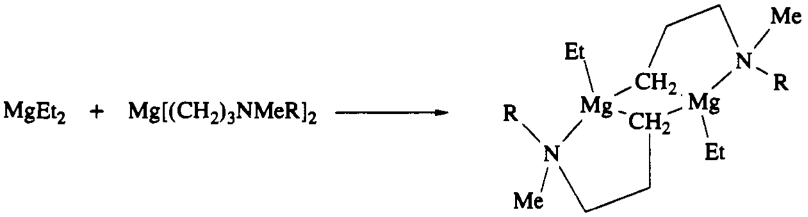

**(77)** R = Me
**(78)** R = cyclohexyl

**(79)** R = Me
**(80)** R = cyclohexyl

A triple ion was crystallized by Richey *et al.* from a solution made up by adding 2,1,1-cryptand to diethylmagnesium.[79] Diffraction analysis reveals that this triple ion consists of $[EtMg^+(2,1,1\text{-cryptand})]_2$ cations and an $(Et_6Mg_2)^{2-}$ anion. The magnesium of the cation is bound to five heteroatoms of the cryptand and to an ethyl group. The two magnesiums in the dianion exhibit identical four coordination and they form a symmetrical dimer with two bridging ethyl groups and four terminal ethyl groups. The anion is depicted as (**81**). A different structure was found for the product of the reaction of dineopentylmagnesium ($Np_2Mg$) with 2,1,1-cryptand.[80] In this latter reaction, crystalline $NpMg^+(2,1,1\text{-cryptand})$ cations and $Np_3Mg^-$ anions are formed. The coordination geometry of magnesium in the Np cation is essentially that of a trigonal bipyramid with bonds to all six heteroatoms of the cryptand and a bond to the neopentyl group. Only the three-coordinate anion (**82**) is illustrated here. The $^1H$ NMR spectrum of a benzene solution of $NpMg^+(2,1,1\text{-cryptand})\cdot Np_3Mg^-$ is consistent with the presence of the same ions in solution. Diethylmagnesium cryptand complex reacts faster with pyridine than the diakylmagnesium reagent alone, and it also modifies the regioselectivity of this reaction.

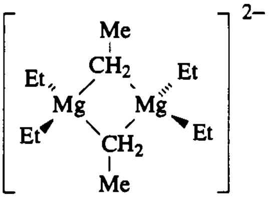

**(81)**

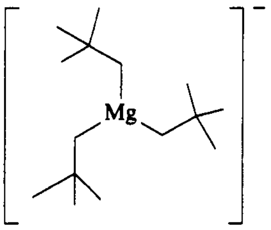

**(82)**

Diethylmagnesium and 18-crown-6 react to form a complex with six oxygens surrounding the magnesium in a quasiequatorial plane and with the ethyl groups occupying *trans* apical positions.[80] This structure is illustrated as (**83**). It has been described as a rotaxane[81] or 'threaded' structure. A related, but slightly different, structure is found for the $MeMg^+(15\text{-crown-}5)\cdot Me_5Mg_2^-$ complex.[82]

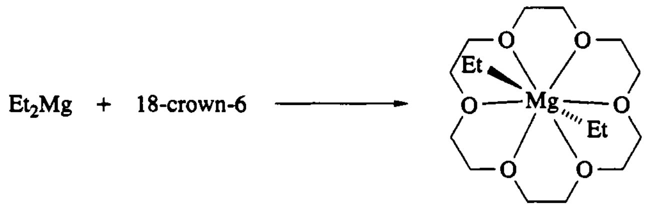

**(83)**

The structures of a few dialkylmagnesium reagents have been characterized. These include $(Me_2Mg)_n$,[83] $(Et_2Mg)_n$,[84] $Me_2Mg{\cdot}TMEDA$,[85] $[(CH_2)_5Mg]_2{\cdot}4THF$,[86] $Me_2Mg{\cdot}(quinuclidine)_2$[87] and *catena*-poly-dineopentylmagnesium-μ-dioxane = $[Mg(C_5H_{11})_2{\cdot}2THF]_n$.[88] While the diakylmagnesium reagents also exhibit several different structural types, all of these complexes are related by the fact that they incorporate magnesium atoms that are four coordinate with distorted tetrahedral geometry. Unsolvated dimethylmagnesium and diethylmagnesium both form linear, polymeric chains with adjoining Mg atoms linked by two bridging alkyl groups. The solvated dimethylmagnesium complex, *i.e.* $Me_2Mg{\cdot}TMEDA$, is illustrated as (**84**) with the bond angle as shown. The pentamethylenemagnesium complex, $[(CH_2)_5Mg]_2{\cdot}4THF$, crystallizes as the dimer (**85**) with two magnesium atoms in a 12-membered ring. This tendency to form a 12-membered ring is ascribed to the large C—Mg—C valence angle of 141° which would cause severe ring strain in a monomeric magnesiocyclohexane. The polymeric dineopentylmagnesium exhibits a structure which consists of dineopentyl units linked through dioxanes forming parallel linear chains as shown in (**86**).

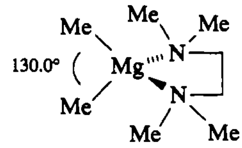

**(84)**

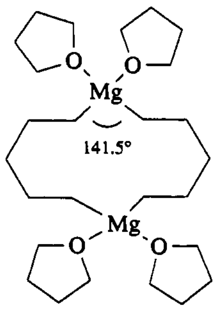

**(85)**

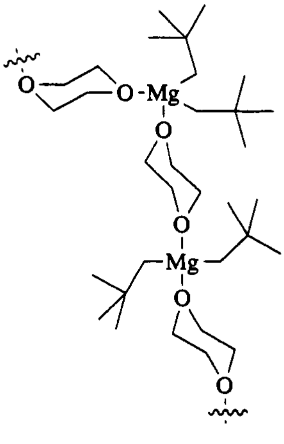

**(86)**

One final diakylmagnesium structure is illustrated as (**87**).[89] This material was obtained from the room temperature crystallization of the magnesium reagent formed from *o*-bis(chloromethyl)benzene in THF. As in all previous dialkylmagnesium reagents, the highly symmetrical trimer (**87**) includes four-coordinate magnesium atoms with distorted tetrahedral geometry.

### *1.1.3.1.2 α-Silyl-substituted aliphatic carbanions*

There are several crystal structures of aliphatic, α-silyl-substituted carbanions. A listing of many of these structures is given in Table 2, along with some references to the original literature where these structures are described. Only a few of these compounds can be considered as generally useful synthetic reagents. The aggregates formed by α-silyl-substituted carbanions are in many cases similar to those described previously for one of the unsubstituted aliphatic alkali metal or magnesium carbanions. A few of the α-silyl-substituted carbanions display unique aggregate structures and these are described as follows.

Tris(trimethylsilyl)methyllithium (**88**), prepared from methyllithium and tris(trimethylsilyl)methane in THF, can be recrystallized from toluene to give colorless, transparent needles of the unique ate complex $[Li(THF)_4]^+[Li\{C(TMS)_3\}_2]^-$.[90] The structure of one of the anions in this complex is shown as (**89**). This

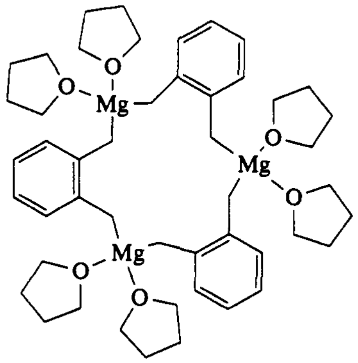

**(87)**

**Table 2** α-Silyl-substitued carbanions

| *Compound* | *Aggregation state* | *CSD refcode* | *Ref.* |
|---|---|---|---|
| TMS-methyllithium $Me_3SiCH_2Li$ | Hexamer | JAFMUY | 205 |
| Bis(TMS)methyllithium $(Me_3Si)_2CHLi$ | Polymer | CIMVUP | 206 |
| Bis(TMS)methyllithium·PMDETA $(Me_3Si)_2CHLi \cdot PMDETA$ | Monomer | BIYXOW | 207 |
| Tris($Me_2PhSi$)*methyllitium·THF* | Monomer | CATZAY | 208 |
| Bis(TMS)-2-methylpyridinelithium | Dimer | CAWMUI | 209 |
| Bis(TMS)-2-methylpyridinelithium·$2Et_2O$ | Dimer | COXTOY | 210 |
| Bis(TMS methyl)pyridinelithium·2TMEDA | Dimer | FERKOC | 211 |
| TMS(cyclopentadiene)·TMEDA | Monomer | CEZTIK | 212 |
| Bis(TMS)methyldiphenylphosphinelithium·TMEDA | Dimer | FIKPUK | 213 |
| TMS-methyl($PMe_2$)Li·TMEDA | Dimer | GIGGOS | 214 |
| TMS-methyl($PMe_2$)Li·THF | Dimer | GIKWS | 215 |
| Bis(TMS)methyl·MgCl·$Et_{2MgCl7Et}$ | Monomer | MSIMMG | 216 |
| 9,10-Bis(TMS)anthracene-9-diylmagnesium | Polymer | FOXBID | 217 |
| Bis(TMS)-2-methylpyridinemagnesium | Dimer | DONVUX | 218 |
| (TMS)methyl(*o*-diphenylphosphinophenyl)lithium | Dimer | VAGHUG | 219 |

anion is linear, with the $C(TMS)_3$ groups staggered about the C—Li—C direction. The cation consists of a lithium tetrahedrally coordinated by four oxygen atoms. Treatment of this ate complex, $[Li(THF)_4]^+[Li\{C(TMS)_3\}_2]^-$, in toluene with pentamethyldiethylenetriamine (PMDETA) containing lithium chloride yields a complex whose formula is given as $[(PMDETA)\text{-}Li\text{-}(\mu\text{-}Cl)\text{-}Li\text{-}(PMDETA)]^+[Li\{C(TMS)_3\}_2]^-$.[91] The anion is the same as in the $Li(THF)_4$ complex, but the new cation contains a PMDETA-complexed, linear Li—Cl—Li geometry depicted as (**90**) (Scheme 6).

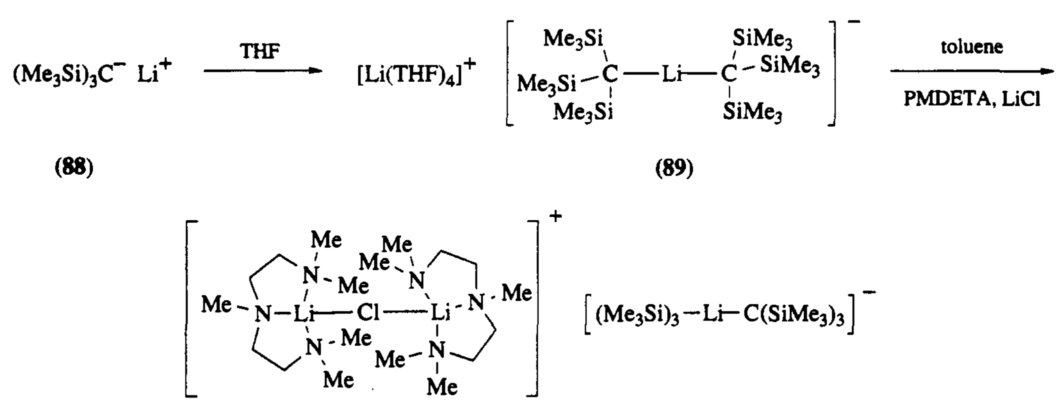

**(90)**

**Scheme 6**

### 1.1.3.2 Allylic Carbanions

Several examples of crystal structures are reported for the allyl carbanion. The first to be considered is allyllithium complexed with TMEDA (**91**).[92] In this complex, the terminal carbon atoms of the allyl group are linked to different lithium atoms forming polymeric chains. Each lithium atom is also coordinated to a chelating TMEDA. There is no evidence of η$^3$-bonding in this allyllithium·TMEDA structure. The structure of monomeric allyllithium solvated by PMDETA subsequently revealed a structure with a single lithium atom having relatively close but unsymmetrical contacts with the terminal carbon atoms and that the $C_3H_5$ anion is not planar.[93] A rough outline of this structure is given in formula (**92**).

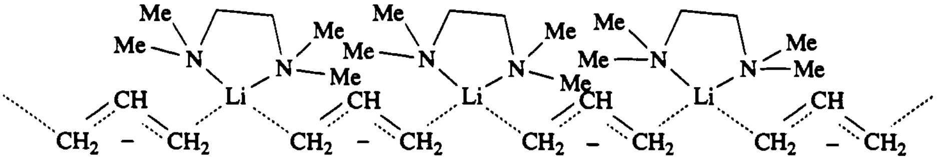

**(91)**

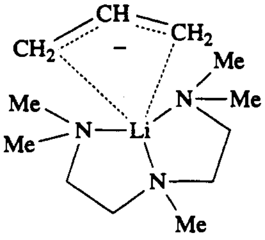

**(92)**

The first example of an η$^3$-allyllithium was reported for the polymeric 1,3-diphenylallyllithium·diethyl ether complex (**93**).[94] In this polymer, the lithium atoms lie almost symmetrically above and below the allyl group. The C(1)—C(2)—C(3) angle is quite large, *i.e.* 131°, similar to that in structures (**91**) and (**92**), but the C(2)—Li distance in (**93**) is shorter than either the C(1)—Li or C(3)—Li distances. The structural features of (**93**) correspond to those found in many allyl transition metal complexes which display η$^3$-bonding of the transition metal to the allyl group.[95]

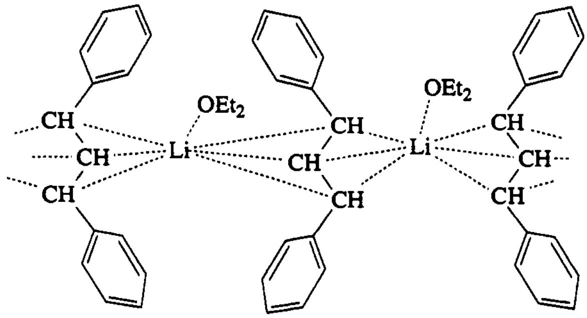

**(93)**

Allylmagnesium chloride crystallizes upon treatment of allylmagnesium chloride in THF with TMEDA.[96] This complex is characterized as the dimer (**94**). A four-membered Mg—Cl—Mg—Cl ring with bridging chlorine atoms forms the core of this dimer. The allyl group is clearly associated with the magnesium at C(1), *i.e.* C(1)—Mg = 2.18 Å, and the other structural features, *i.e.* the C(1)—C(2) and C(2)—C(3) bonds and the tetrahedral geometry at C(1), are commensurate with an η$^1$-structure. The η$^1$-structure of allylmagnesium compounds in solution was confirmed by NMR techniques, as well as by calculations.[97]

Bis(2,4-dimethyl-2,4-pentadienyl)magnesium (**95**), prepared by the reaction of the potassium dienide with anhydrous magnesium halide in THF and TMEDA, also exhibits a terminally bonded η$^1$-structure (**96**), with two dienides attached to a tetrahedral, four-coordinate Mg that is chelated by a single TMEDA

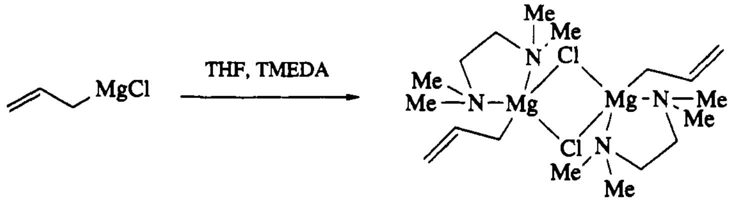

**(94)**

(Scheme 7).[98] This structure is consistent with the hydrolysis product of this complex which is obtained as a 1,3-diene, although either a 1,3-diene or a 1,4-diene is obtained upon addition of (**96**) and similar homologous dienylmagnesium complexes to ketones.

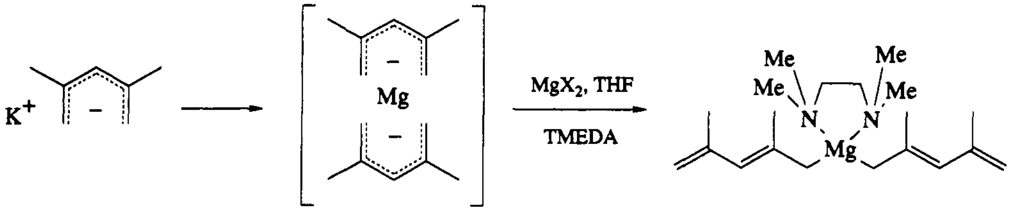

**(95)** **(96)**

**Scheme 7**

The crystal structures of indenyllithium·TMEDA,[99] indenylsodium·TMEDA[100] and bis(indenyl)magnesium[101] are also known. These three structures are all different. The lithium compound is monomeric with $\eta^5$-coordination; the sodium compound is infinitely aggregated with both $\eta^1$- and $\eta^2$-bonding; and the magnesium compound appears to include all three types of interactions, *i.e.* $\eta^1$-, $\eta^2$- and $\eta^5$-bonding, of magnesium to the indenyl anion.

### 1.1.3.3 Vinylic Carbanions

Relatively few vinyl carbanions have been characterized by X-ray diffraction analysis. The majority of these structures were determined by Schleyer and coworkers. Representative examples of some of these compounds are given as (**97**) and (**98**).

Compound (**97**) crystallized as a dimeric, bis-THF-solvated adduct with two different types of lithium atoms, illustrated as (**99**).[102] Compound (**98**) is a doubly lithium bridged dimer chelated with one TMEDA per lithium atom and roughly depicted as (**100**).[103] In the solid state, the sodium anion of (**101**) is monomeric with some of the relevant structural parameters shown in formula (**102**).[104]

The functional equivalent of an enolate dianion (**103**) was prepared by Stork *et al.* by treatment of enamine (**104**) with *t*-butyllithium.[105] This anion crystallized as the symmetrical dimer (**105**) with the carbanionic carbon nearly symmetrically bridging two lithium atoms as shown in (**105**). Doubly bridging carbons represent a characteristic feature of these lithiated vinylic anions and this structural feature is normally expected in these compounds as well as in aryl anions (see ref. 11).

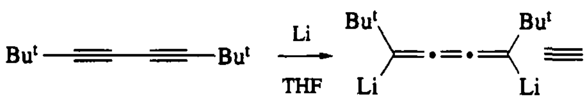

**(97)**

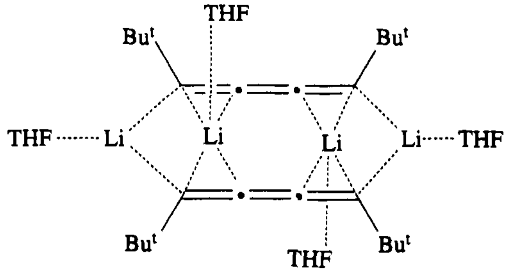

**(99)**

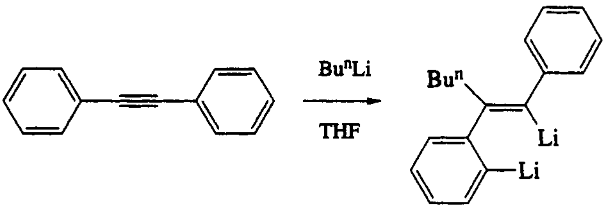

**(98)**

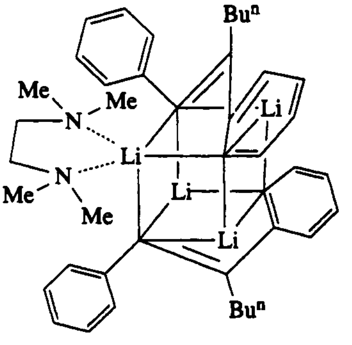

**(100)**

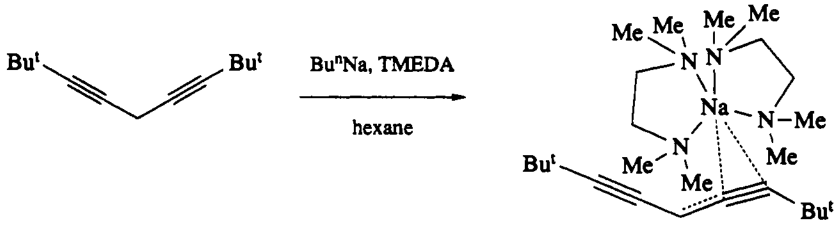

**(101)** **(102)**

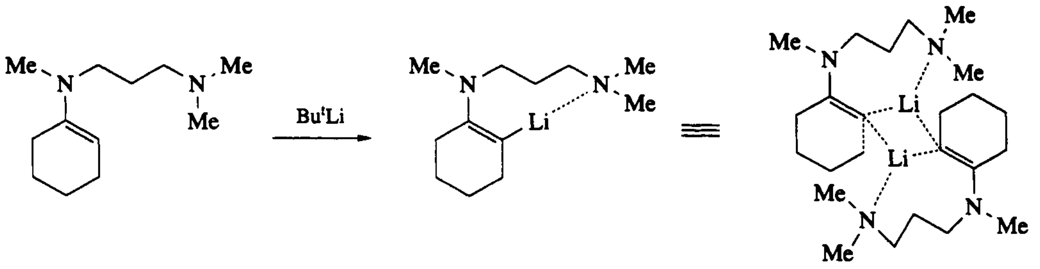

**(104)** **(103)** **(105)**

### 1.1.3.4 Alkynic Carbanions

A systematic investigation of alkynic carbanion structures has been reported by Weiss and coworkers. These structures all incorporate either *t*-butylacetylide or phenylacetylide anion. They differ by the ligand that is incorporated. Perhaps this sequence of structures most aptly demonstrates the rich variety of aggregate structural types that an acetylide anion can choose.

From the reaction of phenylacetylene with *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylpropanediamine (TMPDA) the dimeric complex (**106**) is obtained.[106] Note that the carbanionic acetylene carbon bridges only two lithium atoms in this structure. Dimeric phenylethynyllithium is also detected in THF by low temperature $^{13}$C NMR investigations and by cryoscopic measurements.[107] However, *t*-butylethynyllithium crystallizes from THF-containing solutions as either the tetramer (**107**) of composition $(\mathrm{Bu^tC{\equiv}CLi{\cdot}THF})_4$ or as the dodecamer (**108**) of composition $[(\mathrm{Bu^tC{\equiv}CLi})_{12}{\cdot}4\mathrm{THF}]$.[108] The dodecamer represents a linear combination of three tetramers of (**107**) minus the coordinating THFs. It is not unexpected that under the proper conditions of crystallization an octamer such as (**109**), representing an intermediate between (**107**) and (**108**), can be obtained. Perhaps crystallization of the octamer (**109**) can provide an interesting challenge of the experimental skills of those chemists who are fascinated by crystals and crystallizations of organic compounds.

When crystallized in the presence of of *N*,*N*,*N*′,*N*′-tetramethylhexanediamine (TMHDA) the cubic tetramer (**110**) of phenylethynyllithium was obtained.[109] Adjacent $(\mathrm{PhC{\equiv}CLi})_4$ units in (**110**) are each bound by pairs of TMHDA ligands giving rise to polymer strands with a helix-like structure.

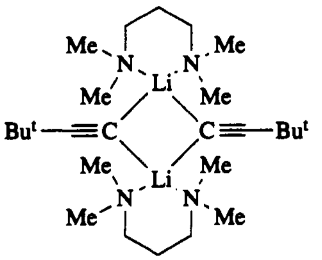

**(106)**

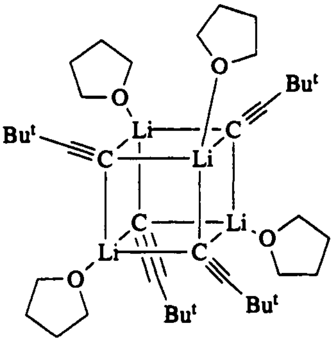

**(107)**

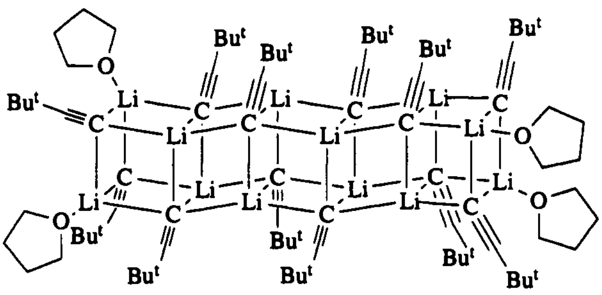

**(108)**

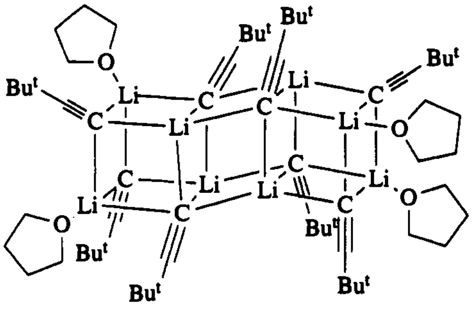

**(109)**

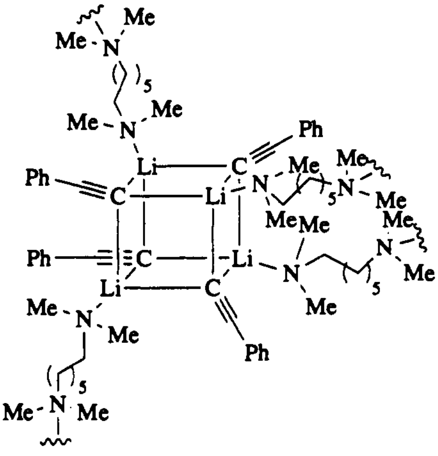

**(110)**

One final structure in this series is the bis-TMEDA-solvated bis(phenylethynyl)magnesium species characterized as a monomer (**111**).[110] Note the octahedral geometry of the central magnesium with two axial ethynyl ligands. This series of alkynic structures, (**106**)–(**111**), serves to underscore the unpredictability of carbanion crystal structures. The alkynic carbanions have coordination numbers of one, two or three in these complexes.

A few simple beryllium acetylide structures are known.[111] In one of these structures, illustrated as (**112**), the metal cation is symmetrically coordinated side-on to a triple bond.

### 1.1.3.5 Aryl Carbanions

As was the case for the alkynic carbanions, the crystalline aryl carbanions also offer the opportunity for observation and comparison of several different structural types for the same or closely related carb-

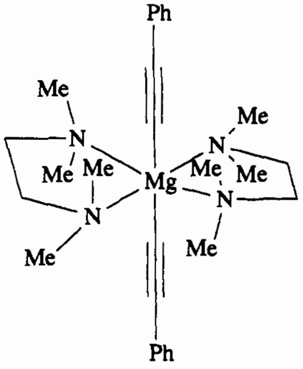

**(111)**

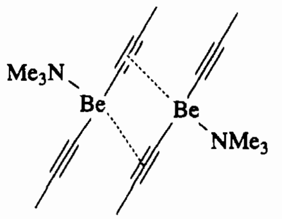

**(112)**

anion substrates. In many of the examples of aryl carbanion structures, the aryl carbanionic carbon is found bridging several different metal atoms. It is important to note that a large number of X-ray crystal structures of aryl carbanions have been determined, and that these have been comprehensively reviewed elsewhere.[11] Hence this discussion is necessarily limited to a subset of these structures which are representative of the whole class and which are also deemed most closely related to synthetic reagents in common usage. It is appropriate to begin this section with the structures of the simplest member of this series, *i.e.* the unsubstituted phenyl carbanion.

Phenyllithium dissolves in hexane by addition of TMEDA. The phenyllithium·TMEDA adduct subsequently crystallizes out of solution as the dimer (**113**) corresponding to general structural type (**16**).[112] With diethyl ether solvation, phenyllithium exists as a solid tetramer (**114**).[113] In ether solution PhLi is known to be either dimeric[114] or tetrameric.[115] Monomeric phenyllithium was successfully crystallized with PMDETA as the ligand.[116] This monomer is depicted as (**115**). Note the difference in the coordination number of the carbanionic center in the monomer (**115**), the dimer (**113**), and the tetramer (**114**), *i.e.* one, two and three, respectively.

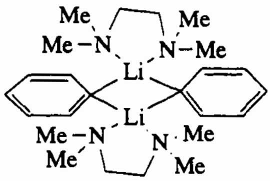

**(113)**

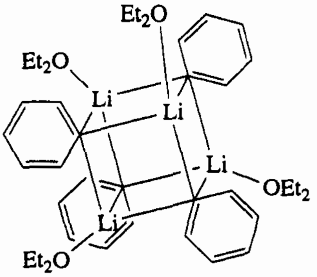

**(114)**

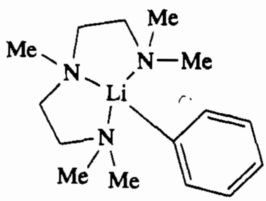

**(115)**

An interesting mixed tetrameric complex containing three equivalents of phenyllithium and one equivalent of lithium bromide, *i.e.* [$(PhLi)_3 \cdot LiBr \cdot 3Et_2O$], depicted as (**116**), has been characterized.[117] In this mixed aggregate the lithium atom diagonally opposite the bromide in the tetramer remains unsolvated by an ether molecule. Recall that the cyclopropyllithium·lithium bromide·diethyl ether complex (**44**) with stoichiometry $[(RLi)_2 \cdot (LiBr)_2 \cdot 4E_2O]$ is structurally related to (**116**), yet in the complex (**116**) all of the lithium atoms are coordinated to a solvent molecule and this is not found in (**44**).

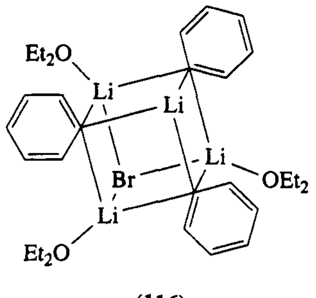

(**116**)

Alkyl substitution at the *ortho* positions of the aromatic ring influences the aggregation state and the structure by providing steric constraints. Whereas unsubstituted phenyllithium·diethyl etherate crystallized as the tetramer (**114**), mesityllithium·diethyl etherate is observed as the dimer (**117**) with stoichiometry $[mesitylLi \cdot Et_2O]_2$.[118] Mesityllithium gains an additional solvent molecule and crystallizes as the bis-solvated dimer (**118**) with stoichiometry $(mesitylLi \cdot 2THF)_2$ from THF-containing solutions.[119] Note that the coordination number of the lithium atoms changes from three to four in these two complexes but that the coordination and the coordination geometry remain the same at the carbon center. The change in solvation of the lithium atoms in the two complexes is also reflected in the interatomic distances. Hence, the three-coordinate lithium is 1.93 Å and 2.25 Å away from the ether oxygen and the aryl carbon respectively in (**117**), whereas the corresponding distances average 2.04 Å and 2.28 Å in (**118**).

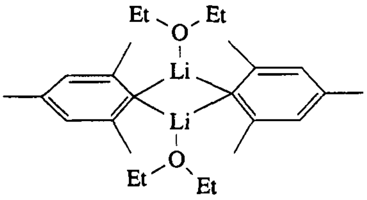

(**117**)

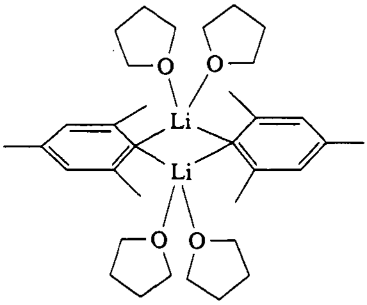

(**118**)

*Ortho* heteroatom substitution provides the opportunity for internal chelation in aryl anions. This effect is successfully utilized in synthetic endeavors, is commonly referred to as '*ortho* metallation', and is reviewed elsewhere.[120] Two different but related structures of *o*-methoxyphenyllithium are known. The most symmetrical of these is the tetramer (**119**) which crystallizes from pentane solution.[121] The solution structure of this compound has been investigated by NMR spectroscopy and by cryscopic measurements and the influence of various Lewis bases on the solution structure are discussed in the same paper as the X-ray structure. A most intriguing variation of the tetramer (**119**) crystallizes from hexane solution in the presence of TMEDA (but in the absence of LiBr). The structure of *o*-methoxyphenyllithium in the presence of TMEDA consists of a pair of unsymmetrical tetramers with the general features of (**119**) but which are linked to each other by a single TMEDA unit.[122] This latter aggregate is represented by the formula (**120**). Obviously the lithium atoms in (**119**) are four coordinate, but participation of the TMEDA in (**120**) forces one of the lithium atoms to be five coordinate. This five-coordinate lithium is in contact with two oxygens of different methoxybenzene residues rather than with an oxygen and a nitrogen of the TMEDA. Hence the symmetry of a tetramer is not maintained in (**120**).

Crystal structures have been reported for 2,6-dimethoxyphenyllithium,[123] for 2,6-dimethylaminophenyllithium[124] and for *o*-*t*-butylthiophenyllithium.[125] The crystal structure of the latter compound is characterized diagrammatically as the infinite polymer (**121**) with relatively planar tetracoordination at the *ipso* carbon. In THF solution this polymer dissociates into monomers. Planar four-coordinate carbons are also observed in the 2,6-dimethoxyphenyl anion (**122**) as a dimeric unit (**123**) which forms the basic building block of the solid of this anion. In this solid two of these simple dimers (**123**) combine to form

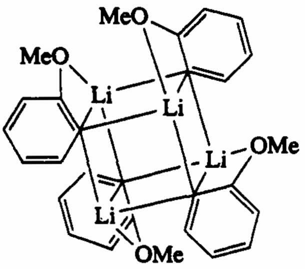

**(119)**

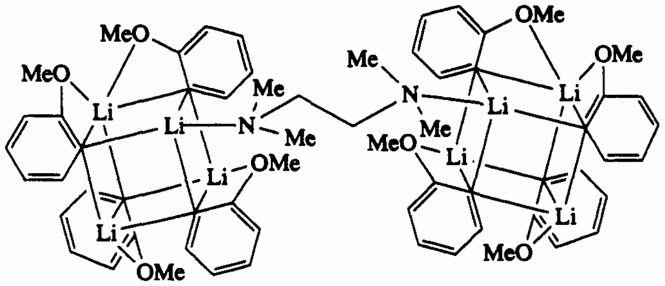

**(120)**

loose tetramers which are characterized as structure (**124**) in both the solid and in solution. In contrast to (**122**), recrystallization of 2,6-dimethylaminophenyllithium from hexane/ether solution yields the trimeric aggregate (**125**).

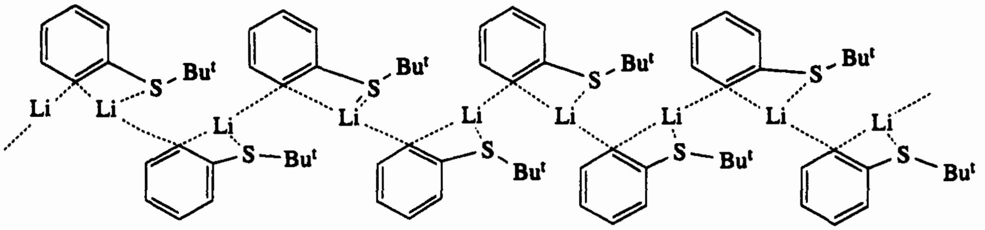

**(121)**

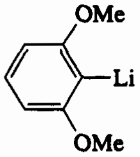

**(122)**

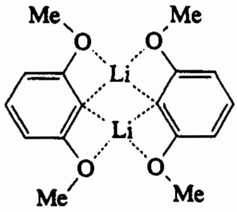

**(123)**

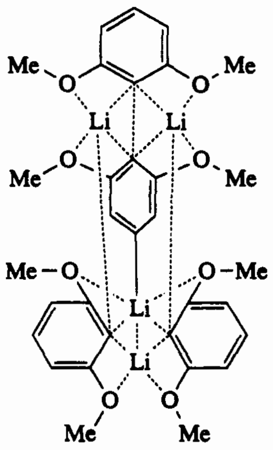

**(124)**

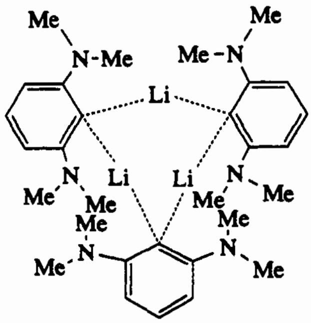

**(125)**

When a methylene group spacer is inserted between the *ortho* heteroatom and the carbanionic center, the coordination geometry of the anionic center is no longer restricted to be planar for intramolecular chelation to occur. Hence, *o*-(dimethylaminomethyl)phenyllithium (**126**) crystallizes from an ether/hexane solution as the internal-chelated tetramer (**127**).[126] This structure is analogous to tetrameric phenyllithium (**119**). When an additional dimethylaminomethyl group is substituted at the *ortho'* position as in 2,3,5,6-tetrakis(dimethylaminomethyl)phenyllithium, the aggregate crystallizes as the dimer (**128**).[127] The lithium atoms in both (**127**) and (**128**) are coordinated to four other nonlithium atoms; this coordination can only be achieved by dimerization and tetramerization respectively.

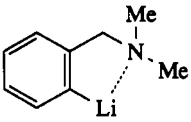

**(126)**

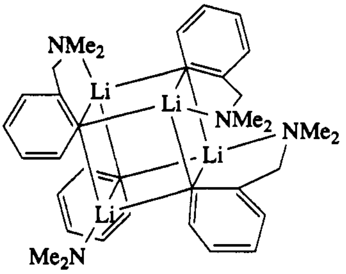

**(127)**

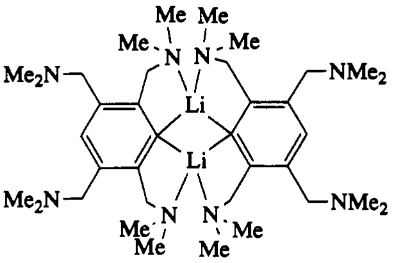

**(128)**

Two additional aryl crystal structures are noteworthy because they represent examples of alternative structural types of aryllithium anions. The first of these is the 2,2′-dianion of biphenyl (**129**). This material is characterized as the bis-TMEDA solvate (**130**) with two lithium atoms doubly bridging the two carbanionic centers.[128] The lithium atoms are located above and below the two aromatic rings. A completely different structure, depicted roughly as (**131**), is obtained for the air- and moisture-sensitive, violet crystals of dilithiobenzophenone.[129]

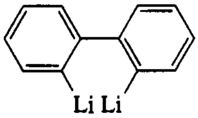

**(129)**

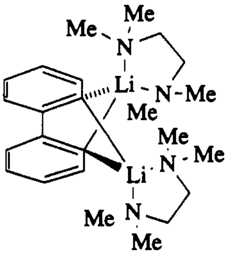

**(130)**

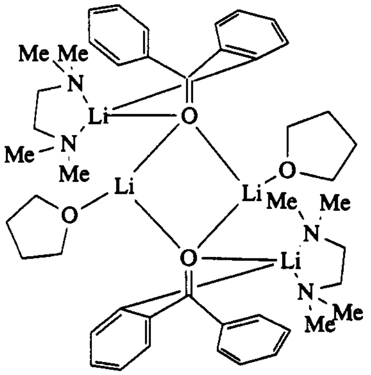

**(131)**

A few arylmagnesium compounds have been characterized crystallographically. As early as 1964, Stucky and Rundle determined that phenylmagnesium bromide·diethyl etherate consists of a magnesium atom tetrahedrally coordinated to two diethyl ether molecules, the phenyl group and a bromide.[130] This Grignard reagent is depicted as (**132**). Diphenylmagnesium·TMEDA also crystallizes as a monomer (**133**) with a tetrahedrally, four-coordinate magnesium atom.[131]

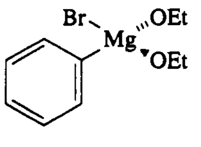

**(132)**

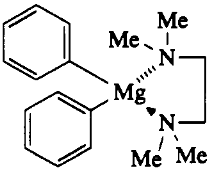

**(133)**

Bickelhaupt and coworkers have determined the crystal structures of a series of crown ether solvated magnesium compounds. A sequence of these compounds is illustrated as the internally coordinated 15-crown-4-xylylmagnesium chloride (**134**)[132] and bromide (**135**),[133] as well as the organometallic, rotaxane (**136**).[134] Note the similarity between these structures and the corresponding aliphatic dialkylmagnesium rotaxane (**83**).

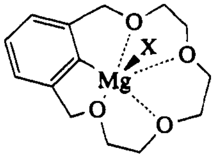

(**134**) X = Cl
(**135**) X = Br

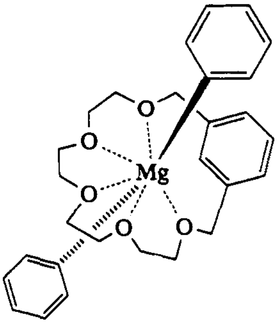

(**136**)

## 1.1.3.6 Enolates and Enamines and Related Species

### *1.1.3.6.1 Ketone enolates*

One of the most relevant and fruitful areas of structural investigation for synthetic organic chemistry during the past decade has been the crystal structure determinations of a variety of enolate and closely related carbanions. Although these species have been considered only as transient reactive intermediates, a number of these enolates can be crystallized out of solution at subambient temperature and stabilized under a stream of cold, dry nitrogen gas during the 24–48 h necessary for X-ray diffraction data collection. A systematic review of these structures known to date begins with the ketone enolates.

Seebach, Dunitz and coworkers first described the THF-solvated tetrameric aggregates obtained from THF solutions of 3,3-dimethyl-2-butanone (pinacolone) and cyclopentanone lithium enolates.[1] These are represented as (**137**). The pinacolone enolate also crystallizes as the unsolvated hexamer (**138**) from hydrocarbon solution, but this hexamer rearranges instantaneously to the tetramer (**137**) in the presence of THF.[135] Williard and Carpenter completed the characterization of both the $Na^+$ and the $K^+$ pinacolone enolates.[136] Quite unexpectedly the $Na^+$ pinacolone enolate is obtained from hydrocarbon/THF solutions as the tetramer (**139**) with solvation of the $Na^+$ atoms by unenolized ketone instead of by THF. The potassium pinacolone enolate is a hexameric THF solvate depicted as (**140**) and described as a hexagonal prism. A molecular model of (**140**) reveals slight chair-like distortions of the hexagonal faces in (**140**) so that the solvating THF molecules nicely fit into the holes between the pinacolone residues.

The pinacolone enolate residue crystallizes as a dimer with solvation by *N,N,N'*-trimethylethylenediamine (TriMEDA) as indicated in formula (**141**).[137] In this structure the NH hydrogen on the secondary amine is relatively close to the terminal carbon of the enolate residue, *i.e.* NH—C═C is 2.60 Å. This

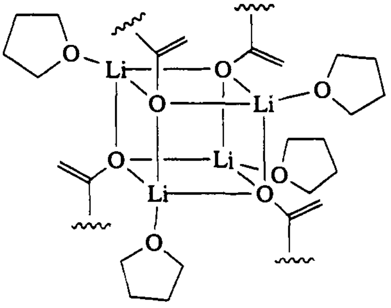

(**137**)

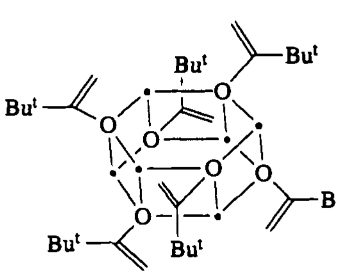

(**138**) • = Li

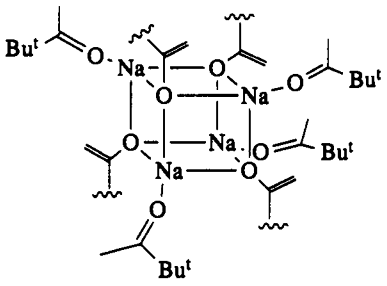

**(139)**

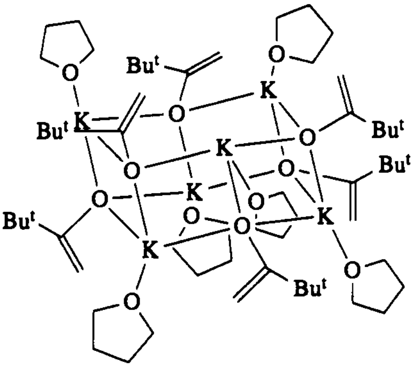

**(140)**

structure can prove useful in a structure–reactivity correlation, since it includes the hydrogen which is transferred in the enolization process. It is also valuable in explaining the fact that incomplete deuterium incorporation is often observed upon 'kinetic' protonation of certain enolates with deuterated acids since the NH proton can be returned directly to the enolate residue rather than a deuterium.

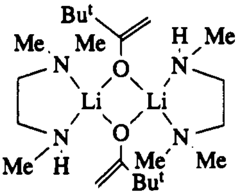

**(141)**

In an attempt to influence the aggregation state of a simple ketone enolate by intramolecular chelation, the homolog of pinacolone (**142**) was prepared.[138] The lithium enolate of this material cocrystallizes with lithium diisopropylamide (LDA) to produce the mixed, dimeric aggregate (**143**). A sequence of mixed enolate/amide base aggregates with five-, six- and eight-membered chelate rings similar to the aggregate (**143**) and depicted as (**144**) have been characterized.[139] It is noteworthy that the bulky silyloxy group serves as a ligand for the terminal, three-coordinate lithium atoms in (**143**).

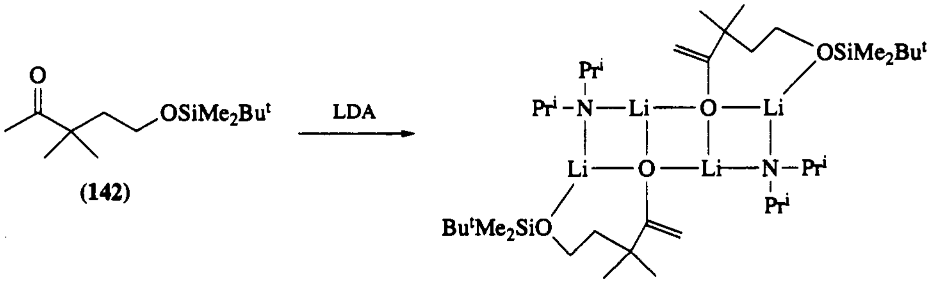

**(142)**

**(143)**

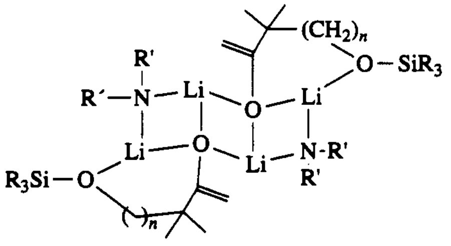

**(144)** $n = 0, 1, 2, 3$

Dimethylaminomethylacetophenone (**145**) reacts with LDA in diethyl ether to produce the tetrameric enolate aggregate (**146**).[140] This aggregate is an internally chelated variation of the tetramer (**137**). The origin of this enolate was not well defined in the original paper describing its characterization.

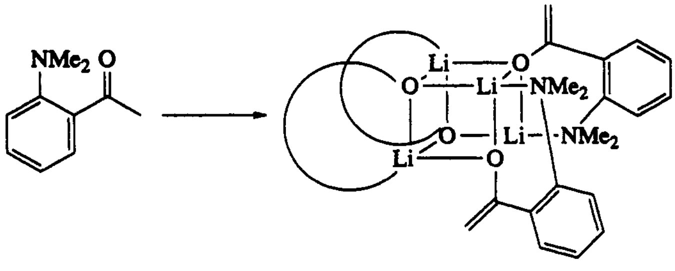

**(145)** **(146)**

The pinacolone lithium enolate condensation product with pivaldehyde (**147**) has been characterized as the tetrameric aggregate (**148**).[141] However, an attempted condensation reaction of pinacolone with itself as shown in Scheme 8 led to crystallization of a product derived from subsequent dehydration and reenolization, *i.e.* (**149**). This dienolate (**149**) was characterized as the dimer (**150**) solvated by dimethylpropyleneurea (DMPU).[142]

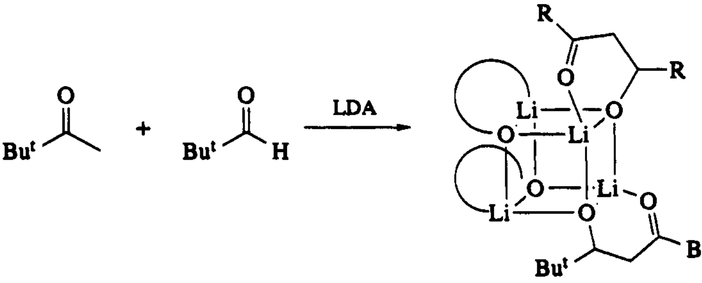

**(147)** **(148)**

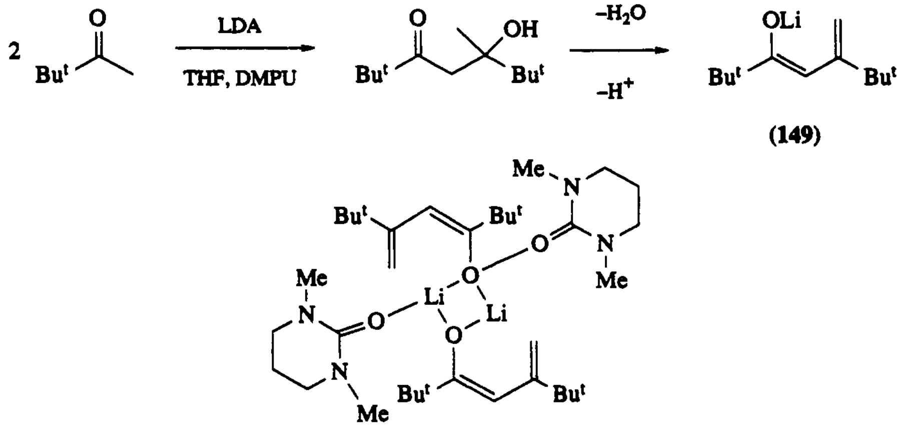

**(150)**

**Scheme 8**

The azaallyl enolates, *i.e.* enolates derived from ketone imines or hydrazones are synthetic equivalents of the ketone enolates and thus two examples of azaallyl enolates are included in this section. Lithiated cyclohexanonephenylimine (**151**) crystallizes out of hydrocarbon solution as the dimeric diisopropylamine solvate (**152**).[143] Significant disorder between the cyclohexyl and the phenyl moieties is observed in this crystal structure; however, it is clear that there are no $\eta^3$-azaallyl carbon contacts in this structure. This lithiated imine structure can be compared with the lithiated dimethylhydrazone of cyclohexanone

(**153**).[144] In this latter structure, roughly depicted as (**154**), there are two different lithium atoms as well as two different anion residues. In one of the residues a lithium is $\eta^5$-coordinated and in the other residue the lithium is $\eta^1$-coordinated. The possible origins of the selectivity of the alkylations of the metallated hydrazones are discussed relative to this structure. The lithiated hydrazone enolate (**155**) prepared from (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone of 2-acetylnaphthalene (**156**) yields the monomeric bis-THF-solvated species (**157**) as ruby red crystals.[145] This is one of the few examples of the crystallization of a resolved enolate substrate.[146]

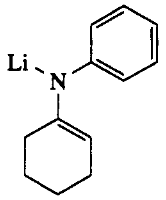

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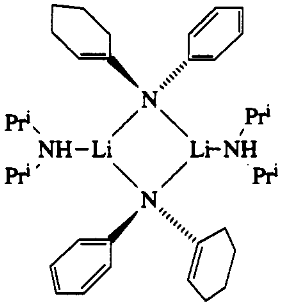

**(151)** **(152)**

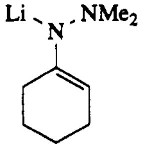

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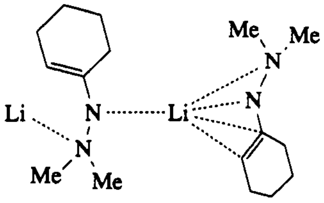

**(153)** **(154)**

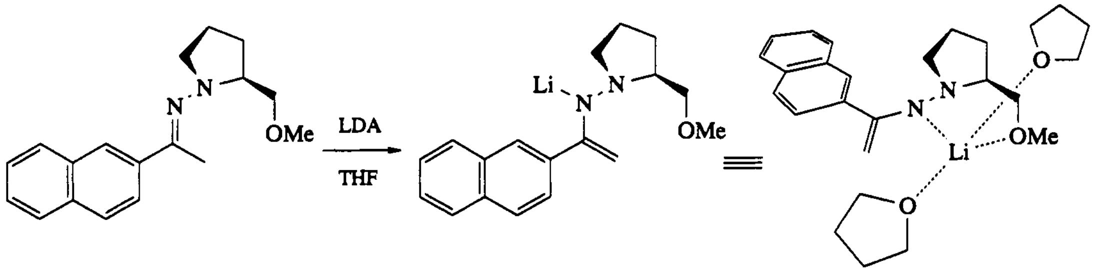

**(156)** **(155)** **(157)**

An uncharacteristic enolate coordination is observed for the α,α′-ketodianion derived from dibenzyl ketone (**158**).[147] The dianion crystallizes as a bis-TMEDA solvate with the general structure shown as (**159**). The two lithium atoms are on opposite sides of the relatively planar carbon skeleton. Each is solvated by TMEDA. Besides coordination to the oxygen, the lithium atoms are in close contact with four additional carbon atoms.

An early prediction about the structure of a magnesium ketone enolate[148] was subsequently modified when the diethyl ether solvated, magnesium bromide enolate derived from *t*-butyl ethyl ketone was characterized as the dimer (**160**) with bridging enolate residues.[149]

Recently the isolation and structure determination of the aldol product of the chiral iron enolate (**161**) with benzaldehyde was obtained as (**162**).[150] This structure is presumed to mimic closely the structure of the cyclic transition state for the aldol reaction.

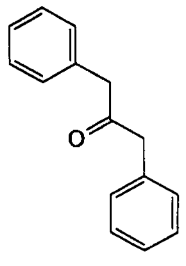

**(158)**

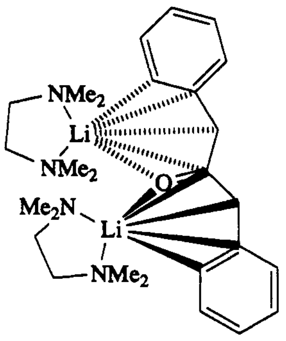

**(159)**

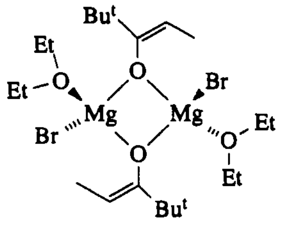

**(160)**

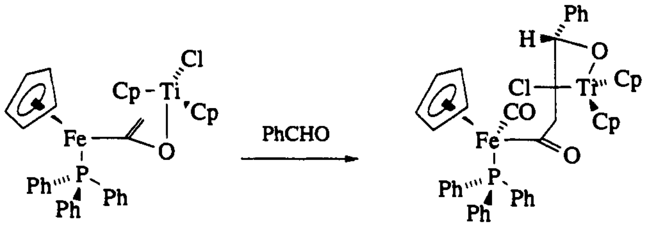

**(161)** **(162)**

### *1.1.3.6.2 Amide and ester enolates*

Few ester enolate crystal structures have been described. The lack of structural information is no doubt due to the fact that the ester enolates undergo α-elimination reactions at or below room temperature. A good discussion of the temperatures at which lithium ester enolates undergo this elimination is presented in the same paper with the crystal structures of the lithium enolates derived from *t*-butyl propionate (**163**), *t*-butyl isobutyrate (**164**) and methyl 3,3-dimethylbutanoate (**165**).[151] It is significant that two of the lithium ester enolates derived from (**163**) and (**165**) are both obtained with alkene geometry such that the alkyl group is *trans* to the enolate oxygen. It is also noteworthy that the two TMEDA-solvated enolates from (**163**) and (**164**) are dimeric, while the THF-solvated enolate from (**165**) exists as a tetramer.

Three additional ester enolates have been characterized and these can be compared to the lithium enolates (**163**)–(**165**). Recently we have obtained the mixed sodium ester/sodium hexamethyldisilazide aggregate derived from *t*-butyl isobutyrate and sodium hexamethyldisilazide as the TMEDA-solvated aggregate (**166**).[152] The second structure of interest is the zinc ester enolate, *i.e.* Reformatsky reagent, derived from *t*-butyl bromoacetate.[153] This zinc enolate (**167**) forms an eight-membered ring with the zinc atoms bonded directly to both enolate oxygens and to the α-carbon of the enolate. The observation of direct metal interaction with the enolate α-carbon of simple substrates is rare for alkali and alkaline earth metal cations. The third lithium ester enolate is derived from ethyl *N*,*N*-diethylglycine (**168**). It crystallizes as the internally chelated hexamer (**169**) which resembles the hexagonal prisms (**138**) and (**140**).[154]

Few amide or amide-like enolates have been characterized. This is somewhat surprising since amide enolates are expected to be less susceptible to ketene formation than the corresponding ester enolates.

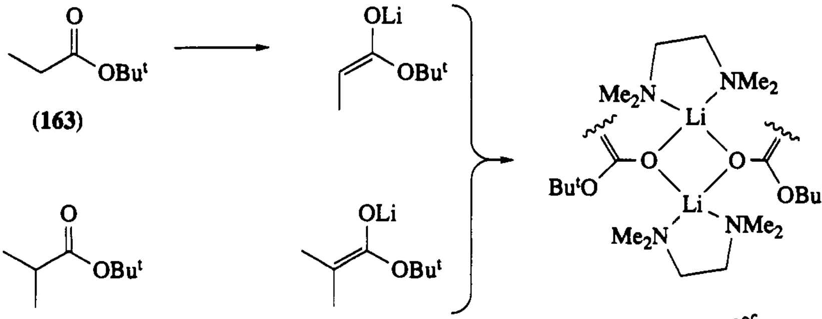

**(163)**

**(164)**

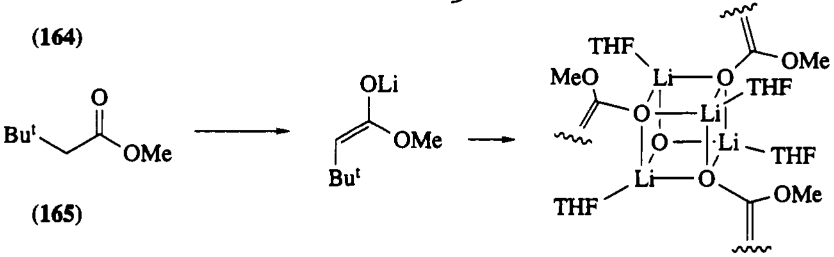

**(165)**

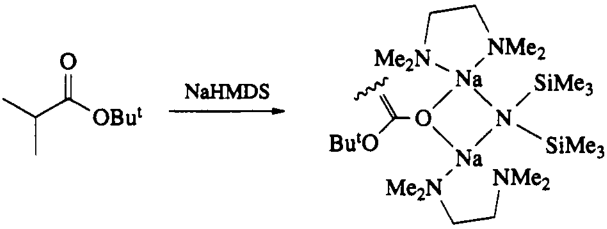

**(166)**

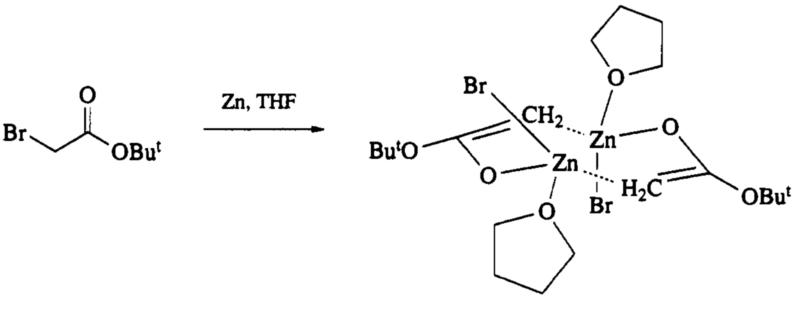

**(167)**

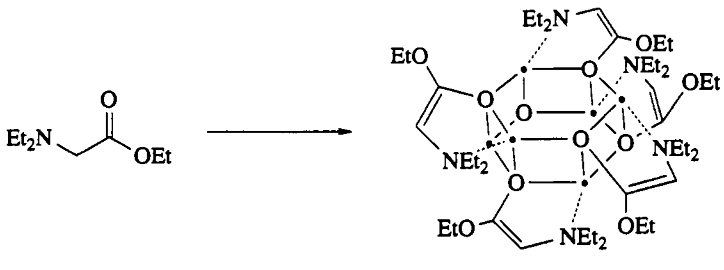

**(168)** **(169)** • = Li

The least highly substituted amide enolate whose structure is known is the lithium enolate of *N,N*-dimethylpropionamide (**170**).[155] This enolate is obtained as a dimer solvated by TriMEDA, *i.e.* (**171**). The alkene geometry in (**171**) is opposite that found in the ester enolates from (**163**) and (**165**). Thus in the dimer (**171**), the terminal methyl group is *cis* to the enolate oxygen and the alkenic residues are on opposite sides of the Li—O—Li—O core. It was noted that the hydrogen atom of the secondary amino group in (**171**) points in the direction of the virtual lone pair of electrons on the amide nitrogen.

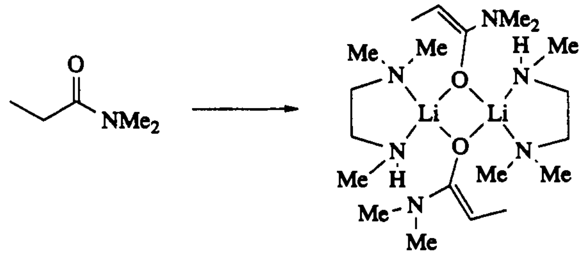

(**170**) (**171**)

The lithium enolate derived from *N*,*N*-dimethylcycloheptatrienecarboxamide (**172**) crystallizes as the bis-THF-solvated dimer (**173**).[156] Neither the amide nitrogens nor the extended π-system participates in complexation to the lithium atoms in this complex.

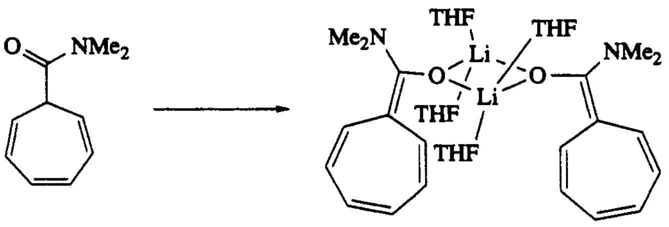

(**172**) (**173**)

Two lithium enolates (**174**) and (**175**) derived from the vinylogous urethanes (**176**) and (**177**) have been crystallized and subjected to X-ray diffraction analysis.[157] Although the individual enolate units combine to form different aggregates, they are very nearly identical in conformation, *i.e.* *s-trans* around the 2,3-bond; however, both the aggregation state and the diastereoselectivity of the enolates differ.[158] The enolate (**175**) is obtained from benzene solution as a tetramer and (**174**) is obtained from THF solution as a dimer. The origin of the diastereoselectivity shown by these enolates is subtle.

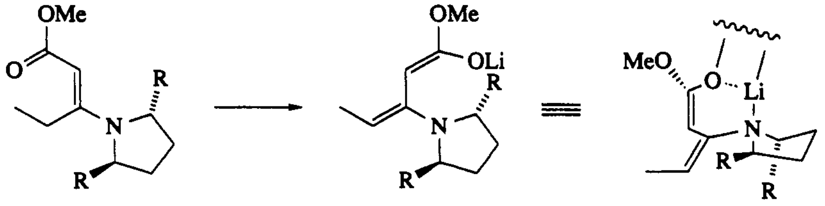

(**176**) R = H
(**177**) R = Me

(**174**) R = H
(**175**) R = Me

### *1.1.3.6.3 Nitrile and related enolates*

Three examples of nitrile-stabilized enolates have been described by Boche *et al.* Two of these structures incorporate the anion of phenylacetonitrile. The TMEDA-solvated dimer (**178**) crystallizes out of benzene solution;[159] however, the mixed nitrile anion·LDA·(TMEDA)$_2$ complex (**179**) is obtained when excess LDA is present.[160] This latter complex has often been mistaken as a geminal dianion since it frequently gives products that appear to arise from a dianion. The crystal structure of the anion 1-cyano-2,2-dimethylcyclopropyllithium (**180**) consists of an infinite polymer (**181**) that is solvated by THF.[161] Interestingly, there are C—Li contacts in this structure and the carbanionic carbon remains tetrahedral.

The tetrahedral carbanion agrees well with the experimental results that optically active cyclopropylnitrile carbanions can undergo reprotonation with retention of configuration under certain conditions.

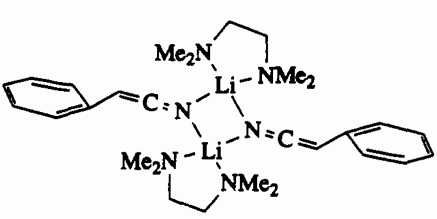
Me2N
Li
NMe2
C
N
N
C
Me2N
Li
NMe2

**(178)**

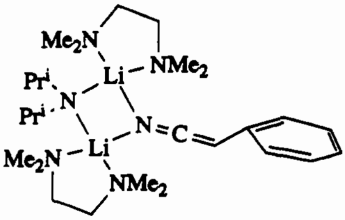
Me2N
Li
NMe2
Pri
Pri
N
N
C
Me2N
Li
NMe2

**(179)**

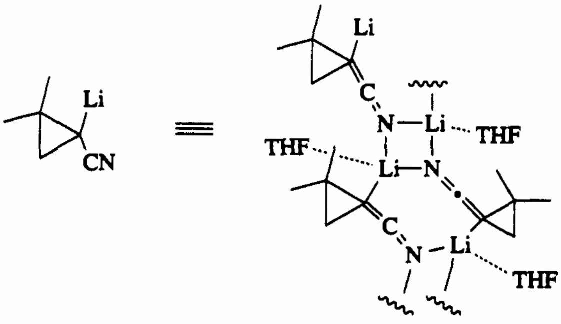
Li
CN
≡
Li
C
N
Li
THF
THF
Li
N
C
N
Li
THF

**(180)** **(181)**

A true dianion (**182**) is obtained in the reaction of (**183**) with base and this dianion crystallizes from ether/hexane solution with the stoichiometry $[(Me_3SiCCN)_{12}{\cdot}Li_{24}{\cdot}(Et_2O)_6{\cdot}(C_6H_{14})]$.[162] The crystal structure exhibits both N—Li and C—Li contacts and is best described in the original manuscript because there is no simple way to redraw this exceedingly complex aggregate structure.

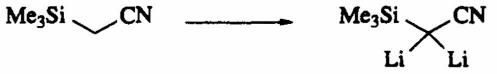
Me3Si
CN
Me3Si
CN
Li
Li

**(183)** **(182)**

The crystal structures of both $Na^+C(CN)_3^-$ [163] and $K^+C(CN)_3^-$ [164] are known for comparison. In all examples of the nitrile-stabilized carbanions except the dianion (**182**), the metal coordination to the organic anion is through the nitrogen. No evidence of interaction between the metal and the nucleophilic carbon atom is seen. Lithiated imine (**184**) is somewhat analogous to dimer (**150**), although this species is not derived from an enolizable substrate.[165]

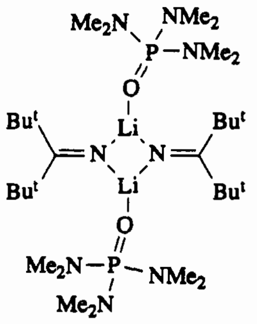
Me2N
NMe2
P
NMe2
O
Li
But
But
N
N
But
But
Li
O
Me2N
P
NMe2
Me2N

**(184)**

### *1.1.3.6.4 Other stabilized enolates*

The crystal structure of a single stabilized nitronate carbanion derived from phenylnitromethane is reported as the polymeric ethanol solvate (**185**).[166] The same geometry found in the nitronate anion (**185**) was also found for the *t*-butyldimethylsilyl ester derived from quenching this nitronate.[167] References to other structures containing carbanions stabilized by a nitro group are given in Table 3; however, it is to be noted that these are derived from highly acidic carbon acids.

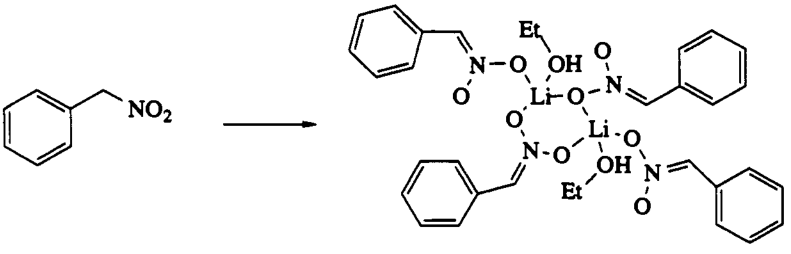

**(185)**

**Table 3** Stabilized Carbanions

| *Compound name* | *CSD refcode* | *Ref.* |
|---|---|---|
| $Ca(acac)_2 \cdot 2H_2O \cdot H_2O)$ | BOLTIF | 220 |
| $Na(acac) \cdot H_2O$ | CAFNEC | 221 |
| $Ca(acac)(CH_3CO_2\text{-}) \cdot 2H_2O)$ | CUHGER | 222 |
| $Li[PhC(O)CHC(O)Ph] \cdot 2H_2O \cdot Et_3N$ | DEKJUY | 223 |
| $Mg_3(acac)_6$ | DENGAE | 224 |
| K-nitromalonamide | NOMLNB | 225 |
| Na(eaa)·15-crown-5 | BODKUG | 226 |
| K(eaa)·18-crown-6 | CREALK, CRKEAC01, CRKEAC10 | 227 |
| $CsC(NO_2)_3$ | CSTNME | 228 |
| K-1,1-dicyano-3-thiabut-1-en-2-olate | FAZBAJ | 229 |
| Na-2-propenal-3-olate | FUSPEO | 230 |
| K-4,4-dinitro-2-butenamide | KDNBUT | 231 |
| K-2,2-dinitroethylacetamide | NEYACM | 232 |

The sodium salt of the stabilized enolate derived from the heteroaryl-substituted 2-oxoglutaric acid ester (**186**) is reported to have the alkene geometry as shown in formula (**187**).[168] Finally, Collum *et al.* have reported the structure of the lithiated anion derived from the *N*,*N*-dimethylhydrazone of 2-methoxycarbonylcyclohexanone (**188**).[169] This enolate crystallizes as the dimeric, bis-THF-solvated aggregate (**189**).

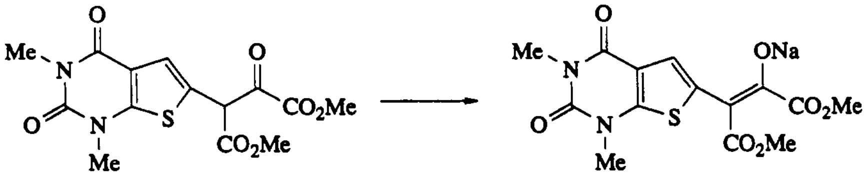

**(186)** **(187)**

## 1.1.3.7 Heteroatom- substituted Carbanions (α-N, α-P or α-S)

To date there are only a few synthetically relevant crystal structures with a nitrogen directly attached to the carbanionic center. X-Ray crystal structure determination of the lithium salt of bis-lactim ether (**190**), derived from alanine, has been characterized and is depicted as (**191**).[170] This structure illustrates

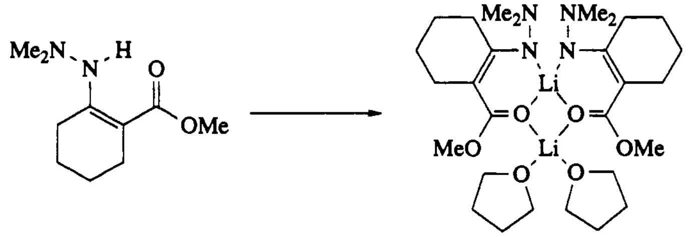

**(188)** **(189)**

that the lithium atoms share very different environments, *i.e.* one five coordinate and one four coordinate. The bromomagnesium derivative of *N*-pivaloyltetrahydroisoquinoline (**192**) crystallizes from THF as a monomer with octahedrally coordinated Mg atoms.[171] This Mg atom coordinates to the carbanion, the amide carbonyl oxygen, a bromine and three THF molecules. A mechanistic proposal is derived from the crystal structure (**193**) to explain the selectivity for addition of this anion to ketones.

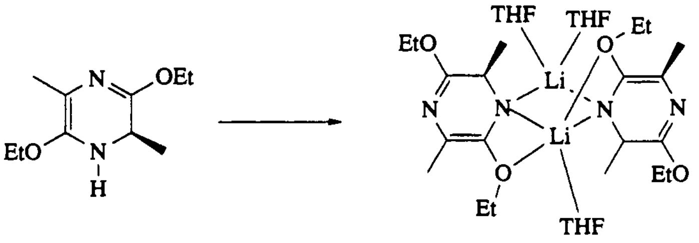

**(190)** **(191)**

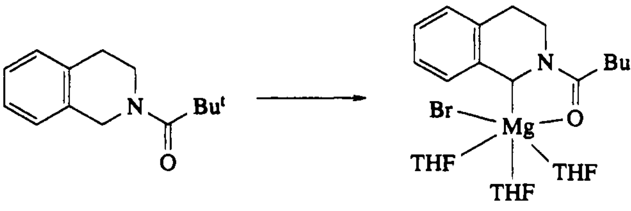

**(192)** **(193)**

*N*-Phenylpyrrole (**194**) is monolithiated at the 2-position of the heterocyclic ring. This monolithium compound crystallizes as the TMEDA-solvated dimer (**195**).[172] This structure agrees well with the $^6$Li–$^1$H 2D heteronuclear Overhauser NMR spectroscopy (2D-HOESY). The structure serves to predict correctly that the second lithiation to a dianion occurs at the *ortho* position of the phenyl ring located closest to the lithium in the monoanion.

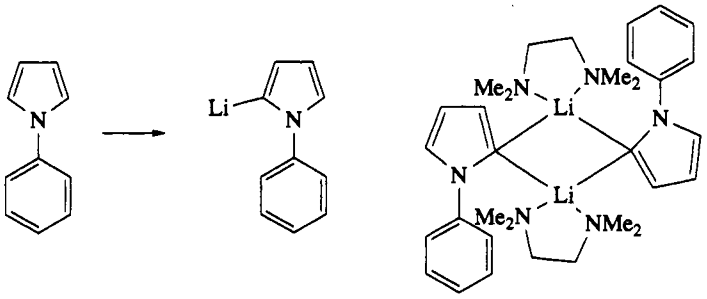

**(194)** **(195)**

Finally, the crystal structure of a lithiated amino nitrile (**196**) has been described in Boche's recent review article as a dimer (**197**) similar to the other nitrile anions (**179**), (**180**) and (**182**).[14] However, there is extended network throughout the solid (**197**) due to coordination of the lithium atoms with the oxygens at the *para* position of the aryl rings of adjacent molecules.

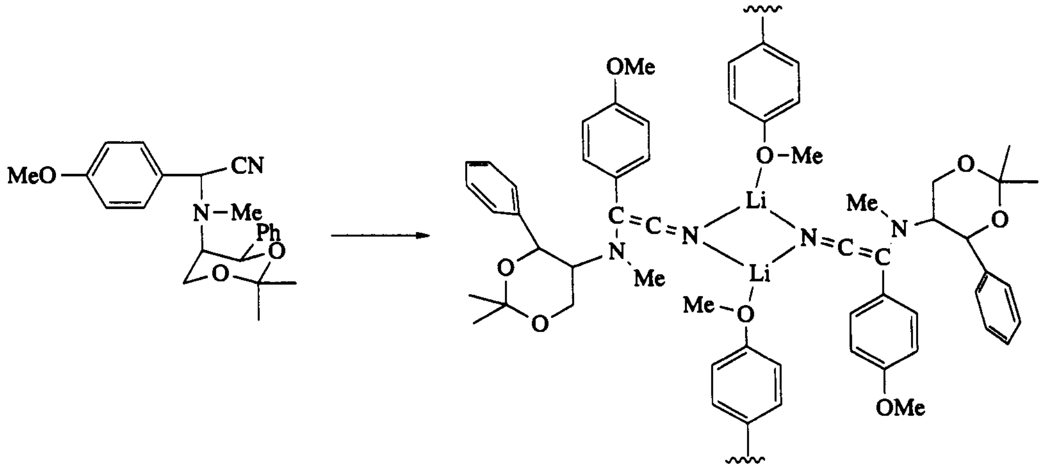

**(196)** **(197)**

Excluding the α-P-, α-Si-substituted carbanions which are listed in Table 2, there exist relatively few simple α-P-substituted carbanions whose structures are known. References to the crystal structures of some tri (alkyl or aryl) substituted phosphines are listed in Table 4. Few if any of these compounds have been utilized as synthetic reagents. Only two synthetically useful phosphorus-stabilized carbanions of Group Ia or IIa metal cations have been examined by X-ray diffraction analysis. The lithium carbanion of 2-benzyl-2-oxo-1,3,2-diazaphosphorinane (**198**) crystallizes as a monomeric bis-THF solvate (**199**) with a tricoordinate lithium atom.[173] The magnesium salt of diethoxyphosphinyl acetone (**200**) is characterized as an intramolecularly chelated trimer[174] similar in structure to $[Mg(acac)]_3$. The Cu salt of this β-keto phosphorus-stabilized anion exists only as a monomer.[175]

There has been much synthetic interest in sulfur-stabilized carbanions. These anions include sulfides, 1,3-dithianes, sulfoxides, sulfones and sulfoximides. Since the structural results in this area have been recently compiled and discussed in excellent detail by Boche,[14] it will suffice to present only the list of compounds in Table 5 whose structures have been reported. Most of these anions have varied and unique

**Table 4** α-Phosphorus-stabilized Carbanions

| *Compound* | *CSD refcode* | *Ref.* |
|---|---|---|
| $LiCH_2PMe_2 \cdot TMEDA$ | CEDSIN, CEDSIN10 | 233, 234 |
| $LiCH_2P(Me)Ph \cdot (-)\text{-sparteine}$ | VAGHOA | 234 |
| $LiCH_2P(Me)Ph \cdot TMEDA$ | VAGHIU | 234 |
| $[(LiCH_2PPh_2)_2(dioxane)_3] \cdot dioxane$ | DUJDIV | 235 |
| $[LiC(PMe_2)_3 \cdot 2THF]_2$ | CESCEI, CESCE10 | 236 |
| $LiCH(PPh_2)_2 \cdot THF$ | GIKXAZ | 237 |

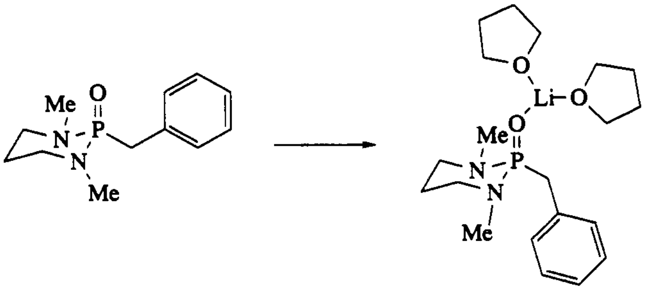

**(198)** **(199)**

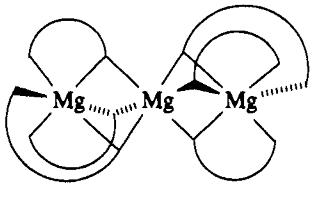

**(200)**

structures. These structures have proven extremely valuable for structure reactivity correlations and this is discussed in the aforementioned review.

**Table 5** α-Sulfur-stabilized Carbanions

| *Compound type* | *Compound* | *CSD refcode* | *Ref.* |
|---|---|---|---|
| Sulfides | (MeSCH$_2$Li)$_2$·(TMEDA)$_2$ | CEPLEO | 238 |
| | (PhSCH$_2$Li)$_2$·(TMEDA)$_2$ | CEPLAK | 238 |
| | [(*E*)-2-Butenyl-1-SBu$^t$]·TMEDA | GAJDAW | 239 |
| 1,3-Dithianes | [Li(2-methyl-1,3-dithiane)]$_2$·(TMEDA) | LIMDTE | 240 |
| | [Li(2-phenyl-1,3-dithiane]$_2$·(TMEDA)$_2$·THF | LIPTHF | 241 |
| Sulfoxides | (α-Methylbenzyl phenyl sulfoxide·Li)$_2$·(TMEDA)$_2$ | FIGHEI | 242 |
| Sulfones | [α-(Phenylsulfonyl)benzyllithium]$_2$·(TMEDA)$_2$ | DIBXIV | 243 |
| | (Phenylsulfonylmethyllithium)$_2$·(TMEDA)$_2$ | DOMSED | 244 |
| | 2,2-Dipehnyl-1-(phenylsulfonyl)cyclopropyllithium·(DME)$_2$·(DME) | VADKIU | 245 |
| | 2,0-Lithium dianion of bis(TMS)methyl phenyl sulfone | GEHZOI | 246 |
| | [α,α-lithium trimethyl(phenylsulfonylmethyl)silane]$_6$·LiO$_2$·(THF)$_{10}$ | GAFXIU | 247 |
| | α-(Phenylsulfonylallyl)lithium·DME | FAGFOI | 248 |
| | α-(Methylbenzyl)phenylsulfonyldilithium·diglyme | GAVYUX | 249 |
| | Isopropylphenylsulfonyldilithium·diglyme | GAVZAE | 249 |
| | Bis(TMS)methyl phenyl sulfone potassium (Et$_2$O)(18-c-6) | SAKXOR | 250 |
| Sulfoximes | [(*S*)-(*N*-methyl-*S*-phenylsulfonimidoyl)methyllithium]$_4$·(TMEDA)$_2$ | FISNOW | 251 |
| | (TMS)[*N*-(TMS)-*S*-phenylsulfonimidoyl][methyllithium]$_4$ | FECRAG | 252 |

## 1.1.3.8 Related Alkali Metal and Alkaline Earth Anions

### *1.1.3.8.1 Amides and alkoxides*

Since most of the synthetically useful enolate anions described in the previous section are prepared by the reactions of enolizable substrates with alkali metal amide bases, it is appropriate to note a few structures of these amide bases. The common bases in synthetic organic chemistry include LDA and LHMDS. The structures of both of these bases are known as the THF solvates.[176,177] Both of these compounds form bis-solvated dimers corresponding to structure (**201**). The diethyl ether solvate of LHMDS also forms a bis-solvated dimer (**202**).[178] Sodium hexamethyldisilazide crystallizes as an unaggregated monomer from benzene solution.[179] Two different crystalline forms of KHMDS are known as the polymeric dioxane solvate (**203**),[180] and the unsolvated dimer (**204**).[181]

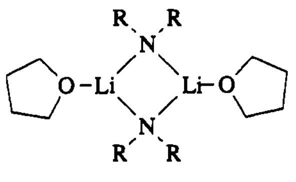

**(201)** R = Pr$^i$ or SiMe$_3$

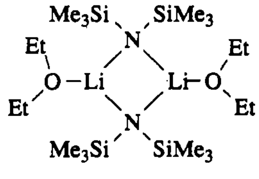

**(202)**

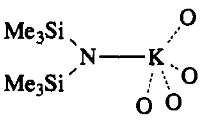

**(203)**

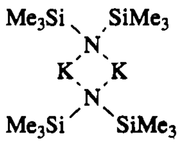

**(204)**

The nonalkali metal bis(trimethylsilyl)amide crystal structures are too numerous to elaborate in detail here, but a partial listing of these includes the bis(trimethylsilyl)amide anion bound to Ti, Sn, Mg, Al, *etc.* Individual references to the structures of these compounds are best found in the CSD.[3] A recent review of the various cage structures available for the main group metal amide bases and alkoxides is given.[182] Recall that a few previously described carbanion crystal structures, *i.e.* **(143)**, **(166)** and **(179)**, form mixed aggregates containing the lithium diisopropylamide moiety or the NHMDS moiety and a carbanion.

Recent structural investigations on lithium organo(fluorosilyl)amides have revealed that the lithium cation can form aggregates with internal lithium coordination to fluorine, and mixed aggregates of the amide and LiF.[183] Structural types such as **(205)**, **(206)**, **(207)** and **(208)** have been found for these compounds.

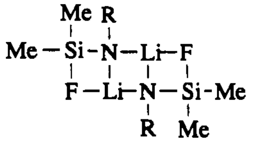

**(205)**

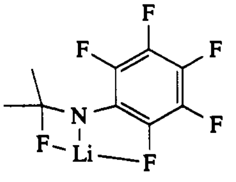

**(206)**

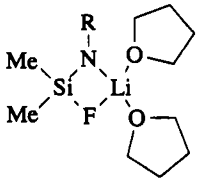

**(207)**

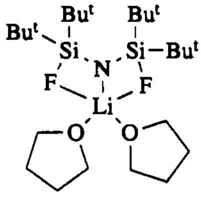

**(208)**

Many of the enolate crystal structures described in Section 1.1.3.6 are coordinated to metal cations only through the enolate oxygen atom. From a structural point of view, these aggregates might be thought of as simple alkoxide anions rather than as carbanions. Because of this structural analogy between the simple enolates and alkoxides, Table 6 is presented. References are given in this table as representative examples of aggregates of alkali metal and alkaline earth salts of relatively simple alkoxides. It is possible to compare the enolate and alkoxide anion structures and perhaps to anticipate new structural types for both groups. Recall also the interesting mixed aggregate that forms between Bu$^n$Li and lithium *t*-butoxide **(45)**. The complex structure of a mixed metal, enolate/alkoxide aggregate has recently been described by our group as **(209)**.[184]

### *1.1.3.8.2 Halides*

The effect of added halide salts on organic reactions is recently undergoing intensive scrutiny.[185] To date only a few mixed aggregate structures containing both carbanion residues and halide anions (excluding the many MgX$^-$ aggregates) have been described. Two of these are previously listed in this chapter as **(44)** and **(116)** plus the few mixed cuprates in the next section. References to the crystal structures of a few simple halide salts are also given in Table 6, with the expectation that these structures may provide some guidance with predicting and preparing mixed carbanion/halide aggregates whose structures remain to be determined.

**Table 6** Representative Alkoxide and Halide Structures

| *Compound* | *CSD refcode* | *Ref.* |
|---|---|---|
| NaOBu$^t$ | NABUOX, NABUOX10 | 253 |
| CsOH·MeOH | GAYCAK | 254 |
| CsOPr$^i$ | IPRXCS | 255 |
| Ba(OMe)$_2$ | MEOXBA | 256 |
| Ca(OMe)$_2$ | MEOXCA | 256 |
| Sr(OMe)$_2$ | MEOXSR | 256 |
| (CuOBu$^t$)$_4$ | CUTBUX | 257 |
| (LiCl)·(HMPA) | CAWSIC | 258 |
| (NaBr)·(acetamide)$_2$ | DIACNB, NABRAA | 259 |
| (LiCl)·(*N*-methylacetamide) | LICMAC, LICMAC10 | 260 |
| (LiBr)·(acetone)$_2$ | DECXEO | 261 |
| (MgCl$_2$)·(*N*-methylacetamide) | NMALIE | 262 |
| (LiI)·(Ph$_3$PO) | LIPPHO | 263 |

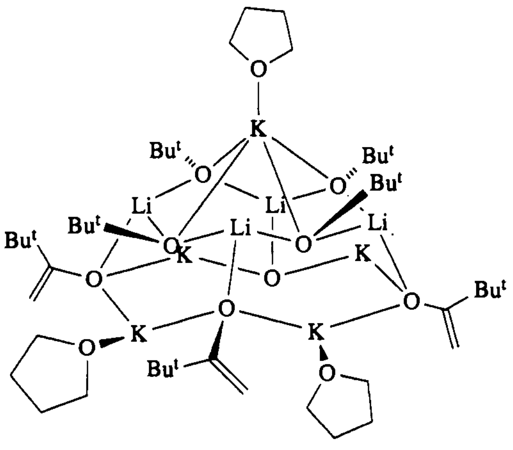

**(209)**

### 1.1.3.9 Mixed Metal Cation Structures

#### *1.1.3.9.1 Without transition metals*

There are a few carbanion aggregates formed with different metal cations in the aggregate. Three of these structures contain both $Li^+$ and $Na^+$ cations. Weiss characterized a $(MeNa)_x{:}(MeLi)_y$ preparation by powder diffraction of this material. These results suggested a geometry analogous to that of the $(MeLi)_4$ tetramer (**38**). A unique diphenyl lithium/sodium·TMEDA complex was characterized also by Weiss with stoichiometry $[Na\text{-}TMEDA]_3$ $[Li\text{-}phenyl_4]$.[186] The single lithium atom, located in the center of the ate complex, forms a pseudo-tetrahedron with four phenyl groups. The lithium atom also lies almost at the center of a triangle formed by TMEDA-coordinated Na atoms. A view from the open face of this structure is approximately as seen in (**210**). A recent characterization of a mixed $Li^+/Na^+$ metal amide aggregate shows a central core as drawn in (**211**).[187] In this aggregate the anion is derived from the imine of *t*-butyl phenyl ketone (**212**).

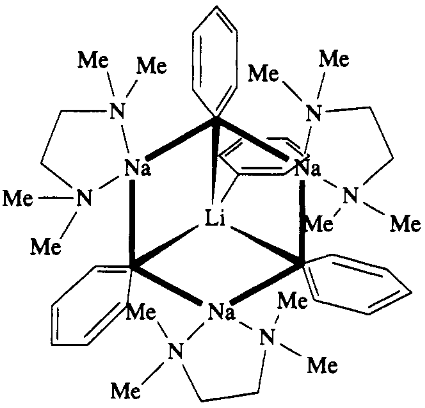

**(210)**

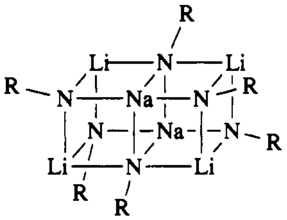

**(211)**

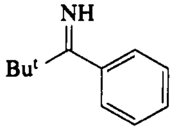

**(212)**

A mixed $Li^+/Mg^+$ aggregate corresponding to (**213**) is formed with either phenyl or methyl carbanions.[188,189] An unusual lithium/magnesium acetylide is formed with stoichiometry $Li_2[(PhC{\equiv}C)_3Mg(TMEDA)]_2$ and is depicted as (**214**). The same authors also report the ion pair characterized as the mixed benzyllithium/magnesium·TMEDA complex (**215**).[190] A different mixed lithium/magnesium aggregate depicted as (**216**) is found for the THF-solvated anion of tris(trimethylsilyl)methyl carbanion.[191]

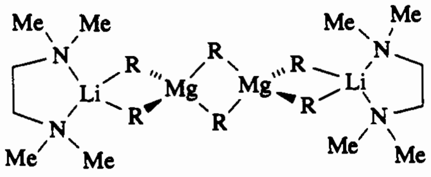

**(213)**

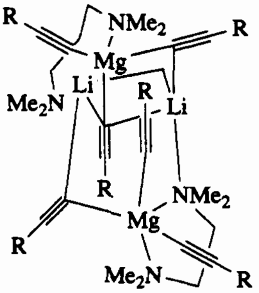

**(214)**

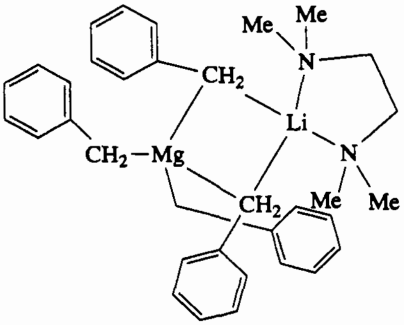

**(215)**

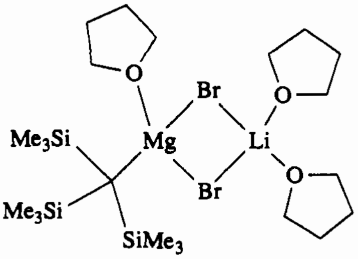

**(216)**

### *1.1.3.9.2 With transition metals (cuprates)*

A dimeric complex of the type $Li_2Cu_2R_4$ where R is phenyl has recently been characterized as the diethyl ether solvate (**217**).[192] This structure is the most recent of an extremely interesting series of diorganocuprate structure determinations. These reagents find many applications in organic synthesis, and there now exist structural models for the sequence of the species as tabulated in Table 7. Almost all of these compounds incorporate aryl groups rather than alkyl groups due to the instability of the simple lithium dialkylcuprates. Many of these structures are complex and the structures are best discussed in the original manuscripts. It is noteworthy that the complexes listed in this table now provide a structural framework for the series of organocopper reagents with a number of different stoichiometries.

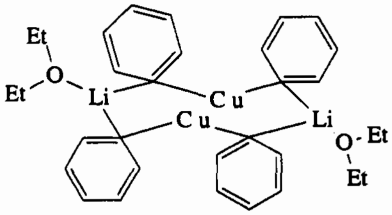

**(217)**

## 1.1.4 CRYSTAL GROWTH AND MANIPULATION

Most of the examples of X-ray crystal structure determinations cited in this review have been carried out at subambient temperature. This is necessary since many, but not all, of the carbanions are only stable as solids at low temperatures. Several special techniques exist for handling temperature- and moisture-sensitive solids. General reviews of these techniques exist.[193] On the average these diffraction analyses require a data collection time spanning the range from 12 to 50 h. The carbanions are most commonly sealed in a thin glass capillary and maintained in a stream of cold, dry nitrogen gas during the

**Table 7** X-Ray Crystal Structure of Cu/Li Carbanions

| *Compound* | *CSD refcode* | *Ref.* |
|---|---|---|
| $[Li(THF)_4]$ | CESDAF | 264 |
| $[Li(12\text{-crown-}4)_2][CuMe_2]$ | DAZWIK | 265 |
| $[Li(THF)(12\text{-crown-}4)_2][CuPh_2]$ | DAZWOQ | 265 |
| $[Li(12\text{-crown-}4)_2][Cu(Br)CH(TMS)_3]\cdot(\text{toluene})$ | DAZWUW | 265 |
| $[Li(THF)_4][Cu_5Ph_6]$ | BEYROM | 266 |
| $[Li(PMDETA)(THF)][Cu_5Ph_6]$ | BEYRUS | 266 |
| $[Li(Et_2O)_4][LiCu_4Ph_6]\cdot(Et_2O)_2$ | CUTCEZ | 267 |
| $[LiCl_2(Et_2O)_{10}][Li_2Cu_3Ph_6]_2$ | CESFIP | 268 |
| $Li_2Cu_2(C_6H_4CH_2NMe_2)_4$ | CUWTUJ | 269 |
| $[Li(THF)_3][CuMe(PBu^t_2)]$ | VACFEK | 270 |
| $[Li_3Cu_2Ph_5(SMe_2)_4]$ |  | 271 |
| $[\{Li(Et_2O)\}(CuPh_2)]_2$ |  | 272 |

period of data collection. All commercial vendors of X-ray diffraction equipment offer as an optional accessory the specialized attachment to their equipment that allows for low temperature data collection. However, the most tedious step in the entire process remains that of obtaining a single crystal suitable for diffraction analysis. Once a suitable crystal is obtained, a specialized piece of glassware for examining, selecting and manipulating the crystal has been described by Seebach *et al.*[151]

A few comments concerning the crystallization of carbanions are in order. These comments are based upon the personal experience developed in our own laboratory and also upon observations noted in the literature in the course of crystallizing enolate anions. Although alkali metal enolate anions are relatively unstable compounds, they have been prepared in the solid state, isolated, and characterized by IR and UV spectroscopy in the 1970s.[194] Thus the α-lithiated esters of a number of simple esters of isobutyric acid are prepared by metallation of the esters with lithium diisopropylamide in benzene or toluene solution. The soluble lithiated esters are quite stable at room temperature in aliphatic or aromatic hydrocarbon solvents and are crystallized out of solution at low temperature (*e.g.* –70 °C.). Alternatively the less soluble enolates tend to precipitate out of solution and are isolated by centrifugation and subsequent removal of the solvent. Recrystallization from a suitable solvent can then be attempted. The thermal stability of the lithiated ester enolates is dramatically decreased in the presence of a solvent with a donor atom such as tetrahydrofuran.

The guidelines we use for obtaining enolate anion crystals are to find a suitable solvent, concentration and temperature combination such that the crystals grow in a matter of 24 h or so. Typically this involved concentrations of 0.5 to 1.0 M in a solvent combination (hydrocarbon plus donor) that allows for complete dissolution of the anion and slow crystallization. It is preferable to crystallize the enolate anions in the range of –20 to –50 °C since the crystals obtained at this temperature can often be transferred directly to the diffractometer with a minimum effort. Exact conditions for the crystallizations of many of the compounds described in this chapter are described in the original literature.

It is noteworthy that Etter has described a recent technique of cocrystallizing stable organic compounds with triphenylphosphine oxide.[195] It is possible that additional enolate anions can be crystallized by addition of this addend to assist with the solid phase formation; however, many of the carbanions already include donors such as TMEDA, THF, *etc.* In summary the crystallization of enolate anions differs little from the crystallization of neutral organic molecules, except that it is often carried out at somewhat lower temperatures. The patience, skill and experience of the chemist often determine whether the crystallization procedure is successful.

## 1.1.5 THEORY, NMR AND OTHER TECHNIQUES

In concluding this review it must be noted that there are many other techniques that are being utilized to increase our understanding about the structure of synthetically important carbanions. A partial listing of these techniques would include the theoretical approaches taken by Schleyer,[196] Streitweiser,[197] Houk[198] and others[199] and classical spectroscopic techniques.[200] There exist also a number of useful NMR techniques in addition to the 2D-HOESY method previously mentioned. These NMR techniques include analysis of $^{13}C$ chemical shifts, $^6Li$–$^{15}N$ spin–spin splitting, $^7Li$ quadrupolar coupling[201] and rapid injection NMR which has proven useful as a technique for structural investigations of aliphatic carbanions.[202] Last, but certainly not least, the excellent thermochemical measurements recently reported by Arnett and coworkers serve to correlate the solid state structural studies with solution species.[203] A comprehensive list and discussion of all of the techniques that have been utilized to analyze carbanion structures is beyond the scope of this review.

In conclusion it must be stated that much work remains before it is possible to predict with confidence the structural characteristics of any new carbanion. That such structures may be utilized to rationalize unusual reactions has already been demonstrated by Grutzner.[204] Although many of the main structural types may have been uncovered already, much additional investigation is necessary before these results can be generally applied to control the stereochemical outcome of reactions of synthetically useful carbanions.

## 1.1.6 REFERENCES

1. R. Amstutz, W. B. Schweizer, D. Seebach and J. D. Dunitz, *Helv. Chim. Acta*, 1981, **64**, 2617 (BEDYOY, BEDYUE).
2. As of January 1990 there exist nearly 1500 structural characterizations of alkali metal cation balanced organic anions.
3. (a) Information about how to obtain the database itself or access thereto is available from Dr. Olga Kennard OBE, FRS, Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK; see also (b) F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B. G. Hummelink-Peters, O. Kennard, W. D. S. Motherwell, J. R. Rodgers and D. G. Watson, *Acta Crystallogr.*, 1979, **B35**, 2331; (c) F. H. Allen, O. Kennard and R. Taylor, *Acc. Chem. Res.*, 1983, **16**, 146.
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# 1.2

# Carbanions of Alkali and Alkaline Earth Cations: (ii) Selectivity of Carbonyl Addition Reactions

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## 1.2.1 ADDITIONS OF ACHIRAL REAGENTS TO CHIRAL SUBSTRATES

### 1.2.1.1 Additions to Acyclic Systems

#### *1.2.1.1.1 Introduction*

The selective nucleophilic addition of Grignard and organolithium reagents to carbonyl compounds has been the subject of extensive study since the early 1900s when McKenzie described the asymmetric synthesis of α-hydroxy acids from the corresponding chiral α-keto esters.[1] This report is the foundation of the seminal work of Prelog,[2] Cram,[3] Cornforth,[4] Karabatsos[5] and Felkin,[6] carried out in the 1950s and 1960s, which provides consistent models of the stereochemical outcome of nucleophilic additions to carbonyl groups. At present, successful application of these models, as well as their theoretical treatment,[7,8] continues to occupy a significant body of the chemical literature. This chapter focuses on the selective addition of carbon nucleophiles generated from organolithium and organomagnesium reagents to carbonyl compounds. The reduction of carbonyl compounds (additions of hydrogen-based reagents) is the subject of Volume 8.

While thorough reviews of this area are available in a number of sources,[9–12] a brief description of the relevant aspects of these models is described below. Cram's 'open-chain model' concerns the addition of a nucleophile to a simple α-alkyl-substituted carbonyl compound.[3] Disposition of the carbonyl oxygen and the largest α-substituent (relative sizes of the substituents are designated L, M, and S) in an *anti* relationship is expected to be the conformation from which nucleophilic addition occurs (Figure 1). In the case of α-halocarbonyls, Cornforth proposes that the carbonyl and carbon–halogen dipoles prefer an *anti* orientation; nucleophilic reaction then takes place from the less-encumbered face (Figure 2).[4] When an α-substituent capable of coordination is present, the 'cyclic chelate model' is invoked. The favored conformation results from formation of a chelate between the cationic reagent, the carbonyl oxygen and the coordinating substituent. Addition then occurs from the least-hindered face (Figure 3).[3]

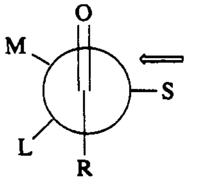

**Figure 1** Open-chain model

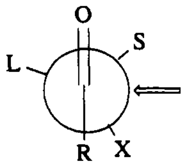

**Figure 2** Dipolar model

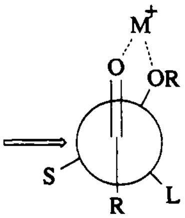

**Figure 3** Cyclic chelate model

The design of reactions based on these models, in particular the cyclic chelation controlled model, often leads to high stereoselectivities. However, discrepancies between theoretical and experimental results have led to the development of alternative theories. Among these, the work of Felkin and coworkers[6] has gained the most acceptance. In an open-chain model, orientation of the largest α-substituent in a conformation perpendicular to the carbonyl group is considered most relevant (Figure 4). Because the carbonyl oxygen is deemed less sterically demanding than the substituent bonded directly to the carbonyl carbon (R), conformation A is favored over B. Calculations by Anh and Eisenstein[7] support the results derived from the Felkin model; however, they propose a different mode of nucleophilic attack. These workers suggest that with the carbonyl substrate in a conformation like that proposed by Felkin, the reacting nucleophile approaches not perpendicularly to the carbonyl bond, but tilted away from it. Preferential attack occurs on a trajectory closest to the smallest substituent (Figure 5). For the purpose of this discussion, the term 'cyclic chelation control' will be used to describe those reactions which adhere to the model depicted in Figure 3. 'Felkin–Anh' or 'nonchelation control' will refer to selective additions which can be described by models such as those shown in Figure 5.

While these models are often useful in predicting the outcome of a reaction in a qualitative sense, the degree of stereoselection can be affected by simple changes in reaction conditions. It has been observed that solvent, temperature and organometallic reagent, as well as other factors, play a vital role in determining which of the reaction modes described predominates. Conditions which enhance, diminish, or even reverse observed stereoselectivities have been reported.[11]

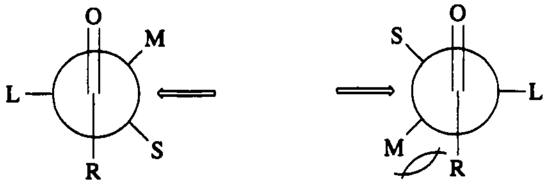

A, favored B, disfavored

**Figure 4** Felkin model

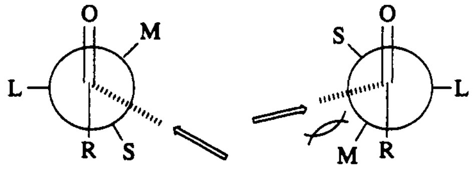

A, favored B, disfavored

**Figure 5** Felkin–Anh model

### 1.2.1.1.2 1,2-Asymmetric induction

The addition of Grignard reagents to chiral α-alkoxy acyclic ketones is one of the most throroughly studied examples of a chelation-controlled reaction. Under certain conditions, these reactions proceed with very high (50–200:1) stereoselectivities, which can be explained by the cyclic chelate model illustrated in equation (1).[13] The nature of the solvent and organometallic reagent has a profound effect on the degree of selectivity observed (equation 2). As shown in Table 1, additions of Grignard reagents in THF are most effective, generating selectivities greater than 99:1. Organolithium nucleophiles, on the other hand, provide no useful selectivity.

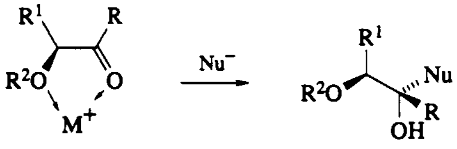

(1) (2)

(1)

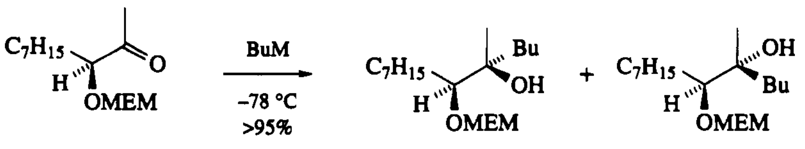

(1a) (2a) (3a)

(2)

**Table 1** Effects of Solvent and Organometallic Reagent on the Selectivity of the Reaction of (**1a**) with BuM

| *Solvent* | *Product ratio (2a):(3a)* | |
|---|---|---|
| | *M = Li* | *M = MgBr* |
| $C_5H_{12}$ | 67:33 | 90:10 |
| $CH_2Cl_2$ | 75:25 | 93:7 |
| $Et_2O$ | 50:50 | 90:10 |
| THF | 41:59 | >99:1 |

The effects of changes in the nature of the alkoxy group (equation 3) are evident in Table 2. High levels of asymmetric induction are achieved by the use of α-substituents such as methoxymethyl ether, benzyl ether, and methylthiomethyl (MTM) ether. The sterically demanding tetrahydropyranyl ether substituent, however, interferes with chelate formation, and its use generates poor selectivities.

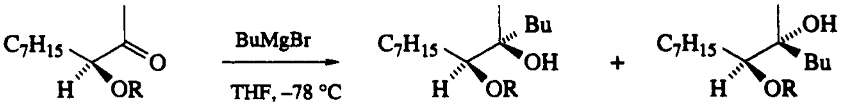

(1b) (2b) (3b) (3)

**Table 2** Effects of Alkoxy Group on the Selectivity of the Reaction of (**1b**) with BuMgBr

| *R* | *Product ratio (**2b**):(**3b**)* |
|---|---|
| —MEM, —MOM, —MTM, —$CH_2$(2-furyl) | >99:1 |
| —$CH_2Ph$ | 99.5:0.5 |
| —$CH_2OCH_2Ph$ | 99:1 |
| —THP | 75:25 |

The high degrees of selectivity (>98:2) found in these reactions are possible not only in acyclic substrates, but also in cyclic α-alkoxy ketones and in more complex systems. The scope of this selective reaction, however, is limited to α-hydroxy ketones, as reaction with β-alkoxy aldehydes proceeds with no selectivity.[13,14]

Similar selectivities (>99:1) are observed in the cyclic chelation controlled reaction of α-benzyloxy carbonyls such as (**4a**; equation 4) with Grignard reagents.[15] However when the α-hydroxy group is protected as a silyl ether (**4b**), the selectivities observed in the addition reaction diminish (60:40), or reverse (10:90; Table 3). The nonchelating nature of a silyl group, as well as its steric bulk, are responsible for this change in selectivity. In the case of (**4b**), nucleophilic addition *via* the Felkin–Anh model effectively competes with the cyclic–chelation control mode of addition.

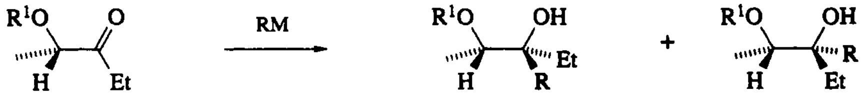

(**4**) a: $R^1 = CH_2Ph$
b: $R^1 = Bu^tMe_2Si$

(**5**) (**6**) (4)

**Table 3** Diastereoselective Additions to Ketones (**4a**) and (**4b**)

| *Ketone* | *Reagent* | *Temperature (°C)* | *Time (h)* | *Solvent* | *Yield (%)* | *Ratio (**5**):(**6**)* |
|---|---|---|---|---|---|---|
| (**4a**) | MeMgCl | -78 | 2 | $Et_2O$ | 85 | >99:<1 |
| (**4a**) | MeLi | -78 | 2 | THF | 90 | 60:40 |
| (**4b**) | MeMgCl | -78 | 2 | $Et_2O$ | 78 | 60:40 |
| (**4b**) | (Allyl)MgCl | -78 | 2 | THF | 90 | 10:90 |

The limited conformations of an α-oxygen substituent within a ring can effectively restrict the possible modes of nucleophilic attack, and lead to highly selective nucleophilic additions. A number of studies using acrolein dimer (**7**; equation 5) illustrate how these ring-constrained systems can be manipulated by taking advantage of either the chelating ability of the α-hydroxy moiety, or the sterically demanding cyclic system.

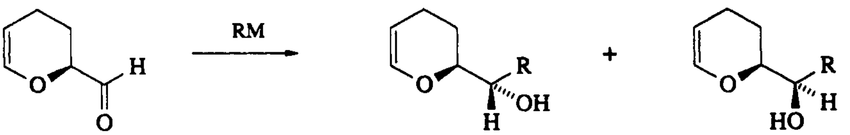

(**7**) (**8**) (**9**) (5)

Simple addition of *n*-decylmagnesium bromide to (**7**) yields an approximately equal ratio of products (**8**) and (**9**).[16] The use of conditions which promote chelation (excess Grignard reagent) produces a shift in the product ratio (63:37). Addition of $ZnBr_2$ to the reaction mixture further increases the amount of chelation-controlled product formed (85:15; Table 4).

**Table 4** Addition of Organometallic Reagents to Acrolein Dimer (**7**)

| *Reagent* | *Conditions* | *Yield (%)* | *Ratio (8):(9)* |
|---|---|---|---|
| (*n*-Decyl)MgBr (1.1 equiv.) | THF, –50 °C | 56 | 48:52 |
| (*n*-Decyl)MgBr (3.0 equiv.) | THF, 15 °C | 90 | 63:37 |
| (*n*-Decyl)MgBr (6.0 equiv.) | $ZnBr_2$ (1.1 equiv.), $Et_2O$, –10 °C | 21 | 85:15 |
| (*n*-Decyl)MgBr (1.5 equiv.) | THF, HMPA (3.5 equiv.), –45 °C | 71 | 21:79 |
| (*n*-Decyl)MgBr (3.0 equiv.) | THF, HMPA (6.0 equiv.), –20 °C | 84 | 15:85 |
| EtLi | $Et_2O$, HMPA (4.0 equiv.), –78 °C | 78 | 12:88 |
| EtLi | $Et_2O$, TMEDA (5.0 equiv.), –78 °C | 81 | 20:80 |
| EtLi | $Et_2O$, –78 °C | — | 28:72 |
| EtMgBr | $Et_2O$, 0 °C → r.t. | 87 | 70:30 |

Addition of HMPA to the reaction mixture to suppress chelation causes a reversal in the stereoselectivity, yielding (**9**) as the dominant product. Similar trends in the addition of ethyl metallics to (**7**) are reported.[17] Use of conditions expected to enhance chelation produces (**8**) as the major product; (**9**) is formed predominantly when chelation is inhibited (Table 4). The proposed modes of addition according to chelation control, yielding (**8**), and Felkin–Anh models, yielding (**9**), are shown in Figures 6 and 7.

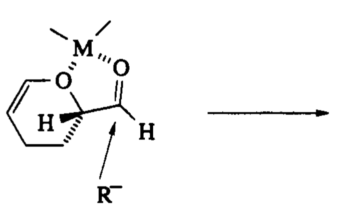

(**8**)

**Figure 6**

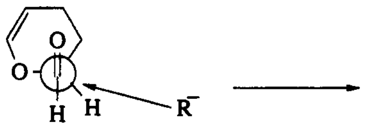

(**9**)

**Figure 7**

Nucleophilic additions to tetrahydrofurfural (**10**; equation 6) proceed under similar constraints. Grignard additions in the presence of HMPT favor formation of product (**11**), arising from Felkin–Anh addition (Table 5). In the absence of HMPT, nucleophilic addition yields the cyclic chelation control product (**12**) as the major isomer.[18]

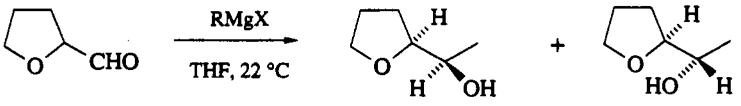

(6)

(**10**) (**11**) (**12**)

**Table 5** Stereoselective Additions to (**10**)

| *RMgX* | *Ratio (11):(12)* | *Yield (%)* |
|---|---|---|
| EtMgBr | 48:52 | 71 |
| EtMgBr, 2 equiv. HMPT | 87:13 | 86 |
| $Bu^nMgBr$ | 43:57 | 71 |
| $Bu^nMgBr$, 2 equiv. HMPT | 90:10 | 81 |
| $Pr^iMgBr$ | 29:71 | 48 |
| $Pr^iMgBr$, 2 equiv. HMPT | 100:0 | 57 |
| PhMgBr | 30:70 | 73 |
| PhMgBr, 2 equiv. HMPT | 68:32 | 64 |

Considerable work has been carried out on nucleophilic additions to more complex carbonyl substrates containing both α- and β-alkoxy substituents. Optically active 2,3-isopropylideneglyceraldehyde (**13**;

equation 7) represents an ideal substrate for systematic study due to the ready availability of either enantiomer, as well as the versatile functionality present in the molecule. Factors to be considered in a stereocontrolled nucleophilic addition to (**13**) include the presence of a rigid dioxolane system adjacent to the carbonyl and the possibility of chelation to three different oxygen atoms (the carbonyl moiety and two ether oxygens).[19]

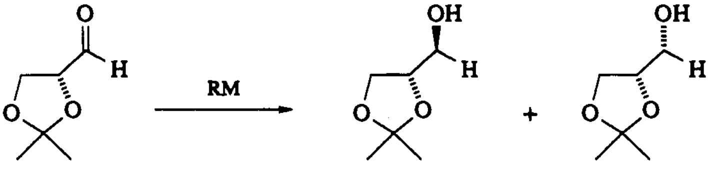

(**13**) (**14**) (**15**)

In general, organometallic additions to (**13**), yielding alcohols (**14**) and (**15**), result in only moderate selectivities when organolithium and Grignard reagents are used.[20] The stereochemistry of the major isomer, and the degree of selectivity, depend on the nature of the organometallic reagent, as well as on the conditions under which the reaction is run. Table 6 illustrates some of these findings. Use of other organometallic reagents (Cr-, Ti- and Zn-based) yields improved selectivities.

**Table 6** Stereoselectivities in the Addition of RM to (**13**)

| *RM* | *Solvent* | *Temperature (°C)* | *(14):(15)* | *Yield (%)* |
|---|---|---|---|---|
| PhLi | $Et_2O$ | −78 | 48:52 | 88 |
| PhMgBr | $Et_2O$ | −78 | 48:52 | 85 |
| MeLi | $Et_2O$ | −70 | 60:40 | 60 |
| MeMgBr | $Et_2O$ | −50 | 67:33 | 57 |
| $Bu^nLi$ | $Et_2O$ | −78 | 69:31 | 83 |
| $Bu^nMgBr$ | $Et_2O$ | −78 | 75:25 | 86 |
| (Allyl)MgBr | $Et_2O$ | −78 | 60:40 | 89 |

The presence of additives in the reaction mixture, however, can significantly enhance the selectivity of nucleophilic addition to (**13**; equation 8).[21] Very high ratios (>95:5) are observed when the addition of furyllithium to (**13**) is carried out in the presence of Zn or Sn salts (Table 7). The stereochemistry of the product is explained by a conformation in which the zinc or tin atom coordinates with the carbonyl oxygen and the 3-oxygen of the dioxolane ring (Figure 8). Nucleophilic attack from the less-hindered face selectively produces (**16**). At present, the applicability of this reaction to other substrates is not known.

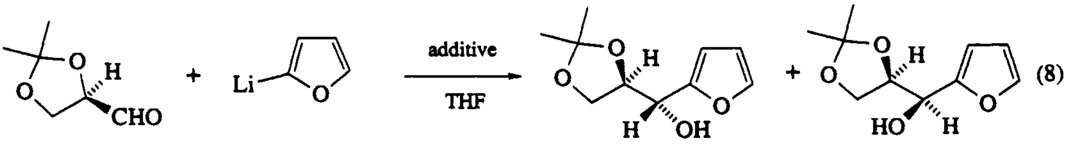

(**13**) (**16**) (**17**)

**Table 7** Effect of Additive on the Stereoselective Reaction of 2-Furyllithium with (**13**)

| *Additive* | *Temperature (°C)* | *Yield (%)* | *(16):(17)* |
|---|---|---|---|
| None | −78 | 68 | 40:60 |
| $MgBr_2$ | 0 | 49 | 50:50 |
| $SnCl_4$ | 0 | 58 | 95:5 |
| $ZnCl_2$ | −78 | 10 | >95:<5 |
| $ZnCl_2$ | 0 | 60 | 90:10 |
| $ZnBr_2$ | 0 | 75 | 95:5 |
| $ZnI_2$ | 0 | 57 | >95:<5 |

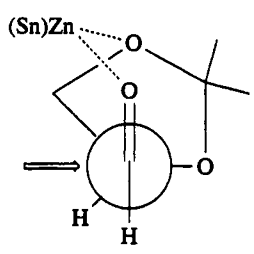

**Figure 8**

Variation of the diol-protecting group or of other substituents on these α,β-dihydroxycarbonyl derivatives does not lead to significant improvements in stereoselection. Moderate selectivities are reported for the Grignard and organolithium additions to the 2,3-*O*,*O*-dibenzylglyceraldehyde (**18**) (ranging from 45:55 to 27:73)[22] and to the homologated cyclohexylideneglyceraldehyde (**19**) (80:20 to 60:40).[23] Synthetically useful ratios can, however, be realized by the use of other organometallic reagents (Ti, Cu). The depressed selectivities seen in the cases of magnesium and lithium reagents may be due to their relatively high reactivity.

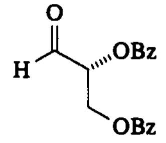

**(18)**

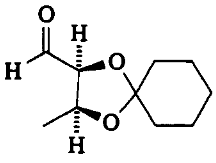

**(19)**

Several reports on selective additions to more complex carbohydrate derivatives suggest that synthetically useful selectivities are indeed obtainable. Grignard addition to aldehyde (**20**) proceeds with a moderate preference for α-chelation-controlled addition. The alcohols (**21**) and (**22**) are isolated in a ratio of about 75:25 (equation 9).[24]

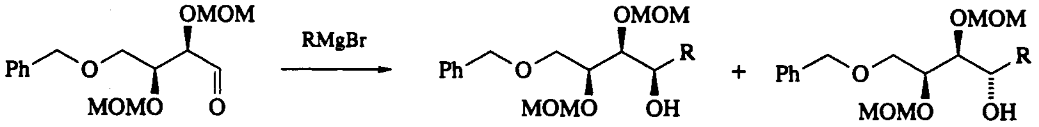

(9)

**(20)** **(21)** **(22)**

In some polyhydroxylated substrates, a specific site of chelation can be favored or disfavored by the appropriate choice of protecting group. Grignard addition to ketone (**23**; equation 10) occurs *via* α-coordination to yield the alcohol (**24**) exclusively.[25] Competitive β-chelation is prevented by the use of a trialkylsilyl protecting group. Alternatively, when the free hydroxy group is present (**25**), addition of the Grignard reagent forms the magnesium alkoxide, and β-chelation control predominates. In this case nucleophilic addition affords (**26**) as the sole product.

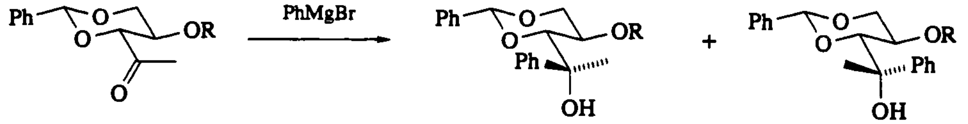

(10)

(**23**) R = $SiMe_2Bu^t$ (**24**) R = $SiMe_2Bu^t$, 100% 0%

(**25**) R = H 0% (**26**) R = H, 100%

A number of other examples have been reported which involve highly selective Grignard or organolithium additions to carbohydrates.[26] Unfortunately, no general trends for these complex systems have been observed. The selectivities reported are often specific for one substrate under a particular set of reaction conditions. Reetz has reviewed the chelation and nonchelation control addition reactions (not confined to organolithium or organomagnesium reagents) of α- and β-alkoxycarbonyl compounds.[27]

In simple carbonyl compounds containing an α-amino substituent, nucleophilic additions generally occur *via* the cyclic chelate model.[9,12] However, just as in the α-hydroxycarbonyl series, selectivities can be greatly influenced by substitution of the amino group. Examples of moderate to high stereoselection in both cyclic chelation and nonchelation controlled additions have been reported.

Grignard addition to the BOC-protected phenylalaninal (**27**; equation 11) occurs mainly through a cyclic chelation controlled mechanism to yield (**28**) and (**29**) in a ratio of 70:30.[28] Conditions which favor coordination of the nitrogen and magnesium atoms (high temperature) are essential for the selectivity observed.

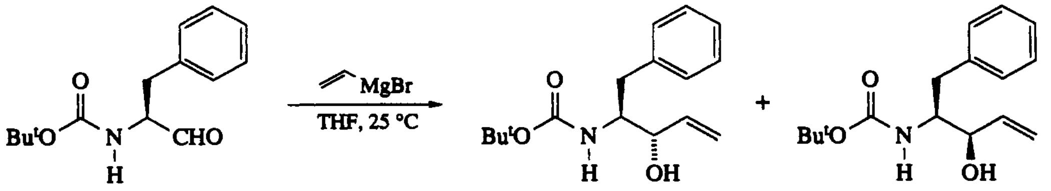

(11)

(**27**) (**28**) (**29**)

In contrast, the use of dibenzyl-protected groups in similar systems shows opposite stereoselectivity.[29] Grignard and alkyllithium additions to dibenzyl-protected α-amino aldehydes such as (**30**; equation 12) proceed with excellent selectivities (usually >95:5) to yield the nonchelate control alcohols (**32**). The high ratios observed (Table 8) regardless of substrate or reagent suggest that the dibenzyl groups act by preventing chelation; Cornforth or Felkin–Anh modes of addition then predominate. Access to the chelation control products is not possible using Grignard or organolithium reagents. The use of titanium or tin reagents, however, provides (**31**) as the major product (Chapter 1.5, this volume).

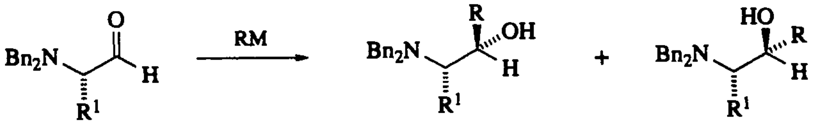

(12)

(**30**) (**31**) (**32**)

Table 8 Stereoselectivities in the Reaction of (**30**) with RM

| *R*$^1$ | *RM* | *Temperature (°C)* | *Yield (%)* | *Ratio (31):(32)* |
|---|---|---|---|---|
| Me | MeMgI | 0 | 87 | 5:95 |
| Me | MeLi | −10 | 91 | 9:91 |
| Me | PhMgBr | 0 | 85 | 3:97 |
| Me | EtMgBr | 0 | 85 | 5:95 |
| Me | Pr$^i$MgBr | 0 | 75 | <3:>97 |
| Me | Bu$^t$MgBr | 0 | 72 | 5:95 |
| Me | Bu$^t$Li | −60 | 88 | <3:>97 |
| $CH_2Ph$ | MeMgI | 0 | 85 | 8:92 |
| $CH_2Ph$ | PhMgBr | 0 | 84 | 3:97 |
| $CH_2Ph$ | $PhC\equiv CLi$ | −78 | 72 | <4:>96 |
| $CH_2Ph$ | $PhCH_2CH_2MgBr$ | −78 | 84 | <4:>96 |
| $CH_2Ph$ | (Allyl)MgCl | −78 | 82 | 28:72 |
| Bu$^i$ | MeMgI | 0 | 85 | 10:90 |
| Bu$^i$ | MeLi | −10 | 89 | 20:80 |
| Bu$^i$ | PhMgBr | 0 | 84 | 3:97 |
| Pr$^i$ | MeMgI | 0 | 87 | 5:95 |
| Pr$^i$ | MeLi | −10 | 81 | 14:86 |
| Pr$^i$ | PhMgBr | 0 | 69 | 9:91 |

Earlier work further illustrates the influence of both size and basicity of the amine-protecting group on the direction and degree of stereoselectivity of nucleophilic additions.[30] While some excellent selectivities are observed in the Grignard reaction to amino aldehydes such as (**33**; equation 13), no general model adequately explains all of the results shown in Table 9.

Except for the α-dibenzylamino substrate cited, Grignard and organolithium additions to protected α-aminocarbonyls are not particularly well understood. Only modest stereoselectivities usually result, and

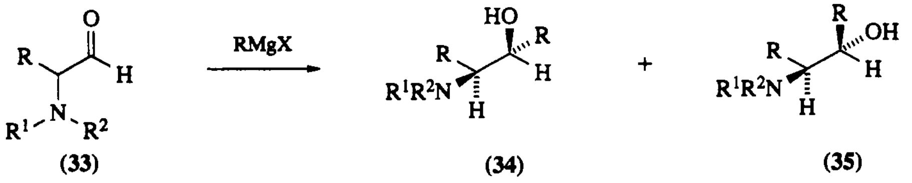

(13)

Table 9 Stereoselectivity in the Reaction of RMgX with (33)

| *R* | *R*$^1$ | *R*$^2$ | *Yield (%)* | *Ratio (34):(35)* |
|---|---|---|---|---|
| Ph | $—CH_2CH_2CH_2CH_2—$ | | 20 | 0:100 |
| Ph | $—CH_2CH_2CH_2CH_2CH_2—$ | | 61 | 16:84 |
| Ph | $—CH_2CH_2OCH_2CH_2—$ | | 72 | 45:55 |
| Ph | Me | Me | 46 | 0:100 |
| Ph | Et | Et | 15 | 12:88 |
| Et | $—CH_2CH_2CH_2CH_2CH_2—$ | | 45 | 0:100 |
| Et | $—CH_2CH_2OCH_2CH_2—$ | | 57 | 34:66 |
| Et | Et | Et | 55 | 52:48 |
| Et | $Pr^i$ | $Pr^i$ | 72 | 100:0 |

the observed selectivities may not be general. However, synthetically useful ratios can be obtained through modifications of reaction conditions, which promote one mode of addition over another.[31]

As described above, the reactions of Grignard or organolithium reagents to α-hydroxy- or α-aminocarbonyls can proceed with extremely high stereoselectivities (>99:1) when cyclic chelation control is in effect. However, attempts to generate products arising from the Cram–Felkin–Anh mode of addition exclusively have been much less successful.[11] These products are available by the use of conditions which favor nonchelation-controlled processes; however, until recently, the selectivities of these reactions (up to 80–90%) never reached those observed in cyclic chelation control additions.

This discrepancy can at least be partially explained by taking into account that in chelation-controlled reactions the acyclic substrate is essentially locked into one rigid cyclic conformation. The reactants taking part in nonchelation-controlled additions have many more degrees of freedom, and exclusive reaction with one conformer is less likely. These reactions rely on reagents which are incapable of chelation and/or substrates containing sterically or electronically differentiated substituents.[27]

Trialkylsilane substituents have been used very effectively to promote nonchelation-controlled nucleophilic reactions. Addition of Grignard and organolithium reagents to chiral acylsilane (36) produces the Cram–Felkin–Anh product (37) almost exclusively (>92:8 selective in most cases).[32] The silyl group in (37) can be stereospecifically replaced with hydrogen to afford the product (40) of formal nucleophilic addition to the parent aldehyde (Scheme 1). This sequence of reactions is one of the first examples of a general procedure for highly efficient nonchelation-controlled additions to aldehyde equivalents. Direct Grignard and organolithium additions to aldehyde (39) are less selective, as shown in Table 10.

Stereoselectivities observed in the reactions of the α-chiral acylsilanes are explained by consideration of the the Felkin–Anh model. The conformers depicted in Figures 9 and 10 are predicted to be those through which nucleophilic addition occurs. The sterically demanding TMS group apparently differentiates between the α-hydrogen (S) and the α-methyl (M) substituents. This preference for the conformation in Figure 9 results in a highly stereoselective reaction.

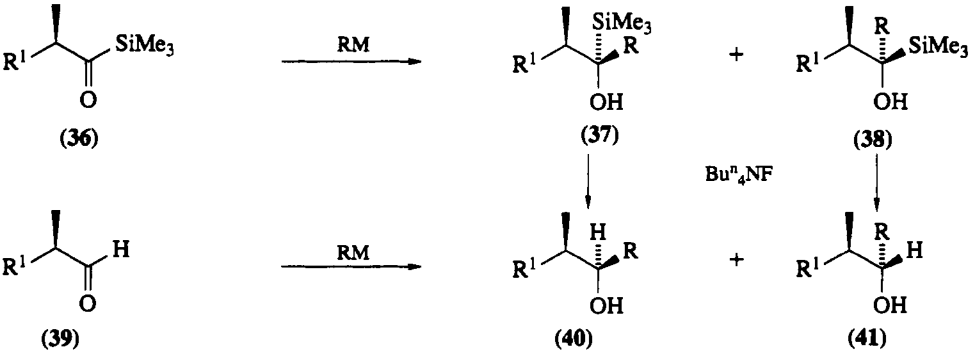

Scheme 1

**Table 10** Selectivities in the Reaction of Nucleophiles with α-Chiral Acylsilanes (**36**) and Aldehydes (**39**)

| *Substrate* | *$R^1$* | *RM* | *Yield (%)* | *Ratio (**37**):(**38**) or (**40**):(**41**)* |
|---|---|---|---|---|
| (**36**) | Ph | $Bu^nLi$ | 92 | >99:1 |
| (**36**) | Ph | MeLi | 96 | >97.5:2.5 |
| (**36**) | Ph | (Allyl)MgBr | 96 | 92:8 |
| (**36**) | 1-Cyclohexenyl | $Bu^nLi$ | 56 | >97:3 |
| (**36**) | 1-Cyclohexenyl | MeLi | 69 | >99:1 |
| (**36**) | 1-Cyclohexenyl | (Allyl)MgBr | 69 | 92:8 |
| (**36**) | Cyclohexyl | $Bu^nLi$ | 98 | 94:6 |
| (**36**) | Cyclohexyl | MeLi | 77 | 96:4 |
| (**36**) | Cyclohexyl | (Allyl)MgBr | 93 | 78:22 |
| (**39**) | Ph | $Bu^nLi$ | 91 | 83:17 |
| (**39**) | Ph | MeLi | 91 | 80:20 |
| (**39**) | Ph | (Allyl)MgBr | 92 | 63:27 |
| (**39**) | 1-Cyclohexenyl | $Bu^nLi$ | 40 | 94:6 |
| (**39**) | 1-Cyclohexenyl | MeLi | 49 | 66:34 |
| (**39**) | 1-Cyclohexenyl | (Allyl)MgBr | 54 | 71:29 |
| (**39**) | Cyclohexyl | $Bu^nLi$ | 96 | 78:22 |
| (**39**) | Cyclohexyl | MeLi | 75 | 67:33 |
| (**39**) | Cyclohexyl | (Allyl)MgBr | 59 | 67:33 |

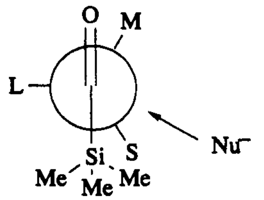

major conformer

**Figure 9**

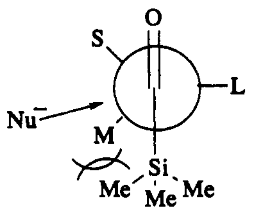

minor conformer

**Figure 10**

Trialkylsilyl groups in other positions on the carbonyl substrate can also influence the direction of nucleophilic addition. Grignard additions to 2-alkyl- and 2-alkoxy-3-trimethylsilylalkenylcarbonyl compounds such as (**42a**), (**42b**) and (**42c**) proceed with high diastereofacial selectivity based on the Cram–Felkin–Anh model.[33] Table 11 lists results of the additions to all three derivatives. Excellent stereoselectivities (>99:1 in most cases) favoring the nonchelation-controlled product (**43**) are evident in all examples except one. Replacement of the trialkylsilyl group in the products with hydrogen, or manipulation to generate other functional groups illustrates the synthetic potential of this procedure. The key role played by the silyl group in obtaining high stereoselectivities is demonstrated by a comparison of reported nucleophilic additions to analogous substrates. In these examples, substrates which do not contain a trialkylsilyl moiety in the carbonyl substrate react with much lower (67:33) selectivities.

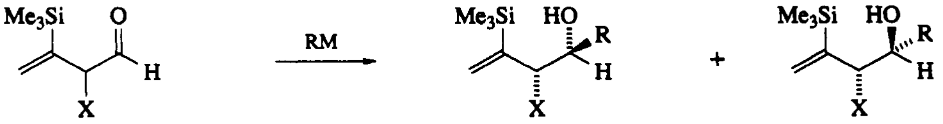

(14)

(**42**) a: X = Me
b: X = OBn
c: X = OMe

(**43**)

(**44**)

### 1.2.1.1.3 Remote asymmetric induction

In general, nucleophilic addition reactions using Grignard or organolithium reagents to β-chiral or other remotely chiral ketones usually yield mixtures of stereoisomers which are not synthetically useful.[9,12,27] However, some specific examples of stereoselective organolithium and Grignard additions to these remotely chiral carbonyl compounds have been reported.

**Table 11** Stereoselectivities in the Reaction of (**42**) with RM

| *Substrate* | *RM* | *Solvent* | *Yield (%)* | *Ratio (**43**):(**44**)* |
|---|---|---|---|---|
| (**42a**) | MeMgI | THF | 84 | 91:9 |
| (**42a**) | EtMgBr | THF | 92 | >99:<1 |
| (**42a**) | $Pr^iMgBr$ | THF | 91 | >99:<1 |
| (**42a**) | PhMgBr | THF | 94 | >99:<1 |
| (**42a**) | $CH_2{=}CH(TMS)MgBr$ | THF | 93 | >99:<1 |
| (**42b**) | EtMgBr | THF | 63 | 50:50 |
| (**42b**) | EtMgBr | $Et_2O$ | 87 | 93:7 |
| (**42c**) | EtMgBr | THF | 68 | 90:10 |
| (**42c**) | EtMgBr | $Et_2O$ | 92 | >99:<1 |

Diastereoselective additions of nucleophiles to the β-alkoxy-γ-hydroxy aldehyde (**45**; equation 15) are reported to generate either chelation- or nonchelation-controlled products, depending on the reaction conditions used. Chelation-controlled additions of organolithium or Grignard reagents in THF take place with reasonable selectivities to produce (**46**) as the major product.[34] These selectivities can be improved with a change of solvent (diethyl ether), and with the addition of Zn salts (Table 12). Figure 11 represents the probable mode of addition in this chelation-controlled reaction. Alternatively, the diol (**47**) results as the major product when the reaction is carried out in ether using alkylmagnesium bromides as nucleophiles. The mode of addition to generate (**47**) under these conditions is not completely understood.

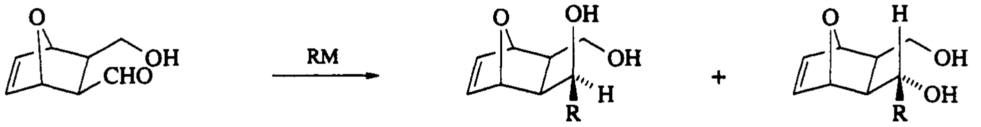

(**45**) (**46**) (**47**) (15)

**Table 12** Diastereoselective Additions of Organometallics to (**45**)

| *RM* | *Solvent* | *Yield (%)* | *Ratio (**46**):(**47**)* |
|---|---|---|---|
| MeMgI | THF | 65 | 70:30 |
| MeMgI | Ether | 82 | 82:18 |
| MeLi | THF/ether | 80 | 78:22 |
| MeLi | Ether | 90 | 83:17 |
| MeMgBr | THF | 60 | 74:26 |
| MeMgBr | Ether | 77 | 15:85 |
| $Bu^nMgBr$ | THF | 65 | 88:12 |
| $Bu^nMgBr$ | Ether | 70 | 15:85 |
| $Pr^iMgBr$ | THF | 73 | 91:9 |
| $Pr^iMgBr$ | Ether | 65 | 15:85 |
| $Bu^nMgBr + ZnI_2$ | THF | 56 | 94:6 |

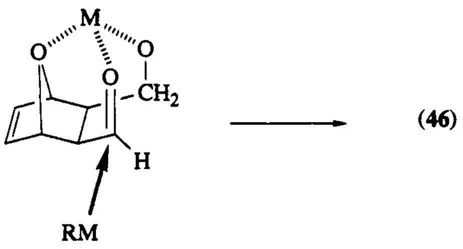

**Figure 11**

Systematic studies on additions to β-asymmetric amino ketones of general structure (**48**; equation 16) result in the following conclusions.[35]

(i) In reactions of (**48**) with organolithiums, isomer (**49**) predominates regardless of the nature of the reagent and the substrate. Selectivities as high as 87:13 are reported. This general trend in stereoselectivity cannot be adequately explained by one model.

(ii) Selectivities in the Grignard additions to (**48**) are highly dependent on the nature of the substrate, as well as the reagents. Neither isomer (**49**) nor (**50**) predominates, and no specific model is consistent with the experimental results. Again, the highest selectivities observed are in the 80:20 range.

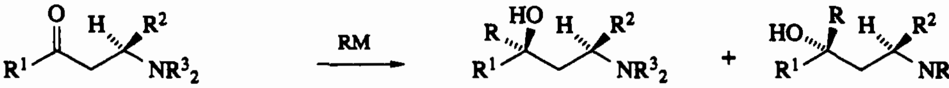
(16)

(**48**) (**49**) (**50**)

In an example of remote asymmetric induction, chiral oxazoline (**51**) undergoes Grignard additions with moderate to good selectivity.[36] The major product formed (**52**) results from coordination of the reagent to the oxazoline moiety, followed by nucleophilic attack from the bottom, as shown in Figure 12. The phenyl substituent of the oxazoline effectively prevents addition from the top face of the molecule. Systems such as (**51**) have been used to synthesize optically active phthalides (**54**), as shown in Scheme 2. Typical optical purities of the isolated aromatic products range from 46–80%. Table 13 lists some of these results.

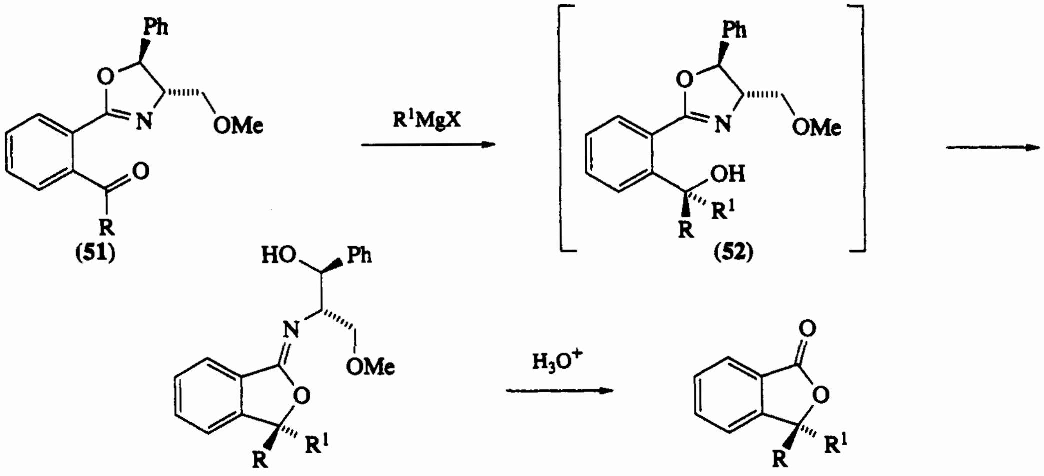

(**51**) (**52**) (**53**) (**54**)

**Scheme 2**

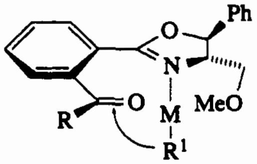

**Figure 12**

**Table 13** Diastereoselectivity of Grignard Additions to (**51**)

| *R* | *R¹MgX* | *Yield (%)* | *(53)* *Diastereomer ratios* |
|---|---|---|---|
| Me | EtMgBr | 96 | 73:27 |
| Me | $Bu^nMgBr$ | 92 | 73:27 |
| Me | $Bu^tMgBr$ | 90 | 83:17 |
| Me | PhMgBr | 97 | 90:10 |
| Ph | MeMgBr | 99 | 88:12 |
| Ph | EtMgBr | 99 | 83:17 |
| Et | MeMgCl | 93 | 82:18 |
| $Bu^t$ | MeMgCl | 66 | 52:48 |
| $p$-$BrC_6H_4$ | MeMgCl | 95 | 87:13 |
| $Bu^n$ | MeMgCl | 89 | 84:16 |

While examples of moderate to good stereoselectivities in remotely chiral molecules, such as those described above, are known, they are usually specific cases, and cannot be generalized to all systems. In general, stereoselective Grignard or organolithium additions which rely on remote or β-chelation are not efficient.

### *1.2.1.1.4 Chiral auxiliaries*

A special class of acyclic diastereoselective reactions involves the use of chiral auxiliaries to control the absolute stereochemistry of nucleophilic additions at carbonyl centers. This process takes advantage of steric and/or electronic factors within the chiral adjuvant to promote nucleophilic addition from one face of the molecule, and thereby generate one predictable diastereomer. Removal of the auxiliary, in the best cases, generates enantiomerically pure products, as well as the recyclable chiral adjuvant. The end result of this process is the synthesis of enantiomerically pure products *via* diastereoselective reactions.

Eliel has extensively studied the 1,3-oxathiane systems (**55**) as a chiral auxiliary to control the addition of organometallics to ketones (Scheme 3).[37] Following nucleophilic addition, cleavage of the oxathiane group generates chiral α-hydroxycarbonyl compounds (**58**). The wide variety of carbonyl substituents, as well as Grignard reagents, amenable to this process is illustrated in Table 14. The enantiomeric auxiliary is available, and affords alcohols of opposite chirality in equivalent yields.

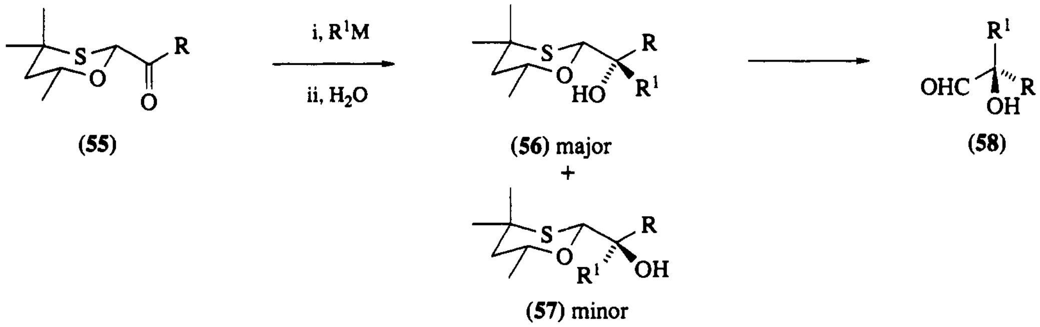

(**55**)

(**56**) major

(**57**) minor

(**58**)

**Scheme 3**

**Table 14** Stereoselective Reactions of (**55**) with Organometallics

| *R* | *R$^1$M* | *Temperature (°C)* | *Solvent* | *Ratio (56):(57)* |
|---|---|---|---|---|
| Ph | MeMgI | Reflux | Et$_2$O | 96:4 |
| Ph | MeLi | Reflux | Et$_2$O | 86:14 |
| Ph | EtMgI | Reflux | Et$_2$O | >99:<1 |
| Ph | Pr$^i$MgI | Reflux | Et$_2$O | 99:1 |
| Me | PhMgBr | Reflux | Et$_2$O | 89:11 |
| Me | Ph$_2$Mg | Reflux | Et$_2$O | 78:22 |
| Me | PhMgI | Reflux | Et$_2$O | 87:13 |
| Me | EtMgI | Reflux | Et$_2$O | 90:10 |
| Me | Pr$^n$MgI | Reflux | Et$_2$O | 90:10 |
| Me | Pr$^n$MgBr | Reflux | Et$_2$O | 83:17 |
| Me | Pr$^n$MgCl | Reflux | Et$_2$O | 79:21 |
| Me | Bu$^n_2$Mg | Reflux | Et$_2$O | 87:13 |
| Me | Pr$^i$MgI | Reflux | Et$_2$O | 67:33 |
| Me | (Vinyl)MgBr | Reflux | THF | 91:9 |
| Me | HC≡CMgBr | Reflux | THF | 94:6 |
| Et | PhMgBr | Reflux | Et$_2$O | 83:17 |
| Et | PhMgBr | −78 | Et$_2$O | 97:3 |
| Et | MeMgI | Reflux | Et$_2$O | 80:20 |
| Vinyl | MeMgI | Reflux | Et$_2$O | 87:13 |
| Vinyl | MeMgI | −78 | Et$_2$O | 95:5 |
| Pr$^i$ | MeMgI | Reflux | Et$_2$O | 68:32 |
| Pr$^i$ | MeMgI | −78 | Et$_2$O | 77:23 |
| Pr$^i$ | MeMgI | Reflux | Et$_2$O | 69:31 |
| Pr$^i$ | PhMgBr | Reflux | Et$_2$O | 85:15 |
| Pr$^i$ | PhMgBr | −78 | Et$_2$O | >99:<1 |
| Bu$^t$ | MeMgI | Reflux | Et$_2$O | 93:7 |
| Bu$^t$ | MeMgI | −78 | Et$_2$O | 96:4 |

Further work towards developing this process into a viable route to enantiomerically pure compounds has led to the use of the 1,3-dioxathiane (**59**; Scheme 4) as a second generation chiral auxiliary.[38] Excellent stereoselectivities (usually >90%) are found in the reaction of (**59**) with a variety of Grignard reagents. The carbinol products (**60**) are readily cleaved to the α-hydroxy aldehydes (**61**) and the sultine (**62**), which is used to regenerate (**59**). Either enantiomer of the desired product is available, by using the diastereomeric oxathiane, or by reversing the order of R-group addition. The nitrogen analog (**63**) has recently been reported to impart excellent stereoselection. Scheme 5 illustrates its utility for the synthesis of a number of α-hydroxy acids in high optical purity (see Table 15).[39]

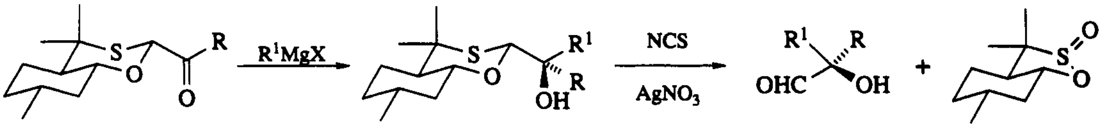

**(59)** **(60)** **(61)** **(62)**

Scheme 4

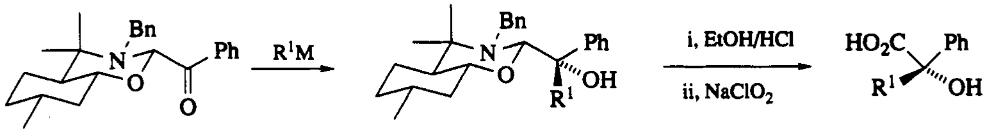

**(63)** **(64)** **(65)**

Scheme 5

Table 15 Synthesis of Optically Active α-Hydroxy Acids from (**63**)

| *$R^1$* | *$R^1M$* | *Temperature (°C)* | *Yield (%)* | *(65) Configuration* | *ee (%)* |
|---|---|---|---|---|---|
| Me | MeMgBr | 20 | 44 | (*S*) | 98 |
| Me | MeMgBr | –70 | — | (*S*) | 98 |
| Me | MeLi | –70 | 47 | (*S*) | 95 |
| Et | EtMgBr | 5 | 77 | (*S*) | 100 |
| HC≡C | HC≡CMgBr | 20 | 63 | (*S*) | 97 ± 1 |
| α-Naphthyl | $C_{10}H_7MgBr$ | 20 | 23 | (*R*) | 82 ± 1 |

The mode of Grignard addition is through the cyclic–chelate conformation shown in Figure 13. The hard magnesium ion coordinates with the carbonyl oxygen and the hard oxygen atom of the oxathiane ring (in preference to the soft sulfur atom). Addition then occurs from the less-hindered side of the auxiliary. All reactions investigated using these ligands have led to the configuration predicted according to this model.[40]

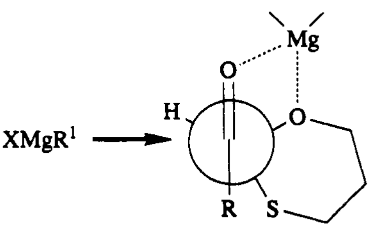

Figure 13

In a study of the factors influencing this nucleophilic addition, it was found that incorporation of an exocyclic oxygen atom into the carbonyl substituent (such as in **66**; equation 17) has a profound effect on the selectivity of the reaction.[41] Alkoxy groups capable of chelation (*e.g.* $CH_2Ph$) can competitively inhibit coordination of the metal to the ring oxygen, thus severely lowering, and in some cases reversing, the stereoselectivities observed. In these cases, the chelating ability of the organometallic reagent, as well as the length of the methylene linker, influence the course of the reaction. The use of a triisopropylsilyl protecting group, however, effectively prevents chelation of the exocyclic alkoxy substituent with the Grignard reagent, and yields high, predictable selectivities (see Table 16).

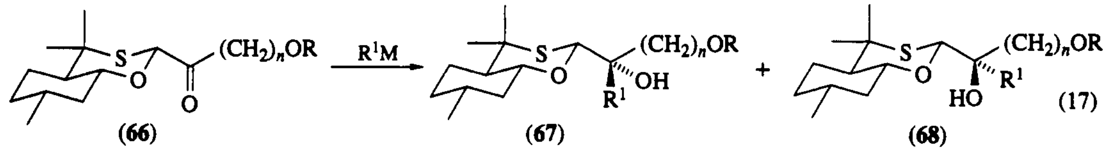

(66) (67) (68) (17)

**Table 16** Stereoselective Nucleophilic Additions to Oxathianyl Alkoxy Ketones (**66**)

| *R* | *n* | *R*¹ | *Reagent* | *(67):(68)* |
|---|---|---|---|---|
| $CH_2Ph$ | 1 | Me | MeMgBr | 33:67 |
| $SiPr^i_3$ | 1 | Me | MeMgBr | 97:3 |
| $CH_2Ph$ | 2 | Me | MeMgBr | 42:58 |
| $SiPr^i_3$ | 2 | Me | MeMgBr | 97:3 |
| $CPh_3$ | 2 | Me | MeMgBr | 86:14 |
| $CH_2Ph$ | 3 | Me | MeMgBr | 81:19 |
| $SiPr^i_3$ | 2 | Me | $(Me)_2Mg$ | 98:2 |
| TMS | 2 | Me | $(Me)_2Mg$ | 73:27 |

The chiral oxathianes have been broadly used for the synthesis of a number of natural products. Through these applications, these chiral auxiliaries have been shown to provide a viable procedure for the synthesis of optically pure compounds.[42]

Chiral acetals can be used as auxiliaries in the diastereoselective reactions of Grignard reagents with acyclic[43] as well as cyclic α-keto acetals.[44] Nucleophilic addition to the monoprotected diketone (**69**; equation 18) occurs with excellent stereoselectivity to generate the corresponding tertiary alcohol (**70**) as the major product, usually with greater than 95:5 selectivity. Removal of the ketal yields α-hydroxy ketones of high optical purity. In most examples, enantiomeric excesses of 95% and higher are observed in the resultant keto alcohols. Table 17 represents the results of additions to cyclic and acyclic substrates.

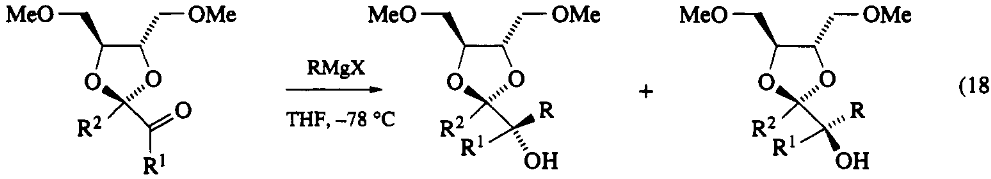

(**69**) (**70**) major (**71**) minor (18)

**Table 17** Diastereoselective Additions to α-Keto Ketals (**69**)

| *R*¹ | *R*² | *RMgX* | *Yield (%)* | *Ratio (70):(71)* |
|---|---|---|---|---|
| $—CH_2CH_2CH_2CH_2—$ | | MeMgBr | 93 | 100:0 |
| $—CH_2CH_2CH_2—$ | | MeMgBr | 91 | 98:2 |
| $—CH_2CH_2CH_2CH_2—$ | | EtMgCl | 95 | 100:0 |
| $—CH_2CH_2CH_2—$ | | EtMgCl | 95 | 100:0 |
| $—CH_2CH_2CH_2CH_2—$ | | (Vinyl)MgBr | 95 | 97:3 |
| $—CH_2CH_2CH_2CH_2—$ | | PhMgBr | 85 | 95:5 |
| Me | Ph | EtMgCl | 98 | >99:1 |
| Me | Ph | (Vinyl)MgBr | 90 | 98:2 |
| Me | Ph | PhMgBr | 84 | 97:3 |
| Me | Et | EtMgCl | 92 | >99:1 |
| Me | Et | (Vinyl)MgBr | 93 | >99:1 |
| Me | Et | PhMgBr | 81 | 98:2 |

The stereoselectivity of these reactions can be explained by chelation of the magnesium metal with the carbonyl oxygen, the proximal methoxy oxygen atom, and one of the acetal oxygens. Migration of the alkyl group from the organometallic reagent then occurs from the least-hindered face (Figure 14). Evidence for this mechanism follows from experiments carried out using a related chiral auxiliary in which the methoxy groups were replaced with hydrogen atoms. Stereoselectivities are considerably lower (10–20% *ee*) in these cases.

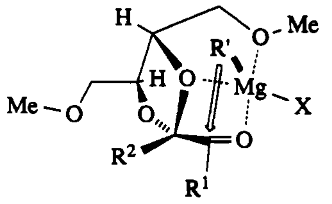

**Figure 14**

Extension of this methodology to the use of chiral acetals such as (**72**; equation 19) to produce optically active secondary alcohols is found to be less efficient than the ketal series. Alkyl Grignard reagents in ether (Table 18) provide the best selectivities (up to 90:10), while aryl and alkynyl organometallics show very little diastereofacial differentiation.[45]

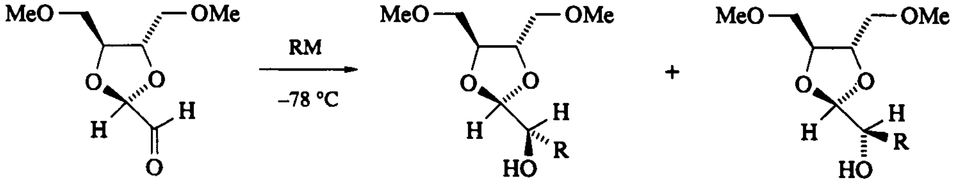

(**72**) (**73**) (**74**) (19)

**Table 18** Diastereoselective Additions to Chiral Acetal (**72**)

| *RM* | *Solvent* | *Yield (%)* | *Ratio (73):(74)* |
|---|---|---|---|
| MeMgI | $Et_2O$ | 70 | 90:10 |
| Bu$^n$MgBr | $Et_2O$ | 65 | 87:13 |
| Bu$^n$Li | $Et_2O$ | 60 | 52:48 |
| Pr$^i$MgBr | $Et_2O$ | 60 | 80:20 |
| PhMgBr | $Et_2O$ | 70 | 34:76 |
| PhMgBr | THF | 70 | 42:58 |
| PhLi | $Et_2O$ | 60 | 49:51 |
| PhC≡CLi | $Et_2O$ | 65 | 48:52 |
| PhC≡CMgBr | THF | 65 | 37:63 |

Advantages of this chiral auxiliary include the ready availability of either enantiomer and its ease of removal, as well as the dual utility of the chiral acetal as both chiral auxiliary, and carbonyl-protecting group. A published synthesis of optically pure (–)-7-deoxydaunomycinone exemplifies the utility of this chiral adjuvant.[46]

The use of ketoaminals based on pyrrolidine as chiral auxiliaries has been demonstrated as another entry to optically active α-hydroxycarbonyls.[47] The aminals (**76**; Scheme 6) are readily obtained from a chiral diamine (**75**) and glyoxal. Addition of Grignard reagents to (**76**), followed by hydrolysis, provides a chiral α-hydroxy aldehyde (**78**) with the (*S*)-configuration. Optical purities are measured in the 94–95% range. The chiral diamine can be recovered unchanged from the reaction mixture.

The source of the asymmetry is thought to occur through two stereoselective steps. First, the preferential formation of one diastereomeric aminal with the structure shown in Figure 15 is expected due to steric arguments. Second, attack of the Grignard reagent from one face of the molecule occurs through the cyclic–chelate mode. The magnesium ion coordinates with the carbonyl oxygen, as well as with the nitrogen (N-1) of the pyrrolidine ring. Complexation with the phenyl-substituted nitrogen (N-2) is dismissed due to its electron deficiency with respect to N-1. This rigid structure leads to alkyl group attack on the carbonyl oxygen from the less-hindered side (see Figure 16).

Extension of this work to the synthesis of α-hydroxy aldehydes with substituents other than phenyl can be carried out by using the methyl ester (**79**; Scheme 7) as precursor.[48] Grignard additions afford a variety of ketoaminals (**80**) in good yield; aldehydes ($R^1$ = H) are available *via* diisobutylaluminum hydride reaction.[49] A second Grignard addition, followed by hydrolysis, generates α-hydroxy aldehydes (**82**) in

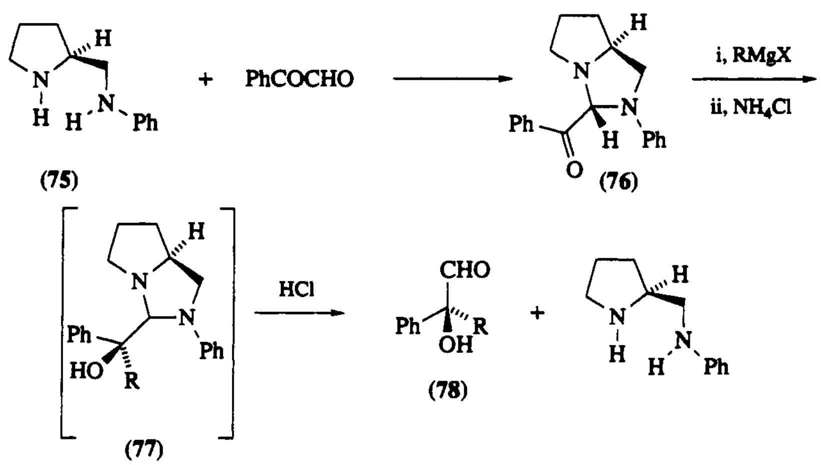

Scheme 6

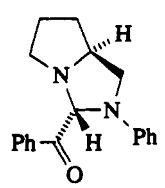

Figure 15

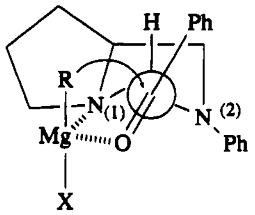

Figure 16

moderate to high optical yields (Table 19). Configurations of the products can be predicted from a model similar to that shown in Figure 16. The corresponding aldehydes (**80**; $R^1$ = H) react with equivalent selectivity to afford secondary alcohols.

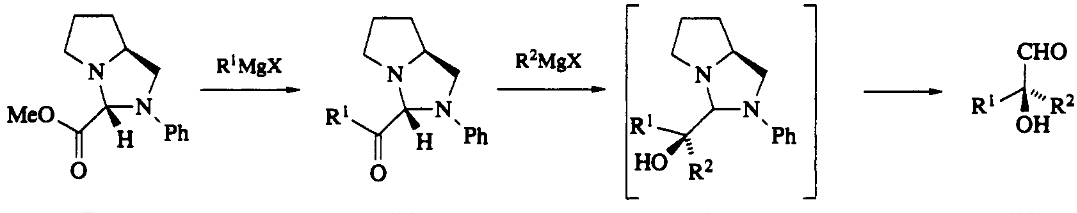

Scheme 7

Table 19 Preparation of α-Hydroxy Aldehydes (**82**)

| $R^1$ | $R^2MgX$ | Yield (%) | (82) ee (%) | Configuration |
|---|---|---|---|---|
| Me | PhMgBr | 76 | 99 | (*R*) |
| Me | EtMgBr | 43 | 78 | (*R*) |
| Me | (Vinyl)MgBr | 44 | 93 | (*R*) |
| Et | PhMgBr | 80 | 100 | (*R*) |
| Et | MeMgI | 41 | 78 | (*S*) |
| $Pr^i$ | PhMgBr | 75 | 94 | (*R*) |

This consecutive Grignard methodology allows the synthesis of either enantiomer of the α-hydroxy aldehyde product, since its stereochemistry is determined only by the order of Grignard reactions. The preparation of natural products such as (+)- and (–)-frontalin[50] and malyngolide[51] in high optical yield has been carried out, and demonstrates the synthetic utility of this chiral auxiliary. The use of pyrrolidine-based chiral auxiliaries is reviewed by Eliel[11] and Mukaiyama.[52]

Glyoxalate esters of phenylmenthols (**83**; equation 20) have been extensively used as chiral auxiliaries for a number of different reactions. Selective Grignard addition from the front face of the molecule affords the α-hydroxy ester (**84**) as the major product (Table 20).[53] Subsequent reduction generates the corresponding diol in optical purities ranging from 88 to 92%.[54] (This methodology is equally applicable to the synthesis of tertiary alcohols using the keto ester as starting material.) The auxiliary suffers from difficulties in its preparation in optically pure form,[55] and from the unavailability of the enantiomeric phenylmenthol. This latter limitation can be overcome by reversal of the order of nucleophilic addition.[56]

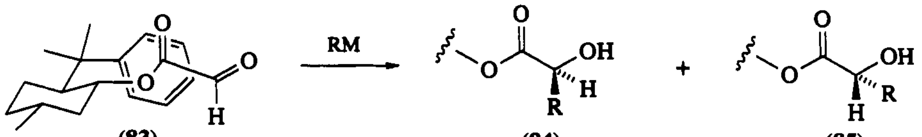

**(83)** **(84)** **(85)** (20)

**Table 20** Selectivities in the Addition of RM to (**83**)

| *Reagent* | *Temperature (°C)* | *Yield (%)* | *Ratio (84):(85)* |
|---|---|---|---|
| MeMgBr | 0 | 62 | 95:5 |
| MeMgBr | –78 | 86 | >99:1 |
| $C_6H_{13}MgBr$ | –78 | 82 | >99:1 |
| $C_8H_{17}MgBr$ | –78 | 80 | 99:1 |
| PhMgBr | –78 | 90 | >99:1 |
| $C_6H_{11}MgBr$ | –78 | 80 | >99:1 |
| MeLi | –78 | 74 | 50:50 |
| MeLi + $LiClO_4$ | –78 | 80 | 80:20 |

Meyers and coworkers report the synthesis of enantiomerically enriched α-hydroxy acids (enantiomeric excesses of the products generally range from 30 to 87%) from chiral ketooxazolines such as (**86**; Scheme 8).[57] In most cases, only moderate selectivities are observed. The highest ratios (62–87% *ee*) result when aryllithiums are employed as the nucleophile (Table 21). Since the course of the reaction seems to depend on a number of subtle conformational and coordinating effects, predictions of the stereochemical outcome of these processes are difficult.

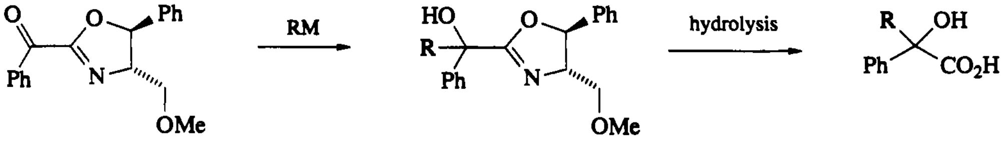

**(86)** **(87)** **(88)**

**Scheme 8**

**Table 21** Synthesis of α-Hydroxy Acids (**88**)

| *Reagent* | *(87)* *Yield (%)* | *Yield (%)* | *(88)* *ee (%)* | *Configuration* |
|---|---|---|---|---|
| MeMgBr/THF | 95 | 70 | 9 | (*S*) |
| MeMgBr/TMEDA/THF | 99 | 72 | 32 | (*R*) |
| MeMgBr/$Et_3N$/toluene | 94 | 76 | 22 | (*S*) |
| MeLi/THF | 93 | 70 | 0 | — |
| MeLi/$LiClO_4$/THF | 99 | 73 | 48 | (*S*) |
| EtMgBr/$Et_3N$/toluene | >99 | 65 | 33 | (*S*) |
| $Pr^n$MgBr/$Et_3N$/toluene | >99 | 62 | 39 | (*S*) |
| $Pr^i$MgBr/$Et_3N$/toluene | 95 | 57 | 41 | (*S*) |
| $Bu^i$MgBr/$Et_3N$/toluene | >99 | 55 | 50 | (*S*) |
| *p*-Tol-Li | 93 | 60 | 76 | (*S*) |
| *p*-Anisyl-Li | 92 | 55 | 62 | (*S*) |
| 1-Naphthyl-Li | >99 | 62 | 65 | (*S*) |
| 2-Thienyl-Li | 90 | 73 | 87 | (*S*) |

### 1.2.1.2 Additions to Cyclic Systems

Nucleophilic additions to cyclic carbonyl compounds differ greatly from those of acyclic systems. In acyclic systems, only the configuration at an adjacent (1,2-asymmetric induction) or nearby center (remote asymmetric induction) is usually considered in predicting the outcome of nucleophilic attack. In cyclic systems, the conformation of the entire molecule (which is in part determined by the individual substituents) must be considered when predicting the mode of nucleophilic attack. Furthermore, a number of other factors such as torsional and electronic effects also play a role in the stereochemical course of additions to cyclic substrates. The relative importance of all of these effects (as well as others) has been the subject of considerable debate in the literature, and has not as yet been adequately resolved.[9,12,58]

Models for the nucleophilic addition of organolithium and Grignard reagents to cyclic ketones assume that the incoming group approaches the carbonyl carbon perpendicularly to the plane of the $sp^2$ center (Figure 17).[58] This line of approach effects maximum overlap of the orbitals in the transition state of the reaction. Whether this perpendicular nucleophilic attack then occurs from an equatorial or an axial trajectory depends on the effects mentioned above. In the case of simple cyclohexanones, if 'steric approach control' influences the reaction, the nucleophile will enter from the less-hindered equatorial position to yield the axial alcohol. Axial addition is disfavored due to steric hindrance from the axial hydrogen atoms at C-3 and C-5. When 'product development control' is in effect, formation of the more stable equatorial alcohol (from axial attack) is favored. The relative importance of all of these effects is highly dependent on the particular nature of the cyclic substrate, and has been the subject of considerable theoretical interest.[59] An excellent review of this field has been written by Ashby and Laemmle.[58]

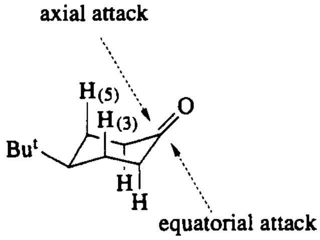

**Figure 17**

The mode of addition to substituted cyclohexanones (equation 21) depends greatly on the nature and position of the substituents, as well as on the structure of the organometallic reagent. Table 22[58] lists results of nucleophilic additions to a variety of cyclohexanones. Some broad generalizations can be made.[12]

(i) With organolithiums (except acetylides) and Grignard reagents, equatorial attack is usually favored. The substitution pattern of the ketone influences the course of the reaction to a lesser extent. With acetylides, axial attack predominates due to torsional effects.

(ii) The degree of selectivity often increases with the size of the incoming nucleophile.

Predictions of the stereochemical outcome of nucleophilic additions to substituted cyclopentanones is less straightforward. The conformation of a 2-substituted five-membered ring (**92**) is such that attack from the least-hindered face (steric approach control) results in the formation of a *cis*-substituted alcohol (**93**; equation 22). Torsional strain controlled additions lead to *trans*-substituted alcohols (**94**).[58] As in the examples of cyclohexanones, steric approach control usually dominates the reaction pathway with the use of organolithiums and Grignard reagents; torsional strain control with ethynyl reagents (Table 23).[12,58] A single substituent at the 3-position of the cyclopentanone has less of an effect on the stereochemical outcome of nucleophilic addition, and product ratios in these systems are generally poor.[58]

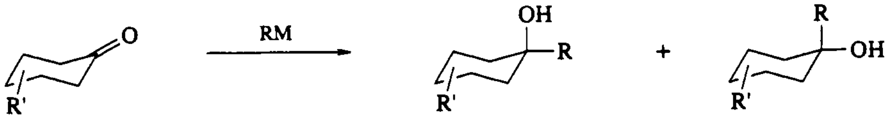

(21)

(**89**) (**90**) equatorial attack (**91**) axial attack

**Table 22** Addition of Organometallic Reagents to Substituted Cyclohexanones (**89**)

| *Reagent (RM)* | *Substituent (R′)* | *Ratio (**90**):(**91**)* |
|---|---|---|
| $MeLi/Et_2O$ | 4-$Bu^t$ | 65:35 |
| $MeLi/Et_2O$ | 2-Me | 84:16 |
| $MeLi/Et_2O$ | 3,3,5-$Me_3$ | 100:0 |
| PhLi | 4-$Bu^t$ | 58:42 |
| PhLi | 4-Me | 53:47 |
| PhLi | 3-Me | 44:56 |
| PhLi | 2-Me | 88:12 |
| $HC{\equiv}CNa/Et_2O + NH_3$ | 4-$Bu^t$ | 12:88 |
| $HC{\equiv}CLi/THF + NH_3$ | 2-Et | 53:47 |
| $HC{\equiv}CLi/THF + NH_3$ | 3-Me | 18:82 |
| $HC{\equiv}CLi/THF + NH_3$ | 2-Me | 45:55 |
| $MeMgI/Et_2O$ | 4-$Bu^t$ | 53:47 |
| $MeMgI/Et_2O$ | 2-Me | 84:16 |
| $MeMgI/Et_2O$ | 3,3,5-$Me_3$ | 100:0 |
| $EtMgBr/Et_2O$ | 4-$Bu^t$ | 71:29 |
| $EtMgBr/Et_2O$ | 3-Me | 68:32 |
| $EtMgBr/Et_2O$ | 2-Me | 95:5 |
| $EtMgBr/Et_2O$ | 3,3,5-$Me_3$ | 100:0 |
| $PhMgBr/Et_2O$ | 4-$Bu^t$ | 49:51 |
| $PhMgBr/Et_2O$ | 4-Me | 54:46 |
| $PhMgBr/Et_2O$ | 3-Me | 59:41 |
| $PhMgBr/Et_2O$ | 2-Me | 91:9 |
| $PhMgBr/Et_2O$ | 3,3,5-$Me_3$ | 100:0 |
| $HC{\equiv}CMgBr$ | 2-Me | 45:55 |
| $HC{\equiv}CMgBr$ | 3,3,5-$Me_3$ | 100:0 |

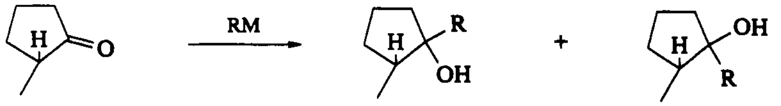

(22)

(**92**) (**93**) *cis*-alcohol (**94**) *trans*-alcohol

**Table 23** Addition of Organometallic Reagents to Substituted Cyclopentanones

| *Reagent* | *Substituent* | *Ratio of alcohols cis:trans* |
|---|---|---|
| $MeMgBr/Et_2O$ | 2-Me | 60:40 |
| PhMgBr/THF | 2-Me | 99:1 |
| $HC{\equiv}CMgBr/THF$ | 2-Me | 50:50 |
| $(Allyl)MgCl/Et_2O$ | 2-Me | 77:23 |
| (Vinyl)MgCl/THF | 2-Me | 92:8 |
| $MeLi/Et_2O$ | 2-Me | 70:30 |
| $Bu^nLi$/Hexane | 2-Me | 86:14 |
| $PhLi/Et_2O$ | 2-Me | 95:5 |
| $HC{\equiv}CLi/THF–NH_3$ | 2-Me | 21:79 |
| $EtMgBr/Et_2O$ | 2-Methoxy | 75:25 |
| $Pr^nMgBr$ | 2-Methoxy | 87:13 |
| $HC{\equiv}CMgBr/THF$ | 2-Methoxy | 42:58 |
| $(Allyl)MgX/Et_2O$ | 2-Methoxy | 82:18 |
| $MeMgI/Et_2O$ | 3-Me | 60:40 |
| $Pr^nMgBr/Et_2O$ | 3-Me | 61:39 |
| $PhMgBr/Et_2O$ | 3-Me | 58:42 |
| $(Allyl)MgCl/Et_2O$ | 3-Me | 65:35 |
| $MeMgBr/Et_2O$ | 3-$Bu^t$ | 54:46 |
| $Pr^iMgBr/Et_2O$ | 3-$Bu^t$ | 61:39 |
| $HC{\equiv}CMgBr/THF$ | 3-$Bu^t$ | 65:35 |
| $MeMgBr/Et_2O$ | 3,4-*cis*-$Me_2$ | 92:8 |
| $PhMgBr/Et_2O$ | 3,4-*cis*-$Me_2$ | 92:8 |

## 1.2.2 ADDITIONS OF CHIRAL REAGENTS TO ACHIRAL SUBSTRATES

### 1.2.2.1 Introduction

A number of reports involving the addition of chiral nucleophiles to prochiral carbonyl compounds have appeared in the literature. While many of these examples involve the use of stabilized carbanions derived from chiral sulfoxides (Chapter 2.4, this volume) or chiral ester enolates (Volume 2), several examples rely on asymmetric derivatives of organolithium and Grignard reagents. Among this class, two subsets of reactions are described. The use of organometallic nucleophiles which are chiral by virtue of covalent bonds has had limited use. A more developed field involves the use of achiral nucleophiles in a chiral environment. In these examples, close association between the nucleophile and the additive generates asymmetric reagents without virtue of a formal chemical bond.

### 1.2.2.2 Covalent Chiral Reagents

The aryllithium reagent (**96**; Scheme 9) can be used as a chiral organometallic reagent in nucleophilic additions to prochiral carbonyl substrates.[60] Addition to a variety of aldehydes affords, after hydrolysis of the aminal, optically active hydroxy aldehydes (**98**) in moderate to high enantiomeric excesses (Table 24). The course of the addition is proposed to occur through intramolecular coordination of the aminal auxiliary to the lithium atom, as shown in Figure 18. The rigid tricyclic structure easily differentiates the faces of the reacting aldehydes. Approach of the aldehydes from the less-hindered face affords asymmetric carbinol centers with the (*S*)-configuration according to this model.

Aromatic oxazolines such as (**99**; Scheme 10) have also been used as chiral nucleophiles.[57b,61] Additions to carbonyl compounds occur with only modest stereoselectivities. The highest ratio of diastereomers produced (64:36) occurs when acetophenone is used as substrate. A sterically undemanding transition state probably accounts for these disappointing results.

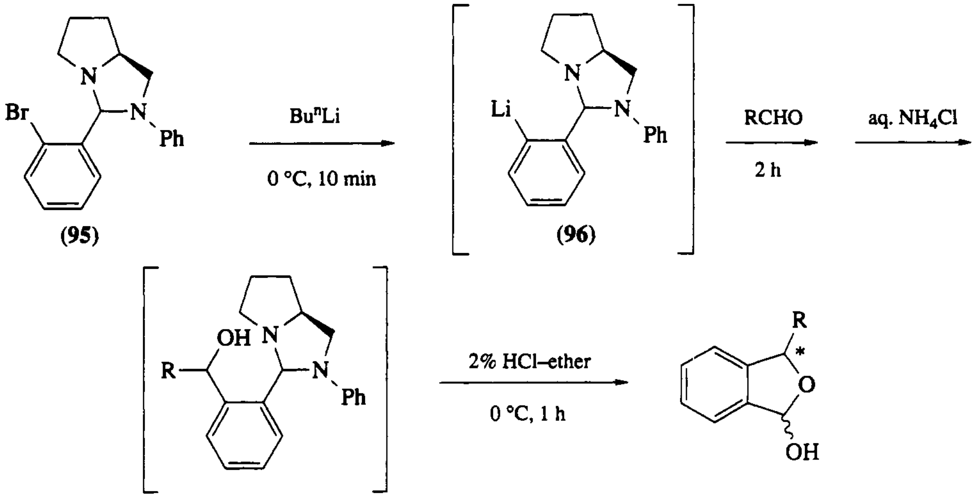

**Scheme 9**

**Table 24** Preparation of Chiral Lactols (**98**)

| *R* | *Solvent* | *Temperature (°C)* | *Yield (%)* | *ee (%)* |
|---|---|---|---|---|
| Bu$^n$ | Toluene | –78 | 73 | 65 |
| Bu$^n$ | Ether | –78 | 63 | 78 |
| Bu$^n$ | Ether | –100 | 62 | 87 |
| Et | Ether | –100 | 51 | 88 |
| Pr$^i$ | Ether | –100 | 52 | >90 |
| n-$C_8H_{17}$ | Ether | –100 | 58 | 90 |
| Allyl | Toluene | –78 | 70 | 20 |

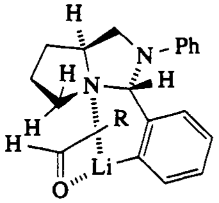

**Figure 18**

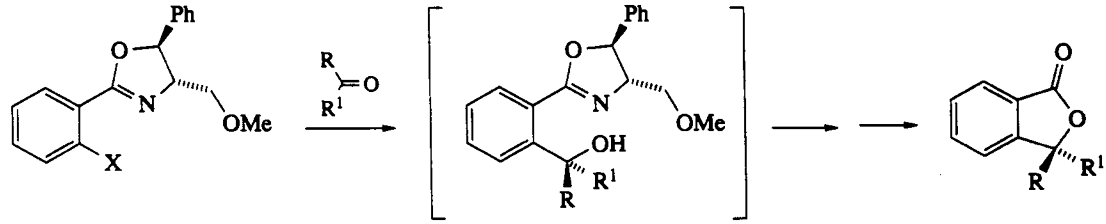

(99) X = Li

(100)

(101)

Scheme 10

### 1.2.2.3 Noncovalent Chiral Reagents

The stereoselective addition of achiral nucleophiles to prochiral carbonyl compounds in the presence of chiral additives is a conceptually elegant method for the synthesis of enantiomerically pure compounds from achiral starting materials. Advantages of this strategy include the ability to recover the chirality 'inducer', and the elimination of steps involving chemically introducing and removing these 'noncovalent chiral auxiliaries'. This latter point represents a significant advantage of this protocol over the use of standard chiral auxiliaries.

Several systems have been developed which exploit the well-known coordination of organolithium reagents to tertiary amines, and of Grignard reagents to ethers. This strong association generates asymmetric nucleophilic reagents; transfer of an alkyl group from this chiral organometallic results in an enantioselective process. Early work in this area led to only low asymmetric inductions. However, a number of groups have recently improved the enantioselectivity to modest, and even high levels in some cases. This area has been reviewed by Solladié.[62]

Seebach has carried out an extensive study on the use of chiral additives based on tartaric acid to induce asymmetry in the addition of *n*-butyllithium to aldehydes.[62,63] After systematically investigating a number of ligands, the tetraamine (**102**) was found to be the most effective, providing alcohols (**103**; equation 23) with optical purities in the range of 15 to 56% (Table 25).

This additive reliably causes nucleophilic attack to occur from the *si* face of the aldehyde to generate the (*S*)-alcohol. The direction of addition is irrespective of the organolithium reagent used. The authors suggest Figure 19 as the conformation responsible for the selectivities observed.

The pyrrolidine derivative (**104**; equation 24) developed by Mukaiyama and coworkers for the enantioselective addition of organolithiums to aldehydes has been one of the most studied.[52,64] Although opti-

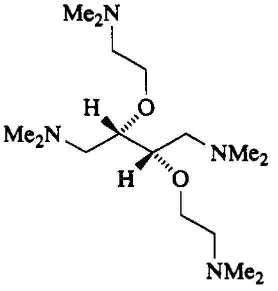

(**102**) (*S*,*S*)-DEB

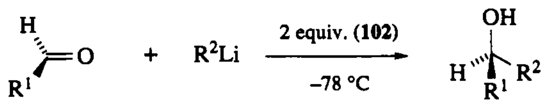

(**103**)

(23)

**Table 25** Enantioselective Additions of $R^2Li$ to Aldehydes ($R^1CHO$) in the Presence of (**102**)

| *$R^1$* | *$R^2$* | *(**103**) ee (%)* |
|---|---|---|
| Me | $Bu^n$ | 46 |
| Et | $Bu^n$ | 35 |
| $Bu^n$ | Me | 34 |
| Ph | $Bu^n$ | 52 |
| $Bu^n$ | Ph | 15 |
| *o*-MePh | $Bu^n$ | 56 |
| *p*-MePh | $Bu^n$ | 49 |
| $Et_2CH$ | $Bu^n$ | 46 |
| $Pr^i$ | $Bu^n$ | 53 |
| $Bu^t$ | $Bu^n$ | 18 |
| $C_6H_{11}$ | $Bu^n$ | 48 |
| Vinyl | $Bu^n$ | 24 |

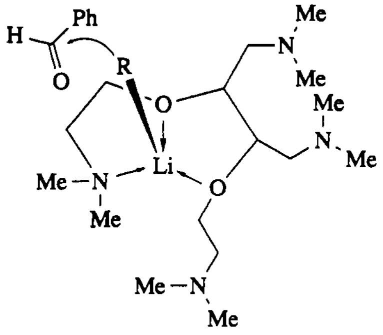

**Figure 19**

cal purities were generally moderate (11–72% *ee*; Table 26), reactions using alkynyllithium reagents show very good selectivities (54–92% *ee*).[65]

Extensive study of (**104**) indicates that both pyrrolidine moieties, as well as the lithiated hydroxymethyl group are crucial for high asymmetric induction. Figures 20 and 21 represent possible modes of the course of the reaction. A rigid structure containing four fused five-membered rings can be formed by coordination of the two nitrogen atoms and the oxygen atom to the lithium of the organometallic reagent.

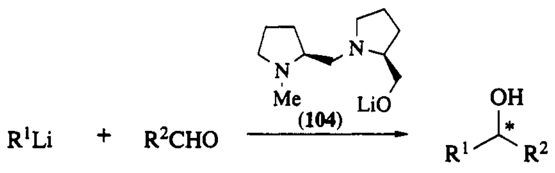

(**105**)

(24)

**Table 26** Enantioselective Additions of $R^1Li$ to Aldehydes ($R^2CHO$) in the Presence of (**104**)

| *$R^1$* | *$R^2$* | *Temperature (°C)* | *Yield (%)* | *Alcohol (**105**) Optical purity (%)* | *Configuration* |
|---|---|---|---|---|---|
| Me | Ph | −78 | 82 | 21 | (*R*) |
| Et | Ph | −123 | 32 | 39 | (*R*) |
| $Pr^n$ | Ph | −123 | 55 | 39 | (*S*) |
| $Bu^n$ | Ph | −123 | 60 | 72 | (*S*) |
| $Bu^i$ | Ph | −123 | 59 | 16 | (*S*) |
| $Bu^n$ | $Pr^i$ | −123 | 47 | 56 | (*S*) |
| Ph | $Bu^n$ | −123 | 46 | 11 | (*R*) |
| HC≡C | Ph | −78 | 76 | 54 | (*S*) |
| TMS—C≡C | Ph | −78 | 99 | 78 | (*S*) |
| TMS—C≡C | Ph | −123 | 87 | 92 | (*S*) |
| $Ph_2MeSi$—C≡C | Ph | −123 | 88 | 80 | (*S*) |

The size of the alkyllithium apparently determines the diastereofacial approach of the aldehyde, and thus determines the stereochemistry of the alcohol product.

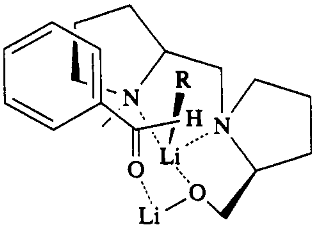

**Figure 20**

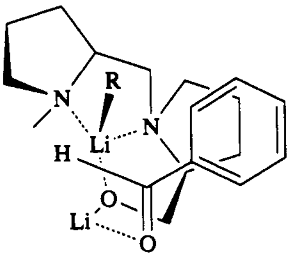

**Figure 21**

Conditions for optimal asymmetric induction include low temperature (–123 °C) and the use of a 1:1 mixture of dimethoxymethane and dimethyl ether as solvent.[66] Investigation of a number of different organometallic species indicated that dialkylmagnesium reagents yield the highest optical purities (equation 25). Table 27 lists representative examples of this enantioselective reaction under these optimal conditions.[67] Interestingly, all of the alcohols produced under these conditions have the (*R*)-configuration.

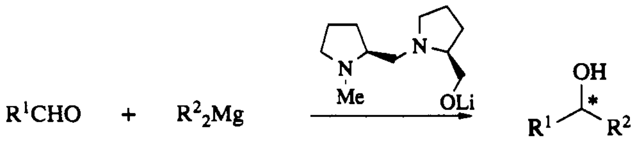

**(105)**

(25)

**Table 27** Synthesis of Optically Active Alcohols (**105**) Using Dialkylmagnesium Reagents in the Presence of (**104**)

| *R*¹ | *R*² | *Yield (%)* | *Optical purity (%)* |
|---|---|---|---|
| Ph | Me | 56 | 34 |
| Ph | Et | 74 | 92 |
| Ph | $Pr^n$ | 90 | 70 |
| Ph | $Pr^i$ | 59 | 40 |
| Ph | $Bu^n$ | 94 | 88 |
| Ph | $Bu^i$ | 81 | 42 |
| $Pr^i$ | $Bu^n$ | 70 | 22 |

This chiral ligand can also be used as an additive in the enantioselective reaction of stabilized anions to carbonyl compounds.[68] Optical purities of these processes are moderate (up to 76% *ee*), and depend on the conditions of the reaction, as well as on the particular reactants involved.

A number of other chiral ligands are available, but have been studied much less extensively. The chiral diamines (**106**) and (**107**) are reported to mediate the reactions between aryl Grignards and aldehydes (Figure 22; equation 26).[69] The alcohols range in optical purity from 40 to 75% *ee*; selectivities increase with the bulkiness of the aldehyde substituent (see Table 28). The use of an aryloxy metal halide to complex the aldehyde moiety enhances the observed enantioselectivities.[70]

Mazaleyrat and Cram have used diamines (**108**) and (**109**) as chiral catalysts in the enantioselective addition of alkyllithiums to aldehydes (equation 27; Table 29). Optical yields of 23–95% are obtained.[71] Highest values are associated with the use of larger alkyllithium reagents, as well as with the more sterically encumbered catalyst (**108**).

A number of other chiral catalysts have been reported, among them the proline (**111**),[72] lithium amides (**112**)[73] and the tetrahydrofurylamine (**113**).[74] The optical yields of the products isolated, however, are only moderate at best. The use of optically active 2-methyltetrahydrofuran in Grignard reactions has also been reported; however, minimal induction is observed.[75]

The use of chiral ligands to enantiofacially bias a nucleophilic reaction of achiral starting materials holds great promise for asymmetric syntheses. Further development of ligands which consistently provide high enantiomeric excess, as well as generate predictable geometries at the chiral center, is necessary.

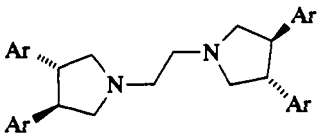

**(106)** Ar = Ph
**(107)** Ar = 3,5-xylyl

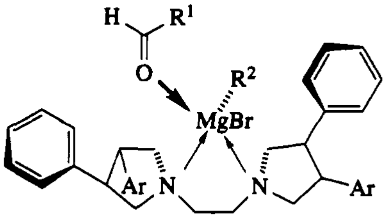

**Figure 22**

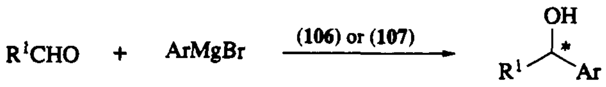

(26)

**Table 28** Enantioselective Additions of Aryl Grignards with Aldehydes Mediated by **(106)** or **(107)**

| *R*$^1$ | *Ar* | *Ligand* | *Temperature (°C)* | *ee (%)* | *Configuration* | *Yield (%)* |
|---|---|---|---|---|---|---|
| Ph | α-Naphthyl | **(106)** | −100 | 71 | (*S*) | 92 |
| Ph | α-Naphthyl | **(106)** | −78 | 64 | (*S*) | 96 |
| Ph | α-Naphthyl | **(106)** | −45 | 55 | (*S*) | 94 |
| Ph | α-Naphthyl | **(107)** | −100 | 75 | (*S*) | 94 |
| Bu$^t$ | Ph | **(106)** | −100 | 60 | (*S*) | 82 |
| $C_6H_{11}$ | Ph | **(107)** | −100 | 55 | (*S*) | 68 |
| Pr$^i$ | Ph | **(106)** | −100 | 47 | (*S*) | 68 |
| Bu$^n$ | Ph | **(106)** | −100 | 40 | (*S*) | 73 |

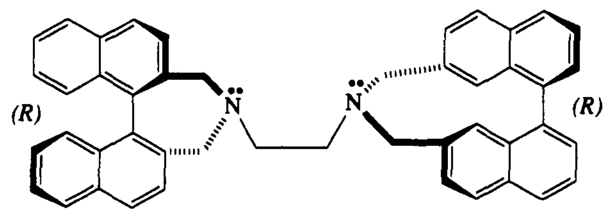

**(108)**

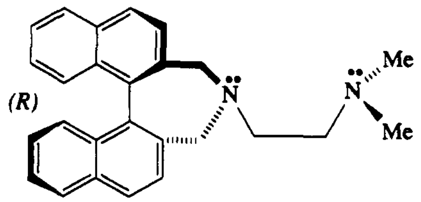

**(109)**

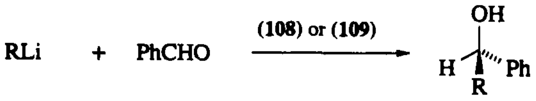

**(110)**

(27)

**Table 29** Enantioselective Additions of Organolithium Reagents (RLi) to Benzaldehyde in the Presence of (**108**) or (**109**)

| *R* | *Ligand* | *Yield (%)* | *(110)*<br>*ee (%)* | *Configuration* |
|---|---|---|---|---|
| $Bu^n$ | 108 | 73 | 95 | (*R*) |
| $Bu^n$ | 108 | 63 | 59 | (*R*) |
| Et | 108 | 75 | 66 | (*R*) |
| Me | 108 | 35 | 36 | (*R*) |
| $Bu^n$ | 109 | 71 | 58 | (*R*) |
| $Pr^n$ | 109 | 75 | 53 | (*R*) |
| Et | 109 | 73 | 30 | (*R*) |
| Me | 109 | 65 | 23 | (*R*) |

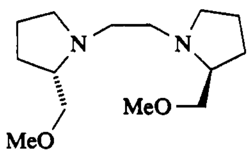

**(111)**

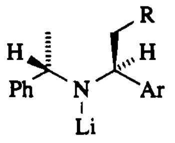

**(112)** **a**: Ar = phenyl, R = H
**b**: Ar = 2-pyridyl, R = H
**c**: Ar = *o*-methoxyphenyl, R = H
**d**: Ar = phenyl, R = OMe

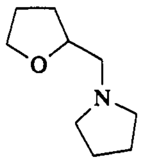

**(113)**

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# 1.3

# Organoaluminum Reagents

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## 1.3.1 INTRODUCTION

Organoaluminums have been reviewed extensively. The first thorough treatise was published in 1972 by Mole,[1] describing the preparation of organoaluminums and their reactions with various functional groups. Negishi[2,4] and Yamamoto[3] have also reviewed the general properties and reactions of organoaluminums. However, Negishi[2] focused on the 1,2-nucleophilic additions of $\alpha,\beta$-unsaturated organoaluminums, which specifically included the reactions of alkenylalanes and alkenylalanates with carbon electrophiles, whereas the Yamamoto review[3] was of a more general nature. The preparation of alkenyl- and alkynyl organoaluminums has also been reviewed by Normant[5] and Zweifel.[6] The portion of the Normant review that focused on organoaluminum reagents described the *syn* specific carbometallation of alkynes by organoaluminums, which provides stereospecific access to alkenylaluminums. In contrast, Zweifel[6] prepared a very detailed review dealing with the preparation and reactions of alkenyl- and alkynyl-aluminums.

The stabilized anions of organoaluminums have also been discussed, inasmuch as there have been extensive reviews of allyl- and crotyl-aluminum reagents.[7–9] Yamamoto has reviewed the preparation and reactions of both allyl-[7] and crotyl-aluminum[9] reagents, while Hoffmann[8] has prepared a more general review of organocrotyl reagents, which includes some discussion of the corresponding aluminum reagents. These reviews also consider in some detail the stereochemical consequences of these processes and include some discussion of the transition state geometries. Not surprisingly, the more recent reviews[10–13] focus on the stereoselectivity and site selectivity of the organoaluminum-mediated reactions, as well as their potential applications to organic synthesis. Most notable in this regard is the review of Yamamoto,[13] which attempts to outline all of the major reactions of organoaluminum reagents not only according to the nature of the reacting substrate, but also in terms of the regioselectivity and stereoselectivity of each reaction.

Since so much has been written about the properties and the preparation of organoaluminums, this review will detail only selected reactions, with a heavy emphasis on site selectivity and stereoselectivity; moreover, the nature of the reactions that are detailed will be limited to 1,2-nucleophilic additions of nonstabilized anions to unsaturated carbon–heteroatom substrates. Obviously, this will limit the scope of the review and the very interesting regioselective and stereoselective challenges presented by stabilized anions, namely, aldol-like processes, will be omitted. Nevertheless, the scope of this review will intensify the focus on the problems of regioselectivity and stereoselectivity furnished by the 1,2-additions of organoaluminum reagents to either carbonyl systems or masked carbonyl systems. Finally, the application of organoaluminum reagents to the synthesis of natural products will be presented, again in the context of regioselective and stereoselective processes.

## 1.3.2 SITE SELECTIVE AND STEREOSELECTIVE ADDITIONS OF NUCLEOPHILES MEDIATED BY ORGANOALUMINUM REAGENTS

### 1.3.2.1 Aluminum-based Additives

In 1975 Ashby[14] extensively reviewed the stereochemical results of the 1,2-additions of a variety of organometallic reagents to prochiral carbonyl substrates. The specific section describing the addition of organoaluminum reagents is extensive, but the most interesting aspect of the review with regard to alkylaluminum-mediated additions is the observation[15,16] that the axial selectivity of alkyl addition to cyclic ketones is greatly enhanced by increasing the ratio of aluminum reagent to substrate. Thus, at ratios of 2:1 or greater, the addition results in 90% axial attack, whereas at a 1:1 ratio equatorial attack predominates. The observation was rationalized by invoking a 'compression effect', which derives from the increased steric bulk about the carbonyl as a result of complexation with the organoaluminum.[17]

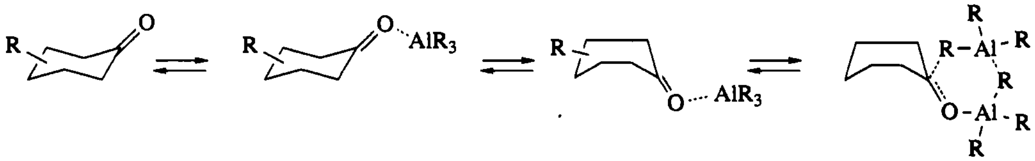

Scheme 1

This seminal observation has recently been utilized by Yamamoto[18] to develop an approach for the stereoselective and site selective addition of organometallics to carbonyl substrates. The approach makes use of the very bulky aluminum reagent (**1**), which is readily prepared *in situ* by exposure of trimethylaluminum to a toluene solution of 2,6-di-*t*-butyl-4-alkylphenols (molar ratio 1:2) at room temperature.

The MAD and MAT reagents are presumably monomeric in solution, since they are very bulky reagents and it is known[19] that a 1:1 mixture of benzophenone and trimethylaluminum exists as a long-lived monomeric complex at room temperature. Although no solid state structure of the complex of reagent (**1**) with carbonyl substrates is available,[20] a reasonable representation is formulated in Scheme 2.

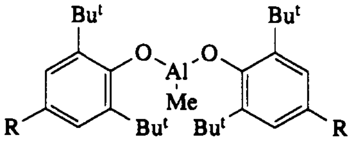

(1) R = Me (MAD); R = Bu$^t$ (MAT)

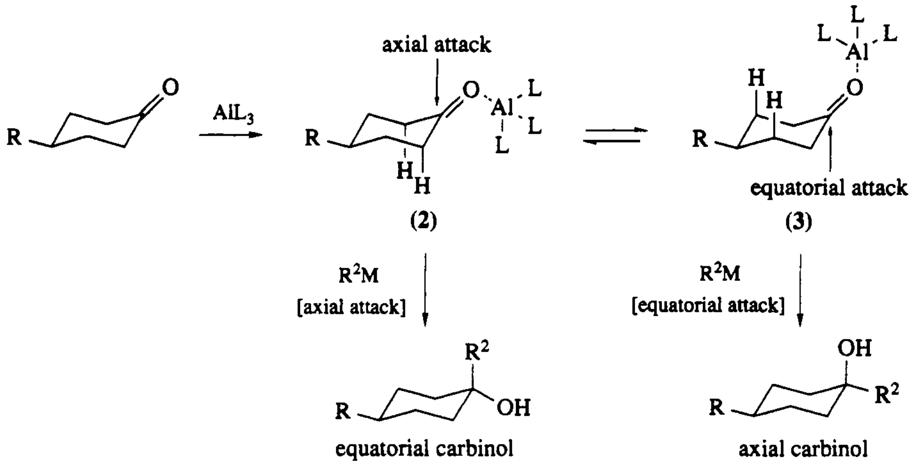

**Scheme 2**

The equilibrium concentration of the reactive species would greatly favor substituted cyclohexanone (**2**; Scheme 2), since it has been demonstrated[14–16] that the steric interaction of the 3,5-axial substituents with a bulky group chelating the carbonyl moiety dominates the torsional strain that develops between the chelating group and the 2,6-diaxial positions. Thus, preexposure of cyclic ketones to reagent (**1**) and subsequent addition of another organometallic would be expected to favor the formation of equatorial carbinols resulting from axial addition of the organometallic ($R^1M$) in Scheme 2. Table 1[8,21] summarizes the results of 1,2-additions of alkyllithium and alkyl Grignard reagents to substituted cyclohexanones in the presence or absence of reagent (**1**). Comparison of entries 4 and 5 as well as entries 6 and 7 illustrates the remarkable effect that the organoaluminum additive (**1**) has on the overall stereoselectivity of the 1,2-additions. For example, exposure of 4-*t*-butylcyclohexanone to methyllithium in the absence of (**1**) results in the preferential formation (*ca.* 4:1) of the corresponding axial alcohol, whereas in the presence of (**1**; R = *t*-butyl; MAT) the 1,2-addition proceeds with almost exclusive formation (99%) of the equatorial alcohol. Although the results outlined in Table 1 support the mechanism outlined in Scheme 2, an additional experiment was conducted attempting to further define the nature of the reacting species. When the ketone substrate is exposed to a mixture of methyllithium and reagent (**1**; R = Me; MAD) at –78 °C, the resulting ratio of axial/equatorial carbinols is similar (ax:eq = 84:16)[21] to that observed for the addition of methyllithium alone. Thus, the possibility of ate complex formation resulting from reaction of methyllithium with the aluminum additive (**1**) appears unlikely. It appears, therefore, that Scheme 2 adequately accommodates the experimental observations.

Unfortunately, this approach has limitations with regard to the nature of the ketone substrate as well as the nature of the organometallic nucleophile. For example, alkylation and reduction occurred when secondary and tertiary alkyl Grignards were utilized as nucleophiles, while attempted reactions with either vinyl or phenyl nucleophiles occurred slowly with no equatorial selectivity. Furthermore, as the steric environment about the carbonyl carbon becomes more congested, the observed stereoselectivity decreases (Table 1, entries 11–14).

The detrimental effect of the steric environment about the carbonyl moiety on the course of the reaction is very well illustrated for cyclopentanones (Table 2). Comparison of the entries in Table 2 reveals that cyclopentanone substrates are very sensitive not only to the steric bulk of the incoming nucleophile (entries 2–4), but also to the substitution pattern on the carbocycle (entries 1, 2 and 5).

**Table 1** Facial Selectivities for the Addition of Organometallics to Substituted Cyclohexanones in the Presence of (**1**)

| *Entry* | *Substrate* | *Reagent (1)* | *Organometallic* | *Yield (%)* | *Axial alcohol: equatorial alcohol* |
|---|---|---|---|---|---|
| 1 | 4-*t*-Butylcyclohexanone | None | MeLi | — | 79:21 |
| 2 | 4-*t*-Butylcyclohexanone | MAD | MeLi | 84 | 1:99 |
| 3 | 4-*t*-Butylcyclohexanone | MAT | MeLi | 92 | 0.5:99.5 |
| 4 | 4-*t*-Butylcyclohexanone | None | EtMgBr | 95 | 48:52 |
| 5 | 4-*t*-Butylcyclohexanone | MAD | EtMgBr | 91 | 0:100 |
| 6 | 4-*t*-Butylcyclohexanone | None | BuMgBr | 58 | 56:44 |
| 7 | 4-*t*-Butylcyclohexanone | MAD | BuMgBr | 67 | 0:100 |
| 8 | 4-*t*-Butylcyclohexanone | None | AllylMgBr | 86 | 48:52 |
| 9 | 4-*t*-Butylcyclohexanone | MAD | AllylMgBr | 90 | 9:91 |
| 10 | 2-Methylcyclohexanone | None | MeLi | — | 92:8 |
| 11 | 2-Methylcyclohexanone | MAD | MeLi | 84 | 14:86 |
| 12 | 2-Methylcyclohexanone | MAT | MeLi | 80 | 10:90 |
| 13 | 2-Methylcyclohexanone | MAD | EtMgBr | 0 | — |
| 14 | 2-Methylcyclohexanone | MAD | BuMgBr | 0 | — |
| 15 | 3-Methylcyclohexanone | None | MeLi | — | 83:17 |
| 16 | 3-Methylcyclohexanone | MAD | MeLi | 69 | 9:91 |
| 17 | 3-Methylcyclohexanone | MAT | MeLi | 95 | 3:97 |
| 18 | 3-Methylcyclohexanone | None | BuMgBr | 86 | 79:21 |
| 19 | 3-Methylcyclohexanone | MAD | BuMgBr | 75 | 1:99 |
| 20 | 3-Methylcyclohexanone | None | AllylMgBr | 95 | 56:44 |
| 21 | 3-Methylcyclohexanone | MAD | AllylMgBr | 72 | 24:76 |

**Table 2** Facial Selectivities for the Addition of Organometallics to Substituted Cyclopentanones in the Presence of (**1**)

| *Entry* | *Substrate* | *Reagent (1)* | *Organometallic* | *Yield (%)* | *Axial alcohol: equatorial alcohol* |
|---|---|---|---|---|---|
| 1 | 2-Butylcyclopentanone | None | MeLi | — | 75:25 |
| 2 | 2-Butylcyclopentanone | MAD | MeLi | 82 | 1:99 |
| 3 | 3-Methylcyclopentanone | None | PrMgBr | 54 | 55:45 |
| 4 | 3-Methylcyclopentanone | MAD | PrMgBr | 79 | 50:50 |
| 5 | 2-Phenylcyclopentanone | MAD | MeMgBr | 0 | — |

### *1.3.2.1.1 Cram* versus *anti-Cram selectivities*

The addition of organometallics to aldehyde substrates incapable of populating intramolecularly chelated conformations preferentially results in a Cram selective process. This result is most easily rationalized by considering an aldehyde conformation that maintains the incoming organometallic reagent and the largest substituent of the aldehyde in an antiperiplanar disposition, as represented by (**5**).[22,23]

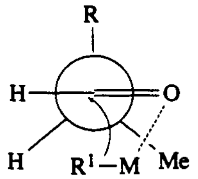

Cram product

(**5**)

Entries 1–4 in Table 3[21] illustrate the tendency for a Cram selective process in additions to aldehydes of type (**4**; equation 1). In contrast, when (**4**) is treated with the aluminum additive (**1**) prior to exposure to organometallics, the nucleophilic addition results in an anti-Cram product. The resulting facial selectivity may be most easily rationalized by considering transition state structure (**6**), which defines the anti-Cram face of the aldehyde to be less hindered by virtue of precoordination of the aluminum reagent (**1**) to the less sterically demanding Cram face. For example, comparison of entries 2, 6 and 9 to the corresponding entries 5, 8 and 10 in Table 3 illustrates the dramatic effect that the aluminum additive (**1**) has on the facial selectivity of the reaction. This approach to anti-Cram selectivity, however, does suffer some limitations. For example, the organometallic reagents in Table 3 are all Grignard reagents, since organolithium based nucleophiles do not work well.[21] Furthermore, additions of $sp^2$-hybridized nucleophiles (*e.g.* vinyl, enolate and phenyl) resulted in no stereoselectivity; also, although the *sp*-hybridized case listed in Table 3 (entry 12) proceeds in good yield, the anti-Cram facial selectivity is unimpressive (41:59; Cram:anti-Cram). Finally, the overall anti-Cram selectivity is adversely affected by increasing steric bulk of the incoming nucleophile (see entries 14, 16, 19, 24 and 28 in Table 3). Presumably, the basis of this result may be rationalized by the enhanced steric crowding of the transition state as represented in (**6**).

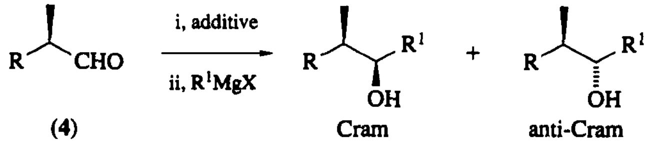

(**4**) Cram anti-Cram (1)

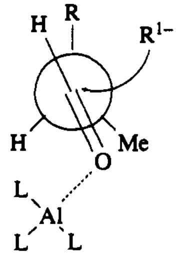

(**6**) Anti-Cram product

**Table 3** Cram *versus* Anti-Cram Selectivity for the Addition of Organometallics to Aldehyde (**4**) in the Presence of (**1**; equation 1).

| *Entry* | *R in (4)* | *Organometallic* | *Additive* | *Yield (%)* | *Cram:anti-Cram* |
|---|---|---|---|---|---|
| 1 | Ph | MeLi | None | — | ~2:1 |
| 2 | Ph | MeMgI | None | 64 | 72:28 |
| 3 | Ph | $MeTi(OPr^i)_3$ | None | — | 88:12 |
| 4 | Ph | $MeTi(OPh)_3$ | None | — | 93:7 |
| 5 | Ph | MeMgI | MAT | 96 | 7:93 |
| 6 | Ph | EtMgBr | None | 78 | 84:16 |
| 7 | Ph | EtMgBr | MAD | 90 | 25:75 |
| 8 | Ph | EtMgBr | MAT | 98 | 20:80 |
| 9 | Ph | BuMgBr | None | 89 | 87:13 |
| 10 | Ph | BuMgBr | MAT | 98 | 33:67 |
| 11 | Ph | BuC≡CMgBr | None | 79 | 78:22 |
| 12 | Ph | BuC≡CMgBr | MAT | 96 | 41:59 |
| 13 | 1-Cyclohexenyl | MeMgI | None | 64 | 79:21 |
| 14 | 1-Cyclohexenyl | MeMgI | MAT | 84 | 2:98 |
| 15 | 1-Cyclohexenyl | EtMgBr | None | 87 | 94:6 |
| 16 | 1-Cyclohexenyl | EtMgBr | MAD | 76 | 34:66 |
| 17 | 1-Cyclohexenyl | EtMgBr | MAT | 98 | 17:83 |
| 18 | 1-Cyclohexenyl | BuMgBr | None | 88 | 94:6 |
| 19 | 1-Cyclohexenyl | BuMgBr | MAT | 97 | 26:74 |
| 20 | Cyclohexyl | MeMgI | None | 81 | 82:18 |
| 21 | Cyclohexyl | MeMgI | MAD | 88 | 22:78 |
| 22 | Cyclohexyl | MeMgI | MAT | 75 | 23:77 |
| 23 | Cyclohexyl | BuMgBr | None | 81 | 89:11 |
| 24 | Cyclohexyl | BuMgBr | MAT | 89 | 77:23 |
| 25 | $PhCH_2$ | MeMgI | None | 52 | 53:47 |
| 26 | $PhCH_2$ | MeMgI | MAT | 96 | 45:55 |
| 27 | $PhCH_2$ | BuMgBr | None | 68 | 50:50 |
| 28 | $PhCH_2$ | BuMgBr | MAT | 94 | 39:61 |

### *1.3.2.1.2 Site selectivity*

#### *(i) 1,2* versus *1,4 site selectivity*

Equation (2) outlines the effect that organoaluminum additives have on the course of nucleophilic additions to α,β-unsaturated carbonyl substrates. Although organolithiums normally undergo 1,2-addition processes to α,β-unsaturated substrates (entry 8 in Table 4[21]), exposure of cyclohexenone substrates to the organoaluminum additive (**1**) prior to exposure to the nucleophile results in a total 1,4-site selective process (compare, for example, entries 1 and 8 in Table 4).

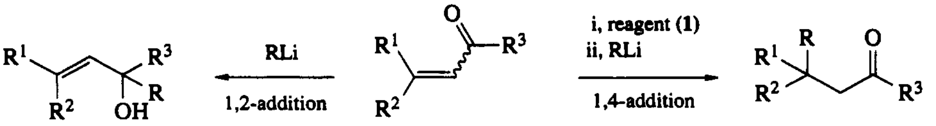

(2)

Table 4 1,2- *versus* 1,4-Regioselectivity for the Addition of Organometallics to Cyclic Enones in the Presence of (1; equation 2)

| *Entry* | *Substrate* | *Organometallic* | *Additive* | *Yield (%)* *1,4-Adduct (cis/trans)* | *1,2-Adduct* |
|---|---|---|---|---|---|
| 1 | a | MeLi | MAD | 68(29:71) | — |
| 2 | a | Bu$^n$Li | MAD | 59(17:83) | — |
| 3 | a | Bu$^t$Li | MAD | 73(18:82) | — |
| 4 | a | PhLi | MAD | 71(33:67) | — |
| 5 | a | $CH_2{=}C(OBu^t)OLi$ | MAD | 87(10:90) | — |
| 6 | a | EtMgBr | MAT | 35(15:85) | — |
| 7 | a | $Bu^nC{\equiv}CLi$ | MAD | Recovered SM | — |
| 8 | a | MeLi | None | — | 75 |
| 9 | b | MeLi | MAD | 70 | — |
| 10 | b | PhLi | MAD | Recovered SM | — |
| 11 | b | $Me_3SiC{\equiv}CLi$ | MAD | Recovered SM | — |
| 12 | c | MeLi | MAD | — | 77 |
| 13 | d | MeLi | MAD | 26 | 11 |
| 14 | e | MeLi | MAD | 65(>95% *trans*) | 16 |
| 15 | e | MeLi | MAT | 63(>95% *trans*) | 31 |
| 16 | e | Bu$^s$Li | MAD | 65(>95% *trans*) | 12 |
| 17 | e | $CH_2{=}C(Me)Li$ | MAD | 75(>95% *trans*) | — |
| 18 | f | MeLi | MAD | Recovered SM | — |
| 19 | g | MeLi | MAD | Recovered SM | — |
| 20 | h | MeLi | MAD | 74(37:63) | — |
| 21 | h | Bu$^t$Li | MAD | 83(24:76) | — |

a
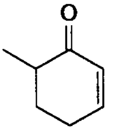

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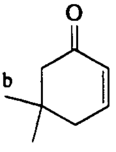

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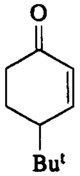

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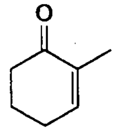

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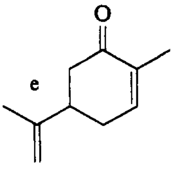

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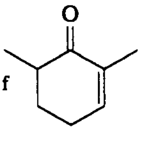

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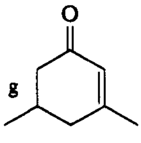

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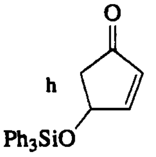

The conjugate addition processes proceed well only when the organometallic is an organolithium reagent. This is in marked contrast to the 1,2-nucleophilic additions to aldehydes detailed in the previous section, which proceeded well when the organometallic was a Grignard reagent. Furthermore, the reaction seems very sensitive to the substitution pattern of the carbonyl substrate. For example, substitution of alkyl substituents at the C-3, C-4 or C-5 position of the cyclohexenone all markedly affect the specificity (see entries 12–19, Table 4). Interestingly, the addition always proceeds with a preference for the *trans* stereoisomer for both five- and six-membered enone substrates, which complements the *cis* preference of cuprate[25] additions (see entries 1–6 and 14–17 in Table 4 for six-membered cases and entries 20 and 21 for five-membered cases). Table 5[21,24] summarizes the site selective additions of nucleophiles to acyclic α,β-unsaturated carbonyl substrates. Entries 1–4 in Table 5 demonstrate that there is a preference for the 1,2-addition products even in the presence of organoaluminum additive (**1**).

**Table 5** 1,2- *versus* 1,4-Regioselectivity for the Addition of Organometallics to Acyclic Enones in the Presence of (**1**; equation 2)

| *Entry* | *Substrate* | *Organometallic* | *Additive* | *Yield (%)*<br>*1,4-Adduct* | <br>*1,2-Adduct* |
|---|---|---|---|---|---|
| 1 | (*E*)-PhCH=CHC(O)Me | MeLi | MAD | — | 78 |
| 2 | PhC≡CC(O)Me | MeLi | MAD | — | 85 |
| 3 | (*E*)-PhCH=CHC(O)Ph | MeLi | MAD | 24 | 60 |
| 4 | (*E*)-PhCH=CHC(O)Ph | MeLi | MAT | 28 | 55 |
| 5 | (*E*)-PhCH=CHC(O)Ph | $Bu^tLi$ | MAD | 77 | 9 |
| 6 | (*E*)-PhCH=CHC(O)$Bu^t$ | MeLi | MAD | Recovered SM | |
| 7 | (*E*)-MeCH=CHCHO | $(Me_3Si)_3Al$ | None | — | — |
| 8 | $(Me)_2C{=}CHC(O)Me^a$ | $(Me_3Si)_3Al$ | None | 85 | — |
| 9 | $(Me)_2C{=}CHC(O)Me^b$ | $(Me_3Si)_3Al$ | None | — | 85 |
| 10 | (*Z*)-PhCH=CHCHO | $(Me_3Si)_3Al$ | None | — | 83 |
| 11 | (*E*)-MeC[$Si(Me)_3$]=CHCHO | $(Me_3Si)_3Al$ | None | — | 91 |
| 12 | HC≡CC(O)Me | $(Me_3Si)_3Al$ | None | 72 (>95% *trans*) | |

[a]Conducted at −78 °C. [b]Conducted at room temperature.

The 1,4-addition product is only preferred when the steric bulk of the nucleophile is increased and the environment about the carbonyl moiety is also sterically encumbered (entry 5 in Table 5). Equation (3) outlines an approach to site selectivity that is not dependent upon additive (**1**), but does require the addition of an organoaluminum.[24]

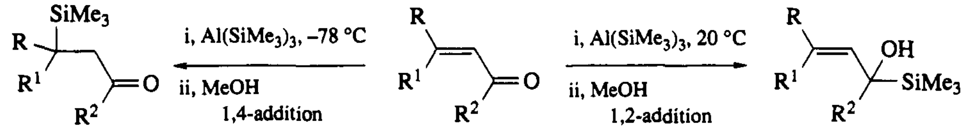

(3)

For example, when acyclic enones are exposed to tris(trimethylsilyl)aluminum (**7**) at room temperature, only the 1,2-addition product is observed, whereas the addition proceeds *via* a 1,4-addition process when the reaction is conducted at −78 °C (compare entries 8 and 9 in Table 5). In contrast, α,β-unsaturated aldehyde substrates only undergo 1,2-additions with reagent (**7**).

### *(ii) Site selective 1,2-additions—discrimination between ketones and aldehydes*

Not surprisingly, there are many examples of site selective processes showing a preference for 1,2-addition to aldehydes in the presence of ketones;[26] however, in contrast, the complementary process is not readily accomplished. Thus, any site selective approach showing a preference for a ketone carbonyl must overcome the inherent reactivity difference favoring aldehydes. Equation (4) outlines an approach to site selective 1,2-nucleophilic additions that takes advantage of the more reactive nature of the aldehyde moiety.[27]

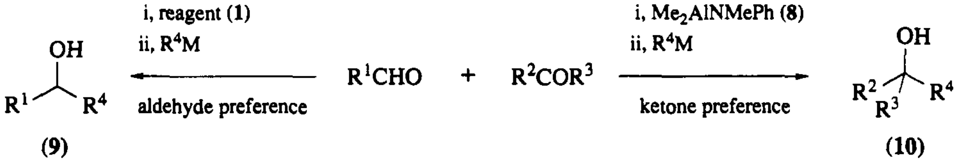

(4)

For example, when a 1:1 mixture of an aldehyde and a ketone is exposed to either an equivalent of an organolithium reagent or an equivalent of a Grignard reagent, the corresponding secondary carbinol (**9**), resulting from preferential addition to the aldehyde component, is usually formed in excess (entries 2, 5, 7, 9 and 12 in Table 6[27]). However, this preference is greatly magnified when the aluminum reagent (**1**) is exposed to the carbonyl substrates prior to the addition of the organometallic (compare entries 1 and 2, 4 and 5, as well as entries 8 and 9 in Table 6).

In contrast, when the experiment is conducted with preexposure of the substrates to aluminum additive (**8**), the corresponding tertiary carbinol (**10**) resulting from preferential addition to the ketone component is produced in excess (compare entries 8 and 10, 11 and 14 in Table 6). Comparison of entries 16 and 17 demonstrates the most dramatic example of total control of this type of site selective process, since in the

**Table 6** Chemospecificity for the Addition of Organometallics to Aldehydes and Ketones in the Presence of (1; equation 4)

| *Entry* | *Substrates* | *Additive* | *Organometallic* | *Ratio (9):(10)* |
|---|---|---|---|---|
| 1 | $C_8H_{17}CHO$ + 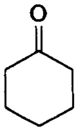 | (1) | EtMgBr | 36:1 |
| 2 | | None | EtMgBr | 8:1 |
| 3 | | (1) | PhMgBr | 14:1 |
| 4 | | (1) | PhLi | 21:1 |
| 5 | | None | PhLi | 1:1 |
| 6 | 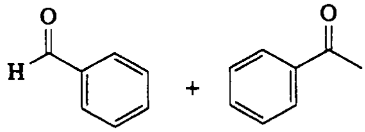 | (1) | MeLi | 6:1 |
| 7 | | None | MeLi | 4:1 |
| 8 | | (1) | MeMgI | 100:0 |
| 9 | | None | MeMgI | 22:1 |
| 10 | | (8) | MeLi | 1:7 |
| 11 | 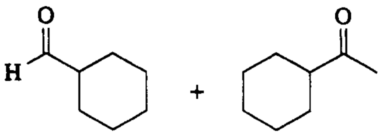 | (1) | MeMgI | 9:1 |
| 12 | | None | MeMgI | 5:1 |
| 13 | | (1) | $Bu^tMgCl$ | 100:1 |
| 14 | | (8) | MeLi | 1:6 |
| 15 | | (8) | PhLi | 1:14 |
| 16 | 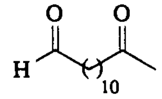 | (1) | MeLi | 100:0 |
| 17 | | (8) | MeLi | 1:62 |

presence of additive (1) site selectivity is total for the aldehyde (100:0), whereas additive (8) gives essentially complete reversal (1:62). The example is most interesting in that the substrate maintains both reactive centers in the same molecule and a competitive experiment of this type (an intramolecular example) is a closer analogy to the problems presented by more complicated, polyfunctional molecules.

Presumably, the selectivity of each process is a result of the generally high oxygenophilicity of aluminum reagents. Thus, aldehydes, which are inherently more reactive than ketones, are being activated by both aluminum additives. In the case of additive (1) this activation leads to an enhancement of the inherent reactivity difference, whereas in the case of additive (8) this reactivity difference results in the formation of a blocked, aminal-like intermediate of the aldehyde moiety (11, equation 5) preventing addition of nucleophiles to the aldehyde. Thus, the preferential addition of nucleophiles to the ketone is observed.

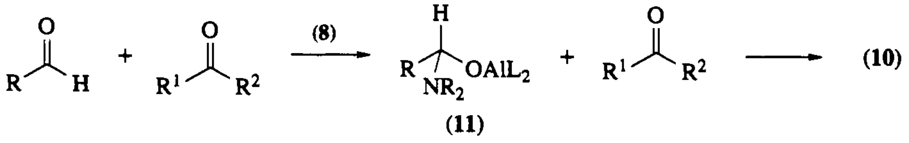

(5)

## 1.3.2.2 Preparation of 1,3-Hydroxy Esters and 1,3-Hydroxy Sulfoxides *via* Organoaluminum Reagents

Although the preparation of 1,3-hydroxycarbonyl species *via* stabilized anions is beyond the scope of this review, the addition of substituted organoaluminums of type (12) to aldehyde or ketone substrates represents an interesting alternative to the typical aldol process.

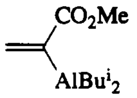

(12)

Reagent (**12**) is readily prepared by the addition of disobutylaluminum hydride in the presence of hexamethylphosphoric triamide to α,β-acetylenic esters.[28] When the organoaluminum (**12**) is exposed to either aldehydes or ketones, the resulting hydroxy ester (**14**) is formed in good yields (equation 6).

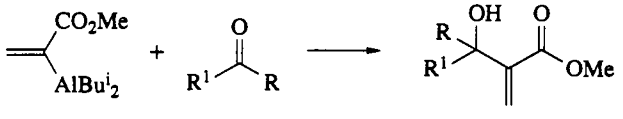

(**12**) (**13**) (**14**) (6)

Table 7[29] lists the aldehyde (entries 1–5) and ketone (entries 6 and 7) substrates that were converted to the corresponding hydroxy ester (**14**). The yields are uniformly good and there appears to be fair generality with regard to the aldehydic substrates; unfortunately, the number of ketone substrates is really not enough to assess the generality of this reaction. The reason for the paucity of ketone substrates may stem from the need to activate the ketone carbonyl with a Lewis acid ($BF_3$–$Et_2O$) in order for the reaction to proceed. The site selectivity of organoaluminum reagent (**12**) was investigated briefly. For example, the addition of (**12**) to (*E*)-2-hexenal (entry 5, Table 7), results in only the 1,2-addition product. In contrast, the addition of (**12**) to cyclohexenone results in no reaction. Since successful additions of (**12**) to the ketone substrates require Lewis acid activation, it would be interesting to expose ketones to chiral Lewis acid complexes prior to their exposure to organoaluminum (**12**). Unfortunately, the stereoselectivity of this reaction was not investigated.

**Table 7** Preparation of Hydroxy Esters from the Addition of Organoaluminum (**12**) to (**13**; equation 6)

| *Entry* | *Substrate (13)*<br>*R* | <br>*$R^1$* | *Yield (%)* | *Temperature (°C)* |
|---|---|---|---|---|
| 1 | H | $Pr^n$ | 87 | 25 |
| 2 | H | $Pr^i$ | 87 | 25 |
| 3 | H | Ph | 83 | 25 |
| 4 | H | Furanyl | 80 | 25 |
| 5 | H | (*E*)-$Pr^nCH{=}CH$ | 90 | 25 |
| 6 | $Pr^n$ | $Pr^n$ | 68 | — |
| 7 | $-(CH_2)_5-$ | | 72 | — |

A substrate related to the 1,3-hydroxy ester (**14**), which does permit a stereochemical investigation of an organoaluminum addition, is represented by chiral keto sulfoxide (**15**) in equation (7). Upon exposure to organometallics, the chiral keto sulfoxides afforded the corresponding diastereomeric β-hydroxy sulfoxides (**16**) and (**17**). Inspection of Table 8[30] reveals that the aluminum reagent provides diastereomer (**17**) in excess (48–92%) and in moderate yield (48–66%), whereas the titanium-based reagent provides diastereomer (**16**) in excess (60–94%) in higher overall yields (60–96%). The keto substituent (R) does have an effect on the overall facial selectivity of the reaction, since oxygen substituents in the *ortho* position of the aromatic ring do improve the relative selectivities for both aluminum- and titanium-mediated processes. The opposite selectivities generated by aluminum and titanium were rationalized on the basis of the transition state structures (**18**) and (**19**).

The titanium-chelated structure (**18**) forces the nucleophilic addition to occur from the less hindered *si*-face (*i.e. syn* to the lone pair of electrons); in contrast, the aluminum-based process proceeds *via* nonchelated transition state (**19**). In this case, the less hindered *re*-face is *syn* to the electron pair. Unfortunately, a test of this transition state hypothesis would require an organoaluminum addition under chelation con-

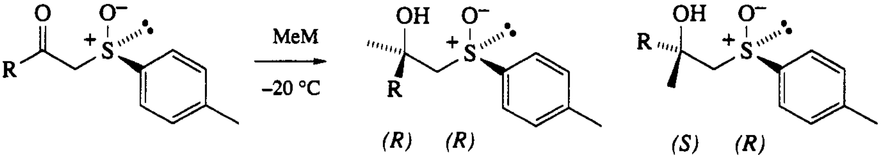

(**15**) (**16**) (**17**) (7)

**Table 8** Comparison of Organoaluminums *versus* Organotitaniums on the Facial Selectivity of Additions to (**15**; equation 7)

| *Entry* | *R* | *MeM* | *Solvent* | *Yield (%)* | *Diastereomer ratio (16):(17)* |
|---|---|---|---|---|---|
| 1 | Ph | $MeTiCl_3$ | $Et_2O$ | 79 | 82:18 |
| 2 | Ph | $Me_3Al$ | Toluene | 66 | 26:74 |
| 3 | *p*-$MeC_6H_4$ | $MeTiCl_3$ | $Et_2O$ | 60 | 80:20 |
| 4 | *p*-$MeC_6H_4$ | $Me_3Al$ | Toluene | 50 | 16:84 |
| 5 | a | $Me_3Al$ | Toluene | 71 | 13:87 |
| 6 | a | $MeTiCl_3$ | $Et_2O$ | 96 | 97:3 |
| 7 | b | $MeTiCl_3$ | $Et_2O$ | 77 | 94:6 |
| 8 | b | $Me_3Al$ | Toluene | 48 | 4:96 |

a

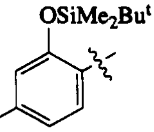

b

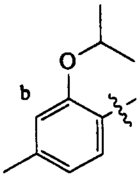

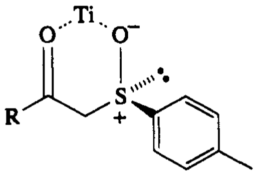

(**18**)

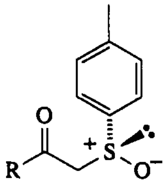

(**19**)

trol conditions. When the addition of trimethylaluminum was performed in the presence of a zinc salt, which is known to provide a chelation control element,[31] there was no reaction.

### 1.3.2.3 Facially Selective 1,2-Additions of Organoaluminum–Ate Complexes to Keto Ester Substrates

The 1,2-addition of chiral aluminum ate complexes to various aldehydes and ketones has been reviewed[32,33] and, generally, this protocol produces very disappointing results with respect to the overall stereospecificity of the process as compared to other organometallics;[34–36] however, the recent extension of this methodology to the preparation of chiral α-hydroxy esters and acids, *via* 1,2-additions to the prochiral ketone moieties of α-keto esters,[37–41] has renewed interest in this area.[42–44] The transformation outlined in equation (8) proceeds in excellent overall yield with exclusive selectivity for the ketone functionality; unfortunately, the stereospecificity is not as impressive.

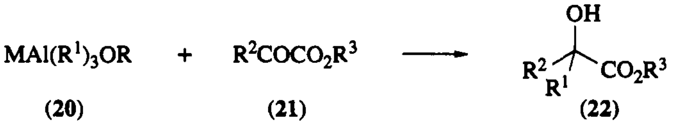

$$\underset{(\mathbf{20})}{MAl(R^1)_3OR} + \underset{(\mathbf{21})}{R^2COCO_2R^3} \longrightarrow \underset{(\mathbf{22})}{R^2C(OH)(R^1)CO_2R^3} \qquad (8)$$

Table 9[37–41] lists the results of the additions of both chiral and achiral alkoxytrialkylaluminates (**20**) to chiral α-keto esters (**21**). Some trends are readily apparent: (i) sodium is a superior cation as compared to lithium and potassium (entries 11–14); (ii) the configuration of the chiral moiety of the ester substrate dictates the facial preference (entries 1–7) and the preference follows the dictates of Prelog's rule;[45] (iii) there is an observable solvent effect with a preference for hexane/ether mixtures; (iv) either (+)- or (±)-(2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Darvon alcohol or Chirald) is the best of the

**Table 9** Results of the Addition of Chiral and Achiral Alkoxy Trialkylaluminates to Keto Esters (equation 8)

| *Entry* | *R* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *M* | *Solvent* | *ee (%)* | *Config.* |
|---|---|---|---|---|---|---|---|---|
| 1 | (–)-*N*-Methylephedrine | Et | Me | (–)-Menthol | Li | Ether/hexane (1:1) | 62 | (*S*) |
| 2 | (+)-*N*-Methylephedrine | Et | Me | (–)-Menthol | Li | Hexane | 15 | (*S*) |
| 3 | (+)-*N*-Methylephedrine | Et | Me | (+)-Menthol | Li | Ether/hexane (1:1) | 58 | (*R*) |
| 4 | (–)-Menthol | Et | Me | (–)-Menthol | Li | Ether/hexane (1:1) | 48 | (*S*) |
| 5 | (+)-Menthol | Et | Me | (–)-Menthol | Li | Ether/hexane (1:1) | 54 | (*S*) |
| 6 | (–)-Menthol | Et | Me | (+)-Menthol | Li | Ether/hexane (1:1) | 50 | (*R*) |
| 7 | (+)-Menthol | Et | Me | (+)-Menthol | Li | Ether/hexane (1:1) | 46 | (*R*) |
| 8 | (–)-*N*-Methylephedrine | Et | Me | (–)-Menthol | Li | Hexane | 49 | (*R*) |
| 9 | (+)-*N*-Methylephedrine | Et | Ph | (–)-Menthol | Li | Hexane | 0.2 | (*R*) |
| 10 | (–)-*N*-Methylephedrine | Me | Ph | (–)-Menthol | Li | Hexane | 38 | (*R*) |
| 11 | (–)-*N*-Methylephedrine | Et | Ph | (–)-Menthol | Na | Toluene/hexane | 52.5 | (*R*) |
| 12 | (–)-*N*-Methylephedrine | Et | Ph | (–)-Menthol | K | Benzene/hexane | 43 | (*R*) |
| 13 | (–)-*N*-Methylephedrine | Et | Ph | (–)-Menthol | Na | Benzene/hexane | 53 | (*R*) |
| 14 | (–)-*N*-Methylephedrine | Et | Ph | (–)-Menthol | Li | Benzene/hexane | 23 | (*R*) |
| 15 | (+)-Darvon alcohol[a] | Et | Ph | (–)-Menthol | Li | Hexane/ether (75:100) | 77 | (*R*) |
| 16 | (+)-Darvon alcohol[a] | Et | Ph | (–)-Menthol | Li | Hexane/ether (30:100) | 82 | (*R*) |
| 17 | (+)-Darvon alcohol[a] | Et | Ph | (+)-Menthol | Li | Hexane/ether (75:100) | 73 | (*S*) |
| 18 | (±)-Darvon alcohol[a] | Et | Ph | (–)-Menthol | Li | Hexane/ether (30:100) | 79 | (*R*) |
| 19 | (±)-Darvon alcohol[a] | Et | Ph | (–)-Menthol | Li | Ether | 84 | (*R*) |
| 20 | *t*-Butyl alcohol | Me | Ph | (–)-Menthol | Li | Hexane | 25 | (*R*) |
| 21 | *t*-Butyl alcohol | Et | Ph | (–)-Menthol | Li | Hexane | 27 | (*R*) |
| 22 | 2-Methyl-2-butanol | Et | Ph | (–)-Menthol | Li | Hexane | 47 | (*R*) |
| 23 | 3-*t*-Butyl-3-pentanol | Et | Ph | (–)-Menthol | Li | Hexane | 60 | (*R*) |
| 24 | 2,4-Dimethyl-3-*t*-butyl-3-pentanol | Et | Ph | (–)-Menthol | Li | Hexane/ether (75:100) | 71 | (*R*) |

[a] Darvon alcohol = (+)- or (±)-(2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol.

chiral ligands (compare entries 15–19 *versus* entries 1–14); and (v) although there appears to be some double stereodifferentiation (entries 4–6 and entries 8, 9), the steric bulk of the alkoxy moiety of the organoaluminum seems to determine the overall enantioselectivity (compare entries 15–17 and 18, 19 as well as entries 20–24).

Since the facial selectivity of the process is controlled by the chiral keto ester and the observed absolute diastereomeric excess of each addition reaction is determined by steric factors within the organoaluminate, there is no apparent need to prepare chiral alkoxytrialkylaluminates. Thus, there should be very good stereodiscrimination for the additions of tetraalkylaluminates to chiral keto ester substrates (equation 9). It is advantageous to utilize tetraalkylaluminates since they are readily prepared by the titanium-catalyzed hydroalumination of alkenes (equation 10).[46,47]

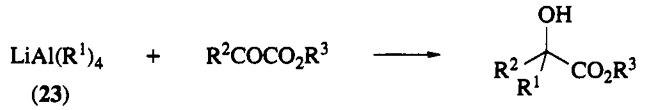

(9)

$$4\text{R–CH=CH}_2 \quad + \quad \text{LiAlH}_4 \xrightarrow[\text{THF}]{5\%\ \text{TiCl}_4} \text{LiAl(CH}_2\text{CH}_2\text{R)}_4 \qquad (10)$$

Table 10 summarizes the data for the addition of various achiral tetraalkylaluminates (**23**) to chiral keto esters as outlined in equation (9). Presumably, the observed diastereoselectivities will reflect the inherent facial bias of the controlling chiral element, namely menthol ($R^3$ in Table 10). In this case the diastereoselectivities are moderate (67 to 75%), but, since Corey,[48] Oppolzer[49] and Whitesell[50] have observed superior inherent facial selectivity for the 8-substituted menthol chiral auxiliary, it would be interesting to attempt the alkyl aluminate additions on substrates incorporating this auxiliary.

**Table 10** Additions of Tetraalkylaluminates to Chiral Keto Esters (equation 9)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *Solvent* | *de* (%) | *Configuration* |
|---|---|---|---|---|---|---|
| 1 | $Me(CH_2)_5$— | Ph | (–)-Menthol | THF | 69 | (*R*) |
| 2 | $Me_2CH(CH_2)_3$— | Ph | (–)-Menthol | THF | 73 | (*R*) |
| 3 | $EtMeCH(CH_2)_2$— | Ph | (–)-Menthol | THF | 74 | (*R*) |
| 4 | 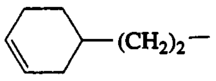 | Ph | (–)-Menthol | THF | 72 | (*R*) |
| 5 | 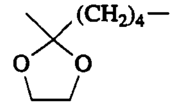 | Ph | (–)-Menthol | THF | 67 | (*R*) |
| 6 | $Me(CH_2)_5$— | Me | (–)-Menthol | THF | 67 | — |
| 7 | $Me(CH_2)_5$— | H | (–)-Menthol | THF | 75 | — |

### 1.3.2.4 Additions of Alkylaluminums to Masked Carbonyl Substrates

#### *1.3.2.4.1 Regioselectivity and stereoselectivity of additions to α,β-unsaturated acetals and ketals*

It is well known that a variety of aluminum hydride reagents cleave acetal substrates with excellent stereoselectivities.[51,53] It is not surprising, therefore, that similar experiments have been attempted with trialkylaluminum reagents. Equation (11) outlines the generalized transformation.

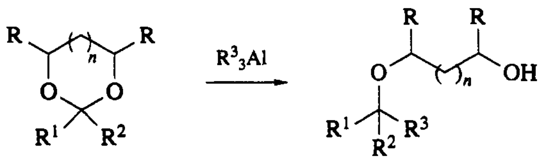

(11)

*n* = 0, 1; R = alkyl, amide; $R^1$ = alkyl, alkenyl, H;
$R^2$ = alkyl, alkenyl, H; $R^3$ = alkyl, alkenyl, alkynyl

In the specific case of *n* = 1, R = Me, $R^1$ = cyclohexyl and $R^2$ = H (equation 12) exposure to trimethylaluminum resulted[52] in poor stereoselectivity and moderate yield (64%). Interestingly, although the diastereomeric ratio was defined by GC methods (2:3), the stereochemistry of the preferred diastereomer was undefined. In contrast to this result, the addition of alkylaluminums to α,β-unsaturated acetals (Scheme 3) proceeds with spectacular regioselectivity and stereoselectivity.

Allylic acetal substrates include both aspects of the selectivity problem, namely, regiochemical control and stereochemical control. Table 11[54] lists the results of alkylaluminum additions to chiral, allylic acetals. The most striking aspect of this work is the total dependence of regiochemical control on the solvent.[54,55] For example, comparison of entries 1 and 3 in Table 11 shows a complete reversal of regiochemical control in going from dichloroethane to chloroform solvent. Furthermore, the stereoselectivity of the process is dependent upon the configuration of the starting acetal. Thus, when one starts with the acetal derived from (*R*,*R*)-(4)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide, the 1,2-addition product with the (*R*)-configuration (88% *ee*) is produced (entry 3, Table 11), whereas the corresponding (*S*,*S*)-isomer produced the 1,2-addition product with the (*S*)-configuration (entry 5, Table 11). It is noteworthy that, although the regioselectivity for the 1,4-process is very good, the 1,2-process is exclusively con-

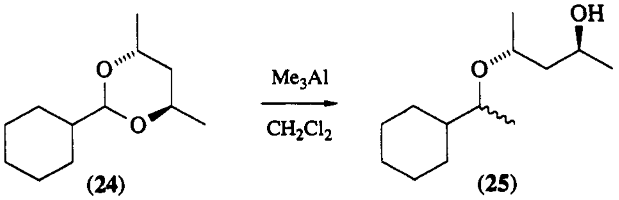

(24) (25)

(12)

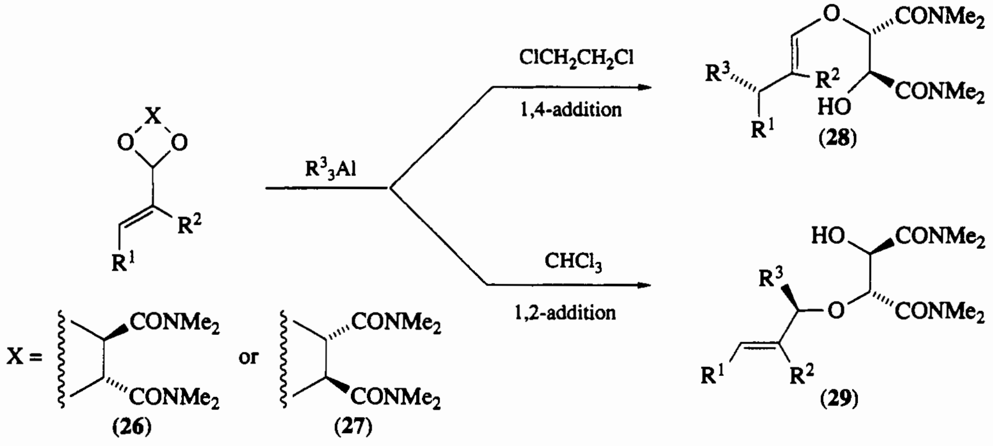
X
O
O
R$^2$
R$^1$
X =
CONMe$_2$
CONMe$_2$
(26)
or
CONMe$_2$
CONMe$_2$
(27)
R$^3_3$Al
ClCH$_2$CH$_2$Cl
1,4-addition
CHCl$_3$
1,2-addition
O
CONMe$_2$
R$^3$
R$^2$
CONMe$_2$
HO
R$^1$
(28)
HO
CONMe$_2$
R$^3$
O
CONMe$_2$
R$^1$
R$^2$
(29)

**Scheme 3**

trolled in chloroform solvent. On the other hand, if one wished to produce only the 1,4-addition product *via* the addition of organoaluminums to acetals, the best method appears to be that of Negishi,[56] which proceeds *via* palladium catalysis (equation 13) to produce exclusively the 1,4-addition products.

**Table 11** Regioselectivity and Stereoselectivity for the Addition of Me$_3$Al to Chiral Allylic Acetals (Scheme 3)

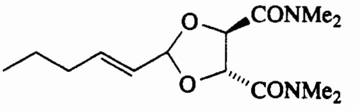
O
CONMe$_2$
O
CONMe$_2$

**(30)**

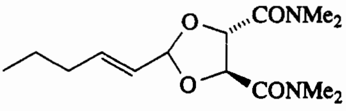
O
CONMe$_2$
O
CONMe$_2$

**(31)**

| *Entry* | *Substrate* | *Solvent* | *Product ratio 1,2 versus 1,4* | *1,2-Product (% ee)* | *Configuration* |
|---|---|---|---|---|---|
| 1 | **(30)** | ClCH$_2$CH$_2$Cl | 1:6.5 | 88 | (*S*) |
| 2 | **(30)** | Toluene | 1:1.7 | 96 | (*S*) |
| 3 | **(30)** | CHCl$_3$ | 1:0 | 88 | (*R*) |
| 4 | **(31)** | Toluene | 1:2.8 | 96 | (*R*) |
| 5 | **(31)** | CHCl$_3$ | 1:0 | 86 | (*S*) |

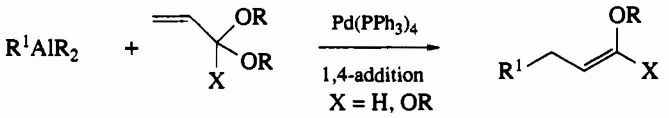
R$^1$AlR$_2$
+
OR
OR
X
Pd(PPh$_3$)$_4$
1,4-addition
X = H, OR
OR
R$^1$
X

(13)

### *1.3.2.4.2 Chiral α-hydroxy acetals and ketals*

The 1,2-addition reaction of organoaluminums may be extended to α-hydroxy ketals. An interesting example of this ketal variant appears in equation (14).

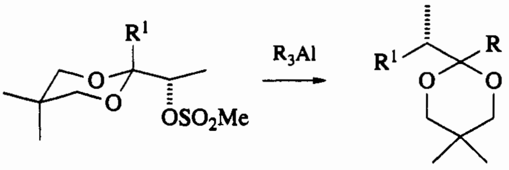
R$^1$
O
O
OSO$_2$Me
R$_3$Al
R$^1$
R
O
O

**(32)** **(33)**

(14)

The reaction presumably takes place *via* attack of the nucleophile at the ketal carbon center with concomitant migration of the R$^1$ moiety to the adjacent center.[58] Organoaluminum reagents are ideally suited for such a transformation since, by virtue of their amphophilic nature, they act as nucleophiles and electrophiles. Thus, organoaluminums will not only donate the nucleophile but also activate the leaving group, which in this case is mesyl. Table 12[57,58] lists the results of alkylaluminum additions to the generalized substrate (**32**).

**Table 12** The Addition of Organoaluminiums to α-Hydroxy Ketals (equation 14)

| *Entry* | $R^1$ | *RAl* | *Yield (%) (double bond geometry)* | *Configuration* [a] | *ee (%)* |
|---|---|---|---|---|---|
| 1 | *p*-$MeOC_6H_4$ | $Me_3Al$ | 39 | *(S)* | >95 |
| 2 | *p*-$MeOC_6H_4$ | $Me_3Al$, $Bu^nLi$ | 89 | *(S)* | >95 |
| 3 | *p*-$MeOC_6H_4$ | $Et_3Al$, $Bu^nLi$ | 90 | *(S)* | >95 |
| 4 | 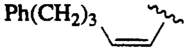 *(cis)* | $Me_3Al$, $Bu^nLi$ | 80 *(cis)* | *(S)* | >95 |
| 5 | 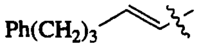 *(trans)* | $Me_3Al$, $Bu^nLi$ | 94 *(trans)* | *(S)* | >95 |
| 6 | *p*-$MeOC_6H_4$ | $Et_2AlC{\equiv}CBu^n$, $Bu^nLi$ | 4 | — | — |
| 7 | *p*-$MeOC_6H_4$ | $EtAl(C{\equiv}CBu^n)_2$ | 81 | *(S)* | >95 |
| 8 | 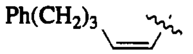 *(cis)* | $Et_2AlC{\equiv}CBu^n$ | 40 *(cis)* | *(S)* | >95 |
| 9 | 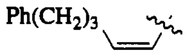 *(cis)* | $EtAl(C{\equiv}CBu^n)_2$ | 84 *(cis)* | *(S)* | >95 |

[a] The enantiomeric excess was determined by NMR methods.

The following generalizations may be drawn from the data in Table 12: (i) the 1,2-addition of alkyl groups is greatly facilitated by preparation of the ate complex (compare entries 1 and 2); (ii) the transfer of alkynyl moieties is retarded by ate complex formation (compare entries 6 and 7); (iii) the integrity of the double bond geometry of the migrating group is maintained (entries 4, 5, 8 and 9); and (iv) the stereospecificity of the process is very high (>95% *ee*). Presumably, the relative differences in nucleophilicity account for the observed reactivities, since it is known that the ate complex of alkylaluminum reagents is more nucleophilic than the corresponding alkylaluminum (as well as a weaker Lewis acid). In contrast, the electron demand of the alkynyl group bestows a reduced Lewis acid character to alkynylaluminum reagents as compared to the corresponding alkylaluminum.

The final example of 1,2-additions of organoaluminums to masked ketone substrates is outlined in equation (15).[59] The addition of a large excess (10 equiv.) of trimethylaluminum to a variety of triol acetals and ketals proceeds in relatively high overall yield. Although ketal substrates where $R^1$ did not equal $R^2$ were not attempted, a number of acetals were prepared and upon exposure to $Me_3Al$ they afforded the corresponding diastereomeric ethers with poor diastereoselectivity (33–17% *de*).

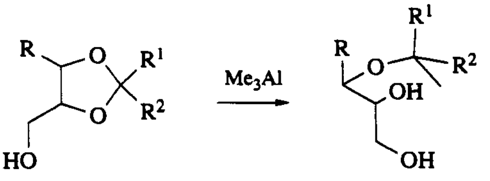

(**34**) (**35**) (15)

The proposed mechanism is outlined in equation (16). A metal alkoxide (**36**) is initially formed, which undergoes a bond reorganization to betaine (**37**). The intermediate (**37**) is presumably the reacting species. Support for this process is derived from the following: (i) essentially no reaction takes place in the absence of an α-hydroxy group (see entries 1–3 in Table 13[59]); (ii) the reaction is extremely sluggish if the environment about the α-hydroxy moiety is highly congested (see entry 4 in Table 13); and (iii) the diastereoselectivity is quite poor (see entries 5 and 6 in Table 13) for the related acetal substrates.

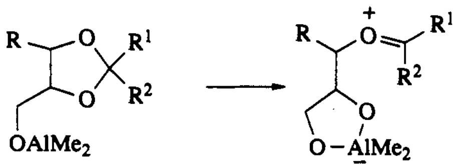

(36) (37)

(16)

**Table 13** The Diastereoselective Addition of Trimethylaluminum Hydroxy Acetals and Ketals (equation 15)

| *Entry* | *Substrate* | *Yield (%)* | *Diastereomeric ratio* |
|---|---|---|---|
| 1 | 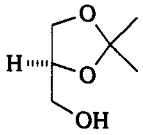 | 83 | — |
| 2 | 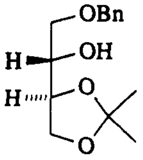 | 91 | — |
| 3 | 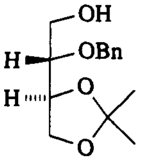 | 16 | — |
| 4 | 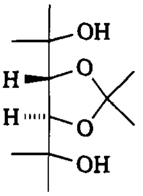 | NR | — |
| 5 | 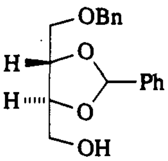 | 73 | 12:1 |
| 6 | 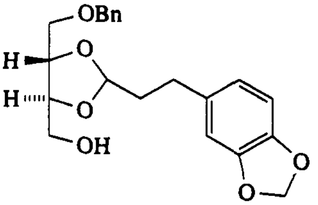 | 77 | 7.2:1 |

#### 1.3.2.4.3 *Application of a masked aluminum enolate in a facially selective sigmatropic protocol*

3,3-Sigmatropic rearrangements (*e.g.* ene and Claisen reactions) are beyond the scope of this review; however, there are specific examples of this transformation, promoted by organoaluminum reagents, which define a 3,3-sigmatropic rearrangement protocol terminating in the 1,2-addition of an organoaluminum to an aldehyde or a ketone. Since it has been demonstrated[60,61] that sterically hindered organoaluminum reagents related to reagent (**38**) permit excellent stereochemical control of the resulting double bond geometry, it is useful to discuss a protocol that, in principle, permits not only control of the double bond geometry, but may also impart considerable bias with regard to facial selectivity.

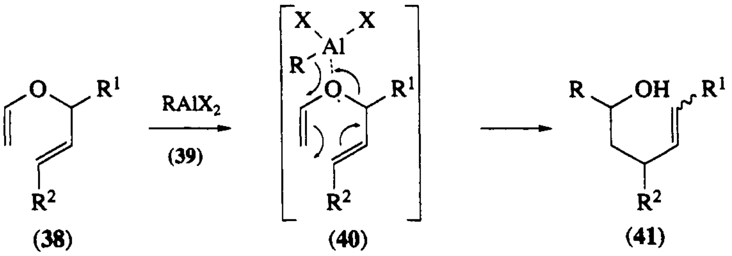

(17)

Equation (17) outlines the organoaluminum-mediated transformation. Although there is no unequivocal definition for the proposed transition state structure,[60] a chair-like version of (**40**) appears reasonable[64] in light of the resulting double bond stereochemistry.[61,62] Table 14[62,63] lists the various substrates and organoaluminum reagents that have been utilized. Although entries 1–3 (Table 14) are simple alkyl and aryl examples, it is interesting to note that the $R^2$ substituent may be something other than a proton (entry 3). Entries 4–8 are examples of the conversion of substituted dihydropyrans to chain-extended, unsaturated six-membered carbocycles. Obviously, in these cases the regiochemistry of the double bond is fixed by the nature of the sigmatropic process; however, an investigation of the possible facial selectivity of the 1,2-addition of the nucleophile to either the intermediate aldehyde (entries 4–7, Table 14) or the intermediate ketone (entry 8) has not been published. The protocol may also be used to prepare seven-membered unsaturated carbocycles (*e.g.* entries 9 and 10, Table 14). The reaction seems general with regard to the organoaluminum, since alkyl, aryl (entries 1–4, 7, 8 and 10), alkenyl (entry 6) and alkynyl (entries 5 and 9) substituents are readily introduced. Interestingly, if an organoaluminum containing a sulfur substituent (**39**; R = SPh, X = Et) is utilized to facilitate the transformation, the corresponding aldehyde or ketone is isolated. Presumably, a thioaryl hemiacetal or ketal is formed, which affords the corresponding aldehyde or ketone upon workup. If the organosulfur substituent is something other than *S*-phenyl (R = SEt or $SBu^t$), there is no rearrangement.

### *1.3.2.4.4 1,2-Addition to enol phosphates*

Although enol phosphates are known to undergo a coupling reaction with nickel-catalyzed Grignard reagents[65] to afford substituted alkenes, the corresponding reaction with organoaluminums does not work; however, it has been demonstrated[66] that the coupling reaction of organoaluminums and enol phosphates does proceed in the presence of palladium (see equation 18 and Table 15[66]).

This reaction sequence produces alkenes in a stereospecific manner, since the double bond geometry of the enol phosphate is retained in the alkene product. Furthermore, the newly formed alkene may be introduced in a regioselective fashion *via* trapping of the regioselectively formed enolate.[67]

The success of the reaction is dependent upon the presence of $Pd(Ph_3)_4$, since the addition fails in the absence of Pd or in the presence of either nickel or $Pd(acac)_2$.[66]

## 1.3.3 REACTIONS OF ORGANOALUMINUM REAGENTS WITH ACID DERIVATIVES

### 1.3.3.1 Reactions with Ester Substrates

The conversion of esters to either amides or hydrazides may be accomplished under relatively mild conditions by the procedure outlined in equation (19).

Reagent (**42**) is readily prepared[68–70] by the treatment of primary and secondary amines and hydrazines (substituted or unsubstituted) or the corresponding hydrochlorides with trimethylaluminum. The aluminum amide reagents (**42**) readily react with a variety of ester substrates, such as conjugated esters (entries 2, 5 and 11, Table 16[68–70]), *N*-blocked amino acid esters (entry 10, Table 16), as well as alkyl esters (en-

**Table 14** The Addition of Organoaluminums to (**40**) (equation 17)

| *Entry* | $R^1$ | $R^2$ | *R* | *X* | *Yield* (%) | *Temperature* (° C) | *Time* (h) |
|---|---|---|---|---|---|---|---|
| 1 | Bu$^n$ | H | Me | Me | 91 | 25 | 0.25 |
| 2 | Ph | H | Me | Me | 78 | 25 | 0.25 |
| 3 | H | Ph | Me | Me | 71 | 25 | 0.25 |
| 4 | 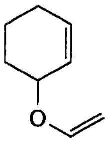 | | Me | Me | 81 | 25 | 0.5 |
| 5 | 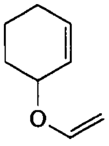 | | $PhC\equiv C$ | Et | 88 | 25 | 0.25 |
| 6 | 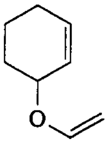 | | | Bu$^i$ | 40 | 25 | 1.5 |
| 7 | 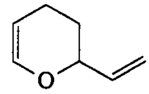 | | Me | Me | 86 | 60 | 2 |
| 8 | 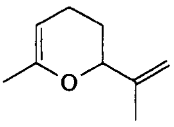 | | Me | Me | 87 | 60 | 2 |
| 9 | 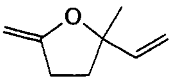 | | $PhC\equiv C$ | Et | 83 | 25 | 2 |
| 10 | 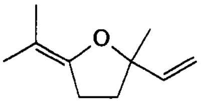 | | Me | Me | 48 | 25 | 1 |

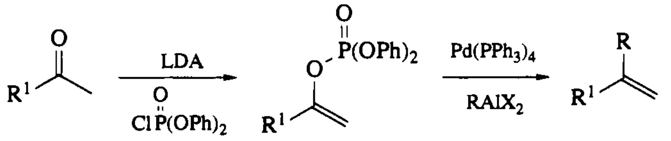

(18)

tries 3, 6–8, Table 16) and aryl esters (entries 1, 4, 9 and 12, Table 16). Dimethylaluminum hydrazides react with esters to afford the corresponding carboxylic acid hydrazides (entries 13–18, Table 16). The reaction is fairly general with regard to the nature of substituted hydrazines, since alkyl and aryl groups are tolerated on the terminal amine of the hydrazine.

Aluminum amides may also be used for the conversion of lactones to the corresponding open chain hydroxy amides (equation 20). For example, exposure of lactone (**45**) to dimethylaluminum amide (**47**; R = H or R = $CH_2Ph$) at 41 °C for about 24 h affords the corresponding hydroxy amide (**46**) in high yield (80%, R = $CH_2Ph$; 83%, R = H); in contrast, exposure of (**45**) to either benzylamine or sodium amide resulted in essentially none of the desired amide (**46**).[68] In general the 1,2-addition of heteroatom-substituted organoaluminum reagents to carboxyl-containing substrates may be rationalized in terms of the

**Table 15** The Addition of Organoaluminums to Enol Phosphates (equation 18)

| *Entry* | $R^2$ | *R* | *X* | *Yield* (%) |
|---|---|---|---|---|
| 1 | 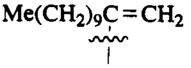 $Me(CH_2)_9C{=}CH_2$ | Me | Me | 91 |
| 2 | | Et | Me | 71 |
| 3 | | PhC≡C | Et | 82 |
| 4 | | $Me(CH_2)_3C{\equiv}C$ | Et | 59 |
| 5 | | 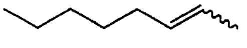 | $Bu^i$ | 66 |
| 6 | 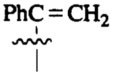 $PhC{=}CH_2$ | Me | Me | 94 |
| 7 | | Et | Et | 80 |
| 8 | | PhC≡C | Et | 67 |
| 9 | 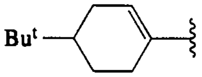 | PhC≡C | Et | 70 |
| 10 | | Me | Me | 72 |

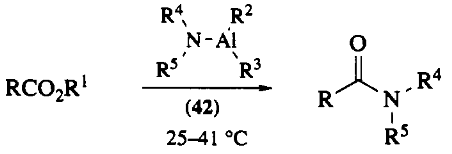

(43) (44) (19)

$R^2 = R^3 = Me$; $R^2 = Cl$, $R^3 = Me$; $R^4 = R^5 = H$, alkyl;

$R^4 =$ alkyl, $R^5 = OMe$; $R^4 = H$, alkyl; $R^5 = NR_2$

**Table 16** The Addition of Aluminum Amide Reagents (42) to Esters (equation 19)

| | *Substrate* | | | *Reagent (42)* | | | *No. of equivalents* | *Yield* | *Reaction conditions* |
|---|---|---|---|---|---|---|---|---|---|
| *Entry* | *R* | $R^1$ | $R^4$ | $R^5$ | $R^2$ | $R^3$ | *(42)* | (%) | *Time* (h)/*Temp.* (°C) |
| 1 | Ph | Me | H | H | Me | Me | 2.2 | 77 | 17/41 |
| 2 | PhCH=CH | Me | H | H | Me | Me | 2.0 | 86 | 12/38 |
| 3 | Cyclohexyl | Mc | H | H | Me | Me | 2.2 | 78 | 17/35 |
| 4 | Ph | Me | H | H | Me | Cl | 3.0 | 83 | 12/50 |
| 5 | PhCH=CH | Et | H | H | Me | Cl | 3.0 | 82 | 12/50 |
| 6 | Cyclohexyl | Me | H | H | Me | Cl | 3.0 | 93 | 12/50 |
| 7 | Cyclohexyl | Me | H | $CH_2Ph$ | Me | Me | 2.0 | 78 | 17/35 |
| 8 | Cyclohexyl | Me | Me | Me | Me | Cl | 2.0 | 76 | 12/50 |
| 9 | Ph | Me | $(CH_2)_4$ | | Me | Me | 1.1 | 94 | 5/40 |
| 10 | $PhCH_2CHNHCO$ Me | Et | $(CH_2)_4$ | | Me | Me | 1.1 | 77 | 40/40 |
| 11 | 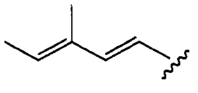 | Me | $(CH_2)_4$ | | Me | Me | 2.0 | 74 | 45/40 |
| 12 | Ph | Me | $(CH_2)_5$ | | Me | Me | 1.1 | 74 | 34/40 |
| 13 | $Me(CH_2)_4$ | Et | H | $NH_2$ | Me | Me | 2.2 | 82 | 16/40 |
| 14 | $Me(CH_2)_4$ | Et | H | PhNH | Me | Me | 2.2 | 91 | 12/25 |
| 15 | $Me(CH_2)_4$ | Et | Me | NHMe | Me | Me | 2.2 | 72 | 16/40 |
| 16 | $4\text{-}MeC_6H_4$ | Et | H | $NMe_2$ | Me | Me | 2.2 | 80 | 16/40 |
| 17 | $4\text{-}MeC_6H_4$ | Et | H | NHPh | Me | Me | 2.2 | 87 | 12/25 |
| 18 | $4\text{-}MeC_6H_4$ | Et | Me | NHMe | Me | Me | 2.2 | 72 | 12/45 |

hard/soft acid and base theory, first defined by Pearson.[71] The aluminum amide reagents discussed in this section all contain a weak bond between aluminum and a relatively soft substituent, when compared to the stronger (and harder) aluminum–oxygen bond which is formed upon reaction.

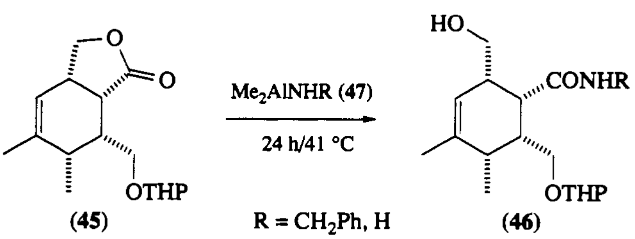

(20)

### 1.3.3.1.1 *Selenol ester formation*

Selenol esters are useful as active acyl equivalents, particularly with regard to macrocycle formation.[72,73] Equation (21) outlines the conversion of esters to selenol esters *via* aluminum reagent (**48**).[6,7]

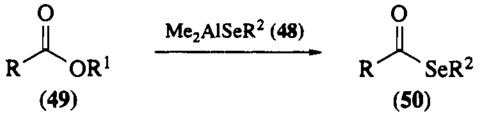

(21)

The reaction is fairly general with regard to the acyl substituent of ester (**49**), since aromatic and alkyl substituents are compatible (entries 1–8, Table 17[73–75]). In contrast, there are restrictions with regard to lactone substrates. For example, the five-membered lactone (entry 11, Table 17) does not undergo reaction, whereas the related six-membered lactone (entry 9, Table 17) is converted to its corresponding selenol ester in good yield (78%). Although the unsubstituted five-membered lactone did not react, the five-membered fused lactone (entry 10, Table 17) did afford the related selenol ester in good yield (80%).[73] The reaction also discriminates between axial and equatorial esters. For example, entry 14 (Table 17) presents a substrate containing an axial, as well as an equatorial, ester, which upon exposure to dimethylaluminum methaneselenolate (**48**; $R^2$ = Me) affords only the equatorial monoselenol ester.[75] The selectivity of this reaction is highly dependent upon the reaction solvent. When axial and equatorial methyl-4-*t*-butylcyclohexanecarboxylates (entries 12 and 13, Table 17) are exposed to organoaluminum (**48**; $R^2$ = Me) in diethyl ether at room temperature, the equatorial selenol ester is formed in 0.5 h, whereas the formation of the axial selenol ester requires 10 h. Equation (22) outlines the results of a site selective process.[73,76]

When cyclohexenone is exposed to either aluminum reagent (**48**) or (**51**), only the 1,4-addition product is observed in high yield (87% and 72% respectively). Thus, there appears to be excellent site selectivity, although the reasons for the selectivity are undefined.

## 1.3.3.2 Reactions with Acyl Chlorides

The reaction of organoaluminums with acyl chlorides typically fails to produce ketones, since the organoaluminum reacts with the desired ketone to produce carbinols.[77] However, organoaluminum reagents, in the presence of transition metal catalysts,[78–80] may be utilized to accomplish this transformation. Equation (23) outlines the overall transformation.

The copper and palladium transition metal catalysts noted in Table 18[78,79] proved to be superior to nickel, ruthenium and rhodium catalysts. The nature of the reacting species has not been unequivocally defined, but the following experimental observations may provide some insight: (i) tetrahydrofuran solvent is essential for the palladium-mediated reactions, since complex reaction mixtures (presumably containing carbinols) were observed when the reactions were performed in either benzene or methylene chloride; (ii) the reaction is truly catalytic with respect to palladium (2 mmol alkylaluminum, 0.05 mmol of $Pd(PPh_3)_4$), whereas the copper catalyst is stoichiometric; and (iii) in the case where a direct comparison may be made (entries 1–8, Table 18), the copper-based system is superior to palladium catalysis with regard to overall yield.

The palladium-catalyzed systems seem quite flexible with regard to the nature of the organoaluminum, since alkyl-, alkenyl- and alkynyl-aluminum reagents were used successfully (entries 8–14, Table 18). Furthermore, the acyl chloride substrates include alkyl, aryl and alkenyl substituents.

**Table 17** The Addition of Selenoaluminum (**48**) to Esters (equation 21)

| | *Substrate (49)* | | | |
|---|---|---|---|---|
| *Entry* | *R* | *$R^1$* | *Yield (50) (%)* | *Solvent* |
| 1 | Ph | Me | 99 | $CH_2Cl_2$ |
| 2 | 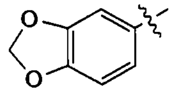 | Me | Quantitative | $CH_2Cl_2$ |
| 3 | $Ph(CH_2)_3$ | Et | 70 | $CH_2Cl_2$ |
| 4 | 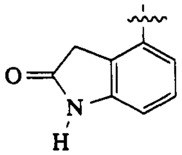 | Et | 80 | $CH_2Cl_2$ |
| 5 | 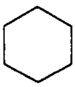 | Me | 93 | $CH_2Cl_2$ |
| 6 | $Me(CH_2)_5$ | Me | 95 | $CH_2Cl_2$ |
| 7 | $H_2C{=}CH(CH_2)_2$ | Me | 84 | $CH_2Cl_2$ |
| 8 | 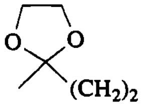 | Me | 94 | $CH_2Cl_2$ |
| 9 | $-(CH_2)_4-$ | | 78 | $CH_2Cl_2$ |
| 10 | 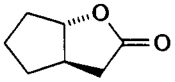 | | 80 | $CH_2Cl_2$ |
| 11 | 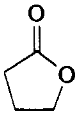 | | 0 | $CH_2Cl_2$ |
| 12 | 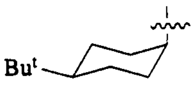 | Me | 92 | $Et_2O$ |
| 13 | 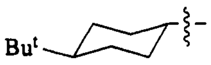 | Me | 96 | $Et_2O$ |
| 14 | 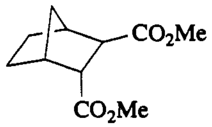 | | 67 (equatorial monoselenol ester) | $Et_2O$ |

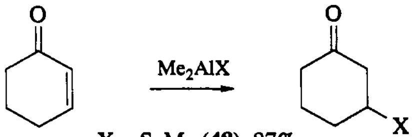

X = SeMe (**48**), 87%
SMe (**51**), 72%

(22)

$$\mathrm{R^1COCl} + \mathrm{R_3Al} \xrightarrow[\substack{\text{THF}\\ \text{metal = Pd, Cu}}]{\text{metal catalyst}} \mathrm{R^1COR} \qquad (23)$$

**Table 18** The Palladium-catalyzed Addition of Organoaluminums to Acyl Chlorides (equation 23)

| *Entry* | *$R^1$* | *R* | *Catalyst* | *Yield (%)* |
|---|---|---|---|---|
| 1 | Ph | Et | $Pd(PPh_3)_4$ | 70 |
| 2 | Ph | Et | $Cu(acac)_2PPh_3$ | 88 |
| 3 | Ph | Me | $Cu(acac)_2PPh_3$ | 95 |
| 4 | Ph | Me | $Pd(PPh_3)_4$ | 74 |
| 5 | $CH_2{=}CH(CH_2)_8$ | Me | $Pd(PPh_3)_4$ | 59 |
| 6 | $CH_2{=}CH(CH_2)_8$ | Me | $Cu(acac)_2PPh_3$ | 90 |
| 7 | $CH_2{=}CH(CH_2)_8$ | Et | $Cu(acac)_2PPh_3$ | 91 |
| 8 | $CH_2{=}CH(CH_2)_8$ | Et | $Pd(PPh_3)_4$ | 71 |
| 9 | Ph | $BuC{\equiv}C$ | $Pd(PPh_3)_4$ | 67 |
| 10 | $PhCH{=}CH$ | $BuC{\equiv}C$ | $Pd(PPh_3)_4$ | 74 |
| 11 | $C_7H_{15}$ | $PhC{\equiv}C$ | $Pd(PPh_3)_4$ | 61 |
| 12 | $CH_2{=}CH(CH_2)_8$ | $Me_3SiC{\equiv}C$ | $Pd(PPh_3)_4$ | 51 |
| 13 | $CH_2{=}CH(CH_2)_8$ | 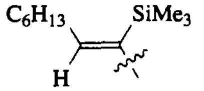 | $Pd(PPh_3)_4$ | 51 |
| 14 | Ph | 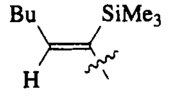 | $Pd(PPh_3)_4$ | 51 |

### *1.3.3.2.1 Preparation of acylsilanes* via *silyl-substituted organoaluminum–ate complexes*

Acylsilanes may be prepared directly from either acyl chlorides or anhydrides by treatment with tris(trimethylsilyl)aluminum–ate complexes (equation 24).[81]

$$\mathrm{RCOCl} \xrightarrow[\text{CuCN}]{\mathrm{LiAl(SiMe_3)_3}\ \textbf{(52)}} \mathrm{RCOSiMe_3} \qquad (24)$$

The silyl organoaluminum reagent (**52**) was prepared either by the addition of 'activated' aluminum to a tetrahydrofuran solution of chlorotrimethylsilane, or by the treatment of sodium tetrakis(trimethylsilyl)aluminate with aluminum chloride. Alternatively, ate complex (**53**) may be prepared by the addition of methyllithium to tris(trimethylsilyl)aluminum.[82]

Table 19[81] lists a variety of alkyl and aryl acyl chlorides that readily undergo the transformation to the corresponding acylsilanes. The ate complex is necessary for the reaction, since tris(trimethylsilyl)aluminum afforded minute quantities of the desired acylsilane; furthermore, catalytic amounts of copper cyanide (10 mol %) are also required, although the role of the copper catalyst has not been defined. Although an excess of either reagent (**52**) or reagent (**53**) (*ca.* 2.5:1 organoaluminum to aryl substrate) is required to obtain an optimum yield of acylsilane, the ate complexes demonstrate remarkable chemoselectivity, in that they do not react with nitriles, esters, ketones, acylsilanes and carbamoyl chlorides.[82] The application of this transformation to a more highly functionalized molecule is outlined in equation (25).

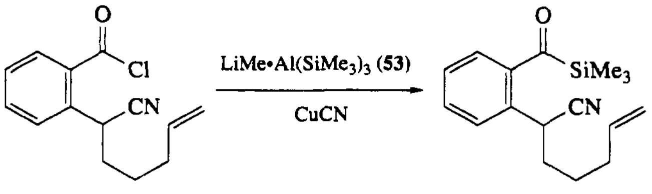

(25)

(**54**) (**55**) 52%

**Table 19** The Copper-catalyzed Addition of Silyl Organoaluminums (**52**) to Acyl Chlorides (equation 24)

| *Entry* | *R* | *Yield* (%) | *Reaction time* (h) |
|---|---|---|---|
| 1 | $C_5H_{11}$ | 95 | 2 |
| 2 | Ph | 93 | 1.5 |
| 3 | $PhCH_2$ | 89 | 1.5 |
| 4 | 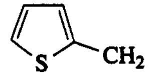 | 90 | 1.5 |
| 5 | $Bu^t$ | 89 | 1.75 |
| 6 | $AcOCH_2$ | 86 | 2.5 |

All reactions were carried out at –78 °C and with a mole ratio (substrate/reagent) of 2.5.

## 1.3.4 1,2-ADDITIONS OF ORGANOALUMINUMS TO CARBON–NITROGEN SYSTEMS

### 1.3.4.1 Stereoselective Additions

Tosylpyrazolines (**56**) stereoselectively react with trimethylaluminum to afford pyrazolols (**57**; equation 26).[83]

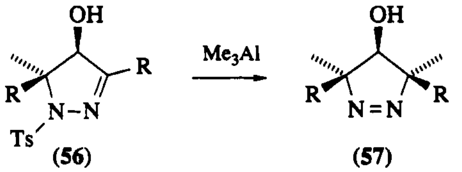

(**56**) (**57**) (26)

The reaction is highly stereoselective since the organoaluminum always approaches the face of the carbon–nitrogen double bond opposite to the hydroxy substituent. Thus, either *cis*- or *trans*-pyrazolols may be selectively prepared. The reaction does not seem to suffer any steric encumbrance since the substituent R was varied from methyl to *t*-butyl without any decrease in the overall yield. Furthermore, attempts to perform the transformation with organolithiums or Grignards failed, which presumably reflects the inherent differences in the Lewis acidity of organoaluminums and other organometallics.

### 1.3.4.2 Organoaluminum-promoted Beckmann Rearrangements

The Beckmann rearrangement proceeds through a transition state represented by structure (**59**) in equation (27). Thus, the organoaluminum-catalyzed protocol presents an opportunity to convert a ketone regiospecifically and stereospecifically into a chain-extended amino substrate.

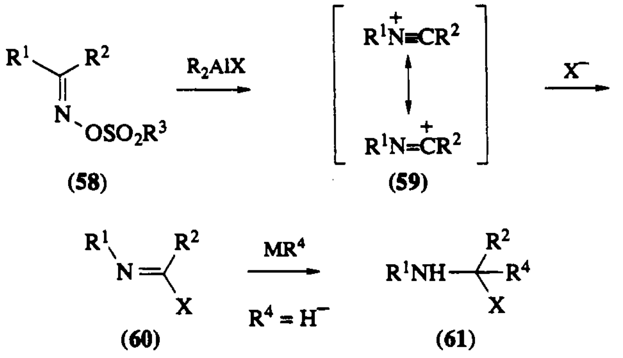

(**58**) (**59**) (27)

(**60**) (**61**)

Table 20[84] summarizes the variety of substrates ($R^1$ and $R^2$) that are compatible with the reaction conditions. For example, cyclic and acyclic thioimidates (entries 1–7) are generally prepared in good to excellent yields (46–90%), with the only reported exception being entry 1. This procedure may also be utilized to stereoselectively synthesize α-monoalkylated amines as well as α,β-dialkylated amines, since the conversion of imine (**60**) to amine (**61**; equation 27) may be accomplished by exposure to either a hydride reagent ($R^4$ = H) or an organometallic ($R^4$ = alkyl). The α-monoalkylated cases are listed in entries 8–13 and the α,α-dialkylated cases are listed in entries 14–20 (Table 20). The reaction has been successfully conducted on both cyclic and acyclic substrates affording the product amines in good overall yield (51–88%). There is reasonable flexibility with regard to the alkyl group (X = methyl, propyl, substituted alkyne; Table 20), although apparently no alkenylaluminum reagents were utilized. Also, in the one case listed in Table 20 that is capable of diastereoselection (entry 10) there was no determination (other than that it was a mixture of *cis–trans* isomers) of the level of facial selectivity.[84] The dialkylated substrates (entries 14–20) are prepared by exposure of intermediate (**60**) to Grignard reagents and, although there does seem to be a fair generality ($R^4$ = allyl, crotyl and propargyl), it is interesting to note that apparently no alkenyl Grignards were utilized.

**Table 20** Organoaluminum-mediated Beckmann Rearrangement (equation 27)

| | *Substrate (58)* | | | *Organoaluminum* | | | | *Temp.* |
|---|---|---|---|---|---|---|---|---|
| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *R* | *X* | *Product* | *Yield (%)* | *(°C)* |
| 1 | $-(CH_2)_4-$ | | $p$-$MeC_6H_4$ | $Bu^i$ | SMe | (**60**) | 5 | 40 |
| 2 | $-CHMe(CH_2)_3-$ | | $p$-$Me$-$C_6H_4$ | $Bu^i$ | SMe | (**60**) | 46 | 40 |
| 3 | $-(CH_2)_5-$ | | Me | Me | SEt | (**60**) | 62 | 0 |
| 4 | $-CHMe(CH_2)_4-$ | | $p$-$MeC_6H_4$ | $Bu^i$ | SMe | (**60**) | 66 | 0 |
| 5 | $-(CH_2)_6-$ | | $p$-$MeC_6H_4$ | Me | SEt | (**60**) | 90 | 0 |
| 6 | Ph | Me | Me | Me | SPh | (**60**) | 88 | –78 |
| 7 | Ph | Me | Me | $Bu^i$ | SMe | (**60**) | 90 | 0 |
| 8 | $-(CH_2)_5-$ | | Me | Me | Me | (**61**)$R^4$ = H | 70 | –78 |
| 9 | $-(CH_2)_5-$ | | Me | Et | $C{\equiv}CBu$ | (**61**)$R^4$ = H | 67 | –78 |
| 10 | 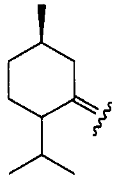 | | Me | Me | Me | (**61**)$R^4$ = H | 57 | –78 |
| 11 | Ph | Me | Me | Me | Me | (**61**)$R^4$ = H | 63 | –78 |
| 12 | Ph | Me | Me | Et | $C{\equiv}CMe$ | (**61**)$R^4$ = H | 60 | –78 |
| 13 | 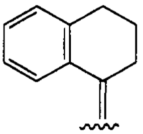 | | Me | Me | Pr | (**61**)$R^4$ = H | 88 | –78 |
| 14 | $-(CH_2)_4-$ | | $p$-$MeC_6H_4$ | Me | Me | (**61**)$R^4$ = allyl | 51 | –78 |
| 15 | $-(CH_2)_5-$ | | Me | Me | Me | (**61**)$R^4$ = allyl | 60 | –78 |
| 16 | $-(CH_2)_5-$ | | Me | Me | Me | (**61**)$R^4$ = propargyl | 55 | –78 |
| 17 | Ph | Me | Me | Me | Me | (**61**)$R^4$ = propargyl | 61 | –78 |
| 18 | Ph | Me | Me | Et | $C{\equiv}CPh$ | (**61**)$R^4$ = allyl | 88 | –78 |
| 19 | Ph | Me | Me | Me | Me | (**61**)$R^4$ = crotyl | 56 | –78 |
| 20 | Ph | Me | Me | Et | $Me(CH_2)_3C{\equiv}C$ | (**61**)$R^4$ = allyl | 74 | –78 |

The regioselectivity of this process is inherent to the Beckmann rearrangement, whereas the potential for useful stereoselectivities derives from the organoaluminum protocol, which permits manipulation of the prochiral imine of intermediate (**60**). Although entry 10 gave disappointing results with regard to stereoselectivity, equation (28) outlines a highly stereoselective example.

The difference in the stereoselectivity for (**64**) and (**65**) is most easily rationalized on the basis of the transition state geometry,[86,87] which is determined by the coordination of aluminum to the nitrogen lone pair of electrons. Scheme 4[85] details the effect that aluminum has on the transition state geometry and, therefore, the course of the overall reaction.

In the presence of the organoaluminum, the substituent (R) on the chiral center adjacent to nitrogen in (**67**) is forced to occupy an axial position to relieve the strain created by the steric interaction with aluminum. This would favor approach by hydride from the top face of (**67**), whereas in the absence of aluminum the favored approach of hydride is from the bottom face of transition state structure (**66**).

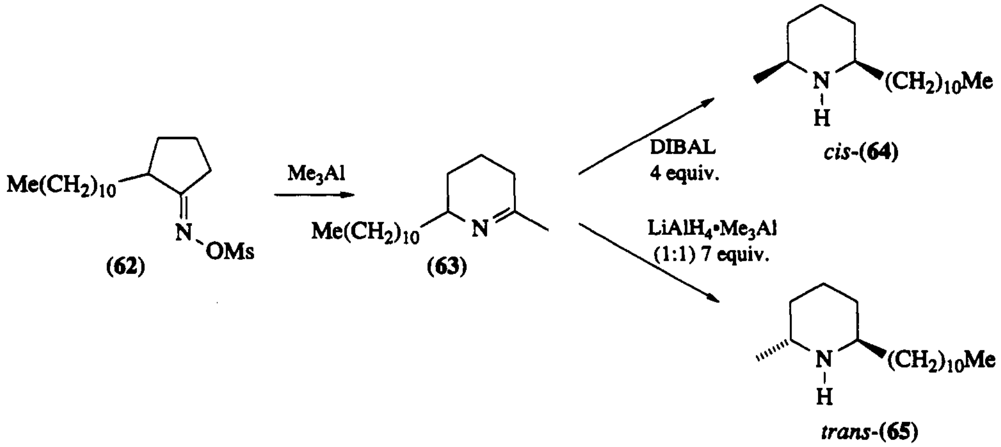
Me(CH2)10
N
OMs
(62)
Me3Al
Me(CH2)10
N
(63)
DIBAL
4 equiv.
LiAlH4•Me3Al
(1:1) 7 equiv.
N
H
(CH2)10Me
cis-(64)
N
H
(CH2)10Me
trans-(65)

(28)

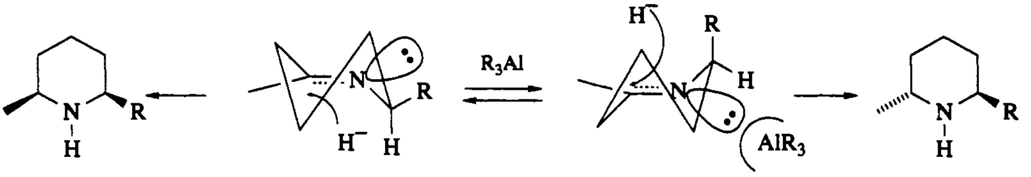
N
H
R
cis-(68)
N
R
H⁻ H
(66)
R3Al
H⁻
R
N
H
AlR3
(67)
N
H
R
trans-(69)

Scheme 4

## 1.3.5 APPLICATIONS TO NATURAL PRODUCT SYNTHESIS

### 1.3.5.1 Application of MAD and MAT to the Synthesis of (±)-3α-Acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene

The synthesis of the title compound (73), which is the defense substance of the termite soldier,[88] is outlined in Scheme 5.[89]

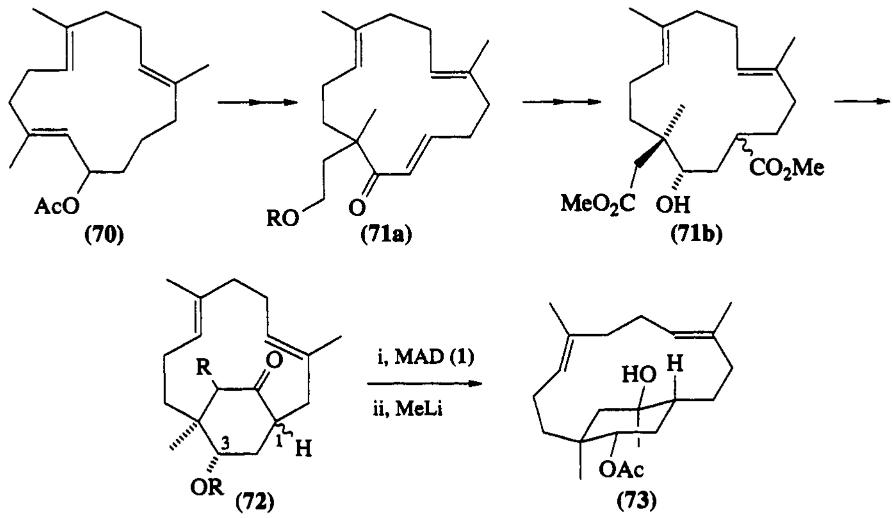
AcO
(70)
RO
O
(71a)
MeO2C
OH
CO2Me
(71b)
R
O
3
1
H
OR
(72)
i, MAD (1)
ii, MeLi
HO
H
OAc
(73)

Scheme 5

The conversion of intermediate (72) to the natural product (73) was accomplished by exposure of a 1:1 complex of (72) and the hindered organoaluminum reagent (1; MAD)[18] to methyllithium (57% yield). This is a fascinating result, not only because attempted methyllithium addition failed, but also because the required configuration of the C-1 position was β with regard to the proton substituent and, therefore, approach of a nucleophile to the C-2 carbonyl moiety would also be from the less hindered β-face; unfortunately, the natural product required a β-hydroxy substituent, which requires a facial selectivity for the more hindered α-face of the carbonyl. Although the facial selectivity of the organoaluminum (**1**) mediated addition was not total, it did give a 3:1 excess of the desired α-face 1,2-addition product, which was identical to the natural product.

### 1.3.5.2 Application of Aminoaluminum Reagents to Natural Product Synthesis

#### *1.3.5.2.1 Synthesis of an FK-506 fragment*

FK-506 (**74**) is an interesting natural product with potent immunosuppressive properties.[90]

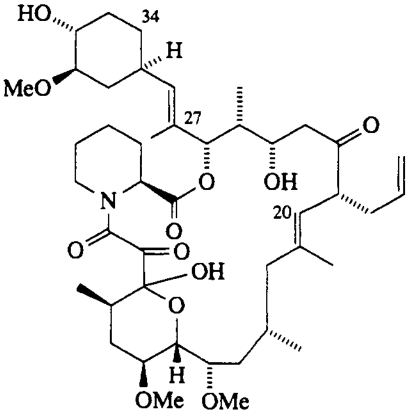

(74)

Recently, there have been a number of publications on the synthesis of various segments of (**74**) in the context of total synthesis and Scheme 6 outlines one approach to the synthesis of the C-20 to C-34 fragment.[91] The synthetic approach to the totally blocked C-20 to C-34 fragment relies on an aminolysis *via* aminoaluminum reagent (**82**) in three different transformations of the sequence, demonstrating the excellent selectivity of (**82**) in a very sensitive array of functionality. For example, the conversion of lactone (**77**) to hydroxyamide (**78**) selectively opens the lactone ring with no undesired epimerization; furthermore, (**82**) was also utilized in the aminolysis of the chiral auxiliary with no apparent epimerization.

#### *1.3.5.2.2 Synthesis of granaticin*

Granaticin (**83**) is a member of the pyranonaphthoquinone group of antibiotics. The portion of the total synthesis of (**83**) which requires the use of the aminoaluminum reagent (**42**) is outlined in Scheme 7.[92]

The conversion of lactone (**86**) to hydroxyamide (**87**) is complicated by the potential for epimerization, which is quite similar to the problem presented by substrate (**77**) in the previous synthesis. Once again, the transformation proceeds smoothly, with no apparent epimerization.

### 1.3.5.3 Application of the Nozaki Protocol

The Nozaki protocol,[93,94] which is an organoaluminum–ate mediated 1,4-addition followed by a 1,2-addition of the resulting enolate, may be considered a 1-acylethenyl anion equivalent, which does fall within the scope of this review. This process may be conducted in either an intramolecular sense or an intermolecular sense. In general, the protocol is compatible with a wide array of functionality; however, the intermolecular process requires an aldehyde, whereas the intramolecular case may be terminated by either an aldehyde or a ketone.

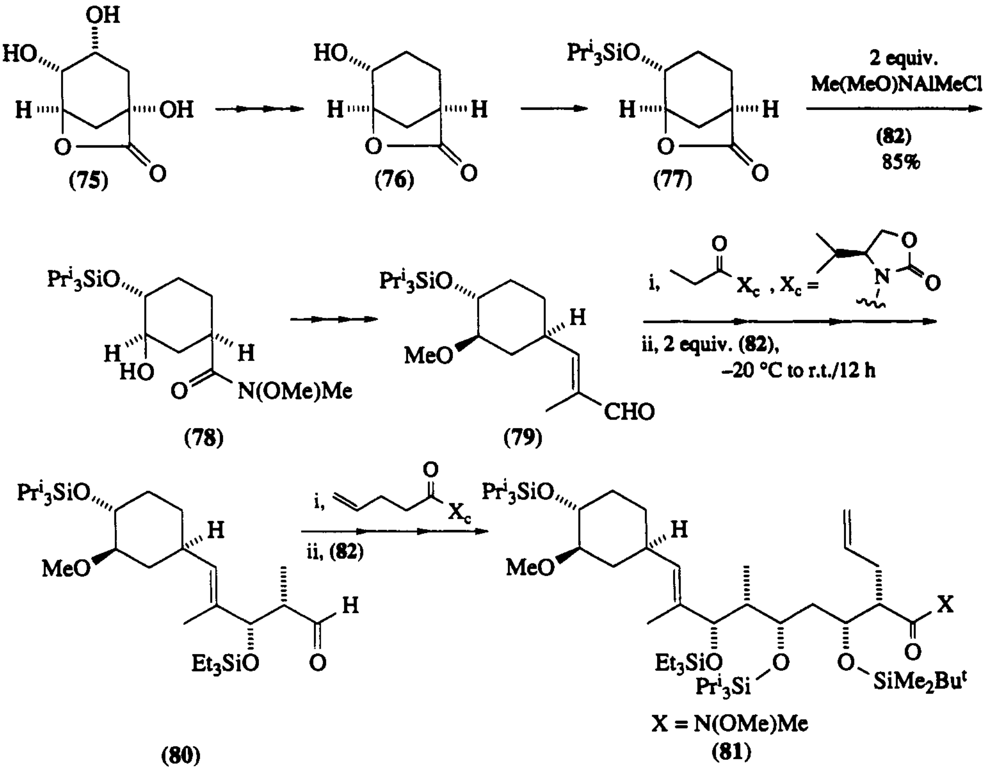
(75)
(76)
(77)
2 equiv. Me(MeO)NAlMeCl
(82)
85%
(78)
(79)
i, Xc = 
ii, 2 equiv. (82), −20 °C to r.t./12 h
(80)
i, ii, (82)
X = N(OMe)Me
(81)

Scheme 6

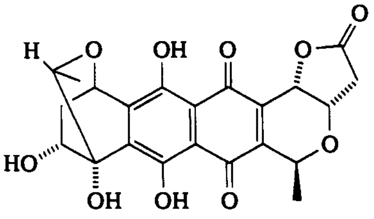

(83)

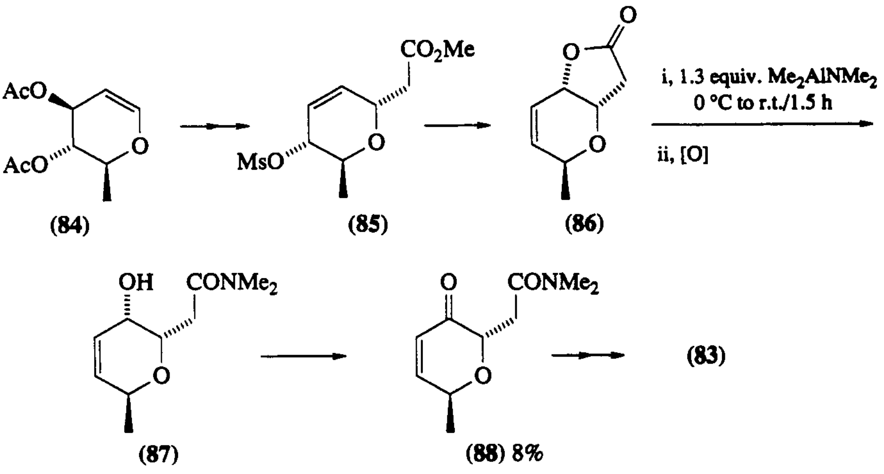
(84)
(85)
(86)
i, 1.3 equiv. Me2AlNMe2 0 °C to r.t./1.5 h
ii, [O]
(87)
(88) 8%
(83)

Scheme 7

### *1.3.5.3.1 Intramolecular protocol — application to avermectins*

An example of an intramolecular Nozaki process was recently described in the total synthesis of an avermectin aglycon (**89**).[95,96] The relevant steps in the sequence are outlined in Scheme 8. The ate complex of lithium thiophenoxide and trimethylaluminum permits the addition of thiophenoxide exclusively in a 1,4-fashion to the α,β-unsaturated aldehyde (**93**), affording an aluminum enolate that is intramolecularly trapped by the electrophilic ketone moiety. The resulting hydroxy sulfide is oxidized to the corresponding hydroxy sulfoxide, which upon exposure to heat (refluxing toluene) affords the cyclized system (**95**) in 76% yield. The addition of the ate complex (**94**) to (**93**) is not only highly regioselective, but also, unlike the typical intermolecular Nozaki process, which has been reported to proceed only when the terminating carbonyl electrophile is an aldehyde,[93,94] this example is terminated by a ketone. Presumably entropic factors are driving the ring closure to the ketone in this intramolecular process.

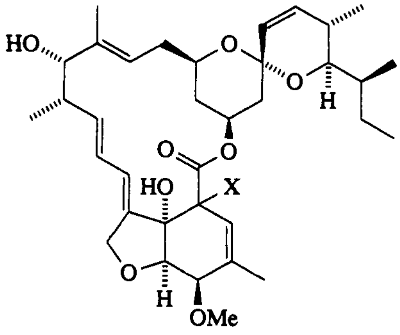

(**89**) X = β-H

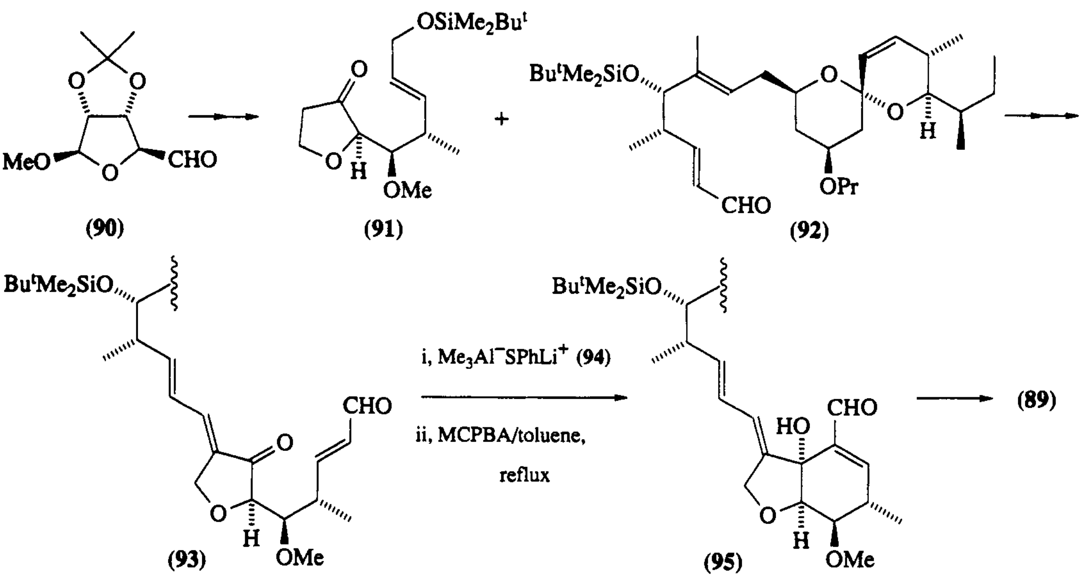

**Scheme 8**

### *1.3.5.3.2 Intermolecular protocol — application to prostanoids*

Scheme 9 outlines the synthesis of a prostanoid[97] intermediate (**99**) that relies on an intermolecular Nozaki process. It is important to note that unlike the intramolecular case described above, the intermolecular version of this protocol requires an aldehyde as the electrophilic trap; however, it is interesting to note that there have been no reports of the addition of Lewis acid activated ketones (presumably, as a preformed complex which would be added *via* cannula at low temperature) to the preformed aluminum enolate. Finally, in this example, the conversion of enone (**96**) to adduct (**98**) is promoted by the less reactive dimethylaluminum phenyl thiolate and not the corresponding ate complex.

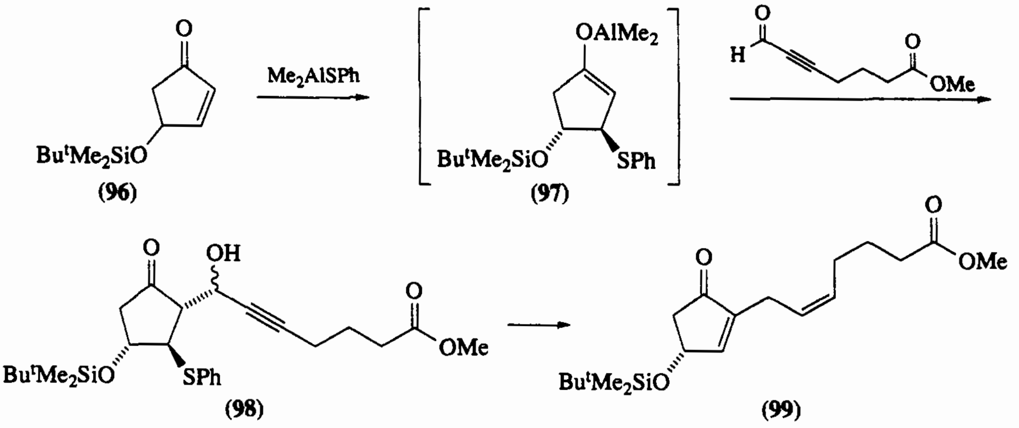
Bu$^t$Me$_2$SiO
(96)
Me$_2$AlSPh
OAlMe$_2$
Bu$^t$Me$_2$SiO
SPh
(97)
H
OMe
OH
Bu$^t$Me$_2$SiO
SPh
OMe
(98)
OMe
Bu$^t$Me$_2$SiO
(99)

Scheme 9

### 1.3.5.4 Synthesis of Nonracemic Sydowic Acid

Sydowic acid (**100**) was prepared as outlined in Scheme 10.[30] The crucial transformation of ketone (**101**) to carbinol (**102**) was accomplished by stereoselective 1,2-addition of trimethylaluminum, which afforded superior facial selectivity for the *re*-face compared to Grignard reagents. In contrast, methyltrichlorotitanium addition resulted in a *si*-face stereoselectivity.

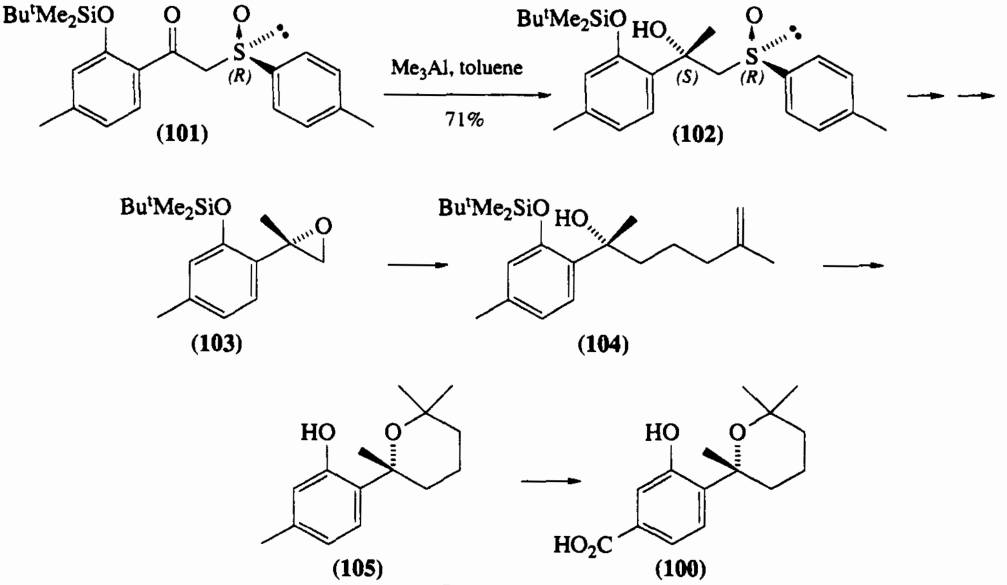
Bu$^t$Me$_2$SiO
(R)
(101)
Me$_3$Al, toluene
71%
Bu$^t$Me$_2$SiO
HO
(S)
(R)
(102)
Bu$^t$Me$_2$SiO
(103)
Bu$^t$Me$_2$SiO
HO
(104)
HO
(105)
HO
HO$_2$C
(100)

Scheme 10

### 1.3.5.5 Synthesis of Racemic Gephyrotoxin-223AB

Gephyrotoxin (**106**), a constituent of the skin extracts of the poison-dart frog, was synthesized as outlined in Scheme 11.[98] The organoaluminum-promoted Beckmann rearrangement produced an imine, which was stereoselectively reduced (essentially total selectivity) with DIBAL to afford piperidine (**109**; 41% yield).

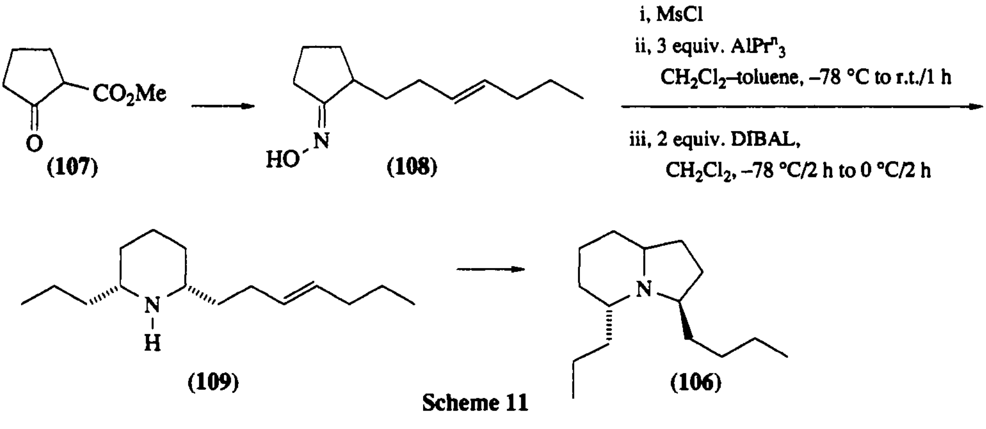

**Scheme 11**

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# 1.4
# Organocopper Reagents

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## 1.4.1 INTRODUCTION

The direct addition of an organocopper or cuprate reagent to a carbon–heteroatom multiple bond might rightfully be considered the forgotten son of transition metal based carbon–carbon bond formation. Indeed, although organocopper reagents are potent Michael donors, their well-recognized hesitation towards competing 1,2-addition may represent their most salient feature. Still, in most circumstances, while many substitution reactions[1] (*e.g.* with a primary iodide) and especially 1,4-additions[2] (*e.g.* with α,β-unsaturated ketones) tend to be far more rapid processes, the appropriately designed substrate can often benefit considerably from a copper reagent mediated 1,2-addition, not only in terms of yield but especially with regard to diastereoselectivity.

Discussed in this chapter, for the most part, are documented cases where complexes derived from (one or more equivalents of) a Grignard or organolithium reagent, in combination with a copper(I) salt, have been used to add to an aldehyde, ketone, imine, amide or nitrile moiety. In the majority of examples, the key issue is one of stereocontrol. Hence, where available, data within the organocopper manifold *versus* those for other organometallic reagents are provided for comparison.

Several different types of copper reagents have been utilized for the 1,2-additions presented herein. Those formed from Grignard reagents (Scheme 1) may be of the type represented as (**1**) or (**2**),[3] depending upon whether ≤0.5 or 1.0 equiv. of CuX (X = I, Br) is involved. In the presence of CuCN, both 'lower order' monoanionic species (**3**)[4] and 'higher order' dianionic salts (**4**)[5] are possible. With the latter class, mixed metal clusters result from treatment of this copper(I) source with one equivalent of both RMgX and R'Li.[6] Reagents derived from organolithium precursors (Scheme 2) include mainly the Gilman cuprates $R_2CuLi$ (**5**),[1,2,7] organocopper species (**6**) akin to (**2**) but containing lithium salts as byproducts of metathesis between the metals,[1,2] and the 'higher order' dilithiocyanocuprates (**7**).[5] Within this group, *i.e.* (**1**) to (**7**), each is distinct from the others, not only insofar as stoichiometric representations are concerned, but in the reactivity profiles displayed, as well as the regio- and stereo-chemical outcomes of their 1,2-additions (*vide infra*).

RMgX + ≤0.5 CuX $\longrightarrow$ $R_2CuMgX$ **(1)** ≡ a 'lower order' magnesium cuprate

RMgX + CuX $\longrightarrow$ $RCu{\bullet}MgX_2$ **(2)** ≡ a Grignard-derived organocopper reagent

RMgX + CuCN $\longrightarrow$ RCu(CN)MgX **(3)** ≡ a 'lower order' Grignard-derived cyanocuprate

RMgX + R'Li + CuCN $\longrightarrow$ RR'Cu(CN)LiMgX **(4)** ≡ a 'higher order' mixed metal cyanocuprate

**Scheme 1**

2 RLi + CuX $\longrightarrow$ $R_2CuLi$ (+ LiX) **(5)** ≡ a 'lower order' or Gilman cuprate

RLi + CuX $\longrightarrow$ $RCu{\bullet}LiX$ **(6)** ≡ an organolithium-derived organocopper reagent

2 RLi + CuCN $\longrightarrow$ $R_2Cu(CN)Li_2$ **(7)** ≡ a 'higher order' dilithium cyanocuprate

**Scheme 2**

## 1.4.2 1,2-ADDITIONS TO ALDEHYDES AND KETONES

### 1.4.2.1 Reactions of Aldehydes

The initial observation that organocuprates react in a synthetically useful fashion with aldehydes was made by Posner in 1972 as part of a study aimed at determining functional group compatibility with $R_2CuLi$ versus temperature.[8] Both benzaldehyde and *n*-heptanal were found to react at –90 °C in less than 10 min with lithium dimethylcuprate to afford the corresponding alcohols in good yields (equation 1).

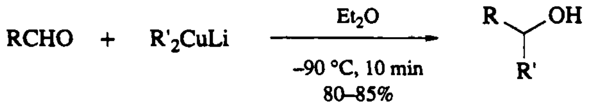

(1)

R = Ph, n-$C_6H_{13}$; R' = Me, $Bu^n$

The facility and efficiency with which copper reagents add to aldehydes has been examined where unsymmetrical α- or β-substitution exists, thereby raising the question of diastereoselection. Two types of situation exist in this regard: (i) where opportunities for chelation-controlled attack by the reagent can lead to a significant preference for one diastereomer; and (ii) the nonchelation-controlled delivery of an organic ligand from copper, where steric and perhaps other factors influence the directionality of addition. The former scenario was first noted by Still and Schneider,[9] concurrent with studies[10] in this group on Grignard reactions with α-alkoxy ketones. Since ketones react relatively sluggishly toward cuprates (*vide infra*), and 1,2-additions to α-alkoxy aldehydes give unimpressive results, a variety of β-alkoxy aldehydes (**8**) have been examined. For these systems, cuprates $Me_2CuLi$ and $Bu^n{}_2CuLi$ tend to afford good ratios in favor of *anti* isomers, irrespective of the protecting group on oxygen (equation 2).[9] Organocopper species derived from vinyllithium, *i.e.* (vinyl)Cu·$PBu_3$ and $(vinyl)_2CuLi$, act in a similar manner, although the ratios are diminished (8:1 and 3:1, respectively) and the aldehyde is only partially consumed (50% conversion) under the standard reaction conditions in the dialkylcuprate cases. By comparison, 1,2-additions employing either the corresponding organolithium or Grignard reagents are essentially stereorandom.[9]

The initially discouraging outcome with α-alkoxy aldehydes[9] has been reexamined in detail by Mead and Macdonald.[11] Both acyclic and cyclic α,β-dialkoxy aldehydes (**9**) and (**10**) served as substrates, and reaction variables including reagents, solvents and temperatures were all considered. Excellent selectivities of the order of 94:6 to 98:2 in favor of the *syn* products (**12a**) were obtained from (**9**) using

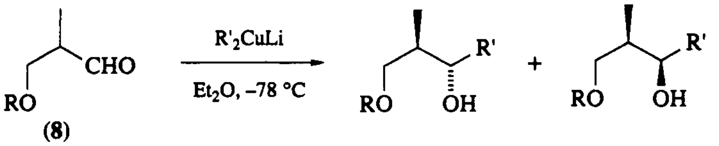
R'$_2$CuLi
Et$_2$O, –78 °C
CHO
RO
R'
OH
+

**(8)**

(2)

| | | | |
|---|---|---|---|
| R = $PhCH_2OCH_2$ | R' = Me | 92% | 30:1 |
| | Bu$^n$ | 82% | 17:1 |
| R = THP, $PhCH_2$ | R' = Me | 90% | >20:1 |

$RCu{\cdot}MgBr_2$ (prepared from RMgBr plus $CuBr{\cdot}Me_2S$) in $Et_2O$ at –78 °C. The α-chelate model (**11**) appears to account for the observed course of addition,[12] without interference from β-chelation or Felkin-predicted[13] modes of attack (equation 3).[14] By contrast, (**10**) did not show the same levels of stereoselectivity under identical conditions, and in fact for the one case studied ($MeCu{\cdot}MgBr_2$) in this report[11] a 2:1 ratio was obtained favoring the *anti* isomer. The corresponding allylcopper·$MgBr_2$ reagent is also not efficient in terms of product ratio (68:32 *syn:anti*) with (**9**),[11] nor was it of value in additions to a trialkoxy example (**13**), where the *anti* material (**14b**) actually dominated, albeit slightly (equation 4).[15] Lithium cation containing Gilman cuprates appear to be unpredictable,[11] as reaction of $Me_2CuLi$ with (**9**) was nonselective (47:53 *syn:anti*), although with (**10**) an improved 82:18 ratio was obtained. Subsequent use of an $MgBr_2$-modified lower order reagent on α-alkoxy aldehyde (**15**), however, did show a preference for *syn* selectivity of 10:1, (**16a**):(**16b**) (equation 5).[16] Reversal of selectivity to give high percentages of *anti* product (**12b**) can be effected using an excess (2 equiv.) of an organotitanium reagent $RTi(OPr^i)_3$ in THF at *ca.* –40 °C.[11]

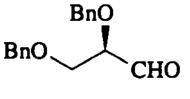

**(9)**

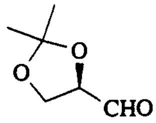

**(10)**

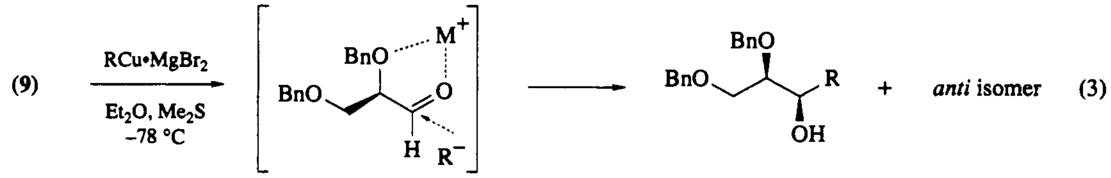
(9)
RCu•MgBr$_2$
Et$_2$O, Me$_2$S
–78 °C
BnO
BnO
M$^+$
O
H
R$^-$
BnO
BnO
R
OH
+
*anti* isomer

(3)

**(11)** **(12a)** **(12b)**

| | | |
|---|---|---|
| R = Me | 83% | 94:6 |
| Bu$^n$ | 78% | 93:7 |
| vinyl | 80% | 98:2 |
| Ph | 69% | 96:4 |

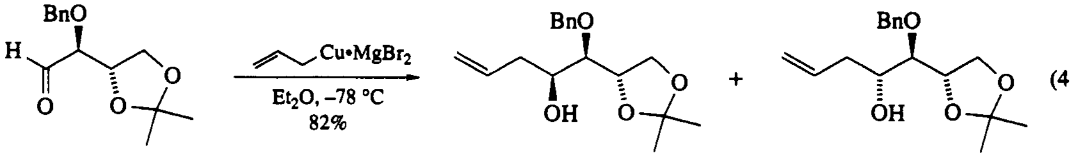
BnO
H
O
O
O
Cu•MgBr$_2$
Et$_2$O, –78 °C
82%
BnO
OH
O
O
+
BnO
OH
O
O

(4)

**(13)** **(14a)** 40:60 **(14b)**

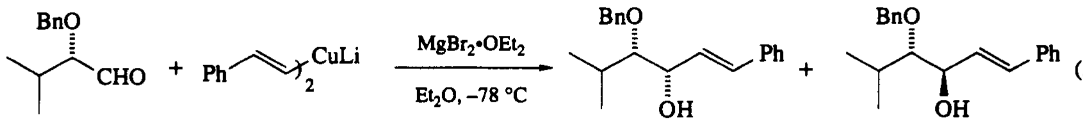
BnO
CHO
+
Ph
CuLi
2
MgBr$_2$•OEt$_2$
Et$_2$O, –78 °C
BnO
Ph
OH
+
BnO
Ph
OH

(5)

**(15)** **(16a)** 10:1 **(16b)**

Further work by Sato on couplings with 2,3-*O*-isopropylideneglyceraldehyde (**10**) using the same class of reagents $RCu{\cdot}MgX_2$ has established the critical role of solvent in determining the diastereomeric outcome.[17] Thus, performing the reaction in THF rather than $Et_2O$ leads to highly selective 1,2-additions producing the *syn* products in high yields. Alkylcopper reagents give ratios ranging from 10:1 to 16:1 for (**17a**):(**17b**) (equation 6), while aryl and vinyl organocopper complexes afford virtually all of the *syn* diastereomer.[17] A cyclic mechanism[12] (*cf.* **18**) which suggests attack by RCu from the direction shown is consistent with the observed data (equation 7).[17] Whether the switch from $Et_2O$ to THF is affecting the ease with which chelate (**18**) can form, or whether the impact is related to changes in the state of the reagent (*e.g.* aggregation), or both, is not clear at this time.

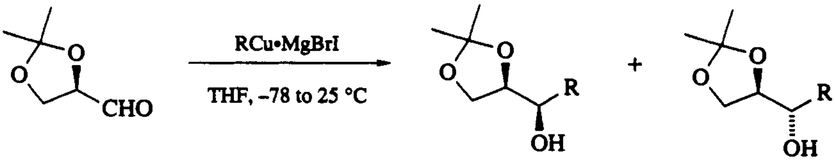

(6)

(**10**) (**17a**) (**17b**)

| | | |
|---|---|---|
| $R = Bu^n$, *n*-pentyl, $n\text{-}C_{10}H_{21}$, $c\text{-}C_6H_{11}$ | 74–89% | 10:1 to 16:1 |
| R = Ph, $p\text{-}ClC_6H_4$, $p\text{-}NO_2C_6H_4$ | 80–93% | >99:1 |
| $R = CH_2{=}C(SiMe_3)$ | 86% | >98:2 |

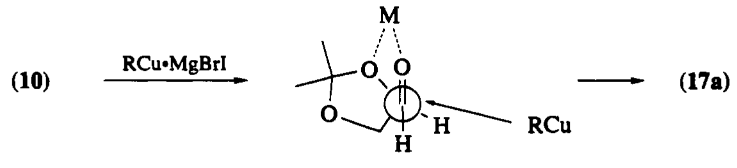

(7)

(**18**) M = MgBrI or CuR

Nonchelation-based 1,2-additions to this same aldehyde, thereby leading to high percentages of the *anti* product (**17b**), have been achieved[18] using higher order cyanocuprate technology.[5] Exposure of CuCN to an equivalent of Grignard reagent (**19a**) and methyllithium forms (stoichiometrically) the mixed metal cuprate (**20**),[6] which upon introduction of (**10**) at –78 °C gave (**21a**) and (**22a**) with a diastereomer excess (*de*) of 90% (75% chemical yield). Likewise, the corresponding reaction with (**19b**) afforded a 73% yield of (**21b**) and (**22b**), with a 96% *de* (Scheme 3). The authors point out that the lower order cuprate analog (**23**) showed considerably reduced stereoselectivity in its reaction with (**10**). Thus, by simply choosing the appropriate organocopper or organocuprate reagent, excellent *syn* or *anti* diastereoselectivity can be realized. The judicious choice of functional group manipulations in (**21a**) and (**22a**) ultimately allows for the conversion of a single starting material (*i.e.* **10**) to carbohydrate derivatives (**24**), (**25**) and (**26**).[18]

Identical treatment of aldehyde (**27**), derived from (**10**) *via* a three-step sequence (proteodesilylation, protection and ozonolysis), once again successfully produces *anti* compound (**28**), this time to the exclusion of the *syn* diastereomer (**29**) (Scheme 4).[19] Pivotal was the role of the hydroxy-protecting group, as use of benzyl in place of *t*-butyldimethylsilyl drastically lowered the selectivity. A Felkin–Anh[13,20] model is proposed to explain the stereochemical results, relying on the bulkiness of the trialkylsilyloxy moiety to assist in strongly maintaining the conformation shown in (**30**). Unfortunately, with the epimer of (**27**), compound (**31**), only a 2:1 selectivity was found (in 75% yield),[19] implying that the stereochemistry of the starting aldehyde is important in determining diastereomeric excesses from these couplings, a finding which corroborates an earlier assessment.[9]

1,2-Additions to aldehydes possessing methoxycarbonyl groups positioned three atoms removed can be an especially attractive route to 4,5-*trans*-disubstituted-γ-butyrolactones (**32**) following acid-catalyzed cyclization.[21] The two possible isomers are formed in a >95:5 ratio using $Me_2CuLi$ or $Bu^n{}_2CuLi$, in yields between 53–82% (equation 8). The authors point to the Felkin–Anh[13,20] model (**33**), where this conformation assumes $R > CH_2CO_2Me > H$. Since this would not apply to the case of R = Me, a stereoelectronic effect due to the ester group may also be involved. Alternatively, the seven-membered chelate (**34**), invoked in their titanium(IV)-induced 1,2-additions,[21] may also be operative.

For aldehydes which lack α-heteroatoms and hence have no avenue for stereocontrol *via* chelation, enhanced Cram selectivity beyond that normally seen with lower order cuprates (*i.e.* 3:1[22] to 7:1[23]) can be

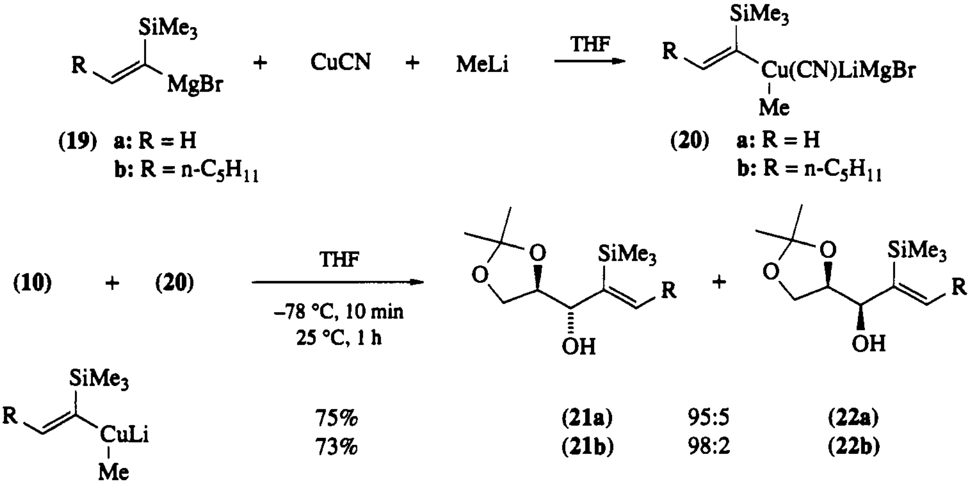
SiMe$_3$
MgBr
R
CuCN
MeLi
THF
Cu(CN)LiMgBr
Me
(10)
(20)
THF
−78 °C, 10 min
25 °C, 1 h
O
OH
SiMe$_3$
CuLi

**(19)** **a:** R = H
**b:** R = n-$C_5H_{11}$

**(20)** **a:** R = H
**b:** R = n-$C_5H_{11}$

**(23)**

| | | | |
|---|---|---|---|
| 75% | **(21a)** | 95:5 | **(22a)** |
| 73% | **(21b)** | 98:2 | **(22b)** |

**Scheme 3**

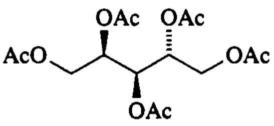

**(24)** D-Lyxitol

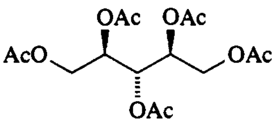

**(25)** Ribitol

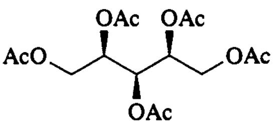

**(26)** Xylitol

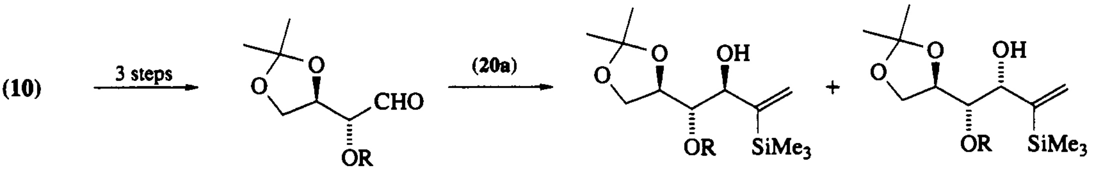
(10)
3 steps
O
CHO
OR
(20a)
OH
SiMe$_3$

**(27)** **(28)** **(29)**

| | | |
|---|---|---|
| R = SiMe$_2$Bu$^t$ | 82% | >98 :<2 |
| R = PhCH$_2$ | 86% | 5:1 |

**Scheme 4**

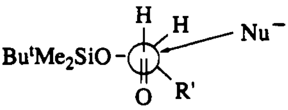
H
H
Nu$^-$
Bu$^t$Me$_2$SiO
O
R'

**(30)**

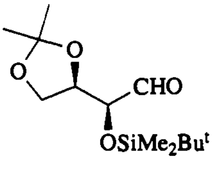
O
CHO
OSiMe$_2$Bu$^t$

**(31)**

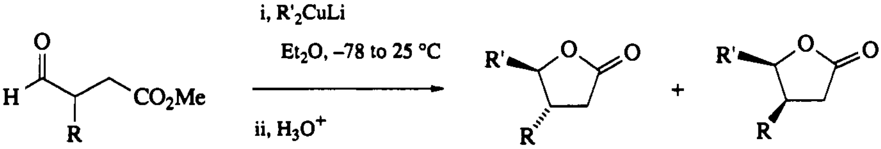
O
H
CO$_2$Me
R
i, R'$_2$CuLi
Et$_2$O, −78 to 25 °C
ii, H$_3$O$^+$
R'
O
R

(8)

R = Me, Bu$^n$

**(32a)** >95:5 **(32b)**

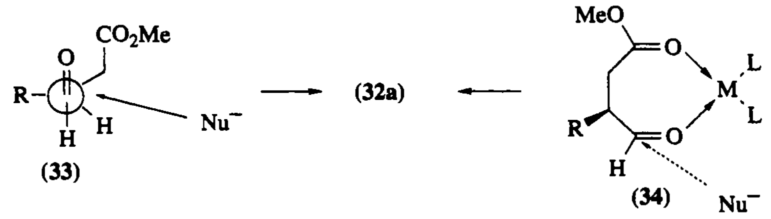

(33) ⟶ (32a) ⟵ (34)

induced using BF$_3$-modified higher order cuprates.[24] Using aldehyde (**35**) as a model with cuprate (**38**), equal amounts of the diastereomers (**36**) and (**37**) are formed at –78 °C over a 3 h period (equation 9). In the presence of both 15-crown-5 ether and BF$_3$·Et$_2$O, however, a quantitative conversion occurs along with an 8:1 to 10:1 ratio of *syn* and *anti* isomers. The crown ether effect could be duplicated using an ether-containing, alkynic nontransferable ligand[25] as part of the mixed cuprate (**39**). In this manner the otherwise room temperature inert reagent (**39**) reacts with BF$_3$·Et$_2$O in the pot at –78 °C to return (**36**) and (**37**) to the extent of 10:1 to 12:1.[24] The importance of the crown ether effect, either internally placed or by external introduction, is clear from the case of reagent (**40**), where a 2-thienyl ligand does not possess the same virtues in this regard. The increase in diastereoselectivity has been attributed to an increase in effective size of the cuprate which bears the BF$_3$ on the nitrile ligand, as well as to the proximity of the crown ether–lithium complex. Hence, regardless of whether perpendicular or nonperpendicular attack prevails, an increase in *syn* selectivity is expected.

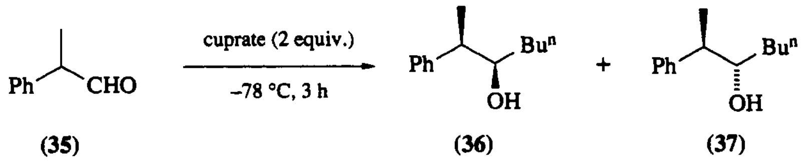

(35) (36) (37) (9)

| | |
|---|---|
| Bu$^n_2$Cu(CN)Li$_2$ (38) | 1:1 |
| (38) + 4 BF$_3$ + 15-crown-5 | 8:1 to 10:1 |
| Bu$^n$(MeO—≡—)Cu(CN)Li$_2$(39) | no reaction |
| (39) + 4 BF$_3$ | 10:1 to 12:1 |
| Bu$^n$(2-Th)Cu(CN)Li$_2$ (40) + 4 BF$_3$ | 4:1 |

Still better ratios of (**36**) to (**37**) have been noted with cuprates (**38**) and (**39**) in the presence of trialkylsilyl halides.[26,27] The presence of Me$_3$SiCl (2 equiv.) improves the otherwise nonselective reaction of (**38**) from 1:1 to 7:1 *syn:anti*, while solutions of cuprate (**39**) containing excess Me$_3$SiBr lead to a 19:1 ratio in excellent yield (equation 10). The critical variable in this scheme is the Me$_3$SiCN produced upon sequestering of the cyano group by the silyl chloride from the higher order cuprate, producing a lower order mixed reagent (**41**; equation 11). Due to the competing reaction between cuprate (**39**) and Me$_3$SiCl and/or Me$_3$SiCN (which consumes active cuprate, forming **42**), an excess of (**39**) is needed for high conversions. The best combination, therefore, is one which utilizes the lower order cuprate (**41**; R = Bu$^n$) together with both Me$_3$SiCl and Me$_3$SiCN in a 1:1 ratio (equation 12). Further improvements in diastereoselectivity may be forthcoming by substituting Me$_3$SiBr for Me$_3$SiCl. The manner in which these additives act in concert (both are required for maximum yield and diastereoselectivity) to give rise to the Cram selectivity is presently unclear.[26]

$$(35) \xrightarrow[\text{THF, - 78 °C}]{\text{cuprate + additive}} (36) \quad + \quad (37) \qquad (10)$$

| | | | |
|---|---|---|---|
| (38) | + 2 Me$_3$SiCl | 45% + SM | 7:1 |
| (39) | + 2 Me$_3$SiCl | 88% | 10:1 to 11:1 |
| (39) | + 2 Me$_3$SiBr | 97% | 17:1 to 19:1 |

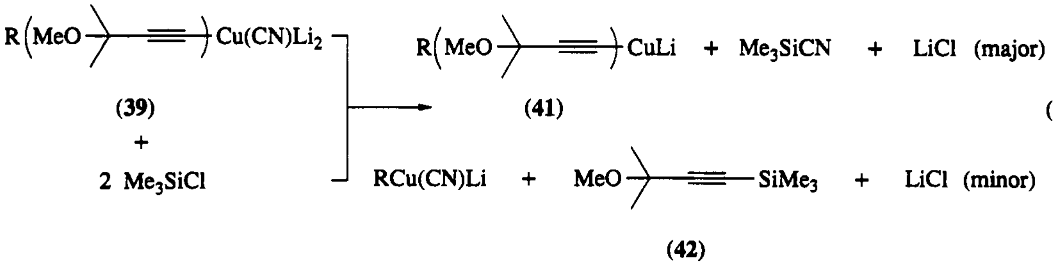
R(MeO)—≡—)Cu(CN)Li2
(39)
+
2 Me3SiCl
R(MeO)—≡—)CuLi + Me3SiCN + LiCl (major)
(41)
RCu(CN)Li + MeO)—≡—SiMe3 + LiCl (minor)
(42)

(11)

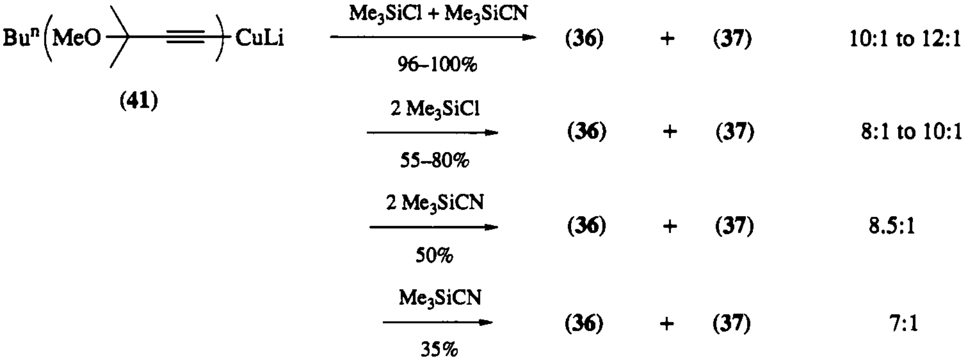

(12)

*syn*-Products are also formed from crotylcopper additions to benzaldehyde in the presence of $BF_3 \cdot Et_2O$.[28] Although the observed 98:2 ratio is impressive, the regiochemistry of attack is, unfortunately, relatively nonselective, the $\alpha$:$\gamma$ ratio being *ca.* 2:1. Without the Lewis acid in the pot, the *syn*:*anti* ratio is reduced to essentially 1:1 (equation 13).

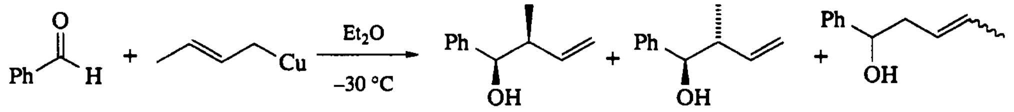

(13)

| | | |
|---|---|---|
| with $BF_3$ | 98 | 2 |
| without $BF_3$ | 48 | 52 |

Interestingly, Florio has noted that by replacing the methyl group characteristic of the crotyl system with heterocyclic arrays, as in (**43**) and (**44**), these allylic copper reagents afford products of exclusive $\gamma$-attack with benzaldehyde.[29] By contrast, the counterions $Li^+$, $MgBr^+$, and $BEt_3Li^+$ strongly favor the $\alpha$-regioisomers. In view of the fact that even the corresponding lithium species are found to add reversibly, it is proposed (Scheme 5) that the 1,2-addition of (**45**) is reversible, and ultimately proceeds perhaps through a four-centered transition state (**47**) to give the thermodynamically preferred products. Since only the (*E*)-stereochemistry is observed in adduct (**48**), it is suggested that complete dissociation of (**46**) does not occur, since some isomerization of the free allylcopper might be expected.

Metallated allylsilanes have also been examined in terms of the effects of various gegenions on $\alpha$- *versus* $\gamma$-additions to aldehydes. Using allylaminosilane (**49**), Tamao and Ito have shown that transmetallation of the lithiated intermediate to copper using CuCN (1 equiv.) leads to a >95% preference for $\gamma$-adduct (**51**; Scheme 6).[30,31] Other metals such as magnesium, zinc and titanium show a strong preference for $\alpha$-attack (>95%), which ultimately leads to dienes (**50**) following Peterson alkenation.

With silicon containing the diethylamino moiety, product (**51**) can be transformed to the isopropoxy derivative (**52**), which is susceptible to oxidation with $H_2O_2$, thereby converting the carbon–silicon bond to a carbon–oxygen bond.[32] In tandem with a prior MCPBA epoxidation of vinylsilane (**52**), a new entry to the 2-deoxy-*C*-nucleoside skeleton is realized (Scheme 7).

Simpler allylic copper reagents, such as lithium diallylcuprate, behave more like allyllithium in their reactions with unsaturated carbonyl systems, usually affording mainly 1,2-adducts.[33] Attempts by Normant to bypass this mode with added TMS-Cl have been completely unsuccessful.[34] High yields of homoallylic alcohols are to be expected using this reagent, even on such highly conjugated enals as cinnamaldehyde,[35,36] or with enolizable ketones (Scheme 8).[37] Recent work from our lab has shown that

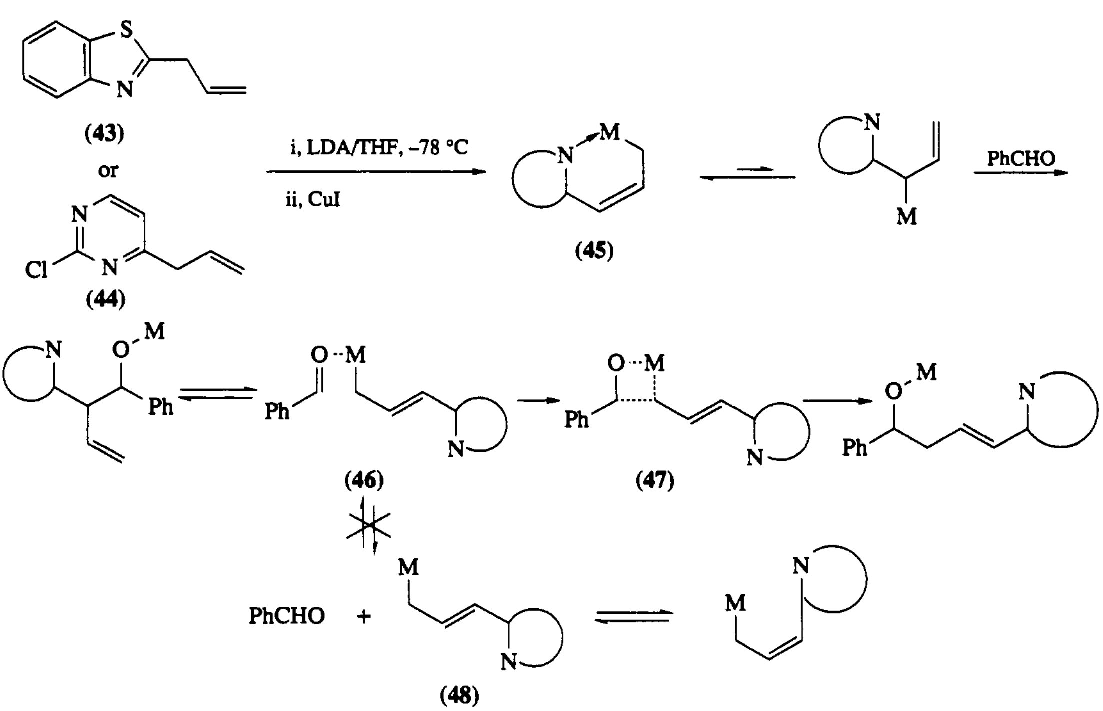
(43)
or
(44)
i, LDA/THF, -78 °C
ii, CuI
(45)
PhCHO
(46)
(47)
PhCHO +
(48)

Scheme 5

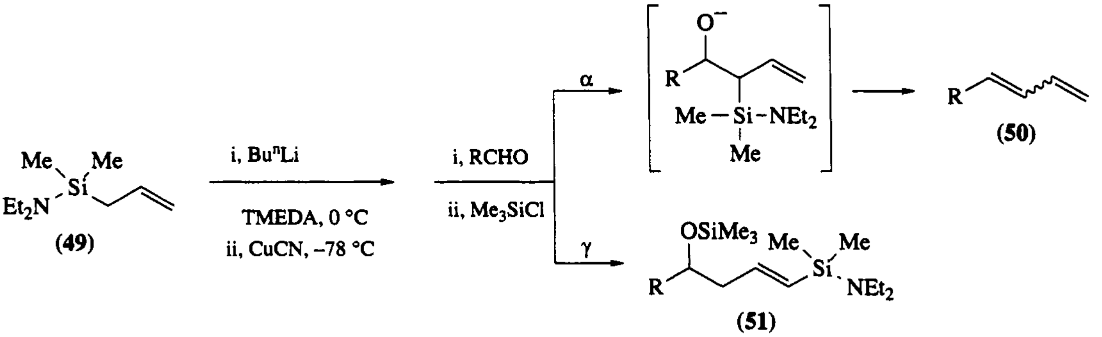
(49)
i, BuⁿLi
TMEDA, 0 °C
ii, CuCN, -78 °C
i, RCHO
ii, Me₃SiCl
α
γ
(50)
(51)

Scheme 6

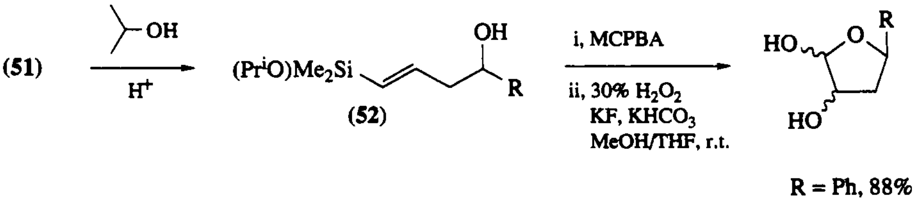
(51)
H⁺
(52)
i, MCPBA
ii, 30% H₂O₂
KF, KHCO₃
MeOH/THF, r.t.
R = Ph, 88%

Scheme 7

allylcuprates are $\sigma$-bound (rather than $\pi$-bound) species, and that the allylic ligands are undergoing rapid $\alpha$–$\gamma$ exchange at –78 °C.[38] In light of these spectral studies, allylcuprates are clearly unique reagents among all those known in organocopper chemistry,[1,2,39] and may find general utility as soft, extremely reactive allylic nucleophiles toward 1,2-addition.

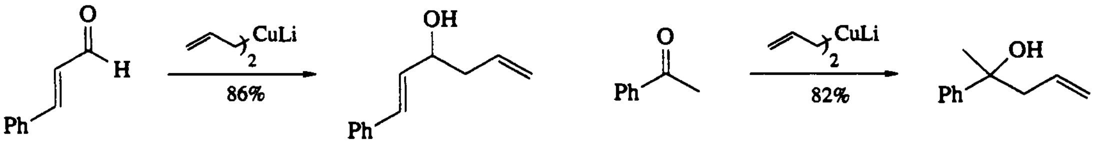

Scheme 8

Gaining preferential entry to the anti-Cram series *via* organocopper chemistry has been achieved, as described by Yamamoto, through the 'surprising'[22] effects of crown ethers on lower order cuprate 1,2-additions.[22] That is, notwithstanding an early report by Langlois,[40] treatment of an aldehyde such as (**35**) with a THF or $Et_2O$ solution of $Bu^n{}_2CuLi$ containing one equivalent of 18-crown-6 ether gave a 1:4:2 ratio favoring the *anti* isomer (**37**; equation 14). The cuprate itself led to a 3:1 mix of *syn*:*anti* products (**36**) and (**37**), and hence these additives completely reverse the normal direction of diastereoselectivity. Similar, although not as pronounced, results were obtained with higher order dilithium ($Bu^n{}_2Cu(CN)Li_2$, 1:2 *syn*:*anti*) and lower order magnesium ($Me_2CuMgBr$, 1:2 *syn*:*anti*) cuprates, as well as with aggregates such as $Bu^n{}_5Cu_3Li_2$ (1:4.4 *syn*:*anti*).[22]

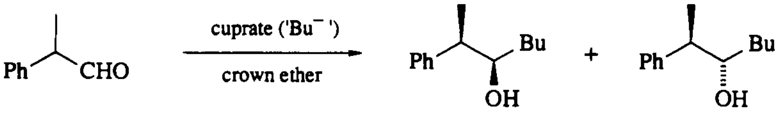

(14)

(**35**) (**36**) (**37**)

| | | | | |
|---|---|---|---|---|
| $Bu^n{}_2CuLi$ | + | 18-crown-6 | 95% | 1:4.2 |
| $Bu^n{}_5Cu_3Li_2$ | + | 18-crown-6 | 96% | 1:4.4 |
| $Bu^n{}_2CuLi$ | | | 95% | 3:1 |

To account for these anti-Cram selectivities, a radical mechanism is proposed based on the ability of $R_2CuLi$–crown ether complexes to transfer electrons more easily than $R_2CuLi$ itself (*e.g.* to dicyclopropyl ketone).[22] If such a mechanism prevails, conformations (**53**) and (**54**) are destabilized in the transition state due to a build-up of negative charge on oxygen and the ensuing Me/$O^-$ interaction. Moreover, the incoming nucleophile may prefer perpendicular attack, all of which taken together favors (**55**) to ultimately afford *anti* products.

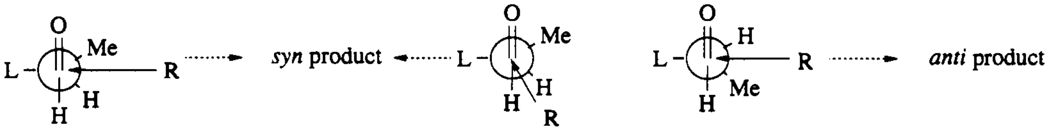

(**53**) (**54**) (**55**)

The use of $BF_3{\cdot}Et_2O$ to accentuate the reactivity of otherwise sluggish cuprates toward 1,2-additions is also the subject of a recent report by Knochel.[41] Functionalized lower order cyanocuprates incorporating $ZnI^+$ as the gegenion in place of $Li^+$ or $MgX^+$ readily add to aldehydes at low temperatures provided excess Lewis acid is present (Scheme 9). Isolated yields of products are very good, and the observation that ketones do not react under similar conditions adds an element of chemospecificity to this method.

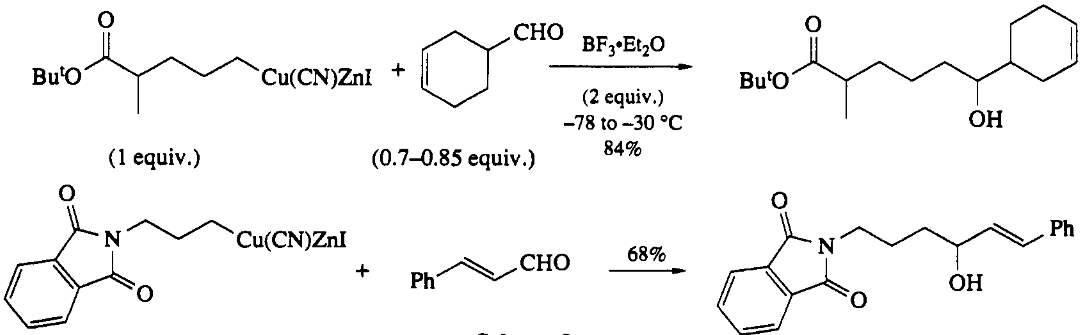

**Scheme 9**

The iron tricarbonyl stabilized form of 2-formylbutadiene (**56**) reacts with various organometallic reagents to produce diastereomeric mixes of products (**57a**) and (**57b**).[42] While the trend is such that Grignard reagents are nonselective, organolithiums tend to add predominantly from the (*exo*) face away from the bulky iron tricarbonyl group, especially when doped with additional LiBr. Interestingly, the diastereoselectivity undergoes a complete turnabout with Gilman's reagent (equation 15). The explanation behind this reversal may involve initial attack either at the metal center or at a CO ligand, which would account for the reduced yield as several other secondary events could occur.[43] Subsequent intramolecular transfer of the methyl group to the aldehyde from the *endo* direction gives initially (**58**), as illustrated in equation (16).

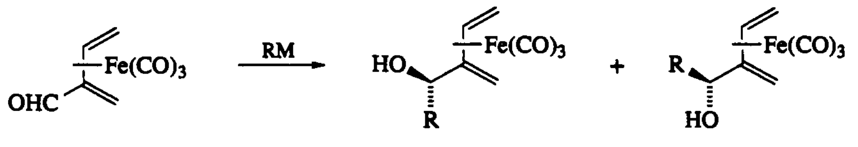

(15)

(**56**) (**57a**) (**57b**)

| | | |
|---|---|---|
| PhMgBr | 88% | 50:50 |
| MeLi/LiBr | 85% | 9:91 |
| $Me_2CuLi$ | 40% | >90:<10 |

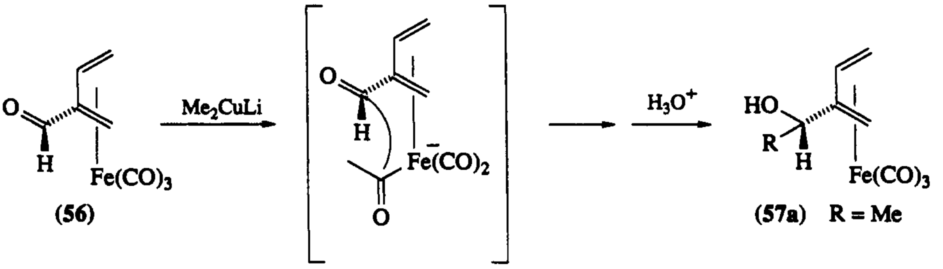

(16)

(**56**) (**58**) (**57a**) R = Me

### 1.4.2.2 Reactions of Ketones

Although unhindered aldehydes are quite susceptible to attack by Gilman cuprates,[8] ketones tend to be far more resistant electrophiles. For example, $Me_2CuLi$ requires temperatures around −10 °C before it will consume, to any significant degree, di-*n*-butyl ketone,[8] while acetophenone gives only 7% of the 1,2-adduct after 24 h at 0 °C.[44] More reactive species, *e.g.* $Bu^n_2CuLi$, are effective above −35 °C,[8] but still a far cry from the −90 °C conditions of aldehydic educts. Not surprisingly, esters are unresponsive at 18 °C towards $Me_2CuLi$, while it takes temperatures in excess of −10 °C for $Bu^n_2CuLi$ to add in a 1,2-manner.[8] Such is not the case, however, with thioesters. As Anderson showed some years ago, thioesters react with lower order cuprates, including $Me_2CuLi$, even at −78 °C (equation 17).[45] Nonetheless, with respect to ketones, conditions are still sufficiently mild such that organocopper 1,2-additions can and have been used to advantage.

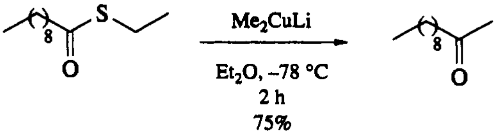

(17)

Most of the early work in this area was done by House[46] in the course of developing a model for cuprate conjugate additions to α,β-unsaturated ketones based on measured (polarographic) reduction potentials.[47] Products of 1,2-addition or reductive elimination (in the case of *e.g.* **59a**, **59b**) can form upon exposure to $Me_2CuLi$ in $Et_2O$ depending upon the α-substitution pattern of the ketone,[48] and whether aryl alkyl[49] or diaryl[50] ketones are involved. Intermediate ketyls are usually produced *via* single-electron transfer, although with more-hindered cases (*e.g.* **60**) additional MeLi is necessary to form the 1,2-adduct.[50] This $Me_2CuLi$/MeLi mixture has been applied to the stereoselective synthesis of axial alcohols by Macdonald and Still.[51] Relative to several of the more common sources of methyl anion, such a cuprate/RLi combination[52] reacts predominantly to deliver the alkyl group from the equatorial face (equation 18).[51,52] The difference between results obtained with RLi or $R_2CuLi$ alone lead to the suggestion that $R_3CuLi_2$ is the species responsible for the observed selectivity. Subsequent work by Ashby, however, who was the first to provide physical evidence for the existence of such higher order cuprates,[53] points to the likely complexation between $R_2CuLi$ and the ketone (*e.g.* **61**) in a Lewis acid–Lewis base sense.[54] The newly activated substrate (**62**) now reacts rapidly with the RLi present, the stereochemistry of addition (favoring **63a** over **63b**) altered with respect to that for RLi alone since the hybridization at the complexed carbonyl carbon has changed, as has its steric environment. The effect is most noticeable in $Et_2O$ but erodes considerably in THF as this solvent is more effective in competing for coordination sites on lithium.[54] Use of MeLi/$LiClO_4$ in $Et_2O$ can effect the same results. Yamamoto's reagent, $RCu\cdot BF_3$, also adds to (**61**), although only a *ca.* 2:1 ratio of axial to equatorial alcohols is obtained.[55]

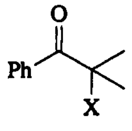

**(59)** **a**: X = OC(O)Me
**b**: X = Br

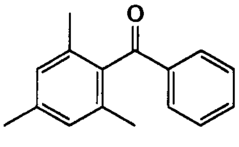

**(60)**

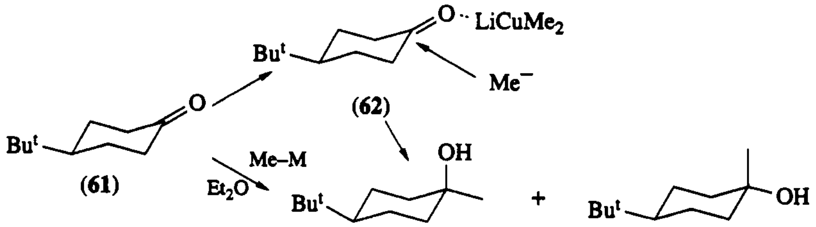

(18)

**(61)** **(62)** **(63a)** **(63b)**

| | |
|---|---|
| M = MgI, 5 °C | 51:49 |
| MgMe | 70:30 |
| Li, –78 °C | 79:21 |
| Li/Me$_2$CuLi, –70 °C | 94:6 |

The (RLi + $R_2CuLi$) mixture was seen by Plumet as a route to the desired tertiary alcohols (**65a**) *via* 1,2-addition to 7-oxabicyclo[2.2.1]hept-5-en-2-one (**64**) from the more-hindered *endo* direction (equation 19).[56] The argument relies on complexation of the carbonyl group and/or ether oxygen with $R_2CuLi$, thereby blocking attack from the *exo* face. While (**65a**) was indeed the major product in all but one case (*i.e.* using PhLi/$Ph_2CuLi$), the supposedly unreactive lower order cuprates themselves gave identical results virtually upon mixing.

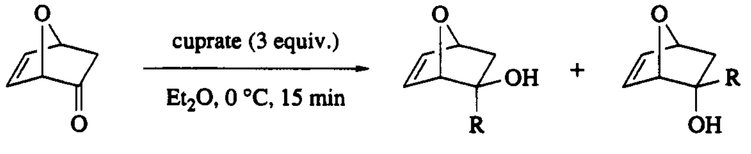

(19)

**(64)** **(65a)** **(65b)**

| *Cuprate* | *Yield* (%) | *Ratio* |
|---|---|---|
| MeLi + Me$_2$CuLi | 80 | 6:1 |
| Me$_2$CuLi | 85 | 6:1 |
| Ph$_2$CuLi | 85 | 6:1 |
| PhLi + Ph$_2$CuLi | 75 | 1:10 |

Preferential 1,2-addition of Gilman's cuprate to a ketone over the usually much more facile 1,4-mode occurs in the case of keto enone (**67**).[57] When Goldsmith and Sakano treated (**67**) with 2 equiv. of $Me_2CuLi$ at –78 °C and quenched the reaction with acetic anhydride, enone (**66**) was formed. At higher temperatures Michael addition begins to take place, although the cuprate also generates products of ketone enolization (**68**) rather than carbon–carbon bond formation (Scheme 10).

Somewhat similar trends have been found by Marino and Floyd concerning their lower order mixed acrylate cuprates (**69**) toward α,β-unsaturated ketones.[58] In $Et_2O$ at –78 °C even simple cyclic enones,

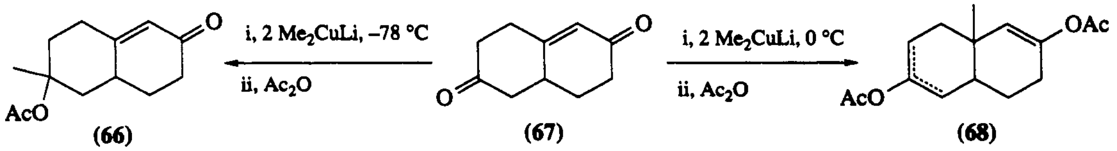

**Scheme 10**

*e.g.* **(70a)** and **(70b)**, give tertiary bisallylic alcohols **(71)** and **(72)**, respectively, in moderate to good yields (equations 20 and 21).

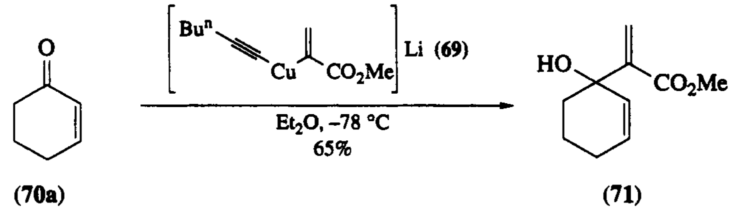

(20)

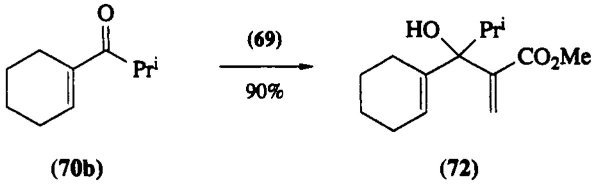

(21)

Although lithium cuprates bearing two alkynic ligands notoriously resist transfer of this group, when admixed with an equal amount of the lithium alkynide (*i.e.* 3RC≡CLi:CuI) exclusive 1,2-addition occurs with cyclic enones.[59] While prior efforts to effect this chemistry in strictly ethereal solvents (dioxane) have been unsuccessful,[60] use of HMPA (~ 20%) as cosolvent now leads to efficient couplings in these cases. The initial products may be isolated as such, or oxidatively worked up to provide, in the case of **(73)**, the rearranged material **(74**; Scheme 11).

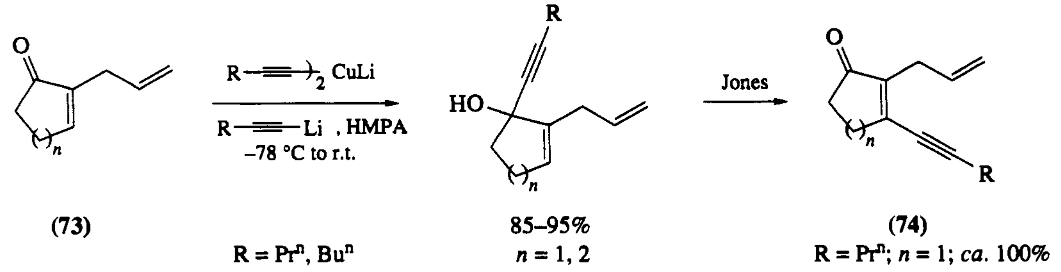

**Scheme 11**

As part of an effort to assess the extent of neighboring group participation in solvolysis reactions of bicyclic systems of type **(76a)**, use of known ketone **(75)** as starting material has been examined.[61] Both MeLi and MeMgI give excellent percentages of the undesired isomer **(76b)**. Switching to $Me_2CuLi$ is based on the notion that electron transfer[46–50] might prevail so as to provide a different stereochemical outcome. Indeed, with this reagent under otherwise identical conditions, net formal attack by methyl from the opposite (desired) direction is realized (equation 22).[61]

The direct conversion of a ketone carbonyl to a *gem*-dimethyl moiety has been accomplished, interestingly enough (*cf.* reactions of **67**[57]) on bicyclic α,β-unsaturated ketones containing a pendant COSR′ group, as in **(78)**, **(79)** and **(80)** (Scheme 12).[62] In sharp contrast, the *O*-ester analog of **(77)** (*i.e.* **78**, X = OEt) leads to a 3:1 mix of tertiary alcohols **(77a)** and **(77b)**, respectively. Intermediate **(82**; Scheme 13) is postulated as the precursor to **(81)**, as its formation from **(78**, X = S) leads to the observed product upon treatment with $Me_2CuLi$.

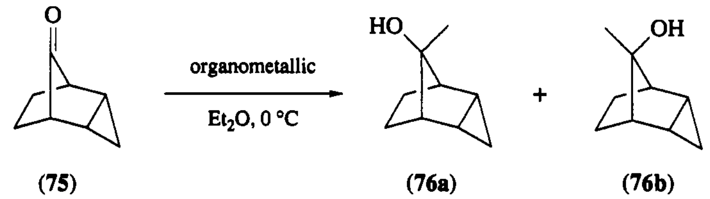
organometallic
$Et_2O$, 0 °C
HO
OH
+
(75)
(76a)
(76b)

(22)

| | |
|---|---|
| MeLi | 5:95 |
| MeMgI | 10:90 |
| $Me_2CuLi$ | 92:8 |

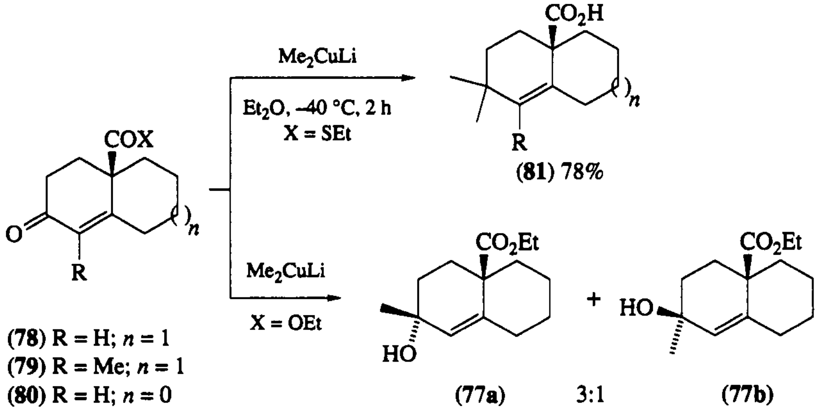
COX
O
R
n
$Me_2CuLi$
$Et_2O$, –40 °C, 2 h
X = SEt
$CO_2H$
n
R
(81) 78%
$Me_2CuLi$
X = OEt
$CO_2Et$
HO
+
HO
$CO_2Et$
(77a)
3:1
(77b)

(78) R = H; $n$ = 1
(79) R = Me; $n$ = 1
(80) R = H; $n$ = 0

Scheme 12

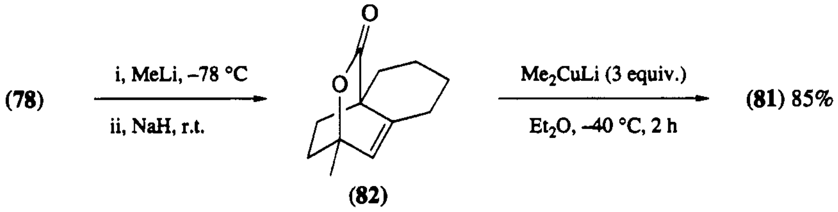
(78)
i, MeLi, –78 °C
ii, NaH, r.t.
O
O
$Me_2CuLi$ (3 equiv.)
$Et_2O$, –40 °C, 2 h
(81) 85%

(82)

Scheme 13

Transmetallation of a lithium enolate to a copper enolate in Davies' iron carbonyl system $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COEt]$ allows for highly stereoselective additions to symmetrical ketones.[63] Lithium enolates (**83**) alone give 2:1 to 6:1 ratios of (**84a**, *RR,SS*) and (**84b**, *RS,SR*), and additives (*e.g.* $SnCl_2$, $BF_3$, $Et_2AlCl$, $ZnCl_2$) either completely suppress the 1,2-addition or do little to influence the diastereoselectivity. Addition of CuCN (1 equiv.), however, gives in most cases 10:1 to 60:1 product ratios (Scheme 14).

A deacylation reaction has been effected by a reactive lower order cuprate when its reaction partner has no other pathway available. Thus, Kunieda and Hirobe have found that (–)-3-ketopinyl-2-oxazolone (**85**) undergoes smooth cleavage of the chiral auxiliary to afford the heterocycle (**86**), subsequent elaboration of which leads to either (2*S*,3*R*)-3-hydroxyglutamic acid (**87**) or (3*R*,4*R*)-4-amino-3-hydroxy-6-methylheptanoic acid (**88**) as their hydrochloride salts (Scheme 15).[64]

## 1.4.3 1,2-ADDITIONS TO IMINES, NITRILES AND AMIDES

### 1.4.3.1 Reactions of Imines

Studies on the additions of organocopper complexes across carbon–nitrogen double bonds are relatively few in number. In terms of stereochemical control in substrates bearing α- and/or β-chiral centers, the information available is even more sparse. That organocopper reagents do add to Schiff bases was shown

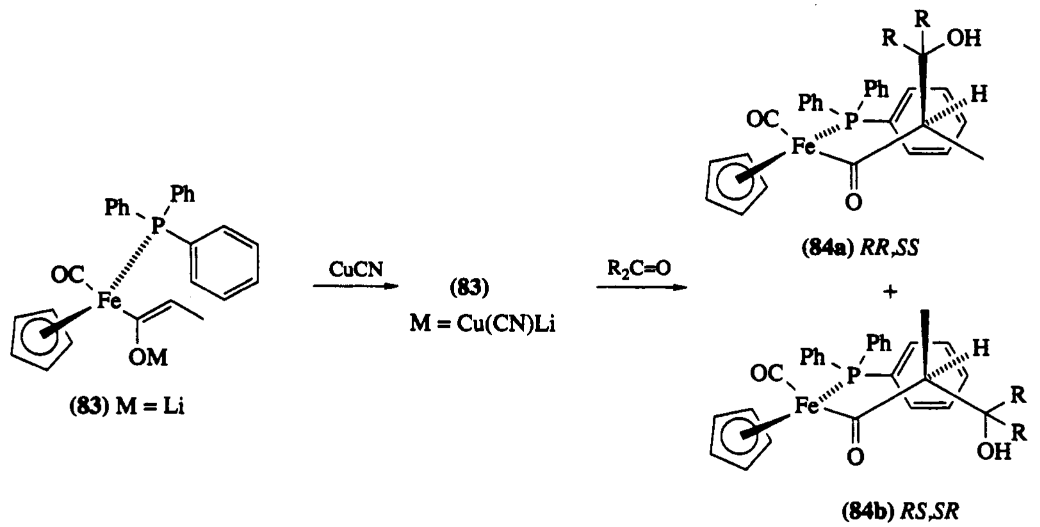
Ph
Ph
P
OC
Fe
OM
(83) M = Li
CuCN
(83)
M = Cu(CN)Li
$R_2C{=}O$
R
R
OH
Ph
Ph
P
OC
Fe
H
O
(84a) *RR,SS*
+
Ph
Ph
P
OC
Fe
H
R
R
OH
O
(84b) *RS,SR*

| *Ketone* | *Ratio (71a):(71b)* | *Yield (%)* |
|---|---|---|
| 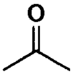 | >40:1 (3:1)[a] | 61 |
| 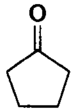 | >60:1 (4:1)[a] | 71 |
| 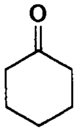 | 10:1 (2:1)[a] | 68 |

[a] Ratio from reactions of Li enolates

Scheme 14

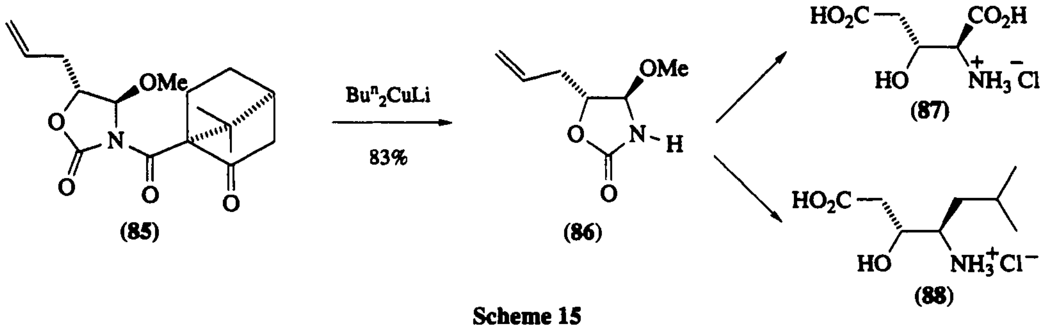
OMe
O
N
O
O
O
(85)
$Bu^n_2CuLi$
83%
OMe
O
N-H
O
(86)
$HO_2C$
$CO_2H$
HO
$\overset{+}{N}H_3\overset{-}{C}l$
(87)
$HO_2C$
HO
$NH_3^+Cl^-$
(88)

Scheme 15

by Akiba, most notably where acidic α-hydrogens are present in these substrates (equation 23).[65] The low basicity of $RCu{\cdot}BF_3$, prepared from CuI and RMgX in THF at –30 °C to which is added $BF_3{\cdot}Et_2O$ (1 equiv.), precludes such typical side reactions as metalloenamine formation that is observed with Grignards, the low yields of 1,2-adducts obtained from alkyl- or aryl-lithiums, and reductive dimerization. Moderate to good yields of secondary amines are normally received from unhindered aldimines, although α-branched aldimines give none of the corresponding products. This limitation can be overcome, however, using $Bu^n_2CuLi{\cdot}BF_3$ (1 equiv.) or the magnesium analog $Bu^n_2CuMgBr{\cdot}BF_3$ (equation 24). The Lewis acid is essential for success in these reactions, as no 1,2-addition is to be expected in its absence. Unfortunately, thus far there has been no success in similar reactions of ketimines.

Attempts to induce asymmetry at an imine carbon using homochiral amines to form Schiff bases followed by 1,2-additions with organocopper reagents has not produced a viable method as yet. Yamamoto

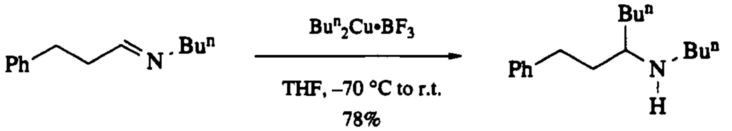
Ph
N
Bu$^n$
Bu$^n_2$Cu•BF$_3$
THF, -70 °C to r.t.
78%
Ph
Bu$^n$
N
Bu$^n$
H

(23)

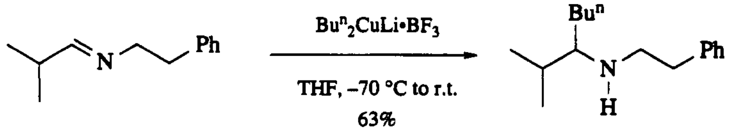
N
Ph
Bu$^n_2$CuLi•BF$_3$
THF, -70 °C to r.t.
63%
Bu$^n$
N
H
Ph

(24)

has found that imine (**89**) reacts with Bu$^n_2$CuLi·BF$_3$ to give an 82:18 mixture of Cram (**90a**) and anti-Cram (**90b**) products (equation 25).[66] Much better results have been obtained using allylic boranes (*e.g.* allyl-9-BBN), where ratios between 94:6 and 100:0 have been achieved. Of course, these borane-mediated allylations share in the benefits associated with a highly ordered cyclic transition state (**91**) not involved with the analogous copper chemistry.

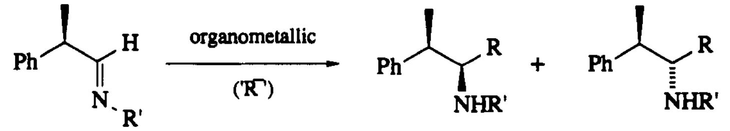
Ph
H
N
R'
organometallic
('R')
Ph
R
NHR'
+
Ph
R
NHR'

(25)

(**89**) R' = CHMePh (**90a**) (**90b**)

Bu$_2$CuLi•BF$_3$ 82:18

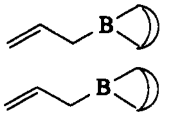

, R' = Pr$^n$ 96:4

, R' = Pr$^i$ 100:0

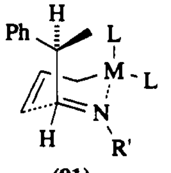

(**91**)

Claremon has briefly looked at the effect of catalytic CuI on the MeLi addition to glyceraldehyde acetonide *N,N*-dimethylhydrazone (**92**).[67] While the organolithium itself leads to a preference for the *anti* product (**93a**) on the order of 3:1 to 6:1 (depending upon the quantity of MeLi and the temperature), the cuprate reverses the ratio to favor the *syn* isomer (**93b**; equation 26). Acyclic α-alkoxyhydrazones, surprisingly, are untouched by organocopper reagents, while organolithiums give excellent (≥97:3) *anti* selectivities in high yields (85–98%).

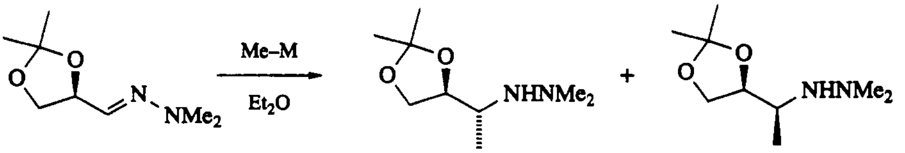
O
O
N
NMe$_2$
Me-M
Et$_2$O
O
O
NHNMe$_2$
+
O
O
NHNMe$_2$

(26)

(**92**) (**93a**) (**93b**)

| | |
|---|---|
| MeLi, -10 to 25 °C, 95% | 3:1 |
| MeLi (5 equiv.), -55 °C, 75% | 6:1 |
| MeLi + CuI (0.1 equiv.), -20 °C, 46% | 1:3 |

Ketoximes have been synthesized by Fujisawa using a catalytic CuI/Grignard addition to *aci*-nitroiminium chlorides, formed by *O*-acylation of a nitroalkane with *N,N*-dimethylchloromethyleniminium chloride.[68] Numerous organomagnesium reagents can be employed, and yields of products resulting from 1,2-addition followed by elimination of DMF range from 61–97% (Scheme 16a).

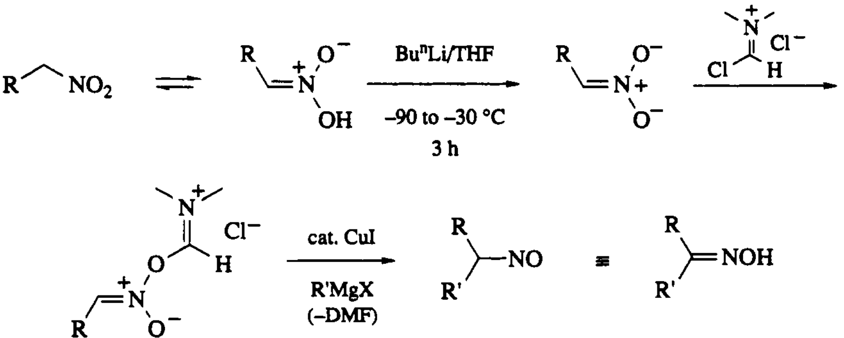

**Scheme 16a**

Copper(I) driven activation of the carbon–nitrogen double bond towards addition by RLi takes place in $Et_2O$, but not THF, where the solvent of poorer Lewis basicity does not compete for nitrogen complexation (*cf.* **95**). On this basis, Bertz converted the bis(tosylhydrazone) (**94**), *via* reaction with '$Me_3CuLi_2$', to the *gem*-dimethylated product (**96**; Scheme 16b).[69] Although several other pathways associated with the various intermediates are followed to account for the five products observed in varying amounts, this study does suggest that otherwise innocuous, soluble copper(I) species may be useful additives for nucleophilic additions to imines and related functional groups.

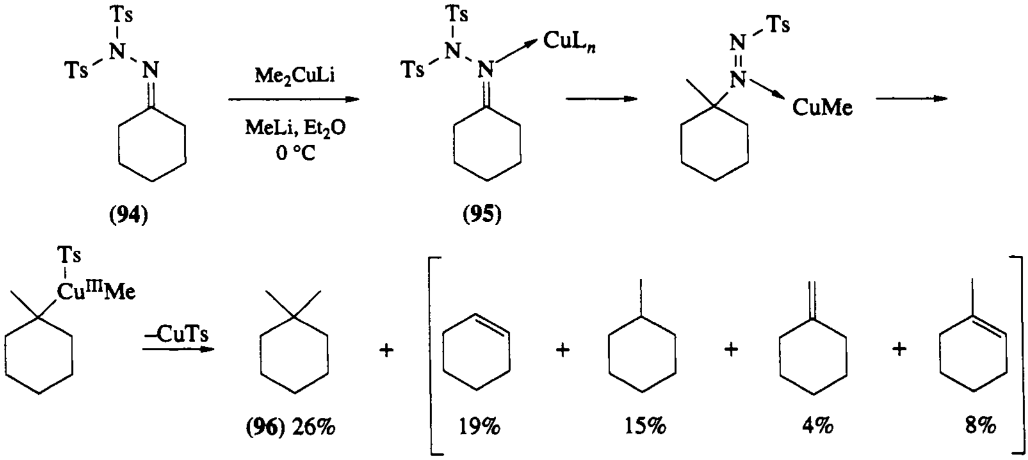

**Scheme 16b**

1,2-Additions of higher order cuprates to acylimines (**97**) provide a novel route to α-alkylated amino acid derivatives (**98**; equation 27).[70] Following generation of amide-stabilized systems (**97**) *via* action of singlet molecular oxygen on trisubstituted imidazoles,[71] products (**98**) can be isolated in 57–75% yields. Since $Bu^nLi$ and $Bu^sLi$ alone (*versus* $Bu^n_2Cu(CN)Li_2$ and $Bu^s_2Cu(CN)Li_2$) raise the yields to 86% and 61%, respectively, there seems to be no particular advantage in using a cuprate, at least for the functionality present in (**97**).

Steglich, however, has found that higher order cuprates are the reagents of choice for additions to acylimines of type (**100**), generated *in situ* from α-bromo amino acid derivatives (**99**).[72] Grignard reagents give modest yields at best, and in some cases fail altogether. Ligands transferred from copper to carbon include primary and tertiary alkyl, phenyl, 1-naphthyl and vinyl, with yields of acylated amino acid esters (**101**) ranging from 30–83%. With $(vinyl)_2Cu(CN)Li_2$, the initial adduct (**101**, R = vinyl), formed at -100 °C, can be easily isomerized to the dehydro derivative (**102**) simply upon warming the reaction mixture to room temperature (Scheme 17).

Similar studies by O'Donnell using the α-acetoxy function as the leaving group (along with the benzophenone Schiff base in **103**),[73] and by Williams on a bromide,[74] come to the same conclusion that $R_2Cu(CN)Li_2$ affords the best results (equation 28). Reactions of the former substrates are highly

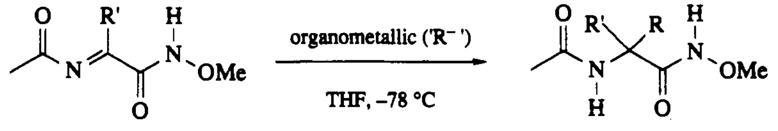

(97) (98) (27)

| | |
|---|---|
| $Bu^n_2Cu(CN)Li_2$ | 75% |
| $Bu^s_2Cu(CN)Li_2$ | 57% |
| $Bu^nLi$ | 86% |
| $Bu^sLi$ | 61% |

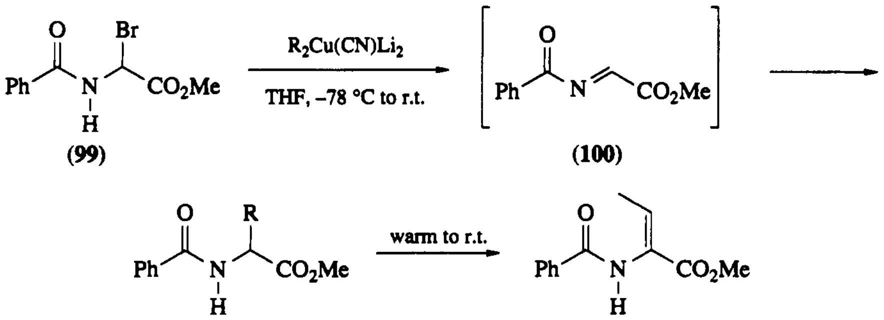

(99) (100) (101) R = vinyl (102)

Scheme 17

sensitive to several parameters, including solvent, temperature and mode of addition. In THF at *ca* ≤5 °C using inverse addition, moderate to good yields of (**104**) are obtained. In $Et_2O$, only products of reduction are observed.

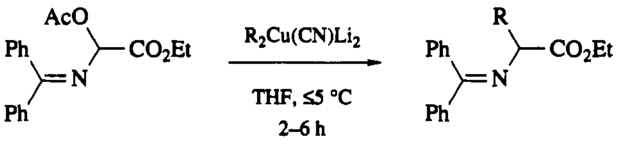

(103) (104) (28)

R = $Bu^n$, $Bu^t$, thienyl, naphthyl

Related 1,2-additions to imines in the β-lactam area employing organocuprates have also met with considerable success.[75–79] Net substitution reactions, proceeding *via* intermediate imino derivatives, have been achieved with lithium diallyl- and dialkyl-cuprates on educts such as (**105**)[76] and (**106**).[77] When a stereochemical label is present as in (**107**)[78] and (**108**),[79] the major products reflect *trans* addition to imines (**109**) and (**110**), respectively (Scheme 18).

### 1.4.3.2 Reactions of Nitriles

Until recently, organocopper-mediated 1,2-additions to nitriles of any consequence were unknown. Most of those reported occurred as undesirable pathways in attempted 1,4-additions to α,β-unsaturated substrates. According to the House model, correlating reduction potentials ($E_{red}$) with substrate reactivity toward lithium cuprates,[47] prior complexation of the reagent with doubly bonded oxygen, rather than nitrogen (presumably of either $sp^2$ or $sp$ hybridization), is an essential ingredient irrespective of $E_{red}$. Hence, attempted reaction of cinnamonitrile (**111**) with $Me_2CuLi$ failed.[47] Years later, reinvestigation of this process with a higher order reagent did slowly produce a product; however, the product turned out to be methyl ketone (**112**), derived from cuprate 1,2-addition followed by hydrolysis of the intermediate imine (equation 29).[80] Nonetheless, this reaction was not synthetically useful, nor was the procedure general, as the *n*-butyl analog led to (**113**) along with several unidentified compounds with the same substrate under similar conditions.

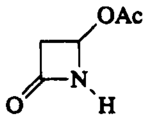

**(105)**

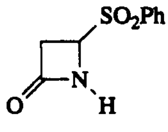

**(106)**

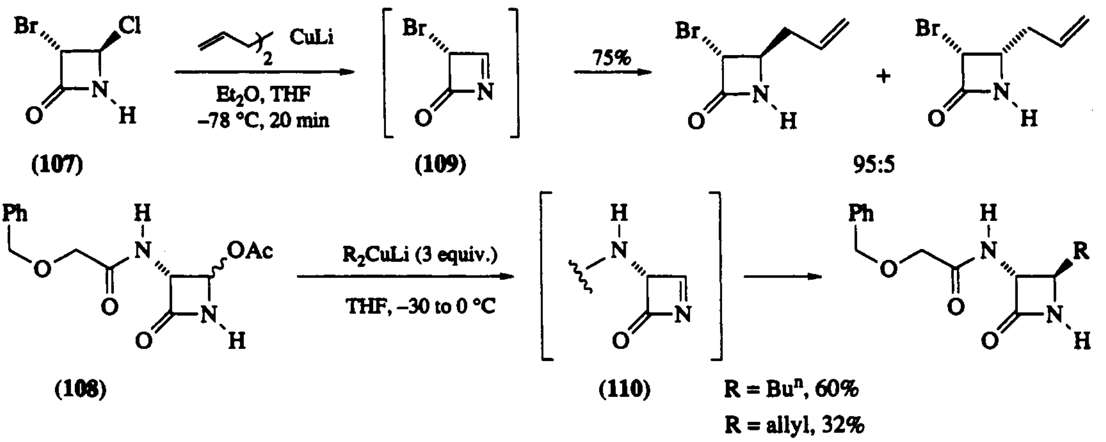

Scheme 18

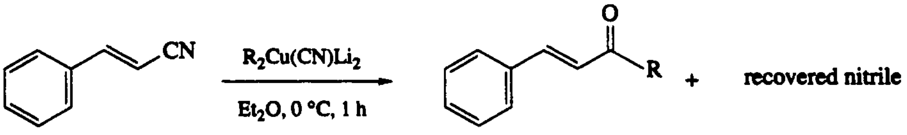

(111)

(112) R = Me

(113) R = Bu$^n$

(29)

Introduction of an additive, *e.g.* TMS-Cl, did lead to good yields of an isolable product; however, the product was shown by Alexakis to be the dialkylated ketone (*e.g.* **114**) in all cases studied (equation 30).[81] Even the softer organometallic, Yamamoto's reagent '$RCu{\cdot}BF_3$', gave mixtures of mono- and dialkylated ketones with acrylonitrile and 1-cyclohexenecarbonitrile.[82]

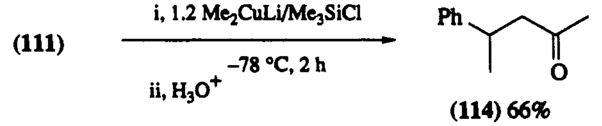

(114) 66%

(30)

A procedure which seems to skirt these problems, as described by Hall, invokes a catalytic copper salt in the presence of a Grignard reagent in refluxing THF, which affords good yields of adducts.[83] The nature of the copper(I) source is not crucial (CuCl, CuBr, CuI, CuCN were all compared), and depending upon manipulation of the initial product, ketones (from hydrolysis), sterically hindered ketimines (from protonolysis) or primary amines (from reduction) can be realized. Since reagents formed from either a 1:1 RMgX:CuX (*i.e.* $RCu{\cdot}MgX_2$) or 2:1 (*i.e.* $R_2CuMgX{\cdot}MgX_2$) ratio are clearly not responsible for the chemistry observed, higher order reagents have been suggested as the reactive species (Scheme 19a).

### 1.4.3.3 Reactions of Amides

Considering the proficiency associated with additions of organolithium and organomagnesium reagents to *N*,*N*-disubstituted amides as a means of preparing aldehydes and ketones,[84] it is not surprising that organocopper reagents are not known to function in this capacity. However, imine formation from amides is another matter, and Feringa has recently demonstrated that lower order lithium and magnesium cuprates can indeed be used with *N*-trimethylsilyl-*N*-alkylformamides to arrive at this functional group.[85]

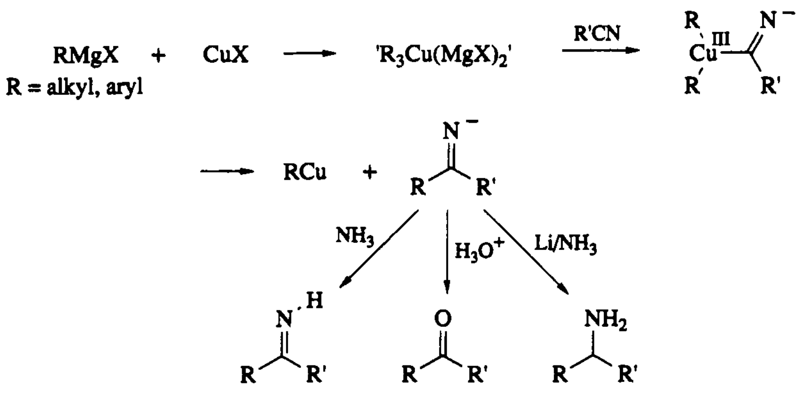

Scheme 19a

Treatment of formamide (**115**) with either $LiCuR_2$ or catalytic CuBr/RMgBr in THF between –80 °C and –20 °C, followed by aqueous work-up, affords aldimine (**116**) exclusively of (*E*)-geometry (equation 31).

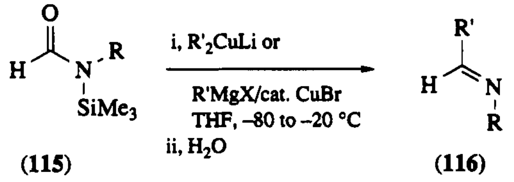

(31)

$R = Bu^n, Bn; R^1 = Bu^n$; 92%

By switching to the corresponding *N*-acrylamide (**115**, R = Ph), secondary amines (**120**) are the major products resulting from double 1,2-additions (Scheme 19b). Presumably, the initial 1,2-adduct (**117**) undergoes a silicon migration from nitrogen to oxygen, the intermediate anion (**118**) being stabilized by the aromatic ring, which subsequently eliminates to reform imine (**119**) now susceptible to a second-stage alkylation. This secondary process does not occur with Grignard reagents, and thus arylaldimines (**119**) are formed in high yields using (**115**, R = Ph) and various RMgX in THF, without the presence of copper(I) salts.

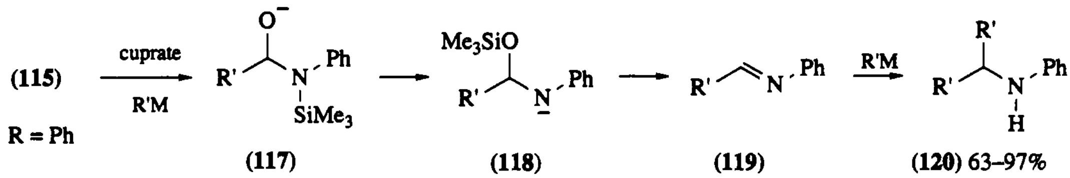

$R' = Et, Bu^n, n\text{-}C_{12}H_{25}$

Scheme 19b

## 1.4.4 APPLICATIONS TO NATURAL PRODUCT SYNTHESIS

As alluded to earlier, in general, 1,2-additions by organocopper reagents especially on more complex, multifunctionalized substrates are statistically few in number compared with the ever popular alkylation,[1] 1,4-addition,[2] and carbocupration[86] processes. Nonetheless, the examples which follow provide strong testimony to the value of organocopper intermediates as an alternative means of delivering a carbanion of attenuated reactivity in a controlled fashion.

Development of a novel route to the C-7 to C-13 portion (*e.g.* **122**) of erythronolides A and B (*i.e.* **121a** and **121b**) by Burke makes use of a stereoselective addition of an isopropenyllithium-derived cuprate to homochiral aldehyde (**123**) as a first, key step (Scheme 20).[87] Formation of allylic alcohol (**124**) as the major product presumably reflects a β chelation controlled pathway (*vide supra*).[9] Subsequent handling of (**124**), which included as the second critical step a dioxanone to dihydropyran enolate Claisen rearrangement,[88] produces three key subunits, including (**122**).

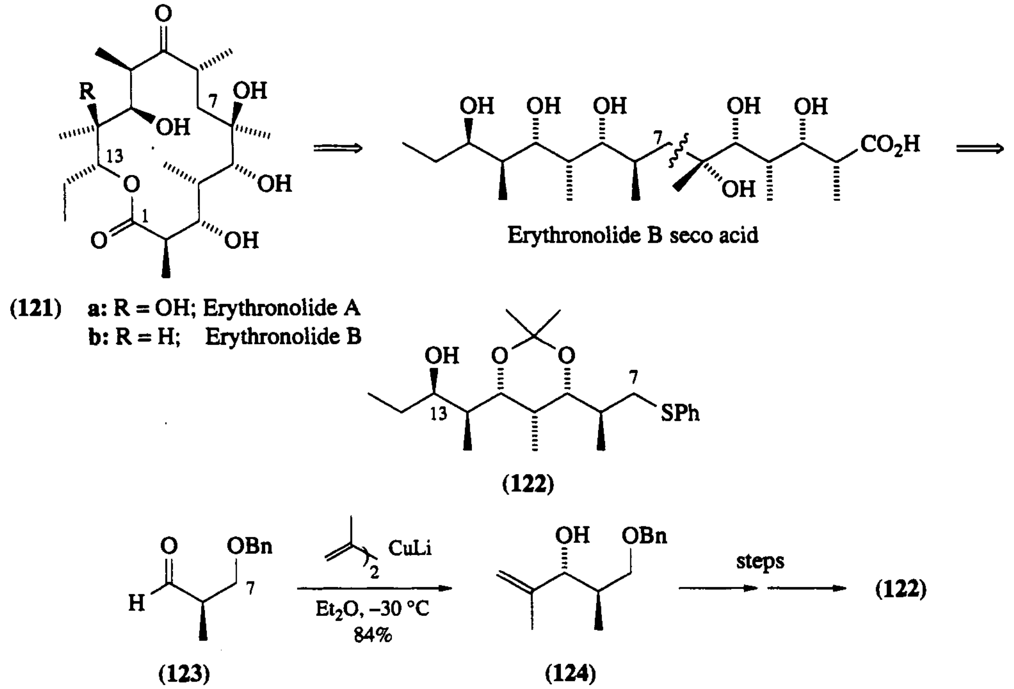

Scheme 20

A similar strategy invoking these two valued processes has also been applied to the 'left wing' of the ionophoric antibiotic indanomycin (X-14547A),[89] and more generally as an entry to *C*-pyranosides (**125**; Scheme 21).[90] Treatment of aldehyde (**126**), itself prepared from elaboration of (**127**), likewise formed from (vinyl)$_2$CuLi addition to aldehyde (**128**),[89] with the Gilman reagent formed from CuI·PBu$_3$ and (*E*)-propenyllithium in Et$_2$O at low temperature affords a 24:1 ratio of alcohols (**129a**) and (**129b**) in good yield (Scheme 22).[89] Unfortunately (**129a**) is of the undesired stereochemistry and necessitates an oxidation (PCC, 93%)–reduction (Zn(BH$_4$)$_2$, 88%) sequence to arrive at (**129b**) (>100:1 **129b**:**129a**). Related model studies on an isopropyl analog of (**126**) (*cf.* **130**) show that the cuprate 1,2-addition approach to (**131**), with or without an intervening oxidation/reduction, could be useful for obtaining dioxanones (**132**) and (**133**) as precursors to *C*-glycosides (**134**) and (**135**), respectively. Thus, individual exposure of (**132**) and (**133**) to the Ireland ester enolate Claisen reorganization,[88] albeit at abnormally high temperatures (*ca.* 110°C for 3–4 h, affords the desired materials following aqueous acid hydrolysis and treatment with ethereal diazomethane of the initially formed silyl esters (Scheme 23).[90]

Indanomycin has also been a target of the Boeckman group, which, while employing a quite different approach to the pyran nucleus, begins the route with a cuprate 1,2-addition to the readily available homochiral aldehyde (**136**).[91] An excellent yield of two diastereomers (**137**) was obtained, epimeric at the carbon bearing the methyl group brought in as part of the cuprate (equation 32). Thus, as confirmed by $^1$H NMR on the Mosher esters of (**137**), the stereoselectivity of the cuprate addition was >98%.

Stereochemical issues associated with polyene macrolide construction, attention being focused on the chiral centers representing C-34 to C-37 in amphotericin B in particular, have been addressed by McGarvey, wherein 1,2-additions by Me$_2$CuLi play an important role.[92] L-Aspartic acid can be parlayed into

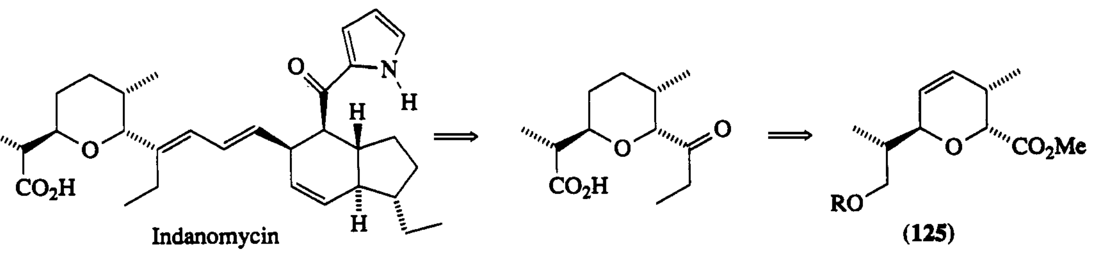

Scheme 21

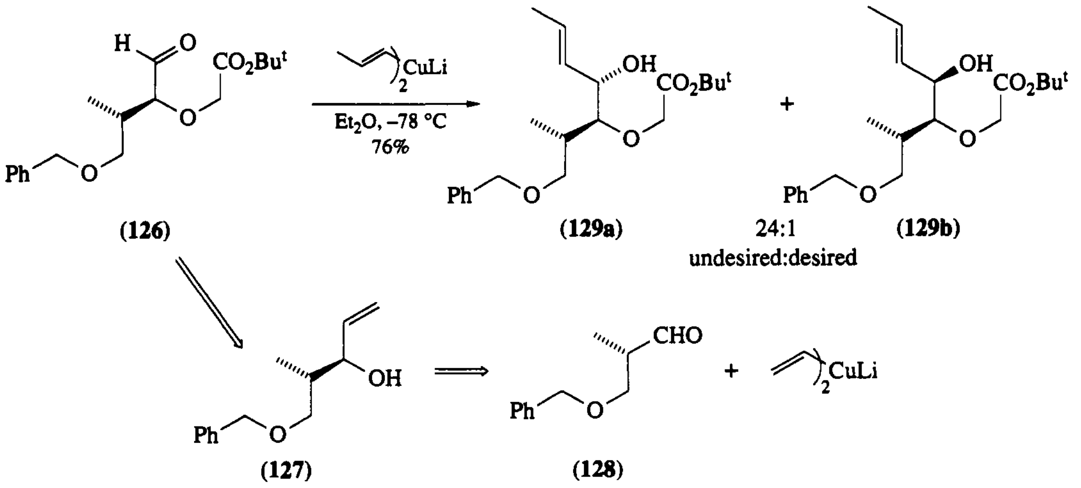
CO₂Buᵗ
CuLi
Et₂O, −78 °C
76%
OH
Ph
(126)
(129a)
24:1
undesired:desired
(129b)
(127)
CHO
(128)

Scheme 22

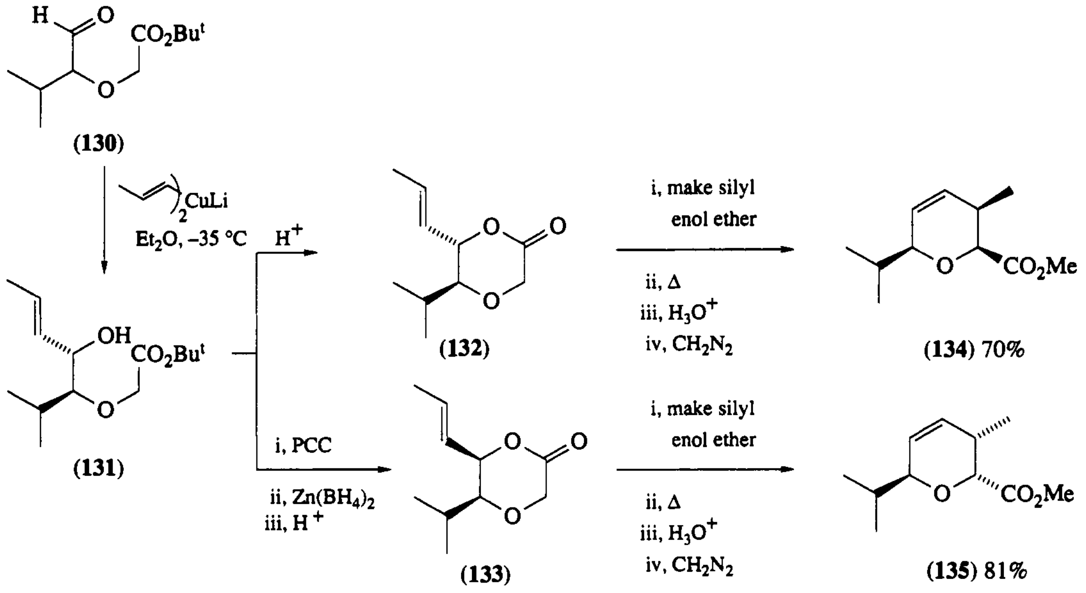
(130)
CuLi
Et₂O, −35 °C
H⁺
i, PCC
ii, Zn(BH₄)₂
iii, H⁺
(131)
(132)
(133)
i, make silyl enol ether
ii, Δ
iii, H₃O⁺
iv, CH₂N₂
CO₂Me
(134) 70%
(135) 81%

Scheme 23

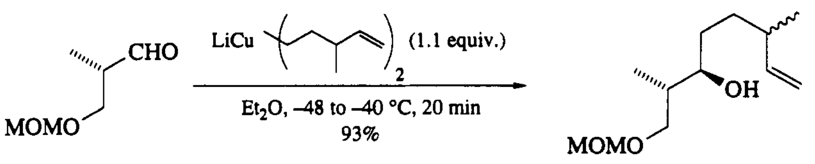
CHO
MOMO
LiCu
(1.1 equiv.)
Et₂O, −48 to −40 °C, 20 min
93%
OH

(32)

(136) (137) 1:1 mix

heterocyclic thioester (**138**) by a series of efficient steps. α-Methylation by either a chelation-controlled or stereoelectronically controlled pathway permits selective generation of the corresponding *anti* (**139a**) or *syn* (**139b**) isomer, respectively (Scheme 24). While DIBAL reduction of each leads cleanly to the aldehyde product (**140**), the greater reactivity of thioesters (relative to esters) towards $Me_2CuLi$ (*vide supra*)[45] permits realization of the ketones (**141**) without epimerization in either type of transformation. Copper-catalyzed reactions using RMgBr/CuBr·$Me_2S$ on (**138**) in THF at −23 °C are also effective (90%).

With aldehydes (**140a**) and (**140b**) in hand, further 1,2-additions of $Me_2CuLi$ have been examined and found to afford results (Scheme 25) opposite to those obtained with, for example, MeMgBr, in good yields (>85%). The preference is explained on the basis of attack onto the chelated bicyclic compound

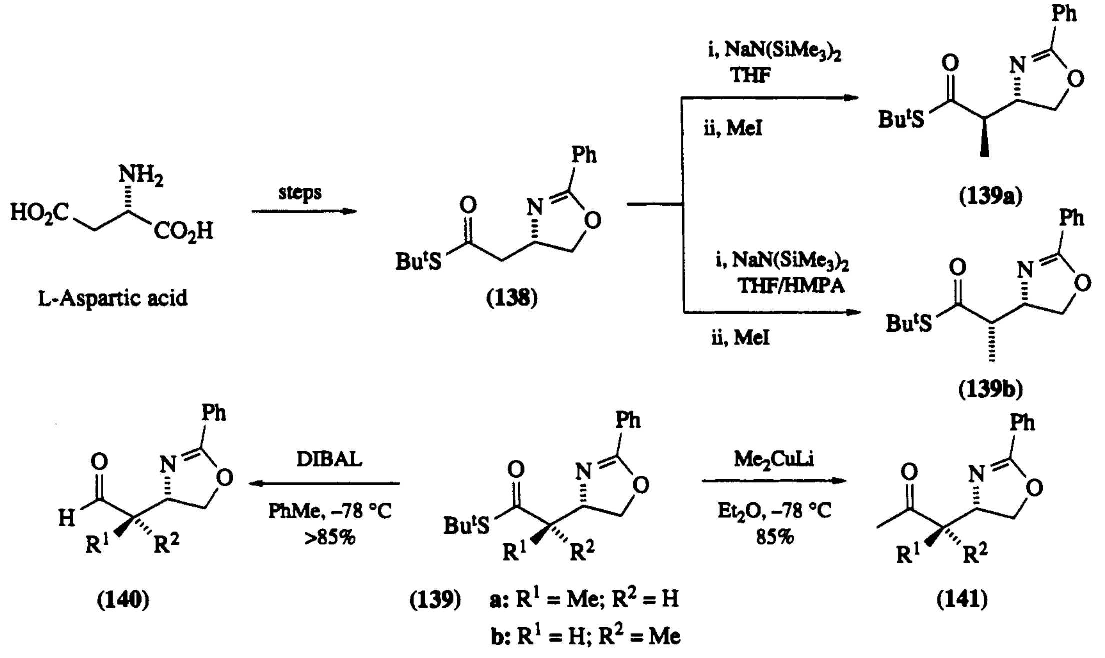
HO2C
NH2
CO2H
L-Aspartic acid
steps
O
N
Ph
O
Bu'S
(138)
i, NaN(SiMe3)2
THF
ii, MeI
i, NaN(SiMe3)2
THF/HMPA
ii, MeI
(139a)
(139b)
DIBAL
PhMe, –78 °C
>85%
Me2CuLi
Et2O, –78 °C
85%
H
R1
R2
(140)
(139) a: R1 = Me; R2 = H
b: R1 = H; R2 = Me
(141)

**Scheme 24**

**(142)** from the axial direction with smaller nucleophiles, while the bulkier cuprate comes in from the bottom to avoid a 1,3-diaxial interaction.

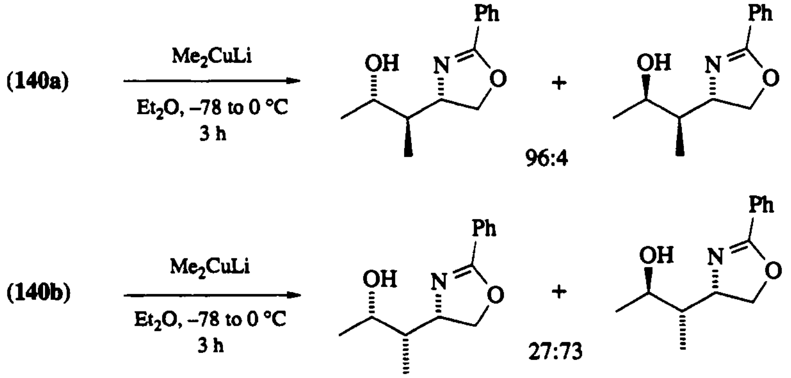
(140a)
Me2CuLi
Et2O, –78 to 0 °C
3 h
OH
N
O
Ph
+
96:4
(140b)
Me2CuLi
Et2O, –78 to 0 °C
3 h
+
27:73

**Scheme 25**

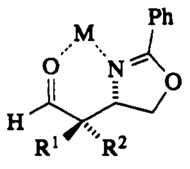
M
O
N
Ph
O
H
R1
R2

≡

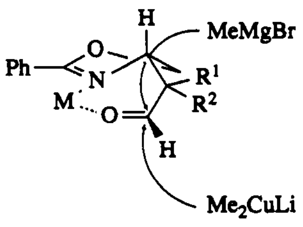
H
MeMgBr
Ph
O
N
M
O
R1
R2
H
Me2CuLi

**(140)** **(142)**

As part of an extensive campaign *en route* to milbemycin $\beta_3$, Smith's synthesis of the 'northern hemisphere' **(143)** relied on the Ireland ester enolate Claisen rearrangements[58] of both diastereomers **(144a)** and **(144b)**.[93] These esters came about from the additions of isopropenyl nucleophiles to aldehyde **(145**; equation 33). The corresponding Grignard reagent added to **(145)** to ultimately give a 2:1 mixture of **(144a)** and **(144b)**, respectively. Although each product could be utilized as part of their 'divergent–

convergent maneuver',[93] a more direct route to (**144b**) was sought. While the reaction of (**145**) with isopropenyllithium occurred in a nondiscriminatory manner, the corresponding lithium cuprate gave a much-improved 7:1 (**144b**):(**144a**) ratio (equation 34). Chelation associated with the β-alkoxyspiroketal oxygen(s), as in the six-membered ring state (**146**), presumably encourages pseudoaxial attack to give mainly (**144b**).

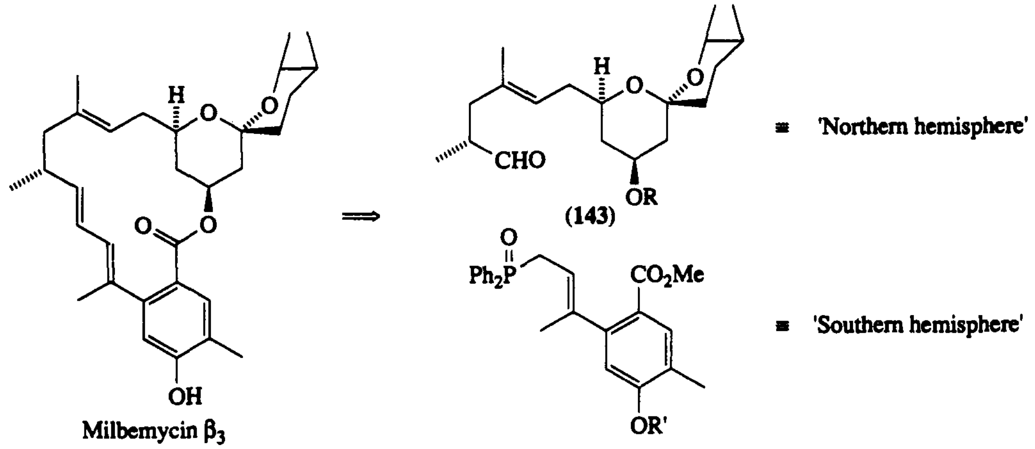
H
O
O
OH
H
O
O
CHO
OR
O
$Ph_2P$
$CO_2Me$
OR'
≡ 'Northern hemisphere'
≡ 'Southern hemisphere'

Milbemycin $\beta_3$

(**143**)

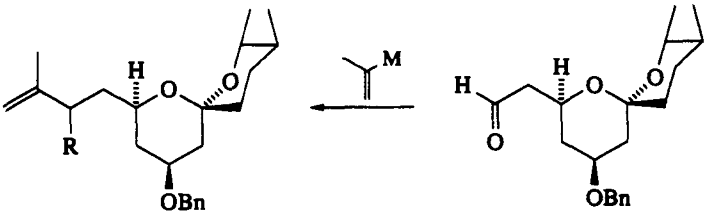
H
O
O
R
OBn
M
H
H
O
O
O
OBn

(33)

(**144**) **a**: R = α-$EtCO_2$
**b**: R = β-$EtCO_2$

(**145**)

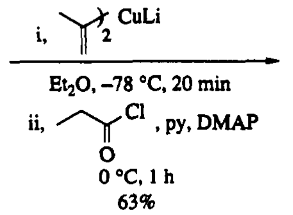
i, CuLi 2
$Et_2O$, −78 °C, 20 min
ii, Cl, py, DMAP
O
0 °C, 1 h
63%

(**145**) → (**144a**) + (**144b**) (34)
1:7

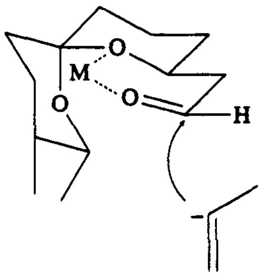

(**146**)

An alternative route to milbemycin β3 by Baker relies on a straightforward sequence of steps to obtain homochiral alkyne (**150**), beginning with (*S*)-methyl 3-hydroxy-2-methylpropionate (**147**).[94] A Gilman cuprate delivers the methyl group to (**148**) in a chelation-controlled manner resulting in the *threo* (*anti*) product (**149**) in high yield (Scheme 26). Coupling of (**150**) with lactone (**151**) to give (**152**), and further handling to give intermediate (**153**),[95] leads to a formal total synthesis (Scheme 27).

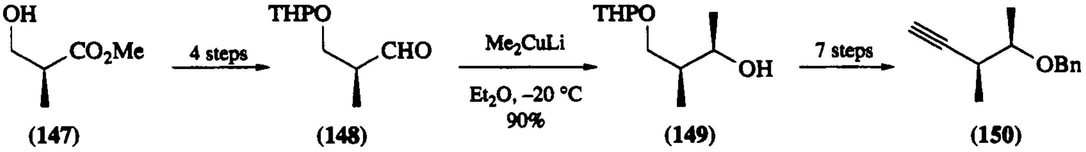
OH
CO2Me
4 steps
THPO
CHO
Me2CuLi
Et2O, –20 °C
90%
THPO
OH
7 steps
OBn
(147)
(148)
(149)
(150)

**Scheme 26**

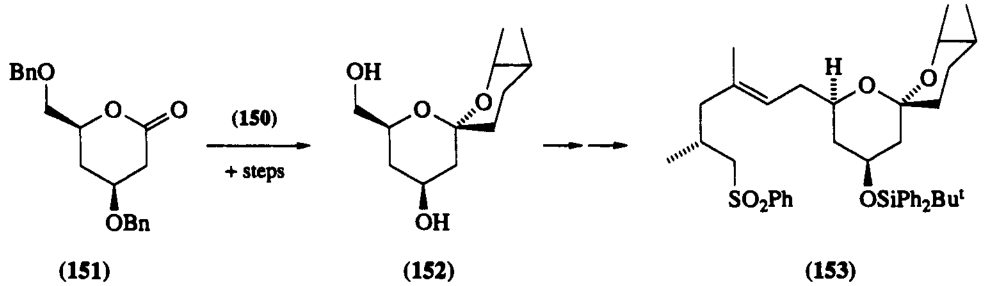
BnO
O
O
OBn
(150)
+ steps
OH
O
O
OH
H
O
O
SO2Ph
OSiPh2Bu^t
(151)
(152)
(153)

**Scheme 27**

Polyether antibiotic X-206, one of the first examples of this venerable class of natural products discovered close to four decades ago,[96] has recently yielded to total synthesis by Evans and coworkers.[97] Assemblage of the left half portion of the ionophore (*i.e.* **154**) requires the adjoining of two substantial homochiral pieces (**155**) and (**156**) such that the (11*R*)-configuration is generated as the C(11)—C(12) bond is made. Use of the organolithium, itself derived from (**156**), affords mainly the (11*S*)-isomer by a factor of 2:1. Incorporation of the organolithium into the higher order cuprate (**157**),[5] however, leads to clean coupling of these segments in not only excellent isolated yield, but with a 49:1 preference for the desired *anti* relationship found in (**158**; equation 35).

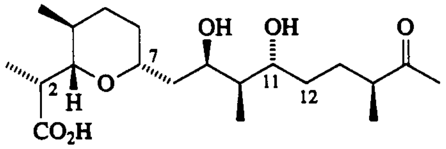
7
2
H
O
CO2H
OH
OH
11
12
O

**(154)**

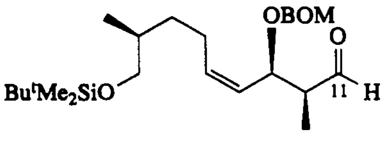
OBOM
O
Bu^tMe2SiO
11
H

**(155)**

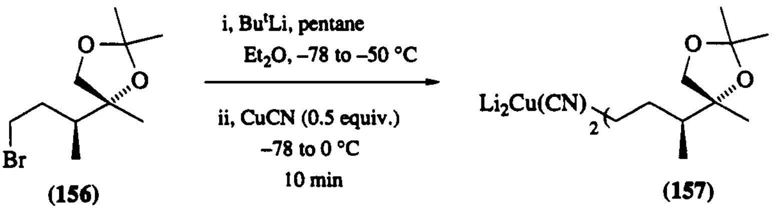
O
O
Br
(156)
i, Bu^tLi, pentane
Et2O, –78 to –50 °C
ii, CuCN (0.5 equiv.)
–78 to 0 °C
10 min
Li2Cu(CN)
2
O
O
(157)

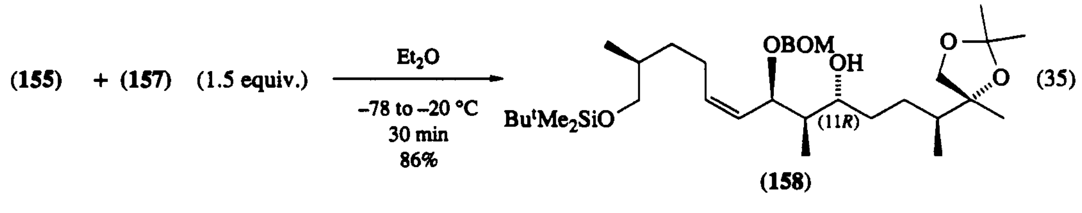
(155)
+
(157)
(1.5 equiv.)
Et2O
–78 to –20 °C
30 min
86%
Bu^tMe2SiO
OBOM
OH
(11R)
O
O
(35)
(158)

As part of an iterative sequence involving successive sigmatropic rearrangements with intervening chelation-controlled additions of vinyl nucleophiles, Kallmerten and Balestra have developed an effective combination for acyclic stereocontrol, successfully applied to the synthesis of the tocopherol side chain (**159**).[98] 1,2-Addition of a $MgBr_2{\cdot}Et_2O$-modified (*E*)-1-propenyllithium-derived reagent to aldehyde (**160**) in Et$_2$O at –78 °C gives a (**161a**):(**161b**) ratio in excess of 50:1 (equation 36). Subsequent acylation to (**162**) sets the stage for the glycolate Claisen rearrangement[99] of the preformed silyl enol ether, the product from which is taken on to (+)-(**159**).

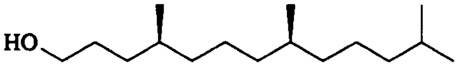

(**159**)

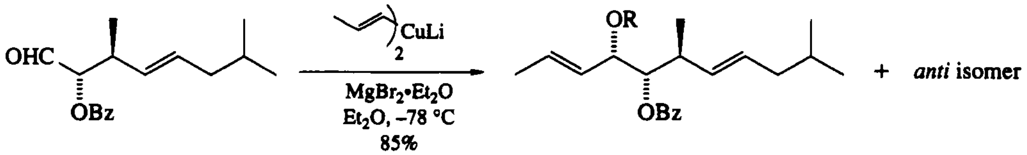

(36)

(**160**) (**161a**) R = H (**161b**)
(**162**) R = BnOCH$_2$CO

In order to arrive at (±)-methyl nonactate (**164**), Baldwin envisioned the addition of a soft organometallic source of methyl anion to aldehyde (**163**), the stereochemical outcome from which would be reagent dependent (equation 37).[100] Although earlier work by Ireland had shown that using Me$_2$CuLi in a hydrocarbon medium on (**163**) is not selective,[101,102] the potential for controlled delivery of 'Me$^-$' is predicated on related work by White,[103] which focussed on reduction of the corresponding methyl ketone. Thus, changing solvents to Et$_2$O does indeed alter the 1:1 ratio to 4.5:1 with Me$_2$CuLi, although the 8-epimethyl nonactate predominates. The desired material (**164**) is best achieved using 'MeTiCl$_3$',[14b] prepared from TiCl$_4$/Me$_2$Zn in CH$_2$Cl$_2$.

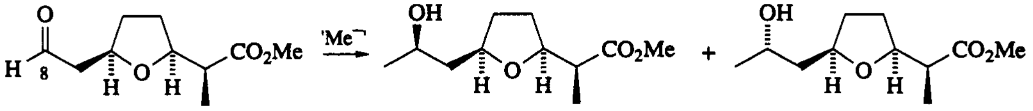

(37)

(**163**) (**164**) (**165**)

| | |
|---|---|
| Me$_2$CuLi, Et$_2$O, –78 °C, 85% | 1:4.5 |
| TiCl$_4$/Me$_2$Zn, CH$_2$Cl$_2$, –78 °C, 78% | 24:1 |

Sato and coworkers have applied the organocopper methodology developed earlier by their group (*vide supra*)[17] to a multigram scale preparation of a commonly used intermediate (**166**) for the synthesis of leukotriene A$_4$ (LTA$_4$).[104] Hydromagnesiation[105] of silylalkyne (**167**), catalyzed by titanocene dichloride, is followed by transmetallation with CuI·Me$_2$S to give the vinylcopper species (**168**; Scheme 28). Addition of (*R*)-glyceraldehyde acetonide leads to the expected *syn* product (**169**) in 85% overall yield from (**167**). The diastereoselectivity is better than 40:1 (*syn*:*anti*), with allylic alcohol (**169**) well suited for Sharpless epoxidation, which establishes C-5 and C-6 in (**166**) and eventually in LTA$_4$. The same protocol can be used to synthesize other homochiral epoxy aldehydes in quantity.[104]

Analogs of leukotriene B$_4$ (LTB$_4$, **170**) have aroused interest based on the potent chemotactic properties of LTB$_4$ itself. The disconnected C-6, C-7 (*Z*)-alkene in (**170**) has been viewed by Taylor, in alkynic form, as a ready means of attaching two residues *via* a carbocupration/1,2-addition scheme (equation 38).[106] Extremely high (*Z*)-stereoselectivity was anticipated for the former step, as discussed by Normant and Alexakis,[107] although trapping of the so-formed vinylcopper complex by an aldehyde was on less secure ground. Model studies showed that lower order lithium cuprates were the most efficacious towards addition across alkynes, while reagents such as RCu·ligand (*e.g.* ligand = Me$_2$S, LiBr or MgBr$_2$) gave

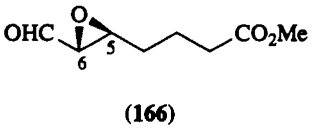

(**166**)

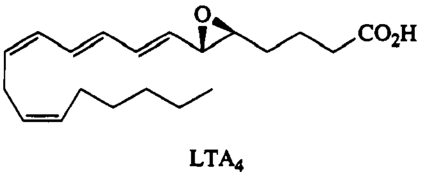

LTA$_4$

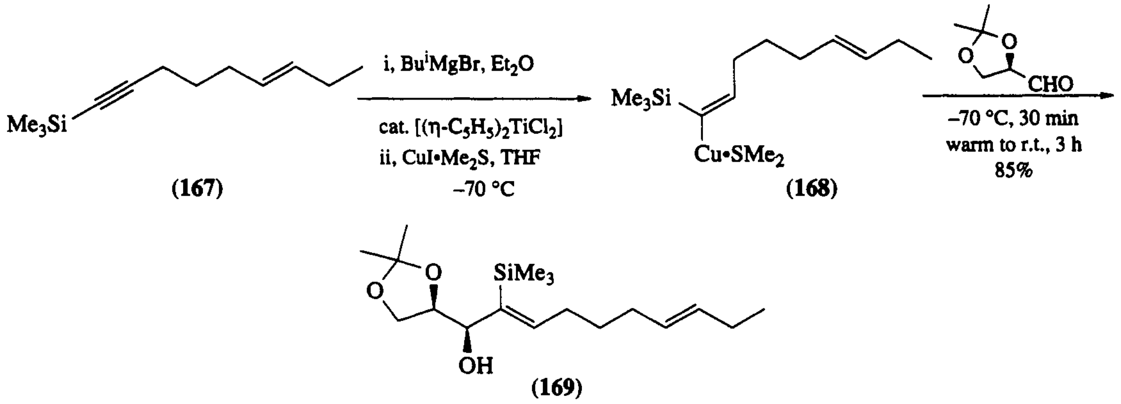
Me3Si
(167)
i, Bu$^i$MgBr, Et$_2$O
cat. [(η-C$_5$H$_5$)$_2$TiCl$_2$]
ii, CuI•Me$_2$S, THF
-70 °C
Me3Si
Cu•SMe2
(168)
O
O
CHO
-70 °C, 30 min
warm to r.t., 3 h
85%
O
O
SiMe3
OH
(169)

Scheme 28

none of the desired product. The same negative results were found with higher order cuprates, although this is likely to be due to their greater basicity and precludes their use (as a source of carbon nucleophiles) in the presence of alkynic protons. Thus, carbocupration of acetylene with mixed cuprate (**171**) afforded vinylcuprate (**172**), the formation of which required unusually high temperatures. The 1,2-addition to ester aldehyde (**173**) was best effected in the presence of $BF_3 \cdot Et_2O$, thereby giving (**174**), saponification of which gave the hexahydro $LTB_4$ analog (**175**; Scheme 29). A double carbocupration,[108] starting with $(C_{11}H_{23})_2CuLi$ and excess acetylene, and thence 1,2-addition to (**173**), ultimately led to the tetrahydro $LTB_4$ analog (**176**; Scheme 30). Both (**175**) and (**176**) can also be converted to their corresponding lactones.

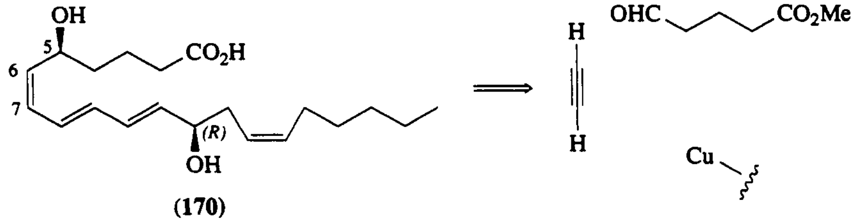
OH
5
6
7
CO2H
(R)
OH
(170)
H
H
OHC
CO2Me
Cu

(38)

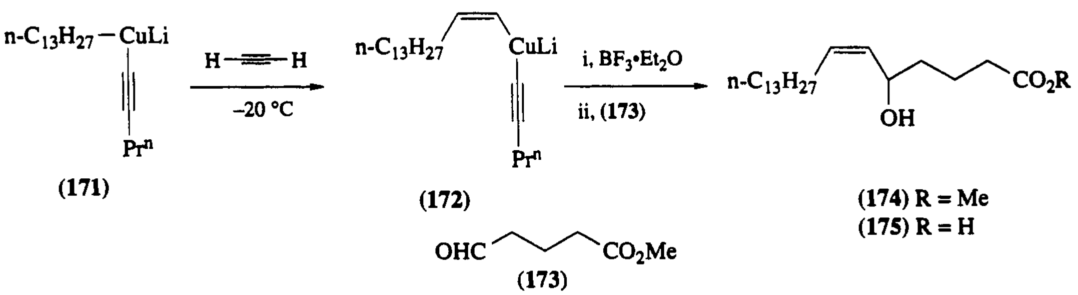
n-C13H27—CuLi
Pr$^n$
(171)
H—≡—H
-20 °C
n-C13H27
CuLi
Pr$^n$
(172)
i, BF$_3$•Et$_2$O
ii, (173)
n-C13H27
OH
CO2R
(174) R = Me
(175) R = H
OHC
CO2Me
(173)

Scheme 29

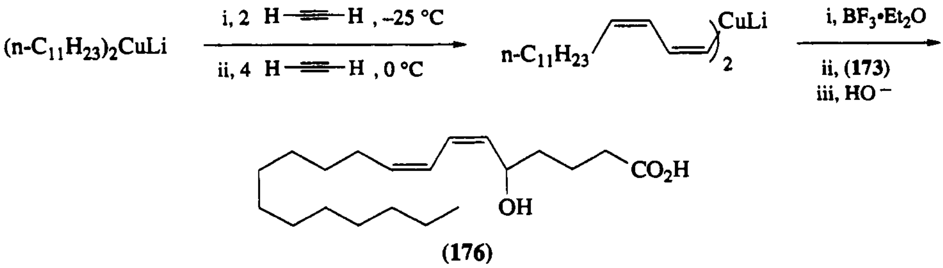
(n-C11H23)2CuLi
i, 2 H—≡—H, -25 °C
ii, 4 H—≡—H, 0 °C
n-C11H23
CuLi
2
i, BF$_3$•Et$_2$O
ii, (173)
iii, HO$^-$
CO2H
OH
(176)

Scheme 30

Also within the domain of arachidonic acid derivatives, a 5-exo-dig cyclization[109] of an α-silyl radical onto an alkyne, followed by proteodesilylation, was applied to a synthesis of isocarbacyclin (**177**), a carbocyclic analog of the potent antihypertensive and platelet aggregation inhibitor prostacyclin (**178**). The necessary functional group array was set in place by Noyori using a 1,2-addition of a higher order silylcuprate to aldehyde (**179**; Scheme 31).[110] A mix of alcohols (**180**)[111] was obtained in good yield, the unspecified ratio being of no consequence. Radical-initiated ring closure, employing either a photochemical step or the action of hot tributyltin hydride on the derived xanthate, formed the bicyclic network (**181**). Conversion to (**177**) was subsequently achieved by cleavage of the silyl–carbon bond with TFA, followed by deblocking, isomerization of the *exo*- to the *endo*-alkene and saponification.

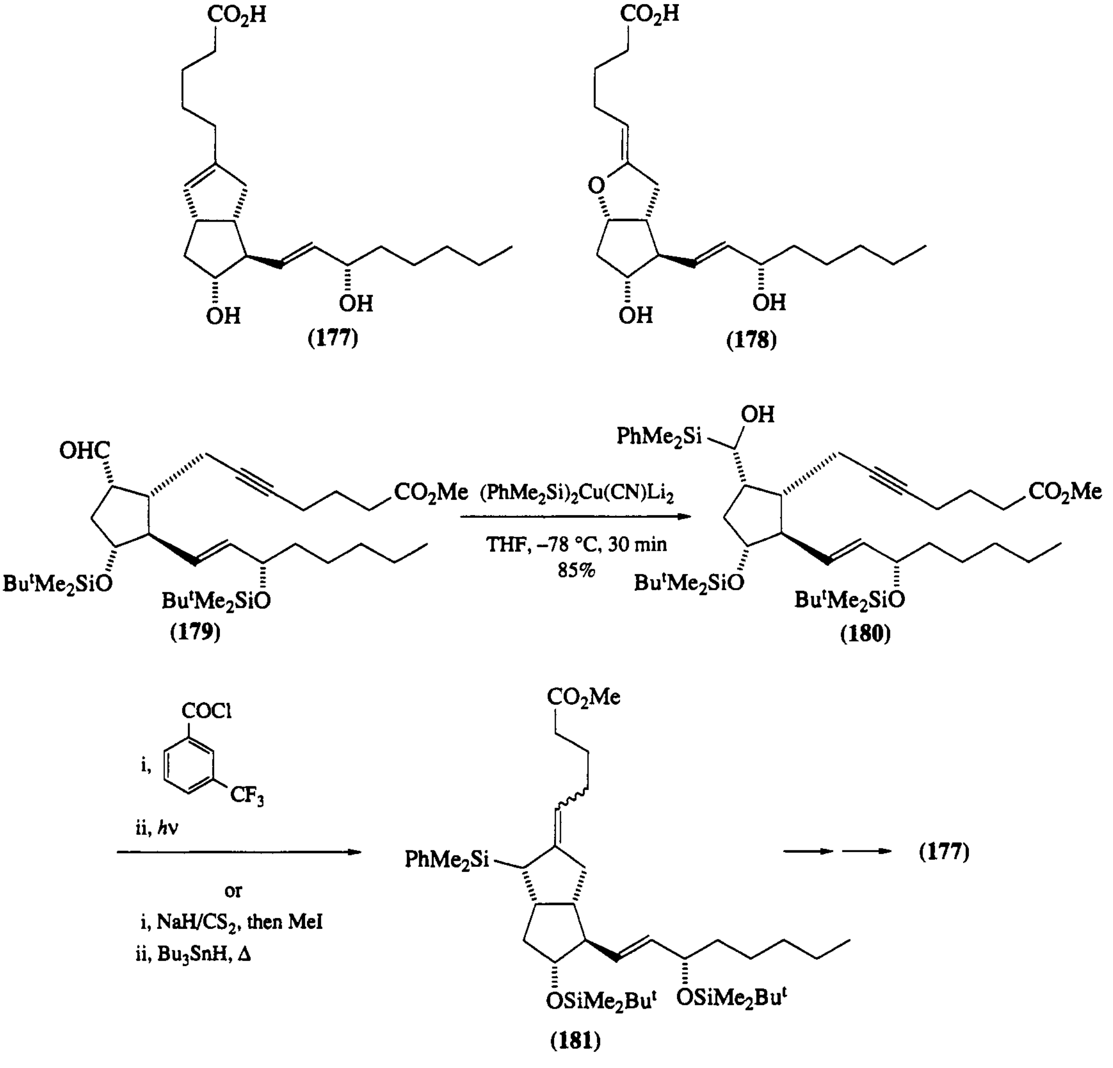
$CO_2H$
OH
OH
(177)
$CO_2H$
O
OH
OH
(178)
OHC
$CO_2Me$
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$
(179)
$(PhMe_2Si)_2Cu(CN)Li_2$
THF, –78 °C, 30 min
85%
OH
$PhMe_2Si$
$CO_2Me$
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$
(180)
COCl
i,
$CF_3$
ii, hν
or
i, NaH/$CS_2$, then MeI
ii, $Bu_3SnH$, Δ
$CO_2Me$
$PhMe_2Si$
$OSiMe_2Bu^t$
$OSiMe_2Bu^t$
(181)
(177)

**Scheme 31**

Tricyclic ketone (**183**), a photoproduct from the intramolecular [2 + 2] cycloaddition of silyl enol ether (**182**), was found by Pattenden and Teague to add methyl stereoselectivity through the agency of $Me_2CuLi/MeLi$.[112] The process occurs in $Et_2O$ at –68 °C following the Macdonald and Still prescription,[51] the product (**184**) from which undergoes facile acid-induced ring expansion to cyclooctenone (**185**). Wittig methylenation, isomerization and Lewis acid promoted transannular cyclization ultimately produces (±)-pentalenene (**186**; Scheme 32).

In the β-lactam area, Grieco *et al.* have applied their development of substituted bicyclo[2.2.1]heptanes to a synthesis of the thienamycin precursor (**188a**), embedded in which are three contiguous asymmetric centers corresponding to C-5, C-6 and C-8 in the natural product (**190**).[113] Readily obtained bromo aldehyde (**187**), upon treatment with the MeLi-derived higher order cuprate $Me_2Cu(CN)Li_2$ in

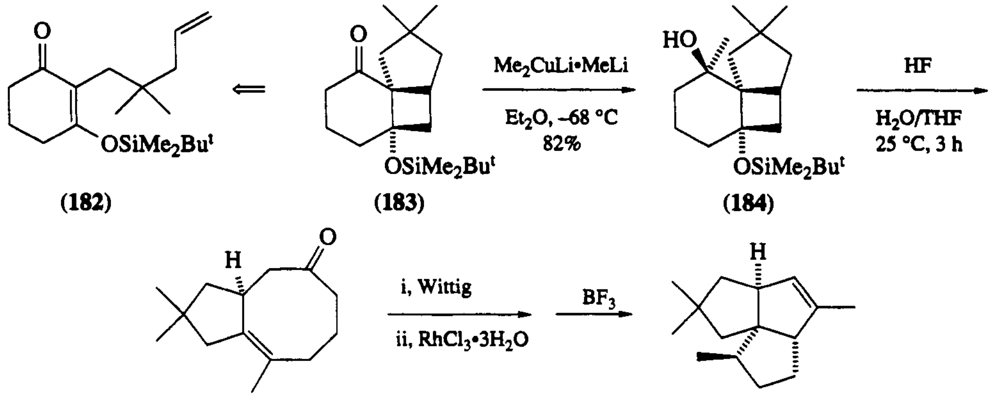
O
OSiMe2Bu^t
(182)
(183)
Me2CuLi•MeLi
Et2O, –68 °C
82%
HO
(184)
HF
H2O/THF
25 °C, 3 h
H
O
(185)
i, Wittig
ii, RhCl3•3H2O
BF3
(186)

Scheme 32

$Et_2O$ at reduced temperatures, gave in good yield (79%) diastereomer (**188a**) together with 8% of the undesired epimer (**188b**). By contrast, MeLi alone showed no preference in its 1,2-addition to (**187**). Further processing of (**188a**) eventually led to β-keto ester (**189**), a known intermediate *en route* to (**190**; Scheme 33).

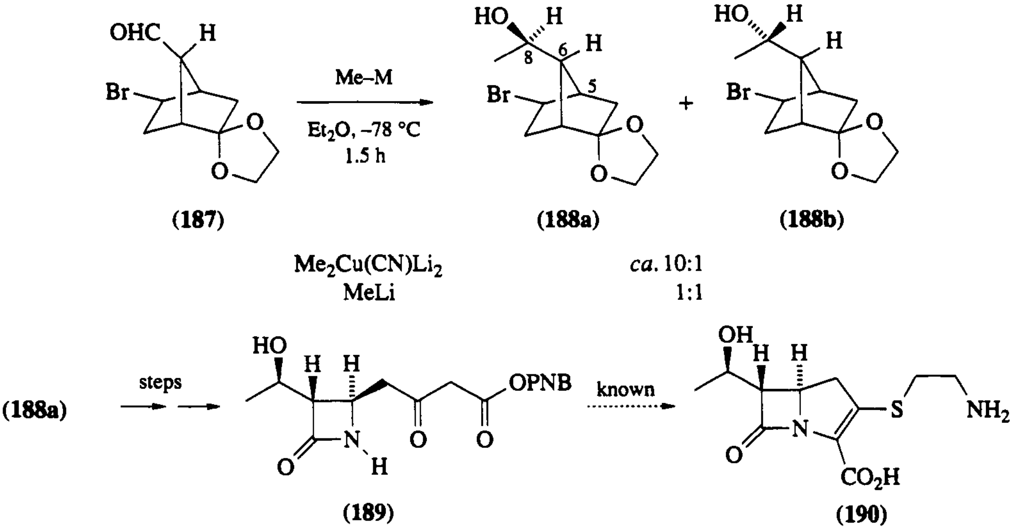
OHC
H
Br
O
(187)
Me–M
Et2O, –78 °C
1.5 h
HO
H
8
6
5
(188a)
+
(188b)
Me2Cu(CN)Li2
MeLi
ca. 10:1
1:1
(188a)
steps
OPNB
N
H
(189)
known
OH
S
NH2
CO2H
(190)

Scheme 33

In search of a practical route to diastereomeric lactones (**193**) and (**194**), potential agents for mosquito control needed by entomologists for evaluation, acrolein dimer (**191**) was deemed as the logical starting point.[114] For compound (**193**), the major component of the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*, the required stereorelationship can be constructed by the initial action of a Grignard reagent on (**191**) at –20 °C in THF doped with HMPA, which minimizes chelation-enhanced *threo* (*syn*) selectivity, thereby favoring (**192a**).[9,11] TMEDA was not an acceptable substitute for HMPA. Addition of CuI to the Grignard, which according to Sato[17] forms the organocopper complex RCuMgBrI, proceeds through a Cram cyclic transition state[12] to arrive at a (**192a**):(**192b**) mix now rich in the *syn* isomer (equation 39). Separation of these 1,2-adducts and subsequent acylation–PCC oxidation culminated this brief approach by Jefford, easily amenable to scale-up (Scheme 34).

Singh and Oehlschlager have used the same starting material (*i.e.* **191**) to study the 1,2-addition of ethylmetallic reagents, in this case with an eye toward both (racemic) *exo*- and *endo*-brevicomin.[115] The *erythro* (*anti*) product (**196b**) can be obtained with the EtLi/$BF_3 \cdot Et_2O$ combination, presumably due to a strong preference for an *anti* configuration of the polar groups as in (**197**) once the Lewis acid complexation has occurred.[116] Ethylcopper reagents reversed the outcome, giving an *ca.* 89:11 split in favor of (**196a**), presumably *via* (**195**; Scheme 35), a result comparable to that obtained by Jefford (*vide supra*).[114]

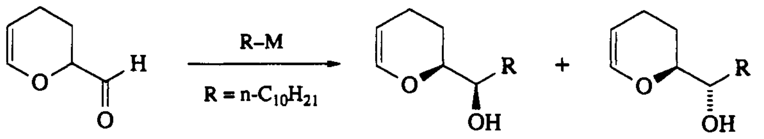
H
O
R–M
R = n-C10H21
O
R
OH
+
O
R
OH

**(191)** **(192a)** *anti* **(192b)** *syn* (39)

| | |
|---|---|
| RMgBr; 84%<br>THF, HMPA (6 equiv.), −20 °C | 5.67:1 |
| RCu•MgBrI; 84%<br>THF, Me$_2$S, −78 to 0 °C | 1:9 |

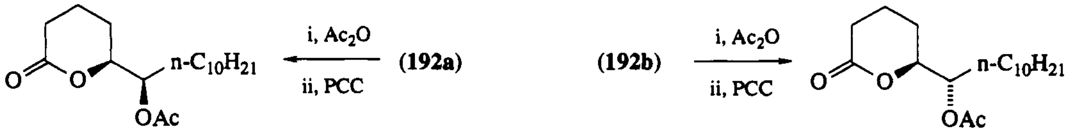
O
O
n-C10H21
OAc
i, Ac2O
ii, PCC
(192a)
(192b)
i, Ac2O
ii, PCC
O
O
n-C10H21
OAc

**(193)** **(194)**

Scheme 34

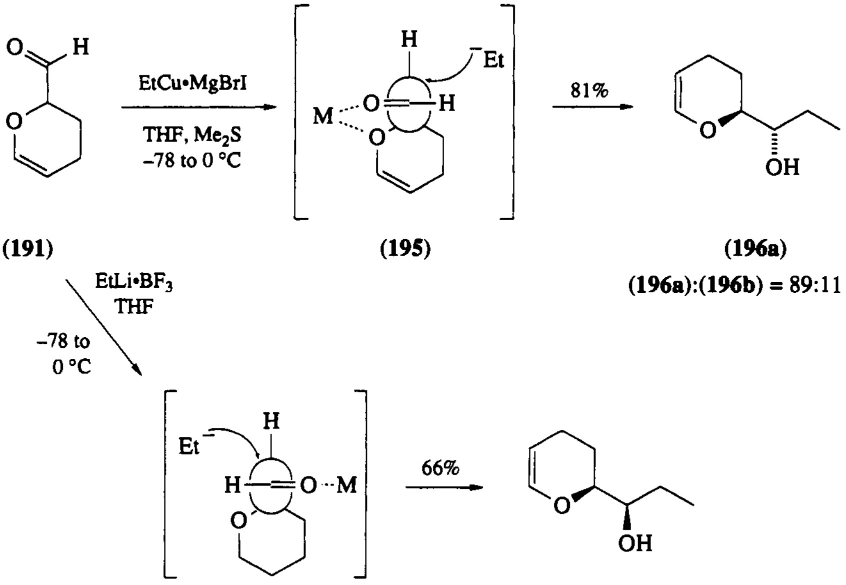
O
H
O
EtCu•MgBrI
THF, Me2S
-78 to 0 °C
H
Et
M
O
H
O
81%
O
OH
EtLi•BF3
THF
-78 to
0 °C
H
Et
H
O
M
O
66%
O
OH

**(191)** **(195)** **(196a)**

**(196a)**:**(196b)** = 89:11

**(197)** **(196b)**

**(196b)**:**(196a)** = 92:8

Scheme 35

Both *exo*- and *endo*-brevicomin (*vide infra*), in optically active form, have been synthesized by elaboration of α-alkoxy aldehyde (**201**).[117] Condensation of the 1-trimethylsilylvinylcopper reagent (**198**) with the (*R*)-glyceraldehyde derivative (**199**) gave *syn* product (**200**) in >85% yield with over 98% diastereoselectivity (Scheme 36). Hydroxy protection, hydrolysis and periodate cleavage of the *vic*-diol converted (**200**) to aldehyde (**201**) in 50–65% overall yields for the two steps.

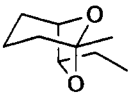

*exo*-Brevicomin

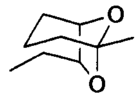

*endo*-Brevicomin

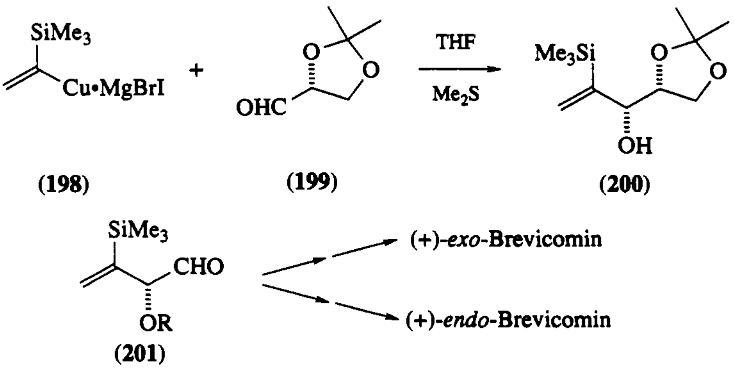

**Scheme 36**

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# 1.5

# Organotitanium and Organozirconium Reagents

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## 1.5.1 INTRODUCTION

In 1861, the first example of an organotitanium reagent was reported.[1] Nevertheless, more than ninety years were necessary before the preparation of the stable compound, phenyltitanium isopropoxide, was achieved.[2] Since then, a tremendous number of organotitanium derivatives have been synthesized,[3–5] in which the metal atom bears a broad variety of ligands sharing both σ- and π-bonds. The stable cyclopentadienyltitanium (titanocene) derivatives became popular following their introduction by Ziegler as reagents for alkene polymerization.[6]

Overcoming the theory that transition metal derivatives could be stable only with a fully coordinated metal atom (18-electron rule), finally opened the route toward the modern application of organotitanium and, later on, organozirconium reagents in synthesis.[7] This was facilitated by the work that had already been performed[8] by inorganic chemists in devising simple and high-yielding methods for the preparation of organo-titanium and -zirconium derivatives. This chapter will not deal with many of the synthetic applications of these reagents, but rather will focus on organo-titanium and -zirconium additions to C=X π-bonds and their advantages in comparison to other organometallic reagents in terms of chemo-, regio-, diastereo- and enantio-selectivity.

## 1.5.2 ORGANOTITANIUM AND ORGANOZIRCONIUM NUCLEOPHILES: A GENERAL VIEW

### 1.5.2.1 Chemical Properties and Comparison with Traditional Organometallic Reagents

The organo-titanium and -zirconium derivatives that will be considered here have the general formula $R_nMX_{4-n}$. The compounds consist of two distinct parts, namely the 'R' nucleophilic moiety and the 'X' ligand system. Considerable stability, selectivity and ease of handling are their most outstanding features as reagents in organic synthesis.

With regard to the 'R' nucleophilic moiety, simple linear alkyl residues should generally be avoided, due to their tendency to decompose through various processes,[9] such as reductive elimination (β-H abstraction; equation 1), and oxidative dimerization (equation 2). Attention must be paid when designing an efficient Ti or Zr nucleophile to minimize decomposition. This is achieved by using organic residues which either do not possess β-hydrogens (*e.g.* methyl, phenyl, benzyl, neopentyl, 1-norbornyl, trimethylsilylmethyl, *etc.*) or are sufficiently hindered that they do not undergo hydrogen abstraction readily.

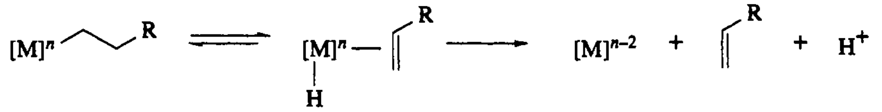
(1)

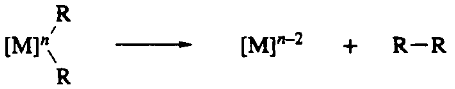

$$[M]^n(R)_2 \longrightarrow [M]^{n-2} + R-R \qquad (2)$$

The 'X' ligands also influence the stability of the above reagents, primarily as a function of the stability of the bonds (σ or π) between the metal and the bond-forming atom. The most commonly used are alkoxy groups, *N,N*-dialkylaminyl groups, chlorine atoms or even mixed chlorine and alkoxy groups. Due to its major ability to donate electrons, nitrogen stabilizes Ti and Zr reagents more than oxygen and, consequently, much more than chlorine.

Considering the energy of the M—X bonds for various $MX_4$ compounds,[10] the bond strengths for Ti, Zr, and Hf decrease in the sequence M—O > M—Cl > M—N > M–C. The M–C bond strength in $Ti^{IV}$ and $Zr^{IV}$ compounds are comparable with that of other metal–carbon bonds,[11] whereas the rather unusual strength[10] of the M—O bond [$E$(Ti—O) = 115 kcal mol$^{-1}$; $E$(Zr—O) = 132 kcal mol$^{-1}$; 1 cal = 4.18 J] serves as a driving force for those reactions involving oxygen coordination by the metal atom. The Ti—O bond is fairly short among the metal–oxygen bonds (compare *e.g.* Li—O, Mg—O and Zr—O; Table 1),[11] a fact relevant to certain stereoselective reactions that will be discussed later (Section 1.5.3.1.4).

**Table 1** Metal–Carbon and Metal–Oxygen Bond Lengths

| *Metal* | *Bond length*<br>*Metal–carbon (Å)* | *Metal–oxygen (Å)* |
|---|---|---|
| Ti | ~2.10 | 1.70–1.90 |
| Zr | ~2.20 | 2.10–2.15 |
| Li | ~2.00 | 1.90–2.00 |
| Mg | ~2.00 | 2.00–2.13 |
| B | 1.5–1.6 | 1.36–1.48 |

Stability aside, the nature of the ligand system determines to some extent the Lewis acid character of $Ti^{IV}$ and $Zr^{IV}$ reagents. As expected, the higher the tendency of the bond-forming atom to share its electrons with the metal, the lower the acidity of the complex (*e.g.* Cl > OR > $NR_2$). This trend can be exploited to modulate the acidity of $Ti^{IV}$ and $Zr^{IV}$ reagents by replacing, for instance in the titanium series, chlorine with alkoxy groups so that their acidity decreases in the sequence $RTiCl_3$ > $RTiCl_2(OR')$ > $RTiCl(OR')_2$ > $RTi(OR')_3$.[12]

One advantage of organo-titanium and -zirconium reagents, relative to more traditional organometallic compounds in the field of nucleophilic additions, is their stability at fairly high temperature (from 0 °C to r.t.) for a reasonably long time. For example, $MeTi(OPr^i)_3$ is a yellow compound, isolated and purified by distillation at 50 °C under reduced pressure,[13,14] and the purple-red crystalline compound $MeTiCl_3$ (m.p. ~29 °C) can be stored at low temperature for several weeks.[15] They are not strongly toxic and do not afford toxic by-products.[9] Easy to handle, they require very simple work-up that includes slightly acidic conditions to avoid $TiO_2$-containing emulsions.[16]

Undoubtedly, the success of organo-titanium and -zirconium complexes as reagents for nucleophilic additions lies in their chemical properties, the most characteristic being chemoselectivity. Grignard reagents, organolithium compounds, and other resonance-stabilized carbanions often react more or less unselectively if two or more target functions are present in the substrate molecule. Even with other more recently reported[17] organometallic reagents, *e.g.* organo-tin, -cadmium and -chromium derivatives, such selectivity is not guaranteed. On the contrary, titanium and zirconium derivatives are capable of discriminating, for example, between an aldehyde and a ketone. More generally speaking, these reagents discriminate between similar functionalities that differ only slightly in their steric and/or electronic environment (Section 1.5.3.1.1). Furthermore, they tolerate several functional groups such as epoxides, ethers, carboxylic acid esters and thioesters, nitriles and alkyl halides.[16] Being less basic than other organometallic reagents, they can be safely utilized for nucleophilic addition to enolizable carbonyl compounds (Section 1.5.3.1.2). 1,2-Addition to α,β-unsaturated carbonyl compounds (Section 1.5.3.1.5), *gem*-dialkylation (Section 1.5.5.1) and one-step amination/alkylation of the carbonyl group (Section 1.5.5.2), represent a few examples of reactions that are more easily realized due to advances in $Ti^{IV}$ and $Zr^{IV}$ chemistry.

Ethyl levulinate (**1**) is reported to afford the lactone (**2**) when treated with methyltitanium triisopropoxide (equation 3).[18] In cases like this, in order to prevent lactonization, it may be expedient to use organozirconium derivatives that have a generally milder reactivity.

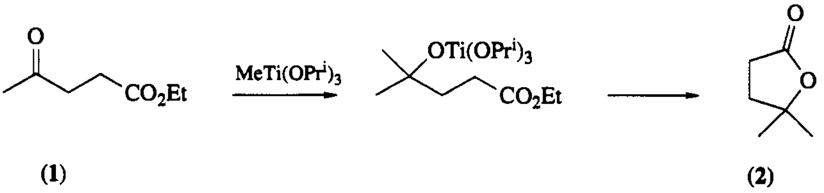

(3)

It is possible that the higher chemoselectivity of $Ti^{IV}$ and $Zr^{IV}$ reagents relative to the classical carbanions may be due to lower reaction rates. However, this cannot be the only reason, and it is likely that chemoselectivity is dependent on the nature of the C—M bond, which in the case of $Ti^{IV}$ and $Zr^{IV}$ is much less polarized than the analogous C—Li or C—Mg bonds.[16] Chemoselectivity is only one of the features of organo-titanium and -zirconium reagents, diastereoselectivity being a second and even more important one. The topic will be broadly covered in Sections 1.5.3.1.3 and 1.5.3.1.4 of this chapter, but as a quick illustration it is useful to compare the results of earlier experiments by Cram *et al.*[19,20] in the addition of either Grignard reagents or alkyllithium compounds to 2-phenylpropanal (**3**), and results from the addition of methyltitanium triisopropoxide to the same aldehyde (equation 4).[21] The diastereomeric products (**4**) and (**5**) are obtained, in the first instance, in about a 2:1 ratio *versus* the 9:1 ratio achieved by the titanium reagent.

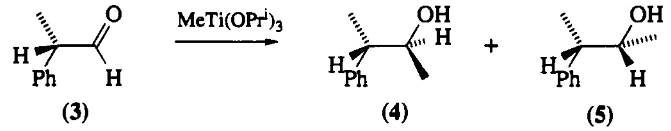

(4)

Enantioselective addition has also been attempted with chirally modified Li or Mg reagents,[22] but only $Ti^{IV}$ and $Zr^{IV}$ derivatives have provided efficient tools for this purpose, due to the stable bond between chiral ligands and metal. In other cases, dissociation leads to a reduced efficacy of the chiral system.

### 1.5.2.2 General Preparation of Principal Organotitanium and Organozirconium Derivatives

Among the $Ti^{IV}$ and $Zr^{IV}$ complexes that are most commonly used for carbonyl nucleophilic additions, monoalkyl and monoaryl derivatives with alkoxylic ligand systems have the longest history of synthetic application.[9] This is likely due to the ease with which they are prepared from the readily available and inexpensive tetraalkoxy compounds (**6**). These, when treated with the tetrachloride of the same metal (equation 5), afford monochlorotrialkoxy metal derivatives (**7**), which in turn can be either alkylated or arylated by numerous lithium or magnesium derivatives[23] or by zinc, cadmium, lead and aluminum derivatives,[9] in various solvents, including THF, $Et_2O$, $CH_2Cl_2$, alkanes, *etc.* Monochlorotrialkoxytitanium compounds (**9**) are also reported to undergo ligand exchange by treatment with alcohols (equation 6),[24] a reaction which can be used to modulate the chemical properties of the reagent, as was discussed in the previous section.

$$\underset{(\mathbf{6})}{3\,M(OR)_4} \xrightarrow{MCl_4} \underset{(\mathbf{7})}{4\,ClM(OR)_3} \xrightarrow[R^1MgX]{R^1Li \text{ or}} \underset{(\mathbf{8})}{R^1M(OR)_3} \qquad (5)$$

$$\underset{(\mathbf{9})}{ClTi(OR^1)_3} \xrightarrow[-R^1OH]{R^2OH} \underset{(\mathbf{10})}{ClTi(OR^2)_3} \qquad (6)$$

Monoalkyl $Ti^{IV}$ and $Zr^{IV}$ reagents having *N,N*-dialkylamino ligand systems (**12**) can be prepared from the corresponding tetra(*N,N*-dialkylamino) metal derivatives (**11**),[23] according to the procedure reported above for the alkoxylic ligand systems (equation 7). Recently, a large scale preparation of both tetra(*N,N*-diethylamino)- and chlorotris(*N,N*-diethylamino)-titanium(IV) compounds (**13**) and (**14**) was devised,[25] starting from lithium *N,N*-diethylamide and $TiCl_4$ (Scheme 1).

$$\underset{(\mathbf{11})}{3\,M(NR_2)_4} \xrightarrow{MX_4} 4\,XM(NR_2)_3 \xrightarrow{R^1Li} \underset{(\mathbf{12})}{4\,R^1M(NR_2)_3} \qquad (7)$$

$$R = Me, Et;\ X = Br, Cl$$

$$\underset{(\mathbf{13})}{Ti(NEt_2)_4} \xleftarrow{TiCl_4\ (0.25\ \text{mol equiv.})} LiNEt_2 \xrightarrow{TiCl_4\ (0.33\ \text{mol equiv.})} \underset{(\mathbf{14})}{ClTi(NEt_2)_3}$$

**Scheme 1**

When the ligand system consists of chlorine atoms, monoalkyl- and monoaryl-titanium(IV) compounds are readily made from $TiCl_4$ by a chlorine atom replacement. The parent compound in this series, $MeTiCl_3$, is made conveniently from the reaction of $TiCl_4$ and dimethylzinc without the use of ethereal solvents,[26] the preparation being carried out in *n*-pentane or dichloromethane. Other methylating species can be used, such as MeMgBr, MeLi and $MeAlCl_2$. When MeLi is used in diethyl ether, an equilibrium takes place between different complexation states of Ti in the resulting $MeTiCl_3$ with the solvent (equation 8).[27] Transmetallation from organotin compounds like (**15**; equation 9) has also been utilized to make trichlorotitanium compounds.[28]

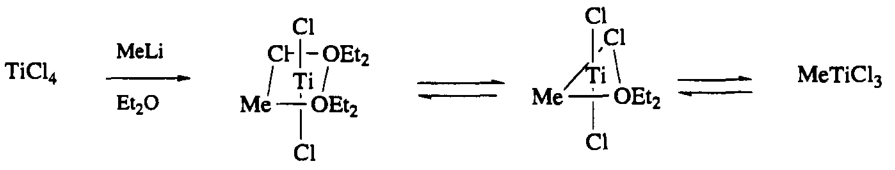

(8)

It is not necessary that the ligands around the metal be homogeneous, in fact mixed ligand systems can be very useful in tuning the chemical properties of the metal complexes. Their preparation is generally effected by ligand interchange, *i.e.* by mixing different $Ti^{IV}$ species in the proper stoichiometric ratio, as is shown in equation (10) for the preparation of $MeTi(OPr^i)Cl_2$ (**16**).[13]

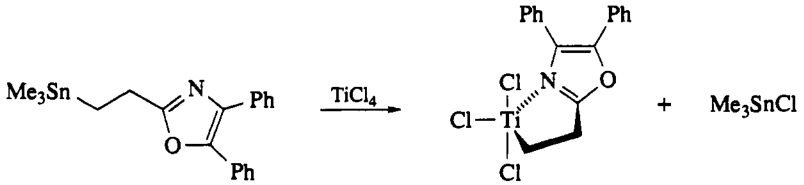

**(15)**

(9)

$$2\,\mathrm{MeTiCl_3} + \mathrm{MeTi(OPr^i)_3} \longrightarrow 3\,\mathrm{MeTi(OPr^i)Cl_2} \qquad (10)$$

**(16)**

Dialkyl and diaryl $Ti^{IV}$ and $Zr^{IV}$ derivatives (**18**) are somewhat less stable than their monosubstituted analogs. They are generally prepared by alkylation of the corresponding dichloro compounds (**17**; equation 11).[13,29,30] The dichloro derivatives themselves can be prepared in turn by reaction of tetrachlorides with the required amount of organometallic species. For example, zirconocene dichloride is prepared by treating zirconium(IV) chloride with cyclopentadienylsodium.[31]

$$\mathrm{Cl_2MCp_2} \xrightarrow{\mathrm{RLi}} \mathrm{R(Cl)MCp_2} \xrightarrow{\mathrm{RLi}} \mathrm{R_2MCp_2} \qquad (11)$$

**(17)** **(18)**

Alkenyl and dienyl groups can be present in $Ti^{IV}$ and $Zr^{IV}$ complexes as well. Vinyltitanium compounds cannot be exploited for nucleophilic additions, however, due to their propensity to undergo oxidative coupling reactions,[32] likewise transition metal derivatives. Vinylzirconium compounds (**20**) can be prepared from alkynes (hydrozirconation; equation 12) by action of zirconium derivatives like (**19**).[33]

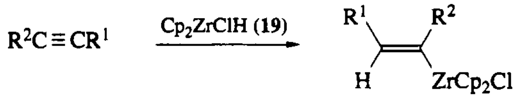

(12)

**(20)**

Allyltitanium complexes (**22**) readily add to carbonyl compounds with high regio- and stereo-selection. They are prepared by reaction of a chlorotitanium complex (**21**) with an allyl-magnesium or -lithium derivative (equation 13).[34] Some of these unsaturated $Ti^{IV}$ complexes, like (**23**)–(**25**) in Scheme 2, obtained from allylmagnesium halides or allyllithium by reaction with titanium tetraisopropoxide or titanium tetramides,[35] are known as 'titanium ate complexes'. The structure of these ate complexes, at least from a formal point of view, can be written with a pentacoordinate Ti atom. Some ate complexes have synthetic interest, as is the case of $(allyl)Ti(OPr^i)_4MgBr$ which shows sharply enhanced selectivity towards aldehydes in comparison with the simple $(allyl)Ti(OPr^i)_3$.[16]

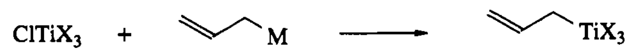

(13)

**(21)** M = MgCl or Li **(22)**

Crotyl-titanocenes and -zirconocenes like (**31**) are readily prepared from the corresponding magnesium and lithium compounds [regardless of (*E*)- or (*Z*)-configuration] by reaction with either dichlorobis(cyclopentadienyl)titanium or its zirconium analog (equation 14).[36,37] Likewise, crotylmagnesium derivatives react with other $Ti^{IV}$ compounds [*e.g.* (**14**), (**26**) and (**27**); Scheme 3] and afford crotyltitanium complexes [*e.g.* (**28**), (**29**) and (**30**), respectively] in a stereoconvergent manner, affording solely the (*E*)-isomer. Finally, some other allylic reagents having a trivalent titanium atom are interesting for their application in synthesis.[38] The parent allyltitanium(III) derivative (**33**) is prepared by reaction of dichlorobis(cyclopentadienyl)titanium (**32**) and allylmagnesium bromide (equation 15).

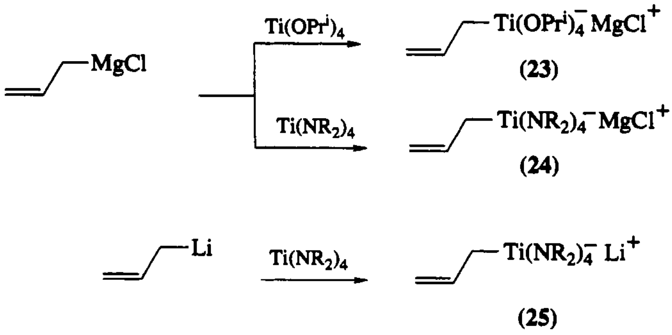
MgCl
Ti(OPr$^i$)$_4$
Ti(NR$_2$)$_4$
Ti(OPr$^i$)$_4^-$MgCl$^+$
(23)
Ti(NR$_2$)$_4^-$MgCl$^+$
(24)
Li
Ti(NR$_2$)$_4$
Ti(NR$_2$)$_4^-$ Li$^+$
(25)

Scheme 2

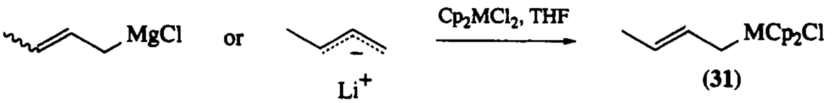
MgCl
or
Li$^+$
Cp$_2$MCl$_2$, THF
MCp$_2$Cl
(31)

(14)

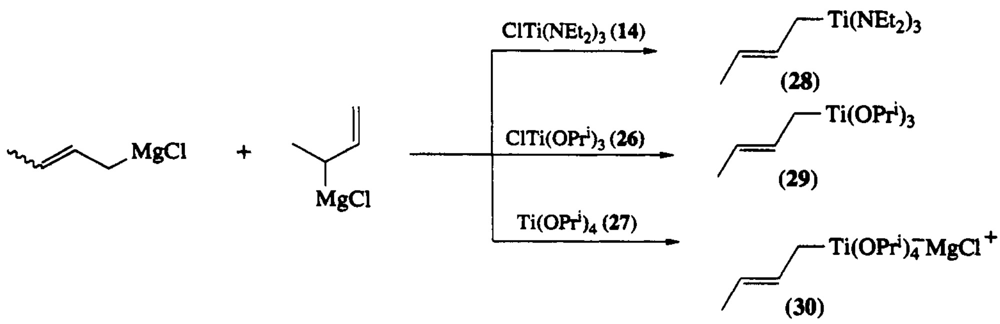
MgCl
+
MgCl
ClTi(NEt$_2$)$_3$ (14)
ClTi(OPr$^i$)$_3$ (26)
Ti(OPr$^i$)$_4$ (27)
Ti(NEt$_2$)$_3$
(28)
Ti(OPr$^i$)$_3$
(29)
Ti(OPr$^i$)$_4^-$MgCl$^+$
(30)

Scheme 3

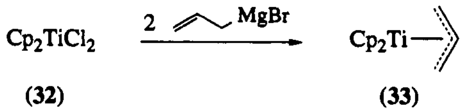
Cp$_2$TiCl$_2$
(32)
2
MgBr
Cp$_2$Ti
(33)

(15)

### 1.5.2.3 Titanium *versus* Zirconium Reactivity

Titanium and zirconium derivatives are in a certain sense complementary as reagents for carbonyl nucleophilic addition. Considering the relative position of both Ti and Zr in the periodic table, the latter is expected to share longer bonds with ligands and with the nucleophilic moiety of the reagent. As a consequence, chelation, when involved, leads to complexes of different structure and thermodynamic stability, factors which directly affect the course of the reaction. Even more important, the lower tendency towards reduction of Zr relative to Ti accounts for the stability of zirconium derivatives at room temperature. Vinylzirconium compounds can be prepared and used as such, whereas their titanium analogs readily undergo oxidative coupling with concomitant reduction of the metal.[39] Enhanced stability has also been verified for those zirconium complexes having branched alkyl groups,[9] that in the case of titanium are quite unstable.[9,11]

Generally speaking, the preparations of Ti$^{IV}$ and Zr$^{IV}$ reagents are quite similar, as was discussed in the previous section, but the Zr$^{IV}$ starting materials, like Zr(OR)$_4$, are generally two or three times more expensive than the corresponding Ti$^{IV}$ compounds and their reactions are slower. This is a characteristic of Zr$^{IV}$ species relative to their Ti$^{IV}$ counterparts that is verified also by the relative rates of nucleophilic addition to carbonyl compounds. The slower reaction rates can lead to side reactions: for example, alkylzirconium trialkoxides will reduce carbonyl compounds to the corresponding carbinol in a Meerwein–Ponndorf–Verley fashion.[40]

With these few exceptions, $Zr^{IV}$ reagents perform nucleophilic additions to carbonyls with the same selectivity features as their titanium analogs,[41] under milder conditions. Moreover, due to their lower basicity,[9] they are generally more suitable to interact with easily enolizable carbonyl compounds. The reaction of (**34**) with $MeZr(OBu^n)_3$ to afford (**35**) serves to illustrate how versatile these reagents are in organic synthesis (equation 16).[39]

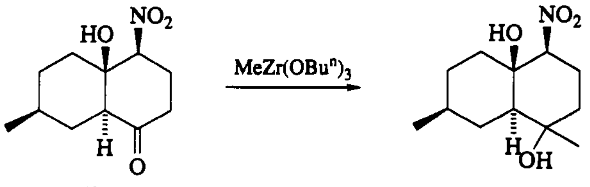

(**34**) (**35**)

(16)

## 1.5.3 CARBONYL ADDITION REACTIONS

### 1.5.3.1 Alkyl and Aryl Titanium and Zirconium Reagents

### *1.5.3.1.1 Addition to simple ketones and aldehydes: chemoselectivity*

Methyltitanium triisopropoxide is probably the oldest and most widely studied organotitanium reagent for nucleophilic addition to carbonyls.[21] Its reaction with aldehydes and ketones (equation 17) is comparable to the reaction of more traditional organometallic reagents, like methylmagnesium halides or methyllithium, with carbonyl compounds. The already cited stability of $MeTi(OPr^i)_3$ and its solubility in various solvents would be sufficient to recommend it as a nucleophilic addition reagent but, more importantly, a wide range of functionalities (*e.g.* nitro, cyano, chloromethyl and thiol groups), as shown in Table 2, are tolerated under the reaction conditions.[16] It is also noteworthy to mention a one-pot procedure that allows the preparation of the reagent *in situ*.[42] A few undesired side reactions of methyl- and other alkyl-titanium triisopropoxides are known which are a result of transfer of the isopropoxy rather than the alkyl group. In fact, the reaction with carboxylic acid esters and with acid chlorides leads to ester interchange[43] and esterification, respectively.[9]

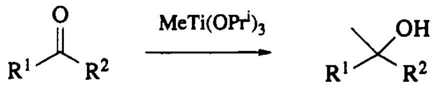

(17)

$R^1$ = or ≠ $R^2$ = H, alkyl or aryl

Aldehydes react very fast and at low temperature (between −70 and 0 °C), whereas ketones require higher temperatures and longer reaction times (Tables 2 and 3). In cross experiments performed using benzaldehyde and acetophenone with $MeTi(OPr^i)_3$ in 1:1:1 molar ratios, only the aldehyde was consumed, leading almost quantitatively to its corresponding methylphenylcarbinol.[42] Such features are fully exploited in the synthesis of macrocyclic lactones like (**36**; equation 18).[45]

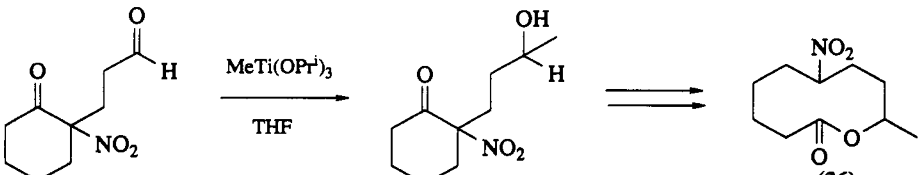

(**36**)

(18)

The chemoselectivity of organo-titanium and -zirconium reagents is practically unaffected by the nature of the nucleophilic moiety of their molecule. Although aldehydes always react much faster than ketones, the addition rates sometimes differ significantly, depending upon steric and electronic properties

**Table 2** Carbonyl Addition Reactions of Various Alkyl- and Aryl-titanium(IV) Nucleophiles[a]

| *Carbonyl compound* | *Nucleophile*[b] | *Solvent* | *Time (h)* | *Temperature (℃)* | *Product* | *Yield (%)*[c] |
|---|---|---|---|---|---|---|
| 2,2-Dimethylpropanal | $MeTi(OPr^i)_3$ | $Et_2O$ | 1.5 | –25 | 3,3-Dimethyl-2-butanol | 60 |
| 3-Methylbutanal | $MeTi(OPr^i)_3$ | $CH_2Cl_2$ | 0.5 | 0 | 4-Methyl-2-pentanol | — (90) |
| Heptanal | $MeTi(OPr^i)_3$ | THF | 4.0 | –50 | 2-Octanol | 97 |
| Benzaldehyde | $MeTi(OPr^i)_3$ | THF | 4.0 | –50 | 1-Phenylethanol | 92 |
| Benzaldehyde | $MeTi(OPr^i)_3$ | $Et_2O$ | 0.2 | 0 | 1-Phenylethanol | 92 |
| 4-Nitrobenzaldehyde | $MeTi(OPr^i)_3$ | THF | 4.0 | –50 | 1-(4-Nitrophenyl)ethanol | 95 |
| Cinnamaldehyde | $MeTi(OPr^i)_3$ | $Et_2O$ | 4.0 | –50 | 4-Phenyl-3-buten-2-ol[d] | 91 |
| Phenylacetaldehyde | $MeTi(OPr^i)_3$ | $Et_2O$ | 2.0 | –40 to 0 | 1-Phenyl-2-propanol | 74 (90) |
| 2-Heptanone | $MeTi(OPr^i)_3$ | $Et_2O$ | 24.0 | +22 | 2-Methyl-2-heptanol | 47 |
| 2-Heptanone | $MeTi(OPr^i)_3$[e] | — | 24.0 | +22 | 2-Methyl-2-heptanol | 83 (90) |
| Cyclohexanone | $MeTi(OPr^i)_3$[f] | THF | 48.0 | r.t. | 1-Methylcyclohexanol | 79 |
| Acetophenone | $MeTi(OPr^i)_3$[f] | $Et_2O$ | 48.0 | r.t. | 2-Phenyl-2-propanol | 96 |
| (+)-1,3,3-Trimethyl-2-norbornanone | $MeTi(OPr^i)_3$[g] | Isooctane | 10.0 | +80 | 1,2,3,3-Tetramethyl-2-norbornanol[h] | 84 |
| α-Tetralone | $MeTi(OPr^i)_3$ | $Et_2O$ | 24.0 | r.t. | 1,2,3,4-Tetrahydro-1-methylnaphthol | 50 |
| Benzaldehyde | $EtTi(OPr^i)_3$ | $Et_2O$ | 6.0 | –30 to +22 | 1-Phenylpropanol | 69 (80) |
| 4-Iodobenzaldehyde | $Bu^nTi(OPr^i)_3$ | $Et_2O$ | 15.0 | –10 to r.t. | 1-(4-Iodophenyl)pentanol | 82 |
| 2-Bromobenzaldehyde | $Bu^nTi(OPr^i)_3$ | $Et_2O$ | 12.0 | –20 | 1-(2-Bromophenyl)pentanol | 92 |
| 4-Cyanobenzaldehyde | $Bu^nTi(OPr^i)_3$ | $Et_2O$ | 15.0 | –10 to r.t. | 1-(4-Cyanophenyl)pentanol | 97 |
| Acetaldehyde | $PhTi(OPr^i)_3$ | THF | 1.0 | –10 | 1-Phenylethanol | 86 (95) |
| Cyclohexanecarbaldehyde | $PhTi(OPr^i)_3$ | THF | 1.0 | –10 | Cyclohexylphenylmethanol | 84 (95) |
| 4-Nitrobenzaldehyde | $PhTi(OPr^i)_3$ | $Et_2O$ | 0.5 | –15 | (4-Nitrophenyl)phenylmethanol | 94 |
| 4-*t*-Butylcyclohexanone | $PhTi(OPr^i)_3$ | $Et_2O$ | 15.0 | r.t. | 1-Phenyl-4-*t*-butylcyclohexanol[i] | 95 |
| Benzaldehyde | $CNCH_2Ti(OPr^i)_3$ | THF | 3.0 | –78 to +22 | 2-Cyano-1-phenylethanol | 81 (95) |
| Benzaldehyde | $CNCH_2Ti(NEt_2)_3$ | THF | 3.0 | –78 to +22 | 2-Cyano-1-phenylethanol | 76 |
| Benzaldehyde | $Me_3SiCH_2Ti(OPr^i)_3$ | THF | 48.0 | +22 | 2-Trimethylsilyl-1-phenylethanol | 41 (60) |
| Benzaldehyde | 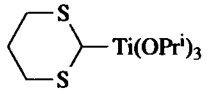 | $Et_2O$ | 16.0 | r.t. | (1,3-Dithian-2-yl)phenylmethanol | — (90) |
| Benzaldehyde | $PhSO_2CH_2Ti(OPr^i)_3$ | THF | 3.0 | –78 to +22 | 2-Benzensulfonyl-1-phenylethanol | 95 (100) |
| Butanal | $Me_2TiCl_2$ | $CH_2Cl_2$ | 1.0 | –40 | 2-Pentanol | — (90) |
| Cyclohexanecarbaldehyde | $Me_2TiCl_2$ | $CH_2Cl_2$ | 1.0 | –40 | 1-Cyclohexylethanol | 78 (95) |
| 3-Methylbutanal | $MeTiCl_3$ | $CH_2Cl_2$ | 0.5 | –30 | 4-Methyl-2-pentanol | — (90) |
| Cyclohexanecarbaldehyde | $MeTiCl_3$ | $CH_2Cl_2$ | 0.5 | –40 | 1-Cyclohexylethanol | — (90) |
| Cyclohexanecarbaldehyde | $Ph_2TiCl_2$ | $CH_2Cl_2$ | 0.5 | –78 | Cyclohexylphenylmethanol | — (90) |

[a] Adapted from the tables reported in refs. 21, 39 and 42–44. [b] 1:1.2 molar ratio unless otherwise specified. [c] Percentages within parentheses are estimated by $^1H$ NMR. [d] No 1,4-adduct formed. [e] In the absence of solvent, using distilled $MeTi(OPr^i)_3$. [f] 1:2 molar ratio. [g] 1:10 molar ratio. [h] One diastereomer only. [i] 1:1 *cis*:*trans* mixture.

**Table 3** Carbonyl Addition Reactions of Various Alkyl- and Aryl-zirconium(IV) Tri-*n*-butoxides[39]

| *Carbonyl compound* | *Nucleophile* | *Solvent* | *Time (h)* | *Temperature (°C)* | *Product* | *Yield (%)* |
|---|---|---|---|---|---|---|
| 2-Methylcyclohexanone | $MeZr(OBu^n)_3$ | $CH_2Cl_2$ | 15 | –20 to +20 | 1,2-Dimethylcyclohexanol[a] | 70 |
| 3β-Acetoxy-5-androsten-17-one | $MeZr(OBu^n)_3$ | $CH_2Cl_2$ | Overnight | –20 to +20 | 17α-Methyl-5-androstene-3β,17β-diol[b,c] | 80 |
| α-Tetralone | $MeZr(OBu^n)_3$ | $Et_2O$ | 24 | r.t. | 1,2,3,4-Tetrahydro-1-methylnaphthol | 90 |
| 4-Phenyl-4-ketobutyric acid | $MeZr(OBu^n)_3$ | $CH_2Cl_2$ | 15 | –20 to +20 | 4-Hydroxy-4-phenylpentanoic acid | 72 |
| 5-Nitro-2-pentanone | $MeZr(OBu^n)_3$ | $CH_2Cl_2$ | 2 | 0 | 2-Methyl-5-nitro-2-pentanol | 72 |
| 2-Methylcyclohexanone | $PhZr(OBu^n)_3$ | $CH_2Cl_2$ | 15 | –20 to +20 | 1-Phenyl-2-methylcyclohexanol[c] | 90 |
| 4-*t*-Butylcyclohexanone | $Bu^nZr(OBu^n)_3$ | $CH_2Cl_2$ | 8 | –80 to +20 | 1-*n*-Butyl-4-*t*-butylcyclohexanol[d] | 78 |
| Benzaldehyde | 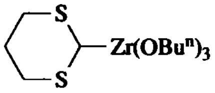 | THF | Overnight | –80 to +20 | (1,3-Dithian-2-yl)phenylmethanol | 85 |

[a] Mixture of diastereomers. [b] After ester hydrolysis. [c] One diastereomer only. [d] 86:14 *cis:trans* mixture.

of the substrate aldehydes as well as the structure of the reagent, including both its nucleophilic moiety and the ligand system (Table 4).[44]

**Table 4** Ligand Influence on the Addition to Benzaldehyde of Various $MeTi(OR)_3$ Derivatives in Ether at –50 °C

| *R* | *Time (min)* | *Yield (%)* |
|---|---|---|
| Propyl | 60 | 20 |
| *i*-Propyl | 60 | 90 |
| *i*-Propyl (distilled) | 30 | 98 |
| (*R*,*S*)-*s*-Butyl | 30 | 99 |
| (*S*)-2-Methylbutyl | 5 | >95 |

The reaction of $MeTi(OPr^i)_3$ with a 1:1 molar ratio of the isomeric hexanal (**37**) and 2-ethylbutanal (**38**) affords a mixture of the carbinols (**39**) and (**40**) in a 92:8 molar ratio (equation 19).[46] Another example of stereocontrol in the chemoselectivity of these reagents is represented by the cross reactions of the ketone pairs (**41**) and (**42**) (equation 20) or (**42**) and (**45**) (equation 21).[16] It is worthy of note that the same 1:1 molar mixture of (**42**) and (**45**) reacts more or less statistically with MeLi, affording about 50% of both (**44**) and (**46**).[16]

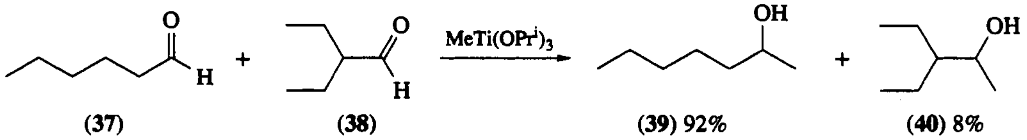
O
H
(37)
+
O
H
(38)
MeTi(OPr^i)_3
OH
(39) 92%
+
OH
(40) 8%

(19)

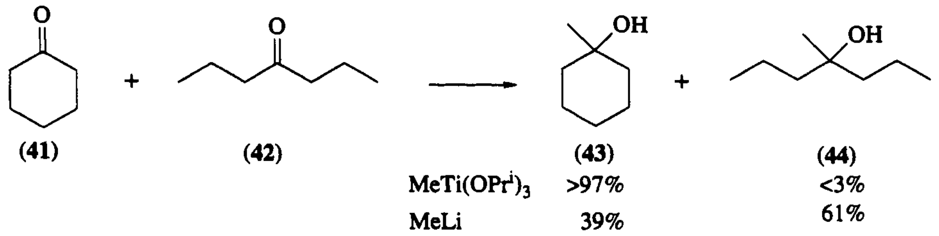
O
(41)
+
O
(42)
OH
(43)
+
OH
(44)
MeTi(OPr^i)_3 >97% <3%
MeLi 39% 61%

(20)

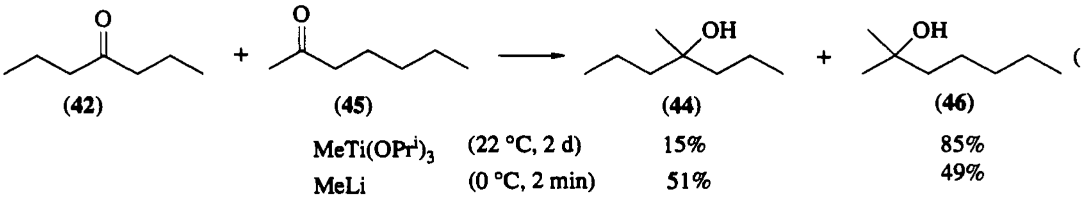
O
(42)
+
O
(45)
OH
(44)
+
OH
(46)
MeTi(OPr^i)_3 (22 °C, 2 d) 15% 85%
MeLi (0 °C, 2 min) 51% 49%

(21)

Chemoselectivity is affected by electronic factors as well. Cross experiments show that small changes in the electrophilic nature of the carbonyl group are responsible for marked differences in the nucleophilic reactivity of $Ti^{IV}$ and $Zr^{IV}$ reagents (equations 22 and 23).[16] The electronic nature of the nucleophilic moiety of the metal reagent also affects the chemoselectivity of the nucleophilic addition. This is the case for some special titanium(IV) triisopropoxide derivatives [*e.g.* (**53**)–(**56**)] which are selective towards aldehydes and give high addition yields, due to their resonance-stabilized residues acting as nucleophiles.[42]

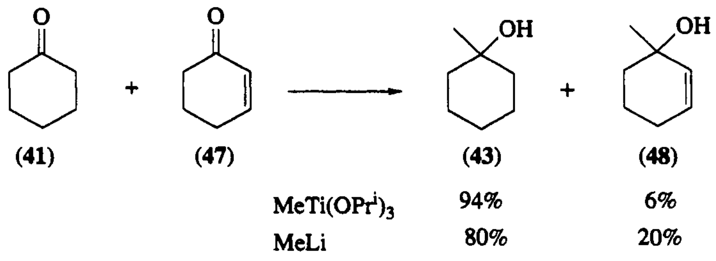
O
(41)
+
O
(47)
OH
(43)
+
OH
(48)
MeTi(OPr^i)_3 94% 6%
MeLi 80% 20%

(22)

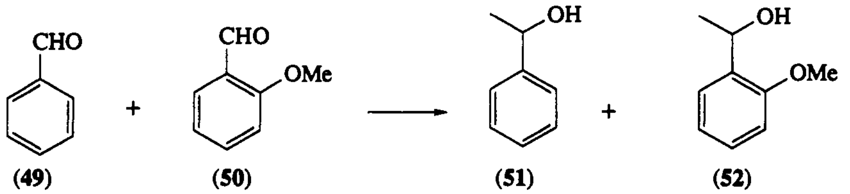

**(49)** **(50)** **(51)** **(52)** (23)

| | (51) | (52) |
|---|---|---|
| $\mathrm{MeTi(OPr^i)_3}$ | 13% | 87% |
| MeLi | 50% | 50% |

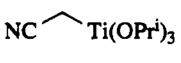

**(53)**

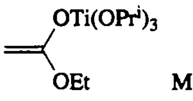

**(54)**

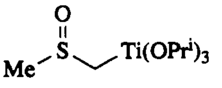

**(55)**

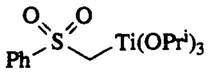

**(56)**

The picture remains substantially unchanged moving from the trialkoxy system to other ligand systems. $\mathrm{(Alkyl)Ti(NMe_2)_3}$, in spite of their appealing stability,[47] fail to give Grignard-type additions, and lead only to low-yielding aminoalkylation reactions (Section 1.5.5.2).[42,48] Alkyl- and aryl-chlorotitanium derivatives, like $\mathrm{MeTiCl_3}$, $\mathrm{Me_2TiCl_2}$ and $\mathrm{Ph_2TiCl_2}$, characteristically exhibit good reactivity leading to nucleophilic addition in high yields (Table 2), accompanied by high chemoselectivity.[21] $\mathrm{MeTiCl_3}$, the parent compound of the series, is a well-known and well-studied chemical. Its coordination complexes with electron-donor species, like TMEDA, glyme, THF and (–)-sparteine, are also well known.[49a] As already mentioned (equation 8), it is easily obtained from MeLi and $\mathrm{TiCl_4}$ in ether and its $\mathrm{Et_2O}$ complex is very reactive towards aldehydes, acting at –30 °C, much faster and higher yielding than $\mathrm{MeTi(OPr^i)_3}$ and having satisfactory chemoselectivity.[27] Recently, an analogous trichlorotitanium derivative (**57**) has been prepared from 1,2-diorganometallic species with $\mathrm{TiCl_4}$.[49b] The reaction of (**57**) with carbonyl compounds is represented in Scheme 4.

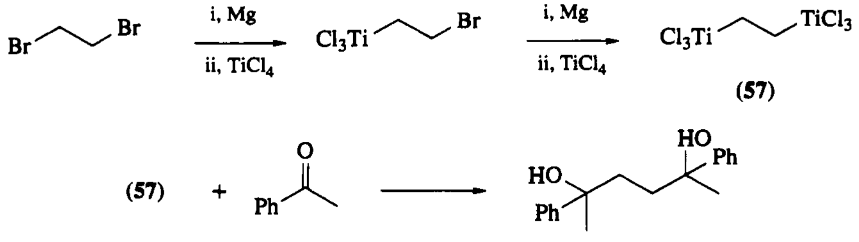

**Scheme 4**

The instability of $\mathrm{Ti^{IV}}$ reagents with branched alkyl groups is due to their tendency to decompose by β-elimination.[9] For this type of compounds the corresponding zirconium reagents are more suitable, since they do not undergo decomposition. For example, *t*-butylzirconium tributoxide (**58b**) is readily prepared from *t*-butyllithium and chlorozirconium tributoxide (**58a**) (equation 24).[39] Alkyl- and aryl-zirconium(IV) tributoxides add to carbonyl compounds (Table 3) in the same fashion as $\mathrm{Ti^{IV}}$ derivatives, with the advantage of low basicity, as is shown by their reactions with enolizable carbonyl compounds (Section 1.5.3.1.2).

$$\underset{\textbf{(58a)}}{\mathrm{ClZr(OBu^n)_3}} + \mathrm{Bu^tLi} \longrightarrow \underset{\textbf{(58b)}}{\mathrm{Bu^tZr(OBu^n)_3}} + \mathrm{LiCl} \qquad (24)$$

A mechanistic interpretation of all the above facts would be attractive at this point. Unfortunately, a comprehensive explanation of the experimental results is not yet available, with the exception of kinetic studies on cyclic ketones[50] and other carbonyls.[51]

### *1.5.3.1.2 Addition to enolizable carbonyl compounds*

2-Phenylcyclopentanone (**59**) is converted to its methylated diastereomeric derivatives (**60**) and (**61**) in reasonably high yield (>90%) (equation 25), by treatment with $Me_2Ti(OPr^i)_2$.[46] When methyllithium is used, under comparable experimental conditions, only a 55% yield and lower selectivity is achieved. This can be accounted for by the relatively low basicity of titanium reagents. There is no general rule that allows one to choose the titanium reagent with the proper balance of nucleophilicity and basicity for a particular substrate. As an example, β-tetralone is methylated in 90% yield, using a $MeLi/TiCl_4$ reagent, *versus* 60% yield obtained with MeLi alone, due to competing enolization.[27]

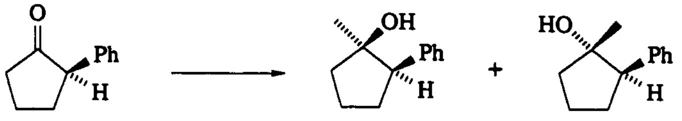

(25)

**(59)** **(60)** **(61)**

| | (60) | (61) | |
|---|---|---|---|
| MeLi | 90% | 10% | (<55%) |
| $Me_2Ti(OPr^i)_2$ | >97% | <3% | (>90%) |

The above-mentioned requirements of low basicity and fast alkyl transfer are combined in alkylzirconium(IV) species,[16,41] like tetramethylzirconium which readily methylates enolizable and highly hindered carbonyl compounds such as (**62**; equation 26). The presence of several alkyl groups on the metal atom imparts enhanced reactivity to the species due to the absence of π-bond-forming electron-donor heteroatoms. In fact, tetramethylzirconium can be regarded as a supermethylating agent, evidenced by the conversion of (**65**) into (**66**; equation 27).[11]

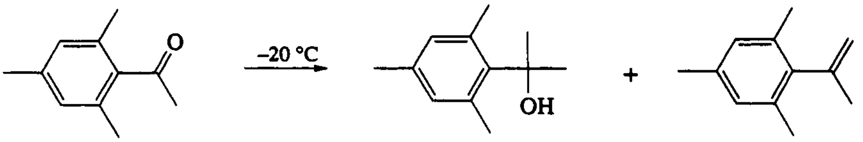

(26)

**(62)** **(63)** **(64)**

| | (63) | (64) | |
|---|---|---|---|
| $Me_4Ti$ | 20% | 35% | (45% SM) |
| $Me_4Zr$ | 45% | 0% | (55% SM) |

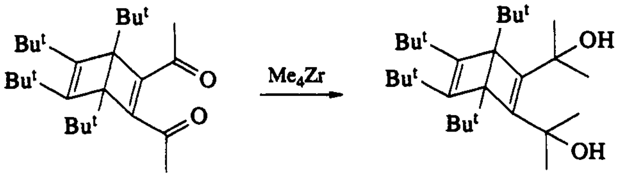

(27)

**(65)** **(66)**

### *1.5.3.1.3 Stereocontrol in nucleophilic addition to carbonyl compounds*

An attempt to prepare (+)-cuparene (**68**), although unsuccessful, illustrates diastereoselectivity of $Ti^{IV}$ reagents.[16] Treatment of (**67**) with $Me_2TiCl_2$ (Scheme 5) does not give the desired dimethylated product, but rather produces the diastereomeric tertiary alcohols (**69**) and (**70**) in a 95:5 molar ratio. The diastereoselectivity, characteristic of $Zr^{IV}$ reagents as well, is influenced by both the electronic nature and the steric hindrance of the metal ligands. Three different types of stereoselection are as follows: (i) diastereofacial selection involving carbonyl substrates bearing a chiral α-carbon atom;[52] (ii) equatorial *versus* axial selection occurring with six-membered cyclic ketones; and (iii) simple diastereoselectivity that is encountered in the reaction of prochiral crotyltitanium(IV) derivatives with prochiral carbonyl compounds. This type of selectivity will be considered in Section 1.5.3.3.

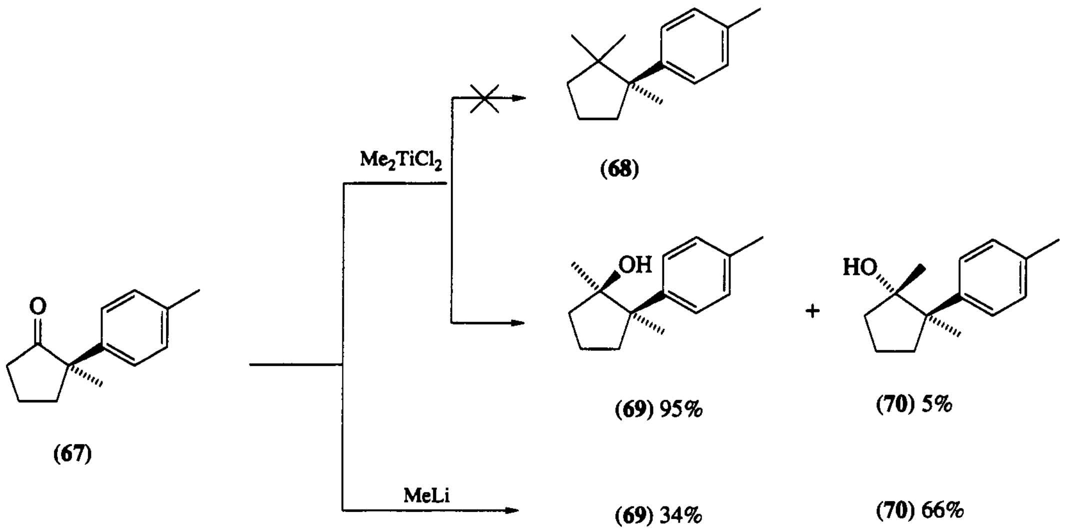

Scheme 5

### *(i) Diastereofacial selection*

Cram's experiments using 2-phenylpropanal with various traditional organometallic reagents have already been mentioned.[19,20] The same substrate was also subjected to several $Ti^{IV}$ and $Zr^{IV}$ complexes (equation 28),[21] the results of which are summarized in Table 5. 2-Phenylbutanal, when treated with $MeTi(OPr^i)_3$ in $Et_2O$, affords preferentially the 'Cram' product (87:13).[53a] $Zr^{IV}$ derivatives, like $MeZr(OPr^i)_3$, follow the same tendency although in some cases the results are somewhat less appealing.[41]

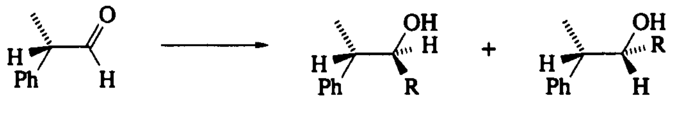

(71) 'Cram' product

(72) '*anti*-Cram' product

(28)

**Table 5** Diastereoselective Addition of $Ti^{IV}$ and $Zr^{IV}$ Complexes to 2-Phenylpropanal (equation 28)

| *Reagent* | *(71):(72)* | *Ref.* |
|---|---|---|
| $MeTi(OPr^i)_3$ | 87:13 | 21 |
| $MeTiCl_3$ | 81:19 | 21 |
| $MeTi(OPh)_3$ | 93:7 | 16 |
| $MeLi/TiCl_4/Et_2O$ | 90:10 | 11 |
| $Ph_2TiCl_2$ | 80:20 | 11 |
| $Bu^nTi(OPr^i)_3$ | 89:11 | 41 |
| $(Allyl)Ti(OPr^i)_3$ | 68:32 | 53 |
| $[(Allyl)Ti(OPr^i)_4]^- MgCl^+$ | 75:25 | 11 |
| $MeZr(OPr^i)_3$ | 90:10 | 41 |

$Ti^{IV}$ complexes have been extensively used for the stereoselective introduction of side chains in steroidal molecules, *e.g.* pregnenolone acetate[53a] and the steroidal[11] C-22 aldehyde (73; equation 29). In these cases satisfactory results are only obtained by using $Ti^{IV}$ reagents, like methyl, $d_3$-methyl and allyl derivatives, due to the strong steric hindrance that affects the position to be attacked. 1,3-*Anti* diastereoselection in the addition of alkyltitanium reagents to chirally β-substituted aldehydes having a dithioacetal group at the α-position (75) was also observed (equation 30).[53b]

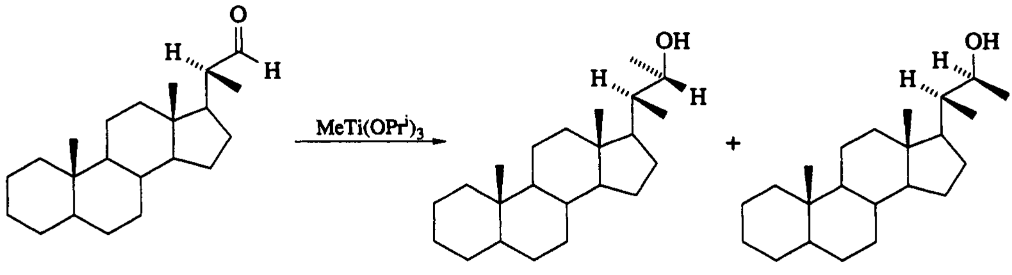

(29)

**(73)** **(74a)** 99% **(74b)** 1%

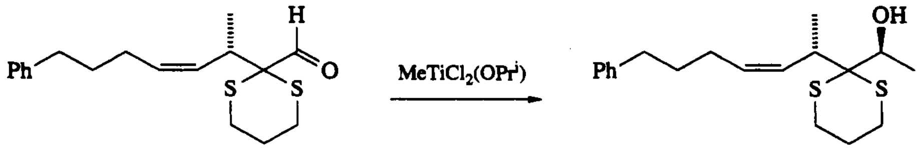

(30)

**(75)** *anti*:*syn* = 99:1

*(ii) Equatorial* versus *axial selection*

Nucleophilic additions to 4-*t*-butylcyclohexanone (**76**; equation 31), by various MeTi$^{IV}$ and MeZr$^{IV}$ reagents (Table 6), are reported to afford mixtures of (**77**) and its C-1 epimer (**78**) with the equatorial methyl bearing isomer (**77**) always predominating. MeTi(OPr$^i$)$_3$ has been used successfully in the steroid field, as in the case of cholestan-3-one[53a] or as in the case of androstane-3,17-dione (**79**; equation 32)[11] which undergoes regio- and diastereo-selective methyl addition. MeTiCl$_3$ is also reported to react with C-2- and C-3-substituted cyclohexanones, leading to significant excesses of the equatorial methyl bearing epimers (88:12 in the case of 3-methylcyclohexanone), whereas MeMgI furnishes random mixtures of both epimers.[27]

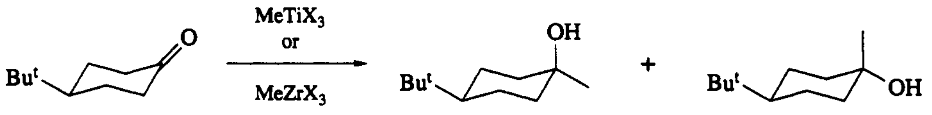

(31)

**(76)** **(77)** **(78)**

**Table 6** Equatorial *versus* Axial Addition of MeTi$^{IV}$ and MeZr$^{IV}$ Reagents to 4-*t*-Butylcyclohexanone (equation 31)

| *Reagent* | *Solvent* | *Temperature (°C)* | *Equatorial:axial (77):(78)* | *Ref.* |
|---|---|---|---|---|
| MeTi(OPr$^i$)$_3$ | CH$_2$Cl$_2$ | +22 | 82:18 | 16 |
| MeTi(OPr$^i$)$_3$ | Et$_2$O | +22 | 86:14 | 16 |
| MeTi(OPr$^i$)$_3$ | Et$_2$O | 0 | 89:11 | 16 |
| MeTi(OPr$^i$)$_3$ | *n*-Hexane | −15 to +22 | 94:6 | 53 |
| Me$_2$TiCl$_2$ | CH$_2$Cl$_2$ | −78 | 82:18 | 21 |
| MeZr(OBu$^n$)$_3$ + LiCl | Et$_2$O | +22 | 80:20 | 39 |

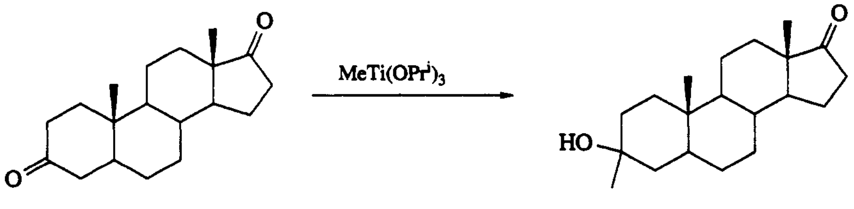

(32)

**(79)** **(80)**

α-alcohol:β-alcohol = 85:15

Mechanistic interpretations of diastereoselectivity, based on the Cram's open chain model as well as more recent models, have been reported.[54,55]

### *1.5.3.1.4 Addition to chiral alkoxycarbonyl compounds*

Chiral α-, β- or γ-alkoxycarbonyl compounds are alkylated by $Ti^{IV}$ and $Zr^{IV}$ reagents with high facial stereoselectivity. This is due to chelation by the metal atom which creates a bridge between the oxygen atoms belonging to the carbonyl function and the alkoxy group, respectively. The resulting cyclic intermediate is then attacked by the nucleophilic moiety of the reagent, preferentially from one side, leading to an excess of one of the potential diastereomeric products. This phenomenon has been observed with other organometallic reagents, though only asymmetric 1,2-induction is known for compounds like RMgX, RLi, $R_2CuLi$ *etc.*,[20,56,57] whereas $Ti^{IV}$ and $Zr^{IV}$ reagents are capable of 1,3- and even 1,4-induction.[58] Furthermore, given that chelation is governed by the Lewis acidity of the metal atom, the chelating properties of the organometallic complexes can be tuned by varying the metal ligand system. The electron-withdrawing halogen ligands increase the acidity and enhance the chelation power. In the presence of electron-donor ligands, like alkoxy and *N,N*-dialkylamino groups, chelation will depend essentially on the nature of the substrates. For example, alkoxy ketones will undergo appreciable chelation, whereas weaker Lewis bases like alkoxy aldehydes will not be chelated, a fact that can be exploited to perform reverse stereochemical control. Examples of asymmetric 1,2- and 1,3-induction are provided by the reactions of the chiral alkoxy aldehydes (**81**) and (**82**), with $MeTiCl_3$ as shown in Scheme 6.[59–61] The induction is consistently over 90%.

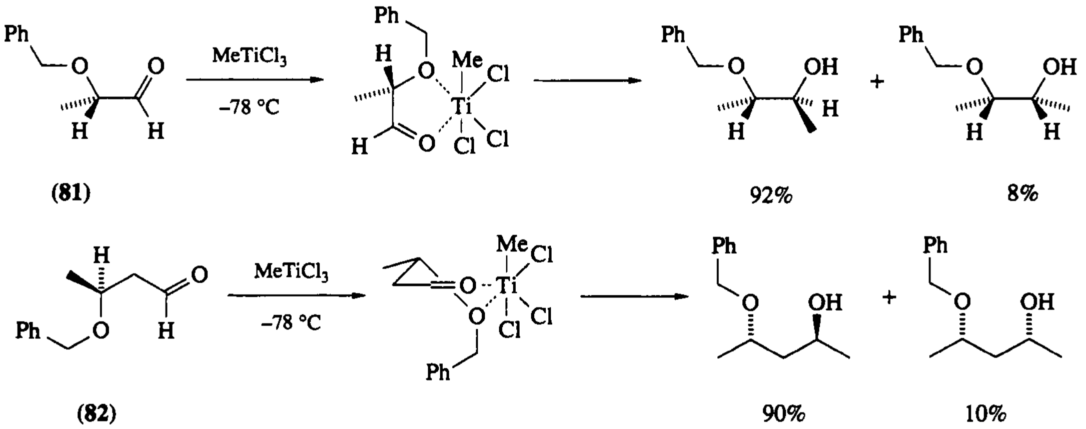

**Scheme 6**

Less acidic than $Ti^{IV}$ and $Zr^{IV}$ chloroderivatives, $MeTi(OPr^i)_3$ performs chelation-controlled addition to chiral alkoxy ketones[59] as well as or better than organomagnesium compounds,[41,58] but fails to chelate to aldehydes or hindered ketones. Should the formation of a cyclic chelation intermediate be forbidden, the reaction is subject to nonchelation control, according to the Felkin–Anh[41] (or Cornforth)[62] model. Under these circumstances, the ratio of the diastereomeric products is inverted in favor of the 'anti-Cram' product(s). In the case of benzil (**83**; Scheme 7) this can be accounted for by the unlikely formation of a cyclic intermediate such as (**85**), and thus the preferential intermediacy of the open chain intermediate (**86**) that leads to the *threo* compound (**88**).[41] This view is substantiated by the fact that replacement of titanium with zirconium, which is characterized by longer M—O bonds, restores the possibility of having a cyclic intermediate and, as a consequence, leads to the *erythro* (*meso*) compound (**87**) thus paralleling the action of Mg and Li complexes.

Nonchelation-controlled addition reactions can be very useful in organic synthesis.[58,59,63,64] An example drawn from carbohydrate chemistry is particularly significant in this regard (Scheme 8).[11] Due to chelation, the aldehyde (**89**) reacts with MeMgBr to give a mixture of the diastereomeric alcohols (**91**) and (**92**) in 88:12 molar ratio, whereas, in the reaction with $MeTi(OPr^i)_3$ under nonchelation control, only the Felkin–Anh product (**92**) is observed. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**93**; equation 33) is also reported to react under nonchelation-controlled conditions with several $RTi(OPr^i)_3$ reagents.[58] Oddly, $PhTi(OPr^i)_3$ favors the formation of the *syn* product, a unique result that is difficult to rationalize.

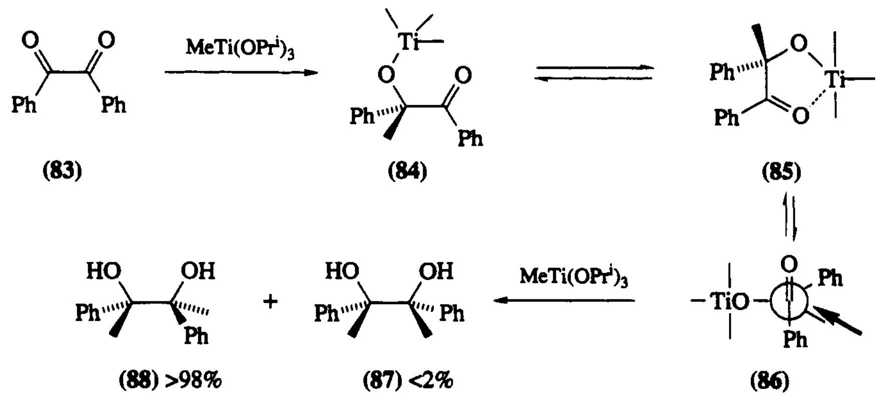

Scheme 7

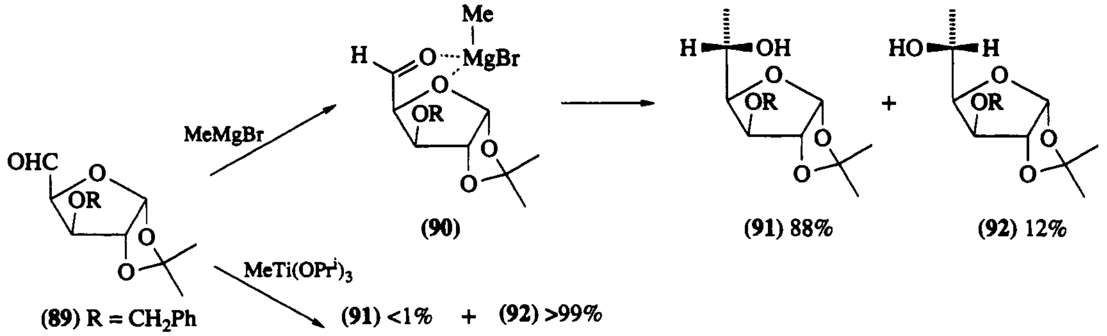

Scheme 8

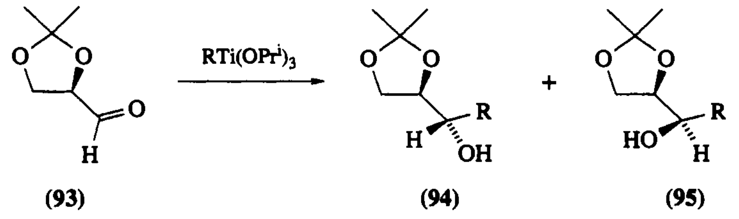

(33)

| | (94) | (95) |
|---|---|---|
| R = Me | 75% | 25% |
| R = Bu$^n$ | 90% | 10% |
| R = Allyl | 71% | 29% |
| R = Ph | 9% | 91% |

Very few examples of asymmetric 1,4-induction are reported in connection with the addition of acidic Ti$^{IV}$ complexes to chiral $\gamma$-alkoxycarbonyl compounds. According to the Cram model, the chelation is expected to afford a flexible seven-membered ring intermediate, resulting in less efficient induction (equation 34).[59] An early example of asymmetric 1,4-induction is provided by the reaction of *o*-phthalaldehyde (**96**; equation 35)[41] with 2 equiv. of MeTi(OPr$^i$)$_3$ which affords an 83:17 molar mixture of *racemic*-(**97**) and *meso*-(**98**), whereas the analogous reaction with MeMgI leads to a 1:1 mixture of the above diastereomers.

The intrinsic difficulty in preparing various titanium derivatives with the desired alkyl group may be overcome by using reagent systems consisting of TiCl$_4$ as the chelating agent, and a suitable nucleophile like dialkylzinc, allylsilanes, allylstannanes, *etc.*[59] The utilization of other nucleophiles, like silyl enol ethers will be covered in Part 1 of Volume 2.

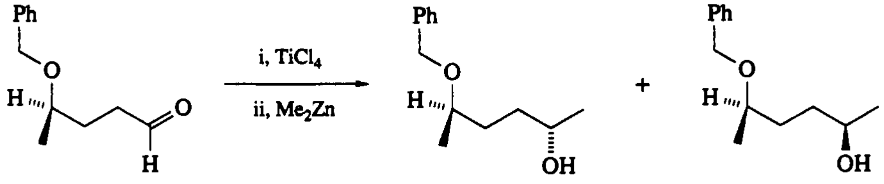

(34)

85% 15%

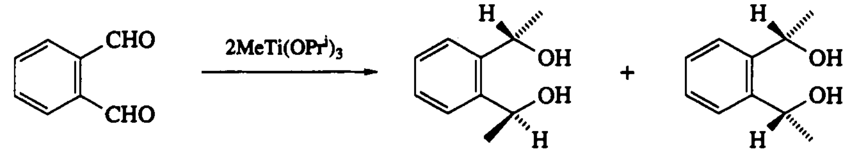

(35)

(**96**) (**97**) 83% (**98**) 17%

### *1.5.3.1.5 Addition to α,β-unsaturated carbonyl compounds*

α,β-Unsaturated carbonyl compounds undergo 1,2-addition by $MeTi(OPr^i)_3$.[16,42,43] A rare case of conjugate addition is reported in the reaction of (**99**; equation 36) with $Ti(CH_2Ph)_4$.[65]

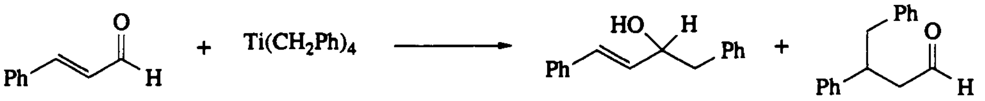

(36)

(**99**) 13% 87%

$Ti^{IV}$ reagents are chemoselective and usually react with α,β-unsaturated carbonyls faster than with their saturated analogs, as is shown by several cross experiments (equation 37).[11] An exception to this generality was observed in the case of cyclohex-2-enone *versus* cyclohexanone,[16] the latter being much more reactive (equation 22, Section 1.5.3.1.1).

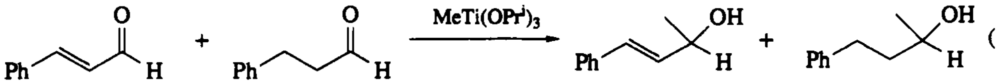

(37)

(**99**) 78% 22%

## 1.5.3.2 Vinylzirconium Reagents: Addition to α,β-Unsaturated Ketones

Vinylzirconium(IV) complexes, unlike their $Ti^{IV}$ analogs (Section 1.5.2.2), are rather stable and can be conveniently used to perform conjugate addition to α,β-unsaturated ketones, sometimes in preference to the more popular alkenylcopper(I) reagents.[66] Vinylzirconium(IV) complexes, as such, are not very reactive and need catalytic amounts of $Ni(acac)_2$ (Scheme 9).[67,68] The reaction has been exploited in a prosta-

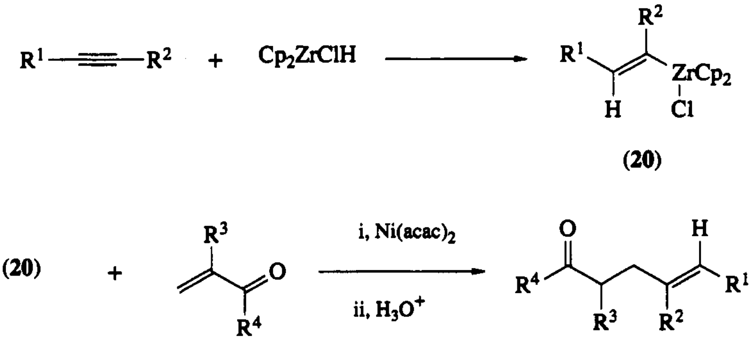

(**20**)

Scheme 9

glandin synthesis.[68] A mechanistic investigation of the addition reaction of vinylzirconium(IV) complexes to carbonyls has been reported.[69]

### 1.5.3.3 Allylic Titanium and Zirconium Reagents

As the general reactivity of allylic metal derivatives will receive proper attention in Part 1 of Volume 2, only those aspects which are very peculiar of allylic $Ti^{IV}$ and $Zr^{IV}$ reagents in organic synthesis will be covered in this section. From a general point of view, the allylic metal derivatives turn out to be fairly more reactive than their alkyl analogs and, as a consequence, show a diminished selectivity. As a matter of fact, (allyl)$Ti(OPr^i)_3$ reacts with a 1:1 molar mixture of heptanal and heptan-2-one (equation 38), leading to the isomeric homoallylic alcohols (**100**) and (**101**) in 86:14 ratio,[35] as well as with a 1:1 molar mixture of benzaldehyde and acetophenone giving (**102**) and (**103**) in 84:16 ratio, (equation 39),[11] whereas ketones remain substantially untouched when alkyltitanium reagents are used likewise in cross reactions (Section 1.5.3.1.1).

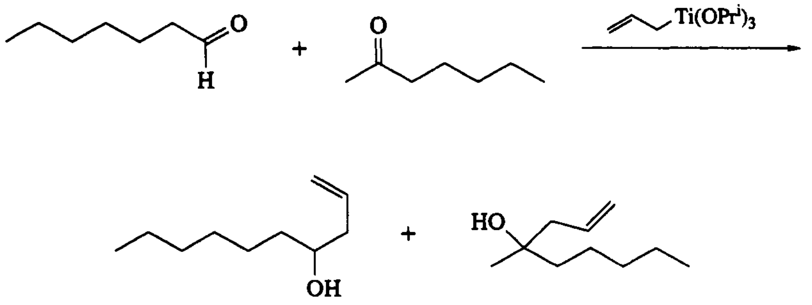

(**100**) 86% (**101**) 14%

(38)

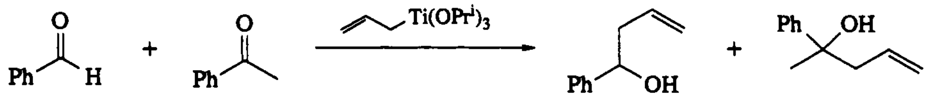

(**102**) 84% (**103**) 16%

(39)

A few examples of chemoselective additions of allyltitanium reagents to aliphatic and aromatic carbonyl compounds are reported in Table 7. Appreciable chemoselectivity toward the aldehydic function is achieved by the titanium ate complex (**23**), whereas the reverse chemoselectivity toward ketones is realized using aminotitanium complex (**104**) and the analogous ate complexes (**24**) and (**25**), as is shown in Table 7. This is very interesting since it represents a rare case of chemoselectivity in favor of carbanion addition to ketones. A tentative explanation of this inverse chemoselection considers a fast transfer of the aminyl ligand onto the aldehyde function which becomes 'protected', as in (**105**), and thus unreactive in respect to the keto group.[35] Ketones react also selectively compared with esters, as is shown by the reaction of ethyl levulinate (**1**) with the ate complex (**23**; equation 40).[35]

**Table 7** Chemoselective Addition of Allyltitanium Reagents to Equimolar Mixtures of Heptanal/Heptan-2-one (equation 38) and Benzaldehyde/Acetophenone (equation 39)[a]

| *Reagent* | | *(**100**):(**101**)* | *(**102**):(**103**)* |
|---|---|---|---|
| (Allyl)$Ti(OPr^i)_3$[b] | | 86:14 | 84:16 |
| $[(Allyl)Ti(OPr^i)_4]^- MgCl^+$ | (**23**) | 98:2 | 98:2 |
| (Allyl)$Ti(NMe_2)_3$[b] | (**104**) | 13:87 | 50:50 |
| $[(Allyl)Ti(NMe_2)_4]^- MgCl^+$ | (**24**) | 4:96 | < 1:99 |
| $[(Allyl)Ti(NMe_2)_4]^- Li^+$ | (**25**) | 2:98 | 9:91 |

[a] Adapted from the tables reported in refs. 11, 16 and 35. [b] Prepared *in situ*.

As far as the stereoselectivity of the addition is concerned, allyltitanium reagents, unlike their alkyl analogs (Section 1.5.3.1.3), give preferentially axial addition to 4-*t*-butylcyclohexanone. The selectivity

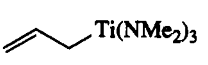

**(104)**

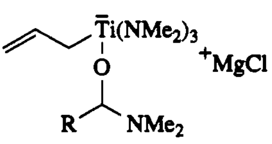
Ti(NMe2)3
O
+MgCl
R
NMe2

**(105)**

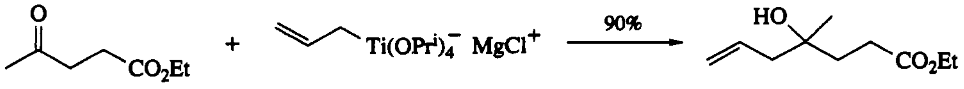
O
CO2Et
+
Ti(OPri)4− MgCl+
90%
HO
CO2Et

(40)

**(1)** **(23)**

is rather low and can be improved by using tris(dialkylamino) ligands.[53a] An example of diastereofacial selectivity of allyl derivatives is offered by tetraallylzirconium in the addition of chiral β-alkoxycarbonyl compounds;[60] 3-hydroxybutanal (**106**) reacts with tetraallylzirconium (Scheme 10) under chelation control conditions (asymmetric 1,3-induction) affording the epimeric diols (**107**) and (**108**) in 19:81 ratio. The chemistry of crotyl-$Ti^{IV}$ and -$Zr^{IV}$ derivatives is definitely more interesting due to their addition reactions which turn out to be sharply chemoselective, regioselective (since they attack the carbonyl substrate by their more substituted $sp^2$-carbon atom), and diastereoselective.

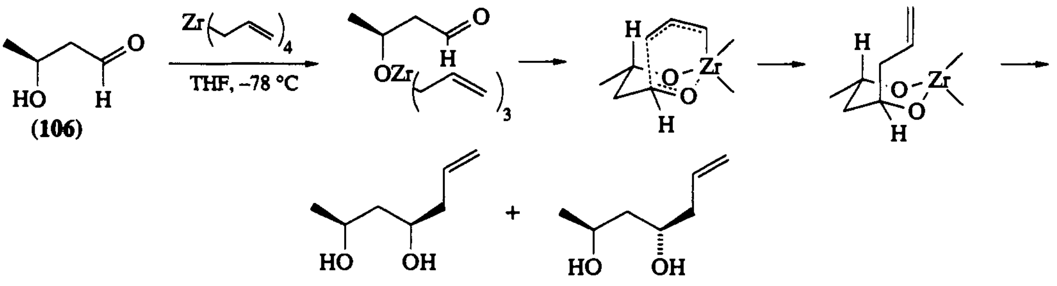
O
HO H
Zr( )4
THF, −78 °C
O
OZr( )3
H
H
O
Zr
O
H
H
O
Zr
O
H
HO OH
+
HO OH

**(106)**

**(107)** 19% **(108)** 81%

**Scheme 10**

Chemoselectivity of these reagents, tested in cross experiments (equations 41 and 42), parallels the one already discussed for the allyl derivatives.[16,35]

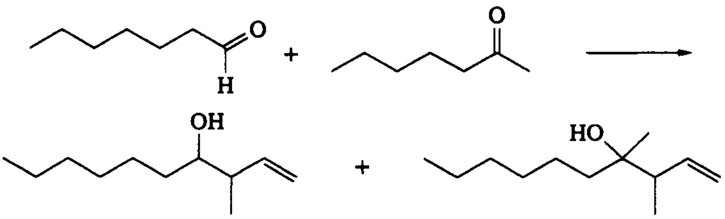

(41)

| | | |
|---|---|---|
| (Crotyl)Ti(OPri)4−MgCl+ | 98% | 2% |
| (Crotyl)Ti(NMe2)4−MgCl+ | <2% | 98% |

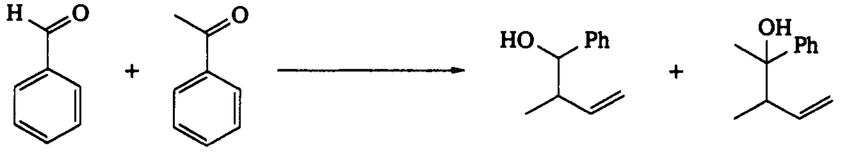
H
O
+
O
HO
Ph
+
OH
Ph

(42)

| | | |
|---|---|---|
| (Crotyl)Ti(OPri)4−MgCl+ | 99% | 1% |
| (Crotyl)Ti(NMe2)4− MgCl+ | 2% | 98% |

Diastereoselectivity is instead extremely important, giving rise to configurationally pure branched homoallylic alcohols. The stereochemistry of the products, which can have *threo* or *erythro* configurations, is dependent on the (*E*)- or (*Z*)-geometry of the starting crotyl metal reagent.[11] Examples of (*Z*)-crotyltitanium(IV) derivatives are not known and only $^1H$ NMR evidences allow such reagents to be assigned, not unambiguously, (*E*)-configuration.[11] The addition of several crotyl-$Ti^{IV}$ and -$Zr^{IV}$ derivatives to various aldehydes and ketones (equation 43) leads invariably to a mixture of *threo* (*anti*) (**109**) and *erythro* (*syn*) (**110**) homoallylic alcohols (Table 8; *cf.* also Table 9). In spite of an influence of the metal ligand system on the diastereoselectivity of the addition (Table 8), the *threo* product appears to be always predominant regardless of the $Ti^{IV}$ reagent used. In this context, no general rule can be put forward about the choice of the suitable ligand system, although the ate complex (**30**) seems to be the most selective in the addition to aromatic aldehydes, whereas the crotyltriamide complex (**28**) should be preferred when aliphatic aldehydes are considered. The triphenoxy ligand system is also interesting, as is shown by some entries in Table 8.

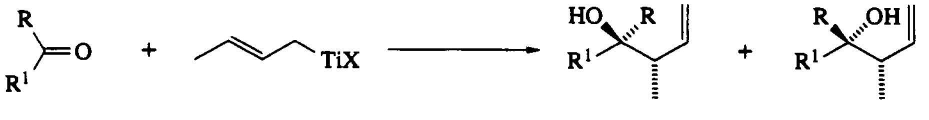

(43)

*threo*-(**109**) *erythro*-(**110**)

R = or ≠ H; $R^1$ = alkyl or aryl; X = $(NEt_2)_3$, $(OPr^i)_3$, $(OPh)_3$, $(OPr^i)_3MgCl$, $(OBu)_3$, 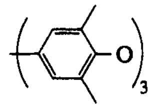

Table 8 Diastereoselective Addition of Various Crotyltitanium(IV) Reagents to Carbonyl Compounds (equation 43)[a]

| *Carbonyl compound* | *Reagent* | *threo:erythro* |
|---|---|---|
| Benzaldehyde | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 69:31 |
| Hexanal | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 82:18 |
| Acetaldehyde | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 67:33 |
| 3-Methylbutan-2-one | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 97:3 |
| Heptan-2-one | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 72:28 |
| 3,3-Dimethylbutan-2-one | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 99:1 |
| Acetophenone | $(Crotyl)Ti(NEt_2)_3$ (**28**) | 85:15 |
| Benzaldehyde | $(Crotyl)Ti(OPr^i)_3$ (**29**) | 80:20 |
| Hexanal | $(Crotyl)Ti(OPr^i)_3$ (**29**) | 75:25 |
| 3-Methylbutan-2-one | $(Crotyl)Ti(OPr^i)_3$ (**29**) | 88:12 |
| Heptan-2-one | $(Crotyl)Ti(OPr^i)_3$ (**29**) | 67:33 |
| Benzaldehyde | $[(Crotyl)Ti(OPr^i)_3]^- MgCl^+$ (**30**) | 84:16 |
| Hexanal | $[(Crotyl)Ti(OPr^i)_3]^- MgCl^+$ (**30**) | 71:29 |
| 3-Methylbutan-2-one | $[(Crotyl)Ti(OPr^i)_3]^- MgCl^+$ (**30**) | 78:22 |
| Heptan-2-one | $[(Crotyl)Ti(OPr^i)_3]^- MgCl^+$ (**30**) | 56:44 |
| Benzaldehyde | $(Crotyl)Ti(OPh)_3$ | 85:15 |
| 3,4-Dihydro-1(2*H*)-naphthalenone | $(Crotyl)Ti(OPh)_3$ | 65:35 |
| Octan-2-one | $(Crotyl)Ti(OPh)_3$ | 70:30 |

[a] Adapted from the tables reported in refs. 11, 16, 53, 70 and 71.

Addition to ketones represents the real field of broad application of crotyltitanium(IV) reagents.[53a] 3-Methylbutan-2-one, by reaction with (**28**), gives a mixture of its *threo* and *erythro* addition products in a 97:3 molar ratio (>95% conversion), other ketones as reported in Table 8 also lead to their addition products in *threo:erythro* molar ratios which are of synthetic relevance. The simple aliphatic ketones react satisfactorily with (**28**). The use of $(crotyl)Ti(OPh)_3$ in this case does not give significant advantages, considering both diastereoselectivity of addition and availability of the reagent relative to (**28**), (**29**) and (**30**).[71] The enormous potential of these reagents can be fully understood considering that the corresponding Grignard reagents show no selectivity in the addition, and allylboranes either react very slowly or do not react at all with ketones.[17,73] Several mechanistic interpretations are also available, accounting for chemo- and diastereo-selectivity of crotyltitanium(IV) reagents.[11,53a,74]

Crotyl-titanocene and -zirconocene complexes, like bis(cyclopentadienyl)-$Ti^{IV}$ and -$Zr^{IV}$ derivatives (**111a–d**) react (equation 44) with aldehydes (Table 9) with pronounced *threo* diastereoselectivity (>90:<10 *threo:erythro* (**112**):(**113**) for $Ti^{IV}$ reagents[37] and approximately 80:20 for their $Zr^{IV}$ analogs).[36]

Less electronegative the halogen atom in (**111a–c**), higher the stereoselectivity of the addition.[17,37] Addition reactions of these reagents to ketones are not reported. The enhanced diastereoselectivity of titanocene-like crotyl derivatives may be ascribed to the strong electron-donating nature of the cyclopentadienyl residues which reduces the Lewis acidity of the complex and, hence, its reactivity.

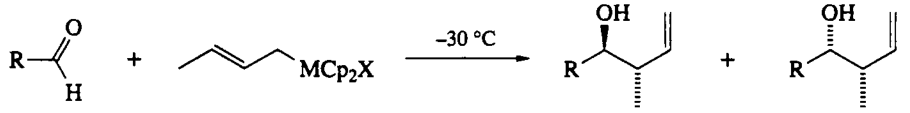

(44)

**(111)** a: X = Cl, M = Ti
b: X = Br, M = Ti
c: X = I, M = Ti
d: X = Cl, M = Zr

**(112)** **(113)**

**Table 9** Diasteroselective Addition of Crotyl-titanocene and -zirconocene Derivatives to Aldehydes (equation 44)[a]

| *Aldehyde* | *Reagent* | *threo:erythro* | *Yield (%)* |
|---|---|---|---|
| Benzaldehyde | $(Crotyl)TiCp_2Cl$ | 60:40 | 96 |
| Benzaldehyde | $(Crotyl)TiCp_2Br$ | 100:0 | 92 |
| Benzaldehyde | $(Crotyl)ZrCp_2Cl$ | 81:19 | 90 |
| Benzaldehyde | $(Crotyl)ZrCp_2Cl + BF_3{\cdot}OEt_2$ | 4:96 | 98 |
| Propanal | $(Crotyl)TiCp_2Cl$ | 66:34 | 92 |
| Propanal | $(Crotyl)TiCp_2Br$ | 96:4 | 92 |
| Propanal | $(Crotyl)ZrCp_2Cl$ | 86:14 | 88 |
| 2-Methylpropanal | $(Crotyl)TiCp_2Br$ | 99:1 | 87 |
| 2-Methylpropanal | $(Crotyl)TiCp_2Br + BF_3{\cdot}OEt_2$ | 9:91 | 75 |
| 2-Methylpropanal | $(Crotyl)ZrCp_2Cl$ | 88:12 | 90 |

[a] Adapted from the tables reported in refs. 36, 37 and 72.

Reverse diastereoselectivity is also reported, as achieved by reaction of crotyl-$Ti^{IV}$ and -$Zr^{IV}$ complexes with aldehydes in the presence of $BF_3{\cdot}OEt_2$ (Table 9).[72,75]

An interesting class of $Ti^{III}$-containing allylic reagents is represented by $(\eta^5\text{-}C_5H_5)_2Ti(\eta^3\text{-allyl})$ compounds (trihaptotitanium compounds), like (**114**), that are readily prepared from $(\eta^5\text{-}C_5H_5)_2TiCl_2$ (**32**) by action of allylic Grignard reagents[76] or, alternatively, alkyl Grignard species and dialkenes (equation 45).[77] When acetone is added to a purple ethereal solution of trihaptotitanium complex (**115**) under argon atmosphere,[38] a reaction takes place spontaneously at room temperature (the reaction medium becomes dark brown) and 2,3-dimethyl-4-penten-2-ol (**116**) is formed in 90% yield (Scheme 11). Benzaldehyde, under the same conditions, affords 1-phenyl-2-methyl-3-buten-1-ol in excellent yield.[38] A further advantage is the possibility of recovering the starting material (**32**), in the end, by simple air oxidation of the acidified reaction mixture (Scheme 11).[38] Due to their pronounced air sensitivity, these π-allyltitanium(III) complexes are most commonly prepared *in situ*.[38] The experiments reported in Table 10 show unambiguously the chemo- and regio-selective nature of their addition reactions.[38] In fact, other functions (*e.g.* halogens, double bonds, carboxylic acid esters) are fully tolerated; furthermore, the attack of the allyl residue occurs at the more substituted γ-carbon atom, with no exceptions. Stereoselectivity is also a relevant feature of a reaction which affords an excess of the *threo* isomer.

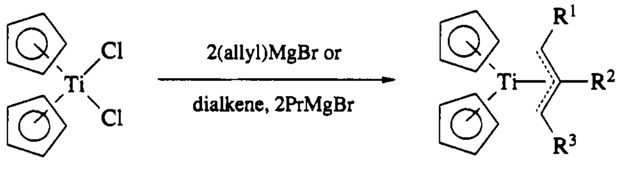

(45)

**(32)** **(114)**

Cyclic allyl residues enable the synthesis of cycloalkenes having a 1-hydroxyalkyl side chain.[78] Cyclic $Ti^{III}$ complexes, like (**118**) and (**119**) are readily obtained (Scheme 12) by treatment of $(\eta^3\text{-}C_5H_5)_2TiCl$ (**117**) with *i*-butylmagnesium chloride and cyclohexadiene or cyclopentadiene respectively, in THF at –40 °C for 10 min.[76,79] Such complexes are quite unstable and can be prepared only *in situ*. Propanal

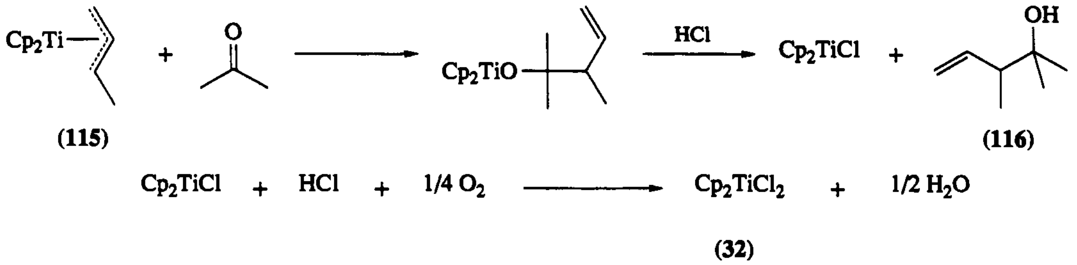
Cp2Ti
+
O
Cp2TiO
HCl
Cp2TiCl
+
OH
(115)
(116)
Cp2TiCl + HCl + 1/4 O2
Cp2TiCl2 + 1/2 H2O
(32)

**Scheme 11**

**Table 10** Addition of Various Allyltitanium(III) Complexes ($RTiCp_2$) to Carbonyl Compounds

| *Carbonyl compound* | *R* | *Product* | *Yield (%)* |
|---|---|---|---|
| Acetone | 1-Methylallyl[b] | 2,3-Dimethyl-4-penten-2-ol | 88 (92)[a] |
| Methyl vinyl ketone | 1-Methylallyl[b] | 3,4-Dimethyl-1,5-hexadien-3-ol[c] | 91 |
| Benzaldehyde | 1-Methylallyl[b] | 2-Methyl-1-phenyl-3-buten-1-ol[d] | 93 |
| Chloroacetone | 1,2-Dimethylallyl[b] | 2,3,4-Trimethyl-1-chloro-4-penten-2-ol | 95 |
| Acrolein | 1,2-Dimethylallyl[b] | 4,5-Dimethyl-1,5-hexadien-3-ol[e] | 90 |
| Levulinic acid methyl ester | 1,2-Dimethylallyl[b] | γ-Methyl-γ-(1,2-dimethylallyl)-γ-butyrolactone | 94 |
| Acetone | 1-Ethylallyl[f] | 2-Methyl-3-ethyl-4-penten-2-ol | 83 (86)[a] |

[a] If isolated $Ti^{III}$ complex is utilized. [b] Prepared from (32), proper diene and PrMgBr. [c] 65:35 mixture of *threo:erythro* diastereomers. [d] 95:5 mixture of *threo:erythro* diastereomers. [e] 90:10 mixture of *threo:erythro* diastereomers. [f] Prepared from (32) and 1-ethylallylmagnesium bromide; m.p. 90.5–91.0 °C.

reacts with (**119**) stereoselectivity,[78] affording exclusively the *erythro* compound (**120**) in 86% yield (Scheme 13); benzaldehyde also shows excellent stereoselection,[78] in spite of a somewhat lower reaction yield (Scheme 13). $\eta^3$-Cyclohexenyltitanium derivative (**118**) reacts likewise (equation 46), although showing diminished stereoselectivity.[78] A mechanistic interpretation of the stereochemical course of such addition reactions is also available.[78]

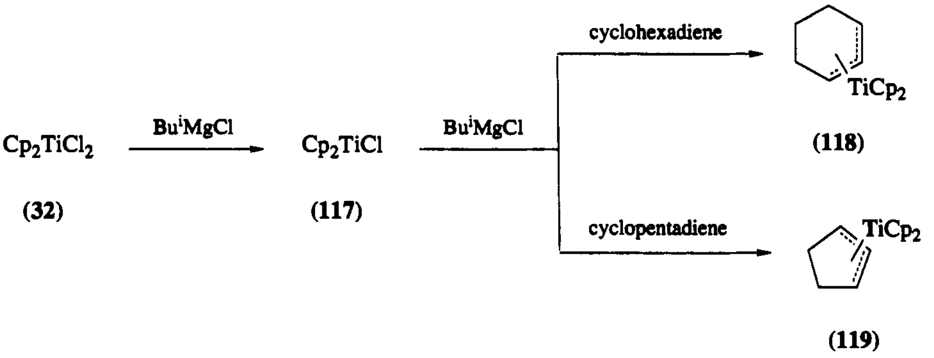
Cp2TiCl2
(32)
BuiMgCl
Cp2TiCl
(117)
BuiMgCl
cyclohexadiene
TiCp2
(118)
cyclopentadiene
TiCp2
(119)

**Scheme 12**

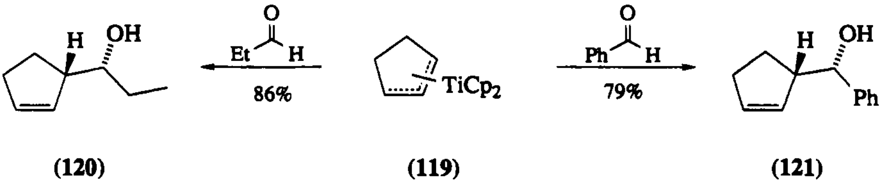
H OH
O
Et H
86%
TiCp2
O
Ph H
79%
H OH
Ph
(120)
(119)
(121)

**Scheme 13**

Modified $\eta^3$-titanium compounds have been prepared from exocyclic dienes.[78] The compound (**123**, *n* = 3) is an example: it is prepared (equation 47) by addition of $Bu^iMgCl$ to a solution of 1-vinylcyclopentene (**122**, *n* = 3) and $(\eta^5\text{-}C_5H_5)_2TiCl$. Its reaction with propanal takes place regiospecifically at the carbon atom belonging to the cycle, in 86% yield, affording the sole *erythro* compound (**124**, *n* = 3) (equation

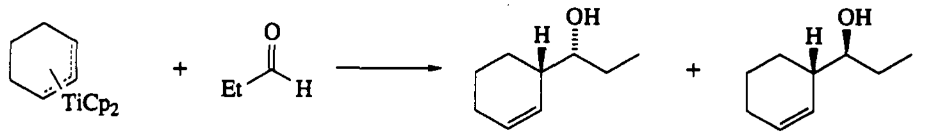
(46)

**(118)** *erythro* 80% *threo* 20%

47), having (*Z*)-configuration of the double bond. The regioselectivity of the attack, however, is a function of the ring dimension and the following order is reported: 90% ($n = 5$), 75% ($n = 6$), 66% ($n = 10$).[78]

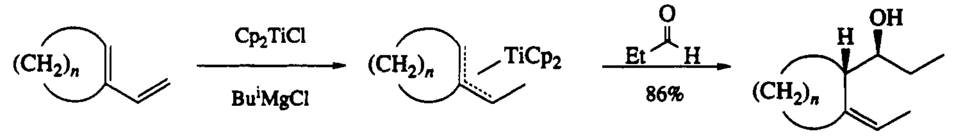
(47)

**(122)** **(123)** **(124)**

### 1.5.3.4 Heterosubstituted Allylic Titanium Reagents

$Ti^{IV}$ reagents bearing heteroatom-substituted allyl residues are conveniently used in analogy with their nonsubstituted analogs to prepare homoallylic alcohols with sulfur,[80–82] silicon,[80,83–85] phosphorus,[86,87] and other β-substituents.[88] These groups can be subsequently exploited to introduce further functions. As the topic will be extensively covered in Part 1 of Volume 2, only a few salient aspects of chemo-, regio- and diastereo-selectivity of such reagents will be considered in this section.

Titanated silyl derivatives, like **(125)**, are among the most interesting of these compounds. They react with carbonyl compounds[35] by addition at the γ-carbon atom and with excellent *threo* diastereoselectivity (equation 48). The reaction of **(125)** with acetophenone affords a 91:9 molar mixture of the corresponding *threo* and *erythro* products (equation 48).[35] Peterson alkenation[35,83] takes advantage of the availability of such products in a stereospecific diene synthesis. Examples of applications of these reagents in the synthesis of natural products are also reported.[89,90] The regiochemistry of the addition is often influenced by the shape and number of substituents on the allyl moiety of the reagent, as is reported for the titanated sulfur-containing compounds **(126)** which, depending upon the nature of the various substituents, perform either α- or γ-attack onto carbonyl compounds (equation 49).[81,82] In Table 11, this substituent effect is illustrated with cyclohexanecarbaldehyde.[81,82]

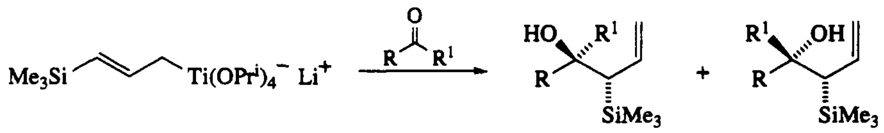
(48)

**(125)**

| | *threo* | *erythro* |
|---|---|---|
| R = Ph, n-$C_6H_{13}$, $Pr^i$; $R^1$ = H | >99% | <1% |
| R = Ph; $R^1$ = Me | 91% | 9% |

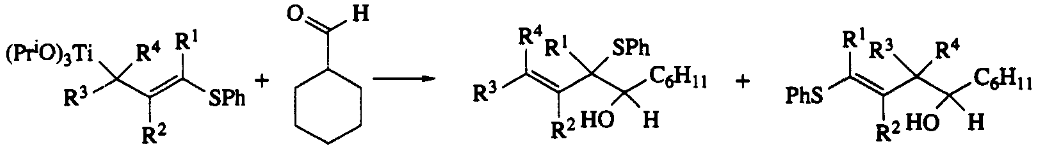
(49)

**(126)** **(127)** **(128)**

Phosphorus-containing allyltitanium(IV) complexes, like **(129)**, have been studied as well.[86,87] The synthetic importance of their addition products to aldehydes lies on their ready deoxygenation to afford dienes stereospecifically (equation 50).

**Table 11** Influence of Substituents on the Addition of Titanated Sulfur-containing Compounds (**126**) to Cyclohexanecarbaldehyde (equation 49)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | (**127**):(**128**) |
|---|---|---|---|---|
| H | H | H | H | 99:1 |
| Me | H | H | H | 99:1 |
| H | Me | H | H | 96:4 |
| H | H | Me | H | 2:98 |
| Me | H | Me | H | 85:4 |
| H | H | Me | Me | <1:99 |

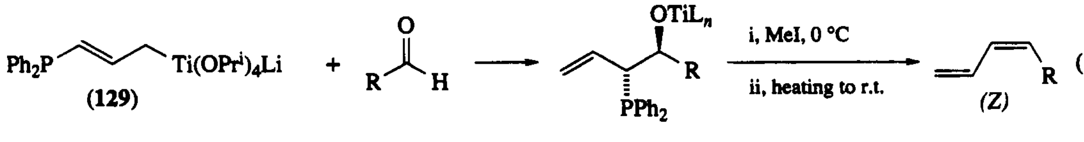

(50)

Metalated *N*,*N*-diisopropyl 2-alkenyl carbamates (**130**) are reported to be successfully utilized to prepare, with high γ-regioselectively (equation 51), 4-hydroxyalkenyl carbamates like (**131**), which are useful intermediates in the synthesis of substituted 4-butanolides.[91]

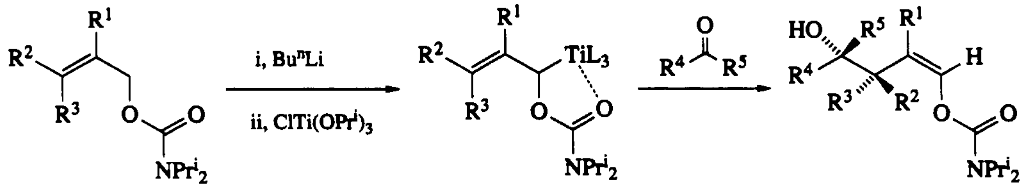

(51)

(**130**) (**131**)

### 1.5.3.5 Dienyl Titanium and Zirconium Reagents

Zirconocene complexes with conjugated dienes can be described in terms of an equilibrium between the *s-trans*-diene zirconocene (**132**) and cyclopentadienyl zirconacyclopentene (**133**) forms (equation 52).[92–94] They are readily prepared either from zirconocene dichloride,[95,96] or diphenyl zirconocene[92] in the presence of conjugated dienes. The equilibrium mixture contains (**132**) and (**133**) in approximately 45:55 molar ratio (at 25°C),[97,98] the former being the most reactive.[94] Addition of the reagent (**132** ↔ **133**) to carbonyl compounds (**134a–f**) (Scheme 14) affords oxazirconacycloheptenes (**135a–f**), which can be hydrolyzed to give alcohol mixtures (**136a–f**) and (**137a–f**).[99]

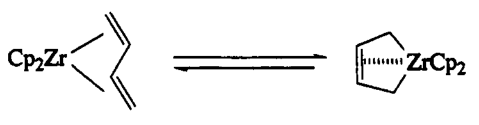

(52)

(**132**) (**133**)

Like allylzirconocene derivatives, conjugated diene zirconocene complexes are highly reactive towards various polar and nonpolar systems, and are characterized by remarkable regioselectivity. For example, isoprene zirconocene (**138**) reacts (Scheme 15) with various systems regioselectively at the sterically more congested C-1 position of isoprene.[100–102] Despite the steric congestion of this reaction site regioselectivity is higher than 95% in reactions with saturated or unsaturated aldehydes as well as with ketones, carboxylic acid esters and nitriles.[94] Furthermore, the yields of such reactions are, without exception, higher than 90%. The highly selective 1,2-addition of diene zirconocene complexes to α,β-unsaturated ketones and esters may be accounted for by the high ionic character of the C—Zr bond and the oxophilic nature of zirconium, in addition to the rigid tetrahedral geometry of the complexes.[94] Analogously, $RTiCl_3$ and alkyllanthanoids are also able to promote selective 1,2-addition to enones.[103,104] Other diene metal complexes of titanium and hafnium are known to give regioselective addition to enones,[94] although their reactivity toward such substrates is considerably lower than that of their $Zr^{IV}$ analogs.

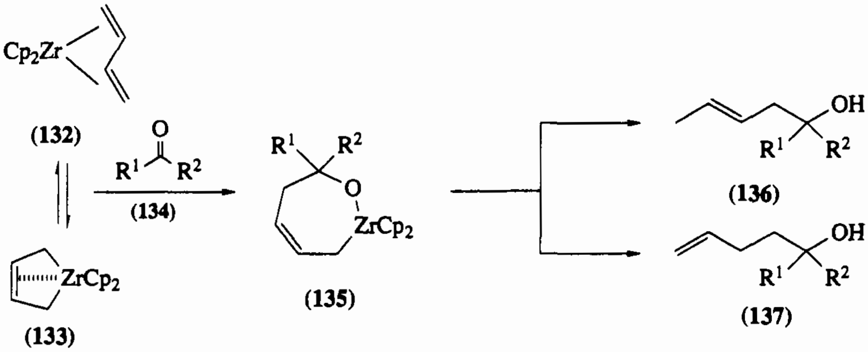

**a**: $R^1 = Me, R^2 = Ph$
**b**: $R^1 = R^2 = Me$
**c**: $R^1—R^2 = —CH_2(CH_2)_9CH_2—$
**d**: $R^1 = R^2 = Ph$
**e**: $R^1 = Pr^i, R^2 = H$
**f**: $R^1 = Bu^t, R^2 = Me$

**Scheme 14**

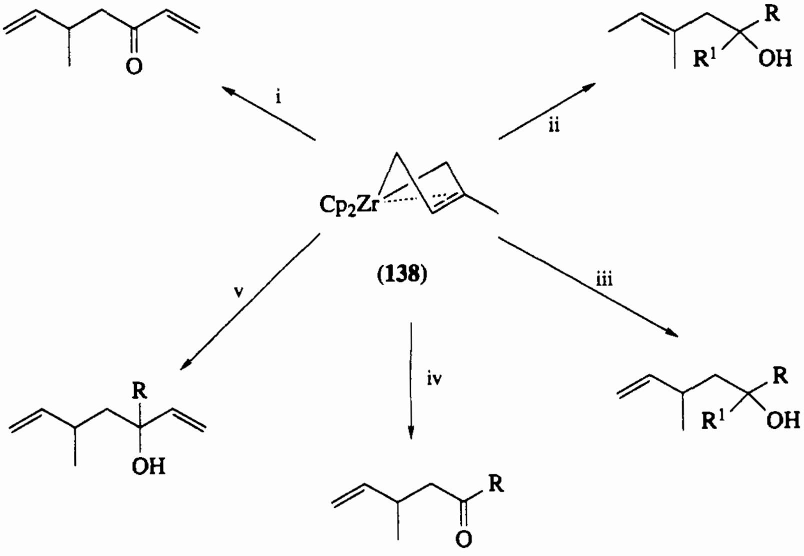

i, $CH_2=CHCO_2R^1$, $H^+$; ii, $RR^1CO$; iii, $RR^1CO$, $H^+$; iv, $RCO_2R^1$ or RCN, $H_2O/H^+$; v, $CH_2=CHCOR$, $H^+$

**Scheme 15**

Reverse regioselectivity is observed when isoprene zirconocene is treated with carbonyl compounds under photochemical conditions, at –70 °C where the thermally induced addition is totally suppressed.[105] As a case in point, 3,3-dimethylbutan-2-one (**139**; Scheme 16) upon reaction with the zirconocene complex of isoprene in benzene at 60 °C for 2 h affords (**140a**), whereas irradiation of the reaction mixture at low temperature in toluene leads to (**140b**). Mixtures of (**140a**) and (**140b**) are obtained by irradiation of isolated (**138**) and ketone (**139**) at higher temperatures. As the reaction temperature is lowered, an increasing amount of (**140b**) is formed. Therefore, it is reasoned that the zirconocene complex reacts in the *cis* form (**138**), under thermal conditions, and in the *trans* form under photochemical conditions.

Zirconocene complexes (with *s-cis* geometry) of isoprene, 2,3-dimethylbutadiene, and 3-methyl-1,3-pentadiene are reported to give exclusively 1:1 addition with carbonyl substrates even if these are used in excess and the reaction temperature is fairly high (*ca.* 100°C).[106] On the contrary, zirconocene complexes of *s-cis*-butadiene, 1,3-pentadiene, and 2,4-hexadiene (*ca.* 1:1 mixture of the *s-cis* and *s-trans* isomers) easily accept (equation 53) 2 equiv. of either butanal or 3-pentanone, at low temperature (*ca.* 30 °C) in high yields (95%).[94,106] This can be exploited for the stepwise insertion of two different electrophiles

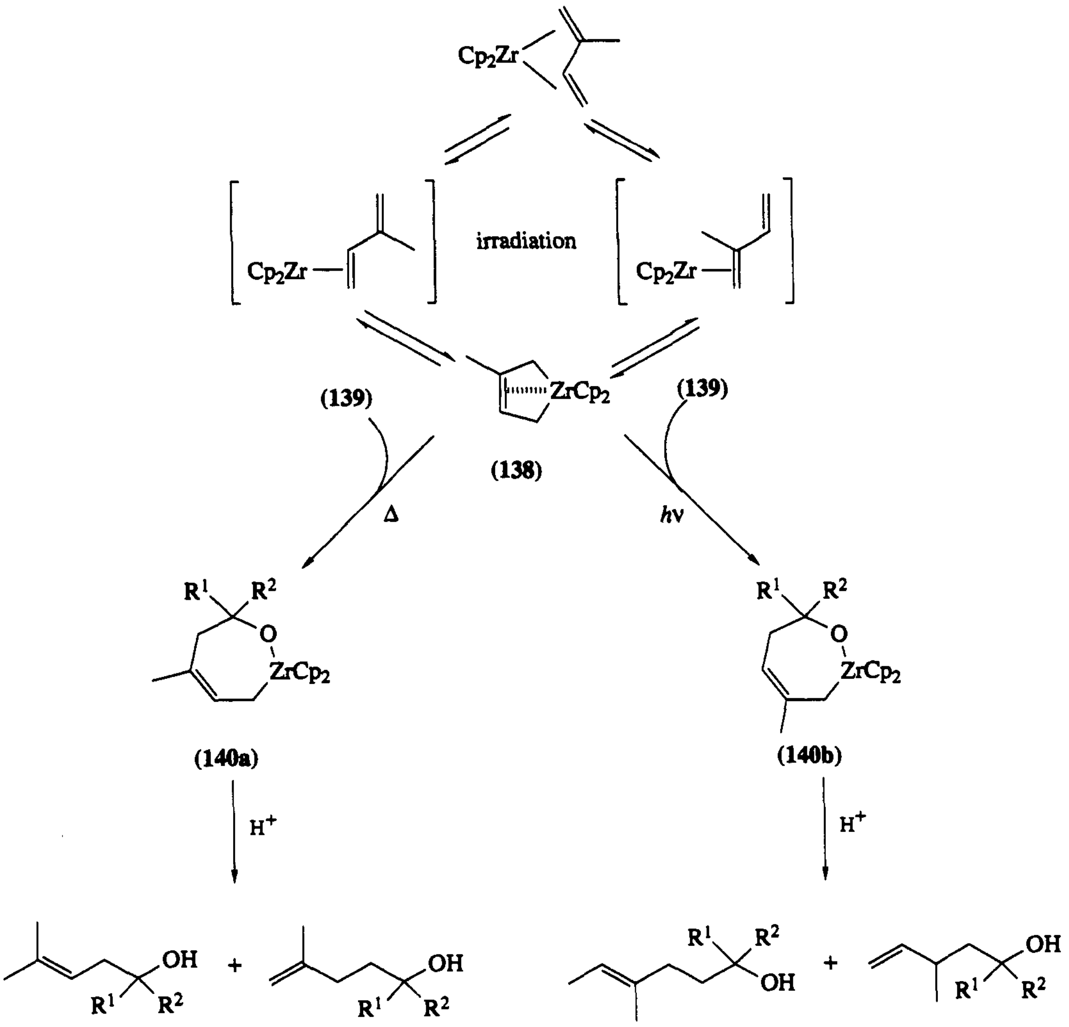
Cp$_2$Zr
irradiation
Cp$_2$Zr
Cp$_2$Zr
(139)
ZrCp$_2$
(139)
(138)
Δ
hν
R$^1$
R$^2$
O
ZrCp$_2$
R$^1$
R$^2$
O
ZrCp$_2$
(140a)
(140b)
H$^+$
H$^+$
OH
R$^1$
R$^2$
OH
R$^1$
R$^2$
R$^1$
R$^2$
OH
OH
R$^1$
R$^2$

R$^1$ = Me, R$^2$ = Bu$^t$

Scheme 16

(*e.g.* isobutanal/pentan-3-one, ethyl acetate/isobutanal, pentan-3-one/acetonitrile) allowing for the preparation of variously substituted diols (Scheme 17).[94] The technique consists of the addition of the first carbonyl compound at 0 °C in hexane, followed by addition of the second electrophile at 60 °C in THF. Attempts to invert the order of addition within the pairs of electrophiles tested (*e.g.* isobutanal/ethyl acetate) are often unsuccessful.[94]

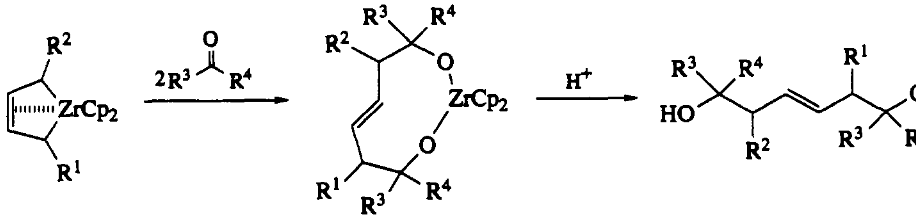
R$^2$
ZrCp$_2$
R$^1$
O
2R$^3$ R$^4$
R$^3$
R$^4$
R$^2$
O
ZrCp$_2$
O
R$^1$
R$^3$
R$^4$
H$^+$
R$^3$
R$^4$
R$^1$
HO
OH
R$^2$
R$^3$
R$^4$

(53)

(133) (*E*)-(141) R$^1$ = or ≠ R$^2$ = H, Me

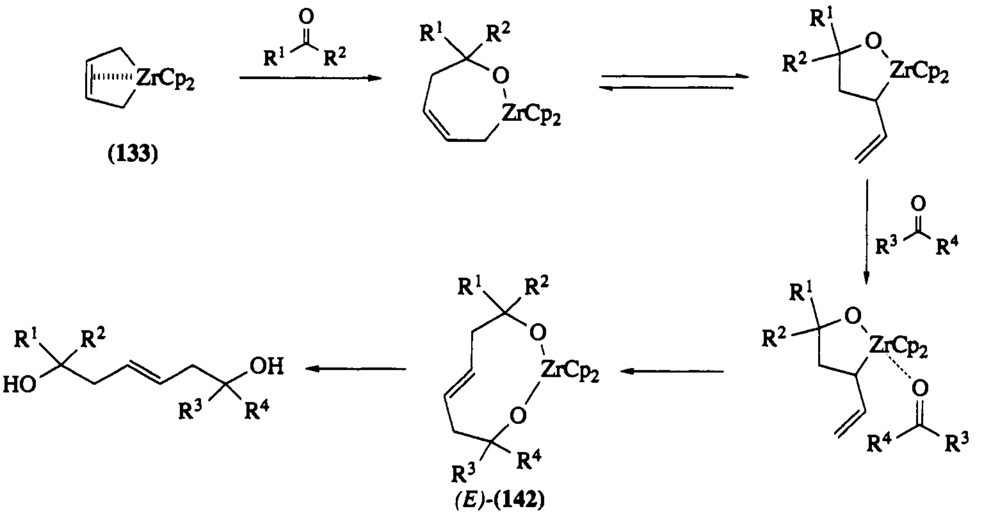

**(133)**

*(E)*-**(142)**

**Scheme 17**

### 1.5.3.6 Propargylic Titanium Reagents

In organic synthesis, propargyltitanium(IV) complexes are unique among the organometallic reagents in that they perform efficient addition of either alkynic or allenic residues to carbonyl compounds.[107]

Since this topic will be covered extensively in Part 1 Volume 2, only the main references concerning their preparation and their more significant synthetic applications are recalled at this point.[108,109] Hetero-substituted propargyltitanium(IV) reagents are also very useful in the synthesis of natural products.[110]

## 1.5.4 CHIRALLY MODIFIED TITANIUM REAGENTS: ENANTIOSELECTIVE ADDITION

Different strategies have been pursued to achieve enantioselection in the addition of specially designed chiral $Ti^{IV}$ reagents to carbonyl compounds. They are essentially based on the use of: (i) organotitanium derivatives having chiral ligands; (ii) complexes having asymmetrically substituted chiral $Ti^{IV}$ atoms; and (iii) $RTiX_3$-like reagents with the nucleophilic moiety bearing a removable chiral auxiliary. Also worthy of mention in this context is an indirect enantioselective addition that is achieved by the reaction of achiral $RTiX_3$ complexes with chiral acetal derivatives of the carbonyl compounds, as is shown in Scheme 18.[111]

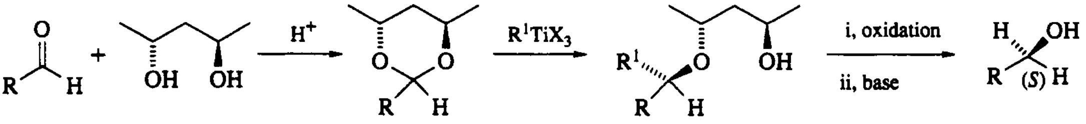

**Scheme 18**

### 1.5.4.1 Organotitanium Derivatives Having Chiral Ligands

Early experiments characterized by low enantiomeric excesses have been reported.[44,46] $Ti^{IV}$ reagents bearing chiral alkoxy ligands are readily prepared from chlorotriisopropoxytitanium by ligand interchange (equation 54) using a chiral alcohol (or phenol), under conditions in which isopropanol can be azeotropically distilled off.[112a] The resulting chiral chlorotitanium derivative is then converted *in situ* to the desired organotitanium complex by reaction with either an RMgX or RLi species. The most commonly used chiral ligands are cinchonine, quinine, (*S*)-1,1′-binaphthol, (–)-menthol, *etc.*[112a] The enantioselectivity of the addition is influenced by the nature of both the carbonyl substrate and the ligand system, as well as by the solvent and the temperature.[112a]

Methyl- and phenyl-$Ti^{IV}$ complexes with different chiral ligands have been tested[112a,b] in reactions with aromatic aldehydes. The enantioselectivity of the addition of chiral $Ti^{IV}$ reagents having a bidentate 1,1′-binaphthol ligand system to aromatic aldehydes (equation 55) has been also extensively examined,

$$\mathrm{ClTi(OPr^i)_3} + \mathrm{R^*OH} \xrightarrow{-3\mathrm{Pr^iOH}} \mathrm{ClTi(OR^*)_3} \xrightarrow[\text{or RLi}]{\text{RMgX}} \mathrm{RTi(OR^*)_3} \qquad (54)$$

and the results obtained are reported in Table 12.[113] The relative topicity of the addition is *lk*, leading to *re* attack of the phenyl group to the carbonyl function by the (*M*)-binaphthol Ti$^{IV}$ reagent [hence, the (*R*)-alcohol] (equation 56) and *si* attack by its (*P*)-binaphthol analog.

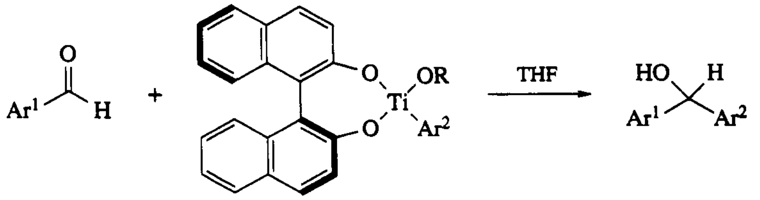

(55)

**Table 12** Enantioselective Addition of (*M*)-Binaphtholphenyltitanium isopropoxide to Aromatic Aldehydes

| *Aldehyde* | *Temperature (°C)* | *Product* | *Yield (%)* | *ee (%)* |
|---|---|---|---|---|
| 2-Methylbenzaldehyde | –2 | (2-Methylphenyl)phenylmethanol | 89 | 85 |
| 4-Methylbenzaldehyde | –2 | (4-Methylphenyl)phenylmethanol | 78 | 86 |
| Anisaldehyde | –69 | (4-Methoxyphenyl)phenylmethanol | 84 | 82 |
| 1-Naphthaldehyde | –15 | 1-Naphthylphenylmethanol | — | 63 |
| 1-Naphthaldehyde | –75 | 1-Naphthylphenylmethanol | 82 | >98 |
| 2-Naphthaldehyde | –17 | 2-Naphthylphenylmethanol | — | 57 |
| 2-Naphthaldehyde | –65 | 2-Naphthylphenylmethanol | 85 | >98 |

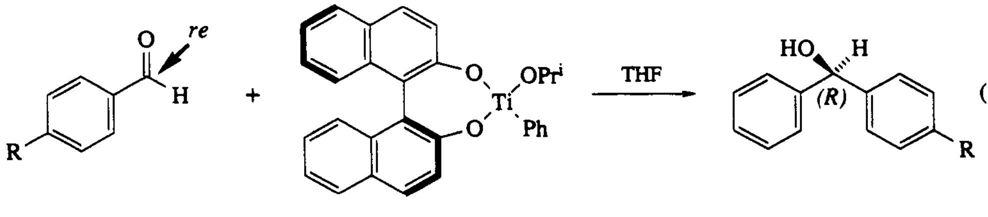

(56)

(*M*)

Attempts to prepare chiral Ti$^{IV}$ reagents capable of transferring groups other than phenyl have been reported.[11] Among these reagents, the methyltitanium (*S*)-acylpyrrolidinylmethoxide diisopropoxides (**144**) are of some interest. They are prepared (Scheme 19) from (*S*)-*N*-acylpyrrolidinylmethanols (**143**) and dimethyltitanium diisopropoxide.[114] Their reactions with either benzaldehyde or 1-naphthaldehyde lead to alcohols with acceptable enantiomeric excesses, as is shown in Table 13.[114]

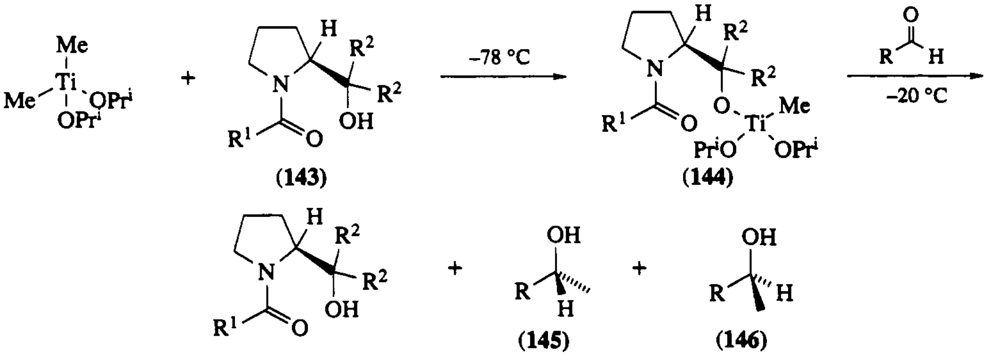

**Scheme 19**

**Table 13** Enantioselective Addition of Methyltitanium (*S*)-*N*-Acylpyrrolidinylmethoxides (**144**) to Aromatic Aldehydes (Scheme 19)

| *Aldehyde* | *R*$^1$ | *R*$^2$ | *Product* | *R* | *ee (%)* |
|---|---|---|---|---|---|
| Benzaldehyde | H | H | (**146**) | Phenyl | 33.0 |
| Benzaldehyde | H | Ph | (**146**) | Phenyl | 17.6 |
| Benzaldehyde | Me | H | (**145**) | Phenyl | 23.9 |
| 1-Naphthaldehyde | Me | H | (**145**) | 1-Naphthyl | 27.6 |
| Benzaldehyde | Me | Me | (**145**) | Phenyl | 18.6 |
| Benzaldehyde | Me | Ph | (**145**) | Phenyl | 39.0 |
| Benzaldehyde | Ph | H | (**145**) | Phenyl | 13.9 |
| Benzaldehyde | $PhCH_2O$ | Me | (**146**) | Phenyl | 23.0 |
| 1-Naphthaldehyde | $PhCH_2O$ | Me | (**146**) | 1-Naphthyl | 27.0 |
| Benzaldehyde | $PhCH_2O$ | Ph | (**145**) | Phenyl | 54.1 |

Further attempts to replace alkoxy groups with other ligand systems, like cyclopentadienyl, in order to reduce the Lewis acidity of the metal atom have been unsuccessful.[11]

### 1.5.4.2 Derivatives Having a Chiral Titanium(IV) Atom

This strategy was devised to enable the chiral center of the reagent to be closer to the carbonyl group during the addition. Ligand systems based on cyclopentadienyls lead to unsatisfactory enantiomeric excesses,[11] as is reported for the reaction of benzaldehyde with the chiral allyltitanium(IV) reagent (**148**) derived from (**147**) by *in situ* treatment with allylmagnesium chloride (Scheme 20).

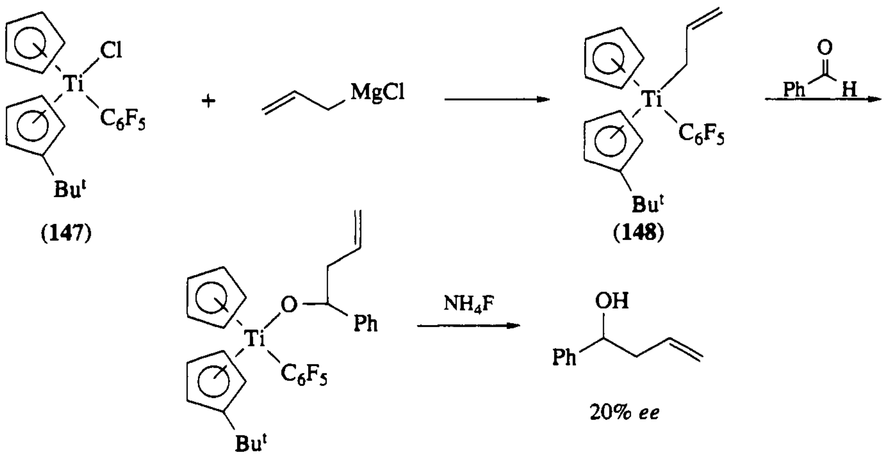

**Scheme 20**

A noteworthy improvement comes from the use of ligand systems which are themselves optically active.[11] This is the case of the complex (**150**), shown in Scheme 21, that is prepared from a sulfenylated norephedrine (**149**). The results reported for the *in situ* reactions of (**150**) with various aldehydes (Scheme 21) are summarized in Table 14.[115] Nothing is reported concerning the mechanism of the enantioselective addition, since the absolute configuration of the asymmetrically substituted Ti$^{IV}$ atom is not known.

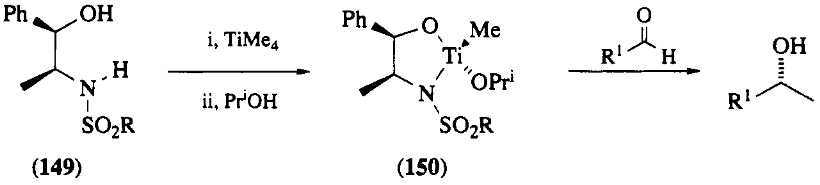

**Scheme 21**

**Table 14** Enantioselective Addition of Methyltitanium(IV) derivatives (**150**) of Various *N*-Sulfonylated Norephedrines to Aldehydes (Scheme 21)

| *R in* (**150**) | *Aldehyde* | *Yield (%)* | *ee (%)*[a] |
|---|---|---|---|
| 4-Tolyl | Benzaldehyde | 78 | 85 |
| 4-Tolyl | 2-Nitrobenzaldehyde | 91 | 79 |
| 4-Tolyl | 1-Naphthaldehyde | 96 | 81 |
| Methyl | Benzaldehyde | 89 | 62 |
| Mesityl | Benzaldehyde | 93 | 88 |
| Mesityl | 2-Nitrobenzaldehyde | 86 | 90 |
| Mesityl | 1-Naphthaldehyde | 92 | 90 |
| 4-Tolyl | Octanal | 81 | 60 |
| Mesityl | Octanal | 82 | 58 |

[a] In all cases the reaction products have the (*R*)-configuration.

### 1.5.4.3 Reagents with the Nucleophilic Moiety Bearing a Removable Chiral Auxiliary

These reagents can be obtained by titanation of a lithium derivative containing the chiral auxiliary (Scheme 22).[116a] Regio- and enantio-selective addition of (**151**) to aldehydes and ketones is reported to afford chiral homoaldol compounds in satisfactory yields and with appreciable enantiomeric excesses (Scheme 22). This reaction has been used in the synthesis of natural products.[116a]

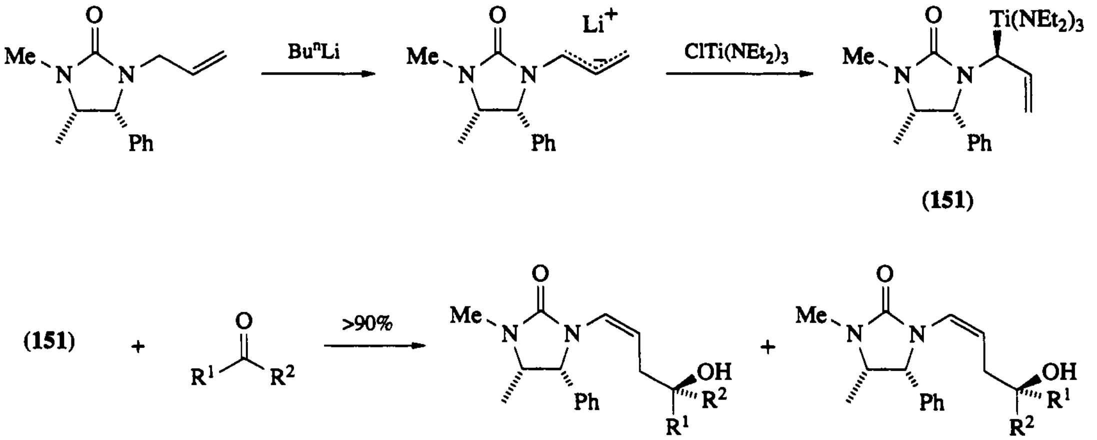

| | | |
|---|---|---|
| $R^1$ = n-$C_8H_{17}$, $R^2$ = H | 94% | 6% |
| $R^1$ = Et, $R^2$ = H | 96% | 4% |
| $R^1$ = $Pr^i$, $R^2$ = H | 96% | 4% |
| $R^1$ = Me, $R^2$ = $Pr^i$ | 98% | 2% |

**Scheme 22**

Lithiated chiral dihydro-1,4-dithiins (**152**) have been recently utilized[116b] in the addition to prochiral aldehydes in the presence of $Ti(OPr^i)_4$ (Scheme 23). Under such conditions (*Z*)-allylic alcohols have been obtained in good yields and with satisfactory enantioselectivity (*ee* >40%), after removal of the chiral sulfur-containing moiety of the addition product. The reaction is likely to proceed *via* the formation of a cyclic five-membered transition state (**153**) involving titanium, oxygen and one of the sulfur atoms.[53b] When $Ti(OPr^i)_4$ is replaced by $TiCl_4$, the addition becomes slower than the uncatalyzed reaction itself.

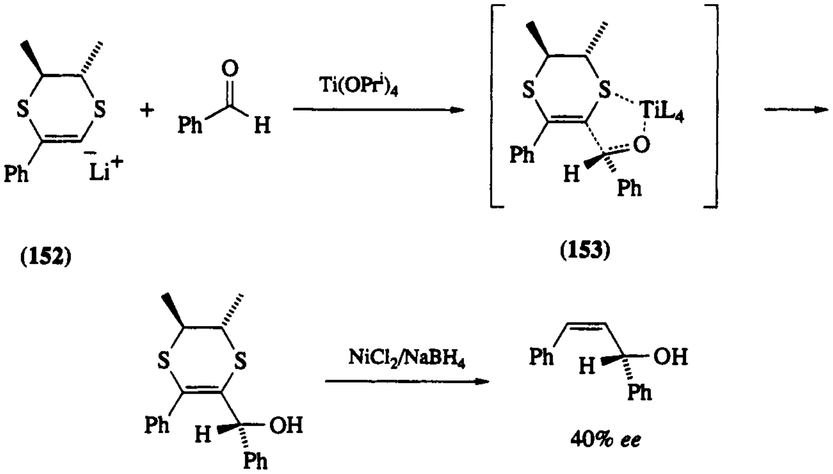

**Scheme 23**

## 1.5.5 MISCELLANEOUS REACTIONS

### 1.5.5.1 Geminal Dialkylation of Aldehydes and Ketones

This represents probably one of the earliest interests in the chemistry of Ti$^{IV}$ compounds.[117] Ketones, like cyclohexanone, are easily dimethylated by $MeTiCl_3$, $Me_2TiCl_2$ and $Me_2Zn/TiCl_4$.[118,119] Depending upon the molecular ratio of $Me_2Zn$ and $TiCl_4$, various products (**43**), (**154**) and (**155**) are obtained from cyclohexanone (equation 57), as is reported in Table 15.[121] The reaction proceeds through cationic intermediates;[120] various functionalities (*e.g.* carboxylic acid esters, primary and secondary alkyl halides) are well tolerated.[120] Some problems arise when α,β-unsaturated ketones are utilized, because of the formation of two distinct dimethylated products (equation 58).[120]

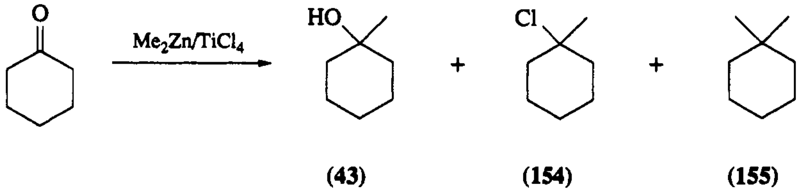

(57)

**Table 15** Geminal Dimethylation of Cyclohexanone (equation 57)

| *Entry* | *TiCl$_4$/ZnMe$_2$ (mmol)*[a] | *Temperature (°C)* | *Time (h)* | *Yield (%)* (**43**) | *Yield (%)* (**154**) | *Yield (%)* (**155**) |
|---|---|---|---|---|---|---|
| 1 | 30/10 | -30 | 4 | — | >90 | — |
| 2 | 10/10 | -30 | 4 | >90 | — | — |
| 3 | 22/22 | -30 to +22 | 2 | — | — | >90 |
| 4 | 10/20 | -30 to +22 | 4 | >90 | — | — |

[a] In all cases 10 mmol of cyclohexanone were used in $CH_2Cl_2$.

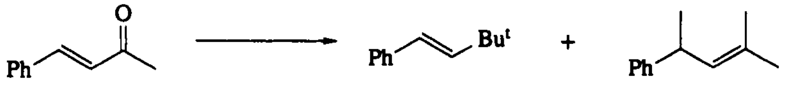

(58)

Aromatic aldehydes are also easily dimethylated by $Me_2TiCl_2$, and aromatic acyl chlorides form *t*-butyl derivatives directly when treated with an excess of $Me_2Zn/TiCl_4$ in methylene chloride.[121] Some examples are also known of application of such a reaction in the synthesis of natural products.[118,119]

### 1.5.5.2 Alkylative Amination

Alkyltitanium(IV) complexes having *N*,*N*-dialkylamino ligand systems, $RTi(NR^1_2)_3$, fail to give nucleophilic additions to carbonyl compounds (Section 1.5.3.1.1). Their reaction with aldehydes leads instead to tertiary amines by addition of both the alkyl moiety of the reagent and one of the *N*,*N*-dialkylamino ligands (equation 59).[48] The synthetic interest of the reaction is restricted to nonenolizable aldehydes, since enolizable carbonyl compounds lead to enamines.[48]

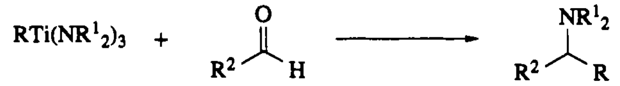

(59)

A few examples of alkylative amination of aldehydes are reported in Table 16.[48]

**Table 16** Alkylative Amination of Various Aldehydes by $RTi(NEt_2)_3$

| *Aldehyde* | *R* | *Product* | *Yield (%)* |
|---|---|---|---|
| Benzaldehyde | Me | *N*,*N*-Diethyl-1-phenylethylamine | 48 |
| 4-Methylbenzaldehyde | Me | *N*,*N*-Diethyl-1-*p*-tolylethylamine | 47 |
| Benzaldehyde | Bu | *N*,*N*-Diethyl-1-phenylpentylamine | 15 |
| 2-Furylaldehyde | Me | *N*,*N*-Diethyl-1-(2′-furyl)ethylamine | 73 |
| Cinnamaldehyde | Me | *N*,*N*-Diethyl-4-phenylbut-3-en-2-ylamine | 44 |
| Pivalaldehyde | Me | *N*,*N*-Diethyl-3,3-dimethylbut-2-ylamine | 55 |

### 1.5.5.3 Protection of Aldehydes

The tendency of $Ti^{IV}$ reagents like $Ti(NR_2)_4$ to release the *N*,*N*-dialkylamino group[42,48] is conveniently exploited to temporarily inactivate a carbonyl function which is fairly reactive (*e.g.* an aldehyde),[122] thus enabling a second, less reactive carbonyl function (*e.g.* a ketone), to react with another nucleophilic reagent. This leads to a sort of reverse chemoselectivity which is highly effective in discriminating between different carbonyl compounds, as well as between carbonyls having different steric environments.

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# 1.6
# Organochromium Reagents

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## 1.6.1 INTRODUCTION

Organochromium(III) complexes were among the first transition metal organometallic compounds to be synthesized and have enjoyed a rich history of investigation and utility.[1] These materials can be prepared either by the addition of Grignard, organolithium or organoaluminum reagents to chromium(III) halides or by the reduction of organic halides with chromium(II) ions. Both routes provide chromium(III) complexes that are believed to possess a Cr—C σ-bond.[1] The organometallic reagents to be described herein serve as carbanion equivalents and participate in a variety of chemo- and stereo-selective carbon–carbon bond-forming reactions *via* the addition to C═X π-bonds. Such processes are the substance of this review.

## 1.6.2 ORGANOCHROMIUM(III) CARBANION EQUIVALENTS

### 1.6.2.1 Synthesis and Structure of Organochromium(III) Complexes

The synthesis of organometallic compounds of chromium was pioneered by Hein in the 1920s and 1930s, and this work has been reviewed in a monogram by Zeiss.[2] However, preparation and adequate characterization of the first simple kinetically stable chromium(III) alkyl in solution was reported by Anet and Leblanc.[3] Pentaaquabenzylchromium(III) perchlorate (**2**) was prepared from benzyl chloride (**1**) and chromium(II) perchlorate in aqueous perchloric acid (equation 1). It is known that readily available chromium(II) salts function effectively as reducing agents for a variety of compounds, including organic halides.[4] The mechanism of chromium(II) ion mediated reductions of organic halides has been thoroughly investigated. Kinetic data have verified the formation of a discrete organochromium intermediate,[5] and mechanistic studies have established that the reaction proceeds by a single-electron reduction of the C—X bond followed by reduction of the resulting radical (**3**) by a second equivalent of chromium(II) ion to provide a chromium(III) organometallic species (**4**; Scheme 1).[6–8] As the reductions are most commonly performed in aqueous media, protonolysis of the organochromium intermediate (**4**) rapidly produces the reduction products (**5**). The coexistence of water in the reaction medium represents an impediment to the mechanistic evaluation of chromium(II) ion reduction of organic halides and a limitation of organochromiums, prepared in this fashion, as potential synthetic reagents. However, the use of anhydrous chromium(II) salts (*e.g.* $CrCl_2$; see Section 1.6.3.1) has more recently allowed for the controlled generation of organochromium compounds and provides for their current and potential utility as carbanion equivalents.[9]

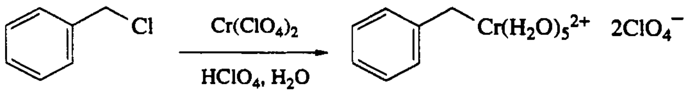

(1)

**(1)** **(2)**

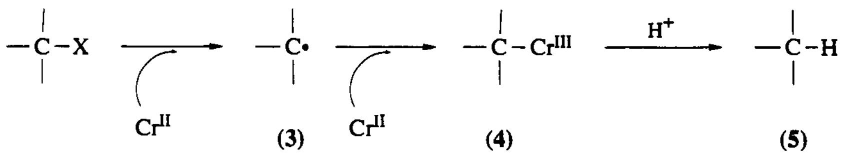

**(3)** **(4)** **(5)**

**Scheme 1**

An alternative synthesis of organochromium(III) compounds involves the addition of organometallic reagents to chromium(III) salts. This route provided the first example of an isolable covalent organochromium(III) compound. Herwig and Zeiss[10] reported that the addition of PhMgBr to $CrCl_3$ provided triphenyltris(tetrahydrofuran)chromium(III) (**6**; equation 2). Verification of Zeiss' structural assignment has more recently been provided in the form of X-ray data reported by Khan and Bau.[11] They have shown that (**6**) maintains three σ-bonded phenyl groups arranged in a *cis* facial fashion, as illustrated in equation (2). A related series of organochromiums was first prepared by Kurras[12] and subsequently investigated by Yamamoto and coworkers.[13] Treatment of $CrCl_3$ with organoaluminums provides organochromium(III) complexes (**7**), as shown in equation (3). The synthesis and X-ray crystal structure of dichlorotris(tetrahydrofuran)-*p*-tolylchromium(III) (**8**) was reported by Sneeden and coworkers (equation 4).[14] The crystal structure reveals a complex of the *mer*-type geometry with the Cr—O distance of the THF ligand *trans* to the σ-aryl bond appearing longer than for the other THF molecules. Other Group VI σ-alkyl and σ-aryl complexes have been studied and this area has been reviewed.[15] However, complexes (**6**), (**7**) and (**8**) are most pertinent to this review as they are representative of organochromiums that have been shown to participate in C—C bond-forming reactions.

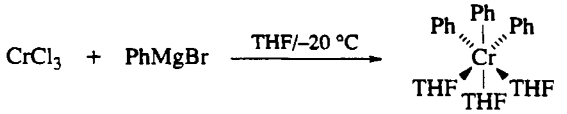

**(6)**

Cr–C 2.060 Å
Cr–O 2.225 Å

(2)

$$\mathrm{CrCl_3} \xrightarrow[\mathrm{THF}]{\mathrm{R_3Al\ or\ R_2AlOEt}} \underset{(\mathbf{7})}{[\mathrm{RCrCl_2(THF)_3}]} \qquad (3)$$

$$\mathrm{R = Ph, Me, Et, Pr^n, Bu^i}$$

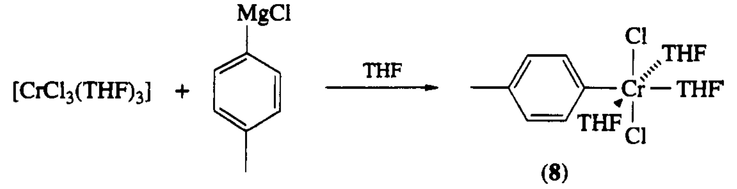

(**8**)

| | | |
|---|---|---|
| Cr–C | 2.015 Å | (4) |
| Cr–O (THF) | 2.045 Å | |
| Cr–O (THF') | 2.214 Å | |
| Cr–Cl | 2.31 Å | |

### 1.6.2.2 Formation of C—C Bonds: Background

The ability of chromium(II) ion generated organochromium(III) species to take part in C—C bond-forming reactions was discovered during mechanistic studies of the chromium(II) ion reduction of halides. Kochi and coworkers[6] have shown that the benzylchromium ion (**2**) when treated with acrylonitrile provides phenylbutyronitrile (**9**) and toluene (**10**) in 40–50% and 40–45% yield, respectively (equation 5). In addition, it was shown that (**2**) in the presence of butadiene afforded a 4–6% yield of 4-phenyl-1-butene (**11**) and 60–80% yield of toluene (equation 6), demonstrating the carbanionic nature of the organochromium species. Barton and coworkers[8] subsequently showed that 9-α-bromo-11-β-hydroxyprogesterone (**12**) when treated with chromium(II) acetate in DMSO provides 11-β-hydroxyprogesterone (**13**), the $\Delta^{9,11}$alkene (**14**) and the 5,9-cyclosteroid (**15**) with the product distribution and yield being a function of solvent and additives (equation 7). These studies[6,8] support the proposed mechanism of chromium(II) ion mediated reductions and also reveal the nucleophilic character of the *in situ* generated organochromium(III) intermediates.

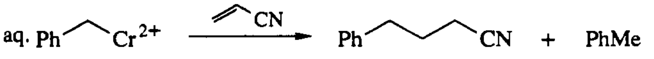

(5)

(**2**) (**9**) 40–50% (**10**) 40–45%

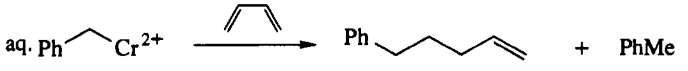

(6)

(**2**) (**11**) 4–6% (**10**) 60–80%

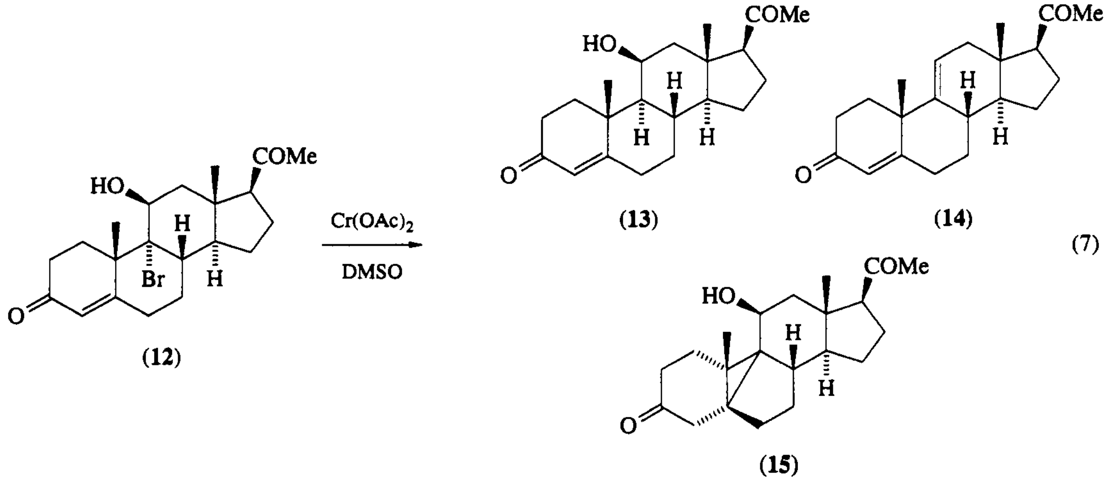

(**12**) (**13**) (**14**) (**15**) (7)

Organochromium compounds prepared from chromium(III) salts and organometallic reagents have been shown to possess carbanionic character and provide the first examples of organochromium additions to carbonyl substrates. Sneeden and coworkers[16] reported that triphenyltris(tetrahydrofuran)chromium(III) (**6**) when treated with carbon monoxide provided benzpinacol (**16**; equation 8). It was also shown that treatment of 3-pentanone (**17**) with the solvated triphenylchromium complex (**6**) afforded diethylphenylcarbinol (**18**) and diol (**19**, R = Ph; equation 9). Cyclohexanone (**20**; equation 10) provided (**21**), (**22**) and (**23**) upon treatment with (**6**). These experiments are noteworthy since they demonstrate the ability of σ-organochromium complexes to add to ketones in a Grignard-like fashion. Interestingly, generation of the aldol and aldol-derived products (**19**), (**22**) and (**23**) occurred without stoichiometric consumption of organometallic reagent. The authors suggested that in these instances (**6**) does not promote aldol condensation by acting as a conventional organic base, but rather that the chromium atom is functioning as a coupling center or a reaction template at which the aldol process occurs. Monoarylchromium complex (**24**) provided addition products with aldehydes and ketones (yields for equations 11 and 12 based on **24**).[17] Reaction of (**24**) with neat acetone produced 2-phenyl-2-propanol (**25**) and mesityl oxide (**26**; equation 11). Also, (**24**) reacted with benzaldehyde to produce benzophenone (**27**) and benzyl benzoate (**28**; equation 12). It was rationalized that the benzophenone arose from a β-hydrogen elimination of the alkoxychromium intermediate (**29**; equation 13), while (**28**) was generated by a chromium-mediated Tischchenko reaction.[18]

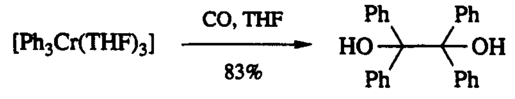

(**6**) (**16**)

(8)

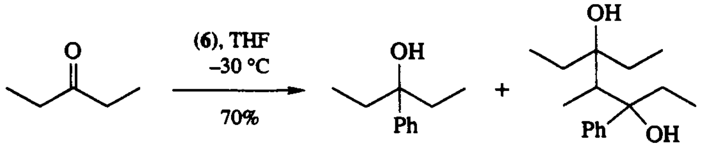

(**17**) (**18**) 81:19 (**19**)

(9)

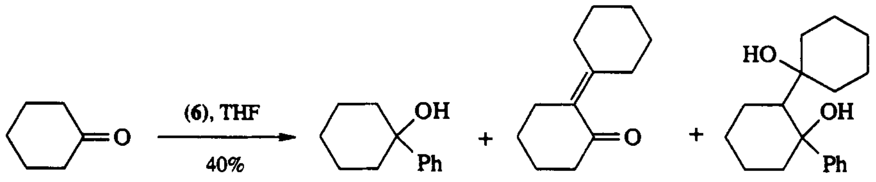

(**20**) (**21**) (**22**) (**23**)

50 : 26 : 24

(10)

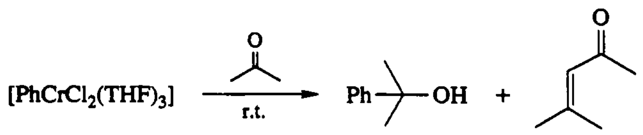

(**24**) (**25**) 71% (**26**) 36%

(11)

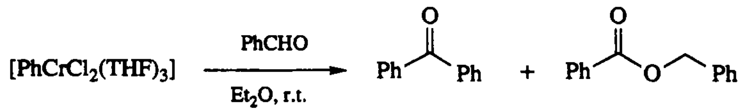

(**24**) (**27**) 84% (**28**) 20%

(12)

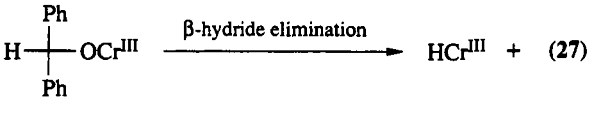

(29)

(13)

## 1.6.3 ALLYL-, METHALLYL-, CROTYL- AND PROPARGYL-CHROMIUM REAGENTS

### 1.6.3.1 Carbonyl Addition Reactions: General Features

The early studies and structural investigations of organochromium(III) compounds revealed the potential synthetic utility of these reagents as carbanion equivalents. However, it was Hiyama and coworkers[9,19] who expanded on the initial findings. These workers reported that the Barbier–Grignard-type addition of allylic halides and tosylates to carbonyl compounds was effectively mediated by anhydrous $CrCl_2$ (equation 14). Anhydrous chromium(II) chloride is commercially available[20] or can be generated *in situ* by the reduction of chromium(III) chloride[21] with either LAH[9,19] or Na(Hg)[22] in THF (equation 15). Although the exact nature of the low valent chromium reagent generated *in situ* has not been established, its functional attributes are indistinguishable from those of the commercially available material.

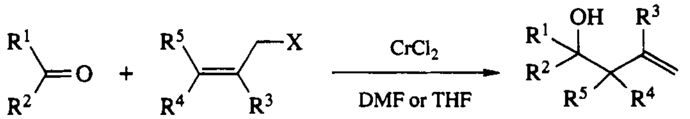

(14)

$$CrCl_3 \xrightarrow[\text{or Na(Hg)}\atop \text{THF}]{\text{LiAlH}_4} CrCl_2 \qquad (15)$$

Reduction of the allylic halide (or tosylate) in this reaction is consistent with expectations.[4] Two mol equivalents of $CrCl_2$ are required for the consumption of each halide. Polar aprotic solvents (*i.e.* DMF) greatly facilitate the reduction and in some cases (*e.g.* chlorides and tosylates) are essential for the generation of the organochromium species. Under these conditions allyl chloride and tosylate add to benzaldehyde (equation 16) to provide the homoallylic alcohol (30). In a similar fashion an allyl group can be delivered to ketones (equations 17 and 18), but requires a larger mol ratio of allylchromium reagent to obtain comparable results. The chemoselective nature of this reagent is further revealed by its ability to

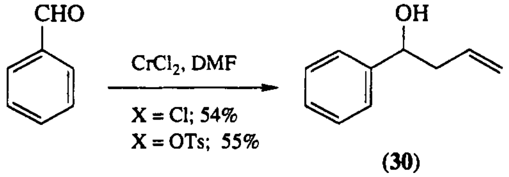

(30)

(16)

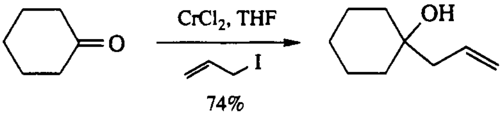

(17)

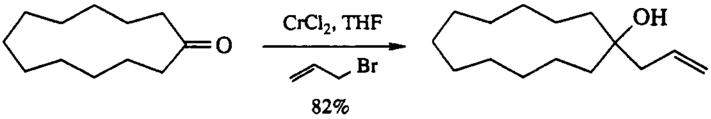

(18)

add selectively to aldehydes in the presence of ketones (equation 19), esters (equation 20) and nitriles (equation 21). In fact, the allylchromium reagent discriminates between ketones of nearly identical reactivity (equation 22). In the same study it was shown that the more-substituted γ-carbon of prenyl bromide adds to the carbonyl carbon of aldehydes (equation 23). This is a general feature of substituted allylchromiums.

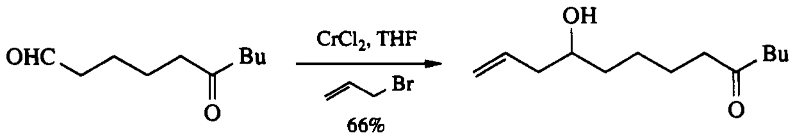
OHC
Bu
O
$CrCl_2$, THF
Br
66%
OH
Bu
O

(19)

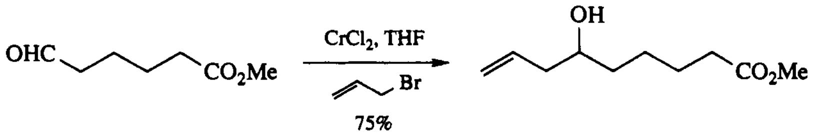
OHC
$CO_2Me$
$CrCl_2$, THF
Br
75%
OH
$CO_2Me$

(20)

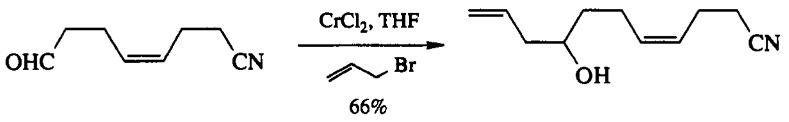
OHC
CN
$CrCl_2$, THF
Br
66%
CN
OH

(21)

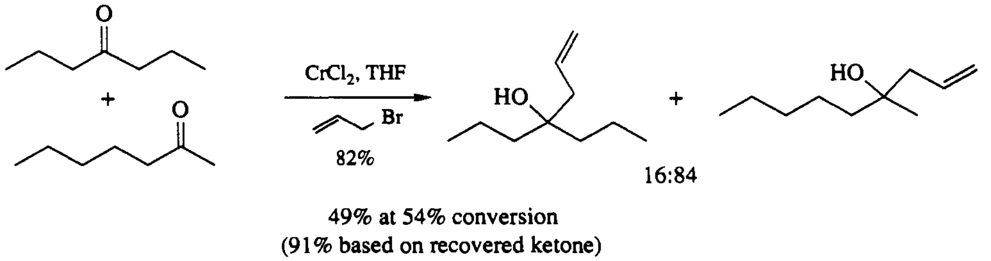
O
+
O
$CrCl_2$, THF
Br
82%
HO
+
HO
16:84
49% at 54% conversion
(91% based on recovered ketone)

(22)

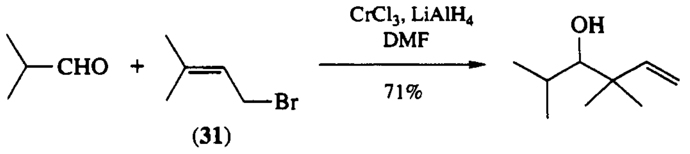
CHO
+
Br
(31)
$CrCl_3$, $LiAlH_4$
DMF
71%
OH

(23)

The addition to α,β-unsaturated aldehydes proceeds exclusively in a 1,2-fashion (equation 24). This regiochemical preference is general for all organochromium compounds. The addition to 4-*t*-butylcyclohexanone (**32**) occurs predominantly *via* equatorial addition (equation 25), as it provides (**33**) and (**34**) in an 88:12 ratio. Allylchromium is one of the most efficient reagents for this transformation (Table 1).

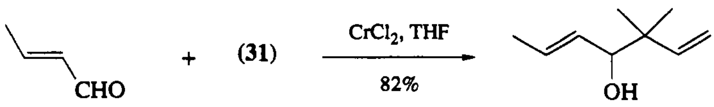
CHO
+
(31)
$CrCl_2$, THF
82%
OH

(24)

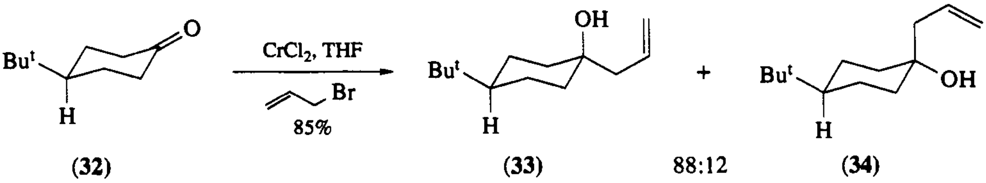
O
$Bu^t$
H
(32)
$CrCl_2$, THF
Br
85%
OH
$Bu^t$
H
(33)
+
88:12
$Bu^t$
OH
H
(34)

(25)

Table 1 Addition of Allyl Organometallics ($CH_2{=}CHCH_2M$) to 4-*t*-Butylcyclohexanone (**32**; equation 25)

| *M* | *Conditions* | *Yield (%)* | *Ratio (33):(34)* | *Ref.* |
|---|---|---|---|---|
| $Cr^{III}$ | THF/r.t. | 85 | 88:12 | 9 |
| ZnBr | THF/5 °C | 79 | 85:15 | 23 |
| $Al_{2/3}Br$ | THF/5 °C | 83 | 68:32 | 23 |
| MgBr | THF/5 °C | 33 | 45:55 | 23 |
| Li | THF/–20 °C | 67 | 35:65 | 23 |
| Na | THF/–20 °C | 68 | 35:65 | 23 |
| K | THF/–20 °C | 30 | 37:63 | 23 |
| $Bu^n{}_3Sn$ | $BF_3{\cdot}Et_2O$ THF/–78 °C | 93 | 92:8 | 24 |
| $Sm^{III}$ | THF/r.t. | 72 | 87:13 | 25 |

### 1.6.3.2 Allylic Chromium Reagents: 1,2-Asymmetric Induction (*Anti*/*Syn* Control)

In the original report of the $CrCl_2$-mediated carbonyl addition reaction Hiyama[9,19] reported that crotyl bromide added to benzaldehyde in the presence of chromium(II) ion and afforded a single diastereomer. Follow-up results from Heathcock and Buse,[26] and subsequent work by Hiyama and coworkers,[27] show that this reaction delivers the *anti* (*threo*) isomer (**35**) exclusively in 96% yield (equation 26). Conversion to the known β-hydroxy acid (**36**) provides proof of the stereochemistry of (**35**). The reaction of crotyl bromide with a variety of aldehydes was investigated (equation 27) and the following trends emerged (Table 2).[27] It was shown that the selective formation of the *anti* addition product occurred with unhindered aldehydes (entries 1–3), but that this preference was reversed for very large substrate aldehydes (entry 4). Moreover, solvent substitution of DMF for THF led to erosion of the *anti* preference (entries 5–8), with concomitant increase in overall chemical yield (entries 6 and 7). Hiyama also showed that the *anti* selectivity was not a function of alkene geometry in the starting bromide since both *cis*- and *trans*-1-bromo-2-butene gave exclusively the *anti* addition product with benzaldehyde. The stereochemical course of addition is rationalized in the following manner. Chromium(III) complexes prefer to exist in an octahedral configuration in which the coordination sphere is often supplemented with solvent molecules (*i.e.* THF).[11,14] A preferred transition state which is consistent with this and the stereochemical data has been proposed[26,27] and is detailed in Scheme 2. The octahedral (*E*)-crotylchromium(III) reagent (**40**) is formed from either (*E*)- or (*Z*)-crotyl bromide with two equivalents of $CrCl_2$. Such double-bond isomer-

Table 2 Addition of Crotyl Bromide (**31**) to Aldehydes (**37**) using Chromium(II) Chloride (equation 27)

| *Entry* | *Aldehyde (37)* | *Solvent* | *Yield (%)* | *Anti:syn (38):(39)* |
|---|---|---|---|---|
| 1 | PhCHO | THF | 96 | 100:0 |
| 2 | $Pr^nCHO$ | THF | 59 | 93:7 |
| 3 | $Pr^iCHO$ | THF | 55 | 95:5 |
| 4 | $Bu^tCHO$ | THF | 64 | 35:65 |
| 5 | PhCHO | DMF | 92 | 75:25 |
| 6 | n-$C_5H_{11}CHO$ | DMF | 77 | 68:32 |
| 7 | $Pr^iCHO$ | DMF | 78 | 66:34 |
| 8 | $Bu^tCHO$ | DMF | 63 | 37:63 |

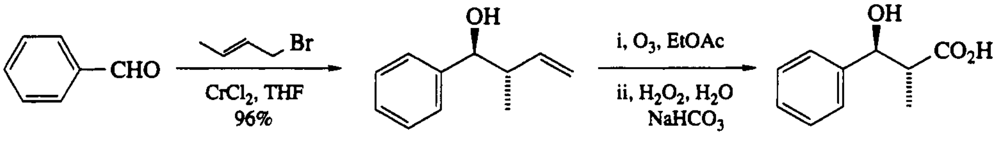

(**35**) (**36**)

(26)

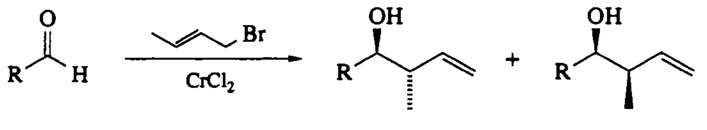

(**37**) (**38**) *anti* (**39**) *syn*

(27)

ization of organometallic reagents to access the more stable (*E*)-double bond geometry is likely to be operative and is the situation which has been noted for crotyl-magnesium,[28] -lithium,[29] -zinc,[30] -titanium[31,41] and -zirconium compounds.[32] Ligand replacement with substrate aldehyde generates reactive complexes (**41**) and (**42**) which on transfer of the crotyl group from Cr to carbon with allylic transposition provides *anti*- and *syn*-homoallylic alcohols (**43**) and (**44**), respectively. The steric requirements of R and L should preclude transition structure (42), favor (43), and as a consequence direct the formation of *anti*-homoallylic alcohol (**43**). If the *gauche* interaction between R and the γ-methyl group becomes highly pronounced, as would be the case with very large aldehydes (*i.e.* R = Bu$^t$), (**41**) will be supplanted by a skew boat (**45**) as the favored transition structure. Finally, the reduction of stereoselectivity when DMF is used is interpreted as a perturbation of the reactive chromium template by the strong donor solvent.

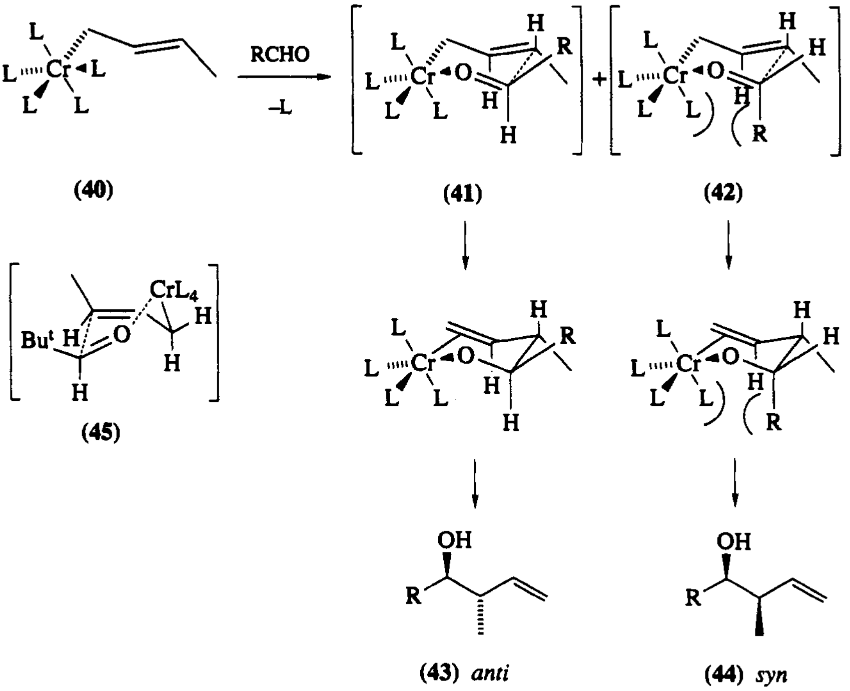

**Scheme 2**

The addition of allyl metal derivatives to aldehydes represents an important and well-developed strategy for the control of acyclic stereochemistry.[33] The transition state models which have been proposed to describe the origin of the 1,2-diastereoselection obtained with γ-substituted allyl organometallics are classified as either synclinal (cyclic) (**46**) or antiperiplanar (acyclic) (**47**; Scheme 3). Involvement of a particular transition state is a function of the metal center and the reaction conditions. Denmark and Weber[34] have suggested that substituted allyl metals are of three types with regard to alkene geometry and 1,2-diastereogenesis (*lk*/*ul*).[50] For type 1, the *anti*:*syn* (*lk*:*ul*) ratio is dependent on the (*Z*):(*E*) ratio of the alkene in the organometallic (B, Al, Si); with type 2; *syn* (*ul*) selective processes are independent of alkene geometry (Sn, Si); and for type 3; *anti* (*lk*) selective reactions are independent of alkene geometry. Examples of types 1–3 crotyl metal reagents are provided in Table 3 and equation (28). The allyl boronates (Table 3, entries 5 and 6)[37] and the pentacoordinate silicates (entries 15 and 16)[43] are crotyl metals of type 1 which react through a synclinal reaction geometry and produce *anti* products from the (*E*)-crotyl metal reagent and *syn* products from the (*Z*)-crotyl metal reagent. Trialkyl-stannanes[38] and -silanes[39] (entries 7, 8 and 9) are type 2 reagents which react under Lewis acid catalysis *via* an open antiperiplanar transition state and consequently produce *syn* products. The type 3 reagents consist of σ- and $\eta^3$-crotyltitanium,[41,42] -crotylzirconium[32,40] and organochromium(III) compounds.[27] These reagents are believed to react exclusively *via* the σ-(*E*)-crotyl metal complex through a synclinal cyclic chair transition state which leads to *anti* addition products. Set against the fabric of crotyl metal additions, the crotylchromiums represent the most convenient and perhaps the most selective reagents for the production of *anti*-homoallylic alcohols. However, with sterically demanding aldehydes, the $\eta^3$-crotyltitanocenes recently reported by Collins[42] exhibit a higher *anti* selectivity than the chromium(III) organometallics.[27]

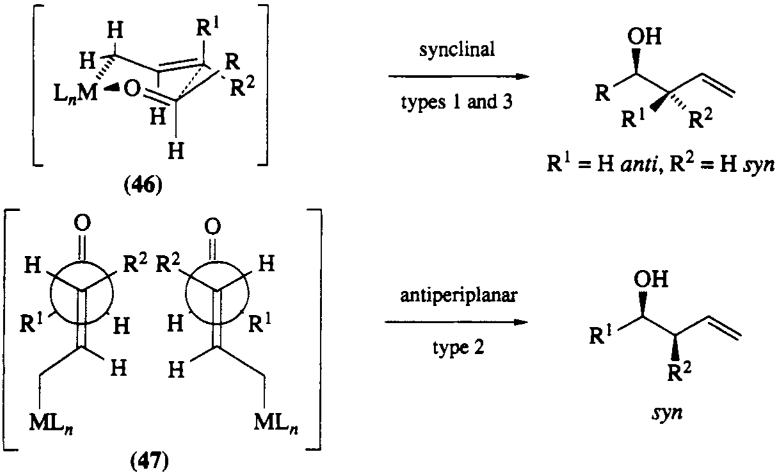

**Scheme 3**

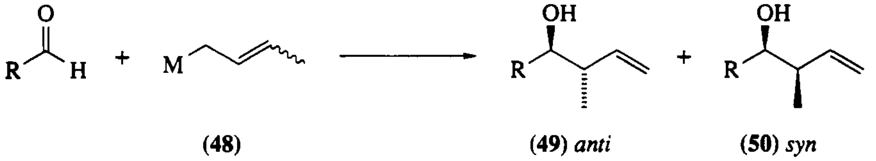

(28)

**Table 3** Addition of Crotyl Organometallics to Aldehydes (equation 28)

| *Entry* | *M* *(48)* | *R* | *Conditions* | *(E):(Z)* *(48)* | *Anti:syn* *(49):(50)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Li | Ph | THF/–78 °C | | 55:45 | 80 | 29 |
| 2 | MgCl | Ph | Ether/–10 °C | | 38:62 | 93 | 35 |
| 3 | $Et_3Al^-$ $Li^+$ | Ph | Ether/–70 °C | | 56:44 | 93 | 36 |
| 4 | $Et_3B^-$ $Li^+$ | Ph | Ether/–70 °C | | 82:18 | 90 | 36 |
| 5 | 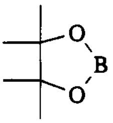 | Ph | Ether/–78 °C | 93:7 | 94:6 | 80 | 37 |
| 6 | | Ph | Ether/–78 °C | <5:>95 | 6:96 | 22 | 37 |
| 7 | $Bu^n_3Sn$ | Ph | $BF_3·Et_2O$<br>$CH_2Cl_2$/–78 °C | 100:0 | 6:96 | 90 | 38 |
| 8 | $Bu^n_3Sn$ | Ph | $BF_3·Et_2O$<br>$CH_2Cl_2$/–78 °C | 0:100 | 6:96 | 90 | 38 |
| 9 | $Me_3Si$ | $Pr^i$ | $TiCl_4/CH_2Cl_2$/–78 °C | >99:<1 | 3:97 | 92 | 39 |
| 10 | $Me_3Si$ | $Pr^i$ | $TiCl_4/CH_2Cl_2$/–78 °C | 3:97 | 36:64 | 98 | 39 |
| 11 | $CrCl_2$ | Ph | THF/r.t. | 100:0 | 100:0 | 96 | 27 |
| 12 | $CrCl_2$ | Ph | THF/r.t. | 0:100 | 100:0 | 96 | 27 |
| 13 | $Cp_2ZrCl$ | Ph | THF/–78 °C | | 86:14 | 90 | 40 |
| 14 | $Cp_2TiBr$ | Ph | Ether/–30 °C | | 100:0 | 92 | 41, 42 |
| 15 | 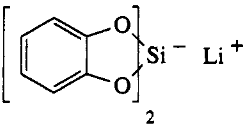 | Ph | THF, hexane/r.t. | 88:12 | 88:12 | 82 | 43 |
| 16 | | Ph | THF, hexane/r.t. | 21:79 | 22:78 | 91 | 43 |

### 1.6.3.3 Crotylchromium Reagents: α- or 2,3-Asymmetric Induction

Addition of crotyl metal reagents to aldehydes bearing a stereogenic center α to the carbonyl (**51**; Scheme 4) has been used as a strategy for the controlled synthesis of the stereo triads.[49] Two of the four possible diastereomers (**52**) and (**53**) are available from the addition of an (*E*)-crotyl metal reagent to (**51**) *via* synclinal cyclic transition states. Synclinal reaction geometries (presumed to be operative for crotylchromiums, (*vide infra*) (**A**) and (**B**) ($R^2$ = Me) are (*lk,ul*) and (*lk,lk*) 1,2-processes, respectively.[50] Both reaction manifolds will afford the *anti*-1,2 stereochemical arrangement (a general feature of crotylchromiums), where (**A**) leads to the 2,3-*anti* product (**52**) and (**B**) leads to the 2,3-*syn* product (**53**). Transition structure (**B**) (and consequently the formation of **53**) was predicted to predominate by Cram's rule[46,48] and is consistent with the Felkin–Ahn model.[47,48] In the general model $R^1$ represents either the largest group or that group whose bond to $C_\alpha$ maintains the greatest $\sigma^*$–$\pi^*$ overlap with orbitals of the carbonyl carbon. In the previous section, the ability of organochromiums to deliver a crotyl group and produce 1,2-*anti* stereochemistry selectively (**52** and **53**) was described. The potential for α- or 2,3- as well as 1,2-asymmetric induction was first addressed by Heathcock and Buse.[26] Addition of crotyl bromide/$CrCl_2$ to aldehyde (**54**; equation 29) provides two of the four possible diastereomers (**55**) and (**56**) in a 2.6:1 ratio, with complete 1,2-stereochemical control. However, the Cram:anti-Cram[46,48] ratio (**55**):(**56**) was modest. The major product (**55**) is that which is predicted by the Felkin–Anh addition model.[47] In a similar fashion (**57**) yields the two *anti* addition products (**58**) and (**59**) in nearly equal amounts (equation 30). Modest 2,3-diastereoselection has also been encountered by Hiyama and coworkers.[27] Crotylchromium addition to (**60**; equation 31) provided a 1,2-*anti*:*syn* selectivity (**61** + **62**):(**63**) of 93:7, and a disappointing Cram:anti-Cram ratio (**61** + **63**):(**62**) of 69:31. The question of 2,3-asymmetric induction has also been addressed by Kishi and coworkers.[44,45] During studies directed toward the construction of the Rifamycin ansa bridge,[44] crotylchromiums were shown to add to more complex substrate

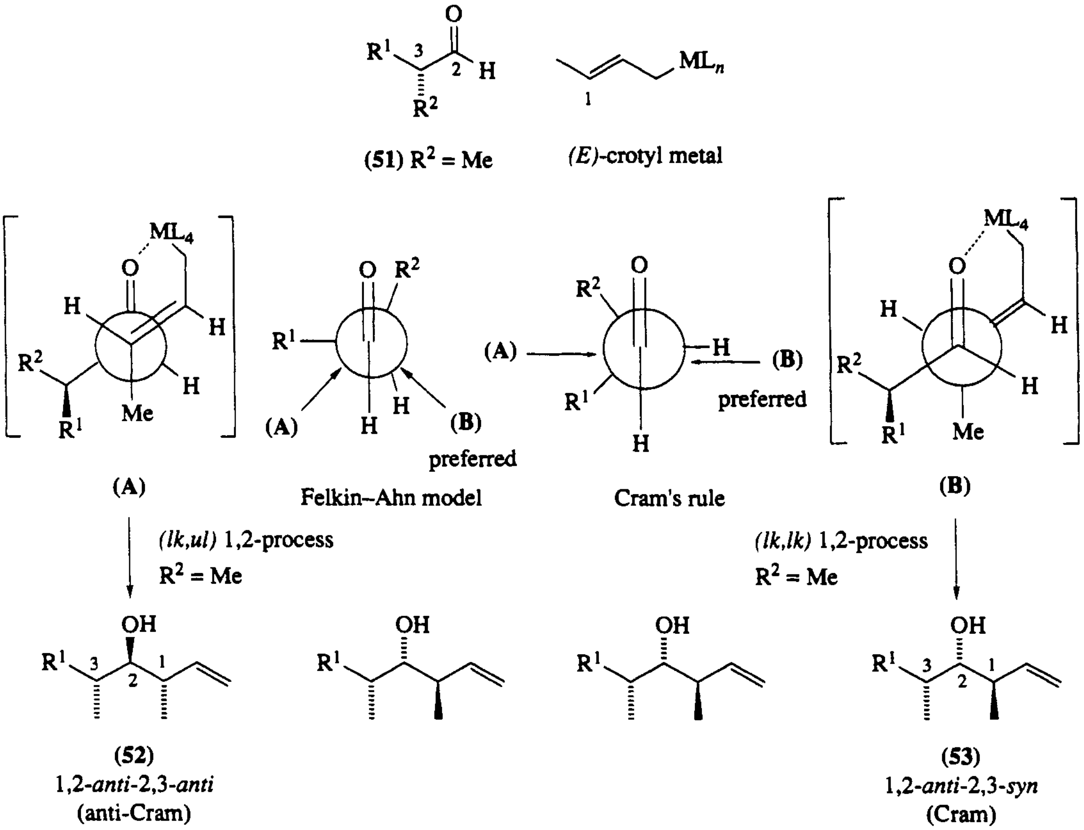
R¹
3
2
H
O
R²
(51) R² = Me
1
MLₙ
(E)-crotyl metal
ML₄
O
H
H
R²
H
R¹
Me
(A)
O R²
R¹
(A)
H
H
(B)
preferred
Felkin–Ahn model
(A)
O
R²
R¹
H
(B)
preferred
H
Cram's rule
ML₄
O
H
H
R²
H
R¹
Me
(B)
(lk,ul) 1,2-process
R² = Me
(lk,lk) 1,2-process
R² = Me
OH
R¹
3
2
1
OH
R¹
OH
R¹
OH
R¹
3
2
1
(52)
1,2-anti-2,3-anti
(anti-Cram)
(53)
1,2-anti-2,3-syn
(Cram)

**Scheme 4**

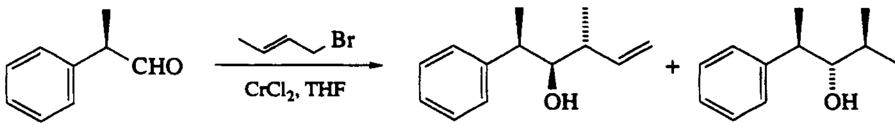
CHO
Br
CrCl₂, THF
OH
+
OH

(29)

(**54**) (**55**) 72:28 (**56**)

aldehydes with excellent 1,2- and 2,3-diastereoselectivity. Aldehyde (**64**) afforded (**65**), which maintains the 1,2-*anti* and 2,3-*syn* (or Cram) diastereochemical relationships. A similar qualitative and quantitative result was realized with aldehyde (**66**). The origin of the selectivity seen for the production of (**65**) and (**67**) was probed in a subsequent study by Kishi and Lewis.[45] The stereochemical outcome was shown not to be a consequence of chelation control[57] as is shown by the insensitivity of the Cram:anti-Cram ratio toward polarity of the reaction medium (equation 34) and toward a variety of hydroxy-protecting groups (R; equation 35). It is apparent that the origin of the 2,3-induction is a function of the steric size and chemical nature of the large α-substituent. Other examples of additions to chiral aldehydes reported by Kishi are provided in Table 4. The major homoallylic alcohols obtained all possess the 1,2-*anti*, 2,3-*syn* (Cram) relationship which arises from an (*lk,lk*) 1,2-process consistent with the expectation for a synclinal transition state and a Felkin–Anh-type approach. Enhanced selectivity with respect to earlier reports and differences in diastereogenesis amongst these cases is rationalized on the basis of predicted torsional preferences about the C(3)—C(4) bond in the substrate aldehydes.[45] In a related transformation, addition of allylchromium to a β-alkoxy-α-methyl aldehyde (**84**) also provided a Cram addition product (**85**) with 91% stereoselectivity (equation 41).[51]

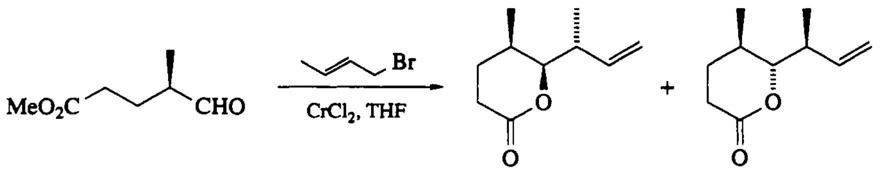

(30)

**(57)** **(58)** 50:50 **(59)**

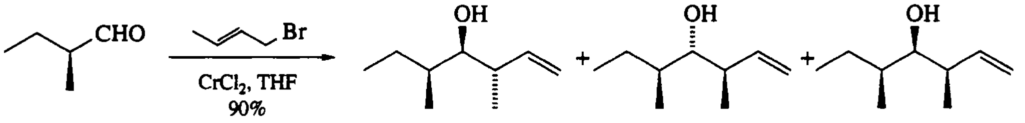

(31)

**(60)** **(61)** **(62)** **(63)**

62 : 31 : 7

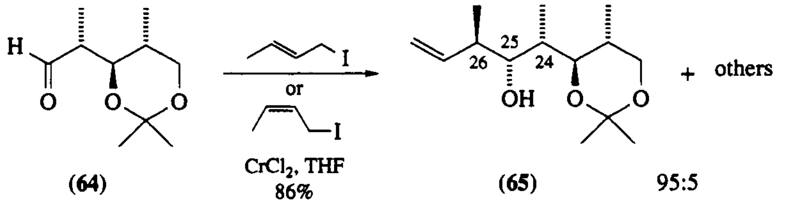

(32)

**(64)** **(65)** 95:5

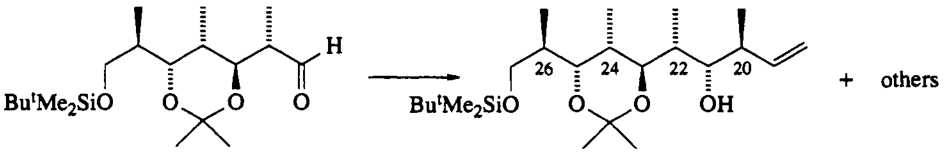

(33)

**(66)** **(67)** >95:<5

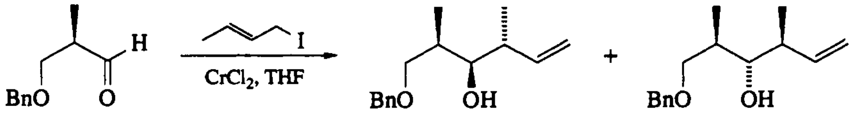

(34)

**(68)** **(69)** **(70)**

| | |
|---|---|
| THF | 61:39 |
| $Et_2O$ | 56:44 |
| PhMe | 61:39 |

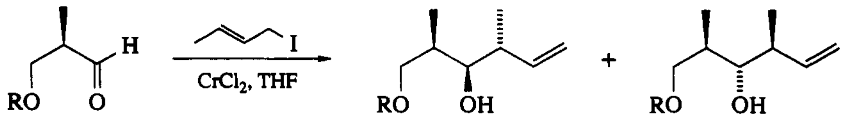
H
RO
O
I
CrCl₂, THF
RO
OH
+
RO
OH

(71) (72) (73) (35)

R = $CH_2OBn$ ~50 : ~50
R = THP ~50 : ~50

**Table 4** Crotylchromium Addition to Chiral Aldehydes with α-Methyl and β-Alkoxy Substituents

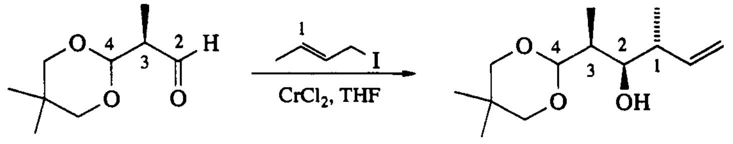
O
4
2
H
3
O
O
1
I
CrCl₂, THF
O
4
2
3
1
O
OH

(74) (75) 92:8[a] (36)

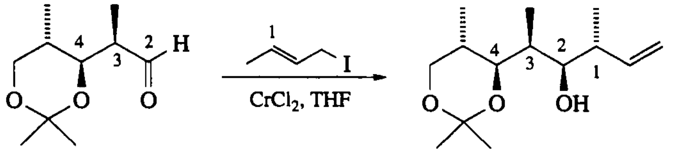
4
2
H
3
O
O
O
1
I
CrCl₂, THF
4
2
3
1
O
O
OH

(76) (77) 80:20[a] (37)

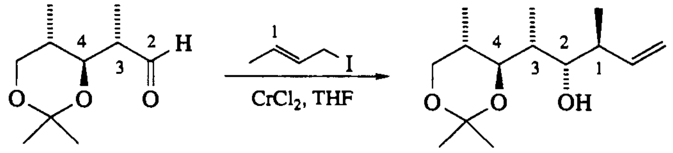
4
2
H
3
O
O
O
1
I
CrCl₂, THF
4
2
3
1
O
O
OH

(78) (79) 95:5[a] (38)

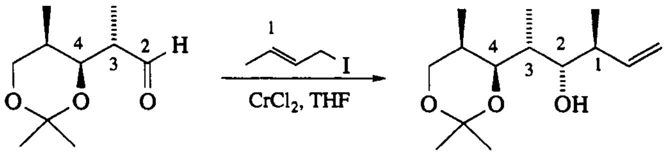
4
2
H
3
O
O
O
1
I
CrCl₂, THF
4
2
3
1
O
O
OH

(80) (81) 80:20[a] (39)

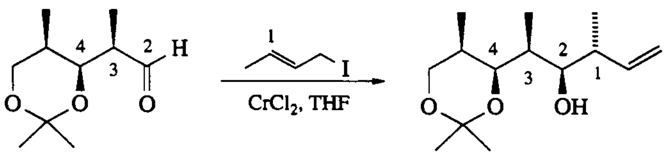
4
2
H
3
O
O
O
1
I
CrCl₂, THF
4
2
3
1
O
O
OH

(82) (83) 91:9[a] (40)

---

[a] Ratio of major diastereomer to next most abundant diastereomer: only structure of major diastereomer was determined.

Reaction of crotylchromium with α-methyl-β,γ-unsaturated aldehyde (**87**) afforded (**88**) as the major diastereomer.[52] The other Cram product (**89**), which is expected to arise from an antiperiplanar transition state (**46**; Scheme 3), is obtained from a $BF_3$-catalyzed tributylcrotylstannane addition. The remaining members of the stereo triad can be accessed by inversion of the C-2 hydroxy (*i.e.* **88** to **91** and **89** to **90**)

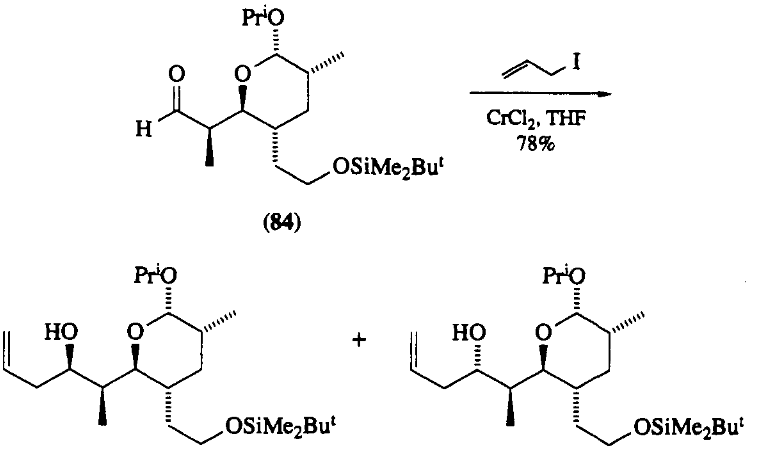

**(84)**

**(85)** 91:9 **(86)** (41)

*via* an oxidation (PDC)–reduction (LiBEt$_3$H) sequence. In general it has been shown that (**87**) and related substrates react with nucleophiles (H$^-$, C$^-$) selectively to give products consistent with the Felkin–Anh mode of addition.[47,54]

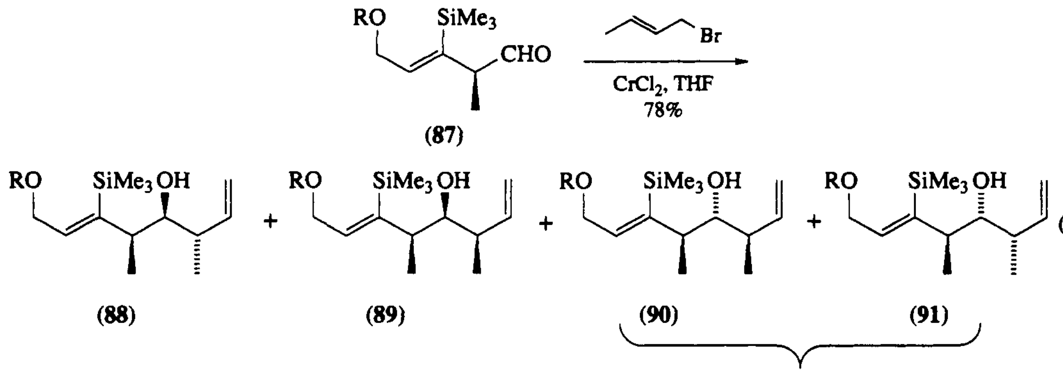

**(87)**

**(88)** **(89)** **(90)** **(91)** (42)

>90 : <1 : 9

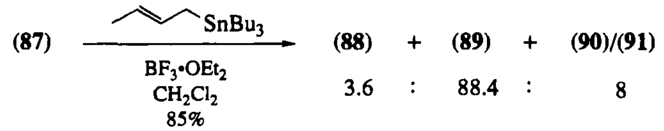

**(87)** → **(88)** + **(89)** + **(90)**/**(91)** (43)

3.6 : 88.4 : 8

Chromium-mediated addition of crotyl halides to α-alkoxy chiral aldehydes has been the subject of several interesting reports. Reaction of crotyl bromide/CrCl$_2$ with 2,3-*O*-isopropylideneglyceraldehyde (**92**; equation 44)[57] provides the 1,2-*anti* products with 98% stereoselectivity, given by the ratio (**93** + **95**):(**94** + **96**),[53] while 2,3-control, given by the ratio (**93** + **94**):(**95** + **96**), was nearly inoperative. However, a related substrate (**97**) produced exclusively 2,3-*syn* products with a 96:4 1,2-*anti*:*syn* ratio (equation 45).[55] Mulzer and coworkers[56] investigated the importance of the γ-substituent of the allylchromium(III) reagent with respect to 1,2- and 2,3-diastereogenesis in the addition reactions to α-alkoxy chiral aldehydes (equation 46 and Table 5). It was found in all cases that the level of 1,2-*anti* selectivity, given by the ratio (**103** + **104**):(**105** + **106**), was complete. Moreover, it was demonstrated that the 2,3-*syn* selectivity increased as a function of increasing the size of R$^2$. This result is consistent with both the transition state models proposed for addition of γ-substituted allylchromiums to aldehydes and with the expectation that products will be generated by Felkin–Anh-type addition (**103** and **106**).[58,60]

The addition of γ-alkoxy allylic chromium(III) reagents to aldehydes has been reported by Takai and coworkers.[76] This work is reviewed in Section 1.6.3.6.

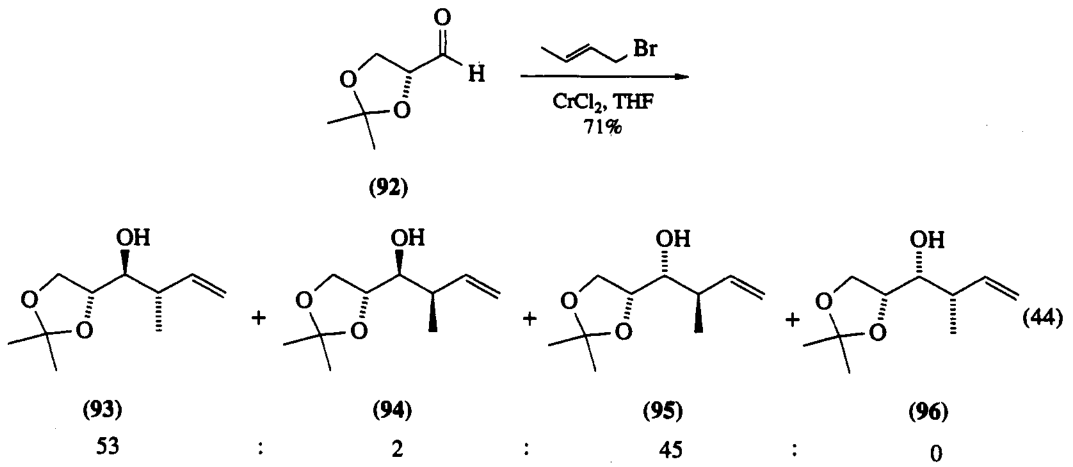
O
H
O
O
Br
CrCl2, THF
71%
OH
OH
OH
OH

(92)

(93) : (94) : (95) : (96)

53 : 2 : 45 : 0

(44)

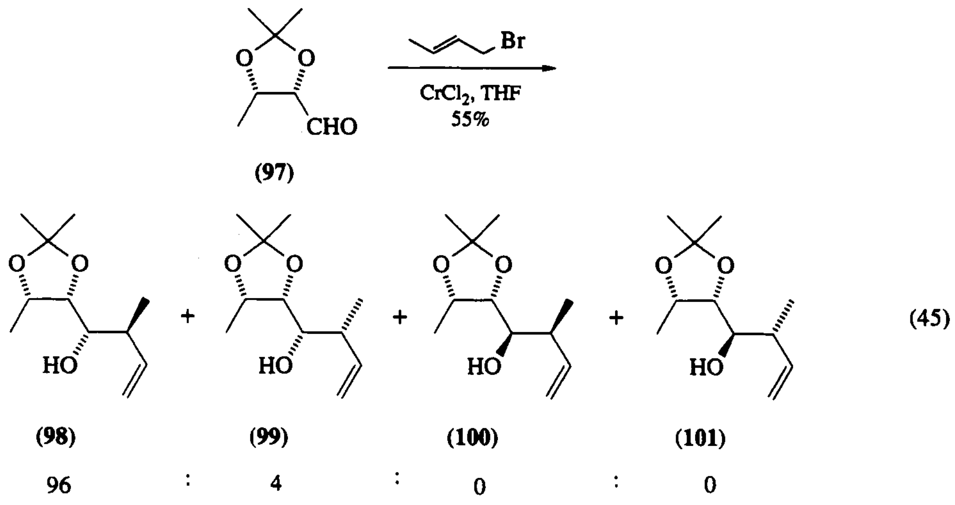
O
O
CHO
Br
CrCl2, THF
55%
HO
HO
HO
HO

(97)

(98) : (99) : (100) : (101)

96 : 4 : 0 : 0

(45)

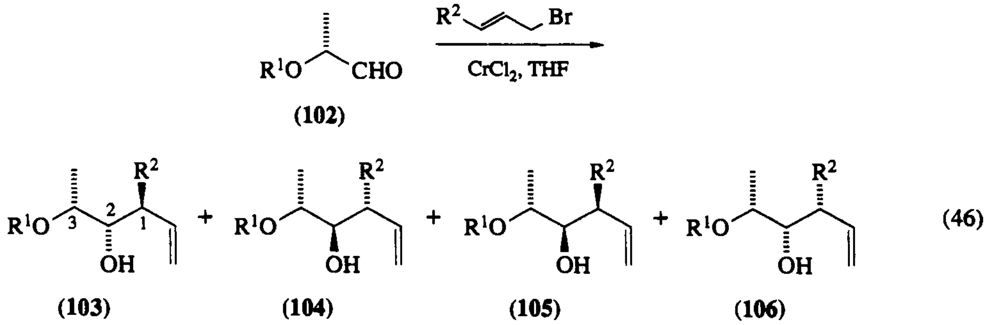
R1O
CHO
R2
Br
CrCl2, THF
R2
R1O
3
2
1
OH
R2
R1O
OH
R2
R1O
OH
R2
R1O
OH

(102)

(103) (104) (105) (106)

(46)

**Table 5** Addition of Substituted Allylchromium Reagents to Protected α-Hydroxy Aldehydes (equation 46)[55]

| *Entry* | $R^1$ | $R^2$ | *(103):(104):(105):(106)* | *Total yield (%)* |
|---|---|---|---|---|
| 1 | THP | Me | 89:11:0:0 | 80 |
| 2 | THP | Ph | 91:9:0:0 | 71 |
| 3 | THP | Bu | >99:<1:0:0 | 75 |
| 4 | TBDMS | Bu | >99:<1:0:0 | 90 |

### 1.6.3.4 Other *n,m*-Asymmetric Induction

The use of allylic chromium reagents to control the relative stereochemistry of remote asymmetric centers has been described by Takeshita and coworkers.[61–64] The condensation of iridoid aldehyde synthon (**107**) and its enantiomer (**109**) with homochiral allylic chloride (**108**) provided in each case only two of the four possible diastereomers equations (47) and (48). In this reaction the γ-carbon of the organochromium offers only its *re*-face to the substrate aldehydes (**107**) and (**109**). Therefore, the two diastereomers arise from addition to either face of the aldehyde with addition to the *re*-face predominating in both cases with good to excellent selectivity. These materials were used in rather inventive syntheses of the 5-8-5 tricyclic sesterterpenes fusicocca-2,8,10-triene (**114**) and cycloaranosine (**115**). The approach to (**115**) uses a second chromium(II)-mediated aldehyde addition reaction (intramolecular) to form the eight-membered ring (see equation 52, Section 1.6.3.5).[62] A similar strategy was developed for the synthesis of ceroplastol II (**116**) and albolic acid (**117**).[63] Reaction of (**108**) with (**118**) in the presence of $CrCl_2$ provided (**120**) selectively with only 3% contamination by the hydroxy epimer (equation 49). The stereochemistry of (**120**) is consistent with the synclinal transition structure (**119**).

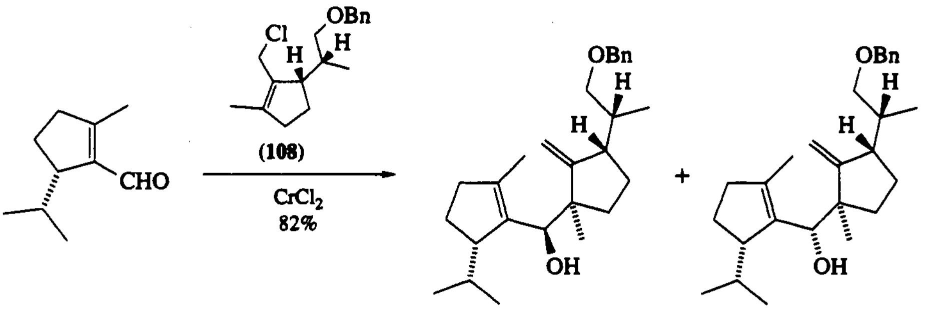

(47)

(**107**) (**110**) 78:22 (**111**)

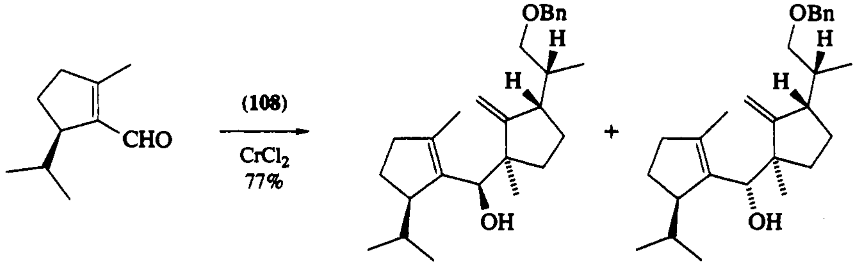

(48)

(**109**) (**112**) 95:5 (**113**)

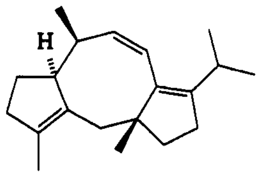

(**114**)

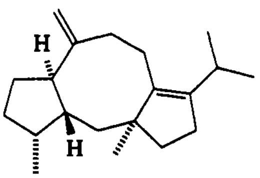

(**115**)

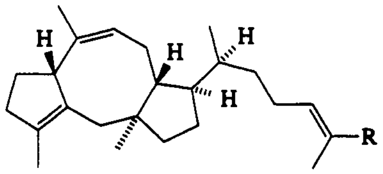

(**116**) R = $CH_2OH$
(**117**) R = $CO_2H$

### 1.6.3.5 Intramolecular Addition Reactions

The intramolecular variant of the chromium(II) ion mediated Barbier–Grignard-type addition reaction was first described by Still and Mobilio[65] in an elegant synthesis of (±)-Asperdiol (**122**; R = H). Chromium(II)-mediated cyclization of (**121**; R = Bn) provided a 4:1 mixture of (**122**) and (**123**) in 64% yield (equation 50). The relative topicity of the process is *lk*. This result is in accord with a synclinal chair transition structure (**124**) in which both hydrocarbon chains diverge from the reacting centers pseudo-

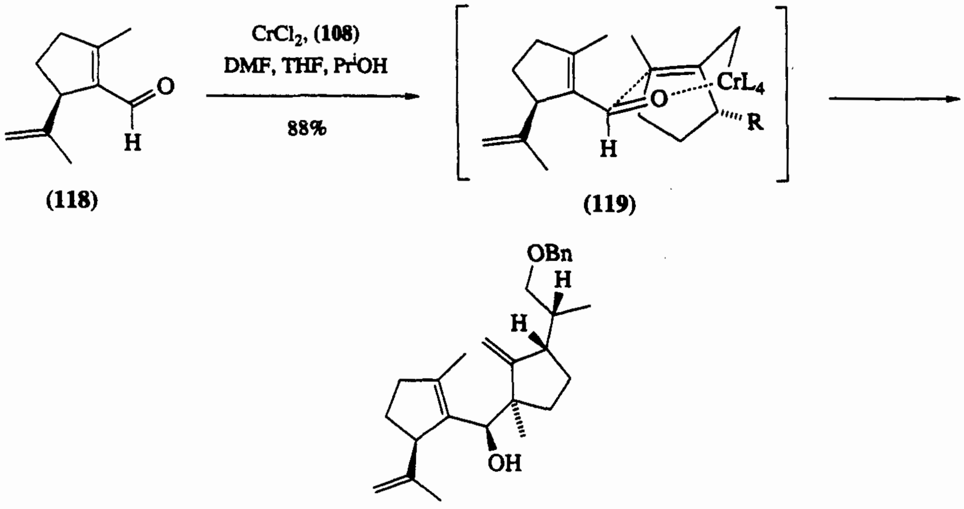

(118) (119) (120)

equatorially (dihedral angle C(2)—C(1)–C(14)—C(13) = *ca.* 30°; **125**). Medium[66,67] and large[68,69] ring closures employing allylstannanes,[68,69] allylzinc[66] and allylnickel[67] compounds are also described in the literature. However, the relative topicity of these intramolecular carbon–carbon bond-forming reactions is *ul* (see equations 55 and 56 in Section 1.6.3.6).[72,73]

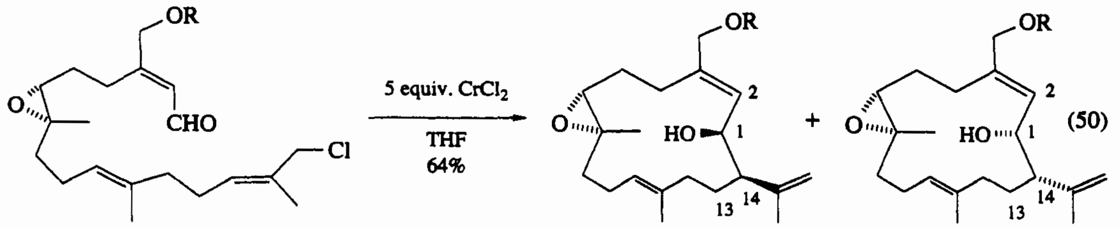

**(121)** **(122)** 80:20 **(123)**

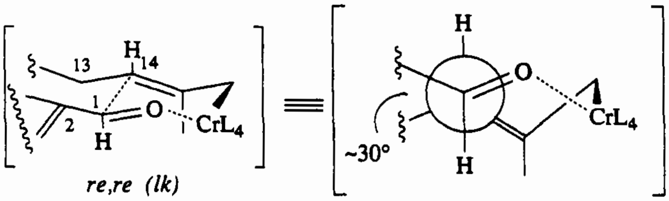

**(124)** **(125)**

A related reaction has been described by Kitagawa and coworkers[70] in which (**126**) exclusively provides (**127**) upon treatment with $CrCl_3$–LAH (equation 51). The relative stereochemical result is qualitatively identical to that reported by Still and Mobilio.[65] Cyclodecadienol (**127**) was subsequently transformed into (±)-costunolide. A third example of a related chromium-initiated cyclization was reported by Takeshita and coworkers[62] in a synthesis of cycloaranosine (**115**). Serial treatment of (**128**) with MsCl/pyridine and $CrCl_3$–LAH provided (**129**) stereospecifically in 95% yield (equation 52). Another example of internal addition of an allylic chromium reagent to an aldehyde has been reported by Oshima and coworkers and is outlined in Section 1.6.3.6.[72]

Intramolecular alkenylchromium additions to aldehydes have been reported[94,95] and are outlined in Section 1.6.4.3. An intriguing example of an intramolecular organochromium reaction has been communicated by Gorques and coworkers.[71] Treatment of (**130**; Scheme 5) with $CrCl_2$ in HMPA elicits a reductive 1,5-acyl transposition and generates chromium phenoxide (**131**). Work-up with aqueous ammonium chloride affords phenol (**132**). However, when the reaction occurs in the presence of boron trifluoride etherate benzo[*b*]furan (**133**) is obtained directly in excellent yield.

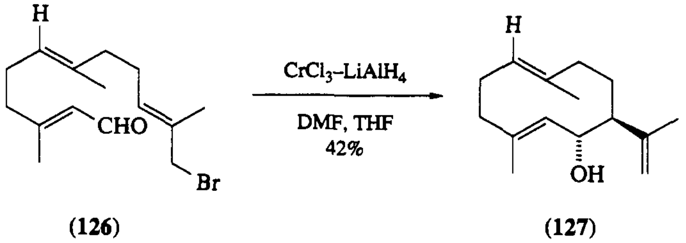

(51)

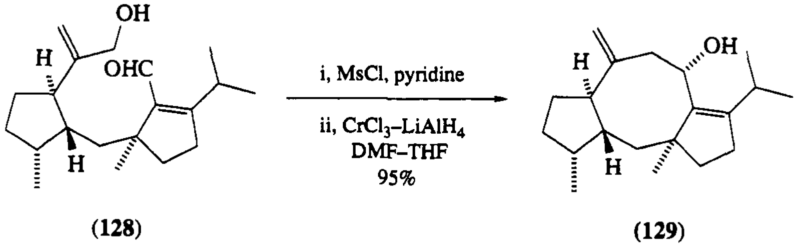

(52)

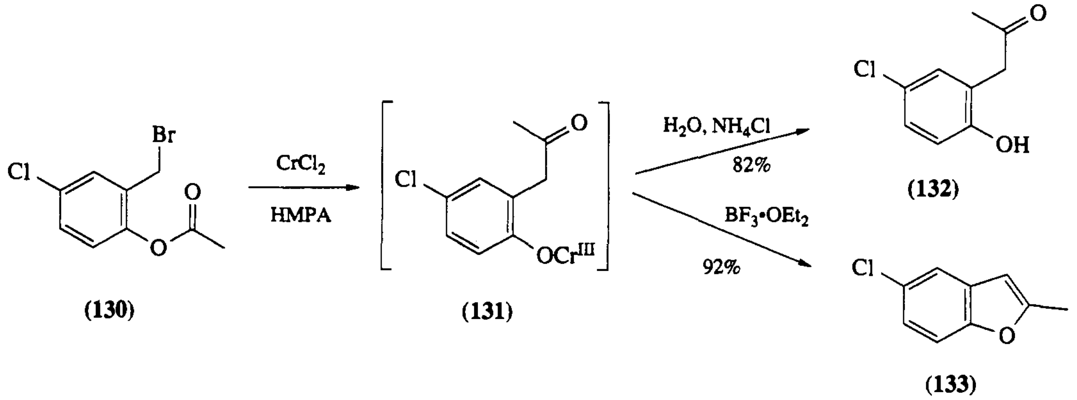

Scheme 5

### 1.6.3.6 Miscellaneous Substituted Substrates

Allylic chromium reagents bearing an electron-withdrawing group at the β-position of the starting halide have been the subject of several reports.[72,75] Oshima and coworkers and Drewes and Hoole have shown that $CrCl_3$–LAH facilitates the addition of ethyl α-bromomethylacrylate (**134**) to benzaldehyde to generate the α-methylenelactone (**135**; equation 53) directly.[72] It was noted that when commercially available $CrCl_2$ was used in place of Hiyama's reagent ($CrCl_3$–LAH) hydroxy ester (**138**) was obtained as the sole product. The reagent prepared from (**134**) and chromium(II) ion added specifically to the aldehyde functionality in (**135**) to provide keto lactone (**137**; equation 54). Appending a substituent at the β-position of (**134**) (*i.e.* Bu; **139**) introduces the possibility for 1,2-asymmetric induction. In sharp contrast to other allylic chromium reagents, (*E*)- or (*Z*)-(**139**) upon treatment with $CrCl_3$–LAH adds to benzaldehyde with *ul* relative topicity to provide the *syn*-α-methylenelactone (**140**) stereospecifically. An intramolecular variant of this reaction reported by Oshima and coworkers,[72] describes the transformation of (**141**) cleanly into (**142**; equation 56). Other reducing metal centers ($Ni^{66,74}$ and $Zn^{67,73}$) have been used to initiate the construction of α-methylenelactones from allylic bromides and aldehydes. These processes also proceed with *ul* relative topicity. Another example of a trisubstituted allylic chromium reagent bearing an electron-withdrawing group at the β-position to the chromium atom was reported by Knochel and coworkers.[75] Sulfone (**143**) adds to isovaleraldehyde (**144**) in the presence of $CrCl_2$. The addition proceeds stereoselectively to provide a 96:4 ratio of *syn*-(**145**) to *anti*-(**146**) in 95% yield (equation 57). The specificity of this transformation was shown to be general (with six examples). The selective *ul* relative topicity of the addition reaction of sulfone (**143**) has been ascribed by Knochel to a synclinal transition structure (**147**). The preferred (*E*)-alkene geometry fixes the γ-substituent of the nucleophile in a pseudoaxial position. Alternatively, Oshima and coworkers explained their results by implicating an antiperiplanar reaction geometry (**148**), which is favored because coordination of the substrate aldehyde is replaced by internal ligation from an ester oxygen.

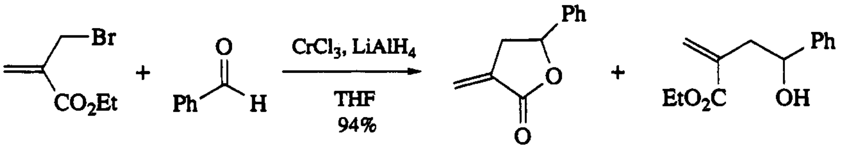
Br
CO2Et
O
Ph
H
CrCl3, LiAlH4
THF
94%
Ph
O
O
Ph
EtO2C
OH

(53)

(**134**) (**135**) (**138**)

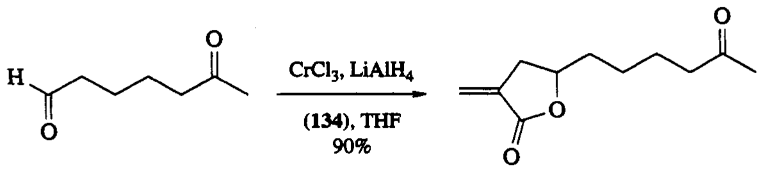
H
O
O
CrCl3, LiAlH4
(134), THF
90%
O
O
O

(54)

(**136**) (**137**)

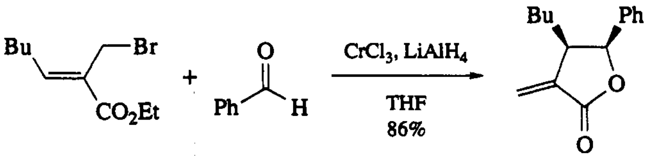
Bu
Br
CO2Et
O
Ph
H
CrCl3, LiAlH4
THF
86%
Bu
Ph
O
O

(55)

(**139**) (**140**)

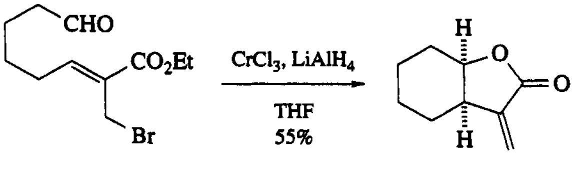
CHO
CO2Et
Br
CrCl3, LiAlH4
THF
55%
H
O
O
H

(56)

(**141**) (**142**)

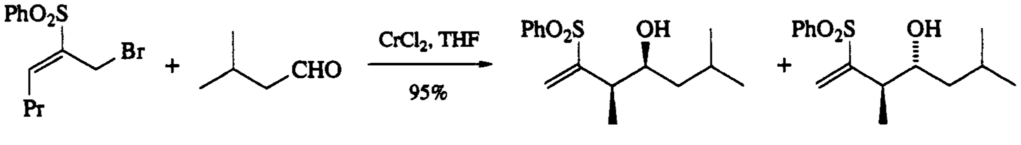
PhO2S
Br
Pr
CHO
CrCl2, THF
95%
PhO2S
OH
PhO2S
OH

(57)

(**143**) (**144**) (**145**) 96:4 (**146**)

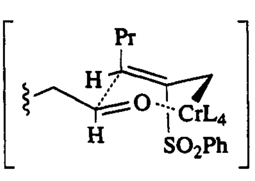
Pr
H
O
CrL4
H
SO2Ph

*re,si (ul)*

(**147**)

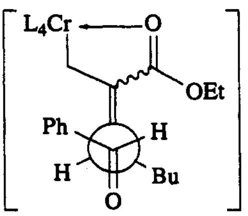
L4Cr
O
OEt
Ph
H
H
Bu
O

*si,re (ul)*

(**148**)

Takai and coworkers have recently reported their findings on the addition of γ-alkoxyallylic chromium compounds to aldehydes.[76] The reagents, which were generated by the reduction of dialkyl acetals (**149**) with $CrCl_2$ in the presence of trimethylsilyl iodide, added to aldehydes (**150**) to produce vicinal diols (equation 58 and Table 6). The addition proceeded efficiently and stereoselectively at −30 °C providing the *erythro*-1,2-diols (**151**) as the major products. The reaction tolerated substitution at the α- and β-positions (Table 6, entries 12 and 13 and entries 10 and 11, respectively) of the acetal. Suprisingly, however, the dibenzyl acetal of crotonaldehyde did not provide a useful chromium-based reagent. *Erythro/threo* selectivity was high in all cases except for addition to pivaldehyde (entry 8). As is the case for other organochromium(III) reagents, the oxygenated analogs generated from acrolein acetals add chemospecifically to aldehydes in the presence of ketones (equation 59). The authors suggest that the organochromium reagent was constrained to an *s-cis* configuration caused by internal ligation of the γ-oxygen atom to the metal center. As a consequence, the possible synclinal transition state geometries are boat-like arrangements (**157**) and (**158**). Preferred complexation of the aldehyde lone pair which is *syn* to hydrogen[77] and the presence of fewer eclipsing interactions make (**157**) the favored transition state and the *erythro* isomer (**151**) the predominant product.

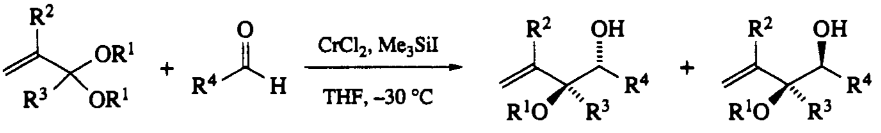

(58)

(**149**) (**150**) (**151**) *erythro* (**152**) *threo*

**Table 6** Reaction of Unsaturated Dialkyl Acetals with Aldehydes using $CrCl_2$/TMS-I (equation 58)[76]

| *Entry* | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *Time (h)* | *Yield (%)* | *Erythro:threo (151):(152)* |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | Ph | 3 | 99 | 88:12 |
| 2 | Bn | H | H | Ph | 1.5 | 97 | 71:29[a] |
| 3 | Bn | H | H | Ph | 3 | 98 | 88:12 |
| 4 | Bn | H | H | Ph | 9 | 33 | 91:9[b] |
| 5 | Bn | H | H | n-$C_8H_{17}$ | 6 | 95 | 87:13 |
| 6 | Bn | H | H | $PhCH_2CH_2$ | 2.5 | 99 | 88:12 |
| 7 | Bn | H | H | Cyclohexyl | 6 | 93 | 88:12 |
| 8 | Bn | H | H | *t*-Butyl | 7 | 91 | 33:67 |
| 9 | Bn | H | H | PhCH=CH | 2 | 97 | 76:24[c] |
| 10 | Bn | Me | H | Ph | 3 | 99 | 85:15 |
| 11 | Bn | Me | H | n-$C_8H_{17}$ | 3 | 99 | 88:12 |
| 12 | Bn | H | Me | Ph | 8 | 88 | 92:8 |
| 13 | Bn | H | Me | n-$C_8H_{17}$ | 5 | 83 | 93:7 |

[a] Reaction performed at 25 °C. [b] Reaction performed at −42 °C; 42% PhCHO recovered. [c] 1,2-Addition.

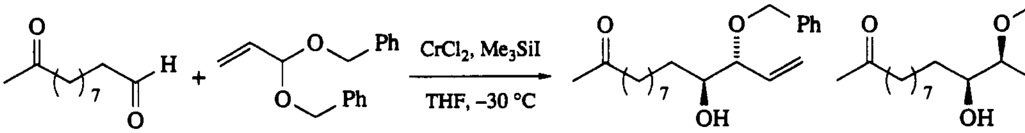

(59)

(**153**) (**154**) (**155**) (**156**)

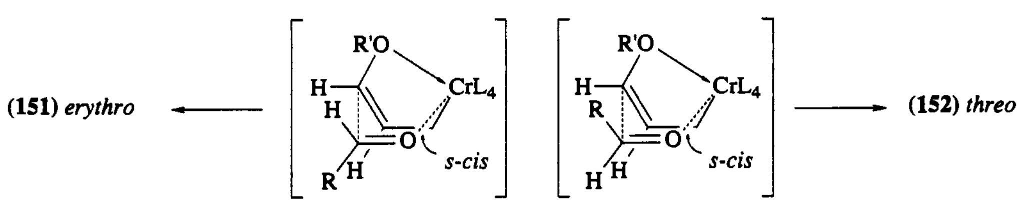

(**157**) (**158**)

## 1.6.3.7 Propargylchromium Reagents

The chromium-mediated addition of propargyl halides to carbonyl compounds was studied by Gore and coworkers.[78–80] Unlike the crotylchromium reagents already described (*vide supra*), which react exclusively with allylic transposition, propargyl systems (**159**) react with carbonyl compounds (**160**) to provide a mixture of alkynic and allenic products (**161**) and (**162**) (equation 60). The regioselectivity was shown to be a function of the propargyl bromide and carbonyl substrate and of the presence of HMPA (hexamethylphosphoramide) in the reaction medium (Table 7). The authors suggest that the organochromium(III) reagent reacts entirely by allylic transposition (Scheme 6). Therefore, the regiochemical outcome reflects the ratio of organochromiums (**165**) and (**166**) which are formed as a mixture or equilibrate *via* mesomeric radical intermediates (**163**) and (**164**).

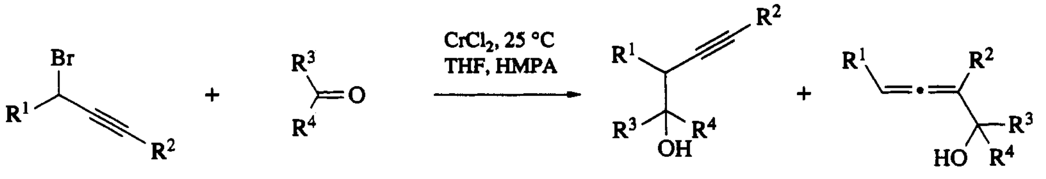

(60)

**(159)** **(160)** **(161)** **(162)**

**Table 7** Chromium(II)-mediated Addition of Propargyl Bromides to Aldehydes and Ketones (equation 60)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *(161):(162)* | *(equiv.) HMPT* | *Yield (%)* |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | n-$C_7H_{15}$ | 85:15 | 0 | 72 |
| 2 | H | H | —$(CH_2)_5$— | | 65:35 | 0 | 68 |
| 3 | H | H | —$(CH_2)_5$— | | 21:79 | 5 | 70 |
| 4 | H | $C_5H_{11}$ | H | $Pr^n$ | 0:100 | 0 | 80 |
| 5 | H | $C_5H_{11}$ | Me | Me | 0:100 | 0 | 78 |
| 6 | H | $C_5H_{11}$ | —$(CH_2)_5$— | | 0:100 | 0 | 78 |
| 7 | n-$C_7H_{15}$ | H | H | $Pr^n$ | 100:0 | 0 | 76 |
| 8 | n-$C_7H_{15}$ | H | Me | Me | 0:100 | 0 | 66 |
| 9 | n-$C_7H_{15}$ | H | —$(CH_2)_5$— | | 60:40 | 0 | 75 |
| 10 | n-$C_7H_{15}$ | H | —$(CH_2)_5$— | | 20:80 | 1 | 68 |
| 11 | $Pr^n$ | Et | H | $Pr^n$ | 100:0 | 0 | 65 |
| 12 | $Pr^n$ | Et | Me | Me | 75:25 | 0 | 60 |
| 13 | $Pr^n$ | Et | —$(CH_2)_5$— | | 80:20 | 0 | 50 |

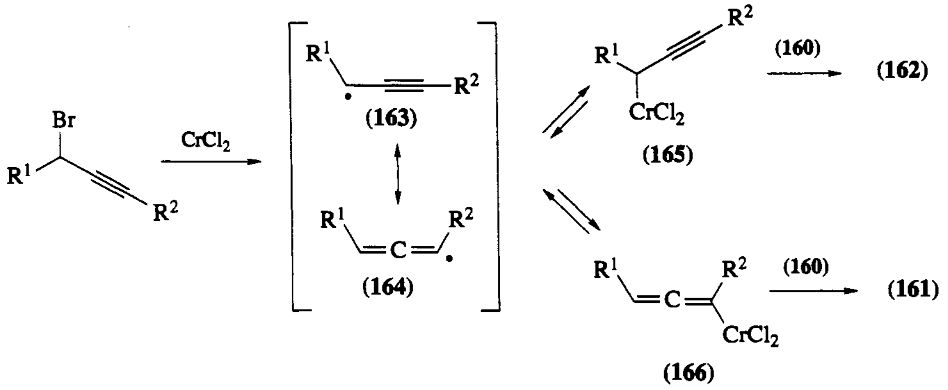

**Scheme 6**

### 1.6.3.8 Enantioselective Addition Reactions

Allylic organometallics modified at the metal center by chiral adjuvants add to aldehydes and ketones to provide optically active homoallylic alcohols. This process has been described for reagents containing boron,[81] tin[82] and chromium[83] metal centers. Gore and coworkers[83] have shown that a chromium-mediated addition reaction of allylic bromides to simple aldehydes that uses a complex of lithium *N*-methylnorephedrine and chromium(II) chloride occurs with modest (6–16% *ee*) enantioselectivity (equation 61, Table 8).

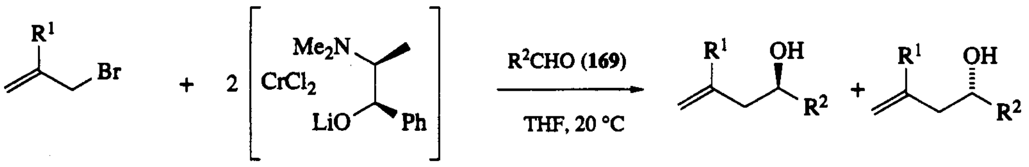

(167) (168) (170) (171)

(61)

**Table 8** Enantioselective Addition of Allylchromium Reagents to Aldehydes (equation 61)

| *Entry* | *$R^1$* | *$R^2$* | *(170):(171)* | *Yield (%)* | *ee (%)* |
|---|---|---|---|---|---|
| 1 | H | Pr | (SR) 58:42 | 49 | 16 |
| 2 | H | $CH_2CHMe_2$ | (SR) 58:42 | 58 | 16 |
| 3 | H | c-$C_7H_{15}$ | a | 48 | a |
| 4 | H | Ph | (RS) 56:44 | 60 | 11.5 |
| 5 | Me | Pr | (SR) 58.5:41.5 | 52 | 17 |
| 6 | Me | Ph | (RS) 53:47 | 53 | 6 |

[a] Not applicable.

## 1.6.4 ALKENYLCHROMIUM REAGENTS

### 1.6.4.1 General Features

The ability of the anhydrous chromium(II) ion to reduce vinyl halides and provide alkenylchromium compounds which participate in aldehyde addition reactions was first described by Takai and coworkers.[84] Treatment of 2-iodopropene (**173**) and benzaldehyde with anhydrous chromium(II) chloride in DMF afforded allylic alcohol (**174**) in quantitative yield (equation 62).[84]

General features of the process are illustrated in Table 9. The addition to aldehydes is more facile than to ketones (entries 1 and 2 *versus* 3). Vinyl bromide (**177**) adds to aldehydes in the presence of $CrCl_2$. The separate addition of (*E*)-bromostyrene (**180**) and (*Z*)-bromostyrene (**182**) to benzaldehyde occurs stereospecifically to provide (*E*)-(**181**) and (*Z*)-(**183**), respectively (entries 6 and 7). However, trisubstituted (*E*)- and (*Z*)-vinyl iodides (**184**) and (**186**) add to benzaldehyde in a stereoconvergent fashion wherein (*E*)-(**185**) is the exclusive product in both cases. Lastly, iodobenzene (**187**) adds more effectively to nonanal than does bromobenzene (**189**) The chemoselectivity of alkenylchromiums mirrors that of crotylchromium reagents (see equations 19 and 21). Selective addition to the aldehyde carbonyl of bifunctional compounds (**190**) and (**192**) yields adducts (**191**) and (**193**), respectively (equation 63 and 64). Takai and coworkers[85] have shown that alkenylchromium reagents can also be generated from enol triflates and chromium(II) chloride under nickel catalysis (equation 65). This work, as well as reports from Kishi and coworkers,[86] shows that nickel, as a trace contaminant in commercially available $CrCl_2$ is essential for most Barbier-like organochromium reactions. Consonant with this finding is the fact that high purity $CrCl_2$, free from nickel salt contamination, does not reproducibly promote organochromium formation. A catalytic cycle which is likely to be operative has been proposed (Scheme 7). Vinyl halide or triflate (**194**) undergoes oxidative addition to nickel(0) to provide a nickel(II) species (**195**)[87] which, after metal exchange with chromium(III), affords an alkenylchromium(III) reagent. The appropriate quantities of nickel(0) and chromium(III) are provided by the facile redox couple between nickel(II) and chromium(II).[88] In cases where (**194**) is an iodide, both nickel(II) and palladium(II) salts promote the catalytic cycle and the addition reaction to aldehydes. However, triflates are converted to competent alkenylchromium reagents only under nickel catalysis. Since it has been shown that palladium(0) undergoes facile oxidative addition to alkenyl and aryl triflates,[89] the alkenylpalladium triflate (**195**; M = Pd,

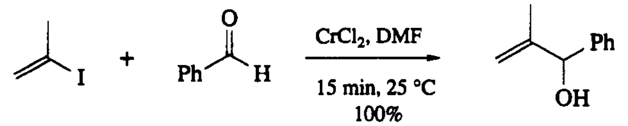

(173) (174)

(62)

**Table 9** $CrCl_2$-mediated Addition of Alkenyl Halides to Aldehydes and Ketones (equation 62)[a]

| *Entry* | *Alkenyl halide* | *Aldehyde/ketone* | *Yield* (%)[b] | *Time* (h) | *Product* |
|---|---|---|---|---|---|
| 1 | 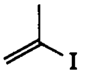 **(173)** | PhCHO | 100 | 0.25 | 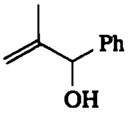 **(174)** |
| 2 | 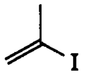 **(173)** | n-$C_8H_{17}$CHO | 100 | 0.25 | 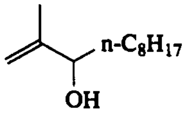 **(175)** |
| 3 | 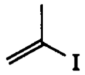 **(173)** | Cyclohexanone **(172)** | 22[c] | 3 | 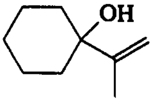 **(176)** |
| 4 | 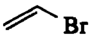 **(177)** | PhCHO | 80 | 15 | 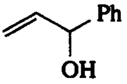 **(178)** |
| 5 | 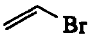 **(177)** | n-$C_8H_{17}$CHO | 77 | 1.5 | 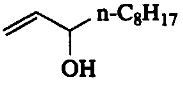 **(179)** |
| 6 | 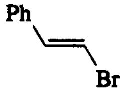 **(180)** | PhCHO | 82 | 1 | 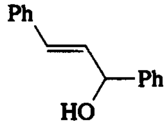 **(181)** (*E*) only |
| 7 | 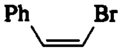 **(182)** | PhCHO | 78 | 1 | 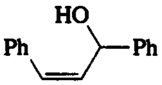 **(183)** (*Z*) only |
| 8 | 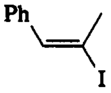 **(184)** | PhCHO | 91 | 3 | 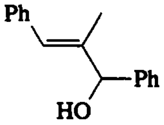 **(185)** (*E*) only |

**Table 9** *(continued)*

| *Entry* | *Alkenyl halide* | *Aldehyde/ketone* | *Yield* (%)[b] | *Time* (h) | *Product* |
|---|---|---|---|---|---|
| 9 | 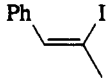<br>**(186)** | PhCHO | 90 | 3 | 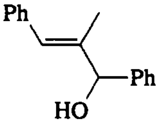<br>**(185)** (*E*) only |
| 10 | PhI **(187)** | n-$C_8H_{17}$CHO | 83 | 3 | 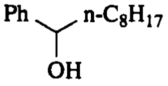<br>**(188)** |
| 11 | PhBr **(189)** | n-$C_8H_{17}$CHO | 13[d] | 5 | 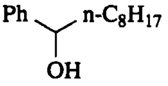<br>**(188)** |

[a] Reaction run at 25 °C, 4 equiv. of $CrCl_2$ used. [b] Isolated yields. [c] 50 °C, 3 h. [d] 90 °C.

X = OTf) may fail to accomplish metal exchange and consequently hinder the formation of the alkenylchromium reagent. Few examples of the use of enol triflates as progenitors of vinyl carbanion equivalents have appeared.[90] Consequently, the work from Takai and coworkers is particularly useful. The alkenylchromiums generated from enol triflates are functionally indistinguishable from those generated from iodoalkenes (equation 65 and table 10).[85] This fact is disclosed by comparison of Table 9 with Table 10.

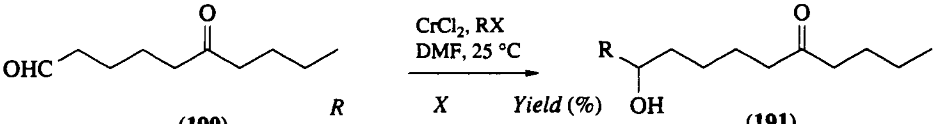

**(190)** **(191)** (63)

| *R* | *X* | *Yield* (%) |
|---|---|---|
| $H_2C{=}C(Me)$ | I | 94 |
| $H_2C{=}CH$ | Br | 86 |
| Ph | I | 81 |

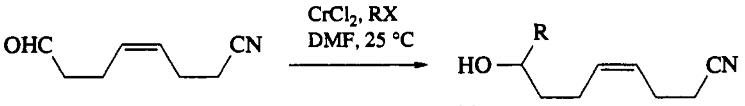

**(192)** **(193)** (64)

| *R* | *X* | *Yield* (%) |
|---|---|---|
| $H_2C{=}C(Me)$ | I | 96 |
| $H_2C{=}CH$ | Br | 92 |
| Ph | I | 87 |

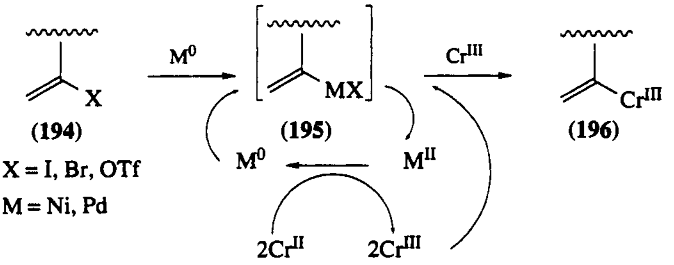

**(194)** **(195)** **(196)**

X = I, Br, OTf
M = Ni, Pd

**Scheme 7**

**Table 10** $CrCl_2$–mediated/$NiCl_2$–catalyzed Addition of Alkenyl Triflates to Aldehydes

| *Entry* | *Triflate* | *Aldehyde* | *Time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|---|---|
| 1 | 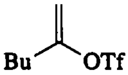 | PhCHO | 1 | 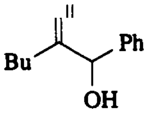 | 72 |
| 2 | 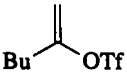 | n-$C_8H_{17}CHO$ | 3 | 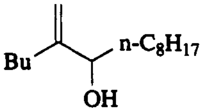 | 81 |
| 3 | 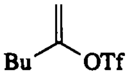 | 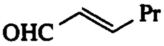 | 4 | 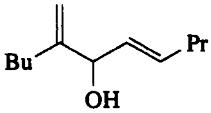 | 64 |
| 4 | 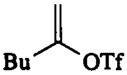 | 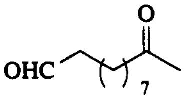 | 1 | 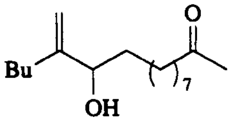 | 87 |
| 5 | 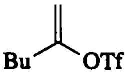 | 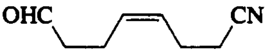 | 2 | 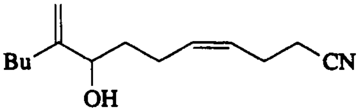 | 78 |
| 6 | 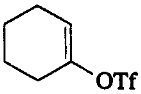 | n-$C_8H_{17}CHO$ | 4 | 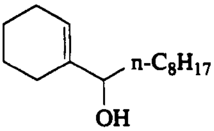 | 74 |
| 7 | 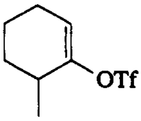 | n-$C_8H_{17}CHO$ | 4 | 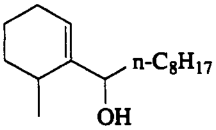 | 76 |
| 8 | 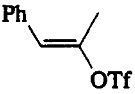 | PhCHO | 1 | 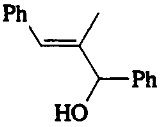 | 92 |
| 9 | 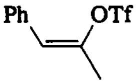 | PhCHO | 3 | 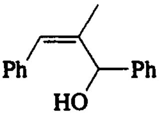 | 46 |
| 10 | 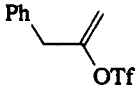 | PhCHO | 1 | 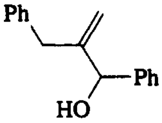 | 85 |
| 11 | 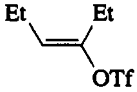 | PhCHO | 2 | 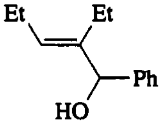 | 72 |

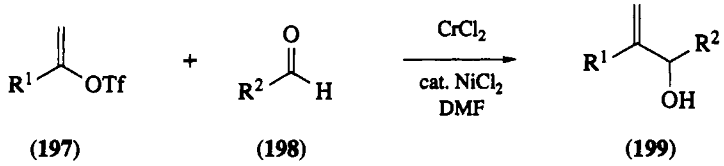
(197)
(198)
CrCl2
cat. NiCl2
DMF
(199)

(65)

## 1.6.4.2 Synthetic Applications

A great portion of the chemical research involving alkenylchromium reagents is described by Kishi and coworkers. During synthetic studies directed towards palytoxin,[92] generation of an organocuprate derived from (**201**) proved untenable. However, the use of an *in situ* prepared organochromium reagent allowed for C(16)—C(17) bond formation (equations 66 and 67). The coupling proceeded with complete

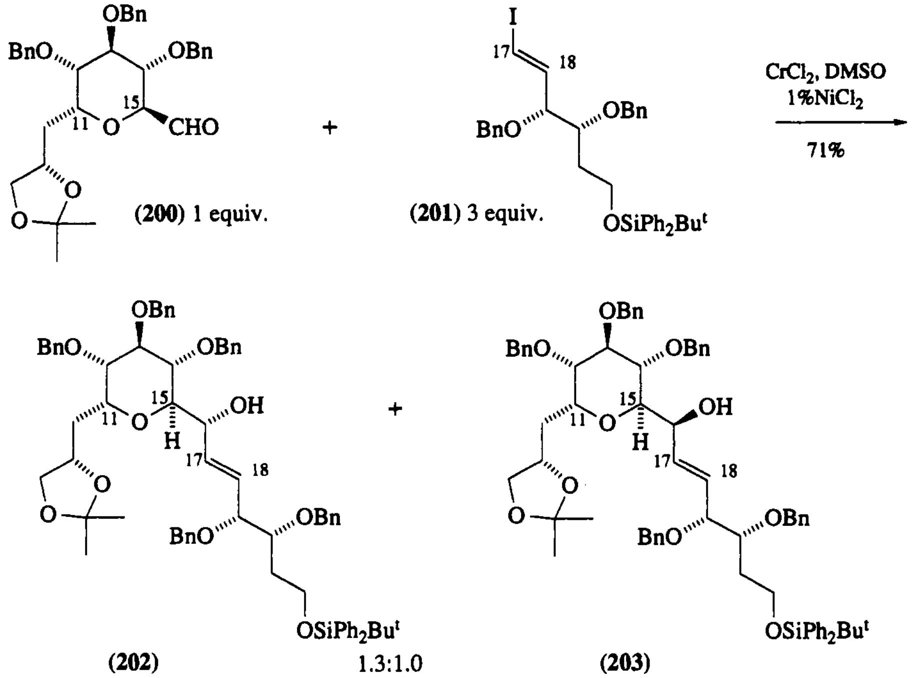
(200) 1 equiv.
(201) 3 equiv.
CrCl2, DMSO
1%NiCl2
71%
(202)
1.3:1.0
(203)

(66)

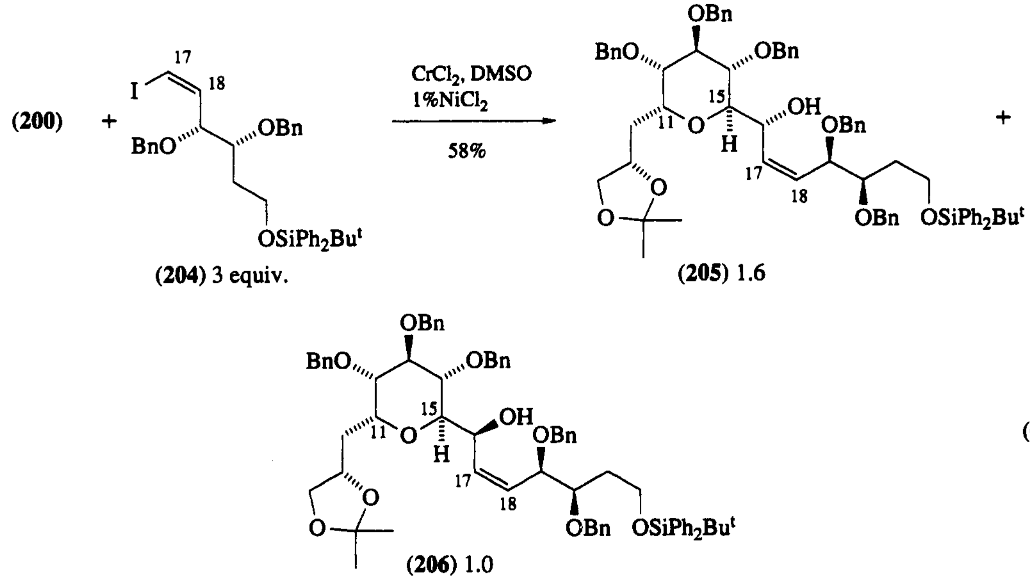
(200)
(204) 3 equiv.
CrCl2, DMSO
1%NiCl2
58%
(205) 1.6
(206) 1.0

(67)

retention of the C(17)—C(18) alkene geometry but with a low level of diastereogenesis at C(16). Retention of double-bond configuration is a general feature of disubstituted alkenylchromium compounds (see also entries 6 and 7, Table 9). However, alkenylchromiums derived from trisubstituted iodoalkenes and trisubstituted β-iodoenones[91] exclusively provide products with an (*E*)-alkene geometry. This stereochemical feature, also noted by Takai and coworkers (entries 8 and 9 in Table 9; entries 8 and 9 in Table 10),[84,85] is evident in equations (68) and (69). Both (*E*)- and (*Z*)-iodoalkenes provide only (*E*)-allylic alcohols as the addition product. Moreover, both reagents provide identical levels of diastereoselection, as seen from the ratios (**210**):(**211**) and (**214**):(**215**). Notwithstanding these similarities, the organometallic prepared from the (*E*)-iodoalkenes provides higher yields of the addition products. The major products obtained, (**210**) and (**215**), are consistent with the Felkin–Anh prediction for diastereoselective addition reactions to α-alkoxy aldehydes.[47] The reactions outlined in equations (68) and (69) serve as useful model studies for the coupling reaction between the C(1)—C(7) and C(8)—C(51) fragments in the actual synthesis of Palytoxin.

Kishi and coworkers[93–95] have also implemented alkenylchromium reagents for the synthesis of glycosides and *C*-methyl glycoside analogs. In the synthesis of the C-analog (**217**) of isomaltose (**216**), the C(5)—C(6) bond was established by the nickel(II) chromium(II)-mediated coupling of (*Z*)-iodoalkene

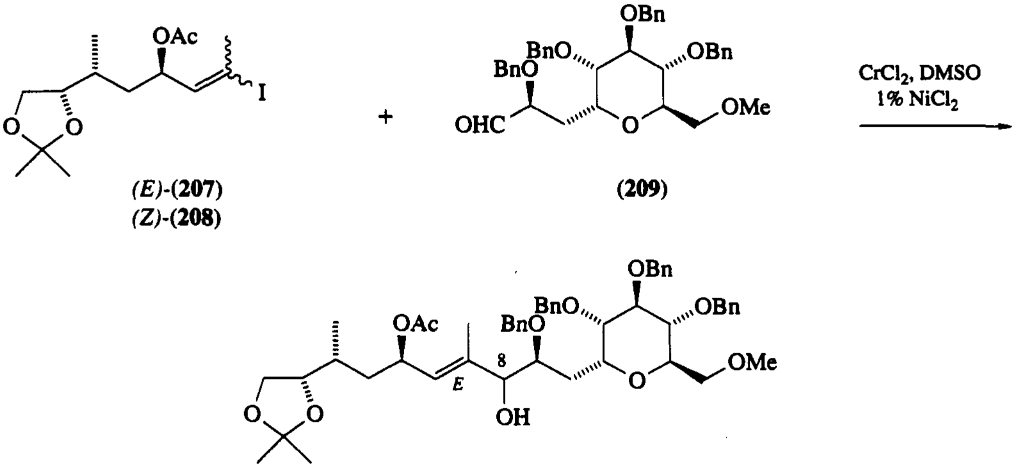

(*E*)-(**207**)
(*Z*)-(**208**)

(**209**)

(68)

| | | 8α-(**210**) | : | 8β-(**211**) |
|---|---|---|---|---|
| From (*E*)-(**207**) | 72% | 2 | : | 1 |
| From (*Z*)-(**208**) | 15% | 2 | : | 1 |

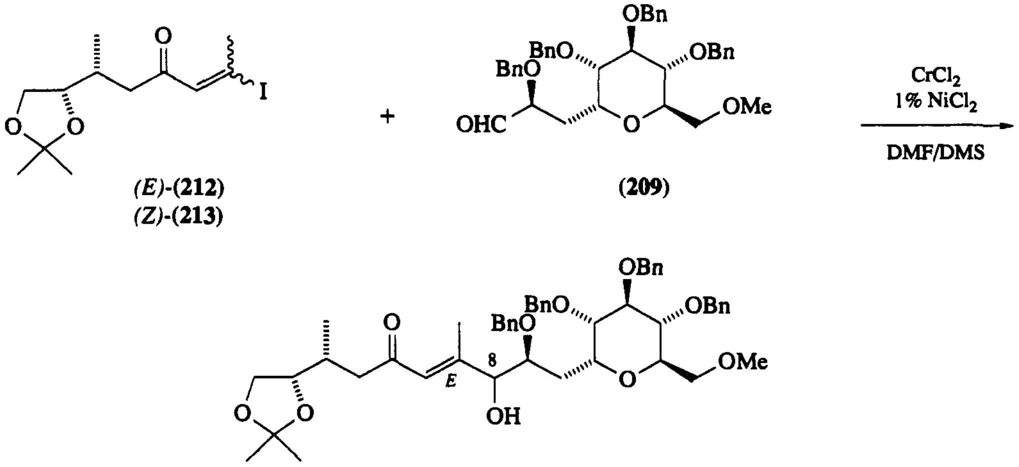

(*E*)-(**212**)
(*Z*)-(**213**)

(**209**)

(69)

| | | 8α-(**214**) | : | 8β-(**215**) |
|---|---|---|---|---|
| From (*E*)-(**212**) | 82% | 5 | : | 1 |
| From (*Z*)-(**213**) | 28% | 5 | : | 1 |

(**218**) with alkoxy aldehyde (**219**; equation 70).[93] The reaction proceeds with excellent stereochemical control *via* a Felkin–Anh approach and provides a >15:<1 ratio of *cis*-allylic alcohols (**220**) and (**221**). Continuing studies in this area include the synthesis of *C*-sucrose (**226**).[94] The nickel(II)/chromium(II) coupling of vinyl iodide (**222**) with α-benzyloxy aldehyde (**223**) affords (**224**) and (**225**; equation 71). The major product (**225**) possesses the 3′,4′-*anti* arrangement which arises rationally from a Felkin–Anh addition pathway. This result is consistent with previously described examples (*vide supra*).

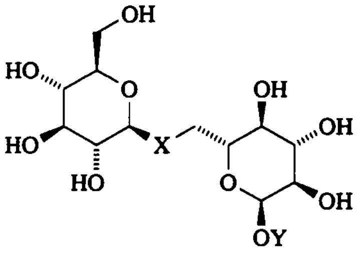
OH
HO
O
OH
OH
HO
X
HO
O
OH
OY

(**216**) Isomaltose: X = O, Y = H
(**217**) Methyl-*C*-glycoside: X = $CH_2$, Y = Me

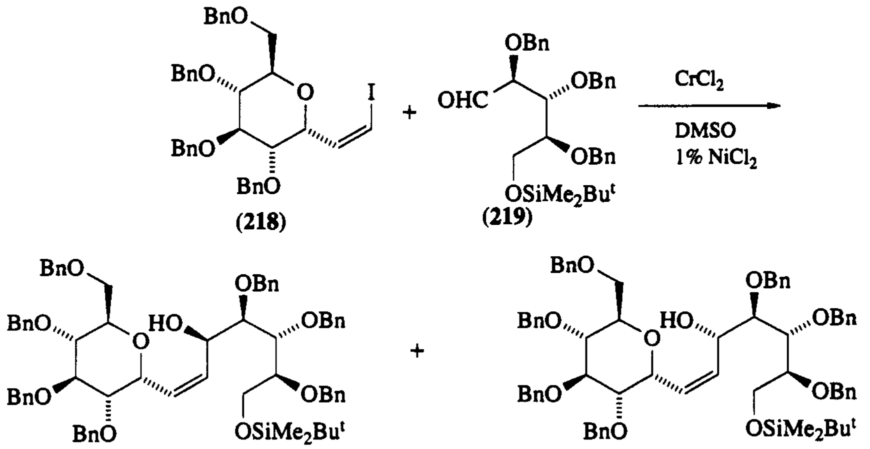
BnO
BnO
O
I
BnO
BnO
+
OBn
OHC
OBn
OBn
OSiMe2But
CrCl2
DMSO
1% NiCl2
BnO
OBn
BnO
HO
OBn
O
BnO
OBn
BnO
OSiMe2But
+
BnO
OBn
BnO
HO
OBn
O
BnO
OBn
BnO
OSiMe2But

(**218**) (**219**)

(**220**) >94% (**221**) <6%

(70)

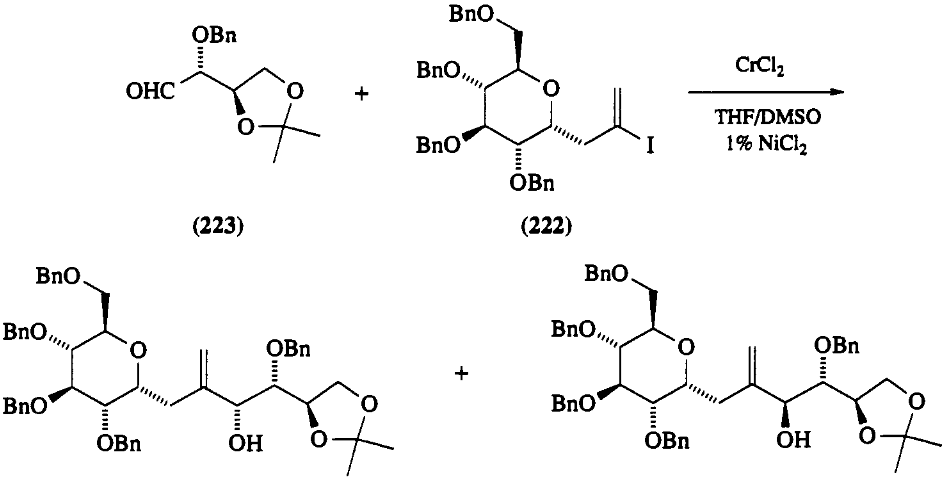
OBn
OHC
O
O
+
BnO
BnO
O
BnO
I
OBn
CrCl2
THF/DMSO
1% NiCl2
BnO
BnO
O
OBn
BnO
OBn
OH
O
O
+
BnO
BnO
O
OBn
BnO
OBn
OH
O
O

(**223**) (**222**)

(**224**) 9% (**225**) 91%

(71)

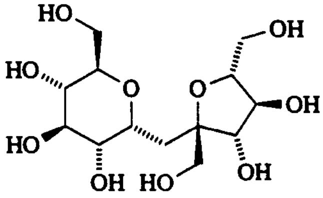
HO
HO
HO
OH
O
O
OH
OH
HO
OH

*C*-Sucrose (**226**)

### 1.6.4.3 Intramolecular Addition Reactions

Examples of intramolecular addition reactions of alkenylchromium reagents to aldehydes have appeared.[96,97] In the course of synthetic studies in the brefeldin structural series, the nickel(II)/chromium(II)-mediated intramolecular addition reactions of (*E*)-iodoalkenes (**227**) and (**230**) were studied by Schreiber and Meyers (equations 72 and 73).[96] Treatment of (**227**) with $CrCl_2$ and a catalytic portion of $[Ni(acac)_2]$ in DMF produced a 4:1 mixture of 4-epibrefeldin C (**228**) and (+)-brefeldin (**229**) in 60% yield. In a similar fashion, precursor iodide (**230**) afforded a >10:1 mixture of cyclized hydroxy lactones (**231**) and (**232**) in 70% yield. An explanation of the stereochemical preference observed has been eloquently offered in a discussion of local conformational preferences found in the starting material and the product lactone, as each is relevant to a transition structure for a 13-membered ring closure.

Another intramolecular addition of an alkenylchromium to an aldehyde was reported by Rowley and Kishi in synthetic studies toward the ophiobolins.[97] Treatment of (**223**; equation 74) with $CrCl_2/NiCl_2$ afforded the cyclized product (**234**) as a single diastereomer in 56% yield.

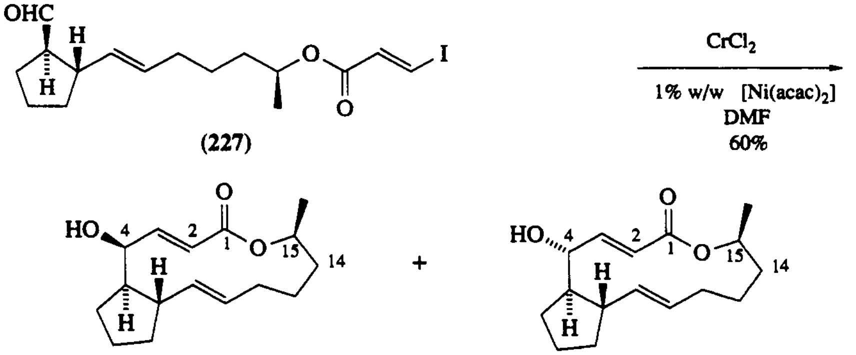
OHC
H
H
O
I
O
CrCl2
1% w/w [Ni(acac)2]
DMF
60%
O
HO
4
2
1
O
15
14
H
H
+
O
HO
4
2
1
O
15
14
H
H

(**227**)

(**228**) 80% (**229**) 20%

(72)

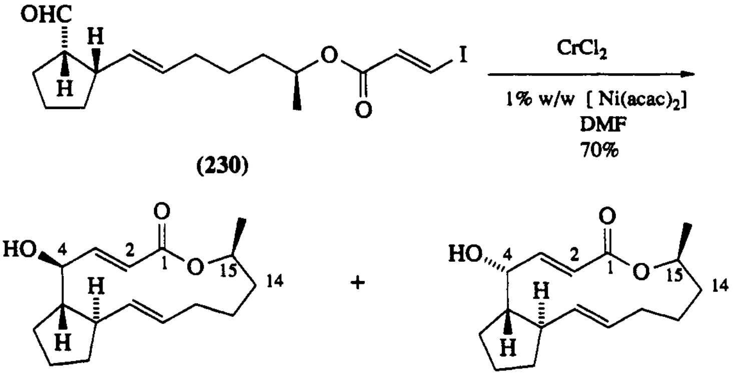
OHC
H
H
O
I
O
CrCl2
1% w/w [Ni(acac)2]
DMF
70%
O
HO
4
2
1
O
15
14
H
H
+
O
HO
4
2
1
O
15
14
H
H

(**230**)

(**231**) >91% (**232**) <9%

(73)

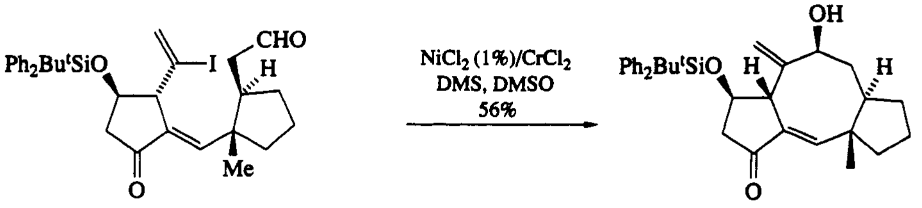
Ph₂BuᵗSiO
CHO
I
H
Me
O
NiCl₂ (1%)/CrCl₂
DMS, DMSO
56%
OH
Ph₂BuᵗSiO
H
H
O

(233) (234)

(74)

## 1.6.5 ALKYNYLCHROMIUM REAGENTS

The generation of alkynylchromium reagents and their addition to carbonyl compounds has been studied by Takai and coworkers.[98] The chemoselectivity of these reagents resembles that of other organochromium(III) reagents. Preparation of alkynylchromiums can be accomplished by treatment of haloalkynes with chromium(II) chloride in DMF. Representative addition reactions of alkynylchromiums are offered in equations (75) to (79).

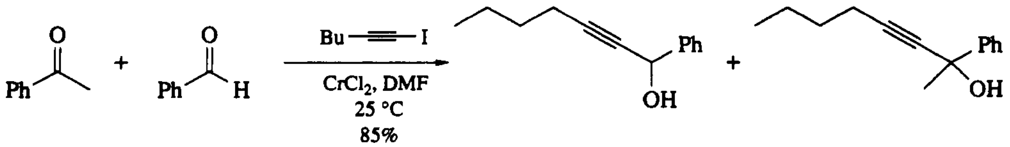
O
Ph
+
O
Ph
H
Bu—≡—I
CrCl₂, DMF
25 °C
85%
Ph
OH
+
Ph
OH

(235) 96% (236) 4%

(75)

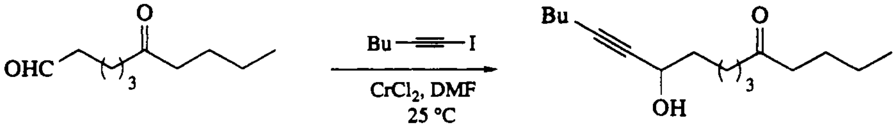
O
OHC
3
Bu—≡—I
CrCl₂, DMF
25 °C
76%
Bu
O
3
OH

(237)

(76)

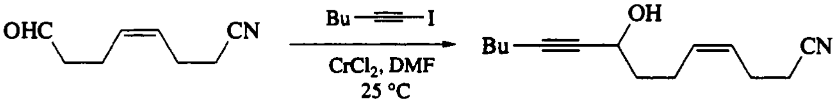
OHC
CN
Bu—≡—I
CrCl₂, DMF
25 °C
78%
OH
Bu
CN

(238)

(77)

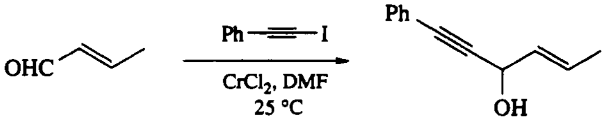
OHC
Ph—≡—I
CrCl₂, DMF
25 °C
83%
Ph
OH

(239)

(78)

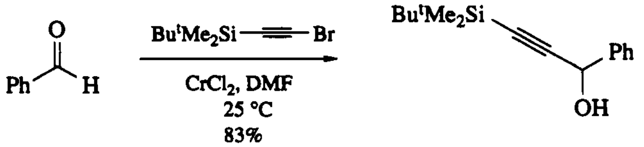

**(240)**

(79)

### 1.6.6 α-ACYLCHROMIUM REAGENTS

The aldol-type reaction of α-bromo ketones with aldehydes, mediated by $CrCl_2$, has been studied by Dubois and coworkers.[99] The reaction is carried out by addition of (**241**; equation 80) to a solution of (**242**) and $CrCl_2$ in THF. The reaction proceeds with high levels of *syn* selectivity with bulky bromo ketones (**241**), independent of the substrate aldehyde used (Table 11, entries 1–6). However, the reaction is stereorandom with bromoacetophenone (entry 7) and selectively *anti* with 2-bromocyclohexanone (entry 8). No explanation of the stereoselectivity has been advanced, but the reaction is believed not to proceed *via* a simple chromium enolate since no condensation reaction is obtained by addition of (**242**) to a solution of (**241**) and $CrCl_2$. Moreover, Nozaki and coworkers[100] have demonstrated that chromium(II) chloride treatment of 1-bromocyclododecanone followed by treatment with either methyl iodide or TMS-Cl produces only cyclododecanone.

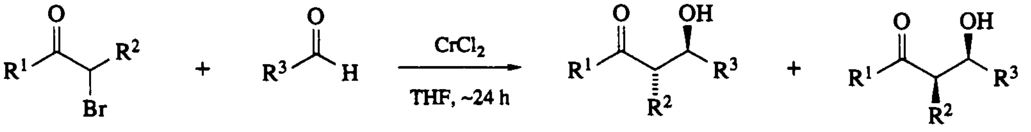

(80)

**(241)** **(242)** **(243)** *anti* **(244)** *syn*

**Table 11** Reaction of α-Bromo Ketones (**241**) with Aldehydes (**242**) using $CrCl_2$ (equation 80)[99]

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *Yield (%)* | *Anti:syn (243):(244)* |
|---|---|---|---|---|---|
| 1 | $Bu^t$ | Me | Me | 50 | 0:100 |
| 2 | $Bu^t$ | Me | Et | 81 | 0:100 |
| 3 | $Bu^t$ | Me | $Pr^i$ | 70 | 0:100 |
| 4 | $Bu^t$ | Me | Pr | 83 | 0:100 |
| 5 | $Bu^t$ | Me | Ph | 75 | 0:100 |
| 6 | $Bu^t$ | Me | $Bu^t$ | 87 | 0:100 |
| 7 | Ph | Me | Ph | 68 | 50:50 |
| 8 | —$(CH_2)_4$— | | Ph | 75 | 100:0 |

### 1.6.7 ALKYLCHROMIUM REAGENTS

Addition of alkylchromium reagents to carbonyl compounds was studied first by Kauffmann and coworkers.[101] Organochromium reagent (**246**) can be generated *in situ* by treatment of trimethylsilylmethylmagnesium chloride (**245**) with $CrCl_3$ (Scheme 8). Condensation with aldehydes provides chromium alkoxide (**247**), which is transformed into the alkenated products (**248**) by warming with aqueous perchloric acid. Ketones are apparently inert to (**246**), providing none of the desired alkene product. A more extensive examination of alkylchromium(III) reagents has been subsequently disclosed.[102] Preparation of a variety of dichlorotris(tetrahydrofuran)alkylchromium(III) complexes (**249**) has been carried out by treatment of $CrCl_3$ with organomagnesium or organolithium reagents in tetrahydrofuran (equation 81). Complexes of this sort can also be prepared from organoaluminums and $CrCl_3$,[12,13] and X-ray data has revealed the structure of one such complex (**249**; R = *p*-tolyl). Addition of (**250**) to aldehydes (equation 82 and Table 12) proceeds smoothly ($R^3$ = H; Table 12, entries 2, 5 and 8), but towards ketones (**250**) is entirely unreactive ($R^3 \neq$ H; entries 3 and 6). The chemoselectivity is underscored by competition experiments (entries 4 and 7). Also, the addition reaction proceeds more efficiently with a molar excess of alkylchromium (entries 1 *versus* 2 and 8 *versus* 9). Generation of alkylchromium(III) reagents from $CrCl_2$ and organic halides has been reported by Takai and coworkers.[103] In particular, it has been demonstrated that α-thioalkylchromium(III) compounds (**254**), prepared by chromium(II) ion reduction of α-iodo sulfides (generated *in situ* from LiI and **253**),[104] add smoothly and selectively to aldehydes to afford thioether carbinols (**256**; equation 83, Table 13), (**257**; equation 84) and (**258**; equation 85). In contrast to the chemoselectivity of this organochromium compound, it has been noted that α-thiomethyllithium exhibits no chemoselectivity for aldehydes in the presence of ketones. The butylchromium reagent prepared by chromium(II) ion reduction of iodobutane provides only 11% of 1-phenyl-1-pentanol (**259**; equation 86) after 24 h. However, Kauffmann and coworkers[102] have demonstrated that the butylchromium reagent prepared from *n*-butyllithium and $CrCl_3$ yields 81% of (**259**) after 18 h. These data reveal the importance of the sulfide group for the efficient reduction of the alkyl iodide.

Diastereoselective addition of thiophenylalkylchromium(III) reagents has been studied by Takai and coworkers.[103] Treatment of aldehyde (**260**) with α-chloro sulfide (**261**), LiI and $CrCl_2$ gives β-phenylthio alcohols (**262**) and (**263**) (equation 87 and Table 14). The *syn* isomer (**262**) was generated diastereoselectively in all cases (**262**:**263** ≥ 4:1). The diastereoselectivity of the addition reactions of thiophenylalkylchromiums is especially noteworthy as the lithium reagent prepared from phenyl ethyl sulfide and Bu$^t$Li–HMPA adds to benzaldehyde in a stereorandom fashion (contrast entry 2, table 14).

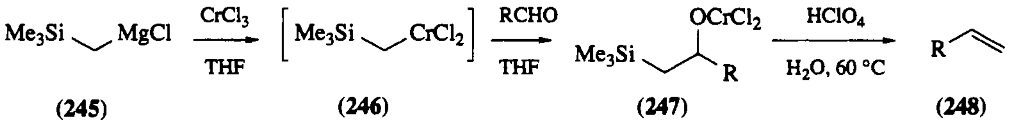
Me3SiCH2MgCl
CrCl3
THF
[Me3SiCH2CrCl2]
RCHO
THF
OCrCl2
Me3Si
R
HClO4
H2O, 60 °C
R
(245)
(246)
(247)
(248)

R = $C_8H_{17}$ 45%
R = $C_6H_{13}$ 47%

**Scheme 8**

$$\mathrm{RMgX\ \ or\ \ RLi} \xrightarrow[\mathrm{THF}]{\mathrm{CrCl_3}} \underset{\textbf{(249)}}{[\mathrm{RCr(THF)_3Cl_2}]} \qquad (81)$$

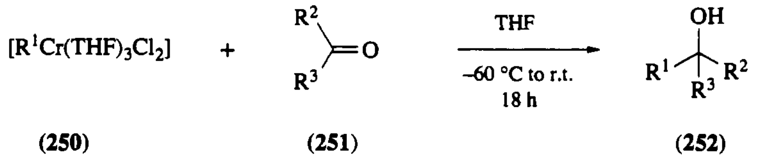
[R1Cr(THF)3Cl2]
+
R2
O
R3
THF
–60 °C to r.t.
18 h
OH
R1
R2
R3
(250)
(251)
(252)

(82)

**Table 12** Addition of Alkylchromium(III) Complexes (**250**) to Carbonyl Compounds (equation 82)

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *(250):(251)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Me | n-$C_6H_{13}$ | H | 1:1 | 36 |
| 2 | Me | n-$C_6H_{13}$ | H | 3:1 | 85 |
| 3 | Me | Me | Me | 1:1 | 0 |
| 4 | Me | n-$C_6H_{13}$<br>Me | H<br>Me | 2:1:1 | 71<br>0 |
| 5 | Pr$^n$ | n-$C_6H_{13}$ | H | 3:1 | 73 |
| 6 | Bu$^n$ | Et | Et | 1:1 | 0 |
| 7 | Pr$^n$ | n-$C_6H_{13}$<br>Et | H<br>Et | 2:1:1 | 66<br>0 |
| 8 | $PhCH_2$ | n-$C_6H_{13}$ | H | 1:1 | 52 |
| 9 | $PhCH_2$ | n-$C_6H_{13}$ | H | 3:1 | 65 |
| 10 | Bu$^n$ | n-$C_6H_{13}$ | H | 1:1 | 81 |

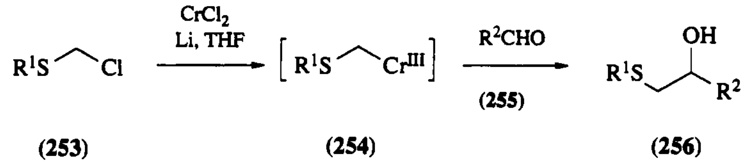
R1S
Cl
CrCl2
Li, THF
R1S
CrIII
R2CHO
(255)
OH
R1S
R2
(253)
(254)
(256)

(83)

**Table 13** Addition of α-Halo Sulfides (**253**) to Aldehydes (**255**) Using $CrCl_2$ (equation 83)

| *Entry* | $R^1$ | $R^2$ | *Temp (°C)* | *Time (h)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Me | Ph | 40 | 5 | 88 |
| 2 | Me | $C_8H_{17}$ | 40 | 9 | 72 |
| 3 | Me | PrCH=CH | 40 | 13 | 64[a] |
| 4 | Ph | Ph | 60 | 10 | 63 |
| 5 | Ph | $C_8H_{17}$ | 40 | 10 | 48 |

[a] 1,2-Product only

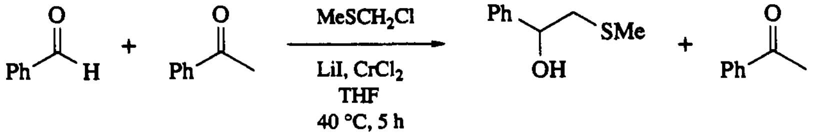
MeSCH₂Cl
LiI, CrCl₂
THF
40 °C, 5 h

(84)

(**257**) 94% 86% recovered

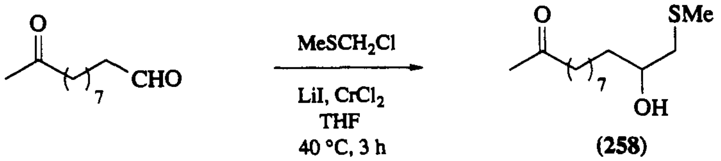
MeSCH₂Cl
LiI, CrCl₂
THF
40 °C, 3 h

(**258**) (85)

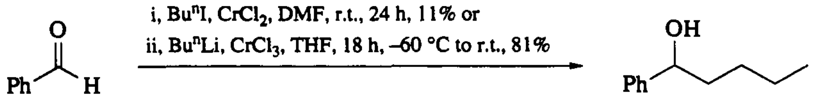
i, BuⁿI, CrCl₂, DMF, r.t., 24 h, 11% or
ii, BuⁿLi, CrCl₃, THF, 18 h, –60 °C to r.t., 81%

(86)

(**259**)

The process is sensitive to solvent additives. Both yields and *syn* selectivities benefit from the addition of TMEDA (entries 1 *versus* 3 and 5 *versus* 6), HMPA (entry 5 *versus* 7), triphenylphosphine (entry 5 *versus* 8) or 1,2-bis(diphenylphosphino)ethane (entry 5 *versus* 9). The effectiveness of a given additive (*vis-a-vis* selectivity and/or % conversion) has been shown to be substrate dependent.

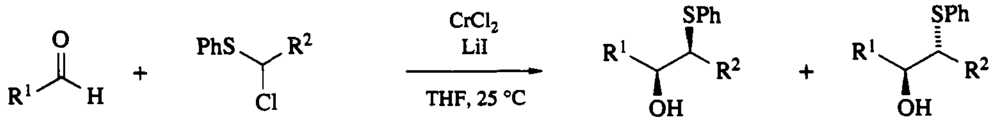
CrCl₂
LiI
THF, 25 °C

(87)

(**260**) (**261**) (**262**) *syn* (**263**) *anti*

**Table 14** Addition of α-Halo Sulfides (**261**) to Aldehydes (**260**) using $CrCl_2$ (equation 87)

| *Entry* | $R^1$ | $R^2$ | *Ligand* | *Time (h)* | *Yield (%)* | *(262):(263)* | *Aldol* | *(261) recovered (%)* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | — | 16 | 58 | 80:20 | — | 17 |
| 2 | Ph | Me | TMEDA | 6 | 96 | 88:12 | — | 0 |
| 3 | Ph | $Pr^n$ | TMEDA | 6 | 95 | 86:14 | — | 0 |
| 4 | Ph | $Pr^i$ | TMEDA | 25 | 46 | 80:20 | — | 25 |
| 5 | $C_8H_{17}$ | Me | — | 17 | 17 | 86:14 | 11 | 0 |
| 6 | $C_8H_{17}$ | Me | TMEDA | 1.5 | 25 | 90:10 | 19 | 0 |
| 7 | $C_8H_{17}$ | Me | HMPA | 20 | 33 | 97:3 | 23 | 5 |
| 8 | $C_8H_{17}$ | Me | $Ph_3P$ | 20 | 23 | 84:16 | 10 | 24 |
| 9 | $C_8H_{17}$ | Me | DIPHOS | 19 | 53 | >98:<2 | <3 | 32 |
| 10 | $C_8H_{17}$ | $Pr^n$ | DIPHOS | 40 | 8 | >98:<2 | <5 | 71 |
| 11 | c-$C_6H_{11}$ | Me | DIPHOS | 18 | 11 | 90:10 | <5 | 50 |
| 12 | c-$C_6H_{11}$ | Me | TMEDA | 18 | 65 | 81:19 | <5 | 13 |

### 1.6.8 ALKYL-*GEM*-DICHROMIUM REAGENTS: ALKENATION REACTIONS

*gem*-Dimetalloorganic compounds are useful reagents for the alkenation of aldehydes and ketones.[105,106] A variety of *gem*-dichromium reagents have also been used for this purpose.[107–109] Takai and coworkers[107] have reported the conversion of aldehydes (**264**) to vinyl halides (**265**) and (**266**) using haloform and chromium(II) salts in THF (equation 88 and Table 15). The (*E*)-alkenyl halide is generated selectively with the exception of the $CHI_3/CrCl_2$ reactions of α,β-unsaturated aldehydes (Table 15, entry 12), which give variable results with respect to alkene geometry. The rate of reaction has been shown to be a function of the haloform and increases in the order Cl < Br < I. In addition, the (*E*):(*Z*) ratio (**265**):(**266**) is also a function of the haloform used and increases in the order I < Br < Cl. The use of $HCBr_3/CrCl_2$ provides a mixture of alkenyl chlorides and bromides (entries 2 and 6). This problem can be alleviated by the use of $CrBr_3$/LAH as the source of $CrBr_2$, which affords the alkenyl bromides cleanly. Haloform–$CrCl_2$ reagents condense selectively with aldehydes in the presence of ketones (equation 89), and provide vinyl halides suitable for alkenylchromium preparation (see Section 1.6.4).

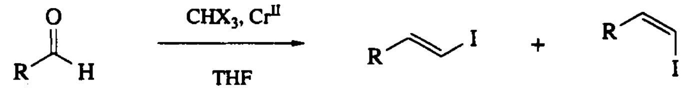

(88)

(**264**) (*E*)-(**265**) (*Z*)-(**266**)

**Table 15** Selective Synthesis of (*E*)-Alkenyl Halides (**265**) from Aldehydes (**264**) and $CHX_3$–$CrCl_2$/THF (equation 88)

| *Entry* | *Aldehyde (264)* | *Haloform X* | *Chromium(II) source* | *Temperature (°C)* | *Time (h)* | *Yield (%)* | *(265):(266)* |
|---|---|---|---|---|---|---|---|
| 1 | PhCHO | I | $CrCl_2$ | 0 | 3 | 87 | 94:6 |
| 2 | PhCHO | Br | $CrCl_2$ | 25 | 1.5 | X = Br 32<br>X = Cl 43 | 95:5<br>95:5 |
| 3 | PhCHO | Br | $CrBr_3/LiAlH_4$ | 50 | 1 | 70 | 95:5 |
| 4 | n-$C_8H_{17}$CHO | Cl | $CrCl_2$ | 65 | 2 | 76 | 95:5 |
| 5 | n-$C_8H_{17}$CHO | I | $CrCl_2$ | 0 | 2 | 82 | 83:17 |
| 6 | n-$C_8H_{17}$CHO | Br | $CrCl_2$ | 25 | 2 | X = Br 37<br>X = Cl 32 | 89:11<br>90:10 |
| 7 | n-$C_8H_{17}$CHO | Br | $CrBr_3/LiAlH_4$ | 50 | 2 | 61 | 87:13 |
| 8 | 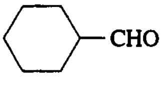 | Cl | $CrCl_2$ | 65 | 4 | 76 | 94:6 |
| 9 |  | I | $CrCl_2$ | 0 | 1 | 78 | 89:11 |
| 10 |  | Br | $CrBr_3/LiAlH_4$ | 50 | 2.5 | 55 | 89:11 |
| 11 | 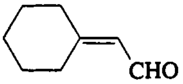 | Cl | $CrCl_2$ | 65 | 2.5 | 55 | 92:8 |
| 12 |  | I | $CrCl_2$ | 0 | 0.5 | 76 | 75:25 to 55:45 |
| 13 | 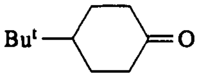 | I | $CrCl_2$ | 25 | 4 | 75 | — |

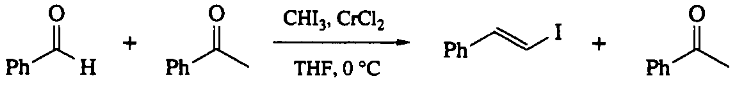

(89)

(**267**) (*E*):(*Z*) 94:6 88% recovered
91%

Takai and coworkers[108] have reported that the formation of alkyl-*gem*-dichromium compounds (**269**) can be achieved by the $CrCl_2$ reduction of *gem*-diiodoalkanes (**268**; equation 90). These reagents add to aldehydes and afford alkylidenation products (**271**) and (**272**) efficiently and with high levels of (*E*)-alkene selectivity (equation 90 and Table 16). The addition of 1,1-diiodoethane to aldehydes proceeds smoothly and with excellent (*E*)-selection (entries 1–5).

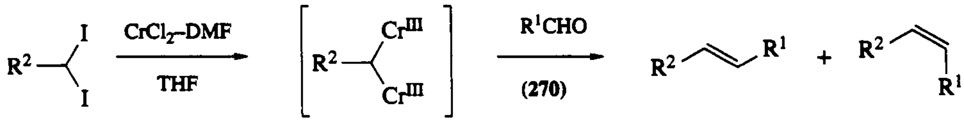

(90)

**(268)** **(269)** **(271)** **(272)**

**Table 16** Alkenation of Aldehydes (**270**) with *gem*-Dichromium Compounds (**269**; equation 90)

| *Entry* | $R^1$ | $R^2$ | *Conditions*[a] | *Time (h)* | *Yield (%)* | *(271):(272)* |
|---|---|---|---|---|---|---|
| 1 | n-$C_5H_{11}$ | Me | A | 4.5 | 94 | 96:4 |
| 2 | n-$C_{11}H_{23}$ | Me | A | 5.0 | 81 | 95:5 |
| 3 | $Ph(CH_2)_2$ | Me | A | 10 | 85 | 97:3 |
| 4 | $Et_2CH$ | Me | A | 2.0 | 99 | 98:2 |
| 5 | 4-$Pr^iC_6H_4$ | Me | A | 10 | 97 | 84:16 |
| 6 | 4$Pr^iC_6H_4$ | Me | C | 5.0 | 84 | 78:22 |
| 7 | n-$C_5H_{11}$ | Pr | A | 24 | 38 | 96:4 |
| 8 | n-$C_8H_{17}$ | Pr | B | 1.5 | 85 | 95:5 |
| 9 | n-$C_8H_{17}$ | Pr | B | 1.0 | 96 | 99:1 |
| 10 | $Bu^t$ | Pr | B | 1.0 | 87 | 88:12 |
| 11 | Ph | Pr | C | 0.5 | 60 | 51:49 |
| 12 | n-$C_5H_{11}$ | $Pr^i$ | A | 24 | 12 | 72:28 |
| 13 | Ph | $Pr^i$ | B | 2.0 | 79 | 88:12 |
| 14 | Ph | $Bu^t$ | B | 2.0 | 80 | 96:4 |
| 15 | Ph | H | A | 24 | 70 | — |
| 16 | Ph | H | B | 3.0 | 92 | — |

[a] A: (**270**) 1.0 mmol, (**268**) 2.0 mmol, $CrCl_2$ 8.0 mmol, THF; B: (**270**) 1.0 mmol, (**268**) 2.0 mmol, $CrCl_2$ 8.0 mmol, DMF 8.0 mmol, THF; C: (**270**) 1.0 mmol, (**268**) 2.0 mmol, $CrCl_3$ 8.0 mmol, Zn* 6.0 mmol, THF.

However, all other *gem*-dichromium reagents ($R^2$ = Pr, H, $Pr^i$) require DMF as a cosolvent to obtain useful yields of alkene products. The effect is attributed to the enhanced reducing ability of chromium(II) in the presence of donor ligands (*vide supra*). Use of Zn/$CrCl_3$ as a source of chromium(II) ion provides inferior stereochemical results (Table 16, entries 6 and 11). Lastly, Takai and coworkers[109] have reported the synthesis of (*E*)-alkenylsilanes. Treatment of dibromotrimethylsilane (**273**) with $CrCl_2$ yields *gem*-dichromium reagent (**274**) which reacts with aldehydes to produce (*E*)- and (*Z*)-vinylsilanes like (**276**) and (**277**). As with other *gem*-dichromiums (equation 88, Table 15; equation 90, Table 16), the alkenation process occurs efficiently with a strong preference for the generation of the (*E*)-vinylsilane (equation 91, Table 17). In corresponding carbon-substituted cases, diiodo substrates are required for useful yields of the alkene to be obtained; however, the presence of the silicon atom allows for the use of dibromo precursors. The general features of reactivity seen with other organochromiums are apparent with this reagent as well (Table 17). The authors believe that the reaction proceeds by the formation of a *gem*-dichromium species (**280**; Scheme 9).[110,111] Subsequent addition to an aldehyde provides the β-oxymetal organometallic (**281**) which then suffers elimination to afford the alkene products (**282**).[106,111] No explanation of the stereochemical outcome has been forwarded.

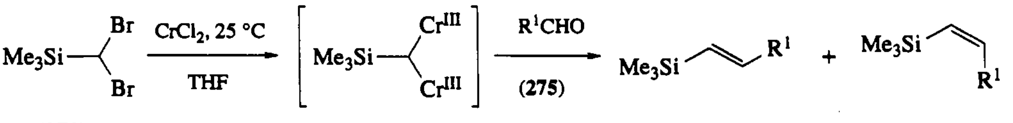

(91)

**(273)** **(274)** **(276)** **(277)**

**Table 17** Synthesis of (*E*)-Alkenylsilanes (**276**) from Aldehydes (**275**) and *gem*-Dichromium Reagents (**274**)

| *Entry* | *Aldehyde (275)* | *Time* (h) | *Yield* (%) | *Comment* |
|---|---|---|---|---|
| 1 | PhCHO | 24 | 82 | |
| 2 | $PhCH_2CH_2CHO$ | 24 | 86 | |
| 3 | n-$C_8H_{17}CHO$ | 24 | 82 | |
| 4 | 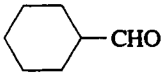 | 18 | 81 | |
| 5 | PhCH=CHCHO | 18 | 79 | 1,2-Addition |
| 6 | 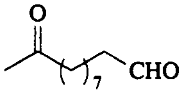 | 16 | 76 | Addition to aldehyde |
| 7 | 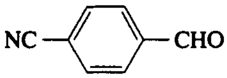 | 24 | 72 | Addition to aldehyde |
| 8 | 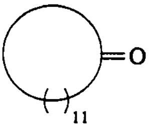 | 60 | 0 | 99% recovery of starting material |

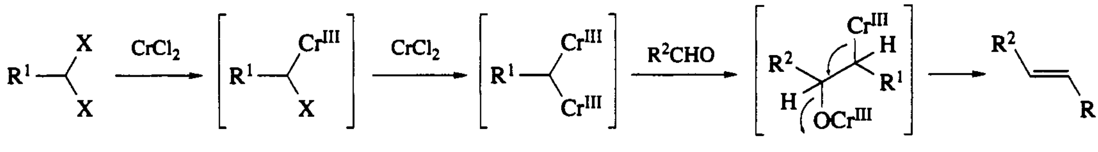

(**278**) (**279**) (**280**) (**281**) (**282**)

$R^1$ = halogen, $SiMe_3$, alkyl

**Scheme 9**

## 1.6.9 CONCLUSION

A large variety of organochromium(III) compounds has been described. The addition reactions of these materials with carbonyl substrates represent an elaborate array of chemoselective and stereoselective processes. Because of the unique reactivity and chemical properties of these reagents, organochromiums are useful reagents for organic synthesis.

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# 1.7
# Organozinc, Organocadmium and Organomercury Reagents

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## 1.7.1 GENERAL CONSIDERATIONS

Organozinc compounds[1,2] are readily prepared by oxidative addition of zinc to alkyl, allylic or benzylic halides, or by transmetallation reactions. Cadmium organometallics are prepared in similar ways, but show a lower thermal stability. Zinc and cadmium derivatives show a much lower reactivity and, consequently, a higher chemoselectivity than their lithium and magnesium counterparts. Organozinc halides containing various important classes of organic functional groups can be prepared in high yields and used, after transmetallation to more reactive copper or palladium organometallics, to form new carbon–carbon bonds. The addition of organozinc compounds to aldehydes and ketones is of considerable synthetic utility. Thus, alkyl- and aryl-zinc and -cadmium reagents add to aldehydes in the presence of Lewis acid catalysts with excellent chemoselectivity. If a chiral catalyst is used, very high enantioselectivities can be achieved. The addition of the more reactive allylic zinc and cadmium compounds to aldehydes and ketones does not require a catalyst and proceeds with high yields, good regioselectivity and, in some cases, excellent diastereoselectivity. The easy preparation of allylic zinc halides, combined with their high reactivity, makes them ideal nucleophilic allylating reagents.

## 1.7.2 PREPARATION OF ORGANOZINC REAGENTS

### 1.7.2.1 Introduction

The carbon–zinc bond,[1,2,3] which is a moderately strong carbon–metal bond (bond energy of $Me_2Zn$ = 42 kcal $mol^{-1}$; 1 cal = 4.18 J), has a high covalent character (85%) and thus is relatively unreactive toward most organic electrophiles. However, this low reactivity allows for the preparation of a wide range of highly functionalized organozinc compounds. The presence of empty *sp*-orbitals of low energy at the zinc atom makes these organometallics very sensitive toward proton sources (such as water and alcohols) and toward oxygen. The two most important classes of zinc organometallics are organozinc halides (RZnX; **1**) and diorganozincs ($R_2Zn$; **2**; see Scheme 1). These are prepared either by the oxidative addition of organic halides to zinc metal or by transmetallation reactions. The organometallics (**1**) and (**2**) show different reactivities and selectivities in addition reactions to carbonyl compounds.

$$\text{Oxidative addition} \qquad 2RX + 2Zn \longrightarrow \underset{(\mathbf{1})}{2RZnX} \xrightarrow[-ZnX_2]{\Delta} \underset{(\mathbf{2})}{R_2Zn}$$

$$\text{Transmetallation} \qquad RM + ZnX_2 \xrightarrow[-MX]{} \underset{(\mathbf{1})}{RZnX} \xrightarrow[-MX]{RM} \underset{(\mathbf{2})}{R_2Zn}$$

**Scheme 1**

### 1.7.2.2 Preparation by Oxidative Addition

Zinc organometallics can be prepared by heating an alkyl halide/zinc mixture without solvent.[1] This procedure initially affords an alkylzinc iodide of type (**1**). Further heating and subsequent distillation converts (**1**) into the corresponding dialkylzinc (**2**; see Scheme 1). A zinc–copper couple has to be used to make the reaction reproducible, and only alkyl iodides or a mixture of alkyl iodide and the corresponding bromide are suitable substrates. This method is successful for low boiling point dialkylzinc reagents (dimethylzinc to dipentylzinc). The preparation of higher analogs requires high distillation temperatures, leading to substantial decomposition of the organometallic and to difficult separations from Wurtz coupling products and unreacted alkyl iodides.[1] The reaction can be performed under much milder conditions and with more elaborate organic halides in the presence of a solvent such as ether, ethyl acetate/toluene, 1,2-dimethoxyethane, THF, DMF, DMSO or HMPA. An alkyl halide is always less readily converted into a zinc organometallic than into the corresponding magnesium organometallic. Only alkyl iodides and activated organic bromides (benzylic, allylic or propargylic) can be used successfully. Allylic or benzylic chlorides can only be converted to the zinc derivative in very polar solvents, such as DMSO,[4] or in THF at high temperatures (50–60 °C).[5] Very mild reaction conditions can be achieved if the zinc metal has been activated. Several procedures for the activation of zinc metal have been developed.[6] The reduction of zinc chloride with various reagents such as potassium,[6b,e] potassium–graphite[6c] ($C_8K$) or lithium in the presence of naphthalene[6d] affords a very reactive zinc powder, which allows otherwise impossible reactions (see Scheme 2).[6d] Activation of zinc by ultrasound wave irradiation[6a] or by the use of active zinc slurries prepared by metal vapor techniques[7] has also been reported. A very convenient activation[8] is realized by the treatment of cut zinc foil or zinc dust with 4 mol % of 1,2-dibromoethane, then with 3 mol % of TMS-Cl. Under these conditions, a wide range of functionalized iodides can be converted, in THF, to the corresponding organozinc iodides in high yields (85–95%; see equation 1). Primary alkyl iodides react between 30 and 45 °C, whereas most secondary alkyl iodides are smoothly converted into the corresponding zinc derivatives between 25 and 30 °C. The tolerance of functional groups in organozinc halides is noteworthy. The zinc organometallics (**3**)–(**13**) have been prepared in THF,[5,8,11,13] benzene/*N*,*N*-dimethylacetamide[9,12,16] or benzene/HMPA[10] in good yields. In polar solvents such as DMF, zinc inserts even into C($sp^2$)—I bonds of aromatic and heteroaromatic iodides affording zinc reagents such as (**11b**).[5a] Iodomethylzinc iodide (**13**) was found to undergo a new 1,2-migration with a variety of copper derivatives NuCu, affording the methylene-homologated organocopper $NuCH_2Cu{\cdot}ZnI_2$.[18] Interestingly, the presence of the THF soluble copper salt $CuI{\cdot}2LiI$ allows iodomethylzinc iodide (**13**) to convert allylic bromides directly to homoallylic iodides in high yields (see Scheme 3).[17]

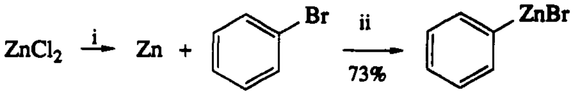
ZnCl2
i
Zn
+
Br
ii
73%
ZnBr

i, Li (2.1 equiv.), naphthalene (10 mol %), DME, 25 °C, 15 h; ii, DME, reflux, 10 h

**Scheme 2**

$$\mathrm{FG{-}R{-}I} \xrightarrow[85\text{–}95\%]{\text{i}} \mathrm{FG{-}R{-}ZnI} \qquad (1)$$

FG = OCOR, $CONR_2$, $CO_2R$, $N(COR)_2$, Cl, $Si(OR)_3$, $P(O)(OR)_2$, SR, S(O)R, $S(O)_2R$

i, Zn (1.5–2.5 equiv.) pretreated with 4 mol % of 1,2-dibromoethane, then 3 mol % of $Me_3SiCl$, addition of the alkyl iodide in THF (2–3 M solution) at 25–45 °C, then 1–12 h at 30–45 °C

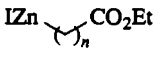

**(3)** *n* = 2, 3 or 4[8–12]

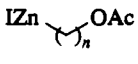

**(4)** *n* = 3, 4 or 5[5,11]

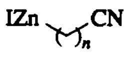

**(5)** *n* = 2 or 3[8,11,13]

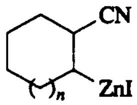

**(6)** *n* = 0 or 1[14]

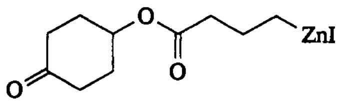

**(7)**[8]

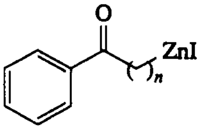

**(8)** *n* = 2–6[15]

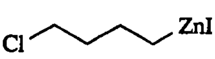

**(9)**[11,16]

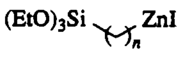
(EtO)3Si
ZnI
n

**(10)** *n* = 2 or 3[5]

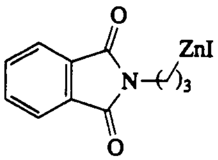

**(11a)**[10]

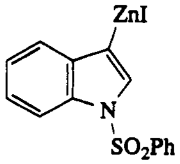

**(11b)**[5]

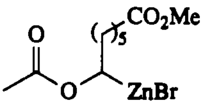
CO2Me
5
O
O
ZnBr

**(12)**[5,17b]

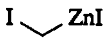

**(13)**[5,17,18]

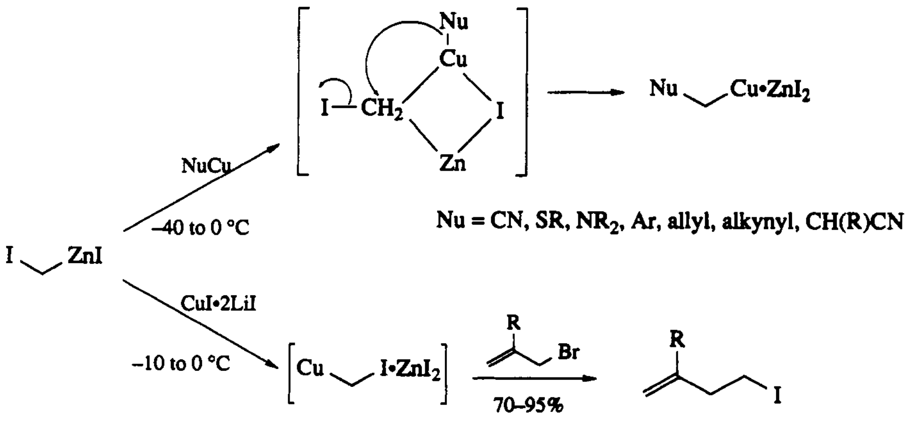
Nu
Cu
I
CH2
I
Zn
NuCu
-40 to 0 °C
Nu
Cu•ZnI2
I
ZnI
CuI•2LiI
-10 to 0 °C
Cu
I•ZnI2
R
Br
70–95%
R
I

Nu = CN, SR, $NR_2$, Ar, allyl, alkynyl, CH(R)CN

**Scheme 3**

The same methodology has been used to prepare various functionalized benzylic zinc organometallics,[19] which are not available by other methods (see equation 2).[20] In the case of electron rich aromatic bromomethyl derivatives, Wurtz coupling can become a major reaction pathway. This side reaction is generally avoided by using the corresponding benzylic chloride. The formation of the zinc reagent[5b] must then be performed at 45 °C instead of 5 °C (see equation 3). *ortho*-Bis(trimethylsilyl)aminobenzylic zinc organometallics can be easily prepared and used for the synthesis of heterocycles such as indoles (see equation 4).[19b]

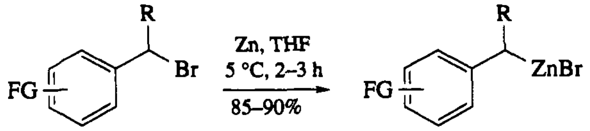

(2)

FG = COR, OAc, OMe, CN, Cl, I, $N(SiMe_3)_2$

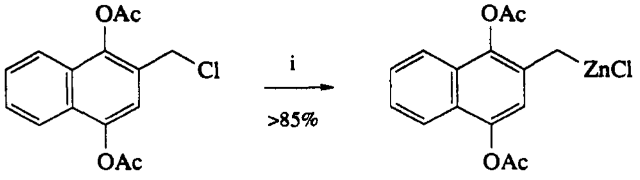

(3)

i, Zn dust (2 equiv.), THF/DMSO (4:1), 45 °C, 4 h

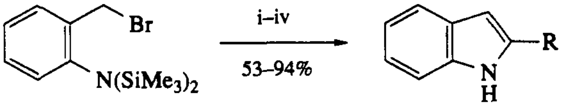

(4)

i, Zn, THF, 0 °C, 5 h; ii, CuCN, 2LiCl, –78 °C to –20 °C, 5 min;
iii, RCOCl, –20 °C, 14 h; iv, aqueous work-up

Various allylic zinc compounds, such as (**14**)–(**16**), can be prepared in good yields from the corresponding allylic bromide and zinc in THF. The tendency to form Wurtz coupling products increases with the number of substituents of the allylic bromide, with the presence of electron-donating groups at the double bond and with higher reaction temperatures. Thus, whereas (**15**) can be prepared[21] in high yields at 25 °C, the preparation of (**14**) has to be performed below 10 °C[22] and (**16**) can only be obtained in good yield[5c] if prepared below –5 °C. Cinnamylzinc bromide has to be prepared at –15 °C.[22a]

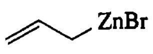

(**14**)

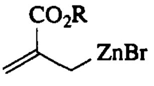

(**15**)

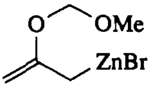

(**16**)

### 1.7.2.3 Preparation by Transmetallation Reactions

Grignard reagents[1,2,3,23] have been used extensively to prepare alkylzinc halides (**1**; see equation 5) and to some extent to prepare dialkylzinc reagents not available by oxidative addition reactions, such as di-*t*-butylzinc[24] or divinylzinc (see Scheme 4).[25] Although moderate yields are often obtained,[1] some optically active dialkylzinc reagents have been prepared in 49–81% yield.[1,26]

$$\mathrm{RMgX} + \mathrm{ZnX_2} \longrightarrow \underset{(\mathbf{1})}{\mathrm{RZnX}} + \mathrm{MgX_2} \qquad (5)$$

Compared to Grignard reagents, lithium organometallics[27] have been used less frequently for the preparation of organozinc compounds. Their high reactivity[28] or their easy availability[29,30] can, however, be

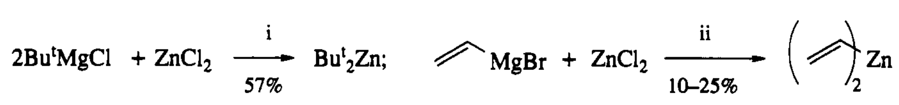

i, ether, 25 °C, then distillation; ii, THF, 55 °C, 12 h, then distillation

**Scheme 4**

useful for the synthesis of several functionalized zinc organometallics, such as (**17**) and (**18**) in Scheme 5. Trialkylaluminum compounds readily react with various zinc salts affording dialkylzinc derivatives in good yields,[1,31] but only one alkyl group per molecule of $R_3Al$ is transferred to zinc (see equation 6).[31a]

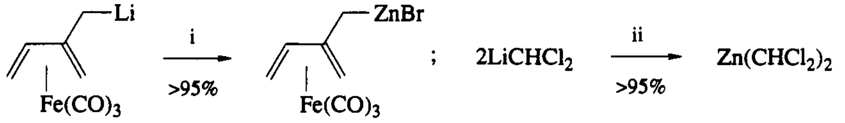

(**17**) (**18**)

i, $ZnBr_2$ (1.1 equiv.), THF, –78 to 25 °C; ii, $ZnCl_2$ (0.5 equiv.), THF, –74 to 25 °C

**Scheme 5**

$$2Me_3Al + Zn(OAc)_2 \xrightarrow[88\%]{i} Me_2Zn + Me_2AlOCOMe \qquad (6)$$

i, decalin, –10 to 10 °C, 2 h, then distillation

In contrast to organoaluminum compounds, the reaction with organoboranes has good synthetic potential.[32] The addition of a triallyl- or tribenzyl-borane to dimethylzinc furnishes, under mild conditions, a diallyl- or dibenzyl-zinc compound and trimethylborane (b.p. –20 °C), which escapes from the reaction mixture and rapidly drives the reaction to completion (see equation 7). Diorganomercury reagents react with zinc at higher temperatures (>100 °C), giving zinc organometallics in satisfactory to good yields.[1,33] Miscellaneous methods, such as the insertion of diazomethane into zinc halides,[34] the electrolysis of alkyl halides,[35] the opening of siloxycyclopropanes,[12b,c] a bromide–zinc exchange reaction,[36] the reduction of π-allylpalladium complexes[37] and the metallation of acidic hydrocarbons,[1,38] have been reported.

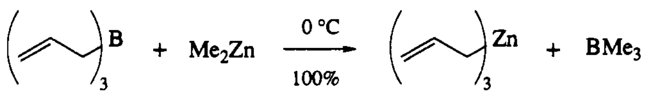

(7)

## 1.7.3 ADDITION REACTIONS OF ORGANOZINC REAGENTS

### 1.7.3.1 Introduction

Allylic, propargylic and, to some extent, benzylic zinc organometallics are more reactive toward addition to carbonyl compounds than alkylzinc derivatives.[1,39] Without catalysts, dialkylzinc reagents display a very low reactivity toward aldehydes and are unreactive toward ketones. The addition of Lewis acids (electrophilic catalysis), such as magnesium or zinc bromide,[40] boron trifluoride etherate,[10] chlorotrimethylsilane,[41] and trimethylsilyl triflate,[42] or the addition of Lewis bases (nucleophilic catalysis) such as tetraalkylammonium halides[43] and amino alcohols,[44,45] can strongly enhance the rate of the addition either by activating the aldehyde, leading to an intermediate of type (**19**), or by activating the organozinc compound by the formation of a more reactive zincate of type (**20**; see Scheme 6). A common side reaction[1,40,43] with zinc organometallics having β-hydrogens is the reduction of the carbonyl compound (see Scheme 7). The carbonyl addition can be favored over the reduction by the addition of tetraalkylammonium salts,[43] as shown in Table 1 (nucleophilic catalysis).

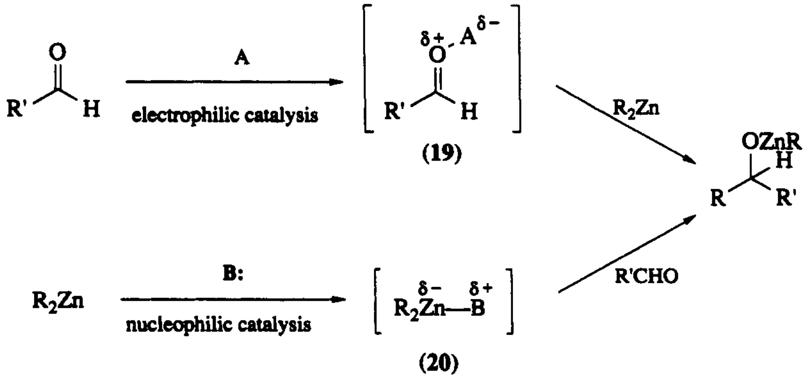

**Scheme 6**

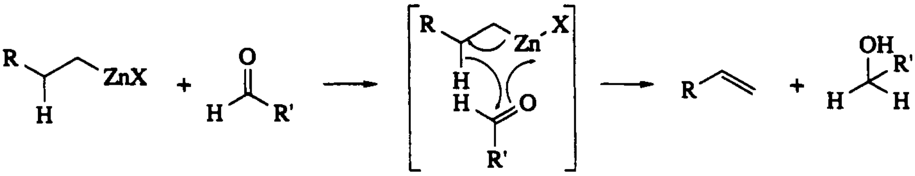

**Scheme 7**

**Table 1** Influence of the Addition of Tetrabutylammonium Salts on the Reaction of Benzaldehyde with Diisopropylzinc in Ether[43]

| *Catalyst* | *Reduction product (%)*<br>*(benzyl alcohol)* | *Addition product (%)*<br>*(1-phenylbutanol)* | *Relative rate* |
|---|---|---|---|
| None | 44 | 56 | 1.0 |
| $Bu_4NI$ | 23 | 77 | 1.1 |
| $Bu_4NBr$ | 8 | 92 | 4.1 |
| $Bu_4NCl$ | 6 | 94 | 8.9 |

### 1.7.3.2 Addition Reactions of Alkyl- and Aryl-zinc Reagents

Without the presence of a catalyst, the addition of alkylzinc organometallics (RZnX or $R_2Zn$) to aldehydes is unsatisfactory and leads to an appreciable amount of reduced product. For example, the reaction of diethylzinc and 4-chlorobenzaldehyde gives a mixture of 4-chlorobenzyl alcohol (45%) and 1-(4-chlorophenyl)propanol (38%).[44] The addition of only 5 mol % of magnesium bromide to the reaction mixture results in faster addition and higher yields.[40] Thus, the treatment of distilled $Bu_2Zn$ with benzaldehyde affords a 15% yield of 1-phenylpentanol, whereas the same reaction in the presence of 2 equiv. of $MgBr_2$ produces 70% of the addition product.[40] Ketones usually do not react; benzophenone is reduced by diethylzinc, and only diphenylzinc gives the addition product under severe conditions (toluene, reflux, 30 h). Preparatively more useful is the reaction of ester-containing alkylzinc iodides with aldehydes in the presence of an excess of TMS-Cl and with DMA or NMP as a cosolvent (see equation 8).[41]

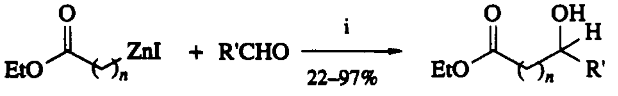 (8)

i, $Me_3SiCl$ (3 equiv.), toluene, DMA, 25–60 °C, 3 h to 3 d

Far milder reaction conditions are possible if a transmetallation of the zinc organometallic (**21**) to the mixed copper–zinc derivative (**22**) is first performed and if the reaction is carried out in the presence of 2 equiv. of $BF_3 \cdot OEt_2$.[10] A wide range of functional groups are tolerated in compounds (**21**) and (**22**), and high yields are usually obtained (68–93%; see Scheme 8), the reaction showing a good chemoselectivity. The treatment of a 1:1 mixture of benzaldehyde and acetophenone with the organozinc iodide (**23**; 2 h at

–30 °C) furnishes the acetoxy alcohol (**24**) in 86% isolated yield, with acetophenone recovered in 93% GLC yield (see equation 9). With an unsaturated aldehyde, such as cinnamaldehyde, a 1,2-addition reaction is observed in the presence of $BF_3·OEt_2$, but only the 1,4-addition product is obtained if the reaction is performed with TMS-Cl as an additive (see Scheme 9).[10]

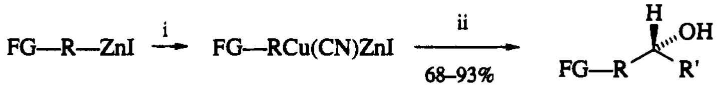

FG—R—ZnI
i
FG—RCu(CN)ZnI
ii
68–93%
H
OH
FG—R
R'

**(21)** **(22)**

ester, nitrile, enoate or imide

i, $CuCN•2LiCl$ (1.0 equiv.), THF, 0 °C, 10 min; ii, R'CHO (0.7–0.85 equiv.), $BF_3•OEt_2$ (2 equiv.), –78 °C, then 4–16 h at –30 °C

Scheme 8

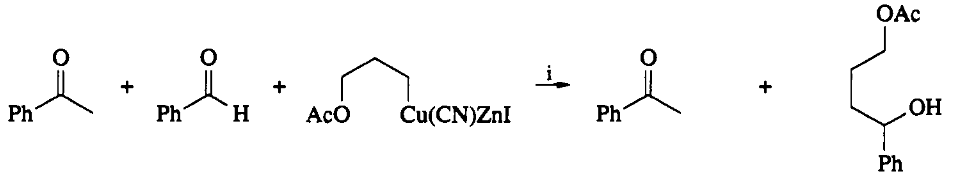

O
Ph
+
O
Ph
H
+
AcO
Cu(CN)ZnI
i
O
Ph
+
OAc
OH
Ph

(9)

1 equiv. 1 equiv. (**23**) 1.4 equiv. 93% (GLC yield) (**24**) 86% (isolated yield)

i, $BF_3•OEt_2$ (2.8 equiv.), –78 to –30 °C, 2 h

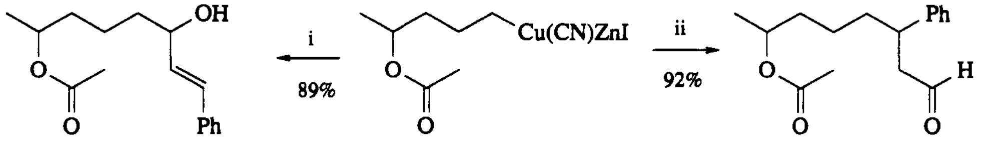

OH
O
O
Ph
i
89%
Cu(CN)ZnI
O
O
ii
92%
Ph
O
O
H
O

i, cinnamaldehyde, $BF_3•OEt_2$ (2 equiv.), –78 to –30 °C, then –30 °C, 4 h;
ii, cinnamaldehyde, $Me_3SiCl$ (2 equiv.), –78 to 25 °C overnight

Scheme 9

A transmetallation to titanium derivatives[12,13,45–47] also promotes the addition of various zinc organometallics to carbonyl compounds. However, the functional group tolerance seems to be limited (see Scheme 10).[10,13,47] Interestingly, diethylzinc reacts with aromatic 1,2-diketones to give α-ethoxy ketones (see equation 10).[48]

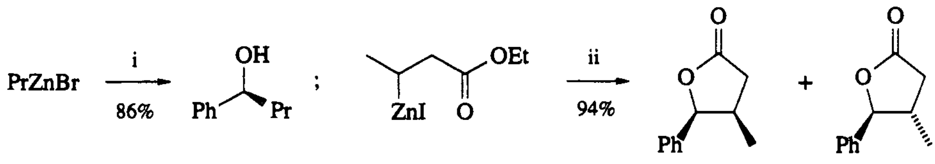

PrZnBr
i
86%
OH
Ph
Pr
;
OEt
ZnI
O
ii
94%
O
O
Ph
+
O
O
Ph

99% 1%

i, $ClTi(OPr^i)_3$ (1 equiv.), –30 °C, then PhCHO (1 equiv.), –20 to –25 °C, 2 h;[46]
ii, $ClTi(OPr^i)_3$ (1 equiv.), –30 °C, then PhCHO (0.75 equiv.), 0 °C, 2 h

Scheme 10

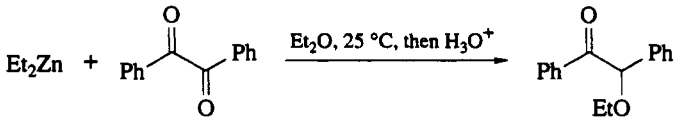

(10)

### 1.7.3.3 Addition Reactions of Allylic and Propargylic Zinc Reagents

The addition of allylic and propargylic zinc bromides to aldehydes and ketones proceeds readily[22,39,49,50] and is of high synthetic interest since the starting allylic and propargylic organometallics are easily prepared (see Scheme 11).[22] Several functionalized aldehydes or ketones can be used.[22,49,51] The reaction of allylzinc bromide with anthraquinone affords a *cis,trans* mixture of the diol (**25**) and produces only the 1,2-addition product with unsaturated ketones (see Scheme 12). Note that trialkylzincates, on the other hand, provide the 1,4-addition product in good yields.[52] Highly functionalized allylic zinc halides[29,53,54] can be prepared and afford, after addition to aldehydes or ketones, a direct approach to five-membered carbo- or hetero-cycles (see Scheme 13). A straightforward approach to the sex pheromone of the bark beetle (**26**) *via* the iron–diene complex (**27**) illustrates the synthetic utility of the Zn–Fe bimetallic isoprenoid reagent (**17**; see Scheme 14).

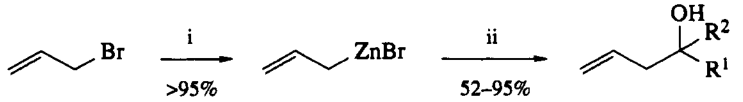

i, Zn (1 equiv.), THF, 10 °C, 3–4 h; ii, $R^1COR^2$ (aldehyde or ketone), 25 °C, several hours

**Scheme 11**

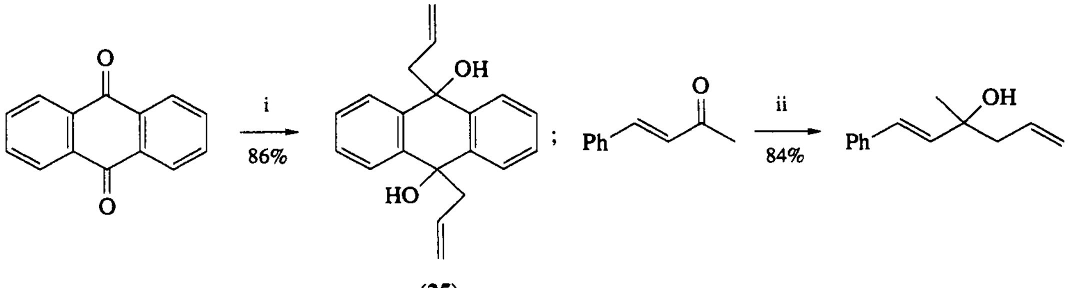

(**25**)

i, $H_2C{=}CHCH_2ZnBr$ (2.5 equiv.), THF, –5 to 0 °C, 2 h; ii, $H_2C{=}CHCH_2ZnBr$ (1.25 equiv.), 25 °C, several hours

**Scheme 12**

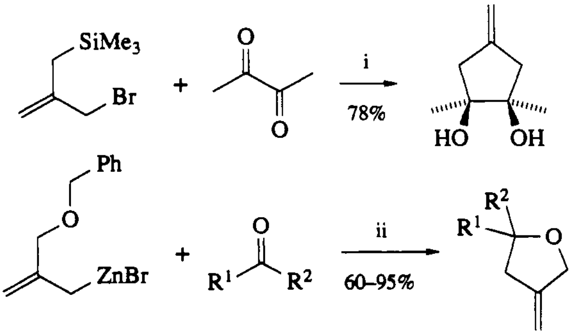

i, Zn, THF, then $Bu_4NF$, then $H_3O^+$;[53]
ii, THF, 25 °C, overnight, then $Pd(PPh_3)_4$ (5–10 mol%), 65 °C, 16–24 h

**Scheme 13**

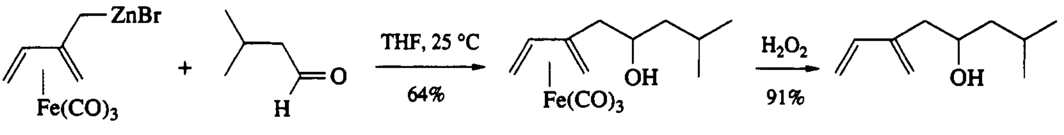

(**17**) (**27**) (**26**)

Scheme 14

The *in situ* generation of allylic zinc reagents in the presence of an electrophile (Barbier conditions)[55] can be advantageous compared to a conventional two-step procedure and allows several new synthetic possibilities, such as: (i) the generation of functionalized zinc organometallics of type (**28**), which add readily to various carbonyl compounds (see Scheme 15); and (ii) the generation of allylic zinc compounds in aqueous medium.[60] In this case, the reaction has a radical character[61] and does not proceed through a true zinc organometallic (see Scheme 16). The addition of substituted allylic zinc bromides proceeds with an allylic rearrangement *via* a cyclic six-membered transition state.[50,62] The new carbon–carbon bond is always formed from the most substituted end of the allylic system (see Scheme 17 and equation 11).

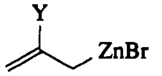

(**28**) Y = $CO_2R$,[56] $SO_2R$,[57] SOR,[42] $PO(OR)_2$,[58,56c] $SiMe_3$[59]

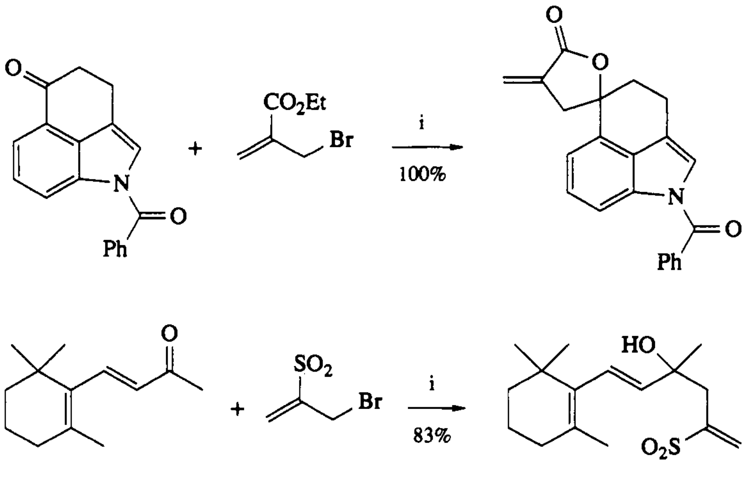

i, Zn, 40–45 °C, 1 h, then $H_3O^+$

Scheme 15

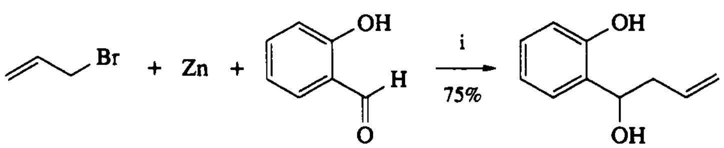

i, aq. $NH_4Cl$, THF, 25 °C, 10–20 min

Scheme 16

Under suitable reaction conditions,[63] the addition of allylic zinc bromides to ketones can be reversible. Thus, the reaction of diisobutyl ketone with 2-pentenylzinc bromide in THF affords, after a short reaction time, a mixture of (**29**) and (**30**) in a 44:56 ratio, whereas after 12 h, only the thermodynamically

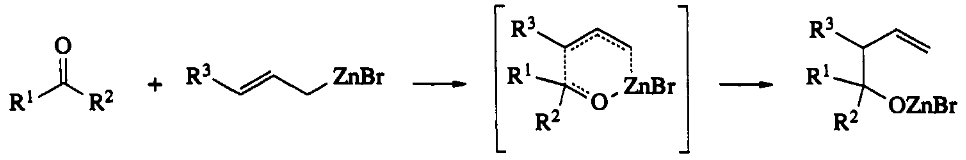

**Scheme 17**

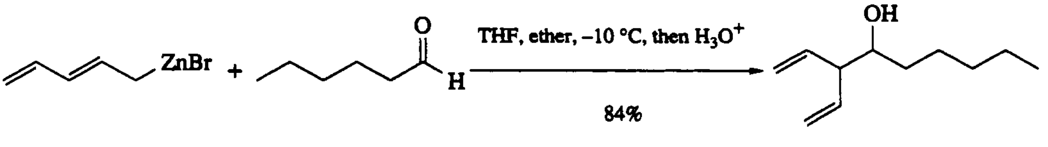

(11)

more stable zinc alcoholate (**29**) is present (see equation 12). Propargylic bromides (**31**)[1,22,64,65,66] are readily converted to the corresponding zinc derivatives (Zn, THF, −10 to −5 °C), which exist as allenic organometallics of type (**32**) if $R^1$ = H or Ph and $R^2$ = alkyl or H, and as a mixture of (**32**) and (**33**) if $R^1$ = alkyl and $R^2$ = H. Their reaction with carbonyl compounds generally affords a mixture of homopropargylic and allenic alcohols of type (**34**) and (**35**) respectively in which the former predominates (see Scheme 18). The ratio between (**34**) and (**35**) strongly depends on the nature of the substituents $R^1$ and $R^2$ of (**31**), on the solvent, and/or on the carbonyl group used. With allenylzinc bromides in which $R^1$ = H and $R^2$ = alkyl, an almost exclusive formation of alkynic alcohols of type (**34**) is observed.[66] In the presence of polar cosolvents like HMPA, a reversible addition to ketones is observed.[65d]

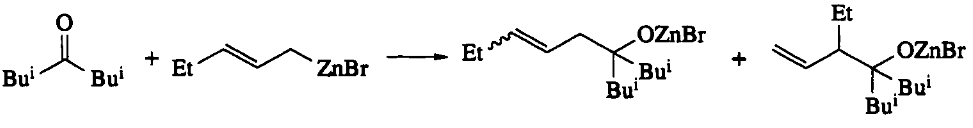

(12)

| | (29) | (30) |
|---|---|---|
| Reaction time = 5 min | 44% | 56% |
| Reaction time = 12 h | 100% | 0% |

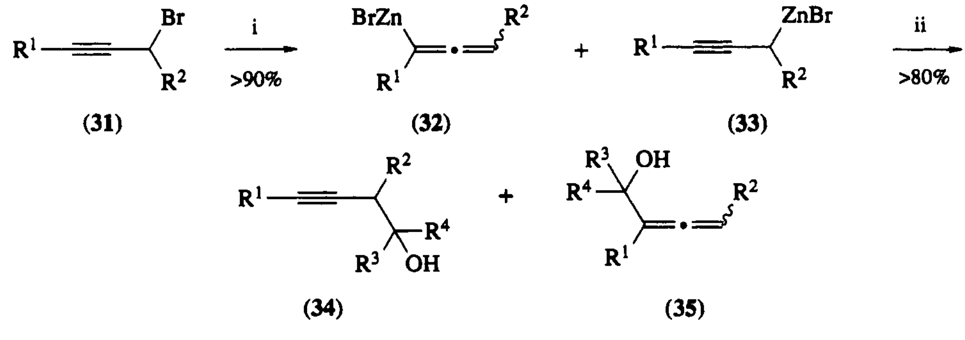

i, Zn (1 equiv.), THF, −10 to −5 °C; ii, $R^3COR^4$, 1 h, 0 °C

**Scheme 18**

### 1.7.3.4 Diastereoselective Addition Reactions

Zinc and cadmium reagents usually add to aldehydes and ketones with good diastereoselectivity compared to Grignard reagents. Dicrotyl-zinc and -cadmium reagents[49] add to sterically hindered aldehydes to produce mostly the *anti*-alcohols (**36**) *via* the cyclic transition state (**37**; see Scheme 19). 2-Substituted allylic zinc bromides display a *syn* diastereoselectivity. The bromo sulfones (**38**) react under Barbier conditions with aldehydes to give the *syn*-alcohols (**39**) with a high selectivity[57b] *via* a transition state such as (**40**), which minimizes the steric interactions between $R^1$, $R^2$ and the $PhSO_2$ group (see Scheme 20).

Remarkable selectivities are observed in the addition of allenic zinc chlorides to aldehydes, affording *anti*-homopropargylic alcohols *via* a transition state of type (**41**) (see Scheme 21). An extension to 1-substituted trimethylsilylallenic zinc chlorides was also possible and gave the *anti*-alcohols (**42**) in 92–99% stereoisomeric purity.

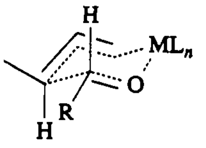

(**37**)

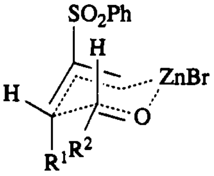
$SO_2Ph$
H
ZnBr
H
O
$R^1R^2$

(**40**)

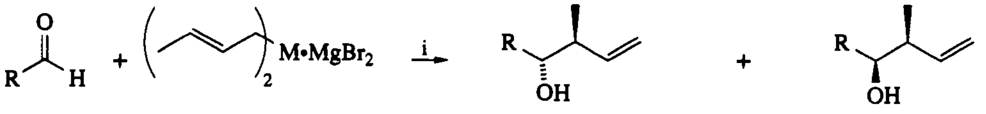
O
R
H
+
M•MgBr$_2$
2
i
R
OH
+
R
OH

(**36**)

| *R* | *M* | *anti (%)* | *syn (%)* |
|---|---|---|---|
| $Pr^i$ | Mg | 58 | 42 |
| | Zn | 70 | 30 |
| | Cd | 80 | 20 |
| $Bu^t$ | Mg | 75 | 25 |
| | Zn | 84 | 16 |
| | Cd | 86 | 14 |

i, ether, –20 °C or –35 °C, 1 h, then $H_3O^+$

**Scheme 19**

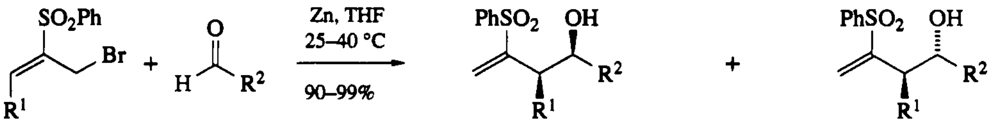
$SO_2Ph$
Br
$R^1$
+
O
H
$R^2$
Zn, THF
25–40 °C
90–99%
$PhSO_2$
OH
$R^2$
$R^1$
+
$PhSO_2$
OH
$R^2$
$R^1$

(**38**) (**39**)

| *R¹* | *R²* | *syn (%)* | *anti (%)* |
|---|---|---|---|
| Me | Ph | 100 | 0 |
| Me | c-$C_6H_{11}$ | 100 | 0 |
| Me | $C_5H_{11}$ | 88 | 12 |
| Pr | Ph | 100 | 0 |
| Pr | $C_5H_{11}$ | 67 | 33 |

**Scheme 20**

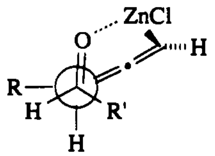
ZnCl
O
H
R
H
R'
H

(**41**)

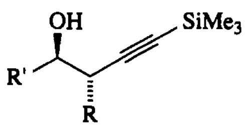

(**42**)

The addition of methylzinc (and cadmium) organometallics to chiral aldehydes[67] proceeds with low stereoselectivity and leads to a mixture of *syn*- and *anti*-alcohols (see Scheme 22). A better diastereoselectivity can be achieved by using the mixed copper–zinc reagents RCu(CN)ZnI.[10] In contrast, the more reactive diallylzinc reacts with several α-alkoxy aldehydes[68] of type (**43**) to give *anti* addition

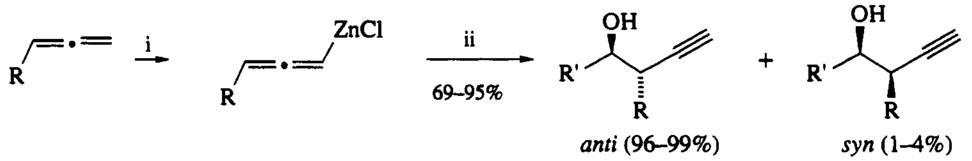
R
i
ZnCl
R
ii
69–95%
OH
R'
R
anti (96–99%)
+
OH
R'
R
syn (1–4%)

i, Bu$^t$Li, THF, –90 °C, 1 h, then $ZnCl_2$ in THF, –74 to –65 °C; ii, R'CHO, –74 to 25 °C, 1 h, then $H_3O^+$

**Scheme 21**

products (**44**) with over 80% *de* (diastereoisomeric excess). The addition follows Cram's rule[69] *via* a transition state such as (**45**). Zinc has a strong ability to complex with oxygen atoms[1,2,3] and this property can be used to perform several chelate-controlled additions to α-alkoxy aldehydes. Thus, diethylzinc adds in ether to the aldehyde (**46**), furnishing the *syn*-alcohol (**47**) as the major diastereoisomer (70% *de*) through a chelate-controlled transition state of type (**48**). The alcohol (**47**) could be converted into *exo*-brevicomin (**49**; see Scheme 23).[70]

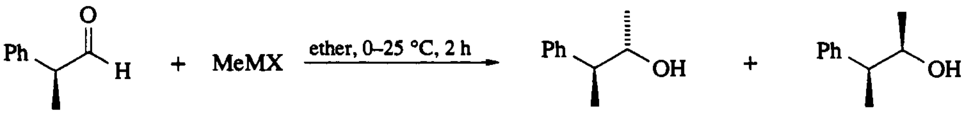
O
Ph
H
+ MeMX
ether, 0–25 °C, 2 h
Ph
OH
+
Ph
OH

| *M* | *X* | *anti (%)* | *syn (%)* |
|---|---|---|---|
| Mg | Br | 69.5 | 30.5 |
| Zn | Br | 56.0 | 44.0 |
| Cd | Br | 62.2 | 37.8 |

**Scheme 22**

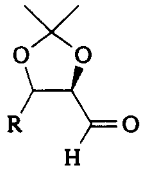

(**43**)

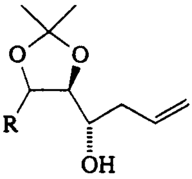

(**44**)

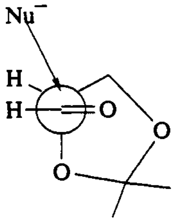

(**45**)

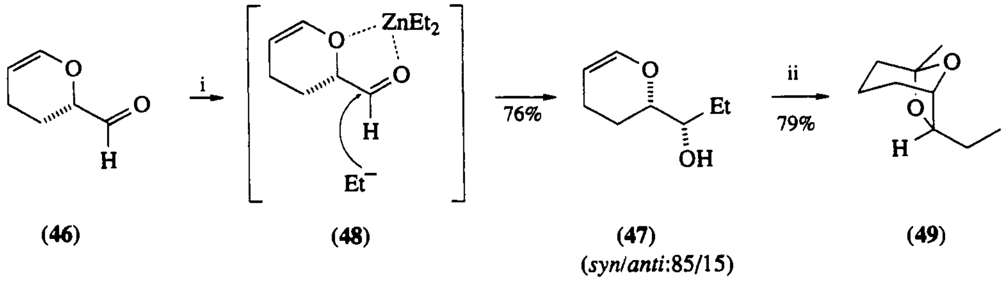
O
O
H
i
ZnEt₂
O
O
H
Et⁻
76%
O
Et
OH
ii
79%
O
O
H
(46)
(48)
(47)
(syn/anti:85/15)
(49)

i, $Et_2Zn$, ether, 0–25 °C, 5 h; ii, TMEDA (0.25 equiv.), BuLi (2.5 equiv.), 0–25 °C, 12 h, then ether, TMEDA (2.5 equiv.), MeI (5 equiv.), 0–25 °C, 1 h, then $H_3O^+$

**Scheme 23**

*In situ* generated perfluoroalkylzinc iodides add to chromium tricarbonyl complexes of aromatic aldehydes with fair diastereoselectivity (44–66% *de*).[71] The low reactivity of $R_2Zn$ toward ketones makes a stereochemical study rather difficult, since extensive reduction is observed. However, it has been found[72a] that methylzinc (and cadmium) derivatives give more axial attack with 4-*t*-butylcyclohexanone than the corresponding magnesium reagents, whereas allyl-[49] and propyl-zinc[72b] and -cadmium compounds mainly furnish the products derived from an equatorial attack (see Scheme 24). The low tendency of $Pr_2Cd$ to reduce 4-*t*-butylcyclohexanone is noteworthy (addition/elimination ratio = 10:1 compared to 1.2–2.0:1 for propyl-zinc and -magnesium reagents). The reactive (–)-menthyl phenylglyoxalate gives α-substituted (–)-menthyl mandelates in good yields and with good stereoselectivity (71–88% *de*; see equation 13).[72c]

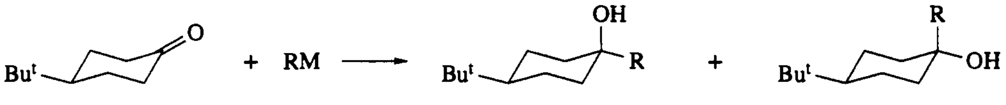

| *M* | *Equatorial attack (%)* | *Axial attack (%)* |
|---|---|---|
| MeMgBr | 68.4 | 31.6 |
| $Me_2Zn•MgBr_2$ | 46.5 | 53.5 |
| $Me_2Cd•MgI_2$ | 51.6 | 48.4 |
| PrMgBr | 69.0 | 31.0 |
| $Pr_2Zn•MgBr_2$ | 75.0 | 25.0 |
| $Pr_2Cd•MgBr_2$ | 80.0 | 20.0 |
| $(Allyl)_2Mg$ | 44.5 | 55.5 |
| $(Allyl)_2Zn$ | 84.0 | 16.0 |
| $(Allyl)_2Cd$ | 77.5 | 22.5 |

Scheme 24

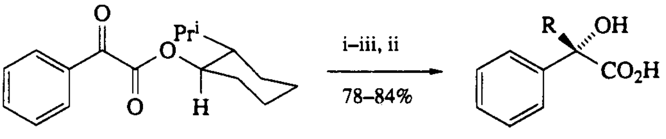

(71–88% *de*) (13)

i, $R_2Zn$, –78 °C, 3 h, then 25 °C, 1 h; ii, $H_3O^+$; iii, $OH^-$

### 1.7.3.5 Enantioselective Addition Reactions

The enantioselective addition of organometallics to aldehydes is a useful approach to optically active secondary alcohols.[52a,73] Diorganozinc reagents[73–84] add with excellent enantioselectivity to aldehydes in the presence of a chiral catalyst such as 1,2- or 1,3-amino alcohols (see equation 14 and Table 2). In most cases, diethylzinc has been used, but the reaction could be extended to some other dialkylzinc reagents and to divinylzinc.[25b] Alkylzinc halides afford secondary alcohols with a substantially lower enantiomeric excess.[82] Many aldehydes are good substrates,[25b,79] but the best results are usually obtained with aromatic aldehydes.[73–84]

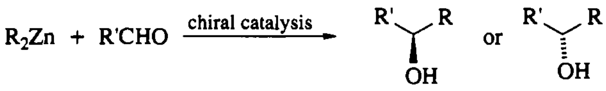

(14)

The mechanism of the reaction has been investigated in detail and it has been established that 2 equiv. of $Et_2Zn$ per molecule of the catalyst are required to observe an addition. If a 1:1 ratio is used, merely the reduction of the aldehyde is observed.[76] Only the ethyl groups coming from the second equivalent of $Et_2Zn$ are transferred to the aldehyde. Thus, the sequential addition of $(C_2H_5)_2Zn$ and $(C_2D_5)_2Zn$ to the catalyst (**64**; see Table 2), followed by benzaldehyde in a 1:1:1:1 ratio affords deuterated 1-phenylpropanol, whereas the addition of $(C_2D_5)_2Zn$ first, followed by $(C_2H_5)_2Zn$ gave only nondeuterated products.[25b] A six-membered bimetallic transition state of type (**66**) has been proposed[73,76b,80,82,85] in which the first equivalent of the diethylzinc (Zn<sub>A</sub>) activates the carbonyl group toward nucleophilic attack (electrophilic catalysis), whereas the second equivalent of $Et_2Zn$, which is made more nucleophilic by the coordination of a donor ligand (nucleophilic catalysis), transfers the ethyl group.[85] The catalytic cycle[73] of Scheme 25 is in agreement with most experimental results. The starting amino alcohol (**67**) is deprotonated by $Et_2Zn$ to afford the tricoordinated ethylzinc derivative (**68**). Complexation of a second molecule of $Et_2Zn$ at the oxygen of the zinc amino alcoholate from the less hindered side[82] affords the di-

**Table 2** Catalysts (**50**)–(**65**) for the Enantioselective Addition of Diorganozinc Reagents to Aldehydes[a]

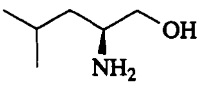
(**50**) *(R)*, 48.8% $ee^{74b}$

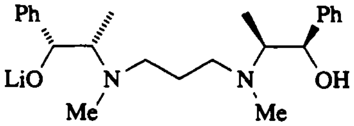
(**51**) *(R)*, 85% $ee^{75}$

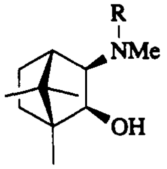
(**52a**) R = Me; *(S)*, 99% $ee^{76a}$
(**52b**) R = polymer; *(S)*, 92% $ee^{76b}$

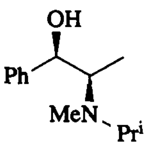
(**53**) *(R)*, 80% $ee^{77}$

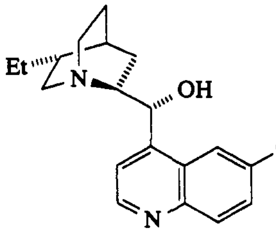
(**54**) *(R)*, 68% $ee^{78}$

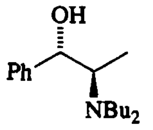
(**55**) *(S)*, 90% $ee^{79}$

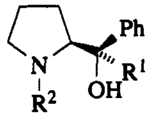
(**56a**) $R^1$ = Ph, $R^2$ = Me; *(S)*, 97% $ee^{80}$
(**56b**) $R^1$ = H, $R^2$ = Me; *(R)*, 74% $ee^{80}$
(**56c**) $R^1$ = H, $R^2$ = n-$C_5H_{11}$; *(R)*, 100% $ee^{80}$

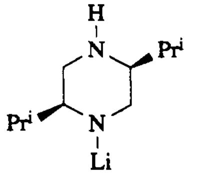
(**57**) *(R)*, 92% $ee^{81}$

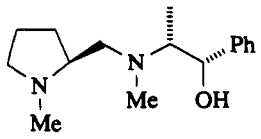
(**58**) *(S)*, 95% $ee^{82}$

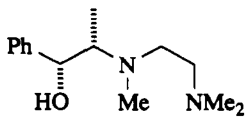
(**59**) *(R)*, 90% $ee^{82}$

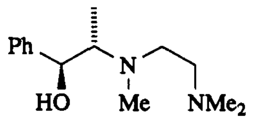
(**60**) *(S)*, 91% $ee^{82}$

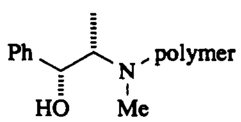
(**61**) *(R)*, 89% $ee^{83}$

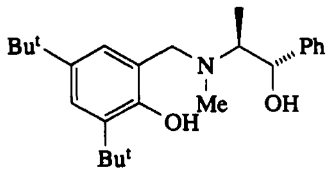
(**62**) *(R)*, 87% $ee^{82}$

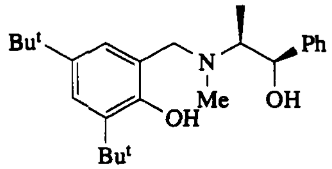
(**63**) *(R)*, 75% $ee^{82}$

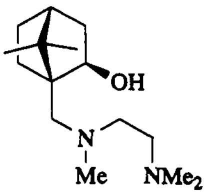
(**64**) *(S)*, 92% $ee^{25b}$

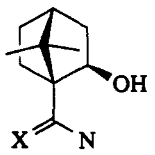
(**65a**) X = O; *(R)*, 91% $ee^{25b}$
(**65b**) X = 2H; *(R)*, 82% $ee^{25b}$

---

[a] The absolute configuration of 1-phenylpropanol obtained by the addition of $Et_2Zn$ to benzaldehyde in the presence of the catalyst as well as the enantiomeric excess (% *ee*) observed are indicated.

metallic reagent (**69**), which coordinates the aldehyde leading to (**70**). This coordination occurs in the half space which contains $Et_2Zn$, unless a tridentate chiral inductor such as (**64**) is used.[25b] The complexation of zinc occurs at the sterically most easily available carbonyl lone pair (*cis* to hydrogen; see **71**). After the transfer of an ethyl group affording the bicyclic zinc alcoholate (**72**), the product (**73**) is liberated, regenerating the catalyst (**68**). Interestingly, the use of a configurationally impure catalyst such as 1-piperidyl-3,3-dimethyl-2-butanol (**74**; 10.7% *ee*) affords, upon addition of $Et_2Zn$ to benzaldehyde, a product of 82% enantiomeric excess. This asymmetric amplification phenomenon[84a] can be explained by diastereomeric interactions between the enantiomers of (**74**). Furthermore, the reaction rate with a 66% *ee* catalyst is 5.5 times faster than with the racemic catalyst. These results indicate that in the case of simple bidentate amino alcohols, the actual mechanism of the enantioselective addition may be more complex than that indicated in Scheme 25. High asymmetric inductions have also been obtained recently by using dialkylzinc–orthotitanate complexes,[84b] chiral oxazaborolidines as catalysts[84c] or secondary amino alcohols derived from camphor.[84d] Applications to the preparation of optically active 2-furylcarbinols have been reported.[84e]

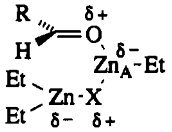
R
δ+
H
O
δ−
Zn$_A$-Et
Et
Zn-X
Et
δ−
δ+

**(66)**

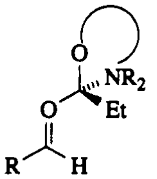

**(71)**

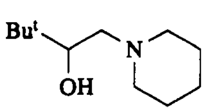

**(74)**

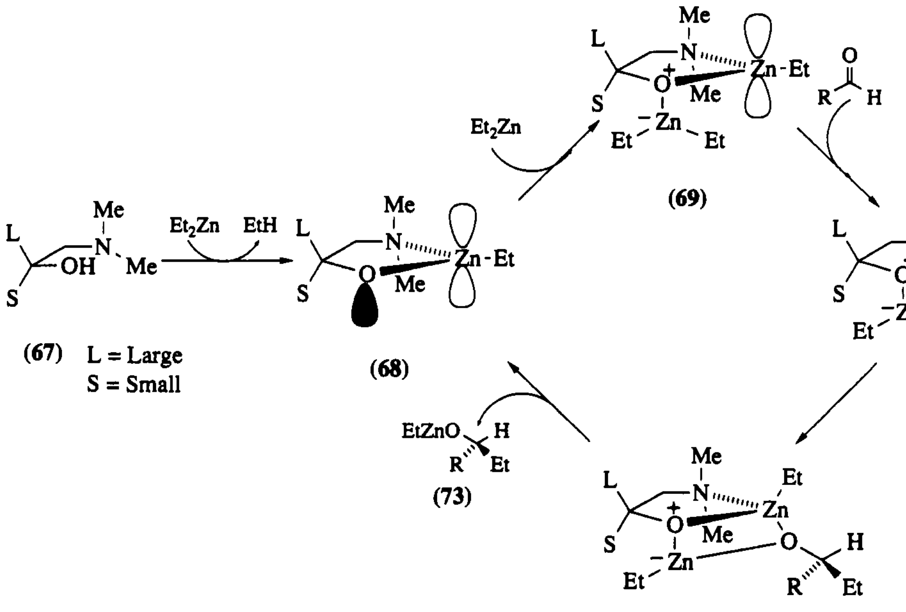
Me
L
N
OH
Me
S
(67) L = Large
S = Small
Et$_2$Zn
EtH
Me
L
N
O
Zn-Et
Me
S
(68)
Et$_2$Zn
Me
L
N
Zn-Et
O
Me
S
Zn
Et
Et
(69)
O
R
H
Me
L
N
Et
Zn
H
O
Me
O
S
Zn
Et
Et
R
(70)
Me
L
N
Et
Zn
O
Me
O
H
S
Zn
Et
R
Et
(72)
EtZnO
H
R
Et
(73)

Scheme 25

## 1.7.4 ADDITION REACTIONS OF ORGANOCADMIUM AND ORGANOMERCURY REAGENTS

### 1.7.4.1 Addition Reactions of Alkyl- and Aryl-cadmium Reagents

Whereas organomercury compounds[86] do not add to aldehydes and ketones, cadmium organometallics show a useful reactivity.[2,39,87,88] As in the case of organozinc derivatives, allylic cadmium compounds are far more reactive than alkyl- or aryl-cadmium organometallics. Alkylcadmium organometallics are prepared in similar ways to the corresponding zinc compounds. However, their high thermal and photochemical instability makes their preparation and isolation more difficult.[87,88] Purified diorganocadmium compounds react very slowly with aromatic aldehydes.[89,90] However, if the reaction is conducted in the presence of magnesium, zinc, lithium or aluminum halides, a fast reaction is observed (electrophilic catalysis; see Section 1.7.3.1). Magnesium bromide and magnesium iodide are the most active promoters (see equation 15).[91] The replacement of ether by THF leads to slower addition rates.[92] Aliphatic aldehydes and ketones react less cleanly and the desired addition product is obtained in low yields (20–40%) together with reduction products.[87,93] The functionalized organocadmium compound (**75**) can be prepared and added in 50–90% yield to aldehydes (see Scheme 26).[94] Synthetically useful is the reaction of dialkylcadmium compounds with certain functionalized ketones[87,95] containing halides, an ester or a nitro group at the α-position, which furnishes polyfunctionalized molecules in fair yields (see Scheme 27). The addition of cadmium organometallics to 4-*t*-butylcyclohexanone has been reported (see Section 1.7.3.4).

$$\mathrm{Et_2Cd} + \mathrm{PhCHO} \xrightarrow[85\%]{\mathrm{i}} \mathrm{Et{-}CH(OH)Ph} \qquad (15)$$

i, $MgBr_2$ (1.2 equiv.), ether, 35 °C, 1 h

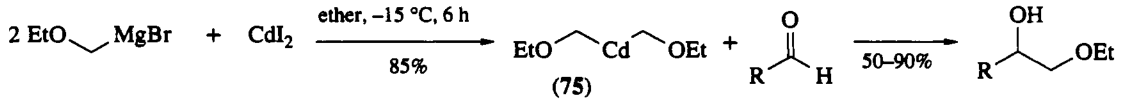

**Scheme 26**

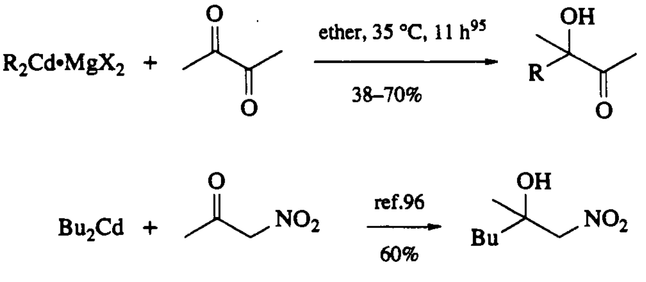

**Scheme 27**

### 1.7.4.2 Addition Reactions of Allylic and Benzylic Cadmium Reagents

Allylic cadmium organometallics react in good yields (50–90%)[49a] with aldehydes and ketones.[49a,87,88] If the allylic reagent is substituted, only the alcohol formed after allylic rearrangement is obtained (see Scheme 28).[49a] If polyfunctionalized substrates are used, the allylic cadmium reagent shows a high

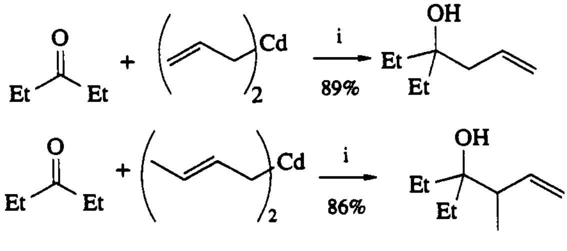

i, ether, 10–20 °C, 3 h then $H_3O^{+}$[49a]

**Scheme 28**

chemoselectivity and attacks only the aldehyde function (see equation 16).[97] Enones react with allylic cadmium organometallics to give only the 1,2-addition product in high yields.[98] Benzylic cadmium[20,99] reagents display a more moderate reactivity, but add cleanly to aliphatic and aromatic aldehydes to furnish various benzylic alcohols in fair to good yields (see equation 17).[99] Sulfur-stabilized allylic cadmium derivatives react with aldehydes with high γ-selectivity.[100]

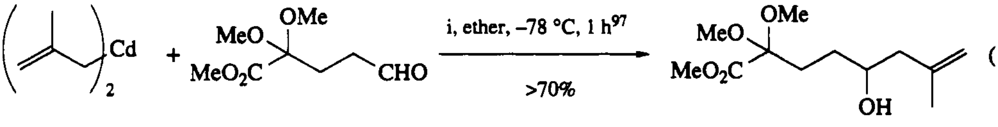

(16)

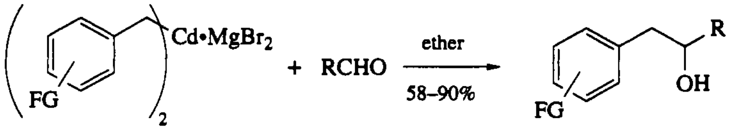

(17)

## 1.7.5 REFERENCES

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# 1.8

# Organocerium Reagents

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## 1.8.1 INTRODUCTION

Elements of the lanthanide series possess unique electronic and stereochemical properties due to their *f*-orbitals, and have great potential as reagents and catalysts in organic synthesis.[1–4] During the 1970s and 1980s many synthetic reactions and procedures using lanthanide elements were reported, in conjunction with significant development in the chemistry of organolanthanides. Several review articles covering this field of chemistry have appeared.[5–11]

Of the 15 elements from lanthanum to lutetium, cerium has the highest natural abundance, and its major inorganic salts are commercially available at moderate prices. The present author and his coworkers have utilized this relatively inexpensive element in reactions which form carbon–carbon bonds, studying the generation and reactivities of organocerium reagents. The cerium reagents, which are prepared from organolithium compounds and cerium(III) halides, have been found to be extremely useful in organic synthesis, particularly in the preparation of alcohols by carbonyl addition reactions. They react with various carbonyl compounds to afford addition products in satisfactory yields, even though the substrates are susceptible to so-called abnormal reactions when using simple organolithiums or Grignard reagents.

This chapter surveys the addition reactions of organocerium reagents to the C—X π-bond. Emphasis is placed on the utility of cerium chloride methodology, and many examples of its practical applications are given. Experimental procedures are also described in detail to enable readers to employ this method immediately in practical organic syntheses.

Other organolanthanide reagents are covered in Chapter 1.10 in this volume, while selective carbonyl addition reactions promoted by samarium and ytterbium reagents are surveyed in Chapter 1.9.

## 1.8.2 ORGANOCERIUM REAGENTS

### 1.8.2.1 Generation of Organocerium Reagents

Organocerium reagents are prepared *in situ* by the reaction of organolithium compounds with anhydrous cerium chloride or cerium iodide, as shown in equation (1).[12–14] A variety of organolithium compounds can be employed, including alkyl-, allyl-, alkenyl- and alkynyl-lithiums, which are all converted to the corresponding cerium reagents.

$$\text{RLi} + \text{CeX}_3 \xrightarrow[\text{X = Cl, I}]{\text{THF}} \text{'RCeX}_2\text{'} + \text{LiX} \qquad (1)$$

No systematic studies on the structure of organocerium reagents have been made so far. Although some experimental results indicate that no free organolithium compounds are present in the reagents, the structure of the reagents has not yet been elucidated. The cerium reagents are presumed to be $\sigma$-($RCeX_2$) or ate [$(RCeX_3)^-Li^+$] complexes, but other possibilities such as a weakly associated complex ($RLi{\cdot}CeX_3$) are not excluded. In this text, organocerium reagents are represented as '$RCeX_2$' for convenience.

#### *1.8.2.1.1 General comments*

Organocerium reagents can be generated without difficulty, but the following suggestions will help to ensure success.

Cerium chloride, rather than cerium iodide, is recommended because preparation of the iodide requires the handling of pyrophoric metallic cerium.[14] Anhydrous cerium chloride is commercially available from Aldrich, but can also be prepared in the laboratory by dehydration of cerium chloride heptahydrate using thionyl chloride,[15] or by reduction of cerium(IV) oxide using $HCO_2H$/HCl followed by dehydration.[16] Heating the hydrate without additive *in vacuo* is a comparatively simple method and is satisfactory for the generation of organocerium reagents.

Ethereal solvents such as tetrahydrofuran (THF) and dimethoxyethane (DME) are employed in the reactions, with THF generally being preferred. Usually, THF freshly distilled from potassium or sodium with benzophenone is used. Use of hot THF is not recommended, because on addition to cerium chloride a pebble-like material, which is not easily suspended, may be formed.

#### *1.8.2.1.2 General procedure for the preparation of anhydrous cerium chloride*

Cerium chloride heptahydrate (560 mg, 1.5 mmol) is quickly ground to a fine powder in a mortar and placed in a 30 mL two-necked flask. The flask is immersed in an oil bath and heated gradually to 135–140 °C with evacuation (*ca.* 0.1 mmHg). After 1 h, a magnetic stirrer is placed in the flask and the cerium chloride is dried completely by stirring at the same temperature *in vacuo* for a further 1 h.

The following procedure is recommended for the small-scale preparation of anhydrous cerium chloride. Cerium chloride heptahydrate (*ca.* 20 g) is placed in a round-bottomed flask connected to a dry ice trap. The flask is evacuated and heated to 100 °C for 2 h. The resulting opaque solid is quickly pulverized in a mortar and is heated again, *in vacuo* at the same temperature, for 2 h with intermittent shaking. A stirrer is then placed in the flask, which is subsequently evacuated, and the bath temperature is raised to 135–140 °C. Drying is complete after 2–3 h of stirring.

Anhydrous cerium chloride can be stored for long periods provided it is strictly protected from moisture. Cerium chloride is extremely hygroscopic; hence, it is recommended that it be dried *in vacuo* at *ca.* 140 °C for 1–2 h before use.

### 1.8.2.1.3 General procedure for the generation of organocerium reagents

Cerium chloride heptahydrate (560 mg, 1.5 mmol) is dried by the procedure described above. While the flask is still hot, argon gas is introduced, after which the flask is cooled in an ice bath. Tetrahydrofuran (5 mL) is added all at once with vigorous stirring. The ice bath is removed and the suspension is stirred well for 2 h or more (usually overnight) under argon at room temperature. The flask is cooled to –78 °C and an organolithium compound (1.5 mmol) is added with a syringe. Stirring for 0.5–2 h at the same temperature, or a somewhat higher temperature (–40 to –20 °C), results in the formation of a yellow or red suspension, which is ready to use for reactions.

### 1.8.2.1.4 Reactions with ketones and similar compounds

The addition reactions are usually carried out at –78 °C, except for reactions of the Grignard reagent/cerium chloride system (Section 1.8.4), which are conducted at 0 °C. A substrate is added to the well-stirred organocerium reagent and the mixture is stirred until the reaction is complete. Work-up is carried out in the usual manner: quenching with dilute HCl or dilute AcOH and extraction with a suitable organic solvent. When the substrates are acid sensitive, work-up using tetramethylenediamine is recommended.[17]

## 1.8.2.2 Scope of the Reactivity

### 1.8.2.2.1 Thermal stability

The reagents are generally stable at low temperature (–78 to –20 °C) and react readily with various carbonyl compounds to give the corresponding addition products in high yields. However, at temperatures above 0 °C, reagents with β-hydrogens decompose; reactions with ketones provide reduction products (secondary alcohols and pinacol coupling products), as shown in Scheme 1. Other reagents, such as methyl- and phenyl-cerium reagents, are stable at around room temperature but decompose at about 60 °C.[13,14,18]

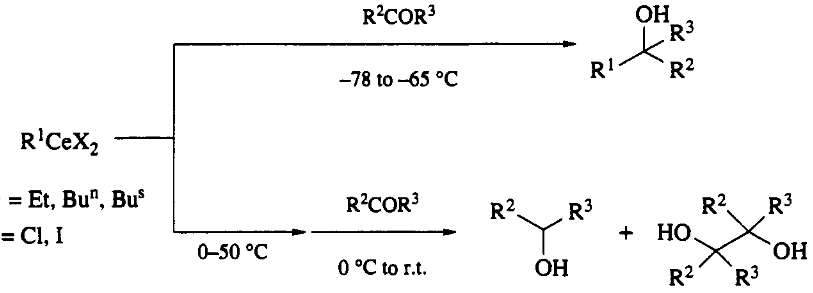

Scheme 1

### 1.8.2.2.2 Reactions with organic halides, nitro compounds and epoxides

The reactivities of organocerium reagents toward organic halides are in sharp contrast to the reactivities of alkyllithiums. No metal–halogen exchange occurs at –78 °C; aryl bromides and iodides are quantitatively recovered unchanged after treatment with *n*-butyl- or *t*-butyl-cerium reagents.[18,19] Alkyl iodides are also inert to prolonged treatment with organocerium reagents at the same temperature. Benzylic halides undergo reductive coupling to give 1,2-diphenylethane derivatives upon treatment with the *n*-butylcerium reagent.[18]

Nitro compounds react immediately with organocerium reagents at –78 °C to give many products,[19] while epoxides undergo ring opening followed by deoxygenation to yield substituted alkenes.[20]

### 1.8.2.3 Reactions with Carbonyl Compounds

Organocerium reagents react readily with various ketones at low temperature to give the addition products in good to high yields.[12–14,21] Some representative results are shown in Table 1,[12,13] together with the results obtained on using the corresponding organolithiums alone.

**Table 1** The Reaction of Organocerium Reagents with Ketones

| *Ketone* | *Reagent* | *Product* | *Yield (%)*[a] |
|---|---|---|---|
| $(PhCH_2)_2CO$ | $Bu^nCeCl_2$ | $(PhCH_2)_2C(OH)Bu^n$ | 96 (33) |
| $(PhCH_2)_2CO$ | $Bu^tCeCl_2$ | $(PhCH_2)_2C(OH)Bu^t$ | 65 (trace) |
| $(PhCH_2)_2CO$ | $HC{\equiv}CCeCl_2$ | $(PhCH_2)_2C(OH)C{\equiv}CH$ | 95 (60) |
| 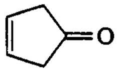 | $PhC{\equiv}CCeCl_2$ | 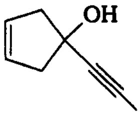 | 89 (30) |
| 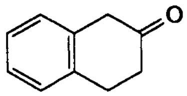 | $Bu^nCeCl_2$ | 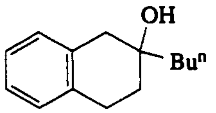 | 88 (trace) |
| 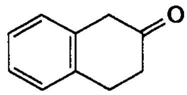 | $H_2C{=}C(Me)CeCl_2$ | 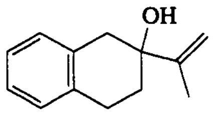 | 88 (12) |
| 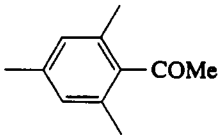 | $Bu^nCeCl_2$ | 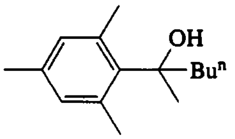 | 57 (<10) |
| $p\text{-}IC_6H_4COMe$ | $Bu^nCeCl_2$ | $p\text{-}IC_6H_4C(OH)(Me)Bu^n$ | 93 (trace) |
| $p\text{-}BrC_6H_4COMe$ | $Bu^nCeCl_2$ | $p\text{-}BrC_6H_4C(OH)(Me)Bu^n$ | 96 (43) |
| $p\text{-}BrC_6H_4COCH_2Br$ | $PhC{\equiv}CCeCl_2$ | $p\text{-}BrC_6H_4C(OH)(CH_2Br)C{\equiv}CPh$ | 95 (trace) |
| $p\text{-}NCC_6H_4COMe$ | $Bu^nCeCl_2$ | $p\text{-}NCC_6H_4C(OH)(Me)Bu^n$ | 48 |
| $m\text{-}O_2NC_6H_4COMe$ | $Bu^nCeCl_2$ | Complex mixture | |
| 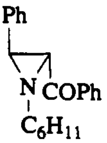 | $Bu^nCeCl_2$ | 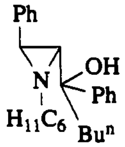 | 93 |
| 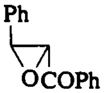 | $Bu^nCeCl_2$ | 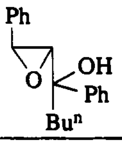 | 52 |

[a] The figures in parentheses indicate the yields obtained by use of the lithium reagent alone.

It is noteworthy that the reagents are only weakly basic and react even with readily enolizable ketones in moderate to good yields. Another important fact is that selective carbonyl addition occurs in the presence of carbon–halogen bonds.

The chemoselectivity between aldehydes and ketones has been studied by Kauffmann *et al.*[22] Cerium reagents exhibit moderate aldehyde selectivities, although these are much lower than those of the organometallic reagents of titanium, zirconium and chromium (Scheme 2).[23–26]

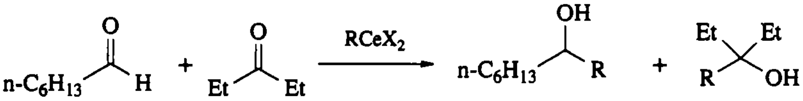

| | | | |
|---|---|---|---|
| $MeCeCl_2$ | 79 | : | 21 |
| $MeCeI_2$ | 87 | : | 13 |
| $Bu^nCeI_2$ | 90 | : | 10 |

**Scheme 2**

Stereoselectivities have been studied by several research groups. In the case of α-heterosubstituted carbonyl compounds, both chelation control and nonchelation control have been observed, depending on the reagents and substrates (Section 1.8.2.6).

### 1.8.2.4 Selective Addition to α,β-Unsaturated Carbonyl Compounds

Organocerium reagents react with α,β-unsaturated carbonyl compounds to give 1,2-addition products in good to high yields (equation 2).[27,28]

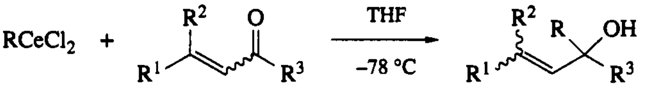

(2)

The reactions of (*E*)- and (*Z*)-1-(4′-methoxyphenyl)-3-phenyl-2-propen-1-ones (**1a** and **1b**; Scheme 3) are representative examples. The 1,2-selectivities are generally higher than those of the corresponding lithium reagents and Grignard reagents (Table 2);[28] however, the selectivity can be severely eroded by steric effects, as exemplified by the reactions of an isopropylcerium reagent.

The reactions of (*Z*)-$PhCH{=}CHCOC_6H_4$-*p*-OMe with cerium reagents provide (*Z*)-allyl alcohols in excellent yields, suggesting that the addition reactions proceed almost exclusively through a polar pathway.

Another notable difference between cerium and lithium reagents has been observed in the reaction of a stabilized carbanion with cyclohex-2-enone. The reaction with α-cyanobenzyllithium is known to be thermodynamically controlled; thus, the initially formed 1,2-adduct dissociates to the starting carbanion and α-enone, which in turn are gradually converted to the thermodynamically stable 1,4-adduct.[29] In contrast, the corresponding cerium reagent affords the 1,2-adduct exclusively in good yield, regardless of reaction time (Scheme 4 and Table 3).[28] Trivalent cerium is strongly oxophilic and intercepts the intermediate 1,2-adduct by virtue of its strong bonding to the alkoxide oxygen, thus suppressing the reverse reaction.

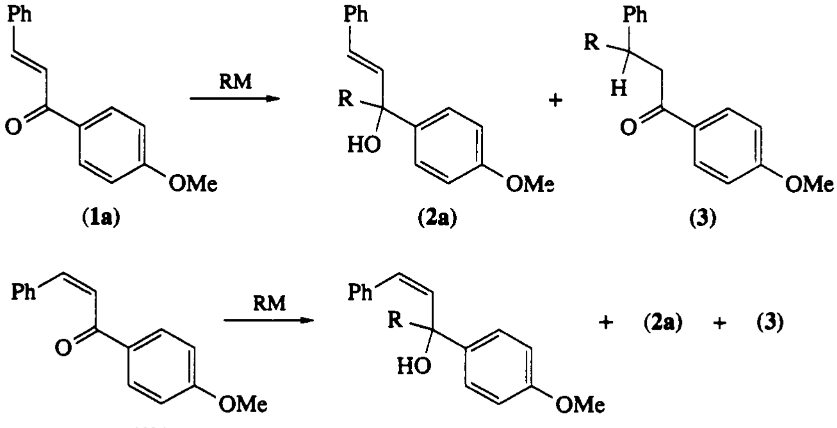

R = Me, Bu, Ph, $Pr^i$; M = $CeCl_2$, Li, MgBr

**Scheme 3**

**Table 2** Reaction of Organocerium, Organolithium or Grignard Reagents with (*E*)- or (*Z*)-$PhCH{=}CHCOC_6H_4$-OMe-*p*

| *Substrate* | *Reagent* | *Conditions*[a] *Solvent* | *Time* (min) | *Yield of products* (%)[b] *(2a)* | *(2b)* | *(3)* |
|---|---|---|---|---|---|---|
| **(1a)** | $MeCeCl_2$ | THF–ether (12:1) | 30 | 98 | 0 | Trace |
| | MeLi | THF–ether (5:1) | 30 | 65 | 0 | 17 |
| | MeMgBr | THF | 30 | 38 | 0 | 65 |
| | $BuCeCl_2$ | THF–hexane (8:1) | 30 | 50 | 0 | 43 |
| | BuLi | THF–hexane (2:1) | 30 | 36 | 0 | 50 |
| | BuMgBr | THF | 30 | 10 | 0 | 76 |
| | $PhCeCl_2$ | THF–ether (8:1) | 30 | 90 | 0 | 4 |
| | PhLi | THF–ether (3:1) | 30 | 85 | 0 | 10 |
| | PhMgBr | THF | 30 | 14 | 0 | 78 |
| | $Pr^iCeCl_2$ | THF–hexane (4:1) | 30 | 42 | 0 | 35 |
| | $Pr^iLi$ | THF–hexane (3:1) | 30 | 39 | 0 | 57 |
| | $Pr^iMgCl$ | THF | 30 | 44 | 0 | 51 |
| **(1b)** | $MeCeCl_2$ | THF–ether (12:1) | 60 | Trace | 97 | Trace |
| | MeLi | THF–ether (5:1) | 60 | Trace | 96 | Trace |
| | MeMgBr | THF | 60 | 26 | 20 | 38 |
| | $BuCeCl_2$ | THF–hexane (8:1) | 60 | Trace | 97 | Trace |
| | BuLi | THF–hexane (2:1) | 60 | Trace | 70 | 20 |
| | BuMgBr | THF | 60 | 20 | 25 | 50 |
| | $PhCeCl_2$ | THF–ether (8:1) | 90 | Trace | 93 | 4 |
| | PhLi | THF–ether (3:1) | 90 | Trace | 90 | 4 |
| | PhMgBr | THF | 90 | 25 | 20 | 45 |

[a] All reactions were carried out at –78 °C. [b] Isolated yield.

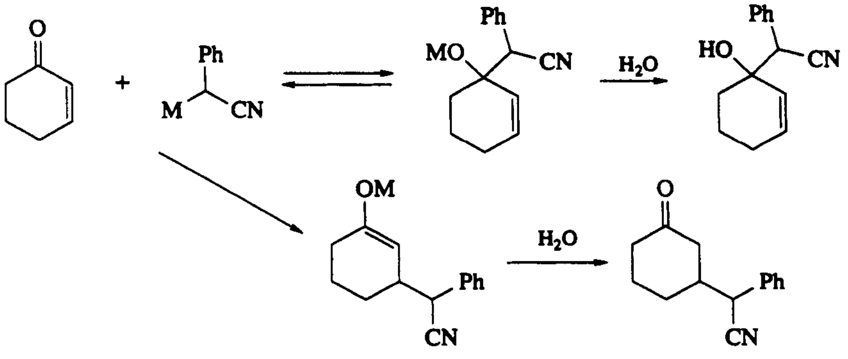

**Scheme 4**

**Table 3**

| *M* | *Conditions*[a] *Temperature* (°C) | *Time* (min) | *Yield* (%) *1,2-Addition* | *1,4-Addition* | *Ref.* |
|---|---|---|---|---|---|
| Li | –70 | 1 | 29 | 36 | 29 |
| Li | –70 | 15 | 21 | 49 | 29 |
| Li | –70 | 180 | 0 | 90 | 29 |
| $CeCl_2$ | –78 | 4 | 61 | 0 | 28 |
| $CeCl_2$ | –78 | 15 | 60 | 0 | 28 |
| $CeCl_2$ | –78 | 240 | 62 | 0 | 28 |

[a] All reactions carried out using THF as solvent.

## 1.8.2.5 Addition to C—N π-Bonds

The reaction of cerium reagents with imines and nitriles which possess α-hydrogens has been studied by Wada *et al.*[30] Available data indicate that the reagents do not effectively add to these substrates, although the results are better than with alkyllithiums themselves. A modification of the procedure improves the yields of addition products. Thus, addition of the organocerium or organolithium reagent to an admixture of cerium chloride and imine or nitrile at –78 °C affords the adducts in acceptable yields, as exemplified in equation (4).[30]

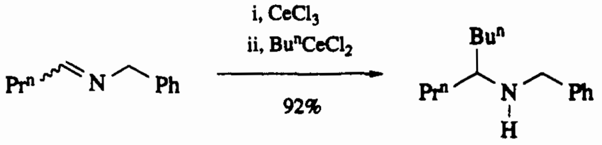

i, $CeCl_3$
ii, $Bu^nCeCl_2$
92%
$Pr^n$
N
Ph
$Bu^n$
H

(4)

It has been reported by Denmark *et al.* that aldehyde hydrazones react smoothly with organocerium reagents to give addition products in good to high yields (Section 1.8.2.6).[31]

## 1.8.2.6 Synthetic Applications

### *1.8.2.6.1 Alkylcerium reagents*

Mash has recently employed a methylcerium reagent in the synthesis of (–)-chokol A.[32] The reagent reacts with the readily enolizable cyclopentanone derivative (4) to give (–)-chokol A in 80% yield, as shown in Scheme 5.

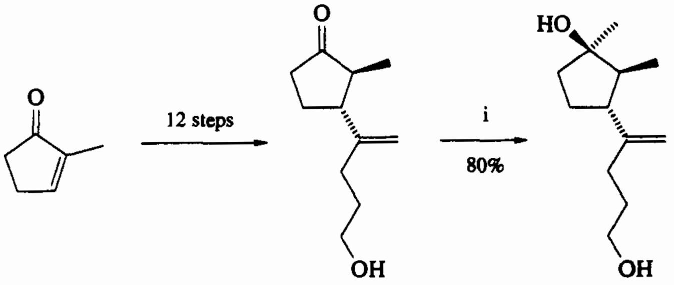

O
12 steps
i
80%
HO
OH

(4)

(–)-Chokol A

i, $MeCeCl_2$ (5 equiv.), THF, –78 °C, 2 h

**Scheme 5**

Corey and Ha have successfully employed a cerium reagent at the crucial step in the total synthesis of venustatriol, as illustrated in Scheme 6.[33]

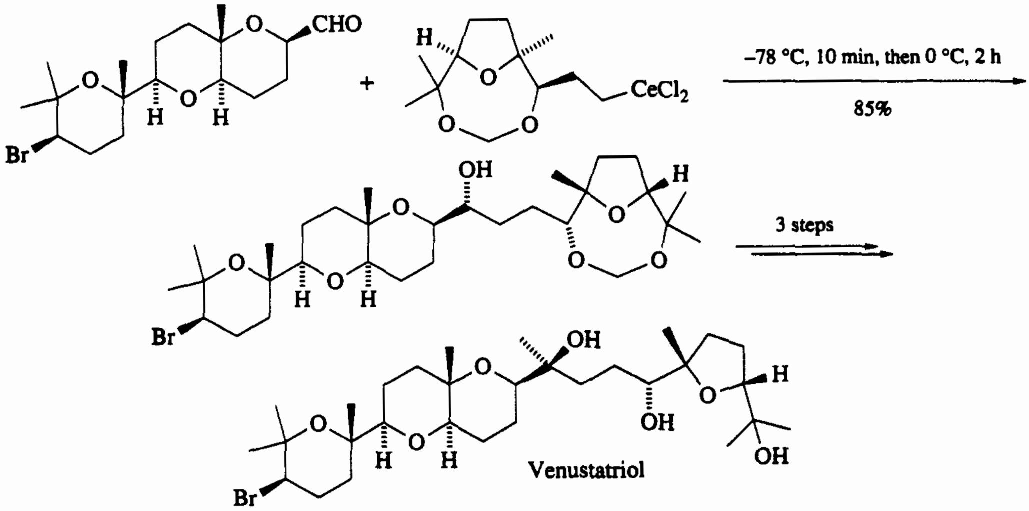

CHO
O
H
Br
+
$CeCl_2$
–78 °C, 10 min, then 0 °C, 2 h
85%
OH
3 steps
Venustatriol

**Scheme 6**

In a total synthesis of (−)-bactobolin, Garigipati and Weinreb used a dichloromethylcerium reagent.[34] The intermediate product (**5**) was isolated in 54% yield as a single isomer, as shown in Scheme 7. Dichloromethyllithium alone in this reaction afforded intractable material.

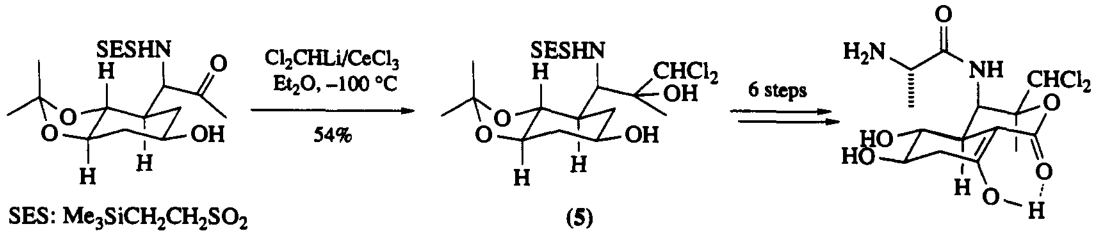
SESHN
H
O
OH
H
$Cl_2CHLi/CeCl_3$
$Et_2O$, −100 °C
54%
$CHCl_2$
OH
6 steps
$H_2N$
NH
$CHCl_2$
HO
HO
O
H

SES: $Me_3SiCH_2CH_2SO_2$

(**5**)

(−)-Bactobolin

**Scheme 7**

The stereochemistry in the reactions mentioned above is consistent with a chelation-controlled addition of the organocerium reagents. On the other hand, nonchelation-controlled addition of alkylcerium reagents to carbonyl components has also been observed, as shown in Scheme 8.[35,36]

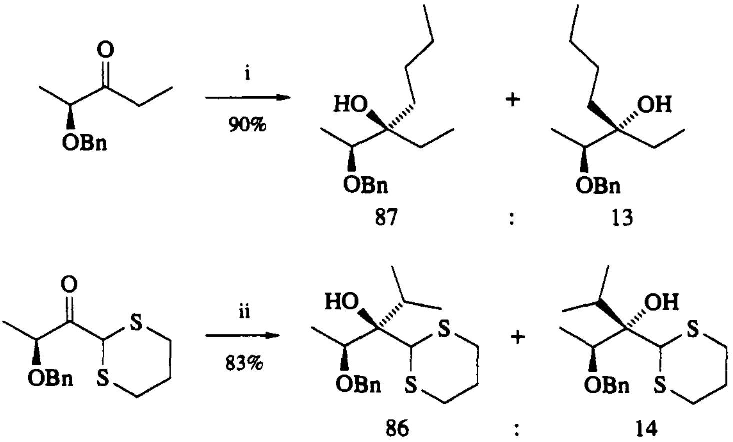
O
OBn
i
90%
HO
OH
87
:
13
ii
83%
S
86
:
14

i, $Bu^nCeCl_2$, THF, −78 °C; ii, $Pr^iCeCl_2$, THF, −78 to −60 °C

**Scheme 8**

Johnson and Tait prepared a trimethylsilylmethylcerium reagent and examined its reaction with carbonyl compounds.[17] The reagent adds to aldehydes and ketones including many readily enolizable ones to afford 2-hydroxysilanes. This modified Peterson reagent gives vastly superior yields in comparison with trimethylsilylmethyllithium. An example is shown in Scheme 9.

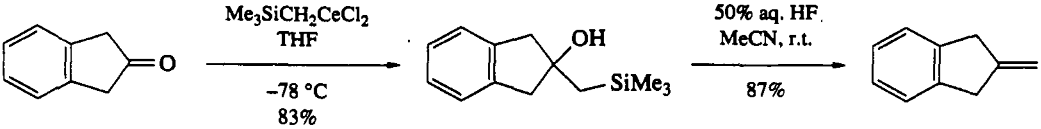
O
$Me_3SiCH_2CeCl_2$
THF
−78 °C
83%
OH
$SiMe_3$
50% aq. HF
MeCN, r.t.
87%

**Scheme 9**

The same reagent reacts with acyl chlorides to afford 1,3-bis(trimethylsilyl)-2-propanol derivatives, which efficiently undergo a trimethylchlorosilane-promoted Peterson reaction to afford allysilanes in high overall yields (equation 5).[37]

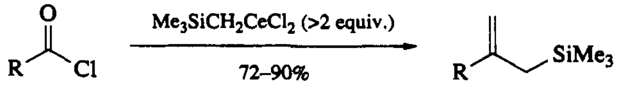 (5)
O
R
Cl
$Me_3SiCH_2CeCl_2$ (>2 equiv.)
72–90%
R
$SiMe_3$

R = n-$C_9H_{19}$, $Ph(CH_2)_2$, PhCH=CH, PhCH=C(Me)

Recently, Mudryk and Cohen have found that reactions of lactones with organocerium reagents provide lactols in good yields, as exemplified in Scheme 10.[38] This reaction leads to an efficient one-pot synthesis of spiroketals, as illustrated in Scheme 11.[38]

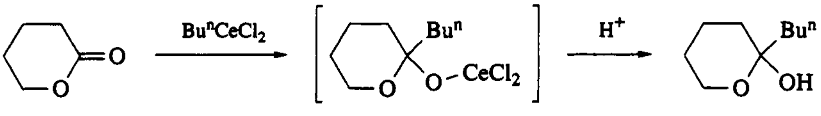

**Scheme 10**

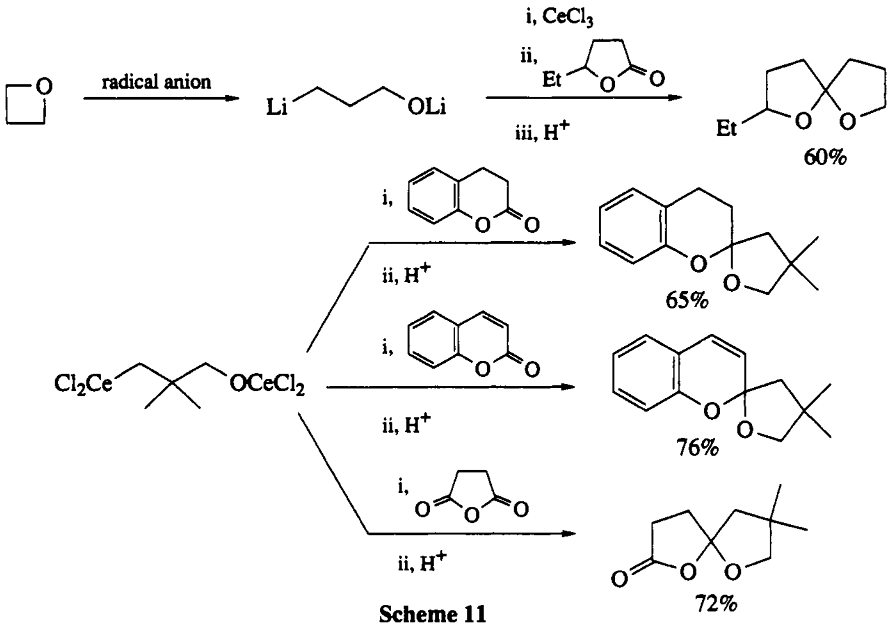

**Scheme 11**

Denmark *et al.* have recently reported that aldehyde SAMP-hydrazones react with various alkylcerium reagents in good yields and with high diastereoselectivities.[31] The method can be applied to the synthesis of optically active primary amines, as exemplified in Scheme 12.

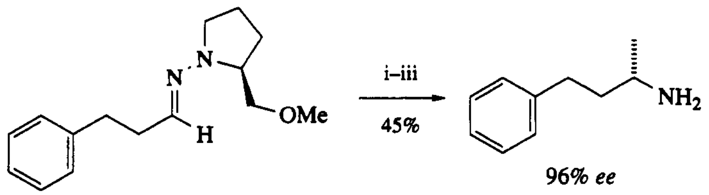

i, $MeCeCl_2$, THF; ii, MeOH; iii, $H_2$ (375 psi = 2.59 MPa), Raney nickel, 60 °C

**Scheme 12**

### 1.8.2.6.2 Allylcerium reagents

Cohen *et al.* have extensively studied the generation and reactivities of allylcerium reagents.[39,40] Allylcerium reagents react with α,β-unsaturated carbonyl compounds in a 1,2-selective fashion. It is particularly noteworthy that unsymmetrical allylcerium reagents react with aldehydes or enals mainly at the least-substituted terminus, as opposed to other allylorganometallics such as allyltitanium reagents. An example is shown in Scheme 13.[39]

Another prominent feature is that the reaction at −78 °C provides (*Z*)-alkenes, while at −40 °C (*E*)-alkenes are formed. Allylcerium reagents have been successfully employed in an economical synthesis of

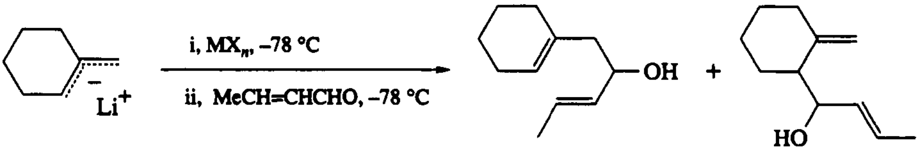
Li+
i, MXn, –78 °C
ii, MeCH=CHCHO, –78 °C
OH
+
HO

$MX_n = CeCl_3$ 82% 95 : 5

$MX_n = Ti(OPr^i)_4$ 90% 10 : 90

**Scheme 13**

some pheromones. Typical examples, which illustrate these characteristic reactivities, are shown in Schemes 14 and 15.[40]

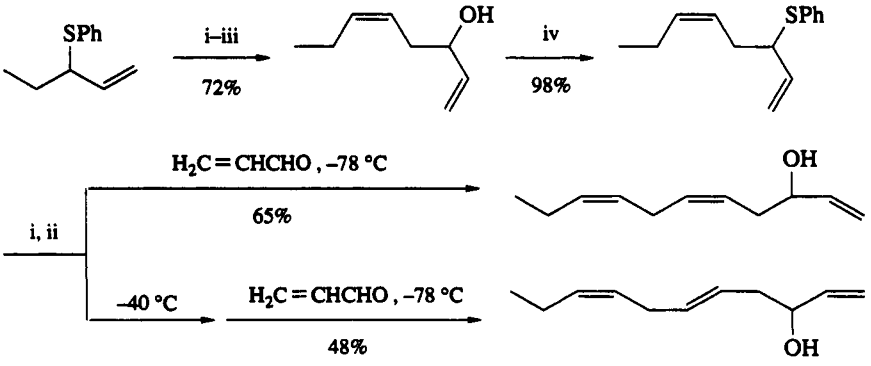
SPh
i–iii
72%
OH
iv
98%
SPh
H2C=CHCHO, –78 °C
65%
OH
i, ii
–40 °C
H2C=CHCHO, –78 °C
48%
OH

i, lithium *p,p'*-di-t-butylbiphenylide (LDBB) or lithium 1-(dimethylamino)naphthalenide (LDMAN), –60 °C; ii, $CeCl_3$, –78 °C; iii, $H_2C{=}CHCHO$; iv, $Bu^n{}_3P/PhSSPh$

**Scheme 14**

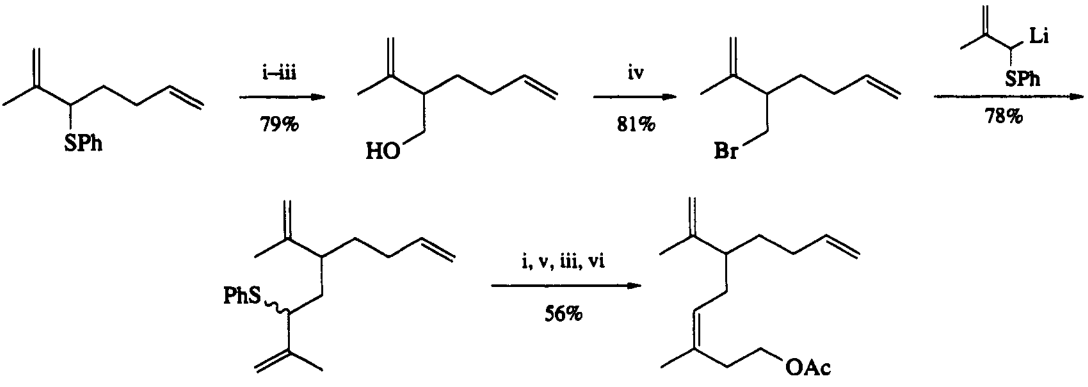
SPh
i–iii
79%
HO
iv
81%
Br
Li
SPh
78%
PhS
i, v, iii, vi
56%
OAc

*(Z)*:*(E)* = 98:2

i, LDBB; ii, $Ti(OPr^i)_4$; iii, $CH_2O$; iv, $Ph_3P/CBr_4$, MeCN; v, $CeCl_3$; vi, $Ac_2O$/pyridine

**Scheme 15**

### *1.8.2.6.3 Alkenyl- and aryl-cerium reagents*

Suzuki *et al.* found that α-trimethylsilylvinylcerium reagents add to readily enolizable β,γ-enones. The method has been employed in the synthesis of (–)-eldanolide, as shown in Scheme 16.[41]

Paquette and his coworkers have employed alkenylcerium reagents in the efficient stereoselective synthesis of polycyclic molecules.[42,43] A typical example is illustrated in Scheme 17. β,γ-Enone (**6**) reacts with alkenylcerium reagent (**7**) with high diastereoselectivity to give adducts (**8**) and (**9**) in a ratio of 95:5. The major product (**8**) undergoes an oxy-Cope rearrangement, creating two chiral centers with high stereoselectivity to furnish (**10**).

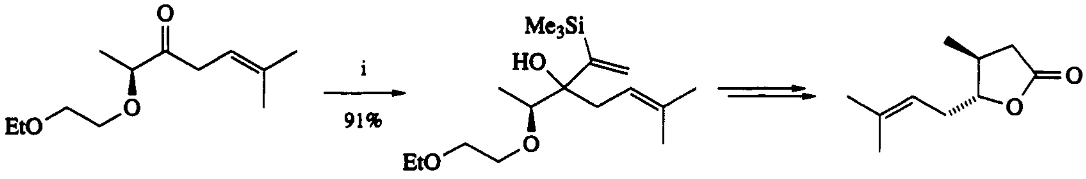

i, $H_2C{=}C(SiMe_3)CeCl_2$, THF–$Et_2O$–hexane (4:1:1), −78 °C, 0.5 h

**Scheme 16**

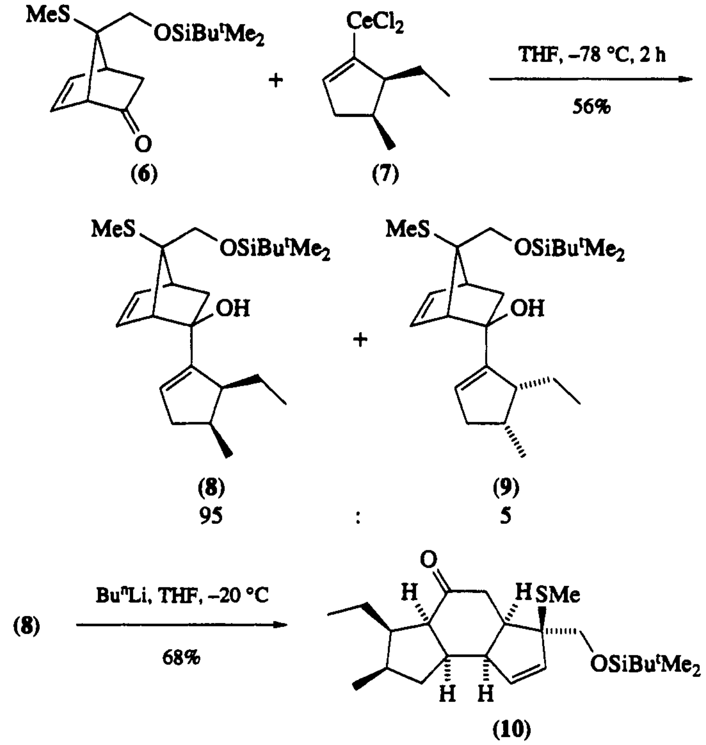

**Scheme 17**

A notably stereoselective reaction of an arylcerium reagent has been reported by Terashima *et al.*[44] As shown in Scheme 18, the cerium reagent provides adducts (**11**) and (**12**) in a ratio of 16:1 in 95% combined yield. In contrast, the organolithium reagent gives a lower and reversed stereoselectivity.

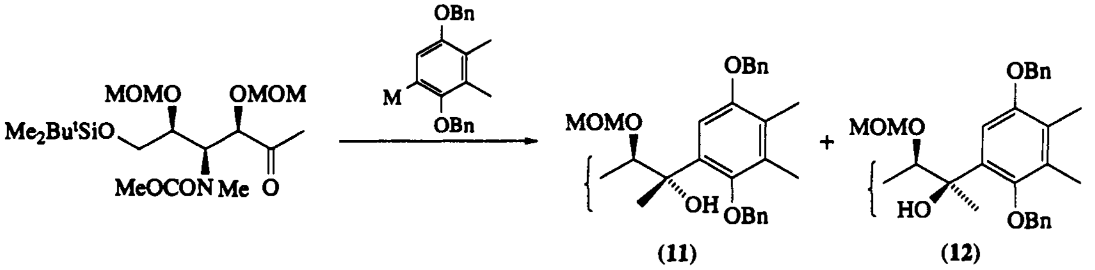

| *M* | *Conditions* | *Yield* (%) | (*11*):(*12*) |
|---|---|---|---|
| $CeCl_2$ | THF, −78 °C | 95 | 94:6 |
| Li | THF, 0 °C | 56 | 12:88 |
| | Ether/THF (4:1), 0 °C | 74 | 11:89 |
| | Ether, 0 °C | 77 | 34:66 |

**Scheme 18**

Recently, a new method for synthesizing coumarin derivatives has exploited the properties of arylcerium reagents, as illustrated in Scheme 19.[45] Interestingly, the bulky arylcerium reagent (**13**) adds to the easily enolizable *t*-butyl acetoacetate in satisfactory yield.

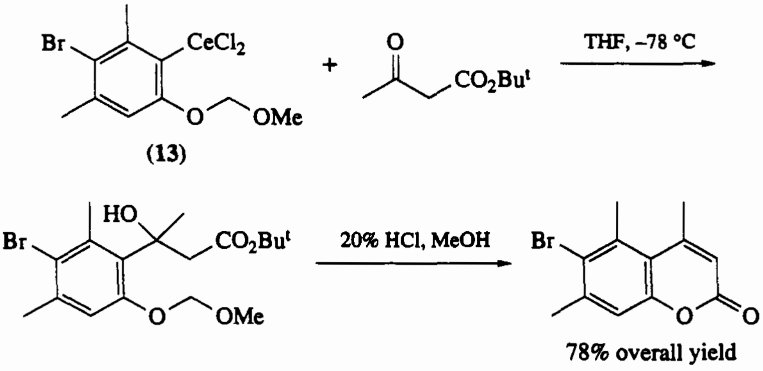
Br
$CeCl_2$
O
OMe
+
O
$CO_2Bu^t$
THF, –78 °C
HO
$CO_2Bu^t$
20% HCl, MeOH
Br
O
O

(**13**)

78% overall yield

**Scheme 19**

An example of the reaction of an alkenylcerium reagent with a cyclopentanone derivative has been reported. As shown in Scheme 20, the (*E*)-cerium reagent adds to the ketone to provide a single adduct in modest yield.[46] However, the (*Z*)-cerium reagent did not react, presumably due to steric effects.

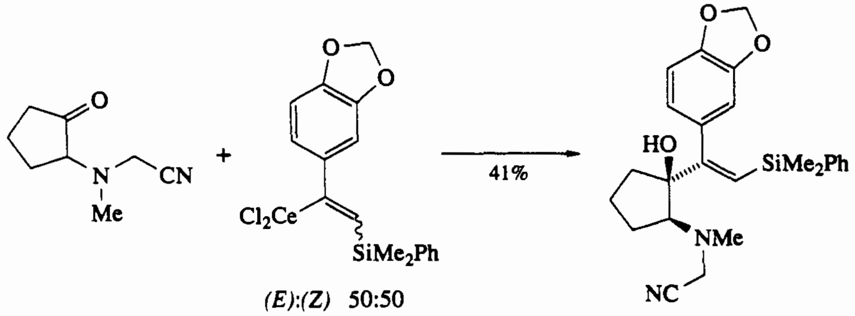
O
N
CN
Me
+
O
O
$Cl_2Ce$
$SiMe_2Ph$
(E):(Z) 50:50
41%
HO
$SiMe_2Ph$
NMe
NC

**Scheme 20**

### 1.8.2.6.4 *Alkynylcerium reagents*

The trimethylsilylethynylcerium reagent, which was initially prepared by Terashima *et al.*, is useful for adding ethynyl groups to carbonyl moieties.[47] This method was successfully employed in the preparation of daunomycinone and related compounds.[47–51] Illustrative examples are shown in Scheme 21.[49]

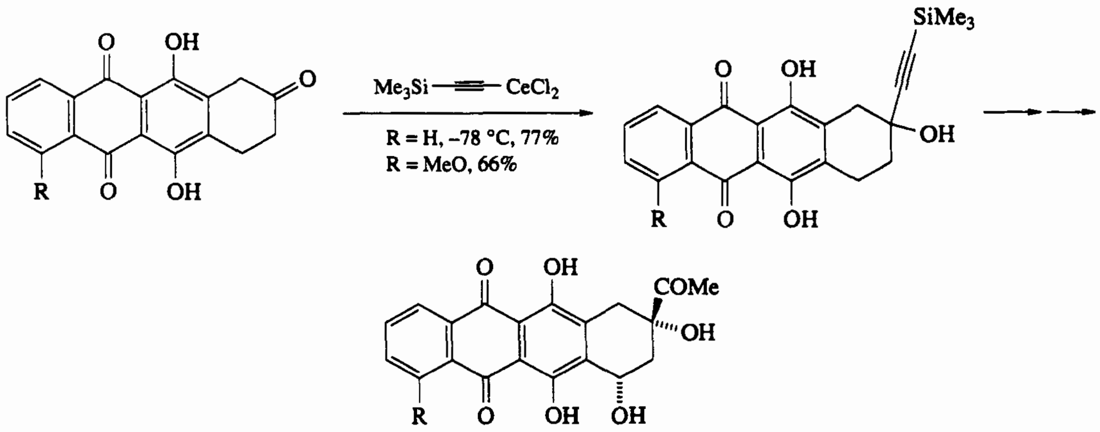
O
OH
O
R
O
OH
$Me_3Si$—≡—$CeCl_2$
R = H, –78 °C, 77%
R = MeO, 66%
$SiMe_3$
OH
COMe
OH
OH

**Scheme 21**

The utility of this reagent has been demonstrated by Tamura *et al.* in its reaction with the readily enolizable ketone (**14**).[52,53] The ethynylation of the ketone proceeds smoothly with the cerium reagent, as shown in Scheme 22; in sharp contrast, the corresponding lithium reagent provides the desired adduct (**15**) in only 11% yield.

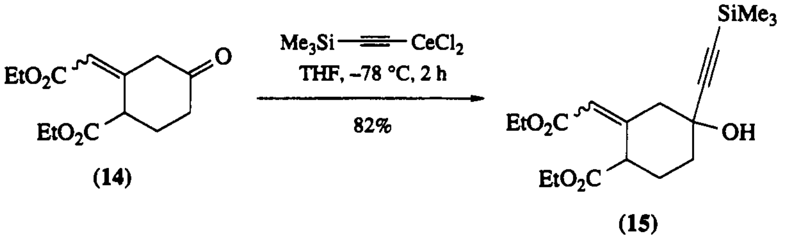

**Scheme 22**

Some other alkynylcerium reagents have been generated and used for the synthesis of alkynyl alcohols and related compounds in good yields.[54–56] An example is illustrated in Scheme 23.

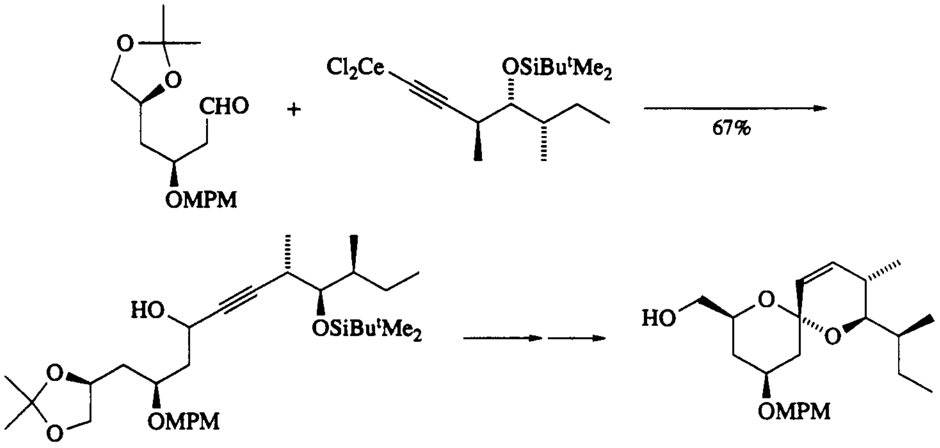

**Scheme 23**

## 1.8.3 CERIUM ENOLATES

Cerium enolates are generated by the reaction of lithium enolates with anhydrous cerium chloride in THF.[57] The cerium enolates react readily with various aldehydes and ketones at –78 °C (Scheme 24). The yields are generally higher than in reactions of lithium enolates. This is presumably due to the relative stabilities of the adducts, that of the cerium reagent being greater by virtue of coordination to the more oxophilic cerium atom. The stereochemistry of the products is almost the same as in the case of lithium enolates, as shown in Table 4. The reaction is assumed to proceed through a six-membered, chair-like transition state, as with lithium enolates.

A synthetic application of this cerium chloride methodology has been reported by Nagasawa *et al.*, as shown in Scheme 25.[58] It is noteworthy that aldol reaction of the cerium enolate proceeds in high yields, even though the acceptor carbonyl group is sterically crowded and is readily enolized by lithium enolates.

Fukuzawa *et al.* found that reduction of α-halo ketones followed by aldol reaction with aldehydes or ketones is promoted by $CeI_3$, $CeCl_3$/NaI or $CeCl_3$/$SnCl_2$.[59,60] These reactions are carried out at room

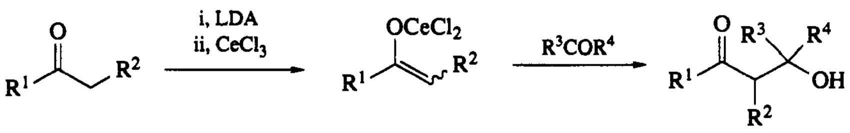

**Scheme 24**

**Table 4**

| *Enolized ketone* | *Acceptor carbonyl compound* | *Reagent* | *Yield (%)* | *Threo:erythro* |
|---|---|---|---|---|
| PhCOCH$_2$Me | MeCOCH$_2$Me | LDA–CeCl$_3$ | 62 | 40:60 |
| | MeCOCH$_2$Me | LDA | 11 | 37:63 |
| 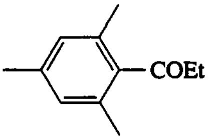 COEt | 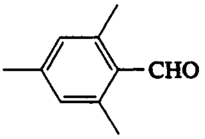 CHO | LDA–CeCl$_3$ | 93 | 20:80 |
| | | LDA | 63 | 20:80 |
| | PhCHO | LDA–CeCl$_3$ | 94 | 91:9 |
| | PhCHO | LDA | 60 | 91:9 |
| | 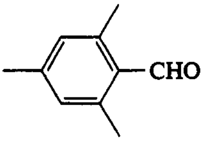 CHO | LDA–CeCl$_3$ | 91 | 93:7 |
| | | LDA | 26 | 88:12 |

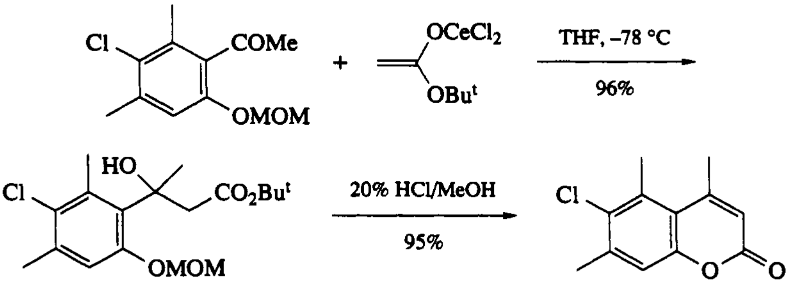
Cl
COMe
OMOM
+
OCeCl2
OBut
THF, –78 °C
96%
HO
CO2But
OMOM
20% HCl/MeOH
95%
O
O

**Scheme 25**

temperature. Use of CeCl$_3$ provides α,β-unsaturated carbonyl compounds, while methods using CeCl$_3$/NaI or CeCl$_3$/SnCl$_2$ afford exclusively β-hydroxy ketones, as shown in Scheme 26.

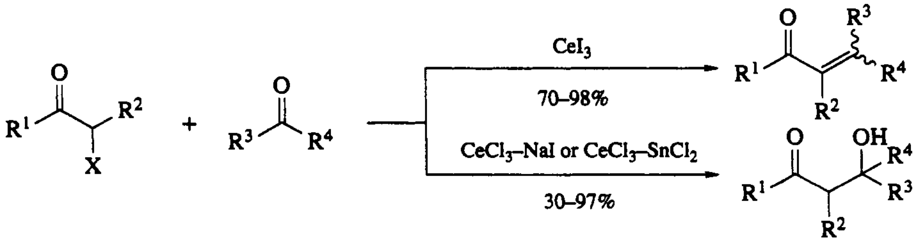
O
R1
R2
X
+
O
R3
R4
CeI3
70–98%
CeCl3–NaI or CeCl3–SnCl2
30–97%
O
R3
R1
R4
R2
O
OH
R4
R1
R3
R2

**Scheme 26**

## 1.8.4 GRIGNARD REAGENT/CERIUM CHLORIDE SYSTEMS

The addition of Grignard reagents to C—X π-bonds is undoubtedly one of the most fundamental and versatile reactions in synthetic organic chemistry. Nevertheless, it is also well recognized that these reactions are often accompanied by undesirable side reactions such as enolization, reduction, condensation, conjugate addition and pinacol coupling. In some cases, such abnormal reactions prevail over the 'normal addition reaction', resulting in poor yields of the desired products.

**Table 5** Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride or with Grignard Reagents Alone[a]

| *Carbonyl compound* | *Reagent* | *Method* | *Product(s)* | *Yield (%)* |
|---|---|---|---|---|
| $Et_3CCOMe$ | $MeMgBr/CeCl_3$ | A | $Et_3CC(OH)Me_2$ | 95 |
| $Et_3CCOMe$ | MeMgBr | | $Et_3CC(OH)Me_2$ | 0 |
| 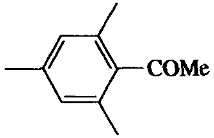 | $MeMgBr/CeCl_3$ | A | 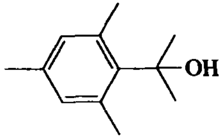 | 47 |
| | MeMgBr | | | Trace |
| 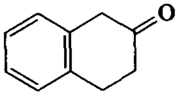 | $EtMgCl/CeCl_3$ | A | 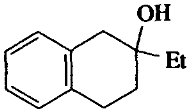 | 76 |
| | EtMgCl | | | 8 |
| 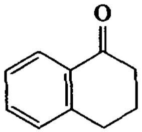 | $Pr^iMgCl/CeCl_3$ | A | 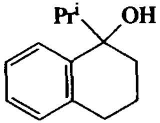 | 73 |
| | $Pr^iMgCl$ | | | 15 |
| PhCOMe | 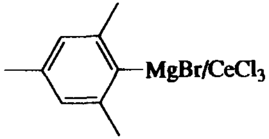 | A | 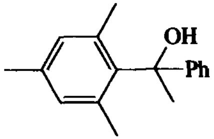 | 73 |
| | 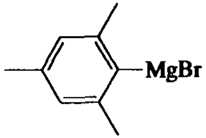 | | | 5 |

**Table 5** *(continued)*

| *Carbonyl compound* | *Reagent* | *Method* | *Product(s)* | *Yield (%)* |
|---|---|---|---|---|
| 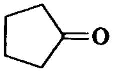 | Pr$^i$MgCl/CeCl$_3$ | B | 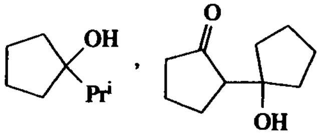 | 3, 80 |
| | Pr$^i$MgCl | | | 72, Trace |
| 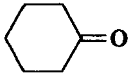 | Pr$^i$MgCl/CeCl$_3$ | B | 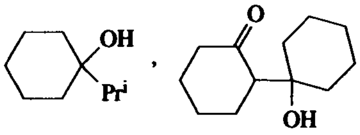 | 80, 0 |
| | Pr$^i$MgCl | | | 30, 35 |
| Pr$^i_2$CO | Pr$^i$MgCl/CeCl$_3$ | A | Pr$^i_3$COH, Pr$^i_2$CHOH | 52, 31 |
| Pr$^i_2$CO | Pr$^i$MgCl | | Pr$^i_3$COH, Pr$^i_2$CHOH | 3, 58 |
| 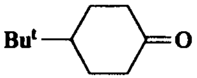 | Bu$^t$MgCl/CeCl$_3$ | A | 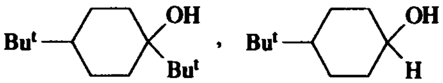 | 89, 10 |
| | Bu$^t$MgCl | | | 38, 40 |
| 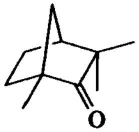 | Me$_2$C=CH(CH$_2$)$_2$MgBr/CeCl$_3$ | B$^b$ | 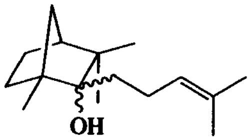 | 72 |
| | Me$_2$C=CH(CH$_2$)$_2$MgBr | | | 0 |
| PhCOCH$_2$Br | H$_2$C=CHMgBr/CeCl$_3$ | A | PhC(OH)(CH$_2$Br)CH=CH$_2$ | 95 |
| PhCOCH$_2$Br | H$_2$C=CHMgBr | | PhC(OH)(CH$_2$Br)CH=CH$_2$ | 66 |
| PhCH=CHCOPh | PhMgBr/CeCl$_3$ | A | PhCH=CHC(OH)Ph$_2$, Ph$_2$CHCH$_2$COPh | 58, 33 |
| PhCH=CHCOPh | PhMgBr/CeCl$_3$ | A$^c$ | PhCH=CHC(OH)Ph$_2$, Ph$_2$CHCH$_2$COPh | 89, 11 |
| PhCH=CHCOPh | PhMgBr/CeCl$_3$ | B$^c$ | PhCH=CHC(OH)Ph$_2$, Ph$_2$CHCH$_2$COPh | 88, 9 |
| PhCH=CHCOPh | MeMgBr/CeCl$_3$ | A | PhCH=CHC(OH)MePh, PhMeCHCH$_2$COPh | 92, 6 |
| PhCH=CHCOPh | MeMgBr | | PhCH=CHC(OH)MePh, PhMeCHCH$_2$COPh | 52, 41 |
| *(Z)*-PhCH=CHCOPh | PhMgBr/CeCl$_3$ | A | PhCH=CHC(OH)Ph$_2$$^d$, Ph$_2$CHCH$_2$COPh | 67, 19 |
| *(Z)*-PhCH=CHCOPh | PhMgBr | | PhCH=CHC(OH)Ph$_2$$^e$, Ph$_2$CHCH$_2$COPh | 15, 83 |

Table 5 *(continued)*

| *Carbonyl compound* | *Reagent* | *Method* | *Product(s)* | *Yield (%)* |
|---|---|---|---|---|
| 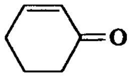 | $Pr^iMgCl/CeCl_3$<br>$Pr^iMgCl$ | A | 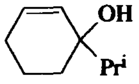 , 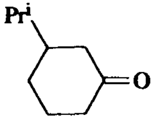 | 91, 5<br>12, 53 |
| $PhCH_2CO_2Me$ | $Pr^iMgCl/CeCl_3$ | A | $PhCH_2C(OH)Pr^i_2$ | 97 |
| $PhCH_2CO_2Me$ | $Pr^iMgCl$ | | $PhCH_2C(OH)Pr^i_2$ | 0 |
| $PhCH{=}CHCO_2Et$ | $H_2C{=}CHMgBr/CeCl_3$ | B | $PhCH{=}CHC(OH)(CH{=}CH_2)_2$, $PhCH{=}CHCO(CH_2)_2CH{=}CH_2$ | 68, 9 |
| $PhCH{=}CHCO_2Et$ | $H_2C{=}CHMgBr$ | | $PhCH{=}CHC(OH)(CH{=}CH_2)_2$, $PhCH{=}CHCO(CH_2)_2CH{=}CH_2$ | 24, 39 |
| $PhCH_2CONMe_2$ | $Bu^nMgBr/CeCl_3$ | B[f] | $PhCH_2COBu^n$ | 66 |
| $PhCH_2CONMe_2$ | $Bu^nMgBr$ | | $PhCH_2COBu^n$ | 8 |

[a] All reactions are carried out in THF at 0 °C with a molar ratio of 1:1.5:1.5 (carbonyl compound:Grignard reagent:$CeCl_3$) unless otherwise stated. [b] Molar ratio 1:2:3 (carbonyl compound:Grignard reagent:$CeCl_3$). [c] Molar ratio 1:1.5:2.5 (carbonyl compound:Grignard reagent:$CeCl_3$). [d] (*Z*):(*E*) = 91:9. [e] (*Z*):(*E*) = 60:40. [f] Molar ratio 1:3:3 (amide:Grignard reagent:$CeCl_3$).

It has been found that use of cerium chloride as an additive effectively suppresses abnormal reactions, resulting in the formation of normal addition products in significantly improved yields.[61,62] The reactions are usually carried out by one of the following two methods.

(i) The Grignard reagent is added to the suspension of cerium chloride in THF at 0 °C, the mixture is stirred well for 1–2 h at the same temperature and finally the substrate is added (method A). As vinylic Grignard reagents decompose rapidly on treatment with cerium chloride at 0 °C, reactions using these reagents should be carried out at a lower temperature.

(ii) The Grignard reagent is added at 0 °C to the mixture of substrate and cerium chloride in THF that has previously been stirred well for 1 h at room temperature (method B).

Representative examples of the reactions of various carbonyl compounds with Grignard reagents under these conditions are listed in Table 5.[62] It is emphasized that enolization, aldol reaction, ester condensation, reduction and 1,4-addition are remarkably suppressed by the use of cerium chloride. Various tertiary alcohols, which are difficult to prepare by the conventional Grignard reaction, can be synthesized by this method.

The Grignard reagent/cerium chloride system has been applied to practical organic syntheses.[63–69] A typical example is shown in Scheme 27.[63] In sharp contrast to the reaction in the presence of cerium chloride, the Grignard reagent alone affords only a 2% yield of the adduct.

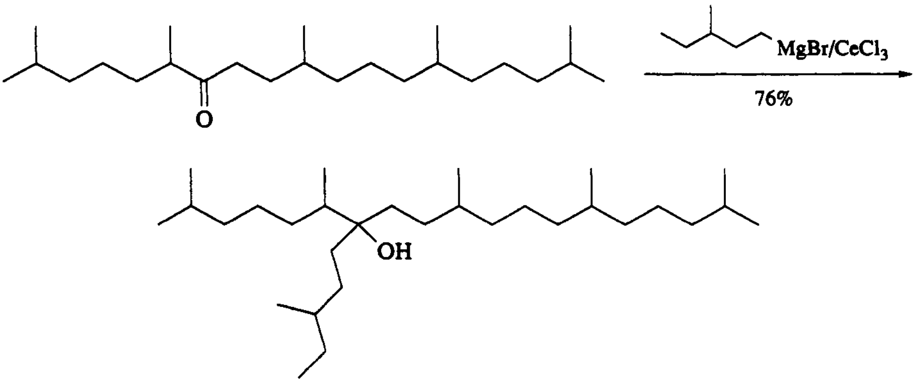

Scheme 27

Recently this method has been successfully applied to the preparation of substituted allylsilanes from esters. A variety of allylsilanes with other functional groups have been synthesized in good yields, as shown in Scheme 28.[70,71]

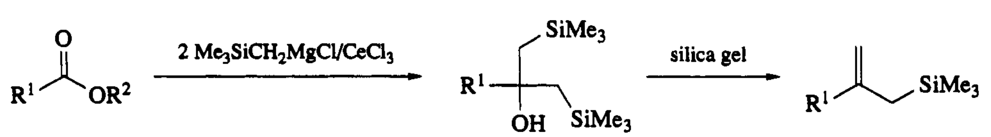

$R^1 = Me_3SiCH_2, Cl(CH_2)_n$ ($n = 1, 3$), $(MeO)_2CH(CH_2)_n$ ($n = 0, 1, 3, 4$), PhCH=CH, *etc.*; $R^2$ = Me or Et

Scheme 28

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# 1.9

# Samarium and Ytterbium Reagents

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## 1.9.1 INTRODUCTION

In contrast to more traditional organometallic nucleophiles, the application of samarium and ytterbium reagents to selective organic synthesis has a relatively brief history. Early studies of lanthanide reagents simply sought to develop reactivity patterns mimicking those of more established organolithium or Grignard reagents. However, as the complexity of organic molecules requiring synthesis increased, demands for more highly selective reagents heightened accordingly. Consequently, the search for reagents which would complement those of the traditional organometallic nucleophiles brought more serious attention to the lanthanides, and an explosive expansion in the application of lanthanide reagents to organic synthesis began. This growth is perhaps best reflected by the publication of a number of excellent review articles.[1] In addition, quite thorough surveys on the synthetic and structural aspects of organolanthanide chemistry have appeared.[2] This chapter concentrates on applications of samarium and ytterbium reagents in selective organic synthesis, and specifically their employment in C—X π-bond addition reactions. Emphasis is placed on transformations that are unique to the lanthanides, and on processes that complement existing synthetic methods utilizing more traditional organometallic reagents. Since additions to C—X π-bonds comprise one of the most essential aspects of carbon–carbon bond formation, fundamental contributions made in this area are by definition of substantial importance to the art of organic synthesis.

The perception that lanthanide metals were rare and therefore inaccessible or expensive was a contributing factor to their long-lasting neglect and slow development as useful synthetic tools. In fact, 'rare earths' in general are relatively plentiful in terms of their abundance in the earth's crust. Samarium and ytterbium occur in proportions nearly equal to those of boron and tin, for example.[3] Modern separation methods have made virtually all of the lanthanides readily available in pure form at reasonable cost.

Unlike many of their main group and transition metal counterparts, inorganic lanthanide compounds are generally classified as nontoxic when introduced orally.[4] In fact, samarium chloride and ytterbium chloride exhibit similar toxicity to that of sodium chloride ($LD_{50}$ of >2000–6700 mg $kg^{-1}$ in mice *versus* 4000 mg $kg^{-1}$ for NaCl). Although toxicity may obviously vary to some extent based on the ligands attached to the metal, in most cases lanthanide complexes are converted to hydroxides immediately on ingestion, and thus have limited absorption through the digestive tract. Moderate toxicity is exhibited by lanthanide salts introduced *via* the intraperitoneal route.

The +3 oxidation state is the most stable oxidation state for both samarium and ytterbium. The +2 oxidation state of ytterbium ($f^{14}$), and samarium ($f^{6}$) is also of great importance with regard to applications in organic synthesis. As expected on the basis of its electronic configuration, $Yb^{2+}$ is the more stable of these two dipositive species, and $Sm^{2+}$ is a powerful one-electron reducing agent ($Sm^{2+}/Sm^{3+} = -1.55$ V, $Yb^{2+}/Yb^{3+} = -1.15$ V). The utility of $Sm^{2+}$ as a reductant in organic synthesis is discussed in detail below, and various aspects of its chemistry have been previously reviewed as well.[1] The type of two-electron redox chemistry on a single metal center, typical of several transition elements, is not observed in lanthanides.

It is the special combination of inherent physical and chemical properties of the lanthanides that sets them apart from all other elements, and provides a unique niche for these elements and their derivatives in selective organic synthesis. The lanthanides as a group are quite electropositive (electronegativities of samarium and ytterbium are 1.07 and 1.06, respectively, on the Allred–Rochow scale[3]) and the chemistry of these elements is predominantly ionic. This is because the 4*f*-electrons do not have significant radial extension beyond the filled $5s^{2}5p^{6}$ orbitals of the xenon inert gas core.[2b] The lanthanides therefore behave as closed-shell inert gasses with a tripositive charge, and in general electrostatic and steric interactions play a greater role in the chemistry of the lanthanides than do interactions between the metal and associated ligand orbitals.[2b,5]

The *f*-orbitals do play a bonding role in complexes in which the coordination number is higher than nine. Compared with transition metals, the ionic radii of the lanthanides are large.[3] Most transition metal ionic radii lie in the range from 0.6 to 1.0 Å, whereas the lanthanides have an average ionic radius of approximately 1.2 Å. Divalent species are, of course, even larger; eight-coordinate $Sm^{2+}$ has an ionic radius of 1.41 Å, for example. The relatively large ionic radii of the lanthanides allow the accommodation of up to 12 ligands in the coordination sphere, and coordination numbers of seven, eight and nine are common. Owing to the well-known 'lanthanide contraction', ionic radii decrease steadily across the row of lanthanides in the periodic table; eight-coordinate $Sm^{3+}$ has an ionic radius of 1.219 Å, whereas the ionic radius of eight-coordinate $Yb^{3+}$ is only 1.125 Å.[3] The lanthanide contraction is a consequence of poor shielding of the 4*f*-electrons, resulting in an increase in effective nuclear charge and a concomitant decrease in ionic radius. As expected, higher coordination numbers are most common in the larger, early lanthanides.

According to the concept of hard and soft acids and bases (HSAB) established by Pearson,[6] lanthanide +3 ions are considered to be hard acids, falling between $Mg^{2+}$ and $Ti^{4+}$ in the established scale. Lanthanides therefore complex preferentially to hard bases such as oxygen donor ligands.

The strong affinity of lanthanides for oxygen is further evidenced by the bond dissociation energies ($D°_0$) for the gas phase dissociation of diatomic lanthanide oxides (LnO).[7] Although they are among the lowest values for the lanthanides, both SmO (136 kcal $mol^{-1}$; 1 cal = 4.18J) and YbO (95 kcal $mol^{-1}$) exhibit values significantly higher than that for MgO (86.6 kcal $mol^{-1}$). This demonstrated oxophilicity (strong metal–oxygen bonds and hard Lewis acid character) has been used to great advantage in organic synthesis. As described below, these properties have been exploited extensively to enhance carbonyl substrate reactivity, and also to control stereochemistry in carbonyl addition reactions through chelation.

## 1.9.2 SAMARIUM REAGENTS

Surprisingly few organosamarium reagents have been synthesized and exploited for their utility in selective organic synthesis. However, examples of both organosamarium(III) and organosamarium(II) reagents are known, and provide some insight into potentially useful areas of further study. By far the most extensive work thus far has been carried out on use of samarium(II) species as reductants and reductive coupling agents in organic synthesis. Applications of all three of these types of reagents to C—X π-bond additions are discussed below.

### 1.9.2.1 Organosamarium(III) Reagents

Organosamarium(III) dihalides are typically generated by a simple transmetalation reaction involving $SmCl_3$ or $SmI_3$ and 1 equiv. of an organolithium or Grignard reagent. Unfortunately, little characterization of such reactions has been performed. As a consequence, limited information is available on the structure of these molecules or the exact nature of the reactive species in such mixtures. While they have been denoted as simple monomeric σ-bonded species ('$RSmX_2$'), certainly other compositions (*e.g.* 'ate' complexes or species resulting from Schlenk-type equilibria) cannot be excluded.

Reagents prepared in this fashion have been demonstrated to undergo facile carbonyl addition reactions. Two promising features of these reactions have emerged. The first is that modest selectivity in reactions of aldehydes over that of ketones can be achieved (equation 1).[8] The second, and perhaps more exciting, development is the efficient reaction of organosamarium(III) reagents with highly enolizable ketones (equation 2).[9] Good yields of 1,2-addition products can be obtained from ketone substrates that produce less than 35% of carbonyl addition product on reaction with organolithium reagents alone. Rigorously anhydrous samarium salts must be used in order to achieve high yields of the alcohols. This carbonyl addition process with enolizable ketones takes advantage of the attenuated basicity of organosamarium reagents as compared to that of their organolithium counterparts, as well as the amplified Lewis acidity of the $Sm^{3+}$ ion. The combination of these factors apparently minimizes enolization of the carbonyl substrate, while at the same time enhancing nucleophilic addition. Although only a limited study of this phenomenon has been carried out to this point, the process rivals that of organocerium reagents (Volume 1, Chapter 1.8), and certainly the results bode well for future exploration.

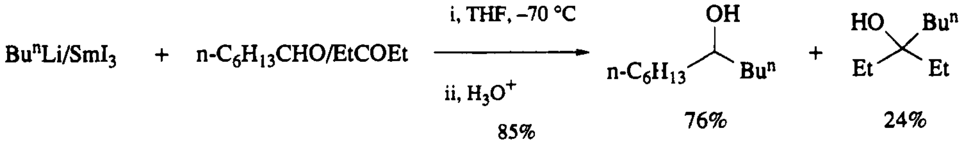

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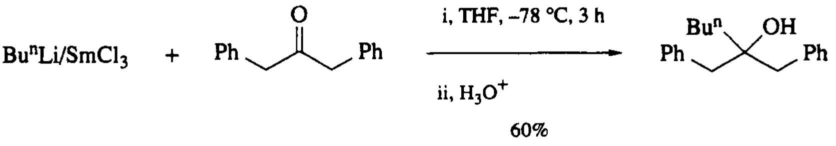

(2)

Reaction of benzylic halides with 2 equiv. of dicyclopentadienylsamarium reportedly generates a benzylsamarium(III) species along with dicyclopentadienylsamarium halide (equation 3).[10] Benzylsamariums undergo carbonyl addition with a variety of aldehydes and ketones, providing high yields of the corresponding alcohols (equation 4).[10,11] These complexes also react with carboxylic acid chlorides, providing modest yields of ketones and minor amounts of dibenzylated tertiary alcohol by-products (equation 5).[10,11]

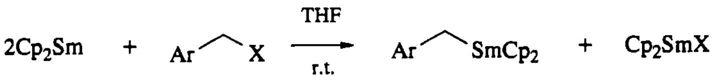

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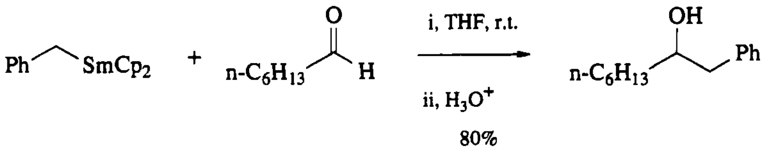

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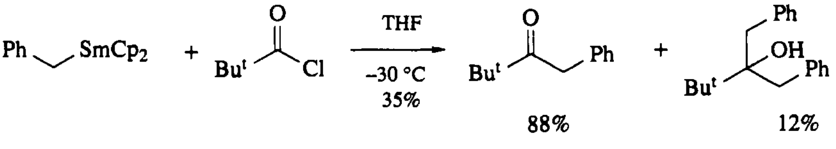

(5)

The preparation and reactivity of organosamarium 'ate' complexes have also been described.[12] By addition of methyllithium to samarium trichloride in $Et_2O$ in the presence of TMEDA, $[Li(TMEDA)]_3[Sm(Me)_6]$ can be isolated in 48% yield as a crystalline solid. This complex is extremely sensitive toward air and moisture, and yet has been fully characterized. Preliminary studies indicate that it provides good selectivity for 1,2-carbonyl addition in reactions with several unsaturated aldehydes and ketones (equation 6). Unoptimized yields in all cases exceed 80%. Chemoselectivity has also been briefly studied with somewhat less impressive results. Reaction of the 'ate' complex with a 1:1 mixture of benzalacetone and cinnamaldehyde demonstrated that addition to the aldehyde was favored by a ratio of only 1.5:1 to 2:1.

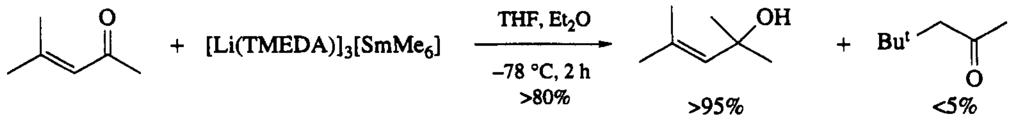

(6)

These preliminary results indicate that substantial promise holds for the further development of organosamarium(III) reagents. The synthesis and characterization of new organosamarium complexes, and application of these reagents to selective synthetic transformations awaits more extensive exploration.

### 1.9.2.2 Organosamarium(II) Reagents

Like the organosamarium(III) reagents discussed in Section 1.9.2.1, few organosamarium(II) reagents have been satisfactorily characterized. In many respects, however, the known chemistry of these reagents mimics that of organomagnesium halides. For example, the preparation of organosamarium(II) halides is apparently best carried out by reaction of samarium metal with organic halides (equation 7).[13] This procedure generates a mixture of divalent and trivalent organosamarium species as determined by magnetic susceptibility measurements and a variety of other analytical methods. Solutions of these reagents exhibit reactivity with ketones that is very similar to that of the corresponding Grignard reagents (equation 8).

$$\text{Sm} + \text{PhI} \xrightarrow[-30\ ^\circ\text{C}]{\text{THF}} \text{'PhSmI'} \qquad (7)$$

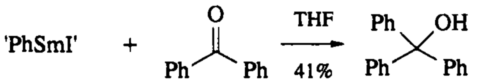

(8)

Reactions of organosamarium(II) halides with aldehydes are somewhat more complicated and synthetically less useful than those with ketones. The ability of $Sm^{2+}$ species to serve as strong reducing agents introduces a number of alternative reaction pathways.[14] For example, reaction of 'EtSmI' with benzaldehyde provides a mixture of benzyl alcohol, benzoin, hydrobenzoin, and benzyl benzoate in low yields. The first three products presumably arise from benzaldehyde ketyl, generated by single-electron transfer from the $Sm^{2+}$ reagent to benzaldehyde. The benzyl benzoate apparently is derived from a Tischenko-type condensation reaction between a samarium alkoxide species and benzaldehyde.[14b]

The intermediate generated by the reaction of samarium metal with methyl β-bromopropionate has found a useful niche in selective synthesis. This reagent, when treated with acetophenone, generates a γ-lactone directly in yields of about 70% (equation 9).[15] Although a significant amount (20%) of pinacol product from the ketone is also generated in this process, the method does provide a useful alternative to the use of other β-metallo ester nucleophiles. Similar processes using zinc or magnesium in place of samarium provide the γ-lactones in yields of less than 30%, with unreacted starting material the predominant substance isolated. A samarium(II) ester homoenolate is postulated as the reaction intermediate in this transformation. Several other lanthanide metals (*e.g.* cerium, lanthanum and neodymium) have been found to work equally well in this transformation.

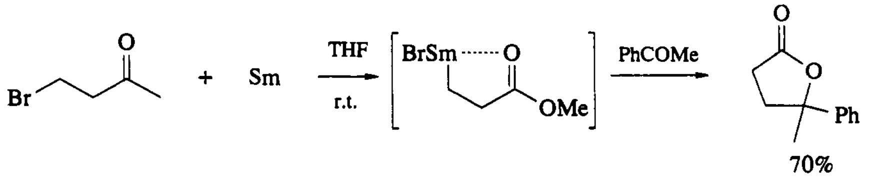

(9)

### 1.9.2.3 Reactions Promoted by Samarium Diiodide and Dicyclopentadienylsamarium

Although organosamarium reagents have made little impact thus far in selective organic synthesis, the emergence of low-valent samarium reagents as reductive coupling agents has had a major influence on the field of C—X π-bond addition reactions. The disclosure of a convenient procedure for generation of samarium diiodide ($SmI_2$) and subsequent development of this reagent by Kagan and his coworkers precipitated explosive growth in the application of this reductant in organic synthesis. Simple functional group reductions as well as a host of reductive coupling reactions have since been investigated. In these processes, $SmI_2$ demonstrates reactivity and selectivity patterns which nicely complement reductants such as zinc, magnesium and other low-valent metal reductants. In addition to the advantages $SmI_2$ provides as a THF-soluble reductant, the $Sm^{3+}$ ion generated as a result of electron transfer can serve as a template to control stereochemistry through chelation in C—X π-bond addition reactions. It has thus become the reagent of choice for numerous synthetic transformations.

Samarium diiodide is very conveniently prepared by oxidation of samarium metal with organic dihalides[16] or with iodine (equations 10–12).[17] Deep blue solutions of $SmI_2$ (0.1 M in THF) are generated in virtually quantitative yields by these processes. This salt can be stored as a solution in THF for long periods when it is kept over a small amount of samarium metal. Tetrahydrofuran solutions of $SmI_2$ are commercially available as well. If desired, the solvent may be removed to provide $SmI_2{\cdot}(THF)_n$ as a powder. For synthetic purposes, $SmI_2$ is typically generated and utilized *in situ*.

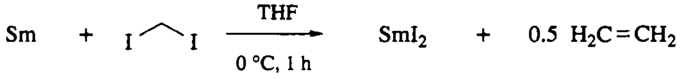
(10)

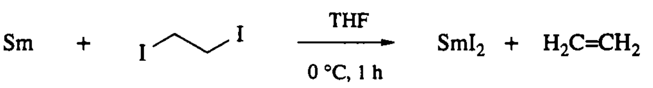
(11)

$$Sm + I_2 \xrightarrow[65\ °C,\ 16\ h]{THF} SmI_2 \qquad (12)$$

Other ether solvents (*e.g.* $Et_2O$, DME) are ineffective for the preparation of $SmI_2$, and samarium(II) salts such as $SmBr_2$ are only slowly generated by procedures analogous to those utilized for preparation of $SmI_2$. Furthermore, $SmBr_2$ is not nearly as soluble in THF as is $SmI_2$. With the exception of studies on dicyclopentadienylsamarium (*vide infra*), little effort has been made in exploring other potential samarium(II) reducing salts.

Samarium diiodide has been characterized in solution by absorption spectroscopy, magnetic susceptibility measurements, titrations of lanthanide ions with EDTA, potentiometric titrations of iodide ion, and acidometric titration and reaction of iodine, which measures the reductive capability of the solutions.[16b,c] All of these analyses are consistent with a species possessing the stoichiometry '$SmI_2$'. However, little is known of the degree of aggregation or solution structure of this reagent. Crystal structure determinations of $SmI_2(NCBu^t)_2$ and $SmI_2[O(CH_2CH_2OMe)_2]_2$ have been performed.[18] The former is an infinite chain of $SmI_2(NCBu^t)_2$ with bridging iodides. The geometry about the samarium ion in this complex is a distorted octahedron. The diglyme complex is monomeric in the solid state; the geometry about the octacoordinate samarium ion is best described as a distorted hexagonal bipyramid.

Dicyclopentadienylsamarium ($Cp_2Sm$) is readily prepared by reaction of $SmI_2$ with dicyclopentadienyl sodium.[19] It is a red powder that can be stored for days at a time under an inert atmosphere without any apparent decomposition. Although it has limited solubility in most organic solvents, $Cp_2Sm$ is emerging as a useful reductant. It appears to have reduction capabilities even greater than those of $SmI_2$.

Both $SmI_2$ and $Cp_2Sm$ have unique characteristics which lend themselves to selective organic synthesis, and their application to a variety of problems in formal C—X π-bond addition reactions is outlined below.

#### *1.9.2.3.1 Barbier-type reactions*

As a homogeneous reductant, $SmI_2$ provides many advantages over more traditional reagents such as magnesium or lithium in Barbier-type syntheses. Both intermolecular and intramolecular variants of the Barbier reaction utilizing $SmI_2$ are finding important uses in the synthesis of complex organic molecules.

Samarium diiodide has been utilized successfully to promote intermolecular Barbier-type reactions between ketones and a variety of organic halides and other substrates.[16c] Allylic and benzylic halides (chlorides, bromides and iodides) react with ketones within a few minutes at room temperature in THF when treated with 2 equiv. of $SmI_2$ (equation 13). Unsymmetrical allylic halides provide mixtures of regioisomers in these coupling reactions. Diallylated (or dibenzylated) tertiary alcohols result from $SmI_2$-promoted reactions of allylic iodides or benzyl bromide with carboxylic acid halides (equation 14).[20] In some instances, homocoupling of the organic halide or carboxylic acid halide effectively competes with the desired cross-coupling reaction.

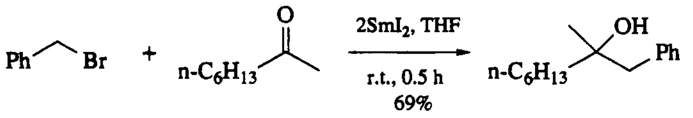

(13)

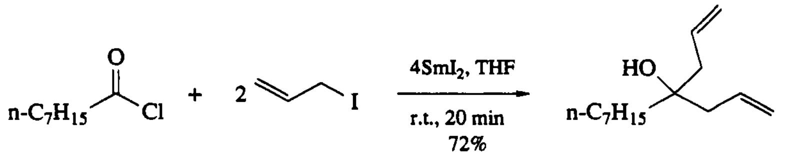

(14)

Allylic halides are not as readily accessible as allylic alcohols or their ester derivatives. Thus, the requirement that allylic halides must be used as precursors for carbonyl addition reactions in conjunction with magnesium and other similar reductants is a severe restriction limiting the convenience of these routes to homoallylic alcohols. In this regard, samarium diiodide can be used to great advantage, because substrates other than allylic halides are suitable precursors for such transformations. For example, allylic phosphate esters have been reported to couple with carbonyl substrates in the presence of $SmI_2$ (equation 15).[21] Since esters and nitriles are unreactive under these conditions, the $SmI_2$-mediated process is likely to be more chemoselective than those promoted by magnesium or lithium.

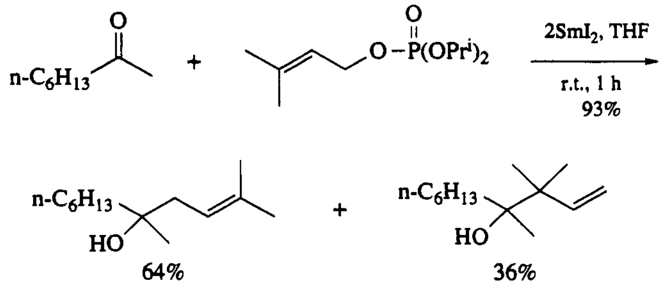

(15)

Curiously, the geometry about the allylic double bond is retained in these reactions (as demonstrated by stereospecific reactions with neryl phosphate and geranyl phosphate), even though the coupling lacks regioselectivity (*i.e.* homoallylic alcohols are isolated as mixtures of products in which coupling has occurred at the α- and γ-positions of the allylic phosphates). The procedure also lacks stereoselectivity; reactions of substituted allylic phosphates with prochiral aldehydes and ketones provide mixtures of diastereomers. The process has other limitations; although alkyl ketones couple nicely utilizing this procedure, aryl ketones and aldehydes provide significant amounts (50–85%) of pinacol by-products. This is a result of the reducing capabilities of $SmI_2$. Furthermore, α,β-unsaturated aldehydes and ketones provide complex mixtures of products.

Allylic acetates can also be utilized as substrates in $SmI_2$-mediated carbonyl addition reactions, but only when these reactions are performed in the presence of palladium catalysts.[22] No reaction occurs in the absence of the palladium catalyst, and a π-allylpalladium species is undoubtedly a key intermediate. Once generated, the π-allylpalladium probably undergoes oxidative–reductive transmetalation with $SmI_2$, generating an allylsamarium species. The latter reacts with the aldehyde or ketone, providing the observed products (Scheme 1). Significantly, palladium(II) salts can also be utilized in the reaction, indicating that $SmI_2$ produces a palladium(0) species *in situ* which is capable of entering the catalytic cycle. In these reactions, there is a type of synergism between the palladium(0) catalyst and $SmI_2$; the latter serves as the stoichiometric reductant in the process, while the palladium catalyst functions as an activator for the relatively unreactive allylic acetate. Samarium diiodide regenerates the catalyst, and brings about a charge inversion in the process by converting the electrophilic π-allylpalladium species to a nucleophilic allylsamarium.

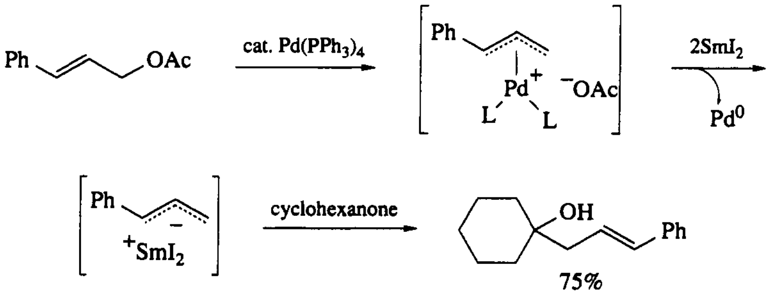

**Scheme 1**

In most cases, carbon–carbon bond formation occurs at the least substituted terminus of the allylic unit. A wide range of aldehydes and ketones can be utilized in the reaction, and one cyclization process has been reported (equation 16). Aromatic and α,β-unsaturated substrates cannot be used owing to competitive pinacolic coupling reactions promoted by $SmI_2$.

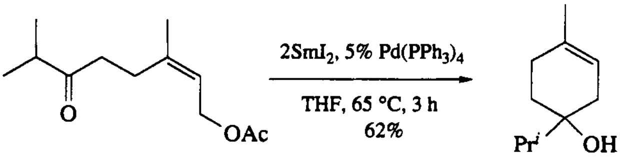

(16)

Propargylic acetates undergo analogous reactions with ketones.[23] Aldehydes can be utilized only with highly reactive propargylic acetates, again due to competitive pinacolic coupling. Primary propargylic acetates produce mixtures of allenic and homopropargylic alcohols, whereas most secondary and all tertiary propargylic carboxylates provide exclusively the allenic alcohols (equation 17). Although other transition metal salts, *e.g.* palladium(II), nickel(II) and cobalt(II), can be utilized as catalysts, lower yields are obtained.

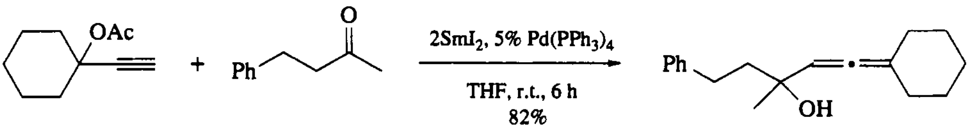

(17)

In addition to reactive allylic and benzylic substrates, other organic precursors have proven suitable for $SmI_2$-promoted intermolecular Barbier-type reactions. Primary organic iodides and even organic tosylates undergo carbonyl coupling, but under much harsher conditions than their allylic halide counterparts. Typically, reactions must be heated for 8–12 h in THF to accomplish complete conversion to product. Again, the ability to utilize organic tosylates in these transformations sets $SmI_2$ apart from more traditional reductants (equation 18). A Finkelstein-type reaction apparently converts alkyl tosylates to the corresponding iodides, which are subsequently involved in the coupling reaction. Addition of a catalytic amount of sodium iodide to the reaction mixture greatly facilitates the coupling. Alkyl bromides are less reactive than corresponding iodides and tosylates, and alkyl chlorides are virtually inert.

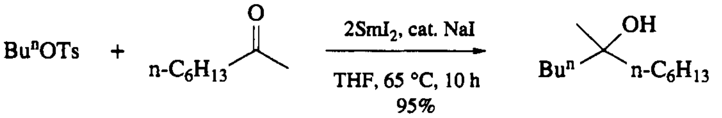

(18)

Much milder reaction conditions in the Barbier-type reaction can be employed by utilizing iron(III) salts as catalysts. For example, when 2 mol % $FeCl_3$ is added to $SmI_2$, the Barbier reaction between a primary organic iodide and a ketone is complete within 3 h at room temperature (equation 19). The iron(III) is probably reduced by $SmI_2$ to a low-valent species which serves as an efficient electron transfer catalyst, thus lowering the activation energy for the coupling process (*vide infra*).

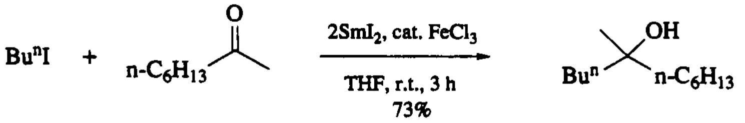
(19)

Utilization of THF–HMPA as solvent for the reaction provides another useful technique for facilitating the $SmI_2$-mediated Barbier-type coupling reaction.[24] Even in the absence of a catalyst, both $Bu^nBr$ and $Bu^sBr$ are cleanly coupled with 2-octanone within 1 min at room temperature in this solvent system, providing greater than 90% yields of the desired tertiary alcohols.

Dicyclopentadienylsamarium ($Cp_2Sm$) presents a third means by which less reactive organic halides can be induced to participate in intermolecular Barbier-type processes (equation 20).[19] Experimental conditions in intermolecular Barbier reactions are much milder with $Cp_2Sm$ (ambient temperature) than with $SmI_2$ (THF heated at reflux). Secondary alkyl iodides, reluctant to undergo $SmI_2$-mediated Barbier coupling under normal conditions, can be efficiently coupled with ketones utilizing $Cp_2Sm$.

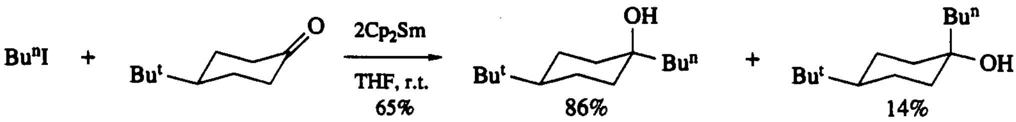
(20)

Alkenyl halides and aromatic halides are unreactive with ketones in the presence of $SmI_2$ in THF.[16c] Pinacolic coupling products can be detected in 10–20% yield under these conditions. In THF/HMPA, iodobenzene reacts in the presence of a ketone to generate a phenyl radical, which abstracts a hydrogen from THF. Samarium diiodide induced coupling of the THF radical to the ketone (or ketyl) provides the major observed product (equation 21).[25]

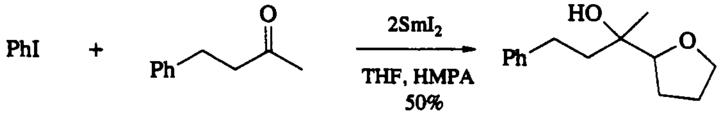
(21)

Aldehydes cannot be coupled to marginally reactive organic halides in $SmI_2$-promoted processes. A mixture of products results as a consequence of a Meerwein–Ponndorf process, initiated by reaction of the secondary samarium alkoxide intermediate with the aldehyde.[26] Highly reactive (allylic and benzylic) halides can be utilized and couple fairly efficiently with aldehydes, since they react quickly enough to suppress the undesired consecutive reaction. A two-step process (Barbier coupling followed by *in situ* oxidation) can be successfully employed with these reactive halides, providing high yields of coupled ketone (equation 22).[26b]

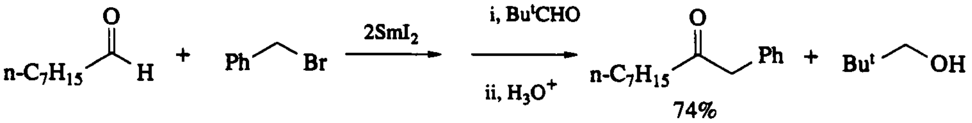
(22)

Dicyclopentadienylsamarium has been utilized to ameliorate the problem of Meerwein–Ponndorf oxidation in Barbier coupling reactions with aldehydes.[19] Dicyclopentadienylsamarium accelerates the coupling process, thereby preventing subsequent oxidation from occurring to any great extent. The enhanced reactivity of $Cp_2Sm$ permits even secondary alkyl iodides to undergo Barbier reactions with aldehydes, providing the desired alcohols in reasonable yields (equation 23). Further studies are likely to uncover other useful reactivity patterns for $Cp_2Sm$ that complement those of $SmI_2$.

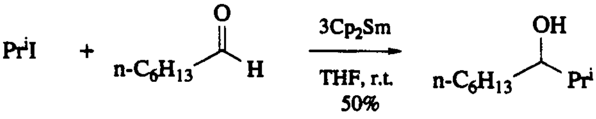
(23)

The mechanism of the intermolecular $SmI_2$-promoted Barbier-type reaction is still open to debate. Direct $S_N2$-type displacement of the halide by a ketyl or a ketyl dianion is unlikely, since optically active

2-bromooctane reacts with cyclohexanone in the presence of $SmI_2$ to provide an optically inactive tertiary alcohol.[27] One caveat concerning this evidence is that $SmI_2$ itself reacts with organic halides in a Finkelstein-type reaction.[16c,27] Thus, racemization of the 2-bromooctane prior to coupling has not been ruled out in these studies.

Reduction of the organic halide to an organosamarium species might also be involved. Subsequent carbonyl addition by this organometallic reagent would provide the observed product. This mechanism finds support in studies utilizing 2-(bromomethyl)tetrahydrofuran as the alkyl halide substrate. Treatment of this halide with $SmI_2$ in the presence of 2-octanone produces a 60% yield of 4-penten-1-ol, and only 3% of coupled product.[27] This is indicative of the generation of a tetrahydrofurfuryl anion, which rapidly rearranges to the ring-opened alkoxide.

Another plausible mechanism for the $SmI_2$-mediated Barbier reaction involves coupling of ketyl and alkyl radicals in a diradical coupling mechanism.[27] Alternatively, addition of an alkyl radical to a $Sm^{3+}$-activated ketone carbonyl may be invoked.[28]

Highly selective synthetic transformations can be performed readily by taking advantage of the chemoselectivity of $SmI_2$. It has been pointed out that there is a tremendous reactivity differential in the Barbier-type reaction between primary organic iodides or tosylates on the one hand, and organic chlorides on the other. As expected, selective alkylation of ketones can be accomplished by utilizing appropriately functionalized dihalides or chlorosulfonates (equation 24).[16c] Alkenyl halides and, presumably, aryl halides can also be tolerated under these reaction conditions.

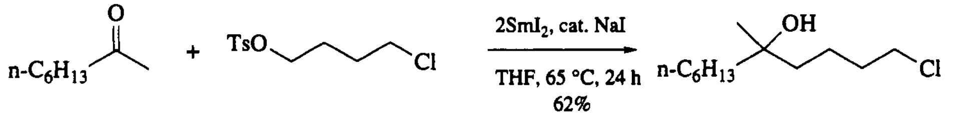

(24)

Nitriles and esters are also unreactive in $SmI_2$-promoted Barbier reactions. A very useful procedure for lactone synthesis has been developed making use of this fact. Treatment of γ-bromobutyrates or δ-bromovalerates with $SmI_2$ in THF/HMPA in the presence of aldehydes or ketones results in generation of lactones through a Barbier-type process (equations 25 and 26).[24] This nicely complements the β-metallo ester or 'homoenolate' chemistry of organosamarium(III) reagents described above (Section 1.9.2.1), and also the Reformatsky-type chemistry promoted by $SmI_2$ (Section 1.9.2.3.2). Further, it provides perhaps the most convenient route to γ- and δ-carbanionic ester equivalents yet devised.

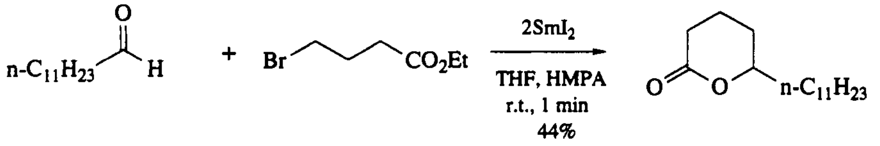

(25)

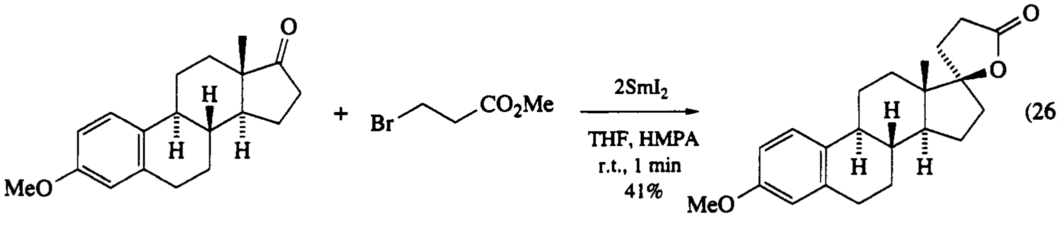

(26)

A very convenient hydroxymethylation process has been developed based on the $SmI_2$-mediated Barbier-type reaction.[29] Treatment of aldehydes or ketones with benzyl chloromethyl ether in the presence of $SmI_2$ provides the alkoxymethylated products in good to excellent yields. Subsequent reductive cleavage of the benzyl ether provides hydroxymethylated products. Even ketones with a high propensity for enolization can be alkylated by this process in reasonable yields. The method was utilized by White and Somers as a key step in the synthesis of (±)-deoxystemodinone (equation 27).[30] This particular ketone substrate resisted attack by many other nucleophilic reagents (such as methyllithium) owing to competitive enolate formation.

A unique alkoxymethylation reaction can be accomplished by treatment of α-alkoxycarboxylic acid chlorides with ketones in the presence of $SmI_2$ (equation 28).[31] The reaction is postulated to proceed by a reductive decarbonylation process, leading to a relatively stable α-alkoxy radical. Addition of this radical to the $Sm^{3+}$-activated carbonyl and further reduction and hydrolysis provides the observed product. An

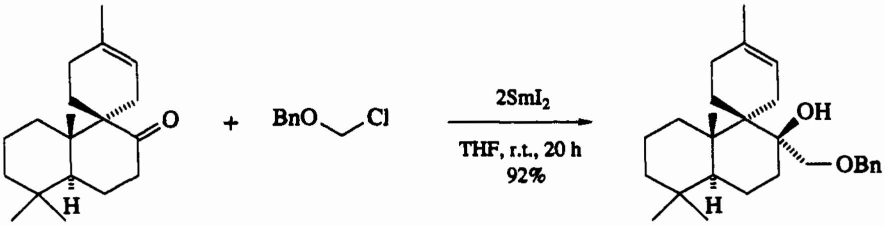
BnO
Cl
2SmI2
THF, r.t., 20 h
92%
OH
OBn
H
H
O

(27)

alternative mechanism involves reduction of the α-alkoxy radical to a transient anion, followed by nucleophilic addition and eventual hydrolysis. These two processes have not been distinguished at this point. With acid halides that do not afford a particularly stable radical on decarbonylation, reduction to the samarium acyl anion becomes competitive with the decarbonylation process. The chemistry of acyl radicals and samarium acyl anions is discussed separately in Section 1.9.2.3.5.

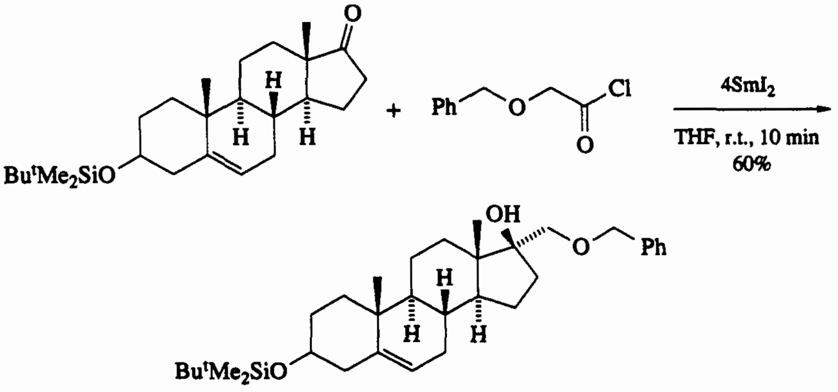
O
H
H
H
Bu^tMe2SiO
Ph
O
Cl
O
4SmI2
THF, r.t., 10 min
60%
OH
O
Ph
H
H
H
Bu^tMe2SiO

(28)

Halomethylation of aldehydes and ketones is difficult to achieve using α-halo organolithium species owing to the thermal instability of these organometallics. As an alternative, $SmI_2$ or samarium metal can be utilized as a reductant in conjunction with diiodomethane to induce an analogous iodomethylation reaction.[32] A wide range of aldehydes and ketones are efficiently alkylated at room temperature under these conditions. Even substrates that are susceptible to enolization react reasonably well, providing moderate yields of the iodohydrin (equation 29).[32a] Only 1,2-addition products are observed with conjugated aldehydes and ketones (equation 30).[32a] Excellent diastereoselectivity is achieved in reactions with both cyclic and acyclic ketones (equations 31 and 32).[32b]

Utilization of dibromomethane also results in the isolation of iodohydrins. Based on this observation and the fact that $SmI_3$ will cleave epoxides to generate iodohydrins, it has been suggested that the iodomethylsamarium alkoxide species that is initially generated cyclizes to an epoxide intermediate. The

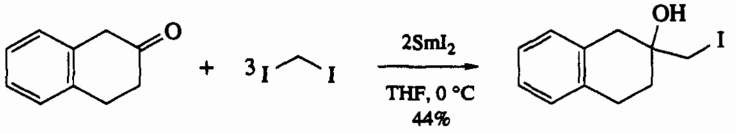
O
+ 3 I I
2SmI2
THF, 0 °C
44%
OH
I

(29)

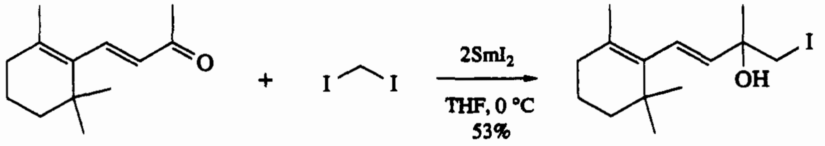
O
+ I I
2SmI2
THF, 0 °C
53%
I
OH

(30)

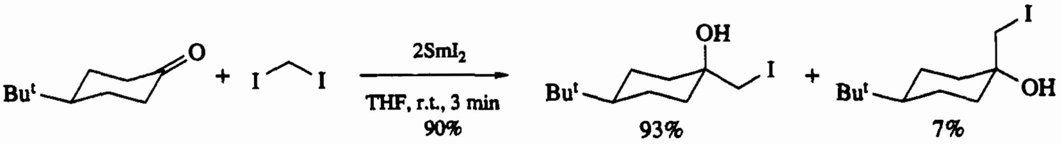
Bu^t
O
+ I I
2SmI2
THF, r.t., 3 min
90%
OH
Bu^t
I
+
93%
I
Bu^t
OH
7%

(31)

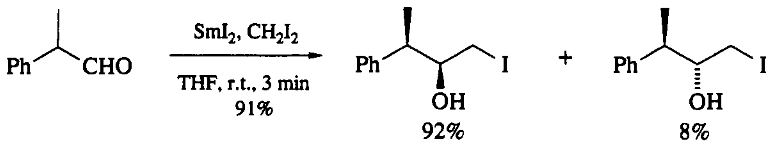

(32)

$SmI_2X$ that is produced as a result of this process then serves to open the epoxide, generating the iodohydrin. Although this appears to be a likely scenario, a more direct route involving a Finkelstein reaction between the bromomethylsamarium alkoxide and various samarium iodide salts[16c,27] cannot be ruled out (Scheme 2).

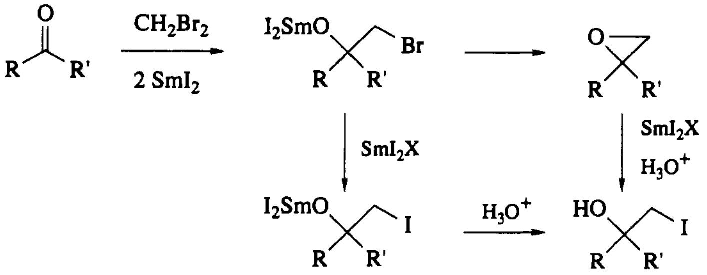

**Scheme 2**

A one-pot carbonyl methylenation reaction has been developed based on this iodomethylenation reaction.[33] Treatment of an iodomethylsamarium alkoxide (generated *in situ* by reaction of aldehydes or ketones with $SmI_2/CH_2I_2$) with $SmI_2$/HMPA and *N*,*N*-dimethylaminoethanol (DMAE) induces a reductive elimination, resulting in the generation of the corresponding methylenated material (equation 33).

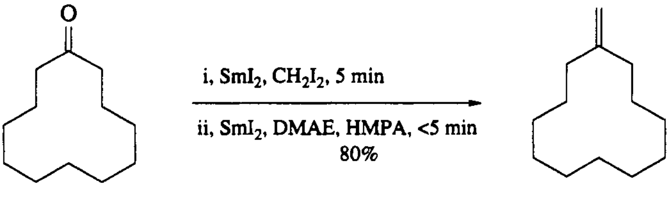

(33)

When α-halo ketones are treated with diiodomethane and samarium at 0 °C, cyclopropanols can be obtained in reasonable yields. Curiously, under the same conditions 1,2-dibenzoylethane also leads to cyclopropanol products (equations 34 and 35).[32a] Several pathways for conversion of α-halo ketones to the observed cyclopropanols can be envisioned. It has been proposed that the mechanism of this reaction involves reduction of the α-halo ketone by Sm (or $SmI_2$) to a samarium enolate. Cyclopropanation of this enolate with a samarium-based carbenoid subsequently provides the observed product.[32c]

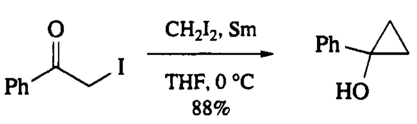

(34)

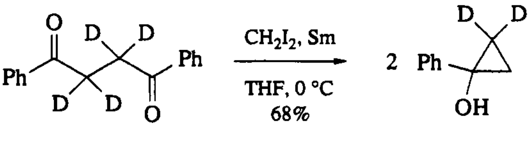

(35)

Although numerous reductants (*e.g.* magnesium, lithium, sodium, organolithiums, organocuprates and chromium(II) salts, to name only a few) have been utilized in attempts to promote intramolecular Barbier-type reactions, $SmI_2$ is by far the most general reductive coupling agent in terms of its utility and its scope of application. It has therefore become the reagent of choice for such processes.

Isolated cyclopentanols can be synthesized with considerable diastereoselectivity when appropriately substituted ω-iodoalkyl ketones are treated with $SmI_2$ in THF at −78 °C and allowed to warm to room temperature (equation 36).[34] The reaction is clearly not subject to steric inhibition about the ketone carbonyl, and provides a useful alternative to intermolecular reactions between organometallic reagents (*e.g.* RLi or RMgX) and α-substituted cyclopentanones. Intermolecular reactions between organometallic reagents and cyclopentanones often suffer from competitive enolization and/or reduction processes.

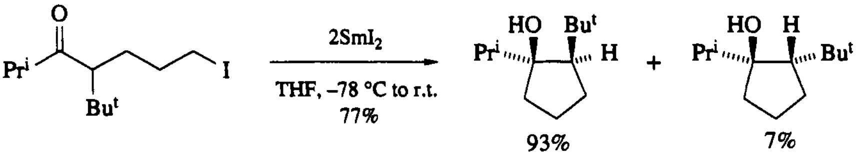

(36)

Perhaps more valuable is the application of the $SmI_2$ reductive coupling technology to the synthesis of bicyclic alcohols. Shiner and Berks have demonstrated that the procedure can be utilized to generate three-membered rings starting from α-tosyloxymethylcycloalkanones (equation 37).[35] An advantage of $SmI_2$ over reductants such as magnesium is that one is not restricted to organic halides in these reactions. As in this example, organic tosylates appear perfectly well suited to the Barbier process also.

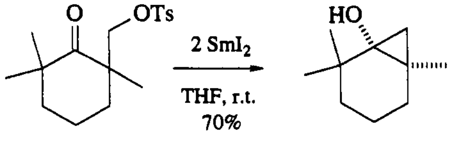

(37)

Although the synthesis of four-membered rings has yet to be thoroughly explored, samarium diiodide can be utilized in the annulation of five- and six-membered rings through an intramolecular Barbier process.[36] The development of this approach to six-membered ring formation in fused bicyclic systems is particularly important. Prior to this discovery there existed no reliable and convenient method to achieve this simple annulation process. The reactions proceed with considerable diastereoselectivity when cyclopentanone substrates are utilized, or when substituents are placed at the α-position of the cycloalkanone (equations 38 and 39). Diastereoselectivity in other systems depends on whether or not an iron(III) catalyst is utilized in the reaction. In addition, in some cases higher diastereoselectivities can be obtained utilizing samarium metal, ytterbium metal, or $YbI_2$ as reductant (Section 1.9.3.3). Unfortunately, the sense and magnitude of stereoselectivity that can be achieved by employing these other reductants are unpredictable from substrate to substrate.

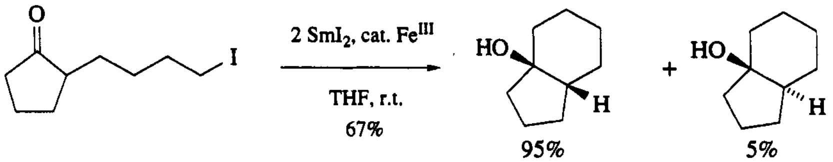

(38)

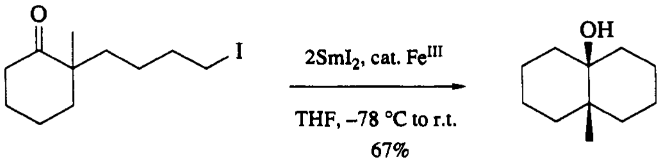

(39)

The $SmI_2$-mediated intramolecular Barbier procedure has been applied to several diverse systems, and in each case has been determined to be superior to other protocols. Suginome and Yamada applied the technique to syntheses of exaltone and (±)-muscone (equation 40).[37] Surprisingly, cyclization in this case generates a single diastereomer. It is claimed that the $SmI_2$ procedure provides better yields than procedures incorporating $Mg/HgCl_2$ or *n*-butyllithium.

Murray and coworkers have used the $SmI_2$-promoted intramolecular Barbier synthesis to produce 3-protoadamantanol (equation 41).[38] Although the yield in this example was not particularly high, it was the only method among several attempted that proved successful.[39]

In an elegant approach to polyquinenes, Cook and Lannoye developed a bisannulation process based on the $SmI_2$-mediated cyclization process (equation 42).[40] Remarkably, both of the carbon–carbon bond-

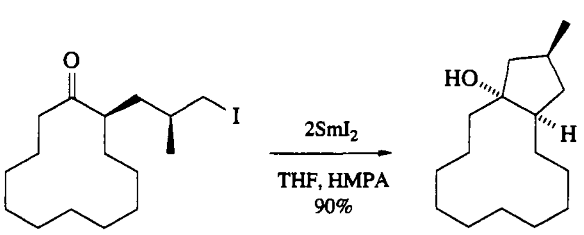

(40)

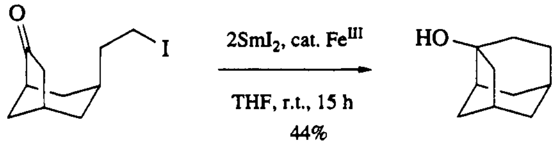

(41)

forming reactions in this process proceed with approximately 90% yield, providing an incredibly efficient entry to these complex molecules.

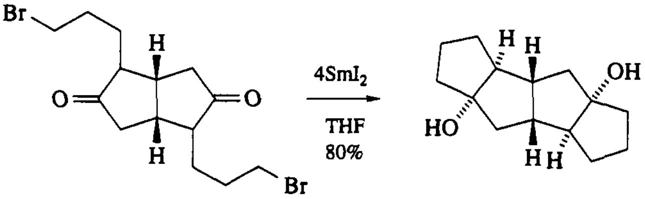

(42)

Exceptionally clean cyclization can be accomplished by utilizing conjugated enones as precursors for the Barbier reaction (equation 43).[41] High diastereoselectivity is achieved in these reactions, and under the mild conditions required for cyclization the TMS ether protecting group remains intact. It is also interesting that a neopentyl halide is effective in the cyclization. This result would appear to exclude an $S_N2$-type displacement of an organic halide by a samarium ketyl as a possible mechanism for the $SmI_2$-promoted intramolecular Barbier reaction.

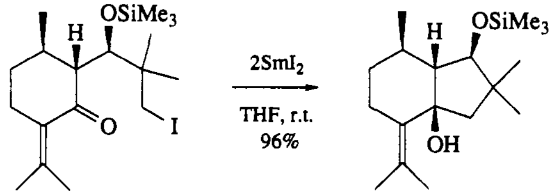

(43)

Ketyls appear to be important intermediates in Barbier-type coupling reactions promoted by $SmI_2$. This provided the very real possibility that the $Sm^{3+}$ ion generated on electron transfer could be utilized as an effective Lewis acid template to control stereochemistry *via* chelation in suitably functionalized substrates. Indeed, a number of systems have been designed with this idea in mind. In β-ketoamide systems, the samarium(III) ion can participate in a rigid, chelated intermediate which serves to control stereochemistry in the cyclization process (equation 44).[42] These particular cyclization reactions appear to proceed under kinetic control; there is no evidence to suggest that any equilibration takes place under the reaction conditions, and a single diastereomer is generated in each example. Six-membered rings can also be constructed by this process, although the yields are lower. By-products derived from simple reduction of the ketone to an alcohol are also isolated in these cases.

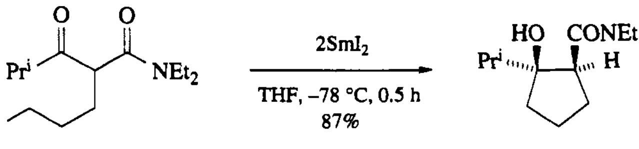

(44)

Allylic halide precursors provide exceptional yields of cyclic products, and both five- and six-membered rings comprising several different substitution patterns can be accessed by the same technology (equations 45 and 46).[42] In some cases, excellent stereochemical control at three contiguous stereocenters is established.

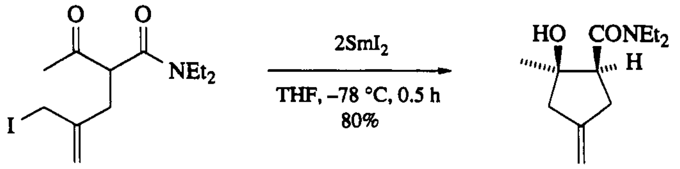

(45)

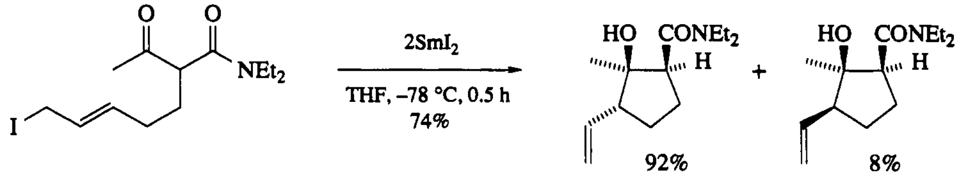

(46)

A number of analogous β-keto esters have also been explored as substrates for intramolecular Barbier cyclization.[42] In the alkyl halide series, a convenient route to 2-hydroxycyclopentanecarboxylates results (equation 47). However, six-membered rings are inaccessible utilizing this procedure. In contrast to β-ketoamide substrates, the β-keto ester series provide products which are clearly under thermodynamic control; that is, the observed diastereoselectivity is the result of a retroaldol–aldol equilibration, which serves to equilibrate the initially formed samarium aldolates. In most cases, diastereoselectivity is high, and the sense of relative asymmetric induction is predictable, based on a simple model for the reaction. However, the degree of diastereoselectivity is highly dependent on substituent and solvent effects. In particular, the use of coordinating solvents or additives (such as tetraglyme, 18-crown-6, or *N,N*-dimethylacetoacetamide) that serve to strip the samarium(III) ion away from the chelating center, radically diminish the diastereoselectivity observed in these reactions. It should be pointed out that these cyclizations cannot be carried out by treating the substrates with activated magnesium. Unreacted starting material is recovered under these conditions.[42]

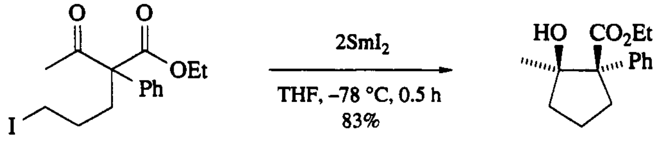

(47)

Evidence for a radical coupling mechanism (as opposed to a carbanionic carbonyl addition mechanism) in the intramolecular $SmI_2$-promoted Barbier reactions has come from studies on appropriately functionalized substrates in the β-keto ester series. It is well known that heterosubstituents are rapidly eliminated when they are adjacent to a carbanionic center. Indeed, treatment of a β-methoxy organic halide (suitably functionalized for cyclization[34,43]) with an organolithium reagent leads only to alkene (equation 48). No cyclized material can be detected. On the other hand, treatment of the same substrate with $SmI_2$ provides cyclized product and a small amount of reduced alcohol, with none of the alkene detected by gas chromatographic analysis (equation 49).[44]

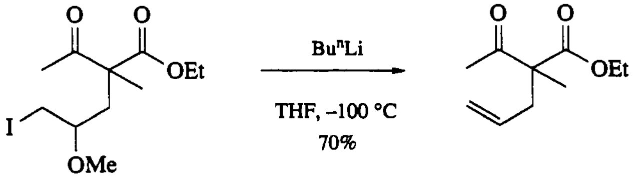

(48)

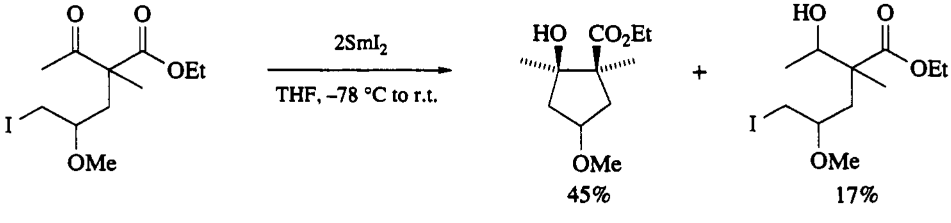

(49)

These results, together with the mechanistic studies by Kagan *et al.*[27] lend strong support for a radical cyclization process. Two general mechanisms are suggested (Scheme 3). In both, initial electron transfer from $SmI_2$ to the ketone carbonyl occurs, generating a ketyl. This chelated intermediate might suffer one of two fates. Dissociative electron transfer from the second equivalent of $SmI_2$ to the halide could occur (pathway A), providing a diradical species. Closure to the samarium aldolate and hydrolysis would result in formation of the observed product. Alternatively, the initially generated ketyl could undergo a dissociative intramolecular electron transfer to the halide (pathway B). Addition of the alkyl radical to the $Sm^{3+}$-activated ketone carbonyl,[28] subsequent reduction of that intermediate with the second equivalent of $SmI_2$ and hydrolysis would again complete the process. Experiments have yet to be designed and carried out to distinguish between a process involving cyclization after single-electron transfer and two-electron cyclization processes. However, it is clear that samarium carbanions are not involved in these intramolecular processes.

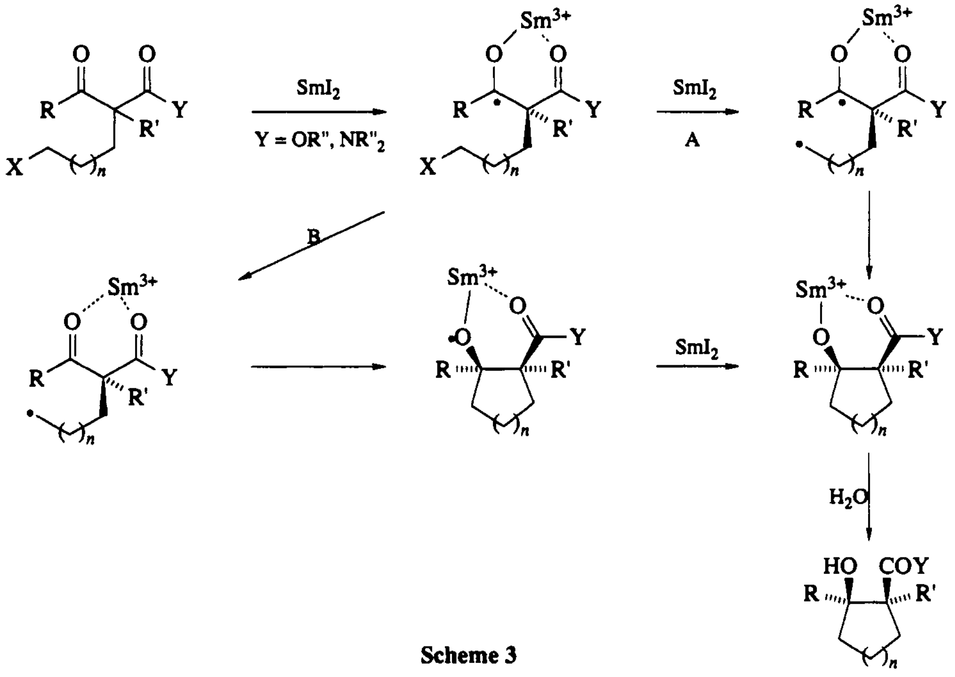

**Scheme 3**

Allylic halide substrates in the β-keto ester series cyclize well, and convenient routes to five-, six- and seven-membered rings have been described (equations 50 and 51).[42] Unfortunately, the diastereoselectivity in these examples again is highly dependent on the substitution patterns about the dicarbonyl substrate.

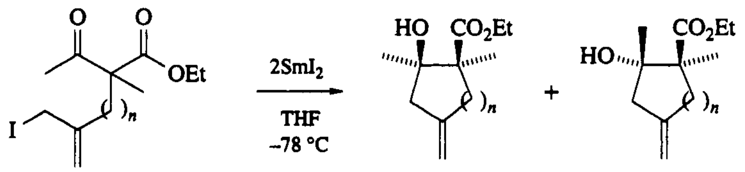

(1) (2) (50)

| *n* | *Yield (%)* | *Diastereoselectivity (1) : (2)* |
|---|---|---|
| 1 | 84 | 86 : 14 |
| 2 | 73 | 64 : 36 |
| 3 | 64 | 50 : 50 |

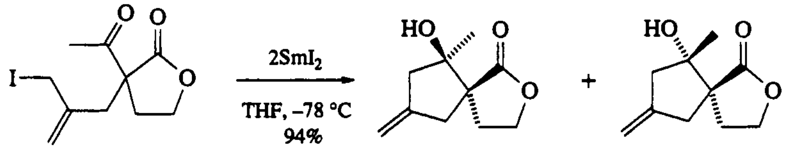

86% 14% (51)

Attempts to cyclize ethyl (*E*)-2-acetyl-2-methyl-6-bromo-4-hexenoate have been unsuccessful, with ethyl 2-methyl-3-oxobutanoate isolated as the major product of the reaction (equation 52).[42] Loss of butadiene, as required for this transformation, is clearly facilitated by the ability of a β-keto ester stabilized (radical or anion) intermediate to serve as an effective leaving group in the reaction. Thus, cyclization of (*E*)-8-bromo-4-methyl-6-octen-3-one proceeds smoothly to provide the expected carbocycle in 91% isolated yield (equation 53).

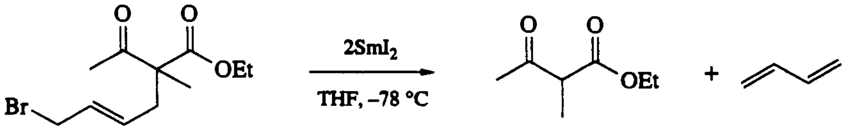

(52)

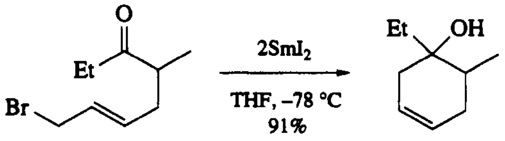

(53)

These examples again have some mechanistic implications in that they appear to rule out cyclization *via* $S_N2$ displacement of the halide by a samarium ketyl. However, one cannot distinguish between a mechanism based on allylsamarium addition to the carbonyl *versus* an electron transfer mechanism as outlined for the alkyl halide substrates above. Both mechanisms allow for isomerization of the double bond (*via* 1,3-allylic transposition in the case of an allylmetallic,[45] or configurational instability in an allylic radical[46] in a diradical coupling mechanism) and also provide reasonable routes for generation of butadiene. Further mechanistic work is clearly required in order to provide a more detailed understanding of all of these intramolecular Barbier-type reactions.

### *1.9.2.3.2 Reformatsky-type reactions*

In addition to serving as a useful replacement for lithium or magnesium in Barbier-type coupling reactions, $SmI_2$ also provides advantages over zinc as a reductant in Reformatsky-type coupling reactions (equation 54).[16c,27] The latter only performs well when an activated form of zinc is utilized, and thus the homogeneous conditions afforded by $SmI_2$ provide the advantage of enhanced reactivity under milder conditions.

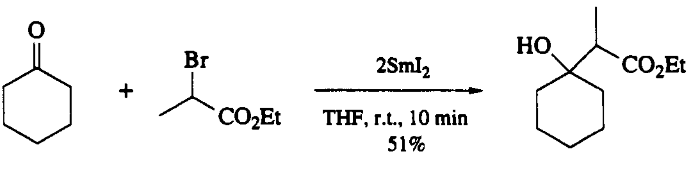

(54)

The procedure has been adapted to permit construction of medium- and large-ring lactones through an intramolecular process (equation 55).[47] Eight- to fourteen-membered ring lactones can be synthesized under high dilution conditions in 75–92% yields, and the process appears much better than procedures involving use of $Zn–Ag/Et_2AlCl$.[48] Diastereoselectivity in the $SmI_2$-mediated cyclizations utilizing α-bromopropionate ester precursors was less than 2.5:1.

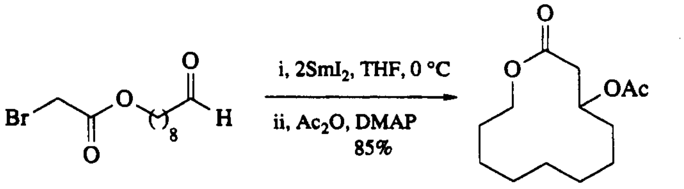

(55)

Vedejs and Ahmad have used this $SmI_2$-promoted macrocyclization technique as a key step in the total synthesis of a cytochalasin (equation 56).[49] In this reaction, the 11-membered ring product is isolated in

46% yield as a single diastereomer. Curiously, the zinc-promoted process provides a 1:1 mixture of diastereomers in 75% yield.

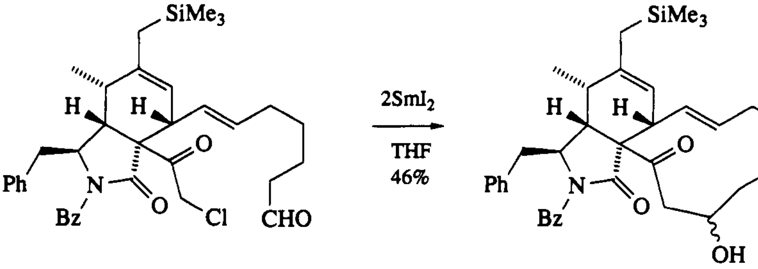

(56)

Reductive cyclizations of β-bromoacetoxy aldehydes and ketones promoted by $SmI_2$ afford β-hydroxyvalerolactones with unprecedented degrees of 1,3-asymmetric induction (equation 57).[50] Numerous attempts at utilizing zinc-mediated intramolecular Reformatsky reactions to access these lactones have failed. The successful development of the $SmI_2$-based methodology therefore provides perhaps the most convenient entry to this important class of molecules.[50]

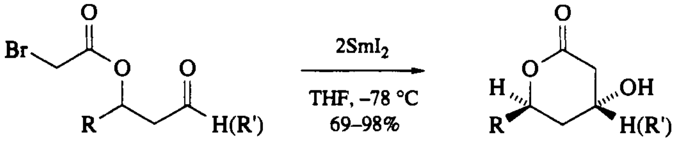

(57)

Yields in the $SmI_2$-promoted intramolecular Reformatsky reaction are typically higher for ketones than for aldehyde substrates, but in both series diastereoselectivity is virtually complete. It has been suggested that reaction of $SmI_2$ with the β-bromoacetoxy initially generates a $Sm^{3+}$ ester enolate, with cyclization taking place through a rigid cyclic transition structure enforced by chelation (Scheme 4).[50]

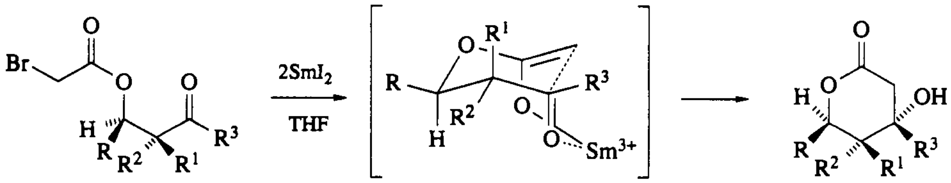

**Scheme 4**

In contrast to other reported methods of 1,3-asymmetric induction, the $SmI_2$-mediated intramolecular Reformatsky procedure permits strict control of stereochemistry even in diastereomeric pairs of substrates bearing α-substituents (equations 58 and 59).[50] Although the diastereoselectivity is somewhat lower for the *syn* diastereomeric substrate, where the α-substituent would be axially disposed in the proposed transition structure leading to the product, 1,3-asymmetric induction is still predominant and overwhelms other effects to an impressive extent.

Only a few exceptions to this general pattern of diastereoselection have been observed.[50,51] Some *syn* diastereomeric α-substituted β-bromoacetoxy aldehydes and ketones provide diastereomeric mixtures of products or the opposite diastereomeric product than is anticipated on the basis of the transition structure proposed in Scheme 4 (equation 60). Steric factors which preclude access to chair transition structures may be responsible for the change in the sense of diastereoselectivity in these examples.

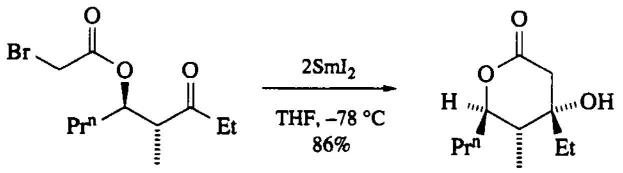

(58)

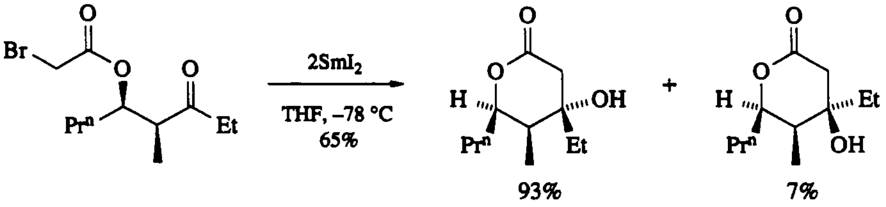

(59)

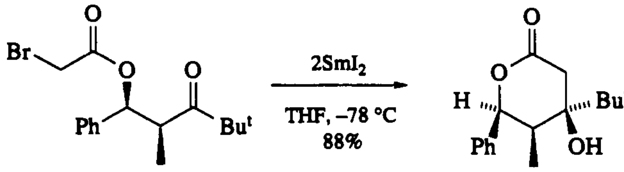

(60)

Surprisingly, 1,3-asymmetric induction can be relayed from a tertiary acetoxy stereocenter (equation 61). The unprecedented degree of stereochemical control exhibited by this process appears to be general for aldehydes and ketones, although the scope of the reaction with regard to substituents at the β-position is limited.[51]

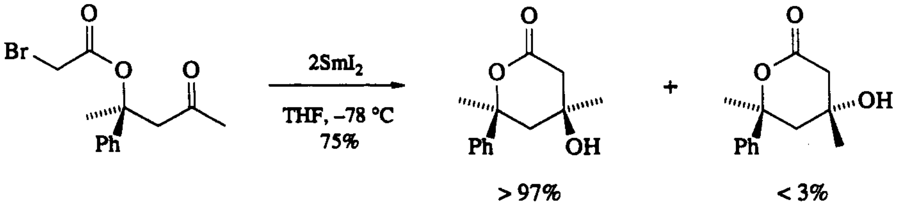

(61)

Seven-membered ring lactones can be accessed in excellent yields by the $SmI_2$-mediated intramolecular Reformatsky reaction as well. Although several substitution patterns provide exceptional relative asymmetric induction in this process (equation 62), it is clear that high diastereoselectivity cannot be achieved for all substitution patterns in the formation of seven-membered ring lactones.[52]

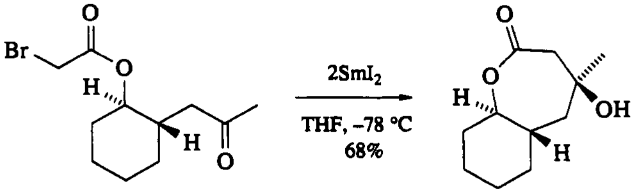

(62)

### *1.9.2.3.3 Ketyl–alkene coupling reactions*

The ability of $SmI_2$ to generate ketyls prompted its use for the reductive cross-coupling of ketones with alkenes. Both intermolecular and intramolecular processes of this type have been described.

Conjugated esters react with aldehydes and ketones in the presence of 2 equiv. of $SmI_2$ and a proton source, affording reasonable yields of butyrolactones (equation 63).[53] The presence of HMPA dramatically enhances reactivity (and yields), permitting reactions to run to completion in 1 min as opposed to 3–6 h without this additive. The method complements electroreductive,[54] photoreductive,[55] and other metal-induced ketone–alkene cyclizations[56] that have been developed. Use of unsaturated esters such as ethyl methacrylate and ethyl crotonate leads to diastereomeric mixtures of products in reactions with prochiral aldehydes and ketones.[53c] Conjugated nitriles do not fare as well as their unsaturated ester counterparts in these reactions. Yields of 17–20% are reported for the nitrile substrates.[53a] In terms of the ketyl precursor, both aliphatic and aromatic ketones and aldehydes can be utilized,[53a] and even formaldehyde is effective to some degree.[53b]

The reaction is considered to proceed by a radical process.[53c] When the reaction is carried out with MeOD as the proton source, α-monodeuterolactone is generated. Two mechanisms can be envisioned which are consistent with this observation. The first involves coupling of a samarium ketyl with an allylic radical derived from single-electron reduction of the unsaturated carbonyl substrate. Protonation

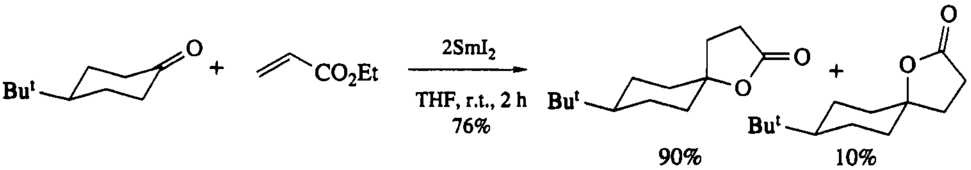

(63)

and cyclization to the lactone completes the process. A more likely mechanism involves simple ketyl addition to the conjugated ester. Subsequent reduction of the radical intermediate, protonation and cyclization would again provide the observed lactones. A third mechanism initially suggested involved reduction of the unsaturated ester by $SmI_2$, generating a stable samarium β-metallo ester intermediate. Direct addition of this intermediate to a ketone or aldehyde would also provide an entry to the lactone (see Section 1.9.2.2). This latter mechanism seems unlikely, since addition of an aldehyde or ketone to a mixture of ethyl acrylate and $SmI_2$ failed to produce a reasonable yield of lactone.

Bicyclic butyrolactones can be generated when intramolecular versions of the reaction are carried out (equation 64).[57] The yields are improved by addition of HMPA, and reactions can be carried out under milder conditions. Addition of a catalytic amount of $FeCl_3$ has little effect on the yields. In most cases, diastereoselectivities range from 2.5:1 to 4:1.

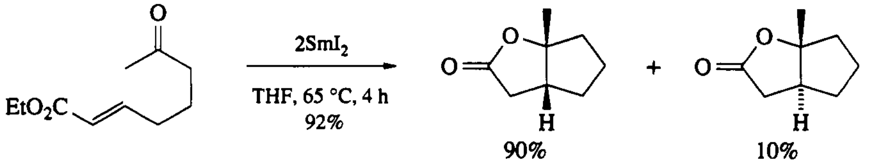

(64)

A much more highly diastereoselective process results when alkenic β-keto ester and β-ketoamide substrates can be utilized in the ketone–alkene reductive coupling process. Both electron deficient and unactivated alkenes can be utilized in the reaction (equations 65 and 66).[58] In such examples, one can take advantage of chelation to control the relative stereochemistry about the developing hydroxy and carboxylate stereocenters. Favorable secondary orbital interactions between the developing methylene radical center and the alkyl group of the ketyl,[54c,56a,59] and/or electrostatic interactions in the transition state[54a,55,59] account for stereochemical control at the third stereocenter.

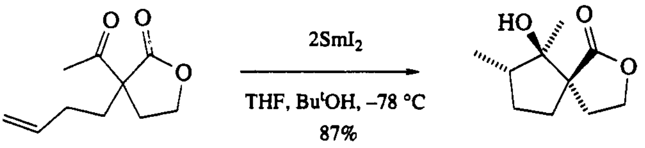

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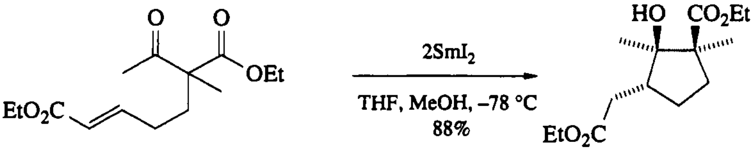

(66)

Since 2 equiv. of $SmI_2$ are required for the reaction, the reductive coupling process must be a two-electron process overall (Scheme 5).[58] Cyclization appears to occur after transfer of a single electron, with $Sm^{3+}$ controlling the stereochemistry at this stage by chelation with the Lewis basic ester carbonyl. Subsequent reduction to a transient carbanion, followed by immediate protonation, accounts for the observed products. Only if a transient anion is generated can one account for >90% deuterium incorporation at the methyl group when the reaction is performed in MeOD (equation 67).[44]

There is an inherent competition between simple reduction of the ketone and the reductive cyclization process with unsaturated carbonyl substrates. Cyclization processes that are slower than that of the ketyl–alkene cyclization forming a five-membered ring, suffer from lower yields owing to this competition. For example, ketyl–alkyne coupling can also be achieved when mediated by $SmI_2$, but yields are lower than those achieved with analogous keto–alkenes (equation 68). This might have been expected on the basis that radical additions to alkynes are slower than corresponding additions to alkenes.[60] Similarly, the rate

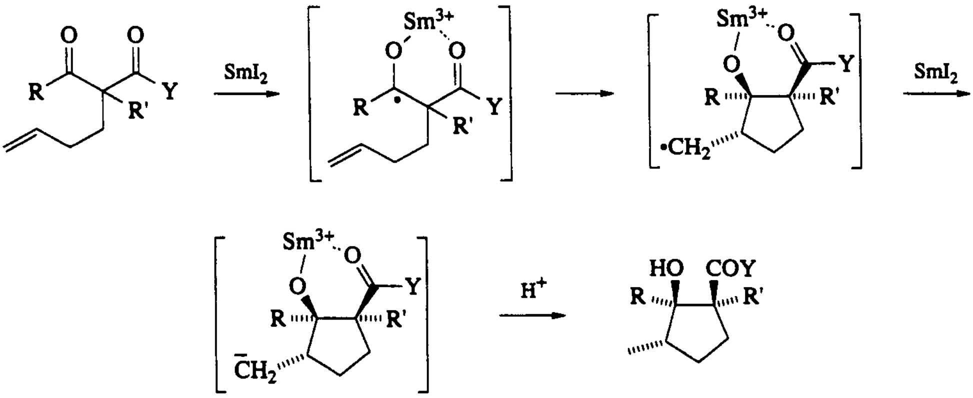

Scheme 5

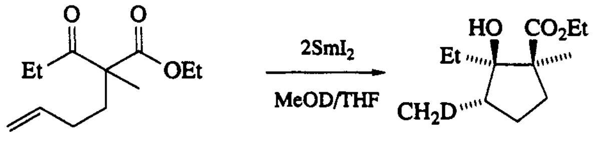

(67)

retardation encountered in formation of six-membered rings by radical processes prevents the construction of 2-hydroxycyclohexanecarboxylates by the SmI$_2$-promoted ketyl–alkene cyclization process.

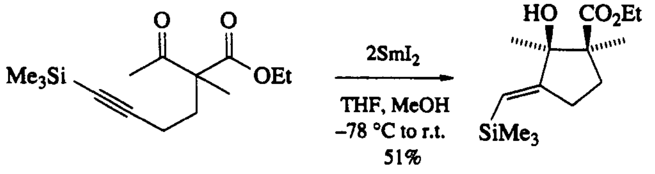

(68)

An elegant tandem radical cyclization process promoted by SmI$_2$ has been developed as a key step in the synthesis of (±)-hypnophilin and the formal total synthesis of (±)-coriolin (equation 69).[61] Cyclization in this case again occurs after transfer of a single electron, and in fact the entire process requires less than 2 equiv. of SmI$_2$. When cyclizations were quenched with D$_2$O, no deuterium was incorporated at the newly formed vinyl carbon. This implies that the alkenyl radical produced after tandem cyclization abstracts a hydrogen from the solvent faster than it is reduced to the anion by SmI$_2$. This and the work by Molander and Kenny described above[58] are completely in line with observations of Inanaga *et al.* in work on the reduction of organic halides with SmI$_2$.[25] Thus, alkyl halides are reduced to hydrocarbons by means of a transient anion (which can be trapped by D$_2$O) with SmI$_2$, whereas aryl (and presumably alkenyl) halides show no deuterium incorporation on reduction. With *sp*$^2$-hybridized radicals, hydrogen abstraction from the THF solvent is thus faster than reduction by SmI$_2$ to the anion. Further studies in ketone–alkene reductive cyclization reactions are bound to lead to exciting new entries to highly complex carbocyclic ring systems.

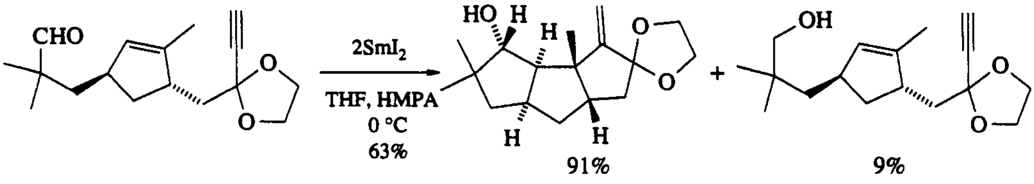

(69)

### 1.9.2.3.4 Pinacolic coupling reactions

As expected with a reagent that is capable of generating ketyls, intermolecular pinacolic coupling reactions can also be carried out with considerable efficiency using SmI$_2$. Treatment of aldehydes or ketones with $SmI_2$ in the presence of a proton source such as methanol results in selective reduction to the corresponding alcohols, and the formation of pinacols is negligible. However, in the absence of a proton source, both aldehydes and ketones can be cleanly coupled in the presence of $SmI_2$ to generate pinacols (equation 70).[62] The yields are excellent in nearly every case, and the method therefore competes effectively with other established procedures for this process. Unfortunately, roughly equimolar ratios of *threo* and *erythro* isomers are generated in these reactions. Aromatic aldehydes and ketones couple within a few seconds at room temperature in THF. Aliphatic aldehydes require a few hours under these conditions, and a day is needed for complete reaction of aliphatic ketones. Amines, nitriles, aryl halides and nitro groups are tolerated under these conditions. Samarium diiodide is thus superior to other reductants in terms of its functional group compatibility. Surprisingly, even carboxylic acids can also be incorporated into substrates with little decrease in the yields of pinacolic products. It is not clear why competitive reduction to the alcohols is not observed in this instance, since a proton source is provided by the acid.

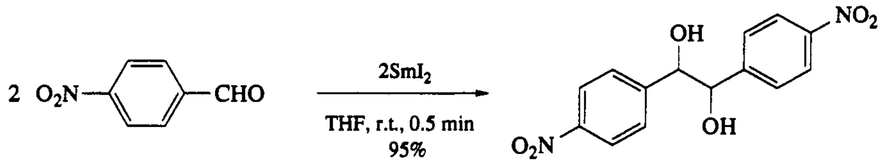

(70)

Dicyclopentadienylsamarium also promotes intermolecular pinacolic coupling reactions with exceptional efficiency.[19] Both benzaldehyde and acetophenone are reported to undergo coupling very rapidly at room temperature in the presence of this reductant. After hydrolysis, pinacols are isolated in virtually quantitative yields.

Samarium diiodide has also been utilized as a reductant to promote pinacolic coupling reactions mediated by low-valent titanium species (equation 71).[63] Utilizing this protocol, high diastereoselectivity can be achieved, although the yields for this particular process were not reported.

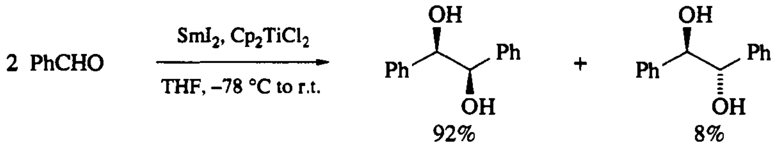

(71)

Intramolecular pinacolic coupling reactions have also proven successful with $SmI_2$. Yields with simple diketones are relatively low.[62b] However, excellent yields and diastereoselectivities are achieved in intramolecular pinacolic coupling reactions of β-keto ester and β-ketoamide substrates (equation 72).[64] A variety of substitution patterns can be tolerated in these reactions to generate five-membered carbocycles. Six-membered rings can also be generated by this process, but substantially lower yields and diastereoselectivities are observed (equation 73).[44] Yields obtained for β-ketoamide substrates are also lower than those observed in the β-keto ester series.

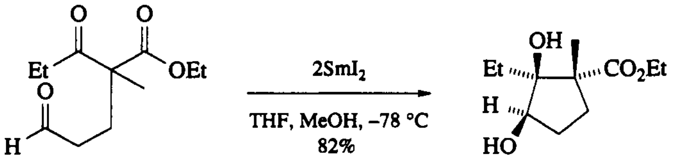

(3)

(72)

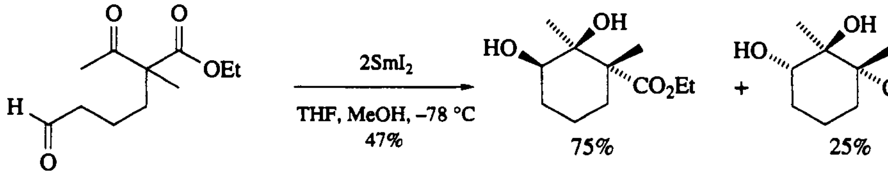

(73)

Curiously, the relative stereochemistry between the carboxylate and the adjacent hydroxy group in the $SmI_2$-mediated intramolecular pinacolic coupling reaction is opposite to that observed in the intramolecular Barbier reactions and ketone–alkene reductive coupling reactions discussed previously (compare equation 72 with equations 47 and 66, for example). From a synthetic point of view, this result is highly advantageous because it provides entry to the manifold of diastereomeric products. The results also have mechanistic implications. Unlike potential substrates for ketone–alkene reductive coupling reactions, precursors for the pinacolic coupling reaction contain two nearly equally reducible functional groups. This complicates any rational assessment of the stereochemical outcome of these reactions. Furthermore, several different mechanisms can be proposed for the intramolecular pinacolic coupling reaction. One scenario involves two-electron reduction followed by cyclization. After initial reduction of one of the carbonyl substituents to a ketyl, intermolecular reduction to generate a dianion could ensue. Subsequent nucleophilic attack by this dianion at the unreduced carbonyl and hydrolysis would provide the observed product. A mechanism of this type can be ruled out. Ketyl dianions are generally inaccessible, even under the most brutal reducing conditions. Reduction of a ketyl is highly endothermic,[65] and certainly $SmI_2$ is not a strong enough reducing agent to generate such a species. Furthermore, a dianion intermediate would quickly become protonated under reaction conditions utilized for these reactions (p$K_a$ Bu$^t$OH = 17, p$K_a$ MeOH = 16, p$K_a$ carbonyl dianion ~ 49–51), resulting in large amounts of uncyclized reduction products.[65a]

The most feasible pathway to coupled products is intramolecular ketyl addition to the $Sm^{3+}$-coordinated ketone (see Scheme 6). Several examples of ketyl addition to Lewis acid activated carbonyls have been reported in the literature.[66] Clerici and Porta have demonstrated in detailed experiments that intermolecular addition of ketyls to carbonyls can be a rapid process.[66a–c] Generally, ketyl addition to carbonyls is a reversible reaction. However, reversibility can be greatly affected by Lewis acid chelation of the complex, and further reduction of the radical intermediate (8) by the second equivalent of $SmI_2$ would serve to make the process irreversible.[65a,66b]

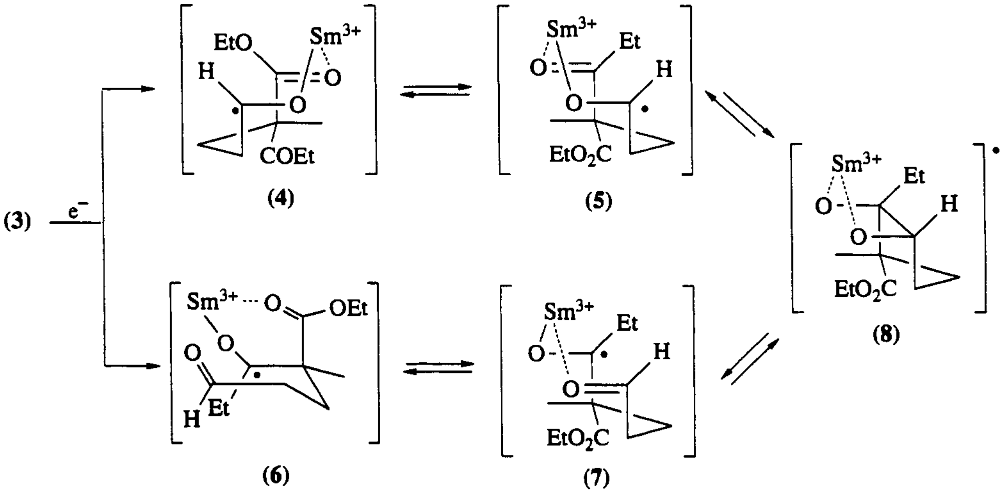

Scheme 6

In the $SmI_2$-promoted pinacolic coupling, two different ketyls can be generated initially. In either of these intermediates, chelation of the resulting $Sm^{3+}$ ion with the carboxylate (carboxamide) moiety (4) and (6) might be of minimal consequence. That is, Lewis acid activation of the unreduced aldehyde or ketone (5) and (7) may be required for efficient cyclization. A frontier molecular orbital approach is useful in thinking about the effects of Lewis acid complexation on the rate of radical addition to activated carbonyl substrates *versus* their unactivated counterparts.[67] Reetz has quantitatively measured the effect of Lewis acid complexation on the HOMO ($\pi_{CO}$) and LUMO ($\pi^*_{CO}$) of carbonyl substrates.[68] Calculations indicate that the LUMO energy decreases by ~50 kcal on coordination with $BF_3$. Thus, the electrophilicity of the carbonyl is greatly enhanced, making it more susceptible to nucleophilic radical addition. In the $SmI_2$-promoted pinacolic coupling reaction, the rate of ketyl addition may be substantially increased by complexation of $Sm^{3+}$ to the ketone as in intermediates (5) and (7). If complexation is required for efficient cyclization, this would explain the *cis*-diol stereochemistry observed for these substrates, regardless of which carbonyl is first reduced to initiate the reductive cyclization process.

Dipolar repulsion between the carboxylate moiety and the developing diol centers in intermediates (5) and (7) would account for the (*trans*) relative stereochemistry between these stereocenters. Following cyclization, intermolecular reduction of the $Sm^{3+}$–chelated complex (8) by the second equivalent of $SmI_2$ and protonolysis by alcohol irreversibly drives the reaction to completion, generating the observed products.

Certainly another plausible mechanism must also be considered. After initial ketyl formation, a second intermolecular reduction could follow, generating a diketyl intermediate. Subsequent carbon–carbon bond formation and protonolysis would again provide the observed products. One cannot unambiguously distinguish between this mechanism and the ketyl addition mechanism. However, both *cis*- and *trans*-diols might be expected from a diketyl coupling reaction. Corey has investigated intramolecular pinacolic coupling reactions promoted by $Ti^{2+}$ (which also lead to generation of *cis*-diols), and argues that a diketyl coupling mechanism is unlikely.[66d] Strong dipolar repulsion between the $Ti^{3+}$-complexed ketyls would appear to favor generation of *trans*-diols. The same argument may apply in the $SmI_2$-mediated process; exclusive formation of *cis*-diols would not seem likely from coupling of a di-$Sm^{3+}$-complexed diketyl. Furthermore, one might speculate that Lewis acid catalyzed intramolecular carbonyl addition (by the ketyl) may be faster than intermolecular reduction of a ketone to a ketyl by $SmI_2$.

In a useful extension of the methodology, highly functionalized nonracemic carbocycles can be synthesized by intramolecular pinacolic coupling reactions utilizing readily available oxazolidinone precursors (equation 74).[44]

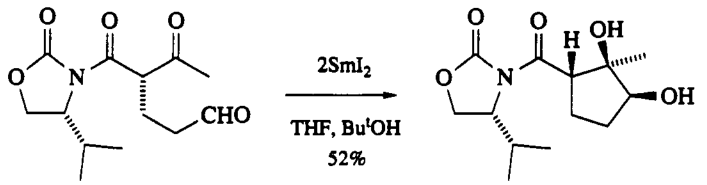

(74)

Related to the intramolecular pinacolic coupling reactions in some respects is a ketone–nitrile reductive coupling process. This process also permits the construction of highly functionalized carbocycles,[44] although the yields are somewhat reduced owing to the reluctance of nitriles to undergo such radical addition reactions (equation 75). Presumably, simple reduction of the ketone to the alcohol competes with the desired process.

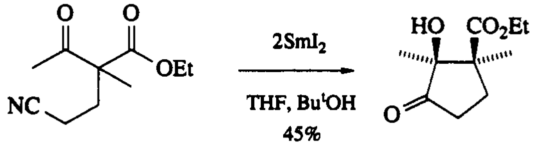

(75)

### 1.9.2.3.5 Acyl anion and acyl radical chemistry

Lithium acyl anions, long sought as unique intermediates, have only recently been synthesized and utilized effectively in synthetic organic chemistry.[69] These reactive organometallics are generated by reaction of organolithiums with carbon monoxide at extremely low temperatures. Samarium acyl anions can be prepared in a somewhat analogous fashion. Thus, when $Bu^tBr$ is added to $Cp_2Sm$ while under an atmosphere of CO in THF at low temperature, a samarium acyl anionic complex is apparently generated (equation 76).[70] Addition of an aldehyde to the reaction mixture at –20 °C, followed by hydrolysis, results in the formation of an α-ketol in modest yields.

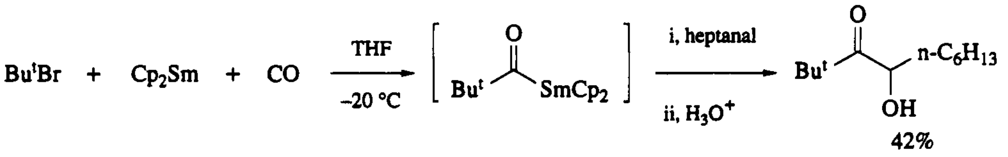

(76)

In the absence of the aldehyde, homocoupled pinacol and a compound resulting from a double carbonylation are isolated in low yields.[70] Both products are consistent with initial formation of a samarium acyl anion.

In addition to the carbon monoxide insertion route, samarium acyl anions can also be prepared under reductive conditions by reaction of $SmI_2$ with acyl halides.[1c,71] In the absence of any other electrophiles, the acyl halides provide moderate yields of α-diketones (equation 77). The main by-product generated in these reactions is the α-ketol.

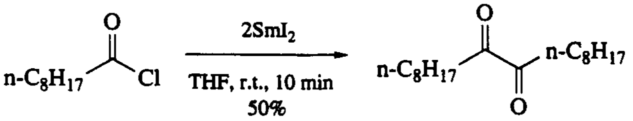
(77)

Mechanistic studies strongly suggest the intermediacy of a samarium acyl anion. For example, the phenylacetyl radical ($PhCH_2CO\cdot$) is known to rapidly decarbonylate ($k = 5.2 \times 10^7$ s$^{-1}$), providing a benzyl radical which dimerizes to bibenzyl.[72] However, addition of phenylacetyl chloride to a solution of $SmI_2$ in THF leads to a 75% yield of the expected diketone, and neither toluene nor bibenzyl is detected. Apparently, intermolecular reduction of this acyl radical to the corresponding anion proceeds at a rate which is greater than $5.2 \times 10^7$ s$^{-1}$.

The acylsamarium species has not been isolated or characterized spectroscopically. Its structure has tentatively been assigned as (**9**) or (**10**), analogous to that of $Cp_2LuCOBu^t$. The latter compound has been prepared from $Cp_2LuBu^t$ and CO.[1c]

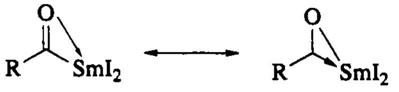
(**9**) (**10**)

Samarium acyl anions can be trapped by electrophiles other than acid halides. For example, addition of a mixture of a carboxylic acid chloride and an aldehyde or ketone to a solution of $SmI_2$ in THF results in the synthesis of α-hydroxy ketones (equations 78 and 79).[73] Intramolecular versions of the reaction have also been performed, although the scope of the reaction is limited owing to the difficulty in obtaining suitable substrates for the reaction (equation 80).[74]

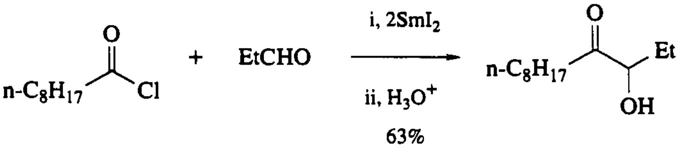
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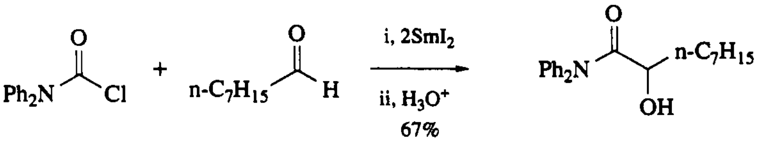
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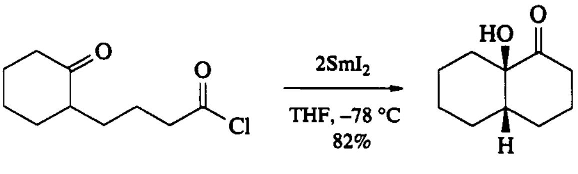
(80)

Intramolecular trapping studies have verified the intermediacy of acyl radicals in the conversion of carboxylic acid chlorides to samarium acyl anions by $SmI_2$.[75] Treatment of 2-allyloxybenzoyl chlorides with $SmI_2$ resulted in a very rapid reaction, from which cyclopropanol products could be isolated in yields of up to 60% (equation 81). Apparently, initial formation of the acyl radical was followed by rapid radical cyclization. The β-keto radical generated by this process undergoes cyclization by a radical or anionic process, affording the observed cyclopropanols (Section 1.9.2.3.1).

### *1.9.2.3.6 Miscellaneous*

A new method for the masked formylation of aldehydes and ketones has been developed which relies on the ability of $SmI_2$ to generate phenyl radicals from iodobenzene. As pointed out previously, aryl

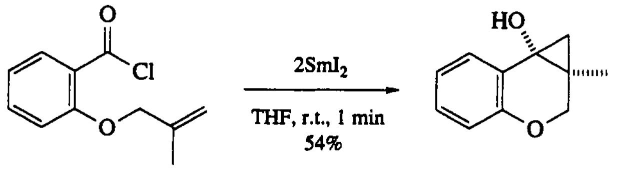

(81)

halides do not undergo Barbier-type coupling reactions with ketones in the presence of $SmI_2$. Instead, THF adducts of the carbonyl compounds are obtained (equation 21).[25] When 1,3-dioxolane is utilized in place of THF, the initially formed phenyl radical can abstract a hydrogen from the dioxolane. The resulting dioxolanyl radical can couple to the carbonyl, generating the observed products (Scheme 7).[76] Both aldehydes and ketones can be utilized in the reaction, with yields ranging from 73–77% for five different substrates.

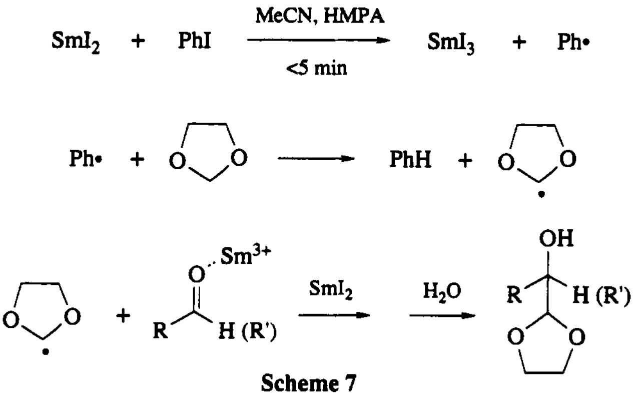

Scheme 7

Martin *et al.* have described the reductive cyclization of ω-unsaturated α-amino radicals mediated by $SmI_2$.[77] Reduction of ω-unsaturated iminium salts by $SmI_2$ in the presence of camphorsulfonic acid generates the ω-unsaturated α-amino radicals, which cyclize to provide good yields of nitrogen heterocycles (equation 82). The process is restricted to the formation of five-membered nitrogen heterocycles, and increased steric bulk adjacent to the radical center was also found to inhibit cyclization. As expected, the presence of an activating group on the acceptor double bond (*e.g.* an aryl substituent) increases the yield of the cyclization. The process could be carried out electrochemically as well as by utilizing cobalt(I) reductants, but the relative strengths and weaknesses of these various approaches has yet to be fully assessed.

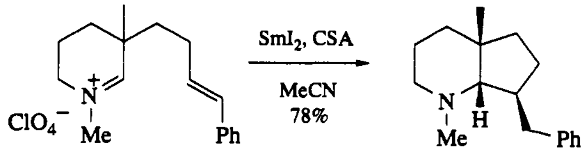

(82)

## 1.9.3 YTTERBIUM REAGENTS

Ytterbium reagents have certainly not attained the status achieved by the corresponding samarium reagents in terms of their utility in selective organic synthesis. Nevertheless, there are indications that ytterbium reagents, too, have the potential to serve as selective nucleophiles in C—X π-bond addition reactions, and eventually will take their place among the other lanthanide reagents with a unique role in organic synthesis. The similarity between samarium and ytterbium reagents in many cases is quite striking. As a consequence, the organization of this section mirrors that of the samarium reagents above, and many resemblances between the two classes of reagents will become apparent.

### 1.9.3.1 Organoytterbium(III) Reagents

Remarkably little chemistry of organoytterbium(III) reagents has been explored as it pertains to selective organic synthesis. These reagents do show promise as useful organic nucleophiles, however. Reaction of 4-*t*-butylcyclohexanone with $Bu^nLi–YbCl_3$ provides a nearly quantitative yield of the expected carbonyl addition product (equation 83).[9] Unfortunately, no mention is made of the diastereoselectivity of this process. Although it might be anticipated that organoytterbium(III) reagents, like their cerium and samarium counterparts, will undergo clean carbonyl addition to highly enolizable ketones, this point has apparently not been addressed.

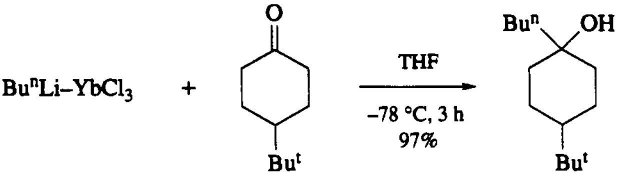

(83)

### 1.9.3.2 Organoytterbium(II) Reagents

The accessibility of a stable +2 oxidation state for ytterbium leads to the possibility of Grignard-type reagents and chemistry. Indeed, both the methods of preparation and reactions of organoytterbiums reported to date closely mimic those of the corresponding Grignard reagents. In spite of rather significant study, these organoytterbium reagents have yet to really assume a special role in organic synthesis. Nevertheless, some unique reactivity patterns have been observed, and with further systematic study one can expect more original reaction manifolds to emerge.

Organoytterbium(II) halides are most conveniently prepared by oxidative metalation of organic iodides with ytterbium metal (equation 84).[13] Since an induction period is often noticed in such reactions, activation of the metal with a trace amount of $CH_2I_2$ can be utilized to facilitate this process.[78]

$$\mathrm{EtI} \ + \ \mathrm{Yb} \ \xrightarrow[\substack{-20\ ^\circ\mathrm{C} \\ 83\%}]{\mathrm{THF}} \ \mathrm{EtYbI} \qquad (84)$$

Compounds prepared in this fashion have been determined to consist largely of 'RYbI' stoichiometries, although the possible existence of Schlenk-type equilibria has never been examined. Ytterbium to iodine ratios determined by elemental analysis, the measured magnetic susceptibilities, and reactivity patterns of these reagents are all consistent with this formulation.[13] From magnetic susceptibilities, the calculated percentages of 'RYbI' generated in solution by this procedure were determined to range from 83–93%, depending on the structure of the organic iodide substrate. This is drastically different from the situation involving samarium reagents discussed in Section 1.9.2.2, in which significant amounts of $Sm^{3+}$ species were also generated. The attenuated reductive capabilities of $Yb^{2+}$ species accounts for the increased selectivity in generation of the organoytterbium(II) reagents.

Oxidative–reductive transmetalation of ytterbium metal with diorganomercury compounds has been utilized as an entry to dialkynyl- and polyfluorinated diaryl-ytterbiums (equations 85 and 86).[79] The dialkynylytterbiums are indefinitely stable in an inert atmosphere at room temperature. On the other hand, the polyfluorinated diarylytterbiums exhibit variable stability. Isolated yields are often low owing to thermal decomposition of these organometallics. However, most can be generated in nearly quantitative yields by this procedure and simply characterized *in situ*.

$$\mathrm{Ph}\!-\!\equiv\!-\mathrm{Hg}\!-\!\equiv\!-\mathrm{Ph} \ + \ \mathrm{Yb} \ \xrightarrow[\substack{19\ ^\circ\mathrm{C},\ 4\ \mathrm{h} \\ 98\%}]{\mathrm{THF}} \ \mathrm{Ph}\!-\!\equiv\!-\mathrm{Yb}\!-\!\equiv\!-\mathrm{Ph} \ + \ \mathrm{Hg} \qquad (85)$$

$$(o\text{-}\mathrm{HC_6F_4})_2\mathrm{Hg} \ + \ \mathrm{Yb} \ \xrightarrow[\substack{0\ ^\circ\mathrm{C},\ 3\ \mathrm{h} \\ 84\%}]{\mathrm{THF}} \ (o\text{-}\mathrm{HC_6F_4})_2\mathrm{Yb} \ + \ \mathrm{Hg} \qquad (86)$$

Metal–hydrogen exchange processes have also been exploited to generate dialkynylytterbiums (equation 87).[79b,d] Clearly, this procedure is of much less synthetic value than the oxidative–reductive transmetalation method described above. Of perhaps greater synthetic utility is the metal–hydrogen exchange reaction of MeYbI with other carbon acids. For example, phenylacetylene and fluorene both react readily to generate reasonable yields of the corresponding organoytterbium iodides (equations 88 and 89).[80] Triphenylmethane and diphenylmethane do not react under these conditions. Incidentally, methyl Grignard reagents provide far lower yields of metalated products than organoytterbiums under comparable reaction conditions.

$$(C_6F_5)_2Yb \; + \; 2\,Ph{-}{\equiv} \; \xrightarrow[41\%]{THF} \; Ph{-}{\equiv}{-}Yb{-}{\equiv}{-}Ph \; + \; 2C_6F_5H \qquad (87)$$

$$MeYbI \; + \; Ph{-}{\equiv} \; \xrightarrow[-20\ ^\circ C]{THF} \; Ph{-}{\equiv}{-}YbI \; + \; CH_4 \qquad (88)$$

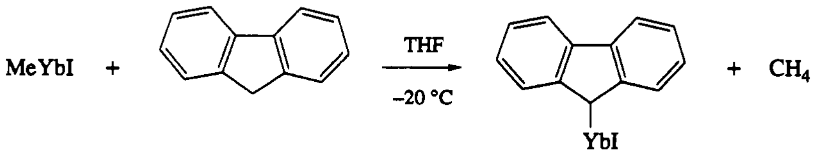

(89)

Useful applications of organoytterbium reagents to organic synthesis pale in comparison to those of organocerium and organosamarium reagents. Most reactivity patterns of organoytterbiums closely mimic those of organomagnesium and organolithium reagents. Carbonation reactions can be carried out on organoytterbiums, but yields are modest. Alkynes can be converted to a one-carbon homologated carboxylic acid in about 50% overall yield (equation 90).[80] Carbonation of bis(pentafluorophenyl)ytterbium generates the expected carboxylic acid in 50% yield, along with nearly 20% of 2,3,4,5-tetrafluorobenzoic acid. It is proposed that the latter is generated by an *ortho* oxidative metalation reaction which is triggered by the initially formed ytterbium(II) carboxylate (equation 91).[81]

$$Ph{-}{\equiv} \; \xrightarrow[\text{iii, } H_3O^+ \\ 50\%]{\text{i, MeYbI} \\ \text{ii, } CO_2} \; Ph{-}{\equiv}{-}CO_2H \qquad (90)$$

$$(C_6F_5)_2Yb \; \xrightarrow[\text{ii, } H_3O^+]{\text{i, } CO_2} \; \underset{50\%}{C_6F_5CO_2H} \; + \; \underset{16\%}{o\text{-}HC_6F_4CO_2H} \qquad (91)$$

Organoytterbium(II) reagents react with aldehydes and ketones to provide modest yields of the corresponding alcohols (equation 92).[82] Significant quantities of pinacol products are generated when diorganoytterbiums are reacted with aromatic ketones, presumably as a result of electron transfer from the ytterbium(II) organometallic. Although principally carbanion transfer reagents, it is clear that organoytterbium(II) reagents can also serve as effective reductants.

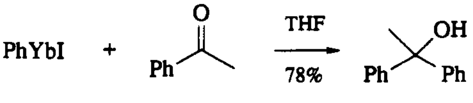

(92)

Organoytterbium(II) halides provide higher 1,2-selectivity in reactions with α,β-unsaturated aldehydes and ketones than their Grignard counterparts, although yields are sometimes low (equation 93).[78,83]

More surprising is the attenuated reactivity of organoytterbium reagents for ketones, especially when compared to carboxylic acid esters. Competitive reaction of phenylytterbium iodide with a 1:1 mixture of

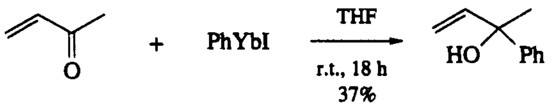

(93)

methyl benzoate and acetophenone results in the formation of 34% benzophenone and only 17% 1,1-diphenylethanol.[9] Unfortunately, no account was made of the remainder of the material. However, these results imply that organoytterbium reagents are more reactive towards esters than ketones. The attenuated reactivity towards ketones has been exploited in the development of a selective ketone synthesis from carboxylic acid derivatives (equation 94).[84] Iron trichloride proved to be an effective catalyst for this reaction, providing higher selectivity than reactions utilizing copper(I) salts or with the organoytterbium reagent alone. Unfortunately, yields reported are too low to be of much value in synthesis.

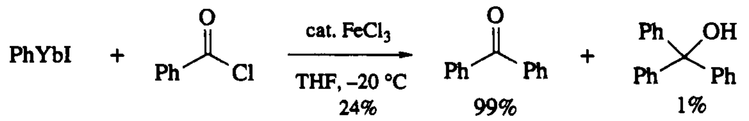

(94)

Phenylytterbium(II) iodide has also been demonstrated to react selectively with *N*,*N*-dimethylbenzamide, affording a 60% yield of benzophenone (equation 95).[14a] Under comparable conditions, the corresponding Grignard reagent provided benzophenone in only 20% yield.

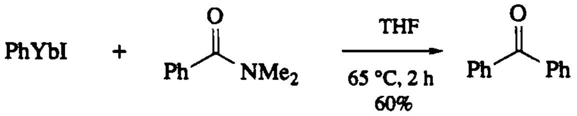

(95)

Nitriles do not undergo efficient reactions with organoytterbium reagents.[9] However, isocyanates are reported to provide good yields of the corresponding amides (equation 96).[13]

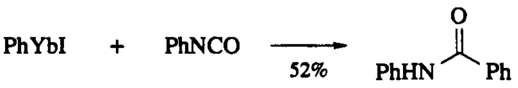

(96)

### 1.9.3.3 Barbier-type Reactions Promoted by Ytterbium Diiodide

Although the application of $SmI_2$ as a reductant and reductive coupling reagent has already had a major impact on selective organic synthesis, utilization of the corresponding ytterbium reagents has lagged behind. There are several important reasons for this. First, although several rapid and convenient syntheses of $SmI_2$ have been reported, preparation of $YbBr_2$ by reaction of ytterbium with 1,2-dibromoethane requires a reaction time of over 2 d. In addition, although $SmI_2$ is relatively soluble in solvents like THF (0.1 M), both $YbI_2$ and $YbBr_2$ have limiting solubilities of <0.04 M in the same solvent.[16b,85] Finally, the redox potential of ytterbium(II) species is borderline for the types of transformations that are of interest to synthetic organic chemists. Nevertheless, some transformations have been reported which nicely complement those accomplished by $SmI_2$.

Intermolecular Barbier-type reactions are reportedly not possible when $YbI_2$ is utilized as the reductant.[16c] However, intramolecular versions of the reaction proceed smoothly.[36] Both five- and six-membered rings can be generated in this process, and in some cases the observed diastereoselectivities exceed those achieved with $SmI_2$ (equation 97). Unfortunately, diastereoselectivity is not always high nor predictable, and thus mixtures of *cis* and *trans* bicyclic alcohols are usually generated.

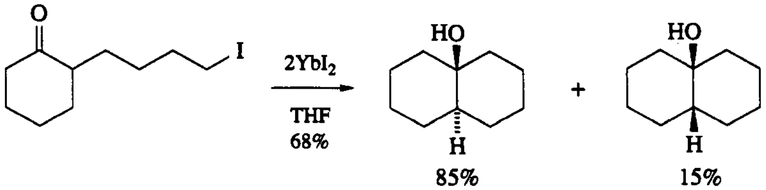

(97)

Other types of reactions that so successfully employ $SmI_2$ as a reductant have yet to be attempted utilizing $YbI_2$. As a milder reductant that might also provide some advantages in terms of diastereoselectivity over $SmI_2$, $YbI_2$ and other ytterbium(II) reagents may have a bright future in synthetic organic chemistry.

### 1.9.3.4 Miscellaneous

Ytterbium metal has been found to promote cross-coupling reactions between diaryl ketones and a variety of C—X $\pi$-bond electrophiles.[86] The reactions reportedly occur by nucleophilic addition of an ytterbium diaryl ketone dianion to the electrophiles. The net result of these transformations is that the diaryl ketones have been converted by the ytterbium from an electrophilic species to a nucleophilic diarylcarbinol anion equivalent. Although this methodology probably will not be a general one from the point of view of the ketone (alkyl ketone dianions are, in general, energetically inaccessible), the procedure does have synthetic utility when nucleophilic incorporation of diarylcarbinols is desired.

The earliest studies on this reaction began with an attempt to generate simple symmetrical pinacols.[86] Reaction of 1 equiv. of ytterbium metal with 2 equiv. of a diaryl ketone in THF/HMPA provided excellent yields of the corresponding symmetrical pinacols (equation 98). Interestingly, when equimolar quantities of ytterbium metal and benzophenone were employed, the sole product isolated after aqueous work-up was benzhydrol. When $D_2O$ was utilized to quench this reaction mixture, *C*-deuterated benzhydrol was formed (equation 99). These latter results indicated that a discrete ketone dianionic intermediate was generated in the reaction between ytterbium metal and diaryl ketones.

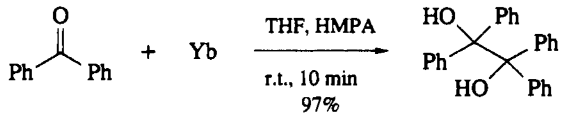

(98)

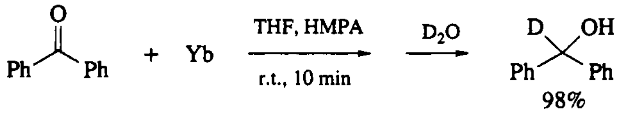

(99)

Spectral studies lend support to the existence of a discrete organoytterbium species. IR spectra taken of reaction mixtures provide evidence for a three-membered oxametallacyclic structure (**11**) incorporating a divalent ytterbium.[86] Of course, the precise nature of this intermediate is still unknown; nevertheless, available evidence does point to a unique type of intermediate which may prove useful in further synthetic transformations.

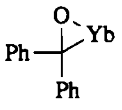

(**11**)

Indeed, it has been found that unsymmetrical pinacols can be generated in surprisingly high yields by treating 1 equiv. of a diaryl ketone with 1 equiv. of ytterbium metal, and subsequently quenching the resultant reaction mixture with a variety of aldehydes and ketones (equation 100).[86] Yields in most cases are high, and this particular transformation represents one of the very few ways in which such a process can be accomplished efficiently. Reaction of benzophenone/ytterbium with 2-cyclohexen-1-one provides mixtures of 1,2- and 1,4-addition products, together with some benzhydrol.

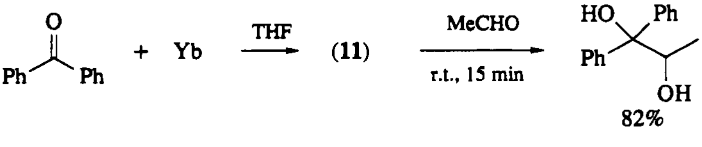

(100)

Recognition that a discrete intermediate could be trapped by aldehydes and ketones led to further studies involving a variety of electrophiles.[86] For example, $CO_2$ was found to react effectively with the ytterbium intermediate, providing good yields of α-hydroxycarboxylic acids (equation 101). Carbonylation did not take place at room temperature under ambient pressures of CO, and carbon disulfide provided a mixture of unidentified products.

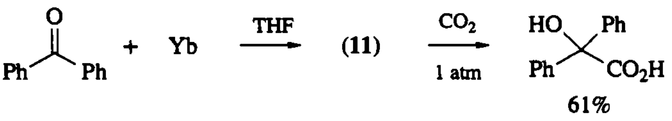

(101)

Carboxylic acid derivatives such as esters and amides undergo nucleophilic acyl substitution reactions with the ketone dianion derived from benzophenone, providing modest yields of the corresponding carbonyl products (equations 102 and 103).[86] Benzhydrol is a significant by-product in these reactions.

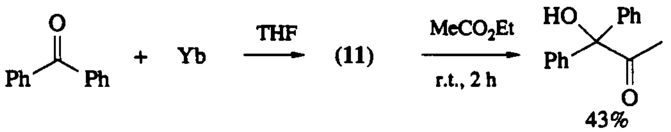

(102)

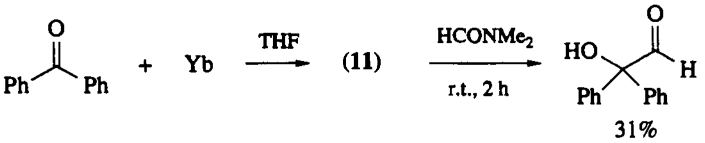

(103)

Isocyanates also react with the ytterbium ketone dianion, providing the expected amides in good yields (equation 104).[86]

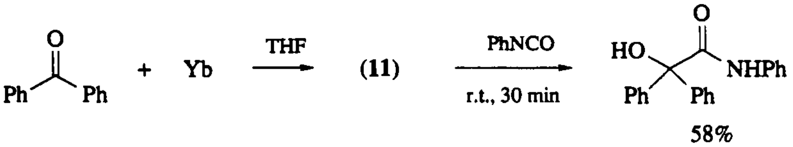

(104)

Finally, nitriles undergo addition with several different diaryl ketone dianions, affording α-hydroxy ketones after hydrolysis of the reaction mixture (equation 105).[86] In some cases, deoxygenated ketones appear as minor by-products of the reaction.

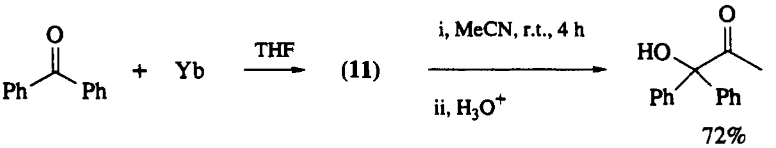

(105)

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# 1.10
# Lewis Acid Carbonyl Complexation

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## 1.10.1 INTRODUCTION

Over 100 years have passed since the appearance of the first report of the formation of crystalline complexes between boron trifluoride and aromatic aldehydes.[1] Since then, Lewis acids have found a prominent role in organic synthesis through their action on carbonyl-containing compounds. They have been used as additives or catalysts in carbonyl addition processes, and in many cases they constitute the essential component of basic carbon–carbon bond forming reactions. Most recently there has been impressive development in the area of asymmetric catalysis by Lewis acids. New chiral reagents possessing near complete asymmetric control are being reported at an increasingly rapid rate. The true origins of the 'Lewis acid effect', however, are still poorly understood. Three examples from simple nucleophilic additions to 4-*t*-butylcyclohexanone (1) are illustrative.

Addition of MeLi to (1) at –78 °C in diethyl ether requires 60 min to reach completion and affords a 65:35 mixture of axial:equatorial alcohols (Figure 1).[2,3] In the presence of $LiClO_4$, however, the same addition is complete within 5 s and proceeds with higher stereoselectivity to give predominantly the axial alcohol in a 92:8 ratio. Precomplexation of the ketone with the bulky Lewis acid, methylaluminum(2,6-di-*t*-butyl-4-methylphenoxide) (MAD), on the other hand, affords the equatorial alcohol almost exclusively.[3]

Rationalization, let alone *a priori* prediction, of these results based on common structural models is not a trivial issue. In order to address such problems one needs a better understanding of the energetics and conformational properties of Lewis acid carbonyl complexes. The aim of this chapter is to survey the lit-

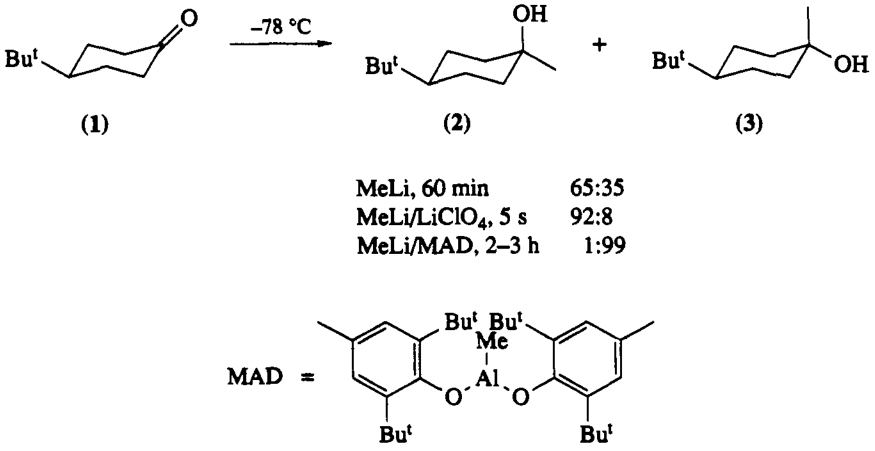

| | |
|---|---|
| MeLi, 60 min | 65:35 |
| MeLi/$LiClO_4$, 5 s | 92:8 |
| MeLi/MAD, 2–3 h | 1:99 |

**Figure 1** Effect of additives on the reaction of MeLi and *t*-butylcyclohexanone

erature that has helped to elucidate the structural consequences of complexation between Lewis acids and a carbonyl moiety. To facilitate the focus and analysis of the large body of available data on this subject, the structural questions of prime interest will be summarized in the following section. The ensuing sections will then draw upon pertinent data in an attempt to explain each particular issue.

## 1.10.2 STRUCTURAL ISSUES

### 1.10.2.1 Effects on Rate and Reactivity

Perhaps the best known effect of Lewis acids on the reaction of carbonyl-containing compounds concerns their ability to enhance reactivity. For example, the $AlCl_3$-catalyzed Diels–Alder reaction of anthracene and maleic anhydride in dichloromethane at room temperature is complete in 90 s, while the uncatalyzed reaction has been estimated to require 4800 h for 95% completion.[4] Such dramatic rate enhancements in Lewis acid promoted reactions are generally rationalized in terms of an increase in the polar character of the carbonyl group. This suggestion has direct implications for the structure of Lewis acid carbonyl complexes. Possible consequences include a longer C—O bond, increased dipole moment[5] and an influence on the conformational preferences of groups proximal to the carbonyl ligand. An examination of the theoretical and experimental results that pertain to these issues may, in turn, shed some light on the origins of rate enhancement.

### 1.10.2.2 $\sigma$- *versus* $\pi$-($\eta^2$)-Bonding

In principle, a carbonyl ligand can coordinate to a Lewis acidic metal center either through its lone pair electrons to form a $\sigma$-bond or through the carbonyl $\pi$-system to afford $\eta^2$-metallooxirane complexes (Figure 2). A preference for one mode of bonding over the other will not only depend on the nature of the Lewis acid but also on the steric and electronic requirements of the carbonyl ligand. Moreover, different modes of bonding impose different constraints upon the conformation and reactivity of the ligand. For example, $\eta^2$-bonding necessarily blocks one face of the carbonyl ligand, thereby directing the approach of a reactive reagent to the opposite face. However, a simple rule of face selectivity is not available for the $\sigma$-bound carbonyl complex. On the other hand, the conformational biases of substituents *syn* and *anti* to the metal (Figure 2; $R^1$ and $R^2$) in these systems would be quite different than for $\eta^2$-complexes, where $R^1$ and $R^2$ occupy symmetric volumes of space with respect to an achiral Lewis acid. Furthermore, one might expect a more polar and perhaps more reactive C—O bond for $\sigma$-complexes. Therefore, it would be helpful to know if any preference for Lewis acid $\sigma$- or $\pi$-($\eta^2$)-coordination and *syn* or *anti* to particular substituents, exists.

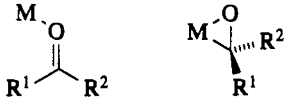

Figure 2 σ-Bonding *versus* π-bonding

### 1.10.2.3 Conformational Issues

#### *1.10.2.3.1 Conjugated carbonyls:* s-cis versus s-trans

Although there are many conformational issues which can influence the stereochemical outcome of the reaction of carbonyls, the central question for most simple α,β-unsaturated carbonyl systems is whether the reactive intermediate adopts an *s-cis* or *s-trans* conformation (Figure 3). Since the *s-cis* and *s-trans* arrangements expose different faces of an α,β-unsaturated moiety, this issue becomes particularly important in enantioselective additions to these systems. The question can now be posed as to how coordination to a Lewis acid may affect the equilibrium between the *s-cis* and *s-trans* arrangements.

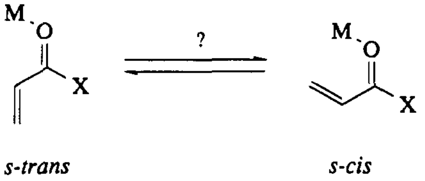

Figure 3 *s-cis versus s-trans*

#### *1.10.2.3.2 Nonconjugated carbonyls*

Despite the great deal of attention devoted to nucleophilic additions to α-chiral carbonyls, the source of stereoselectivity in these reactions (predicted by Cram's rules of asymmetric induction[6]) remains largely unresolved. Neither direct structural studies nor correlation of reactant and product stereochemistries have yielded any conclusive support for a single comprehensive model. Similarly, the effect of Lewis acids on these systems is only understood at the level of chelation-controlled additions (*vide infra*).

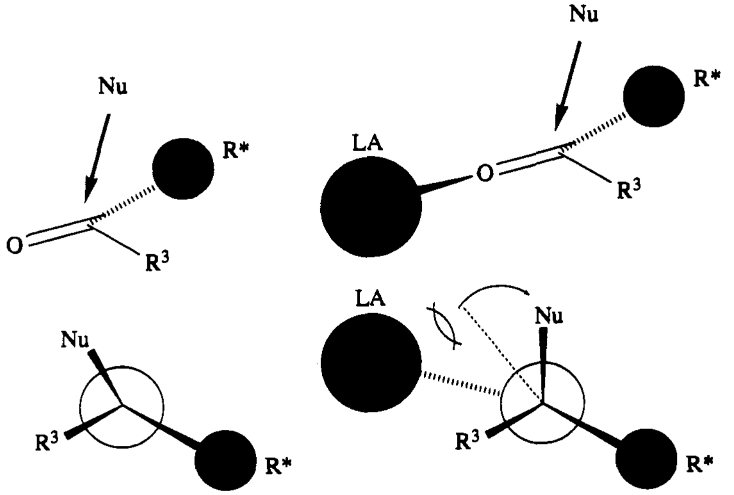

Figure 4 Postulated effect of Lewis acids (LA) on the trajectory of nucleophilic attack

It has been suggested that Lewis acids could affect the trajectory of nucleophilic additions to carbonyl electrophiles (Figure 4).[7] For α-chiral carbonyls this change may translate to a more acute angle of attack, and thereby closer proximity of the nucleophile and the center of chirality. This hypothesis is supported by MNDO calculations of the $H^-$/pivalic aldehyde system,[8] and also by an investigation of nucleophilic additions to chiral thionium ions.[9] Higher levels of diastereoselectivity are observed with larger aryl substituents on the thionium species (Figure 5).[9] Bulky aryl groups can thus be envisioned as playing a role similar to that of a coordinating Lewis acid and increasing the stereoselectivity by reorientation of the trajectory of attack. Still, this proposal does not address the question of the influence of Lewis acids on the inherent conformational preferences α to a carbonyl. A structural model of this effect would undoubtedly be of great value for the design of stereospecific reactions of this type, and it may also provide some insight into the origins of Cram selectivity itself.

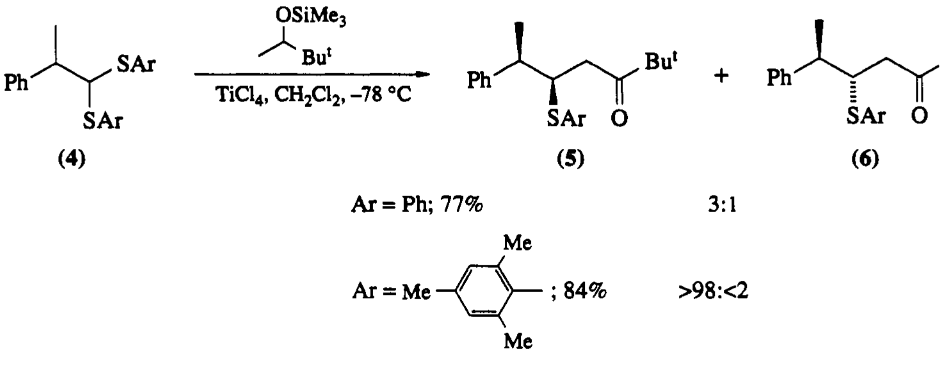

Figure 5 Diastereoselectivity in nucleophilic additions to chiral thionium ions

## 1.10.3 THEORETICAL STUDIES

Most of the early theoretical studies of Lewis acid carbonyl interactions focused on alkali metal cations such as $Li^+$ and $Na^+$, partly due to the significance of such interactions in biological systems and partly due to computational limitations. In 1973 some of the first calculations on the formaldehyde/$Li^+$ system were performed.[10] Using both *ab initio* (SCF–LCAO–MO) and semiempirical (CNDO/2) methods the researchers found that in the ground state the complex possesses $C_{2v}$ symmetry in which $Li^+$ lies on the axis of the carbonyl C—O bond with an O—Li distance of 1.77 Å.

Interestingly, the energy of interaction showed a strong preference for the linear geometry of C—O—Li, whereas little out of plane angular dependence was observed (Figure 6).[10] A second study of the same complex, using larger basis sets and a full configuration interaction (CI) analysis, later confirmed these results (linear C—O—Li, $C_{2v}$ symmetry, $d$[O—Li] = 1.70 Å) and also indicated that the C—O bond length of the complex (1.23 Å) is close to that of isolated formaldehyde at equilibrium.[11] Thus it was argued that structural relaxation of the carbonyl group was not important. However, a Mulliken population analysis revealed a pronounced polarization of the formaldehyde electron density towards oxygen, indicating that complex stabilization is achieved mainly through electrostatic ion–dipole interactions with little covalent character for the O—Li bond.

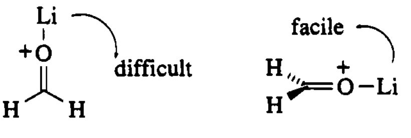

Figure 6 Relative ease of distortions for the $Li^+$/formaldehyde complex

(based on *ab initio* results of ref. 10)

In 1979 the results of *ab initio* calculations at the 4-31G and 6-31G level on the same complex as well as a formaldehyde/$H^+$ complex were reported.[12,13] Structural and energetic comparisons of the two complexes showed that while $Li^+$ prefers a linear geometry for electrostatic ion–dipole bonding, the proton coordinates to the carbonyl through a largely covalent bond, resulting in a bent structure ($C_s$ symmetry) for the $H_2CO—H^+$ complex with a CO—H angle of 124.5°. The energy of the $Li^+$/formaldehyde complex was then compared to the energy of $Li^+$ complexes of urea, acetone, carbonyl fluoride and carbonic acid. Based on these calculations the order of $Li^+$ affinities of Lewis bases with the general formula $R_2C{=}O$ could be assigned as R = $NH_2$ > Me > OH > H > F, consistent with intuitive notions of electron-donating or electron-withdrawing abilities of the substituents R.

Complexation of acetone with a sodium cation was investigated through a combination of *ab initio* and semiempirical calculations.[14] The investigators concluded that, similar to the lithium complexes, $Na^+$/acetone adopts a linear geometry, with Na 1.22 Å from the carbonyl oxygen. These results are in full accord with an extensive *ab initio* study of proton, lithium and sodium affinities of first and second row bases.[15] Both groups, however, also pointed out deficiencies in their theoretical methods which could account for some of the discrepancies with experimentally determined Lewis acid–base bonding energies.[16]

The geometries found for the complexes of formaldehyde with first and second row cations in theoretical studies were analyzed in terms of molecular orbitals.[17] Based on the results of photoelectron spectroscopy,[18] it was argued that the carbonyl group contains two nonequivalent lone pairs; an *sp*-hybridized orbital contains one pair of electrons along the C=O axis and a second, higher energy lone pair in a *p*-like orbital lies perpendicular to the C=O axis (Figure 7).[17]

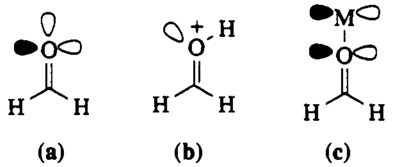

**Figure 7** Proposed molecular orbital scheme for uncomplexed and complexed formaldehyde

When the Lewis acid interacts with only one lone pair of the carbonyl a bent geometry is observed, since the second lone pair can be stabilized by acquiring more *s*-character in an $sp^2$-like orbital (Figure 7b). The linear geometry is favored for Lewis acids with a second vacant orbital that can accommodate additional electron donation from the second *p* lone pair (Figure 7c). The structures of a number of Lewis acid/formaldehyde complexes were thus rationalized and it was also noted that these geometric preferences may be weak, since in some cases strong Lewis acid carbonyl interactions were found in structures distorted by as much as 30° from their optimum (bent or linear) geometries.

It has been noted that although the linear geometry is consistently predicted for cationic Lewis acid carbonyl complexes in *ab initio* calculations, extrapolation of these results to neutral Lewis acid complexes may not be justified.[19] Semiempirical MNDO calculations predicted the bent conformation as the lowest energy structure for neutral Lewis acidic derivatives of beryllium, boron and aluminum complexed with *trans*-2,3-dimethylcyclopropanone, whereas linear structures were predicted for the cationic complexes of beryllium and aluminum (Table 1).[19]

**Table 1** Geometric Preferences for the Complexes of Dimethylcyclopropanone with Lewis Acids; MNDO-calculated Heats of Formation for the Bent and Linear Geometries

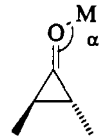

| *M* | *Bent* *Angle (α)* | *ΔH* (kcal mol$^{-1}$) | *Linear* *Angle (α)* | *ΔH* (kcal mol$^{-1}$) | *ΔΔH* |
|---|---|---|---|---|---|
| $BeH^+$ | 150.0° | 138.7 | 180.0° | 137.1 | 1.6 |
| $BeH_2$ | 149.8° | −27.04 | 179.9° | −26.63 | 0.41 |
| $AlMe_2^+$ | 136.0° | 111.7 | 179.5° | 108.8 | 2.9 |
| $AlMe_3$ | 138.8° | −52.24 | 180.0° | −49.49 | 2.75 |
| $BF_2^+$ | 133.5° | −11.27 | 180.0° | −6.85 | 4.42 |
| $BF_3$ | 133.4° | −270.8 | 180.0° | −265.6 | 5.2 |

In a recent article the question of the effect of Lewis acids on the conformational preferences of α,β-unsaturated carbonyl systems was addressed.[20] Calculations were first conducted on three uncomplexed α,β-unsaturated carbonyl compounds and the relative energies of the *s-cis* and *s-trans* conformations were compared. As can be seen from Table 2,[20] while the *s-trans* conformation is favored for uncomplexed acrolein, both acrylic acid and methyl acrylate prefer the *s-cis* conformation, although this preference is not strong.

**Table 2** Relative Ground State Energies of α,β-Unsaturated Carbonyls

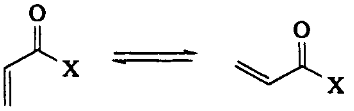

| *Entry* | *X* | *Relative energies* (kcal mol$^{-1}$) *s-trans* | *s-cis* | $E_a$[b,c] | *Basis set* |
|---|---|---|---|---|---|
| 1 | —H | 0.0 | 1.8 | 8.9 (5.0) | 6-31G*//3-21G* |
| 2 | —OH[a] | 0.6 | 0.0 | 7.5 (3.8) | 6-31G*//3-21G* |
| 3 | —OMe[a] | 0.7 | 0.0 | 7.4 | 6-31G*//3-21G* |

[a] Values are for the (*Z*)-conformations of acrylic acid and methyl acrylate. [b] Barriers to rotation: calculated relative energies for an optimized structure with the τ(C═C—C═O) angle constrained to 90°. [c] Experimentally determined values given in parentheses when available.

Next, complexation with various Lewis acids was studied extensively. Protonation of acrolein, for example, affords a bent complex in which both the C—O and the C—C double bonds are longer by 0.03–0.07 Å. The C—C single bond is comparably (0.06 Å) shorter than in uncomplexed acrolein. Although protonation *anti* to the C═C bond seems to have little effect on the equilibrium between *s-cis* and *s-trans* (compare entries 1 from Tables 2 and 3), *syn* protonation seems to strongly disfavor the *s-cis* conformation, presumably due to steric interactions (Table 3; entry 2). *Anti* coordination is slightly favored for the *s-trans* conformation but strongly preferred for the *s-cis* complex. Protonation of acrylic acid and methyl acrylate is more complicated since in addition to the *s-cis*/*s-trans* and *syn*/*anti* issues, (*E*)/(*Z*) conformational preferences of the acid or ester should also be considered. It was found that the (*E*)/(*Z*) equilibrium is not strongly influenced by Lewis acid coordination. Here the more stable (*Z*)-conformer will be assumed in order to focus on the two other issues. Thus, for both protonated (*Z*)-acrylic acid and protonated (*Z*)-methyl acrylate the *syn*, *s-trans* structure has the lowest energy (Table 3).[20] As compared to acrolein, the *syn*–*anti* preference is now reversed but the greater *s-trans* stability is maintained.

**Table 3** Conformational Preferences of Protonated α,β-Unsaturated Carbonyls

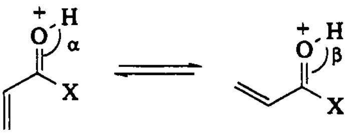

| *Entry* | *X* | | *Relative energies* (kcal mol$^{-1}$) *s-trans* | *α* | *s-cis* | *β* | *Basis set* |
|---|---|---|---|---|---|---|---|
| 1 | —H | (*Anti*)[a] | 0.0 | 121° | 1.8 | 120° | 6-31G*//3-21G* |
| 2 | —H | (*Syn*)[a] | 0.4 | 239° | 6.0 | 236° | 6-31G*//3-21G* |
| 3 | —OH[b] | (*Syn*)[a] | 0.0 | 239° | 4.2 | 123° | 6-31G*//3-21G* |
| 4 | —OH[b] | (*Anti*)[a] | 5.6 | 123° | | | 6-31G*//3-21G* |
| 5 | —OMe[b] | (*Syn*)[a] | 0.0 | 240° | 3.6 | 238° | 6-31G*//3-21G* |

[a] The terms *syn* and *anti* refer to the position of the Lewis acid relative to the C═C double bond. [b] Calculated relative energies for the (*Z*) conformers.

It was noted that a fourth low energy complex for methyl acrylate is structure (7), which is conceptually related to (*Z*)-acrylic acid by coordination of the Lewis acid Me$^+$ *syn* to the double bond.

At this point, a simple steric argument seems capable of rationalizing these results. Thus, the problem can be viewed in the following manner: protonation occurs on the least-hindered lone pair regardless of

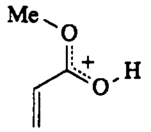

(7)

the inherent *s-cis*/*s-trans* preference of the substrate but always with retention of a (*Z*)-acid or -ester conformer; *syn* to H for acrolein and *syn* to the double bond for (*Z*)-methyl acrylate. In the latter case (*syn* to C=C) steric interactions between the Lewis acid and the double bond locks the *s-trans* conformation, yielding the (*Z*)-*syn*-*s-trans* structure. All other planar conformations suffer from one or more severe steric interactions, which lead to higher energy structures. Such a 'gearing effect' has been proposed before for other Lewis acid carbonyl complexes[110] and will be discussed further in light of some experimental results in the ensuing sections.

Two other Lewis acids were also included in these studies. Lithium cation coordination with acrolein gave a linear, *s-trans* complex as the most stable structure (Table 4).[20] An increase of the *s-cis–s-trans* gap by 1.4 kcal mol$^{-1}$ is now difficult to rationalize on steric grounds since the C=O-Li bond is nearly linear. The researchers have suggested that this effect is due to an increase in the electron density on the carbonyl oxygen upon complexation, which in turn would increase 'nonbonded electron pair–hydrogen repulsion of the alkene termini in the *s-cis* conformer'. A similar effect is observed with (*Z*)-acrylic acid, where the linear *s-trans* structure is once again more stable than the *s-cis* complex by 1.5 kcal mol$^{-1}$.

**Table 4** Conformational Preferences of α,β-Unsaturated Carbonyls Coordinated to Lithium Cation

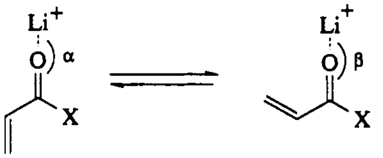

| *Entry* | *X* | *Relative energies* (kcal mol$^{-1}$) *s-trans* | *α* | *s-cis* | *β* | $E_a$[a] | *Basis set* |
|---|---|---|---|---|---|---|---|
| 1 | —H | 0.0 | 178° | 3.2 | 169° | 12.0 | 6-31G*//3-21G |
| 2 | —OH | 0.0 | 189° | 1.5 | 180° | 8.5 | 6-31G*//3-21G |

[a] Rotational barrier for isomerization calculated for an optimized structure with τ(C=C—C=O) angle constrained to 90°.

The borane complexes of acrylic acid and methyl acrylate were studied next (Table 5).[20] The *syn*, *s-trans* conformers are again preferred. Notably, the steric arguments discussed previously can nicely rationalize these results. Single point calculations on a linearly restricted BH$_3$ complex (α = β = 180°) revealed only a 0.1 kcal mol$^{-1}$ preference for the *s-trans* structure, thereby supporting the notion that, in contrast to the Li$^+$ case, the steric gearing effect is dominant in determining the structure here.

**Table 5** Conformational Preferences of α,β-Unsaturated Carbonyls Coordinated to Borane

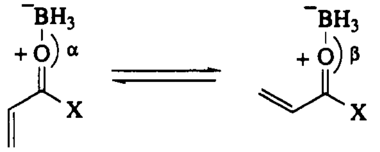

| *Entry* | *X* | | *Relative energies* (kcal mol$^{-1}$) *s-trans* | *α* | *s-cis* | *β* | *Basis set* |
|---|---|---|---|---|---|---|---|
| 1 | —OMe | (*Syn*) | 0.0 | 230° | 1.4 | 221° | 3-21G//3-21G |
| 2 | —OMe | (*Anti*) | 5.4 | 154° | 4.4 | 154° | 3-21G//3-21G |
| 3 | —OH | (*Syn*) | 0.0 | 230° | 1.3 | 221° | 3-21G//3-21G |

LePage and Wiberg have analyzed the rotational barriers of Lewis acid coordinated aldehydes and ketones.[21] Calculations on formaldehyde complexes of $BH_3$, $BF_3$, $AlH_3$ and $AlCl_3$ revealed a number of interesting effects. A planar [τ(R—C—O—M) = 0°] bent geometry with a C—O—M angle of 120° seems to be optimal for these neutral Lewis acids (Table 6; Figure 8). Small distortions (15°) in the nodal plane, however, can be accommodated fairly readily, with aluminum complexes being more flexible than the complexes of boron (Figure 8).[21]

**Table 6** Calculated Relative Energies for the Bent and Linearly Coordinated Complexes of Formaldehyde

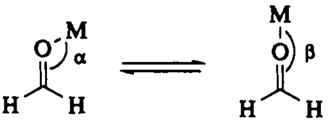

| *Entry* | *M* | *Relative energies* (kcal mol$^{-1}$)<br>*bent* | *α* | *linear* | *β* | *Basis set* |
|---|---|---|---|---|---|---|
| 1 | $H^+$ | 0.0 | 117.4° | 24.2 | 180° | MP3/6-31G*//6-31G* |
| 2 | $BH_3$ | 0.0 | 122.5° | 10.4 | 180° | MP3/6-31G*//6-21G* |
| 3 | $BF_3$ | 0.0 | 122.1° | 4.00 | 180° | MP2/6-31G*//6-21G* |
| 4 | $AlH_3$ | 0.0 | 125.1° | 5.95 | 180° | MP2/6-31G*//6-21G* |
| 5 | $AlCl_3$ | 0.0 | 141.2° | 4.63 | 180° | 6-31G*//6-21G* |

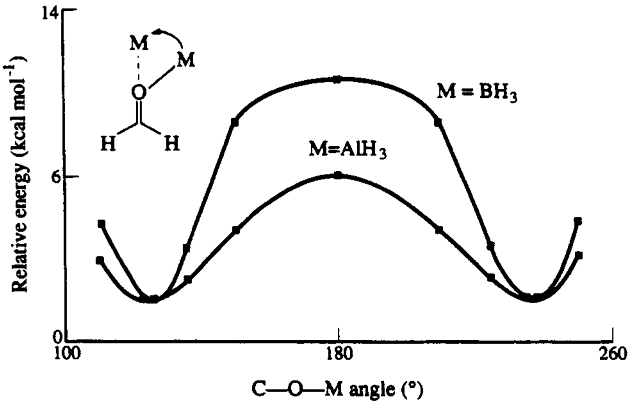

**Figure 8** Rotational profile for formaldehyde complexes of $BH_3$ and $AlH_3$ [τ(H—C—O—M) = 0°]

Perpendicular π-bonding is predicted to be energetically even less favorable than the linear mode of coordination in the nodal plane (Figure 9).[21] Once again small distortions are facile, although aluminum seems to be less tolerant of π-bonding than boron.

With propanal, borane ($BH_3$) coordinates through the less-hindered, *anti* (*syn* to H) lone pair to yield a complex which is 2.8 kcal mol$^{-1}$ more stable than the *syn* complex. Surprisingly, the rotational restrictions about the C—C—C—O bond of propanal are somewhat relaxed upon coordination of a Lewis acid (Figure 10).[21]

This phenomenon was rationalized by arguing that the C=O dipole moment is decreased upon Lewis acid complexation, thereby reducing dipole-induced dipole stabilization of the lowest energy (methyl) eclipsed conformer.

In addition to these provocative results several important shortcomings of theoretical methods, even at this level of sophistication, were emphasized. Among other things, the calculated coordination energies and rotational barriers are both strongly basis set and electron correlation dependent. Moreover, there are also many discrepancies with empirical results and no consistent trends in the theoretical disagreements with experiment can be found. The rotational barrier for the $BH_3$/formaldehyde complex was calculated to be 4–6 kcal mol$^{-1}$ lower than the spectroscopically determined value (8–10 kcal mol$^{-1}$). In contrast, the coordination energy of $BF_3$ with dimethyl ether was found to be much larger than the experimental value.

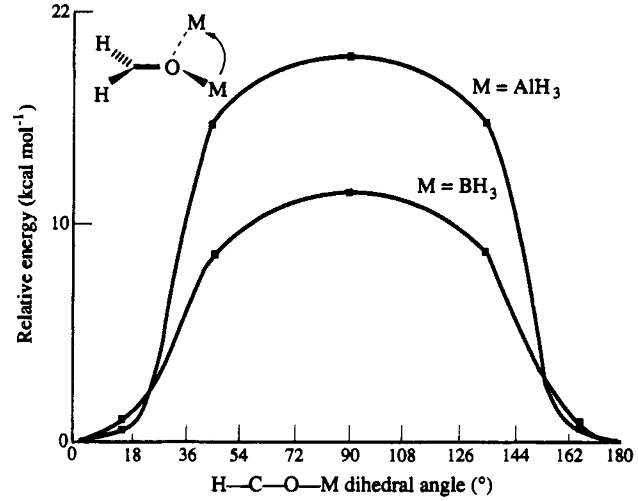

**Figure 9** Energy profile for out of plane bending for formaldehyde complexes of $BH_3$ and $AlH_3$ (C—O—M = 120°C)

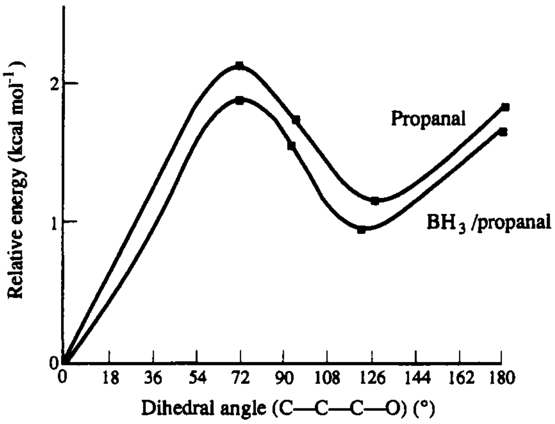

**Figure 10** Energy profile for rotation about the $C_\alpha$ bond of propanal and the effect of $BH_3$ complexation

These points prompt a few words of caution regarding the results discussed in this section and some comments on theoretical results in general. In particular, besides considerations of the size and effect of basis sets, one needs to examine the energy dependence on electron correlation. For donor–acceptor complexes, such as Lewis acid–carbonyls, electron correlation seems to be crucial. It is also instructive to consider the dipole moments of various structures in theoretical studies. Assumption of a gas phase environment may overestimate destabilization due to a large dipole, as dipoles can often be stabilized quite effectively in solution.[22] At times the interpretation of theoretical results are the source of trouble and confusion. Thus two different groups propound apparently conflicting and opposite views on the effect of Lewis acids on the carbonyl dipole.

In recent years theoreticians have exhibited a serious interest in some of the central questions of experimental organic chemistry. Unfortunately, at present, due to computational limitations, theory is unable to reliably address systems of great complexity. Larger basis sets and more efficient computing machines would naturally facilitate the examination of larger systems with increasing reliability. Another essential component, however, appears to be sensitivity towards the true origins of the observed effects or the source of disagreement among different theoretical studies or with experimental values. Difficult as they may be to achieve, coherent conceptual frameworks with strong powers of prediction are central to any theory that hopes to explain a complex problem such as Lewis acid carbonyl complexation. Thus from the experimentalist's viewpoint, a predictive tool that can be readily tested and utilized is invariably more useful than the actual numerical results which may or may not be an accurate reflection of reality.

As a final note to this discussion, one may recognize that, despite their discrepancies and disagreements, the *ab initio* calculations point to a few general observations. To begin with, ionic and covalently bound Lewis acid complexes can be regarded as two distinct categories. Ionic complexes (except for that of $H^+$) have a primarily ion–dipole mode of coordination with a preference for a linear or near linear geometry. Slight (up to 15°) geometric distortions of these complexes seem to occur with relative ease and are independent of the direction of bending.

Covalently bound Lewis acids, on the other hand, prefer a planar, bent conformation in the direction of one of the $sp^2$-hybridized carbonyl lone pairs. When the two sites of coordination on the carbonyl are nonequivalent, steric effects appear to determine the coordination geometry. The Lewis acid generally lies *syn* to the small group. For α,β-unsaturated carbonyls Lewis acid coordination increases the *s-trans* preference through steric and/or electronic influences. For nonconjugated carbonyls conformational effects on the substituents of the carbonyl group are either negligible or undetectable by theory. As will be shown in the following sections many of these generalizations are manifest in experimental observations.

## 1.10.4 NMR SPECTROSCOPY

The nature of donor–acceptor complexes has been the subject of various NMR studies conducted as early as the 1960s. Early calorimetric studies[23–25] showed that boron trihalides are capable of forming donor–acceptor complexes with a number of Lewis bases and the heats of adduct formation for some of these complexes were determined. Gaseous boron trifluoride, for example, was shown to form a complex with ethyl acetate in a highly exothermic reaction ($-\Delta H = 32.9 \pm 0.2$ kcal $\text{mol}^{-1}$).[25] IR and UV analysis of $BF_3$ complexes of aromatic aldehydes indicated a σ-complex with a lengthened C=O bond and a highly delocalized π-system.[26] More detailed structural information, however, was acquired only after closer inspection by low temperature $^1H$, $^{11}B$, $^{13}C$ and $^{19}F$ NMR studies.[27]

Initially, it was established that boron trihalides form complexes of 1:1 stoichiometry with ethereal and carbonyl-containing Lewis bases. Alkyl ethers appeared to form stronger complexes than acetone and dimethyl formamide. In addition, dimethyl ether was found to complex more strongly than dimethyl sulfide, a trend which is the opposite to that observed with gallium and tin Lewis acids.[28] Low temperature $^1H$ NMR spectra of $BF_3$/methyl ketone complexes further revealed that, while $BF_3$ exchange is rapid at room temperature, separate signals due to free and bound species can be observed at –90 °C.[29] The Lewis acidity of various boron derivatives was correlated with the chemical shift differences between the free and complexed ligand, and the order of decreasing Lewis acidity was established as $BBr_3 > BCl_3 > BF_3 > BH_3$.

*Syn–anti* isomerization about the C=O bond of $BF_3$/diethyl ketone adduct at low temperatures gave the first indication of an asymmetrical, bent structure.[30] At –125 °C two separate signals could be distinguished for the methylene protons α to the carbonyl. Since intermolecular exchange is slow even at –90 °C it was argued that the two sets of signals are due to protons *syn* and *anti* to the Lewis acid. A coalescence temperature of –111 °C ($\Delta\upsilon = 30$ Hz) suggested a barrier of *ca.* 8 kcal $\text{mol}^{-1}$ for the *syn–anti* isomerization.

Low temperature (–50 °C) $^1H$ and $^{19}F$ NMR spectra of α- or β-substituted ketones, esters and nitriles complexed to boron trifluoride showed that boron coordinates preferentially at the most basic and least-hindered base when more than one coordination site is present in the ligand.[31] Ordinarily a relative measure of chemical shifts for each type of complex would be derived from the spectra of a number of model complexes. For example, $^{19}F$ chemical shifts for $BF_3$ complexes of ketones (acetone), esters (methyl acetate), nitriles (acetonitrile) and ethers (diethyl ether) were measured as 149 p.p.m., 150 p.p.m., 144 p.p.m. and 156 p.p.m., respectively. Inspection of the resonance frequency and relative intensities of each peak would then reveal the types and ratios of the complexes present in solution.

Methoxyacetonitrile showed exclusive coordination at the methoxy oxygen while methoxymethyl acetate indicated interactions with $BF_3$ at both the ether and the carbonyl oxygens. Interestingly, a large difference was observed in the preferred site of coordination between methyl methoxyacetate and methoxymethyl acetate (equations 1 and 2). The apparent lower basicity of the ether oxygen in the latter was attributed to the electron-withdrawing effects of the proximal acetate group.

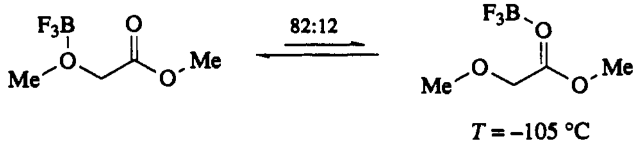

(1)

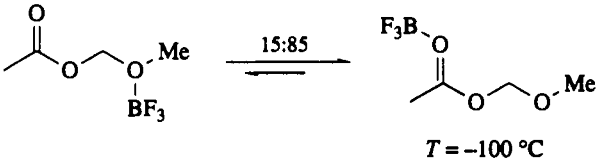

(2)

The $BF_3$/2-methoxyethyl acetate system showed a marked temperature dependence. Complexation at the carbonyl oxygen is dominant at low temperature (63% carbonyl complex at –105 °C) but a shift to the methoxy base is observed upon warming to –60 °C (61% ether complex).

A systematic study of cycloalkanones established the order of their basicity towards boron trifluoride.[32] It was concluded that steric effects control the extent of complexation. For simple cycloalkanones $C_n$ (where *n* depicts the size of the ring) the basicities were shown to decrease in the order $C_8 > C_5 > C_7 > C_6 = C_9 > C_{10} > C_4$.

NMR spectra of various carbonyl-containing steroids were investigated.[33,34] Here, intermolecular exchange was slow even at 0 °C. In the presence of hydroxy or ether functionality little or no complexation at the carbonyl sites was observed.[34] For $BF_3$/androstene-3,17-dione (Figure 11a) complexation occurred solely on the enone carbonyl of the A-ring, in contrast to 5β-androstane-3,17-dione (Figure 11b), where the carbonyls of the A- and the D-ring were complexed in a 64:36 ratio.[33]

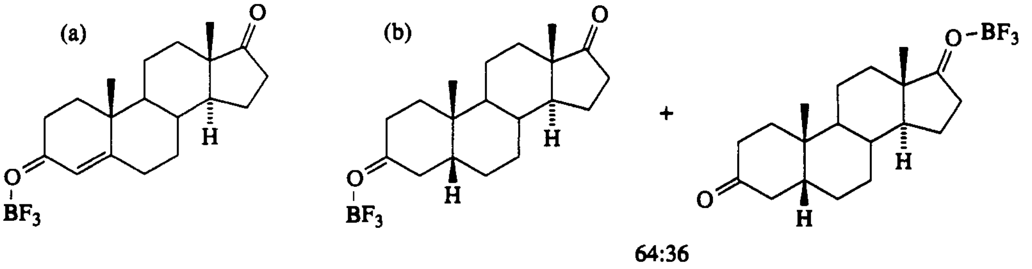

**Figure 11** Complexation of steroids to boron trifluoride

In the same study, 2-cyclohexen-1-one was studied as a model enone. The $^{13}C$ NMR spectrum at –85 °C showed two sets of signals for both the C-α and C-β carbons of the complexed ligand, presumably due to slow *syn–anti* isomerization of $BF_3$. However, it was not determined which conformer predominates or what the barrier to isomerization might be.

$^1H$ and $^{13}C$ NMR studies of cyclic and acyclic $BF_3$/ketone complexes clearly demonstrated the unsymmetrical, bent nature of their structures and suggested a barrier of 8–10 kcal mol$^{-1}$ for *syn–anti* isomerization about the carbonyl group of simple alkyl ketones.[35–37] Cyclopentanone, for example, displayed two separate sets of signals for the methylene groups *syn* and *anti* to $BF_3$ at –100 °C with a coalescence temperature of –64 °C ($\Delta G$ = 10.3 kcal mol$^{-1}$). An interesting comparison can be made between the complexes of acetone (**8**) and ethyl methyl ketone (**9**).[35] Complexation of acetone at –30 °C resulted in a slight shift (0.1 p.p.m.) of the α-carbon resonance, while for ethyl methyl ketone the two α-carbons showed a much larger shift (*ca.* 2 p.p.m.), one upfield and the other downfield from their original frequencies (Figure 12).[35]

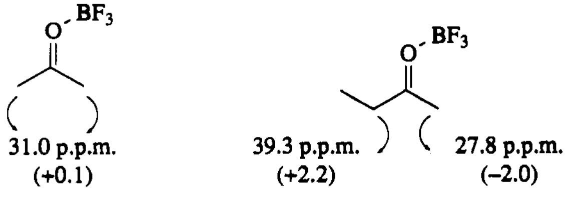

(**8**) (**9**)

**Figure 12** Selected $^{13}C$ chemical shifts of $BF_3$-coordinated ketones. Numbers in parentheses depict the change in chemical shifts from those of the free ligand in p.p.m.

These results are consistent with a single preferred conformation for (**9**) with slow *syn–anti* exchange and probably an averaging effect for the rapidly isomerizing acetone complex. It is noteworthy that the relatively small difference in the steric bulk of the methyl and ethyl substituents can affect the *syn–anti* equilibrium.

For simple cyclic ketones ($C_n$) the barrier for *syn–anti* isomerization of $BF_3$ was shown to decrease in the order $C_5 > C_7 = C_6 > C_4$, a trend which closely follows the order of their basicities towards $BF_3$ (*vide supra*).

In contrast to boron-centered Lewis acids, tin and titanium derivatives prefer a 1:2 (acid:base) stoichiometry in complexation with carbonyls. $^{13}C$ and $^{1}H$ NMR spectra of an equimolar solution of $SnCl_4$ and 4-*t*-butylbenzaldehyde showed signals only for free ligand and a 1:2 (acid:base) complex over a wide temperature range.[38] Only with excesses of $SnCl_4$ was any 1:1 adduct observed and even in the presence of 10 equiv. of Lewis acid, only 25% of the 1:1 complex could be detected. Intermolecular exchange in this case was shown to be slow below –40 °C and no *syn–anti* isomerization could be detected.

Similar observations were made in a study of $TiCl_4$/carbonyl complexes but over a smaller temperature range and to a more limited extent.[39–41] Thus, $^{1}H$ NMR studies showed that $TiCl_4$ forms 1:2 adducts with ketones, esters, ethers and nitriles. Ethers and esters were once again stronger ligands than ketones.[39] $TiCl_4$ has also been used as a diagnostic shift reagent for NMR studies of β-lactams and several α,β-unsaturated carbonyls.[40,41] Both functionalities form strong complexes (as deduced from the changes in $^{1}H$ and $^{13}C$ chemical shifts) but more detailed structural information has not been obtained.

The structure of carbonyls complexed to lanthanide shift reagents [LSR, *e.g.* Eu(fod)$_3$] has been the subject of some debate in the literature.[42–45] The two prevailing models for the structure of these complexes are known as the one-site and the two-site models, simply referring to the linear and bent geometries of coordination, respectively. The position of the lanthanide Lewis acid is generally determined by comparing the observed induced shifts with calculated values for randomly generated structures followed by a search for the best fit. The choice between a linear geometry and a 'time-averaged geometry' of two bent structures may be a difficult one, since the corresponding calculated values are probably quite similar. Although crystallographic studies of LSR complexes show a bent geometry,[47] strong spectroscopic evidence for the linear, one-site model has also been obtained.[44–46] Both models, however, agree that the location of the Lewis acid is strongly affected by the steric environment of the carbonyl group, and also that in line with *ab initio* predictions, distortions away from the lowest energy geometry appear facile.

NMR spectroscopy of Lewis acids complexed with α,β-unsaturated carbonyls has shed light on their structure and conformational preferences. Low temperature $^{1}H$ and $^{13}C$ NMR spectra of $BF_3$/2-cyclohexenone indicated slow exchange at –80 °C.[48] A mixture of *syn* and *anti* complexes was detected but the *anti* preference seemed to increase with increasing bulk at the α-carbon.

$^{1}H$ and $^{13}C$ NMR of a wide range of Lewis acids complexed with crotonaldehyde, tiglic aldehyde, 3-pentenone and methyl crotonate were investigated.[49] Correlation of $^{1}H$ and $^{13}C$ shifts at –20 °C consistently showed an *anti, s-trans* conformation for crotonaldehyde complexed with 12 different Lewis acids. Notably, $^{13}C$ NMR shifts suggested significant decrease of electron density on C-1 and C-3 but an increase of charge on C-2. This observation may be the result of a greater contribution from the enol resonance structure of the complex (Figure 13).

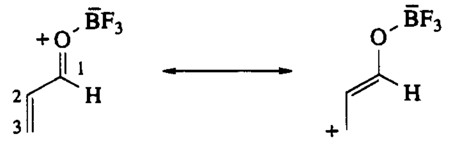

**Figure 13** Enol resonance structure of $BF_3$/enal complexes

The linear correlation between the changes in chemical shifts (Δδ) of different protons for complexed and uncomplexed crotonaldehyde has a somewhat different character for α,β-unsaturated ketones and esters. Conformational isomerization, for example, was found to be rapid for enones (2-cyclohexenone, 2-pentenone) even at low temperatures, although it was evident that the *syn* conformation, in which the Lewis acid and H-2 are in close proximity, is one of the low energy conformers. The change in the resonance frequency of H-2 was attributed to 'through-space deshielding' due to the anisotropy of the Lewis acid. Complexes of methyl crotonate provided further evidence for the predominance of the *syn* conformation. Correlation of the changes in chemical shifts of the H-2 resonances of this system with those of the crotonaldehyde complexes suggested through-space interactions of the Lewis acid with H-2, consistent with an abundance of conformer (**10**).

Finally, a scale of Lewis acidity based on the induced changes in chemical shifts was established (Table 7). Of special relevance for synthetic applications may be the relative powers of $BF_3$ and $TiCl_4$.

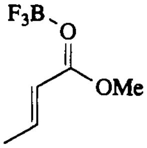

**(10)**

These results suggest that the mildness of $BF_3/Et_2O$ (relative to $TiCl_4$) may simply be due to the low effective concentrations of free Lewis acid, since uncomplexed $BF_3$ seems to be a much stronger Lewis acid. Furthermore, in cases where a second potential site of coordination (*e.g.* an ether functionality) is present in the ligand, the effective concentration of $BF_3$ may be even lower.

**Table 7** Relative Lewis Acidities as determined by $^1H$ NMR Spectroscopy.[a]

| *Lewis acid* | *Relative power* | *Lewis acid* | *Relative power* |
|---|---|---|---|
| $BBr_3$ | 1.00 ± 0.005 | $EtAlCl_2$ | 0.77 |
| $BCl_3$ | 0.93 ± 0.020 | $TiCl_4$ | 0.66 ± 0.030 |
| $SbCl_5$ | 0.85 ± 0.030 | $Et_2AlCl$ | 0.59 ± 0.030 |
| $AlCl_3$ | 0.82 | $SnCl_4$ | 0.52 ± 0.040 |
| $BF_3$ | 0.77 ± 0.020 | | |

[a] Relative power refers to the induced Δδ-values of the H-3 resonances of various α,β-unsaturated carbonyl bases.

Lewis acids that possess two empty sites of coordination are capable of imposing conformational constraints on a carbonyl ligand either by forming 2:1 complexes or *via* chelation when a second basic site is present in the ligand. Despite the popularity of the 'chelation-control' model since its original proposal in 1952 by Cram and coworkers,[50] rigorous and direct experimental evidence for chelation in α- and β-alkoxycarbonyls was only obtained recently from variable temperature $^1H$ and $^{13}C$ NMR.[51–54]

NMR titration experiments with 2-methoxycyclohexanone (**11**; equation 3) and $TiCl_4$ at 23 °C indicated the formation of a conformationally rigid 1:1 adduct, in which both the carbonyl carbon and the carbon bearing the methoxy group had lower field chemical shifts with respect to the free ligand.[51,52] The reaction of $MeTiCl_3$ and 2-benzyloxy-3-pentanone was monitored by $^{13}C$ NMR spectroscopy (equation 4). At –45 °C two new sets of carbonyl signals (downfield from those of the free ligand) appeared immediately upon addition of $MeTiCl_3$. Additionally, broadening and an upfield shift of the titanium-bound

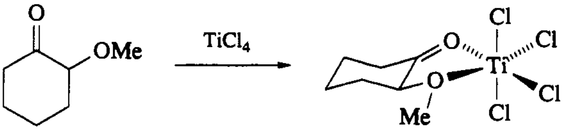

**(11)** **(12)**

(3)

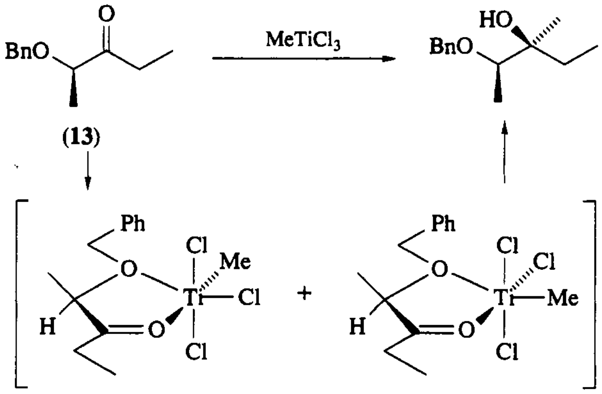

**(14)** **(15)**

(4)

methyl group indicated formation of an octahedral complex. These signals were assigned to the two diastereomeric structures (**14**) and (**15**), in which the methyl group occupies a meridional position *cis* or *trans* to the carbonyl ligand. Structures with axially disposed methyl substituents were discarded, based on precedence from previous NMR and crystallographic studies. Kinetics and crossover experiments also showed that product formation is due to bimolecular rather than intramolecular methyl transfer.[53]

β-Alkoxycarbonyls can also form stable and conformationally rigid chelates. Spectroscopic evidence for these structures was provided by a study of titanium-, tin- and magnesium-derived Lewis acids and β-alkoxy aldehydes (**16**) and (**17**).[54] Variable temperature (–80 °C to –20 °C) $^{13}C$ and $^{1}H$ NMR spectra showed that (**16**) can form conformationally rigid 1:1 adducts with $TiCl_4$, $SnCl_4$ and $MgBr_2/Et_2O$.

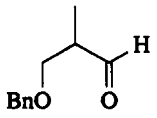

**(16)**

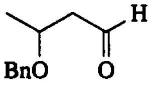

**(17)**

The splitting pattern and coupling constants for the C-2 methine hydrogen ($J_{ax-ax}$ = 9.7 Hz, $J_{ax-eq}$ = 3.5 Hz) further indicated its pseudo-axial disposition, and structure (**18**) was proposed for the $TiCl_4$ complex (equation 5).

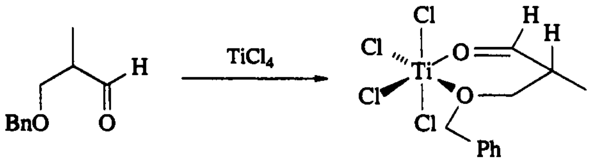

**(16)** **(18)** (5)

Aldehyde (**17**) behaved somewhat differently (equation 6). In this case, the splitting pattern for the C-3 methine hydrogen suggested a pseudo-equatorial location in the $TiCl_4$ complex, but no discreet, stable chelate could be detected with $SnCl_4$ even at –93 °C. The preference for structure (**19**) with an axial methyl group was rationalized based on the observation that the alternative conformation (**20**) would be disfavored due to an $A^{1,3}$-like interaction between the equatorial methyl group and the benzyl protecting group. The benzyl group, in turn, should be locked in its conformation due to steric interactions with the chlorine ligands of the Lewis acid.

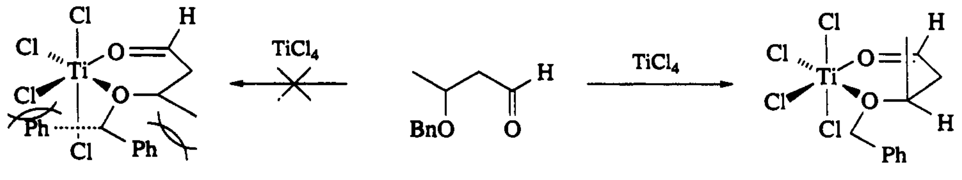

**(20)** **(17)** **(19)** (6)

Further support for this hypothesis was obtained by studying systematic changes in the steric and electronic requirements of the oxygen-protecting group.[55] The *O*-methyl derivative (**21a**), for example, was shown to form a rigid chelate with $TiCl_4$, in which the C-3 methyl substituent is equatorially ($J_{ax-ax}$ = 10 Hz, $J_{ax-eq}$ = 1 Hz) disposed (equation 7). Apparently, the size of the oxygen-protecting group in (**22**) is

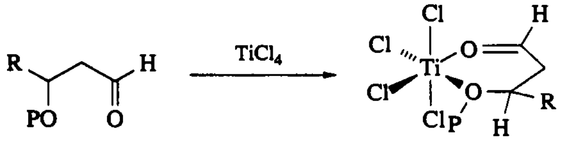

(7)

**(21a)** R = *n*-hexyl, P = Me
**(21b)** R = *n*-hexyl, P = Et

**(22)**

reduced to the extent that an equatorial substituent can now be accommodated. To appreciate the delicate balance of various influential factors here, it can be noted that in the *O*-ethylated complex (**21b**) the C-3 alkyl group is once again forced to adopt an axial disposition (*cf.* **19**).

Yet another interesting observation was made in the study of β-siloxy aldehydes.[56] $^1H$ and $^{13}C$ NMR spectra of silyl ether (**23**; equation 8) showed only 1:2 (acid:base) adduct formation and no evidence for chelation over a wide range of concentration and temperature (–80 °C to –20 °C). The researchers proposed that the reason for lack of chelation with silicon protecting groups may be electronic in nature: delocalization of the oxygen lone pair electrons into empty silicon *d*-orbitals could reduce oxygen basicity. *Ab initio* calculations on a number of alcohols, ethers and silyl ethers supported this proposal by indicating a large Si—O—C bond angle (131°), which may result from Si—O π-interactions, thereby ascribing double bond character to the Si—O bond.[57] A search of the Cambridge Structural Database (CSD) for the silyl ether [Si—O—C ($sp^3$)] substructure indicated a mean value of 126 ± 9 °C for the Si—O—C bond angle and 1.65 ± 0.05 Å for the Si—O bond length in the solid state.[58] Moreover, the Si—O bond length shows a linear decrease with increasing Si—O—C bond angle (Figure 14), suggesting that the Si—O—C bond angle may be a valid measure of the Si—O double bond character. No such correlation was found between the Si—O—C angle and the C—O bond length (Figure 15).

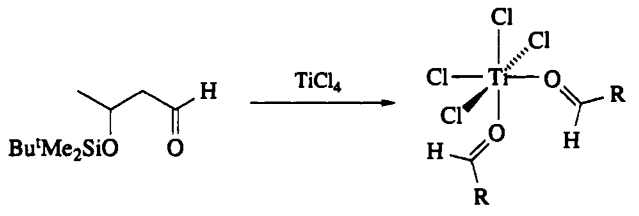

(8)

**(23)** **(24)**

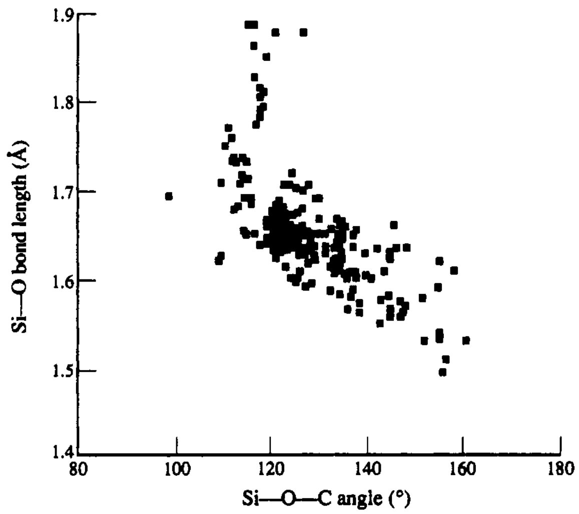

**Figure 14** Correlation of the Si—O bond lengths and Si—O—C ($sp^3$) bond angles (data from Cambridge Crystallographic Data Base)

From this discussion it is quite clear that NMR spectroscopy is one of today's most powerful tools in the pursuit of structural information. Not only can NMR spectroscopy provide accurate and easily accessible structural data regarding a large variety of chemical species, but its ability to reveal energetic and solution dynamics data is unmatched even by X-ray crystallography.[59] Detection of Lewis acid carbonyl complexes by these methods has produced several noteworthy results. It is quite evident that Lewis acids form strong and stable complexes with a variety of oxygen bases. The order of Lewis basicity of some of the most common oxygen-containing functional groups towards Lewis acids has been established. Thermodynamically, ethers seem to be stronger bases than carbonyls, although kinetic basicities of these groups have not been measured. Carbonyl-containing compounds listed in the order of reducing basicity towards common Lewis acids are amides > esters > enones > ketones > aldehydes. Effective basicity seems to be dependent on both electronic and steric effects. Thus a sterically congested ester may

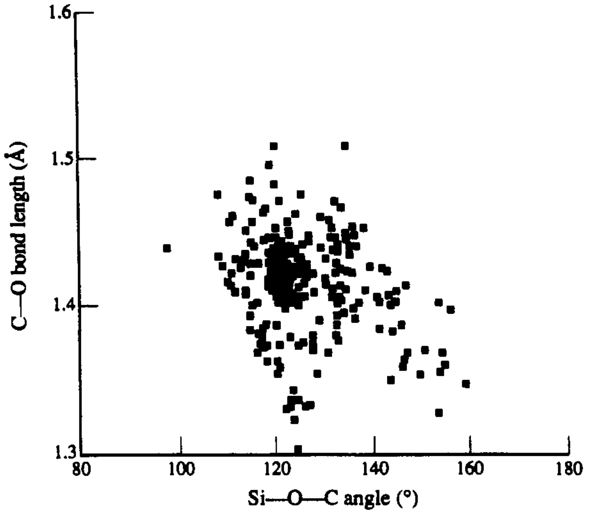

**Figure 15** Correlation of the C—O bond lengths and Si—O—C ($sp^3$) bond angles (data from Cambridge Crystallographic Data Base)

coordinate more weakly than an unhindered aldehyde. An order of Lewis acidity towards carbonyl bases has also been deduced from NMR spectroscopy (Table 7), which may prove helpful in fine-tuning the reactivity of Lewis acidic catalysts.

Most of the available data point to a bent, planar conformation for Lewis acid carbonyl complexes. *Syn–anti* isomerization seems to be fast at room temperature on the NMR timescale but at low temperature individual isomers can be observed. The barrier to isomerization is estimated as 8–10 kcal $mol^{-1}$, but the mechanism of this process (*i.e.* through a parallel or perpendicular arrangement) is unresolved. The *syn–anti* equilibrium is quite sensitive towards the relative size of the carbonyl substituents and the Lewis acid prefers to lie *syn* to the smaller substituent.

In agreement with *ab initio* predictions, Lewis acid complexation with α,β-unsaturated carbonyls seems to encourage adoption of the *s-trans* conformation. In the complexes of conjugated esters and ketones the gearing effect discussed previously may be responsible for the abundance of the (*Z*)-*syn*-*s-trans* conformation.

Strong evidence for Lewis acid chelation with bidentate bases has been gathered. Subtle and intricate factors seem to contribute to the overall conformation of the chelated complex but the importance of protecting groups for the alkoxy ligands should be emphasized. Silicon protecting groups reduce oxygen basicity probably through a combination of steric and electronic effects and thereby disfavor chelation. Alkyl ethers, on the other hand, are strong chelators, but small differences in the size of the protecting group may result in large differences in the overall conformation of the Lewis acid chelate.

There are also a few interesting topics which have not yet been addressed. The question of the conformational preferences of α-chiral aldehydes upon Lewis acid complexation is among the most important issues. Theoretical predictions imply that the small magnitude of the differences in energy may prevent detection of individual conformers even at very low temperatures. However, it is not inconceivable that through the proper choice of Lewis acid and design of an appropriate carbonyl ligand one may exaggerate the energetic differences such that detection becomes possible.

Stereoelectronic effects of various remote substituents on the basicity of the carbonyl is yet another intriguing question. Electronic effects of remote substituents have been postulated to be responsible for stereoselective additions to carbonyls in rigid adamantanone systems.[60] If present, such stereoelectronic effects would similarly be expected to bias the energetics and structural features of Lewis acid complexation.

Finally, the mechanism of *syn–anti* isomerization remains elusive. Is π-bonding truly higher in energy than the linear, planar arrangement as predicted by theory? The answers to these questions will undoubtedly help to clarify our emerging view of the interactions of the carbonyl group with Lewis acids.

## 1.10.5 X-RAY CRYSTALLOGRAPHY

There are two distinct approaches to the analysis of X-ray structural data. In one approach a detailed consideration of individual angles and distances in single crystal structures is used to attain insights into the properties and reactivity patterns of a particular compound or class of compounds. On the other hand, a statistical analysis of a large number of crystal structures that share a common structural feature can be used to extract generalizations regarding particular types of interactions or molecular properties. Clearly, the latter approach is more useful and more reliable in deriving a general sense of a bond length or bond angle, while a detailed analysis is preferred when various factors which may contribute to the final structure of a complex (especially those with unusual structures) are to be determined. Since both methods have their merits, a combination of the two has been adopted throughout this section.

Such a combination was used in connection with a study of the crystal structure of the LiBr/acetone complex.[61] In this dimeric complex (Figure 16) each lithium ion is coordinated by two molecules of acetone through the carbonyl lone pair electrons with a bent, planar geometry in a tetrahedral environment. The Li—O bond length is measured as 2.0 Å with an Li—O—C angle of 145°. Although the observed Li—O distance is very close to various theoretical predictions (*vide supra*) the nonlinear coordination geometry disagrees with *ab initio* calculations. To probe the source of this discrepancy and to determine the true low energy conformation of alkali metal/carbonyl complexes the researchers conducted a general search of the Cambridge Structural Database (CSD). Of the nine crystal structures that were analyzed in this study, six contained $Li^+$, two $Na^+$ and one $K^+$ as the Lewis acid bound to the carbonyl ligands. The coordination angle for $Li^+$ was consistently found to be bent (120°–156.3°) but large distortions from planarity (up to 55°) seemed to occur randomly. The Li—O bond distance showed no linear dependence on the Li—O—C—X dihedral angle.

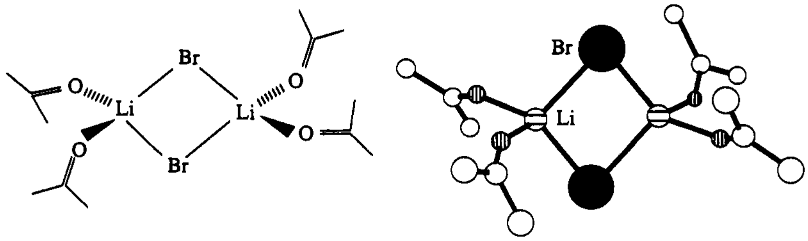

**Figure 16** Crystal structure of LiBr•(acetone)$_2$ complex

The crystal structures of $Na^+$ complexes, however, showed that linear and bent geometries are equally accessible and bending out of the plane of the carbonyl was once again observed (Figure 17).[62]

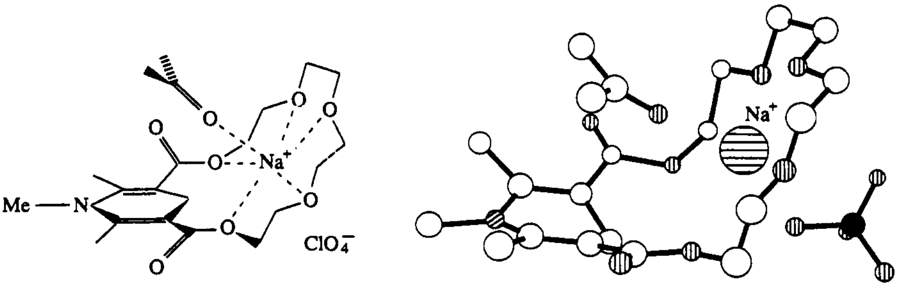

**Figure 17** Linear complexation of a $Na^+$/acetone complex

The workers concluded that the potential energy surface for carbonyl coordination to alkali metals is likely to be fairly flat with respect to changes in the M—O=C angle and the M—O=C—X dihedral angle. This proposal would also account for the discrepancy between theory and the experimental results regarding the exact structure of the lowest energy species.

A more recent search of the CSD for alkali metal/carbonyl crystal structures also confirmed these results.[63] The average Li—O bond length and the Li—O—C bond angle were found to be 1.99 ± 0.07 Å and 139 ± 3°, respectively. Of the 23 examples found, 9 exhibited coordination by more than 10° out of the plane of the carbonyl group.

Thus, cationic alkali metal Lewis acids do not exhibit any strong directional preferences in coordination to carbonyls.[64] In particular, bending towards the π-cloud of the carbonyl with no significant lengthening of the M—O bond is commonly observed. Coordination seems to occur from the direction that best satisfies the cation's electron demand and minimizes steric interactions. These, in turn, depend on the coordination number of the cation, the relative size and electronic properties of the ligands, and, in the solid state, on crystal-packing forces. It is, therefore, not at all surprising that gas phase calculations, which assume a 1:1 stoichiometry and necessarily ignore packing forces, predict different low energy structures, since under those conditions the linear geometry might very well be favored. What theory would predict as the lowest energy conformation of a multicoordinated, alkali metal/carbonyl complex is an interesting question which, at present, remains unanswered.

Finally, the biological relevance and importance of metal cation/carbonyl interactions, although beyond the scope of the present discussion, should be noted. Such interactions may play a significant role in determining the structures and conformations of metal-binding peptides or metalloproteins. Two provocative crystal structures of $Li^+$ bound to the cyclic decapeptides antamanide and perhydroantamanide have been reported.[65,66] In the former, lithium was found to be pentacoordinated to four carbonyl oxygens and the nitrogen atom of an acetonitrile solvent molecule in a pseudo square pyramidal arrangement (Figure 18).[65] In this structure, the Li—O bond lengths and Li—O—C bond angles are similar to the values discussed previously and are consistent with the principles of the foregoing discussion.

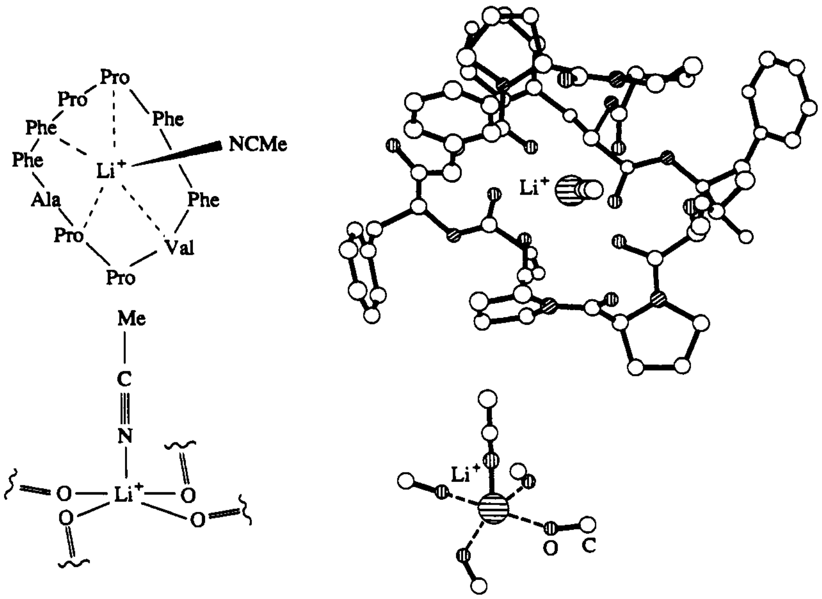

**Figure 18** Crystal structure of $Li^+$/antamanide complex

Relative to alkali metals, neutral Lewis acids seem to perform much more consistently. Crystal structure of the $BF_3$/benzaldehyde complex may serve as a representative example (Figure 19).[67] Here the Lewis acid is placed 1.59 Å from the carbonyl oxygen, along the direction of the oxygen lone pair and *anti* to the larger phenyl substituent.[68]

Although crystal structures of other bimolecular complexes of carbonyls with boronic Lewis acids have not been reported, a number of intramolecular chelates have been detected in the solid state.[69–71] In all these cases boron is found to lie in the direction of the carbonyl lone pair with no more than 11° distortion away from the best plane of the carbonyl group. The average B—O bond length is 1.581 ± 0.019 Å and the B—O—C angle lies between 112° and 119°.

A search of the CSD files for the Al—O═C substructure revealed 30 such interactions with Lewis acidic aluminum atoms from 23 crystal structures.[72] Mean values for the Al—O distances and Al—O—C bond angles were found to be 1.88 ± 0.09 Å and 136 ± 4°, respectively. Aluminum was found to lie within ±8° of the carbonyl plane where θ in Figure 20 had a mean value of 83 ± 1°.

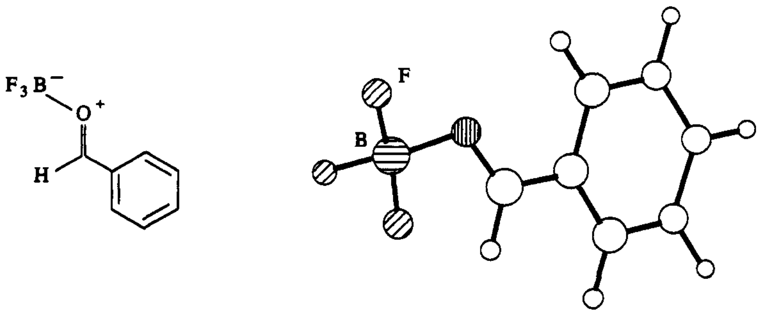

Figure 19 Crystal structure of $BF_3$/benzaldehyde complex

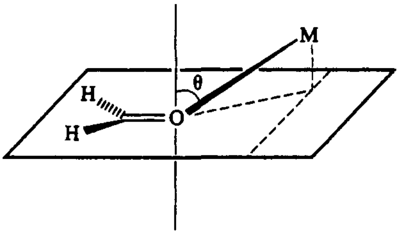

Figure 20

The crystal structure of the $AlCl_3$/tetramethylurea ($AlCl_3$/TMU) complex shows a 1:1 adduct, in which aluminum binds to the carbonyl lone pair electrons at an angle of 132.5° and at a distance of 1.78 Å (Figure 21).[73] The C—O bond length (1.239 Å) is approximately 0.06 Å longer than that of unbound TMU and 0.03 Å longer than in the corresponding $Me_2SnCl_2$/TMU complex. The Lewis acid is once again coplanar with the carbonyl, although the dimethylamino group *syn* to aluminum is twisted out of conjugation to avoid steric interactions.

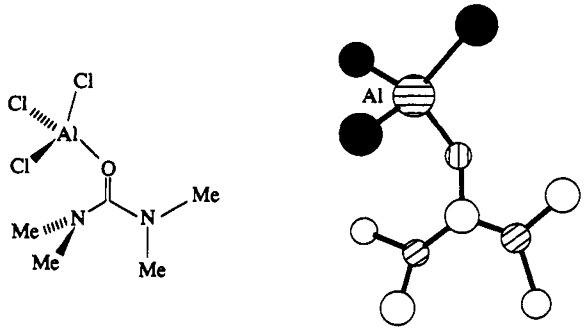

Figure 21 Crystal structure of $AlCl_3$/TMU complex

Based on statistical analyses it may be reasonable to propose that this structure reflects the idealized or low energy mode of coordination to carbonyls for aluminum-centered Lewis acids. It would be interesting to see how distortions away from such an arrangement may come about. Imposition of steric congestion through bulky substituents is one way to address this question. The crystal structure of (2,6-di-*t*-butyl-4-methyl)phenoxydiethylaluminum/methyl toluate was recently reported (Figure 22).[74]

In this structure a pseudo-tetrahedral aluminum is positioned 1.89 Å from the carbonyl ligand. The Al—O—C angle of 145.6° is on the more linear end of the Al—O—C angle spectrum, but, more interestingly, the Al—O=C—C torsion angle (49.9°) shows considerable bending towards the π-plane. Clearly, this distortion from the 'idealized' structure is a result of the unusually bulky phenoxide ligand on the Lewis acid, coupled with the fact that in (*Z*)-aromatic esters both $sp^2$-lone pairs are fairly hindered. Notice that other available mechanisms for relief of steric strain were not employed. Either twisting of the

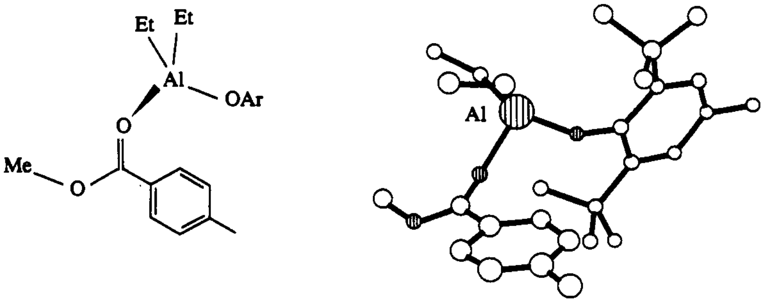

**Figure 22** Crystal structure of $Et_2Al(OAr)$/methyl toluate complex

phenyl substituent or alteration of an idealized (*Z*)-ester conformation could have accommodated a more planar Lewis acid complex, but neither occurs to any considerable extent [$\tau$(O=C—O—O) = 4.1°, $\tau$(O=C—C=C) = 12.1°]. Furthermore, a linear Lewis acid complex would also avoid steric interactions with the carbonyl substituents but this mode of coordination seems to be excluded as well. These results suggest that the energetic barrier for out-of-plane bending of the Lewis acid is less steep and probably lower than the barrier for either (*E*)/(*Z*) ester isomerization, rotation about the phenyl–carbonyl C—C bond or in-plane distortion to a linear structure. The latter proposition is in sharp contrast to theoretical predictions.

When a Lewis acid possesses two empty coordination sites, another degree of complexity is added to the structural issues discussed above. Titanium(IV) Lewis acids, for example, show a strong preference for a six-coordinate, octahedral arrangement. Thus, the acid:carbonyl stoichiometry for these complexes is often 1:2 or, when only a single equivalent of the carbonyl base is present, dimeric structures with bridging ligands are observed. The crystalline 1:1 adduct of $TiCl_4$ and ethyl acetate, for example, contains dimeric units of two octahedral titaniums with bridging chlorine atoms (Figure 23).[75] The 2.03 Å long Ti—O bond is almost coplanar with the carbonyl group [$\tau$(Ti—O=C—C) = 2.86°] and the Ti—O—C angle is measured as 152°.

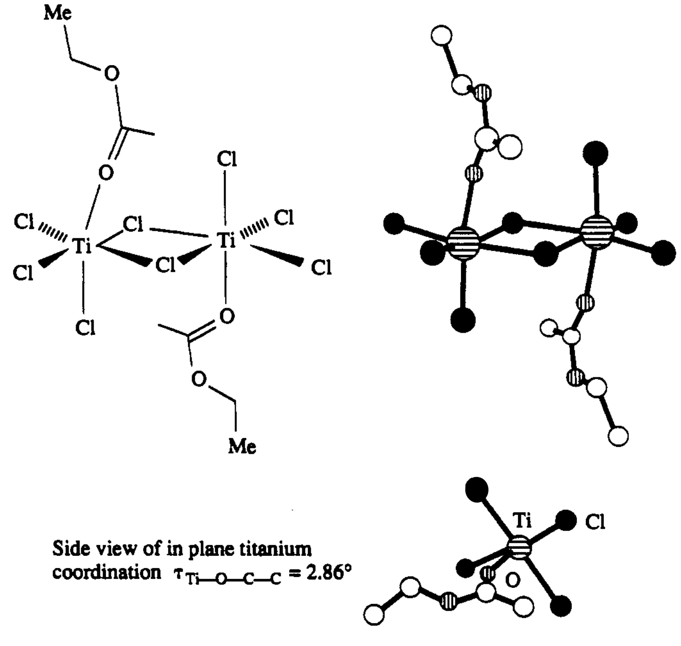

Side view of in plane titanium coordination $\tau_{Ti—O—C—C}$ = 2.86°

**Figure 23** Crystal structure of $TiCl_4$/ethyl acetate complex

These values agree well with the average Ti—O═C bond lengths and bond angles derived from searches of the CSD files (Ti—$O_{mean}$ = 2.14 ± 0.07 Å), although the Ti—O—C angle is on the wider side of the observed range (Ti—O—$C_{mean}$ = 125 ± 12°).[76] Meanwhile, the (*Z*)-conformation of the ester is retained [$\tau$(O═C—O—C) = 2.6°] by coordinating the Lewis acid *syn* to the methyl substituent.

In line with the behavior of aluminum-centered Lewis acids, deviations from the 'idealized' conformation are observed when steric congestion is imposed on the structure. This point is illustrated in the crystal structure of the $TiCl_4$/ethyl anisate complex (Figure 24).[77] Although at first glance the main features of this complex (dimeric complex, octahedral titanium, *etc.*) are very similar to those of the $TiCl_4$/ethyl acetate structure, out-of-plane bonding to the carbonyl clearly distinguishes the two structures. The Ti—O—C—C dihedral angle is 45.7° and the Ti—O—C angle has now opened up to 168.7°. The (*Z*)-conformation of the ester is still intact [$\tau$(O═C—O—C) = 1.4°] and the Lewis acid is bound more or less *syn* to the phenyl substituent, which, in turn, is twisted out of conjugation and away from the Lewis acid by 13.0°. These structural features are very similar to those of the bulky aluminum Lewis acid complex discussed previously and one may expect them to be quite general in similar systems. Interestingly, distortions from the 'idealized' structures are more prominent for the titanium complex, which may suggest that, in the dimeric form, $TiCl_4$ is in fact even larger than the aryloxyaluminum reagent, or that $\pi$-distortion occurs more readily for Ti than for Al.

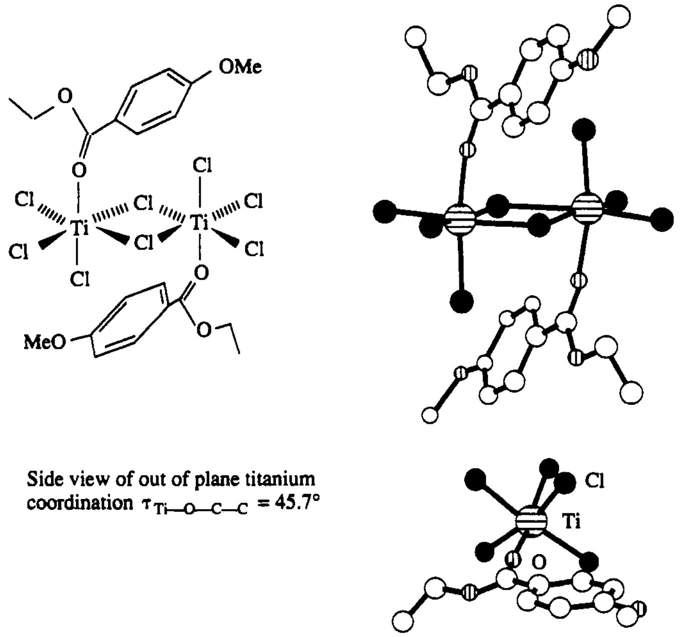

Side view of out of plane titanium coordination $\tau_{Ti—O—C—C}$ = 45.7°

**Figure 24** Crystal structure of $TiCl_4$/ethyl anisate complex

Extreme out-of-plane bonding is observed in the crystalline complex of $TiCl_4$ and acryloylmethyl lactate (Figure 25).[78] In this structure Ti is bound by two ester carbonyls in a seven-membered ring chelate. Both carbonyls are $\pi$-bonded with $\tau$(Ti—O(1)═C—C) = 63.6° and $\tau$(Ti—O(2)═C—C) = 48.1°. Both esters, however, remain very close to planarity ($\tau_1$ = 8.8°, $\tau_2$ = 4.1°) and in the preferred (*Z*)-conformation. Furthermore, due to the presence of a chelate ring the Lewis acid is *anti* to the acrylate double bond and the enoate adopts an *s-cis* geometry. It is difficult to rationalize $\pi$-bonding in this case since direct steric interactions appear to be unimportant. Moreover, $\pi$-bonding cannot be the result of chelation since crystal structures of $TiCl_4$ chelated by acetic anhydride[79] or 3,3-dimethyl-2,4-pentanedione[80] show no evidence for $\pi$-bonding. Even the seven-membered ring diester chelate of $TiCl_4$ with diethyl phthalate has the Lewis acid coplanar with the carbonyl ligands (Figure 26).[79,81] Another noticeable feature of the chelated structures is that they are all monomeric, probably due to the ability of the bidentate ligands to satisfy titanium's desire for hexacoordination and octahedral geometry.

In the previous section it was noted that in solution tin-derived Lewis acids, like titanium, prefer to form 1:2 acid:carbonyl or 1:1 chelated adducts. Consistent with these findings, the crystal structure of

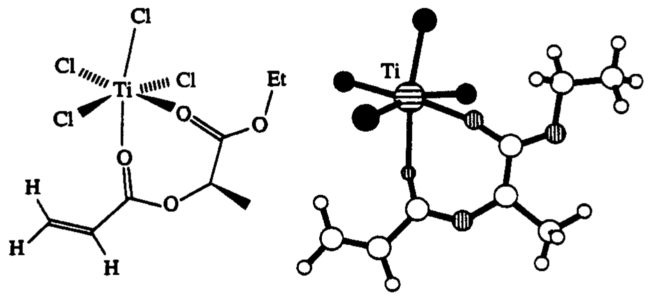
Cl
Cl
Ti
Cl
Cl
Et
O
O
O
O
H
H
H
Ti

**Figure 25** Crystal structure of $TiCl_4$/acryloylmethyl lactate complex

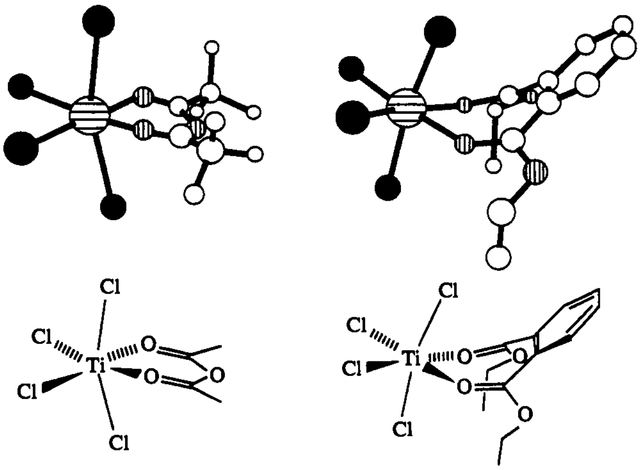
Cl
Cl
Ti
O
O
O
Cl
Cl
Cl
Cl
Ti
O
O
O
Cl
Cl

**Figure 26** Crystal structures of two $TiCl_4$ chelates

$SnCl_4$/4-*t*-butylbenzaldehyde shows a 1:2 stoichiometry with two nonequivalent aromatic aldehydes, *cis* to one another around the octahedral tin atom (Figure 27).[38]

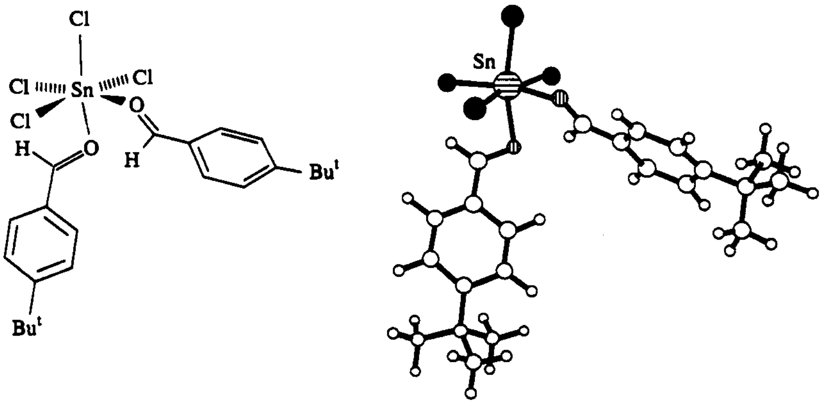
Cl
Cl
Sn
Cl
Cl
O
H
O
H
Bu$^t$
Bu$^t$
Sn

**Figure 27** Crystal structure of the $SnCl_4$ /4-*t*-butylbenzaldehyde complex

Similarly to the $BF_3$/benzaldehyde complex, tin lies within the carbonyl plane with respect to both aldehydes ($\tau_1$ = 2°, $\tau_2$ = 4°), in the direction of $sp^2$-hybridized lone pairs (Sn—O(1)—C(1) = 128°, Sn—O(2)—C(2) = 126.2°) and *anti* to the aromatic ring.

These measurements and the Sn—O bond lengths (2.23 Å) are close to the average values of tin–carbonyl bond angles and bond lengths found in the CSD files (Sn—O = 2.3 ± 0.1 Å; Sn—O—C = 127 ± 10°).[82] However, the 1:2 stoichiometry and the *cis* relationship of the carbonyl ligands are not universal. Only slight alterations in the nature of the Lewis acid or its ligands are necessary to alter this arrangement. For example, an X-ray analysis of $Ph_2SnCl_2$/*p*-dimethylaminobenzaldehyde shows a monomeric 1:1 complex with a pentacoordinated, trigonal bipyramidal tin atom (Figure 28).[83]

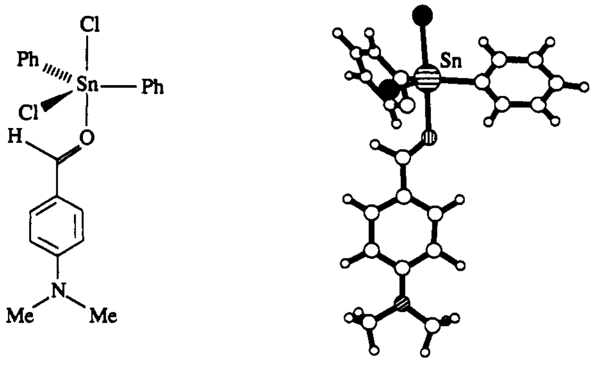

**Figure 28** Crystal structure of $Ph_2Sn_2$/*p*-$NMe_2C_6H_4CHO$ complex

Although neither the Sn—O bond length (2.3 Å) nor the bond angles [Sn—O—C = 121°, τ(Sn—O═C—C) = 4°] nor the *anti* geometry of coordination have changed significantly compared to the $SnCl_4$ complex, the environment about the Sn atom is clearly different. It is likely that these changes are caused by the substitution of chlorines for aryl groups on the Lewis acid. Thus, crystal structures of $Ph_3SnCl$/tetramethylurea (TMU),[84] $Me_2SnCl_2$/TMU,[85] $Me_3SnCl$/triphenylphosphoranyldiacetone[86] and $Me_2SnCl_2$/salicylaldehyde[87] all feature pentacoordinated, trigonal bipyramidal 1:1 adducts, while $SnX_4\cdot 2L$ (X = Cl, Br, I; L = urea or thiourea) complexes contain *cis*-octahedral tin centers.[88] The *cis* and *trans* stereochemistry of the octahedral complexes seems to depend on the size and the basicity of the base, as well as the nature of the Lewis acid. $Me_2SnCl_2$/DMU[85] and $SnCl_4$/ethyl cinnamate[89] are both *trans*-octahedral 1:2 complexes. The latter complex is particularly relevant to the discussion of the conformational preferences of α,β-unsaturated carbonyl complexes (Figure 29).[89] Here the ligand adopts a *(Z)-s-trans* conformation with tin coordinated *syn* to the double bond. The Sn—O—C—C dihedral angle of 21° indicates some out-of-plane bonding, although not as much as in the titanium complexes.

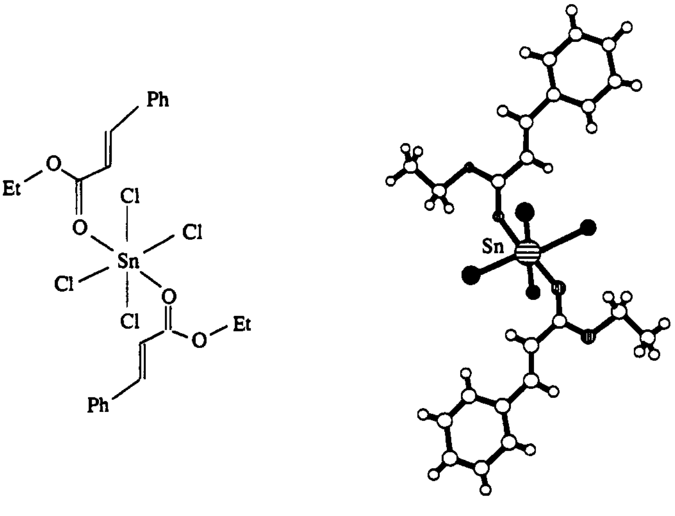

**Figure 29** Crystal structure of $SnCl_4$/ethyl cinnamate complex

Crystal structures of chelated tin Lewis acids have also been obtained. Recently, X-ray analysis of two five-membered chelates of $SnCl_4$ were reported.[90] $SnCl_4$ complexes of 2-benzyloxy-3-pentanone and methoxyacetophenone are both 1:1 monomeric chelates with distorted octahedral geometry (Figure 30).[90] In the former complex, tin is apparently coplanar with the carbonyl plane (10° puckering of the stannacycle) at a distance of 2.184(3) Å away from the carbonyl oxygen. More importantly, the ether oxygen is planar and seems to coordinate to the Lewis acid through an $sp^2$-like lone pair. This point lends credence to the assumption of $A^{1,3}$-like interactions between the oxygen-protecting group and an α-substituent, as discussed in the last section.[54] It should also be noted that coordination along the direction of a trigonal lone pair of ether oxygen atoms is not altogether unexpected and is, in fact, well documented for other Lewis acids such as lithium cation.[91]

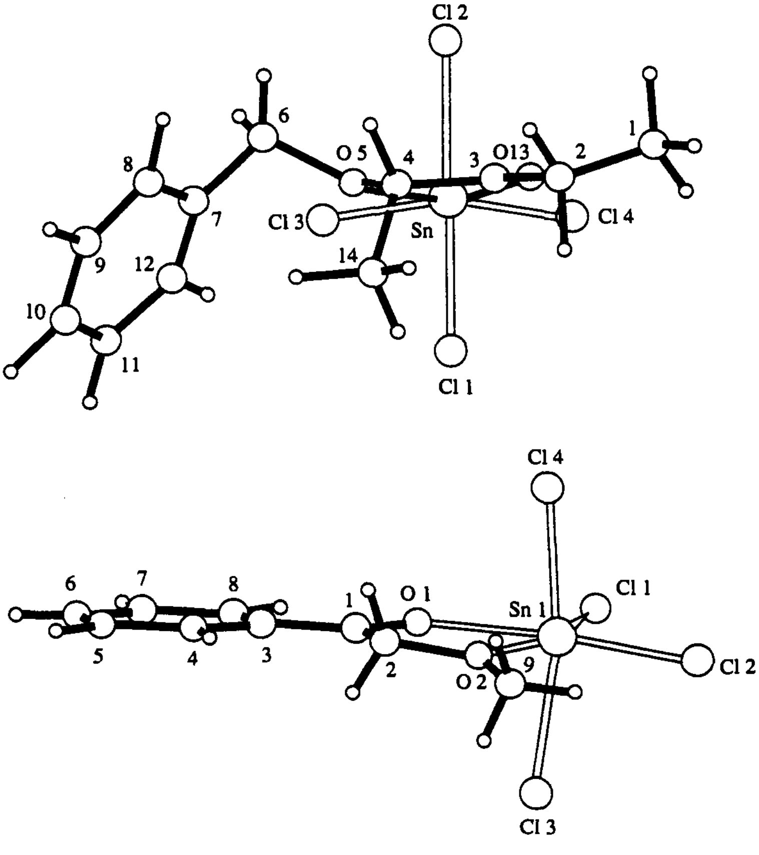

**Figure 30** Crystal structures of two $SnCl_4$ chelates

Methoxyacetophenone chelates $SnCl_4$ in much the same way.[90] There are, however, two distinct conformations about the ether oxygen in these crystals. In one conformer, the ether group is planar with $sp^2$-like donation to the Lewis acid, while in the second conformer the ether oxygen is better described as $sp^3$-hybridized and pseudo-tetrahedral.

In summary, crystallographic studies have provided a wealth of structural information regarding carbonyl complexation of various Lewis acids. More specifically, it has been shown that alkali metal cations do not show a strong directional preference for binding to carbonyls and for these complexes coordination numbers and coordination geometries vary greatly. Boron, aluminum, titanium and tin Lewis acids all accept electron density from $sp^2$-lone pairs of a carbonyl ligand at *ca.* 130–140°, but in the presence of steric interactions they easily distort from their optimal geometry. For aluminum, titanium and tin complexes there is fairly strong evidence that, contrary to theoretical predictions, these distortions are invariably out of plane, towards the π-cloud of the carbonyl group rather than the linear, in-plane geometry. This may also suggest a mechanism for *syn–anti* isomerization of the Lewis acid, although this point is less clear.

The stoichiometry of complexation is ordinarily 1:1 (acid:carbonyl) for boron- and aluminum-centered Lewis acids, which give pseudo-tetrahedral complexes, and 1:2 for octahedral $Ti^{IV}$ complexes. Tin(IV)-derived Lewis acids can form either 1:2 octahedral or 1:1 trigonal bipyramidal complexes, depending on the nature of their ligands and on the carbonyl base.

Lewis acids prefer to lie *syn* to the smaller substituent of the carbonyl, *e.g. syn* to H for aldehydes, *anti* to —OR for simple alkyl esters. In α,β-unsaturated systems, Lewis acid coordination *syn* to the double bond favors the *s-trans* conformation, but in two crystal structures, where coordination *anti* to the alkene occurs, *s-cis* complexes are observed.[78,111] Finally, chelation with titanium and tin occurs readily and yields stable, crystalline complexes.

Some of the shortcomings and difficulties encountered in the attainment of structural data from crystalline compounds should also be noted here. The single most important difficulty in X-ray crystallographic analyses is the task of obtaining suitable, X-ray diffracting crystals. This task is made even more formidable for the highly reactive and often unstable Lewis acid carbonyl complexes. Most of the crystal structures discussed here were obtained by crystal growth and data collection at low temperatures, under inert atmospheres. Once the X-ray diffraction data are available, care should be taken to avoid overinterpretation of single structures and invalid generalizations. In this section, statistical analyses of a large number of crystal structures have been used to distinguish the ordinary from the unusual. In unusual systems, crystal-packing forces may be the cause of deviations from the norm, and it is always important to take this factor into consideration. Lastly, it is worth noting that crystal structures represent static single point conformations and their relevance to dynamic chemical reactions is not clear. Nevertheless, in the past chemical dynamics have been cleverly inferred from crystallographic data,[59] although performing such a task for the case at hand would require a very serious and systematic effort.

## 1.10.6 TRANSITION METALS AS LEWIS ACIDS

Despite the focus of this chapter on the most commonly utilized Lewis acids in organic synthesis, a much larger body of data regarding the structure of donor/acceptor complexes of transition metals with carbonyls exists. Although a comprehensive treatment of this subject is beyond the scope of the present discussion, it is nonetheless worthwhile to consider the structural features of some of these complexes briefly, since many demonstrate novel and unusual ways of interacting with the carbonyl group.[92]

To begin with, one can consider those high valent transition metals that seem to behave analogously to the Lewis acids discussed thus far. The crystal structure of a cationic iridium complex $[IrH_2(Me_2CO)_2PPh_3]BF_4$ shows *cis* coordination of two acetone ligands to an octahedral iridium atom (Figure 31).[93] Iridium is coordinated to the lone pairs of the acetone ligands, coplanar with the carbonyl at an Ir—O═C angle of 133.1° for one acetone ligand and 134.9° for the other. Aside from the interest in this complex due to its role as an active dehydrogenation catalyst,[94] one can also regard it as an effective Lewis acid towards acetone, since it seems to possess all the necessary structural characteristics.

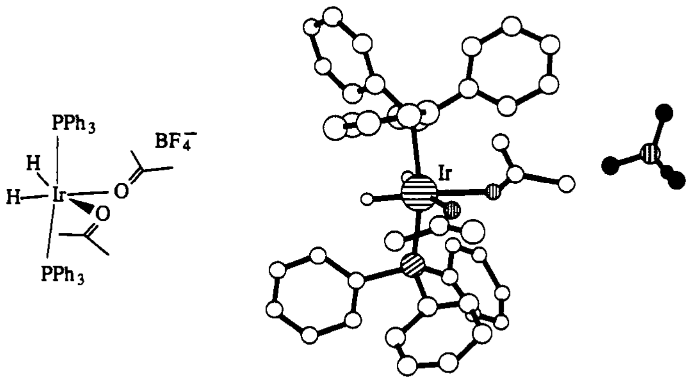

**Figure 31** Crystal structure of $[IrH_2(Me_2CO)_2PPh_3]BF_4$

Dicarbonylcyclopentadienyliron cation ($Fp^+$) is another reactive Lewis acid. This 16-electron complex is known to coordinate ethers, nitriles and various carbonyl-containing compounds quite effectively and with 1:1 stoichiometry. The resultant 18-electron complexes are often stable, crystalline compounds and the crystal structures of a few of them have been solved.[95–97] X-ray analysis of Fp(cyclohexenone)$BF_4$, for instance, shows iron $\sigma$-bonded in the plane of the carbonyl [$\tau$(Fe—O═C—C) = 3.7(9)°] at 132.81(4)° (Figure 32).[95,97] Interestingly, iron is coordinated *syn* to the double bond, which could be explained by steric or electronic arguments. Sterically, coordination next to the smaller methine, as opposed to the methylene, $\alpha$ to the carbonyl should be favored. A similar preference may be expected if the enone moiety is envisioned in an enol ether resonance structure (*cf.* Figure 33). Thus, the known preference of enol ethers to adopt a (*Z*)-conformation may be extended to this case to explain the observed result. The latter, electronic argument, however, does not appear to override steric factors in an aldehyde complex. Preliminary results from a crystal structure of Fp(cinnamaldehyde)$PF_6$ indicate metal coordination *cis* to the aldehydic hydrogen and *trans* to the enal double bond.[97]

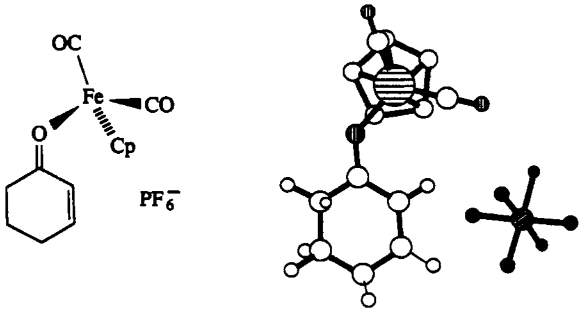

**Figure 32** Crystal structure of Fp(cyclohexenone)$PF_6$

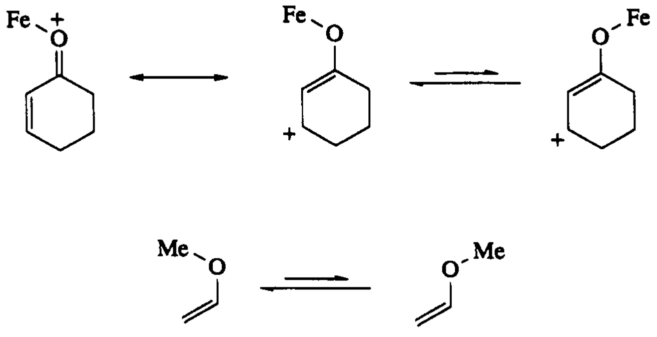

**Figure 33** Analogy between *syn*/*anti* Lewis acid complexes and (*E*)/(*Z*) enol ethers

Fp(4-methoxy-3-butenone)$BF_4$ also shows coordination *syn* to the double bond, *s-trans* geometry and no evidence for $\pi$-bonding [Figure 34; $\tau$(Fe—O═C—C—O) = 0(1)°].[97] Fp(tropone)$BF_4$ is yet another complex whose crystal structure has been solved.[96] In this case, the complex is particularly stable due to

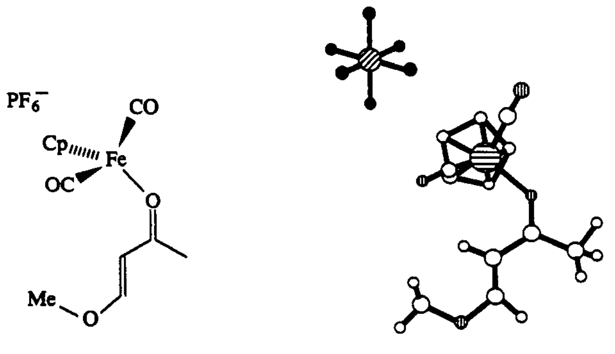

**Figure 34** Crystal structure of Fp(4-methoxy-3-butenone)$BF_4$

the high basicity of the tropone ligand and the crystal shows very similar structural features to other Fp(carbonyl) complexes.

A tungsten-derived Lewis acid, $[(Me_3P)(CO)_3(NO)W]^+SbF_6^-$, was recently reported to catalyze diene polymerization and Diels–Alder reactions.[98] A crystal structure of the acrolein-bound complex (Figure 35) shows tungsten σ-coordinated $[\tau(\mathrm{W{-}O{=}C{-}C}) = 180°]$, *syn* to hydrogen, at an angle of 137.1°. In line with *ab initio* predictions, acrolein adopts an *s-trans* conformation, despite the absence of any obvious steric interactions in the *s-cis* conformer. It is apparent from this crystal structure that the tungsten complex behaves in a similar fashion to classical Lewis acids, and its structure can be predicted based on the same principles.

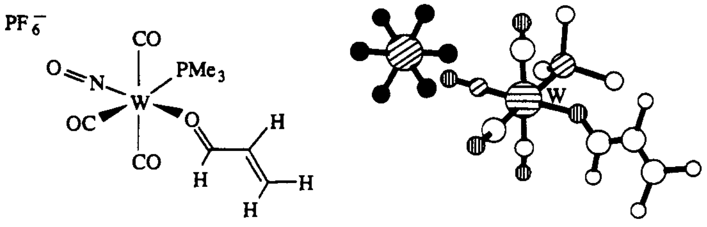

**Figure 35** Crystal structure of $(Me_3P)(CO)_3(NO)WFSbF_5$

The cationic complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (Z) is capable of binding carbonyls either $\eta^2$, through the π-system, or by σ-bonding through the lone pair electrons.[99,100] Crystal structures of Z(phenylacetaldehyde) and Z(acetophenone) clearly show the two different modes of complexation (Figure 36).

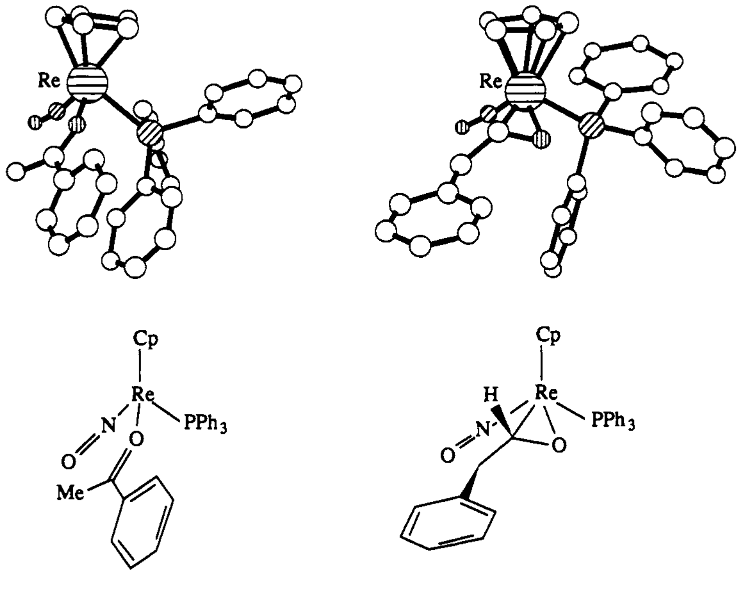

**Figure 36** σ- and $\eta^2$-bonding for $Cp(Ph_3P)(CO)Re^+$

The authors attributed the difference in binding to increased steric bulk and lower π-acidity of ketones as compared to aldehydes. No crystal structures of $Fp^+$/aldehyde complexes are available in order to determine whether $Fp^+$ has a similar 'amphichelic' binding property but $(Ph_3P)(CO)_2Fe^0$ binds cinnamaldehyde in an $\eta^4$ fashion.[101] Additionally, it is worth noting that both of the rhenium complexes shown here are chiral and it has been shown that in the enantiomerically pure form, they undergo nucleophilic additions to the carbonyls with high enantioselectivities.[99,100] Finally, the significance of the phenylacetaldehyde crystal structure should not escape attention. This is the first crystal structure of a nonchelated, α-substituted Lewis acid/aldehyde complex. Despite the unusual $\eta^2$-bonding in this complex there may be direct implications for the conformational preferences of Lewis acid/α-chiral aldehyde complexes. Remarkably, the phenyl ring lies nearly perpendicular to the plane of the carbonyl at a dihedral angle of τ(C—C—C=O) = 94°, which is reminiscent of the Felkin–Anh proposal for the reactive conformation of α-substituted carbonyl systems.[102] However, it also seems reasonable to argue that the phenyl group occupies the sterically least congested area of space, and that the observed conformation is merely an artifact of the steric requirements of this particular complex, rather than a general, electronic phenomenon.

$\eta^2$-Bonding appears to occur with electron rich metals and electron deficient carbonyls. This combination allows for better back-bonding from the metal to the carbonyl $\pi^*$-orbital and disfavors competitive σ-coordination by lowering the carbonyl lone pair basicity. Hexafluoroacetone, for example, is $\eta^2$-bound to $Ir(Ph_3P)_2(CO)Cl$[103] (*cf.* ref. 93), and electron rich $Ni^0$ complexes show π-bonding to both aldehydes[104] and ketones.[105] The crystal structure of $(TMEDA)Ni(C_2H_4)(H_2CO)$, for example, shows formaldehyde bound in a metallooxirane structure in which the C—O bond has lengthened to 1.311 Å (Figure 37).[106] Similarly, a molybdenum Lewis acid bound to benzaldehyde shows $\eta^2$-π-bonding and a C—O bond length of 1.333 Å.[107] Acetone bound to pentamineosmium(II) (C—O = 1.322 Å) has also been detected in the solid state and π-bonding is observed in this case as well.[108]

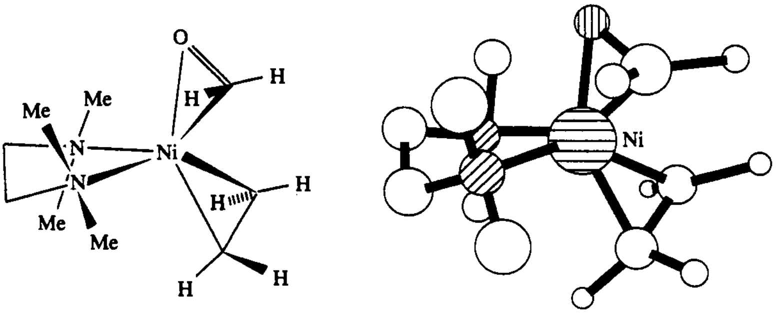

Figure 37 Crystal structure of $(TMEDA)Ni(C_2H_4)$/formaldehyde complex

Finally, carbonyls can bind two metals at once. The crystal structure of a bridging (μ), $\eta^2$-bound acetaldehyde complex, for example, shows the carbonyl coordinated to two molybdenum atoms (Figure 38).[109] It appears that in this structure the carbonyl utilizes its π as well as its lone pair electrons to bond to the two metal centers. Conceptually one can think of this molybdenum complex as a bidentate Lewis acid that chelates the carbonyl group.

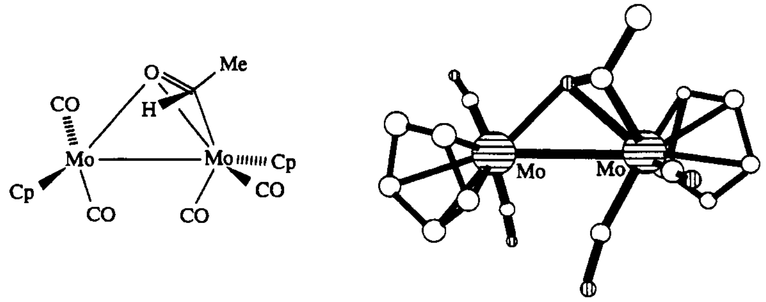

Figure 38 Crystal structure of $(\eta^2\text{-}\mu\text{-}MeCHO)Cp_2(CO)_4Mo_2$

In conclusion, it can be noted that high valent transition metals seem perfectly capable of serving as effective Lewis acids. Many of the systems discussed here exhibit exceptional robustness, stability and a propensity to form crystalline complexes. This would facilitate the task of crystallization and structural analysis, and one can imagine that transition metal complexes can be used as structural probes of Lewis acid–carbonyl interactions. In this vein, the first glimpse of the origins of Cram selectivity in α-chiral aldehydes may have been obtained from the crystal structure of a rhenium aldehyde complex. Lastly, the variety of ligands and metals that can be exploited in this field provide a useful handle for the custom design of Lewis acidic reagents. These constructs may also benefit from the large body of structural (especially crystallographic) data that is available for transition metal complexes.

## 1.10.7 STRUCTURAL MODELS FOR LEWIS ACID MEDIATED REACTIONS

A significant aim of the structural theory of organic chemistry is to acquire the ability to predict the behavior of molecules of known chemical structure. Ideally, one would be able to predict such 'structure–reactivity' relationships based on the principles of quantum mechanics, but such an accomplishment is, at present, not possible. The shortcomings of modern theoretical chemistry in performing a reliable analysis of complex organic molecules have already been mentioned. An even greater hurdle, however, may lie still further ahead in answering the question of chemical selectivity. Thus, even if one were to predict the structure and energy of a molecular system correctly, to choose between a large number of available reaction paths and to predict the lowest lying transition state remain very difficult tasks indeed.

As a corollary, reliable prediction of the structure of Lewis acid carbonyl complexes is by no means a solution to the problem of predicting their reactivity. To address the latter problem one needs to correlate the structural information with the observed patterns of reactivity and *vice versa*.

In this section the stereochemical implications of the structural knowledge gained in the previous sections will be discussed briefly. In some cases, this knowledge has resulted in the confirmation and/or development of various transition state models. In other instances, where compounds of known structure behave contrary to the predictions of structural theory, it has revealed inadequacies in, and limitations of, a model or collection of models.

### 1.10.7.1 Additions to α,β-Unsaturated Carbonyls

Asymmetric Diels–Alder reactions have been the subject of some of the more thorough mechanistic studies. Fairly reliable structural models for predicting the outcome of these reactions exist. In a review of the subject, it has been suggested that the stereochemical course of the reaction of a variety of chiral acrylates could be consistently predicted based on two models (Figures 39 and 40).[110] Model A positions the complex in a *(Z)-syn-s-trans* conformation and presumes attack from the least-hindered face of the double bond. This model is consistent with almost all of the structural data for systems of this type (*e.g.* $SnCl_4$/ethyl cinnamate X-ray diffraction study). Contrapuntally, the large number of experimental observations that can be explained by this model support the assumption that the crystal structure conformation (**26**) is relevant to the course of these reactions.

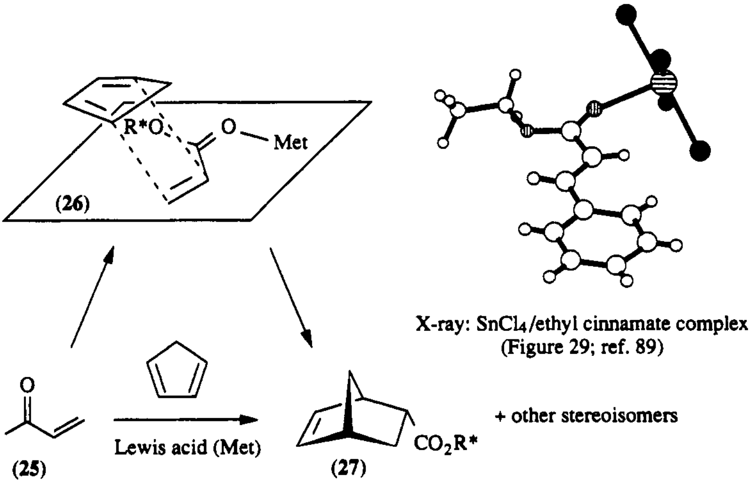

**Figure 39** Model A for Lewis acid mediated Diels–Alder reactions

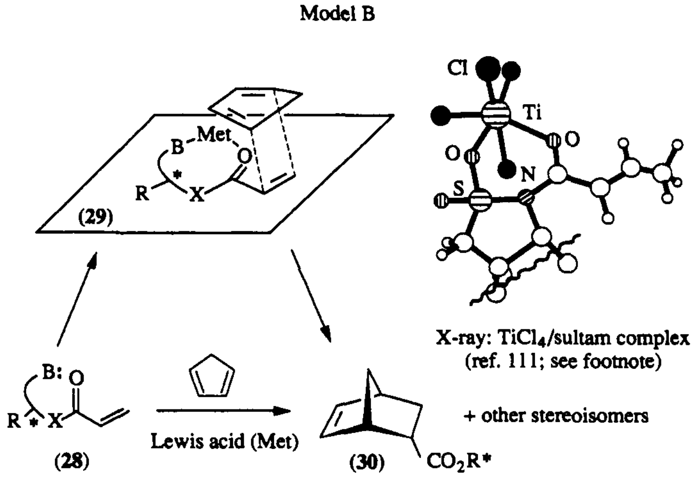

**Figure 40** Model B for Lewis acid mediated Diels–Alder reactions

Model B describes the case in which a chelating group is present in the dienophile, as shown in Figure 40. In contrast to model A, the Lewis acid complex is now *anti-s-cis*, although the (*Z*)-ester conformation is still intact. The *s-cis* conformation is also observed in two crystal structures of chelated complexes, although one of these (*cf.* Figure 25) is somewhat unusual.[111]

A similar model was proposed in describing the asymmetric Diels–Alder reaction of chiral α,β-unsaturated *N*-acyloxazolidinones (**31**).[112–114] The researchers noted that the reaction stoichiometry and the nature of the Lewis acid are crucial in obtaining high levels of diastereoselection (Table 8).[112–114] In particular, stoichiometric amounts of chelating Lewis acids (*i.e.* $SnCl_4$, $TiCl_4$, $ZrCl_4$) resulted in increased stereoselectivities relative to Lewis acids with only a single coordination site (*i.e.* $AlCl_3$, $EtAlCl_3$, $Et_2AlCl$). The most diastereoselective reactions, however, were observed when a slight excess (1.4 equiv.) of $Et_2AlCl$ was used. These results were interpreted in terms of the action of the ionic species $Et_2Al^+(Et_2AlCl_2^-)$ as the effective Lewis acid. Faster reaction rates, improved *endo* selectivity and Lewis acid concentration studies were all consistent with this interpretation and structure (**34**) was proposed as a transition state model.[112] In support of this hypothesis, the researchers have pointed to

**Table 8** Lewis Acid Promoted Diels–Alder Reaction of Chiral α,β-Unsaturated Acyloxazolidinones

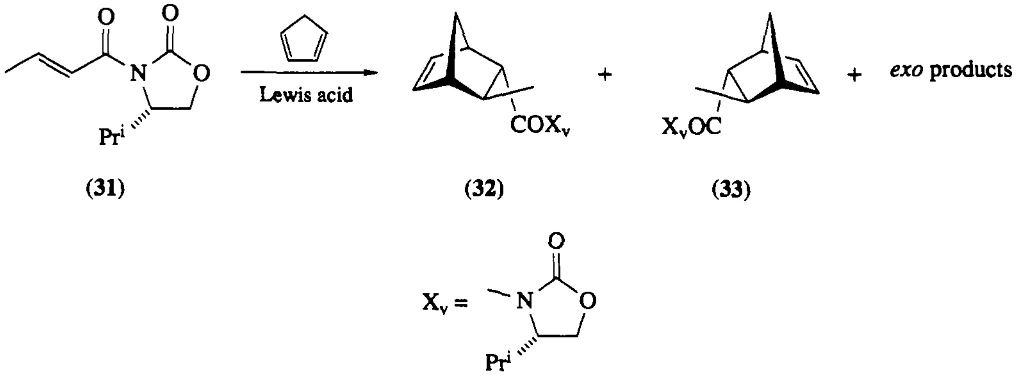

| *Lewis acid (equiv.)* | *Temperature* (°C) | *Time* (h) | *Conversion* (%) | *(32):(33)* | *Σ(endo):Σ(exo)* |
|---|---|---|---|---|---|
| $SnCl_4$ (1.1) | −78 | 2 | 70 | 3.1:1 | 14.9:1 |
| $TiCl_4$ (1.1) | −78 | 3 | 100 | 2.7:1 | 9.9:1 |
| $ZrCl_4$ (1.4) | −78 | 3 | 100 | 7.2:1 | 99:1 |
| $AlCl_3$ (1.0) | −78 | 3 | 60 | 1.5:1 | 4.2:1 |
| $EtAlCl_2$ (1.1) | −78 | 3 | 50 | 1.7:1 | 11:1 |
| $Et_2AlCl$ (0.8) | 0 | 6 | 100 | 6.5:1 | 15:1 |
| $Et_2AlCl$ (1.4) | −78 | 2.5 | 100 | 17:1 | 50:1 |

work on the complexation of dialkylaluminum chlorides and amine bases, where similiar phenomena were observed.[115]

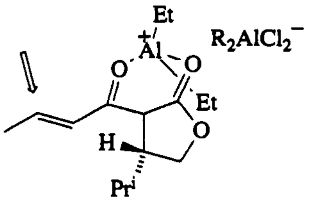
Et
Al
O
O
Et
O
H
Pr^i
$R_2AlCl_2^-$

(34)

Some of the Lewis acid catalyzed Michael additions to α,β-unsaturated carbonyls can also be rationalized based on these models. For example, $BF_3$-mediated additions of organocopper reagents to chiral α,β-unsaturated esters such as (–)-8-phenylmenthyl crotonate (35) occur with high levels of diastereoselectivity.[116–118] The product stereochemistries for these reactions could be predicted by assuming the reactive conformation (36), which follows the basic structural tenets of model A (Figure 41).[117]

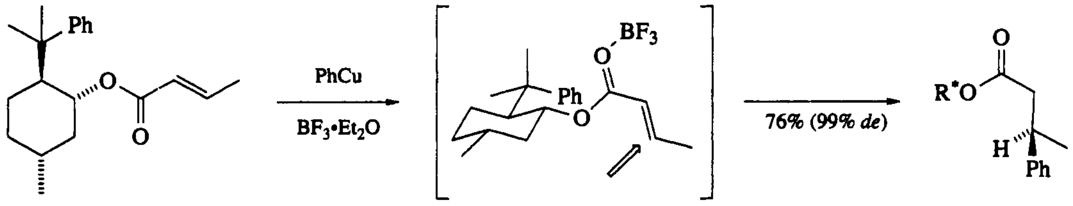
Ph
O
O
PhCu
$BF_3 \cdot Et_2O$
$BF_3$
O
Ph
O
76% (99% *de*)
O
R*O
H
Ph

(35) (36) (37)

**Figure 41** $BF_3$-mediated asymmetric Michael additions to chiral crotonates

The inventors of the chiral catalyst (38) for asymmetric 1,4-additions to α,β-unsaturated ketones[119] have proposed the transition structure depicted in (40) as a possible model for the Lewis acid catalyzed 1,4-addition to cyclohexenone (Figure 42).[120]

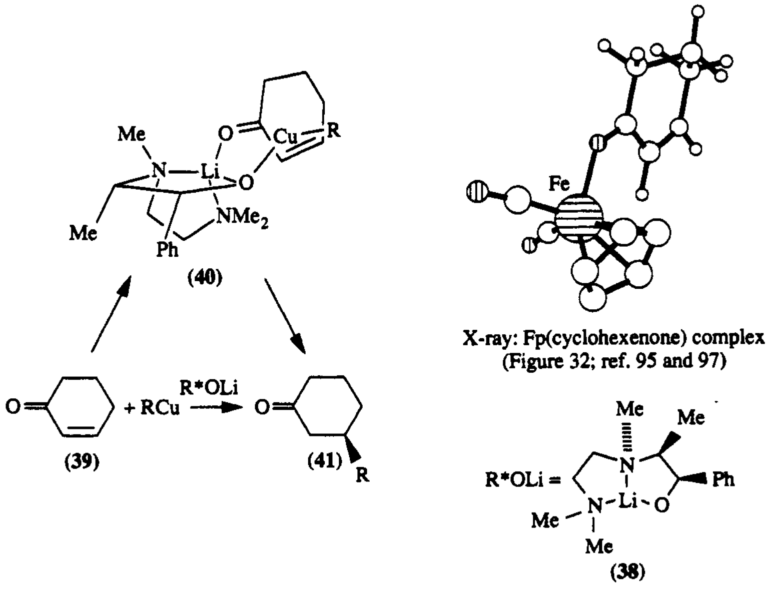
Me
O
Cu
R
N
Li
O
NMe₂
Me
Ph
(40)
O
+ RCu
R*OLi
O
(39)
(41)
R
Fe
Me
Me
R*OLi =
N
Ph
N
Li
O
Me
Me

X-ray: Fp(cyclohexenone) complex (Figure 32; ref. 95 and 97)

(38)

**Figure 42** A model for catalytic asymmetric 1, 4-addition to cyclohexenone

This model is consistent with the conformation found in the structure of Fp(cyclohexenone)$BF_4$[95,97] and the similarities can be seen in Figure 42.[119,120] Notice that the assumption that Lewis acid ($Li^+$) coordination occurs *syn* to the double bond is essential for mediation of attack on the *re face* of the double bond. *Anti* coordination (if all else is retained) would result in *si face* addition.

Catalytic asymmetric induction in Diels–Alder reactions is somewhat more difficult to analyze based on these models. The chiral Lewis acids shown in Figure 43 all promote asymmetric Diels–Alder cycloaddition with variable degrees of enantioselectivity.[121–128]

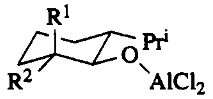

(42) $R^1, R^2 = H$
(43) $R^1 = H, R^2 = Me$

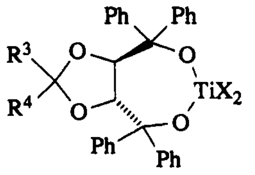

$X = Cl, OPr^i$

(44) $R^3 = Me, R^4 = Bu^t$
(45) $R^3 = H, R^4 = Ph$

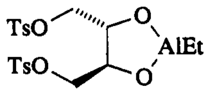

(46)

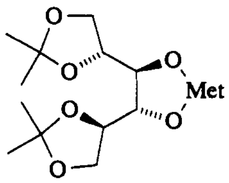

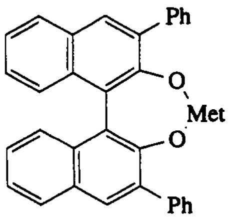

(47) Met = $TiX_2$ (49)
(48) Met = AlX (50)

Figure 43 Chiral catalysts for asymmetric Diels–Alder reactions

Construction of useful structural models for these reactions, however, would require not only a full structural characterization of the Lewis acid, but also knowledge of the preferred conformation of the chiral ligands. In many cases the catalysts are generated *in situ* and the stoichiometry or the aggregation state of the Lewis acid are not well defined. The latter point is particularly important since both titanium and aluminum alkoxides are known to form dimeric or polymeric species.[129]

The well-characterized aluminum Lewis acid (**52**) has been reported to catalyze hetero Diels–Alder reactions of aldehydes with high enantioselectivity (Figure 44).[130]

The model proposed for the reaction of simple aromatic aldehydes (**54**) places the Lewis acid *syn* to the aldehydic hydrogen, consistent with the frequent observation of this preference in crystal structures of Lewis acid–aldehyde complexes (*cf.* Figures 19, 27 and 28).

Chiral lanthanide shift reagents (LSR) also promote asymmetric hetero Diels–Alder reactions (Figure 45).[131–134] Lack of rigorous structural information regarding LSR/carbonyl interactions, however, does not allow meaningful speculation on the source of chirality transfer.

In addition, chiral dienes seem to exhibit a curious behavior in the presence of chiral LSRs (Table 9).[131–134] Diastereoselection is highest when a 'mismatched' diene/catalyst pair is used. The researchers have proposed a novel 'interactivity' between the catalyst and the chiral auxiliary, the nature of which is at this point unclear.

### 1.10.7.2 Additions to Nonconjugated Carbonyls

The design of novel Lewis acidic reagents for additions to nonconjugated carbonyls, based on structural information, has attracted much attention in recent years. An excellent overview of this subject has recently appeared, in which the mechanistic aspects of and various models for carbonyl addition processes are highlighted.[135] In particular, attention was directed towards the *ab initio* treatment of solvation effects in additions to the carbonyl group.[136,137] These calculations indicated that in the addition of water

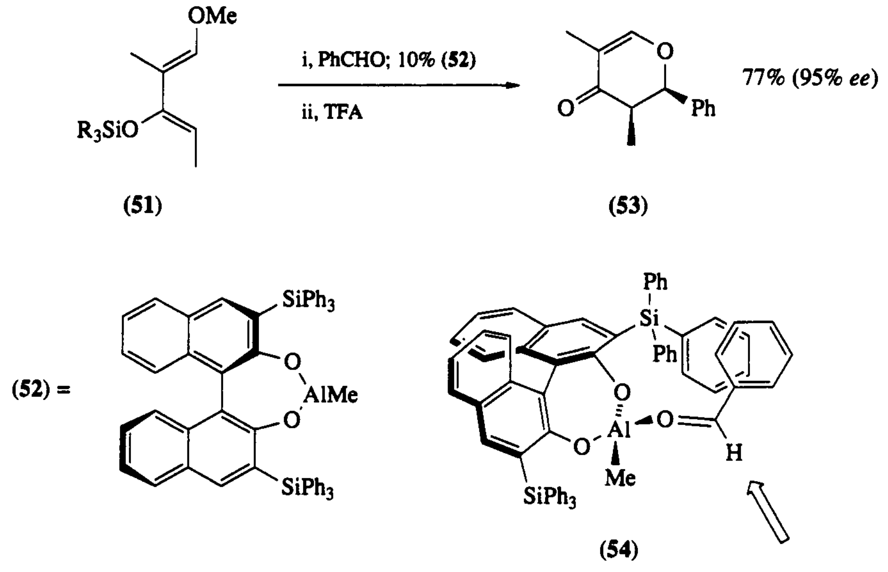
OMe
R3SiO
i, PhCHO; 10% (52)
ii, TFA
O
O
Ph
77% (95% ee)
SiPh3
O
AlMe
O
SiPh3
Ph
Si
Ph
O
Al
O
O
Me
H
SiPh3

(51) (53)

(52) =

(54)

**Figure 44** Catalytic asymmetric hetero-Diels–Alder reaction

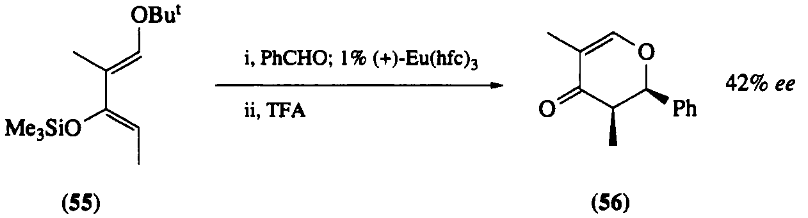
OBu$^t$
Me3SiO
i, PhCHO; 1% (+)-Eu(hfc)3
ii, TFA
O
O
Ph
42% ee

(55) (56)

**Figure 45** Asymmetric hetero-Diels–Alder reactions catalyzed by chiral lanthanide shift reagents

**Table 9** Interactivity of Lanthanide Shift Reagents and Chiral Dienes in Hetero-Diels–Alder Reactions

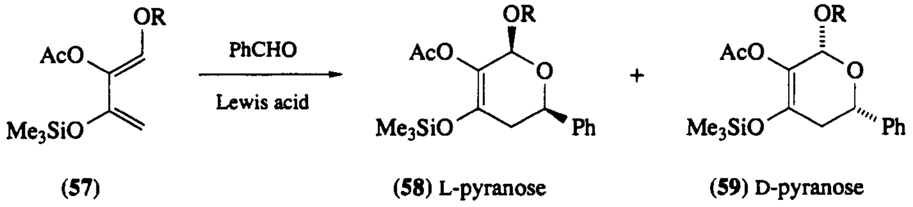
OR
AcO
Me3SiO
PhCHO
Lewis acid
OR
AcO
O
Me3SiO
Ph
+
OR
AcO
O
Me3SiO
Ph

(57) (58) L-pyranose (59) D-pyranose

| *Lewis acid* | *R* | *Product* | *ee (%)* |
|---|---|---|---|
| Eu(fod)$_3$ | (–)-Menthyl | D-Pyranose | 10 |
| (+)Eu(hfc)$_3$ | Bu$^t$ | L-Pyranose | 42 |
| (+)Eu(hfc)$_3$ | (+)-Menthyl | L-Pyranose | 18 |
| (+)Eu(hfc)$_3$ | (–)-Menthyl | L-Pyranose | 86 |

or ammonia to formaldehyde, the intermediacy of a molecule of water in a six-membered transition state can considerably lower the transition energy, relative to a four-membered transition state (Figure 46).[135–137]

This seemingly simple result may have far reaching consequences. For example, it may help to explain the effect of added lithium salts in nucleophilic additions to cyclohexanones as discussed earlier in this chapter. Thus, model (63) shown in Figure 47[2,135–137] can explain the enhancement of rate and may also be relevant to the origins of stereoselectivity in this reaction. Of course, the exact location of the lithium atom and the aggregation state of the adding nucleophile are subject to speculation, since for lithium these parameters seem to be highly variable.

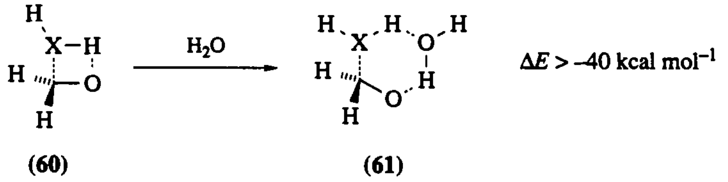
H
X–H
H
O
H
H₂O
H
X
H
O
H
H
H
O
H
$\Delta E > -40$ kcal mol$^{-1}$
(60)
(61)

**Figure 46** Four-membered *versus* six-membered transition states; role of a bridging catalyst

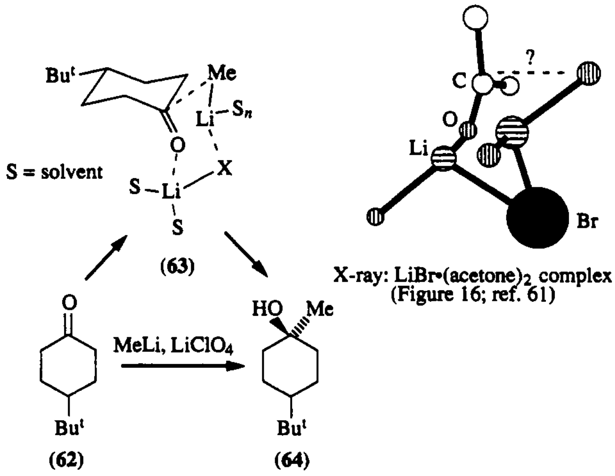
Bu^t
Me
Li
S_n
O
X
S = solvent
S–Li
S
(63)
O
MeLi, LiClO₄
HO
Me
Bu^t
Bu^t
(62)
(64)
O
C
?
O
Li
Br

X-ray: LiBr•(acetone)$_2$ complex
(Figure 16; ref. 61)

**Figure 47** A model for $LiClO_4$-mediated addition of MeLi to 4-*t*-butylcyclohexanone

It may be recalled that an opposite stereochemical result is obtained by employing the bulky aluminum reagents MAD and MAT.[3] This observation has been explained by invoking out-of-plane complexation of the Lewis acid in a direction which would prevent equatorial attack (Figure 48).[3,74] The X-ray crystal structure of methyl toluate complexed with a bulky aluminum Lewis acid is fully consistent with this model.[74] However, it is worth mentioning that a six-membered transition state, perhaps involving $[Me_2(ArO)Al]^-Li^+$, has not been considered as an alternative mechanism.

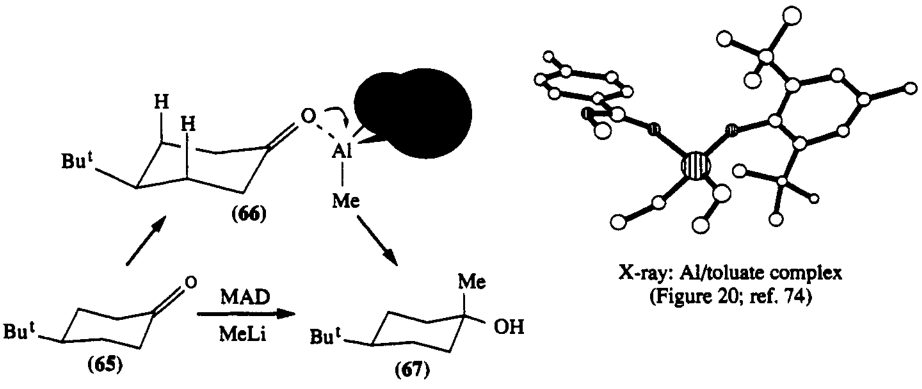
H
H
Bu^t
O
Al
Me
(66)
O
MAD
MeLi
Bu^t
(65)
Me
OH
Bu^t
(67)

X-ray: Al/toluate complex
(Figure 20; ref. 74)

**Figure 48** A model for MAD-mediated addition of MeLi to 4-*t*-butylcyclohexanone

It is more difficult to account for the remarkable anti-Cram selectivity observed in the MAT-mediated nucleophilic additions to α-chiral aldehydes, although out of plane coordination may play an important role (Figure 49).[3]

Chiral Lewis acidic catalysts derived from β-amino alcohols constitute a major field of recent development. These reagents have been used for enantioselective reduction of ketones[138–145] and for dialkylzinc additions to aldehydes.[146–155]

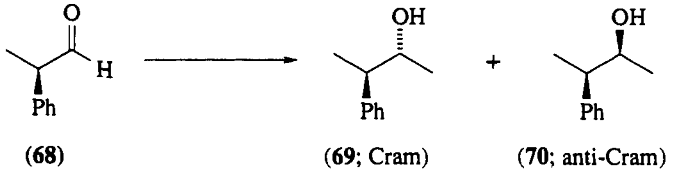

| | |
|---|---|
| MeMgBr | 72:28 |
| MeMgBr/MAT | 7:93 |

**Figure 49** Anti-Cram addition of MeMgBr to α-phenylpropanal mediated by the bulky aluminum Lewis acid MAT

The isolation and characterization of the reagent derived from the reaction of β-amino alcohols and borane accompanied the first report of a truly catalytic procedure for the enantioselective reduction of ketones.[143,144] A representative example is shown in Figure 50.[135,143,144] Based on $^1$H and $^{11}$B NMR spectroscopy, a six-membered, boat-like transition state model (**73**) was postulated.[135,143]

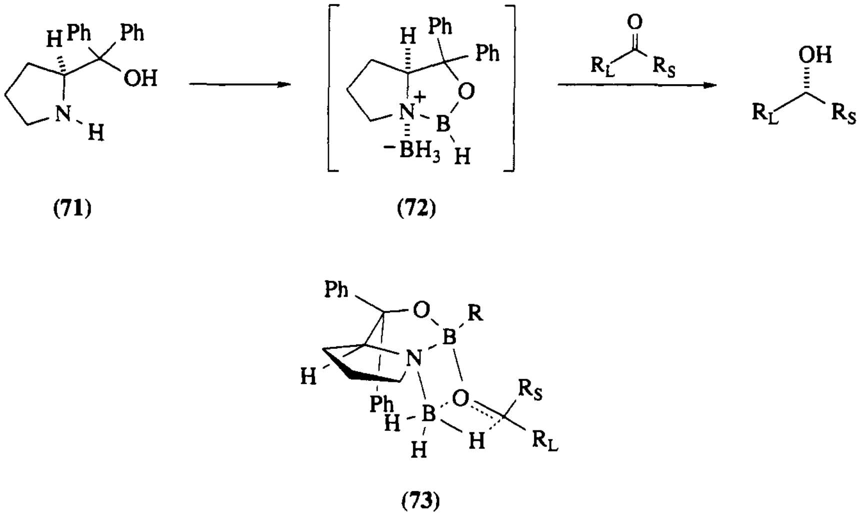

**Figure 50** Catalytic asymmetric reduction of ketones

In this model the sense of asymmetric induction is controlled by two principle factors: (i) coordination of borane on the least-hindered face of the bicyclic ring system; and (ii) coordination of the Lewis acid *syn* to the small group ($R_S$). The latter point is in good agreement with the structural data that has been presented in this chapter, and is further supported by results from the asymmetric reduction of oxime ethers (Figure 51).[145] As predicted by the model (**75** and **78**), (*E*)- and (*Z*)-oxime ethers afford enantiomeric amines upon reduction by the reagent derived from (–)-norephedrine and borane (2 equiv.). Here, Lewis acid coordination is dictated by the (*E*)/(*Z*) stereochemistry of the oxime ether rather than by the rule of coordination *syn* to the small group.

A very similar model can be invoked to explain the results of catalytic enantioselective dialkylzinc additions to aldehydes.[135] The catalysts used in these reactions are invariably lithium- or zinc-centered Lewis acids. The transition structure shown in Figure 52[135,146,150] has been put forward by several groups and predicts the stereochemical outcome of many systems of this general type (**83–89**; Figure 53) quite nicely. In this model a dialkylzinc molecule is coordinated to a basic site (X) on the least-hindered face of the catalyst. The Lewis acidic metal can then deliver a molecule of aldehyde by coordination *syn* to the aldehydic hydrogen. The assumption of a boat transition state can be justified by invoking Zn–O interactions along the reaction path and comparison with various zinc–alkoxide crystal structures (*e.g.* MeZnOMe).

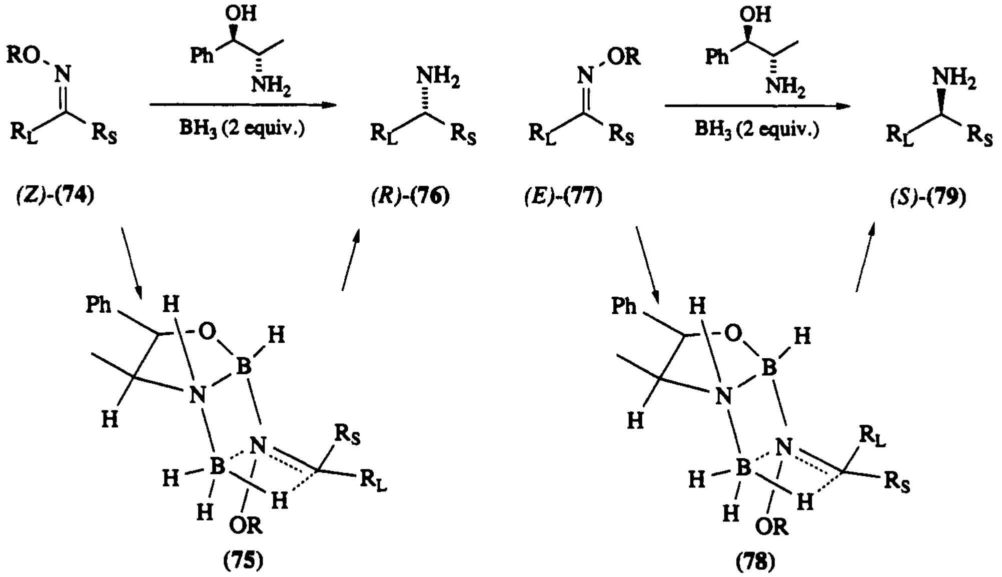
(Z)-(74)
BH3 (2 equiv.)
(R)-(76)
(E)-(77)
BH3 (2 equiv.)
(S)-(79)
(75)
(78)

**Figure 51** Asymmetric reduction of oxime ethers

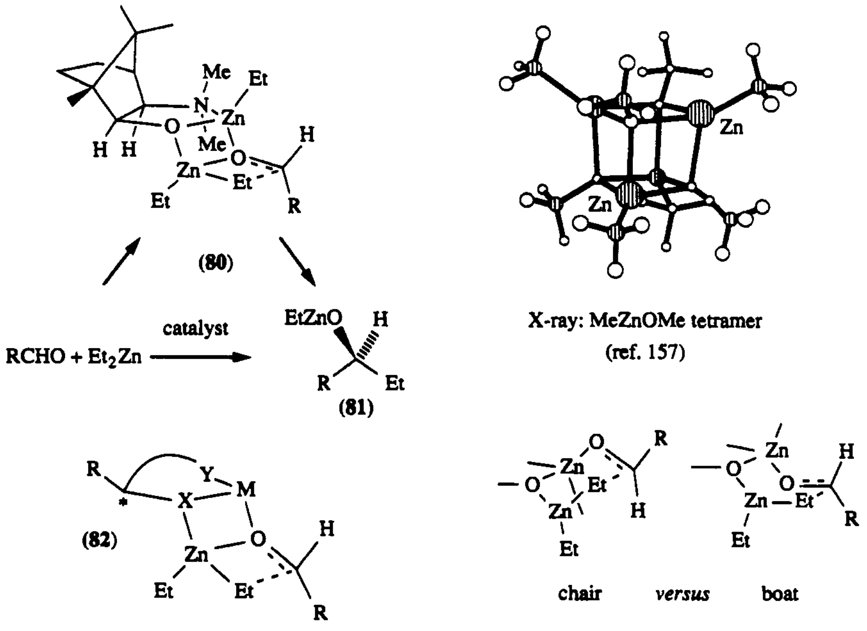
(80)
catalyst
RCHO + Et2Zn
EtZnO
(81)
X-ray: MeZnOMe tetramer
(ref. 157)
(82)
chair
versus
boat

**Figure 52** A model for catalytic asymmetric dialkylzinc additions to aldehydes

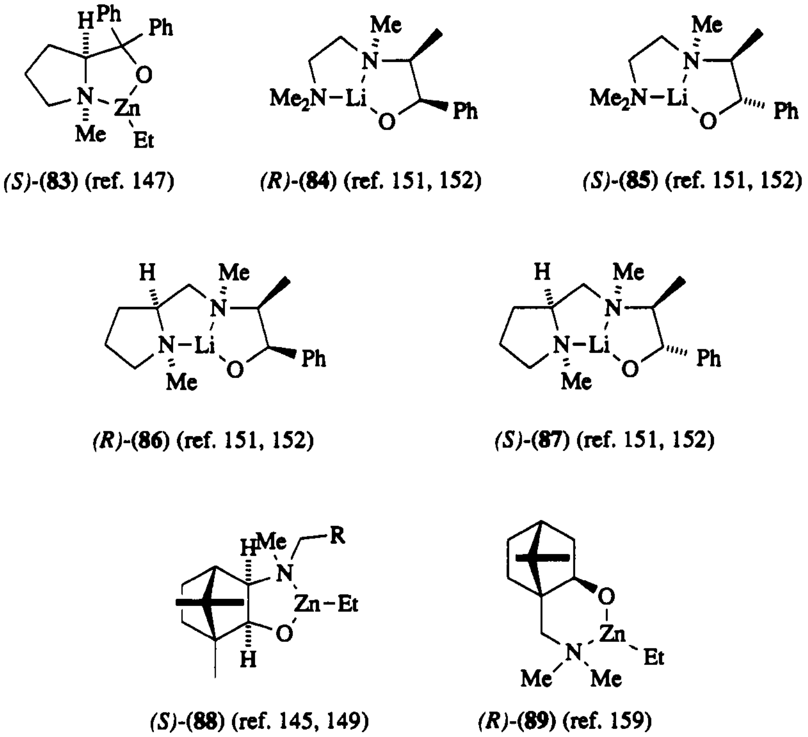

*(S)*-(**83**) (ref. 147) *(R)*-(**84**) (ref. 151, 152) *(S)*-(**85**) (ref. 151, 152)

*(R)*-(**86**) (ref. 151, 152) *(S)*-(**87**) (ref. 151, 152)

*(S)*-(**88**) (ref. 145, 149) *(R)*-(**89**) (ref. 159)

**Figure 53** Chiral catalysts for asymmetric dialkylzinc additions to carbonyls

Two interesting features of these models include the presence of an acid/base pair for organization of a well-defined six-membered transition state, and the role of the asymmetry adjacent to the basic group (X), which determines the face selectivity of the reaction. Note that for some catalysts (*i.e.* **85** and **87**) the 'least-hindered' site of coordination is not necessarily the convex face of a polycyclic system.

Lastly, the similarities between (**73**) and (**82**) suggest that these catalysts may be used interchangeably for reductions and dialkylzinc additions. Furthermore, the choice of small and large groups may not always be obvious. For example, in simple α,β-unsaturated ketones or in 1-chloroacetophenone the large group is not well defined.[144] Enone (**90**) is reduced to the (*R*)-allylic alcohol upon treatment with one equivalent of borane and a catalytic amount of (**91**; Figure 54).[144] Assuming that (**73**) is a valid transition structure, this result would suggest that the Lewis acid coordinates *anti* to the enone double bond, which, in light of the structural data, is somewhat surprising.

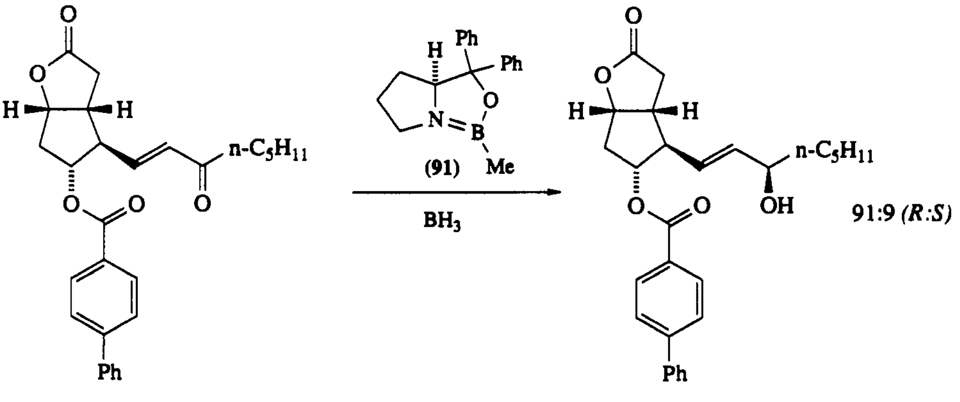

(**90**) (**92**)

**Figure 54** Catalytic asymmetric reduction of enones

In this particular substrate one should also consider other potential sites of coordination for boron, such as the ester or the lactone carbonyl, which may be considered more basic than the carbonyl of the ketone.

Recent reports by two groups propose two new and entirely different models for similar catalytic dialkylzinc additions.[154,155] One of these[154] assumes a pentavalent, pseudotrigonal bipyramidal zinc(II) catalyst (**93**)[157] and the other[155] purports transfer of the alkyl group from the carbonyl-bearing metal (**94**; Figure 55).

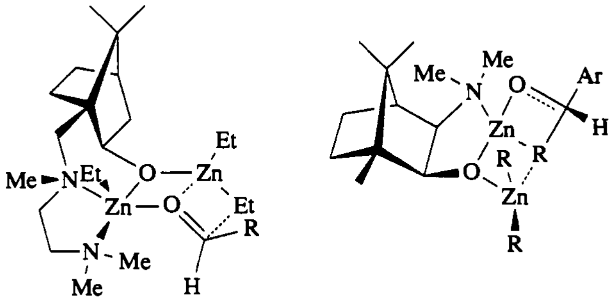

**(93)** **(94)**

**Figure 55** Two models for catalytic dialkylzinc additions to carbonyls

Structural evidence for these models has been gathered from X-ray crystal structures and, in the case of (**94**), from crossover experiments. Use of two different dialkylzinc reagents for the generation of the catalyst and the nucleophile gave a statistical mixture of possible products.[155] This result is in contrast to the findings of another group,[149] who found no crossover in a very similar system. It is interesting to note that model (**94**) essentially represents metal coordination to the π-face of the carbonyl as opposed to σ-bonding in all other models. Clearly, more mechanistic details are needed in order to identify the true mechanism of these reactions. This problem, however, is a good demonstration of a case where the validity of several plausible models cannot be discerned despite the availability of crystallographic and spectroscopic data.

The aldol reactions of isocyanoacetates and a variety of aldehydes proceeds with very high levels of asymmetric induction under the influence of catalytic amounts of a chiral Au$^I$ complex (Figure 56).[158,159] This remarkable transformation provokes speculation regarding the possible mechanism of catalysis and provides a challenge to model-building exercises. Although a crystal structure of an Au$^I$/carbonyl complex is not presently available, one may draw analogies with the isoelectronic, square planar Ni$^0$/$\eta^2$-benzaldehyde complex (Figure 56).[160] Note that both the nickel and the gold compounds can be formally viewed as $d^8$-transition metal complexes with a preference for the square planar geometry.[161] Accordingly, one may expect Au$^I$ Lewis acids to form $\eta^2$-square planar complexes with carbonyls, although the presence of other bases (*i.e.* isocyanate, tertiary amines) may completely alter this bias.[162] Thus, it should be emphasized that the proposed transition structure (**95**) is highly speculative and neither the orientation of the aldehyde nor the role and structure of the diamine linker can be predicted reliably.

## 1.10.8 CONCLUSIONS

Interactions of the carbonyl group with Lewis acids are colorful and varied, but by no means unpredictable. The structural information gathered in this chapter points, fairly consistently, to the same set of principles. 'Rules of complexation' such as coordination *syn* to the small substituent, *s-trans* preference due to gearing effects and distortions towards the π-cloud in response to steric strain are among these principles. Section 1.10.7 illustrated a few examples of how the predictive power of such structural rules have been applied to the design of novel and highly selective Lewis acidic catalysts.

In the context of future prospects in catalysis, transition metal complexes seem to provide a particularly diverse source of useful Lewis acids. Although the structural features of these complexes were not discussed extensively in this chapter, $\eta^2$-bonding seems unique to these complexes and warrants further exploration.

For the design of new reagents one would also like to understand the conformational changes of the carbonyl group upon complexation. The *s-trans* effect on unsaturated carbonyls is a clear example of such effects. More subtle, and perhaps more interesting, are the conformational consequences of Lewis

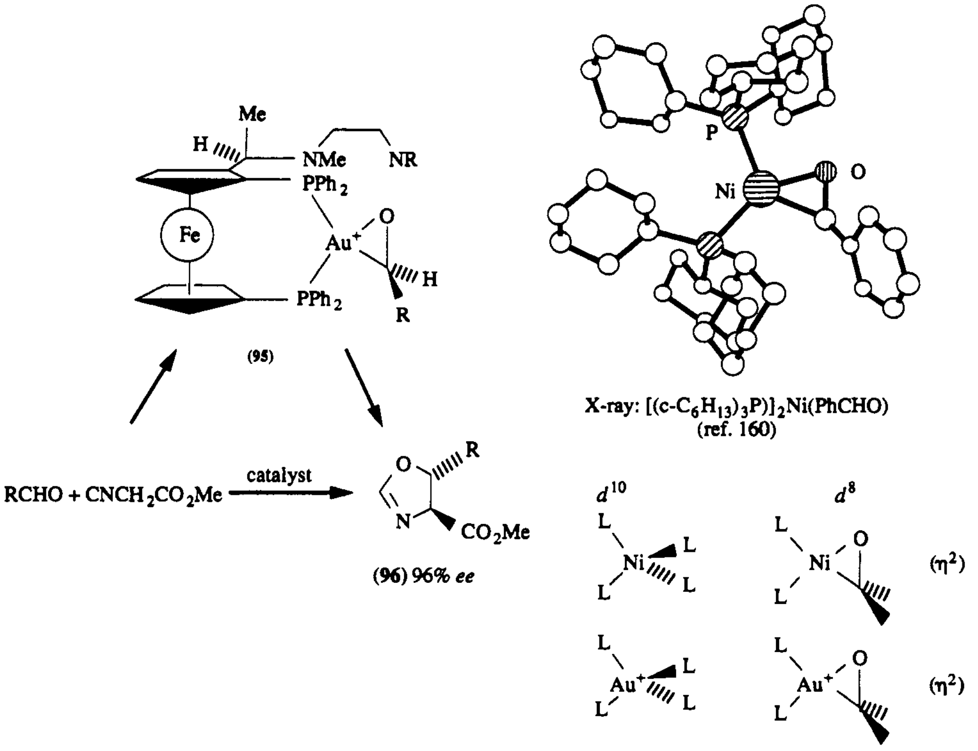

X-ray: $[(c\text{-}C_6H_{13})_3P)]_2Ni(PhCHO)$ (ref. 160)

**Figure 56** A possible model for the catalytic asymmetric aldol reaction of isocyano acetates and aldehydes

acid complexation for nonconjugated carbonyls. The relevance of these issues to the topic of chelation-controlled additions was discussed at length. Similar effects for nonchelating carbonyls, however, are completely unresolved, but one may hope to generate a coherent set of rules in these systems as well. Impressive achievements of the past and worthy rewards of the future provide a strong incentive to pursue this and other structural problems of Lewis acid–carbonyl complexation with vigor and optimism.

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# 1.11

# Lewis Acid Promoted Addition Reactions of Organometallic Compounds

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## 1.11.1 INTRODUCTION

The importance of the Lewis acidic nature of organometals in addition reactions to C═X bonds (X = heteroatom) has been well documented.[1] The complexation of organometallic compounds with C═X bonds is considered to be the origin of the promotion of the addition reactions and the generation of chemo-, regio- or stereo-selectivities. The complexation phenomena are discussed in detail in Chapter 1.10, of this volume. In reactions of simple organometals such as alkyl-magnesiums or -aluminums, a single organometallic species undertakes both of the tasks involved in the C—C bond formation process: complexation and nucleophilic attack. For example, reaction of benzophenone with $Me_3Al$ in a 1:1 ratio is reported to give a monomeric 1:1 complex at room temperature, which decomposes to dimethylaluminum 1,1-diphenylethoxide at 80 °C (equation 1).[2]

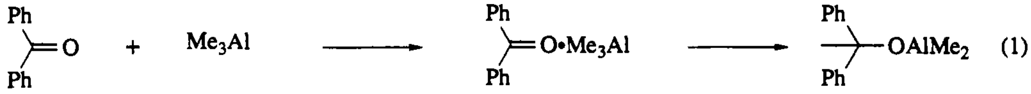

In recent years, a new type of addition reaction to C═X bonds is emerging in organic synthesis which utilizes a *binary reagent system* composed of a nucleophilic organometal and a Lewis acid. In contrast to the addition of simple organometals mentioned above, this new methodology assigns the task of the nucleophilic attack and the complexation to the two separate reagents. Consequently, the selection of an appropriate Lewis acid allows a modification of the nature of the C═X bonds through complexation, which dramatically enhances the rate of organometal addition reactions, increases the yields, changes the regio- or stereo-selectivities and allows chemoselective reactions to be conducted in complex molecules possessing other sensitive functional groups. It should also be noted that the complexation of a Lewis acid with an organometal can modify the nature of the nucleophiles, for example by the ate complex formation, which offers another advantage of these reagent systems. The development of the binary reagents, especially that of effective Lewis acids, is one of the hot topics in contemporary organic synthesis. The synthetic aspects of these useful reagent systems will be reviewed here.

The addition reactions can be divided into two categories depending on the nature of the nucleophilic organometals employed: (i) the Lewis acid promoted addition reactions of relatively unreactive organometals such as alkyl-silanes, -stannanes, *etc.*, where, although the reagents are stable and storable, they turn to highly reactive species in the presence of appropriate Lewis acids; and (ii) the Lewis acid promoted addition reactions of reactive organometals such as alkyl-lithiums, -magnesiums, *etc.*, where, although the reagents themselves are generally capable of reaction with the electrophiles, the presence of the Lewis acids results in the variation of the reaction course. The present review deals with both of these categories with some emphasis on the latter.

Although these methodologies have proved to be quite useful in organic synthesis, the precise mechanisms are still not known in many cases because of the lack of mechanistic studies. The following can be presented as the candidates in the reaction of an $\mathrm{R{-}ML}_n/\mathrm{M'L}_m$ system, in which $\mathrm{R{-}ML}_n$ represents the nucleophilic organometals and $\mathrm{M'L}_m$ the Lewis acids: (i) the original organometallic compound $\mathrm{R{-}ML}_n$ attacks a C=X bond activated by a Lewis acid $\mathrm{M'L}_m$; (ii) the ate complex $\mathrm{ML}_n{}^+[\mathrm{RM'L}_m]^-$, generated from $\mathrm{R{-}ML}_n$ and $\mathrm{M'L}_m$ (equation 2), adds to a C=X bond; or (iii) a new organometallic species $\mathrm{R{-}M'L}_{m-l}$ formed by the transmetalation, which produces another Lewis acid $\mathrm{ML}_{n+l}$ (equation 3), reacts with a C=X bond.

$$\mathrm{RML}_n \;+\; \mathrm{M'L}_m \longrightarrow \mathrm{ML}_n^{+}\left[\mathrm{RM'L}_m\right]^{-} \qquad (2)$$

$$\mathrm{RML}_n \;+\; \mathrm{M'L}_m \longrightarrow \mathrm{RM'L}_{m-1} \;+\; \mathrm{ML}_{n+1} \qquad (3)$$

This chapter focuses the attention on the reactions of nonstabilized carbanionic compounds such as alkyl, vinyl, aryl, alkynyl metals, *etc.*, and the chemistry of the stabilized system, *i.e.* allylic, propargylic or oxaallylic carbanions is presented in Volume 2 of this series. Electrophiles with C=X bonds which are discussed include aldehydes, ketones, epoxides, aziridines, acetals, orthoesters and imines, all of which turn into highly reactive electrophiles in the presence of Lewis acids.

## 1.11.2 LEWIS ACID PROMOTED REACTIONS OF ALDEHYDES AND KETONES

### 1.11.2.1 Control of the Reactivity

A classic example of a Lewis acid promoted addition reaction is that of organocadmiums to aldehydes or ketones.[3,4] Despite the conventional use of the alkylcadmiums in the ketone synthesis from acid halides, organocadmium compounds add rapidly and efficiently to simple carbonyl compounds, provided that *in situ* reagents prepared from Grignard reagents and cadmium halides are employed.[5,6] Pure dialkylcadmiums show almost no reactivity towards ketones. However, addition of magnesium halides greatly increases the reactivity. These phenomena have been interpreted in terms of a prior complexation of the carbonyl group with $MgX_2$, followed by an attack of $R_2Cd$ on the resultant complex. Magnesium halides promote addition reactions far more effectively than zinc, cadmium, lithium or aluminum salts (equation 4).[7]

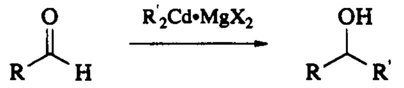

| | | |
|---|---|---|
| R = Me | R' = $n\text{-}C_6H_{13}$ | 60% |
| R = Me | R' = Ph | 60% |
| R = Ph | R' = Me | 55% |
| R = Ph | R' = $Bu^n$ | 65% |

(4)

Organozinc reagents behave similarly. Reagents prepared *in situ* from Grignard reagents and $ZnBr_2$, or reconstituted reagents from distilled $R_2Zn$ and $MgBr_2$ react smoothly with aldehydes and ketones (equation 5).[8,9] $TiCl_4$-promoted addition reaction of alkylzincs has also been developed. It is carried out by adding $R_2Zn$ to a solution of the carbonyl component and $TiCl_4$. Another procedure, the addition of carbonyl compounds to a solution of $R_2Zn$ and $TiCl_4$, is reported to be less effective (equation 6).[10]

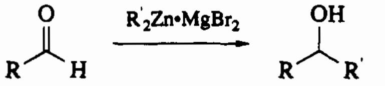

| | | |
|---|---|---|
| R = Et | R' = Et | 70% |
| R = Et | R' = Bu$^n$ | 70% |
| R = Ph | R' = Et | 70% |
| R = Ph | R' = Bu$^n$ | 50% |

(5)

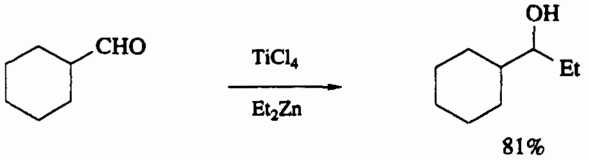

(6)

TMS-Cl or TMS-I, formed *in situ*, works as the promoter in addition reactions of zinc homoenolates (β-metallocarbonyl compounds), generated from 1-alkoxy-1-siloxycyclopropanes and $ZnX_2$ (equation 7). No reaction takes place with the purified zinc homoenolates. In contrast, titanium homoenolates are reactive enough to add to aldehydes in the absence of the Lewis acid promoter.[11] Related reactions of zinc esters with aldehydes in the presence of $(Pr^iO)_3TiCl$ have been reported (equation 8).[12]

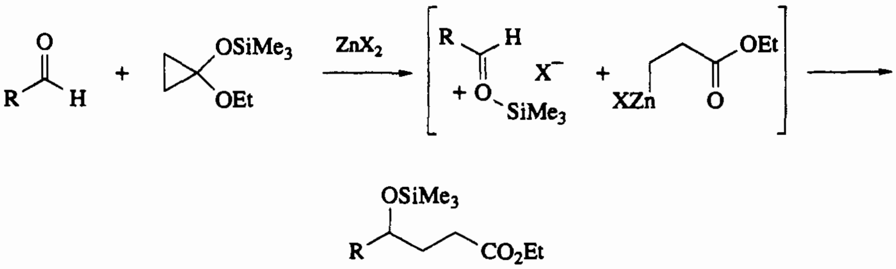

(7)

R =Ph, 89%; R = MeCH=CH, 72%; R = n-$C_6H_{13}$, 44%

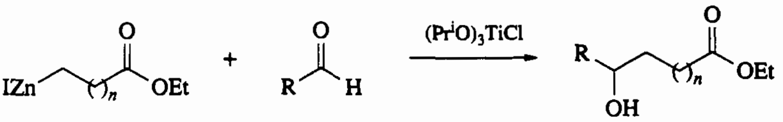

(8)

Organic synthesis utilizing the Group IVB organometals has been a growing field in the past decade.[13] Various organo-silanes or -stannanes with activated carbon–metal bonds can be used in addition reactions to ketones and aldehydes. Although certain organostannanes add to carbonyls in the absence of the Lewis acid, the presence of the promoters dramatically enhances the rate and allows the reaction to be conducted under mild conditions. In the presence of $TiCl_4$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, TMSOTf, $Me_3O^+$ $BF_4^-$, $TrClO_4$, *etc*., allylation of aldehydes with allyl-silanes or -stannanes proceeds smoothly, and homoallylic alcohols are obtained in high yields.[14,15] The Lewis acid promoted aldol reactions of silyl enol ethers are reviewed in Scheme 1.[16]

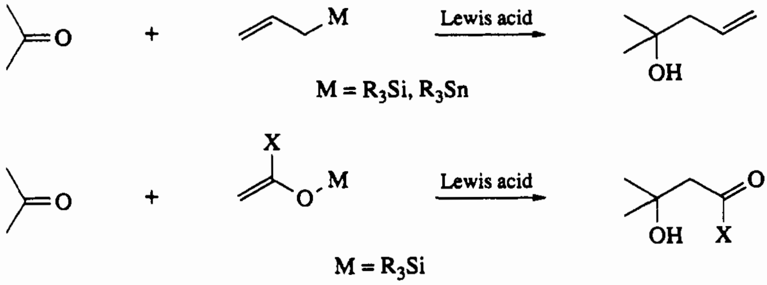

**Scheme 1**

Organo-silanes and -stannanes possessing *sp* carbon–metal bonds also add to carbonyls in the presence of Lewis acids. Alkynylation with silyl- and stannyl-alkynes is promoted by $AlCl_3$ or $ZnCl_2$ (equations 9 and 10).[17–19] Notably, the reaction of 1,3-bis(trimethylsilyl)-1-propyne with chloral affords alkynic alcohol instead of allenylic alcohol, showing the preferential cleavage of *sp* C—Si bonds (equation 11).[17]

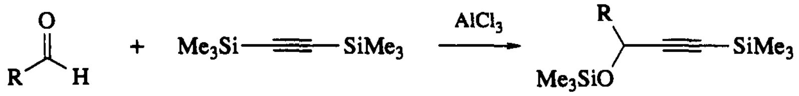
AlCl3
Me3Si
SiMe3
Me3SiO
R
H

(9)

R = Et, 67%; R = $Pr^i$, 51%; R = n-$C_8H_{17}$, 46%

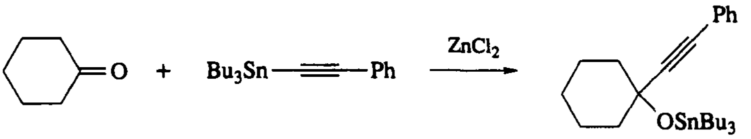
ZnCl2
Bu3Sn
Ph
OSnBu3

(10)

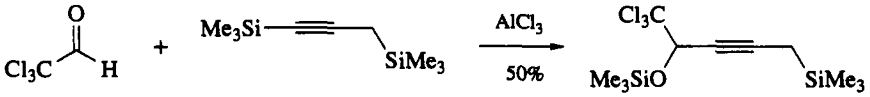
AlCl3
50%
Cl3C
Me3Si
SiMe3
Me3SiO

(11)

Trialkylsilyl cyanides, which also possess *sp* C—Si bonds, react with carbonyls.[20] $ZnI_2$,[21–24] $AlCl_3$,[25] TMSOTf,[26] $LnCl_3$ (Ln = La, Ce, Sm),[27] *etc.*, are employed as the promoter, and cyanohydrin silyl ethers are obtained in high yields even from hindered ketones (equation 12). The products are converted to various synthetically important intermediates such as cyanohydrins, α,β-unsaturated nitriles or amino alcohols.

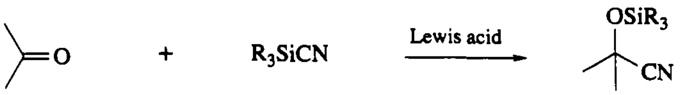
R3SiCN
Lewis acid
OSiR3
CN

(12)

Other organo-silanes and -stannanes are relatively inert, and addition reactions to aldehydes or ketones have been quite limited. However, there seems to be no reason why these organometals should not find applications in the future through the development of appropriate promoters. Actually, several examples appear in the literature. Aryl- or vinyl-silanes, which possess $sp^2$ C—Si bonds, add to chloral in the presence of $AlCl_3$ (Scheme 2).[17] The intramolecular addition reactions of alkylstannanes to ketones proceed with $TiCl_4$ (equations 13 and 14).[28,29]

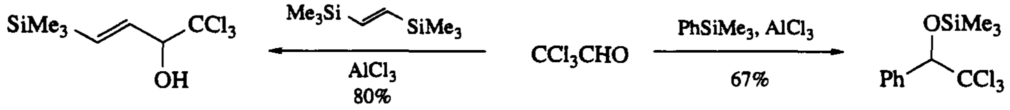
SiMe3
CCl3
OH
Me3Si
SiMe3
AlCl3
80%
CCl3CHO
PhSiMe3, AlCl3
67%
OSiMe3
Ph
CCl3

**Scheme 2**

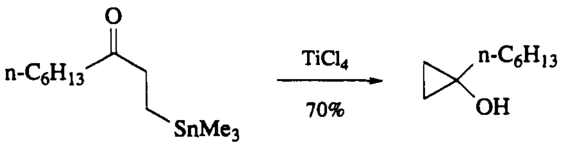
n-C6H13
SnMe3
TiCl4
70%
n-C6H13
OH

(13)

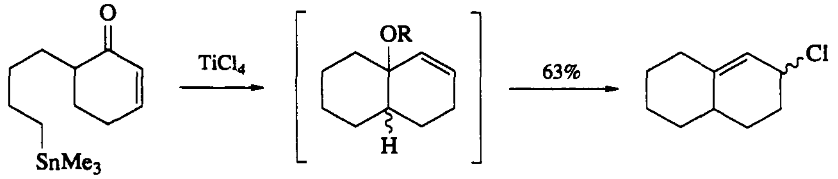
SnMe3
TiCl4
OR
H
63%
Cl

(14)

In contrast to the inertness of alkyl-silanes and -stannanes, alkylplumbanes in the presence of $TiCl_4$ add to aldehydes. The effectiveness of $BF_3$ as the promoter eliminates the possibility of organotitanium species occurring as intermediates. Addition of $R_4Pb$ to a mixture of an aldehyde and $TiCl_4$ is important, as clean reaction does not occur when the order of addition is reversed, *i.e.* addition of the aldehyde to a mixture of $R_4Pb$ and $TiCl_4$. As the reagent reacts only with aldehydes and not with ketones, octanal can be butylated selectively in the presence of 2-octanone (equation 15).[30]

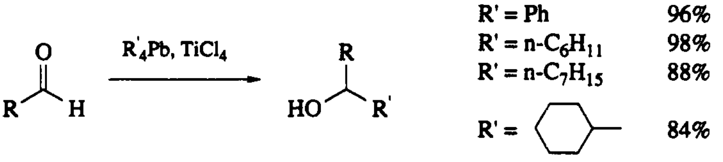

(15)

Alkylcoppers (RCu) were shown to add to aldehydes in the presence of $BF_3{\cdot}OEt_2$ (equation 16).[31,32]

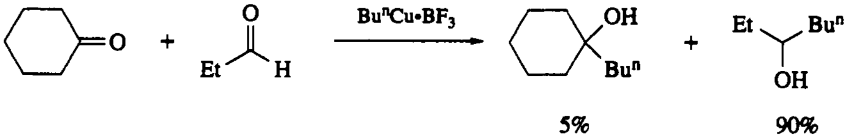

(16)

Organolithiums are widely used nucleophiles in organic synthesis, and normally add to aldehydes and ketones smoothly. However, they sometimes fail to react for such reasons as the presence of sensitive functionalities, the deprotonation side reactions, steric hinderance, *etc.* One of the popular modifications of the alkyllithium reactions is the addition of magnesium salts. The coupling reaction of lithiated sulfones with enolizable aldehydes or ketones gives a low yield of β-hydroxy sulfones because of the deprotonation. The process is greatly improved by the presence of $MgBr_2$ (Scheme 3).[33,34] The reaction is successfully employed in the total synthesis of zincophorin (equation 17).[35] A vinyllithium–$MgBr_2$ complex is used instead of vinyllithium in the synthesis of (–)-vertinolide (equation 18).[36]

Lithium salts are also effective for promoting the organolithium or magnesium addition reactions. $LiClO_4$ was found to enhance the rate of MeLi or $Me_2Mg$ addition to 4-*t*-butylcyclohexanone.[37] Another example is shown in the reaction of 2-acetylpyridine with alkyllithiums, where added LiBr raises the yields of the adducts.[38] This phenomenon is explained by the coordination of LiX to the carbonyl oxygen prior to the C—C bond formation.

Recently, $BF_3$ has also been found to be an effective promoter of organolithium reactions. At low temperatures, various organolithiums are able to coexist with the Lewis acid in solution without provoking transmetalation, which would give unreactive alkylboranes. Addition of lithiated sulfones to the enolizable aldehydes is carried out in the presence of $BF_3{\cdot}OEt_2$ at –78 °C (Scheme 4).[39,40] $BF_3{\cdot}OEt_2$ promotes the reaction of the sterically demanding vinyllithium reagents with aldehydes (equation 19).[41] $RLi{\cdot}BF_3$ reagents are finding wide use in organic synthesis, and further examples are shown in the following sections.

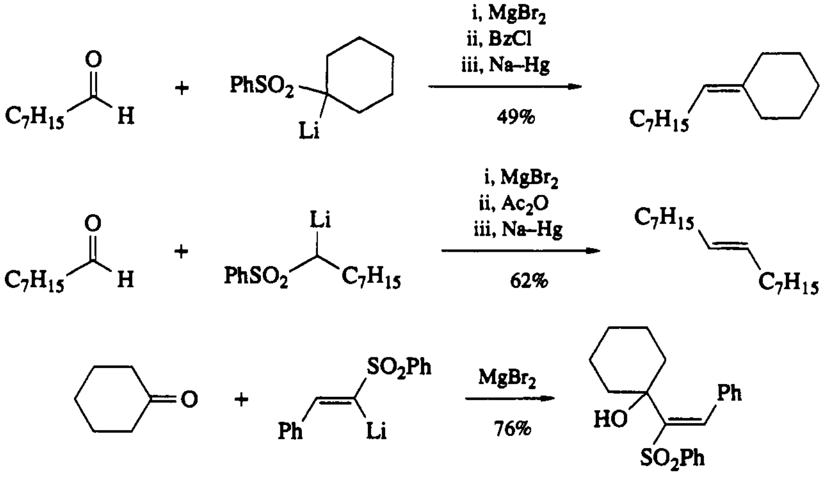

Scheme 3

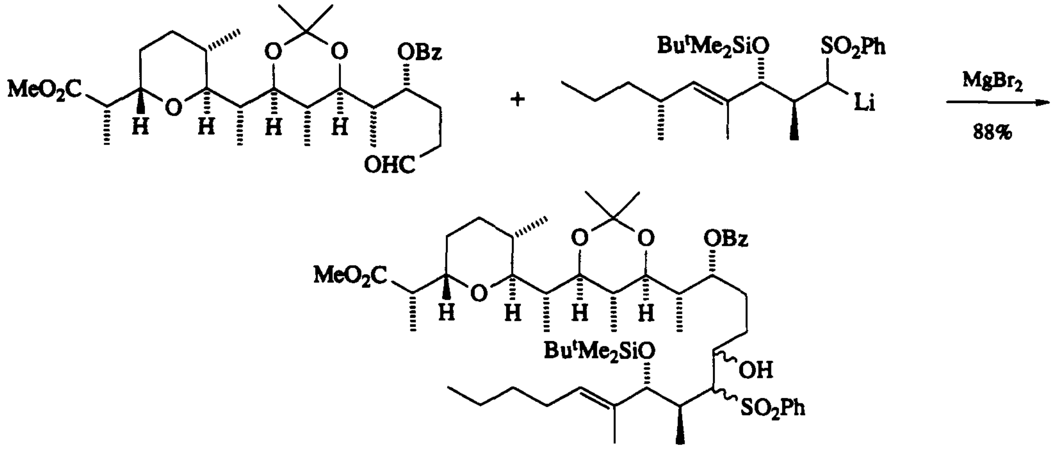

MeO2C
OBz
OHC
Bu<sup>t</sup>Me2SiO
SO2Ph
Li
MgBr2
88%
OH

(17)

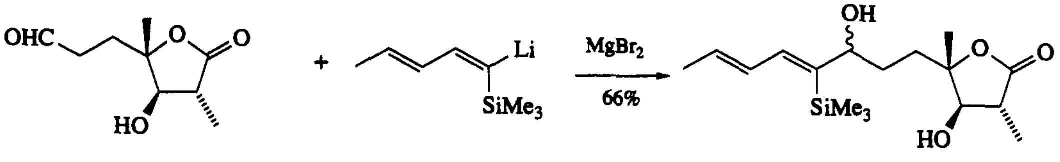

OHC
HO
Li
SiMe3
MgBr2
66%
OH

(18)

The complex reagents of organo-lithiums and -magnesiums with transition metal halides ($TiCl_4$, $CrCl_3$, $UCl_4$, $MnI_2$, $CeCl_3$, $VCl_3$, *etc.*) have been developed. Although the actual reacting species or the effect of the Lewis acids is not fully clear, they provide unique and useful methodologies in organic synthesis.

The chemistry of organotitanium reagents has been explored by Reetz[42–44], Weidmann and Seebach.[45] The MeLi–$TiCl_4$ system provides a nonbasic reagent which reacts chemo- and stereo-selectively. Nitro,

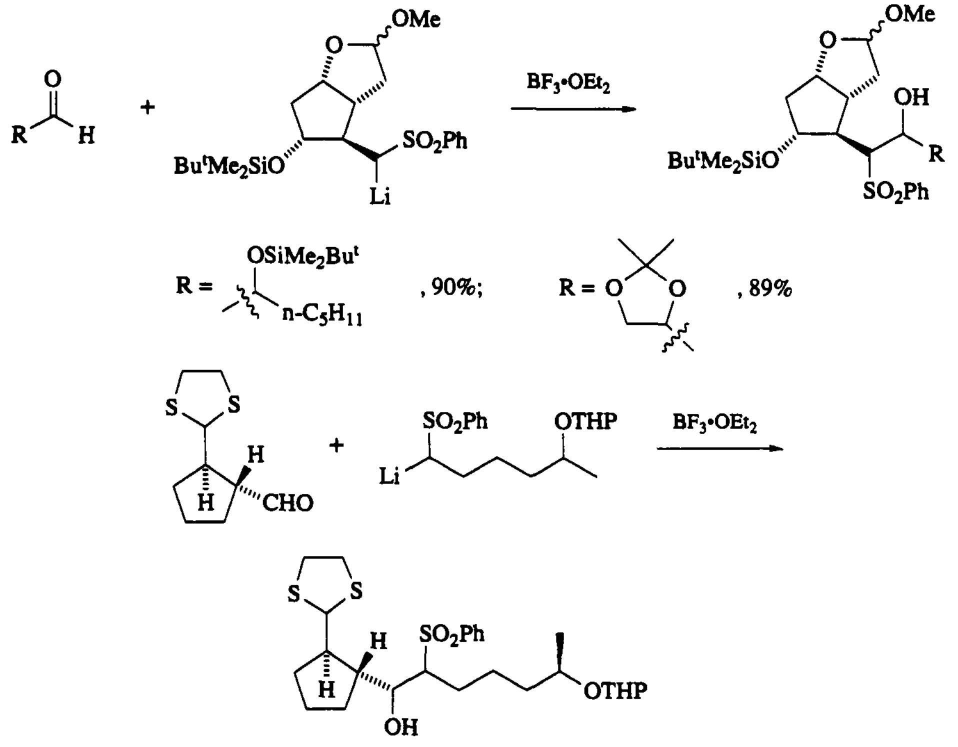

OMe
SO2Ph
Li
Bu<sup>t</sup>Me2SiO
BF3•OEt2
OH
R
R = OSiMe2Bu<sup>t</sup> n-C5H11 , 90%;
R = , 89%
CHO
OTHP
BF3•OEt2

Scheme 4

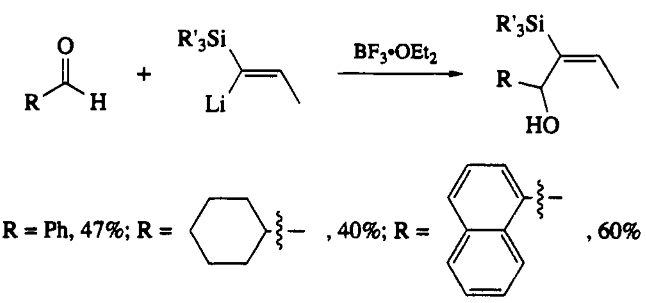
R'$_3$Si
Li
BF$_3$•OEt$_2$
R'$_3$Si
R
HO
R = Ph, 47%; R =
, 40%; R =
, 60%

(19)

cyano or ester groups do not interfere with the carbonyl addition. The reaction proceeds smoothly with enolizable ketones without proton abstraction (Scheme 5).[46]

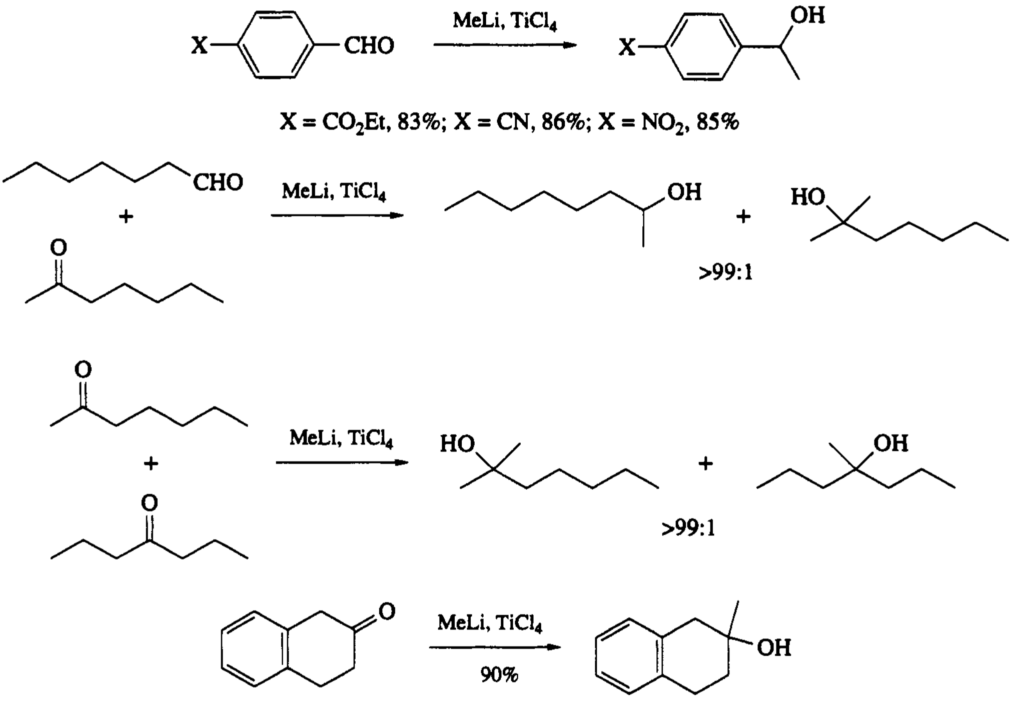
X
CHO
MeLi, TiCl$_4$
X
OH
X = CO$_2$Et, 83%; X = CN, 86%; X = NO$_2$, 85%
CHO
O
MeLi, TiCl$_4$
OH
HO
>99:1
O
O
MeLi, TiCl$_4$
HO
OH
>99:1
O
MeLi, TiCl$_4$
90%
OH

**Scheme 5**

Organochromium reagents generated from alkyl-lithiums or -magnesiums and $CrCl_3$ react with aldehydes selectively in the presence of ketones (equation 20).[47,48] RLi–$UCl_4$ reagents, developed recently, are also aldehyde selective.[49]

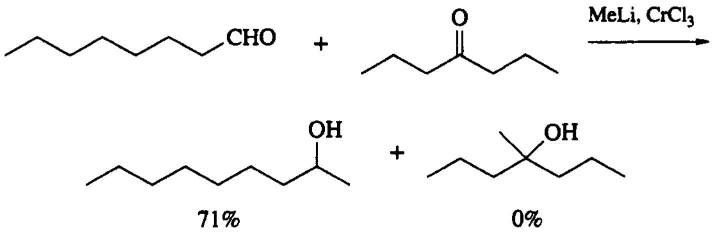
CHO
O
MeLi, CrCl$_3$
OH
OH
71%
0%

(20)

A similar chemoselectivity is observed with alkylmanganese compounds prepared from alkyl-lithiums or -magnesiums and $MnI_2$. The organometallic compounds react with aldehydes at –50 °C, while ketone addition occurs only at higher temperatures (Scheme 6).[50,51]

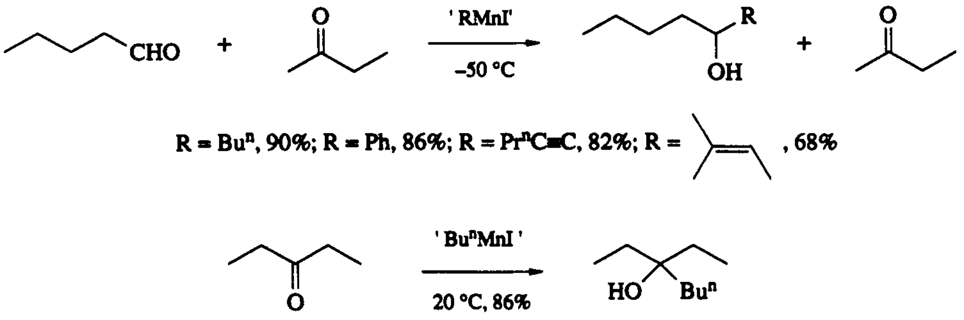
CHO
+
O
'RMnI'
-50 °C
R
OH
+
O
R = Bu$^n$, 90%; R = Ph, 86%; R = Pr$^n$C≡C, 82%; R =
, 68%
O
'Bu$^n$MnI'
20 °C, 86%
HO
Bu$^n$

**Scheme 6**

RLi–CeCl$_3$ is an effective alkylating reagent for easily enolizable ketones, which give very low yields of the adducts with alkyl-lithiums or -magnesiums.[52,53] Selective 1,2-addition reactions with α,β-unsaturated ketones can be conducted with the cerium reagents (Scheme 7).[54]

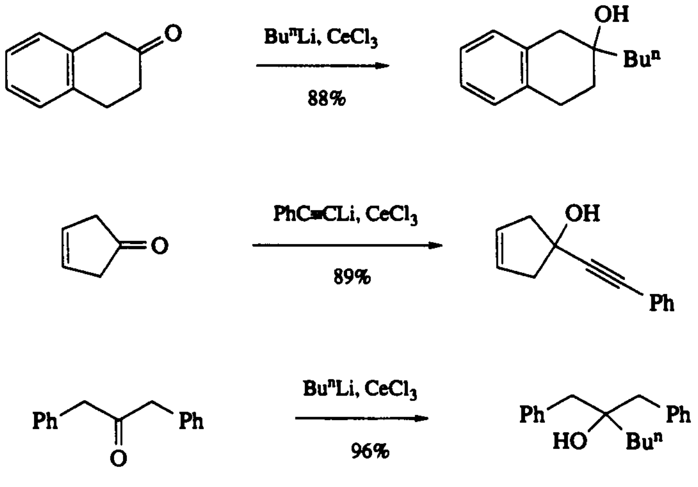
O
Bu$^n$Li, CeCl$_3$
88%
OH
Bu$^n$
O
PhC≡CLi, CeCl$_3$
89%
OH
Ph
Ph
Ph
O
Bu$^n$Li, CeCl$_3$
96%
Ph
Ph
HO
Bu$^n$

**Scheme 7**

The reactions of RLi–VCl$_3$ or RMgX–VCl$_3$ with aldehydes result in oxidative carbon–carbon bond formation, affording ketones. Since a lithium alkoxide is converted to a ketone in the presence of VCl$_3$, the vanadium(III) species is considered to work as an oxidant (Scheme 8).[55,56]

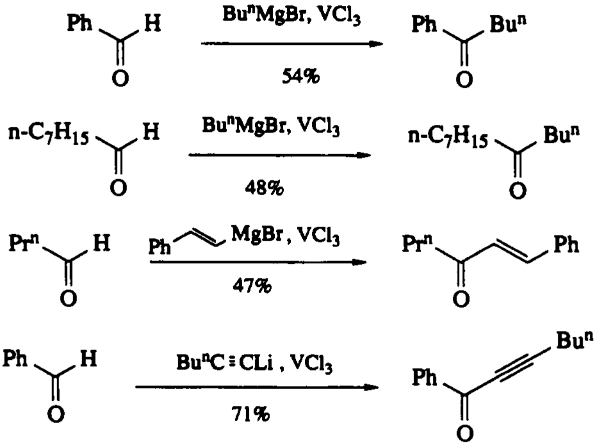
Ph
H
O
Bu$^n$MgBr, VCl$_3$
54%
Ph
Bu$^n$
O
n-C$_7$H$_{15}$
H
O
Bu$^n$MgBr, VCl$_3$
48%
n-C$_7$H$_{15}$
Bu$^n$
O
Pr$^n$
H
O
Ph MgBr, VCl$_3$
47%
Pr$^n$
Ph
O
Ph
H
O
Bu$^n$C≡CLi, VCl$_3$
71%
Bu$^n$
Ph
O

**Scheme 8**

### 1.11.2.2 Control of the Stereoselectivity

The stereochemistry of organometal additions to cyclic ketones has been extensively studied using various alkyl metals. The results are used to gain knowledge concerning the solution state of the particular organometals and to explore the driving force behind the steric course of the addition.

Addition to cyclohexanones is considered to be influenced by two factors: (i) the steric interaction of the incoming groups with 3,5-axial substituents; and (ii) the torsional strain of the incoming groups with 2,6-axial substituents. Steric strain hinders axial attack, whereas torsional strain hinders equatorial attack. The actual stereochemistry of the addition depends upon which factor is greater in a particular case.[1] The production of the desired isomer in high stereoselectivity is required from the synthetic point of view.

In a large number of studies on the addition reactions to 4-*t*-butylcyclohexanone, acceptably high selectivities have been attained with only a limited number of methods. Selective equatorial attack is obtained with bulky nucleophiles, since steric interactions of the incoming bulky reagents with 3,5-axial hydrogens outweigh torsional effects. For example, $\mathrm{Bu^tMgBr}$ gives the axial alcohol exclusively.[1] Similarly, $\mathrm{MeTi(OPr^i)_3}$, which possesses bulky ligands, is superior to MeLi for equatorial attack.[57]

The use of organometal–Lewis acid complex reagents is quite effective in controlling the axial–equatorial problem, since the reaction course can be modified by the Lewis acid complexation to carbonyl oxygen. Although MeLi showed a low selectivity in the addition to 4-*t*-butylcyclohexanone, the presence of an appropriate Lewis acid dramatically enhances either equatorial or axial attack. The $\mathrm{MeLi–Me_2CuLi}$ reagent shows a high tendency to deliver a methyl moiety from an equatorial site.[58] A high equatorial selectivity as well as a considerable rate enhancement is also observed with the $\mathrm{MeLi–LiClO_4}$ reagent, and the results are interpreted as the complexation of $\mathrm{Li^+}$ to carbonyl followed by the addition of MeLi (Figure 1).[37,59]

| *ax:eq* | *Reagent* |
|---|---|
| 88:12 | $\mathrm{Me_3Al}$ (3 equiv.) |
| 99:1 | MeLi-MAD |
| 99.5:0.5 | MeLi-MAT |

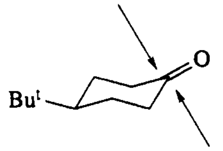

| *Reagent* | *eq:ax* |
|---|---|
| $\mathrm{Bu^tMgBr}$ | 100:0 |
| $\mathrm{MeTi(OPr^i)_3}$ | 94:6 |
| $\mathrm{MeLi–LiClO_4}$ | 92:8 |
| $\mathrm{MeLi–Me_2CuLi}$ | 94:6 |

**Figure 1**

Axial attack has been rather difficult to attain. The treatment of the ketone with 3 equiv. of $\mathrm{Me_3Al}$ has been known to give equatorial alcohol predominantly, although low selectivity was obtained using 1 equiv. of reagent. Methylation of the $\mathrm{Me_3Al}$-complexed carbonyl was suggested. This methodology, however, was not applicable to ethyl- or butyl-aluminum because of the competitive carbonyl reduction.[1]

A selective axial attack is achieved by employing bulky organoaluminum ligands; methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) or methylaluminum bis(2,4,6-tri-*t*-butylphenoxide) (MAT). Treatment of carbonyl compounds with the aluminum reagents prior to alkyllithium or Grignard addition gives equatorial alcohols in high selectivities. Various alkyl groups can be introduced by this reaction (Figure 1). Since addition of ketones to a mixture of MeLi and MAD resulted in low selectivity, the possibility of the ate complex $\mathrm{Li^+}$ $\mathrm{[Me{\cdot}MAD]^-}$ as the reactive intermediate was excluded. Preferential formation of the sterically favored isomer (**1b**) rather than the alternative (**1a**) was suggested for the transition state (Figure 2).[60,61]

Similar tendencies are observed with other cyclic ketones. With 2- or 3-methylcyclohexanone, MeLi–LiX (X = $\mathrm{CuMe_2}$, $\mathrm{ClO_4}$) or $\mathrm{MeTi(OPr^i)_3}$ favors equatorial attack, whereas $\mathrm{Me_3Al}$ (3 equiv.), MeLi–MAT, or MeLi–MAD attacks from the axial site (Figure 3).[58–61]

In relation to the synthesis of chain molecules with a series of asymmetric centers, macrolides or polyether antibiotics, asymmetric induction in the addition reactions of organometals to chiral aldehydes

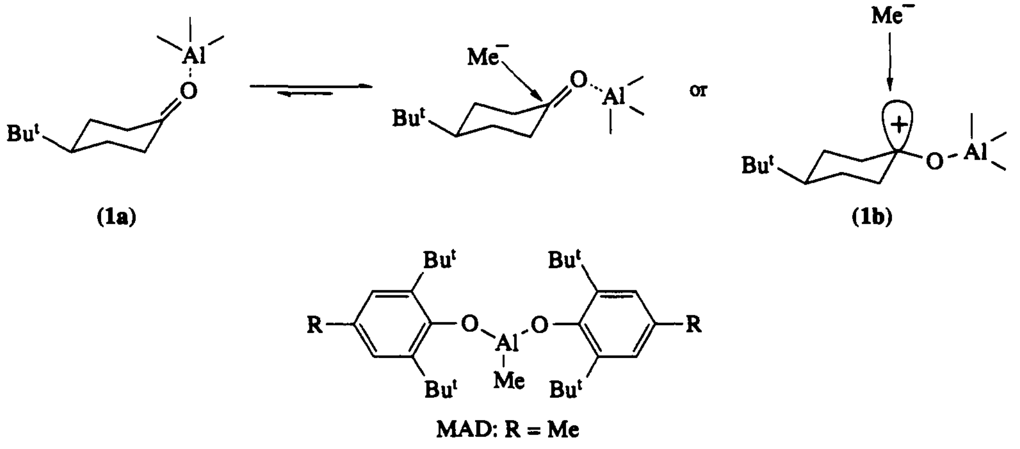

MAD: R = Me

MAT: R = Bu^t

**Figure 2**

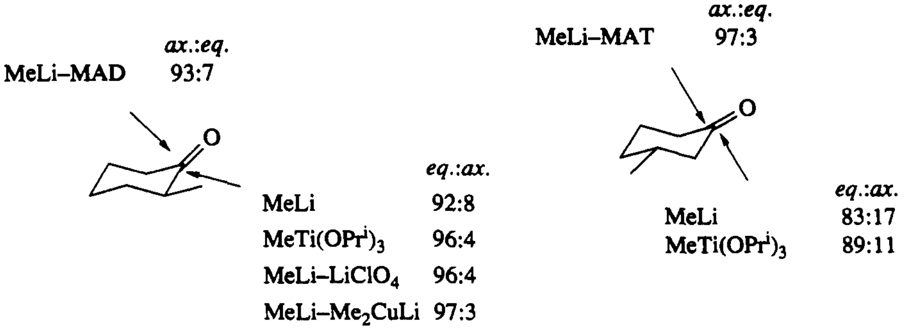

| | *eq.:ax.* |
|---|---|
| MeLi | 92:8 |
| $MeTi(OPr^i)_3$ | 96:4 |
| $MeLi–LiClO_4$ | 96:4 |
| $MeLi–Me_2CuLi$ | 97:3 |

| | *eq.:ax.* |
|---|---|
| MeLi | 83:17 |
| $MeTi(OPr^i)_3$ | 89:11 |

**Figure 3**

has been extensively studied.[42,62] In the following part, Cram/anti-Cram selectivity, and the chelation/nonchelation problem is discussed.

Addition to chiral aldehydes which have no additional functional group capable of interacting with metal species is governed by electronic and/or steric factors. Of several mechanistic rationalizations provided since Cram, the Felkin model best agrees with the prediction based on *ab initio* calculations. In this model, M and S represent medium and small groups, respectively, attached to the chiral α-carbon, and L represents either the largest group or the group whose bond to the α-carbon provides the greatest $\sigma^*–\pi^*$ overlap with the carbonyl $\pi^*$ orbital. A nucleophile approaches from the opposite side of the L group (Figure 4). Although the selectivity of this type of reaction had not previously been very high, the Lewis acid promoted addition methodologies succeeded in attaining high Cram selectivities, or even anti-Cram selectivities (equations 21 and 22).

MeLi–$TiCl_4$[46] or $PbEt_4$–$TiCl_4$[30] reagents show high Cram selectivities in addition reactions to 2-phenylpropanal. An explanation was presented by Heathcock for the selectivities achieved by the Lewis acid promoted additions compared to simple organometal additions. In the latter cases, a trajectory is followed that brings the nucleophiles closer to H rather than to $R^*$, and asymmetry in $R^*$ is transferred

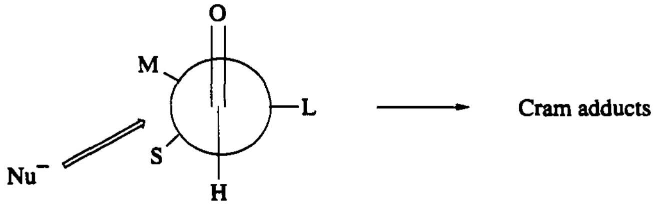

**Figure 4**

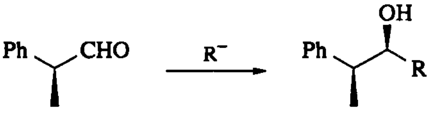

(21)

| | |
|---|---|
| MeTi(OPr$^i$)$_3$ | 93:7 |
| MeLi–TiCl$_4$ | 90:10 |
| PbEt$_4$–TiCl$_4$ | 93:7 |
| MeLi–K[2.2.1] | 9:1 |
| Bu$_2$CuCNLi$_2$–15-crown-5–BF$_3$ | 8–10:1 |

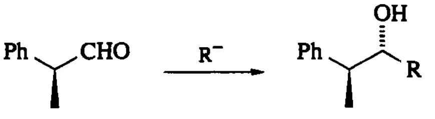

(22)

| | |
|---|---|
| MeMgI–MAT | 93: 7 |
| EtMgBr–MAT | 87:13 |
| Bu$_2$CuLi–K[2.1] | 5:1 |

imperfectly. When a Lewis acid coordinates with an aldehyde occupying the position *syn* to H,[63] the nucleophile may be forced to approach the carbonyl plane in a perpendicular fashion, resulting in greater stereoselectivity (Figure 5).[64]

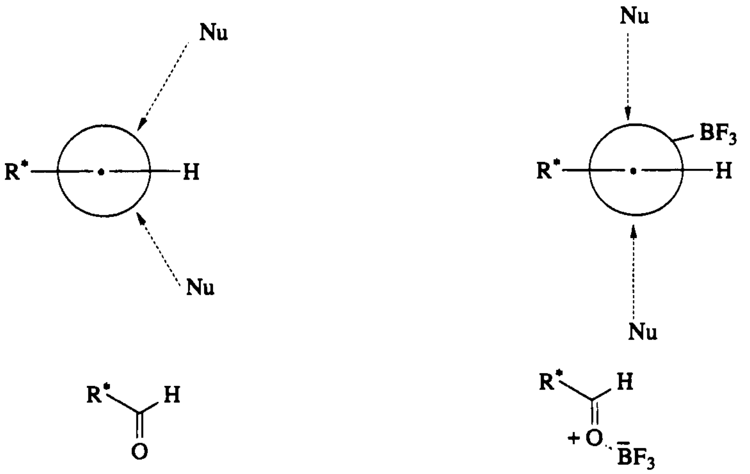

**Figure 5**

The presence of crown ethers was found to enhance the Cram selectivity. The MeLi/18-crown-6 reagent system shows a similar level of selectivity to the above reagents, and BuLi/15-crown-5 and allyllithium/18-crown-6 add to 2-phenylpropanal in Cram fashion almost exclusively.[65] Since a bulky reagent MeTi(OPr$^i$)$_3$ also exibits a high Cram selectivity,[57] the bulkiness of the RLi–crown ether reagent might be one of the important factors which control the selectivity. Interestingly, R$_2$CuCNLi$_2$–crown ether–BF$_3$ reagent also shows Cram selectivity.[66]

Stannylalkynes in the presence of TiCl$_4$ react with a steroidal aldehyde in a highly Cram selective manner. The use of lithium derivatives gives 1:1 mixtures of two diastereomers (equation 23).[67]

Recently it has been reported that the addition of Grignard reagents to MAT or MAD complexed aldehydes results in anti-Cram products in high stereoselectivities. Formation of a sterically least hindered complex and subsequent attack of the organometal from the opposite site to the bulky ligand is suggested by Yamamoto (Figure 6).[60,61] The R$_2$CuLi–crown ether system is also reported to show anti-Cram selectivities. An electron transfer mechanism has been suggested for this reaction.[65]

Although the stereochemistry of the organometal addition reactions to carbonyls with α-alkyl (typically α-methyl) substituents is explained mostly by the Felkin–Ahn model, different phenomena are observed with α-alkoxy- or α-hydroxy-carbonyls, which make the opposite π-face sterically more

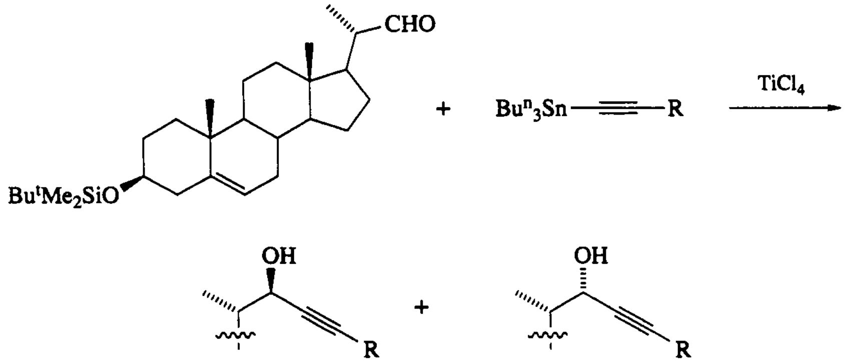

(23)

| | | | |
|---|---|---|---|
| R = Pr$^i$ | 90 | : | 10 |
| R = Bu$^n$ | 90 | : | 10 |
| R = Ph | 85 | : | 15 |

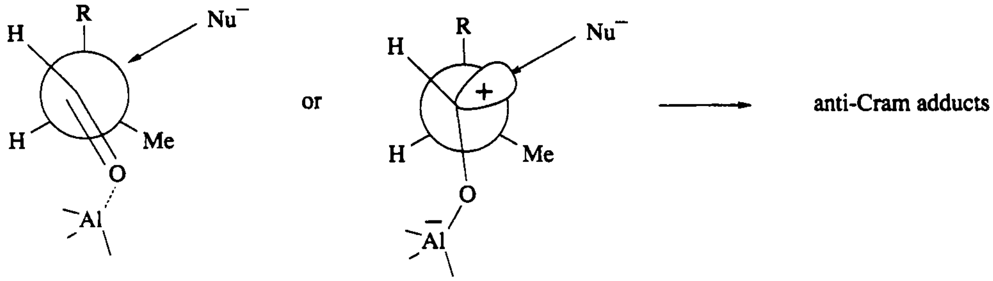

**Figure 6**

accessible. In such cases, Cram's cyclic model pertains, which assumes a chelation of the metal species between the carbonyl oxygen and the α-oxygen atom (chelation control).

Systematic studies on the chelation-controlled additions were carried out, varying the type of alkoxy group, the carbon nucleophile, the solvent and the temperature. It was found that α-alkoxy ketones react highly stereoselectively with Grignard reagents in THF (equation 24). Alkyllithiums were not effective.[68,69] The generalization was made use of in the synthesis of the polyether antibiotic monensin.[70]

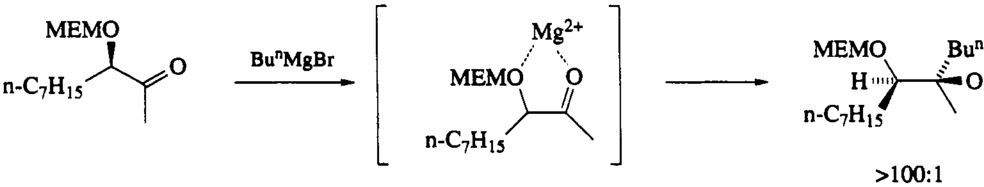

(24)

The high levels of 1,2-asymmetric induction observed with ketones did not extend to aldehydes. However, Asami and coworkers achieved it by pretreating α-alkoxy aldehydes with $ZnBr_2$.[71,72] The reaction is used in the synthesis of *exo*-(+)-brevicomin[71] and L-rhodinose (Scheme 9).[73] Chelation-controlled addition of a Lewis acidic reagent $MeTiCl_3$ is reported,[74] and a chelation intermediate is actually detected by low temperature NMR techniques (equation 25).[75] A 'tied-up' method, which involves the precomplexation of α-alkoxy aldehydes with a Lewis acid and addition of soft C-nucleophiles, shows a high level of asymmetric induction. $SnCl_4$ and $TiCl_4$, capable of forming six-coordinate octahedral complexes, are well suited. $R_2Zn$, TMS-CN, allylsilanes or silyl enol ethers are employed as the nucleophiles (equation 26).[76,77]

In order to obtain the other isomer in addition reactions to α-alkoxy aldehydes, reagents incapable of chelation must be used, and electronic and/or steric factors relied upon (nonchelation control). Treatment of α-alkoxy aldehydes with an excess of gaseous $BF_3$ followed by silyl enol ethers results in the nonchelation-controlled adducts. Formation of a rigid conformation due to electronic repulsion is expected (equation 27). $BF_3 \cdot OEt_2$ is reported to be considerably less efficient.[78,79] The use of $RTi(OPr^i)_3$, which

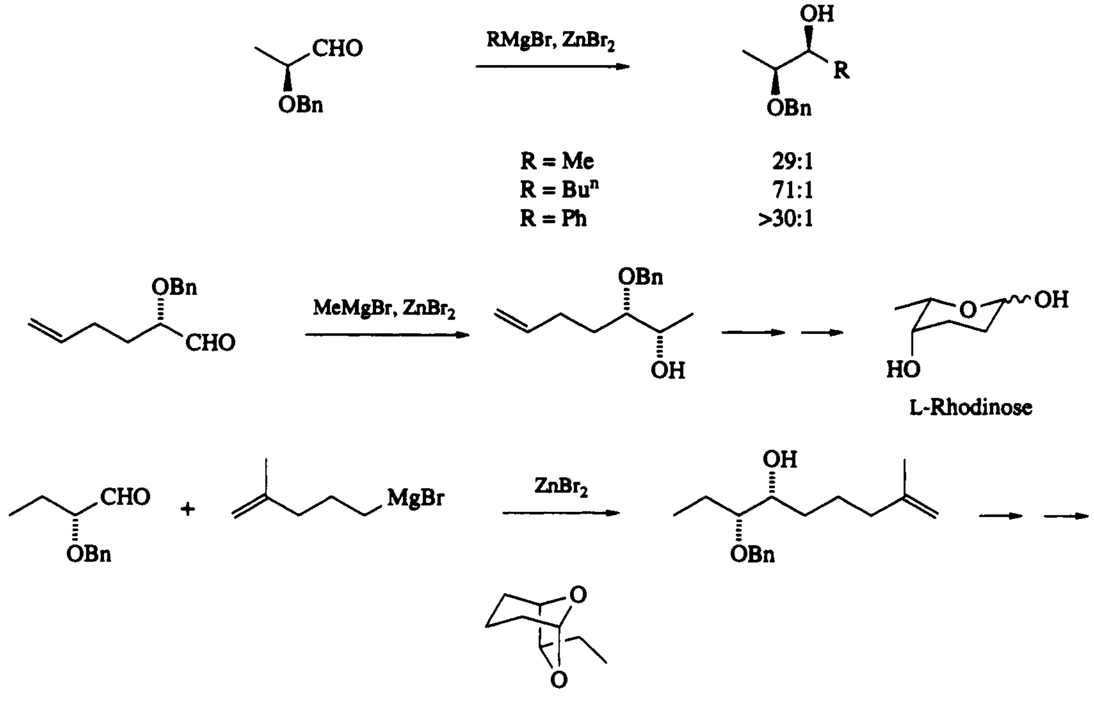
CHO
OBn
RMgBr, ZnBr$_2$
OH
R
OBn
R = Me 29:1
R = Bu$^n$ 71:1
R = Ph >30:1
OBn
CHO
MeMgBr, ZnBr$_2$
OBn
OH
O
OH
HO
L-Rhodinose
CHO
OBn
+
MgBr
ZnBr$_2$
OH
OBn
O
O

*exo*-(+)-Brevicomin

**Scheme 9**

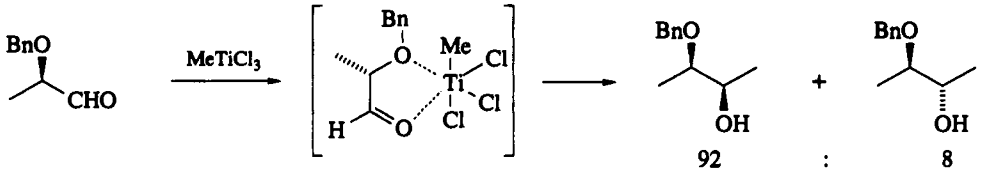
BnO
CHO
MeTiCl$_3$
Bn
O
Me
Cl
Ti
Cl
Cl
H
O
BnO
OH
+
BnO
OH
92 : 8

(25)

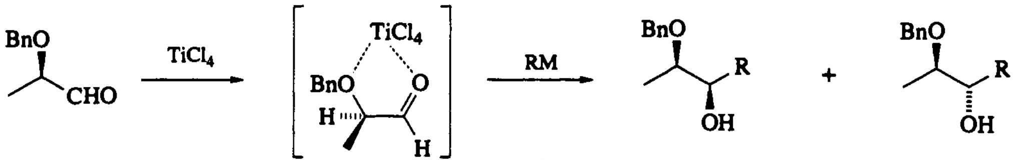
BnO
CHO
TiCl$_4$
TiCl$_4$
BnO
O
H
H
RM
BnO
R
OH
+
BnO
R
OH

(26)

| RM | | | |
|---|---|---|---|
| Bu$^n_2$Zn | 90 | : | 10 |
| Me$_3$SiCN | 80 | : | 20 |
| SiMe$_3$ | 93 | : | 7 |
| OSiMe$_3$ Ph | 96 | : | 4 |

are weakly Lewis acidic and incapable of chelation, provides another method for nonchelation-controlled addition (equation 28).[57]

Novel nonchelation phenomena are observed with a steroidal α-hydroxy aldehyde. The reaction of a lithium or magnesium alkynide with the aldehyde gives the (20*R*,22*R*)-diastereomer predominantly, the formation of which was explained by Cram's cyclic model. When $BF_3·OEt_2$ is added to the lithium alkynide prior to the addition of the aldehyde, the stereoselectivity is inverted, and the (20*R*,22*S*)-isomer is obtained as the principal product. Transformation of α-alkoxy aldehyde to the boron 'ate' complex is suggested. Other Lewis acids, such as $B(OMe)_3$, $AlCl_3$, *etc.*, are less effective (equation 29).[80]

Organometal addition reactions to α,β-dihydroxy aldehyde derivatives have been extensively studied in relation to the stereoselective synthesis of sugar derivatives. Protecting groups play an important role in the chelation/nonchelation problem. With a benzyl protecting group at the α-oxygen, similar behavior to simple α-alkoxy aldehydes is observed. $TiCl_4$- or $SnCl_4$-promoted reactions of organo-silanes, -plum-

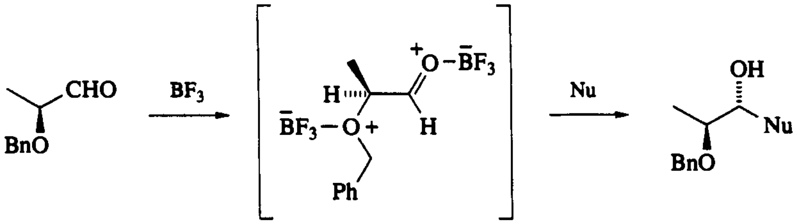
CHO
BnO
BF3
H
BF3−O+
O−BF3
H
Ph
Nu
OH
Nu
BnO

(27)

Nu = $CH_2COBu^t$, 90:10; Nu = $CMe_2CO_2Me$, 84:16

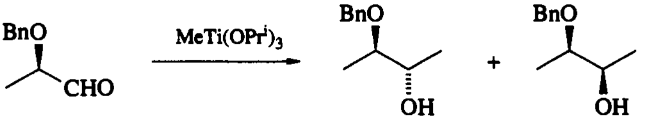
BnO
CHO
MeTi(OPr^i)3
BnO
OH
+
BnO
OH

(28)

92:8

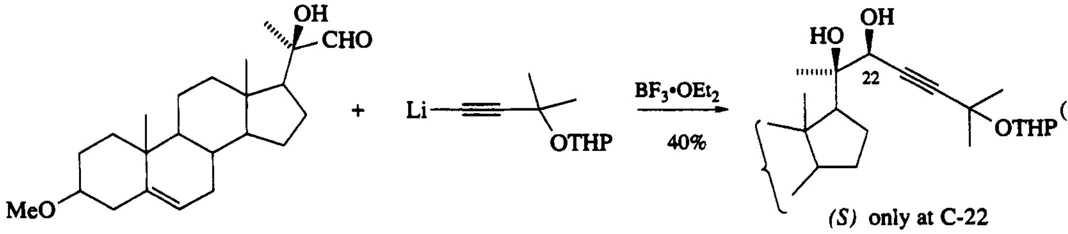
OH
CHO
MeO
+
Li
OTHP
BF3•OEt2
40%
HO
OH
22
OTHP

(29)

(*S*) only at C-22

banes or -zincs give chelation-controlled addition products, while $BF_3$ reverses the selectivity. Bulky $RTi(OPr^i)_3$ also shows nonchelation selectivities (Scheme 10).[81–83] $RCu–MgBr_2$ reagents are reported to be superior to RLi or RMgX in conducting chelation-controlled addition to an α,β-dibenzyloxy aldehyde (equation 30).[83]

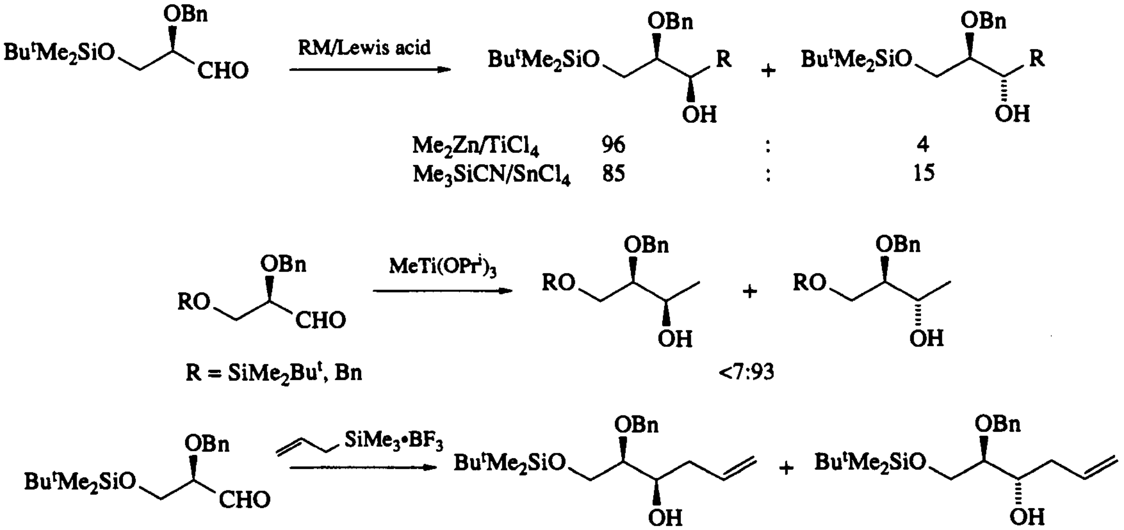
OBn
Bu^tMe2SiO
CHO
RM/Lewis acid
OBn
Bu^tMe2SiO
R
OH
+
OBn
Bu^tMe2SiO
R
OH
OBn
RO
CHO
MeTi(OPr^i)3
RO
OBn
OH
+
RO
OBn
OH
OBn
Bu^tMe2SiO
CHO
SiMe3•BF3
Bu^tMe2SiO
OBn
OH
+
Bu^tMe2SiO
OBn
OH

$Me_2Zn/TiCl_4$ 96 : 4
$Me_3SiCN/SnCl_4$ 85 : 15

R = $SiMe_2Bu^t$, Bn

<7:93

19:81

**Scheme 10**

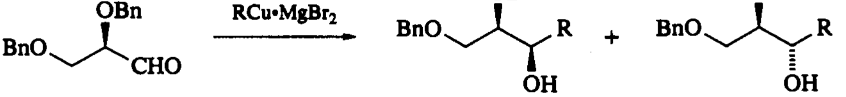
OBn
BnO
CHO
RCu•MgBr2
OBn
BnO
R
OH
+
OBn
BnO
R
OH

(30)

>93:7

In contrast to the α-alkoxy aldehydes, acetonide-protected α,β-dihydroxy aldehydes generally exhibit nonchelation selectivities in simple organometal addition reactions and the Lewis acid promoted reactions.[84] The presence of $ZnX_2$ was found to enhance the selectivity of furyllithium addition to acetonide aldehydes (Scheme 11). $ZnX_2$ is more efficient than $SnCl_4$ or $MgBr_2$. Notably, $ZnX_2$ enhances both nonchelation and chelation selectivity, depending on the protecting groups (*cf.* Scheme 9). The reaction is employed in the synthesis of the rare sugars L-tagatose and D-ribulose.[85] These peculiarities of acetonide aldehydes are explained by the inhibition of chelation formation, since a Felkin–Ahn type transition state predominates as a consequence of: (i) the significant ring strain which develops in the chelate structure; (ii) the depressed donor abilities of the acetonide oxygen due to inductive electron withdrawal; and (iii) the steric inhibition to chelate formation due to nonbonded interaction between the metal ligands and the acetonide methyl group.[82] Another explanation has been made which attributes the selectivity to a chelation between the β-oxygen and the carbonyl oxygen (Scheme 11).[85,86]

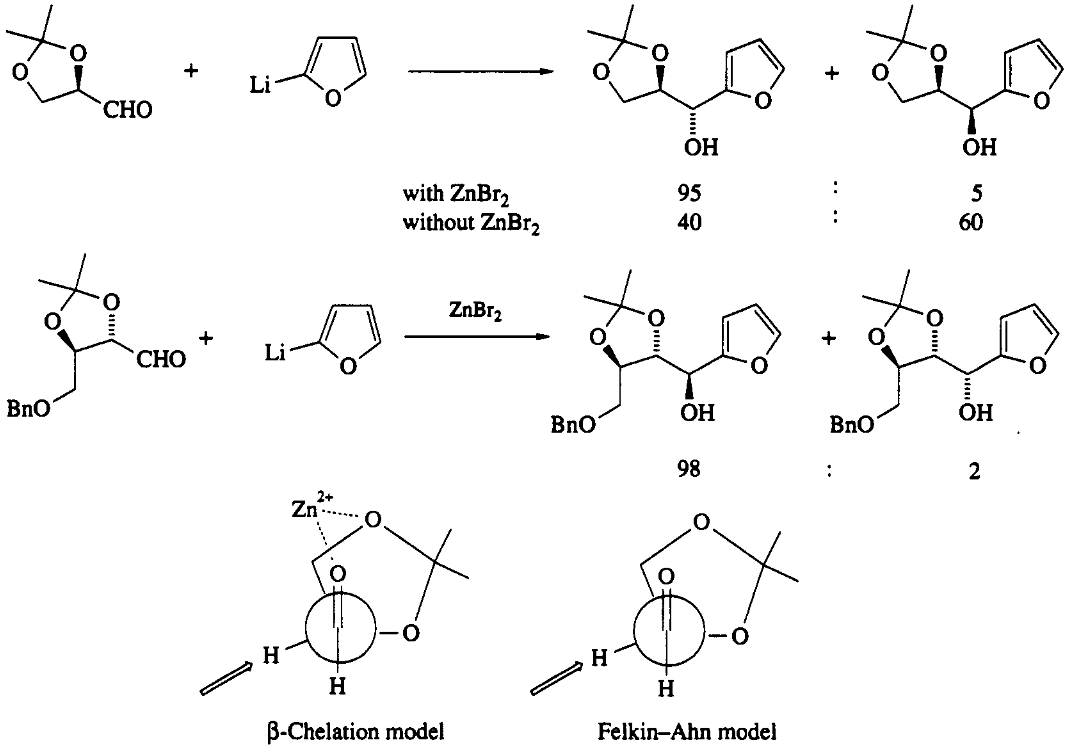

Scheme 11

An exception to the general rule regarding nonchelation stereoselectivities of acetonide aldehydes has been published. RCu·$MgBr_2$ in THF adds to 2,3-*O*-isopropylideneglyceraldehyde to give chelation products. In ether the reagent shows almost no selectivity (equation 31).[87,88]

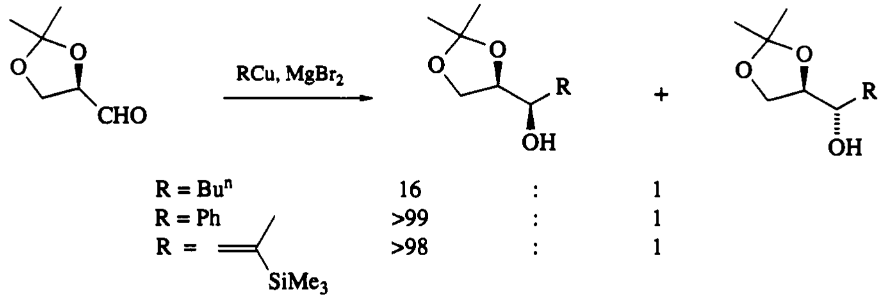

(31)

Addition of organometallic compounds to α,β-epoxy aldehydes gives predominantly nonchelation-controlled adducts. Grignard reagents or allylstannanes in the presence of $BF_3{\cdot}OEt_2$ give good results (equation 32).[89]

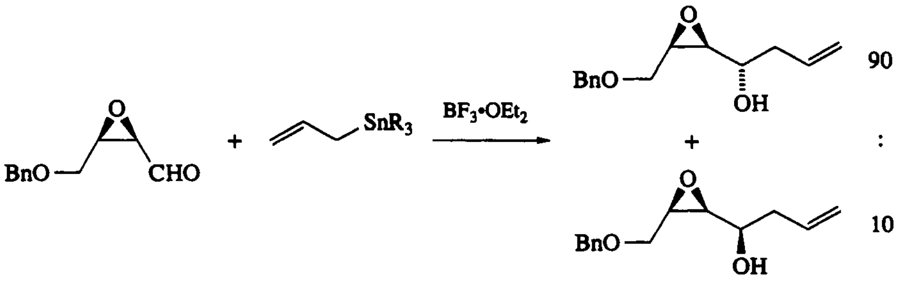

(32)

A high level of 1,3-asymmetric induction was achieved by the assistance of a Lewis acid. Complexation of a β-alkoxy aldehyde with $TiCl_4$ followed by addition of $Bu_2Zn$, allylsilane or silyl enol ethers at −78 °C results in chelation-controlled products in >85% selectivities (Scheme 12).[77,79] Even a considerable level of 1,4-asymmetric induction is observed with the $Me_2Zn–TiCl_4$ system (equation 33).[74]

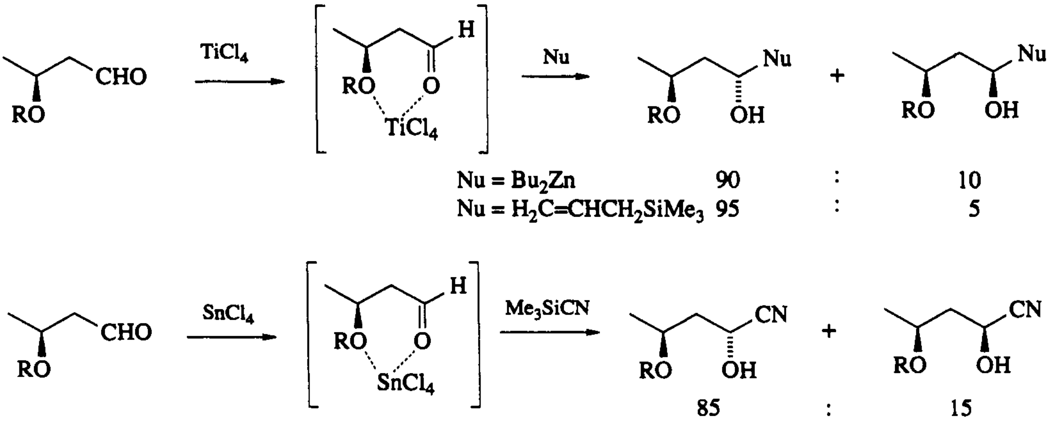

**Scheme 12**

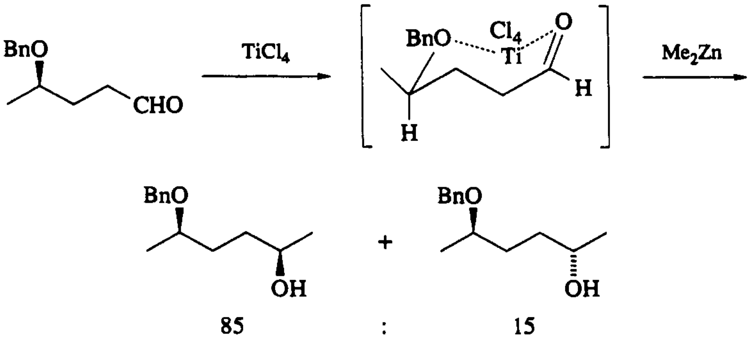

(33)

*Erythro/threo* selectivity in the reactions of crotyl-type organometals with aldehydes (simple diastereoselectivity) is markedly influenced by the presence of a Lewis acid. Crotyltitanium reagents react with aldehydes to afford *threo* adducts preferentially,[90] while *erythro* isomers are obtained in high selectivity by the addition of the organometal to a mixture of an aldehyde and $BF_3{\cdot}OEt_2$.[91] A pericyclic transition state is assumed for the former, and an open-chain transition state, in which the nucleophile attacks the $BF_3$-complexed aldehyde, is suggested for the latter (Scheme 13). A similar reversal of the diastereoselectivity was reported in the reactions of crotyl $Cu^{I}$, Cd, $Hg^{II}$, $Tl^{I}$, $ZrCp_2Cl$ and $VCp_2Cl$.[92] The mechanistic aspects of the Lewis acid promoted addition reactions of allyl-stannanes or -silanes have been studied in detail.[93]. Configurationally defined α-alkoxylithium is readily accessible from the corresponding organostannanes, and the addition to aldehydes has been examined. *syn*-1,2-Diol derivatives are obtained predominantly in the presence of $MgBr_2$. Enantiofacial discrimination is considered to result

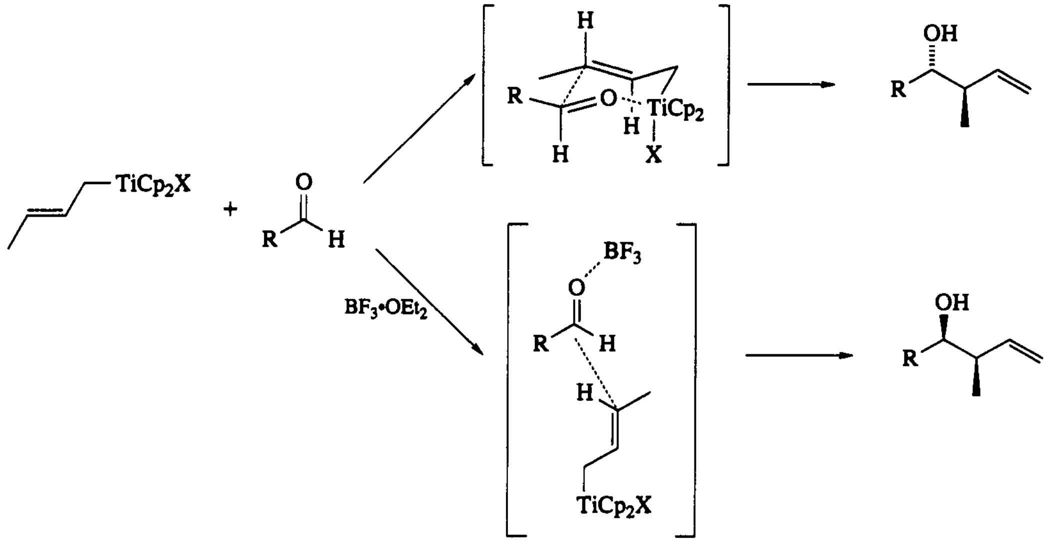

Scheme 13

from the unfavorable interaction which is absent in the transition state (**2a**), although the stereoregulating effect of the metal salt remains unclear (Scheme 14).[94]

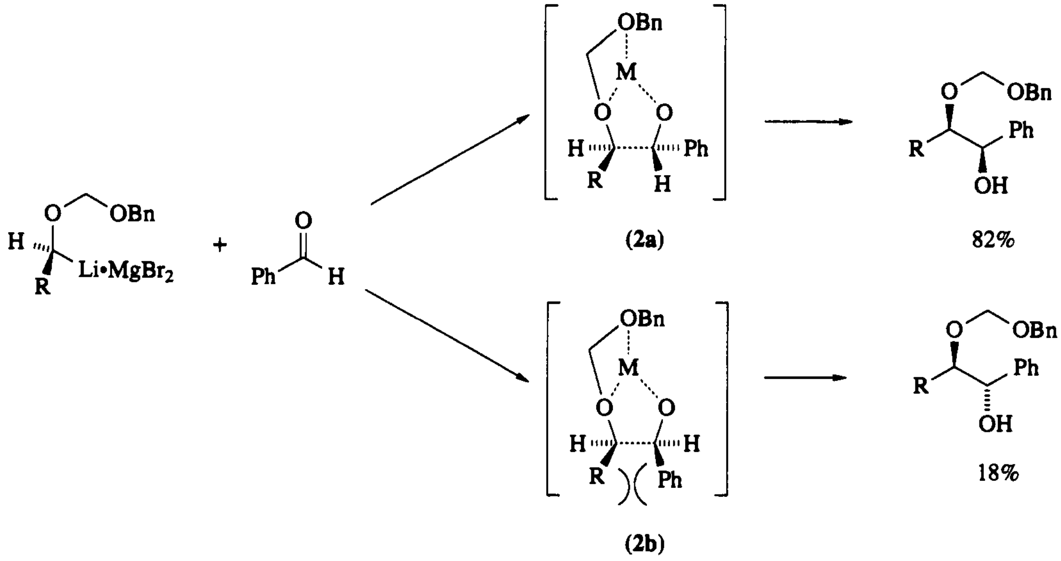

Scheme 14

Although lithiated 1,2,3,4-tetrahydroisoquinoline reacts with aldehydes with little diastereoselectivity, the presence of $MgBr_2$ dramatically enhances the selectivity. *l*-Isomers are obtained from 2-pivaloyl-1,2,3,4-tetrahydroisoquinoline in >97% *de*, and a *u*-isomer predominantly from a formamidine.[95] In the latter case, an organomagnesium reagent (**3**) formed by transmetalation was shown to be the reactive intermediate (Scheme 15).[96]

Stereoselectivity in the addition of α-lithiated (*R*)-methyl-*p*-tolyl sulfoxide to aromatic aldehydes is enhanced from 1:1 to 4:1 by the presence of $ZnCl_2$ (equation 34).[97]

Chiral organotitanium reagents generated from aryl Grignards transfer aryl groups to aromatic aldehydes with high enantiofacial selectivity. The use of aryllithium resulted in lower selectivity indicating the important role of $MgX_2$ in the asymmetric induction (equation 35).[98]

Tomioka found that, by the pretreatment of benzaldehyde with 2,4,6-$Me_3C_6H_2OAlCl_2$, the enantiofacial addition reaction of an RMgBr–chiral diamine complex led to carbinols with considerably higher optical purities. Steric modification of the benzaldehyde carbonyl by the complexation of the aluminum

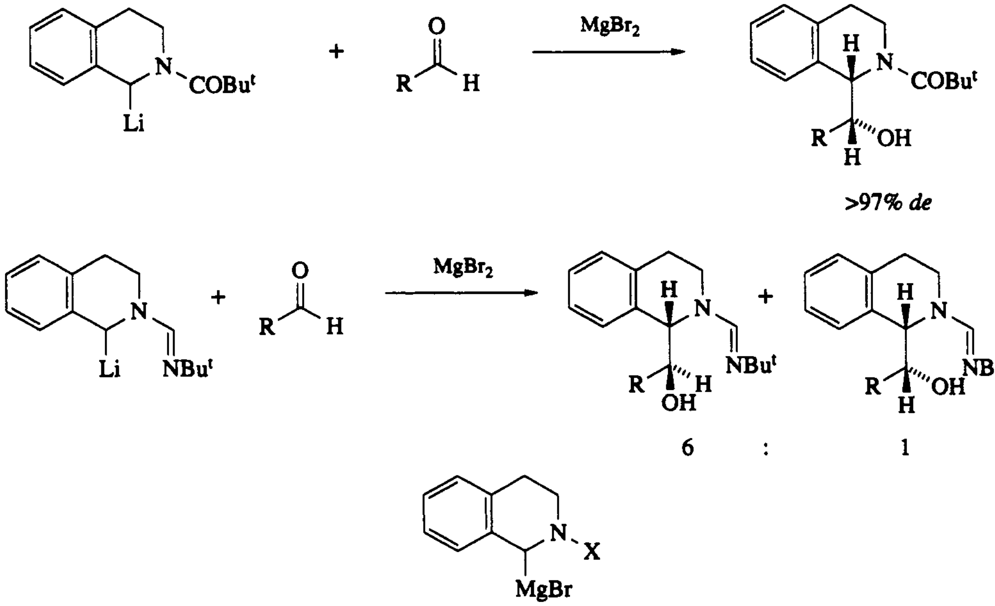
COBu^t
Li
R
H
MgBr$_2$
H
COBu^t
R
OH
H
>97% de
Li
NBu^t
R
H
MgBr$_2$
H
R
H
OH
NBu^t
H
R
OH
H
NBu^t
6 : 1
N
X
MgBr

(3)

**Scheme 15**

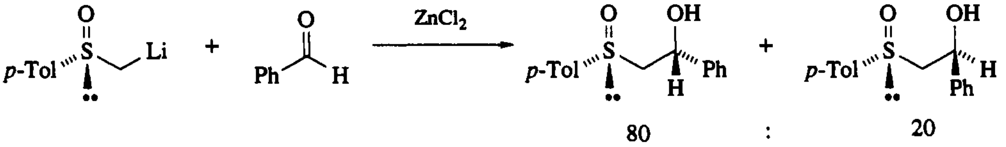
p-Tol
S
Li
Ph
H
ZnCl$_2$
p-Tol
OH
Ph
H
p-Tol
OH
H
Ph
80 : 20

(34)

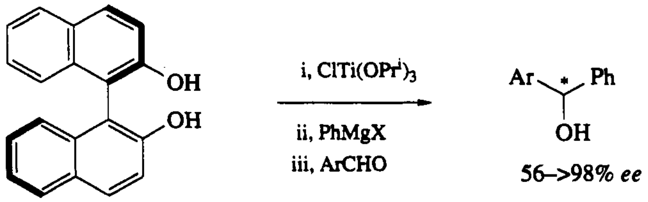
OH
OH
i, ClTi(OPr$^i$)$_3$
ii, PhMgX
iii, ArCHO
Ar
Ph
OH
56–>98% ee

(35)

reagent was presumed (equation 36).[99] This type of approach including chiral modifications of carbonyls with chiral Lewis acids will undoubtedly find wide use in asymmetric synthesis.

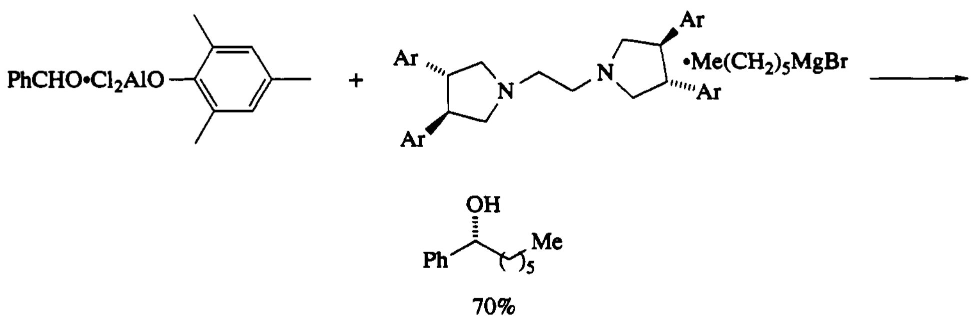
PhCHO•Cl$_2$AlO
Ar
N
N
Ar
Ar
•Me(CH$_2$)$_5$MgBr
Ar
OH
Ph
Me
5
70%

(36)

## 1.11.3 LEWIS ACID PROMOTED REACTIONS OF EPOXIDES

Although nucleophilic ring opening of epoxides with organometals is a well-documented technology in organic synthesis, the reaction sometimes fails to occur due to the unreactiveness and the facile isomerization of the electrophile. The presence of an appropriate Lewis acid, notably $BF_3$, greatly promotes the C—C bond cleavage.

Alkynylation of oxiranes or oxetanes with lithium alkynides is effectively carried out in the presence of $BF_3 \cdot OEt_2$ at −78 °C. The use of $BF_3$ gives better results than $TiCl_4$, $SnCl_4$ or $AlCl_4$. The reaction takes place stereospecifically with *anti* opening, and the attack generally occurs at the less hindered site. Several functional groups such as halogens, acetals or certain esters survive the reaction conditions (Scheme 16).[100–102]

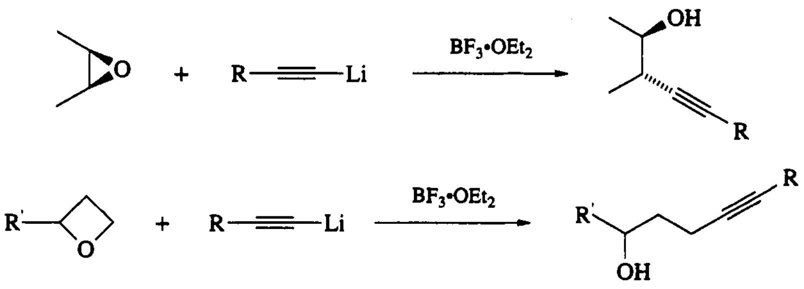

**Scheme 16**

A novel regioselectivity is observed with *trans*-2,3-epoxy alcohols. The C-1 attack of 1,2-epoxy alcohol formed by the Payne rearrangement proceeds predominantly, and *anti*-β,γ-dihydroxyalkynes are obtained stereospecifically (equation 37).[103] The reaction is employed in the synthesis of a pheromone, *erythro*-6-acetoxyhexadecan-5-olide.

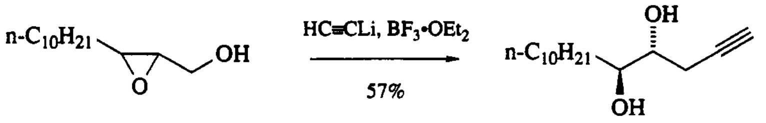

(37)

The mechanistic aspects of this Lewis acid promoted reaction have been examined by low temperature NMR studies, and reaction of the lithium alkynides with the Lewis acid activated epoxides is indicated.[104,105] The order of the addition of the reagents does not affect the product yields provided that the reaction is carried out at −78 °C; addition of $BF_3 \cdot OEt_2$ to a mixture of an epoxide and an alkynide or addition of an epoxide to a mixture of an alkynide and $BF_3 \cdot OEt_2$ are both possible. The transmetalation between RLi and $BF_3$ which produces unreactive organoboron compounds is shown to be very slow at this temperature.[102,104,105]

The alkynylation reactions have been applied to polyfunctionalized molecules (Scheme 17),[106–110] and have proved to be quite useful in natural product synthesis.

The use of $Me_3Ga$ allows a catalytic mode of the reaction to be carried out (equation 38).[111]

Related syntheses using a variety of organolithium compounds have also been developed. Alkyllithiums, vinyllithiums or phenyllithiums in the presence of $BF_3 \cdot OEt_2$ give the oxirane and oxetane opening products in high yields (equation 39).[105] Enolate-type nucleophiles can also be employed for this purpose (Scheme 18).[112–114]

The reaction rates of organocopper and cuprate reagents with less reactive epoxides are enhanced by the presence of $BF_3 \cdot OEt_2$.[115,116] $R_2CuCNLi_2$–$BF_3$ reagents are especially effective, and even mesitylation or *t*-butylation of cyclohexene oxide can be carried out in high yields. Similar stereo- and regio-chemical features with RLi–$BF_3$ reagents — *anti* opening and attack at the less hindered site — are observed. The order of the addition of reagents again does not affect the yields of the products. The cleavage of sterically hindered epoxysilanes was carried out with the cuprate–$BF_3$ reagent, and applied to the synthesis of pheromones (Scheme 19).[117] Aziridines are cleaved effectively with $R_2CuLi$ in the presence of $BF_3 \cdot OEt_2$ (equation 40).[118]

A novel stereoselectivity is observed in the Lewis acid mediated $S_N2'$-type reactions of an epoxycycloalkene and methylating reagents. *Syn* attack occurs with MeLi–$LiClO_4$ in high selectivity, and exclusive *anti* attack with MeCu–$Me_3Al$. Chelation of MeLi to the epoxide or to the epoxide–$LiClO_4$ complex is suggested for the former, while attack of MeCu on the $Me_3Al$-coordinated epoxide from the less hindered site is presumed for the latter. The use of MeLi gives a mixture of several compounds (Scheme 20).[119]

Lewis acid promoted ring opening of oxiranes with organo-silanes or -stannanes is reported. TMS-CN cleaves the C—O bond in the presence of $AlCl_3$,[120] $Et_2AlCl$,[121] $Ti(OPr^i)_4$[122] or $LnX_3$,[27] and β-hydroxy-

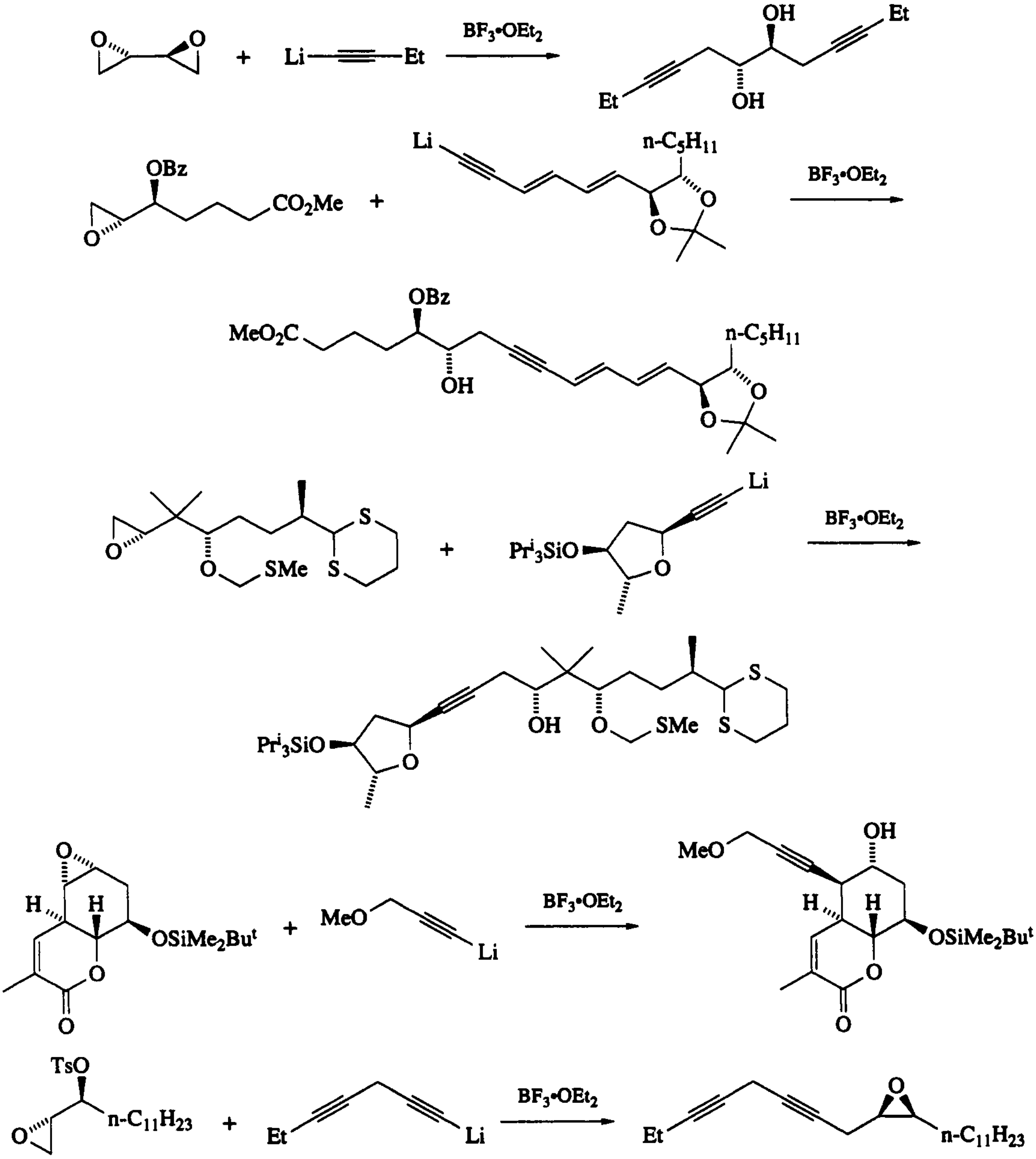
BF₃•OEt₂
Li
Et
OH
OBz
CO₂Me
MeO₂C
n-C₅H₁₁
SMe
Pr^i₃SiO
OSiMe₂Bu^t
MeO
TsO
n-C₁₁H₂₃

**Scheme 17**

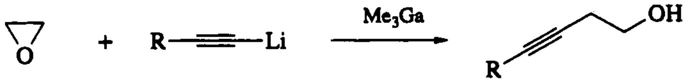
Me₃Ga
R
Li
OH

(38)

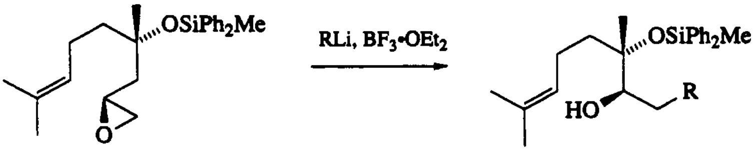
RLi, BF₃•OEt₂
OSiPh₂Me
HO
R

(39)

R = $Bu^t$, 95%; R = Ph, 85%; R = $CH_2$=C(Me)OEt, 99%

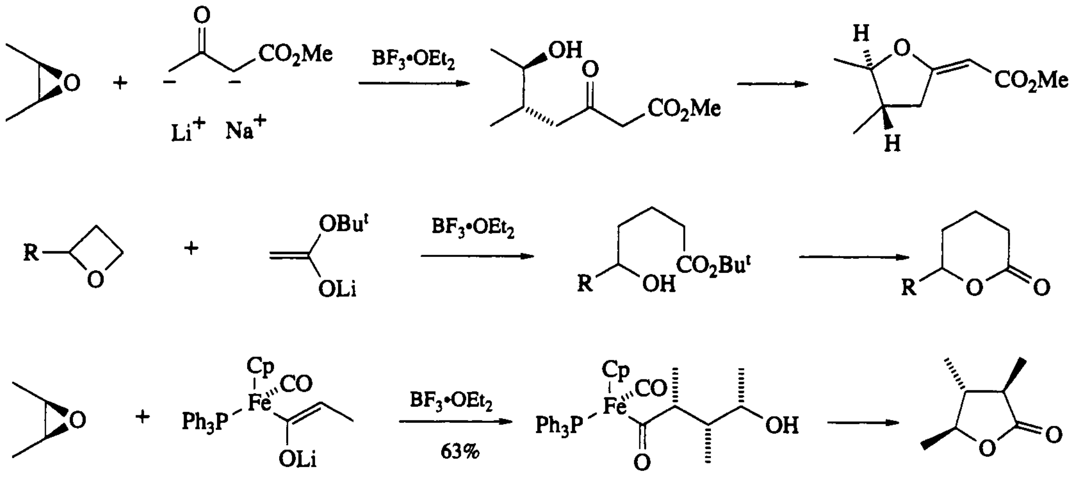

Scheme 18

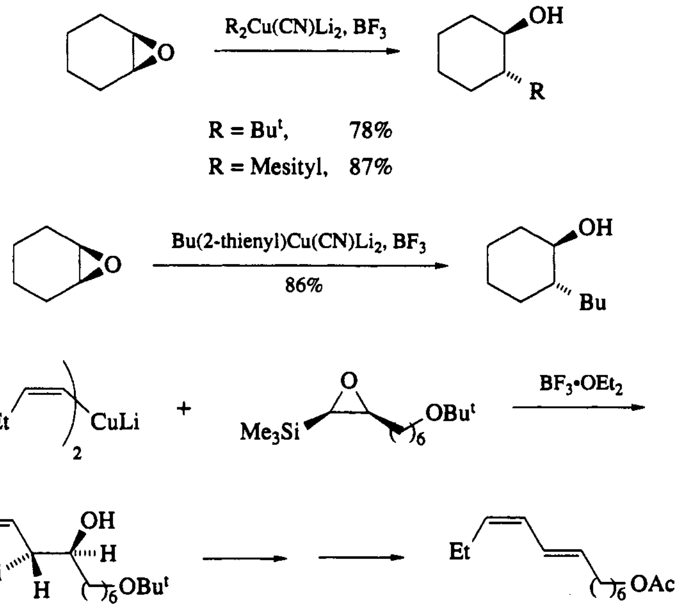

Scheme 19

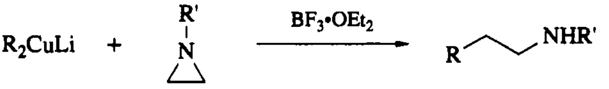 (40)

nitriles are obtained. With aluminum catalysts, propylene oxide is cyanated at the less hindered site, while attack at the more hindered site proceeds with isobutene oxide. Apparently, the cationic nature of the Lewis acid coordinated epoxide plays an important role in the latter case (Scheme 21).[120,121] Ti(OPr$^i$)$_4$ promotes the reaction of TMS-CN or KCN with 2,3-epoxy alcohols, C-3 attack predominating over C-2 attack (equation 41).[122] Organostannanes with unactivated C—Sn bonds alkylate epoxides intramolecularly in the presence of TiCl$_4$, and cyclopropyl alcohols are obtained (Scheme 22).[123,124]

## 1.11.4 LEWIS ACID PROMOTED REACTIONS OF ACETALS

Acetals are quite unreactive towards simple organometallic compounds and have been employed as a convenient protecting group. However, they turn into highly reactive species in the presence of Lewis

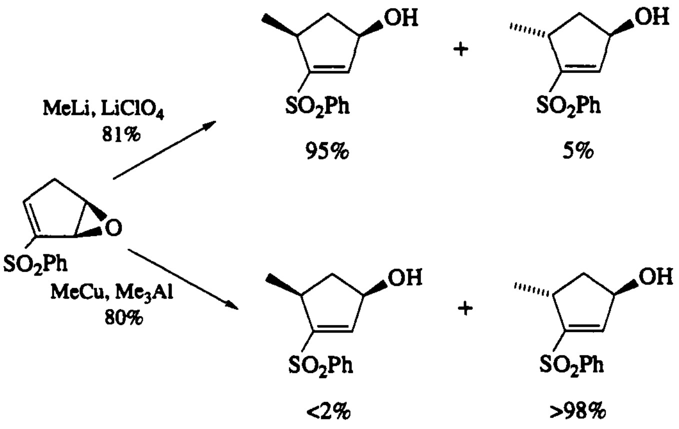
MeLi, LiClO4
81%
MeCu, Me3Al
80%
SO2Ph
OH
95%
5%
<2%
>98%

Scheme 20

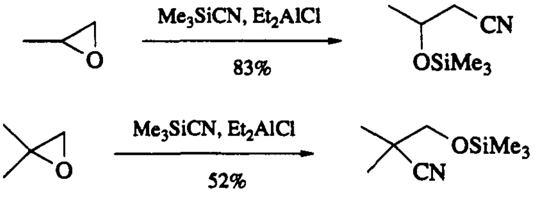
Me3SiCN, Et2AlCl
83%
52%
CN
OSiMe3

Scheme 21

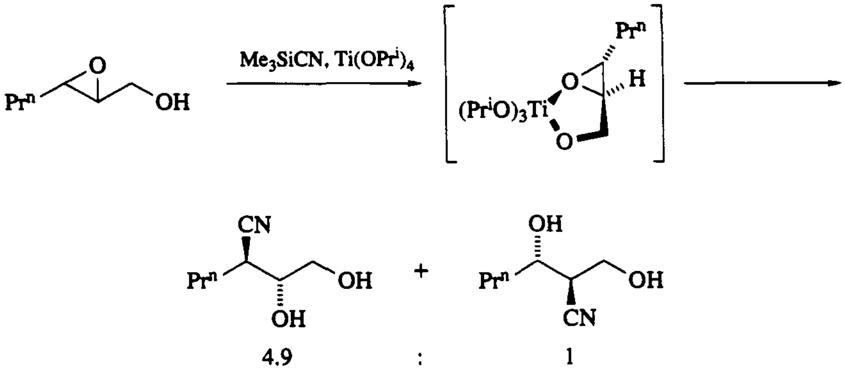
Me3SiCN, Ti(OPri)4
Prn
OH
(PriO)3Ti
CN
4.9
:
1

(41)

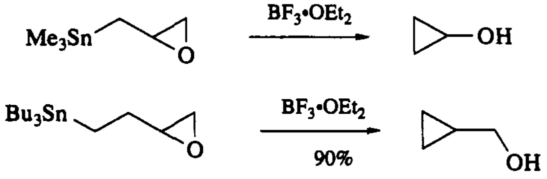
Me3Sn
Bu3Sn
BF3•OEt2
90%
OH

Scheme 22

acids. Aldol reactions with silyl enol ethers[16] and allylations with allylsilanes,[14] which utilize stabilized carbanionic species, have been extensively investigated in the past decade.

In recent years, nonstabilized carbanions have also been used in this type of reaction. The earliest example is the combination of an organomagnesium compound and $TiCl_4$ developed by Mukaiyama. Alkyl Grignard reagents react with α,β-unsaturated acetals activated by $TiCl_4$ at the α-position to give allylic ethers (equation 42). PhMgBr, on the other hand, gives γ-addition products.[125] Although normal alkyl acetals of aromatic and aliphatic aldehydes are unreactive towards $RMgX–TiCl_4$, reactive acetals give the corresponding products. For example, 2-alkyltetrahydropyrans are synthesized from 2-(2,4-dichlorophenoxy)tetrahydropyran (equation 43).[126,127] Reactions of $RMgBr–BF_3$ with *N,O*-acetals have also been reported, which give amines by the preferential cleavage of the C—O bond (equation 44).[128]

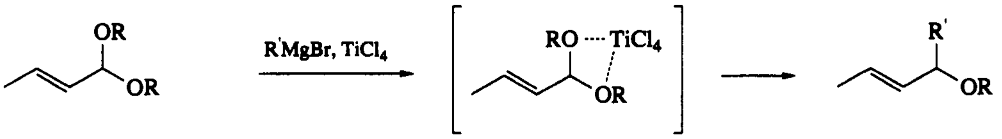

(42)

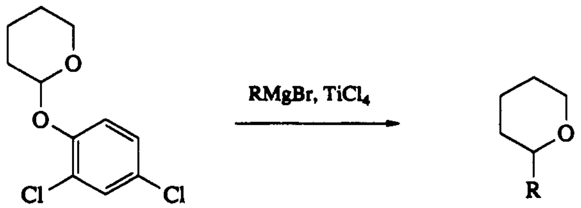

(43)

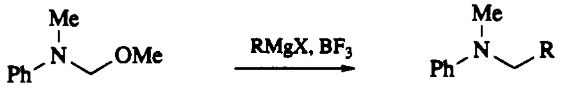

(44)

Organolithium compounds also react with acetals or orthoesters in the presence of BF$_3$·OEt$_2$. Dialkoxymethylations of lithium enolates with triethyl orthoformate are carried out by adding BF$_3$·OEt$_2$ to the mixture (equation 45). Prior mixture of an enolate and the Lewis acid results in a drastic decrease of the product yield. Lithium enolates are generated from silyl enol ethers and MeLi, and C—C bond formation proceeds regiospecifically with respect to the enolates. The condensation is applicable to a fully substituted enolate.[129] Butenolide anions add to acetals or orthoesters pretreated with BF$_3$·OEt$_2$ at the C-5 position (equation 46).[130]

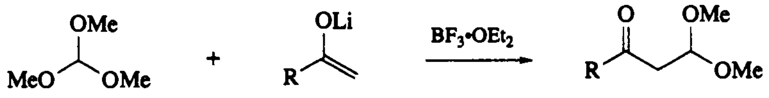

(45)

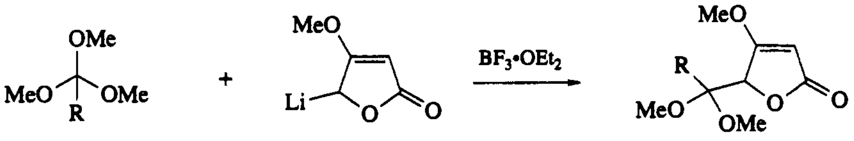

(46)

The association of BF$_3$ with organocopper and cuprate reagents greatly increases the reactivity towards acetals (equation 47). The reaction can be carried out by either of the following procedures with the same experimental results: (i) copper reagents are premixed with BF$_3$·OEt$_2$ at –78 °C and the electrophile is added, or (ii) copper reagents are premixed with the electrophile and BF$_3$·OEt$_2$ is added. These procedures can also be applied to α,β-unsaturated acetals, giving allylic ethers. In the case of tetrahydropyranyl acetal, ring-opening products are obtained exclusively, in contrast to the reaction of RMgX–TiCl$_4$, which gives 2-alkyltetrahydropyrans (*cf.* equation 43). Orthoesters are more susceptible to the Lewis acid promoted reactions.[131]

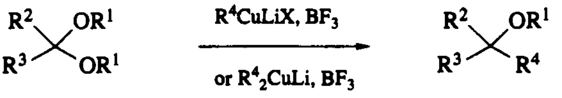

(47)

In the presence of a Lewis acid such as SnCl$_2$, BF$_3$·OEt$_2$,[132–134] or TiClO$_4$,[135] TMS-CN reacts with acetals to give cyanohydrin ethers. D-Ribofuranosyl cyanide, an important intermediate of C-nucleoside synthesis, is prepared from a furanosyl acetate (Scheme 23).[133]

Acetals prepared from chiral diols and carbonyl compounds serve as a chiral synthetic equivalent of aldehydes or ketones. 1,3-Dioxanes synthesized from chiral 2,4-pentanediols are especially useful, and high asymmetric inductions are observed in the Lewis acid promoted reactions of a variety of organometallic compounds. After the removal of the chiral auxiliary by the oxidation and β-elimination procedures, optically active alcohols are obtained. Optically active propargylic alcohols and cyanohydrins are synthesized from organosilane compounds, TMS-C≡CR or TMS-CN in the presence of TiCl$_4$ (Scheme 24).[136–138] Reactive organometals such as alkyl-lithiums, -magnesiums or -coppers also react with chiral

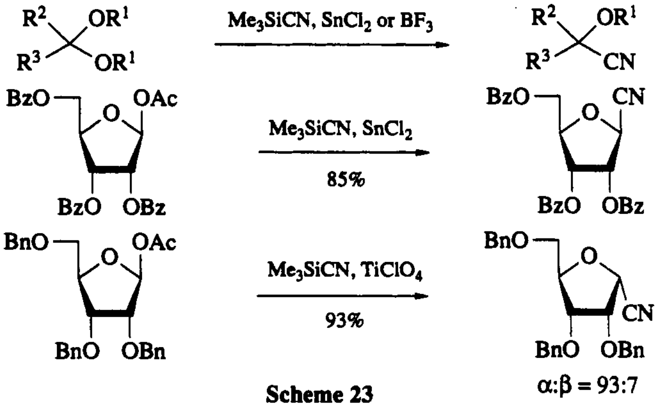
Me3SiCN, SnCl2 or BF3
Me3SiCN, SnCl2
85%
Me3SiCN, TiClO4
93%
α:β = 93:7

**Scheme 23**

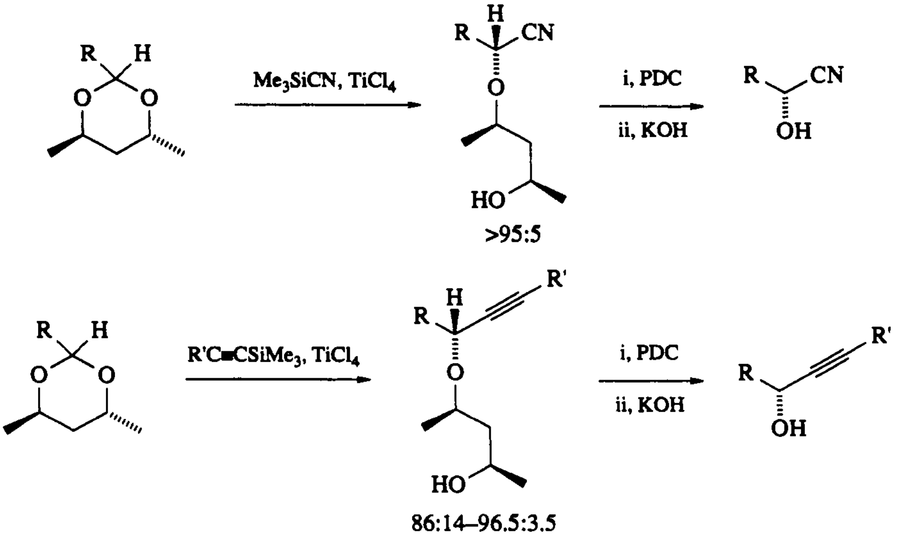
Me3SiCN, TiCl4
i, PDC
ii, KOH
>95:5
R'C≡CSiMe3, TiCl4
i, PDC
ii, KOH
86:14–96.5:3.5

**Scheme 24**

acetals activated by $TiCl_4$ or $BF_3$ (Scheme 25).[139–141] An $S_N2$-like transition state, which relieves 1,3-diaxial interaction between hydrogen and the axial methyl group by a lengthening of a C—O bond, has been proposed by Johnson for the interpretation of the highly asymmetric induction (Figure 7).[138,142]

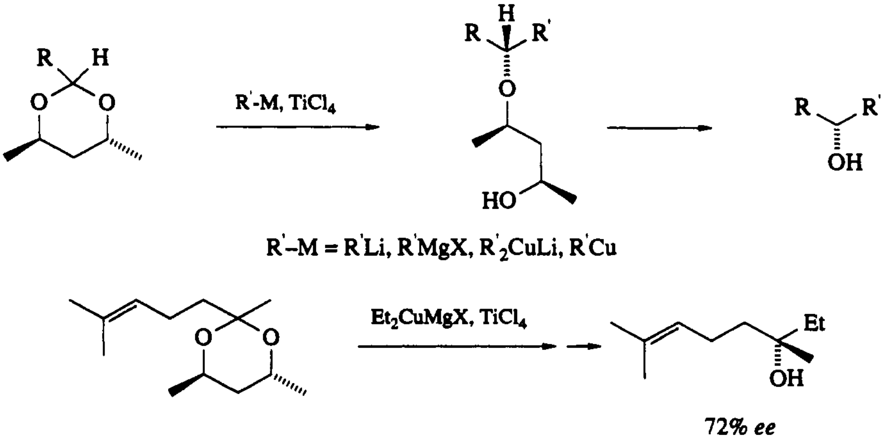
R'-M, TiCl4
R'-M = R'Li, R'MgX, R'2CuLi, R'Cu
Et2CuMgX, TiCl4
72% ee

**Scheme 25**

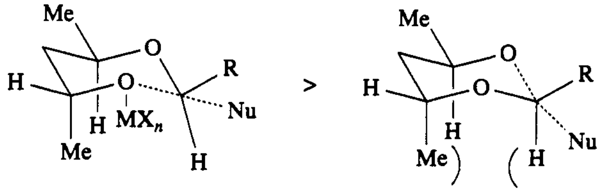
Me
O
O
R
H
H
MX$_n$
Nu
Me
H
>
Me
O
O
R
H
H
Me
H
Nu

**Figure 7**

## 1.11.5 LEWIS ACID PROMOTED REACTIONS OF IMINES

Compared with aldehydes and ketones, aldimines and ketimines are less reactive towards nucleophilic addition. Furthermore, imine additions are subject to steric constraints, and rapid deprotonation proceeds with imines bearing α-hydrogen atoms. The Lewis acid promoted addition methodology has provided a solution to these problems.

In the presence of $MgX_2$, organo-cadmium and -zinc compounds add smoothly to imines derived from aromatic aldehydes and arylamines. Yields are very low with isolated alkyl-cadmiums or -zincs which lack a Lewis acid promoter (equation 48).[143–145]

A catalytic amount of Lewis acid, such as $ZnI_2$, $AlCl_3$, $TiCl_4$, $Al(OPr^i)_3$, $Al(acac)_3$, *etc.*, promotes the addition reactions of TMS-CN to imines and oximes, giving *N*-TMS-α-aminonitriles.[146,147] The product is a useful precursor of α-aminonitriles, α-aminoamides or α-amino acids. Cyanosilylation of (–)-*N*-alkylidene-(1-methylbenzyl)amines catalyzed by $ZnCl_2$ affords α-aminonitriles in 57–69% *de*. The use of $ZnCl_2$ gives better results than $AlCl_3$ or $Al(OPr^i)_3$ (Scheme 26).[148] It is also noted that the optical purities of the adducts obtained by the Lewis acid promoted reaction are much higher than those attained by the simple addition of hydrogen cyanide to imines.

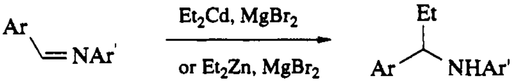
Ar
=NAr'
Et$_2$Cd, MgBr$_2$
or Et$_2$Zn, MgBr$_2$
Et
Ar
NHAr'

(48)

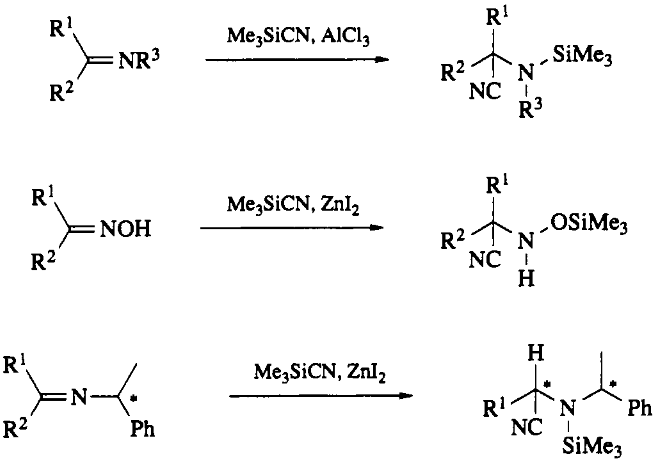
R$^1$
=NR$^3$
R$^2$
Me$_3$SiCN, AlCl$_3$
R$^1$
R$^2$
N
SiMe$_3$
NC
R$^3$
R$^1$
=NOH
R$^2$
Me$_3$SiCN, ZnI$_2$
R$^1$
R$^2$
N
OSiMe$_3$
NC
H
R$^1$
=N
R$^2$
Ph
Me$_3$SiCN, ZnI$_2$
H
R$^1$
N
Ph
NC
SiMe$_3$

57–70% *de*

**Scheme 26**

In the presence of $ZnBr_2$, nonchelation controlled addition of lithiated *N*,*N*-dimethylacetamide to 2,3-*O*-cyclohexylidene-4-deoxy-L-threose benzylimine proceeds in high stereoselectivity. The absence of the Lewis acid results in a slight preference for the other isomer. The product is used in the synthesis of L-daunosamine (equation 49).[149]

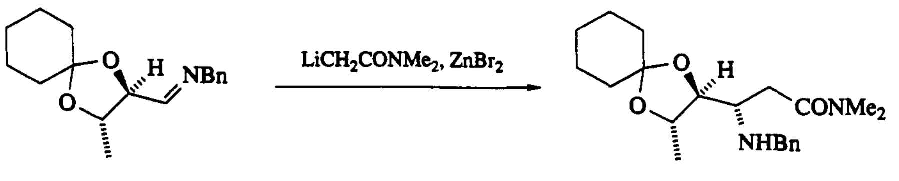

(49)

3-Thiazolines activated with an equivalent of $BF_3$ readily react with a wide range of organometals, giving *trans*-4,5-disubstituted thiazoles stereoselectively. Alkyllithiums, Grignard reagents, lithium alkynides, nitronates, ester and ketone enolates have been employed as the nucleophile. Stereocontrolled construction of three contiguous asymmetric centers is performed with a lithiated isothiocyanatoacetate, and the product is successfully transformed to (+)-biotin (Scheme 27).[150,151]

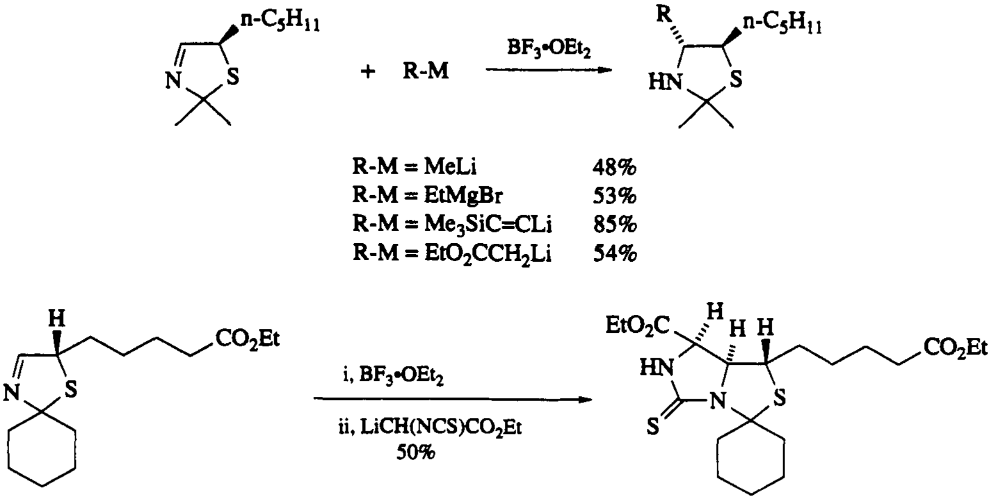

| | |
|---|---|
| R-M = MeLi | 48% |
| R-M = EtMgBr | 53% |
| R-M = $Me_3SiC{\equiv}CLi$ | 85% |
| R-M = $EtO_2CCH_2Li$ | 54% |

**Scheme 27**

RCu, prepared from alkylmagnesiums and CuI, reacts with aldimines in the presence of $BF_3{\cdot}OEt_2$. Grignard or copper(I) reagents do not give the addition product at all, and the starting imines are recovered. Interestingly, preparation of an RCu–$BF_3$ complex prior to the C—C bond formation reaction is necessary, and the addition of RCu to a mixture of an imine and $BF_3{\cdot}OEt_2$ results in low yield. $R_2CuM$–$BF_3$ (M = Li or Mg) are effective for more hindered aldimines.[152] Lithium alkynide–$BF_3$ reagents also add to aldimines at –78 °C, and aminoalkynes are obtained in good yields. Again the presence of the Lewis acid is reported to be essential (Scheme 28).[153]

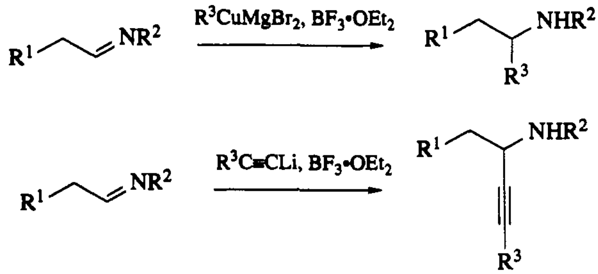

**Scheme 28**

Perfluoroalkyllithiums, generated from perfluoroalkyl iodide and MeLi, add to imines pretreated with $BF_3{\cdot}OEt_2$. Since the addition of an imine to a mixture of $C_6F_{13}Li$ and $BF_3{\cdot}OEt_2$ results in the recovery of the starting material, activation of the imine, rather than an ate complex formation, is suggested as the role of the Lewis acid. In the presence of $BF_3{\cdot}OEt_2$, an imine is more reactive than the carbonyl of methyl benzoate towards the addition of $C_6F_{13}Li$. A high Cram-type asymmetric induction is observed in the addition of $C_6F_{13}Li$ to 2-phenylpropanal imine (Scheme 29).[154] The reaction of the dianion of (4-phenylsulfonyl)butanoic acid with imines activated by $BF_3{\cdot}OEt_2$ has also been reported (equation 50).[155]

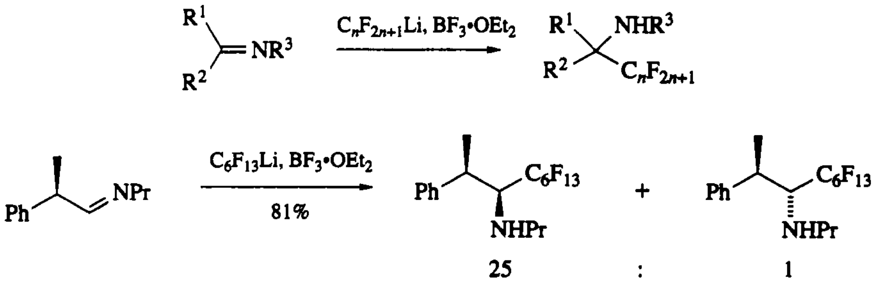

Scheme 29

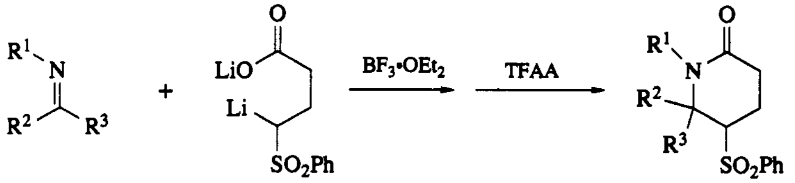

(50)

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# 1.12

# Nucleophilic Addition to Imines and Imine Derivatives

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## 1.12.1 SCOPE

Synthetic and biological interest in highly functionalized acyclic and cyclic amines has contributed to the wealth of experimental methodology developed for the addition of carbanions to the carbon–nitrogen double bond of imines/imine derivatives (azomethines). While a variety of practical methods exist for the enantio- and stereo-selective syntheses of substituted alcohols from aldehyde and ketone precursors, related imine additions have inherent structural limitations. Nonetheless imines, by virtue of nitrogen substitution, add a synthetic dimension not available to ketones. In addition, improved procedures for the preparation and activation of imines/imine derivatives have increased the scope of the imine addition reaction.

This chapter will attempt to provide a comprehensive picture of nonstabilized carbanion additions to the carbon–nitrogen double bond of imines/imine derivatives. Included are organometallic condensations with cyclic and acyclic azomethines [including *N*-(trimethylsilyl)imines, sulfenimines and sulfonimines], iminium salts, *N*-acylimines (*N*-acyliminium salts), hydrazones, oximes and nitrones (Scheme 1). While 1,4-additions to azadienes (including α,β-unsaturated and aromatic aldimines) are presented, the addition of organometallic reagents to the carbon–nitrogen bond of aromatic compounds (*i.e.* pyridines and quinolines) is not. Because the structural features of each imine derivative (class) are uniquely responsible for the chemistry of azomethines, this chapter is organized by imine structure. In concert with the theme of 'Comprehensive Organic Synthesis,' recent scientific contributions, particularly those involved in the control of stereochemistry, are highlighted. Essential background for each class of azomethines is provided. For an extensive evaluation of areas, the reader is urged to also consult appropriate review articles.

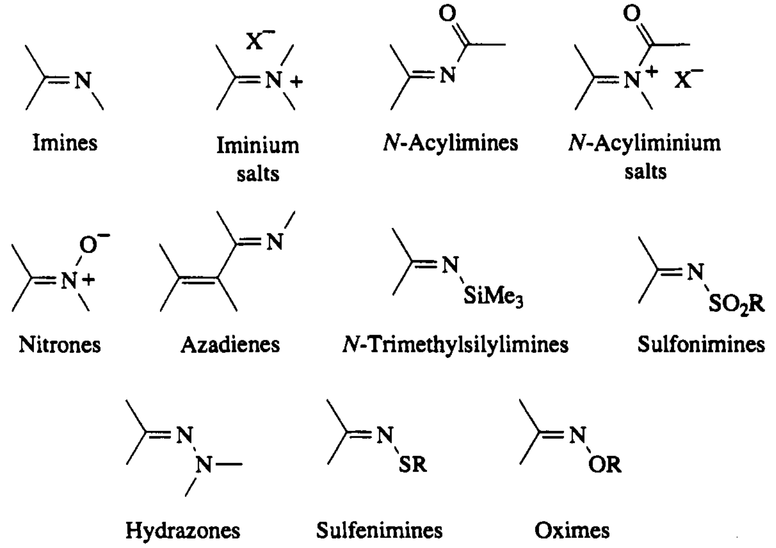

**Scheme 1** Azomethines

## 1.12.2 INTRODUCTION

The inability of certain nucleophiles to add to the carbon–nitrogen double bond of imines/imine derivatives, coupled with the propensity of basic reagents to preferentially abstract protons α to the imine double bond, has limited the utility of the group in synthetic organic chemistry. While unique solutions exist for individual reactions, they are at best only applicable to a particular structural class of azomethines. Since structurally diverse imine derivatives have been utilized for the preparation of highly functionalized amines, an overview of some of the structural features of azomethines and nonstabilized carbanions responsible for (i) azomethine reactivity, (ii) proton abstraction, and (iii) stereochemical control in azomethine additions is included.

### 1.12.2.1 Azomethine Reactivity

A systematic evaluation of the relationship between azomethine structure and reactivity with nonstabilized carbanions has not been reported. Some imines/imine derivatives are inert to nucleophilic addition. The electrophilicity of imines can, however, be increased by *N*-alkylation to form highly reactive iminium salts, by *N*-oxidation to form reactive nitrones, or by *N*-acylation or *N*-sulfonylation to form reactive acylimines and sulfonimines. Sulfonimines and nitrones condense with organometallic reagents to generate sulfonamide and hydroxylamine products. 'Activated' imines need not be isolated, as the *in situ* preparation of acylimines, iminium and acyliminium salts can be employed for the generation of substituted amines (amine derivatives). These activating groups, however, do not provide a general solution to this fundamental problem of imine reactivity, since they are in certain cases not easily removed. For this reason, Lewis acid activation with $BF_3{\cdot}OEt_2$ and the *in situ* formation of iminium salts with TMS-OTf have been recently employed in amine synthesis.

### 1.12.2.2 Deprotonation of Azomethines

While the abstraction of protons adjacent to the carbon–nitrogen double bond of imines/imine derivatives has been utilized for the regioselective generation of azaallyl anions (which are useful in asymmetric ketone synthesis), it competes with and often prevents the addition of nucleophiles to imines. For this reason, imine additions often involve azomethines (*e.g.* benzylidineanilines) which are not capable of enolization. Many potentially useful additions, however, involve substrates capable of proton abstraction. By avoiding in certain instances some of the structural features of imines/imine derivatives and the reaction conditions responsible for proton abstraction, products resulting from this serious side reaction can be minimized.

The regioselectivity of imine deprotonations[1] is considerably more complicated than similar ketone deprotonations,[2] and can be influenced by imine geometry, nitrogen substitution, steric accessibility of α-hydrogen atoms and the deprotonation conditions (base, solvent) employed. Chelation-directed proton abstraction is implicated for metallated oximes and tosylhydrazones. For example, organometallic-mediated deprotonation of oximes (**1**) occurs with *syn* selectivity[3] (*syn* to the nitrogen alkoxide group) and provides a regioselective route to reactive azirines.[4] Likewise, the failure of aliphatic aldehyde tosylhydrazones (**2**; (*E*)-configuration) to form dianions at low temperatures is consistent with the strong preference for proton abstraction *syn* to the $NSO_2Ar$ moeity and is presumably responsible for the susceptibility of (**2**) to nucleophilic addition.[5] Proton abstraction of ketone dimethylhydrazones and ketimines can lead to isomeric azaallyl anions. Ketone dimethylhydrazones generally deprotonate on the less-substituted α-carbon, regardless of the C═N geometry.[6] Alkyllithium-mediated deprotonation of ketimines, however, generally occurs *anti* to the nitrogen substituent.[7] For example, Bu$^s$Li (THF) treatment of 2-methylcyclohexanone-derived *N*,*N*-dimethylhydrazone (**3**) and *N*-cyclohexylimine (**4**) followed by the addition of benzyl chloride results in *syn* (100:0) and *anti* (87:13) α-alkylation, respectively.

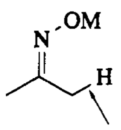

(**1**)

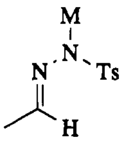

(**2**)

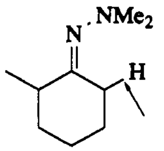

(**3**)

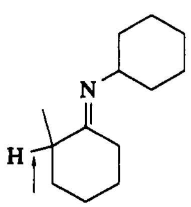

(**4**)

Regardless of the kinetic regioselectivity, Fraser, Houk and coworkers[8] have demonstrated that the nitrogen substituents of most metallated (lithio) aldehyde- and ketone-derived azomethines prefer the (*Z*)-orientation (Scheme 2). This thermodynamic preference is postulated to result from a minimization of dipole–dipole (electrostatic) interaction between nitrogen lone pair electrons and the carbanion.

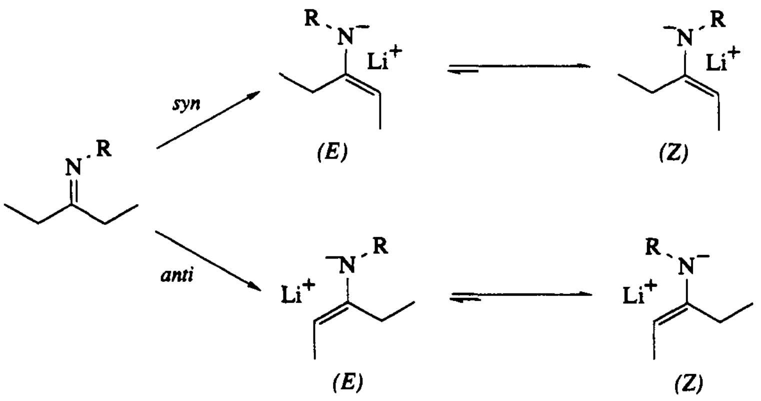

**Scheme 2** Metallation of imines/imine derivatives

On the other hand, endocyclic ketimines such as 2-alkyl-1-pyrroline (**5**) have a thermodynamic bias for the (*E*)-azaallyl anion (which is postulated to result from excessive angle strain of the (*Z*)-azaallyl anion). This result suggests that by judicious selection of nucleophiles, proton abstraction might be minimal in additions to endocyclic aldimines which are devoid of 2-alkyl substitution, such as 1-pyrroline (**6**).

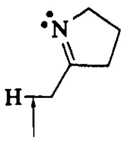

(**5**)

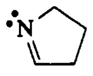

(**6**)

Highly basic (organolithium) reagents are employed for the abstractions of protons adjacent to the carbon–nitrogen double bond of imines/imine derivatives. To minimize proton abstractions in nucleophilic additions, less basic reagents (many of which are outside the scope of this chapter)[9] such as allylboranes, allylboronates, allyl Grignards, allylzincs, allylstannanes, alkylcoppers, alkylcuprates, organocerium reagents and metal enolates (Li, B, Al, Zr, Sn, Zn) are used.

### 1.12.2.3 Stereochemical Control in Azomethine Additions

The design of practical methods for effectively controlling product stereochemistry in nucleophilic additions remains an important challenge in synthetic organic chemistry. The addition of carbon nucleophiles to aldehydes and ketones possessing an adjacent asymmetric center has been extensively investigated.[10] Two strategies for controlling product stereochemistry, which generally lead to opposite diasteriofacial selectivity, have emerged: (i) chelation control, in which Lewis acid reagents form intermediate chelates, rendering one face of the carbonyl moeity more accessible for nucleophilic addition (Cram's cyclic model, Figure 1a); and (ii) nonchelation control, in which the addition of reagents to substrates incapable of internal chelation is governed by steric and/or electronic factors. The bias for addition from a diastereotopic face in nonchelation-controlled additions was predicted empirically by Cram and is supported by the Cornforth and Felkin–Ahn models shown in Figures 1b and 1c.

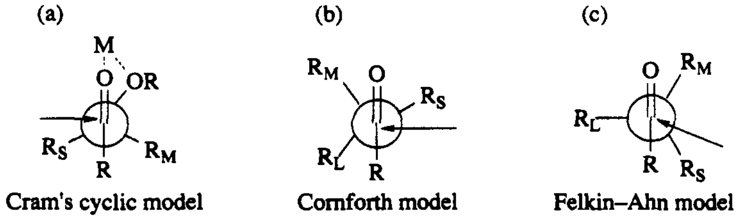

**Figure 1**

The relevance of these models for the addition of carbon nucleophiles to structurally similar acyclic imine/imine derivatives has not been adequately tested. Products which are consistent with chelation control are obtained in the addition of organolithium reagents to dimethylhydrazones (**7**) of α-alkoxyacetaldehydes.[11] In contrast to allylorganometallic and ester enolate additions,[9] only a few examples suggestive of nonchelation (Felkin–Ahn) control in the additions of nonstabilized organometallic reagents to chiral aldimines have been reported.[12,13] The paucity of any in depth systematic investigations examining the additions of nonstabilized carbanions to aldimines/aldimine derivatives containing an adjacent asymmetric center is not surprising. The propensity of acyclic imines to isomerize, the presence in these derivatives of other heteroatoms which are capable of chelation (*e.g.* hydrazones), and poor imine reactivity all contribute to the complexity of the problem.

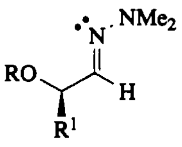

(**7**)

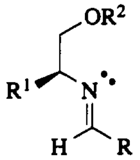

(**8**)

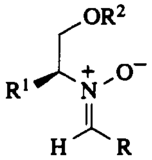

(**9**)

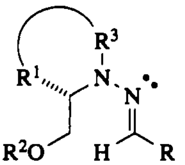

(**10**)

A major synthetic effort, however, has been focused on asymmetric induction resulting from the addition of organometallic reagents to aldimines/aldimine derivatives derived from chiral amines/hydrazines. A variety of chiral aldimines (**8**),[14] nitrones (**9**)[15] and hydrazones (**10**)[16–18] (all of which contain as part of the chiral auxilary a terminal alcohol, ether or ester moiety capable of chelation) have been examined. High diastereoselectivity can be obtained in these additions and, while the intimate mechanistic details which account for the stereoselectivity are not known, mechanisms involving: (i) chelation control (Figure 2a); and (ii) chelation-mediated delivery of the organometallic reagent (Figure 2b) have been suggested. The susceptibility of nitrogen–oxygen, nitrogen–nitrogen and nitrogen–aryl alkyl bonds within the addition products to reductive cleavage contributes to their value for the enantioselective synthesis of amines.

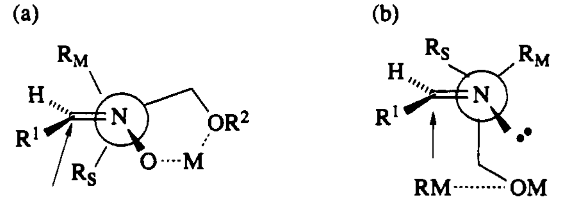

**Figure 2** (a) Chelation control, *e.g.* nitrones; (b) Organometallic delivery, *e.g.* aldimines

The 1,4-addition of organometallic reagents to α,β-unsaturated aldimines (**11**)[19] and aromatic aldimines (**12**)[20] resembles additions to oxazolines (**13**)[21] and (**14**),[22] and provides a valuable method for generating a remote stereocenter (1,5-asymmetric induction). Other strategies have been employed for controlling azomethine diastereofacial selectivity. For example, organometallic treatment of chiral chromium complexes (**15**)[23] of *N*-arylaldimines leads to high stereoselectivity (presumably a result of steric control). Further investigations are required to assess the value of the chromium tricarbonyl complexes in asymmetric amine synthesis.

By constructing rigid endocyclic imines/imine derivatives (either isolated or generated *in situ*) some of the problems associated with acyclic stereocontrol can be avoided. The addition of organometallic reagents to 3-thiazolines (**16**)[24] or the putative piperidine intermediate (**17**)[25] provides excellent stereocontrol.

In summary, notable advances have been made in controlling stereoselectivity resulting from the addition of nonstabilized carbanions to chiral imine/imine derivatives. Unfortunately our level of mechanistic understanding in these additions is unsatisfactory. While additions involving chiral nitrones, hydrazones and some cyclic imines have been evaluated in reasonable detail, few systematic studies of other aldimine/aldimine derivatives are available.

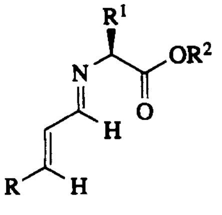

**(11)**

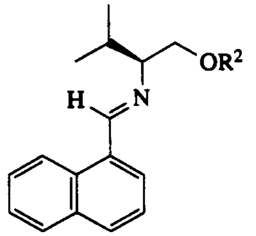

**(12)**

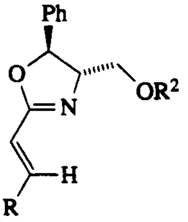

**(13)**

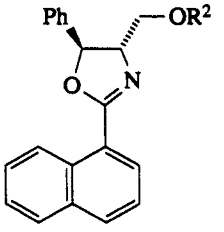

**(14)**

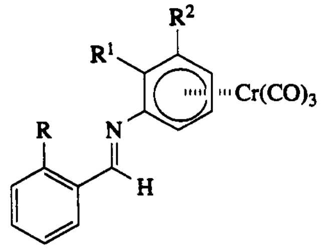

**(15)**

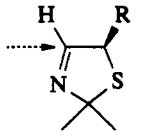

**(16)**

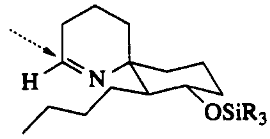

**(17)**

## 1.12.3 ORGANOMETALLIC ADDITIONS TO IMINES

The addition of organometallic agents to aldimines and ketimines provides a useful route to substituted amines, although this reaction is sensitive to imine/organometallic substitution. Along with addition, competitive enolization, reduction and bimolecular reduction (coupling) reactions are also possible.

### 1.12.3.1 Nonenolizable Imines

Addition to imines derived from aryl aldehydes has been investigated extensively and has been reviewed.[26] The addition of Schiff base (**18**) to excess Grignard reagent (2 equiv.) provides a route to secondary amines (**19**; equation 1). As the size of R and branching of $R^1$ increases, addition yields decrease (entries 1–3, Table 1),[12,27,28] and reduction products such as (**20**) are often generated.

**Table 1** The Reaction of Organometallic Reagents with Azomethine (**18**)

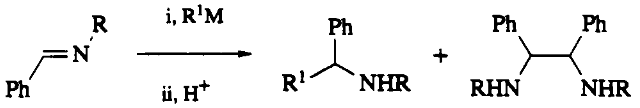

**(18)** **(19)** **(20)**

(1)

| Entry | R | $R^1M$ ($Et_2O$) | Yield (19) | Yield (20) | Ref. |
|---|---|---|---|---|---|
| 1 | Me | MeMgI, Δ | 72% | — | 27 |
| 2 | $Bu^t$ | MeMgI, Δ | — | — | 28 |
| 3 | Bu | $Pr^iMgI$, Δ | — | 56% | 27 |
| 4 | $Bu^t$ | $2C_6F_{13}Li(BF_3)$, –78 °C | 68% | — | 12 |

In reactions with *N*-benzylidineaniline (PhCH=NPh), the addition of $MgBr_2$ (2 equiv.) to solutions of EtMgBr, $Et_2Cd$ and $Et_2Zn$, or, in the case of $Et_2Mg$, lowering the solvent basicity (DME and $Et_2O$ preferred over THF) results in dramatic yield improvements.[29] In the absence of other metal salts, Grignard addition yields increase if a 1:2 ratio of Schiff base to organometallic agent is employed.[30]

The effect of phenyl substitution on the rate of Grignard addition to *N*-benzylidineaniline has been examined. The reaction rate in ether for ethylmagnesium bromide conforms to $r = k[R^1{}_2Mg{\cdot}MgX_2][\text{Schiff base}]$. A four-centered reaction mechanism (Scheme 3) has been suggested.[30]

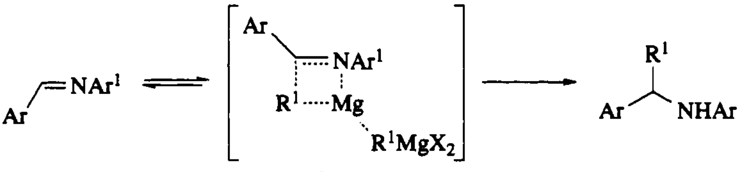

**Scheme 3**

In certain cases, Grignard reagents do not add to azomethines, but organolithium compounds (alone[28,31] or in the presence of $BF_3{\cdot}OEt_2$)[12] have been reported to add to many of these Schiff bases (entry 4, Table 1).

The addition of organometallic agents to *N*-methylenamines (**22**) has been utilized for the generation of unsymmetrical secondary amines. Even though these formaldehyde imines rapidly trimerize to yield 1,3,5-trialkylhexahydro-1,3,5-triazines (**24**), they can be generated *in situ* and treated with organolithium and Grignard reagents to provide secondary amines (**23**; Scheme 4). *N*-(Alkoxymethyl)aryl-,[32a] *N*-alkyl-*N*-(alkylthiomethyl)-,[32b] *N*-(cyanomethyl)-,[33] and *N*-(aminomethyl)-amines[33] (**21**) have been utilized for the preparation of formaldehyde imines (**22**). Primary, secondary, tertiary, aryl and alkenyl organometallic agents (a minimum of 2 equivalents is required) have been condensed with *N*-methylenamine precursors.

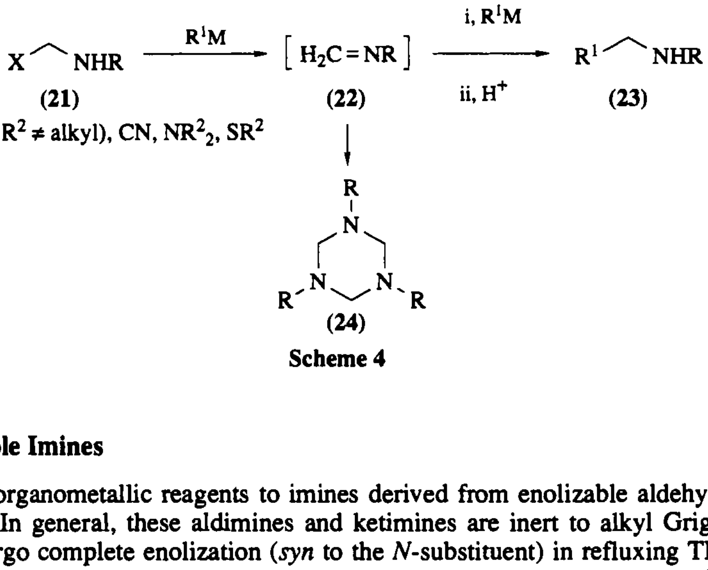

**Scheme 4**

### 1.12.3.2 Enolizable Imines

The addition of organometallic reagents to imines derived from enolizable aldehydes and ketones is more problematic. In general, these aldimines and ketimines are inert to alkyl Grignards and in their presence will undergo complete enolization (*syn* to the *N*-substituent) in refluxing THF.[34] On the other hand, aryl- and alkyl-lithiums condense with enolizable aldimines in low/moderate yields (~30–60%).[31] However, the reaction is not general; lithium alkynides[35b] and alkyllithiums[12] that are not stable above − 78 °C often do not add. Ketimines containing α-hydrogen atoms are resistant to organometallic addition. Sakurai and coworkers[7] have treated these ketimines with organolithium reagents to regioselectively generate substituted α-lithiated imines (deprotonation occurs preferentially *anti* to the *N*-substituent).

Activation of the C=N moiety by the addition of $BF_3{\cdot}OEt_2$[35,36] has increased the scope of organometallic additions (Table 2). Akiba and coworkers[35b] have shown that lithium alkynides treated with $BF_3{\cdot}OEt_2$ add to substituted aldimines (entry 1, Table 2).[12,13,35] $BF_3$ complexes of organocopper and dialkylcuprate reagents provide good yields of addition products. Dialkylcuprates are preferred in the condensation of branched aldimines (entry 2, Table 2).[35a]

**Table 2** The Addition of Organometallic Reagents to Activated Imines Containing α-Hydrogen Atoms

| *Entry* | *Organometallic* | *Imine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 2 $LiC{\equiv}C(CH_2)_4Me$/<br>$BF_3{\bullet}OEt_2$/THF | $Ph(CH_2)_2CH{=}NPr^i$ | 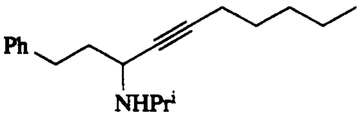 | 82 | 35b |
| 2 | $Bu_2CuLi{\bullet}BF_3$/THF | $Me_2CHCH{=}N(CH_2)_2Ph$ | 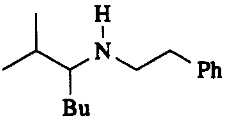 | 63 | 35a |
| 3 | $C_6F_{13}I/MeLi/BF_3/Et_2O$ | $Me(Ph)C{=}NPr^n$ | 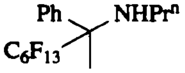 | 84 | 12 |
| 4 | $C_6F_{13}I/MeLi/BF_3/Et_2O$ | $Me(Ph)CHC{=}NPr^n$ | 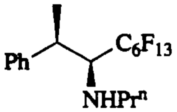<br>(25:1) | 81 | 12 |
| 5 | $Bu_2CuLi{\bullet}BF_3$ | $Me(Ph)CHC{=}NPr^n$ | 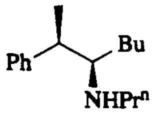<br>(4:1) | NA | 13 |

While Lewis acid activation has not provided a general solution for ketimine additions, isolated examples such as the condensation of perfluoroalkyllithiums with imines derived from acetophenone (entry 3, Table 2) have been reported.[12]

### 1.12.3.3 Stereochemical Control

Asymmetric induction is not high in the addition of organometallic agents to chiral aldehydes whose substituents have no chelating ability (such as 2-phenylpropanal). Although few examples involving nonstabilized carbanions to chiral aldimines have been reported, the presence of a stereogenic center adjacent to the aldimine can provide good diastereoselectivity; *e.g.* 60:40 *versus* 84:16, Cram/anti-Cram selectivity for 2-phenylpropanal *versus* its corresponding *N*-propylaldimine (**25**; equation 2) in the addition of allyl Grignard.[13] In the case of dialkylcuprate and perfluoroalkyllithium additions, $BF_3$ is required. Again good Cram/anti-Cram (Felkin–Ahn) selectivity is obtained (entries 4 and 5, Table 2).[12,13] Chelation/nonchelation control in the addition of stabilized allyl (crotyl) organometallics to chiral aldimines has been reviewed.[9b]

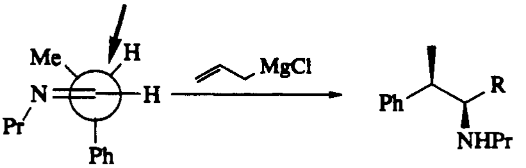

(**25**) (**26**)

major

(84:16, Cram:anti-Cram)

(2)

Fiaud and Kagan[37] examined the addition of organometallic agents to *N*-substituted imines of (–)-menthyl glyoxylates with the intention of producing substituted amino acids. Grignard condensations with *N*-[(*S*)-α-methylbenzyl]iminoacetate (**27**) produced, in modest yields, varying amounts of secondary and tertiary amines (**28**) and (**29**), demonstrating the molecules ambident electrophilicity (equation 3). While the problem of regiochemical control (**29** *versus* **28**) can be solved by the use of organocadmium agents, stereochemical control in the production of (**29**) is modest (*de* ≈ 40–50%). The menthyl ester moiety is the major stereochemical determinant, as replacement of the *N*-[(*S*)-α-methylbenzyl] substituent with the corresponding (*R*)-isomer had little effect on reaction diastereoselectivity (for $R^1$ = $Pr^n$, 40 *versus* 41% *ee*).

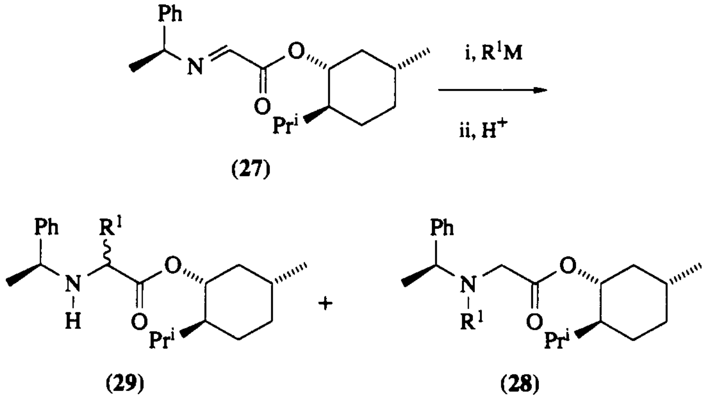

**(27)**

**(29)** **(28)**

(3)

Diastereoselectivity produced by 1,3-asymmetric induction in the reaction of (*S*)-valinol-derived imines with organometallic agents can be high. Takahashi, Suzuki and coworkers (equation 4) have examined the condensation of chiral azomethines (**8**), which are reported to exist exclusively as the (*E*)-isomer, with organolithium and Grignard reagents (≥4 equiv.).[14] Addition occurs predominantly from the *si*-face of Figure 3 and is consistent with an alkoxy-mediated delivery of the organometallic agent. The size of substituent $R^1$ at the resident stereogenic center of Figure 3 is a key stereochemical determinant of the diastereoselectivity ($R^1$ = $Pr^i$, $Bu^i$ and $Bu^s$ are superior to $R^1$ = Me; entries 1 and 2, Table 3).[14] Conversion of the alcohol funtionality to the corresponding methyl ether has little effect on the stereochemical course of the addition (entries 3, 4, 6 and 7, Table 3). By appropriate selection of azomethine and organometallic agent, both diastereomeric amines can be obtained (entries 1 and 5, Table 3).

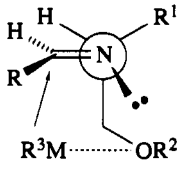

**Figure 3**

**Table 3** The Reaction of Organometallic Reagents with Chiral Aldimines (**8**)

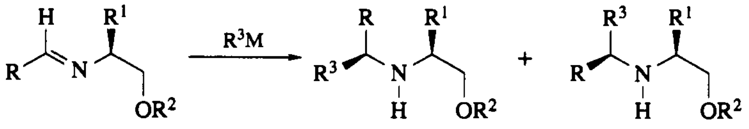

**(8)** **(30)** **(31)**

(4)

| *Entry* | *R* | *R*$^1$ | *R*$^2$ | *R*$^3$*M* | *Overall yield (%)* | *(30) (%)* | *(31) (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | $Pr^i$ | H | $PhCH_2MgCl$/THF | 73 | >98 | — | 14a |
| 2 | Ph | Me | H | $PhCH_2MgCl$/THF | 53 | 78 | 22 | 14b |
| 3 | Ph | $Pr^i$ | H | EtMgBr/$Et_2O$ | 63 | 78 | 22 | 14e |
| 4 | Ph | $Pr^i$ | Me | EtMgBr/$Et_2O$ | 81 | 91 | 9 | 14e |
| 5 | $CH_2Ph$ | $Pr^i$ | H | PhLi/$Et_2O$ | 35 | >98 | — | 14a |
| 6 | Et | $Pr^i$ | H | PhLi/$Et_2O$ | 68 | >97 | — | 14e |
| 7 | Et | $Pr^i$ | Me | PhLi/$Et_2O$ | 60 | 95 | 5 | 14e |

### 1.12.3.4 Cyclic Imines

Cyclic imines, such as 1-pyrroline (**6**) and $\Delta^1$-piperidine (**32**), which are prone to trimerization, can be prepared from *N*-halopyrrolidine and *N*-halopiperidine respectively and treated *in situ* with organolithium reagents to provide 2-alkylated and 2-arylated pyrrolidines and piperidines in modest yield.[38] Corey *et al.*[25] treated substituted piperidine (**17**) generated in this fashion with *N*-pentyllithium to establish the stereochemistry of the remote pentyl side chain of perhydrohistrionicotoxin (**33**), as condensation occurred from the more accessible *re*-face of the imine π-system of (**17**).

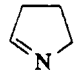

**(6)**

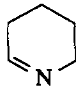

**(32)**

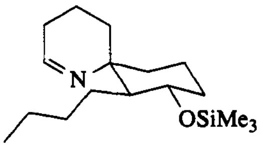

**(17)**

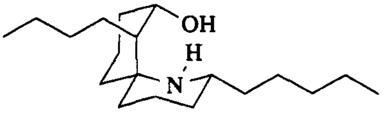

**(33)**

Difficulties in generating highly functionalized alicyclic imines have limited their synthetic utility. *In situ* generation of piperidines from highly substituted α-aminonitriles has been employed in the Grignard-mediated conversion of the 1-α-cyano-1-deoxynojirimycin derivative (**34**) to the 1-α-substituted amine (**35**; equation 5).[39]

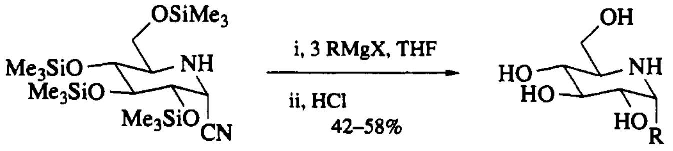

**(34)** **(35)**

(5)

Substituted 3-thiazolines (**16**) are stable and easily prepared, but are inert to organometallic addition. Activation of (**16**) with $BF_3{\cdot}OEt_2$ followed by organometallic addition ($R^1MgX$, $R^1Li$) provides *trans*-4,5-disubstituted thiazolidines (**36**) (masked 2-aminothiols) in which $R^1$ = aryl, alkyl or alkynyl (equation 6).[24]

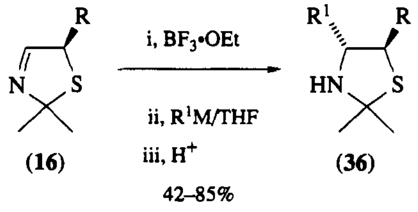

**(16)** **(36)**

(6)

The addition of organolithium agents to bicyclic imines such as (**37**) provides modest yields of alkylated product (**38**; equation 7).[40] These condensations have been reviewed.[26]

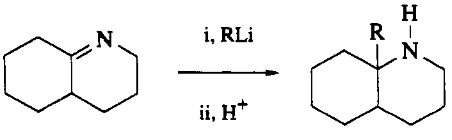

**(37)** **(38)**

(7)

### 1.12.3.5 Chiral Chromium Complexes

Solladie-Cavallo and Tsamo (equation 8) have investigated the addition of Grignard reagents to chiral chromium tricarbonyl complexes of diarylimines (**15**).[23] Results of these additions are shown in Table 4. While the absolute stereochemistry of the product(s) (**39**) formed has not been determined, the results demonstrate that high diastereoselectivity can be obtained in the addition of benzyl Grignards to azomethine (**15**), in which ring A is *ortho* substituted (entries 4–6, Table 4).

**Table 4** Addition of Grignard Reagents to Chiral Chromium Tricarbonyl Complexes of Diarylimines (**15**)

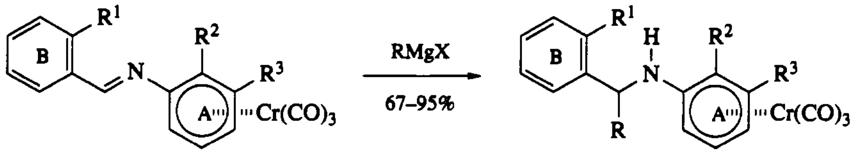

(**15**) (**39**)

(8)

| *Entry* | *RMgX* | $R^1$ | $R^2$ | $R^3$ | *Diastereomeric ratio*[a] |
|---|---|---|---|---|---|
| 1 | MeMgI | H | Me | H | 67:33 |
| 2 | MeMgI | Me | Me | H | 67:33 |
| 3 | MeMgI | Me | Ph | H | 66:34 |
| 4 | $PhCH_2MgCl$ | Me | Me | H | 100:0 |
| 5 | $PhCH_2MgCl$ | OMe | Me | H | 100:0 |
| 6 | $PhCH_2MgCl$ | Cl | Me | H | 100:0 |
| 7 | $PhCH_2MgCl$ | Me | H | Me | 57:43 |

[a] Determined by $^1H$ NMR (250 MHz).

The diastereoselectivity has been rationalized by the authors with the transition state model shown in Figure 4a, in which the $Cr(CO)_3$ moiety is situated in the plane of the azomethine group ($\sigma_I$) and approach of the Grignard occurs nearly orthogonal to this plane. The facial selectivity is postulated to arise from interactions of the incoming Grignard reagent and the substituents on ring A. Determination of the absolute configuration of the product(s) (**39**) should probe the relevance of this model since organometallic addition to (**15**) in which $Cr(CO)_3$ is orthogonal to the plane of the azomethine group (Figure 4b) would generate the opposite diastereomer.

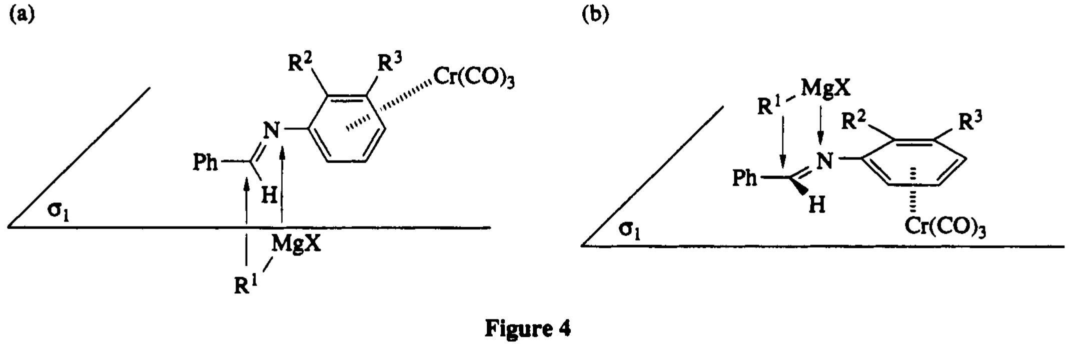

**Figure 4**

Alkyllithium addition to the ($\eta^6$-arene) dicarbonylchromium imine chelates has been examined.[41] Treatment of optically pure chelate (**41**) with methyllithium provides amine (**42**) with an enantiomeric excess of 94% (Scheme 5). No diastereoselectivity was reported for alkyllithium additions to (arene)tricarbonylchromium complex (**40**). In the absence of additional examples, the generality of this chromium chelate methodology for asymmetric amine synthesis cannot be assessed.

## 1.12.4 ORGANOMETALLIC ADDITIONS TO IMINIUM SALTS

### 1.12.4.1 Background

While the addition of organometallic reagents to acyclic or cyclic imines (**43**) is often compromised by poor imine reactivity, these reagents readily condense with structurally diverse, more electrophilic iminium salts (**44**), bearing a positive charge on the nitrogen atom, to provide substituted tertiary amines (**45**; Scheme 6). A review of the literature describing additions to cyclic iminium salts prior to 1966 is avail-

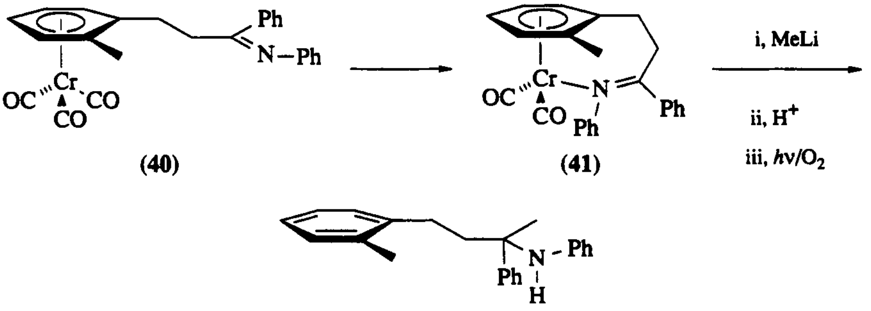

(40) (41)

(42) 72% (*ee* 94%)

**Scheme 5**

able.[42] More recent reviews (up to 1976) summarize the addition of organometallic reagents to iminium salts derived from aliphatic, aromatic or heteroaromatic aldehydes as well as from aromatic or aliphatic ketones.[43]

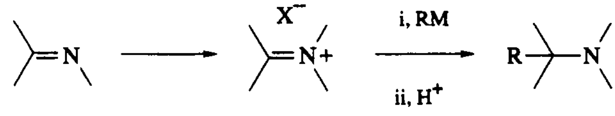

(43) (44) (45)

**Scheme 6**

### 1.12.4.2 Preformed Iminium Salts

Preformed iminium salts have been used extensively in organic synthesis. The facility of the condensation is a function of iminium salt substitution. Treatment of formaldehyde-derived *N*,*N*-dimethyl(methylene)ammonium halides (or trifluoroacetates) (**46**) with Grignard and lithium reagents results in the high yield formation of dimethylaminomethyl-containing compounds (**47**).[44] Subsequent oxidation[45] or alkylation[46] of these products has been employed to generate terminal alkenes (**48**; Scheme 7). As expected, addition yields are modest for the more-hindered iminium salts derived from other aldehydes and are somewhat lower for those derived from cyclic ketones.[47]

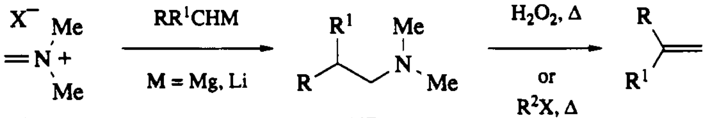

(46) (47) (48)

**Scheme 7**

Addition to cyclic iminium salts has been utilized in alkaloid synthesis. A zinc-promoted reductive coupling reaction of iminium salts and alkyl halides has been reported by Shono *et al.* (Scheme 8).[48] Evidence delineating the mechanistic course (organozinc addition or electron transfer reaction) of the addition has not been established. In contrast to organolithium or Grignard additions, aromatic halogen and alkoxycarbonyl substituents are compatible with this methodology. The intramolecular version of this reaction has been employed for the synthesis of tricyclic amines (**53**; equation 9).

The quaternization of imines to form more reactive iminium salts has had limited synthetic utility since the activating substituents are often not easily removed. For this reason Lewis acids have been utilized to activate imines. MacLean and coworkers[49] have also addressed this problem and found that silylation of 3,4-dihydroisoquinolines and 3,4-dihydro-β-carbolines with trimethylsilyl triflate (TMS-OTf) provides a reactive, yet labile, silyl iminium salt which undergoes nucleophilic addition (Scheme 9). With this procedure, 3,4-dihydro-6,7-dialkoxyisoquinoline (**54**) was converted to amidine (**56**) in 98% yield. In the absence of TMS-OTf no addition occurred.

While 2-substituted-4,4,6-trimethyl-5,6-dihydro-1,3-oxazines[50] 2-substituted-4,4-dimethyl-2-oxazolines[51] and 1-benzyl-2-alkyl-4,5-dihydroimidazoles[52] are inert to organometallic addition, their corresponding methiodide salts (**57**)–(**59**) are reactive and have been utilized for the synthesis of ketones (**60**;

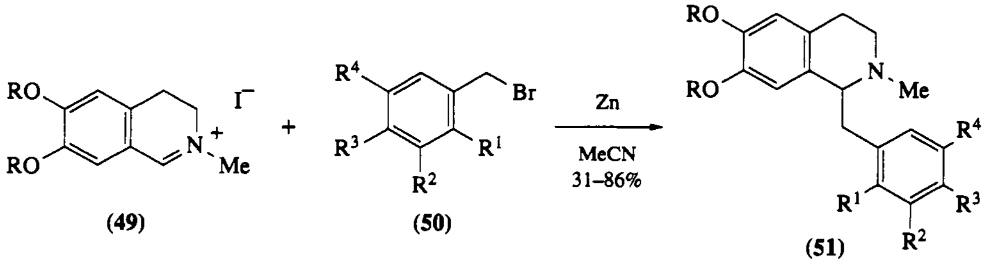
RO
RO
I⁻
N
+
Me
(49)
+
R4
R3
R2
R1
Br
(50)
Zn
MeCN
31–86%
RO
RO
N
Me
R4
R3
R2
R1
(51)

Scheme 8

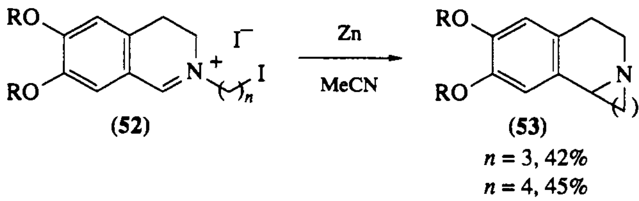
RO
RO
I⁻
N
+
I
n
(52)
Zn
MeCN
RO
RO
N
n
(53)
n = 3, 42%
n = 4, 45%

(9)

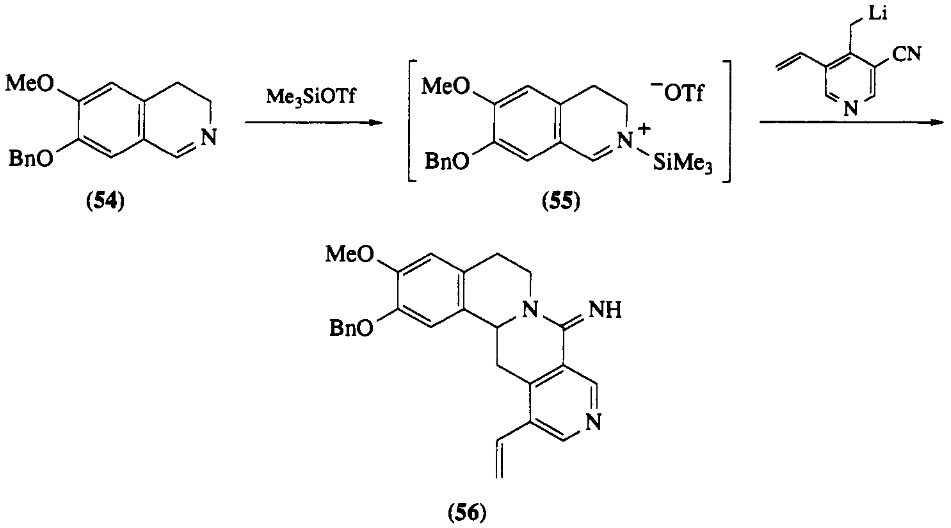
MeO
BnO
N
(54)
Me3SiOTf
MeO
BnO
⁻OTf
N
+
SiMe3
(55)
Li
CN
N
MeO
BnO
N
NH
N
(56)

Scheme 9

Scheme 10). The use of this methodology in ketone synthesis is not widespread, given the lack of availability of these salts and the sensitivity of this reaction to substrate/organometallic substitutions.

Addition to vinylogous iminium salts has also been explored. Moriya *et al.*[53] have examined the addition of nucleophiles to 3-(1-pyrrolidinylmethylene)-3*H*-indolium salt (**61**) in the synthesis of 3-(1-dialkylamino)alkyl-1*H*-indoles (**62**; equation 10).

Similarly, Gupton *et al.*[54] have shown that acyclic amidinium salts (**63**) and vinylogous amidines (**65**) are reactive and can be utilized for the synthesis of structurally diverse aldehydes (Scheme 11).

In addition, functionalized piperidines (**68**) have been generated by the addition of organometallic reagents to 5,6-dihydropyridinium salts (**67**; equation 11).[55]

### 1.12.4.3 Iminium Salts Generated *In Situ*

Difficulties associated with the preparation and purification of anhydrous, soluble iminium salts (**44**) suitable for organometallic additions can in certain instances be avoided by an *in situ* generation of these reactive molecules.[56] *N*,*N*-(Disubstituted)aminomethyl ethers (or acetates) (**69**), sulfides (**70**) and nitriles (**71**) are frequently utilized in the generation of these salts. In addition, *N*,*N*-(disubstituted)aminomethylamides (**72**), -sulfonates (**73**) and halides (**74**) have been employed (Scheme 12).

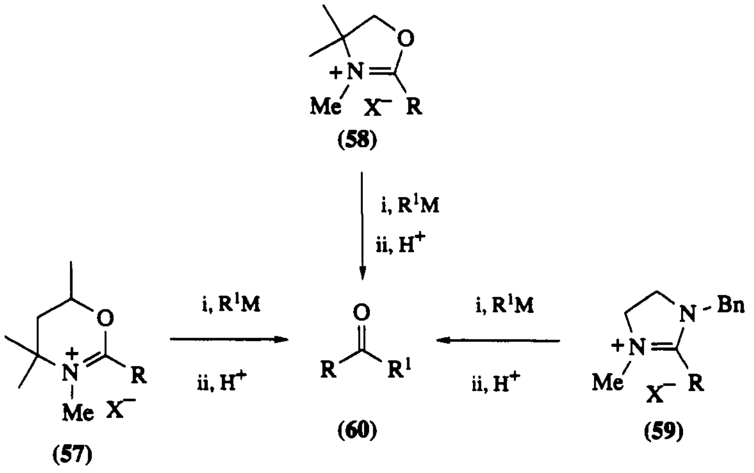

**Scheme 10**

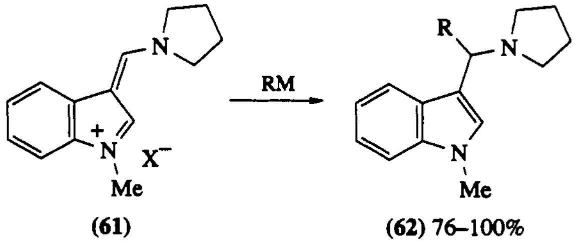

(10)

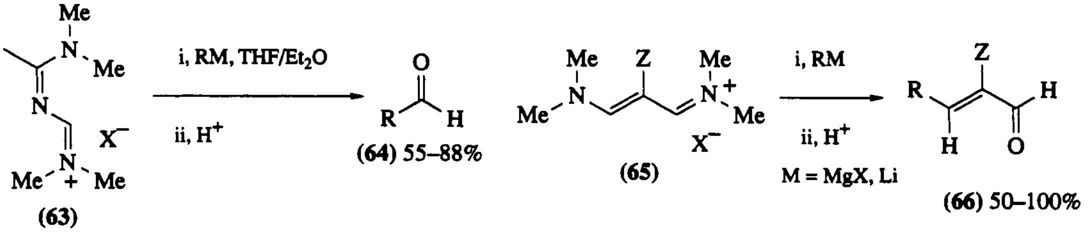

**Scheme 11**

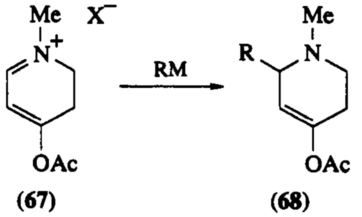

(11)

The reaction of *N*,*N*-(disubstituted)aminomethyl ethers (**69**) with Grignard reagents has been extensively investigated[56] and provides good yields of substituted tertiary amines. Representative examples are shown in Table 5. Acyclic[57] as well as cyclic[58] ethers (entries 1 and 2, Table 5) have been studied. Grignard treatment of bis(alkoxymethyl)amines (entry 3, Table 5)[59] and dialkylformamide acetals (entry 4, Table 5)[60] results in the displacement of both alkoxy substituents. In addition, β,γ-unsaturated-α-amino esters can be easily accessed by organozinc ($R_2Zn$) addition to alkoxy(dialkylamino)acetates (entry 5, Table 5).[61]

The propensity of formaldehyde imines (**22**) to trimerize to give hexahydro-1,3,5-triazines (**24**) has limited their synthetic utility. Sekiya and coworkers[62] and Bestmann *et al.*[63] have shown that *N*,*N*-bis(trimethylsilyl)methoxymethylamine (**75**) is a useful synthetic equivalent of formaldehyde imine. Treatment

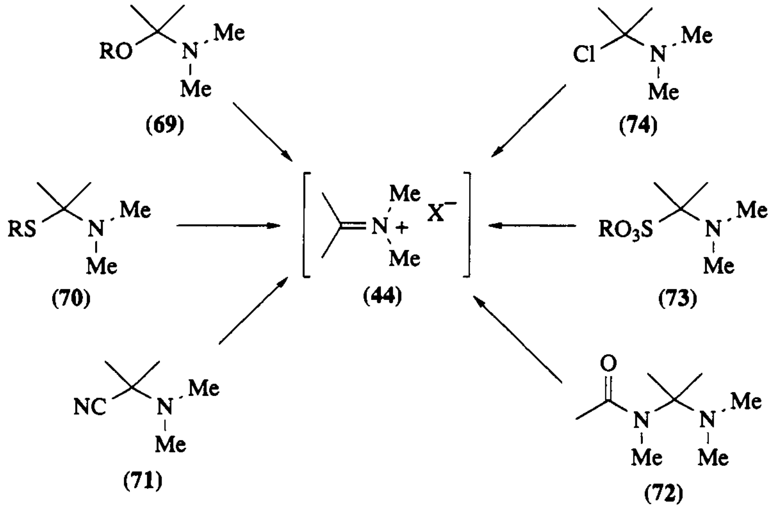

Scheme 12

Table 5 Addition of Organometallic Reagents to *N,N*-Disubstituted Aminoalkyl Ethers

| *Entry* | *Substrate* | *Organometallic reagent/conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 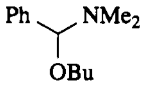 | 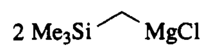<br>THF/0–20 °C/15 h | 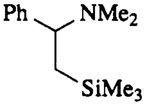 | 84 | 57 |
| 2 | 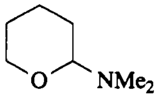 | 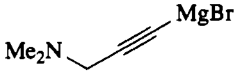 | 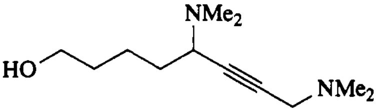 | 89 | 58 |
| 3 | 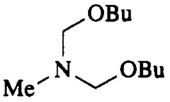 | 2 $\equiv$—MgBr<br>THF/50 °C/15 h | 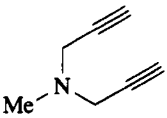 | 44 | 59 |
| 4 | 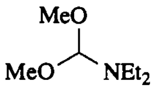 | 2.5 PhMgBr<br>$Et_2O$/0 °C to r.t./30 min | 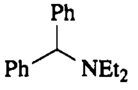 | 93 | 60 |
| 5 | 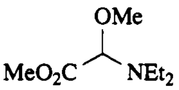 | 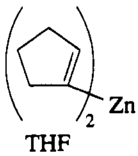 | 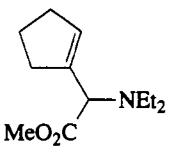 | 63 | 61 |

of aryl, heteroaryl, primary and secondary alkyl Grignards (organolithium reagents can also be used but require the addition of $MgBr_2$) with (**75**) generates in good yield *N,N*-bis(trimethylsilyl)amines (**76**), which can be readily desilylated to generate primary amines (**77**; Scheme 13).

α-Amino ethers need not be isolated in the synthesis of tertiary amines. α-Substituted phenethylamines (**81**), for example, have been generated in good yield from aldehydes and benzylmagnesium chloride using titanium amide complexes.[64a] The intermediacy of a titanium amide tetraisopropoxide ate complex (**79**) which can condense with aldehydes to form the reactive titanium complex (**80**), has been proposed (Scheme 14).

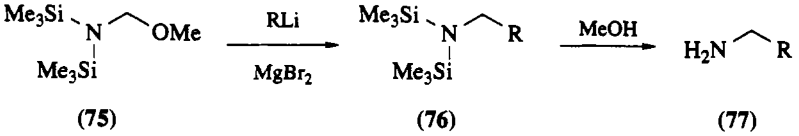
Me3Si
N
OMe
Me3Si
RLi
MgBr2
Me3Si
N
R
Me3Si
MeOH
H2N
R
(75)
(76)
(77)

Scheme 13

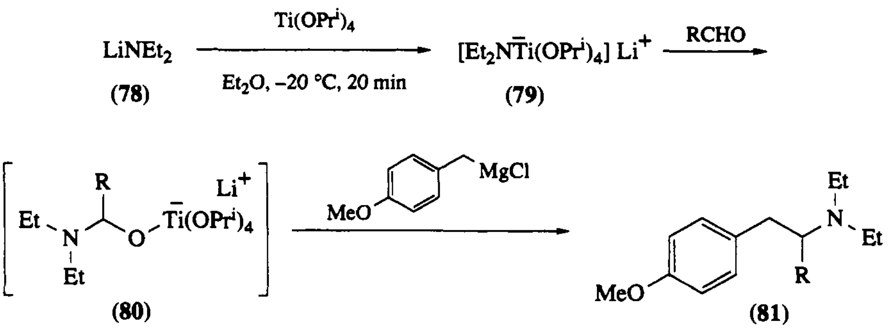
LiNEt2
(78)
Ti(OPri)4
Et2O, -20 °C, 20 min
[Et2NTi(OPri)4] Li+
(79)
RCHO
R
Li+
Et
N
O
Ti(OPri)4
Et
(80)
MgCl
MeO
MeO
Et
N
Et
R
(81)

Scheme 14

In addition, amine *N*-oxides (**82**) can be treated with trialkylsilyl triflates to generate, after methyllithium treatment, α-siloxyamines (**83**) which, when allowed to react with Grignard reagents (or trialkylaluminum), generate tertiary amines (**84**) in modest yields (Scheme 15).[65]

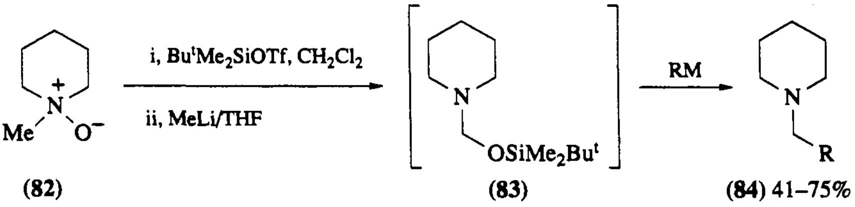
+
N
Me
O−
i, ButMe2SiOTf, CH2Cl2
ii, MeLi/THF
N
OSiMe2But
RM
N
R
(82)
(83)
(84) 41–75%

Scheme 15

O'Donnell *et al.*[66] have examined benzophenone-derived glycine acetate (**85**) as a glycine cation equivalent. Higher order mixed cuprates [$R_2Cu(CN)Li_2$] react with (**85**) to afford alkylated Schiff base (**86**) in moderate yields. The reaction is sensitive to reaction conditions and reduction competes with organometallic addition. Hydrolysis of (**86**) provides access to aryl- or alkyl-substituted amino acids (**87**; Scheme 16).

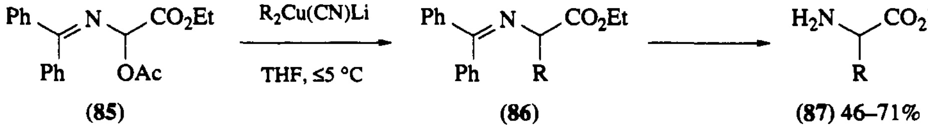
Ph
N
CO2Et
Ph
OAc
R2Cu(CN)Li
THF, ≤5 °C
Ph
N
CO2Et
Ph
R
H2N
CO2H
R
(85)
(86)
(87) 46–71%

Scheme 16

*N*-(Arylthiomethyl)amines, which are easily prepared and reportedly have better shelf stability[67] than the corresponding *N*-(alkoxymethyl)amines,[56] have also been utilized to prepare tertiary amines. Alkenyl cuprate addition to *N*,*N*-diethylphenylthiomethylamine produces allylic amines in high yield (entry 1, Table 6).[68] Both alkenyl groups of the cuprate react. *S*-(Dialkylaminomethyl) dithiocarbamates (entry 2, Table 6),[69] sulfonates (entry 3, Table 6)[70] and amides[71] also generate iminium salts *in situ*. Of a variety of amides examined, imides such as dialkylaminomethyl-succinimides (entry 4, Table 6)[71] and -phthalimides provide the best overall yields. Organolithium reagents are rarely utilized in aminomethylation reactions. However, *N*-chloromethylamines condense readily with lithiated anisole derivatives (entry 5, Table 6).[72]

The condensation of Grignard reagents with *N*,*N*-(disubstituted)aminomethylnitriles has been widely studied.[56] The reaction can accommodate hindered α-aminonitriles as exemplified by the condensation of phenyl Grignard with 1-piperidinocyclohexane carbonitrile to afford phencyclidine (entry 6, Table

**Table 6** Addition of Organometallic Reagents to Iminium Salts Generated *In Situ*

| *Entry* | *Substrate* | *Organometallic reagent/conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 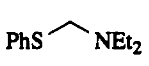 | 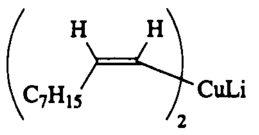<br>THF/–40 °C to r.t./3 h | 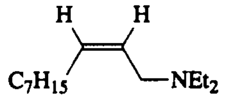 | 95 | 68 |
| 2 | 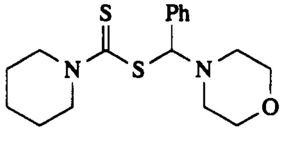 | PhMgBr, $Et_2O$ | 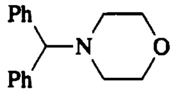 | 81 | 69 |
| 3 | 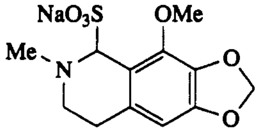 | EtMgBr, $Et_2O$ | 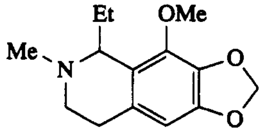 | 94 | 70 |
| 4 | 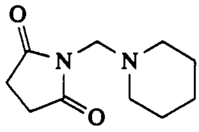 | $PhCH_2CH_2MgBr$, $Et_2O$ | 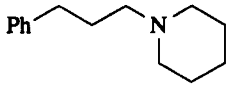 | 80 | 71 |
| 5 | 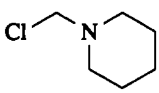 | 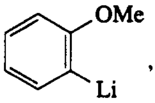 , $Et_2O$ | 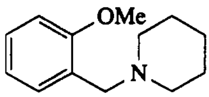 | 82 | 72 |
| 6 | 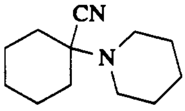 | PhMgBr, $Et_2O$, Isooctane<br>Δ, 1 h | 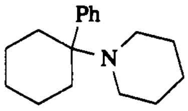 | 54 | 73 |

6).[73] In general, Grignards add to the α-carbon atom, while alkyllithiums add to the nitrile carbon atom of *N*,*N*-(disubstituted)aminomethylnitriles. If the α-aminonitrile has an active hydrogen atom on nitrogen, both Grignards and organolithium reagents add to the α-carbon atom. On the other hand, if the aminonitriles have an acetyl group on the amine nitrogen atom, both reagents condense with the nitrile moiety.[74]

## 1.12.5 ORGANOMETALLIC ADDITIONS TO *N*-ACYLIMINES AND *N*-ACYLIMINIUM SALTS

### 1.12.5.1 Background

The α-amidoalkylation reaction, which involves the addition of carbon nucleophiles (primarily aromatic rings, alkenes, cyanides, isocyanides, alkynes, organometallic and active methylene-containing compounds) to substituted amides (**89**) where X is a leaving group (Scheme 17), has been extensively reviewed.[75] A variety of organometallic condensations have since been reported which extend the scope of this reaction.[76] The reactive intermediates in these reactions are considered to be *N*-acylimines (**88**) or *N*-acyliminium salts (**90**). Direct displacement of the α-haloalkylamide precursors (**89**; X = halogen) cannot in certain cases be discounted.

A comprehensive kinetic study examining the reactivity of *N*-acylimines/*N*-acyliminium salts *versus* imines/iminium salts has not, to date, been published. Spectral data ($^{13}C$ NMR), however, would suggest

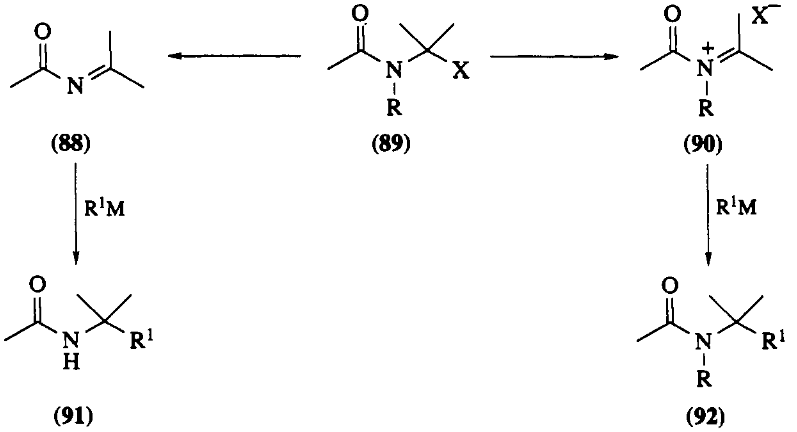

Scheme 17

that *N*-acyliminium salts could be even more reactive than iminium salts, since the imine carbon atom in (**93**) and (**94**) is shifted about 5 p.p.m. downfield from that in iminium salt (**95**).[75e,77]

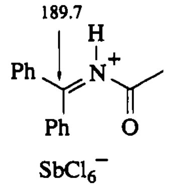

(**93**)

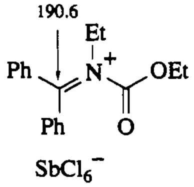

(**94**)

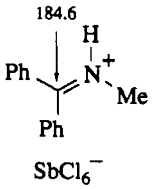

(**95**)

### 1.12.5.2 α-Amidoalkylation Reactions Involving Substituted Azetidin-2-ones

No α-amidoalkylation reaction has been studied in recent years in greater detail than the addition of nucleophiles to substituted azetidin-2-ones such as (**96**), bearing a leaving group (X) in the 4-position. The addition of oxygen and sulfur nucleophiles has been employed for the synthesis of oxapenam and penem antibiotics, while the addition of stabilized and nonstabilized carbanions has been utilized for the synthesis of carbapenems (**97**; Scheme 18).[78] While a thorough comparative study examining the effect of leaving groups (X) on the reactivity of these 4-substituted azetidin-2-ones is not available, cross comparisons[79] (many of which are outside the scope of this chapter) suggest an approximate order of reactivity of Cl > $SO_2Ph$ > OAc > SCSOEt, $SCS_2Et$ > $N_3$ > OEt > SEt. High yields of 4-alkyl-, 4-allyl-, 4-vinyl- and 4-ethynyl-azetidin-2-ones have been obtained by treatment of 4-phenylsulfonylazetidin-2-ones with either lithium organocuprates or Grignard reagents.[80] Yields for the organocuprate additions are, in general, superior to those of the Grignard condensations.

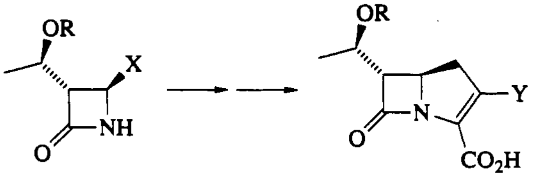

Scheme 18

In the addition of phenylthioethynyl Grignard to 3-substituted azetidinone (**98**), the stereochemistry of addition is exclusively *trans*, consistent with the intermediacy of azetinone intermediate (**99**; Scheme 19).[81]

*N*-Substituted azetidin-2-ones are more stable than their unsubstituted counterparts and as a result are more resistant to nucleophilic additions. However, treatment of either 4β- or 4α-chloroazetidinone (**101**)

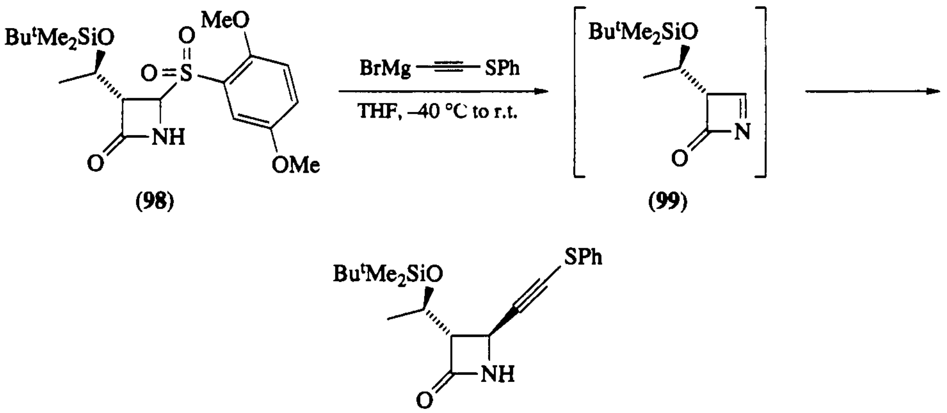

**(98)** **(99)**

**(100)** 80%

**Scheme 19**

with allylcopper reagents provides the same product ratio of substituted azetidinones (**102**), suggesting the intermediacy of an acyliminium ion (equation 12).[82]

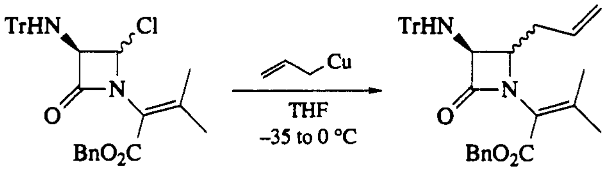

(12)

**(101)** **(102)** 4β:4α = 33:67

### 1.12.5.3 *N*-Acylimines/*N*-Acyliminium Salts

The addition of organometallic reagents to substituted *N*-halomethylamides (**103**) has been utilized to generate substituted amides (**104**; equation 13). Selected examples are shown in Table 7.[84–92]

*N*-Acylimine intermediates stabilized by electron-withdrawing groups can be isolated (entries 3–6, Table 7) and readily undergo nucleophilic addition. In most cases, however, *N*-acylimines need not be isolated since the addition of organometallic reagents (2 equiv.) to *N*-halomethylamide precursors provides the products in comparable yields. Almost all substituted *N*-halomethylamides lack β-hydrogen atoms due to the propensity of *N*-acylimines to tautomerize to acyl enamides.[83]

Complex alkenyl-copper and -cuprate derivatives, and also alanates, have been generated with high stereochemical purity, and upon treatment with *N*-chloromethyl-*N*-methylformamide or *N*-chloromethylphthalimide provide access to highly functionalized allylic amides (entries 1 and 2, Table 7).[84] Addition to acyliminomalonic esters[85] or acyliminophosphonates[86] provides acylaminomalonates and acylaminoalkylphosphonates in modest yield (entries 3 and 4, Table 7).

Carbanion amidoalkylations provide a versatile means of generating α-amino acids. The ability to oxidize alkenes[87] or hydrolyze trichloromethyl groups[88] of amidoalkylation products (entries 5 and 6, Table 7) to acids provides access to these compounds. α-Halo-*N*-(*t*-butoxycarbonyl)glycine esters have been used as 'electrophilic glycinates' for the preparation of broadly substituted amino acids (entry 7, Table 7).[89] Several approaches have been examined as possible enantioselective routes to relatively inaccessible, synthetic amino acids. The reactions of vinylmagnesium bromide with *N*-Cbz-L-Phe-α-chloro-Gly-OMe resulted in no asymmetric induction as a 1:1 mixture of diastereomeric β,γ-unsaturated

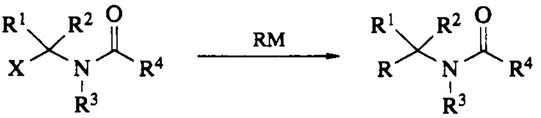

(13)

**(103)** **(104)**

**Table 7** The Addition of Organometallic Reagents to *N*-Acylimines

| *Entry* | *Electrophiles* | *Organometallic Reagent* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 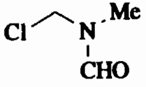 | 0.62 equiv. 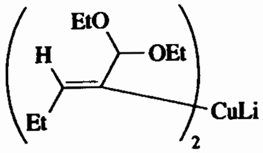 | THF, –20 °C to r.t., 3 h | 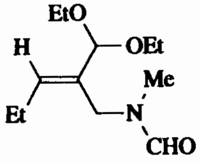 | 89 | 84 |
| 2 | 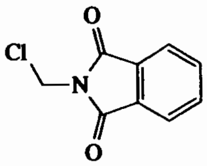 | 1.2 equiv. 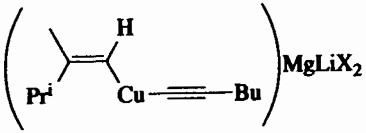 | THF, –20 °C to r.t., 3 h | 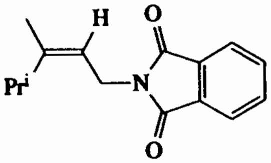 | 47 | 84 |
| 3 | 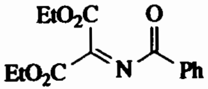 | 1 equiv. 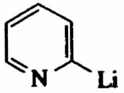 | THF, –100 to –78 °C | 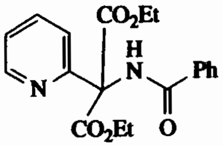 | 50 | 85 |
| 4 | 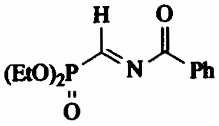 | 1.1 equiv. 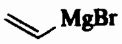 | THF, –78 °C | 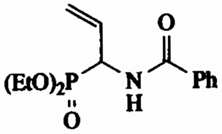 | 45 | 86 |
| 5 | 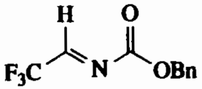 | 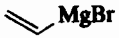 | THF, 0 °C | 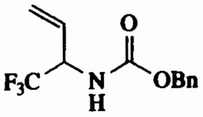 | 81 | 87 |
| 6 | 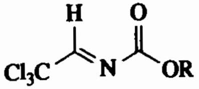 | 1 equiv. MeMgBr | Et$_2$O, 0 °C, 12 h | 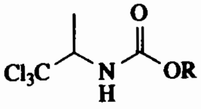 | 56 | 88 |

**Table 7** *(continued)*

| *Entry* | *Electrophiles* | *Organometallic Reagent* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 7 | 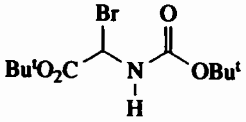 | 2.2 equiv. 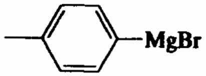 | THF, −78°C to r.t., 12 h | 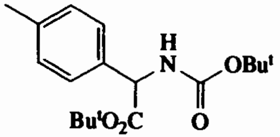 | 91 | 89 |
| 8 | 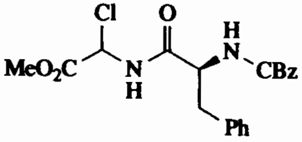 | Excess 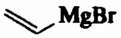 | THF, −70 °C, 2 h | 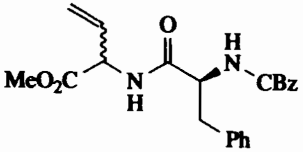 | 60 | 90 |
| 9 | 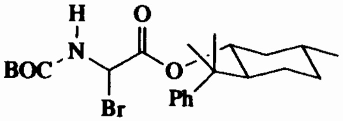 | $Bu^iMgBr$ | $Et_2O$, 0 °C | 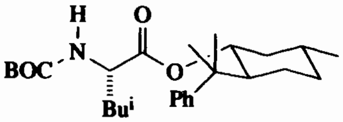 | 65<br>(95% *ee*)[a] | 91 |
| 10 | 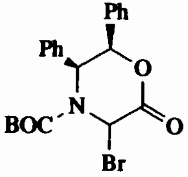 | $Bu_2CuCNLi_2$ | THF, −78 °C, 30 min | 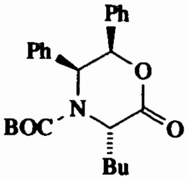 | 48<br>(99.5% *ee*)[a] | 92 |

[a] Optical purity of the L-norleucine produced using the chiral auxiliary.

α-amino acid esters was produced (entry 8, Table 7).[90] Obrecht and coworkers[91] have examined the addition of Grignard reagents to α-bromo-*N*-Boc-glycine-(–)-phenylmenthyl ester (entry 9, Table 7). The high enantioselectivity (82–95% *ee*, 4 examples) can be rationalized by the shielding of the *re*-face of the imine double bond by the aromatic ring of the (–)-8-phenylmenthyl moiety, as illustrated in Figure 5. A two-step conversion of these products to amino acids was developed as a result of the resistance of phenylmenthyl esters to hydrolysis.

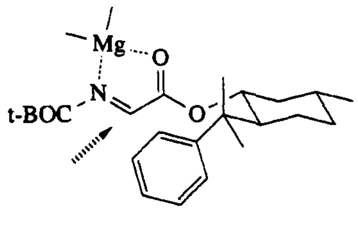

**Figure 5**

Williams and coworkers have constructed a rigid 3-bromotetrahydrooxazin-2-one ring from D- or L-erythro-α,β-diphenyl-β-hydroxyethylamine as a chiral template for electrophilic glycinate condensations (entry 10, Table 7).[92] Upon nucleophilic addition, very high diastereoselectivity is obtained (>91%, 11 examples) and is rationalized by a sterically controlled nucleophilic addition to a putative iminium species (Figure 6) or its bromoamide precursor. Hydrogenation or dissolving metal reduction of these products provides amino acids directly in excellent yield. The methodology is best suited for 'neutral' nucleophiles (*e.g.* silyl enol ethers, allyltrimethylsilanes) since the more basic organometallic agents competitively reduce the α-bromo ketones, resulting in lower overall yields.

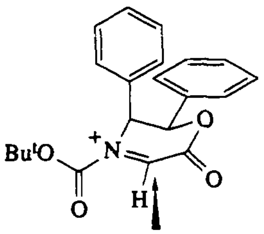

**Figure 6**

Lipshutz *et al.*[93] have described a singlet oxygen based approach for the conversion of 1,2,4-trisubstituted imidazoles (**105**) to *N*-acylimines (**106**) containing either alkyl or aryl substituents (Scheme 20). *N*-Acylimines (**106**; $R^1$ = Bu$^n$, Bu$^i$, Ph; R = $CH_2Ph$, $CH_2CH_2Ph$) are inert to organometallic reagents. Remarkably, hydroxamic *N*-acylimines (**106**; $R^1$ = Bu$^n$, Bu$^i$, Ph; R = OMe) react with a variety of aryl, vinyl, ethynyl, primary and secondary organometallic reagents (2.5 equiv.) to afford α,α-disubstituted amino acid bis-amides (**107**) in good yield (52–94%). The fact that hydroxamic acid acylimine derivatives react and amide acylimines are inert to nucleophilic attack is unexpected. The authors speculate that organometallic complexation with the hydroxamic moiety might be responsible for organometallic delivery. A chelation-mediated acylimine activation of (**106**) cannot be discounted.

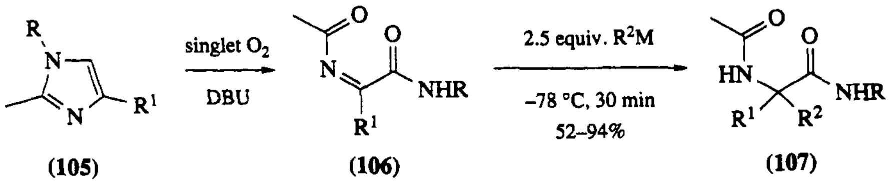

**Scheme 20**

Weinreb *et al.*[94] have described a procedure for the preparation of acyclic *N*-alkylamides (**110**) which involves the addition of trialkylalanes (4 equiv.) to amide methylols (**108**; Scheme 21). While the methodology has also been extended to ureas and carbamates, all efforts to couple hydroxylactams such as (**111**; R = H) with trialkylalanes failed.

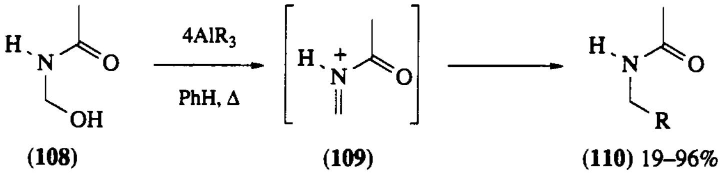

Scheme 21

Treatment of lactam methyl ether (**111**; R = Me) with trialkylalanes, however, generated desired product (**112**) in modest yield (equation 14).[95] Similarly, Shono *et al.*[96] have treated α-methoxy carbamates (**113**) with Grignard reagents in the presence of boron trifluoride etherate to afford substituted pyrrolidines (**114**; equation 15).

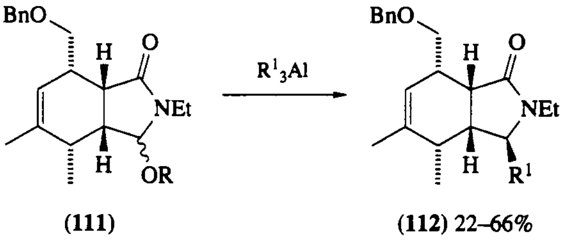

(14)

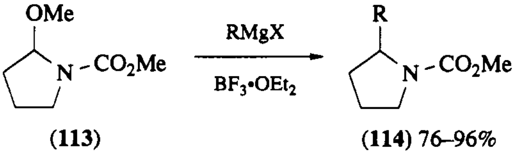

(15)

## 1.12.6 ORGANOMETALLIC ADDITIONS TO HYDRAZONES

### 1.12.6.1 Tosylhydrazones

The reaction of alkyllithium reagents with acyclic and cyclic tosylhydrazones can lead to mixtures of elimination (route A) and addition (route B) products (Scheme 22). The predominant formation of the less-substituted alkene product in the former reaction (Shapiro Reaction) is a result of the strong preference for deprotonation *syn* to the *N*-tosyl group.[97] Nucleophilic addition to the carbon–nitrogen tosylhydrazone double bond competes effectively with α-deprotonation (and alkene formation) if abstraction of the α-hydrogens is slow and excess organolithium reagent is employed.[97a,98] Nucleophilic substitution is consistent with an $S_N2'$ addition of alkyllithium followed by electrophilic capture of the resultant carbanion.

Treatment of 5α-cholestan-3-one tosylhydrazone (**115**) with excess (8 equiv.) alkyllithium reagent (primary, secondary and tertiary carbanions) provides, after axial protonation, 3β-alkylcholestane products (**116**) in addition to minor amounts of the anticipated alkene by-products (equation 16).[99]

In the case of verbenone tosylhydrazone (**117**), δ-pinene (**118**) is produced along with verbenene (**119**) following methyllithium treatment (equation 17).[100]

Good yields of substitution products can be obtained if elimination is precluded. Alkyllithium addition to fluorenone tosylhydrazone (**120**) provides access to 9,9-disubstituted fluorenes (**121**; equation 18).[101]

In a number of cases, the addition of lithium reagents to ketone mono- and di-tosylhydrazones can be improved by the inclusion of $Cu^I$, which activates the carbon–nitrogen bond toward nucleophilic addition.[102] However, the formation of complex product mixtures with many ketone tosylhydrazones limits its synthetic utility.[103]

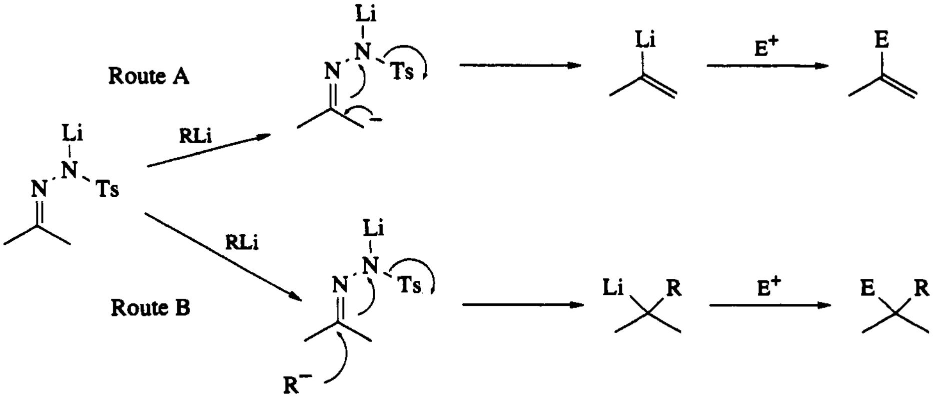

Scheme 22

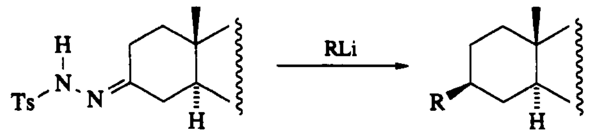

**(115)** **(116)**

R = Bu$^n$, 55%; R = Bu$^s$, 50%; R = Bu$^t$, 48% (16)

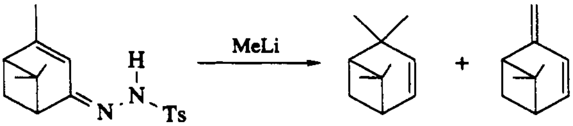

**(117)** **(118)** **(119)** (17)

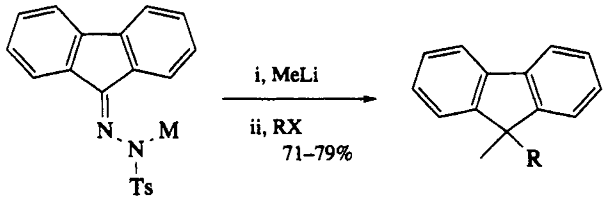

**(120)** **(121)** (18)

The failure of aldehyde tosylhydrazones (**122**), which exist predominantly in the (E)-configuration,[6,104] to form stable dianions at low temperature, as opposed to many ketone tosylhydrazones which do, is consistent with the strong preference for deprotonation *syn* to the *N*-tosyl group. As a result, alkyllithium reagents add rapidly to the aldehyde tosylhydrazone C═N bond. The addition of primary, secondary and tertiary alkyllithiums to aldehyde tosylhydrazones provides modest yields of the expected coupled hydrocarbons (**127**), accompanied by carbanion-derived side products (**124**–**126**) (Scheme 23).[5]

Vedejs *et. al.*[105] have shown that carbanions bearing leaving groups condense with aldehyde tosylhydrazones to generate disubstituted (**128**) and trisubstituted alkenes (**129**) (Scheme 24). While stereochemical control (*cis:trans*) is poor in the generation of disubstituted alkenes (compared, for example, to the Wittig reaction), the methodology is well suited for the synthesis of structurally diverse terminal alkenes.

As expected, the presence of $Cu^I$ promotes addition to the lithium and magnesium salts of secondary and tertiary aldehyde tosylhydrazones.[106] Dilithiotrialkylcuprates react with tosylhydrazones (**130**) to generate in high yield hindered cuprates (**131**), which undergo typical cuprate reactions (Scheme 25).

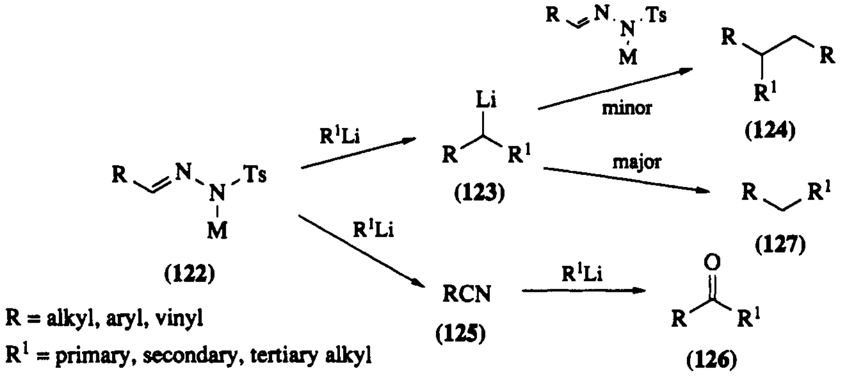
(122)
R = alkyl, aryl, vinyl
R¹ = primary, secondary, tertiary alkyl
R¹Li
(123)
minor
major
(124)
(127)
(125)
(126)
RCN

Scheme 23

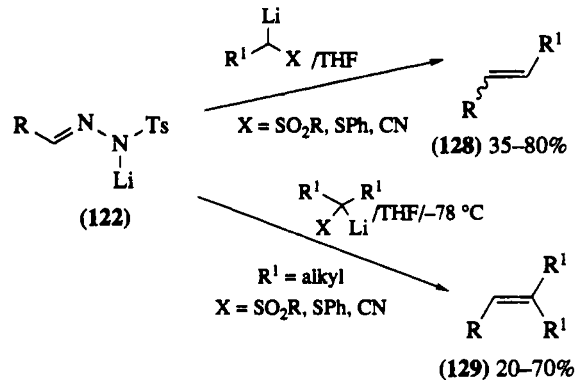
(122)
/THF
X = SO2R, SPh, CN
(128) 35–80%
/THF/–78 °C
R¹ = alkyl
X = SO2R, SPh, CN
(129) 20–70%

Scheme 24

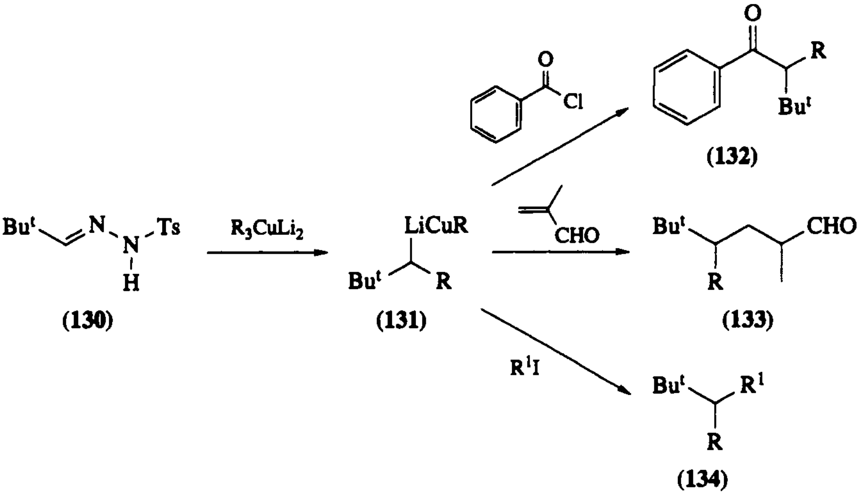
(130)
R3CuLi2
(131)
(132)
(133)
R¹I
(134)

Scheme 25

### 1.12.6.2 Chiral *N*,*N*-Dialkylhydrazones

Organometallic reagents condense with aldehyde-derived *N*,*N*-dialkylhydrazones.[107] This methodology has since been utilized for enantioselective syntheses of amines. The addition of Grignard reagents to *N*-aminoephedrine and L-valinol derived hydrazones **(135)**[16a–c] and **(138)**[16d] to provide, after hydrogenolysis, access to (*R*)- and (*S*)-1-phenylalkylamines **(137)** and **(140)** has been studied by Takahashi *et al.* (Scheme 26). Diastereoselectivity is >98% for alkyl Grignards (Me, Et, $Pr^i$) but erodes (<50%) with the addition of arylalkyl(benzyl) Grignards. The *re*-facial selectivity of **(135)** and *si*-facial selectivity of

**(138)** can be rationalized by the formation of the six-membered magnesium chelates shown in Figures 7a and 7b, with the diastereoselectivity resulting from a sterically controlled Grignard addition.

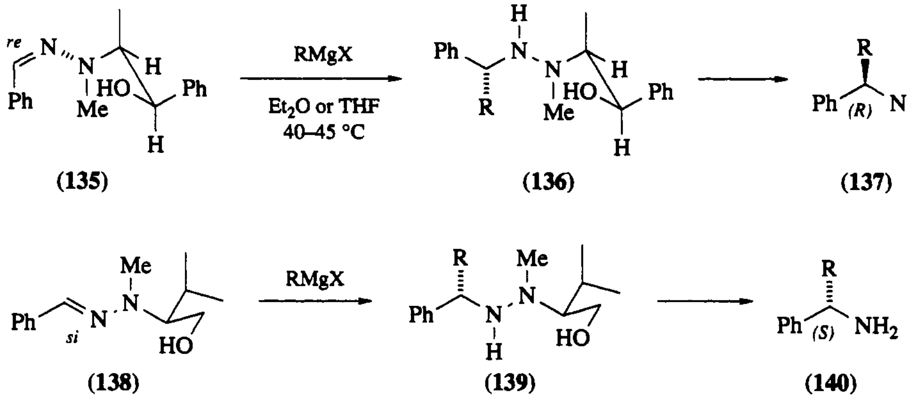

Scheme 26

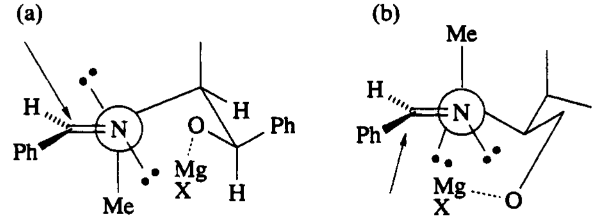

Figure 7

## 1.12.6.3 SAMP (RAMP) Hydrazones

Enders and Denmark have shown that SAMP (RAMP) hydrazones apparently provide a more versatile route to optically pure amines. Organolithium[17] and organocerium[18] reagents add to structurally diverse SAMP aldehyde hydrazones (**141**; Scheme 27). Representative examples are shown in Table 8. While addition diastereomeric selectivity is similar for both the organo-lithium and -cerium substrates, the overall yields in the organocerium additions are superior to those of various organometallic reagents ($R^1Li$, $R^1MgX$, $R^1_2CuLi$) alone or in conjunction with additives ($BF_3{\cdot}Et_2O$, TMEDA). The preferred reagent stoichiometry is $R^1M{:}CeCl_3{:}$hydrazone = 2:2:1. Vinyl, primary, secondary and tertiary organocerium reagents give addition products with high diastereomeric selectivity. Aliphatic, aromatic, α,β-unsaturated and highly enolizable aldehyde hydrazones are suitable for nucleophilic addition (entries 1–4, Table 8). Only 1,2-addition is observed with α,β-unsaturated SAMP hydrazones (entry 4, Table 8). Although the intimate mechanistic details of this addition are not known, these results suggest the organolithium or organocerium ($RCeCL_2$) reagent possibly coordinates to the methoxymethyl group and delivers $R^1$ to the *re*-face of (**141**) to generate preominantly (**142**).

## 1.12.6.4 α-Alkoxyaldehyde Dimethylhydrazones

Organolithium reagents (primary, secondary, tertiary, aryl and vinyl) also add in excellent yield to α-alkoxyaldehyde dimethylhydrazones (**146**); equation 19) with high *threo* diastereoselectivity (Table 9).[11] Hydrogenolytic cleavage of the resultant hydrazines provide an attractive route to *threo*-2-amino alcohols.

*Threo* diastereoselectivity is consistent with a chelation-controlled (Cram cyclic model) organolithium addition (Figure 8a). Since five-membered chelation of lithium is tenuous, an alternative six-membered chelate involving the dimethylamino nitrogen atom of the thermodynamically less stable (*Z*)-hydrazone (in equilibrium with the (*E*)-isomer) cannot be discounted. The trityl ether (entry 4, Table 9) eliminates the chelation effect of the oxygen atom such that the *erythro* diastereomer predominates (*via* normal Felkin–Ahn addition) (Figure 8b).

**Table 8** Addition of Organolithium and Organocerium Reagents to SAMP Hydrazones (141)

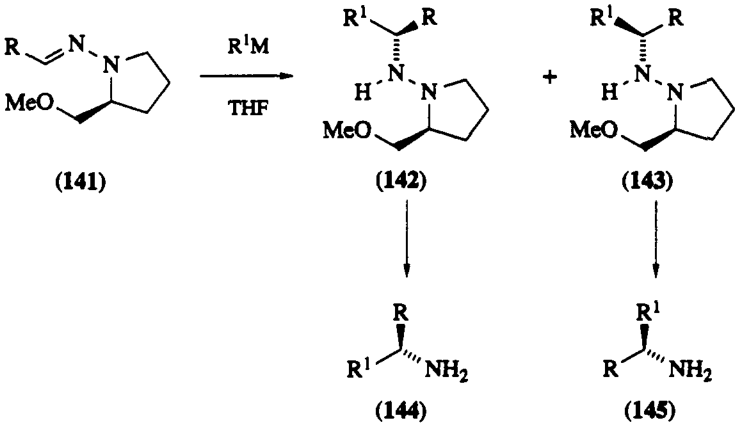

Scheme 27

| Entry | R | $R^1M$ (2 equiv.) | Yield (%) | Diastereomeric ratio (142):(143) | Ref. |
|---|---|---|---|---|---|
| 1 | $PhCH_2CH_2$ | $MeLi/CeCl_3$ | 81[a] (59)[b] | 98:2 (98:2)[c] | 18 |
| 2 | $PhCH_2$ | $MeLi/CeCl_3$ | 66 (0) | 96:4 (—) | 18 |
| 3 | Ph | $MeLi/CeCl_3$ | 59 (47) | 91:9 (90:10) | 17, 18 |
| 4 | (*E*)-$MeCH{=}CH_2$ | $MeLi/CeCl_3$ | 82 (52) | 96:4 (95:5) | 18 |

[a] Yield after chromatography of the corresponding methyl carbamates. [b] Yield for the addition without $CeCl_3$ (2 equiv. MeLi). [c] Diastereomeric ratio for the addition without $CeCl_3$ (2 equiv. MeLi).

**Table 9** Addition of Organolithium Reagents to α-Alkoxyaldehyde Dimethylhydrazones (146)

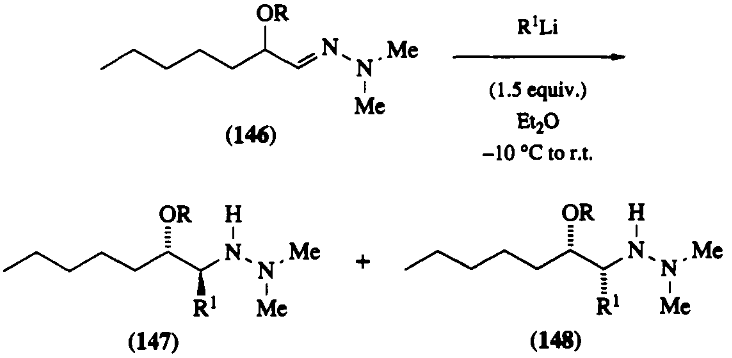

(19)

| Entry | R | $R^1Li$ | Yield (%) | Diastereomeric ratio (147):(148) |
|---|---|---|---|---|
| 1 | Bn | MeLi | 98 | 97:3 |
| 2 | Bn | $Bu^tLi$ | 98 | >98:2 |
| 3 | $CMe_2OMe$ | PhLi | 85 | >98:2 |
| 4 | Tr | MeLi | 85 | 1:10 |

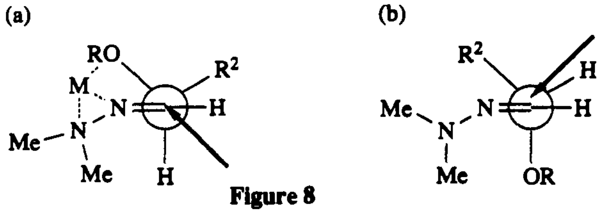

**Figure 8**

Only fair selectivity was obtained using the dimethylhydrazone of (*R*)-glyceraldehyde acetonides (**149**; equation 20). The addition of catalytic CuI reversed the diastereoselectivity (Table 10).[11]

**Table 10** Addition of Organolithium Reagents to (*R*)-Glyceraldehyde Acetonide Dimethylhydrazones (**149**)

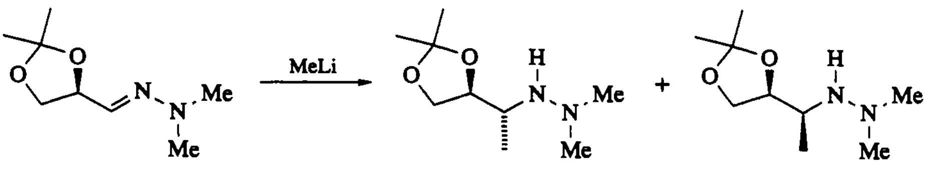

(20)

**(149)** **(150)** **(151)**

| *Entry* | *Organolithium reagent* | *Threo (150)* | *Erythro (151)* |
|---|---|---|---|
| 1 | MeLi | 3 | 1 |
| 2 | MeLi (0.1 equiv. CuI) | 1 | 3 |

## 1.12.7 ORGANOMETALLIC ADDITIONS TO AZADIENES

### 1.12.7.1 Chiral α,β-Unsaturated Aldimines

Koga and coworkers[19] have examined the addition of organometallic reagents to chiral α,β-unsaturated aldimines (**11**) derived from amino acid esters (equation 21). While *n*-butyllithium and lithium di-*n*-butylcuprate add to the aldimine moiety (1,2-addition), 1,4-addition occurs preferentially with Grignard reagents (Table 11).[19a,b]

**Table 11** Addition of Organometallic Reagents to Chiral α,β-Unsaturated Aldimines (**11**)

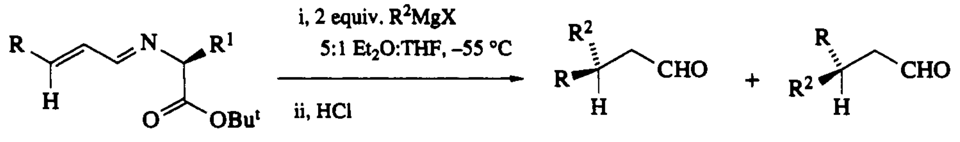

(21)

**(11)** **(152)** **(153)**

| *Entry* | *R* | *R*$^1$ | *R*$^2$ | *Isolated yield*$^a$ *(%)* | *(152) (%)* | *(153) (%)* |
|---|---|---|---|---|---|---|
| 1 | Me | Pr$^i$ | Ph | 42 | 65 | 35 |
| 2 | Me | Bu$^t$ | Ph | 52 | 91 | 9 |
| 3 | Ph | Bu$^t$ | Et | 56 | 95 | 5 |
| 4 | Me | Bu$^t$ | $(CH_2)_2CH{=}CMe_2$ | 48 | 98 | 2 |
| 5 | Me | Bu$^t$ | Bu$^n$ | 40 | 98 | 2 |

[a] Isolated as the corresponding alcohol.

Incorporation of a bulky substituent (R$^1$ = Bu$^t$) at the stereogenic center of the aldimine prevents deprotonation at this center and in addition is responsible for the high diastereoselectivity (entries 1 and 2, Table 11). The absolute configuration of the major β,β-disubstituted aldehydes produced after hydrolysis of the aldimine addition products is postulated to result from a chelation-mediated Grignard addition from the less-hindered *re*-face of the α,β-unsaturated aldimine existing in the *s-cis* conformation (Figure 9). Both diastereomeric products are accessible in theory, since R- and R$^2$-substituents can be reversed (entries 2 and 3, Table 11).

Similarly, Grignard addition to cycloalkenecarbaldehyde-derived aldimines (**154**) affords, upon hydrolytic work-up, optically enriched *trans*-2-substituted cyclohexenecarbaldehydes (**156**; Scheme 28).[19c–e] The magnesioenamine intermediate (**155**) generated by the Grignard additions (only phenyl and vinyl reported) can be alkylated with methyl iodide to give, in most instances, the aldehyde (**158**).[19d,e] The amino ester bidentate ligand dictates the stereochemical control in the alkylation. The formation of the other

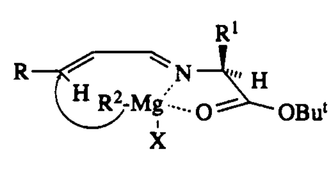

**Figure 9**

diasteriomeric aldehyde (**157**) in refluxing THF presumably results from a thermal isomerization of the (*Z*)-magnesioenamine (**155**), followed by methyl iodide alkylation.

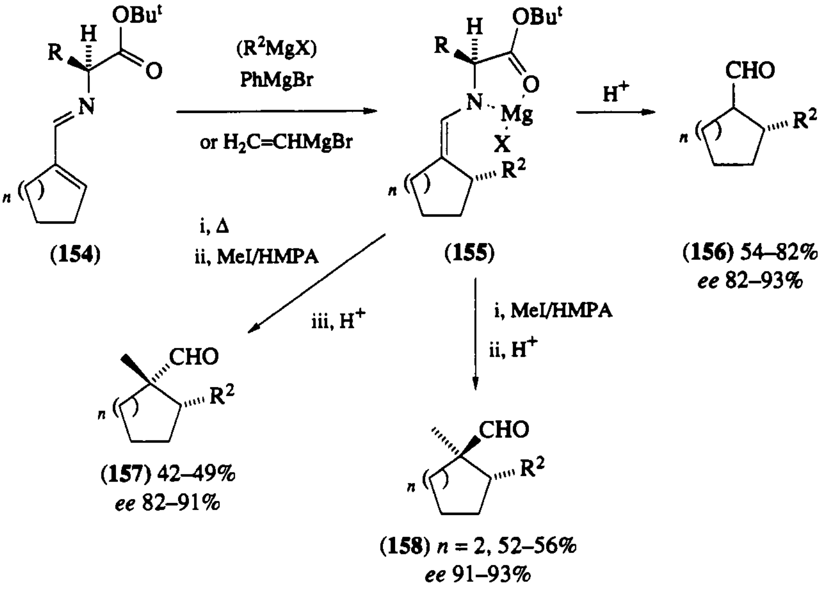

**Scheme 28**

### 1.12.7.2 2-Azadienes

Metalloenamines produced in the addition of organometallic reagents to 2-azadienes have synthetic advantages over related enolates and enamines since they are formed regioselectively, exhibit a low tendency to suffer equilibration by proton transfer processes and are very nucleophilic. Wender and Eissenstat[108] have shown that *N*-allylic and α,β-unsaturated imines undergo facile prototropic isomerization to *N*-alkenylimines (2-azadienes) in the presence of potassium *t*-butoxide. Addition of organolithium reagents to *N*-alkenylimines (**160**) provides in high yield a regiospecific generation of lithioenamine (**161**), which can be smoothly alkylated or condensed with aldehydes (directed aldol condensation) (Scheme 29).[109] A potential limitation of this methodology, involving the existence of unfavorable α,β-unsaturated-*N*-alkenylimine equilibriums (*e.g.* **159** *versus* **160**, can be circumvented by manipulating aromatic ring substitution (*p*-OMe substituent favors azadiene formation).

The one-pot procedure involving the *in situ* generation of metalloenamines has been utilized by Martin *et al.* in the synthesis of the cyclohexenone (**164**); Scheme 30).[110]

### 1.12.7.3 Aromatic Aldimines

Gilman *et al.*[111] first investigated the 1,4 addition of Grignard reagents to benzophenone anil under forcing conditions. Meyers *et al.*[20] have shown that conjugative addition of organometallic reagents to 1-naphthylimines provides an alternative to naphthyloxazolines[21,22] for the preparation of substituted dihydronaphthalenes. Treatment of organolithium reagents (R = Pr^i, Bu^n, Bu^t) with *O*-*t*-butylvalinol-derived imine (**12**),[20] followed by a methyl iodide quench, generates (**165**) in >95% *ee* (Scheme 31). Addition to (**12**; Figure 10) is consistent with a chelation-mediated (butoxy moiety) delivery of the organolithium reagent, paralleling the stereochemical course of the valinol-derived aldimine additions described by

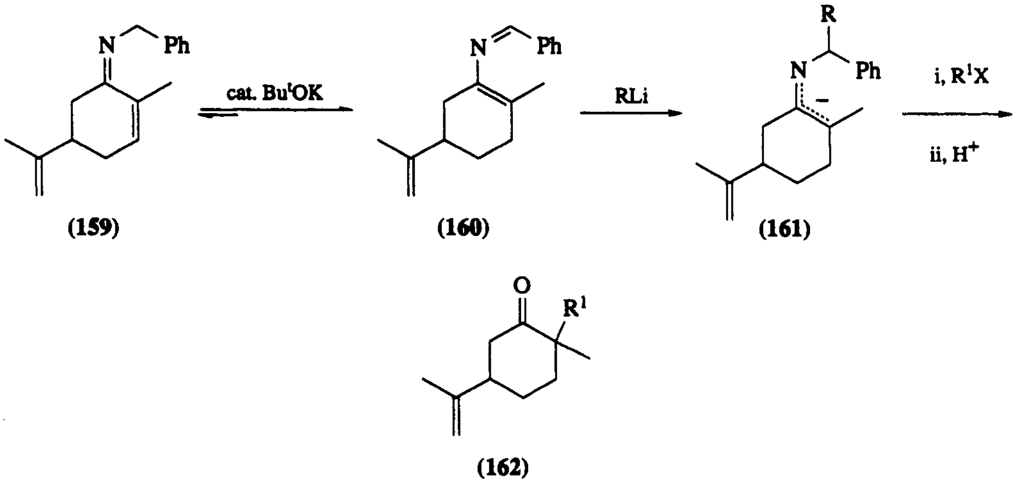
cat. Bu$^t$OK
RLi
i, R$^1$X
ii, H$^+$
(159)
(160)
(161)
(162)

Scheme 29

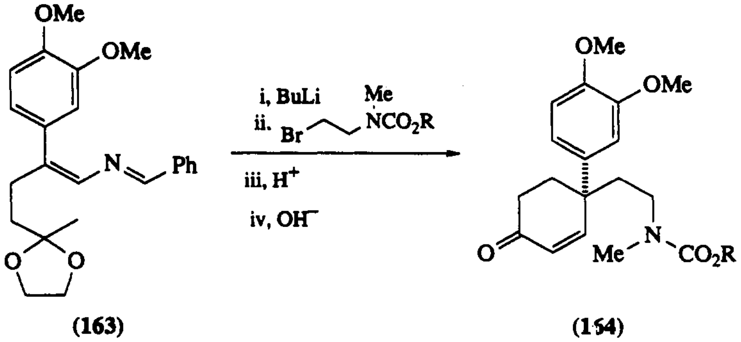
i, BuLi
ii. Br NCO$_2$R Me
iii, H$^+$
iv, OH$^-$
(163)
(164)

Scheme 30

Takahashi and Suzuki (equation 4).[14] The use of methyl-, benzyl- and 2-propenyl-lithium gave exclusive 1,2-addition. Demonstration that this methodology can be extended to 2-naphthyl, 3-pyridyl and 3-quinolyl aldimines (paralleling oxazoline chemistry)[21,22] has not been reported.

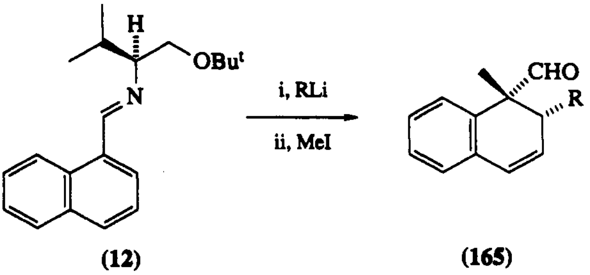
i, RLi
ii, MeI
(12)
(165)

Scheme 31

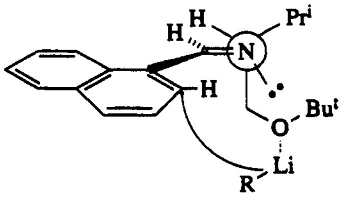

Figure 10

## 1.12.8 ORGANOMETALLIC ADDITIONS TO OXIMES AND OXIME ETHERS

In addition to providing hydroxy (alkoxy) amines, the reaction of oximes[112] or oxime ethers[107] with organometallic reagents can generate additional products. The propensity for proton abstraction α to the carbon–nitrogen double bond, the existence of mixtures of (*E*)- and (*Z*)-oxime isomers, the lability of the nitrogen–oxygen bond coupled with the poor oxime reactivity all contribute to the variability of this reaction.

### 1.12.8.1 Aldoxime Ethers/BF$_3$-Activated Oxime Ethers

Treatment of benzaldehyde oxime ether (**166**) with butyllithium (pentane/–10 °C) demonstrates the complexity of the reaction (Scheme 32) as the desired alkoxyamine (**167**; R = Bu) is accompanied by other oxime-derived side products[113] (entry 1, Table 12). Selectivity is reagent/solvent dependent as allyl Grignard (ether),[113] allylzinc bromide (THF),[113] and butyllithium (THF)[114] treatment produce predominantly amine (**171**; R = allyl) (the Beckmann rearrangement derived product), alkoxyamine (**167**; R = allyl) (the oxime addition product) and ketone (**169**; R = Bu) (the nitrile-derived product), respectively (entries 2–4, Table 12).

**Table 12** Addition of Organometallic Reagents to Benzaldehyde Oxime

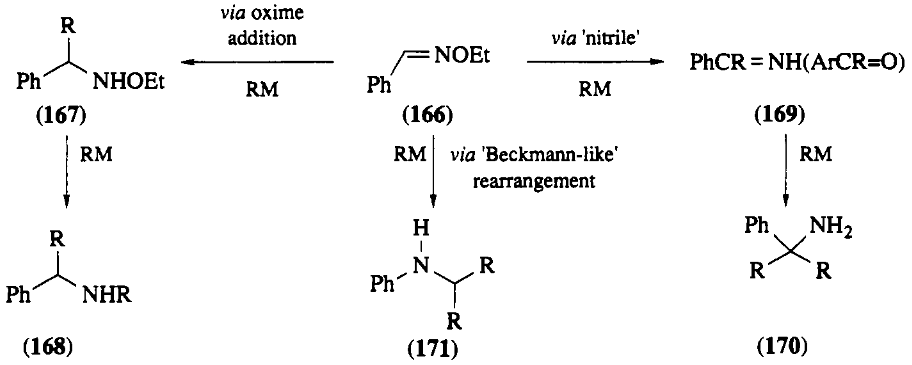

**Scheme 32**

| *Entry* | *Organometallic Reagent (RM)* | *R* | *(167)* | *(168)* | *(169)* | *(170)* | *(171)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| | | | *Products (%)* | | | | | |
| 1 | 3BuLi (pentane/–10 °C/1 h) | Butyl | 57 | 10 | 20 | 1 | 3 | 113 |
| 2 | 3Allylmagnesium bromide (ether/20 °C/16 h) | Allyl | | | | | 96 | 113 |
| 3 | 3Allylzinc bromide (THF/20 °C/16 h) | Allyl | 60 | | | | 7 | 113 |
| 4 | 2BuLi (THF/0 °C/1 h) | Butyl | | | 80 | | | 114 |

The addition of organometallic reagents to formaldoxime ethers[115] has been employed to incorporate aminomethyl substituents. Lithium carbanions add rapidly (–40 °C) to formaldoxime ether (**172**) to generate lithium alkoxyamide (**173**); Scheme 33).[116] Lithium alkoxyamides (LiRNOR$^1$), in contrast to alkoxyamines (RNHOR$^1$), react under mild conditions with organolithium reagents (R$^2$Li) to provide amines (RNHR$^2$).[117,118] Displacement of the benzyloxy moiety of (**173**) with a second equiv. of organometallic reagent requires somewhat higher temperatures (0–40 °C) and thereby permits sequential addition of two different organolithium reagents. Benzyloxyamide (**173**) and secondary amide (**174**) can be protonated or quenched with typical acylating or alkylating agents.

Reaction with (**172**) and other aldoximes may require oxime activation, which can be achieved with the addition of 1 equiv. of BF$_3$·OEt$_2$.[119–121] Yields in the addition of organometallic reagents to substituted aldoximes are modest and are a function of the isomeric composition of the oxime ethers, as the (*Z*)-oxime isomers are reported to preferentially react with organolithium reagents (entries 1 and 2, Table 13).[120] The reaction has been employed for the preparation of 6-aminoalkyl-substituted pencillins (entry 3, Table 13).[119] Cyclic oxime ether additions have also been evaluated (entries 4 and 5, Table 13).[120,121] With the lability of the nitrogen–oxygen bond, addition to 5-substituted isoxazolines provides a potential avenue for stereospecific synthesis of substituted 3-aminoalcohols (entry 5, Table 13).

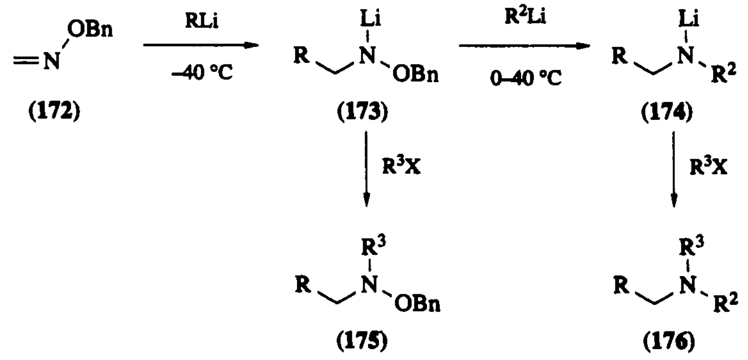

**Scheme 33**

**Table 13** The Addition of Organometallic Reagents to Oxime Ethers in the Presence of $BF_3 \cdot OEt_2$ [a]

| *Entry* | *Organometallic reagent* | *Oxime* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 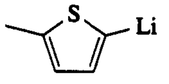 | 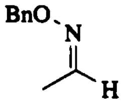 | 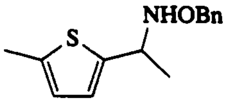 | 64 | 120 |
| 2 | 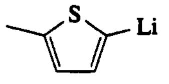 | 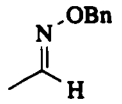 | 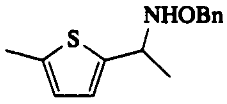 | 7 | 120 |
| 3 | 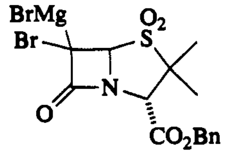 | 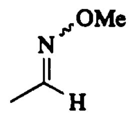 | 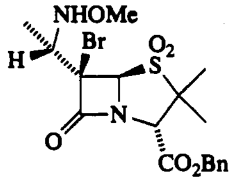 | 40 | 119 |
| 4 | 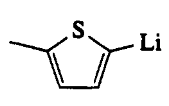 | 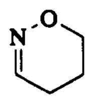 | 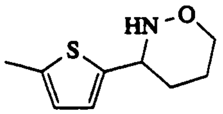 | 61 | 120 |
| 5 | $Me_3Si-C\equiv C-Li$ | 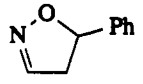 | 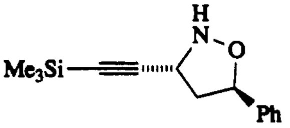 | 50 | 121 |

[a] THF/–78 °C.

Corey *et al.*[122] have elegantly exploited the ability of oxime ethers to stabilize carbanions *syn* to the *N*-alkoxy substituent in the boron trifluoride mediated addition of the mixed cuprate reagent derived from **(177)** to α,β-unsaturated oxime ether **(178**; Scheme 34). Stereochemistry is established by the ring *t*-butyldimethylsiloxy group. The addition does not occur in the absence of boron trifluoride. The alkylation of the cuprate adduct of **(178)** by iodoalkyne **(179)** provides the $PGE_2$ skeleton.

The condensation of organolithium reagents (2 equiv.) with glyoxylate-derived oxime ethers **(182)** provides a direct method for the synthesis of α-*N*-hydroxy amino acids (equation 22).[123] Both glyoxylic acid and glyoxylamide oxime ethers are compatible with this process. *N*-hydroxyaminoacetamides are also produced in low/moderate yields by the addition of isonitriles to oximes (oxime ethers) analogous to the four component condensation described by Ugi.[124]

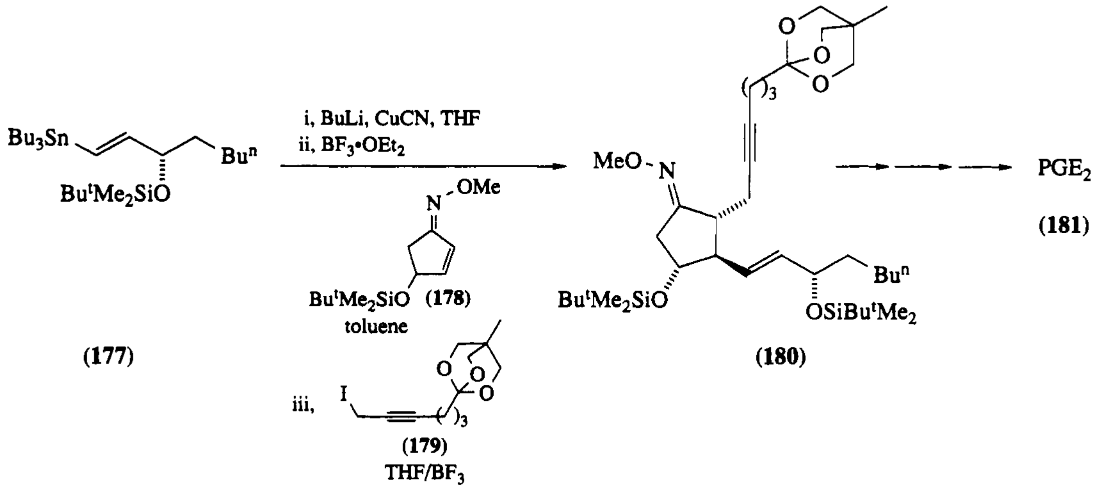
Bu3Sn
Bun
ButMe2SiO
(177)
i, BuLi, CuCN, THF
ii, BF3•OEt2
N-OMe
ButMe2SiO (178)
toluene
iii, (179)
THF/BF3
MeO-N
ButMe2SiO
OSiButMe2
(180)
PGE2
(181)

Scheme 34

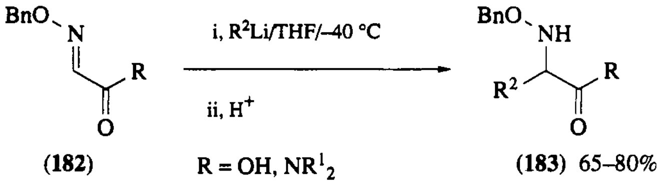
BnO
N
R
O
(182)
i, R2Li/THF/–40 °C
ii, H+
R = OH, NR12
BnO
NH
R2
(183) 65–80%

(22)

## 1.12.8.2 Ketoximes/Ketoxime Derivatives

The reaction of ketoximes with Grignard reagents has been extensively investigated and provides aziridines in low/moderate yields.[125–133] Examples are shown in Table 14. The stereochemical preference for substituted aziridines is consistent with the formation of an azirine intermediate (**185**; Scheme 35) followed by Grignard addition from the less-hindered side of the ring (entries 5 and 6, Table 14).[129] Azirine ring formation in turn occurs predominantly *syn* to the oxime hydroxy group (entries 1, 2, 3, 5 and 6, Table 14).[126,129] The regiospecificity of azirine formation is solvent dependent (entries 1 and 2, Table 14). Replacement of the oxime functionality with dimethylhydrazone methiodides[134] provides in many instances superior yields to substituted aziridines (entries 4 and 7, Table 14).

The acid-catalyzed Beckmann rearrangement of ketoximes provides a reliable synthetic tool for the synthesis of amides and lactams. A methyllithium-promoted Beckmann rearrangement of oxime tosylates to give substituted amines was reported by Gabel.[135] Yamamoto and coworkers[136] have in recent years increased the synthetic scope and utility of this rearrangement with the discovery of an organoaluminum-mediated reaction. Successive treatment of oxime sulfonates (**187**) with trialkylaluminum, which induces the Beckmann rearrangement and captures the intermediary iminocarbocation, followed by a progargylic or allylic Grignard reagent generates acyclic and cyclic amines (**190**) in synthetically useful yields (Scheme 36).

For example, treatment of oxime mesylate (**191**) with $Me_3Al$ (2 equiv.) in $CH_2Cl_2$ (–78 °C) followed by allylmagnesium bromide (2 equiv., –78 to 0 °C) yields amine (**192**; equation 23).[136]

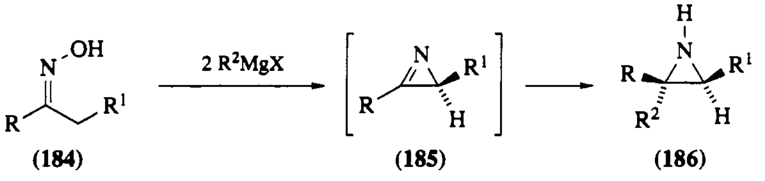
N-OH
R
R1
(184)
2 R2MgX
N
R1
R
H
(185)
H
N
R
R1
R2
H
(186)

Scheme 35

**Table 14** Preparation of Aziridines from Oximes (Quaternary Hydrazones) and Grignard Reagents

| *Entry* | *Substrate* | *Grignard* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 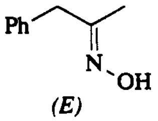 (*E*) | 5 EtMgBr, toluene | 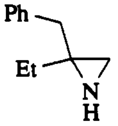 | 33 | 126 |
| 2 | 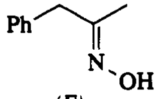 (*E*) | 5 EtMgBr, THF | 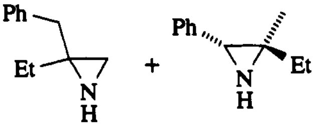 85% 15% | — | 126 |
| 3 | 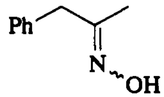 (*E*):(*Z*) = 7:3 | 5 EtMgBr, toluene | 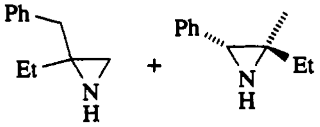 52% 48% | 46 | 126 |
| 4 | 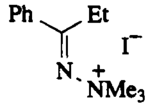 | PhMgBr | 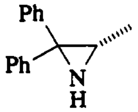 | 80 | 134 |
| 5 | 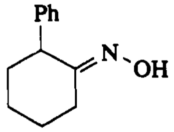 | 2 EtMgBr, toluene | 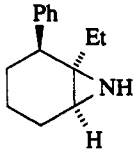 | 35 | 129 |
| 6 | 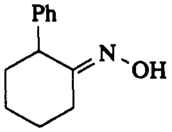 | 2 MeMgBr, toluene | 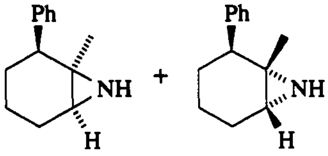 75% 25% | 53 | 129 |
| 7 | 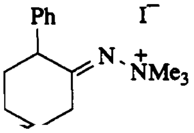 | MeMgBr | 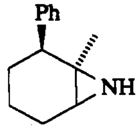 | 93 | 134 |

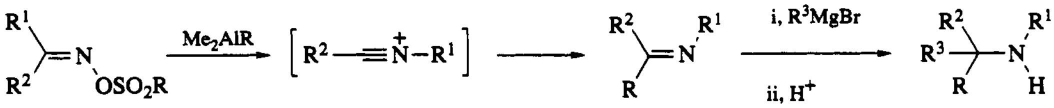

(187) (188) (189) (190)

**Scheme 36**

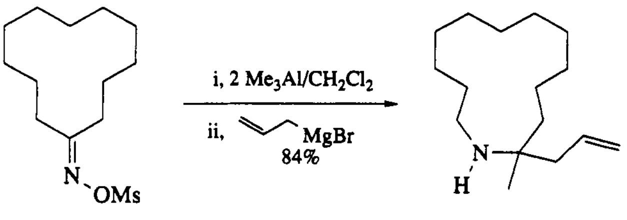

**(191)** **(192)** (23)

## 1.12.9 ORGANOMETALLIC ADDITIONS TO *S*-ARYL SULFENIMINES

The addition of organometallic reagents to *S*-aryl sulfenimines (**193**) yields, upon aqueous work-up, substituted primary amines (**195**). The scope of these additions has not been extensively explored, largely because of the difficulties encountered in sulfenimine preparation. Recently, the generation of sulfenimines from *N*,*N*-bis(trimethylsilyl)sulfenamides and aldehydes or ketones has provided a more convenient access to these molecules.[137]

Davis and Mancinelli[138] examined the addition of aryl- and alkyl-lithium reagents to nonenolizable and enolizable *S*-aryl sulfenimines (Table 15). The intermediate sulfenamides (**194**) contain a relatively weak sulfur–nitrogen bond, which is cleaved on aqueous work-up to generate amines (**195**) directly. The ability to add organometallic reagents to enolizable sulfenimines (in addition to providing good diastereoselectivity in several diallylzinc[139] and enolate condensations)[140] demonstrates synthetic advantages over the corresponding oximes or trimethylsilyl imines. On the other hand, sulfenimine condensations are plagued by the functionality's ambient electrophilicity, as demonstrated in the attempted condensation of sulfenimine (**196**) with methyllithium.[141] In this case only products indicative of nitrogen–sulfur bond cleavage (imine **197** and thioanisole) were formed. Hart and coworkers[140] have found that nucleophilic attack on the sulfenimine sulfur atom can be minimized by replacement of the *S*-aryl moiety with the bulky *S*-trityl substituent.

**Table 15** The Addition of Organometallic Reagents to *S*-Aryl Sulfenimines (**193**)

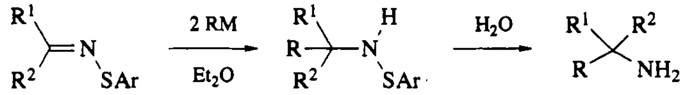

**(193)** **(194)** **(195)**

**Scheme 37**

| *Entry* | $R^1$ | $R^2$ | *RM (excess)* | *Product (195)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Ph | H | MeLi | PhCH(Me)$NH_2$ | 79 |
| 2 | Me | H | PhLi | PhCH(Me)$NH_2$ | 61 |
| 3 | Me | Me | $Bu^tLi$ | $Bu^tCMe_2NH_2$ | 43 |
| 4 | —$(CH_2)_5$— | | MeLi | 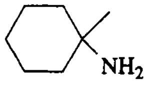 $NH_2$ | 68 |

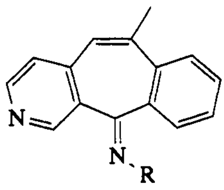

**(196)** R = SPh
**(197)** R = H

## 1.12.10 ORGANOMETALLIC ADDITIONS TO SULFONIMINES

Nucleophiles readily add to *N*-(arylsulfonyl)imines (**198**; Equation 24).[142] The reaction has limited synthetic utility for amine syntheses due to the harsh conditions required for the removal of the product's *N*-(arylsulfonyl) protecting group.

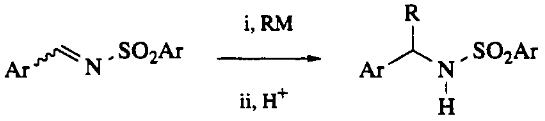

(24)

(**198**) (**199**)

Diaryl sulfamides (**201**) produced in the condensation of Grignard (primary, tertiary or aryl) and organolithium (primary or aryl) reagents with sulfamylimines (**200**) can, however, be hydrolyzed in refluxing aqueous pyridine to afford arylamines (**202**) in good (75–95%) overall yield (Scheme 38).[143]

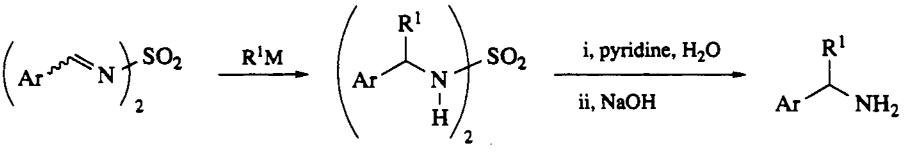

(**200**) (**201**) (**202**)

**Scheme 38**

## 1.12.11 ORGANOMETALLIC ADDITIONS TO *N*-TRIMETHYLSILYLIMINES

While organometallic reagents condense with *N*-substituted imines (Schiff bases) to afford, after hydrolysis, good yields of substituted amines, the reaction with *N*-unsubstituted imines (**203**)[26a] derived from ammonia (which are easily hydrolyzed and self condense) is not synthetically useful. As a result, the use of masked imines containing labile silicon– or sulfur–nitrogen bonds, such as *N*-trimethylsilylimines (**204**) or *N*-sulfenimines (**205**), has been explored.

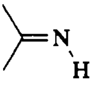

(**203**)

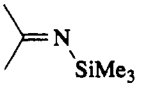

(**204**)

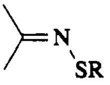

(**205**)

Demonstration that *N*-trimethylsilylimines (which are sometimes too unstable to isolate) can be generated and treated *in situ* with organometallic reagents has increased the scope and utility of these reactions for the preparation of substituted primary amines.[144] Nonenolizable aldehydes, for instance, condense with lithium bis(trimethylsilyl)amide to afford solutions of *N*-trimethylsilylaldimines. Hart[144] *et al.* and Nakahama and coworkers[145] have independently shown that trimethylsilylimines (**206**) react with organolithium and Grignard reagents to give, after aqueous work-up, primary amines (**207**) in moderate/excellent yields (equation 25). The isolation of phenyltrimethylsilane, albeit in low yield, in the addition of phenylmagnesium bromide to (**206**; $R^1 = H$) suggests that silicon attack may, in certain instances, compete with azomethine addition.

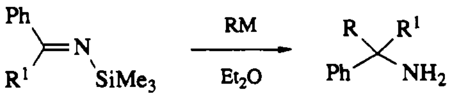

(25)

(**206**) (**207**)

$R^1 = H$; $R = Me, Bu^n, Ph, Bu^t$ (87–100%); $R^1 = Ph$; $R = Bu^t$ (68%)

Several other preparative methods, involving the condensation of (i) *N*-(trimethylsilyl)phosphinimines and carbonyl compounds;[146] and (ii) organometallic reagents with nitriles followed by quenching with chlorotrimethylsilane,[147] have been used for the preparation of other aldehyde- and ketone-derived silylimines. Organolithium reagents add to nonenolizable ketone-derived silylimines such as (**206**; $R^1$ = Ph) to generate tertiary carbinamines (**207**).[145]

Attempts to extend the organometallic addition reaction to *N*-trialkylsilylimines derived from enolizable ketones have been frustrated by difficulties encountered in the preparation of these silylimines (due to competitive enolization), in addition to the existence of a tautomeric equilibrium between desired silylimines and the corresponding enamines. As a result, addition products (formed in low yield) are accompanied by significant amounts of starting materials (presumably generated *via* enamine hydrolysis).[145] However, silylimines derived from enolizable aldehydes reportedly can be generated and trapped *in situ* with ester enolates to form β-lactams (18–60% yield).[148]

Iminium salts bearing a labile trimethylsilyl group can be generated *in situ* and undergo nucleophilic addition (see Sections 1.12.4.2 and 1.12.7.3). Bis(trimethylsilyl)methoxymethylamine (**75**), for example, has been used as a formaldehyde equivalent for the preparation of primary amines.[62,63] Cyclic imines, such as 3,4-dihydroquinolines, react with trimethylsilyl triflate (TMS-OTf) to provide reactive labile iminium salts (**55**), which condense with picoline anions.[49] The addition of nonstabilized Grignard and organolithium reagents to acyclic aromatic ketimines and aldimines, however, is often not facilitated by the presence of TMS-OTf.[149]

## 1.12.12 ORGANOMETALLIC ADDITIONS TO NITRONES

The highly polarized imine double bond of nitrones is responsible for the group's high electrophilic activity. The susceptibility of nitrones to nucleophilic addition has been exploited particularly in dipolar [3 + 2] cycloaddition reactions. The addition of organometallic reagents to acyclic and cyclic nitrones has been reviewed.[150] Grignards add to acyclic aldonitrones (**208**) bearing alkyl and aryl substituents to generate after work-up *N*,*N*-disubstituted hydroxylamines (**209**). *N*,*N*-disubstituted hydroxylamines can be further elaborated *via* oxidation[151,154] to substituted nitrones (**210**) or by reduction[152] to secondary amines (**211**). Acyclic ketonitrones are resistant to organometallic addition and have been reduced by Grignard reagents to the corresponding Schiff bases.[153]

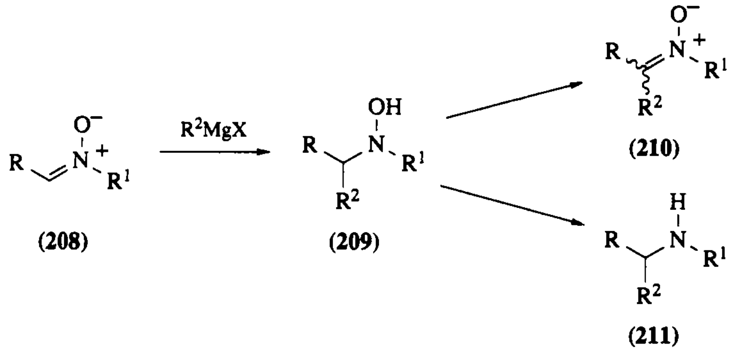

**Scheme 39**

### 1.12.12.1 Acyclic Chiral Nitrones

Chang and Coates[15] have examined the addition of organometallic reagents to nitrones (**212**; equation 26) containing a chiral nitrogen auxiliary (Table 16). These nitrones are prepared by the condensation of chiral *N*-alkylhydroxylamines with alkyl and aryl aldehydes and are assumed to exist in the (*Z*)-configuration. High diastereoselectivity (determined by $^1$H NMR) is obtained in the addition of organolithium and Grignard reagents to nitrones bearing a β-alkoxy group on nitrogen (entries 1, 2, 4, 5 and 6, Table 16).

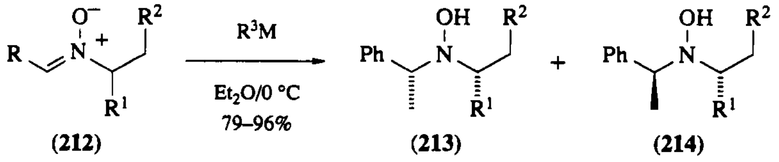

(26)

**Table 16** Additions of Organometallic Reagents to Racemic Nitrones (212; equation 26)

| *Entry* | | *Nitrone (212)* | | $R^3M$ | *(213) (%)* | *(214) (%)* |
|---|---|---|---|---|---|---|
| | *R* | $R^1$ | $R^2$ | | | |
| 1 | Me | Ph | OMe | PhMgBr | 97 | 3 |
| 2 | Me | Ph | OBn | PhMgBr | 90 | 10 |
| 3 | Me | Ph | H | PhMgBr | 54 | 46 |
| 4 | Me | $Pr^i$ | OMe | PhMgBr | 95 | 5 |
| 5 | Me | $Pr^i$ | OMe | PhLi | 94 | 6 |
| 6 | Ph | Ph | OMe | MeMgBr | 5 | 95 |
| 7 | Ph | $Pr^i$ | OTBDMS | MeMgBr | 92 | 8 |

The absolute configuration of the major products (**213**) or (**214**) can be predicted by the chelation model shown in Scheme 40, as the resident stereogenic substituent controls the facial selectivity in the organometallic additions. The diastereoselectivity is affected by the β-alkoxy functionality. The methoxy substituent is preferred, as the selectivity erodes with benzyloxy substitution (entries 1 and 2, Table 16) and is reversed with the bulky *t*-butyldimethylsiloxy group (entries 6 and 7, Table 16). As expected, selectivity is poor for nitrones devoid of β-alkoxy substituents (entry 3, Table 16). By appropriate nitrone/organometallic substitution, both diastereomeric products can be preferentially generated (entries 1 and 6, Table 16).

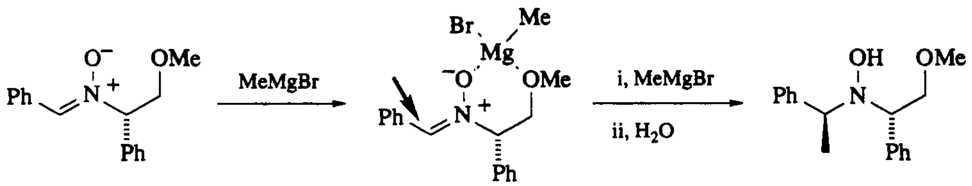

**Scheme 40**

Stereochemical control in the addition of Grignard reagents to chiral racemic *N*-(2-phenylpropylidene)alkylamine *N*-oxides (**215**) has been observed (equation 27).[154] Diastereoselectivity is modest (**216**:**217** = 2:1–5:1). The formation of hydroxylamines (**216**) as the major products is consistent with Felkin–Ahn Grignard addition (Figure 11).

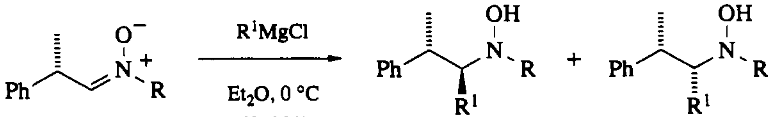

(**215**) (**216**) (**217**) (27)

$R = C_6H_{11}$, Me; $R^1$ = Me, Et, $Pr^i$

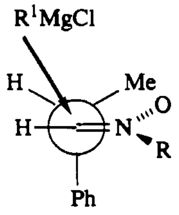

**Figure 11**

### 1.12.12.2 Cyclic Nitrones

Additions have been reported for both cyclic aldo- and keto-nitrones and have been utilized in the synthesis of structurally diverse heterocyclic systems (see Table 17).[155–157] The condensation of 3,4-dimethoxybenzyl Grignard with 3,4-dihydroisoquinoline *N*-oxide (entry 1, Table 17) provides an access to pellefierine alkaloids.[155] A synthetic use of cyclic ketonitrone condensations is demonstrated in the addition of allylmagnesium bromide to 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxides, as the resultant hydroxylamine product can be readily oxidized and trapped internally to generate useful bridged isoxazolidines (entry 2, Table 17). Nitrones need not be isolated for organometallic addition as Grignard reagents readily condense with dimeric nitrones (entry 3, Table 17).[156] In addition, the condensation of alkyllithiums and Grignards with heterocyclic *N*-oxides such as 2,4,4-trialkyloxazoline *N*-oxides followed by $Cu(OAc)_2$ exposure provides a flexible entry into biologically useful Doxyl (4,4-dimethyloxazolidine-*N*-oxyl) nitroxide spin labels (entry 4, Table 17).[157]

**Table 17** Additions of Organometallic Reagents to Cyclic Nitrones

| *Entry* | *Nitrone* | *Organometallic* | *Product* | *Ref.* |
|---|---|---|---|---|
| 1 | 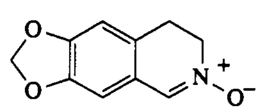 | 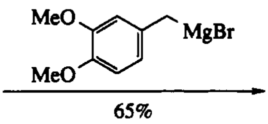 | 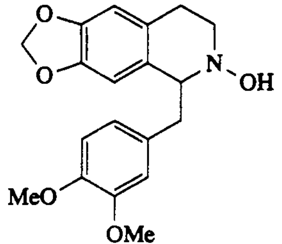 | 155 |
| 2 | 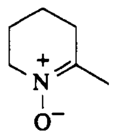 | 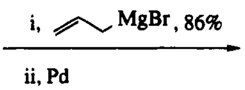 | 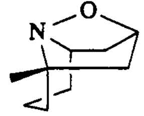 | 155 |
| 3 | 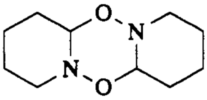 | 2PhMgBr<br>93% | 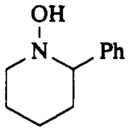 | 156 |
| 4 | 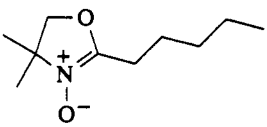 | i, MeLi<br>ii, $Cu^{2+}$ | 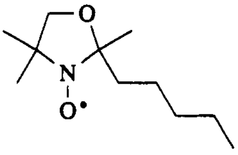 | 157 |

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# 1.13

# Nucleophilic Addition to Carboxylic Acid Derivatives

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## 1.13.1 INTRODUCTION

The reaction of carbon-based nucleophiles and carboxylic acid derivatives often presents a sophisticated problem in reaction chemoselectivity, especially when selective acylation of organometallics to form a ketone is required (equation 1). Historically, this transformation has been plagued by the formation of by-products due to subsequent nucleophilic addition to the desired product. A great deal of effort has been directed toward developing gentler techniques which avoid overaddition. Alternatively, the preparation of a ketone from a carboxylic acid equivalent often relies on a three-step approach, as shown in equation (2).

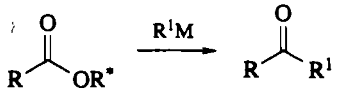

(1)

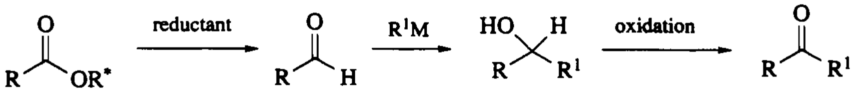

(2)

This familiar protocol begins with the selective reduction of an ester to an aldehyde. The aldehyde is then subjected to a nucleophilic addition with an organometallic to form a secondary alcohol (see Chapters 1.1 and 1.2 of this volume and Chapters 1.11 and 1.12, Volume 8). The required ketone is obtained through oxidation by one of several known reagents for the task (see Chapters 2.7 and 2.8, Volume 7). Although made simple by the ready availability of reducing reagents for the seemingly nontrivial first step and the facile oxidation depicted in the third step, it seems apparent that, even with high yields in each step, the overall transformation suffers from extended linearity. Considering methodology currently available, the development of a single-step general ketone synthesis through direct transformation of the acid derivative would be more expeditious. The goal of this chapter is to document the success of the latter approach, and to influence current practitioners to consider this strategy when designing synthetic approaches to target molecules.

The extent of the challenge can be rationalized as follows: reaction of a weakly electrophilic species such as an ester with a powerful nucleophile such as a Grignard reagent affords initially a ketone. By comparison with the ester, this highly electrophilic species cannot shield itself from the sea of excess nucleophile present in the reaction mixture and thus undergoes a second nucleophilic addition. For example, reaction of methylmagnesium bromide with ethyl acetate affords the intermediate 2-propanone only momentarily before succumbing to further nucleophilic attack with formation of *t*-butyl alcohol. It is often not possible to control a reaction of this type simply by the choice of solvents, temperature, order of addition or by the amount of the carbanionic reagent used. Although in most cases the desired product is a more reactive moiety than the starting carboxylic acid derivative, new reagents and substrates have been devised that allow for sophisticated manipulation of these reactivities. As we shall see, solutions to this problem are now abundant and our discussion will concentrate on methodology which has been developed recently for promoting ketone formation.

While most of the chemistry discussed in this chapter has been developed in the past decade, several important methods have withstood the test of time and have made important contributions in areas such as natural product synthesis. Methods such as cuprate acylation[1] and the addition of organolithiums[2] to carboxylic acids have continued to enjoy widespread use in organic synthesis, whereas older methods including the reaction of organocadmium reagents with acid halides, once virtually the only method available for acylation, has not seen extensive utilization recently.[3] In the following discussion, we shall be interested in cases where selective monoacylation of nonstabilized carbanion equivalents has been achieved. Especially of concern here are carbanion equivalents or more properly organometallics which possess no source of resonance stabilization other than the covalent carbon–metal bond. Other sources of carbanions that are intrinsically stabilized, such as enolates, will be covered in Chapter 3.6, Volume 2.

Related chemistry not covered in this chapter includes the acylation of stabilized organometallics and the broad category of enolate or metalloenamine *C*-acylation (Volume 2), the Claisen or Dieckman condensations (Chapter 3.6, Volume 2), the acylation of heteroatom-stabilized carbanions (Part 2, Volume 1), the Friedel–Crafts acylation of alkenes, aromatics or vinyl silanes (see Chapters 3.1 and 2.2, Volume 2), nor will methods that involve radical-mediated acylation be discussed in this section.

Finally, ketone formation by acylation of carbanions can proceed in several ways, including masking of the ketonic product until isolation, the use of carbanion equivalent reagents which do not readily react with the product or the use of substrates which are more reactive than the ketone towards acylation. An alternative approach involves substrates which selectively coordinate the organometallic and thus activate the substrate towards acylation. As we shall see, examples of successful acylation can occur even when the ketone is present in the reaction mixture. Additionally, transition metal mediated acylation provides a mechanistic alternative where carbon–carbon bond formation is the result of an electronic reorganization of the metal, driven by the stability of the particular oxidation state. This chapter will discuss these approaches in detail, as well as some other types of reactions that selectively result in the formation of ketones, by the presentation of examples from the natural products literature, and simultaneously review the scope and limitations of many of these methods.

## 1.13.2 ACYLATION OF ORGANOLITHIUM AND GRIGNARD REAGENTS

### 1.13.2.1 Acylation with *N*-Methoxy-*N*-methylamides

In 1981, Nahm and Weinreb reported an effective and versatile method for the direct acylation of unstabilized organometallics.[4] Organolithium and Grignard reagents, the most readily available nucleophilic agents in this class, have been used interchangeably in this ketone synthesis (equation 3). The approach has been successful in large part because of the exceptional stability of tetrahedral intermediate (**1**), the primary adduct from organometallic addition to *N*-methoxy-*N*-methylamides. The inertness of (**1**) prevents premature release of the ketone functionality and thus avoids products from secondary addition of the nucleophile. Subsequently, we shall discuss methods in which the ketone was released into the reaction mixture during acylation without seriously affecting the selectivity of acylation; however, the Weinreb approach has become one of the most generally effective for preventing overaddition. Furthermore, it is likely that prior coordination of the metal alkyl to the carbonyl and methoxyamide groups can serve to accelerate addition and limit enolization. Prior to this disclosure, few methods provided selective monoaddition of a nucleophile to carboxylic acid derivatives with stoichiometric quantities of both the acylating agent and organometallic.[4] The present method avoids the preparation of specialized organo-cadmiums[3] or -zincs for acylation, and complements the use of *S*-(2-pyridyl) thioates as acylating agents as demonstrated by Mukaiyama (see Section 1.13.2.2).

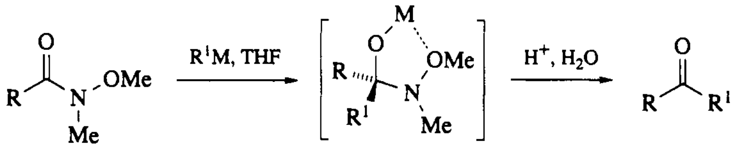

(**1**)

(3)

While nucleophilic addition to an *N*-methoxy-*N*-methylamide with an organolithium or Grignard reagent affords a ketone, the reduction of the same substrate may also be preformed with excess lithium aluminum hydride, or (more conveniently) DIBAL-H, thus providing an aldehyde directly. Table 1 shows the scope of both of these transformations.[4]

**Table 1** Addition of Organometallics to *N*-Methoxy-*N*-methylamides

| *R* | *$R^1M$* | *Equiv.* | *Reaction time* | *Temperature (°C)* | *Product* | *Yield (%)* |
|---|---|---|---|---|---|---|
| Ph | MeMgBr | 1.1 | 1.0 h | 0 | PhCOMe | 93 |
| Ph | MeMgBr | 75 | 1.0 h | 0 | PhCOMe | 96 |
| Ph | $Bu^nLi$ | 2.0 | 1.0 h | 0 | $PhCOBu^n$ | 84 |
| Ph | $PhC\equiv CLi$ | 1.1 | 1.0 h | 20 | $PhC\equiv CCOPh$ | 90 |
| Ph | $PhC\equiv CMgBr$ | 1.5 | 1.5 h | 65 | $PhC\equiv CCOPh$ | 92 |
| Ph | DIBAL-H | Excess | 1.0 h | −78 | PhCHO | 71 |
| Ph | $LiAlH_4$ | Excess | 8 min | −78 | PhCHO | 67 |

The requisite *N*-methoxy-*N*-methylamides may be prepared from acid chlorides by employing a slight excess of the commercially available *N*,*O*-dimethylhydroxylamine hydrochloride[5] in the presence of pyridine. They have also been prepared from acylimidazoles[6] and from mixed anhydrides of carboxylic acids.[7] Once prepared, these systems possess stability equivalent to that of most tertiary amides and, in this section, we shall discuss several cases where extensive manipulation of ancillary functionality was accomplished without interference from the amide.

Recently, Hlasta has shown that *N*-methoxy-*N*-methylamides may be prepared through the addition of organolithiums to *N*-methoxy-*N*,*N'*,*N'*-trimethylurea (2) or the symmetrical reagent (3) (Scheme 1).[8] Interestingly, it is possible in some cases to introduce a second alkyllithium in order to produce a ketone directly without isolation of the intermediate amide.

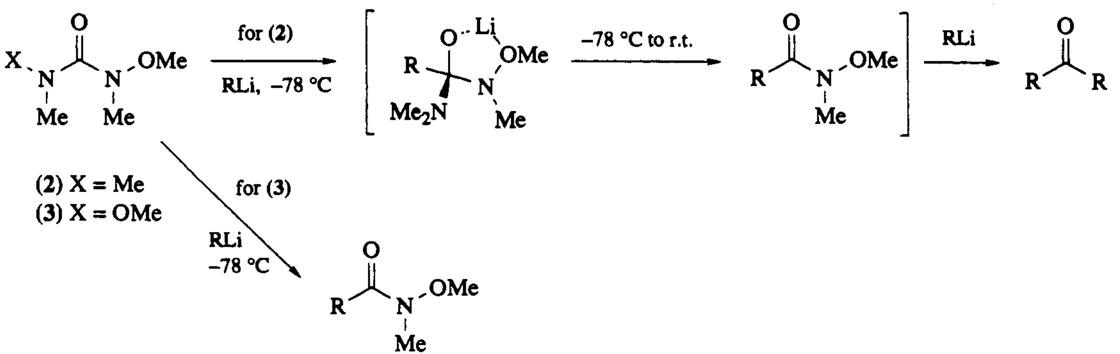

Scheme 1

As an extension of their chiral aldol and alkylation technology, Evans and coworkers have reported a variety of methods for cleaving and replacing the chiral oxazolidinone auxiliary once chain construction has been completed.[9] Included in this methodology was the direct transformation of a chiral imide to an *N*-methoxy-*N*-methylamide through the use of aluminum amides (prepared *in situ*).[10] This reaction has been shown to be rather general for complex substrates (Scheme 2).[11]

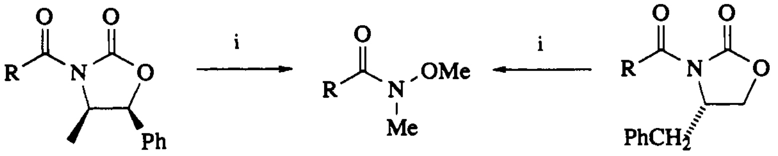

i, $MeONHMe{\bullet}HCl$, $AlMe_3$, $CH_2Cl_2$, –15 to 0 °C, >90%

Scheme 2

Since it had been determined that ketone or aldehyde functionality was not directly accessible from chiral *N*-acyloxazolidinones, the transamination–metal alkyl addition procedure provided a conveniently expeditious alternative. The first step, transamination, proceeded in high yield by introduction of the *N*-acyloxazolidinone into a solution of the aluminum amide in dichloromethane at –15 °C. The reaction is favored by the presence of α-heteroatom substituents and by β-alcohol functionality (aldol adducts). Acceleration of the transamination in the latter case is most likely due to formation of a chelated intermediate (5) which serves to activate only the exocyclic carbonyl towards attack (equation 4). Because of the indicated activation, these aldol adducts are often the best substrates for this permutation. The effectiveness of the transamination in the case of (4) is noteworthy, as retroaldol fragmentation of this substrate usually occurs under mild base catalysis.[11a]

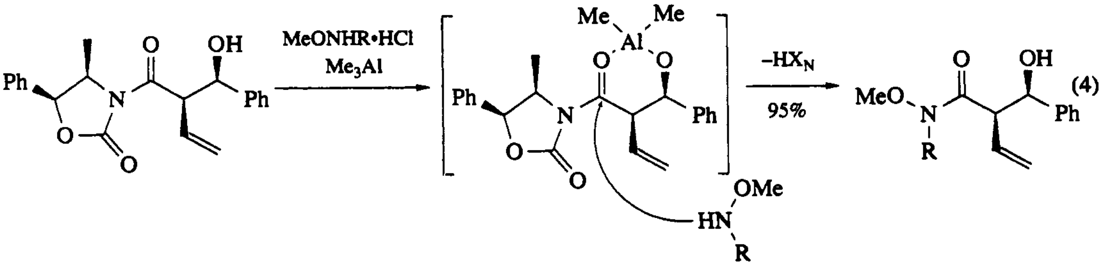

(4) (5)

In the case of a simple α-alkylated adduct such as (**6**), which cannot form a chelated intermediate of the type (**5**) or which does not contain α-heteroatom activation, and for cases that are especially hindered, attempted transamination often leads to competing attack upon the oxazolidinone carbonyl (equation 5).[15]

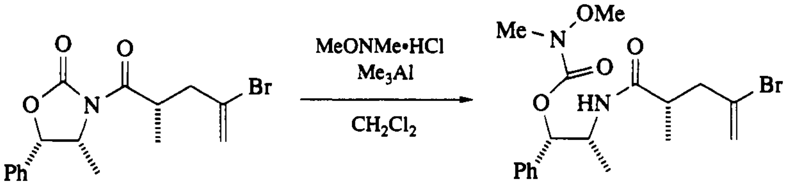

(**6**) (**7**)

(5)

The preparation of fully elaborated ketones and aldehydes was demonstrated by Evans in the context of the total syntheses of the antibiotic X-206[12] and the antitumor cytovaricin.[14] The exceptional stability of the *N*-methoxy-*N*-methylamide allows application of an array of functional group transformations on distant portions of the molecule before organometallic addition is carried out. Early intermediates towards X-206, compounds (**8**) and (**9**), readily suffer ozonolytic cleavage to the aldehyde amide (**10**). (Notice that either terminus of (**9**) may later be converted in a single operation to an aldehyde.) When imide or ester functionality is substituted for the *N*-methoxy-*N*-methylamide of (**8**), attempted protection of the secondary alcohol results in retroaldolization. However, *O*-benzylation was accomplished with intermediate (**8**) without competing retroaldol cleavage, even when the sodium aldolate was used! Intermediate (**10**) was subjected to the Wittig reaction in toluene and the resulting (**11**) was then reduced by DIBAL-H to aldehyde (**12**). No epimerization was observed at either stereogenic center during these modifications (Scheme 3).

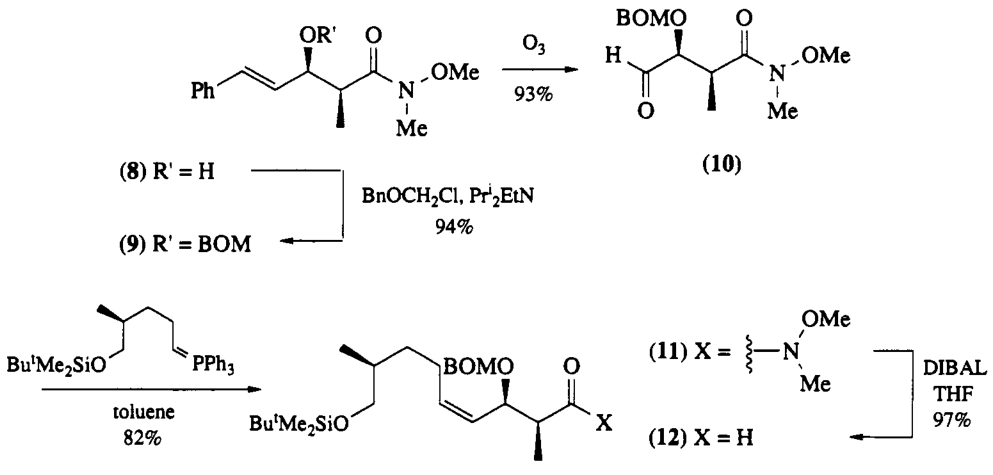

**Scheme 3**

The synthesis of cytovaricin passes through several highly functionalized intermediates including compound (**13**).[13] Glycosidation of the alcohol at C-3 was carried out with the *N*-methoxy-*N*-methylamide functionality in place. The addition of methyllithium and deprotection of the alcohol completes the formation of ketone (**14**) without competing epimerization or elimination (equation 6).

The acylation of vinylorganometallics was also possible with this technology. In equation (7), taken from the cytovaricin study, the acylation was completed directly after transamination of the starting imide (not shown), without racemization or retroaldolization and apparently without the necessity of protection of the β-hydroxy alcohol.[14]

A model study, directed at the total synthesis of X-206, showed that more functionalized vinyllithiums could be acylated in very high yield.[15] The product, an α-methylene ketone, does not suffer further attack by the vinyllithium reagent because the enone is concealed until after quenching of the reaction mixture.

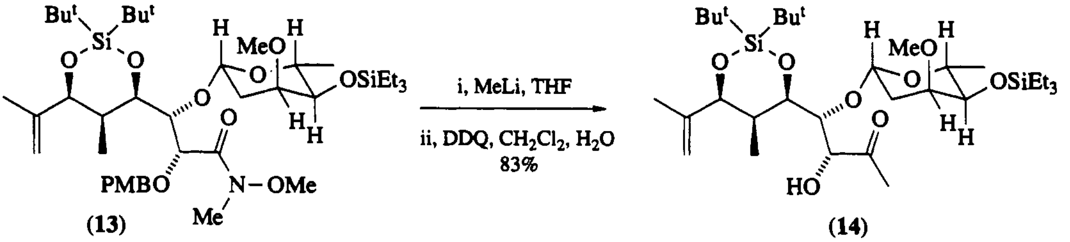
(13)
PMBO
N–OMe
Me
OSiEt$_3$
MeO
i, MeLi, THF
ii, DDQ, CH$_2$Cl$_2$, H$_2$O
83%
(14)
HO

(6)

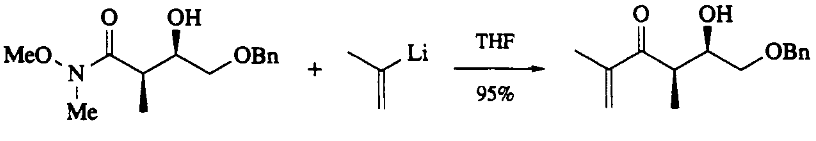
MeO
N
Me
OH
OBn
Li
THF
95%

(7)

The tetrahedral intermediate generated by organometallic addition thus provides '*in situ*' protection of the ketone (equation 8).

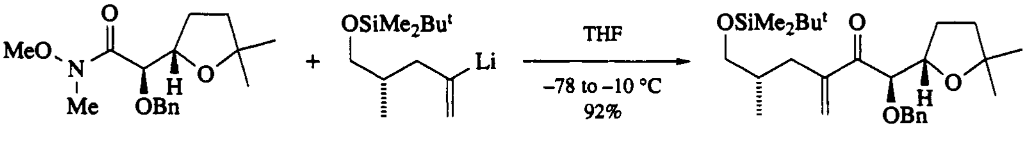
MeO
N
Me
OBn
OSiMe$_2$Bu$^t$
Li
THF
–78 to –10 °C
92%

(8)

Organometallic addition to the *N*-methoxy-*N*-methylamide (**15**) also affords an exceptionally stable tetrahedral intermediate (**16**) and carbonyl-protecting group, first used in the synthesis of X-206.[12] Deprotonation of the hydrazone in intermediate (**16**) was subsequently carried out with lithium diisopropylamide. The resulting dianion initiated a novel attack upon epoxide (**17**) and in the ensuing transformation was followed by tetrahydrofuran ring formation as depicted, in 71% yield, all in one pot (Scheme 4).

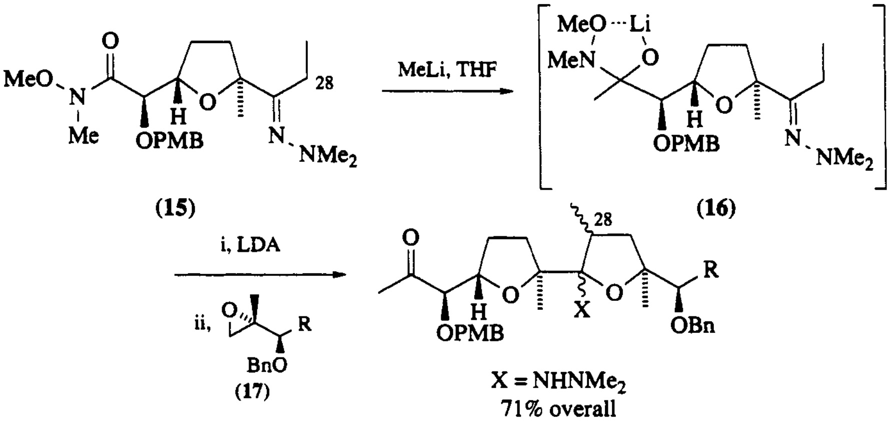
MeO
N
Me
OPMB
28
NMe$_2$
(15)
MeLi, THF
MeO···Li
MeN
OPMB
NMe$_2$
(16)
i, LDA
ii,
R
BnO
(17)
OPMB
OBn
X = NHNMe$_2$
71% overall

**Scheme 4**

A similar transformation was carried out on the less-oxygenated substrate (**18**) during the synthesis of a portion (C-10 to C-20) of the antibiotic ferensimycin (Scheme 5).[16]

The most complex example of this type of consecutive organometallic acylation, subsequent deprotonation, and tetrahydrofuran ring formation was recorded during the synthesis of the right hand portion of X-206 (Scheme 6).[12] The high overall yield obtained in this process is a testament to the method's generality.

This method has been applied by other researchers as well. The recent total synthesis of (–)-FK 506 by the Merck Process Group employed *N*-methoxy-*N*-methylamide functionality as a mild route to complex aldehydes (equation 9).[17]

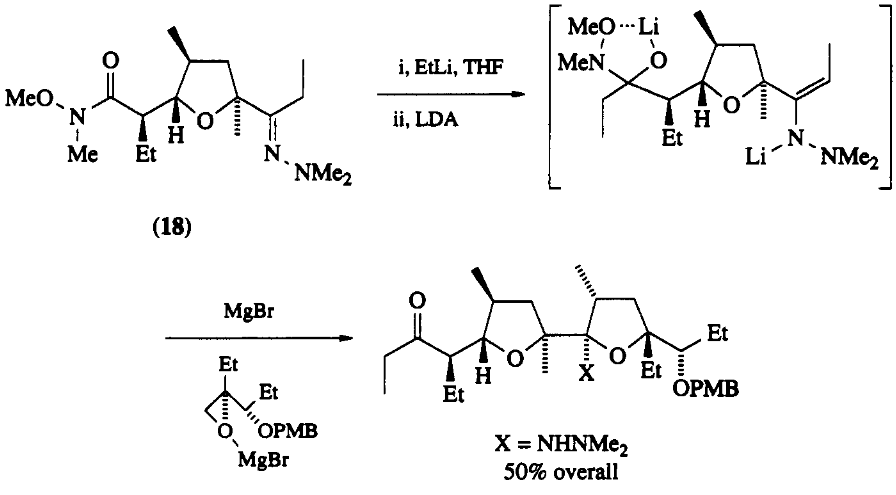
MeO
N
Me
O
Et
H
O
N
NMe2
i, EtLi, THF
ii, LDA
MeO···Li
MeN
O
Et
H
O
Li
N
NMe2
MgBr
Et
Et
O
OPMB
MgBr
O
Et
H
O
X
O
Et
Et
OPMB
X = NHNMe2
50% overall

(18)

**Scheme 5**

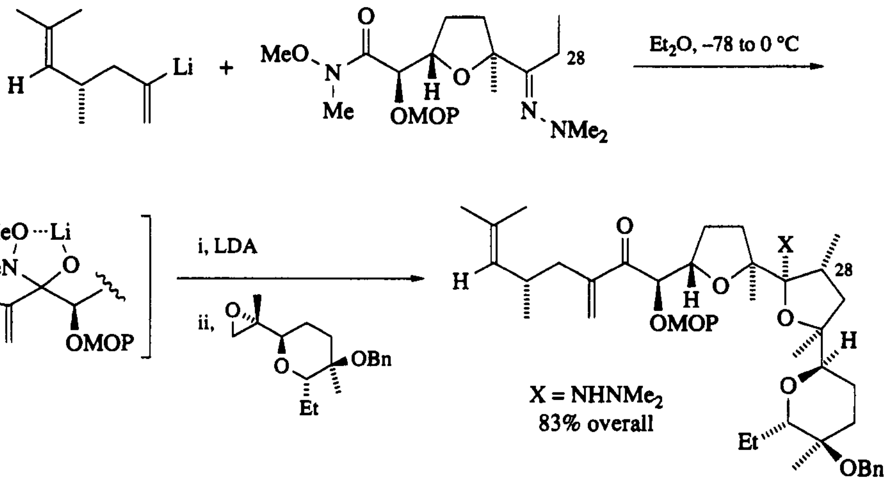
H
Li
+
MeO
N
Me
O
H
OMOP
O
28
N
NMe2
Et2O, –78 to 0 °C
MeO···Li
MeN
O
OMOP
i, LDA
ii,
O
O
OBn
Et
H
O
H
OMOP
O
X
28
O
H
O
Et
OBn
X = NHNMe2
83% overall

**Scheme 6**

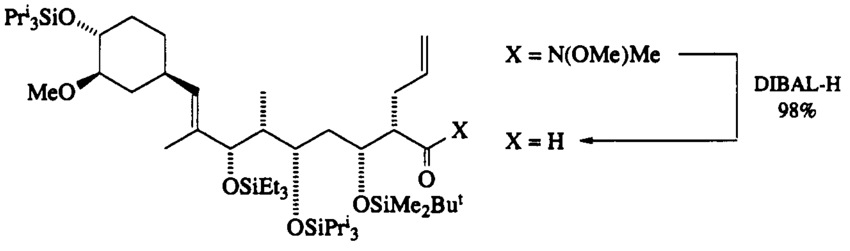
Pri3SiO
MeO
OSiEt3
OSiPri3
OSiMe2But
O
X
X = N(OMe)Me
X = H
DIBAL-H
98%

(9)

Patterson has prepared ethyl ketone (**20**) without racemization and in good overall yield by the sequence shown in Scheme 7. The preparation of (**20**) by standard organometallic addition to the corresponding aldehyde followed by Swern oxidation resulted in substantial racemization.[18]

By way of comparison, a very similar transformation has been accomplished without the use of the *N*-methoxy-*N*-methylamide. Hydrolysis of methyl ester (**19**) affords the corresponding carboxylic acid which was treated directly with methyllithium to afford a 70% overall yield of methyl ketone.[19]

The acetylation of a precursor to the natural respiratory toxin (±)-anatoxin-a was best achieved under the Weinreb protocol as depicted in equation (10). Other methods which relied on organocuprate or Grignard addition to thioacetates were totally unsuccessful. A proton-transfer side reaction consumed up

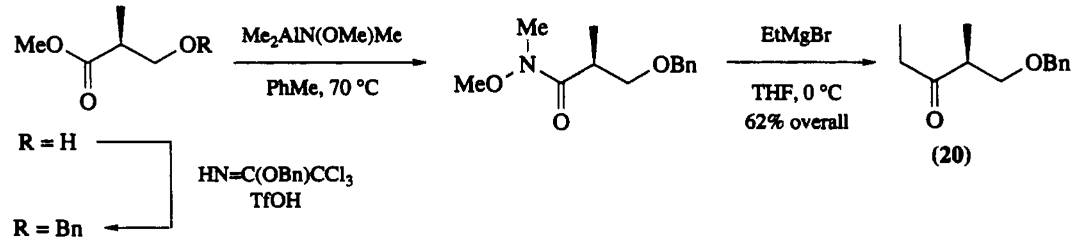
MeO
OR
O
R = H
R = Bn
Me₂AlN(OMe)Me
PhMe, 70 °C
HN=C(OBn)CCl₃
TfOH
Me
N
MeO
OBn
O
EtMgBr
THF, 0 °C
62% overall
OBn
O

(19)

(20)

**Scheme 7**

to 10% of the vinyllithium, formed by lithium–halogen exchange under standard conditions (>2 equiv. Bu$^t$Li), but it was not clear whether this was due to deprotonation of the acetylating agent or *t*-butyl bromide.[20]

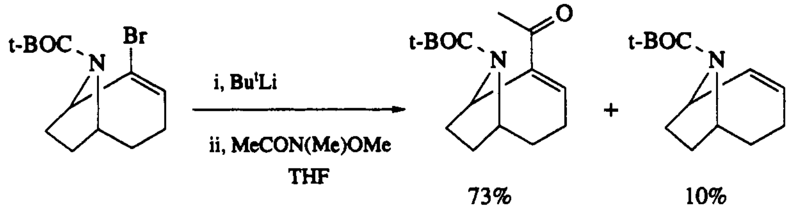
t-BOC
N
Br
i, Bu$^t$Li
ii, MeCON(Me)OMe
THF
O
+
73%
10%

(10)

Weinreb has reported the total syntheses of (+)-actinobolin and (–)-bactobolin from common intermediate (**21**). Both the reductive cleavage and Grignard addition proceeded in high overall yield (equation 11).[21]

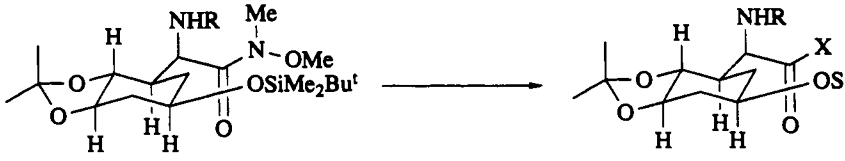
NHR
Me
N
OMe
OSiMe₂Bu$^t$
H
O
H
X

(11)

(**21**)

(–)-Bactobolin intermediate; MeMgBr, THF, 88% X = Me
(+)-Actinobolin intermediate; $LiAlH_4$, THF, 89% X = H

A highly selective acylation of assorted organometallics by β-lactam (**22**) was achieved through the use of the *N*-methoxy-*N*-methylamide. There was no attack at the β-lactam carbonyl and the overall yields were quite good (equation 12).[22]

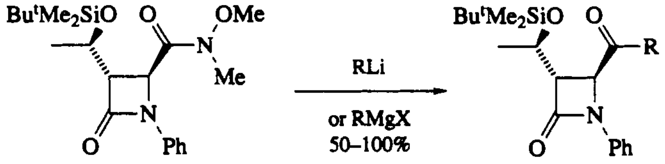
Bu$^t$Me₂SiO
O
OMe
N
Me
N
Ph
RLi
or RMgX
50–100%
R

(12)

(**22**)

Williams has reported that *ortho*-lithiated anisole may be acylated with the *N*-methoxy-*N*-methylamide of 2-(benzyloxy)acetic acid (equation 13) in higher yield than previously demonstrated with organocadmium reagents (90% *versus* 40%). The ketone (**23**) is an early intermediate in an approach to quinocarcin.[23] Acylation of lithium 3-lithiopropoxide, generated from the stannane, afforded a hydroxy ketone without racemization at the α-position (equation 14).[24]

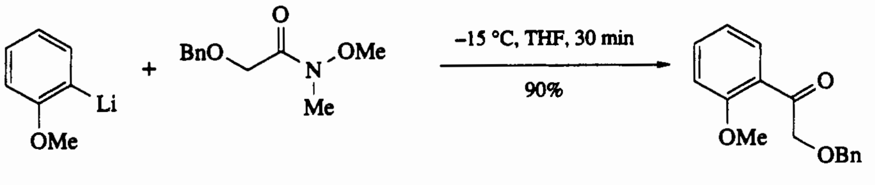

**(23)**

(13)

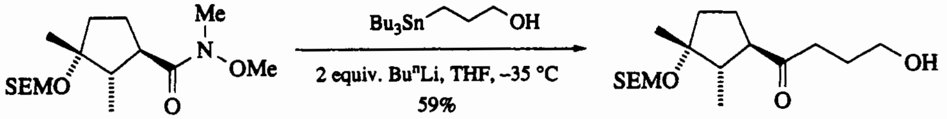

(14)

### 1.13.2.1.1 *Formation of alkynic ketones*

Alkynic ketones have been used extensively in natural product synthesis, due in large part to the contributions of Midland and coworkers and the development of general methods for enantioselective reduction of this moiety to afford optically active propargyl alcohols using chiral trialkylboranes.[25] Furthermore, the derived alkynic alcohol is a versatile system which can be manipulated directly into *cis*- or *trans*-allylic alcohols and as a precursor for vinylorganometallic species. This section will briefly cover progress made in the direct acylation of alkynic organolithiums with the acylation protocol developed by Weinreb (see also Section 1.13.2.7).

Several examples of alkynic ketone formation have been recorded since Weinreb's first examples.[4] A Diels–Alder strategy for the synthesis of mevinolin required the preparation of alkynic ketone (**24**). Standard methods, calling for the addition of the alkynide anion to an aldehyde followed by oxidation, lead to extensive degradation and by-product formation. The Weinreb methodology was clearly more effective (Scheme 8).[26]

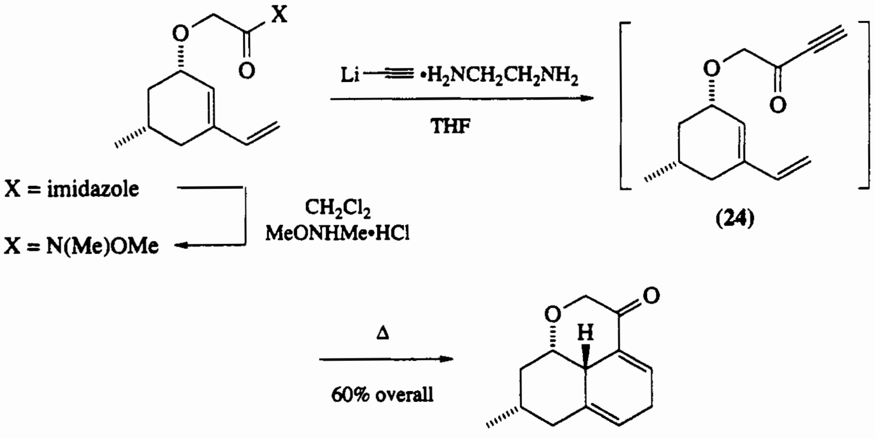

**(24)**

**Scheme 8**

Trost has prepared several alkynic ketones by direct acylation of *N*-methoxy-*N*-methylamides. Because of subsequent transformations on the product, the addition served as a method for introducing a dienylanion. Interestingly, the methoxyamide moiety is specifically activated towards nucleophilic addition, and the neighboring ester of the lactate system (**25**) was not disturbed during this transformation (equation 15). Prior coordination of the organolithium within the amide subunit and subsequent activated addition of the nucleophile serves as a reasonable explanation for the unusual selectivity of this process.[27]

Rapoport has compared the leaving-group ability of a variety of activated acyl groups towards metal alkynides and has demonstrated the usefulness of acylisoxazolidides such as (**27**) for the preparation of α′-amino-α,β-ynones (equation 16). Qualitatively, these acylating agents bear a strong resemblance to the simpler *N*-methoxy-*N*-methylamides (**26**) and appear to be as effective in acylation. The advantage of

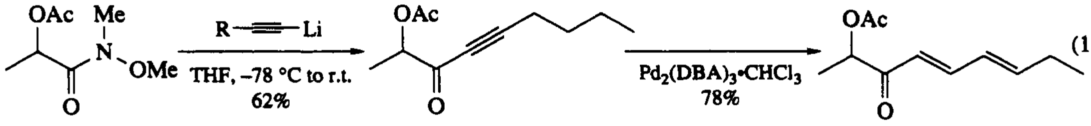

(25) (15)

the former substrate appears to stem from the crystalline nature of many of the resulting adducts. The ynones prepared by this route retain the optical purity of the *N*-carboethoxyamino acids. Interestingly, the study also found that the *N*-protected amino acids themselves were unreactive towards lithium alkynides, whereas alkyl- or alkenyl-lithiums added rapidly to these substrates (*vide infra*).[28]

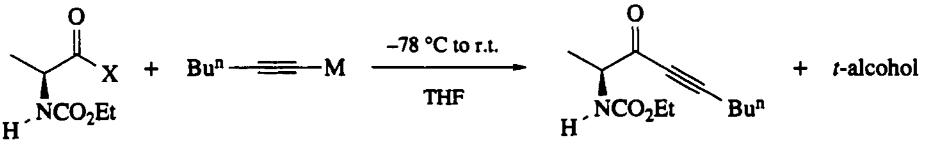

(16)

| X | M | % ynone | ynone:*t*-alcohol |
|---|---|---|---|
| X = 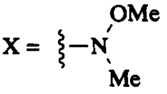<br>**(26)** | M = Li (250 mol %) | 84 | >100:1 |
| X = 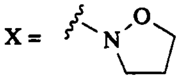<br>**(27)** m.p. = 95–96 °C | M = Li (250 mol %) | 88 | >100:1 |
| X = 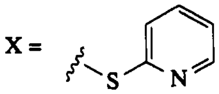<br>**(28)** | M = MgBr (200 mol %) | <1 | 1:20 |
| X = 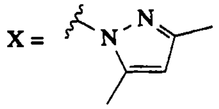<br>**(29)** | M = Li (100 mol %) | <5 | 1:10 |

Rapoport found that *S*-(2-pyridyl) thioates such as (**28**) did not function as selective acylating agents, and substantial amounts of tertiary alcohol were formed through overaddition (equation 16). Presumably, the tetrahedral intermediate, derived from nucleophilic addition to the *S*-(2-pyridyl) thioate, was not a stable entity in the reaction mixture. As will be discussed shortly, the lability of these intermediates had been recognized previously.[30] The novel dimethylpyrazolide moiety of substrate (**29**) also did not confer any additional stability to the tetrahedral intermediate and tertiary alcohol was the major product (equation 16). Tertiary amides, such as those derived from pyrrolidine or dimethylamine, were reactive towards lithium alkynides in the presence of $BF_3$, but analysis of the product indicated that it had undergone substantial racemization.[28]

Jacobi's synthesis of (±)-paniculide-A involves an intramolecular Diels–Alder reaction of the alkynic ketone (**31**). This compound was prepared in >90% yield (Scheme 9) by acylation of a lithium alkynide with the *N*-methoxy-*N*-methylamide (**30**). Addition of the anion to other derivatives related to (**30**) such as an acid chloride, a trifluoroacetic mixed anhydride, an acyl imidazole, *S*-(2-pyridyl) thiolates and a mixed carbonic anhydride (from ethyl chloroformate) led to either bis-addition or to proton abstraction. Notice should be made of the stability exhibited by the *N*-methoxy-*N*-methylamide group while the oxazole moiety was being introduced.[29]

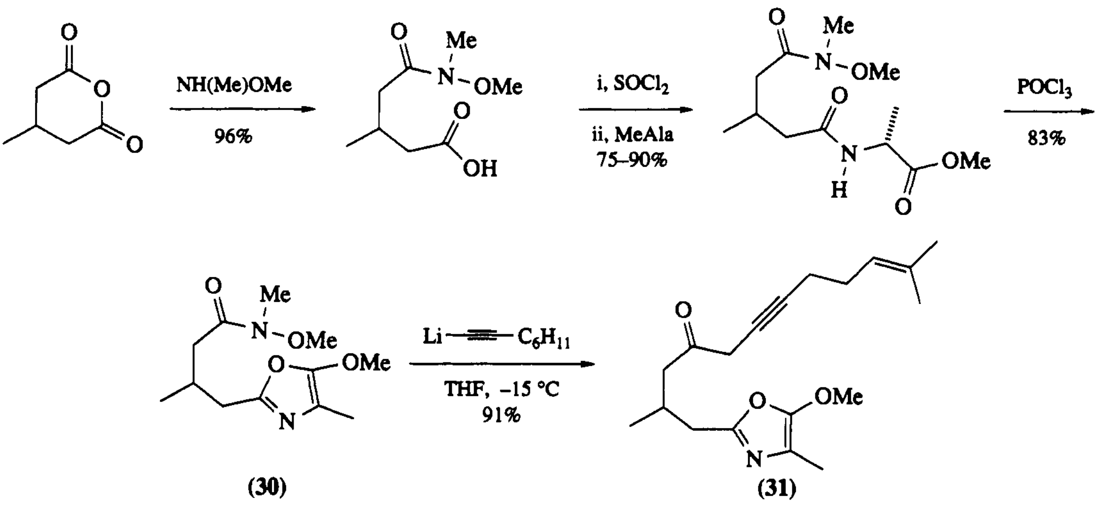

Scheme 9

### 1.13.2.2 Acylation with *S*-(2-Pyridyl) Thioates

During the previous discussion, mention was made of the acylation of Grignard reagents with *S*-(2-pyridyl) thioates as developed by Mukaiyama. In principle, this method also avoids the preparation of cuprates and organocadmiums in favor of the more readily available Grignard reagents; however, the approach often needs modification, usually through the use of copper(I) salts, in cases where overaddition is encountered (*vide infra*). Some other limitations of the Grignard addition have surfaced during the synthesis of complex natural products; however, the original method is successful in many cases and is exemplified by the preparation of an intermediate for the synthesis of *cis*-jasmone (equation 17).[30]

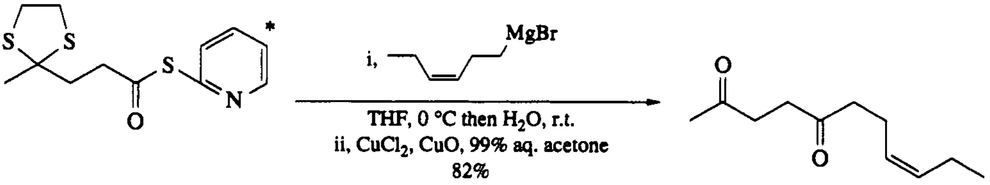

(17)

* from levulinic acid in 2 steps and 97% overall yield: i, $HS(CH_2)_2SH$; ii, 2,2′-pyr disulfide, $PPh_3$

The reaction depicted was run in THF at 0 °C, other solvents having been found to be inferior. The *S*-(2-pyridyl) thioates may be prepared through reaction of the corresponding acid chloride and 2-pyridinethiol in the presence of a tertiary amine. They are also available directly from carboxylic acids by reaction with 2,2′-dipyridyl disulfide (Aldrithiol-2) and triphenylphosphine.[31] In the case illustrated above, protection of the ketone would seem unnecessary if Grignard addition was selective for the thiol ester; however, the starting material, *S*-(2-pyridyl) γ-oxopentanethioate, is not stable to the lactonization shown in equation (18).

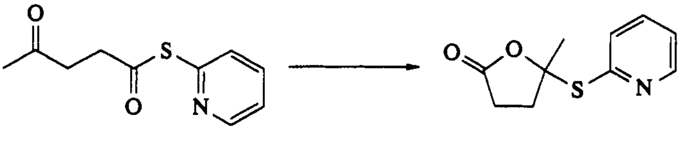

(18)

Mukaiyama has shown that in cases where lactonization was not possible, oxothioates can be used in the acylation process with selective addition only to the thiol ester (equations 19 and 20).[32]

Mechanistic studies have shown that the tetrahedral intermediate (33) is not stable during the course of the reaction (Scheme 10). By monitoring the reaction mixture with infrared spectroscopy, Mukaiyama demonstrated that the ketone is released before the quench and therefore could compete with the more reactive thiol ester in nucleophilic addition.[33] The authors postulate that selective addition occurs to the

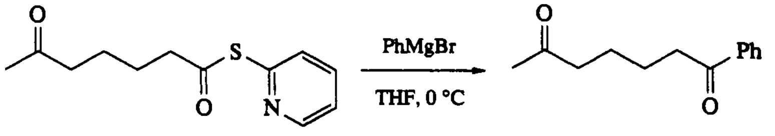
PhMgBr
THF, 0 °C
S
N
O
Ph

(19)

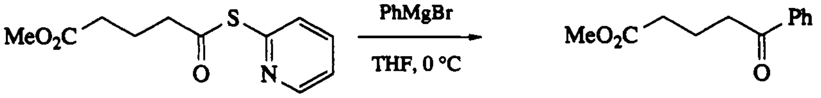
MeO2C
PhMgBr
THF, 0 °C
S
N
O
Ph

(20)

thiol ester because of the formation of the activated chelate (32); unfortunately, the apparently strong chelation provided by tetrahedral intermediate (33) is not sufficient to maintain the integrity of this species before quenching.[34] This is a conceptually different situation than was observed for Weinreb's method wherein the tetrahedral intermediate is exceptionally stable. In terms of the chemoselectivity of Mukaiyama's approach, the reactivity differences between the pyridyl thiol ester and other ketones have been shown to be substrate dependent and may not be general.

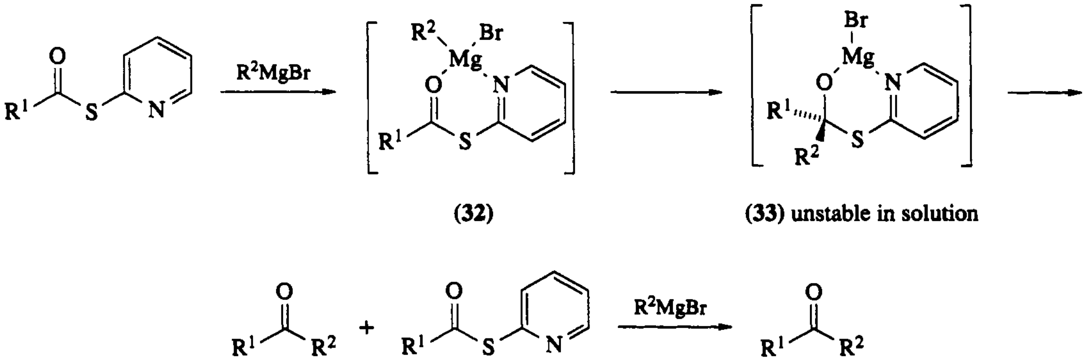
R2MgBr
R1
S
N
O
Mg
Br
R2

(32)

(33) unstable in solution

Scheme 10

The formation of a late-stage intermediate for the total synthesis of erythronolide B by Corey and co-workers takes advantage of this methodology. The coupling of pyridyl thiol ester (36) with Grignard reagent (35), prepared indirectly from iodide (34), affords the erythronolide B intermediate (37) in high yield without racemization or attack at the lactone (Scheme 11).[35] The corresponding reaction in the erythronolide A series which contains additional oxidation at pro-C-12, indicated on (37), results in overaddition (see Section 1.13.3.2). Another case of overaddition by functionalized Grignard reagents has been recorded by Still (see Section 1.13.3.1).

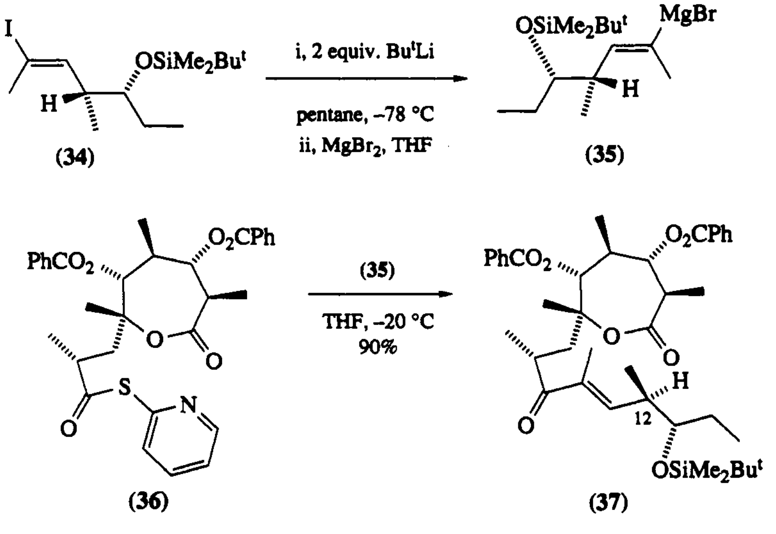
I
OSiMe2Bu^t
H
i, 2 equiv. Bu^tLi
pentane, –78 °C
ii, MgBr2, THF
MgBr
PhCO2
O2CPh
O
S
N
(35)
THF, –20 °C
90%
H
12

(34)

(35)

(36)

(37)

Scheme 11

The interesting antibiotics X-14547A and A-23187 (calcimycin) contain a novel 2-ketopyrrole moiety, which is apparently important for biological activity. Nicolaou has developed a simple method for incorporation of this unit into the sensitive intermediates required for preparation of the natural products.[36] Through use of the Mukaiyama protocol, formation of the 2-pyridyl thiol ester was effected with 2,2′-dipyridyl disulfide and triphenylphosphine. The reaction mixture was then cooled to –78 °C and was treated with a solution of pyrroylmagnesium chloride in THF (equation 21).

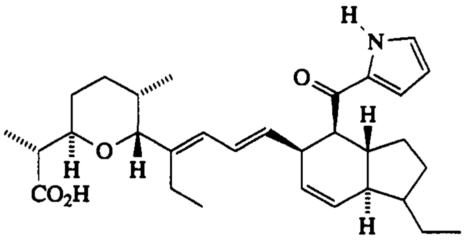
X-14547A

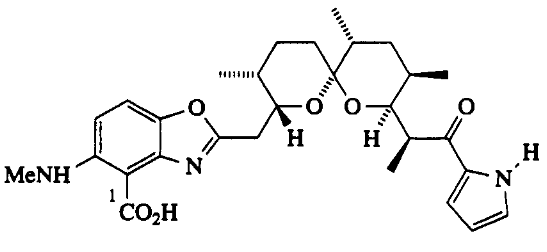
A-23187

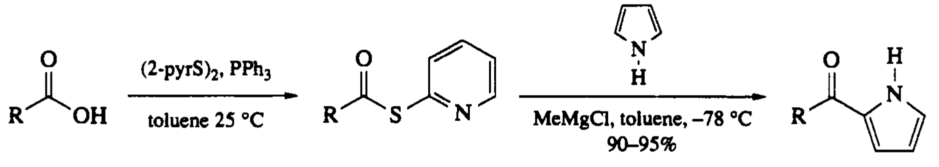

(21)

The use of the acid chloride instead of the 2-pyridyl thiol ester also results in formation of the 2-ketopyrrole functionality, but significant amounts of the 3-ketopyrrole isomer were also formed. Several rather complex substrates were used as acylating agents in this process with a high degree of success. Some examples of the 2-ketopyrroles that have been prepared are shown in Scheme 12.

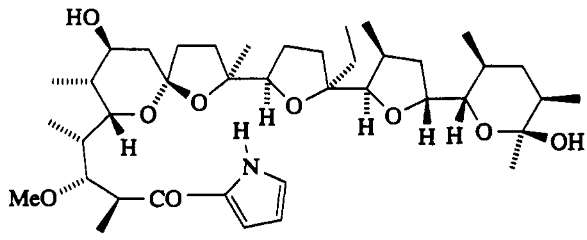
90% from monensic acid and pyrroylmagnesium bromide

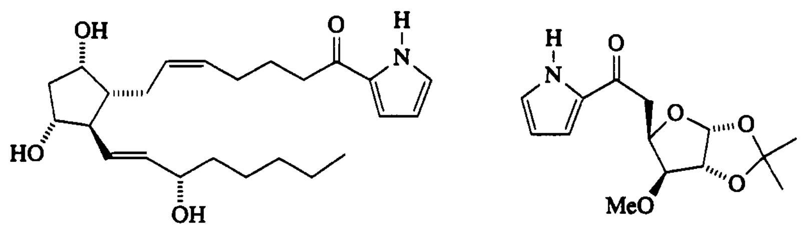
95% from PGF$_{2\alpha}$ 89% from carboxylic acid

**Scheme 12**

The synthesis of X-14547 A was completed by the transformation shown in equation (22).[37] Interestingly, the reaction proceeded without interference from the carboxylic ester group even though excess pyrrolylmagnesium chloride was used. At higher temperatures, it was possible to observe addition at both the desired position and at the distant carboxylic ester in 95% yield.

The antibiotic (–)-A-23187 (calcimycin) has been prepared by Boeckman using similar methodology (equation 23).[38] No racemization was observed at the position α to the thiol ester.

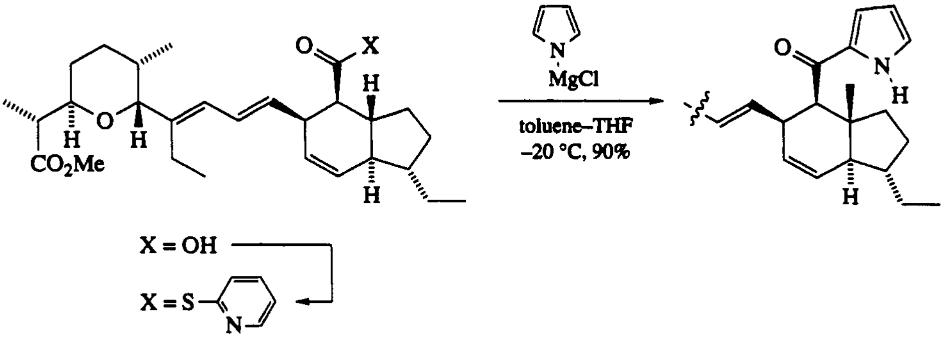
H
CO2Me
O
H
O
X
H
H
N
MgCl
toluene–THF
-20 °C, 90%
O
N
H
H
X = OH
X = S
N

(22)

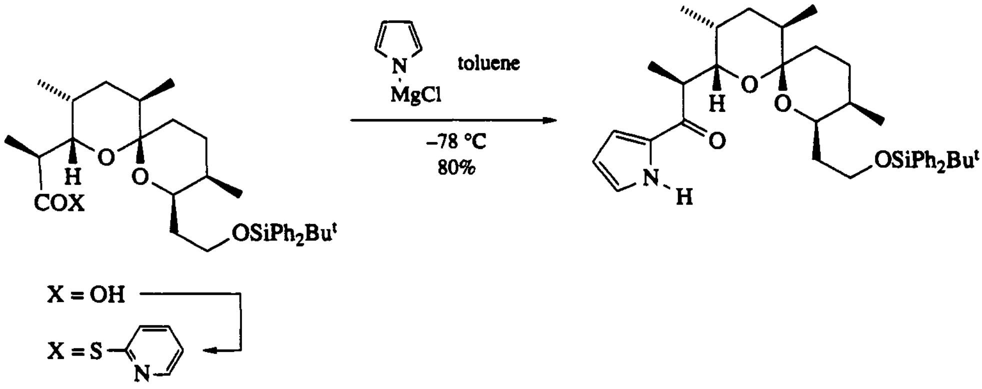
H
COX
O
O
OSiPh2Bu^t
N
MgCl
toluene
-78 °C
80%
H
O
O
O
N
H
OSiPh2Bu^t
X = OH
X = S
N

(23)

A similar transformation has been carried out by Nakahara and Ogawa; however, these workers reported no success in adding the pyrrole functionality to the penultimate precursor containing the benzoxazole ring.[39] Most recently, French workers have demonstrated the late stage introduction of the pyrrole unit by prior formation of the methyl ester at position 1 and use of a catalytic amount of copper(I) iodide in the acylation step.[40] Finally, for substrates that require protection at the ring nitrogen, acylation of 2-lithio-*N*-(*N′*,*N′*-dimethylamino)pyrrole has been demonstrated by Grieco. The reaction is exemplified by the synthesis of a model system for calcimycin (equation 24).[41] Although extra steps are involved in this transformation the overall yield is slightly higher than the previous case.

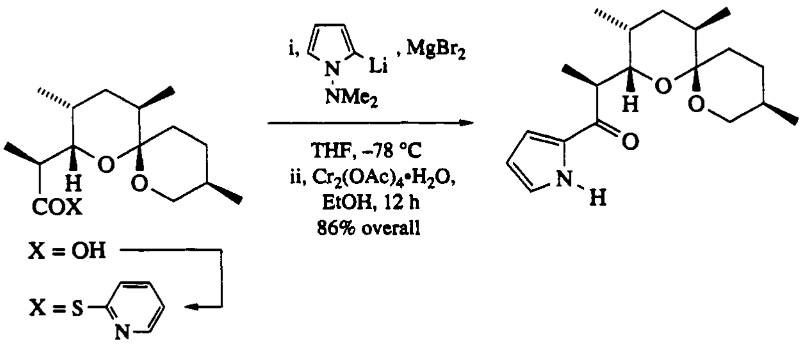
H
COX
O
O
i,
N
Li
, MgBr2
NMe2
THF, -78 °C
ii, Cr2(OAc)4•H2O,
EtOH, 12 h
86% overall
H
O
O
O
N
H
X = OH
X = S
N

(24)

### 1.13.2.3 Acylation by Carboxylic Acids

Methyl ketones are often directly prepared from carboxylic acids by reaction with methyllithium. Other simple alkyl ketones may also be prepared in the same fashion, making this a method that should be considered whenever these substrates are required.[42] An important demonstration of this protocol was reported by Masamune and coworkers in their synthesis of chiral propionate surrogates (Scheme 13).[43] The ethyl and cyclopropyl[44] ketones are important starting materials for macrolide total synthesis and have been prepared on a large scale. The overall yield for the ethyl ketone is 65% using 3.5 equiv. of ethyllithium without protection of the hydroxy group.

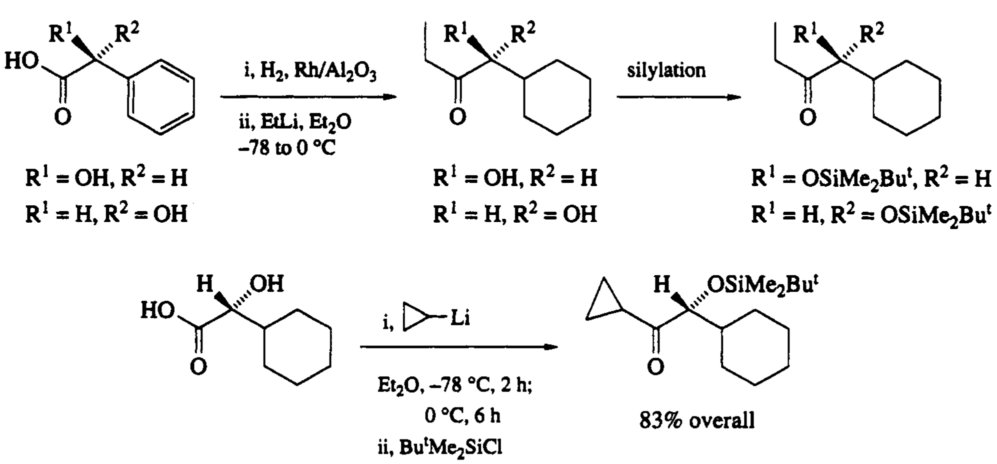

**Scheme 13**

Many experimental procedures have been discussed for effectively converting a carboxylic acid to a ketone through the use of organolithium reagents. House has advocated a procedure which begins with formation of the lithium carboxylate in dimethoxyethane. A slight excess of methyllithium is then added at 0 °C to form a 1,1-dilithium dialkoxide. Subsequently, the manner in which the geminal dialkoxide was quenched had a dramatic effect on the yield. Breakdown of the intermediate dialkoxide can in some instances precede protonation of the alkyllithium reagent. Rapid addition of the organometallic to the exposed ketone can then take place and result in the formation of a tertiary alcohol. For this reason, House favored inverse addition of the reaction mixture to a vigorously stirred solution of dilute hydrochloric acid at 0 °C. In this way high yields of the ketone may be obtained. This procedure may be even more important for reactions which are conducted with large excesses of alkyllithiums.[45] Excess methyllithium can also be quenched by addition of ethyl formate to the reaction mixture followed by aqueous acid, as was demonstrated by Mander.[46]

Other improvements in the standard methodology for addition of alkyllithiums to carboxylic acids and esters have been reported by Rubottom[47] and Cooke.[48] Both methods utilize trimethylsilyl chloride (TMS-Cl) at some point during ketone preparation; the former method of Rubottom introduces TMS-Cl once addition of the alkyllithium to the carboxylic acid is complete. This was done in an effort to trap residual methyllithium and allow the use of large excesses of reagent. However, it is known that most simple alkyllithiums react only sluggishly with trialkylsilyl chlorides,[49] thus the actual mechanism may involve silylation of the geminal dialkoxide. The method of Cooke uses a preformed solution of TMS-Cl and carboxylic ester. The reaction mixture was then treated with an alkyllithium whilst maintaining the reaction mixture at -78 °C. Previous use of carboxylic esters in this reaction often led to the formation of tertiary alcohols. The success of this procedure has been attributed to the formation of the *O*-silylated tetrahedral intermediate (**38**) which was apparently stable to the reaction conditions (Table 2).[47,48]

**Table 2** Use of Trimethylsilyl Chloride (TMS-Cl) in Acylation of Carboxylic Acids and Esters

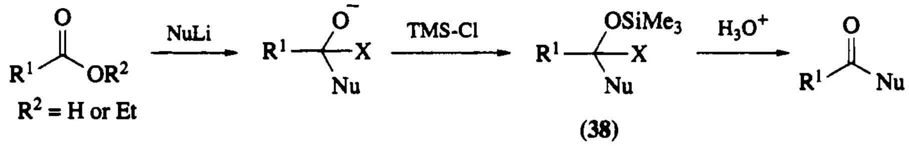

(**38**)

| *R*¹ | *X* | *Nu* | *Equiv. TMS-Cl* | *Temperature (°C)* | *Yield (%)* | | *Ref.* |
|---|---|---|---|---|---|---|---|
| | | | | | *R*¹*CONu* | *R*¹*(Nu)*₂*OH* | |
| Buⁿ | OEt | Buⁿ | 25 | -100 | 90 | 8 | 48 |
| Et | OEt | Buⁿ | 5 | -100 | 87 | 15 | 48 |
| Ph | OEt | Buⁿ | 5 | -100 | 82 | 21 | 48 |
| $C_6H_{11}$ | OTMS | Me | 20 | 0 | 92 | 2 | 47 |
| Ph | OTMS | Me | 20 | 0 | 97 | 0 | 47 |
| *p*-$OHC_6H_4$ | OTMS | Me | 20 | 0 | 87 | <5 | 47 |

The acylation of organolithiums with carboxylic acids has often been used in natural product synthesis. Certainly, the method is one of the easiest approaches available when analysis of a target structure indicates that organometallic acylation may be more efficient than the two-step nucleophilic addition to an aldehyde followed by oxidation. Many simple organolithiums are commercially available or may be prepared easily by standard methodology.[50] A case in which this plan was effective can be seen in Stork's synthesis of the corticosteroid ring system (C-11 oxygenated steroid) which embodied the transformations shown in equation (25).[51] Addition of the readily available lithium reagent proceeded in greater than 90% yield, reacting with both the acid and ketone functional groups. After an *in situ* dehydration, Diels–Alder ring closure afforded the penultimate precursor to the C-11 steroid system (equation 25). The addition of vinyllithium reagents to carboxylic acids was first reported by Floyd.[52] Interestingly, the latter investigation demonstrated that the reaction of vinyllithium with stearic acid actually had to be heated to 40 °C to achieve a 70% yield of product.

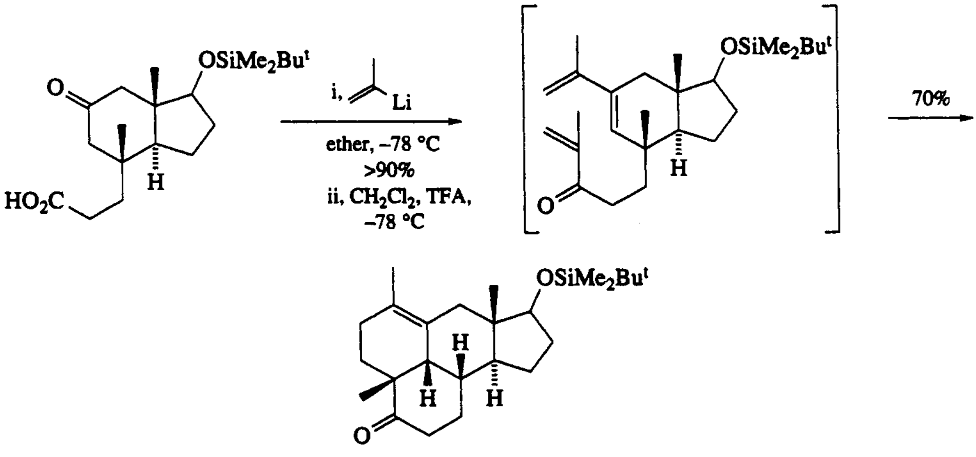

(25)

The intermediate 1,1-dialkoxide which was formed from the addition of ethyllithium to carboxylic acid (**39**) functioned as a masked form of a ketone, and facilitated a subsequent Wittig reaction on aldehyde (**40**; equation 26).[53]

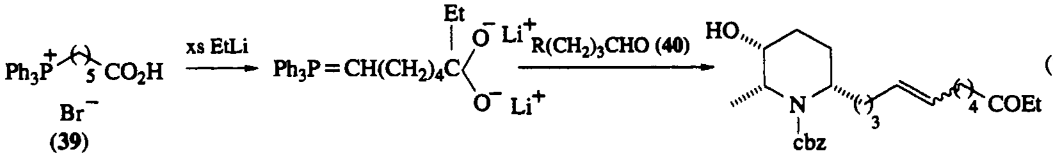

(**39**)

(26)

The well-known Parham cyclization of bromoaromatic carboxylic acid derivatives can be exemplified by the examples in equations (27)–(29). The reaction is usually run at very low temperature in ether or THF and provides surprisingly good yields of aromatic ketones. The method has been reviewed recently.[54]

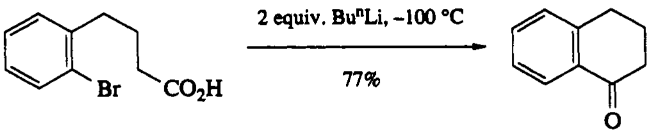

(27)

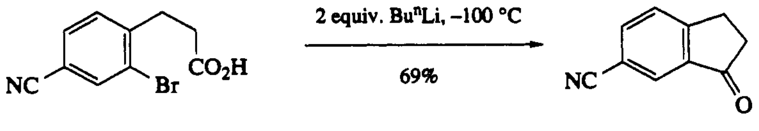

(28)

The simple homochiral adduct from Diels–Alder cycloaddition of (*R*)-pantolactone acrylate ester with cyclopentadiene was hydrolyzed and converted to the methyl ketone in 89% yield through addition of 3

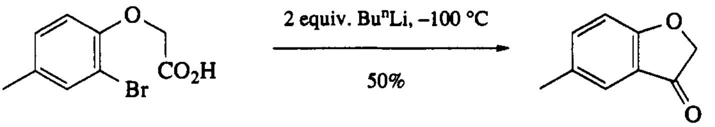

(29)

equiv. of methyllithium (equation 30). The reaction mixture was treated with TMS-Cl before addition of aqueous ammonium chloride under the conditions of Rubottom.[55]

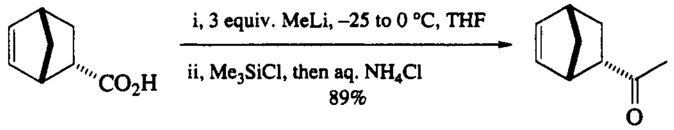
CO2H
i, 3 equiv. MeLi, –25 to 0 °C, THF
ii, Me3SiCl, then aq. NH4Cl
89%
O

(30)

Paquette's synthesis of africanol advanced through the α,β-unsaturated acid (**41**). Addition of 2.2 equiv of methyllithium followed by standard work-up gave a 71% yield of the methyl ketone (**42**; equation 31).[56]

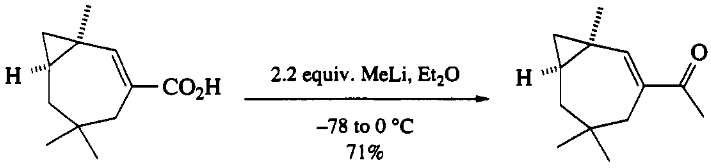

(31)

**(41)** **(42)**

There has been an isolated report dealing with the direct acylation of Grignard reagents by carboxylic acids mediated by nickel(II) salts. Large excesses of Grignard reagents must be used (6 equiv.) but the reaction can be run at room temperature with only 7 mol % Ni(DPPE)$Cl_2$. Normally, Grignard reagents are not useful in carboxylic acid acylation because the tetrahedral intermediate breaks down rapidly and the ketone is attacked by the organometallic. The role and generality of the nickel-mediated process has not been elucidated as yet.[57]

### 1.13.2.4 α-Amino Acids as Acylating Agents

α-Amino acids can be directly converted to ketones through the addition of alkyl- or vinyl-organometallics. This approach complements the addition of lithium alkynides to activated amino acid derivatives (Section 1.13.2.1.1) but is much simpler to carry out. Rapoport has shown that 3 equiv. of the organolithium are necessary to transform a protected amino acid such as *N*-(ethoxycarbonyl)alanine to an aryl or alkyl ketone. The first 2 equiv. of the organometallic function only as a base, resulting in dianion formation. This species is crucial to the process because further deprotonation is not possible and the intermediate is thus protected from racemization. *N*,*N*-Disubstituted amino acids were found to be racemized under the same conditions presumably because enolization was no longer impeded by nitrogen deprotonation. In the interest of economy, carboxylate anion formation may be carried out with *n*-butyllithium prior to addition of the desired nucleophile, but the acylation of a Grignard reagent requires prior formation of the lithium carboxylate to avoid breakdown of the tetrahedral intermediate in solution. The choice for nitrogen protection does not include the popular t-BOC or cbz groups but ethoxycarbonyl, benzoyl, acetyl and phenylsulfonyl may be used interchangeably (Table 3).[58]

The addition of allyllithium provides access to β,γ-unsaturated amino ketones or α,β-unsaturated amino ketones, depending upon the conditions chosen for work-up. In Scheme 14, simple interchange of the acidic reagent in the quench affected the positioning of the double bond.[58]

A stereospecific total synthesis of the antibiotic sibirosamine was carried out using this methodology. In the first step, addition of methylmagnesium iodide to *N*-(phenylsulfonyl)-L-allothreonine afforded the α-amino methyl ketone in modest yield.[59] This reaction afforded a diminished yield compared with *N*-(phenylsulfonyl)-L-threonine for some unexplained reason. A clever use of the L-amino acid serine allows for a straightforward preparation of D-amino acids such as D-dopa as is shown in Scheme 15.[60]

**Table 3** Formation of α-Amino Ketones from Various α-*N*-Acylated Amino Acids and Organometallic Reagents

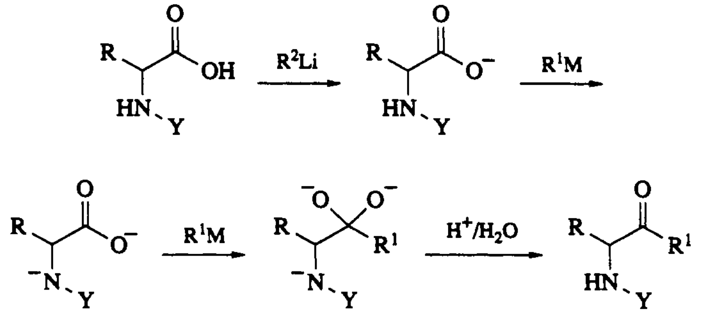
$R^2Li$
$R^1M$
$R^1M$
$H^+/H_2O$
R
$R^1$
HN
Y
OH
O

| *Compound* | *R* | *$R^1$* | *Y* | *$R^2$* | *M* | *Yield (%)* |
|---|---|---|---|---|---|---|
| a | Me | $CH_2CH{=}CH_2$ | COMe | $Bu^n$ | MgBr | 40 |
| b | Me | $CH_2CH{=}CH_2$ | COPh | $Bu^n$ | MgBr | 87 |
| c | Me | $CH_2CH{=}CH_2$ | $CO_2Et$ | $CH_2CH{=}CH_2$ | Li | 74 |
| d | $Pr^i$ | $CH_2CH{=}CH_2$ | $SO_2Ph$ | $Bu^n$ | MgBr | 62 |
| e | $MeSCH_2CH_2$ | $CH_2(CH_2)_2CH_3$ | $SO_2Ph$ | $Bu^n$ | Li | 54 |
| f | $MeSCH_2CH_2$ | $CH{=}CH_2$ | $SO_2Ph$ | $Bu^n$ | MgBr | 35 |
| g | $o$-$BnOC_6H_4CH_2$ | $CH_2CH{=}CH_2$ | $CO_2Et$ | $Bu^n$ | MgBr | 71 |
| h | $EtO_2CNH(CH_2)_3CH_2$ | $CH_2CH{=}CH_2$ | $SO_2Ph$ | $Bu^n$ | MgBr | 52 |
| i | $HOCH_2$ | $CH_2CH{=}CH_2$ | $SO_2Ph$ | $Bu^n$ | MgBr | 53 |
| j | $HOCH_2$ | $CH{=}CH_2$ | $SO_2Ph$ | $Bu^n$ | MgBr | 48 |

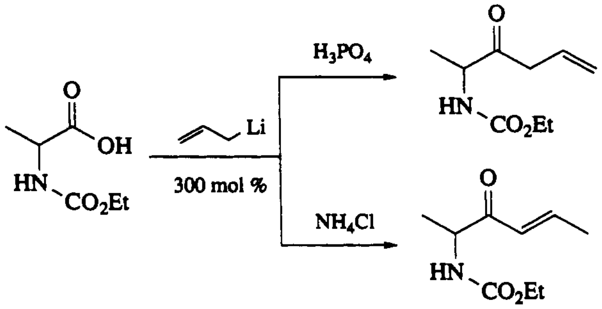
$H_3PO_4$
Li
300 mol %
$NH_4Cl$
OH
HN
$CO_2Et$
O

**Scheme 14**

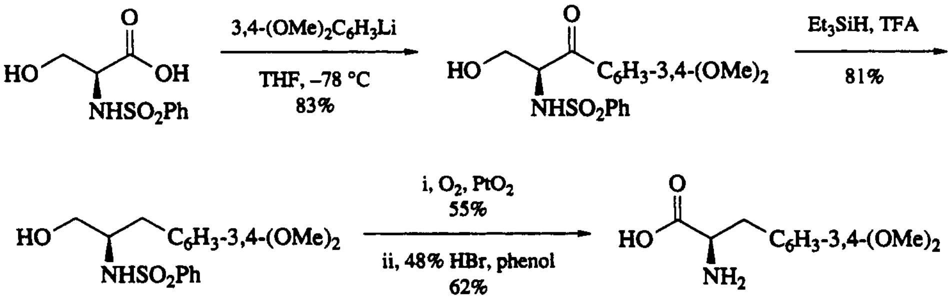
$3,4\text{-}(OMe)_2C_6H_3Li$
THF, −78 °C
83%
$Et_3SiH$, TFA
81%
i, $O_2$, $PtO_2$
55%
ii, 48% HBr, phenol
62%
HO
OH
O
$NHSO_2Ph$
$C_6H_3\text{-}3,4\text{-}(OMe)_2$
$NH_2$

**Scheme 15**

### 1.13.2.5 Acylation with Acid Chlorides

The synthesis of ketones from acid chlorides has been demonstrated with several organometallic reagents (see Sections 1.13.3, 1.13.4 and 1.13.5); however, the acylation of organolithiums often leads to substantial amounts of overaddition product. Initially, acid chlorides appear to be a poor choice for ketone synthesis considering highly electrophilic nature and the poor stability of the tetrahedral intermediate produced by nucleophilic addition. For these reasons, substantial amounts of ketone may reside in solution during addition of the organometallic. In addition, acid chlorides offer no site for prior coordination of the organometallic, as was the case with the *S*-(2-pyridyl) thioate of Mukaiyama (Section 1.13.2.2).[30]

The fact that organomagnesium reagents can often be acylated with acid chlorides to provide high yields of ketones as the exclusive product is somewhat surprising. Although the reaction is not well understood in its present form, the scope of the process can be illustrated by the following examples. Sato and coworkers have found the choice of solvent and temperature are important for the acylation of simple Grignard reagents.[61] A partial list of examples is given in Table 4.

**Table 4** Acylation of Grignard Reagents by Acid Chlorides

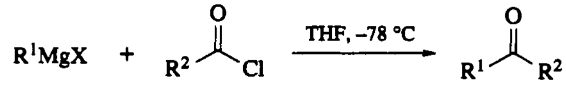

| $R^1$ | *Equiv.* | *X* | $R^2$ | *Product* | *Yield (%)* |
|---|---|---|---|---|---|
| Ph | 1.0 | Br | Ph | PhCOPh | 89 |
| *p*-$MeC_6H_4$ | 1.0 | Br | Ph | *p*-$MeC_6H_4COPh$ | 84 |
| $Pr^n$ | 2.0 | Cl | $Bu^t$ | $Pr^nCOBu^t$ | 88 |
| n-$C_6H_{13}$ | 2.0 | Br | Me | n-$C_6H_{13}COMe$ | 93 |

To avoid overaddition, the reaction was conducted by slowly introducing the Grignard reagent to a solution of the acid chloride at –78 °C. These workers reported that replacing tetrahydrofuran with diethyl ether caused a dramatic increase in the amount of tertiary alcohol formed, indicating that Grignard reagents reacted more rapidly with acid chlorides in THF rather than in ether, and that the reaction must be executed at low temperature. Many of the aromatic cases use a molar equivalent amount of $R^1MgX$; however, the best yields were obtained in the nonaromatic series by using 0.5 equiv. of Grignard reagent. Similar observations were reported by Eberle[62] and they also showed that functional groups such as carboxylic esters, halides and alkenes could be tolerated in the reaction. 1 equiv. of Grignard reagent was utilized and unlike the previous case the acylating agent was added directly to a cold solution of the organometallic. This should maximize the chances for tertiary alcohol formation; however, none was obtained. A characteristic example is shown in equation (32).

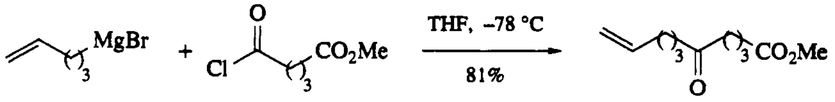

(32)

An isolated example of Grignard acylation by proline acid chloride was achieved by the use of a large excess of acid chloride (**43**). The keto aldehyde (**45**) was obtained in 71% yield (equation 33).[63] Unfortunately, the reaction with stoichiometric amounts of the acid halide were not discussed. In light of the results of Sato[61] and Eberle,[62] the real capabilities of this reaction were apparently not explored.

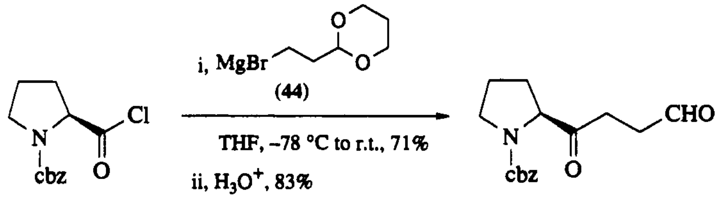

(43) (45)

(33)

To show the potential of the method, the related Grignard reagent (**46**) has been acylated in good yield through use of a stoichiometric mixture of organomagnesium and acid halide (equation 34). The use of low temperatures and THF was critical to the process.[64]

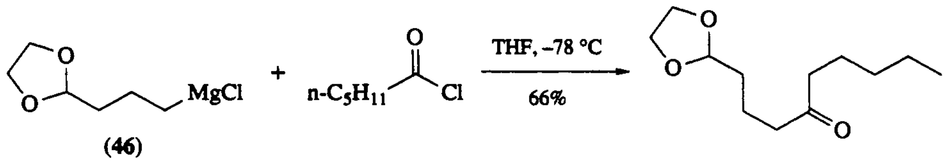

(46)

(34)

Sworin[65] has studied several interesting reactions of the Grignard reagent (**47**) which may indicate it reacts as the dialkylmagnesium (**48**) in THF at −78 °C (Schlenck equilibrium; equation 35).[66] The proposal was advanced that internal coordination of magnesium by the flanking oxygen moieties resulted in a softer nucleophile, 'similar in reactivity to an organocuprate'. The dimeric material may be responsible for the somewhat 'anomalous behavior' observed in reactions of this Grignard reagent and may point to the importance of temperature and solvent for successful acylations of other Grignard reagents. These workers also recommend that at least 2 equiv. of (**47**) be employed per mole of substrate to insure that (**48**) is the sole reactive intermediate. At room temperature, the equilibrium is believed to shift to the left with formation of the monomeric and harder nucleophile (**47**). Reactions at this temperature take a different course and favor 1,2-addition to the ketone.

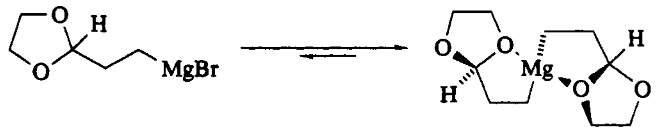

(47) (48)

(35)

Grignard reagents can also be monoacylated in the presence of iron(III) salts. The reaction uses catalytic amounts of iron and reproducible yields of ketones have been obtained.[67] The addition can be conducted at room temperature with stoichiometric amounts of the acid chloride and Grignard reagent. Only very simple substrates were considered initially; however, a synthesis of the methyl ketone derived from Mosher's acid was reported in very high yield (equation 36), as well as a synthesis of a heptatrienyl ketone (equation 37).[68] The reaction may be mediated by an acyl iron complex, although at room temperature one would have expected overaddition products from the Grignard reagent. No mechanistic studies have been carried out as yet.

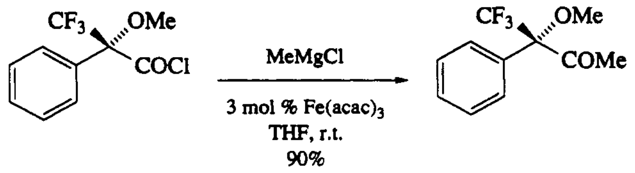

(36)

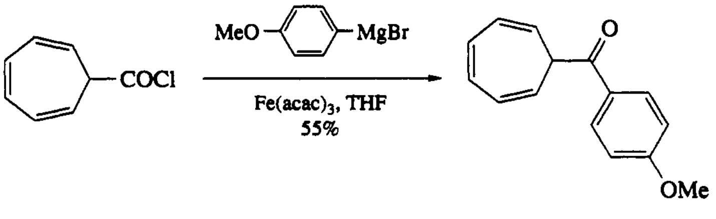

(37)

## 1.13.2.6 Acylation with Carboxylic Esters

Carboxylic esters have also been used to acylate Grignard reagents with some success. Workers at Shionogi research laboratories demonstrated that the combination of methylmagnesium bromide and triethylamine could be acylated in good yield by substrates such as (**49**; equation 38). The reaction did not require THF as a solvent, but an excess of triethylamine was needed to achieve the best results. Presumably the amine alters the usual aggregation of the organomagnesium reagent and/or influences the Schlenck equilibrium between MeMgBr and $Me_2Mg$, as discussed above. This combined reagent may selectively add to the ester functionality in preference to the newly formed ketone. On the other hand, the authors postulate that triethylamine aids in the deprotonation of the resulting methyl ketone, which is then protected from further attack. To provide evidence for this they quenched a reaction mixture with $D_2O$ and obtained deuterium incorporation at the newly introduced methyl group. Therefore if the ketone was converted to the enolate, then the combination of the Grignard reagent and triethylamine must be capable of serving as a base as well as a nucleophile (2 equiv. of reagent were used). Further investigations of this result would be of interest.[69]

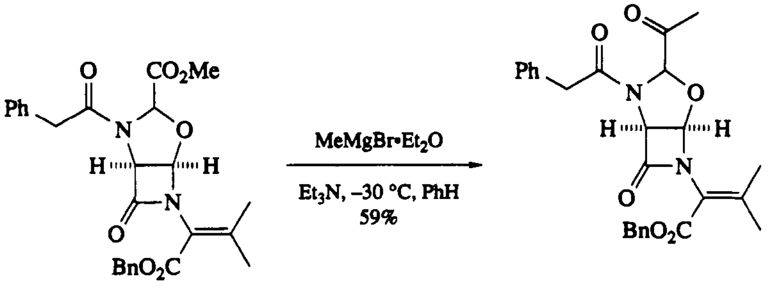

**(49)**

(38)

The use of other mixed reagents to promote acylation and subsequent enolization of the ketone during its formation have been reported by Fehr.[70] The success of the method depends on the ease of ketone deprotonation and thus was limited to substituted allylic nucleophiles. The final product was obtained entirely in the form of the α,β-unsaturated ketone. A combination of the nucleophilic Grignard reagent and the nonnucleophilic base lithium diisopropylamide converts sterically hindered ester (**50**) into α-damascone (**52**) *via* (**51**) (Scheme 16). The ratio of ketone to tertiary alcohol was 98:2 (many cases gave selectivity greater than 9:1); however, a few examples showed a substantial amount of tertiary alcohol formation.

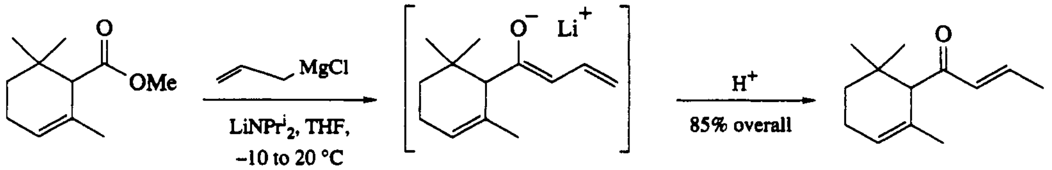

**(50)** **(51)** **(52)**

**Scheme 16**

The proposed enolate has been trapped in the case of amide (**53**) but there was no report if this could be accomplished on the ester substrates (equation 39). In general the amides did give higher yields of ketone and less tertiary alcohol, but this is expected based purely on the enhanced stability of the tetrahedral intermediate. It is not clear to what extent the amide base may influence the degree of aggregation of the Grignard reagent and thus alter its reactivity. All of the cases studied were extremely sterically congested, which could have influenced the rate of tetrahedral intermediate collapse and enolate formation. It should be noted that the previously discussed combination of Grignard reagent and triethylamine failed to give ketones selectively in these cases.[69]

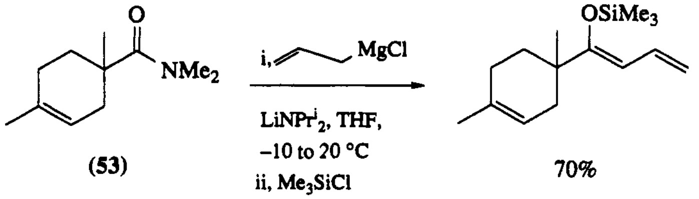

**(53)**

(39)

Comins has reported that simple esters can be converted to secondary alcohols in one step with a mixture of Grignard reagent and lithium borohydride ($LiBH_4$) in THF. The reaction is conducted at 0 to -10 °C to preclude undesired reduction of the ester by $LiBH_4$. Once acylation has occurred, reduction of the intermediate ketone occurs more rapidly than does addition of a second equivalent of the Grignard reagent.[71] Burke has modified the procedure slightly so as to include DIBAL-H as the reducing agent. In this fashion, either isomer of alcohol (**54**) may be obtained (equation 40).[72]

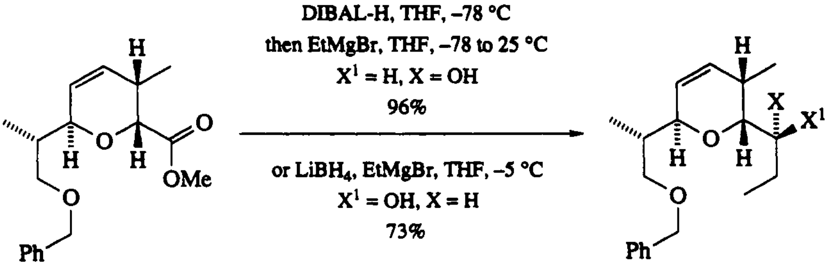

(40)

**(54)**

Seebach has also studied the utility of esters in organometallic acylation. In this case, preformed ester enolates of 2,6-di(*t*-butyl)-4-methylphenyl esters (BHT esters) were slowly warmed above –20 °C to form the corresponding ketene. If this was done in the presence of an additional equivalent of alkyllithium the ketene was trapped to give a ketone enolate in high yield. The same reaction failed to give any product when simple esters such as methyl, ethyl or *t*-butyl were used.[73] Scheme 17 is illustrative of the method.

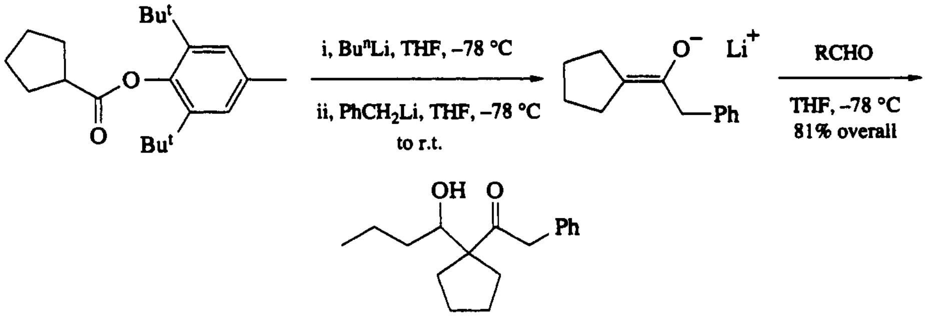

**Scheme 17**

A variety of alkyllithiums could be acylated by this method. The enolate was then quenched with electrophiles such as aldehydes and chlorosilanes. Unfortunately only branched chain carboxylic acids could be used in this process, as monosubstituted ketenes were unstable in the presence of butyllithium.[74]

### 1.13.2.7 Preparation of Alkynic Ketones from Lactones

Lactones are convenient acylating agents for lithium alkynides and have been used extensively for this purpose. Lactones are stable, readily available substances with a reactivity substantially different from simple esters. The first report discussing this strategy was by Ogura in 1972.[75] This work demonstrated that γ-valerolactone undergoes monoaddition with simple lithium alkynides, but suffers multiple addition with the corresponding magnesium alkynide. Chabala discussed the effect of lactone ring size on acylation as well as proposing the mechanism by which they undergo addition.[76] In this study, simple esters were found to undergo bis-addition when treated with lithium alkynides, due to the poor stability of the tetrahedral intermediate. However, in the case of δ-valerolactone, the intermediate ketal alkoxide was found to be stable in the reaction mixture and thus serves to protect the carbonyl function from further attack (equation 41). Other ring sizes do not seem to work as well, although acceptable yields of alkynic ketones can be obtained from γ-butyrolactone (50–60%).

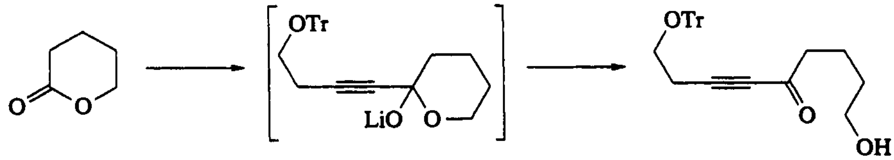

(41)

Recent evidence for the formation of hemiketal intermediates upon acylation of alkynides has been obtained from glucopyranolactones. Treatment of tetrabenzyl (**55**) with the anion from 1-benzyloxy-3-butyne gave a quantitative yield of hemiketal (**56**) which showed IR absorptions for the OH and alkyne portions of the molecule ($\lambda = 3350\ \text{cm}^{-1}$ and $2250\ \text{cm}^{-1}$, respectively). This compound was stereospecifically reduced to the *C*-glycoside (**57**) with triethylsilane/$BF_3$·etherate (overall yield 72%; Scheme 18). None of the other stereoisomer or ring-opened product was obtained.[77]

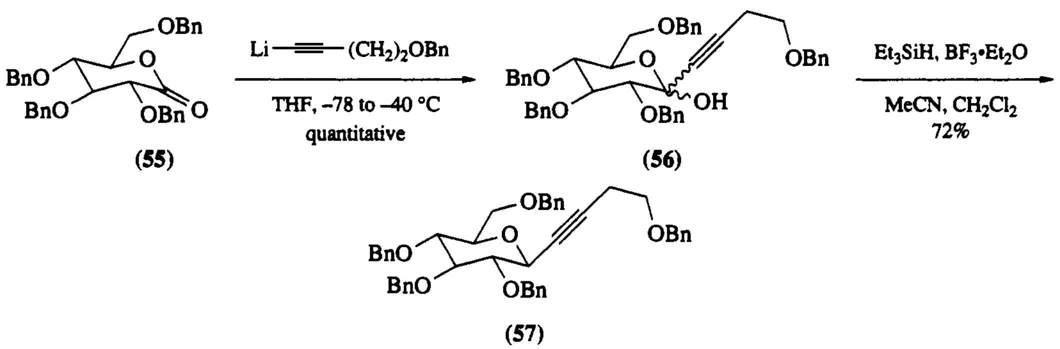

(**55**) (**56**) (**57**)

**Scheme 18**

The first important test of this methodology came in Hanessian's investigation of the spiroketal portion of avermectin $B_{1a}$. This highly convergent approach incorporates all the oxidation levels and functionality required for carbons C(15)–C(28), except for the necessity of alkyne to alkene conversion. The lithium alkynide was prepared at –78 °C and then mixed with boron trifluoride etherate under the conditions of Yamaguchi (Scheme 19).[78] (Direct condensation of the lithium salt and lactone lead to substantial amounts of α,β-unsaturated lactone.) Addition of the lactone in stoichiometric amounts to the solution of the modified alkynide led to the formation of the desired hemiketal in acceptable yield. Further improvements could be obtained by the recycling of starting material.[79]

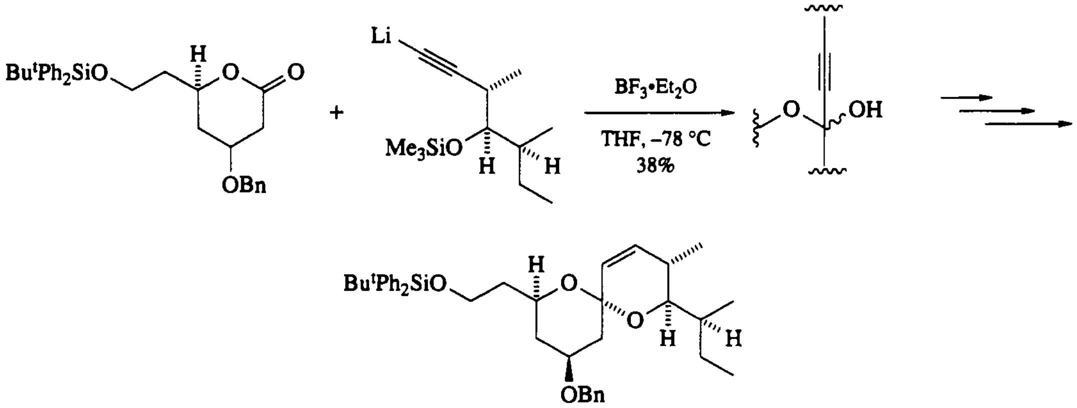

**Scheme 19**

A more recent example of a functionalized alkyne addition can be seen in Crimmin's synthesis of talaromycin A (equation 42).[80] This particular alkynide is an equivalent of the formyl acetone dianion and its use has been generalized as an entry into the spiroketal portion of the milbemycins (Scheme 20).[81] This approach differs from the Hanessian strategy in that formation of the C(17)–C(21) pyran ring is constructed last, through use of the alkynic unit.

An alternative construction which incorporates much of the alkyl functionality on to the alkyne portion and which carries the required methoxycarbonylalkyl substituent in the correct configuration at C-17 was reported by Langlois (equation 43).[82] This process and recently modified versions of the Hanessian spiroketal synthesis seem to correlate well.[79]

In the lactone acylations discussed above, there was never any evidence for a competing side reaction due to break down of the hemiketal moiety and Michael addition of the alcohol to the newly formed propargylic ketone. This may be taken as further evidence for the stability of the ketal-alkoxide intermediate; however, hemiketal ring opening and intramolecular Michael addition would provide an

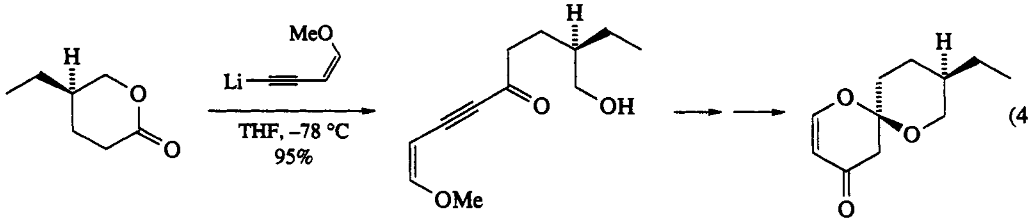

(42)

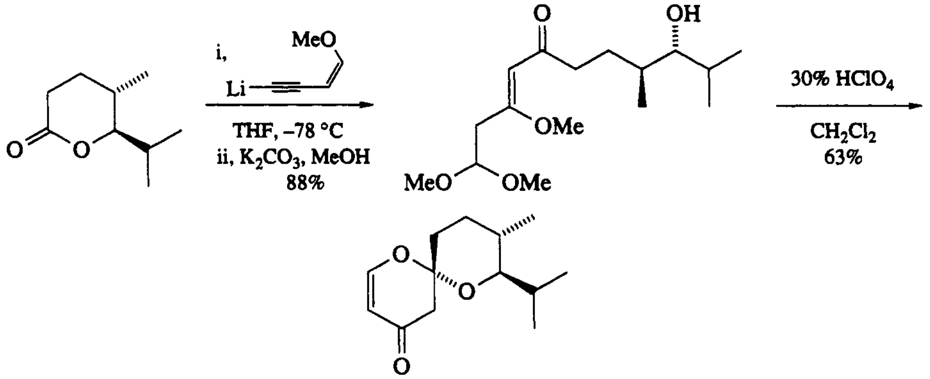

Scheme 20

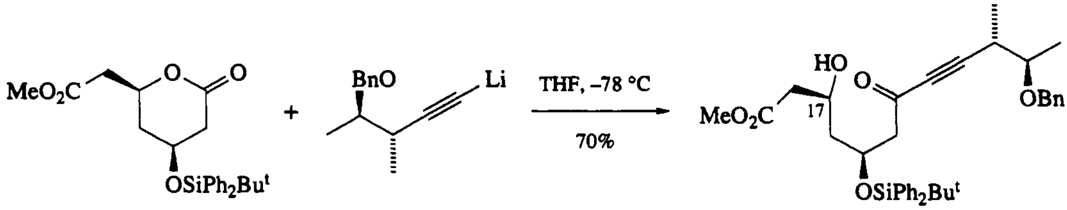

(43)

eight-membered ring vinylogous ester, seemingly a difficult process. Schreiber has discussed a method for achieving this nontrivial ring expansion in the context of the total synthesis of gloeosporone (equation 44).[83]

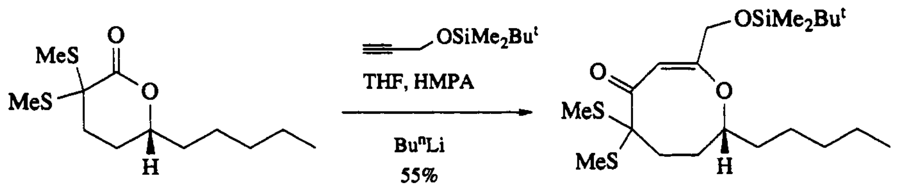

(44)

The initial hemiketal addition product is most likely induced to undergo ring opening as the reaction is warmed to room temperature and while in the presence of HMPA. Conjugate addition of the alkoxide to the alkynic ketone completes the ring formation. The reaction is promoted by α,α-disubstitution of the δ-lactone, as well as by the presence of electron-withdrawing groups on the alkynic fragment.

In a related fashion, certain types of vinylogous amides can be prepared by a modification of this same method, as reported by Suzuki (equations 45 and 46).[84] The triphenylsilyl moiety is essential for this transformation. The corresponding *t*-butyldimethylsilylacetylene gave the simple acylation product without subsequent Michael addition of the amine. In the ring expansion process the use of unmodified lithium acetylide (LiC≡CH) lead to the formation of by-products. A similar ring expansion process was reported for α-lactams with formation of five-membered ring vinylogous amides.[85]

An elegant 'reconstruction' of monensin from two chromic acid degradation products serves as an excellent example of the generality of alkynide addition to activated carboxylic acid derivatives. The alkynide (**59**) was prepared in eight steps from one degradation product and was then sequentially deprotonated with *n*-butyllithium and treated with magnesium bromide. The resultant magnesium salt

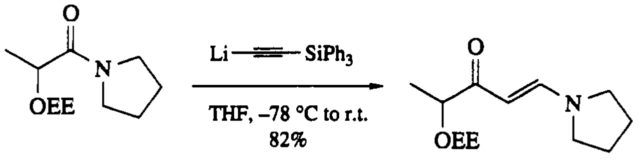
O
N
OEE
Li—≡—SiPh3
THF, –78 °C to r.t.
82%
O
N
OEE

(45)

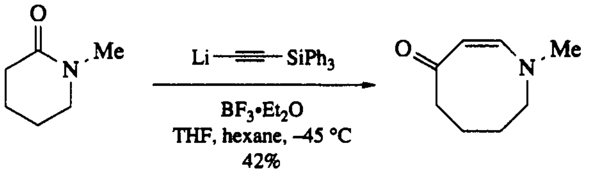
O
N
Me
Li—≡—SiPh3
BF3•Et2O
THF, hexane, –45 °C
42%
O
N
Me

(46)

was then acylated with mixed anhydride (**58**), derived from another degradation fragment. This α,β-ynone was obtained in 87% yield (equation 47).[86] Lewis acid mediation of alkynide addition as provided by magnesium bromide or boron trifluoride[87] often improves the efficiency of the process and is useful for reactions which give substantial quantities of by-products.

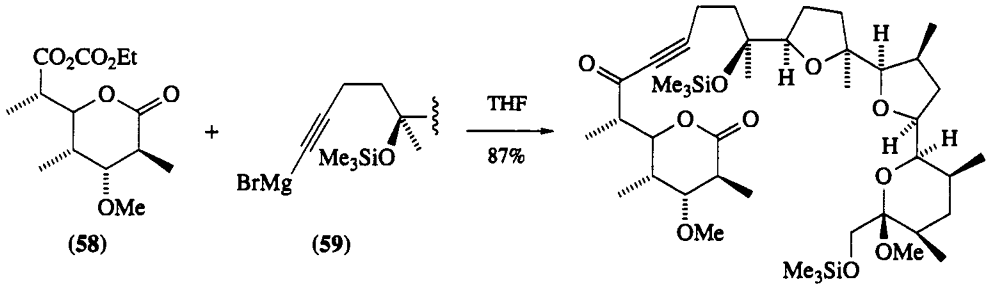
CO2CO2Et
O
O
OMe
+
Me3SiO
BrMg
THF
87%
O
Me3SiO
H
O
H
O
O
O
H
H
O
OMe
OMe
Me3SiO

**(58)** **(59)** (47)

The highly reactive carbonyl of lactone (**60**), an intermediate in the synthesis of forskolin, was easily converted to propargyl ketone (**61**) by addition of the lithium alkynide as shown in equation (48).[88] It is possible that the intermediate ketal alkoxide was not stable in solution because of ring strain; however, no multiple addition products were reported, nor was there any Michael addition of the alkoxide to the resulting ynone.

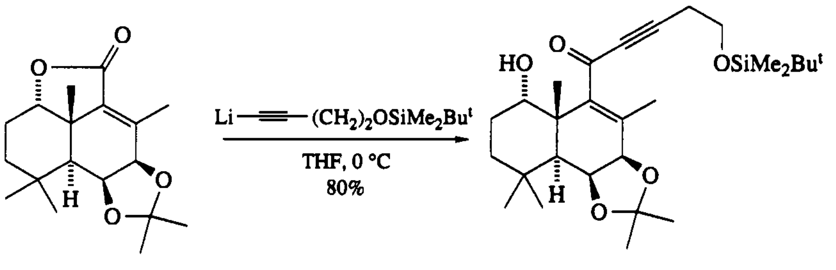
O
O
H
O
O
Li—≡—(CH2)2OSiMe2Bu$^t$
THF, 0 °C
80%
O
HO
OSiMe2Bu$^t$
H
O
O

**(60)** **(61)** (48)

One final example of acylation of alkynes by lactones forms part of the synthesis of neomethynolide by Yamaguchi. The Prelog–Djerassi lactone serves as the acylating agent (equation 49). The functionalized alkynide undergoes addition very selectively at the lactonic carbonyl group, despite the presence of a relatively unhindered primary ester.[89]

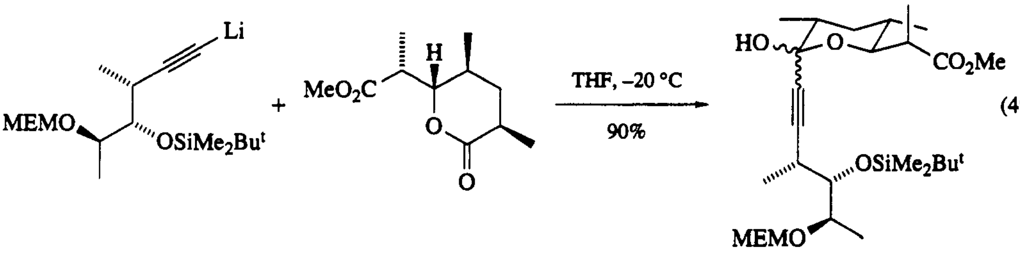
Li
MEMO
OSiMe2Bu$^t$
+
MeO2C
H
O
O
THF, –20 °C
90%
HO
O
CO2Me
OSiMe2Bu$^t$
MEMO

(49)

## 1.13.2.8 Other Activated Acylating Agents for Ketone Synthesis

In this section, several additional types of acylating agents for ketone synthesis will be discussed. Nearly all of these reagents are designed to preassociate with the organometallic reagent prior to acylation. At the present time, very infrequent use has been made of these new acylating agents, and their particular advantage remains to be demonstrated.

### *1.13.2.8.1 Acylating agents derived from pyridine or quinoline*

Sakan and Mori have described the reaction of Grignard reagents with carboxylic esters formed from 8-hydroxyquinoline.[90,91] This acylating agent was designed to complex the organomagnesium with the substrate prior to formation of the tetrahedral intermediate, as indicated in Scheme 21. The actual tetrahedral species is not stable to the reaction conditions and a strong insoluble complex is formed between magnesium ion and 8-hydroxyquinoline. Although it is apparent that free ketone exists in solution simultaneously with complex (**62**), little if any tertiary alcohol formation was reported in the few simple cases investigated.[91] This may be due to the higher reactivity of the complexed oxoquinoline ester relative to the ketone.

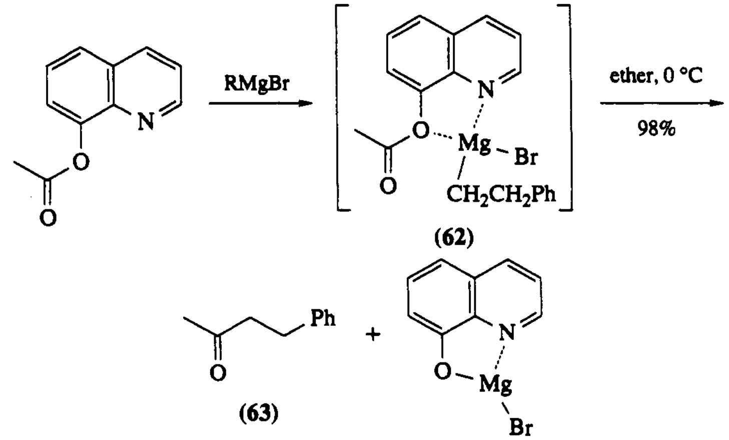

**Scheme 21**

A competition experiment (Scheme 22) was conducted to test the acylation abilities of the 8-acyloxyquinoline system and another metal-induced acylating agent, the 2-acyloxypyrazines (**65**) and (**67**). A mixture of quinoline (**64**) and pyrazine (**65**) was treated with phenethylmagnesium bromide under conditions which had previously afforded a 98% yield of the ketone (**63**) with the 8-acyloxyquinoline system. Surprisingly, the only product was that derived from addition to the acyloxypyrazine reagent, *i.e.* ketone (**68**). When substrates (**66**) and (**67**) were treated in the same fashion again only the product derived from addition to the acyloxypyrazine system was observed.[92] These results support the notion that the effect of prior complexation of the organometallic with the acylating agent may be as important to the rate of acylation as an incremental amplification in electrophilicity.

Similar results were obtained through the acylation of Grignard reagents with *O*-acyloximes (Scheme 23), although a higher degree of metal to substrate interaction is possible in this case.[93] The extent to which the species drawn in Scheme 23 actually participates in the reaction is unknown.[94]

Meyers and Comins have reported acylation of Grignard reagents with *N*-methylaminopyridylamides as a chemoselective method of ketone formation (equation 50). Once again chelation is expected to play a role in activating the substrate towards nucleophilic attack. However, as in the previously described cases, the resulting tetrahedral intermediate is not stable in the reaction mixture and a second equivalent of either a Grignard reagent or an alkyllithium can be introduced to form unsymmetrical tertiary alcohols. Alkyllithium reagents did not function as well in the formation of ketones; tertiary alcohols were the major product.[95]

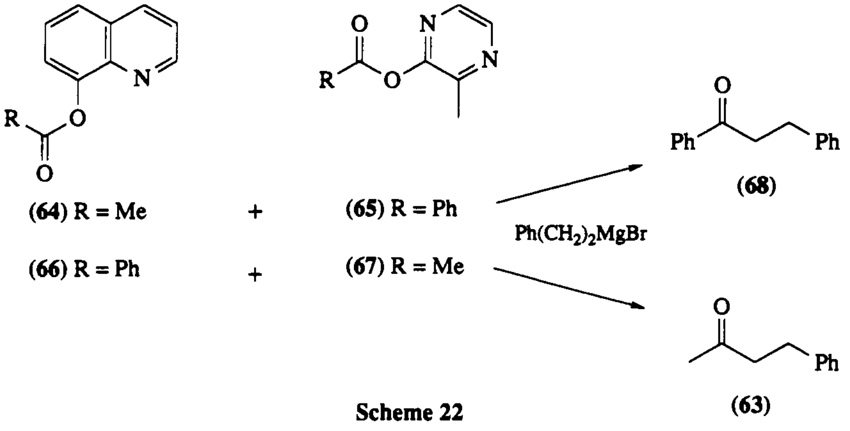
(64) R = Me
(66) R = Ph
(65) R = Ph
(67) R = Me
Ph(CH2)2MgBr
(68)
(63)

Scheme 22

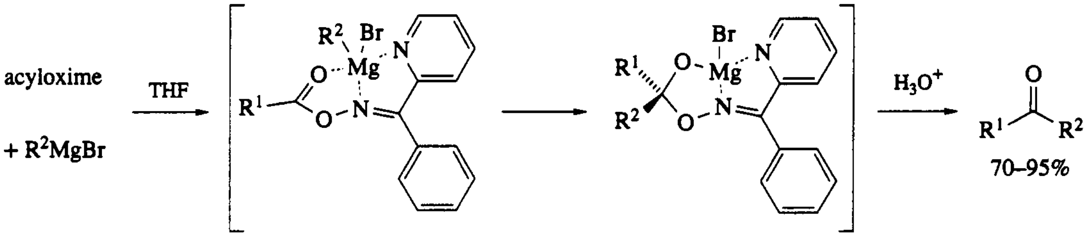
acyloxime
+ R2MgBr
THF
H3O+
70–95%

Scheme 23

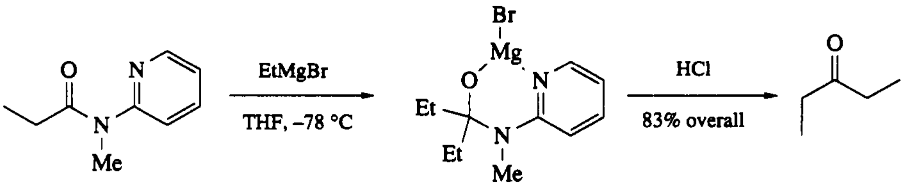
EtMgBr
THF, –78 °C
HCl
83% overall

(50)

### 1.13.2.8.2 Carboxymethyleniminium salts

The generation of active acylating agents *in situ* has certain advantages over methods which require a separate step for their preparation. Acylating agents that have previously been prepared *in situ* and used for ketone synthesis have included anhydrides and acyl imidazoles.[96] A frequent side reaction with these rather reactive agents is the formation of tertiary alcohols. Fujisawa and coworkers advocated the use of carboxymethyleniminium salts, prepared directly from carboxylic acid salts, and then subjected to reaction with Grignard reagents (Scheme 24). Good yields of ketones were observed in most cases.[97] The

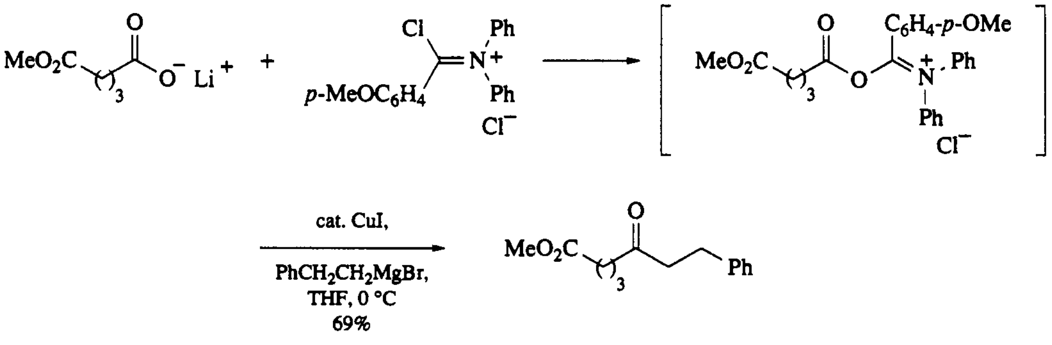
cat. CuI,
PhCH2CH2MgBr,
THF, 0 °C
69%

Scheme 24

particular example shown in Scheme 24 indicates the selectivity obtained in competition with a carboxylic ester. No other acylated products or tertiary alcohols were present.

Bearing in mind that the exact nature of the intermediate in this and the following case has not been elucidated, together with the often surprising ability of acid chlorides to provide ketones when treated with Grignard reagents or organocuprates, the same authors have discussed the reaction of carboxylic acids with α-chloroenamines as a way to prepare acylating agents for ketone synthesis (Scheme 25).[98] In this case, the overall yield for the addition of organometallics may be slightly higher than the previously described method. The possible advantage is the direct transformation of a free acid to an acylating agent without the need for an extra equivalent of base.

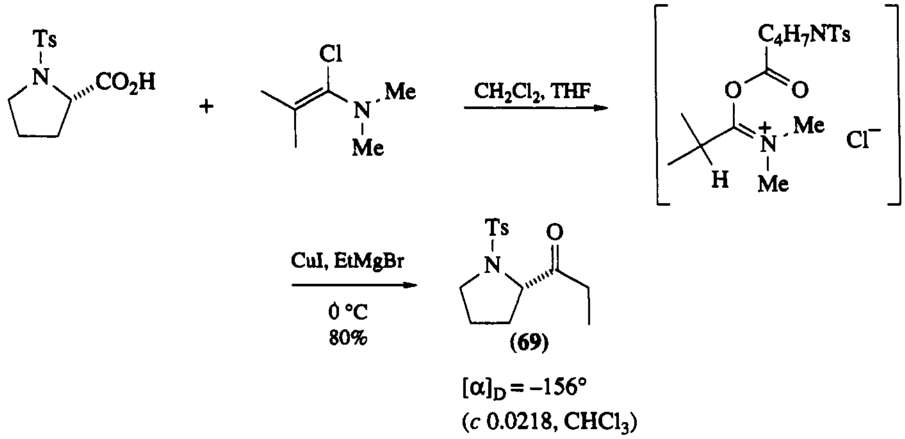

**Scheme 25**

A comparison of the example in Scheme 25 with the results of earlier investigations with *N*-tosylproline demonstrates that the use of α-chloroenamines has some advantage. *N*-Tosylproline when treated with methyllithium in ether gave a 50% yield of methyl ketone of ≥95% *ee*. Similarly, preparation of the mixed anhydride with pivaloyl chloride followed by addition of ethylmagnesium bromide affords (**69**) in 53% yield[99] utilizing the conditions of Mukaiyama (equation 51).[100] No racemization was observed in any of these cases. Surprisingly in equation (51), the acylation of the mixed anhydride proceeds with only 1 equiv. of Grignard reagent, although there is an equimolar amount of triethylamine hydrochloride present.

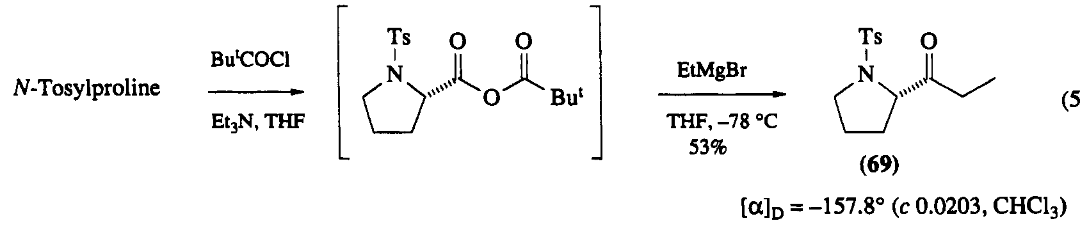

(51)

### 1.13.2.8.3 Acylation with the mixed anhydrides of phosphorus

Kende has demonstrated that the mixed anhydride from carboxylic acids and diphenylphosphinic chloride would acylate Grignard reagents to afford ketones in moderate to good yield. Tertiary carbinols were not observed unless excess Grignard reagent was added. The intermediate anhydrides were generally isolated and made free of triethylamine hydrochloride before addition of the nucleophile. The reaction shown in equation (52) gave improved yields over the simple addition of methyllithium to the carboxylic acid.[101]

Another procedure which was thought to pass through a mixed phosphorus anhydride was the acylation of Grignard reagents with an adduct formed between lithium carboxylates and triphenylphosphine dichloride (Scheme 26). The betaine (**70**) was the proposed tetrahedral intermediate; however, since no evidence is provided, the reaction may have also proceeded by way of the acid chloride. Surprisingly, good yields of ketone are preserved even in the presence of excess nucleophile and no tertiary alcohol formation was observed. Triethylamine can be used for prior deprotonation of the carboxylic acid; how-

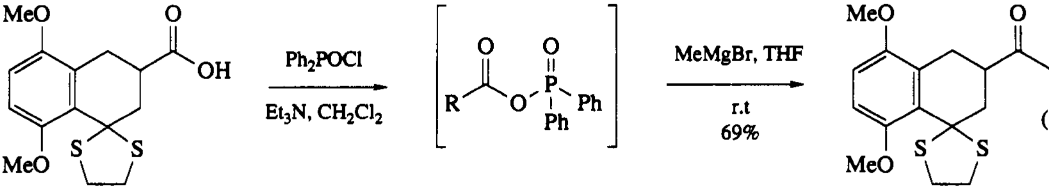
MeO
O
OH
MeO
S
S
Ph$_2$POCl
Et$_3$N, CH$_2$Cl$_2$
O
O
R
O
P
Ph
Ph
MeMgBr, THF
r.t
69%
MeO
O
MeO
S
S

(52)

ever, unlike the case of mixed carboxylic anhydrides, 2 equiv. of Grignard reagent were required to complete the addition.[102]

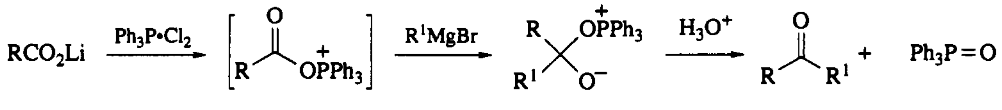
RCO$_2$Li
Ph$_3$P•Cl$_2$
O
R
+
OPPh$_3$
Cl$^-$
R$^1$MgBr
R
+
OPPh$_3$
R$^1$
O$^-$
H$_3$O$^+$
O
R
R$^1$
+
Ph$_3$P=O

(70)

60–95%

**Scheme 26**

### 1.13.2.9 Addition to Oxalic Acid Derivatives

General methods for α-keto ester synthesis are important for the preparation of a wide variety of natural substances of current interest. The direct addition of alkyllithiums or Grignard reagents to oxalate esters has been reported to give good yields of α-keto esters.[103] Presumably the tetrahedral intermediate formed from such an addition is stabilized by the strong electron withdrawal of the adjacent ester carbonyl, thus preventing or retarding reformation of the $sp^2$ center. Trapping of this intermediate is possible by the addition of acetyl chloride (equation 53).[104]

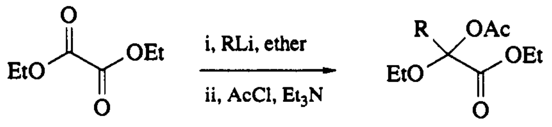
O
EtO
OEt
O
i, RLi, ether
ii, AcCl, Et$_3$N
R
OAc
EtO
OEt
O

R = Me, Ph

(53)

A second example of this methodology comes from the Merck synthesis of homo-tyrosine, an intermediate for a potent dopamine agonist (Scheme 27).[105] The Grignard reagent is added to a solution of 2 equiv. of diethyl oxalate at –20 °C.

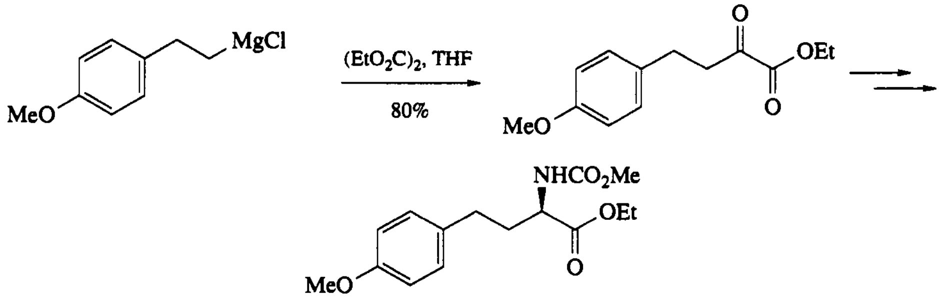
MgCl
MeO
(EtO$_2$C)$_2$, THF
80%
O
OEt
MeO
O
NHCO$_2$Me
OEt
MeO
O

**Scheme 27**

Preparation of the tricarbonyl region of the immunosuppressive FK-506 can be accomplished through acylation of a heavily functionalized dithiane as shown in equation (54).[106]

Previously, Corey had established a similar type of oxalate acylation using functionalized dithianes in the synthesis of aplasmomycin.[107] One additional entry into the α-keto ester system was through the reaction of triethoxyacetonitrile and alkyllithium reagents.[108] Only simple alkyl- and aryl-lithium reagents have been applied thus far, with yields in the range of 80%. Interestingly, the reaction took a different course with Grignard reagents; simple esters were the exclusive products.

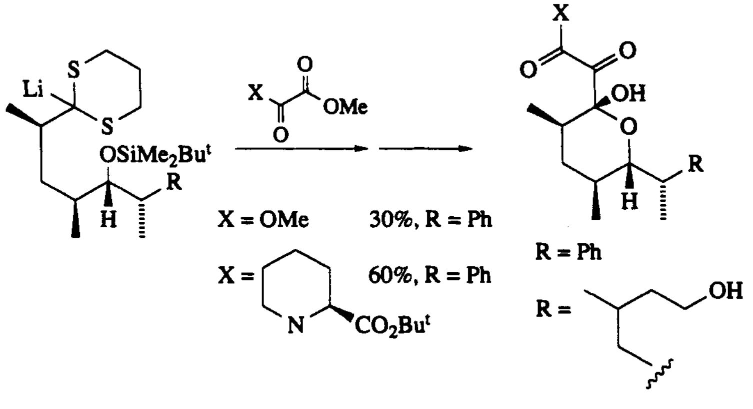

(54)

## 1.13.3 ACYLATION BY ORGANOCOPPER REAGENTS

### 1.13.3.1 Stoichiometric Organocopper Reagents

A great deal of study has surrounded the usefulness of preformed organocopper reagents (both stoichiometric and dialkylcuprates) and the utility of copper-catalyzed organometallics in ketone synthesis. When this methodology first became useful there were few other reliable methods for the direct synthesis of ketones from carboxylic acid derivatives.[109] The addition of organolithiums to carboxylic acids, or the reaction of organocadmium or organozincs with acid chlorides was often accompanied by side reactions or suffered from low yields. It was apparent that ketones did not generally react with organocuprates at low temperature, unlike the situation with the corresponding aldehydes. The conditions for acylation were therefore mild enough to prevent side reactions. Stoichiometric alkylcopper species (RCu) were found to afford lower yields of the ketone than were obtained from lithium dialkylcuprates and acid chlorides.[110] These reagents are much less reactive than dialkylcuprates and often require catalysis for addition to take place (*vide infra*). The work of Rieke represents the most recent study of the acylation of simple organocopper reagents.[111] Treatment of a functionalized alkyl bromide with a 'highly reactive copper solution' (formed *in situ* by reduction of copper(I) iodide triphenylphosphine complex with lithium naphthalide) results in the formation of an alkylcopper. This reagent adds rapidly to acid chlorides at –35 °C, affording ketones in good yield. The approach allows the preparation of organocopper reagents unavailable by methods which use organo-lithium or -magnesium reagents and copper(I) iodide. A drawback of the chemistry is that an excess of the acid chloride is required due to a serious side reaction which takes place between any excess of soluble copper metal and the acylating agent. Benzoyl chloride reacts rapidly with this form of copper(0) to form *cis*-stilbene diol dibenzoate thus consuming 4 equiv. of the reagent. Some examples of the method are included in Table 5.[111]

**Table 5** Formation and Acylation of Stoichiometric Organocuprate Reagents prepared from Rieke Copper

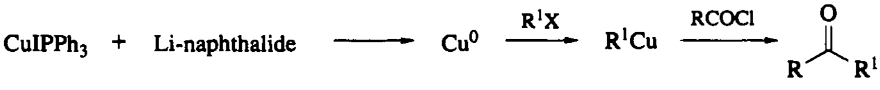

| *Alkyl halide* | *Acid chloride* | *Equiv.* | *Temperature (°C)* | *Product* | *Yield (%)* |
|---|---|---|---|---|---|
| $Br(CH_2)_3CO_2Et$ | PhCOCl | 2.75 | –35 | $PhCO(CH_2)_3CO_2Et$ | 81 |
| $Br(CH_2)_6Cl$ | PhCOCl | 2.80 | –35 | $PhCO(CH_2)_6Cl$ | 77 |
| 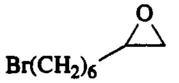 | PhCOCl | 2.80 | –35 | 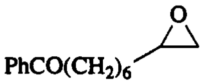 | 58 |
| $Br(CH_2)_3CN$ | $Me(CH_2)_2COCl$ | 2.85 | –35 | $Me(CH_2)_2CO(CH_2)_3CN$ | 61 |
| $o$-$NCC_6H_4Br$ | PhCOCl |  | 0 | $o$-$NCC_6H_4COPh$ | 71 |

One of the advantages of using stoichiometric organocopper reagents (RCu) instead of the more common dialkylcuprates ($R_2CuLi$) is that only 1 equiv. of RCu is necessary for good yields of ketones, whereas 3 equiv. of the dialkylcuprate are usually required in acylations. In many cases it is possible to substitute the more readily available alkyl or aryl Grignard reagent in the presence of stoichiometric, or in some cases catalytic, amounts of copper iodide.[112] These modified Grignard reagents are then used in equal molar amounts relative to the acid chloride. An important example of this methodology appeared in the synthesis of monensin by Still.[113] The central fragment (**71**) comprising carbons C(8)–C(15) was prepared through copper(I)-catalyzed Grignard addition to the *S*-pyridyl thiol ester (**72**), comprising carbons C(16)–C(25) (equation 55). The direct reaction of the Grignard reagent with the *S*-pyridyl thiol ester under the conditions of Mukaiyama resulted in multiple addition (Section 1.13.2.2).[30]

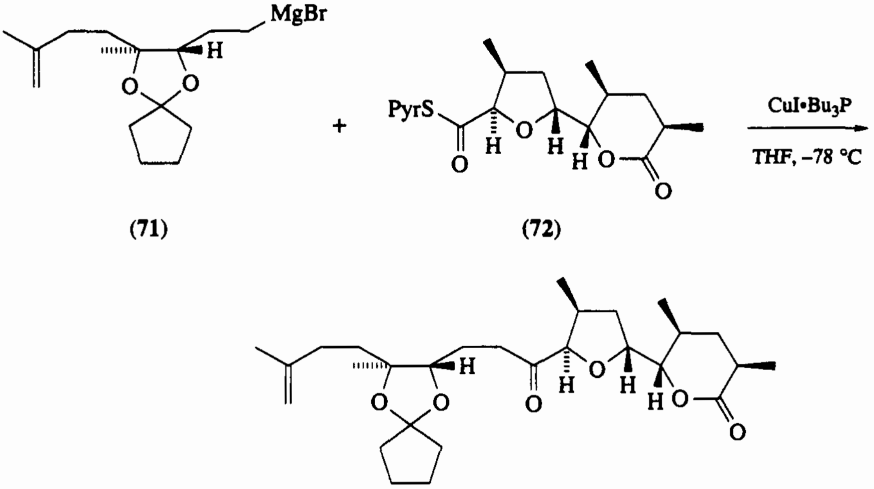
MgBr
H
O
O
+
PyrS
O
H
O
H
H
O
O
CuI•Bu3P
THF, –78 °C
H
O
O
O
H
H
H
O
O

(**71**) (**72**) (55)

A recent example by McGarvey demonstrates the formation of chiral derivatives (**73**)–(**76**) which are useful for elaboration into the ubiquitous propionate unit through stereoselective enolate-based alkylation (equation 56).[114] The thiol ester substrates were derived from aspartic acid in seven steps. The acylation of either dimethylcuprate or the Grignard-derived organocopper reagent was extremely clean when these organometallics were used in excess. No epimerization of the adjacent center was observed during the addition.

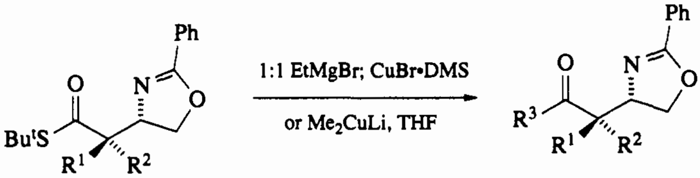
Ph
O
N
O
Bu$^t$S
R$^1$
R$^2$
1:1 EtMgBr; CuBr•DMS
or Me$_2$CuLi, THF
Ph
O
N
O
R$^3$
R$^1$
R$^2$

(56)

(**73**) $R^3 = Et, R^1 = R^2 = H$; 90%

$R^3$ = Me approx. 85% yield for all below

$R^1 = R^2 = H$ (**74**) $R^1 = R^2 = H$

$R^1 = Me, R^2 = H$ (**75**) $R^1 = Me, R^2 = H$

$R^1 = H, R^2 = Me$ (**76**) $R^1 = H, R^2 = Me$

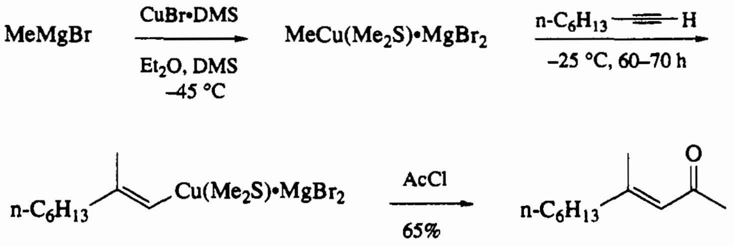
MeMgBr
CuBr•DMS
Et$_2$O, DMS
–45 °C
MeCu(Me$_2$S)•MgBr$_2$
n-C$_6$H$_{13}$—≡—H
–25 °C, 60–70 h
n-C$_6$H$_{13}$
Cu(Me$_2$S)•MgBr$_2$
AcCl
65%
n-C$_6$H$_{13}$
O

**Scheme 28**

### *1.13.3.1.1 Acylation of vinylcuprates*

The extension of organocopper-based technology to the synthesis of α,β-unsaturated ketones was accomplished by acylation of vinylcopper reagents (Scheme 28). This represented something of an unexpected advance due to the potential for subsequent conjugate addition to the product.[115] The approach has not seen extensive utility, compared to approaches using organotransition metal and organolithium methodology which have become more general. The first specific example was generated through adaptation of Normant's method for the formation of 1,1-disubstituted alkenylcuprates.[116] This trisubstituted alkene synthesis proceeds with retention of the stereochemistry generated initially by organocopper addition to an alkyne. The vinylcopper reagent must be β,β-disubstituted to avoid subsequent conjugate addition to the product. This restriction is removed when acylation is carried out with the more reactive acid bromide.[117]

The method was made considerably more general by inclusion of a catalytic amount of a palladium(0) complex during addition of the organometallic. Alkenylcopper reagents actually react relatively slowly with acid halides but, in a fashion analogous to other alkenyl metal species (see Section 1.13.4), they may be readily transmetallated to form an acylpalladium(II) complex which then undergoes reductive elimination to the product (Scheme 29).[118] A further discussion of acylation mediated by palladium complexes is included in Section 1.13.4. Interestingly, α,β-unsaturated acid chlorides react under these conditions to form divinyl ketones.

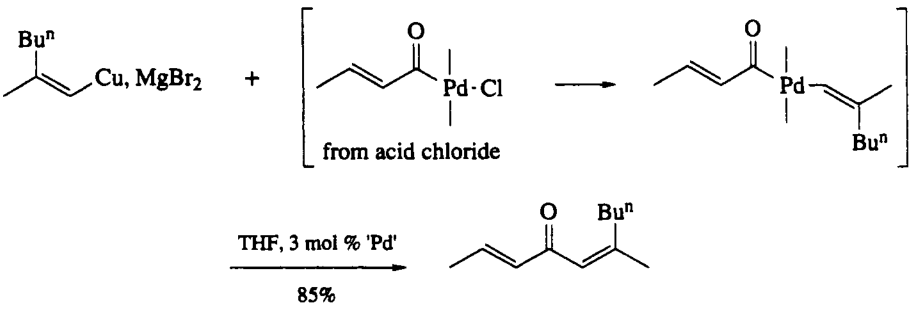

Scheme 29

γ-Silylated vinylcopper reagents are acylated with acid chlorides followed by palladium-catalyzed 1,5-sigmatropic rearrangement to form silyloxy dienes in moderate yield (equation 57).[119]

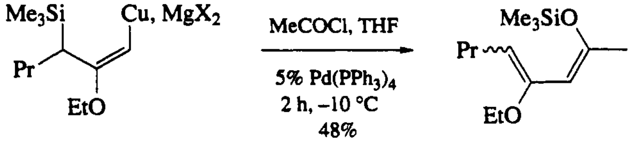 (57)

The more reactive lithium dialkenylcuprates ($R_2CuLi$) cannot be directly acylated even at low temperature, because further addition to the product takes place. These reagents can be modified *in situ* so that the actual species undergoing reaction is an organozinc (requires palladium catalysis); however, other methods for generating organozincs are available that do not involve prior organocopper formation (Section 1.13.4.4). Stoichiometric vinylcopper and other copper-mediated acylations were not directly applicable to the case shown in equation (58)[120] (however, see Section 1.13.2.1).

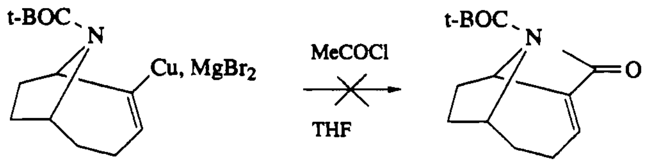 (58)

## 1.13.3.2 Acylation of Lithium Dialkylcuprates with Acid Chlorides or Thiol Esters

The use of the more reactive lithium dialkylcuprate ($R_2CuLi$) species in acylation requires the complete exclusion of moisture and air.[121] This fact makes application of organocuprate acylation early in a synthetic route rather difficult if large amounts of material are to be handled or complex transferrable ligands are to be prepared. Nevertheless, the reaction has been widely used at mM scale with simple alkyllithiums. Posner has shown that lithium dimethyl- and other di-*n*-alkyl-copper reagents react with primary, secondary and tertiary acid chlorides at low temperature to provide good to excellent yields of simple ketones (equations 59 and 60).[121,122]

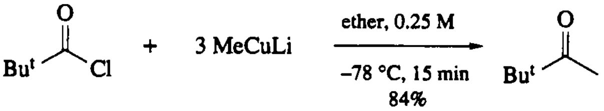

(59)

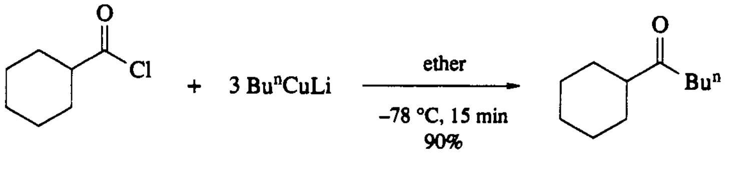

(60)

An interesting transformation, carried out by Paquette, demonstrates the selectivity that can be achieved with these reagents. The reaction of the acid chloride (**77**) and cuprates (**78**) or (**79**) takes place selectively in the presence of the lactone. The cuprates must be added to a solution of the acid chloride to obtain high yields. A later transformation demonstrated that a lactone can be converted easily to the ketone with phenyllithium (Scheme 30).[123] No loss of stereochemistry occurs in either permutation.

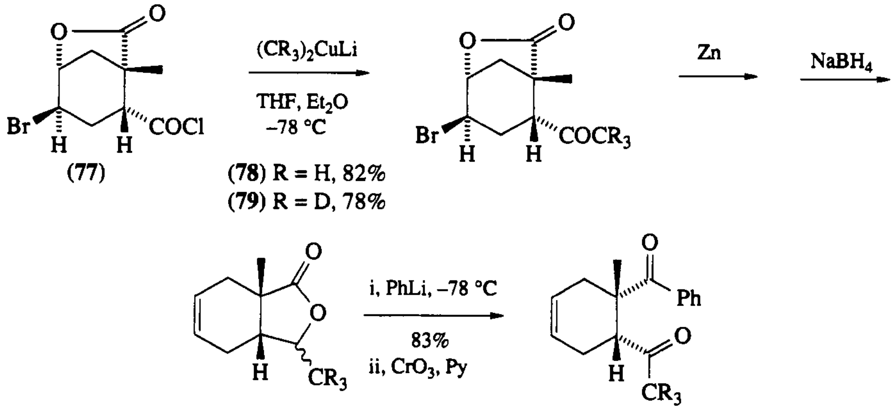

**Scheme 30**

The diacid chloride (**80**) can be easily converted to a diketone without epimerization or aldol condensation (equation 61).[124] In this case, inverse addition was not required for high yields.

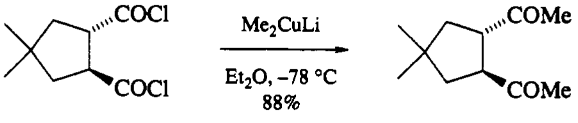

(61)

**(80)**

Walba has used cuprate technology for the synthesis of the septamycin A-ring fragment shown in Scheme 31.[125] The use of the well-known anhydride (**81**) in this transformation was unsatisfactory.

The same acid chloride formed part of the premonensin synthesis of Sih.[126] Somewhat later in this synthesis, one of the final transformations before union of two large fragments was acylation of dimethylcuprate by acid chloride (**82**). The reaction proceeded in good yield but the requisite acid chloride had to be prepared from a methyl ester in two steps. A very similar dissection was used by Evans except that the methyl ketone (**84**) was prepared directly from the corresponding dimethylamide (**83**) using methyl-

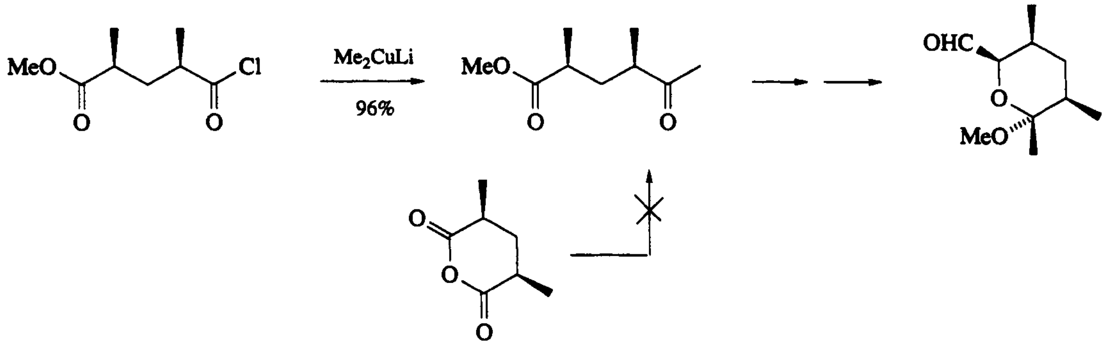

**(81)**

Scheme 31

lithium (equation 62).[127] Although both procedures gave high yields, the amide was perhaps the more useful functional group, since it was carried intact through several prior synthetic permutations before acylation.

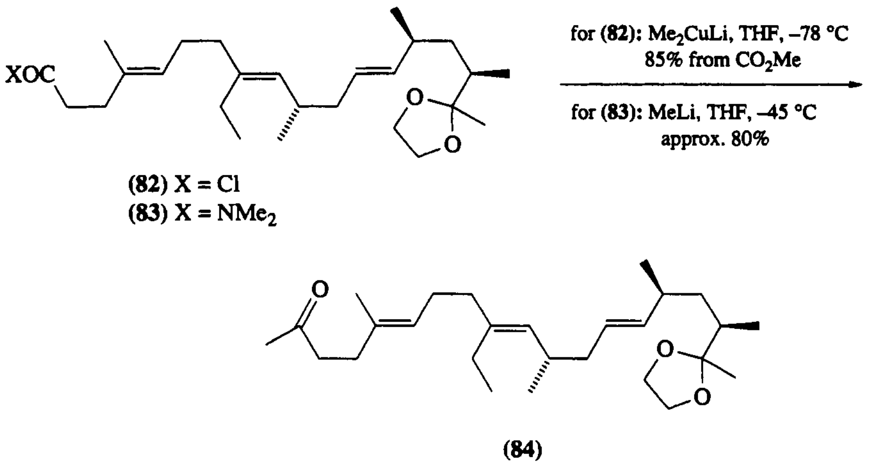

for (**82**): $Me_2CuLi$, THF, –78 °C
85% from $CO_2Me$

for (**83**): MeLi, THF, –45 °C
approx. 80%

(**82**) X = Cl
(**83**) X = $NMe_2$

(62)

(**84**)

Because 3 equiv. of the organocuprate are usually required for the synthesis of ketones, the method is less effective for substrates of limited availability. Corey has described a class of mixed homocuprates $R_rR_tCuLi$ in which one of the groups attached to copper is a nontransferable ligand ($R_r$) while the other group ($R_t$) is designed to be selectively introduced into the substrate.[128] Although this reagent was first used in the conjugate addition of valuable prostaglandin side chains to cyclopentenones, it has also found utility in acylation chemistry. Most often the residual groups are copper(I) alkynides which become strongly complexed to copper. Copper alkynides are somewhat more susceptible to acylation[129] than they are towards conjugate addition to enones, and the choice of acylating agent is more consequential. The most useful nontransferable ligand in this class is that derived from 3-methyl-3-methoxy-1-butyne.[130] In Corey's erythronolide A synthesis, the coupling of vinyl iodide (**85**) and the *S*-pyridyl thiol ester (**36**) could not be accomplished through Mukaiyama's direct acylation of Grignard reagents,[131] despite close analogy between related transformations in the erythronolide B series (see Section 1.13.2.2). The obstacle was overcome by the formation of mixed homocuprate (**86**) in which a nontransferrable ligand was used. The cuprate was selectively acylated by the *S*-pyridyl thiol ester with formation of ketone (**87**; Scheme 32).[132] The reaction was also quite solvent dependent and only a minimum amount of THF can be used in relation to nonpolar cosolvents (hexane/pentane:THF 1.2:1).

Attention should be drawn to the subtle differences between the reaction shown in Scheme 32 and the formation of the related erythronolide B intermediate (Scheme 11) by Corey and coworkers.[35] As mentioned earlier (Section 1.13.2.2), the addition of the Grignard reagent derived from iodide (**34**) was carried out easily on the identical substrate, *S*-(pyridyl) thiol ester (**36**) used in the A series, providing erythronolide B intermediate (**37**). The reaction in the erythronolide A series appears to be sensitive to the presence of the MTM-protected alcohol.

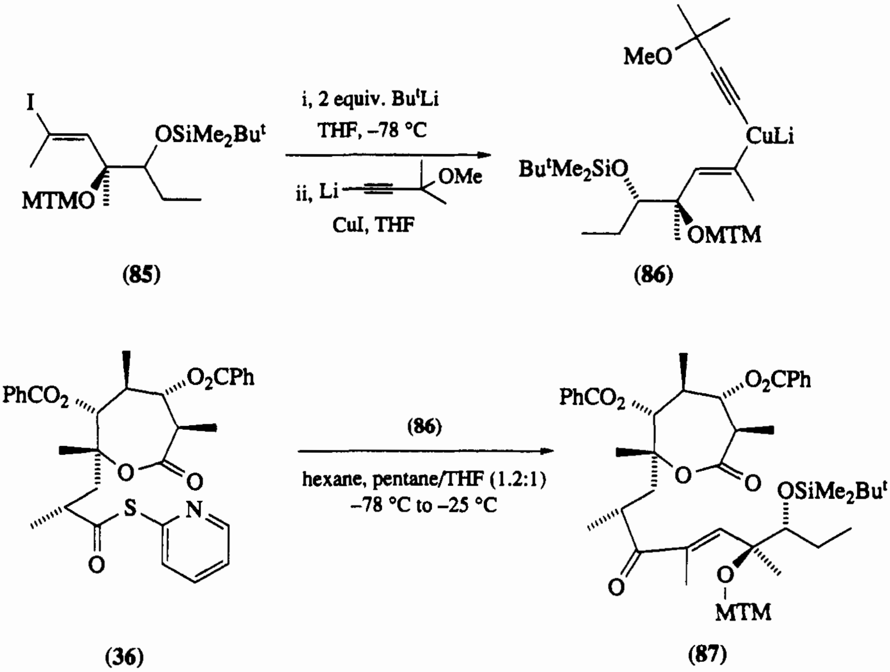
I
OSiMe2But
MTMO
i, 2 equiv. ButLi
THF, –78 °C
ii, Li
OMe
CuI, THF
MeO
CuLi
ButMe2SiO
OMTM
(85)
(86)
PhCO2
O2CPh
O
O
S
N
O
(86)
hexane, pentane/THF (1.2:1)
–78 °C to –25 °C
OSiMe2But
O
MTM
(36)
(87)

**Scheme 32**

There have been few transformations of vinylcuprate reagents with acid chlorides (Section 1.13.3.1.1). Marino and Linderman have reported a general preparation of divinyl ketones useful in a Nazarov sense for the formation of cyclopentenones (Scheme 33). Addition of various cuprate species to ethyl propiolate formed a mixed cuprate which is perhaps best represented as the allene (**91**). In the case of heterocuprates (**89**) and (**90**), acylation proceeded in good yield to form the divinyl ketone. Dimethylcuprate afforded none of the desired product but instead produced 1-acetylcyclohexene. The method was generalized for several different acid chlorides.[133]

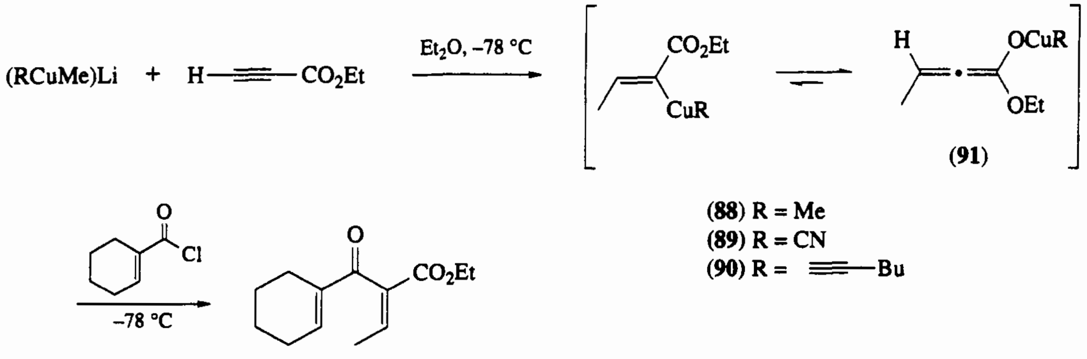
(RCuMe)Li
+
H
CO2Et
Et2O, –78 °C
CO2Et
CuR
H
OCuR
OEt
(91)
O
Cl
–78 °C
O
CO2Et
(88) R = Me
(89) R = CN
(90) R =
Bu

Reagent (**88**) none of desired product
(**89**) 80%
(**90**) 85%

**Scheme 33**

### 1.13.3.3 Acylation of Heterocuprates

The addition of secondary and tertiary dialkylcuprates is often impractical due to the thermal instability of these reagents. For instance it is known that solutions of *s*- and *t*-alkylcopper(I) reagents cannot be cleanly prepared from 2 equiv. of the organolithium and copper(I) iodide even at –78 °C.[134] Posner has developed a method which makes preparation and acylation of these species more practical.[135] The method uses heterocuprates [$R(R^1X)CuLi$] in which $R^1X$ is an alkoxide ion, thiolate or lithium amide ion and R is the transferrable ligand. The most satisfactory results have been obtained when $R^1X$ was derived from *t*-butoxide. The reagents were prepared by addition of lithium *t*-butoxide to copper(I) iodide with formation of copper(I) *t*-butoxide. Addition of *s*-butyl- or *t*-butyl-lithium resulted in formation of the heterocuprate which has been shown to add efficiently to acid chlorides (Table 6).[135] As with many heterocuprates, these reagents are generally stable only to –50 °C, but acylation can proceed in high yield utilizing only 1.2–1.3 equiv. of reagent and product isolation was relatively facile. Similar organocuprates can be prepared from primary alkyllithium reagents and acylation is also facile. Unfortunately, these reagents have not seen a great deal of use in natural product synthesis as yet.

**Table 6** Acylation of Heterocuprate Reagents Derived from Organolithiums and Cuprous *t*-Butoxide

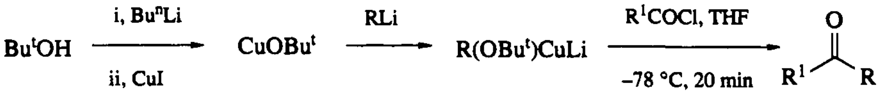

| *Acid halide* | *Cuprate (equiv.)* | *Product* | *Isolated yield (%)* $R = Bu^t$ | $R = Bu^s$ | $R = Bu^n$ |
|---|---|---|---|---|---|
| $Br(CH_2)_{10}COCl$ | 1.2–1.3 (1.5%) | $Br(CH_2)_{10}COR$ | 78 (83) | 83 | |
| PhCOCl | 1.2–1.3 | PhCOR | 82 | 87 | 70 |
| $MeO_2C(CH_2)_2COCl$ | 1.2–1.3 | $MeO_2C(CH_2)_2COR$ | 61 | 66 | |
| $Bu^nCO(CH_2)_4COCl$ | 1.2–1.3 | $Bu^nCO(CH_2)_4COR$ | 73 | 86 | |

Posner has also studied the effect of various other nontransferable ligands in the process. It was concluded that phenylthio was equivalent to *t*-butoxide as a nontransferable ligand, but phenoxy, dimethylamino and *t*-butylthio were inferior (equations 63 and 64).[136]

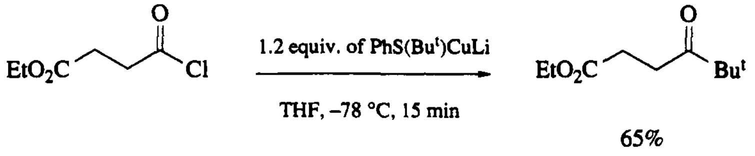

(63)

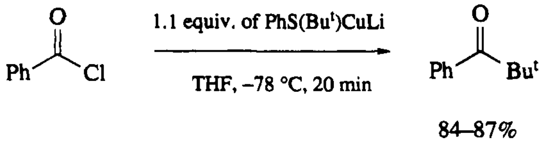

(64)

The importance of achieving the combined goals of high thermal stability for the organometallic and for improving the efficiency of alkyl group transfer has led Bertz and Dabbagh to continue the study of heterocuprates in a variety of transformations including acylation. Although these workers were primarily interested in assaying the thermal stability of new types of heterocuprates, they showed that $Bu^nCu(PPh_2)Li$ or $Bu^nCu(PCy_2)Li$ can be quantitatively acylated by excess PhCOCl after the cuprates had been aged for 30 min at 0 °C and 25 °C (Table 7). They provided a comparison of the reactivity of these reagents with other heterocuprates developed by other workers.[137]

An important development in cuprate acylation methodology that addresses several of the most objectionable properties of the reagents themselves has come from Knochel and his associates.[138] New highly functionalized copper reagents, represented by the formula RCu(CN)ZnI, can be prepared from readily available primary and secondary alkylzinc iodides by transmetallation with the soluble complex $CuCN\cdot 2LiX$ in THF (equation 65).

These reagents have several advantages in acylation chemistry. Once prepared, these lower order cuprates may be used at temperatures near 0 °C rather that the usual –78 °C needed for alkylheterocuprates. Only one transferable ligand is involved per mole of reagent, which avoids the loss of precious substrates. Reaction work-up and product isolation is simplified relative to heterocuprates containing sulfur or phosphorus ligands. The organozinc and the corresponding organocuprate tolerate a wide variety of

Table 7 Comparison of Heterocuprate Reagents for Acylation with Benzoyl Chloride

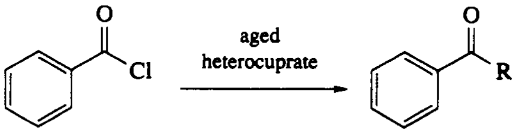

| Entry | Reagent | Solvent | Temperature (°C) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 | $Bu^nCu(PPh_2)Li$ | Ether | 0 (25) | 99 (95) | |
| 2 | $Bu^nCu(PCy_2)Li$ | Ether | 0 (25) | 97 (89) | |
| 3 | $Bu^nCu(NCy_2)Li$ | Ether | 0 (25) | 98 (89) | |
| 4 | $Bu^nCu(NPr^i_2)Li$ | Ether | 0 (25) | 100 (87) | |
| 5 | $Bu^nCu(NEt_2)Li$ | Ether | 0 (25) | 98 (73) | 224 |
| 6 | $Bu^nCu(SPh)Li$ | Ether | 0 (25) | 19 (0)[a] | |
| 7 | $Bu^nCu(C{\equiv}CBu^t)Li$ | Ether | 0 (25) | 92 (89) | 225 |
| 8 | $Bu^nCu(CH_2SO_2Ph)Li$ | THF | 0 (25) | 99 (91) | 226 |
| 9 | $Bu^n_2Cu(CN)Li_2$ | Ether | 0 (25) | 95 (84) | 227 |

[a] The yields after 30 min at –50 °C and –25 °C were 100% and 97%.

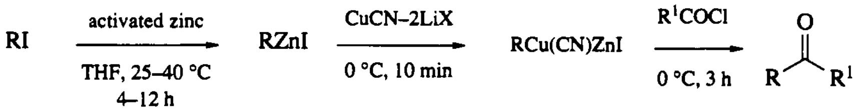

(65)

functionality contained within the original iodide substrate. Ketone, ester and nitrile functionality do not interfere with the generation of the organometallic. In addition, α,β-unsaturated esters are not attacked by these reagents. The yields of acylated organometallic are quite high (Table 8).[138] Further developments of this class of reagent should prove rewarding.

Table 8 Acylation of RCu(CN)ZnI with Acid Chlorides

| Reagent | Acyl halide | Product | Yield (%) |
|---|---|---|---|
| $NC(CH_2)_2Cu(CN)ZnI$ | $PhCOCl$ | $NC(CH_2)_2COPh$ | 83 |
| $NC(CH_2)_2Cu(CN)ZnI$ | $Cl(CH_2)_3COCl$ | $NC(CH_2)_2CO(CH_2)_3Cl$ | 77 |
| $NC(CH_2)_2Cu(CN)ZnI$ | $C_6H_{11}COCl$ | $NC(CH_2)_2COC_6H_{11}$ | 79 |
| $Pr^iCu(CN)ZnI$ | $Ph(OAc)CHCOCl$ | $Ph(OAc)CHCOPr^i$ | 82 |
| $EtO_2C(CH_2)_3Cu(CN)ZnI$ | $PhCOCl$ | $EtO_2C(CH_2)_3COPh$ | 87 |
| $C_6H_{11}Cu(CN)ZnI$ | $PhCOCl$ | $C_6H_{11}COPh$ | 84 |
| $Bu^sCu(CN)ZnI$ | $Cl(CH_2)_3COCl$ | $Cl(CH_2)_3COBu^s$ | 94 |

### 1.13.3.4 Acylation with Thiol Esters

Because of the requirement for a large excess of dialkylcuprate in the reaction with acid chlorides, other acylating agents have been studied. Anderson has shown that *S*-ethyl thiol esters or *S*-phenyl thiol esters react in stoichiometric fashion with homocuprates to provide good yields of ketones (Table 9).[139]

Table 9 Acylation of Dialkylcuprates with *S*-Ethyl Thiol Esters

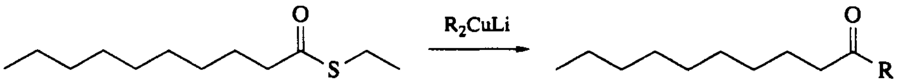

| Homocuprate | Equiv. | Solvent | Temperature (°C) | Time (h) | R | Yield (%) |
|---|---|---|---|---|---|---|
| $Me_2CuLi$ | 1.2 | $Et_2O$ | –78 | 2 | Me | 75 |
| $Bu^n_2CuLi$ | 0.55 | $Et_2O$ | –40 | 2.5 | $Bu^n$ | 89 |
| $Bu^n_2CuLi$ | 1.0 | $Et_2O$ | –40 | 2.5 | $Bu^n$ | 87 |
| $Pr^i_2CuLi$ | 1.1 | THF | –40 | 2 | $Pr^i$ | 66 |

In contrast to the results obtained during the acylation of acid chlorides, nearly quantitative substitution of the thiol ester by each alkyl group of the cuprate takes place. Presumably, the intermediary heterocuprate R(EtS)CuLi, related to those prepared by Posner (*vide supra*), was also sufficiently reactive to provide the ketone from the thiol ester. The yields obtained depend on the reaction temperature and solvent. The transformation was performed by the rapid introduction of the thiol ester to a solution of copper(I) reagent in ether at –40 °C. Reaction times varied from one to several hours and quenching was carried out at low temperature with ammonium chloride. Methyl ketones must be prepared in ether at –78 °C to avoid selfcondensation. These thiol esters undergo bis-addition with standard Grignard or organolithium reagents to form tertiary alcohols unlike the *S*-(2-pyridyl) thioates of Mukaiyama (see Section 1.13.2.2). However, reaction of the thiol esters with 1.5 equiv. of $Bu^nMgBr{\cdot}CuI$ in THF gave *n*-butyl ketones in >80% yield.

The selective addition of diethyl cuprate to the dodecadienethioate shown in equation (66) demonstrates the utility of this methodology. Notice that there is only a small amount of conjugate addition product.[139] In diethyl ether, a large percentage of conjugate addition product is formed, even at –78 °C (equation 66).

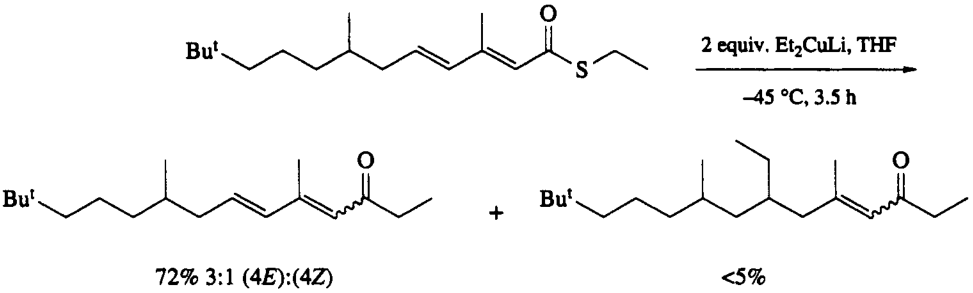

(66)

Another example of this methodology has appeared recently from Masamune and coworkers in connection with a total synthesis of bryostatin (equation 67).[140] The salient point here is the demonstrated utility of the thiol ester, prepared directly through stereoselective boron enolate aldol condensation. Notice that no further activation or removal of a chiral auxiliary is necessary for this transformation, unlike other related aldol methodology.

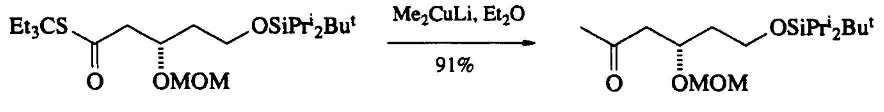

(67)

Researchers at Merck have studied the synthesis of the simple carbapenem system (**94**) through Wittig cyclization of the keto ylide (**93**). This interesting precursor was prepared directly from the thiol ester (**92**) by reaction with lithium dimethylcuprate or magnesium diphenylcuprate (Scheme 34).[141]

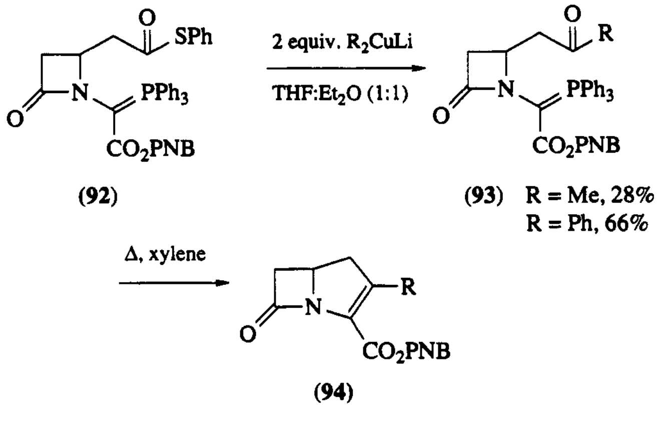

**Scheme 34**

Other acylating agents are similarly effective in the formation of ketones by reaction with homocuprates. Kim has demonstrated that activated esters such as the 2-pyridyl carboxylates are satisfactory cuprate traps.[142] These esters can be prepared from carboxylic acids and 2-pyridyl chloroformate, provided a catalytic amount of DMAP is utilized (Scheme 35).

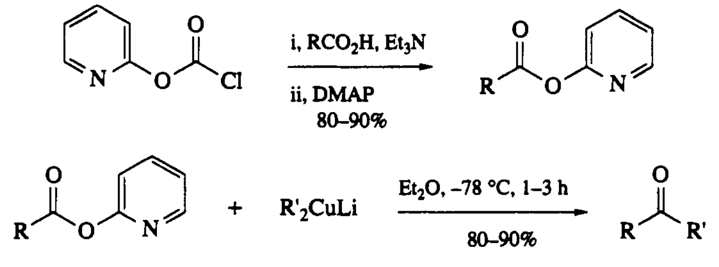
i, RCO2H, Et3N
ii, DMAP
80–90%
+
R'2CuLi
Et2O, –78 °C, 1–3 h
80–90%

**Scheme 35**

Once again these acylating agents are useful for the stoichiometric introduction of simple nucleophilic groups (methyl and *n*-butyl) into multifunctionalized substrates because the intermediate heterocuprate is also acylated (equations 68–70).

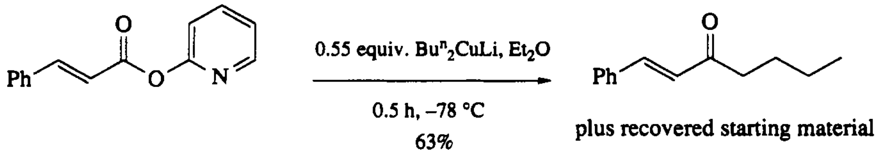
0.55 equiv. BunCuLi, Et2O
0.5 h, –78 °C
63%
plus recovered starting material

(68)

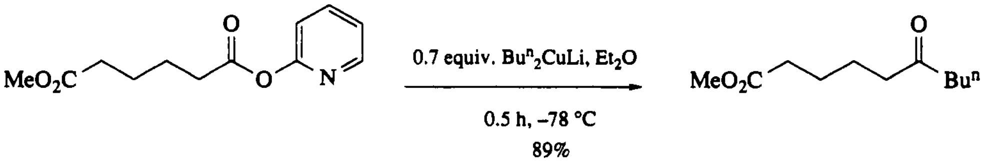
0.7 equiv. Bun2CuLi, Et2O
0.5 h, –78 °C
89%

(69)

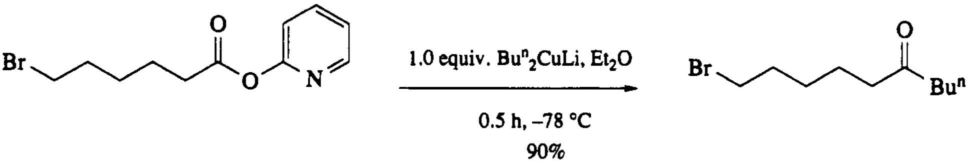
1.0 equiv. Bun2CuLi, Et2O
0.5 h, –78 °C
90%

(70)

Kim[143] has also studied the corresponding acylation of homocuprates by *S*-(2-pyridyl) thioates, discussed earlier in the context of total synthesis of monensin and erythronolide A (Sections 1.13.2.2 and 1.13.3.2). Under the standard anaerobic conditions necessary for cuprate formation, good yields of ketones could be derived from acylation of lithium dimethylcuprate (or lithium dibutylcuprate) by *S*-(2-pyridyl) thiobenzoate and other simple *S*-(pyridyl) thiol esters (equation 71). Interestingly, if the homocuprate is intentionally placed under an oxygen atmosphere before acylation and then reacted with the *S*-(2-pyridyl) thioate in oxygen at –78 °C, one obtains good yields of the corresponding ester (equation 72).

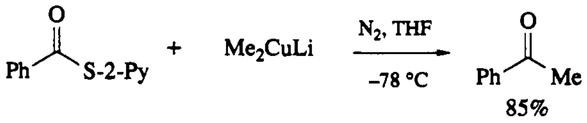
+
Me2CuLi
N2, THF
–78 °C
85%

(71)

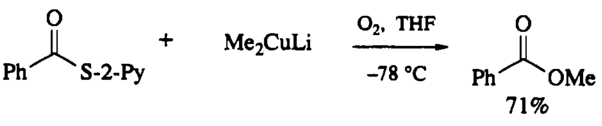
+
Me2CuLi
O2, THF
–78 °C
71%

(72)

### 1.13.3.5 Acylation of α-Trimethylsilylmethylcopper

Potentially useful β-silyl ketones[144] may be obtained through acylation of the trimethylsilylmethylcopper reagent generated from 1 equiv. of copper(I) iodide and trimethylsilylmagnesium bromide. The results obtained with this reagent have varied depending upon the exact conditions used. Normant has found that acylation of trimethylsilylmethylcopper magnesium bromide under palladium catalysis results in the direct formation of the silyl enol ether without formation of β-silyl ketone.[145] It appears that under the latter conditions, the initial product is a β-silyl ketone which then undergoes a palladium- or acid-catalyzed C to O isomerization. Several previous investigations including one by Akiba indicate this is the case. Akiba has shown that β-silyl ketones can be obtained from the stoichiometric copper reagent in good yield, but when treated with a catalytic amount of triflic acid, they underwent immediate isomerization to silyl enol ethers.[146,147] Kishi had earlier prepared 1-(trimethylsilyl)-2-butanone by addition of $Me_3SiCH_2MgBr{\cdot}CuI$ to acetyl chloride affording an 80–90% yield.[148] The report indicated that this transformation is superior to methods which use the corresponding trimethylsilylmethyllithium.[149,150]

The construction of the naturally derived narbomycin[151] and tylosin-aglycones[152] by Masamune and coworkers employ identical methodology for seco-acid formation. In each case, Peterson alkenation of a functionalized aldehyde (not shown) and the silyl ketones (**96**; R = $SiMe_3$; Scheme 36) or (**99**; Scheme 37) efficiently introduced the required (*E*)-α,β-unsaturation. Silyl ketone formation is accomplished in each case through cuprate acylation by an activated carboxylic acid derivative. Formation of an acid chloride was not possible in the sensitive tylosin-aglycone intermediate; however, selective acylation of the silylcuprate proceeded at the pyridyl thiol ester moiety of (**98**) and not with the *t*-butyl thiol ester. In a related investigation,[153] (**97**), an advanced intermediate for 6-deoxyerythronolide B, was obtained from (**95**) *via* addition of lithium diethylcuprate to the acid chloride (84% yield). In all the above cases, no addition was observed at the *t*-butyl thiol ester.

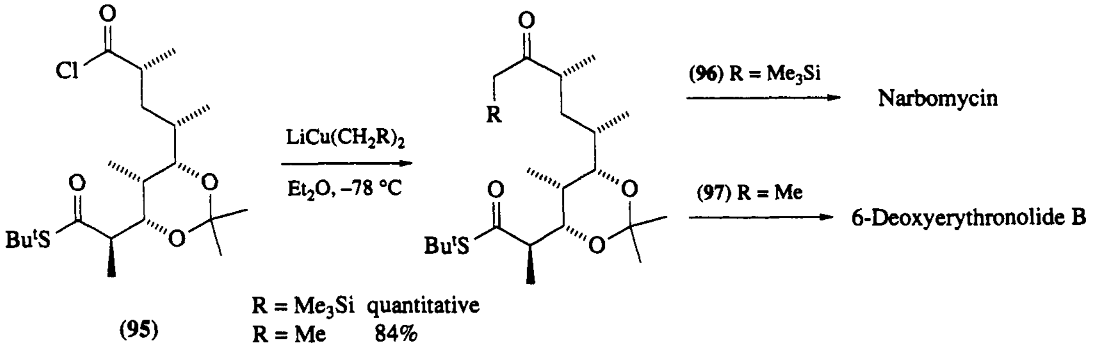

Scheme 36

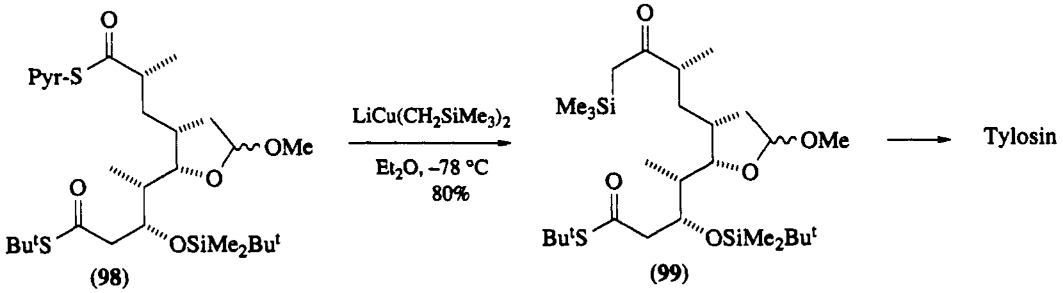

Scheme 37

## 1.13.4 ACYLATION MEDIATED BY LOW-VALENT PALLADIUM COMPLEXES

### 1.13.4.1 Acid Chlorides and Organostannanes

The acylation of the mildly nucleophilic organostannanes was first reported by Migita in 1977[154] through the use of palladium catalysis. However, the reported conditions were harsh and of limited scope. Nearly simultaneously, Stille and Milstein reported a more comprehensive study of this method,[155] including mechanistic and synthetic studies. Their work also formed the basis for the discovery of improved reaction conditions for acylation.[156] Equimolar amounts of an acid chloride and tetrasubstituted organotin undergo acylation with palladium catalysis in HMPA to afford high yields of ketones wherein one of the tin substituents has been acylated (equation 73). Transfer of a second substituent from $R_3SnCl$ is 100 times slower than transfer from $R_4Sn$ but can still be useful. $R_2SnCl_2$ and $RSnCl_3$ do not under go acylation. The reaction can be carried out in the presence of the following functional groups without interference: $NO_2$, $RC{\equiv}N$, aryl halide (≠ Br), vinyl, methoxy, carboxylic esters and aldehydes. The latter functional group is not tolerated by any other method of ketone formation that involves organometallic addition to a carboxylic acid derivative. An especially interesting case is that of *p*-acetylbenzaldehyde (equation 74) which serves to introduce the method. The product, a keto aldehyde, is generally difficult to prepare by other methods since it undergoes rapid selfcondensation.

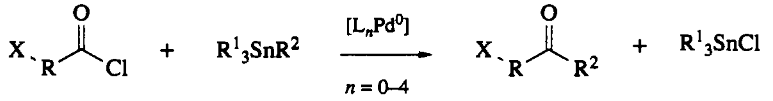

(73)

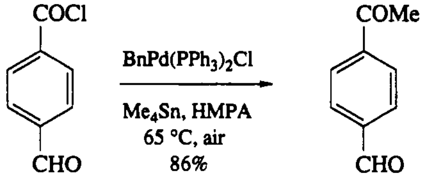

(74)

Other aromatic and aliphatic acid chlorides give good to excellent yields of the desired ketones using this procedure. Hindered or α,β-unsaturated acid chlorides also function effectively, the latter forms α,β-unsaturated ketones without competing conjugate addition (equations 75 and 76).

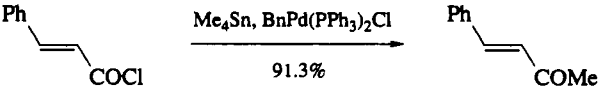

(75)

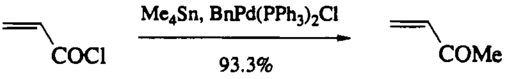

(76)

There is no need for an inert atmosphere as both the catalyst and organostannane are air stable; in fact the reaction is accelerated by the presence of oxygen. Depending on the solvent, reaction times are very short, an hour or less in HMPA and under 24 h for solvents like chloroform, THF and dichloroethane. The end of the reaction is dramatically signaled by the precipitation of metallic palladium from the clear reaction solution.

The acylation is limited to the use of acid chlorides due to their unique ability to oxidatively add palladium(0); other acylating agents are not generally useful in this context. It was also known that acid chlorides do not react with organotins without Lewis acid catalysis and more importantly organotins do not generally react with the expected product, the ketone, except under very strong Lewis acidic conditions.[157] Even diacid chlorides may be utilized in this process (equation 77); however, oxalyl chloride cannot be used due to the indicated decarbonylation of the intermediate acid chloride (equation 78).[155]

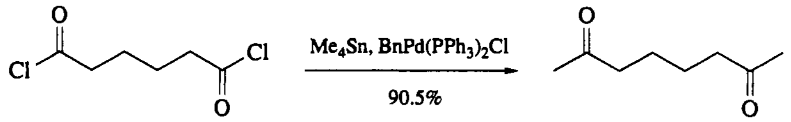

(77)

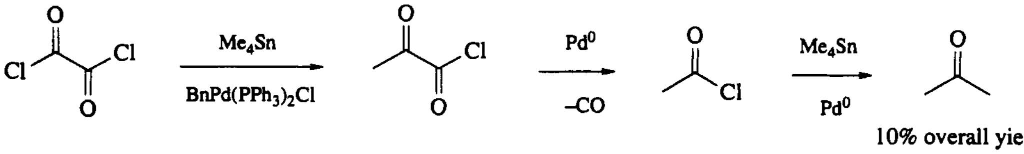

(78)

α-Diketones have been prepared by the reaction of acylstannanes and acid chlorides.[158] Few cases have been studied thus far and the yields for unsymmetrical α-diketones were moderate at best. Two by-products have been observed in the reaction. Decarbonylation made up 4–20% of the material balance and degradation of acyl-tri-*n*-butyltin resulted in *n*-butyl ketone, although the latter mode of decomposition only accounted for a few percent of the reaction product (Scheme 38).

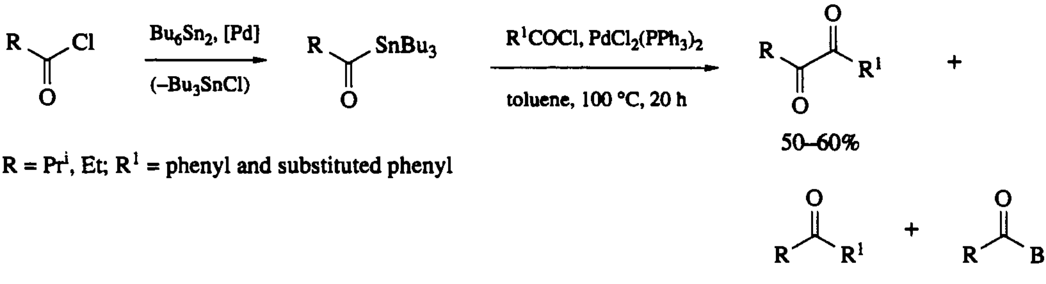

R = $Pr^i$, Et; $R^1$ = phenyl and substituted phenyl

Scheme 38

Symmetrical diketones have been prepared in a similar fashion from 2 mol of the acid chloride and 1 mol of hexabutylditin with palladium catalysis (equation 79). The yields were still moderate.[159]

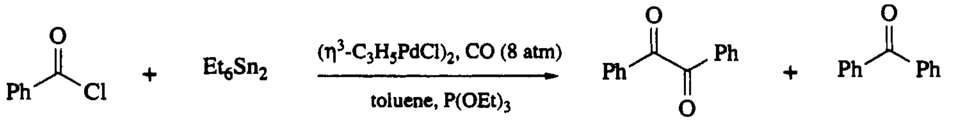 (79)

Soderquist has reported a slightly more effective method not subject to the losses due to decarbonylation of intermediates.[160] Acylation of α-methoxyvinyltin (**100**) under palladium(0) catalysis afforded a good yield of the α-methoxyenone (**101**). Hydrolysis in acetone/aqueous acid releases the diketo functionality (equation 80). Only the unsubstituted vinyl system has been employed thus far.

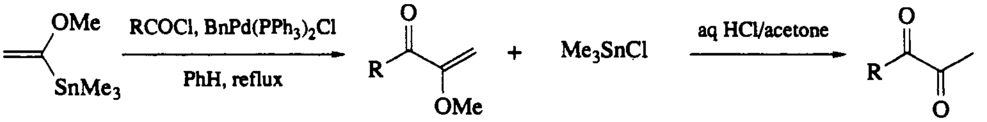 (80)

**(100)** **(101)**

R = Me, 65%
R = Ph, 75%

R = Me, 44%; R = Ph , 73%; R = $Bu^t$, 79%

Prior to the studies which uncovered the utility of organotin acylation as described in the preceding paragraphs, acid chlorides were also found to undergo a similar rhodium(I)-mediated acylation with allyltins to form β,γ-unsaturated ketones.[161] The palladium(0)-catalyzed coupling has been found to be more general with respect to varied substitution patterns of both reagents and could be conducted under essentially neutral conditions (see Section 1.13.5.1).

### *1.13.4.1.1 Mechanistic studies of palladium-catalyzed acylation*

The mechanism of palladium-catalyzed coupling of organic halides with tetrasubstituted organotins has been widely studied by Stille[162] and a general understanding of the mechanism is critical to further developments in this area. The use of other organometallics in palladium-catalyzed acylation will follow this discussion, as well as further examples where this method has been used.

Thus far we have discussed numerous examples whereby selective ketone formation has been achieved through organometallic acylation. The problem was approached by choosing a less nucleophilic organometallic which can be acylated but does not interact with the desired product. Thus far, few reagents with this type of selectivity have been found (organocuprates). Most often, the strategy was to either preserve the tetrahedral intermediate formed upon nucleophilic addition or to activate the substrate towards nucleophilic attack by prior coordination of the organometallic. A conceptually different approach, achieved through the use of transition metals, alters the mechanism of acylation such that carbon–carbon bond formation is not part of the rate-determining step. Many examples of the formation of acylmetal complexes have been reported in the literature.[163] Depending upon the nature of the metal and the degree of coordination, these complexes can function as nucleophiles or as electrophiles in reactions with organic substrates. An example of a nucleophilic acylmetal complex used in ketone synthesis was reported by Collman. Nucleophilic acyliron(0) complexes such as (**102**) readily undergo oxidative addition (akin to nucleophilic displacement) with alkyl halides to form the hexacoordinate acylalkyliron(II) species (**104**) or (**105**). These are unstable with respect to reductive elimination of the alkyl and acyl ligands and the complex degrades to form a ketone and complexed iron(0).[164] The carbon–carbon bond formation is therefore a result of electronic reorganization of the metal driven by the stability (or lack thereof) of the particular oxidation state with the given ligands.

The acyliron(0) complex (**102**) has been isolated and subjected to the same nucleophilic displacement (or equivalently oxidative addition) with excellent correlation (Scheme 39). The same species is also readily available from acid chlorides (*i.e.* formation of **103**), but the overall process has not been widely used in the synthesis of ketones (Scheme 40).[165] The final step of the process, a reductive elimination of acyliron(II) complex (**104**) or (**105**), is quite rapid and it has not been possible to isolate and identify the presumed intermediates in this case (Scheme 41). Since the oxidative addition of the acyliron complex with the alkyl halide is extremely mild, the corresponding ketone formed in the reaction is not subject to attack by organometallic reagents and no tertiary alcohol is formed.

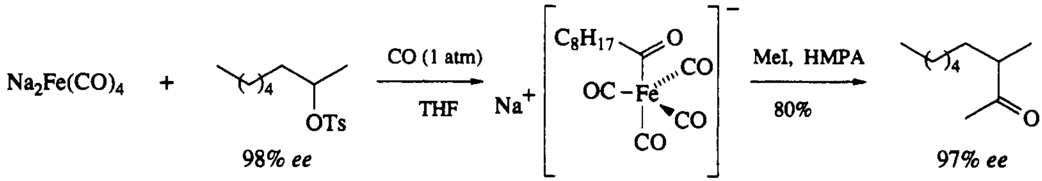

(**102**)

**Scheme 39**

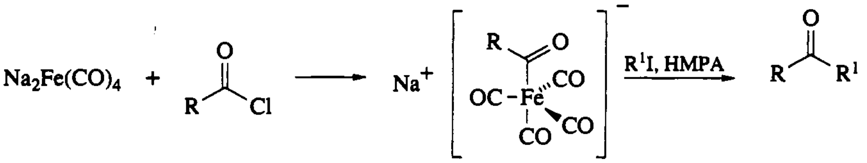

(**103**)

**Scheme 40**

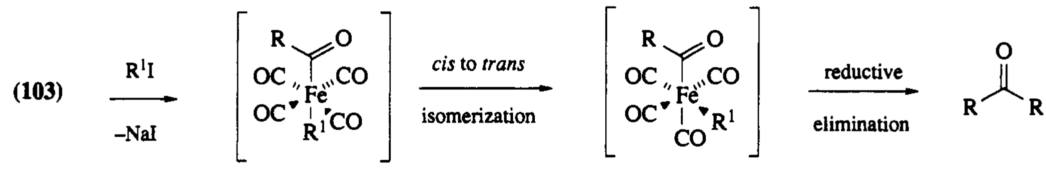

(**104**) (**105**)

**Scheme 41**

Palladium(0) complexes are well known to suffer oxidative addition with acid chlorides.[166] The resulting acylpalladium(II) complex (**106**) is, in contrast to the acyliron(II) complex discussed above, an electrophilic species which is subject to nucleophilic attack by various organometallics. Stille has studied the addition of organotins because they undergo rapid nucleophilic addition to the acylpalladium(II) complex, but do not add to either the acid chloride or react with the ketone (Scheme 42). There are also several other organometallics useful in this sense (*vide infra*).

Both of the described processes, nucleophilic acyliron or electrophilic acylpalladium, rely upon the rapid degradation of organoacyl metal complexes by a net reduction of the metal to a low-valent form with creation of a carbon–carbon bond. The precise mechanism involved in the formation of each high-valent complex is complementary and interesting but irrelevant to the resulting ketone formation, due to

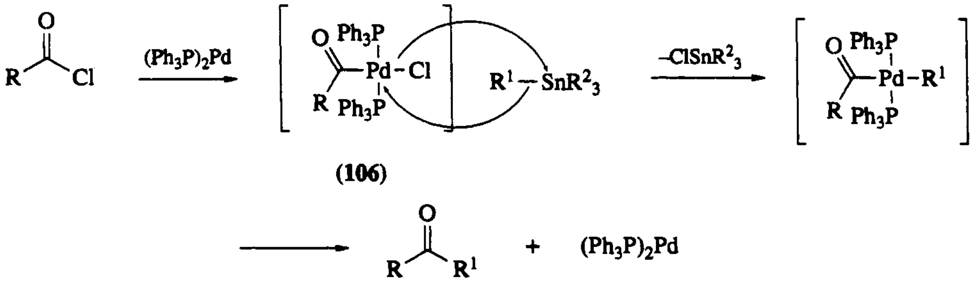

**(106)**

**Scheme 42**

reductive elimination. Many examples of these processes have been described with other metals, but are beyond the scope of this discussion.[167] The particular case of organocuprates may also fit into the same model. One can envision an oxidative addition of a dialkylcuprate (a copper(I) complex) to the acid chloride forming an acylcopper(III) species. Reductive elimination returns copper(I) and generates the ketone. At present, however, there is no evidence for this latter supposition, none of the intermediates in the organocuprate acylation have been characterized and researchers are only now beginning to understand the complex chemistry of organocuprates.[168]

### *1.13.4.1.2 Effect of the catalyst*

Returning to the palladium-catalyzed process, we begin with a discussion of the catalytic cycle and particularly the function of the metal, the effect of phosphine ligands and the identity of the organopalladium intermediates along the route. What will become important is the rate at which these intermediates are transformed along the reaction pathway, and whether or not a step in the catalytic cycle is made rate limiting through the addition or omission of a particular reagent, solvent or ligand.

The rapid rate of oxidative addition of palladium(0) to an acid chloride has been attributed to the extended bond length and highly polarized nature of the carbon–chlorine bond.[169] The half life for oxidative addition of tetrakis(triphenylphosphine)palladium(0) to benzoyl chloride has been measured at approximately 10 min at –40 °C.[170] Palladium(0) is required for oxidative addition but large effects on the reaction rate may be observed depending on the degree and type of ligation around this metal. Electron-donating ligands, such as triarylphosphines, tend to make palladium more nucleophilic, but they also increase steric interaction with the substrate.[172] Palladium(0) catalysts are also air sensitive making their handling a problem. It is often beneficial to introduce the catalyst in the form of a palladium(II) species that is more stable to atmospheric conditions. In a separate step, reduction of the palladium(II) complex occurs by one of several mechanisms to a suitable form of solvated or ligated palladium(0), which undergoes reaction. Stille has found that benzyl(chloro)bis(triphenylphosphine)palladium(II), formed as shown in equation (81), is an excellent catalyst precursor for acylation of organotins by acid chlorides.[155]

$$Pd^0(PPh_3)_4 + PhCH_2Cl \longrightarrow PhCH_2Pd^{II}(PPh_3)_2Cl + 2\,PPh_3 \qquad (81)$$

The actual acylation catalyst for alkyltins and acid chlorides is generated through sacrificial transmetallation of the organotin to form a new palladium(II) complex with release of trialkyltin halide (see Scheme 43). Reductive elimination then forms a small amount of benzylated adduct and the coordinatively unsaturated and highly nucleophilic catalyst bis(triphenylphosphine)palladium(0) [$Pd^0(PPh_3)_2$]. The generalized mechanism for acid chloride insertion and coupling is depicted in Scheme 43. Oxidative addition of $Pd^0(PPh_3)_2$ to the acid chloride forms an observable and isolable palladium(II) complex (**107**).[155] Transmetallation of a single tin ligand affords *trans*-acylalkylpalladium(II) complex (**108**) which is not observable but then undergoes a rapid *trans* to *cis* migration, possibly involving dissociation of one of the ligands.[190] The *cis* complex (**109**) immediately undergoes reductive elimination to the product and returns the palladium(0) complex.

Commercially available $Pd^0(PPh_3)_4$ also catalyzes the process depicted above, but observations indicate that the reaction rate is significantly depressed over those seen with $PhCH_2Pd^{II}(PPh_3)_2Cl$.[155] This is true even though the same coordinately unsaturated complex, $Pd^0(PPh_3)_2$, is responsible for catalysis in both cases through the well-known dissociative process shown in equation (82).[171]

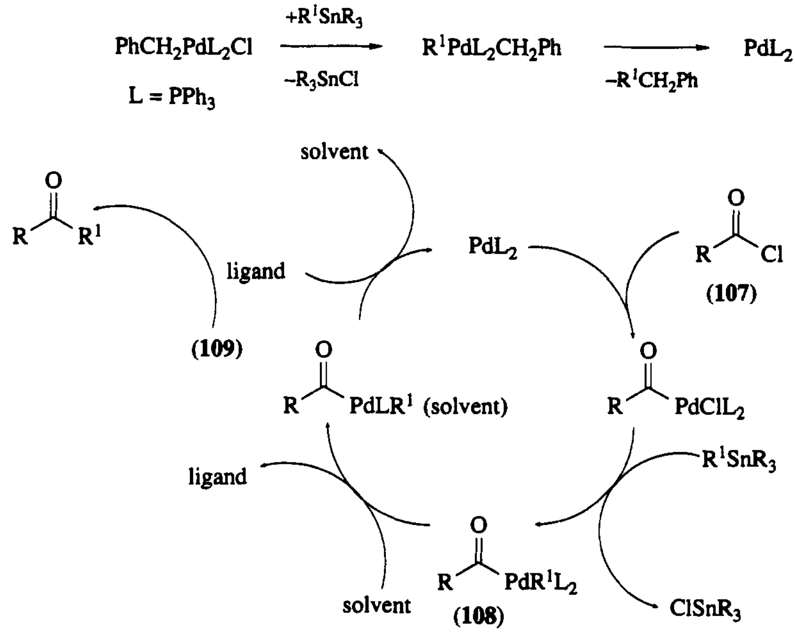

**Scheme 43**

$$\mathrm{Pd^0(PPh_3)_4} \rightleftharpoons \mathrm{Pd^0(PPh_3)_2} + \mathrm{2PPh_3} \qquad (82)$$

The inclusion of additional triphenylphosphine in reactions catalyzed by $PhCH_2Pd(PPh_3)_2Cl$ results in a deceleration of the oxidative addition process. The highly reactive coordinatively unsaturated catalyst $Pd^0(PPh_3)_2$ now becomes part of the equilibrium shown above. Since in this case coordinatively saturated $Pd^0(PPh_3)_4$ first undergoes dissociation, the added ligand shifts the equilibrium towards the left and decreases the rate of oxidative addition.[172] In mechanistic studies to be discussed later, the effect of added triphenylphosphine was found to be the greatest during oxidative addition. Smaller effects of this ligand were observed in the ensuing transmetallation and reductive elimination.

Other potential sources of catalyst for the acylation include the air- and moisture-stable dibenzylideneacetone complex of palladium(0); $Pd^0_2(DBA)_3{\cdot}CHCl_3$.[173] This complex reacts with triphenylphosphine to form coordinatively unsaturated complexes *in situ* but has been used infrequently for acylation.[174] So-called 'ligandless catalysts' have been exploited with promising results. Ligandless palladium complexes such as $RPd^0XL_2$ (L = solvent) contain no phosphine-derived ligands but instead are merely solvated by the reaction medium. These complexes are among the most active catalysts for cross-coupling and can be formed *in situ* from either $(\eta^3\text{-}C_3H_5Pd^{II}Cl)_2$, $(MeCN)_2Pd^{II}Cl_2$ or $Pd^{II}Cl_2{\cdot}LiCl$ through metathesis with the organotin. Acid chlorides will suffer oxidative addition by these complexes and good yields of ketones are obtained (Scheme 44).[175]

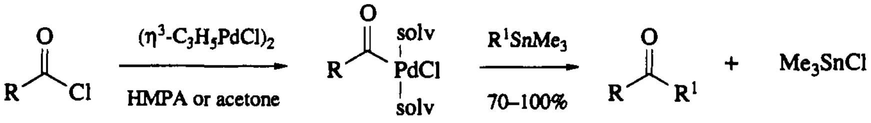

R = Ph; $R^1$ = Me, Bn, vinyl, Ph, *p*-$ClC_6H_4$, *p*-$CNC_6H_4$, *p*-$NO_2C_6H_4$, 2-thenoyl,
R = Me, *o*-$FC_6H_4$, Bn, PhCH=CH, *p*-$ClC_6H_4$; $R^1$ = Ph, Me

**Scheme 44**

Aromatic or α,β-unsaturated acid chlorides were found to undergo rapid oxidative addition with these palladium complexes, and the subsequent acylation of an organotin proceeded smoothly in HMPA (1–60 min) or in acetone. Formation of simple aliphatic acylpalladium(II) complexes proceeds at markedly reduced rates and the acylation of organotins is slower but still useful (10–24 h).

The formation of the acylated palladium(II) species has been formulated as shown in Scheme 45. The sequence relies on strong solvent participation to prevent precipitation of palladium(0) during reductive elimination of intermediate complex (**110**). When tetramethyltin or benzyltrimethyltin is to be used in this process it is necessary to introduce a small amount of $Me_6Sn_2$ to aid in the formation of the active catalyst. These organotins are slow to react with $(\eta^3\text{-}C_3H_5PdCl)_2$.

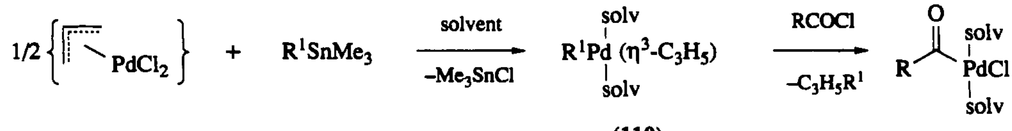

**(110)**

**Scheme 45**

### *1.13.4.1.3 Effect of solvent, catalyst concentration and oxygen*

Several factors were found to influence the rate of the Stille acylation process, including an acceleration effect by oxygen and also acceleration by the use of polar solvents such as HMPA. Oxidative addition to the acid chloride forms a *trans*-acylpalladium(II) complex which can in principle degrade by the loss of carbon monoxide. In some cases it is advantageous to use an atmosphere of CO to reverse this process.[176] The initial rate was also found to be critically dependent on catalyst concentration. Surprisingly, high catalyst concentrations do not accelerate the reaction and are in fact only slightly more effective than low levels of palladium (see Table 10). The initial rate and $t_{1/2}$ were found to be sensitive to the concentration of palladium complex between 0 and $3 \times 10^3$ M, but became constant above this concentration. The optimal catalyst concentration for the reaction shown in Table 10 is about $7 \times 10^{-4}$ M in $PhCH_2Pd(PPh_3)_2Cl$.[155]

**Table 10** Dependence of Reaction on Catalyst Concentration

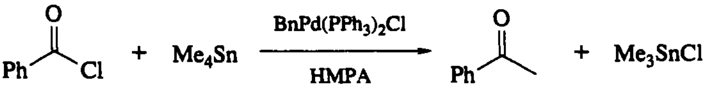

| *[Catalyst] (mol $L^{-1} \times 10^{-4}$)* | *Turnover number* | *Initial rate (mol $L^{-1}$ $min^{-1}$ × $10^{-4}$)* | *$t_{1/2}$ (min)* |
|---|---|---|---|
| 0.866 | 14925 | 30.72 | 125 |
| 1.73 | 7692 | 76.80 | 60 |
| 6.94 | 1852 | 172.80 | 38 |
| 8.30 | 1563 | 70.40 | 50 |
| 30.4 | 422 | 46.08 | 128 |
| 75.5 | 170 | 40.96 | 115 |
| 149.4 | 86 | 42.24 | 120 |

[PhCOCl] = 1.28 M, $[Me_4Sn]$ = 1.40 M.

The exact reasons for this behavior are not clear; however, deactivation at high concentrations may be due to dimerization of the catalyst which liberates triphenylphosphine as shown in equation (83). As discussed, the reaction is significantly impeded by added phosphine.

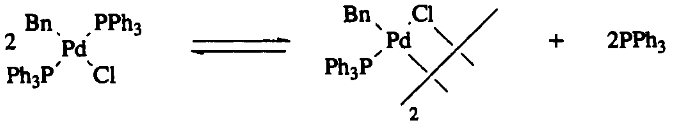

(83)

Although it is not certain by what mode added oxygen accelerates the catalytic process, it has been proposed that oxygen initiates a radical-based oxidative addition to palladium which is several orders of magnitude faster than the alternative nucleophilic displacement occurring largely under inert atmosphere.[177] Radical scavengers predictibly override the rate enhancement due to oxygen. It is possible that at least two mechanisms are active to some extent during oxidative addition.[178] One path involves nucleophilic addition, displacement of chloride with possible formation of a cationic metal complex, and collapse to RCOPd(L$_2$)X.[179] The other process may involve halide abstraction, electron transfer to form a radical pair (L$_2$Pd$^{I}$X + RCO·) which can collapse to RCOPd(L$_2$)X.[179] In this case oxygen can act as the electron acceptor to initiate the process. The latter proposition is based upon CIDNP effects observed during oxidative addition of platinum and palladium complexes to alkyl halides.[180] Latter stages of the process, including transmetallation and reductive elimination, are not enhanced. The stoichiometric reaction of isolated acylpalladium complex (**107**) (Scheme 43; R = Ph) with tetraalkyltins (transmetallation, *trans* to *cis* isomerization and reductive elimination) was actually shown to be retarded by the presence of oxygen.[181]

Originally, it was felt that a polar solvent such as HMPA was a requirement for the reaction; however, subsequent work has shown that even nonpolar solvents such as chloroform can be used with only a small decrease in yield and in reaction rate.[182] The work-up was made considerably simpler by this change and in some cases the reaction is made more selective over similar reactions using HMPA. Bromoaromatic compounds such as 4-bromobenzoyl chloride are converted to the acetophenone without replacement of the halogen. In HMPA, up to 26% of the 4-methylacetophenone is produced. No bromination or elimination was observed from substrates such as 6-bromohexanoyl chloride. It is known that cyclic ethers such as THF may be cleaved with acylpalladium(II) halide complexes in the absence of tetraalkyltins, but this solvent can still be used effectively for ketone synthesis since the rate of organotin acylation exceeds that of the degradation reaction.[183] A strong coordination of the acylpalladium complex by THF is indicated by these observations. Interestingly, solvent effects play a role in the selectivity of acylation when using allylic stannanes. In equations (84)–(86), the use of CHCl$_3$ rather than THF led to multiple addition products.[182]

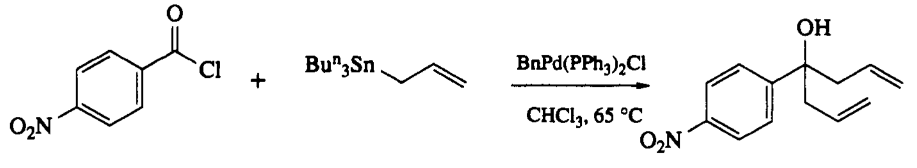

(84)

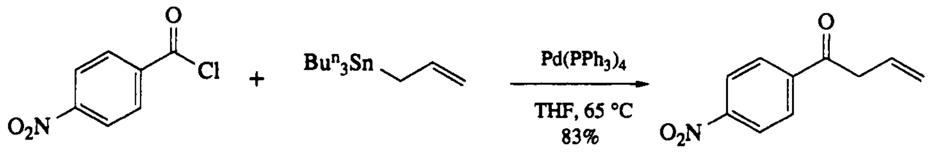

(85)

90:10 β,γ:α,β

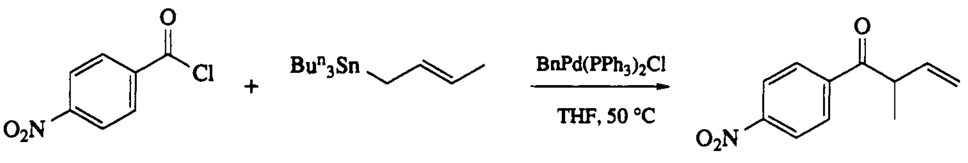

(86)

83:17 mixture with γ-isomer

The palladium(II) catalyst, because of its Lewis acidity, may play a role in the addition of allylic tin to the ketone; however, acylation of crotyltin was not reported to form a tertiary alcohol using palladium(II). It appears that solvent effects dominate in these cases. As part of the same study, substituted vinylstannanes were shown to undergo acylation with retention of configuration; however, the resulting α,β-unsaturated ketones were not configurationally stable to the reaction conditions. Isomerically pure (*Z*)-1-propenylstannane was acylated to afford a 50:50 mixture of alkenes (equation 87). The (*Z*)-α,β-unsaturated ketone was shown to isomerize to a mixture of (*Z*)- and (*E*)-isomers under the reaction conditions. Mixtures of (*Z*)- and (*E*)-2-substituted vinylstannanes were acylated to afford mainly the (*E*)-α,β-unsaturated ketone (equation 88).[184]

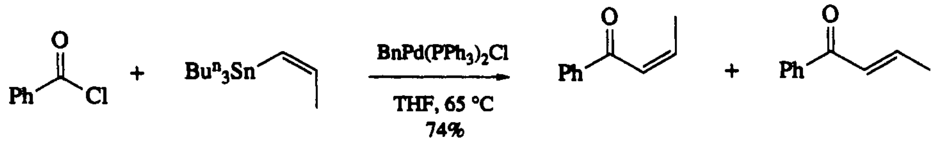

(87)

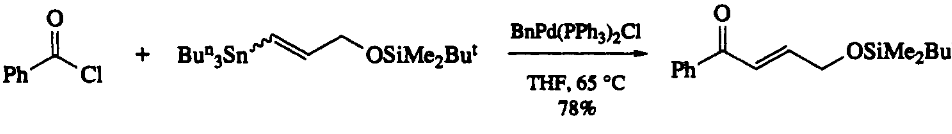

(88)

### 1.13.4.1.4 *Transmetallation and reductive elimination*

The acceleration of palladium-catalyzed acylation of organostannanes with polar solvents is thought to originate in the transmetallation and reductive elimination sequence. Kinetic studies have shown that the transmetallation of the tin substituent is rate limiting for reactions catalyzed by BnPd$^{II}$(PPh$_3$)$_2$Cl and in the absence of excess triphenylphosphine. Support for transmetallation of the acylpalladium(II) chloride by the stannane, and direct evidence for the existence of the acylpalladium complex in solution was obtained from $^{31}$P NMR using the reaction shown in equation (89).[185] After the reaction had proceeded for 1.5 h at 65 °C, the $^{31}$P resonance due to BnPd$^{II}$(PPh$_3$)$_2$Cl at δ 28.7 disappeared and a new resonance at δ 19.8 was observed. The latter correlated exactly with spectra of independently prepared PhCO-Pd$^{II}$(PPh$_3$)$_2$Cl.[186] The build up of this intermediate in the catalytic process suggests the transmetallation was rate limiting. Acylarylpalladium(II) complexes (**108**) and (**109**) (Scheme 43) were not observed spectroscopically, intimating that the reductive elimination was not a rate-limiting process. Also, it was not possible to observe the presence of the presumed palladium(0) catalyst (PPh$_3$)$_2$Pd$^0$ which demonstrates that oxidative addition was not rate limiting.

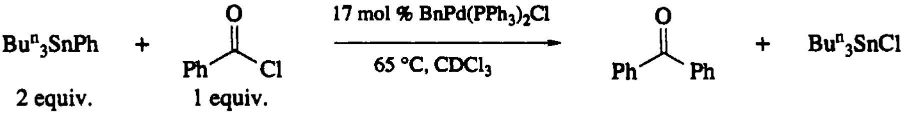

(89)

The order of reactivity in the transmetallation of organostannanes to the acylpalladium(II) complex (**107**) has been found to be PhC≡C > PrC≡CH > PhCH=CH, CH$_2$=CH > Ar > allyl, benzyl > MeOCH$_2$ > Me > Bu.[185] The order of reactivity indicates that substantial amount of charge is borne by the migrating group and is consistent with electrophilic attack by the acylpalladium(II) complex. In most cases with diverse substituents attached to tin, alkyl groups will not be transferred and the better migrating ligand is always the one to be consumed. Alkyl groups can only be transferred with tetraalkylstannanes. Tetramethyltin is commercially available and has been used for the purpose of preparing methyl ketones. The tetraorganotin reagents transfer the first group rapidly but the second leaves about 100 times slower. Usually stoichiometric amounts of acid chloride and stannane are used.

As discussed earlier, the transmetallation segment occurs with retention of stereochemistry in the case of vinylstannanes, although the thermodynamic isomer usually predominates. Stille has provided evidence that transmetallation of alkyl substituents occurs with inversion of configuration based upon the acylation of (*S*)-(–)-(α-deuteriobenzyl)tributyltin ([α]$^{20}_D$ –0.328° (neat) approx. 75% *ee*). Although the final product was sensitive to racemization, the authors could conclude that at least 65% stereospecificity was realized in this process. The last step, reductive elimination has been shown to proceed with retention of configuration (equation 90).[187]

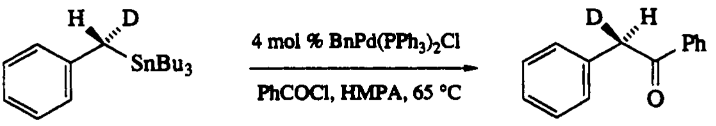

(90)

Reductive elimination from the acylorganopalladium(II) complex is generally a facile process. The rate is influenced by the solvent polarity and added triphenylphosphine.[188] Reductive elimination has been shown to be faster than the elimination of palladium hydride from intermediate (**111**) in both chloroform and HMPA (Scheme 46).[189] This makes the process useful even for alkyl group acylation.

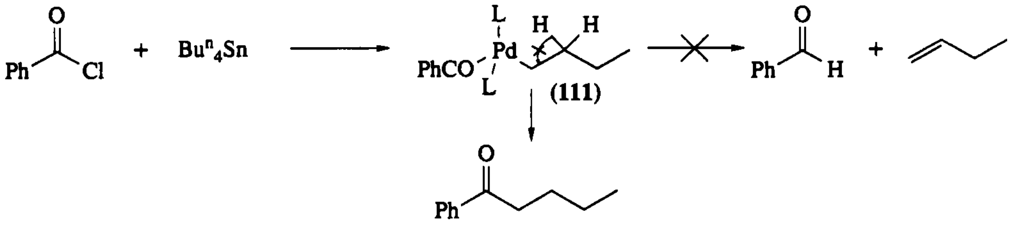

Scheme 46

Kinetic studies indicate that reductive elimination is preceded by a dissociation step in which a phosphine ligand is removed. This places the migrating groups on adjacent sites for elimination from a tricoordinate species. Recall the rate retardation caused by addition of triphenylphosphine to a stoichiometric reaction of RCOPd$^{II}$L$_2$Cl and R$'_4$Sn. This would be expected if ligand dissociation is a necessary step in *trans* to *cis* migration prior to reductive elimination (Scheme 47).[190]

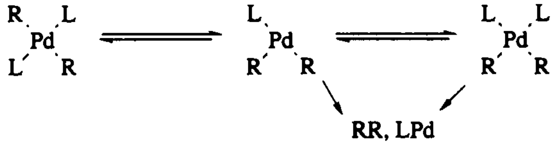

Scheme 47

Polar solvents may lower the activation energy needed for removal of a phosphine ligand by substitution with a weaker solvent ligand at the site of unsaturation. During reductive elimination, palladium obtains two electrons from the displaced groups, therefore strong $\sigma$-donation from these groups is more important than continued electron donation from a phosphine. Strongly donating phosphine ligands tend to reduce the rate of reductive elimination by keeping the electron density on the metal relatively high.[190] Although additional phosphine ligand was observed to slow the rate of reductive elimination by displacing the equilibrium shown in Scheme 47, the overall rate of the catalytic reaction is effected to a much greater extent, indicating a more substantial hindering effect during oxidative addition.[155] Beletskaya has shown that oxidative addition of palladium to the acid chloride is not dependent upon the $\sigma$-donation of phosphine ligands and advocates the use of ligandless palladium in these reactions.[175]

The end of the reaction is signified by the precipitation of metallic palladium as bis(triphenylphosphine)palladium(0) undergoes disproportionation in the absence of the acid chloride (equation 91).

$$2\mathrm{Pd(PPh_3)_2} \longrightarrow \mathrm{Pd(PPh_3)_4} + \mathrm{Pd} \qquad (91)$$

### 1.13.4.2 Sources of Tetrasubstituted Stannanes

Aromatic, heterocyclic, alkynyl, alkenyl and alkyl stannanes have all been shown to be useful as the nucleophilic partner in palladium-catalyzed acylation.[191] The organostannanes are not water or air sensitive and may be prepared easily by one of several general strategies;[192] a few simple organotins are commercially available. The application of trimethyl- or tri-*n*-butyl-stannyl anions with organic electrophiles provides the most versatile approach to these derivatives; a wide range of functionality may be tolerated as part of the electrophilic substrate. Alternatively, trialkyltin halides or sulfonates may be reacted with common organometallic agents, including Grignard, organolithium and organoaluminum reagents. The functionality which is to be introduced into the organostannane by the latter method is limited by the choice of the organometallic; however, both approaches have seen a great deal of use. Once tin is incorporated into an organic substrate, selective manipulation of other functional groups on the molecule may subsequently be carried out. Selective reactions such as lithium aluminum hydride reduction or permanganate- and chromium-mediated oxidation have been demonstrated, as well as a variety of nucleophilic addition and acid–base chemistry. The organotins may be purified by distillation or silica gel chromatography. Other methods of organotin construction, which have been employed recently, include the free radical addition of organotin hydrides to substituted alkenes or alkynes, the palladium-catalyzed coupling of hexaalkyldistannanes with aryl or benzylic and allylic systems and the formation of $\alpha$-stannylated ketones through reaction of trialkyltin amides with simple ketones.

### 1.13.4.3 Acylation of Organostannanes with Acid Chlorides

Several interesting uses of palladium-mediated acylation in organic synthesis have appeared recently. In the synthesis of the marine natural product diisocyanoadociane completed by Corey, formation of optically active enone ester (**112**) was accomplished under the conditions shown in equation (92).[193] Note that tetrakis(triphenylphosphine)palladium(0) was used as the catalyst and the reaction was conducted under an inert atmosphere without severely impeding its completion (2 h).

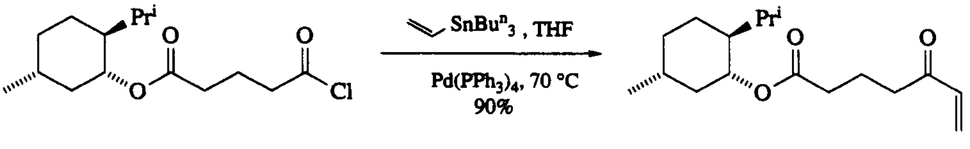

(92)

**(112)**

The conditions used by Stille provided an increased rate of conversion in a related synthesis of a steroid precursor (equation 93); however, HMPA was the solvent.[194] Enone (**113**) was previously synthesized in 40–44% yield by aluminum chloride mediated acylation of ethylene.[195]

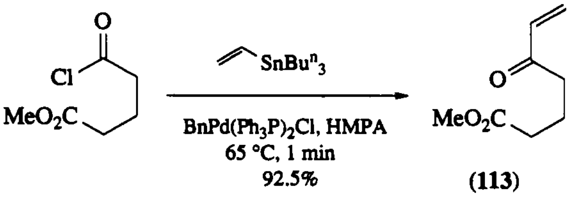

**(113)**

(93)

Preparation of the macrolide antibiotic pyrenophorin may be accomplished through Mitsunobu coupling of two identical fragments derived from (**114**; equation 94). Stille has completed a formal synthesis of this molecule with minimal protection of the precursor, through palladium-mediated acylation of organotins.[196,197] Several modifications of the original procedure[155] were incorporated as part of this synthesis to facilitate isolation of the product and to avoid side reactions caused by decomposition of the intermediate acylpalladium species. Replacement of the preferred solvent HMPA with chloroform caused a reduction in the reaction rate but the work-up was considerably easier. Reaction times in chloroform vary depending on the degree of substitution on the organotin. Unsubstituted vinyltins react in less than an hour; however, di- and tri-substituted vinylstannanes transfer the alkene group at progressively slower rates, ranging from 20 to 72 h, respectively. In the synthesis of enone ester (**114**) shown in equation (94), two charges of the stannane were required during the 30 h reaction period before complete consumption of the acid chloride was noted. A total of 1.6 equiv. of stannane were added. Additionally, carbon monoxide was necessary to reverse the observed decomposition of the intermediate acylpalladium complex; the latter modifications served to improve the yield by 40%.

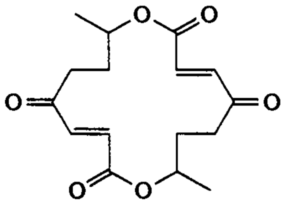

Pyrenophorin

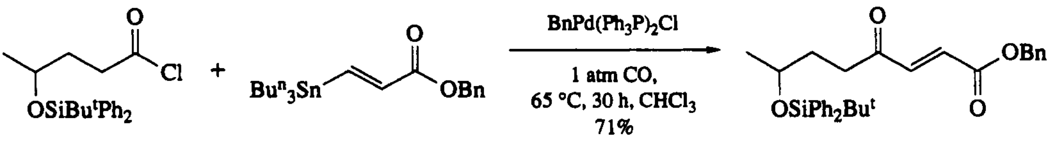

(94)

**(114)**

In Kende's formal total synthesis of the antitumor agent quadrone[198], a late stage intermediate, prior to closure of the third carbocyclic ring, was prepared using the method of Stille. The reaction appears to be exceedingly slow, even when HMPA is used as the solvent (equation 95). This points to the fact that transfer of simple alkyl groups from tin to the acylpalladium complex is not facile. No mention was made of alternative nucleophiles for this transformation such as dimethylcuprate or methylmagnesium chloride.

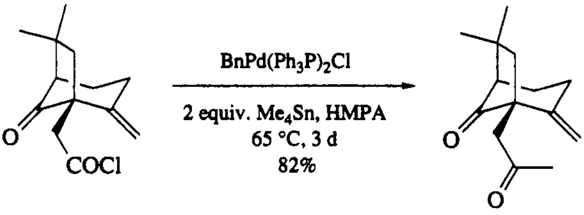

(95)

In contrast, early in the synthesis of the hexahydrobenzofuran portion of the avermectins, Ireland reported that palladium-catalyzed acylation of tetramethyltin was the most effective method for preparing the required methyl ketone as shown in equation (96).[199] The sensitive 3,4-*O*-isopropylidene-L-threonyl chloride was converted in high yield to the corresponding methyl ketone without epimerization at C-3. To avoid decarbonylation, the reaction was run under a carbon monoxide atmosphere until completion (4 h).

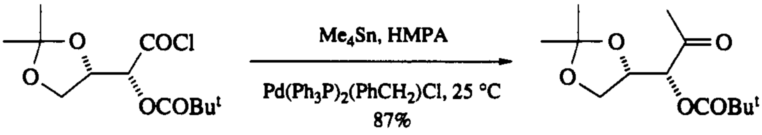

(96)

The acylation of organocadmium reagents with acid chlorides such as (**115**) formed an early method for synthesis of progesterone derivatives such as 21-methyl progesterone (equation 97). The same transformation may be accomplished more easily with palladium-catalyzed organotin acylation in 45% yield.[200]

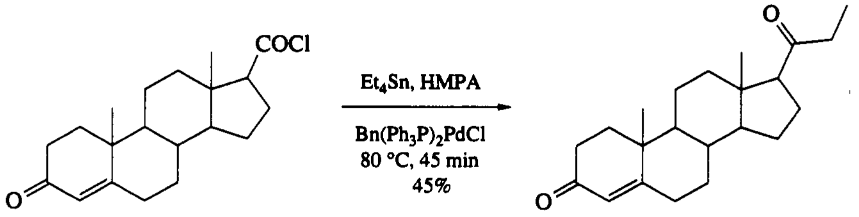

(**115**)

(97)

Holton has demonstrated that certain palladium(II) complexes can function as nucleophiles towards powerful acylating agents such as acetyl chloride.[201] These reactions proceed through the intermediacy of the palladium(IV) species (**116**) formed through oxidative addition as depicted in equation (98). Palladium(IV) intermediates had been proposed earlier to explain rate acceleration by reactive alkylating agents such as methyl iodide or benzyl bromide in metal-catalyzed carbon–carbon bond formation.[202] Logue has studied a substantial number of palladium-catalyzed acylations of (1-alkynyl)tributylstannanes.[203] Alkynylstannanes were acylated under very mild conditions which allowed a variety of functional groups to be present; however, in many cases the alkynylstannanes themselves had to be prepared from alkynyllithiums. Recall the earlier discussion of the acylation of alkynyllithiums by *N*-methoxy-*N*-methylamides (Section 1.13.2.1.1), and lactones (Section 1.13.2.7). In addition, it is also possible to acylate terminal alkynes directly with copper(I) iodide and palladium dichloride bistriphenylphosphine complex without the necessity of tin mediation.[204,214]

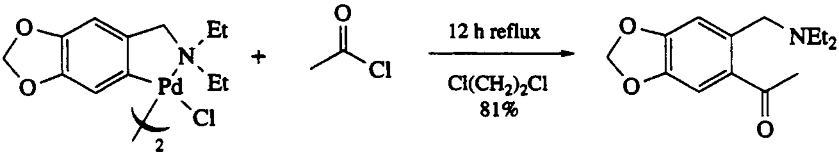

(98)

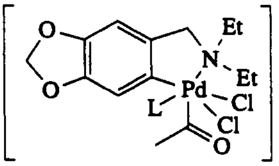

(116)

### 1.13.4.4 Palladium-catalyzed Acylation of Organozincs

Organometallics derived from the reaction of zinc chloride and Grignard reagents or organolithiums can be efficiently acylated by acid chlorides in the presence of palladium(0). The reaction is quite similar to the acylation of organostannanes but depending upon the case, may be easier to carry out for relatively simple alkyl organometallics which do not transfer well from tin. On the other hand, the need for an organometallic limits the functionality that can reside on the intended nucleophile. Unlike the case of organotins and acid chlorides there is some uncatalyzed acylation of zinc organometallics by the substrate; however, the latter process in and of itself is not useful. Organozinc reagents do not appear to add to ketones without Lewis acid activation.

Although not intensely studied, the mechanism of acylation with zinc reagents is expected to take the same course as that proposed for organotins. The most reactive catalyst, $(Ph_3P)_2Pd$ can be generated *in situ* from $(Ph_3P)_4Pd$ as discussed previously (Section 1.13.4.1.2) or by reduction of $Cl_2Pd^{II}(PPh_3)_2$ and $Cl_2Pd(DPPF)$ with diisobutylaluminum hydride.[206] Also Stille's catalyst, $BnPd^{II}(PPh_3)_2Cl$, is reported to be as effective for acylation under these conditions as with the organotins.[208] As with stannane acylation triphenylphosphine has a rate-retarding effect on oxidative addition of the acid chloride and would be expected to have a somewhat smaller rate-retarding effect on reductive elimination. Reactive halides such as benzylic bromides may be directly acylated with acid chlorides in the presence of zinc powder and palladium(0).[205] The most effective catalyst precursor was $Cl_2Pd^{II}(PPh_3)_2$ and the rate was decreased by suboptimal catalyst concentrations as was observed for organotins. Many of the examples have been substituted alkenyl or alkynyl zincs (equations 99–101). The acylation is >98% stereospecific for retention of configuration with disubstituted alkenes.[206]

The reaction was recently applied to the synthesis of 1,4- and 1,5-diketones (equation 102).[207] Perhaps not surprisingly, the β- and γ-ketozincs are stable to selfcondensation and proton abstraction. HMPA or some polar aprotic solvent must be used for high yields.

The corresponding dialkyl zinc reagents have also been used in acylation (equation 103). Under the reaction conditions with aromatic acid chlorides, substituted benzaldehydes are often a by-product. The

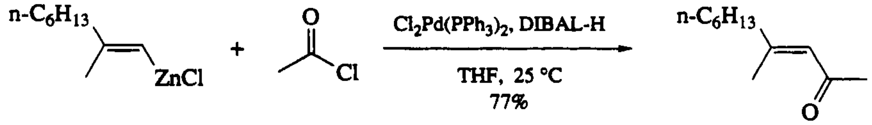

(99)

>98% *(E)*

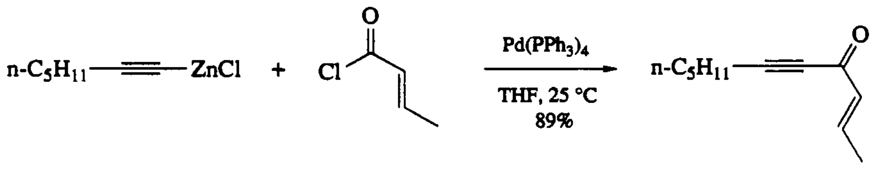

(100)

*(E)*:*(Z)* = 95:5 *(E)*:*(Z)* = 95:5

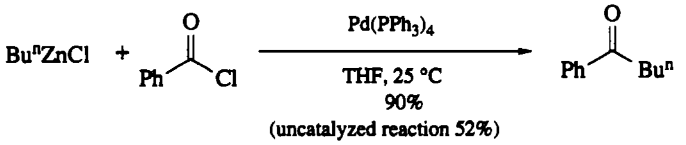
Bu^nZnCl
+
O
Ph
Cl
Pd(PPh3)4
THF, 25 °C
90%
(uncatalyzed reaction 52%)
O
Ph
Bu^n

(101)

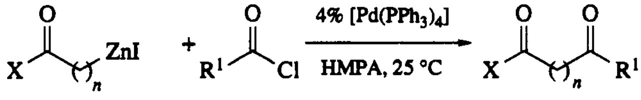
O
X
ZnI
n
+
O
R1
Cl
4% [Pd(PPh3)4]
HMPA, 25 °C
O
O
X
n
R1

(102)

$X = Et; n = 2$ $R^1 = Ph$ 53%

$X = Me; n = 3$ $R^1 = H_2C{=}CH$ 85%

yield of desired product can be maximized by using ether as the solvent and the bidentate DPPF ligand which prevents the elimination of palladium hydride. Alkyl acid chlorides do not require these special conditions in acylation.[208]

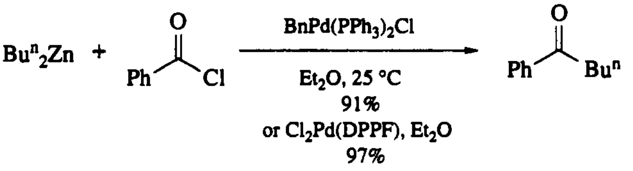
Bu^n2Zn
+
O
Ph
Cl
BnPd(PPh3)2Cl
Et2O, 25 °C
91%
or Cl2Pd(DPPF), Et2O
97%
O
Ph
Bu^n

(103)

Amino acid synthons can be prepared from iodoalanine with no loss of optical integrity (Scheme 48). The amino acid was transformed into a novel zinc reagent through reductive metallation with a zinc–copper couple in benzene/dimethyl acetamide. This organometallic was acylated under palladium catalysis in good overall yield.[209]

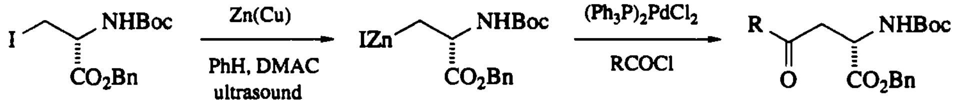
I
NHBoc
CO2Bn
Zn(Cu)
PhH, DMAC
ultrasound
IZn
NHBoc
CO2Bn
(Ph3P)2PdCl2
RCOCl
R
O
NHBoc
CO2Bn

$R = Ph$, 70%; $R = 2\text{-furyl}$, 90%; $R = Me$, 80%; $R = Bu^tCH_2$, 84%

**Scheme 48**

In a related procedure, the Diels–Alder substrate (**118**) was prepared from the iodide (**117**) through reductive metallation with a zinc–copper couple followed by palladium-catalyzed acylation (Scheme 49).[210] This was a very rapid acylation in contrast to the related organotin-mediated coupling.

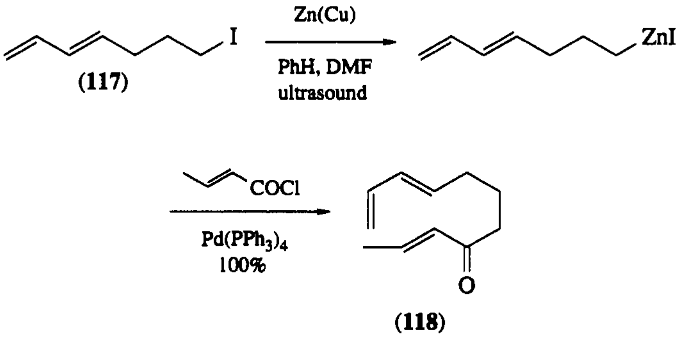
I
(117)
Zn(Cu)
PhH, DMF
ultrasound
ZnI
COCl
Pd(PPh3)4
100%
O
(118)

**Scheme 49**

### 1.13.4.5 Palladium-catalyzed Acylation of Organomercurials and other Organometallics

Many other types of organometallics which are not acylated directly by acid chlorides and which do not undergo addition to ketones may still transmetallate into the acylpalladium(II) complex. Simple alkyl organomercurials have been acylated in this fashion to give moderate to good yields of ketones.[211] Larock has studied the palladium-catalyzed acylation of vinylmercury(II) compounds with acyl halides (equation 104).[212] The reaction was only modestly productive and could not compare to the yield provided by aluminum chloride catalysis.

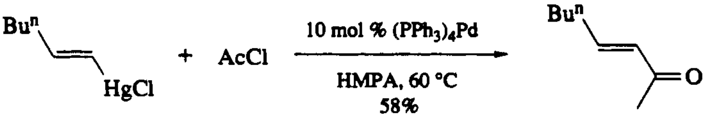

(104)

Organoaluminum reagents are known to react with ketones to form geminal dialkyl compounds, thus their use in acylation chemistry has been limited. For instance treatment of benzoyl chloride with triethylaluminum in THF gave less than 5% of propiophenone. Surprisingly, the corresponding palladium(0)-catalyzed process afforded this ketone in 70% yield with 5 mol % $Pd^0(PPh_3)_4$ (equation 105). The rate of acylation must be substantially faster than addition of the trialkylaluminum reagent to the ketone. Transmetallation of the organoaluminum with the acylpalladium(II) intermediate must also be facile. Palladium catalysts generated *in situ* from $Pd^{II}(OAc)_2$ and 2 equiv. $PPh_3$ were effective, as were other sources including $Cl_2Pd^{II}(PPh_3)_2$.[213] Presumably, the actual catalyst, $Pd^0(PPh_3)_2$, was generated by sacrificial transmetallation of a portion of the organoaluminum as in the analogous case of organotins (Section 1.13.4.1.2).

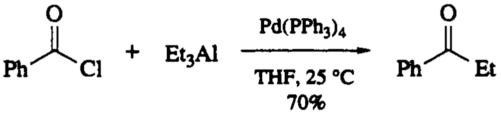

(105)

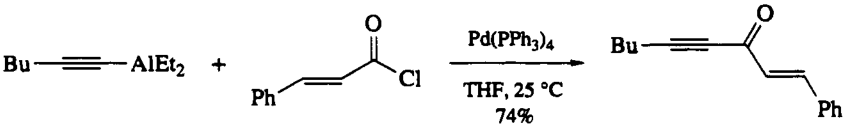

(106)

We have previously discussed the acylation of organocopper(I) reagents under palladium catalysts as a method for the preparation of α,β-unsaturated ketones (Section 1.13.3.1.1). An additional example of what must be a palladium(II)-catalyzed process for the synthesis of furanones comes from the work of Inoue (Scheme 50).[214]

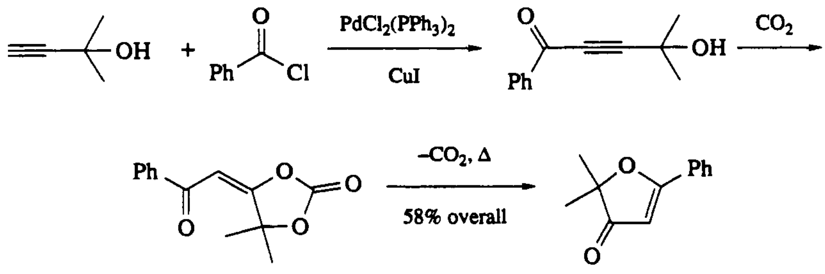

**Scheme 50**

## 1.13.5 ACYLATION WITH NICKEL AND RHODIUM CATALYSIS

### 1.13.5.1 Acylation with Alkylrhodium(I) Complexes and Acid Chlorides

The use of nickel and rhodium in acylation has largely been supplanted by the growing use of palladium complexes. This is in large part due to the lethargic nature of reductive elimination from nickel(II) complexes and the need for stoichiometric amounts of rhodium in the original protocol. Nevertheless, an exceedingly mild method for the acylation of simple primary alkyl-, aryl- or allyl-lithiums (or Grignard reagents) by acid halides is achieved through the prior transformation of these organometallics into substituted rhodium(I) complexes.[217] Although this method has not found widespread acceptance in the literature, it was one of the first examples of transition metal mediated organic synthesis applied to the preparation of ketones. Substrates complicated with extensive functionality and which are sensitive to strongly basic conditions can be acylated in much the same way that palladium mediates acylation of a variety of nucleophiles. For this reason, a short discussion of the applications of this technology are included.

Although the scope of nucleophilic reagents that can be used in this approach is not exceedingly broad, many different functional groups such as aldehydes, esters and nitriles as well as α-chloro ketones are tolerated as part of the substrate molecule. The conditions are mild and the rhodium(I) complex is returned unchanged from the reaction mixture. The addition of allyllithiums or Grignard reagents offers a selective method for the preparation of β,γ-unsaturated ketones. As mentioned, it is necessary to employ stoichiometric amounts of a rhodium complex, usually in the form of chloro(carbonyl)bis(triphenylphosphine)rhodium(I).[215] This is because of the high nucleophilicity of the organometallics chosen. The reaction is thought to proceed by addition of the nucleophile to form rhodium(I) complex (**119**) which then oxidatively adds to the acid chloride forming rhodium(III) complex (**120**). Reductive elimination releases the ketone and returns the original form of the rhodium complex, ready for reuse (Scheme 51). Attempts to isolate the intermediate rhodium(I) or rhodium(III) complex have thus far failed; however, the reaction may be monitored by infrared spectroscopy. A clear transformation of the initial rhodium complex (**121**) to the alkylrhodium(I) complex (**119**) was observed by a shift of the carbonyl absorption to lower energy, expected of the more electron-rich complex. It was not possible to observe the rhodium(III) complex (**120**) by this method. After addition of the acid chloride, infrared bands for the expected carbonyl product and for the starting rhodium(I) complex become evident. The expectation of a rhodium(III) intermediate was based upon other work in this area, but still remains a supposition. Oxidative addition to the acid chloride was not observed to take place with complex (**121**) and formation of the alkyl complex (**119**) increases the ability of the metal to add oxidatively by electron donation. Other more nucleophilic forms of rhodium such as $Rh(PMe_2Ph)_3Cl$ are known to oxidatively add to acid chlorides but have not been used in this acylation process.[216]

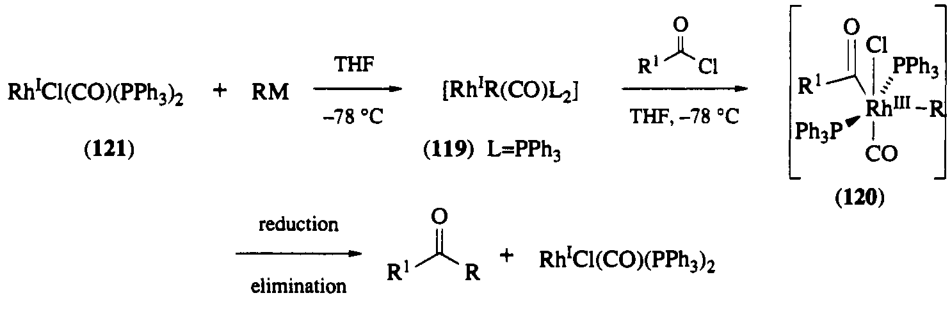

**Scheme 51**

Some examples of this method are given in Table 11.[217] Most of the entries proceed in about 60–80% yield, with the exception of secondary and tertiary alkyllithiums. In these cases, the facility of β-hydride elimination in the intermediate alkylrhodium complex predominates over oxidative addition to the acid halide. One example of formation of an optically active ketone proceeded without racemization at the α-center.

**Table 11** Acylation of Alkylrhodium Complexes with Acid Chlorides

| *Acid chloride* | *RM* | *Product* | *Yield (%)* |
|---|---|---|---|
| n-$C_{11}H_{23}COCl$ | MeLi | n-$C_{11}H_{23}CO$ | 77 |
| n-$C_{11}H_{23}COCl$ | MeMgBr | n-$C_{11}H_{23}COMe$ | 58 |
| PhCOCl | PhLi | PhCOPh | 94 |
| PhCOCl | $CH_2{=}CHCH_2MgBr$ | $PhCOCH_2CH{=}CH_2$ | 71 |
| *trans*-PhCH=CHCOCl | MeLi | *trans*-PhCH=CHCOMe | 68 |
| $ClCH_2COCl$ | Bu$^n$Li | $ClCH_2COBu^n$ | 55 |
| (*S*)-(+)-PrCH(Me)COCl | EtLi | (*S*)-(+)-PrCH(Me)COEt | 83 |
| PhCOCl | EtCH(Me)Li | EtCH(Me)COPh | 3 |

In an extension of this work, Pittman has found that the rhodium(I) complex may be anchored to polystyrene resin thus enabling facile catalyst regeneration (Scheme 52). Unfortunately, certain acid chlorides such as *p*-nitrobenzoyl do not oxidatively add to the rhodium(I) complex at an appreciable rate; other unreactive substrates include *p*-methoxybenzoyl and some hindered acid chlorides.[218]

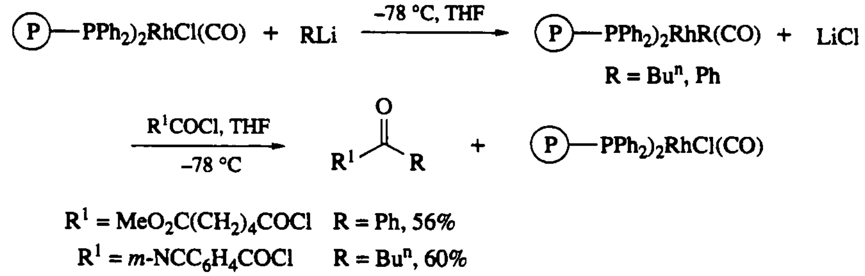

**Scheme 52**

The advantage of the previously described palladium-mediated acylation of organotins actually lies in the fact that the tin reagents do not directly react with the acid chlorides in the same way as organolithiums and Grignard reagents. The substituent on tin readily transmetallates or acts as the nucleophile towards the acylated palladium(II) complex which then undergoes rapid reductive elimination to form the product and reform the palladium(0) catalyst. Since organolithiums and magnesiums are not compatible with acid halides, stoichiometric quantities of the rhodium complex are necessary to preform the alkylrhodium(I) complex. To make the rhodium-mediated process catalytic in metal, Migita and coworkers demonstrated that the combination of allyltins and acid chlorides will afford ketones in good yield using 2 mol % $ClRh^I(PPh_3)_3$ (equations 107 and 108).[219] They propose the mechanism of this process to involve addition of the allyltin to the rhodium(I) complex, which then suffers oxidative addition with the acid chloride. An alternative possibility begins with oxidative addition of the acid chloride to the rhodium(I) complex, followed by transmetallation of the allyltin, and reductive elimination. In equation (108) introduction of the tin substituent occurs without allylic rearrangement, as is also the case with palladium catalysis; however, compared to the methodology developed for the corresponding palladium-catalyzed process, the use of rhodium in acylation has not been shown to be advantageous.

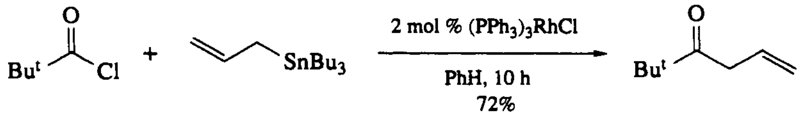

(107)

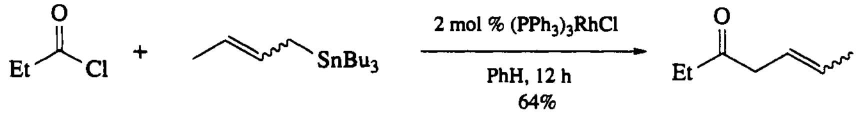

(108)

### 1.13.5.2 Acylation by Organonickel Complexes

Only scattered examples of the use of nickel salts in acylation have been reported in the past few years. Marchese and coworkers in a series of papers have discussed their discovery that $Ni^{II}$ complexes such as $Ni(DPPE)Cl_2$ will moderate the acylation of Grignard reagents to afford ketones (see also Sections 1.13.2.5 and 1.13.2.6). In a particularly interesting synthesis of 1,4-diketones or 1,4-keto aldehydes, these workers selectively monoacylated the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane with *S*-phenyl carbonochloridothioate using catalytic amounts of nickel(II) (Scheme 53). Subsequently, a second equivalent of another Grignard reagent was added to the resulting product, this time with mediation from iron(III) acetylacetonate.

Each step of the process proceeds in high yield without formation of tertiary alcohol by-products. The reaction can be run at 0 °C in THF, which is somewhat of an advantage compared to the low temperatures normally required in Grignard acylations. Both steps can also be conducted in one pot, although yields are higher if the intermediate thiol ester is isolated before the next step.[220]

Mukaiyama has described the use of nickel(II) salts as catalysts for the acylation of weakly nucleophilic organozincs. The advantage of this methodology is that the zinc reagent is prepared *in situ* from

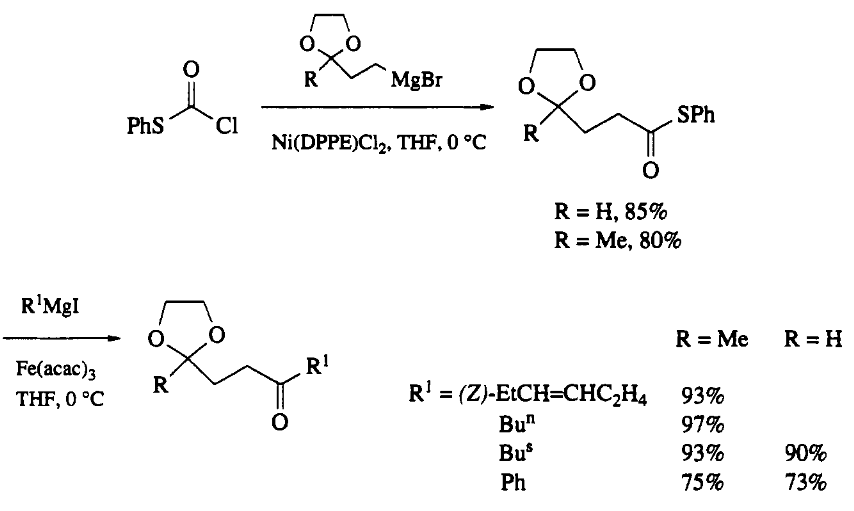

| | R = Me | R = H |
|---|---|---|
| $R^1$ = (Z)-EtCH=CHC$_2$H$_4$ | 93% | |
| Bu$^n$ | 97% | |
| Bu$^s$ | 93% | 90% |
| Ph | 75% | 73% |

Scheme 53

the corresponding alkyl iodide (equation 109). Many types of functional groups are tolerated, including ketones, esters, chlorides and α,β-unsaturated carboxylic acid derivatives. Only 10 mol % of nickel catalyst is needed for this acylation.[221]

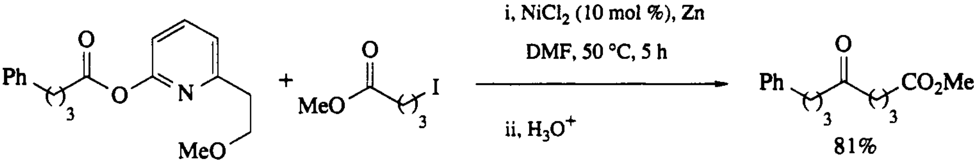

(109)

Generally only primary and some secondary iodides have been useful in this process; tertiary iodides do not react. It was also observed that no reaction occurred between the alkyl iodide and zinc unless the nickel catalyst was present. Several carboxylic acid derivatives were tested as acylating agents; however, the best yields were afforded by the 2-[6-(2-methoxyethyl)pyridyl] carboxylate shown in equation (109). Presumably, the higher degree of coordination attainable between this functionality and the organometallic, activates the acylating agent towards nucleophilic addition. This important effect has been seen in several other acylating agents including the *S*-(2-pyridyl) thiol ester. Both the *S*-(2-pyridyl) thiol ester and the 2-pyridyl carboxylic ester gave lower yields in this reaction.[221]

β,γ-Unsaturated ketones have been prepared in moderate yield through the acylation of π-allylnickel complexes with activated 2-pyridyl carboxylates. But, isomerization of the initially formed unconjugated alkene resulted in mixtures of products and limited the value of the method. Substituted π-allylnickel complexes derived from crotyl bromide or cinnamyl bromide were acylated in 79% and 50% yields, respectively, without formation of the α,β-unsaturated ketone.[222]

Rieke and coworkers have found that a special type of activated metallic nickel, available through reduction of nickel(II) iodide with lithium metal, suffers oxidative addition of benzylic and allylic halides. The resulting nickel(II) complexes readily undergo cross-coupling with acid chlorides to form ketones. Once again it was difficult to obtain β,γ-unsaturated ketones from this method. Moderate to good yields of simple ketones may be prepared by this method.[223]

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# 2.1

# Nitrogen Stabilization

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## 2.1.1 INTRODUCTION

This chapter covers the carbonyl addition chemistry of carbanions stabilized by a nitrogen atom or a nitrogen-containing functional group in which the nitrogen is responsible for the stabilization. In most cases, the carbanions are formed by deprotonation, but metal–halogen exchange is occasionally important. A carbanion that is stabilized by a nitrogen may exist in three oxidation states: *sp*, $sp^2$ or $sp^3$. The simplest nitrogen-stabilized carbanion is cyanide, the *sp*-hybridized case. In recent years, most efforts in this area have been expended on developing the chemistry of $sp^2$- and $sp^3$-carbanions. This chapter deals with the addition of these types of anions to carbonyl compounds. Alkylation reactions of $sp^3$-hybridized species are covered in Volume 3, Chapter 1.2, and alkylation of $sp^2$-hybridized carbanions is covered in Volume 3, Chapter 1.4. Specifically excluded from this chapter are additions of carbanions stabilized by a nitro group (the Henry nitroaldol reaction) and azaenolates, which are covered in Volume 2, Chapters 1.10, 1.16 and 1.17.

Each section of this chapter is subdivided according to the type of species being metalated: acyclic, carbocyclic or heterocyclic. The site of metalation is the criterion for classifying each species. Thus, the *ortho* metalation of anisole is classified as a carbocyclic system, whereas metalation of the *N*-methyl group of a heterocycle is an acyclic system and the α-metalation of a piperidinecarboxamide is a heterocyclic system.

## 2.1.2 *sp*-HYBRIDIZED CARBANIONS (CYANIDE)

The addition of HCN to aldehydes has been a well-known reaction since the 19th century, especially in the context of the Kiliani–Fischer synthesis of sugars. Even older is the Strecker synthesis of amino acids by simultaneous reaction of aldehydes with ammonia and HCN followed by hydrolysis. The challenge in recent years has been to achieve face-selectivity in the addition to chiral aldehydes. These face-selective additions, known as 'nonchelation-controlled' processes, refer to the original formulation of Cram's for the reaction of nucleophiles with acyclic chiral carbonyl compounds.[1] The 'chelation-controlled' reactions refer also to a formulation of Cram's, but whose stereochemical consequences sometimes differ.[2]

An example of this type of effort is as follows. Complexation of the carbonyl oxygen of *N*,*N*-dibenzyl-α-amino aldehydes with Lewis acids such as $BF_3$, $ZnBr_2$ or $SnCl_4$, followed by addition of trimethylsilyl cyanide leads to adducts formed by a nonchelation-controlled process.[3] Complexation with $TiCl_4$ or $MgBr_2$ affords the opposite stereochemistry preferentially, through a chelation-controlled process (Scheme 1).[3]

*Nonchelation control*

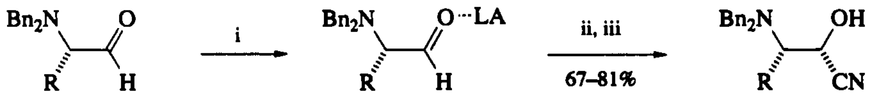

R = Me, Bn, $Bu^i$, $Pr^i$

selectivity 87:13–95:5

i, $BF_3$, $ZnBr_2$ or $SnCl_4$, $CH_2Cl_2$; ii, $Me_3SiCN$; iii, $H_2O$ or citric acid, MeOH

*Chelation control*

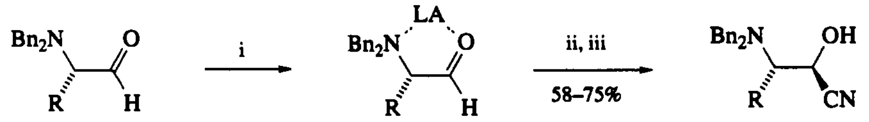

R = Me, Bn, $Bu^i$, $Pr^i$

selectivity 78:22–88:12

i, $TiCl_4$ or $MgBr_2$, $CH_2Cl_2$; ii, $Me_3SiCN$; iii, $H_2O$ or citric acid, MeOH

**Scheme 1**

## 2.1.3 *sp*²-HYBRIDIZED CARBANIONS

### 2.1.3.1 Introduction

There are two common methods for forming *sp*²-hybridized carbanions: deprotonation and metal-halogen exchange. In their 1979 review of heteroatom-facilitated lithiations, Gschwend and Rodriguez contend that there are two mechanistic extremes for a heteroatom-facilitated lithiation: a 'coordination only' mechanism and an 'acid–base mechanism'.[4] They further state that: 'between these extremes there is a continuous spectrum of cases in which both effects simultaneously contribute in varying degrees to the observed phenomena'.[4] Because the subject of this chapter is nitrogen-stabilized carbanions, and because this stabilization is most often exerted by coordination to the cation (usually lithium), it turns out that most of the deprotonations are best rationalized by prior coordination of the base to a heteroatom (the coordination only mechanism). Because these effects often render a deprotonation under conditions of kinetic control, this phenomenon has been termed a 'complex-induced proximity effect'.[5] The most important manifestation of this coordination in the examples presented below is a high degree of regioselectivity in proton removal.

We have not restricted our coverage to instances of cation coordination to a nitrogen atom, since there are a number of important functional groups (such as secondary and tertiary amides) where coordination occurs at oxygen but stabilization is also provided by nitrogen. Thus, most of the developments of the last 10 years have been in the area commonly known as 'directed metalations'. Several reviews have appeared on various aspects of these subjects.[5–9]

### 2.1.3.2 Additions *via* Metalation of Acyclic Systems

A novel method has been reported for the elaboration of carbonyl compounds, which is discussed in Section 2.1.4.2.[10,11] However, one of the examples falls into the present category: the transformation of cyclohexanone to keto alcohol (**4**), *via* enamidine (**1**; equation 1). Treatment of (**1**) with *t*-butyllithium effects regioselective deprotonation of the vinylic hydrogen to give (**2**), which adds to propanal to give (**3**). Hydrolysis then provides keto alcohol (**4**).[10,11]

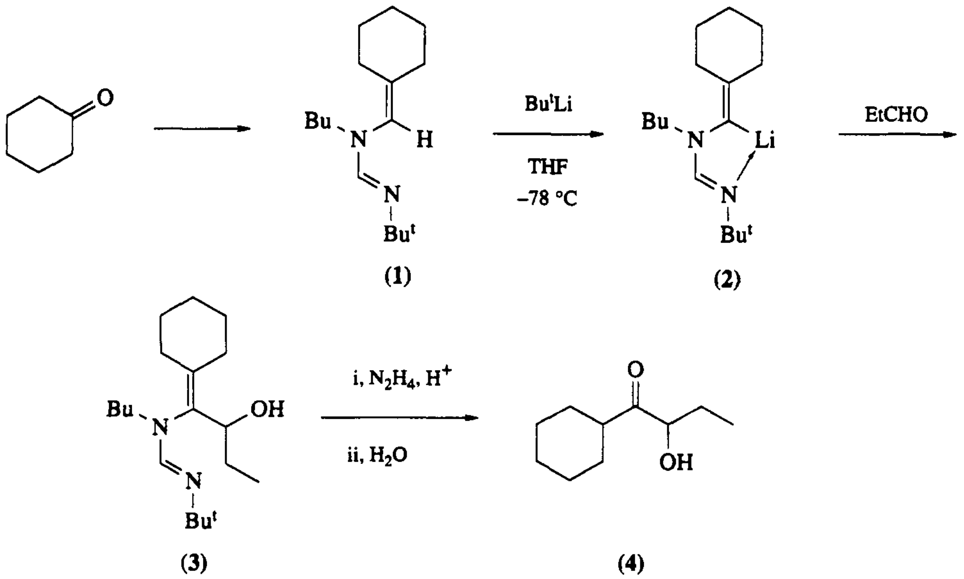

(1)

A synthesis of pyrroles and pyridines is possible by addition of dilithium species (**5**) to carbonyls (Scheme 2). The *syn* lithiation to give (**5**) was established by quenching (**5**) with trimethylsilyl chloride.[12]

### 2.1.3.3 Additions *via* Metalation of Carbocyclic Systems

#### *2.1.3.3.1* Ortho *metalation*

The vast majority of the species discussed in this and the following sections are formed by *ortho* lithiation (equation 2). In that the regioselective metalation of a given substrate at a given position is predicated on the 'directing ability' of the directing functional group, it is important to know what functional groups might take precedence over others. This ordering may be the result of either kinetics or thermodynamics. At one extreme for example, a strongly basic atom in a functional group might coordinate a lithium ion so strongly that coordination (and therefore *ortho* lithiation) is precluded at any other site (a kinetic effect). At the other extreme, metalation might occur to produce the most stable anion (a thermodynamic effect).

The relative directing abilities of several functional groups have been evaluated by both inter- and intra-molecular competition experiments.[9,13–15] The strongest directing group is a tertiary amide, but groups such as 3,3-dimethyloxazolinyl and secondary amides are also effective. The p$K_a$ values of a

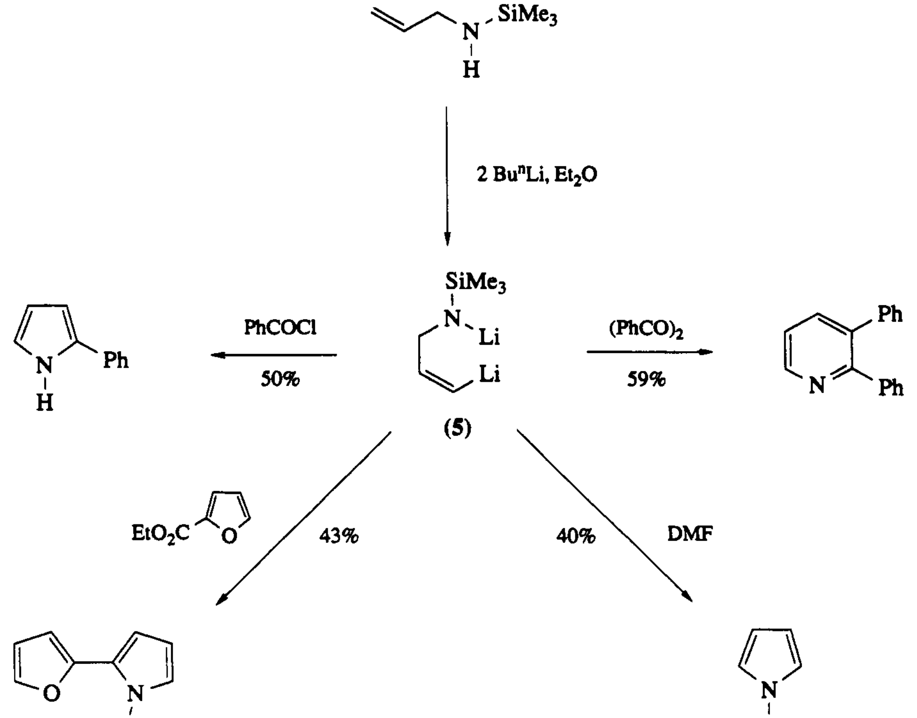

**Scheme 2**

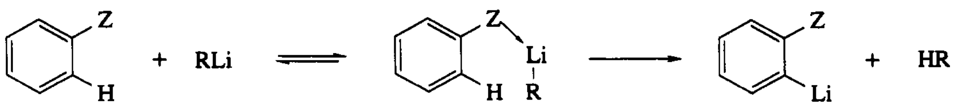

(2)

number of monosubstituted benzenes (*ortho* lithiation) were measured against tetramethylpiperidine ($pK_a$ = 37.8) by NMR spectroscopy.[16] The results, shown in Table 1,[16] are accurate to ±0.2 $pK_a$ units. By and large, the thermodynamic acidities parallel the directing ability of the substituent. Thus, the acidity imparted to the *ortho* position is a useful guideline for determining relative directing ability. Also pertinent to the mechanism of nitrogen-directed lithiations is a recent theoretical study on the lithiation of enamines, which concludes that 'a favorable transition state involves the achievement of both the stereoelectronic requirement for deprotonation and stabilizing coordination of the lithium cation with the base, the nitrogen of the enamine and the developing anionic center'.[17]

**Table 1** $pK_a$ Values for *Ortho* Lithiation of Substituted Benzenes in THF at 27 °C

$PhR + LITMP \rightleftharpoons o\text{-}RC_6H_4Li + HTMP$

| *R* | *$pK_a$ (±0.2)* | *R* | *$pK_a$ (±0.2)* |
|---|---|---|---|
| —$NMe_2$ | ≥40.3[a] | —OPh | 38.5 |
| —$CH_2NMe_2$ | ≥40.3[a] | —$SO_2NEt_2$ | 38.2[b] |
| —C≡CPh | ≥40.3[a] | 3,3-Dimethyloxazolinyl | 38.1[b] |
| —$NHCOBu^t$ | ≥40.5[a] | —CN | 38.1 |
| —OLi | ≥40.5[a] | —$CONPr^i_2$ | 37.8[b] |
| —OTHP | 40.0 | —$OCONEt_2$ | 37.2[c] |
| —OMe | 39.0 | | |

[a]No metalation observed. [b]−40 °C. [c]−70 °C.

From a synthetic standpoint, a highly useful consequence of the directed metalation strategy for aromatic substitution is the cooperativity exerted by two directing groups that are *meta*: metalation and substitution occur at the hindered position between the two directing groups (equation 3). However, exceptions have been noted in certain instances.[18] Metalation may be directed elsewhere by the use of a trimethylsilyl blocking group at the preferred position.[19]

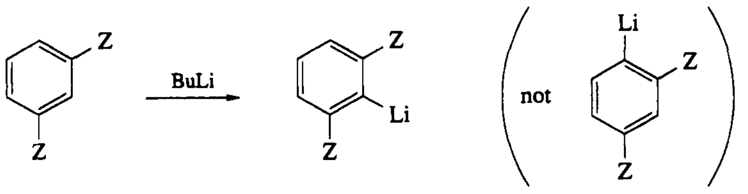

(3)

### 2.1.3.3.2 Meta *metalation*

In some cases, aniline or indole derivatives can be substituted *meta* to the nitrogen by lithiation of the appropriate chromium tricarbonyl complexes.[20–22] Examples are given in Scheme 3. One of the Cr—C═O bonds eclipses the C—N bond, and therefore the other carbonyls eclipse the *meta* C—H bonds. Two suggestions have been offered for the *meta* selectivity: (i) the butyllithium coordinates the chromium carbonyl oxygen and then removes the proximate proton (a kinetic effect);[20] (ii) the eclipsed conformation produces a lower electron density at the *meta* position, which in turn renders the *meta* protons more acidic (a thermodynamic effect).[21]

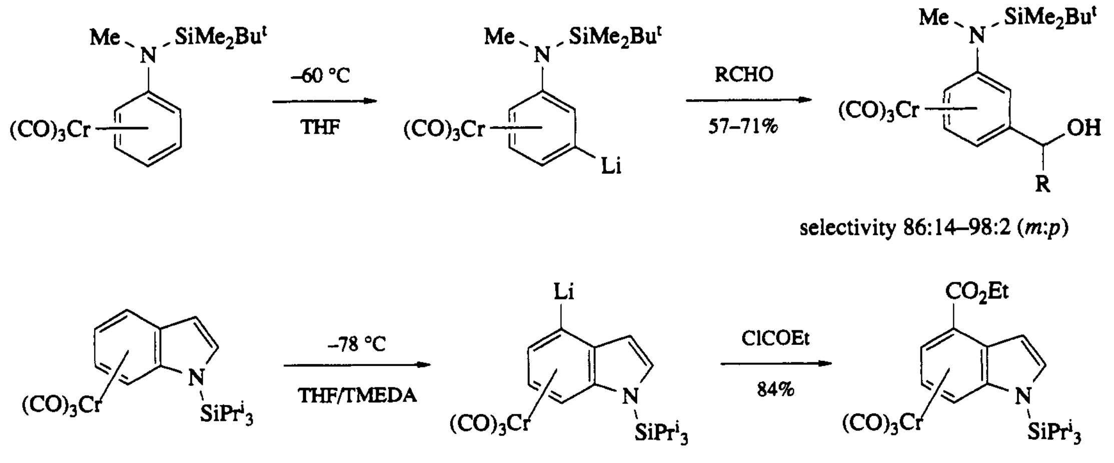

selectivity 86:14–98:2 (*m*:*p*)

Scheme 3

### 2.1.3.3.3 *Amines and anilides*

The classic example of amines as directing groups, and the reaction cited by Gschwend and Rodriguez as the best example of a 'coordination only' mechanism,[4] is the *ortho* metalation of *N,N*-dialkylbenzylamines, reported by Hauser in 1963.[23] Recent applications of the same directing group, working cooperatively with a *meta* methoxy to produce substitution between the two, are shown in Scheme 4.[24–26] In the illustrated examples, paraformaldehyde is the electrophile, and the benzylic alcohol (**6**) is obtained in 92% yield. The conversion of (**6**) to isochromanones such as (**7**) and berberines such as (**8**) illustrates the advantages of directed metalations over more traditional aromatic substitution methods such as Pictet–Spengler cyclizations.

Imidazolidines may also act as *ortho* directing groups: the lithiation of 1,3-dimethyl-2-phenylimidazolidine followed by addition to benzophenone proceeds in 63% yield.[27] Carbazole aminals can be metalated *ortho* to the nitrogen, while benzo[*a*]carbazole may be dilithiated at nitrogen and the 1-position.[28] A 2-amino group of a biphenyl directs lithiation to the 2′-position of the other ring in a novel synthesis of a phenanthride.[29]

Lithium amides add to benzaldehydes to form α-aminoalkoxides that direct *ortho* metalation, as shown in Scheme 5.[30,31] In a related process, the α-aminoalkoxides may be metalated by lithium–halogen exchange.[32]

In an aliphatic system, Stork has reported the regioselective lithiation of chelating enamines such as (**9**), to give vinyl carbanions such as (**10**; Scheme 6). Work-up often results in hydrolysis of the enamine, and in the case of addition to aldehydes, dehydration.[17,33]

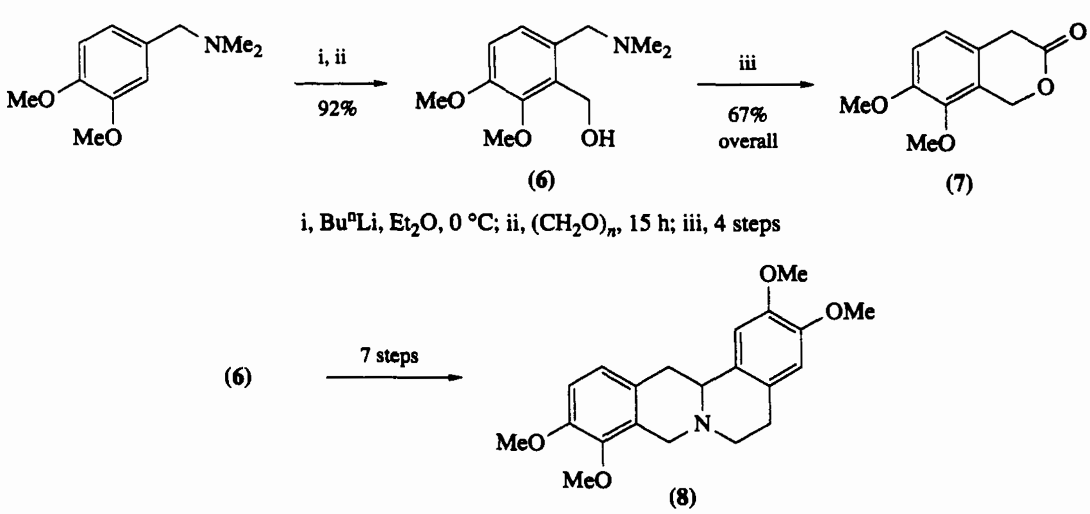

i, Bu$^n$Li, $Et_2O$, 0 °C; ii, $(CH_2O)_n$, 15 h; iii, 4 steps

**Scheme 4**

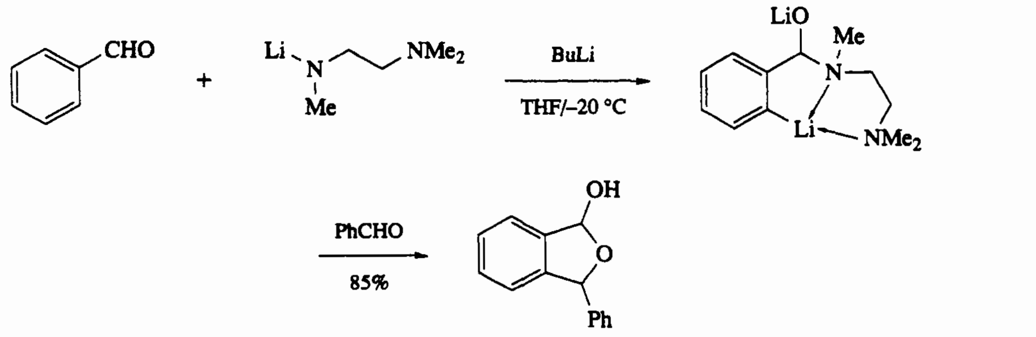

**Scheme 5**

Gschwend reported the *ortho* lithiation of aniline pivalamides and subsequent addition to nitriles and carbonyls in 1979.[34] A few years later, Wender used a similar aryllithium (**11**), obtained by metal–halogen exchange, in a new synthesis of indoles (Scheme 7).[35] An analogous metalation occurs when *N*-phenylimidazol-2-ones are treated with LDA in THF at –78 °C.[36]

### *2.1.3.3.4 Amides*

Secondary amides may direct *ortho* lithiation, but they must first be deprotonated. This makes them somewhat weaker *ortho* directors than tertiary amides, but they may still serve the purpose quite well. For example, the lithiation and addition of benzamide (**12**) to aldehyde (**13**) was used in a synthesis of 11-deoxycarminomycinone (Scheme 8).[37] More recently, it has been shown that the amide monoanion may be obtained by addition of a phenylsodium to an isocyanate.[38]

The p$K_a$ data listed in Table 1 note that tertiary amides are more acidic than several other functional groups, suggesting thermodynamic acidity as an important component of the mechanistic rationale for their lithiation. Indeed tertiary amides are the strongest *ortho* directing group, taking preference over all other functional groups tested in both intra- and inter-molecular competition experiments.[9,13–15] *N,N,N',N'*-Tetramethylphosphonic diamides also promote efficient *ortho* metalation.[39] The use of tertiary amides as *ortho* directors was reviewed in 1982,[9] so this discussion will focus only on developments since then.

Beak has reported an aromatic ring annelation using *ortho* lithiation to regioselectively introduce an aldehyde, which is then converted to a carbene. Subsequent Diels–Alder cycloaddition of the resultant isobenzofurans result in adducts that may be oxidized to naphthalenes or reduced to tetralins.[40,41] A typical example is shown in Scheme 9.

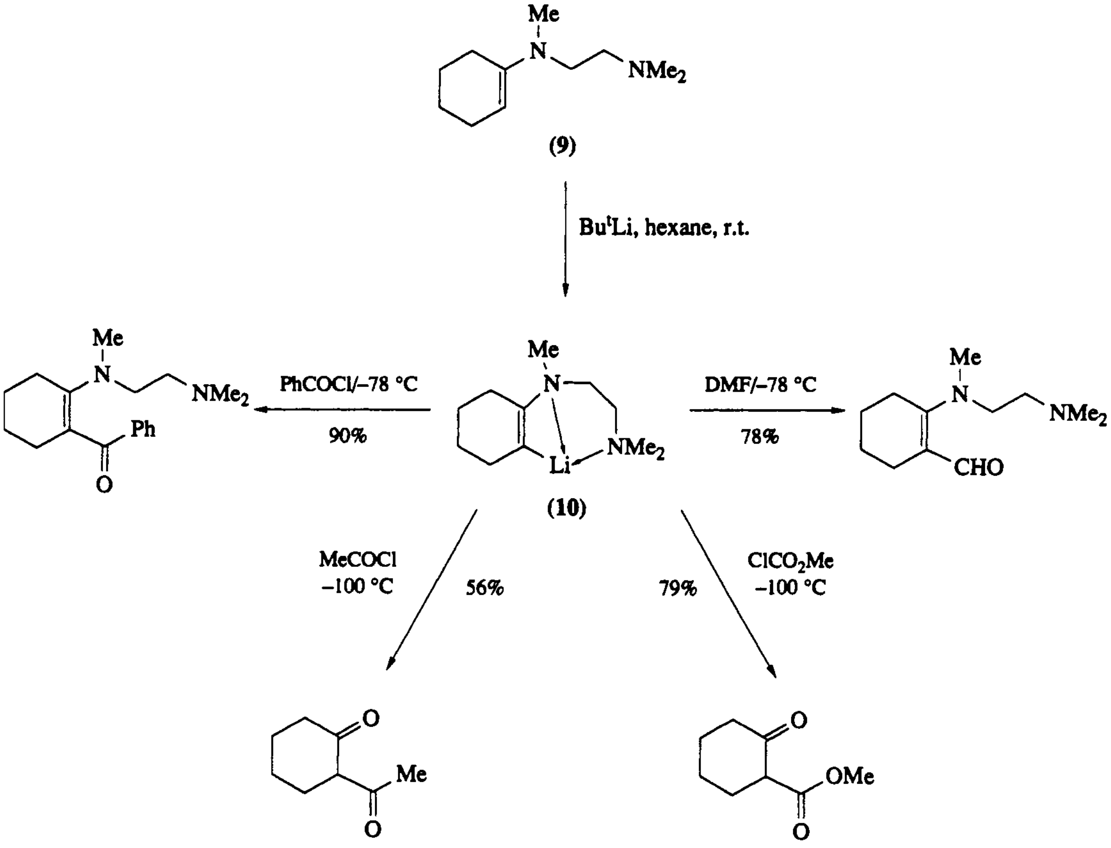
(9)
Bu$^t$Li, hexane, r.t.
(10)
PhCOCl/–78 °C
90%
DMF/–78 °C
78%
MeCOCl
–100 °C
56%
ClCO$_2$Me
–100 °C
79%

**Scheme 6**

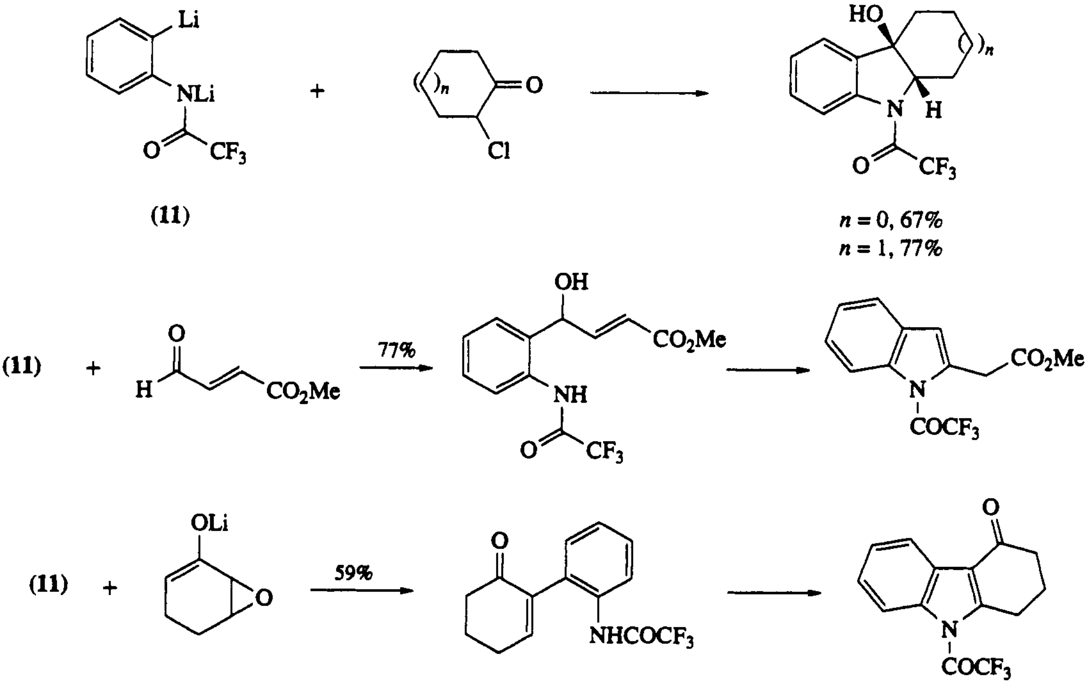
(11)
n = 0, 67%
n = 1, 77%
(11)
77%
(11)
59%

**Scheme 7**

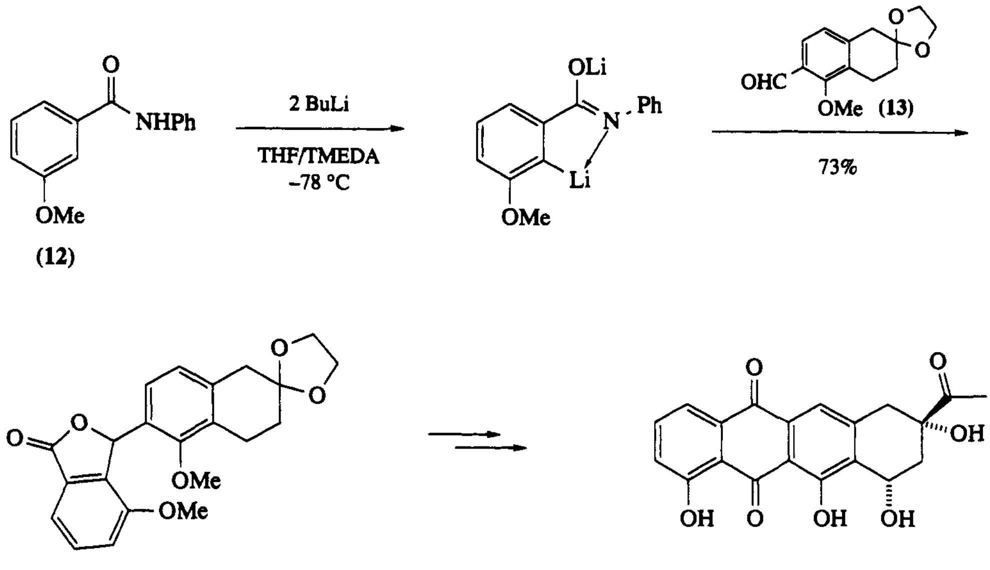
NHPh
OMe
(12)
2 BuLi
THF/TMEDA
-78 °C
OLi
N
Ph
Li
OMe
OHC
OMe (13)
73%
OMe
OMe
OH
O
OH
OH

Scheme 8

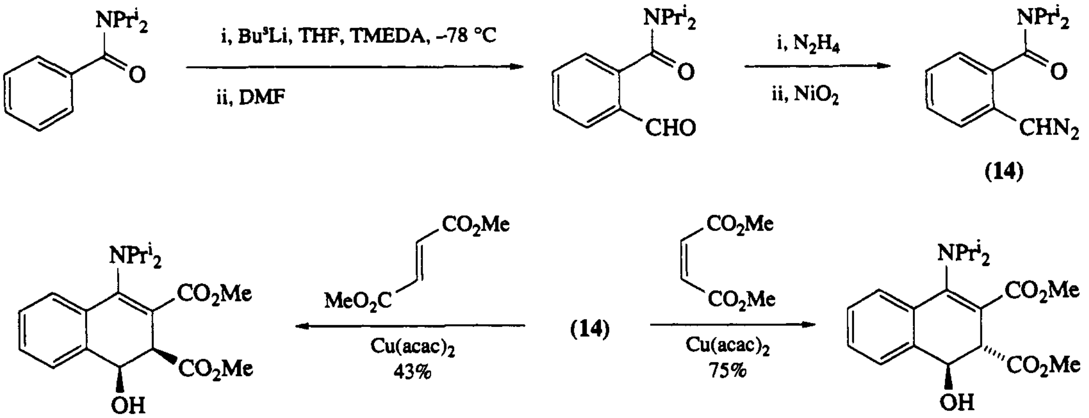
NPr$^i_2$
i, Bu$^s$Li, THF, TMEDA, -78 °C
ii, DMF
CHO
i, N$_2$H$_4$
ii, NiO$_2$
CHN$_2$
(14)
CO$_2$Me
MeO$_2$C
Cu(acac)$_2$
43%
(14)
Cu(acac)$_2$
75%
OH

Scheme 9

*Ortho* lithiation of a tertiary amide and addition to 3-(phenylthio)acrolein, followed by a second lithiation *in situ*, provides a convenient 'one-pot' synthesis of naphthoquinones.[42] One of the several examples reported is shown in Scheme 10.

Two groups report the addition of metalated benzamides to aldehyde carbonyls.[43,44] The methods differ in the metal. Lithiated diethylamides must be transmetalated with MgBr$_2$ before addition to the aldehyde, but β-aminoamides react similarly as the lithium derivative. Following addition, the hydroxyamide is hydrolyzed to afford phthalides in moderate overall yield (Scheme 11).

The lithiation of a 1,6-methano[10]annulenamide occurs selectively at the '*peri*' position,[45] but the lithiation of fused ring aromatics takes place preferentially at the *ortho* (rather than *peri*) position,[46,47] as shown by the examples in Scheme 12. Subsequent transformations of the phthalides obtained in the naphthalene example also illustrate the usefulness of this method for the annelation of aromatic rings. The preference for *ortho* over *peri* lithiation holds true for phenanthrenes as well. The selective metalation of trimethoxyphenanthrenamide (**15**) followed by phthalide synthesis as above constitute the key steps in the synthesis of the phenanthroquinolizidine alkaloid cryptopleurine and the phenanthroindolizidine alkaloid antofine (Scheme 13).[48,49]

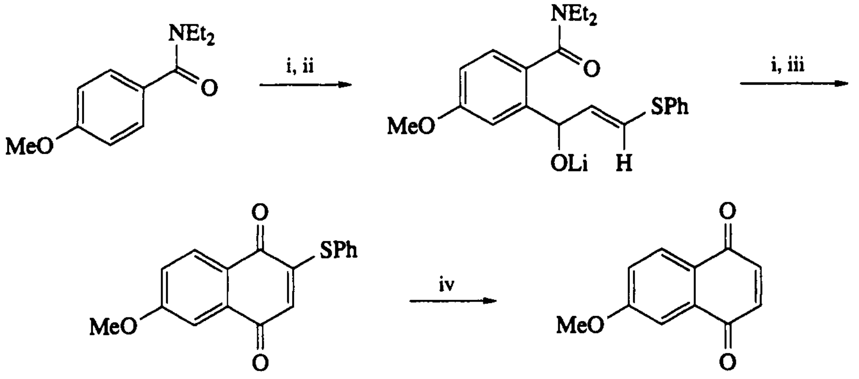
NEt2
O
MeO
i, ii
NEt2
O
MeO
SPh
OLi
H
i, iii
O
SPh
MeO
O
iv
O
MeO
O

i, Bu$^s$Li, THF, TMEDA, –78 °C; ii, PhSCH=CHCHO; iii, air, r.t.; iv, $Bu_3SnH$

**Scheme 10**

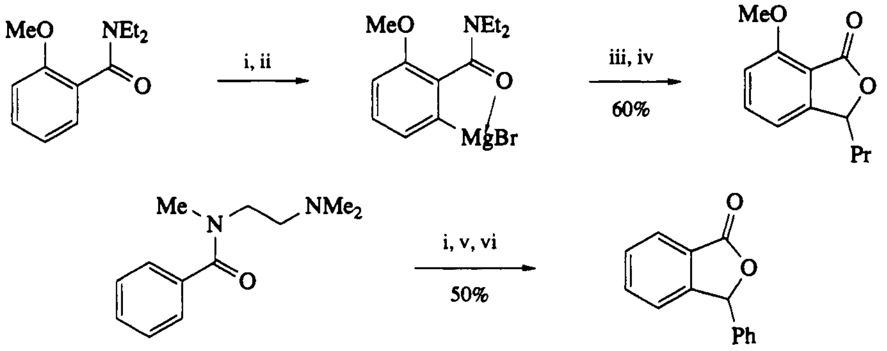
MeO
NEt2
O
i, ii
MeO
NEt2
O
MgBr
iii, iv
60%
MeO
O
O
Pr
Me
N
NMe2
O
i, v, vi
50%
O
O
Ph

i, Bu$^s$Li, THF, TMEDA, –78 °C; ii, $MgBr_2$-$Et_2O$, to r.t.; iii, PrCHO, –78 °C;
iv, TsOH, PhH, reflux; v, PhCHO, to r.t.; vi, 6M HCl, reflux

**Scheme 11**

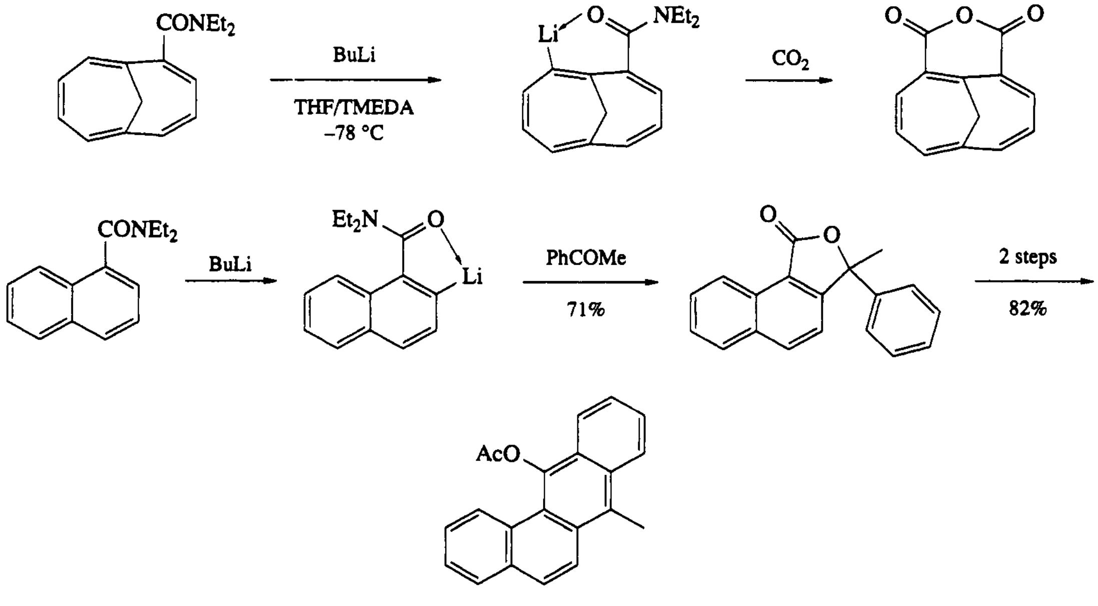
CONEt2
BuLi
THF/TMEDA
-78 °C
Li
O
NEt2
CO2
O
O
O
CONEt2
BuLi
Et2N
O
Li
PhCOMe
71%
O
O
2 steps
82%
AcO

**Scheme 12**

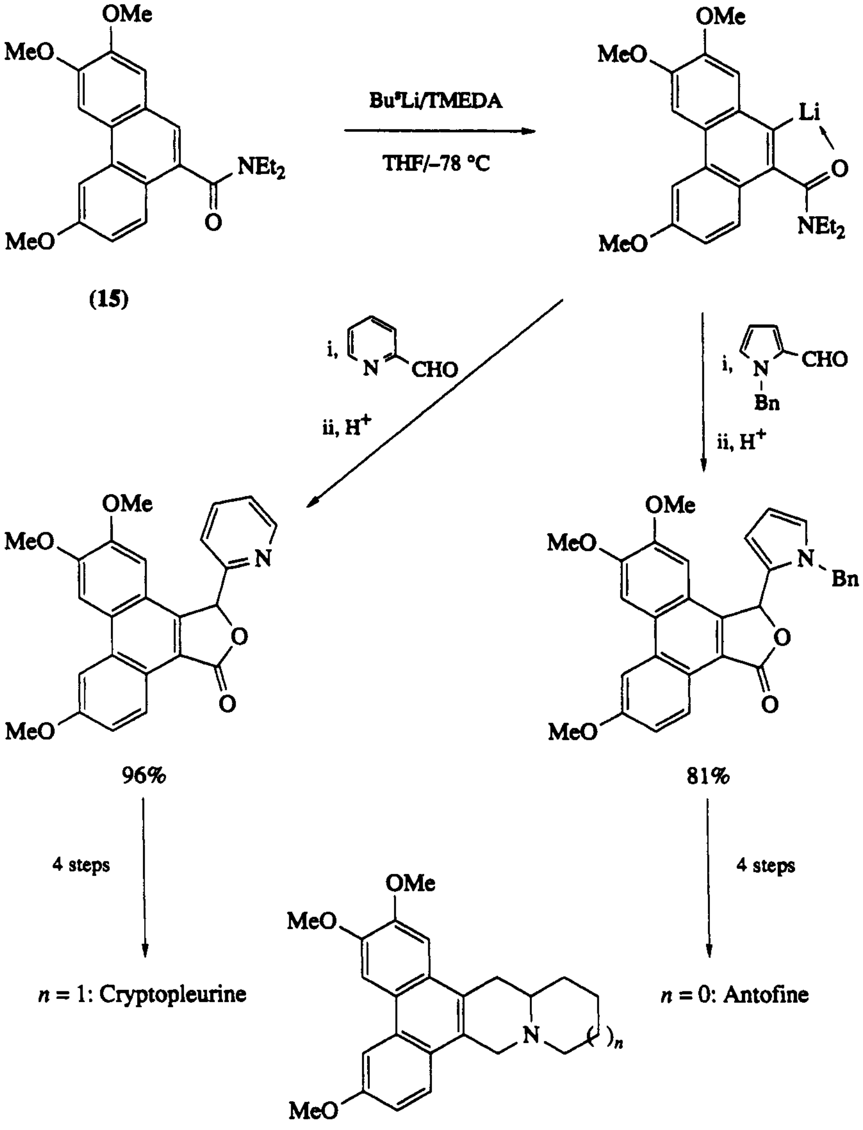

**Scheme 13**

### 2.1.3.3.5 *Nitriles*

In spite of the acidity imparted to the *ortho* position by a cyano group (Table 1), little use has been made of it as a directing group. Two examples are shown in Scheme 14. Because of the susceptibility of the nitrile function to addition by organometallics, the bases used are lithium amides.[50,51]

### 2.1.3.3.6 *Oxazolines*

Oxazolines may be used as *ortho* directors in phthalide syntheses analogous to those shown in Schemes 11–14. The phthalides derived from oxazolines have been further transformed to polycyclic aromatics by a route that is analogous to, and perhaps more general than, those shown in Scheme 12.[52,53] An efficient synthesis of the lignin lactones chinensin and justicidin along such lines was reported by Meyers (Scheme 15).[54]

The use of a chiral oxazoline to achieve an enantiofacial-selective addition to aldehydes was also reported by Meyers.[55] Although the selectivities were not high (51:49–64:36), the diastereomeric products could be separated by crystallization. A typical example is shown in Scheme 16. In this[55] and another

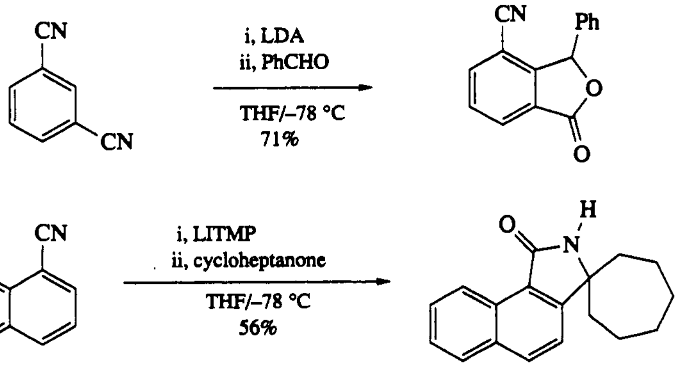

**Scheme 14**

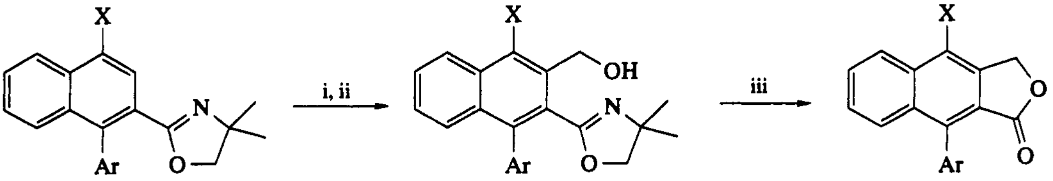

46–50%

Chinensin: X = H; Ar = 3,4-dimethoxyphenyl
Justicidin: X = OMe; Ar = 3,4-methylenedioxyphenyl

i, $Bu^sLi$, TMEDA, THF, –78 °C; ii, $(CH_2O)_n$ or DMF then $NaBH_4$; iii, HCl

**Scheme 15**

study,[56] it is shown that the alcohol addition product may subsequently attack the oxazoline causing ring opening.

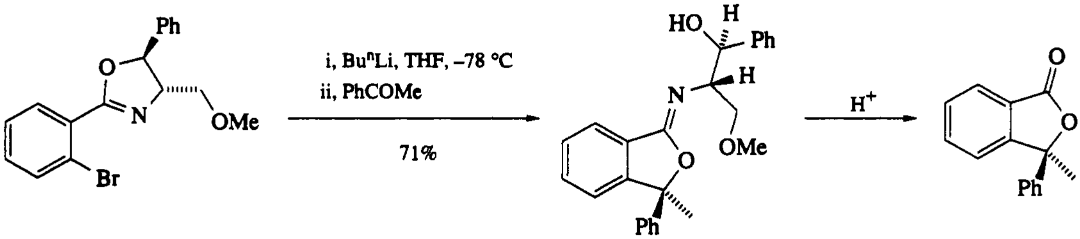

selectivity 64:36; enriched to 100% by crystallization

**Scheme 16**

### *2.1.3.3.7 Urethanes*

Lithiation of both *N*-phenyl- and *O*-phenyl-urethanes has been reported. The *ortho* lithiation of *N*-*t*-butoxycarbonylaniline and subsequent addition to carbonyls, nitriles and several other electrophiles was first reported by Muchowski in 1980.[57] In some cases the adduct cyclized by attacking the urethane carbonyl. Typical examples are shown in Scheme 17. Lithiation of an *N*-*t*-butoxycarbonylaniline derivative served as one of two directed lithiation steps in Snieckus' synthesis of anthramycin (**17**; Scheme 18).[58]

Treatment of phenothiazines with 2 equiv. of butyllithium affords an *N*,*o*-dilithium species, but reaction with electrophiles occurs at both sites. Katritzky has shown that the sequence of *N*-lithiation, carbonation and *o*-lithiation protects the nitrogen from alkylation (Scheme 19).[59]

The *ortho* lithiation of phenolic urethanes was reported by Snieckus in 1983.[60] In addition to being an efficient *ortho* director (as expected considering the $pK_a$ data in Table 1), the *O*-phenylurethane also is capable of an 'anionic Fries rearrangement'. This rearrangement allows substitution *ortho* to the urethane, then lithiation and rearrangement at the *ortho*′ position, resulting in introduction of a tertiary

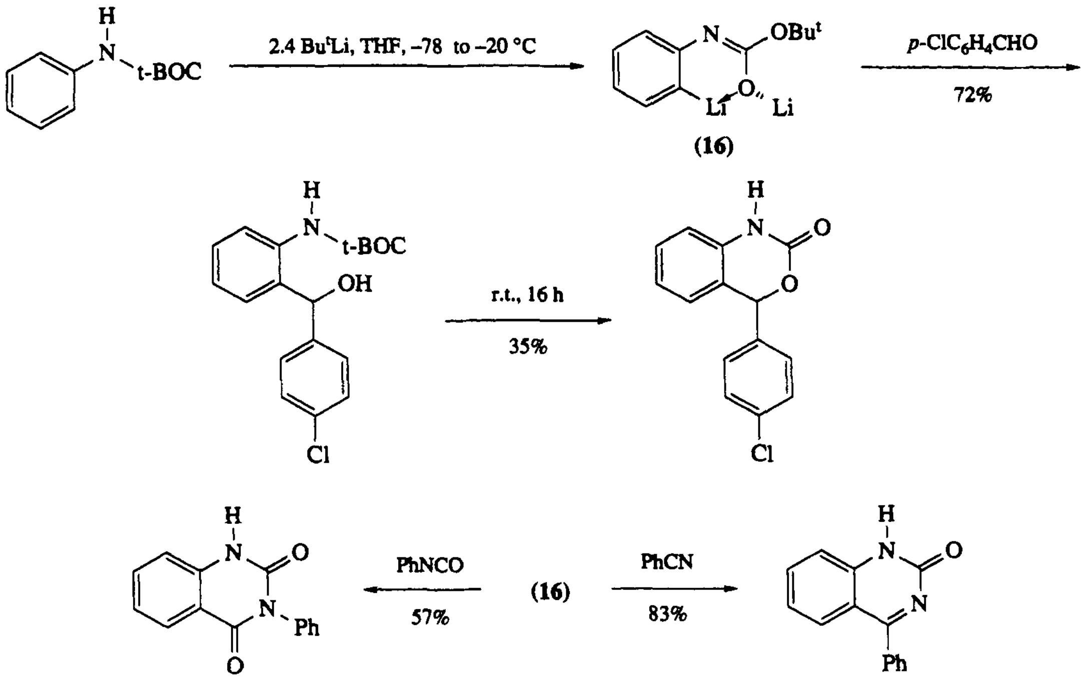
t-BOC
2.4 BuᵗLi, THF, –78 to –20 °C
OBuᵗ
Li
(16)
p-ClC₆H₄CHO
72%
OH
Cl
r.t., 16 h
35%
PhNCO
57%
(16)
PhCN
83%
Ph

Scheme 17

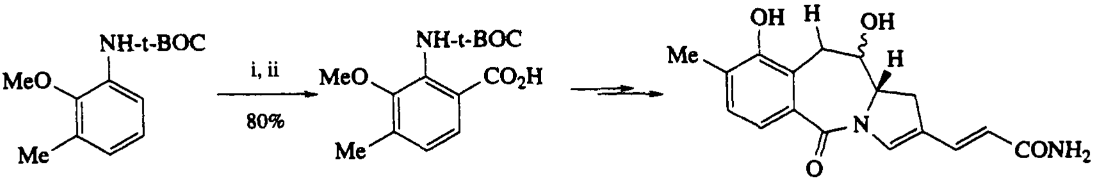
NH-t-BOC
MeO
Me
i, ii
80%
CO₂H
OH
H
CONH₂

i, 2.5 BuᵗLi, THF, –78 to –20 °C; ii, $CO_2$ (17)

Scheme 18

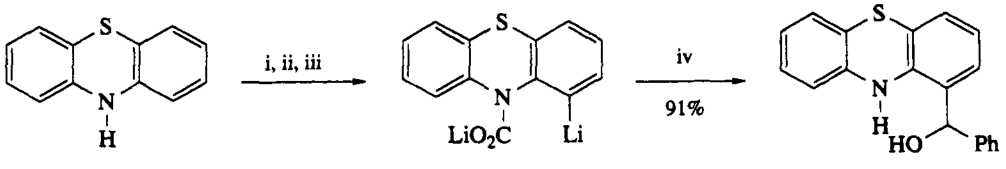
i, ii, iii
LiO₂C
Li
iv
91%
HO
Ph

i, BuⁿLi, THF, –78 °C; ii, $CO_2$; iii, 2 BuᵗLi, –78 to –20 °C; iv, PhCHO, –78 °C, then $H^+$

Scheme 19

amide. An *ortho* lithiation, carbonyl addition and anionic Fries rearrangement (**18** → **19**) are illustrated by the sequence shown in Scheme 20, which is part of a formal synthesis of ochratoxins A and B.[61] Noteworthy in this scheme is the selective lithiation of (**18**) *ortho* to the urethane, in preference to the tertiary amide.

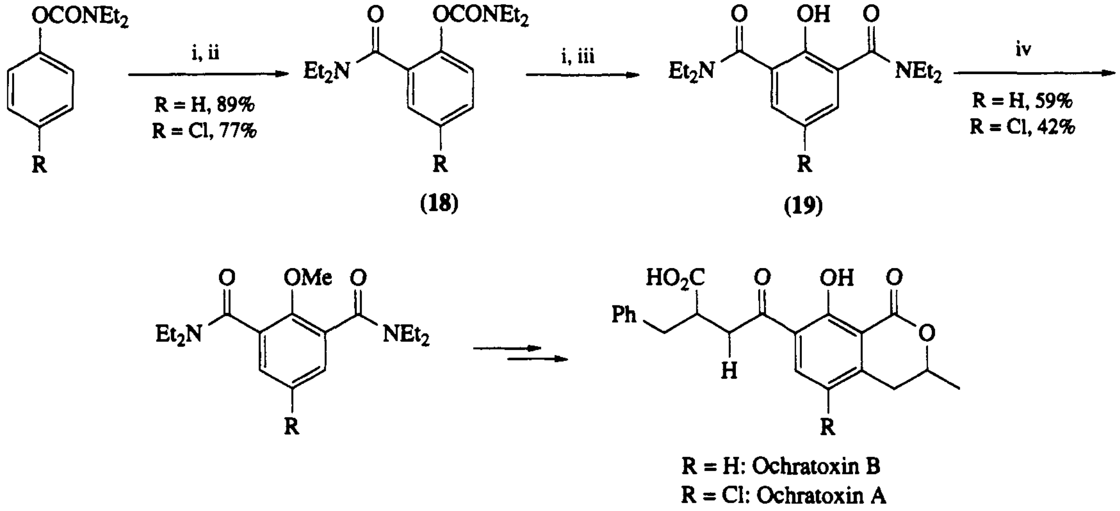

i, $Bu^sLi$, THF, TMEDA, –78 °C; ii, $ClCONEt_2$; iii, –78 °C to r.t.; iv, MeI, $K_2CO_3$, acetone

Scheme 20

### 2.1.3.4 Additions *via* Metalation of Heterocyclic Systems

#### *2.1.3.4.1 α-Metalation*

The metalation of heterocycles is possible without the aid of a directing group. This type of reaction is most common in the π-excessive heterocycles, and is most important for thiophenes.[4] For nitrogen heterocycles, examples of unactivated lithiation of π-excessive azoles have been reported, and are summarized below. π-Deficient heterocycles such as pyridine are resistant to unactivated lithiation,[4] although pyridine can be metalated with low regioselectivity using butylsodium.[62] Pyridines also form weak complexes with fluoro ketones; the complex of 4-*t*-butylpyridine and hexafluoroacetone can be lithiated and added to benzaldehyde in 60% yield.[63]

A review on the metalation and metal–halogen exchange reactions of imidazole appeared in 1985.[64] Generally, *N*-protected imidazoles metalate at the 2-position;[65] 1,2-disubstituted imidazoles usually metalate at the 5-position, unless sterically hindered.[64] Even 2,5-dilithiation of imidazoles has been achieved.[66] 1-Substituted 1,3,4-triazoles can be metalated at the 5-position and added to carbonyls in good yield.[67] Oxazoles are easily lithiated at the 2-position, but the resultant anion readily fragments.[68] 1-(Phenylthiomethyl)benzimidazole can be lithiated at the 2-position at low temperature (Scheme 21), but higher temperatures afford rearrangement products.[69]

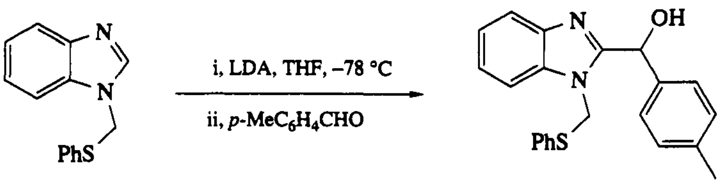

Scheme 21

Pyrrolopyridines can be lithiated at the 2-position,[70] in direct analogy to pyrrole itself. The reaction is sufficiently mild that it has been applied to the functionalization of purine nucleosides, as illustrated by the examples in Scheme 22.[71]

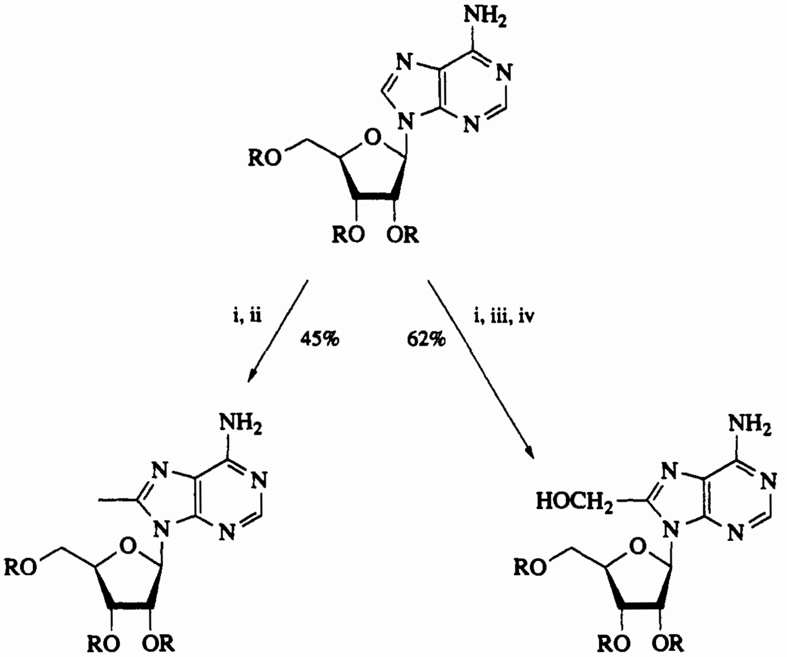
NH2
N
N
N
N
RO
O
RO OR
i, ii
45%
62%
i, iii, iv
HOCH2

R = $SiMe_2Bu^t$

i, 5 LDA, THF, −78 °C; ii, MeI; iii, $HCO_2Me$; iv, $NaBH_4$

Scheme 22

### 2.1.3.4.2 Ortho *metalation*

As will be seen in the examples below, the use of an activating group usually determines the site of lithiation for π-excessive heterocycles, and facilitates the lithiation of π-deficient ones.

Furans and thiophenes normally undergo α-lithiation,[4] but when substituted at the 2-position by an activating group, a competition arises between metalation at the 3-position (*ortho* lithiation) and the 5-position (α-lithiation).[4,72–74] 2-Oxazolinylthiophenes may be lithiated selectively at either the 3- or 5-position by adjusting the reaction conditions;[73] tertiary amides give little or no *ortho* selectivity,[74] but secondary amides direct *ortho* lithiation reasonably well, as seen in Scheme 23.[74] Both thiophenes and furans that are substituted with an oxazoline or tertiary amide at the 2-position may be dilithiated at the 3- and 5-positions.[75,76] Although secondary amides are less successful at directing *ortho* lithiation of furans than thiophenes,[74] *N,N,N′,N′*-tetramethyldiamido phosphates work quite well. Subsequent hydrolysis affords access to butenolides.[77] A typical example is shown in Scheme 24.

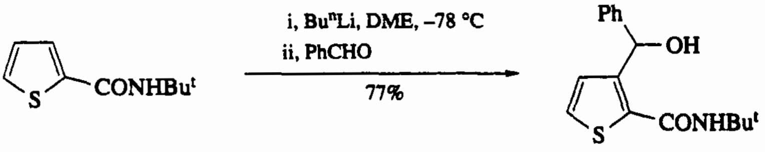
S
CONHBu^t
i, Bu^nLi, DME, −78 °C
ii, PhCHO
77%
Ph
OH
S
CONHBu^t

Scheme 23

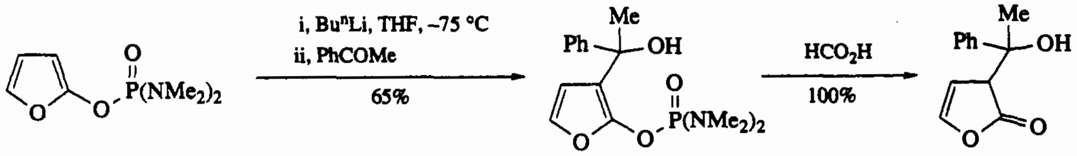
O
O
O
P(NMe2)2
i, Bu^nLi, THF, −75 °C
ii, PhCOMe
65%
Me
Ph
OH
O
O
O
P(NMe2)2
HCO2H
100%
Me
Ph
OH
O
O

Scheme 24

*N*-Substituted pyrroles and indoles normally undergo lithiation at the 2-position (α-metalation),[4,78] so when there is an *ortho* director on the nitrogen, metalation is facilitated. For example, the lithiation of *N*-t-BOC pyrrole and its addition to benzaldehyde occurs in 75% yield.[79] Similar lithiations of *N*-t-BOC indole[79] and *N*-benzenesulfonylindole[80,81] have also been reported. Examples of these reactions are illustrated in Scheme 25.

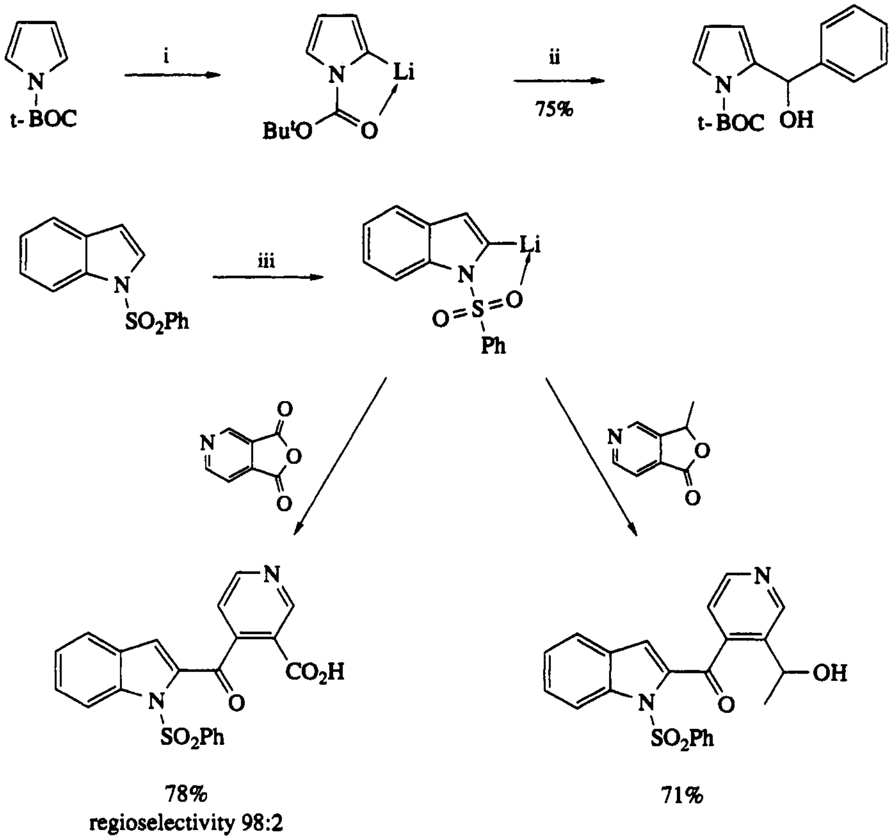

i, LITMP, THF, –80 to –20 °C; ii, PhCHO; iii, Bu$^n$Li or LDA, THF, –78 to 0 °C

Scheme 25

The recently reported dilithiation of the azafulvene dimer (**20**) is the key step in a synthesis of 5-substituted pyrrole-2-carbaldehydes.[82] This synthesis offers a reasonable alternative to the Vilsmeier–Haack formylation for the synthesis of such compounds. An example is shown in Scheme 26.

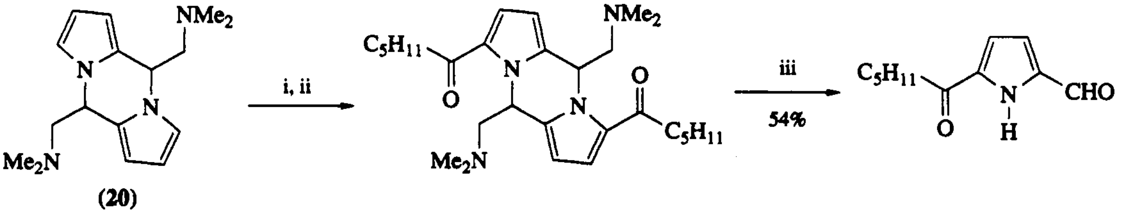

i, Bu$^t$Li, THF, –15 °C; ii, $C_5H_{11}CON(Me)OMe$, –78 °C to r.t.; iii, NaOAc, $H_2O_2$, reflux

Scheme 26

The regioselective functionalization of $\Delta^2$-pyrrolines at the 2-position by metalation of the derived *t*-butylformamidine (**21**) is shown in Scheme 27.[11] Metalation at the 2-position of a pyrrole having an *ortho* director at the 3-position is readily achieved.[42] Functionalization of a pyrrole at the 3-position by *ortho* metalation of a 2-substituted derivative is more problematic, with a mixture of 3- and 5-substituted products usually resulting,[74,83] as summarized in a recent review.[84] An intriguing possibility is *ortho* palladation, as shown in Scheme 28.[85]

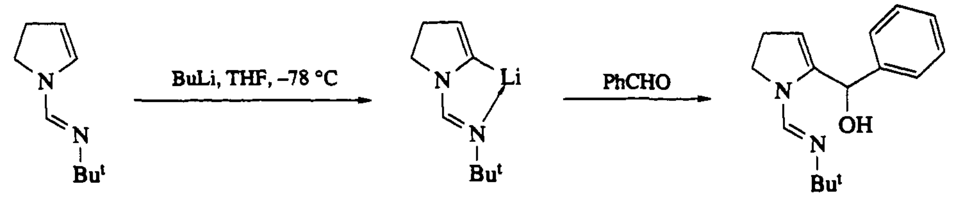

**Scheme 27**

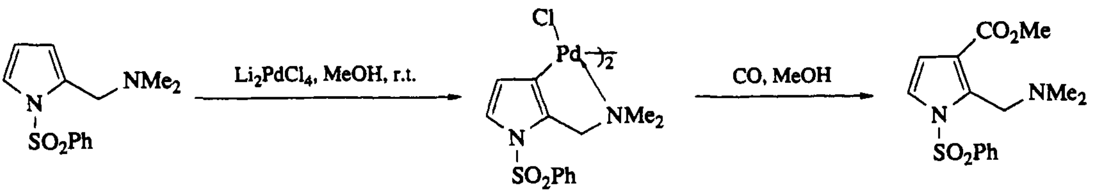

**Scheme 28**

*Ortho* lithiation of 2-substituted indoles occurs readily, but fragmentation to an alkynylanilide may occur in some instances.[86] The use of a 2-pyridyl group to facilitate the 3-lithiation of an indole was recently used in a synthesis of some indolo[2,3-*a*]quinolizine alkaloids;[87] an example is the synthesis of flavopereirine (**22**; Scheme 29).

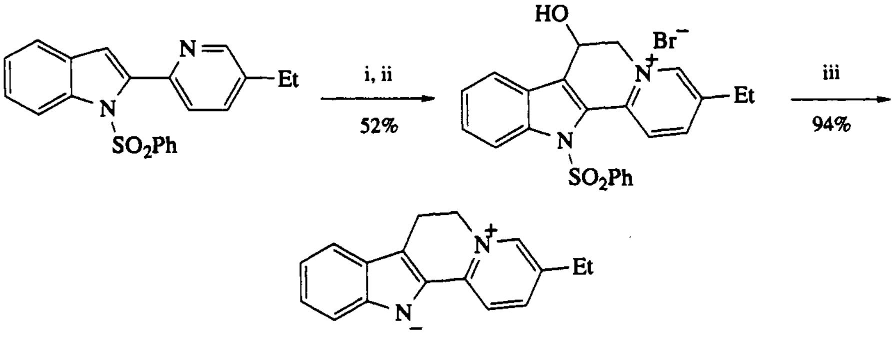

**(22)**

i, Bu$^n$Li, THF, –78 °C; ii, BrCH$_2$CHO, then AcOH; iii, NaOH, H$_2$O, MeOH, reflux

**Scheme 29**

In pyridines,[88] the *ortho* lithiation of 2-substituted secondary[89–91] and tertiary[90,92,93] amides and sulfonamides[94] has been reported. All three afford regioselective metalation at the 3-position, as illustrated by Kelly's synthesis of berninamycinic acid (**23**; Scheme 30).[95] A recent development is the use of catalytic amounts of diisopropylamine for the *ortho* metalation of 2-methoxypyridine.[96]

Pyridines substituted at the 3-position by a urethane,[97] halogen,[98,99] secondary amide[90,100] or tertiary amide[90,92] metalate regioselectively at the 4-position. An exception appears to be 3-alkoxypyridines, which metalate selectively at the 2-position.[101] The lithiation of halopyridines may be accomplished by metal–halogen exchange, or by *ortho* lithiation. In the latter instance, lithium amides are used as the base, and the temperature must be kept low to prevent pyridyne formation.[98,102,103] For 3-halo-4-lithiopyridines, the order of stability is F >> Cl > Br >> I.[98] Selective lithiation at the 4-position, directed by a tertiary amide, has been used in the synthesis of bostrycoidin (**24**)[104] and sesbanine (**25**; Scheme 31).[105]

Pyridines having a directing group at the 4-position undergo *ortho* metalation. Groups reported in this category include sulfonamides,[94] secondary amides,[90,91] tertiary amides,[106,107] halogens[98] and oxazolines.[56,108,109] As was the case in the carbocyclic series, a pyridine having directing groups in

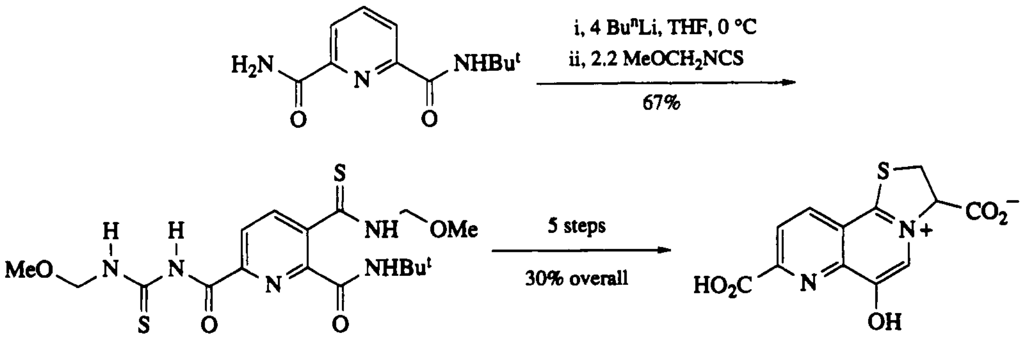

i, 4 Bu^nLi, THF, 0 °C
ii, 2.2 MeOCH2NCS
67%
5 steps
30% overall

(23)

**Scheme 30**

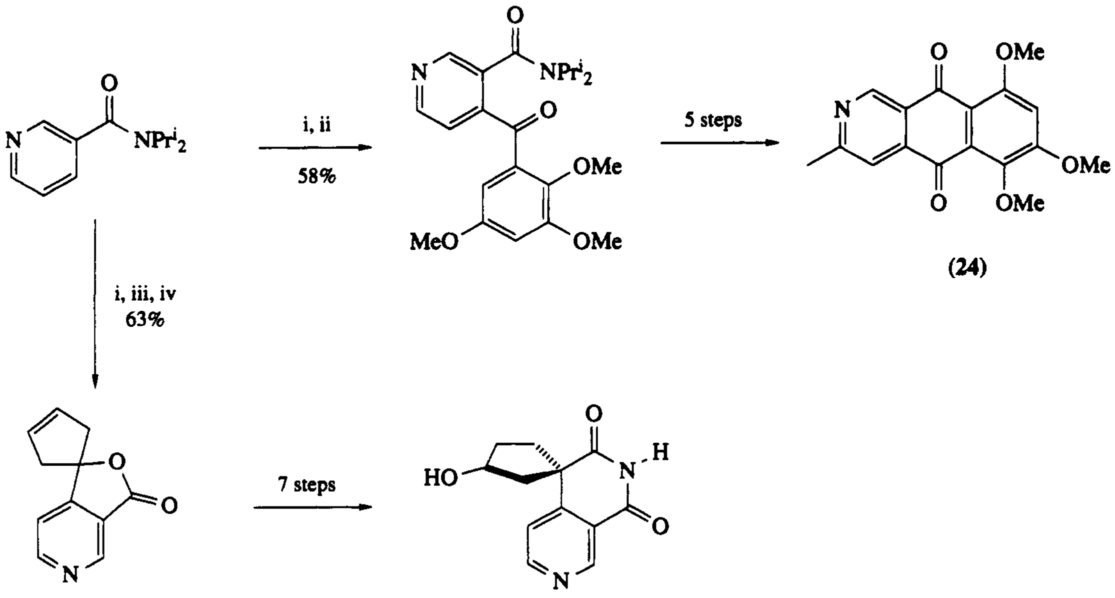

i, ii
58%
5 steps
(24)
i, iii, iv
63%
7 steps

(25)

i, LITMP, DME, −78 °C; ii, 2,3,5-$(MeO)_3C_6H_2CONMe_2$; iii, cyclopent-3-en-1-one; iv, TFA, $CH_2Cl_2$

**Scheme 31**

positions 2 and 4 is metalated in between, at the 3-position. This has been used in a synthesis of (*g*)-fused isoquinolines, whose key step is shown in Scheme 32.[109]

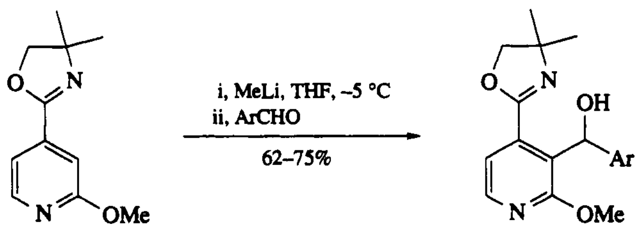

i, MeLi, THF, −5 °C
ii, ArCHO
62–75%

Ar = 1-naphthyl, 2-naphthyl, 3-methoxyphenyl, 3-thienyl

**Scheme 32**

## 2.1.4 *sp*³-HYBRIDIZED CARBANIONS

### 2.1.4.1 Introduction

The deprotonation of an *sp*³-hydrogen α to a nitrogen atom, although a relatively recent development synthetically, is now a common phenomenon. It has been stated that the 'normal' reactivity of carbon atoms attached to nitrogen or oxygen is $a^1$, meaning it is an acceptor site in polar reactions.[110] The deprotonation of such a site has therefore been called a charge affinity inversion or reactivity umpolung.[111] There is ample precedent in the literature to support the notion of $a^1$ reactivity α to nitrogen, of course, but we contend that this classification is inappropriate. The α-deprotonation of dimethyldodecylamine[112] and of triethylamine[113] were reported over 20 years ago, although the former was in low yield and no products of reaction of the latter with electrophiles were found. However in 1984, Albrecht reported that *s*-butylpotassium readily deprotonates *N*-methylpiperidine, *N*-methylpyrrolidine and trimethylamine, and that the derived organometallics add readily to aldehydes, ketones and alkyl halides.[114] In 1987, it was found that *t*-butyllithium deprotonates a methyl group of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), whereas *n*-butylpotassium ($Bu^nLi/KOBu^t$) deprotonates a methylene.[115]

Furthermore, it was first shown nearly 20 years ago that α-lithioamines could be produced by the transmetalation of α-aminostannanes.[116] Thus, the thermodynamic stability of α-amino anions is reasonably good, even if the kinetic acidity of the conjugate acids is low. Although some authors have suggested that α-amino carbanions constitute a reversal of 'normal' reactivity,[110,111] we suggest that this notion is inappropriate and should be discontinued.

Most of the chemistry described in the following sections involves two types of anion stabilization by nitrogen: resonance and dipole stabilization. Since these topics were reviewed in 1984,[111] this discussion is restricted to recent developments. By and large, the chemistry of resonance-stabilized species (azaenolates) is covered in Volume 2 of this series; however, there are a few species whose inclusion here seems appropriate and consistent with the present discussion. One such example is removal of a benzylic proton by a base that is coordinated to a nitrogen or nitrogen-containing functional group.

Another resonance-stabilized species discussed here is nitrosamine anions, whose chemistry has been reviewed several times.[111,117–119] Cyclic nitrosamines normally lose the axial proton *syn* to the nitrosamine oxygen,[120] and alkylate by axial approach of the electrophile.[121] In these respects, nitrosamine anions are similar to their isoelectronic counterparts, oxime dianions, as shown in equation (4).[122,123]

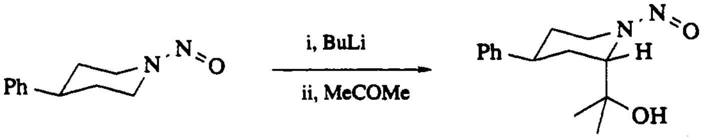

(4)

Dipole-stabilization is a term coined by Beak to describe the situation that results when a carbanion is stabilized by an adjacent dipole.[117] Such a situation arises when, for example, an amide is deprotonated α to nitrogen. The chemistry of these systems has been reviewed,[111,117] so only a few pertinent points will be made here. Firstly, metalation occurs *syn* to the carbonyl oxygen, and when the system is cyclic, the equatorial proton is removed selectively, and the electrophile attacks equatorially, as shown in equation (5).[124,125] Thus, in contrast to nitrosamines, amide anions give the less stable equatorial product.[124,125]

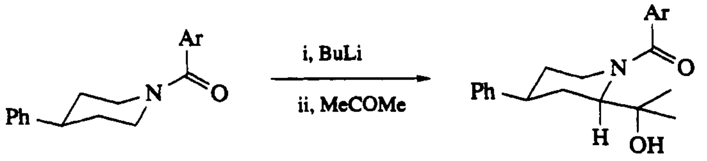

(5)

Considerable theoretical work has been done to explain equatorial alkylations such as the one illustrated in equation (5).[125–127] The simplest model of a dipole-stabilized anion is *N*-methylformamide anion, $HCONHCH_2^-$. The geometric requirements for this system are strict: the lone pair on carbon is 16–18 kcal mol⁻¹ more stable when oriented in the nodal plane of the amide π-system than when rotated 90° into conjugation.[126,127] To explain the removal of an equatorial hydrogen, it has been suggested that 'the electronic effects of extended amide conjugation should be felt relatively early along the reaction coordinate for proton removal'.[126] Thus equatorial protons are removed for stereoelectronic reasons, and the anions of piperidinecarboxamides[124,125] and amidines[128,129] are configurationally stable and do not invert. Note, however, that if the carbanion is also benzylic, pyramidal inversion is possible.[130,131] In spite of the intervention of pyramidal inversion in benzylic systems, the anion is still in the nodal plane of the amide π-system. Semiempirical calculations on lithiated oxazolines[129,131] and an X-ray crystal structure of a pivaloylisoquinoline Grignard[132] confirm the location of the carbon–metal bond in or near the nodal plane of the amide or amidine. At the same time, the theoretical and crystal structures show considerable overlap with the benzene *p*-orbitals, thus providing a possible explanation for the inversion process.

The mechanism of the deprotonation of dipole-stabilized anions has been studied in detail. It has been shown by IR spectroscopy that a preequilibrium exists between the butyllithium base and the amide[133,134] or amidine,[135] forming a coordination complex prior to deprotonation. A recent mechanistic study has shown that, in cyclohexane solvent, this prior coordination is between the amide (or added TMEDA) and aggregated *s*-butyllithium, and that the effect of the coordination is to increase the reactivity of the complex.[134] The diastereoselectivity of proton removal in chiral benzylic systems has also been examined,[130,131,136] but since the anions invert, this selectivity is of little consequence in the alkylation step.

### 2.1.4.2 Additions *via* Metalation of Acyclic Systems

The directed metalation of aromatic systems that was discussed in Section 2.1.3.3 has one ramification that was not mentioned there: the directed lithiation of an *o*-methyl group. Although the resultant species is formally a resonance-stabilized anion, and therefore covered in Volume 2 of this series, we mention it here for consistency with the other topics covered. In particular, the examples that have appeared in recent years involve substrates having a methyl *ortho* to a tertiary amide. Intentional use of such a directed lithiation has been used in the synthesis of the isocoumarin natural products hydrangenol and pyllodulcin.[137,138] Interestingly, the directed metalation of 5-methyl-oxazoles and -thiazoles occurs in preference to deprotonation at a 2-methyl group (azaenolate) (Scheme 33).[139]

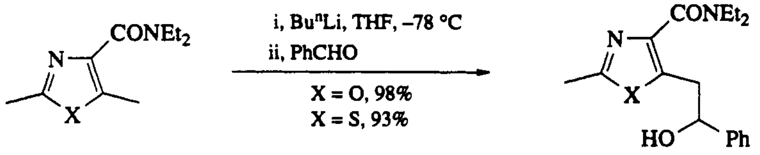

**Scheme 33**

*N*-Alkyl π-excessive heterocycles such as pyrazoles,[140] imidazoles[141] and triazoles[141,142] can be lithiated. In the example shown in Scheme 34, lithiation occurs selectively on the *N*-methyl in preference to the *C*-methyl (azaenolate).[140]

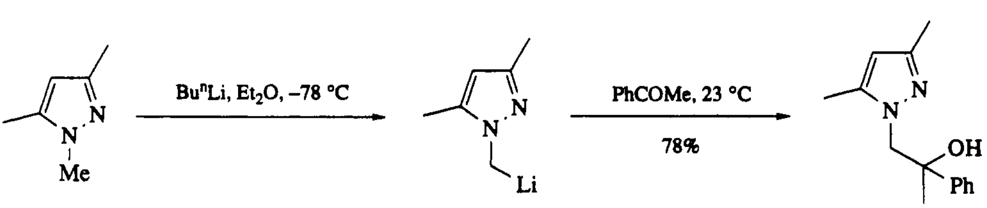

**Scheme 34**

As was mentioned in Section 2.1.4.1, the metalation (at an *N*-methyl group) of tertiary amines by *s*-butylpotassium was reported in 1984.[114] The derived potassium species are strong bases and tended to deprotonate enolizable carbonyl compounds, but transmetalation with lithium bromide afforded a more nucleophilic species. Several examples are shown in Scheme 35.

The γ′-lithiation of allylic amines affords a nitrogen-chelated allylic lithium species by regioselective deprotonation. An example is shown in Scheme 36.[143]

Baldwin has shown that monoalkyl hydrazones may be used as acyl anion ('RCO$^-$')[144,145] or α-amino anion equivalents ('CH$_2$NH$_2$$^-$').[146] An example of the former is shown in Scheme 37. Note that the isomerization step (**26** → **27**) is necessary to avoid reversion to the parent hydrazone and ketone.[144]

In spite of considerable potential synthetically, nitrosamines have not received a lot of attention because of their high toxicity.[111,117–119] One potentially important development, reported by Seebach, is a

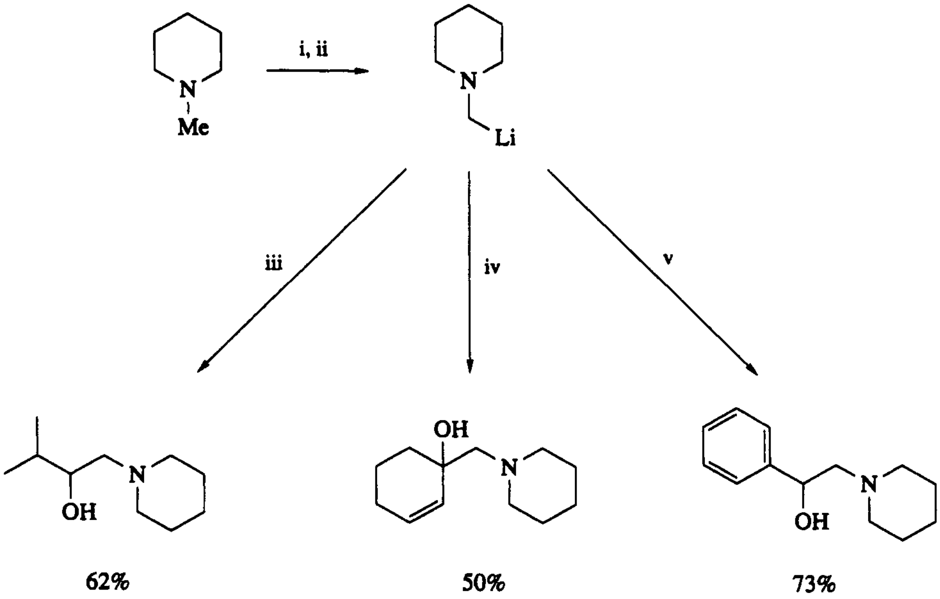

i $Bu^sLi$, $KOBu^t$, isopentane, –78 °C to 0 °C; ii, LiBr, $Et_2O$, –78 °C to 0 °C; iii, $Pr^iCHO$; iv, cyclohexenone, HMPA; v, PhCHO

**Scheme 35**

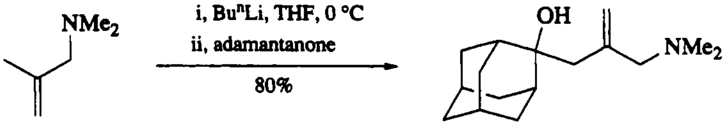

**Scheme 36**

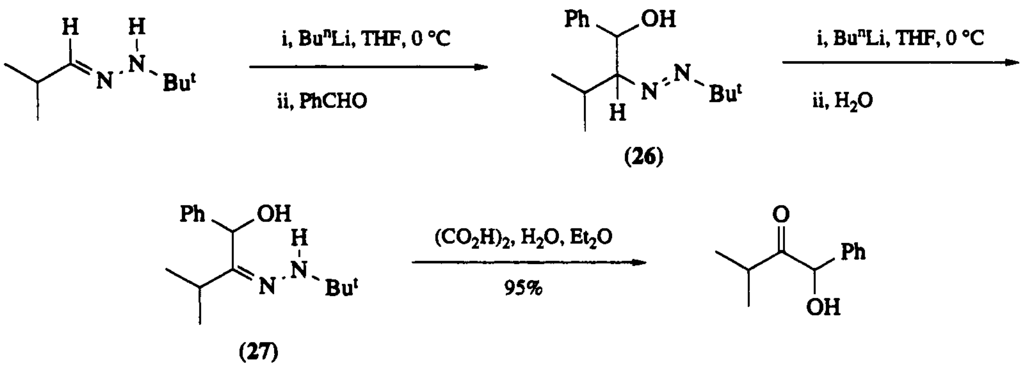

**Scheme 37**

one-pot alkylation and reduction protocol for the synthesis of secondary amines.[147] An example is shown in Scheme 38.

An interesting method for the synthesis of amines and the homologation of carbonyl compounds has been reported that utilizes the condensation of a lithiated formamidine with a carbonyl compound.[10,11] Typical examples are shown in Scheme 39.

A number of heterocyclic *N*-alkyllactams have been metalated to dipole-stabilized anions, and the yields of addition to carbonyls are reasonably good.[36] An experimental and theoretical study of the competitive metalation to form enolates or dipole-stabilized anions of a series of alicyclic *N*-benzyllactams has been reported by Meyers and Still.[148] Experimentally, the regioselectivity of the deprotonation varies inconsistently with ring size. Specifically: 5-, 6- and 11-membered rings are deprotonated in the ring to form enolates (**29**), whereas 7- and 8-membered rings are deprotonated at the *N*-benzyl to form dipole-

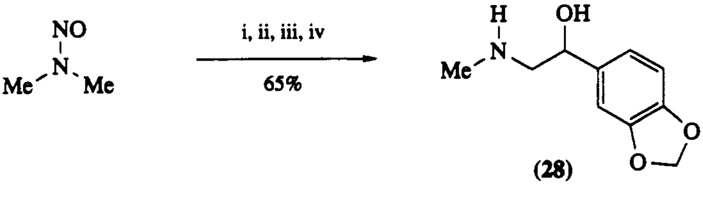

**(28)**

i, Bu$^n$Li; ii, piperonal; iii, LiAlH$_4$; iv, Raney Ni, H$_2$

Scheme 38

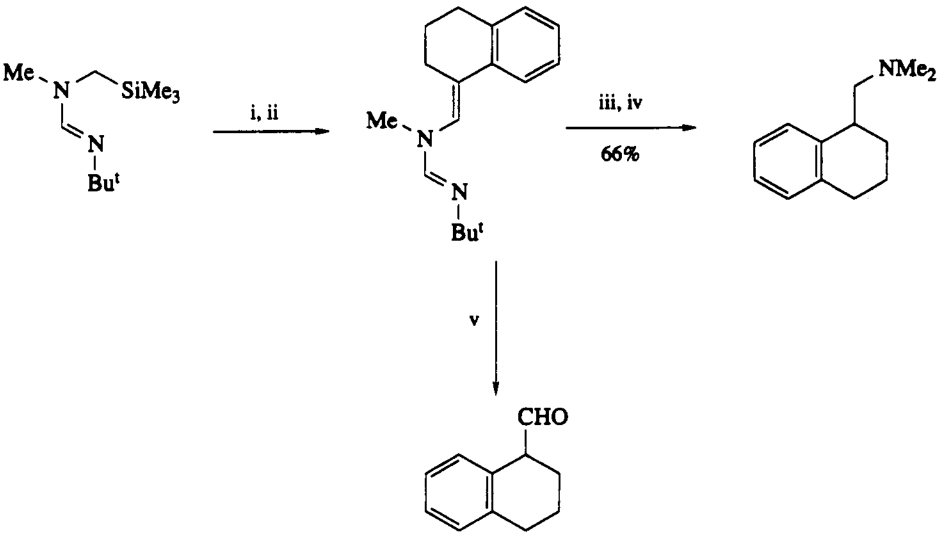

60%

i, Bu$^s$Li, THF, –78 to –20 °C; ii, α-tetralone, –78 °C to r.t.; iii, NaBH$_4$; iv, dilute HCl; v, N$_2$H$_4$, H$^+$

Scheme 39

stabilized anions (30; Scheme 40). In contrast, 9-, 10- and 13-membered ring lactams give mixtures of enolization and benzylic metalation. A simplistic molecular mechanics model was found to predict the regioselectivity that evaluates the strain energy necessary to achieve the optimal geometry for enolate formation. The model restrains the lactam α-hydrogen in a stereoelectronically preferred 90° O═C—C—H alignment, then compares the resulting minimized energy calculated using the MM2 force field with the global minimum for each lactam. When the differences in strain energies are small (<0.1 kcal mol$^{-1}$), enolization is the preferred course of deprotonation. When the differences are between 1.3 and 2.2 kcal mol$^{-1}$, mixtures of enolization and benzylic metalation are found, and when the differences are large, 2.25 and ≥3.5 kcal mol$^{-1}$, exclusive benzylic metalation is found.

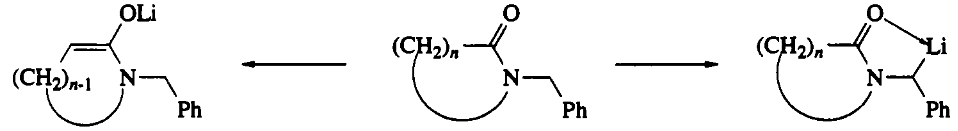

**(29)** **(30)**

Scheme 40

The formation of α-aminolithium reagents by transmetalation of α-aminostannanes was first reported in the early 1970s.[116] However, the exploitation of this protocol was delayed until better methods were developed for the synthesis of the requisite stannanes. Quintard has shown that tributyltin Grignard reagents afford α-aminostannanes when reacted with amino acetals[149] or iminium ions,[150] as shown in Scheme 41. Transmetalation of the α-aminostannanes and addition to aldehydes and ketones has been reported for simple tertiary amines[149,150] as well as carbamates.[151] Representative examples are shown in Scheme 42.

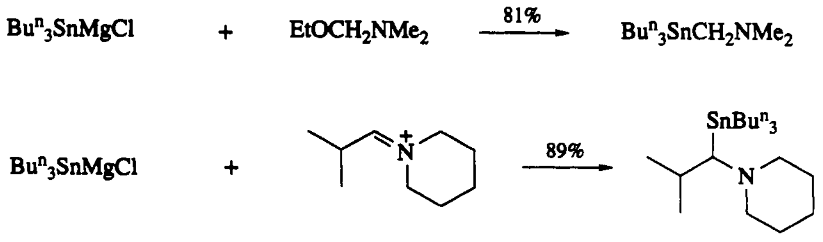

$Bu^n{}_3SnMgCl$ + $EtOCH_2NMe_2$ 81% $Bu^n{}_3SnCH_2NMe_2$
$Bu^n{}_3SnMgCl$ +
89%
$SnBu^n{}_3$
N

**Scheme 41**

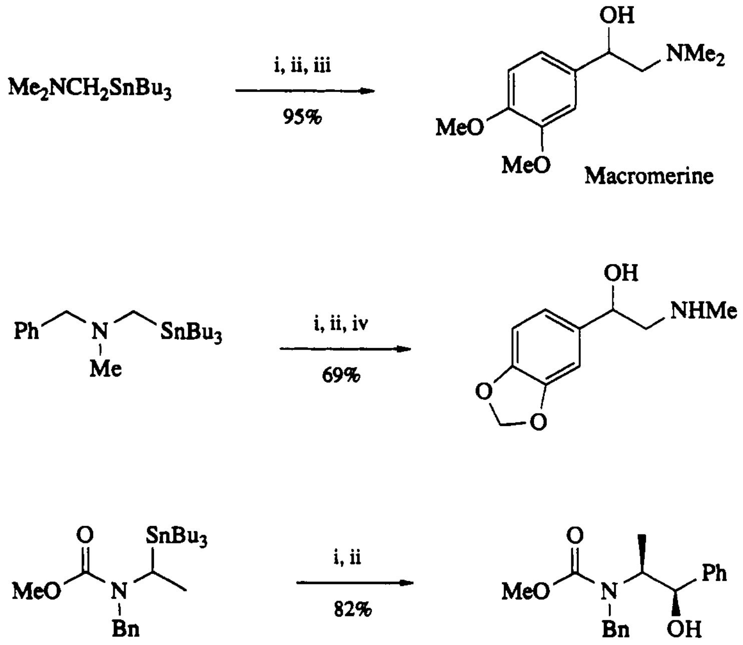

$Me_2NCH_2SnBu_3$
i, ii, iii
95%
OH
$NMe_2$
MeO
MeO
Macromerine
Ph
N
Me
$SnBu_3$
i, ii, iv
69%
OH
NHMe
O
O
O
MeO
N
Bn
$SnBu_3$
i, ii
82%
O
MeO
N
Bn
Ph
OH

i, BuLi; ii, ArCHO; iii, $H^+$; iv, $H_2$, Pd/C

**Scheme 42**

### 2.1.4.3 Additions *via* Metalation of Carbocyclic Systems

The regioselective *syn*, vicinal lithiation of cyclopropane and cubane amides has been reported.[152–154] Transmetalation to organomercury[153,154] or zinc[152] compounds facilitates functionalization, as shown in Scheme 43.

Directed lithiations of α,β- and γ,δ-unsaturated amides[155–157] have been extensively studied.[158,159] Illustrative examples are shown in Scheme 44. Prior complexation of the alkyllithium base with the amide carbonyl oxygen directs the base to the thermodynamically less acidic β′-position in α,β-unsaturated amide (**31**), which adds to benzophenone and subsequently lactonizes. Analysis of the NMR spectrum reveals that the organolithium added the benzophenone in the equatorial position.[156,158] A different kinetic deprotonation is seen in γ,δ-unsaturated amide (**32**), where β-lithiation to form an allylic anion predominates over α-lithiation to form an enolate.[157,159] Addition of the lithium anion to acetone affords poor regioselectivity, but transmetalation to magnesium before carbonyl addition yields a species which adds exclusively at the δ-position.[157,159]

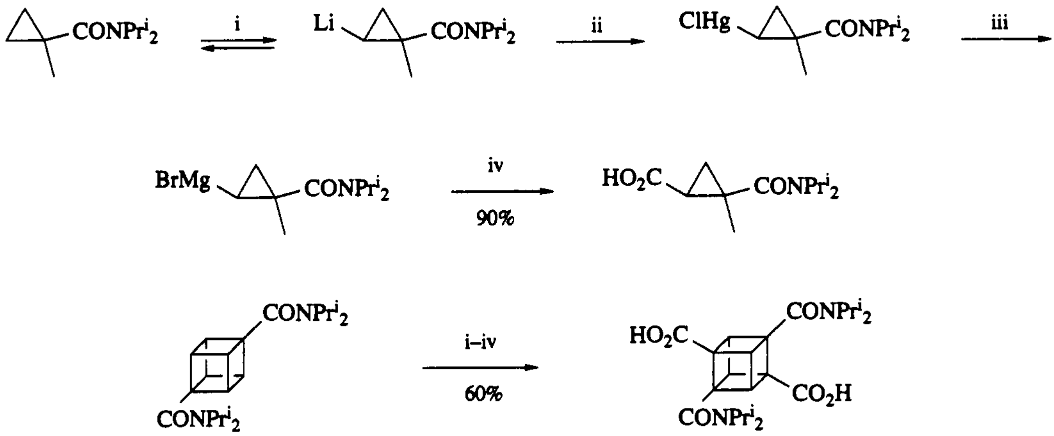

i, LITMP, THF, 0 °C; ii, $HgCl_2$; iii, MeMgBr, –20 °C; iv, $CO_2$

Scheme 43

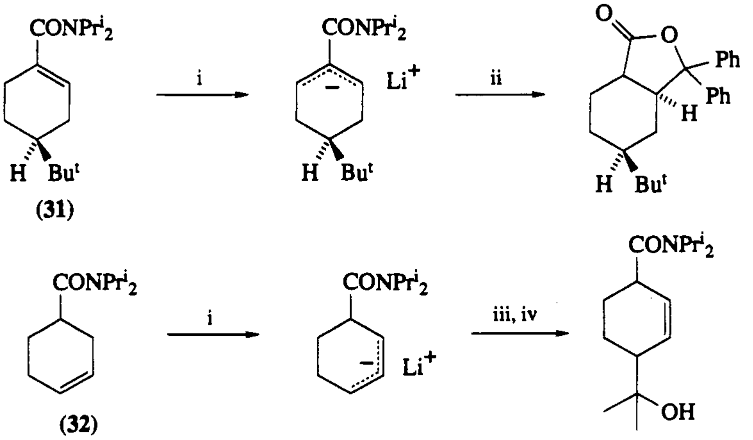

(31)

(32)

i, $Bu^sLi$, TMEDA, THF, –78 °C; ii, $Ph_2CO$; iii, $MgBr_2{\bullet}Et_2O$; iv, $Me_2CO$

Scheme 44

### 2.1.4.4 Additions *via* Metalation of Heterocyclic Systems

A one-pot procedure for the activation and metalation of tetrahydroisoquinoline involves the carbonation of the lithium amide anion and then further metalation. As is illustrated in Scheme 45, the dipole-stabilized anion species may be added to carbonyl compounds in good yield.[160] For the activation of tetrahydroisoquinoline Grignards, Seebach examined benzamides, pivalamides and phosphoramides, and found that the benzamides would not metalate, and that although the phosphoramides were most easily removed, the pivalamides were the most nucleophilic species. As is shown in Scheme 46, the lithiated pivaloylisoquinoline adds to cyclohexanone in good yield.[161]

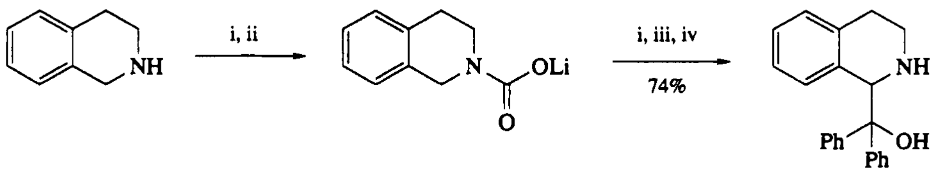

i, $Bu^nLi$, THF, –20 °C; ii, $CO_2$; iii, $Ph_2CO$; iv, 2M HCl

Scheme 45

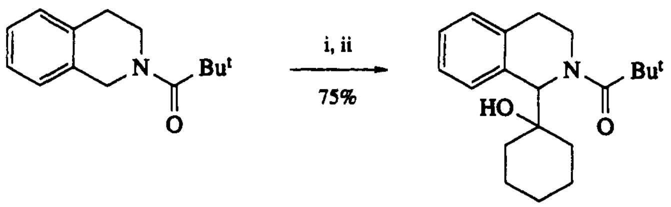

i, $\mathrm{Bu^tLi}$, TMEDA, THF, −78 °C; ii, cyclohexanone

Scheme 46

Seebach also compared the same pivaloylisoquinoline to a tetrahydroisoquinoline formamidine to evaluate the face-selectivity in the addition of the metalated derivatives to aldehydes.[132,162,163] In both cases, the organolithium showed significantly lower diastereoselectivity than the Grignard obtained by transmetalation with $\mathrm{MgBr_2{\cdot}Et_2O}$, as shown by the examples in Scheme 47. The transmetalation protocol was used to prepare a number of racemic isoquinoline alkaloids.[162]

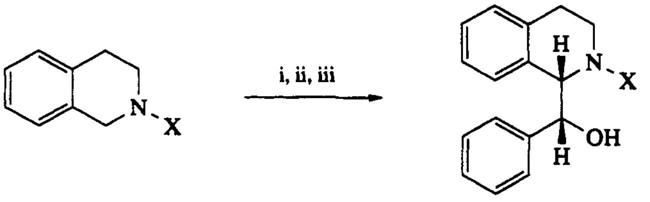

major diastereomer

selectivity:
X = $\mathrm{COBu^t}$: >97:3
X = $\mathrm{CHNBu^t}$: 86:14

i, $\mathrm{Bu^tLi}$, THF, −78 °C; ii, $\mathrm{MgBr_2{\bullet}Et_2O}$; iii, PhCHO

Scheme 47

Similarly low face-selectivity was found in the addition of lithiated formamidines of tetrahydroquinoline,[164] dihydroindole[164] and β-carboline[165] to benzaldehyde, although addition of the lithiated β-carboline to methyl chloropropyl ketone afforded an 8.5:1 selectivity (Scheme 48).[166] Lithiated formamidines of pyrrolidine and piperidine also add to benzaldehyde in excellent yield, but the diastereoselectivity was not reported.[128]

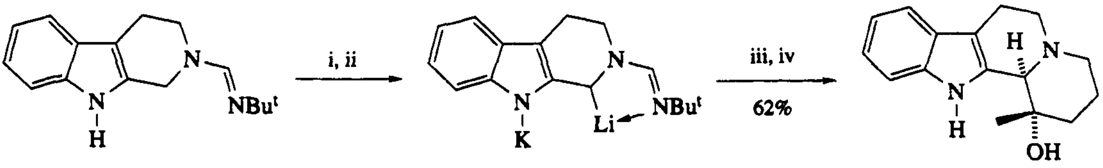

major diastereomer
diastereoselectivity = 89:11

i, $\mathrm{KOBu^t}$ or KH; ii, $\mathrm{Bu^nLi}$, THF, −78 °C; iii, $\mathrm{MeCO(CH_2)_3Cl}$; iv, $\mathrm{N_2H_4}$, $\mathrm{H^+}$

Scheme 48

Formamidines whose α-protons are allylic are easily metalated, but the predominant site of electrophilic attack is the γ-position, as shown by the example in Scheme 49.[128]

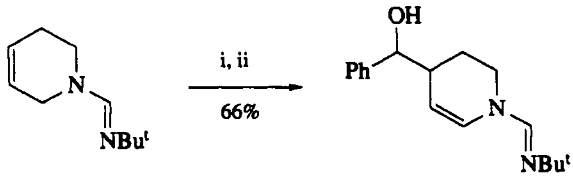

major isomer
regioselectivity = 100:0
diastereoselectivity = 66% *threo*, 34% *erythro*

i, $\mathrm{Bu^nLi}$, THF, −78 °C; ii, PhCHO, −78 °C to r.t.

Scheme 49

The lithiation and carbonyl additions of piperidinecarboxamides has been studied by both Beak[167] and Seebach.[168] An example of the addition of a lithiated derivative to propionaldehyde is shown in Scheme 50.[167] Beak found that although the face-selectivity of the addition shown in Scheme 50 is not high, acid hydrolysis affords a single diastereomer of the product of *N*- to *O*-acyl migration. The stereospecificity must be obtained before the acyl migration; the suggested mechanism is illustrated in Scheme 51.[167]

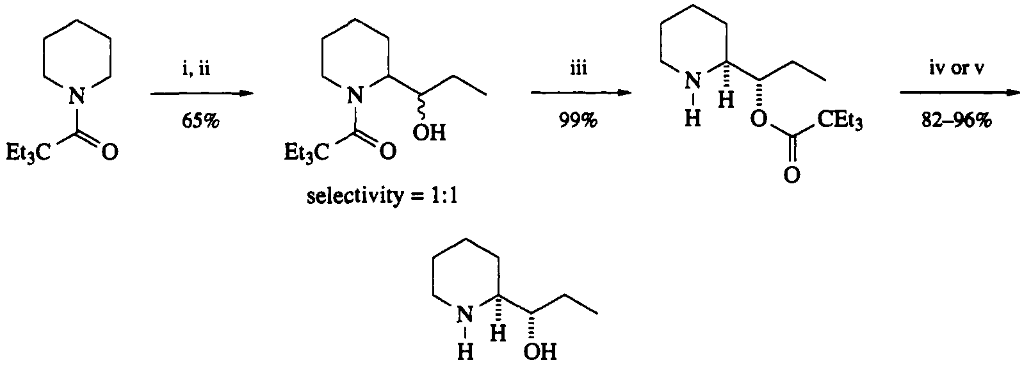

i, $Bu^sLi$, TMEDA, $Et_2O$; ii, EtCHO; iii, conc. HCl, MeOH; iv, $KOBu^t$, $H_2O$, diglyme; v, $LiAlH_4$

**Scheme 50**

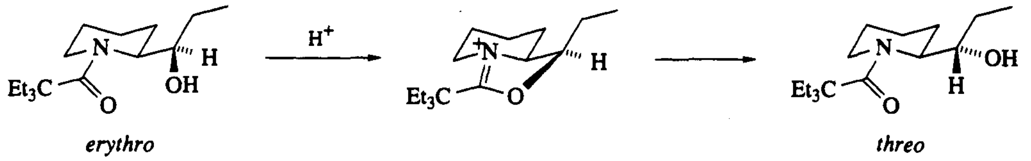

**Scheme 51**

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# 2.2

# Boron Stabilization

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## 2.2.1 INTRODUCTION

Based upon their knowledge of the chemistry of carbonyl, nitro, sulfonyl, cyano compounds *etc.*, organic chemists have long believed that carbanions $XCH_2^-$ are stabilized if the group X is electron withdrawing.

Recently, calculations have been carried out on anions $XCH^-_2$ in which X is a member of the first row element set: Li, BeH, $BH_2$, $CH_3$, $NH_2$, OH and F.[1–4] Schleyer's calculations (Table 1)[1] suggest that the methyl group is destabilizing, the amino group is borderline, while all other groups are stabilizing. These results are qualitatively similar to those obtained from other calculations. In particular, very large π-effects are exhibited by BeH and planar $BH_2$ groups, while inductive stabilization by the electronegative F and OH groups is less effective.

In Table 2 are given similar calculations for stabilization by first row elements, together with calculated and experimental values for a variety of stabilizing organic groups.[4]

Clearly, whichever method of calculation is used, there is a remarkable stabilization by a boron atom, comparable with that of a carbonyl group. When diffuse function-augmented basis sets are used, the stabilization energies calculated are generally lower,[1] and in the case of organic stabilizing groups this brings them closer to the experimental values (Table 2).

There is an appreciable C—B bond shortening of 0.13 Å in planar $H_2B—CH_2^-$ when compared to the perpendicular form, and at the 4-31G level the planar form is 57.2 kcal $mol^{-1}$ (1 cal = 4.18 J) lower in energy than the perpendicular form.[4]

**Table 1** Calculated[1] Stabilization Energies (kcal mol$^{-1}$) for Carbanions $XCH_2^-$

| *X* | *STO-3G//<br>STO-3G* | *4-31G//<br>4-31G*[2,3] | *6-31G*//<br>4-31G*[3] | *MP2/6-31G*//<br>4-31G*[3] | *4-31+G//<br>4-31+G* | *MP2/4-31+G//<br>4-31+G* | *6-31+G*//<br>4-31+G* | *MP2/6-31+G*//<br>4-31+G* |
|---|---|---|---|---|---|---|---|---|
| Li | –54.9 | –17.5 | –13.7 | –25.8 | –2.4 | –6.6 | –4.8 | –8.1 |
| BeH | –65.8 | –40.4 | –38.1 | –46.9 | –31.8 | –33.3 | –31.3 | –32.9 |
| $BH_2$ | –81.6 | –67.7 | –61.4 | –71.8 | –54.7 | –58.0 | –53.2 | –57.4 |
| $CH_3$ | –9.0 | –2.1 | –1.4 | –3.3 | +5.7 | +4.8 | +4.0 | +3.0 |
| $NH_2$ | –16.6 | –5.2 | –3.3 | –5.6 | +1.9 | +0.6 | +1.5 | –0.6 |
| OH | –20.0 | –15.8 | –7.9 | –10.9 | –7.7 | –8.1 | –3.7 | –5.6 |
| F | –21.7 | –24.6 | –14.6 | –16.1 | –15.6 | –13.3 | –9.3 | –9.0 |

**Table 2**[4] Calculated and Experimental Stabilization Energies (kcal mol$^{-1}$) for Carbanions $XCH_2^-$

| *X* | *4-31G* | *6-31G** | *MP2/6-31G** | *Experimental* |
|---|---|---|---|---|
| Li | –17.4 | –13.7 | –25.8 | — |
| BeH | –40.4 | –38.1 | –46.9 | — |
| $BH_2$ | –67.6 | –61.4 | –71.8 | — |
| $CH_3$ | –2.1 | –1.4 | –3.3 | — |
| $NH_2$ | –5.2 | –3.3 | –5.6 | — |
| OH | –15.7 | –7.9 | –10.9 | — |
| F | –24.6 | –14.6 | –16.1 | — |
| CN | –61.1 | –55.0 | –57.9 | –44.4 |
| $NO_2$ | –98.1 | –75.9 | — | –57.9 |
| $CH_3CH_2$ | –5.6 | –4.4 | — | — |
| $CH_2{=}CH$ | –37.5 | –31.8 | –37.1 | –25.8 |
| $HC{\equiv}C$ | –44.1 | –42.9 | –46.5 | –35.2 |
| $CF_3$ | –57.0 | –37.0 | — | — |
| CHO | –71.5 | –60.5 | –66.2 | –50.2 |
| Ph | –44.4 | — | — | –37.6 |

Since the degree of stabilization of boron-stabilized carbanions is similar to that for anions stabilized by a formyl or a cyano group, the comparative lack of knowledge of boron-stabilized carbanions must be due either to kinetic factors associated with their production or to the availability and nature of their precursors.

Boron-stabilized carbanions are expected to assume a geometry which allows maximum overlap between the lone pair on the α-carbon atom and the vacant boron orbital. Dynamic NMR studies[5] on $Mes_2BC^-HPh$ (Mes = 2,4,6-trimethylphenyl) demonstrate this by showing that the anion decomposes at 140 °C, before observation of rotation effects about the B—C$^-$HPh bond. This gives a $\Delta G^{\ddagger}$ rotation of >22 kcal mol$^{-1}$, which is similar to that of the isoelectronic $Mes_2B{-}NHR$[6,10] and greater than that found[7,10] for rotation about the B—S bond in $Mes_2B{-}SR$ (19.25 kcal mol$^{-1}$; calc.[8] 22 kcal mol$^{-1}$) and for rotation about the B—O bond in $Mes_2B{-}OMe$ (13.2 kcal mol$^{-1}$).[9,10] The B—C rotational barrier[11] of $(Mes_2B)_2CHLi$ is 17 kcal mol$^{-1}$, very similar to that found for a series of isoelectronic substituted allyl cations.[12] It was concluded[11] that structure (**1**) makes a significant contribution to the overall electronic structure of $Mes_2BCH_2^-$.

The crystal structure of (**2**), as its 12-crown-4 derivative, has been determined.[13] The $C_2BCH_2$ core of the molecule is essentially planar and the length of the B—$CH_2$ bond is 1.444 Å. This is within the 1.42–1.45 Å predicted for $B{=}CH_2$ and quite distinct from the B—Me distance of the parent compound (**3**).[13] The distances and angles found are in accord with formulation (**1**), as is the upfield shift of 43.2 p.p.m. in the $^{11}B$ NMR spectrum on passing from (**3**) to (**2**).[13] Thus there is a high degree of orbital overlap in species of type (**4**), which might be better represented in general as the highly stabilized forms (**5**).

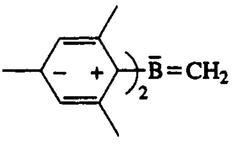

(**1**)

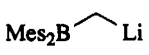

(**2**)

$Mes_2BMe$

(**3**)

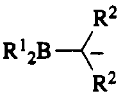

(4)

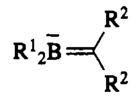

(5)

## 2.2.2 PREPARATION OF BORON-STABILIZED CARBANIONS

### 2.2.2.1 Introduction

This topic has been summarized in references 14 and 15, of which the former is the most recent and wide ranging of the reviews available over the whole field of boron chemistry.

There are currently three general methods for the production of boron-stabilized carbanions, each of which has analogies in carbonyl chemistry. The cleavage of a 1,1-diborylalkane by base readily yields the desired anion in a fashion similar to the base cleavage of a β-dicarbonyl compound. Deprotonation α to a boron atom can be accomplished directly in special circumstances, as can the addition of an organometallic compound to a vinylborane, which is similar to conjugate addition to an α,β-unsaturated carbonyl compound. Each of these methods is treated in detail in the next three sections.

### 2.2.2.2 Preparation and Cleavage of 1,1-Diboryl Compounds

1,1-Diboryl compounds (**6**) are made by reaction of certain dialkylboranes, generally dicyclohexylborane [$(C-C_6H_{11})_2BH$], disiamylborane ($Sia_2BH$) or 9-borabicyclo[3.3.1]nonane (9-BBN-H), with 1-alkynes (equation 1).[14,16–18]

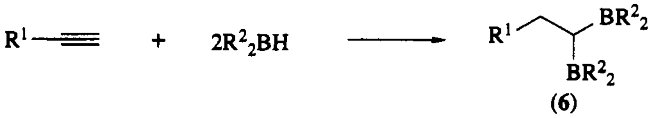

(1)

The products (**6**) are very prone to hydrolytic cleavage by base; this is presumably due to the ready production of an intermediate carbanion followed by its rapid protonation. This possibility was tested[19] by treating a series of compounds (**6**; $R^2$ = cyclohexyl) with $Bu^nLi$ at –78 °C in THF. The products had properties consistent with the production of (**7**; equation 2). The by-product, a simple trialkylborane, also reacts with butyllithium, and so 2 equiv. of the latter must be added. Thus, the process is wasteful in that one atom of boron and 1 equiv. of base are consumed in an unproductive fashion (equation 3).

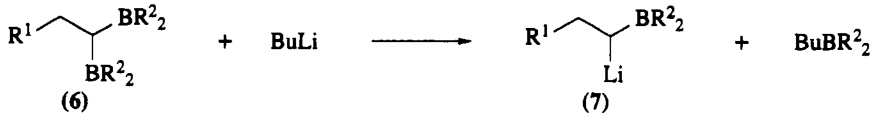

(2)

$$BuBR^2_2 + BuLi \longrightarrow Bu_2\bar{B}R^2_2Li^+ \qquad (3)$$

The reaction of pent-1-yne with borane, followed by base cleavage, has been studied,[20] yields having been estimated by alkylation with ethyl bromide. Although the reaction occurred with sodium and lithium methoxides, it went better with butyllithium and best with 2 equiv. of methyllithium. It was later shown[17] that diborane gave *ca.* 10% of 1,2-addition, which did not occur with dicyclohexyl- and disiamyl-borane. Hydroboration with 9-BBN-H[21] readily gave (**6**) ($BR^2_2$ = 9-BBN), which on cleavage with 2.5 mol equiv. of MeLi gave high yields of the corresponding product (**7**).

Tris(dialkoxyboryl)alkanes such as (**8**), produced as in equation (4), may also be used as precursors of boron-stabilized carbanions.[22] Reaction of (**8**) with base gives (**9**),[22,23] which is stabilized by two boron atoms (equation 5). It is not clear whether a similar reaction succeeds with $CH_2[B(OR)_2]_2$.

Although cleavage of *gem*-diboryl compounds is a mild and general process for the production of boron-stabilized carbanions, it nevertheless suffers from two disadvantages. Firstly, although

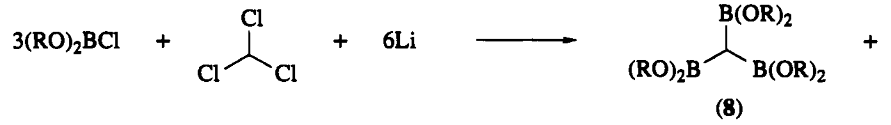

(4)

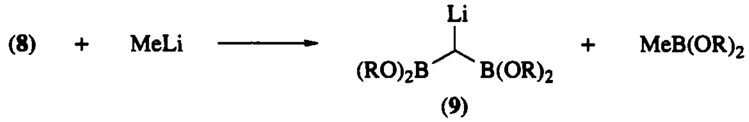

(5)

1,1-diborylalkanes are available from terminal alkynes, *gem*-diboryl compounds within a carbon chain are not readily available. Compounds such as (**8**) are very interesting as one-carbon synthons, but are confined to this function as yields drop when CH is replaced by CMe or CPh.[24] Secondly, there is the wasteful use of base and boron referred to previously.

### 2.2.2.3 Cleavage of α-Substituted Organoboranes

Boron-stabilized carbanions may also be produced by selective cleavage of a heteroatom group from an α-substituted organoborane such as a borylstannylmethane (equations 6–8).[25,26]

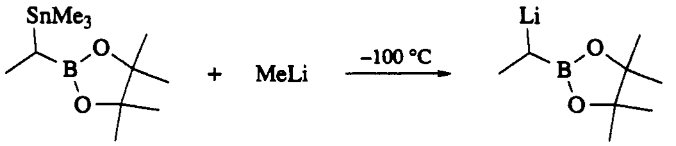

(6)

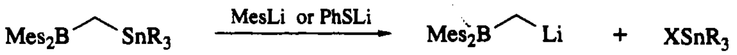

(7)

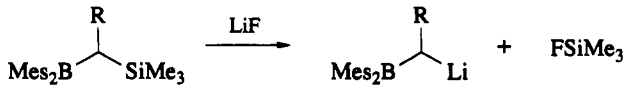

(8)

The reactions of bases with borylstannylalkanes generally lead to cleavage of the tin moiety,[25,26] and lithium thiophenoxide is especially specific.[25] It is of interest that the reaction of fluoride anion with dimesitylboryl(trimethylsilyl)alkanes also gives α-boryl carbanions, thus obviating the need to use organometallics.[26,27]

### 2.2.2.4 Deprotonation of Organoboranes

It appears that the first example of deprotonation to give a boron-stabilized carbanion was that shown in equation (9).[28] In general, however, early attempts to deprotonate organoboranes (equation 10) foundered because borate formation (equation 11) was favored.

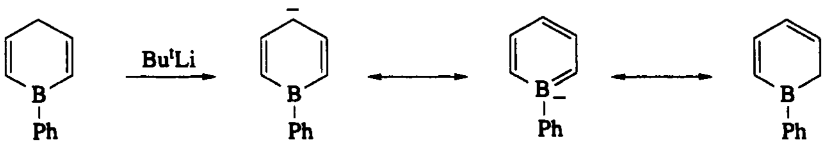

(9)

Successful deprotonations must discourage equation (11) so as to allow equation (10) to proceed. This may be achieved in several ways as follows: (a) the reagent can be a very hindered, non-nucleophilic base; (b) the groups around boron can be large so that attack on boron is inhibited on steric grounds; or (c) the electrophilicity of the boron atom may be lowered by the use of heteroatom substituents (*e.g.* equation 10; X = OR). All three of these approaches have been used, either separately or in conjunction with one another.

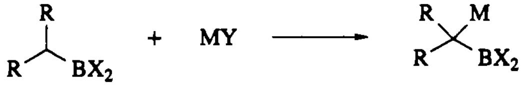

(10)

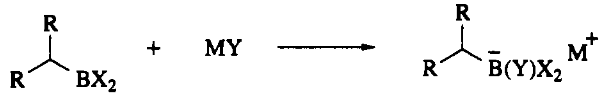

(11)

The first successful attempt to deprotonate a simple alkylborane is shown in equation (12).[29] *B*-Methyl-9-BBN (**10**) was reacted with a variety of lithium amides and the yield of (**12**) estimated by deuterium incorporation on quenching with $D_2O$. Neither lithium diethylamide nor lithium diisopropylamide gave any of (**12**) at all, but the hindered piperidide (**11**) (LITMP) produced up to 75% of (**12**) using 100% excess of base.

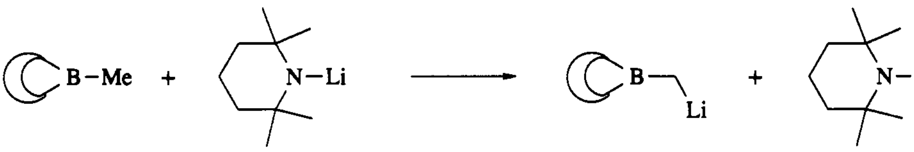

(12)

**(10)** **(11)** **(12)**

Even using LITMP it was not possible to convert (**13**) into (**14**) when X = H (equation 13). It appears that stabilization by one dialkoxyboryl group is not sufficient and that at least one other stabilizing group is required for anion formation.[30] Deprotonation with LITMP was successful for (**13**) with X = Ph,[30] SPh,[31] TMS,[32,33] $Ph_3P^+$ [33] and $CH{=}CH_2$,[33] but failed for X = $Me_2S^+$ [33] and $R_3N^+$.[34] Compound (**15**; X = H; equation 14) is successfully deprotonated by LITMP in the presence of TMEDA to give (**16**; X = H). Unfortunately, with (**15**; X = Ph), cleavage takes precedence over deprotonation and (**14**; X = Ph) is produced rather than (**16**; X = Ph).[30]

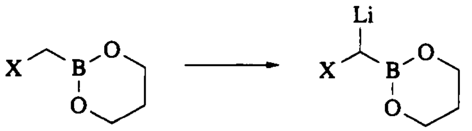

(13)

**(13)** **(14)**

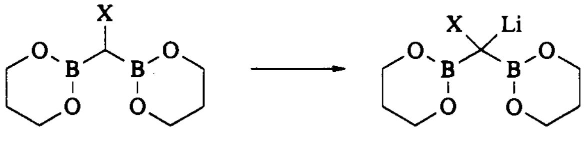

(14)

**(15)** **(16)**

Compound (**17**; equation 15) is deprotonated by LDA to give (**19**), but treatment with butyllithium leads to cleavage of the B—C bond (equation 16).[35]

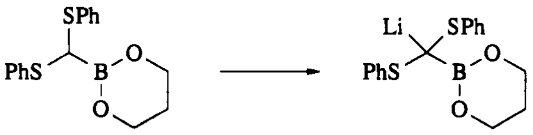

(15)

**(17)** **(18)**

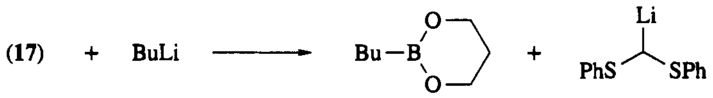

(16)

The production of boron-stabilized carbanions using steric hindrance on the borane to inhibit borate formation was first demonstrated[36] as part of a study of the properties of dimesitylboryl derivatives. Unlike the situation with dialkoxyboryl derivatives, it was possible to carry out the deprotonation with only one boron atom present and with no extra stabilizing groups. Either LDA or lithium dicyclohexylamide may be used as base, the latter being rather more efficient (equation 17).[36] The initial study showed that the reaction with $Mes_2BCHR^1R^2$ was successful with: $R^1, R^2 = H$; $R^1 = H, R^2 = Me$; $R^1 = H, R^2 = Ph$; and $R^1, R^2 = Me$.

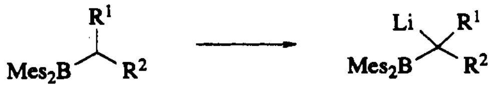

(17)

A study of the reactions of various bases with dimesitylmethylborane (Scheme 1) showed that the outcome critically depends on the nature of the base used.[5] Both mesityllithium and lithium dicyclohexylamide give high yields of the required anion, mesityllithium proving to be a superior base for a wide variety of alkyldimesitylboranes. *n*-Butyllithium attacks at boron to give the borate and *t*-butyllithium gives the hydroborate by β-hydrogen transfer. Sodium hydride also gives the hydroborate, while potassium metal gives the radical anion.

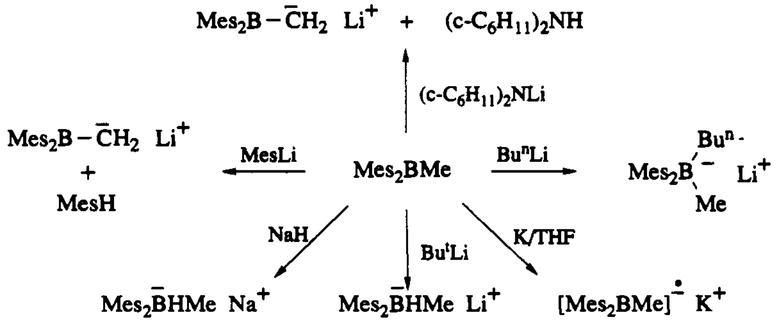

Scheme 1 Reactions of various bases with dimesitylmethylborane

Further studies showed that a variety of substituted anions, $Mes_2BCHLiX$, in which X = SPh,[37] TMS,[37] $SnPh_3$[26] amd $BMes_2$,[37] are available by deprotonation of the corresponding boranes. It is noteworthy that the triphenyltin derivative gives the anion without cleavage, while both the trimethyltin and tri-*n*-butyltin derivatives are cleaved at the carbon–tin bond by treatment with mesityllithium.

Vinylboranes, readily available by the hydroboration of 1-alkynes with dialkylboranes such as $Sia_2BH$,[38] react readily with LITMP to give high yields of the corresponding allyl carbanions (equation 18).[38]

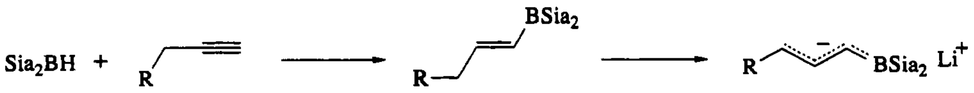

(18)

Mesityllithium or lithium dicyclohexylamide react similarly with allyldimesitylborane (equation 19).[39] Thus, boron-stabilized allyl units are available from either allyl- or vinyl-boranes.

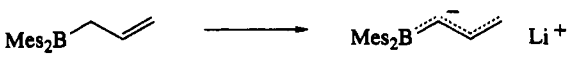

(19)

### 2.2.2.5 Addition to Vinylboranes

As vinylboranes are electronically similar to α,β-unsaturated ketones, reactions analogous to conjugate addition might be expected. Unfortunately, many attempts to add organometallic compounds to simple alkenyldimesitylboranes gave only very low yields (*ca.* 5%) of the required carbanions.[40] However, additional steric hindrance and/or carbanion-stabilizing ability at the α-position, caused by the introduction of a TMS group, allows the process to be realized and so a wide variety of organometallics have been added to 1-dimesitylboryl-1-trimethylsilylethylene (**19**; $R^1 = H$; equation 20).[41]

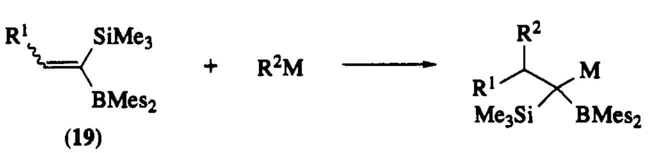
SiMe3
BMes2
+ R2M
R2
M
R1
Me3Si
BMes2
**(19)**

(20)

For the case of $R^1$ = H, $R^2M$ can be $\mathrm{Bu^nLi}$, $\mathrm{Bu^tLi}$, PhLi, $\mathrm{(RS)_2CHLi}$, $\mathrm{Bu^tO_2CCH_2Li}$, $\mathrm{CH_2{=}CH(CH_2)_4Li}$ and $\mathrm{Bu_2Cu(CN)Li}$. However, there was no addition of BuMgCl or PhC≡CLi, nor could an enolate anion be added. For (**19**; $R^1$ = Ph or $\mathrm{CH{=}CH_2}$) addition of butyllithium was successful and in the latter case the addition was entirely to the terminal position (equation 21).[41] Somewhat strangely, the addition of BuLi to (**19**; $R^1$ = $\mathrm{Bu^n}$) was unsuccessful.[41]

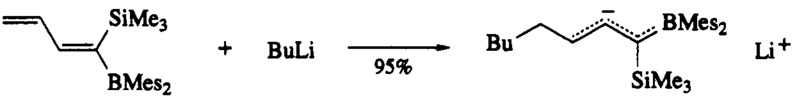
SiMe3
BMes2
+ BuLi
95%
Bu
BMes2
SiMe3
Li+

(21)

Of particular interest is the process shown in equation (22), in which the (*E*)-alkene geometry of (**20**) precludes intramolecular ate complex formation and hence an addition–cyclization reaction occurs to give the α-unsubstituted carbanion (**21**), which may be trapped by protonation, deuteration or alkylation.[41]

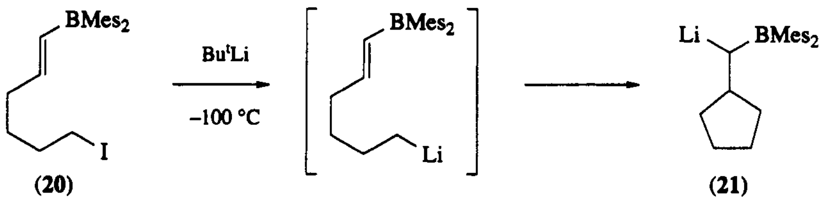
BMes2
I
ButLi
-100 °C
BMes2
Li
Li
BMes2
**(20)** **(21)**

(22)

As much recent work has concerned dimesitylboryl species, it is worth remarking that the related compounds (**22**)–(**24**) also readily yield carbanions.[42] Unlike mesityl compounds, (**22**) cannot be deprotonated at the 4′-methyl group, while compounds (**23**) have some special properties due to the great increase in steric hindrance around boron.[42a] Compounds (**24**) promise to be of utility due to their very ready solvolysis with water or alcohols in the presence of catalytic quantities of mineral acid. They are even selectively hydrolyzed in preference to vinyl as well as alkyl groups (equation 23).[42b]

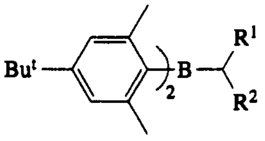

**(22)**

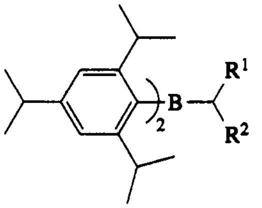

**(23)**

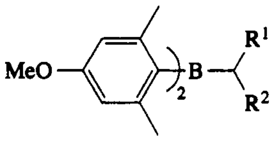

**(24)**

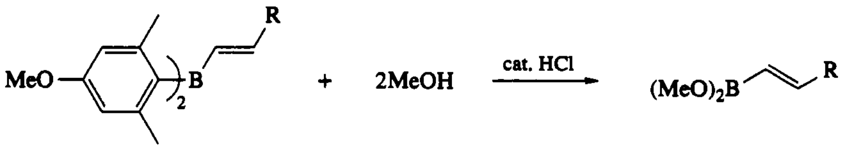
R
MeO
B
2
+ 2MeOH
cat. HCl
(MeO)2B
R

(23)

## 2.2.3 REACTIONS OF NONALLYLIC BORON-STABILIZED CARBANIONS

### 2.2.3.1 Reactions with Metal Halides

The reactions shown in equation (24) proved relatively facile for M = Ge, Sn or Pb. Although chlorotriphenylsilane failed to react, the corresponding TMS derivative was readily produced.[22]

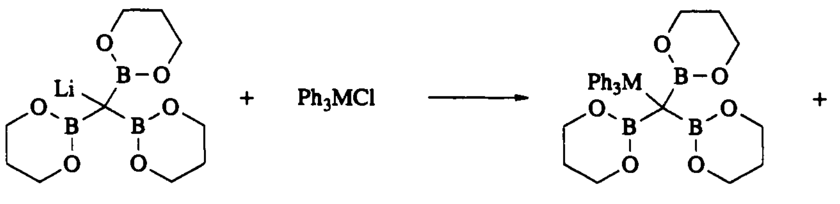
Li
+ Ph$_3$MCl
Ph$_3$M
+ LiCl

(24)

**(25)**

The products (**25**; M = Ge, Sn, Pb) react with butyllithium to give (**26**) by C—B cleavage and further reactions of these anions with Ph$_3$M′Cl (M′ = Sn, Pb) proceed to give compounds (**27**; equation 25) with no evidence of disproportionation.[22] If (**28**; equation 26) is treated in a similar fashion, the very stable tristannylmethylborane (**29**) results.[22]

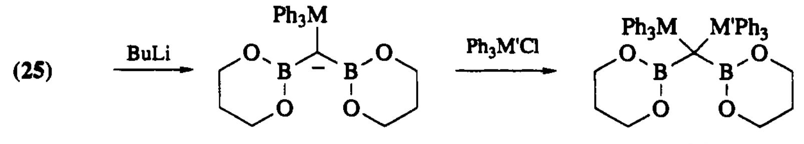
(25)
BuLi
Ph$_3$M
Ph$_3$M′Cl
Ph$_3$M
M′Ph$_3$

(25)

**(26)** **(27)**

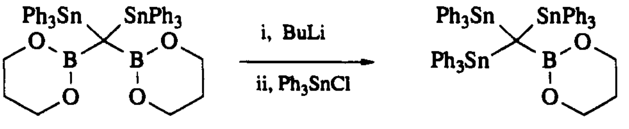
Ph$_3$Sn
SnPh$_3$
i, BuLi
ii, Ph$_3$SnCl
Ph$_3$Sn
SnPh$_3$
Ph$_3$Sn

(26)

**(28)** **(29)**

To obtain analogous organometallic compounds containing α-protons, it is better to use ethylenedioxyboryl derivatives (equation 27).[43]

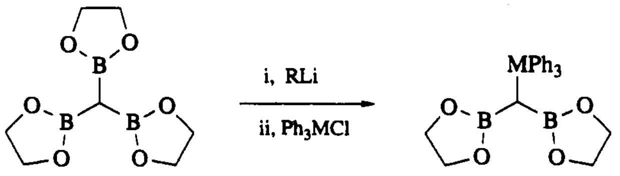
i, RLi
ii, Ph$_3$MCl
MPh$_3$

(27)

The reactions shown in equation (28) have been used[37] to make a set of dimesitylboryl compounds (**30**) in which M = Si, R = Me, $n$ = 3; M = Sn, R = Me, Bu, Ph, $n$ = 3; M = S, R = Ph, $n$ = 1; M = Hg, R = $CH_2BMes_2$, $n$ = 1. In most cases $R_nMCl$ was used as the reactant, but for introducing sulfur to give (**31**), $PhSSO_2Ph$ was advantageous in yielding pure product.[26] Otherwise the reaction shown in equation (29) was utilized.[37] Products (**30**) are stable, crystalline compounds that may act as precursors of boron-stabilized carbanions.[37]

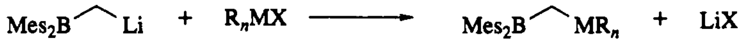
Mes$_2$B
Li
+ R$_n$MX
Mes$_2$B
MR$_n$
+ LiX

(28)

**(30)**

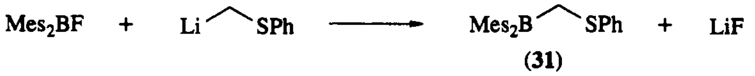
Mes$_2$BF
+ Li
SPh
Mes$_2$B
SPh
+ LiF

(29)

**(31)**

### 2.2.3.2 Alkylation Reactions

In general, all types of boron-stabilized carbanions are readily alkylated by primary alkyl halides. The situation for the alkylation of dimesitylboryl compounds is summarized in Scheme 2.[44] These reactions represent highly efficient homologation processes. Oxidation of the tertiary alkyl organoboranes is slow, but use of 4-methoxy-2,6-dimethylphenyl groups instead of mesityl groups renders the products sensitive to solvolysis.[42]

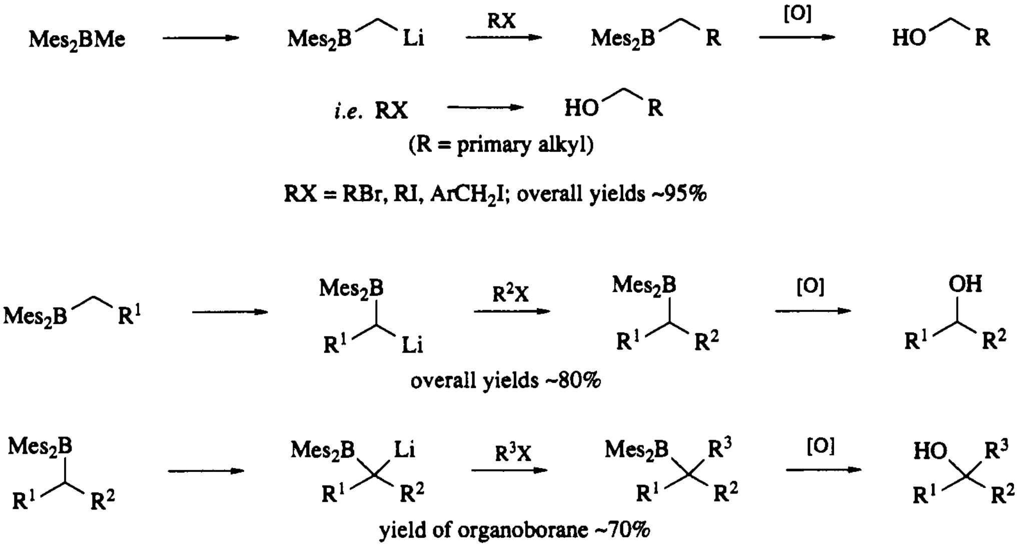

(R = primary alkyl)

RX = RBr, RI, ArCH$_2$I; overall yields ~95%

overall yields ~80%

yield of organoborane ~70%

**Scheme 2** Alkylation of alkyldimesitylboranes

Alkylations with *s*-alkyl halides give lower yields due to competitive elimination reactions.[44]

Alkylations of boron-stabilized carbanions have been carried out with primary alkyl halides containing acetal,[22,45] alkene,[41] alkyne,[22] chloride,[45] cyano,[45] ester[41] and tosylate[45] groups, though a ketone group was not tolerated.[22]

The anion derived from (**31**) reacted in a remarkable fashion with primary alkyl halides so that alkylation occurred only on sulfur to give the corresponding ylide (equation 30).[46]

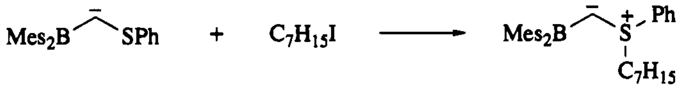

(30)

Alkylations of bis(dialkoxyboryl)methyl anions give products that may be oxidized to aldehydes or ketones (Scheme 3).[31]

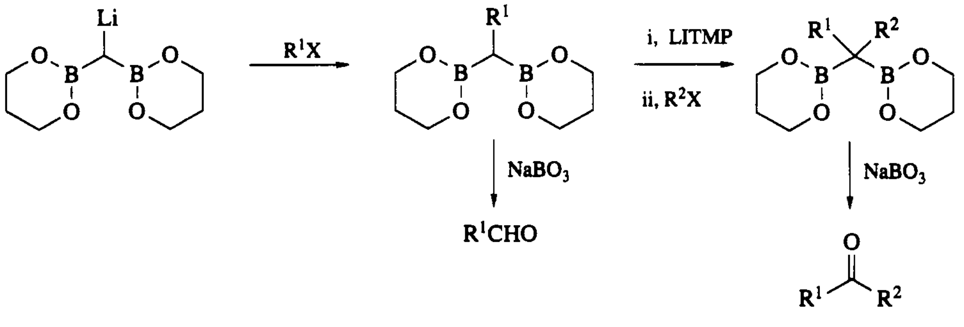

**Scheme 3** Alkylation of bis(dialkoxyboryl)methyl anions

Monoalkylation of (**32**)[31] gives products that are readily converted by NCS into monothioacetals (equation 31).[47]

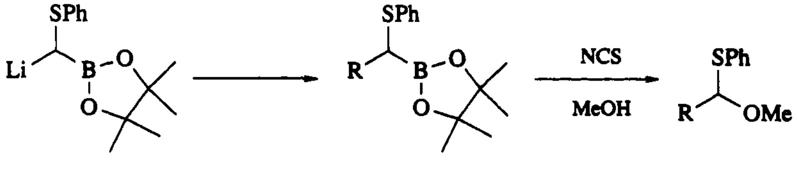
SPh
Li
B
O
O
SPh
R
B
O
O
NCS
MeOH
SPh
R
OMe

(32)

(31)

### 2.2.3.3 Reactions with Epoxides

The reactions of epoxides with dialkoxyboryl-stabilized carbanions are complicated by interaction of the oxyanion produced with the dialkoxyboryl grouping. When such an interaction is sterically inhibited, as with cyclohexene oxide, a single product results (equation 32).[31]

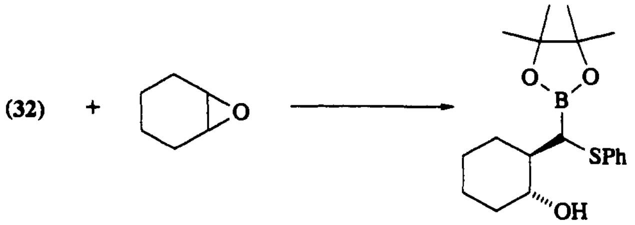
(32)
+
O
O
B
O
SPh
OH

(32)

Dimesitylboryl-stabilized anions generally react readily with epoxides to give products that can be oxidized to 1,3-diols (Scheme 4).[48] The regioselectivity is high and is dominated by the bulk of the dimesitylboron group, so that even (2), the anion derived from methyldimesitylborane, attacks styrene oxide regiospecifically. While (2) shows little regioselectivity in its reaction with *trans*-1-methyl-2-pentyl-

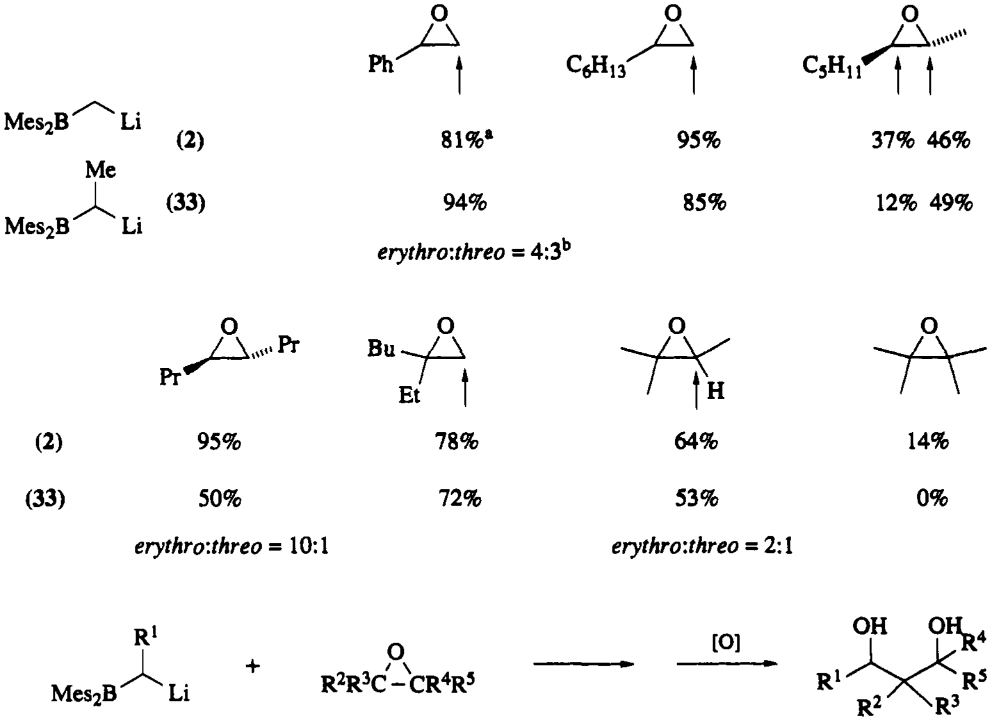
Mes2B
Li
(2)
Me
Mes2B
Li
(33)
O
Ph
O
C6H13
O
C5H11
81%a
95%
37% 46%
94%
85%
12% 49%
erythro:threo = 4:3b
O
Pr
Pr
O
Bu
Et
O
H
O
(2)
95%
78%
64%
14%
(33)
50%
72%
53%
0%
erythro:threo = 10:1
erythro:threo = 2:1
R1
Mes2B
Li
+
O
R2R3C–CR4R5
[O]
OH
OH
R1
R2
R3
R4
R5

[a] Yields are of isolated 1,3-diol and are based on starting organoboranes. The arrows indicate the position(s) of attack on the epoxide based on the isolated diol. For symmetrical epoxides no arrows are shown.

[b] The *erythro*:*threo* ratio is defined by the relationship of the 1,3-alcohol units.

**Scheme 4** Reactions of dimesitylboryl-stabilized carbanions with epoxides oxirane, anion (**33**), derived from ethyldimesitylborane, reacts with unusual selectivity with the same epoxide. In certain cases, stereo- as well as regio-selectivity is obtained. The *erythro:threo* ratio of 10:1 in the 1,3-diols derived by reaction of (**33**) with *trans*-1,2-di-*n*-propyloxirane is extremely unusual.[48]

With more hindered epoxides, yields are lower but only become negligible with tetrasubstituted epoxides. The method therefore provides a widely applicable synthesis of 1,3-diols.

### 2.2.3.4 Acylation Reactions

The overall process shown in equation (33) has been fairly well investigated. The presumed initial acylation products (**34**) undergo rearrangement to give alkenyloxyboranes (enol borinates) (**35**), the isolable products of the reaction. There has been no recorded instance of polyacylation in this process.

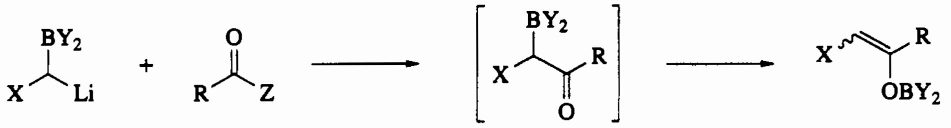
BY2
X
Li
+
O
R
Z
BY2
X
R
O
X
R
OBY2

(**34**) (**35**)

(33)

A specific example of the process, useful for the synthesis of phenyl ketones, is shown in equation (34).[21] Unfortunately, the further reactions of the intermediate enol borinates (**36**) with aldehydes show little diastereoselectivity (equation 35).[21]

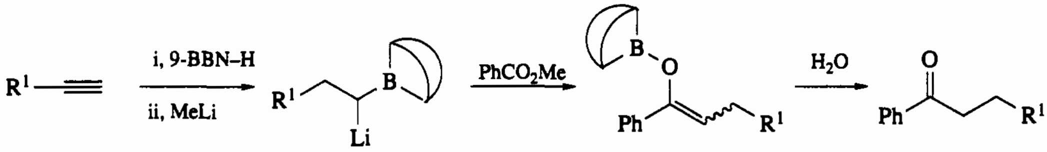
R1
i, 9-BBN-H
ii, MeLi
R1
B
Li
PhCO2Me
B
O
Ph
R1
H2O
O
Ph
R1

(**36**)

(34)

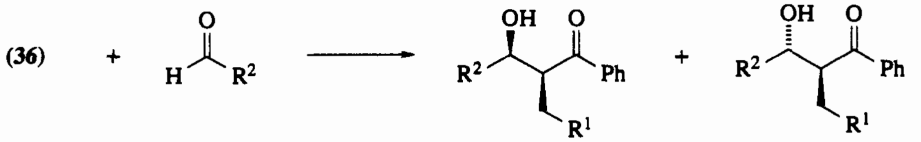
(36)
+
O
H
R2
OH
O
R2
Ph
R1
+
OH
O
R2
Ph
R1

(35)

The reactions of (**37**) with esters give poor or moderate yields of ketones (equation 36).[30]

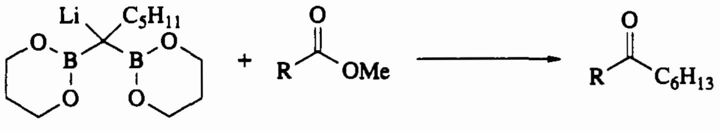
Li
C5H11
O
B
B
O
O
O
+
O
R
OMe
O
R
C6H13

(**37**)

(36)

The reactions with esters of stabilized anions (**32**) and (**38**) give α-phenylthio ketones in yields of 75–82% (equation 37).[31] Acylations with succinic anhydride and butyrolactone to give γ-keto acids and γ-hydroxy ketones respectively, also proceed in good yields.[31]

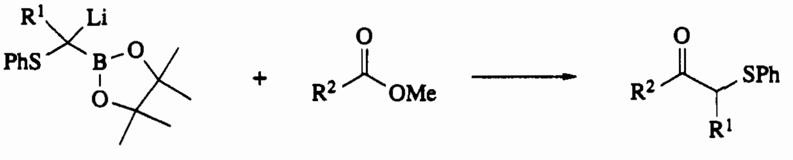
R1
Li
PhS
B
O
O
+
O
R2
OMe
O
R2
SPh
R1

(**38**)

(37)

The acylation of the pinacol derivative of dihydroxy[lithio(trimethylsilyl)methyl]borane with methyl benzoate has been recorded.[33] No details were given due to difficulties in the isolation of the products.

Acylation of $Mes_2BCH_2Li$ (**2**) with methyl benzoate for 5 min gave a 72% yield of acetophenone, marginally better than for use of benzoyl chloride or benzoic anhydride.[49] However, acylation of other dimesitylboryl-stabilized anions does not appear to be of general use, often giving only modest yields.[49]

The ethoxycarbonylation shown in equation (38) leads to ethyl octanoate in 50% yield.[49] When dimethyl carbonate was used, α-methylation occurred in preference to ester homologation.[49]

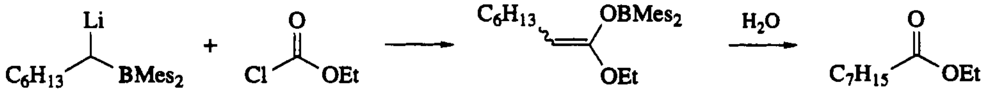

(38)

Acylation of (**2**) with benzonitrile gives an intermediate which yields acetophenone (52%) on hydrolysis with 3 M HCl.[49] This seems to be the only recorded reaction of a boron-stabilized carbanion with a nitrile.[49]

The carboxylation of boron-stabilized carbanions followed by acidification has been reported to give malonic acids in yields of 65–70% (equation 39).[19] The carboxylation of (**39**), however, did not yield any of the corresponding malonic acids.[26]

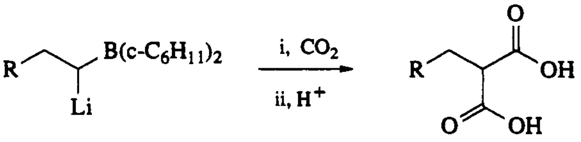

(39)

### 2.2.3.5 Reactions with Aldehydes and Ketones

It was early reported[50] that boron-stabilized carbanions reacted with benzaldehyde and ketones to yield alkenes (equation 40). The reaction gave a 45–50% yield in the one case quantified, with (*E*):(*Z*) ratios varying over a wide range with temperature. Benzophenone gave a similar yield but the yields with aliphatic ketones were considerably less.[50]

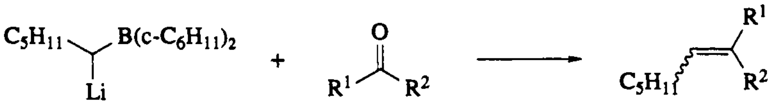

(40)

An analogous reaction with cyclohexanone gave methylenecyclohexane in 55–60% yield (equation 41).[29]

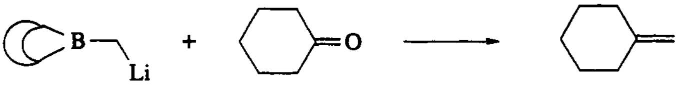

(41)

The reactions of dimesitylboryl-stabilized carbanions (**39**; R = H, Me, $C_7H_{15}$) with aldehydes and ketones are extremely interesting as they can lead to different products, depending on the nature of R, the carbonyl compounds and the reagents used in the work-up.

Aromatic ketones react to give excellent yields (70–90%) of the corresponding alkenes directly (equation 42), a reaction that was postulated to proceed by *syn* elimination from oxaboretane intermediates by analogy with the Wittig and Peterson reactions.[51] In one case an intermediate β-hydroxyborane has been isolated by chromatography, and in many cases intermediate salts separate, but dissolution of the salts in chloroform gives alkenes upon warming.[51]

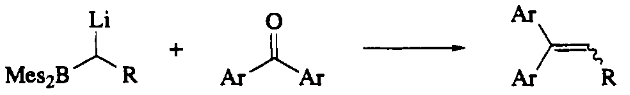

(**39**)

(42)

The direct reactions of (**39**) with benzaldehyde are complex, giving products as shown in equation (43) in proportions varying with the conditions. The alkene, however, was overwhelmingly (*E*)-alkene, in contrast to the similar reactions of 'unstabilized' Wittig reagents.

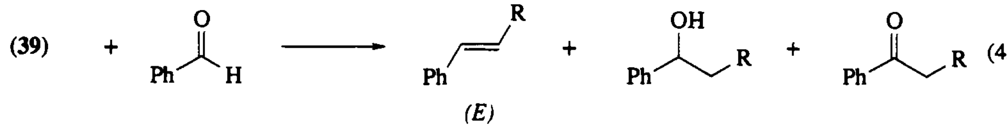

(43)

If the reactions are carried out at low temperature and the reaction mixtures then oxidized also at low temperature, the products are *erythro*-1,2-diols (**41**) obtained in good yields. This is a synthetically useful process, unique among Wittig-type reactions.[52] On the assumption that the oxidation proceeds with retention of configuration at carbon, as for all other C—B bond cleavages by alkaline hydrogen peroxide,[18] then the intermediate has the stereochemistry (**40**; Scheme 5). This can exist as the acyclic form (**40a**) or the cyclic form (**40b**). The latter, however, would have to give (*Z*)-alkene, whereas (*E*)-alkene is actually observed. This must arise therefore by *anti* elimination from (**40a**), which is a most unusual pathway in Wittig-type reactions.

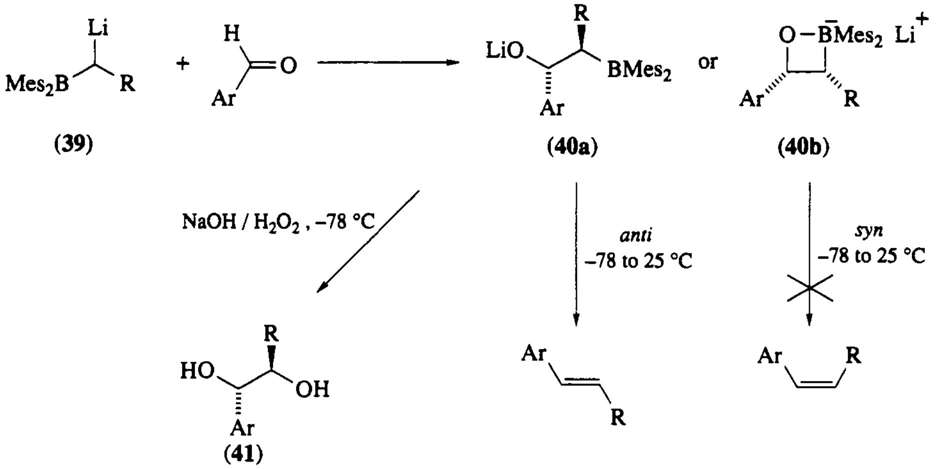

**Scheme 5** Reactions of aromatic aldehydes with dimesitylboryl-stabilized carbanions

Intermediates (**40**) react at −110 °C with TMS-Cl to give compounds (**42**), which are stable, readily purified products. The $^1H$ NMR of (**42**) is in accord with the assigned stereochemistry and shows that the oxidation of (**40**) had indeed proceeded with retention of configuration. Reaction of (**42**) with HF/MeCN gives (*E*)-alkenes in excellent yields (Scheme 6) with none of the many by-products seen in the original reaction. The (*E*):(*Z*) ratios range from 100:0 to 95:5 and the reaction tolerates $NO_2$, Cl, OMe and alkyl groups in the aromatic aldehyde.[53]

By contrast if (**40a**) is reacted with trifluoroacetic anhydride (TFAA) at low temperatures and the reaction then allowed to warm, the (*Z*)-alkene is obtained, presumably by a cyclic ester type elimination (Scheme 6).[53] The isolated yields (72–77%) of (*Z*)-alkene are rather lower than the yields for the (*E*)-alkene process, as are the stereoselectivities. In the case of 4-nitrobenzaldehyde the process shows little stereoselectivity.[53]

The reactions of (**39**; R = H) with aliphatic aldehydes give alkenes in yields that are strongly temperature dependent.[51] If the reaction is carried out in the presence of TFAA, then excellent yields of the methylene compounds result.[54] However, reaction of aliphatic aldehydes with (**39**; $R = C_7H_{15}$) in the same conditions proceeds by a most unexpected redox process to yield ketones in good yields after aqueous work-up.[54] The appearance of ketones as products is unique in any Wittig-type of reaction at this oxidation level. Alkenyloxyboranes appear to be the intermediates in the reactions, and these react with excess TFAA to give enol trifluoroacetates, which can be isolated and characterized.[54] A possible sequence is shown in Scheme 7.[54]

If the added aldehyde is premixed with a protic acid, the intermediates (**43**) are still formed, but are immediately discharged to give (**44**), which then decompose to give alkenes in good yields. Acetic acid shows little stereochemical discrimination in the production of alkenes except when R = Bu$^t$ (100% of *Z*)

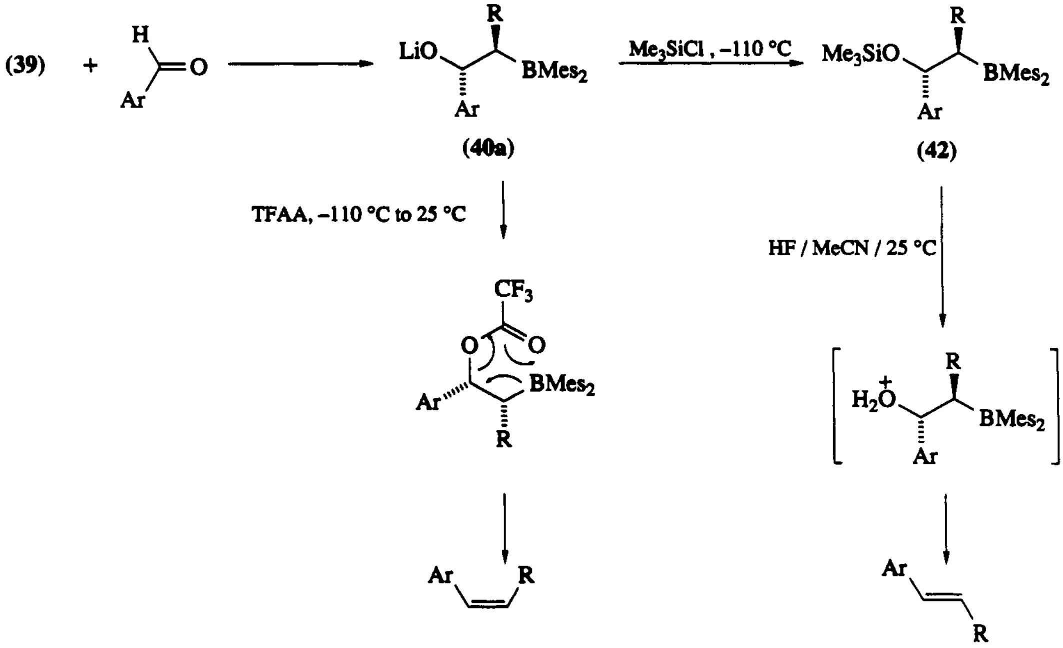
(39)
Me3SiCl, −110 °C
(40a)
(42)
TFAA, −110 °C to 25 °C
HF / MeCN / 25 °C

**Scheme 6** Stereoselective alkene formation using the boron Wittig reaction

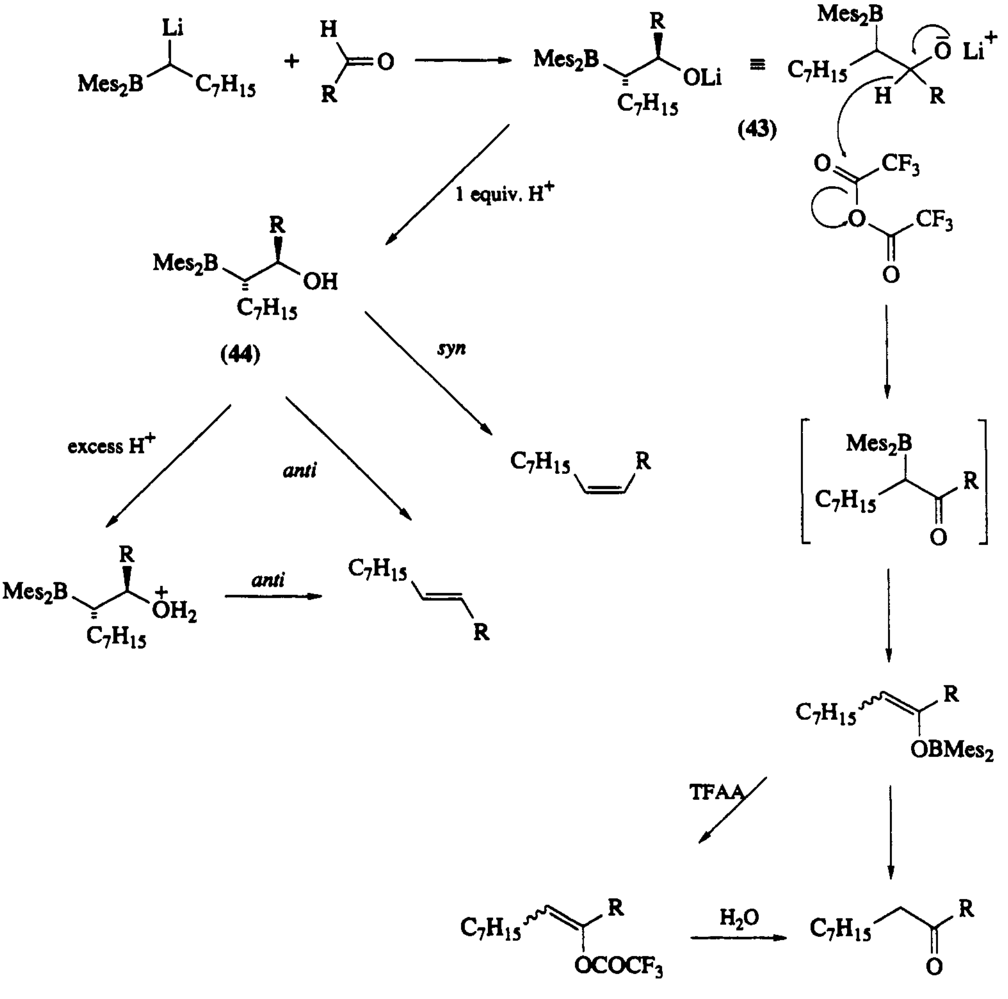
1 equiv. H+
(43)
(44)
syn
excess H+
anti
anti
TFAA
H2O

**Scheme 7** Reactions of 1-dimesitylboryl-1-lithiooctane with aliphatic aldehydes and cyclohexyl (90% of *Z*), but excess of stronger acids (HCl, $CF_3SO_3H$) gives >90% of (*E*)-alkene for less hindered aldehydes.[54] The overall situation for (**39**; R = $C_7H_{15}$) is summarized in Scheme 7.

Bis(dialkoxyboryl)-stabilized anions react with aldehydes to give alkenylboranes which may be oxidized to the homologated aldehydes (equation 44).[29] Addition of TMEDA and careful control of conditions are required to give good yields.

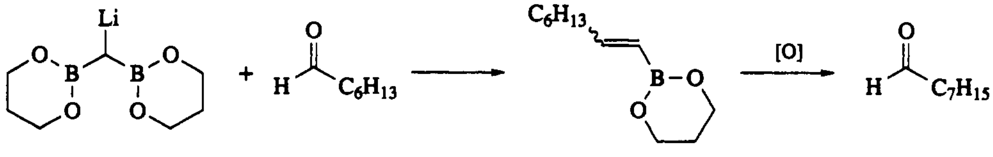

(44)

The reactions of α-TMS-substituted boranes with aldehydes proceed with elimination of the TMS group to give alkenylboranes as in equations (45) and (46). Such products can be hydrolyzed to alkenes or oxidized to aldehydes.[33] The intermediate in the case of the dimesitylborane reaction was directly oxidized to aldehyde in 95% overall yield, a good formyl homologation process.[37]

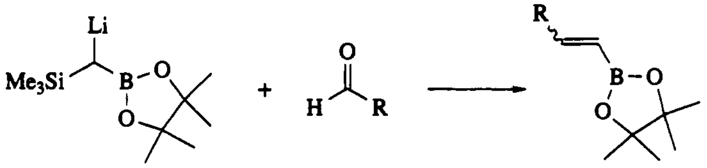

(45)

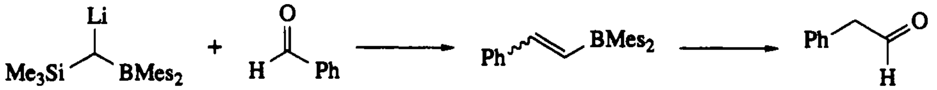

(46)

In reactions with benzophenone and cyclohexanone the dialkoxyboryl-stabilized carbanions still eliminate silicon[33] but the dimesitylboryl derivatives eliminate boron and silicon competitively so that a mixture of products results.[36]

1-Lithio-1-phenylthioalkane-1-boronates react with aldehydes or ketones to give phenylthioalkenes as mixtures of geometric isomers, when this is possible, in yields of 61–86% (equation 47).[31]

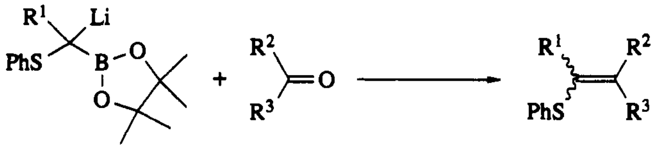

(47)

The dialkoxyboryl-substituted Wittig reagent (**45**) also loses boron upon reaction with benzophenone to yield another Wittig reagent that has been used in the synthesis of allenes (equation 48).[33]

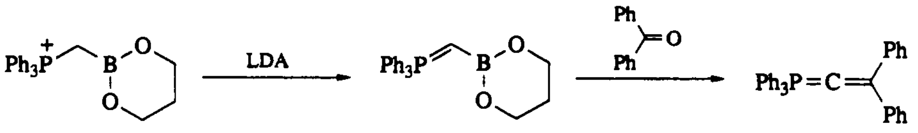

(**45**)

(48)

## 2.2.3.6 Halogenation Reactions

The halogenation of boryl-substituted carbanions has received little attention. However, bromination of the appropriate carbanions has been accomplished to give compounds (**46**),[22] (**47**)[22] and (**48**).[31] The latter undergoes reaction with phenylmagnesium bromide to give (**49**), though only 57% of impure material has been isolated. With aliphatic Grignard reagents only cleavage products were isolated.[31]

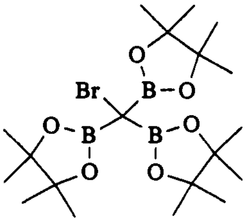
**(46)**

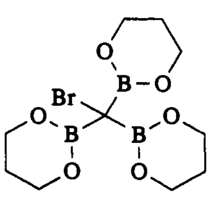
**(47)**

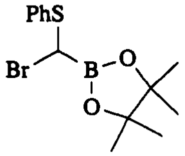
**(48)**

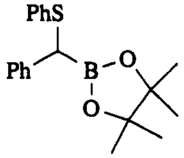
**(49)**

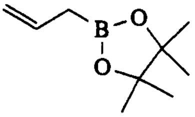
**(50)**

### 2.2.4 REACTIONS OF ALLYLIC BORON-STABILIZED CARBANIONS

The anion derived from (**50**) gives mixtures of products from reactions with $D_2O$, MeI, BuI and TMS-Cl and it was concluded that it cannot function as a useful synthetic reagent.[33]

Anion (**51**) protonates and methylates at the α-position but reacts with TMS-Cl and acetone (equation 49) specifically at the γ-position. No product derived from a boron-Wittig reaction was noted in the reaction with acetone, which upon work-up with propionic acid gave the corresponding alkene (**52**).[38]

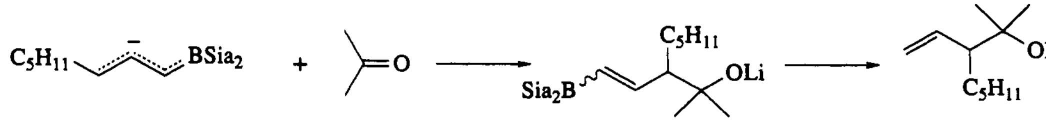

(**51**) (**52**) (49)

Anions (**53**) undergo only α-attack with TMS-Cl or $Bu_3SnCl$ to give (**54**; equation 50).[55] The stereochemistry of compounds (**54**) has not been defined, but upon reaction with water they give only the (*Z*)-allyl-silicon or -tin derivatives (**55**).[55]

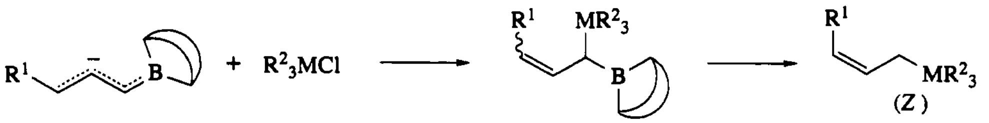

(**53**) (**54**) (**55**) (50)

The reactions of anion (**56**) proceed entirely at the γ-position with $D_2O$, $Me_2SO_4$, EtI, PrI, $C_6H_{13}I$, $C_7H_{15}I$, $C_8H_{17}I$, $PhCH_2I$ and TMS-Cl, and in every case (*E*)-alkenylboranes result.[39] Alkylations proceed in high yields (90–96%) and buffered oxidation of the products gives aldehydes (90–95% overall), giving an efficient three-carbon homologation of alkyl iodides (equation 51).[39]

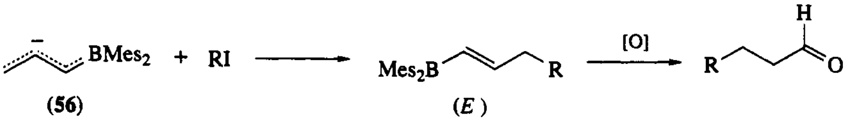

(**56**) (51)

Benzaldehyde also reacts with (**56**) at the γ-position and oxidation of the intermediate yields γ-lactols (equation 52).[39]

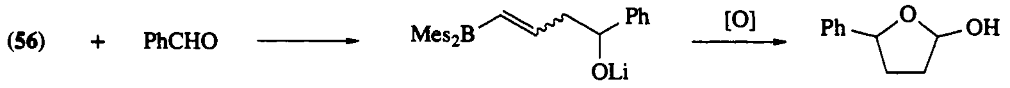

(52)

## 2.2.5 CONCLUSION

It is clear that the chemistry of carbanions stabilized by boron is so far undeveloped compared, say, with the chemistry of carbanions stabilized by sulfur. Despite this, a variety of unique reactions have been produced and it is certain that more await discovery and development.

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# 2.3
# Sulfur Stabilization

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*Chiba University, Japan*

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## 2.3.1 INTRODUCTION

Sulfur is one of the most frequently employed elements in organic synthesis. Typical functionalities containing sulfur atoms are illustrated below (**1a–1d**); they all stabilize the adjacent carbanion, which serves as a nucleophile. The carbanion reacts with alkyl halides or adds to C═X π-bonds (X = C, O, N, *etc.*) to form a C—C bond, which is an essential process in organic synthesis.

This section deals with addition reactions of sulfur-stabilized carbanions to C═X π-bonds from the standpoint of stereo- and regio-selectivity.

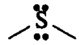

**(1a)** Sulfide

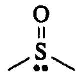

**(1b)** Sulfoxide

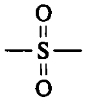

**(1c)** Sulfone

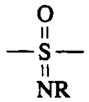

**(1d)** Sulfoximine

### 2.3.2 SULFENYL-STABILIZED CARBANIONS

#### 2.3.2.1 Configuration of the Carbanion

The action of butyllithium on thioanisole in THF generates (phenylthio)methyllithium in a low yield of 35%.[1,2] Corey and Seebach found that reaction of equimolar amounts of butyllithium, DABCO and thioanisole in THF at 0 °C produces (phenylthio)methyllithium in *ca.* 97% yield.[3] Dimethyl sulfide can be metalated with a butyllithium–TMEDA complex at room temperature (equation 1).[4] Treatment of chloromethyl *p*-tolyl sulfide with magnesium produces the corresponding Grignard reagent; a reaction temperature between 10 and 20 °C is crucial for its efficient generation (equation 2).[5]

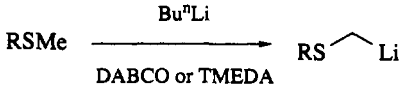

(1)

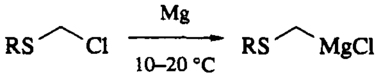

(2)

The p$K_a$ value for 2-$CH_2$ of 1,3-dithiane is 31.1,[6] indicating that the sulfenyl group stabilizes the adjacent carbanion. Theoretical studies present convincing evidence for the unimportance of *d*-orbital participation in the acidification of C—H bonds α to sulfur atoms.[6,7] Whether or not 3*d*-orbitals are included in the basis set, the preferred conformation of $^-CH_2SH$ is predicted to be that of an $sp^3$ carbanion (**2**).[8] The calculation, NMR studies and crystallography all support a tetrahedral structure for the α-lithiated sulfide.[9]

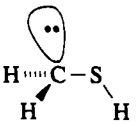

**(2)**

Anderson and coworkers emphasized the polarizability of sulfur, which accounts for the regiochemistry of C—H acidification by sulfur.[10] Epiotis *et al.* developed a hyperconjugative model involving delocalization of the unshared pair on carbon into the low-lying adjacent S—R antibonding orbital,[11] which accounts for the stereochemical aspects of C—H bond acidification by sulfur.

#### 2.3.2.2 Addition to C═O Bonds

(Phenylthio)methyl metal (metal = Li or MgCl) adds to the carbonyl group of ketones and aldehydes [3–5,12,13] Benzoyl derivatives of these adducts are converted to alkenes by reductive elimination with Li–$NH_3$,[14] $TiCl_4$–Zn[15] or Ti.[16] Transformation of (**3**) into an alkene *via* its phosphoric ester has also been reported (equation 3).[17]

The above ketone methylenation is applicable to highly hindered ketones, which are usually inert to the Wittig method. For example, a highly hindered tricyclic ketone (norzizanone, **4a**) undergoes the methylenylation to give zizaene (**4b**; equation 4). $\Delta^5$-Cholesten-3-one (**5a**) was also converted to the nonconjugated diene 3-methylene-$\Delta^5$-cholestene (**5b**; equation 5).[14]

Condensation of the lithio derivative of benzyl phenyl sulfide (**6**) with benzaldehyde gave two diastereomers of 2-phenylthio-1,2-diphenyl-1-ethanol (**7**) in a ratio of 60:40 (equation 6).[18]

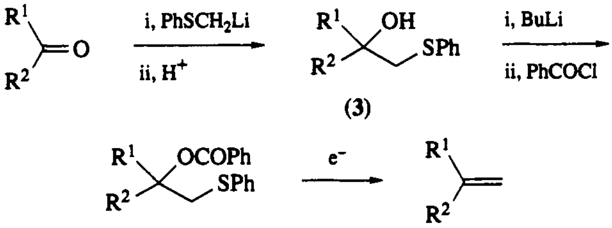

i, PhSCH2Li
ii, H+
(3)
i, BuLi
ii, PhCOCl
e-

(3)

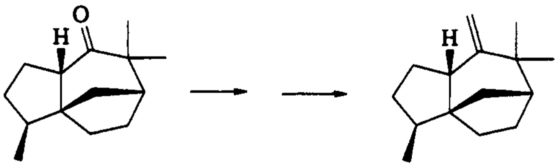

**(4a)** **(4b)**

(4)

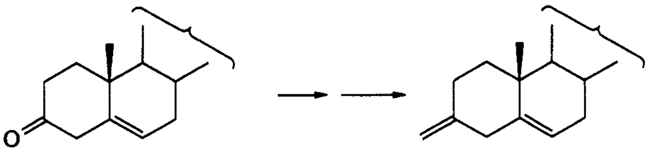

**(5a)** **(5b)**

(5)

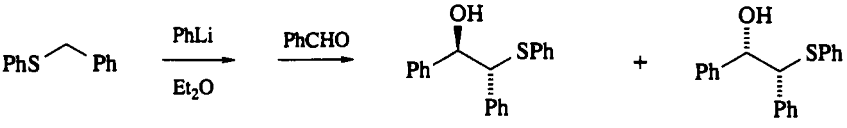

**(6)** **(7a)** **(7b)**

PhLi
Et2O
PhCHO

(6)

In the addition of the sulfide (**8**), which has a chiral center at the β-position, 1,2-induction was completely stereoselective, while 1,3-asymmetric induction occurred with 80% efficiency (Scheme 1). It has been shown that the critical factor for obtaining high stereoselectivity is a thermodynamic preference in the lithio derivative (**9**) and not a diastereoselective deprotonation. In essence, C—Li bonds to sulfur are similar to their oxygen and nitrogen counterparts and differ only in the fact that the epimerization rate of (**9**) is seemingly faster.[19]

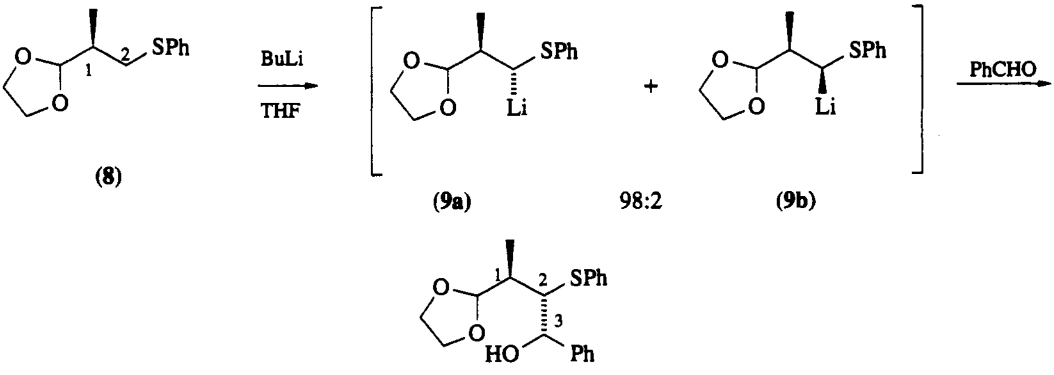

BuLi
THF
PhCHO
(8)
(9a)
98:2
(9b)

α-OH:β-OH = 4:1

**Scheme 1**

### 2.3.2.3 α-Sulfenylated Allylic Carbanions

The reaction of α-sulfenylated allylic carbanions with electrophiles may give both the α- and γ-products (equation 7). Regiochemical control of this ambident anion is dependent upon many factors, including substituents, counterions, the solvent system, the type of electrophile and steric effects.

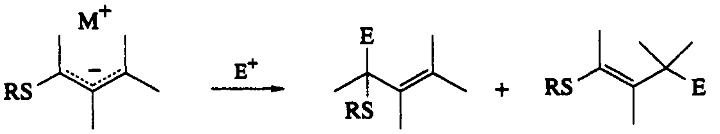

(7)

When the counterion is lithium, the α:γ regioselectivity depends in part upon the electrophile employed (Scheme 2). 3-Methyl-2-butenyl phenyl sulfide generates an allylic carbanion by the action of *n*-butyllithium–THF. Methyl iodide reacts with α-selectivity (exclusively α at –78 °C), whereas acetone predominantly affords the γ-adduct (α:γ = 25:75). The regioselectivity of alkylation and of reaction with acetone also depends on the presence of solvating species. The results are best explained by assuming that in THF without a complexing agent, the carbanion exists as an ion pair, the lithium ion being closely associated with the α-carbon. In contrast, the cryptate [2.2.2] accommodates the lithium in its cavity so that solvent-separated ion pairs or free anions are present. The reaction now occurs at both α- and γ-carbons with methyl iodide (α:γ = 60:40) and only at the α-carbon with acetone.[20] Addition of the lithio derivative of an aryl allyl sulfide to benzaldehyde (equation 8) was also reported to afford predominantly the corresponding γ-adduct (α:γ = 15:85 or 28:72 in the cases of aryl = phenyl or *p*-methoxyphenyl, respectively). The diastereomeric ratio of the product resulting from α-attack ranges from 34:66 (aryl = mesityl) to 25:75 (aryl = *p*-methoxyphenyl).[21]

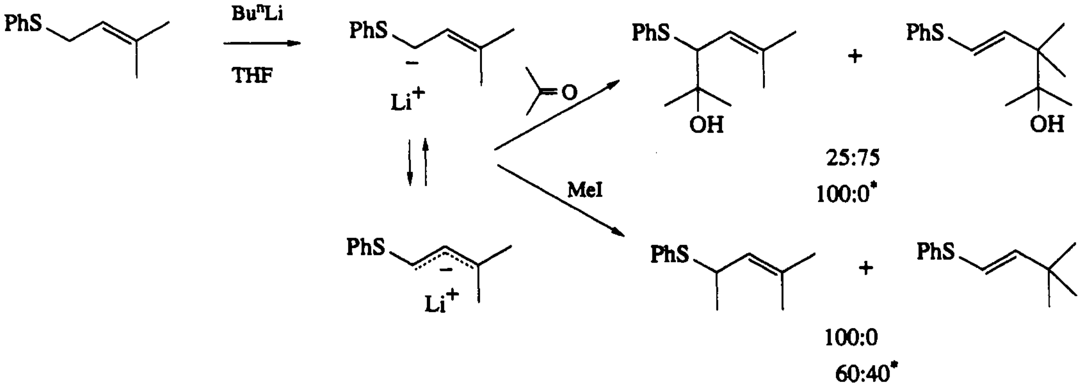

* In the presence of cryptate [2.2.2]

**Scheme 2**

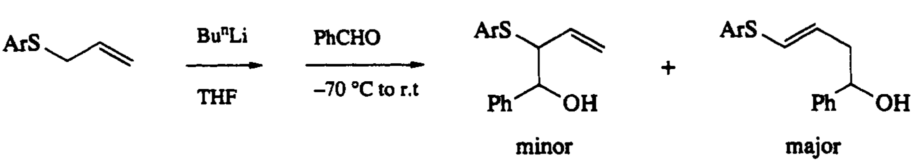

(8)

In contrast to lithio derivatives, (isopropylthio)allyl copper reacts with acetone in ether at –78 °C to yield an α-adduct as a major product (Scheme 3).[22]

The reaction between a wide variety of (alkylthio)allyltitanium reagents of type (**11**) and carbonyl compounds has also been reported (equation 9). Table 1 illustrates how the relative proportions of α- and γ-adduct formed vary according to the reagent.

The substitution pattern of the starting sulfide (**10**) can have a pronounced effect on the α:γ ratio in the final condensation products. With unsubstituted sulfides ($R^1 = R^2 = R^3 = R^4 = H$) or α- and β-mono- and di-substituted sulfides ($R^1$ and/or $R^2$ = Me), the α-selectivities are about 97–99%. On the other hand, a dramatic alteration in product distribution occurs when the condensation with aldehydes is carried out using γ-substituted sulfides ($R^3$ and/or $R^4$ = Me); excellent γ-selectivity was observed. It is highly interesting that α- and γ-disubstituted sulfide ($R^1 = R^3$ = Me) gives the α-adduct almost exclusively. The

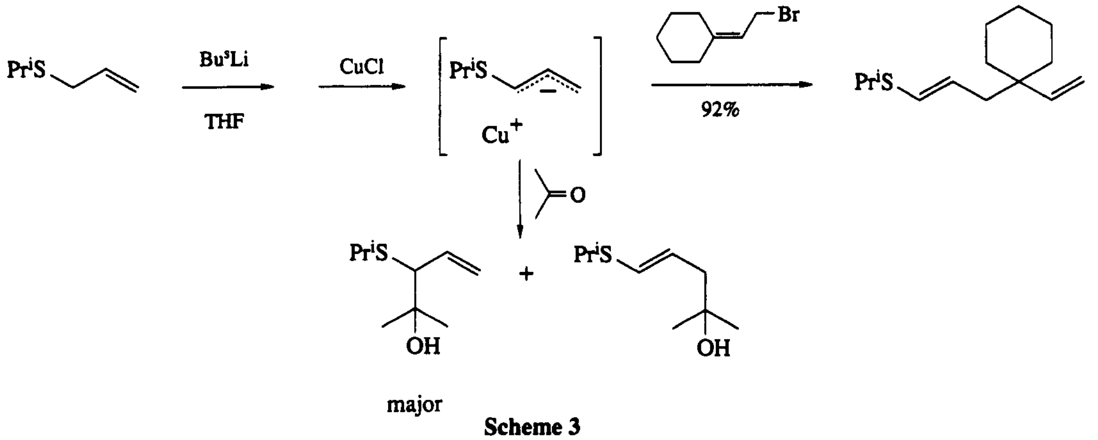

**Scheme 3**

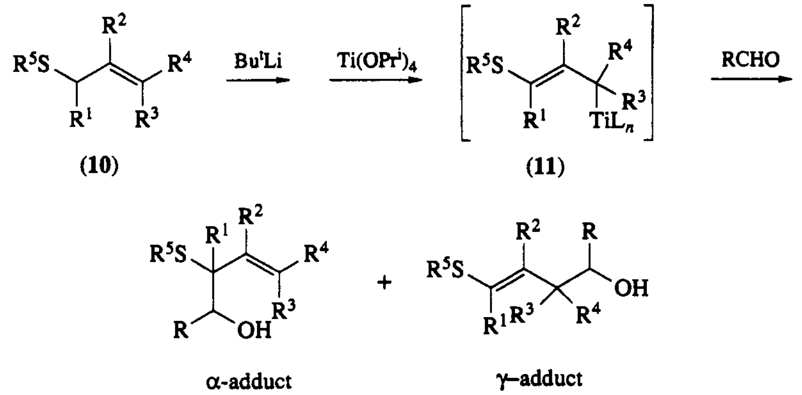

(9)

**Table 1** Reaction of the Anion (11) with Aldehydes

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *R*$^5$ | *RCHO* | *Yield (%)* *α-Adduct*[a] | *Yield (%)* *β-Adduct* |
|---|---|---|---|---|---|---|---|
| H | H | H | H | Ph | $c\text{-}C_6H_{11}CHO$ | 99 (>30:1) | <1 |
| H | H | H | H | Et | $n\text{-}C_5H_{11}CHO$ | 87 (>30:1) | 5 |
| H | H | H | H | Et | PhCHO | 94 (6:1) | 2 |
| Me | H | H | H | Ph | $c\text{-}C_6H_{11}CHO$ | 99 (>30:1) | <1 |
| H | Me | H | H | Et | $c\text{-}C_6H_{11}CHO$ | 98 (>30:1) | 2 |
| H | H | Me | H | Et | $c\text{-}C_6H_{11}CHO$ | >1 | 93 |
| Me | Me | H | H | Ph | $c\text{-}C_6H_{11}CHO$ | 83 (>30:1) | <1 |
| Me | H | Me | H | Ph | $c\text{-}C_6H_{11}CHO$ | 71 (>30:1) | 4 |
| H | H | Me | Me | Ph | $c\text{-}C_6H_{11}CHO$ | >1 | 99 |

[a] The value in parenthesis is the ratio of *erythro*:*threo*.

second important trend is the exceedingly high *erythro* selectivity of the reaction. Even an aromatic aldehyde gives the *erythro*-alcohol selectively. Furthermore, the *erythro* stereoselectivity is not affected by the α-branches of the starting sulfides.[23]

The well-known procedure for desulfurization *via* sulfonium salt formation followed by base-catalyzed cyclization converts this reaction into a stereoselective alkenyloxirane synthesis. Some examples are illustrated in Scheme 4.

The triethylaluminum or triethylborane ate complexes (**12**) of the (isopropylthio)allyl carbanion react with carbonyl compounds at the α-position (equation 10). In the reactions with carbonyl compounds, very high regioselectivity (for example, butanal 95:5, 3-methylbutanal 99:1, cyclohexanone 92:8 and acetophenone 95:5) was achieved by using the aluminum ate complex. On the other hand, the α-regioselectivity with ketones decreases if the boron ate complex is used (cyclohexanone 72:28, acetophenone 45:55). It is noteworthy that the stereoselectivity of the α-adduct from an aldehyde is low. Presumably the geometry of the double bond in the ate complex (**12**) is not homogeneous.[24]

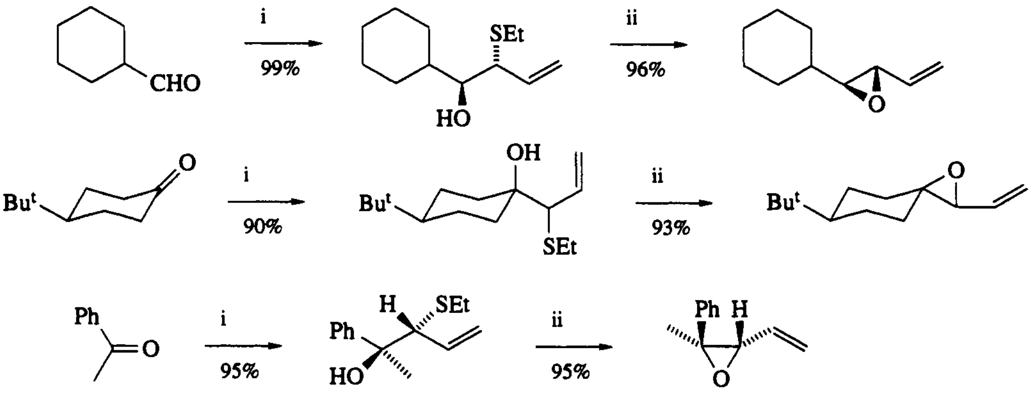

i, $CH_2{=}CHCH_2SEt/Bu^tLi/Ti(OPr^i)_4$, THF, –78 °C; ii, $Me_3OBF_4$, $CH_2Cl_2$, 0 °C, then aqueous NaOH, 25 °C

**Scheme 4**

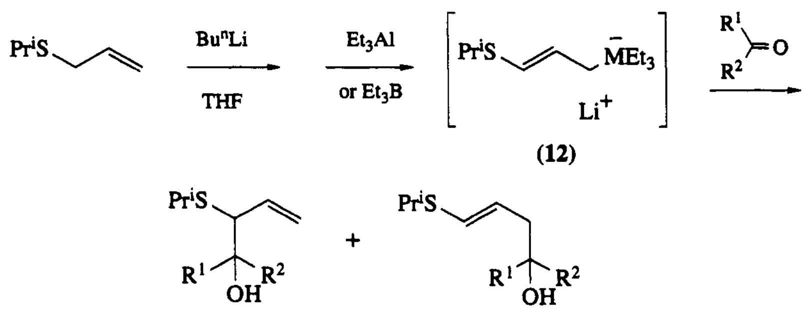

(12)

(10)

Seebach and coworkers reported that the doubly lithiated 2-propenethiol (**13**) reacts preferentially in the γ-position with a variety of electrophiles, including aldehydes and ketones. The selectivity is 67–75%.[25] The magnesium derivative (**14**), readily accessible by addition of $MgBr_2$ (1 equiv.), reacts with aldehydes and ketones to give α-adducts almost exclusively (more than 90%). Successive addition of a saturated or α,β-unsaturated aldehyde or ketone followed by methyl iodide to a solution of the magnesium derivative at –80 °C affords very high yields of the α-adducts, which are synthetic precursors for vinyloxiranes (Scheme 5).[26]

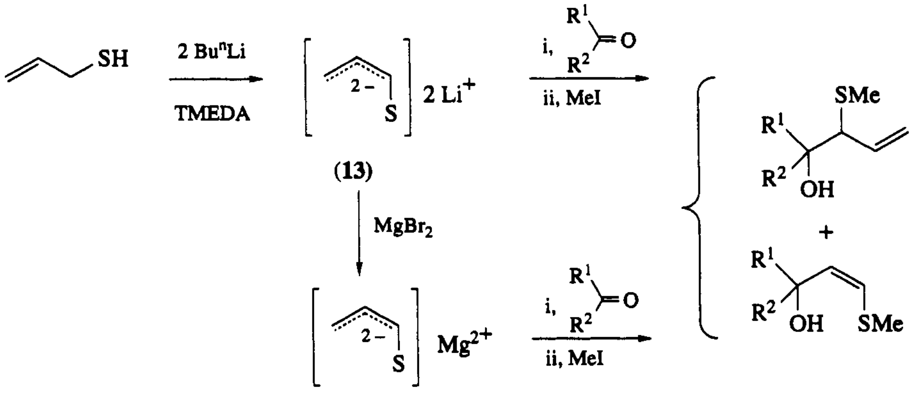

(13)

(14)

**Scheme 5**

### 2.3.2.4 Miscellaneous

Formaldehyde dithioacetals are often utilized as synthetic equivalents of formyl anion ($^-CHO$) and carbonyl dianion ($^{2-}C{=}O$). 1,3-Dithiane is commonly used; its 2-H is quite acidic ($pK_a = 31.1$)[6] due to stabilization by its two adjacent sulfenyl groups. 2-Lithio-1,3-dithiane adds to aldehydes and ketones. Its addition to 4-*t*-butylcyclohexanone proceeds under kinetic control, and the rates of equatorial and axial attack are comparable.[27] 2-Phenyl-1,3-dithiane generates a more stable carbanion at the 2-position (p$K_a$ = 28.5 in cyclohexylamine), thus enabling thermodynamic control, under which attack is exclusively equatorial. The dianion (**15**) of 2-hydroxymethyl-1,3-dithiane adds to an epoxycyclohexanone (**16**) in a highly stereoselective manner, which is the key step in a novel approach to the avermectin southern hexahydrobenzofuran unit (Scheme 6).[28]

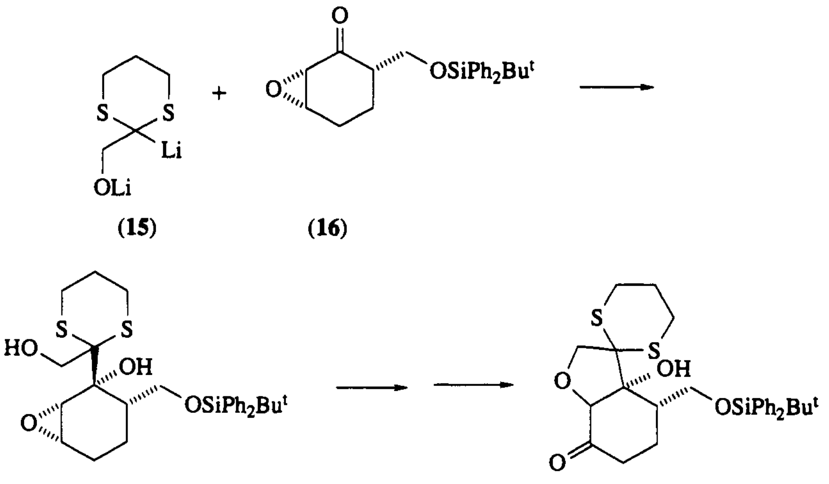

**Scheme 6**

In the reaction with α,β-unsaturated ketones (**18**), 2-lithio-1,3-dithiane (**17**; R = H) produces 1,2-adduct (**20**) in THF. By addition of HMPA (1–2 equiv.) to the reaction mixture, 1,4-addition is successfully attained (equation 11).[29] It is noteworthy that the lithio derivative of 2-aryl-1,3-dithiane regiospecifically adds to 2-cyclohexenone in a 1,4-manner (25 °C in THF).[30]

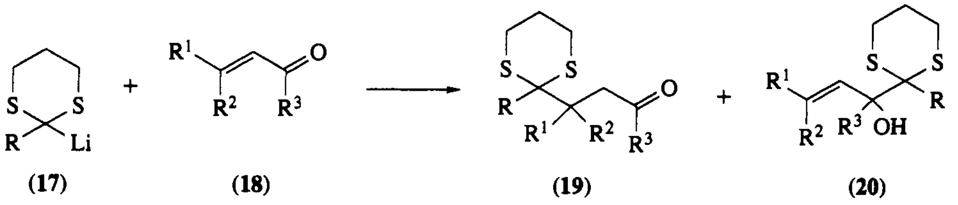

(11)

The reactions of lithiated tris(phenylthio)-,[31] methoxyphenylthiotrimethylsilyl-,[32] bis(methylthio)trimethylsilyl- and bis(methylthio)stannylmethanes[33] with conjugated ketones give the corresponding 1,4-adducts exclusively.

The allyllithium derived from 2-ethylidene-1,3-dithiane (**22**) and LDA reacts with an aldehyde (**21**) at predominantly the α-position (α:γ = 90:10). When the counterion is changed from lithium to cadmium, the regioselectivity is reversed (α:γ = 10:90), as shown in Scheme 7.[34]

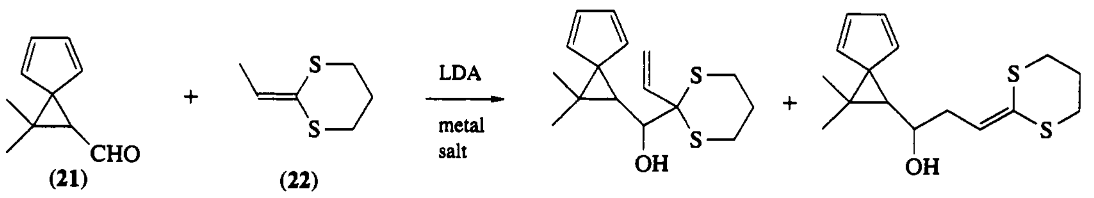

| | | | |
|---|---|---|---|
| LDA | 96% (90:10) | LDA/CuI•P(OMe)$_3$ | 61% (35:65) |
| LDA/ZnCl$_2$ | 70% (60:40) | LDA/CdCl$_2$ | 90% (10:90) |

**Scheme 7**

The crotyllithium compound (**23**) generated from (*E*)-2-(1-propen-1-yl)-1,3-dithiane reacts with aldehydes to give exclusively γ-adducts, which favor the *anti* isomer (Scheme 8).[35] However, crotyllithium (**23**) reacts with ketones at either the α- or the γ-site, depending on the nature of the ketone (for 2-butanone, α:γ = 84:16, *anti*:*syn* = 77:23). To account for the high regioselectivity and *anti* selectivity of the aldehyde addition, a chelation model with a chair-like transition state (**25**) was proposed. This regio- and diastereo-selective reaction is applicable to syntheses of *trans*-β,γ-disubstituted γ-lactone (**27**). The *anti* γ-adducts are prone to cyclization to afford (**26**), which undergoes hydrolysis with $HgCl_2$, leading to (**27**; equation 12).

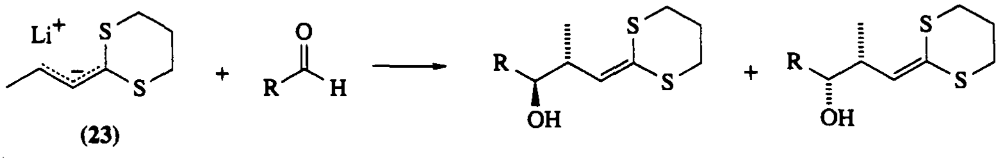

(**23**)

*anti*-(**24**)

*syn*-(**24**)

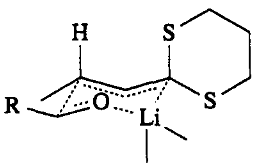

(**25**)

| | | | | |
|---|---|---|---|---|
| R = Me, | 86% | (80:20) | R = $Me_2C$=CH, | 88% (84:16) |
| R = Et, | 91% | (~100:0) | R = PhCH=CH, | 86% (85:15) |
| R = $Pr^i$, | 93% | (~100:0) | | |

**Scheme 8**

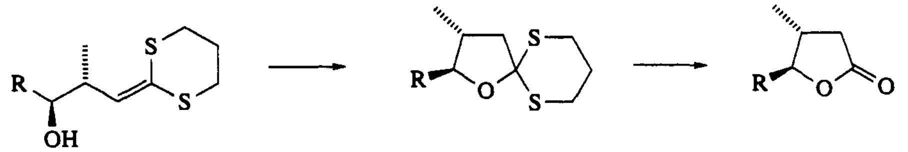

*anti*-(**24**) (**26**) (**27**) (12)

## 2.3.3 SULFINYL-STABILIZED CARBANIONS

### 2.3.3.1 Configuration of the Carbanion

Sulfoxides bearing two different substituents are dissymmetric and resolvable into optically active enantiomeric forms. Since the sulfinyl group is pyramidal, a diastereotopic relationship exists for the methylene protons ($H_R$ and $H_S$) and differential acidity of these protons is observed.

It has been demonstrated that *pro-(R)* hydrogen ($H_R$) of (*S*)-benzyl methyl sulfoxide undergoes exchange in alkaline $D_2O$ or in MeOD containing NaOMe at a rate approximately 16 times faster than the *pro-(S)* hydrogen ($H_S$). The results hitherto reported are summarized in Figure 1.[36–40] Deuteration and methylation of benzyl methyl sulfoxide occur with opposite stereospecificity, whereas the corresponding actions of benzyl *t*-butyl sulfoxide in THF proceed with the same stereospecificity. The lithiated α-sulfinyl carbanions produced from ($S_S$) and ($R_S$)-benzyl methyl sulfoxides may have ($S_C$,$S_S$) and ($S_C$,$R_S$) configurations, respectively. Water comes from the lithiated side of the carbanions because its polarization causes it to interact initially with the countercation. However, methyl iodide is a nonpolar substrate and prefers to react on the more nucleophilic side, which is *anti* to the sulfur lone pair. Thus, the sulfur lone pair can exert an α-effect to make the *anti* lone pair more polarizable.[41]

*Ab initio* MO calculations on the hypothetical anion $^-CH_2S(O)H$ suggest a nonplanar geometry to be preferable at the anionic center, and the order of carbanion stability is shown in Figure 2.[42,43]

This order is not in agreement with most of the results from experiments conducted to determine the conformational preferences of α-sulfinyl carbanions in solution, where solvation and ion-pairing effects are important. For example, Biellmann found that the product stereochemistry varies with solvent and temperature, and with the presence or absence of lithium chelating agents such as cryptate.[44] Lithium cation–oxygen chelation may control the conformation in THF (Figure 3), while a free anion is predominant in the presence of the chelating agent.

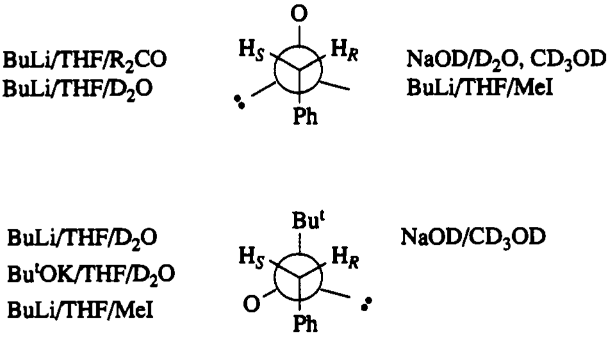

**Figure 1**

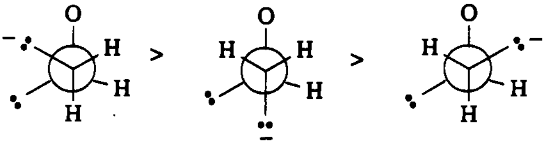

**Figure 2**

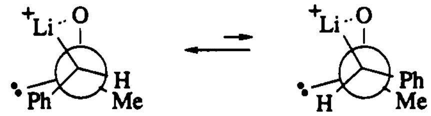

**Figure 3**

Even the widely accepted assumption of pyramidal $sp^3$-hybridized α-sulfinyl carbanions has been challenged. A $^{13}C$ NMR study provides evidence for a chelated α-lithio thiane *S*-oxide with a planar metalated carbon.[45] The stereoselectivity observed in methylation with MeI is completely reversed with $(MeO)_3PO$. These results are explained in terms of *trans* approach of MeI to the chelated face and *cis* approach of $(MeO)_3PO$, which requires coordination to $Li^+$. It was also reported that the carbanion carbon of PhCHLiS(O)Me or $Bu^tS(O)CH_2Li$ is primarily $sp^2$-hybridized or intermediate between $sp^2$- and $sp^3$-hybridized, respectively.[46]

### 2.3.3.2 Addition to C=O Bonds

In 1972, Tsuchihashi disclosed that the carbanion (**28**; Ar = *p*-tolyl), generated from (*R*)-methyl *p*-tolyl sulfoxide with lithium diethylamide, adds to benzaldehyde or α-tetralone to give an adduct (**29**) in a diastereomeric ratio of 50:50 or 64:36, respectively.[47] Additions of this carbanion to various unsymmetrical ketones are also reported to be poorly diastereoselective (for example, EtCOMe 50:50, Bu^tCOMe 55:45, Bu^tCOPh 70:30).[48] Note that in the case of Ar = 2-pyridyl a chiral sulfinyl group increases the asymmetric induction observed in the addition of the corresponding carbanion to carbonyl compounds (PhCHO 80:20, *n*-$C_9H_{19}CHO$ 70:30).[49] Since diastereomer pairs of (**29**) are separable, chromatographic separation followed by reductive desulfurization with Raney Ni provides a method for obtaining optically active alcohols (**30**; Scheme 9).

Reaction of the α-carbanion of an alkyl aryl sulfoxide ($RCH_2SOAr$) with aldehydes may give four diastereomers. In general, the reaction is highly diastereoselective with respect to the α-sulfinyl carbon, but poorly diastereofacially selective with respect to attack on the carbonyl component. In fact, the α-carbanion (**31**) of benzyl *t*-butyl sulfoxide adds to an aldehyde to produce only two diastereomers (**32a**) and (**32b**). As shown in Scheme 10, the selectivity increases when the counterion is $Zn^{2+}$. A transition state structure (**33**) is proposed to account for the *anti* stereoselection.[50] Addition of the dianion of (*R*)-3-(*p*-tolylsulfinyl)propionic acid (**34**) to aldehydes affords two main diastereoisomeric β-(*p*-tolylsulfinyl)-γ-lactones (**35**; R = Ph and Bu^t, *ca.* 60:40). These isomers (**35**) were separated by chromatography, and their

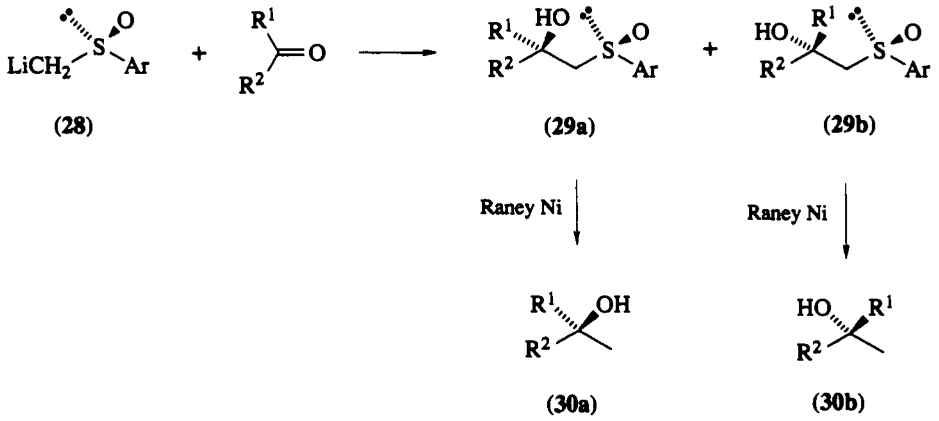

Scheme 9

pyrolysis gave optically pure 5-substituted furan-2(5*H*)-ones (**36**; Scheme 11).[51] Analogously, optically active *cis*-7,8-epoxy-2-methyloctadecane (**39**), the sex attractant of the gypsy moth, was synthesized by utilizing the addition of the α-carbanion of optically active *t*-butyl 5-methylhexyl sulfoxide (**37**) to undecanal (**38a**:**38b** = *ca*. 67:33) as shown in Scheme 12.[52]

Condensation of α-sulfinyl carbanions with aldehydes provides a useful method for generating 1,2-asymmetry as well as construction of 1,3-asymmetric relationships in acyclic systems. α-Sulfinyl carbanions such as (**40**) undergo condensation with aldehydes, yielding the β-hydroxy sulfoxides (**41**), thus generating two asymmetric centers at C-4 and C-5 (equation 13). Successive treatment of the sulfoxide (**42a**) with LDA and then with benzaldehyde at −78 °C gave adducts (**43**) and (**44**) in 85% yield in a 91:9 ratio, whereas the diastereomer (**42b**) gave four adducts (**45**, **46**, **47** and **48**) in 94% yield of 67:17:13:3 composition, respectively (Scheme 13). In analogous fashion, condensation of the racemic sulfoxides which have the opposite configuration of the β-methyl substituent at C-3 afforded 85–90% yields with benzaldehyde.[53–55] It is noteworthy that major products (**43**) and (**45**) share the same relative stereochemistry along the carbon backbone, in spite of the inversions of sulfinyl configuration. The general mode of the addition demonstrates the same preference for '*erythro*' orientations at C-4 and C-5 as observed in the addition of an anion to a carbonyl compound, which presumably does not involve a cyclic, chair-like, transition state. An indolizidinyl sulfoxide (**49**) also adds to butanal *via* its α-sulfinyl carbanion to afford two diastereomers (**50a**) and (**50b**) in a ratio of 2:1. Since the configuration of the newly created

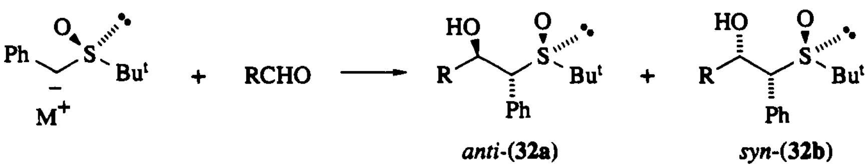

| | | | |
|---|---|---|---|
| R = Ph, countercation = | Li$^+$ | 63 : 37 | (81%) |
| | Zn$^{2+}$ | 84 : 16 | (98%) |
| R = Pr$^i$, countercation = | Li$^+$ | 78 : 22 | (90%) |
| | Zn$^{2+}$ | 91 : 9 | (72%) |
| R = PhCH=CH, countercation = | Li$^+$ | 49 : 51 | (100%) |
| | Zn$^{2+}$ | 57 : 43 | (82%) |

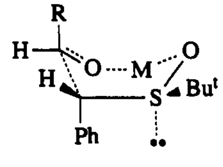

(33)

Scheme 10

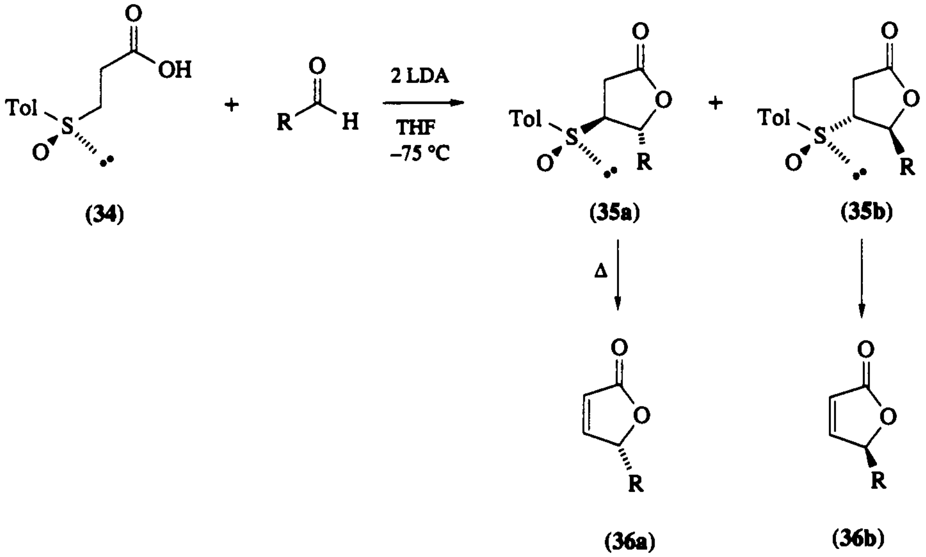
Tol
S
O
OH
(34)
+
R
H
2 LDA
THF
-75 °C
(35a)
(35b)
Δ
(36a)
(36b)

Scheme 11

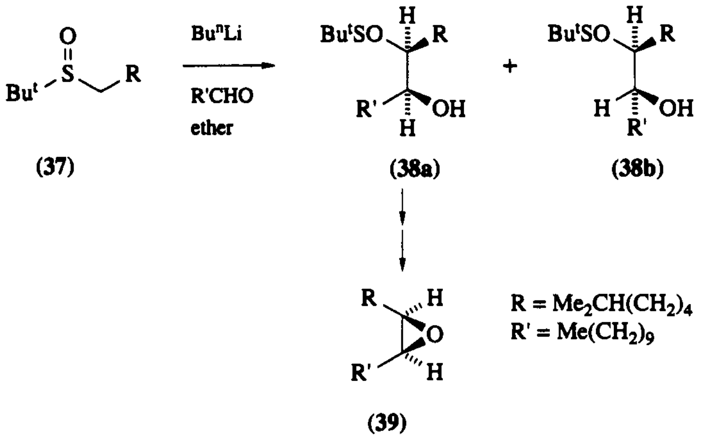
Bu<sup>t</sup>
S
R
(37)
Bu<sup>n</sup>Li
R'CHO
ether
Bu<sup>t</sup>SO
H
R'
OH
(38a)
(38b)
(39)
R = Me<sub>2</sub>CH(CH<sub>2</sub>)<sub>4</sub>
R' = Me(CH<sub>2</sub>)<sub>9</sub>

Scheme 12

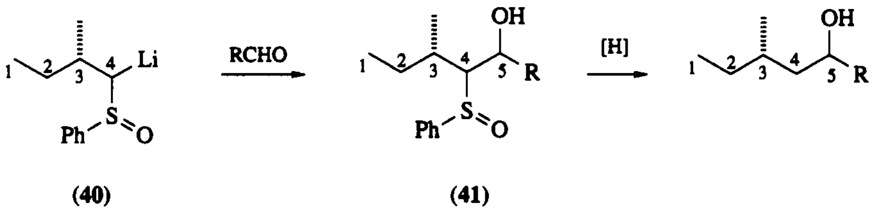
Li
Ph
S
O
(40)
RCHO
OH
R
(41)
[H]
1
2
3
4
5

(13)

hydroxycarbon is always (*S*), pyrolytic dehydrosulfinylation of (**50a**) and (**50b**) furnishes the same product, (−)-elaeokanine B.[56]

## 2.3.3.3 Addition to C=N Bonds

In 1973, addition of a carbanion (**52**; Ar = *p*-tolyl) to benzylideneaniline (**51a**; Scheme 15) at −10 to −20 °C was found to be a highly diastereoselective process.[57] Later, this and its related reactions were reexamined in detail.[58] An anion (**52**; Ar = Ph) adds smoothly to (**51a**) at −78 °C over a period of 5 h to give a mixture of the diastereoisomeric adducts with modest diastereoselection (18:82). Longer reaction

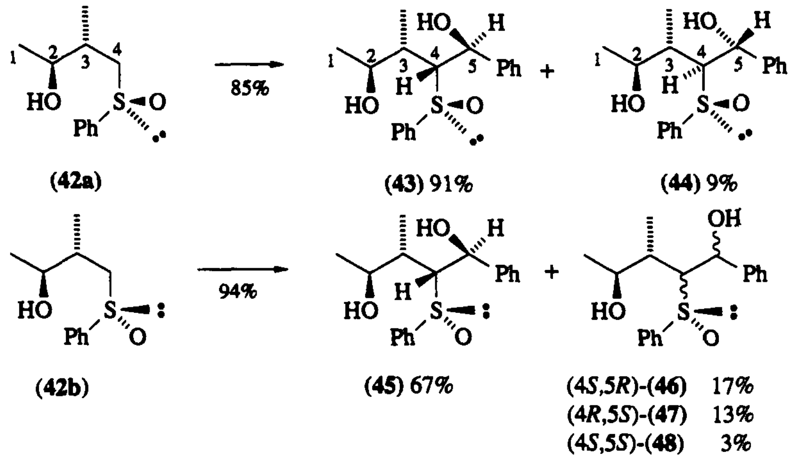

Scheme 13

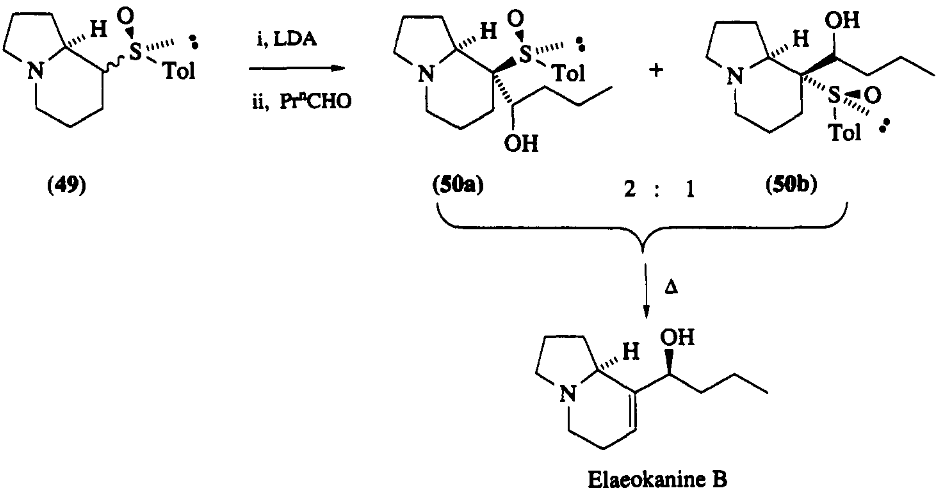

Scheme 14

times (0.5–20 h) at 0 °C result in very poor diastereoselection (30:70–43:57), suggesting an equilibrium between the anions (**53**) of the diastereoisomeric adducts. Under kinetically controlled conditions (0 °C/10 min), the reaction of (**52**; Ar = *p*-tolyl) with (**51b**) or (**51c**) is highly diastereoselective (9:91). The chair transition state (**55**; equation 14) can account for the preference of the diastereoisomeric adduct (**54a**) over (**54b**).

Addition of (**52**; Ar = *p*-tolyl) to 3,4-dihydro-6,7-dimethoxyisoquinoline (**56**) gives a diastereomeric mixture of the adduct (**57a**:**57b** = 77:23) under kinetically controlled conditions (–78 °C ~ –40 °C/2 h), whereas the diastereoselection was reversed to a high degree (8:92) at 0 °C (equation 15).

Since these adducts undergo reductive desulfurization with Raney Ni, the optically active aryl methyl sulfoxide is a versatile reagent for the synthesis of optically active amines from imines.

### 2.3.3.4 Addition to Nonactivated C═C Bonds

Intramolecular addition of an α-sulfinyl carbanion to an isolated double bond occurs on treatment of medium-ring *E*-homoallylic sulfoxides (**58**), (**59**), (**60**) and (**61**) with butyllithium (0.5 equiv.; equations 16–19)[59,60] Kinetic data suggest that this process is a nucleophilic addition of a carbanion (an α-lithiated sulfoxide) to a nonactivated double bond and takes place readily, provided a suitable proton source is available. Normally the free sulfoxide is the proton donor species.[60]

Under the same conditions, the corresponding (*Z*)-isomers are inert, even though the *E*–*Z* differential strain is negligible in 9- and 10-membered ring systems. The presence of an (*E*) double bond induces a

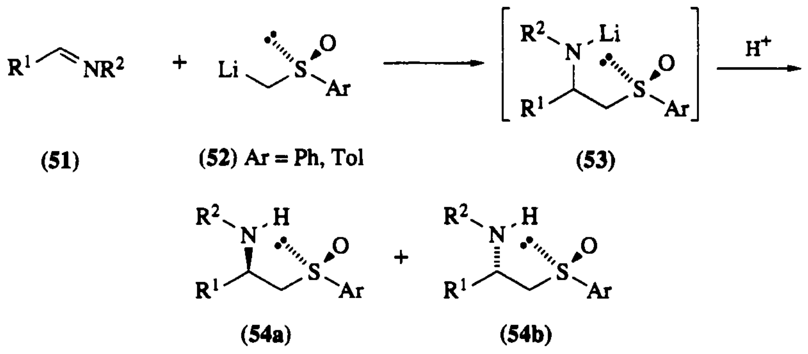

**(51)** **(52)** Ar = Ph, Tol **(53)**

**(54a)** **(54b)**

$R^1 = R^2 = Ph$ 18:82

$R^1 = Ph$, $R^2 = Me$; or $R^1$ = 2-furyl, $R^2 = Ph$ 9:91

**Scheme 15**

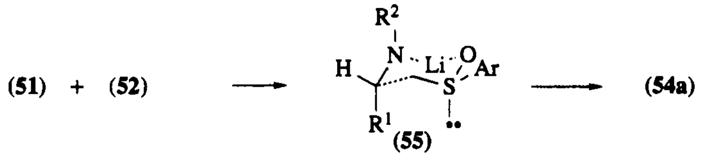

(14)

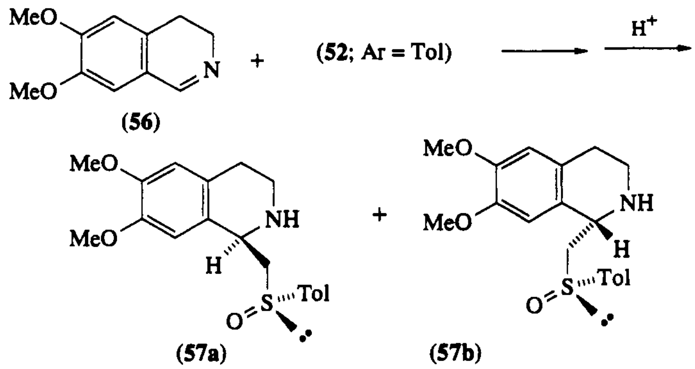

(15)

conformation in which the double bond lies in a plane almost perpendicular to the mean ring plane and is faced transannularly by the anionic orbital α to the sulfinyl group. Although the cyclization of (**58**) and (**59**) is stereospecific, treatment of (**60**) or (**61**) with butyllithium (0.5 equiv.) at –30 °C or –20 °C for 2 h produces two isomeric products in about equal amounts. This result is due to kinetic control. When the resulting mixture is allowed to stand at room temperature in the presence of butyllithium, an equilibrium is established between these products to afford the *trans*-junction isomer (**64b**) or (**65b**) exclusively or predominantly.[61]

This transannular addition of α-sulfinyl carbanions to nonactivated double bonds is utilized as the key step in a synthesis of *trans*-1-thiadecalin (**70**) in enantiomerically pure form.[62] The required (*E*)-thiacyclodec-4-ene *S*-oxide (**66a,b**) was prepared *via* several steps from (*R*,*R*)-1,6-dibromo-3,4-hexanediol. Upon treatment with butyllithium, a 4:1 mixture of isomeric sulfoxides (**66a** and **66b**) undergoes smooth cyclization to give a mixture of isomeric bicyclic sulfoxides (**67a** and **67b**) in the same 4:1 ratio as the starting material, suggesting that the cyclization is essentially stereospecific. The major isomer (**67a**) is reduced with $PCl_3$ to a sulfide (**68**) from which the desired (**70**) is derived *via* a thiaoctaline (**69**; Scheme 16).

### 2.3.3.5 Addition of Allylic Sulfinyl Carbanions to C=O Bonds

Deprotonation of allyl sulfoxides with LDA generates the corresponding allylic carbanions, which are able to add to aldehydes. Addition of the anion of aryl allyl sulfoxides to aromatic aldehydes proceeds

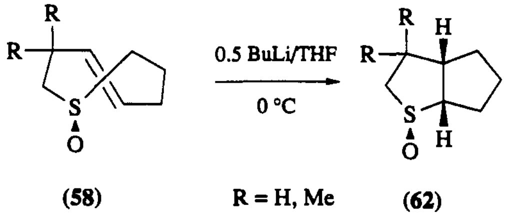
R
R
S
O
0.5 BuLi/THF
0 °C
R
H
R
S
O
H
(58)
R = H, Me
(62)

(16)

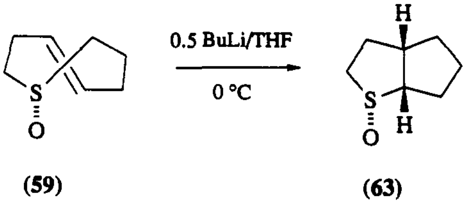
S
O
0.5 BuLi/THF
0 °C
H
S
O
H
(59)
(63)

(17)

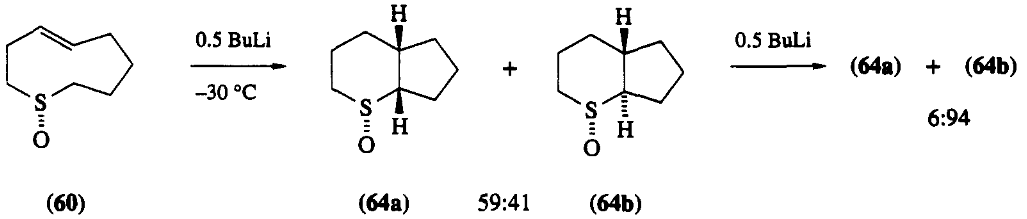
S
O
0.5 BuLi
-30 °C
H
S
O
H
+
H
S
O
H
0.5 BuLi
(64a) + (64b)
6:94
(60)
(64a)
59:41
(64b)

(18)

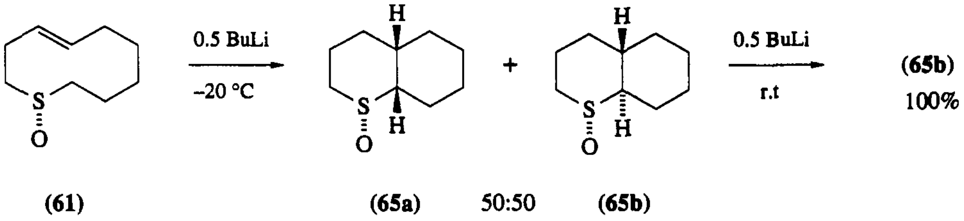
S
O
0.5 BuLi
-20 °C
H
S
O
H
+
H
S
O
H
0.5 BuLi
r.t
(65b)
100%
(61)
(65a)
50:50
(65b)

(19)

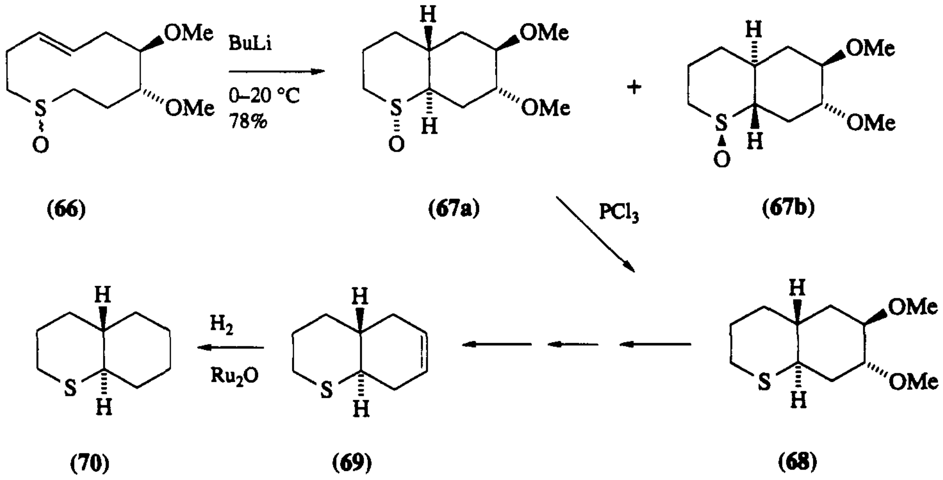
OMe
OMe
S
O
BuLi
0–20 °C
78%
H
OMe
OMe
S
O
H
+
H
OMe
OMe
S
O
H
(66)
(67a)
PCl₃
(67b)
H
S
H
H₂
Ru₂O
H
S
H
H
OMe
OMe
S
H
(70)
(69)
(68)

**Scheme 16**

readily in moderate yields to afford a mixture of products resulting from α- and γ-attack on the allyl anion (equation 20). All four possible diastereomers are formed from α-attack. Rapid epimerization at two chiral centers (sulfinyl sulfur and α-carbon) occurs *via* allylic sulfoxide–sulfenate 2,3-sigmatropic rearrangement, causing the low stereoselection summarized in Table 2. The γ-product possesses (*E*)-geometry at the double bond, and 1,5-asymmetric induction is observed to the extent that the major/minor diastereomeric ratio exceeds 2:1. The metalated carbon in the α-lithiated sulfoxide should be planar and the lithium cation should chelate with the sulfinyl oxygen. By analogy with the model proposed to explain diastereoselection in the reaction of aldehydes with enolates, the transition states (**71**) and (**72**), involving coordination in a six-membered ring, were proposed (Scheme 17).[63,64]

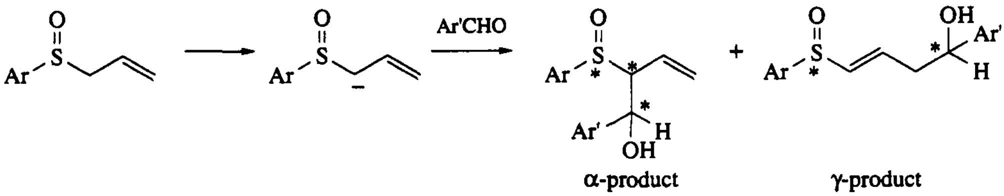

(20)

**Table 2** Results of the Addition Reaction in Equation (20)

| *Ar* | *Ar'* | *α/γ* | *Diastereomer ratio*<br>*a-Product* | <br>*γ-Product* |
|---|---|---|---|---|
| Ph | Ph | 1/2.1 | 3/6/7/2 | 3.0/1 |
| *p*-Tol | Ph | 1/1.7 | 3/3/6/2 | 3.0/1 |
| *p*-$NO_2C_6H_4$ | Ph | 1/2.2 | 5/5/5/1 | 2.0/1 |
| *p*-Tol | *p*-$MeOC_6H_4$ | 1/1.0 | 4/3/1/1 | 2.0/1 |
| *p*-Tol | *o*-$MeOC_6H_4$ | 1/1.1 | 8/5/2/1 | 3.4/1 |
| *p*-Tol | *p*-$NO_2C_6H_4$ | 1/1.5 | 6/3/2/1 | 2.5/1 |
| *p*-Tol | 2-naphthyl | 1/1.2 | 5/4/2/1 | 2.4/1 |

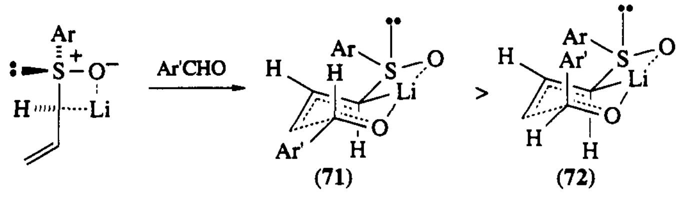

**Scheme 17**

Treatment of allyl *p*-tolyl sulfoxide with LDA followed by addition of HMPA (4.4 mol equiv.) and chiral 2-methylalkanal (3 mol equiv.) at –78 °C gave a mixture of readily separable α- and γ-adducts, where the α:γ regioisomer ratios are markedly higher than those obtained in the reaction with aromatic aldehydes. Exposure of the α-adduct to an excess of a thiophile (trimethyl phosphite or dimethylamine in MeOH) results in quenching of the allylic sulfoxide–sulfenate equilibrium and affords diastereoisomeric mixtures of the *syn*- and *anti*-diols (Scheme 18),[65,66] for which some yields and product ratios are shown in Table 3.

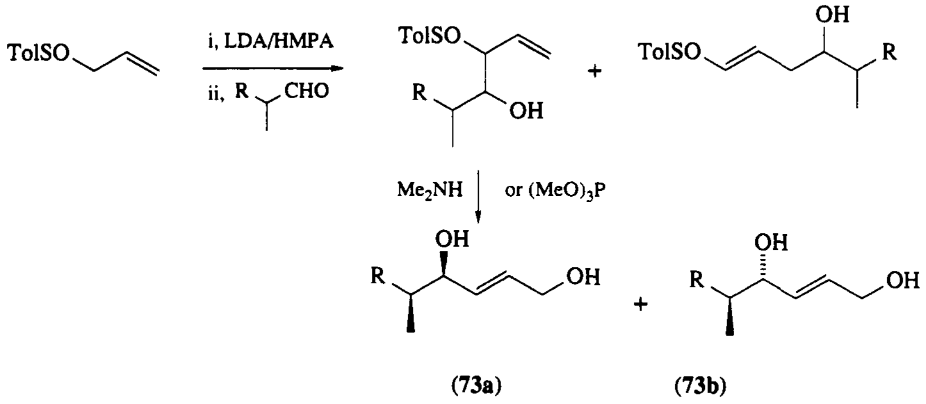

**Scheme 18**

**Table 3** Synthesis of Diols (73)

| *R* | *α/γ* | *Yield (%)* | *Syn/anti* |
|---|---|---|---|
| Et | 6.1/1 | 40 | 2.1/1 |
| $Pr^i$ | 10/1 | 40 | 5.1/1 |
| c-$C_6H_{11}$ | 5.6/1 | 57 | 6.4/1 |
| Ph | 9/1 | 67 | 28/1 |

Tandem condensation of chiral α-alkoxy aldehydes with the anion of allyl 2-pyridyl sulfoxide and $(MeO)_3P$-promoted desulfurization of the resulting α-adduct provide (*E*)-alkoxydiols. The major stereochemical path in their preparation may be accounted for by the Felkin–Anh (nonchelation control) model (Scheme 19).[67]

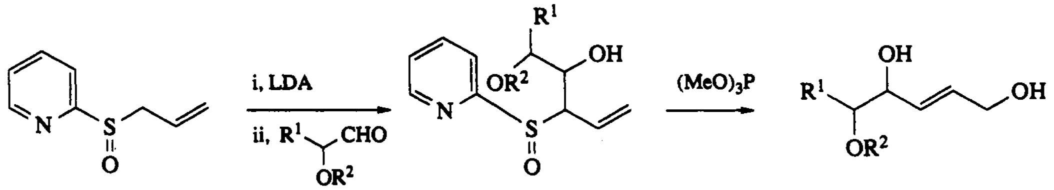

| *R¹* | *R²* | *Yield (%)* | *syn/anti* |
|---|---|---|---|
| Me | $PhCH_2$ | 51 | 1 / 2.5 |
| Me | $Bu^tMe_2Si$ | 40 | 1 / 5.5 |
| $PhCH_2OCH_2$ | $PhCH_2$ | 68 | 1 / 3.0 |
| $C_6H_{10}(Me)CH_2O$ |  | 60 | 1 / 6.5 |

**Scheme 19**

### 2.3.3.6 Addition of Allylic Sulfinyl Carbanions to C=C—C=O Bonds

In preliminary reports, the γ-carbon of the carbanion of allyl phenyl sulfoxide has been shown to attack cyclopentenone and cyclohexenone by 1,4-addition to deliver vinyl sulfoxides.[68–71] The lithiated carbanion (**75**) of 1-(phenylsulfinyl)-2-octene (*E*:*Z* = 85:15) adds to 4-*t*-butoxycyclopent-2-en-1-one (**74**) to give *syn-(E)*-vinylic sulfoxide (**76**) and *anti-(E)*-vinylic sulfoxide (**77**) in the ratio of 79:21. It has been suggested that (**76**) arises almost exclusively from the (*E*)-(**75**), and (**77**) derives from the (*Z*)-(**75**). Both the products have the same geometry about the double bond, but differ in configuration at the allylic carbon atom (equation 21).[72,73]

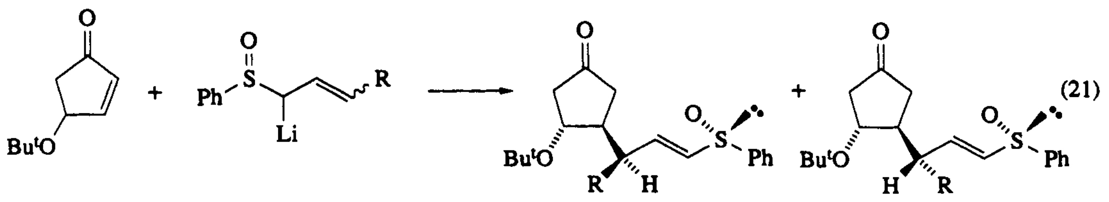

(21)

(**74**) (**75**) R = n-$C_5H_{11}$ (**76**) (**77**)

Since the 1,4-γ-adducts can be converted to various types of bicyclic compounds,[74] 1,4-addition of allylic sulfoxides to enones provides a useful tool for stereoselective synthesis of cyclic compounds. Further, the 1,4-addition can be utilized in a three-component coupling process for synthesis of prostanoic acid derivatives (Scheme 20).[75] Typical examples of addition of the lithio derivative (**78**) of (*R*)-allyl *p*-tolyl sulfoxide to cyclic enones are summarized in Scheme 21.[76]

Only 1,4-γ-adducts are formed in the five-membered ring system and the carbanion, which has *trans* geometry, attacks from the *si* face. The '*trans*-fused 10-membered' cyclic transition state offers an explanation for this highly stereoselective reaction. Six- and seven-membered cyclic enones provide both 1,4-γ- and 1,2-γ-adducts, with the larger ring providing a greater percentage of the 1,2-γ-adduct. With the seven-membered ring, a 58% yield of the 1,2-γ-adduct is isolated. These 1,4- and 1,2-addition re-

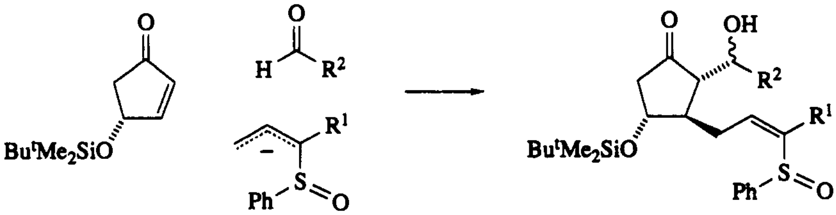

$R^1 = (CH_2)_4Me$, $R^2 = (CH_2)_5CO_2Me$ 68%

$R^1 = (CH_2)_3CO_2Bu^t$, $R^2 = CH{=}CHCH(OSiMe_2Bu^t)(CH_2)_3Me$ 62%

**Scheme 20**

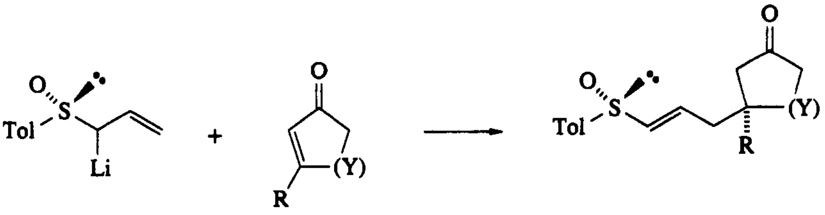

**(78)**

| | | |
|---|---|---|
| $Y = CH_2$, | $R = H$ | 91% (96% *ee*) |
| $Y = CH_2$, | $R = Me$ | 80% (95% *ee*) |
| $Y = O$, | $R = H$ | 70% (95% *ee*) |
| $Y = CH_2CH_2$, | $R = H$ | 79% (50% *ee*)[a] |
| $Y = CH_2CH_2CH_2$, | $R = H$ | 25% (59% *ee*)[b] |

[a] 1,2-adduct 14% (50% *ee*)

[b] 1,2-adduct 58% (50% *ee*)

**Scheme 21**

actions appear to be kinetically controlled. The same product or product ratio is observed whether the addition reactions are performed at −100 °C or at −50 °C, and the 1,2-γ- and 1,4-γ-adducts do not interconvert under these reaction conditions, or even at 25 °C.

Kinetic resolution is operative in the reaction with 4-substituted cyclopent-2-en-1-ones.[76] For instance, when 2 equiv. of racemic 4-(1-methyl-1-phenylethoxy)-2-cyclopentenone (**79**) is reacted with the carbanion (**78**), (*S*)-(**79**) reacts to yield predominantly the product derived by approach of the carbanion from the *si* face of (**79**). The formation of the *cis* adduct probably results from the chelation of lithium counterion with the C-4 oxygen (equation 22). Kinetically selective resolution of a bicyclic enone (**80**) is also effected. On treatment of the carbanion of (*R*)-(**78**) with racemic (**80**) (2 equiv.), an enantiomer of (**82**) and (*S*)-(**80**) are obtained in 80% and 45% yields respectively. Addition of the lithio derivative (2 equiv.) of

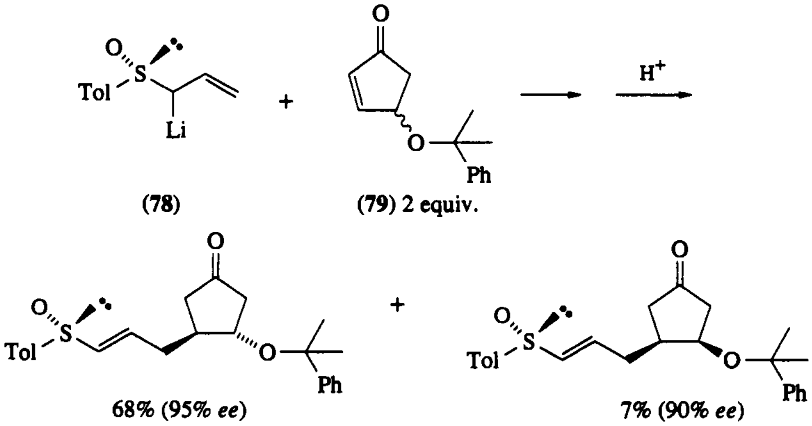

**(78)** **(79)** 2 equiv.

68% (95% *ee*) 7% (90% *ee*)

(22)

racemic *cis*-crotyl phenyl sulfoxide (**81**) to (*S*)-(**80**) affords a 1,4-$\gamma$-adduct (**83**; 91% yield/82% *ee*), which is a synthetic precursor of (+)-pentalenene (Scheme 22).[76,77]

Stereospecific 1,4-addition of the carbanion (**78**) to (siloxymethyl)bicyclooctenone (**84**) yields mainly the corresponding 1,4-$\gamma$-adduct. In seven steps, this adduct is converted into the known $\delta$-lactol (**85**), from which pentalenolactone (*E*)-methyl ester (**86**) may then be derived (Scheme 23).[78]

In addition, the 1,4-addition reaction of the anion (**87**) derived from various cyclic allylic sulfoxides with 2-cyclopentenones (**88**) were investigated (Scheme 24).[79] Methyl substitution at C-3 of (**88**) hinders the 1,4-addition. An activated enone (**88e**), however, affords excellent chemical and optical yields of the 1,4-adducts (**89**). (+)-12,13-Epoxytrichothec-9-ene (**91**) and its antipode have been enantioselectively synthesized from (*S*)-4-methyl-2-cyclohexenone (**90**) in 11 steps (Scheme 25).[79]

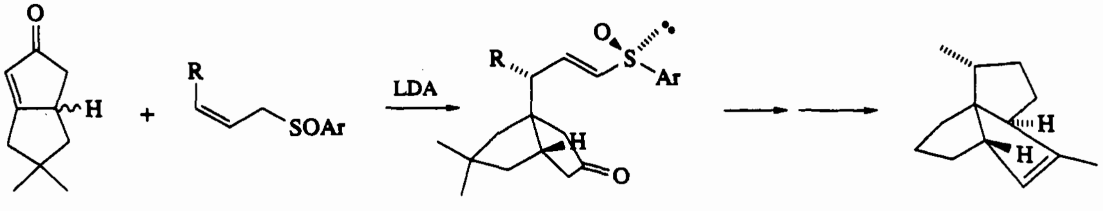

**(80)** **(78)** Ar = Tol, R = H; **(81)** Ar = Ph, R = Me **(82)** Ar = Tol, R = H; **(83)** Ar = Ph, R = Me (+)-Pentalenene

**Scheme 22**

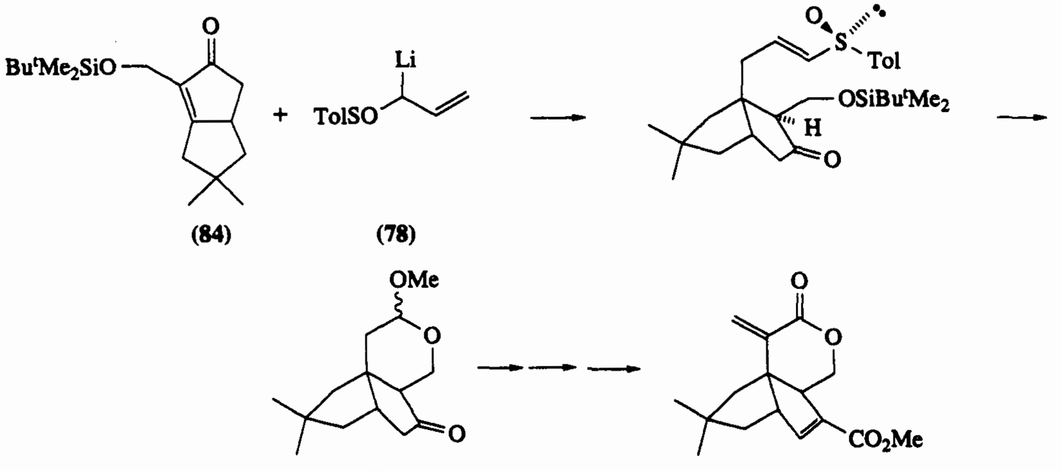

**(84)** **(78)**

**(85)** **(86)**

**Scheme 23**

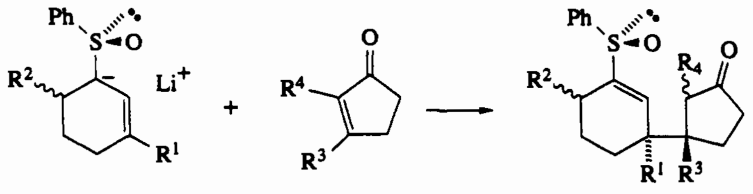

**(87)** **(88)** **(89)**

| | |
|---|---|
| **a**: $R^1 = R^2 = R^3 = R^4 = H$ | 50% |
| **b**: $R^1 = Me, R^2 = R^3 = R^4 = H$ | 60% |
| **c**: $R^1 = R^2 = Me, R^3 = R^4 = H$ | 61% |
| **d**: $R^1 = R^2 = R^3 = Me, R^4 = H$ | 5% |
| **e**: $R^1 = R^2 = R^3 = Me, R^4 = CO_2Me$ | 87% |

**Scheme 24**

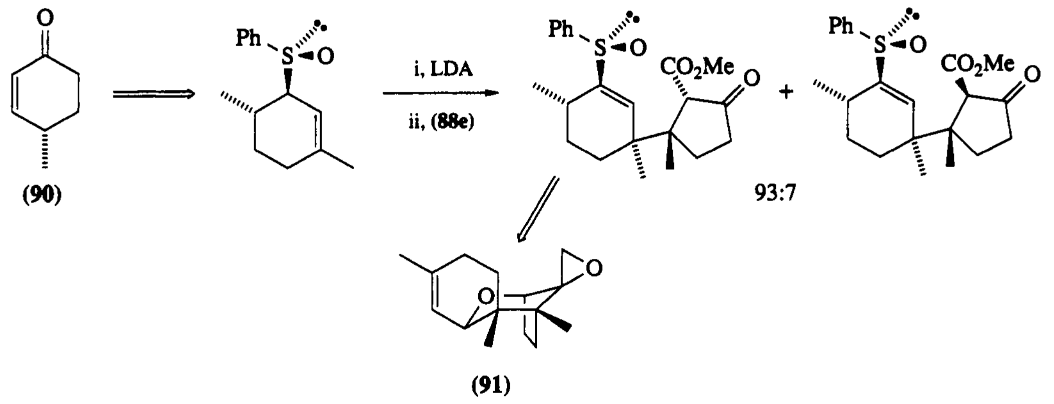

Scheme 25

## 2.3.3.7 Addition of α-Sulfinyl Carbonyl Compounds to C=O Bonds

The metal enolate of *(R)*-*N*,*N*-dimethyl-α-(*p*-tolylsulfinyl)acetamide (**92**) reacts with an aldehyde to afford a diastereomeric mixture of adduct (**93**), which undergoes desulfurization with 10% Na(Hg) in MeOH ($NaH_2PO_4$) to give an optically active β-hydroxyamide (**94**). By the use of $Li^+$ as a countercation, low to medium levels of enantioselection are achieved. However, the magnesium enolate of (**92**) realizes a high enantioselectivity, as summarized in Table 4. A rigid chelation model, shown in Scheme 26, is suggested for the transition state of this addition.[80]

Similarly, the magnesium enolate of *t*-butyl (*R*)-(*p*-tolylsulfinyl)acetate adds to aldehydes and ketones. The subsequent reductive desulfurization yields the corresponding optically active β-hydroxy esters (Scheme 27).[81,82] This process can be utilized for preparation of a synthetic intermediate (**95**) of maytansine with a selectivity of 93:7 (equation 23).[83] Michael-type addition of *t*-butyl (*R*)-(*p*-tolylsulfinyl)acetate to crotonic ester with NaH in DMF has also been reported, but the enantiomeric excess of the desulfurized product is very low (12%).[84]

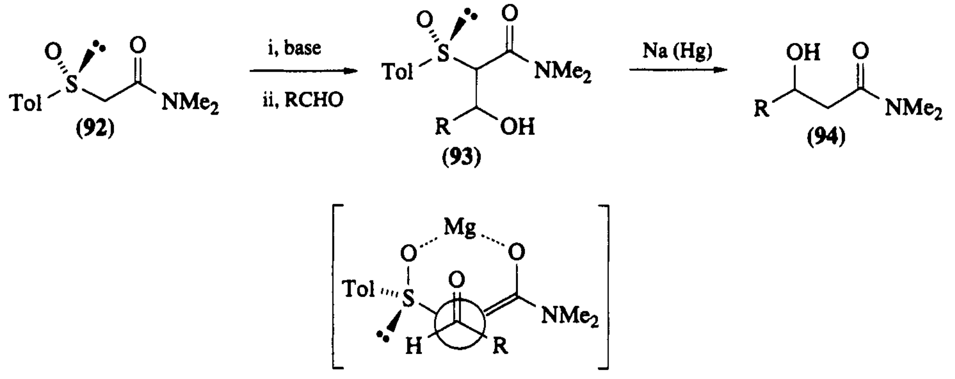

Scheme 26

Table 4 Addition of (92) to RCHO

| R | BuLi as base<br>Yield (%) | ee (%) | α | Bu$^t$MgBr as base<br>Yield (%) | ee (%) | α |
|---|---|---|---|---|---|---|
| Me | 65 | 47 | + | 68 | >>99 | – |
| Bu$^i$ | 77 | 45 | + | 71 | 98 | – |
| Pr$^i$ | 78 | 31 | + | 66 | 95 | – |
| Bu$^t$ | 20 | 8 | + | 56 | 90 | – |

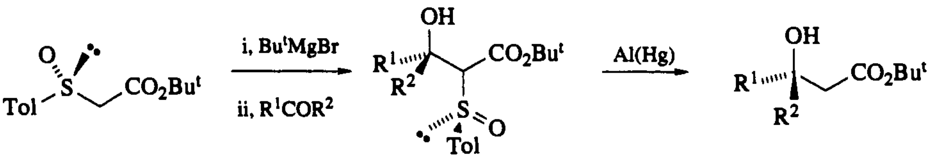

| *R$^1$* | *R$^2$* | *Yield (%)* | *ee (%)* |
|---|---|---|---|
| H | Ph | 85 | 91 (*S*) |
| Me | Ph | 75 | 68 (*S*) |
| H | n-$C_7H_{15}$ | 80 | 20 (*R*) |
| Me | 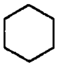 | 88 | 95 (*S*) |
| Me | $CO_2Et$ | 80 | 85 (*S*) |

**Scheme 27**

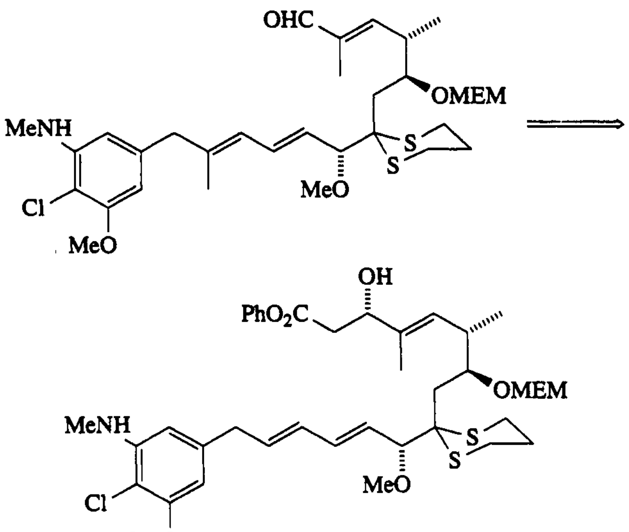

**(95)**

(23)

Direct condensation of (*p*-tolylsulfinyl)methyl ketones (**96**) with aldehydes followed by reductive desulfurization is an alternative method for obtaining optically active β-hydroxy ketones (**97**), but this reaction occurs with only moderate enantiomeric excess (Scheme 28).[85]

Aldol-type condensation of chiral α-sulfinyl hydrazones with aldehydes also provides a route leading to chiral β-hydroxy ketones.[86,87] This is exemplified by the synthesis of (–)-(*R*)-[6]-gingerol (**98**; equation 24).[88]

### 2.3.3.8 Addition of α-Halo Sulfoxides to C═X Bonds

Durst reported that lithiation of chloromethyl phenyl sulfoxide (**99**) with butyllithium followed by treatment of a symmetrical ketone (–78 °C to –20 °C) affords an adduct (**100**). This reaction is so highly stereoselective that only one diastereomer is produced. Reaction of (**100**) with dilute methanolic KOH gives an epoxy sulfoxide (**101**; equation 25).[89,90]

When chloromethyl *p*-tolyl sulfoxide (**102**; R = *p*-tolyl) is treated with carbonyl compounds (**103**) and potassium *t*-butoxide in *t*-butyl alcohol ether, (*p*-tolylsulfinyl)oxiranes (**104**) are directly formed.[91] Chloromethyl methyl sulfoxide (**102**; R = Me) exhibits the same behavior (Scheme 29).[92] These reactions proceed with high stereoselection at the position α to the sulfinyl group. The stereochemical course proposed for the attack of the carbanion of an α-halo sulfoxide on a carbonyl compound is shown in Figure 4.[93]

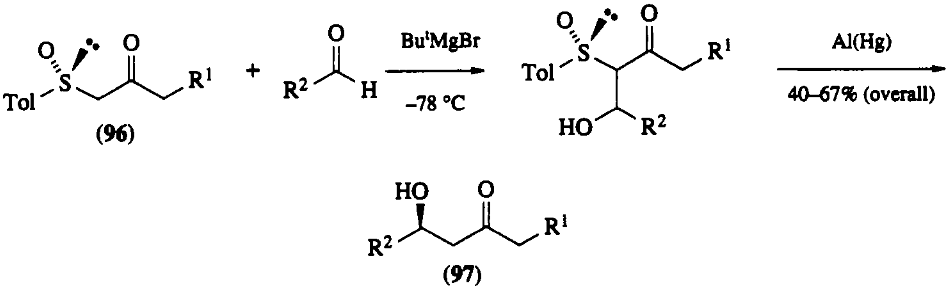
(96)
Bu$^t$MgBr
-78 °C
Al(Hg)
40–67% (overall)
(97)

| *R¹* | *R²* | *ee (%)* | *R¹* | *R²* | *ee (%)* |
|---|---|---|---|---|---|
| H | Et | 64 | Et | Et | 78 |
| H | 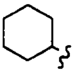 | 54 | Et | 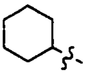 | 74 |
| H | Ph | 72 | | | |

**Scheme 28**

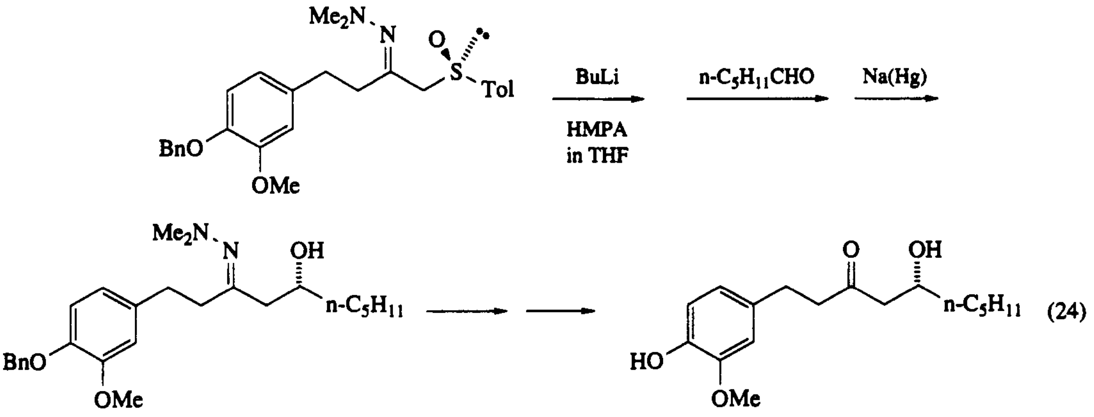
BuLi
HMPA in THF
n-C$_5$H$_{11}$CHO
Na(Hg)

optical purity of 60%
(98)

(24)

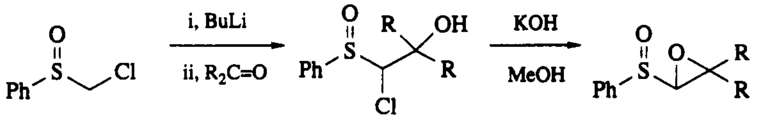
i, BuLi
ii, R$_2$C=O
KOH
MeOH

(99)
(100) a: R = Me
b: 2R = -(CH$_2$)$_5$-
c: R = Ph
(101) one diastereomer

(25)

It is noteworthy that the sterically hindered epoxide is preferentially formed in this Darzens-type condensation, which is in sharp contrast with that of α-halo sulfones (see Section 2.3.4.4). This intriguing

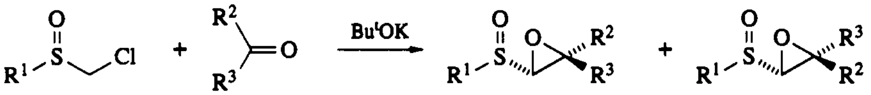

(102) (103) (104a) (104b)

R$^1$ = Tol, R$^2$ = Ph, R$^3$ = H, 100:0
R$^1$ = Me, R$^2$ = Bu$^t$, R$^3$ = Me, 75:25

**Scheme 29**

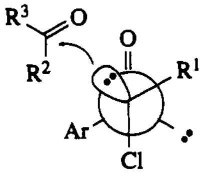

**Figure 4**

phenomenon may be rationalized in terms of a kinetically controlled approach of the anion of α-halo sulfoxide to aldehydes or ketones.[92]

Lithio-fluoro (or -chloro) methyl phenyl sulfoxide reacts with *N*-(benzylidene)aniline derivatives (**105**) to afford the corresponding aziridines (**106**) in good yields. Two diastereomeric isomers are produced, but the *trans* isomer is the major product except in the case of *N*-benzylidene-*p*-nitroaniline (Scheme 30).[94]

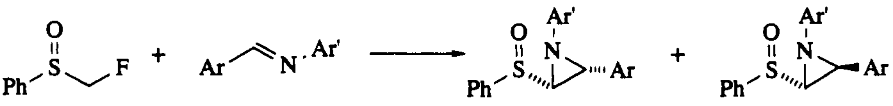

**(105)** **(106a)** **(106b)**

| | | |
|---|---|---|
| Ar = Ph, | Ar' = Ph, | 38:72 |
| Ar = $p$-ClC$_6$H$_4$, | Ar' = Ph, | 45:55 |
| Ar = $p$-NO$_2$C$_6$H$_4$, | Ar' = Ph, | 100:0 |
| Ar = Ph, | Ar' = $p$-BrC$_6$H$_4$, | 29:71 |

**Scheme 30**

The Darzens-type products from α-halo sulfoxides and carbonyl compounds undergo reductive desulfurization by the action of butyllithium. This is a useful synthetic route to various epoxides. Yamakawa and coworkers disclosed a novel asymmetric synthesis of epoxides (**109**) using optically active 1-chloroalkyl *p*-tolyl sulfoxide (**107**).[93,95] This method is most effective when the starting ketones are symmetrical, because only one diastereomer is then formed in the Darzens-type condensation (equation 26).

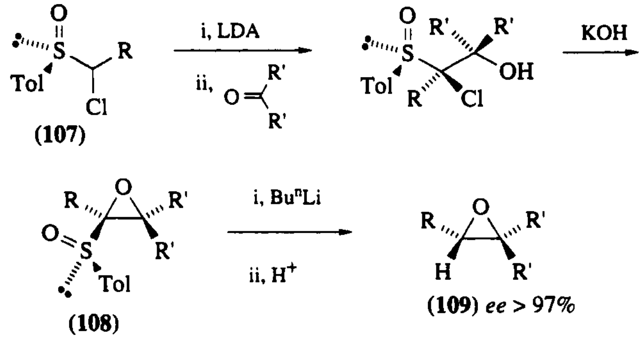

**(107)** **(108)** **(109)** *ee* > 97% (26)

R = n-C$_{10}$H$_{23}$, R' = Me or 2R' = (CH$_2$)$_5$ or (CH$_2$)$_4$

### 2.3.3.9 Addition of Dithioacetal *S*-Oxides and *S*,*S*'-Dioxides to C=X Bonds

Dropwise addition of butyllithium to a solution of (±)-1,3-dithiane *S*,*S*'-dioxide (**110**) in pyridine–THF (1.5:1) generates an anion (**111**), which reacts with an aldehyde to give an adduct (**112**) as a 1:1 diastereomeric mixture. The reaction is extremely rapid at –78 °C, but the kinetic selectivity is moderate. In the reaction with benzaldehyde or pivalaldehyde, equilibration is attained at 0 °C to give predominantly a single diastereomer in good yield (Scheme 31).[96]

Formaldehyde dimethyl dithioacetal *S*-oxide (FAMSO; **113**) and its ethyl analog are widely used as synthetic carbonyl equivalents.[97,98] Addition of the lithio derivative of (**113**) to aldehydes and ketones followed by acidic hydrolysis is a preparative method for α-hydroxy aldehyde derivatives (equation 27).[99] A chiral analog of (**113**), (*S*)-formaldehyde di-*p*-tolyl dithioacetal *S*-oxide (**114**), can be synthesized from (–)-mentyl *(R)-p*-toluenesulfinate.[5,100] The reaction of the lithio derivative of (*S*)-(**114**)

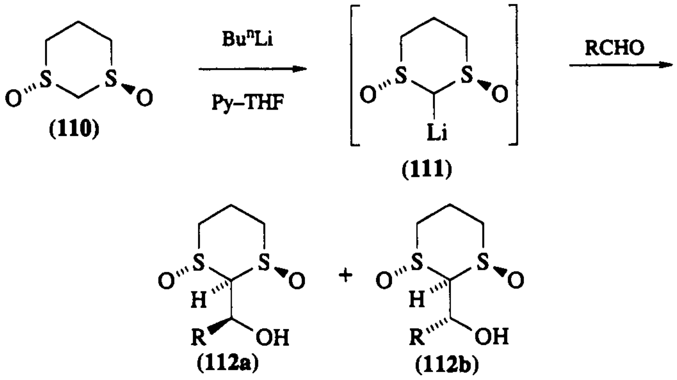

Bu^nLi
Py–THF
RCHO
(110)
(111)
(112a)
(112b)
Li
H
R
OH

| | |
|---|---|
| $\mathrm{Bu^nCHO}$, –78 °C | 63:37 |
| 0 °C/60 min | 49:51 |
| $\mathrm{Bu^tCHO}$, –78 °C | 64:36 |
| 0 °C/60 min | 14:86 |
| PhCHO, –78 °C | 66:34 |
| 0 °C/60 min | 36:64 |

**Scheme 31**

with benzaldehyde in THF at –78 °C affords an adduct (**115**), which is transformed into (*R*)-α-methoxyphenylacetaldehyde (**116**) with an enantiomeric excess of more than 70%.[101,102] The intermediary adduct (**115**) should consist of four stereoisomers, but the ratio is reported to be 55:30:15:0 [tentatively assigned (1*S*,2*S*,3*R*):(1*S*,2*R*,3*R*):(1*S*,2*S*,3*S*):(1*S*,2*R*,3*R*)]. It is noteworthy that a highly stereoselective formation of the adduct is achieved by $NaBH_4$ reduction of the benzoyl derivative (**117**) in MeOH–$NH_3$ (Scheme 32).[103]

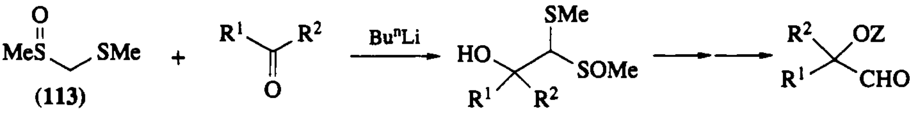

MeS
SMe
(113)
R¹
R²
O
Bu^nLi
HO
SMe
SOMe
OZ
CHO

(27)

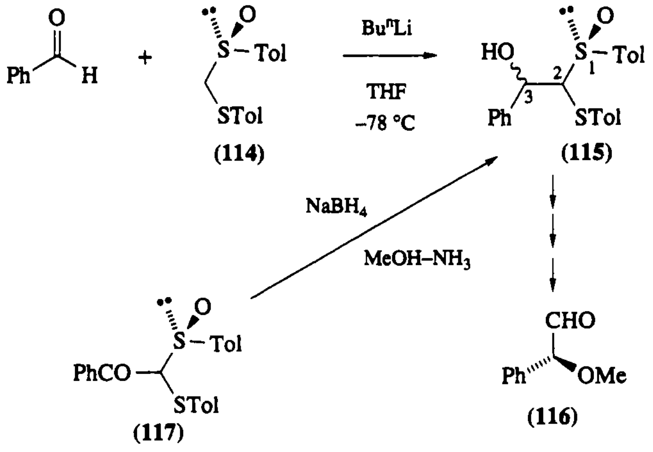

Ph
H
O
S–Tol
STol
(114)
Bu^nLi
THF
–78 °C
HO
1
2
3
(115)
NaBH₄
MeOH–NH₃
PhCO
(117)
CHO
OMe
(116)

**Scheme 32**

The anion of an aldehyde dithioacetal *S*-oxide is well known to add to α,β-unsaturated carbonyl compounds.[104–106] Conjugate addition of formaldehyde di-*p*-tolyl dithioacetal *S*-oxide (**114**) to open-chain and cyclic enones is achieved by using HMPA as a polar cosolvent in THF (–78 °C).[107] The lithio derivative of (*S*)-(**114**) was found to add to 2-cyclopentenone with asymmetric induction. Transformation of the dithioacetal part into a formyl group gives 3-formylcyclopentanone in 39% enantiomeric excess (equation 28).[107] Interestingly, highly asymmetric induction is observed in the conjugate addition of the lithiated (*S*)-(**114**) to 2-[6-(methoxycarbonyl)-1-hexyl]-2-cyclopentenone (**118**).[108] The enone (**118**) was added at −78 °C to the anion of (*S*)-(**114**) in THF containing HMPA (10 mol equiv.). After 30 min at −78 °C, usual work-up gave the 1,4-addition product (**119**) in 45% yield. The ratio of the four *trans* diastereomers was 48:44:5:3 [(1*S*,2*R* or *S*,3*R*,4*S*):(1*S*,2*S* or *R*,3*R*,4*S*):(1*S*,2*R* or *S*,3*S*,4*R*):(1*S*,2*S* or *R*,3*S*,4*R*)]. Formation of significant amounts (>90%) of only two diastereomers should be noted. The key step of this asymmetric synthesis is the addition of a chiral formyl anion equivalent to the enone (**118**). The reaction proceeds with high β- and γ-asymmetric induction of 92% and with poor α-stereoselection (52:48), probably due to the presence of α- and β-substituents of (**118**), which create a more demanding steric array in the transition state.

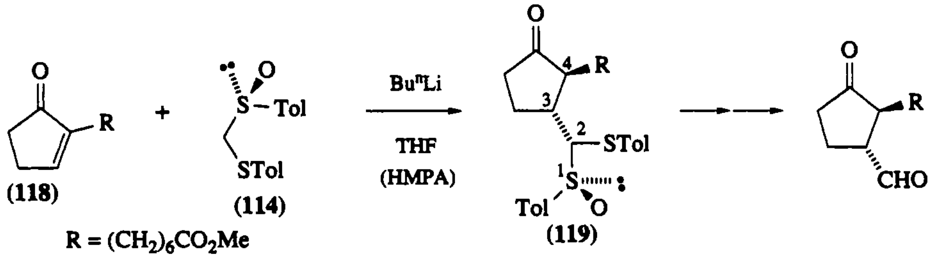

(**118**) (**114**) (**119**)

R = $(CH_2)_6CO_2Me$

(28)

## 2.3.4 SULFONYL-STABILIZED CARBANIONS

### 2.3.4.1 Configuration of the Carbanion

Configuration of an α-sulfonyl carbanion has been much investigated both theoretically and experimentally. Several experiments were designed to distinguish between planar and pyramidal structures for α-sulfonyl carbanions, which investigated: (i) the rate of H/D exchange of 1-phenylethyl phenyl sulfone;[109,110] (ii) the intramolecular H/D exchange of cyclopropyl alkyl sulfones;[111–114] and (iii) the base-catalyzed decarboxylation of optically active 2-methyltetrahydrothiophene-2-carboxylic acid 1,1-dioxide derivatives. The results suggest that α-sulfonyl carbanions are symmetrical (planar) as discrete reaction intermediates in asymmetric environments.[115]

*Ab initio* calculations on the hypothetical α-sulfonyl carbanion $HSO_2CH^-{}_2$ suggested that the geometry of the anionic carbon is intermediate between $sp^2$ and $sp^3$ structures.[116] Further, $HSO_2CH_2Li$ was calculated to have only an unsymmetrically chelated structure (**120**; Figure 5).[117] Bors and Streitwieser, Jr. also reported theoretical (*ab initio*) studies of the anion of dimethyl sulfone, showing that the pyramidal anion is 0.57 kcal $mol^{-1}$ (1 cal = 4.184 J) higher in energy over the planar form. The most stable geometry of the lithium salt of this anion is a structure (**121**), which is similar to (**120**). Another minimum with an unusual structure (**122**), is 1.1 kcal $mol^{-1}$ higher in energy than (**121**; see Figure 6).[118]

It should be noted that the crystal structure of the Li/TMEDA salt of benzyl phenyl sulfone reported by Boche[119] is conceptually similar to the theoretical structure (**122**). X-Ray structure determination of α-(phenylsulfonyl)benzyllithium–TMEDA, α-(phenylsulfonyl)allyllithium and the potassium salt of bis(methylsulfonyl)-3-(2,6-dimethyoxypyridyl)sulfonylmethane shows that the coordination about the anionic carbon atom is nearly planar, and that the *p*-orbital on the anionic carbon is approximately *gauche* to the two oxygen atoms on the sulfur.[119–122] The anionic carbon atom can be described as interacting with the sulfur atoms in an ylide-like manner with a barrier to rotation about the $^-C$—$SO_2$ bond.

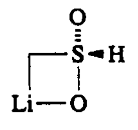

(**120**)

**Figure 5**

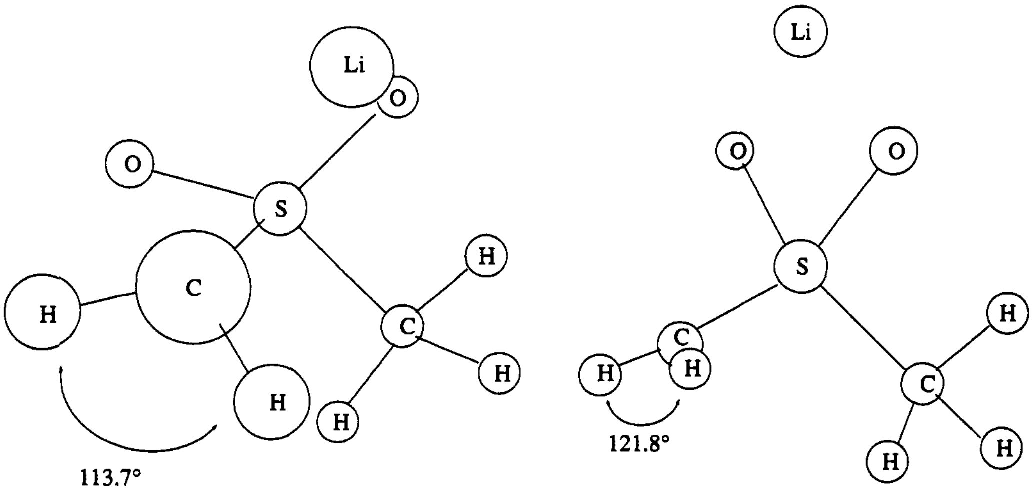

**(121)** **(122)**

**Figure 6**

### 2.3.4.2 Addition to C═O Bonds

Sulfonyl groups are useful for organic synthesis, and several methods have been elucidated for generation of their α-anions, for example: (i) action of butyllithium; (ii) treatment of α-silyl sulfone with fluoride anion; (iii) addition of an anion to an α,β-unsaturated sulfone, and so on. Although the carbanion α to the sulfonyl group has the ability to add inter- or intra-molecularly to C═O bonds, the stereoselectivity of this addition is relatively low. Fluoride-induced reaction of (**123**) gave a cyclization product (**124**) as a 75:25 mixture of two diastereomers (equation 29).[123] Therefore, addition of the α-sulfonyl carbanion to a formyl group is usually utilized in combination with a subsequent reaction to delete the newly created asymmetry. In the above case, reductive cleavage of (**124**) gave the corresponding alkene (**125**). Intermolecular addition of an α-sulfonyl carbanion to an aldehyde was utilized as an efficient method for coupling of subunits in a synthesis of FK506. The lithium salt of (**126**) reacted with an aldehyde (**127**) in THF at −78 °C. Oxidation of the resultant product mixture (**128**) with Dess–Martin periodinane afforded keto sulfone diastereomers which, upon reduction with lithium naphthalenide, were converted into the homogeneous ketone (**129**) in 60% overall yield (equation 30).[124]

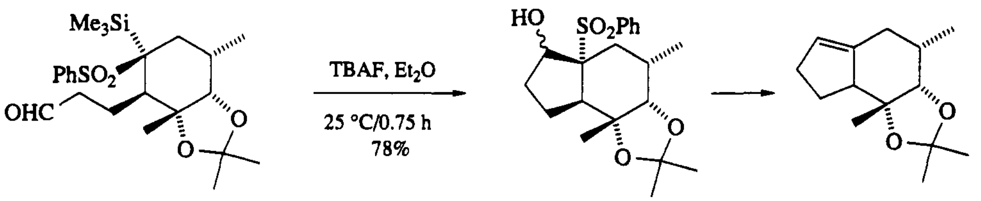

**(123)** **(124)** 75:25 **(125)** (29)

### 2.3.4.3 Addition of Allylic Sulfonyl Carbanions to C═X Bonds

The butyllithium-generated anion of an allylic sulfone was reported to add to conjugate enones, but different regioselectivity was observed for 2-cyclohexenone (1,4-γ) and 3-penten-2-one (1,4-α), as shown in equation (31).[125] Clean 1,4-α additions to both acyclic and cyclic enones can be realized when the lithio carbanions are allowed to react in the presence of HMPA (2 mol equiv.) at −78 °C.[126] Under these conditions, allyl phenyl sulfone reacts with 2-cyclohexenone, 2-methyl-2-cyclopentenone and 3-methyl-2-cyclohexenone, giving the corresponding 1,4-α adducts as a 75:25 mixture of two diastereoisomers. In the reaction of allylic phenyl sulfone with an acyclic enone, 4-methyl-3-penten-2-one,

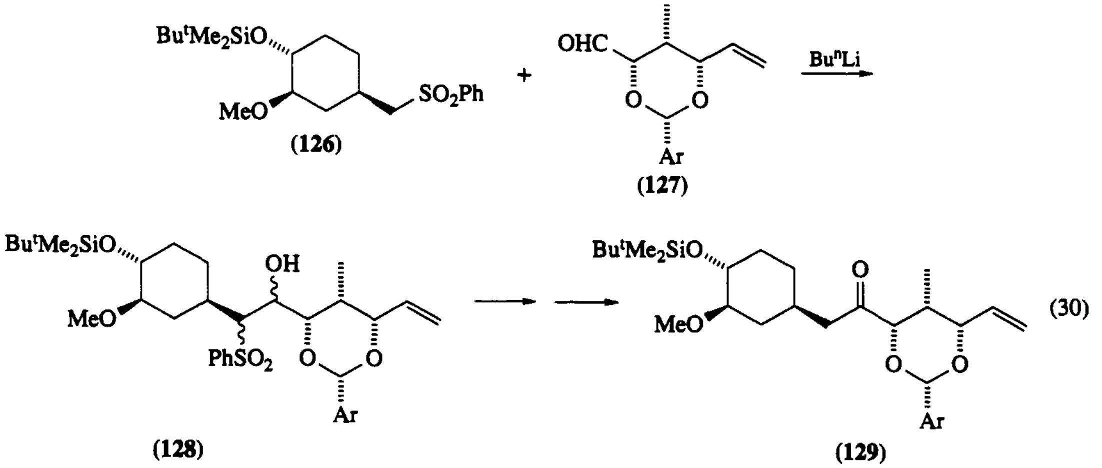
Bu^tMe2SiO
MeO
SO2Ph
(126)
+
OHC
O
O
Ar
(127)
Bu^nLi
Bu^tMe2SiO
MeO
OH
PhSO2
O
O
Ar
(128)
Bu^tMe2SiO
MeO
O
O
O
Ar
(129)
(30)

a 1,4-α adduct is exclusively produced. From several experiments, it has been concluded that the rapid and highly regioselective formation of 1,4-α adduct in the THF–HMPA (2 mol equiv.) system results from a direct conjugate addition rather than a kinetically controlled 1,2-α-addition followed by a rearrangement.

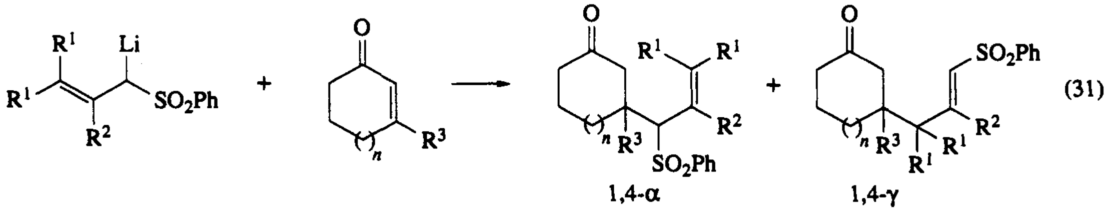
R1
Li
R1
SO2Ph
R2
+
O
R3
n
O
R1
R1
R2
n
R3
SO2Ph
1,4-α
+
O
SO2Ph
R2
n
R3
R1
R1
1,4-γ
(31)

### 2.3.4.4 Addition of α-Halo Sulfones to C=O Bonds

When chloromethyl phenyl sulfone (**130**; Ar = phenyl) was subjected to the Darzens-type reaction with an aldehyde, a thermodynamically stable *trans* isomer (**133**) was produced exclusively (equation 32). This is in sharp contrast with the corresponding reaction of chloromethyl phenyl sulfoxide. Tavares proposed that the initial nucleophilic attack of the α-sulfonyl carbanion upon a carbonyl compound is rapidly reversible due to its stability, and that the product-determining step is the ring closure. Thermodynamic equilibrium between the two diastereomers of (**132**) allows predominant formation of the thermodynamically stable isomer (**133**) from the preferred transition state.[127]

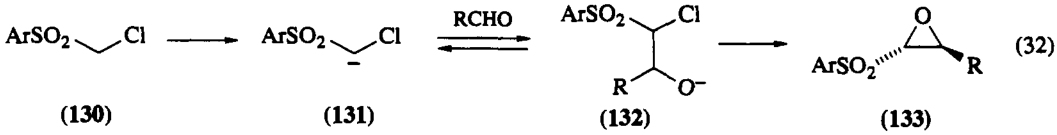
ArSO2
Cl
(130)
ArSO2
Cl
-
(131)
RCHO
ArSO2
Cl
R
O-
(132)
O
ArSO2
R
(133)
(32)

Treatment of the epoxy sulfones obtained thus with $MgBr_2$ produces α-bromo ketones or α-bromo aldehyde.[128] This conversion can be applied to stereoselective preparations of α-bromo methyl ketones from cyclohexanone derivatives. Thus, treatment of 17-β-hydroxy-5-α-androstan-3-one (**134**) with 1-chloroethyl phenyl sulfone provides an epoxy sulfone (**135**), which is cleaved by $MgBr_2$ to give a 99:1 mixture of 3-acetyl-3-bromoandrostanes (**136** and **137**; equation 33), whereas similar treatment of 17-β-hydroxy-5-β-androstan-3-one (**138**) gives a 4:96 mixture of 3-acetyl-3-bromoandrostanes (**139** and **140**; equation 34). These facts may reflect the steric course of the initial attack of the α-sulfonyl carbanion on the carbonyl face.

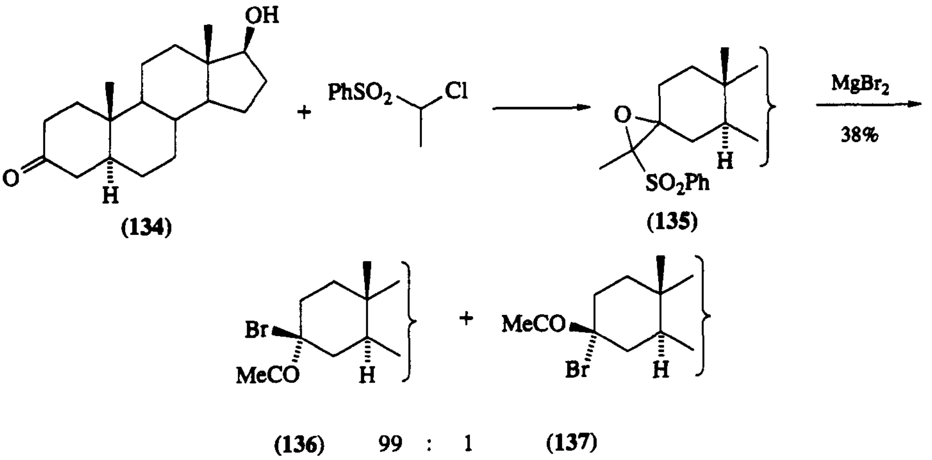

(134) (135) (136) (137)

(33)

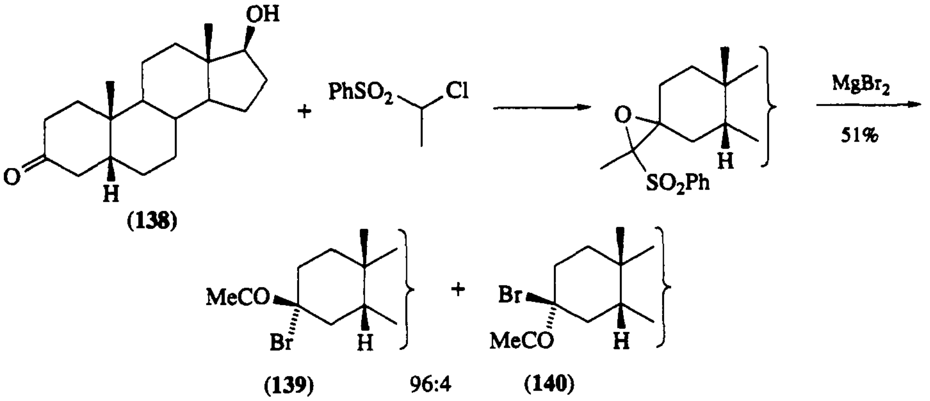

(138) (139) (140)

(34)

## 2.3.5 SULFONIMIDOYL-STABILIZED CARBANIONS

### 2.3.5.1 Configuration of the Carbanion

Bordwell estimated the p$K_a$ of *N*,*S*-dimethyl-*S*-phenylsulfoximine (**141**) in DMSO to be about 33, less acidic than methyl phenyl sulfone by about 4 p*K* units. From a cyclopropyl effect on the equilibrium acidity of *N*-phenylsulfonyl-*S*-methyl-*S*-phenylsulfoximine (**142**), it was concluded that the carbanion is planar or nearly planar to the sulfonimidoyl group.[129] However, on the basis of the $^1J_{CH}$ coupling constant in a $^{13}$C NMR spectroscopic study, it was concluded by Marquet that the configuration of the lithiated α-carbon (**142**) is pyramidal.[130]

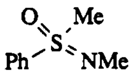

**(141)**

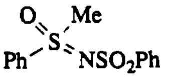

**(142)**

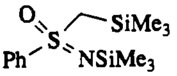

**(143)**

X-Ray structure analyses of the α-lithiated (**141**) and *N*-trimethylsilyl-*S*-trimethylsilylmethyl-*S*-phenylsulfoximine (**143**) were reported.[131,132] The latter compound can be crystallized as a tetramer including two molecules of cyclohexane, and its α-carbon is shown to be markedly pyramidalized. The $^1J_{CH}$ value of its α-carbon varies depending on the solvent employed, suggesting a hybrization between $sp^2$ and $sp^3$ in cyclohexane and a nearly $sp^2$ hybrization in THF.[133]

### 2.3.5.2 Addition to C=O Bonds

In 1971, Johnson and a coworker reported that the lithio derivative of (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (**141**) added to benzaldehyde in THF at room temperature to give an adduct as a 75:25 mixture of two diastereomers. Fractional crystallization gave one of the diastereomers in a pure form. Treatment of this material with aluminum amalgam in aqueous THF yielded optically pure (*R*)-1-phenylethanol.[134] This preliminary result was extended to a general method for syntheses of optically active alcohols. By addition of the lithium derivative of (*S*)-(**141**) to prochiral ketones and aldehydes, optically active β-hydroxysulfoximines were prepared as diastereomeric pairs. The ketone adducts (**144**) showed moderate diastereoselectivities (for example, 60:40 for propiophenone). After separation by medium pressure chromatography on silica gel, each diastereomer was desulfurized with Raney nickel to yield an optically active tertiary alcohol (**145**; Scheme 33). When the aldehyde adducts (**146**) are treated with Raney nickel without separation into each diastereomer, the corresponding secondary alcohols (**147**) are yielded in optical purities of 25–46% (equation 35).[135]

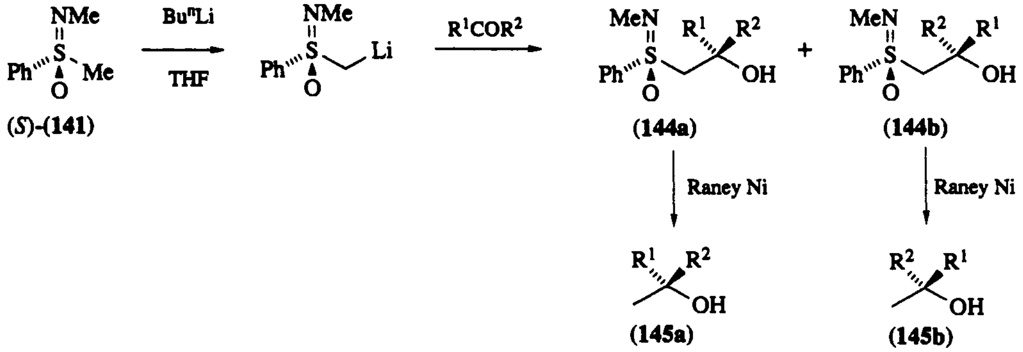

Scheme 33

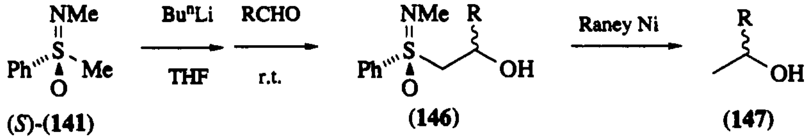 (35)

*N*-Silyl-*S*-methyl-*S*-phenylsulfoximine (**148**) adds to aldehydes in ether at –78 °C. Desilylation of the resulting adducts with hydrochloric acid affords *N*-unsubstituted β-hydroxyalkylsulfoximines (**149**; Scheme 34).[136] The product ratios are insensitive to the steric bulk of the reacting aldehydes and to reaction temperature (–78 to –10 °C). The use of a larger *N*-silyl group enhances the diastereoselectivity of 1,2-addition, particularly when a sterically bulky aldehyde is used. The oxygen-coordinated model (**150**) provides for interaction of the silylated sulfoximine nitrogen with the R group of the incoming aldehyde.

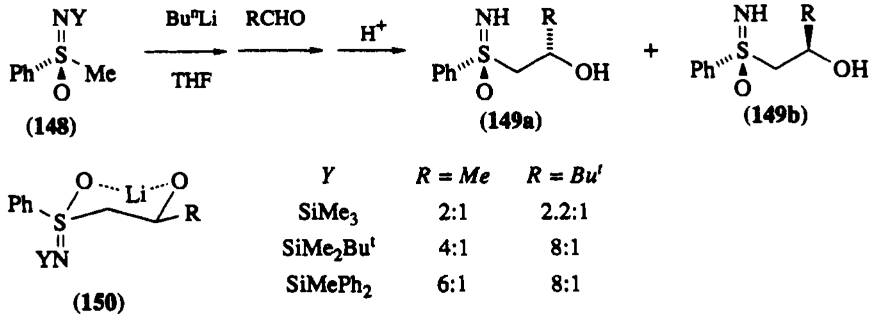

| *Y* | *R = Me* | *R = Bu$^t$* |
|---|---|---|
| $SiMe_3$ | 2:1 | 2.2:1 |
| $SiMe_2Bu^t$ | 4:1 | 8:1 |
| $SiMePh_2$ | 6:1 | 8:1 |

Scheme 34

(*S*)-(**141**) is also known to be a reagent for ketone methylenation with optical resolution.[137] Thus, addition of (*S*)-(**141**) to a racemic tricyclic ketone (**151**) resulted in the production of two diastereomers, (+)-(**152**) and (+)-(**153**), which were readily separated by flash chromatography. Treatment of (+)-(**152**) with aluminum amalgam and acetic acid in aqueous THF gave (–)-β-panasinsene (**154**) in 96% yield. Similar treatment of (+)-(**153**) gave the unnatural enantiomeric (+)-β-panasinsene (**155**; Scheme 35).

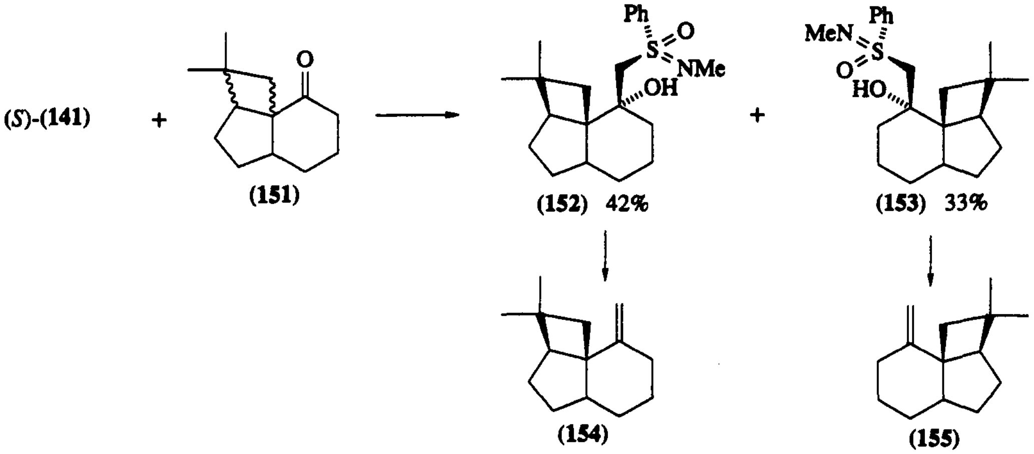
(*S*)-(141)
+
O
(151)
Ph
S
O
NMe
OH
(152) 42%
+
MeN
Ph
S
O
HO
(153) 33%
(154)
(155)

**Scheme 35**

The adduct (**157**) derived from (*S*)-(**141**) and an α,β-unsaturated ketone (**156**) undergoes Simmons–Smith cyclopropanation which is directed by the coexisting β-hydroxysulfoximine chiral center. As outlined in Scheme 36, this is a new methodology for optical activation of cyclopropyl ketones (**159**).[138] Indeed, optically active tricyclic ketones (–)-(**161**) and (+)-(**161**) were synthesized from a bicyclic ketone (**160**) in optical purities of 96% and 94%, respectively (equation 36).

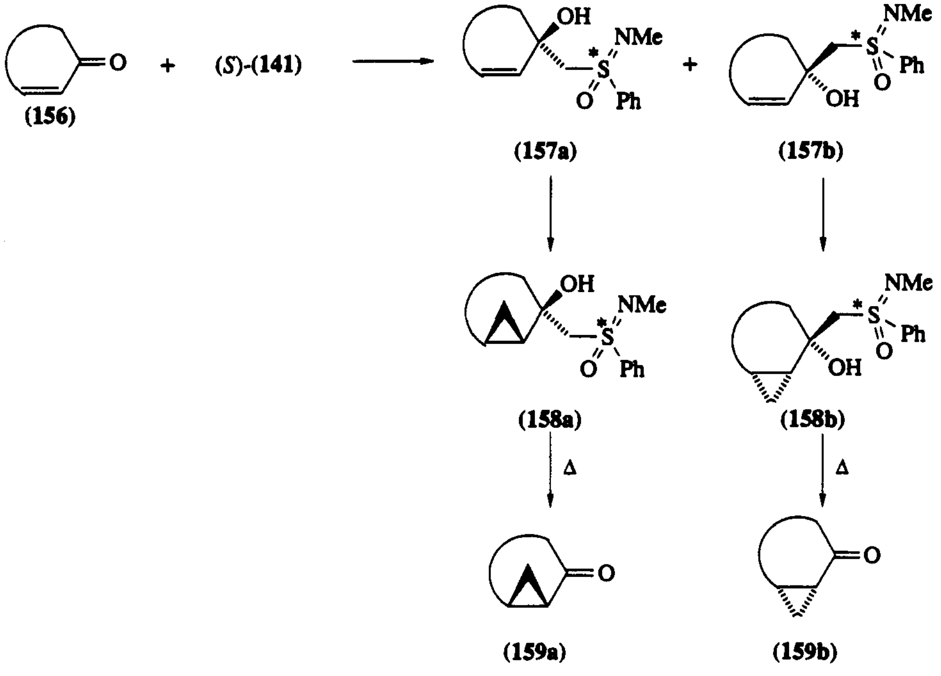
O
+
(*S*)-(141)
(156)
OH
NMe
*
S
O
Ph
(157a)
+
NMe
*
S
Ph
O
OH
(157b)
OH
NMe
*
S
O
Ph
(158a)
NMe
*
S
Ph
O
OH
(158b)
Δ
Δ
O
(159a)
O
(159b)

**Scheme 36**

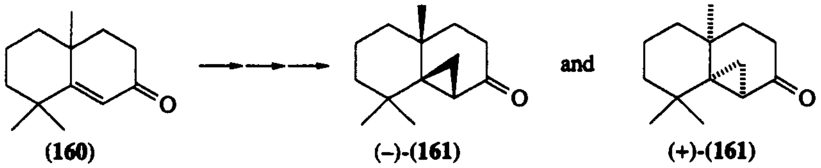
O
(160)
O
(–)-(161)
and
O
(+)-(161)

(36)

The same type of process using osmylation instead of the Simmons–Smith reaction leads to a synthesis of enantiomerically pure 2,3-dihydroxycycloalkanones from 2-cycloalkenones.[139] Addition of (*S*)-(**141**) to 3,5,5-trimethyl-2-cyclohexenone (**162**) produces a mixture of diastereomers (**163a**) and (**163b**), which are easily separable by silica gel chromatography. Treatment of the individual diastereomers with triethylamine *N*-oxide and $OsO_4$ (5 mol %) affords crude triols. In each case, a single diastereomeric product is produced. The subsequent thermolysis of the diastereomeric triols gives enantiomeric 2,3-dihydroxy-3,5,5-trimethyl-2-cyclohexanones (**164**; Scheme 37).

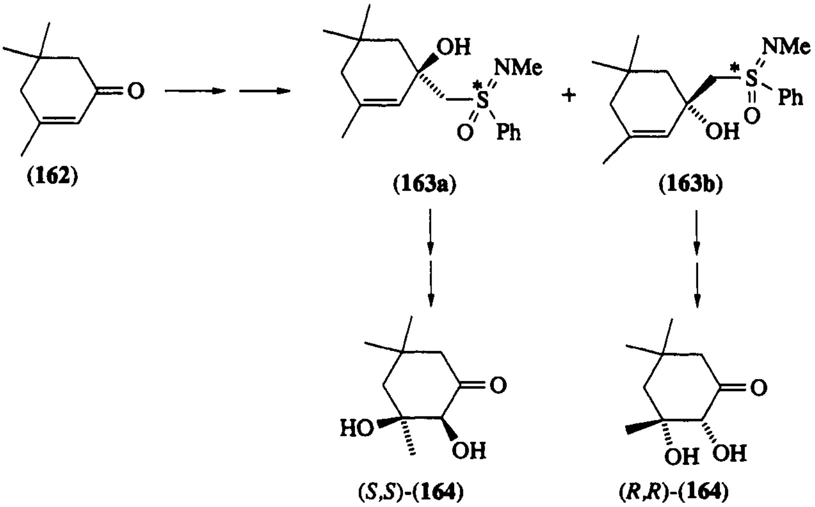

**Scheme 37**

Optical resolution of ketones using (*S*)-(**141**) has also been reported. As mentioned above, the addition of (*S*)-(**141**) as its α-lithio derivative to ketones occurs readily and irreversibly at –78 °C to give an adduct in excellent yield. The adduct usually consists of two or three diastereomers, which are separated by chromatography. Envelope-shaped bicyclic ketones such as (**165**) and (**166**) give diastereofacial specificity on addition of the lithio derivative of (*S*)-(**141**) to form two diastereomers in a 50:50 ratio. Simple 2-substituted cyclohexanones such as (**167**) and (**168**) generally give rise to three diastereomeric adducts (61:22:17 and 57:25:18, respectively): two major adducts resulting from equatorial addition and a single minor product resulting from axial addition. Steric complications arise during axial attack, but with only one of the two diastereomeric transition states. The diastereofacial selectivity of chiral acyclic ketones (or aldehydes) is usually low, and four diastereomers result from the addition of (*S*)-(**141**). Thermolysis of the individual diastereomers occurs smoothly at 80–120 °C to regenerate the optically active ketone and the starting (*S*)-(**141**).[140,141] This technique is applicable to resolving various cyclic ketones (**169**, **170** and **171**), which are useful intermediates for the synthesis of biologically active compounds.[140,142,143]

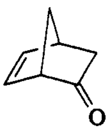

**(165)**

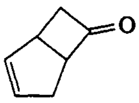

**(166)**

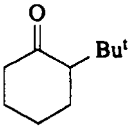

**(167)**

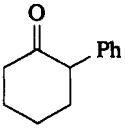

**(168)**

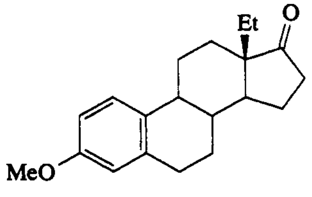

**(169)**

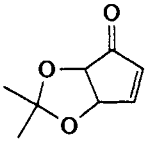

**(170)**

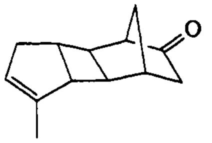

**(171)**

### 2.3.5.3 Others

The α-carbanion of an *N*-substituted sulfoximine adds to cycloalkadiene–molybdenum complexes (**173**) with asymmetric induction.[144] Although the reaction of *N*-substituted *S*-methyl-*S*-phenylsulfoximine is problematic, giving multiple products, the enolate ion of its *S*-(methoxycarbonyl)methyl analog (**172**) satisfactorily reacts with these complexes. It was established that the enolates derived from (*R*)-(**172**) preferentially add to the *pro*-(*R*) terminus of the complexes. Desulfonylation of the adducts (**174**) gave enantiomerically enriched monoester derivatives (**175**; equation 37), which could be further functionalized by hydride abstraction and a second nucleophilic addition. Typical results are summarized in Table 5. The reactions show a marked dependence on the sulfoximine *N*-substituent. The corresponding sodium and potassium enolates gave quite similar enantiomeric excesses, higher in all cases than those observed for the lithium enolates. The asymmetric inductions observed for reactions of complexes (**173**) are quite respectable and synthetically useful. To explain this stereoselectivity, open transition state models are proposed. The similar reaction of (**172**) to give dienyliron complexes (**176**) and (**177**) was also reported. Since the observed asymmetric inductions are lower, these reactions seem to be less useful.

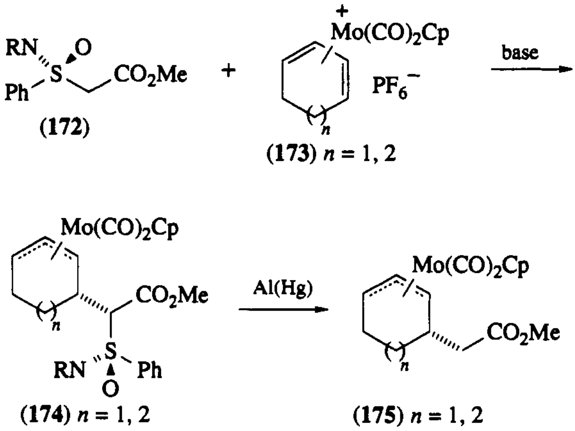

(37)

**Table 5** Asymmetric Induction in Equation (37)

| *n* | *(173)* *R*[a] | *Base* | *(175)* *Yield (%)*[b] | *ee (%)*[a] |
|---|---|---|---|---|
| 1 | Ts (+) | Bu$^t$OK | 79 | 16 (+) |
| 1 | Me (+) | NaH | 45 | 35 (+) |
| 1 | TBDMS (+) | Bu$^t$OK | 80 | 78 (–) |
| 1 | DMTS (–) | LDA | 77 | 55 (–) |
| 1 | DMTS (–) | NaH | 83 | 75 (–) |
| 1 | DMTS (–) | Bu$^t$OK | 80 | 80 (–) |
| 2 | DMTS (–) | Bu$^t$OK | 80 | 85 (–) |

[a] (+) or (–) indicates enantiomer. [b] Overall yield after desulfonylation.

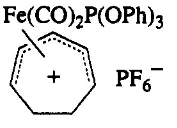

(**176**)

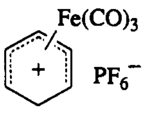

(**177**)

Recently Gais and coworkers disclosed an asymmetric synthesis of alkyl-substituted exocyclic alkenes from ketones by the use of optically active *N*,*S*-dimethyl-*S*-phenylsulfoximine (**141**).[145] Scheme 38 shows the conversion of 4-*t*-butylcyclohexanone (**178**) into optically active 4-*t*-butyl-1-ethylidenecyclohexane (**182**). Addition of the lithiated (*S*)-(**141**) to (**178**) affords two diastereomeric adducts (**179**) and (**180**), which are easily separable.[146] Trimethylsilylation followed by action of butyllithium brings about asymmetric elimination of $LiOSiMe_3$, leading to an alkenylsulfoximine (**181**).[147] Treatment of (**181**) with dimethylzinc in the presence of $MgBr_2$ (2 equiv.) gives the enantiomerically pure alkene (**182**) in 74% yield. This method is effectively applicable to stereoselective synthesis of a precursor (**186**) for carbacyclins. Highly selective *exo* addition of the lithiated (*R*)-(**141**) to bicyclic ketone (**183**) yields the β-hydroxysulfoximine (**184**). Silylation and then subsequent asymmetric elimination of $LiOSiMe_3$ affords the (*Z*)-alkenylsulfoximine (**185**) with more than 98% diastereoselectivity.[147] In the reaction of (**185**) with a dialkylzinc in ether in the presence of $NiCl_2(DPPP)$, a carbacyclin precursor (**186**) is obtained in 70% yield with 99:1 diastereoselectivity (Scheme 39).[145]

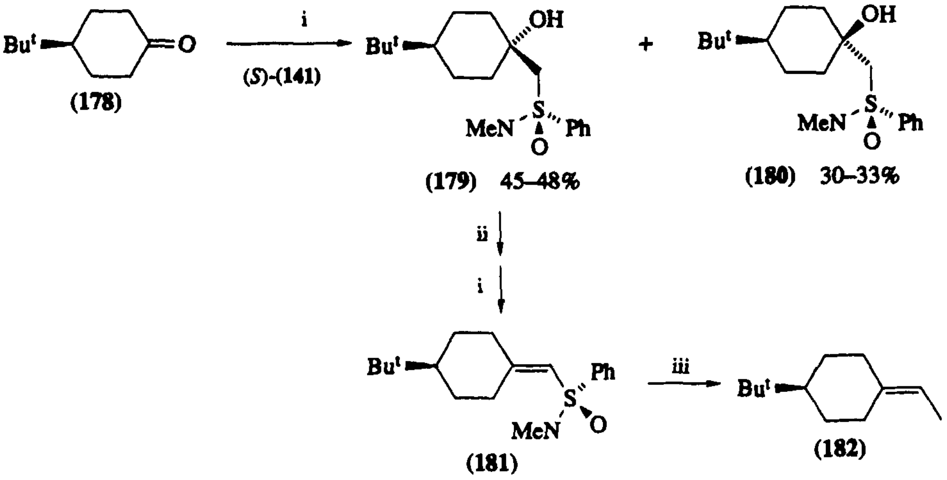

Bu<sup>t</sup>
(178)
i
(S)-(141)
OH
MeN S Ph O
(179) 45–48%
+
(180) 30–33%
ii
i
Ph
(181)
iii
(182)

i, $Bu^nLi$, THF, –78 °C; ii, $Bu^nLi$, THF, –78 °C, then $Me_3SiCl$, –78 to 25 °C;
iii, $Me_2Zn/MgBr_2/NiCl_2(DPPP)$, ether

Scheme 38

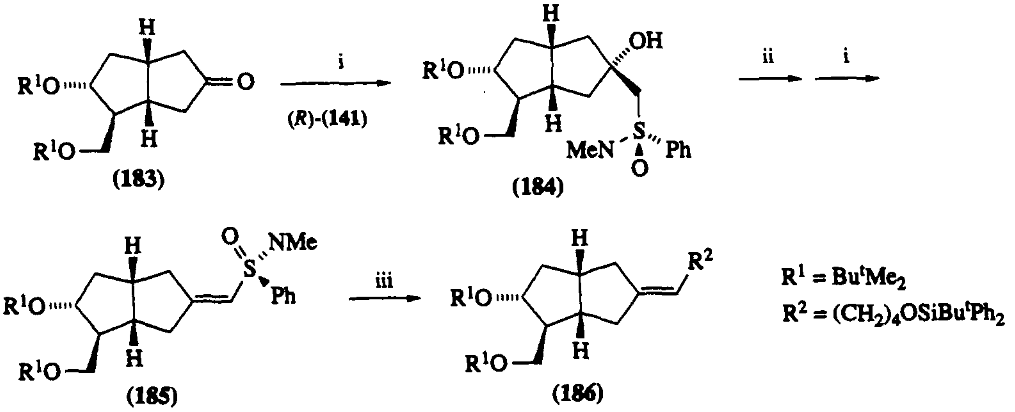

H
R1O
(183)
i
(R)-(141)
OH
MeN S Ph O
(184)
ii
i
NMe
(185)
iii
R2
(186)
R1 = ButMe2
R2 = (CH2)4OSiButPh2

i, $Bu^nLi$, THF, –78 °C; ii, $Bu^nLi$, THF, –78 °C, then $Me_3SiCl$, –78 to 25 °C;
iii, $R^2{}_2Zn/MgBr_2/NiCl_2(DPPP)$, ether

Scheme 39

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# 2.4

# The Benzoin and Related Acyl Anion Equivalent Reactions

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## 2.4.1 INTRODUCTION

C—C bond formation is a pivotal process in organic synthesis.[1,2] An effective pathway for C—C bond formation involves the reaction of an enolate at the α-position of a carbonyl compound with a carbon electrophile (alkyl halide, epoxide, carbonyl or unsaturated carbonyl compound). An alternative pathway would involve reaction of an acyl anion with an electrophile. Since acyl anions are in general unattainable, a great deal of effort has been expended to find masked acyl anions (acyl anion equivalents),[3] usually compounds of type $^-$RCXY, in which CXY can be reconverted into a carbonyl group. The benzoin condensation (Scheme 1), one of the oldest reactions in organic chemistry, represents a special case of such masked acyl anions. In this chapter we do not aim at exhaustive coverage of the subject but rather to give examples that highlight the utility of acyl anion equivalents, especially those related to cyanohydrins, in synthetic manipulations.

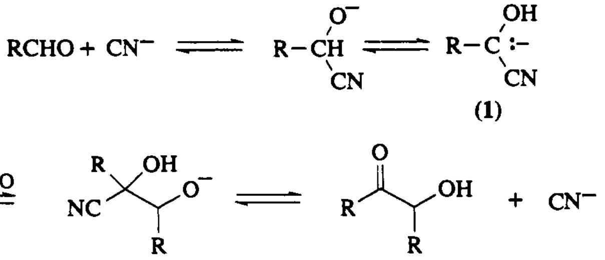

Scheme 1

In the benzoin condensation, both aromatic and heterocyclic aldehydes are transformed into α-hydroxy ketones of the general formula ArCHOHCOAr, often called benzoins.[4–6] This class of compounds is frequently encountered in natural products, hence the benzoin and related reactions have received much attention.[7–13] The reaction employs a cyanide ion as the catalyst and the mechanism, proposed by Lapworth,[4] involves formation of carbanions stabilized by the nitrile group (Scheme 1).

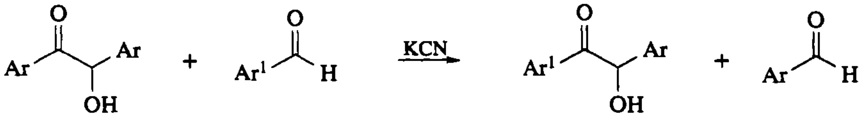

(1)

The fact that treatment of a benzoin with potassium cyanide in the presence of a second aldehyde leads to mixed benzoins indicates that all the steps are reversible (equation 1).

The carbanion (**1**) can be generated independently from cyanohydrins and can be added to the double bond of α,β-unsaturated ketones, esters and nitriles by an irreversible reaction which ultimately leads to γ-diketones, 4-oxocarboxylic esters and 4-oxonitriles.[7]

Studies on thiamine (vitamin $B_1$) catalyzed formation of acyloins from aliphatic aldehydes and on thiamine or thiamine diphosphate catalyzed decarboxylation of pyruvate[7,8] have established the mechanism for the catalytic activity of 1,3-thiazolium salts in carbonyl condensation reactions. In the presence of bases, quaternary thiazolium salts are transformed into the ylide structure (**2**), the ylide being able to exert a catalytic effect resembling that of the cyanide ion in the benzoin condensation (Scheme 2). Like cyanide, the zwitterion (**2**), formed by the reaction of thiazolium salts with base, is nucleophilic and reacts at the carbonyl group of aldehydes. The resultant intermediate can undergo base-catalyzed proton transfer to give a carbanion (**3**), which is stabilized by the thiazolium ring. The carbanion (**3**), like (**1**), undergoes 1,4-addition to α,β-unsaturated esters, ketones or nitriles.

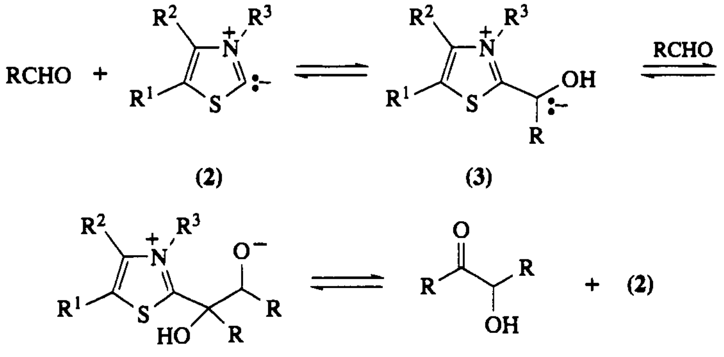

**Scheme 2**

### 2.4.1.1 Catalysts for Benzoin Formation

Generally benzoins are generated by the action of sodium cyanide or potassium cyanide on aromatic aldehydes in aqueous ethanol *via* cyanohydrin intermediates.[4] Benzoins may also be prepared in good yields by treating aromatic aldehydes with potassium cyanide in the presence of crown ethers in water or aprotic solvents.[14] Other sources for cyanide in this type of condensation are tetrabutylammonium cyanide,[5] polymer-supported cyanide[15] and acetone cyanohydrin with $K_2CO_3$.[16] Similarly, addition of aromatic aldehydes to α,β-unsaturated ketones can be accomplished by means of cyanide catalysis in DMF.[7]

The use of thiazolium salts enables the benzoin condensation to proceed at room temperature.[5] It can also be performed in dipolar aprotic solvents or under phase transfer conditions.[5] Thiazolium salts such as vitamin $B_1$,[17] thiazolium salts attached to γ-cyclodextrin,[18] macrobicyclic thiazolium salts,[19] thiazolium carboxylate,[20] naphtho[2,1-*d*]thiazolium and benzothiazolium salts catalyze the benzoin condensation[8] and quaternary salts of 1-methylbenzimidazole and 4-(4-chlorophenyl)-4*H*-1,2,4-triazole are reported to have similar catalytic activity.[7,8] Alkylation of 2-hydroxyethyl-4-methyl-1,3-thiazole with benzyl chloride, methyl iodide, ethyl bromide and 2-ethoxyethyl bromide yields useful salts for catalyzing 1,4-addition of aldehydes to activated double bonds.[8] Insoluble polymer-supported thiazolium salts are catalysts for the benzoin condensation and for Michael addition of aldehydes.[21–24] Electron rich alkenes such as bis(1,3-dialkylimidazolidin-2-ylidenes) bearing primary alkyl substituents at the nitrogen atoms[25] or bis(thiazolin-2-ylidene) bearing benzyl groups at the nitrogen atoms[26] are examples of a new class of catalyst for the conversion of ArCHO into ArCHOHCOAr.

The yeast-mediated condensation of benzaldehyde with acetaldehyde is of particular interest since it represents one of the first industrially useful microbial transformations, with the acyloin produced being subsequently converted chemically to D-ephidrine.[27] Other illustrations of synthetic value are the yeast-induced condensation of aldehyde (**4a,b**) with fermentatively generated acetaldehyde. The initially formed acyloins (**5a,b**) are not isolated but are further reduced, again with enantiotopic specificity, to give the pheromone synthon (**6a**; R = β-styryl) and the α-tocopherol chromanyl moiety precursor (**6b**; R = 2-propenylfuran) respectively (Scheme 3).[28]

α-Hydroxy ketones bearing a trifluoromethyl group were prepared from an aromatic aldehyde in high yield *via* a hydrazone.[29]

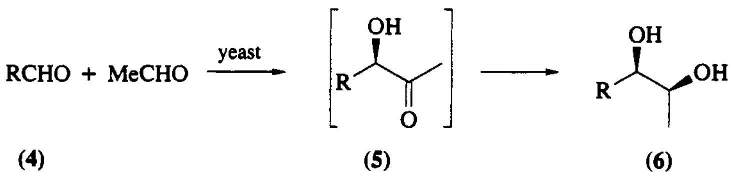

**Scheme 3**

### 2.4.1.2 Masked Acyl Anion Equivalents

The benzoin condensation has recently been recognized as belonging to the general class of reactions that involve masked acyl anions as intermediates.[5,8,11,12] For example, an aldehyde is converted into an addition product RCH(OX)Y, which renders the C—H acidic. Then under basic conditions, a masked acyl anion (see **1**) can be formed and may react with an electrophilic component $E^+$. Decomposition of the product RCE(OX)Y should regenerate the carbonyl group with formation of RC(O)E. Intermediates such as (**1**) are used in the conversion of aldehydes into α-hydroxy ketones, α-diketones and 1,4-dicarbonyl compounds, proving to be a powerful strategy in the development of new synthetic methods.[3,8–12]

The most systematically investigated acyl anion equivalents have been the TMS ethers of aromatic and heteroaromatic aldehyde cyanohydrins,[30] TBDMS-protected cyanohydrins,[31,32] benzoyl-protected cyanohydrins,[33] alkoxycarbonyl-protected cyanohydrins,[34] THP-protected cyanohydrins,[35] ethoxyethyl-protected cyanohydrins,[36] α-(dialkylamino)nitriles,[8] cyanophosphates,[37] diethyl 1-(trimethylsiloxy)-phenylmethyl phosphonate[38] and dithioacetals.[3] Deprotonation of these masked acyl anions under the action of strong base, usually LDA, followed by treatment with a wide variety of electrophiles is of great synthetic value. If the electrophile is another aldehyde, α-hydroxy ketones or benzoins are formed. More recently, the acyl carbanion equivalents formed by electroreduction of oxazolium salts[39] were found to be useful for the formation of ketones, aldehydes or α-hydroxy ketones (Scheme 4). α-Methoxyvinyllithium also can act as an acyl anion equivalent and can be used for the formation of α-hydroxy ketones, α-diketones, ketones, γ-diketones[40] and silyl ketones.[13,41,42]

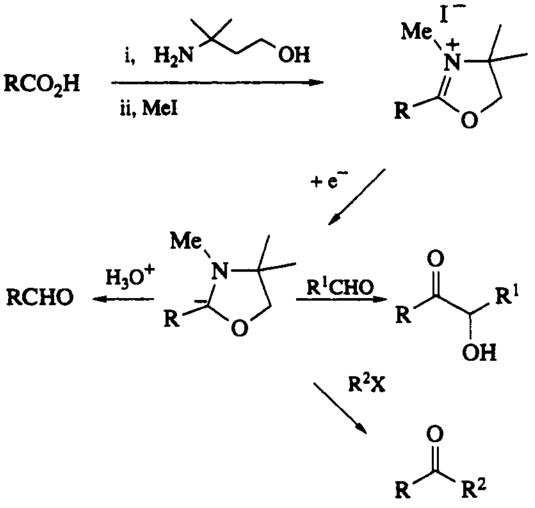

Scheme 4

### 2.4.1.3 Electrophiles

In the benzoin condensation, one molecule of aldehyde serves as an electrophile. If a carbanion is generated from protected cyanohydrins, α-aminonitriles or dithioacetals, it can react with electrophiles such as alkyl halides, strongly activated aryl halides or alkyl tosylates to form ketones. Amongst other electrophiles which are attacked by the above carbanions are heterocyclic *N*-oxides, carbonyl compounds, α,β-unsaturated carbonyl compounds, α,β-unsaturated nitriles, acyl halides, Mannich bases, epoxides and chlorotrimethyl derivatives of silicon, germanium and tin.

### 2.4.1.4 Miscellaneous

Benzoins can also be synthesized by the photolysis of aldehydes at high concentration.[43] The formation of benzoin can be rationalized as arising from intermolecular hydrogen abstraction followed by collapse of the radicals.

The addition of lithium and Grignard reagents to isocyanides which do not contain α-hydrogens proceeds by an α-addition to produce a metalloaldimine (**7**, an acyl anion equivalent). The lithium aldimines are versatile reagents which can be used as precursors for the preparation of aldehydes, ketones, α-hydroxy ketones, α-keto acids, α- and β-hydroxy acids, silyl ketones and α-amino acids (Scheme 5).[44,45]

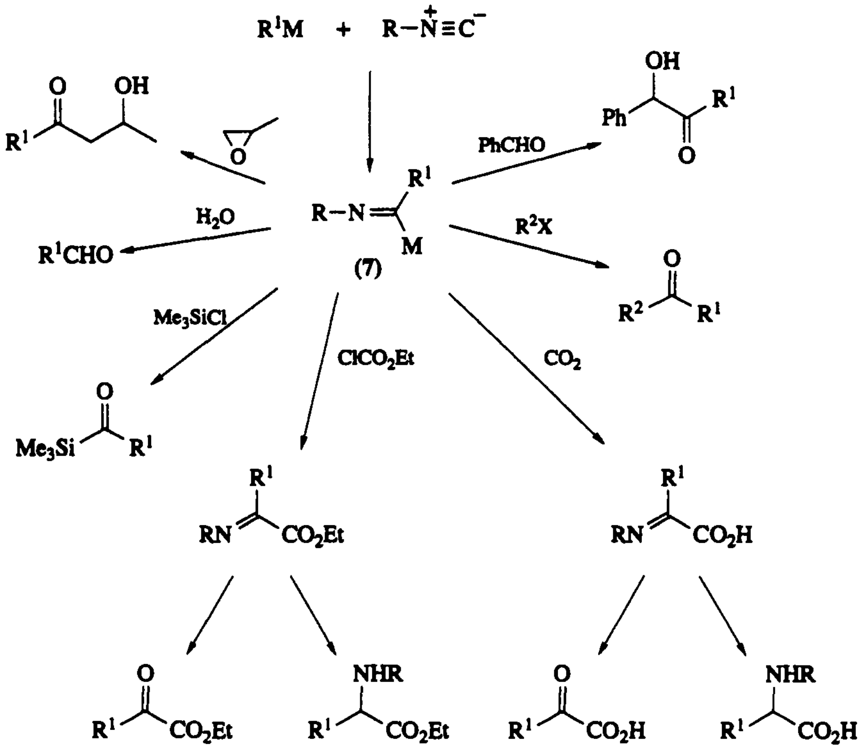
R¹M + R−N≡C
H₂O
R¹CHO
PhCHO
R²X
Me₃SiCl
ClCO₂Et
CO₂
(7)

Scheme 5

The lithium salts of aldehyde *t*-butylhydrazones react with electrophiles (aldehydes, ketones, alkyl halides) to form C-trapped *t*-butylazo compounds; isomerization and hydrolysis give α-hydroxy ketones or ketones in good yields, thereby providing a convenient path *via* a new acyl anion equivalent (Scheme 6).[46] Reaction of these lithium salts with aldehydes and ketones, followed by elimination, provides a new route to azaalkenes,[47] whereas homolytic decomposition of C-trapped azo compounds of trityl and diphenyl-4-pyridylmethylhydrazones lead to the formation of alkanes, alkenes, alcohols or saturated esters.[48]

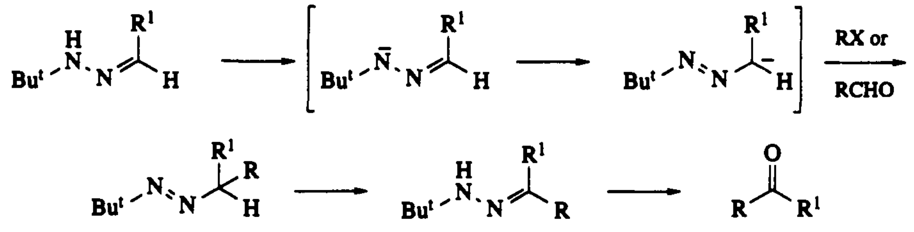

Scheme 6

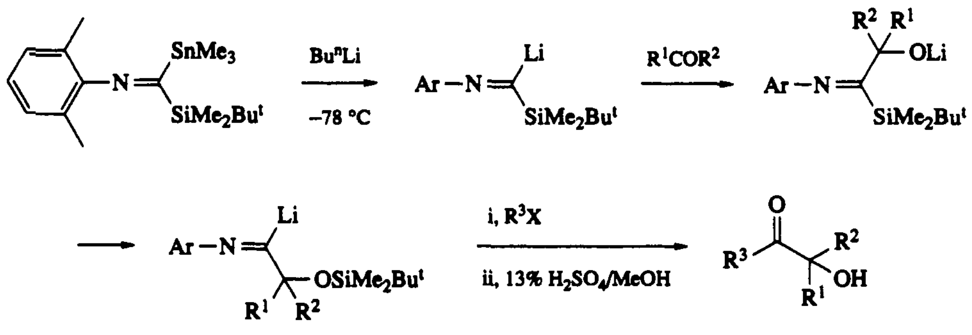
BuⁿLi
−78 °C
R¹COR²
i, R³X
ii, 13% H₂SO₄/MeOH

Scheme 7

When the 2,6-xylylimine of trialkylsilyl trimethylstannyl ketone is selectively transmetallated at −78 °C with Bu$^n$Li to generate a derivative, the latter serves as a versatile masked acyl anion that can react with various electrophiles. For example, α-hydroxy ketones were prepared using this new reagent (Scheme 7).[49]

## 2.4.2 CHIRAL CYANOHYDRINS

Asymmetric synthesis by means of a cyanohydrin is an important process in organic synthesis, because the cyanohydrin can be easily converted into a variety of valuable synthetic intermediates, such as α-hydroxy ketones, α-hydroxy acids, γ-diketones, β-amino alcohols, 4-oxocarboxylic esters, 4-oxonitriles, α-amino acids and acyl cyanides. More specifically, the (*S*)-cyanohydrin of *m*-phenoxybenzaldehyde is a building block for the synthesis of the insecticide deltamethrin,[50] or (1*R*)-*cis*-pyrethroids.[51]

In catalytic processes with enzymes such as D-oxynitrilase[52] and (*R*)-oxynitrilase (mandelonitrilase)[53] or synthetic peptides such as cyclo[(*S*)-phenylalanyl-(*S*)-histidyl],[54] or in reaction with TMS-CN promoted by chiral titanium(IV) reagents[55,56] or with lanthanide trichlorides,[57] hydrogen cyanide adds to numerous aldehydes to form optically active cyanohydrins. The optically active Lewis acids (**8**) can also be used as a catalyst.[58] Cyanation of chiral cyclic acetals with TMS-CN in the presence of titanium(IV) chloride gives cyanohydrin ethers, which on hydrolysis lead to optically active cyanohydrins.[59] An optically active cyanohydrin can also be prepared from racemic RR′C(OH)CN by complexation with brucine.[60]

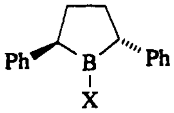

(**8**) X = OMe or Cl

### 2.4.2.1 1,2-Addition to Aldehydes and Ketones

The oldest known reaction involving masked acyl anions of the type (**1**) is the preparation of benzoin from aromatic aldehydes as illustrated in Scheme 1 (R = Ph). The reaction is applicable only to aldehydes with no α-hydrogen atoms (otherwise the aldol reaction competes); attempts to prepare a mixed acyloin yield a mixture of products. It is essential that the reaction be carried out in aprotic solvents, general preference being given to DMF. Aldehydes which normally give poor yields of benzoin in aqueous alcohol react in DMF–DMSO to give good yields of benzoins, especially if tetrabutylammonium cyanide is used as the base.[5,7] Under these conditions, the cyanide ion becomes more nucleophilic and basic; the reaction is usually complete in a few hours at room temperature.

Quite often the products of the benzoin condensation are unstable to oxygen and lead to α-diketones.[5] This is the case in intramolecular condensations when the initial product is an *o*-quinol, which is easily oxidized to the quinone.[5] 4-Substituted tetramides can be prepared by the reaction of an aromatic aldehyde with oxalaldehyde in the presence of cyanide ion, *via* the benzoin condensation (Scheme 8).[6]

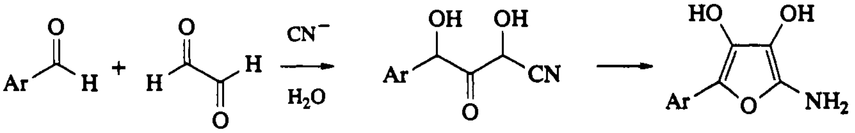

**Scheme 8**

### 2.4.2.2 1,4-Addition to α,β-Unsaturated Carbonyl Compounds

The most suitable technique for addition of aromatic aldehydes to α,β-unsaturated ketones utilizes cyanide catalysis in DMF (equation 2).[7] Unsubstituted aromatic aldehydes and those bearing substituents in the ring, except for *ortho*-substituted benzaldehydes, can add to an aliphatic, aromatic or heterocyclic α,β-unsaturated ketone. Addition of heterocyclic aldehydes can be catalyzed by cyanide ion as well. The products are γ-diketones, which can be converted to cyclopentenones, furans, pyrroles, thiophenes and pyrazines, as illustrated for the synthesis of *N*-methyl-2,3,5-tris(3-pyridyl)pyrrole, quinolizidines and 1-(3-phenyl-1-indolizidinyl)-1-propanol.[7]

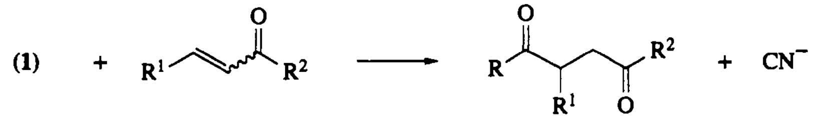
(2)

Aromatic or heterocyclic aldehydes also add smoothly to α,β-unsaturated esters and nitriles.[7]

Dialdehydes such as 2,5-thiophenedicarbaldehyde can be added to acrylonitrile in the presence of cyanide ion and the product can be converted to 4,9-dioxododecanedioic acid.[7]

### 2.4.2.3 Addition to Mannich Bases

Aromatic and heterocyclic aldehydes add readily to Mannich bases in a cyanide-catalyzed reaction in DMF to produce γ-diketones (equation 3).

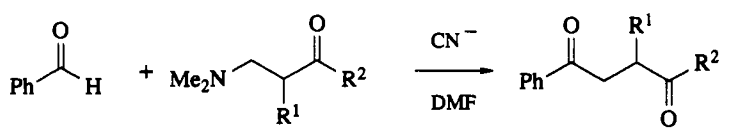
(3)

$R^1$ = H, Me, Ph; $R^2$ = Me, $Pr^i$, Ph; $R^1R^2$ = $-(CH_2)_n-$

Examples include the reactions of 3-pyridinecarbaldehyde with 3-dimethylamino-1-phenyl-1-propanone, of furfural with 3-dimethylamino-1-(2-furyl)-1-propanone and of 2-thiophenecarbaldehyde with 3-dimethylamino-1-(2-thienyl)-1-propanone.[7]

### 2.4.2.4 Miscellaneous Reactions of Cyanohydrins

Direct conversion of aldehydes to esters was carried out *via* oxidative benzoin reactions, using an aromatic nitro compound as an oxidizing agent under the catalytic action of cyanide ion or of a conjugate base of a thiazolium ion (Scheme 9).[61]

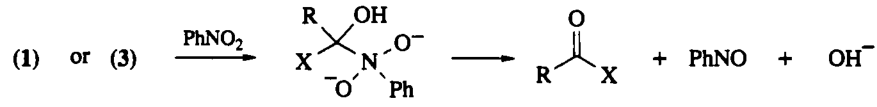

X = CN, Tz

Scheme 9

## 2.4.3 *O*-PROTECTED CYANOHYDRINS

The mechanism of the benzoin condensation,[4] as depicted in Scheme 1, suggested that anions derived from a protected aldehyde cyanohydrin should function as nucleophilic acylating reagents. The use of protected cyanohydrins as carbanion equivalents has been studied by Stork[62] and by Hunig[63] and has found wide applicability in chemical synthesis. Such species may serve as either acyl anion equivalents[12] or homoenolate anions.[25,36]

Anions of protected cyanohydrins of aliphatic, aromatic or α,β-unsaturated aldehydes undergo 1,4-addition to cyclic and acyclic enones. The synthetic utility of protected cyanohydrins in 1,4-addition depends on regioselectivity, since a competing reaction is 1,2-addition to the carbonyl group. The regioselectivity of these reactions (1,4- *versus* 1,2-addition) is dependent on the structure of the protected cyanohydrin, the enone and the reaction solvent.[8] Some general principles which influence the regioselectivity can be defined.

Conjugate additions predominate with bulky anions or with an enone containing a hindered carbonyl function. Anions derived from protected cyanohydrins of α,β-unsaturated aldehydes favor 1,4-additions. Anions derived from aryl aldehydes, especially if substituted with electron-withdrawing substituents, give predominantly conjugate addition. Increased bulk at the β-position of the enone, such as in β,β-disubstituted enones, leads to increased amounts of 1,2-addition.[8]

The anions of protected cyanohydrins are excellent nucleophiles in reaction with both primary and secondary alkyl halides.[8]

### 2.4.3.1 *O*-Silyl-protected Cyanohydrins

*O*-Silylated cyanohydrins have found considerable utility in the regioselective protection of *p*-quinones,[64] as intermediates for the preparation of β-amino alcohols[65] and as precursors to acyl anion equivalents.[36] Such compounds are typically prepared in high yield by either thermal or Lewis acid catalyzed addition of TMS-CN across the carbonyl group.[64] This cyanosilylation has a variety of disadvantages and modified one-pot cyanosilylation procedures have been reported.[31,66] The carbonyl group can be regenerated by treatment with acid, silver fluoride[64] or triethylaluminum hydrofluoride followed by base.[63]

### *2.4.3.1.1 1,2-Addition to aldehydes and ketones*

The anion of the adduct of TMS-CN with benzaldehyde reacts with aldehydes and ketones to form acyloin silyl ethers, by way of a 1,4-*O*-silyl rearrangement (Scheme 10). This method gives α-hydroxy ketones in excellent yield (80–90%) and allows the selective synthesis of unsymmetrical benzoins.[67]

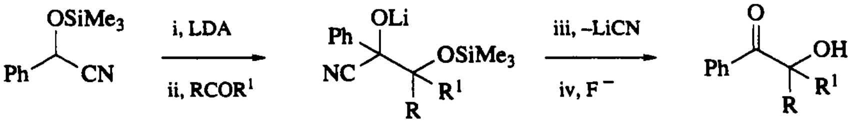

Scheme 10

Trimethylsiloxy cyanohydrins (**9**) derived from an α,β-unsaturated aldehyde form ambident anions (**9a**) on deprotonation. The latter can react with electrophiles at the α-position as an acyl anion equivalent (at –78 °C)[7] or at the γ-position as a homoenolate equivalent (at 0 °C).[36] The lithium salt of (**9**) reacts exclusively at the α-position with aldehydes and ketones.[36] The initial kinetic product (**10**) formed at –78 °C undergoes an intramolecular 1,4-silyl rearrangement at higher temperature to give (**11**). Thus the initial kinetic product is trapped and only products resulting from α-attack are observed (see Scheme 11). The α-hydroxyenones (**12**), γ-lactones (**13**) and α-trimethylsiloxyenones (**11**) formed are useful precursors to cyclopentenones and the overall reaction sequence constitutes a three-carbon annelation procedure.

### *2.4.3.1.2 1,4-Addition to α,β-unsaturated carbonyl compounds*

The anion (**9a**) derived from crotonaldehyde reacts with 2-cyclohexen-1-one (**14**) to give exclusively a 1,4-addition product (equation 4).[8] Both the solvent and the nature of the protecting group affect the regioselectivity in the reactions of anions (**9**) with 4-methyl-3-penten-2-one (**15**). For instance, in THF the 1,2-adduct (**16**) is formed in 74% yield (equation 5), while in ether only the 1,4-addition product (**17**) is isolated.

The introduction of electron-donating or electron-withdrawing substituents in the *para* position of anion (**18**) strongly influences the regioselectivity in additions to (**15**).[8] In DME the amount of 1,4-addition increases from 0% for the *p*-dimethylamino to 100% for the *p*-cyano derivative. In ether only the 1,4-product (**19**) is observed when the *para* substituent is hydrogen, chloro, trifluoromethyl or cyano. The *p*-OMe derivative in ether gives 70% of (**19**), while the *p*-dimethylamino derivative gives mainly 1,2-product (**20**; equation 6; 86%).

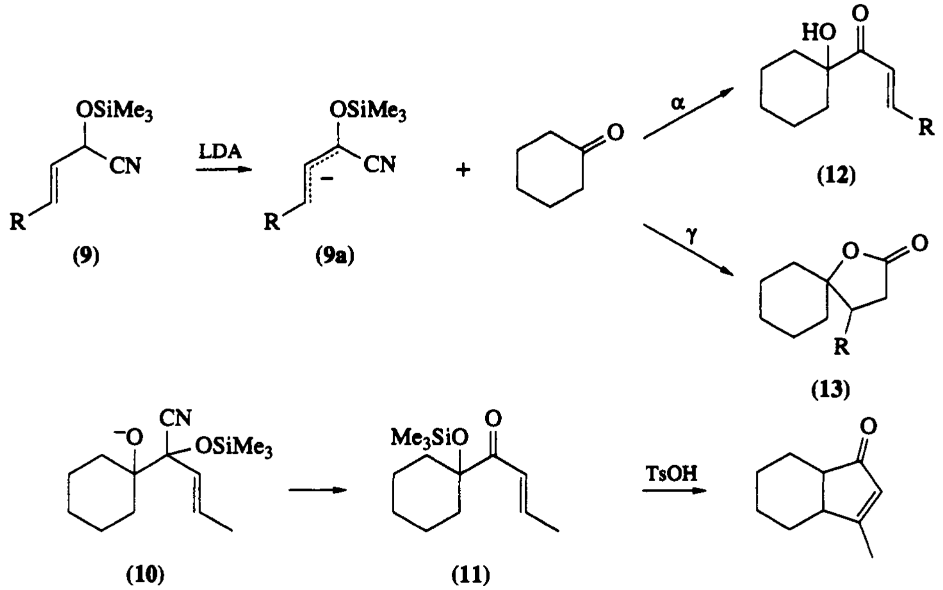
OSiMe3
CN
R
(9)
LDA
OSiMe3
CN
R
(9a)
+
O
α
HO
O
R
(12)
γ
O
O
R
(13)
CN
⁻O
OSiMe3
(10)
Me3SiO
O
(11)
TsOH
O

**Scheme 11**

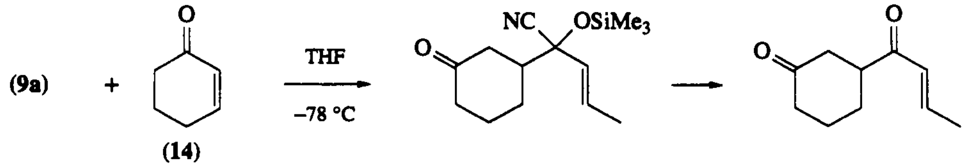
(9a)
+
O
(14)
THF
−78 °C
NC
OSiMe3
O
O
O

(4)

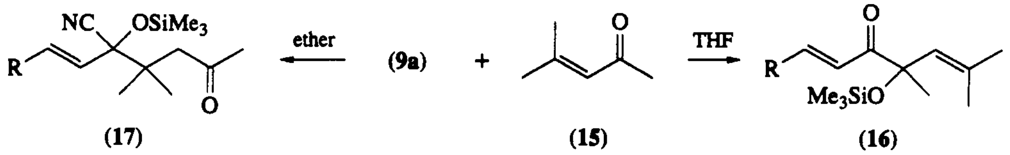
NC
OSiMe3
R
O
(17)
ether
(9a)
+
O
(15)
THF
O
R
Me3SiO
(16)

(5)

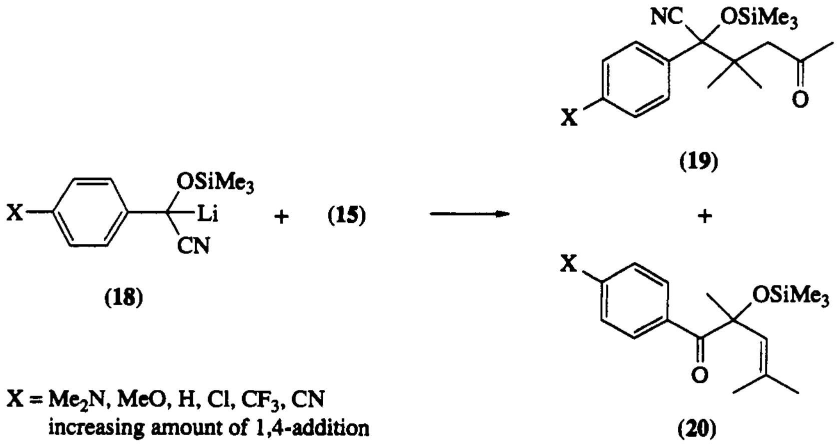
NC
OSiMe3
X
O
(19)
X
OSiMe3
Li
CN
(18)
+
(15)
+
X
OSiMe3
O
(20)

X = $Me_2N$, MeO, H, Cl, $CF_3$, CN
increasing amount of 1,4-addition

(6)

Addition of the α,β-unsaturated anion (**21**) to the Michael acceptor (**22**), in which either alkylation or 1,4-addition is possible, affords only the Michael product. Internal alkylation of the intermediate ester enolates leads to cyclopropyl derivatives (equation 7).[8] Terpenoid polyenes are prepared through conjugate addition of the lithiated protected cyanohydrins (**23**) to dienyl sulfoxide (**24**; equation 8).[8]

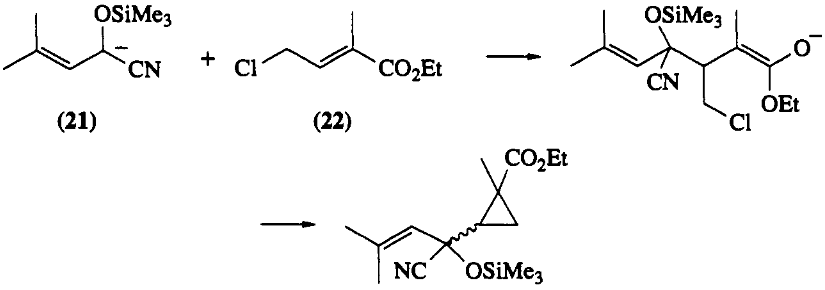
OSiMe3
CN
+
Cl
CO2Et
OSiMe3
O−
CN
Cl
OEt
CO2Et
NC
OSiMe3

(**21**) (**22**)

(7)

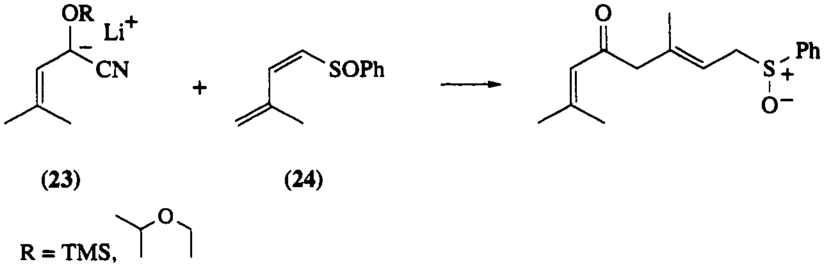
OR
Li+
CN
+
SOPh
O
Ph
S+
O−

(**23**) (**24**)

R = TMS,

(8)

### 2.4.3.1.3 Alkylation with R—X

Anions (**25**) derived from aryl and heterocyclic aldehydes have been used by Hunig *et al.* for the preparation of a large number of ketones in which one residue is aromatic or heterocyclic (equation 9).[8] In view of the competition between displacement and elimination so frequently encountered in reactions of nucleophiles with secondary halides, it is striking that alkylation of (**25**; R = Ph) proceeds well even with a tertiary iodide. 1-Bromo-4-*t*-butylcyclohexane reacts with (**25**) to give the *trans* product (**26**) with inversion of configuration (equation 10).

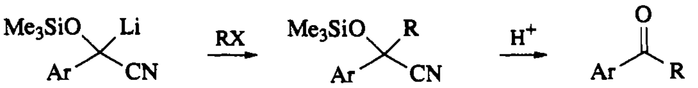
Me3SiO
Li
Ar
CN
RX
Me3SiO
R
Ar
CN
H+
O
Ar
R

(**25**)

(9)

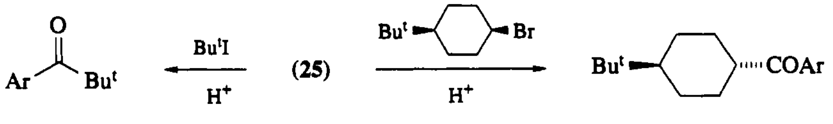
O
Ar
Bu^t
Bu^tI
H+
(25)
Bu^t
Br
H+
Bu^t
COAr

(**26**)

(10)

An intramolecular $S_N2$ displacement at a neopentyl center in (**27**) gave (**28**), a precursor for the total synthesis of steroids (equation 11).[8]

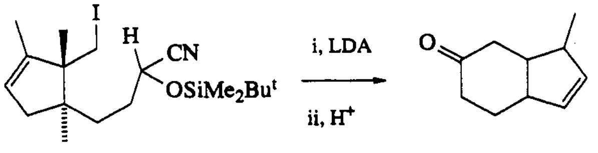
I
H
CN
OSiMe2Bu^t
i, LDA
ii, H+
O

(**27**) (**28**)

(11)

#### 2.4.3.1.4 Miscellaneous reactions of O-silylated cyanohydrins

Oxidation of a cyanohydrin derived from a conjugated aldehyde (as the O-TMS derivative) using pyridinium dichromate (PDC) in DMF gave an α,β-unsaturated lactone ($\delta^2$-butenolide) as the major product (equation 12).[68] Simple nonconjugated cyanohydrins are not satisfactory substrates for the synthesis of acyl cyanides using PDC, because they seem to add to the initially formed acyl cyanides, leading ultimately to cyanohydrin esters. Oxidation of cyanohydrin to acyl cyanides can be carried out either by means of manganese dioxide,[69] ruthenium-catalyzed oxidation with *t*-butyl hydroperoxide[70] or NBS.[71]

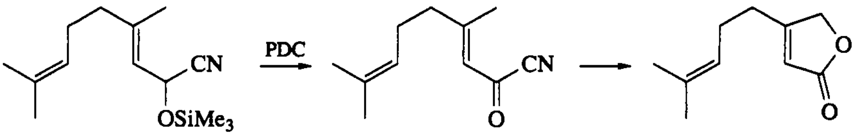

(12)

Tetronic acids and β-keto-γ-butyrolactones are easily prepared by reaction of an *O*-trimethylsilylated cyanohydrin with α-bromo esters in the presence of a Zn–Cu couple in a Reformatsky-type reaction (Scheme 12).[72,73]

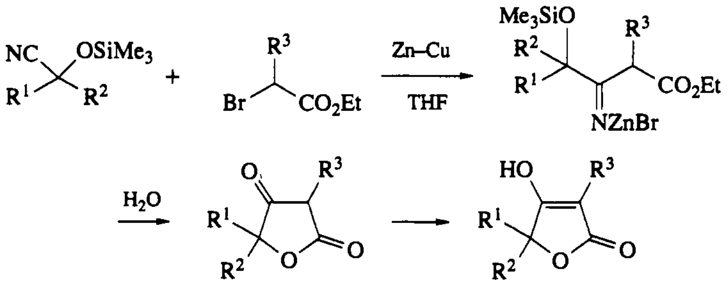

Scheme 12

Acyloins are prepared in high yields by attack of a Grignard reagent on the cyano group of *O*-trimethylsilylated cyanohydrins. The method is particularly useful for the preparation of unsymmetrical acyloins.[74]

### 2.4.3.2 Cyanohydrin Ethers and Esters

Acid-catalyzed addition of aliphatic, aromatic or heteroaromatic cyanohydrins to ethyl vinyl ether, *n*-butyl vinyl ether or dihydro-4*H*-pyran provides base stable, protected cyanohydrin derivatives.[9] Phase transfer catalyzed alkylation of aliphatic cyanohydrins with allylic bromides gave α-substituted α-allyloxyacetonitrile.[75] Carbonyl compounds react with cyanide under phase transfer catalysis to give cyanohydrin anions, which are trapped by an acyl chloride or ethyl chloroformate to give acyl- or alkoxycarbonyl-protected cyanohydrins respectively.[34] The reduction of the carbonyl group of an acyl cyanide by $NaBH_4$ under phase transfer conditions followed by esterification serves as an alternative route to aldehyde-derived cyanohydrin esters.[76]

Cyanation of acetals was achieved either by means of *t*-butyl isocyanide or β-trimethylsilylethyl isocyanide in the presence of titanium(IV) chloride (equation 13)[77] or by TMS-CN in the presence of electrogenerated acid.[78]

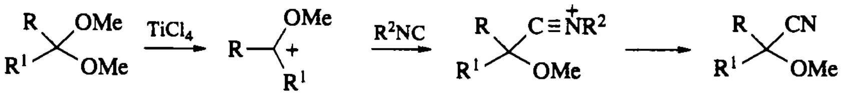

(13)

#### 2.4.3.2.1 1,2-Addition to aldehydes and ketones

The condensation of cyanohydrin ethers with aldehydes or ketones provides α-hydroxy ketones.[9] *O*-Benzoyl-protected cyanohydrins react with aldehydes to give α-hydroxy ketones *via* intramolecular deprotective benzoylation analogous to TMS-protected cyanohydrins (Scheme 10).[33]

A comparative study was reported using 1,3-dithianes and *O*-benzoylated cyanohydrins respectively for the synthesis of several analogs of secoisoquinoline alkaloids bearing a dimethylamino side chain and a benzilic or reduced benzilic group.[79]

### 2.4.3.2.2 1,4-Addition to α,β-unsaturated carbonyl compounds

The anions of protected cyanohydrins derived from saturated aliphatic aldehydes undergo competitive 1,2- and 1,4-addition to unsaturated carbonyl electrophiles. The proportion of the adducts appears to vary as a function of both structure and solvent. Steric interactions that favor dissociation of the reversibly formed 1,2-addition product increase the proportion of the 1,4-addition product. For example, increasing the size of the substituent R in a protected cyanohydrin (**29**) from methyl to *n*-pentyl increases the ratio of 1,4-addition product (**30**) to 1,2-addition product (**31**) from 1.5:1 to 2.7:1 (equation 14).[62]

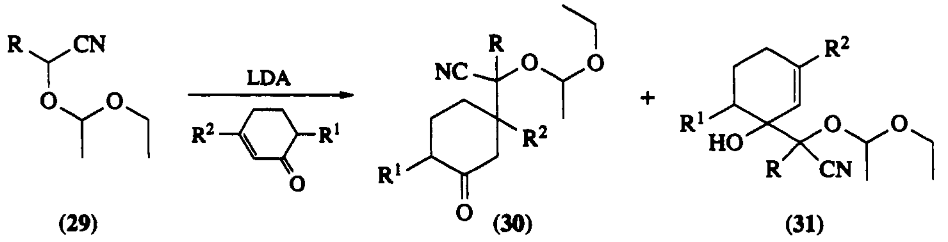

(14)

Conjugate addition of an aryl cyanohydrin has been used in the synthesis of tetracyclines, 13-oxyprostanoids and β-cuparenone.[8]

### 2.4.3.2.3 Alkylation with R—X

The alkylation of protected cyanohydrin anions constitutes an excellent method for ketone synthesis.[9,62] Generally the anions are generated from aliphatic or aromatic aldehyde protected cyanohydrins with LDA under nitrogen at –78 °C. The addition of an alkyl halide produces the protected ketone cyanohydrin. The carbonyl group is then liberated by successive treatment with dilute acid and dilute aqueous base. This method is applicable for the synthesis of buflomedil.[80]

Regiocontrolled synthesis of 2,4-disubstituted pyrroles is achieved using the alkylation of a protected cyanohydrin with an alkynyl bromide (equation 15).[81]

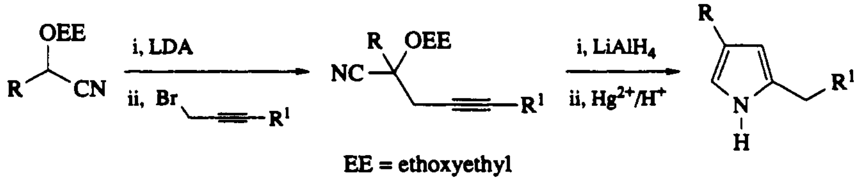

(15)

The side chain of brassinolide, (20*S*,22*R*), can be stereoselectively introduced by alkylation ($S_N2$) of the (20*R*)-tosyloxy steroid with a protected cyanohydrin followed by the stereoselective reduction of the resulting 23-en-22-one.[82]

α-Hydroxy-γ-butyrolactones are prepared by the alkylation of a protected cyanohydrin with an epoxide.[83] Maldonado *et al.* applied this method to the synthesis of α-bisbololone (equation 16).[84]

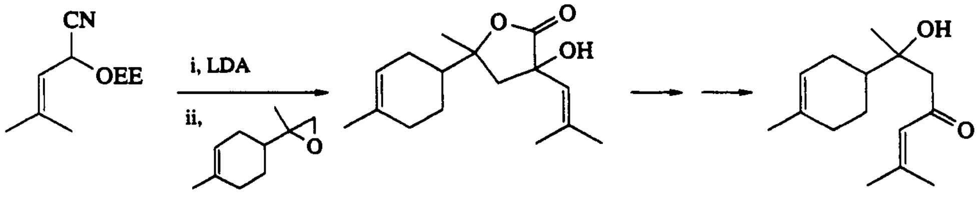

(16)

Of special interest is the use of protected cyanohydrins in the formation of carbocyclic rings. Ring closure of an acyclic intermediate to form a five-membered ring (75–85%) has been described in the synthesis of prostaglandins (equation 17).[85,86] In addition this method is applicable to the formation of cyclopropyl,[87] cyclobutyl[85] and cyclohexyl rings (60–70%).[88]

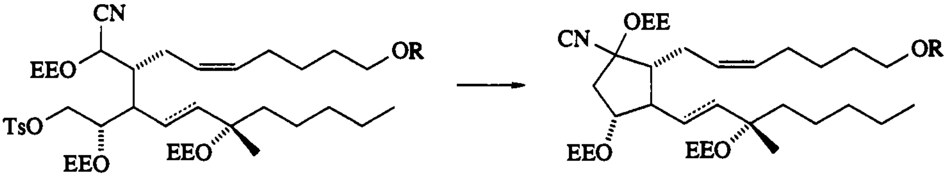

(17)

Macrocyclic ketones are prepared by intramolecular alkylation without the use of high dilution conditions.[89] These cyclizations have the following characteristic features:[85,87] (i) the alkylation is irreversible and very rapid, and the cyclized product is stable under basic conditions. Therefore, this method of cyclization requires short reaction times and no high dilution conditions and provides the macrocycle in a satisfactory yield; (ii) the carbanion derived from an α,β-unsaturated cyanohydrin acts *via* α-attack, so that γ-attack and isomerization of double bonds are not observed; and (iii) the cyclized products are easily converted by mild acid and base treatment to the corresponding enones in high yields with excellent stereoselectivity. This cyclization method can be applied to the synthesis of a wide variety of naturally occurring compounds such as the pheromone periplanone B,[90] the sesquiterpenes acoragermacrone (equation 18),[91] germacrone,[92] humulene,[93] mukulol,[91] germacrone lactones such as costunolide and haagenolide,[94] (*E*,*E*)- and (*E*,*Z*)-2,6-cyclodecadienones,[95] *trans*-2-cyclopentadecanone, a precursor of the natural products (+)-muscone and exaltone,[89] zearalenone,[96] dihydroxy-*trans*-resorcylide[97] and the 14-membered (*E*,*E*,*E*)-macrocyclic triene, a precursor for the Diels–Alder synthesis of a steroid skeleton (equation 19).[98] Such cyclizations have been carried out on a 60 mmol scale.[90]

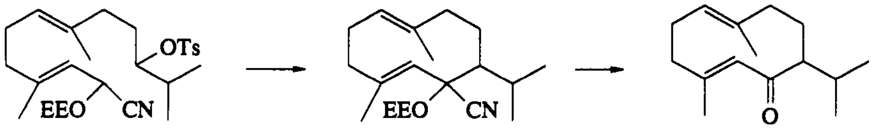

(18)

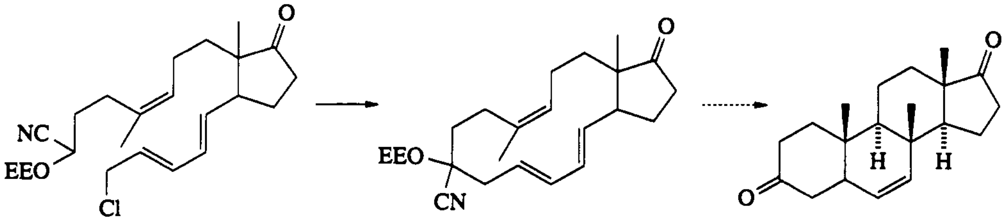

(19)

### 2.4.3.2.4 Miscellaneous reactions

The classic $S_NAr$ substitution of activated aryl halides by protected cyanohydrin anions provides substituted benzophenones.[8] Another procedure for the arylation of protected cyanohydrin anions involves the use of aromatic substrates activated as their π-chromium tricarbonyl complexes.[9,99] Addition of the anion of (**32**) to the 1,3-dimethoxybenzene complex, for example, leads principally to the *meta*-substituted isomer (**33**; equation 20). Preferential *meta* regioselectivity is also noted with other π-chromium tricarbonyl complexes of arenes. Other arylations of cyanohydrin anions include interesting but synthetically limited additions at the α-position of quinoline *N*-oxides.[8] In a similar manner, cyanohydrin carbonates of aromatic aldehydes react with *N*-oxides of quinoline and isoquinoline.[34]

β,γ-Unsaturated ethers of cyanohydrins, on formation of lithio derivatives, undergo a 2,3-sigmatropic rearrangement[8] to form β,γ-unsaturated ketones (equation 21), whereas benzylic ethers of aliphatic cyanohydrins gave *o*-methylaryl ketones.[8] The method has been used to prepare 3-methyl-1-(3-methyl-2-furyl)-1-butanones, a naturally occurring $C_{10}$ terpene,[8] α-allenic ketones[8] and enolic monoethers of γ-keto aldehydes *via* 2,3-sigmatropic rearrangement of their respective carbanions.[8]

An annelation reaction of α,β-unsaturated carbonyl compounds with cyanophthalides (**34**) can be used for the construction of naphthoquinone and anthraquinone systems in biologically active natural

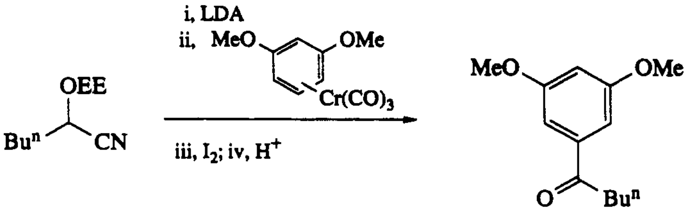

(32) (33) (20)

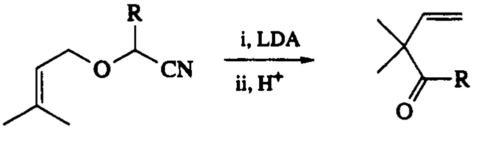

(21)

products.[100] For example, synthesis of racemic 1-fluoro-, 4-fluoro-, 2,3-difluoro- and 1,4-difluoro-4-demethoxy-daunomycinones (**35**) is achieved by annelation of highly functionalized quinone monoketal with the appropriate cyanophthalide anion followed by deprotection (equation 22).[101,102] Annelative reactions of arynes generated *in situ* from haloarenes and LDA in THF with lithiated cyanophthalide provide a convenient way of preparing a wide variety of anthraquinones and anthracyclinones.[103] More recently, Yoshii *et al.* utilized a tetracyclic cyanophthalide anion in an annelative reaction with 5-*t*-butoxy-2-furfurylideneacetone in their synthesis of (±)-granticin.[104]

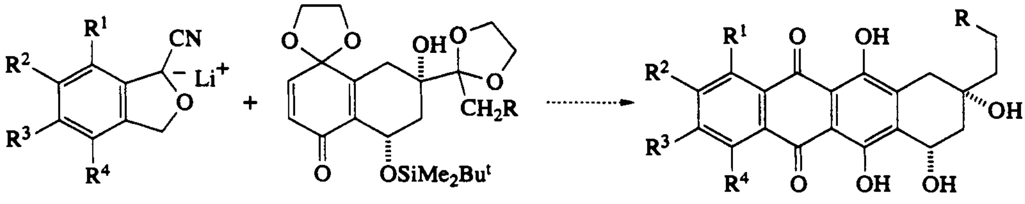

(34) (35) (22)

2-Substituted cyclohexenones are prepared by the alkylation of 2-cyano-6-methoxytetrahydropyran, a cyclic protected cyanohydrin (Scheme 13).[105]

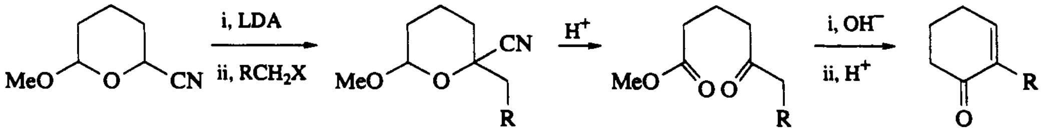

**Scheme 13**

An interesting variant of these Michael-type additions is the 1,6-addition of the anion of type (**29**) to a dienyl sulfone as a route to tagetones[106] and 1,4-addition to nitrostyrene to form β-nitro ketones.[107] A key step in a synthesis of 11-deoxyanthracyclinone involves the regioselective reaction of complexed styrene with lithiated protected acetaldehyde cyanohydrin.[108]

## 2.4.4 α-(DIALKYLAMINO)NITRILES

From a historical perspective, the α-(dialkylamino)nitrile anions were the first acyl anion equivalents to undergo systematic investigation.[9] More recent studies indicate that anions of α-(dialkylamino)nitriles derived from aliphatic, aromatic or heteroaromatic aldehydes intercept an array of electrophiles[9] including alkyl halides, alkyl sulfonates, epoxides, aldehydes, ketones, acyl chlorides, chloroformates, unsaturated ketones, unsaturated esters and unsaturated nitriles. Aminonitriles are readily prepared and their anions are formed with a variety of bases[9] such as sodium methoxide, KOH in alcohol, NaH, LDA, PhLi, sodium amide, 70% NaOH and potassium amide. Regeneration of the carbonyl group can be achieved either by the usual acid hydrolysis or by other mild hydrolytic agents such as copper sulfate,[109] iron(II) sulfate,[109] copper acetate,[110] silver nitrate in $D_2O$–THF–diethyl ether[111] and silica gel.[111]

Aromatic and aliphatic aldehydes in the presence of dialkylamines and an equivalent of acid such as hydrochloric, perchloric or *p*-toluenesulfonic acid give iminium salts, which add cyanide ion to form α-(dialkylamino)nitriles.[9] An alternative preparation involves the reaction of the aldehyde with dialkylamines in the presence of acetone–cyanohydrin, α-(*N*,*N*-dialkylamino)isobutyronitriles,[112] diethyl phosphorocyanidate[113] or TMS-CN.[114] Another route to α-aminonitrile starts with an aldehyde, the salt of an amine and KCN in organic solvents under solid–liquid two-phase conditions by combined use of alumina and ultrasound.[115] Chiral α-aminonitriles were prepared by Strecker-type reactions,[116] cyanosilylation of Schiff's bases,[117] amination of α-siloxynitriles[118] or from an *N*-cyanomethyl-1,3-oxazolidine synthon.[119] Reaction of tertiary amines with $ClO_2$ in the presence of 5.7 mol equiv. of aqueous NaCN as an external nucleophile affords α-aminonitrile.[120]

### 2.4.4.1 1,2-Addition to Aldehydes and Ketones

α-Hydroxy ketones can be prepared by the addition of carbanions derived from easily accessible α-(dialkylamino)nitriles to carbonyl compounds followed by hydrolysis.[121] Optically active α-hydroxy ketones are obtained by the nucleophilic acylation of chiral α-aminonitriles.[122] 1,2-Addition to cyclic ketones, aryl aldehydes and aliphatic aldehydes leads to ethanolamines.[8a] Stereoselectivity in favor of the *threo* isomer occurs with α-(dimethylamino)propionitrile, while reversed stereoselectivity is observed with the open chain Reissert compound (**36**; Scheme 14).[8b] A high degree of stereoselectivity is also observed in the condensation of *N*-benzoyl-2-cyanopiperidine with propanal, a key step in the synthesis of (+)-conhydrine (*erythro*-α-ethyl-2-piperidinemethanol) (**37**; Scheme 15).[8]

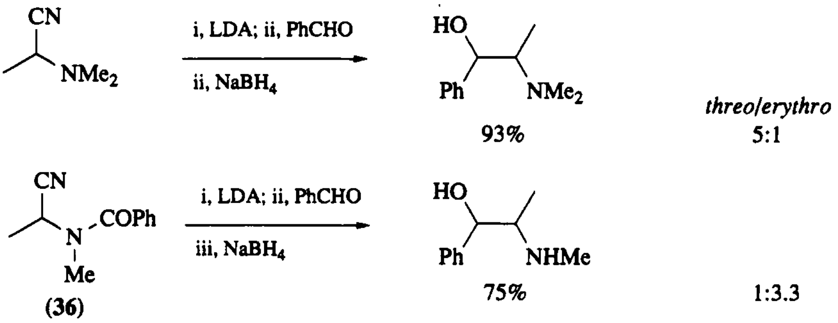

**Scheme 14**

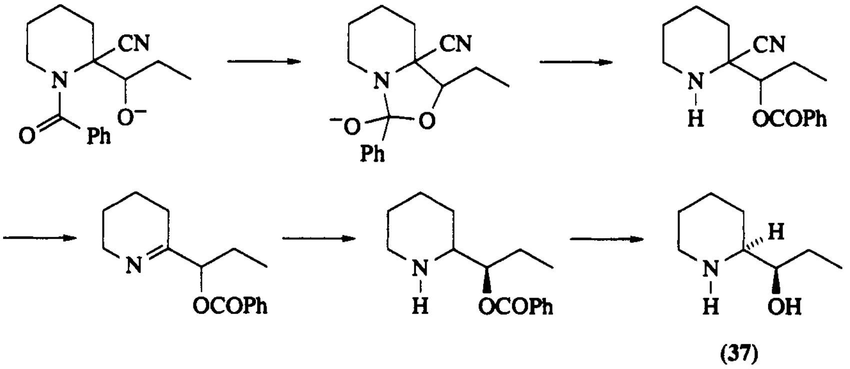

**Scheme 15**

Unsymmetrical amino ketones were prepared by 1,2-addition of an α-aminonitrile to an aldehyde (Scheme 16).[123]

α-(Dialkylamino)nitriles (**38**) can react as either acyl anion or β-homoenolate ion equivalents on varying the reaction conditions.[8] This constitutes a general entry to the formation of cyclopentenone derivatives (Scheme 17).

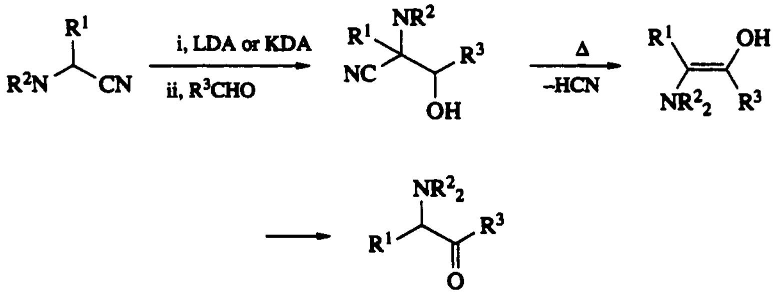

Scheme 16

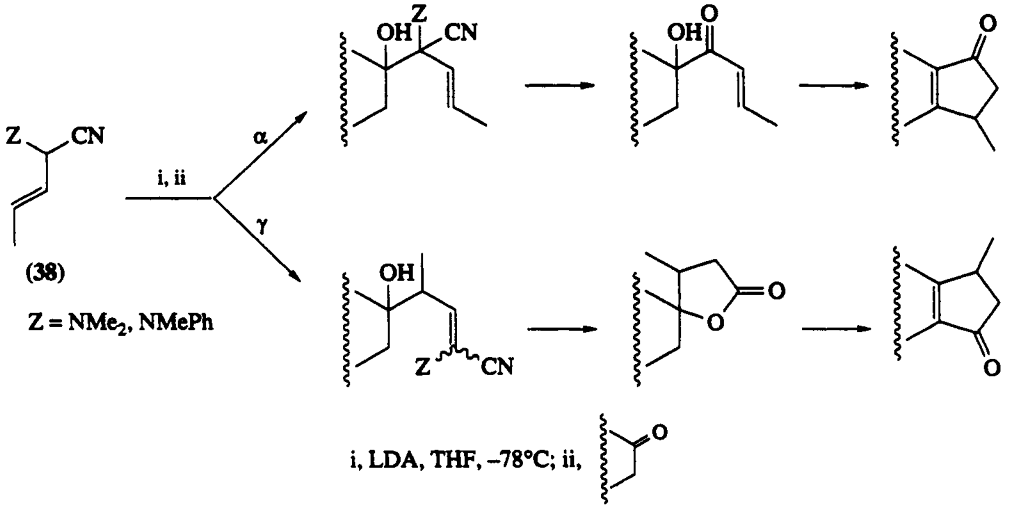

(38)

Z = $NMe_2$, NMePh

i, LDA, THF, −78°C; ii,

Scheme 17

The lithium salt of the unsaturated α-aminonitrile (39) reacts as a homoenolate (γ-attack) with aldehydes or ketones to give 1,2-addition products (40). Deprotonation of the masked carbonyl affords substituted lactones (equation 23).[8]

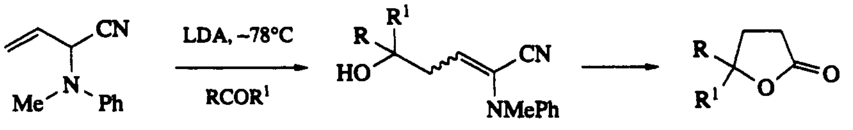

(39) (40) (23)

### 2.4.4.2 1,4-Addition to α,β-Unsaturated Carbonyl Compounds

Addition of α-aminonitriles to an α,β-unsaturated ketone affords 1,4-diketones. High yields are also observed in 1,4-additions to ethyl acrylate or acrylonitrile.[7,109] α-Phenyl-α-(*N*-morpholino)acetonitrile gives good yields of 1,4-adducts with methyl crotonate, methyl methacrylate, diethyl maleate and ethyl propiolate under catalysis of sodium methoxide in THF. Reaction of the lithium salt of (41) with methyl acrylate is reported to give pyrrole derivatives (Scheme 18).

Conjugate addition of the benzoyl anion equivalent (42) to unsubstituted and 2-substituted cyclic enones can be highly stereoselective (equation 24).[124] Lewis acids such as $BF_3{\cdot}Et_2O$, $Ti(OPr^i)_4$ or $ZnCl_2$ make possible the Michael addition of (42) even to β,β-disubstituted α-enones.[125]

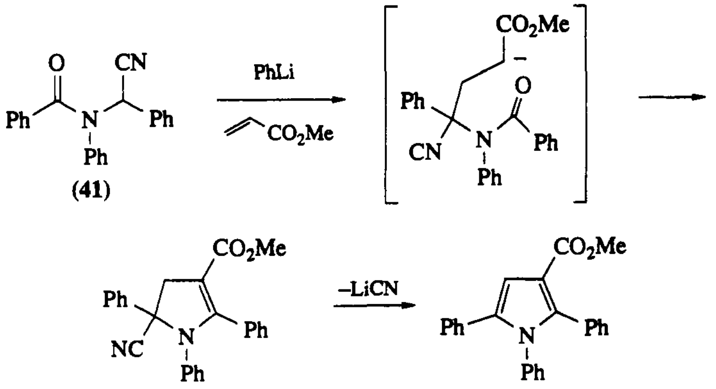

Scheme 18

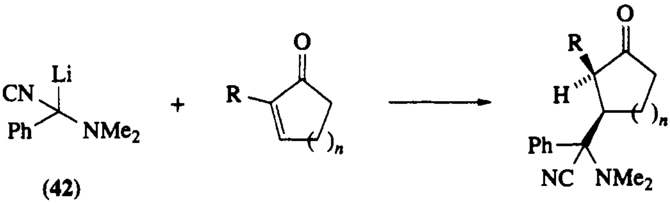

(24)

### 2.4.4.3 Alkylation with R—X

Alkylation of metallated α-(dialkylamino)nitriles with alkyl halides, epichlorohydrin, allyl halides or ethyl bromoacetate followed by hydrolysis furnishes an array of ketones in good yield.[8,9] For example, reaction of (**42**) with benzyl chloride leads to the formation of deoxybenzoins.[8] Alkylation of α-(dialkylamino)nitriles is also possible if the latter are derived from aliphatic aldehydes.[8,9]

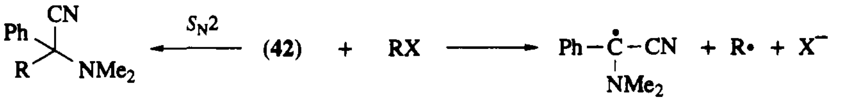

Scheme 19

The alkylation of (**42**) with chiral 1-methylheptyl halides in liquid ammonia proceeds with partial inversion of configuration. The accompanying racemization is dependent on the basic reagent, on the configuration of the alkylating agent and on the extent of participation of the electron transfer process in the alkylation (Scheme 19).[111]

The key step for the conversion of open-chained α,β-unsaturated aldehydes to their corresponding cyclized carbonyl compounds involves the regioselective alkylation of (**39**) with dihalides.[126]

2-Alkyl- and 2,6-dialkyl-piperidine alkaloids have been synthesized by the alkylation of cyclic α-aminonitriles such as *N*-benzyl-2-cyano-6-methylpiperidine[127,128] or 1-benzyl-2,6-dicyanopiperidine.[129]

Unsaturated α-(dialkylamino)nitriles (**43**) form ambident anions which are alkylated at either the α- or γ-position.[8] Alkylation of (**43a**) with methyl iodide is completely selective to give only the γ-alkylated regioisomer, while alkylation of (**43b**) with ethyl bromide gave exclusively the α-alkylated product (equation 25). The structure of the secondary α-amino group as well as the steric bulk of the alkylating reagent influence the regioselectivity. With dimethylamine or piperidine as the amine component, the alkylation with methyl iodide gives approximately equal amounts of α- and γ-alkylation product, while with the morpholino derivative (**43b**) α-alkylation is the major product. Increased amounts of γ-alkylation are observed with isopropyl bromide.

Ring closures through intramolecular alkylation of Reissert compounds have been described.[8] The sequential dialkylation of dimethylaminoacetonitrile (**44**) first with methallyl chloride and then isopentenyl bromide, followed by hydrolysis and isomerization, affords artemesia ketone in 77% overall yield (Scheme 20).[130]

3-Substituted pyrazoles can be prepared by the alkylation of α-(dimethylamino)nitriles with bromodiethyl acetal followed by heating with hydrazine dihydrochloride in ethanol.[131] 3,5-Dialkylpyrazoles were

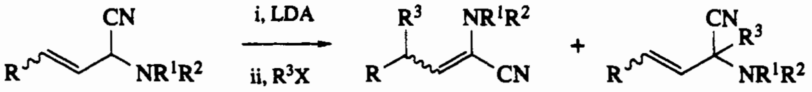
CN
NR¹R²
R
i, LDA
ii, R³X
R³
NR¹R²
CN
+
R³

(25)

**(43a)** R = H; $R^1$ = Me; $R^2$ = Ph
**(43b)** R = Me; $R^1R^2$ = $-(CH_2)_2O(CH_2)_2-$

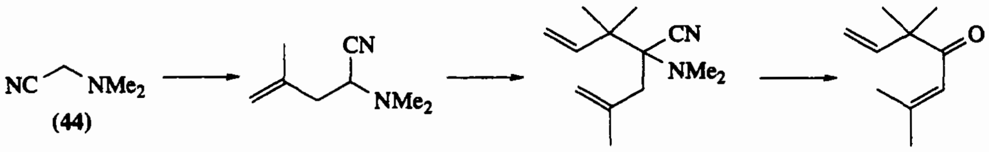
NC
NMe2
(44)
CN
NMe2
CN
NMe2
O

**Scheme 20**

synthesized by reaction of α,γ-dialkyl-α,γ-dipyrrolidinylglutaronitriles with hydrazine.[132] Vinyl ketones in general and the himachalene skeleton specifically can be synthesized by the alkylation of (**45**) with an alkyl halide, *e.g.* (**46**; Scheme 21).[133]

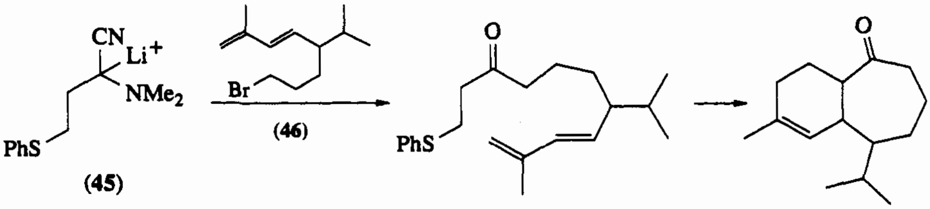
CN
Li+
NMe2
PhS
(45)
Br
(46)
O
PhS
O

**Scheme 21**

Reaction of 1-benzyl-2,5-dicyanopyrrolidine with an alkyl halide gives unsymmetrical 2,5-dialkylated products (**47**) in high yield. Hydrolysis of (**47**) provides a γ-diketone, which serves as a precursor for jasmone analogs (Scheme 22).[134]

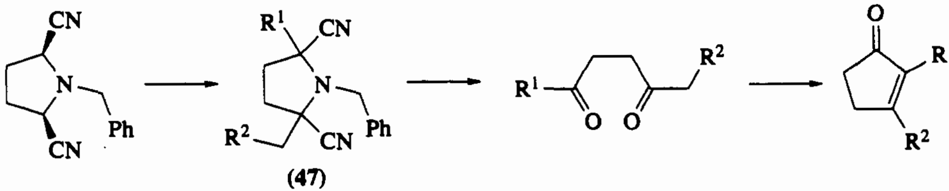
CN
N
Ph
CN
R¹
CN
N
Ph
R²
CN
(47)
R¹
R²
O
O
O
R¹
R²

**Scheme 22**

δ-Diketones and their aldol-derived cyclohexenones are obtained from alkylation of 1-benzyl-2,6-dicyanopiperidine followed by hydrolysis.[135,136] This dicyano analog of (**47**) provides a new method for the synthesis of *trans*-2-methyl-6-undecylpiperidine (solenopsin), α-propylpiperidine (coniine) and other 2,6-dialkylpiperidine alkaloids.[129]

The pyrrolidine synthon (**48**)[137] is useful for the chiral synthesis of pyrrolizidine,[138] pyrrolidine,[139,140] indolizidine[138] and azabicyclic alkaloids[141] (see Scheme 23).

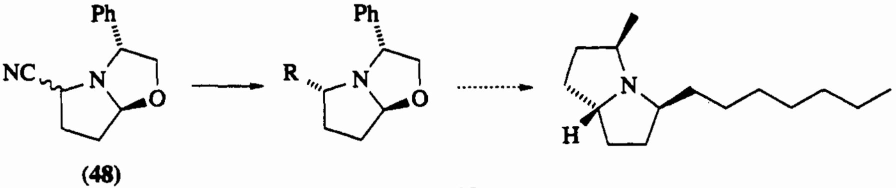
Ph
NC
N
O
(48)
Ph
R
N
O
N
H

**Scheme 23**

In a similar manner, the 2-cyano-6-oxazolopiperidine synthon is useful for the chiral synthesis of indolizidine (monomerine I),[142] piperidine [(+)- and (–)-coniine and dihydropinidine][143] and quinolizidine alkaloids.[144,145] 2-Hydroxymethyl-1-amino-1-cyclopropanecarboxylic acid[146] (–)-(2*R*)-hydroxy-(3*S*)-nonylamine[147] and α-substituted phenylethylamines[148] are obtained in optically active form from (–)-*N*-cyanomethyl-4-phenyloxazolidine.

Alkylation of the α-aminonitrile (**49**) with propyl bromide followed by reductive decyanation gives the key intermediate (**50**), which on treatment with diethyl cyanophosphonate leads to the formation of a new α-aminonitrile (**51**). Compound (**51**) reacts with K and 18-crown-6 in THF to form gephyrotoxin-223AB, an indolizidine alkaloid (Scheme 24).[149]

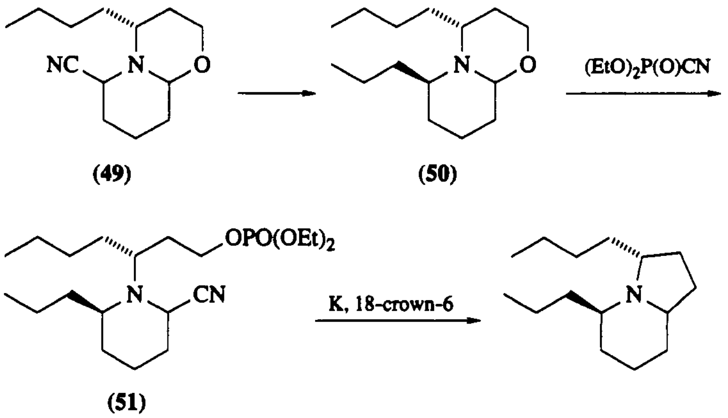

**(49)** **(50)** **(51)**

Scheme 24

α-Ethoxyurethanes react with TMS-CN in the presence of Lewis acid to afford the corresponding α-cyanourethanes, analogous to α-aminonitrile, which *via* the carbanion are transformed to α-alkylated products in moderate yield.[150] This synthon is useful for the synthesis of coniine and *trans*-quinolizidines.[151]

### 2.4.4.4 Miscellaneous Reactions of α-Aminonitriles

1,2,5-Trisubstituted pyrroles are obtained in 50–100% yields by the addition of open chain analogs of a Reissert compound to the vinyltriphenylphosphonium cation, with subsequent cyclization by an intramolecular Wittig reaction and base-catalyzed elimination of HCN (Scheme 25).[152]

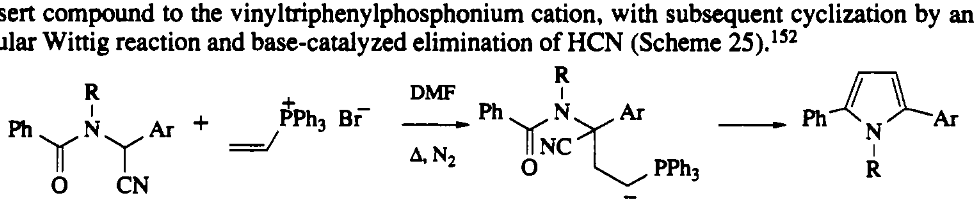

Scheme 25

Allylamines are prepared regio- and stereo-selectively by reaction of Grignard reagents with an α-aminonitrile.[153] α-Phenyl-4-morpholinoacetonitrile (**52**) reacts with 4-chlorobenzoyl chloride to give diketone (**53**; equation 26).[109]

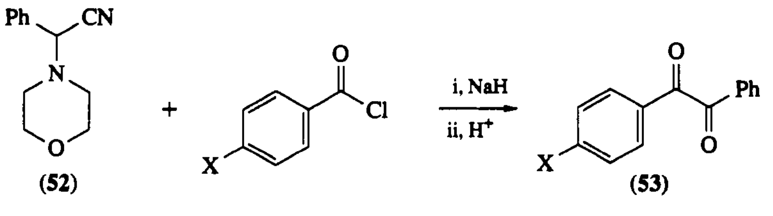

**(52)** **(53)**

(26)

The phenylcyanoamine derivative (**54**) has been used as a benzoyl anion equivalent in an intramolecular process to effect the replacement of the hydroxy group of enols or phenols by the benzoyl group (Scheme 26).[154]

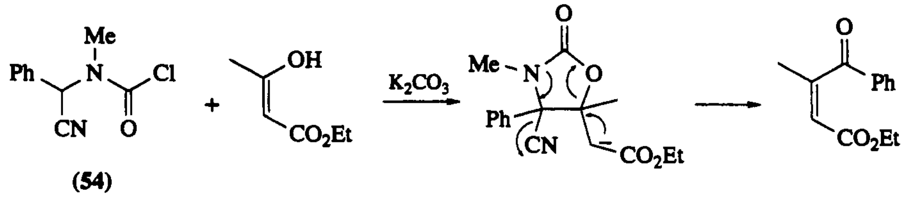

**Scheme 26**

A particularly interesting development involves the alkylation of the nitrogen of an α-aminonitrile with allylic halides and subsequent 2,3-sigmatropic rearrangement of the allylic ammonium ylides.[9] This method provides a convenient route to 2-methyl-3-formylpyridines or 2-methyl-3-acylpyridines. With the use of 1-(cyanomethyl)pyrrolidine, the reaction with various allylic halides proceeds with a stereochemical bias that varies with the substrate to give β,γ-unsaturated aldehydes, as illustrated in the preparation of (**55**; equation 27). The procedure also succeeds with benzylic halides to furnish *ortho*-oriented carbonyl and methyl groups on an aromatic ring.

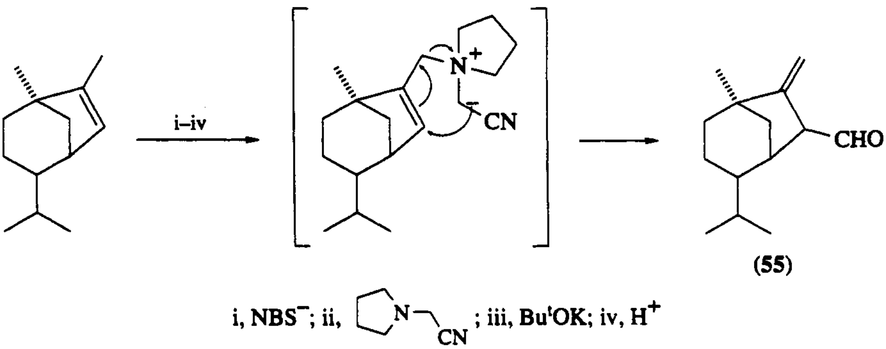

(27)

i, NBS$^-$; ii, (1-(cyanomethyl)pyrrolidine); iii, Bu$^t$OK; iv, H$^+$

Ester-stabilized ammonium ylides of α-(dialkylamino)nitriles, formed by treatment of ammonium salts with DBU (1,5-diazabicyclo[5.4.0]undec-5-ene), undergo spontaneous fragmentation to give α,β-unsaturated nitriles.[8]

Asymmetric induction is observed in 2,3-sigmatropic rearrangements *via* chiral ammonium chlorides such as (**56**), which was obtained from (*S*)-proline ethyl ester.[8] Ylide formation with potassium *t*-butoxide, rearrangement and acid hydrolysis of the aminonitrile affords (*R*)-(+)-methyl-2-phenyl-3-butenal (90% optical purity) (equation 28). Application of this sequence furnishes intermediates in a new approach to steroids, to various sesquiterpenes such as α-sinsenal and to a highly substituted pyridine, as part of an impressive synthesis of streptonegrin.[9]

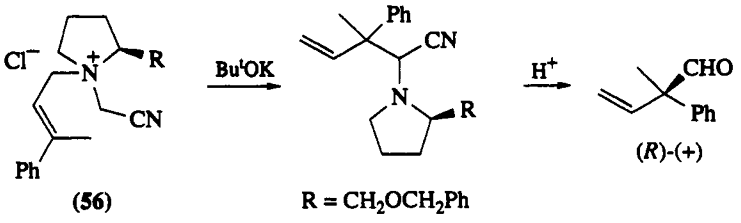

(28)

## 2.4.5 CYANOPHOSPHATES

Cyanophosphates can be prepared from aromatic or α,β-unsaturated aldehydes with diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$) in THF using LiCN[37] or LDA as a base.[155] Deprotonation of a cyanophosphate with Bu$^n$Li in the presence of tetramethylethylenediamine in THF at −78 °C, followed by reaction with alkyl (or acyl) halides, carbonyl compounds and α,β-unsaturated nitriles or esters, as well as cyanophosphates themselves, affords alkylated (or acylated) products, mixed benzoin and acyloin phosphates, polysubstituted cyclopropanes and diarylfumaronitriles in moderate yields respectively (Scheme 27).[37,156]

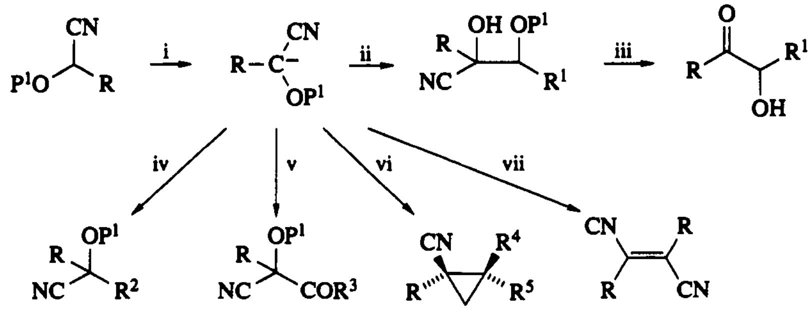

i, Bu$^n$Li/TMEDA; ii, $R^1CHO$; iii, NaOH; iv, $R^2X$; v, $R^3COX$;
vi, $CH_2{=}CR^4R^5$, $R^4$ = H, Me, $R^5$ = CN, $CO_2Et$; vii, $RCH(OP^1)CN$

Scheme 27

## 2.4.6 α-THIONITRILES

α-Thionitriles also serve as acyl anion equivalents. The parent compound $RSCH_2CN$ is accessible by the reaction of $RSCH_2Cl$ with $Hg(CN)_2$, or by an $S_N2$ process involving $ClCH_2CN$ and RSNa. Aliphatic nitriles on treatment with two equivalents of LDA followed by RSSR afford α-thionitriles (**57**), as does the reaction of thioacetals (alkyl or aryl) with TMS-CN in the presence of $SnCl_4$ (Scheme 28).[157] They can also be prepared by the reaction of thioacetals with $Hg(CN)_2$ and iodine[158] or from a 1-(phenylthio)vinylsilane with TMS-CN *via* a thionium ion intermediate.[159] Alternatively such compounds are prepared by the reaction of an aldehyde with phenyl thiocyanate and tributylphosphine.[160]

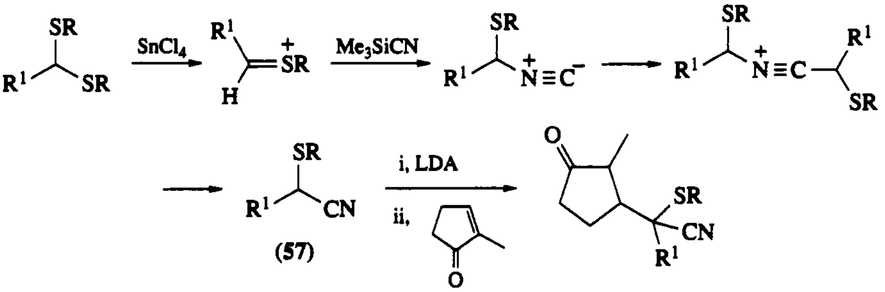

(**57**)

Scheme 28

Reaction of an α-(phenylthio)nitrile with base, such as LDA, followed by an aldehyde or a ketone gives a 1,2-addition product in good yield, while the use of α,β-unsaturated aldehydes and ketones usually leads to the 1,4-addition product.[161] Conjugate addition of the α-(phenylthio)acetonitrile anions to 2-methyl- or 2-phenyl-2-cyclohexenones or 2-methyl-2-cyclopentenones, followed by acid quenching under kinetic control, leads to different ratios of *cis*- and *trans*-2,3-disubstituted cyclanones depending on ring size.[162]

An intramolecular alkylation of α-thionitrile (**58**) leads to a macrocycle, an intermediate for the synthesis of the sesquiterpene (–)-dihydrogermacrene D (Scheme 29).[163] Alkylation of an α-cyanosulfone followed by reduction gave α-substituted acetonitriles.[164] Cyclization of a 1,3-dibromoalkane with (methylthio)acetonitrile yields a 1-cyano-1-(methylthio)cyclobutane, a precursor for the synthesis of cyclopentanones.[165] Reaction of α-(arylthio)nitriles with aryl halides in the presence of LDA and $Bu_3P$ at –78 °C affords cyanostilbenes.[160]

A chiral cyclopentenoid building block (**60**) has been reported to result in a one-pot cyclization process from epoxide (**59**) (readily accessible from (*R*,*R*)-(+)-tartaric acid) with the carbanion derived from (phenylthio)acetonitrile (equation 29).[166]

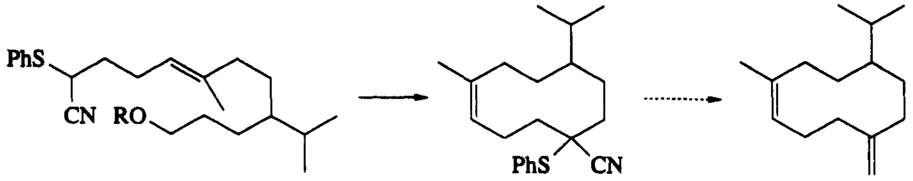

(58)

Scheme 29

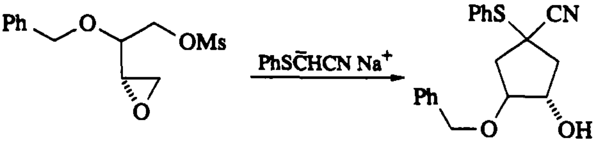

(59) (60)

(29)

## 2.4.7 α-(ARYLSELENO)NITRILES

Cyanoselenation of aldehydes with phenyl selenocyanate in the presence of $Bu_3P$ gave α-(arylseleno)nitriles.[167] Selenylation of nitriles after treatment with 2 equiv. of base also led to the formation of α-selenonitriles.[168] Their lithiated derivatives undergo smooth alkylation with methyl iodide (80%) and Michael addition to cyclohexenone in 90% yield (Scheme 30).[167]

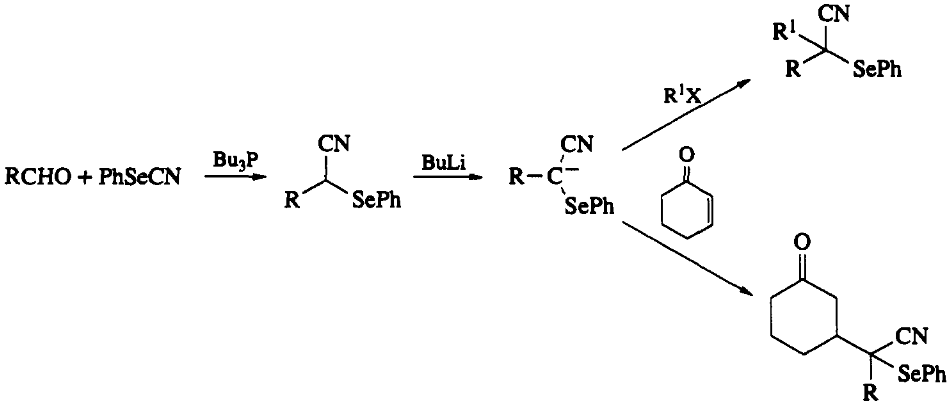

Scheme 30

## 2.4.8 α-HETEROSUBSTITUTED PHOSPHONATE CARBANIONS AS ACYL ANION EQUIVALENTS

A system analogous to a cyanohydrin is a siloxyalkylphosphonate. Thus, the diethyl 1-phenyl-1-trimethylsiloxymethylphosphonate carbanion derived from (**61**) on treatment with LDA[169] acts as an effective acyl anion equivalent in the preparation of α-hydroxy ketones and ketones.[38] The phosphonate (**61**) is formed from triethyl phosphite, benzaldehyde and TMS-Cl in excellent yield.[170]

### 2.4.8.1 1,2-Addition to Aldehydes and Ketones

When the carbanion of (**61**) reacts with aldehydes or ketones, a 1,4-silicon migration from O to O with subsequent loss of diethyl phosphite is observed (Scheme 31).[38] Hydrolysis of the resulting rearranged product leads to α-hydroxy ketones in good yield.

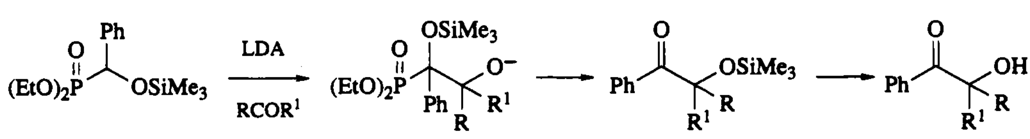

**(61)**

**Scheme 31**

### 2.4.8.2 Alkylation with R—X

Unsymmetrical ketones result from the alkylation of the carbanion generated *in situ* from phosphonate (**61**) with LDA, as shown in equation (30).[171]

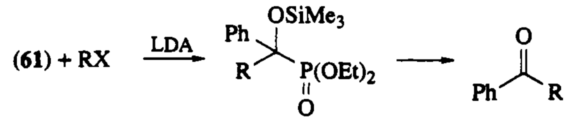

(30)

A new acyl anion equivalent derived from an aldehyde, a secondary amine and diphenylalkylphosphine oxide, *e.g.* (*N*-morpholinomethyl)diphenylphosphine oxide, reacts with aldehydes or ketones to form enamines, which on acid hydrolysis afford aldehydes or ketones (Scheme 32).[172,173] The usefulness of this acyl anion equivalent is demonstrated by the synthesis of dihydrojasmone and (*Z*)-6-henicosen-11-one.[174]

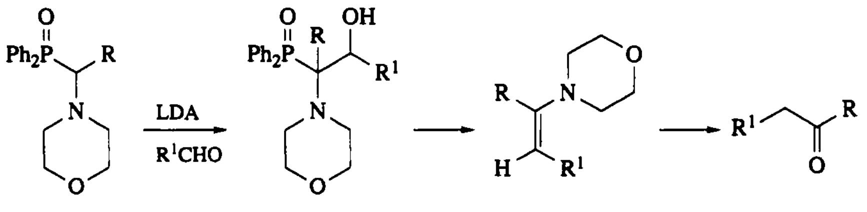

**Scheme 32**

## 2.4.9 DITHIOACETALS AND DITHIANES

In dithioacetals the proton geminal to the sulfur atoms can be abstracted at low temperature with bases such as Bu$^n$Li. Lithium ion complexing bases such as DABCO, HMPA and TMEDA enhance the process. The resulting anion is a masked acyl carbanion, which enables an assortment of synthetic sequences to be realized *via* reaction with electrophiles.[3,12,13,175,176] Thus, a dithioacetal derived from an aldehyde can be further functionalized at the aldehyde carbon with an alkyl halide, followed by thioacetal cleavage to produce a ketone. Dithiane carbanions allow the assemblage of polyfunctional systems in ways complementary to traditional synthetic routes. For instance, the β-hydroxy ketone systems, conventionally obtained by an aldol process, can now be constructed from different sets of carbon groups.[176]

Dithioacetals, 1,3-dithianes or 1,3-dithiolanes are prepared by reaction of the corresponding carbonyl compound in the presence of an acid catalyst (conc. HCl, Lewis acids such as $ZnI_2$, $BF_3{\cdot}Et_2O$, TMS-Cl, *etc.*) with a thiol or dithiol.[177] Silica gel treated with thionyl chloride was found to be an effective as well as selective catalyst for thioacetalization of aldehydes.[178] Thioacetalization can also be achieved using a (polystyryl)diphenylphosphine–iodine complex as a catalyst.[179] Conversion of aldehydes or acetals into 1,3-dithianes is achieved with the aid of organotin thioalkoxides and organotin triflates[180] or with 2,2-dimethyl-2-sila-1,3-dithiane.[181] Direct conversion of carboxylic acids to 1,3-dithianes can be carried out by reaction with 1,3,2-dithiabornenane–dimethyl sulfide and tin(II) chloride[182] or 1,3,2-dithiaborolene with trichloromethyllithium followed by basic hydrolysis.[183]

The dithiane-derived anion can be generated by the action of Bu$^n$Li in THF at –78 °C or with complex bases $NaNH_2$–RONa at room temperature.[184] Lithiated dithiane can also be prepared *in situ* by sonication of *n*-butyl chloride with lithium in the presence of dithiane.[185] Dithioacetals or ketals are resistant to acidic or basic hydrolysis. Regeneration of the carbonyl group from the dithioketal sometimes presents difficulties but can be carried out by hydrolysis in polar solvents (acetone, alcohols, acetonitrile) in the presence of metallic ions such as Hg$^{II}$, Cu$^{II}$, Ag$^{I}$, Ti$^{IV}$[177] or Tl$^{III}$.[186] Alternatively, alkylative hydrolysis using methyl iodide, methyl fluorosulfonate or Meerwein salts, or oxidative cleavage using chloramine-T, *N*-halosuccinimides, peroxy acids, ceric ammonium nitrate (CAN) or 1-chlorobenzotriazoles leads to the carbonyl compound.[177] In other cases one can use *n*-tributyltin hydride, trialkoxonium tetrafluoroborate, isopentyl nitrite, thionyl chloride–silica gel–water, $Fe(NO_3)_2$ or $Cu(NO_3)_2$ supported on clay,[187] nitrosonium ion ($NO^+$) sources,[188] methyltriphenylphosphonium tribromide, trimethylphenylammonium tribromide,[189] phenyldichlorophosphonate–DMF–NaI[190] or photochemistry[3,177] to achieve the hydrolytic cleavage.

It has been shown that thioacetal monosulfoxides undergo hydrolysis with greater ease than thioacetals or dithianes, *i.e.* the hydrolysis can be carried out with dilute sulfuric or perchloric acid.[175] Not only is the hydrolysis of the thioacetal monosulfoxides more facile but the addition of the lithium salt proceeds 1,4 rather than 1,2 to α,β-unsaturated carbonyl compounds.[175,191]

### 2.4.9.1 1,2-Addition to Aldehydes and Ketones

1,2-Addition of lithiodithianes to carbonyl compounds followed by hydrolysis gives α-hydroxy ketones in good yield (equation 31).[3,175,192] The reaction of sugar lactones with lithiodithiane provides a preparative route to higher sugars.[193] The reaction of 2-phenyl-1,3-dithianyllithium with 4-*t*-butylcyclohexanone in cyclohexane or THF proceeds with thermodynamic control, involving exclusively equatorial attack on the carbonyl group. In contrast only kinetic control (axial attack) is seen in the reaction of the same ketone with 1,3-dithianyllithium.[194]

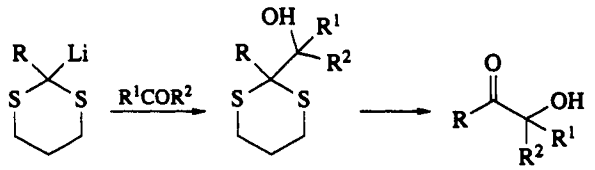

(31)

Stereoselective addition of a dithiane anion to chiral 2-methyl-3-trimethylsilyl-3-butenal combined with the stereoselective addition of a Grignard reagent to the chiral α-alkoxy ketone affords a practical method for the construction of α,γ-dimethyl-α,β-dihydroxy compounds, useful intermediates for the synthesis of erythronolides (Scheme 33).[195] β-Hydroxy carboxylic esters were synthesized by the addition of ethyl 1,3-dithiolanyl-2-carboxylate enolate to a chiral aldehyde, followed by desulfurization.[196]

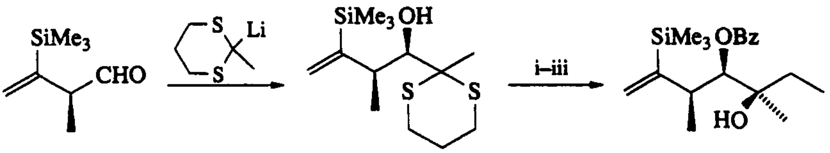

i, BzBr, NaH; ii, $HgCl_2$–$CaCO_3$; iii, EtMgBr

Scheme 33

The intramolecular carbonyl addition of a lithiated dithiane to a ketone was used in the synthesis of rocaglamide, an anticancer compound, in 64% yield.[197]

α-Hydroxy ketones having fungicidal activity were prepared from the reaction of lithiated 2-alkyldithianes with 3-pyridyl ketones.[198]

The reaction of 2-cyclohexenone with 2-lithiodithiane occurs in a 1,2-fashion to give the unsaturated hydroxy derivative, which, after rearrangement followed by deprotection, gives 3-hydroxy-1-cyclohexenecarbaldehyde.[199]

1,2-Addition of dithianyl anion to the appropriate aldehydes is a key step in the multistep synthesis of (i) amphotericin B (Scheme 34);[200,201] (ii) the dioxabicyclononane unit of tirandamycin (Scheme 35);[202] (iii) secoisoquinoline alkaloids such as peshawarine, cryptopleurospermine, (±)-corydalisol, (±)-aobamine and hypercornine[203] and baldulin; and (iv) sesquiterpene lactones[204] and chiral lycoserone.[205]

Reaction of dianion (**62**) with nicotinaldehyde or *N*-methylpiperidone gave the corresponding alcohols in good yield (equation 32),[206] whereas the *N*-protected anion led to the formation of the ring-opened alkyne derivative (equation 33).

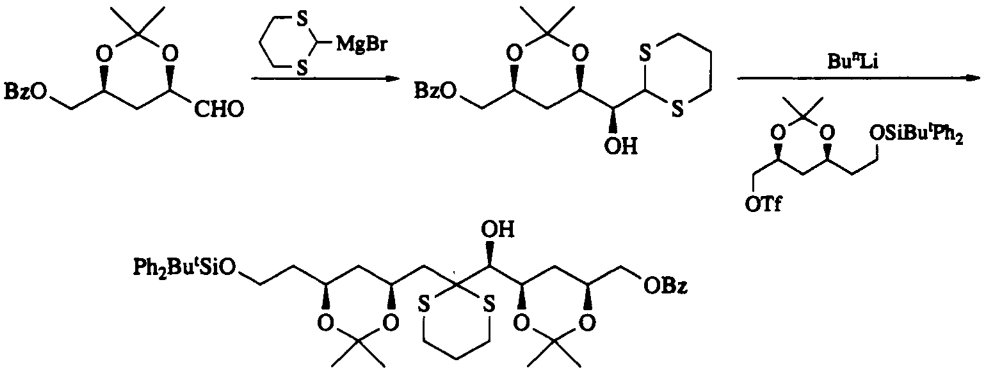
BzO
CHO
MgBr
BzO
OH
Bu$^n$Li
OSiBu$^t$Ph$_2$
OTf
OH
Ph$_2$Bu$^t$SiO
OBz

Scheme 34

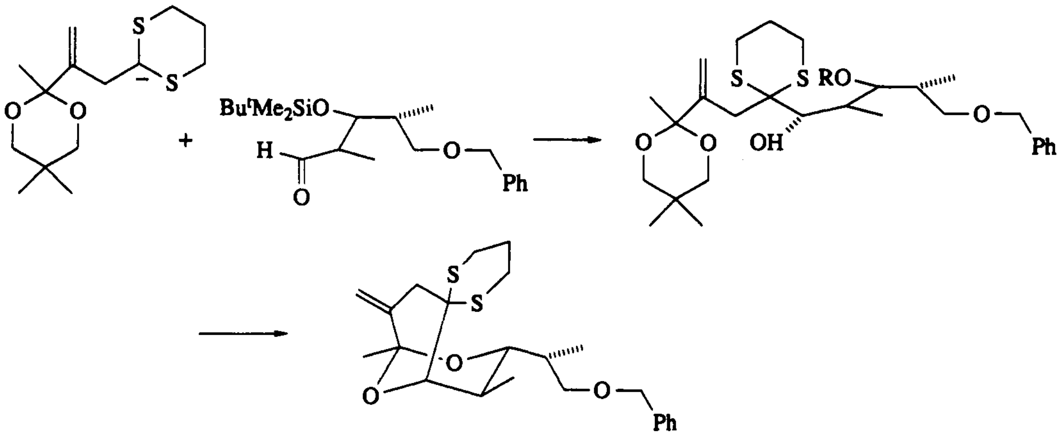
Bu$^t$Me$_2$SiO
H
O
Ph
RO
OH
Ph
Ph

Scheme 35

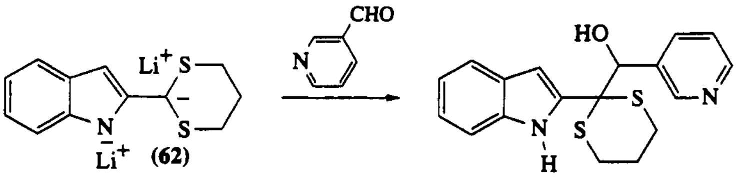
Li$^+$
Li$^+$
(62)
CHO
HO
H

(32)

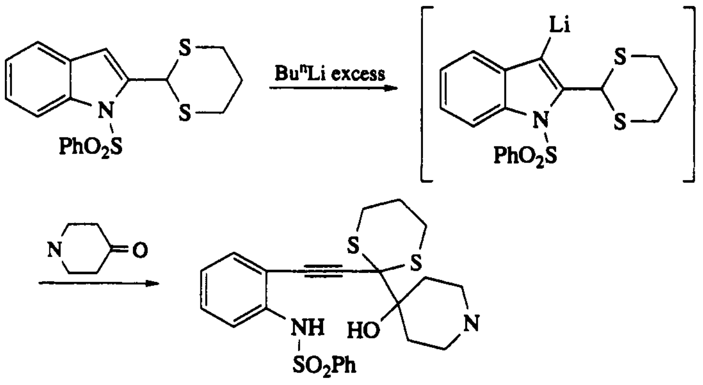
Bu$^n$Li excess
PhO$_2$S
Li
PhO$_2$S
NH
SO$_2$Ph
HO

(33)

The regio- and diastereo-selective reaction of the anion generated from 2-(1-propen-1-yl)-1,3-dithiane with an aldehyde is applicable to the synthesis of *trans*-β,γ-disubstituted γ-lactones, including the natural products (±)-eldnolide and (±)-*trans*-quercus lactone.[207]

2-Lithio-2-(1-methyl-2-alkenyl)-1,3-dithianes showed 1,3-*syn* selectivity on addition to aldehydes (equation 34). The presence of a bulky substituent $R^3$ on the aldehyde gave increased *syn* selectivity in the following order: alkyl > phenyl > 1-silylalkenyl > alkenyl > alkynyl. Activation of an aldehyde by $BF_3 \cdot Et_2O$ reduced the ratio.[208]

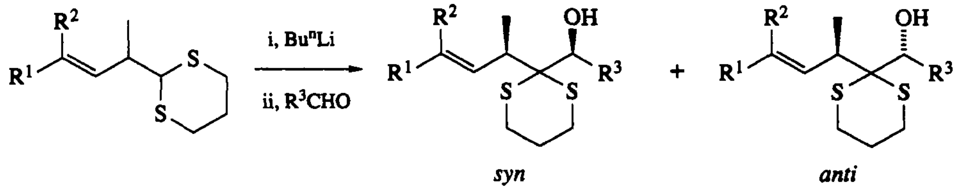

(34)

Intramolecular addition of lithiodithiane to an acetal leads to the formation of cyclic derivatives (equation 35).[209] Carbonyl additions have been extended to the analogous imonium salts ($R_2C{=}^{+}NR_2$), which furnish α-amino ketones.[210]

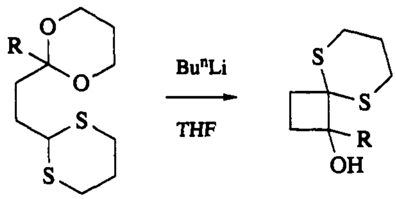

(35)

The reaction of 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose with 2-lithiodithiane yields an unsaturated open chain heptose derivative (equation 36).[211]

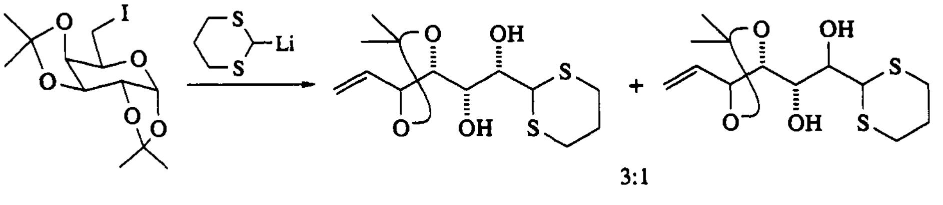

(36)

### 2.4.9.2 1,4-Addition to α,β-Unsaturated Carbonyl Compounds

This reaction is of importance since it enables the conversion of α,β-unsaturated carbonyl systems into 1,4-dicarbonyl compounds, which are precursors of cyclopentenones (*e.g.* jasmonoids, rethronoids and prostanoids).[212] The 1,4-addition proceeds in the presence of 1–2 equiv. of HMPT[213] and additional anion-stabilizing groups on the alkene enhance the tendency of metallated *S,S*-acetals to undergo the conjugate addition.

Chirally mediated conjugate addition reactions of lithiated dithioacetals to a prochiral α,β-unsaturated ester proceed enantioselectively to the corresponding adduct.[214] Alkylation of an acyclic α,β-unsaturated ester was achieved with high diastereoselectivity using a dithioacetal as the stereocontrolling unit (Scheme 36).[215] The conjugate addition of 2-lithiodithiane to 2-cyclohexenones, followed by quenching of the intermediate enolate anion with 2-chloroacyl chloride, affords 2-substituted 4-(1,3-dithian-2-yl)-4,5,6,7-tetrahydro-3(2*H*)-benzofuranones.[216]

The benzylic alcohols (**63**) are readily prepared by the conjugate addition of appropriate sulfur-stabilized carbanions, either as aryldithianes or as arylbis(phenylthiomethanes), to butenolides, followed by trapping of the generated enolate with an aromatic aldehyde.[217] Cyclization of the derived ketone provides a short efficient synthesis of clinically important podophyllotoxin derivatives (Scheme 37),[218] whereas Raney nickel desulfurization, followed by hydrolysis under various conditions, gave lignan lactones like (–)-burseran, (–)-cubebin, hinokinin[219] and podorhizol.[217] More significantly, the use of a chiral butenolide leads to an asymmetric synthesis of the lignans (+)-burseran, isostegane and (+)-steganacin.[217]

A total synthesis of (±)-aromatin has utilized the lithium anion of the dithiane of (*E*)-2-methyl-2-butenal as a functional equivalent of the thermodynamic enolate of methyl ethyl ketone in an aprotic

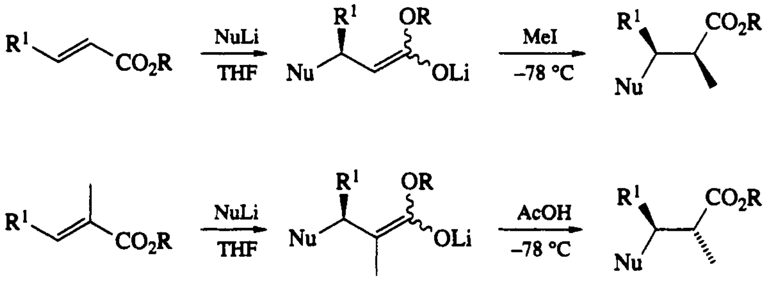

Nu = dithiane

Scheme 36

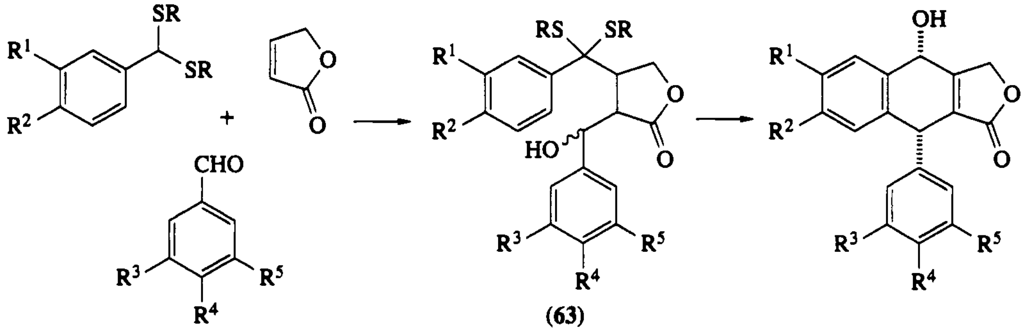

(63)

Scheme 37

Michael addition.[220] The synthesis of the naturally occurring benz[*a*]anthraquinones, X-14881 (**64**; R = Me) and ochromycinone (R = H) utilizes 2-phenyldithiane anion (Scheme 38),[221] while 11-deoxydaunomycinone was prepared using 2-methyldithiane.[222] The formation of bicyclo[3.3.0]oct-1(5)-ene-2,6-dione utilizes 2-(2,2-diethoxyethyl)-1,3-dithiane anion.[223] Conjugate addition of the highly stabilized anion (**65**) occurs readily with enamide (**66**), whereas the related acyclic anion (**67**) appears to be less reactive than the cyclic analog (Scheme 39).[12] Conjugate addition of lithiated α-alkylthio monosulfoxide provides a new route for the synthesis of dihydrojasmone.[224]

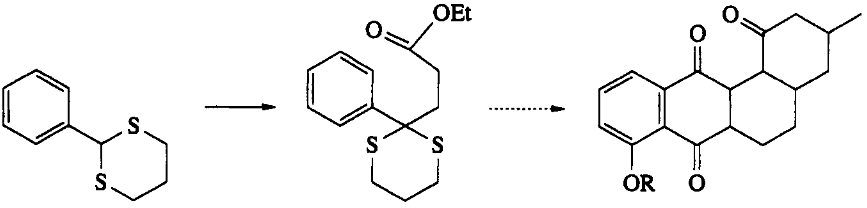

(64)

Scheme 38

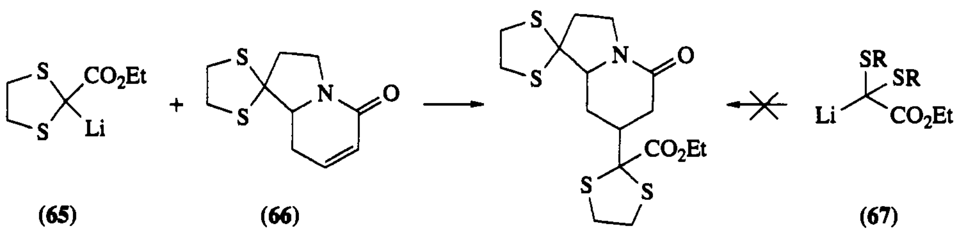

(65) (66) (67)

Scheme 39

### 2.4.9.3 Alkylation with R—X

The lithio derivatives of 1,3-dithiane react readily with alkyl halides to afford 2-alkylated dithianes in excellent yields.[3,225] Dithiane anions are useful for the formation of small- and medium-sized rings *via* alkylation.[226]

The alkylation method has been used for the multistep synthesis of vermiculine,[3] homofernascene, the trail pheromone components of the fire ant *Solinopis invicta*,[227] the spiroacetal fragment of milbemycin E,[228] chiral segments of roflamycin, the macrolide gloeosporone,[229] an autoinhibitor of spore germination,[230] antibiotic A23187, calcimycin,[231] a fragment containing the backbone of the antibiotic boromycin,[232] taloromycin B, an acute avian toxin,[233] and baiyunol, an aglycon of a sweat substance.[234]

Alkylation of 2-lithio-2-ethoxycarbonyl-1,3-dithiane with 5-bromo-1,2-pentadiene gave a precursor for the total synthesis of lycorenine alkaloids.[235]

The aliphatic portion of (±)-zearalenone has been synthesized starting from 2,3-dihydropyran and iodopentanone ketal by employing dithiane for C—C bond formation *via* alkylation.[236] The method also proved to be useful for the preparation of long chain alcohols starting from 5-alkyl-2-(1,3-dithianyl)thiophene.[237] Similarly two rigid crown ethers (**68**), which possess a tripyridine subunit, are prepared by the construction of the middle pyridine moiety *via* a dithiane precursor (Scheme 40).[238]

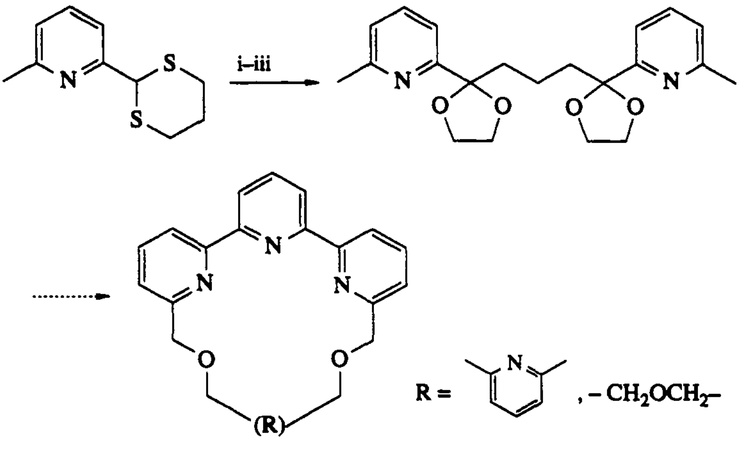

(**68**)

i, $Bu^nLi$, $Br(CH_2)_3Br$, −35 °C; ii, HgO, $HgCl_2$, 90% MeOH, THF; iii, $HO(CH_2)_2OH$, TsOH

**Scheme 40**

Cyclization of 1,ω-dihalo [or bis(tosyloxy)] alkanes with methyl methylthiomethyl sulfoxide in the presence of a base such as $Bu^nLi$ or KH gave three-, four-, five- and six-membered 1-methylsulfinyl-1-methylthiocycloalkanes that are easily converted to the corresponding ketone by acid hydrolysis.[239] This is applicable to the formation of the key intermediate for the synthesis of isocarbacyclin, a potent prostacyclin analog.[240]

Bis(benzenesulfonyl)methane[241] and 1,3-benzodithiole tetroxide[242] are useful formyl anion equivalents for alkylation as well as cycloalkylation reactions.

### 2.4.9.4 Acylation with Lithiodithianes

Reaction of lithiodithianes with acyl chlorides, esters or nitriles leads to the formation of 1,2-dicarbonyl compounds in which one of the carbonyl groups is protected as the thioacetal.[175,176,243,244] Optically active amino ketones of type (**69**) are prepared *via* acylation of dithiane with an oxazoline-protected (*S*)-serine methyl ester (Scheme 41).[245] Optically active (*S*)-2-alkoxy-1-(1,3-dithian-2-yl)-1-propanones were prepared by the reaction of the corresponding methyl (*S*)-lactate with 2-lithio-1,3-dithiane, which can be used for the enantioselective synthesis of (−)-trachelanthic acid.[246] Enantioselective synthesis of L-glyceraldehyde involves the acylation of a dithiane glycolic acid derivative followed by bakers' yeast mediated reduction.[247]

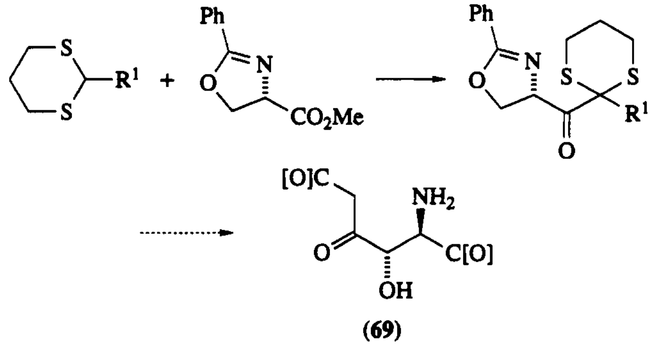

(69)

Scheme 41

### 2.4.9.5 Miscellaneous Reactions of Dithioacetals

Arylation of dithiane can be achieved by the reaction of the anion with activated haloarenes such as halopyridines or haloarylchromium(tricarbonyls).[3]

α-Diketones are prepared either by the reaction of 2-lithio-1,3-dithianes with a nitrile oxide (Scheme 42)[248] or by the reaction of 2-lithiodithiolane with iron(pentacarbonyl) followed by alkylation with an alkyl halide.[249]

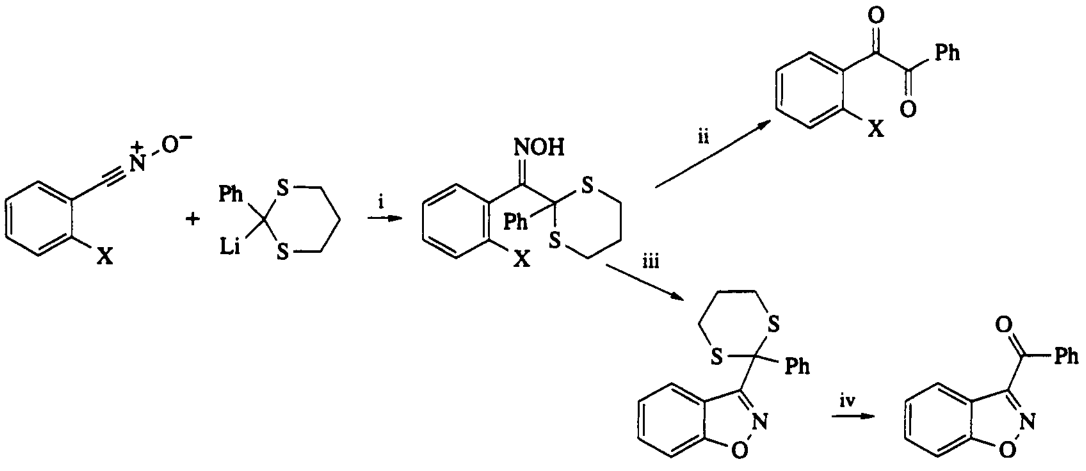

i, THF; ii, $CF_3CO_2H$, 35%; iii, KOH, EtOH; iv, HgO

Scheme 42

Epoxides and oxetanes react readily with lithiodithiane to give derivatives of β- or γ-hydroxy aldehydes or ketones.[176] The method has been used for the multistep synthesis of an inomycin fragment,[250] thietane prostaglandin analogs,[251] branched-chain nucleoside sugars,[252] the southern hexahydrobenzofuran unit avermectin,[253] the anti-Gram-positive bacterial elaiphylin[254] and *syn*-1,3-polyols.[255]

Allylic anions generated from 2-propenyl-1,3-dithiane and 2-styryl-1,3-dithiane react exclusively at α-carbon atoms either with carbonyl compounds[256] or with three- to six-membered cyclic ethers in the presence of $BF_3 \cdot Et_2O$.[257]

Reaction of dithiolane (**70**) with BuLi followed by a hindered organoborane gives (**71**), which after oxidative work-up affords an unsymmetrical ketone in good yield (Scheme 43).[258]

Reaction of dithiane with DMF leads to the formation of an aldehyde, a key intermediate for the synthesis of the macrocyclic antibiotic (±)-pyrenophorin.[259,260]

2-Diethoxyphosphinyl-2-buten-4-olide reacts with lithiated dithianes followed by an intermolecular Wittig–Horner reaction to produce fused γ-lactones (equation 37).[261] The reaction of 2-lithio-1,3-dithianes with nitroarenes gives 2- or 4-[(1,3-dithian)-2′-yl]cyclohexa-3,5(or 2,5-)-diene-1-nitronate compounds (conjugate addition products), free nitroarene radical anions (redox products), 1,3-dithianes and 2,2′-bis(1,3-dithianes).[262]

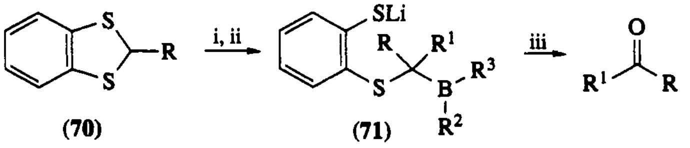

**(70)** **(71)**

i, $Bu^nLi$, THF, 30 °C; ii, $BR^1R^2R^3$; iii, $NaOH/H_2O_2$, r.t.

**Scheme 43**

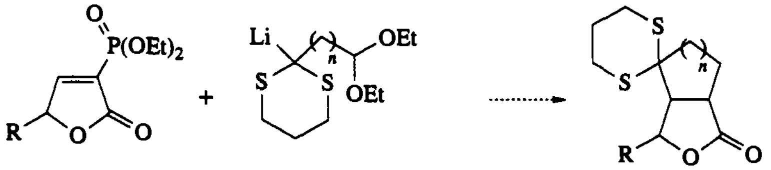
(37)

A key step for the synthesis of prostaglandin $D_1$ methyl ester involves the reaction of dithiane (**72**) with (1-methylthiovinyl)triphenylphosphonium chloride (**73**; Scheme 44).[263]

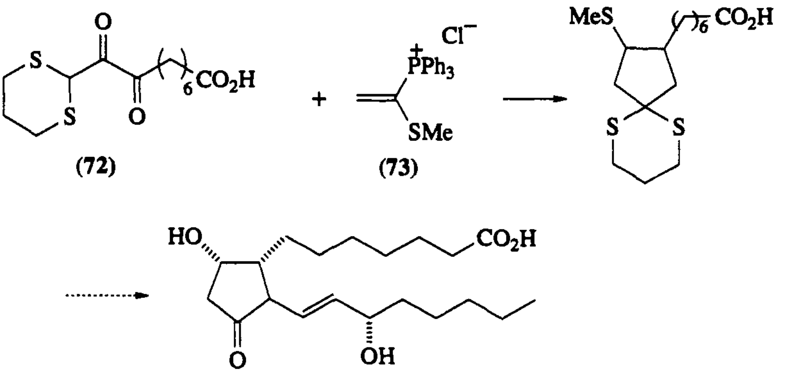

**(72)** **(73)**

**Scheme 44**

Lithiodithiane is aminated by reaction with a vinyl azide, as shown in equation (38).[264]

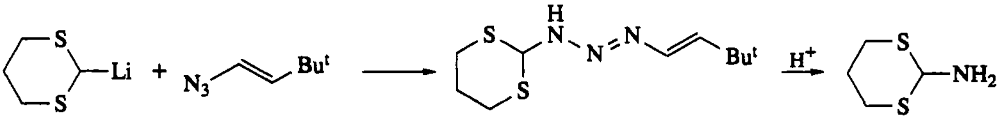
(38)

Methoxy(phenylthio)methane and methoxy(phenylsulfonyl)methane are useful formyl anion equivalents for one-carbon homologation.[265] For instance, addition of methoxy(phenylthio)methyllithium to ketones, followed by rearrangement of the adduct, provides a new method for the preparation of α-(phenylthio) aldehydes (equation 39). The rearrangement is stereospecific.[266] This method has been used for the total synthesis of annelated furans such as (+)-euryfuran,[267] butenolides such as isoderminin and confertifolin[268] and spirocyclic tetrahydrofurans and butenolides.[269]

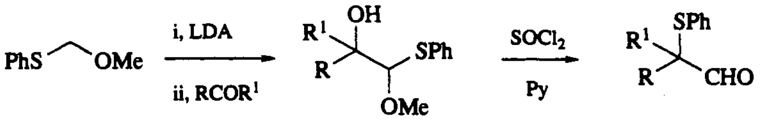

(39)

Alkylation of phenylthiomethyl(trimethyl)silane or phenylthiophenyl(trimethylsilyl)methane with alkyl halides followed by deprotection gave aldehydes[270] or ketones[271] respectively.

### 2.4.10 DISELENOACETALS

Diselenoacetals are also useful for the protection or umpolung of the carbonyl group.[2,272,273] Bis(alkylseleno)alkanes and arylseleno analogs are prepared by the reaction of carbonyl compounds with selenols and trimethylsilyl selenides in the presence of acid catalysts (conc. HCl, conc. $H_2SO_4$, Lewis acids such as $BF_3{\cdot}Et_2O$, $TiCl_4$, $ZnCl_2$ or $AlCl_3$) or with tris(methylseleno)borane in the presence of LAH and $BF_3{\cdot}Et_2O$.[274]

The selenium-stabilized carbanions derived by deprotonation of selenoacetals by strong bases, such as a mixture of KDA–lithium *t*-butoxide, LiTMP in HMPT/THF or LBDA in THF at –78 °C, react readily with a variety of electrophiles including primary or secondary halides, epoxides, ketones, aldehydes and enones, followed by deprotection, to give ketones, β-hydroxy ketones, α-hydroxy ketones and 1,4-dicarbonyl compounds respectively.[2,275,276]

Regeneration of the carbonyl group from a diseleno-ketal or -acetal can be carried out by clay-supported iron(III) or copper(II) nitrate,[277] $HgCl_2/CaCO_3/MeCN$, $(PhSeO)_2O/THF$, $NaIO_4/EtOH–H_2O$, HgOAc/MeCN or $CuCl_2/CuO$.[275]

The presence of DME or HMPT allows the C-3 regio- and stereo-selective 1,4-addition of 1,1-bis(methylseleno)alkanes to methylcyclohexenones (see Scheme 45). The resulting adducts have been stereoselectively transformed into *cis*- or *trans*-3-ethyl-2-methylcyclohexanone using $Bu_3SnH$ and AIBN.[278]

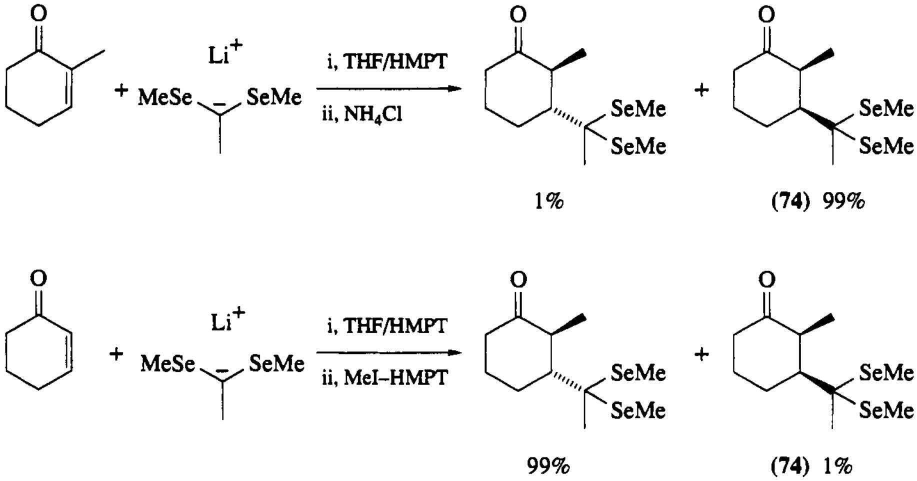

**Scheme 45**

Selective transformation of the diseleno-substituted cyclohexanone to the corresponding diketone can be carried out from the *cis* product (**74**), whereas the *trans* isomer does not produce the desired diketone but instead leads to a ketovinyl selenide.[275]

α-Phenylselenyl cyclic ethers prepared by the reactions of either lactols or lactol acetate with benzeneselenol in the presence of a Lewis acid act as acyl anion equivalents, which on deprotonation with BuLi followed by reaction with alkyl halides lead to the formation of alkylated products.[279]

The lithio reagents generated from silylselenylmethanes ($Me_3SiCH_2SePh$) and $Me_3SiCH(SePh)CH_2R$ are useful synthetic equivalents of a protected formyl anion and an acyl anion respectively.[2] Silylselenylmethanes are valuable reagents for the transformation of halides to aldehydes.[2]

### 2.4.11 TOSYLMETHYL ISOCYANIDE

Tosylmethyl isocyanide (TosMIC) (**75**; R = H), a versatile reagent in synthesis, can also be used as an acyl anion equivalent. For instance symmetrical and unsymmetrical diketones were prepared by using this TosMIC synthon (equation 40).[280] Ketones are homologated to enones by alkylating the condensation product derived from TosMIC, followed by acid hydrolysis (Scheme 46).[281]

1-Isocyano-1-tosyl-1-alkenes (**76**), formed by the reaction of TosMIC with an aldehyde or ketone, react with a primary amine or ammonia to give 1,5-disubstituted (or 5-monosubstituted) imidazoles in high yield (Scheme 47).[282]

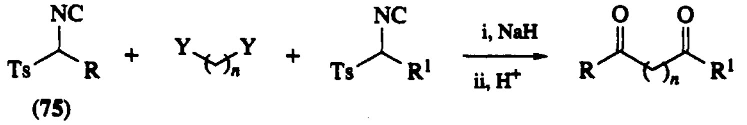

(40)

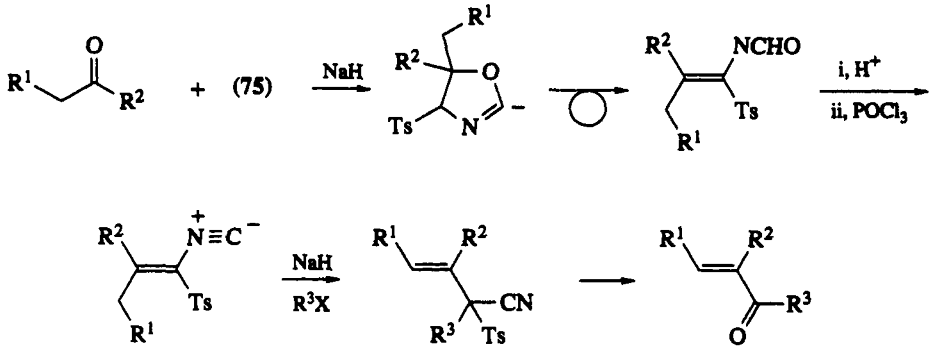

Scheme 46

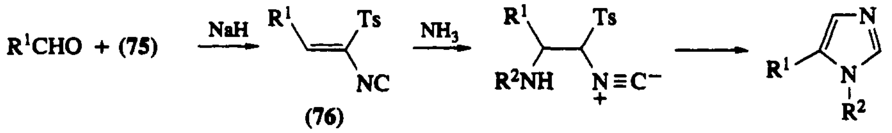

Scheme 47

## 2.4.12 REFERENCES

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# 2.5
# Silicon Stabilization

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## 2.5.1 INTRODUCTION

The chemistry of organic silicon compounds is one of the fastest growing fields in synthetic organic chemistry. Consequently, it has become one of the most important areas of research and the development of new methodology which provides general stereoselective reaction processes continues to be actively investigated.[1] This chapter will review the synthetic utility of silicon-stabilized carbanion equivalents and their use in addition reactions to C=X π-bonds. No attempt has been made to provide an exhaustive literature search, rather the discussion focuses on more recent developments in stereoselective bond-forming processes and their practical usage. The chapter has been organized by the various types of stabilized carbanion equivalents, with issues of selectivity being treated in the context of each specific type. Particular attention has been given to the treatment of σ–π-bonded silicon-stabilized carbanions, *e.g.* vinylsilanes, allenylsilanes, alkynylsilanes, propargylsilanes, allylsilanes and α-metallated organosilanes. Primary emphasis has been placed on practical enantio- and stereo-selective synthetic methods and yields; reaction conditions and proposed mechanisms, however, are frequently discussed. Reactions which have not been judged to be synthetically useful, due to isolation of the desired addition product in low yield, have been neglected.

## 2.5.2 CHARACTERISTICS OF ORGANOSILICON COMPOUNDS

Organic silicon compounds display a multitude of functions in organic synthesis.[1] The wide applicability of organosilicon reagents in stereoselective bond-forming reactions can be attributed to the large number of functional groups and the variety of reaction conditions that can be accommodated by silicon, and to its ability to function as an electron donor and acceptor. The reactivity and selectivity of reactions involving organosilanes is dependent upon both steric requirements and electronic contributions. The electronic effects associated with silicon include: (i) inductive effects; (ii) field effects; (iii) *p–d* π-bonding; and (iv) hyperconjugative effects. A brief summary of the physical properties of organosilicon compounds is helpful.

### 2.5.2.1 Inductive Effects

Inductive effects are generally considered to be transmitted through the σ-framework of a molecule. The electronegativity of an element is usually a measure of its ability to attract σ-electrons.[2] In many synthetic operations selectivity reflects the energy differences between reagents, activated intermediates and transition states. Thus, caution must be exercised when considering the influence of electronic effects on selectivities of reactions involving organosilanes. Through purely inductive effects trialkylsilyl groups are electron donating; however, the inductive effects of silicon are weak and in general only influence atoms directly bonded to it.

### 2.5.2.2 Field Effects

Field effects describe the polarization of an adjacent π-system to the σ-dipole moment of the entire $R_3Si$ group.[2,3] A π-inductive effect alters a nearby π-system without charge transfer to or from that system. Two types of π-inductive effects have been described.[4] The first is termed $\pi_\sigma$ and is the result of charge differences in the σ-bonding system, as a consequence of inductive effects. The effect is illustrated in Figure 1, where an electropositive substituent Y induces a partial positive charge at the C-1 position of the benzene ring. This induces redistribution of the π-electron density in a fashion that can be predicted by consideration of the contributing resonance forms in the illustrated structures. In the case of an electron-withdrawing substituent Y, the $\pi_\sigma$-effect predicts diminished electronegativity at C-2 and C-3 and increased electron density at C-1 and C-4.

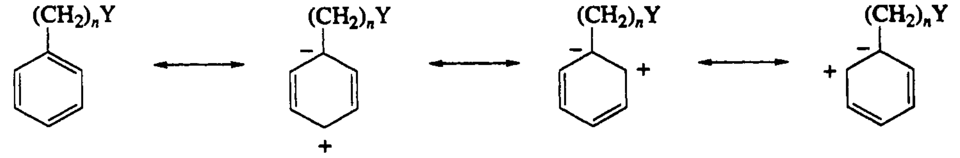

Figure 1

The second π-inductive effect, $\pi_F$, is the field effect, which arises when the electric dipole of $(CH_2)_nY$ affects the entire π-system through polarization. This process is illustrated in Figure 2.[2] Both $\pi_\sigma$ and $\pi_F$ contribute to the overall π-electron density, but it is difficult to separate these effects when they operate mainly at the C-1 position. For trialkylsilyl groups it is not easy to predict the magnitude of the field effect because although the Si—C bond is polarized such that silicon bears a partial positive charge, the trialkylsilyl group can be electron withdrawing, depending on the alkyl substituents.

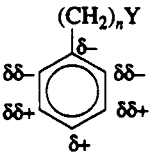

**Figure 2**

### 2.5.2.3 *p–d* π-Bonding

The mechanism by which the trialkylsilyl group can function as a π-electron-withdrawing group is influenced by the physical properties of silicon. The most widely recognized explanation is that the low-lying, unoccupied silicon *d*-orbitals can participate in *p–d* π-bonding, as illustrated in Figure 3.[2,5] In this illustration the electron density from the *p*-orbital on X can be delocalized onto silicon through a donor–acceptor interaction with the vacant Si 3*d*-orbital. Pauling was the first to introduce this concept to provide an explanation for the short lengths of silicon–oxygen and silicon–halogen bonds.[6] The *p–d* π-bonding model is most easily applied to systems in which electron density in a *p*-type orbital adjacent to silicon is transferred onto the silicon atom.

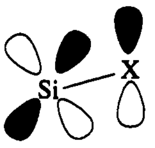

**Figure 3**

### 2.5.2.4 Hyperconjugation

When two adjacent molecular orbitals are relatively close in energy and have appropriate symmetry, they can undergo perturbation resulting in the lowering of the energy of one orbital and an increase in the other. This phenomenon is shown in Figure 4 for the interaction of the Si—C σ*- orbital with a π-orbital.[1f,2] In this example the *p*-orbital is lowered in energy through hyperconjugation, as reflected in the ionization potential. The magnitude of the hyperconjugative interaction is directly proportional to the orbital energy difference and the orbital coefficients.

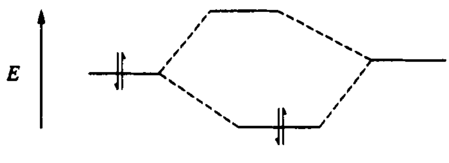

**Figure 4** The hyperconjugative interaction of π- and σ*- orbitals

The hyperconjugation model when applied to carbocation stabilization in organosilane systems is illustrated in Figure 5.

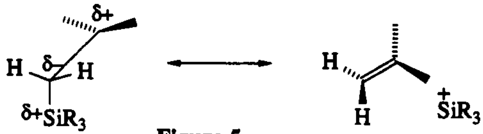

**Figure 5**

For organosilicon compounds the conformational requirements are well defined; for maximum stabilization of the carbocation β to the silicon group it is necessary for the C—Si bond to be orientated antiperiplanar to the empty *p*-orbital. Another system that is amenable to the simple hyperconjugation model is the α-silyl carbanion, $R_3SiCH_2^-$, as illustrated in Figure 6. Since the C—Si bonding orbital is higher in energy than C—C or C—H bonding orbitals and has a large coefficient on the adjacent carbon atom, through-space hyperconjugative stabilization by silicon is more influential in stabilizing an electron deficient center than that of an alkyl substituent or hydrogen.[1a,f,2]

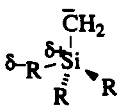

**Figure 6**

### 2.5.2.5 Nucleophilic Substitution Reactions

In the periodic table a column of elements will exhibit a trend of electronegativity that decreases in magnitude from top to bottom. The same trend is observed for silicon and carbon; the Pauling electronegativity of carbon is 2.5 eV, while that of silicon is 1.8,[1b,6] indicating that the C–Si bond is polarized such that silicon is the electron deficient atom and is responsible for accelerating nucleophilic attack at silicon (Figure 7). The reaction rate is in fact accelerated if the group undergoing displacement is a good leaving group.[1b] As a result, organosilanes are relatively nonpolar compounds compared to other organometallic reagents, so they can tolerate the presence of a wide variety of functional groups and in most cases can be handled without special precaution.

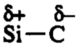

$$\overset{\delta+}{Si}-\overset{\delta-}{C}$$

**Figure 7**

The σ-bonds between silicon and electronegative elements such as the halogens are quite strong. A comparison of the bond dissociation energies between carbon/halogen and silicon/halogen is listed in Table 1.[1b]

**Table 1** Bond Energies ($kJ\ mol^{-1}$)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C—F | 552 | Si—F | 552.7 ± 2.1 | C—Br | 280 ± 21 | Si—Br | 343 ± 50 |
| C—Cl | 397 ± 29 | Si—Cl | 456 ± 42 | C—I | 209 ± 21 | Si—I | 293 |

The driving force for many addition reactions involves the formation of a new silicon compound with a stronger bond to the silicon atom. Treatment of the trimethylsilyl ether (**1**) with fluoride ion ($F^-$) results in the formation of fluorotrimethylsilane (**2**) because the derived Si—F bond has a higher bond dissociation energy (BDE) than the Si—O bond undergoing heterolytic bond cleavage (Scheme 1). The facile removal of the silyl group by use of a fluoride ion is commonly referred to as desilylation and is responsible for the extensive use of trialkylsilanes as protecting groups in synthesis.[7]

$$\underset{\textbf{(1)}}{RO-SiMe_3} \xrightarrow{F^-} \underset{\textbf{(2)}}{FSiMe_3} + RO^-$$

**Scheme 1**

The result of carbon–silicon σ-bond stabilization of an adjacent carbocation in electrophilic additions to C—X π-bonds is that the reactions normally occur with high levels of stereo- and regio-control. For instance, Lewis acid catalyzed addition reactions of allylsilanes to C—X π-systems proceed with C-3-regiospecificity and electrophilic additions of vinylsilanes occur predominantly at the silicon-bearing carbon. Trapping of the β-carbocation through the loss of the silyl group (or silicon substituent) then gives the addition product.

### 2.5.3 SILICON ATTACHED TO PARTICIPATING π-BONDED CARBON NUCLEOPHILES

The spectrum of silicon-stabilized carbanions containing σ-bonded silyl groups attached to a participating π-bond (π-nucleophile) and their use in organic synthesis has grown considerably over the last few years. In this context vinylsilanes, alkynylsilanes and allenylsilanes have emerged as remarkably useful and versatile carbon nucleophiles for the regio- and stereo-selective formation of carbon–carbon bonds. This section will discuss the stereochemical aspects of σ–π-bonded silicon-stabilized carbanions in addition reactions to C—X π-systems. Excellent reviews have appeared covering vinylsilane-[1a,8] and alkynylsilane-terminated cyclization reactions.[8]

#### 2.5.3.1 Vinylsilanes

Vinylsilanes function as vinyl anion equivalents in addition reactions to C—X π-systems. The reaction has been successfully conducted under a variety of conditions. The strong σ-donating capability of the silyl group is primarily responsible for directing the initially formed cation along a single reaction pathway. The adjacent carbanion center is stabilized by overlap with the low energy, unoccupied 3*d*-orbital of silicon or by σ → σ* orbital overlap (Figure 8). As a consequence, characteristic regio- and stereoselectivity are observed in vinylsilane addition reactions; as shown in Figure 9, electrophilic substitution takes place at the silicon-bearing carbon and occurs stereospecifically with retention of configuration.[8]

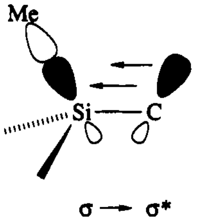

**Figure 8**

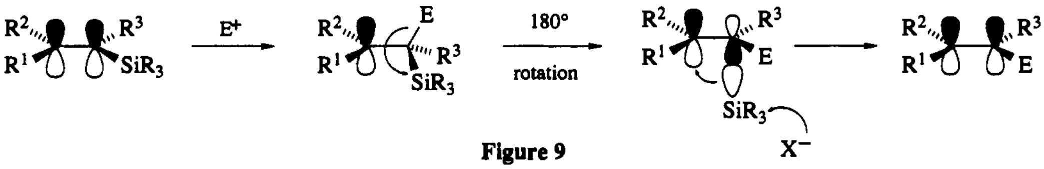

**Figure 9**

The intermolecular addition of vinylsilanes to C—X π-systems is a well-studied reaction;[1j,8a,b] however, not until 1981 had the intramolecular variant been demonstrated. Thus, coverage of vinylsilane additions in this chapter will focus on the regio- and stereo-selectivity in intramolecular (cyclization) reactions. Two modes of cyclization are possible, as determined by the position of the alkene with respect to the ring system: cyclization can occur in an endocyclic or an exocyclic mode with respect to the vinylsilane group (Figure 10).

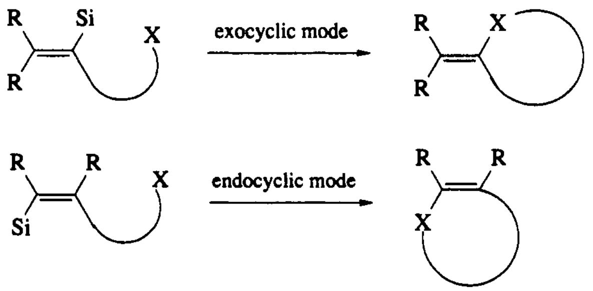

X = electrophilic initiating center; Si = nucleophilic terminating center

**Figure 10**

The first report of an intramolecular addition of a vinylsilane came from the Burke laboratory.[9] The reaction was used for the preparation of spiro[4.5]decadienones. As shown in Scheme 2, the addition of the vinylsilane to the intermediate acylium ion generated using titanium tetrachloride resulted in the formation of the enone system (3) → (4).

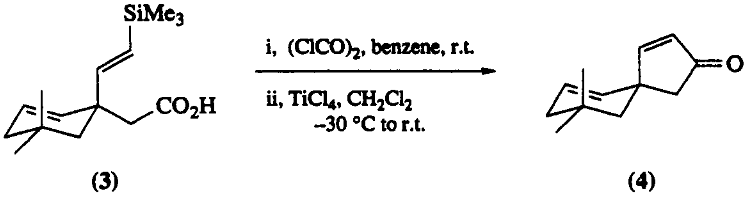

Scheme 2

Kuwajima has reported similar internal addition reactions resulting in the formation of spirocyclic enones. Treatment of the acyl chlorides (**5a**,**b**; Scheme 3) with $TiCl_4$ resulted in the formation of enone systems (**6a**) and (**6b**) in good yields.[10]

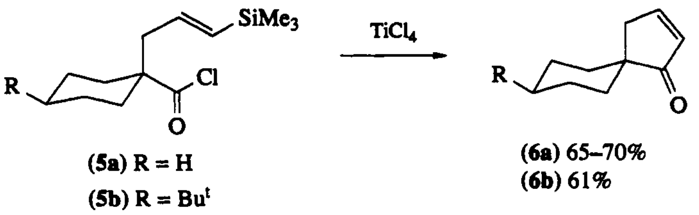

Scheme 3

Competition studies reported by Kuwajima,[10] which also complement the results of Nakai,[11] illustrate the limitations of the β-effect as a tool for predicting the outcome of vinylsilane-terminated cyclizations (Scheme 4). Acylium ion initiated cyclizations of (**7a**) and (**7b**) gave the expected cyclopentenones (**8a**) and (**8b**). However, compound (**7c**), upon treatment with titanium tetrachloride, gave exclusively the cyclopentenone product (**8c**) arising from the chemoselective addition on the 1,1-disubstituted alkene followed by protodesilylation of the vinylsilane. The reversal observed in the mode of addition may be a reflection of the relative stabilities of the carbocation intermediates. The internal competition experiments of Kuwajima indicate that secondary β-silyl cations are generated in preference to secondary carbocations (compare Schemes 3 and 4), while tertiary carbocations appear to be more stable than secondary β-silyl carbocations, as judged by the formation of compound (**8c**).

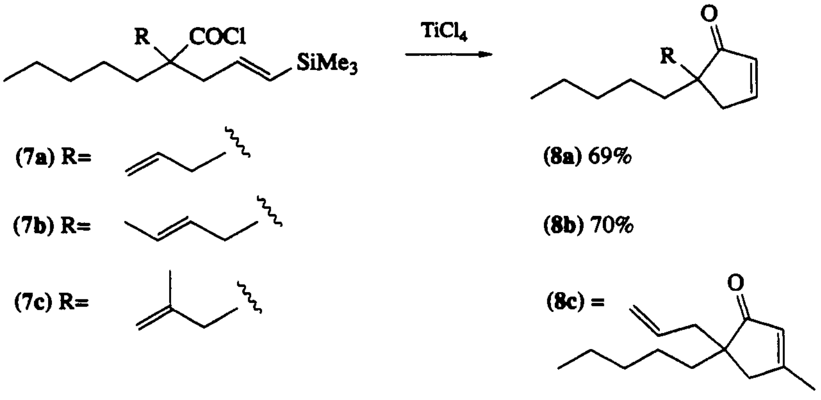

Scheme 4

### *2.5.3.1.1 Regiospecific cyclopentenone annelations: vinylsilane-terminated annelations*

The efficient conversion of a ketone to a fused cyclopentenone of the general type outlined in Scheme 5 has been demonstrated by Paquette and coworkers.[12] The overall strategy is illustrated in Scheme 6 and begins with Freidel–Crafts acylation of the cyclic vinylsilane (**8**) to give the enone (**9**), which undergoes tin tetrachloride mediated cyclization to give the fused 5,5-pentenones (**10a**) and (**10b**), as a 10:1 mixture of double bond isomers.

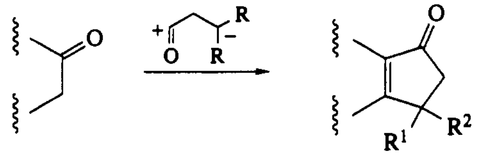

Scheme 5

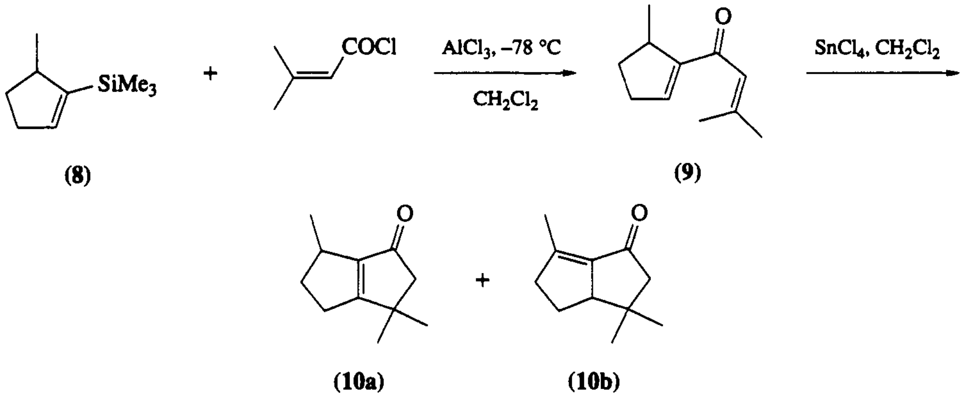

Scheme 6

Subsequent investigations by Denmark have shown that vinylsilanes can direct the course of Nazarov-type cyclization reactions.[13] Once again the regiochemical outcome is controlled by the β-effect as substitution takes place at the carbon bearing the silyl group (Scheme 7). This clever modification provided a solution to the serious problem of double bond isomerization that is frequently observed in the classical Nazarov reaction. Treatment of the enone (**11**) with commercially available 'anhydrous' iron(III) chloride ($FeCl_3$) promoted cyclization to give one double bond isomer of the *cis*-hydrindinone (**12**) in excellent yield. Table 2 summarizes a representative collection of cyclization reactions catalyzed by $FeCl_3$.

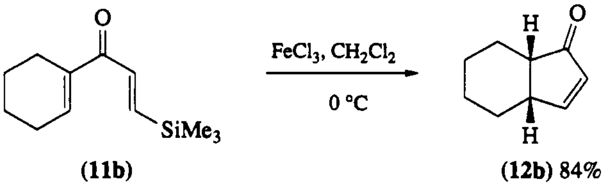

Scheme 7

### *2.5.3.1.2 Acetal- and carbonyl-initiated cyclizations*

In general, carbonyl groups do not function as good initiators in vinylsilane-mediated cyclization reactions and relatively few examples exist. The cyclization of vinylsilanes with ketones or aldehydes as initiators is a highly underdeveloped reaction that holds considerable potential. As reported by Tius and coworkers,[14] treatment of aldehyde (**13**) with a catalytic amount of *p*-toluenesulfonic acid gave a mixture of the tetralins (**14**) and (**15**) in a combined yield of 53%, with lesser amounts of the enone (**16**; Scheme 8). The enone system presumably arises from the intramolecular 1,3-hydride transfer of the intermediate α-silyl carbocation (**17**). Similarly, the vinylsilane (**18**) undergoes cyclization to produce the disubstituted benzene derivative (**19**), although yields are low.

Activated carbonyl groups serve as excellent substrates in Lewis acid catalyzed cyclization reactions, with faster reaction rates and higher yields being obtained in related cyclization processes involving acetals and ketals.[15] Thus, treatment of the dimethyl acetals (**20a–c**) with $TiCl_4$ at −78 °C afforded the biaryl

**Table 2** Iron(III) Chloride Induced Cyclizations of Vinylsilanes

| *Substrate* | *Solvent* | *Temperature* (° C) | *Time* (h) | *Product* | *Yield* (%)[a] |
|---|---|---|---|---|---|
| 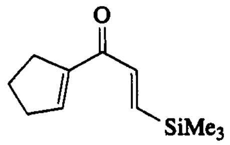<br>**(11a)** | $(CH_2Cl)_2$[b] | 20 | 2.5 | 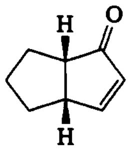<br>**(12a)** | 55 |
| 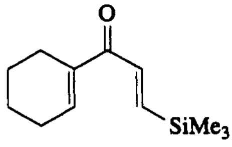<br>**(11b)** | $CH_2Cl_2$ | 0 | 4.0 | 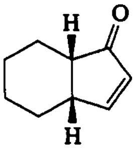<br>**(12b)** | 84 |
| 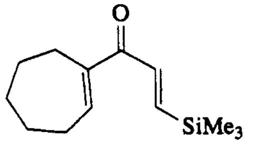<br>**(11c)** | $CH_2Cl_2$ | 0 | 1.0 | 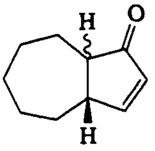<br>**(12c)** | 74 |
| 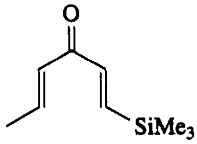<br>**(11d)** | $CH_2Cl_2$ | 20 | 12.0 | 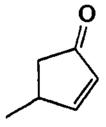<br>**(12d)** | 54 |
| 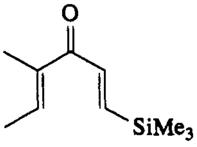<br>**(11e)** | $CH_2Cl_2$ | 20 | 12.0 | 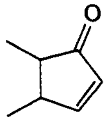<br>**(12e)** | 95 |

[a] All reactions were run with 1.05 equiv. of $FeCl_3$ (0.08 M) in vinylsilane. [b] $CH_2Cl_2$ gave poor yields.

ring systems (**23a–c**). It was presumed by the authors that the products arose through the intermediates (**21**) and (**22**) (Scheme 9).

### 2.5.3.1.3 *Effect of vinylsilane double bond configuration*

Both vinylsilane dimethyl acetals (*E*)-(**24**) and (*Z*)-(**24**) undergo cyclization to form the substituted cyclohexene (**25**; Scheme 10).[1a,16] The vinylsilane (*Z*)-(**24**) cyclizes nearly twice as fast as the (*E*)-stereoisomer and in higher yield. This greater efficiency may be due to the lability of the product allyl ether to the Lewis acid catalyst.

Trost has reported the use of dithioacetals as initiators in vinylsilane-terminated cyclizations (Scheme 11).[17] Reaction of the dimethyl thioketal (**26**) with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[18] led to the formation of the allylic sulfide (**28**) *via* a 2,3-sigmatropic rearrangement of the initially formed sulfonium salt (**27a**), which may have been catalyzed by complexation with excess DMTSF.

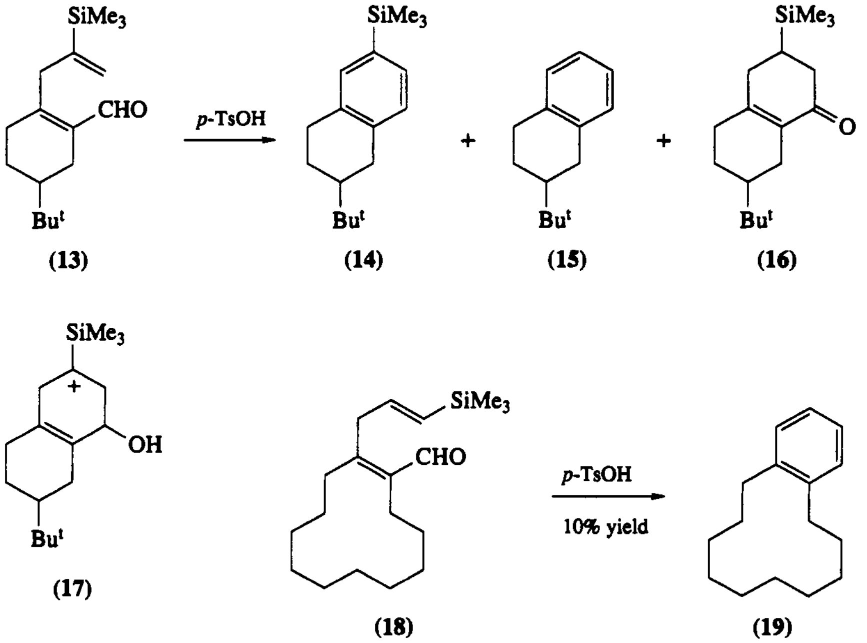
SiMe3
CHO
p-TsOH
Bu^t
OH
+
O
10% yield

(13) (14) (15) (16)

(17) (18) (19)

**Scheme 8**

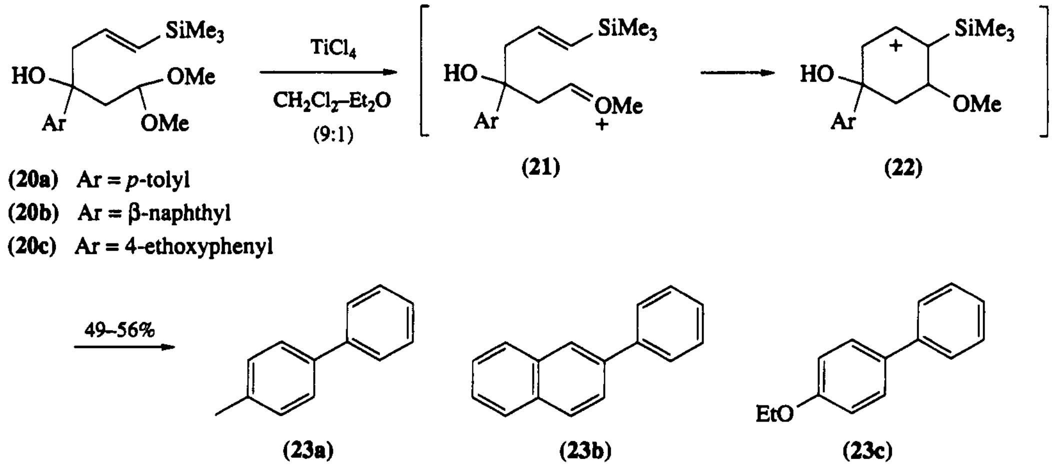
SiMe3
HO
OMe
Ar
TiCl4
CH2Cl2–Et2O
(9:1)
+
49–56%
EtO

(20a) Ar = *p*-tolyl
(20b) Ar = β-naphthyl
(20c) Ar = 4-ethoxyphenyl

(21) (22)

(23a) (23b) (23c)

**Scheme 9**

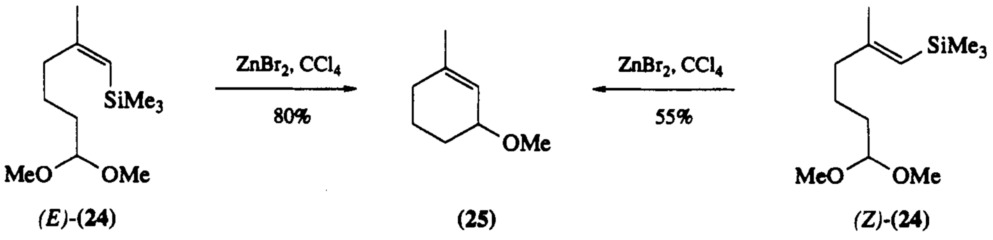
SiMe3
MeO
OMe
ZnBr2, CCl4
80%
55%

(*E*)-(24) (25) (*Z*)-(24)

**Scheme 10**

Competition experiments between two π-bonded nucleophiles within the same molecule were studied in an attempt to identify reaction parameters and factors responsible for regioselectivity.[17] These experiments, summarized in Scheme 12, demonstrated that the dithioacetal (initiating carbocation) is in competition with two nucleophilic functional groups within the same molecule, a silyl enol ether and a vinylsilane. In this instance, when the thioacetal (29) was treated with DMTSF, complete chemoselectiv-

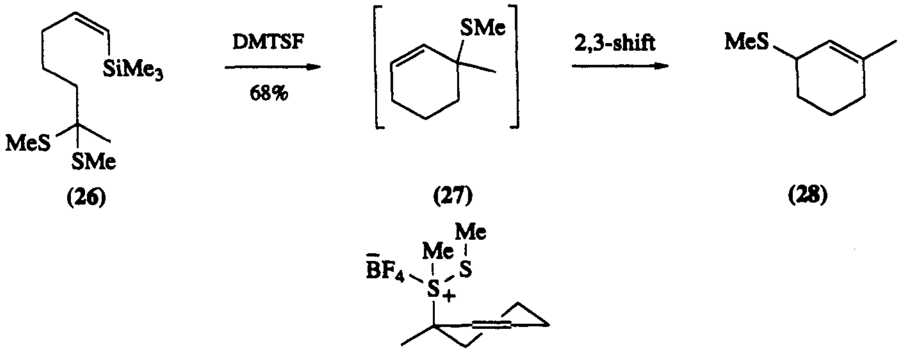
SiMe$_3$
MeS
SMe
DMTSF
68%
SMe
2,3-shift
MeS
Me
Me
$\bar{B}F_4$
S
S+

**(26)** **(27)** **(28)**

**(27a)**

**Scheme 11**

ity was observed for the addition of the more nucleophilic enol ether to the intermediate thionium ion to give the cyclohexanone derivative (**30b**). Cyclization product (**30a**), arising from reaction with the vinylsilane functional group, was not detected. However, cyclization of the corresponding ketone (**31**) gave the spirocyclic ketone (**32**). In this case, the first of the two consecutive cyclizations must occur *via* addition of the vinylsilane moiety, as neither ketone (**30b**) nor enone (**30a**) yielded the spirocyclic ketone (**32**) upon treatment with DMTSF (Scheme 13).

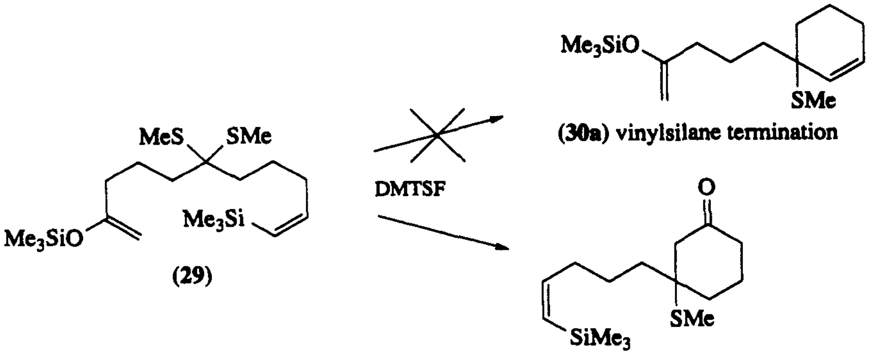
MeS
SMe
Me$_3$SiO
Me$_3$Si
DMTSF
Me$_3$SiO
SMe
O
SMe
SiMe$_3$

**(29)**

**(30a)** vinylsilane termination

**(30b)** silyl enol ether termination

**Scheme 12**

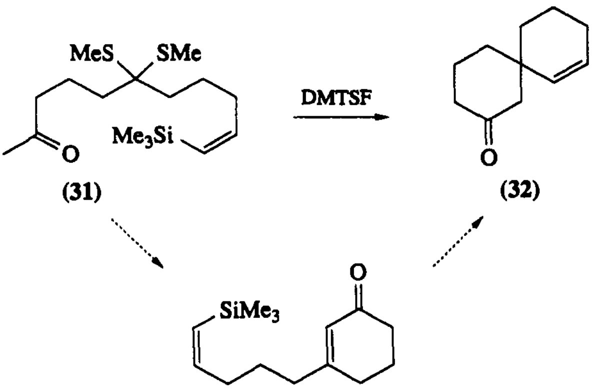
MeS
SMe
O
Me$_3$Si
DMTSF
O
O
SiMe$_3$

**(31)** **(32)**

**(31a)**

**Scheme 13**

Related cyclizations that occur in an endocyclic mode with respect to the initiating acetal function lead to a variety of different sized oxygen heterocycles, including eight-membered cyclic ethers. As summarized earlier by Blumenkopf and Overman, four modes of oxonium ion promoted cyclizations are possible.[8a] The sense of cyclization is dependent on the orientation of the initiating and terminating functional groups (Figure 11; equations 1–4).

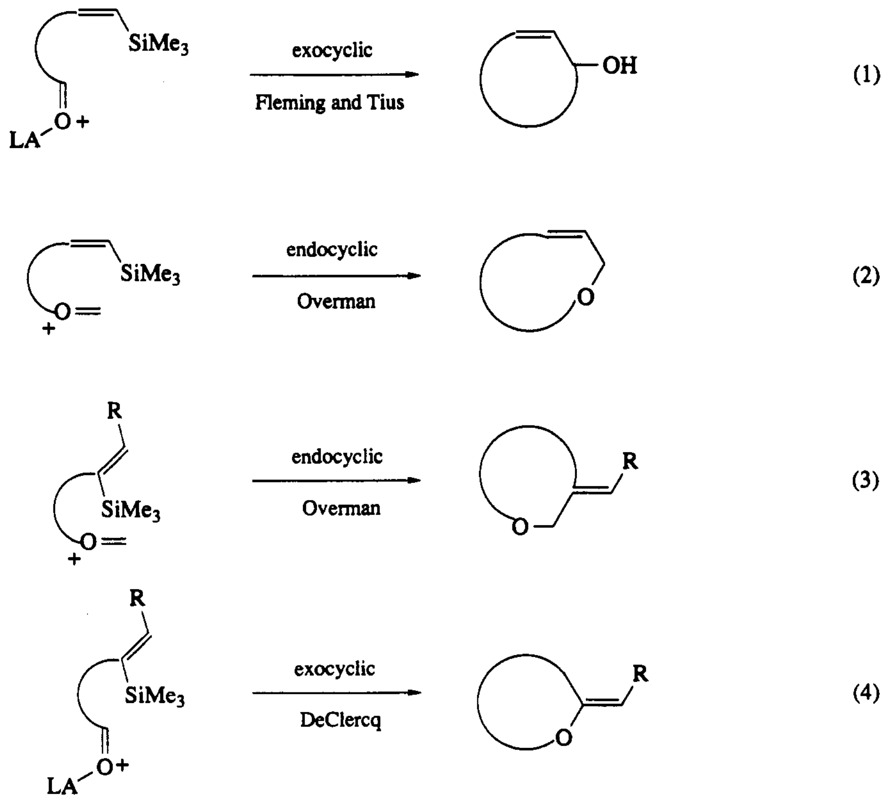

**Figure 11** Oxonium ion initiated cyclization modes of vinylsilanes

An efficient approach to the synthesis of oxygen heterocycles has been described by Overman and coworkers. It utilizes the internal trapping of an oxonium ion, generated by the action of a Lewis acid on methoxyethoxymethyl ether (MEM ether) by a vinyltrimethylsilane, as illustrated in Scheme 14.[8a,19] For instance, 5,6-dihydro-2*H*-pyrans (**34a**)–(**34d**) were prepared as single double-bond regioisomers from the reaction of vinylsilane acetals (**33a**)–(**33d**) under Lewis acid catalysis (Table 3).[8a] An interesting example is shown in entry (**33d**). In this case the 1-bromo-1-(trimethylsilyl)alkene, presumably a weaker nucleophile due to the inductive destabilization of the intermediate $\beta$-silyl carbocation by the bromine atom, still underwent cyclization in good yield. More importantly, from a synthetic viewpoint the reaction resulted in the formation of a regiospecifically functionalized pyran system in good yield.

The construction of medium-sized ring systems has been a persistent and difficult problem in organic synthesis. The cyclizations that occur in an exocyclic mode with respect to the vinylsilane terminator have been used to prepare five-, six- and even seven- and eight-membered oxygen heterocycles.[19,20a,b] As illustrated in Scheme 15, for the construction of pyran systems, acetals (**35a**) and (**35b**) underwent cyclization to yield the tetrahydropyrans (**36a**) and (**36b**) in excellent yields with high levels of stereoselection (>99.5% retention of stereochemistry about the double bond).

The first stereocontrolled method for the preparation of 3-alkylideneoxepanes was demonstrated using this cyclization strategy.[20] Thus, Lewis acid promoted cyclizations of vinylsilane acetals (**37a**) and (**37b**) yielded the seven-membered ring alkylideneoxacycles (**38a**) and (**38b**), as illustrated in Scheme 16.

The vinylsilane-terminated cyclization strategy has been extended to the preparation of eight-membered cyclic ethers.[20a,b] Oxocenes (Scheme 17) with $\Delta^4$-unsaturation (3,6,7,8-tetrahydro-2*H*-oxocins) were prepared efficiently by the $SnCl_4$-catalyzed cyclization of the mixed acetals (**39**) with complete regiochemical control. Electrophilic addition on the 2-(trimethylsilyl)-1-alkene occurs predominantly at the terminal position of the alkene to form a tertiary $\alpha$-silyl, rather than a primary $\beta$-silyl, carbocation.[8a] The

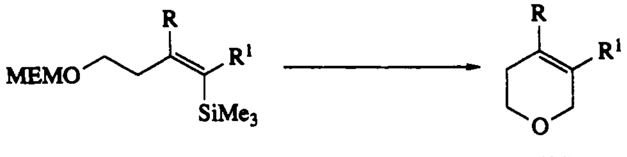
R
MEMO
$R^1$
$SiMe_3$
R
$R^1$
O

(33) (34)

Scheme 14

Table 3 Preparation of Dihydro-2*H*-pyrans (34)

| *Entry* | *R* | *R*$^1$ | *Lewis acid* | *Temperature* (°C) | *Time* (h) | *Yield* (%) |
|---|---|---|---|---|---|---|
| **(33a)** | H | H | $SnCl_4$ | –20 | 1.0 | 71 |
| **(33b)** | H | $(CH_2)_3Ph$ | $SnCl_4$ | –20 | 1.0 | 65 |
| **(33c)** | Me | H | $TiCl_3(OPr^i)$ | –20 | 2.0 | 83 |
| **(33d)** | H | Br | $TiCl_4$ | –60 | 2.0 | 78 |

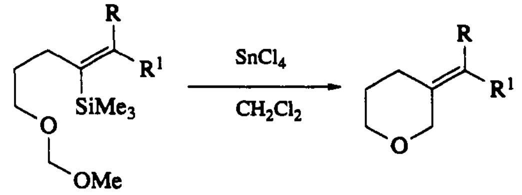
R
$R^1$
$SiMe_3$
O
OMe
$SnCl_4$
$CH_2Cl_2$
R
$R^1$
O

**(35a)** R = H, $R^1$ = $Bu^n$

**(35b)** R = $Bu^n$, $R^1$ = H

**(36a)** 89%

**(36b)** 92%

Scheme 15

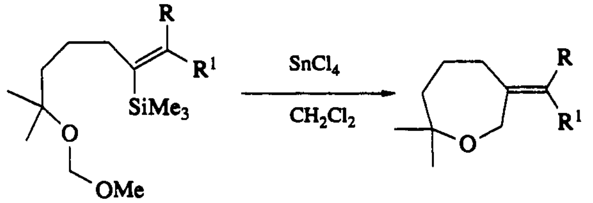
R
$R^1$
$SiMe_3$
O
OMe
$SnCl_4$
$CH_2Cl_2$
R
$R^1$
O

**(37a)** R = H, $R^1$ = $Bu^n$

**(37b)** R = $Bu^n$, $R^1$ = H

**(38a)** 71%

**(38b)** 57%

Scheme 16

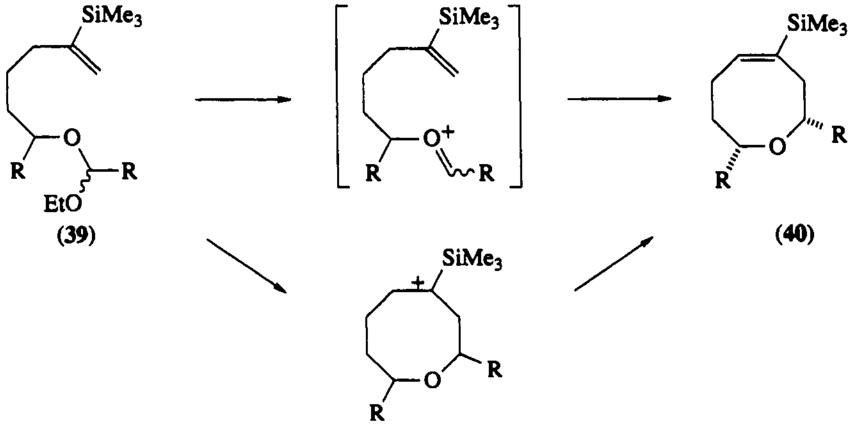
$SiMe_3$
O
R
R
EtO
$SiMe_3$
$O^+$
R
R
$SiMe_3$
O
R
R
$SiMe_3$
+
O
R
R

(39)

(40)

Scheme 17

*cis* stereochemistry of cyclizations that form 2,8-disubstituted-$\Delta^4$-oxocenes of structural type (**40**) can be rationalized on the basis that cyclization of the more stable (*E*)-oxonium ion (**41**) → (**42**) should occur preferentially in the conformation having the hydrogen (smallest substituent) at the α-carbon in the plane of the partial C—O π-bond (Scheme 18). Alternatively, Overman has suggested that the *cis* stereochemistry could arise from trapping of the (*E*)-oxonium ion in an intramolecular ene reaction, which proceeds through a boat–chair bicyclo[3.3.1]nonane transition state, as illustrated in Scheme 19.[20b]

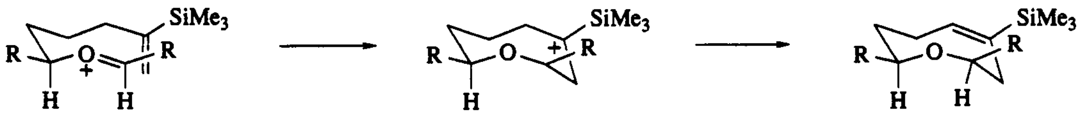

(*E*)-Oxonium ion (**41**)

(**42**)

**Scheme 18**

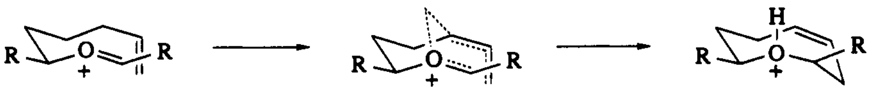

**Scheme 19** Oxonium ion trapping *via* an intramolecular ene reaction

In contrast, vinylsilane acetals (**43a**)–(**43c**), with a two-carbon tether between the vinylsilane and the MEM group, cyclize in the presence of tin tetrachloride to form tetrasubstituted alkylidenetetrahydrofurans (**44a**)–(**44c**). However, little or no stereochemical preference for either (*E*)- or (*Z*)-alkene stereoisomers was observed in these reactions (Scheme 20 and Table 4).[19]

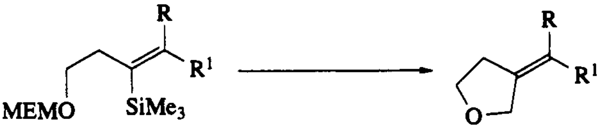

(**43**)

(**44a**) R = Et, $R^1 = Bu^n$

(**44b**) $R = Bu^n$, $R^1$ = Et

(**44c**) $R = Bu^n$, $R^1$ = H

**Scheme 20**

**Table 4** $SnCl_4$-catalyzed Cyclizations of MEM Ethers

| *Entry* | *R* | *$R^1$* | *Lewis acid* | *(E):(Z) ratio* | *Yield (%)* |
|---|---|---|---|---|---|
| (**43a**) | Et | $Bu^n$ | $SnCl_4$ | 40:60 | 81 |
| (**43b**) | $Bu^n$ | Et | $SnCl_4$ | 40:60 | 86 |
| (**43c**) | $Bu^n$ | H | $SnCl_4$ | 97:3 | 81 |

Through the efforts of the Overman research group, the acetal–vinylsilane cyclization reaction has been shown to be a useful strategy for the stereoselective preparation of a variety of medium-sized oxygen heterocycles. This cyclization strategy has been used successfully in the asymmetric synthesis of the marine natural product (–)-laurenyne (**40a**), an eight-membered cyclic ether.[21] These molecules are members of an unusual class of C-15 nonisoprenoid metabolites.

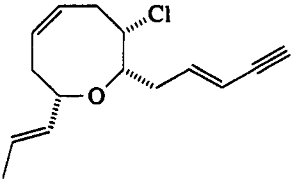

(**40a**) (–)-Laurenyne

In contrast, the related cyclizations used to form carbocyclic systems have been of limited synthetic value due to the acid sensitive nature of the derived allylic ether product (equation 1; Figure 11). The sensitivity of these carbocycles may be rationalized by considering the poor orbital overlap between the allylic C—O bond with the adjacent π-bond in a five-, six- or seven-membered ring.[8a,20a]

### 2.5.3.1.4 Acyliminium and iminium ion initiated cyclizations

Activated C═N bonds have been used extensively as initiators in cyclization reactions. In particular, acyliminium and iminium ions serve as reliable initiators in vinylsilane-terminated cyclizations and thus represent an exceptionally useful method for the construction of nitrogen heterocycles.[8a] As with oxonium ions, iminium ions may be generated using similar conditions that are compatible with the terminating vinyltrimethylsilanes. Acyliminium and iminium ions have been applied in key ring-forming reactions in a number of alkaloid syntheses. This section will examine the use of this methodology in stereoselective bond-forming reactions relevant to the synthesis of nitrogen heterocycles (Scheme 21).

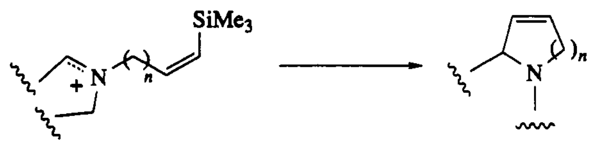

Scheme 21

An acyliminium ion terminated cyclization served as the key step in a short synthesis of the indolizinone alkaloids elaeocanines B (**47a**) and A (**47b**).[22] The key intermediates and cyclizations are summarized in Scheme 22.

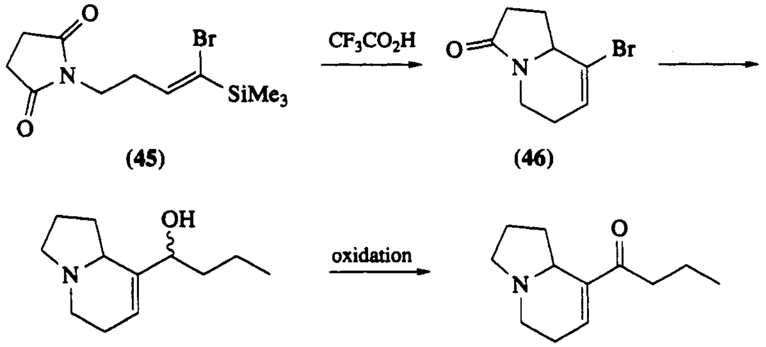

(**45**) (**46**) (**47a**) (**47b**)

Scheme 22

The reported synthesis of the Amaryllidaceae alkaloid (±)-epielwesine (**50**) also employed an iminium ion–vinylsilane in the key cyclization step (Scheme 23).[23] Reaction of the (*Z*)-vinyltrimethylsilane (**48**) with TFA generated an intermediate iminium ion, which was trapped by the vinylsilane nucleophile to yield the *cis* fused heterocycle (**49**).

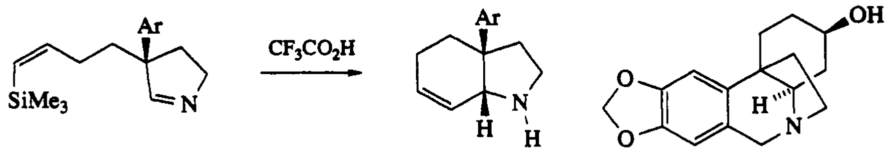

(**48**) (**49**) (**50**) (±)-Epielwesine

Scheme 23

The synthesis of the indoloquinolizadine alkaloid deplancheine (**52**; Scheme 24), using an exocyclic variant of an iminium ion initiated vinylsilane cyclization, has been reported by Malone and Overman.[24] Thus, treatment of vinylsilane (**51**) with formaldehyde resulted in the generation of an intermediate iminium ion that underwent smooth cyclization, forming the carbon framework of deplancheine. The (*Z*)-vinylsilane (**51b**) also cyclized to the (*Z*)-stereoisomer of deplancheine (**52b**) *via* the corresponding iminium ion to give the tetracyclic ring system in greater than 98% isomeric purity. This series of experiments provides an excellent demonstration of the high levels of stereoselection that can be achieved in vinylsilane cyclization reactions that occur in the exocyclic mode with respect to the attacking nucleophile.

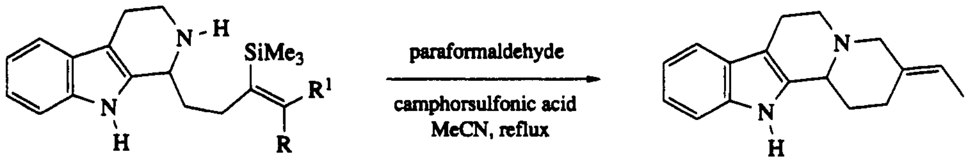

(**51a**) R = Me, $R^1$ = H

(**51b**) R = H, $R^1$ = Me

(**52**) (±)-Deplancheine

**Scheme 24**

A successful enantioselective approach to the pumiliotoxin class of alkaloids has been developed using vinylsilane cyclization strategies.[25] Three members of this class, pumiliotoxin A (**55**), pumiliotoxin B (**56**) and pumiliotoxin 251D (**57**) have been synthesized in optically active forms through the use of iminium ion–vinylsilane cyclization reactions. The strategy employed in these syntheses relied on the chiral pool to provide optical activity. L-Proline was used as the optically active starting material; its (*S*)-stereocenter became the C-8a stereocenter of the indolidizidine ring system in all three alkaloids. The iminium ion–vinylsilane strategy was employed in constructing the piperidine ring and establishing the (*Z*)-stereochemistry of the alkylidene side chain. The key bond-forming reaction in each synthesis is detailed in Scheme 25 and involved the generation and subsequent trapping of an iminium ion by the vinylsilane. The total syntheses of (+)-geissoschizine (**58**) and (±)-(*Z*)-isositsirkine (**59**) have also been documented. The general strategy is outlined in Scheme 26 below and utilized, as a key step, stereocontrolled formation of the ethylidene side chain by stereospecific cyclization of an (*E*)- or (*Z*)-vinylsilane iminium (**A**) → (**B**).

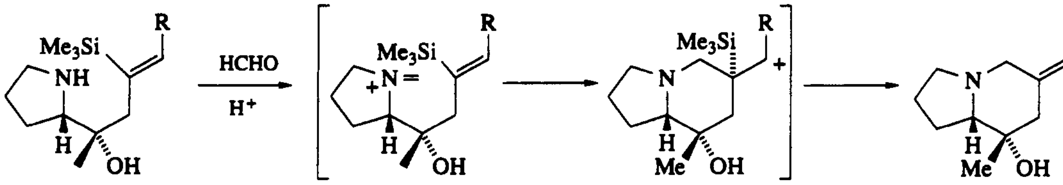

(**53**)

(**54**)

**Scheme 25**

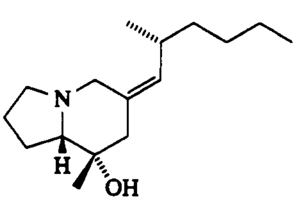

(**55**) Pumiliotoxin A

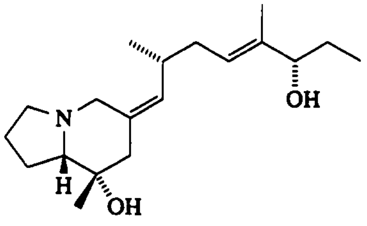

(**56**) Pumiliotoxin B

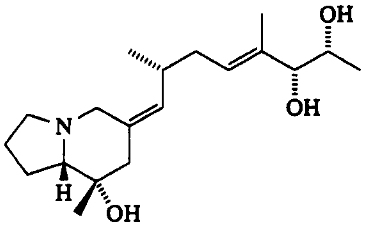

(**57**) Pumiliotoxin 251D

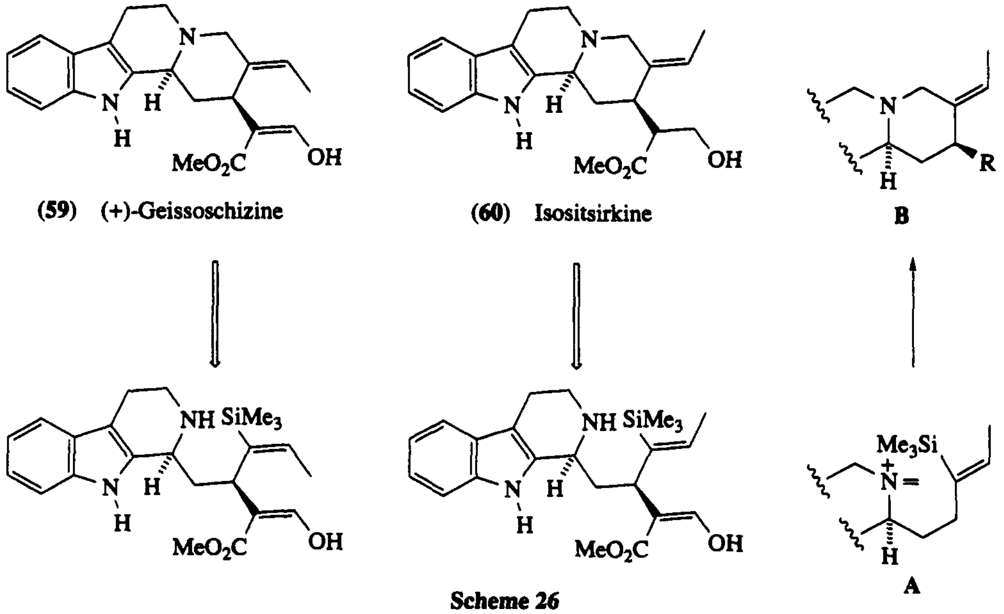
(59) (+)-Geissoschizine
(60) Isositsirkine
B
A

**Scheme 26**

An efficient enantiodivergent synthesis of levorotatory (1*S*,2*R*,8a*S*)-1,2-dihydroxyindolizidine (**62a**) and its antipode (**62b**) has been developed starting from commercially available D-isoascorbic acid (**61**; Scheme 27).[27] This strategy illustrates the complementary use of iminium and *N*-acyliminium ion inter-

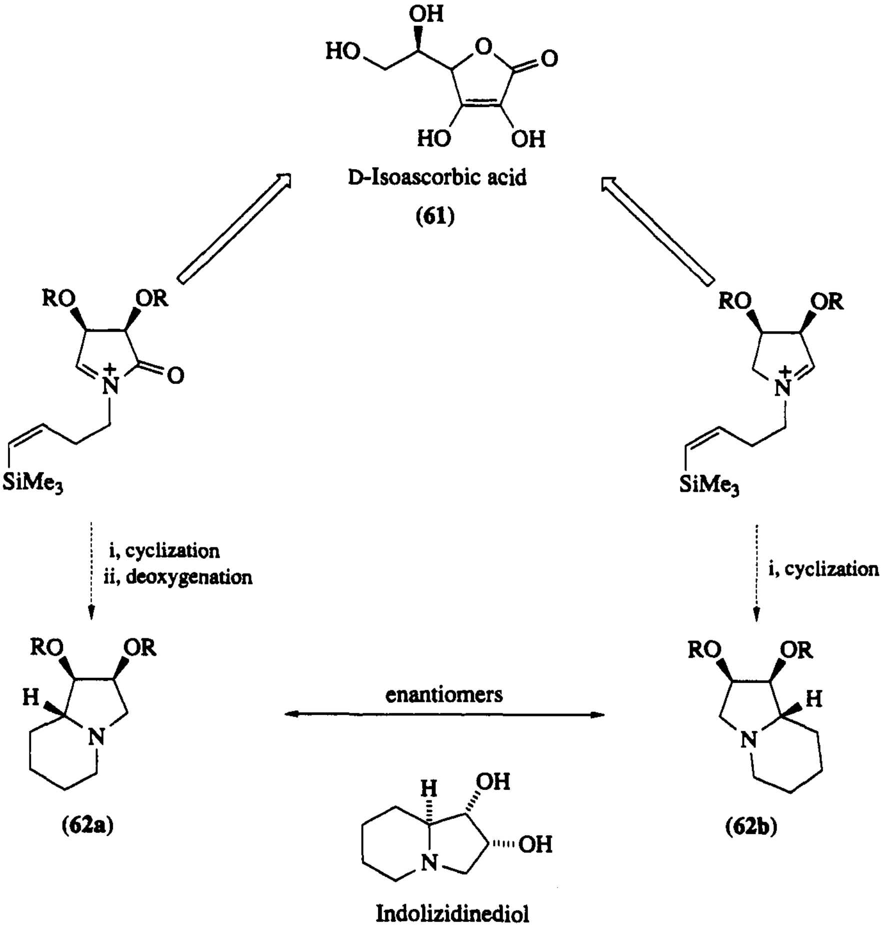
D-Isoascorbic acid
(61)
i, cyclization
ii, deoxygenation
i, cyclization
enantiomers
(62a)
(62b)
Indolizidinediol

**Scheme 27**

mediates as initiators for the enantiodivergent synthesis of the indolizidinediol alkaloids. The different types of iminium ion initiated cyclizations, and their related electron deficient intermediates, have become some of the most useful methods for the preparation of nitrogen heterocycles. These studies have illustrated the compatibility of iminium ion–vinylsilane cyclizations with complex alkaloids containing sensitive functional groups.[8a,25–27]

### 2.5.3.2 Allenylsilanes: Multifunctional Propargylic Anion Equivalents

Alkynic intermediates serve as important functional groups in organic synthesis. Many important reactions exploiting the unique and versatile chemistry of the carbon–carbon triple bond have been devised over the last few years.[28] A general strategy for the synthesis of substituted alkynes involves substitution and addition reactions of propargylic anion equivalents; this approach is particularly well suited for the preparation of homopropargylic alcohols (Scheme 28).

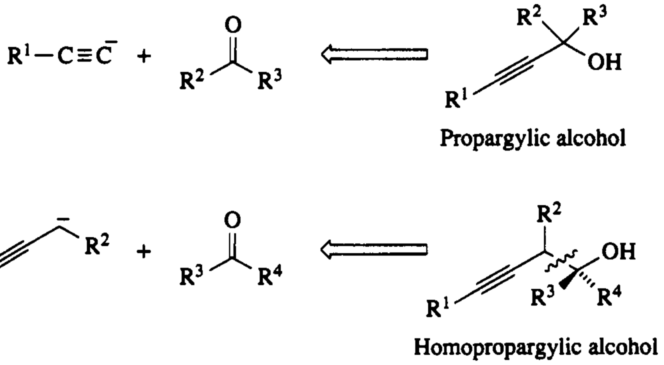

Scheme 28

This methodology has been limited by the tendency of metallated propargylic anions to add to electrophiles to produce a mixture of regioisomers. This lack of regiochemical control results from the fact that these anions exist as an equilibrating mixture of allenic and propargylic anions, which can both add to electrophiles to produce allenic and propargylic alcohols (Scheme 29). Thus, product ratios are determined by the position of the equilibrium between the two organometallic species. Pioneering work by Danheiser and coworkers has resulted in the development of allenylsilanes as useful propargylic anion equivalents.[29] Importantly, these readily available organometallic compounds do not participate in the dynamic equilibrium described above and, as a result, undergo additions with virtual regiospecificity. As described in Sections 2.5.4.1 to 2.5.4.8, allenylsilanes have proven to be useful carbon nucleophiles and are known to participate in regio- and stereo-controlled addition reactions to a variety of electrophiles.

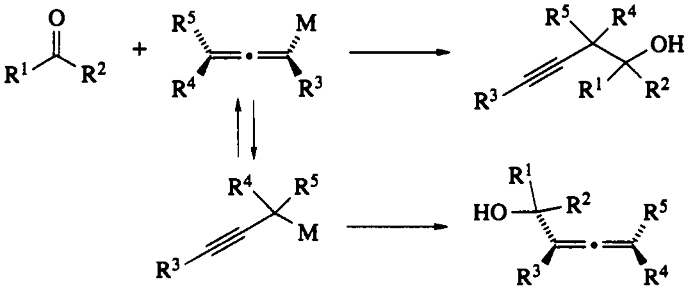

Scheme 29

#### *2.5.3.2.1 Titanium tetrachloride promoted additions of allenylsilanes to carbonyl compounds*

The $TiCl_4$-mediated addition of allenylsilanes (**66**; Scheme 30) to aldehydes and ketones provides a general regiocontrolled route to a wide variety of substituted homopropargylic alcohols.[29] Importantly, all three types of homopropargylic alcohols (**63**, **64** and **65**) are accessible through allenylsilane methodology.

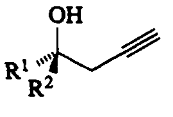

**(63)**

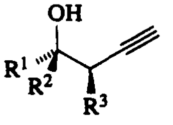

**(64)**

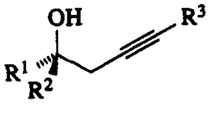

**(65)**

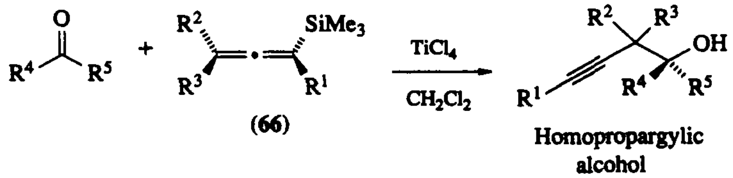

a: $R^1$ = Me, $R^2$ = $R^3$ = H    d: $R^1$ = $R^3$ = H, $R^2$ = $-(CH_2)_2Ph$
b: $R^1$ = $Pr^i$, $R^2$ = $R^3$ = H    e: $R^1$ = $R^2$ = H, $R^3$ = Me
c: $R^1$ = $R^3$ = H, $R^2$ = Me    f: $R^1$ = Me, $R^3$ = Et, $R^3$ = H

**Scheme 30**

Reactions of chiral allenes proceed with a preference for the formation of the *syn* diastereomer. The stereochemical outcome of these reactions can be rationalized by invoking an open transition state model for the addition reactions (Figure 12), which depicts an antiperiplanar orientation of the chiral allenylsilane to the aldehyde carbonyl. In this model, steric repulsion between the allenyl methyl and the aldehyde substituent is most likely responsible for the destabilization of transition state (**B**), which leads to the *anti* (minor) stereoisomer. This destabilizing interaction is minimized in transition state (**A**). Table 5[29] illustrates representative examples and summarizes the scope of the regiocontrolled synthesis of homopropargylic alcohols using allenylsilanes.

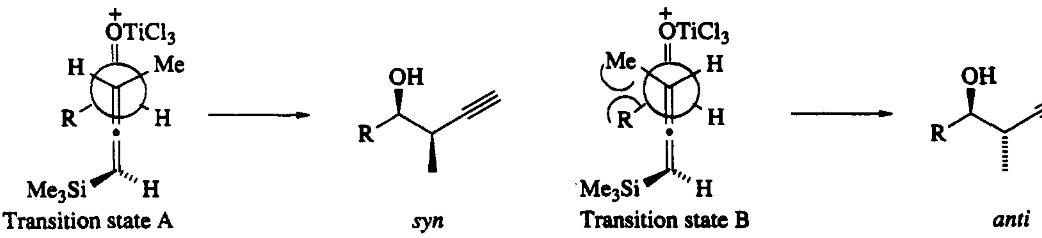

**Figure 12**

### *2.5.3.2.2 [3 + 2] annelation strategies involving allenylsilanes*

[3 + 2] annelation tactics involving allenylsilanes as the three-carbon nucleophile have been extensively investigated by Danheiser and coworkers.[30] Their efforts in this area have resulted in the generation of an effective strategy for the preparation of a variety of both carbocyclic and heterocyclic compounds. These processes are summarized in Figure 13 with the illustrated transformations. The allenylsilane (**66**) reacts with α,β-unsaturated carbonyl compounds to give carbocyclic derivatives (**67a**)–(**69a**). Allenylsilanes react with heteroallenophiles, *e.g.* aldehydes, acylium, acyliminium, iminium and nitronium ions to yield the corresponding heterocyclic products (**70**)–(**72**). Sections 2.5.4.2–2.5.4.8 offer a detailed discussion of these reactions.

### *2.5.3.2.3 Additions to α,β-unsaturated carbonyl compounds*

The reaction of allenylsilanes with electron deficient π-systems constitutes a powerful and general method for the regio- and stereo-selective preparation of substituted cyclopentenes.[30] As first reported, (trimethylsilyl)allenes function as three-carbon nucleophiles in $TiCl_4$-promoted (trimethylsilyl)cyclopentene annelations (Scheme 31). The annelation process involves the polarization of an α,β-unsaturated carbonyl compound by $TiCl_4$ to generate an alkoxyallylic cation. Regiospecific electrophilic substitution of this cation at C-3 of the allenylsilane produces a silicon-stablized vinyl cation. A 1,2-shift of the trimethylsilyl group then yields an isomeric vinyl cation, which is trapped by the titanium enolate to generate the annelated (trimethylsilyl)cyclopentene products (**67b**).

**Table 5** Regiocontrolled Synthesis of Homopropargylic Alcohols (see Scheme 30)

| *Entry* | *Carbonyl compound* | *Allenylsilane* | *Method*[a] | *Product(s)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Cyclohexanecarbaldehyde | **66a** | A | 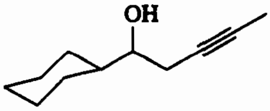 | 68 |
| 2 | $PhCH_2CH_2CHO$ | **66a** | A | 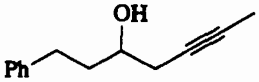 | 85 |
| 3 | $Pr^iCOMe$ | **66a** | A | 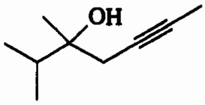 | 86 |
| 4 | $PhCH_2CH_2CHO$ | **66b** | A | 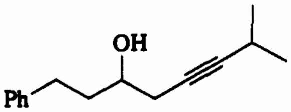 | 89 |
| 5 | Cyclohexanone | **66b** | A | 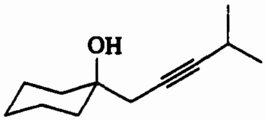 | 84 |
| 6 | $Pr^iCOMe$ | **66b** | A | 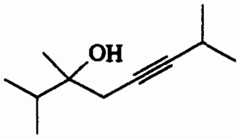 | 51 |
| 7 | $PhCH_2CH_2CHO$ | **66c** | B | 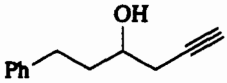 | 84 |
| 8 | $PhCH_2COMe$ | **66c** | B | 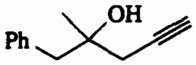 | 72 |
| 9 | Cyclohexanone | **66c** | B | 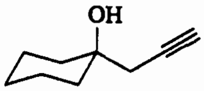 | 89 |
| 10 | MeCOMe | **66d** | B | 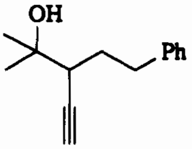 | 38 |
| 11 | Cyclohexanone | **66d** | B | 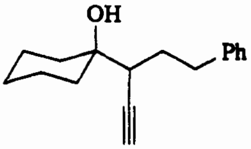 | 49 |

**Table 5** *(continued)*

| *Entry* | *Carbonyl compound* | *Allenylsilane* | *Method*[a] | *Product(s)* | *Yield (%)* |
|---|---|---|---|---|---|
| 12 | $PhCH_2CH_2CHO$ | **66e** | B | 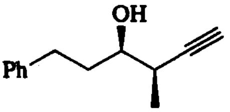<br>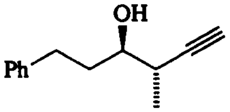 | 89 (3.1:1) |
| 13 | Cyclohexanecarbaldehyde | **66e** | B | 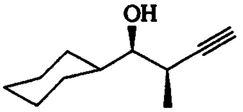<br>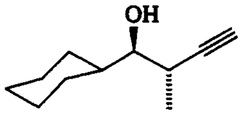 | 81 (4.1:1) |
| 14 | Cyclohexanone | **66e** | B | 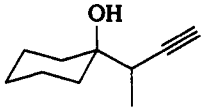 | 77 |

[a] Method A: $TiCl_4$ (1.15 equiv.), −78 to 25 °C. Method B: $TiCl_4$ (1.15 equiv.), −78 to 25 °C then 2.0–2.5 equiv. of KF in DMSO.

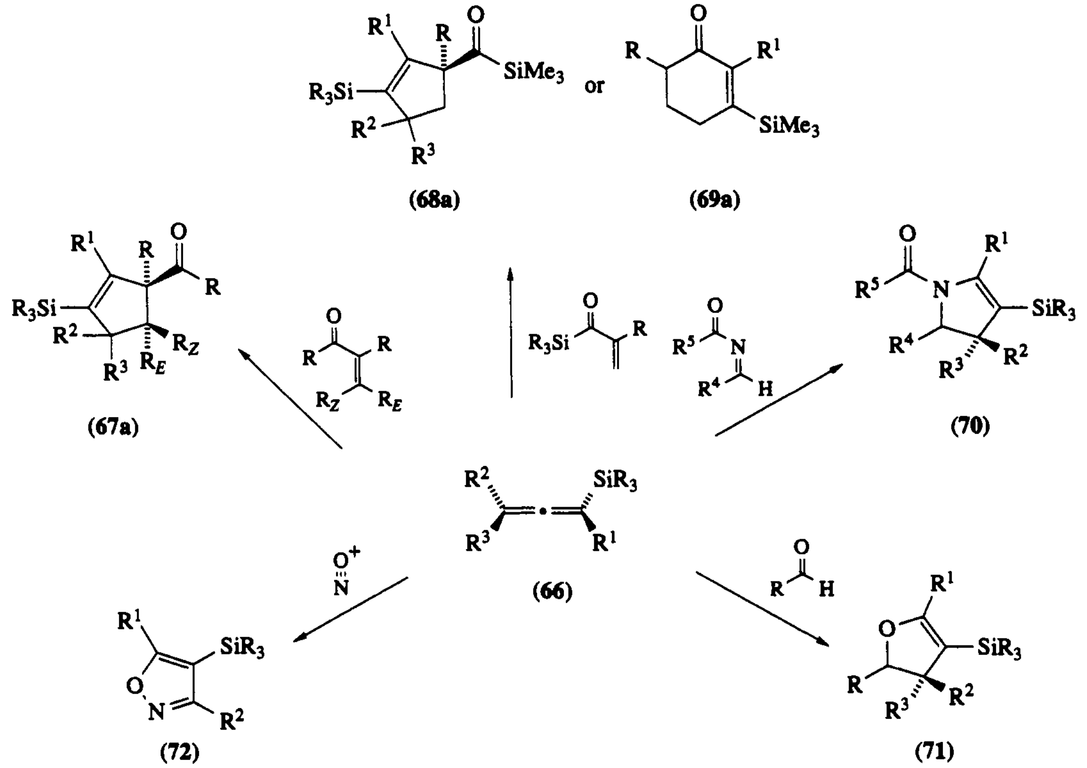

**Figure 13**

**Table 6** (Trimethylsilyl)cyclopentene Annelations (see Scheme 30)

| *Entry* | *α,β-Unsaturated ketone* | *Allenylsilane* | *(Trimethylsilyl)cyclopentene product* | *Yield (%)* |
|---|---|---|---|---|
| 1 | Methyl vinyl ketone | **66a** | 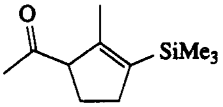 | 68–75 |
| 2 | Cyclohexenone | **66a** | 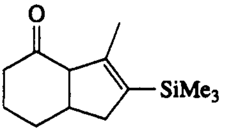 | 85 |
| 3 | Cycloheptenone | **66a** | 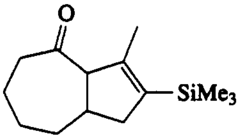<br>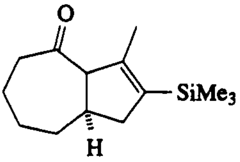 | 90–94 (*cis*:*trans* = 83:17) |
| 4 | Cyclopentenone | **66a** | 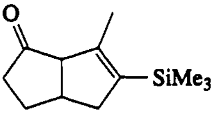 | 48 |
| 5 | *trans*-3-Penten-2-one | **66a** | 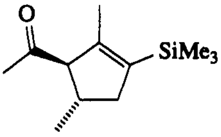 | 79 |
| 6 | Carvone | **66a** | 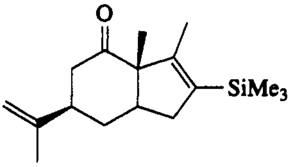 | 87 |
| 7 | 1-Acetylcyclohexene | **66a** | 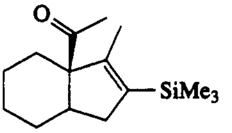 | 91 |
| 8 | 2-Methylene-α-tetralone | **66a** | 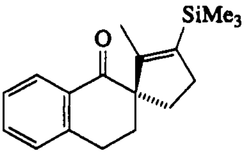 | 80–84 |

**Table 6** *(continued)*

| *Entry* | *α,β-Unsaturated keton* | *Allenylsilane* | *(Trimethylsilyl)cyclopentene product* | *Yield (%)* |
|---|---|---|---|---|
| 9 | Phenyl vinyl ketone | **66b** | 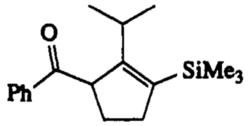 | 69–73 |
| 10 | Cyclohexenone | **66b** | 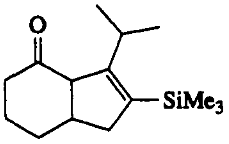 | 81–85 |
| 11 | Cyclohexenone | **66b** | 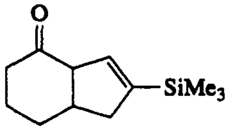 | 17–19 |
| 12 | Methyl vinyl ketone | **66e** | 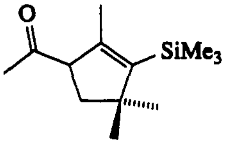 | 80 |
| 13 | Cyclohexenone | **66e** | 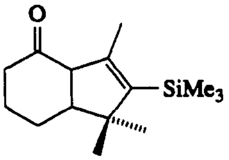 | 61–63 |
| 14 | Cyclohexenone | **66f** | 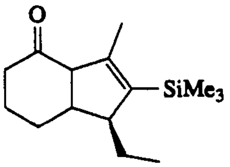<br>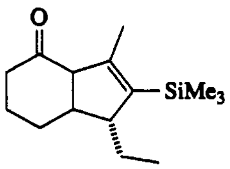 | 79 (*cis*:*trans* = 95:5) |
| 15 | Cyclopentenone | **66c** | 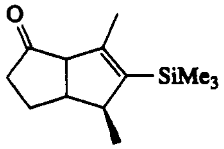<br>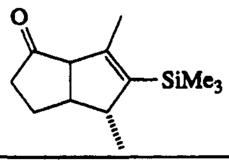 | 68 (*cis*:*trans* = 75:25) |

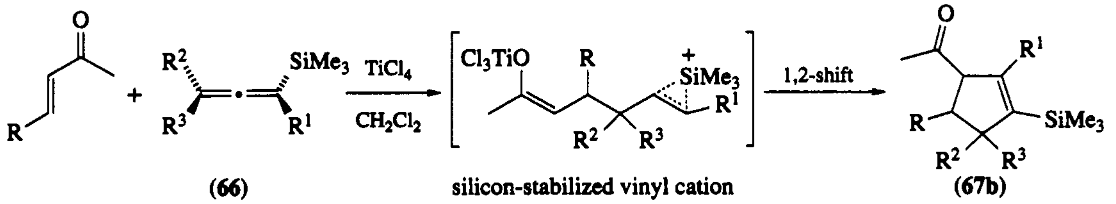

**Scheme 31**

Both cyclic and acyclic enone systems participate in the (trimethylsilyl)cyclopentene annelation (Table 6).[40] α-Methylene ketones react to form spiro-fused systems and the intermediates derived from acetylcyclohexanone, cyclohexenone and cyclopentanone cyclize to yield 5,5- and 6,5-fused ring systems.[30]

### *2.5.3.2.4 Additions to α,β-unsaturated acylsilanes*

α,β-Unsaturated acylsilanes serve as highly reactive carboxylic acid equivalents in conjugate addition reactions with allenylsilanes.[31] The trimethylsilyl acylsilanes provide the basis for a [3 + 3] annelation approach to six-membered carbocycles. By manipulating the trialkylsilyl group of the acylsilane, the course of the annelation reaction can be controlled to produce either five- or six-membered rings (**68** and **69**; Figure 13 and Scheme 32). α,β-Unsaturated acylsilanes combine with allenylsilanes at –78 °C in the presence of $TiCl_4$ to produce trimethylsilyl–cyclopentene annelation products in good yield (Table 7).[31]

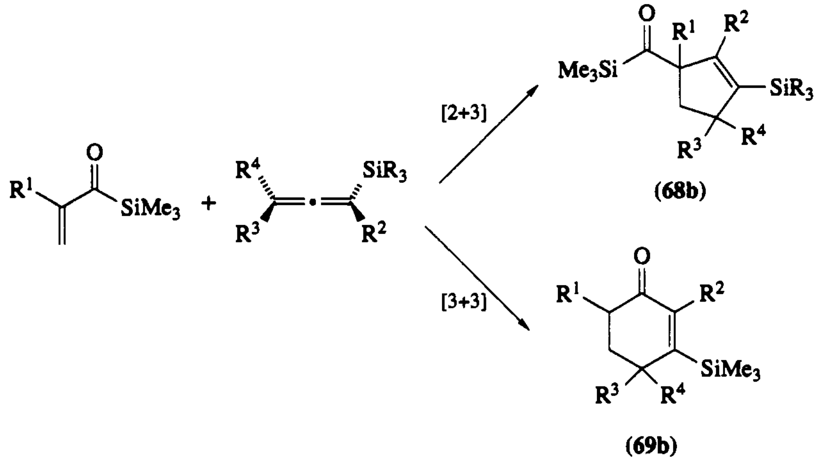

**Scheme 32**

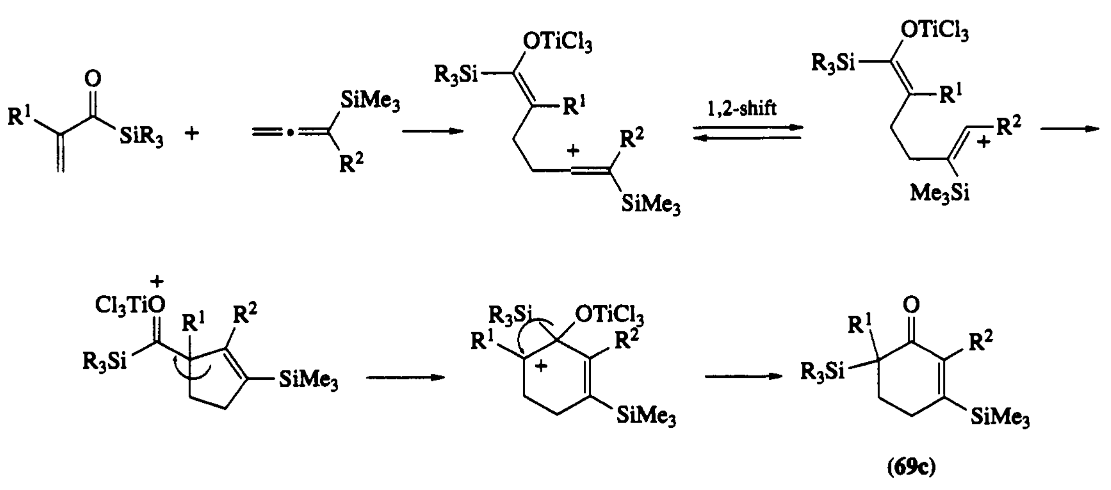

**Scheme 33**

The annelation products derived from 2-alkyl-substituted α,β-unsaturated acylsilanes undergo a rearrangement to β-silylcyclohexanone derivatives when treated with $TiCl_4$. The proposed mechanism is illustrated in Scheme 33.[31] The annelation process commences with the regiospecific electrophilic substitution at the C(3)-position of the allenylsilane, producing a vinyl carbocation which undergoes a 1,2-cationic trimethylsilyl shift to yield an isomeric vinyl carbocation. Cyclization then gives the [3 + 2] annelation product. Ring expansion of the cyclopentene generates a tertiary carbocation, which undergoes a second 1,2-anionic trimethylsilyl shift to produce the cyclohexanone (**69c**).

**Table 7** Annelations of α,β-Unsaturated Acylsilanes

| *Acylsilane* | *Allenylsilane* | *Product* | *Yield (%)*[a] |
|---|---|---|---|
| 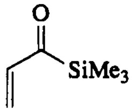 | 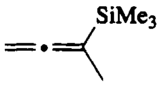 | 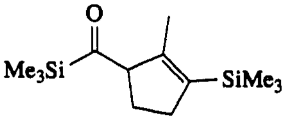 **(68c)** | 72 |
| 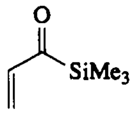 | 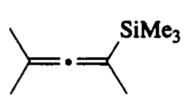 | 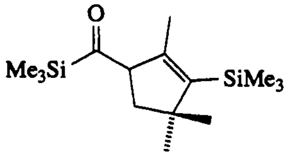 **(68d)** | 55 |
| 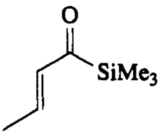 | 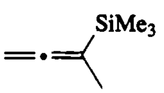 | 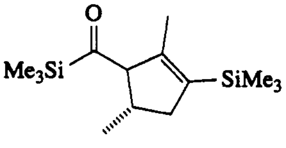 **(68e)** | 66 |
| 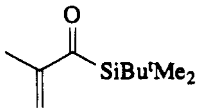 | 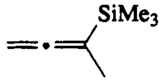 | 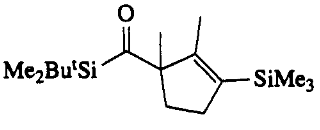 **(68f)** | 78 |
| 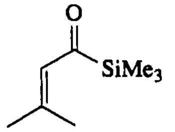 | 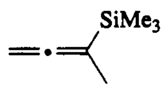 | 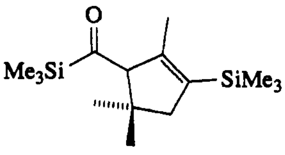 **(68g)** | 74 |

[a] Reactions were conducted using 1.0–1.5 equiv. of allenylsilane and $TiCl_4$ (1.5 equiv.) in methylene chloride at –78 °C for 0.5–1.0 h or 30 s in the case of (**68e**).

### *2.5.3.2.5 Additions to acyliminium ions*

The reactions of sterically encumbered allenylsilanes of structure type (**66**) with *N*-acyliminium ions generated by the titanium tetrachloride promoted reaction of ethoxypyrrolidinone produced the nitrogen heterocycle (**70**), as depicted in Figure 13. In this reaction it is likely the lactam product is generated by a pathway similar to that involved in the [3 + 2] cyclopentene annelation.[32] Thus, a regiospecific electrophilic substitution of the *N*-acyliminium ion derived from substitution at the C-3 position of the allenylsilane produces a vinyl cation stabilized by the hyperconjugative interaction of the adjacent σ-donor silicon group. A 1,2-cationic trialkylsilyl shift then occurs, affording an isomeric vinyl cation, which is intercepted by the nucleophilic nitrogen atom to form the new heterocycle (**70**) as summarized in Table 8.[32]

**Table 8** Preparation of Nitrogen Heterocycles *via* [3 + 2] Annelation

| *Allenophile* | *Allene* | *Annelation product(s)* | *Yield (%)* |
|---|---|---|---|
| 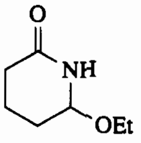 | 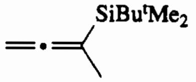 | 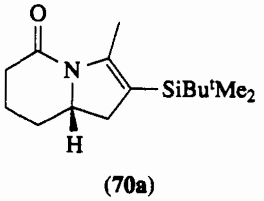<br>**(70a)** | 67 |
| 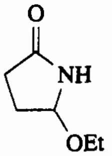 | 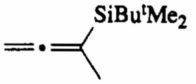 | 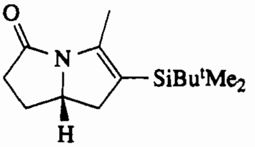<br>**(70b)** | 63 |
| 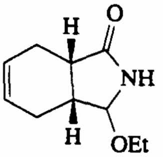 | 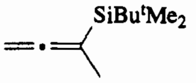 | 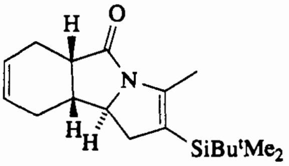<br>**(70c)** | 76 |
| 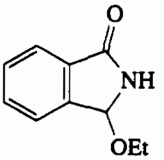 | 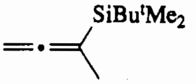 | 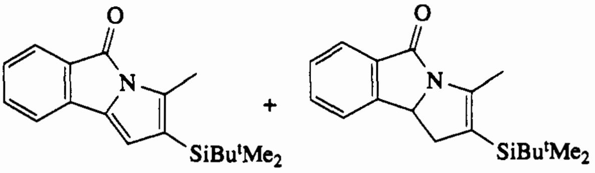<br>**(70d)** 2.8:1 | 76 |
| 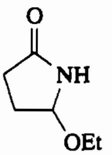 | 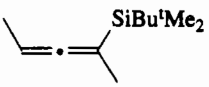 | 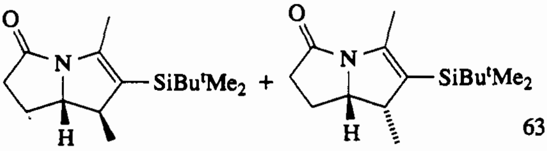<br>**(70e)** 1.2:1 | 63 |

### *2.5.3.2.6 Additions to aldehydes*

A variety of aldehydes can function as heteroallenophiles in this [3 + 2] annelation (Figure 13 and Table 9).[32] Reactions of the C(3)-substituted allenylsilanes (**66**) gave predominantly the *cis*-substituted dihydrofurans (**71**). The *cis* stereochemistry was anticipated, based on the well-documented stereochemical course of Lewis acid catalyzed additions of 3-substituted allylsilanes to aldehydes.[32]

**Table 9** Preparation of Oxygen Heterocycles *via* [3 + 2] Annelation

| *Allenophile* | *Allene* | *Annelation product(s)* | *Yield (%)* |
|---|---|---|---|
| 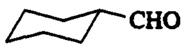 | 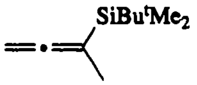 | 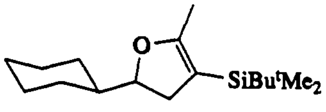<br>**(71a)** | 76 |
| 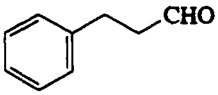 | 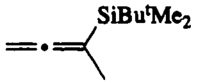 | 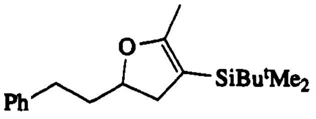<br>**(71b)** | 70 |
| MeCHO | 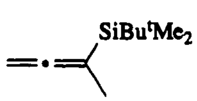 | 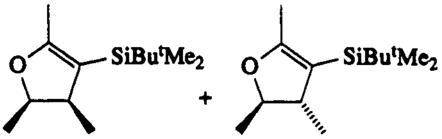<br>**(71c)** 1.4:1 | 78 |
| 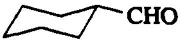 | 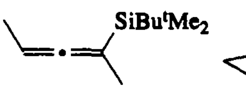 | 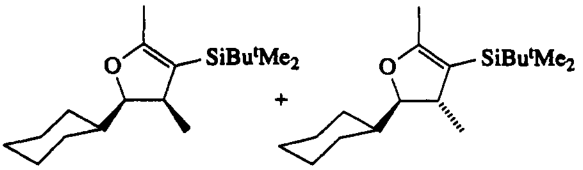<br>**(71d)** 7:1 | 97 |
| Bu$^t$CHO | 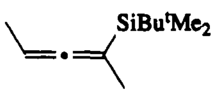 | 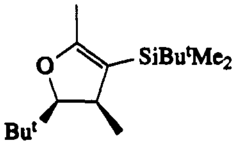<br>**(71e)** | 92 |
| 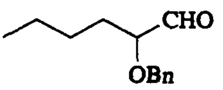 | 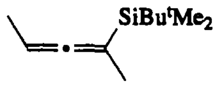 | 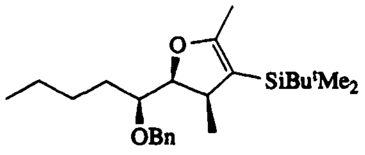<br>**(71f)** | 88 |

### *2.5.3.2.7 Additions to activated C═N π-bonds*

A general strategy for the synthesis of five-membered heteroaromatic compounds has been developed which involves the reaction of allenylsilanes with π-bonded electrophilic species of the general type $X{=}Y^+$ (heteroallenophile).[33] Scheme 34 details a stepwise mechanism to interpret the annelation. Addition of the heteroallenophile at the C-3 carbon of the allenylsilane produces a vinyl carbocation, which rapidly rearranges to the isomeric vinyl cation. The trialkylsilyl group serves two roles in this initial step: (i) it directs the regiochemical course of the electrophilic addition reaction (*i.e.* β-silicon effect); and (ii) it promotes the transfer of electrophilic character from the central carbon to the terminus of the three-carbon annelation unit, indicating the high migratory aptitude of silyl groups in cationic rearrangements. Cyclization furnishes the intermediate, which subsequently undergoes proton elimination to generate the aromatic heterocycle.

This [3 + 2] annelation strategy has been employed in a regiocontrolled synthesis of 4-silylisoxazoles. In this instance, nitrosonium tetrafluoroborate functions as a heteroallenophile in the isoxazole annelation (Scheme 35). The electrophilic addition of nitrosonium tetrafluoroborate ($NOBF_4$) to the C-3 position of the allenylsilane produces the silicon-stabilized vinyl cation. A 1,2-trialkylsilyl shift then occurs affording an isomeric vinyl cation, which is trapped by the nucleophilic oxygen of the nitroso group to form the intermediate (**73**). Deprotonation yields the aromatized 4-silylisoxazole system (**72**). This regiocontrolled, one-step annelation method allows access to a wide range of substituted 4-silylisoxazoles.

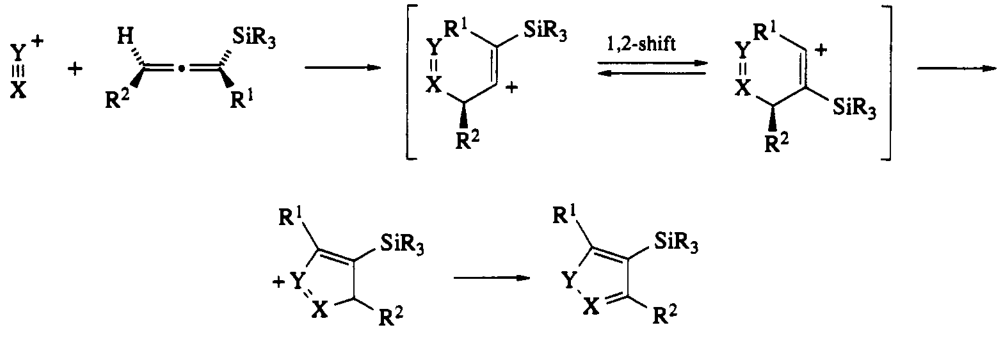

**Scheme 34**

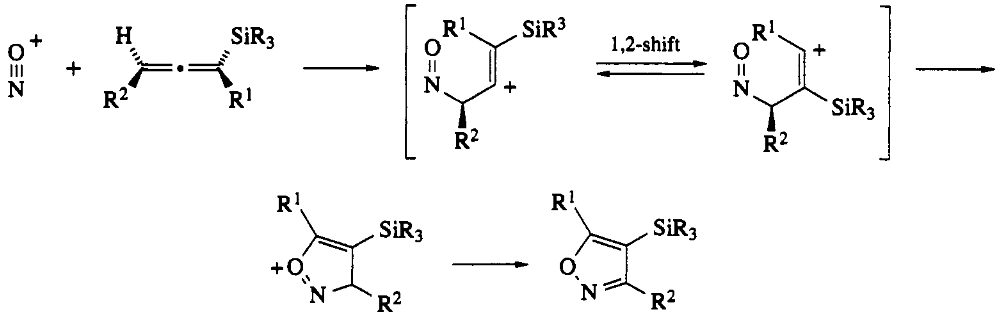

**(73)** **(72)**

**Scheme 35**

### *2.5.3.2.8 Additions to tropylium ions*

A new [3 + 2] annelation route to azulenes has been reported and involves the addition of a tropylium cation to allenylsilanes. The approach is based on the general [3 + 2] annelation strategy used in the preparation of five-membered carbocycles and heterocycles and uses tropylium tetrafluoroborate ($TpBF_4$) as the tropylium cation source.[34] The proposed mechanism is depicted in Scheme 36 and begins with addition of the tropylium ion to the C(3)-position of the allenylsilane, generating a vinyl cation which rapidly rearranges by a 1,2-shift to the isomeric vinyl cation. Cyclization of the latter cation furnishes the cycloheptyldienyl cation, which undergoes deprotonation to generate the dihydroazulene. Dehydrogenation occurs if a second equivalent of tropylium ion is added to the reaction: hydride abstraction by the tropylium ion generates a more stable (delocalized) tropylium ion derivative, which finally aromatizes by the elimination of the C(3)-proton to yield the product azulene (**74**). As indicated in Table 10,[34] azulene annelations which employ TBDMS alkenes are more efficient than those involving TMS derivatives, since TMS allenes undergo desilylation of the intermediate vinyl cations to produce propargyl-substituted cycloheptatrienes as by-products.

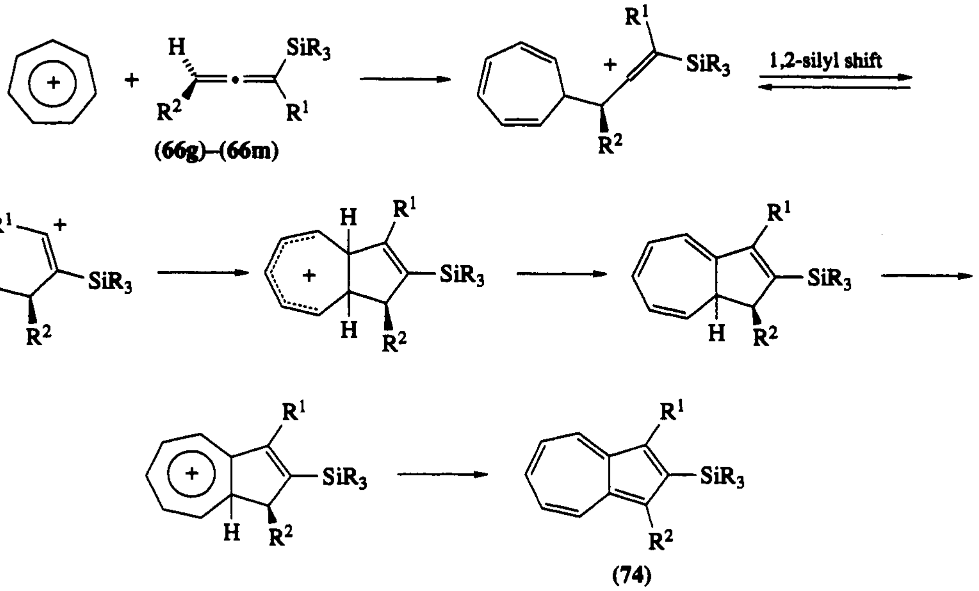

**Scheme 36**

**Table 10** Synthesis of Substituted Azulenes (see Scheme 36)

| *Entry* | *Allenylsilane* | *Method*$^a$ | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 1 | (**66g**) $R^1 = R^2 = Me$ | A | 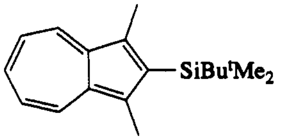 (**74a**) | 52–59 |
| 2 | (**66h**) $R^1 = Me$; $R^2 = (CH_2)_3Ph$ | B | 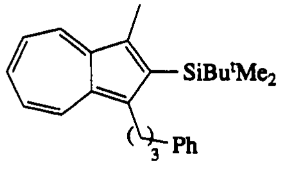 (**74b**) | 57 |
| 3 | (**66i**) $R^1 = Me$; $R^2 = (CH_2)_3CH{=}CH_2$ | B | 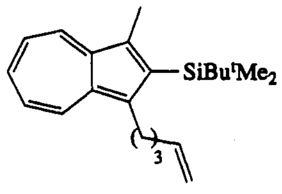 (**74c**) | 43 |

**Table 10** *(continued)*

| *Entry* | *Allenylsilane* | *Method*[a] | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 4 | **(66j)** $R^1$ = cyclohexyl; $R^2$ = $CH_2Me$ | B | 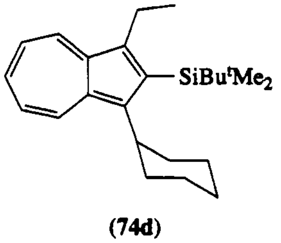 <br>**(74d)** | 44 (58) |
| 5 | **(66k)** $R^1$ = Me; $R^2$ = $(CH_2)_4Br$ | B | 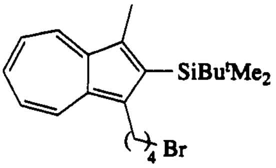 <br>**(74e)** | 55 |
| 6 | **(66l)** $R^1$ = Me; $R^2$ = $(CH_2)_2(o\text{-}BrC_6H_4)$ | B | 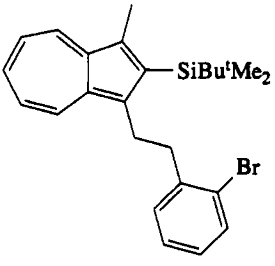 <br>**(74f)** | 63 |
| 7 | **(66m)** $R^1$ = Me; $R^2$ = H | C | 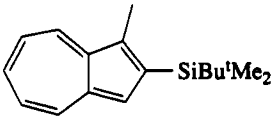 <br>**(74g)** | 22 |

---

[a] Method A: $TpBF_4$ (2.0 equiv.) and 158 mg poly(4-vinylpyridine) $mmol^{-1}$ of $TpBF_4$ in MeCN at 25 °C for 24 h. Method B: $TpBF_4$ (4.0 equiv.) $MeSi(OMe)_3$ in MeCN at 25 °C for 48 h. Method C: $TpBF_4$ (3.0 equiv.) and 123 mg poly(4-vinylpyridine) $mmol^{-1}$ of $TpBF_4$ in MeCN/heptane (1:1) at 65 °C for 2.0 h.

### 2.5.3.3 Alkynylsilanes: Additions to C—X π-Bonds

Alkynylsilanes can function as carbon nucleophiles in addition reactions to electrophilic π-systems. In principle electrophilic addition reactions to alkynylsilanes can occur to produce α- or β-silyl-substituted vinyl cations, as illustrated in Scheme 37. The α-silyl carbocation is not the most stabilized cation, the reason being that the carbon–silicon bond can achieve coplanarity with the vacant orbital on the β-carbonium ion, making possible β-stabilization through hyperconjugation. Depending on the configuration of the carbocation, the developing vacant orbital can exist as a *p*-orbital, as in structure **(75a)**, or an *sp*$^2$-hybrid, as in structure **(75b)**.

Alkynylsilanes have been used as terminators in allylic alcohol and ketene thioacetal initiated cyclizations. In the late 1970s Heathcock[35] and Johnson[36] independently established the utility of alkynylsilanes in cyclization reactions. The example reported by Heathcock illustrated the electronic effect of silicon in the formic acid promoted transformation of the alkynylsilane (**76**) to the bicyclic ketone (**78**) in 76% yield. In contrast cyclization of the analogous alkyne (**77**) produced the bicyclo[2.2.2]octene (**79**), as illustrated in Scheme 38.

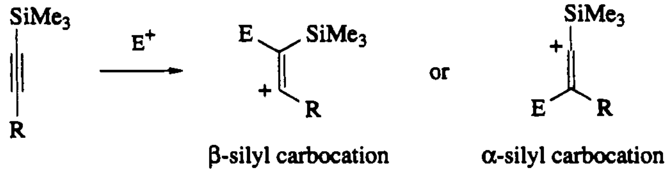

**Scheme 37**

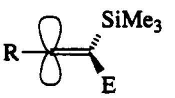

empty *p*-orbital (**75a**)

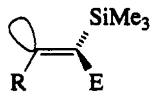

$sp^2$-hybridized (**75b**)

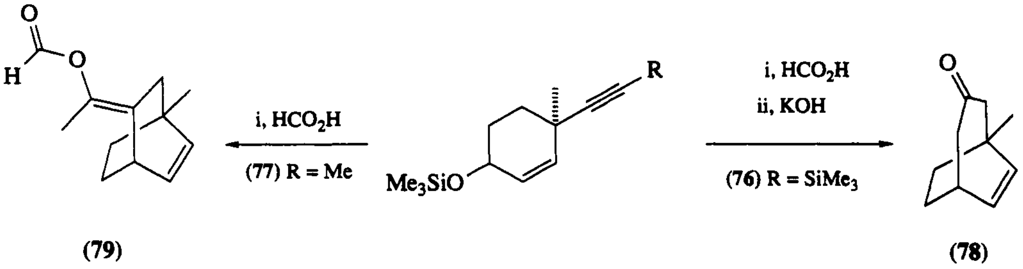

**Scheme 38**

Johnson *et al.* have investigated the use of alkynylsilanes as terminators in the synthesis of steroids and triterpenes through biomimetic polyene cyclizations.[37] This strategy was used in the stereospecific synthesis of the tetracyclic ketone (**81**) using an alkynylsilane as a terminator. Thus, treatment of (**80**) with trifluoroacetic acid under carefully optimized reaction conditions yielded, after hydrolysis of the ortho ester, the tetracyclic ketone (**81**; Scheme 39).

Clearly the course of these cyclization reactions is dependent upon the silicon group. In this regard, cyclization of (**82**) affords the steroid nucleus (**83**; Scheme 40). The formation of (**83**) was attributed, in part, to a transition state preference for the formation of the linear vinyl carbocation (**84b**) rather than the bent vinyl cation (**84a**), which would be produced in an endocyclic cyclization.[38,39] The formation of (**81**) was controlled by the generation of the β-silyl carbocation (**85a**), which may be a precursor to an α-silyl ketone, which undergoes protodesilylation. It is not known whether the formation of (**81**) as the major cyclization product occurs through a kinetic pathway or by Wagner–Meerwein rearrangement[40] of the kinetically preferred linear carbocation (**85b**).

Ketene dithioacetals have also been used as initiators for alkynylsilane-terminated cyclization reactions.[41] Treatment of the thioacetal (**86**) with trifluoroacetic acid gave the bicyclic ketodithioketal (**87**) in 76% yield. In this reaction the protonated ketene dithioacetal functions as an acylium ion equivalent, which is trapped by the nucleophilic alkynylsilane.

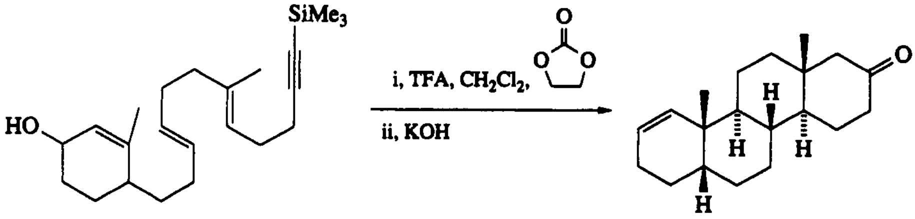
SiMe$_3$
HO
i, TFA, CH$_2$Cl$_2$,
ii, KOH
O
H
H
H
H

**(80)** **(81)**

**Scheme 39**

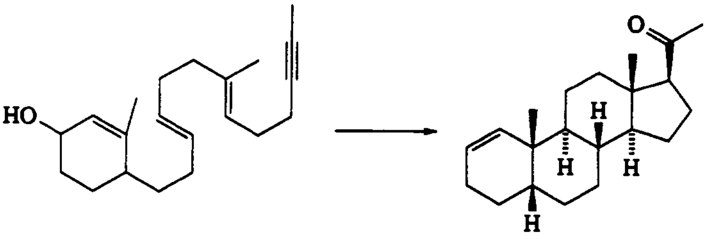

**(82)** **(83)**

**Scheme 40**

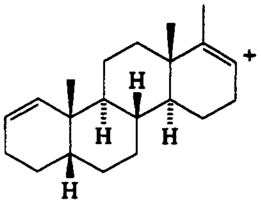

**(84a)**

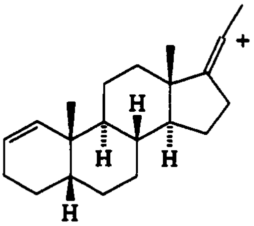

**(84b)**

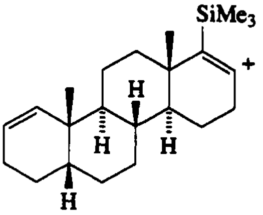

**(85a)**

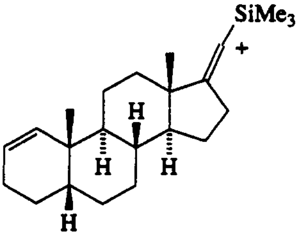

**(85b)**

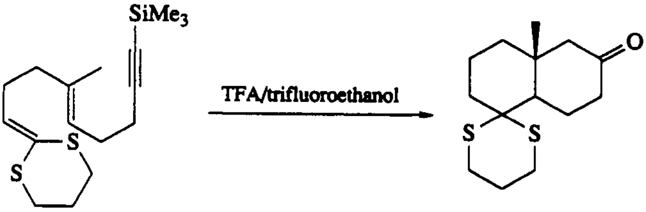
SiMe$_3$
S
S
TFA/trifluoroethanol
O
S
S

**(86)** **(87)**

**Scheme 41**

## 2.5.4 SILICON ATTACHED TO ADJACENT PARTICIPATING π-BONDED CARBON SYSTEMS

### 2.5.4.1 Allylsilanes

Fleming has published a comprehensive review on the chemistry of allylsilanes.[1a] The following sections will provide an overview of the mechanistic proposals currently used to rationalize the regio- and stereo-selectivities in addition reactions involving allylsilanes, and focus on recent contributions to this important area of research. Allylsilanes have proven to be an exceedingly useful class of organometallic reagents and continue to show enormous potential in stereoselective bond formation reactions. They participate in addition reactions with a wide variety of C—X π-systems. Their use as carbon nucleophiles has received considerable attention due in part to the large number of chemical transformations that can be achieved and the wide range of reaction conditions that can be tolerated by these reagents.

#### *2.5.4.1.1 Stereochemistry of addition reactions involving allylsilanes*

Generally, electrophilic addition reactions to acyclic allylsilanes proceed with *anti* stereochemistry.[42–44] The stereochemistry of these reactions has been interpreted on the basis of ground state conformational energies of the allylsilane. As illustrated in Figure 14, the preferred ground state conformer (**88a**) *versus* (**88b**) orients the smallest substituent, usually hydrogen, in a position eclipsing (inside) the adjacent double bond.[45] The bulky silicon group may direct attack of the electrophile to the opposite face of the π-system, generating a secondary carbocation. Subsequent bond rotation orients the C—Si bond periplanar to the empty *p*-orbital, providing stabilization through hyperconjugation to the electron deficient center. Apparently this additional stabilization is responsible for the high levels of selectivity that are observed in the elimination reaction (second step) to form the (*E*)-double bond, as illustrated for structure (**89a**).

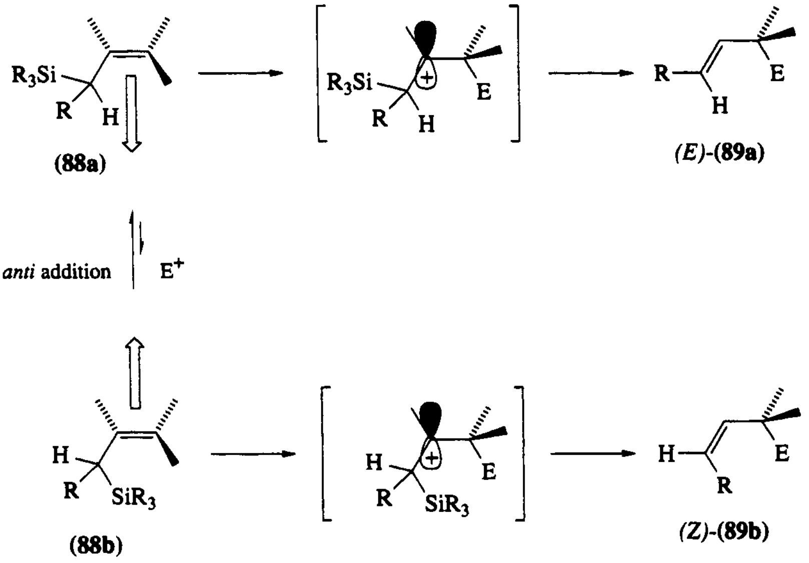

Figure 14 Stereochemistry of electrophilic additions to chiral allylic silanes

#### *2.5.4.1.2 Intermolecular additions to aldehydes, ketones and acetals*

C(3)-substituted allylsilanes (crotylsilanes) participate in chelation-controlled addition reactions with aldehydes to give *syn* addition products as the major stereoisomers.[1a,2a] Generally, the (*E*)-crotylsilanes are highly selective in the *syn* sense (>95:5). In contrast, the (*Z*)-crotylsilanes are much less selective (60–70:40–30 *syn*:*anti*; Scheme 42). Hayashi and Kumada have reported a successful approach to optically active homoallyl alcohols using this strategy.[46] They have reported that useful levels of asymmetric induction can be achieved in Lewis acid catalyzed addition reactions of optically active (*R*)-(*E*)- and (*R*)-(*Z*)-crotylsilanes (**90**) and (**92**) to achiral aldehydes (Schemes 43 and 44).

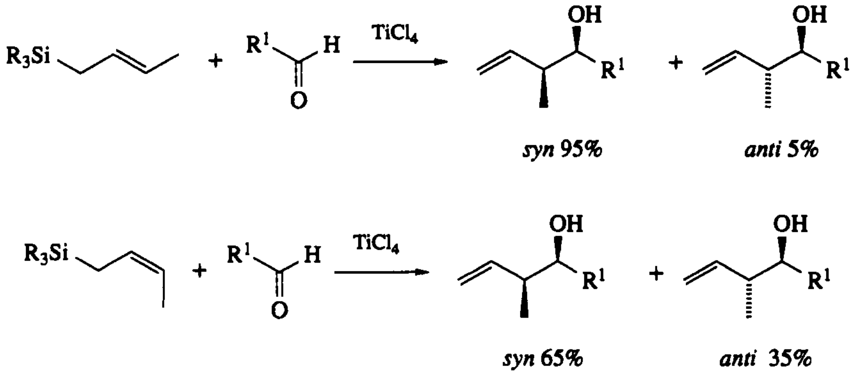

**Scheme 42**

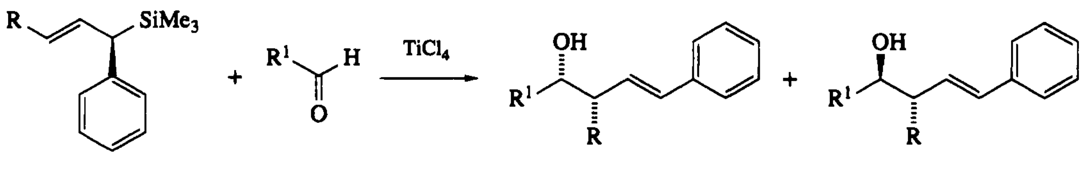

(*R*)-(*E*)-(**90**) *syn*-(**91**) *anti*-(**91**)

**Scheme 43**

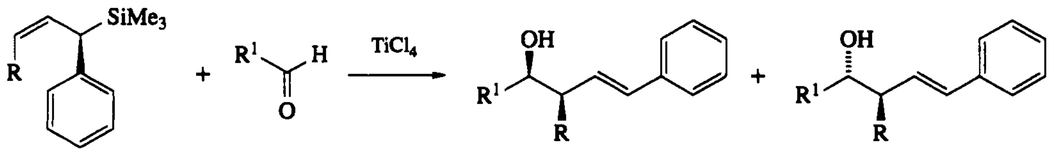

(*R*)-(*Z*)-(**92**) *syn*-(**93**) *anti*-(**93**)

**Scheme 44**

Table 11[46] summarizes the important results of asymmetric induction in addition reactions of optically active allylsilanes (**90**) and (**92**). The origin of the π-facial selectivity in these reactions can be traced to the *anti* selectivity that is commonly observed for $S_E2'$ reactions of allylsilanes (Figure 14).[1a,2a] The *syn* stereochemistry with respect to the double bond configuration (*E* or *Z*) is also very high even with aldehydes bearing sterically bulky substituent groups, as illustrated by entry (*R*)-(*Z*)-(**92b**).

**Table 11** Asymmetric Induction in Additions of Optically Active Allylsilanes (*R*)-(*E*)-(**90**) and (*R*)-(*Z*)-(**92**) to Achiral Aldehydes

| *Allylsilane* | *R* | *$R^1$CHO* | *(**91**) syn:anti* | *(**93**) syn:anti* | *Yield (%)* |
|---|---|---|---|---|---|
| (*R*)-(*E*)-(**90a**) | Me | Bu$^t$CHO | >99:1 | | 47 |
| (*R*)-(*Z*)-(**92a**) | Me | Bu$^t$CHO | | >99:1 | 27 |
| (*R*)-(*E*)-(**90a**) | Me | Pr$^i$CHO | >95:5 | | 67 |
| (*R*)-(*Z*)-(**92a**) | Me | Pr$^i$CHO | | >65:35 | 61 |
| (*R*)-(*E*)-(**90b**) | Ph | Bu$^t$CHO | >99:1 | | 44 |
| (*R*)-(*Z*)-(**92b**) | Ph | Bu$^t$CHO | | >99:1 | 10 |

The stereochemical outcome of these reactions has been interpreted on the basis of two types of transition state models. These models use very different orientations of the reacting double bonds to explain the stereoselectivities. The first is referred to as an 'open' or 'extended' antiperiplanar transition state model, illustrated in Figure 15 for both (*E*)- and (*Z*)-crotylsilanes. In this case the carbon nucleophile and the activated carbonyl (aldehyde) are *anti* to each other and also coplanar. Using this model transition states (I) and (II) are favored due to diminished steric interactions between the aldehyde substituent and the vinylmethyl group. The destabilizing interactions created by these substituents are greatest for transition states (III) and (IV), which place them in a *gauche* orientation.[1a]

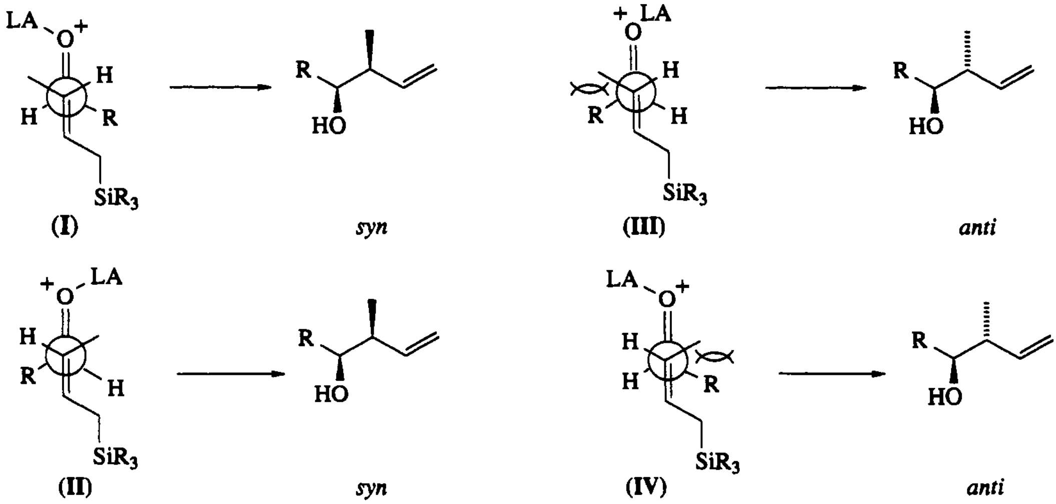

**Figure 15** Open transition state models for intermolecular additions of C(3)-substituted allylsilanes

An alternate model using the transition states (V)–(XII) can be used to rationalize the selectivities in these reactions (Figure 16). This model requires synclinal orientation of the reacting double bonds. The transition states (V) or (VI) and (IX) or (X) are favored over (VII), (VIII), (XI) and (XII) because steric interactions between the Lewis acid bonded to the oxygen lone pair *anti* to the R substituent of the aldehyde and the vinyl methyl group are minimized.

Useful levels of stereoselectivity were obtained in intermolecular addition reactions of C(3)-substituted allylsilanes to chiral aldehydes. Lewis acids that are capable of chelating to heteroatoms have been used to direct the stereochemical course of allylsilane additions to α-alkoxy and α,β-dialkoxy carbonyl compounds. The allylation of α-benzyloxy aldehyde (**94**) in the presence of $TiCl_4$ and $SnCl_4$ furnished products with high levels of *syn* stereoselection (*syn*-**95**).[47] In contrast, under nonchelation-controlled reaction conditions ($BF_3{\cdot}OEt_2$) allyltrimethylsilane reacted to form predominantly the *anti*-1,2-diol product (*anti*-**95**), as shown in Scheme 45.

Taddei and coworkers reported that chiral allyltrimethylsilanes containing an optically active ligand derived from (–)-myrtenal attached to silicon (**96**) underwent enantioselective addition reactions with achiral aldehydes (Scheme 46) to give, after acid hydrolysis, optically active homoallyl alcohols (**98**).[48] A variety of Lewis acids were examined to optimize enantiomeric excess, and $TiCl_4$ was found to be the most effective catalyst. The results of the $TiCl_4$-promoted additions are reported in Table 12.[48]

### 2.5.4.1.3 Intramolecular additions of allyltrimethylsilanes to aldehydes and ketones

Intramolecular addition of allylsilanes performed under chelation-controlled conditions represents an efficient method in which useful levels of stereoselectivity can be achieved. This process has been demonstrated for a variety of α-alkoxy, α,β-dialkoxy and β-dicarbonyl compounds, including β-keto esters, β-keto amides and β-keto lactones.

The use of chelation to direct the stereochemical outcome of intramolecular additions of allylsilanes to β-dicarbonyl compounds can provide excellent levels of diastereoselectivity.[49] Cyclizations of this type proceed at low temperature under mild reaction conditions and are highly chemoselective, providing routes to highly functionalized five-, six- and seven-membered rings (**100a**, **100b** and **100c**; Scheme 47). For the cases examined, $SnCl_4$ and $FeCl_3$ proved to be less effective than $TiCl_4$ in the cyclization of ethyl 2-alkyl-2-alkanoyl-4-(trimethylsilyl)methyl-4-pentenoate (**99**; *n* = 1; Table 13).[49]

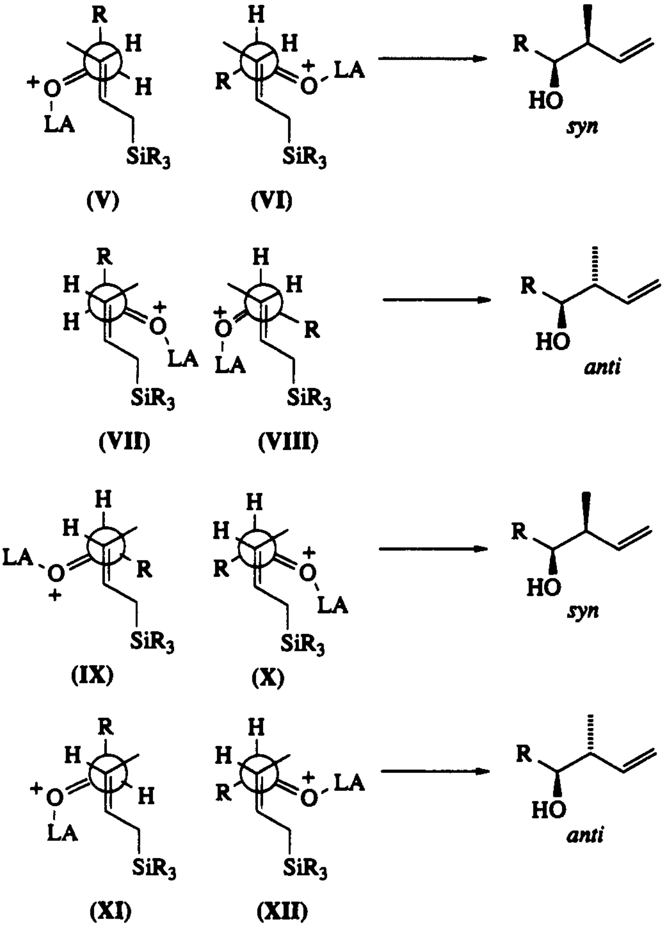
R
H
LA
SiR3
(V)
(VI)
syn
(VII)
(VIII)
anti
(IX)
(X)
syn
(XI)
(XII)
anti

**Figure 16** Synclinal transition state model for the intermolecular addition of C(3)-substituted allylsilanes to aldehydes

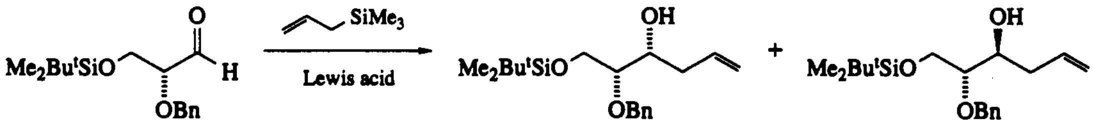
SiMe3
Lewis acid
Me2ButSiO
OBn
OH
H
O

(94)

| | *syn*-(95) | *anti*-(95) |
|---|---|---|
| $TiCl_4$ | >98% | <2% |
| $SnCl_4$ | >98% | <2% |
| $BF_3{\cdot}OEt_2$ | 19% | 81% |

**Scheme 45**

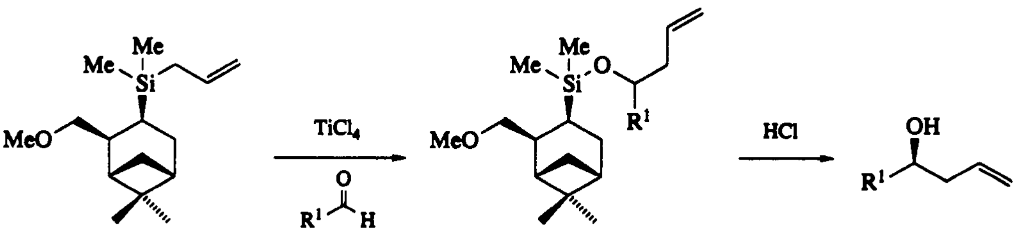
Me
Si
MeO
TiCl4
R1
H
O
HCl
OH

(96) (97) (98)

**Scheme 46**

**Table 12** Enantioselective Allylation of Achiral Aldehydes Catalyzed by $TiCl_4$

| *Aldehyde* | *Product* | *Yield (%)* | *ee (%)*[a] |
|---|---|---|---|
| 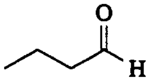 | 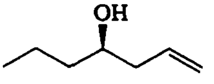<br>**(98a)** | 58 | 46 |
| 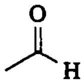 | 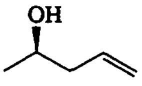<br>**(98b)** | 61 | 40 |
| 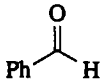 | 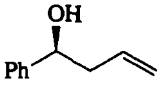<br>**(98c)** | 45 | 21 |
| 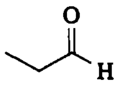 | 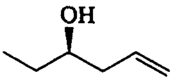<br>**(98d)** | 39 | 40 |

[a] Enantiomeric excess determination performed by Mesher analysis and literature comparison.

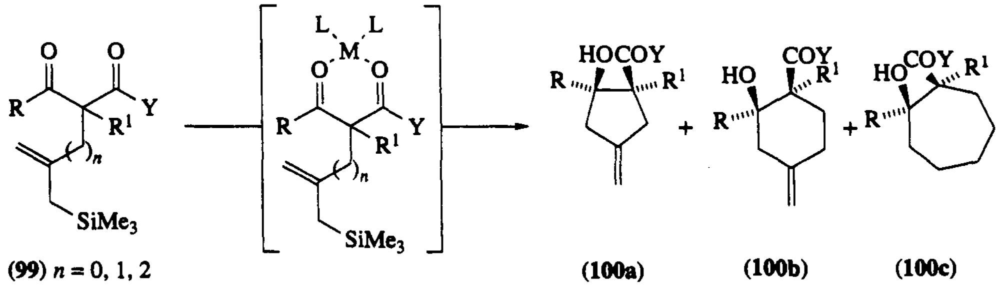

**Scheme 47**

**Table 13** Cyclizations of Ethyl 2-Alkyl-2-alkanoyl-4-(trimethylsilyl)methyl-4-pentenoate (99) Catalyzed by Titanium Tetrachloride (Scheme 47)

| *Substrate* | *R* | *$R^1$* | *Isolated yield of (100) (%)*[a] |
|---|---|---|---|
| (99a) | Me | Me | 88 |
| (99b) | Me | Et | 78 |
| (99c) | Me | $Pr^i$ | 65 |
| (99d) | Me | Ph | 72 |
| (99e) | Et | Me | 78 |
| (99f) | $Pr^i$ | Me | 66 |
| (99g) | $Bu^t$ | Me | 74 |
| (99h) | Ph | Me | 74 |
| (99i) | Me | H | 57 |

[a] Diastereomer ratio was >200:1.

The Lewis acid promoted intramolecular additions of β-allylsiloxy aldehydes represent an efficient method for the construction of 1,3-stereocenters, as illustrated in Scheme 48.[50] The sense of 1,3-asymmetric induction in $TiCl_4$-catalyzed allylsilane addition to *O*-allylsilyl-protected aldehydes is opposite (>90% *syn* selection) to that reported for the intermolecular addition to the *O*-benzyl derivative.

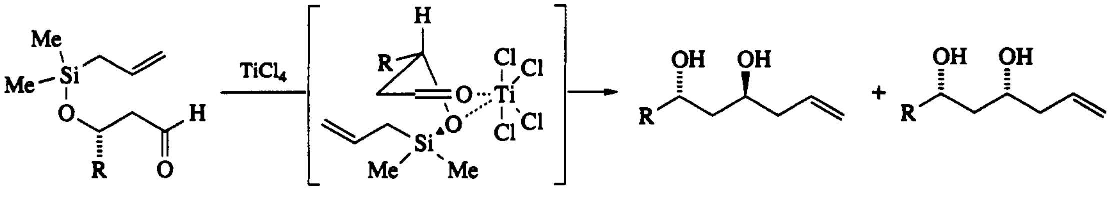

**(101a)** R = Me

**(101b)** R = $Bu^n$

*anti*-**(102a)** *syn*-**(102a)**

*anti*-**(102b)** *syn*-**(102b)**

**Scheme 48**

Reaction of aldehydes **(101a)** and **(101b)** containing equivalent amounts of the Lewis acids $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}OEt_2$ are summarized in Table 14. Interestingly, $TiCl_4$ and $SnCl_4$ lead to opposite diastereomers (*syn versus anti*). The results of $TiCl_4$-mediated reactions (Table 14)[50] support the original hypothesis of an internal allyl transfer in which silicon and titanium act as templates. However, as pointed out by Reetz,[50] the levels of stereoselection do not unequivocally demonstrate an intramolecular pathway.

**Table 14** Lewis Acid Catalyzed Intramolecular Additions of β-Allylsiloxy Aldehydes

| *β-Allylsiloxy aldehyde* | *R* | *Lewis acid* | *Yield (%)* | *(**102**) anti:syn* |
|---|---|---|---|---|
| **(101a)** | Me | $TiCl_4$ | 70 | 8:92 |
| **(101a)** | Me | $SnCl_4$ | 70 | 92:8 |
| **(101a)** | Me | $BF_3{\cdot}OEt_2$ | 60 | 70:30 |
| **(101b)** | $Bu^n$ | $TiCl_4$ | 80 | 10:90 |

### *2.5.4.1.4 Stereochemistry of internal allylsilane additions to aldehydes and acetals*

In view of the importance of stereoselective addition reactions of allylsilanes to C—X π-bonds, the stereochemical course of intramolecular addition reactions involving aldehydes has been investigated by Denmark and coworkers.[51] The results are summarized below in Tables 15[51] and 16.[52] In the cases involving additions to aldehydes, the authors have made the assumption that the coordination of the Lewis acid to the carbonyl oxygen generates the '(*E*)-complex' (**103**; Scheme 49), which after cyclization generates the *syn* and *anti* bicyclic alcohols (**104**). The major steric contribution arises from interaction between the Lewis acid and the trimethylsilylmethyl group. This interpretation suggests that there may

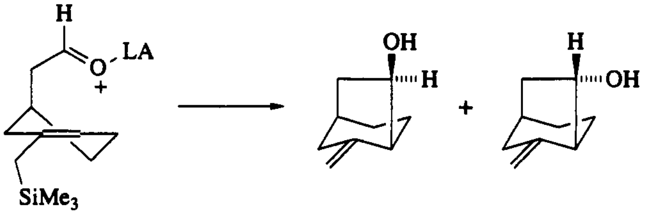

**(103)** *syn*-**(104)** *anti*-**(104)**

**Scheme 49**

**Table 15** Lewis Acid Catalyzed Cyclization of Aldehyde (**103**)

| *Lewis acid* | *Solvent* | *Temperature (°C)* | *(**104**) syn:anti* |
|---|---|---|---|
| $SnCl_4$ | $CH_2Cl_2$ | -70 | 49:51 |
| $Et_2AlCl$ | $CH_2Cl_2$ | -70 | 66:34 |
| $FeCl_3$ | $CH_2Cl_2$ | -70 | 70:30 |
| $AlCl_3$ | $CH_2Cl_2$ | -70 | 79:21 |
| $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | -70 | 80:20 |
| $Bu^n{}_4NF$ | THF | 67 | 30:70 |

be a stereoelectronic advantage for the synclinal orientation of reactants under electrophilic conditions. Reactions catalyzed by fluoride ions show a reversal of stereoselectivity and most likely involve a different mechanism.

Analogous systems related to the models for allylsilane–acetal cyclizations have been studied.[52] In these cases, however, cyclization of the acetals (**105**; Scheme 50) forms the corresponding *syn* and *anti* bicyclic ethers (**106**). The authors concluded that the stereochemistry of cyclization of acetal models (**105**) is dependent upon the mechanism of activation. In the presence of TMS-OTf the acetals (**105a–c**) reacted through an $S_N2$-type process, while the isopropyl acetal (**105d**) reacted through prior ionization to oxonium ion (**107**).

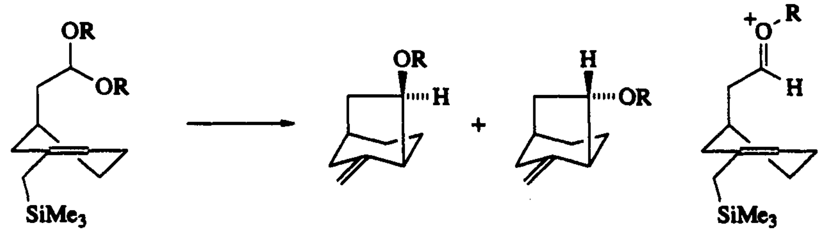

(**105a**) = Me
(**105b**) = Et
(**105c**) = Bu$^i$
(**105d**) = Pr$^i$

*syn*-(**106**) *anti*-(**106**) (**107**)

**Scheme 50**

**Table 16** Effect of Lewis Acid in the Cyclization of Dimethyl Acetal (**105a**)

| *Reagent* | *Temperature* (°C) | *(106) Syn:anti* | *Yield* (%) |
|---|---|---|---|
| TMS-OTf | –70 | 96:4 | 100 |
| TfOH | –70 | 96:4 | 62 |
| $Ti(OPr^i)_2Cl_2$ | –20 | 87:13 | 21 |
| $AlCl_3$ | –20 | 86:14 | 33 |
| $BCl_3$ | –70 | 82:18 | 57 |
| $BF_3{\cdot}OEt_2$ | –20 | 77:23 | 95 |
| $TiCl_4$ | –90 | 47:53 | 55 |
| $SnCl_4$ | –70 | 45:55 | 35 |
| $SnCl_4$ | –60 | 71:29 | 81 |

For the cases examined, the structure of the acetal had a dramatic effect on the stereochemical outcome of the reaction. Thus, allylsilanes (**105a–c**) all showed *syn* selectivity. However, the isopropyl case (**105d**) showed a slight *anti* preference. This reversal of selectivity has been interpreted as a change in mechanism rather than a steric phenomenon related to the added steric bulk of the diisopropyl acetal. The results of these experiments are summarized in Table 17.[52]

**Table 17** Effect of Acetal Structure on the Stereochemical Outcome of the Cyclization of (**105a**)–(**105d**) with TMS-OTf[a]

| *Substrate* | *R* | *syn* (%) | *anti* (%) |
|---|---|---|---|
| (**105a**) | Me | 96 | 4 |
| (**105b**) | Et | 92 | 8 |
| (**105c**) | Bu$^i$ | 90 | 10 |
| (**105d**) | Pr$^i$ | 38 | 62 |

[a] All reactions were run in $CH_2Cl_2$ (0.05 M) with 1.0 equiv. of TMS-OTf.

### 2.5.4.2 Propargylsilanes

Propargylsilanes undergo electrophilic addition reactions to generate β-silyl carbocations (**109**) that can, in principle, react further to give either addition (**110**) or substitution (**111**) products, as illustrated in Scheme 51. As in the case of allylsilanes, however, substitution predominates.[2a]

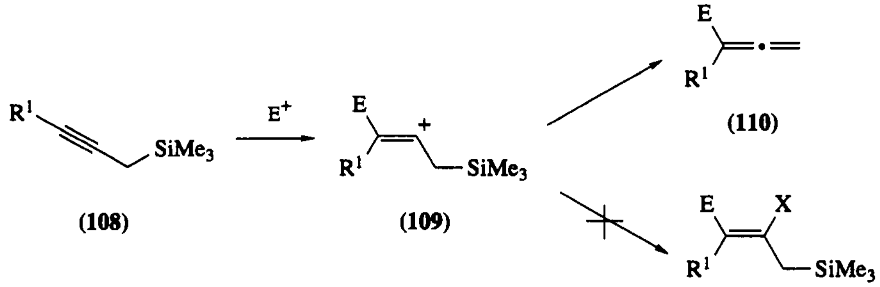
R$^1$
SiMe$_3$
E$^+$
E
+
R$^1$
SiMe$_3$
E
R$^1$
E
X
R$^1$
SiMe$_3$
(108)
(109)
(110)

**Scheme 51**

The stereochemical course of the addition reactions to propargylsilanes can be rationalized using a mechanism similar to that for allylsilanes (Scheme 52).[53] The propargylsilane would be expected to exist in conformation (**113**; Scheme 53) with the carbon–silicon bond overlapping with the π-lobes of one of the carbon–carbon π-bonds. The electrophile attacks the π-bond conjugated with the carbon–silicon bond *anti* to the trialkylsilane group, generating the stabilized vinyl cation (**114**). Loss of the trialkylsilicon group then affords the expected allene.

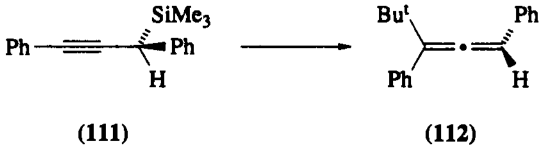
SiMe$_3$
Ph
Ph
H
Bu$^t$
Ph
Ph
H
(111)
(112)

**Scheme 52**

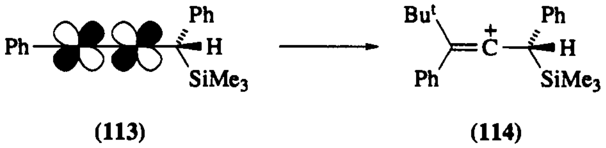
Ph
Ph
H
SiMe$_3$
Bu$^t$
+
C
Ph
Ph
H
SiMe$_3$
(113)
(114)

**Scheme 53**

Propargylsilanes show predictable behavior as cyclization terminators. Internal additions of propynylsilanes to acyclic *N*-acyliminium ions promoted by Lewis acids or protic acids yield α-allenic amides or carbamates (Scheme 54).[54]

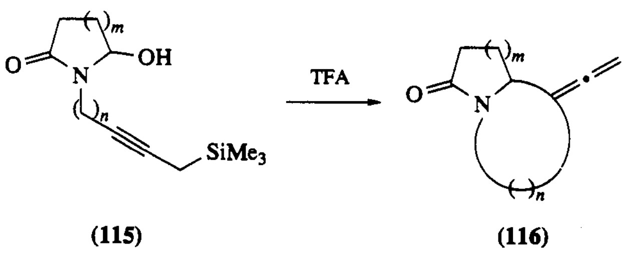
O
N
OH
m
n
SiMe$_3$
TFA
O
N
m
n
(115)
(116)

**Scheme 54**

The intramolecular acid-catalyzed reaction of 2-propargylsilanes of structural type (**117**) with *N*-acyliumion ion precursors leads to bridged azabicyclic ring systems (**118**; Scheme 55) which contain an α-allenic amide function. These bicyclic products serve as intermediates to highly functionalized *trans*-fused ring systems possessing a 1,3-diene moiety.

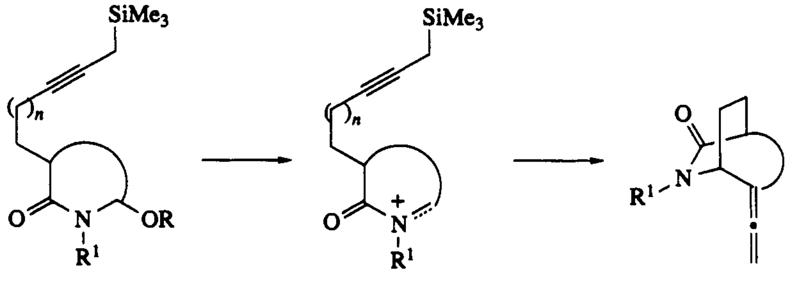

**(117)** **(118)** **(119)**

**Scheme 55**

## 2.5.5 α-SILYLORGANOMETALLIC REAGENTS

Silicon is capable of stabilizing an adjacent carbon–metal bond although it is more electropositive than hydrogen or carbon. The origins of this stabilization are discussed in Sections 2.5.2.1–2.5.2.5.

### 2.5.5.1 General Methods for the Formation of α-Silyl Carbanions

The variety of methods available for the formation of α-silyl carbanions can be divided into four categories.

(i) Deprotonation: alkyllithium reagents (*e.g.* Bu$^n$Li) can easily abstract protons adjacent to trialkylsilyl groups (**120** → **121**; Scheme 56) generating the α-silyl carbanion.[55]

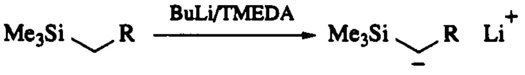

**(120)** **(121)**

**Scheme 56**

(ii) Metal–halogen exchange: α-halosilanes undergo metal–halogen exchange upon treatment with alkyllithium reagents (**122** → **123**; Scheme 57).[56]

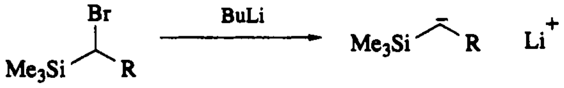

**(122)** **(123)**

**Scheme 57**

(iii) Transmetallation: α-selenosilanes are transmetallated in the presence of alkyllithium reagents (**124** → **125**; Scheme 58).[57] Included in this category are desilylation of bis(silyl) compounds (**126**) by fluoride and alkoxide anions.[58] This procedure has been shown to be a particularly clean method for the generation of α-silyl carbanions (**127**), as illustrated in Scheme 59.

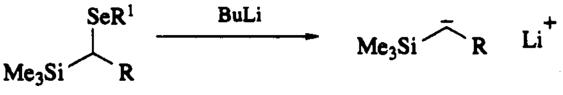

**(124)** **(125)**

**Scheme 58**

(iv) Addition of an organometallic reagent to vinylsilanes: The example provided in Scheme 60 illustrates the ability of silicon to activate and direct the formation of carbon nucleophiles. These addition

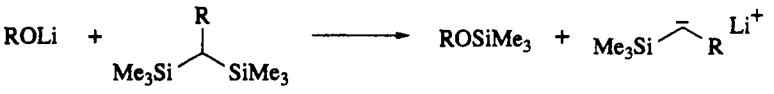

**(126)** **(127)**

**Scheme 59**

reactions proceed with excellent levels of selectivity, as only α-silyl carbanions are observed; such levels of selectivity are not reached with unsubstituted or unsymmetrical alkenes.[59]

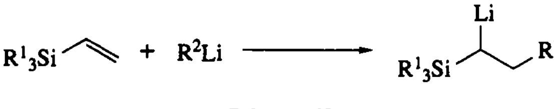

**Scheme 60**

The directing ability of silicon is further illustrated by the observation that isopropylmagnesium chloride adds to the triethoxyvinylsilane (**128**) to generate the addition product (**129**; Scheme 61); however, the triethoxyallylsilane (**130**) undergoes clean substitution at silicon when treated with isopropylmagnesium chloride to yield the substitution product (**131**; Scheme 62).

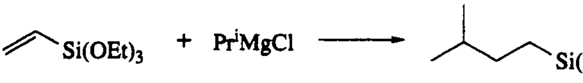

**(128)** **(129)**

**Scheme 61**

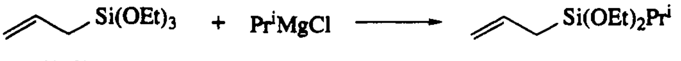

**(130)** **(131)**

**Scheme 62**

Both organolithium[60] and Grignard reagents[61] undergo additions to vinylsilanes to yield α-silyl carbanions. This directing effect can be overcome by the influence of a stronger electron-withdrawing group, such as a nitro group, adjacent[62] to the silicon group, as illustrated in Scheme 63 with the transformation of (**132**) to (**133**).

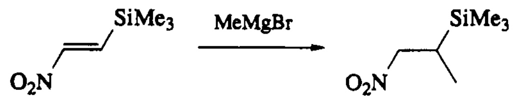

**(132)** **(133)**

**Scheme 63**

One of the most significant demonstrations of the ability of silicon to promote nucleophilic attack at carbon–carbon bonds was reported by Stork within the context of the development of an improved variant of the Robinson annelation.[63,64] Existing annelation methods which depend on conjugate addition of an enolate to an α,β-unsaturated ketone suffer from a variety of drawbacks, which are consequences of the reversible nature of the Michael addition reaction and the ease with which most electrophilic alkenes undergo multiple additions and oligomerization. α-Silylvinyl ketones of structure type (**134**) are not prone to these problems and thus serve as excellent four-carbon components (Michael acceptors) in the Robinson annelation. The ability of silicon to stabilize adjacent carbanions is shown in Scheme 64 with the α-silyl carbanion and its resonance form (**135** and **136**). The additional stabilization of the intermediate enolate ion halts the reversibility of the process, ultimately generating the octalone system in good yield with minimum side reactions. The added steric bulk created by the trialkylsilane group diminishes the reactivity of the intermediate enolate, thus providing an increase in chemoselectivity.

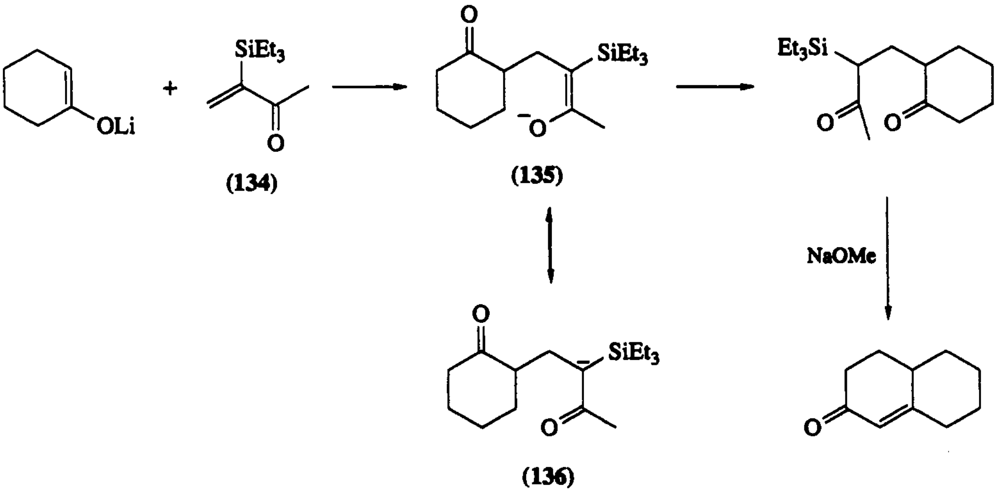

(134) (135) (136)

Scheme 64

### 2.5.5.2 The Peterson Reaction: Introduction

The use of α-silyl organometallic reagents, principally lithium and Grignard reagents, to convert aldehydes and ketones to alkenes has been applied extensively in organic synthesis. Peterson was the first to investigate this type of reaction sequence and many useful applications were derived from these initial observations and experiments. The reaction has been reviewed by Ager.[65] This section is concerned with the mechanism of the Peterson reaction and some recent applications of the Peterson-type alkenation of carbonyl compounds.

As illustrated in Scheme 65, the intermediate β-silyl alkoxide (**138**) is subject to either protonation to give the corresponding β-silyl alcohol (**139**), or elimination of $R_3SiO$ to generate the alkene (**140**). The pathway leading to the alkene is known as the carbonyl alkenation reaction, or the Peterson reaction.[55]

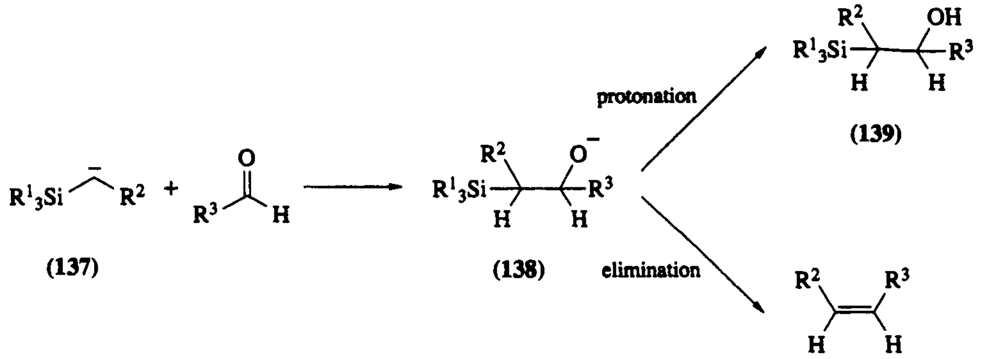

(137) (138) (139) (140)

Scheme 65

### 2.5.5.2.1 The mechanism of the Peterson reaction

As a consequence of the presumed irreversibility of the first step of the Peterson reaction, the stereochemistry of the elimination was determined solely by the relative rates ($k_1$ and $k_1'$) of formation of *threo-* and *erythro*-β-silyl alkoxides (**141**) and (**142**), as indicated in Scheme 66. Support for the irreversibility of this step comes from the experiments on the nucleophilic opening of the diastereomeric epoxides (**143**) and (**144**). Thus, the *syn-* and *anti*-epoxides, when treated with lithium dipropyl cuprate, yielded the *threo-* and *erythro*-β-silyl alcohols (**145**) and (**146**), respectively.[66] Treatment of the *threo* isomer with base gave the (*Z*)-alkene exclusively and the *erythro* isomer gave the (*E*)-alkene. The high levels of selectivity for this elimination indicated that the initial addition is not reversible. The elimination was also shown to be stereospecific and only the *syn* stereoisomer was generated under basic conditions. Under acidic conditions the stereochemistry of the elimination product is inverted. Thus, β-silyl alcohols **(143)** and **(144)** yield the (*E*)-alkene **(147)** and the (*Z*)-alkene **(148)** respectively, resulting from *anti* elimination (Scheme 66).

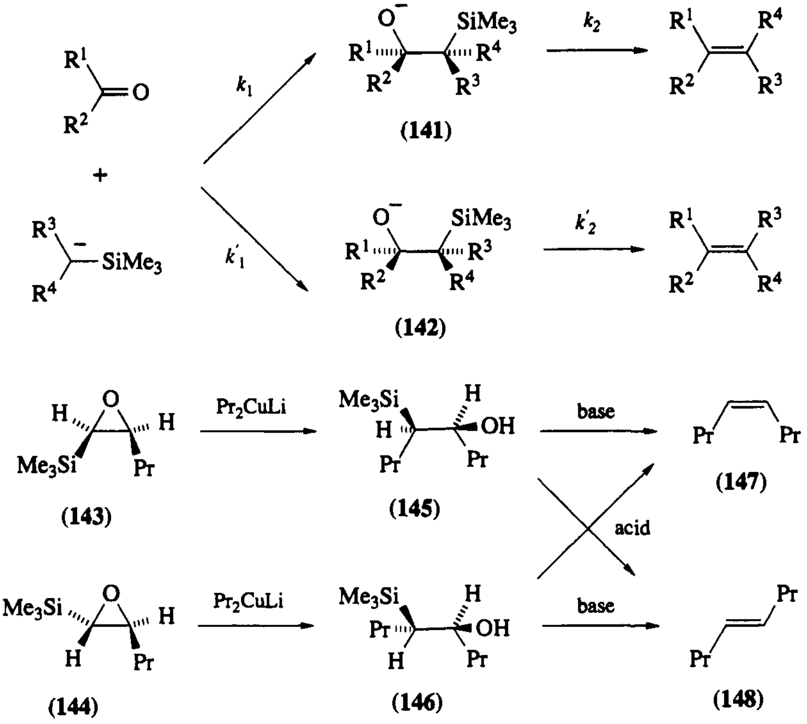

Scheme 66 Mechanism of the Peterson reaction

### 2.5.5.2.2 *Stereochemistry of the Peterson reaction*

The *(E):(Z)* ratio of the derived alkene varied considerably with the size of the silyl group. A transition state model has been developed to rationalize the relative transition state energies.[67] Nucleophilic attack on carbonyl compounds occurs in the plane of the C—O π-bond with a Nu—C—O angle of approximately 109°.[68,69] The smallest group R, usually a hydrogen, is placed in the least sterically demanding position and attack occurs between the hydrogen and the R substituent of the aldehyde in order to minimize steric repulsion. The remaining substituents are arranged such that the largest group is positioned *anti* to the R substituent of the aldehyde. Thus, as the steric size of the silyl group increases, transition state **(149)** becomes more favorable than transition state **(150)**, resulting in the preferential formation of the *erythro* isomer leading to formation of the (*Z*)-alkene.

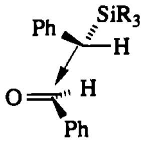

**(149)**

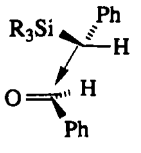

**(150)**

### 2.5.5.3 Functionalized α-Silyl Carbanions

The addition of trimethylsilylmethyllithium to enolizable ketones generally gives significant amounts of the enolized carbonyl compound. Johnson and Tait[70] have shown that when the lithium anion is converted to the cerium reagent it gives high yields of the addition product. For example, α-tetralone **(151)** reacts with trimethylsilylmethyllithium to give after protonation an ~1:1 mixture of the desired exocyclic alkene (**152**) and recovered ketone. In sharp contrast, the corresponding cerium reagent gave a 95:5 ratio of alkene to ketone (see Scheme 67).

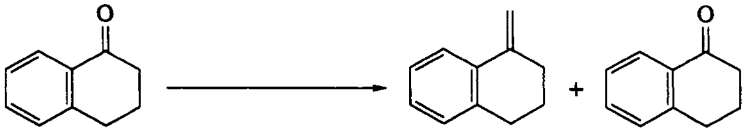

(**151**) (**152**)

| | | |
|---|---|---|
| $Me_3SiCH_2Li$ | 50 | 50 |
| $Me_3SiCH_2Li/CeCl_3$ | >95 | 5 |

**Scheme 67**

Anions of α-silyl phosphonates of type (**153**) also undergo additions to carbonyl compounds. The corresponding addition products, β-silyl alkoxides, can react with ketones to yield the product of the Peterson alkenation or the Wittig reaction. In practice only the Peterson product (**154**) is obtained, indicating that loss of $OSiMe_3$ is faster than elimination of $O{=}PPh_3$ (Scheme 68).[71,72] If the α-silyl carbanion is adjacent to a chlorine atom (**155**), an internal displacement reaction follows the initial formation of the β-silyl alkoxide, and epoxides (**156**) are formed (Scheme 69).[73,74]

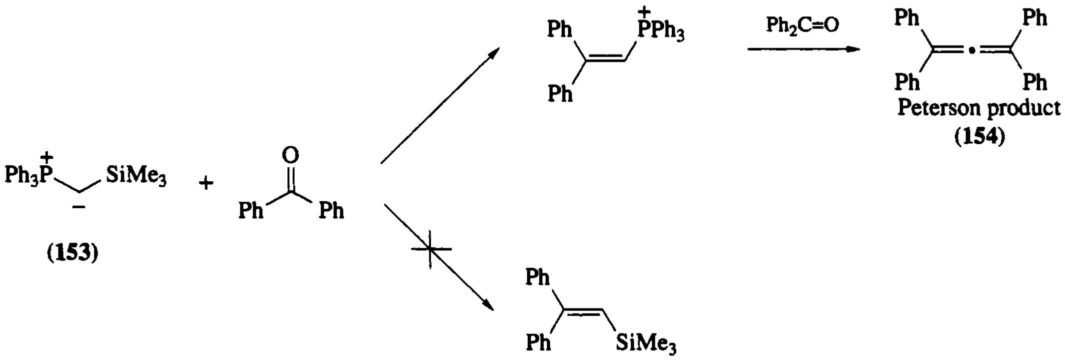

Ph
PPh3
Ph
Ph2C=O
Ph
Ph
Ph
Ph
Ph3P
SiMe3
O
Ph
Ph
Ph
Ph
SiMe3

Peterson product (**154**)

(**153**)

Wittig product

**Scheme 68**

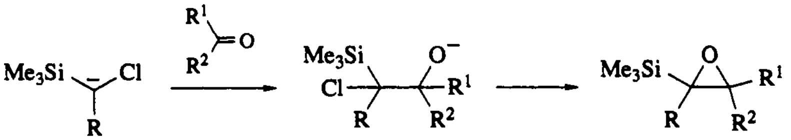

Me3Si
Cl
R
R1
O
R2
Me3Si
O−
Cl
R1
R
R2
Me3Si
O
R1
R
R2

(**155**) (**156**)

**Scheme 69**

Mixed ketene *O*,*S*-acetal derivatives (**157**) can be readily prepared from the reaction of [methoxy(phenylthio)(trimethylsilyl)methyl]lithium,[75] generated from the mixed acetal (**158**), with aldehydes and ketones (Scheme 70).

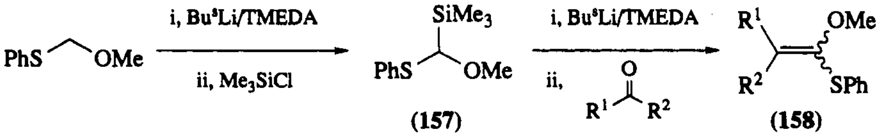

i, Bu$^s$Li/TMEDA
ii, Me3SiCl
PhS
OMe
SiMe3
PhS
OMe
i, Bu$^s$Li/TMEDA
ii,
O
R1
R2
R1
OMe
R2
SPh

(**157**) (**158**)

**Scheme 70**

The lithium reagent of phosphonate (**159**) reacts with aldehydes and ketones to produce vinylphosphonate (**160**). These compounds were oxidized ($OsO_4$/NMO) and deprotected to provide a convenient and high yielding route to α-hydroxy acids[76] of structure type (**161**; Scheme 71).

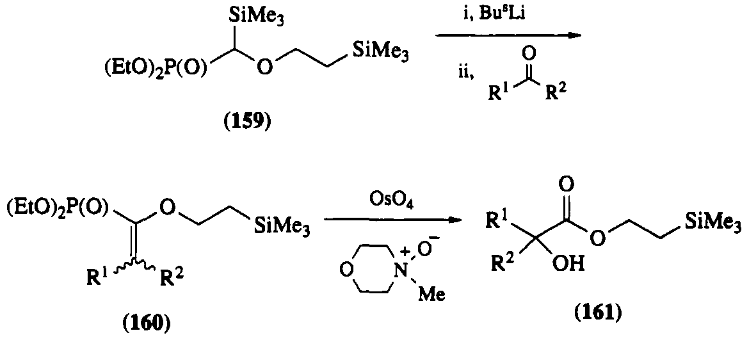

**(159)** **(160)** **(161)**

**Scheme 71**

### 2.5.5.3.1 *Reactions involving ambient silyl-substituted carbanions*

The Peterson reaction has been successfully employed using α-silylallyl anions (**162a** and **162b**; Figure 17).

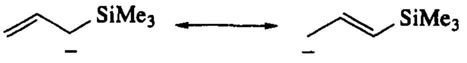

**(162a)** **(162b)**

**Figure 17**

In addition reactions to carbonyl compounds C-3 attack generally predominates,[77–79] as illustrated in Scheme 72 with the formation of vinylsilane (**163**). C-1 addition also predominates in alkylation and acylation reactions involving α-silylallyl anions when alkyl halides[80] and acyl halides[81] are used as electrophiles.

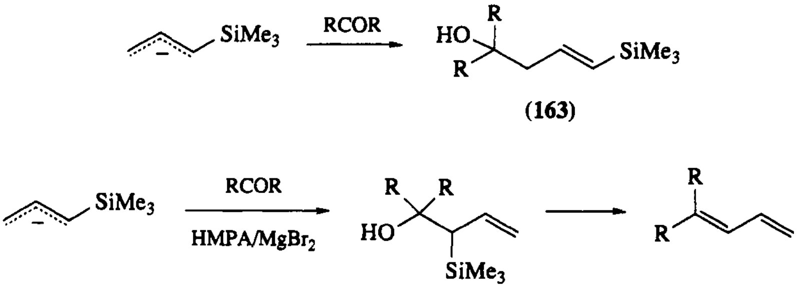

**(163)**

**Scheme 72**

Interestingly, in the presence of HMPT and magnesium bromide, C-1 attack predominates and is followed by elimination, yielding the 1,3-diene system[82] as shown in Scheme 72. Similarly, allylboronates of structural type (**164**) bearing a vinylsilane at the C-3 position gave predominantly C-1 addition products to form the *syn (erythro)* isomer (**165**) as the major diastereomer (Scheme 73).[83]

Metallation of the bis(silyl) derivative (**166**) generates a symmetrical carbanion (**167**), which also reacts stereoselectively with aldehydes to produce *anti* β-silyl alcohol derivatives (**168**), which undergo base-catalyzed elimination reactions to generate the *(E)/(Z)* diene system (**169**; Scheme 74).[84]

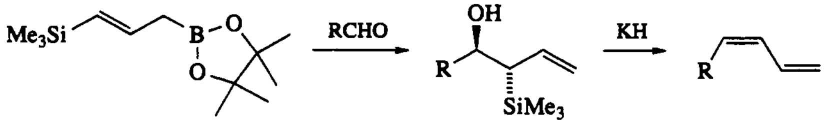
Me₃Si
B
O
O
RCHO
OH
R
SiMe₃
KH
R

**(164)** **(165)**

**Scheme 73**

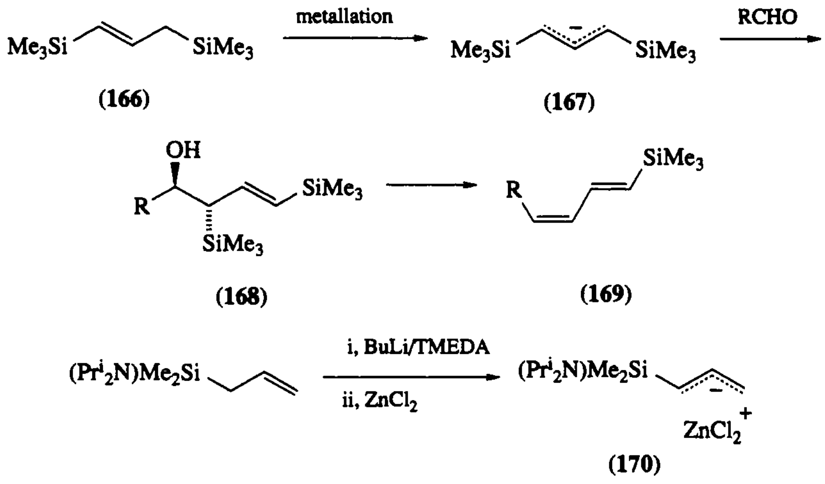
Me₃Si
SiMe₃
metallation
Me₃Si
SiMe₃
RCHO
OH
R
SiMe₃
SiMe₃
R
SiMe₃
(Pr^i₂N)Me₂Si
i, BuLi/TMEDA
ii, ZnCl₂
(Pr^i₂N)Me₂Si
ZnCl₂+

**(166)** **(167)** **(168)** **(169)** **(170)**

**Scheme 74**

### *2.5.5.3.2 Metallated allylaminosilanes*

The organozinc reagent (**170**) derived from allyl(diisopropylamino)dimethylsilane reacts with aldehydes to form *anti*-3-silyl-2-alken-4-ols (**171**), which are further oxidized ($KHCO_3/H_2O_2$) to *anti*-1-alkene-3,4-diols (**172**).[85] The use of a sterically bulky $Pr^i_2NMe_2Si$ group in the zinc reagent was required to suppress the elimination pathway and the formation of conjugated 1,3-diene systems. These allylamino anions thus function as useful α-alkoxyallyl anion equivalents, as illustrated in Scheme 75. The important results of these experiments are summarized in Table 18.[85]

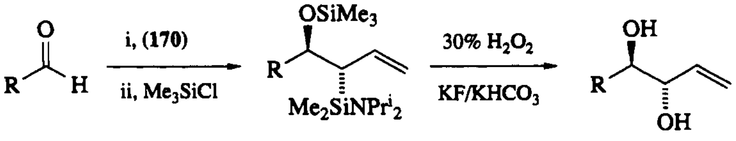
O
R
H
i, (170)
ii, Me₃SiCl
OSiMe₃
R
Me₂SiNPr^i₂
30% H₂O₂
KF/KHCO₃
OH
R
OH

**(171)** **(172)**

**Scheme 75**

### *2.5.5.3.3 Addition reactions of α-silyl anions to C=N π-bonds*

An interesting variant of the Peterson reaction involves the addition of an α-silylbenzylic anion (**173**) to a carbon–nitrogen double bond such as an imine. In this case the loss of RN—$SiMe_3$ occurs less readily than the loss of alkoxytrialkylsilane (O—$SiR_3$).[86] The initial addition reaction is reversible and the stereochemistry of the elimination reaction is predominantly *trans* (Scheme 76). Both acid- and base-catalyzed elimination reactions lead to the *trans* product (**174**).

**Table 18** Stereoselective Additions of Metallated Aminosilanes to Aldehydes

| *Aldehyde* | *α-Silyloxysilane* | *Yield (%)* | *Diol* | *Yield (%)* |
|---|---|---|---|---|
| 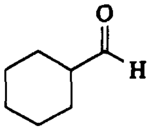 | 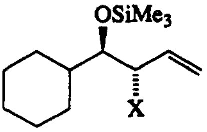<br>**(171a)** | 54 | 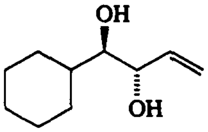<br>**(172a)** | 78 |
| 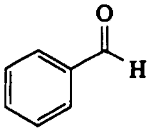 | 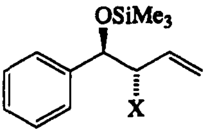<br>**(171b)** | 97 | 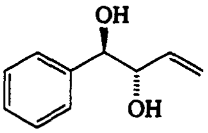<br>**(172b)** | 80 |
| 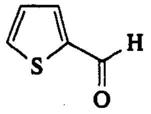 | 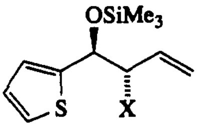<br>**(171c)** | 87 | 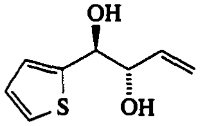<br>**(172c)** | 72 |
| 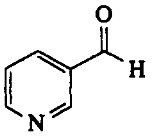 | 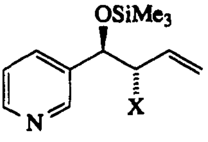<br>**(171d)** | 75 | 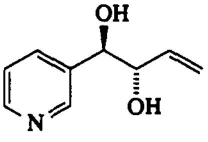<br>**(172d)** | 93 |

X = $SiMe_2(NPr^i_2)$.

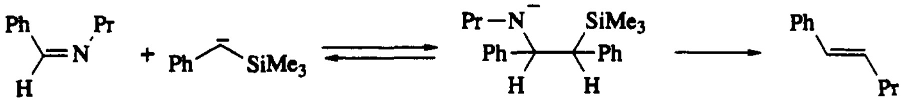
**(173)** **(174)**

**Scheme 76**

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# 2.6

# Selenium Stabilization

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## 2.6.1 INTRODUCTION

Over the past 15 years, organoselenium reagents have been increasingly used in organic synthesis, especially for the construction of complex molecules.[1] This is due to the ease with which selenium can be introduced into organic molecules,[2–7] and the large variety of selective reactions which can be performed on organoselenium compounds. These allow the synthesis of different selenium-free functional groups or molecules.[1–15] Organometallics bearing a selenium-stabilized carbanion have played an important role in such developments.[7,9,12,16,17] They are usually readily available and can be particularly good nucleophiles, especially towards compounds bearing an electrophilic carbon atom. In this respect they have been widely used, since they allow the synthesis of more complex organoselenium compounds with the concomitant formation of a new carbon–carbon bond attached at one end to the selenium-containing moiety. This review article deals with the synthesis of selenium-stabilized carbanions and only discloses their reactivity towards carbonyl compounds, especially aldehydes and ketones. Some further transformations of functionalized selenides to selenium-free molecules will also be discussed. We have in most cases chosen examples involving the trapping of organometallics, with aldehydes and ketones, as a definite proof of their existence. In some cases, however, such information was not available and we have therefore described trapping experiments with alkylating agents instead.

## 2.6.2 SYNTHESIS OF ORGANOMETALLICS BEARING A SELENIUM-STABILIZED CARBANION

### 2.6.2.1 Generalities on Selenium-stabilized Carbanions

### *2.6.2.1.1 Reaction of alkyl metals with selenides and functionalized selenides*

Organometallics bearing a selenium-stabilized carbanion[7,9,12,16,17] belong to the well-known family of α-heterosubstituted organometallics which have proved particularly useful in organic synthesis over the past 30 years.[7,18–33] Although they share similar features with other members of this family, they possess exceptional properties due to the special behavior of the selenium atom.[1–4,6–9,12,14–16,34]

Several organometallics bearing a seleno moiety and belonging to the aryl- (especially phenyl-) and methyl-seleno series, having their selenium atom in different oxidation states (Scheme 1), such as α-metalloalkyl selenides, α-metalloalkyl selenoxides, α-metalloalkyl selenones and α-metalloalkyl selenonium salts, as well as α-metallovinyl selenides and α-metallovinyl selenoxides, have been prepared, usually by metallation of the corresponding carbon acid with lithium or potassium amide or with potassium *t*-butoxide.

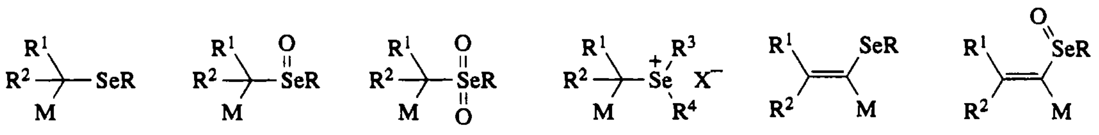

Scheme 1

These bases, however, are not strong enough to metallate[35,36] dialkyl and alkyl aryl selenides. Amylsodium[37,38] and alkyllithiums,[7,37–39] which have proved particularly useful for the metallation of the corresponding sulfides and phosphines, are not useful for the metallation of dialkyl or alkyl aryl selenides[7,17] owing to their tendency to react on the selenium atom and to produce a novel selenide and a novel organometallic (Scheme 2).[7,37–45] This latter reaction is easier when carried out in THF than in ether (Scheme

2, a),[16,17,43] is faster with *s*- or *t*-butyllithium[16,17,43,44] than with *n*-butyllithium[7,16,35,36,38–40,43–50] or methyllithium (Scheme 2, a)[45] and delivers the organometallic with the more stable carbanionic center of the three possible carbanions (Scheme 2, compare a with b). Thus butyllithiums react with methyl phenyl selenide and produce butyl methyl selenides and phenyllithium.[16,38–40,44] Substitution of the methyl group of methyl phenyl selenide by a group able to stabilize a carbanionic center, such as a vinyl,[45] aryl,[43,44,46] thio[47–49] or seleno[7,16,35,36] moiety, not only increases the reactivity of the selenide (the cleavage reaction takes place faster and at lower temperature: Scheme 2; compare a with b) but also dramatically changes the regiochemistry of the reaction. Phenyllithium is no longer produced but instead allyl-,[45] benzyl-,[43,44,46] thiomethyl-[47–49] and selenomethyl-lithiums[7,16,35,36] are obtained, respectively, in almost quantitative yield (Scheme 2, b).

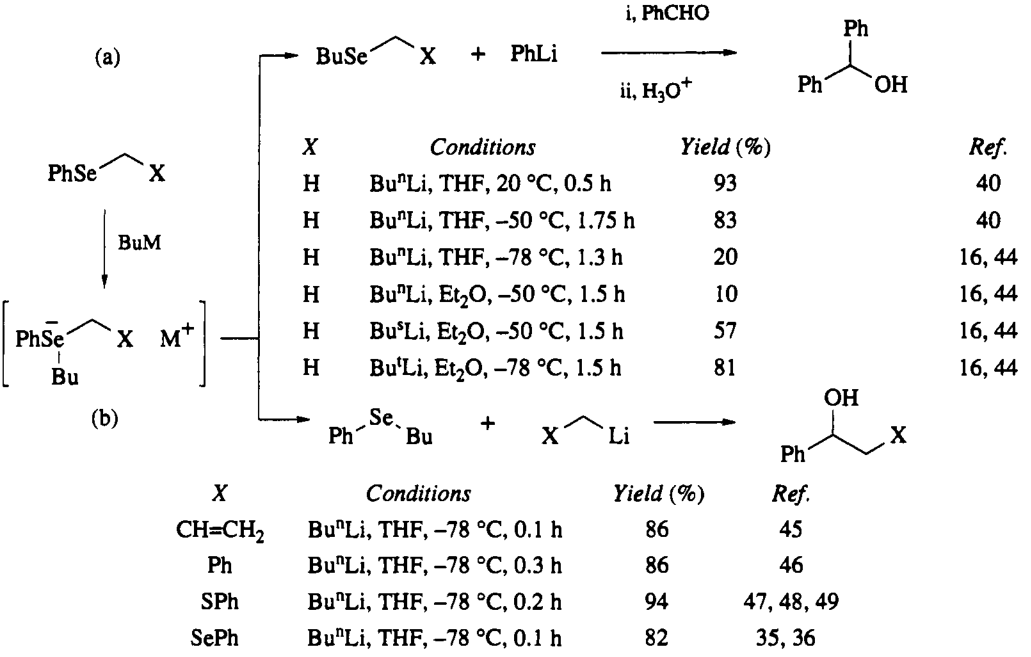

| X | Conditions | Yield (%) | Ref. |
|---|---|---|---|
| H | $\mathrm{Bu^nLi}$, THF, 20 °C, 0.5 h | 93 | 40 |
| H | $\mathrm{Bu^nLi}$, THF, −50 °C, 1.75 h | 83 | 40 |
| H | $\mathrm{Bu^nLi}$, THF, −78 °C, 1.3 h | 20 | 16, 44 |
| H | $\mathrm{Bu^nLi}$, $\mathrm{Et_2O}$, −50 °C, 1.5 h | 10 | 16, 44 |
| H | $\mathrm{Bu^sLi}$, $\mathrm{Et_2O}$, −50 °C, 1.5 h | 57 | 16, 44 |
| H | $\mathrm{Bu^tLi}$, $\mathrm{Et_2O}$, −78 °C, 1.5 h | 81 | 16, 44 |

| X | Conditions | Yield (%) | Ref. |
|---|---|---|---|
| $\mathrm{CH{=}CH_2}$ | $\mathrm{Bu^nLi}$, THF, −78 °C, 0.1 h | 86 | 45 |
| Ph | $\mathrm{Bu^nLi}$, THF, −78 °C, 0.3 h | 86 | 46 |
| SPh | $\mathrm{Bu^nLi}$, THF, −78 °C, 0.2 h | 94 | 47, 48, 49 |
| SePh | $\mathrm{Bu^nLi}$, THF, −78 °C, 0.1 h | 82 | 35, 36 |

**Scheme 2**

This reaction has proven to be of wide applicability: the selenium–metal exchange is a valuable alternative to the hydrogen–metal, halogen–metal or tin–metal exchange. Although less general than the two former methods, it takes advantage of the easy synthesis of selenides and functionalized selenides and of their thermal stability, even in the case of allyl or benzyl derivatives. Moreover, the butyl selenides produced concomitantly with the organometallic and resulting from the C—Se bond cleavage are generally inert in the reaction medium.[7,12,16] This differs markedly from the halogen–metal exchange by butyllithiums, which instead leads to butyl halides that react further with the organometallics present in the reaction medium.[51,52]

For the synthesis of α-selenoalkyllithiums, the selenium–lithium exchange reaction is a good alternative to the almost impossible metallation of unactivated selenides.[7,16,17] Thus it has been found that a large variety of selenoacetals, often readily available from carbonyl compounds and selenols,[35,53] react with butyllithiums to provide α-selenoalkyllithiums[4,7,9,12,16,17,35,36,40,48,49,54–56] in very high yields (Scheme 2; see also Section 2.6.2.3).

### *2.6.2.1.2 Stabilization of carbanionic centers by selenium-containing moieties*

The seleno moiety, when linked to a carbanionic center, provides[17,56–59] an extra stabilization of about 10 $\mathrm{p}K_\mathrm{a}$ unit. This is of the same order of magnitude as that provided by the corresponding thio moiety,[17] which stabilizes an $sp^3$ carbanion slightly better than does a seleno moiety.[7,17,57,60] These results differ greatly from those obtained by calculation,[59] which suggest a much higher difference (4 kcal; 1 cal = 4.18 J) and in the reverse order. Recent results from our laboratory[7,16,60] seem to show that heteroatom substituents affect the stabilization of an $sp^3$-hybridized carbanionic center much more than the heteroatom itself (S, Se). Thus a phenylseleno group stabilizes a carbanionic center to a higher extent than a methylseleno or (probably) a methylthio moiety.[60] Results which support the above mentioned tendencies are collected in Schemes 3, 4, 5 and 6.[60]

| *Compound* | *Conditions* | *Measured* | *Sulfur/selenium* | *Ref.* |
|---|---|---|---|---|
| $PhXCD_3$ | $KNH_2$, $NH_3$, −33 °C | $k_{isotop}$ | 10 | 64 |
| $m$-$CF_3C_6H_4XMe$ | LiTMP, THF, −78 °C | $k_{dep}$ | 3.8 | 56 |
| $PhXCH_2CH{=}CH_2$ | LDA, THF, −78 °C | $k_{dep}$ | 7.5 | 65 |
| $PhXCH_2C{\equiv}CH$ | NaOEt, EtOH, 25 °C | $k_{isom}$[a] | 12.6 | 62, 63 |
| $PhXCH{=}C{=}CH_2$ | NaOEt, EtOH, 25 °C | $k_{isom}$[b] | 7 | 62, 63 |
| $PhCOCH_2XPh$ | $MeSOCH_2Na$, DMSO | $K_{eq}$ | 32 | 66 |
| $Me_3XI$ | NaOD, $D_2O$, 62 °C | $K_{isotop}$ | 45 | 67 |
| $(PhX)_2CH_2$ | 0 °C | $pK_S/pK_{Se}$[c] | 32/35 | 36 |

[a] Isomerization of propargyl to allenyl selenide. [b] Isomerization of allenyl to 1-propynyl selenide.
[c] $pK_{aS} = 17.1$, $pK_{bSe} = 18.6$

**Scheme 3** Relative kinetic and thermodynamic acidity of sulfides and selenides

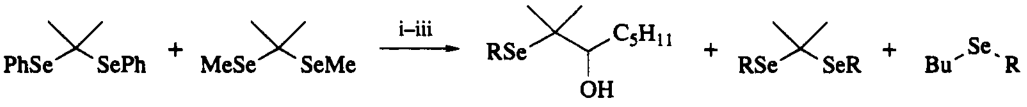

| | | | |
|---|---|---|---|
| R = Ph | 62% | 65% | 77% |
| R = Me | 10% | 10% | 23% |

i, Bu$^n$Li, THF–hexane, −78 °C, 0.1 h; ii, $C_5H_{11}CHO$; iii, $H_3O^+$

**Scheme 4**

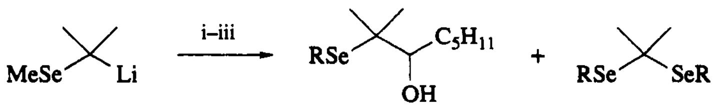

(ref. 60)

| *Solvent* | *Temperature* (°C) | *Time* (h) | *R* | *Yield* (%) | |
|---|---|---|---|---|---|
| THF–hexane | −78 | 0.1 | Me | 44 | 12 |
| | | | Ph | 30 | 50 |
| THF–hexane | −78 | 0.3 | Me | 30 | 20 |
| | | | Ph | 40 | 40 |

i, $Me_2C(SePh)_2$; ii, $C_5H_{11}CHO$; iii, $H_3O^+$

**Scheme 5**

The results in Schemes 3 to 6 are derived[17,36,56,61–67] from kinetic or thermodynamic acidity measurements on functionalized selenides and on the corresponding sulfides (Scheme 3), as well as from equilibration reactions[7,60] involving 2-phenylseleno-2-propyllithium and 2-phenylseleno-2-phenylthiopropane, and those involving 2-phenylthio-2-propyllithium and 2,2-bis(phenylseleno)propane (Scheme 6).

Surprisingly, for $sp^2$-hybridized carbanionic centers the reverse order of stabilization is found.[17,65,68] The seleno moiety is now more stabilizing than a thio moiety (Scheme 7, *cf.* Scheme 3).[17,69]

Several factors[59,66,69] might govern the relative stabilization of a negative charge by sulfur and selenium. The selenium atom is larger and more polarizable than sulfur, and is therefore expected to disperse the charge more efficiently. Sulfur, however, is slightly more electronegative and better stabilizes the charge by an inductive effect.[69] Conjugative interactions *via* $d$-orbitals should be more favorable for sulfur; however, conjugation is less favorable for $sp^2$-hybridized carbanions for which the greater polarizability of selenium dominates.

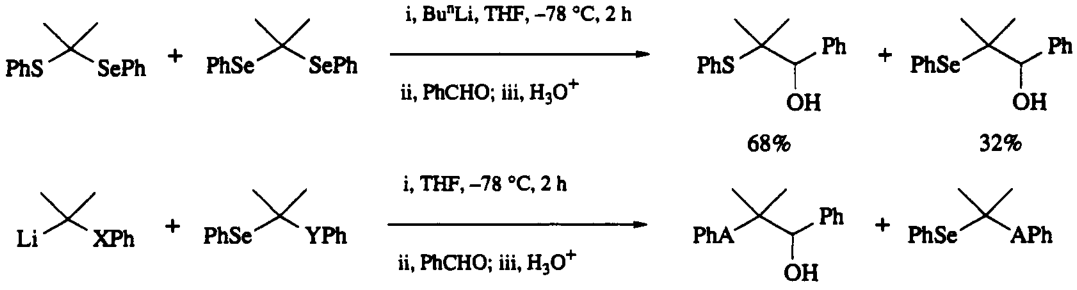
PhS SePh + PhSe SePh
i, Bu$^n$Li, THF, -78 °C, 2 h
ii, PhCHO; iii, $H_3O^+$
PhS Ph OH + PhSe Ph OH
68%
32%
Li XPh + PhSe YPh
i, THF, -78 °C, 2 h
ii, PhCHO; iii, $H_3O^+$
PhA Ph OH + PhSe APh

(ref. 60)

| | *A* | *Yield* (%) | |
|---|---|---|---|
| X = S, Y = Se | S | 66 | 19 |
| | Se | 33 | 66 |
| X = Se, Y = S | S | 66 | 25 |
| | Se | 33 | 63 |

**Scheme 6**

| *Compound* | *Conditions* | *Measured* | *Sulfur/selenium* |
|---|---|---|---|
| 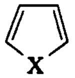 | KOBu$^t$, DMSO, 25 °C | $K_{isotop}$ | 0.67 |
| 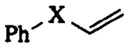 | LDA, THF, -78 °C | $K_{eq}$ | 0.21 |
| | LiTMP, THF, -78 °C | $k_{dep}$ | 0.37 |
| 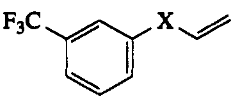 | LDA, THF, -78 °C | $K_{eq}$ | 0.37 |
| | LiTMP, THF, -78 °C | $k_{dep}$ | 0.42 |

**Scheme 7** Relative kinetic and thermodynamic acidity of vinyl sulfides and selenides (refs. 17 and 69)

The group attached to the seleno moiety modulates its ability to stabilize a carbanionic center (this effect is often higher than the one produced by the heteroatom itself). Thus a *m*-$CF_3PhSe$ group enhances[56,69,70] the kinetic acidity of a methylene group by approximately a factor of 20 over a PhSe group (Scheme 8),[7,71,72] which is in turn a much better stabilizing group than MeSe.

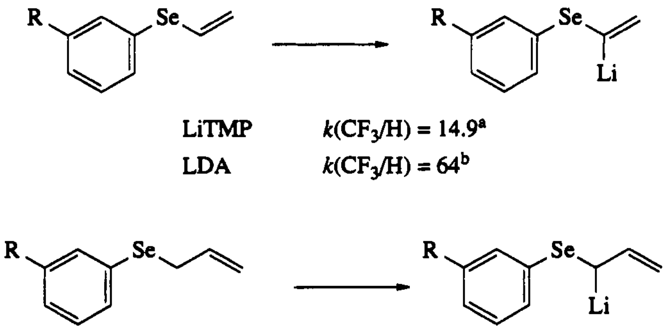
R Se
R Se Li
R Se
R Se Li

LiTMP $k(CF_3/H) = 14.9^a$

LDA $k(CF_3/H) = 64^b$

LDA $k(CF_3/H) = 11.7^a$

[a] $k(CF_3/H)$ is the relative rate of deprotonation, $k(CF_3/k_H) = \log M(CF_3)/\log M(H)$, where $M(CF_3)$ and $M(H)$ are the mole fractions of components *m*-$CF_3RH$ and RH remaining when the reaction is quenched.

[b] Equilibrium constant $K(CF_3/H)$ where $K = [CF_3RH][CF_3RLi]/RH/RLi$ (ref. 69)

**Scheme 8**

Thus, whereas 1,1-bis[(*m*-trifluoromethyl)phenylseleno]alkanes[65] and 1,1-bis(phenylseleno)-alkanes[35,36,71,73] are successfully metallated under various conditions (see below), their methylseleno analogs are not.[71] 1-Phenylseleno- and 1-methylseleno-1-arylethanes exhibit[72] a similar tendency, since the former is efficiently metallated with KDA in THF but not the latter (Scheme 9, compare c to f).

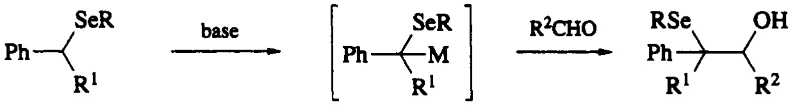

| *Entry* | *R* | *R¹* | *Conditions* | *R²* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| a | Ph | H | LDA, THF–hexane, –78 °C, 0.1 h | Et | 70 | 56 |
| b | Ph | Me | LDA, THF–hexane, –78 °C, 0.1 h | Ph | 0 | 72 |
| c | Ph | Me | KDA, THF–hexane, –50 °C, 0.3 h | Ph | 87 | 72 |
| d | Ph | Bu | KDA, THF–hexane, –50 °C, 0.3 h | Ph | 70 | 72 |
| e | Me | H | KDA, THF–hexane, –50 °C, 0.3 h | Ph | 79 | 72 |
| f | Me | Me | KDA, THF–hexane, –50 °C, 0.3 h | Ph | 0 | 72 |

**Scheme 9**

It also has been found that butyllithiums react faster with 2,2-bis(phenylseleno)propane than with its methylseleno analog.[60] Thus, addition of *n*-butyllithium to a 1:1 mixture of 2,2-bis(phenylseleno)propane and 2,2-bis(methylseleno)propane leads selectively to the formation of 2-lithio-2-phenylselenopropane under kinetically controlled conditions, providing the α-selenoalkyllithium with the more stable carbanionic center (Scheme 4). Furthermore, 2-methylselenopropyllithium reacts[60] with 2,2-bis(phenylseleno)propane and leads, under thermodynamically controlled conditions, to 2-phenylseleno-2-propyllithium, thus demonstrating the better propensity of a phenylseleno moiety over a methylseleno moiety to stabilize a carbanionic center (Scheme 5).

The presence of a group able to delocalize the charge from the carbanionic center favors the synthesis of the carbanion whatever the method used, whereas substitution of the carbanionic center by alkyl groups disfavors it. Thus, whereas methyl phenyl and dimethyl selenide cannot be metallated with LDA at –78 °C or 0 °C, phenylseleno and methylseleno acetates and propionates lead, on reaction with the same base at –78 °C, to the corresponding organometallics (Scheme 10).[74,75]

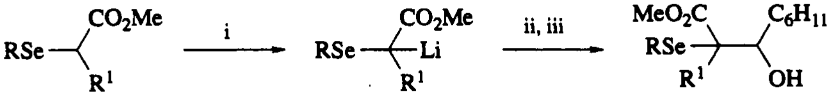

(ref. 74)

| *R* | *R¹* | *Yield (%)* |
|---|---|---|
| Ph | H | 93 |
| Ph | Me | 60 |
| Me | H | 80 |
| *p*-$ClC_6H_4$ | H | 96 |

i, LDA, THF–hexane. –78 °C, 0.5 h; ii, $C_6H_{13}CHO$; iii, $H_3O^+$

**Scheme 10**

Yet another important difference of reactivity towards *n*-butyllithium has been found between phenyl selenoacetals derived from aldehydes and ketones.[60] This distinction allowed,[60] when the reaction was performed in ether–hexane, the selective synthesis of an α-selenoalkyllithium derived from the phenyl selenoacetal of an aldehyde in the presence of the phenyl selenoacetal of a methyl ketone, which remained untouched (Scheme 11).[60]

α-Selenoalkyl metals have been prepared[7,9,12,16,17] by a large array of methods such as metallation of selenides, selenoxides, selenones and selenonium salts; selenium–metal exchange between selenoacetals and alkyllithiums or metals; halogen–lithium exchange between α-haloalkyl selenides and alkyllithiums; addition of organolithiums to vinyl selenides; and selenophilic addition of organometallics to selones (Scheme 12).

Among these methods, the metallation reaction is the method of choice for selenides bearing electron-withdrawing groups able to stabilize the carbanionic center. This also applies to selenoxides, selenones and selenonium salts.

The reaction of selenoacetals with butyllithiums allows the synthesis of a large variety of α-selenoalkyllithiums whose carbanionic centers are unsubstituted, monoalkyl substituted or dialkyl substituted.

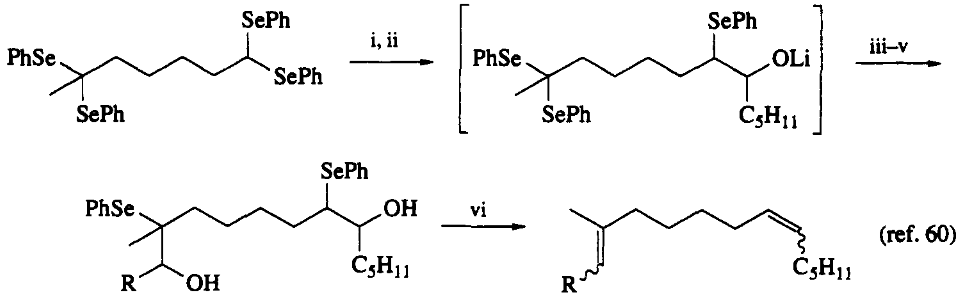
SePh
PhSe
SePh
SePh
i, ii
SePh
PhSe
OLi
SePh
$C_5H_{11}$
iii–v
SePh
PhSe
OH
R
OH
$C_5H_{11}$
vi
R
$C_5H_{11}$
(ref. 60)

R = $C_5H_{11}$, 76%; R = Ph, 66% R = Ph, $C_5H_{11}$, 76% overall

i, $Bu^nLi$ (1 equiv.), ether–hexane, 45 °C, 0.5 h; ii, $C_5H_{11}CHO$; iii, $Bu^sLi$ (1 equiv.), ether–hexane, −78 °C, 0.5 h; iv, RCHO; v, $H_3O^+$; vi, $P_2I_4$

Scheme 11

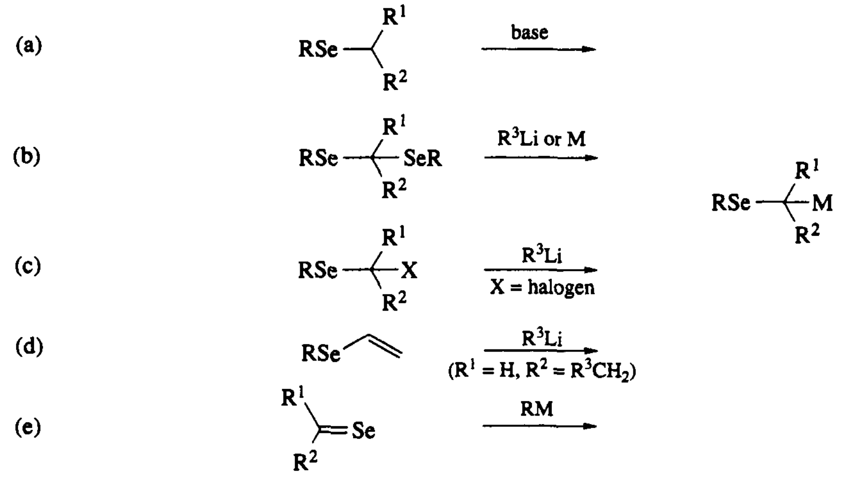
(a)
RSe
$R^1$
$R^2$
base
(b)
RSe
SeR
$R^1$
$R^2$
$R^3Li$ or M
(c)
RSe
X
$R^1$
$R^2$
$R^3Li$
X = halogen
(d)
RSe
$R^3Li$
($R^1$ = H, $R^2$ = $R^3CH_2$)
(e)
$R^1$
Se
$R^2$
RM
RSe
M
$R^1$
$R^2$

Scheme 12

The other methods cited above are synthetically less useful, especially the selenophilic addition to selones.[76]

All the different types of selenium-substituted organometallics with almost all the possible substitution patterns around the carbanionic center are now available, and therefore the intermediates are among the few α-heterosubstituted organometallics to be so widely available.[7]

## 2.6.2.2 Synthesis by Metallation of Organometallics Bearing a Selenium-stabilized Carbanion

### *2.6.2.2.1 Synthesis of α-selenoalkyl metals by metallation of selenides*

Alkyl aryl and dialkyl selenides, aside from the parent compounds methyl phenyl selenide (Scheme 13, a)[36] and trifluoromethylphenyl methyl selenide (Scheme 13, b),[56] cannot be easily metallated. It was expected that the extra stabilization provided by the cyclopropyl group would be sufficient to permit the metallation of cyclopropyl selenides, but that proved not to be the case.[56,77]

Cyclopropyl phenyl selenides are inert towards lithium diisopropylamide (LDA) and lithium tetramethylpiperidide (LiTMP) (Scheme 14, a). Butyllithiums instead react on the selenium atom and produce[77] butyl cyclopropyl selenides and phenyllithium rather than cyclopropyllithiums and butyl phenyl selenides (Scheme 14, b).

Aryl methyl selenides with the methyl group substituted by an aryl (Scheme 9 and 15),[56,70,72,78,79] a vinyl (Schemes 16–18),[56,69,80–90] a 1-butadienyl (Scheme 17, d)[91] or an ethynyl (Schemes 19 and

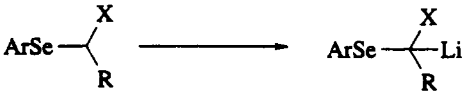
ArSe
X
R
ArSe
X
Li
R

| | *Ar* | *X* | *R* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Ph | H | H | $Bu^nLi$-TMEDA, THF, 0 °C | 38 | 38 |
| (b) | 4-$CF_3C_6H_4$ | H | H | LiTMP, THF–hexane, –55 °C, 2 h | 100 | 56 |
| (c) | 4-$CF_3C_6H_4$ | H | Me | LiTMP, THF–hexane, –55 °C, 2 h | 0 | 56 |

**Scheme 13**

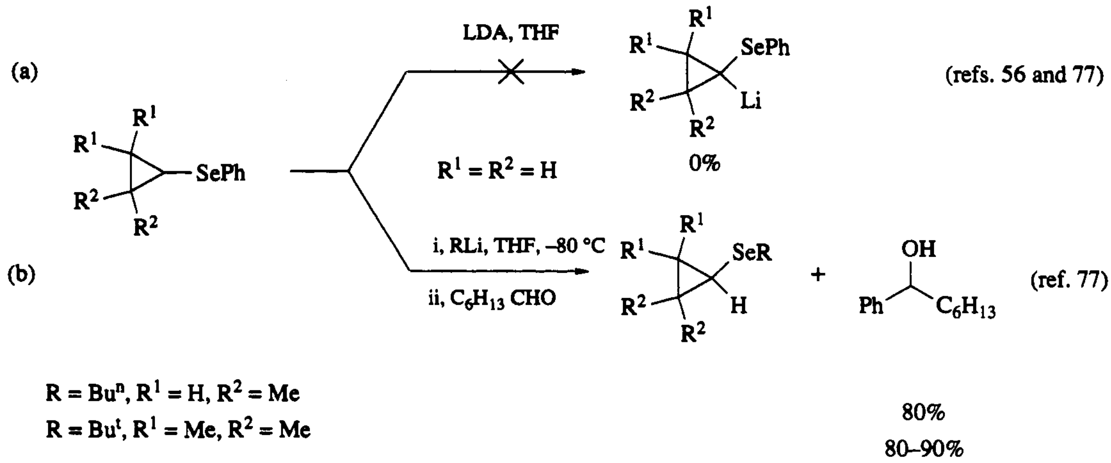
(a)
(b)
R1
R1
SePh
R2
R2
LDA, THF
R1 = R2 = H
R1
R1
SePh
R2
Li
R2
0%
(refs. 56 and 77)
i, RLi, THF, –80 °C
ii, C6H13 CHO
R1
R1
SeR
R2
H
R2
+
OH
Ph
C6H13
(ref. 77)
R = Bun, R1 = H, R2 = Me
R = But, R1 = Me, R2 = Me
80%
80–90%

**Scheme 14**

20)[56,92,93] group, or a methoxy (Scheme 21, a),[56] a phenylthio (Scheme 22),[94] an arylseleno (Scheme 21, b; Scheme 23, a),[35,36,49,56,65,71,73,95–97] a silyl (Scheme 24, a–d)[56,70,98–100] or a telluryl (Scheme 25, a)[101] moiety, some of which provide a further stabilization of the carbanionic center, have been successfully metallated by metalloamides.

As a general trend in this series of compounds, *m*-trifluoromethylphenyl selenides are more efficiently metallated than phenyl selenides, methylseleno derivatives are scarcely reactive, and the presence of an alkyl substituent on the carbon to be metallated often inhibits the reaction (Scheme 9 and Schemes 13–25).

As far as the basic system is concerned, KDA in THF–hexane (a 1:1 mixture of lithium diisopropylamide (LDA) and potassium *t*-butoxide)[45,72,73] is by far more efficient than lithium tetramethylpiperidide (LiTMP) (in THF–HMPA[71] or THF–hexane[45,56,71,72]) which is in fact at least a power of 10 more reactive[17,56] than lithium amides (in HMPA[41] or THF–hexane[35,36,41,56,65,70,78–82,84–86,90,92,93,95,97,99,101–103]). Thus, although bis(phenylseleno)methane[35,36] and its bis(*m*-trifluoromethyl) analogs[65] are almost quantitatively metallated with lithium diisobutyramide or LDA in THF, respectively (Scheme 21, b and c;

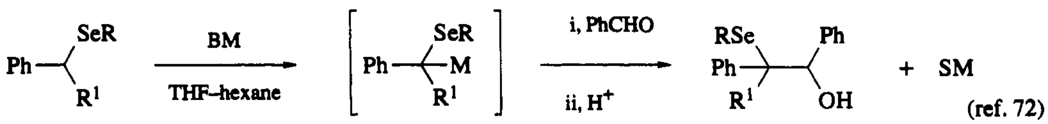
SeR
Ph
R1
BM
THF–hexane
SeR
Ph
M
R1
i, PhCHO
ii, H+
RSe
Ph
Ph
R1
OH
+ SM
(ref. 72)

| | *R* | *R¹* | *Conditions* | *Yield (%)* | |
|---|---|---|---|---|---|
| (a) | Ph | Me | KDA, –50 °C, 0.3 h | 87 | 0 |
| (b) | Ph | Me | LDA, 0 °C, 0.5 h | 15 | 85 |
| (c) | Ph | Me | LiTMP, 20 °C, 0.5 h | 62 | 0 |
| (d) | Me | H | KDA, –78 °C, 0.3 h | 79 | — |
| (e) | Me | H | LDA, –50 °C, 0.5 h | 61 | 16 |
| (f) | Me | H | LiTMP, –78 °C, 0.3 h | 67 | 17 |

**Scheme 15**

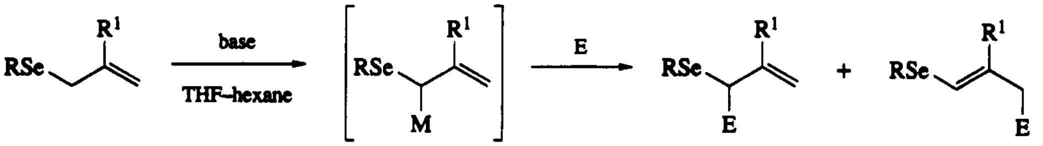
RSe
R1
base
THF–hexane
RSe
R1
M
E
RSe
R1
E
+
RSe
R1
E

| | *R* | *R¹* | *Conditions* | *E* | *Yield (%)* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | Ph | H | LDA, –78 °C, 0.2 h | $Ph(CH_2)_3Br$ | 68 | 100:0 | 80 |
| (b) | Ph | H | LDA, –78 °C, 0.2 h | PhCOMe | 70–85 | 15:85 | 80 |
| (c) | Ph | H | LDA, –78 °C, 0.2 h, then $Et_3Al$ | PhCOMe | 70–85 | 64:36 (64:36)$^a$ | 81, 82 |
| (d) | Ph | H | LDA, –78 °C, 0.2 h | EtCHO | 70–85 | 12:88 | 81, 82 |
| (e) | Ph | H | LDA, –78 °C, then $Et_3Al$ | EtCHO | 70–85 | 100:0 (81:19)$^a$ | 81, 82 |
| (f) | Ph | Me | LDA, –78 °C, 0.5 h | $Bu_3SnCl$ | 100 | 0:100 | 84 |
| (g) | Me | H | LiTMP | PhCHO | 76 | 18:82 | 45 |

$^a$ *Threo*:*erythro* ratio

Scheme 16

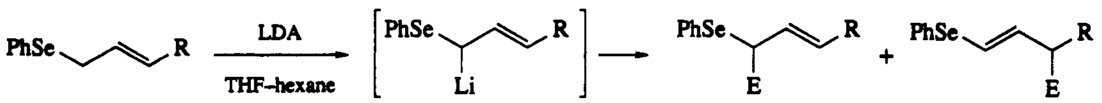
PhSe
R
LDA
THF–hexane
PhSe
R
Li
PhSe
R
E
+
PhSe
R
E

| | *R* | *Conditions* | *E* | *Yield (%)* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Me | –78 °C, 0.6 h | $Ph(CH_2)_2Br$ | 80 | 100:0 | 80 |
| (b) | Ph | –78 °C, 0.1 h | $Me_2CO$ | 55 | 100:0 | 80 |
| (c) | SePh | –78 °C, 0.1 h | $Pr^iCHO$ | 88 | — | 85 |

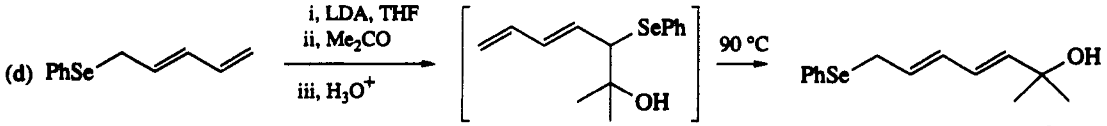
(d) PhSe
i, LDA, THF
ii, Me2CO
iii, H3O+
SePh
OH
90 °C
PhSe
OH

71% overall (ref. 91)

Scheme 17

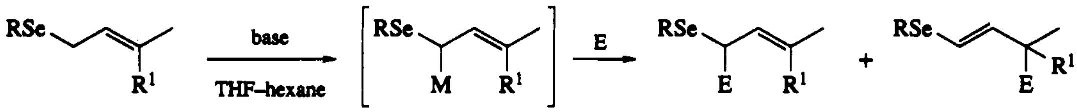
RSe
R1
base
THF–hexane
RSe
M
R1
E
RSe
E
R1
+
RSe
R1
E

| | *R* | *R¹* | *Conditions* | *E* | *Yield (%)* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | Ph | Cl | LDA, –78 °C, <0.1 h | $Ph(CH_2)_2Br$ | 85 | 100:0 | 80 |
| (b) | Ph | Me | LDA, 0 °C, 0.5 h | $Me_2PhSiCl$ | 71 | 100:0 | 80 |
| (c) | Me | Me | LiTMP, –78 °C, 0.5 h | PhCHO | 11 | 0:100 | 45 |
| (d) | Me | Me | LiTMP, –25 °C, 0.5 h | PhCHO | 47 | 0:100 | 45 |
| (e) | Me | Me | KDA, –78 °C, 0.3 h | PhCHO | 78 | 35:65 | 45 |

Scheme 18

Scheme 23, a), bis(methylseleno)methane remains untouched[71] under these or even under stronger conditions. Higher homologs in the arylseleno series require the concomitant use of LiTMP and HMPT,[71] or better, KDA in THF (Scheme 23, b–d).[73]

In fact, the metallation of some of these compounds can be achieved in minute amounts using even LDA or Bu$^t$OK, but the equilibrium between the different partners is not in favor of the formation of the

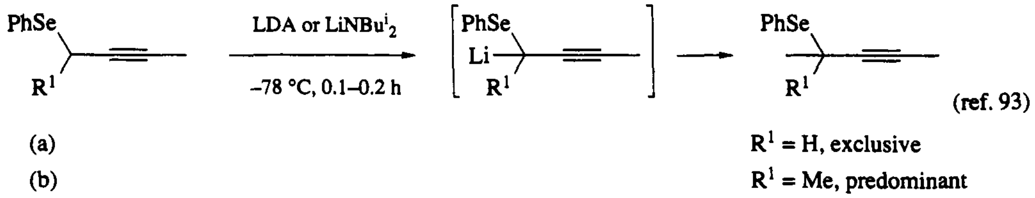
PhSe
R¹
LDA or LiNBuⁱ₂
-78 °C, 0.1–0.2 h
PhSe
Li
R¹
PhSe
R¹
(ref. 93)
(a)
(b)
R¹ = H, exclusive
R¹ = Me, predominant

Scheme 19

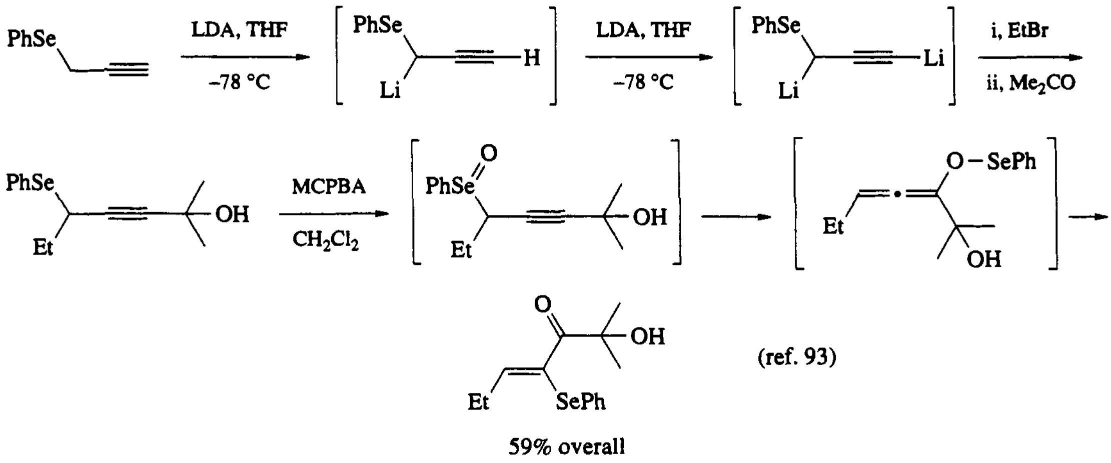
PhSe
LDA, THF
-78 °C
PhSe
Li
H
LDA, THF
-78 °C
PhSe
Li
Li
i, EtBr
ii, Me₂CO
PhSe
Et
OH
MCPBA
CH₂Cl₂
O
PhSe
Et
OH
O–SePh
Et
OH
O
OH
Et
SePh
(ref. 93)
59% overall

Scheme 20

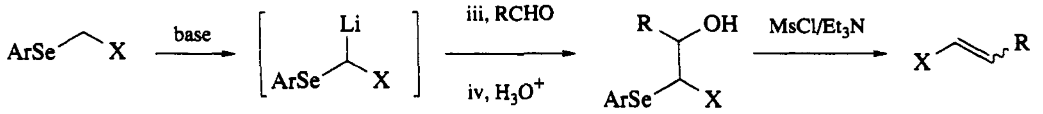
ArSe
X
base
Li
ArSe
X
iii, RCHO
iv, H₃O⁺
R
OH
ArSe
X
MsCl/Et₃N
X
R

| | *Base/conditions* | *Ar* | *X* | *R* | *Yield (%)* | *Temperature/time* | *Yield (%)* | *(Z):(E)* |
|---|---|---|---|---|---|---|---|---|
| (a) | i | $m$-$CF_3C_6H_4$ | OMe | Ph | 76 | | 72 | 46:54 |
| (b) | ii | Ph | SePh | Ph | 95 | 0 °C, 0.2 h | 74 | 0:100 |
| | ii | Ph | SePh | Me | 92 | 0 °C, 0.2 h | 84 | 50:50 |
| | ii | Ph | SePh | Et | 98 | 0 °C, 0.2 h | 74 | 50:50 |
| | ii | Ph | SePh | $Pr^i$ | 71 | 0 °C, 0.2 h | 81 | 25:75 |
| (c) | ii | $m$-$CF_3C_6H_4$ | $m$-$CF_3C_6H_4Se$ | Ph | - | 20 °C, 3 h | 85 | 0:100 |
| | ii | $m$-$CF_3C_6H_4$ | $m$-$CF_3C_6H_4Se$ | Me | 91 | 20 °C, 3 h | 63 | 50:50 |
| | ii | $m$-$CF_3C_6H_4$ | $m$-$CF_3C_6H_4Se$ | Et | 98 | 20 °C, 3 h | 72 | 50:50 |
| | ii | $m$-$CF_3C_6H_4$ | $m$-$CF_3C_6H_4Se$ | $Pr^i$ | 98 | 20 °C, 3 h | 79 | 30:70 |

i, LiTMP, THF, -78 °C, 0.1 h; ii, LDA, THF, -78 °C, 0.5 h (refs. 56 and 65)

Scheme 21

α-selenoalkyl metal. In some cases, however, the equilibrium can be driven to the other side by, for example, trapping the organometallic, once it is formed, with an alkylating agent. This is effectively the case for 3-chloro-1,1-bis(phenylseleno)propane and its bis(methylseleno) analogs, as well as 3-chloro-1,1-bis(phenylseleno)hexane, which produce[104] the corresponding selenoacetals of cyclopropanone on reaction with LDA in THF (Scheme 26, a and b). 3-Chloro-1,1-bis(methylseleno)hexane, however, does not react under similar conditions (Scheme 26, d). Such difference of reactivity between phenylseleno and methylseleno derivatives is also observed when potassium *t*-butoxide is used as the base. Thus, whereas 3-chloro-1,1-bis(phenylseleno)propane is almost quantitatively cyclized (Scheme 26, b),[12,77] its methylseleno analogs unexpectedly produce[12,77] 1,1-bis(methylseleno)-1-propene (Scheme 26, c). 1,1-Bis(phenylseleno)cyclopropane has also been prepared by Reich[97] from 3-tosyloxy-1-phenylseleno-

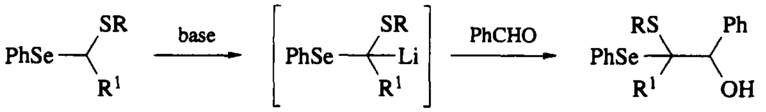

(ref. 94)

| *R* | *R¹* | *Base/conditions* | *Yield* (%) | *Recovered SM* (%) |
|---|---|---|---|---|
| Ph | H | LiTMP, THF, −24 °C, 1.5 h | 91 | – |
| Ph | Me | LiTMP, THF, −24 °C, 1.5 h | 68 | 10 |
| Ph | $C_5H_{11}$ | LiTMP, THF, −24 °C, 1.5 h | 0 | 85 |
| Ph | $C_5H_{11}$ | LiTMP, diglyme, −24 °C, 0.5 h | 65 | 17 |
| Me | $C_5H_{11}$ | LiTMP, diglyme, −78 °C, 1 h | 75 | 0 |

**Scheme 22**

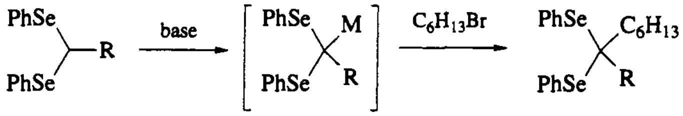

|  | *Conditions* | *R* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| (a) | $Bu^i_2NLi$, THF, −78 °C, then −30 °C, 0.2 h | H | 80 | 35, 36 |
| (b) | LDA, THF–HMPA, −30 °C, then 20 °C, 0.2 h | Me | 74 | 71 |
|  | LDA, THF–HMPA, −30 °C, then 20 °C, 0.2 h | $C_6H_{13}$ | 44 | 71 |
| (c) | LiTMP, THF–HMPA, −30 °C, then 20 °C, 0.2 h | Me | 83 | 71 |
|  | LiTMP, THF–HMPA, −30 °C, then 20 °C, 0.2 h | $C_6H_{13}$ | 86 | 71 |
| (d) | KDA, THF, −78 °C | Me | 95 | 73 |

(e)

(f)

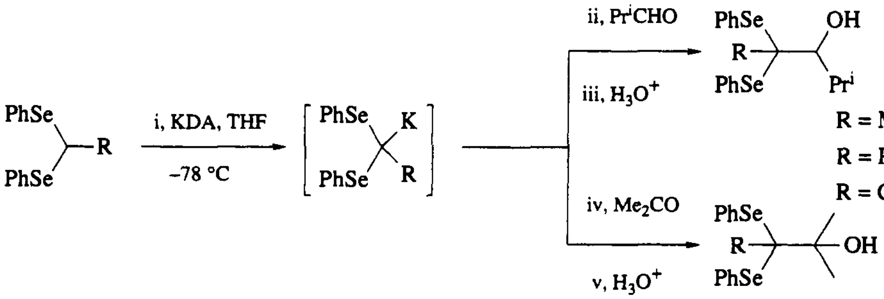

(ref. 73)

R = Me, 90%

R = $Pr^i$, 63%

R = $C_{10}H_{21}$, 84%

(ref. 73)

R = Me, 77%

**Scheme 23**

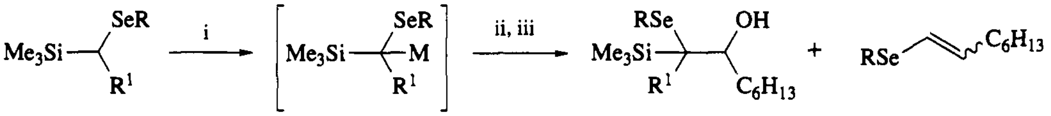

|  | *R* | *R¹* | *Conditions* | *Yield* (%) | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Me | H | −30 °C, 0.5 h | 0 | – | 100 |
| (b) | Ph | H | −78 °C, 0.5 h | 5 | 100:0 | 100 |
| (c) | Ph | H | −30 °C, 0.5 h | 30 | 57:43 | 100 |
| (d) | *m*-$CF_3C_6H_4$ | H | −78 °C, 0.5 h | 83 | – | 70 |
| (e) | Ph | $C_{10}H_{21}$ | −30 °C, 0.5 h | 0 | – | 100 |
| (f) | Ph | Ph | 0 °C, 0.5 h | 77 | – | 70 |
| (g) | *m*-$CF_3C_6H_4$ | Ph | −78 °C, 0.8 h | 81 | – | 70 |

i, LDA, THF–hexane; ii, $C_6H_{13}CHO$; iii, $H_3O^+$

**Scheme 24**

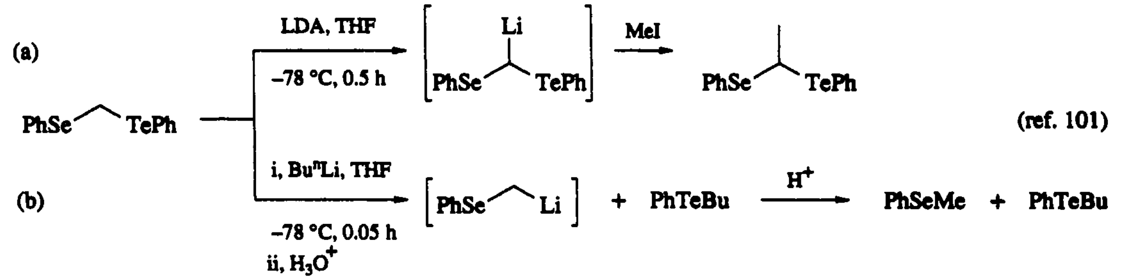
(a)
LDA, THF
−78 °C, 0.5 h
Li
PhSe
TePh
MeI
PhSe
TePh
(ref. 101)
PhSe
TePh
(b)
i, Bu<sup>n</sup>Li, THF
−78 °C, 0.05 h
ii, H3O+
PhSe
Li
+ PhTeBu
H+
PhSeMe + PhTeBu

**Scheme 25**

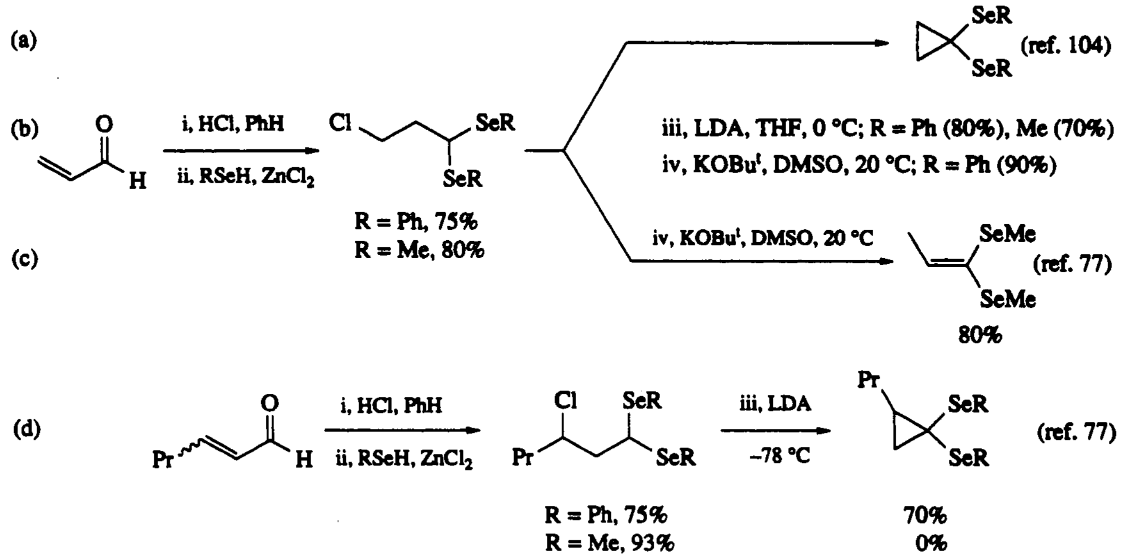
(a)
SeR
SeR
(ref. 104)
(b)
O
H
i, HCl, PhH
ii, RSeH, ZnCl2
Cl
SeR
SeR
R = Ph, 75%
R = Me, 80%
iii, LDA, THF, 0 °C; R = Ph (80%), Me (70%)
iv, KOBu<sup>t</sup>, DMSO, 20 °C; R = Ph (90%)
(c)
iv, KOBu<sup>t</sup>, DMSO, 20 °C
SeMe
SeMe
(ref. 77)
80%
(d)
Pr
O
H
i, HCl, PhH
ii, RSeH, ZnCl2
Cl
SeR
Pr
SeR
iii, LDA
−78 °C
Pr
SeR
SeR
(ref. 77)
R = Ph, 75%
R = Me, 93%
70%
0%

**Scheme 26**

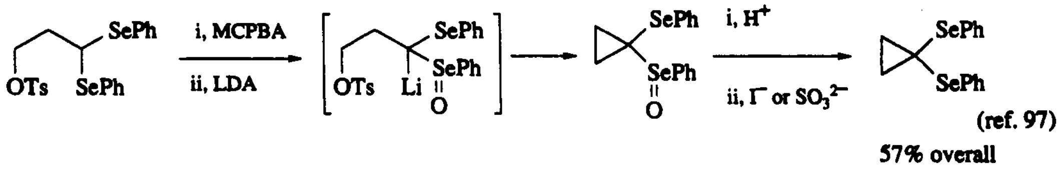
SePh
OTs
SePh
i, MCPBA
ii, LDA
SePh
SePh
OTs
Li
O
SePh
SePh
O
i, H+
ii, I− or SO3 2−
SePh
SePh
(ref. 97)
57% overall

**Scheme 27**

1-phenyl-selenoxypropane and LDA in THF followed by reduction of the resulting cyclopropyl phenyl selenoxide with, for example, iodide anion (Scheme 27).[97]

Benzyl selenides exhibit a similar pattern of reactivity. Thus, although the parent aryl benzyl selenides are successfully metallated with LDA at −78 °C,[56,72,78,79] their higher homologs, as well as benzyl methyl selenides,[72] are not. Use of stronger bases such as LiTMP, or better, KDA, allows the metallation of various aryl benzyl selenides, even those bearing an alkyl substituent at the benzylic site (Scheme 13, c; Scheme 15 a and c; Scheme 23, b–d). They are, however, of limited use in the methylseleno series since the parent compound is the only one to react (Scheme 15, d–f).[72]

Allylic[45,80–82,84,85] and propargylic[93] selenides seem to be more acidic. In the phenylseleno series, for example,[80–82,84,85] the synthesis of those compounds bearing an alkyl substituent on the carbanionic center has been already achieved with LDA and does not require the use of stronger bases (Schemes 16–20). In the methylseleno series,[45] however, the use of LiTMP (Scheme 16, h; Scheme 18, c and d) or KDA (Scheme 18, e compared with c and d) is often needed.

Finally, the metallation is particularly difficult with selenides bearing a methoxymethyl substituent,[56] and is only successful[56] when a *m*-(trifluoromethyl)phenyl moiety is attached to the selenium atom (Scheme 21, a).

As already mentioned, LiTMP acts usually as a stronger base than LDA or lithium diethylamide; in some rare cases the reverse order of reactivity has been observed. Thus it has been found[56] that the trimethylsilyl substituent reduces the kinetic acidity of $CF_3PhSeCH_2SiMe_3$ as compared with $CF_3PhSeMe$ towards LiTMP by a factor of 2.8. With LDA as base, however, the silyl substituent has the opposite effect,[56] since *m*-$CF_3PhSeCH_2SiMe_3$ is deprotonated at least 25 times as fast as *m*-$CF_3PhSeMe$ (Scheme 24, d). Presumably, steric effects cancel the normal acidifying effect of the trimethylsilyl group when a hindered base such as LiTMP is used.

Phenylselenomethyl phosphonates[102] and (phenylseleno)chloromethane[105] have been metallated by NaH and $Bu^tOK$, respectively (Scheme 28, a and b; Scheme 29). The former organometallics react with carbonyl compounds and directly produce vinyl selenides (Scheme 28, a and b),[102] whereas the second decomposes to phenylselenomethylene[105] which adds stereospecifically to alkenes and leads to phenylselenocyclopropanes in reasonably good yields (Scheme 29).[105]

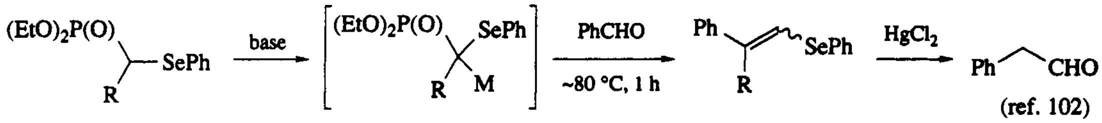

(ref. 102)

| | *Conditions* | *R* | *Yield (%)* | *(Z):(E)* | *Yield (%)* |
|---|---|---|---|---|---|
| (a) | NaH, THF–HMPA (10:1), 80 °C, 1 h | H | 80 | 6:94 | 90 |
| (b) | NaH, THF–HMPA (10:1), 80 °C, 6 h | Me | 86 | 47:53 | – |
| | NaH, THF–HMPA (10:1), 80 °C, 6 h | Et | 70 | 8:92 | – |
| (c) | $Bu^nLi$, THF–hexane, –78 °C, 4 h | H | 70 | 16:84 | – |

**Scheme 28**

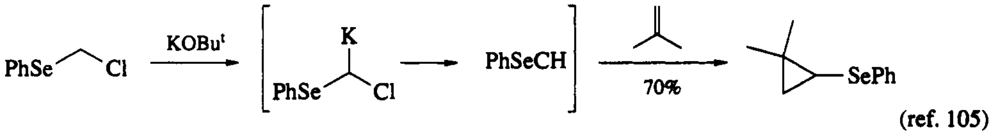

(ref. 105)

**Scheme 29**

$Bu^nLi$, which usually performs the Se–Li exchange[7,9,12,16,17] in selenides, effects the metallation of some functionalized selenides. This is particularly the case of phenylselenomethyl phosphonates[102] and phosphonium salts (Scheme 28, c).[106,107] This is also the case of methyl phenyl selenide (Scheme 13, a compared with Scheme 2, a),[36] phenyl trimethylsilylmethyl selenide (Scheme 30, a)[98] and bis(phenylseleno)methane (Scheme 30, c and d),[36,71] which are metallated with butyllithium but only in coordinating solvents such as TMEDA,[36,98] dimethoxyethane (DME)[71] or HMPA.[71]

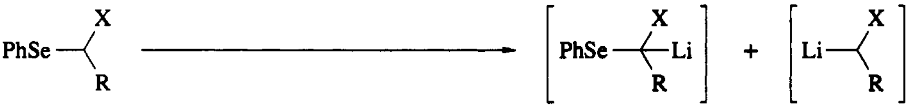

| *X* | *R* | *Conditions* | *Yield (%)* | | *Ref.* |
|---|---|---|---|---|---|
| (a) $Me_3Si$ | H | $Bu^sLi$–TMEDA, 25 °C, 1.5 h | 83 | 15 | 98 |
| (b) PhSe | H | $Bu^nLi$, DME–hexane, –78 °C, 1 h | 50 | 40 | 71 |
| (c) PhSe | Me | $Bu^nLi$, DME–hexane, –78 °C, 1 h | 25 | 35 | 71 |

**Scheme 30**

Selenides bearing two groups capable of stabilizing a carbanionic center on the α-carbon are much more acidic than the above mentioned derivatives and both the phenylseleno and the methylseleno derivatives can be readily metallated. Thus, tris(phenylseleno)methane,[35,36] tris(methylseleno)methane (Scheme 31),[71,108] arylbis(phenylseleno)methane and arylbis(methylseleno)methane (Scheme 32)[72] lead to the corresponding methyllithiums with LiDBA,[35,36] LDA,[71,72,100] LiTMP[72] or KDA[72] in THF. Surprisingly, with arylbis(seleno)methanes selenophilic attack of LiTMP[72] and LDA,[72] which produces α-selenobenzyllithiums, competes with the metallation reaction (Scheme 32, d and e). This reaction can be prevented if KDA is used instead of LDA (Scheme 32, a and b).[72]

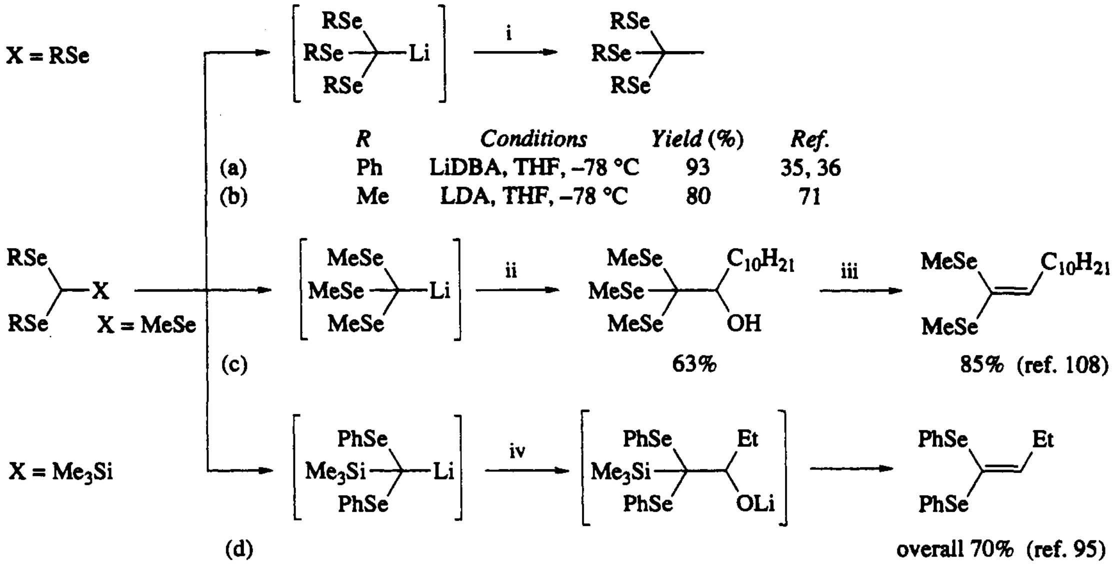

|  | *R* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| (a) | Ph | LiDBA, THF, –78 °C | 93 | 35, 36 |
| (b) | Me | LDA, THF, –78 °C | 80 | 71 |

i, MeI; ii, $C_{10}H_{21}CHO$; iii, $PI_3$, $Et_3N$, $CH_2Cl_2$, 20 °C, 1 h; iv, EtCHO

Scheme 31

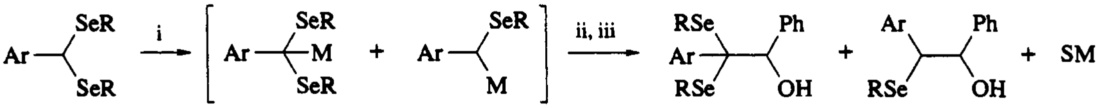

|  | *R* | *Ar* | *Base* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|---|
| (a) | Me | Ph or 4-$MeOC_6H_4$ | KDA | 79 | 100:0:0 |
| (b) | Ph | Ph or 4-$MeOC_6H_4$ | KDA | 81 | 100:0:0 |
| (c) | Me | Ph | LDA | – | 50:0:50 |
| (d) | Me | Ph | LiTMP | – | 16:30:54 |
| (e) | Ph | Ph | LDA | – | 26:11:50[a] |

(ref. 72)

[a] Other products are formed.

i, base, THF–hexane, –78 °C, 0.3 h; ii, PhCHO; iii, $H^+$

Scheme 32

It has been noticed that lithium diethylamide is far superior to LDA for the metallation of vinyl-[85] and phenyl-(trimethylsilyl)phenylselenomethane (Scheme 33).[70] Presumably, the steric hindrance due to the trimethylsilyl group prevents the attack of the bulky LDA.

The situation is clearly different for α-seleno ketones (Schemes 34–36),[96,109–111] α-seleno esters (Schemes 10 and 37),[56,74,75,112,113] selenolactones (Scheme 38),[74,114] α-seleno acids (Scheme 39)[56,115] and α-selenonitriles (Scheme 40),[116,117] which have been easily metallated according to Rathke's procedure[118,119] using LDA as a base. The reaction is reasonably general and takes place on a large variety of arylseleno and methylseleno derivatives including those that bear an alkyl group in the α-position. In the latter case, however, some competitive C—Se bond cleavage has been observed from time to time.[96,111]

α-Phenylselenonitroalkanes (Scheme 41)[120] and α-phenylseleno-β-lactams (Scheme 42, a) derived from penicillin[121] have been transformed to their enolates on reaction with calcium hydroxide and butyllithium, respectively. In the latter case, however, successful metallation has been achieved exclusively on the stereoisomer bearing an *endo*-phenylseleno moiety (Scheme 42, compare a with b).[121]

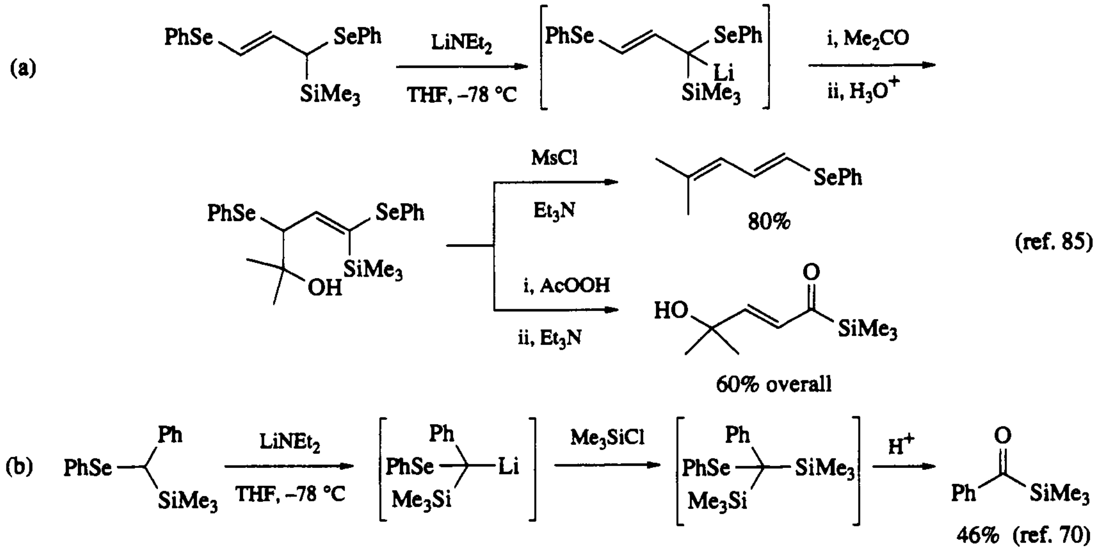
(a)
PhSe
SePh
SiMe3
LiNEt2
THF, −78 °C
Li
i, Me2CO
ii, H3O+
OH
MsCl
Et3N
80%
i, AcOOH
ii, Et3N
HO
O
SiMe3
60% overall
(ref. 85)
(b)
Ph
Me3Si
Me3SiCl
H+
46% (ref. 70)

**Scheme 33**

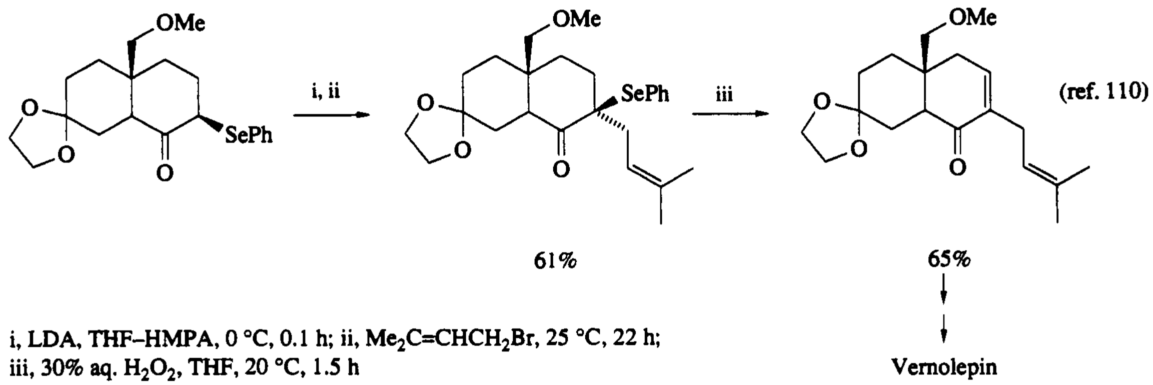
OMe
O
SePh
i, ii
iii
61%
65%
Vernolepin
(ref. 110)

i, LDA, THF–HMPA, 0 °C, 0.1 h; ii, $Me_2C{=}CHCH_2Br$, 25 °C, 22 h;
iii, 30% aq. $H_2O_2$, THF, 20 °C, 1.5 h

**Scheme 34**

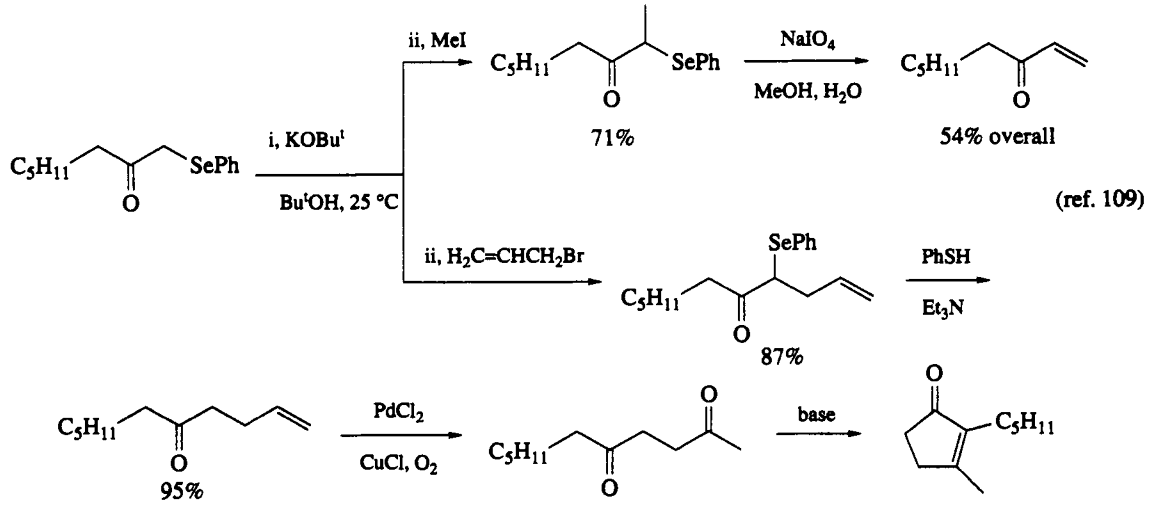
C5H11
SePh
O
i, KOBut
ButOH, 25 °C
ii, MeI
71%
NaIO4
MeOH, H2O
54% overall
(ref. 109)
ii, H2C=CHCH2Br
87%
PhSH
Et3N
95%
PdCl2
CuCl, O2
base

**Scheme 35**

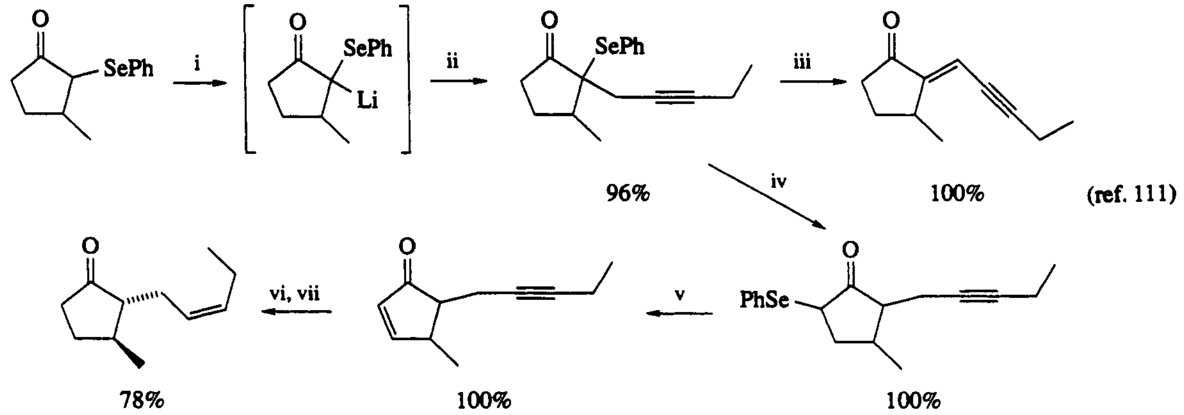
SePh
i
Li
ii
SePh
iii
96%
iv
100%
(ref. 111)
vi, vii
v
PhSe
78%
100%
100%

i, LDA, THF, −78 °C, 0.2 h; ii, EtC≡CCH$_2$Br, THF–HMPA, −78 °C, 2 h, then 20 °C, 10 h;
iii, 30% aq. H$_2$O$_2$, CH$_2$Cl$_2$; iv, LDA, THF–HMPA, −78 °C, 0.5 h, then 20 °C, 1 h;
v, 30% aq. H$_2$O$_2$, 20 °C, 1 h; vi, NaOMe, 20 °C, 5 h; vii, H$_2$, BaSO$_4$, EtOAc

**Scheme 36**

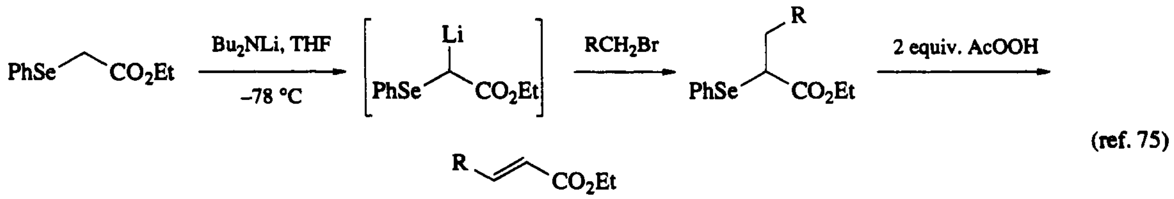
PhSe
CO2Et
Bu2NLi, THF
−78 °C
Li
PhSe
CO2Et
RCH2Br
R
PhSe
CO2Et
2 equiv. AcOOH
(ref. 75)
R
CO2Et

Overall yields: R = Me, 66%; R = Ph, 65%

**Scheme 37**

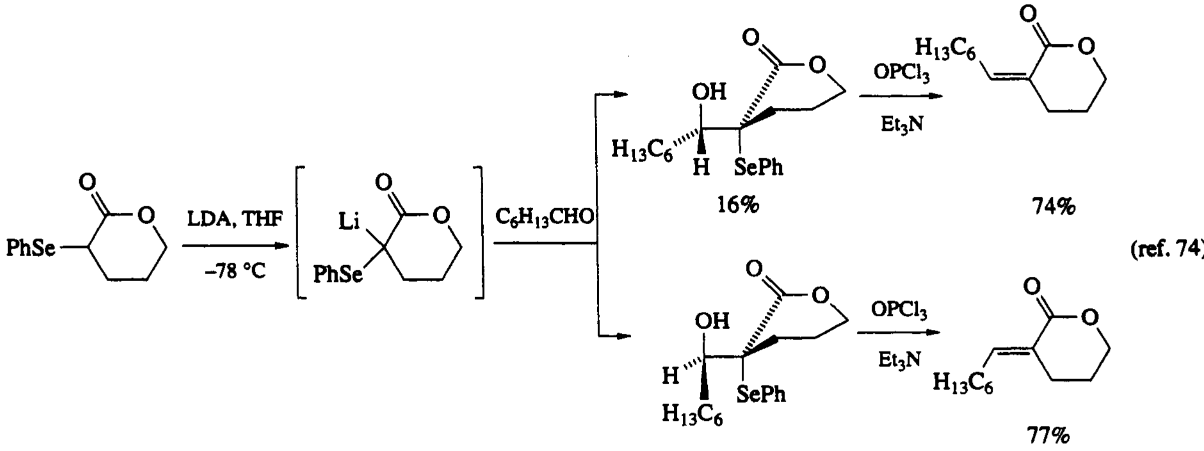
PhSe
LDA, THF
−78 °C
Li
PhSe
C6H13CHO
OH
H13C6
H
SePh
16%
OPCl3
Et3N
H13C6
74%
(ref. 74)
OH
H
SePh
H13C6
OPCl3
Et3N
H13C6
77%

**Scheme 38**

### *2.6.2.2.2 Synthesis of α-selenovinyl metals (1-seleno-1-alkenyl metals) by metallation of vinyl selenides*

Metallation of vinyl selenides can be more readily achieved than that of alkyl selenides since two different effects now work in the same direction. Hydrogens linked to an *sp*$^2$ carbon are more acidic than those linked to an *sp*$^3$ carbon, and the selenium atom stabilizes the resulting *sp*$^2$ carbanion to a larger extent than it does in the *sp*$^3$ case (see Section 2.6.2.1.2).[17,65,68] Except in the special cases of selenophene[122] and benzoselenophene (Scheme 43),[123] which also belong to that series of compounds, butyllithiums are not suitable metallating agents. Depending upon the solvent and the nature of the vinyl

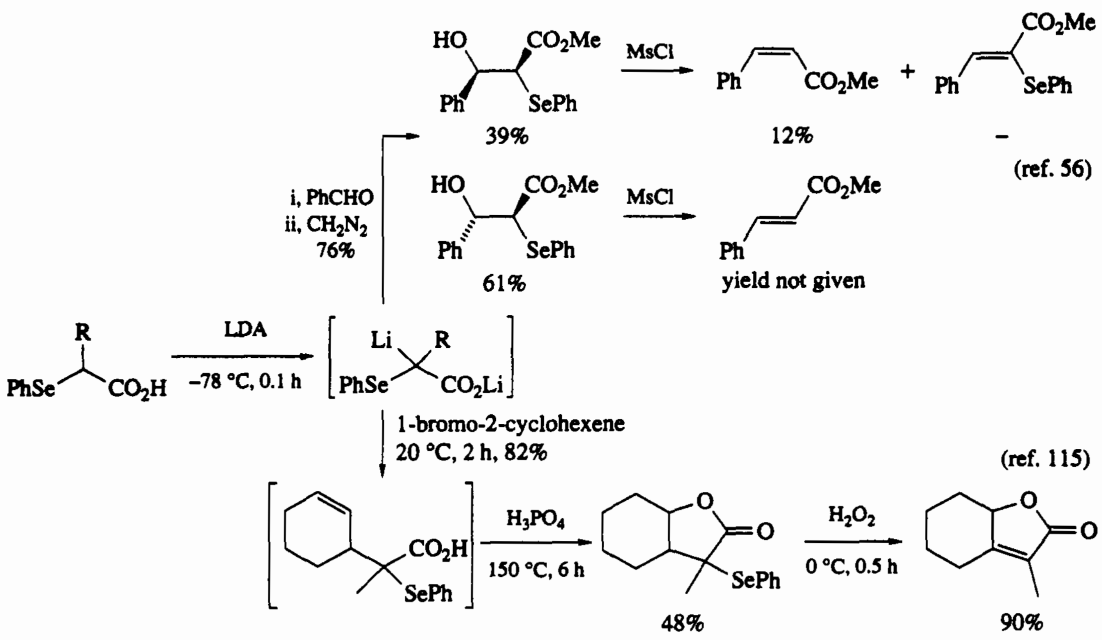
MsCl
39%
12%
(ref. 56)
i, PhCHO
ii, CH2N2
76%
61%
yield not given
LDA
−78 °C, 0.1 h
1-bromo-2-cyclohexene
20 °C, 2 h, 82%
(ref. 115)
H3PO4
150 °C, 6 h
48%
H2O2
0 °C, 0.5 h
90%

**Scheme 39**

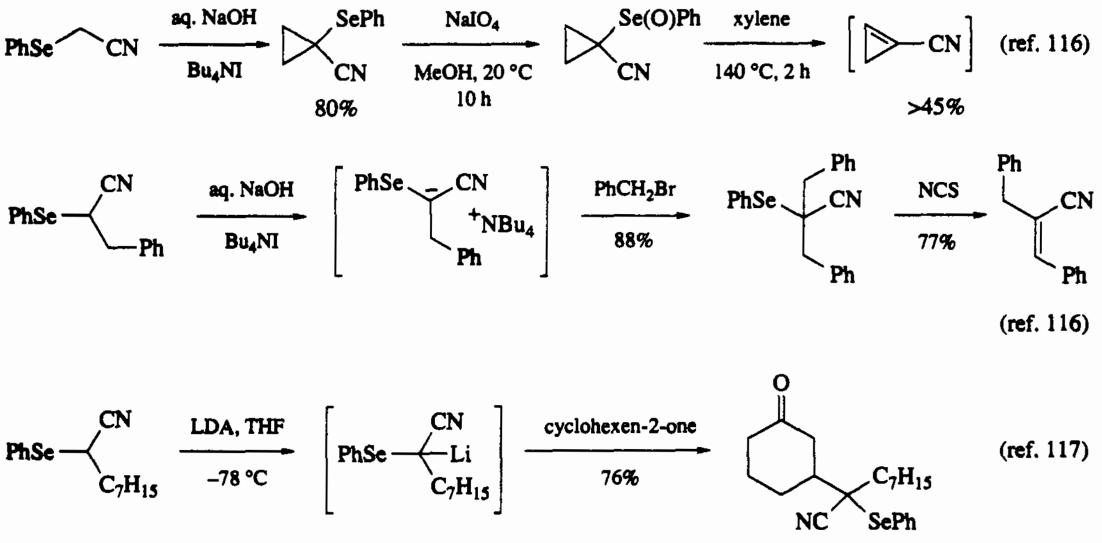
aq. NaOH
Bu4NI
80%
NaIO4
MeOH, 20 °C
10 h
xylene
140 °C, 2 h
>45%
(ref. 116)
aq. NaOH
Bu4NI
PhCH2Br
88%
NCS
77%
(ref. 116)
LDA, THF
−78 °C
cyclohexen-2-one
76%
(ref. 117)

**Scheme 40**

selenide different reactions take place. Thus, alkyllithiums in ether[41,65,124] or DME[42] add across the carbon–carbon double bond of phenyl vinyl selenide (see Section 2.6.2.5), whereas the C—Se bond cleavage leading to phenyllithium and butyl vinyl selenide occurs[41,65,125] when the reaction is performed in THF at

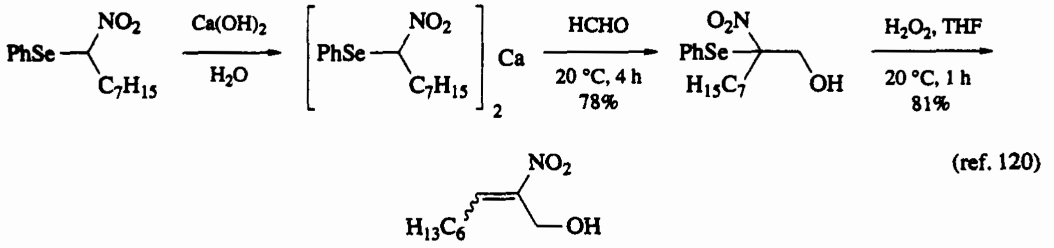
Ca(OH)2
H2O
HCHO
20 °C, 4 h
78%
H2O2, THF
20 °C, 1 h
81%
(ref. 120)

**Scheme 41**

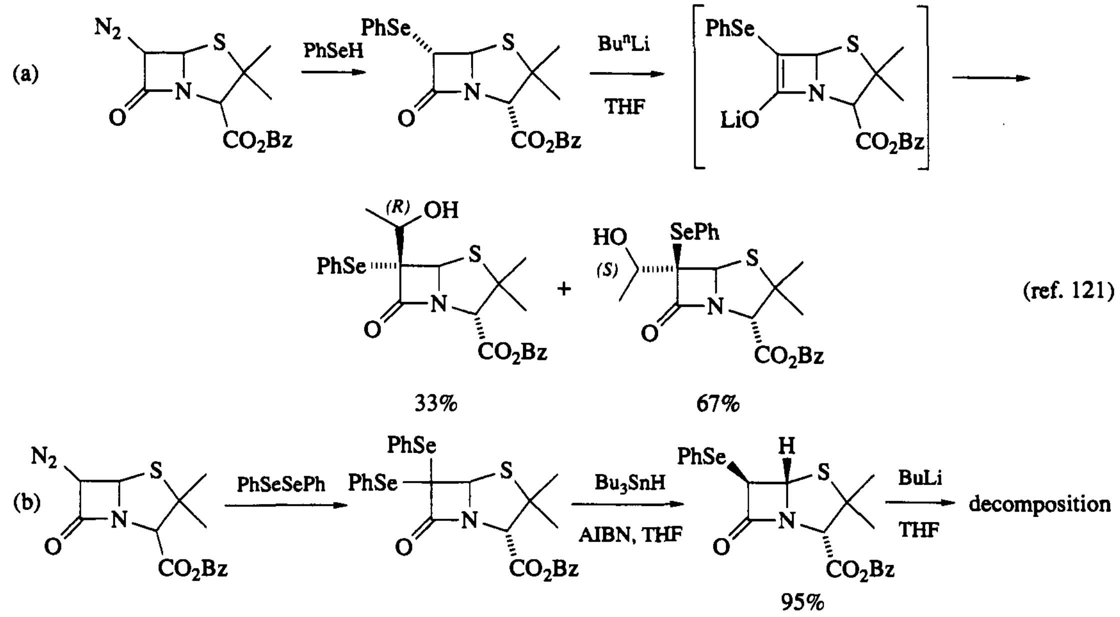
(a)
PhSeH
Bu^nLi
THF
33%
67%
(ref. 121)
(b)
PhSeSePh
Bu3SnH
AIBN, THF
95%
BuLi
THF
decomposition

**Scheme 42**

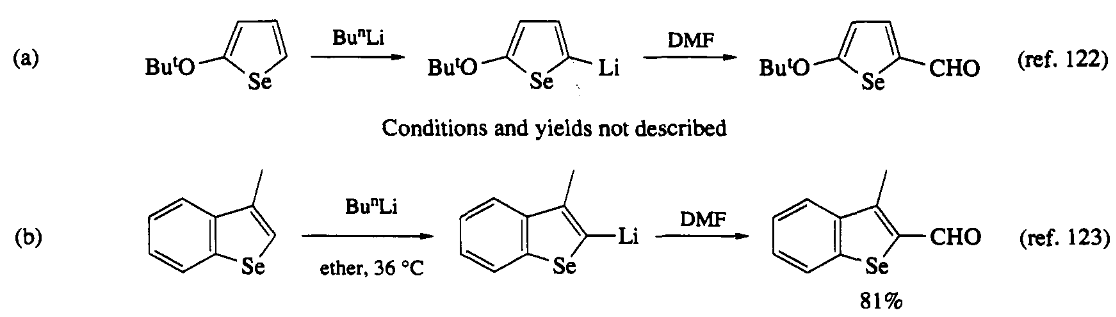
(a)
Bu^nLi
DMF
(ref. 122)
(b)
Bu^nLi
ether, 36 °C
DMF
81%
(ref. 123)

Conditions and yields not described

**Scheme 43**

low temperature. Under the latter conditions methyl vinyl selenides are metallated instead on their methyl group.[125]

Metalloamides are suitable for the synthesis of 1-metallovinyl aryl selenides (Scheme 44)[41,65,73] and 1-metalloallenyl phenyl selenides (Scheme 45)[93] from the corresponding vinyl or allenyl selenides. The synthesis of the latter organometallics is even more conveniently achieved[93] by metallation of 1-phenylseleno-1-propyne or by a two-step, one-pot sequence of reactions from 2-chloroallyl phenyl selenide (Scheme 45).

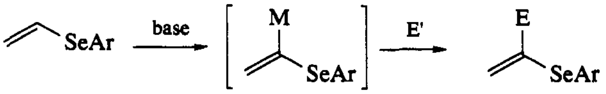
SeAr
base
M
SeAr
E'
E
SeAr

| | *Ar* | *Conditions* | *E'* | *E* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Ph | LDA (1.5 equiv.), THF, -78 °C, 1 h | $D_2O$ | D | 80 | 65 |
| (b) | Ph | LDA (1.5 equiv.), THF, -78 °C, 1 h | $Me_2CO$ | $Me_2CHOH$ | 80 | 65 |
| (c) | Ph | LDA (1.5 equiv.), THF, -78 °C, 1 h | $C_6H_{13}CHO$ | $C_6H_{13}CHOH$ | 40 | 41 |
| (d) | Ph | LDA (1.5 equiv.), THF, -78 °C, 1 h | $CO_2$ | $CO_2H$ | 77 | 65 |
| (e) | Ph | LDA (1 equiv.), THF–HMPA (20:1), -78 °C | $C_{10}H_{21}Br$ | $C_{10}H_{21}$ | 80 | 41 |
| (f) | Ph | KDA (1 equiv.), THF, -78 °C | $C_{10}H_{21}Br$ | $C_{10}H_{21}$ | 94 | 73 |
| (g) | 4-$CF_3C_6H_4$ | LDA (1 equiv.), THF, -78 °C | $CO_2$ | $CO_2H$ | 80 | 65 |
| (h) | 4-$CF_3C_6H_4$ | LDA (1 equiv.), THF–HMPA, -78 °C | BuI | Bu | 85 | 65 |

**Scheme 44**

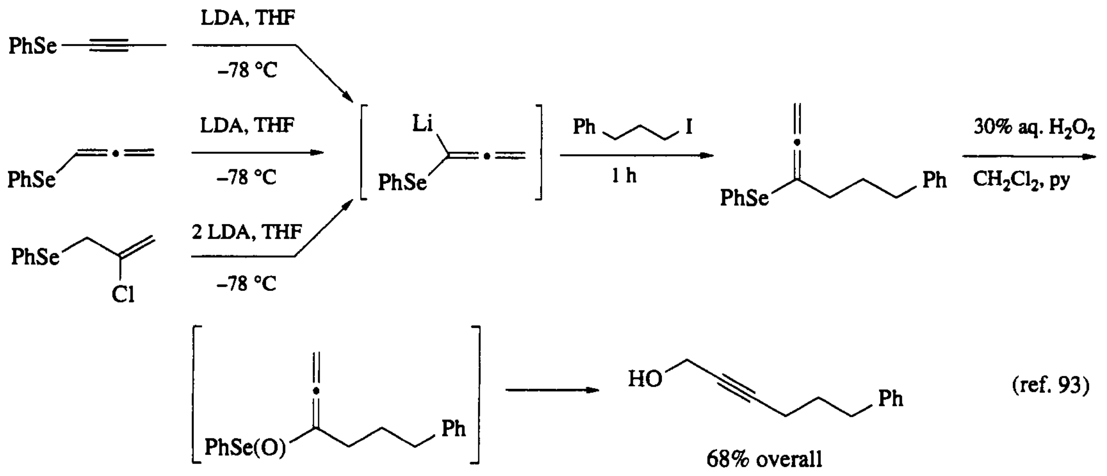

(ref. 93)

**Scheme 45**

LDA in THF[41,65] or in THF–HMPT,[41] LiTMP in THF[65] and KDA in THF[73] have all been successfully used for the metallation of phenyl[41,65,73] or *m*-(trifluoromethyl)phenyl[65] vinyl selenide (Scheme 44). The deprotonation was shown to be reversible[65] with LDA in THF and irreversible with LiTMP[65] when performed in the same solvent. Extension of this reaction to homologous derivatives proved difficult[65,73] since metallation at the allylic sites often competes. Allylic metallation is particularly favorable with aryl 1-propenyl selenides (Scheme 46)[65,73] and, whatever the conditions used (LiTMP[65] or KDA[73]), with aryl 1-(2-methyl-1-propenyl) selenides (Scheme 47). In the latter case both the (*Z*)- and the (*E*)-methyl groups have been metallated leading to the corresponding α-metalloallyl selenides (Scheme 47).[65,73]

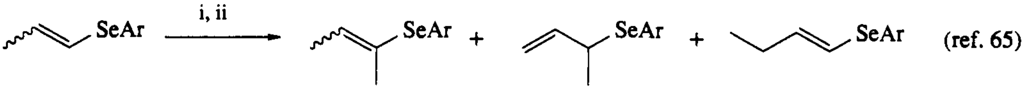

| *Ar* | *Time* (h) | *Overall yield* (%)[a] | *Ratio* |
|---|---|---|---|
| Ph | 2 | 42 | 9:73:12 |
| Ph | 9 | 88 | 4:74:18 |
| *m*-$CF_3C_6H_4$ | 1 | 66 | 30:51:7 |
| *m*-$CF_3C_6H_4$ | 7 | 93 | 12:68:11 |

[a] Products resulting from decomposition of the carbanion are also formed.

i, LDA (1.25 equiv.), THF, –78 °C, times as above; ii, MeI

**Scheme 46**

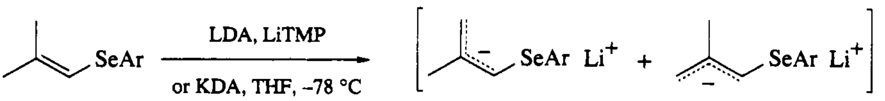

Ar = Ph or *m*-$CF_3C_6H_4$

(refs. 55 and 73)

**Scheme 47**

Increasing the substitution of the alkyl group on the β-carbon of 1-alkenyl phenyl selenides again favors metallation at the vinylic site (Scheme 48).[65,73] KDA in THF has proved to be, without contest, the most successful reagent for this purpose.[73] The reaction takes place at low temperature (–78 °C) and the 1-phenylselenoalkenyl metal, produced in almost quantitative yield,[73] retains its stereochemistry (Scheme 48, b–d).

Satisfactory deprotonations of 1-(*E*)-butenyl and 1-(3-methyl-1-(*E*)-butenyl) selenides in either the phenyl or *m*-(trifluoromethyl)phenyl series cannot be achieved[65] with LDA in THF (Scheme 48, compare a, e and g). Even LiTMP does not deprotonate the phenyl vinyl selenides (Scheme 48, a), and complete

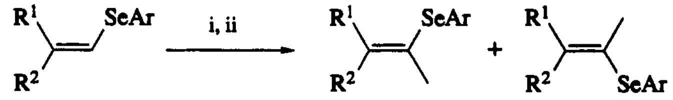

| | *Ar* | *$R^1$* | *$R^2$* | *Reagent* | *Yield (%)* | | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | Ph | H | Et or $Pr^i$ | LDA or LiTMP | Unsatisfactory metallation | | 65 |
| (b) | Ph | H | Bu | KDA | 85 | – | 73 |
| (c) | Ph | Bu | H | KDA | – | 85 | 73 |
| (d) | Ph | H | $Pr^i$ | KDA | 80 | – | 73 |
| (e) | $m$-$CF_3C_6H_4$ | H | Et | LDA | Unsatisfactory metallation | | 65 |
| (f) | $m$-$CF_3C_6H_4$ | H | Et | LiTMP | 32 | 32 | 65 |
| (g) | $m$-$CF_3C_6H_4$ | H | $Pr^i$ | LDA | Unsatisfactory metallation | | 65 |
| (h) | $m$-$CF_3C_6H_4$ | H | $Pr^i$ | LiTMP | 43 | 19 | 65 |
| (i) | Py | H | $C_6H_{13}$ | LDA | 94 | – | 126 |
| (j) | Py | $C_6H_{13}$ | H | LDA | 100 | – | 126 |

i, LDA (1.5 equiv.), THF, –78 °C or LiTMP (1.5 equiv.), THF, –50 °C or KDA (1 equiv.), THF, –78 °C; ii, MeI

Scheme 48

deprotonation of the $m$-$CF_3$ aryl substituted selenides requires[65] the use of an excess of LiTMP (1.5 equiv.) and a higher temperature (–50 °C instead of –78 °C). Methylation of the resulting organometallics, furthermore, leads to the corresponding vinyl selenides in modest yield and as a mixture of (*Z*)- and (*E*)-stereoisomers. These results differ substantially[65] from those obtained with KDA (see above).

Related results have been described[126] from pyridyl alkenyl selenides which, contrary to other aryl alkenyl selenides (see below),[65] are easily metallated at the vinyl site with LDA (Scheme 48, compare i and j with f and h). The ready deprotonation and stereoselective methylation of these selenides have been ascribed[126] to the presence of the nitrogen atom which can reduce the electron density of the double bond and also chelate with the lithium counterion.[65,103]

Phenyl vinyl selenoxide was expected to be considerably more acidic than the corresponding selenide and it was thought that it might be deprotonated more easily and with greater selectivity at the vinylic carbon. Deprotonation with LDA occurs[65] at –78 °C as well as at –90 °C (Scheme 49), but the decomposition of the resulting α-lithiovinyl selenoxide is so rapid ($t_{1/2}$ = 0.5 h at –78 °C in THF) that the methylation product is formed in less than 50% yield (Scheme 49).[65]

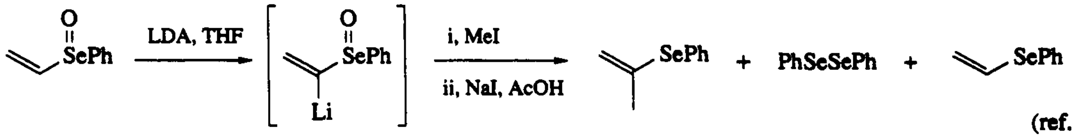

(ref. 65)

| | | | | |
|---|---|---|---|---|
| (a) | 0.2 h, –78 °C | 35% | 44% | 22% |
| (b) | 0.5 h, –78 °C | 19% | 67% | 14% |

Scheme 49

### 2.6.2.2.3 Synthesis of α-metalloalkyl selenoxides, selenones and selenonium salts

Alkyl selenoxides,[97,98,127,128] selenones[129–131] and selenonium salts[132–137] are far more acidic than the corresponding selenides and have been successfully deprotonated by LDA,[98,127,128,132] KDA[130,131] or $Bu^tOK$[129–132,135,136] in THF or DMSO, KOH in DMSO[134,135] or $NaNH_2$ in liquid ammonia.[137]

Alkyl metals are not suitable for the metallation of these compounds. For example, $Bu^nLi$ reacts at –78 °C on the selenium atom of selenonium salts and produces a novel organolithium in which the carbanionic center is more stabilized (Scheme 50, a and b), whereas alkylmagnesium bromides and chlorides unexpectedly lead[129] to decyl bromide and chloride respectively on reaction with decyl phenyl selenone (Scheme 50, c).

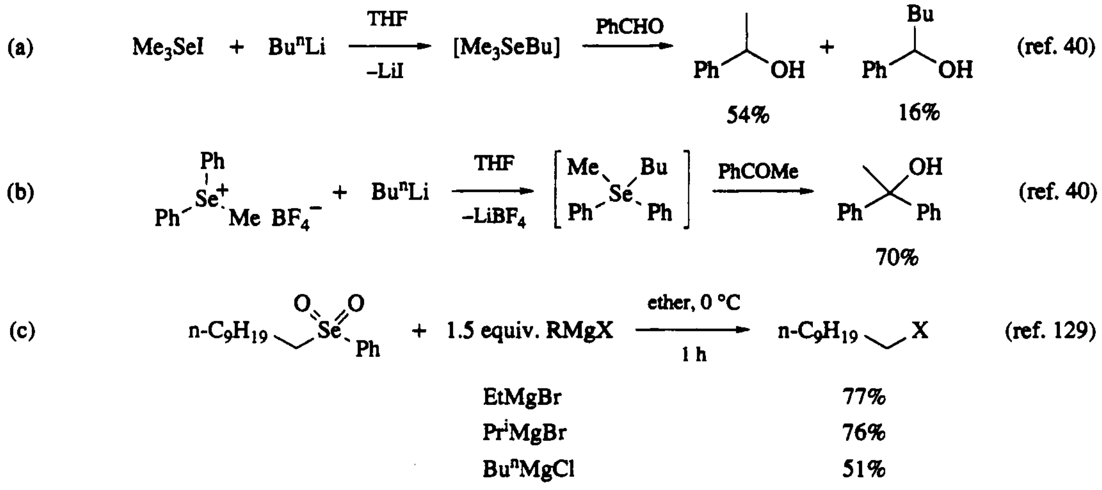
(a)
Me3SeI + BunLi
THF
-LiI
[Me3SeBu]
PhCHO
54%
16%
(ref. 40)
(b)
+ BunLi
THF
-LiBF4
PhCOMe
70%
(ref. 40)
(c)
+ 1.5 equiv. RMgX
ether, 0 °C
1 h
(ref. 129)
EtMgBr 77%
PriMgBr 76%
BunMgCl 51%

Scheme 50

### (i) *Metallation of selenoxides*

Due to the thermal instability and hygroscopicity of alkyl phenyl selenoxides their metallation is best achieved in the same pot in which they are prepared. Thus, differently substituted selenides have been oxidized[97,98] at low temperature (–78 °C) with ozone or a stoichiometric amount of *m*-chloroperoxybenzoic acid and the resulting mixture has been directly subjected[97,98] to the reaction of 2 equiv. of LDA, which neutralizes the benzoic acid present in the medium and at the same time achieves the desired metallation (Schemes 51–54). This reaction has been used for the synthesis of a large variety of organolithium reagents including those bearing two hydrogens, one alkyl or two alkyl groups on the carbanionic center,[97,98,127,128] as well as those bearing functionalized alkyl substituents there.[97,128]

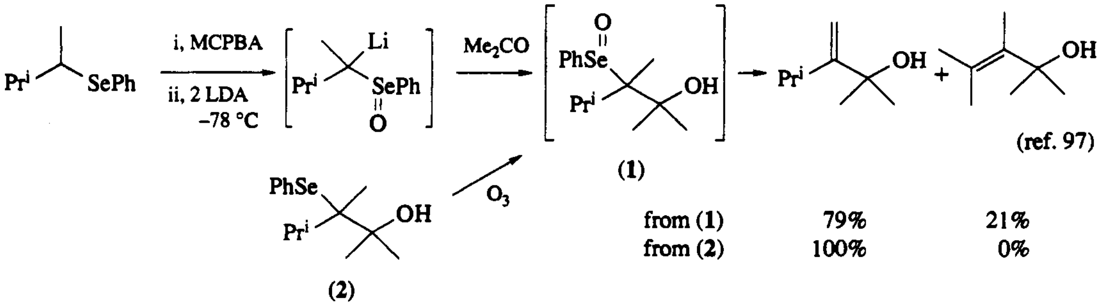
i, MCPBA
ii, 2 LDA
-78 °C
Me2CO
O3
(1)
(2)
(ref. 97)
from (1) 79% 21%
from (2) 100% 0%

Scheme 51

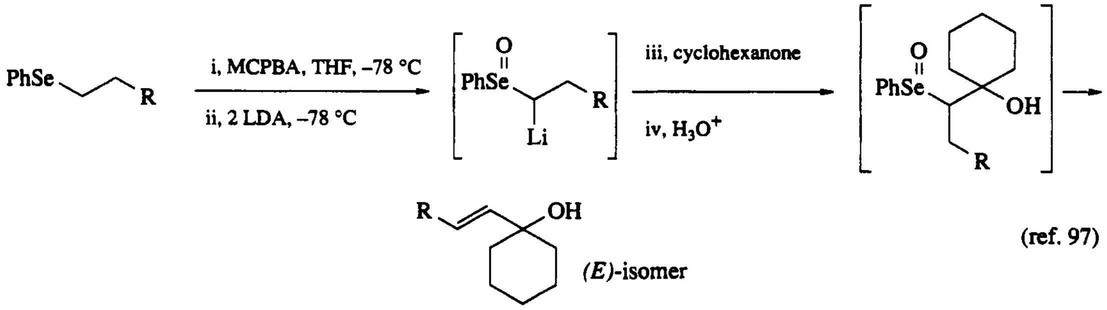
i, MCPBA, THF, -78 °C
ii, 2 LDA, -78 °C
iii, cyclohexanone
iv, H3O+
(*E*)-isomer
(ref. 97)

R = H (66%), R = Et (78%)

Scheme 52

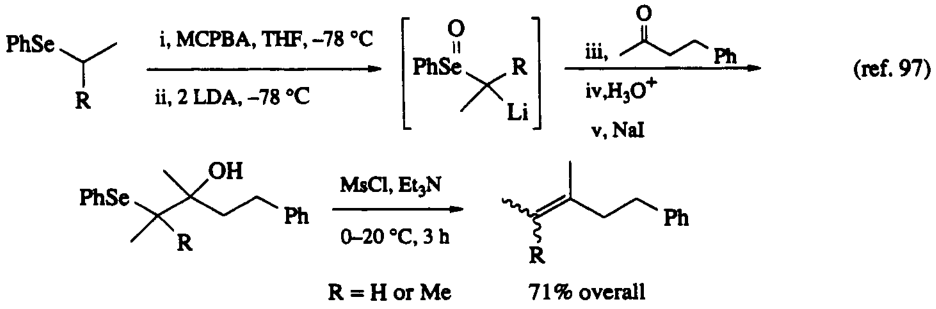

**Scheme 53**

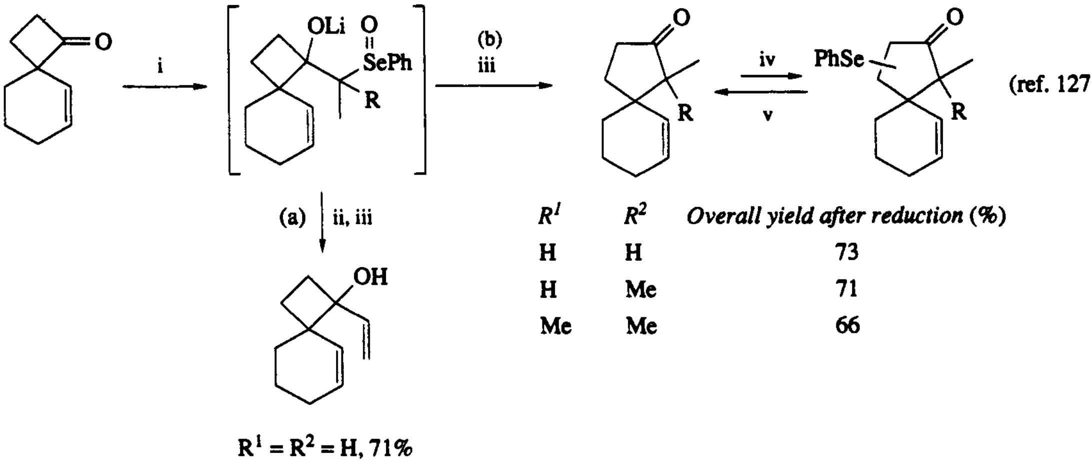

| *R¹* | *R²* | *Overall yield after reduction (%)* |
|---|---|---|
| H | H | 73 |
| H | Me | 71 |
| Me | Me | 66 |

i, PhSe(O)CR$^1$R$^2$Li, THF, –78 °C; ii, AcOH, THF; iii, 55 °C, 0.1 h, –PhSeOH; iv, PhSeOH; v, Al–Hg

**Scheme 54**

Further reaction of these species with carbonyl compounds and hydrolysis of the resulting alkoxide leads to β-oxidoalkyl selenoxides which have been transformed[97,127] into allyl alcohols on thermal decomposition (Schemes 51, 52 and 54, entry a; see Section 2.6.4.4) or reduced to β-hydroxyalkyl selenides[97] or to alkenes (Scheme 53).[97] β-Oxidoalkyl selenoxides derived from cyclobutanones react in a different way since they rearrange[127,128] to cyclopentanones upon heating (Scheme 54, b, Schemes 120 and 121 and Section 2.6.4.5.3).

### *(ii) Metallation of selenones*

Alkyl phenyl selenones can be metallated with LDA in THF but the reaction is slow and suffers from side reactions attributed to the substitution of the starting material with LDA or with the α-lithioalkyl selenones produced. KDA[131] and Bu$^t$OK[129–131,138] are much more efficient. The former base allows for the deprotonation of methyl,[131,138] *n*-alkyl[129] and cyclopropyl[130,131] phenyl selenones at low temperature (–78 °C), but α-potassioalkyl selenones have to be used immediately upon generation since they are particularly unstable. Otherwise, metallation of phenyl selenones is even more conveniently achieved with Bu$^t$OK in THF, and it even occurs in the presence of carbonyl compounds (Schemes 55 and 56)[129,130,138] or α,β-unsaturated esters (Schemes 57 and 58)[131] to provide epoxides and cyclopropyl esters, respectively, in reasonably good yields.

One of the major drawbacks of these reactions is clearly the unavailability of the whole set of alkyl phenyl selenones due to side reactions which occur during their preparations. Methyl, *n*-alkyl and some cyclopropyl phenyl selenones are available from the corresponding selenides and potassium permanganate,[130,139] peroxycarboxylic acids[130,139] or hydrogen peroxide/seleninic acids mixtures,[131] whereas *s*-alkyl phenyl selenones,[139] 2,2,3,3-tetramethylcyclopropyl selenone[130] and benzyl phenyl selenone[139] are not available in these ways.

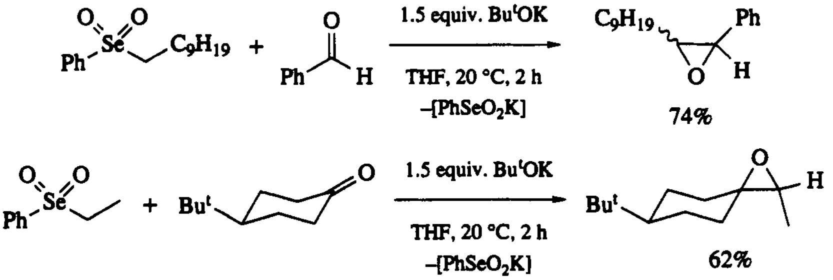
1.5 equiv. Bu$^t$OK
THF, 20 °C, 2 h
–[PhSeO$_2$K]
74%
1.5 equiv. Bu$^t$OK
THF, 20 °C, 2 h
–[PhSeO$_2$K]
62%

(ref. 129)

(ref. 138)

**Scheme 55**

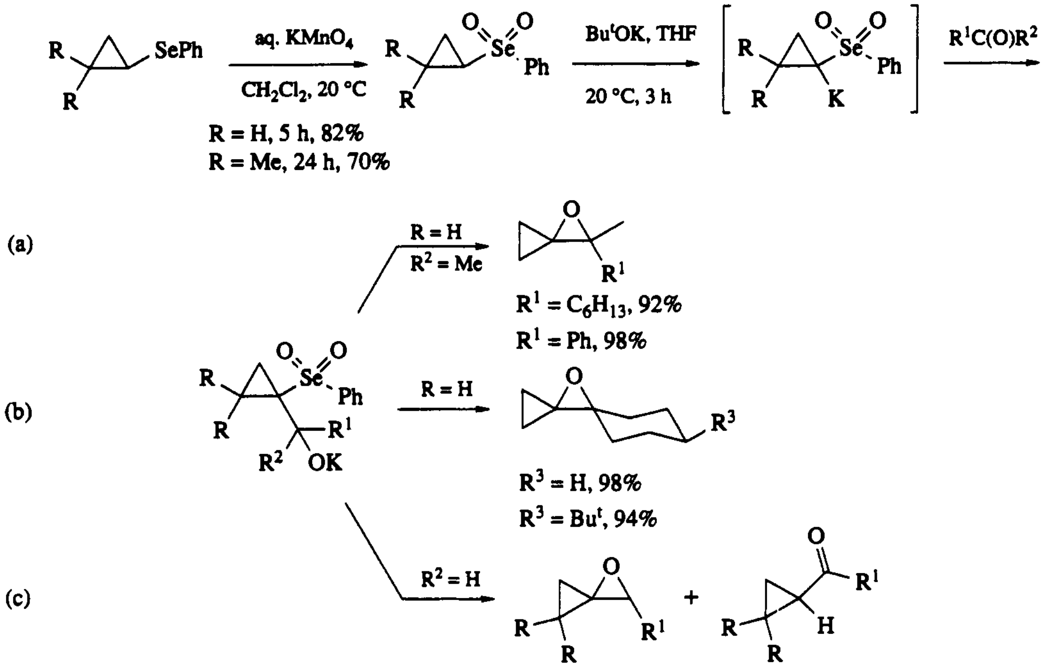
aq. KMnO$_4$
CH$_2$Cl$_2$, 20 °C
R = H, 5 h, 82%
R = Me, 24 h, 70%
Bu$^t$OK, THF
20 °C, 3 h
R$^1$C(O)R$^2$
(a)
R = H
R$^2$ = Me
R$^1$ = C$_6$H$_{13}$, 92%
R$^1$ = Ph, 98%
(b)
R = H
R$^3$ = H, 98%
R$^3$ = Bu$^t$, 94%
(c)
R$^2$ = H

| *R* | *R$^1$* | *Yield (%)* | *Ratio* | | |
|---|---|---|---|---|---|
| H | Ph | 70 | 50 | : | 50 |
| H | $C_6H_{13}$ | 74 | 75 | : | 25 |
| Me | Ph | 45 | 30 | : | 70 |

(ref. 130)

**Scheme 56**

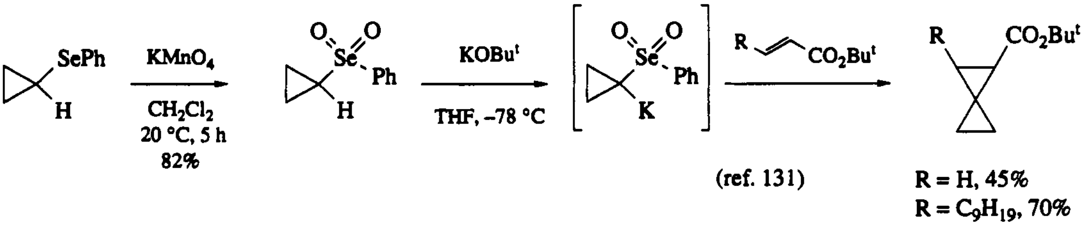
KMnO$_4$
CH$_2$Cl$_2$
20 °C, 5 h
82%
KOBu$^t$
THF, –78 °C
(ref. 131)
R = H, 45%
R = C$_9$H$_{19}$, 70%

**Scheme 57**

### *(iii) Metallation of selenonium salts*

Methyl- and ethyl-selenuranes, prepared from trimethyl-, methyldiphenyl- and ethyldiphenyl-selenonium salts, respectively, and Bu$^t$OK in DMSO, react with aromatic aldehydes and ketones, including those that are α,β-unsaturated, to produce the corresponding epoxides in good yields (Scheme 59).[132] Metal-

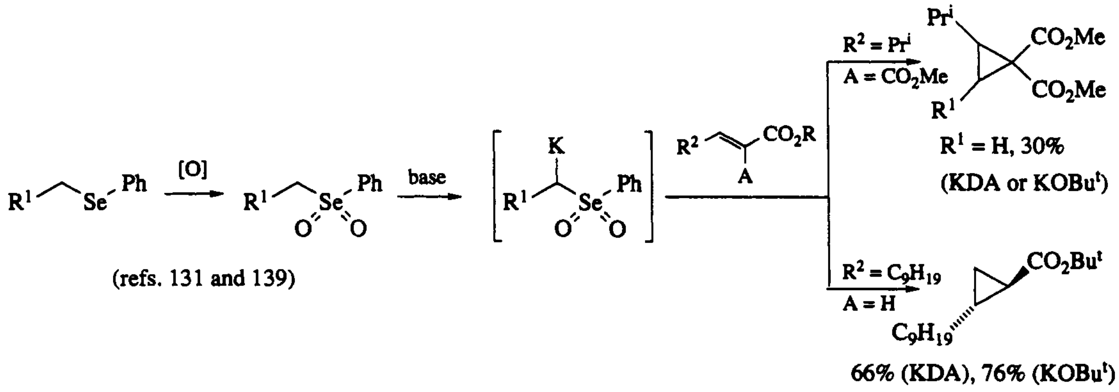
[O]
base
(refs. 131 and 139)
R² = Prⁱ
A = CO₂Me
R¹ = H, 30%
(KDA or KOBuᵗ)
R² = C₉H₁₉
A = H
66% (KDA), 76% (KOBuᵗ)

Scheme 58

lation of trimethylselenonium iodide has been performed at –30 °C using dichloromethyllithium in DME (Scheme 60), but further reaction with acetophenone leads to oxidomethylstyrene in low yield.

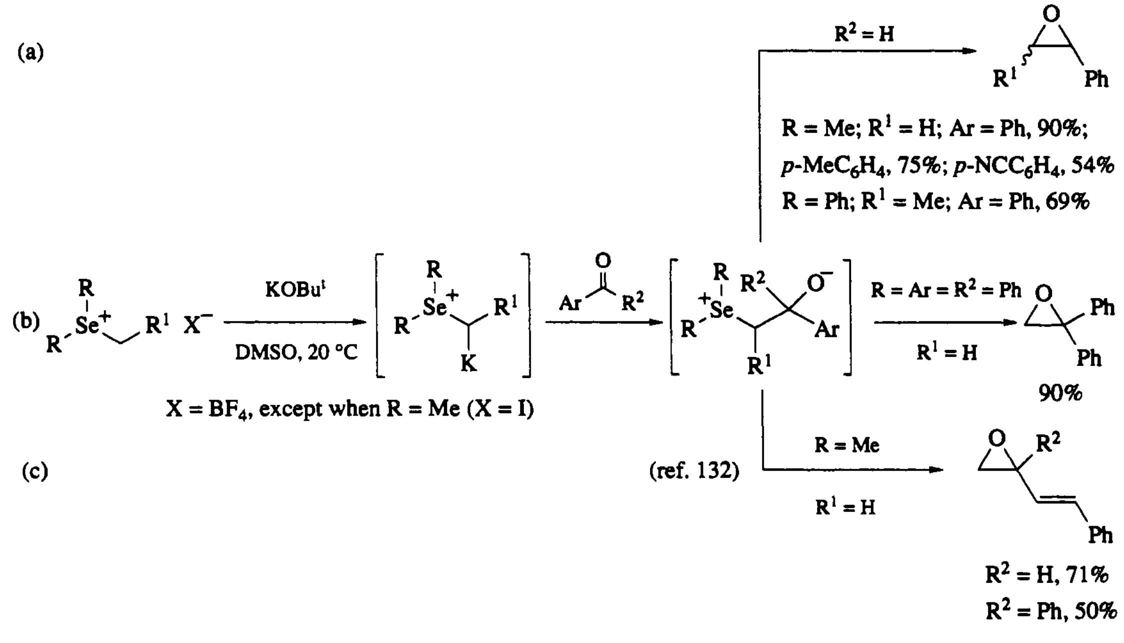
(a)
(b)
(c)
R² = H
R = Me; R¹ = H; Ar = Ph, 90%;
p-MeC₆H₄, 75%; p-NCC₆H₄, 54%
R = Ph; R¹ = Me; Ar = Ph, 69%
KOBuᵗ
DMSO, 20 °C
X = BF₄, except when R = Me (X = I)
R = Ar = R² = Ph
R¹ = H
90%
(ref. 132)
R = Me
R¹ = H
R² = H, 71%
R² = Ph, 50%

Scheme 59

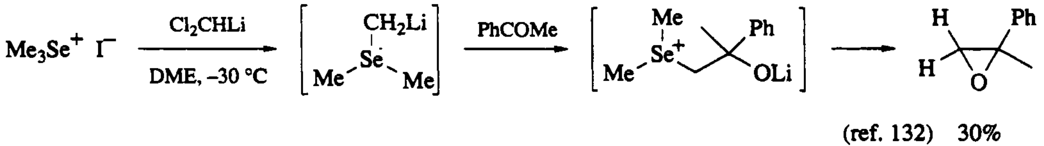
Cl₂CHLi
DME, –30 °C
PhCOMe
(ref. 132) 30%

Scheme 60

Interestingly, the same reaction performed on decyldimethylselenonium fluoroborate and benzaldehyde exclusively leads[77] to styrene oxide and decyl methyl selenide (Scheme 61, a). If benzaldehyde is omitted, 1-decene is formed[133] in very good yield (Scheme 61, b). The above mentioned observations, as well as the fact that decyldiphenylselenonium fluoroborate does not produce 1-decene when reacted with potassium *t*-butoxide, suggests that a *syn* elimination formally related to the selenoxide[140] *syn* elimination reaction is taking place on the decylmethylmethyleneselenurane intermediate. Although the selenoxide elimination reaction offers the advantage of taking place in a neutral medium, the ylide elimination reaction offers the advantage of permitting the synthesis of alkylidenecyclopropanes[133] in very high yields from the corresponding selenides (Scheme 62, a),[141] and the synthesis of allylidenecyclopropane from 1-vinylcyclopropyl methyl selenide (Scheme 62, b).[7,135] These are unavailable *via* the selenoxide elimination reaction on related derivatives.[141]

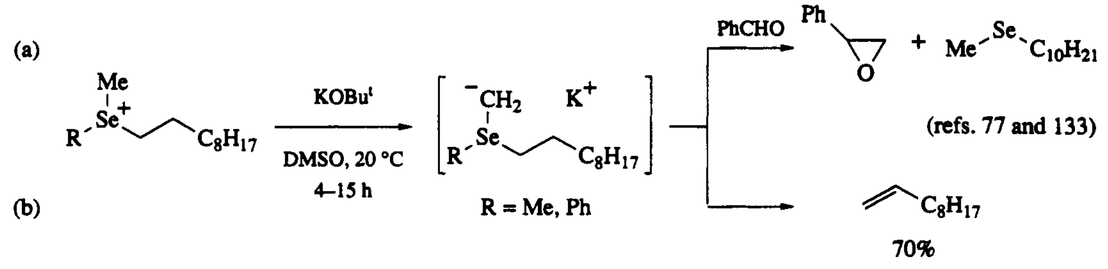
(a)
(b)
KOBu$^t$
DMSO, 20 °C
4–15 h
R = Me, Ph
PhCHO
(refs. 77 and 133)
70%

Scheme 61

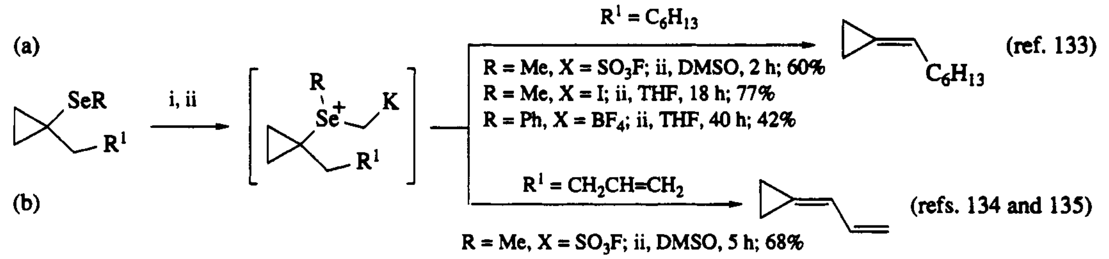
(a)
(b)
i, ii
$R^1 = C_6H_{13}$
R = Me, X = $SO_3F$; ii, DMSO, 2 h; 60%
R = Me, X = I; ii, THF, 18 h; 77%
R = Ph, X = $BF_4$; ii, THF, 40 h; 42%
(ref. 133)
$R^1 = CH_2CH{=}CH_2$
R = Me, X = $SO_3F$; ii, DMSO, 5 h; 68%
(refs. 134 and 135)

i, MeX, 20 °C; ii, KOBu$^t$, solvent, 20 °C

Scheme 62

The regiochemistry of this reaction is reminiscent of the related selenoxide elimination since it mainly leads to the less-substituted alkene (Scheme 63).[133] However, striking differences exist in the case of 1-octylcyclobutyl methyl selenide, where the reaction regioselectively produces octylidenecyclobutane *via* the ylide route (Scheme 64, a),[136] whereas a 1:1 mixture of octylidenecyclobutane and 1-octylcyclobutene is formed *via* the selenoxide route (Scheme 64, b).[136]

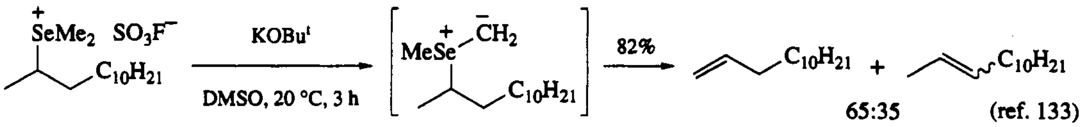
KOBu$^t$
DMSO, 20 °C, 3 h
82%
65:35
(ref. 133)

Scheme 63

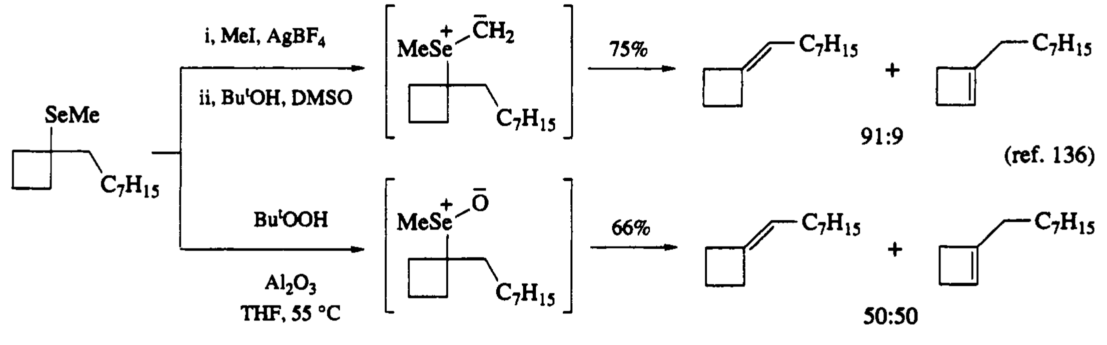
i, MeI, $AgBF_4$
ii, Bu$^t$OH, DMSO
75%
91:9
(ref. 136)
Bu$^t$OOH
$Al_2O_3$
THF, 55 °C
66%
50:50

Scheme 64

Allyldimethyl- and allylmethylphenyl-selenonium salts react under similar conditions with potassium *t*-butoxide (THF, 20 °C, 20 h) and lead to homoallyl selenides in very high yields, including the particularly strained alkylidenecyclopropane derivatives (Scheme 65, b).[141] These result from the metallation of the methyl group of the selenonium salts, leading to the corresponding ylides which then suffer a [2,3] sigmatropic rearrangement.

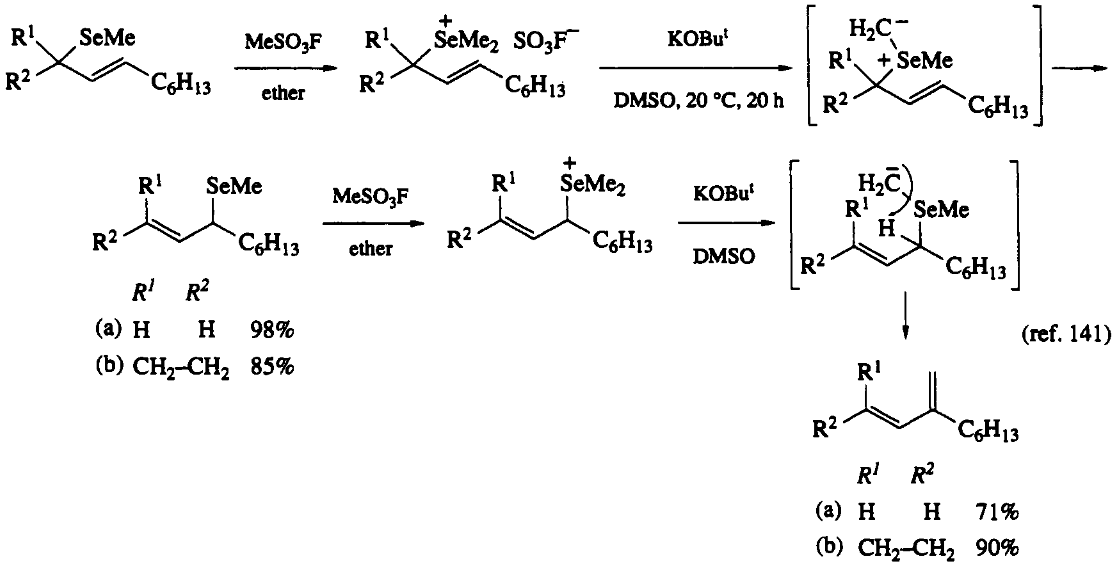
MeSO$_3$F
ether
KOBu$^t$
DMSO, 20 °C, 20 h
MeSO$_3$F
ether
KOBu$^t$
DMSO
R$^1$ R$^2$
(a) H H 98%
(b) CH$_2$–CH$_2$ 85%
(ref. 141)
R$^1$ R$^2$
(a) H H 71%
(b) CH$_2$–CH$_2$ 90%

Scheme 65

Homoallyl selenides are valuable precursors of dienes and allylidenecyclopropanes (Scheme 65).[141] The dienes have been produced using the same sequence of reactions outlined above (Schemes 63 and 64), which involves the alkylation of the homoallyl selenide followed by treatment of the resulting salt with Bu$^t$OK in DMSO (Scheme 65).

Treatment of benzylmethylphenylselenonium tetrafluoroborate with potassium *t*-butoxide gave[137] a 9:1 mixture of methyl phenyl and benzyl phenyl selenides but no products which would have resulted had the appropriate ylide been formed (Scheme 66, a). This demonstrated that at least this salt is extremely susceptible to nucleophilic attack, even by nucleophiles as hindered as the *t*-butoxide anion (Scheme 66, a).[137]

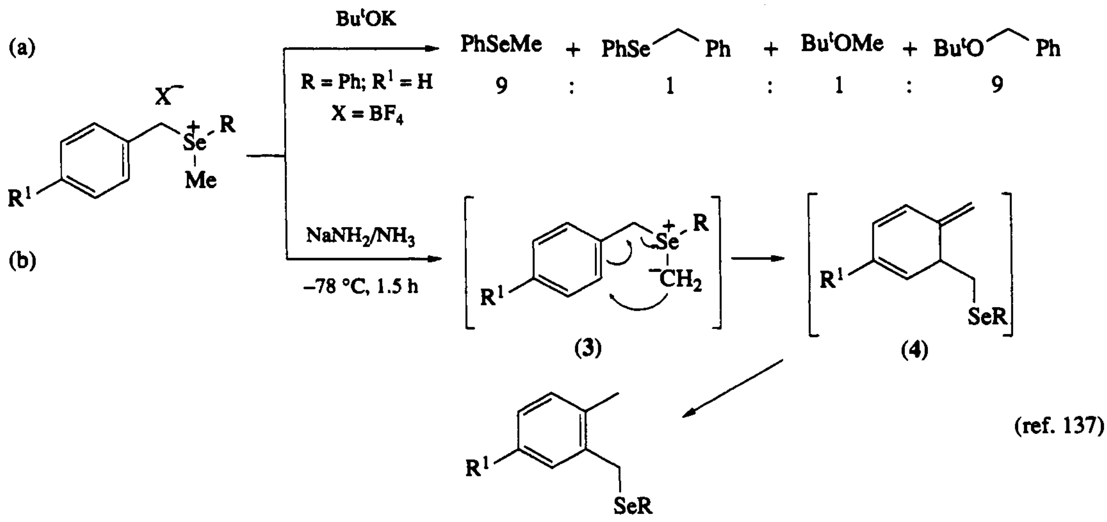
(a)
(b)
Bu$^t$OK
R = Ph; R$^1$ = H
X = BF$_4$
PhSeMe + PhSe⌒Ph + Bu$^t$OMe + Bu$^t$O⌒Ph
9 : 1 : 1 : 9
NaNH$_2$/NH$_3$
–78 °C, 1.5 h
(3)
(4)
(ref. 137)

R = Ph; X = BF$_4$; R$^1$ = H, 17%; Me, 38%; Cl, 37%
R = Me; X = SO$_3$F; R$^1$ = H, 43%; Cl, 50%

Scheme 66

Ylide formation has been accomplished, however, through the use of sodium amide in liquid ammonia.[137] This reaction has been extended to analogous salts (Scheme 66, b and Scheme 67). *o*-Methylbenzyl phenyl and methyl selenides are produced in modest to good yields, respectively, by metallation on the methyl group of the corresponding selenonium salts followed by spontaneous [2,3] sigmatropic rearrangement and rearomatization of the methylidenecyclohexadiene intermediate (**4**; Scheme 66).[137] Stilbenes, probably resulting from metallation at the benzylic site, are also produced in this reaction (Scheme 67, for example).[137]

Of special interest were the results obtained from the *m*-chlorobenzyldimethylselenonium fluoroborate since the chlorine appears to direct the attack of the ylide predominantly to the more-hindered position *ortho* to itself (Scheme 67).

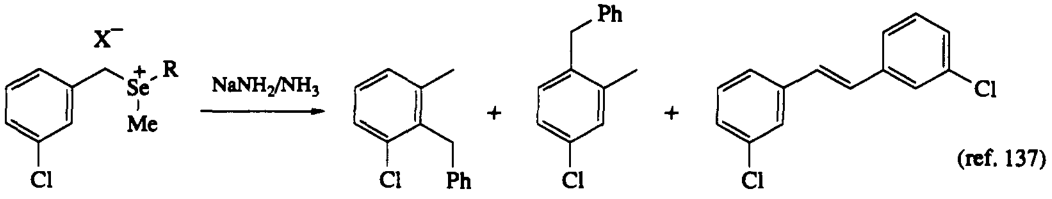

| | | | |
|---|---|---|---|
| R = Ph | 23% | - | 28% |
| R = Me | 56% | 14% | - |

**Scheme 67**

Phenacylmethyl(dimethyl)selenonium bromide is far more acidic than the selenonium salts presented above since deprotonation can be achieved with aqueous potassium hydroxide (Scheme 68).[142] The resulting ylide is stable at room temperature and decomposes to 1,2,3-triphenacylcyclopropane on irradiation or heating (Scheme 68, a).[142] It reacts with benzalacetophenone in a different manner from methylene(dimethyl)selenurane (Scheme 59, c)[132] and provides, rather than the oxirane, 1-phenyl-2,3-phenacylcyclopropane in very high yield (Scheme 68, b).[142]

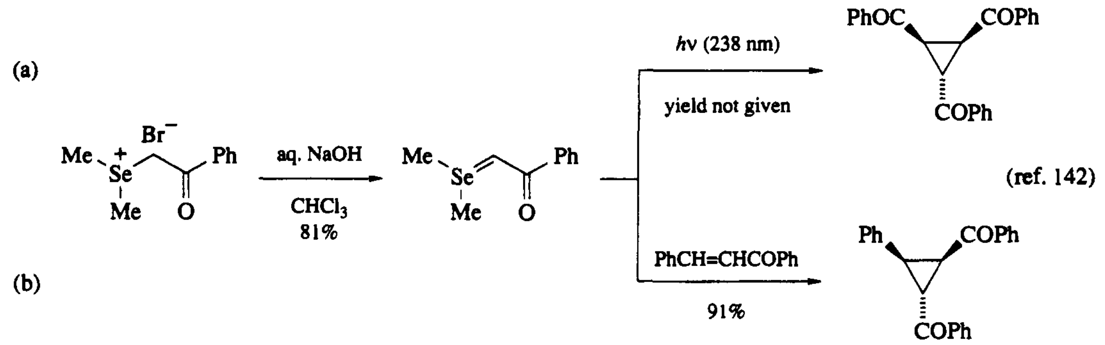

**Scheme 68**

### 2.6.2.3 Synthesis of Organometallics Bearing an α-Seleno Carbanion by Selenium–Metal Exchange

#### *2.6.2.3.1 Synthesis of α-selenoalkyllithiums by selenium–lithium exchange*

*(i) Generalities*

α-Selenoalkyllithiums with carbanionic centers bearing hydrogens or alkyl groups and which cannot be synthesized by metallation of selenides (see Section 2.6.2.2.1) have been conveniently prepared from selenoacetals and butyllithiums. This approach relies not only on the great availability of selenoacetals, which are accessible from a wide range of commercially available starting materials, but also on the efficiency of the Se–Li exchange. It finally allows wider structural variations on the α-selenoalkyllithium than those possible for related α-heterosubstituted organometallics[7] usually prepared by metallation.

Although the work has been routinely carried out with both phenyl and methyl selenoacetals with equal success, the compounds belonging to the last series are, in some specific cases, much more accessible and the resulting organometallic more reactive towards electrophiles in general and towards carbonyl compounds in particular.[7,9,12,16,17]

### *(ii) Synthesis of selenoacetals*

Selenoacetals are readily available compounds which have been prepared: (i) by selenoacetalization[53] of carbonyl compounds with selenols[36,40,49,55,143–145] in acidic media, with tris(seleno)boranes[53,144,146–148] in neutral or acidic media or with trimethylsilyl selenides and aluminum trichloride (Schemes 69 and 70);[53,144] (ii) by trans-selenoacetalization of *O,O*-acetals with selenols[77] or triselenoboranes (Scheme 71);[149] (iii) by substitution of dihaloalkanes with selenolates (Scheme 72);[36,55,56] (iv) by insertion of carbenes into diselenides (Scheme 73);[53,121,150–153] and (v) by addition of selenols to vinyl selenides (Scheme 74),[154] by selenenylation of α-selenoalkyl anions (Scheme 75)[155,156] and by alkylation of 1,1-bis(seleno)alkyl metals (Schemes 26, 76 and 77).[12,35,36,71,73,100,104]

The direct selenoacetalization of carbonyl compounds by selenols is by far the shortest and most convenient route to selenoacetals.[53] The reaction is usually carried out at 20 °C with zinc chloride (0.5 equiv. *versus* the carbonyl compound) and delivers rapidly (<3 h) and in reasonably good yields methyl and phenyl selenoacetals derived from aliphatic aldehydes and ketones and cyclic ketones (Scheme 69). Selenoacetalization is more difficult to achieve with hindered ketones, such as adamantanone and diisopropyl ketone, and with hindered aromatic carbonyl compounds.[53] In these cases the reaction is best achieved[53] with titanium tetrachloride instead of zinc chloride and is often limited to the methylseleno derivatives (Scheme 78). Tris(methylseleno)borane offers the advantage of not requiring an acid catalyst and is particularly useful for the selenoacetalization of acid labile aldehydes such as citronellal (Scheme 70, e).

Transacetalization in our opinion does not offer a definite advantage over the direct method except for those cases, such as that of cyclopropanone,[77] where the *O,O*-acetal is more accessible than the parent carbonyl compound (Scheme 71). The reaction, however, does not seem to be general (Scheme 71, b).

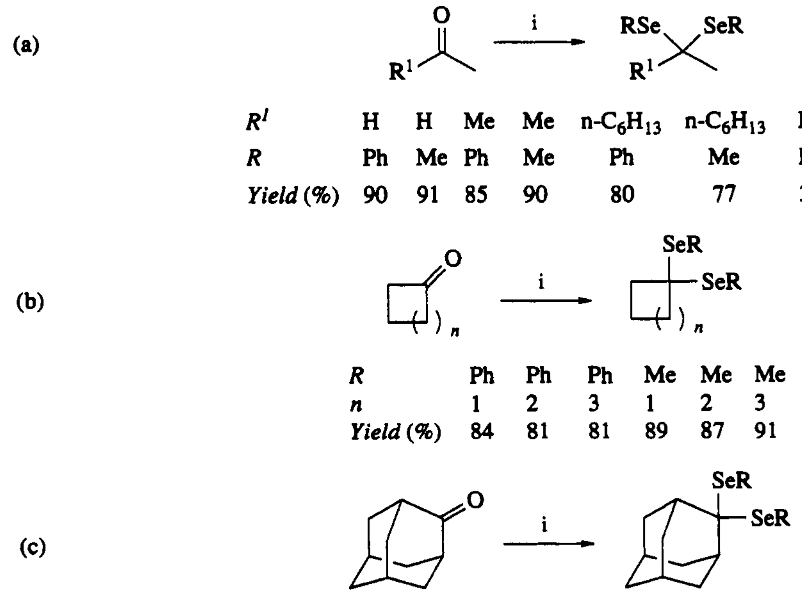

(a)

| *R¹* | H | H | Me | Me | n-$C_6H_{13}$ | n-$C_6H_{13}$ | Bu$^t$ | Bu$^t$ |
|---|---|---|---|---|---|---|---|---|
| *R* | Ph | Me | Ph | Me | Ph | Me | Ph | Me |
| *Yield* (%) | 90 | 91 | 85 | 90 | 80 | 77 | 32 | 81 |

(b)

| *R* | Ph | Ph | Ph | Me | Me | Me |
|---|---|---|---|---|---|---|
| *n* | 1 | 2 | 3 | 1 | 2 | 3 |
| *Yield* (%) | 84 | 81 | 81 | 89 | 87 | 91 |

(c)

R = Ph, 27%
R = Me, 88%

i, RSeH, $ZnCl_2$, 20 °C, 3 h (ref. 53)

Scheme 69

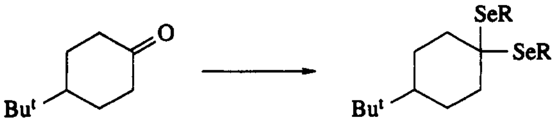
O
Bu$^t$
SeR
SeR
Bu$^t$

| | *Conditions* | *R* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| (a) | RSeH, $ZnCl_2$, 20 °C, 6 h | Ph | 70 | 53 |
| (a) | RSeH, $ZnCl_2$, 20 °C, 6 h | Me | 85 | 53 |
| (b) | $B(SeMe)_3$, $CHCl_3$, 20 °C, 31 h | Me | 84 | 53 |
| (c) | $Me_3SiSeR$, $AlCl_3$, 3 h | Ph | 82 | 53 |
| (c) | $Me_3SiSeR$, $AlCl_3$, 3 h | Me | 90 | 53 |

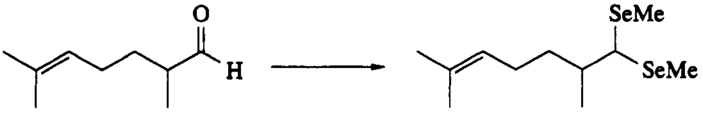
O
H
SeMe
SeMe

| | *Conditions* | *Yield* (%) | *Ref.* |
|---|---|---|---|
| (d) | MeSeH, $ZnCl_2$, 20 °C | 0 | 144 |
| (e) | $B(SeMe)_3$, $CHCl_3$, 20 °C, 5 h | 60 | 144 |
| (f) | $Me_3SiSeMe$, $AlCl_3$, $CHCl_3$, 20 °C | 8 | 144 |

**Scheme 70**

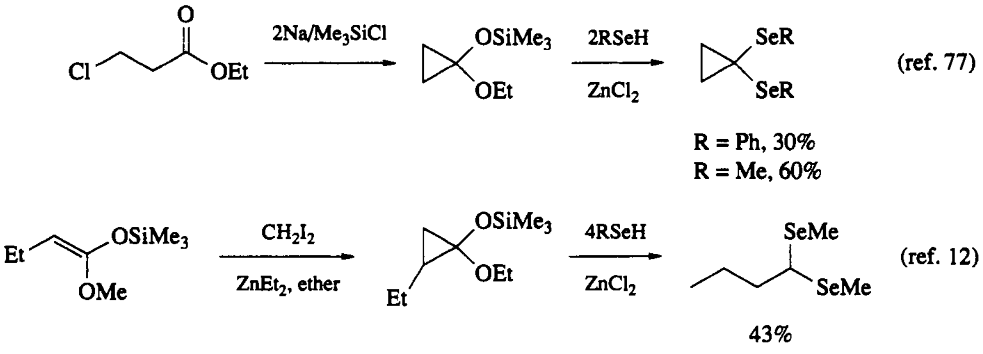
O
Cl
OEt
2Na/Me$_3$SiCl
OSiMe$_3$
OEt
2RSeH
ZnCl$_2$
SeR
SeR
(ref. 77)
R = Ph, 30%
R = Me, 60%
Et
OSiMe$_3$
OMe
CH$_2$I$_2$
ZnEt$_2$, ether
OSiMe$_3$
OEt
Et
4RSeH
ZnCl$_2$
SeMe
SeMe
(ref. 12)
43%

**Scheme 71**

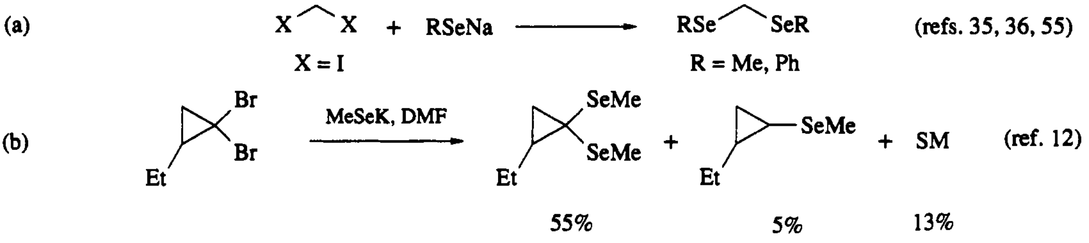
(a)
X
X
+ RSeNa
X = I
RSe
SeR
R = Me, Ph
(refs. 35, 36, 55)
(b)
Br
Br
Et
MeSeK, DMF
SeMe
SeMe
Et
+
SeMe
Et
+ SM
(ref. 12)
55%
5%
13%

**Scheme 72**

The reaction of 1-metallo-1,1-bis(seleno)alkanes with electrophiles is another interesting approach to selenoacetals (Schemes 76 and 77),[36,71,73] which *inter alia* allows the synthesis of 1,1-bis(seleno)cyclopropanes (Scheme 26, a, b and d; Scheme 77, c) and also permits the synthesis of functionalized selenoacetals by concomitant C—C bond formation (Scheme 79).[157] Other methods listed above are of limited use. The substitution of dihaloalkanes by selenolates is the method of choice for the synthesis of bis(seleno)methanes (Scheme 72, a),[36,55,56] and can be applied to the synthesis of the relatively unhindered selenoacetal of cyclopropanone (Scheme 72, b).

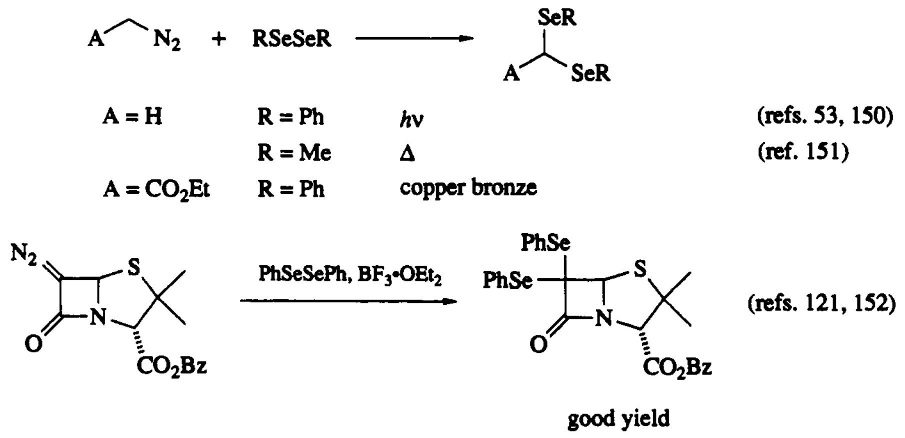

| A | R | | |
|---|---|---|---|
| A = H | R = Ph | *hν* | (refs. 53, 150) |
| | R = Me | Δ | (ref. 151) |
| A = $CO_2Et$ | R = Ph | copper bronze | |

PhSeSePh, $BF_3•OEt_2$
$CO_2Bz$
(refs. 121, 152)
good yield

**Scheme 73**

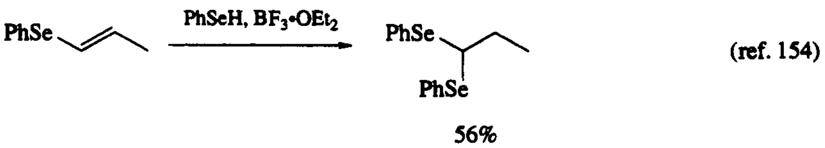

PhSeH, $BF_3•OEt_2$
(ref. 154)
56%

**Scheme 74**

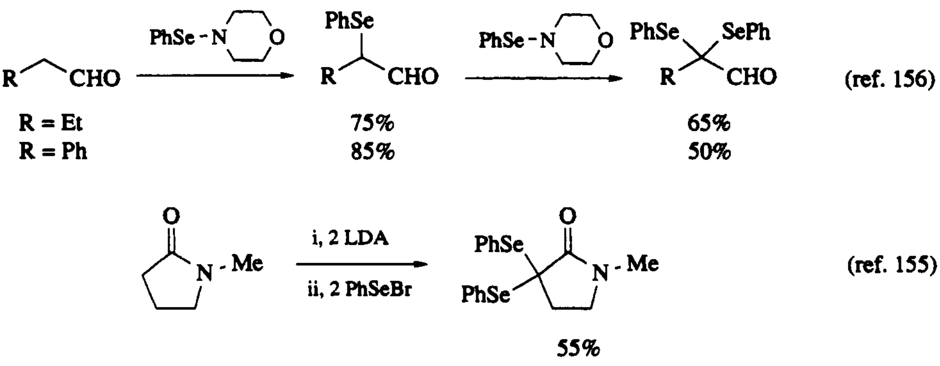

(ref. 156)
i, 2 LDA
ii, 2 PhSeBr
(ref. 155)
55%

| | | |
|---|---|---|
| R = Et | 75% | 65% |
| R = Ph | 85% | 50% |

**Scheme 75**

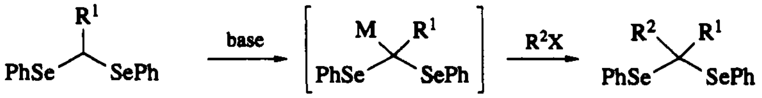

| $R^1$ | *Conditions* | $R^2X$ | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| H | $LiNBu_2$, THF, –78 °C | MeI | 91 | 35, 36 |
| $C_6H_{13}$ | LiTMP, THF–HMPA, –30 °C | $C_6H_{13}Br$ | 86 | 71 |
| $C_{10}H_{21}$ | KDA, THF, –78 °C | $PhCH_2Br$ | 98 | 73 |

**Scheme 76**

### *(iii) Synthesis of α-selenoalkyl metals by selenium–metal exchange*

Phenyl and methyl selenoacetals usually react with butyllithiums and produce the corresponding α-selenoalkyllithiums and butyl selenides.[4,7,9,12,13,16,17,35,36,48–50,54,55,60,158] The reaction is usually carried out at –78 °C (a temperature at which these organometallics are stable for a long period), with *n*-butyllithium in THF or *s*-butyllithium in ether. It provides a large variety of α-selenoalkyllithiums including

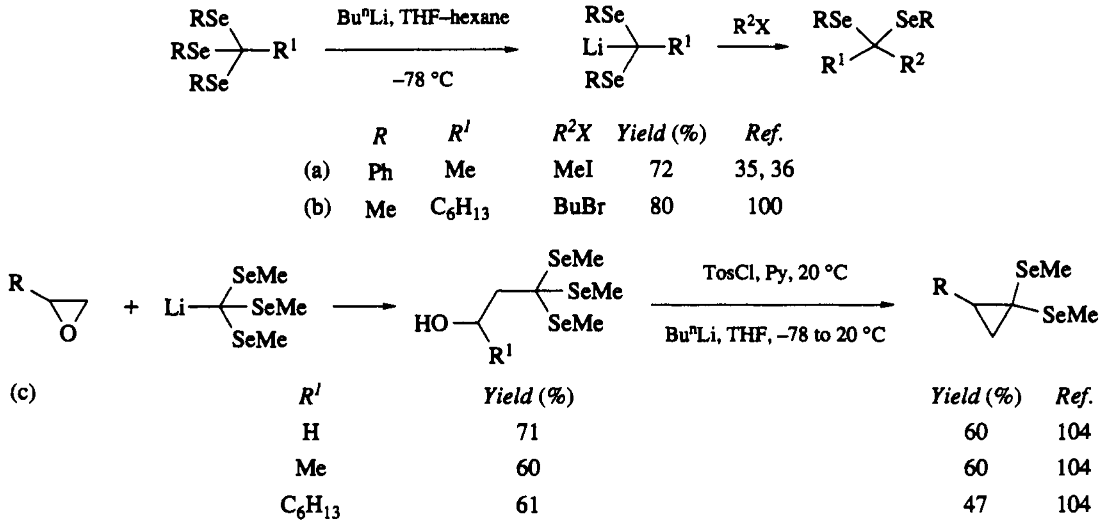

| | R | R¹ | R²X | Yield (%) | Ref. |
|---|---|---|---|---|---|
| (a) | Ph | Me | MeI | 72 | 35, 36 |
| (b) | Me | $C_6H_{13}$ | BuBr | 80 | 100 |

(c)

| R¹ | Yield (%) | Yield (%) | Ref. |
|---|---|---|---|
| H | 71 | 60 | 104 |
| Me | 60 | 60 | 104 |
| $C_6H_{13}$ | 61 | 47 | 104 |

**Scheme 77**

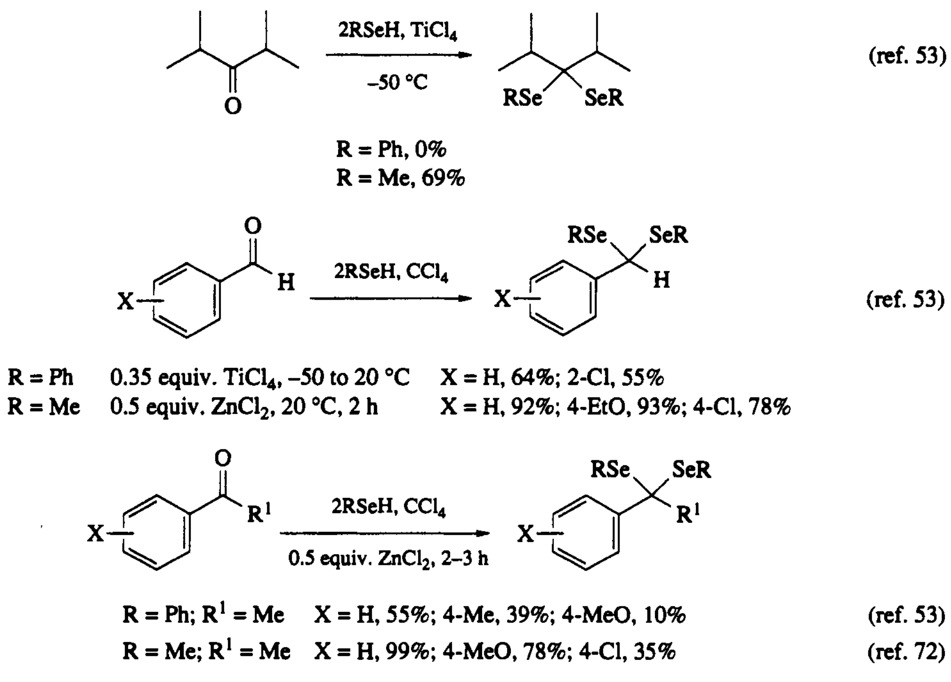

(ref. 53)

R = Ph, 0%
R = Me, 69%

(ref. 53)

R = Ph 0.35 equiv. $TiCl_4$, −50 to 20 °C X = H, 64%; 2-Cl, 55%
R = Me 0.5 equiv. $ZnCl_2$, 20 °C, 2 h X = H, 92%; 4-EtO, 93%; 4-Cl, 78%

R = Ph; R¹ = Me X = H, 55%; 4-Me, 39%; 4-MeO, 10% (ref. 53)
R = Me; R¹ = Me X = H, 99%; 4-MeO, 78%; 4-Cl, 35% (ref. 72)

**Scheme 78**

those where the carbanionic center is unsubstituted,[35,36,54,55,160] monoalkyl[40,48–50,54,55] or dialkyl substituted,[40,48–50,54,55,104,135,136,159–163] or that bear an aryl[54,164] or a heteroaryl[158] moiety (Scheme 80).[54]

In general, the Se–Li exchange is easier: (i) when carried out in THF rather than in ether; (ii) when *s*- or *t*-butyllithium is used instead of *n*-butyllithium. Methyllithium is almost unreactive in most cases; and (iii) if a better stabilization of the carbanionic center can be achieved. Thus phenyl selenoacetals react more rapidly than their methyl analogs (see Section 2.6.2.1.2), and α-selenoalkyllithiums where the carbanionic center is part of a three-membered cycle or is substituted by an aryl group are more readily obtained than those which are monoalkyl or dialkyl substituted.

The presence of bulky groups around the reactive site does not have a marked effect[54] on the reactivity of selenoacetals derived from aldehydes but it dramatically lowers[54] the reaction rates of those derived from ketones such as adamantanone or diisopropyl ketone. In these cases, the reaction rate is greatly enhanced when *s*- or *t*-butyllithium is used in place of *n*-butyllithium.[54]

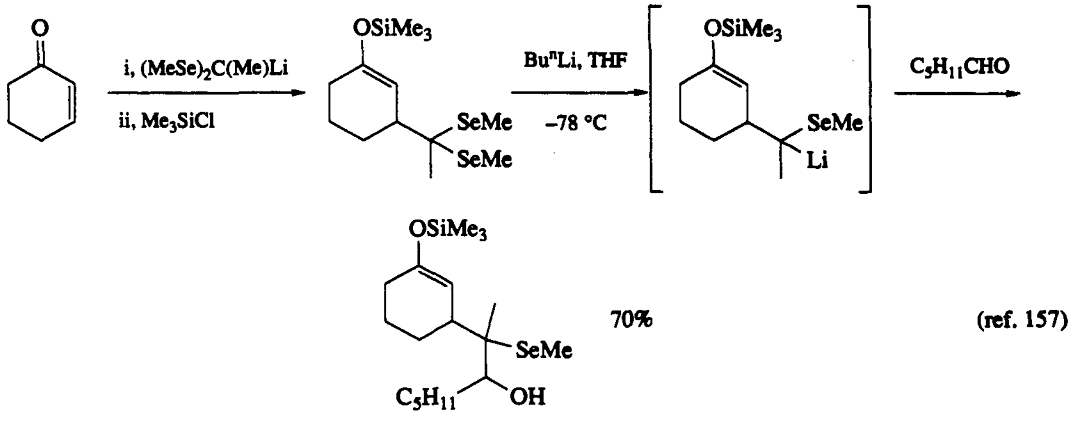
O
i, (MeSe)2C(Me)Li
ii, Me3SiCl
OSiMe3
SeMe
SeMe
BunLi, THF
–78 °C
OSiMe3
SeMe
Li
C5H11CHO
OSiMe3
SeMe
C5H11
OH
70%
(ref. 157)

**Scheme 79**

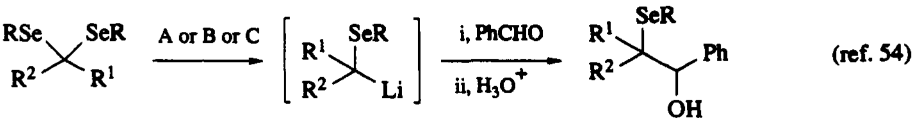
RSe
SeR
R2
R1
A or B or C
R1
SeR
R2
Li
i, PhCHO
ii, H3O+
R1
SeR
R2
Ph
OH
(ref. 54)

| *Intermediate* | *R* | *Yield (%)* | *Method* | *Intermediate* | *R* | *Yield (%)* | *Method* |
|---|---|---|---|---|---|---|---|
| $RSeCH_2Li$ | Me | 80 | A | $RSeC(Me)(n\text{-}C_6H_{13})Li$ | Me | 90 | A, 2 h |
| | Me | 82 | B | | Ph | 78 | A |
| | Ph | 82 | A | $RSeC(Me)(Bu^t)Li$ | Me | 32 | A |
| $RSeCH(Me)Li$ | Me | 80 | A | | Me | 77 | A, 2 h |
| | Ph | 70 | A | | Ph | 59 | A |
| $RSeCH(n\text{-}C_6H_{13})Li$ | Me | 84 | A | $RSeC(n\text{-}C_6H_{13})_2Li$ | Me | 17 | A |
| | Me | 82 | B | | Me | 93 | A, 4 h |
| | Ph | 89 | A | | Ph | 47 | A |
| | Ph | 74 | B | 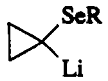 | Me | 91 | A |
| $RSeCH(Bu^t)Li$ | Me | 82 | A | | Me | 68 | B |
| | Ph | 92 | A | | Ph | 80 | A |
| $RSeCMe_2Li$ | Me | 75 | A | 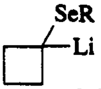 | Me | 87 | A |
| | Me | 80 | B | | Ph | 90 | A |
| | Ph | 94 | A | 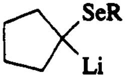 | Me | 82 | A |
| | Ph | 83 | B | | Ph | 91 | A |
| $RSeCPr^i_2Li$ | Me | 77 | A, 2 h | 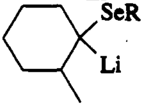 | Me | 25 | A |
| 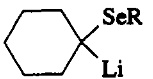 | Me | 87 | A, 2 h | | Me | 78 | B |
| | Ph | 88 | A | | Me | 87 | C |
| 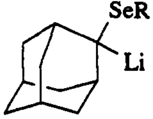 | Me | 0 | A | | Ph | 55 | A, 4 h |
| | Me | 81 | C | | Ph | 79 | B |

A = $Bu^nLi$, THF–hexane, –78 °C, 0.9 h; B = $Bu^sLi$, ether–hexane, –78 °C, 0.5 h; C = $Bu^sLi$, THF–hexane, –78 °C, 0.5 h

**Scheme 80**

Metallation is never a competing reaction even for those selenoacetals derived from aromatic aldehydes (Scheme 81).[54] Only in the case of phenyl selenoacetals derived from formaldehyde and acetaldehyde are the corresponding 1-metallo-1,1-bis(seleno)alkanes produced (Scheme 82).[54] In fact these compounds arise from the metallation of the selenoacetals not by the butyllithium but by the α-selenoalkyllithium just produced.[54] This side reaction, which does not occur with methylseleno analogs and with higher homologs in the phenylseleno series, can be prevented by slow reverse addition of the reactants (Scheme 82).[54]

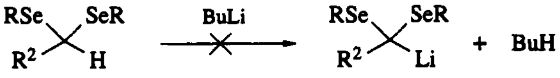
RSe
SeR
R2
H
BuLi
RSe
SeR
R2
Li
+ BuH

(ref. 54)

Scheme 81

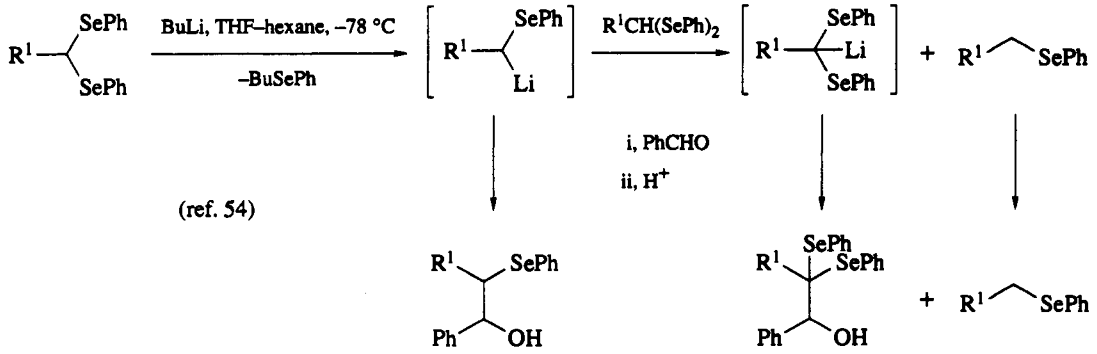
SePh
R1
SePh
BuLi, THF–hexane, –78 °C
–BuSePh
SePh
R1
Li
R1CH(SePh)2
SePh
R1
Li
SePh
+ R1
SePh
i, PhCHO
ii, H+
(ref. 54)
R1
SePh
Ph
OH
SePh
R1
SePh
Ph
OH
+ R1
SePh

| | *Reaction* | *R¹* | *Yield (%)* | | |
|---|---|---|---|---|---|
| (a) | 'Normal addition' | H | 61 | 23 | 16 |
| (b) | 'Normal addition' | Me | 70 | 8 | 8 |
| (c) | 'Reverse addition' | H | 82 | 6 | 5 |

Scheme 82

Except for the case shown in Scheme 83,[165,166] α-selenoalkyllithiums are stable intermediates at or below –78 °C.[7,16,54] They do not have a high tendency to decompose to carbenes (Scheme 84, a), nor are the phenyl selenoacetals transformed to their ring-metallated isomers (Scheme 84, b) or to the more stable α-alkylselenomethyllithiums (methylseleno derivatives) (Scheme 84, c).[54] Interestingly, they are not alkylated by the concomitantly produced butyl selenide (Scheme 85, a).[54]

Reaction of *n*-butyllithium with 1,1-bis(seleno)-4-*t*-butylcyclohexane,[54,167a–c] 1,1-bis(methylseleno)-2-methylcyclohexane[54] or 1,1-bis(phenylseleno)-3-silyloxybutane[167d] leads to, in each case, one of the stereoisomers of the α-selenoalkyllithium, as observed by $^{77}$Se NMR and trapping experiments (Scheme 86). In the former case, the reaction exclusively produces the axially oriented lithio derivative and in the latter case it leads almost exclusively to the stereoisomer shown in Scheme 86. It has been secured in the case of 1,1-bis(seleno)-4-*t*-butylcyclohexanes, that the C—Se bond cleavage is operating stereoselectively on the axial seleno group.

Only a few functionalized α-selenoalkyllithiums have been synthesized apart from the ones shown in Schemes 11,[60] 79[157] and 86.[167]

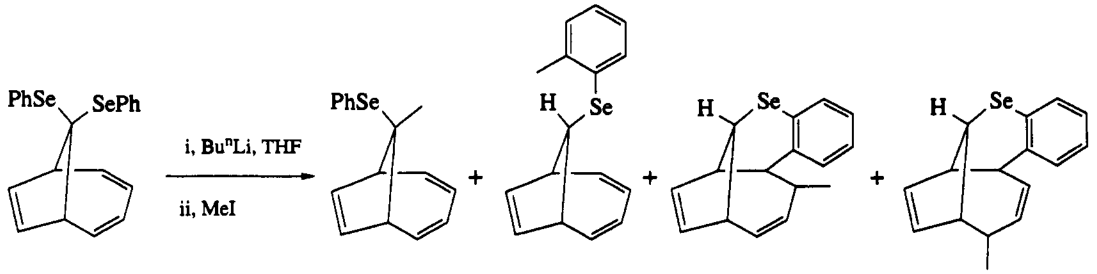
PhSe
SePh
i, BunLi, THF
ii, MeI
PhSe
+
H
Se
+
H
Se
+
H
Se

| | *Conditions* | *Yield (%)* | | | *Ratio* | | | |
|---|---|---|---|---|---|---|---|---|
| (a) | –78 °C, 0.1 h | 96 | 15 | : | 85 | – | | – |
| (b) | 20 °C, 1 h | 84 | – | | – | 73 | : | 27 |

(ref. 165)

Scheme 83

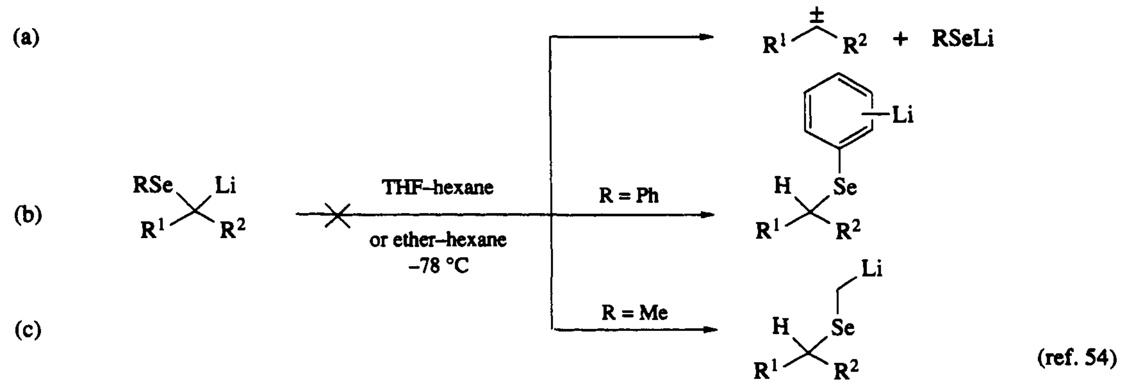

Scheme 84

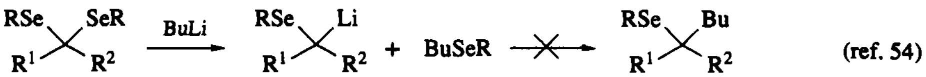

$R^1, R^2$ = H, alkyl, allyl, aryl

Scheme 85

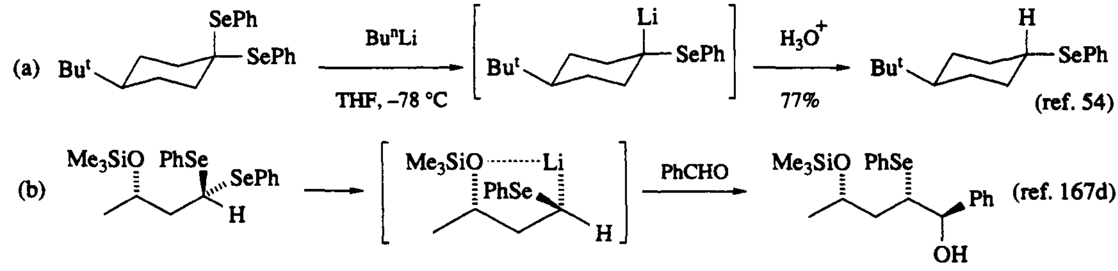

Scheme 86

It has been shown that the methyl selenoacetal resulting from the reaction of 1-lithio-1,1-bis(methylseleno)methane with 5-methyl-2-cyclohexen-1-one and trimethylsilyl chloride is efficiently cleaved by *s*-butyllithium in THF to afford[157] the corresponding α-selenoalkyllithium in very high yield (Scheme 79). Chemoselective cleavage of a selenoacetal derived from an aldehyde has been achieved[60] in the presence of a selenoacetal derived from a ketone (Scheme 11). The best results have been observed[60] in the phenylseleno series when the reaction is carried out at −42 °C in ether–hexane. Under these conditions the difference of reactivity between the two selenoacetals is so high that almost complete discrimination can be achieved (Scheme 87).[60]

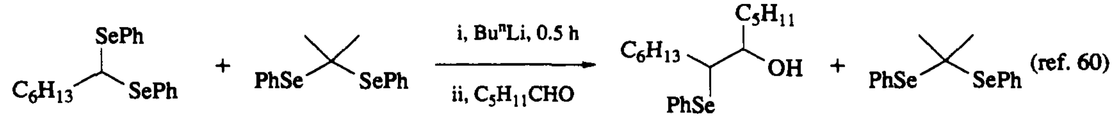

| *Conditions* | *Yield (%)* | |
|---|---|---|
| Ether, −42 °C | 82 | 94 |
| THF, −78 °C | 70 | 75 |

Scheme 87

The same selectivity cannot be achieved under similar conditions in the methylseleno series due to the inertness of these selenoacetals. Performing the reaction with *s*-butyllithium in THF–hexane (at −110 °C to −78 °C) leads[60] to rather poor selectivity (Scheme 88). A somewhat better chemoselection is achieved if the reaction is performed in THF–hexane at −78 °C and then the medium warmed to −40 °C prior to the addition of the electrophile (Scheme 88).[60] We believe that under these conditions a thermodynamic control is operative. Application of these observations has allowed the selective synthesis of 1,7-dienes from 1,1,6,6-tetrakis(phenylseleno)heptane (Scheme 11).[60]

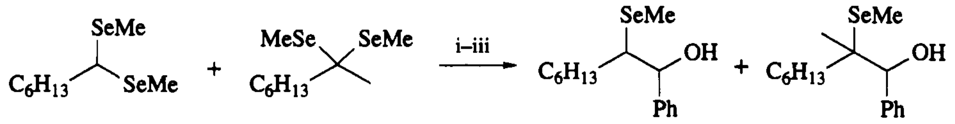

(ref. 60)

| | *Conditions* | *Yield (%)* | *Yield (%)* | *Chemoselectivity (%)* |
|---|---|---|---|---|
| (a) | $Bu^sLi$, ether/hexane, –78 °C, 0.5 h | 55 | 25 | 73 |
| (b) | $Bu^nLi$, THF/hexane, –100 °C, 0.5 h | 15 | 5 | 75 |
| (c) | $Bu^nLi$, THF/hexane, –78 °C, 0.05 h | 37 | 11 | 77 |
| (d) | $Bu^nLi$, THF/hexane, –78 °C, 1 h | 63 | 23 | 74 |
| (e) | $Bu^nLi$, THF/hexane, –78 °C, 0.1 h, then –40 °C, 1 h | 78 | 8 | 90 |

i, RLi; ii, PhCHO; iii, $H_3O^+$

**Scheme 88**

As already mentioned, α-selenoalkyllithiums are stable for several hours at –78 °C. However, they start to decompose when the temperature is raised to around –50 °C or –40 °C. The exact temperature at which this process begins, the rate of decomposition and the nature of the products formed clearly depends upon the structure of the selenoacetal. Those bearing two alkyl groups on the carbanionic center often decompose below –40 °C. The resulting products are not always identical and in most cases their structures have not been identified. A more detailed work has been carried out on 1-seleno-1-heptyllithiums. In the methylseleno series, whatever the solvent used, only a trace amount of the expected 1-methylseleno-1-heptyllithium is present after standing for 3.5 h at 0 °C; 1-methylselenoheptane, which probably results from the protonation of the organometallic by the solvent, and 1-methylseleno-1-heptene, resulting from a hydride elimination, are produced instead (Scheme 89).[54]

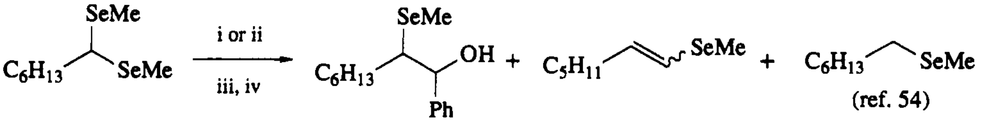

(ref. 54)

| | *Conditions* | | *Yield (%)* | |
|---|---|---|---|---|
| (a) | i | 25 | 27 | small amount |
| (b) | ii | trace | 36 | 35 |

i, $Bu^nLi$, THF–hexane, –78 °C, 0.2 h, then –78 to 0 °C, then 0 °C, 1 h; ii, $Bu^nLi$, THF–hexane, –78 °C, 0.2 h, then –78 to 0 °C, then 0 °C, 3.5 h; iii, PhCHO; iv, $H_3O^+$

**Scheme 89**

The decomposition takes another course with 1-phenylseleno-1-heptyllithium (Scheme 90).[54] In ether and THF the reagent is still present (±20%) after 3.5 h at 0 °C, along with heptylselenophenyllithiums resulting from the isomerization of the original organometallic to the more stable aryllithiums (Scheme 90). Heptyl phenyl selenide (15%) arising from the protonation of the organometallic by the solvent and substantial amounts of phenyllithium (trapped as diphenyl carbinol, ±21%) from unknown origin are also found as by-products when the reaction is carried out in THF–hexane or in ether–hexane, respectively.

The same type of exchange occurs,[165,166] but unexpectedly more rapidly and at –78 °C, with the α-selenoalkyllithium shown in Scheme 83. At higher temperature (20 °C)[165,166] the addition of the β-selenoaryllithium across the carbon–carbon double bond present in the molecule also occurs (Scheme 83, b).

α-Selenoalkyllithiums usually do not have a high tendency to add across carbon–carbon double bonds even intramolecularly. However, it has been found that 1-phenyl-2-methylseleno-2-oct-5-enyllithium cyclizes at 0 °C and leads to the benzylidenecyclopentane shown in Scheme 91.[168] The mechanism of this reaction is being investigated.[168]

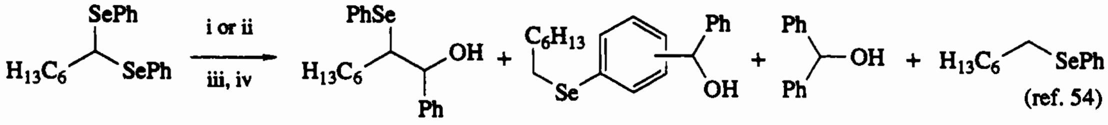

| | *Conditions* | *Yield* (%) | | | |
|---|---|---|---|---|---|
| (a) | i | 25 | 11 | trace | 15 |
| (b) | ii | 21 | 25 | 21 | 0 |

i, Bu$^n$Li, THF–hexane, –78 °C, 0.2 h, then –78 to 0 °C, then 0 °C, 3.5 h; ii, Bu$^n$Li, ether–hexane, –78 °C, 0.2 h, then –78 to 0 °C, then 0 °C, 3.5 h; iii, PhCHO; iv, $H_3O^+$

**Scheme 90**

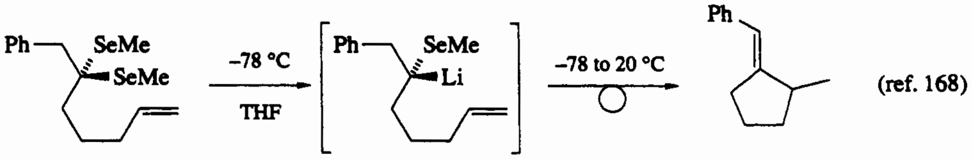

**Scheme 91**

α-Selenobenzyllithiums are much more prone to add to alkenes.[169,170] Although they are stable around –78 °C (Scheme 92, a), the addition reaction usually takes place around 0 °C and produces [3.1.0]bicyclohexanes and [4.1.0]bicycloheptanes in reasonably good yields when a carbon–carbon double bond is present in a suitable position with respect to the organometallic group (Scheme 92, b).[169,170]

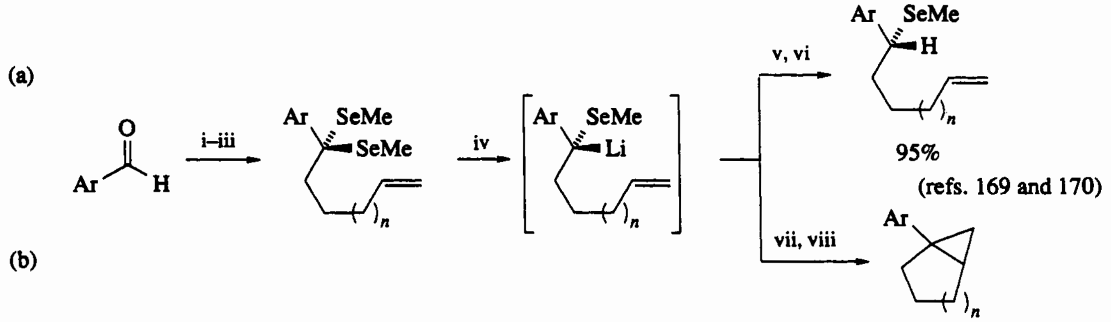

Ar = Ph; *n* = 1, 80%; *n* = 2, 80%
Ar = 4-MeOC$_6$H$_4$; *n* = 1, 45%

i, MeSeH (2 equiv.), $ZnCl_2$; ii, KDA, THF, –78 °C; iii, $H_2C{=}CH(CH_2)_3Br$, iv, Bu$^n$Li, THF, –78 °C; vi, –78 °C, 0.5 h; vii, –78 °C, 0.5 h; viii, 0 °C, 1 h

**Scheme 92**

Addition also occurs[169,170] with ethylene and with activated alkenes, such as styrene, butadiene, trimethylsilylethylene and phenylthioethylene, and provides in all cases the corresponding cyclopropanes in good yield (Scheme 93).[200,201] Interestingly, the α-selenoalkyllithiums do not react with the C—C bond at lower temperatures so that the anion is still available for reaction with alkyl halides or carbonyl compounds (Scheme 92, compare a with b).

The synthesis of α-selenoalkyl metals reported above is not limited to those compounds which possess alkyl or aryl groups on an *sp*$^3$ carbanionic center. For example, α-selenoalkyllithiums bearing a vinyl (Scheme 94),[87] furfuryl (Scheme 95),[158] silyl (Scheme 96),[100,171] methoxy (Scheme 97)[56] or seleno moiety (Schemes 77 and 98)[35,36,71] have been obtained in almost quantitative yield from the corresponding functionalized selenoacetals[56,87,100,171] or orthoesters[36,71] and Bu$^n$Li. The Se–Li exchange is in all these cases, except that of tris(phenylseleno)methane,[36] exclusively observed even with those compounds which possess a hydrogen susceptible to metallation. The 6,6-bis(phenylseleno)-β-lactam shown

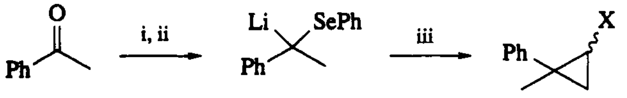

i, ii
Li
SePh
Ph
iii
Ph
X

(refs. 169 and 170)

|  | *Conditions* | *X* | *Yield (%)* |
|---|---|---|---|
| (a) | 0 °C, 1–2 h | H | 50 |
|  | 0 °C, 1–2 h | Me | 0 |
|  | 0 °C, 1–2 h | Ph | 60 |
| (b) | −30 °C, 0.2–3 h | $CH=CH_2$ | 70 |
|  | −30 °C, 0.2–3 h | $SiMe_3$ | 81 |
|  | −30 °C, 0.2–3 h | SPh | 59 |

i, MeSeH, $TiCl_4$, 0 °C; ii, $Bu^nLi$, THF; iii, $H_2C=CHX$

**Scheme 93**

in Scheme 99 also reacts[121] with *n*-butyllithium and provides the corresponding 6-lithio-6-phenylseleno derivative (compare to Scheme 42, a) resulting from an attack on the selenium atom rather than on the carbonyl group. Interestingly, methylmagnesium bromide, which is usually inert towards selenoacetals, reacts efficiently with the above mentioned selenoacetal to produce the 6-phenylselenoenolate derivative (Scheme 99, b). This is probably due to efficient stabilization of the carbanionic center by delocalization on the carbonyl group.

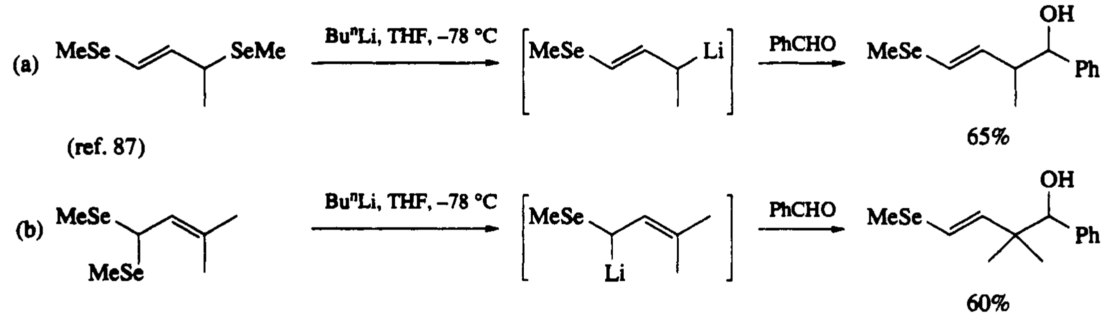

(a)
MeSe
SeMe
BunLi, THF, −78 °C
MeSe
Li
PhCHO
MeSe
OH
Ph
(ref. 87)
65%
(b)
MeSe
MeSe
BunLi, THF, −78 °C
MeSe
Li
PhCHO
MeSe
OH
Ph
60%

**Scheme 94**

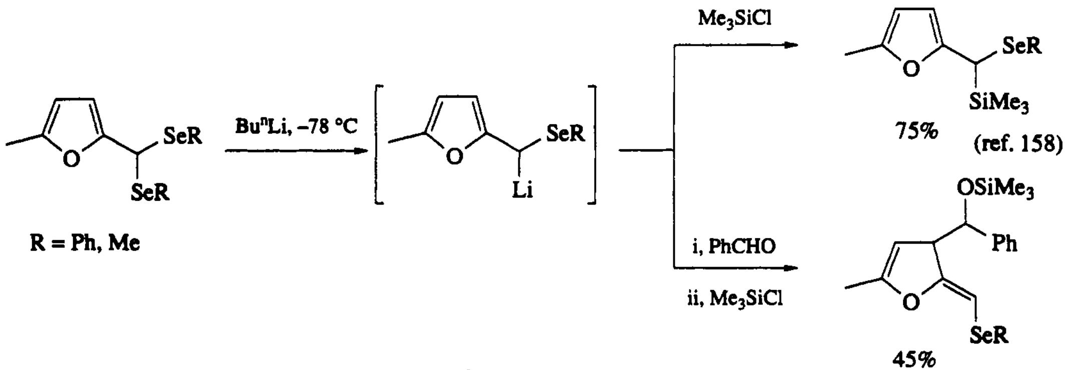

SeR
SeR
R = Ph, Me
BunLi, −78 °C
O
SeR
Li
Me3SiCl
SeR
SiMe3
75%
(ref. 158)
i, PhCHO
ii, Me3SiCl
OSiMe3
Ph
SeR
45%

**Scheme 95**

### *2.6.2.3.2 Synthesis of α-selenovinyl metals by selenium–metal exchange*

1,1-Bis(phenylseleno)alkenes, readily prepared from vinylcarbenes and diselenides (Scheme 100),[172] trimethylsilylbis(phenylseleno)methyllithium and carbonyl compounds (Scheme 31, d),[95] orthoselenoesters[35,36] and diphosphorus tetraiodide ($P_2I_4$)[174] or tin tetrachloride ($SnCl_4$),[175] and from β-hydroxyalkyl orthoesters and $P_2I_4$ (Scheme 101, b),[108] efficiently react with *n*-butyllithium in THF and provide, even at

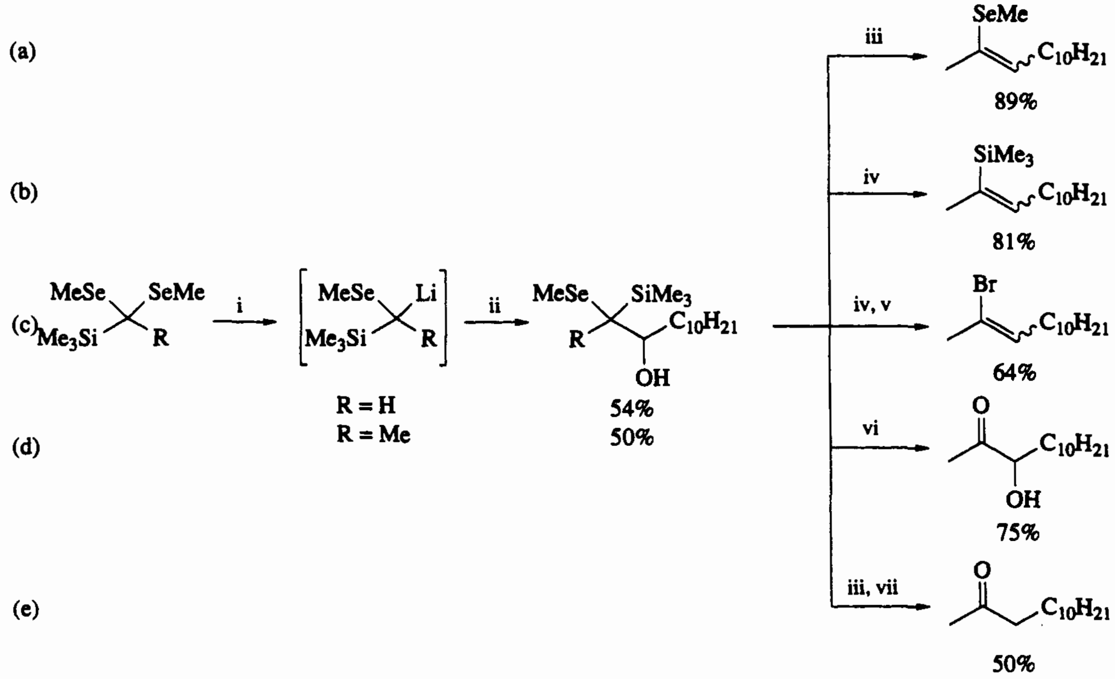

i, Bu$^n$Li, THF, −78 °C, 0.1 h; ii, $C_{10}H_{21}CHO$; iii, Bu$^t$OK, THF, 55 °C; iv, $POCl_3$, $Et_3N$, 20 °C; v, $Br_2$, $CCl_4$, 20 °C; vi, $H_2O_2$, THF, 20 °C, vii, $HgCl_2$, aq. MeCN, 20 °C, 12 h (ref. 171)

Scheme 96

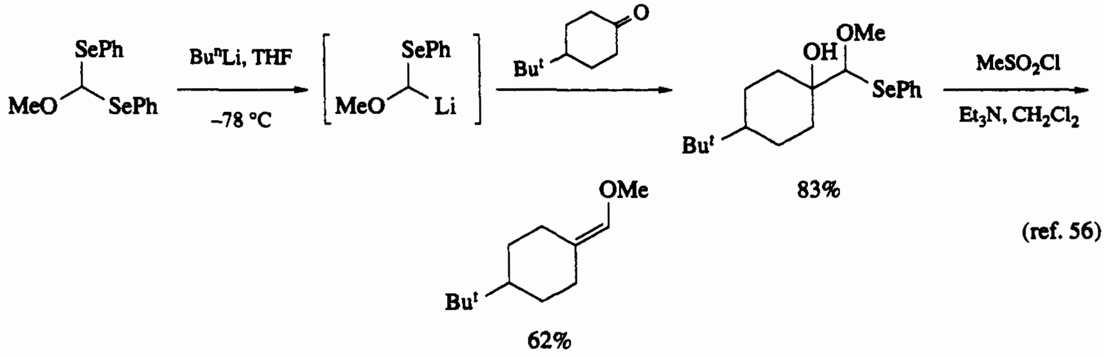

(ref. 56)

Scheme 97

−78 °C, 1-phenylseleno-[173] and 1-methylseleno-1-alkenyllithiums[176] in almost quantitative yields (Scheme 101). The stereochemistry of the reaction is not well defined and the only available results are those concerning the stereochemistry of the compounds resulting from further reaction of these organometallics with electrophiles.[173,176] Both stereoisomers are formed if the methylselenoalkenyllithium is hydrolyzed[176] or reacted[176] with an aldehyde or a ketone, whereas only one stereoisomer of an α,β-unsaturated carbonyl compound is found from 1-methylseleno-1-alkenyllithiums and DMF[176] and from the 1-phenylseleno-1-alkenyllithiums and phenacyl bromide.[173]

### 2.6.2.4 Miscellaneous Syntheses of α-Selenoalkyl Metals

More recently, lithium naphthalenide, lithium dimethylaminonaphthalenide and lithium 4,4′-dimethoxybiphenylide have been successfully reacted with selenoacetals to produce the corresponding α-selenoalkyllithiums is moderate yields.[168] Phenylselenomethyllithium has been prepared[101] from (phenylseleno)(phenyltelluro)methane and butyllithium (Scheme 25, b), and α-phenylselenoalkyllithiums have also been obtained[177] from α-bromoalkyl phenyl selenides and *n*-butyllithium in THF. The

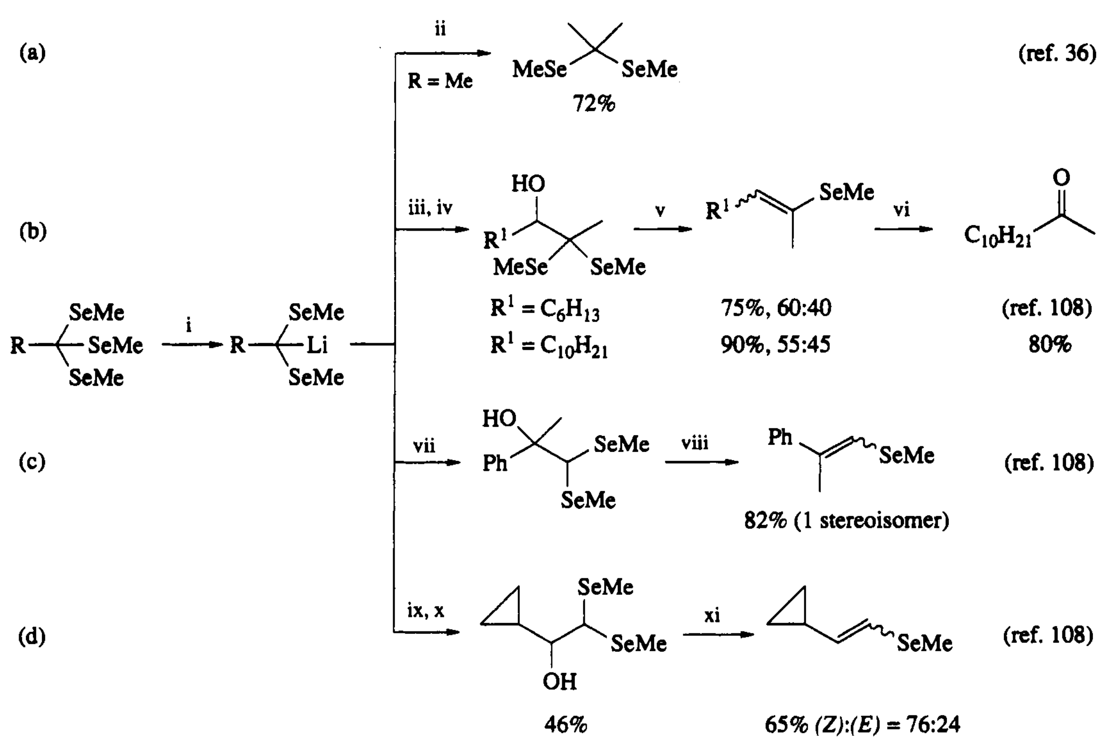
(a)
(b)
(c)
(d)
i
ii
R = Me
72%
iii, iv
v
vi
$R^1 = C_6H_{13}$
$R^1 = C_{10}H_{21}$
75%, 60:40
90%, 55:45
(ref. 36)
(ref. 108)
80%
vii
viii
82% (1 stereoisomer)
(ref. 108)
ix, x
xi
46%
65% (Z):(E) = 76:24
(ref. 108)

i, $Bu^nLi$, THF, –78 °C; ii, MeI; iii, $R^1CHO$; iv, $H_3O^+$; v, $P_2I_4$, $Et_3N$, $CH_2Cl_2$, 20 °C; vi, $HgCl_2$, $H_2O$, MeCN, 20 °C; vii, PhCOMe; viii, $P_2I_4$, $Et_3N$, $CH_2Cl_2$, 20 °C; ix, cyclopropylaldehyde; x, $H_3O^+$; xi, $P_2I_4$, $Et_3N$, $CH_2Cl_2$, 20 °C

**Scheme 98**

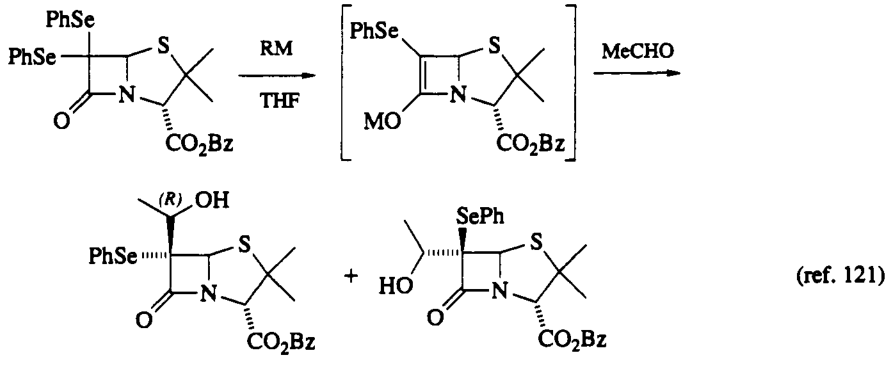
RM
THF
MeCHO
(R)
(ref. 121)

| | *RM* | *Yield (%)* | *Ratio* |
|---|---|---|---|
| (a) | BuLi, –78 °C | – | 40:60 |
| (b) | MeMgBr, –60 °C | 78 | 97:3 |

**Scheme 99**

latter reaction is highly selective, readily occurs at –78 °C and provides a wide range of α-phenylselenoalkyllithiums in about 60% yield (Scheme 102).

The halogen–lithium exchange is, however, far less general than the selenium–metal exchange from selenoacetals for the synthesis of α-selenoalkyllithiums. It does not provide α-phenylselenoalkyllithiums from α-chloroalkyl phenyl selenides[177] and does not allow the synthesis of methylselenoalkyllithiums from α-haloalkyl methyl selenides.[177] It also suffers from the instability of the α-bromoalkyl phenyl selenides, especially those which produce the α-selenoalkyllithiums where the carbanionic center is dialkyl substituted.[177] Furthermore the butyl bromide produced concomitantly with the α-selenoalkyllithium

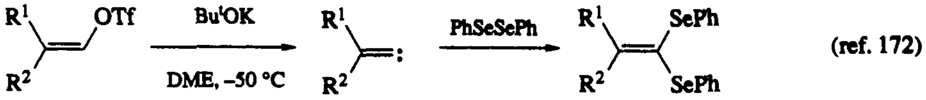
R¹
R²
OTf
Bu<sup>t</sup>OK
DME, −50 °C
R¹
R²
PhSeSePh
R¹
R²
SePh
SePh
(ref. 172)

| *R¹* | *R²* | *Yield* (%) |
|---|---|---|
| Me | Me | 47 |
| $CH_2(CH_2)_3CH_2$ | | 61 |

**Scheme 100**

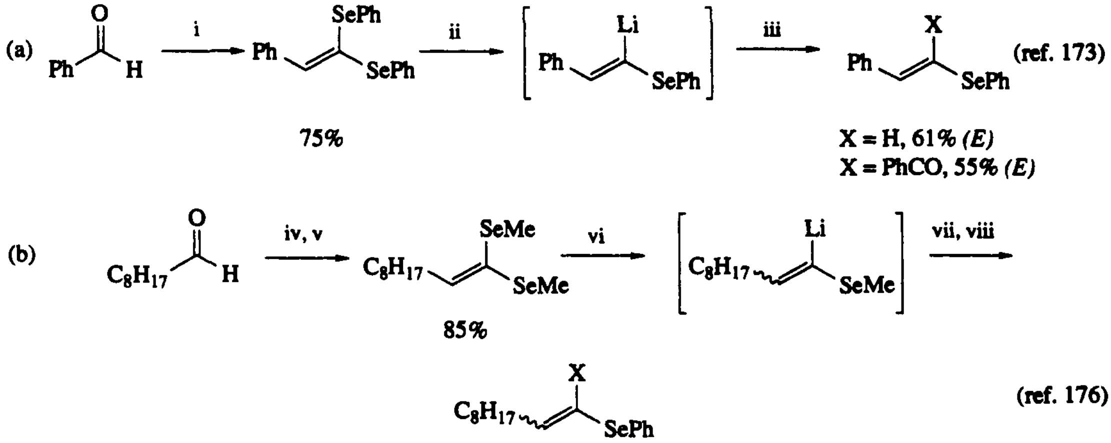
(a)
O
Ph
H
i
SePh
Ph
SePh
75%
ii
Li
Ph
SePh
iii
X
Ph
SePh
(ref. 173)
(b)
O
C8H17
H
iv, v
SeMe
C8H17
SeMe
85%
vi
Li
C8H17
SeMe
vii, viii
X
C8H17
SePh
(ref. 176)

X = H, 61% *(E)*
X = PhCO, 55% *(E)*

X = $C_6H_{13}CHOH$, 69% (Z + *E*)
X = $CO_2H$, 80% (Z + *E*)
X = CHO, 79%, *(E)*

i, $Me_3SiCLi(SePh)_2$, THF, −78 °C, 1 h, then 30 °C, 14 h; ii, $Bu^nLi$, THF, −78 °C; iii, $H_2O$ or PhCOBr; iv, $LiC(SeMe)_3$; v, $P_2I_4$, $Et_3N$, $CH_2Cl_2$, 20 °C, 1 h; vi, $Bu^nLi$, THF, −78 °C; vii, $C_6H_{13}CHO$ or $CO_2$ or $Me_2NCHO$; viii, $H_3O^+$

**Scheme 101**

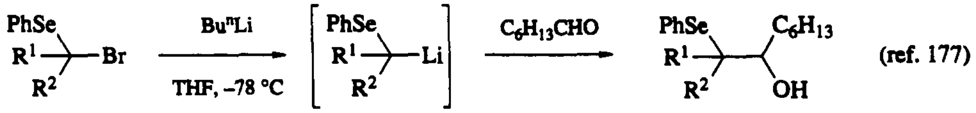
PhSe
R¹
R²
Br
BunLi
THF, −78 °C
PhSe
R¹
R²
Li
C6H13CHO
PhSe
R¹
R²
C6H13
OH
(ref. 177)

| *R¹* | *R²* | *Yield* (%) |
|---|---|---|
| H | H | 69 |
| H | Me | 63 |
| Me | Me | 62 |

**Scheme 102**

competes with other electrophiles in further reactions.[177] The Br–Li exchange has been successfully used for the synthesis of 2-lithioselenophene[122] and 2-lithiobenzoselenophene (Scheme 103).[123]

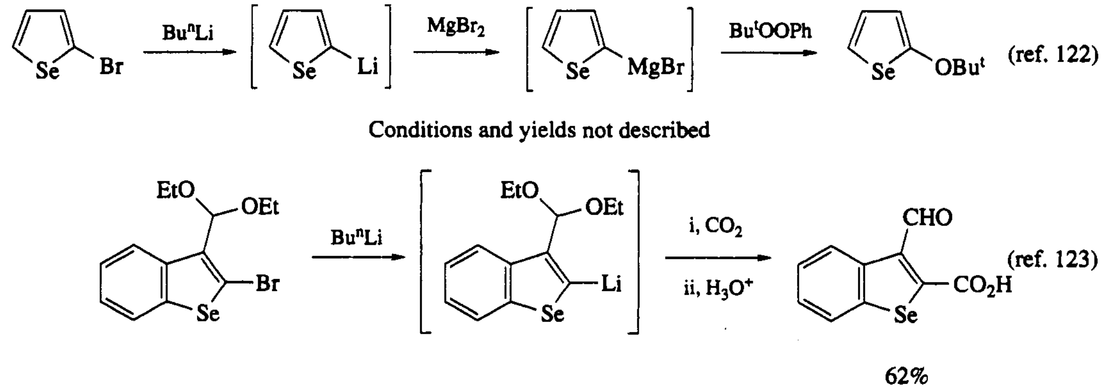

Conditions and yields not described

Scheme 103

## 2.6.2.5 Synthesis of α-Selenoalkyl Metals by Addition of Organometallics to Vinyl Selenides, Vinyl Selenoxides and Vinyl Selenones

The reaction of organolithium compounds with phenyl vinyl selenides[11,41,42,124,174,178,179] proceeds by at least three different routes which involve: (i) metallation, which leads to 1-phenylseleno-1-vinyllithium (Section 2.6.2.2.2);[41,65,125] (ii) Se–Li exchange, which produces phenyllithium and a novel vinyl selenide (Scheme 104, a);[41,42] or (iii) addition of the organolithium across the carbon–carbon double bond leading to α-selenoalkyllithiums (Scheme 104, b).[41,42,124] The choice of the experimental conditions, especially the solvent, is crucial for chemoselective reactions.

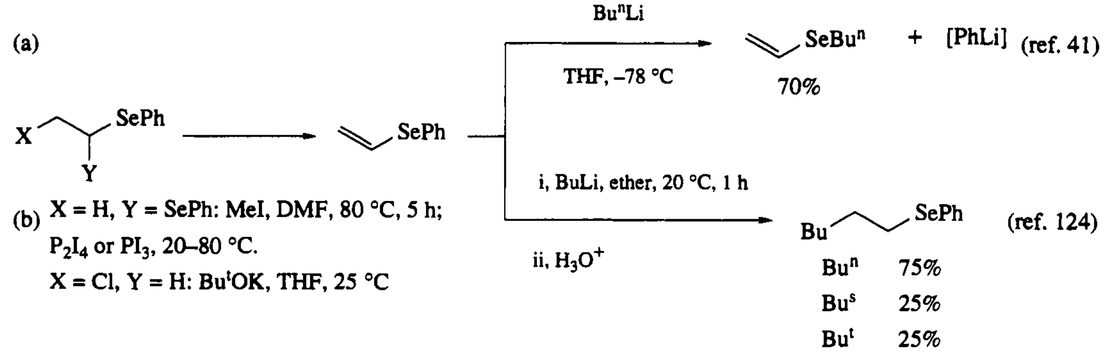
(a)
Bu$^n$Li
THF, −78 °C
SeBu$^n$ + [PhLi] (ref. 41)
70%
(b) X = H, Y = SePh: MeI, DMF, 80 °C, 5 h; P$_2$I$_4$ or PI$_3$, 20–80 °C.
X = Cl, Y = H: Bu$^t$OK, THF, 25 °C
i, BuLi, ether, 20 °C, 1 h
ii, H$_3$O$^+$
(ref. 124)
Bu$^n$ 75%
Bu$^s$ 25%
Bu$^t$ 25%

Scheme 104

The addition reaction is particularly favored[41,42,124] when carried out in ether or DME (Scheme 104, b; Scheme 105). Addition takes place between 0 °C and 20 °C, under conditions at which the α-phenylselenoalkyllithium isomerizes rapidly to the corresponding aryllithium (Scheme 106).[7,16,41,180] So, further reaction with electrophiles, for example, must be carried out as soon as possible (compare Scheme 106 with Scheme 105). The reaction takes another course when performed in THF since 1-phenylseleno-1-vinyllithium and phenyllithium are produced from, respectively, the metallation and C—Se bond cleavage of the vinyl selenide (Scheme 104, a).[41] Interestingly, the temperature has an important effect on the course of this reaction, since in THF the Se–Li exchange becomes predominant if the reaction is carried out at low temperature (−78 °C instead of 0 °C).[41]

α-(Methylseleno)benzyllithiums also react with phenyl vinyl selenide but surprisingly give 1-phenyl-1-methylselenocyclopropanes. This result has been tentatively rationalized in Scheme 107.[169,170]

A reaction related to those mentioned above involves an addition–cyclization sequence of 2-azaallyllithiums on phenyl vinyl selenide, which leads to seleno-substituted pyrrolidines (Scheme 108).[181,182]

γ-Selenoalkylmetals have been suggested as intermediates in a large array of reactions. Thus organocuprates efficiently add at the C-3 site of α-seleno-α,β-unsaturated ketones to produce enolates which can be further trapped with various alkyl or propargyl halides to give α,β-dialkyl-α-seleno ketones (Scheme 109). These, after proper control of the relative stereochemistry at the α- and β-carbons to the carbonyl group, have been selectively transformed to cycloalkenones (Schemes 36 and 109, a)[111,183] or

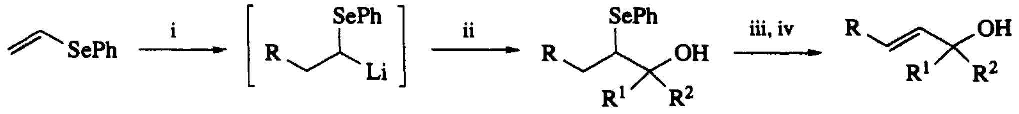
SePh
i
R
SePh
Li
ii
R
SePh
OH
R1
R2
iii, iv
R
OH
R1
R2

| | *RLi* | *Conditions* | *Carbonyl compound* | *Yield* (%) | | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Bu$^n$Li | Ether, 20 °C, 0.2 h | $C_6H_{13}CHO$ | 40 | | 41 |
| (b) | Bu$^n$Li | DME, 0 °C | PhCHO | 71 | | 42 |
| (c) | Pr$^i$Li | Ether, 0 °C | $Me_2CO$ | 72 | 81 | 42 |

i, RLi; ii, $R^1R^2CO$; iii, $O_3$, –78 °C, 0.1 h; iv, $Pr^i{}_2NH$, $CCl_4$, 80 °C, 0.5 h

**Scheme 105**

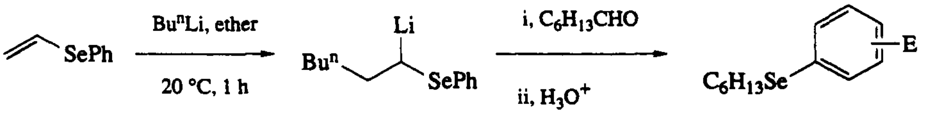
SePh
Bu$^n$Li, ether
20 °C, 1 h
Li
Bu$^n$
SePh
i, $C_6H_{13}CHO$
ii, $H_3O^+$
$C_6H_{13}Se$
E

(ref. 41)

E = H, 30%; E = $C_6H_{13}CHOH$, 18%

**Scheme 106**

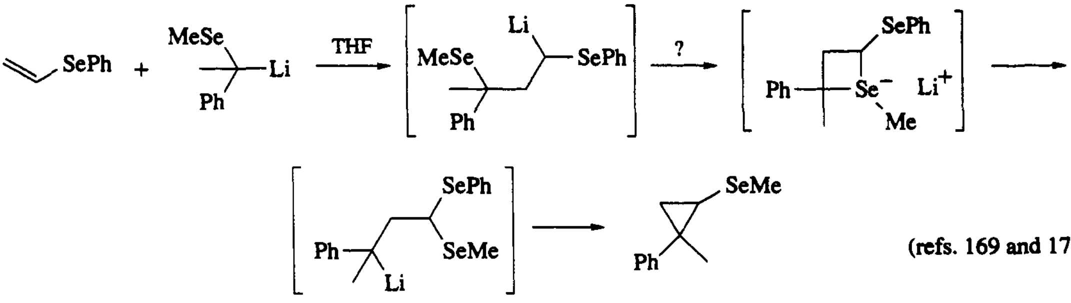
SePh
+
MeSe
Li
Ph
THF
Li
MeSe
SePh
Ph
?
SePh
Ph
Se$^-$
Li$^+$
Me
SePh
Ph
SeMe
Li
SeMe
Ph

(refs. 169 and 170)

**Scheme 107**

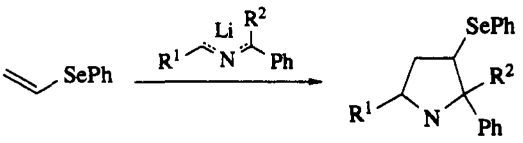
SePh
Li
R2
R1
N
Ph
SePh
R2
R1
N
Ph

(refs. 181 and 182)

| $R^1$ | $R^2$ | *Conditions* | *Yield* (%) |
|---|---|---|---|
| Ph | H | –40 °C, 22 h | 77 |
| H | Ph | –50 to –10 °C, 6 h | 42 |

**Scheme 108**

alkylidenecycloalkanes (Scheme 109, b)[183] using the well-established selenoxide *syn* elimination reaction.

Lithium enolates derived from methyl ketones and acetates successfully add to vinyl selenoxides[184,185] and to vinyl selenones to give cyclopropyl ketones and esters (Scheme 110).[185,186] The α-lithioalkyl selenoxide or selenone intermediates presumably exchange to the lithium enolates which, after displacement of the seleno or selenoxy group, lead to the observed products.

Additions of various nucleophiles to vinyl selenoxides[184,185,187] and vinyl selenones[17,185–187] have been described. Thus potassium hydroxide[187] and amines[17] add to vinyl selenones and directly produce epoxides and aziridines, respectively, whereas 3-methoxyoxetanes have been obtained from γ-hydroxy-α-alkenyl selenones and sodium methoxide (Scheme 111).[185]

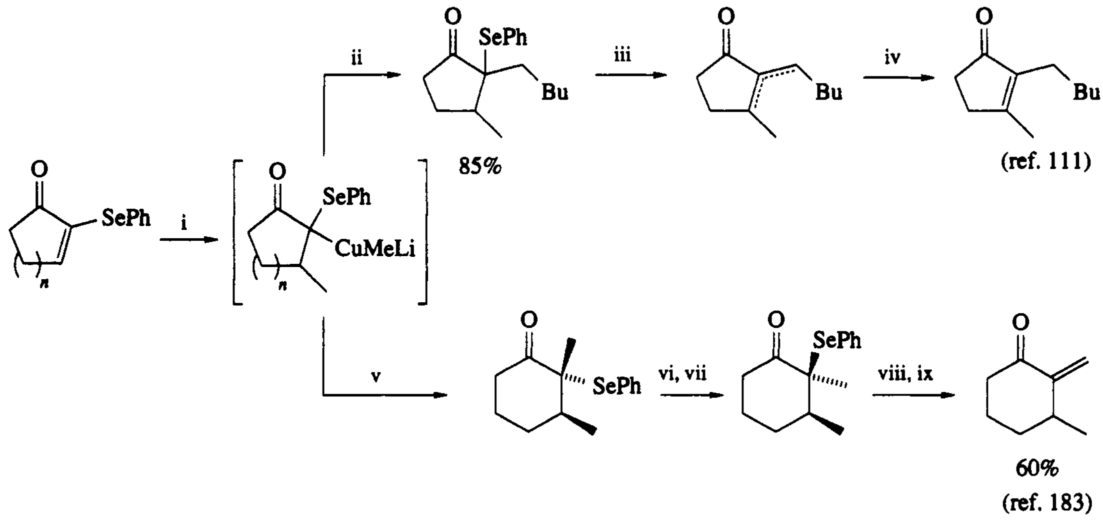

SePh
ii
iii
iv
Bu
85%
(ref. 111)
i
CuMeLi
n
v
vi, vii
viii, ix
60%
(ref. 183)

i, $Me_2CuLi$, $Et_2O$, 20 °C, 0.3 h; ii, $Bu^nLi$, THF–HMPA; iii, aq. $H_2O_2$, $CH_2Cl_2$; iv, HCl, $Bu^nOH$, 90 °C, 1 h; v, MeI, THF–HMPA; vi, PhSeLi; vii, PhSeCl; viii, $O_3$, $CH_2Cl_2$; ix, $Et_2NH$, 50 °C

**Scheme 109**

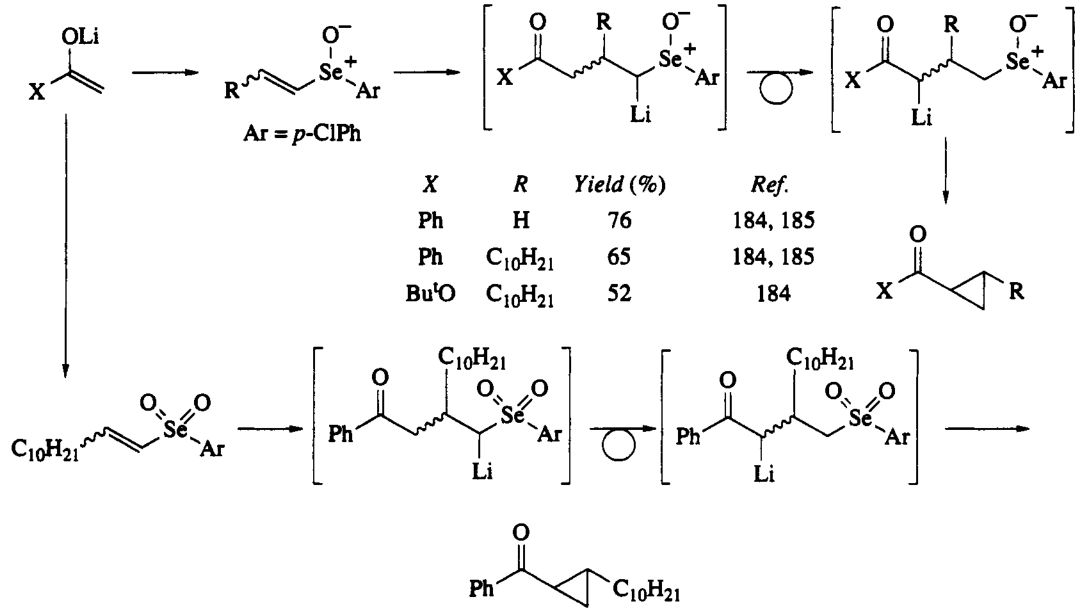

OLi
X
Ar = p-ClPh
Se
Ar
R
Li
Ph
$C_{10}H_{21}$

| X | R | Yield (%) | Ref. |
|---|---|---|---|
| Ph | H | 76 | 184, 185 |
| Ph | $C_{10}H_{21}$ | 65 | 184, 185 |
| $Bu^tO$ | $C_{10}H_{21}$ | 52 | 184 |

29% (ref. 185)

**Scheme 110**

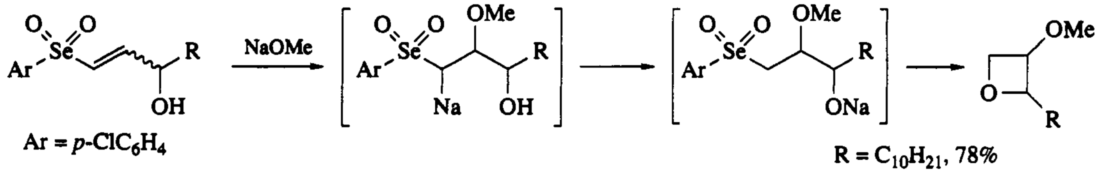

Ar
Se
R
OH
NaOMe
OMe
Na
ONa
Ar = p-ClC6H4

(ref. 185)

R = $C_{10}H_{21}$, 78%
R = $C_5H_{11}CHCO_2Bu^t$, 81%

**Scheme 111**

## 2.6.3 REACTIVITY OF CARBONYL COMPOUNDS WITH ORGANOMETALLICS BEARING A SELENIUM-STABILIZED CARBANION

### 2.6.3.1 Generalities

The organometallics bearing a selenium atom directly attached to the carbanionic center, the synthesis of which has been discussed above, have been reacted with a large variety of electrophiles.[1,4,5,7–9,12,13,16,17] Among these electrophiles, aldehydes and ketones occupy a place of choice, usually leading, after hydrolysis, to β-hydroxyalkyl selenides. Some examples are gathered in Schemes 112 to 118.

Examples of organometallics bearing a selenium-stabilized carbanion include: (i) α-selenoalkylhydroxylithiums bearing hydrogens or alkyl groups on the carbanionic[4,7–9,13,16,17,35,36,40,48–50,54–56,77,159,160,162,163,166,177,188–206] center; (ii) α-selenocyclopropyllithiums[7,12,16,77,104,159–161] and α-selenocyclobutyllithiums;[7,12,16,136,162,163] (iii) α-selenoallyllithiums (Schemes 16–18, 94 and 119);[16,17,45,80–82,84–87,91] (iv) α-selenobenzyllithiums (Schemes 9, 15 and 118, b)[54,56,72,164,203] and (phenylseleno)(furfuryl)methyllithium (Scheme 95);[158] (v) 1-phenylselenovinyllithiums (Scheme 44);[41,65,73,176] (vi) 1-methoxy-1-phenylselenomethyllithium (Scheme 21, a; Scheme 97);[56] (vii) 1-phenylseleno-1-thioalkyllithiums (Scheme 22);[94] (viii) 1-phosphonato-1-phenylselenoalkyllithiums (Scheme 28);[102] (ix) 1-seleno-1-silylalkyllithiums (Scheme 24, b and c; Scheme 96),[100,171] 1-seleno-1-silylallyllithiums (Scheme 33, a)[85] and 1-seleno-1-silylbenzyllithiums (Scheme 33; b);[70] (x) 1,1-bis(seleno)alkyllithiums (Scheme 23, e and f),[35,36,56,65,71,73,98,108,192] 1,1-bis(seleno)benzyllithiums (Scheme 32),[72] 1,1-bis(seleno)(trimethylsilyl)methyllithiums (Scheme 31, d)[95] and tris(seleno)methyllithiums (Scheme 31, a–c);[36,71,108] (xi) selenonium ylides (Schemes 59 and 60; Scheme 61, a);[77,132,206] (xii) α-metalloalkyl selenoxides (Schemes 51–54);[97,127,128] (xiii) α-metallovinyl selenoxides (Scheme 179);[103] (xiv) α-metalloalkyl selenones (Schemes 55 and 56);[129,130,138,206] and (xv) α-selenometalloenolates derived from esters (Scheme 10),[74] lactones (Scheme 38),[74] lactams[121,207] including β-lactams[121] (Scheme 42, a; Scheme 99), and nitroalkanes (Scheme 41).[120] Most of the organometallics listed produce the corresponding alcohols by reaction with aldehydes and ketones and further hydrolysis of the resulting alcoholates.

β-Oxidoalkylselenonium salts (Schemes 59–61)[77,132,206] and β-oxidoalkyl selenones (Schemes 55 and 56)[129,130,138,206] are unstable too, and directly collapse to epoxides even at –78 °C. The former reaction is limited to nonenolizable carbonyl compounds.[132] In the case of acetophenone and trimethylselenonium iodide, for example, polymethylation of the carbonyl compound occurs (Scheme 122).[132] The results can be rationalized by considering enolate formation and alkylation of the enolate by the selenonium salt.

β-Oxidoalkyl selenides bearing a phosphonato (Scheme 28),[102] phosphonio[106,107] or silyl group (Scheme 24, b and c; Scheme 31, d)[95,100,171] are unstable too, and have a high tendency to produce vinyl selenides *via* the well-known Wittig–Horner or Peterson elimination reaction. Lithium alkoxides derived from 1-trimethylsilyl-1-selenoalkyllithiums can be trapped with water and lead to the corresponding alcohols in modest yields (Scheme 96). Their potassium analogs, as well as lithium alkoxides derived from bis(phenylseleno)trimethylsilylmethane, however, directly collapse to the corresponding alkenes (Scheme 31, d).

### 2.6.3.2 Nucleophilicity of α-Selenoalkyllithiums Towards Aldehydes and Ketones

α-Selenoalkyllithiums, even those where the carbanionic center is monoalkyl, dialkyl[55,188,189,193,194] or benzyl substituted,[208] are particularly nucleophilic towards carbonyl compounds (Schemes 112–116). There is some evidence that they are far more reactive with carbonyl compounds than with alkyl halides (Scheme 123).[12,77]

Phenylseleno- and methylseleno-alkyllithiums usually exhibit a closely related reactivity towards carbonyl compounds whether the reaction is performed in THF or in ether. As expected, the nucleophilicity of such species often decreases[189] by increasing the substitution around the carbanionic center (**6** and **8**; Scheme 112), but interestingly they are often far more nucleophilic than the corresponding alkyllithiums.[51] However, in some rare cases employing particularly hindered reaction partners there is a significant difference of reactivity between phenyl- and methyl-selenoalkyllithiums when the reactions are performed in THF, since the former reagents are much less nucleophilic than the latter (compare **11** and **12** in Scheme 113 and **17a**–**17f** in Scheme 114). As general trends, α-methylselenoalkyllithiums are more nucleophilic in ether than in THF (compare **15** in Scheme 113, **17d** and **17e** in Scheme 114 and **24** in Scheme 116).

β-Hydroxyalkyl selenides have been transformed to epoxides (see Section 2.6.4.5.2)[7,16,206] and to alkenes (see Section 2.6.4.3).[7,12,16] These are therefore produced from two carbonyl compounds, one of them being activated as a selenoacetal and then as an α-selenoalkyllithium. Best results are obtained

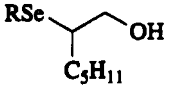

**(5)**

R = Me, 58%, method A (ref. 195)
R = Ph, 78%, method A

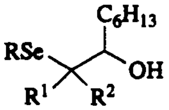

**(6)**

| | *R* | *R¹* | *R²* | *Yield (%)* | *Method* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Ph | H | n-$C_6H_{13}$ | 75 | A | 193 |
| (b) | Me | H | n-$C_6H_{13}$ | 82 | A | 193 |
| (c) | Ph | H | Et | 50 | A | 196 |
| (d) | Me | Me | Et | 82 | A | 55 |
| (e) | Me | $(CH_2)_5$ | | 76 | A | 55 |
| (f) | Me | H | $Bu^t$ | 79 | A | 189 |
| (g) | Me | Me | $Bu^t$ | 57 | A or B | 189 |

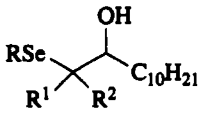

**(7)**

| | *R* | *R¹* | *R²* | *Yield (%)* | *Method* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Ph | H | H | 71 | A | 193 |
| (b) | Me | H | H | 71 | A | 193 |
| (c) | Ph | H | Me | 80 | A | 193 |
| (d) | Me | $(CH_2)_2CH(n\text{-}C_5H_{11})$ | | 67 | A | 159 |

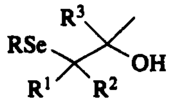

**(8)**

| | *R* | *R¹* | *R²* | *R³* | *Yield (%)* | *Method* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | Ph | H | $Bu^t$ | $C_6H_{13}$ | 75 | A | 193 |
| (b) | Me | H | $Bu^t$ | $C_6H_{13}$ | 44 | B | 189 |
| (c) | Me | Me | $Bu^t$ | $C_6H_{13}$ | 9 | B | 180 |
| (d) | Ph | Me | Me | $C_6H_{13}$ | 79 | B | — |
| (e) | Me | Me | Me | $C_6H_{13}$ | 73 | B | — |
| (f) | Me | Me | Me | $C_9H_{19}$ | 63 | A | 194 |

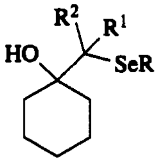

**(9)**

| | *R* | *R¹* | *R²* | *Yield (%)* | *Method* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Me | H | Me | 94 | A | 55 |
| (b) | Me | H | $C_6H_{13}$ | 60 | A | 55 |
| (c) | Me | Me | Et | 60 | A | 55 |
| (d) | Ph | $(CH_2)_5$ | | 70 | B | 223 |
| (e) | Ph | Me | Me | 78 | A | 132 |

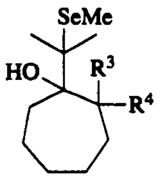

**(10)**

| | *R³* | *R⁴* | *Yield (%)* | *Method* | *Ref.* |
|---|---|---|---|---|---|
| (a) | H | H | 64 | B | 223 |
| (b) | H | Me | 64 | B | 223 |
| (c) | Me | Me | 64 | B | 223 |
| (d) | $(CH_2)_4$ | | 88 | B | 223 |

A = $Bu^nLi$, THF–hexane, –78 °C; B = $Bu^sLi$, ether–hexane, –78 °C; C = $Bu^sLi$, THF–hexane, –78 °C;
D = $Bu^tLi$, ether–hexane, –78 °C

**Scheme 112**

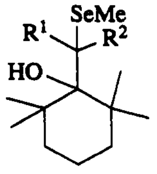

**(11)**

| | $R^1$ | $R^2$ | Method A Yield (%) | Method B Yield (%) | Ref. |
|---|---|---|---|---|---|
| (a) | H | H | 83 | 87 | 188, 189 |
| (b) | H | Me | 83 | 85 | 188, 189 |
| (c) | Me | Me | 77 | 85 | 188, 189 |

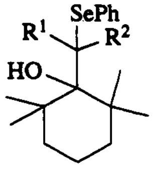

**(12)**

| | $R^1$ | $R^2$ | Method A Yield (%) | Method B Yield (%) | Ref. |
|---|---|---|---|---|---|
| (a) | H | H | 22 | 85 | 188, 189 |
| (b) | H | Me | 5 | 63 | 188, 189 |
| (c) | Me | Me | 0 | 60 | 188, 189 |

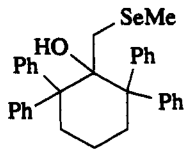

**(13)**

0% by method A, C or D (ref. 188)

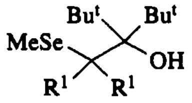

**(14)**

| | $R^1$ | Yield (%) | Method | Ref. |
|---|---|---|---|---|
| (a) | H | 81 | C | 189, 206 |
| (b) | Me | 76 | D | 189, 206 |

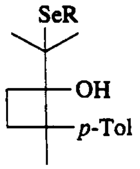

**(15)**

| | R | Yield (%) | Method | Ref. |
|---|---|---|---|---|
| (a) | Me | 0 | A | 160 |
| | Me | 66 | B | 160 |
| (b) | Ph | 0 | A | 160 |
| | Ph | 49 | B | 160 |

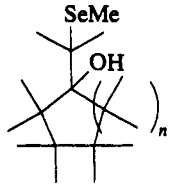

**(16)**

| | n | Yield (%) | Method | Ref. |
|---|---|---|---|---|
| (a) | 0 | 73 | B | 190, 191 |
| (b) | 1 | 73 | B | 190, 191 |

A = $Bu^nLi$, THF–hexane, –78 °C; B = $Bu^sLi$, ether–hexane, –78 °C; C = $Bu^sLi$, THF–hexane, –78 °C;
D = $Bu^tLi$, ether–hexane, –45 °C

Scheme 113

when the less hindered or the less enolizable of the two carbonyl compounds is transformed to the α-selenoalkyllithium (compare **8b** and **8c** in Scheme 112 to **14** in Scheme 113).

α-Selenoalkyllithiums react efficiently with highly hindered carbonyl compounds such as 2,2,6-trimethylcyclohexanone (see **17**; Scheme 114),[12,77,188,189] 2,2,6,6-tetramethylcyclohexanone (see **11** and **12**; Scheme 113),[12,77,188,189] permethylcyclobutanone,[190,191] permethylcyclopentanone (see **16**; Scheme 113)[190,191] and di-*t*-butyl ketone (see **14**; Scheme 113). However, they do not add to 2,2,6,6-tetraphenylcyclohexanone (see **13**; Scheme 113).[189] Their reactivity towards highly enolizable carbonyl com-

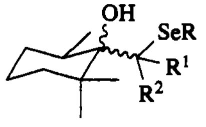

**(17)**

| | *R* | *R¹* | *R²* | *Yield* (%) | *Ax:eq*$^a$ | *Method* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | Me | H | H | 92 | 18:82 | A | 188, 189 |
| (b) | Me | H | H | 85 | 31:69 | D | 188, 189 |
| (c) | Me | H | Me | 85 | 95:5 | A or C | 188, 189 |
| (d) | Me | Me | Me | 48 | 33:67 | A | 188, 189 |
| (e) | Me | Me | Me | 85 | 95:5 | D | 188, 189 |
| (f) | Ph | Me | Me | 0 | – | A | 188, 189 |
| (g) | Ph | Me | Me | 84 | 95:5 | D | 188, 189 |

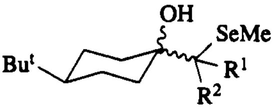

**(18)**

| | *R¹* | *R²* | *Yield* (%) | *Ax:eq*$^a$ | *Method* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | H | H | 85 | 75:25 | A | 189, 210 |
| (b) | H | H | 75 | 69:31 | D | 189, 210 |
| (c) | H | Me | 70 | 90:10 | A | 189, 210 |
| (d) | H | Me | 79 | 90:10 | D | 189, 210 |
| (e) | Me | Me | 75 | 100:0 | A or D | 189, 210 |

A = $\mathrm{Bu^nLi}$, THF–hexane, –78 °C; B = $\mathrm{Bu^sLi}$, ether–hexane, –78 °C; C = $\mathrm{Bu^sLi}$, THF–hexane, –78 °C; D = $\mathrm{Bu^tLi}$, ether–hexane, –78 °C.

[a] Axial alcohol:equatorial alcohol.

**Scheme 114**

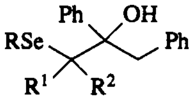

**(19)**

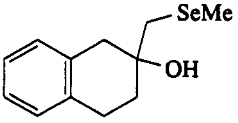

**(20)**

44%, method A (refs. 189, 206)

| | *R* | *R¹* | *R²* | *Yield* (%) | *Method* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Ph | H | H | 82 | A | 196 |
| (b) | Ph | H | Me | 69 | A | 196 |
| | Me | H | Me | 88 | A | 55 |
| (c) | Me | H | n-$C_6H_{13}$ | 75 | A | 189 |
| | Me | H | n-$C_6H_{13}$ | 80 | D | 189 |
| (d) | Me | Me | Me | 88 | A | 55 |

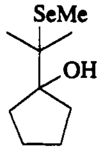

**(21)**

45%, method A (refs. 189, 206)

A = $\mathrm{Bu^nLi}$, THF–hexane, –78 °C; D = $\mathrm{Bu^tLi}$, ether–hexane, –78 °C

**Scheme 115**

pounds is somewhat capricious. Deoxybenzoin, a particularly enolizable derivative, is efficiently transformed to β-hydroxyalkyl selenides (**19** in Scheme 115; **24** in Scheme 116),[55,193,194] whereas β-tetralone[189] and cyclopentanone[189] are partially enolized (**20** and **21**; Scheme 115).

α-Selenoalkyllithiums exhibit towards carbonyl compounds a nucleophilicity almost identical to that of the corresponding α-thioalkyllithiums[12,77,209] but slightly superior to that of α-metalloalkyl selenoxides[98,127,128,192] and several orders of magnitude superior to that of selenium[132,206] and sulfur ylides.[25,32,33] The reasons for such exceptional nucleophilicity are not yet understood. Reactions involving single- electron transfer could take place but experimental support is not available.

α-Selenoalkyllithiums which bear another heteroatomic moiety on the carbanionic center are still valuable nucleophiles towards carbonyl compounds but they are not as efficient as the α-selenoalkyllithiums reported above.[71,100] Even so, the presence of a trimethylsilyl substituent on the carbanionic center substantially decreases[100,171] the reactivity of these organometallics (Scheme 96), whereas a phospho-

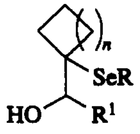

**(22)**

| *n* | *R* | *R*$^1$ | *Yield* (%) | *Method* | *Ref.* |
|---|---|---|---|---|---|
| 0 | Me | $C_{10}H_{21}$ | 72 | A | 12, 77 |
| 0 | Ph | c-$C_6H_{11}$ | 63 | A | 12, 77 |
| 0 | Me | c-$C_6H_{11}$ | 73 | A | 12, 77 |
| 1 | Ph | $C_{10}H_{21}$ | 71 | D | 136, 156 |
| 1 | Me | $C_{10}H_{21}$ | 90 | D | 136, 156 |

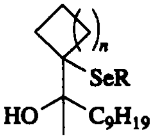
n
SeR
HO
C9H19

**(23)**

| *n* | *R* | *Yield* (%) | *Method* | *Ref.* |
|---|---|---|---|---|
| 0 | Ph | 54 | A | 12, 77 |
| 0 | Me | 69 | A | 136 |
| 1 | Ph | 70 | A | 136 |
| 1 | Me | 78 | A | 136 |

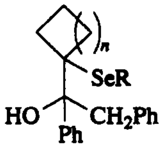
n
SeR
HO
CH2Ph
Ph

**(24)**

| *n* | *R* | *Yield* (%) | *Method* | *Ref.* |
|---|---|---|---|---|
| 0 | Ph | 61 | A | 12, 77 |
| 0 | Me | 56 | A | 12, 77 |
| 0 | Me | 70 | B | 12, 159 |
| 1 | Me | 68 | A | 12, 77 |

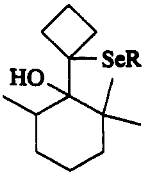

**(25)**

| *n* | *R* | *Yield* (%) | *Method* | *Ref.* |
|---|---|---|---|---|
| 0 | Ph | 47 | A | 12, 77 |
| 0 | Me | 64 | C | 12, 159 |
| 0 | Ph | 35 | A | 12, 159 |
| 1 | Me | 54 | A | 12, 159 |
| 1 | Me | 68 | C | 12, 159 |

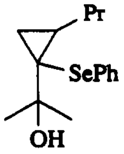

**(26)**

58%, method A (refs. 12 and 77)
60%, method B (refs. 12 and 77)

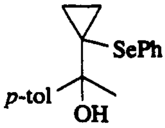
SePh
p-tol
OH

**(27)**

R = Ph, 81%, method C (ref. 160)
R = Me, 85%, method C (ref. 160)

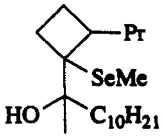
Pr
SeMe
HO
C10H21

**(28)**

71%, method A (refs. 12 and 77)

A = $\mathrm{Bu^nLi}$, THF–hexane, –78 °C; B = $\mathrm{Bu^sLi}$, ether–hexane, –78 °C; C = $\mathrm{Bu^sLi}$, THF–hexane, –78 °C; D = $\mathrm{Bu^tLi}$, ether–hexane, –78 °C

**Scheme 116**

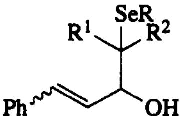

**(29)**

| | R | R¹ | R² | Yield (%) | Method | Ref. |
|---|---|---|---|---|---|---|
| (a) | Me | H | Me | 90 | A | 222 |
| (b) | Ph | H | Me | 66 | A | 223 |
| (c) | Ph | H | n-$C_6H_{13}$ | 68 | A | 223 |
| (d) | Me | Me | Me | 85 | A | 222 |
| (e) | Ph | Me | Me | 78 | A | 221 |

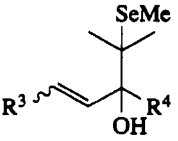

**(30)**

| | R³ | R⁴ | Yield (%) | Method | Ref. |
|---|---|---|---|---|---|
| (a) | $Pr^n$ | Me | 74 | B | 223 |
| (b) | $Pr^n$ | Et | 74 | B | 223 |
| (c) | H | Me | 55 | A | 221 |
| (d) | Me | Me | 45 | A | 221 |

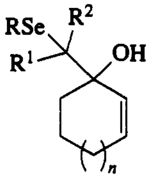

**(31)**

| | n | R | R¹ | R² | Yield (%) | Method | Ref. |
|---|---|---|---|---|---|---|---|
| (a) | 1 | Me | H | n-$C_6H_{13}$ | 64 | A | 222 |
| (b) | 1 | Me | Me | Me | 55 | A | 221 |
| (c) | 1 | Ph | Me | Me | 83 | B | 225 |
| (d) | 2 | Me | Me | Me | 57 | B | 225 |
| (e) | 2 | Ph | Me | Me | 51 | B | 225 |
| (f) | 7 | Me | Me | Me | 54 | B | 225 |
| (g) | 1 | Me | $CH_2$-$CH_2$ | | 86 | A | 12, 77 |
| (h) | 1 | Ph | $CH_2$-$CH_2$ | | 88 | A | 12, 77 |

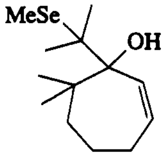

14%, method A
46%, method B (ref. 225)

**(32)**

A = $Bu^nLi$, THF–hexane, –78 °C; B = $Bu^sLi$, ether–hexane, –78 °C; C = $Bu^sLi$, THF–hexane, –78 °C; D = $Bu^tLi$, ether–hexane, –78 °C

**Scheme 117**

nio[106,107] or a phosphonato[102] group dramatically lowers its reactivity. For example, α-phosphonio- and α-phosphonato-α-selenoalkyl metals[102] efficiently react with aldehydes[102,106] but not with ketones.[102,106,107]

### 2.6.3.3 Stereochemistry of the Addition of α-Selenoalkyllithiums to Aldehydes and Ketones

The reactions of α-selenoalkyllithiums with aliphatic and aromatic aldehydes and ketones are not usually stereoselective regardless of the solvent used (ether or THF). Even in the most favorable cases, such as that of 1-methylseleno-2,2-dimethylpropyllithium and heptanal, in which well-differentiated bulky groups are involved, the stereoisomeric ratio ranges from 1:1 to 3:2 (Scheme 124).[189,206] However, in the case shown in Scheme 86, b,[167d] in which the lithium can coordinate to the silyloxy group, only one of the two stereoisomeric β-hydroxyalkyl selenides is formed.

α-Selenoalkyllithiums react stereoselectively with rigid cyclohexanones such as 4-*t*-butylcyclohexanone (**17**; Scheme 114)[210] and 2,2,6-trimethylcyclohexanone (**18**; Scheme 114).[188,189] In most cases the axial alcohols resulting from the equatorial attack of the organometallic are produced (either in THF or

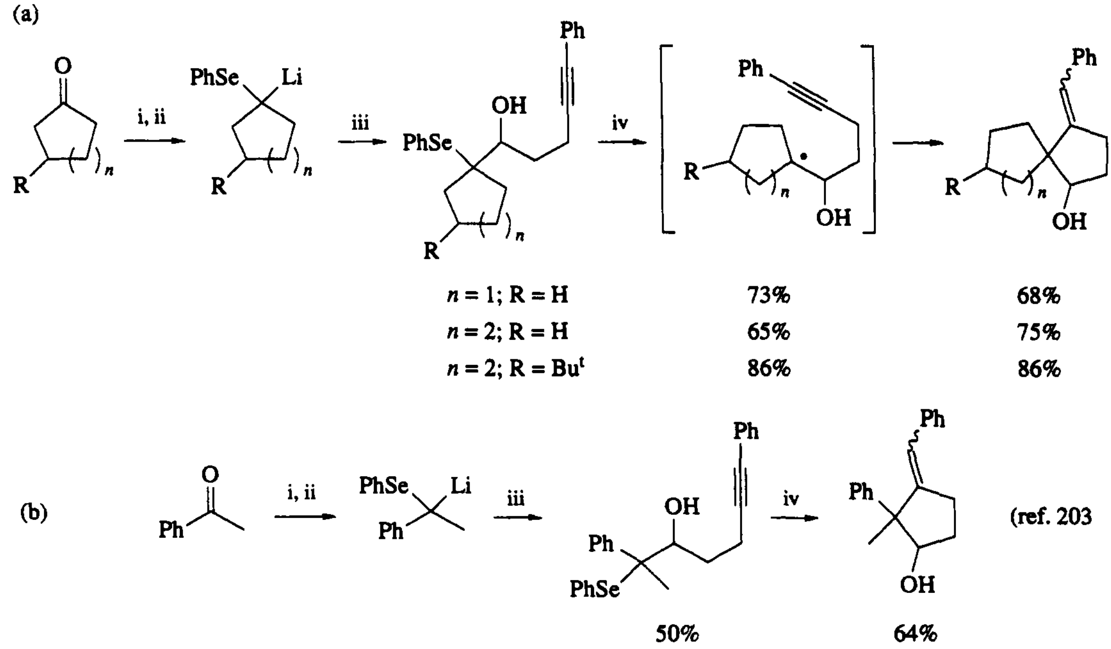
(a)
O
R
n
i, ii
PhSe
Li
iii
Ph
OH
PhSe
iv
Ph
OH
n = 1; R = H 73% 68%
n = 2; R = H 65% 75%
n = 2; R = Bu$^t$ 86% 86%
(b)
O
Ph
i, ii
PhSe
Li
Ph
iii
Ph
OH
Ph
PhSe
iv
Ph
Ph
OH
(ref. 203
50%
64%

i, PhSeH, ZnCl$_2$; ii, Bu$^n$Li; iii, PhC≡C(CH$_2$)$_2$CHO; iv, Ph$_3$SnH, AIBN, benzene, 90 °C, 14 h

Scheme 118

ether). In rare cases, such as that of 2-seleno-2-propyllithium and 2,2,6-trimethylcyclohexanone (**17d** and **17e**; Scheme 114),[188] however, the axial: equatorial ratio is highly dependent upon the solvent used (see also **17a**, **17b**, **18a** and **18b** in Scheme 114). Otherwise, 1-selenocyclopropyllithiums react stereoselectively with α-methylseleno aldehydes and lead to β-hydroxyalkyl methyl selenides with stereochemistry that can be accounted for by the Cram[211,212] and Felkin rules (Scheme 125).[213,214] Finally, methylselenomethyllithium adds on the less-hindered face of protected pregnenolone and related steroidal ketones to produce the (20*R*)-derivatives in good yield (Scheme 126).[206,215,216]

### 2.6.3.4 The Ambident Reactivity of α-Selenoallyllithiums

α-Metalloallyl selenides are ambident nucleophiles which can react[30] at their α- and γ-sites with electrophiles. The regiochemistry of the reaction not only depends upon the nature and the number of substituents present on the allylic or vinylic carbons but also upon the nature of the metallic counterion. Thus aldehydes (Scheme 16, e)[45,81,82] and ketones (Scheme 16, c),[80] except cyclopentenone (Scheme 127, a),[83,90] exhibit a high propensity to react at the γ-site of the parent phenylseleno-[80–82,90] and methylseleno-allyllithiums.[45]

The presence of one alkyl[80] or vinyl[91] group at the γ-site usually inverts the regiochemistry of the reaction which now takes place almost exclusively at the α-site (Scheme 17, b–d), except in the case

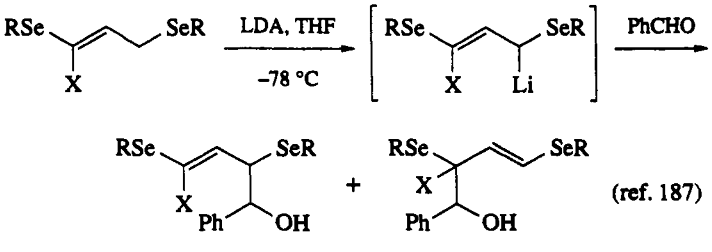
RSe
SeR
X
LDA, THF
-78 °C
RSe
SeR
X
Li
PhCHO
RSe
SeR
X
Ph
OH
+
RSe
SeR
X
Ph
OH
(ref. 187)

R = Ph; X = H; 71%; 50:50
R = Me; X = SeMe; 81%; 61:39

Scheme 119

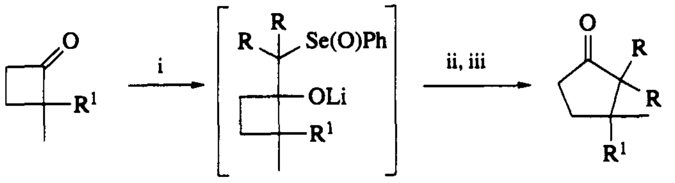

| | *R* | *R¹* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| (a) | H | n-$C_6H_{13}$ | 78 | 128 |
| | H | $Bu^t$ | 9 | 128 |
| | H | $CH_2CH{=}CMe_2$ | 56 | 128 |
| (b) | Me | n-$C_6H_{13}$ | 36 | 128 |
| (c) | Me | *p*-tol | 39 | 127 |

i, $PhSe(O)CR_2Li$, THF, –78 °C; ii, 55 °C, 1 h; iii, Al–Hg

**Scheme 120**

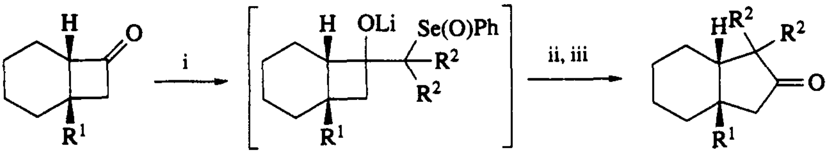

| *R¹* | *R²* | *Yield (%)* |
|---|---|---|
| H | H | 48 |
| Ph | H | 34 |
| Me | Ph | 46 |

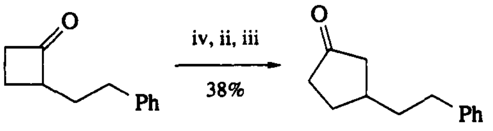

(ref. 128)

i, $PhSe(O)CR^2_2Li$, THF, –78 °C; ii, 55 °C, 2–3 h; iii, Al–Hg; iv, $PhSe(O)CH_2Li$, THF, –78 °C

**Scheme 121**

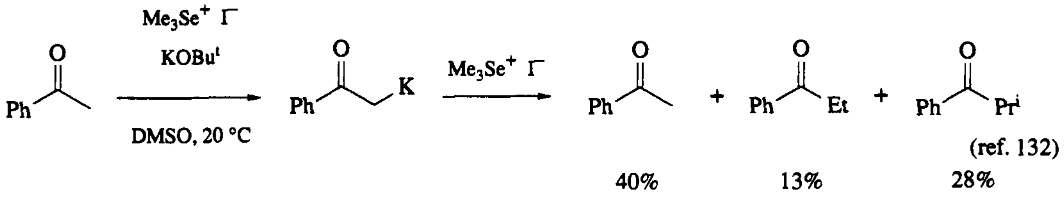

**Scheme 122**

shown in Scheme 94, a.[87] 1-Lithio-1-seleno-3-methylpropene[45,87] reacts exclusively from its α-site with benzaldehyde (Scheme 18, c and d), whereas a mixture of the two regioisomers is produced when the potassium analog is used instead (Scheme 18, e).[45] Presumably the metal coordinates to the less-hindered carbon and the reaction takes place through a six-membered cycle, implying a precoordination of the oxygen of the carbonyl compound with the metal counterion.

Although carbonyl compounds add at the γ-site of phenylselenoallyllithium, the reversed regioselectivity is realized[81,82] by using a triethylaluminum ate complex (Scheme 16, compare b with c and d with e; Scheme 128). Unfortunately, with benzaldehyde and acetophenone the degree of regiochemical convergence is not so high,[82] presumably owing to the steric effect of the carbonyl group. The *threo*

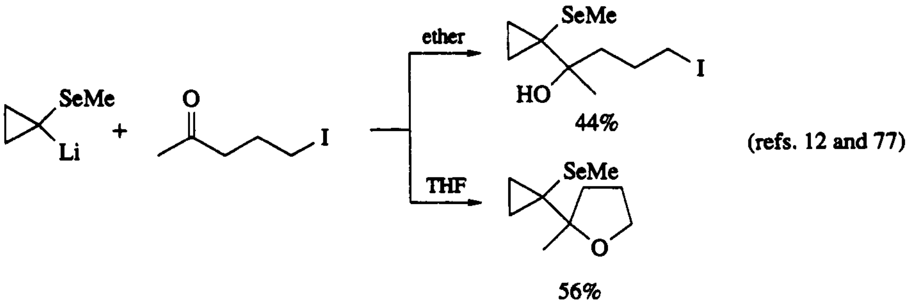
SeMe
Li
+
I
ether
THF
SeMe
HO
I
44%
SeMe
O
56%

(refs. 12 and 77)

**Scheme 123**

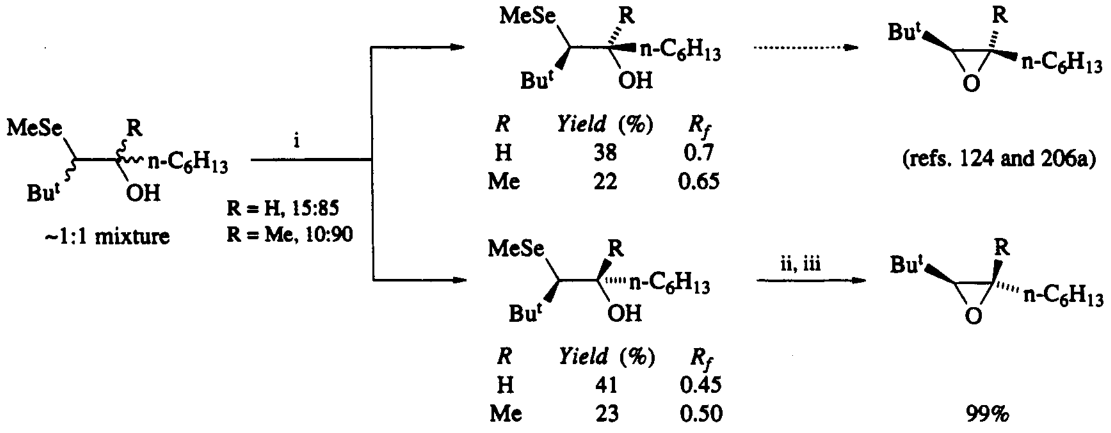
MeSe
R
n-C$_6$H$_{13}$
Bu$^t$
OH
~1:1 mixture
i
R = H, 15:85
R = Me, 10:90
MeSe
R
n-C$_6$H$_{13}$
Bu$^t$
OH
Bu$^t$
R
n-C$_6$H$_{13}$
O
MeSe
R
n-C$_6$H$_{13}$
Bu$^t$
OH
ii, iii
Bu$^t$
R
n-C$_6$H$_{13}$
O
99%

(refs. 124 and 206a)

| *R* | *Yield* (%) | $R_f$ |
|---|---|---|
| H | 38 | 0.7 |
| Me | 22 | 0.65 |

| *R* | *Yield* (%) | $R_f$ |
|---|---|---|
| H | 41 | 0.45 |
| Me | 23 | 0.50 |

i, TLC, $SiO_2$, ether/pentane; ii, $MeSO_3F$, ether; iii, 10% KOH, ether

**Scheme 124**

isomer is predominantly produced and results[82] probably from the *trans* geometry of the intermediate ate complex. This reaction has been successfully applied[82] to the synthesis of 9,11-dodecadien-1-yl acetate, a pheromone of *Disparosis castanea* (Scheme 128). The reaction is highly chemoselective, since ordinary organic halides, trimethylsilyl chloride and trimethylsilyl acetates, which usually react[80] with the lithium derivative, are unreactive towards the aluminum ate complex.[82]

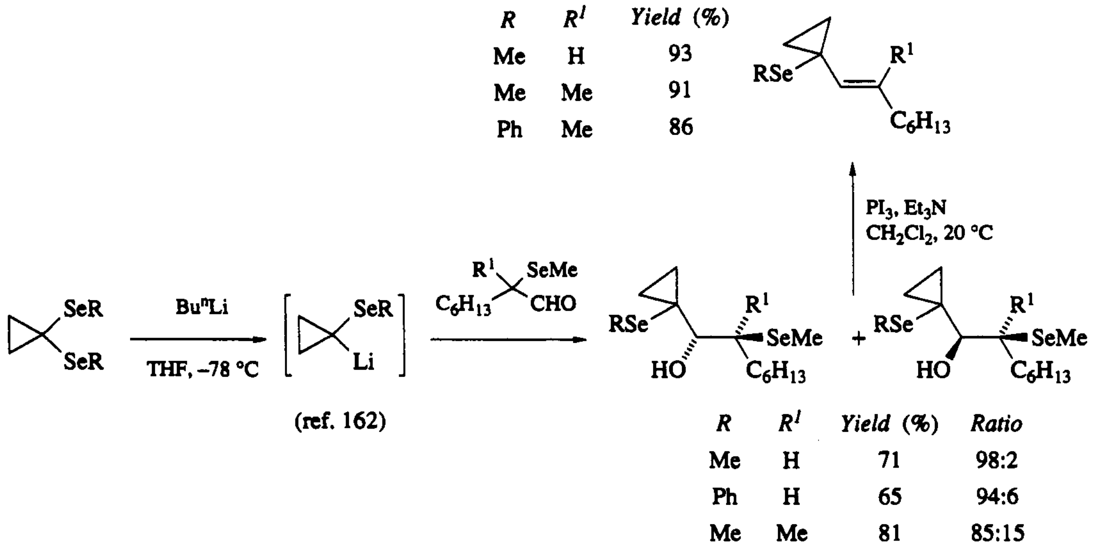
RSe
R$^1$
C$_6$H$_{13}$
SeR
SeR
Bu$^n$Li
THF, –78 °C
SeR
Li
R$^1$
SeMe
C$_6$H$_{13}$
CHO
RSe
R$^1$
SeMe
HO
C$_6$H$_{13}$
+
RSe
R$^1$
SeMe
HO
C$_6$H$_{13}$
PI$_3$, Et$_3$N
CH$_2$Cl$_2$, 20 °C

(ref. 162)

| *R* | $R^1$ | *Yield* (%) |
|---|---|---|
| Me | H | 93 |
| Me | Me | 91 |
| Ph | Me | 86 |

| *R* | $R^1$ | *Yield* (%) | *Ratio* |
|---|---|---|---|
| Me | H | 71 | 98:2 |
| Ph | H | 65 | 94:6 |
| Me | Me | 81 | 85:15 |

**Scheme 125**

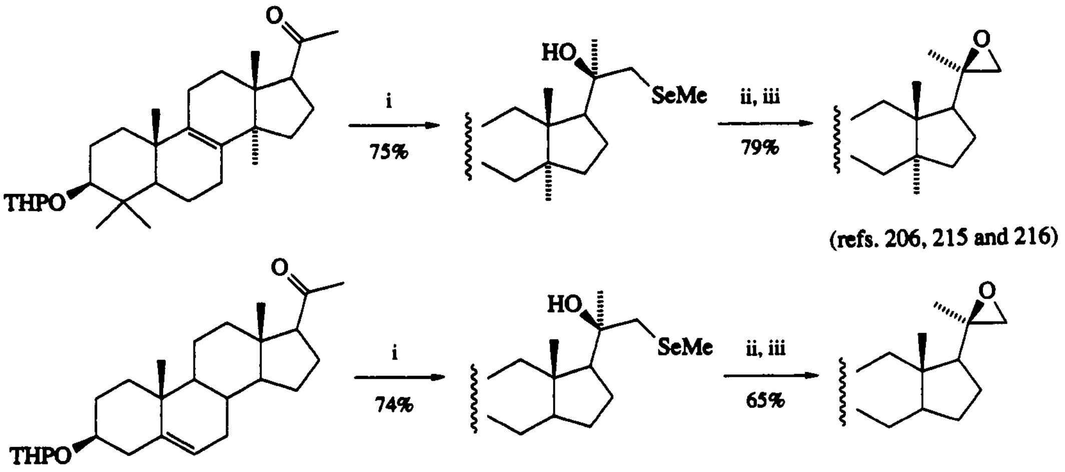
THPO
i
75%
HO
SeMe
ii, iii
79%
O
i
74%
ii, iii
65%

(refs. 206, 215 and 216)

i, $MeSeCH_2Li$, ether–hexane; ii, $MeSO_3F$, 0 to 20 °C, 1 h; iii, 10% aq. KOH, ether, 20 °C, 16 h

**Scheme 126**

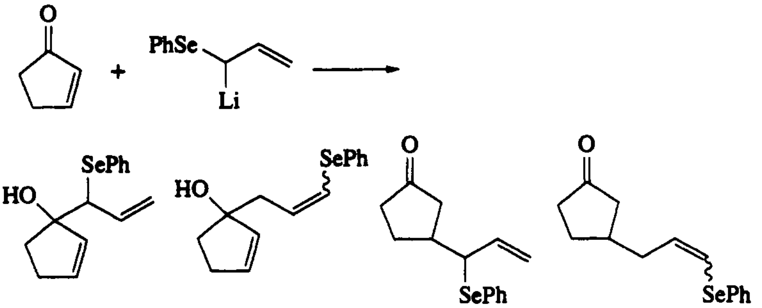
O
PhSe
Li
SePh
HO
SePh
HO
O
SePh
O
SePh

(refs. 83 and 90)

| | *Conditions* | *Yield (%) (stereoisomeric ratio)* | | | |
|---|---|---|---|---|---|
| (a) | i, THF, −78 °C; ii, $H^+$ | 46 (48:52) | 16 (48:52) | 10 | 8 (41:59) |
| (b) | i, THF–HMPA, −78 °C; ii, $H^+$ | — | — | 81 (54:46) | 5 |

**Scheme 127**

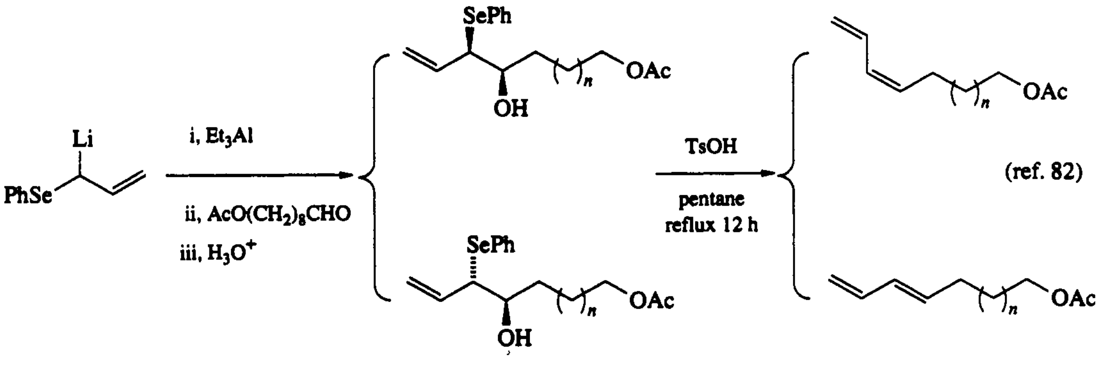
SePh
OAc
OH
Li
PhSe
i, $Et_3Al$
ii, $AcO(CH_2)_8CHO$
iii, $H_3O^+$
SePh
OAc
OH
TsOH
pentane
reflux 12 h
OAc
(ref. 82)
OAc

70% overall
86:14 *(syn:anti)*

77% *(E):(Z)* = 86:14

pheromone of *Diparopsis castanea* (*E:Z* ~ 90:10)

**Scheme 128**

α-Heterosubstituted allyl metal–boronate complexes[82] usually behave like their aluminum analogs. This is not the case of allyl metals bearing a seleno moiety.[217] These in fact undergo a facile migration from boron to the α-carbon. The allylic rearrangement of the resulting boron–selenium complex (**33** to **34**; Scheme 129) is slow[217] in comparison with the usual allylic boranes rearrangement. Thus the trialkylborane–α-phenylselenoallylithium complex produced at –78 °C rapidly leads to the ate complex (**33**) after 1 h at 0 °C and to the complex (**34**) after 12 h at 20 °C. Each one reacts regioselectively with carbonyl compounds at the position where the boron was attached (Scheme 129). Otherwise, 1-lithio-1,3-bis(phenylseleno)-2-propene bearing an α-trimethylsilyl group regioselectively reacts with acetone at the γ-carbon (Scheme 33, a),[85] whereas a mixture of regioisomers is produced from benzaldehyde and 1,1,3-tris(methylseleno)propene (Scheme 130).[87]

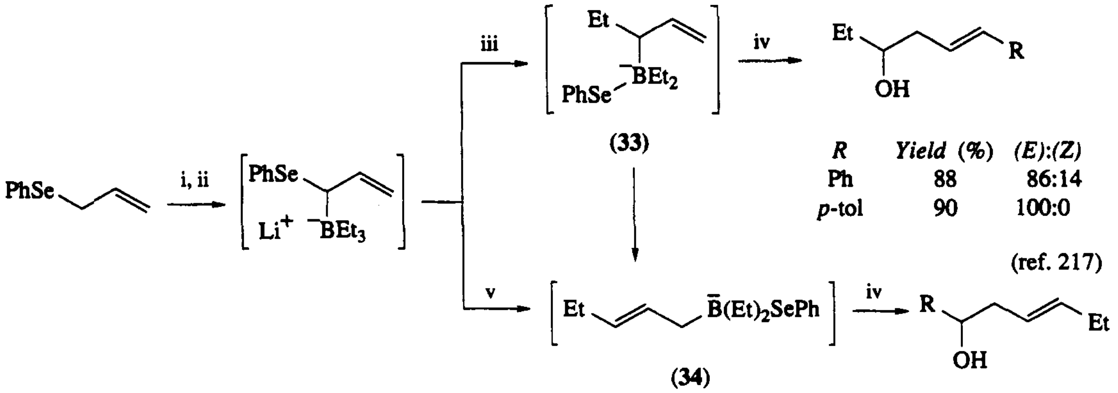

| R | Yield (%) | (E):(Z) |
|---|---|---|
| Ph | 88 | 86:14 |
| p-tol | 90 | 100:0 |

(ref. 217)

| R | Yield (%) | Erthyro:threo |
|---|---|---|
| Ph | 89 | 24:76 |
| p-tol | 92 | 36:64 |
| p-$NO_2C_6H_4$ | 93 | 18:82 |
| $Pr^n$ | 85 | 25:75 |

i, LDA, –78 °C; ii, $Et_3B$, –78 °C; iii, 0 °C, 1 h; iv, RCHO; v,excess $BEt_3$, 20 °C, 12 h

Scheme 129

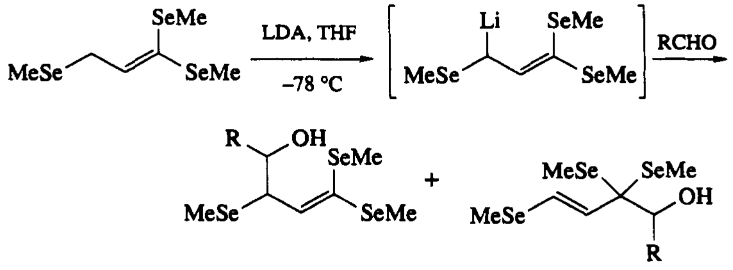

(ref. 87)

| | | |
|---|---|---|
| R = Ph | 49% | 32% |
| R = n-$C_6H_{13}$ | 37% | 48% |

Scheme 130

### 2.6.3.5 Control of the Regiochemistry of Addition of α-Selenoalkyl Metals to Enones, Enals and Enoates

#### *2.6.3.5.1 Generalities*

The control of the regiochemistry of addition of organometallic α-enones, α-enals and α-ene esters has attracted the attention of many chemists from the early age of organic chemistry. Not only have α-selenoalkyllithiums not escaped the rule, but fundamental discoveries made at the occasion of this work have been successfully extended to other organometallics.[7]

The structure of the organometallic and of the α,β-unsaturated carbonyl compound, as well as the experimental conditions, play a crucial role in controlling the regiochemistry of the reaction. In general, enals possess a higher tendency to react at their C-1 site than enones and ene esters and increasing the substitution around the C-1 (or the C-3) site favors the reaction at the C-3 (or at the C-1) site of the enones. Furthermore, the compounds which possess either a privileged cisoid conformation, or the lowest half-wave potential of electrolytic reduction,[218] or the lower level of their LUMO orbitals,[219,220] react predominantly at the C-3 site (PhCH=CHC(=O)Ph >> PhCH=CHC(=O)Me ≈ MeCH=CHC(=O)Ph >> MeCH=CHC(=O)Me).

Performing the reaction at a higher temperature and in a more polar solvent usually increases[7] the amount of the C-3 over the C-1 adduct. The C-1:C-3 ratio is also highly dependent upon the nature of the α-selenoalkyllithium. In this respect, organometallics where the carbanion is directly linked to a selenium atom can be classified into three different categories, each of which behaves differently towards α,β-unsaturated carbonyl compounds: (i) α-selenoalkyllithiums bearing hydrogens or alkyl groups on the carbanionic center which possess, whatever the solvent and the conditions used, the highest propensity to add at the C-1 site of enones; (ii) 1,1-bis(seleno)-1-alkyllithiums where the C-1:C-3 reactivity can be adjusted under kinetically controlled conditions by the proper choice of the solvent; and (iii) enolates derived from α-seleno esters which possess a tendency to add at the C-1 site of α,β-unsaturated carbonyl compounds under kinetically controlled conditions and at the C-3 site under thermodynamic control.

### *2.6.3.5.2 Reactivity of α-selenoalkyl metals, α-selenoxy-γ-alkyl metals and selenium ylides with enals and enones*

α-Selenoalkyllithiums bearing hydrogen or alkyl groups on the carbanionic center possess the highest tendency to react at the C-1 site of enals (Schemes 117, 131 and 132)[12,221–225] and enones (Schemes 117, 133 and 134).[56,77,221,225–227] They usually provide stereoisomeric mixtures of β-hydroxy-γ-alkenyl selenides in good yields.

The reaction takes another course[221] with chalcone since a mixture of β-hydroxyalkyl selenides and γ-selenoalkyl phenyl ketones resulting from C-1 and C-3 attack, respectively, is produced (Scheme 135, compare b and c with a). This enone is the only one among those tested to react in such a way.[221] Interes-

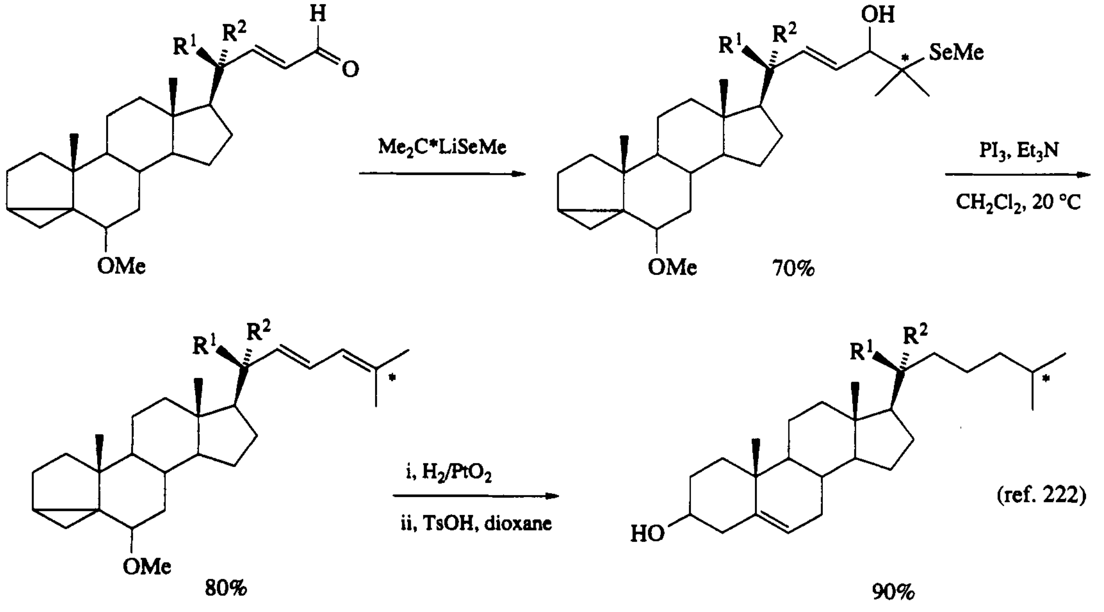

$R^1$ = H; $R^2$ = Me, Cholesterol

$R^1$ = Me; $R^2$ = H, Iso-(20S)-cholesterol

*C = $^{14}$C 12 500 d.p.m. nmol$^{-1}$

**Scheme 131**

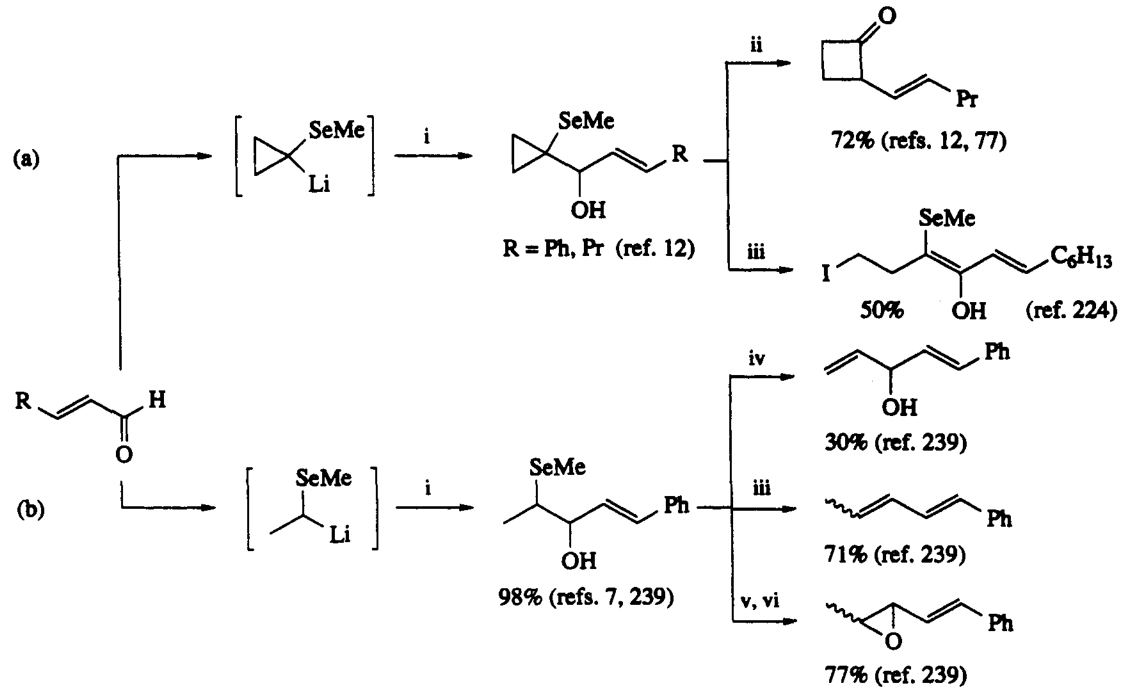
(a)
SeMe
Li
i
SeMe
R
OH
R = Ph, Pr (ref. 12)
ii
O
Pr
72% (refs. 12, 77)
iii
SeMe
I
C6H13
50%
OH
(ref. 224)
R
H
O
(b)
SeMe
Li
i
SeMe
Ph
OH
98% (refs. 7, 239)
iv
Ph
OH
30% (ref. 239)
iii
Ph
71% (ref. 239)
v, vi
O
Ph
77% (ref. 239)

i, THF, −78 °C; ii, TsOH, wet benzene, 80 °C; iii, $PI_3$, $Et_3N$, $CH_2Cl_2$, 20 °C; iv, $Bu^tOOH$, $Al_2O_3$, THF, 55 °C; v, MeI (neat), 20 °C; vi, aq. KOH, ether, 20 °C

**Scheme 132**

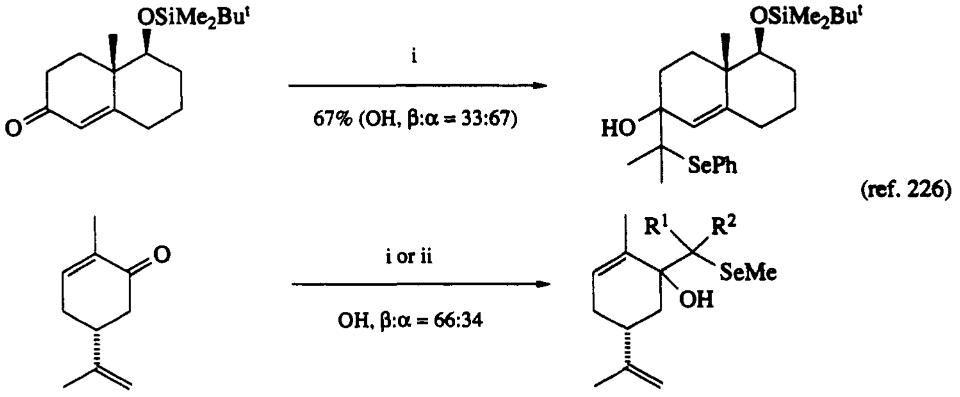
OSiMe2But
O
i
67% (OH, β:α = 33:67)
OSiMe2But
HO
SePh
(ref. 226)
O
i or ii
OH, β:α = 66:34
R1
R2
SeMe
OH

i, $R^1 = R^2 =$ Me; 82%: ii, $R^1 =$ H, $R^2 = C_5H_{11}$; 90%

i, $PhSeCMe_2Li$, THF, −78 °C; ii, $PhSeCH(C_5H_{11})Li$

**Scheme 133**

tingly, the higher percentage of C-3 attack is observed[221] with the α-selenoalkyllithium which possesses the more alkyl substituted carbanionic center. Furthermore, in all these cases the best yields have been observed when the reactions are performed at low temperature (−78 °C) in ether, but it has been noticed that the C-1:C-3 ratio of attack is not affected by the type of solvent (ether, THF or THF–HMPA), the temperature at which the reaction is performed or the reaction time.

α-Selenoxyalkyllithiums in THF (Scheme 136)[97] and methylenedimethylselenurane (generated from trimethylselenonium iodide and potassium *t*-butoxide) in DMSO (Scheme 59, c)[132] also react at the C-1 site of α,β-unsaturated carbonyl compounds. It is interesting to note that whereas methylenedimethylselenurane adds[132] at the C-1 site of chalcone and produces the corresponding α,β-unsaturated epoxide (Scheme 59, c), the more stabilized phenacylmethylenedimethylselenurane exclusively adds[142] at the C-3 site of chalcone and leads to the corresponding cyclopropane (Scheme 68b).

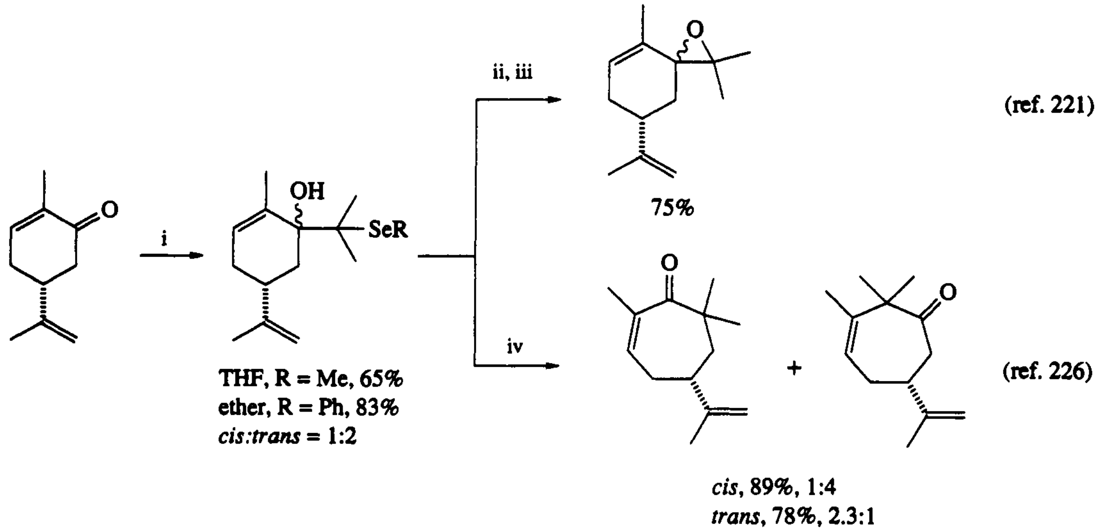
i
ii, iii
iv
OH
SeR
O
75%
(ref. 221)
(ref. 226)
THF, R = Me, 65%
ether, R = Ph, 83%
*cis*:*trans* = 1:2
*cis*, 89%, 1:4
*trans*, 78%, 2.3:1

i, $Me_2CLi(SeR)$, solvent (THF or ether), –78 °C; ii, MeI; iii, $KOBu^t$, DMSO; iv, TlOEt (5.5 equiv.), $CHCl_3$

**Scheme 134**

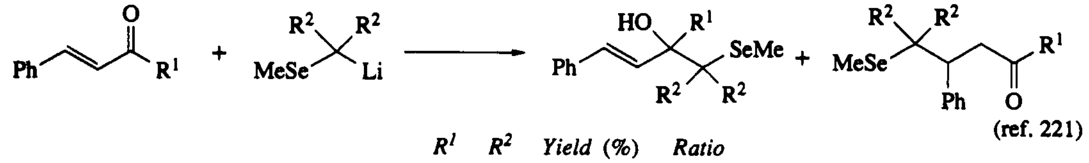
Ph
O
$R^1$
$R^2$
MeSe
Li
HO
SeMe
MeSe
Ph
(ref. 221)

| | *$R^1$* | *$R^2$* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (a) | Me | H | 87 | 100:0 |
| (b) | Ph | H | 70 | 50:50 |
| (c) | Ph | Me | 68 | 30:70 |

Conditions: THF, –78 °C, or THF, –78 to 20 °C, or ether –78 °C

**Scheme 135**

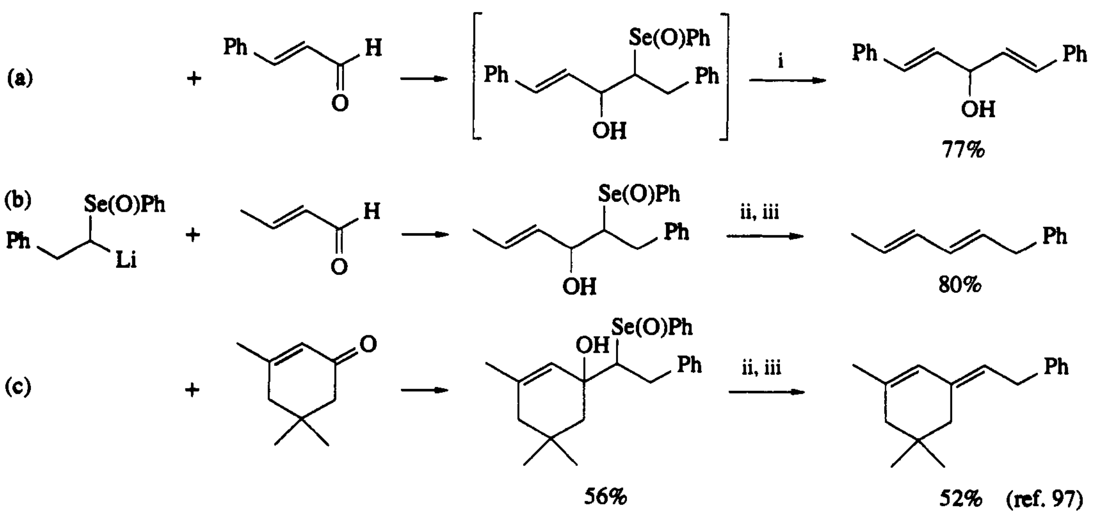
(a)
(b)
(c)
Ph
H
O
Se(O)Ph
Li
OH
i
ii, iii
77%
80%
56%
52% (ref. 97)

i, Δ; ii, $EtCO_2H$, $P(OMe)_3$; iii, MsCl, $Et_3N$

**Scheme 136**

A great deal of attention has been paid to the addition of α-selenoalkyl metals at the C-3 site of enones. Performing the reaction in the presence of the copper iodide–dimethyl sulfide complex does not lead to the expected results, although a novel species is produced[135] which exhibits different behavior from α-selenoalkyllithiums towards, for example, allyl halides.[135] This novel species, which has even been observed[135] by $^{77}$Se NMR, does not react at –78 °C with enones and decomposes in THF or in ether at around –45 °C with no addition to enones. In fact, α-selenoalkyllithiums react at low temperature with the copper iodide–dimethyl sulfide complex in THF or ether to provide,[16,135,228] around –45 °C, alkenes resulting formally from the reductive coupling of the organometallic followed by elimination of the two seleno moieties present on the adjacent carbons (Scheme 137). This reaction is reasonably general since it allows the synthesis of α,β-disubstituted and tetrasubstituted alkenes as mixtures of stereoisomers from α-selenoalkyllithiums bearing one or two alkyl substituents on the carbanionic center. The reaction takes another course when the putative α-selenoalkylcuprate is reacted[229] with the enone in the presence of trimethylsilyl chloride (Scheme 138, compare c with a, b and d), since after hydrolysis the C-3 adducts are obtained from α-selenoalkyllithiums with carbanionic centers that are monoalkyl substituted. Unfortunately, this reaction is not general and those organometallics which bear two alkyl groups on the carbanionic center do not react with enones under such conditions.[229]

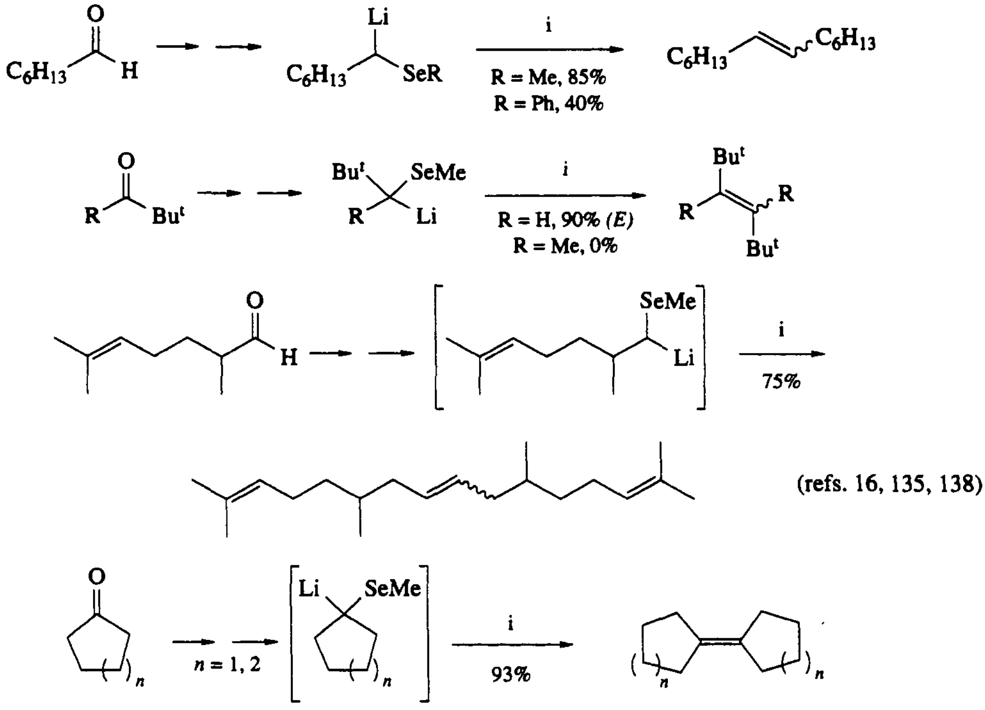

i, CuI•SMe$_2$ (0.5 equiv.), ether, –78 to 20 °C

Scheme 137

### 2.6.3.5.3 *Reactivity of 1,1-bis(seleno)-1-alkyl metals and α-selenocarbonyl compounds with enals and enones*

#### *(i) Generalities*

α-Selenoalkyl metals with carbanionic centers that are substituted with another seleno moiety[7,73,230–234] or an electron-withdrawing group such as an ester[112,113] or a nitrile[117] behave differently. In these cases the nature of the solvent, the seleno moiety attached to the carbanionic center and the metal have an influence on the regiochemical outcome of the reaction. However, whereas the temperature does not affect the regioisomeric ratio with 1-metallo-1,1-bis(seleno)alkanes,[230–232] it plays an especially crucial role with ester enolates derived from α-seleno esters.[112,113,157]

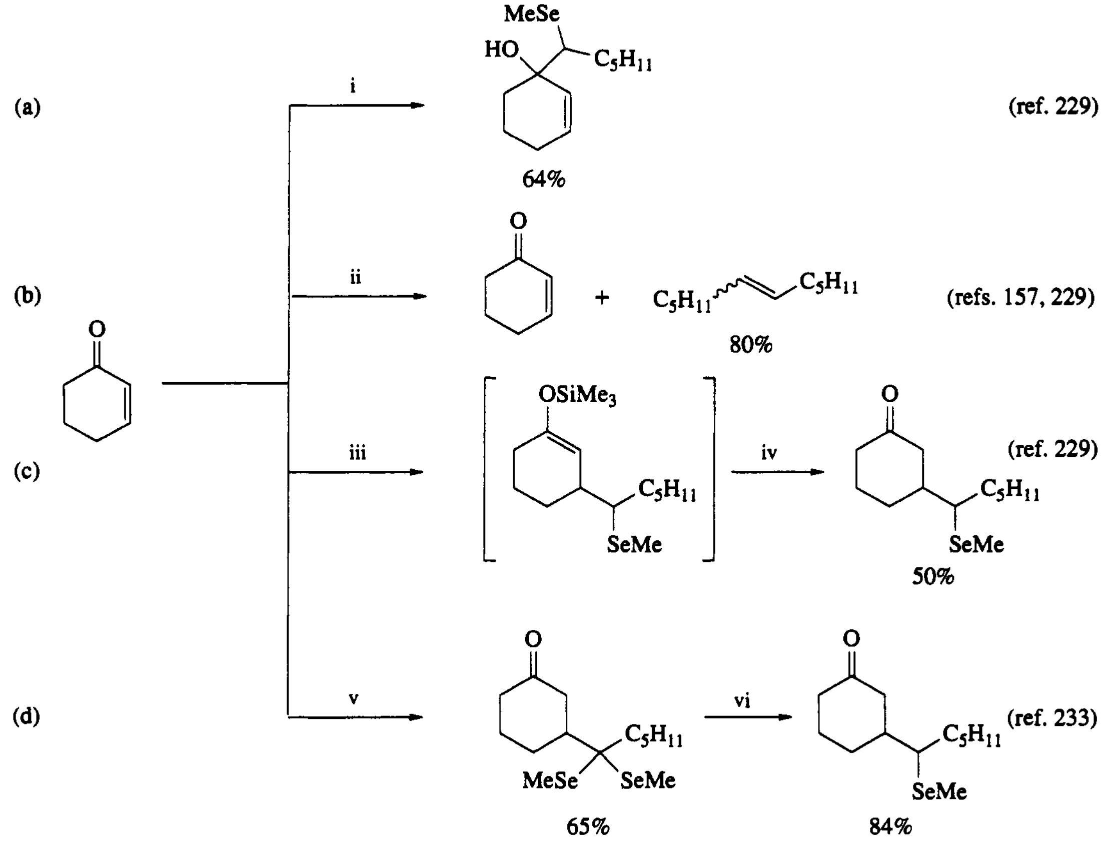

i, $C_5H_{11}CH(SeMe)Li$, THF, –78 °C; ii, $[C_5H_{11}CH(SeMe)]_2CuLi$, $Me_2S$, –78 to 30 °C;
iii, $[C_5H_{11}CH(SeMe)]_2CuLi$, $Me_2S$, $Me_3SiCl$, –78 °C; iv, $H_3O^+$; v, $C_5H_{11}C(SeMe)_2Li$, THF–HMPA;
vi, $Bu_3SnH$, toluene, 100 °C

**Scheme 138**

Furthermore, although similar behavior will be often observed with these two classes of compounds, some fundamental differences exist. In fact with 1,1-bis(seleno)alkyllithiums regiochemical control both at C-1 and C-3 has been achieved under kinetically controlled conditions,[7,16,157,230,231] whereas the ester enolates tend to add at C-1 under kinetically controlled conditions[112,113,157] and at C-3 under thermodynamic control.[7,16,112,113,157] The case of 1-lithio-1-(phenylseleno)cyanoalkanes is somewhat different, since they already react at –78 °C in THF with, for example, cyclohexenone to give the C-3 adduct exclusively (Scheme 40, c), and C-1 attack has not yet been achieved.

### *(ii) Reactivity of 1,1-bis(seleno)-1-alkyl metals with enals and enones*

*(a) Generalities.* 1,1-Bis(seleno)alkyl metals are valuable synthetic intermediates which *inter alia* play the role of acyl anion equivalent. Some synthetic uses of these intermediates are displayed in Schemes 139 and 140, whereas various results concerning the reactivity of such species with enals and enones are gathered in Schemes 141–147.[157]

*(b) Control of the C-1 attack.* The formation of the C-1 over the C-3 adduct is usually favored if the reactions are carried out: (i) in the less polar and basic solvent compatible with the formation of the organometallic (compare Scheme 140, a to b in Scheme 142, a to b; Scheme 143, a to b; Scheme 144, a to b, c and d; Scheme 145, a with Scheme 146, c and d) THF–hexane is often reasonably good.[230,231] but ether–hexane is even better (Schemes 140, a; Scheme 141; Scheme 144, a; Scheme 145).[233] Generally the better overall yields are obtained when the reactions are carried out in the less polar solvent and at the

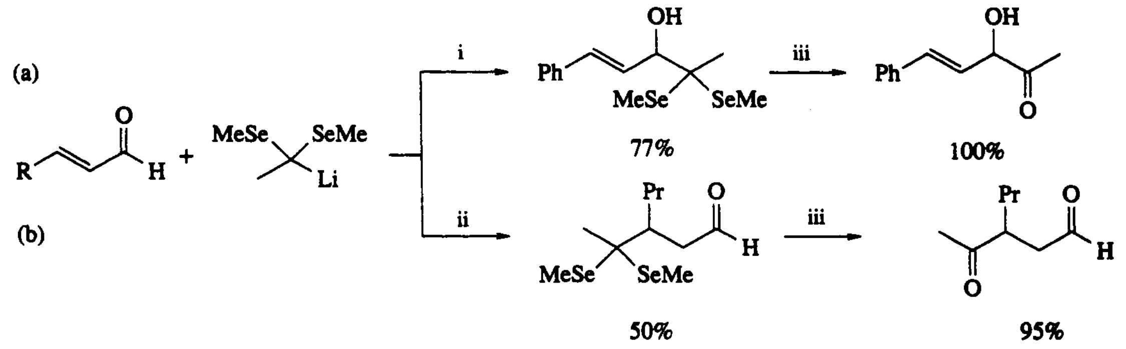

i, THF, −78 °C, 0.2 h; ii, THF, HMPA (2 equiv.), −78 °C, 0.2 h; iii, $CuCl_2$, CuO (4 equiv.), aq. acetone, 20 °C, 0.1 h (ref. 157)

**Scheme 139**

lowest temperature; (ii) with 1,1-bis(methylseleno)alkyllithiums rather than their phenylseleno analogs (compare Scheme 147, a with Scheme 146, c); and (iii) when potassium[73] rather than lithium salts are involved (compare Scheme 147, a and c).

Enals[232] have the highest propensity to react (Scheme 142, a; Scheme 143, a; compare to Scheme 144, b) at C-1 than straight chain ketones,[157] and this is also the case for cyclohexenones (Scheme 146)[7,230,231] as compared to cyclopentenones[157] and cycloheptenones.[157] Chalcone, however, is a very special compound. It apparently shows a different behavior since the C-1 adduct is undoubtedly favored in the more basic solvents (Scheme 148).[234] In all the cases cited above it has been proven[231] that the reactions proceed under kinetic control, so that once the C-1 adduct is formed it is stable and does not produce the C-3 adduct if the temperature of the medium is raised or if a more basic solvent is added before hydrolysis of the alcoholate.

*(c) Control of the C-3 attack.* In general, the C-3 adducts can be produced when the reactions are carried out in a more polar or basic solvent, such as THF containing at least 1.1 equiv. of HMPA per mol of organometallic (Scheme 139, b; Scheme 140, b–e; Scheme 141; Scheme 142, b; Scheme 143, b; Scheme 144, c and d; Scheme 146, b, d and f; Scheme 147, b).[230,231] Use of more HMPA, which usually increases the C-3:C-1 ratio, often leads,[231] due to competing enolization, to a much lower yield of γ-oxo selenoacetal (Scheme 141).

HMPA is not the only additive which leads to the formation of the C-3 adduct. Performing the reaction in ether but in the presence of an 18-crown-6 ether (Kryptofix, trade name (Merck) for hexaoxa-4,7,13,16,21,24-diaza-1,10-bicyclo[8.8.8]hexaiosane) or in DME also favors the formation of the C-3 adduct. However, HMPA is by far the best and the more reliable alternative.

The conditions mentioned above are applicable to various enals (Scheme 139, compare b to a; Scheme 141, compare e to d; Scheme 142, compare b to a; Scheme 143, compare b to a)[157,232,233] and straight chain ketones (Scheme 144, compare c and d to a and b),[157,233] although the regiochemical control is less spectacular than with cyclic enones, especially cyclopentenones and cyclohexenones (Scheme 140, compare b–e with a; Scheme 146, compare b, d and f with a, c and e; Scheme 147, compare b to c; Scheme 149).[157,230,231,233] Surprisingly, 1-metallo-1,1-bis(methylseleno)alkanes are more prone than their phenylseleno analogs to react under these conditions at the C-3 site of enals[232] when the reactions are carried out in THF–HMPA, although the reverse was found with cyclohexenone in THF (compare Scheme 147, b with Scheme 146, c; and Scheme 142, c and d with b). Finally, and surprisingly, the addition of 1-lithio-1,1-bis(seleno)alkanes at the C-3 site of chalcone can be achieved[234] if the reaction is performed in a less basic solvent (Scheme 148, compare a to b).

The addition of 1,1-bis(seleno)alkyllithiums at the C-3 site of enals and enones produces enolates which can be trapped with various electrophiles (Scheme 140, b–d; Schemes 149 and 150).[157,230,233] Silylation of the lithium enolates with trimethylsilyl chloride leads to the corresponding silyl enol ethers (Scheme 140, c),[157,230] which can then be subjected to further reactions.

Methylation of the lithium enolates derived from cyclohexen-2-one and 1,1-bis(methylseleno)ethyllithium takes place[230] regioselectively but requires the use of more than one equivalent of HMPA (5 equiv., 0 °C, 1 h). The product consists[230] quite exclusively of the *trans* stereoisomer (99%) with a trace (1%) of the *cis* (Scheme 140, d and e). The latter can be obtained as a single stereoisomer on hydrolysis of the adduct resulting from the reaction of the same organometallics with 2-methylcyclohexen-2-one

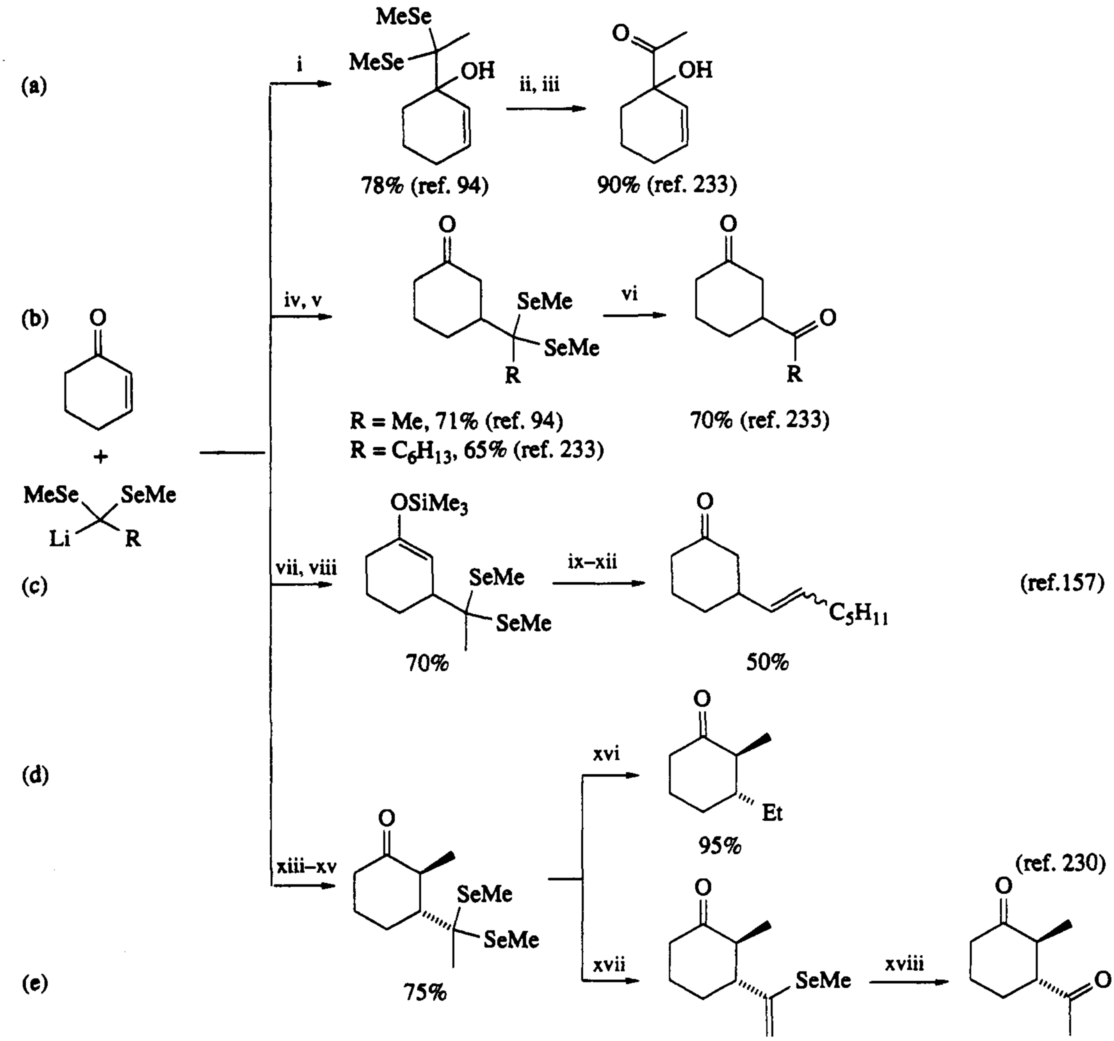

i, ether, –78 °C, 0.2 h; ii, $CuCl_2$–CuO (1:4), aq. acetone, 20 °C; iii, $NaIO_4$, EtOH, 20 °C;
iv, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h; v, $H_3O^+$; vi, $CuCl_2$–CuO (1:4), aq. acetone, 20 °C;
vii, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h; viii, $Me_3SiCl$; ix, $Bu^nLi$, THF, –78 °C; x, $C_5H_{11}CHO$, then $H_3O^+$;
xi, MeLi, 20 °C, then $H_3O^+$; xii, $P_2I_4$, $Et_3N$, $CH_2Cl_2$, 20 °C, xiii, THF–HMPA (1.1 equiv.), –78 °C, 0.2 h;
xiv, MeI (5 equiv.), HMPA (5.5 equiv.), 0 °C, 1 h; xv, $H_3O^+$; xvi, $Bu_3SnH$ (3 equiv.), AIBN (0.1 equiv.),
toluene, 80 °C, 0.3 h; xvii, $CuCl_2$–CuO (1:4), aq. acetone, 20 °C, 0.1 h; xviii, $HgCl_2$, MeCN, 85 °C, 0.3 h

**Scheme 140**

(Scheme 149).[230] Unfortunately, the methylation of the lithium enolate derived from cyclopentenone is less regioselective (Scheme 150).[157]

The reaction between 1,1-bis(methylseleno)-1-propyllithium and other methylcyclohexenones has also been investigated (Scheme 151).[230] No adduct was obtained[230] from 3-methylcyclohexen-2-ones whatever the conditions used (THF–HMPA or DME), whereas γ-keto selenoacetals are produced from 4-, 5- and 6-methyl-2-cyclohexen-2-ones in yields ranging from 58 to 76% when the reactions are carried out in THF–HMPA (Scheme 151). Yields are lowered by 10% when DME is used instead.[230]

Most of the above mentioned derivatives have been reduced[230] by tributyltin hydride to methyl-3-ethylcyclohexanones. These have been produced with a stereochemical control often superior to that observed from the copper chloride catalyzed addition of ethylmagnesium bromide in ether to the same ketones (Scheme 149, b; Scheme 151, a). Reaction of the C-1 and C-3 adducts with copper chloride (1

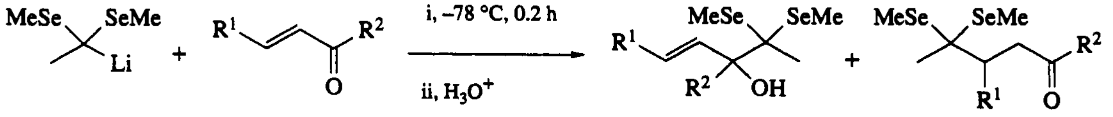
MeSe
SeMe
Li
+
R1
R2
O
i, –78 °C, 0.2 h
ii, H3O+
MeSe
SeMe
R1
R2
OH
+
MeSe
SeMe
R2
R1
O

| | | SM is cyclohexanone | | SM is hexenal | |
|---|---|---|---|---|---|
| | *Conditions*[a] | *Yield (%)* | *Ratio* | *Yield (%)* | *Ratio* |
| (a) | $Et_2O$ | 80 | 98:2 | | |
| (b) | $Et_2O$, HMPA (0.5 equiv.)[b] | 74 | 75:25 | | |
| (c) | $Et_2O$, Kryptofix 2.2.2 | 60 | 28:72 | | |
| (d) | THF | 63 | 73:27 | 74 | 100:0 |
| (e) | THF–HMPA (1:1.1) | 78 | 1:99 | 68 | 28:72 |
| (f) | THF–HMPA (1:4.4) | | | 27 | 18:82 |
| (g) | THF–Kryptofix 2.2.2 | | | | 86:14 |
| (h) | THF–Kryptofix 1.1.1 | | | | 68:32 |
| (i) | THF–$Ph_3PO$ | 68 | 23:77 | | |
| (j) | THF–TPPT[c] | | | 58 | 24:76 |
| (k) | DME | 61 | 13:87 | | 83:17 |
| (l) | DME–HMPA (1:1.1) | | | | 24:76 |

[a] Hexane present in each case. [b] Refers to the additive:organometallic ratio.
[c] TPPT = tripyrrolidinophosphoroimide.

**Scheme 141**[157, 231]

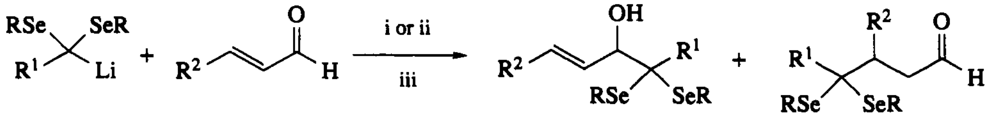
RSe
SeR
R1
Li
+
R2
O
H
i or ii
iii
OH
R2
R1
RSe
SeR
+
R2
O
R1
H
RSe
SeR

| | *R* | *R¹* | *R²* | *Conditions* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|---|---|
| (a) | Me | Me | Pr | i | 74 | 100:0 |
| | Me | Me | Ph | i | 74 | 100:0 |
| (b) | Me | Me | Pr | ii | 63 | 28:72 |
| | Me | Me | Ph | ii | 67 | 57:43 |
| (c) | Ph | H | Pr | ii | 55 | 100:0 |
| (d) | Ph | Me | Pr | ii | 60 | 100:0 |

i, THF, –78 °C, 0.2 h; ii, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h; iii, $NH_4Cl$, –78 °C

**Scheme 142**[118, 157]

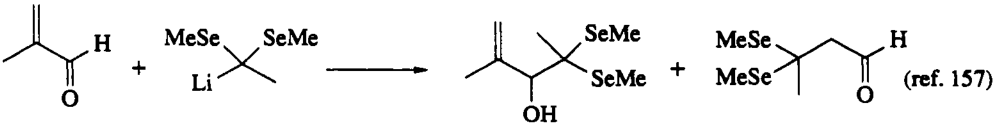
H
O
+
MeSe
SeMe
Li
SeMe
SeMe
OH
+
MeSe
MeSe
H
O
(ref. 157)

| | *Conditions* | *Yield (%)* | *Ratio* |
|---|---|---|---|
| (a) | THF, –78 °C, 0.2 h | 80 | 100:0 |
| (b) | THF, HMPA (1.1 equiv.), –78 °C, 0.2 h | 56 | 25:75 |

**Scheme 143**

equiv.) and copper oxide (4 equiv.) in aqueous acetone (1%) allows the synthesis of the corresponding α-hydroxy-β,γ-unsaturated carbonyl compounds[73,233] or γ-ketocarbonyl compounds.[233] Therefore,

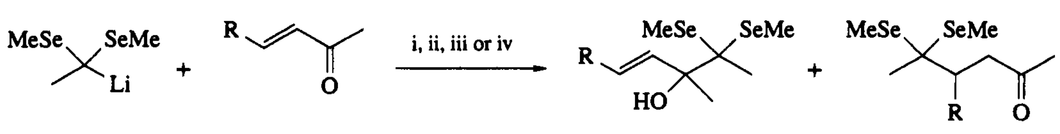

(ref. 157)

| | *R* | *Conditions* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (a) | Me | i | 73 | 100:0 |
| | Pr | i | 81 | 100:0 |
| (b) | Me | ii | 51 | 75:25 |
| | Pr | ii | 54 | 95:5 |
| (c) | Me | iii | 70 | 15:85 |
| | Pr | iii | 60 | 40:60 |
| (d) | Pr | iv | 38 | 35:65 |

i, $Et_2O$, –78 °C, 0.2 h; ii, THF, –78 °C, 0.2 h; iii, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h;
iv, THF, HMPA (2.2 equiv.), –78 °C, 0.2 h

**Scheme 144**

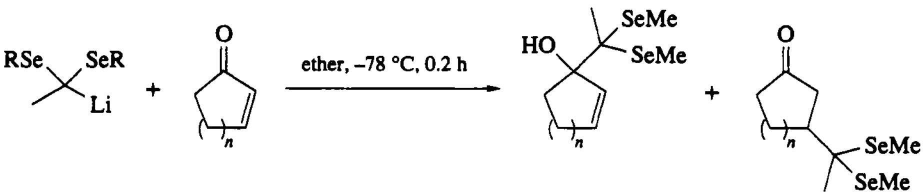

(ref. 94)

| | *R* | *n* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (a) | Me | 1 | 68 | 100:0 |
| (b) | Me | 2 | 78 | 97:3 |
| (c) | Ph | 2 | 71 | 93:7 |

**Scheme 145**

1,1-bis(seleno)alkyl metals play the role of valuable acyl anion equivalents (Scheme 139; Scheme 140, a, b and e; Scheme 149, b).

Regiochemical control of the addition of 1-phenylselenoallyllithium to cyclopentenone has been achieved[83,90] in a manner similar to that mentioned above. In THF alone the C-1 adducts resulting from the attack of the ambident nucleophile at its α- and γ-sites prevail (Scheme 127, a),[83,90] whereas the C-3 adducts resulting from the almost exclusive reaction of the α-selenoallyllithium at its α-site are produced[83,90] if the reaction is performed instead in the presence of HMPA (Scheme 127, b). Therefore, this solvent mixture allows the simultaneous control of the sites of attack of these two ambident species.

### *(iii) Reactivity of enolates derived from α-selenocarbonyl compounds*

Lithium enolates derived from α-seleno esters have a marked tendency to produce the C-3 adduct, and in fact the C-1 adducts are the most difficult to obtain. Representative results are collected in Schemes 152–154.

The best control of addition of these organometallics at the C-1 site of enones is achieved[157,231] by performing the reaction in a less basic solvent, such as ether or THF, at a lower temperature (–110 or –78 °C), and within a shorter time, so that not only the formation of the C-1 adducts is favored, but also there is a lower chance of them isomerizing to the more stable C-3 adducts (Scheme 152, compare f to g; Scheme 153, compare a with b–d; Scheme 154, compare c to a). This control is particularly efficient with cyclohexenone (Scheme 153, a and b)[112,157] and straight chain enones (Scheme 152, e)[112] and particularly poor with cyclopentenone (Scheme 154, a and b).[157] Such control cannot be achieved with chalcone (Scheme 152, a–d).[113]

The formation of the C-3 adduct relies on the fact that the α,β-unsaturated alcoholate, produced, as mentioned above, by attack of the organometallic at the α-site of the α,β-unsaturated carbonyl compound, can rearrange to the enolate resulting from C-3 attack. This isomerization has been more conveniently achieved by raising the temperature to 20 °C (Scheme 153, compare d to b; Scheme 154 compare c to b).[112] It has also been performed by adding HMPA[112] to the medium (Scheme 152, g; Schemes 153 and 154).[157] Otherwise, the C-3 adduct can be obtained directly, and even at –78 °C, by using potassium

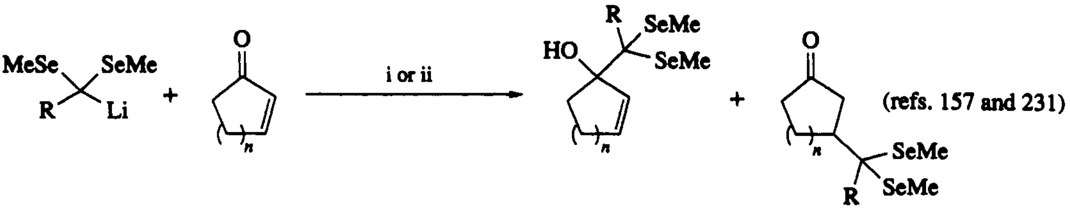

(refs. 157 and 231)

C-1 C-3

|  | *R* | *Conditions* | *n* | *Yield (%)* | *C-1:C-3* |
|---|---|---|---|---|---|
| (a) | H | i | 1 | 55 | 75:25 |
|  | H | i | 2 | 75 | 92:8 |
|  | H | i | 3 | 67 | 87:13 |
| (b) | H | ii | 1 | 75 | 0:100 |
|  | H | ii | 2 | 78 | 0:100 |
|  | H | ii | 3 | 29 | 20:80 |
| (c) | Me | i | 1 | 31 | 70:30 |
|  | Me | i | 2 | 63 | 73:27 |
|  | Me | i | 3 | 50 | 80:20 |
| (d) | Me | ii | 1 | 78 | 0:100 |
|  | Me | ii | 2 | 78 | 0:100 |
|  | Me | ii | 3 | 72 | 11:89 |
| (e) | $C_6H_{13}$ | i | 1 | 22 | 40:60 |
|  | $C_6H_{13}$ | i | 2 | 63 | 100:0 |
| (f) | $C_6H_{13}$ | ii | 1 | 68 | 0:100 |
|  | $C_6H_{13}$ | ii | 2 | 59 | 0:100 |

i, THF, –78 °C, 0.2 h; ii, THF–HMPA (1:1.1), –78 °C, 0.2 h

**Scheme 146**

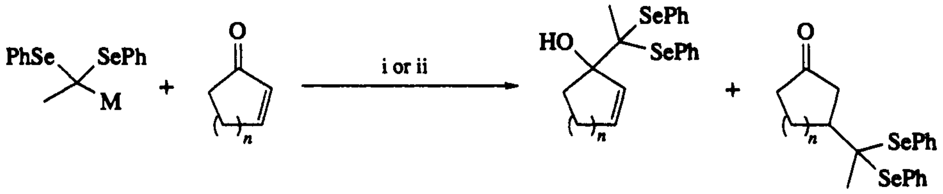

|  | *M* | *Conditions* | *n* | *Yield (%)* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | Li | i | 2 | 56 | 0:100 | 94 |
|  | Li | i | 3 | 80 | 0:100 | 94 |
| (b) | Li | ii | 2 | 94 | 0:100 | 94 |
|  | Li | ii | 3 | 80 | 0:100 | 94 |
| (c) | K | ii | 2 | 76 | 100:0 | 73 |

i, THF, –78 °C, 0.2 h; ii, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h

**Scheme 147**

instead of lithium enolates derived from α-seleno esters (Schemes 152, d; Scheme 153, e and f; Scheme 154, d).

The mechanism of this C(1)–C(3) isomerization has been investigated,[113] starting from the alcohols resulting from the hydrolysis of the C-1 adducts of cyclohexenone. Reaction of these alcohols with bases leads to the alcoholates which then rearrange to the C-3 adducts. This rearrangement takes place[113] almost instantaneously with potassium alcoholates and is substantially less efficient with the lithium analogs (Scheme 155). In the latter case it is faster[113] with phenylseleno than with methylseleno derivatives and with adducts bearing an alkyl group on the carbon next to the ester group (Scheme 155, compare a to b).

Each of the two stereoisomeric C-1 adducts shown in Scheme 156, when subjected to the reactions mentioned above, leads to a different ratio of the C-3 stereoisomers (Scheme 156, a).[113] It was also found

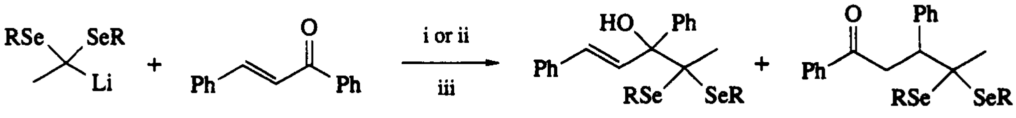
RSe
SeR
Li
+
O
Ph
Ph
i or ii
iii
HO
Ph
Ph
RSe
SeR
+
O
Ph
Ph
RSe
SeR

| | *R* | *Conditions* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (a) | Me | i | 91 | 25:75 |
| | Ph | i | 60 | 55:45 |
| (b) | Me | ii | 77 | 95:5 |
| | Ph | ii | 63 | 98:2 |

(ref. 234)

i, THF, –78 °C, 0.2 h, ii, THF, HMPA (1.1 equiv.), –78 °C, 0.2 h, iii, $H_3O^+$, –78 °C

**Scheme 148**

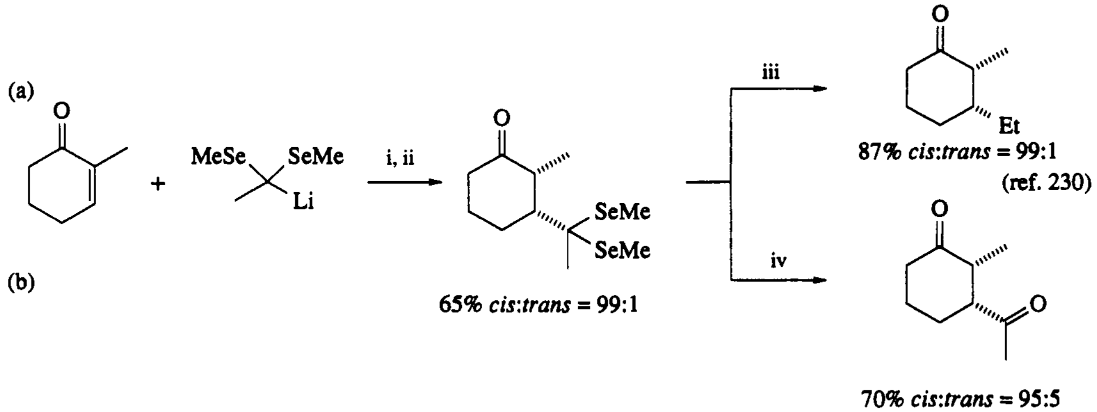
(a)
(b)
O
+
MeSe
SeMe
Li
i, ii
O
SeMe
SeMe
65% cis:trans = 99:1
iii
iv
O
Et
87% cis:trans = 99:1
(ref. 230)
O
O
70% cis:trans = 95:5

i, THF–HMPA, –78 °C, 0.2 h, ii, $H_3O^+$; iii, $Bu_3SnH$ (3 equiv.), AIBN (0.1 equiv.), toluene, 80 °C;
iv, CuCl (1 equiv.), CuO (4 equiv.), aq. acetone, 20 °C, 0.1 h

**Scheme 149**

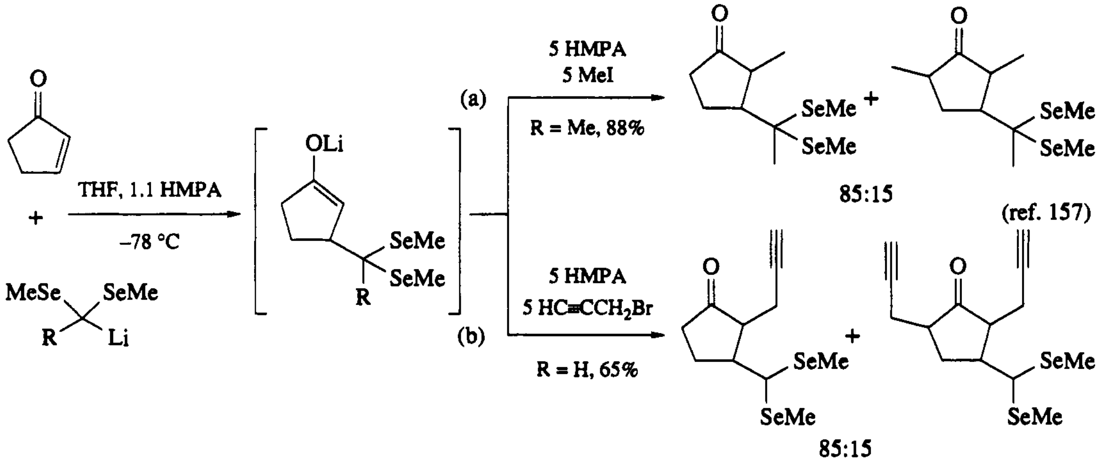
O
+
MeSe
SeMe
R
Li
THF, 1.1 HMPA
–78 °C
OLi
SeMe
SeMe
R
(a)
5 HMPA
5 MeI
R = Me, 88%
(b)
5 HMPA
5 HC≡CCH2Br
R = H, 65%
O
SeMe
SeMe
+
O
SeMe
SeMe
85:15
(ref. 157)
O
SeMe
SeMe
+
O
SeMe
SeMe
85:15

**Scheme 150**

that the C(3)–C(1) isomerization involves the dissociation of the C-1 adduct to cyclohexenone and α-metallo-α-seleno esters.[113] Since the isomerization is performed in the presence of chalcone the ester enolate moiety is transferred to the latter enone (Scheme 156, b).[113]

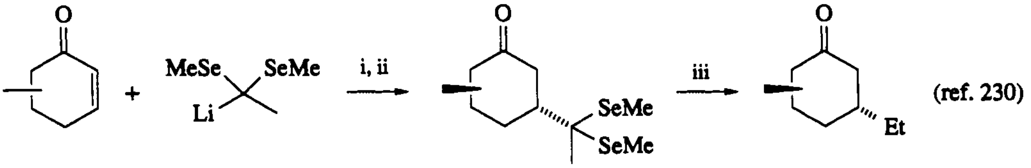

| | | |
|---|---|---|
| 4-Me | 58%, 95:5[a] | 74% |
| 5-Me | 76%, 13:87 | 90% |
| 6-Me | 74%, 32:68 | 85% |

[a] The first number in the ratio refers to the compound shown.

i, THF–HMPA (1:1.1), –78 °C; ii, aq. $NH_4Cl$; iii, $Bu_3SnH$ (3 equiv.), AIBN (0.1 equiv.), toluene, 0.3 h

Scheme 151

### *2.6.3.5.4 Reaction of organometallics bearing an α-seleno carbanion with carboxylic acid derivatives and related compounds*

*(i) Reactions involving α-selenoalkyllithiums and α-selenoxyalkyllithiums*

α-Selenoalkyllithiums have also been reacted with other carbonyl compounds such as esters,[235] acid chlorides,[235,236] carboxylic anhydrides,[235] dimethylformamide[12,162,235,237] and nitriles,[42] as well as chlorocarbonates,[235] carbonic anhydride (Scheme 157, a–d; Scheme 158)[12,77,235] and α,β-unsaturated lactones.[238] In the last case the C-3 adduct, produced when the reaction is performed in THF–HMPA, has been successfully used in an efficient synthesis of pederin (Scheme 159).[238] Finally, it is possible to acylate[98] α-selenoxyalkyllithiums but, except for special cases, yields are unsatisfactory (Scheme 157, e).

*(ii) Reactions involving 1,1-bis(seleno)alkyllithiums*

1,1-Bis(seleno)alkyllithiums exclusively add[232] at the C-1 site of α,β-unsaturated esters in THF (Scheme 160, a).[157] The reaction does not in fact stop at that stage since the organometallic reacts further on the α′,α′-bis(seleno)-α-enone intermediate to give an α-seleno-α-enone and 1,1,1-tris(methylseleno)-

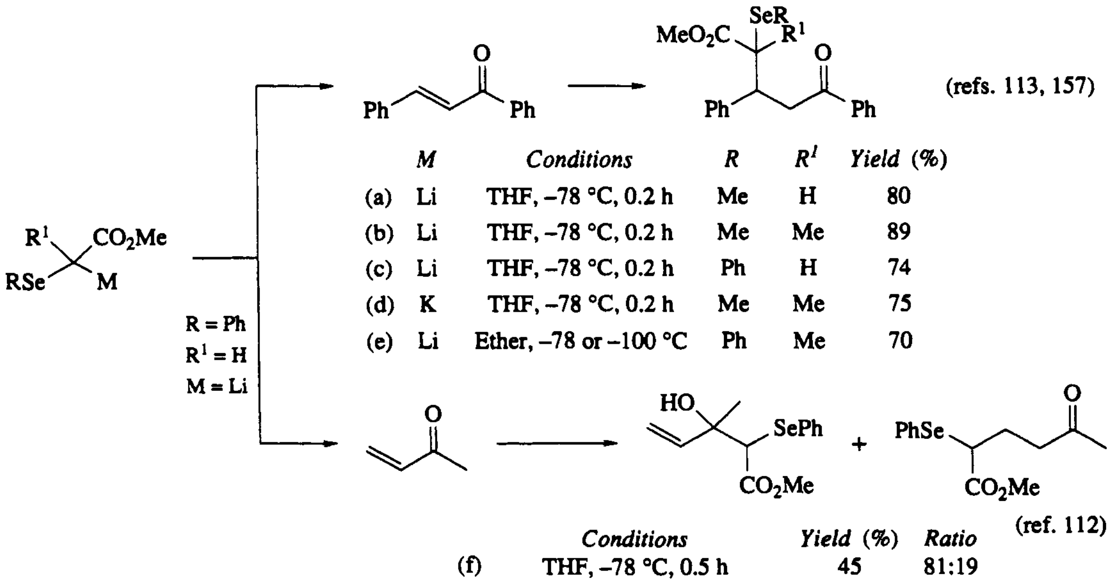

| | M | Conditions | R | $R^1$ | Yield (%) |
|---|---|---|---|---|---|
| (a) | Li | THF, –78 °C, 0.2 h | Me | H | 80 |
| (b) | Li | THF, –78 °C, 0.2 h | Me | Me | 89 |
| (c) | Li | THF, –78 °C, 0.2 h | Ph | H | 74 |
| (d) | K | THF, –78 °C, 0.2 h | Me | Me | 75 |
| (e) | Li | Ether, –78 or –100 °C | Ph | Me | 70 |

| | Conditions | Yield (%) | Ratio |
|---|---|---|---|
| (f) | THF, –78 °C, 0.5 h | 45 | 81:19 |
| (g) | THF–HMPA, –78 °C, 0.5 h | 41 | 15:85 |

Scheme 152

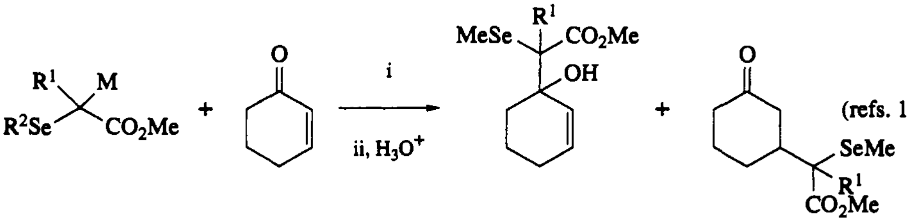

(refs. 112, 157)

| | *M* | *Condition i*[a] | *R* | *R[1]* | *Yield* (%) | *Ratio* |
|---|---|---|---|---|---|---|
| (a) | Li | Ether–hexane (80:20) | Me | Me | 71 | 100:0 |
| | Li | Ether–hexane (80:20) | Ph | Me | 66 | 100:0 |
| (b) | Li | THF–hexane (80:20) | Me | Me | 75 | 85:15 |
| | Li | THF–hexane (80:20) | Ph | Me | 85 | 85:15 |
| (c) | Li | THF–HMPA–hexane (70:7:23) | Me | H | 54 | 60:40 |
| (d) | Li | THF–hexane (80:20), –78 to 20 °C, 1 h | Me | Me | 72 | 0:100 |
| | Li | THF–hexane (80:20), –78 to 20 °C, 1 h | Ph | Me | 70 | 0:100 |
| (e) | Na | THF–pentane (80:20) | Me | Me | 65 | 0:100 |
| | K | THF–pentane (80:20) | Me | Me | 69 | 0:100 |
| (f) | K | Ether–pentane (80:20), –100 °C | Me | Me | 74 | 0:100 |

[a] At –78 °C, 0.2 h unless otherwise stated.

**Scheme 153**

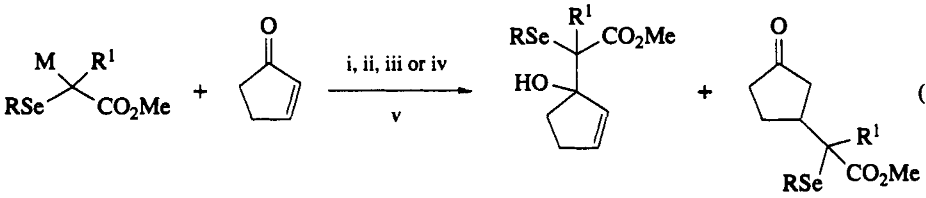

(ref. 157)

| | *Conditions* | *R* | *R[1]* | *Yield* (%) | *Ratio* |
|---|---|---|---|---|---|
| (a) | i | Me | H | 40 | 75:25 |
| | i | Ph | H | 46 | 63:37 |
| (b) | ii | Me | H | 69 | 54:46 |
| | ii | Ph | H | 68 | 41:59 |
| | ii | Me | Me | 73 | 35:65 |
| | ii | Ph | Me | 66 | 0:100 |
| (c) | iii | Me | H | 61 | 0:100 |
| (d) | iv | Ph | H | 68 | 0:100 |

i, M = Li, ether, –78 °C, 0.2 h; ii, M = Li, THF, –78 °C, 0.2 h; iii, M = Li, THF, –78 °C, 0.2 h, then 20 °C, 0.2 h; iv, M = K, THF, –78 °C, 0.2 h; v, $H_3O^+$

**Scheme 154**

alkane after hydrolysis.[157] If the reaction is performed instead in THF–HMPA or in DME, an alkyl γ,γ-(dimethylseleno)alkylcarboxylate, resulting from the addition of the organometallic at the C-3 site of the α,β-unsaturated ester, is produced exclusively (Scheme 160, b).[157]

Otherwise, α-selenoxyalkyllithiums have been reacted with aromatic esters,[97,98] and 1-metallo-1-selenoalkenes efficiently react with acyl bromides,[173] dimethylformamide (Schemes 43 and 101),[122,123,176] chlorocarbonates[176] and carbonic anhydride (Schemes 101 and 103).[65,123,176]

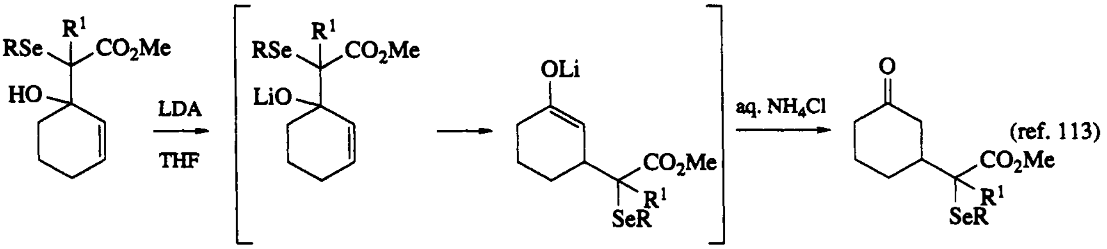
RSe
R1
CO2Me
HO
LDA
THF
RSe
R1
CO2Me
LiO
OLi
CO2Me
R1
SeR
aq. NH4Cl
O
(ref. 113)
CO2Me
R1
SeR

| | *R* | *R¹* | *Temperature* (°C) | *Time* (h)[a] |
|---|---|---|---|---|
| (a) | Ph | H | −25 | 1 |
| (b) | Ph | Me | −60 | 0.2 |
| | Ph | Me | −40 | 0.1 |
| | Ph | Me | −25 | Instantaneous |

[a] Minimum required for complete C(1)–C(3) isomerization.

**Scheme 155**

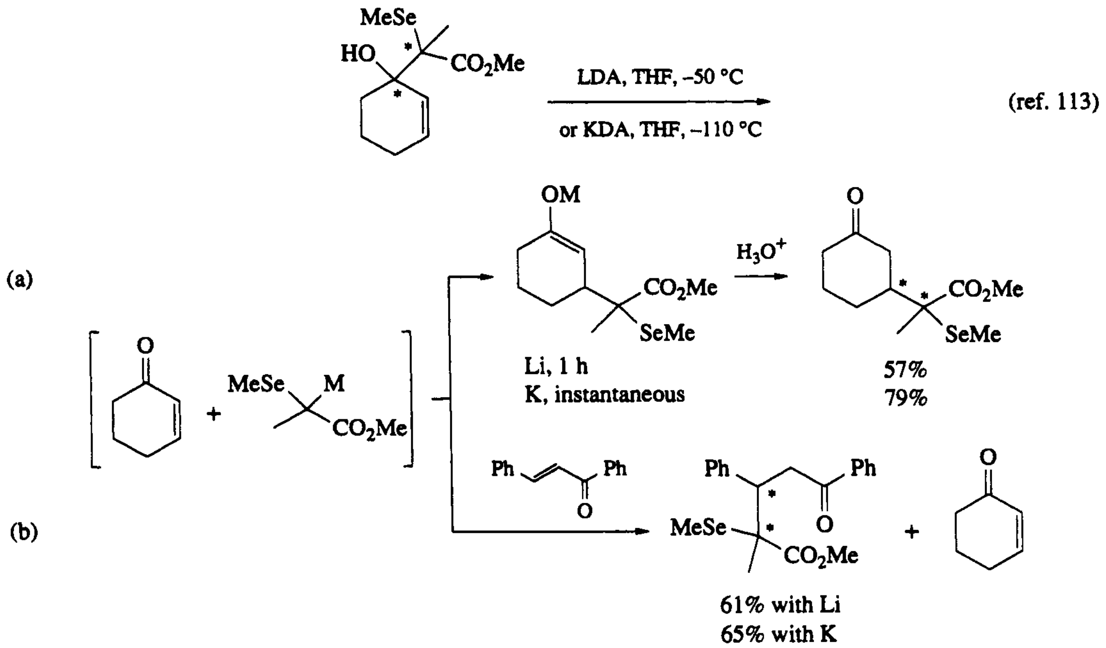
MeSe
HO
CO2Me
LDA, THF, −50 °C
or KDA, THF, −110 °C
(ref. 113)
(a)
(b)
O
MeSe
M
CO2Me
OM
CO2Me
SeMe
Li, 1 h
K, instantaneous
H3O+
O
CO2Me
SeMe
57%
79%
Ph
Ph
O
Ph
Ph
MeSe
O
CO2Me
O
61% with Li
65% with K

**Scheme 156**

## 2.6.4 β-HYDROXYALKYL SELENIDES AS VALUABLE SYNTHETIC INTERMEDIATES

### 2.6.4.1 Generalities

β-Hydroxyalkyl selenides are valuable intermediates for the synthesis of various selenium-free compounds. Although typical reactions of alcohols and selenides can often be achieved on such functionalized derivatives, some other reactions involve at the same time both functionalities. In fact, β-hydroxyalkyl selenides can be viewed as 'super' pinacols, since they possess two very well differentiated functionalities. The oxygen atom is hard and is linked to a hydrogen, whereas the selenium atom is softer and is attached to an alkyl or an aryl group. Typical reactions of β-hydroxyalkyl selenides, including those that are functionalized, are displayed in Schemes 96 and 161–167. β-Hydroxyalkyl selenides have been, amongst other things: (i) oxidized to α-selenocarbonyl compounds, β-hydroxyalkyl selenoxides (precursors of allyl alcohols) and β-hydroxyalkyl selenones (precursors of epoxides or rearranged

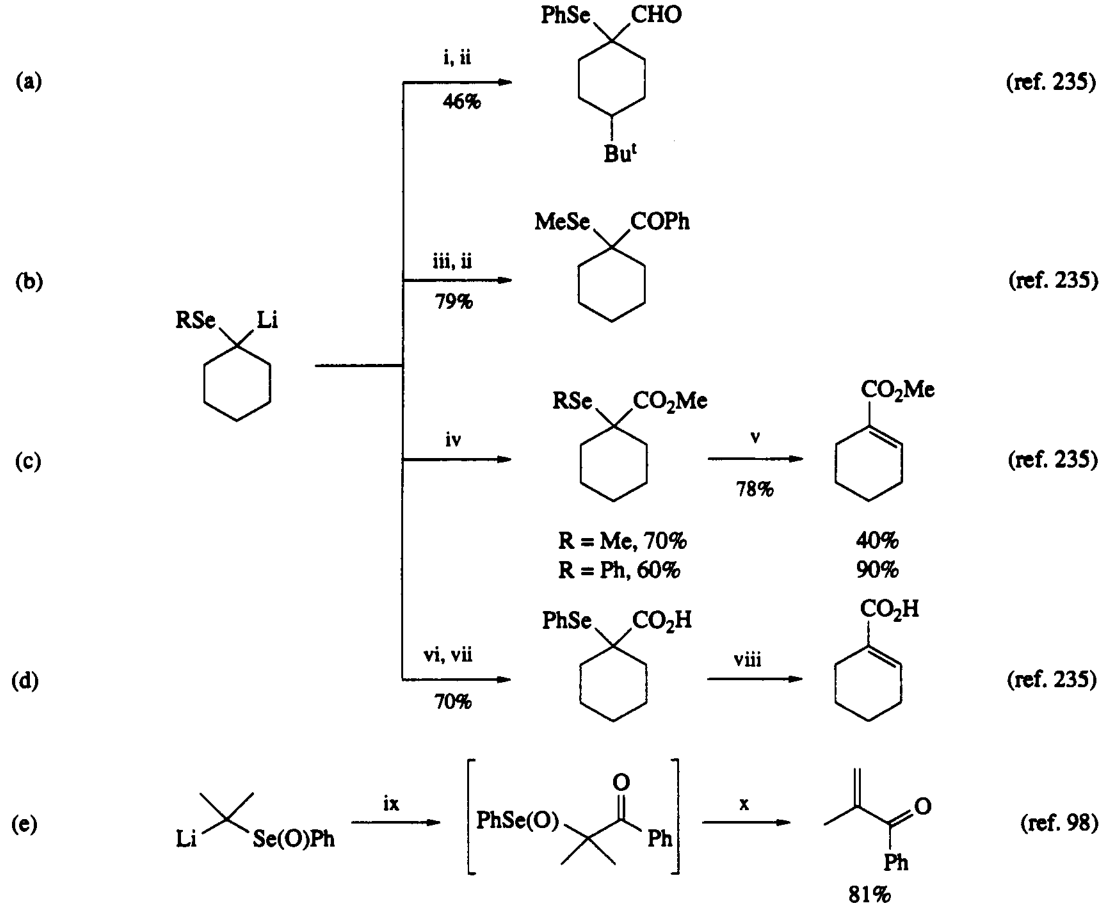
(a)
(b)
(c)
(d)
(e)
RSe
Li
i, ii
46%
PhSe
CHO
Bu$^t$
iii, ii
79%
MeSe
COPh
iv
RSe
CO$_2$Me
v
78%
CO$_2$Me
R = Me, 70%
R = Ph, 60%
40%
90%
vi, vii
70%
PhSe
CO$_2$H
viii
CO$_2$H
Li
Se(O)Ph
ix
PhSe(O)
O
Ph
x
O
Ph
81%
(ref. 235)
(ref. 235)
(ref. 235)
(ref. 235)
(ref. 98)

i, $Me_2NCHO$; ii, $H_3O^+$; iii, PhCOCl; iv, MeOCOCl; v, $H_2O_2$, THF; vi, $CO_2$; vii, $H_3O^+$; viii, $H_2O_2$/THF; ix, $PhCO_2Me$; x, Δ

**Scheme 157**

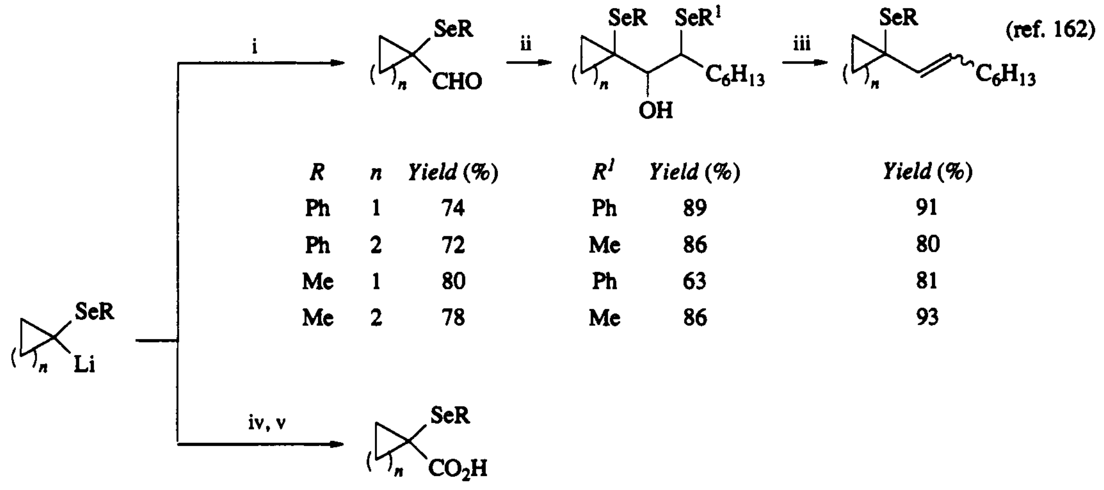
SeR
Li
( )$_n$
i
SeR
CHO
ii
SeR
SeR$^1$
C$_6$H$_{13}$
OH
iii
SeR
C$_6$H$_{13}$
(ref. 162)
iv, v
SeR
CO$_2$H

| *R* | *n* | *Yield* (%) | *R*$^1$ | *Yield* (%) | *Yield* (%) |
|---|---|---|---|---|---|
| Ph | 1 | 74 | Ph | 89 | 91 |
| Ph | 2 | 72 | Me | 86 | 80 |
| Me | 1 | 80 | Ph | 63 | 81 |
| Me | 2 | 78 | Me | 86 | 93 |

*n* = 1, R = Ph, 42% (ref. 97); *n* = 2, R = Ph, 88%; R = Me, 79% (ref. 94)

i, $Me_2NCHO$; ii, $C_6H_{13}CH(SeR^1)Li$; iii, $PI_3/Et_3N$, $CH_2Cl_2$, 20 °C; iv, $CO_2$; v, $H_3O^+$

**Scheme 158** [12,136,162]

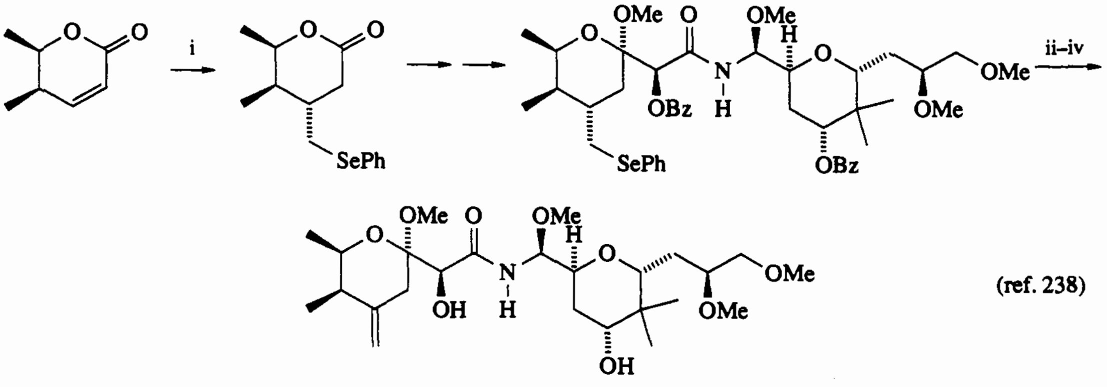

Pederin, 78% overall

i, $PhSeCH_2Li$, THF–HMPA, –85 °C, 1 h; ii, $NaIO_4$, $MeOH–H_2O$, 20 °C; iii, benzene, $Et_3N$, reflux, 0.04 h; iv, LiOH, $MeOH–H_2O$, 50 °C, 5 h

**Scheme 159**

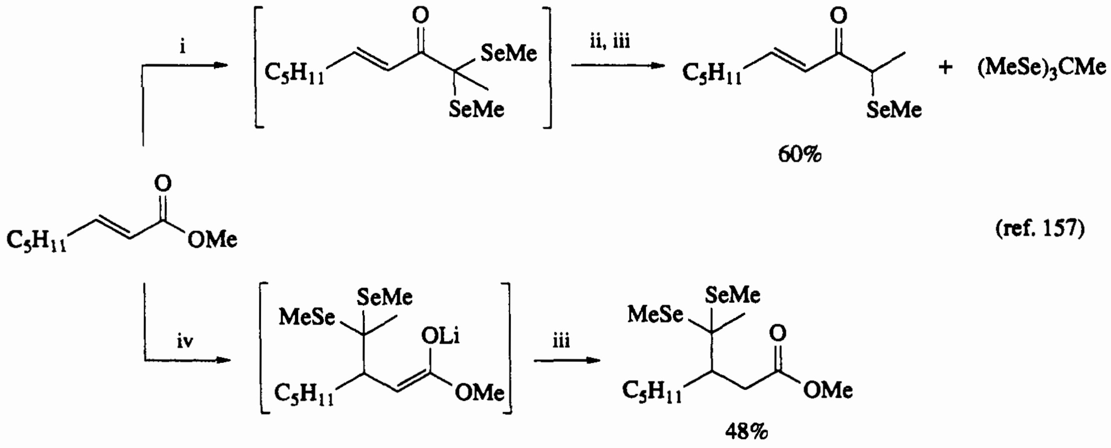

i, $(MeSe)_2C(Me)Li$, THF, –78 °C; ii, $(MeSe)_2C(Me)Li$; iii, $H_3O^+$; iv, $(MeSe)_2C(Me)Li$, THF–HMPA (1:1.1)

**Scheme 160**

ketones); (ii) reduced to alcohols; (iii) transformed to halohydrins, β-haloalkyl selenides, vinyl selenides, alkenes, epoxides and rearranged ketones; and (iv) transformed to β-hydroxyalkylselenonium salts (precursors, *inter alia*, of epoxides).

Although some reactions, such as the transformation of β-hydroxyalkyl selenides to β-haloalkyl selenides (Scheme 161, b)[7] or to vinyl selenides,[7] enones (Scheme 161, f),[7,240] α,α-dihalocyclopropanes (Scheme 162, f)[198] or β-hydroxyalkyl halides (Scheme 161, h; Scheme 162, g),[223,241] have been occasionally described or found only with specific types of β-hydroxyalkyl selenides, especially those having a strained ring [*e.g.* their transformation to allyl selenides (Scheme 163, b),[12,161] 1-selenocyclobutenes (Scheme 163, c)[12,161] and cyclobutanones (Scheme 163, f),[12,159,160,163]] others are far more general. This is particularly the case of their reductions to alcohols (Scheme 161, a; Scheme 162, a; Scheme 163, a; Scheme 164, a; Scheme 165, a)[7,188,189,246] or alkenes (Scheme 161, c; Scheme 162, c; Scheme 163, d; Scheme 164, c; Scheme 165, a; Scheme 166, c),[7,188,189,194,239] their transformation to allyl alcohols (Scheme 161, e; Scheme 162, b; Scheme 164, b; Scheme 166, b),[188,195] epoxides (Scheme 161, g; Scheme 162, d; Scheme 163, e; Scheme 164, d; Scheme 165, b; Scheme 166, d)[7,188,189,206] and rearranged carbonyl compounds (Scheme 162, e; Scheme 164, e; Scheme 165, a, c; Scheme 166, e),[188,198,244] as well as oxidation to α-selenocarbonyl compounds (Scheme 161, d).[240,242,248–251]

### 2.6.4.2 Reduction of β-Hydroxyalkyl Selenides to Alcohols

The reduction of β-hydroxyalkyl selenides to alcohols has been achieved[7,12,188,189,247,254] by lithium in ethylamine (Scheme 161, a; Scheme 162, a; Scheme 163, a; Scheme 167)[246] or triphenyl- or tributyl-tin hydride in toluene,[188,247,254] with or without AIBN. Most of these reactions proceed through radicals. The reactions involving tin hydrides can be carried out thermally around 120 °C[247] or photochemically at much lower temperature (0–20 °C).[148,252] The cleavage of the C—SePh bond is faster[255] than that of the

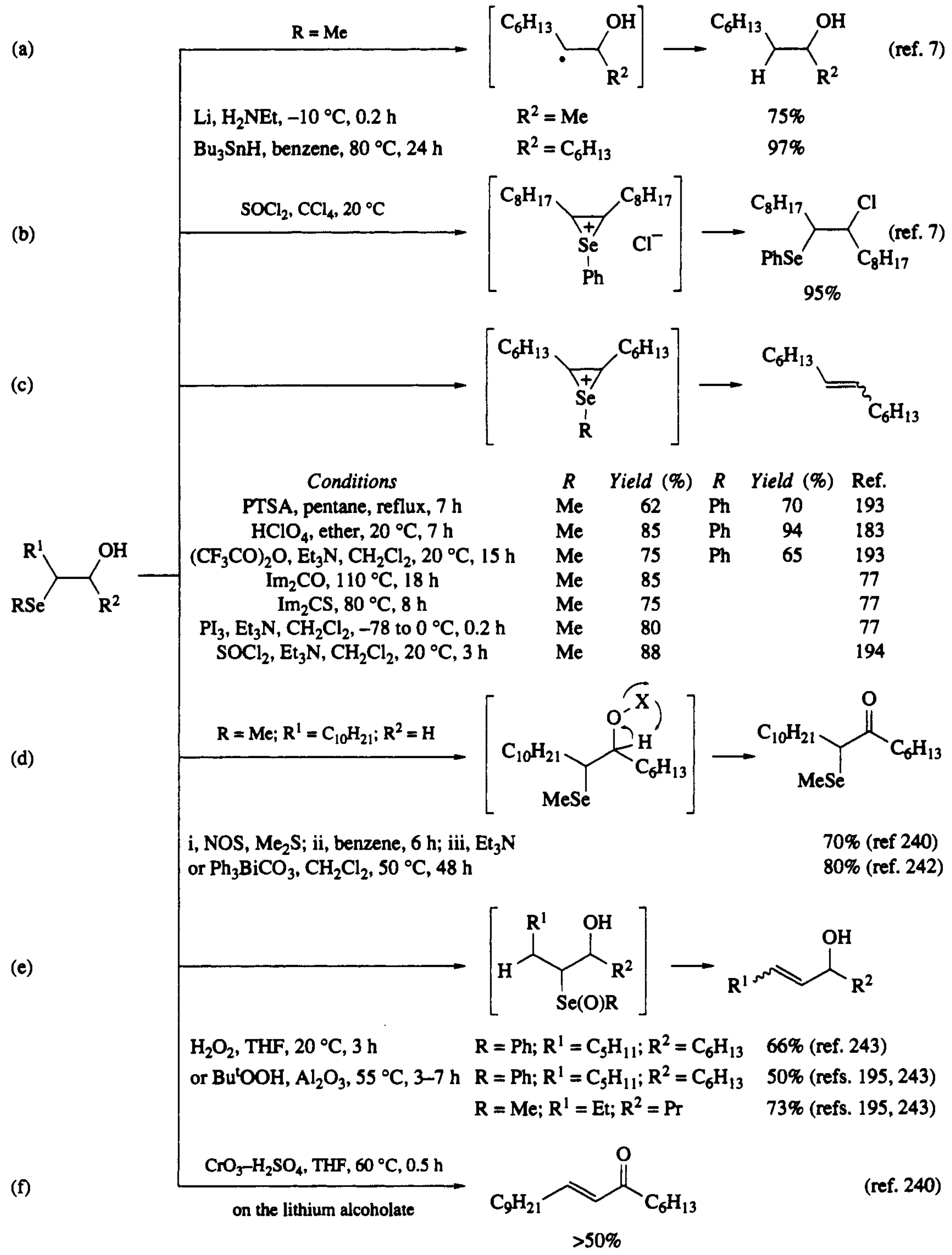
(a)
R = Me
$C_6H_{13}$
OH
$R^2$
H
(ref. 7)
Li, $H_2NEt$, –10 °C, 0.2 h
$Bu_3SnH$, benzene, 80 °C, 24 h
$R^2 = Me$
$R^2 = C_6H_{13}$
75%
97%
(b)
$SOCl_2$, $CCl_4$, 20 °C
$C_8H_{17}$
Se
Ph
$Cl^-$
Cl
PhSe
(ref. 7)
95%
(c)
$C_6H_{13}$
Se
R
$R^1$
OH
RSe
$R^2$
(d)
R = Me; $R^1 = C_{10}H_{21}$; $R^2$ = H
$C_{10}H_{21}$
O
X
H
$C_6H_{13}$
MeSe
i, NOS, $Me_2S$; ii, benzene, 6 h; iii, $Et_3N$
or $Ph_3BiCO_3$, $CH_2Cl_2$, 50 °C, 48 h
70% (ref 240)
80% (ref. 242)
(e)
$R^1$
OH
H
$R^2$
Se(O)R
$H_2O_2$, THF, 20 °C, 3 h
or $Bu^tOOH$, $Al_2O_3$, 55 °C, 3–7 h
R = Ph; $R^1 = C_5H_{11}$; $R^2 = C_6H_{13}$ 66% (ref. 243)
R = Ph; $R^1 = C_5H_{11}$; $R^2 = C_6H_{13}$ 50% (refs. 195, 243)
R = Me; $R^1$ = Et; $R^2$ = Pr 73% (refs. 195, 243)
(f)
$CrO_3$–$H_2SO_4$, THF, 60 °C, 0.5 h
on the lithium alcoholate
$C_9H_{21}$
O
$C_6H_{13}$
(ref. 240)
>50%

| *Conditions* | *R* | *Yield (%)* | *R* | *Yield (%)* | Ref. |
|---|---|---|---|---|---|
| PTSA, pentane, reflux, 7 h | Me | 62 | Ph | 70 | 193 |
| $HClO_4$, ether, 20 °C, 7 h | Me | 85 | Ph | 94 | 183 |
| $(CF_3CO)_2O$, $Et_3N$, $CH_2Cl_2$, 20 °C, 15 h | Me | 75 | Ph | 65 | 193 |
| $Im_2CO$, 110 °C, 18 h | Me | 85 | | | 77 |
| $Im_2CS$, 80 °C, 8 h | Me | 75 | | | 77 |
| $PI_3$, $Et_3N$, $CH_2Cl_2$, –78 to 0 °C, 0.2 h | Me | 80 | | | 77 |
| $SOCl_2$, $Et_3N$, $CH_2Cl_2$, 20 °C, 3 h | Me | 88 | | | 194 |

Scheme 161

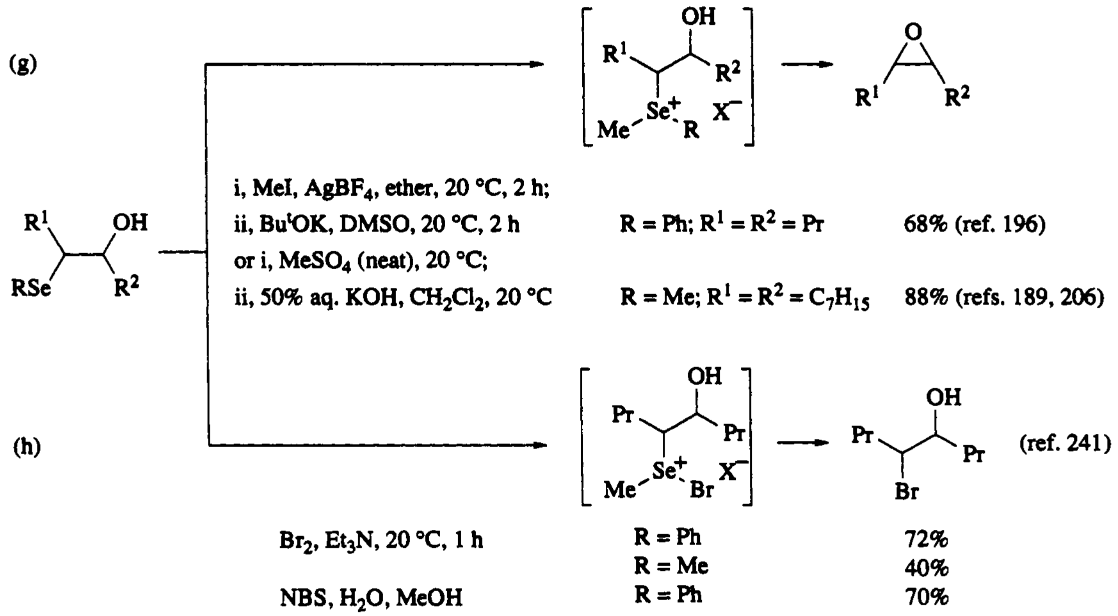

**Scheme 161** *(continued)*

C—SeMe and the C—Cl bonds and often faster than that of the C—Br bond. The reduction is highly chemoselective and leads to alcohols usually in almost quantitative yield (Scheme 161, a; Scheme 164, a; Scheme 168, a and b). In rare cases, however, such as when a carbon–carbon double or triple bond is present in a suitable position, the formation of a five- or six-membered ring takes place by trapping of the radical intermediate (Scheme 118).[203] Tin hydride reduction has been advantageously extended[176] to β-hydroxy-γ-alkenyl and β-hydroxy-α-alkenyl selenides displayed in Scheme 166 (a) and Scheme 168 (a and b) and derived from α-selenoalkyllithiums and enenones, and from 1-seleno-1-alkenyl metals and carbonyl compounds, respectively.

### 2.6.4.3 Reductive Elimination of β-Hydroxyalkyl Selenides to Alkenes

β-Hydroxyalkyl selenides are valuable precursors of alkenes. This reduction reaction, the mechanism of which is tentatively presented in Scheme 169, is observed[194] when the hydroxy group is transformed to a better leaving group and occurs by formal *anti* elimination of the hydroxy and selenyl moieties. It takes advantage of: (i) the difference in reactivity between the hard oxygen and the soft selenium atom which allows the selective activation of the hydroxy group when a hard electrophile is used; (ii) the high propensity of the selenium atom to favor the substitution of the oxygen-containing moiety by participation, thus allowing the intermediate formation of a seleniranium ion; and (iii) the attack of an exogeneous nucleophile on the charged selenium atom of the seleniranium ion which finally leads to the alkene.

This reaction has been performed on various β-hydroxyalkyl selenides bearing a phenylseleno (Scheme 21, b; Scheme 33, a; Schemes 38, 39, 53 and 128; Scheme 136, b and c; Scheme 161, c; Scheme 170),[16,56,74,82,85,97,136,194,236,256] *p*-chlorophenylseleno (Scheme 170),[74] (*m*-trifluoromethyl)phenylseleno (Scheme 21, a and c; Scheme 128)[56,65] or a methylseleno moiety (Scheme 31, c; Scheme 96, c; Scheme 98, b–d; Schemes 125 and 131; Scheme 132, b; Scheme 140, c; Scheme 161, c; Scheme 162, c; Scheme 163, d; Scheme 164, c; Scheme 165, a; Scheme 166, c; Scheme 168, c; Schemes 169 and 170),[7,12,77,108,136,159,162,189,193,194,221,222,236] with different reagents able to react selectively on the hydroxy group, such as perchloric or *p*-toluenesulfonic acids[193] in pentane or ether, as well as mesyl chloride,[56,65,97,166,192,202,257] thionyl chloride,[108,194,207,236,258] trifluoroacetic anhydride,[193] phosphorus oxychloride,[74,112,171,239] or diphosphorus tetraiodide[108,188,245] or phosphorus triiodide[108,136,159,162,188,189,245,259] in the presence of an amine or trimethylsilyl chloride and sodium iodide in acetonitrile.[260] The reactions usually proceed at room temperature with the above reagents (Scheme 158, a and b; Scheme 161, c; Scheme 162, c; Scheme 163, d; Scheme 164, c), but require heating to 50 °C or to 110 °C when *p*-toluenesulfonic acid (Scheme 128; Scheme 161, c; Scheme 165, a)[82,193,236] or carbonyl or thiocarbonyl diimidazole (Scheme 161, c; Scheme 163, d),[7,77,159] respectively, is used.

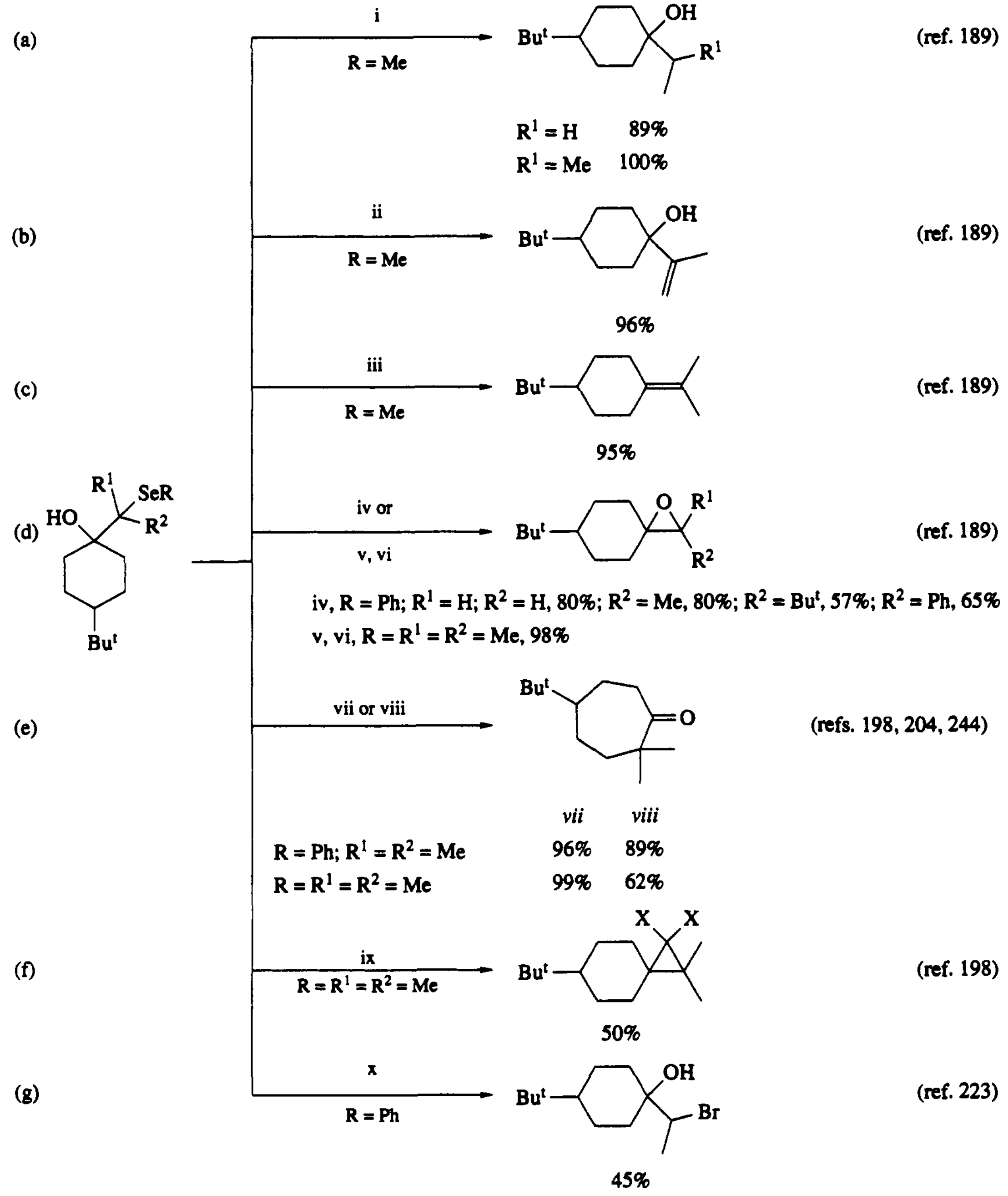
(a)
i
R = Me
Bu$^t$
OH
R$^1$
R$^1$ = H 89%
R$^1$ = Me 100%
(ref. 189)
(b)
ii
R = Me
96%
(ref. 189)
(c)
iii
R = Me
95%
(ref. 189)
(d)
HO
R$^1$
SeR
R$^2$
iv or
v, vi
O
iv, R = Ph; R$^1$ = H; R$^2$ = H, 80%; R$^2$ = Me, 80%; R$^2$ = Bu$^t$, 57%; R$^2$ = Ph, 65%
v, vi, R = R$^1$ = R$^2$ = Me, 98%
(ref. 189)
(e)
vii or viii
(refs. 198, 204, 244)
vii viii
R = Ph; R$^1$ = R$^2$ = Me 96% 89%
R = R$^1$ = R$^2$ = Me 99% 62%
(f)
ix
R = R$^1$ = R$^2$ = Me
X X
50%
(ref. 198)
(g)
x
R = Ph
Br
45%
(ref. 223)

i, Li, $EtNH_2$, –10 °C; ii, Bu$^t$OOH, $Al_2O_3$, THF, 55 °C; iii, $PI_3$, $Et_3N$, $CH_2Cl_2$, 20 °C; iv, TlOEt (5.5 equiv.), $CHCl_3$, 20 °C, 20 h; v, $MeSO_3F$, ether; vi, 10% aq. KOH, ether; vii, TlOEt (5.5 equiv.), $CHCl_3$, 20 °C, 8 h; viii, $AgBF_4$ (1.3 equiv.), $CHCl_3$; ix, Bu$^t$OK (10 equiv.), $CHCl_3$; x, TlOEt (5.5 equiv.), $CHBr_3$, 20 °C

**Scheme 162**

Except in rare cases which will be discussed below, all these methods work equally well and allow the synthesis of almost all of the different types of alkene such as terminal, α,α- and α,β-disubstituted, tri- and tetra-substituted, including alkylidenecyclobutanes[77,136] and alkylidenecyclohexanes (Scheme 162, c),[39,77,159,189,192,202] especially those that are particularly hindered, as depicted in Scheme 164.[159,188] Specific examples are gathered in: Scheme 53; Scheme 125; Scheme 140, c; Scheme 158, a and b; Scheme 161, c; Scheme 162, c; Scheme 163, d; Scheme 164, c; Scheme 165, a; Scheme 166, c; Scheme 170 and Scheme 171.

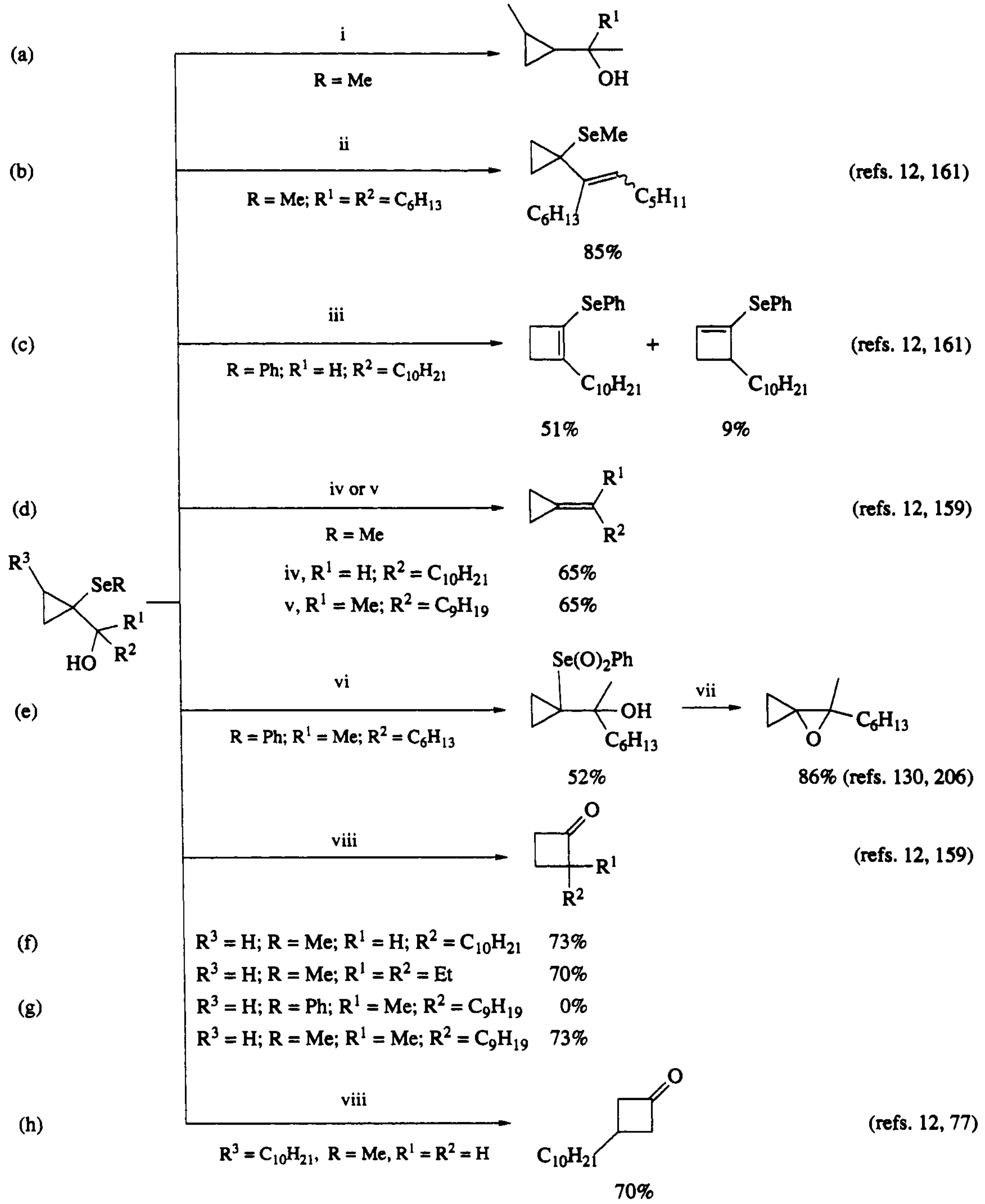
(a)
i
R = Me
R1
OH
(b)
ii
R = Me; R1 = R2 = C6H13
SeMe
C6H13
C5H11
85%
(refs. 12, 161)
(c)
iii
R = Ph; R1 = H; R2 = C10H21
SePh
C10H21
+
SePh
C10H21
51%
9%
(refs. 12, 161)
(d)
iv or v
R = Me
iv, R1 = H; R2 = C10H21
v, R1 = Me; R2 = C9H19
R1
R2
65%
65%
(refs. 12, 159)
R3
SeR
R1
HO
R2
(e)
vi
R = Ph; R1 = Me; R2 = C6H13
Se(O)2Ph
OH
C6H13
52%
vii
O
C6H13
86% (refs. 130, 206)
viii
O
R1
R2
(refs. 12, 159)
(f)
R3 = H; R = Me; R1 = H; R2 = C10H21 73%
R3 = H; R = Me; R1 = R2 = Et 70%
(g)
R3 = H; R = Ph; R1 = Me; R2 = C9H19 0%
R3 = H; R = Me; R1 = Me; R2 = C9H19 73%
(h)
viii
R3 = C10H21, R = Me, R1 = R2 = H
O
C10H21
70%
(refs. 12, 77)

i, Li, $NH_3$; ii, $MeO_2CNSO_2$, $Et_3N$, toluene, 110 °C; iii, $MeO_2CNSO_2$, $Et_3N$; iv, $Im_2CO$, toluene, 110 °C; v, $PI_3$, $Et_3N$, $CH_2Cl_2$, 20 °C; vi, MCPBA (22 equiv.), $CH_2Cl_2$, 20 °C, 36 h; vii, Bu$^t$OK, THF, 20 °C, 2 h; viii, TsOH, $C_6H_6$, $H_2O$, 80 °C

**Scheme 163**

The reactions are usually easier with methylseleno[199] than with phenylseleno,[39,199] *p*-chlorophenylseleno[74] or (*p*-trifluoromethyl)phenylseleno[39,56] derivatives, and allenes[176] and alkylidenecyclopropanes[159] are much more difficult to synthesize than other alkenic compounds. Thus, although allyl selenides resulting from selective elimination of the hydroxy and the methylseleno moiety are usually produced from β-(methylseleno)-β′-(phenylseleno) alcohols,[77,162,199] in the case of 1-seleno-1-(1′-hydroxy-2′-seleno)-

cyclopropanes the elimination takes place away from the cyclopropane ring and exclusively leads to 1-seleno-1-vinylcyclopropanes, and not to alkylidenecyclopropanes, whatever the nature of the seleno moiety (Scheme 125; Scheme 158, a and b).

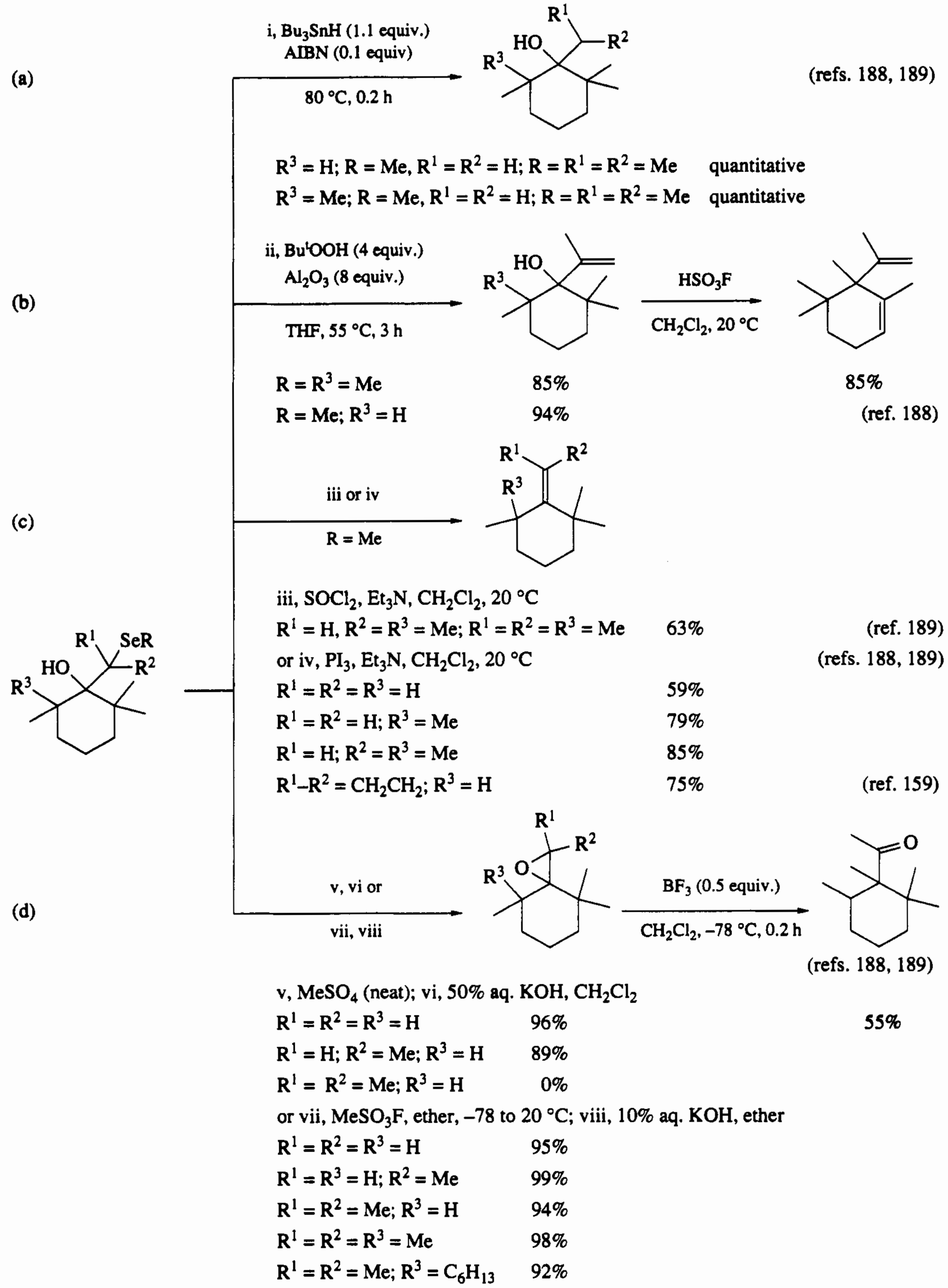
(a)
i, $Bu_3SnH$ (1.1 equiv.)
AIBN (0.1 equiv)
80 °C, 0.2 h
$R^1$
HO
$R^2$
$R^3$
(b)
ii, $Bu^tOOH$ (4 equiv.)
$Al_2O_3$ (8 equiv.)
THF, 55 °C, 3 h
HO
$R^3$
$HSO_3F$
$CH_2Cl_2$, 20 °C
(c)
iii or iv
R = Me
$R^1$
$R^2$
$R^3$
$R^1$
SeR
HO
$R^2$
$R^3$
(d)
v, vi or
vii, viii
$R^1$
$R^2$
$R^3$
O
$BF_3$ (0.5 equiv.)
$CH_2Cl_2$, −78 °C, 0.2 h
O

(refs. 188, 189)

$R^3$ = H; R = Me, $R^1$ = $R^2$ = H; R = $R^1$ = $R^2$ = Me quantitative
$R^3$ = Me; R = Me, $R^1$ = $R^2$ = H; R = $R^1$ = $R^2$ = Me quantitative

R = $R^3$ = Me 85% 85%
R = Me; $R^3$ = H 94% (ref. 188)

iii, $SOCl_2$, $Et_3N$, $CH_2Cl_2$, 20 °C
$R^1$ = H, $R^2$ = $R^3$ = Me; $R^1$ = $R^2$ = $R^3$ = Me 63% (ref. 189)
or iv, $PI_3$, $Et_3N$, $CH_2Cl_2$, 20 °C (refs. 188, 189)
$R^1$ = $R^2$ = $R^3$ = H 59%
$R^1$ = $R^2$ = H; $R^3$ = Me 79%
$R^1$ = H; $R^2$ = $R^3$ = Me 85%
$R^1$–$R^2$ = $CH_2CH_2$; $R^3$ = H 75% (ref. 159)

(refs. 188, 189)

v, $MeSO_4$ (neat); vi, 50% aq. KOH, $CH_2Cl_2$
$R^1$ = $R^2$ = $R^3$ = H 96% 55%
$R^1$ = H; $R^2$ = Me; $R^3$ = H 89%
$R^1$ = $R^2$ = Me; $R^3$ = H 0%
or vii, $MeSO_3F$, ether, −78 to 20 °C; viii, 10% aq. KOH, ether
$R^1$ = $R^2$ = $R^3$ = H 95%
$R^1$ = $R^3$ = H; $R^2$ = Me 99%
$R^1$ = $R^2$ = Me; $R^3$ = H 94%
$R^1$ = $R^2$ = $R^3$ = Me 98%
$R^1$ = $R^2$ = Me; $R^3$ = $C_6H_{13}$ 92%

**Scheme 164**

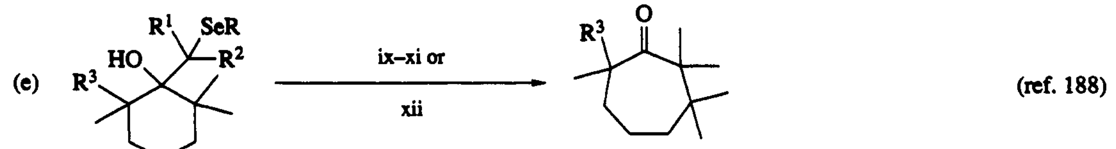

ix, $MeSO_3F$, ether; x, MeMgBr; xi, $CH_2Cl_2$, 50 °C $R^3$ = Me, 95%
or xii, $MeSO_3F$, $CH_2Cl_2$, 20 °C $R^3$ = H, 95%

**Scheme 164** *(continued)*

Acidic conditions are,[193,194] in most cases, as good as others but they have,[166,194] at least in the case of β-hydroxyalkyl selenides bearing two alkyl substituents at the selenium-bearing carbon, a tendency to produce rearranged compounds besides the expected alkenes (Scheme 165, a). These become the exclusive compounds obtained[12,159,160] when 1-seleno-1-(1′-hydroxyalkyl)cyclopropanes are involved (Schemes 132, a; Scheme 163, f–h). This behavior is general for almost all cyclopropylcarbinols bearing a heterosubstituent (*e.g.* OR, $NR_2$, SR, SeR) at that position on the cyclopropane ring (see Section 2.6.4.5.3).[12]

In general, the best combination, at least in our hands, involves phosphorus triiodide or diphosphorus tetraiodide and β-hydroxyalkyl methyl selenides. These conditions allow the high yield synthesis of: (i) highly hindered alkenes[188,189] derived from, for example, bulky selenoalkyllithiums such as those bearing two alkyl groups on the carbanionic center, and particularly hindered 2,2,6-trimethylcyclohexanone, 2,2,6,6-tetramethylcyclohexanone (Scheme 164) and di-*t*-butyl ketone; (ii) highly strained and hindered alkylidenecyclopropanes[12,159] derived from 1-methylselenocyclopropyllithium and ketones including 2,2,6-trimethylcyclohexanone (Scheme 163, d); and (iii) allenes from β-hydroxyalkenyl methyl selenides derived from 1-seleno-1-alkenyllithiums (Scheme 167, c).[176]

These successful conditions take advantage of (i) the high affinity of trivalent phosphorus for oxygen; (ii) the ease with which a methylseleno moiety (compared to phenylseleno) is able to participate in order

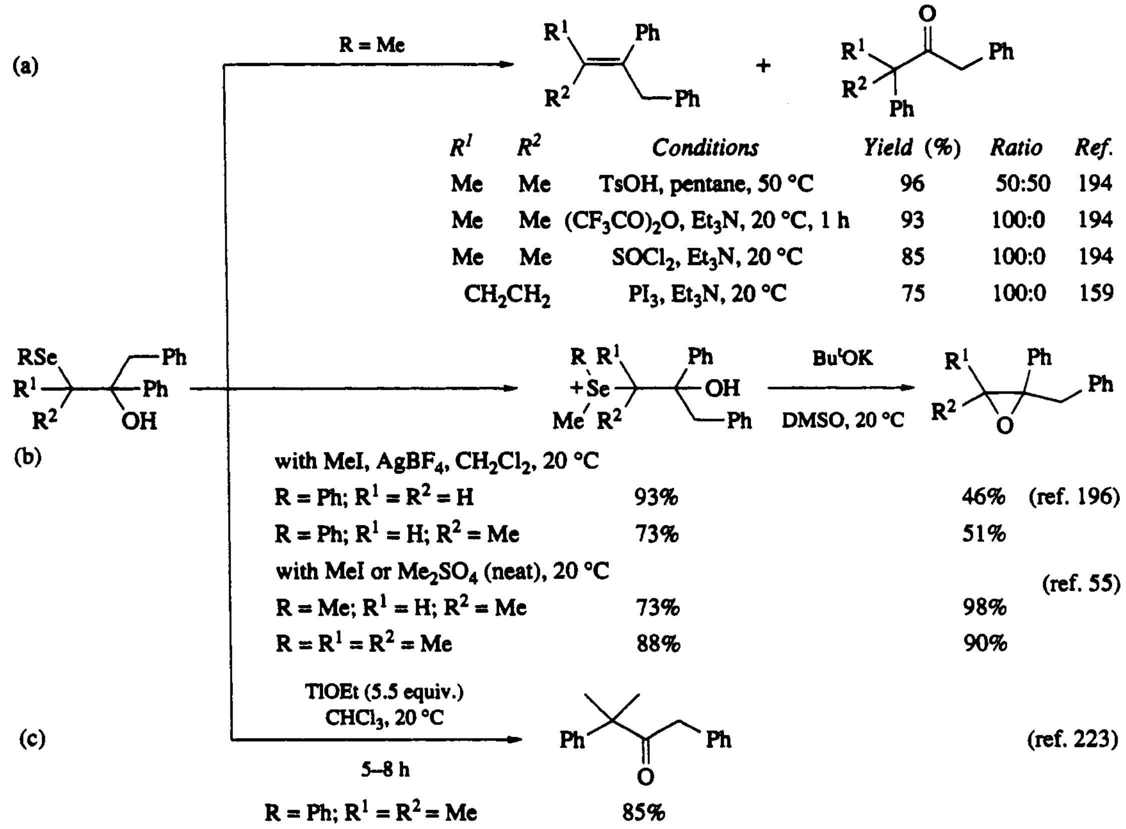

| *R¹* | *R²* | *Conditions* | *Yield (%)* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|
| Me | Me | TsOH, pentane, 50 °C | 96 | 50:50 | 194 |
| Me | Me | $(CF_3CO)_2O$, $Et_3N$, 20 °C, 1 h | 93 | 100:0 | 194 |
| Me | Me | $SOCl_2$, $Et_3N$, 20 °C | 85 | 100:0 | 194 |
| $CH_2CH_2$ | | $PI_3$, $Et_3N$, 20 °C | 75 | 100:0 | 159 |

with MeI, $AgBF_4$, $CH_2Cl_2$, 20 °C

| | | | |
|---|---|---|---|
| R = Ph; $R^1 = R^2$ = H | 93% | 46% | (ref. 196) |
| R = Ph; $R^1$ = H; $R^2$ = Me | 73% | 51% | |

with MeI or $Me_2SO_4$ (neat), 20 °C

| | | | |
|---|---|---|---|
| R = Me; $R^1$ = H; $R^2$ = Me | 73% | 98% | (ref. 55) |
| R = $R^1 = R^2$ = Me | 88% | 90% | |

R = Ph; $R^1 = R^2$ = Me 85% (ref. 223)

**Scheme 165**

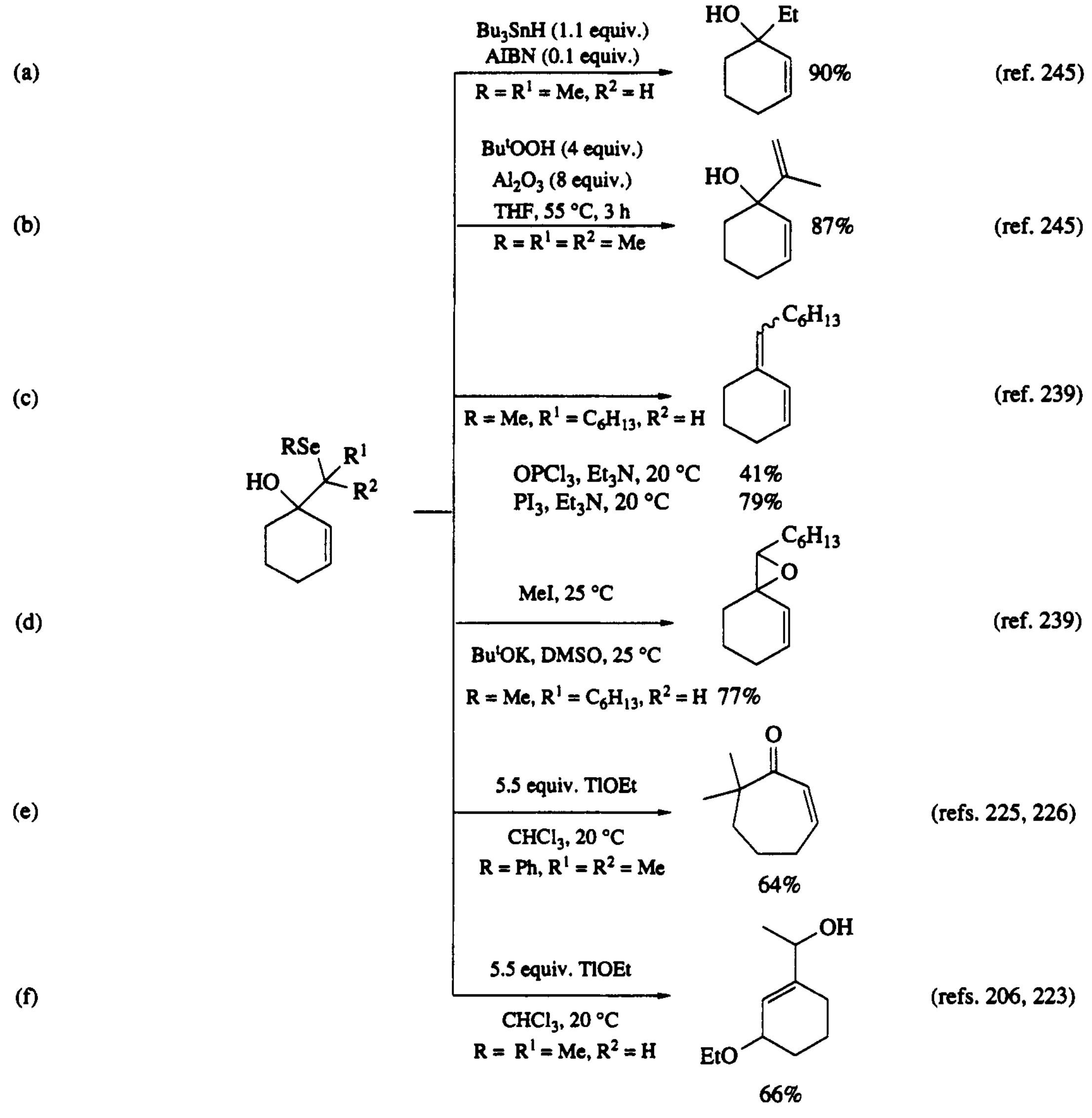
(a)
(b)
(c)
(d)
(e)
(f)
RSe
R1
HO
R2
Bu3SnH (1.1 equiv.)
AIBN (0.1 equiv.)
R = R1 = Me, R2 = H
HO
Et
90%
(ref. 245)
ButOOH (4 equiv.)
Al2O3 (8 equiv.)
THF, 55 °C, 3 h
R = R1 = R2 = Me
HO
87%
(ref. 245)
C6H13
R = Me, R1 = C6H13, R2 = H
OPCl3, Et3N, 20 °C 41%
PI3, Et3N, 20 °C 79%
(ref. 239)
C6H13
O
MeI, 25 °C
ButOK, DMSO, 25 °C
R = Me, R1 = C6H13, R2 = H 77%
(ref. 239)
O
5.5 equiv. TlOEt
CHCl3, 20 °C
R = Ph, R1 = R2 = Me
64%
(refs. 225, 226)
OH
5.5 equiv. TlOEt
CHCl3, 20 °C
R = R1 = Me, R2 = H
EtO
66%
(refs. 206, 223)

**Scheme 166**

to expel the activated oxygen-containing group; and (iii) the softness of the iodide counterion which favors its reaction on the selenium atom rather than on the carbon atom of the intermediate seleniranium ion (see, for example, Scheme 169).

The reductive elimination reported above allows[56,74,171,193,194,222,236,259] the stereoselective synthesis of each of the two stereoisomers of several alkenes, including those that are disubstituted, trisubstituted and functionalized, from each of the two stereoisomers of β-hydroxyalkyl selenides (Schemes 170–172).

The reductive elimination has been successfully applied to the synthesis of various functionalized alkenes such as: (i) dienes, including α,ω-dienes (Scheme 11)[60,245] and 1,3-dienes (Schemes 128 and 131; Scheme 132, d; Scheme 136, b and c; Scheme 166)[7,56,82,97,194,221,222,239] at the exclusion of allylidenecyclopropanes (Scheme 132, a);[224] (ii) vinyl ethers (Scheme 21, a; Scheme 97);[56] (iii) vinylsilanes (Scheme 96);[171] (iv) vinyl selenides (Scheme 21, b and c; Scheme 98, b–d)[56,65,108] and 1,3-dienyl selenides (Scheme 33, a);[85] (v) ketene selenoacetals (Scheme 31, c);[108] (vi) allyl sulfides;[77,199] (vi) allylsilanes;[12,199,202] (vii) allyl selenides (Scheme 125; Scheme 158, a and b);[12,77,162,199] and (viii) α,β-unsaturated esters (Schemes 39 and 170)[56,74] and lactones (Scheme 38).[74]

Particularly interesting results have been observed from β-hydroxy-α-trimethylsilylalkyl selenides since vinylsilanes are exclusively produced[171] under conditions where both the selenyl and the silyl moieties are removed with the hydroxy moiety. Apparently the selenyl moiety seems to stabilize a β-carbenium ion to a better extent than a silyl group.

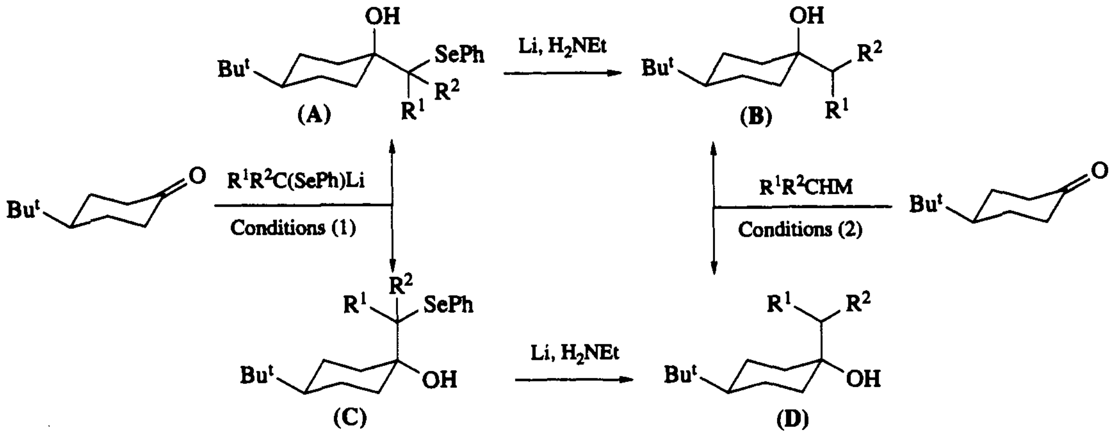
OH
SePh
Bu^t
R^2
R^1
(A)
Li, H2NEt
(B)
O
R^1R^2C(SePh)Li
Conditions (1)
R^1R^2CHM
Conditions (2)
(C)
(D)
OH

| $R^1$ | $R^2$ | *Conditions (1)* | *Yield (%)* [a] | *Yield (%)* [b] | *Conditions (2)* | *Yield (%)* [c] |
|---|---|---|---|---|---|---|
| H | H | THF, −78 °C, 1 h | 68, 85:15 | 93, 85:15 | MeMgI, ether | 95, 56:44 |
| | | | | | MeLi, ether | —, 68:12 |
| H | Me | Ether, −78 °C, 2 h | 78, 100:0 | 89, 100:0 | EtMgBr, ether | 80, 68:12 |
| Me | Me | Ether, −78 °C, 2 h | 75, 100:0 | 92, 100:0 | $Pr^iMgBr$, ether | 47, 83:17 |
| | | | | | $Bu^tMgCl$ | 22, 100:0 |

[a] Yield is (A) + (C), ratio is (A):(C). [b] Yield is (B) + (D), ratio is (B):(D), from reactions (A) to (B) and (C) to (D). [c] Yield is (B) + (D), ratio (B):(D).

**Scheme 167** [210]

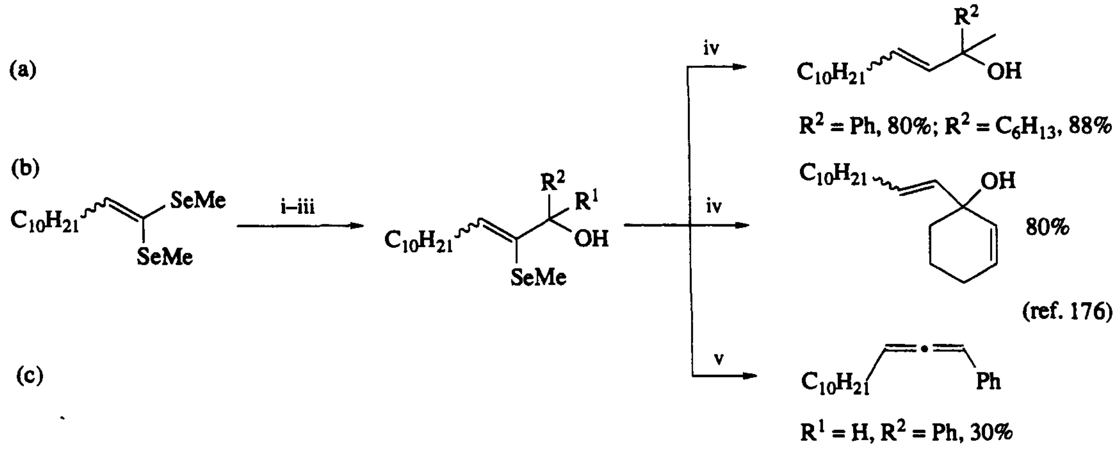
(a)
(b)
(c)
C10H21
SeMe
SeMe
i–iii
R^2
R^1
OH
SeMe
iv
iv
v
R^2 = Ph, 80%; R^2 = C6H13, 88%
80%
(ref. 176)
Ph
R^1 = H, R^2 = Ph, 30%

i, $Bu^nLi$, THF; ii, $R^1R^2CO$; iii, $H_3O^+$; iv, $Bu_3SnH$, AIBN, toluene, 110 °C, 3 h; v, $P_2I_4$, $Et_3N$, 20 °C, 1.5 h

**Scheme 168**

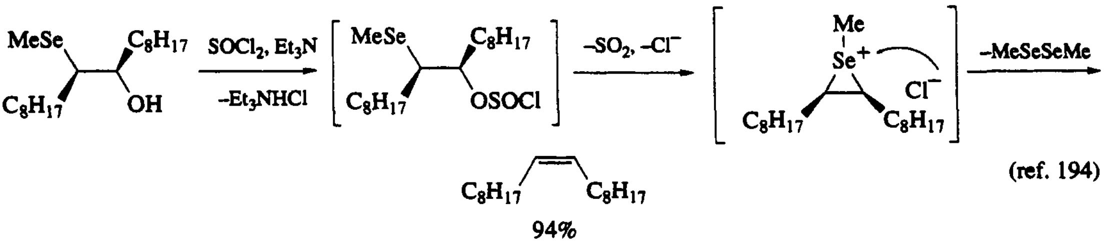
MeSe
C8H17
OH
SOCl2, Et3N
−Et3NHCl
OSOCl
−SO2, −Cl^−
Me
Se+
Cl^−
−MeSeSeMe
(ref. 194)
94%

**Scheme 169**

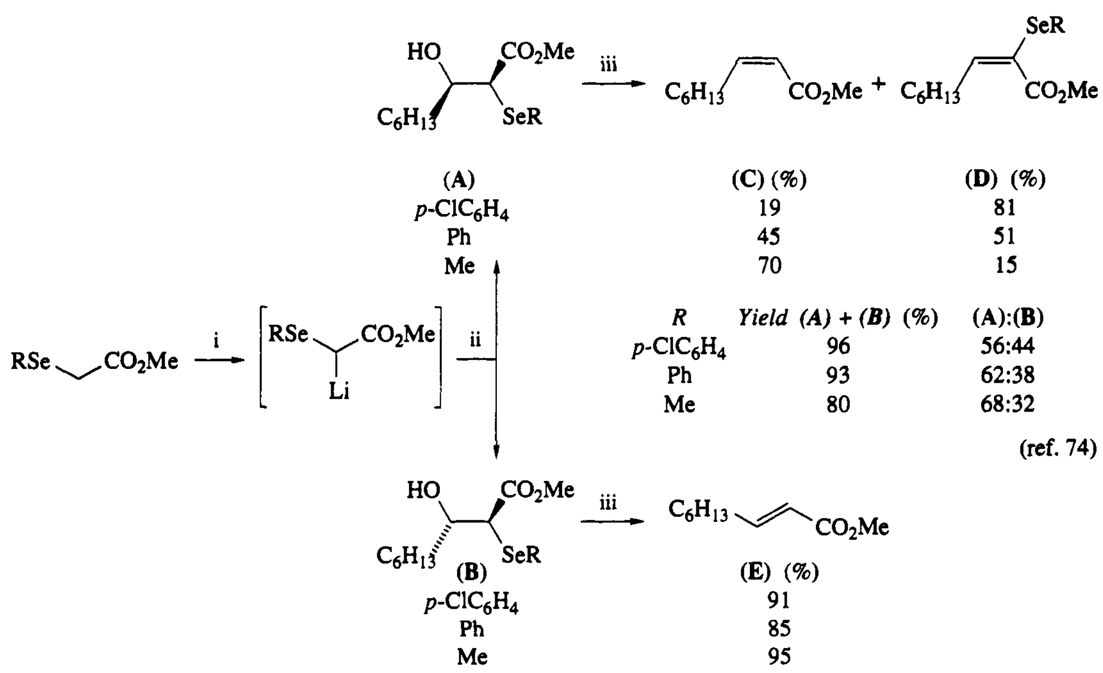

| (A) | (C) (%) | (D) (%) |
|---|---|---|
| $p$-ClC$_6$H$_4$ | 19 | 81 |
| Ph | 45 | 51 |
| Me | 70 | 15 |

| *R* | *Yield (A) + (B)* (%) | (A):(B) |
|---|---|---|
| $p$-ClC$_6$H$_4$ | 96 | 56:44 |
| Ph | 93 | 62:38 |
| Me | 80 | 68:32 |

(ref. 74)

| (B) | (E) (%) |
|---|---|
| $p$-ClC$_6$H$_4$ | 91 |
| Ph | 85 |
| Me | 95 |

$R_{fB} - R_{fA} = 0.1$–$0.2$; SiO$_2$, ether–pentane (2:8)

i, LDA, THF, –78 °C; ii, $C_6H_{13}CHO$; iii, $OPCl_3$, $Et_3N$, 20 °C, 2 h

**Scheme 170**

The elimination is completely chemoselective with 1-(1-hydroxyalkyl)-δ-lactones[74] and with methyl β-hydroxy-α-selenoalkylcarboxylates (precursors of (*E*)-α,β-unsaturated methyl carboxylates; Scheme 39, b and Scheme 170),[56,74] but not with the other stereoisomer which produces a mixture of (*Z*)-α,β-unsaturated methyl carboxylates (by formal selenenic elimination) and α-seleno-α,β-unsaturated methyl carboxylates (by formal elimination of water).

Elimination of water is particularly favored from *p*-chlorophenyl[74] and (*p*-trifluoromethyl)phenyl[56] selenides, whereas elimination of seleninic acid is mainly observed from methylseleno derivatives. Here, two different effects work in the same direction. The arylseleno group, more than the methylseleno group, makes the α-hydrogen acidic, and has at the same time a lower tendency to stabilize a β-carbenium ion *via* the formation of a seleniranium ion.

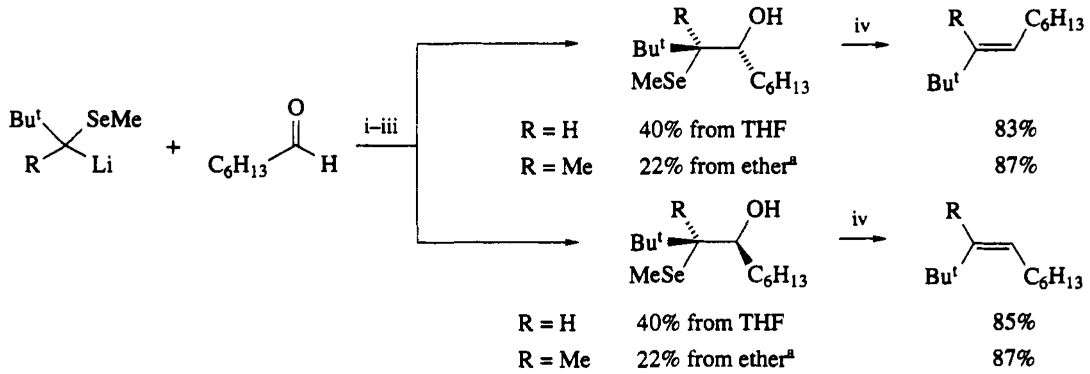

| | | |
|---|---|---|
| R = H | 40% from THF | 83% |
| R = Me | 22% from ether[a] | 87% |

| | | |
|---|---|---|
| R = H | 40% from THF | 85% |
| R = Me | 22% from ether[a] | 87% |

[a] Refers to the yield after separation of the 1:1 mixture of stereoisomers

i, –78 °C, 1–1.5 h; ii, $H_3O^+$; iii, separation by TLC; iv, $PI_3$, $Et_3N$

**Scheme 171** [189]

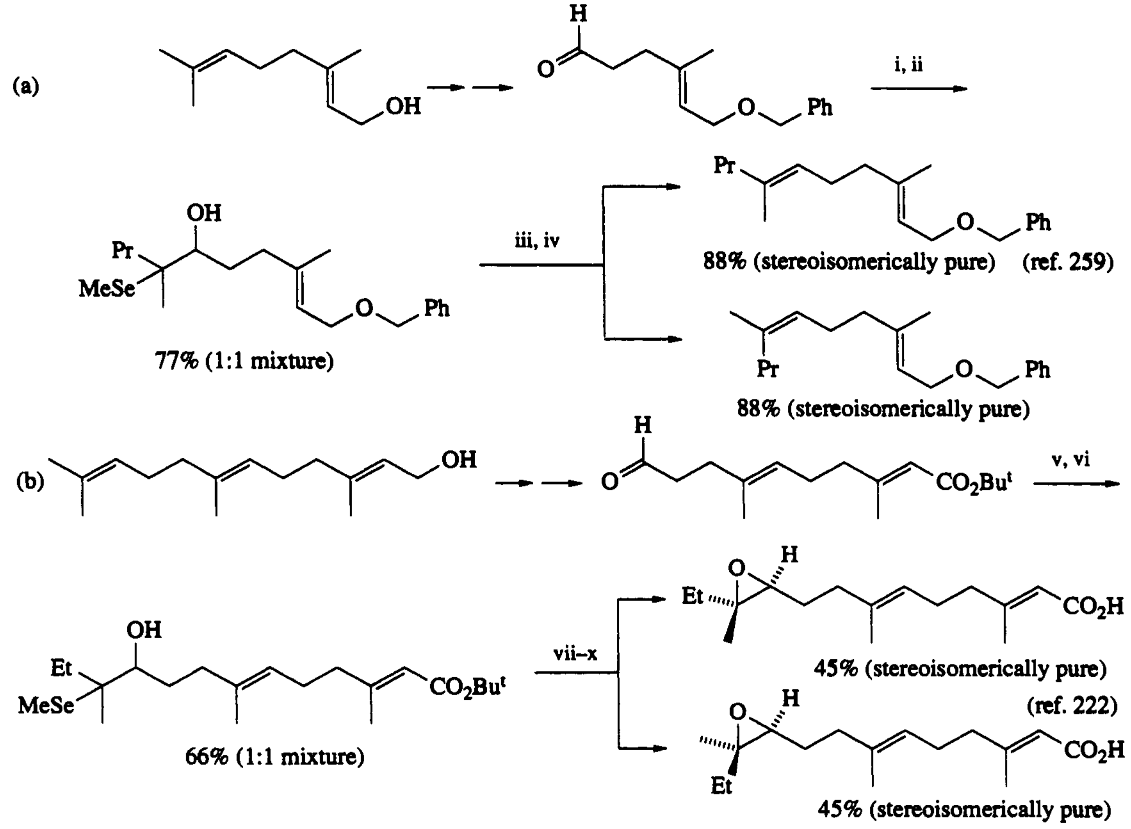
(a)
OH
H
O
O
Ph
i, ii
OH
Pr
MeSe
O
Ph
77% (1:1 mixture)
iii, iv
Pr
O
Ph
88% (stereoisomerically pure) (ref. 259)
Pr
O
Ph
88% (stereoisomerically pure)
(b)
OH
H
O
$CO_2Bu^t$
v, vi
OH
Et
MeSe
$CO_2Bu^t$
66% (1:1 mixture)
vii–x
O
H
Et
$CO_2H$
45% (stereoisomerically pure)
(ref. 222)
O
H
Et
$CO_2H$
45% (stereoisomerically pure)

i, PrC(SeMe)(Me)Li, THF, –78 °C; ii, $H_3O^+$; iii, separation ($SiO_2$, hexane–ethyl acetate); iv, $PI_3$, $Et_3N$, $CH_2Cl_2$ on each stereoisomer; v, EtC(SeMe)(Me)Li, THF, –78 °C; vi, $H_3O^+$; vii, separation; viii, $MeSO_3F$; ix, aq. KOH, ether; x, $H_3O^+$

**Scheme 172**

### 2.6.4.4 Synthesis of Allyl Alcohols

β-Hydroxyalkyl selenoxides directly available from α-lithioalkyl selenoxides or by oxidation of β-hydroxyalkyl selenides are valuable precursors of allyl alcohols (Schemes 51 and 52; Scheme 54, a; Scheme 105; Scheme 161, e; Scheme 162, b; Scheme 164, b; Scheme 166, b; Schemes 173 and 174).[7,40,42,48,49,97,98,120,127,128,136,188,189,195,253,261] In the former case the reaction is usually performed on thermolysis at around 70 °C in carbon tetrachloride[98] and in the presence of an amine[97,243] able to trap the selenenic acid concomitantly produced.

In general, the elimination rection is easier: (i) with arylseleno derivatives bearing an electron-withdrawing group at the *ortho* or *para* position of the phenyl ring than with their phenylseleno or methylseleno analogs; and (ii) when it provides a relatively more-substituted carbon–carbon double bond.

On β-hydroxyalkyl phenyl selenides, the oxidation–elimination is best achieved with an excess of 30% aqueous hydrogen peroxide according to the original description of Sharpless (Scheme 174, c and d).[261] Although 1-(1′-hydroxyalkyl)cyclohexyl phenyl selenide produces[49] under these conditions a hydroperoxide (Scheme 174, a), the desired elimination reaction has been successfully achieved[49] with sodium periodate in ethanol (Scheme 174, b).

The above conditions are not suitable for β-hydroxyalkyl methyl selenides (Scheme 175, a)[195,243] or for β-hydroxyalkyl phenyl selenides bearing a primary hydroxy group (Scheme 176, a).[195] Several other conditions including ozone and *t*-butyl hydroperoxide are not efficient for that purpose (Schemes 175 and 176).[195,243] The best reagent is *t*-butyl hydroperoxide supported on basic alumina. The reaction takes place at reflux in THF, and allows the synthesis from β-hydroxyalkyl methyl selenides of a large variety

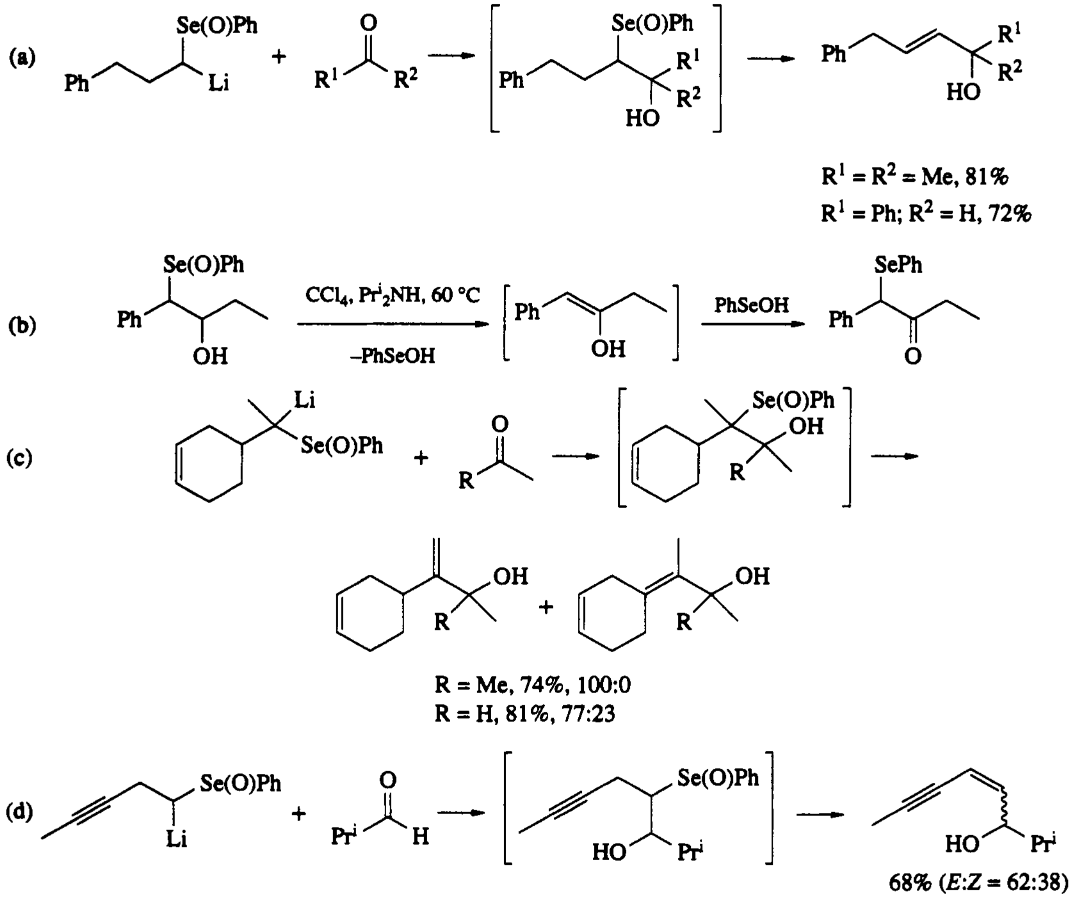

Scheme 173 [97]

of allyl alcohols, even those bearing a primary hydroxy group (Scheme 161, e; Scheme 162, b; Scheme 164, b; Scheme 174, c; Scheme 175, c; Scheme 176, c).[195]

This reaction, which is related to the well-known amine oxide pyrolysis,[262] involves a *syn* elimination of the selenenic acid, but proceeds under milder conditions (20 °C to 60 °C instead of 400 °C). It is more regioselective, takes place away from the oxygen and leads to allyl alcohols instead of enols, except when the only available hydrogen is the one α to the hydroxy group (Scheme 173, b).[97]

Selenoxides normally show[97] a preference for elimination towards the least-substituted carbon (Scheme 173, c), and for the formation of conjugated over unconjugated alkenes.

In the case presented in Scheme 51 the differences in behavior of the β-hydroxyalkyl selenoxides of different origin may be due to different diastereoisomeric ratios the equilibration of which is hampered by steric crowding. Therefore, there is a pronounced stereochemical effect on the regiochemistry of selenoxide *syn* elimination reactions. This elimination reaction leads to allyl alcohols where the α,β-disubstituted double bond possesses exclusively the (*E*)-stereochemistry when reasonably bulky groups are present (Scheme 52; Scheme 105, c; Scheme 174, d).[7,40,42,97,195,243] Those substituted with smaller groups such as a primary hydroxy group (Scheme 176, c)[195] or an ethynyl moiety (Scheme 173, d)[97] lead, however, to a mixture of stereoisomers in which the (*E*)-isomer prevails.

This reaction allows the synthesis of: (i) β,β′-dienols by oxidation of β-hydroxy-γ-alkenyl selenides[239,245] or more conveniently from α-lithioalkyl selenoxides and enones (Scheme 136 and 166);[97] (ii) β,δ-dienols from 1-lithio-3-alkenyl phenyl selenoxides and carbonyl compounds (Scheme 177);[97] and (iii) 2-(1′-hydroxyalkyl)-1,3-butadienes from 1-methylselenocyclobutyllithium and carbonyl compounds (Scheme 178).[136] α,β-Unsaturated alcohols bearing a methylselenoxy or a phenylselenoxy group at the α-position do not lead on thermolysis to propargyl alcohols; however, those bearing a (trifluoromethylphenyl)selenoxy moiety at the α-position are valuable precursors of such compounds (Scheme 179).[103]

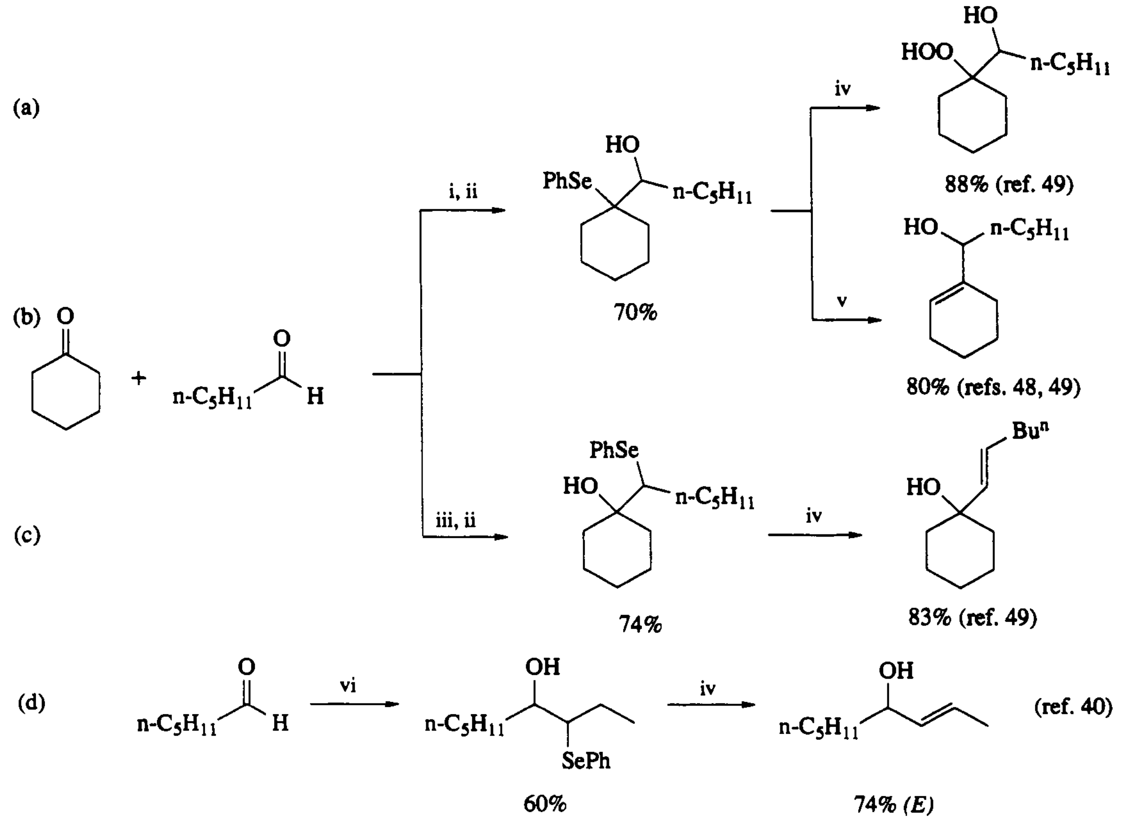
(a)
(b)
(c)
(d)
n-C5H11
i, ii
iii, ii
iv
v
vi
PhSe
HO
HOO
OH
SePh
Bun
70%
74%
88% (ref. 49)
80% (refs. 48, 49)
83% (ref. 49)
60%
74% (E)
(ref. 40)

i, cyclohexanone, PhSeH, HCl; ii, Bu$^n$Li, THF, –78 °C; iii, hexanal, PhSeH, $ZnCl_2$; iv, 30% $H_2O_2$, THF, 20 °C, 0.2 h; v, $NaIO_4$, MeOH–$H_2O$, 0 °C, 1 h, then 20 °C, 1 h; vi, EtC(Li)SePh

**Scheme 174**

Finally, 1-(1-selenoalkyl)cyclobutanols provide the expected 1-(1′-alkenyl)cyclobutanols (Scheme 54, a),[127,128] whereas a ring enlargement reaction leading to a mixture of cyclopentanones and α-phenylselenocyclopentanones (Scheme 54, b) occurs with the corresponding alcoholates.[127,128] The last reaction is strictly limited to strained compounds such as cyclobutanols and cyclopropanols, and does not take place with higher homologs.

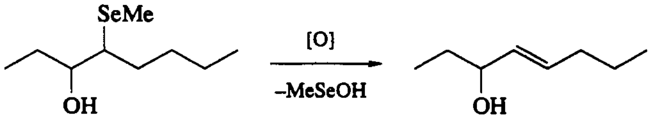
SeMe
OH
[O]
–MeSeOH
OH

| | Conditions | Yield (%) at 20 °C | Yield (%) at 55 °C |
|---|---|---|---|
| (a) | $H_2O_2$, THF, 5 h | 14 | 27 |
| (b) | $H_2O_2$–$Al_2O_3$, THF, 4 h | 43 | 63 |
| (c) | Bu$^t$OOH, $Al_2O_3$, THF, 3 h | 39 | 43 |
| (d) | $O_3$, $CDCl_3$, 2 h | — | 50 (50% SM) |
| (e) | i, $O_3$, $CDCl_3$, –78 °C; ii, 3 $Et_3N$, $CH_2Cl_2$ | — | 62 (40 °C) |

**Scheme 175** [188, 195]

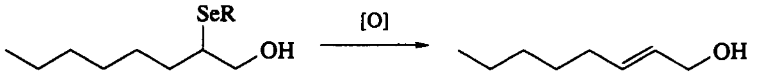

(ref. 195)

| | Conditions | Yield (%) R = Ph | Yield (%) R = Me |
|---|---|---|---|
| (a) | 30% $H_2O_2$, THF, 16 h | 35 | — |
| (b) | 30% $H_2O_2$, $Al_2O_3$, THF, 55 °C, 3–6 h | 74 | 47 |
| (c) | $Bu^tOOH$–$Al_2O_3$, THF, 55 °C, 5 h | 78 | 80 (E:Z = 75:25) |

**Scheme 176**

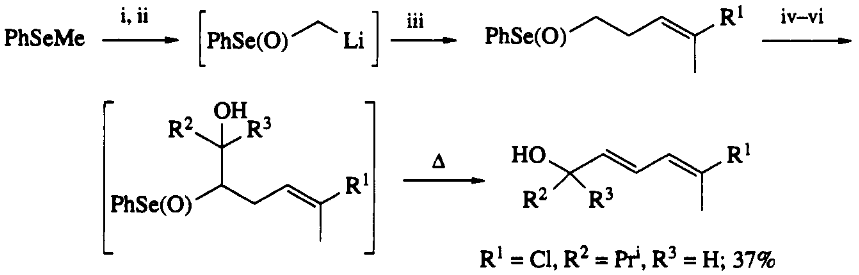
PhSeMe
i, ii
PhSe(O)
Li
iii
PhSe(O)
R1
iv–vi
R2
OH
R3
PhSe(O)
R1
Δ
HO
R1
R2
R3

(ref. 97)

$R^1$ = Cl, $R^2$ = $Pr^i$, $R^3$ = H; 37%
$R^1$ = Me, $R^2$ = Et, $R^3$ = Me; 69%

i, MCPBA, THF, –78 °C; ii, LDA, –78 °C; iii, (E)-$R^1$(Me)C=CHC$H_2$X; iv, LDA; v, $R^2R^3$CO; vi, $H_3O^+$

**Scheme 177**

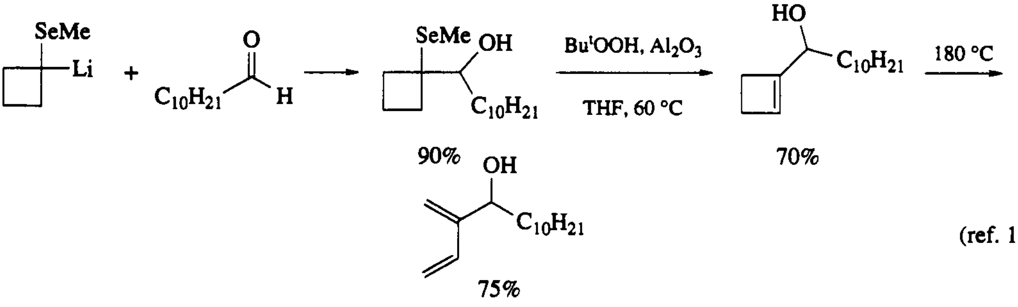
SeMe
Li
+
O
C10H21
H
SeMe
OH
C10H21
ButOOH, Al2O3
THF, 60 °C
HO
C10H21
180 °C
90%
70%
OH
C10H21
75%

(ref. 136)

**Scheme 178**

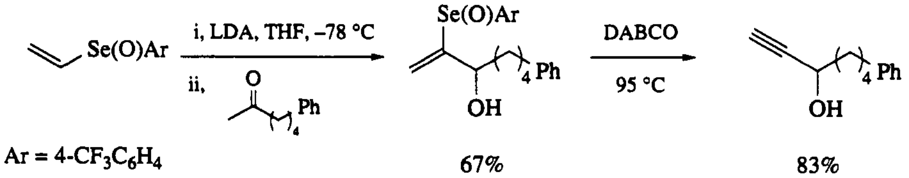
Se(O)Ar
i, LDA, THF, -78 °C
ii,
O
Ph
4
Ar = 4-CF3C6H4
Se(O)Ar
Ph
4
OH
67%
DABCO
95 °C
Ph
4
OH
83%

**Scheme 179** [103]

### 2.6.4.5 β-Hydroxyalkyl Selenides as Precursors of Epoxides and Carbonyl Compounds

#### 2.6.4.5.1 Generalities

The presence of two potential leaving groups β to each other makes β-hydroxyalkyl selenides valuable candidates for epoxide synthesis,[206a] as well as for pinacol-type rearrangement.[206b] These concurrent transformations, which usually require the selective activation of the selenyl moiety to a better leaving group, have been successfully achieved by three distinct ways: (i) by alkylation to β-hydroxyalkyl selenonium salts; (ii) by oxidation to β-hydroxyalkyl selenones; and (iii) by complexation with metal salts where the metal is a soft acceptor. The first two methods can provide either the epoxide or the rearranged carbonyl compounds, whereas the last one exclusively leads to rearranged carbonyl compounds only when the carbon bearing the seleno moiety is alkyl disubstituted.

### 2.6.4.5.2 *Synthesis of epoxides*[7,12,16,199,206]

The transformation of β-hydroxyalkyl selenides to epoxides (Schemes 124, 132b, 134a, 161g, 162d, 163e, 164d, 165b, 166d and 180–185) has been achieved under three different sets of conditions: (i) by alkylation of the selenium atom, leading to stable β-hydroxyalkylselenonium salts, with MeI,[55,136,163,206,221,236,239,263] MeI–$AgBF_4$[55,163,196,206,221] $Me_2SO_4$,[55,189,196,206,265] $Et_3OBF_4$[206,258,264] or $MeFSO_3$.[163,188,206,215,216,222] The selenonium salts are then cyclized on reaction with a base such as Bu$^t$OK/DMSO,[55,136,163,196,206,221,236,239,265] 50% aqueous KOH/$CH_2Cl_2$[189,206] 10% aqueous KOH/$Et_2O$,[136,163,206,215,216,222,239,263] KH/DME[258] or NaH/THF;[264] (ii) by reaction of dichlorocarbene, generated[206,266] from chloroform and thallous ethoxide (5.5 equiv. TlOEt, $CHCl_3$, 20 °C, 8–24 h), or more conveniently from 50% aqueous potassium hydroxide solution in the presence of a phase transfer catalyst (50% aq. KOH, $CHCl_3$, 20 °C, 1–2 h);[206,266] and (iii) by oxidation to β-hydroxyalkyl selenones (2.5 equiv. MCPBA, $CHCl_3$),[130,201,206] which are cyclized in the presence of a base (Bu$^t$OK/DMSO or $K_2CO_3$/$CHCl_3$).[130] All these reactions proceed stereoselectively by complete inversion of the configuration at the substituted carbon.[206,236,263,264,266]

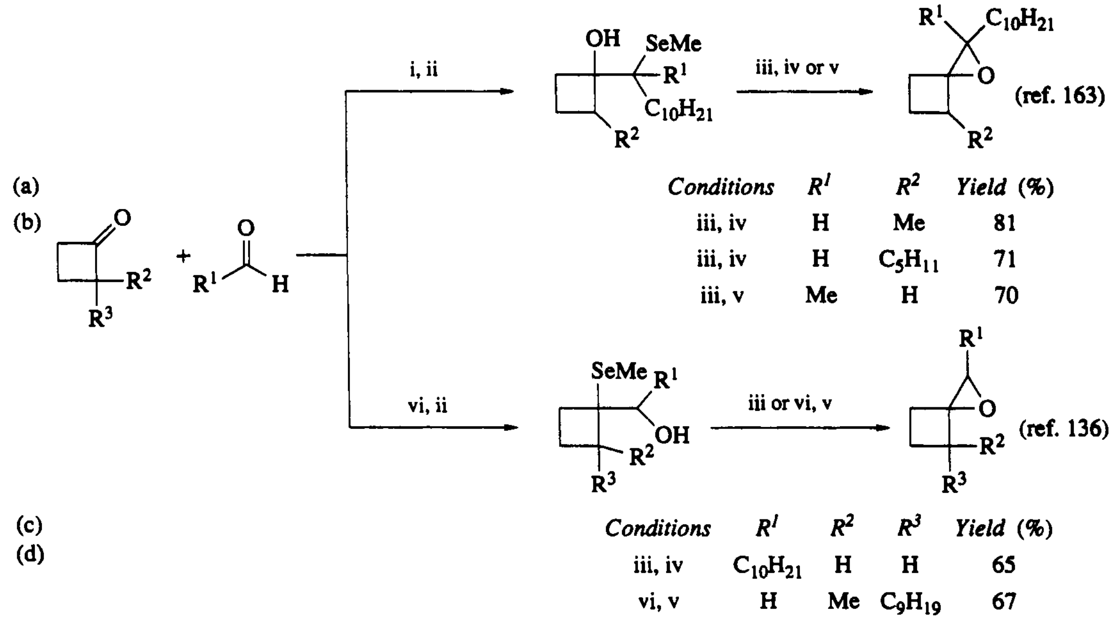

| *Conditions* | *R¹* | *R²* | *Yield* (%) |
|---|---|---|---|
| iii, iv | H | Me | 81 |
| iii, iv | H | $C_5H_{11}$ | 71 |
| iii, v | Me | H | 70 |

| *Conditions* | *R¹* | *R²* | *R³* | *Yield* (%) |
|---|---|---|---|---|
| iii, iv | $C_{10}H_{21}$ | H | H | 65 |
| vi, v | H | Me | $C_9H_{19}$ | 67 |

i, $R^1CHO$, MeSeH, $ZnCl_2$; ii, Bu$^n$Li, THF, –78 °C; iii, MeI (neat), 20 °C; iv, Bu$^t$OK, DMSO, 20 °C; v, 10% KOH, ether, 20 °C; vi, cyclobutanone, MeSeH, $ZnCl_2$; vi, MeI•$AgBF_4$

**Scheme 180**

The reaction involving the alkylation of β-hydroxyalkyl selenides to give β-hydroxyalkylselenonium salts which are then cyclized with a base is by far the most general. It allows the synthesis of a large variety of epoxides such as terminal, α,α- and α,β-disubstituted, tri-[55,196] and tetra-substituted,[55,188] as well as oxaspiro[2.0.*n*]-hexanes,[136,163] -heptanes[189] and -octanes (Scheme 161, g; Scheme 162, d; Scheme 164, d; Scheme 165, b)[55,188,196] and vinyl oxiranes (Schemes 166 and 181)[221,239] from both β-hydroxyalkyl methyl[55,136,163,215,221,222,236,263] and phenyl selenides.[163,196,258,264]

The most successful combination involves methylseleno derivatives as starting materials, methyl iodide (neat) as the alkylating agent and 10% aqueous potassium hydroxide solution in ether as the base.[188] In some difficult cases, such as those involving hindered β-hydroxyalkyl selenides,[188] where the

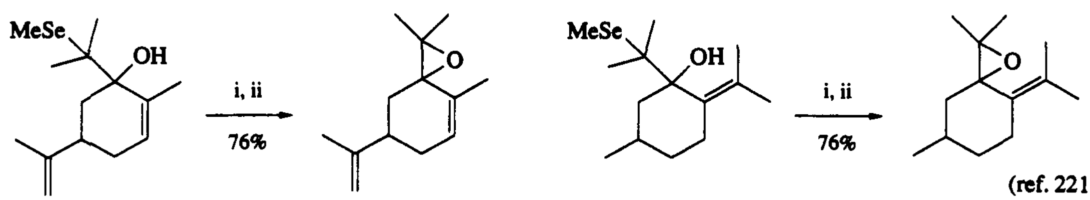

MeSe
OH
i, ii
76%
O
MeSe
OH
i, ii
76%
O

(ref. 221)

i, neat MeI, 20 °C; ii, Bu$^t$OK, DMSO, 20 °C

**Scheme 181**

seleno moiety is linked to a cyclohexane ring$^{55,189}$ or to a primary alcohol$^{189}$ (Scheme 164, d; Schemes 182 and 183),$^{189}$ the consecutive use of methyl fluorosulfonate and aqueous potassium hydroxide in ether or pentane is required in order to avoid the concomitant formation of carbonyl compounds, allyl alcohols$^{188}$ or alkenes$^{189}$ which are observed when other conditions are used.

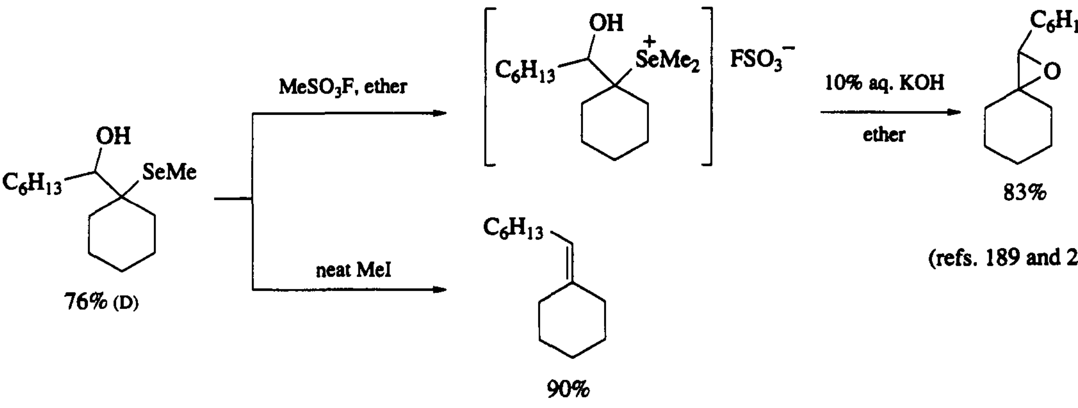

OH
$C_6H_{13}$
SeMe
76% (D)
$MeSO_3F$, ether
neat MeI
OH
$C_6H_{13}$
$\overset{+}{S}eMe_2$
$FSO_3^-$
10% aq. KOH
ether
$C_6H_{13}$
O
83%
$C_6H_{13}$
90%

(refs. 189 and 206)

**Scheme 182**

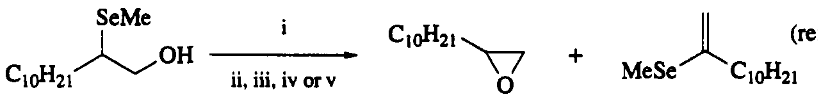

SeMe
$C_{10}H_{21}$
OH
65% (D)
i
ii, iii, iv or v
$C_{10}H_{21}$
O
+
MeSe
$C_{10}H_{21}$

(refs. 189 and 206)

| | *Conditions* | *Yield* (%) | *Yield* (%) |
|---|---|---|---|
| (a) | ii | 5 | 45 |
| (b) | iii | 65 | 30 |
| (c) | iv | 85 | 15 |
| (d) | v | 78 | 3 |

i, $MeSO_3F$, ether; ii, 50% aq. $KOH/CH_2Cl_2$; iii, aq. $K_2CO_3$/ether; iv, 10% aq. KOH/ether;
v, 10% aq. KOH/pentane

**Scheme 183**

Methylseleno derivatives offer the advantage of being more easily methylated than their phenylseleno analogs (MeI instead of MeI–$AgBF_4$) and allowing the synthesis of a wide range of β-hydroxyalkylselenonium salts, including those which have two alkyl groups on the carbon bearing the selenium atom. These are unavailable from phenylseleno derivatives;$^{196}$ therefore, tetrasubstituted epoxides can only be produced from methylseleno compounds.$^{55}$

The reaction involving dichlorocarbene also provides a wide range of epoxides,$^{206,266}$ including terminal, α,α- and α,β-dialkyl-substituted and trialkyl-substituted compounds, from a large variety of β-hydroxyalkyl methyl and phenyl selenides (Scheme 162, d). The thallous ethoxide reaction, although it takes place more slowly (especially with phenylseleno derivatives) than under phase transfer catalysis conditions,$^{206,266}$ has to be in several instances preferred since it avoids the concomitant formation of alkenic or dihalocyclopropane derivatives often observed under the latter conditions.[206,223,266] This reaction is less general than that involving the discrete formation of β-hydroxyalkylselenonium salts since it takes another course with β-hydroxyalkyl selenides where the carbon bearing the seleno moiety is dialkyl substituted, and instead delivers rearranged ketones (see Section 2.6.4.5.3). This method, therefore, does not allow the synthesis of tetraalkyl-substituted epoxides (Scheme 162, compare d and e). However it offers the definite advantage of taking place in one step and avoiding the use of expensive silver tetrafluoroborate[196] or triethyloxonium tetrafluoroborate.[264]

The reaction involving β-hydroxyalkyl selenones[130,201,206] is by far the less attractive route to epoxides among those cited above due to the difficulties usually encountered in the oxidation step and the easy rearrangement of the β-hydroxyalkyl selenones to carbonyl compounds (Scheme 184, b and c).[130] This method is, however, particularly useful for the synthesis of oxaspiropentanes[130,206] (especially for those bearing a fully alkyl-substituted epoxide ring) from 1-seleno-1-(1′-hydroxyalkyl)cyclopropanes (Scheme 163, e; Scheme 185), which cannot be obtained under other conditions.[12]

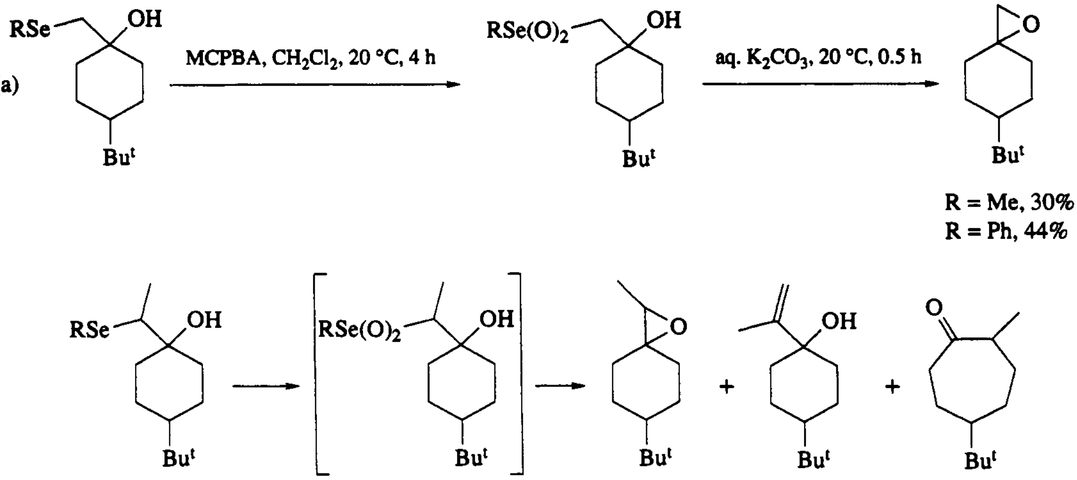

R = Me, 30%
R = Ph, 44%

| | Conditions | | Yield (%) | |
|---|---|---|---|---|
| (b) | MCPBA (3 equiv.), $CH_2Cl_2$, 20 °C, 3 h | 4 | 21 | 56 |
| (c) | excess $K_2CO_3$, MCPBA (3 equiv.), $CH_2Cl_2$, 20 °C, 3 h | 44 | — | 9 |

Scheme 184

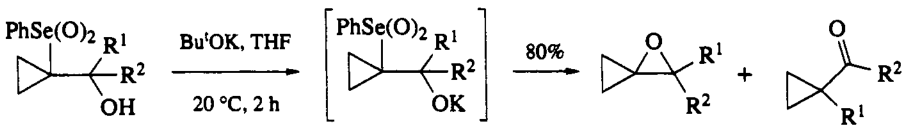

$R^1 = H, R^2 = Ph$ 33:67

Scheme 185 [130]

### 2.6.4.5.3 *Rearrangement of β-hydroxyalkyl selenides to carbonyl compounds*[16,206b]

The rearrangement of β-hydroxyalkyl selenides to carbonyl compounds has been carried out under different conditions, which have to be chosen with regard to the structure of the starting material and especially the substitution pattern around the carbon bearing the seleno moiety. The rearrangement of β-hydroxyalkyl selenides possessing two hydrogen atoms on the carbon bearing the seleno moiety has not yet been achieved. However, the rearrangement of monoalkyl-substituted derivatives takes place on oxidation with *m*-chloroperoxybenzoic acid (2.5 equiv. of MCPBA in $CHCl_3$[130] or in MeOH;[201] Scheme 184), and the rearrangement of dialkyl-substituted compounds occurs on reaction with silver tetrafluoroborate[190,191,204,227] in dichloromethane and chloroform or silver tetrafluoroborate supported on basic alumina[197,204] in the same solvents (Scheme 162, e; Scheme 186, a; Scheme 187), or silver nitrate,[267] or with dichlorocarbene generated from chloroform and thallous ethoxide[197,225–227,244] or a 50% aqueous solution of potassium hydroxide in the presence of a phase transfer catalyst ($PhNEt_3Cl$, TEBAC)

(Scheme 162, e; Scheme 165, c; Scheme 166, e; Scheme 186, b; Scheme 188, a; Scheme 189, a and b).[197,198,227]

The above conditions allow the synthesis of a large variety of α,α-dialkyl substituted ketones including spiro derivatives and cyclopentanones, cyclohexanones, cycloheptanones and cyclododecanones bearing two alkyl groups at the α-position (Scheme 162, e; Scheme 165, c; Scheme 166, e; Scheme 186, a and b; Scheme 187; Scheme 188, a; Scheme 189, a and b).[160,198,204,244]

The reactions are less selective when the dichlorocarbene is generated from bromodichloromethane[223] and lead to *gem*-dichlorocyclopropanes if the dichlorocarbene is produced from chloroform and potassium *t*-butoxide (Scheme 162, f; Scheme 188, b; Scheme 189, c).[198]

Particularly crowded or strained derivatives lead to carbonyl compounds under special conditions. Thus, β-hydroxyalkylselenonium salts, obtained on alkylation of particularly hindered β-hydroxyalkyl selenides and the selenium-bearing carbon of which is dialkyl substituted, have been rearranged[160,188] to ketones by heating or by simple dissolution in dichloromethane (Scheme 164, e; Scheme 186, c).

Strained β-oxidoalkyl phenyl selenoxides, such as 1-oxido-1-(1′-phenylselenoxyalkyl)cyclopropanes, derived from oxaspiropentanes with tetraalkyl-substituted oxirane rings,[268] and 1-(1′-hydroxyalkyl)-1-selenoxycyclobutanes,[127,128] obtained on oxidation of the corresponding selenides or on reaction of α-lithioalkyl selenoxides with cyclobutenones, possess a high propensity to rearrange to cyclobutanones

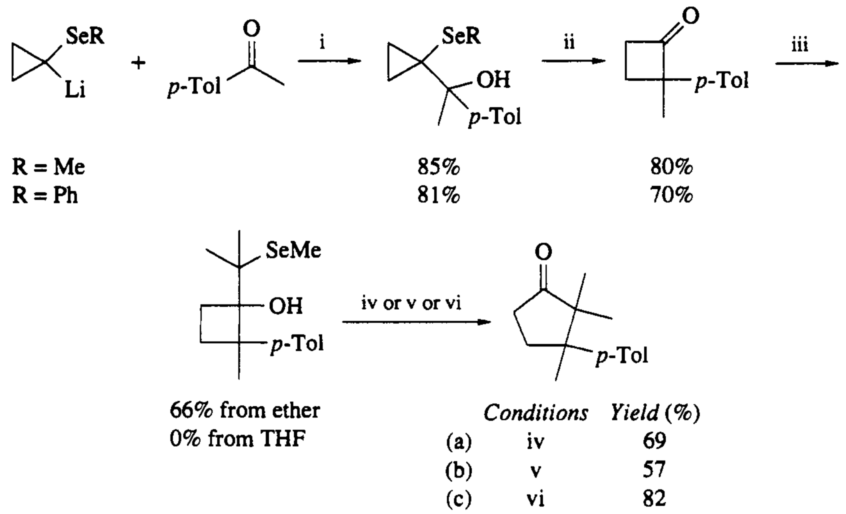

| | *Conditions* | *Yield* (%) |
|---|---|---|
| (a) | iv | 69 |
| (b) | v | 57 |
| (c) | vi | 82 |

i, ether, –78 °C; ii, *p*-TsOH, benzene/$H_2O$, 80 °C, 12 h; iii, $Me_2C(SeMeLi)$, solvent, –78 °C; iv, $AgBF_4$–$Al_2O_3$, $CH_2Cl_2$; v, TlOEt,$CHCl_3$; vi, $MeSO_3F$, ether

**Scheme 186** [160]

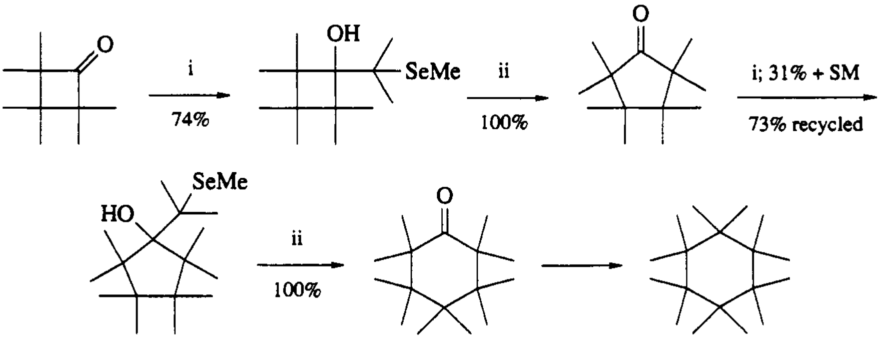

i, $Me_2C(SeMe)Li$, ether, –78 °C; ii, $AgBF_4$, $CHCl_3$

**Scheme 187** [190]

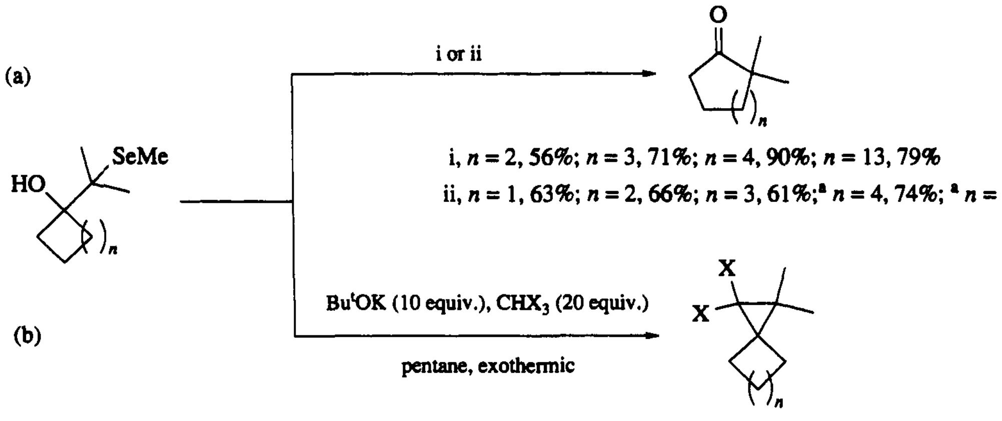

i, $n$ = 2, 56%; $n$ = 3, 71%; $n$ = 4, 90%; $n$ = 13, 79%
ii, $n$ = 1, 63%; $n$ = 2, 66%; $n$ = 3, 61%;[a] $n$ = 4, 74%;[a] $n$ = 13, 73%
(ref. 198)

X = Cl; $n$ = 3, 39%; $n$ = 4, 50%; $n$ = 12, 40%
X = Br, $n$ = 3, 46%

i, TlOEt (5.5 equiv.), $CHCl_3$, 20 °C, 8 h; ii, 50% aq. KOH, $CHCl_3$, TEBAC, 20 °C, 1 h
[a] Allyl alcohols also produced (4–13%)

Scheme 188

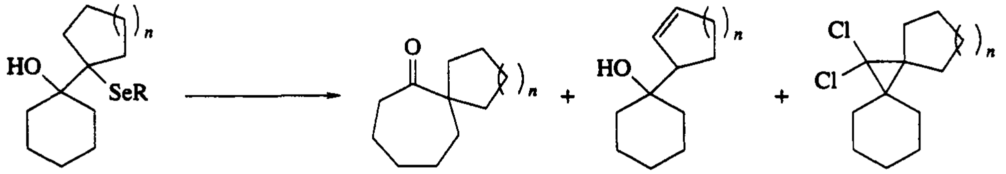

| | *Conditions* | *R* | *n* | *Yield (%)* | | | | | | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|
| (a) | i | Ph | 1 | 87 | 100 | : | 0 | : | 0 | 198, 244 |
| | i | Ph | 2 | 92 | 100 | : | 0 | : | 0 | 198, 244 |
| (b) | ii | Ph | 1 | 89 | 68 | : | 32 | : | 0 | 198 |
| | ii | Me | 1 | 91 | 78 | : | 22 | : | 0 | 198 |
| (c) | iii | Me | 1 | 47 | 40 | : | 17 | : | 43 | 198 |

i, TlOEt (5.5 equiv.), $CHCl_3$, 20 °C, 8 h; ii, 10% aq. KOH, $CHCl_3$ (3 equiv.), TEBAC, $CH_2Cl_2$, 20 °C;
iii, BuᵗOK (10 equiv.), $CHCl_3$ (10 equiv.), pentane, 20 °C

Scheme 189

(Scheme 190)[268] and cyclopentanones (Schemes 54b and 121),[127,128] respectively, rather than produce the corresponding allyl alcoholates *via* the well-established seleninic acid elimination (Section 2.6.4.4). The latter reaction, however, becomes important with oxaspiropentanes where the oxirane ring is trialkyl substituted (Scheme 191).[268]

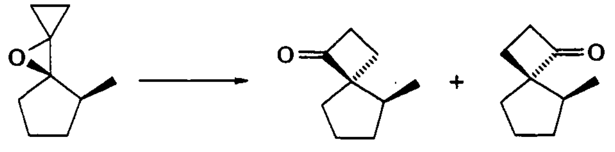

(ref. 268)

| | *Conditions* | *Yield (%)* | *Ratio* |
|---|---|---|---|
| (a) | PhSeNa, EtOH, then MCPBA | 48 | 4:96 |
| (b) | $LiBF_4$ | 61 | 100:0 |

Scheme 190

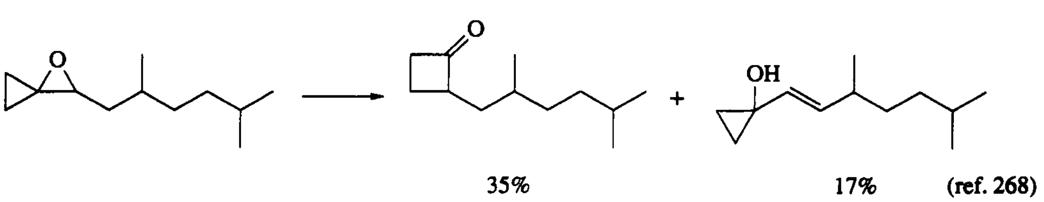

i, PhSeNa, EtOH; ii, MCPBA, $CH_2Cl_2$, –25 °C, 4.5 h, then 0 °C, 1 h

**Scheme 191**

The stereochemistry of the spirocyclobutanones shown in Scheme 190 seems to be determined by the rate of the ring expansion compared with that of bond rotation.[268] Indeed, in several cases high stereoselectivity is observed (Scheme 190, a),[268] which is quite opposite to that found[268] with lithium tetrafluoroborate (Scheme 190, b).

Finally, 1-(1′-hydroxyalkyl)-1-(methylseleno)cyclopropanes and some rare phenylseleno analogs belonging to the phenylcarbinol series produce cyclobutanones on reaction with *p*-toluenesulfonic acid in a similar manner to the phenylthio analogs.[12] This reaction has allowed the synthesis of a large variety of cyclobutanones, including those that are polyalkylated (Scheme 163; f–h),[12,77,159,160,199] aryl substituted or vinyl substituted (Scheme 132, a; Scheme 186),[12,77,160] by selective migration of the more-substituted carbon (Scheme 163, compare h with f).[12,77,160]

The conditions involving dichlorocarbene generated from chloroform and thallium ethoxide give the best chemoselectivity, yields and reproducibility (Scheme 162, e; Scheme 165, c; Scheme 166, e; Scheme 186, b; Scheme 188, a; Scheme 189, a).[160,197,225–227,244] The reactions are usually carried out at room temperature and require at least 8 h to go to completion.[244] They are faster with methylseleno than with phenylseleno derivatives when performed at a higher temperature.[244] The reactions performed under phase transfer catalysis conditions are valuable[198] owing to the simplicity of the reagents used and the particularly rapid reaction rate (20 °C, 1–2 h). They lead,[198] however, to appreciable amounts of allyl alcohol (5–20%) besides the rearranged ketones (Scheme 188, a; Scheme 189, b). They are valuable for the synthesis of the most water soluble and volatile ketones, such as 2,2-dimethylcyclopentanone, since they avoid the presence of ethanol and chloroform, difficult to remove from the desired compounds. The same transformation can also be performed[204] with silver tetrafluoroborate or silver tetrafluoroborate supported on basic alumina. The latter conditions are usually better than the former since they avoid the presence of fluoroboric acid, responsible for the concomitant formation of alkenes (by formal elimination of RSeOH).

When two different groups are susceptible to migrate on reaction of β-hydroxyalkyl selenides with dichlorocarbene or silver salts, the tendency to migrate follows the order $CH_2SiMe_3 < H < Ph <$ alkyl (Scheme 192; Scheme 165, c).[197,223,244,267] In general, the more alkyl substituted carbon possesses the highest propensity to migrate whatever the conditions used (Scheme 192). In the case of 2-methylcyclohexanols, however, low selectivity has been observed[197] with thallium(I) ethoxide (Scheme 192, a and b) and, surprisingly, when the reaction is instead performed with silver tetrafluoroborate, the less-substituted carbon has the highest tendency to migrate (Scheme 192, c).[197]

The case of β-hydroxy-γ-alkenyl selenides merits further comments.[225–227] The rearrangement efficiently takes place using the thallium(I) ethoxide method and the presence of an additional double bond in the reactant does not introduce a serious problem associated with unwanted reaction with the dichlorocarbene intermediate.[225,226] This is not the case when silver tetrafluoroborate is used.

The thallium ethoxide method almost selectively provides α,α-dialkyl-β-enones by vinyl migration in sterically unconstrained straight chain derivatives (Scheme 193),[225,226] whereas alkyl migration leading to α-enones takes place almost exclusively with the 2-cyclohexen-1-ol derivatives[225,226] shown in Scheme 194. This is probably due to interrelationships of steric and conformational influences associated with proper antiperiplanar alignment of the $RSeCCl_2H$ leaving group. However, such high selectivity in favor of the alkyl over the vinyl migration is not observed[225] with 2-cycloalken-1-ols of lower (2-cyclopenten-1-ols) and of higher (2-cycloocten-1-ols) ring size (Scheme 194), and although the alkyl migration is favored[225] with 6-alkyl-substituted 2-cyclohexen-1-ols, the vinyl migration is observed[225,226] if the cyclohexene ring is substituted at the 2- or 3-position (Schemes 134 and 195).

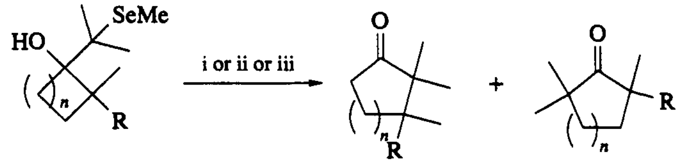

| | R | Conditions | n | Yield (%) | Ratio | Ref. |
|---|---|---|---|---|---|---|
| (a) | H | i | 2 | 76 | 90:10 | 197, 244 |
| | H | i | 3 | 77 | 60:40 | 197, 244 |
| | H | i | 4 | 65 | 78:22 | 197, 244 |
| (b) | H | ii | 2 | 69 | 92:8 | 197 |
| | H | ii | 3 | 58 | 62:38 | 197 |
| | H | ii | 4 | 56 | 84:16 | 197 |
| (c) | H | iii | 2 | 74 | 90:10 | 204 |
| | H | iii | 3 | 54 | 22:78 | 204 |
| | H | iii | 4 | 49 | 72:28 | 204 |
| (d) | Me | i | 3 | 81 | 100:0 | 197, 244 |
| | Me | i | 4 | 81 | 99:1 | 197, 244 |
| (e) | Me | ii | 3 | 54 | 100:0 | 197 |
| | Me | ii | 4 | 52 | 99:1 | 197 |
| (f) | Me | iii | 3 | 65 | 100:0 | 204 |
| | Me | iii | 4 | 55 | 70:30 | 204 |

i, TlOEt (5.5 equiv.), $CHCl_3$, 20 °C; ii, 10% aq. KOH, $CHCl_3$, TBEAC, 20 °C; iii, $AgBF_4$–$Al_2O_3$, $CH_2Cl_2$, 20 °C

**Scheme 192**

### 2.6.4.5.4 Mechanism of epoxide and ketone formation from β-hydroxyalkyl selenides

Striking differences exist between silver tetrafluoroborate and dichlorocarbene mediated reactions since they proceed differently in several instances.[200,206] Although the dichlorocarbene reaction takes place with almost all kinds of β-hydroxyalkyl selenides,[160,197,225–227,244] the silver tetrafluoroborate mediated reaction only works with those β-hydroxyalkyl selenides which possess[190,191,204] two alkyl groups on the carbon bearing the seleno moiety and on the condition that no unsaturation is present around the active site. Furthermore, detailed investigations carried out on the β-hydroxyalkyl selenides (**35**) and (**36**) shown in Scheme 196 shed some light on the intimate mechanism of these reactions and on the subtle differences which exist between dichlorocarbene and silver tetrafluoroborate mediated reactions, although both often lead to identical products from the same starting materials.[20,200,206]

Thus, the β-hydroxyalkyl selenides (**35a**) and (**35b**) react[266] with dichlorocarbene and stereoselectively lead to *trans*- and *cis*-9,10-epoxyoctadecene (**37a** and **37b**; Scheme 196). Under similar conditions the β-hydroxyalkyl selenide (**36a**) regio- and stereoselectively leads to the cycloheptanone (**38a**) resulting from the migration of the most-substituted carbon, and its diastereoisomer (**36b**) produces a mixture of the regioisomeric cycloheptanones (**38b**) and (**39a**) in which the latter, arising from the migration of the least-substituted carbon, prevails (Scheme 196, c and e).[200] In all cases the reactions take place apparently in a concerted manner with inversion of the configuration at the substituted carbon,[200,206,266] and in the

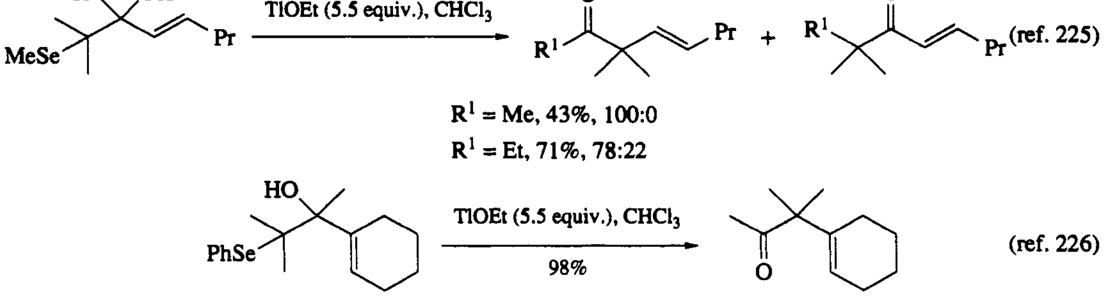

$R^1$ = Me, 43%, 100:0
$R^1$ = Et, 71%, 78:22

**Scheme 193**

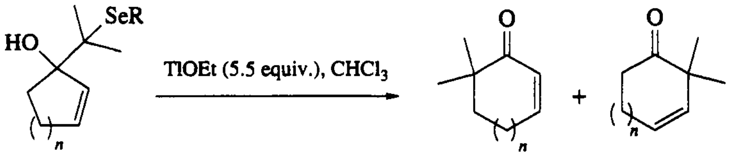

| | *n* | *R* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (a) | 1 | Me | — | 43:57 |
| (a) | 2 | Me | 68 | 91:9 |
| (b) | 2 | Ph | 84 | 95:5 |
| (a) | 3 | Me | 69 | 51:49 |
| (b) | 3 | Ph | 88 | 56:44 |
| (a) | 8 | Me | 87 | 42:58 |

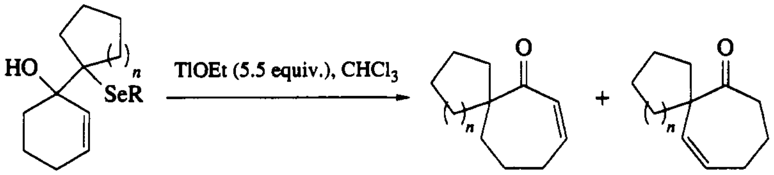

| | *n* | *R* | *Yield (%)* | *Ratio* |
|---|---|---|---|---|
| (c) | 1 | Ph | 95 | 80:20 |
| (d) | 2 | Me | 80 | 90:10 |

(refs. 225 and 226)

**Scheme 194**

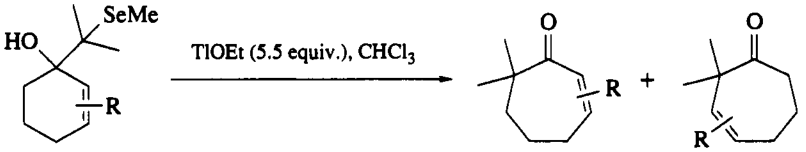

(ref. 225)

| | | *Yield (%)* | *Ratio* |
|---|---|---|---|
| (a) | 2-Me | 64 | 78:22 |
| | 3-Me | 67 | 73:27 |
| | 4-Me | 77 | 91:9 |
| | 6-Me | 71 | 100:0 |
| (b) | 6-Ph | 70 | 100:0 |

**Scheme 195**

case of the ring enlargement reaction with complete retention of the configuration at the migrating carbon.[200]

The reactions of the same β-hydroxyalkyl selenides (**35**) and (**36**) with silver tetrafluoroborate take a somewhat different course. Although cycloheptanones are produced from (**36**), (**35**) is unreactive and gives only the starting materials on heating (Scheme 196). Furthermore, with the β-hydroxyalkyl selenides (**36**) the structure and stereochemistry of the cycloheptanones obtained are different from those disclosed when the reaction is carried out with dichlorocarbene. Not only the least-substituted carbon now migrates, regardless of whether (**36a**) or (**36b**) is involved, but also the ring enlargement proceeds with almost complete racemization from (**36b**) (leading to a mixture of **39a** and **39b**; Scheme 196) and with apparent complete retention of configuration from (**36a**) (leading to **39a**; Scheme 196). The latter might be the result of two consecutive inversions involving the intermediate formation of an epoxide, but this remains to be confirmed.

The reaction of dichlorocarbene with β-hydroxyalkyl selenides is believed[200,206,226,266] to take place selectively on the selenium atom, thus producing the corresponding β-hydroxyalkyldichloromethyleneselenonium ylide (**40**; Scheme 197). This, after an intramolecular proton transfer leading to (**41**; Scheme 197), which probably occurs in a six-membered transition state, collapses selectively to the epoxide[206,266] or to the carbonyl compound depending upon the substitution pattern around the substituted carbon.[200] The regiochemistry of the latter reaction depends upon the stereochemistry of the starting material, and the regioisomeric ratio without doubt reflects the ratio of the two conformers (**43** and **44**; Scheme 197)

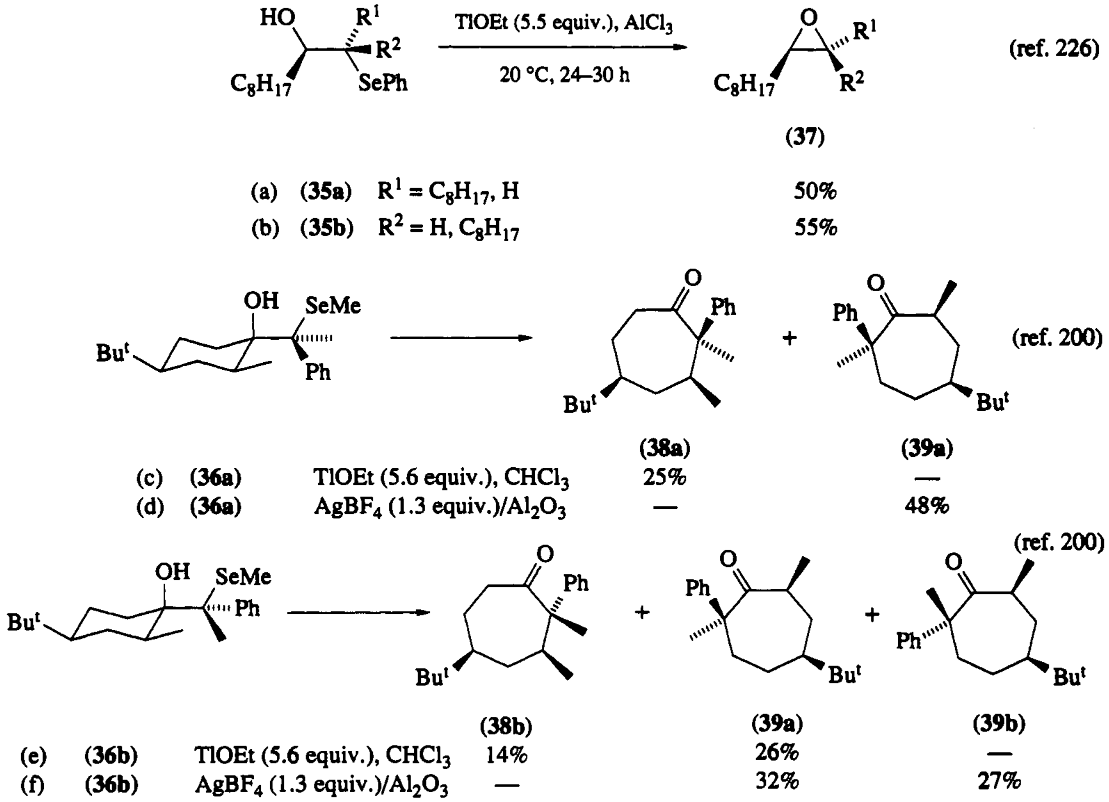
TlOEt (5.5 equiv.), AlCl3
20 °C, 24–30 h
(37)
(ref. 226)
(38a)
(39a)
(ref. 200)
(38b)
(39a)
(39b)
(ref. 200)

(a) (35a) $R^1 = C_8H_{17}$, H — 50%

(b) (35b) $R^2 = H, C_8H_{17}$ — 55%

| | | | (38a) | (39a) |
|---|---|---|---|---|
| (c) | (36a) | TlOEt (5.6 equiv.), $CHCl_3$ | 25% | — |
| (d) | (36a) | $AgBF_4$ (1.3 equiv.)/$Al_2O_3$ | — | 48% |

| | | | (38b) | (39a) | (39b) |
|---|---|---|---|---|---|
| (e) | (36b) | TlOEt (5.6 equiv.), $CHCl_3$ | 14% | 26% | — |
| (f) | (36b) | $AgBF_4$ (1.3 equiv.)/$Al_2O_3$ | — | 32% | 27% |

Scheme 196

which have the different groups involved in the rearrangement properly aligned for antiparallel migration.[200,226] These two conformations are not isoenergetic and will not be attained with equal probability.[200,226]

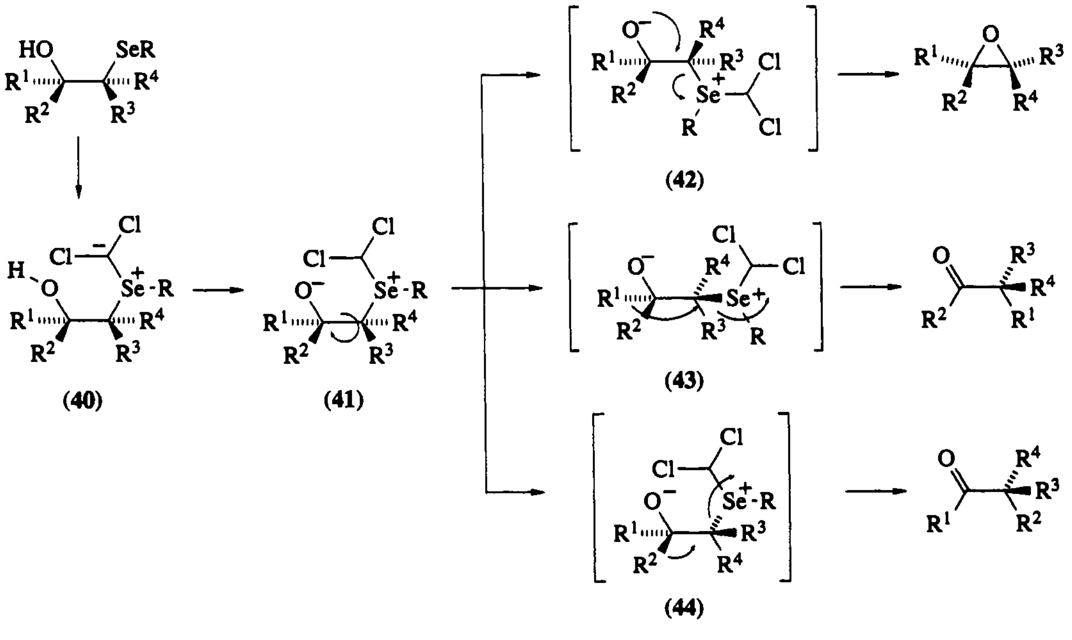
(40)
(41)
(42)
(43)
(44)

Scheme 197

### 2.6.4.6 Synthetic Uses of β-Hydroxyalkyl Selenides: Comparison with Well-established Related Reactions

#### 2.6.4.6.1 *Generalities*

The combination of reactions described above (Sections 2.6.4.2 to 2.6.4.5) allows the selective synthesis of a large variety of alcohols, allyl alcohols, alkenes, epoxides and carbonyl compounds from β-hydroxyalkyl selenides. These products often can be obtained from two carbonyl compounds by activation of one of them as an α-selenoalkyllithium (Schemes 161–196).

#### 2.6.4.6.2 *Synthesis of alcohols*

The whole process involving the reaction of an α-selenoalkyllithium with a carbonyl compound and further reduction of the C—Se bond in the resulting β-hydroxyalkyl selenide leads to an alcohol which can be directly produced from an alkyl metal and the same carbonyl compound (Section 2.6.4.2). This two-step procedure offers, in some cases, interesting advantages due to the larger size of α-selenoalkyllithiums, which favors a better stereochemical control (see, for example, Scheme 167 for comparison between the two approaches).[210]

#### 2.6.4.6.3 *Synthesis of allyl alcohols*

Allyl alcohols have been prepared from α-selenoalkyllithiums or from α-selenoxyalkyllithiums and carbonyl compounds (Section 2.6.4.4). Although the former route is less connective than the latter, it usually provides allyl alcohols in similar yields (Scheme 198) and offers the advantage of a higher nucleophilicity of the organometallic, which becomes valuable for the more-hindered carbonyl compounds (Scheme 164, b). Both α-selenoalkyllithiums and α-selenoxyalkyllithiums in these processes are synthetically equivalent to vinyl anions. The principal advantage over the classical alkenyllithium route is in the availability of the starting materials (selenoacetals and alkyl selenides), in contrast to the difficulty of obtaining the simplest vinyl halides. Furthermore, since allyl alcohols can be obtained[7,49] *via* the selenoacetal route from two carbonyl compounds, the activation of each of the two derivatives allows the regioselective synthesis of one of the two isomeric allyl alcohols (Scheme 174, b and c).[7,49]

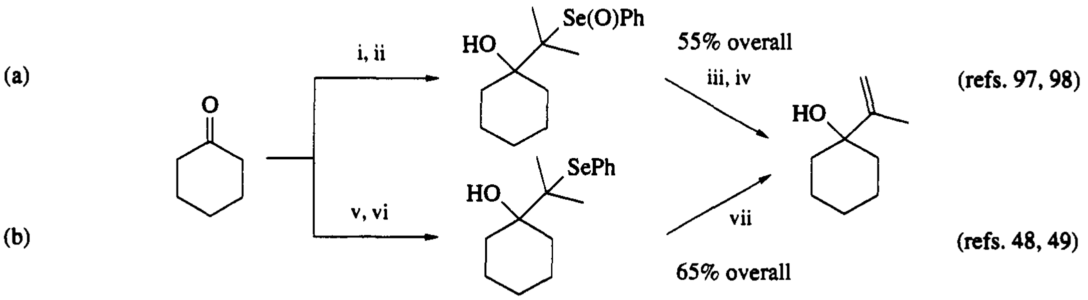

i, LiC(Me)$_2$Se(O)Ph, THF; ii, 10% AcOH, THF; iii, CCl$_4$, 70 °C; iv, 20 °C; v, LiC(Me)$_2$SePh, THF; vi, H$_3$O$^+$; vii, H$_2$O$_2$, THF, 20 °C

Scheme 198

#### 2.6.4.6.4 *Synthesis of epoxides, alkenes and carbonyl compounds*

Alkenes, epoxides and carbonyl compounds have been conveniently prepared from β-hydroxyalkyl selenides (Sections 2.6.4.3 and 2.6.4.5). These often can, in turn, be obtained from two carbonyl compounds by activation of one of them as an α-selenoalkyllithium. Although each of the two carbonyl compounds can be formally transformed to an α-selenoalkyllithium, in practice a judicious selection is often of some value and even in some cases crucial for the success of the transformations. The following rules might help for the choice. It is better to transform to an α-selenoalkyllithium the carbonyl compound which is: (i) the most readily available; (ii) the least substituted; (iii) the least hindered; and (iv) not aryl or vinyl substituted. Since α-selenoalkyllithiums belong to the well-known family of α-hetero-substituted organometallics,[7] some of them, such as phosphorus ylides[7,25,269–275] or α-silylalkyllithiums,[7,16,31,276] sulfur ylides[7,25,32,33] or α-thioalkyllithiums,[7,16,33] and diazoalkanes[277] have been intensively and successfully used for the one-pot synthesis from carbonyl compounds of alkenes and epoxides, as well as for the ring enlargement of cyclic ketones. The selective synthesis of the same compounds can also be achieved from α-selenoalkyllithiums by the multistep sequences already discussed, which involve the formation of the same bonds (shown in bold in Scheme 199).

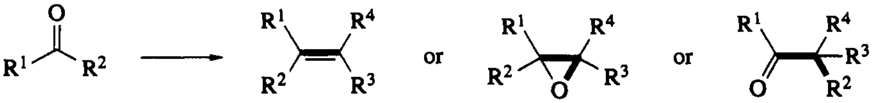

Scheme 199

Although in many instances the well-established, one-step procedures presented above are very efficient and should be preferred to the α-selenoalkyllithium route, there remain several cases for which the latter approach offers definite advantages.

The synthesis of the starting α-selenoalkyllithiums is, as already mentioned, easy and straightforward. Differently substituted reagents, including those bearing two alkyl groups on the carbanionic center, are available from carbonyl compounds and *via* a sequence of reactions which regioselectively allow the replacement of the carbonyl oxygen atom by the seleno moiety and the lithium atom. This compares very well to the synthesis of: (i) phosphorus and sulphur ylides, which require the use of lengthy procedures when *s*-alkyl-phosphonium[7,25,269–275] or -sulphonium salts[7,25,32,33] (with the exclusion of 2-propyl and cyclopropyl derivatives) are needed; and (ii) α-silyl-[7,16,31,276] or α-thio-alkyllithiums,[7,16,33] which is limited to the unsubstituted and monoalkyl-substituted derivatives.

The high nucleophilicity of α-selenoalkyllithiums towards carbonyl compounds, even those that are the most hindered or enolizable, such as 2,2,6-trimethyl- and 2,2,6,6-tetramethyl-cyclohexanone (Schemes 113 and 164),[188] di-*t*-butyl ketone,[189] permethylcyclobutanone,[190,191] permethylcyclopentanone (Schemes 113 and 187)[190,191] and deoxybenzoin (Schemes 115, 116 and 165),[159,194,196,223] allows the synthesis of related alkenes, epoxides and rearranged ketones which are not available from the same carbonyl compounds on reaction with phosphorus or sulfur ylides[278,279] or diazoalkanes.[206a]

The high tendency of α-selenoalkyllithiums, even those that bear alkyl substituents on the carbanionic center, to add at the C-1 site of enones allows the high yield synthesis of vinyl oxiranes (Schemes 132, 134 and 166).[221,239] These cannot be prepared from sulfur ylides since they add across the carbon–carbon double bond of enones to produce cyclopropyl ketones (Scheme 200).[280]

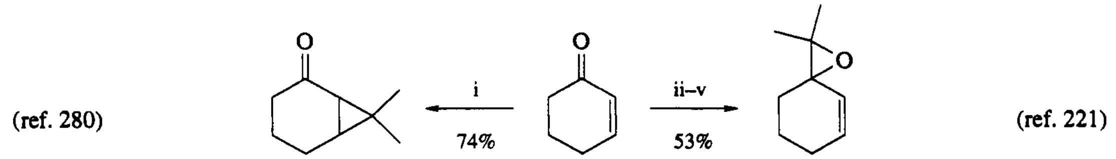

i, $Me_2C{=}SPh_2$, $LiBF_4$, DME; ii, $Me_2C(SeMe)Li$, THF; iii, $H_3O^+$; iv, MeI; v, $Bu^tOK$, DMSO

Scheme 200

In the rearrangement reaction, the multistep sequence offers the definite advantage of avoiding the polyhomologation of cyclic ketones, often encountered with diazoalkanes[277] due to the presence of the reagent with both the starting and rearranged ketone.

The stereoisomeric mixture of β-hydroxyalkyl selenides resulting from the reaction of the α-selenoalkyllithium and the carbonyl compound has been often cleanly and easily separated into its constituents by liquid chromatography on silica gel (Schemes 124, 133, 134, and 170–172).[200,206,222,226,229,258,259] This has, therefore, allowed the synthesis of each of the two stereoisomers of various di- and tri-substituted alkenes (Schemes 124, 170 and 171; Scheme 172, a) and epoxides (Scheme 124; Scheme 172, b),[206] which are otherwise obtained as intractable mixtures of stereoisomers through the conventional phosphorus or sulfur ylide methods. Last but not least, 2-lithio-2-methylselenopropane can be used as the precursor of various compounds bearing *gem* dimethyl substituted carbons, such as squalene,[222] oxidosqualene,[206,222,229] lanosterol[222] and cholesterol.[222] Use of commercially available perdeuterated or $^{14}C_1$ or $^{14}C_1$—$^{14}C_2$ acetone allows the straightforward synthesis of the corresponding labelled compounds (Schemes 131 and 201), which otherwise would have required a more lengthy synthetic route.

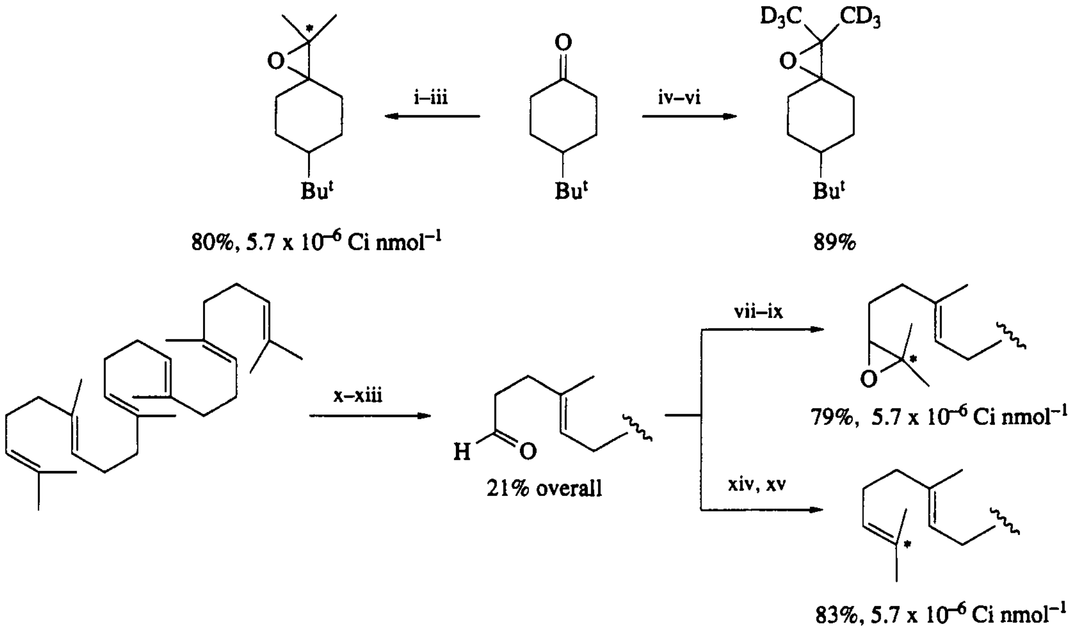
i–iii
iv–vi
Bu^t
O
D3C CD3
80%, 5.7 x 10^-6 Ci nmol^-1
89%
x–xiii
H O
21% overall
vii–ix
xiv, xv
79%, 5.7 x 10^-6 Ci nmol^-1
83%, 5.7 x 10^-6 Ci nmol^-1

* = $^{14}C$

i, $MeSe^{14}CMe_2Li$; ii, MeI, 20 °C; iii, 10% aq. KOH, ether; iv, $MeSeC(CD_3)_2Li$, ether; v, MeI, 20 °C; vi, 10% aq. KOH, ether; vii, $MeSe^{14}CMe_2Li$; viii, $MeSO_3F$, ether; ix, 10% aq. KOH, ether; x, NBS (1.1 equiv.), DME, $H_2O$; xi, 10% aq. KOH; xii, $HClO_4$; xiii, $NaIO_4$; xiv, $MeSe^{14}CMe_2Li$; xv, $PI_3$, $Et_3N$, $CH_2Cl_2$

**Scheme 201** [222]

## 2.6.5 MISCELLANEOUS REACTIONS INVOLVING FUNCTIONALIZED α-SELENOALKYL METALS AND CARBONYL COMPOUNDS

### 2.6.5.1 α-Selenoalkyl and α-Selenoxyalkyl Metals as Vinyl Anion Equivalents

α-Selenoalkyllithiums and α-selenoxyalkyllithiums have at several occasions played the role of vinyllithium equivalents. Thus, various β-seleno-[235] and β-selenoxy-carbonyl[98] compounds have been transformed to α,β-unsaturated carbonyl compounds by taking advantage of the well-established elimination of the corresponding selenoxide (Scheme 157, c, d and e).

### 2.6.5.2 1,1-Bis(seleno)alkyl Metals and 1-Silyl-1-selenoalkyl Metals as Acyl Anion Equivalents

#### *2.6.5.2.1 1,1-Bis(seleno)alkyl metals as acyl anion equivalents*

1,1-Bis(seleno)alkyl metals are valuable acyl anion equivalents. Thus β-hydroxybis(seleno)alkanes,[281] as well as β-hydroxy-γ,δ-unsaturated bis(seleno)alkanes or γ-oxobis(seleno)alkanes, selectively obtained on reaction of enals, or enones and 1-metallo-1,1-bis(seleno)alkanes in ether or THF–HMPA, immediately react[73,94,233,281] with copper chloride–copper oxide in acetone and lead, respectively, to β-hydroxy-β,γ-unsaturated carbonyl[73,94,233] compounds or γ-diketones (Scheme 139; Scheme 140, a, b and e; Scheme 149, b).[94,233] In some rare cases (see Scheme 140, e), the reaction proceeds[233] differently and instead leads to a vinyl selenide, which can be further transformed to a carbonyl compound when reacted with mercury(II) chloride.

#### *2.6.5.2.2 1,1-Silyl-1-selenoalkyl metals as acyl anion equivalents*

α-Hydroxycarbonyl compounds have also been synthesized[171] from β-hydroxy-α-silylalkyl selenides and hydrogen peroxide (Scheme 96, d). The reaction proceeds smoothly under mild conditions and might involve a Pummerer-type rearrangement.

### 2.6.5.3 Homologation of Carbonyl Compounds from α-Heterosubstituted-α-selenoalkyl Metals

α-Selenoalkyl metals bearing on the carbanionic center a phosphono,[106] phosphonato (Scheme 28),[102] silyl (Scheme 96, e)[171] or seleno moiety (Scheme 98, b) allow the homologation of carbonyl compounds. The three former reagents immediately lead to vinyl selenides on reaction with carbonyl compounds, whereas the latter requires the reductive elimination of the β-hydroxybis(seleno)alkane intermediate to provide the same vinyl selenides (Scheme 98, b).[108] These have been later transformed to carbonyl compounds on reaction with mercury(II) chloride.[11,102,106,108,171]

### 2.6.5.4 Conclusion

Most of the reactions described in this section have not been carried out on a large array of compounds. It is therefore difficult to compare their scope to the related reactions which use other α-heterosubstituted alkyl metals.[7]

## 2.6.6 GENERAL CONCLUSION

In conclusion, α-selenoalkyllithiums and α-selenoxyalkyl metals are versatile building blocks, readily available, and particularly prone to produce β-hydroxyalkyl selenides and β-hydroxyalkyl selenoxides which, after proper activation, have allowed the selective synthesis of various selenium-free compounds.

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# 3.1

# Alkene Synthesis

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## 3.1.1 INTRODUCTION

In this chapter, the various methods of converting a carbonyl derivative to an alkene are discussed. Particular focus has been given to recently developed methods and their use in the context of natural product synthesis. Formally this volume in the series is devoted to nonstabilized carbanion additions, but this mechanistic definition has not been strictly adhered to in this chapter. The methods are categorized according to the type of alkene synthesized, and the stabilizing group attached to the anion or carbene. In addition, all of the methods discussed involve the addition of a carbon unit to the carbonyl, followed by some type of elimination or cleavage to the alkene. To further narrow the scope of this chapter, the added carbon unit and the original carbonyl carbon must form the units of the alkene, as shown in Scheme 1.

Aldehydes, ketones, esters and lactones, and amides and lactams are all featured in these sections, depending on the synthetic method being discussed.

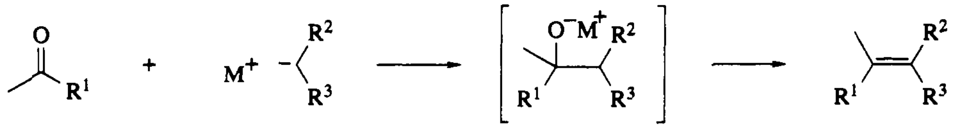

**Scheme 1**

## 3.1.2 METHYLENATION REACTIONS: INTRODUCTION

The methylenation of ketones and aldehydes by the Wittig reaction is a well-established and selective methodology. Unlike addition–elimination methods of alkene formation, the Wittig proceeds in a defined sense, producing an alkene at the original site of the carbonyl. The Wittig reaction is not considered here, but is used as the standard by which the methods discussed are measured.[1] The topics covered in the methylenation sections include the Peterson alkenation, the Johnson sulfoximine approach, the Tebbe reaction and the Oshima–Takai titanium–dihalomethane method.

## 3.1.3 SILICON-STABILIZED METHYLENATION: THE PETERSON ALKENATION

The conversion of a carbonyl to an alkene can be effected by the addition of a α-silyl-substituted alkyl anion to an aldehyde or ketone, followed by either alkoxide attack on the silicon and elimination of silanolate, or acid-catalyzed elimination (Scheme 2).[2]

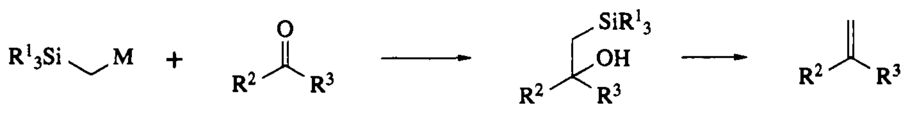

**Scheme 2**

In the case of base-induced elimination, the Peterson alkenation relies on the strong bond formed between silicon and oxygen, and the ready propensity for silicon to be attacked by alkoxide, to drive the reaction.[3] In the original study by Peterson, the β-silylcarbinols were prepared by the addition of (trimethylsilyl)methylmagnesium chloride to the carbonyl. The carbinols were subsequently eliminated by treatment with sodium or potassium hydride or with sulfuric acid to form the methylene derivatives in excellent yield. The Peterson reaction has proven to be of general utility in the synthesis of alkenes.[4]

### 3.1.3.1 Methylenation in Comparison with the Wittig Reaction

The Peterson reagent is more basic and is sterically less hindered than the phosphorus ylide.[4] Therefore, the reagent has the advantage of being more reactive than the Wittig reagent and the side product, hexamethyldisiloxane, is simpler to remove than the various phosphorus by-products of the Wittig reaction. One of the most frequently cited comparisons of the Wittig reaction with the Peterson is the synthesis of β-gorgonene (2) by Boeckman and coworkers, where the Wittig failed and the Peterson methodology was successful (equation 1).[5]

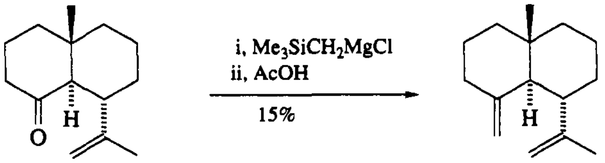

(1) (2)

(1)

In an interesting comparison of the propensity for alkoxide attack on silicon, given the option of elimination in the direction of phosphorus or silicon, it is the silicon elimination that prevails, to give the vinylphosphonium salt (Scheme 3).[2] For use with enolizable carbonyls, the basicity of the reagent can be greatly reduced by the use of cerium chloride, as discussed in Section 3.1.3.4.2.

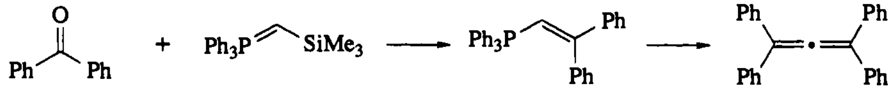

Scheme 3

### 3.1.3.2 Elimination Conditions

As Peterson outlined in his preliminary communication of the method, either basic (KH, KOBu$^t$ or NaH) or acidic conditions (acetic acid, sulfuric acid or boron trifluoride etherate) may be utilized to effect the elimination of the silylcarbinol.[2] Alternatively the initial adduct may be treated *in situ* with thionyl or acetyl chloride.[6] This procedure may be advantageous in cases where isomerization of the alkene is problematic, and is particularly useful in the synthesis of terminal alkenes. As discussed in Section 3.1.3.4.2, the Johnson group has successfully employed aqueous HF to effect the elimination and this method may also have advantages in situations complicated by base-catalyzed isomerization.[7]

### 3.1.3.3 Variation of the Metal Anion

The most prevalent applications of the Peterson methodology are with the readily available lithium or magnesium anions, which have similar reactivity with both aldehydes and ketones.[8] Recent examples of the Peterson methylenation in organic synthesis are presented in Table 1.

In addition to the examples in Table 1, the Peterson methylenation has been used in several interesting natural product syntheses, as the examples in equation (2)–(6) indicate. Danishefsky and coworkers used the Peterson reaction in an approach to mitomycins (**4**; equation 2).[16] This application demonstrated the use of unique elimination conditions. The hydroxysilane intermediate was stable to direct Peterson elimination. Therefore, the removal of the silyl protecting group and the elimination of the silyloxy group were carried out with DDQ in quantitative yield.

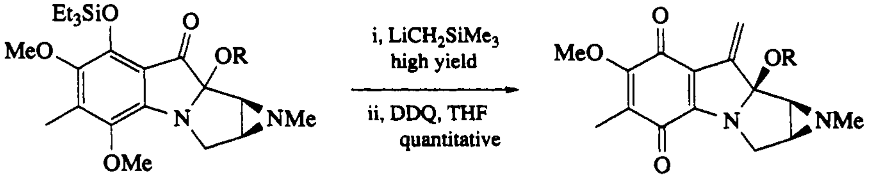

(2)

(**3**) R = H, Me (**4**)

The Peterson methodology has seen wide application in the synthesis of carbohydrates. The preparation of 3-*C*-methylene sugars (**6**) was demonstrated by Carey and coworkers, with the methylenation proceeding without elimination of the anomeric alkoxy group (equation 3).[17] A more recent example of Peterson methylenation of a carbohydrate is the synthesis of a deoxyamino sugar (**8**) by Fraser-Reid (equation 4).[18] In this case, the carbonyl failed to react with the methylenetriphenylphosphorane at room temperature, and forcing conditions resulted in decomposition. Application of the Oshima–Takai–Lombardo method also failed.[19] The Peterson reagent added in excellent yield, and the elimination resulted in the formation of the desired methylene (**8a**) as well as the vinylsilane (**8b**).

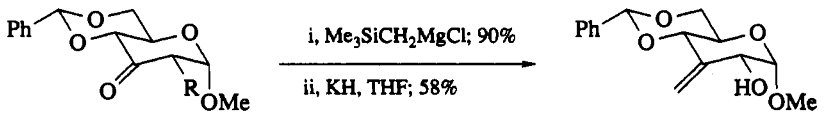

(3)

(**5**) R = OCOPh (**6**)

Further examples of the Peterson methylenation successfully being applied when other techniques failed are shown in equations (5) and (6). In the synthesis of bicyclomycin, a diazabicyclodecane dione, both the Wittig and the Tebbe procedures failed.[20] (Trimethylsilyl)methylmagnesium chloride was added to ketone (**9**) in 52% yield. The usual elimination procedures failed. The trifluoroacetate was formed, and this derivative was treated with $Bu^n{}_4NF$ to effect the elimination. Following deprotection, the desired methylene derivative (**10**) was isolated in 81% yield (equation 5). In studies directed toward the synthesis of senoxepin (**12**), $CH_2Br_2/Zn/TiCl_4$ methylenation destroyed the oxepin.[21] The Peterson reagent was successfully added, and further elaboration of the ring skeleton was carried out to complete the synthesis (equation 6).

**Table 1** Methylenation by the Addition of Lithium or Magnesium Trimethylsilylmethyl Anion to Carbonyls

| *Substrate* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 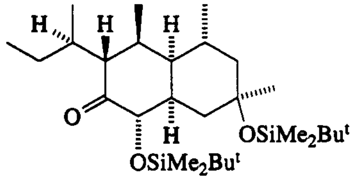 | i, $LiCH_2SiMe_3$; ii, KH, THF; iii, $Bu^n{}_4NF$<br>no epimerization | 35 (3 steps) | 9 |
| 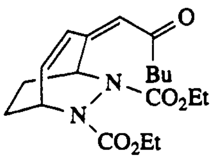 | i, $ClMgCH_2SiMe_3$; ii, $SOCl_2$ | 50–60 | 10 |
| 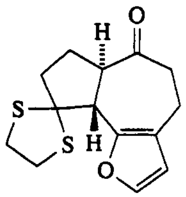 | i, $LiCH_2SiMe_3$; ii, NCS, $AgNO_3$ | 80 | 11 |
| 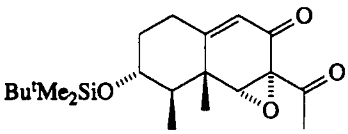 | i, $ClMgCH_2SiMe_3$; ii, $H_2SO_4$, THF; iii, HF, MeCN | 88[a] (3 steps) | 12 |
| 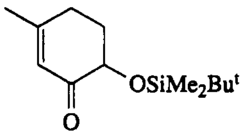 | i, $ClMgCH_2SiMe_3$; ii, cat. oxalic acid, MeOH<br>base not effective | 72 | 13 |
| 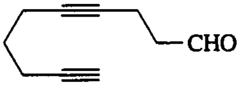 | i, $ClMgCH_2SiMe_3$; ii, MeCOCl, $MeCO_2H$ | 60 | 14 |
| 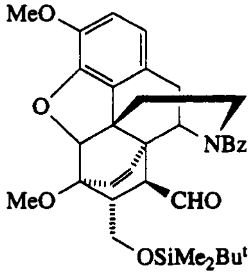 | i, $ClMgCH_2SiMe_3$, 84%; ii, KH, THF, 89% | 75 | 15 |

[a] Yield of product methylenated at side chain carbonyl only.

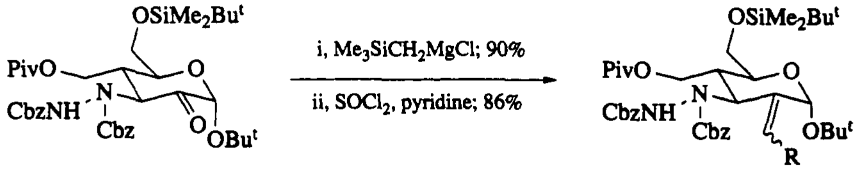
OSiMe2Bu<sup>t</sup>
PivO
O
CbzNH
N
Cbz
O
OBu<sup>t</sup>
i, Me3SiCH2MgCl; 90%
ii, SOCl2, pyridine; 86%
R

(7) Cbz = benzyloxycarbonyl

(8a) R = H; 75%
(8b) R = $Me_3Si$; 25%

(4)

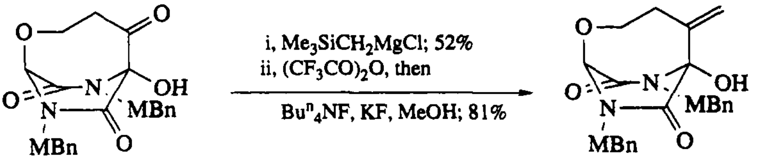
O
OH
N
MBn
i, Me3SiCH2MgCl; 52%
ii, (CF3CO)2O, then
Bu<sup>n</sup>4NF, KF, MeOH; 81%

(9) (10)

(5)

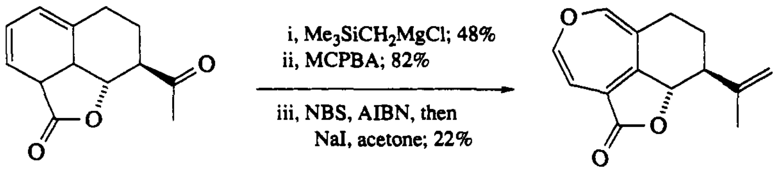
O
i, Me3SiCH2MgCl; 48%
ii, MCPBA; 82%
iii, NBS, AIBN, then
NaI, acetone; 22%

(11) (12)

(6)

## 3.1.3.4 Chemoselectivity

### *3.1.3.4.1 Titanium*

Recently, the chemoselective addition of the α-silylmethyl anion to aldehydes has been accomplished with titanium (equation 7). In studies by Kauffmann, the Grignard derivative was treated with $TiCl_4$ to prepare the titanium species *in situ*.[22] As indicated in Table 2,[22] this reagent added in good yield to aldehydes to produce the desired methylene compounds but was ineffective for the conversion of ketones to the corresponding methylene compound.[23]

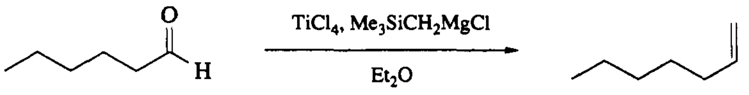
O
H
TiCl4, Me3SiCH2MgCl
Et2O

(7)

**Table 2** Titanium Peterson Methylenation[22]

| *Substrate* | *Yield (%)* | *Substrate* | *Yield (%)* |
|---|---|---|---|
| Hexanal | 60 | Benzaldehyde | 59 |
| Heptanal | 65 | 3,3-Dimethyl-3-butanone | 0 |
| Octanal | 59 | 4-*t*-Butylcyclohexanone | 8 |
| Nonanal | 61 | Acetophenone | 3 |

### *3.1.3.4.2 Cerium*

Johnson has studied the cerium modification of the Peterson methylenation.[24] (Trimethylsilyl)methyllithium was added to $CeCl_3$ and the addition carried out in the presence of TMEDA (equation 8). The cerium lithium reagent proved to be superior to the lithium, magnesium or cerium magnesium mixed species on reaction with base sensitive aldehydes and ketones.[25] The addition is chemoselective for aldehydes and ketones in the presence of amides, esters and halides. The elimination was carried out with HF or KH. Aqueous hydrogen fluoride (with or without pyridine) gave superior yields of the desired products without isomerization. Several examples are listed in Table 3.[24,26]

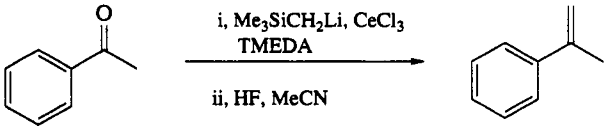

**(13)** **(14)** (8)

**Table 3** Cerium Modification of the Peterson Methylenation[24]

| *Carbonyl* | *Me$_3$SiCH$_2$Li* | *Me$_3$SiCH$_2$Li/CeCl$_3$* | *HF* |
|---|---|---|---|
| 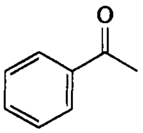 | 78% | 93% | 84% |
| 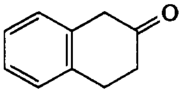 | 0% | 82% | 80% |
| 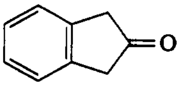 | 6% | 83% | 87% |
| 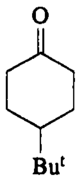 | 78% | 91% | 94% |
| 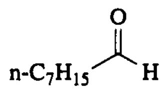 | 56% | 86% | 93% |

In addition, this approach has been utilized in the synthesis of allylsilanes, as shown in Scheme 4. An ester was reacted with an excess of the reagent prepared from TMSCH$_2$MgCl and CeCl$_3$ to give the bis(silylmethyl)carbinol (**16**).[27] Treatment with silica gel resulted in the formation of the allylsilane (**17**). Examples are listed in Table 4.

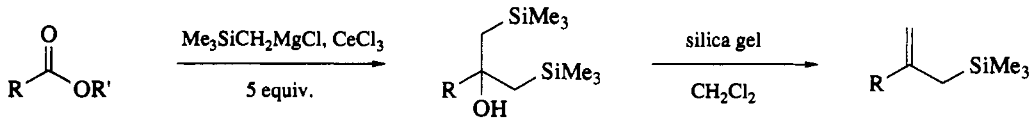

**(15)** **(16)** **(17)**

**Scheme 4**

As in the work by Johnson, a distinct difference was noted in the magnesium- and lithium-derived cerium species. The lithium/cerium complex has been used by Fuchs and coworkers to synthesize allylsilane derivatives (**20**) from acyl chlorides (**18**; Scheme 5).[28] This work is summarized in Table 5.

**Table 4** Reaction with Esters[27]

| *Ester* | *Yield of allylsilane (%)* | *Ester* | *Yield of allylsilane (%)* |
|---|---|---|---|
| 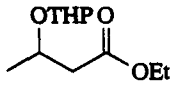 | 90 | 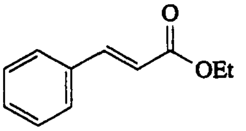 | 93 |
| 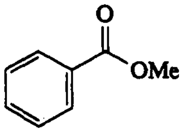 | 95 | 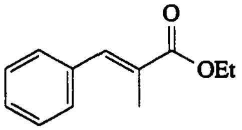 | 92 |

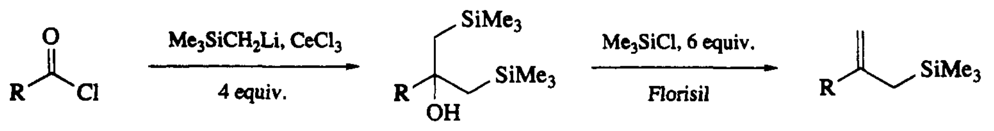

**(18)** **(19)** **(20)**

**Scheme 5**

**Table 5** The Addition of the Cerium Peterson Reagent to Acid Chlorides to Form Allylsilanes[28]

| *Substrate* | *$Me_3SiCH_2MgCl$* | *$Me_3SiCH_2Li$* | *$Me_3SiCH_2Li/CeCl_3$* |
|---|---|---|---|
| 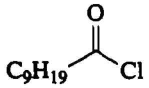 | 20% | 61% | 87% |
| 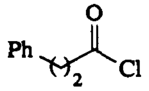 | 0% | 40% | 72% |
| 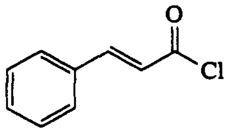 | 22% | 40% | 90% |
| 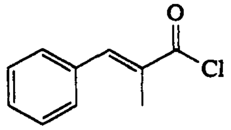 | 7% | 64% | 80% |

Interestingly, the lithium/cerium reagent was not effective on reaction with esters. Besides the differences in counterion, the Fuchs and Bunnelle groups utilized different methods for forming the cerium complex. Johnson and Bunnelle formed the cerium Peterson reagent by heating $CeCl_3 \cdot 7H_2O$ to 140–150 °C under high vacuum for 2 h.[24,27] The flask is cooled and THF is added. The $CeCl_3$ in THF is stirred at room temperature for 2 h, then cooled to –78 °C, and the lithium or magnesium Peterson reagent is added. After this solution has been stirred for 30 min to 1 h the carbonyl derivative is added. The Fuchs anion is derived from commercially available $CeCl_3$.[28] It is stirred at room temperature in THF for 12–24 h, and then the solution is cooled and the Peterson anion added. It is unknown what effect the different preparations has on the additions to the various carbonyl derivatives. The cerium reagent has proven to be highly advantageous for the synthesis of allylsilanes from esters or acid chlorides that are sterically hindered, without competitive enolization.

### 3.1.3.5 Substitution on Silicon[29]

(Phenyldimethylsilyl)methylmagnesium chloride has recently been demonstrated to be an effective alternative to the trimethylsilyl derivative.[30] This reagent has been used in the methylenation of pyranosides (**21**). It forms a stable α-hydroxysilane that can be purified by silica gel chromatography. The intermediate may be oxidized to the diol or quantitatively cleaved to the methylene derivative (**22**; equation 9).

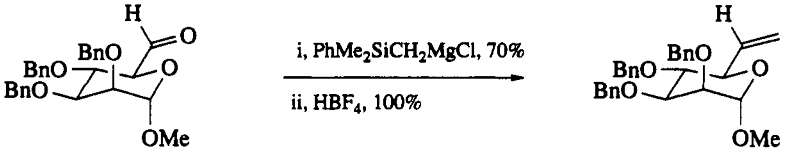

**(21)** **(22)** (9)

### 3.1.3.6 Other Reactions

α,β-Epoxysilanes can be synthesized directly from an aldehyde or a ketone by the addition of chloromethyl(trimethylsilyl)lithium (Scheme 6).[31] This functional group can be used to form the homologated aldehyde or ketone (**24**), or, as discussed in Section 3.1.10, additions may be carried out on the epoxide, and the β-hydroxysilane eliminated to form the alkene (**25**).

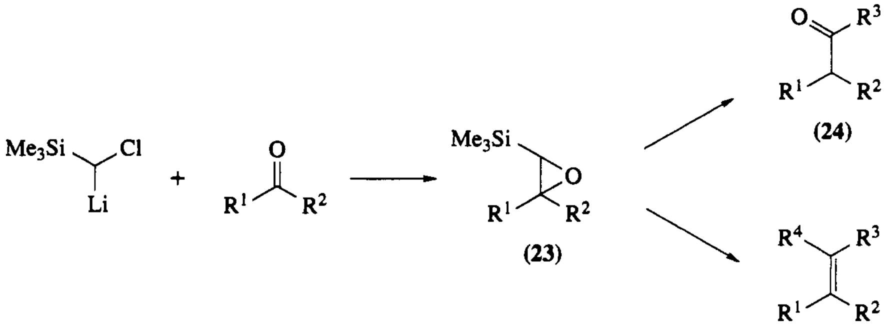

**Scheme 6** **(25)**

## 3.1.4 SULFUR-STABILIZED METHYLENATION: THE JOHNSON (*N*-METHYLPHENYLSULFONIMIDOYL)METHYLLITHIUM METHOD

In 1973, Johnson reported the use of (*N*-methylphenylsulfonimidoyl)methyllithium (**26**) for addition to carbonyls, followed by reductive elimination to produce the methylene derivative (**28**; Scheme 7).[32] As with the Tebbe and Oshima procedures discussed in Sections 3.1.5 and 3.1.6, this method can be applied to enones, ketones and, with comparatively diminished efficiency, aldehydes.[33] The anion appears to be more nucleophillic than methylenetriphenylphosphorane, and there are several examples, detailed below, in which the Wittig reaction failed but the Johnson procedure succeeded. The addition and reductive cleavage can be combined into a single operation without isolation of the β-hydroxysulfoximine.[33]

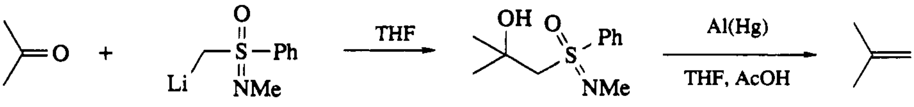

**(26)** **(27)** **(28)**

**Scheme 7**

### 3.1.4.1 Reductive Elimination

In addition to aluminum amalgam, several other methods were explored for the elimination of the β-hydroxysulfoximine.[33] Acetylation, followed by attempted elimination under a variety of conditions, was not effective, and therefore reducing agents were explored. Of the various metals investigated, magnesium amalgam, zinc and chromium did not have high enough oxidation potentials to give good ratios of the desired alkene. While sodium, magnesium, aluminum and aluminum amalgam were all effective, only the latter reagent, in the presence of acetic acid, was high yielding and gave acceptable ratios of alkene to alcohol. The proposed mechanism of reductive cleavage entails a two-electron transfer from the aluminum to the sulfoximine (**29**). Collapse of this intermediate results in a carbanion (**31**) and the sulfinamide (**32**). The sulfur derivative may be further reduced to thiophenol and the carbanion can either be protonated to yield the alcohol or eliminated to yield the alkene (**33**; Scheme 8).[33] It was found that the methylenation of aryl aldehydes is complicated by the reaction of the styrene (**34**) with the thiophenol produced in the reduction to give the sulfide (**35**; equation 10). While this side reaction can be abated by the use of less aluminum amalgam, this gave diminished yields, so the best choice would be an alternative method of methylenation.

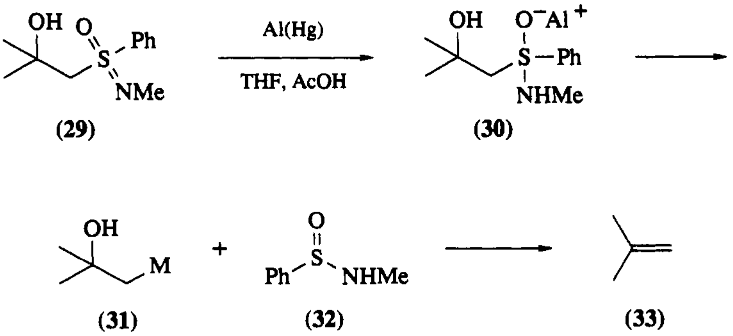

(29) (30) (31) (32) (33)

Scheme 8

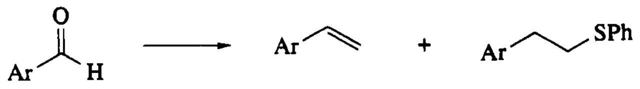

(34) (35) (10)

### 3.1.4.2 Examples of the Johnson Methylenation Procedure

Examples of the Johnson methylenation procedure are outlined in Table 6. As the examples indicate, the methodology is compatible with a wide variety of ethers, as well as amides and esters.

### 3.1.4.3 Comparison with the Wittig Procedure

Of particular note in comparison with the Wittig procedure is Boeckman's total synthesis of gascardic acid (equation 11). It was found that direct Wittig methylenation was low yielding in the reaction with (**36**).[39] It was hypothesized that this was because of interference with the two-carbon side chain. The problem was solved by hydrolyzing the esters, followed by addition and elimination of the sulfoximine and reesterification to obtain the desired adduct (**37**) in 70% overall yield. The Johnson method was also utilized to selectively methylenate the less-hindered ketone (**38**) in the synthesis of (–)-picrotoxinin (equation 12).[40]

### 3.1.4.4 Resolution

The tremendous advantage of this method of methylene formation over the various other procedures is that it is capable of producing optically pure material through the addition of an enantiomer of (methyl-

**Table 6** Reaction of *N*-Methylphenylsulfonimidoylmethyl Anion with Ketones

| *Entry* | *Substrate* | *Reagent* | *Yield of RR'CCH$_2$ (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 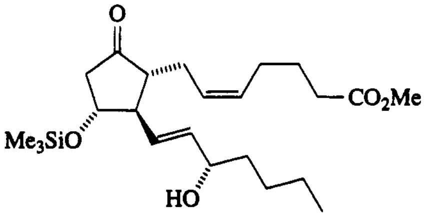 | BrMgCH$_2$SOPhNMe | 75 | 34 |
| 2 | 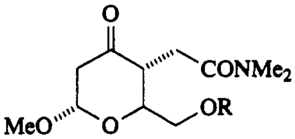 | R = COPh<br>LiCH$_2$SOPhNMe<br>R = CH$_2$Ph | 59<br><br>50 | 35 |
| 3 | 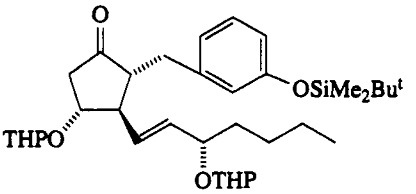 | LiCH$_2$SOPhNMe | 72 | 36 |
| 4 | 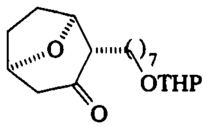 | LiCH$_2$SOPhNMe | 66 | 37 |
| 5 | 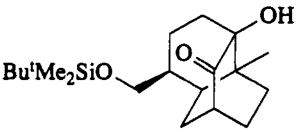 | LiCH$_2$SOPhNMe | 67 | 38 |

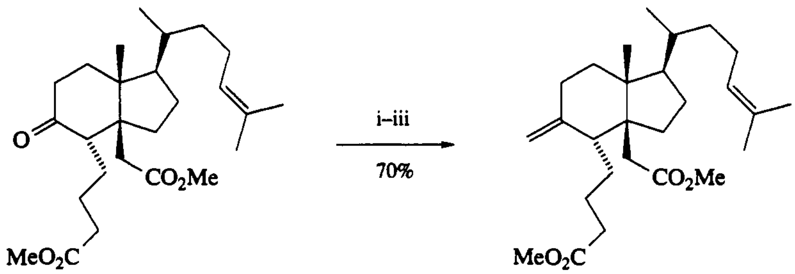

**(36)** **(37)** (11)

i, Na$_2$CO$_3$, aq. MeOH; ii, PhSO(NMe)CH$_2$Li, THF, –78 °C, then *in situ* Al(Hg), AcOH; iii, CH$_2$N$_2$, Et$_2$O

phenylsulfonimidoyl)methyllithium to the ketone.[41] As demonstrated in the synthesis of (–)-β-panasinsene (**43**), the diastereomers (**41**) and (**42**) can be separated (frequently by simple column chromatography) and taken on to the enantiomeric methylenes (**43**) and (**44**).[42] Johnson observed excellent facial diastereoselectivity in the addition of the sulfoximine to the racemic ketone (**40**; Scheme 9). In another interesting comparison to the Wittig reaction, the same ketone was reported to be unreactive to the Wittig reagent in DMSO.[42]

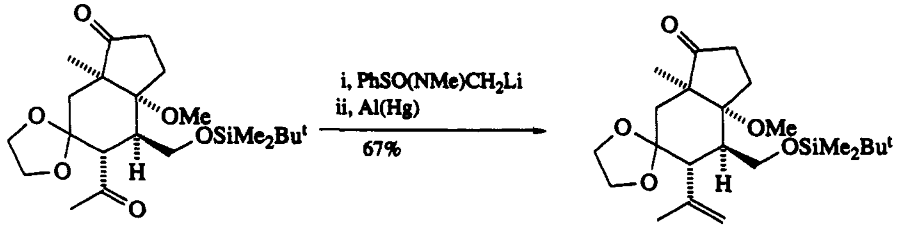
i, PhSO(NMe)CH$_2$Li
ii, Al(Hg)
67%
OMe
OSiMe$_2$Bu$^t$
H

(12)

**(38)** **(39)**

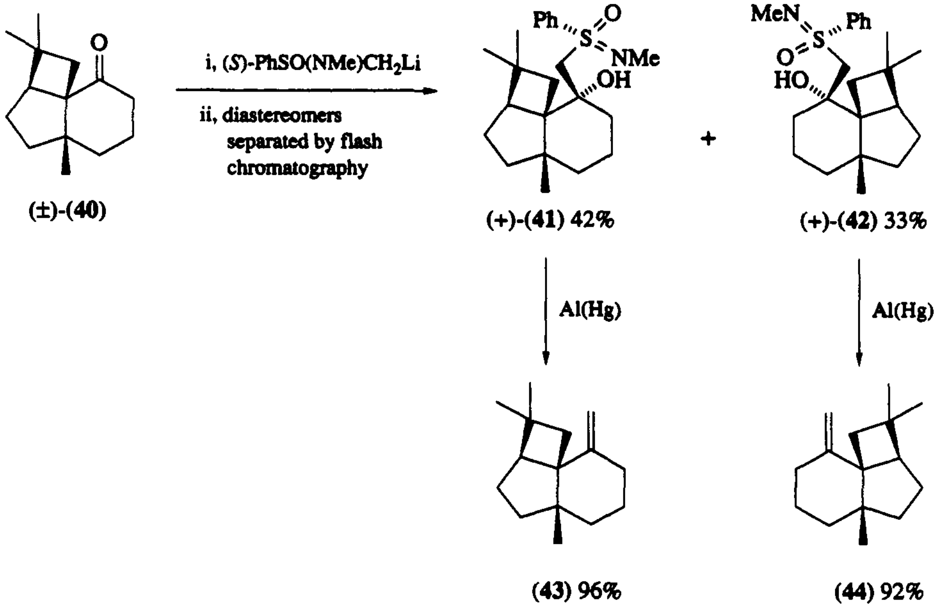
i, (S)-PhSO(NMe)CH$_2$Li
ii, diastereomers separated by flash chromatography
(±)-(40)
Ph
NMe
OH
MeN
Ph
HO
+
(+)-(41) 42%
(+)-(42) 33%
Al(Hg)
Al(Hg)
(43) 96%
(44) 92%

**Scheme 9**

In addition to synthesizing optically pure alkenes, this method can be utilized to produce chiral ketones and alcohols as shown in Scheme 10.[43] The intermediate sulfoximine (**45**) can either be reduced with Raney nickel to the chiral alcohol (**46**) or, because it is not stable to thermolysis, heated to revert back to the ketone (**47**).

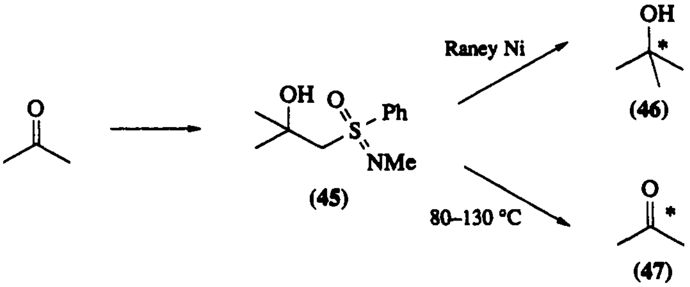
Raney Ni
OH
Ph
NMe
(45)
80–130 °C
(46)
(47)

**Scheme 10**

As detailed in Scheme 11, Paquette has taken advantage of both the methylenation and the thermolysis in studies concerning the nucleus of cerorubenic acid.[44] Since the absolute configuration of the natural product was unknown, the route made use of the symmetry of the diketone (**48**) to produce either enantiomer of the ketoalkenes (**52**) and (**53**). Paquette observed the same high facial selectivity that Johnson had observed on the addition of the sulfoximine to the ketone.[43b] The diastereomers produced, (**49**) and (**50**), could be readily separated by silica gel chromatography, reduced with Raney nickel and dehydrated with the Burgess reagent. Although the reductive cleavage with Al(Hg) was attempted, in this example it proved unsuccessful.[44] The overall efficiency of the process was improved by first carrying out the Wittig reaction to produce methylene (**51**), followed by the addition of the sulfoximine. Once again the diastereomers could be separated and, having served its purpose of resolution, the sulfoximine was cleaved thermally back to the ketoalkenes (**52**) and (**53**).

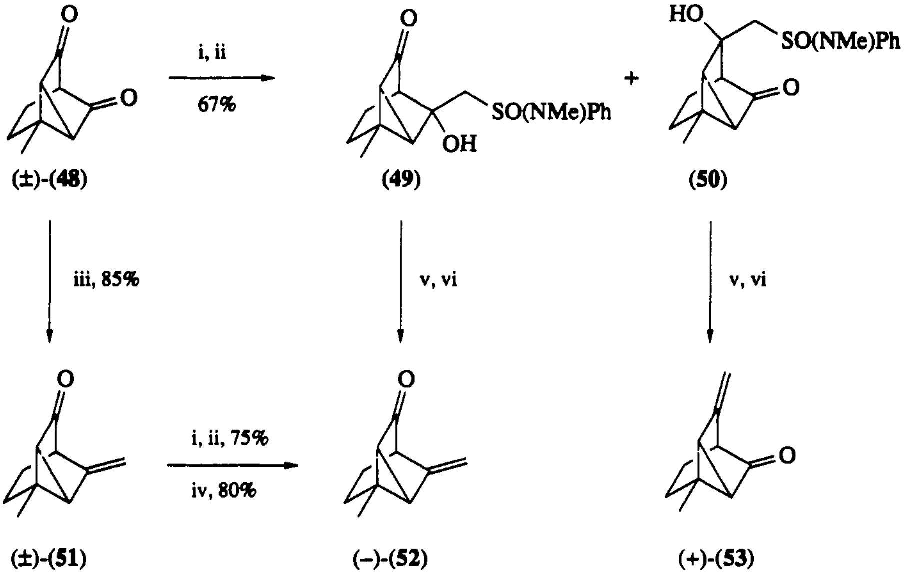

i, (+)-PhSO(NMe)CH$_2$Li; ii, separate diastereomers; iii, $Ph_3\overset{+}{P}\overset{-}{C}H_2$;
iv, 130 °C, PhH; v, Raney Ni, EtOH; vi, $MeO_2C\overset{-}{N}SO_2\overset{+}{N}Et_3$

Scheme 11

Besides serving as a useful tool for resolution, the sulfoximine addition adduct can be utilized to direct such reactions as the Simmons–Smith cyclopropanation and $OsO_4$ addition to an alkene.[43]

### 3.1.4.5 Halogen Incorporation

Finch has demonstrated that the sulfoximine approach is a viable alternative for fluoromethylenation (Scheme 12). The fluorosulfoximine (**54**) is deprotonated with LDA in THF and the aldehyde or ketone added to the anion. Conversion to the alkene is carried out with the standard aluminum amalgam procedure to yield a 1:1 mixture of (*E*)- and (*Z*)-alkenes (**56**). The reaction is very effective for aromatic and aliphatic aldehydes and aliphatic and alicyclic ketones, but, while aromatic and α,β-unsaturated ketones give good yields of the addition adduct, the reductive elimination results in a variable amount of product formation. This method was applied to the synthesis of prostaglandin 9-fluoromethylene (**58**; equation 13).[45]

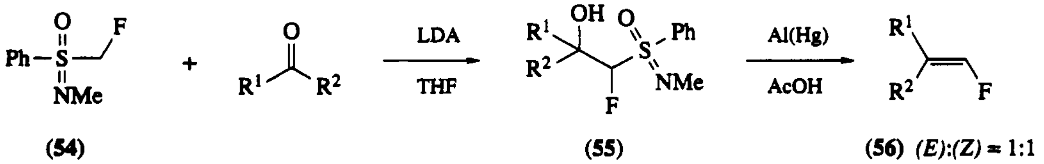

Scheme 12

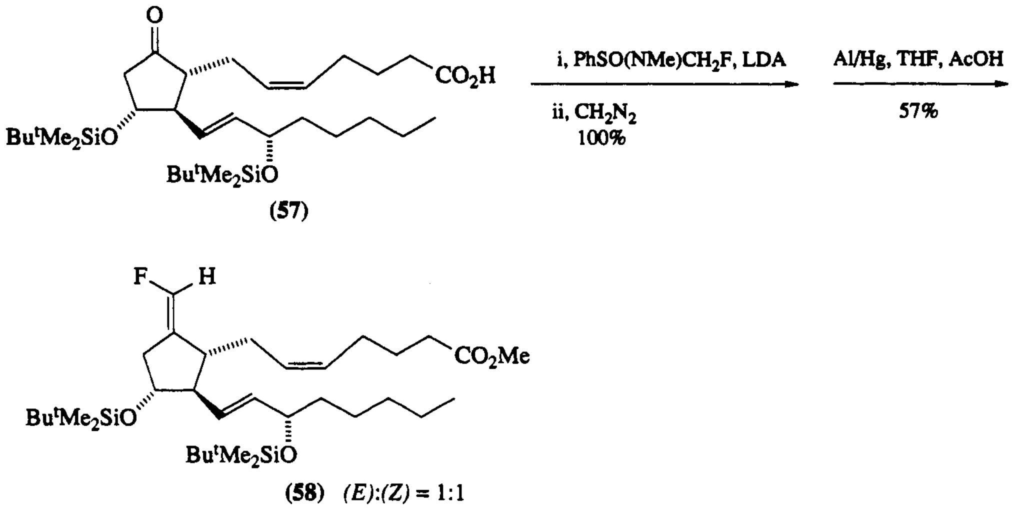

(57)

(58) (E):(Z) = 1:1

(13)

### 3.1.4.6 Di-, Tri- and Tetra-substituted Alkenes

The Johnson procedure may not be applied to tetrasubstituted alkenes. The explanation is that the reduced nucleophilicity of the sulfoximine causes it to function as a strong base, rather than add to the ketone.[33] The reaction of higher analogs of the methyl sulfoximine may be applied to the synthesis of di- and tri-substituted alkenes but, while the reactions proceed to give *trans*-alkene as the major product, the *trans*/*cis* selectivity is not high.[33] An excellent comparison between the sulfoximine and Wittig reactions is found in the synthesis of 6a-carbaprostaglandin $I_2$ (**60**; equation 14).[46] Initial attempts to incorporate the top portion by a Wittig reaction were complicated by apparent enolization of the carbonyl (**59**). While this was effectively solved by employing the more nucleophilic Johnson sulfoximine procedure, the *trans*/*cis* ratio was approximately 1:1. It was subsequently discovered that the difficulties encountered with the Wittig could be solved if an excess of the ylide was utilized.[46]

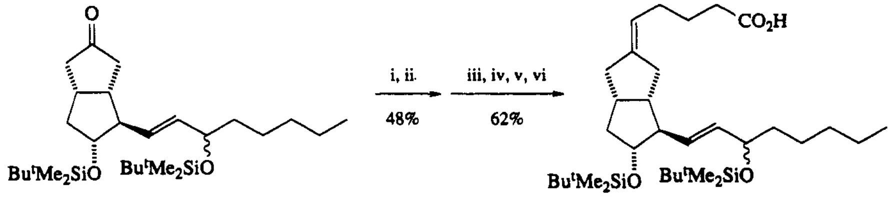

(59)

(60)

(14)

i, $PhSO(NMe)CH_2(CH_2)_4OTHP$, MeMgBr; ii, Al/Hg, THF, AcOH; iii, $Bu^n{}_4NF$; iv, $Ac_2O$, Py; v, AcOH; vi, Jones reagent

It has been demonstrated that the mechanism (see Section 3.1.4.1) for the reductive cleavage of the sulfoximine explains the mix of alkenes.[33] Other effects, such as interconversion of the hydroxysulfoximines, alcohol elimination or equilibration of the alkenes, were experimentally eliminated as the cause of the *trans*/*cis* ratios.[33]

### 3.1.4.7 Phenylphosphinothioic Amide

In addition to the sulfoximines, Johnson has studied phosphinothioic amides as alkene precursors.[47] This reagent has not achieved the popularity of the sulfoximines. It can be utilized for ketone methylenation with resolution, as well as for the synthesis of more highly substituted alkenes.[48] Rigby has found that in the synthesis of guaianolides this reagent was effective where Peterson and Wittig reactions gave only β-elimination.[49]

## 3.1.5 TITANIUM-STABILIZED METHYLENATION: THE TEBBE REACTION

The application of Wittig technology to higher oxidation state carbonyls, such as esters and amides, is complicated by the undesired cleavage of the ester or amide bond. In addition, any basic method of alkene formation has the inherent possibility of enolizing a sensitive carbonyl derivative. In the course of studies directed toward reagents for the alkene metathesis reaction, a secondary observation was made by Schrock that lead to the discovery of higher oxidation state metal analogs of the Wittig reagent. These alkylidene complexes have filled an important gap in synthetic methodology.

Schrock discovered that the *t*-butylalkylidene complex of tantalum (and in lower yield, niobium) was a structural analog to the phosphorus ylide.[50] The complex proved to be a reagent for *t*-butylalkene formation. Of the Wittig-type reactions tried, most notable was the ability of the complex to react with esters and amides to form the corresponding *t*-butylalkenes in good yields.

### 3.1.5.1 Methylenation

Stimulated by these findings, the titanium methylenation reagent, known as the Tebbe reagent (**61**), was first introduced in 1978 and has been widely used for the one-carbon homologation of carbonyls.[51] As discussed in a footnote in the Tebbe paper, the reagent reacts with aldehydes, ketones and esters to produce the methylene derivatives. This observation was expanded by Evans and Grubbs to include a wide range of both esters and lactones.[52] It was observed that the rate of reaction was increased by the presence of donor ligands such as THF and pyridine. This effect has been noted in the reaction of the Tebbe reagent with alkenes.[53] The explaination provided is that the Lewis acid removes $Me_2AlCl$ from the metallocycle, allowing the reactive $[Cp_2TiCH_2]$ fragment to be trapped by the carbonyl or alkene. In addition, Evans and Grubbs discovered that the Tebbe reagent tolerated ketal and alkene functionality. The stereochemical integrity of unsaturated carbonyls is maintained. Pine and coworkers found that the reactivity of the reagent towards ketones was higher than that towards esters,[52] allowing for selective methylenation of dicarbonyl compounds.[54] In addition to ester functionality, the reaction can be performed on amides to produce the corresponding enamines. The methylenation reaction is summarized in Scheme 13. Inspection of Tables 7–10 reveals the wide variety of substrates and functional groups with which the reaction is compatible.

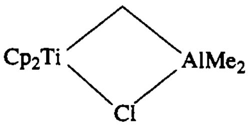

(**61**)

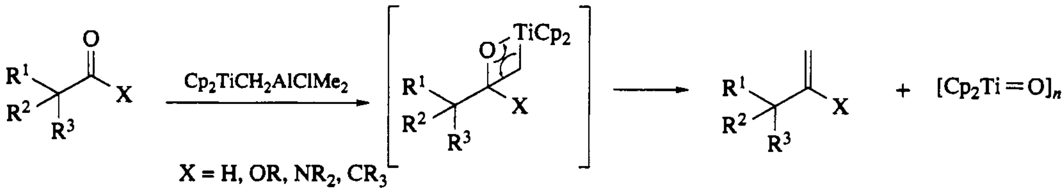

**Scheme 13**

If the reaction is applied to anhydrides or acid chlorides, however, another reaction pathway predominates. In cases where a good leaving group is attached to the carbonyl, the enolate is formed (Scheme 14) and, after work-up, the methyl ketone is isolated in moderate yield.[65] Grubbs found that the enolate was best formed with titanocyclobutane (see Section 3.1.5.3), instead of the Tebbe reagent itself.[66] With a 50% excess of the acid chloride, the enolates are synthesized in high yield and do not isomerize. These enolates can be used directly in the aldol condensation. In addition to failing to transfer a methylene in these cases, the method also fails with extremely hindered ketones such as (–)-fenchone.[67] In some cases, as depicted in Scheme 15, α,α-disubstitution results in enolate formation rather than methylene transfer.[67] Anhydrides form enolates as well, but, unlike the products from acid chlorides, they are not efficiently utilized in subsequent reactions.[68] The anhydride enolates can react with starting materials, resulting in mixtures of products.

**Table 7** Tebbe Reaction on Lactones

| *Entry* | *Substrate* | *Solvent* | *Yield of $RR'CCH_2$ (%)* | | *Ref.* |
|---|---|---|---|---|---|
| 1 | 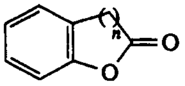 | Toluene/THF | $n = 1$<br>$n = 2$ | 85<br>85 | 52 |
| 2 | 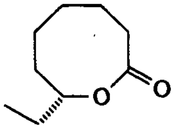 | THF/DMAP | | Not isolated | 55 |
| 3 | 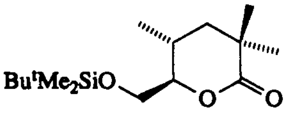 | Toluene/THF | | 76 | 56 |
| 4 | 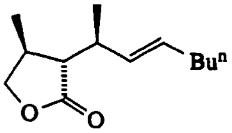 | Toluene/THF/pyridine | | Not isolated | 57 |
| 5 | 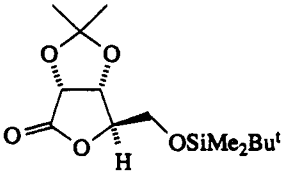 | Toluene/THF | | 85 | 58 |
| 6 | 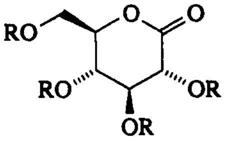 | Toluene/THF/pyridine | R = $CH_2Ph$<br>R = $SiMe_3$<br>R = $SiEt_3$ | 82<br>54<br>86 | 59 |
| 7 | 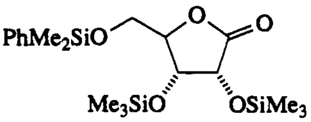 | Toluene/THF/pyridine | | 70 | 59 |
| 8 | 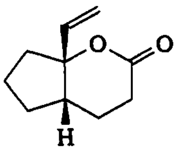 | Toluene/THF/pyridine | | 92 | 60 |
| 9[a] | 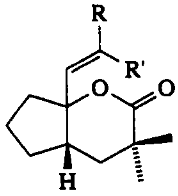 | Toluene/THF/pyridine | | Not isolated | 60 |

**Table 7** *(continued)*

| *Entry* | *Substrate* | *Solvent* | *Yield of RR'CCH$_2$ (%)* | *Ref.* |
|---|---|---|---|---|
| 10$^b$ | 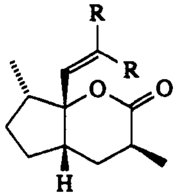 | Toluene/THF/pyridine | Not isolated | 60 |

$^a$ R, R' = Me, H. $^b$ R = H, Me.

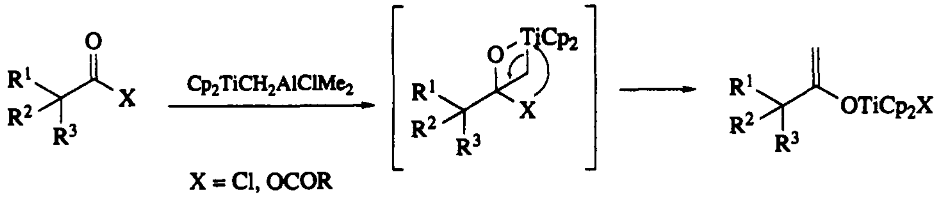
Cp$_2$TiCH$_2$AlClMe$_2$
X = Cl, OCOR
OTiCp$_2$X

**Scheme 14**

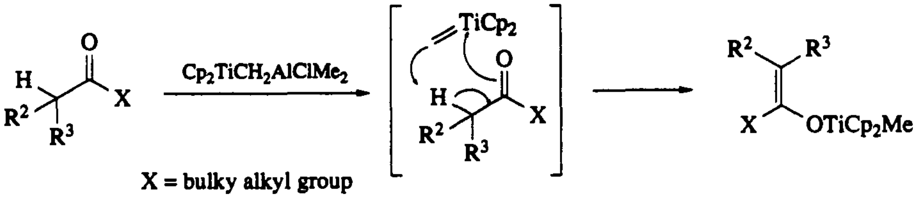
Cp$_2$TiCH$_2$AlClMe$_2$
X = bulky alkyl group
OTiCp$_2$Me

**Scheme 15**

Succinimides (**62**) react to form the corresponding mono- (**63**) or di-methylenated products (**64**). If two alkyl substituents are present in the α-position, a high degree of regioselectivity is observed for reaction at the less-hindered carbon. All of the diaddition compounds have the potential of isomerization to the pyrrole (**65**; Scheme 16). Piperidinediones (**66**), however, react predominantly by the enolization pathway to give (**67**; equation 15).[68]

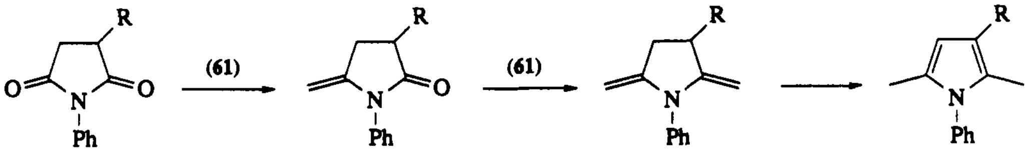

(**62**) (**63**) (**64**) (**65**)

**Scheme 16**

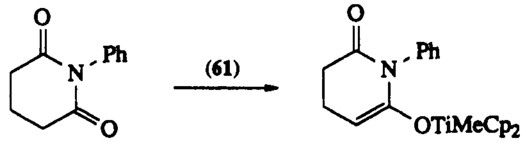

(**66**) (**67**) (15)

**Table 8** Tebbe Reactions on Ketones

| *Entry* | *Substrate* | *Solvent* | *Yield of RR'CCH$_2$ (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 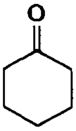 | Toluene | 65 | 51 |
| 2 | 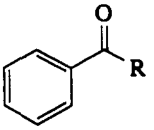 | Toluene/THF | R = Me 88<br>R = Ph 97<br>R = Bu$^t$ 96<br>R = CF$_3$ 50 | 54 |
| 3 | 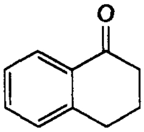 | Toluene/THF | 73 | 54 |
| 4 | 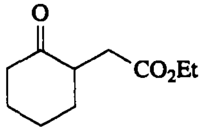 | Toluene/THF | 67 | 54 |
| 5 | 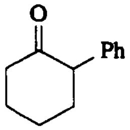 | THF | 93 | 67 |
| 6 | 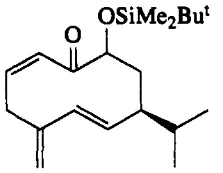 | THF/pyridine | 45 | 61 |
| 7 | 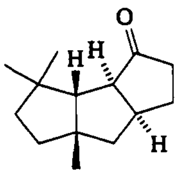 | Et$_2$O/DMAP | 93 | 62 |

### 3.1.5.2 Metals Other Than Aluminum

The $AlMe_3$ used in the production of the Tebbe reagent (**61**) is thought to inhibit decomposition of $Cp_2TiMe_2$. Further, the use of Al dictates the abstraction of the hydrogen from the methyl group rather than the cyclopentadienyl.[51] Other metals have been utilized in conjunction with [$Cp_2TiCH_2$], including $Me_2Zn$,[51] $CH_2(ZnI)_2$[69] and $MgBr_2$.[70] In addition Grubbs has studied a variety of metal complexes with the $Cp_2TiCH_2$ system.[71] These complexes provide interesting mechanistic information on the Tebbe reaction. Some of the reagents exhibit modified reactivity compared to the original reagent. For example, Eisch's Zn compound does not form the methyl ketone as the major product when reacted with acid

**Table 9** Tebbe Reactions on Esters[a]

| *Entry* | *Substrate* | | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 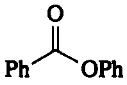 | | 94 | 52 |
| 2 | 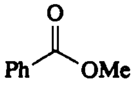 | | 81 | 52 |
| 3 | 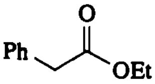 | | 90 | 52 |
| 4 | 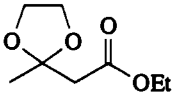 | | 87 | 52 |
| 5 | 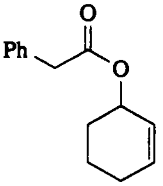 | | 96 | 52 |
| 6 | 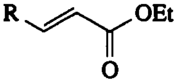 | R = Me<br>R = Ph | 82<br>96 | 52 |
| 7 | 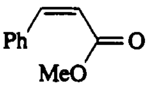 | | 79 | 52 |
| 8 | 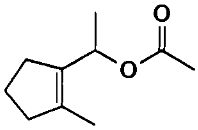 | | 85 | 80a |
| 9 | 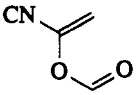 | | No yield | 63 |
| 10 | 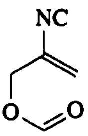 | | No yield | 63 |
| 11 | 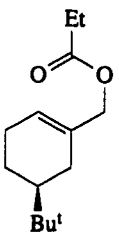 | | 86 | 64 |

---

[a] All reactions were carried out in toluene/THF

**Table 10** Tebbe Reactions with Amides

| *Entry* | *Substrate* | *Solvent* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 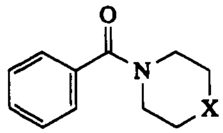 | Benzene/toluene | X = CH$_2$ 76<br>X = O 67 | 54 |
| 2 | 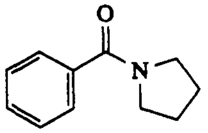 | Benzene/toluene | 80 | 54 |
| 3 | 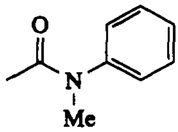 | Benzene/toluene | 97 | 54 |

chlorides.[69] By and large, these modified reagents do not appear to offer any significant synthetic advantage over the Tebbe reagent, and have not found application in organic synthesis.

### 3.1.5.3 Metallacyclobutane Complexes

Grubbs discovered that the reaction of the Tebbe reagent (**61**) with alkenes to form metallacycles that can then be used for methylene transfer, has distinct advantages over the Tebbe reagent itself.[72] These complexes are stable to air and are more easily handled that the Tebbe reagent. In addition, the aqueous work-up required in the Tebbe reaction (it is typical to quench with a 15% aqueous NaOH solution) can result in isomerization.[73] A comparative study on the two methods found that similar yields were obtained with both.[67,68] Grubbs applied both types of reactivity to a synthesis of capnellene.[74] As depicted in Scheme 17, the Tebbe reagent (**61**) first reacts with the alkene to form the metallacycle (**69**). Heating the reaction results in the ring opening to the alkene alkylidene (**70**). The *t*-butyl ester is then trapped intramolecularly to form the cyclobutene enol ether (**71**).

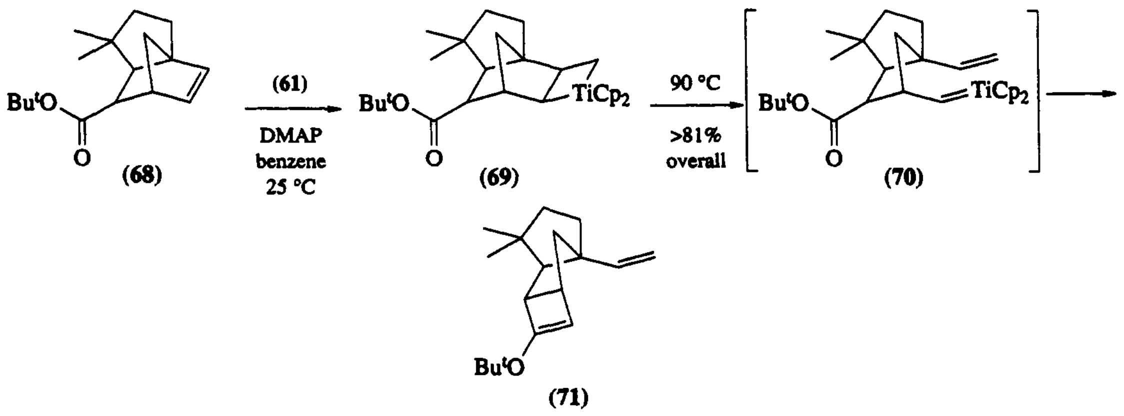

**Scheme 17**

### 3.1.5.4 Methylene *versus* Alkylidene Transfer

Unfortunately the Tebbe reagent (**61**) cannot be extended to higher alkyl analogs. When the complex is formed with β-hydrogens present on the aluminum reagent, alternative products are formed.[75] Tebbe found that the use of $Et_3Al$ resulted in a bridged cyclopentadienyl group in a dimeric complex.[76] Although the problems of higher order complex synthesis can be circumvented,[78] these reagents do not react with the high conversion of the Tebbe reagent, and have not been utilized in total synthesis.[77] As discussed in Section 3.1.12, there are many metals that form alkylidene complexes.[78] The Tebbe reagent has proven to be of widespread generality and use in organic synthesis. Schwartz has developed a Zr alkylidene reagent that will add to carbonyls in analogy to the Tebbe reaction in high yield.[317] Many of these complexes require special techniques for synthesis. Takai has discovered that alkylidenation occurs with a dibromoalkyl in the presence of $TiCl_4$, Zn and TMEDA *in situ*, resulting in the preparation of (*Z*)-alkenyl ethers.[79] This reagent is discussed in Section 3.1.12.2

### 3.1.5.5 Miscellaneous Reactivity

As originally pointed out by Evans and Grubbs, one of the advantages of the Tebbe reagent is the facile preparation of the intermediate allyl vinyl ethers for the Claisen rearrangement.[52] It has also been observed that the Tebbe reagent itself can behave as a Lewis acid catalyst for the rearrangement.[80] Negishi and Grubbs have studied the ability of the Tebbe reagent to form allene derivatives.[81]

## 3.1.6 TITANIUM–ZINC METHYLENATION[82]

A reaction that appears to be mechanistically similar to the Tebbe reaction was developed by Oshima in 1978.[83] Diiodomethane or dibromomethane in the presence of zinc is treated with a Lewis acid to form, presumably, a divalent complex (**72**), which reacts with aldehydes and ketones to produce the corresponding methylene derivative (**73**; Scheme 18).[84] This reagent complements the reactivity of the Tebbe reagent, in that the zinc methylenation is not reactive towards esters or lactones.[85] Because it is an electrophilic reagent, it is suitable for the methylenation of enolizable ketones and aldehydes.

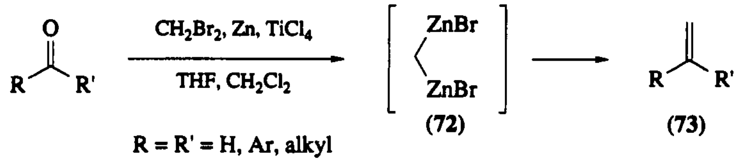

**Scheme 18**

### 3.1.6.1 Other Lewis Acids

In addition to titanium tetrachloride, a variety of Lewis acids have been utilized by Oshima.[86] The choice centers around the type of reactivity desired, and this is further discussed below in Section 3.1.6.2. Dibromomethane and zinc combined with $TiCl_4$ is the most commonly used reagent for the methylenation of ketones.[87] Lombardo discovered, during work on the gibberellins (**74**; equation 16), a method of synthesizing the $CH_2Br_2/Zn/TiCl_4$ reagent that results in an extremely active catalyst that can be stored in the freezer.[87] Lombardo's catalyst may have advantages over the original procedure for

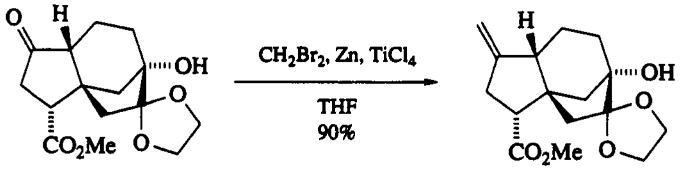

(16)

**(74)** **(75)**

compounds that are sensitive to titanium tetrachloride, but no comparative study of the catalyst formed by the two methods has been done.[87]

### 3.1.6.2 Chemoselectivity

It is possible to exclusively methylenate a ketone in the presence of an aldehyde by precomplexing the aldehyde (*e.g.* **76**) with $Ti(NEt_2)_4$, followed by treatment with the usual methylene zinc/$TiCl_4$ reagent (equation 17).[88] Takai also studied the chemoselective methylenation of aldehydes (**78**) in the presence of ketones, and found the use of diiodomethane, zinc and titanium isopropoxide or trimethylaluminum to be effective (equation 18).[88]

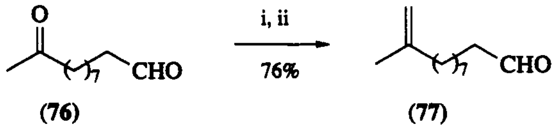

(17)

i, $Ti(NEt_2)_4$, $CH_2Cl_2$; ii, $CH_2I_2$, Zn, $TiCl_4$, THF

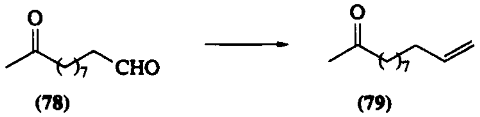

(18)

$CH_2I_2$, Zn, $Ti(OPr^i)_4$, 83%; $CH_2I_2$, Zn, $Me_3Al$, 96%

### 3.1.6.3 Examples of the Reaction with Aldehydes

It is advantageous to utilize either titanium isopropoxide or trimethylaluminum complexes with aldehydes in general, because pinacol-coupled diols form with the $Zn/CH_2Br_2/TiCl_4$ systems as minor side products.[86] No evidence of Simmons–Smith-type side products was observed with any of the methylenation reagents.[83] Additional examples of the reaction with aldehydes are presented in Table 11.

### 3.1.6.4 Examples of the $TiCl_4/CH_2X_2/Zn$ Reaction Compared with the Wittig

Some of the more intriguing examples of the use of the $TiCl_4/CH_2X_2/Zn$ reagent are in cases where the Wittig or other methods of methylenation have failed, and the Oshima method has proved a successful solution. Specific examples are outlined in Table 12.

### 3.1.6.5 Examples of the $TiCl_4/CH_2Br_2/Zn$ Reaction with Ketones Where Stereochemistry is Preserved

As the examples indicate, the reaction is compatible with a wide range of functional groups, including alcohols, esters, acetates, carboxylic acids, ethers, halogens, silyl groups, acetinides, lactones, alkenes, ketals and amines. The methylenation proceeds with allylic carbonyls, without loss of stereochemistry. One of the tremendous advantages of the $TiCl_4/CH_2X_2/Zn$ reaction is that sensitive ketones can be methylenated without loss of stereochemistry. Additional examples of the reactions of ketones with the reagent are summarized in Table 13. The $CH_2Br_2/Zn/TiCl_4$ reagent has proven to be of broad utility in natural products synthesis.

### 3.1.6.6 Isotopic Labeling

When the methylenation reagent is generated using zinc, $CD_2Br_2$ or $CD_2Cl_2$, and titanium tetrachloride, it can be utilized to synthesize the deuterated analogs (**82**). In addition, Trost has demonstrated that a $^{13}C$ label may be incorporated in a ketone (**81**) using $H_2{}^{13}CI_2$ (Scheme 19).[108]

**Table 11** Zinc, $CH_2X_2$ Reaction with Aldehydes

| *Entry* | *Substrate* | *Reagent* | *Yield of $RR'CCH_2$ (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 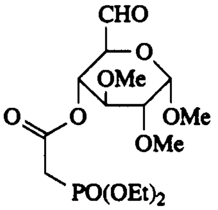 | $TiCl_4$–$CH_2Br_2$–Zn | 60–75 | 89 |
| 2 | 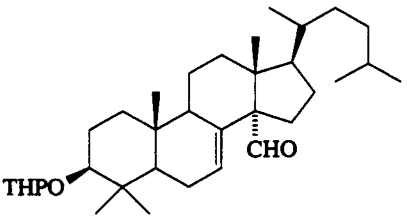 | $TiCl_4$–$CH_2Br_2$–Zn | — | 90 |
| 3 | 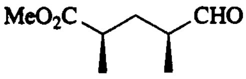 | $TiCl_4$–$CH_2Br_2$–Zn | 70 | 91 |
| 4 | 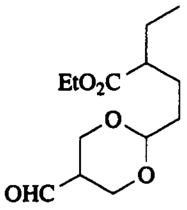 | $TiCl_4$–$CH_2Br_2$–Zn | 35, 2 steps | 92 |
| 5 | 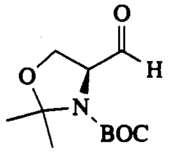 | $AlMe_3$–$CH_2I_2$–Zn | 75, >99% *ee* | 93 |

### 3.1.6.7 Halogen Incorporation

The zinc procedure has been extended to $CF_3CCl_3$ to form 2-chloro-1,1,1,-trifluoro-2-alkenes (**84**; equation 19). and α-fluoro-α,β-unsaturated carboxylic acid methyl esters (**87**) with methyl dichlorofluoroacetate (**85**; equation 20).[109] Both of these transformations are carried out with zinc and acetic anhydride. Several variations of this reaction have appeared in the literature.[109] The mechanism appears to be dramatically different from the Oshima methylenation. In this case, the reaction proceeds through the alcohol intermediate, which is converted to the acetate and reductively cleaved.

## 3.1.7 OTHER METHODS OF METHYLENATION

### 3.1.7.1 Samarium-induced Methylenation

Inanaga has studied the use of $SmI_2$ deoxygenation of aldehydes and ketones.[110] The reaction proceeds by a two-step mechanism, where $SmI_2$ and $CH_2I_2$ react with the carbonyl to form an O—SmIX species (**88**), which is converted to a better leaving group and reductively eliminated with $SmI_2$.[111] As the examples depicted in Scheme 20 indicate, no studies of chemoselectivity have been undertaken.[112]

**Table 12** Examples of $TiCl_4$–$CH_2Br_2$–Zn Reaction Compared with Wittig

| *Entry* | *Substrate* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 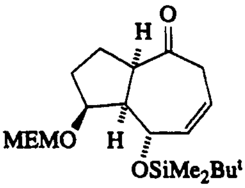 | THF, $CH_2Cl_2$ | 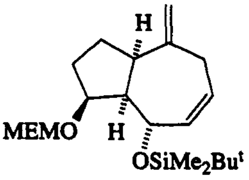 | 99[a] | 94 |
| 2 | 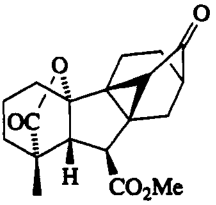 | $CH_2Cl_2$ | 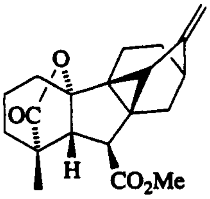 | 87 | 95 |
| | | | 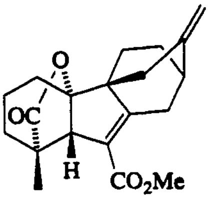 | b | 95 |
| 3 | 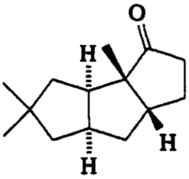 | $CH_2Cl_2$ | 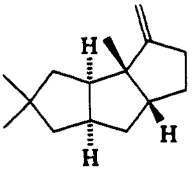 | 98[c] | 96 |
| 4 | 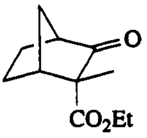 | THF | 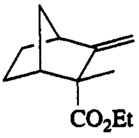 | 40[d] | 97 |
| 5 | 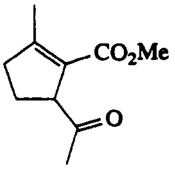 | THF, $CH_2Cl_2$ | 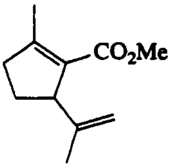 | 95[e] | 98 |
| 6 | 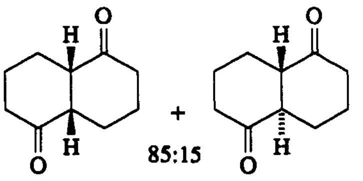 | | 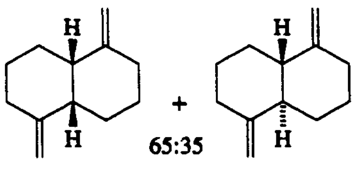 | 75[f] | 99 |

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[a] Wittig and Johnson sulfoxime fail. [b] Wittig results in retro Michael (poor recovery). [c] Wittig 70%, capricous.
[d] Wittig and acetalization conditions fail. [e] Wittig yield only 22%. [f] Wittig fails.

**Table 13** Examples of $TiCl_4$–$CH_2Br_2$–Zn Reaction with Ketones Where Stereochemistry is Preserved

| *Entry* | *Substrate* | | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 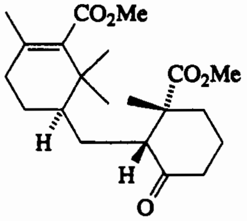 | | 60 | 100 |
| 2 | 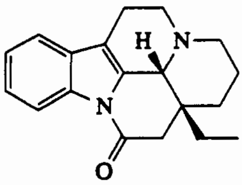 | | 85 | 101 |
| 3 | 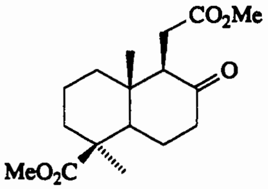 | | 86 | 102 |
| 4 | 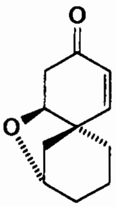 | used $CH_2I_2$ | 62 | 103 |
| 5 | 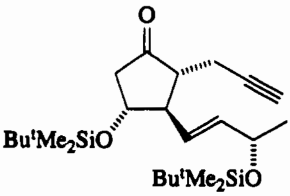 | | 78 | 104 |
| 6 | 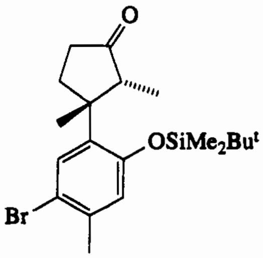 | | 84 | 105 |

**Table 13** *(continued)*

| *Entry* | *Substrate* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 7 | 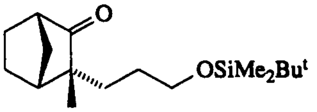 O<br>OSiMe$_2$Bu$^t$ | 75 | 106 |
| 8 | 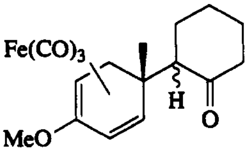 Fe(CO)$_3$<br>H<br>O<br>MeO | 80 | 107 |

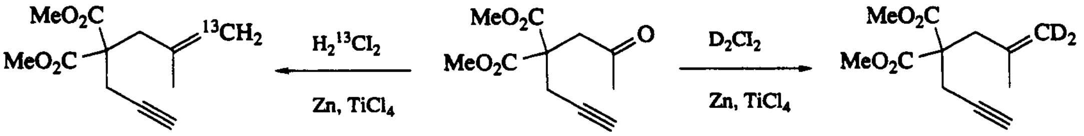

MeO$_2$C
MeO$_2$C
$^{13}$CH$_2$
H$_2$$^{13}$Cl$_2$
Zn, TiCl$_4$
MeO$_2$C
MeO$_2$C
O
D$_2$Cl$_2$
Zn, TiCl$_4$
MeO$_2$C
MeO$_2$C
CD$_2$

(81) (80) (82)

Scheme 19

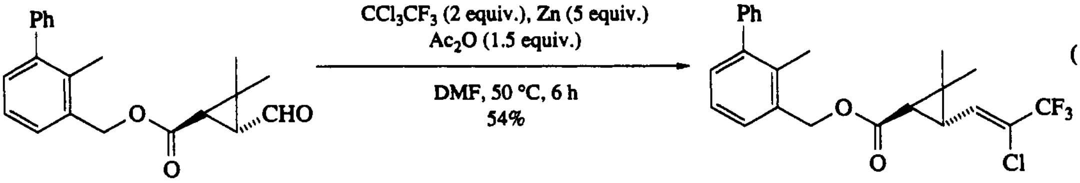

Ph
O
CHO
O
CCl$_3$CF$_3$ (2 equiv.), Zn (5 equiv.)
Ac$_2$O (1.5 equiv.)
DMF, 50 °C, 6 h
54%
Ph
O
CF$_3$
O
Cl

(83) (84) (19)

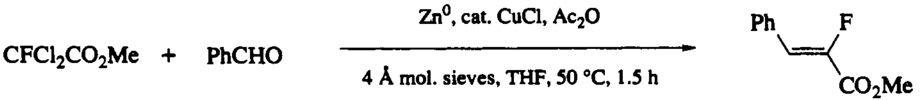

CFCl$_2$CO$_2$Me + PhCHO
Zn$^0$, cat. CuCl, Ac$_2$O
4 Å mol. sieves, THF, 50 °C, 1.5 h
78%, 100% (Z)
Ph
F
CO$_2$Me

(85) (86) (87) (20)

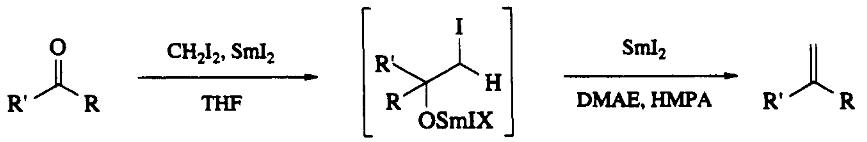

O
R'
R
CH$_2$I$_2$, SmI$_2$
THF
I
R'
H
R
OSmIX
SmI$_2$
DMAE, HMPA
R'
R

(88) (89)

R' = Me(CH$_2$)$_{10}$, R = H; 73%
R, R' = —(CH$_2$)$_{10}$— ; 80%

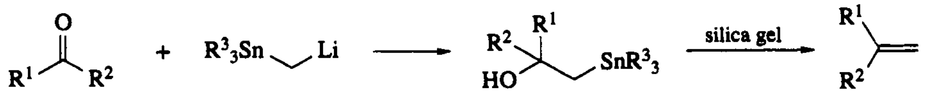

O
R$^1$
R$^2$
+ R$^3$$_3$Sn
Li
R$^1$
R$^2$
HO
SnR$^3$$_3$
silica gel
R$^1$
R$^2$

(90) (91) (92) (93)

R$^1$ = Ph, R$^2$ = Et; 78%
R$^1$, R$^2$ = 1-tetralone; 91%
R$^1$ = *p*-MeOC$_6$H$_4$, R$^2$ = H; 94%

R$^1$, R$^2$ = *cis*-1-decalone; 91%
R$^1$, R$^2$ = *trans*-1-decalone; 96%

Scheme 20

#### 3.1.7.2 Tin-induced Methylenation

In direct analogy to the Peterson methylenation, the triaryl- and trialkyl-stannylmethyllithium reagent (**91**) can be added to aldehydes and ketones (**90**), followed by elimination of the hydroxystannane (**92**) to obtain the methylene derivative (**93**; Scheme 20).[113] This reaction, like the titanium and cerium modifications of the Peterson methylenation of Kaufmann and Johnson, may prove advantageous, in comparison to the Wittig reaction, for enolizible substrates.

## 3.1.8 ALKENE FORMATION: INTRODUCTION

Many of the methods discussed in the previous sections may be extended to more complex substitution patterns. The sections covering alkene formation are divided according to the stabilizing substituent on the anion component. For each stabilizing element, its application to the synthesis of alkenes with precise geometries is discussed.

## 3.1.9 PHOSPHORUS-STABILIZED ALKENATION

The Wittig reaction is one of the most effective and general methods of alkene formation from carbonyl derivatives.[114] Prior to the development of phosphorus-stabilized anion addition and elimination, the synthesis of an alkene from a carbonyl entailed anion addition and subsequent elimination with nonspecific alkene position and configuration. The Wittig reaction proceeds with defined positional selectivity, in addition to chemo- and stereo-selectivity. It has become the standard by which all subsequent methodology is judged. This section is organized according to the type of Wittig reagent used. Section 3.1.9.1 discusses phosphonium ylides and is further subdivided depending on the presence of stabilizing or conjugating functionality in the Wittig reagent. Phosphoryl-stabilized carbanions are covered in Sections 3.1.9.2, 3.1.9.3 and 3.1.9.4; this discussion includes the phosphonate and phosphine oxide carbanions. Since the Wittig reaction has been the subject of many excellent reviews, this section will briefly discuss expected stereochemical trends and will emphasize new methods, with particular focus on attaining (*E*)- and (*Z*)-selectivity.[115]

### 3.1.9.1 Phosphonium Ylides

The general representation of the classic Wittig reaction is presented in equation (21). The (*E*)- and (*Z*)-selectivity may be controlled by the choice of the type of ylide (**95**), the carbonyl derivative (**94**), the solvent and the counterion for ylide formation. As a general rule, the use of a nonstabilized ylide (**95**; X and Y are H or alkyl substituents and $R^3$ is phenyl) and salt-free conditions in a nonprotic, polar solvent favors the formation of the (*Z*)-alkene isomer (**96**) in reactions with an aldehyde. A stabilized ylide with strongly conjugating substituents such as an ester, nitrile or sulfone forms predominantly the (*E*)-alkene.

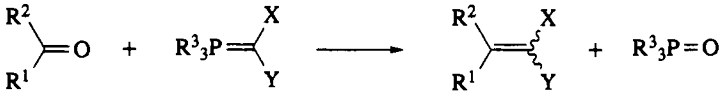

(**94**) (**95**) (**96**) (**97**)

(21)

#### *3.1.9.1.1 Mechanism*

Mechanistic studies have been the subject of a great deal of recent work.[116] Although at one time the Wittig reaction was thought to occur through the formation of zwitterionic betaine intermediates (**100**) and (**101**), the reaction of a nonstabilized triphenylphosphorus ylide (**99**) with an aldehyde forms observable (by NMR) 1,2-oxaphosphetanes (**104**) and (**105**), which eliminate to produce the alkene (**102**) and phosphine oxide (**103**) (Scheme 21).[117]

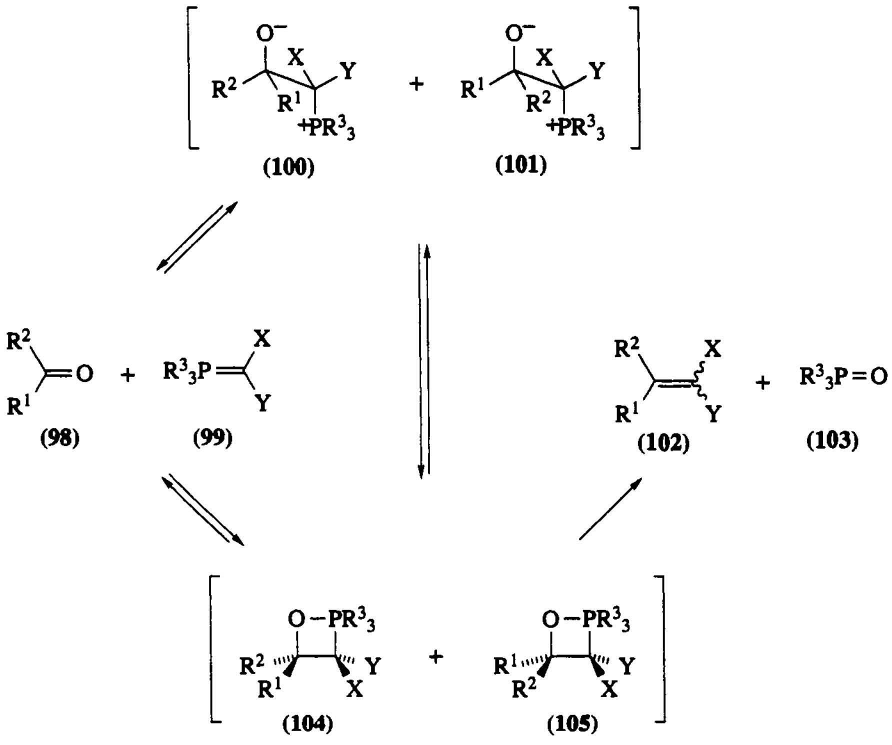

Scheme 21

There are two steps to the reaction that define the stereochemical outcome. The first is the intial addition of ylide and carbonyl, with inherent preferences for the formation of *cis*- and *trans*-oxaphosphetane intermediates (**104**) and (**105**), and the second is the ability of the intermediates to equilibrate. Maryanoff has studied numerous examples in which the final (*E*)/(*Z*) ratio of the alkene (**102**) produced does not correspond to the initial ratios of oxaphosphetanes (**104**) and (**105**) and has termed this phenomenon 'stereochemical drift'.[116b] The intermediate oxaphosphetanes are thought to interconvert by reversal to reactants (**98**) and (**99**), followed by recombination. In this case the final ratio of alkene can be substantially different from the initial addition ratio.

Interconversion and the intermediacy of betaine structures (**100**) and (**101**) are still matters of debate and ongoing research. There are distinct differences in the reactions of aliphatic and aromatic aldehydes, and also of aromatic and aliphatic phosphonium ylides, with regard to reversibility of the initial addition adducts.[116] Vedejs and coworkers have evidence that salt-free Wittig reactions with unbranched aliphatic aldehydes occur with less than 2% equilibration and are therefore under kinetic control.[116d–f] These studies suggest the (*Z*):(*E*) alkene ratios correspond to the kinetic selectivity of the initial addition step. While *cis*-oxaphosphetanes can equilibrate, the more stabile *trans* isomer does not. Elimination of phosphine oxide occurs stereospecifically *syn*. Factors that are known to enhance equilbration of the *cis*-oxaphosphetane are the presence of an alkyl or donor ligand on phosphorous, lithium salts, and steric hindrance in either the aldehyde or ylide.[118] Mechanistic studies have been done largely on nonstabilized ylides, due to the fact that intermediates can be followed by NMR. Vedejs has developed a unified theory to explain the stereoselectivity of stabilized and nonstabilized Wittig reactions.[116f] Nonstabilized ylides add in an early transition state to give a high ratio of *cis*- to *trans*-oxaphosphetanes, while stabilized ylides have a later transition state and a larger portion of *trans* isomer. Equilibration is thought to occur only under special circumstances, and both reactions are thought to be under kinetic control.

### *3.1.9.1.2 Nonstabilized ylides*

#### *(i) Nonstabilized ylides giving (Z)-stereoselectivity*

Typically, nonstabilized ylides are utilized for the synthesis of (*Z*)-alkenes. In 1986, Schlosser published a paper summarizing the factors that enhance (*Z*)-selectivity.[119] Salt effects have historically been defined as the response to the presence of soluble lithium salts.[114] Any soluble salt will compromise the (*Z*)-selectivity of the reaction, and typically this issue has been resolved by the use of sodium amide or sodium or potassium hexamethyldisilazane (NaHMDS or KHMDS) as the base. Solvent effects are also vital to the stereoselectivity. In general, ethereal solvents such as THF, diethyl ether, DME and *t*-butyl methyl ether are the solvents of choice.[119] In cases where competitive enolate formation is problematic, toluene may be utilized. Protic solvents, such as alcohols, as well as DMSO, should be avoided in attempts to maximize (*Z*)-selectivity. Finally, the dropwise addition of the carbonyl to the ylide should be carried out at low temperature (–78 °C). Recent applications of phosphonium ylides in natural product synthesis have been extensively reviewed by Maryanoff and Reitz.[114]

#### *(ii) α-Oxygenated substrates*

As discussed in the following sections, there are notable exceptions to the general rules of selectivity in the Wittig reaction. Carbonyl derivatives with α-oxygenation reverse normal selectivity with stabilized ylides. This effect does not predominate in the reactions of nonstabilized ylides. A systematic study of Wittig reactions of ethylidenetriphenylphosphorane and derivatives of hydroxyacetone (**106**) was undertaken by Still.[120] Optimal (*Z*)-selectivity was obtained with KHMDS as the base with 10% HMPA in THF (equation 22). This procedure was applied to the synthesis of α-santalol (**109**), with alkene formation proceeding in 85% yield and greater than 99% stereochemical purity (equation 23).[121] Other recent examples of successful (*Z*)-alkenations in the presence of oxygenated substrates are the syntheses of isoquinuclidines by Trost, in which alkenation of an epoxy ketone occurred to produce only the (*Z*)-isomer, and of the C(7)–C(13) fragment of erythronolide by Burke, in which a pyran derivative was homologated to the ethylene with high (*Z*)-selectivity.[122]

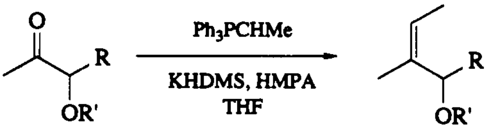

(22)

**(106)** **(107)**

R = H, R' = $CH_2Ph$; *(Z)*:*(E)* = 12:1
R = H, R' = $SiMe_2Bu^t$; *(Z)*:*(E)* = 14:1
R = H, R' = THP; *(Z)*:*(E)* = 41:1, 83%
R = Me, R' = THP; *(Z)*:*(E)* = 200:1, 95%

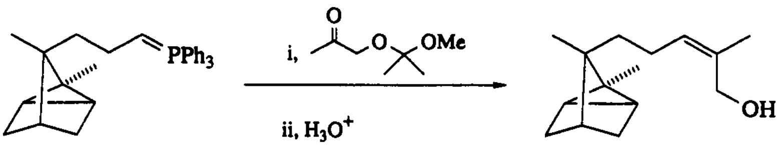

(23)

**(108)** 85% **(109)** >99% *(Z)*

### *(iii) (E)-Selective alkenation*

Application of the Wittig reaction of a nonstabilized ylide to the synthesis of an (*E*)-alkene is practically and effectively carried out by the Schlosser modification.[123] Alternatively, the use of a trialkylphosphonium ylide can produce high ratios of (*E*)-alkene.[116] Recently, Vedejs has developed a reagent using dibenzophosphole ylides (**110**) to synthesize (*E*)-disubstituted alkenes (**111**) from aldehydes (equation 24).[124] The initial addition of ylide occurs at –78 °C, but the intermediate oxaphosphetane must be heated to induce alkene formation. The stereoselectivity in the process is excellent, particularly for aldehydes with branched substitution α to the reacting center. Both the ethyl and butyl ylides have been utilized.

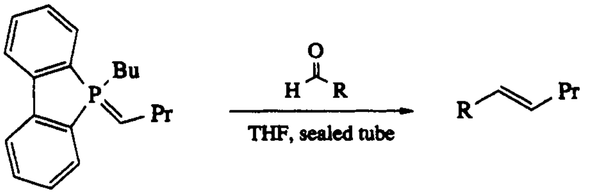

(24)

**(110)** **(111)**

R = $CH_2CH_2Ph$; *(E)*:*(Z)* = 20:1, 66%
R = $CMe_2CH_2Ph$; *(E)*:*(Z)* = 12:1, 82%
R = $CHMeC_9H_{19}$; *(E)*:*(Z)* = 124:1, 91%
R = c-$C_6H_{11}$; *(E)*:*(Z)* = 84:1, 97%

The presence of an oxido, carboxy or amide group in the ylide (**112**) can shift selectivity to produce (*E*)-alkenes. The effect of various nucleophilic groups at different distances away from the phosphorus has been systematically studied by Maryanoff.[116a] There is an optimal chain length for the nucleophile in order to maximize (*E*)-alkene formation. In the case of oxido ylides, short chain lengths and the use of lithium as the counterion maximized (*E*)-selectivity. Oxido ylides form significant amounts of (*E*)-alkene with both benzaldehyde (*E*:*Z* = 94:6) and hexanal (*E*:*Z* = 52:48) relative to an ylide that does not possess an nucleophilic group. Carboxy ylides, on the other hand, only showed dramatic increases in (*E*)-selectivity with benzaldehyde (*E*:*Z* = 93:7). In addition, the effect of short chain length was critical, but interestingly the selectivity was not strongly dependent on the type of counterion. Significant effects with amino substitution on the ylide were observed if 2 equiv. of base were added to generate the amido species (*E*:*Z* = 87:13 with benzaldehyde).

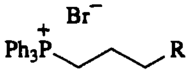

(**112**) R = OH, $CO_2H$, $CONH_2$

### *3.1.9.1.3 Semistabilized ylides*

As a general rule, ylides with allylic or benzylic functionality do not proceed with a high degree of stereoselectivity.[125] There have been recent examples of arachidonic acid derivatives in which the coupling of an allylic phosphonium salt with an unsaturated aldehyde resulted in (*Z*)-selective alkenation.[126] As in the case of nonstabilized ylides, replacing aromatic phosphorus substituents with allylic (**113**; equation 25) or alkyl (**115**; equation 26) groups dramatically increases the production of the (*E*)-alkene.[127]

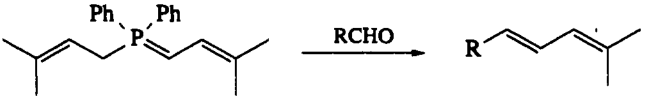

(25)

**(113)** **(114)**

R = Ph, $NaNH_2$ as base; *(E)*:*(Z)* = 15:1, 93%
R = c-$C_6H_{11}$, $NaNH_2$ as base; *(E)*:*(Z)* = 40:1, 99%

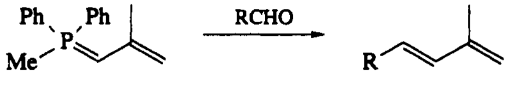

**(115)** **(116)** (26)

R = Ph, KOBu$^t$ as base; *(E)*:*(Z)* = 2:1, 96%
R = c-$C_6H_{11}$, $NaNH_2$ as base; *(E)*:*(Z)* = 26:1, 73%

In cases were the allylic fragment is inexpensive, the phosphonium salt is formed by reacting lithiated diphenylphosphine with 2 equiv. of the allylic bromide. Alternatively, diphenylmethylphosphonium salts can be selectively deprotonated in the allylic position. The highest ratios were obtained with sodium/ammonia as the base, but KOBu$^t$ in THF provides a practical and selective route to (*E*)-1,3-dienes. Tamura and coworkers have demonstrated that allylic nitro or acetate compounds (**117**) can be converted to allylic tributylphosphonium ylides by palladium(0) catalysis.[128] This procedure may be carried out in one pot by forming the ylide in methanol and THF, followed by addition of KOBu$^t$ and the aldehyde (equation 27). These reactions proceed in good overall yield, and stereoselectivity is high for bulky phosphonium ylides and a range of aldehydes. A comparison of the selectivity of tributyl- and triphenyl-phosphonium ylides has been carried out.[129] Le Corre has demonstrated the use of diphenylphosphinopropanoic acid in the semistabilized Wittig reaction.[130] Enhanced ratios of (*E*)-isomer were observed and because of the increased water solubility of the phosphine oxide produced, work-up is simplified.

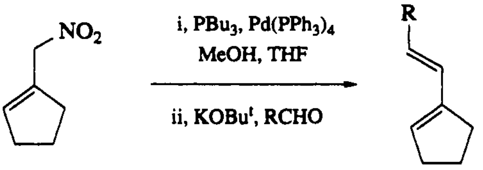

**(117)** **(118)** (27)

R = Ph; *(E)*:*(Z)* = 95:1, 83%
R = $Me(CH_2)_5CHO$; *(E)*:*(Z)* = 93:7, 82%

### *3.1.9.1.4 Stabilized ylides*

Ylides which have conjugating functionality present tend to produce (*E*)-alkenes stereoselectively.[114] A significant departure from this anticipated selectivity is the reaction of α-alkoxy substrates with stabilized phosphonium ylides to produce (*Z*)-conjugated esters.[114] In an application of the Wittig reaction to aldehydosugars (**119**), two important factors were noted to obtain high selectivity.[131] The sugars which had polar groups, such as ether substituents with lone pairs, *cis* to the aldehyde in the β-position formed (*Z*)-alkenes (**120**; equation 28). This stereoselectivity is solvent dependent and (*Z*)-alkene formation can be minimized by using DMF and maximized in methanol. Several comparative studies have been carried out with sugar derivatives.[132] It is important that the α-oxgenated functionality be protected as an ether. The reaction of stabilized ylides with α-hydroxy ketones forms the normal (*E*)-alkene.[133] Wilcox and coworkers have studied the reaction of lactols and found that in dichloromethane the lactol (**121**) selectively produced the (*Z*)-isomer (**122**), while the methyl ether (**123**) formed the corresponding *trans*-alkene (**124**) (Scheme 22).[134]

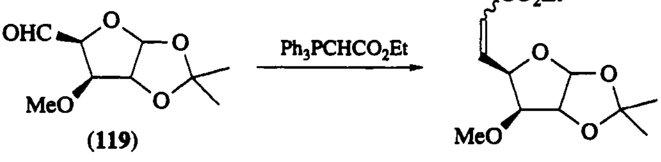

**(119)** **(120)** (28)

DMF; *(Z)*:*(E)* =14:86
$CHCl_3$; *(Z)*:*(E)* = 60:40
MeOH; *(Z)*:*(E)* = 92:8

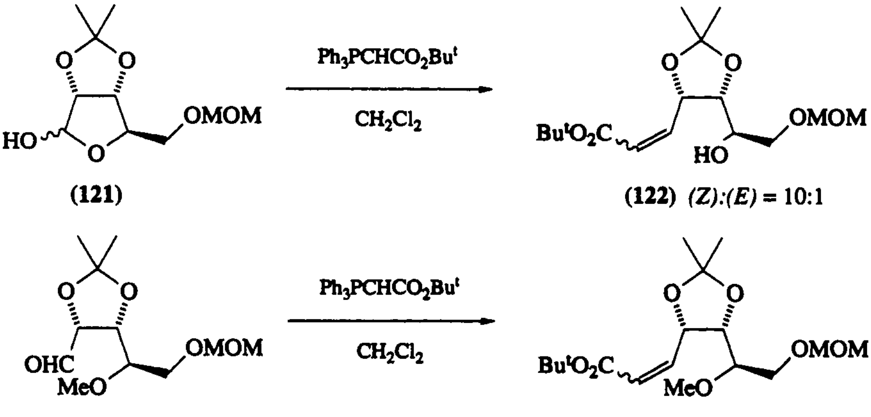
Ph3PCHCO2Bu^t
CH2Cl2
OMOM
HO
MeO
OHC
Bu^tO2C
Ph3PCHCO2Bu^t
CH2Cl2

**(121)** **(122)** *(Z):(E)* = 10:1

**(123)** **(124)** *(Z):(E)* = 1:19

**Scheme 22**

Although this reaction is general for ester-stabilized Wittig reagents, (formylmethylene)triphenylphosphorane was reacted with a pyranose (**125**) to form the expected (*E*)-alkene (**126**; Scheme 23).[135] Reduction of (**126**) and (**127**) supplied (*E*)- and (*Z*)-allylic alcohols selectively. Precise rules for the prediction of (*E*)- and (*Z*)-selectivity with α-oxygenated substrates are difficult to formulate.[114]

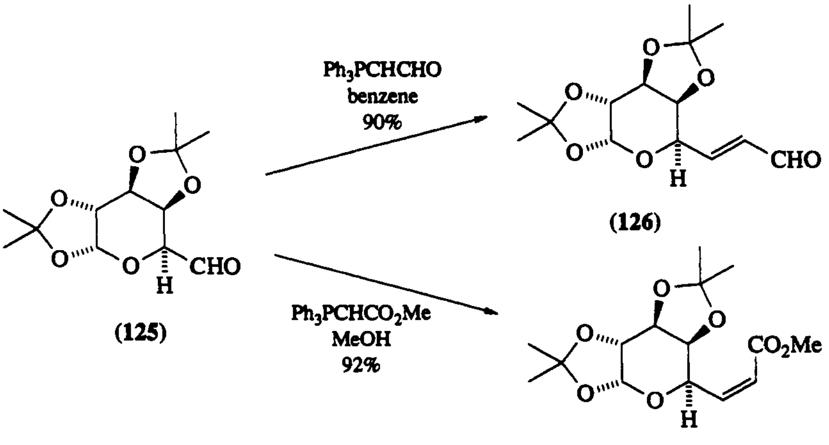
Ph3PCHCHO
benzene
90%
Ph3PCHCO2Me
MeOH
92%
CHO
H
CO2Me

**(125)** **(126)** **(127)**

**Scheme 23**

The synthesis of conjugated (*Z*)-enones (**129**) can be undertaken with a stabilized ylide (**128**) and an aliphatic aldehyde.[136] The reactivity of the ylide is altered by *in situ* deprotonation with 2 equiv. of NaH in THF with a small amount of water (equation 29). Stereoselectivity was approximately 9:1 in favor of the (*Z*)-isomer. This ratio could be improved with aldehydes with α-branched substitution. As discussed

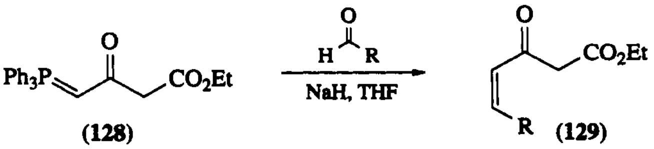
Ph3P
O
CO2Et
O
H R
NaH, THF
O
CO2Et
R

**(128)** **(129)** (29)

R = Et; *(Z):(E)* = 85:15, 65%
R = $(CH_2)_9Me$; *(Z):(E)* = 86:14, 91%
R = $Pr^i$; *(Z):(E)* = 84:16, 90%

with the nonstabilized and semistabilized ylides, substitution of phenylphosphonium ylides with alkyl functionality has been studied on stabilized ylides.[137] Both the ylide and the dianion species demonstrate enhanced reactivity with ketones to produce (*E*)-alkenes (**131**; equation 30). Replacement of the phenyl ligands on the phosphorus by alkyl groups increases the proportion of (*E*)-alkene, even in the absence of stabilizing functionality, by increased reversibility of the *cis*-oxaphosphetane for these substrates.[116]

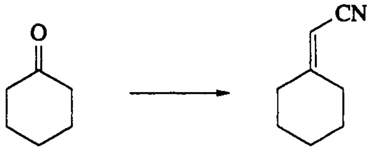

(30)

**(130)** **(131)**

$Ph_3PCH_2CN$, Bu$^n$Li, THF; 6%
$Ph_2P(CH_2CN)_2$, Bu$^n$Li, THF; 81%

### 3.1.9.2 Phosphoryl-stabilized Carbanions

The use of anions derived from a phosphine oxide (**132**) or a diethyl phosphonate (**133**) to form alkenes was originally described by Horner.[138] Although these papers laid the foundations for the use of phosphoryl-stabilized carbanions for alkene synthesis, it was not until Wadsworth and Emmons published a more detailed account of the general applicability of the reaction that phosphonates became widely used.[139] Since the work of Wadsworth and Emmons was significant and crucial to the acceptance of this methodology, the reaction of a phosphonate carbanion with a carbonyl derivative to form an alkene is referred to as a 'Horner–Wadsworth–Emmons' reaction (abbreviated HWE).[114] The phosphine oxide variation of the Wittig alkenation is called the 'Horner' reaction.

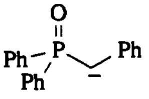

**(132)**

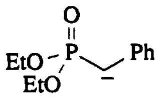

**(133)**

### 3.1.9.3 Phosphonates: the Horner–Wadsworth–Emmons Reaction

Phosphonates are the most commonly used phosphoryl-stabilized carbanions.[140] These reagents are more nucleophilic than the corresponding phosphonium ylides. Additional advantages of the HWE reagents are that the by-products of the alkenation are water soluble and reaction conditions can be altered to yield either the (*E*)- or the (*Z*)-isomer. The disadvantage of the phosphonate reagents is that a stabilizing group must be present in the α-position, unless a two-step addition and elimination strategy is employed. The stabilizing functionality is frequently a carboxyl derivative; however, aryl, vinyl, sulfide, amine and ether functionalities have also proven to stabilize the anion sufficiently for alkene formation to take place.

#### *3.1.9.3.1 Mechanism*

The mechanism of phosphonate anion (**135**) addition to carbonyl derivatives is similar to the phosphonium ylide addition; however, there are several notable features to these anion additions that distinguish the reactions from those of the classical Wittig. The addition of the anion gives a mixture of the *erythro* (**136** and **137**) and *threo* (**139** and **140**) isomeric β-hydroxyphosphonates (Scheme 24). In the case of phosphine oxides, the initial oxyanion intermediates may be trapped. The anion intermediates decompose by a *syn* elimination of phosphate or phosphinate to give the alkene. The elimination is stereospecific, with the *erythro* isomer producing the *cis*-alkene (**138**), and the *threo* addition adduct producing the *trans*-alkene (**141**). The ratio of (*E*)- to (*Z*)-alkene is dependent on the initial ratio of the *erythro* and *threo* adducts formed, as well as the ability of these intermediates to equilibrate.

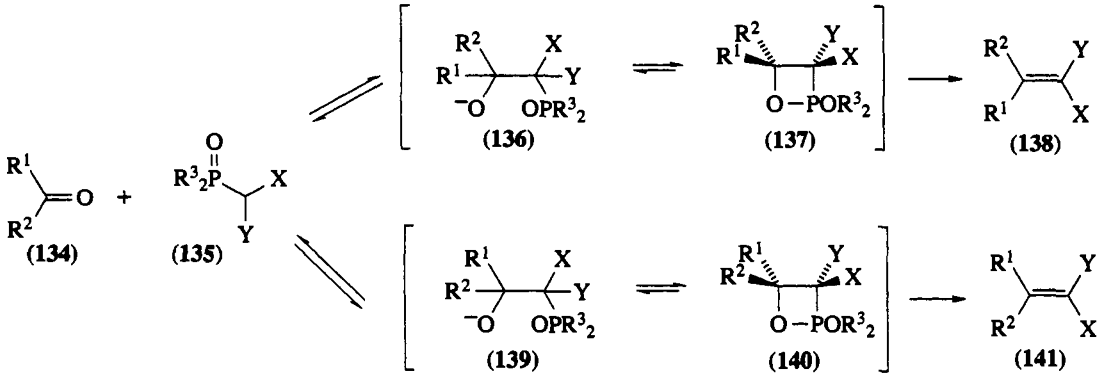

Scheme 24

### 3.1.9.3.2 Formation of (E)-alkenes

The most common applications of the HWE reaction are in the synthesis of disubstituted (*E*)-alkenes. The stereoselectivity of the reaction can be maximized by increasing the size of the substituents on the phosphoryl portion. In cases where the stabilizing functionality is a carboxy group, the size of the ester may be 'tuned' to enhance (*E*)-alkene formation.

The HWE reaction can be carried out on a ketone, but often the stereoselectivity is not as good as the reaction of a substituted phosphonate carbanion with the corresponding aldehyde. Because of the greater reactivity of the phosphonate reagent relative to the phosphonium carbanion, the HWE reaction has proven to be effective with hindered ketones that were unreactive toward classical Wittig ylides.

### 3.1.9.3.3 (E)-Selectivity, effect of phosphonate size

Several studies have described the successful enhancement of the (*E*)-selectivity in alkene formation by increasing the steric requirements of the phosphonate. This selectivity may be derived by increasing the selective formation of the *threo*-β-hydroxyphosphonate.

Kishi and coworkers noted the importance of the phosphonate structure in the synthesis of monensin, where a methyl phosphonate was used to maximize (*Z*)-alkene formation.[141] These observations were expanded upon in the synthesis of rifamycin S.[142] Several interesting Wittig reactions from this synthesis are presented in Table 14.

**Table 14** Rifamycin S Studies by Kishi and Coworkers

| *Carbonyl* | *Reagent* | *(Z):(E) ratio* |
|---|---|---|
| 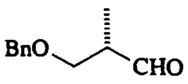 | $Ph_3PCH_2CO_2Et$, $CH_2Cl_2$, 0 °C | 1:7 |
| | $(Pr^iO)_2POCH_2CO_2Et$, $KOBu^t$, THF, −78 °C | 5:95 |
| | $(MeO)_2POCH_2CO_2Me$, $KOBu^t$, THF, −78 °C | 3:1 |
| 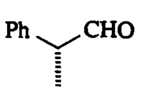 | $Ph_3PCH(Me)CO_2Et$, $CH_2Cl_2$, r.t. | 5:95 |
| | $Ph_3PCH(Me)CO_2Et$, MeOH, r.t. | 15:85 |
| | $(MeO)_2POCH(Me)CO_2Me$, $KOBu^t$, THF, −78 °C | 95:5 |
| | $(MeO)_2POCH(Me)CO_2Et$, $KOBu^t$, THF, −78 °C | 90:10 |
| | $(EtO)_2POCH(Me)CO_2Et$, $KOBu^t$, THF, −78 °C | 60:40 |
| | $(Pr^iO)_2POCH(Me)CO_2Et$, $KOBu^t$, THF, −78 °C | 10:90 |
| | $(Pr^iO)_2POCH(Me)CO_2Pr^i$, $KOBu^t$, THF, −78 °C | 5:95 |

In order to maximize the (*E*)-selectivity, it was found best to use the bulky isopropyl substitutent on the phosphonate as well as on the stabilizing ester. Alternatively, in the case of an aromatic aldehyde, the stabilized phosphonium ylide provided high (*E*)-alkene formation. When the (*Z*)-isomer was desired, it was best to use a methyl substituent on the phosphonate and ester functionalities. Strongly dissociating basic conditions and a hindered aldehyde can result in reversal of the normal (*E*)-selectivity of a phosphonate. This effect is strongly dependent on the reactants and is further discussed in Section 3.1.9.3.4. The importance of steric effects were exemplified in the synthesis of the C–D fragment of amphotericin B by Masmune and coworkers.[143] The methyl and ethyl phosphonates, respectively, formed 1:1.2 and 1.75:1 ratios of (*E*)- to (*Z*)-alkenes. By using isopropyl or 3-pentyl phosphonates, the (*E*)-isomer (**144**) was formed exclusively. The yield of the reaction was improved by using lithium tetramethylpiperidide (**143**) in THF (equation 31). The diisopropyl phosphonate was recently applied to the synthesis of brefeldin C.[144] In this example, the (*E*)-alkene (**146**) was selectively synthesised without epimerization (equation 32).

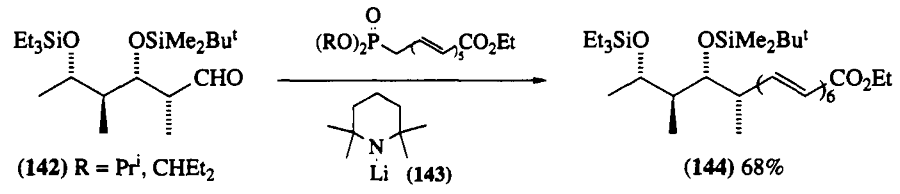

(**142**) R = Pr$^i$, CHEt$_2$ (**143**) (**144**) 68% (31)

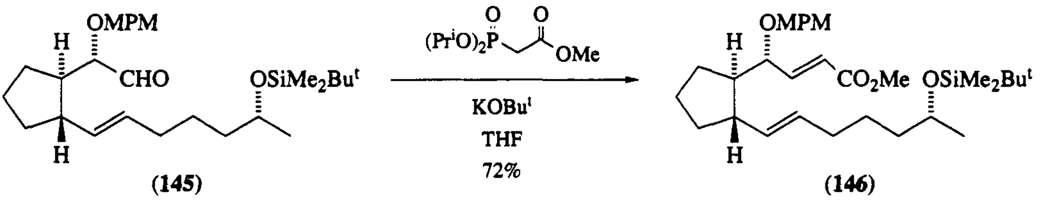

(**145**) (**146**) (32)

### 3.1.9.3.4 *Formation of (Z)-alkenes*

As noted in the discussion of (*E*)-selective alkene formation, Kishi has found that α-substituted aldehydes reacted with trimethylphosphonopropionate and KOBu$^t$ to produce the (*Z*)-alkene selectively. A strongly dissociating base is critical to this approach. In addition to the examples already presented in the discussion of (*E*)-alkene formation, the (*Z*)-selective reaction has recently been applied to the synthesis of macrolide antibiotics.[145] In this example, a trisubstituted alkene was formed and closed to the lactone (**148**; equation 33). In an application to diterpenoids, Piers encountered an example of how substrate-specific the alkene formation can be.[146] With α-dimethoxyphosphonyl-γ-butyrolactone (**150**), the reactions with simple aldehydes proceeded with very high selectivity [(*Z*):(*E*) = 99:1]. On application of the reaction to the more complex aldehyde (**149**) the (*Z*):(*E*) stereoselectivity dropped to 3:1 in 58% yield (equation 34). No selectivity was observed on reaction with benzaldehyde. Although for hindered substrates, strongly basic conditions with a dimethyl phosphonate can be a simple and effective method for the synthesis of (*Z*)-isomers, the reaction is not general. In 1983, Still and coworkers introduced methodology that used bis(trifluoroethyl)phosphonoesters (**153**) to provide a facile approach to (*Z*)-alkenes (**154**) when reacted with aldehydes (equation 35).[147]

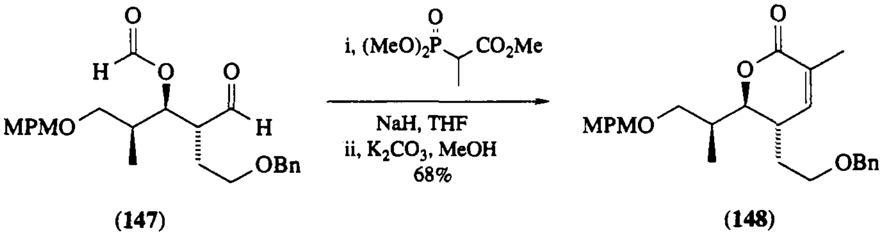

(**147**) (**148**) (33)

The (*Z*)-selectivity is presumed to occur because of rapid elimination of the β-hydroxyphosphonate before equilibration can take place. Several base and solvent combinations were explored, including triton B, K$_2$CO$_3$ and KOBu$^t$, but potassium hexamethyldisilazide with 18-crown-6 in THF gave the most

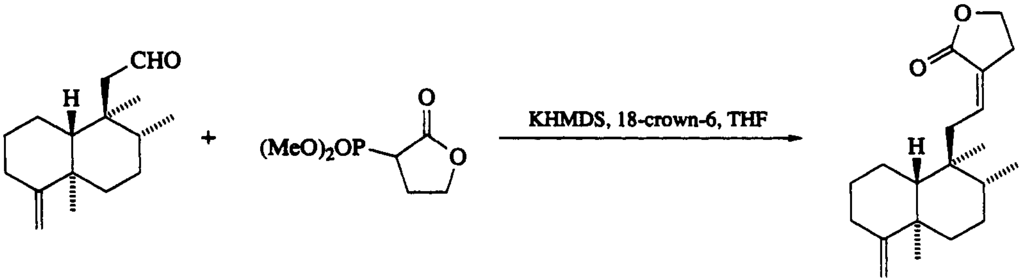
CHO
H
(MeO)$_2$OP
O
KHMDS, 18-crown-6, THF

(34)

**(149)** **(150)** **(151)**

**(150)** + PhCHO; *(Z)*:*(E)* = 1:1, 91%
**(150)** + Bu$^i$CHO; *(Z)*:*(E)* = 99:1, 86%
**(150)** + n-$C_6H_{13}$CHO; *(Z)*:*(E)* = 99:1, 94%

*(Z)*:*(E)* = 3:1, 58%

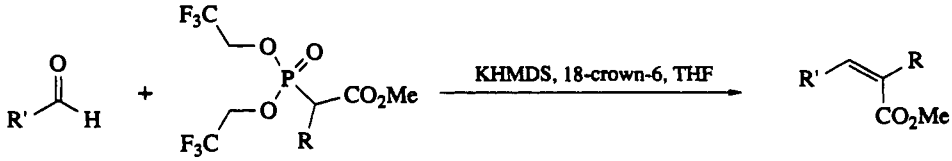
O
R'
H
F$_3$C
O
P
CO$_2$Me
R
KHMDS, 18-crown-6, THF
R'
R
CO$_2$Me

(35)

**(152)** **(153)** R = H, Me **(154)**

consistent and highest (*Z*)-selectivities. A comparison was carried out with trimethyl phosphonoacetate under the same conditions and (*Z*)-alkene formation occurred to a high degree [(*Z*):(*E*) = 12:1] in the reaction with cyclohexanal, which was consistent with the observations of Kishi and coworkers.[147] This was the only instance in which the trimethyl phosphonate formed the (*Z*)-alkene with higher selectivity than the trifluoroethyl analog. The diminished selectivity for α-alkyl-substituted aldehydes does not appear to be general, as two recent syntheses by Baker and Roush demonstrate. Baker synthesized macbecin 1 using a Still phosphonate to form the (*Z*)-alkene (**156**) and a standard stabilized ylide to form the (*E*)-linkage (**157**; Scheme 25).[148] Roush used the trifluoroethyl phosphonate in a synthesis of the C(1)–C(15) segment of streptovaricin, and in this case (**159**) the (*Z*):(*E*) selectivity was at least 10:1 (equation 36).[149]

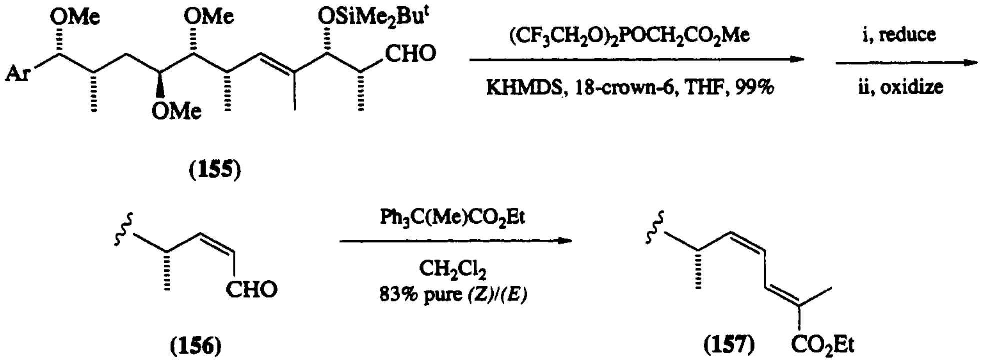
OMe
OMe
OSiMe$_2$Bu$^t$
CHO
Ar
OMe
(CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$Me
KHMDS, 18-crown-6, THF, 99%
i, reduce
ii, oxidize
(155)
CHO
Ph$_3$C(Me)CO$_2$Et
CH$_2$Cl$_2$
83% pure (Z)/(E)
(156)
(157)
CO$_2$Et

**Scheme 25**

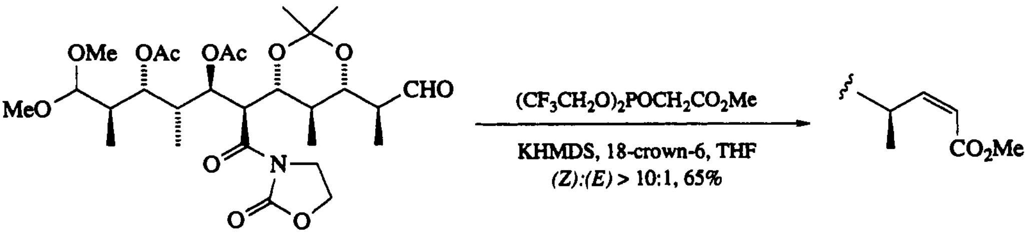
OMe
OAc
OAc
O
O
CHO
MeO
O
N
O
O
(CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$Me
KHMDS, 18-crown-6, THF
(Z):(E) > 10:1, 65%
CO$_2$Me

(36)

**(158)** **(159)**

An aldehyde with α-ether functionality was used in the synthesis of *N*-acetylneuraminic acid by Danishefsky (equation 37).[150] A series of *cis*- and *trans*-alkenes with α-oxygen functionality were synthesized by Cinquinin and coworkers.[151] Of the examples generated, the HWE reaction proceeded in the expected (*E*)-selective manner (**164**), while the trifluoroethyl phosphonate was used to form the (*Z*)-alkenes (**163**) selectively (Scheme 26). Interestingly, 18-crown-6 was not used for (*Z*)-alkene formation.

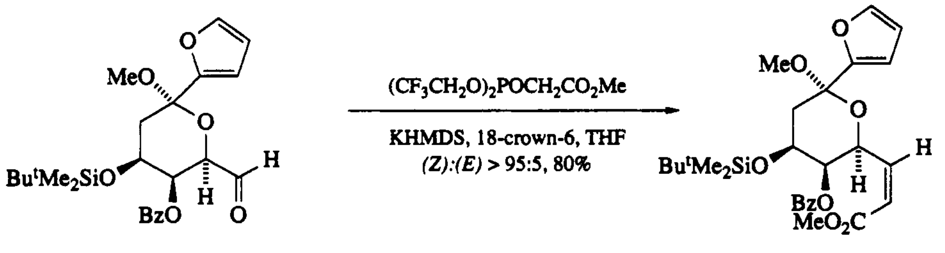

**(160)** **(161)** (37)

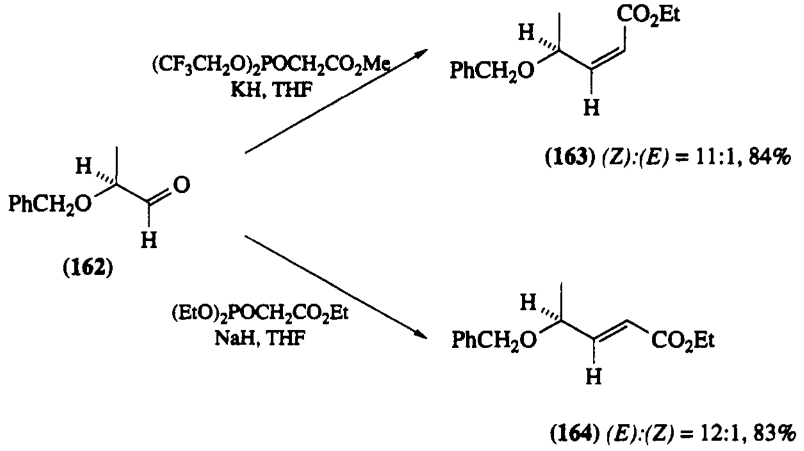

**Scheme 26**

Several examples are presented in Table 15 which indicate that α-heteroatom substitution is compatible with this reagent. The tremendous advantage of the trifluoroethyl phosphonate reagent is the selective formation of (*Z*)-alkene with aromatic aldehydes, while the trimethyl phosphonate gives the normal selectivity.

The trifluoroethyl phosphonate reagent is effective with a number of carbanion-stabilizing groups, including carboalkoxy, cyano and vinylogous cyano. Liu and coworkers have utilized a conjugated nitrile phosphonate (**166**) to synthesize all-*cis*-retinal (**167**; equation 38).[165] In this example, the Wittig reaction gives a mixture of products that were separated by HPLC. The crude yield was 45%, with 72% of the product having the *cis* configuration at the alkene formed. The type of ester stabilizing the phosphonate does not appear to have an large effect on the selectivity. Both the methyl and ethyl esters are routinely used. Recently, Boeckman used the allyl ester in the synthesis of (+)-ikarugamicin to produce the desired (*Z*)-alkene (**169**), the (*Z*):(*E*) ratio being 19:1 (equation 39).[166]

Still's original communication demonstrated that this approach was effective for the synthesis of trisubstituted alkenes by the reaction of a methyl-substituted Wittig reagent with an aldehyde. Examples of the synthesis of methyl-trisubstituted alkenes are presented in Table 16.

Fuchs has published a comparative study of the methyl, ethyl, isopropyl and trifluoroethyl phosphonates, stabilized with either an ester or nitrile, in reaction with an α-amino aldehyde (**170**; equation 40).[174] Although the use of strongly basic conditions improved the ratio of (*Z*)-alkene produced with methyl phosphonate, the (*Z*):(*E*) ratios were 2:3 with either potassium or sodium anions. Interestingly, the HWE reagent stabilized with a nitrile demonstrated far less sensitivity to the size of the phosphonate functionality. With sodium hydride as the base, the diisopropyl phosphonate gave higher (*Z*)-selectivity (7:1) than that of the corresponding ethyl derivative (3.3:1). Fuchs hypothesized that the sterically less demanding nitrile produces a higher ratio of the *erythro* intermediate than the ester-stabilized phosphonate. The trisubstituted alkene was best prepared by using the trifluoroethyl phosphonate, (*Z*):(*E*) = 70:1,

**Table 15** Synthesis of Disubstituted Alkenes by Trifluoroethyl Phosphonate Esters in THF with KHMDS and 18-Crown-6[a]

| *Carbonyl* | *Yield (%)* | *(Z):(E) ratio* | *Notes* | *Ref.* |
|---|---|---|---|---|
| 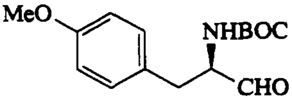 MeO<br>NHBOC<br>CHO | >80 | All *(Z)* | | 152 |
| 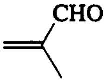 | 78 | 7:1 | | 153 |
| 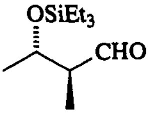 | 70 | All *(Z)* | In $Et_2O$ | 143 |
| 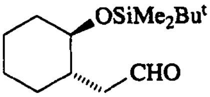 $OSiMe_2Bu^t$<br>CHO | 56 | All *(Z)* | *(E)* with $Ph_3PCHCO_2Me$, $CHCl_3$, 90%, *(Z):(E)* = 1:12 | 154 |
| 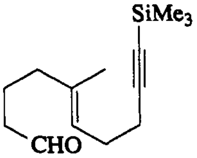 | >61 | 9.4:1 | | 155 |
| 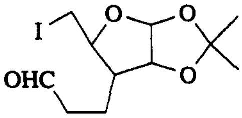 | 75 | All *(Z)* | *(E)* with $Ph_3PCHCO_2Et$, toluene, 95% | 156 |
| 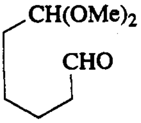 | 94 | 5:1 | | 157 |
| 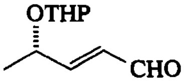 | 75 | 15:1 | No 18-Crown-6, 1:1 | 158 |
| 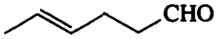 | 75 | 7:1 | | 159 |
| 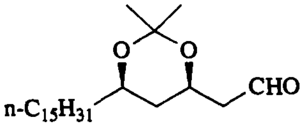 O<br>O<br>CHO<br>$n-C_{15}H_{31}$ | 77 | 9% *(E)* | | 160 |
| 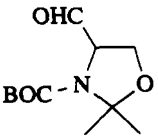 | >87 | *(Z)* >65% | | 161 |
| 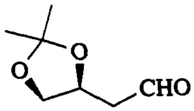 | 89 | 5:1 | In $Et_2O$ with NaH | 162 |

**Table 15** *(continued)*

| *Carbonyl* | *Yield (%)* | *(Z):(E) ratio* | *Notes* | *Ref.* |
|---|---|---|---|---|
| 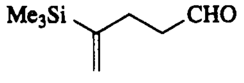 | >62 | 25:1 | | 163 |
| 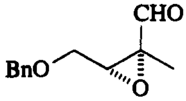 | 80 | | | 164 |

[a] Exceptions to these reaction conditions are noted.

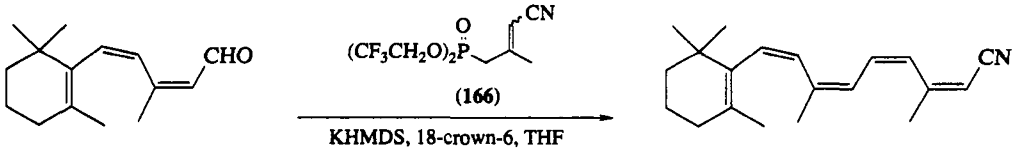

**(165)** **(167)** (38)

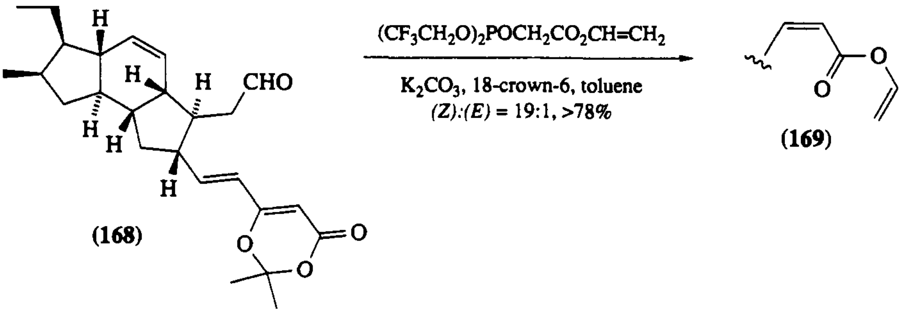
(CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$CH=CH$_2$
K$_2$CO$_3$, 18-crown-6, toluene
(Z):(E) = 19:1, >78%

**(168)** **(169)** (39)

even in the absence of a crown ether. Marshall and coworkers investigated the extension of the trifluoroethyl phosphonate to trisubstituted alkenes with more complex substitution patterns.[175] The reaction of aldehydes lacking α-substitution with methyl α-(dimethylphosphono)propionate and KHMDS/18-crown-6 gave an increased percentage of (*Z*)-isomer, but still gave predominantly the (*E*)-alkene. In examining Kishi's conditions, Marshall found it critical to have a large excess of phosphonate for optimum (*Z*)-selectivity. Alkyl substituents larger than methyl appear to slow the rate of phosphonate oxide elimination. This in turn increases the amount of equilibration that occurs and compromises the (*Z*)-selectivity. The best results observed were for the trifluoroethyl phosphonate (**172**), which formed the (*Z*)-alkene (**173**) on reaction with nonanal in 94% yield and (*Z*):(*E*) = 87:13 (equation 41).

Several other examples of highly substituted applications of the Still phosphonate have appeared. In work very similar to Marshall's, a substituted methyl phosphonate directed toward furancembraolides demonstrated a (*Z*):(*E*) selectivity of 4:5, while the trifluoroethyl phosphonate gave 4:1.[176] Recently an application to squalinoids was demonstrated with a (*Z*)-selectivity similar to Marshall's examples [(*Z*):(*E*) = 6.5:1].[177] Marshall has also investigated an intramolecular ring closure for formation cembraolides and in this application the Still phosphonate did not have any inherent advantage over an alkyl phosphonate in terms of yield or (*E*)-selectivity.[178] Recently, two other examples of substituted phosphonate applications have appeared. Oppolzer has used the methodology to generate an allylic acetate (**175**) with excellent yield and high (*Z*)-selectivity (equation 42).[179]

In an application of (*Z*)-selective alkene formation to enolizable aldehydes, it was noted that the combination of LiCl and DBU was effective for deprotonation by lithium complexation of the Still phosphonate.[180] In this example, the cyclopropyl aldehyde (**176**) reacted chemoselectively in the presence of the ketone (equation 43). In addition, the (*E*)-alkene could be synthesized by lithium coordination with a standard HWE methyl phosphonate. As this example illustrates, the trifluoroethyl phosphonate can fill an important void by providing trisubstituted alkenes with sensitive substrates in good selectivity. From the examples of Marshall and Oppolzer it appears that the application of the reaction to higher order trisubstituted alkenes is selective for the (*Z*)-isomer. The magnitude of the selectivity is substrate specific and dependent on the rapid rate of *erythro*-α-oxyphosphonate decomposition.

**Table 16** Synthesis of Trisubstituted Alkenes by $(CF_3CH_2O)_2POCH(Me)CO_2R$ in THF with KHMDS and 18-Crown-6[a]

| *Carbonyl* | *Yield* (%) | *(Z):(E) ratio* | *Notes* | *Ref.* |
|---|---|---|---|---|
| 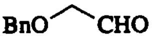 | 60 | 58% *(Z)* | | 167 |
| 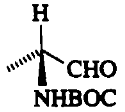 | 68 | 99:1 | | 168 |
| 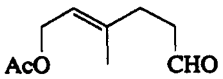 | 71 | >99% *(Z)* | | 169 |
| 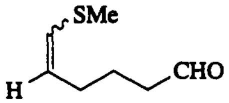 | 93 | 98:2 | *(E)* with $Ph_3PC(Me)CO_2Me$, 86%, *(E)* only | 170 |
| 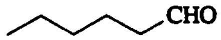 | 63 | 91:9 | *In situ* DIBAL and Wittig<br>*(E)* with diethyl phosphonate, 77%, 18:82 *(Z):(E)* | 171 |
| 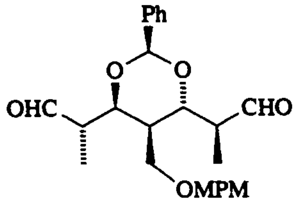 | 78 (4 steps) | | | 172 |
| 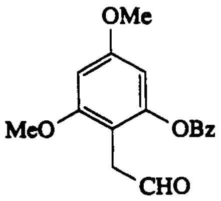 | 77 | All *(Z)* | | 173 |

[a] Exceptions to these conditions are noted.

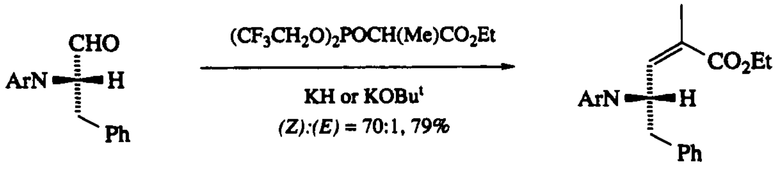
$(CF_3CH_2O)_2POCH(Me)CO_2Et$
KH or KOBu$^t$
*(Z):(E)* = 70:1, 79%
CHO
ArN
H
Ph
$CO_2Et$

**(170)** Ar = Ts, Bn **(171)** (40)

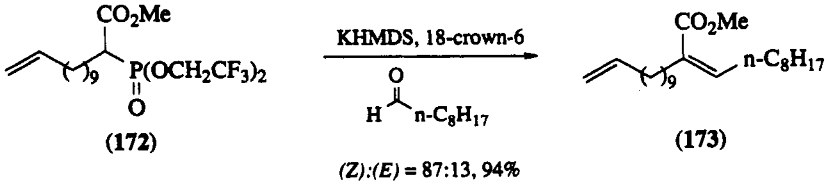
$CO_2Me$
$P(OCH_2CF_3)_2$
O
9
KHMDS, 18-crown-6
O
H
n-$C_8H_{17}$
*(Z):(E)* = 87:13, 94%
$CO_2Me$
n-$C_8H_{17}$
9

**(172)** **(173)** (41)

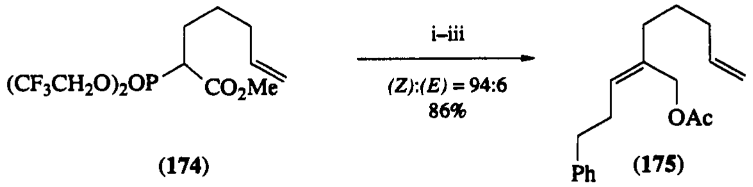

(174) (175) (42)

i, KHMDS, 18-crown-6, THF, $Ph(CH_2)_2CHO$; ii, DIBAL-H; iii, $Ac_2O$, $Et_3N$

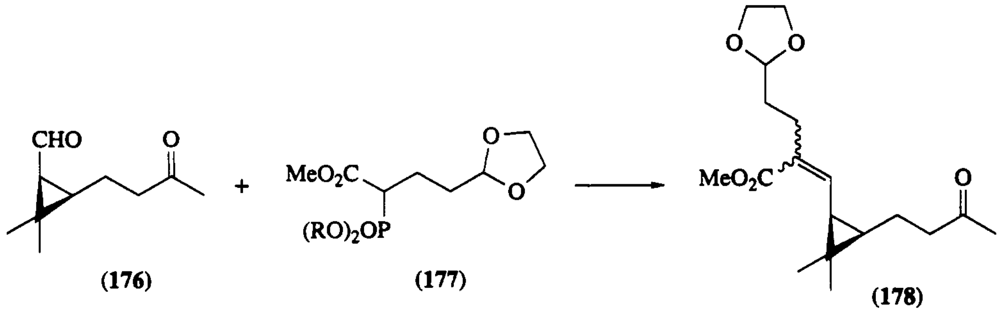

(176) (177) (178) (43)

R = Me; LiHMDS, DME; (Z):(E) = 14:86, 100%
R = $CF_3CH_2$; DBU, LiCl, MeCN; (Z):(E) = 75:25, 100%

### *3.1.9.3.5 Effect of bases*

As noted in the work of Seyden-Penne, and demonstrated in numerous examples such as those by Still and Kishi, higher (*Z*)-selectivity is observed by using base systems that have minimally complexing counterions in order to increase the rate of elimination relative to equilibration.[181] Coordination has been used to advantage by Massamune and Roush, who found that the addition of lithium chloride to a phosphonate formed a tight complex (**180**; equation 44) that could be deprotonated with a weak base such as DBU or diisopropylethylamine.[182] This method is a mild and extremely effective modification for substrates in which racemization or β-elimination are processes competitive with alkene formation. Rathke and coworkers have demonstrated that TEA and LiBr or $MgBr_2$ may also be used to form a reactive HWE reagent.[183] Acetonitrile and THF are the most frequently used solvents. These conditions do not alter the normal course of stereoselectivity for alkene formation. As noted above, the method was utilized with the Still phosphonate to produce (*Z*)-alkenes. There is some indication that this technique may enhance inherent (*E*)-stereoselectivity in alkenations with a standard HWE reagent.[182] Other stabilizing functionalities are compatible with this method. As outlined in Table 17, ester, ketone, sulfone, amide and allylic ketone groups have been demonstrated to be effective as stabilizing functionalities.

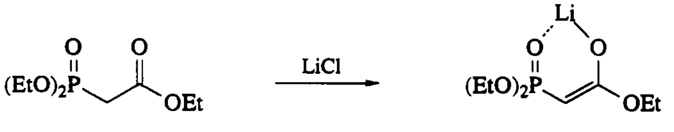

(179) (180) (44)

This reaction has been utilized in the context of natural product synthesis. A recent example is the synthesis of colletodiol by Keck, shown in equation (45).[194] In this example, no problems were encountered with epimerization or ester cleavage. The desired (*E*)-ester (**182**) was synthesized in 80% yield. Two examples are outlined (in equations 46 and 47) in which epimerization was a substantial problem with sodium or potassium salts, while the LiCl/amine method effectively suppressed this side reaction. When the phosphonate was allowed to react with the cyclohexanal derivative (**183**), the sodium salt gave epimerized material. Use of LiCl and diisopropylethylamine gave an 88% yield of alkene (**184**), free of epimer (equation 46).[195] In the synthesis of norsecurinine, Heathcock found that the phosphonate anion

**Table 17** Synthesis of Alkenes Utilizing LiX and Amine Base

| *Carbonyl* | *Phosphonate* | *Comments* | *Ref.* |
|---|---|---|---|
| 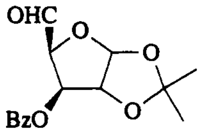 | 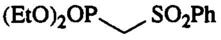 | LiCl, $\mathrm{Pr^i_2NEt}$, 63%, (*E*) | 184 |
| 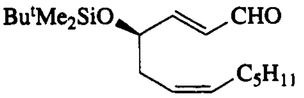 | 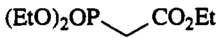 | LiCl, DBU, 60%, (*E*) | 185 |
| 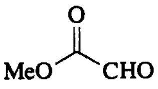 | 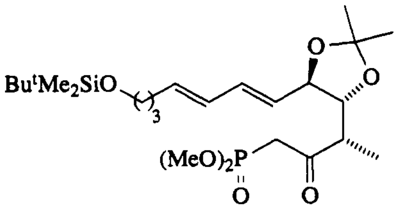 | LiCl, $\mathrm{Pr^i_2NEt}$, 99%, (*E*) | 186 |
| 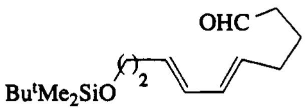 | 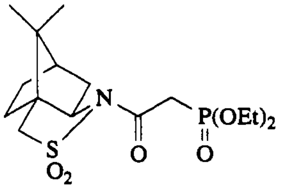 | LiCl, DBU, 89%, (*E*) | 187 |
| 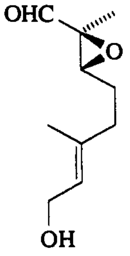 | 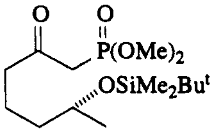 | LiCl, $\mathrm{Pr^i_2NEt}$, 88%, (*E*) | 188 |
| 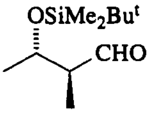 | 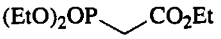 | LiCl, DBU, 90%, (*E*) | 189 |
| PhCHO | 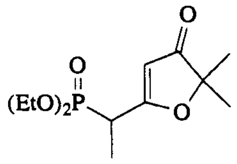 | LiBr, $\mathrm{Et_3N}$, 85%, 83:7 (*E*) | 190 |
| $\mathrm{Pr^iCHO}$ | 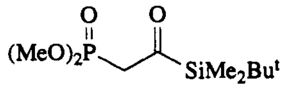 | LiCl, DBU, 87%, >95% (*E*) | 191 |

**Table 17** *(continued)*

| *Carbonyl* | *Phosphonate* | *Comments* | *Ref.* |
|---|---|---|---|
| 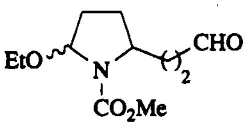 | 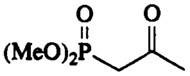 | LiCl, $Pr^i_2NEt$, 83% *(E)* | 192 |
| 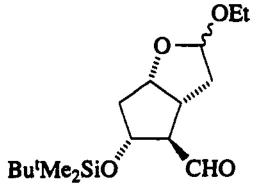 | 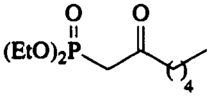 | LiCl, $Pr^i_2NEt$, 93% *(E)* | 193 |

generated with $KOBu^t$ gave an excellent (96%) yield of the desired alkene (**186**), but the material was racemic.[196] Use of DBU and LiCl produced (**186**) in 84% yield and 93% *ee* (equation 47).

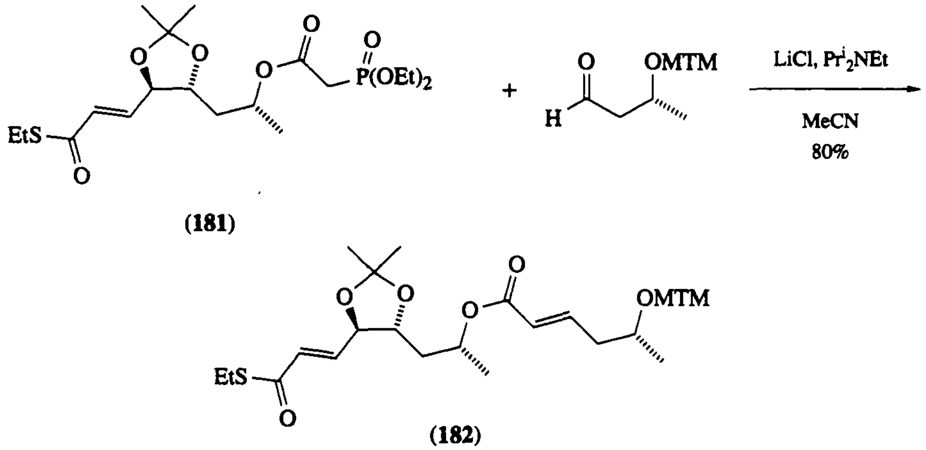
LiCl, $Pr^i_2NEt$
MeCN
80%

(**181**)

(**182**)

(45)

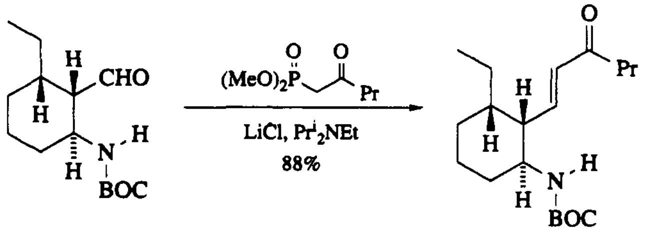
LiCl, $Pr^i_2NEt$
88%

(**183**) (**184**)

(46)

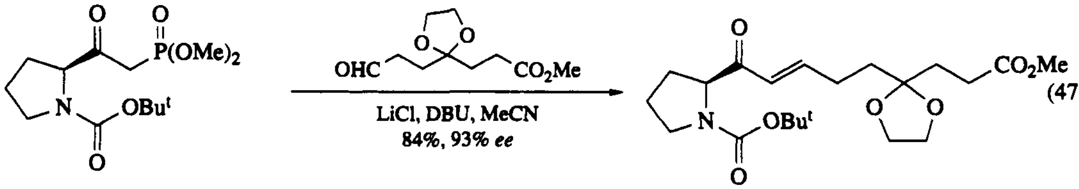
LiCl, DBU, MeCN
84%, 93% *ee*

(**185**) (**186**)

(47)

As with all reactions with phosphonates, these conditions are sensitive to the steric environment of the carbonyl and phosphonate. In a reaction directed at intermediates for synthesis of the erythronolides, Paterson and coworkers found that the unsubstituted phosphonate (**188**) added in 82% yield in the presence of molecular sieves (equation 48).[197] When R was methyl the reaction failed with DBU because of competitive elimination of $OSiMe_2Bu^t$. Model studies with the phosphonate and isopropyl aldehyde were successful, providing the alkene in 78% yield in an (*E*):(*Z*) ratio of 8:1. The Roush–Masamune modification of the HWE reaction was utilized by Heathcock and coworkers in the synthesis of mevinic acids.[198] The coupling was very clean and resulted in 35–60% yields of alkene (**192**), along with 35–50% of recovered aldehyde (**191**; equation 49). This methodology is also effective for macrolide synthesis by intramolecular ring closure. An example of the utility of this approach is the synthesis of amphotericin B by Nicolaou.[199] In this example, the macrolide could be formed from (**193**) either with potassium carbonate and 18-crown-6, or with LiCl and DBU at 0.01 M in 70% yield to form the (*E*)-alkene. Other applications of intramolecular cyclization have appeared for the cembranolides[200] and rubradirins.[201]

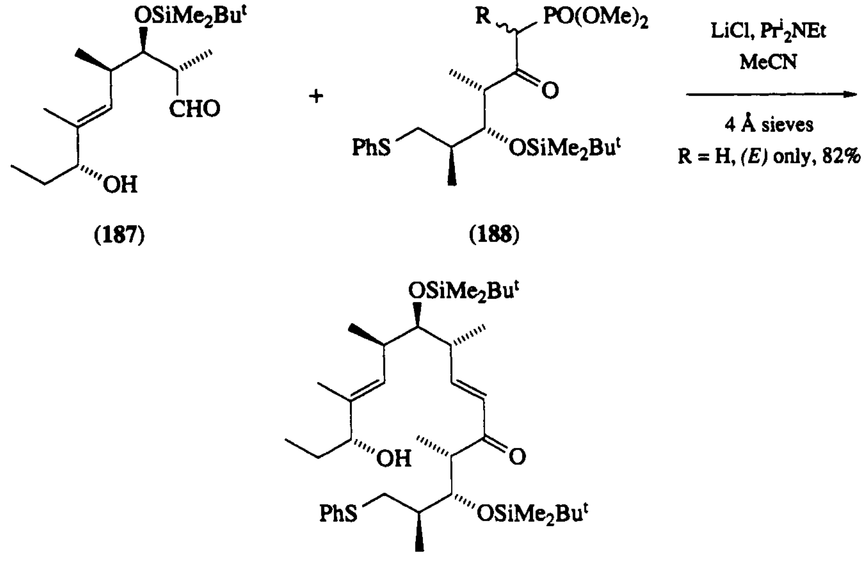
OSiMe2But
CHO
OH
+
R
PO(OMe)2
O
PhS
OSiMe2But
LiCl, Pri2NEt
MeCN
4 Å sieves
R = H, (E) only, 82%
OSiMe2But
OH
O
PhS
OSiMe2But

**(187)** **(188)**

**(189)**

(48)

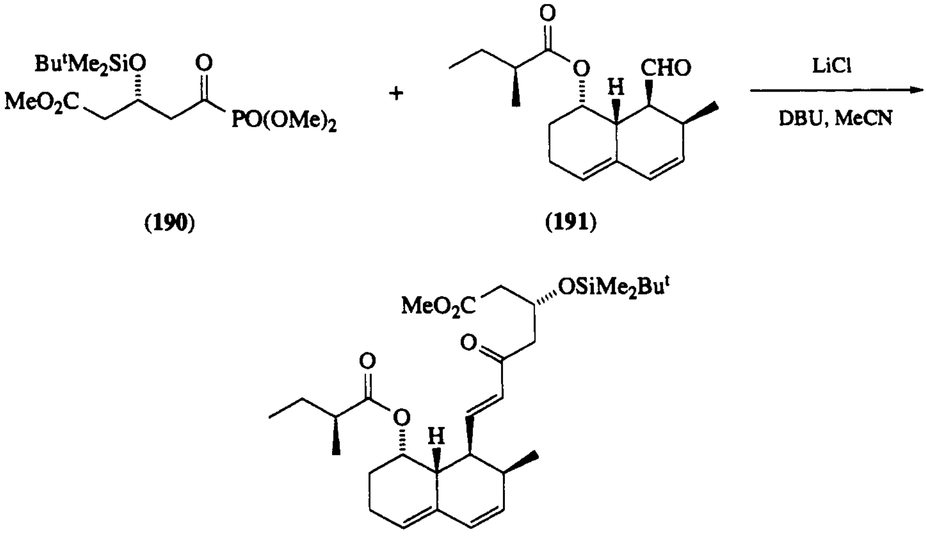
ButMe2SiO
O
MeO2C
PO(OMe)2
+
O
O
CHO
H
LiCl
DBU, MeCN
MeO2C
OSiMe2But
O
O
O
H

**(190)** **(191)**

(49)

**(192)** 35–60%

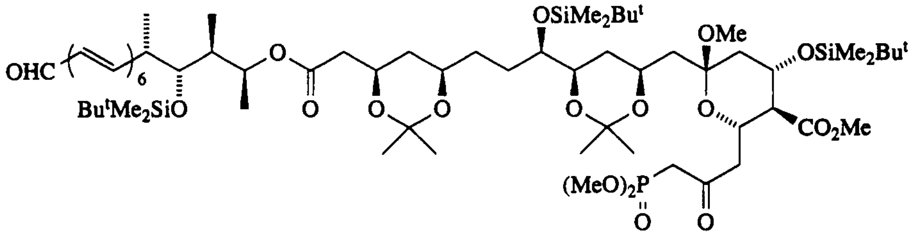

(193)

### 3.1.9.3.6 *Asymmetric Horner–Wadsworth–Emmons*

Hanessian and coworkers have prepared a homochiral bicyclic phosphonamide (**194**) that reacted with cyclohexanone derivatives to form (*E*)-ethylenes with good optical purity.[202] The phosphonamide (**194**) was deprotonated with KDA in THF and reacted with 4-*t*-butylcyclohexanone (**195**) to give a 82% yield of 90% optically pure alkene (**196**; Scheme 27). Either the (*R*,*R*)- or the (*S*,*S*)-phosphonamide (**194**) can be synthesized, and on reaction with (+)-3-methylcyclohexanone (**197**) it is possible to obtain (*E*),(3*R*)-alkene (**198**) with (*R*,*R*)-reagent and (*Z*),(3*R*)-alkene with the (*S*,*S*)-phosphonamide. Gais and Rehwinkel have demonstrated the use of a chiral phosphonate in which the stabilizing carbonyl is an 8-phenylmenthyl ester.[203] This methology was applied to the synthesis of carbacylins (**200** and **201**; equation 50). Whereas a methyl phosphonate gives a 1:1 mixture of (*E*)- and (*Z*)-alkenes, the presence of a chiral ester gives good selectivity for either the (*E*)- or (*Z*)-alkene, depending on the enantiomer of the phenylmenthyl chosen. This reaction is temperature sensitive and, if heated, the (*E*)-alkene predominates.[203b] The choice of solvent is not as critical a factor as temperature, and better ratios were observed with potassium as the counterion. Other esters were examined, including (+)-menthyl and (–)-*trans*-2-phenylcyclohexyl, but the phenylmenthyl ester proceeded with higher selectivity.[203a] This reaction has been applied to achiral ketones to produce diastereomeric esters.[203]

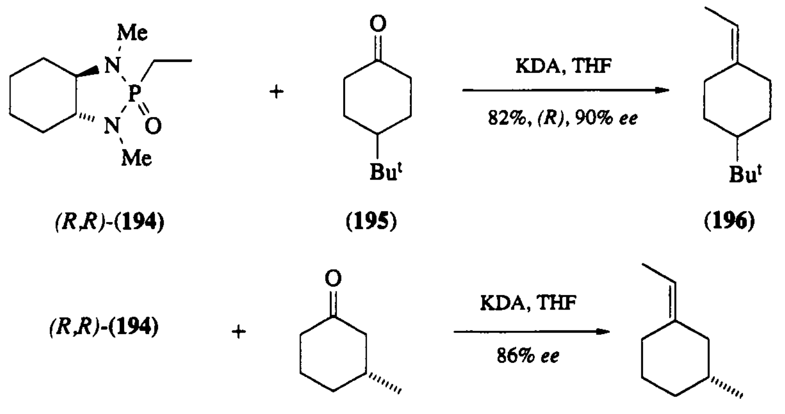

(197) (198)

Scheme 27

### 3.1.9.4 Phosphine Oxides: the Horner Reaction

In Horner's original work, phosphine oxides (**202**) were treated with potassium *t*-butoxide or sodamide and allowed to react with an aldehyde or ketone to form the alkene (**203**) directly (Scheme 28). Horner observed that the use of a lithium anion resulted in the isolation of the β-hydroxyphosphine oxide (**204**).[204] In addition, he found that the intermediate hydroxyphosphine oxide could be obtained by LAH reduction of the ketophosphine oxide. Warren and coworkers have utilized and expanded upon these techniques by isolating and separating the diastereomeric, frequently crystalline, β-hydroxyphosphine

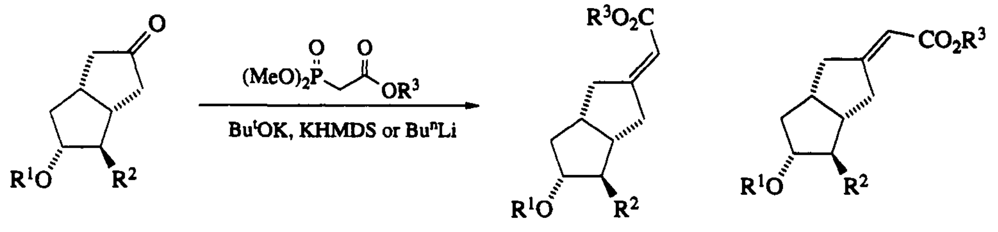

(199) (E)-(200) (Z)-(201)

(50)

$R^1 = SiMe_2Bu^t$, $R^2 = OSiMe_2Bu^t$, $R^3$ = (+)-8-phenylmenthyl; *(E)*:*(Z)* = 86:14, 95%

$R^1 = SiMe_2Bu^t$, $R^2 = OSiMe_2Bu^t$, $R^3$ = (–)-8-phenylmenthyl; *(E)*:*(Z)* = 23:77, 89%

$R^1 = H$, $R^2 =$ 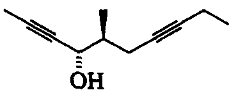 , $R^3$ = (+)-8-phenylmenthyl; *(E)*:*(Z)* = 86:14, 92%

$R^1 = H$, $R^2 =$ 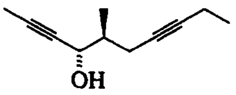 , $R^3$ = (+)-8-phenylmenthyl; *(E)*:*(Z)* = 15:85, 95%

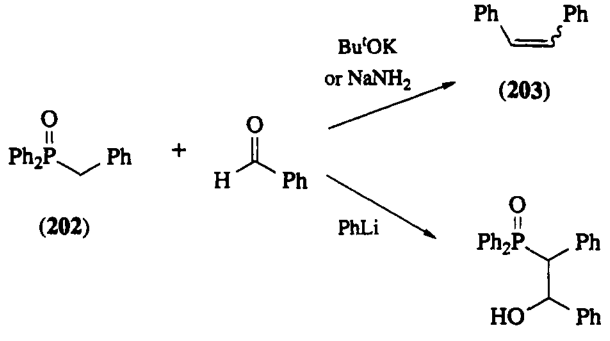

(202) (203) (204)

**Scheme 28**

oxides (**206**) and (**207**).[205] The *erythro* and *threo* adducts are then subjected to *syn* elimination, with the *erythro* isomer producing the (*Z*)-alkene (**208**), and the *threo* the (*E*)-isomer (**209**; Scheme 29).[206]

Unlike the Peterson alkenation, which is in principle similar, the phosphine oxide anion addition can be controlled to produce predominantly the *erthyro* isomer (**206**). The *threo* isomer can be obtained by selective reduction of the α-ketophosphine oxide (**210**), allowing highly stereoselective alkene formation. Since a two-step sequence is employed, this reaction does not require a stabilizing functionality to be conjugated to the phosphine oxide in order to produce the alkene. In fact, unlike the phosphonate HWE reagents, the reaction of a ketophosphine oxide (**211**) with a carbonyl derivative does not occur to produce the unsaturated carbonyl (**213**; Scheme 30).[207] The addition step is presumably too rapidly reversible and the elimination of phosphine oxide too slow.

The use of diphenylcyanomethylphosphine oxide is effective for the synthesis of (*E*)-α,β-unsaturated nitriles.[208] Phosphine oxides can be used to synthesize a variety of functionalized alkenes, including vinyl ethers (**215**; equation 51),[209] vinyl sulfides (**217**; equation 52),[210] allylic amines (**219**) and amides (equation 53),[211] ketene acetals (**221**; equation 54)[212] and ketene thioketals (**223**; equation 55).[213] In the examples of α-thio substitution, the alkenes are formed directly.

### *3.1.9.4.1 Elimination*

The intermediate β-hydroxyphosphine oxide is isolated only if lithium is used to deprotonate the phosphine oxide. Sodium or potassium anions eliminate *in situ* to form the alkene directly. Eliminations of

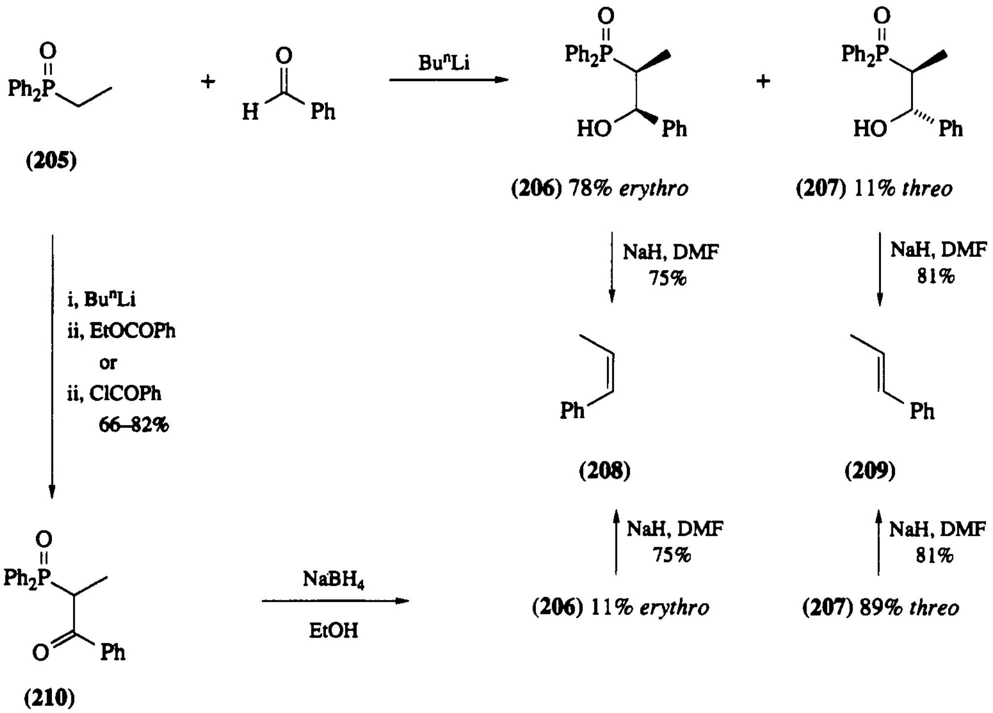
(205)
Bu^nLi
(206) 78% erythro
(207) 11% threo
NaH, DMF 75%
NaH, DMF 81%
(208)
(209)
i, Bu^nLi
ii, EtOCOPh
or
ii, ClCOPh
66–82%
NaBH4
EtOH
NaH, DMF 75%
NaH, DMF 81%
(206) 11% erythro
(207) 89% threo
(210)

**Scheme 29**

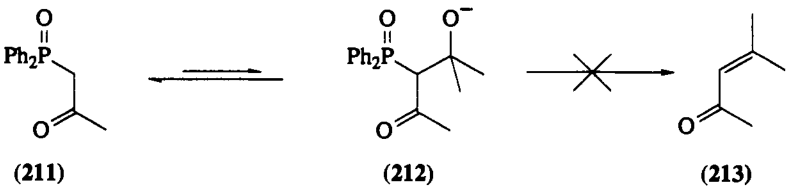

**Scheme 30**

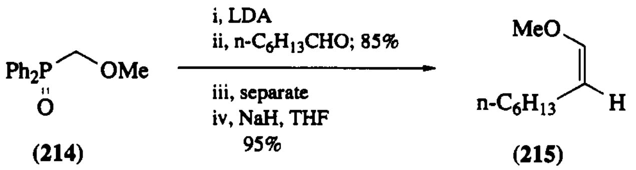
(214)
i, LDA
ii, n-C6H13CHO; 85%
iii, separate
iv, NaH, THF
95%
(215)

(51)

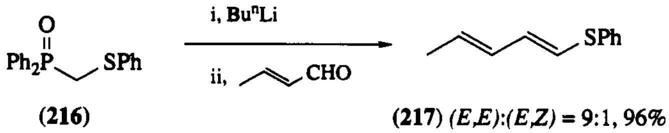
(216)
i, Bu^nLi
ii, CHO

(217) *(E,E):(E,Z)* = 9:1, 96%

(52)

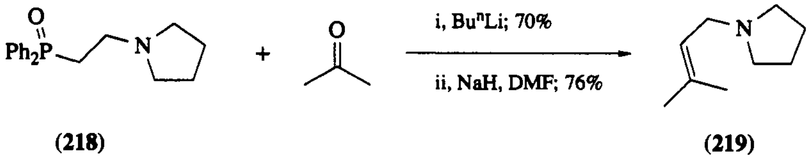
(218)
i, Bu^nLi; 70%
ii, NaH, DMF; 76%
(219)

(53)

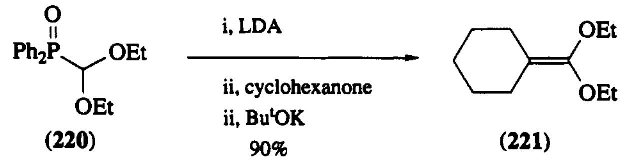

**(220)** **(221)** (54)

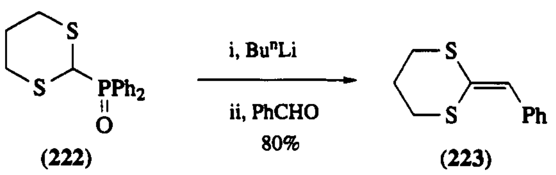

**(222)** **(223)** (55)

the *threo*-hydroxyphosphine oxide intermediates are stereospecifically *syn* and produce the (*E*)-alkene, but the reaction of *erythro* adducts can be complicated by equilibration with starting materials, particularly in the case of aromatic aldehydes.[214] Typically, bases such as NaH, KOH and KOBu$^t$ are used in DMF, DMSO or THF to effect elimination.

### *3.1.9.4.2* Erythro *selectivity,* cis*-alkene*

The addition of the phosphine oxide anion to the carbonyl is dramatically affected by solvent, base and temperature.[214] These conditions can be modified in order to maximize the *erythro* isomer formation. In nonpolar solvents the addition proceeds with virtually no selectivity. Substantial improvements are seen by the use of ethers, and the highest ratios of *erythro* adduct (**225**) are obtained in THF with the lithium complexing reagent TMEDA present at –78 °C or lower temperatures (equation 56).

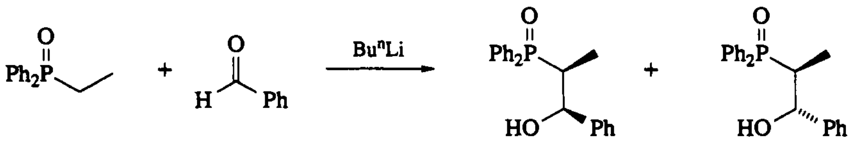

(56)

**(224)**

| *Solvent* | (**225**) *erythro* (%) | (**226**) *threo* (%) |
|---|---|---|
| Pentane | 55 | 45 |
| THF | 85 | 15 |
| THF, TMEDA, –78 °C | 88 | 12 |

Substituent effects are also important to the selectivity. Branching α to the phosphine oxide can significantly erode the ratios of *erythro* to *threo* intermediates. For example, changing the α-substituent from methyl to isopropyl gives a 64:36 ratio of *erythro* to *threo* isomers on reaction with benzaldehyde.[214] Increasing the branching of the aldehyde component also diminishes the selectivity, but the effect is smaller. Cyclohexanal combines with the lithium anion of ethylphosphine oxide to give a 79:21 mixture of *erythro* to *threo* adducts in 79% yield. Although the elimination of phosphine oxide to form the alkene is *syn*, a certain amount of (*E*)-alkene is formed from *erythro* intermediates with a conjugating functionality α to the phosphine oxide.[206] This loss of selectivity is thought to occur by cleavage back to the starting anion and the carbonyl, resulting in equilibration to higher ratios of *threo* adduct and therefore (*E*)-alkene. The equilibration can be minimized by using a polar solvent such as DMF or DMSO and higher temperatures to ensure rapid elimination of phosphinate. An additional solution is demonstrated in the selective synthesis of (*Z*)-stilbene (**229**) using dibenzophosphole oxide in the Horner reaction (Scheme 31).[215] The cyclic phosphine oxide shifts the equilibrium so that phosphinate elimination is favored relative to the reverse aldol process. This is because of the marked acceleration of elimination when phosphorus is incorporated in a five-membered ring. The *erythro* adduct was generated by ring-opening the epoxide. Elimination with NaH in DMSO gives a 91% yield with a (*Z*):(*E*) ratio of 89:11. This ratio can be dramatically improved to >99:1 by using DBU.

Warren has also studied dibenzophosphole oxides.[216] The ketophosphine oxide (**230**) substrate can be formed and selective reduction to either the *erythro* (**233**) or the *threo* (**231**) adducts carried out. The normal NaBH$_4$ conditions were used for reduction to the *threo* isomer and CeCl$_3$ was added to obtain the *erythro* adduct. This methodology was applied to the synthesis of (*E*)- and (*Z*)-isosafroles (**232**) and

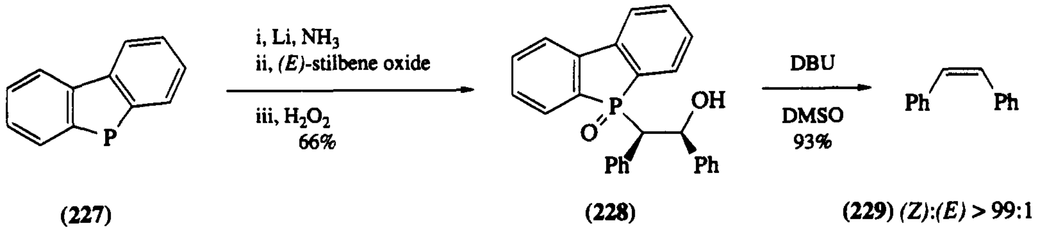
i, Li, NH$_3$
ii, (*E*)-stilbene oxide
iii, H$_2$O$_2$
66%
P
P
O
OH
Ph
Ph
DBU
DMSO
93%
Ph
Ph
(227)
(228)
(229) (*Z*):(*E*) > 99:1

**Scheme 31**

(**234**), respectively, from a single ketophosphine oxide intermediate (**230**; Scheme 32). The application of this approach to diphenylphosphine oxides would provide a method by which either alkene isomer could be readily obtained from a single intermediate. Unfortunately, the Luche reduction, which is vital to this strategy, is highly substrate specific.[216b]

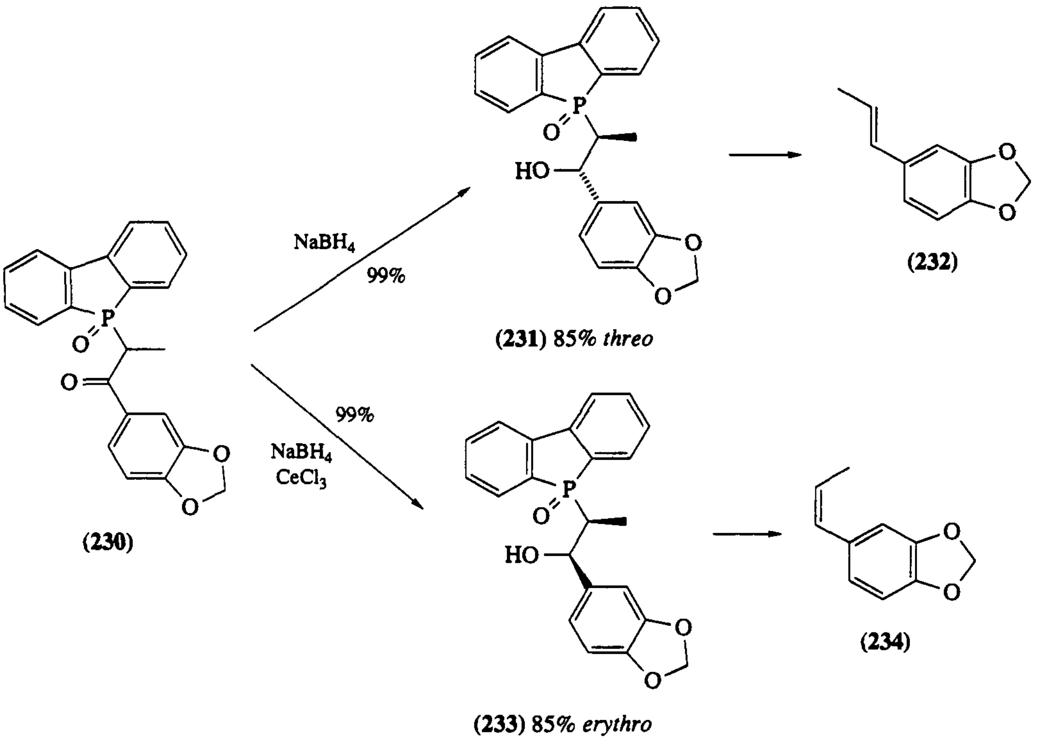
P
O
O
O
O
(230)
NaBH$_4$
99%
99%
NaBH$_4$
CeCl$_3$
P
O
HO
O
O
(231) 85% *threo*
(232)
P
O
HO
O
O
(233) 85% *erythro*
(234)

**Scheme 32**

### *3.1.9.4.3* Threo *selectivity,* trans-*alkene*

*Trans*-alkenes can be synthesized by the Horner reaction from the ketophosphine oxide, which is reduced selectively to the *threo* adduct.[217] This intermediate is typically formed by reaction of the phosphine oxide with an ester or acid chloride. Alternatively, the keto intermediate may be obtained by oxidation of β-hydroxyphosphine oxides. This sequence was applied to the synthesis of the pure (*E*)-triene (**237**) by Warren (equation 57).[217]

Unlike the elimination of *erythro* adducts, the elimination of the *threo* intermediate is stereospecific for aromatic and aliphatic substituents. A study of various methods of reduction found that NaBH$_4$ in EtOH gave the best combination of *threo* selectivity and yield.[218]

This methodology has been applied to the synthesis of oudemansins by Kallmerten.[219] In this example, the Wittig alkenation gave mixtures of (*E*)- and (*Z*)-products, as well as epimerizing the ether position. These problems were solved by acylating the phosphine oxide (**239**) and carrying out reduction and

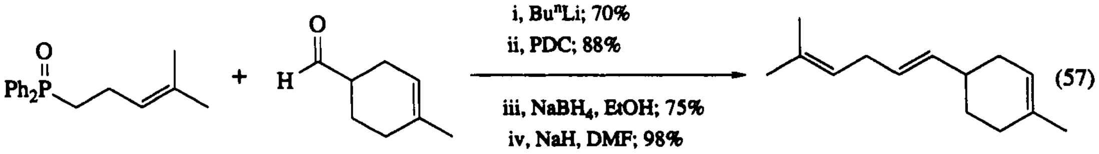
Ph₂P
O
H
i, BuⁿLi; 70%
ii, PDC; 88%
iii, NaBH₄, EtOH; 75%
iv, NaH, DMF; 98%

(235) (236) (237) (57)

elimination to (**240**) with $LiBH_4$ (Scheme 33). It was not anticipated that the reduction conditions would also cause elimination. It is unknown whether this effect is general for conjugated alkenes. Recently, Warren has studied the effect of additional chiral centers on the reduction of the ketophosphine oxide intermediate.[220] In simple alkyl-substituted cases (**241**) it is possible to reduce the intermediate with high diastereoselectivity to produce (*E*)-alkenes (**242**). Alternatively an anion addition can be carried out on the ketophosphine oxide (**243**) to synthesize trisubstituted alkenes (**245**). Yields of these processes are good and alkene ratios are high (Scheme 34).

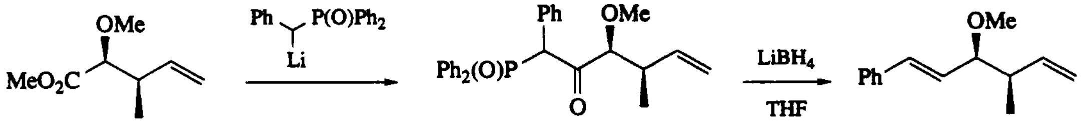
OMe
MeO₂C
Ph P(O)Ph₂
Li
Ph OMe
Ph₂(O)P
O
LiBH₄
THF
OMe
Ph

(238) (239) (240) (*E*) only, 32%

Scheme 33

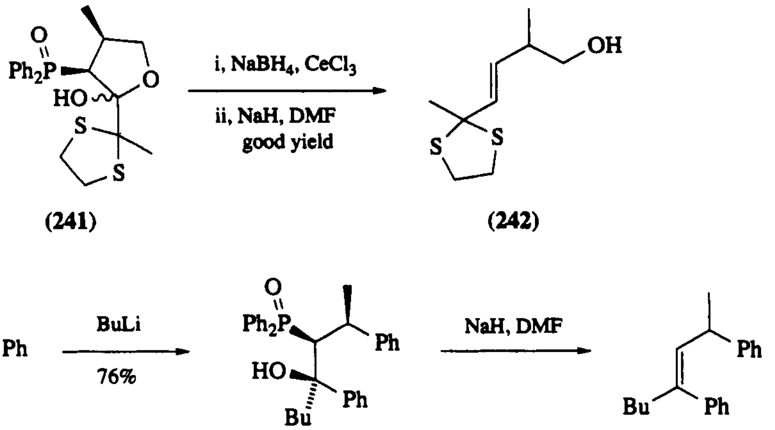
O
Ph₂P
HO
O
S
S
i, NaBH₄, CeCl₃
ii, NaH, DMF
good yield
OH
S
S
(241)
(242)
O
Ph₂P
Ph
O
Ph
BuLi
76%
O
Ph₂P
Ph
HO
Bu
Ph
NaH, DMF
Ph
Bu
Ph

(243) (244) (245)

Scheme 34

### 3.1.9.4.4 Disubstituted alkenes

For the synthesis of disubstituted alkenes by the Horner reaction, there are general guidelines that can be followed to maximize selectivity, as shown in structure (**246**).[221] It is best to have the larger of the two substituents of the double bond to be formed derived from the carbonyl moiety. This is particularly important if the substituent is anion-stabilizing since this will erode the selectivity at the elimination. These rules can be followed, regardless as to the stereochemistry of the alkene desired.

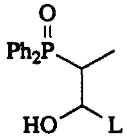

(246) L = large, conjugating group

The Wittig and Horner processes can be combined in a cyclic process to form (*E,Z*)-dienes (**249**; Scheme 35).[222] The initial Wittig process proceeded in 63% yield with 68:32 to (*Z*)-selectivity. Deprotonation of the phosphine oxide (**248**) and reaction with benzaldehyde gave exclusively the *erythro* isomer in 82% yield. The phosphine oxide was eliminated with NaH in DMF to give the (*E,Z*)-1,6-diene in an isomer ratio of 92:8 with the (*E,E*)-diene.

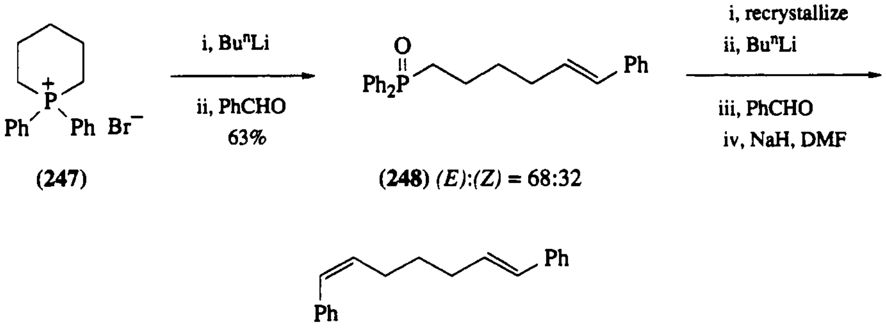

**(247)**

**(248)** (*E*):(*Z*) = 68:32

**(249)** (*E,Z*):(*E,E*) = 92:8

**Scheme 35**

The Horner–Wittig process has been utilized in the synthesis of vitamin D and its metabolites. Recently, a process was developed for the synthesis of hydrindanols by the 1,4-addition of the phosphine oxide to cyclopentenone.[223] After further elaboration, the phosphine oxide formed (**250**) can be utilized to incorporate side chains (**251**; equation 58).

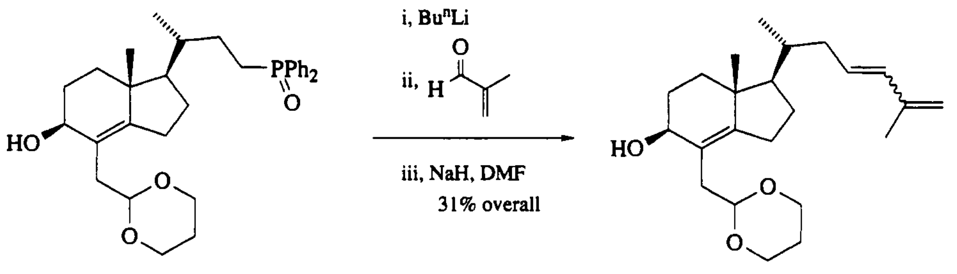

(58)

**(250)**

**(251)** (*E*):(*Z*) = 71:29

Recently, the Horner coupling was utilized by Smith and coworkers in the total synthesis of milbemycin (equation 59).[224] In an excellent example of the sensitivity of the alkene stereochemistry to the base utilized, when the phosphine oxide anion (**253**) was generated with NaH as the base the (*E*):(*Z*) ratio was 7:1, but epimerization occurred at the aldehyde methine (**252**) and the yield was only 15%. Switching to KHMDS, the yield improved to 74% but virtually a 1:1 ratio of alkenes formed. Use of sodium hexamethyldisilazide solved these difficulties, forming the desired (*E*)-diene (**254**) in a 7:1 ratio with the (*Z*)- in 85–95% yield. Additional examples of the use of phosphine oxides in the synthesis of milbemycins and FK-506 are presented in Section 3.1.11.4.

Warren has applied the Horner reaction to the synthesis of isoxazoles (equation 60).[225] Either the 3-alkyl or the 5-alkyl substitution is effective, and in either case good yields of (*E*)-alkenes are obtained. The isoxazoles can be cleaved with $Mo(CO)_6$. The Horner reaction can be utilized in the synthesis of polyenes. For example, Nicolaou utilized this methodology in the synthesis of a pentaene (equation 61).[226] The addition was carried out with LDA and the elimination effected with $KOBu^t$ to give the (*E*)-isomer (**258**).

### *3.1.9.4.5 Trisubstituted alkenes*

The Horner reaction can be applied to the synthesis of trisubstituted alkenes. As in the case of HWE reactions, the yield obtained by adding a disubstituted phosphine oxide to an aldehyde is frequently higher than that obtained by adding an anion to a ketone. This methodology was applied to the synthesis

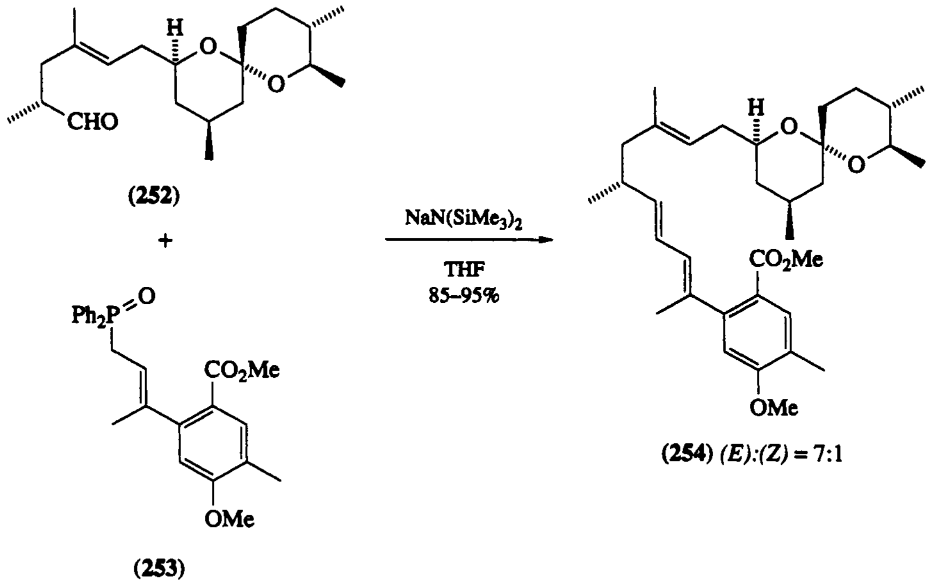
H
O
O
CHO
Ph2P=O
CO2Me
OMe
NaN(SiMe3)2
THF
85–95%
H
O
O
CO2Me
OMe

**(252)** + **(253)** → **(254)** *(E)*:*(Z)* = 7:1 (59)

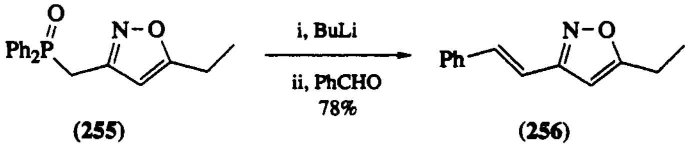
O
Ph2P
N−O
i, BuLi
ii, PhCHO
78%
Ph
N−O

**(255)** → **(256)** (60)

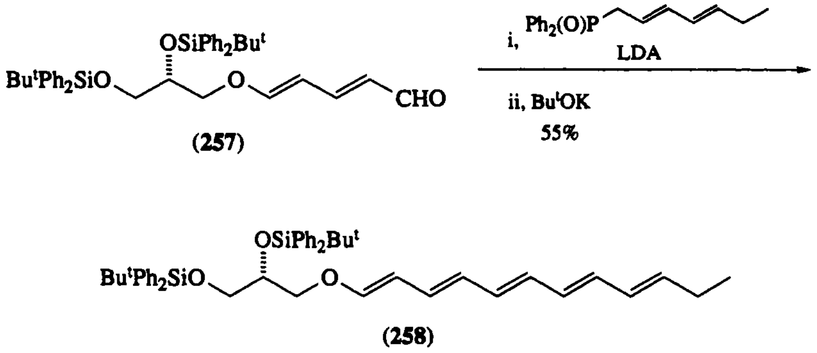
OSiPh2But
ButPh2SiO
O
CHO
i, Ph2(O)P
LDA
ii, ButOK
55%
OSiPh2But
ButPh2SiO
O

**(257)** → **(258)** (61)

of (*Z*)-α-bisabolene (**261**; equation 62).[227] As stated above, heteroatom substitution is compatable with the formation of alkenes by phosphine oxide. This technique has been used by Ley and coworkers to synthesize intermediates for spiroketal formation (**263**; equation 63).[228] The Horner coupling has been utilized by many groups for the synthesis of the diene portion of vitamin D and its metabolites (**266**; equation 64).[229] These reactions occur with excellent stereoselectivity for the diene formation.

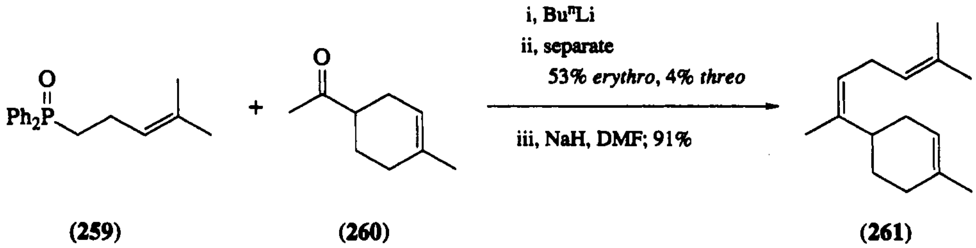
O
Ph2P
+
O
i, BunLi
ii, separate
53% erythro, 4% threo
iii, NaH, DMF; 91%

**(259)** + **(260)** → **(261)** (62)

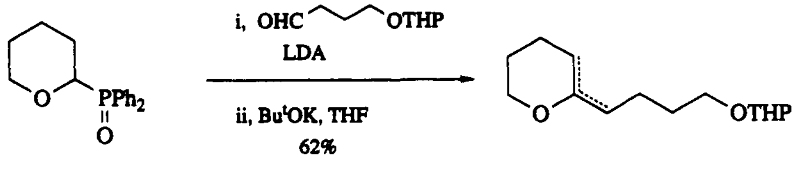
i, OHC OTHP
LDA
ii, Bu$^t$OK, THF
62%
PPh$_2$
O
OTHP

**(262)** **(263)**

(63)

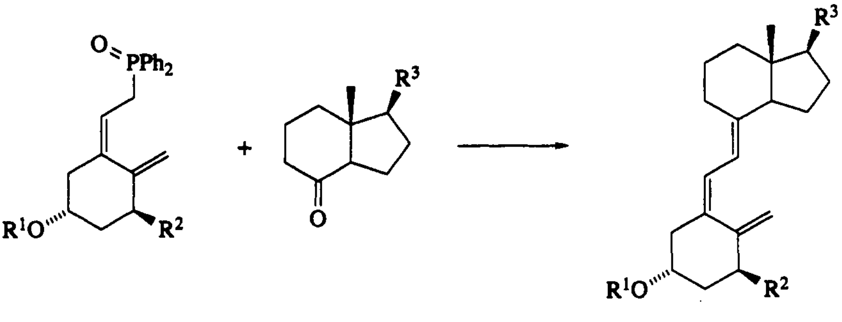
PPh$_2$
R$^1$O
R$^2$
R$^3$
O
R$^3$
R$^1$O
R$^2$

**(264)** **(265)** **(266)**

(64)

R$^1$ = CHMeOEt, R$^2$ = H, R$^3$ = C$_8$H$_{17}$; 60%

R$^1$ = SiMe$_2$Bu$^t$, R$^2$ = H, R$^3$ = 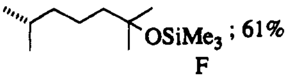 ; 61%

R$^1$ = SiMe$_2$Bu$^t$, R$^2$ = OSiMe$_2$Bu$^t$, R$^3$ = 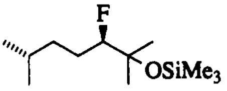 ;90%

### *3.1.9.4.6 Alternative approaches*

In analogy to the Peterson alkenation, the intermediate hydroxyphosphine oxides (**269**) can be prepared by addition to epoxide derivatives (**268**; Scheme 36).[230] Overall yields are high for this process, and this sequence can be applied to the synthesis of phosphonate intermediates as well. Warren has studied hydroxy-directed epoxidation.[230b] Provided the allylic phosphine oxide is trisubstituted, as is (**270**) in equation (65), these oxidations proceed with good selectivity. Ring opening can then be undertaken to generate the hydroxyphosphine oxide.

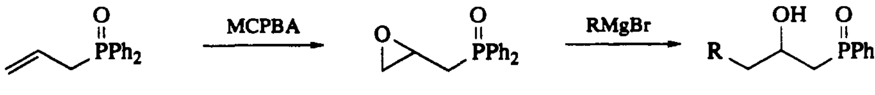
O
PPh$_2$
MCPBA
O
O
PPh$_2$
RMgBr
OH
O
R
PPh$_2$

**(267)** **(268)** **(269)**

Scheme 36

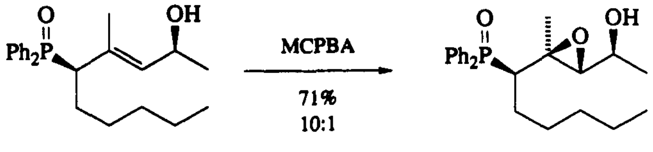
O
Ph$_2$P
OH
MCPBA
71%
10:1
O
Ph$_2$P
O
OH

**(270)** **(271)**

(65)

Acylated phosphine oxides have been used as intermediates to unsaturated acids such as (**276**; Scheme 37).[231] These compounds cannot be formed by the direct addition of an acid derivative of the phosphine oxide to a carbonyl (**273**). Instead, the ketophosphine oxide (**274**) is reduced and the lactones (**275**) are separated. The sequence is completed by treatment with KOH in aqueous THF followed by elimination in DMSO. The application of the Horner reaction to the synthesis of *homo*-allylic alcohols (**279**) was studied by Warren and coworkers.[232] These derivatives were formed by an intramolecular acyl transfer to the ketophosphine oxide (**278**; Scheme 38). The acyl group may be alkyl or aromatic and the reduction of the ketone, followed by elimination to the alkene, takes place under the standard protocol. This reaction was also applied to systems with chiral centers present in the phosphine oxide chain.[233] The intermediate phosphine oxide can also be converted to a hydroxy ketone and a cyclopropyl ketone by treatment with base. An alternative approach to *erythro*-phosphine oxides is to add the phosphine imide anion (**280**) in a selective manner to the aldehyde and hydrolyze to the hydroxyphosphine oxide (**282**; Scheme 39).[234] In comparing the imide to the phosphine oxide, the *erythro* selectivity of the phosphine imide addition was higher (98:2 *versus* 88:12 for the methyl- and phenyl-substituted alkene), and it remains to be demonstrated whether this alternative will prove to have practical applications in organic synthesis.

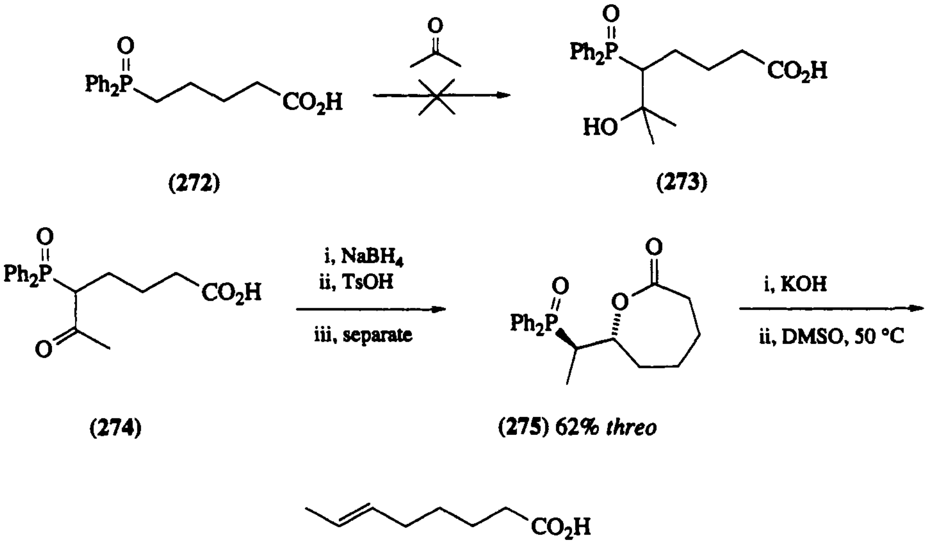

**(272)** **(273)**

**(274)** **(275)** 62% *threo*

**(276)** 93%

Scheme 37

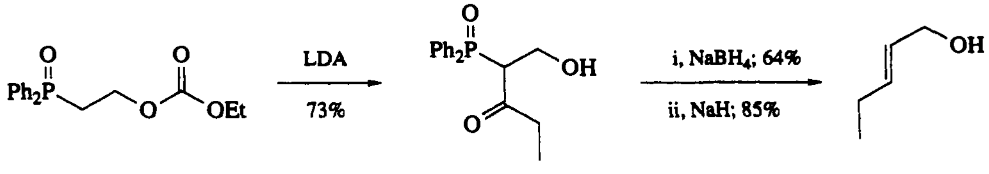

**(277)** **(278)** **(279)**

Scheme 38

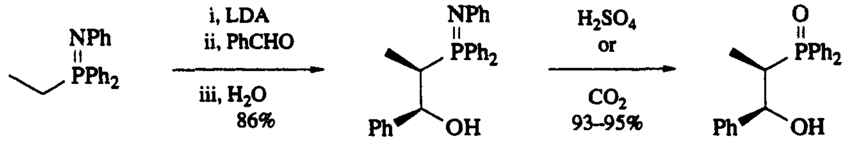

**(280)** **(281)** **(282)**

Scheme 39

### 3.1.10 SILICON-MEDIATED ALKENE FORMATION

In Section 3.1.3.1, the advantages of the Peterson alkenation in comparison to the Wittig reaction were detailed. The by-product (hexamethyldisiloxane) is volatile and is easier to remove than the phosphine oxides, and it is a more basic and more reactive anion. On the other hand, the anion can be more arduous to obtain than the Wittig anion for more complex applications, and the stereochemistry of the elimination is such that control of alkene isomers requires separation of the β-silylcarbinols.

### 3.1.10.1 Anion Formation

The α-silyl carbanions necessary to apply the Peterson reaction to higher substituted examples are limited by the ability to efficiently produce the anion. A clever example of an alternative to the Wittig reaction for ethylidene formation to give (**285**) with α-(trimethylsilyl)vinyllithium was utilized by Jung in the synthesis of coronafacic acid (Scheme 40).[235]

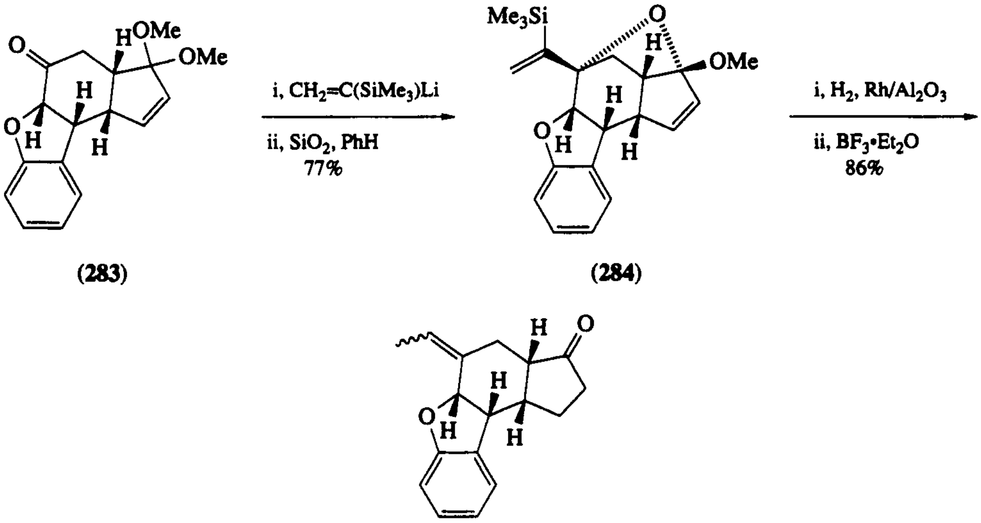

(**283**) (**284**)

(**285**)

**Scheme 40**

As a general rule, unless an anion-stabilizing group, such as phenyl, or a heteroatom such as sulfur is present, the alkylsilane is not readily deprotonated.[236] The α-halosilane can be deprotonated but, unlike the readily available chloromethyltrimethylsilane, there are few general methods to this approach. Alkyllithium reagents add to vinylsilanes (**286**) to produce the carbanion (**287**).[237] Silyl derivatives with heteroatoms, such as sulfur, selenium, silicon or tin, in the α-position (**288**) may be transmetallated (Scheme 41).[4d] Besides the difficulty in synthesizing the anion, alkene formation lacks specificity for simple di- and tri-alkyl-substituted alkenes. As a result, the Peterson reaction of an α-silyl carbanion with a carbonyl has found the greatest utility in the synthesis of methylene derivatives, (as discussed in Section 3.1.3), heterosubstituted alkenes and α,β-unsaturated esters, aldehydes and nitriles.

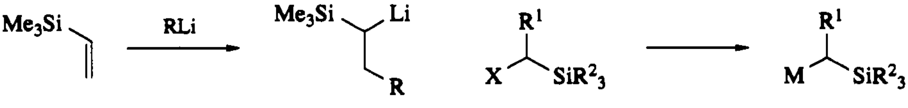

(**286**) (**287**) (**288**) (**289**)

$X = SR^3, SeR^3, SnR^3_3, SiR^2_3$

**Scheme 41**

### 3.1.10.2 Elimination

In a study by Hudrlik, the elimination was demonstrated to be stereospecific.[238] Diastereomeric β-hydroxysilanes were synthesized by the reduction of the corresponding ketones. In this way, each distinct diastereomer (**290**) and (**293**) was monitored in the elimination reaction. The elimination of the silane was stereospecific, with the acid-promoted eliminations being *anti* and the base-induced reaction following the *syn* pathway (Scheme 42).

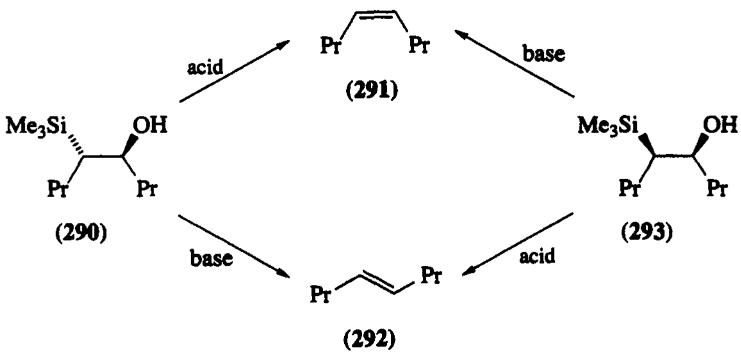

Scheme 42

The implication of this observation is that if one can form the silylcarbinol selectively, the ratios of *cis*- and *trans*-alkenes should be controllable and high. Unfortunately, the addition of the silyl anion to a carbonyl does not result in formation of a single carbinol. Unlike the Wittig reaction, the initial addition step is not reversible (the reaction is under kinetic control), therefore the inherent ratios in the addition step define the ratio of *cis*- to *trans*-alkenes produced.[239] The reaction is not influenced significantly by solvent, counterion effects, added salts or temperature. Because of these combined factors, the Peterson alkenation generally yields equal amounts of *cis*- and *trans*-alkenes.[240] To take advantage of the stereospecific elimination, either the substrate must be synthesized by an approach other than anion addition to the carbonyl, or the diasteromeric β-silylcarbinols must be separated.[241] Examples of successful formation of the stereodefined carbinol are the selective reduction of the α-silyl carbonyl (**294**; equation 66),[242] the addition of an alkyl anion to an α-silyl carbonyl (**296**; equation 67),[243] the addition of a silyl anion to an epoxide (**298**; equation 68)[4d] and the ring opening of a silyl epoxide (**300**; equation 69).[244]

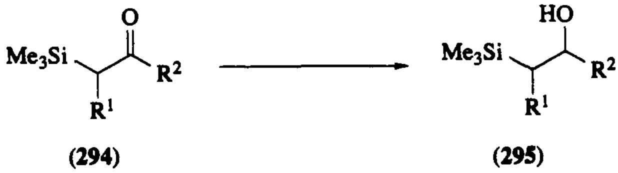

(66)

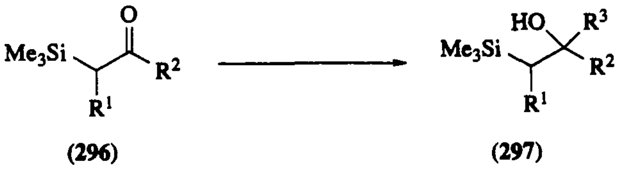

(67)

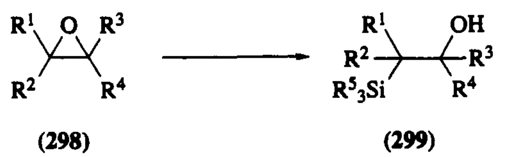

(68)

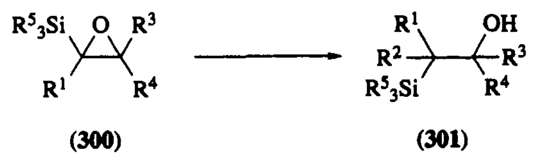

(69)

The term 'Peterson alkenation' has been used to describe the elimination of a functionalized organosilicon compound with alkene formation for substrates synthesized by these methods. In accordance with the mechanistic definition outlined in the introduction to this chapter, such topics are not considered in detail in this review.[245] For the purpose of this discussion, the Peterson alkenation will be considered as the addition of an anion derivative to a carbonyl compound, followed by elimination to the alkene.

### 3.1.10.3 Mechanism

As mentioned in the previous section, the Peterson reaction proceeds by an irreversible addition of the silyl-substituted carbanion to a carbonyl. It has generally been assumed that an intermediate β-oxidosilane is formed and then eliminated. In support of this mechanistic hypothesis, if an anion-stabilizing group is not present in the silyl anion, the β-hydroxysilanes can be isolated from the reaction, and elimination to the alkene carried out in a separate step. Recent studies by Hudrlik indicate that, in analogy to the Wittig reaction, an oxasiletane (**304**) may be formed directly by simultaneous C—C and Si—O bond formation (Scheme 43).[246] The β-hydroxysilanes were synthesized by addition to the silyl epoxide. When the base-induced elimination was carried out, dramatically different ratios of *cis*- to *trans*-alkenes were obtained than from the direct Peterson alkenation. While conclusions of the mechanism in general await further study, the Peterson alkenation may prove to be more closely allied with the Wittig reaction than with β-elimination reactions.

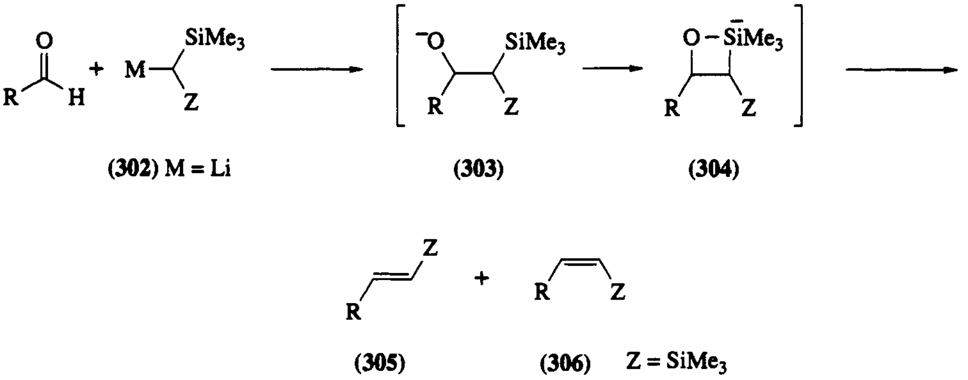

Scheme 43

The stereochemistry of the elimination of the β-hydroxysilane at silicon has been investigated.[247] In studies by Larson and coworkers, the β-hydroxyalkyl(1-naphthyl)phenylmethylsilanes (**307**) and (**309**) were isolated and subjected to elimination conditions to ascertain the stereochemistry of the elimination on the silyl group (Scheme 44). The acid-catalyzed eliminations proceed with inversion of stereochemistry at silicon, while the base-catalyzed elimination occurred with retention. These results are in agreement with the mechanism proposed of *anti* elimination under acidic conditions and *syn* elimination under basic. While the optically pure silicon was useful for determining the course of the elimination, it could not be utilized in asymmetric synthesis. Addition of the anion to various carbonyls afforded virtually no diastereoselectivity, and it was not possible to separate the diastereomers formed either by crystallization or by chromatography.

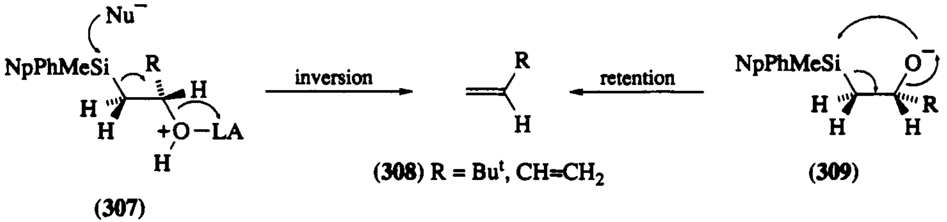

Scheme 44

### 3.1.10.4 Alkene Formation

The Peterson reaction, as shown in equation (70), has been applied to the synthesis of alkenes that are hindered and difficult to form by the Wittig reaction. In the case of trisubstituted alkenes (**311**) in which $R^1$ and $R^2$ are components of a ring or are identical, the reaction may prove to be the method of choice.

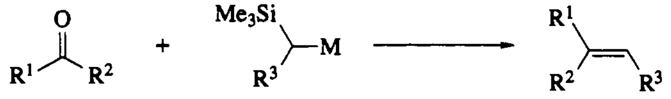

(70)

**(310)** **(311)**

An example is the preparation of allylidenecyclopropanes (Scheme 45).[248] The 1-(trimethylsilyl)cyclopropane (**312**) is reductively lithiated with lithium 1-(dimethylamino)naphthalenide (LDMAN) followed by addition of an aldehyde to form the β-silylcarbinol (**314**).[249] This method of anion formation is general[17a] but has seen greatest application in the synthesis of cyclopropyl compounds. The intermediate can be eliminated *in situ* with KOBu$^t$ to form the alkene (**315**). Yields are good but, as discussed in the mechanistic section, in unsymmetrical cases a mixture of products results. This reaction has been extended by Halton and Stang to the synthesis of cycloproparenes.[250]

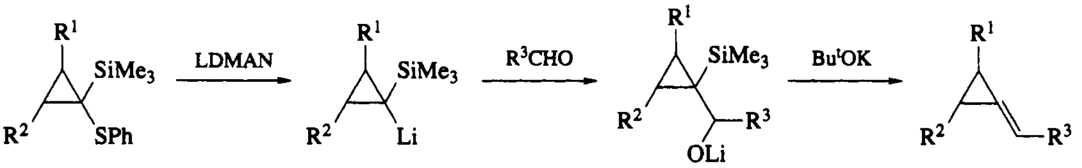

**(312)** **(313)** **(314)** **(315)**

**Scheme 45**

### 3.1.10.5 Heteroatom Substitution

#### *3.1.10.5.1 Silicon*

The Peterson reaction can be used to synthesize a number of heterosubstituted alkenes. Methoxydimethylsilyl(trimethylsilyl)methyllithium (**316**) can be added to aldehydes and ketones, including enolizable substrates, to form the vinylsilane (**317**; equation 71). Modest (*E*):(*Z*)-selectivity was observed in unsymmetrical cases. This reagent may represent an improvement over the bis(trimethylsilyl)methyl anion, which is ineffective for enolizable substrates.

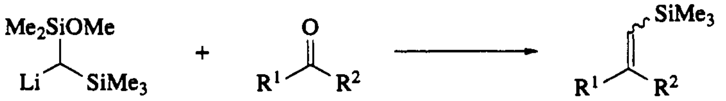

(71)

**(316)** **(317)**

#### *3.1.10.5.2 Sulfur*

In the original study by Peterson, the alkenation procedure was found to be compatible with sulfur and phosphorus substitution.[251] The alkenation reaction has been applied successfully to a variety of substituted alkenes.[252] Because of the anion-stabilizing nature of the thiophenyl, the β-hydroxysilane is not isolated and the elimination to the alkene takes place directly to form a 1:1 mixture of (*E*)- and (*Z*)-isomers. Ager studied the reaction of the lithio anions of phenyl (trimethylsilyl)methyl sulfides (**318**) with a variety of carbonyl compounds (equation 72).[14] Yields of this process were good, and addition occurred even with enolizable substrates. This reaction was extended to vinyl sulfones. In contrast to the sulfide case, the substituted sulfone silyl anion behaves as a base, leading to undesired enolization. The best yields were observed for the case where $R^1$ is a hydrogen or phenyl.

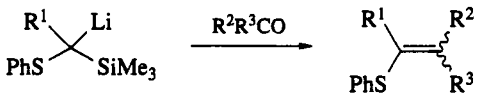
R¹
Li
PhS
SiMe₃
R²R³CO
R¹
R²
PhS
R³

**(318)** **(319)**

$R^1, R^2, R^3$ = H, Me, Et, Bu, $C_5H_{11}$, Ph, *etc.*

(72)

Ley and coworkers have done studies with phenyl (trimethylsilyl)methyl sulfones (**320**; equation 73).[253] The lithio anion was generated with $Bu^nLi$ in DME to form vinyl sulfones (**321**) in good to excellent yields as isomeric mixtures. There is some indication that the reaction should best be carried out in DME at –78 °C, rather than in THF as in the initial Ager work.[16] Trapping the intermediate alkoxide as the acetate, followed by attempts at stereospecific elimination did not prove to be successful in forming a single alkene isomer.

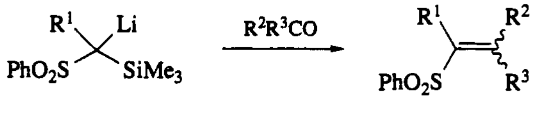
R¹
Li
PhO₂S
SiMe₃
R²R³CO
R¹
R²
PhO₂S
R³

**(320)** **(321)**

$R^1, R^2, R^3$ = H, Me, $C_5H_{11}$, Ph, *etc.*

(73)

Addition of sulfides and sulfones to acid derivatives has been investigated by Agawa.[254] Phenyl and methyl (trimethylsilyl)methyl sulfides and sulfones added to amides (**323**) to produce the aminovinyl sulfides (**324**; equation 74) and sulfone (**326**; equation 75). The reactions proceeded in good yield with some examples of stereocontrolled synthesis of the (*E*)-isomer. Other acid derivatives such as esters, carbonates and ureas were investigated, but gave inconsistent results.

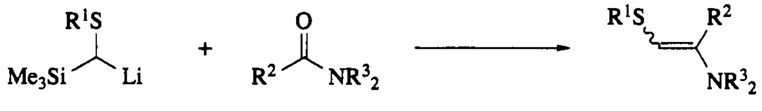
R¹S
Me₃Si
Li
+
O
R²
NR³₂
R¹S
R²
NR³₂

**(322)** **(323)** **(324)**

(74)

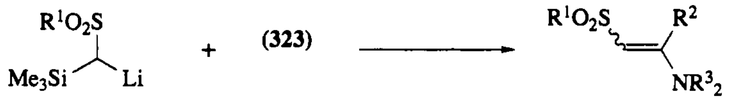
R¹O₂S
Me₃Si
Li
+
(323)
R¹O₂S
R²
NR³₂

**(325)** **(326)**

(75)

In studies directed toward intermediates for the synthesis of quadrone, Livinghouse demonstrated the utility of lithiated methoxy(phenylthio)(trimethylsilyl)methane (**327**) for the conversion of aldehydes and ketones to ketene *O*,*S*-acetals (**328**) in good to excellent yields (Scheme 46).[255] These Peterson alkenations gave predominantly the (*E*)-double bond isomer. As the example depicted in the scheme demonstrates, this procedure may be used to homologate a carbonyl to the phenyl thioester (**329**) in excellent yields.

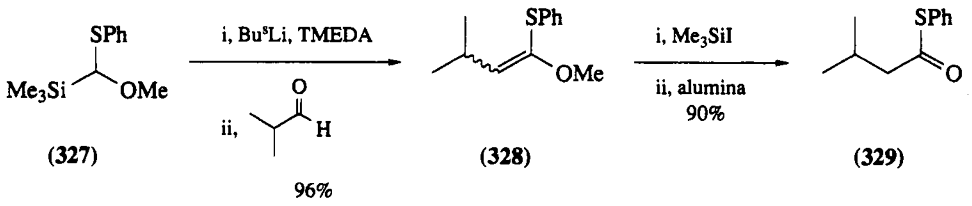
SPh
Me₃Si
OMe
i, BuˢLi, TMEDA
ii,
O
H
96%
SPh
OMe
i, Me₃SiI
ii, alumina
90%
SPh
O

**(327)** **(328)** **(329)**

**Scheme 46**

The use of sulfur in the Peterson reaction can be extended to the optically pure lithio anion of *S*-phenyl-*S*-(trimethylsilyl)methyl-*N*-tosylsulfoximine (**330**; equation 76).[256] Unlike most Peterson alkenations this reaction is selective for the formation of the (*E*)-alkene isomer (**331**) with aldehydes. In addition, the stereochemistry of the sulfoximine is maintained.

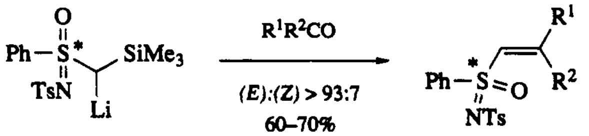

(76)

(**330**) $R^1, R^2$ = H, Me, Ph, $\mathrm{Pr^i}$, $\mathrm{Bu^t}$, *etc.* (**331**)

### *3.1.10.5.3 Phosphorus*

As in the case of sulfur-substituted analogs to the Peterson alkenation, the compatibility of the reaction with a phosphorus substituent was demonstrated in the original work of Peterson. An *in situ* procedure for the preparation and reaction of the lithio anion of (trimethylsilyl)alkylphosphonates has been developed (**333**; Scheme 47).[257] The phosphonate (**332**) was treated with 2 equiv. of LDA followed by TMS-Cl and after warming to −20 °C, the aldehyde. The overall yields were good, but (*E*):(*Z*) selectivities for this reaction were low. Zbiral and coworkers developed a method for the homologation of a carbonyl compound to an α-hydroxy ester with a silylphosphonate derivative (**335**; Scheme 48).[258] The reactions produced a 1:1 mixture of alkene isomers (**336**). The intermediate vinylphosphonate was oxidized with $OsO_4$ to form the α-hydroxy ester (**337**). Recently, both sulfur and phosphorus functionalities were combined in a Peterson reagent.[259] The lithium anion of the (methylthio)phosphonate (**338**) reacted with high (*E*)-selectivity with aldehydes (equation 77). The reaction was ineffective with ketones.

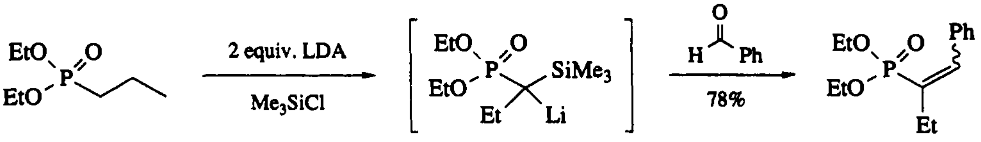

(**332**) (**333**) (**334**)

Scheme 47

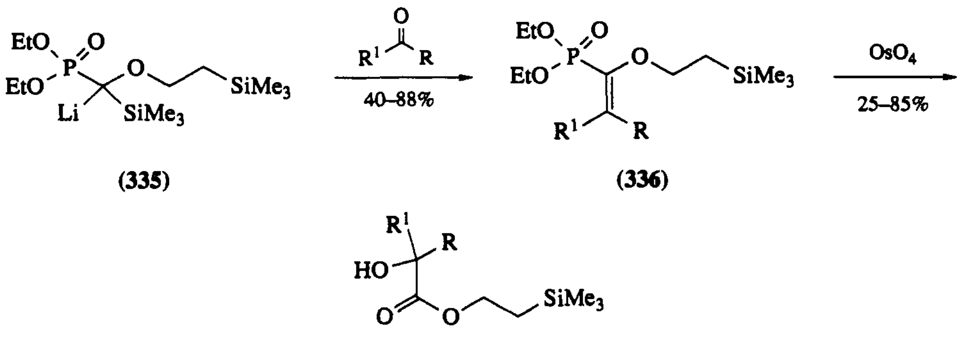

(**335**) (**336**)

(**337**)

Scheme 48

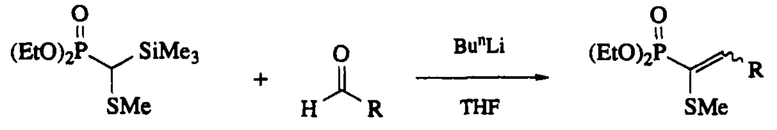

(77)

(**338**) (**339**) R = H, Me, Ph

### 3.1.10.6 Synthesis of Conjugated Alkenes

In the application of the Peterson alkenation to the synthesis of α,β-unsaturated esters, the full advantage of the greater reactivity of the silyl-stabilized anion as well as the ease of by-product removal can be realized. In addition, the Peterson reagent can be directly formed by deprotonation if an activating group, in these cases a carbonyl or similar conjugating functionality, is present, making the anion readily accessible. Selectivity for (*E*)- and (*Z*)-alkene isomers is highly substrate specific and no general predictive rule can be stated, but selectivity is enhanced by increasing the steric bulk of the silyl substituent, and in some instances by altering the counterion, as the following examples illustrate.

The reaction of a silylacetate derivative with an aldehyde or ketone was initially studied by Rathke and Yamamoto.[260] Rathke and coworkers studied the addition of the lithium anion of *t*-butyl (trimethylsilyl)acetate (**340**) with a variety of aldehydes and ketones (equation 78). The anion can be formed directly from the silyl compound on treatment with LDA. The reaction proceeded to give the conjugated alkenes in excellent yields. Unsaturated compounds reacted *via* 1,2-addition. No discussion of alkene geometry was presented. In the Yamamoto work, the ethyl (trimethylsilyl)acetate derivative (**342**) was used in a variety of reactions with aldehydes and ketones (equation 79). The anion was formed with dicyclohexylamide in THF. It was stated in the experimental section that the (*E*):(*Z*) ratios of alkenes were dependent on the reaction conditions. In all the examples presented in this work, the (*E*)-isomer was predominantly formed.

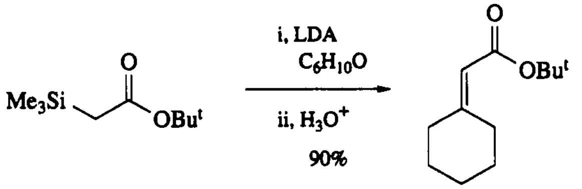

**(340)** **(341)** (78)

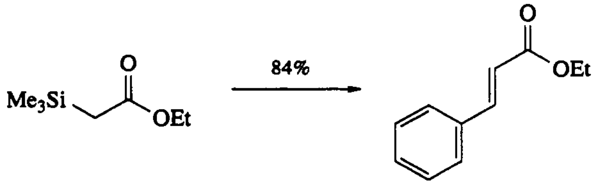

**(342)** **(343)** (*E*):(*Z*) = 3:1 to 9:1 (79)

The ability to define the alkene geometry by modification of the anion was investigated by Debal.[261] In this work, the intermediate β-hydroxysilanes were either isolated and the elimination carried out with $BF_3{\cdot}Et_2O$ to synthesize the (*E*)-isomers (**347**), or the addition adduct (formed in the presence of $MgBr_2$) was treated with HMPT and eliminated *in situ* to give predominantly the (*Z*)-isomer (**346**), as shown in Scheme 49.[262b]

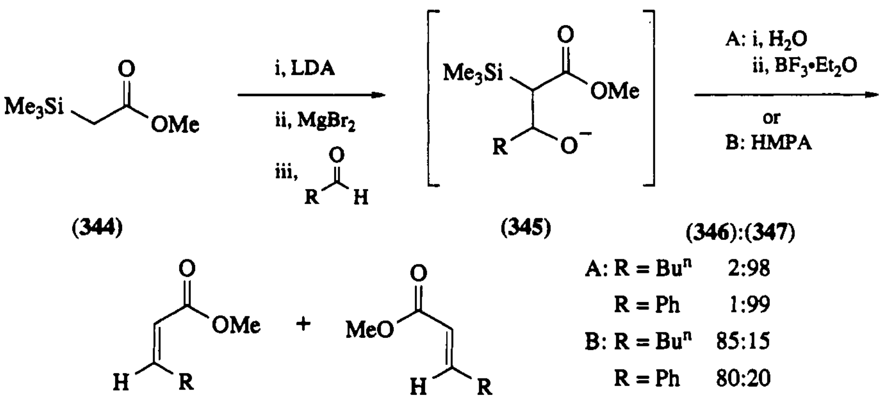

**(344)** **(345)** **(346)** **(347)**

| | | (346):(347) |
|---|---|---|
| A: | R = Bu$^n$ | 2:98 |
| | R = Ph | 1:99 |
| B: | R = Bu$^n$ | 85:15 |
| | R = Ph | 80:20 |

**Scheme 49**

Comparative examples of the Wittig reaction and the Peterson alkenation with ketones (**353**; equation 82) and (**355**; equation 83), epoxy ketones (**351**; equation 81), or protected α-hydroxy ketones (**348**; equation 80) have appeared.[262] The reactions can proceed with high kinetic control for the (*Z*)-isomer and, as a result, the Peterson technology may form complementary isomers to the Wittig reaction.[114]

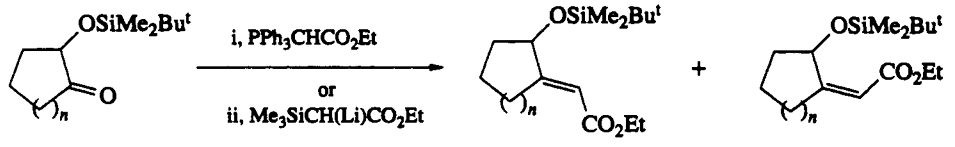
OSiMe$_2$Bu$^t$
O
n
i, PPh$_3$CHCO$_2$Et
or
ii, Me$_3$SiCH(Li)CO$_2$Et
OSiMe$_2$Bu$^t$
CO$_2$Et
+
OSiMe$_2$Bu$^t$
CO$_2$Et

(80)

**(348)** **(349)** **(350)**

| | | |
|---|---|---|
| i, | $n = 1$, 52% | 97:3 |
| | $n = 2$, 80% | 96:4 |
| | $n = 3$, 27% | 94:6 |
| ii, | $n = 1$, 64% | 33:67 |
| | $n = 2$, 68% | 14:86 |
| | $n = 3$, 50% | 8:92 |

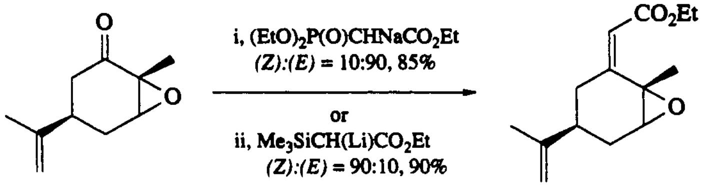
O
O
i, (EtO)$_2$P(O)CHNaCO$_2$Et
(*Z*):(*E*) = 10:90, 85%
or
ii, Me$_3$SiCH(Li)CO$_2$Et
(*Z*):(*E*) = 90:10, 90%
CO$_2$Et
O

(81)

**(351)** **(352)**

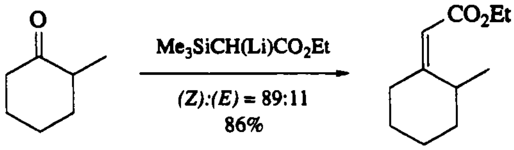
O
Me$_3$SiCH(Li)CO$_2$Et
(*Z*):(*E*) = 89:11
86%
CO$_2$Et

(82)

**(353)** **(354)**

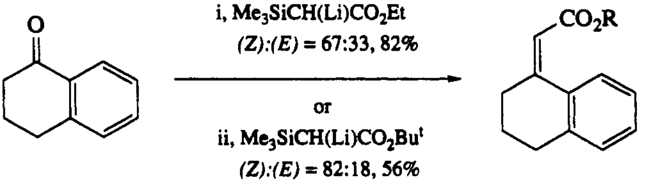
O
i, Me$_3$SiCH(Li)CO$_2$Et
(*Z*):(*E*) = 67:33, 82%
or
ii, Me$_3$SiCH(Li)CO$_2$Bu$^t$
(*Z*):(*E*) = 82:18, 56%
CO$_2$R

(83)

**(355)** **(356)**

The reaction has been extended to α-silyl lactones and lactams.[263] Other stabilizing groups have been demonstrated to be effective. For example, the Peterson reagent formed from bis(trimethylsilyl)propyne (**357**) and that formed from α-silyl acetonitrile derivatives (**358**) both give the (*Z*)-alkene as the predominant product (equation 84).[264]

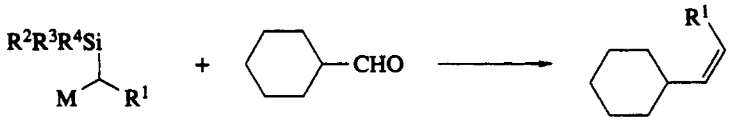
R$^2$R$^3$R$^4$Si
M
R$^1$
+
CHO
R$^1$

(84)

(**357**) $R^1 = C{\equiv}CSiMe_3$, $R^2 = Bu^t$, $R^3 = R^4 = Me$, $M = MgBr$; (*Z*):(*E*) = 30:1, 75%
(**358**) $R^1 = CN$, $R^2 = R^3 = R^4 = Ph$, $M = MgI$; (*Z*):(*E*) = 9:1, 80%

Increasing the steric bulk of the silyl group enhances the ratios of (Z)- to (E)-alkene isomers. The size of the ester group can also affect the (*E*):(*Z*) ratios of alkenes.[265] An example is the synthesis of butenolides (**360**) by Peterson alkylation of α-keto acetals (**359**; equation 85). Increasing the ester from methyl to isopropyl and *t*-butyl resulted in a corresponding increase in (*Z*)-alkene formation.

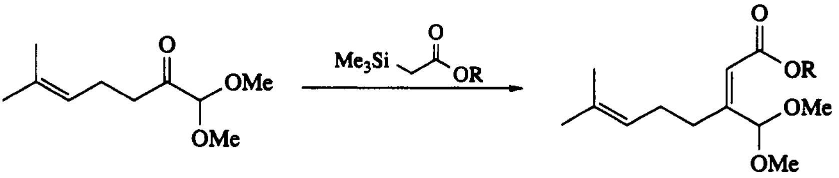

(85)

**(359)** **(360)**

R = Me; *(Z)*:*(E)* = 43:57, 70%
R = Pr$^i$; *(Z)*:*(E)* = 80:20, 73%
R = Bu$^t$; *(Z)*:*(E)* = 88:12, 77%

Boeckman and coworkers studied the reaction of bis(trimethylsilyl) ester (**361**) with aldehydes to form the silyl-substituted unsaturated ester (**362**; equation 86).[266] The anion was formed with potassium or lithium diisopropylamide. Other metals, such as magnesium or aluminum, were introduced by treating the lithium anion with Lewis acids. The addition step produced a single diastereomer, enabling the effects of counterion and steric bulk on the elimination to be ascertained. Excellent selectivity for the (*E*)-isomer (**362**) may be obtained by using K or Li cations and a sterically hindered aldehyde. In studies directed toward the synthesis of substituted pseudomonic acid esters, the Peterson alkenation was utilized to form a mixture of (*Z*)- and (*E*)-alkene isomers, one example of which (**365**) is depicted in equation (87).[267] In this example the conditions were optimized to form the highest degree of selectivity for the (*Z*)-alkene.

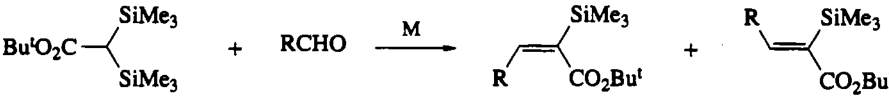

(86)

**(361)** R = Pr$^i$, Bu$^t$; M = K, Li **(362)** >100:1 **(363)**

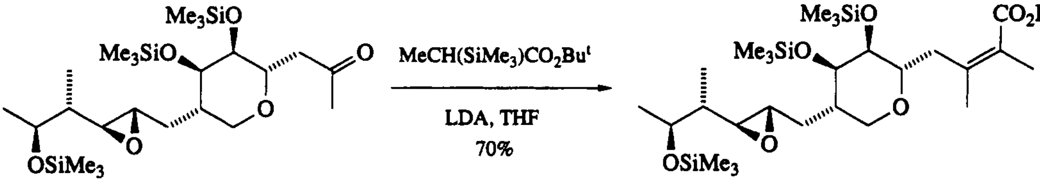

(87)

**(364)** **(365)** *(Z)*:*(E)* = 7.2:1

A comparison of the Wittig and Peterson alkenation procedures for the conversion of an aldehyde to its α,β-unsaturated vinylog was carried out by Schlessinger (Scheme 50).[268] The Wittig methodology was more effective for the base-sensitive lactone substrate (**366**), while the Peterson reaction was the preferred method for the hindered aldehyde (**368**). An additional comparative example of the Peterson and Wittig methods to synthesize an unsaturated aldehyde is found in studies on the streptogramin antibiotics by Meyers (Scheme 51).[269] Higher yields and (*E*)-alkene isomer selectivity (**371**) were obtained with the Wittig reagent. The Schlessinger method was recently used in the synthesis of FK-506 by Mills and coworkers (equation 88).[296a] Addition to the hindered aldehyde (**372**) produced the α,β-unsaturated aldehyde (**373**) in 78% yield and an (*E*):(*Z*) ratio of >100:1.

While these examples point to the possible use of the Wittig and the Peterson reactions as complementary methods for (*Z*)- and (*E*)-alkene formation in cases with conjugating functionality, it must be emphasized that no systematic predictive rule can be applied to the possible selectivity, and this area remains one of active research.

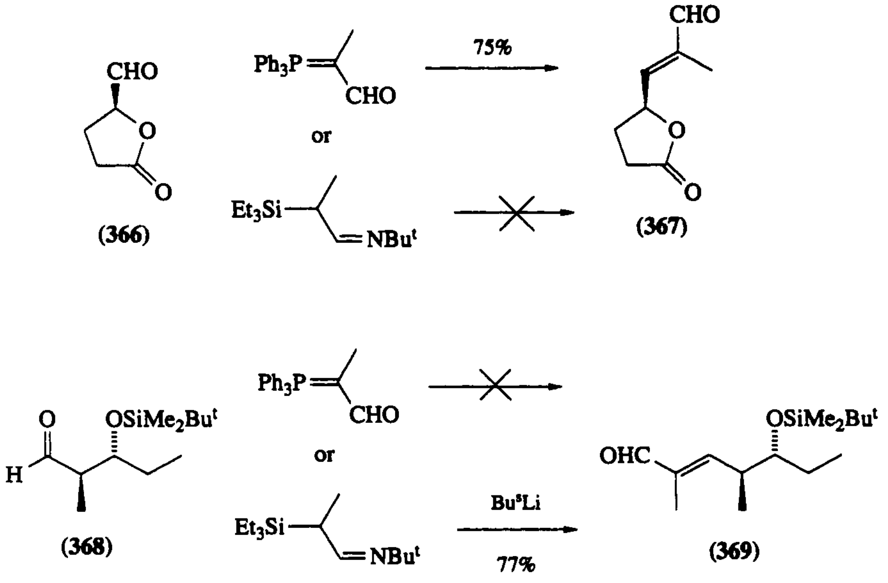
CHO
(366)
$Ph_3P$
CHO
or
$Et_3Si$
NBu$^t$
75%
CHO
(367)
O
OSiMe$_2$Bu$^t$
H
(368)
$Ph_3P$
CHO
or
$Et_3Si$
NBu$^t$
Bu$^s$Li
77%
OHC
OSiMe$_2$Bu$^t$
(369)

**Scheme 50**

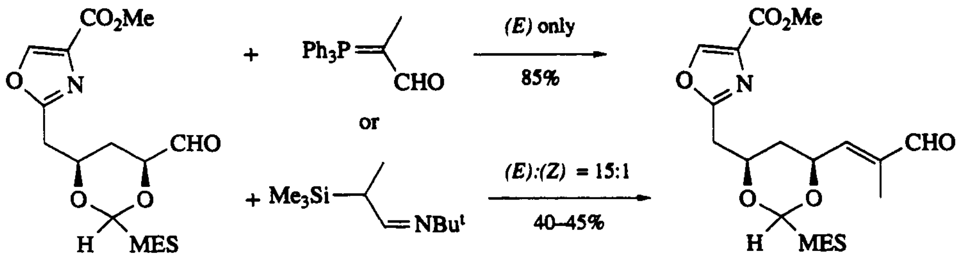
CO$_2$Me
O
N
CHO
O
O
H
MES
(370)
+ $Ph_3P$
CHO
or
+ $Me_3Si$
NBu$^t$
(E) only
85%
(E):(Z) = 15:1
40–45%
CO$_2$Me
CHO
H
MES
(371)

MES = mesityl

**Scheme 51**

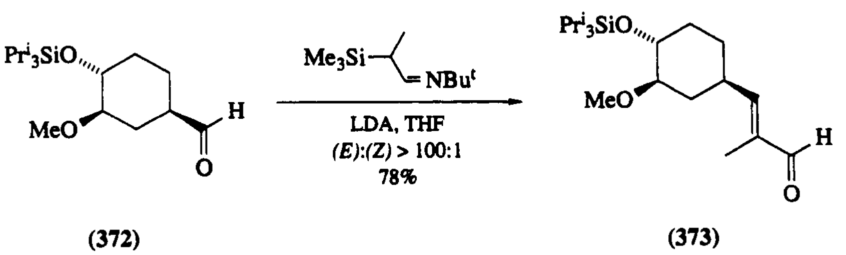
Pr$^i_3$SiO
MeO
H
O
(372)
$Me_3Si$
NBu$^t$
LDA, THF
(E):(Z) > 100:1
78%
Pr$^i_3$SiO
MeO
H
O
(373)

(88)

### 3.1.10.7 Lewis Acid Catalysis

The use of cerium trichloride for the Peterson alkenation has been applied by Ueda and coworkers for nucleoside synthesis (Scheme 52).[270] The anion was generated with LDA/cerium trichloride and condensed with the aldehyde (**375**). The product was treated with KH in THF and the pyrimidopyridine (**377**) isolated in 50% yield.

## 3.1.11 SULFUR-STABILIZED ALKENATIONS: THE JULIA COUPLING

In 1973, Julia introduced the reaction depicted in Scheme 53, that bears his name.[271] The sulfone derivative is metallated (**378**) and added to the carbonyl, followed by functionalization (**380**), and reductive elimination, to produce the alkene (**381**). The yield for the transformation from carbonyl to alkene is ex-

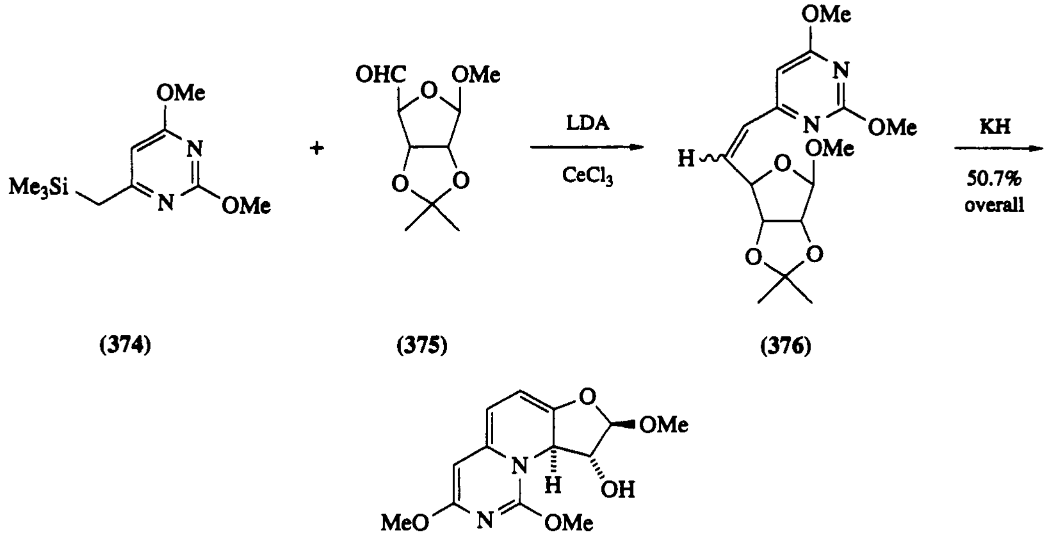

(374) (375) (376)

(377)

Scheme 52

tremely high; usually greater than 80% overall. In the original communication, the Julia coupling was applied to the synthesis of mono-, di- and tetra-substituted alkenes, and since then has been employed to solve many challenging synthetic problems.[272] The selectivity can be extremely high for the production of disubstituted (*E*)-alkenes and it is this particular aspect of the Julia coupling in the synthesis of complex molecules that will be considered below.

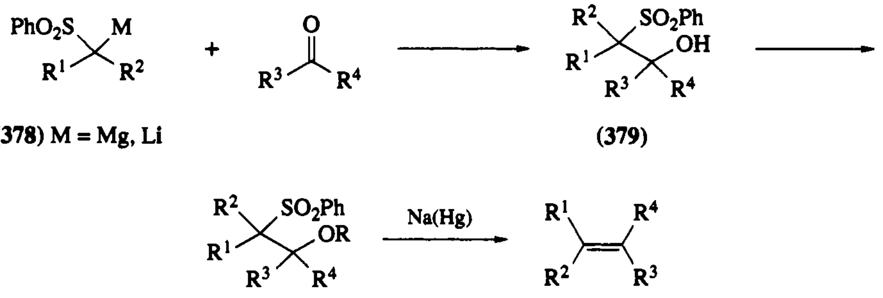

(378) M = Mg, Li (379)

(380) R = Ms, Ac, Ts, COPh (381) overall yield >80%

Scheme 53

### 3.1.11.1 (*E*)-/(*Z*)-Selectivity

A study carried out by Kocienski and Lythgoe first demonstrated the *trans* selectivity of the Julia coupling process.[273] The authors found the reductive elimination could best be carried out with the acetoxy or benzoyloxy sulfones. If the lithio sulfone derivative is used for addition to the carbonyl, the reaction can be worked up with acetic anhydride or benzoyl chloride to obtain the alkene precursor. In cases where enolization of the carbonyl is a complication, the magnesium derivative can frequently be used successfully.[274] A modification of the reductive elimination was found to be most effective. Methanol, ethyl acetate/methanol or THF/methanol were the solvents of choice and a temperature of –20 °C was effective at suppressing the undesired elimination of the acetoxy group to produce the vinyl sulfone. With these modifications of the original procedure, the ability of the reaction to produce dienes as well as *trans*-disubstituted alkenes was demonstrated. The diastereoisomeric *erythro*- and *threo*-acetoxy sulfones could be separated and it was demonstrated that both isomers were converted to the *trans*-alkene. It was hypothesized that the (*E*)-selectivity is derived from the reductive removal of the phenylsulfonyl group, generating an anion (**383**) that assumes the low energy *trans* configuration before loss of the acylate anion (Scheme 54). As demonstrated by numerous examples, the mechanism for reductive elimination is consistent with the finding that the alkenes obtained are the thermodynamic mixture and that increased branching at the site of elimination should, for steric reasons, increase the *trans* selectivity.[273c,d]

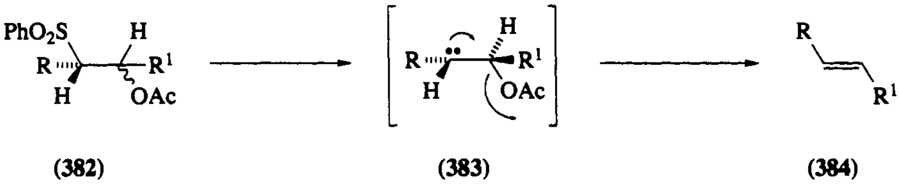

**Scheme 54**

### 3.1.11.2 Reductive Cleavage

The reduction of the β-acyloxy sulfone is most often carried out with sodium amalgam, as the examples below indicate. The reductive elimination can be buffered with disodium hydrogenphosphate for sensitive substrates.[275] In certain applications it has proven advantageous to utilize lithium or sodium in ammonia. For example, Keck's synthesis of pseudomonic acid C made use of the lithium/ammonia reductive elimination to simultaneously form an alkene and deprotect a benzyl ether.[281] In studies directed toward the same target, Williams made use of a reductive elimination procedure developed by Lythgoe, involving the formation of the xanthate ester followed by reduction with tri-*n*-butyltin hydride.[276]

### 3.1.11.3 The Synthesis of (*E*)-Disubstituted Alkenes: Comparison with the Wittig Reaction

#### *3.1.11.3.1 The synthesis of pseudomonic acid C*

The Julia coupling can be utilized as an alternative to the Schlosser–Wittig reaction to form (*E*)-alkenes.[277] Several reported syntheses of pseudomonic acid C (**385**) have provided interesting clues as to variability of applications of the Julia coupling in the context of natural product synthesis.

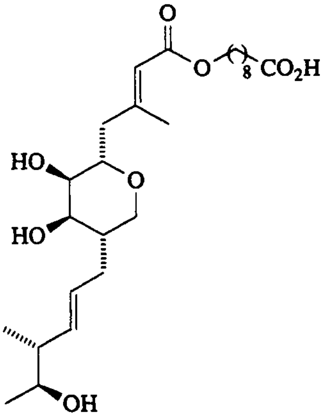

**(385)**

The (*E*)-disubstituted alkene has been extensively studied with several applications of the Julia coupling attempted.[278] The first synthesis of the natural product was accomplished by Kozikowski.[279] In this approach, the aldehyde (**386**) was reacted with 2 equiv. of the Wittig reagent (**387**) to produce (**388**), with an (*E*):(*Z*) ratio of 60:40 (equation 89; no yield given). This first synthesis establishes the baseline selectivity achievable with the Wittig reaction and is useful for subsequent comparison to the Julia coupling. Further studies by Kozikowski on methyl deoxypseudomonate B utilized the Julia coupling to form a similar alkene (equation 90).[280] The aldehyde (**389**) was coupled with the anion of the sulfone (**390**) and the hydroxyl group isolated as the benzoate. The alkene (**391**) was produced by treatment with Na(Hg) to give the desired (*E*)-alkene (no yield specified).

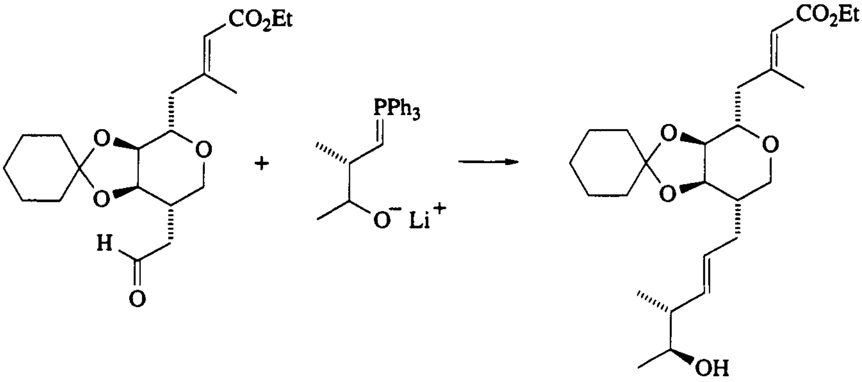

(89)

**(386)** **(387)** **(388)** *(E):(Z)* = 60:30

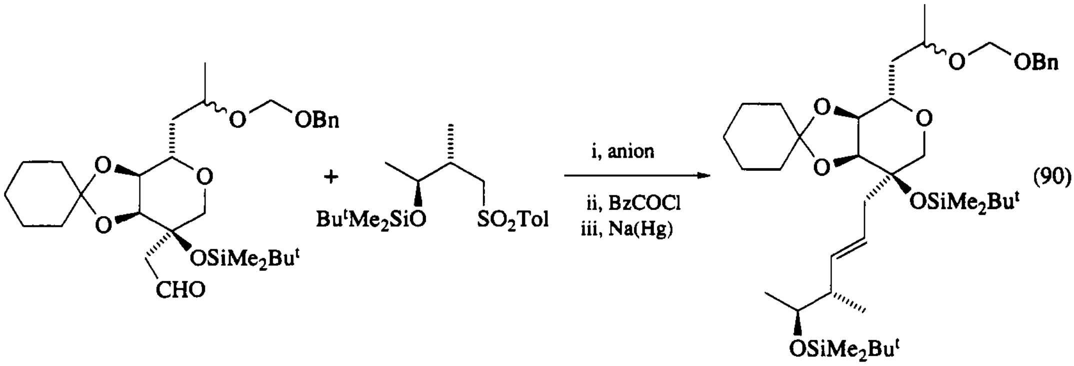

(90)

**(389)** **(390)** **(391)**

Keck attempted to apply the Julia coupling to the synthesis of pseudomonic acid C.[281] Despite the success of the sulfone (**393**) in reactions with simple aldehydes, only modest yields of the desired coupling were observed. This problem was solved by reversing the aldehyde (**395**) and sulfone components (**394**), as shown in Scheme 55. The anion was formed with LDA in THF and condensed with the aldehyde. The β-hydroxysulfone was converted to the mesylate, and the reduction and simultaneous deprotection of the benzylglycoside was carried out with lithium and ammonia to produce the (*E*)-alkene (**396**), in 37% overall yield with excellent selectivity.

Williams carried out a Julia coupling similar to the Keck example. With the removal of the acetal functionality, the coupling step of the Julia reaction was efficient, but the usual reductive elimination procedure failed.[282] As an alternative to the acetylation and reductive elimination procedure, the β-sulfonyl xanthate was formed by quenching the addition reaction with carbon disulfide and methyl iodide. Reductive elimination was then carried out with tri-*n*-butyltin hydride to yield the desired (*E*)-alkene (**399**) in an 85:15 ratio with the (*Z*)-alkene in 83% overall yield (equation 91).

Finally, White has utilized a substrate (**400**) with which the Wittig reagent (**401**) gave a 37% yield of a 57:43 mixture of (*E*)- and (*Z*)-isomers (Scheme 56). Using the preparation of the sulfone (**393**) developed by Keck, White formed the anion with *n*-butyllithium in THF and condensed it with the aldehyde (**400**). The β-hydroxy sulfone was acetylated and reduced with sodium amalgam to produce a 17:3 ratio of (*E*)- to (*Z*)-alkenes (**402**) in 62% overall yield.

These four examples of the successful application of the Julia coupling in natural product synthesis indicate the sensitivity of various substrates to the anionic conditions. The solutions, interchanging the aldehyde and sulfone portions, modification of the substrate or altering the reductive elimination conditions, are all techniques that can enable the successful use of the Julia coupling for (*E*)-alkene synthesis.

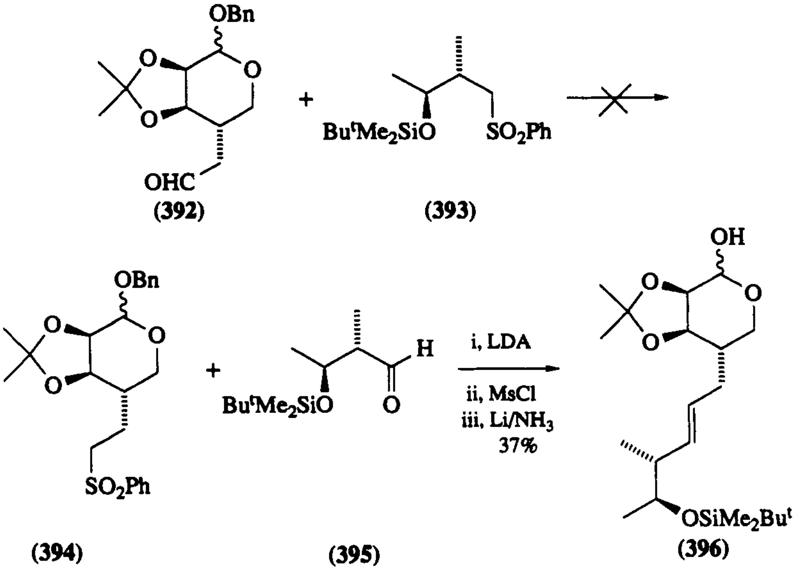
OBn
OHC
BuᵗMe₂SiO
SO₂Ph
OBn
SO₂Ph
BuᵗMe₂SiO
H
O
i, LDA
ii, MsCl
iii, Li/NH₃
37%
OH
OSiMe₂Buᵗ

(392) (393) (394) (395) (396)

Scheme 55

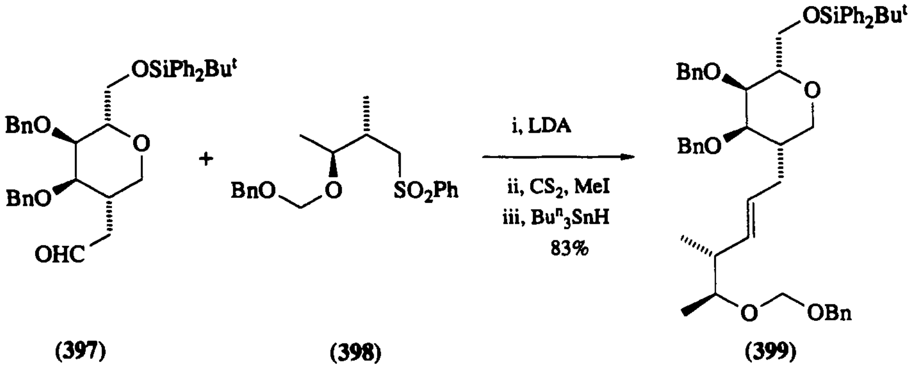
OSiPh₂Buᵗ
BnO
BnO
OHC
BnO
SO₂Ph
i, LDA
ii, CS₂, MeI
iii, Buⁿ₃SnH
83%
OSiPh₂Buᵗ
BnO
BnO
OBn

(397) (398) (399)

(91)

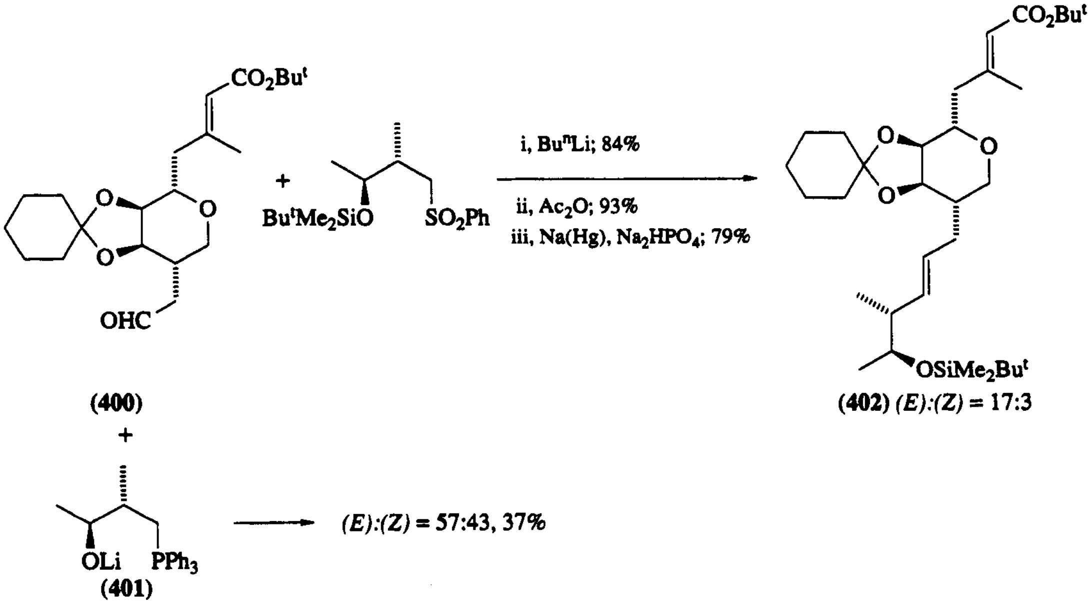
CO₂Buᵗ
OHC
BuᵗMe₂SiO
SO₂Ph
i, BuⁿLi; 84%
ii, Ac₂O; 93%
iii, Na(Hg), Na₂HPO₄; 79%
CO₂Buᵗ
OSiMe₂Buᵗ
OLi
PPh₃
(E):(Z) = 57:43, 37%

(400) (401) (402) (E):(Z) = 17:3

Scheme 56

### *3.1.11.3.2 Other examples*

An interesting comparative example of the unstabilized Wittig reaction and the Julia coupling is found in the synthesis of the capsaicinoids by Gannett.[283] A selective route to both the (*E*)- and (*Z*)-isomers (**405**) and (**406**), respectively, is depicted in equation (92). The Wittig was carried out with potassium *t*-butoxide in DMF as the base, to form the (*Z*)-alkene (**406**) as the major product in a 91:9 ratio to the (*E*)-isomer. The Julia coupling and subsequent elimination produced the isomer (**405**) as a 9:1 mixture with the (*Z*)-isomer in 70–80% yields. Other examples of the Julia coupling for the synthesis of (*E*)-disubstituted alkenes are outlined in Table 18. From the examples cited, is apparent that the sulfone anion adds chemoselectively to aldehydes in the presence of esters and amides. The reagent is also compatible with a wide range of protecting groups, including ethers, acetals and amines.

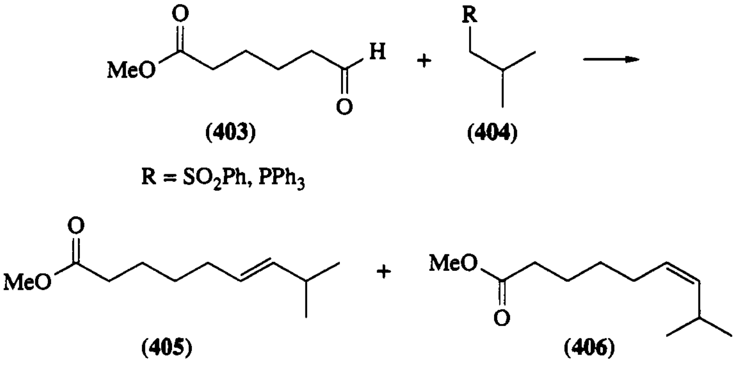

(**403**) (**404**)

R = $SO_2Ph$, $PPh_3$

(**405**) (**406**)

(92)

## 3.1.11.4 (*E*)-Trisubstituted Alkene Synthesis

The Julia coupling has also been successfully utilized for the synthesis of more complex alkenes.[277] There are limitations to the application of the method to tri- and tetra-substituted alkenes, since the addition of the sulfone anion to a highly substituted ketone forms a β-alkoxy sulfone that is difficult to trap and isolate.[273d] There is a tendency for highly substituted β-alkoxy sulfones to revert back to the ketone sulfone. There have been several recent examples of the synthesis of trisubstituted (*E*)-alkenes worthy of note.

### *3.1.11.4.1 The milbemycins and avermectins*

The milbemycins and the structurally related avermectins contain an (*E*)-trisubstituted alkene linkage that has been formed by the Julia coupling. The first application of the Julia coupling to avermectin was undertaken by Hanessian.[292] In this synthesis, the spiroketal portion was added as the sulfone (**407**) to the ketone (**408**; equation 93). The yield for the anion addition was 40%, but based on recovered sulfone (**407**) was 95%. The β-hydroxy sulfone was directly reduced to the (*E*)-trisubstituted alkene with excellent selectivity. In the synthesis of milbemycin, Barrett carried out a very similar transformation, but with the two components reversed (equation 94).[293] The sulfone (**410**) was metallated and condensed with the aldehyde (**411**). The adduct was isolated as the acetate in 86% yield and the mixture of isomers reduced with sodium amalgam in 86% overall yield. Although the conversion to the alkene (**412**) was efficient, the (*E*)- to (*Z*)-selectivity was 5:3. Hirama and coworkers have also applied the Julia coupling to the trisubstituted alkene portion of the avermectins (equation 95).[294] In this case, the addition of the sulfone anion (**414**) to the ketone (**413**; R = Me) failed and the starting materials were recovered. It was hypothesized that the lack of reactivity was due to the presence of oxygen substituents in the ketone which coordinate with the metal cation. In support of this theory, 3-methyl-2-butanone did undergo coupling with the sulfone and subsequent reductive elimination in satisfactory yield; however, the geometric selectivity in forming the trisubstituted alkene was a disappointing 2:1. In this case, the problem was solved by addition of the sulfone (**414**) to the aldehyde (**413**; R = H). The β-hydroxy sulfone (**415**) was converted to the enol triflate and displaced with dimethylcuprate.[295]

**Table 18** Julia Coupling to Produce (*E*)-Disubstituted Alkenes[284]

| *Entry* | *Carbonyl* | *Sulfone* | *Yield (%)* | *(E):(Z) ratio* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 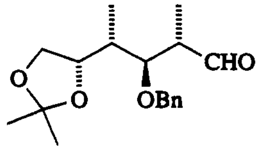 | 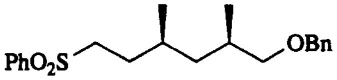 | 60 | 9:1 | 285 |
| 2 | 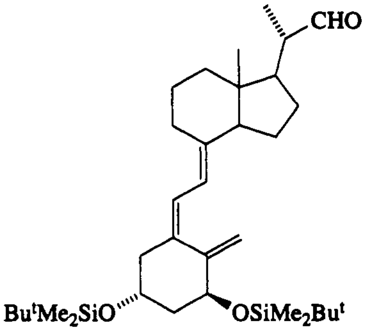 | 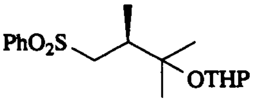 | 36 | (*E*) | 286 |
| 3 | 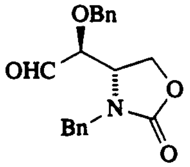 | $PhO_2S-C_{14}H_{29}$ | 28 | (*E*) | 287 |
| 4 | 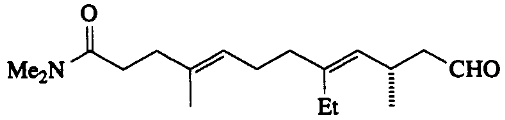 | 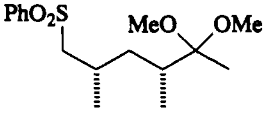 | 68 | 4:1 | 288 |
| 5 | 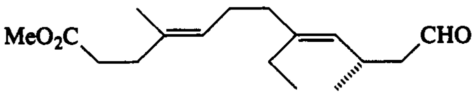 | 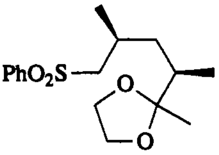 | 35 | (*E*) | 289 |
| 6 | 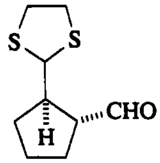 | 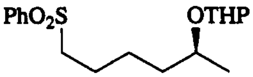 | 46 | (*E*) | 290 |
| 7 | 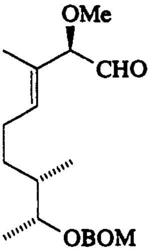 | 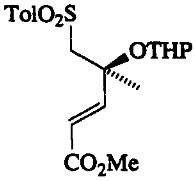 | 30 | (*E*) | 291 |

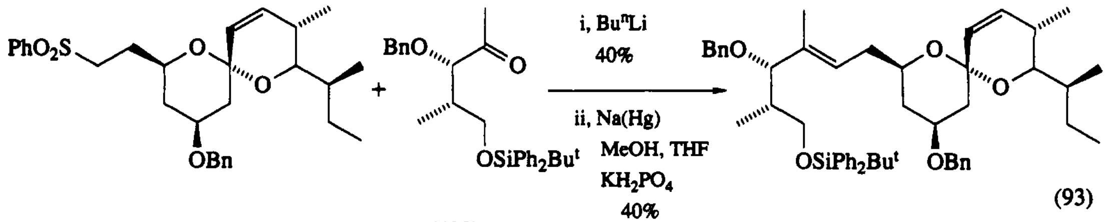
i, Bu$^n$Li
40%
ii, Na(Hg)
MeOH, THF
KH$_2$PO$_4$
40%
PhO$_2$S
OBn
BnO
OSiPh$_2$Bu$^t$
(93)

(407) (408) (409)

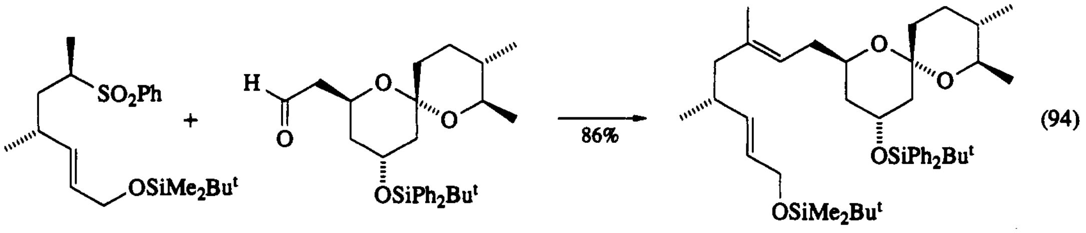
SO$_2$Ph
OSiMe$_2$Bu$^t$
H
O
OSiPh$_2$Bu$^t$
86%
(94)

(410) (411) (412) $(E)$:$(Z)$ = 5:3

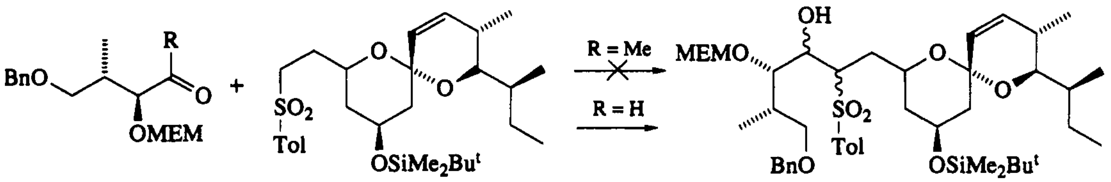
BnO
R
OMEM
SO$_2$
Tol
OSiMe$_2$Bu$^t$
R = Me
R = H
OH
MEMO
BnO
(95)

(413) (414) (415)

### 3.1.11.4.2 FK-506

Most recently, the immunosuppressive agent FK-506 (**416**) has been the target of total synthesis. To date several approaches to the trisubstituted alkene region at C-19 and C-20 have appeared. These preliminary studies allow the comparison between the Warren phosphine oxide approach and the Julia coupling. In the first total synthesis of FK-506, Jones and coworkers at Merck formed the the alkene by deprotonation of the phosphine oxide (**418**) and condensation with the aldehyde (**417**).[296] The hydroxyphosphine oxides were formed in a ratio of 1:1 in 77% yield. The less polar diastereomer was treated with base to obtain the ($E$)-alkene (**419**) in 32% overall yield from the aldehyde (equation 96). Danishefsky utilized the Julia coupling for the formation of the trisubstituted alkene region.[297] The sulfone anion (**420**) was treated with isobutyraldehyde as a model, followed by acetylation and reductive elimination to

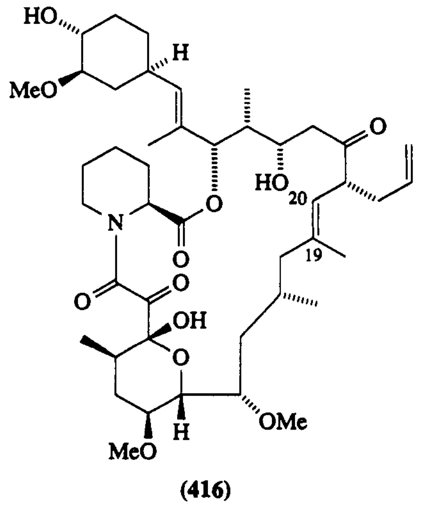
HO
H
MeO
O
HO
20
19
N
O
O
O
O
OH
O
H
OMe
MeO

(416)

give a 2–2.5:1 (*E*)- to (*Z*)-alkene mixture (**421**) in 83% yield for the addition and 33% yield for the acetylation and reductive elimination (equation 97).

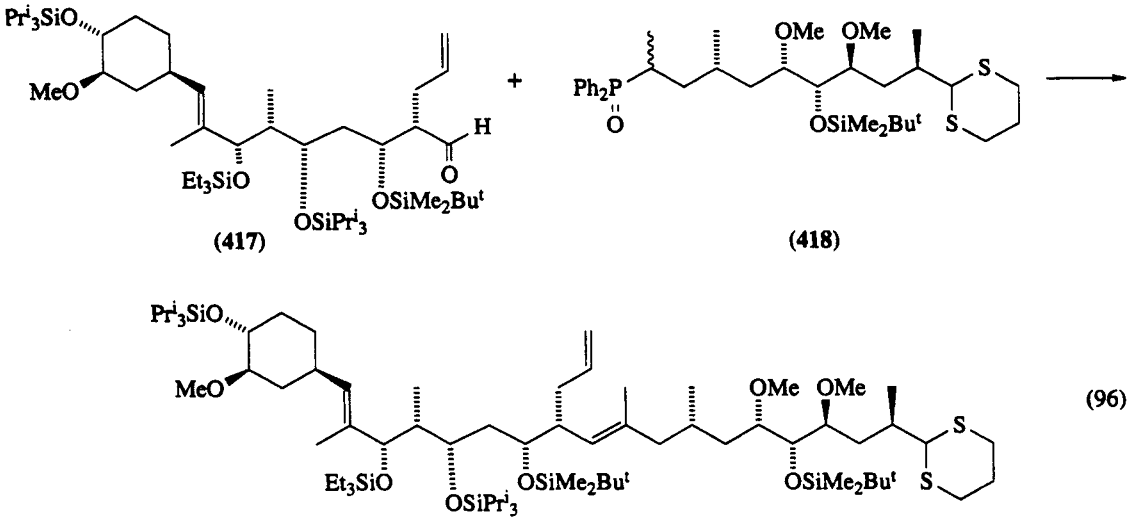

(**417**)

(**418**)

(**419**)

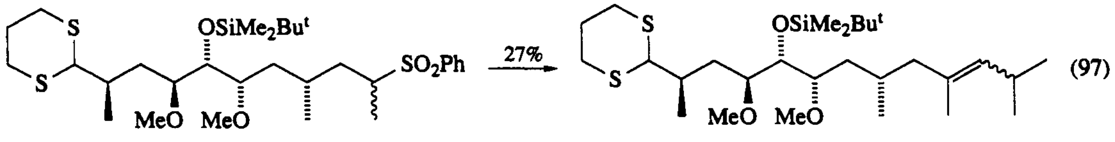

(**420**)

(**421**)

In a more direct comparison of the phosphine oxide elimination with the sulfone, Schreiber employed a identical system to Danishefsky, but used the phosphine oxide (**422**).[298] Reaction with isobutyraldehyde and subsequent elimination resulted in a 1:1 mixture of the (*E*)- and (*Z*)-alkenes (**421**; equation 98). It appears from the more complex example of the Merck synthesis and from this example, that the Julia coupling proceeds with higher (*E*)-selectivity, in similar yield.

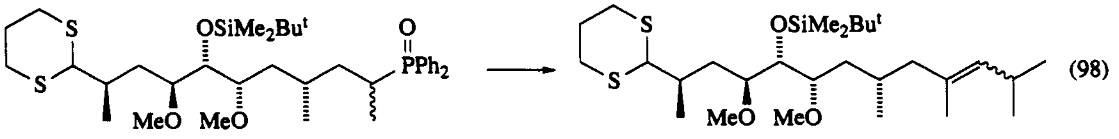

(**422**)

(**421**)

### 3.1.11.5 Diene Synthesis

Use of the Julia coupling for complex natural product synthesis has provided some of the most significant examples of the broad utility of the reagent. The coupling procedure can be a very selective method of (*E*,*E*)-diene synthesis, as the examples below indicate.

### *3.1.11.5.1 X-14547 A*

Ley synthesized the antibiotic X-14547 A using Julia coupling to form the (*E*,*E*)-diene portion (**424**; equation 99).[299] The sulfone anion was generated with $Bu^nLi$ in THF/HMPA and the addition adduct trapped with benzoyl chloride. The alkene generated from the mixture of sulfones was found to be exclusively the (*E*,*E*)-isomer (**424**). In studies directed to the same target by Roush, an interesting comparative study of the Julia coupling, Horner–Wadsworth–Emmons, Wittig and phosphine oxide methods of alkene formation was discussed (see Scheme 57).[300] The synthesis of the key polyene intermediate was carried out by the addition of the phosphonate (**426**) to the aldehyde (**425**) to produce a 95% yield of a 95:5 mixture of the desired (*E*)-alkene (**427**). The corresponding phosphorane and phosphine oxide proceed with significantly lower selectivity (3.5:1) and lower yield (37%) respectively. As an alternative route, the Julia coupling of (**429**) and (**428**) formed the alkene in 49% overall yield and an (*E*):(*Z*) selectivity of 10:1.

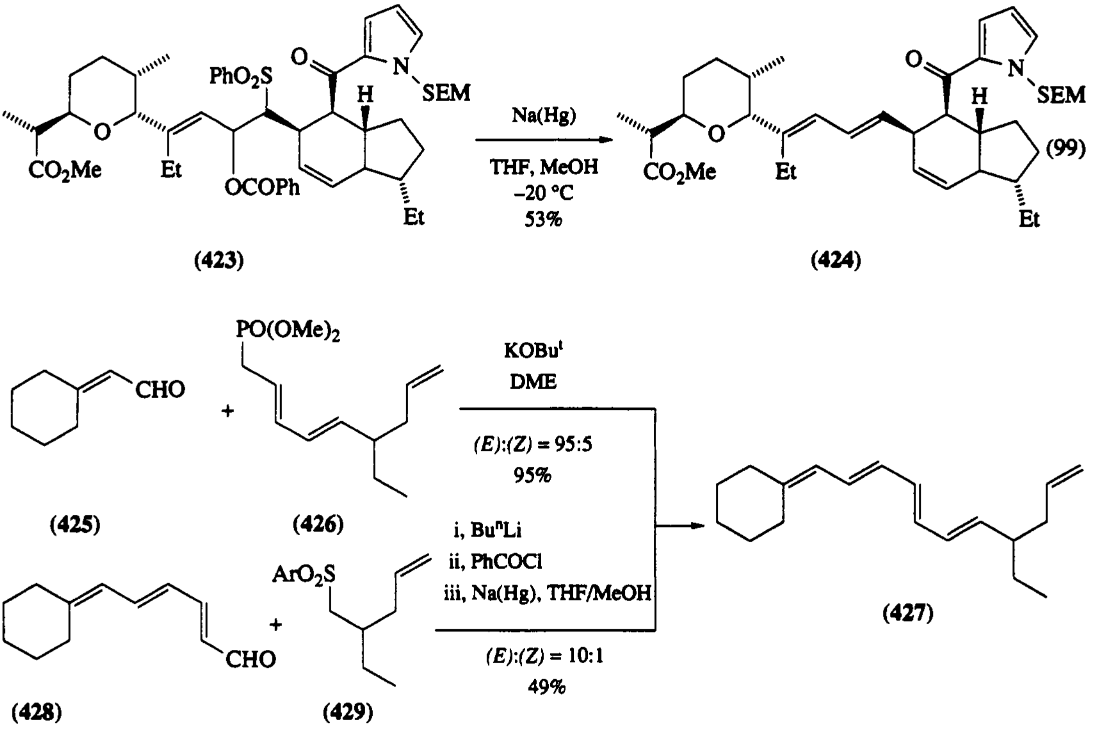
PhO₂S
O
N
SEM
H
CO₂Me
Et
OCOPh
Et
Na(Hg)
THF, MeOH
-20 °C
53%
PO(OMe)₂
CHO
+
KOBuᵗ
DME
(E):(Z) = 95:5
95%
i, BuⁿLi
ii, PhCOCl
iii, Na(Hg), THF/MeOH
ArO₂S
(E):(Z) = 10:1
49%

(**423**) (**424**) (99)

(**425**) (**426**) (**427**) (**428**) (**429**)

**Scheme 57**

### *3.1.11.5.2 The diene portions of avermectin and milbemycin*

The diene portions of avermectin and milbemycin have been synthesized by application of the Julia coupling. For the total synthesis of milbemycin $\beta_3$ by Baker and coworkers, the aromatic ring was incorporated as the aldehyde (**431**) and the spiroketal portion added as the sulfone (**430**; equation 100).[301] The overall yield was 70–80% of the (*E,E*)-alkene (**432**), exclusively. The identical bond disconnection was studied by Kocienski, but with the aldehyde (**433**) and sulfone (**434**) components reversed (equation 101).[302] The anion was formed with LDA and, following functionalization and reductive elimination, the alkene was isolated in 39% yield in a 5:1 ratio of the (*E*)- and (*Z*)-isomers (**435**).

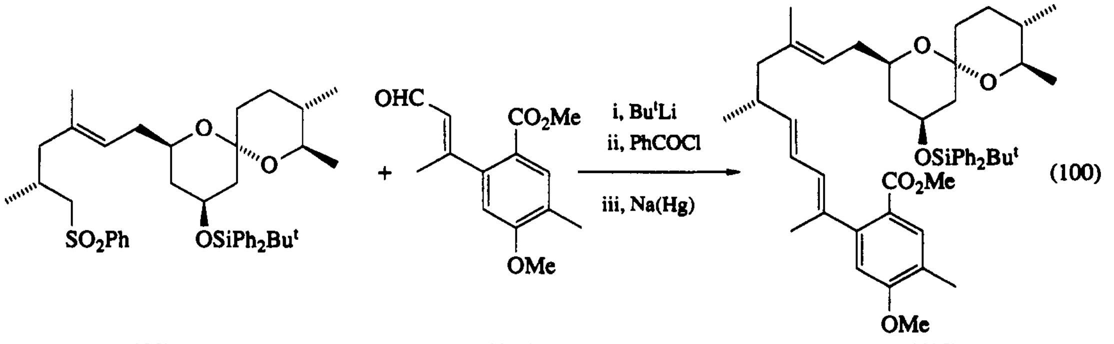
O
O
SO₂Ph
OSiPh₂Buᵗ
OHC
CO₂Me
+
OMe
i, BuᵗLi
ii, PhCOCl
iii, Na(Hg)
OSiPh₂Buᵗ
CO₂Me
OMe

(**430**) (**431**) (**432**) (100)

An interesting variation upon these approaches was published by Ley and coworkers.[303] In studies directed toward the synthesis of milbemycin $\beta_1$, a vinyl sulfone (**437**) was deprotonated to form the diene

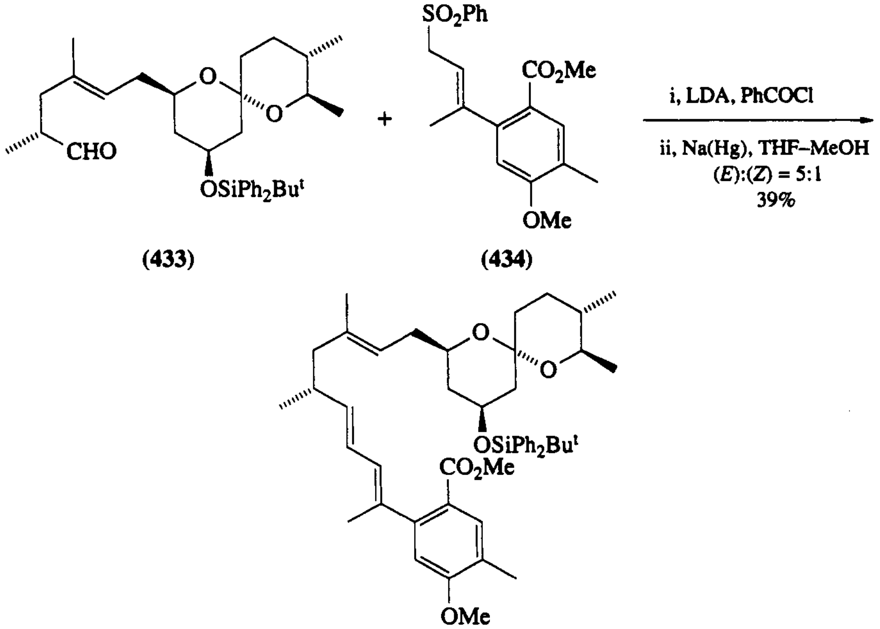

**(433)** **(434)**

**(435)**

(101)

unit (**438**; equation 102). The anion couples at the α-carbon with the aldehyde (**436**), and the β-hydroxy sulfone is derivatized with benzoyl chloride and subjected to reductive cleavage to form the desired diene (**438**) without contamination from the other isomers, in 25% overall yield.

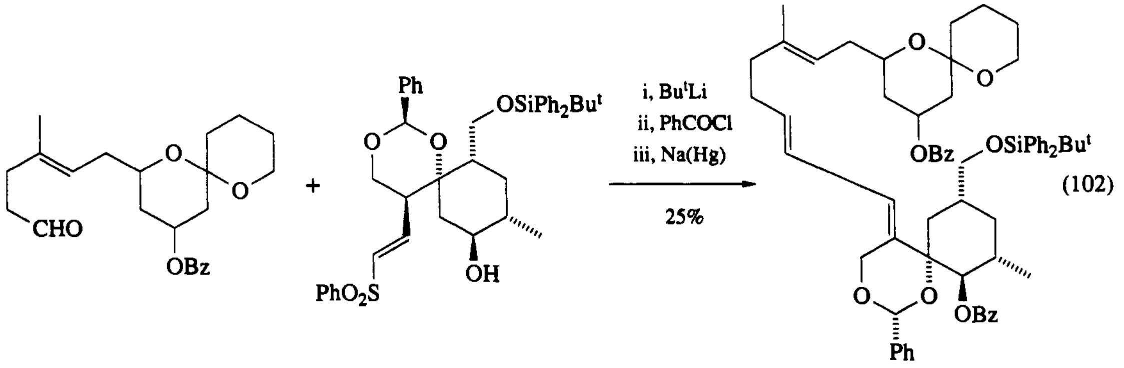

(102)

**(436)** **(437)** **(438)**

In Hanessian's approach to avermectin discussed in Section 3.1.11.4.1, the Julia coupling was used for the trisubstituted alkene and the diene portion of the molecule.[292] The sulfone (**439**) was deprotonated with $Bu^nLi$ and the aldehyde (**440**) added to it to obtain a 47% yield (77% based on recovered sulfone) of β-hydroxy sulfones (equation 103). The alcohol was converted to the chloride and the reductive cleavage carried out with sodium amalgam in 35% yield. The desired diene was the only detectable isomer (**441**). From the examples cited, it is apparent that the synthesis of (*E,E*)-dienes by the Julia coupling is an extremely successful process, in terms of both yield and selectivity.

### *3.1.11.5.3 The double elimination of the sulfone and the hydroxy component*

An alternative approach to diene synthesis using the basic methodology of the Julia coupling has been studied by Otera. Polyenes (**445**) and alkynes (**443**) can be formed by double elimination of the sulfone and the hydroxy component (Scheme 58).[304]

The addition portion of the Julia coupling is run as usual. The β-hydroxy sulfone is functionalized and treated with $KOBu^t$ to effect the elimination. If an allylic hydrogen is present in the substrate, the

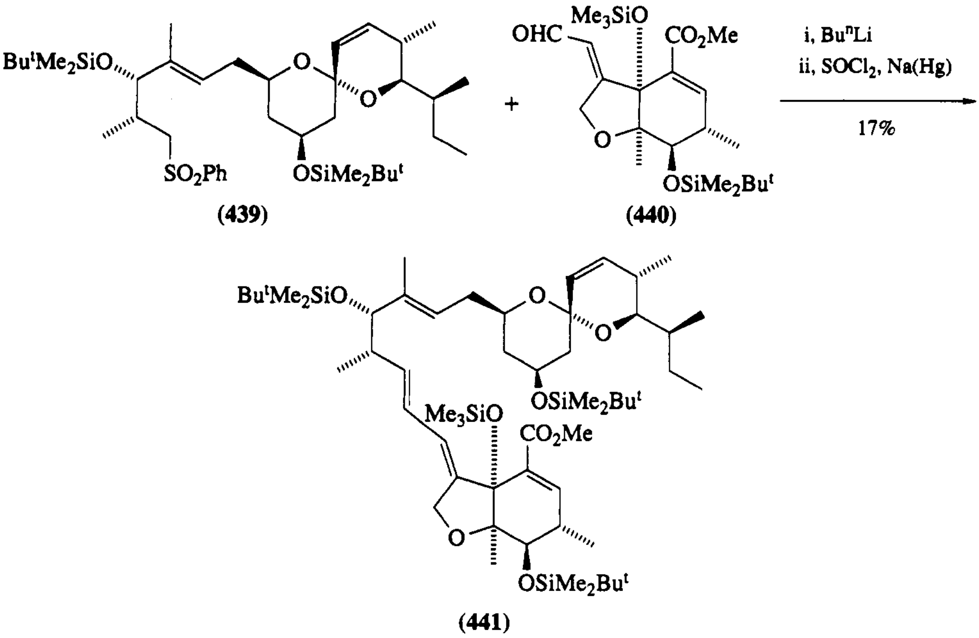
Bu$^t$Me$_2$SiO
SO$_2$Ph
OSiMe$_2$Bu$^t$
OHC
Me$_3$SiO
CO$_2$Me
OSiMe$_2$Bu$^t$
i, Bu$^n$Li
ii, SOCl$_2$, Na(Hg)
17%

**(439)** **(440)** **(441)**

(103)

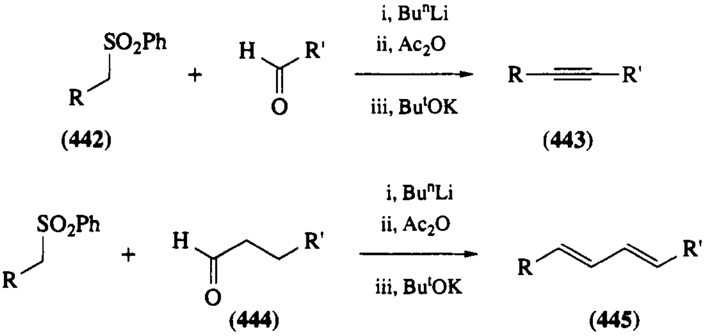
SO$_2$Ph
R
H
R'
O
i, Bu$^n$Li
ii, Ac$_2$O
iii, Bu$^t$OK
R—≡—R'

**(442)** **(443)** **(444)** **(445)**

**Scheme 58**

polyene is formed, otherwise the alkyne is the product. Mechanistically, the alkyne formation proceeds by elimination of the acetoxy or alkoxy group to the vinyl sulfone, followed by elimination of the sulfone.[305] In the case of the polyene, the vinyl sulfone is formed, followed by isomerization to produce allyl sulfone. This substrate then undergoes 1,4-elimination to form the polyene. This sequence has been applied to the synthesis of muscone, methyl retinoate and vitamin A.[306]

In cases where the alkene is conjugated to a carbonyl, the polyene is formed with virtually exclusively the (*E*)-geometry.[307] In the case of the dienamides (**447**) the selectivity was 88–95% for the production of the (*E*,*E*)-isomer (equation 104).

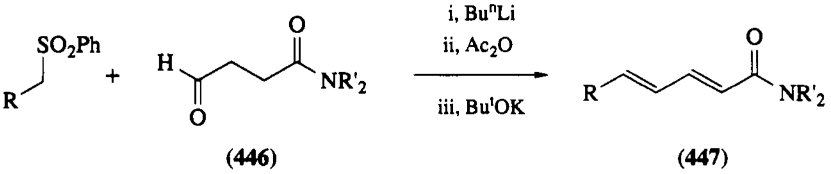
SO$_2$Ph
R
H
O
O
NR'$_2$
i, Bu$^n$Li
ii, Ac$_2$O
iii, Bu$^t$OK
O
NR'$_2$
R

(104)

**(446)** **(447)**

### 3.1.11.6 Reaction with Esters

As discussed in the sections above, the sulfonylmethane anion reacts with ketones and aldehydes chemoselectively in the presence of an ester or amide. It is possible to obtain the keto sulfone on addition to an ester (**448**) when the reaction is carried out without competing carbonyl groups (equation 105). The keto sulfone (**450**) can either be reduced to the β-hydroxy sulfone (**451**) and carried through to the alkene (**452**), or the ketone can be trapped as the enol phosphinate (**453**), and either reduced to the alkene (**452**), eliminated to the vinyl sulfone (**454**)[308] or cleaved to the alkyne (**455**),[313] as shown in Scheme 59.

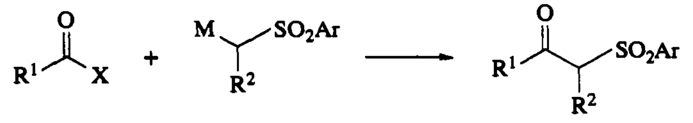

(105)

(**448**) X = OR$^3$, Cl (**449**) (**450**)

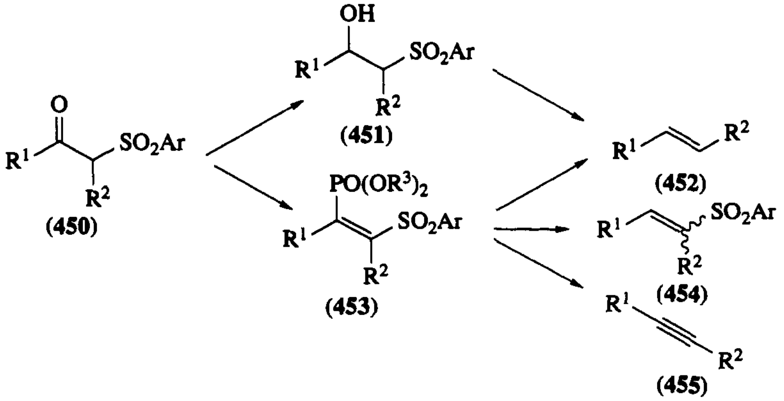

**Scheme 59**

### 3.1.11.6.1 Alkene formation

As discussed in Section 3.1.11.1, which covers the reductive cleavage of the β-hydroxy sulfone derivatives to alkenes, the Julia reaction proceeds by the formation of an anion that is able to equilibrate to the thermodynamic mixture prior to elimination. Therefore, there is no inherent advantage in producing the *erthyro-* or *threo-*β-hydroxy sulfone selectively from the keto sulfone. The (*E*)/(*Z*)-mixture of alkenes should be the same.[273] This method is used to produce alkenes in cases where the acid derivative is more readily available or more reactive. The reaction of the sulfone anion with esters to form the keto sulfone, followed by reduction with metal hydrides has been studied.[308] The steric effects in the reduction do become important for the reaction to produce vinyl sulfones, which are formed from the *anti* elimination of the β-hydroxy sulfone adduct, as mentioned in Section 3.1.11.6.2. Some examples of the use of esters are presented below.

An interesting intramolecular application of the Julia coupling through an ester was carried out by Kang and coworkers in the total synthesis of trinoranastreptene (**458**; Scheme 60).[309] The reduction produced isomeric alcohols, which were separated by chromatography. The major isomer was carried through the sequence shown in Scheme 60, while the minor isomer was resistant to functionalization.

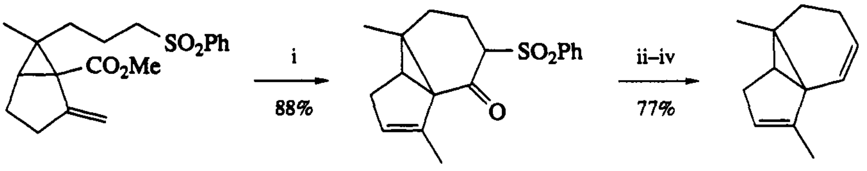

(**456**) (**457**) (**458**)

i, LDA, THF, 0 °C; ii, NaBH$_4$, Et$_2$O, MeOH; iii, Ac$_2$O; iv, Na(Hg), EtOAc, MeOH

**Scheme 60**

The reaction of lactone (**459**) with *p*-tolylsulfonylmethylmagnesium iodide, followed by reduction of the keto sulfone to the β-hydroxy sulfone has been studied.[310] In this paper, the β-hydroxy sulfone was reduced to the alkene (**460**) electrochemically (equation 106). The method was applied to a wide variety of esters and lactones. The yield of the reduction to the methylene derivative was 70–87%.

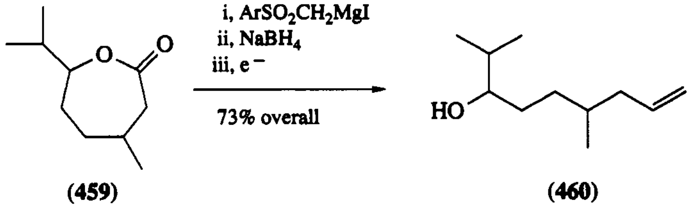
i, $ArSO_2CH_2MgI$
ii, $NaBH_4$
iii, e⁻
73% overall
HO
(459)
(460)

(106)

Both the enol phosphate method, and the reduction of the keto sulfone to the β-hydroxy sulfone followed by reductive cleavage to produce (*E*)-alkenes, have been applied to the synthesis of brefeldin A. Gais and coworkers added the sulfone (**462**) to the lactone (**461**), formed the enol phosphate and reduced with sodium and ammonia to the (*E*)-alkene (**463**), in a 65% overall yield (equation 107).[311]

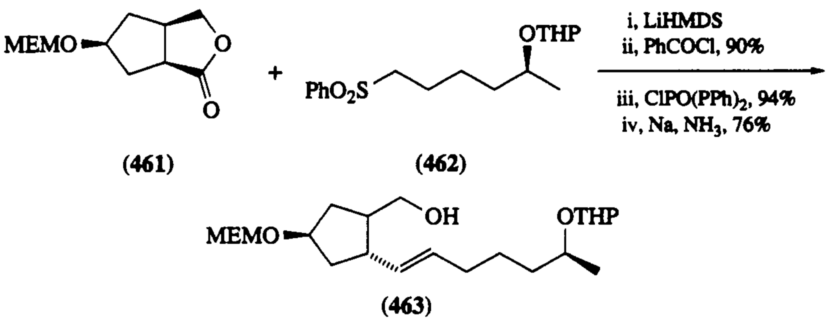
MEMO
O
O
+
$PhO_2S$
OTHP
i, LiHMDS
ii, PhCOCl, 90%
iii, $ClPO(PPh)_2$, 94%
iv, Na, $NH_3$, 76%
(461)
(462)
MEMO
OH
OTHP
(463)

(107)

Trost added the sulfone (**465**) to the ester (**464**), and reduced the ketone to the alcohol.[312] In this example the formation of the enol derivative of the keto sulfone failed. The hydroxy group was functionalized with acetic anhydride, and the reduction to the alkene (**466**) carried out with the standard sodium amalgam conditions in 54% overall yield, as shown in equation (108).

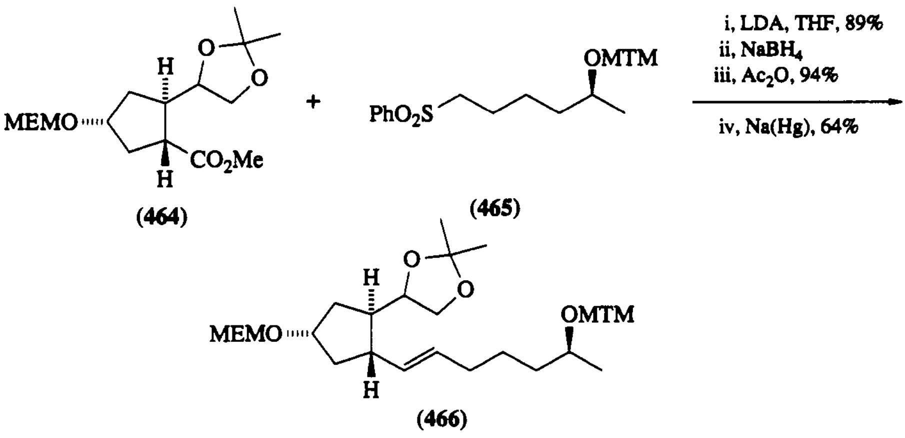
O
O
H
MEMO
$CO_2Me$
H
+
$PhO_2S$
OMTM
i, LDA, THF, 89%
ii, $NaBH_4$
iii, $Ac_2O$, 94%
iv, Na(Hg), 64%
(464)
(465)
O
O
H
MEMO
OMTM
H
(466)

(108)

### 3.1.11.6.2 *Vinyl sulfone formation*

Julia has undertaken studies on the selective reduction of keto sulfones, followed by the *trans* elimination to the vinyl sulfone.[308] These intermediates can then be reacted with Grignard reagents to produce trisubstituted alkenes.[295]

### 3.1.11.6.3 *Alkyne formation*

In 1978, Bartlett published a study of the reaction of esters and acid chlorides to produce β-keto sulfones (**467**), which could be converted to the enol phosphinates (**468**) and reduced with sodium in ammonia to the alkyne (**469**; Scheme 61).[313] The overall yields for the process are good. As discussed in

Section 3.1.11.5.3, the double elimination developed by Otera can also be employed in the synthesis of alkynes.

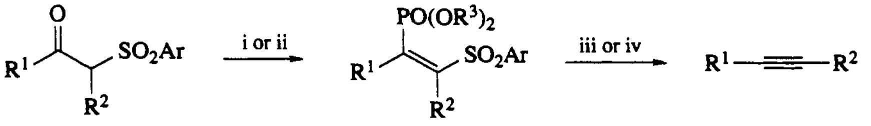
O
$R^1$
$SO_2Ar$
$R^2$
i or ii
$PO(OR^3)_2$
$R^1$
$SO_2Ar$
$R^2$
iii or iv
$R^1$
$R^2$

**(467)** **(468)** **(469)**

i, NaH or KH, $(R^3O)_2POCl$; ii, DMAP, $Et_3N$, $(R^3O)_2POCl$; iii, $Na/NH_3$; iv, Na(Hg)/THF

**Scheme 61**

### 3.1.11.7 Lewis Acid Catalyzed Additions of Sulfone Anions to Carbonyls

In a study by Wicha directed to the synthesis of prostaglandins from the Corey lactone, the use of $BF_3{\cdot}Et_2O$ to catalyze the addition of the lithium sulfone anion (**470**) to aldehydes was demonstrated (equation 109).[314] The use of Lewis acid catalysis results in significantly improved yields for the addition component of the Julia coupling. In this example, the addition of either the lithium or the magnesium sulfone anion proceeded in low yield. With the addition of $BF_3{\cdot}Et_2O$, the β-hydroxy sulfone can either be isolated, or directly converted to an alkene in one pot. This sequence was originally developed to deal with the specific problem of α-hydroxy aldehydes, and the difficulty of sulfone anion addition to these adducts. Other problems with addition of the sulfone adduct may be amenable to this solution as well.

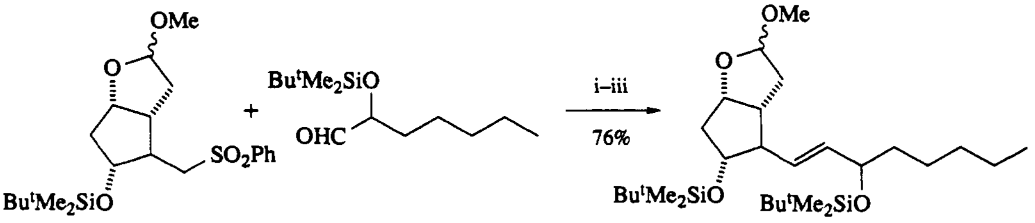
OMe
O
+
$SO_2Ph$
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$
OHC
i–iii
76%
OMe
O
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$

(109)

**(470)** **(471)** **(472)**

i, $Bu^nLi$, $BF_3{\bullet}OEt_2$; ii, MsCl; iii, Na(Hg), MeOH, $Na_2HPO_4$

A second application of the use of Lewis acid catalysis in the Julia coupling can be found in the synthesis of *trans*-alkene isosteres of dipeptides (**478**; Scheme 62).[315] Initially, attempts to couple aldehydes derived from amino acids (**473**) resulted in poor overall yield of the alkene. This difficulty was solved by reversing the substituents, and introducing the amino acid portion as the anion of sulfone (**476**) to the chiral aldehyde (**477**). The dianion of the sulfone was formed and to it were added 2 equiv. of aldehyde and 1 equiv. of diisobutylaluminum methoxide. The resulting β-hydroxy sulfone was taken on to the reductive elimination step to produce the desired (*E*)-alkene (**478**), in 74% overall yield.

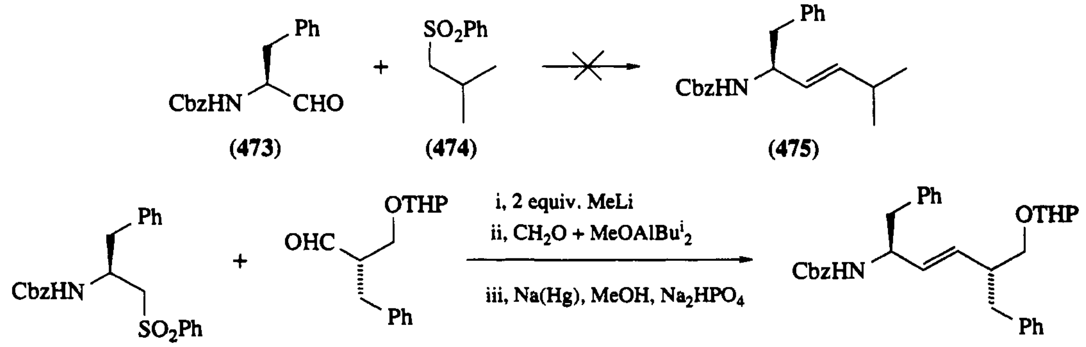
Ph
CbzHN
CHO
+
$SO_2Ph$
Ph
CbzHN
(473)
(474)
(475)
Ph
CbzHN
$SO_2Ph$
+
OTHP
OHC
Ph
i, 2 equiv. MeLi
ii, $CH_2O$ + $MeOAlBu^i_2$
iii, Na(Hg), MeOH, $Na_2HPO_4$
Ph
OTHP
CbzHN
Ph

**(476)** **(477)** **(478)** 74% overall

**Scheme 62**

## 3.1.12 METHODS OF ALKENE FORMATION BY METAL CARBENE COMPLEXES

There are many metals that form alkylidene complexes.[316] Among these, the Tebbe reagent has proven to be of widespread generality and use in organic synthesis for the transfer of a methylene unit. As discussed in Section 3.1.6, a method using titanium and zinc has recently been applied for the methylenation of aldehydes and ketones. In the quest to extend this technology to longer chain alkyl groups, other metals have been investigated. Unfortunately the dimetallo precursors to metal carbene complexes are prone to β-hydride elimination, and this has limited the application of this methodology to alkylidenation. In addition, the methods of forming the metal carbene complexes can be arduous.[316] Consequently, these methods have not found widespread application in the context of natural product synthesis. Recently some mild and practical solutions to this problem have been discovered. These results are discussed in the following sections.

### 3.1.12.1 Chromium

A chromium carbene generated *in situ* from $CrCl_2$ and a dihaloalkyl derivative, has been utilized to form a variety of (*E*)-disubstituted alkene compounds (**480**). The general reaction is summarized in equation (110). Alkenyl halides, sulfides and silanes, as well as dialkyl-substituted alkenes, have been synthesized by this method.

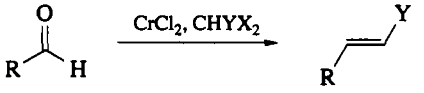

**(479)** **(480)**

(110)

#### *3.1.12.1.1 Alkenyl halides*

Aldehydes may be converted to (*E*)-alkenyl halides[317] by the reaction of $CrCl_2$ with a haloform in THF.[318] The highest overall yields for the conversion were with iodoform, but somewhat higher (*E*):(*Z*) ratios were observed with bromoform or chloroform. Other low-valent metals, such as tin, zinc, manganese and vanadium, were ineffective. As the examples in Table 19 indicate, the reaction is selective for the (*E*)-isomer, except in the case of an α,β-unsaturated aldehyde. In addition, the reaction with ketones is sufficiently slow for chemoselectivity to be observed for mixed substrates.

**Table 19** The Reaction of $CrCl_2$ with Dihalo Derivatives to Produce Alkenes

| *Substrate* | *Reagent* | *Yield (%)* | *(E):(Z)* | *Ref.* |
|---|---|---|---|---|
| PhCHO | $CHI_3$ | 87 | 94:6 | 318 |
| | $CHCl_3$ | 43 | 95:5 | 318 |
| | $TMSCHBr_2$ | 82 | (*E*) only | 322 |
| | $PhSCHCl_2$, LiI | 83 | 82:18 | 322 |
| | $Pr^nCHI_2$ | 87 | 88:12 | 324 |
| | $Pr^iCHI_2$ | 79 | 88:12 | 324 |
| | $Bu^tCHI_2$ | 80 | 96:4 | 324 |
| | $CH_2I_2$ | 70 | — | 324 |
| $Me(CH_2)_7CHO$ | $CHI_3$ | 82 | 83:17 | 318 |
| | $TMSCHBr_2$ | 82 | (*E*) only | 322 |
| | $PhSCHCl_2$, LiI | 68 | 71:29 | 322 |
| 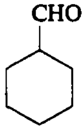 | $CHI_3$ | 78 | 89:11 | 318 |
| | $TMSCHBr_2$ | 81 | (*E*) only | 322 |
| 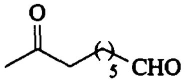 | $CHI_3$ | 75 | 81:19 | 318 |
| | $TMSCHBr_2$ | 76 | (*E*) only | 322 |
| $Ph(CH_2)_2CHO$ | $MeCHI_2$ | 85 | 97:3 | 324 |
| $Et_2CHCHO$ | $MeCHI_2$ | 99 | 98:2 | 324 |

This procedure has been utilized by Nicolaou to prepare the vinyl iodide (**482**) in the synthesis of lipotoxins $A_5$ and $B_5$ (equation 111).[319] The synthesis of vinyl iodides was also utilized by Bestmann in a stereospecific synthesis of (4*E*,6*E*,11*Z*)-hexadecatrienal. A Wittig reaction was used to create the (*E*)-alkene (**484**), and the (*E*)-diene portion was synthesized *via* vinyl iodide (**485**) formation and coupling (Scheme 63).[320] This method has been applied to the synthesis of $^{13}C$-labeled vinyl iodide (**488**; equation 112).[321] Labeled iodoform (**486**) was made and the reaction conditions altered from those employed by Takai and coworkers in order to use smaller quantities of the valuable iodoform, relative to $CrCl_2$.

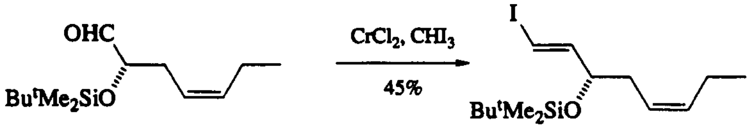

**(481)** **(482)** (111)

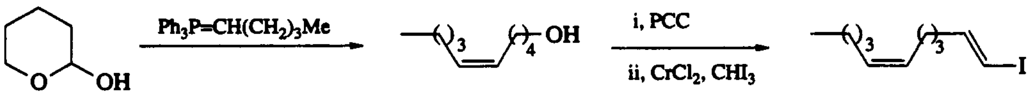

**(483)** **(484)** **(485)**

Scheme 63

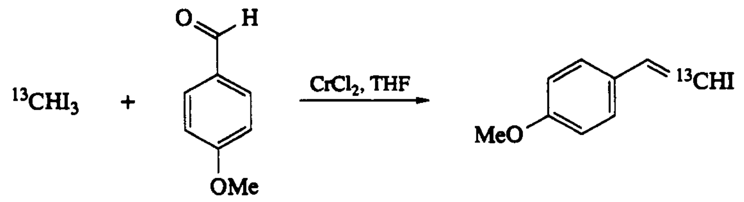

**(486)** **(487)** **(488)** (112)

### 3.1.12.1.2 Substituted examples

This reaction has been extended to alkenylsilanes and alkenyl sulfides, as summarized in Table 19.[322] In addition to various heteroatom-substituted examples, the reagent formed from $CrCl_2$ and a *gem*-diiodoalkane can be reacted with an aldehyde to selectively form the (*E*)-alkene. For the transfer of groups larger than ethylene with an aldehyde, it was found advantageous to add DMF. The conditions are compatible with nitriles, esters, acetals, alkynes and alkyl halides.[323] In the case of ethylidenation, the chromium carbene reacts with ketones in good yields.[324] It has not proven to be of general utility for the synthesis of trisubstituted alkenes either by the addition of a Cr derivative to a ketone or by the addition of a disubstituted Cr species to an aldehyde. An interesting comparative study of the Wittig reaction and the alkylidenation with Cr was carried out by Maxwell in the synthesis of several long chain ketones.[325] The all-(*Z*)-isomers (**490**) were synthesized by the salt-free Wittig reaction, while the all-(*E*)-isomers (**491**) were obtained by the $CrCl_2$ coupling of the diiodide (Scheme 64). The reaction has been applied to the synthesis of a segment of macbecins.[326] The aldehyde was treated with $CrCl_2$ and $MeCHI_2$ to produce the desired alkene (**493**) in 91% yield with 99% (*E*)-selectivity (equation 113).

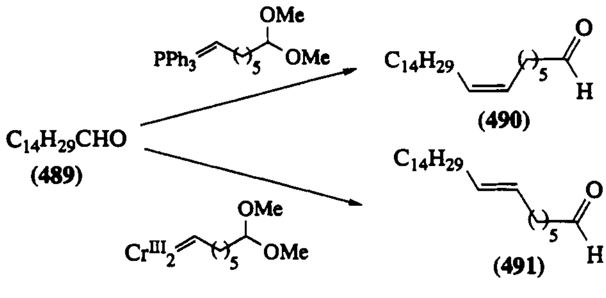

Scheme 64

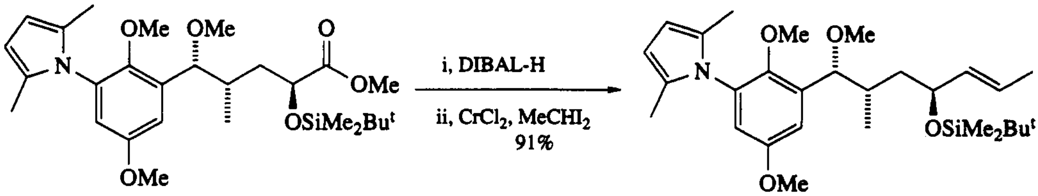

**(492)** **(493)** (113)

As pointed out in this work, the mild conditions of the Cr reaction resulted in no observed epimerization, and offered an excellent alternative to the Schlosser modification of the Wittig reaction. Both the $CrCl_2$ chemistry and the $TiCl_4/Zn$ method discussed in Section 3.1.12.1.2 have the advantage of preparing the metallocarbene complex *in situ*.

### 3.1.12.2 Titanium–Zinc

The chemistry of Oshima and Takai, previously discussed in Section 3.1.6, has been extended to the incorporation of alkylidene (**495**) units when reacted with esters (**494**; equation 114).[327] The essential additive is TMEDA. The reaction is highly selective, producing the disubstituted (*Z*)-enol ether in good yield. The ratio of (*Z*)- to (*E*)-isomer is enhanced by increasing the steric repulsion of substituents $R^1$ and $R^2$ relative to the size of the ester functionality. In addition, the rate of reaction was increased with aromatic or unsaturated esters.[330] Although diiodoalkanes can be used in the reaction, better yields were obtained with the dibromo compounds. This reaction is complementary to the Tebbe reagent discussed in Section 3.1.5. The $CH_2Br_2/Zn/TiCl_4$ system does not react with esters even in the presence of TMEDA.[328] Therefore this method can be utilized to selectively form more highly substituted enol ethers, while the Tebbe reaction may be used to synthesize methylene derivatives. Examples are presented in Table 20.

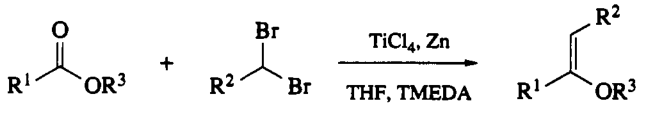

**(494)** **(495)** **(496)** (114)

The reaction is effective with electron-rich carbonyls such as trimethylsilyl esters and thioesters, as Table 20 indicates.[329] Lactones are substrates for alkylidenation; however, hydroxy ketones are formed as side products, and yields are lower than with alkyl esters.[327,330] Amides are also effective, but form the (*E*)-isomer predominantly. This method has been applied to the synthesis of precursors to spiroacetals (**499**) by Kocienski (equation 115).[330] The reaction was found to be compatible with THP-protected hydroxy groups, aromatic and branched substituents, and alkene functionality, although complex substitution leads to varying rates of reaction for alkylidenation. Kocienski and coworkers found the intramolecular reaction to be problematic.[330] As with the $CrCl_2$ chemistry, this reaction cannot be used with a disubstituted dibromoalkane to form the tetrasubstituted enol ether. Attempts were made to apply this reaction to alkene formation by reaction with aldehydes and ketones, but unfortunately the (*Z*):(*E*)-ratio of the alkenes formed is virtually 1:1.[327]

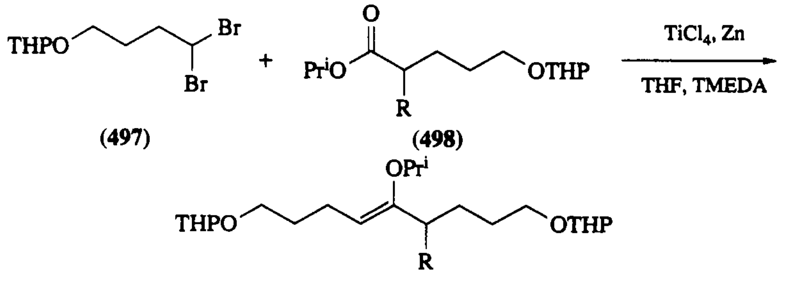

**(497)** **(498)**

(115)

R = H, 88%; R = Et, 89%

**(499)**

**Table 20** Synthesis of Enol Ether Derivatives by Zn, $TiCl_4$ and TMEDA

| *Carbonyl compound* | *Alkyl halide* | *Yield (%)* | *(Z):(E)* | *Ref.* |
|---|---|---|---|---|
| $PhCO_2Me$ | $MeCHBr_2$ | 86 | 92:8 | 327 |
| $PhCO_2Me$ | n-$C_5H_{11}CHBr_2$ | 89 | 95:5 | 327 |
| $PhCO_2Me$ | c-$C_6H_{11}CHBr_2$ | 61 | 90:10 | 327 |
| $PhCO_2Bu^t$ | $MeCHBr_2$ | 81 | 71:29 | 327 |
| $Pr^iCO_2Me$ | n-$C_5H_{11}CHBr_2$ | 89 | 100:0 | 327 |
| $MeCHCHCO_2Et$ | n-$C_5H_{11}CHBr_2$ | 90 | 94:6 | 327 |
| $BuCO_2CH_2CHCH_2$ | n-$C_5H_{11}CHBr_2$ | 52 | 92:8 | 327 |
| $PhCO_2TMS$ | $MeCHBr_2$ | 90 | 73:27 | 329a |
|  | $BuCHBr_2$ | 84 | 73:27 | 329a |
|  | c-$C_6H_{11}CHBr_2$ | 74 | 80:20 | 329a |
| n-$C_9H_{19}CO_2TMS$ | $MeCHBr_2$ | 77 | 86:14 | 329a |
| c-$C_6H_{11}CO_2TMS$ | $MeCHBr_2$ | 80 | 100:0 | 329a |
| $PhCHCHCO_2TMS$ | $MeCHBr_2$ | 65 | 96:4 | 329a |
| $PhCOSMe$ | $MeCHBr_2$ | 77 | 80:20 | 329b |
|  | $Bu^nCHBr_2$ | 75 | 84:16 | 329b |
| n-$C_8H_{17}COSMe$ | $MeCHBr_2$ | 94 | 73:27 | 329b |
| c-$C_6H_{11}COSMe$ | $MeCHBr_2$ | 88 | 94:6 | 329b |
|  | $PhCH_2CHBr_2$ | 95 | 100:0 | 329b |
| 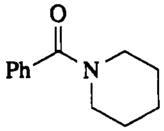 | $MeCHBr_2$ | 70 | 2:98 | 329b |
|  | $PhCH_2CHBr_2$ | 87 | 1:99 | 329b |
| 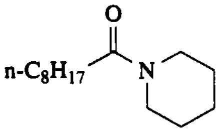 | $MeCHBr_2$ | 79 | 1:99 | 329b |
| 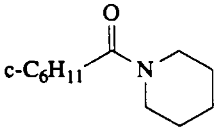 | $MeCHBr_2$ | 82 | 47:53 | 329b |

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# 3.2
# Epoxidation and Related Processes

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## 3.2.1 INTRODUCTION

This chapter concerns the net conversion of a C═X π-bond (X = O and N) to various three-membered ring heterocycles. The most common such process is the conversion of an aldehyde or ketone to a homologous epoxide. These reactions will be discussed along with the analogous process which takes place on imines and related compounds. Additionally, methods to effect the addition of elements other than carbon across either unsaturated system will be considered. The synthesis of thiiranes by the addition of carbon across the C═S π-bond is the subject of a recent comprehensive review[1] and will not be covered here.

## 3.2.2 ADDITIONS TO C═O π-BONDS

### 3.2.2.1 General Considerations

The particular attributes of carbonyl epoxidation reactions, in addition to the importance of forming any carbon–carbon bond, result from the fact that the newly introduced carbon substituent is functionalized and, due to its presence in a three-membered ring, activated. The lability of epoxides toward nucleophiles is well known and accounts for the bulk of their utility in synthesis.[2,3] In addition, epoxides undergo a variety of rearrangement reactions, such as chain elongation or ring expansion processes. Emphasis is placed here on techniques which allow the conversion of a carbonyl to a homologous isolable epoxide in a one-pot procedure, although pertinent multistep methods will be briefly noted.

All of these methods require the formation of an alkoxide with a leaving group $X^n$ (the formal charge $n$ is usually 0 or +1) in the β-position which collapses with the expulsion of an $X^{n-1}$ species to afford the epoxide, as shown in Scheme 1. Rearrangement processes often compete with epoxidation and sometimes constitute the major reaction pathway. The bulk of these approaches entail the formation of this intermediate by the addition of an anionic species $R^3R^4XC^-$ to the electrophilic carbonyl group (path a). Very often, the leaving group serves the additional function of stabilizing the carbanionic species as well. Some mention will be made of alternative routes in which a nucleophile attacks a carbonyl compound which contains an adjacent leaving group (path b).

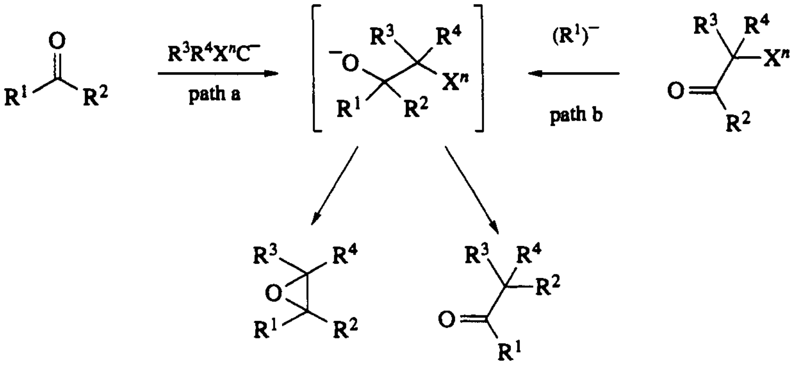

Scheme 1

### 3.2.2.2 Sulfur Ylides

The most commonly used reagents to effect the addition of a methylene group to an aldehyde or ketone are sulfur ylides such as dimethylsulfonium methylide (**1**) or dimethyloxosulfonium methylide (**2**)[4] (Corey–Chaykovsky reaction).[5] This reaction is well reviewed in standard treatises of organic synthesis[6,7] and several useful monographs.[8,9] This update will concentrate on progress attained from 1975. The reader is also encouraged to consult reviews on the chemistry of the related sulfoximine-derived ylides such as (**3**).[10,11]

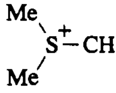

$Me_2\overset{+}{S}{-}\overset{-}{C}H_2$

(**1**)

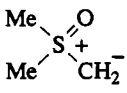

$Me_2\overset{+}{S}(O){-}\overset{-}{C}H_2$

(**2**)

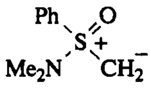

$Ph(Me_2N)\overset{+}{S}(O){-}\overset{-}{C}H_2$

(**3**)

Sulfur ylides are primarily synthesized by deprotonation of a sulfonium salt, which in turn is usually prepared by alkylation of a sulfide.[12] Branched chain sulfonium salts are not generally preparable by simple sulfide displacement, although some can be made by other routes.[9,12] While ylide solutions are most commonly prepared and used immediately, frozen stock solutions of the more stable (**2**) can be stored for several months in DMSO at –20 °C.[13]

The reaction between sulfur ylides and carbonyl compounds entails attack of the ylide on the carbonyl to form a betaine, which then collapses with expulsion of the neutral sulfide or sulfoxide (Scheme 1; $X^n = R_2S^+$).[6,7,9] A theoretical study of this mechanism has appeared.[14] Ylides belonging to the general classes of (**1**) and (**2**) differ in stability and in the relative rates of the two mechanistic steps. Specifically, the more stable (**2**) reacts reversibly with carbonyl groups, whereas (**1**) undergoes a kinetic addition to the substrate followed by a rapid collapse of the betaine to an epoxide. Differences in chemoselectivity and stereoselectivity between the ylides are attributed to this key difference.[6,7,9]

The structural variety of epoxides available through the above technology is limited by the availability of the starting sulfonium salt, the reactivity of the desired ylide, and the propensity of either species to undergo a variety of side reactions. For simple methylene addition, (**1**) and (**2**) are the most general and reliable reagents available. The rearrangement reactions observed with other reagents (most notoriously, diazoalkanes) are much less common with sulfur ylides. Even so, some electron-rich epoxides are prone to undergo rearrangement prior to isolation, yielding aldehydes or ketones.[15] In addition, (**2**) or (**3**) reacts with epoxides under rather forcing conditions (50 °C, 3 d) giving rise to oxetanes.[16,17]

A particularly interesting and useful group of ylides are those derived from diphenylcyclopropyl sulfonium halides, such as (**4**) and (**5**).[18] These reagents react with ketones and aldehydes to afford oxaspiropentanes, which are versatile synthetic intermediates.[19] Ylide (4) exhibits stereochemical and regiochemical tendencies similar to (1).

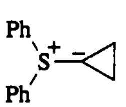

(4)

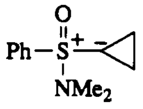

(5)

New methods for the generation of ylide (1) in the presence of a substrate have been introduced. Solid potassium hydroxide in nonpolar solvents containing trace amounts of water has proven a highly effective medium for the promotion of methylene[20] and benzylidene[21] transfer reactions (equation 1). The counterion of the sulfonium salt and the base used has a substantial effect on the success of the reaction.[22]

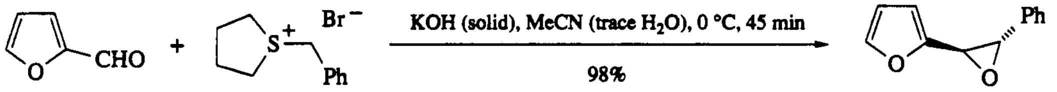

(1)

Two-phase systems, usually consisting of a strongly alkaline aqueous phase and methylene chloride, are also effective and convenient. Trialkylsulfonium salts with methylsulfate counterions can be used alone under these conditions,[23] whereas those with halide counterions generally benefit from added phase transfer catalysts (equation 2).[24] Dodecyldimethylsulfonium chloride was found to be an effective phase transfer reagent.[24] A sulfonium salt covalently attached to a polymeric resin was found most effective when a phase transfer agent was also employed.[25]

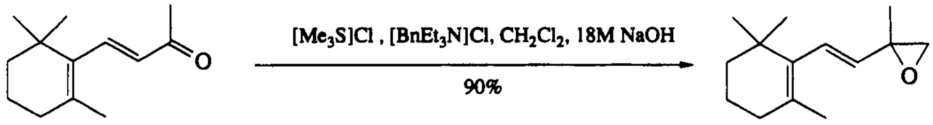

(2)

Epoxidations can be effected by adsorption of sulfonium salts and substrate on potassium fluoride impregnated alumina.[26] Soluble fluoride ion allowed the generation of a methylide from a TMS-substituted precursor, which underwent equilibration to the more stable benzylide prior to addition (equation 3).[27] The reaction failed with ketones or imines.

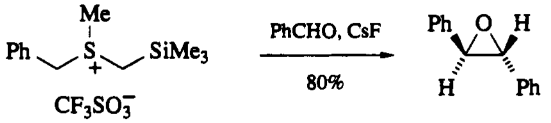

(3)

Several groups have investigated the use of complex sulfur ylide reagents for a key carbon–carbon bond formation step in leukotriene synthesis (equation 4).[28,29] For example, tetraene (6) reacted with methyl 5-oxopentanoate to give an 85% yield of the desired epoxides as a mixture of *cis* and *trans* isomers. Significantly, only small amounts of by-products resulting from elimination or rearrangement of the sulfonium salt were observed.

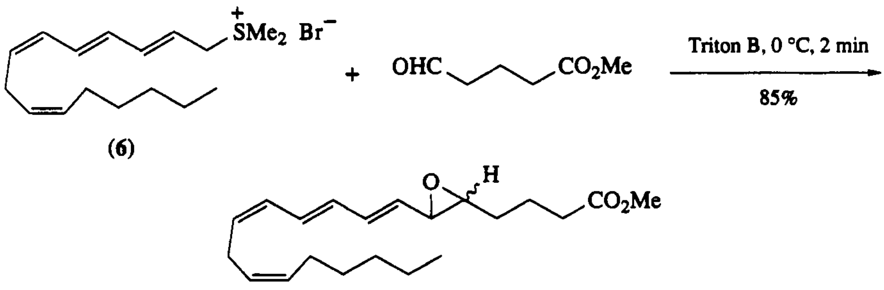

(4)

Several examples of intramolecular epoxide formation have been reported.[30,31] In general, a keto sulfide is reacted with a trialkyloxonium tetrafluoroborate to yield a sulfonium salt, which cyclizes upon treatment with base. A particularly clever variation involves the *in situ* generation of an allylic ylide (Scheme 2).[32]

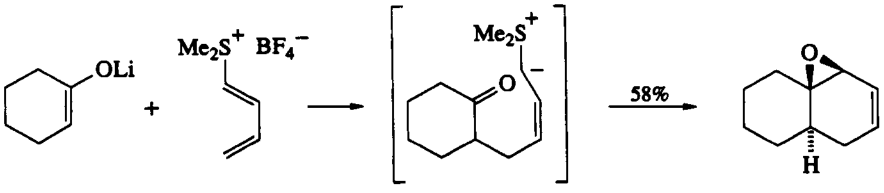

**Scheme 2**

Compared to unstabilized ylides, ylides bearing an electron-withdrawing group on the adjacent carbon can be generated under milder conditions and are considerably more stable. However, most reactive aldehydes or ketones are not epoxidized by these reagents and classical Darzens-type reactions are usually preferred for the synthesis of epoxides bearing an electron-stabilizing group (see Volume 2, Chapter 1.13). However, ylide (**7**)[33] does react with ketones to afford α,β-epoxy carboxylic acids (equation 5).[34] Notably, ketone (**8**) did not react with standard Darzens reagents.

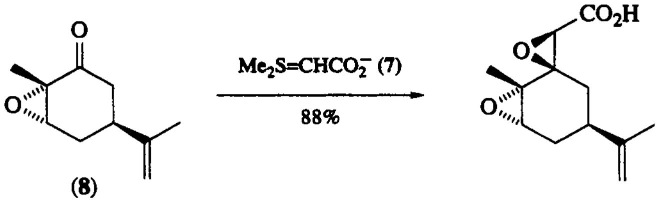

(**8**)

(5)

Early efforts to probe the stereochemistry of sulfur ylide additions have been reviewed.[35] Ylide (**1**) reacts with unhindered cyclohexanone derivatives to give products resulting from axial attack, whereas (**2**) gives rise to net equatorial addition. This is again due to the tendency of (**1**) to undergo kinetically controlled reactions and (**2**) to give products resulting from thermodynamic control. However, equatorial attack may prevail even in kinetically controlled reactions if axial attack is rendered sufficiently hindered, *e.g.* by 1,3-diaxial interactions or by additional steric bulk adjacent to the reactive carbonyl.[6,7,9] For example, the addition of (**1**) to ketone (**9**) affords the β-epoxide shown in equation (6) exclusively.[36] Other cyclic systems react with fairly predictable stereoselectivities in accord with the above observations.[9,19]

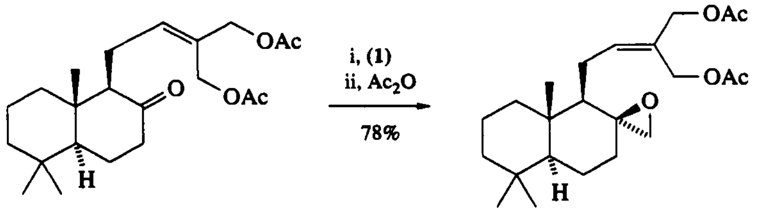

(**9**)

(6)

Ylide (**1**) adds selectively to the least hindered side of a spirocyclic cyclobutanone to afford epoxide (**10**) as the sole product in ≥65% yield (Scheme 3).[37] Where only steric factors are likely to be important, complementary stereochemical results are often possible by methylene addition to a carbonyl group or alternatively, by carrying out an epoxidation reaction on the derived alkene. In each case, the reagent approaches a double bond from the same stereochemical face. This point is nicely illustrated by the synthesis of epoxide (**11**).

Several workers have observed differences in the stereoselectivity of the reactions of (**1**) and (**2**) with ketones related to the trichothecene family of natural products (Scheme 4).[38,39] Reaction of ketone (**12**) with (**1**) stereoselectively led to epoxide (**13**), whereas ylide (**2**) gave (**14**) instead. Very high diastereoselection was obtained in the late stages of a synthesis of (+)-phyllanthocin: treatment of ketone

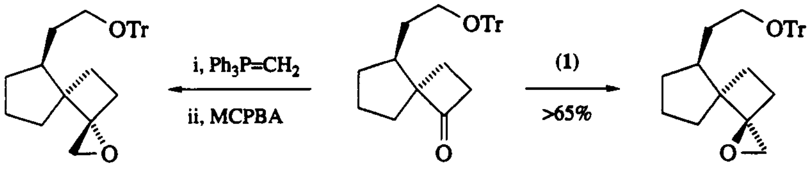

**(11)** **(10)**

**Scheme 3**

**(15)** with a large excess of **(2)** afforded a 98% yield of epoxide **(16)** in 97% diastereomeric purity (equation 7).[13]

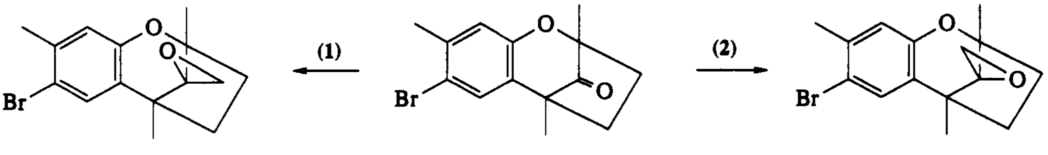

**(13)** **(12)** **(14)**

**Scheme 4**

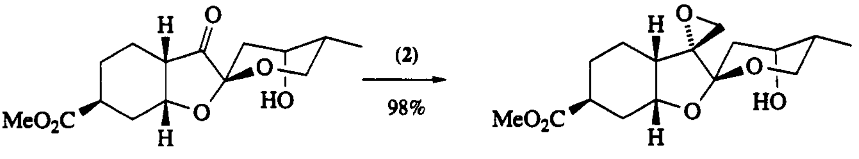

**(15)** **(16)** (7)

In contrast with the considerable effort which has gone into delineating the stereochemistry of sulfur ylide additions to cyclic ketones, studies in acyclic stereoselection have been sparse, and generally anecdotal. An interesting example is shown in Scheme 5.[40] Here treatment of ketone **(17)** with **(2)** gave an approximately 78:22 preference for **(18)**; addition of zinc chloride or magnesium chloride reversed the sense of the diastereoselection (with ratios of **(18)**:**(19)** ranging from 23:77 to 10:90). The authors propose cyclic intermediates with significant bond formation between nitrogen and sulfur in the uncatalyzed reaction. The selectivity was thus explained by the preferential decomposition of the betaine containing an *exo*-methyl group. The Lewis acids were postulated to disrupt the cyclic structures.

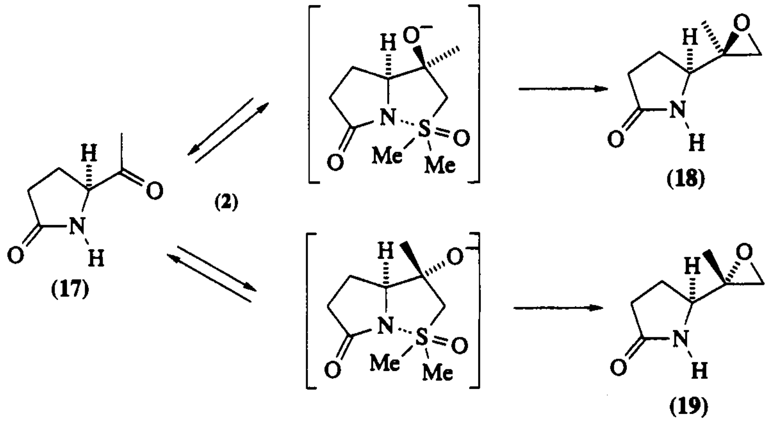

**Scheme 5**

Other examples of stereoselective additions of sulfoxonium methylide **(2)** to chiral aldehydes are shown in equations (8),[41,42] (9)[43] and (10).[44a] At present, no one model is able to account for all of these results. Equations (10a)[44b] and (10b)[44c] show the effect of a nitrogen protecting group on the stereoselectivity of addition of unstabilized ylide **(1)** to α-amino acid derived aldehydes. The major products of epoxidation of *N*,*N*-dibenzylamino aldehydes result from nonchelation-controlled attack of the nucleophile.

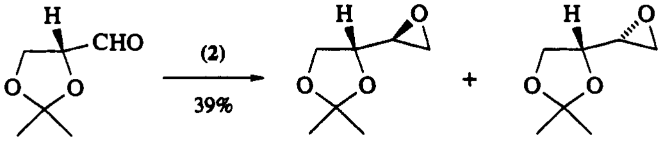

**(20)** **(21)** 68% 32%

(8)

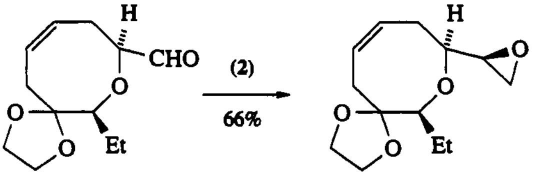

(9)

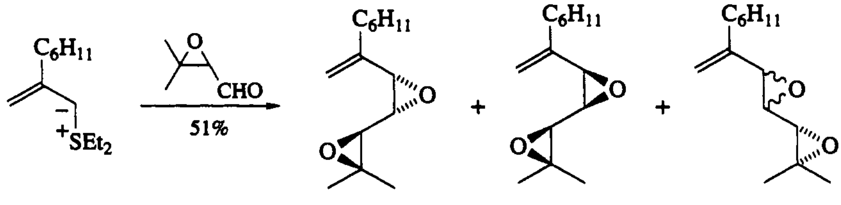

49% 8% 43%

(10)

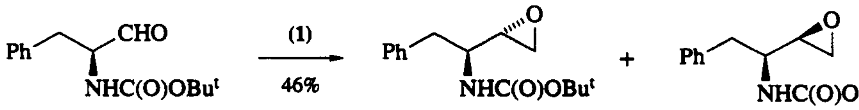

50% 50%

(10a)

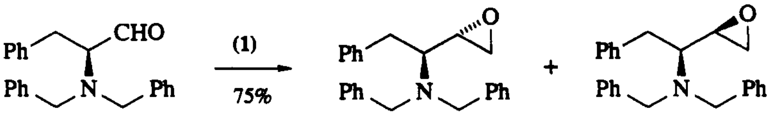

86% 14%

(10b)

In a synthetic effort directed toward a segment of erythronolide A, the addition of (**2**) to aldehyde (**22**) gave, after treatment with MeMgBr/CuI, an approximately 80:20 mixture of ring-opened products (**23**) and (**24**; equation 11).[45] Interestingly, direct alkylation of this aldehyde (as a mixture of double bond isomers) with ethyllithium gave an 18:82 mixture of adducts. The factors responsible for the complementary face selectivity shown by (**2**) *versus* ethyllithium are unclear. Comparisons are particularly difficult due to the fact that most organolithium additions to carbonyl compounds are irreversible, kinetically controlled processes, whereas reactions of (**2**) can be reversible.

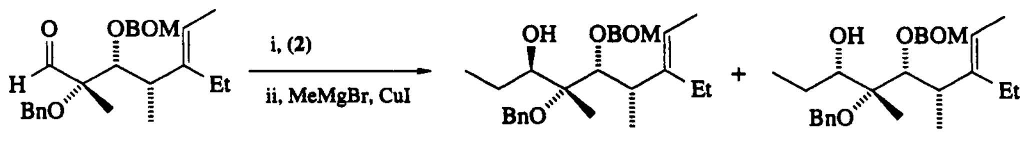

**(22)** BOM = $CH_2OBn$ **(23)** **(24)**

(11)

Reactions with substituted ylides give rise to questions of relative stereochemistry in the product epoxides. (*E*)/(*Z*)-Selectivity is usually low in the absence of other stereochemical control elements.[35] An exception is diphenylsulfonium benzylide, which reacts stereoselectively with aldehydes to give *trans*-stilbene oxides (*e.g.* see equations 1 and 3). Another example of modest stereocontrol in a cyclic example is shown in equation (12).[46] Arsenic ylides are generally more stereoselective.

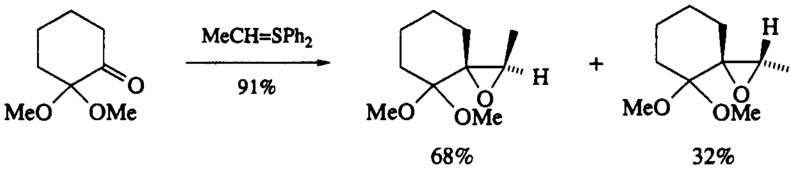

(12)

Another stereochemical feature of potential utility arises from the basic nature of many ylide generation conditions, in which enolizable ketones may undergo epimerization faster than epoxidation.[19] This means that a stereochemically heterogeneous ketone can undergo equilibration prior to reaction. A recent example is shown in equation (13).[47]

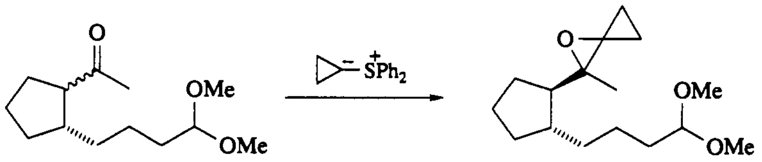

(13)

The few published attempts at the asymmetric epoxidation of carbonyl compounds with chiral sulfur ylides have been reviewed.[48] Thus far, such processes have not been very useful synthetically. For example, reaction of benzaldehyde with an optically pure sulfoximine ylide only afforded an epoxide in 20% enantiomeric excess.[49] More recently, chiral sulfur methylides have provided *trans*-stilbene oxides in up to 83% *ee*.[50] An example of optical induction observed in reactions taking place with a chiral phase transfer reagent was reported,[51] but later disputed.[24]

### 3.2.2.3 Other Ylides

A number of elements form ylides which are analogous to the sulfur-based reagents discussed above, and these reagents display chemistry which is very similar to that obtained with the sulfur compounds. The following discussion will emphasize processes which appear to offer real advantages to better-known techniques.

Arsonium ylides were discovered near the turn of the century, but their reactions with carbonyl compounds did not become elucidated until the 1960s.[8,52] In a broad sense, arsonium ylides are midway in chemical behavior between ylides of phosphorus and those of sulfur. Stabilized arsonium ylides react with carbonyl compounds to afford alkenes, whereas the unstabilized analogs give rise to epoxides. More subtly, the nature of the substituents on either the ylide arsenic or carbon atom can alter the course of the reaction; the choice of solvent can exert a similar effect.[53]

The synthesis of the arsonium ylides most commonly involves deprotonation of arsonium salts utilizing a variety of bases. Simple arsonium salts are available *via* direct alkylation of triphenylarsine, but more highly substituted compounds require specialized methods. These include the use of highly electrophilic triflate salts, alkylation of triphenylarsonium methylide, and double alkylation of lithiodiphenylarsine. For some purposes, formation of the tetrafluoroborate salts is desirable and can be effected in good yield by cation exchange.[54]

The reactions of substituted arsonium ylides with carbonyl compounds can be carried out with high stereoselectivity in favor of *trans*-disubstituted epoxides (equation 14).[54] Equatorial attack is observed for addition to 4-*t*-butylcyclohexanone. Good stereoselectivity ($\geq$9:1) was observed for the addition of triphenylarsonium methylide to some (*N,N*-dibenzyl)amino aldehydes at −78 °C in THF.[44c] Interestingly, the initial hydroxy tetraalkylarsonium adducts were isolated under these conditions, and had to be cyclized under the action of sodium hydride in a separate step.

Another arsonium ylide reaction involves a notable 'transylidation' reaction between a phosphorus and an arsenic ylide (Scheme 6).[55] A useful arsenic ylide which provides a hydroxymethyl epoxide has been reported (equation 15); note the use of biphasic reaction conditions for ylide generation.

Selenium and tellurium ylides take part in chemistry which is analogous to the reactions discussed thus far, and the subject has been well reviewed.[56,57] Both alkenes and epoxides are formed in their reactions,

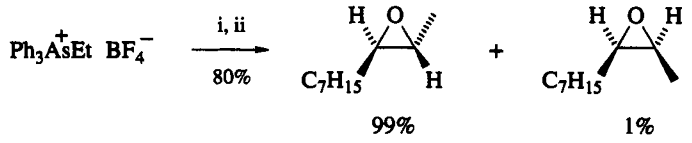
$Ph_3\overset{+}{As}Et\ BF_4^-$
i, ii
80%
H
O
H
$C_7H_{15}$
H
+
H
O
H
$C_7H_{15}$
99%
1%

(14)

i, $KN(SiMe_3)_2$, THF/HMPA, 40 °C; ii, $Me(CH_2)_6CHO$

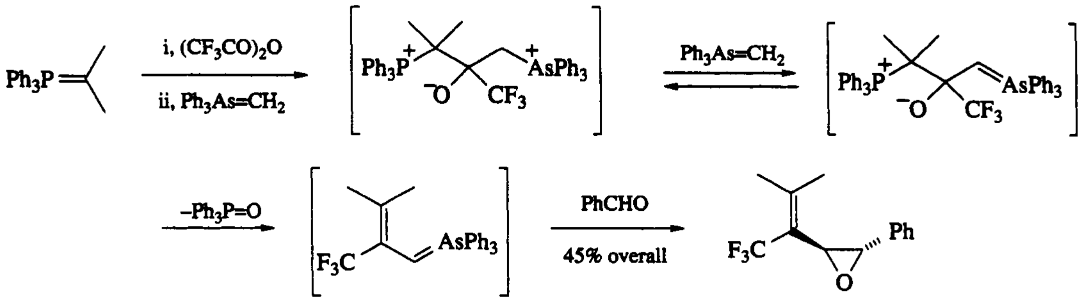
$Ph_3P$
i, $(CF_3CO)_2O$
ii, $Ph_3As{=}CH_2$
$Ph_3\overset{+}{P}$
$\overset{+}{As}Ph_3$
$^-O$
$CF_3$
$Ph_3As{=}CH_2$
$Ph_3\overset{+}{P}$
$AsPh_3$
$^-O$
$CF_3$
$-Ph_3P{=}O$
$F_3C$
$AsPh_3$
PhCHO
45% overall
$F_3C$
Ph
O

**Scheme 6**

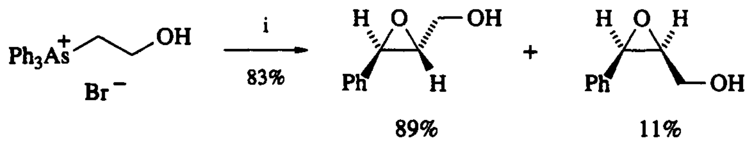
$Ph_3\overset{+}{As}$
OH
$Br^-$
i
83%
H
O
OH
Ph
H
+
H
O
H
Ph
OH
89%
11%

(15)

i, PhCHO, KOH (solid), THF (trace water)

as with the arsonium ylides above. The stereoselectivities obtained using these ylides are generally less satisfactory than those observed in the arsenic counterparts.

### 3.2.2.4 Addition of Anionic Species

Strategies employing α-heterosubstituted organometallic reagents often provide useful alternatives to ylide chemistry for methylene transfer.[58] The carbonyl compound is treated with a heteroatom-stabilized organometallic reagent, which gives rise to an isolable β-hydroxy adduct. These are transformed into the desired epoxide either: (a) spontaneously; (b) under the action of base; or (c) following an intermediate activation step in which X is converted into a better leaving group.

A powerful class of epoxidation reagents in this category are the anions derived from *N*-*p*-tolylsulfonylsulfoximines[10,11] (equation 16).[59] These reagents form epoxides directly upon addition to carbonyl compounds and are available in a number of alkyl substitution patterns. Their chemistry is similar to that of dimethyloxosulfonium methylide, to which they often provide a practical alternative due to their greater nucleophilicity.

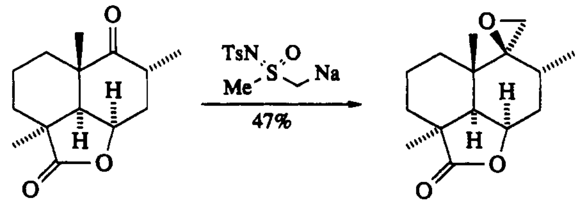
O
H
H
O
O
TsN
O
Me
S
Na
47%
O
H
H
O
O

(16)

Deprotonation of thioanisole and addition of a carbonyl compound affords an isolable hydroxy sulfide which can then be alkylated (Scheme 7).[60] Treatment with base generates the same betaine that would have been formed using the sulfur ylide approach, and effects the intramolecular displacement reaction. The addition of methylthiomethyllithium to 2-cyclohexenone exclusively provides the 1,2-addition product;[61] the dianions derived from phenylmethanethiol[62] or allylthiol[63] react in a similar manner. In one case a 6-keto steroidal substrate was found to undergo smooth methylenation using this procedure, whereas attempted epoxidation using either ylide (**1**) or (**2**) exclusively gave rearrangement products such as (**25**; equation 17).

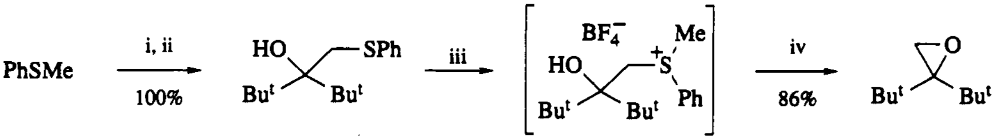

i, Bu$^n$Li, DABCO; ii, Bu$^t_2$C=O; iii, [$Me_3O$]$BF_4$ ; iv, $CH_2Cl_2$, 0.5M NaOH

Scheme 7

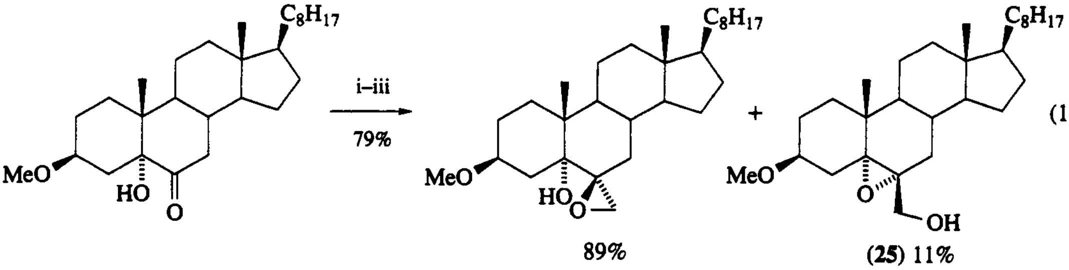

(17)

i, $PhSCH_2Li$; ii, [$Me_3O$]$BF_4$ ; iii, aq. NaOH

The lithiation of ethyl allyl sulfide followed by transmetallation with titanium isopropoxide engenders an allyltitanium reagent formulated as (**26**; Scheme 8).[64a] This and related reagents add to aldehydes or ketones to afford hydroxy sulfides, which are converted to epoxides as shown. The power of this method for the stereoselective generation of even trisubstituted epoxides is evident from Scheme 8 and equation (18). Reagent (**26a**), prepared as shown in Scheme 8a, undergoes addition to ketone (**26b**) to afford product exclusively resulting from chelation-controlled diastereofacial addition (as a mixture of epimers at the position shown).[64b]

Early efforts to synthesize optically active epoxides using chiral α-lithio sulfoxide anions or chiral complexes of α-lithio sulfides have been reviewed.[65] These approaches usually yield epoxides of low optical purity. More successful, if indirect, approaches are outlined in Section 3.2.2.7.

Chloromethyl phenyl sulfone and related compounds can undergo deprotonation and addition to ketones under a variety of conditions.[66,67] These procedures appear most prominently as part of one-

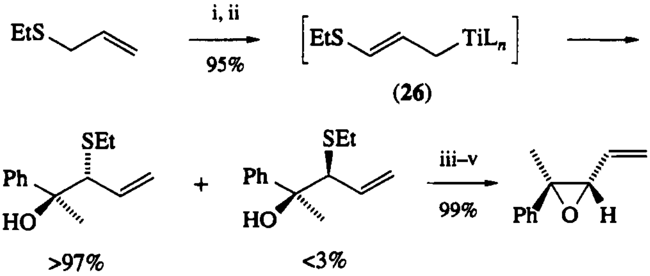

i, Bu$^t$Li, Ti(OPr$^i$)$_4$; ii, PhC(O)Me; iii, separate; iv, [$Me_3O$]$BF_4$ ; v, NaOH

Scheme 8

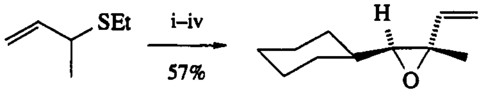

(18)

i, Bu$^t$Li, Ti(OPr$^i$)$_4$; ii, $C_6H_{11}CHO$; iii, [$Me_3O$]$BF_4$ ; iv, Bu$^n$Li, –78 °C

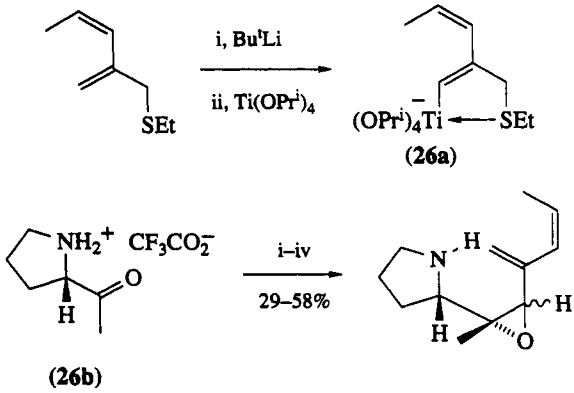

i, (**26a**); ii, $(CF_3CO)_2O$; iii, $[Me_3O]BF_4$ ; iv, NaOH

**Scheme 8a**

carbon homologation procedures; alternatively, the sulfur substituent can be removed by treatment with *n*-butyllithium at low temperature (Scheme 9).[68] This reaction has recently been featured in a stereoselective approach to a functionalized steroid side chain.[69] Attempts to extend this reaction to asymmetric epoxide synthesis using chiral phase transfer catalysis[70] or a chirally substituted sulfone[71] have been reported.

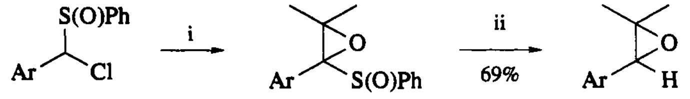

Ar = *p*-$MeOC_6H_4$

i, NaOH, MeCN, acetone; ii, Bu$^n$Li, –100 °C

**Scheme 9**

Procedures which utilize selenides are similar, but α-lithio selenides are not generally preparable *via* simple deprotonation chemistry, due to facile selenium–lithium exchange.[56–58,72,73] Selenium-stabilized anions are available, however, by transmetallation reactions of selenium acetals and add readily to carbonyl compounds. The use of branched selenium-stabilized anions has been shown to result exclusively in 1,2-addition to unhindered cyclohexenones, in contrast to the analogous sulfur ylides. The resulting β-hydroxy selenides undergo elimination by treatment with base after activation by alkylation[58,73] or oxidation[74,75] (Scheme 10). An alternative method of activating either β-hydroxy selenides or sulfides toward elimination involves treatment of a chloroform solution of the adduct with thallium ethoxide (Scheme 11).[76] A mechanism involving the intermediacy of a selenium ylide is proposed.

Although much less is known about the chemistry of selenones, these compounds can be converted into epoxides upon reaction with carbonyl compounds in a single-step procedure, which succeeds due to the greater leaving group ability of the benzeneselenonyl anion.[77] A series of cyclopropylselenonyl anions have been prepared and they afford oxaspiropentanes in excellent yields.[78]

α-Chloro-substituted silicon[79] and germanium[80] anions also afford substituted epoxides upon treatment with base and carbonyl compounds. The reactions give disubstituted epoxides with modest levels of *trans* selectivity (equation 19). These reagents undergo addition to chiral aldehydes and ketones with face selectivities analogous to the sulfur ylides described earlier.[79] The resulting silicon-substituted epoxides are useful precursors for chain elongation and ring expansion processes, and can be stereospecifically converted to silyl enol ethers.[81]

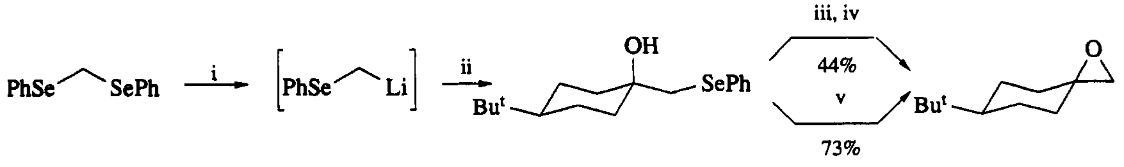

i, Bu$^n$Li; ii, 4-*t*-butylcyclohexanone; iii, MeI; iv, base; v, MCPBA

**Scheme 10**

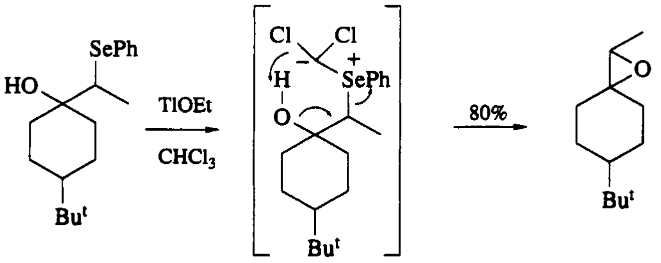
SePh
HO
Bu$^t$
TlOEt
CHCl$_3$
Cl
Cl
H
SePh
O
Bu$^t$
80%
O
Bu$^t$

**Scheme 11**

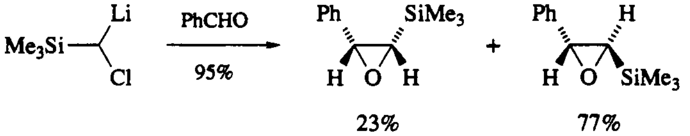
Li
Me$_3$Si
Cl
PhCHO
95%
Ph
SiMe$_3$
H
O
H
23%
Ph
H
H
O
SiMe$_3$
77%

(19)

The additions of metallated 2-allyloxybenzimidazoles to carbonyl compounds are tunable according to the nature of the transition metal counterion. The parent allyl ethers can be deprotonated by *n*-butyllithium and converted to the corresponding allyl-cadmium[82] or -aluminate[83] species by transmetallation (Scheme 12). The authors speculate that the allylcadmium reagent exists primarily in the (*Z*)-configuration, whereas the allylaluminum species is mostly (*E*). Each is presumed to react through a boat-like transition state to yield *erythro* or *threo* adducts, respectively, along with varying amounts of γ-attack. Ring closure with sodium hydride completes the sequence. Addition of the allylcadmium reagent to a chiral aldehyde predominantly afforded the Cram–Felkin isomer.[84]

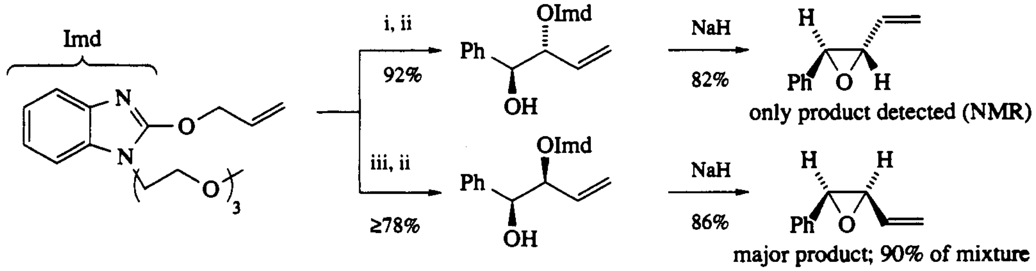
Imd
N
O
N
O
3
i, ii
92%
iii, ii
≥78%
OImd
Ph
OH
OImd
Ph
OH
NaH
82%
NaH
86%
H
Ph
O
H
only product detected (NMR)
H
H
Ph
O
major product; 90% of mixture

i, Bu$^n$Li, CdI$_2$; ii, PhCHO; iii, Bu$^n$Li, Et$_3$Al

**Scheme 12**

Other α-alkoxylithium carbanions have been generated by tin–lithium exchange at low temperature,[85] by metallation of (alkoxymethyl)trimethylsilane,[86] or by using samarium iodide.[87] These reagents do not directly form epoxides due to the poor nucleofugicity of alkoxide anion. However, the resultant protected diols can be considered as particularly robust precursors to epoxides when deprotected and manipulated in any number of standard ways. A notable example of this strategy is shown in Scheme 13.[88]

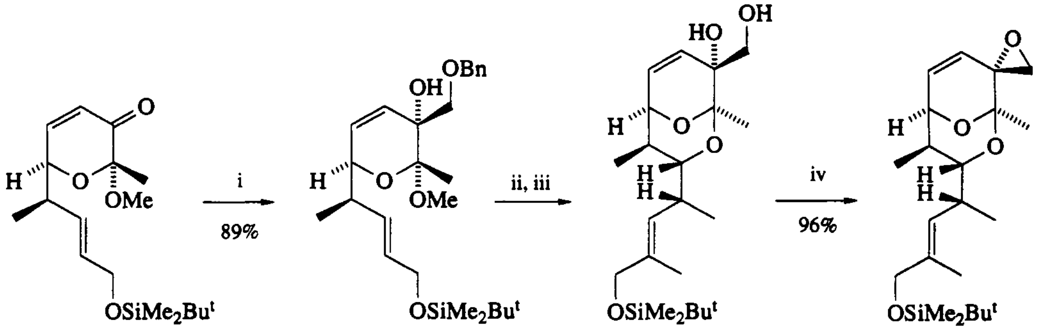
O
H
O
OMe
OSiMe$_2$Bu$^t$
i
89%
OBn
OH
H
O
OMe
OSiMe$_2$Bu$^t$
ii, iii
OH
HO
H
O
O
H
H
OSiMe$_2$Bu$^t$
iv
96%
O
H
O
O
H
H
OSiMe$_2$Bu$^t$

i, BnOCH$_2$Li; ii, 9 steps; iii, debenzylation; iv, (tolylsulfonyl)imidazole, NaH

**Scheme 13**

### 3.2.2.5 Halogen-stabilized Carbenoids

Another important group of stabilized anions which have a built-in leaving group suitable for epoxide formation are carbenoids (Köbrich reagents). These reagents are both highly reactive and thermally unstable. Several reviews on the varied chemistry of these reagents are available.[89,90]

The mechanistic outline of carbenoid/carbonyl reactivity follows the paradigm illustrated at the outset of this chapter (Scheme 1; X = halogen). The nucleophilic lithium species adds to the carbonyl compound and suffers elimination to provide the epoxide. Competition from molecular rearrangements emanating from the intermediate halohydrin or the product epoxides is sometimes a problem, particularly with cyclic ketones. Also, the initial adduct frequently fails to cyclize when the reaction is quenched at low temperature, but it is usually a simple matter to effect ring closure by treatment of the halohydrin with mild base in a separate step.

Lithium halocarbenoids are generated by either direct metallation (deprotonation), or lithium–halide exchange. Early efforts to use the former route were limited to vinyl halides or carbenoids bearing at least two chlorine atoms. Lithium–halide exchange has the advantages of offering a greater variety of structural types, and more importantly, often occurring even at ≤–100 °C. In the case of especially unstable carbenoids, such as those bearing additional alkyl substitution, those having a single chlorine atom, or when X = Br or I, this method of generation is crucial.

Solvent plays an important role in these reactions. A highly basic solvent, usually THF, is used to provide stabilization of the lithium halocarbenoid, due to coordination which disrupts the internal Li–Br interaction which would otherwise lead to α-elimination (equation 20).[91] The extreme low temperature of many of the reactions requires special solvent systems, commonly a mixture of THF, diethyl ether, and petroleum ether or pentane in a ratio of 4:1:1 (Trapp mixture). Solvent has also been noted to alter the mechanistic course of the reaction; for example, reaction of ketones with lithiobromomethane in hexane was observed to give rise to alkenes rather than epoxides.[92]

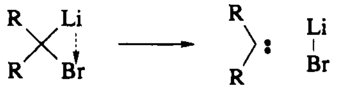

(20)

Contemporary work on the development of *in situ* methods for the generation of the classical carbenoid species or providing additional stabilization by other transition metals has permitted the more convenient use of these reagents. A chief advance involved the generation of the lithiohalocarbenoid by exchange with *n*-butyllithium, lithium metal, or lithium amalgam in the presence of the carbonyl partner at –78 °C.[90,92] Simple methylene transfer or epoxidations involving more highly substituted epoxides can be effected under these conditions. For example, the use of chloroiodomethane as the carbenoid precursor affords epoxides in very high yield (equation 21).[93,94] Epoxidations involving more highly substituted epoxides can also be effected under these conditions.[90]

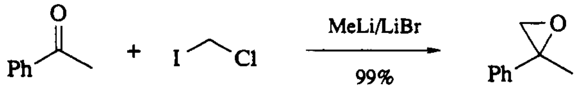

(21)

A later modification of the original Köbrich procedure entails the generation of carbenoids in the presence of an added equivalent of lithium bromide salt (equation 22).[91] Apparently, the Lewis acid character of the added salt helps to stabilize the carbenoid by coordination with the halogen atom. The lithium salt is also implicated in Lewis acid complexation to the oxygen atom of the C═O bond, and seems to assist in the cyclization step as well.

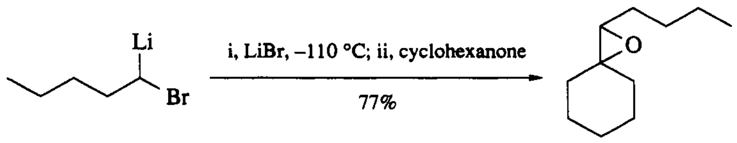

(22)

Lithium–bromine exchange of bromochloromethane can be accomplished using sonication at temperatures as high as –15 °C.[95] The apparent generation of a dichloromethyl anion was effected at room temperature using phase transfer catalysis (equation 23).[96] A practical route involving the selective deprotonation of several dihaloalkane solutions containing a ketone or aldehyde substrate using hindered lithium amide bases has been reported (equation 24).[97] Fluoride catalysis liberates a 'naked' carbenoid anion from a TMS-containing precursor, which adds in good yields to a variety of aldehydes at 0 °C to room temperature.[98] Addition to 2-phenylpropanal predominantly afforded the isomer predicted by Cram's rule (equation 25). Similar results were obtained by generating (presumably) the same anion under electrochemical conditions.[99]

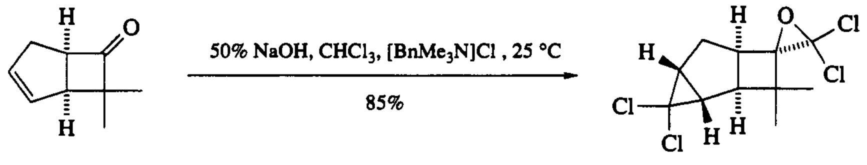
50% NaOH, CHCl3, [BnMe3N]Cl, 25 °C
85%
H
O
H
Cl
Cl
Cl
H
Cl
H
H

(23)

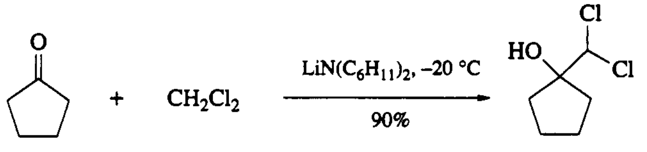
O
+
CH2Cl2
LiN(C6H11)2, -20 °C
90%
HO
Cl
Cl

(24)

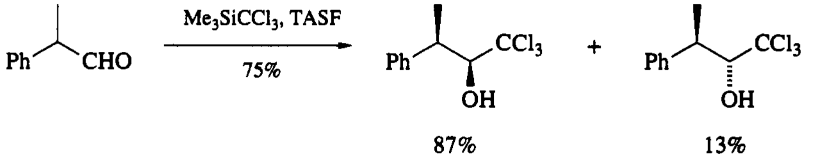
Ph
CHO
Me3SiCCl3, TASF
75%
CCl3
OH
+
87%
13%

(25)

A number of methods to increase the thermal stability of Köbrich reagents have centered around replacement of the lithium counterion normally present with a variety of transition metals, chiefly titanium, hafnium and copper.[100] For example, the reagent derived from transmetallation of lithium dichloromethane with titanium isopropoxide could be reacted with various ketones and aldehydes to afford halohydrin adducts in good yields at temperatures as high as 0 °C. Competition experiments established the chemoselectivity of this reagent (Scheme 14). The direct activation of several allylic halides has been accomplished with tin[101] and chromium[102] reagents (equation 26). Transmetallation of an alkyllead precursor has also been noted.[103]

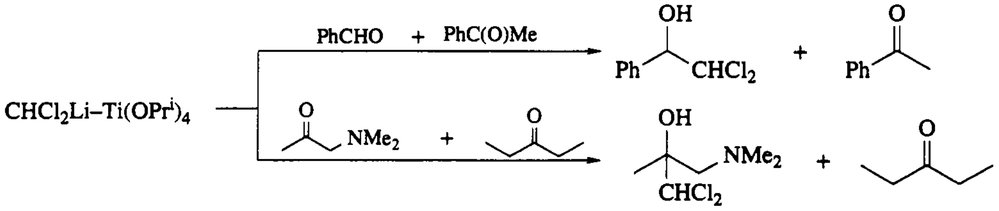
CHCl2Li–Ti(OPri)4
PhCHO + PhC(O)Me
OH
Ph
CHCl2
+
O
Ph
O
NMe2
+
O
OH
NMe2
CHCl2
+
O

**Scheme 14**

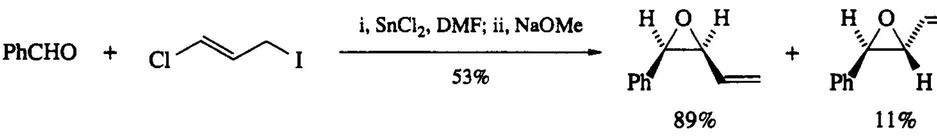
PhCHO
+
Cl
I
i, SnCl2, DMF; ii, NaOMe
53%
H O H
Ph
+
H O
Ph H
89%
11%

(26)

Activation of dibromo- and diiodo-methanes can also be effected using samarium powder, which generates $SmI_2$ *in situ*. This procedure allows the isolation of the formal adduct of iodomethane to ketones and aldehydes at room temperature with very short reaction times.[104,105] The iodohydrin so isolated can, of course, be readily converted to the corresponding epoxide. The reaction is thought to occur by a radical chain process. The stereoselectivity of the reaction was briefly investigated (equations 27 and 28).

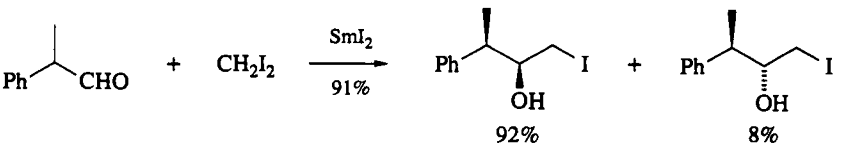
Ph
CHO
+
CH2I2
SmI2
91%
Ph
I
OH
+
92%
8%

(27)

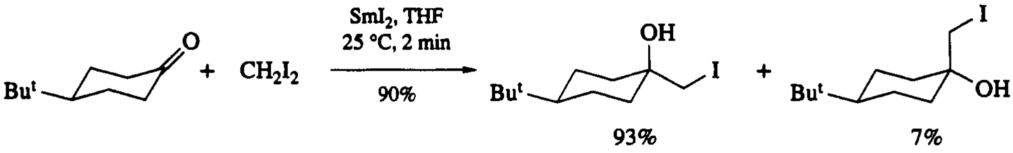

(28)

There are few reports which deal with questions of chemo- and stereo-selectivity of Köbrich reagents. Lithiobromomethane reacted preferentially with a saturated ketone in the presence of an α,β-unsaturated ketone in a steroidal substrate, although the reaction was not stereoselective.[92] However, addition of a related reagent to an acyclic chiral ketone was reported to occur with complete diastereoselectivity (equation 29).[106]

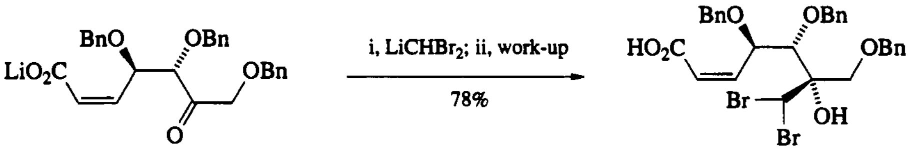

(29)

Chemically distinct halogen atoms can undergo selective exchange in substrates containing a Lewis base site capable of internal coordination.[107] A provocative example involves an exchange reaction which occurs with diastereotopic group selectivity (Scheme 15).[108]

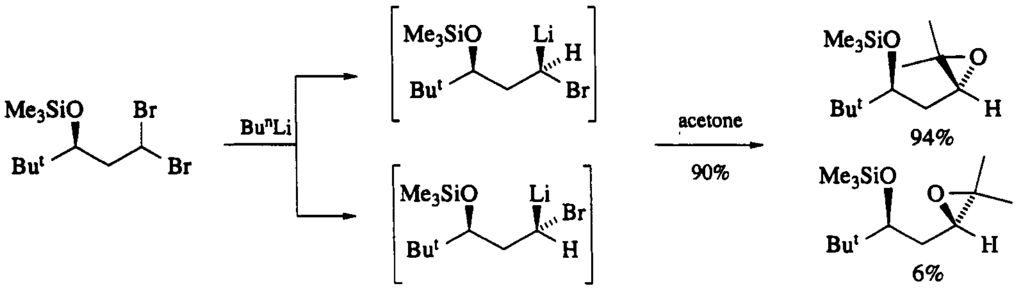

Scheme 15

### 3.2.2.6 Diazoalkane Reactions

Although historically important, the epoxidation of ketones and aldehydes using diazoalkanes is of less contemporary interest as a synthetic tool. This is due to the much greater propensity of the adducts resulting from addition of the diazo compound to the carbonyl group to react along other pathways. Products arising from chain elongation and ring expansion tend to predominate in these reactions, particularly with cyclic ketones. The interested reader is directed to several good reviews on the subject,[109,110] an older but still useful *Organic Reactions* chapter,[111] and a review dedicated to diazomethane chemistry.[112]

The mechanism for the addition of diazoalkanes to a C=O double bond is generally written along lines similar to those discussed so far (Scheme 1; $X^n = N_2^+$). The initial adduct is also the progenitor of the various rearrangement pathways. However, the subject of mechanism is by no means settled, with 1,3-dipolar cycloadditions[109] and carbonyl ylide formation[113] considered to be prominent alternatives. In general, successful epoxidation of carbonyl compounds improves with increasing electron-poor character of the C=O bond. When the diazoalkane is electron poor, yields of epoxide diminish.

An epoxidation reaction utilizing a complex diazo compound is shown in equation (30).[114] The addition of diazomethane to highly electron-deficient esters has been reported to yield 2-alkoxy-2-substituted epoxides (equation 31).[115] The stereoselectivity of the addition of diazomethane to pentulose derivative (**20**) was shown to be superior to that obtained using sulfur ylides, giving ratios of 95:5 in favor of (**21**; equation 8). However, the yields were unstated, and the products were accompanied in most cases by significant amounts of homologous ketone.[41]

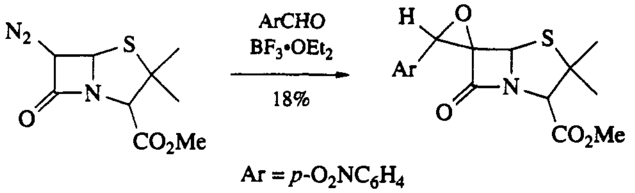

(30)

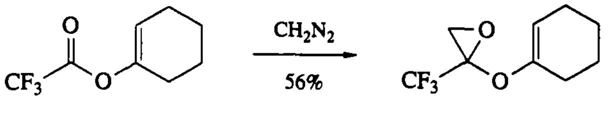

(31)

### 3.2.2.7 Additions to C═O π-Compounds Bearing Adjacent Leaving Groups

Although the bulk of this section is concerned with the formal addition of a single atom across both ends of a C═O double bond, halohydrins also result from the addition of a nucleophile ($H^-$ or $R^-$) to carbonyl compounds bearing an adjacent leaving group or its equivalent (path b, Scheme 1). The use of this approach for epoxide synthesis was pioneered by Cornforth and coworkers as early as 1959.[116] The scope of this process is very wide, so only a few highlights will be covered here.

The most simple example of this reaction type is the reduction of a ketone RC(O)CH$_2$X to afford a monosubstituted epoxide. Recently, several strategies for performing this reaction to give epoxides in optically active form have appeared. The corresponding β-keto sulfoxides are available in optically pure form by the deprotonation of resolved $p$-tolylmethyl sulfoxide and addition to esters (Scheme 16).[117] The adducts can be stereospecifically reduced[118] to afford either diastereomer, depending upon the reaction conditions: DIBAL-H in THF gives a 95:5 mixture of (**27**) and (**28**), whereas carrying out the reaction in the presence of zinc chloride[118,119] reversed the ratio to 5:95. The stereochemistry of the former reduction is rationalized by an *anti* conformation resulting from dipole–dipole repulsions between the S—O and C═O bonds, whereas a chelation-controlled transition state best explains the latter result. Reduction to the corresponding sulfide, alkylation and elimination afforded optically pure styrene oxide in high yield. An even more direct approach utilizes a chiral reducing agent (**29**) (equation 32).[120]

The preparation of disubstituted epoxides is similarly accomplished by the addition of nucleophiles to more highly substituted ketones. Selective reduction of keto sulfides with either L-Selectride or zinc

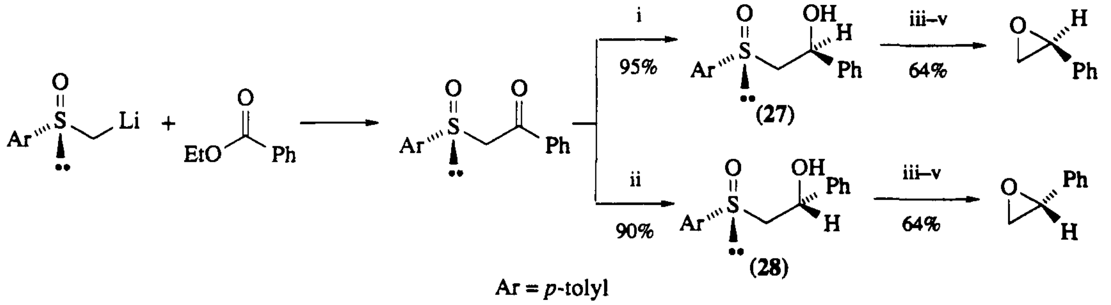

i, DIBAL-H; ii, DIBAL-H, ZnCl$_2$; iii, LiAlH$_4$; iv, [Me$_3$O]BF$_4$ ; v, NaOH

**Scheme 16**

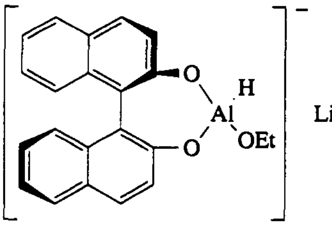

(**29**)

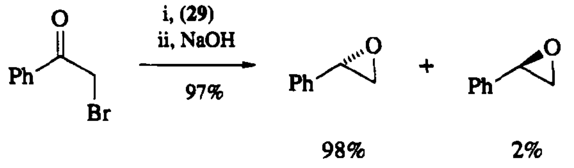

O
Ph
Br
i, (29)
ii, NaOH
97%
Ph
O
+
Ph
O
98%
2%

(32)

borohydride ultimately affords *cis-* or *trans*-epoxides, respectively, as the major products (Scheme 17).[121a] This route was extended to the preparation of optically active epoxides.[121b] The optically active keto sulfides were prepared in 50–85% enantiomeric excess by carrying out an asymmetric sulfenylation reaction on the parent ketones. β-Ketosulfonium salts can also be stereoselectively reduced to give *trans*-epoxides after cyclization.[122]

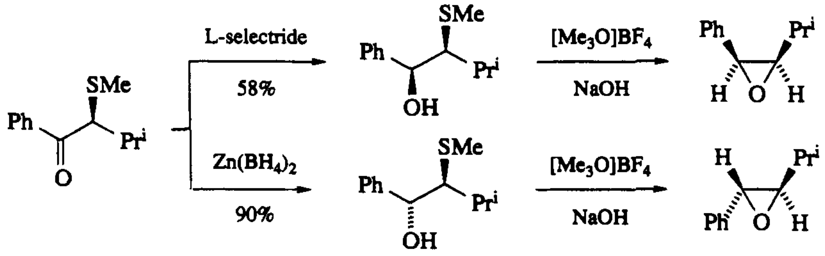

SMe
Ph
Pr^i
O
L-selectride
58%
Zn(BH4)2
90%
SMe
Ph
Pr^i
OH
[Me3O]BF4
NaOH
Ph
Pr^i
H
O
H

Scheme 17

A three-step procedure leads to trisubstituted epoxides from an acid chloride (Scheme 18).[123] A palladium-catalyzed addition of an allyltin reagent to α-chloro ketones was reported to yield trisubstituted epoxides in moderate yield.[124]

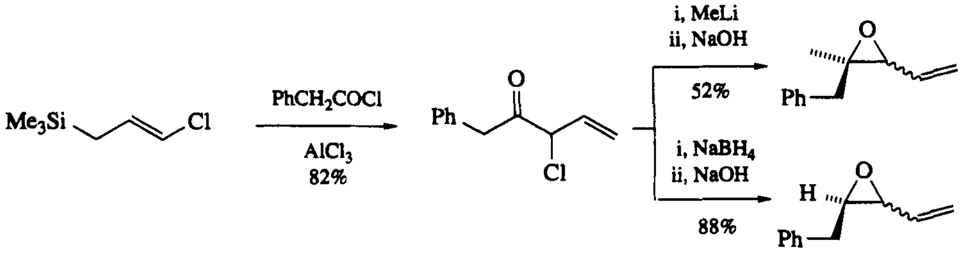

Me3Si
Cl
PhCH2COCl
AlCl3
82%
O
Ph
Cl
i, MeLi
ii, NaOH
52%
i, NaBH4
ii, NaOH
88%
O
Ph
H

Scheme 18

### 3.2.2.8 Other Heterocyclic Syntheses

The formal addition of an oxygen atom across the carbonyl group gives rise to dioxiranes (equation 33). In practice, this reaction is effected with Oxone, and dimethyldioxirane (**30**) and other dioxiranes have been generated in solutions of their parent ketones.[125] Dioxirane (**30**) has been implicated in oxidations of alkenes,[126] sulfides[127] and imines.[128] The formal addition of nitrogen across a carbon–oxygen double bond to afford oxaziridines has been reviewed (equation 34).[129,130] There are also many methods available for the indirect conversion of carbonyl compounds to aziridines[131] and thiiranes[1] using multistep conversions.

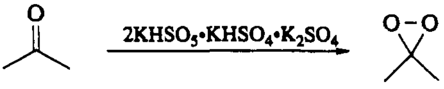

O
$2KHSO_5{\bullet}KHSO_4{\bullet}K_2SO_4$
O–O

(**30**)

(33)

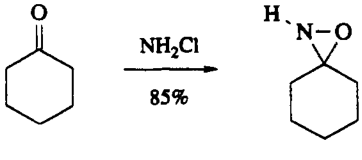

O
NH2Cl
85%
H
N–O

(34)

A number of techniques are available for the one-pot conversions of carbonyl substrates to thiiranes.[1] These entail the addition of a lithiated thiol derivative to the substrate, transfer of either an acyl group or heterocycle to the oxygen atom, and cyclization. A recent example is depicted in Scheme 19.[132]

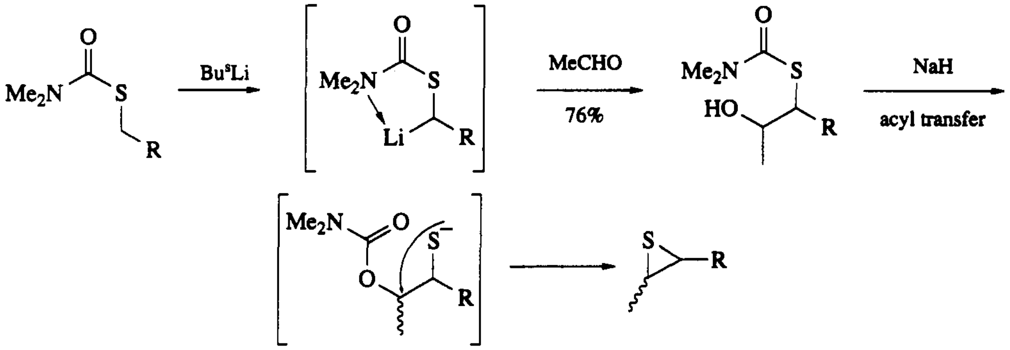

Me2N
O
S
R
BusLi
Li
MeCHO
76%
HO
NaH
acyl transfer

Scheme 19

## 3.2.3 ADDITIONS TO C=N π-BONDS

### 3.2.3.1 Addition of Carbon

The addition of a carbon atom to the C=N double bond has been reported using sulfur (equation 35)[135] and arsenic ylides, halogen-stabilized carbenes, and diazo compounds.[131,133] The best substrates are imines in which the nitrogen is substituted with an aromatic ring, substituted oximes, and hydrazones.

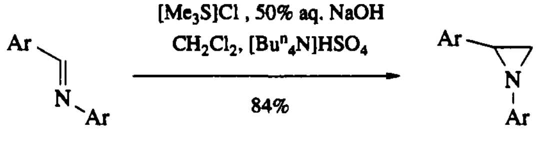

[Me3S]Cl, 50% aq. NaOH
CH2Cl2, [Bun4N]HSO4
84%
Ar
N

(35)

$Ar = m\text{-}MeOC_6H_4$

Reactions of halogen-stabilized carbenoids with imines have been carried out using preformed lithium species (*e.g.* equation 36),[131,134] or *via* a carbenoid generated from diiodomethane utilizing zinc–copper couple (Simmons–Smith conditions).[136] A stereospecific ring closure is observed after the addition of lithiodichloromethane to a benzaldimine (equation 37).[137] The addition of lithiochloro(phenylsulfonyl)methane to aromatic imines affords 2-phenylsulfonyl-substituted aziridines, which can be deprotonated and alkylated in excellent yield (Scheme 20).[138]

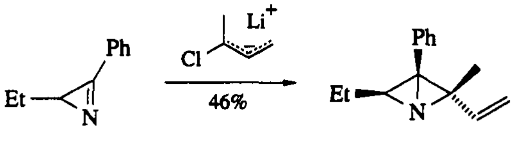

Ph
Et
N
Li+
Cl
46%

(36)

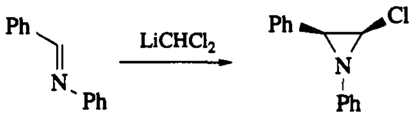

Ph
N
LiCHCl2
Cl

(37)

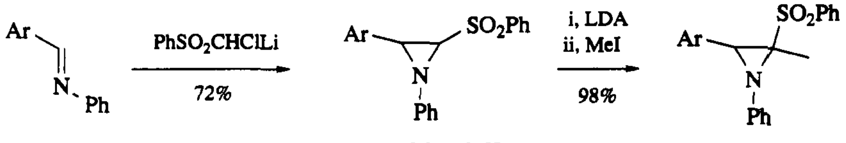

Ar
N
Ph
PhSO2CHClLi
72%
SO2Ph
i, LDA
ii, MeI
98%

$Ar = m\text{-}MeOC_6H_4$

Scheme 20

The anion of (**31**) reacts with *O*-methyl oximes[139] or nitrones[140] to afford *trans* *N*-unsubstituted aziridines in modest yields (*e.g.* equation 38). Nitrones also react with stabilized phosphonate esters (equation 39).[131,141]

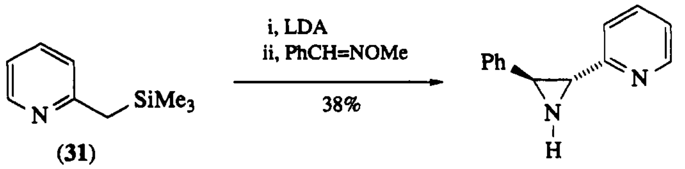
SiMe3
i, LDA
ii, PhCH=NOMe
38%
Ph
N
H

(**31**)

(38)

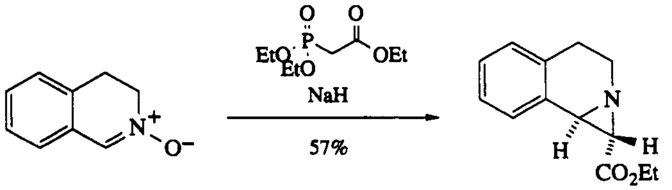
EtO
EtO
P
O
O
OEt
NaH
57%
N+
O−
N
H
H
CO2Et

(39)

The reactions of diazoalkanes and imines occur in generally low yields, but Lewis acid catalysis is of some help (equation 40).[142] The reaction involves a 1,3-dipolar mechanism which proceeds through an isolable triazoline intermediate (Scheme 21). Treatment of the latter with acid affords aziridine in modest yield.

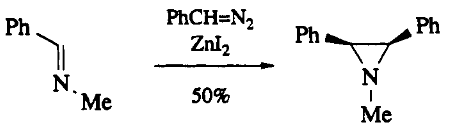
Ph
N
Me
PhCH=N2
ZnI2
50%
Ph
Ph
N
Me

(40)

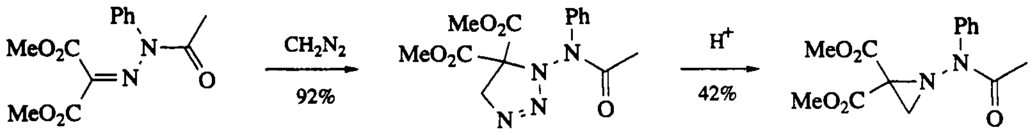
Ph
MeO2C
MeO2C
N
N
O
CH2N2
92%
MeO2C
MeO2C
Ph
N
N
N
N
O
H+
42%
MeO2C
MeO2C
Ph
N
N
O

**Scheme 21**

In contrast, the addition of various diazoalkanes to preformed iminium ions can be a highly efficient process, leading to aziridinium salts, which may undergo further chemistry prior to isolation.[131,143] The intermediacy of a diazonium ion which may react with nearby nucleophilic centers prior to cyclization has been postulated (Scheme 22).[144] This and similar stereoselective reactions have been investigated as potential approaches to morphinoid analgesics.[145,146]

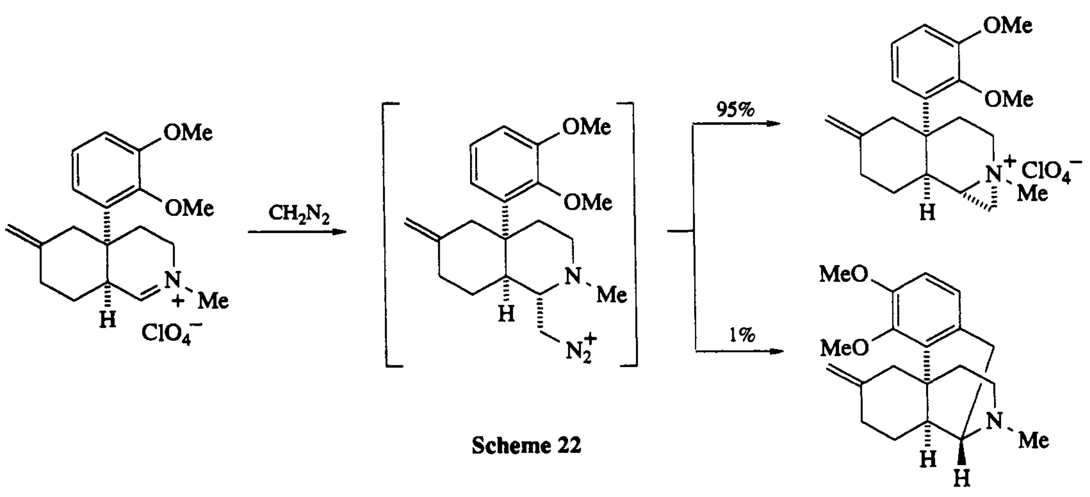
OMe
OMe
N
+ Me
H
ClO4−
CH2N2
OMe
OMe
N
Me
H
N2+
95%
OMe
OMe
N+ ClO4−
Me
H
1%
MeO
MeO
N
Me
H
H

**Scheme 22**

The asymmetric synthesis of aziridines *via* these routes has been sparingly investigated. Aziridines bearing an *N*-alkoxy substituent can be resolved into nitrogen stereoisomers. Modest asymmetric induction was observed in the reaction of a chiral *O*-alkyl oxime with dimethylsulfonium methylide (equation 41).[147] The analogous reaction with diazomethane was not stereospecific. Earlier work in this area has been reviewed.[148]

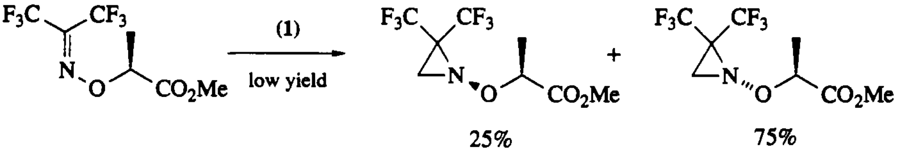

(41)

Synthetic methods which utilize the addition of nucleophiles to α-halo oximes and similar compounds (the Hoch–Campbell reaction) have been reviewed.[131]

### 3.2.3.2 Addition of Oxygen and Nitrogen

The addition of oxygen across the C=N double bond is a common and synthetically useful process.[149] The product oxaziridines are of interest for theoretical reasons (largely due to the high configurational stability of the chiral nitrogen), as reagents (such as oxygen transfer moieties), and as synthetic intermediates.[150] The stereochemical aspects of oxaziridine synthesis and reactivity have been reviewed.[148]

Oxaziridines can be conveniently classified by the substituent on nitrogen. *N*-Alkyloxaziridines and *N*-aryloxaziridines often differ in behavior from those compounds bearing an electron-poor nitrogen substituent, usually an *N*-sulfonyl or *N*-sulfamyl group.

The nitrogen atom in oxaziridines usually constitutes a stable stereogenic center. The nitrogen atoms in *N*-alkyloxaziridines and *N*-aryloxaziridines have barriers to inversion of the order of *ca.* 30–33 kcal mol$^{-1}$ (1 cal = 4.18 J),[148] rendering these compounds configurationally stable at ambient temperature. Alternatively, the various *N*-sulfonyloxaziridines appear to be more readily epimerized, with inversion barriers of *ca.* 19–21 kcal mol$^{-1}$.[151,152] 3-Alkoxyoxaziridines readily epimerize at room temperature, possibly through zwitterionic intermediates.[153]

The most common method for the synthesis of *N*-alkyloxaziridines and *N*-aryloxaziridines from imines is through the oxidation of imines with an organic peroxy acid.[129,154] Two mechanisms for this reaction have been advanced (Scheme 23). The concerted mechanism is exactly analogous to that usually accepted for the oxidation of alkenes with electron-deficient peracids. Unlike the latter conversion, however, the oxidation reaction of imines is not stereospecific. To account for this observation, it is necessary to presume that the imine isomers equilibrate more rapidly than the oxidation occurs, and that the *cis* isomer is more reactive.[155] Neither of these possibilities can be convincingly ruled out. However, an alternative, Baeyer–Villiger type of mechanism seems more likely. Addition of the active oxygen atom to the carbon of the C=N double bond followed by expulsion of the acid by-product gives rise to oxaziridine. Intermediate (32) must be sufficiently long lived to allow nitrogen inversion to occur prior to ring closure. The two-step mechanism has been supported by an *ab initio* molecular orbital study.[156]

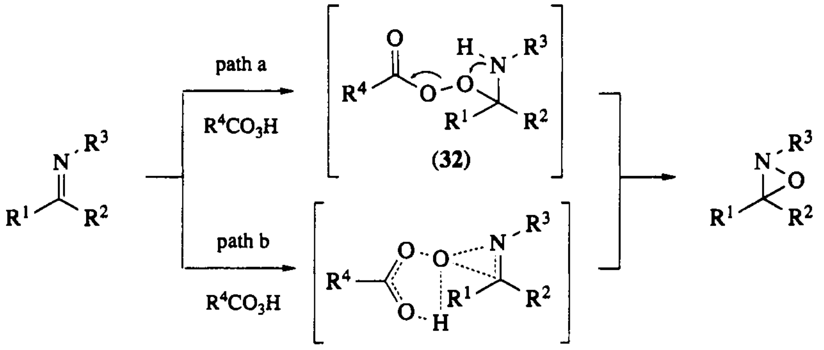

Scheme 23

Methods utilizing MCPBA[157,158] or Oxone[159] in buffered biphasic systems usually suffice for the stereoselective synthesis of *trans*-sulfonyl- and sulfamyl-substituted oxaziridines. The stereoselectivity is rationalized by the greater ability of the *N*-sulfonyl moiety to stabilize a negative charge in the intermediate resulting from addition to the imine carbon atom, allowing more time for bond rotation or nitrogen inversion before the ring closure step.[160]

The oxidation of imines derived from substituted cyclohexanones occurs predominantly from the equatorial direction. However, the product oxaziridines can undergo subsequent equilibration to favor a more stable conformation which places the bulkier nitrogen substituent in an equatorial conformation (Scheme 24).[161] A particularly useful oxaziridine derived from camphor was formed exclusively *via exo* approach of the reagent (equation 42).[162]

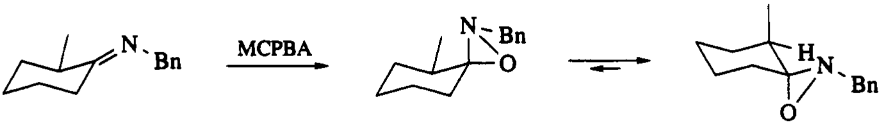

Scheme 24

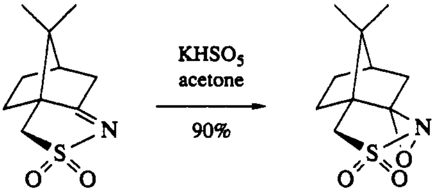

(42)

A chiral substituent on nitrogen can direct the predominant attack of an oxidizing agent to one diastereotopic face of an imine. Ratios as high as 97:3 were observed in a series of imines derived from α-methylbenzylamine (equation 43).[163] The oxidation of achiral imines with optically active peroxy acids, most notably monoperoxycamphoric acid [(+)-MPCA], do afford optically active oxaziridines, but not generally in synthetically useful optical ratios,[148] but ratios as high as 80:20 have been reported.[164]

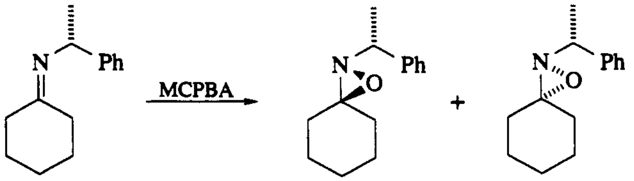

(43)

Reactions involving the use of chiral substrates in conjunction with chiral reagents have been reported. A seminal experiment was the oxidation of both enantiomers of a chiral imine with (+)-MPCA.[148,165] In another example, the cumulative effect of equatorial attack in prochiral cyclohexanones with diastereoselectivity induced by a chiral nitrogen substituent allowed the synthesis of spirocyclic oxaziridines with a high induction of axial disymmetry (Scheme 25).[166,167] The major oxaziridine isomer (**33**) results from both the favored equatorial attack and oxidation *anti* to the chiral nitrogen substituent (as drawn in Scheme 25). The isomers (**34**) and (**35**) result from a combination of one favored and one disfavored process and are minor products, whereas (**36**), which would result from a doubly disfavored trajectory, is not observed. The oxidation of a cyclic imine which involved a synergism between control by the chiral nitrogen substituent and attack from the convex face of the ring system was reported (equation 44).[168] Oxaziridines of the type (**37**) have been utilized in the synthesis of racemic[169,170] and optically active[167,168] indole alkaloids.

Imines and substituted oximes react with several nitrogen-containing nucleophiles to provide a general synthesis of diaziridines or diazirines.[171]

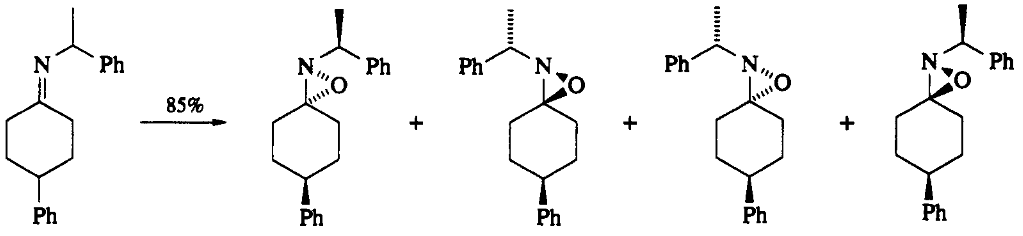

(33) 70% (34) 22% (35) 8% (36) 0%

**Scheme 25**

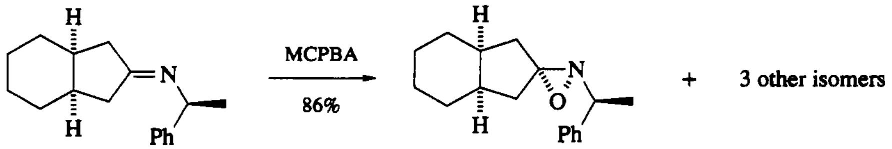

(44)

mixture of C=N isomers (37) 66% 34%

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# 3.3

# Skeletal Reorganizations: Chain Extension and Ring Expansion

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## 3.3.1 INTRODUCTION

The utilization of homologation reactions as a general synthesis strategy may be considered for various reasons, such as a greater accessibility of the lower homolog, the opportunity to introduce additional functionality, or simply the need for a regular series of homologs. The merit of an expansion/extension reaction which may be considered for incorporation into a synthetic plan will, to a large extent, be measured by the efficiency, technical simplicity, and regio- and/or stereo-selectivity of the overall operation. The persistent growth of new methodologies is testimony to the continuing demand for strategies which offer greater selectivity or versatility.

An exhaustive review[1] on the general topic of carbocyclic ring expansions was recorded over twenty years ago, while a number of more specialized reviews,[2a–g] each not necessarily devoted to but incorporating some aspects of homologation reactions, have appeared during the interim. The intention of this chapter is to present a variety of methodologies with illustrative examples, focusing on the processes which achieve an overall homologation with preservation of the original carbonyl group, as illustrated in Scheme 1. This criterium emphasizes rearrangement processes over simple homologation protocols such as the methoxymethylenation/hydrolysis of carbonyl groups, alkylation with acyl anion equivalents, carbonyl group transpositions and so on. Since the orientation is primarily towards synthetic transformations, detailed mechanistic discussions will be held to a minimum, although in-depth analyses may usually be found in the accompanying references. The intention is to cover a variety of methods with sufficient examples to display both the advantages and disadvantages of the process, in the hope that the advantages will be exploited and the disadvantages will be taken as opportunities for improvement.

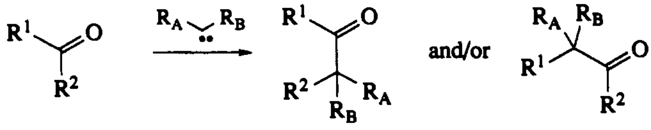

Scheme 1

## 3.3.2 DIAZOALKANES AND RELATED REACTIONS

### 3.3.2.1 Arndt–Eistert Homologation

One of the more commonly applied chain extension reactions for carboxylic acids utilizes the unique reactivity of diazoalkanes. This sequence, generally referred to as the Arndt–Eistert synthesis, is a two-step process which, in the first step, involves the formation of an α-diazo ketone by reaction of the corresponding acyl chloride with an excess of diazoalkane (Scheme 2).[3a–c] In the second stage of the sequence, the α-diazo ketone is induced to undergo rearrangement by photochemical or thermal means or by exposure to metal salts (*e.g.* Ag, Cu), with concomitant loss of nitrogen to produce an intermediate ketene, which reacts *in situ* with water or alcohol to form the homologated acid or ester. This rearrangement of α-diazo ketones, known as the Wolff rearrangement, has been reviewed elsewhere in sufficient depth with regard to mechanism and synthetic utility that no comprehensive treatment will be given here.[4,5a–d]

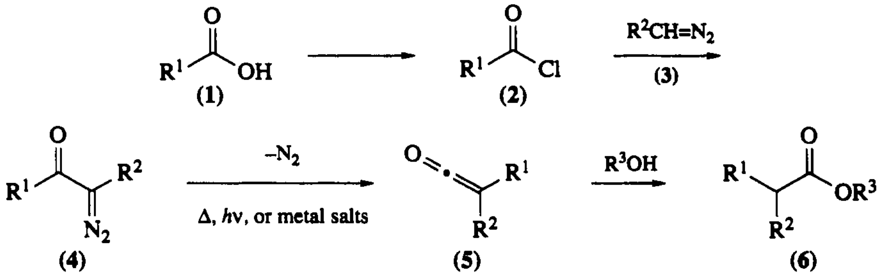

Scheme 2

The Arndt–Eistert synthesis, usually carried out with diazomethane, is fairly general and tolerates a wide range of substituents on both the carboxylic acid and alcohol.[5e] An obvious limitation is the reactivity of other functional groups, such as carboxylic acids or phenols, with diazomethane. The use of the more stable trimethylsilyldiazomethane as a replacement for diazomethane has been reported.[6] While the use of diazoalkanes other than diazomethane is fairly rare, it does offer the opportunity to introduce additional functionality. For example, when sulfonyldiazomethanes (7) are used, the result is an α-sulfonyl carboxylic ester (Scheme 3).[7]

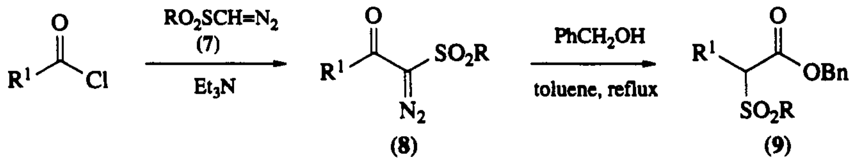

R, R$^1$ = alkyl, aryl

Scheme 3

### 3.3.2.2 Reactions of Aldehydes and Ketones

The reaction of diazomethane derivatives with aldehydes and ketones, though a fairly well-studied field now, continues to be a source of practical extension/homologation technology.[8a–f,9] The general reaction is outlined in Scheme 4. The diazoalkane, shown in resonance forms (11a) and (11b), reacts with the carbonyl carbon to form an intermediary betaine (**12**). Depending on the circumstances, the intermediate may be isolated in the form of the β-hydroxy diazo compound (**13**) or may lose nitrogen to produce an intermediate (**14**), which may then undergo rearrangement with migration of a substituent $R^2$ or $R^1$ to give the homologated compounds (**15**) and (**16**) respectively. Alternatively, simple collapse of (**14**) without migration of a substituent leads to epoxide (**17**). In general, the course of the reaction is influenced by the substituents and by the reaction conditions.

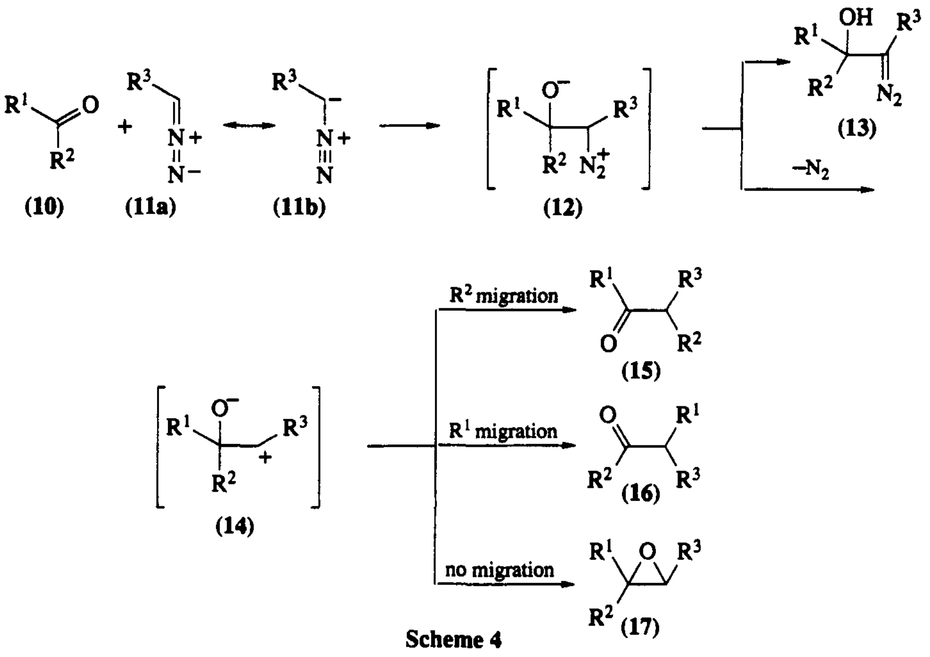

**Scheme 4**

While the reaction of aldehydes with diazomethane is, in general, not a practical method for homologating aldehydes, it illustrates the influence of the relative migratory aptitudes of substituents on the outcome of the reaction. With aliphatic aldehydes, the preferential migration of hydrogen *versus* an alkyl group produces fair to good yields of the methyl ketones (**18**), along with varying amounts of epoxides (Scheme 5). Aromatic aldehydes are more variable, being influenced by substituents and solvent. For example, the addition of methanol or water favors aryl group migration; however, the resulting aldehyde reacts further to produce the homologated methyl ketone (**21**).[10] A compilation of these reactions may be found in refs 8b and 9.

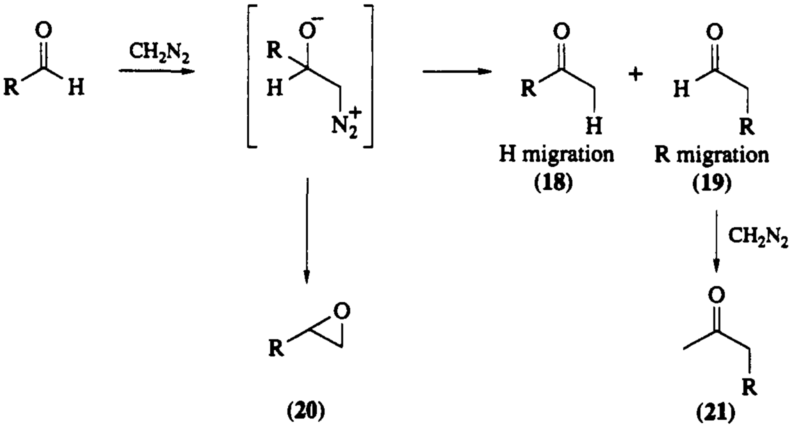

**Scheme 5**

The reaction of diazomethane and its derivatives with ketones has been a rich source of chemistry. The major part of the developmental work with regard to reagents and mechanisms emerged from extensive studies in this area. Relative to aldehydes, aliphatic ketones are much less reactive to diazomethane and yield, in addition to homologation products, substantial amounts of epoxides.[9] The use of Lewis acids to activate the ketone carbonyl has greatly improved the situation, by increasing the rate of reaction and by reducing the degree of epoxide formation. The general trend for the migration of substituents, aryl > methyl ≥ substituted alkyl, may be seen in Scheme 6.[11,12]

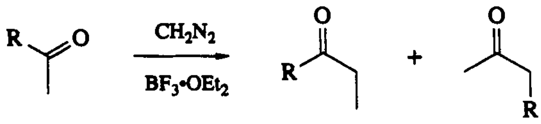

methyl *versus* R migration

| *R* | |
|---|---|
| $Pr^n$ | 50:50 |
| $Pr^i$ | 67:33 |
| $Bu^t$ | 74:26 |
| $PhCH_2$ | 78:22 |
| Ph | 22:78 |
| $CH{=}CMe_2$ | 29:71 |

**Scheme 6**

Similar results were obtained on application of the related Tiffeneau–Demjanov reaction. This semipinacol-type reaction,[13,14] an extension of the Demjanov rearrangement, involves the rearrangement of a diazonium ion (**25**; Scheme 7), which is generated by the diazotization of the corresponding amino alcohol (**24**).[15] The amino alcohol is obtained from the ketone by reduction of a nitromethane adduct (**23a**),[16] cyanohydrin (**23b**) or trimethylsilyl cyanohydrin (**23c**).[17] This procedure allows for a controlled addition–rearrangement sequence in cases where the use of diazomethane is complicated by the further reaction of the product ketone.

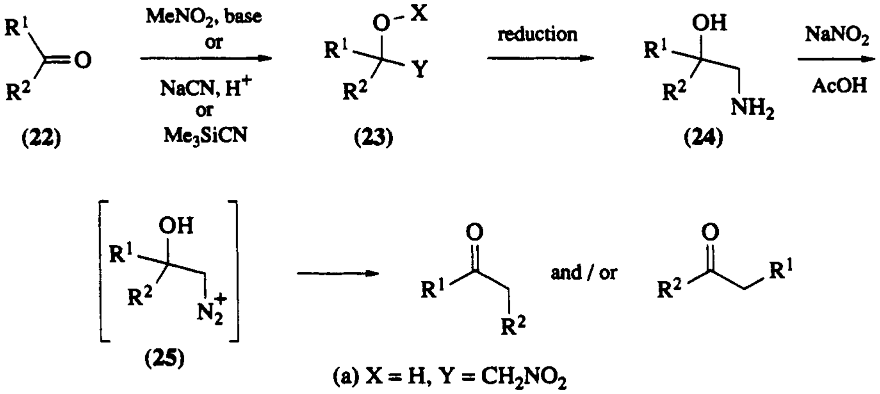

(a) X = H, Y = $CH_2NO_2$
(b) X = H, Y = CN
(c) X = $SiMe_3$, Y = CN

**Scheme 7**

The hydroxide-catalyzed addition of α-acyldiazomethane derivatives, while quite facile with aldehydes to produce stable aldol adducts, is poor with aliphatic ketones.[18a–c] However, the lithium or magnesium anion (**26**) adds smoothly to produce the corresponding aldol adducts (**27**) in good yield (Scheme 8). On treatment with acid,[19a,b] thermolysis[18a] or metal catalysts,[20] these adducts lose nitrogen and rearrange to the β-keto esters (**28**) and (**29**). The analogous reaction with α-diazo ketones has also been carried out; however, with bulkier substituents, the retro-aldol reaction competes with rearrangement.

In a mechanistic study on the Lewis acid catalyzed addition of ethyl diazoacetate to ketones a similar profile of rearrangement to the β-keto esters was observed (Scheme 9).[21] In the same reaction with acetophenones, substitution on the benzene ring was found to only slightly affect the otherwise 90:10 preference for migration of aryl *versus* methyl.[22]

Application of the above series of homologation reactions to cyclic ketones provides a route to ring-expanded products. Due to the constraints of ring systems, the preference for the migration of one bond over the other during these reactions is influenced by an additional set of factors, among which include

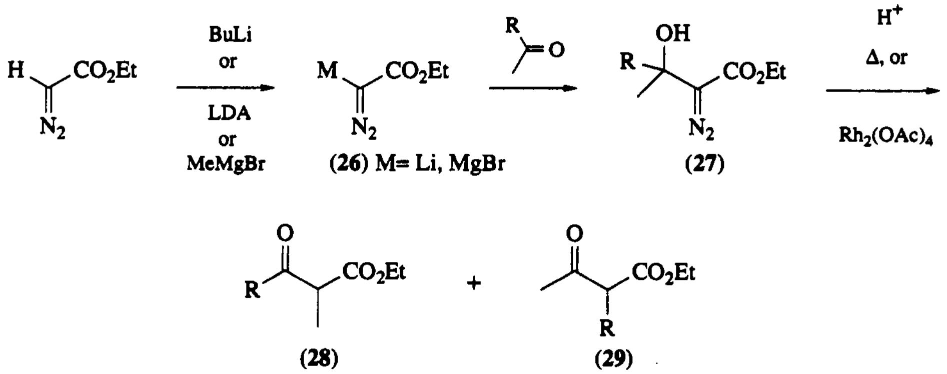
BuLi
or
LDA
or
MeMgBr
(26) M= Li, MgBr
(27)
H⁺
Δ, or
Rh₂(OAc)₄
(28)
(29)

| *R* | *Adduct yield (%)* | *Overall yield (%)* | **(28)**:**(29)** | *Ref.* |
|---|---|---|---|---|
| Me | 93 | 74 | — | 19b |
| Ph | 94 | 72 | 0:100 | 18 |
| Et | 65 | 87 | 55:45 | 20 |
| Bu | 80 | 68 | 55:45 | 20 |
| Bu$^t$ | 76 | 58 | 100:0 | 20 |
| PhCH$_2$ | - | 73 | 38:62 | 20 |
| Ph | 47 | 80 | 8:92 | 20 |

**Scheme 8**

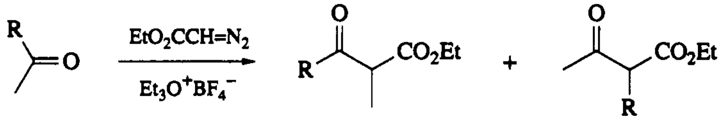
EtO₂CCH=N₂
Et₃O⁺BF₄⁻

| *R* | *Yield (%)* | *Product ratio* |
|---|---|---|
| Me | 78 | - |
| Et | 89 | 50:50 |
| Pr$^i$ | 54 | 66:33 |
| Bu$^t$ | 10 | 95:5 |
| PhCH$_2$ | 96 | 62:38 |
| Ph | 78 | 10:90 |
| CH=CMe$_2$ | 10 | 2:98 |

**Scheme 9**

ring strain, steric effects, stereochemical relationships in the approach of the diazoalkane, and conformational effects in the intermediate betaine (Scheme 10). Earlier work in this area has been reviewed.[9,15,23]

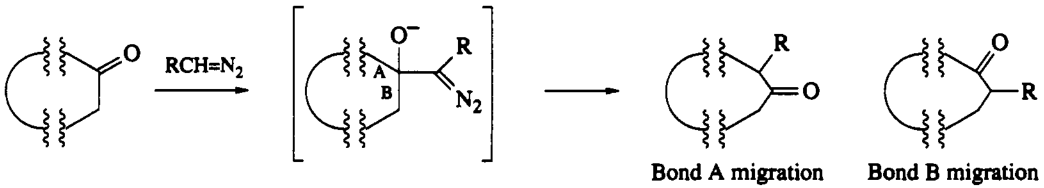
RCH=N₂
Bond A migration
Bond B migration

**Scheme 10**

For monocyclic and many fused bicyclic ketones the general order of reactivity of 3 > 4 > 6 > 7 ≥ 5 has been observed in the reaction with diazomethane and derivatives.[1,9] Cyclopropanones react smoothly with diazomethane and diazoethane in the absence of catalysts to form cyclobutanones (equations 1 and 2).[24]

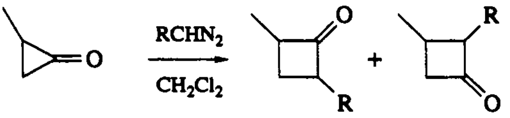
RCHN$_2$
CH$_2$Cl$_2$
O
R
+
R
O

(1)

R = H 43 : 57, 85%
R = Me 43 : 57, 85%

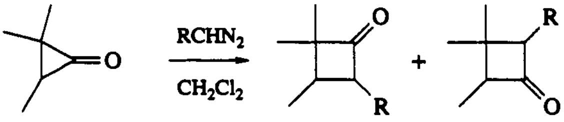
RCHN$_2$
CH$_2$Cl$_2$
O
R
+
R
O

(2)

R = H 33 : 67, 80%
R = Me 70 : 30, 80%

The ready availability of cyclobutanones from the [2 + 2] cycloaddition of ketenes with alkenes makes cyclobutanones attractive precursors to cyclopentanones. These react with diazomethane in ether/methanol to give the ring-expanded products (equations 3[25] and 4[26]). The presence of an α-halo substituent both accelerates the reaction of ketones with diazomethane and strongly shifts the migratory preference to the nonhalogenated carbon (equation 5a).[27] It is noteworthy that the Tiffeneau–Demjanov expansion produces the opposite regiochemistry for expansion in the nonhalogenated case (equation 5b).[15] Additional examples in mono-, bi- and tri-cyclic cyclobutanones are given in equations (6)–(10).

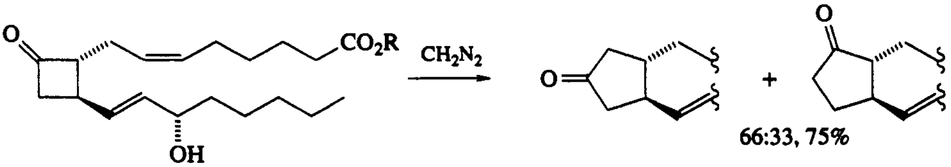
O
CO$_2$R
OH
CH$_2$N$_2$
O
+
O

66:33, 75%

(3)

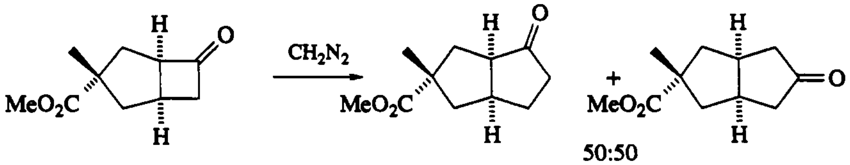
H
O
MeO$_2$C
H
CH$_2$N$_2$
H
O
MeO$_2$C
H
+
H
MeO$_2$C
O
H

50:50

(4)

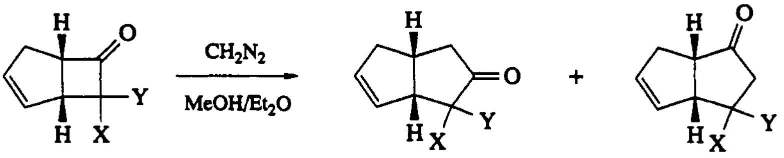
H
O
Y
H X
CH$_2$N$_2$
MeOH/Et$_2$O
H
O
H X
Y
+
H
O
H X
Y

(5a)

X = Y = H 55:45
X = H, Y = Cl 90:10
X = Y = Cl 95:5

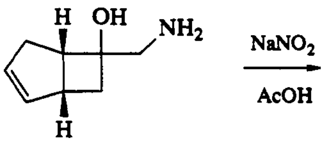
H OH
NH$_2$
H
NaNO$_2$
AcOH

X = Y = H 16:84

(5b)

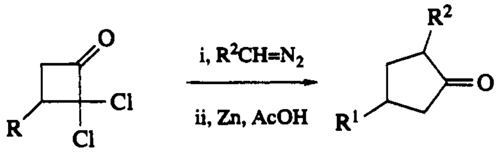
O
Cl
R
Cl
i, R$^2$CH=N$_2$
ii, Zn, AcOH
R$^2$
O
R$^1$

(ref. 27) (6)

R$^1$ = Ph, R$^2$ = H 82% overall
R$^1$ = Ph, R$^2$ = Me 74%
R$^1$ = C$_8$H$_{17}$, R$^2$ = H 75%

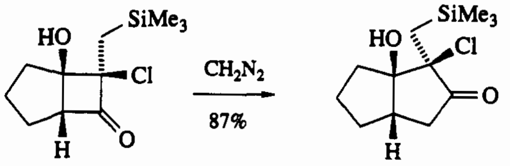
SiMe3
HO
Cl
H
O
CH2N2
87%
SiMe3
HO
Cl
O
H

(ref. 28) (7)

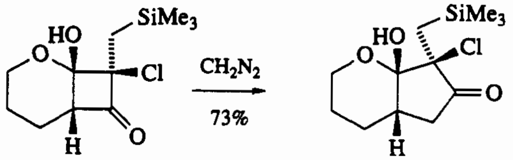
SiMe3
HO
O
Cl
H
O
CH2N2
73%
SiMe3
HO
O
Cl
O
H

(ref. 28) (8)

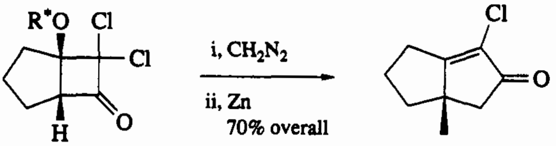
R*O
Cl
Cl
H
O
i, CH2N2
ii, Zn
70% overall
Cl
O

(ref. 29) (9)

R* = (–)-8-phenylmenthol

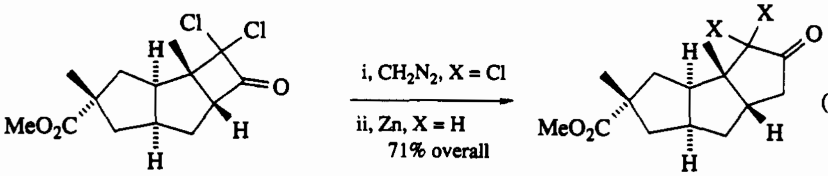
Cl
Cl
H
O
MeO2C
H
H
i, CH2N2, X = Cl
ii, Zn, X = H
71% overall
X
X
H
O
MeO2C
H
H

(ref. 26) (10)

The Lewis acid catalyzed expansion with ethyl diazoacetate also gives good regioselectivity, with a preference for migration of the non-ring-fusion carbon (equations 11–16). The use of $SbCl_5$ as the Lewis acid at –78 °C was reported to improve the regioselectivity in one case (equation 14).[26]

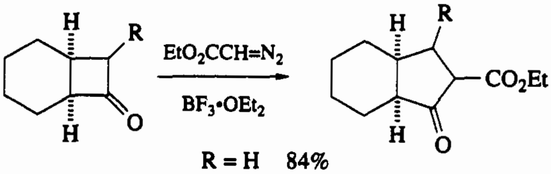
H
R
H
O
EtO2CCH=N2
BF3•OEt2
H
R
CO2Et
H
O

(ref. 30) (11)

R = H 84%
R = Me 100%

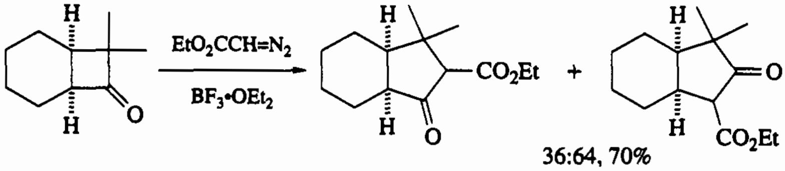
H
H
O
EtO2CCH=N2
BF3•OEt2
H
CO2Et
H
O
+
H
O
H
CO2Et

36:64, 70%

(ref. 30) (12)

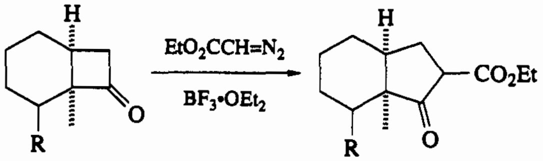
H
O
R
EtO2CCH=N2
BF3•OEt2
H
CO2Et
R
O

(ref. 30) (13)

R = α-Me 83%
R = β-Me 92%

The diminished reactivity of cyclopentanones toward diazomethane, while an asset in the ring expansion of cyclobutanones, has also proven to be a disadvantage. Some examples in the older literature demonstrate the problem of further reaction to higher homologs. The successful expansion reactions with

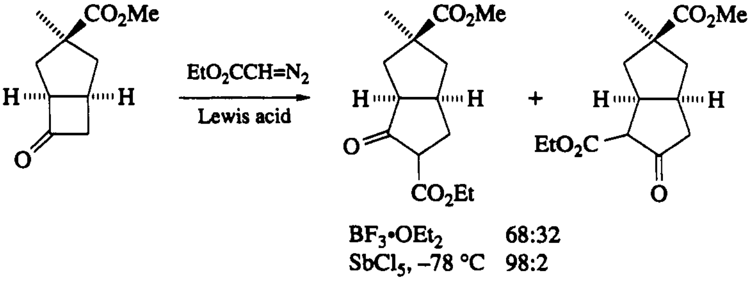
CO2Me
H
H
O
EtO2CCH=N2
Lewis acid
CO2Me
H
H
O
CO2Et
+
CO2Me
H
H
EtO2C
O
BF3•OEt2 68:32
SbCl5, −78 °C 98:2

(ref. 26) (14)

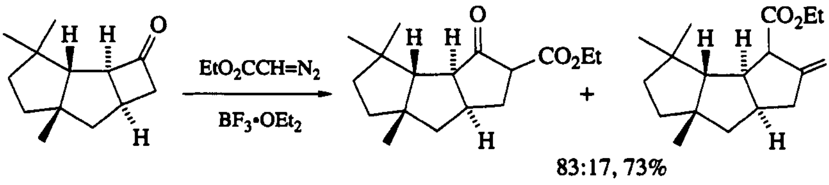
H H
O
H
EtO2CCH=N2
BF3•OEt2
H H
O
CO2Et
H
+
H H
CO2Et
O
H
83:17, 73%

(ref. 31) (15)

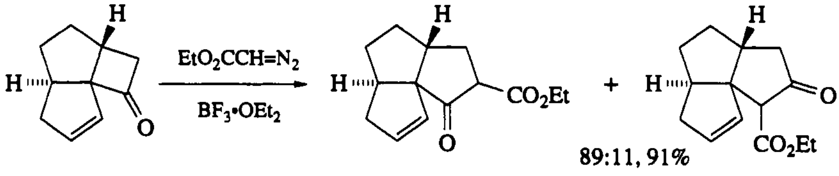
H
H
O
EtO2CCH=N2
BF3•OEt2
H
H
CO2Et
O
+
H
H
O
CO2Et
89:11, 91%

(ref. 32) (16)

ethyl diazoacetate are a likely consequence of the relatively unreactive β-keto ester products (equations 17 and 18). The sequential addition of the lithium anion of ethyl diazoacetate (**26**) to form the aldol product followed by rearrangement has also been found to be a viable tactic for the ring expansion of cyclopentanones (Scheme 11).[19b]

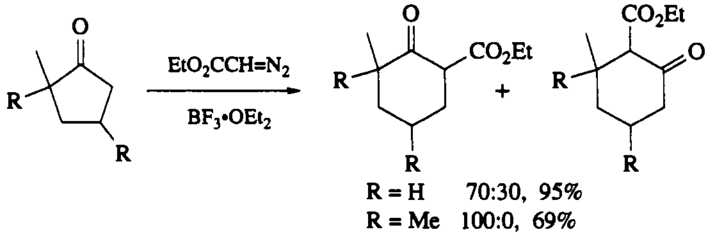
O
R
R
EtO2CCH=N2
BF3•OEt2
O
CO2Et
R
R
+
CO2Et
O
R
R
R = H 70:30, 95%
R = Me 100:0, 69%

(ref. 33) (17)

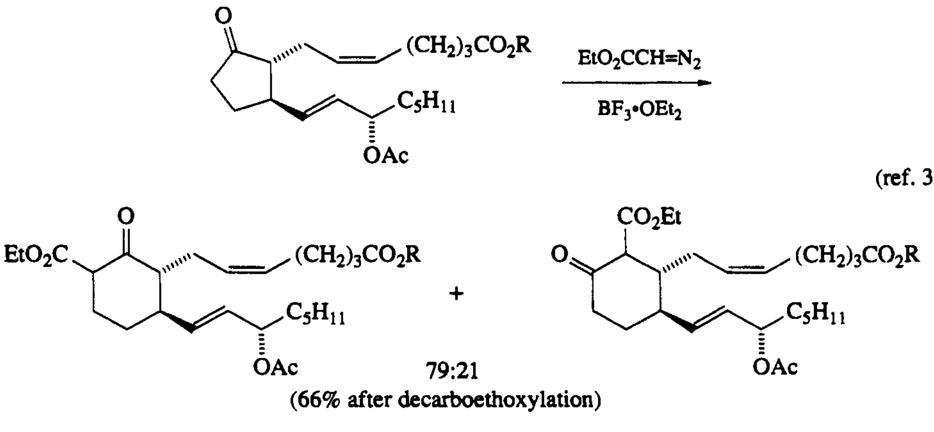
O
(CH2)3CO2R
C5H11
OAc
EtO2CCH=N2
BF3•OEt2
O
EtO2C
(CH2)3CO2R
C5H11
OAc
+
CO2Et
O
(CH2)3CO2R
C5H11
OAc
79:21
(66% after decarboethoxylation)

(ref. 34) (18)

There is an abundance of literature dealing with the diazomethane, diazomethane derivatives and Tiffeneau–Demjanov expansions of six-membered and larger ring ketones, with most of the simpler examples reported in the older literature.[9,15] For example, the diazomethane expansion of cyclohexanone

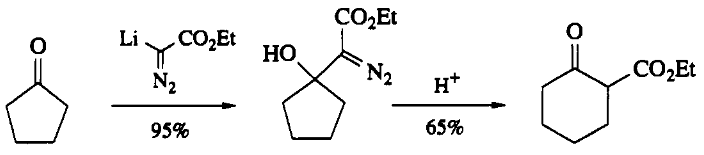

**Scheme 11**

produces cycloheptanone in 33–36% yield on a preparative scale,[35] and the corresponding Tiffeneau–Demjanov expansion provides a 41% overall yield.[16] The preparative scale expansion of cyclohexanone with phenyldiazomethane to 2-phenylcycloheptanone has also been recorded and provides a route to 2-arylcycloheptanones.[36] A series of 4-substituted cyclohexanones have been expanded with diazoethane to yield the 2-methylcycloheptanones in good yield as *ca.* 1:1 *cis/trans* mixtures (equation 19).[37] As in the case with diazomethane, the addition of alcohol to the reaction mixture with diazoethane had a beneficial effect.

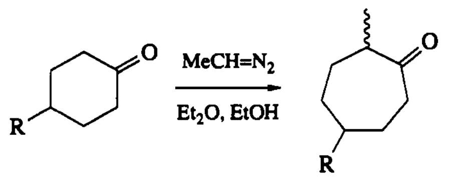

(19)

| *R* | *Yield (%)* | *R* | *Yield (%)* |
|---|---|---|---|
| H | 84% | $Me_2COH$ | 81% |
| Me | 81% | $CO_2Et$ | 89% |
| $Pr^i$ | 75% | | |

The use of Lewis acids for the diazomethane and diazoethane homologations of a series of $C_6$–$C_{14}$ ketones has been reported to reduce the amount of epoxide formation, although as the ring size increases the amount of unreacted starting material increases (Scheme 12).[12] The expansion of 2-allylcyclohexanone with diazomethane in the presence of $AlCl_3$ proceeds with migration of the less-substituted bond,[12] in contrast to the Tiffeneau–Demjanov expansion of 2-methyl- and 2-isopropyl-cyclohexanone wherein the alkyl-substituted bond migrates preferentially (Scheme 13).[38,39]

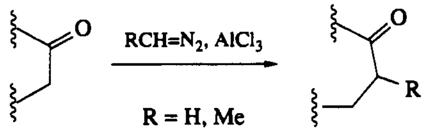

| | *R = H* | *Me* |
|---|---|---|
| $C_6 \rightarrow C_7$ | 58% | - |
| $C_7 \rightarrow C_8$ | 50% | 82% |
| $C_8 \rightarrow C_9$ | 46% | 66% |
| $C_9 \rightarrow C_{10}$ | 45% | 72% |
| $C_{10} \rightarrow C_{11}$ | 25% | 57% |
| $C_{12} \rightarrow C_{13}$ | 26% | 66% |

**Scheme 12**

The trimethylsilyldiazomethane–$BF_3{\cdot}Et_2O$ homologation of 2-methylcyclohexanone also proceeds with high regioselectivity to give 2-methylcycloheptanone in 69% yield. A particular advantage for this reagent over diazomethane appears to be for the homologation of larger rings where the yields are good (equations 20[40] and 21[41]). The Tiffeneau–Demjanov expansion also displays good regioselectivity with larger ketones containing a fused benzene ring (equations 22[42] and 23[43]), although a loss of selectivity was noted in a 12-membered ring ketone (equation 24).[44]

The one-carbon expansion of cyclohexanones with introduction of a carbonyl group, trifluromethyl, cyano, phosphonate or benzenesulfonate has also been reported to proceed in the presence of Lewis acids (Scheme 14). The analogous reactions of larger ring ketones [expressed as ring size (yield)] with ethyl diazoacetate[21] [7 (81%), 8 (85%)] and phenylsulfonyldiazomethane[47] [7 (86%), 8 (27%), 12 (43%), 14 (48%), 15 (54%) and 16 (58%)] have also been reported. In the reaction of ethyl diazoacetate and

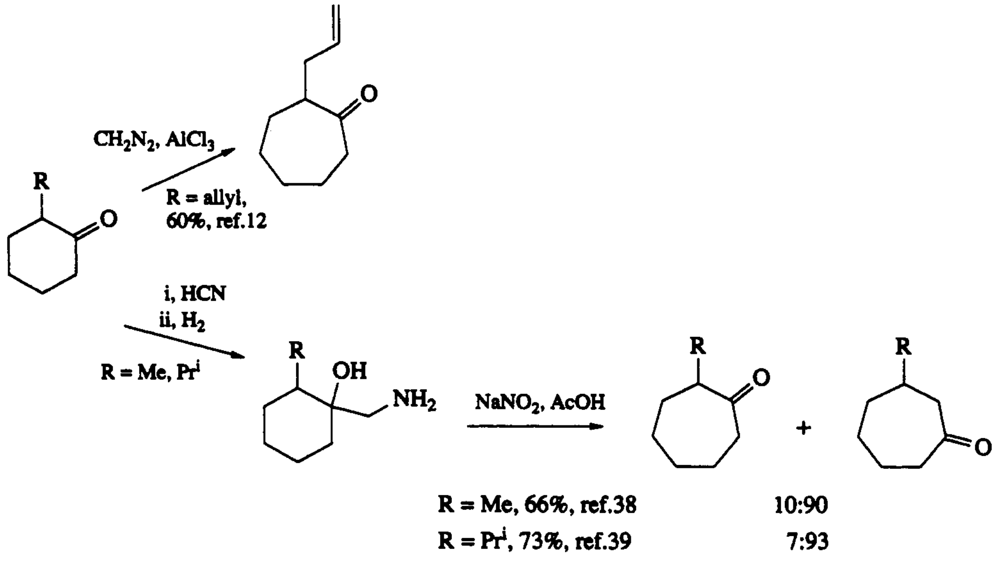
CH₂N₂, AlCl₃
R = allyl,
60%, ref.12
R
O
i, HCN
ii, H₂
R = Me, Prⁱ
R
OH
NH₂
NaNO₂, AcOH
R
O
+
R
O
R = Me, 66%, ref.38
10:90
R = Prⁱ, 73%, ref.39
7:93

**Scheme 13**

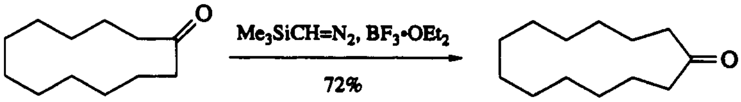
O
Me₃SiCH=N₂, BF₃•OEt₂
72%
O

(ref. 40) (20)

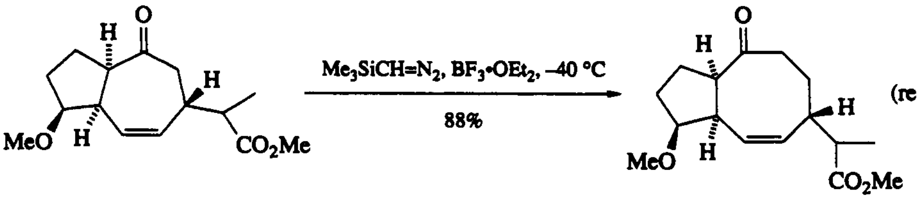
H
O
H
MeO
H
CO₂Me
Me₃SiCH=N₂, BF₃•OEt₂, –40 °C
88%
O
H
H
MeO
H
CO₂Me

(ref. 41) (21)

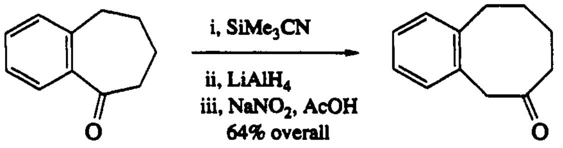
O
i, SiMe₃CN
ii, LiAlH₄
iii, NaNO₂, AcOH
64% overall
O

(22)

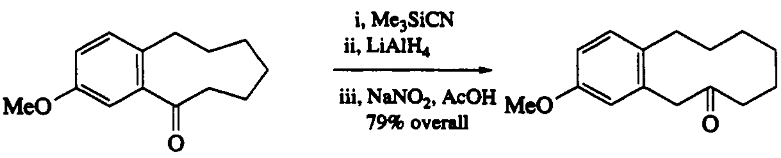
MeO
O
i, Me₃SiCN
ii, LiAlH₄
iii, NaNO₂, AcOH
79% overall
MeO
O

(23)

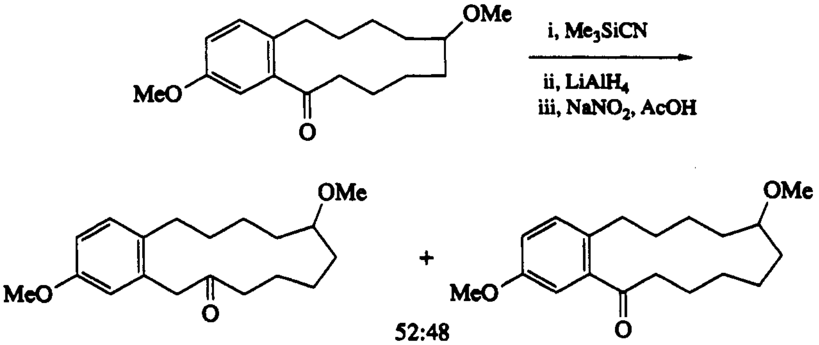
OMe
MeO
O
i, Me₃SiCN
ii, LiAlH₄
iii, NaNO₂, AcOH
OMe
MeO
O
+
OMe
MeO
O
52:48

(24)

2-substituted cyclohexanones, a preference for the migration of the unsubstituted carbon was observed (Scheme 15). The regioselectivity of this rearrangement promoted by $BF_3{\cdot}OEt_2$ was improved by the use of $SbCl_5$ at −78 °C.

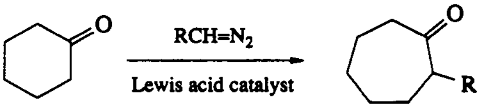

| *R* | *Catalyst* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| $CO_2Et$ | $Et_3O^+BF_4^-$ | 90 | 21 |
| $CO_2Bn$ | $BF_3{\bullet}Et_2O$ | 66 | 45 |
| $CO_2Bu^t$ | $Et_3O^+BF_4^-$ | 46 | 21 |
| CN | $Et_3O^+BF_4^-$ | 58 | 21 |
| $CF_3$ | $Et_3O^+BF_4^-$ | 85 | 21 |
| $PO(OMe)_2$ | $Et_3O^+BF_4^-$ | 65 | 21 |
| $COC_6H_4OMe$ | $BF_3{\bullet}Et_2O$ | 92 | 46 |
| $SO_2Ph$ | $TiCl_4$ | 71 | 47 |

**Scheme 14**

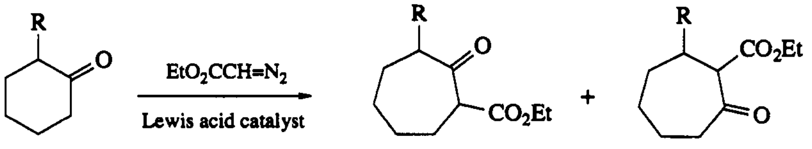

| *R* | *Catalyst* | *Ratio* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| Cl | $Et_3O^+BF_4^-$ | 100:0 | 90 | 21 |
| Me | $Et_2O{\bullet}BF_3$ | 83:17 | 66 | 33 |
| Me | $Et_3O^+BF_4^-$ | 85:15 | 46 | 21 |
| Me | $SbCl_5$ | 94:6 | 58 | 21 |
| Et | $Et_3O^+BF_4^-$, $Et_2O{\bullet}BF_3$ | 80:20 | 85 | 21, 33 |
| $Pr^i$ | $Et_3O^+BF_4^-$ | 90:10 | 65 | 21 |
| $Bu^t$ | $Et_3O^+BF_4^-$ | 73:27 | 92 | 21 |
| Ph | $Et_3O^+BF_4^-$ | >95:5 | 71 | 21 |

**Scheme 15**

The powerful directing effect of halogen substitution has been studied in the reaction of a series of cholestane derivativers with ethyl diazoacetate. In both the 5α and 5β series, essentially no selectivity was observed for the nonhalogenated series, while with halogen substitution only the products arising from migration of the unhalogenated carbon were observed (Scheme 16).[48] A similar effect was observed for an acetoxy substituent.

The sequential lithioethyl diazoacetate addition–Rh catalyzed rearrangement proved to be advantageous in a pseudoguanolide synthesis, where the corresponding one-step ethyl diazoacetate–$BF_3{\cdot}OEt_2$ method produced an 80:20 mixture of regioisomers (Scheme 17).[49] An investigation for a guaiane synthesis utilized a similar sequence, again with only one regioisomer being observed (Scheme 18).[50]

The reaction of diazomethane and its derivatives with bridged polycyclic ketones continues to provide a convenient source of the next higher homologs, and also serves as a reactivity probe with which the effects of ring strain and steric and electronic interactions may be unveiled. In cases where further ring expansion occurs due to a lower reactivity of the starting ketone relative to the product, the Tiffeneau–Demjanov ring expansion is especially useful. Moreover, this sequence allows for the study of bond migration preferences in relation to the stereochemistry of leaving groups when the intermediate amino alcohols can be isolated as separate stereoisomers. The reader is referred to an excellent review on the ring expansion of bridged bicyclic compounds for a detailed analysis of the factors which influence rearrangements in general for this class of compounds.[2c] Illustrative examples are provided in Table 1.

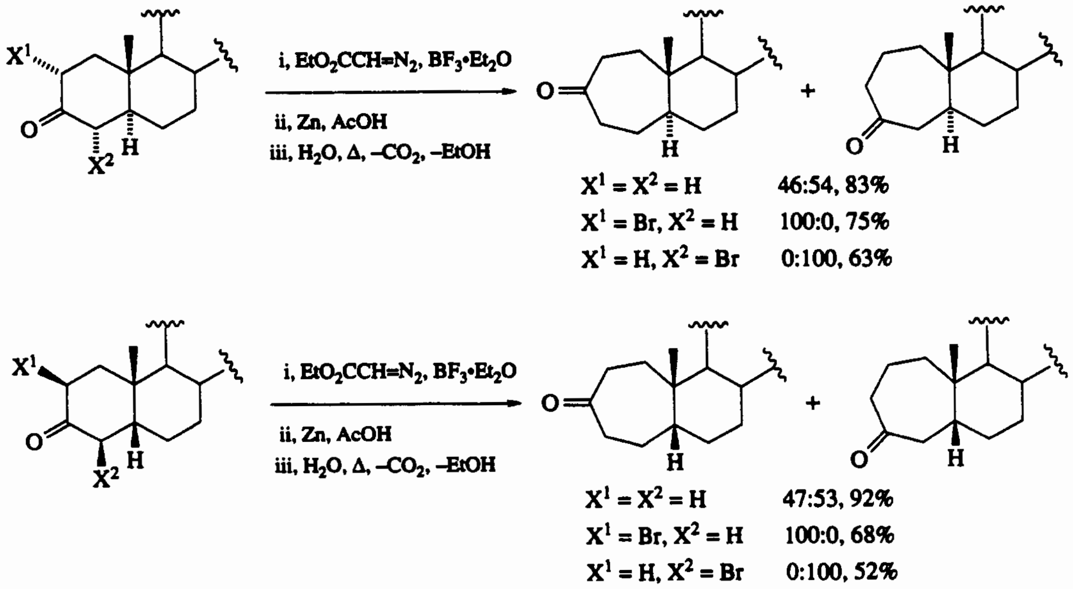
i, EtO2CCH=N2, BF3•Et2O
ii, Zn, AcOH
iii, H2O, Δ, –CO2, –EtOH
X1
X2
O
H
+

$X^1 = X^2 = H$ 46:54, 83%
$X^1 = Br, X^2 = H$ 100:0, 75%
$X^1 = H, X^2 = Br$ 0:100, 63%

$X^1 = X^2 = H$ 47:53, 92%
$X^1 = Br, X^2 = H$ 100:0, 68%
$X^1 = H, X^2 = Br$ 0:100, 52%

Scheme 16

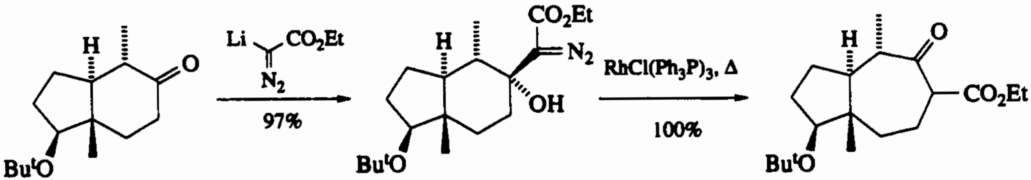
H
O
ButO
Li
CO2Et
N2
97%
OH
RhCl(Ph3P)3, Δ
100%

Scheme 17

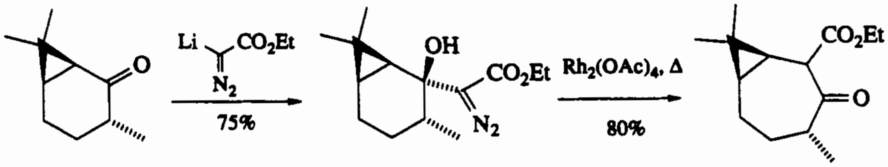
O
Li
CO2Et
N2
75%
OH
Rh2(OAc)4, Δ
80%

Scheme 18

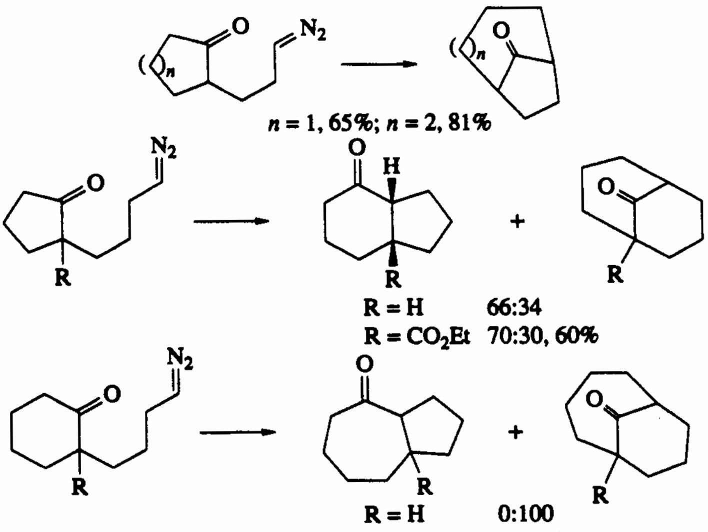

$n = 1$, 65%; $n = 2$, 81%

R = H 66:34
R = $CO_2Et$ 70:30, 60%

R = H 0:100
R = $CO_2Et$ 91:9, 70%

Scheme 19

**Table 1** Ring Expnasion of Bridged Bicyclic Ketones with Diazoalkanes or Tiffeneau–Demjanov Rearrangement

| *Ketone* | *Conditions* | *Intermediates if isolated* | *Conditions* | *Products* | | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 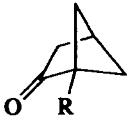 | a | 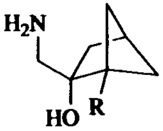 | b | 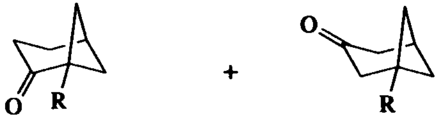 | | | 51 |
| | | | | R = H | 81:19 | 85 | |
| | | | | R = Me | 93:7 | 80 | |
| | | | | R = F | 100:0 | 65 | |
| | | | | R = Cl | 100:0 | 66 | |
| 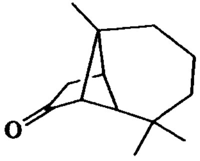 | c | 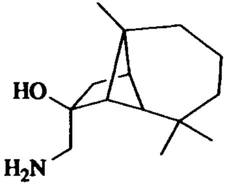 | b | 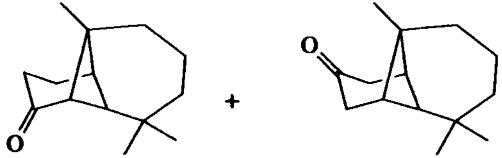 | | | 52 |
| | | | | | 94:6 | | |
| 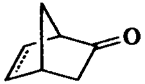 | d | — | — | 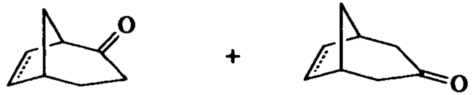 | | | 53 |
| | | | | single bond | 60:40 | | |
| | | | | double bond | 42:58 | | |
| 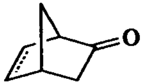 | e | 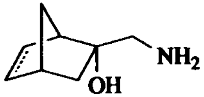 | b | 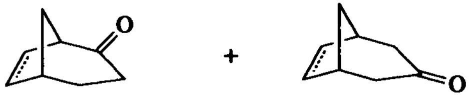 | | | 53 |
| | | | | single bond | 62:38 | | |
| | | | | double bond | 50:50 | | |

**Table 1** *(continued)*

| *Ketone* | *Conditions* | *Intermediates if isolated* | *Conditions* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 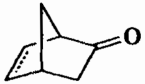 | e | 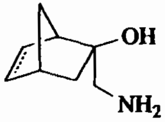 | b | 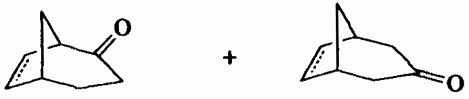<br>single bond 91:9<br>double bond 77:23 | | 53 |
| 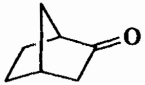 | f | — | — | 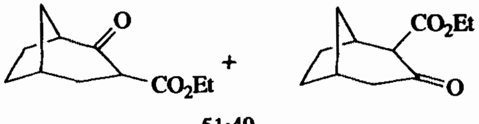<br>51:49 | 52 | 22 |
| 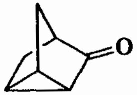 | g | — | — | 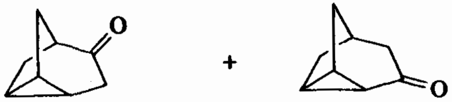<br>90:10 | 42 | 54 |
| 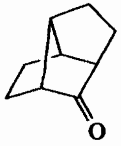 | a | 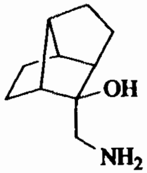<br>95% | b | 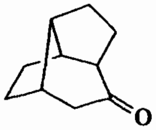 | 99 | 55 |
| 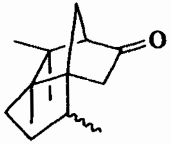 | a | 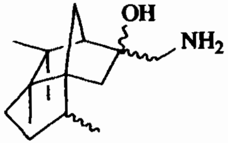 | b | 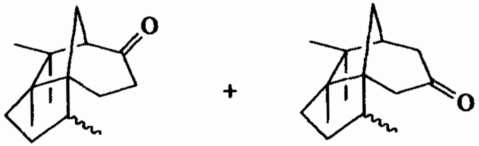<br>78:22 | 93 | 56 |

Table 1 *(continued)*

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| 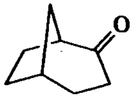 | e | — | — | 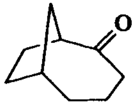 + 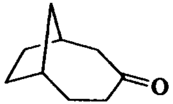<br>68:32 | | 57 |
| 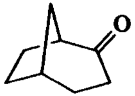 | e | 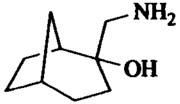<br>and | b | 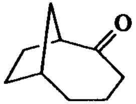 + 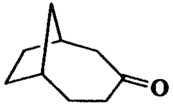<br>88:12 | | 57 |
| 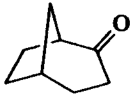 | e | 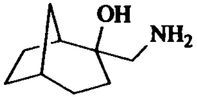 | b | 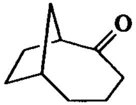 + 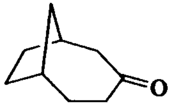<br>50:50 | | 57 |
| 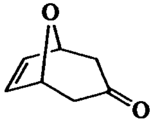 | a | — | b | 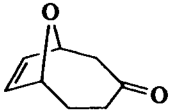 + 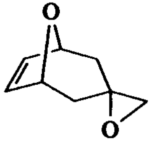<br>75:25 | 71 | 58 |
| 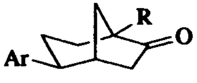 | i | — | — | 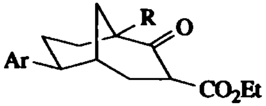 + 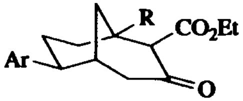<br>~75:25 (R = H, Me) | | 59 |

Table 1 (continued)

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| 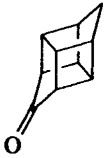 | j | — | — | 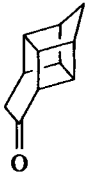 | 70 | 60 |
| 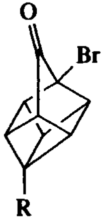 | g | — | — | 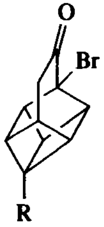 |  | 61 |
|  |  |  |  | $R = CO_2Me$ | 50 |  |
|  |  |  |  | R = Br | 45 |  |
|  |  |  |  | R = Me | 45 |  |
| 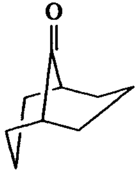 | g | — | — | 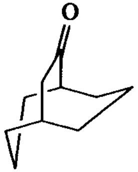 | 75 | 62 |
| 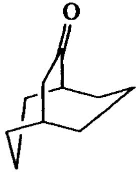 | k | 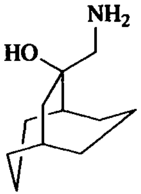 | b | 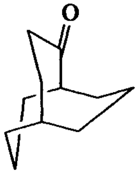 + 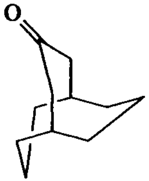<br>66:34 |  | 62 |

**Table 1** *(continued)*

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| 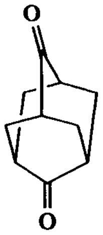 | g | — | — | 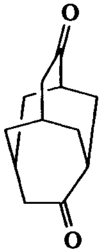 | 80 | 63 |
| 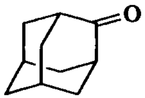 | l | — | — | 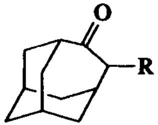 <br>R = H<br>R = $CO_2Et$ | <br>85<br>63 | <br>64<br>21 |
| 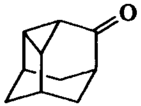 | a | 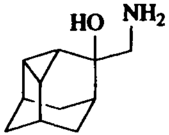 | b | 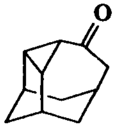 | 70 | 65 |
| 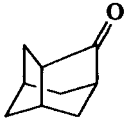 | g | — | — | 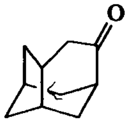 | 90 | 66 |
| 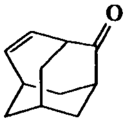 | a | 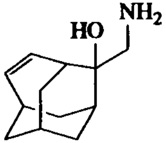 | b | 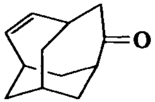 <br>+<br>90:10<br>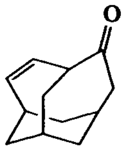 | 75 | 67 |

**Table 1** *(continued)*

| *Ketone* | *Conditions* | *Intermediates if isolated* | *Conditions* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 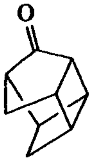 | m | — | — | 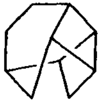 + next higher homolog<br>72:28 | 64 | 68 |
| 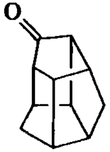 | g | — | — | 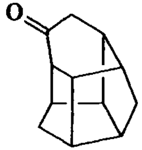 | 56 | 69 |
| 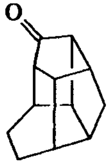 | m | — | — | 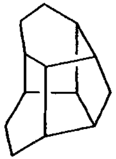 | 71 overall | 70 |

[a] i, $Me_3SiCN$; ii, $LiAlH_4$. [b] $NaNO_2$. [c] i, $Me_2C{=}CH_2$; ii, $NaN_3$; iii, $H_2$, $PtO_2$. [d] $CH_2N_2$, 17–20% completion. [e] i, HCN; ii, $H_2$, $PtO_2$. [f] Ethyl diazoacetate/$BF_3{\bullet}OEt_2$. [g] Excess $CH_2N_2$. [h] 0.06 equiv. $CH_2N_2$. [i] Ethyl diazoacetate, $Et_3O^+ BF_4^-$. [j] $CH_2N_2$, $Et_2O$, MeOH. [k] i, $Ph_3P{=}CH_2$, ii, MCPBA; iii, $NaN_3$; iv, $H_2$, $PtO_2$. [l] $RCH{=}N_2$ (R = H or $CO_2Et$). [m] i, $CH_2N_2$; ii, Wolff–Kishner reduction.

The intramolecular reaction of diazo groups with ketones has also been examined in several systems. Early work studied the variation in ring size, substitution and chain length on the reaction outcome (Scheme 19).[71] Despite the interesting synthetic potential for an intramolecular ring expansion reaction, relatively few examples have been reported (equations 25,[21] 26,[72] 27[73] and 28[73]).

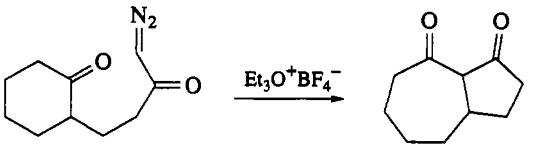
$N_2$
O
O
$Et_3O^+BF_4^-$
O
O

(25)

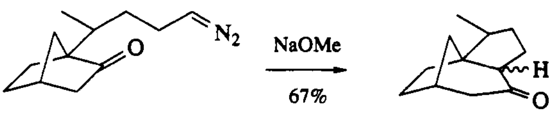
O
$N_2$
NaOMe
67%
H
O

(26)

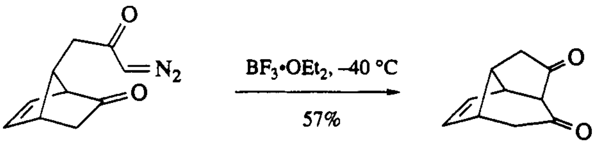
O
$N_2$
O
$BF_3•OEt_2$, –40 °C
57%
O
O

(27)

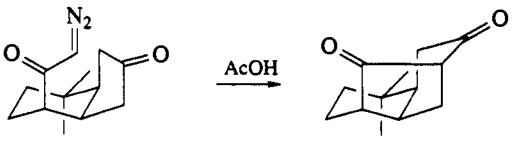
$N_2$
O
O
AcOH
O
O

(28)

## 3.3.3 PINACOL-TYPE REACTIONS OF β-HYDROXY SULFIDES AND SELENIDES

In a related addition–elimination with rearrangement sequence, the chain extension–ring expansion reactions of ketones with sulfur- and selenium-stabilized anions has, relative to diazoalkanes, only been examined fairly recently. The general reaction involves the addition of a sulfur- or selenium-stabilized carbanion (**30**) to the ketone carbonyl to form adduct (**31**; Scheme 20). The expulsion of the sulfur or selenium may be induced by alkylation, complexation with metal salts, reaction with carbenes or oxidation, which leads to the rearranged products and/or epoxides. While the mechanistic details of the rearrangement aspect may differ substantially, depending on the reaction conditions, this set of expansion reactions is organized according to a common first step, the addition of a sulfur- or selenium-stabilized anion to a carbonyl group and will be presented in the order of the number of heteroatoms on the nucleophile (**30**).

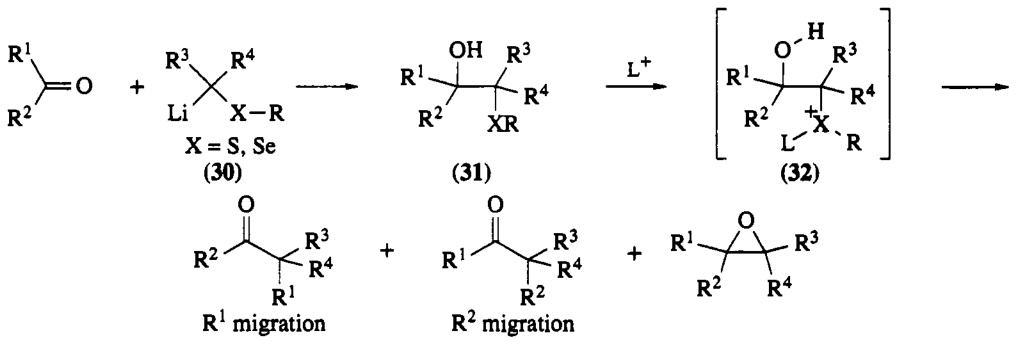
$R^1$
$R^2$
O
+
$R^3$
$R^4$
Li
X–R
X = S, Se
(30)
OH
$R^1$
$R^2$
$R^3$
$R^4$
XR
(31)
$L^+$
H
O
$R^1$
$R^2$
$R^3$
$R^4$
X
L
R
(32)
O
$R^2$
$R^3$
$R^4$
$R^1$
$R^1$ migration
+
O
$R^1$
$R^3$
$R^4$
$R^2$
$R^2$ migration
+
O
$R^1$
$R^2$
$R^3$
$R^4$

Scheme 20

When one heteroatom is present on the nucleophilic unit, the overall result is similar to the carbon insertion with diazomethane. While the addition of $PhSeCH_2Li$ or $MeSeCH_2Li$[74] to ketones is an efficient process, the elimination step using methyl iodide and base (*e.g.* KOH), dichlorocarbene generated from thallium(I) ethoxide and chloroform, or oxidation with peroxy acids leads, in general, to high yields of epoxides from aliphatic ketones. For cyclobutanones the resulting epoxides have been rearranged to the cyclopentanones with preferential migration of the more-substituted carbon (Schemes 21[75a,b] and 22[76]).

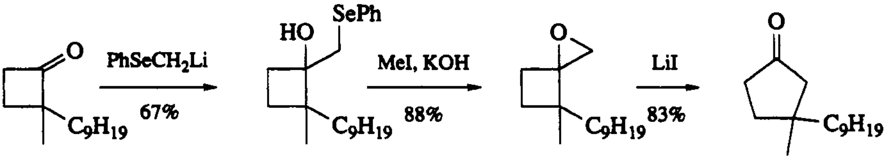

Scheme 21

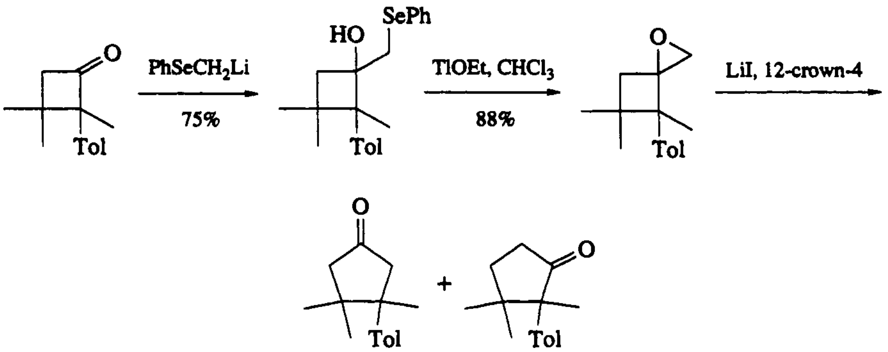

94:6, 95%

Scheme 22

The β-hydroxy phenyl selenide products from the reaction of aryl-substituted ketones and $PhSeCH_2Li$ eliminate the phenylselenyl group on treatment with peroxy acid, with migration of the aromatic group to give the one-carbon extended ketones or, in the case of cyclic ketones, the ring-expanded products (Schemes 23 and 24).[77] Cyclobutanones have been ring-expanded in a two-step procedure by reaction of the lithium anion of methyl 2-chlorophenyl sulfoxide followed by heating the β-hydroxy sulfoxide with potassium hydride in tetrahydrofuran. Rearrangement with elimination of sulfur proceeds with the exclusive migration of the more-substituted carbon atom (Scheme 25). This method has also been applied to cyclobutanones with substituted sulfoxides to provide 2-substituted cyclopentanones (Table 2).[78] The precise mechanistic details have yet to be elucidated, as well as the extension of the reaction to other ketones.

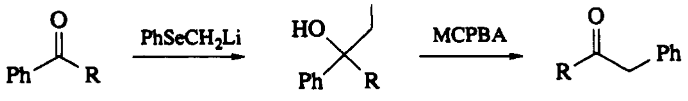

R = Me, 60%; R = Ph, 50%

Scheme 23

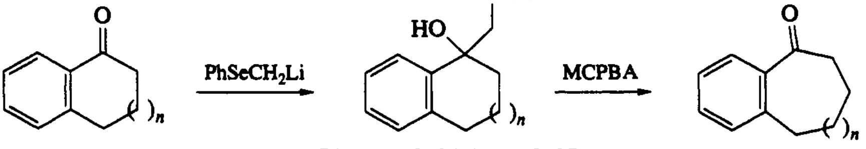

*n* = 1, 74%; *n* = 2, 84%; *n* = 3, 97%

Scheme 24

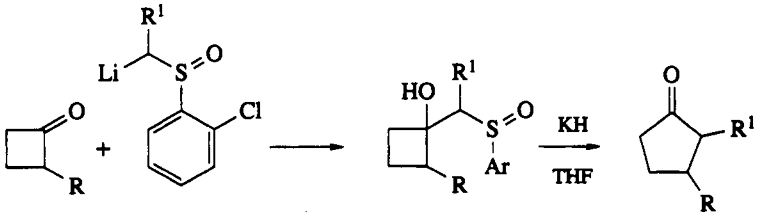
R1
Li
S
O
O
Cl
R
+
HO
R1
S
O
Ar
R
KH
THF
O
R1
R

$R^1$ = H, alkyl, aryl

**Scheme 25**

**Table 2** Ring Expansion of Cyclobutanones with Lithium Alkyl Aryl Sulfoxides

| *Sulfoxide $RCH_2SOAr$*[a] | *Cyclobutanone* | *Product* | *Yield (%)* |
|---|---|---|---|
| R = H | 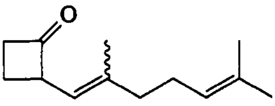 | 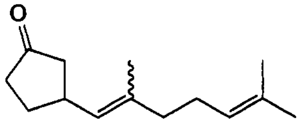 | 58 |
| R = H | 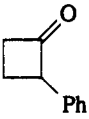 | 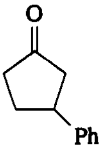 | 52 |
| R = H | 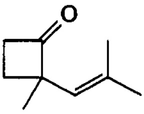 | 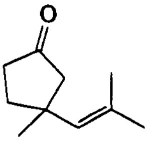 | 72 |
| R = H | 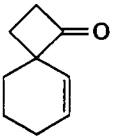 | 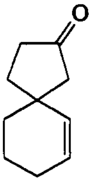 | 94 |
| R = H | 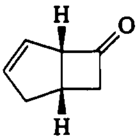 | 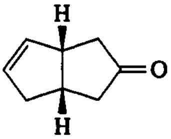 | 63 |
| R = Me | 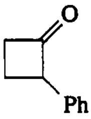 | 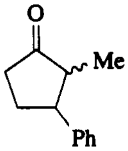 | 52 |
| R = Me | 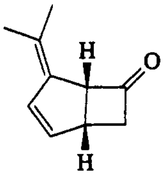 | 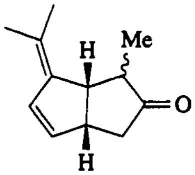 | 52 |

**Table 2** *(continued)*

| *Sulfoxide $RCH_2SOAr$* [a] | *Cyclobutanone* | *Product* | *Yield (%)* |
|---|---|---|---|
| R = $CH_2CH_2CH{=}CH_2$ | 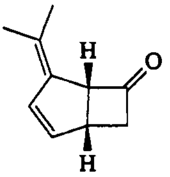 | 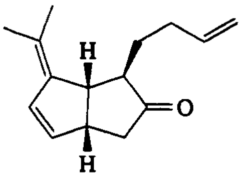 | 69 |
| R = $(CH_2)_7OSiMe_2Bu^t$ | 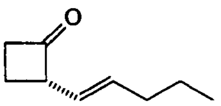 | 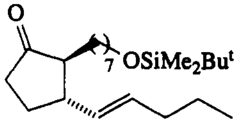 | 53 |
| R = $CH_2CH_2Ph$ | 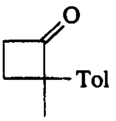 | 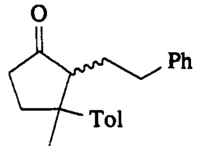 | 53 |

[a] Ar = 2-chlorophenyl.

The selenium-based methodology is particularly well suited for the homologation of ketones with the incorporation of a geminally disubstituted carbon because, in this instance, the formation of epoxides is minimal. Representative examples are given in Table 3. The regioselectivity of the expansion reaction is sensitive to steric effects and stereochemical relationships, as well as to the method used for activation of the selenium for elimination. For cyclic enones, ring sizes larger than six begin to show a decline in regioselectivity. It is noteworthy that the thallium(I) ethoxide/chloroform generated dichlorocarbene can be utilized in the presence of double bonds. The last entry of Table 3 is of particular interest with regard to the mechanistic aspects of the overall reaction. This example indicates that the configuration of the migrating carbon is preserved regardless of the elimination method used, while the center from which the selenium departs undergoes net inversion with $TlOEt/CHCl_3$ and varying amounts of net retention or inversion with the silver tetrafluoroborate induced elimination.

When the lithium reagent added to the carbonyl group bears two heteroatoms, the net result following rearrangement is the incorporation of a carbon bearing a heteroatom. The hydroxy diphenyl dithioacetals, readily formed from the addition of the anion of the formaldehyde diphenyl dithioacetal to ketones, have been shown to rearrange in the presence of copper(I) triflate to produce the α-benzenesulfenyl homologated ketones. The preferred migration of the more-substituted carbon atom is observed for aliphatic and cyclic ketones, while hydrogen migration is still preferred in the case of aldehyde adducts (Table 4).[85] The presence of an epoxide intermediate has been observed and may bear some relevance to the failure of the rearrangement process to homologate cycloheptanone. Complementary to the copper(I) triflate induced elimination is the base-induced loss of thiophenol. Treatment of the hydroxy diphenyl dithioacetal adduct with two equivalents of *s*-butyllithium at –78 °C produces a dianion, which on warming undergoes a carbenoid-type reaction (*cf.* the next section for a discussion) to the ring-expanded ketone (Scheme 26).[86] In general the yields and regioselectivity for the bond migrations appear to be comparable to the copper(I) triflate reaction, with the notable improvement that ring size does not appear to be a restriction.

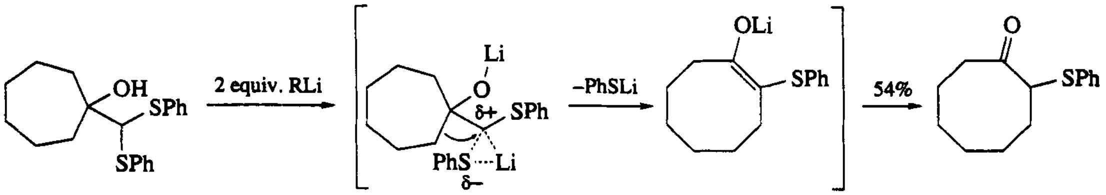

Scheme 26

Another variation on the Lewis acid catalyzed homologation process is to raise the oxidation level on one of the sulfur groups to the level of sulfone.[87] The addition of the less nucleophilic lithium anion of (phenylthio)methyl phenyl sulfone to ketones requires the presence of a Lewis acid (diethylaluminum chloride). The rearrangement step, which did not occur in ether solvents, is conducted at low temperature in dichloromethane in the presence of diethylaluminum chloride and provides good yields of the ring-enlarged ketones. The general trend of the more-substituted bond migration also follows here, except for a bridged bicyclic system, the last entry of Table 5.

A nitro group has been found to perform the same leaving group function as the phenyl sulfone in an analogous procedure using the addition of the dianion of $PhSCH_2NO_2$ to ketones.[88] The rearrangement step is catalyzed by the action of aluminum chloride, is apparently general for four- through seven-membered ring ketones and also displays a high regioselectivity for migration of the more-substituted carbon. An illustrative example is shown in Scheme 27.

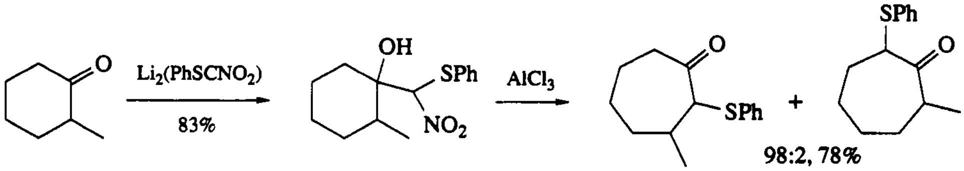

**Scheme 27**

This general procedure has also been extended to allow for the insertion of a methoxy-containing carbon. The uncatalyzed addition of the lithium anion of methoxymethyl phenyl sulfone to ketones proceeds readily at low temperature in dimethoxyethane to form the intermediate adduct. Addition of a Lewis acid (ethylaluminum dichloride or diisobutylaluminum diisopropylamide) directly to the reaction mixture effects the rearrangement reaction to produce the ring-expanded α-methoxy ketone. This sequence, illustrated by the example in Scheme 28, is limited to the expansion of four- and five-membered ring ketones.[87]

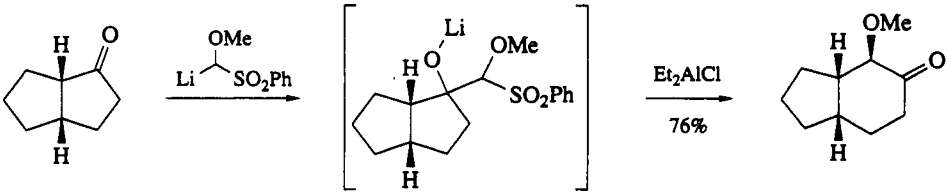

**Scheme 28**

Insertion of a latent carbonyl group, in the form of a dithioketal, may be achieved through the same sulfur-based strategy by employing a nucleophile containing three heteroatoms such as the lithium anion of tris(methylthio)methane. The rearrangement, with loss of one thiomethyl group, has been carried out in a separate step on the anion of the adduct in the presence of $CuClO_4 \cdot 4MeCN$, $CuBF_4 \cdot 4MeCN$ in toluene or in a strained case simply by treatment with acid (Scheme 29). The reaction proceeds well for the expansion of four- and five-membered ring ketones, but is diverted to nonexpanded products for cyclohexanone and other ketones, a result rationalized by the isomerization through epoxides. As may be seen from the examples in Table 6, the regioselectivities in general are high.

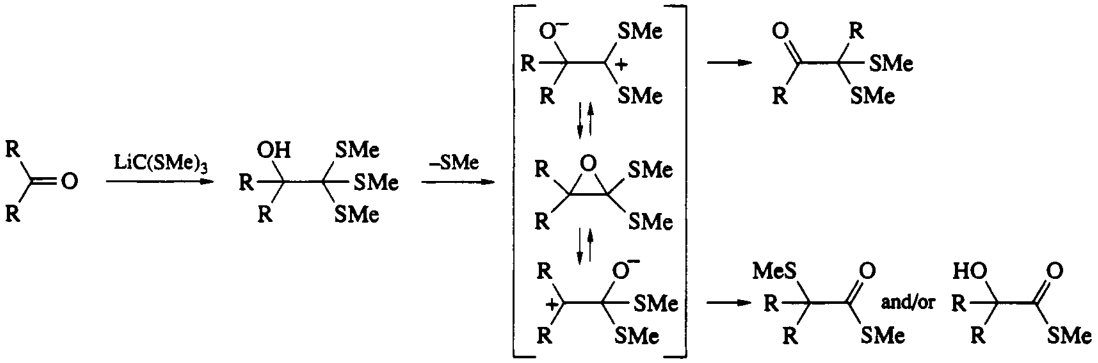

**Scheme 29**

**Table 3** Ring Expansion of Ketones by Se-based Addition–Rearrangement Reactions

| *Lithioselenide* | *Ketone* | *Adducts* | *Yield (%)* | *Rearrangement method* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 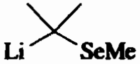 | 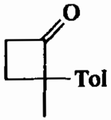 | 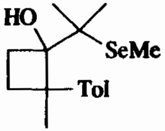 | 66 | a<br>c | 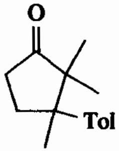 | 57<br>83 | 79 |
| 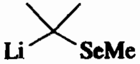 | 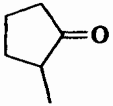 | 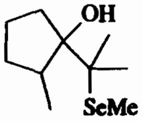 | 20 | a | 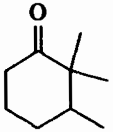<br>+<br>90:10<br>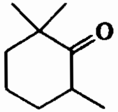 | 76 | 79 |
| 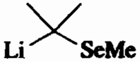 | 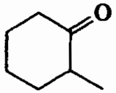 | 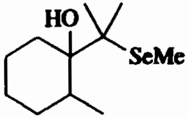 | | | 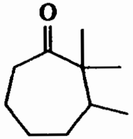<br>+<br>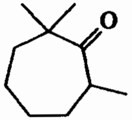 | | 79 |
| | | | | a | 60:40 | 77 | |
| | | | | b | 22:78 | 54 | |
| 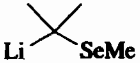 | 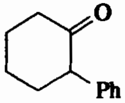 | 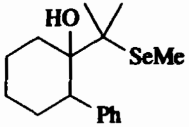 | 89 | a | 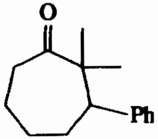<br>+<br>81:19<br>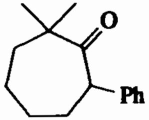 | 79 | 79 |
| 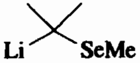 | 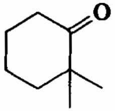 | 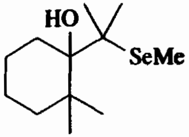 | 68 | a | 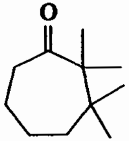<br>+<br>99:1<br>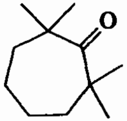 | 81 | 79 |

**Table 3** *(continued)*

| *Lithioselenide* | *Ketone* | *Adducts* | *Yield (%)* | *Rearrangement method* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 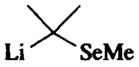 | 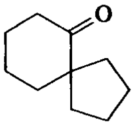 | 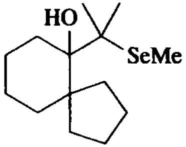 | 70 |  | 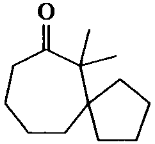 + 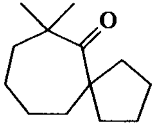 |  | 79 |
|  |  |  |  | a | 99:1 | 77 |  |
|  |  |  |  | b | 34:66 | 45 |  |
| 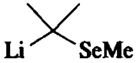 | 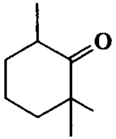 | 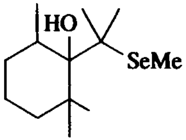 |  | c | 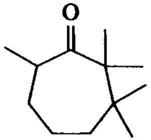 | 88 | 79 |
| 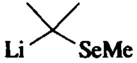 | 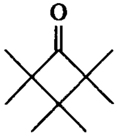 | 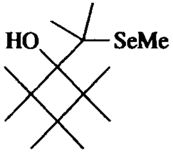 |  | a | 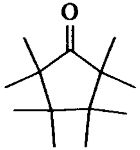 | 71 | 80 |
| 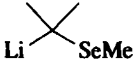 | 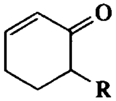 | 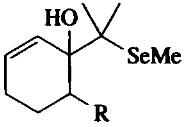 |  | a | 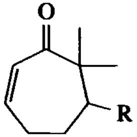 + 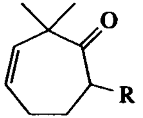 |  | 81 |
|  | R = H |  | 58 |  | 91:9 | 68 |  |
|  | R = Me |  | 70 |  | 100:0 | 71 |  |
|  | R = Ph |  | 74 |  | 100:0 | 67 |  |

**Table 3** *(continued)*

| *Lithioselenide* | *Ketone* | *Adducts* | *Yield (%)* | *Rearrangement method* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 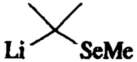 | 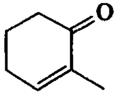 | 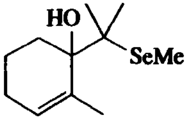 | 39 | a | 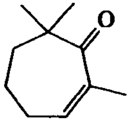 + 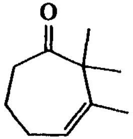<br>78:22 | 64 | 81 |
| 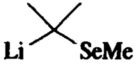 | 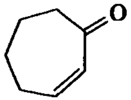 | 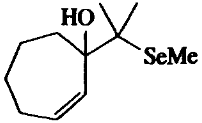 | 51 | a | 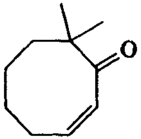 + 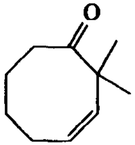<br>56:44 | 88 | 81 |
| 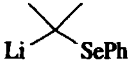 | 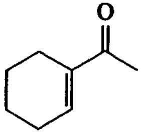 | 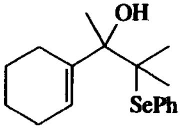 | | a | 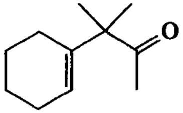 | 98 | 82 |
| 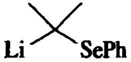 | 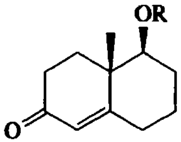 | 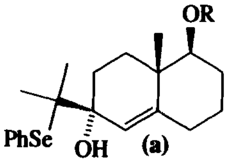 (a)<br>(a):(b) = 34:66 | 67 | a | 94:6<br>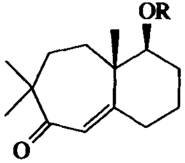 + 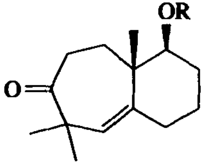 | 93 | 82 |
| | | 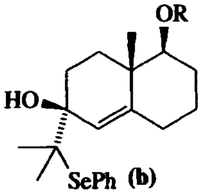 (b) | | a | 77:23 | 72 | |

**Table 3** *(continued)*

| *Lithioselenide* | *Ketone* | *Adducts* | *Yield (%)* | *Rearrangement method* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 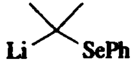 | 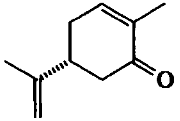 | 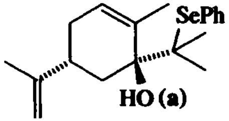 (a) | 83 | a | 20:80<br>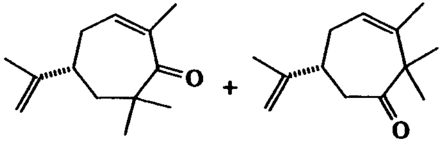 | 89 | 82 |
| | | (a):(b) = 34:66<br>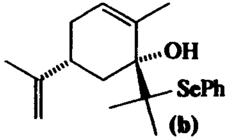 (b) | | a | 70:30 | 78 | |
| 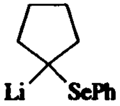 | 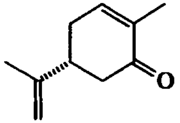 | 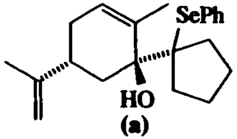 (a) | | a | 4:96<br>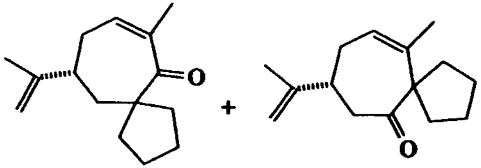 | 65 | 82 |
| | | (a):(b) = 34:66<br>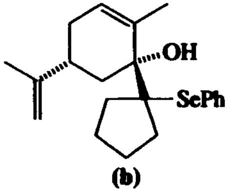 (b) | | a | 32:68 | 20 | |
| 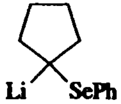 | 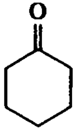 | 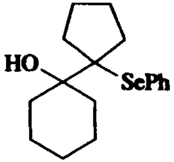 | | a | 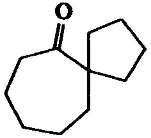 | 87 | 83 |

**Table 3** *(continued)*

| *Lithioselenide* | *Ketone* | *Adducts* | *Yield (%)* | *Rearrangement method* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 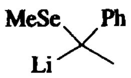 | 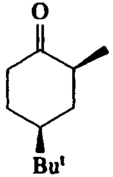 | 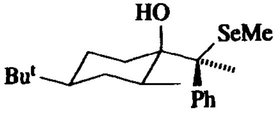<br>(a)<br>(a):(b) = 50:50<br>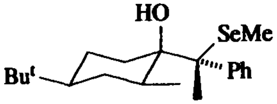<br>(b) | 84 |  | 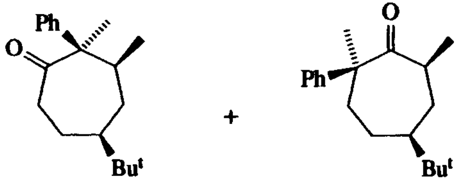 |  | 84 |
|  |  |  |  | a | 100:0 | 25 |  |
|  |  |  |  | b | 0:100 | 48 |  |
|  |  |  |  |  | 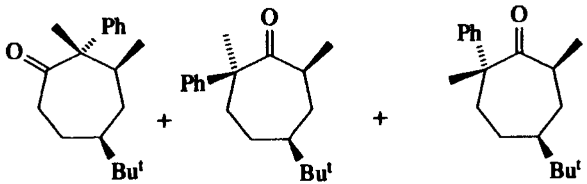 |  |  |
|  |  |  |  | a | 35:65:0 | 40 |  |
|  |  |  |  | b | 0:54:46 | 89 |  |

[a] TlOEt/$CHCl_3$. [b] $AgBF_4$/$CH_2Cl_2$. [c] $MeSO_3F$.

**Table 4** Homologation of Carbonyls by Reaction with $(PhS)_2CHLi$ and Rearrangement with $Cu^+$

| *Carbonyl* | *Adduct yield (%)* | *Homologated ketone* | *Yield (%)* |
|---|---|---|---|
| 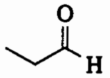 | 80 | 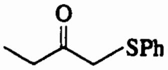 | 66 |
| 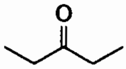 | 90 | 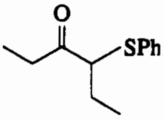 | 88 |
| 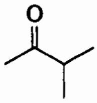 | 85 | 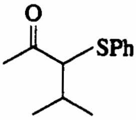 | 81 |
| 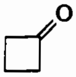 | 86 | 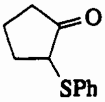 | 72 |
| 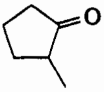 | 84 | 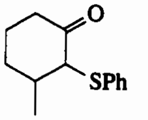<br>+<br>89:11<br>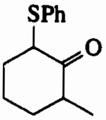 | 83 |
| 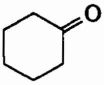 | 74 | 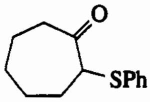<br>+<br>82:18<br>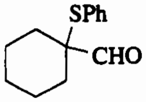 | 71 |

**Table 5** Ring Expansion of Ketones with $PhS(PhSO_2)CHLi$

| *Ketone* | *Adduct* | *Yield (%)* | *Expansion product* | *Overall yield (%)* |
|---|---|---|---|---|
| 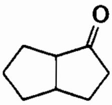 | 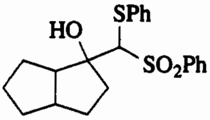 | 92 | 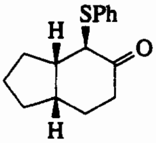 | 79 |
| 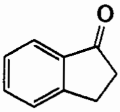 | 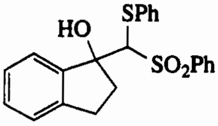 | 94 | 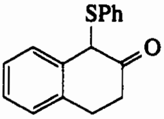 | 77 |
| 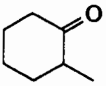 | 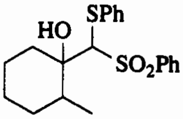 | 92 | 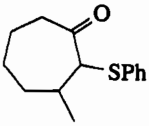 | 69 |
| 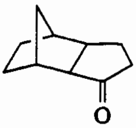 | 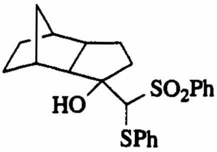 | 93 | 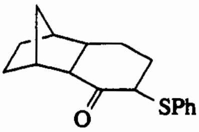 | 74 |

**Table 6** Ketone Ring Expansions *via* $(MeS)_3CLi$

| *Ketone adduct* | *Yield* (%) | *Expansion product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| 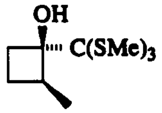 | 73 | 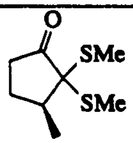 | 73 | 89 |
| 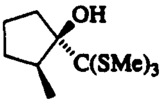 | 85 | 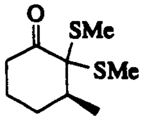 | 58 | 89 |
| 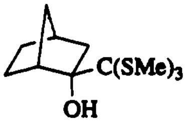 | 95 | 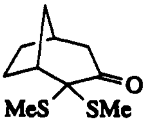 | 61 | 89 |
| 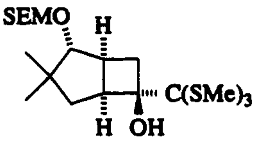 | 95 | 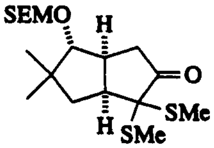 | 84 | 89 |
| 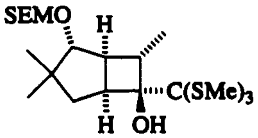<br>(a)<br>(a):(b) = 48:52<br>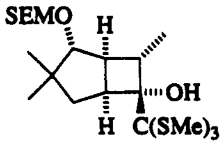<br>(b) | 87 | 21:79<br>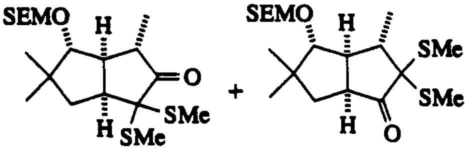<br>69:31 | 92<br>83 | 89 |
| 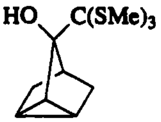 | 74 | 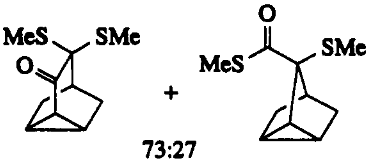<br>73:27 | 99 | 90 |
| 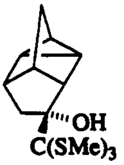 | 75 | 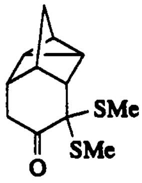 | 71 | 90 |
| 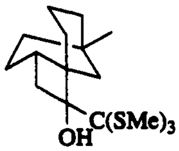 | | 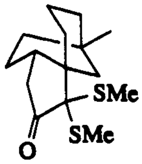 | 66 | 91 |

### 3.3.4 REARRANGEMENT OF β-OXIDO CARBENOIDS

A novel homologation method arises from the base-induced rearrangement of dihalohydrins.[92] On an historical note, this reaction is mechanistically distinct from an earlier ring expansion protocol that employed the known tendency of the magnesium salts of monohalohydrins to undergo rearrangement. That procedure involved the addition of benzylmagnesium chloride to ketones and bromination of the resulting alcohols at the benzylic position with *N*-bromosuccinimide to form the bromohydrin.[93] On heating with one equivalent of isopropylmagnesium bromide, the bromohydrin underwent rearrangement to the homologated ketone, either through a pinacol-like reaction, or possibly *via* an epoxide. Examples are shown in Schemes 30 and 31. While the regioselectivity for bond migration is moderate for the 2-methylcyclopentanone expansion, the corresponding expansion for the 2-methylcyclohexanone is near unity.

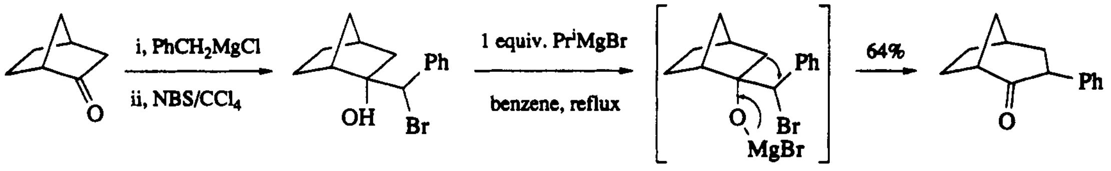
i, PhCH$_2$MgCl
ii, NBS/CCl$_4$
O
Ph
OH
Br
1 equiv. Pr$^i$MgBr
benzene, reflux
Ph
O
Br
MgBr
64%
Ph
O

Scheme 30

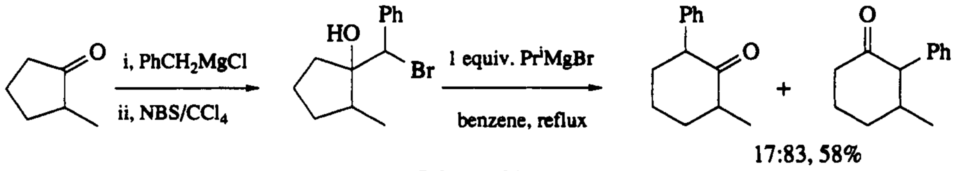
O
i, PhCH$_2$MgCl
ii, NBS/CCl$_4$
HO
Ph
Br
1 equiv. Pr$^i$MgBr
benzene, reflux
Ph
O
+
O
Ph
17:83, 58%

Scheme 31

On the other hand, dichlorohydrins, produced by the addition of dichloromethyllithium to ketones, may be deprotonated at low temperature by two equivalents of alkyllithiums or lithium dialkylamides to form the corresponding dianion. This dianion loses LiCl on warming, and rearranges either directly or through a carbenoid intermediate to the enolate of the homologated α-chloro ketone (Scheme 32).[92,94] As a homologation, the reaction proceeds well for aliphatic (Scheme 33)[92,95a] and cyclic ketones (Scheme 34),[92,95b] but suffers with aldehydes due to the preferred migration of hydrogen ~ phenyl >> alkyl.

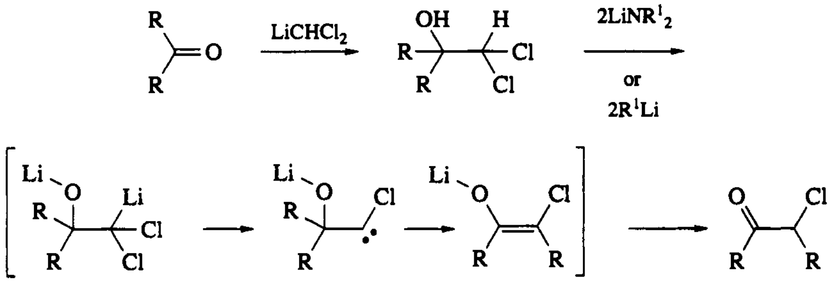
R
R
O
LiCHCl$_2$
OH
H
R
R
Cl
Cl
2LiNR$^1_2$
or
2R$^1$Li
Li
O
Li
R
R
Cl
Cl
Li
O
Cl
R
R
Li
O
Cl
R
R
O
Cl
R
R

Scheme 32

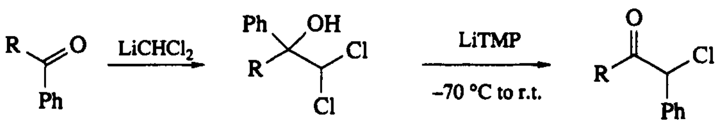
R
O
Ph
LiCHCl$_2$
Ph
OH
Cl
R
Cl
LiTMP
-70 °C to r.t.
O
R
Cl
Ph

R = Me, 56%; R = Ph, 86%

Scheme 33

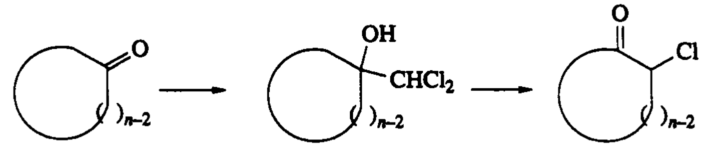

$n = 5$, 90%; $n = 6$, 70%; $n = 7$, 68%; $n = 8$, 48%

Scheme 34

In contrast, when the analogous dibromohydrins are exposed to two equivalents of butyllithium at low temperature, lithium–halogen exchange occurs to produce the monobromo dianion. On warming, this intermediate loses LiBr to give a carbene, which rearranges with migration of a substituent to form the enolate of the expanded ketone (Scheme 35).[96] This procedure appears to be fairly general for the one-carbon expansion of cyclic ketones (Table 7). It is noteworthy that the intermediate enolate anion has been trapped as the trimethylsilyl enol ether. The preferred regioselectivity for the migration of the more-substituted carbon atom has been rationalized in terms of a preferred orientation of the dianion in which the departing bromine atom is situated opposite the more sterically hindered center (Scheme 36).[96b] For the few cases examined, it has been determined that the configuration at the migrating carbon atom is preserved: examples are given in Table 7.

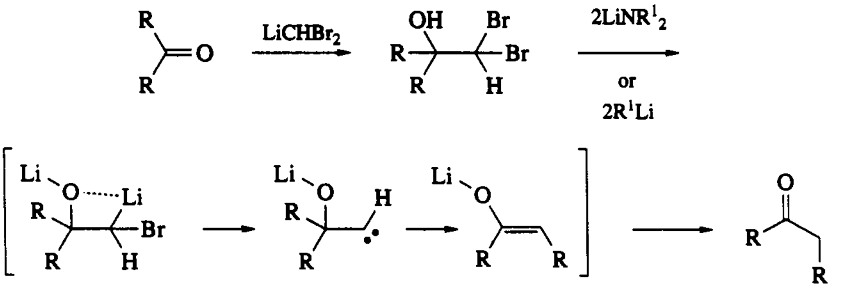

Scheme 35

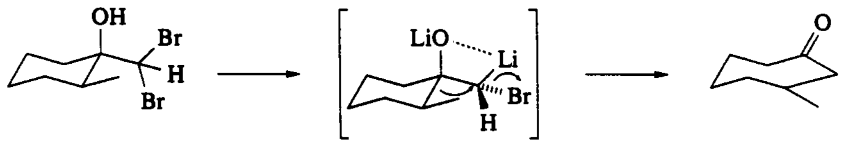

Scheme 36

This rearrangement process has also been developed into a homologation procedure for esters. The low temperature addition of dibromomethyllithium to esters produces the primary adduct, which, depending on substitution may collapse to the dibromo enolate (Scheme 37). A rapid metal–halogen exchange occurs on addition of butyllithium to produce the dilithio anion, which then undergoes a rearrangement on warming. The resulting lithium ynolate is quenched with acidic ethanol to give the homologated ester. This one-flask process appears to be general for esters and lactones (Table 8).[103] The rearrangement aspect of the reaction has been verified by carbon-13 labeling, and proceeds with retention of configuration at the migrating carbon. An interesting adjunct to this homologation procedure is the observation that the intermediate ynolate may be reduced to the enolate by lithium hydride generated *in situ* from butyllithium and 1,3-cyclohexadiene (Scheme 38).[104] The esters shown in Table 8 have been converted to the corresponding aldehydes or enol acetates in 50–60% overall yield by this procedure.

**Table 7** β-Oxido Carbenoid Ring Expansion

| *Ketone* | *Adduct* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 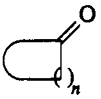 | 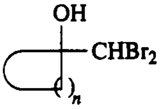 | 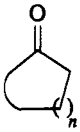 | | 96b |
| | | $n = 5$ | 92 | |
| | | $n = 6$ | 70 | |
| | | $n = 7$ | 80 | |
| | | $n = 8$ | 87 | |
| | | $n = 12$ | 89 | |
| | 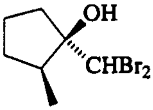<br>**(a)** | 69:31 | 90 | |
| 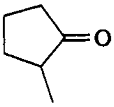 | **(a)**:**(b)** = 70:30 | 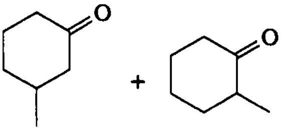 | | 96b |
| | 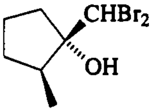<br>**(b)** | 49:51 | 73 | |
| 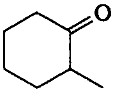 | 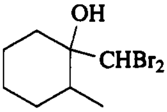 | 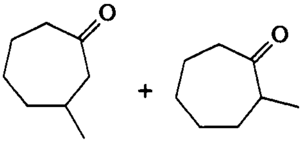<br>97:3 | 86 | 96b |
| 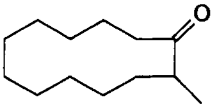 | 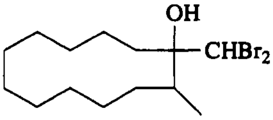 | 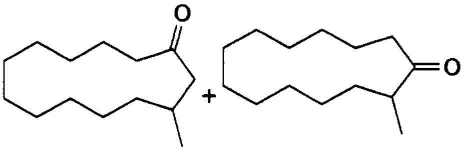<br>99:1 | 96 | 96b |
| 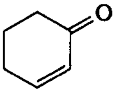 | 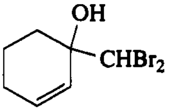 | 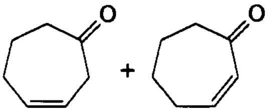<br>95:5 | 76 | 96b |
| 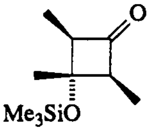 | 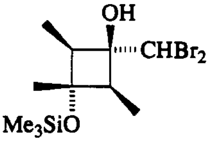 | 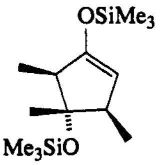 | 85 | 97 |

**Table 7** *(continued)*

| *Ketone* | *Adduct* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 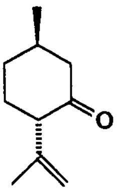 | 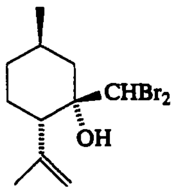 | 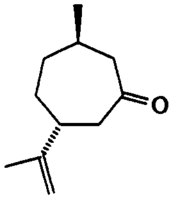 | 60 | 50 |
| 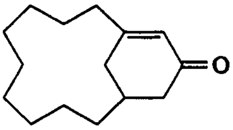 | 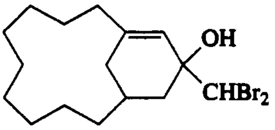 | 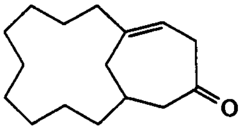 | 50 | 98 |
| 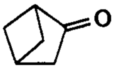 | 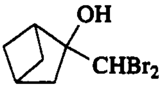<br>98% | 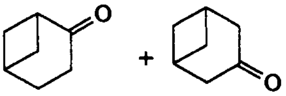<br>85:15 | 68 | 99 |
| 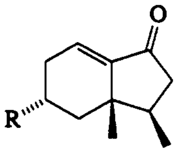 | 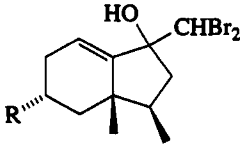 | 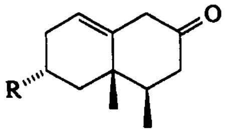 | | 100 |
| R = H | 86% | | 41 | |
| R = $MeC(=CH_2)$– | 60% | | 83 | |
| 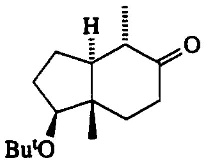 | 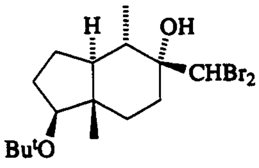 | 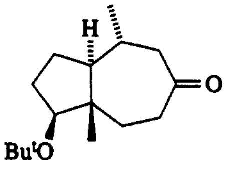 | 58 | 49 |
| 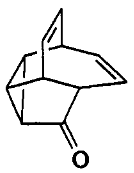 | 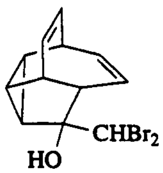 | 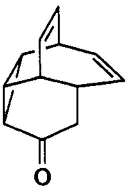 | 53 | 101 |
| 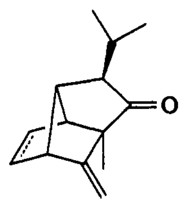 | 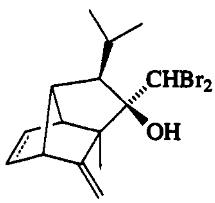 | 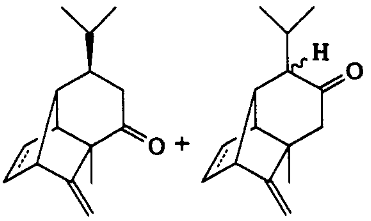 | | 102 |
| double bond | 63% | 73:27 | 56 | |
| single bond | 62% | 80:20 | 50 | |

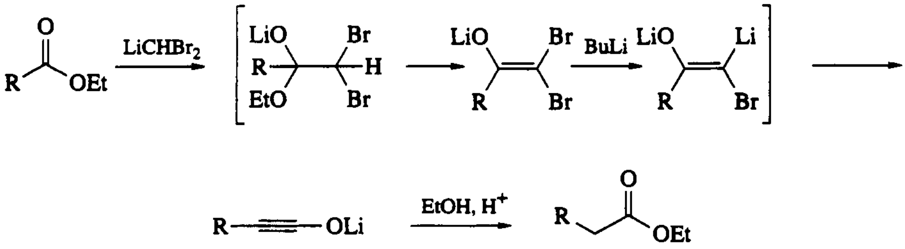
LiCHBr2
BuLi
EtOH, H+

Scheme 37

Table 8 Ester Homologation

| *Starting ester* | *Product* | *Yield (%)* |
|---|---|---|
| $PhCO_2Et$ | $PhCH_2CO_2Et$ | 65 |
| $PhCH_2CO_2Et$ | $PhCH_2CH_2CO_2Et$ | 74 |
| 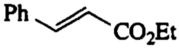 | 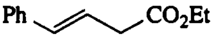 | 53 |
| 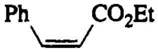 | 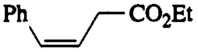 | 55 |
| 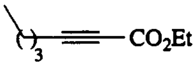 | 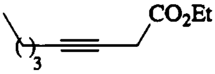 | 60 |
| 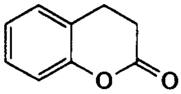 | 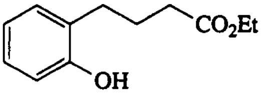 | 72 |
| 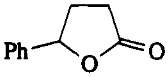 | 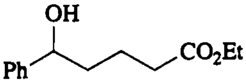 | 75 |
| 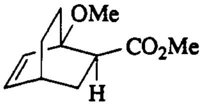 | 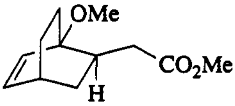 | 57 |
| 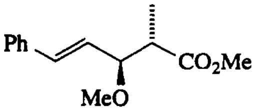 | 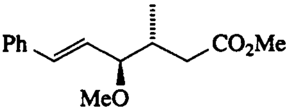 | 60 |
| 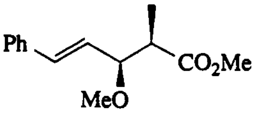 | 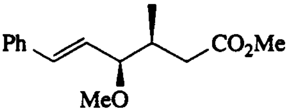 | 65 |

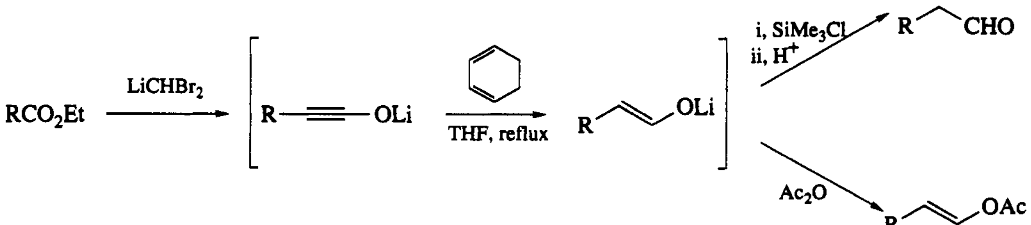
LiCHBr2
THF, reflux
i, SiMe3Cl
ii, H+
Ac2O

Scheme 38

### 3.3.5 MISCELLANEOUS HOMOLOGATION METHODS

In this section are homologation/expansion procedures which do not fit a strict addition–elimination with rearrangement type of process such as those described above. Included among these are known carbon–carbon bond-forming processes which, when applied to cyclic ketones, achieve ring expansions by forming, either transiently or in a stepwise manner, bicyclic systems that suffer fragmentations to the homologated ketone (Scheme 39). Several of these protocols provide the opportunity to introduce more than one carbon atom at a time.

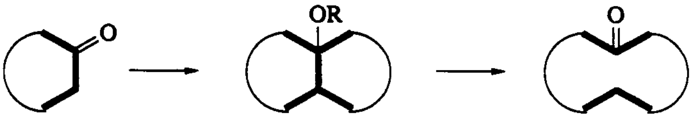

Scheme 39

#### 3.3.5.1 Rearrangement of Cyclopropanol Derivatives from Ketone Enols

This method is based on the known tendency of dihalocyclopropanol ethers to undergo solvolytic rearrangements.[105] Addition of dihalocarbenes[106] to enol ethers and acetates of cyclic ketones produces the corresponding dihalocyclopropane derivatives (Scheme 40). The cyclopropyl derivative may undergo an ionic ring-opening, either thermally or in the presence of silver salts, to provide either the α-halo-α,β-unsaturated ketone or the corresponding enol ether. Early studies with ethyl enol ethers indicated that, while homologation for the six-membered ring worked well, expansions of seven- and eight-membered ring ketones were not successful.[107] When the ring-opening step was carried out on the corresponding acetate derivatives in the presence of LiAlH$_4$, conditions which may alter the mechanistic aspects of the reaction, the expanded α-halo-α,β-unsaturated ketones could be obtained as the corresponding alcohols in good yields for five- through eight-membered ring ketones.[108]

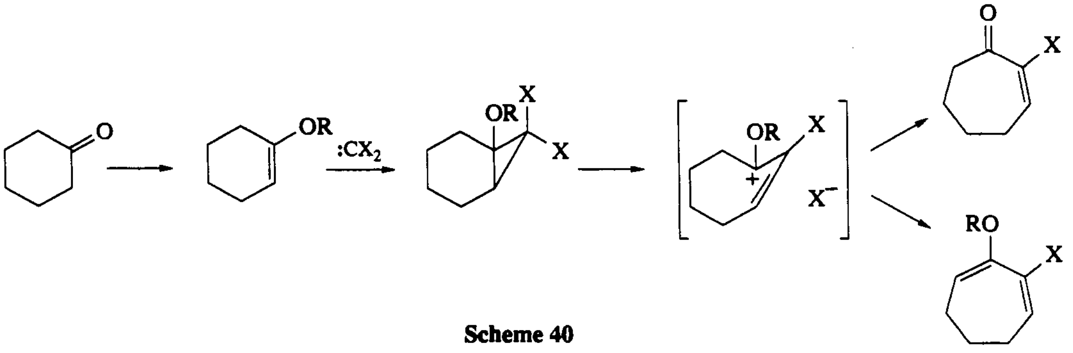

Scheme 40

Along these lines, cyclic enol esters, after reaction with dichlorocarbene, were found to undergo smooth expansion to the 2-chlorocycloheptenones on room temperature treatment with ethanolic potassium carbonate (Scheme 41).[109]

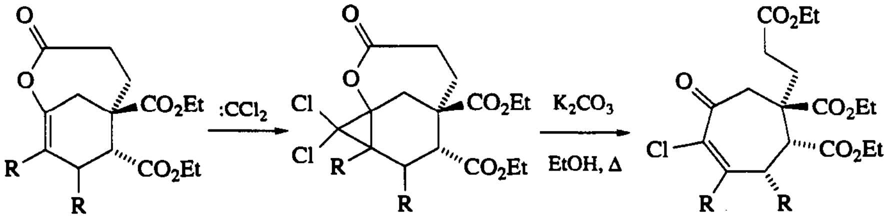

| *R* | *Yield* (%) | *Yield* (%) |
|---|---|---|
| Me | 80 | 62 |
| (CH$_2$)$_3$ | 66 | 65 |
| (CH$_2$)$_4$ | 80 | 55 |

Scheme 41

Similarly, the rearrangement of trialkylsilyloxycyclopropanes, obtained from the reaction of the silyl enol ethers of cyclic ketones with halocarbenes, may be carried out under either acidic (alcohol/HCl) or basic (alcohol/$Et_3N$) conditions. Since the regiochemistry of the expansion is fixed by the position of the starting enol ether, this variation has the further advantage that methods for the convenient regioselective generation of the silyl enols are well established.[110] Examples showing rearrangements from mono- and dihalo-cyclopropyl derivatives are given in Table 9.[111a–e]

**Table 9** Ring Expansion of Ketones *via* Halo Carbene Addition to Silyl Enol Ethers

| *Silyl enol ether* | *Carbene adduct* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 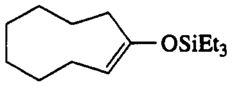 | 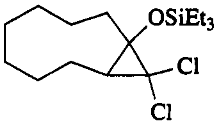 OSiEt3<br>Cl<br>Cl | 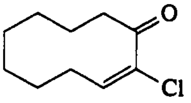 | 66 | 111a |
| 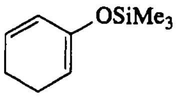 | 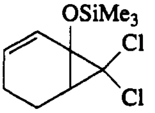 OSiMe3<br>Cl<br>Cl | 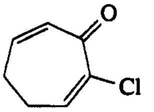 | 73 | 111b |
| 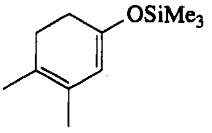 | 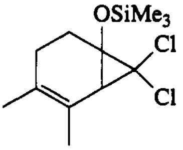 OSiMe3<br>Cl<br>Cl | 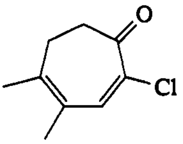 | 72 | 111b |
| 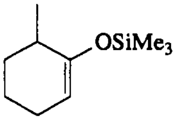 | 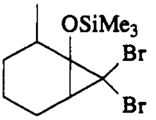 OSiMe3<br>Br<br>Br | 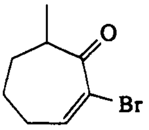 | 40 | 111c |
| 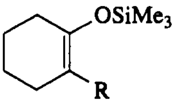 | 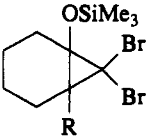 OSiMe3<br>Br<br>Br<br>R | 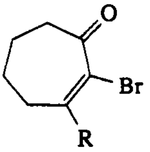 |  | 111c |
| R = H |  |  | 90 |  |
| R = Me |  |  | 40 |  |
| 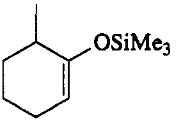 | 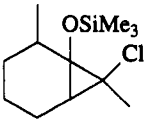 | 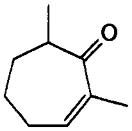 | 56 | 111d |
| 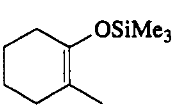 | 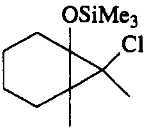 | 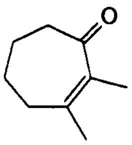 | 56 | 111d |
| 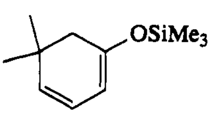 | 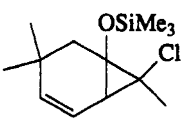 | 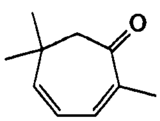 | 52 | 111e |

A similar, but mechanistically different, ring expansion sequence has been described using the iron(III) chloride induced opening of nonhalogenated cyclopropyl derivatives. In this case, the silyl enol ethers are cyclopropanated under Simmons–Smith conditions[112] and then exposed to $FeCl_3$ in dimethylformamide. The ring fission, rationalized in terms of a radical mechanism, produces the β-chloro-expanded ketone which, either spontaneously or with sodium acetate–methanol, eliminates chloride to yield the corresponding expanded enone (Scheme 42).[113] This protocol has been demonstrated for the homologation of five-, six-, seven- and twelve-membered ring ketones. An example which demonstrates a regioselective expansion by taking advantage of the *in situ* trapping of a regiospecifically generated enolate is shown in Scheme 43.[114]

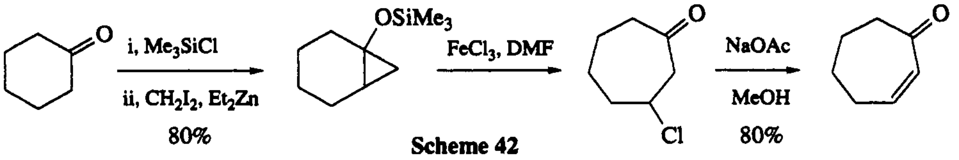

Scheme 42

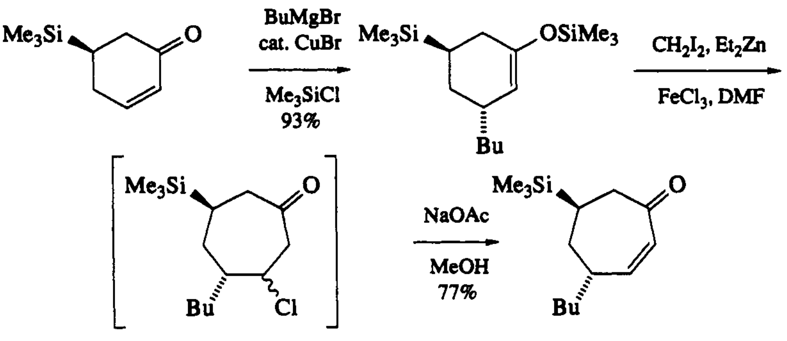

Scheme 43

### 3.3.5.2 Homologations *via* 3,3-Rearrangements

The 3,3-rearrangement of allylvinylcarbinols and their derivatives, also referred to as the oxy-Cope rearrangement, is a well-studied bond reorganization process that has found substantial use in synthesis. Since this topic has already been reviewed in depth in this series with regard to mechanistic detail and general synthetic application, the coverage here will be limited to those particular instances where simple ring homologations have been achieved.[115] The overall two-step process, illustrated in Scheme 44, first involves the addition of a vinyl organometallic to a ketone bearing a vinyl substituent. The thermal 3,3-rearrangement step is carried out on the carbinol (R = H), the ether derivatives (R = alkyl or $Me_3Si$) or, with a substantial rate increase,[116] the alkoxide (R = Na, K) to produce the enol derivative, which is subsequently transformed to the ketone. The net result of this operation is the insertion of a four-carbon unit, which for cyclic ketones ($R^1$ and $R^2$ are joined) translates to a four-carbon ring expansion.

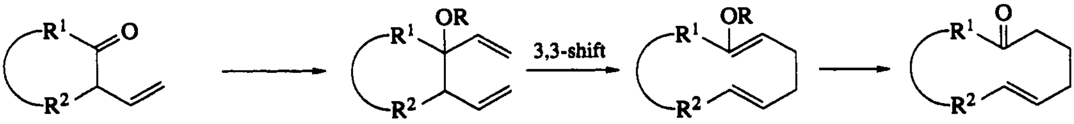

Scheme 44

The placement of the substituents on the ring establishes the regiochemistry of the expansion process, while the stereochemistry of the vinylcarbinol adduct influences the double bond geometry in the products and is illustrated in the following example. Addition of a vinyl organometallic to 2-vinylcyclohexanone produces two vinylcarbinols (Scheme 45).[117] The major isomer on thermolysis (220 °C, 3 h) produces the 10-membered ring ketone as a single isomer in 90% yield, while, on the other hand, the minor carbinol isomer produces a mixture of *cis*- and *trans*-enones. These results have been interpreted in terms of the preferred conformations of the the carbinols during rearrangement assuming a chair-like transition state.

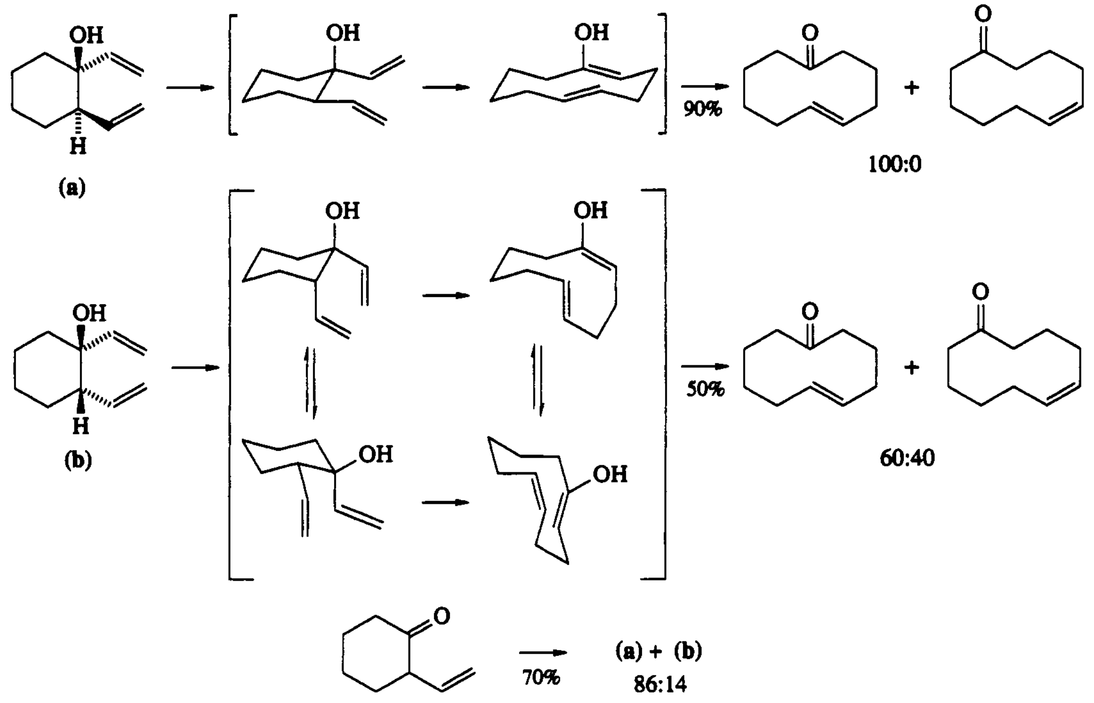
OH
H
(a)
OH
OH
90%
O
O
+
100:0
OH
H
(b)
OH
OH
OH
OH
50%
O
O
+
60:40
O
70%
(a) + (b)
86:14

Scheme 45

The ring size also influences the course of the reaction. For example, both the *cis*- and *trans*-divinylcyclopentanols lead to a single (*E*)-nonenone, while for the divinyldodecanols the *trans* isomer produces only the (*E*)-enone, whereas the *cis* isomer produces mostly the (*Z*)-enone (Scheme 46).[118] Relief of ring strain can provide a considerable driving force for the rearrangement, such as in the example shown in Scheme 47, where rearrangement of the carbinol occurs at only 50 °C.[119]

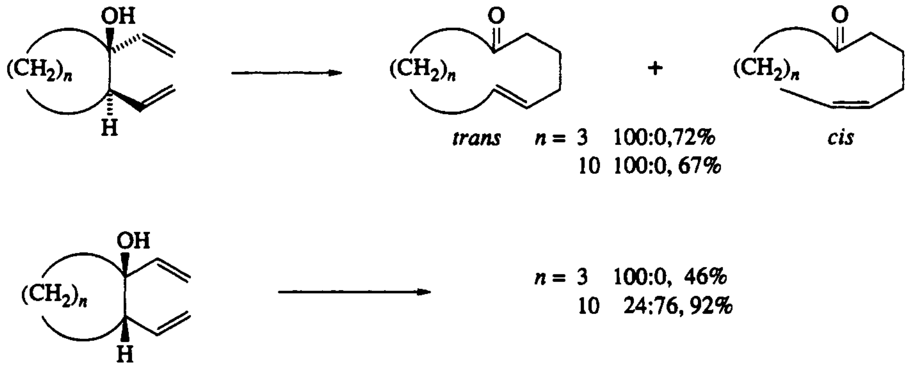
OH
(CH2)n
H
O
(CH2)n
+
O
(CH2)n
trans
n = 3 100:0,72%
10 100:0, 67%
cis
OH
(CH2)n
H
n = 3 100:0, 46%
10 24:76, 92%

Scheme 46

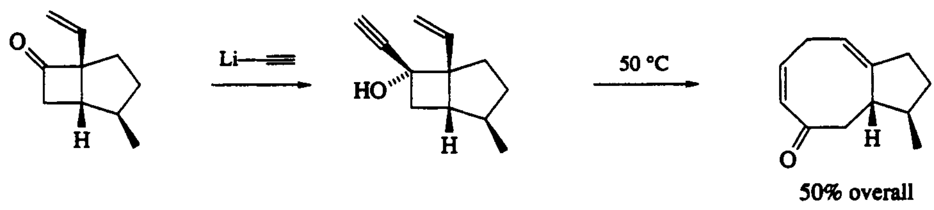
O
H
Li—≡
HO
H
50 °C
O
H
50% overall

Scheme 47

This basic strategy has found application in the synthesis of germacranes (Schemes 48,[120] 49[121] and 50[122]), where the initial addition of the vinyl organometallic to the ketone proceeded with a high level of stereoselectivity, which in turn led to the selective 3,3-rearrangement of the potassium alkoxides. The sequence depicted in Scheme 50 demonstrates the trapping of the regiospecifically generated enolate as a trimethylsilyl ether, and its subsequent reaction to form an α-hydroxy ketone as a single isomer. The regiospecific generation of the enol has also allowed for the regiospecific repetitive ring expansion process shown in Scheme 51.[123]

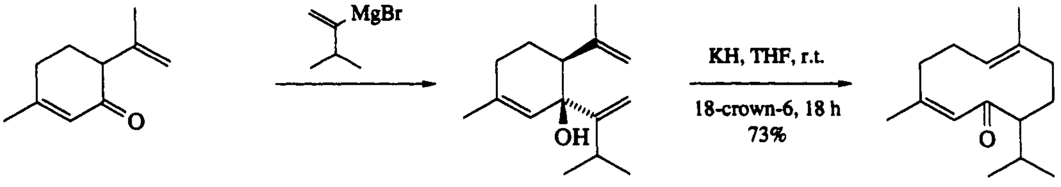

MgBr
O
OH
KH, THF, r.t.
18-crown-6, 18 h
73%
O
single isomer

**Scheme 48**

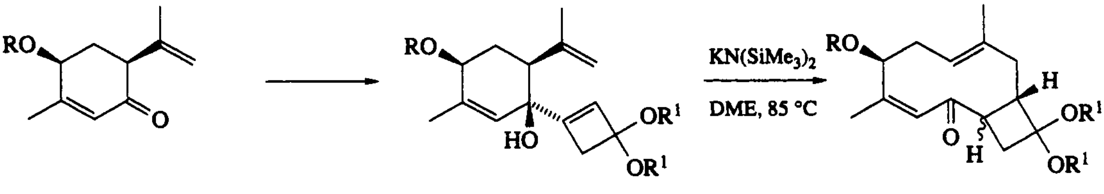

RO
O
RO
HO
OR1
OR1
KN(SiMe3)2
DME, 85 °C
RO
H
OR1
OR1
O
H

**Scheme 49**

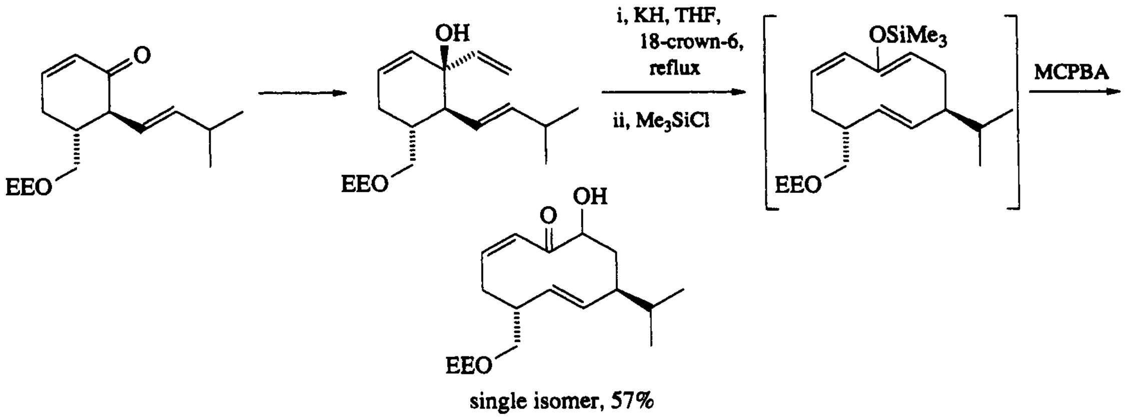

O
EEO
OH
EEO
i, KH, THF, 18-crown-6, reflux
ii, Me3SiCl
OSiMe3
EEO
MCPBA
O
OH
EEO
single isomer, 57%

**Scheme 50**

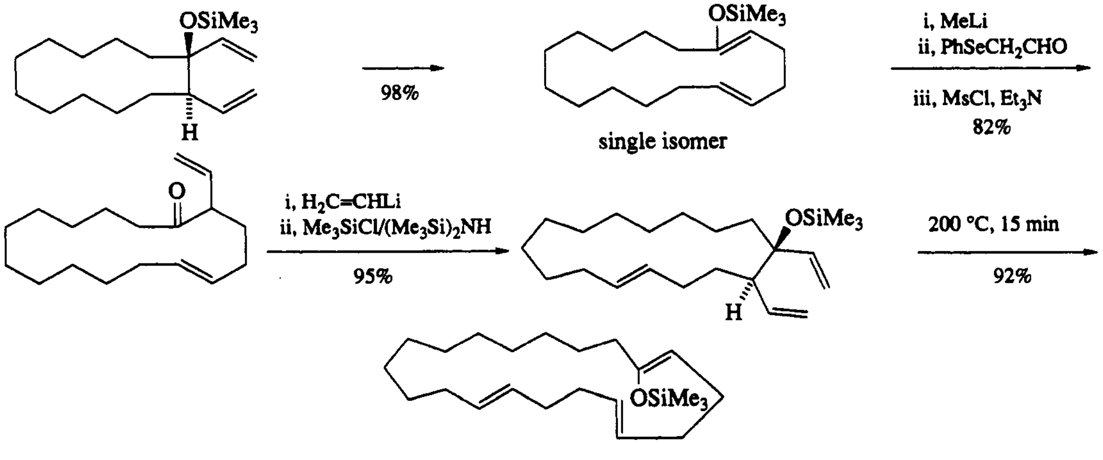

OSiMe3
H
98%
OSiMe3
single isomer
i, MeLi
ii, PhSeCH2CHO
iii, MsCl, Et3N
82%
O
i, H2C=CHLi
ii, Me3SiCl/(Me3Si)2NH
95%
OSiMe3
H
200 °C, 15 min
92%
OSiMe3

**Scheme 51**

A highly efficient route to the ophiobolin nucleus is a noteworthy application of the *in situ* enolate-trapping strategy (Scheme 52).[124] The 3,3-rearrangement of the intermediate divinyl alkoxide, produced from the addition of a cyclopentenyl anion to the bicyclic ketone, proceeds at low temperature *via* a boat-like transition state to generate the enolate. Subsequent trapping with methyl iodide provides the expanded, alkylated ketones in good overall yield. Transannular alkylations are feasible when an alkylating moiety resides on the reacting molecule, as illustrated in Scheme 53.[125] A stereochemical dependence for the transannular alkylation step has been observed in an unusual use of allylic ethers as alkylating agents. While the stereospecific 3,3-rearrangement proceeds for both the (*E*)- and (*Z*)-isomers shown in Scheme 54,[126] only the intermediate from the (*Z*)-enol ether undergoes the internal alkylation.

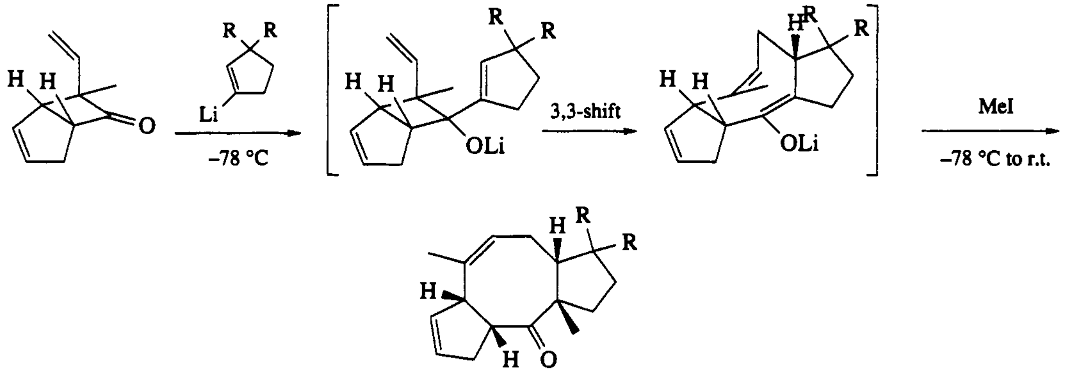

R = H, 96%; R = $SCH_2CH_2S$, 71%

Scheme 52

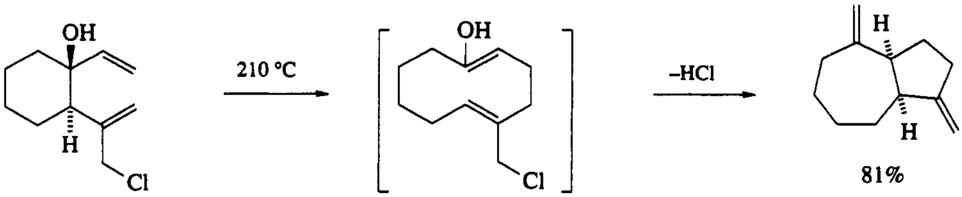

Scheme 53

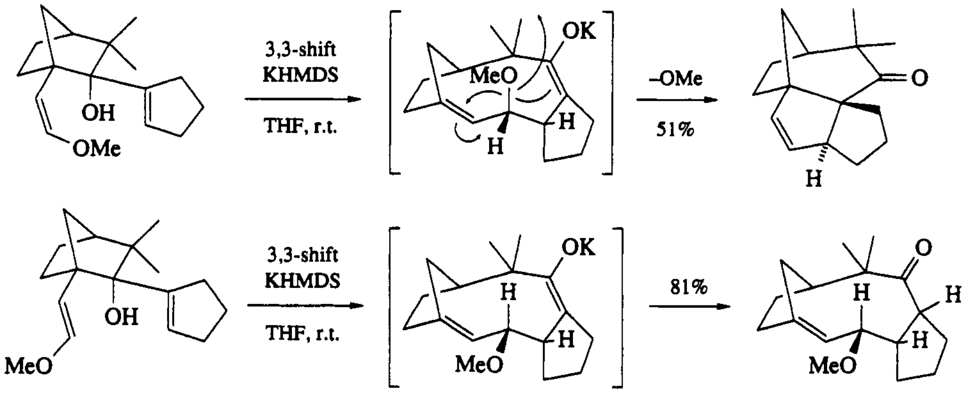

Scheme 54

Other variations of the 3,3-rearrangement have been reported where the vinyl unit is incorporated into a ring. Addition of vinyllithium to a cyclohexanespirocyclobutanone produces a mixture of two stereoisomeric alkoxides, one of which on warming to room temperature undergoes a smooth anionic oxy-Cope rearrangement to the octahydrobenzocyclooctene, while the other suffers ring fission (Scheme 55).[127] Interestingly, if the carbinols are isolated first by a low temperature quench and then transformed to the potassium alkoxides, the isomer with the *trans*-disposed vinyl units undergoes rearrangement to the hexahydronaphthalene ketone. This alternate reaction course, rationalized in terms of either a fragmentation–recombination process or a 1,3-rearrangement, has been utilized in other systems as a ring expansion process (see Section 3.3.5.3). The formation of bicyclo[5.3.1]undecenes has been made feasible *via* the anionic oxy-Cope rearrangement arising from either spirocyclobutanone systems or bicyclo[2.2.2]octane systems (Table 10). Significantly, a base-induced stereoisomerization has been suggested to explain the fact that, in the case of the spirocyclobutanones, either stereoisomer of the vinylcarbinol undergoes the rearrangement to the same product.[127]

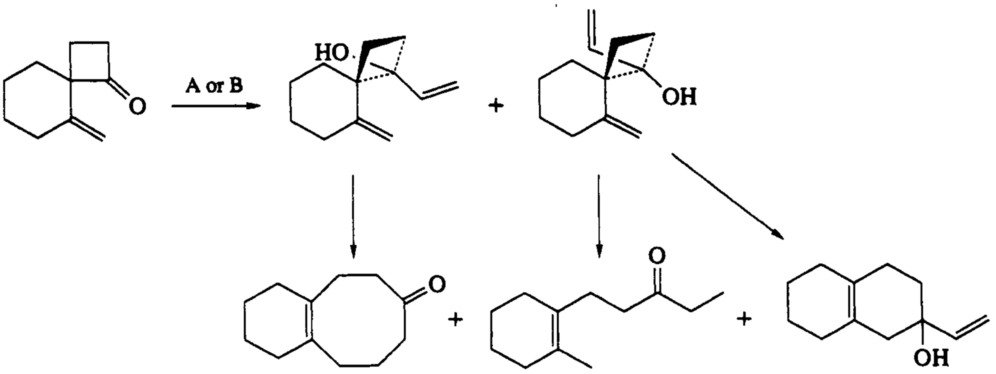

(A) i, $H_2C{=}CHLi$, –78 °C to r.t. 44:56:0 78%

(B) i, $H_2C{=}CHLi$, ii, quench, iii, KH, THF 44:0:56 43%

**Scheme 55**

**Table 10** Ring Expansion of Ketones *via* 1,3-Rearrangements

| *Ketone adduct* | *Rearrangement product* | | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 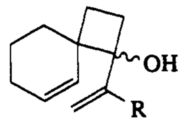 | 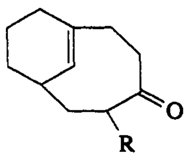 | R = H<br>R = Me | 80<br>72 | 128<br>127 |
| 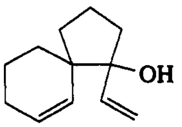 | 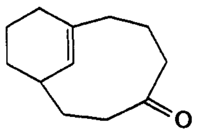 | | 83 | 129 |
| 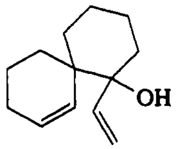 | 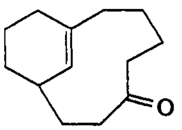 | | 79 | 129 |
| 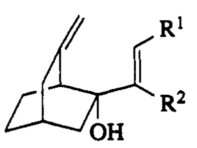<br>$R^1 = R^2 = H$<br>$R^1 = H, R^2 = Me$<br>$R^1 + R^2 = -(CH_2)_4-$ | 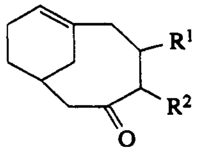 | | 70–85 | 130 |

**Table 10** *(continued)*

| *Ketone adduct* | *Rearrangement product* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 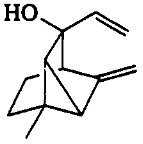 | 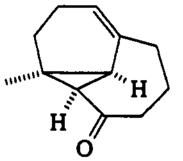 R = H<br>R = Me | 80<br>72<br>90 | 128<br>127<br>131 |
| 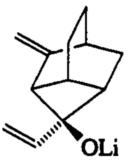 | 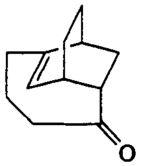 | 62 | 132 |

Even larger ring expansions are possible when bis(butadienyl) systems are employed. As exemplified in Schemes 56,[133a] 57[133b] and 58[133c] the process involves the addition of a butadienyl organometallic to a ketone bearing a butadienyl side chain. The 5,5-bond reorganization process of the resulting carbinol, which may in fact be the outcome of two consecutive 3,3-rearrangements, is conducted thermally as for the 3,3-rearrangements above.[133a–c]

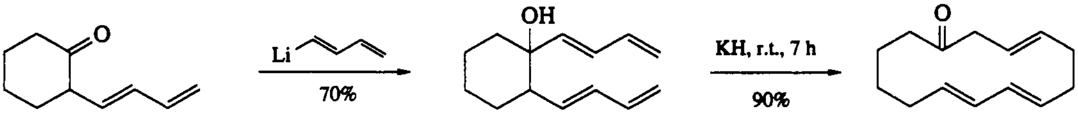
O
Li
70%
OH
KH, r.t., 7 h
90%
O

Scheme 56

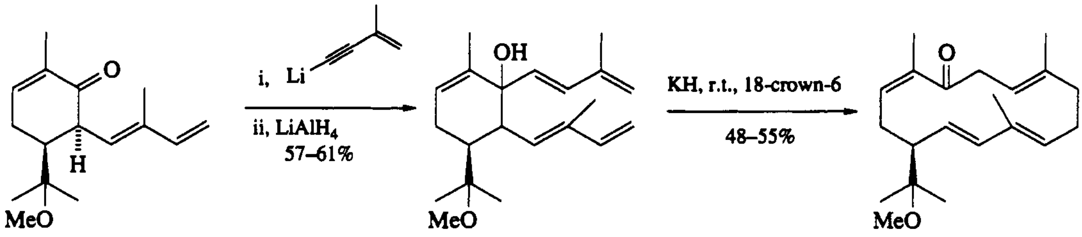
O
H
MeO
i, Li
ii, LiAlH4
57–61%
OH
MeO
KH, r.t., 18-crown-6
48–55%
O
MeO

Scheme 57

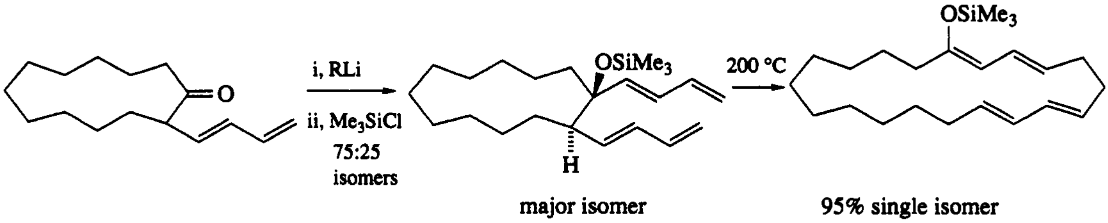
O
i, RLi
ii, Me3SiCl
75:25
isomers
OSiMe3
H
major isomer
200 °C
OSiMe3
95% single isomer

Scheme 58

### 3.3.5.3 Homologations *via* 1,3-Rearrangements

During the course of investigations on the 3,3-rearrangement of allylvinylcarbinols, some cases were found where 1,3-reaction pathways predominate (Scheme 59).[134] This alternative reaction sequence has been used to advantage for the two-carbon ring expansion in a number of ring systems. As in the 3,3-rearrangements, a substantial rate acceleration has been observed in the 1,3-rearrangements for the corresponding alkoxides, although this modification may well alter the reaction mechanism. Shown in Scheme 60 are examples of systems where the ring expansion *via* 1,3-rearrangement predominates in a synthetically useful manner over the alternative nonexpanding 3,3-rearrangement.[135]

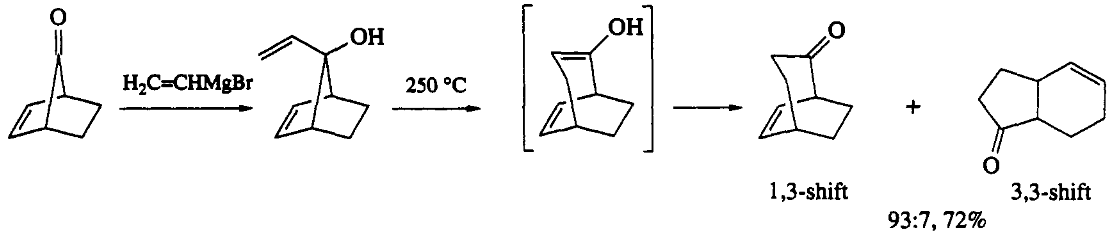
O
H₂C=CHMgBr
OH
250 °C
OH
O
+
O
1,3-shift
3,3-shift
93:7, 72%

Scheme 59

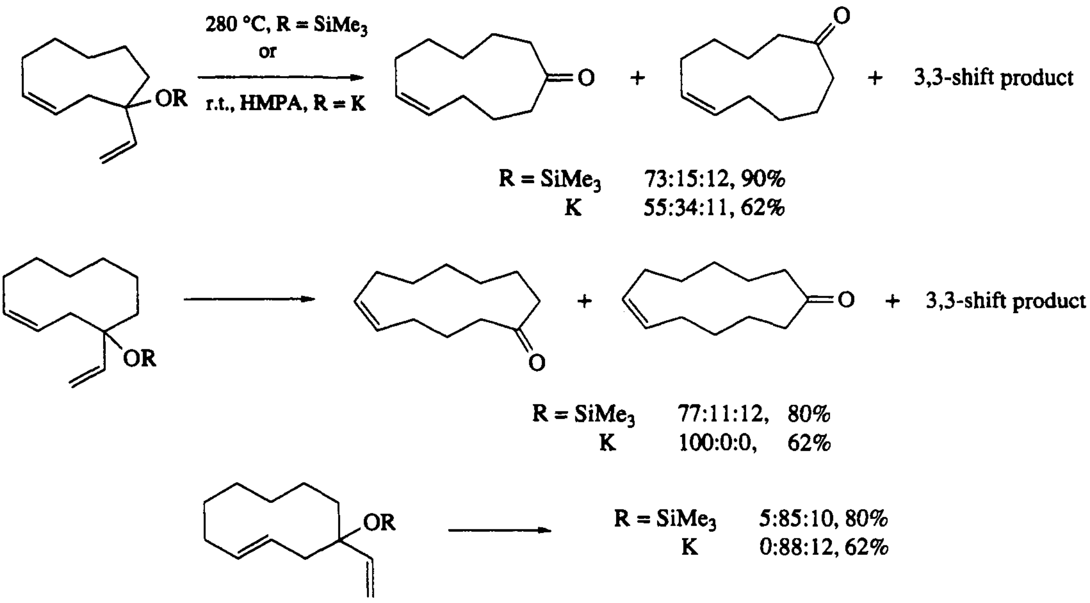
280 °C, R = SiMe₃
or
r.t., HMPA, R = K
OR
O
+
O
+ 3,3-shift product
R = SiMe₃ 73:15:12, 90%
K 55:34:11, 62%
OR
+
O
O
+ 3,3-shift product
R = SiMe₃ 77:11:12, 80%
K 100:0:0, 62%
OR
R = SiMe₃ 5:85:10, 80%
K 0:88:12, 62%

Scheme 60

This process for large rings is somewhat substrate sensitive. For example, the corresponding saturated ring systems do not undergo the rearrangement; however, the presence of a phenyl group on the carbon adjacent to the carbinol restores the facility of the 1,3-rearrangement.[136] In similar fashion, incorporation of an aromatic moiety into the ring system, also adjacent to the original ketone, allows for the execution of a two-carbon ring expansion (Schemes 61 and 62).[42,43] In the 13- to 15-membered ring ketone expansion, the competition between 1,3- and 3,3-rearrangement is dependent on both the rearrangement conditions and substitution patterns on the vinyl moiety (Scheme 63).[137]

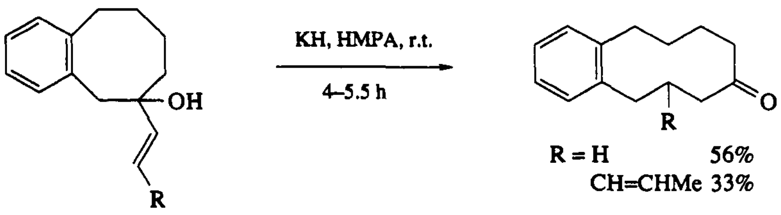
OH
R
KH, HMPA, r.t.
4–5.5 h
O
R
R = H 56%
CH=CHMe 33%

Scheme 61

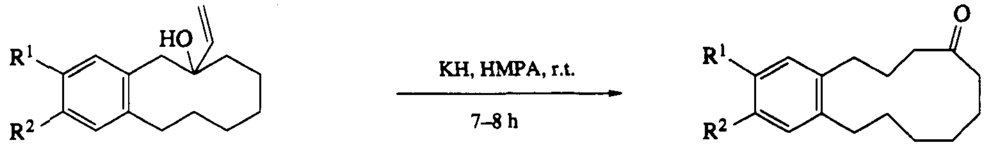

$R^1 = R^2 = H$ 70%
$R^1 = H, R^2 = OMe$ 90%
$R^1 = OMe, R^2 = H$ 54%

Scheme 62

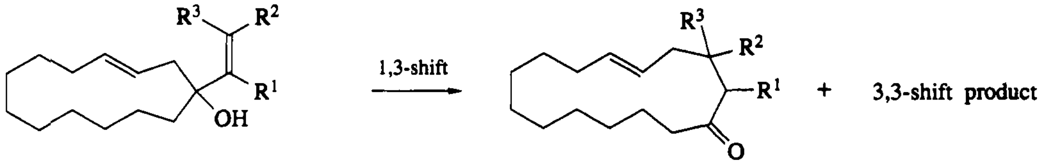

| *R¹* | *R²* | *R³* | *via TMS ether* | *via KH, HMPA* |
|---|---|---|---|---|
| H | H | H | 46:54, 79% | 13:87, 70% |
| Me | H | H | 15:85, 47% | 18:82, 62% |
| H | Me | H | 98:2 , 47% | 55:45, 39% |
| H | H | Me | 98:2, 55% | 46:54, 62% |

Scheme 63

The relief of ring strain in cyclobutanols also provides the driving force for alkoxide-induced 1,3-rearrangements (Scheme 64).[138] The reduction of α-vinyl-substituted cyclobutanones with borohydride reagents followed by methyllithium generates the intermediate alkoxides which, on warming, undergo the 1,3-rearrangement to the cyclohexanol derivatives. Examples are provided in Table 11. A reversal of the stereochemical outcome of the 1,3-rearrangement has been achieved by altering the reaction conditions. Further investigation of the intermediate isomeric alcohols has revealed that, for the example shown in Scheme 65, the *cis*-alcohol isomerizes to the *trans*-alcohol, which then undergoes the 1,3-rearrangement.[139] Moreover, this isomerization is accelerated by the addition of 18-crown-6, a modification which also changes the product distribution. This effect has been rationalized in terms of a fragmentation-recombination process where the geometry of the recombination step is changed according to whether the potassium ion is intramolecularly coordinated by the carbonyl oxygen or externally coordinated by the crown ether.

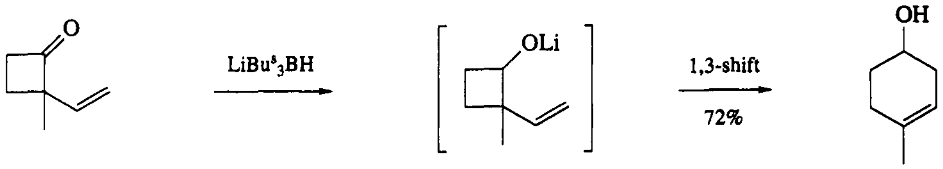

Scheme 64

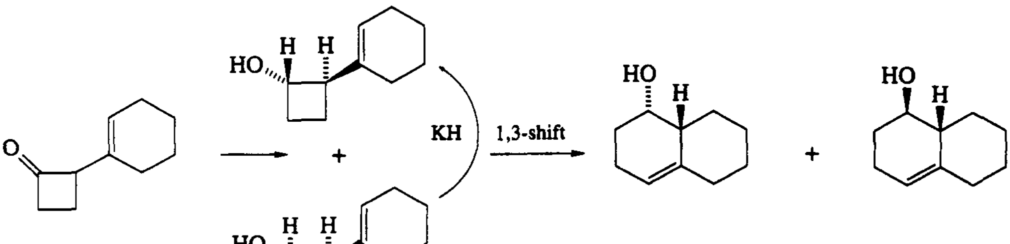

| | |
|---|---|
| KH/THF/reflux | 70:30, 88% |
| KH/18-crown-6/r.t. | 10:90, 98% |

Scheme 65

**Table 11** Ring Expansion of Cyclobutanones *via* 1,3-Rearrangements

| *Ketone* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 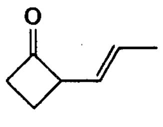 | 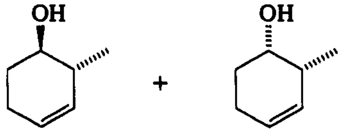<br>84:16 | 65 | 138 |
| 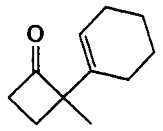 | 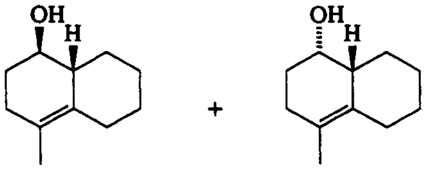<br>94:6 | 75 | 138 |
| 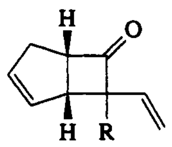 | 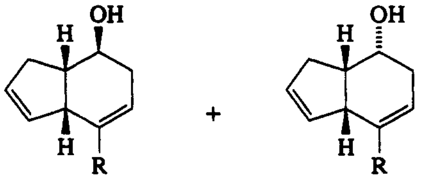 |  | 138 |
| R = H | 17:83 | 65 |  |
| R = Me | 83:17 | 70 |  |
| R = Bu | 90:10 | 89 |  |
| 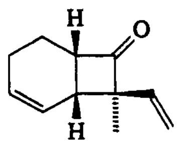 | 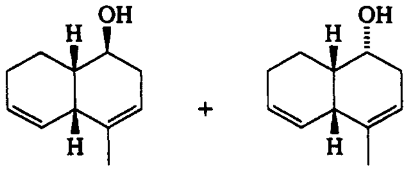<br>97:3 |  | 138 |
| 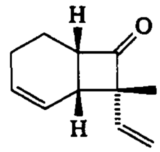 | 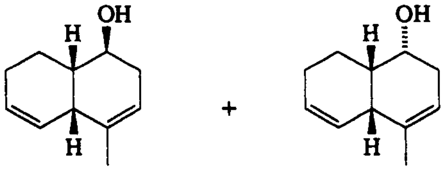<br>22:78 |  | 138 |
| 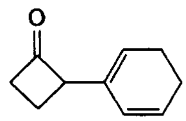 | 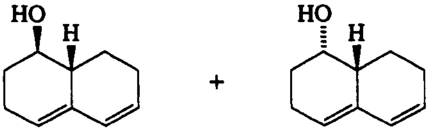<br>*trans*[a] 92:8<br>*cis*[a] 72:28 |  | 139 |

---

[a] Intermediate alcohols were isolated and treated separately with KH/THF.

### 3.3.5.4 Cationic Variations of the 3,3-Rearrangement

Ring expansions of appropriately α-substituted ketones *via* their vinyl carbinol derivatives has also been carried out under cationic conditions. The basic sequence, outlined in Scheme 66, begins with the addition of a vinyl organometallic to an α-substituted ketone, where X is carbon or a heteroatom. Departure of a leaving group Y then produces a cationic species, which may react further to form products. Two main pathways appear to be operative: one is a cationic alkene cyclization, followed by a pinacol-like rearrangement; while the other is a 3,3 or 3,3-like rearrangement, followed by an intramolecular alkylation of the intermediate enol.

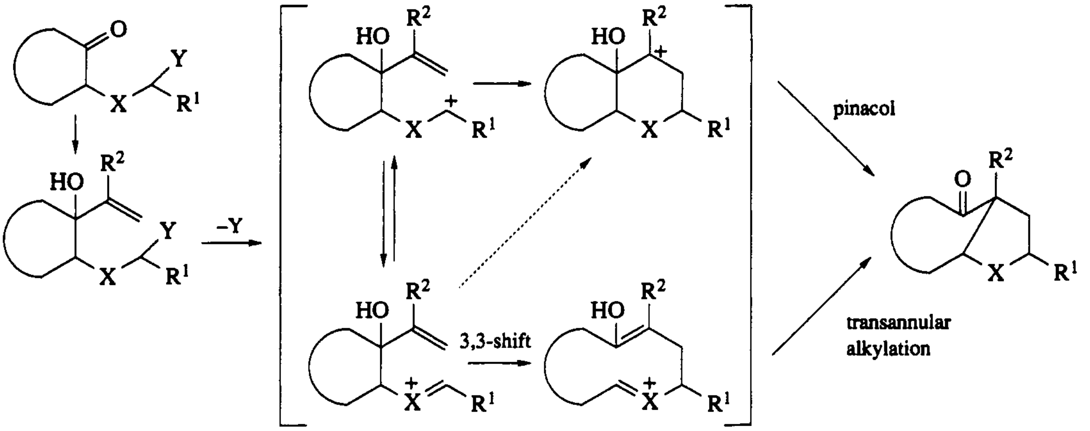

Scheme 66

When X is nitrogen, the overall process achieves ring expansion with a pyrrolidine annulation. Representative of this protocol is the addition of aryl-substituted vinyllithium reagents to the α-amino-substituted ketones, as shown in Scheme 67.[140] The vinylcarbinols, produced as *cis/trans* mixtures, are reduced to the secondary amines with sodium cyanoborohydride. On exposure of either isomer to paraformaldehyde and acid in dimethyl sulfoxide, intermediate iminium ions are formed that rearrange preferentially to the *cis*-fused bicyclic systems. Alternatively, the iminium ions may be generated through the acid or silver ion induced loss of cyanide from the related *N*-cyanomethyl derivatives. The process, shown in Scheme 68, involves the addition of a vinyllithium reagent in a *trans* fashion to the α-amino-substituted ketone.[141] Treatment with camphorsulfonic acid in refluxing benzene or silver nitrate at room temperature yields the *cis*-fused ring-expanded product. The procedure appears to be general for four- to five-, five- to six- and six- to seven-membered ring expansion–annulations, and has found utility in alkaloid synthesis, examples of which are depicted in Schemes 69[142] and 70.[143]

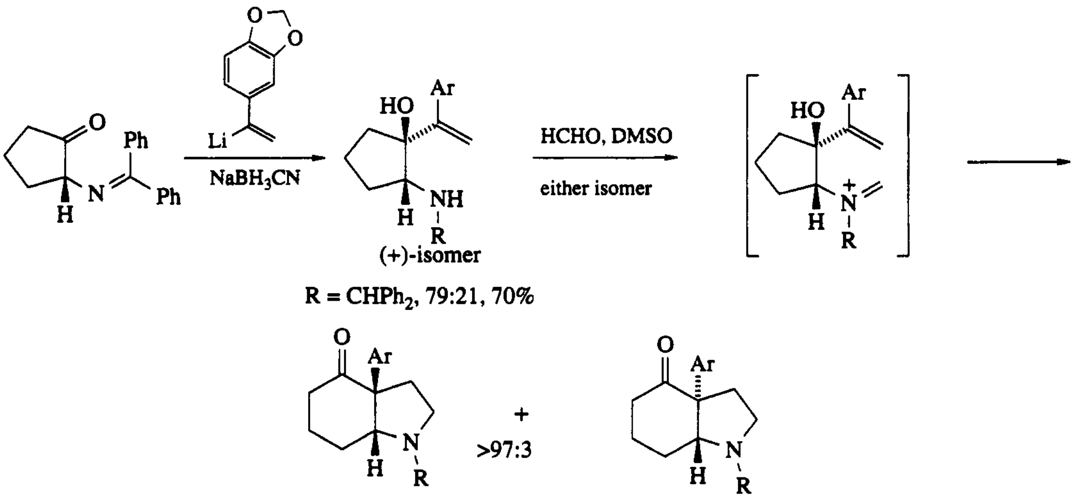

Scheme 67

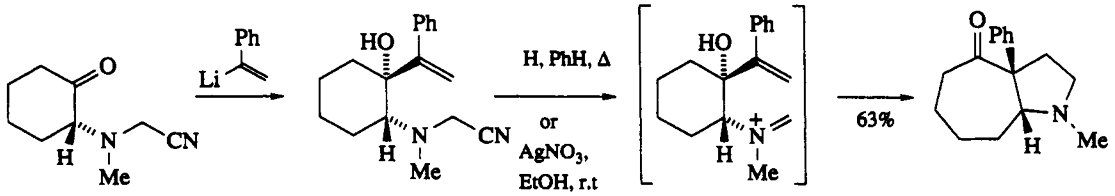

**Scheme 68**

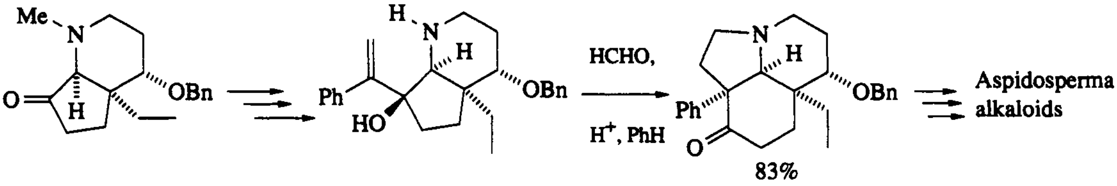

**Scheme 69**

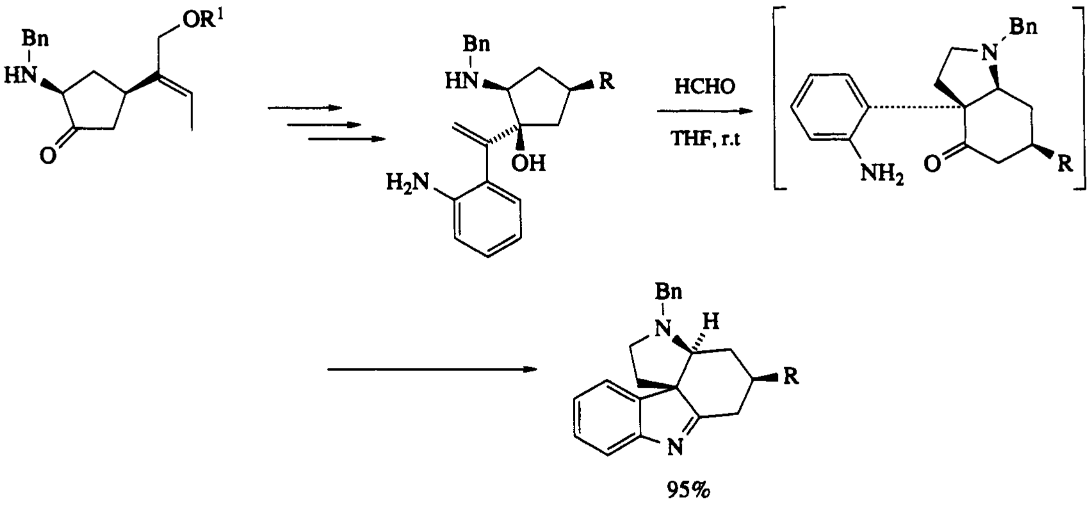

**Scheme 70**

The mechanistic interpretation of these results has favored the 3,3-like rearrangement–transannular alkylation pathway. Detailed conformational analyses on this basis have been advanced for the stereochemical outcome of the reaction.[140–144] Evidence in favor of the 3,3-rearrangement comes in part from the example in Scheme 71.[144] If a cationic alkene cyclization–pinacol-like rearrangement mechanism were operative and the substrate and product did not racemize under the reaction conditions, the optically active amino alcohol derivative would be expected to produce an optically active product. That a racemic product is formed suggests that the intermediate enol–iminium ion, which if formed in a chiral conformation by a 3,3-rearrangement, undergoes racemization by rotation around the single bond prior to ring closure. Supporting evidence comes from the example presented in Scheme 72,[145] where the rearrangement of optically active starting material produced optically pure product. The preservation of chirality is attributed to the restricted bond rotation imposed by the cyclic structure of the asymmetric enol conformation prior to the alkylation step.

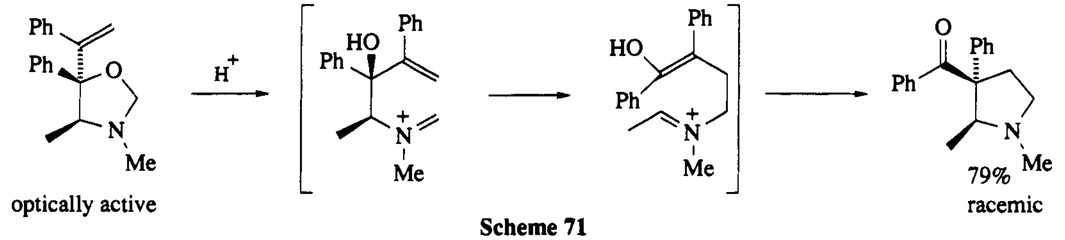
Ph
Ph
O
N
Me
optically active
H+
HO
Ph
Ph
N
Me
HO
Ph
Ph
N
Me
O
Ph
Ph
N
Me
79%
racemic

Scheme 71

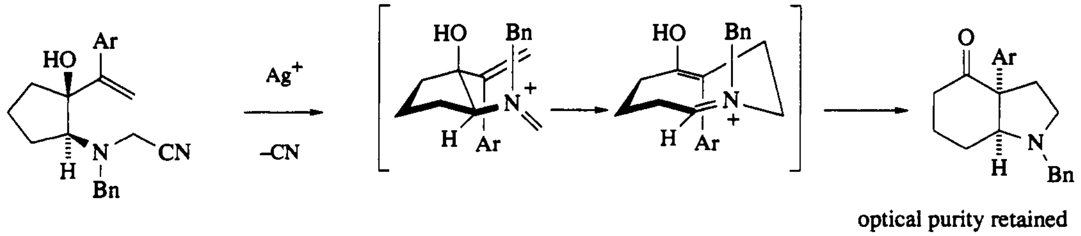
HO
Ar
N
CN
H
Bn
Ag+
-CN
HO
Bn
N
H
Ar
HO
Bn
N
H
Ar
O
Ar
N
H
Bn
optical purity retained

Scheme 72

In contrast, when the X group is oxygen, the reaction appears to follow the cationic alkene cylization–pinacol-like rearrangement pathway. In this case, reaction of an optically pure acyclic oxygen-containing analog of the system in Scheme 71 leads to a product with preservation of optical activity.[146] This reaction protocol, which accomplishes an overall ring expansion with a tetrahydrofuran annulation, has been examined for α-hydroxy-cyclopentanones and -cyclohexanones (Scheme 73 and equations 29–31).[147]

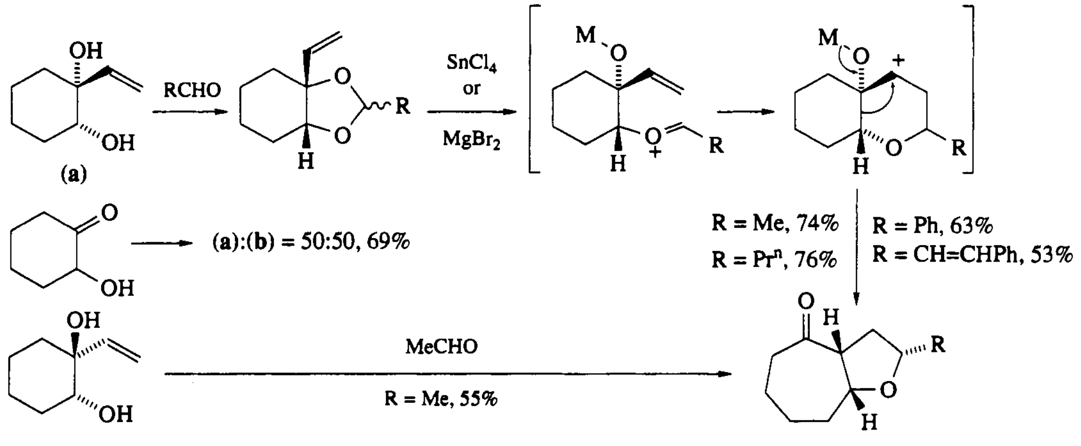
OH
OH
(a)
RCHO
O
O
R
H
SnCl4
or
MgBr2
M
O
O
R
H
M
O
O
R
H
O
OH
(a):(b) = 50:50, 69%
R = Me, 74%
R = Prn, 76%
R = Ph, 63%
R = CH=CHPh, 53%
OH
OH
(b)
MeCHO
R = Me, 55%
O
H
R
O
H

Scheme 73

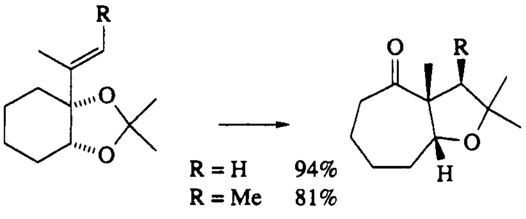
R
O
O
R = H 94%
R = Me 81%
O
R
O
H

(29)

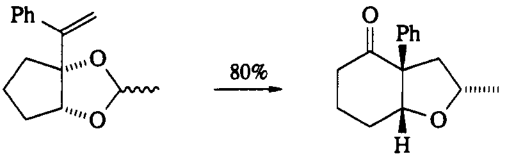
Ph
O
O
80%
O
Ph
O
H

(30)

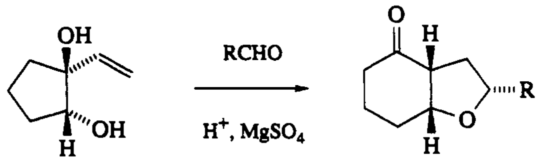

(31)

| R = | Yield |
|---|---|
| Ph | 47% |
| $CH=CH_2$ | 63% |
| $CH_2OBu^t$ | 56% |

The process has also been extended to the X = C series. The ring expansion–cyclopentane annulation provides good yields for the five- to six- (82%), six- to seven- (90%) and seven- to eight-membered ring (75%) ketone series studied (Scheme 74 and equations 32 and 33).[148,149]

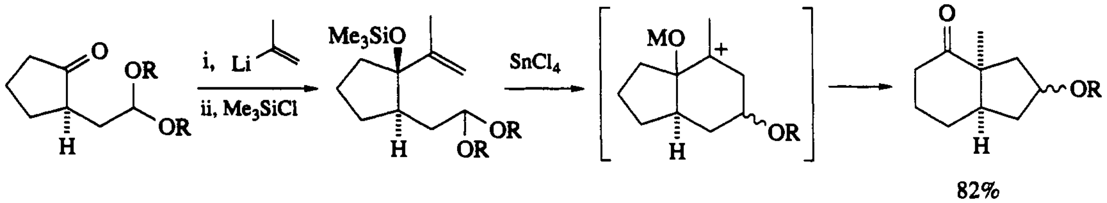

**Scheme 74**

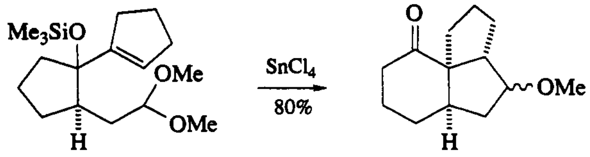

(32)

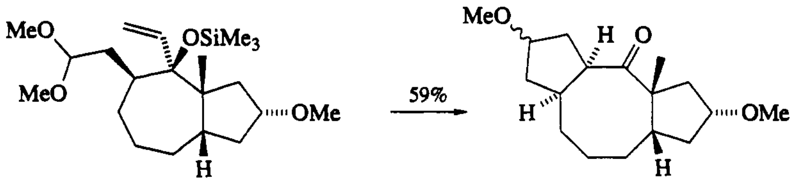

(33)

### 3.3.5.5 Expansion by Intramolecular Addition–Fragmentation

Another homologation strategy is the intramolecular addition of nucleophiles to the ketone carbonyl followed by a fragmentation reaction, which may be facilitated by a charge-stabilizing group X (Scheme 75).[150] The reaction, with X = $SO_2Ph$, $NO_2$ or CN, has been examined mostly for the expansion of cyclic ketones, although a few acyclic examples exist. The sequence does have the virtue that the presence of the electron-withdrawing group X allows for the convenient attachment of the requisite side chain. The sulfone-based methodology utilizes the fluoride-induced intramolecular addition of an allyl silane to the ketone catalytically in the first stage and stoichiometrically for the fragmentation step (Scheme 76). The reaction works well for the three-carbon expansion of five-, eight- and twelve-membered ring ketones, as well as an acyclic case (equation 34), but fails at the fragmentation step for six- and seven-membered ring ketones.[151]

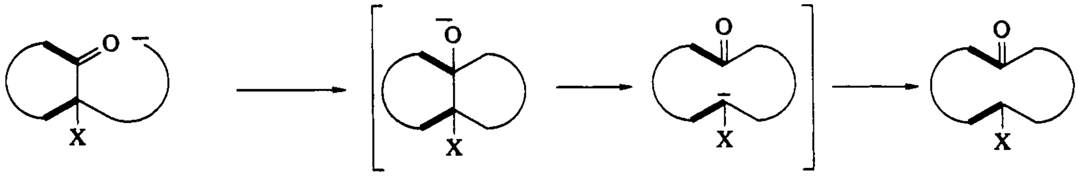

**Scheme 75**

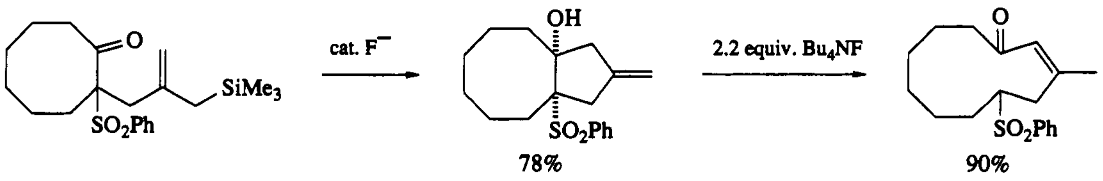
O
SiMe$_3$
SO$_2$Ph
cat. F$^-$
OH
SO$_2$Ph
78%
2.2 equiv. Bu$_4$NF
O
SO$_2$Ph
90%

**Scheme 76**

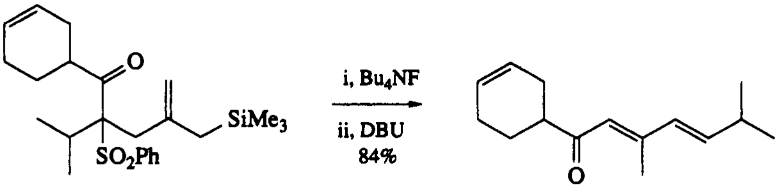
O
SiMe$_3$
SO$_2$Ph
i, Bu$_4$NF
ii, DBU
84%
O

(34)

A four-carbon ring expansion, where X is nitro, has been reported to proceed well for seven- and eight-membered ring ketones, poorly for the 12-membered ring ketone, and fails at the fragmentation step for five- and six-membered ring ketones (equation 35).[152] A successful three-carbon expansion has been reported for the octanone where X is cyano (equation 36).[153] For these anionic type addition–fragmentation reactions, the success of the sequence is dependent to a large extent on the fragmentation of the intermediate carbinol derivative, which in turn has been correlated in part with the release of ring strain.

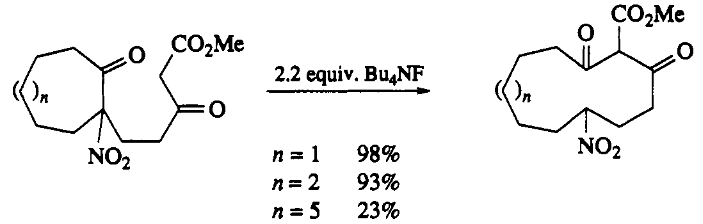
O
CO$_2$Me
( )$_n$
O
NO$_2$
2.2 equiv. Bu$_4$NF
$n$ = 1 98%
$n$ = 2 93%
$n$ = 5 23%
CO$_2$Me
O
O
( )$_n$
NO$_2$

(35)

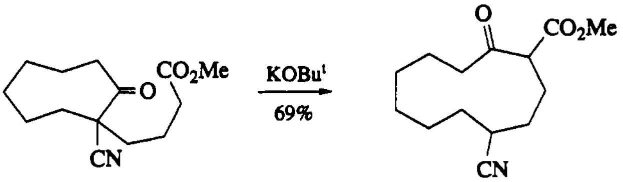
CO$_2$Me
O
CN
KOBu$^t$
69%
O
CO$_2$Me
CN

(36)

More recently, a radical-mediated variation of this addition–fragmentation has been explored. The reaction, summarized in Scheme 77 for a one-carbon expansion, involves the generation of a radical at the terminus of a chain by homolytic cleavage of a carbon–heteroatom bond. Addition of the radical to the carbonyl produces a bicyclic intermediate, which on cleavage of the alternate bond regenerates the ketone carbonyl group with formation of a new radical. The sequence is terminated by the reduction of the radical with the tributyltin hydride reagent. The near neutral conditions of the reaction avoid the reclo-

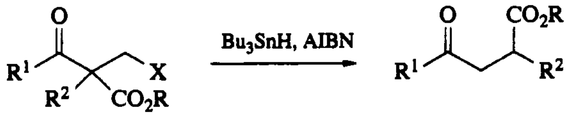
O
R$^1$
X
R$^2$
CO$_2$R
Bu$_3$SnH, AIBN
O
CO$_2$R
R$^1$
R$^2$

(37)

| *R$^1$* | *R$^2$* | *X* | *Yield* (%) |
|---|---|---|---|
| CO$_2$Et | H | Br | 76 |
| Me | H | Br | 64 |
| SEt | Me | I | 91 |

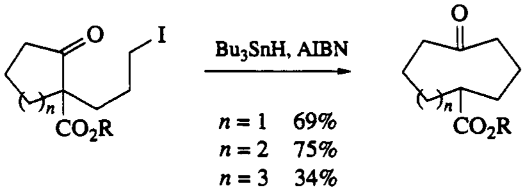

(38)

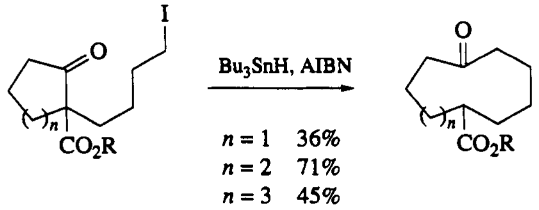

(39)

sure or nonfragmentation complication encountered in the anionic series above. The sequence proceeds in good yield for the one-carbon expansion of the five-, six-, seven- and eight-membered ring ketones studied (Scheme 77) as well as acyclic ketones (equation 37).[154,155] While the corresponding two-carbon homologation has not been successful, three- and four-carbon expansions are viable, although in some cases reduction at the chain terminus competes with the expansion reaction (equations 38 and 39).[154–156]

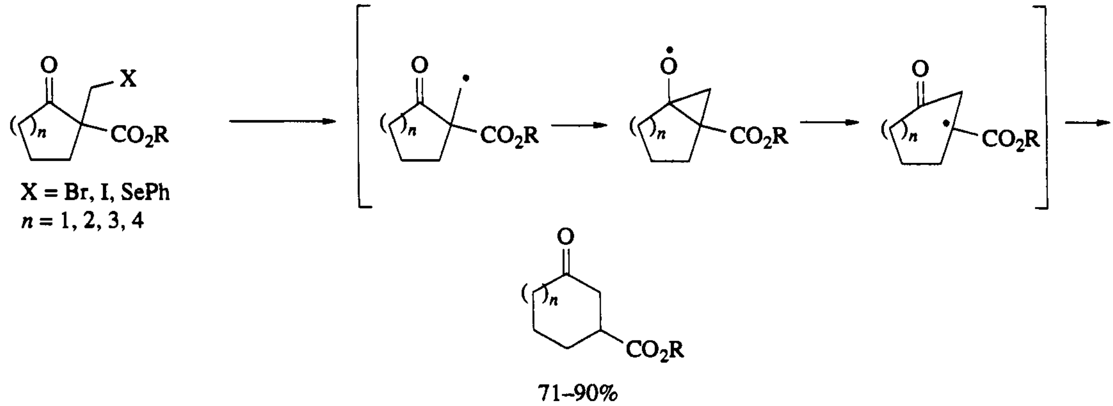

**Scheme 77**

A slightly different approach has been utilized for the three-carbon expansion in a system which does not contain a carboalkoxy group. The initial intramolecular addition step is carried out separately with butyllithium or samarium diiodide to give a bicyclic alcohol (Scheme 78).[157] The radical-induced fragmentation step is carried out photochemically in the presence of mercury(II) oxide and iodine to provide the expanded iodo ketone.

An alternate radical-induced addition–fragmentation sequence relies on the 1,4-elimination of a leaving group to drive the reaction.[158] In this sequence, because the fragmentation is accompanied by the expulsion of a tributylstannyl radical, the requirement for the initial tributyltin hydride is only catalytic (Scheme 79).[159] The stereospecificity of the reaction course has been rationalized in terms of a conformational preference for the elimination step, as depicted in Scheme 79 where the *trans*-substituted cyclohexanone forms only one double bond geometry in the product.[160] As shown in equations (40) and (41), the *cis*-substituted cyclohexanones undergo the four- and three-carbon expansions stereospecifically to give the (*Z*)-alkenes.

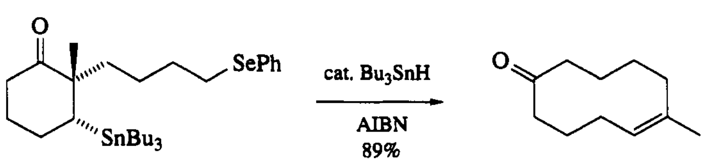

(40)

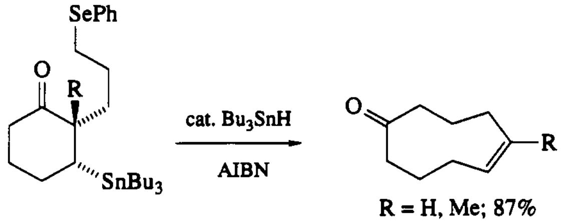

(41)

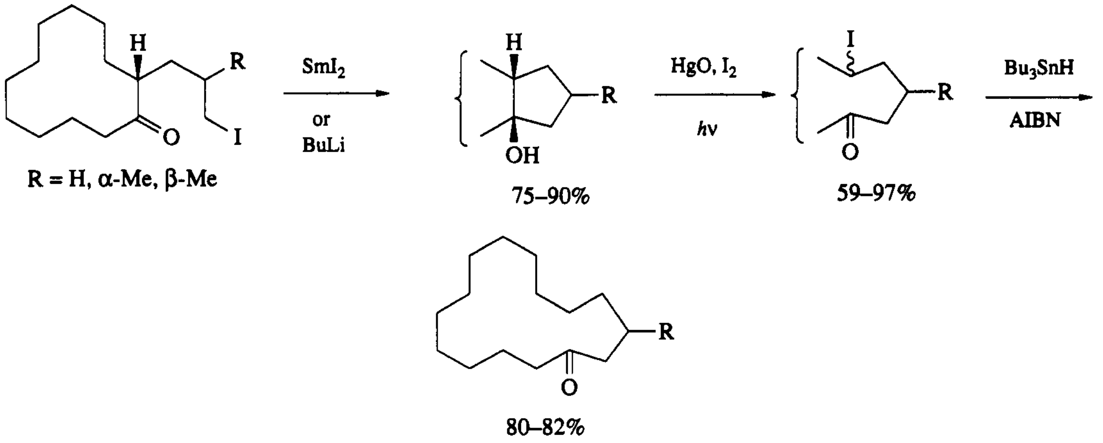

**Scheme 78**

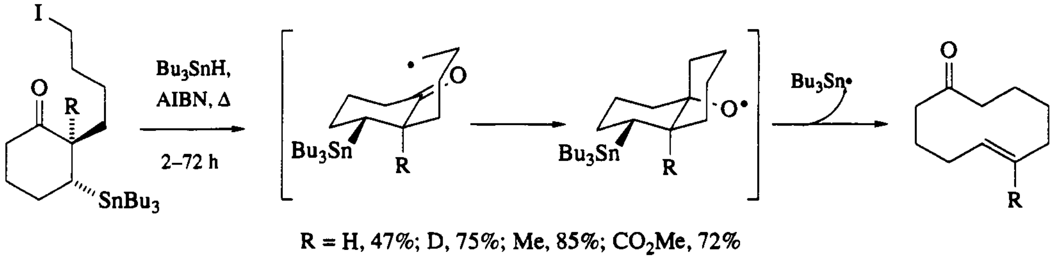

**Scheme 79**

## 3.3.6 REFERENCES

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# Author Index

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Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

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The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# 1.1

# Allyl Organometallics

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## 1.1.1 INTRODUCTION

The widespread occurrence and biological significance of the macrolide ansamycin and polyether antibiotics, and of polyhydroxylated natural products, including rare carbohydrates, among others, has stimulated considerable interest in the development of concise, efficient synthetic methodology for the stereo- and enantio-selective construction of stereochemically adorned acyclic molecules.[1,2] Indeed, considerable effort has been devoted towards the development of highly stereoselective syntheses of the so-called propionate (*e.g.*—CHMe—CHOH—CHMe—CHOH—), acetate (*e.g.*—CHOH—$CH_2$CHOH—$CH_2$—)

and glycolate (*e.g.*—CHOH—CHOH—CHOH—) segments that are commonly found in these natural products.[3]

Methods that involve C—C bond formation with the establishment of two new stereogenic centers are of considerable interest in this context. The aldol reaction has proven very useful in this regard, particularly in view of the development of powerful chiral enolates capable of controlling the stereochemical course of reactions with chiral aldehydes *via* the principle of double asymmetric synthesis.[4,5]

The reactions of allyl metal reagents and carbonyl compounds offer a complementary approach to the aldol reaction for acyclic stereocontrol.[6] Many allyl metal reagents are known, many react with high stereoselectivity with carbonyl compounds and imines, and in nearly all cases the reactions are operationally straightforward. Additional synthetic versatility is provided by the ease of preparation of many substituted and highly functionalized allyl organometallic reagents, and the ability to store many of these (*e.g.* B, Si and Sn based reagents) until needed. Besides serving as 'aldol equivalents', the homoallylic alcohol products are easily manipulated to other useful synthetic intermediates by transformations of the double bond (Scheme 1).

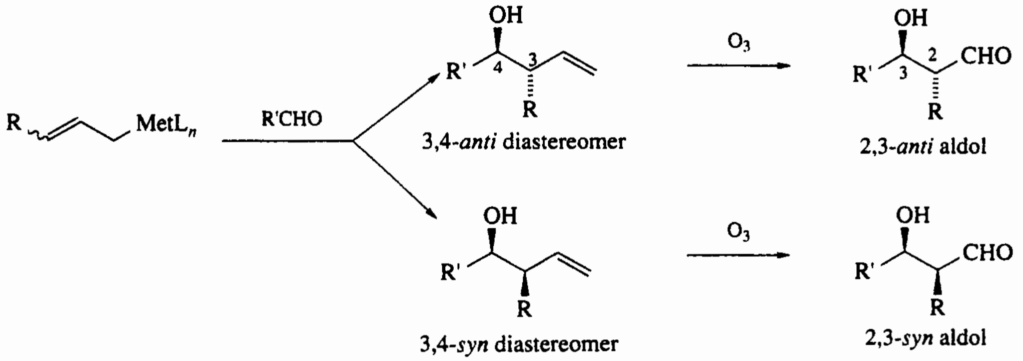

**Scheme 1**

Several factors must be considered in selecting a crotyl metal or allyl metal reagent for use in an acyclic stereoselective synthesis. First, it is necessary that the new stereocenters generated in concert with the new C—C bond (Scheme 1) be formed with a high degree of stereoselectivity. This is the problem of simple diastereoselectivity. Two diastereomeric products may be produced, and in this chapter Masamune's *syn*/*anti* nomenclature system will be used to describe them.[7] Second, the issue of diastereofacial selectivity is encountered if the aldehyde (or other C═X reaction partner) is chiral. This is a problem of relative diastereoselectivity, and four products may be produced in the reactions of the crotyl organometallics (Scheme 2). The diastereofacial selectivity issue is also critical in the reactions of allyl metal reagents and chiral C═X electrophiles.

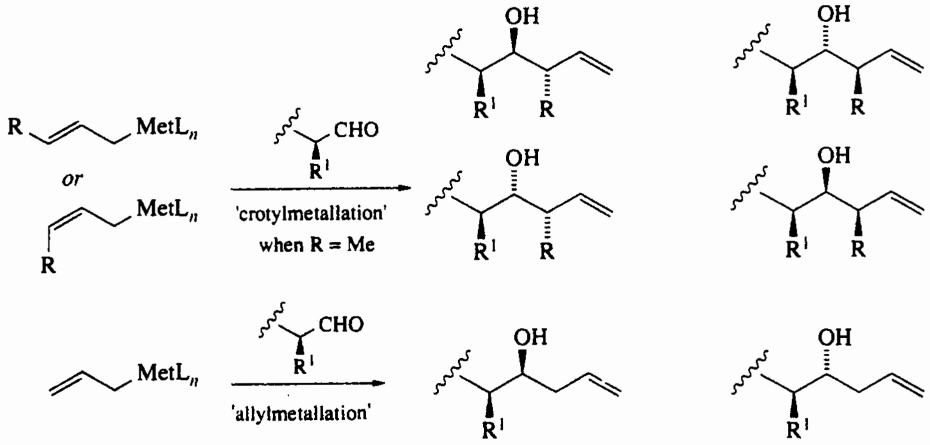

**Scheme 2**

A major goal of research in the allyl metal area has been the development of a family of allyl organometallic reagents that provide highly selective access to each of the four possible crotyl adducts and the two possible allyl adducts indicated in Scheme 2. While many crotyl organometallic solutions exist to the problem of simple diastereoselection, the issue of aldehyde diastereofacial selectivity (relative diastereoselection) has been much more difficult to solve. Although specific cases have been reported, and are reviewed here, that proceed with excellent selectivity, these are exceptions to the general rule that poor to moderate diastereofacial selectivity is obtained in reactions of chiral aldehydes and achiral allyl or crotyl metal compounds. Thus, recourse to the powerful technique of double asymmetric synthesis is generally required to achieve synthetically useful levels of selectivity in reactions of the type summarized in Scheme 2.

The purpose of this review is to provide a summary (through to the end of 1988) of the uncatalyzed reactions of type I and type III allyl organometallics with C═X electrophiles. Most of the examples involve aldehydes and ketones, but the reactions of allyl organometallics with imines are also covered. Because the focus of this review is on selectivity and synthetic efficiency, this review is not intended to be as comprehensive as an 'Organic Reactions' chapter or a *Chemical Reviews* article. Rather, we have attempted to define and illustrate the factors that influence stereoselectivity, to provide access to the most pertinent literature, and, most importantly, to provide a basis for selection of an allyl organometallic reagent for application in specific synthetic problems.

## 1.1.2 SIMPLE DIASTEREOSELECTION

### 1.1.2.1 General Considerations

#### *1.1.2.1.1 Mechanistic classification of crotyl organometallics*

The reactions of carbonyl compounds and imines with allyl metal and crotyl metal reagents derived from a variety of metals, including aluminum, antimony, bismuth, boron, cadmium, chromium, cerium, copper, indium, lithium, magnesium, manganese, molybdenum, potassium, silicon, tin, titanium, zinc and zirconium, among others, have been investigated.[6] Prior to approximately 1978 the major interest was in controlling the $S_E2$ or $S_E2'$ regioselectivity in the coupling of allylic organometallics and electrophiles.[6a] Roughly 10 years ago, however, significant synthetic interest began to emerge in the control of the stereochemistry of the C—C bond formed in the reactions with carbonyl electrophiles.[8] Heathcock reported in 1978 that the Hiyama (*E*)-crotylchromium(II) reagent undergoes highly *anti* selective additions to aldehydes,[9] and in 1979 Hoffmann reported that (*Z*)-crotylboronates provide the *syn*-homoallylic alcohol products stereoselectively.[10]

Three classes of crotyl organometallics have now been identified, based on mechanistic and stereochemical preferences.[11]

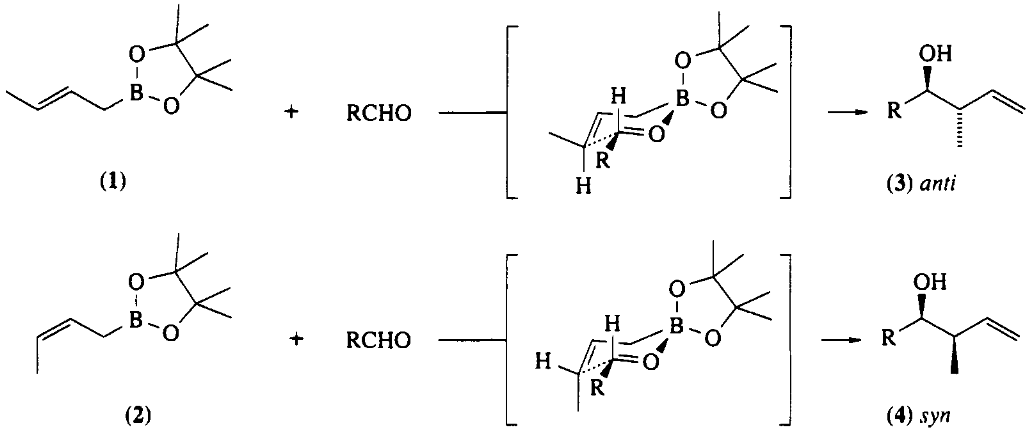

Scheme 3 Type I aldehyde addition reactions of crotylboronic esters

Type I crotyl organometallics react with aldehydes, presumably *via* chair-like transition states, such that the stereochemical information present in the reagent is transmitted to an *anti* (from (*E*)-alkene precursors) or a *syn* (from (*Z*)-alkene precursors) relationship about the new C—C bond of the product (Scheme 3). A detailed analysis of possible transition states appears in a subsequent section. Type I stereoselectivity has been observed for crotyl organometallics incorporating boron, aluminum, silicon and tin (thermal reactions).

Type II crotyl organometallic reagents undergo Lewis acid catalyzed carbonyl additions *via* pathways that tend to be stereoconvergent. That is, both geometric isomers of the reagent preferentially lead to the same (*syn*) product diastereomer (Scheme 4). Reagents based on tin, silicon and titanium, among others,[14b] belong in this category.[12–14]

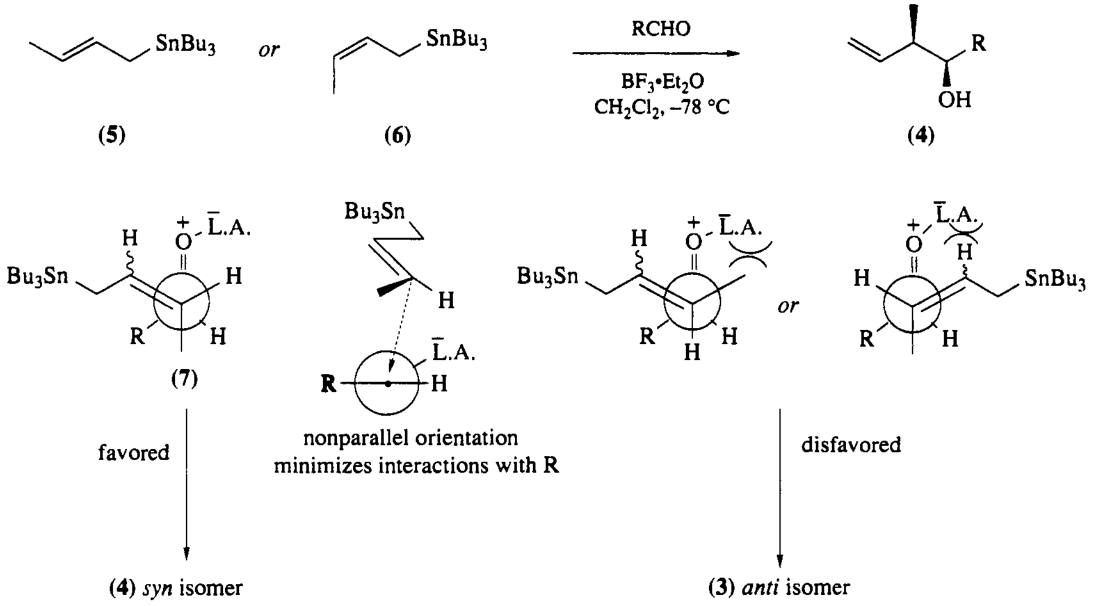

SnBu3
or
SnBu3
RCHO
BF3•Et2O
CH2Cl2, –78 °C
R
OH
(5)
(6)
(4)
Bu3Sn
L.A.
H
R
(7)
or
favored
nonparallel orientation
minimizes interactions with R
disfavored
(4) syn isomer
(3) anti isomer

**Scheme 4** Type II Lewis acid catalyzed aldehyde addition reactions of crotylstannanes

The stereoconvergence of the Lewis acid catalyzed reactions of aldehydes and crotylstannanes (**5**) and (**6**) is particularly striking, with very high *syn* selectivity being realized with either reagent and $BF_3·Et_2O$ as catalyst.[12a,c] These reactions have been reported to proceed through open, acyclic transition states in which the carbonyl oxygen is coordinated with a Lewis acid and the reagent double bond approaches the carbonyl oxygen in an antiperiplanar fashion.[12a] However, stereochemical studies performed by Denmark suggest that a synclinal orientation may be preferred.[15] The stereoconvergence is most easily ra-

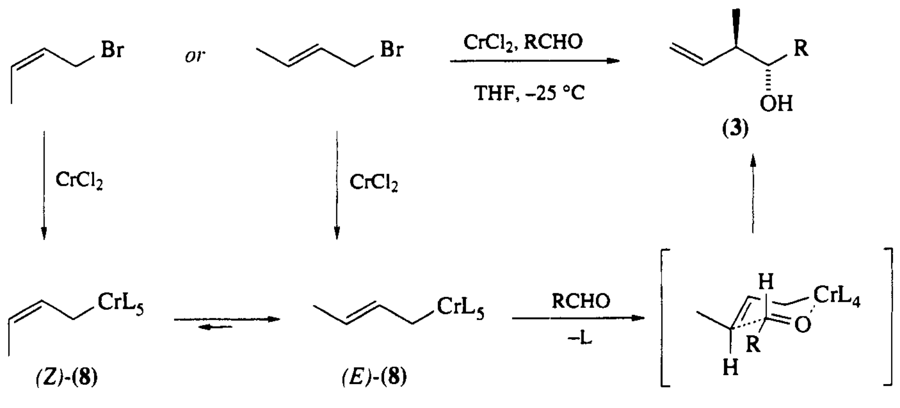

Br
or
Br
CrCl2, RCHO
THF, –25 °C
R
OH
(3)
CrCl2
CrCl2
CrL5
CrL5
(Z)-(8)
(E)-(8)
RCHO
–L
H
CrL4
O
R
H

**Scheme 5** Type III reactivity of crotylchromium(II) reagents tionalized if it is assumed that the two reactants approach in a nonparallel manner so as to minimize interactions between the allyl metal reagent and R (see 7 in Scheme 4).[16]

The type II Lewis acid catalyzed additions of allyl organometallics with C═X electrophiles are not covered in this chapter, since this is the topic of a separate survey elsewhere in this volume (see Chapter 2.2).

Type III crotyl organometallics react with aldehydes to give mainly the *anti* addition product regardless of the alkene geometry of the reagent (or its precursors).[9b,c,17–19] Type III crotyl metal reagents typically are generated *in situ* and presumably equilibrate to the more stable and/or more reactive (*E*)-isomer, which then reacts *via* a cyclic transition state to give the *anti* adduct (Scheme 5). This is strikingly demonstrated by the reactions of the crotylchromium reagent (**8**) generated either from (*E*)- or (*Z*)-crotyl bromide and $CrCl_2$: both experiments provide the *anti*-homoallyl alcohol (**3**) from PhCHO with very high diastereoselectivity.[9b,c] Other well-studied, synthetically useful type III crotyl organometallics are based on Ti and Zr.[17–19]

### *1.1.2.1.2 Configurational stability of crotyl organometallics*

The principal difference between type I and type III crotyl organometallics is their configurational stability (type I), or lack thereof (type III), under the conditions of the reactions with C═X electrophiles. The stereochemical integrity of type I allyl organometallics is obviously critical to their successful application in synthesis, since any (*E*) to (*Z*) isomerization prior to reaction will have a detrimental effect on the ratio of 3,4-*anti*/*syn* product diastereomers. It is obviously necessary as well that they be accessible by highly stereoselective synthetic routes, and preferably also be stable to storage. The lack of configurational stability of type III reagents, however, means that high stereochemical control need not be exercised over the construction of allylic halide or other organometallic precursors. Thus, for example, many type III crotyl-titanium and -zirconium reagents are prepared from crotyllithium or crotylmagnesium bromide, which exist as mixtures of rapidly equilibrating (*E*)- and (*Z*)-isomers,[20] since the (*Z*)-crotyl-titanium or -zirconium species equilibrates rapidly to the (*E*)-isomer, which is either highly favored at equilibrium or the more reactive of the two.[17,19] Crotyllithium or crotylmagnesium bromide, however, cannot be used in the preparation of type I crotyl organometallics since mixtures of (*E*)- and (*Z*)-isomers will be produced. One route to configurationally defined type I crotyl organometallics thus involves the (*E*)- and (*Z*)-crotylpotassiums that can be generated with high isomeric purity and are configurationally stable in the absence of traces of $O_2$.[20a,21]

Allyl metal compounds can exist in either the monohapto $\eta^1$- or trihapto $\eta^3$-forms. Crotyl metal compounds that exist in the $\eta^1$-form, including those classified as type I reagents, are generally sensitive to metallotropic rearrangements (sequential 1,3-shifts) which affect (*E*) to (*Z*) isomerization *via* the intermediacy of the methallyl metal isomer (Scheme 6). Trihapto, or π-bound, allyl metal reagents can exist in either of two forms: the extended or (*E*)-isomer, and the U-shaped or (*Z*)-isomer. These $\eta^3$-reagents can also isomerize if a pathway for interconversion with the $\eta^1$-methallyl intermediate is energetically accessible.

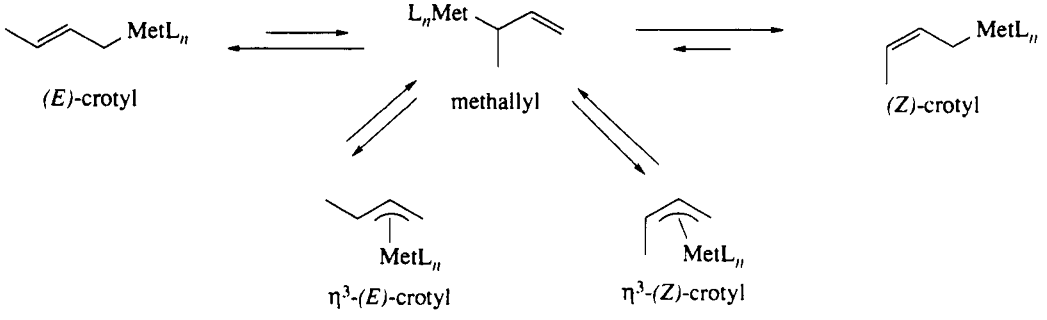

**Scheme 6**

Allylboron compounds have been the most widely studied of the type I allyl organometallics.[6b] Of these, the dialkylcrotylboranes isomerize most readily and often require handling at temperatures below –78 °C for isomerization to be suppressed.[22] Thus, it is probably more appropriate to view such compounds (*e.g.* crotyl-9-BBN) as type III crotyl organometallics. The boratropic isomerization of dialkylcrotylboranes, however, is sensitive to steric factors. For example, the (*E*)- and

(*Z*)-crotyldiisopinocampheylboranes undergo highly stereoselective additions to aldehydes at –78 °C.[23] Nevertheless, these reagents are too labile to be prepared and stored for subsequent use.[23c] The boratropic shift may also be suppressed by replacing the alkyl ligands on boron with electron-donating alkoxy or amino groups that stabilize the electrophilic boron atom by resonance. Replacement of one alkyl ligand of an allyldialkylborane with an alkoxy group stabilizes the reagent at temperatures up to –20 °C, but using an amino ligand suppresses the boratropic rearrangement at temperatures up to 150 °C.[24] Replacement of both alkyl ligands with alkoxy groups gives allylboronic acid esters that can be handled at room temperature without isomerization; many have been distilled and their isomeric purity determined by capillary GC analysis.[25] These heteroatom-stabilized allylboron reagents, however, readily isomerize in the presence of Lewis acids.[10b,26]

Type I crotyl metal reagents based on silicon and tin have also proven useful synthetically. Crotyltrimethylsilane is reported to be configurationally stable at elevated temperatures,[27] but only type II carbonyl addition reactions (Lewis acid catalyzed) have been reported for this compound. Type I reactivity has been demonstrated for pentacoordinate crotyl silicates, and available stereochemical evidence suggests that these reagents are configurationally stable.[28] The crotyltrialkylstannanes, on the other hand, undergo carbonyl additions either thermally (type I reactivity)[8a] or in the presence of Lewis acid catalysts (type II reactivity).[12] These compounds readily isomerize in the presence of Lewis acids,[12c,29] and there are also indications that they may spontaneously isomerize (uncatalyzed) at temperatures below 100 °C.[30] Configurational instability, however, has not been demonstrated under the conditions of thermal additions to aldehydes.[8] Crotylstannanes such as (crotyl)SnX$_3$ and (crotyl)SnR$_n$X$_{3-n}$ are more reactive than the trialkylcrotylstannanes,[31] and are probably highly prone to isomerization because of the Lewis acidity of the tin atom.[29,32]

Configurational lability is desirable in type III reagents, in as much as one geometric isomer is more reactive and/or highly favored at equilibrium. $\eta^1$-Crotyl-chromium, -titanium and -zirconium compounds apparently satisfy these requirements,[9,17,18] while $\eta^3$-crotyltitanium reagents such as dicyclopentadienylcrotyltitanium appear to be configurationally stable.[19] $\eta^3$-Cyclopentadienylcrotylmolybdenum complexes also appear to be stable.[33]

Many other crotyl organometallics that would be classified as type III reagents based on their configurational instability, including crotyl-cadmium, -lithium, -magnesium and -zinc, are not generally useful for diastereoselective synthetic conversions since mixtures of *syn*- and *anti*-homoallyl alcohols are obtained in reactions with achiral aldehydes.[6d] The equilibrium between the (*E*)- and (*Z*)-crotyl isomers is not highly biased in these cases,[20] consequently the poor diastereoselectivity suggests that the two isomers have comparable reactivity towards carbonyl electrophiles. Synthetically useful results have been obtained with reagents containing these metals only in cases where the crotyl metal compound is sterically biased or contains chelating substituents such that one geometric isomer is substantially favored at equilibrium.[34]

### 1.1.2.1.3 Transition states for the reactions of type I and type III crotyl organometallics with C=X electrophiles

Another factor that influences the diastereoselectivity of the C—C bond-forming process concerns the selectivity for reaction through a single transition state. Clearly, if two or more diastereomeric transition states are accessible, the reaction diastereoselectivity will suffer.

Possible transition states for the reactions of type I and III crotyl organometallics with aldehydes are depicted in Scheme 7. Most of the available stereochemical evidence suggests that these reactions proceed preferentially through transition state (**12**) in which the metal is coordinated to the carbonyl oxygen *syn* to the smallest carbonyl substituent, H. This necessitates that R of RCHO adopt an equatorial position if the transition state is chair-like, an arrangement that is structurally similar to the Zimmerman–Traxler model commonly invoked for many aldol reactions.[4a] Transition states (**13**) and (**14**), however, may potentially intervene and are frequently cited to rationalize the production of minor diastereomers (**17**).

These reactions are probably initiated by the coordination of the carbonyl group with the Lewis acidic metal center (see structures **10** and **11**). Complex (**10**) should be highly favored as suggested by solution and X-ray structural investigations of Lewis acid aldehyde complexes.[35] It is productive then to view the conversion of complex (**10**) (or **11**) to products as a [3,3] sigmatropic rearrangement of a 2-oxa-3-metalla-1,5-diene system. It would be expected then that chair-like transition state (**12**) would be favored over boat-like (**13**) for the same reasons that acyclic Claisen and other [3,3] sigmatropic rearrangements are usually highly chair selective.[36] The alternative chair-like transition state (**14**) is usually viewed as unfavorable owing to the interactions of the axial R of RCHO with the axial metal ligand. It should be noted further that the pathway *via* (**14**) is also kinetically disfavored owing to the location of the metal unit in the more highly sterically congested position *syn* to R in (**11**).

It is difficult to assess the relative importance of transition states (**12**)–(**15**) in the reactions of type III crotyl organometallics since their configurational instability provides an alternative set of pathways for generation of the minor diastereomer (**17**). This question can be addressed more easily with configurationally stable type I reagents as long as the isomeric purity of the reagent is known. In a recent detailed study of the stereochemistry of the reactions of tartrate crotylboronates (**18**) and (**19**) with achiral aldehydes, for example, it has been shown that in most cases the (*E*)-crotyl reagent (**18**) of 98% isomeric purity provides the 3,4-*anti* diastereomer (**16**; $R^1$ = Me, $R^2$ = H) with ≥98% diastereoselectivity, while

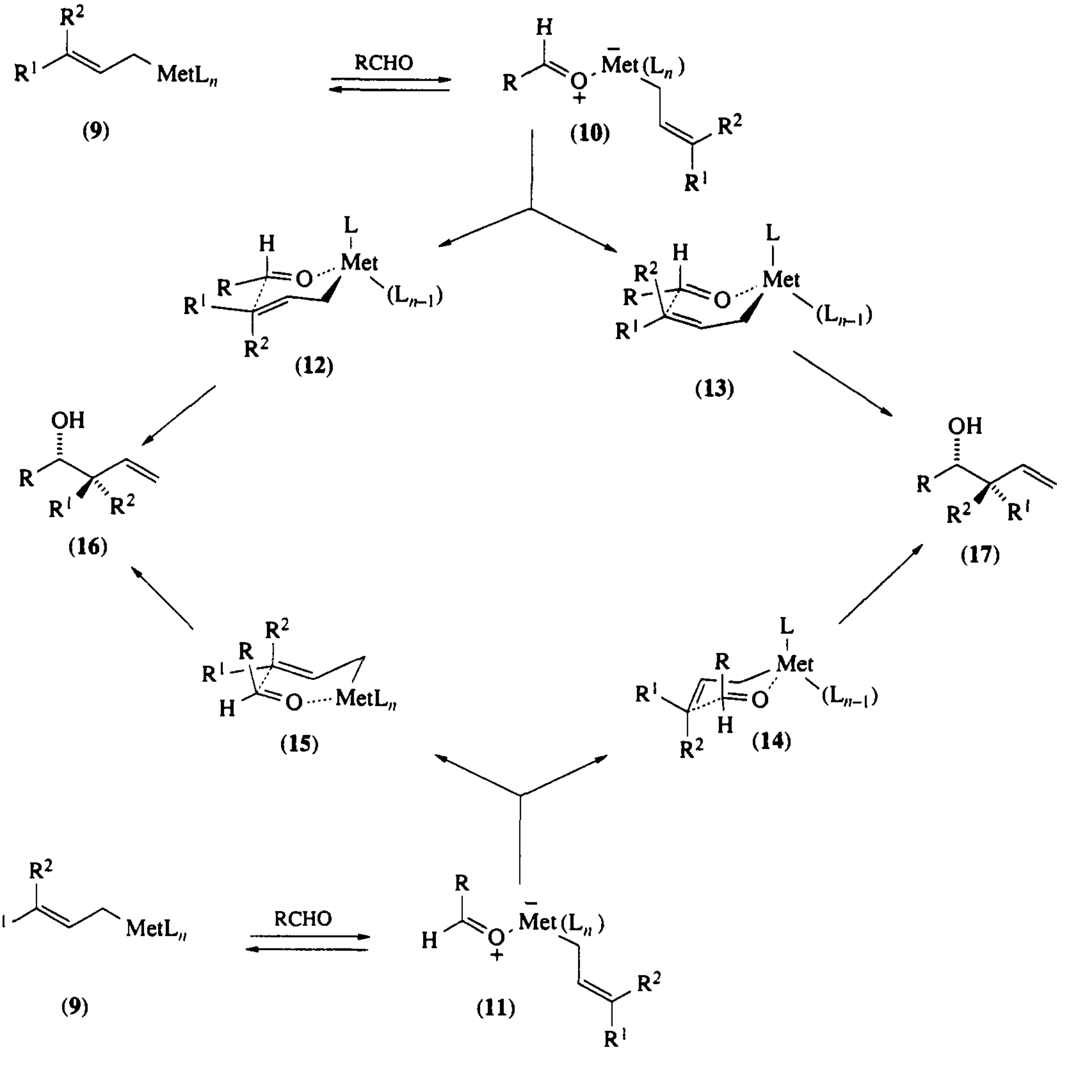

**Scheme 7**

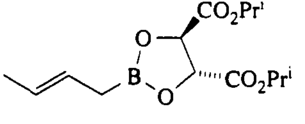

(*R,R*)-(**18**)

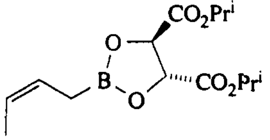

(*R,R*)-(**19**)

with ≥98% pure (*Z*)-crotyl reagent (**19**) the 3,4-*syn* diastereomer (**16**; $R^1$ = H, $R^2$ = Me) is usually obtained with at least 97% selectivity.[37] These reactions thus are highly selective for transition state (**12**), providing evidence that (**13**)–(**15**) must be highly disfavored.

The diastereoselectivity of the reactions of crotyl metal reagents with ketones is frequently lower than with aldehydes, owing presumably to greater competition between transition states (**20**) and (**21**) analogous to (**12**) and (**14**). The possibility that boat-like transition states similar to (**13**) and (**15**) may also be accessible, however, cannot be ruled out.

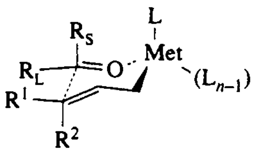
L
Met
$R_S$
$R_L$
O
$(L_{n-1})$
$R^1$
$R^2$

**(20)**

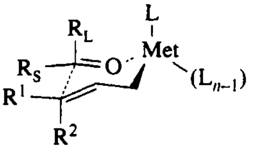
L
Met
$R_L$
$R_S$
O
$(L_{n-1})$
$R^1$
$R^2$

**(21)**

Additional insight into the competition between the various cyclic transition states is provided by a recent study of the reactions of crotylboronates (**22**) and (**23**) with the two isomers of oxime silyl ether (**24**; Scheme 8).[38] The stereoselectivities of these reactions were found to be independent of the geometry of (**24**), both isomers of which were shown to be configurationally stable under the reaction conditions. Since the oxime stereochemistry defines the site of coordination to the boron atom, it seems likely that the (*Z*)-oxime isomer reacts preferentially through the chair-like transition state (**28**), while the (*E*)-oxime reactions proceed preferentially *via* boat-like transition state (**27**). Evidently, the chair-like arrangement

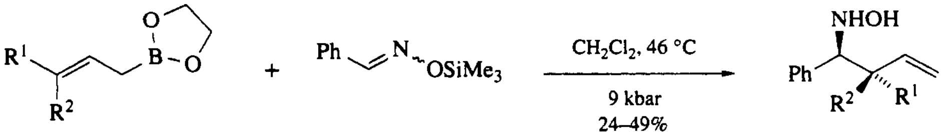
$R^1$
$R^2$
B
O
O
+
Ph
N
OSiMe$_3$
CH$_2$Cl$_2$, 46 °C
9 kbar
24–49%
NHOH
Ph
$R^2$
$R^1$

(**22**) $R^1$ = Me, $R^2$ = H
(**23**) $R^1$ = Me, $R^2$ = Me

(**24**)

(**25**) $R^1$ = Me, $R^2$ = H
(**26**) $R^1$ = H, $R^2$ = Me

| *Crotyl boronate* | *Oxime ether* | *(25):(26)* |
|---|---|---|
| (**22**) | (**24**) (*E*) | 95:5 |
| (**22**) | (**24**) (*Z*) | 95:5 |
| (**23**) | (**24**) (*E*) | 13:87 |
| (**23**) | (**24**) (*Z*) | 15:85 |

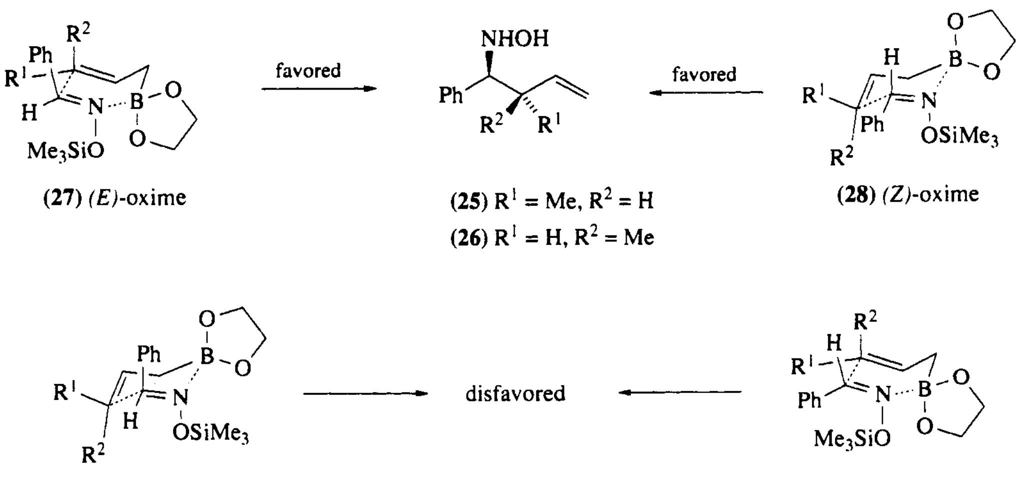
$R^2$
Ph
$R^1$
H
N
B
O
O
Me$_3$SiO
favored
NHOH
Ph
$R^2$
$R^1$
favored
O
H
B
O
$R^1$
N
Ph
OSiMe$_3$
$R^2$
O
Ph
B
O
$R^1$
N
H
OSiMe$_3$
$R^2$
disfavored
$R^2$
H
$R^1$
Ph
N
B
O
O
Me$_3$SiO

(**27**) (*E*)-oxime

(**25**) $R^1$ = Me, $R^2$ = H
(**26**) $R^1$ = H, $R^2$ = Me

(**28**) (*Z*)-oxime

(**29**)

(**30**)

**Scheme 8**

(**29**) is destabilized by the 1,3-interaction between the axial phenyl group and the axial alkoxy ligand on boron. It may be inferred, therefore, that transition state (**14**) in Scheme 7 is less stable than (**15**), and consequently also that any stereochemical leakage in the reactions of type I crotyl organometallics with aldehydes probably occurs *via* boat transition state (**13**).

### 1.1.2.2 Reactions of Type I Crotyl Metal Reagents with Achiral Aldehydes, Ketones and Imines

#### *1.1.2.2.1 Reagents based on aluminum*

The parent crotylaluminum reagents have not been thoroughly investigated. (*Z*)-Crotyldiethylaluminum (**31**) has been generated at –78 °C by the reaction of (*Z*)-crotylpotassium with diethylaluminum chloride.[39] The reaction of (**31**) with (**32**) displayed good 3,4-*syn* selectivity, as expected for a type I (*Z*)-crotyl metal reagent, and 3:1 diastereofacial selectivity with respect to the preexisting chirality of (**31**).

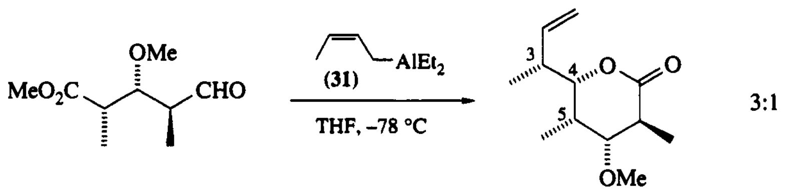
OMe
MeO2C
CHO
AlEt2
(31)
THF, –78 °C
3
4
O
O
5
OMe
3:1

(**32**) (**33**)

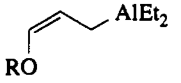

(**34**) R = Me
(**35**) R = CMe$_2$OMe

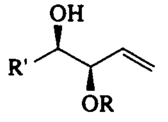

(**36**)

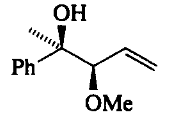

(**37**)

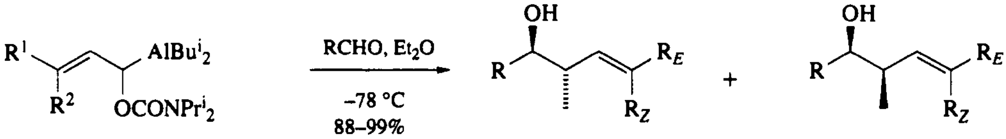
R1
R2
AlBui2
OCONPri2
RCHO, Et2O
–78 °C
88–99%
OH
R
RE
RZ
+
OH
R
RE
RZ

(**38**) R$^1$ = Me, R$^2$ = H
(**39**) R$^1$ = H, R$^2$ = Me

(**40**) R$_E$ = OCONPr$^i_2$, R$_Z$ = H (**42**)
(**41**) R$_E$ = H, R$_Z$ = OCONPr$^i_2$ (**43**)

| *Reagent* | *R* | *(40)*: | *(41)*: | *(42)*: | *(43)* | *anti:syn* |
|---|---|---|---|---|---|---|
| (**38**) | Ph | 77 | 6 | 16 | <1 | 83:17 |
| (**38**) | Me | 78 | 13 | 8 | <1 | 91:9 |
| (**38**) | Pr$^i$ | 90 | 4 | 5 | <1 | 94:6 |
| (**38**) | Bu$^t$ | 87 | 10 | 2 | <1 | 97:3 |
| (**39**) | Ph | 8 | 2 | 87 | 3 | 10:90 |
| (**39**) | Me | 8 | 7 | 79 | 6 | 15:85 |
| (**39**) | Pr$^i$ | 7 | 7 | 80 | 6 | 14:86 |

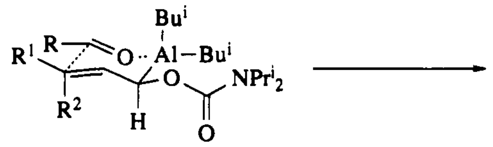
Bui
R1
R
O
Al
Bui
O
NPri2
R2
H
O

(**40**)/(**42**)

**Scheme 9**

The stereochemical outcome of this reaction is surprising because it is opposite to the diastereofacial selectivity observed in reactions of (*Z*)-crotylboronates and α-methyl chiral aldehydes. Rather, the preferential production of (**33**) parallels the results observed in the type II Lewis acid catalyzed additions of tributylcrotylstannanes and α-methyl chiral aldehydes.[12b,40]

Alkoxy-substituted allylaluminum reagents (**34**) and (**35**) have been prepared by treatment of the corresponding alkoxyallyllithiums with $Et_2AlCl$ in THF at –78 °C.[41] These species provided *syn* diastereomers (**36**) with 9–11:1 selectivity in reactions with aldehydes at –78 °C, while (**37**) was obtained with 4:1 selectivity from the reaction of (**34**) and acetophenone.

(*E*)- and (*Z*)-crotylaluminum reagents (**38**) and (**39**) have been generated at low temperature by treating the corresponding crotyllithium reagents with either $Bu^i_2AlCl$ or $Bu^i_2AlOMe$.[42] These reagents display reasonable levels of stereoselectivity in reactions with aliphatic aldehydes (Scheme 9), and type I diastereoselection is clearly evident in the data. These reactions occur presumably *via* cyclic transition states with preferential equatorial placement of the allylic $OCONPr^i_2$ substituent. Diastereomer (**41**) is available with much greater stereoselectivity by using the corresponding titanium reagent.[43]

Ate complex (**44**) generated from crotyllithium and triethylaluminum displayed poor diastereoselectivity (56:44, *anti:syn*) in a reaction with benzaldehyde.[44] Heterosubstituted aluminate complexes such as (**45**), however, give good diastereoselectivity in aldehyde addition reactions.[45] The reactions of (**45a**) with aldehydes at –100 °C give the *syn*-3,4-diol monoether (**36**) with ≥95% diastereoselectivity and ≥80% regioselectivity.[45a] Reagents (**45b**) and (**45c**) are significantly more regioselective at –78 °C and show >99% *syn* selectivity with aliphatic aldehydes; the *syn:anti* selectivity with PhCHO, however, is somewhat lower (92:8).[45b] The heteroatom-substituted ate complexes (**46**) have also been examined, but their reactions with aldehydes are not as selective as those of alkoxy substituted reagents (**45**).[45b] The reagent generated by treatment of trimethylsilylallyllithium and $EtAlCl_2$, however, shows excellent selectivity for the *anti* diastereomer (86–100%).[46]

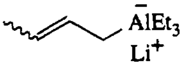

(**44**)

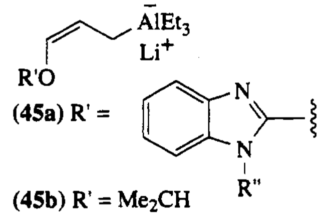

(**45a**) R' =

(**45b**) R' = $Me_2CH$

(**45c**) R' = $MeOCH_2O$

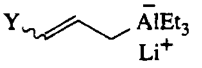

(**46**) Y = $SPr^i$, SePh, $SiMe_3$

### *1.1.2.2.2 Reagents based on boron*

#### *(i) Reactions with aldehydes and ketones*

The dialkylcrotylboranes are the most reactive but also the least configurationally stable of the allylboron reagents.[22] Mixtures of *anti*- and *syn*-homoallyl alcohols, enriched in the *anti* isomer, are obtained in the reactions of aldehydes with crotyl-9-BBN (**47**) and other $R_2BCH_2CH{=}CHR$ (**48**) reagents. For example, the reactions of (**47**) and glyoxylate esters provide the *anti* diastereomer with up to 3:1 selectivity,[47] while the reactions of (**48**; R = Et, Bu) with various aldehydes at –78 °C provide the *anti* diastereomer with 61–88% selectivity.[48] Mixtures of *anti* and *syn* diastereomers are similarly obtained when (**49**) is treated with aldehydes at –78 °C.[22c] When (**49**) is generated and used at –100 °C, however, the *anti* diastereomer (**50**) is obtained with >95% diastereoselectivity. The boratropic shift is also sensitive to and retarded by steric factors, as evidenced by the crotyldiisopinocampheylboranes (**51**) and (**52**) that are generated at –78 °C and undergo highly diastereoselective additions to aldehydes at that temperature.[23]

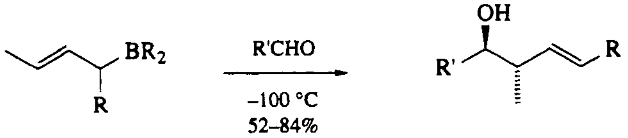

(**49**) R = Et, Bu

(**50**)

≥95% selectivity

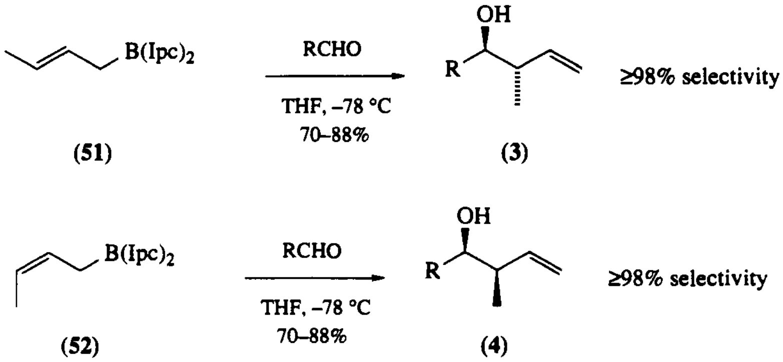
B(Ipc)$_2$
(51)
RCHO
THF, −78 °C
70–88%
OH
R
(3)
≥98% selectivity
B(Ipc)$_2$
(52)
RCHO
THF, −78 °C
70–88%
OH
R
(4)
≥98% selectivity

The reactions of crotyl-9-BBN (**47**) and pyruvate esters have been studied.[49] As was observed in reactions with glyoxylates,[47] stereoselectivity depends on the steric bulk of the ester group (Scheme 10). Interestingly, the stereochemistry of the major product (**54**) suggests that the $CO_2R$ substituent adopts an equatorial position in the cyclic transition state like (**20**).

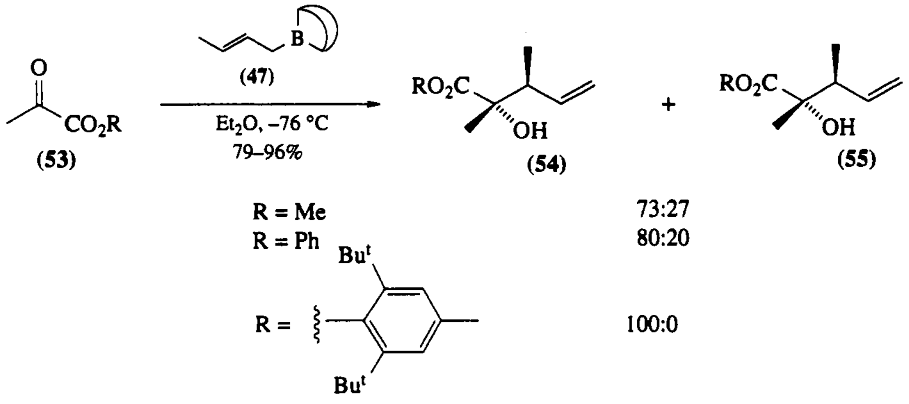
O
CO$_2$R
(53)
B
(47)
Et$_2$O, −76 °C
79–96%
RO$_2$C
OH
(54)
+
RO$_2$C
OH
(55)
R = Me
R = Ph
R =
Bu$^t$
Bu$^t$
73:27
80:20
100:0

**Scheme 10**

The reactions of aldehydes with crotylboron ate complexes have also been investigated. Ate complex (**56**), generated by the addition of $Et_3B$ to crotyllithium, exists mainly as the (*E*)-isomer and displays moderate selectivity (68–85%) for the *anti* diastereomer in reactions with various aldehydes (Scheme 11).[44] Greater selectivity has been achieved by using ate complexes generated *in situ* from (**57**; Scheme 12).[50] Diastereoselectivity is extremely high (>98:2) in reactions in which (**57**) is first treated with *n*-butyl- or *s*-butyl-lithium, but yields are only moderate (50–62%) due to competitive transfer of the alkyl group introduced as RLi. Yields of (**58**) are generally improved when pyridine is the additive, but overall stereoselectivity is somewhat lower (typically 88–92%).

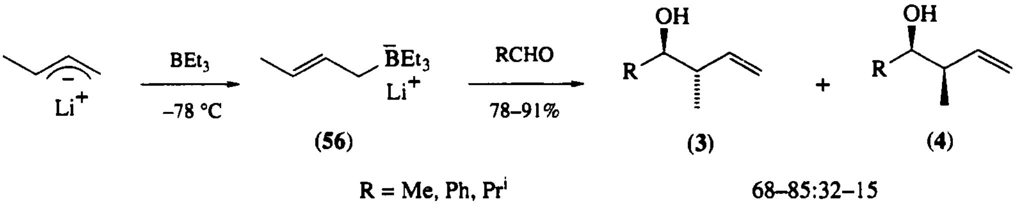
Li$^+$
BEt$_3$
−78 °C
$\bar{B}$Et$_3$
Li$^+$
(56)
RCHO
78–91%
OH
R
(3)
+
OH
R
(4)
R = Me, Ph, Pr$^i$
68–85:32–15

**Scheme 11**

Yamamoto has rationalized these results by invoking cyclic transition states such as (**59**) for the reactions of (**57**).[44,50] This transition state seems unlikely, however, since the boron atom in the ate complex has a full octet and so no association with the carbonyl oxygen is possible prior to the transition state. A concerted pathway in which the new C—C and B—O bonds form as the allylic C—B bond

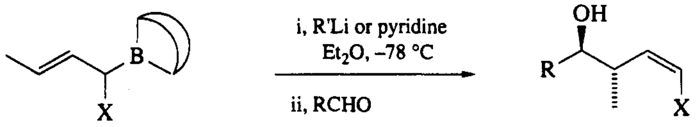
i, R'Li or pyridine
Et$_2$O, −78 °C
ii, RCHO
X
B
OH
R
X

**(57)** **a**: X = SiMe$_3$; **b**: X = SnMe$_3$

**(58)**

| *Reagent* | *R* | *Additive* | *Yield (%)* | *(58):Others* |
|---|---|---|---|---|
| **(57a)** | Ph | Bu$^n$Li | 50 | >98:2 |
| **(57a)** | Ph | Bu$^s$Li | 56 | >98:2 |
| **(57a)** | Bu$^n$ | Bu$^n$Li | 62 | >98:2 |
| **(57a)** | Ph | Pyridine | 75–90 | 88–92:12–8 |
| **(57b)** | Ph | Pyridine | 90 | Not determined |
| **(57a)** | Bu$^n$ | Pyridine | 70 | 90:10 |

**Scheme 12**

breaks is also unreasonable for stereoelectronic reasons, since this would constitute an *S*N2 reaction at boron with an angle of *ca.* 110° relating the incoming and departing groups. An alternative explanation involves a synclinal transition state such as **(60)** in which the carbonyl group is coordinated to a lithium cation that is held in close proximity to the negatively charged boron atom.[51] The X substituent will preferentially adopt a conformation in the plane of the C═C double bond so as to minimize interactions with the 9-BBN unit, which in turn reinforces a much higher preference for an (*E*)-alkene in the reactions of **(57)** than **(56)**, which lacks a bulky allylic X group. The reactions of **(57)** in the presence of pyridine are adequately explained by cyclic transition state **(61)**, since the carbonyl group should be capable of displacing pyridine as a ligand on boron.

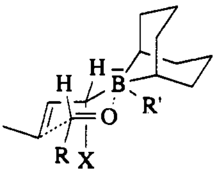

**(59)**

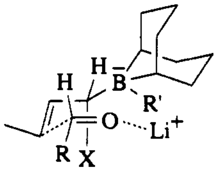

**(60)**

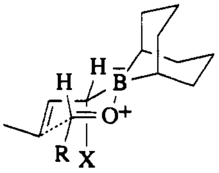

**(61)**

In contrast to the crotylboranes, crotylboronates have found widespread application in acyclic diastereoselective synthesis owing to their ease of preparation, configurational stability and highly stereoselective reactions with aldehydes.[3,6b,10,25] Substituted allylboronates are accessible by one of two general routes: (i) functionalization of a configurationally defined allyl anion **(62)** with an electrophilic boron reagent **(63)**; or (ii) substitution of an α-haloalkylboronate **(65)** with a vinyl organometallic reagent (**64**; Scheme 13).

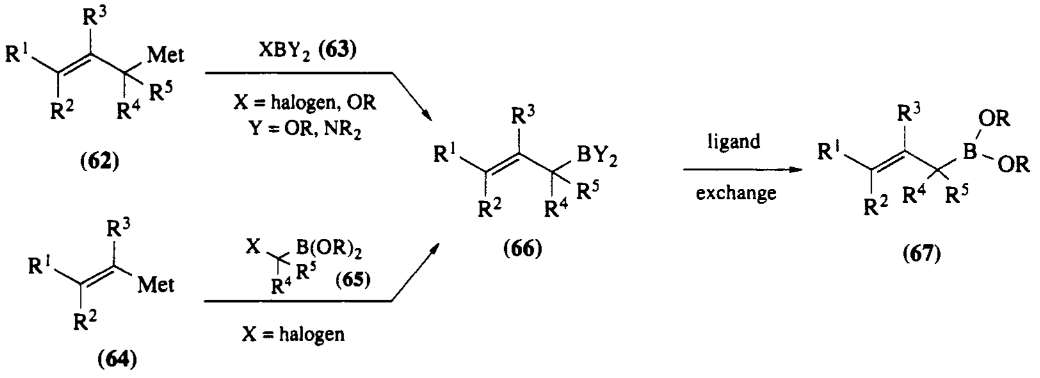
R$^3$
R$^1$
Met
R$^2$
R$^4$
R$^5$
(62)
XBY$_2$ (63)
X = halogen, OR
Y = OR, NR$_2$
R$^3$
R$^1$
Met
R$^2$
(64)
X B(OR)$_2$
R$^4$ R$^5$ (65)
X = halogen
R$^3$
R$^1$
BY$_2$
R$^2$
R$^4$
R$^5$
(66)
ligand
exchange
R$^3$
OR
R$^1$
B
OR
R$^2$
R$^4$
R$^5$
(67)

**Scheme 13**

Crotylboronates such as (**1**) and (**2**) are best prepared starting from (*E*)- and (*Z*)-crotylpotassium.[21] The crotylpotassiums have been functionalized with electrophilic boranes including $FB(OMe)_2$,[21,25] $ClB(NEt_2)_2$[10] and $B(OPr^i)_3$,[37] the products of which are either hydrolyzed to the crotylboronic acids and then treated with the appropriate diol[25,37] or directly transesterified as in the $ClB(NEt_2)_2$ procedure.[10] An advantage to the $FB(OMe)_2$ method is that crotylboronates (**68**) and (**69**) are generated *in situ* and may be directly treated with an aldehyde in a one-pot operation.[21] Substituted crotylboronates (**70**)–(**72**), among others, have also been prepared in this way.[21c,52] Recent optimization studies involving the synthesis of tartrate crotylboronates (**18**) and (**19**), however, have revealed that the yield (14–35%) and isomeric purity (92–96%) drop substantially as the $FB(OMe)_2$ procedure is scaled up.[37] Consistently good results have been obtained when the crotylpotassiums are treated with $(Pr^iO)_3B$ (70–75% yields of **18** and **19**, ≥98% isomeric purity), and it is this procedure that should be adopted for the large-scale preparation of achiral crotylboronates such as (**1**) and (**2**).

Substituted allylboronates (**73**)–(**79**) have been prepared by using similar methods. Of these, only the (*E*)-γ-alkoxyallylboronates (**73**) and (**75**) have proven particularly troublesome to prepare owing to the difficulty of generating (*E*)-alkoxyallylpotassium with high isomeric purity.[53]

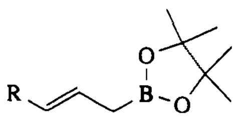

(**1**) R = Me
(**73**) R = OMe
(**75**) R = $OCH_2CH_2SiMe_3$
(**78**) R = $SiMe_3$

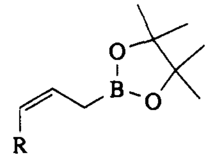

(**2**) R = Me
(**74**) R = OMe
(**76**) R = $OCH_2CH_2SiMe_3$
(**77**) R = OMOM
(**79**) R = SMe

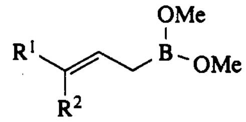

(**68**) $R^1$ = Me, $R^2$ = H
(**69**) $R^1$ = H, $R^2$ = Me
(**70**) $R^1$ = H, $R^2$ = Et
(**71**) $R^1$ = CH=CHMe *(Z)*, $R^2$ = H
(**72**) $R^1$ = H, $R^2$ = CH=CHMe *(E)*

The α-halomethylboronate alkylation method (Scheme 13) is extremely useful for the preparation of substituted allylboronates that cannot be prepared *via* the allyl anion route. Notable examples that fall into this category are (**80**)–(**82**).[10,25,56] The only limitation to this method as a preparative route is the occasional coproduction of alkenylboronates that presumably arise *via* an α-elimination pathway involving the ate complex generated upon addition of (**64**) to (**65**).[25,57]

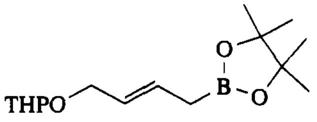

(**80**)

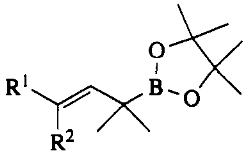

(**81**) $R^1$ = Me, $R^2$ = H
(**82**) $R^1$ = H, $R^2$ = Me

Results of representative reactions of substituted allylboronates and achiral aldehydes are summarized in Table 1. It is noteworthy that in the majority of cases the reaction diastereoselectivity closely parallels the isomeric purity of the reagents, thus underscoring the requirement that the allylboronate synthesis be highly stereoselective. Dimethyl crotylboronates (**68**) and (**69**) are more reactive than (**1**) and (**2**), as indicated by the fact that the reactions of (**68**) and (**69**) are complete within a few hours at –78 °C while those of (**1**) and (**2**) include an overnight period at room temperature.[59] Reagents (**73**)–(**79**) are even less reactive than (**1**) and (**2**), their reactions requiring several days at room temperature to reach completion.[60] A detailed study of the temperature dependence of diastereoselectivity, however, has not been reported to date.

Several studies have noted that (*E*)-allylic boronates are more reactive than their (*Z*)-alkene isomers.[10,25,53,55,58] Thus, by using an (*E*)-allylic boronate as the excess reagent, it is possible to achieve a kinetic enhancement of the reaction diastereoselectively. This is nicely illustrated by the data in entries 15–19 of Table 1: reagents (**73**) and (**75**) of *ca.* 90% isomeric purity were treated with 0.9 equiv. of aldehyde and the *anti* diastereomer (**83**) was obtained with 94 to >98% selectivity.[53] Similarly, Schlosser has

**Table 1** Diastereoselectivity in the Reactions of Aldehydes and Substituted Allylboronates

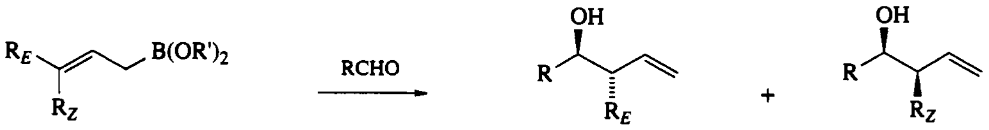

**(83)** **(84)**

| *Entry* | *RCHO* | *Reagent* | $R_E$ | $R_Z$ | *Isomeric purity* | *Yield (%)* | *(**83**):(**84**)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | PhCHO | (**1**) | Me | H | 93:7 | 80 | 94:6 | 10 |
| 2 | PhCHO | (**68**) | Me | H | a | $50^b$ | 99:1 | 21c |
| 3 | MeCHO | (**1**) | Me | H | 93:7 | 40 | 93:7 | 10 |
| 4 | EtCHO | (**1**) | Me | H | 93:7 | 62 | 93:7 | 10 |
| 5 | EtCHO | (**68**) | Me | H | a | $61^b$ | 97:3 | 21c |
| 6 | $Me_2CHCHO$ | (**1**) | Me | H | 93:7 | 59 | 94:6 | 10 |
| 7 | $C_5H_{11}CHO$ | (**80**) | $THPOCH_2$ | H | 93:7 | 86 | 93:7 | 56a |
| 8 | $AcOCH_2CH_2CHO$ | (**80**) | $THPOCH_2$ | H | 93:7 | 71 | 93:7 | 56a |
| 9 | PhCHO | (**2**) | H | Me | 5:95 | 80 | 5:95 | 56a |
| 10 | PhCHO | (**2**) | H | Me | 5:>95 | 22 | 6:94 | 10 |
| 11 | PhCHO | (**69**) | H | Me | a | $40^b$ | 4:96 | 21c |
| 12 | MeCHO | (**2**) | H | Me | 5:>95 | 20 | 7:93 | 10 |
| 13 | EtCHO | (**2**) | H | Me | 5:>95 | 26 | 7:93 | 10 |
| 14 | EtCHO | (**69**) | H | Me | a | $62^b$ | 2–4:96–98 | 21c,58 |
| 15 | $Me_2CHCHO$ | (**2**) | H | Me | 5:>95 | 51 | 6:94 | 10 |
| 16 | PhCHO | (**73**) | MeO | H | ~90:10 | 87 | 95:5 | 53 |
| 17 | PhCHO | (**75**) | $Me_3SiCH_2CH_2O$ | H | ~90:10 | 92 | 94:6 | 53 |
| 18 | EtCHO | (**73**) | MeO | H | ~90:10 | 68 | 95:5 | 53 |
| 19 | $Me_2CHCHO$ | (**73**) | MeO | H | ~90:10 | 77 | >98:2 | 53 |
| 20 | $Me_2CHCHO$ | (**75**) | $Me_3SiCH_2CH_2O$ | H | ~90:10 | 86 | >95:5 | 53 |
| 21 | PhCHO | (**74**) | H | MeO | 5:>95 | 86 | 5:>95 | 53 |
| 22 | PhCHO | (**76**) | H | $Me_3SiCH_2CH_2O$ | 5:>95 | 98 | 5:>95 | 53 |
| 23 | EtCHO | (**74**) | H | MeO | 5:>95 | 94 | 8:92 | 53 |
| 24 | $Me_2CHCHO$ | (**74**) | H | MeO | 5:>95 | 94 | 11:89 | 53 |
| 25 | $Me_2CHCHO$ | (**76**) | H | $Me_3SiCH_2CH_2O$ | 5:>95 | 76 | 11:89 | 53 |
| 26 | $Me_2CHCHO$ | (**77**) | H | MOMO | 5:>95 | 90 | 20:80 | 53 |
| 27 | PhCHO | (**78**) | $Me_3Si$ | H | a | 89 | >98:2 | 54 |
| 28 | n-$C_7H_{15}CHO$ | (**78**) | $Me_3Si$ | H | a | 78 | >98:2 | 54 |
| 29 | $AcO(CH_2)_8CHO$ | (**78**) | $Me_3Si$ | H | a | 92 | >98:2 | 54 |
| 30 | PhCHO | (**79**) | H | MeS | 5:>95 | 95 | 2:98 | 55 |
| 31 | $Me_2CHCHO$ | (**79**) | H | MeS | 5:>95 | 90 | 5:95 | 55 |

[a] Isomeric purity was not determined. [b] The indicated yields include the preparation of the substituted allylboronate that was generated *in situ*. Yields in all other cases are for experiments in which purified allylboronates were used.

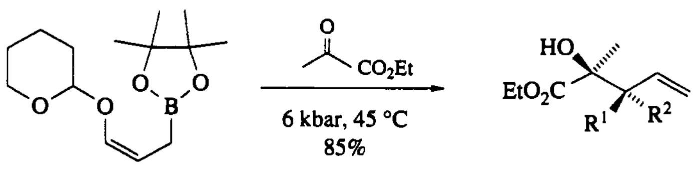

**(85)**

**(86a)** $R^1$ = OTHP, $R^2$ = H

**(86b)** $R^1$ = H, $R^2$ = OTHP

noted that the diastereoselectivity of the reactions of (*Z*)-crotylboronate (**69**) can be enhanced by first treating the reagent with 0.05–0.1 equiv. of acetaldehyde to consume any contaminating (*E*)-crotyl isomer.

The only reactions in Table 1 where diastereoselectivity deviates markedly from the reagent isomeric purity involve the (*Z*)-γ-alkoxyallylboronates (entries 21–26), and then only when a sterically demanding aldehyde (isobutyraldehyde, entries 24–26) or a bulky protecting group is employed.[53] Under these circumstances it appears that boat-like transition state (**13**) becomes competitive with the otherwise favored chair arrangement (**12**; Figure 7).

Relatively few studies of the reactions of allylboronates and ketones have appeared.[61] The reaction of (**85**) and ethyl pyruvate, for example, was conducted under 6 kbar pressure at 45 °C for 80 h to give a 9:1 mixture of diastereomers (**86a**) and (**86b**). The stereochemistry of this reaction parallels that seen with crotyl-9-BBN (Figure 10) in that the structure of the major isomer is consistent with a transition state in which the —$CO_2Et$ unit adopts an equatorial position. The same result could occur, however, *via* a boat-like transition state with an axial —$CO_2Et$ group.

### *(ii) Reactions with C═N electrophiles*

Reactions of allylboronates (**87**)–(**89**) and aldoximes,[62] imines[62a] and sulfenimides[63] have been described. These reactions are considerably slower than those of aldehydes, and consequently reagents (**87**) and (**88**) are generally used in preference to the less reactive pinacol ester (**89**). The reactions of imines and (**87**) proceed at room temperature, while those of (**88**) and oximes and sulfenimides generally require heating in refluxing $CCl_4$ or toluene. The reaction of (**88**) and oximes can be performed at room temperature if a pressure of several kilobars is applied.[62a]

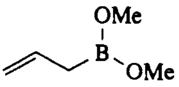

**(87)**

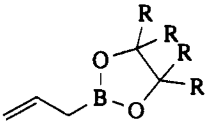

**(88)** R = H
**(89)** R = Me

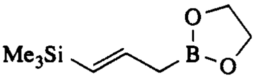

**(90)**

The stereochemistry of the reactions of oxime ethers and crotylboronates (**22**) and (**23**) have been discussed earlier (Scheme 8).[38] The reactions of the corresponding oximes with (**22**) and (**23**) appear to follow a similar stereochemical course (Scheme 14).[38] Stereoselectivity, however, is not as high with the isobutyraldehyde and pentanal oximes as it is with phenylaldoxime. The reaction of $Me_3Si$-substituted allylboronate (**90**) and acetaldehyde oxime performed in refluxing $CCl_4$ similarly provides a 79:21 mixture of the *anti* and *syn* product diastereomers ($Me_3Si$ replacing Me in **25** and **26**).[64] Excellent stereoselectivity for *syn*-homoallylamines has been achieved *via* the Lewis acid catalyzed reactions of aldimines and crotyltributylstannane.[65]

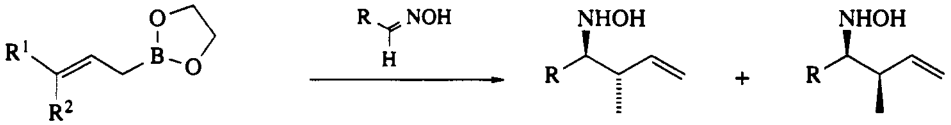

(**22**) $R^1$ = Me, $R^2$ = H
(**23**) $R^1$ = H, $R^2$ = Me

**(25)** **(26)**

| *Reagent* | *R* | *Pressure* (kbar) | *Temp.* (°C) | *Yield* (%) | *(25):(26)* |
|---|---|---|---|---|---|
| (**22**) | Ph | 9 | 46 | 64 | 95:5 |
| (**22**) | $Pr^i$ | 9 | 46 | 81 | 81:19 |
| (**22**) | $Bu^n$ | 4 | 25 | 84 | 75:25 |
| (**23**) | Ph | 9 | 46 | 38 | 12:88 |
| (**23**) | $Pr^i$ | 9 | 46 | 65 | 20:80 |
| (**23**) | $Bu^n$ | 9 | 46 | 60 | 30:70 |

**Scheme 14**

Yamamoto and coworkers have studied the reactions of crotyl-9-BBN (**47**) and achiral aldimines (Scheme 15).[66] These reactions occur at much lower temperature than those involving crotylboronates because of the greater reactivity of (**47**). No clear stereochemical pattern, however, is apparent in the data. Assuming that (**47**) reacts preferentially as the (*E*)-crotyl isomer, one would expect *anti* diastereomer (**93**) to be the major product *via* transition state (**95a**; Scheme 16) by analogy to Hoffmann's results with oximes and oxime ethers (Schemes 8 and 14).[38] Only in entries 1, 6, 7 and 8 of Scheme 15, however, is this stereochemical result realized. Yamamoto argues that *syn* diastereomer (**92**), the major product in entries 2–5 and 9–11, is formed by way of chair-like transition state (**94a**). This seems unlikely, however, since the analogous transition state (**29**) is highly disfavored in the reactions of oximes and crotylboronates (Figure 8). The interactions involving the axial R and the 9-BBN unit in (**94a**) are probably more serious than those involving the axial OR group in (**29**). Thus, (**92**) is probably produced *via*

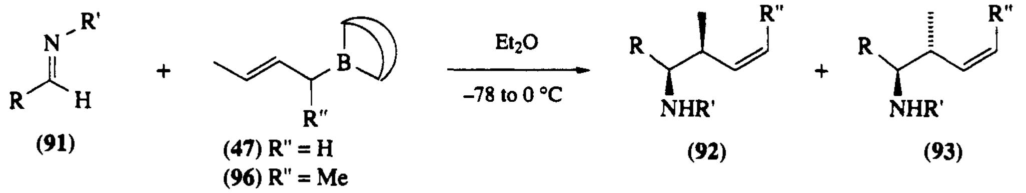

R'
N
R
H
(91)
+
B
R''
(47) R'' = H
(96) R'' = Me
Et₂O
−78 to 0 °C
R
R''
NHR'
(92)
+
R
R''
NHR'
(93)

| *Entry* | *R* | *R'* | *R''* | *Yield (%)* | *(92):(93)* |
|---|---|---|---|---|---|
| 1 | Ph | Ph | H | 93 | 0:100 |
| 2 | Ph | $Pr^n$ | H | 95 | 85:15 |
| 3 | Ph | $Pr^i$ | H | 79 | 65:35 |
| 4 | $Pr^n$ | $Pr^n$ | H | 90 | 75:25 |
| 5 | $Pr^n$ | $Pr^i$ | H | 97 | 100:0 |
| 6 | $Pr^i$ | $Pr^n$ | H | 95 | 34:66 |
| 7 | $Pr^i$ | $Pr^i$ | H | 60 | 30:70 |
| 8 | Ph | Ph | Me | 90 | 8:92 |
| 9 | Ph | $Pr^n$ | Me | 84 | 100:0 |
| 10 | $Pr^n$ | $Pr^i$ | Me | 75 | 100:0 |
| 11 | $Pr^i$ | $Pr^n$ | Me | 78 | 85:15 |

**Scheme 15**

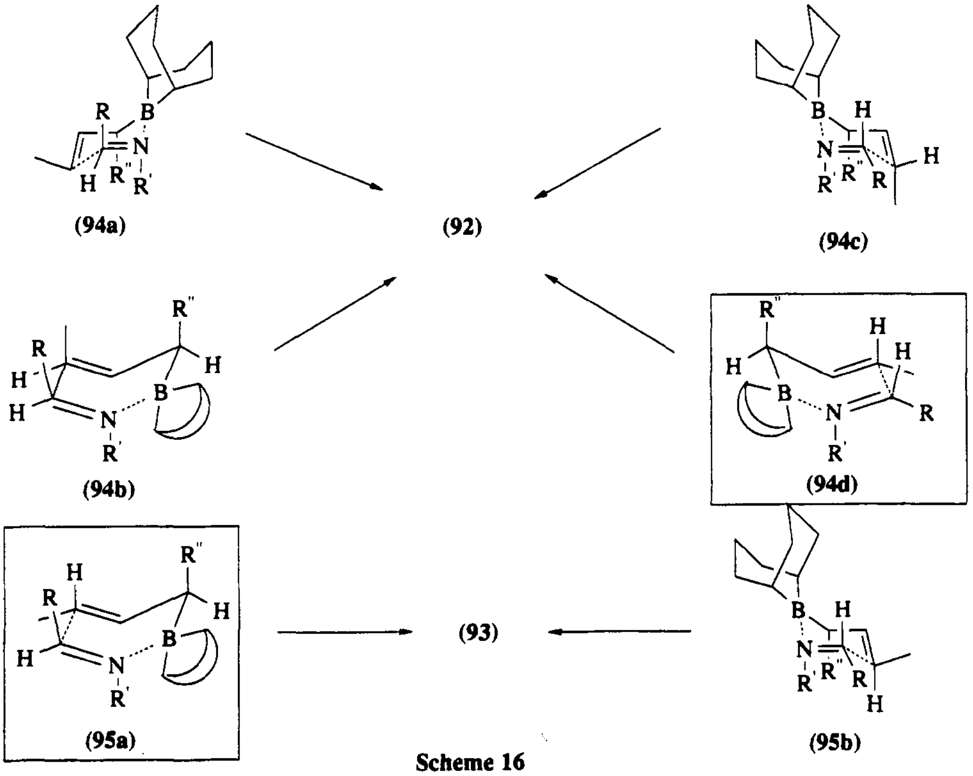

R
B
N
H
R''
R'
(94a)
(92)
B
H
N
R'
R''
R
H
(94c)
R''
R
H
H
H
B
N
R'
(94b)
R''
H
H
H
B
N
R
R'
(94d)
H
R''
R
H
H
B
N
R'
(95a)
(93)
B
H
N
R'
R''
R
H
(95b)

**Scheme 16**

one of the alternative transition states (**94b**) in which the crotylborane has (*Z*)-configuration, (**94c**) in which the imine has isomerized and the crotyl unit is (*Z*), or (**94d**) in which only the imine has isomerized. It is likely that (**94d**) is the most important one in view of the exclusive generation of (**92**) in the reaction of (**96**; R″ = Me): transition states (**94b**) and (**94c**) clearly suffer from serious interactions involving R″.

In the final analysis, it appears that the diastereoselectivity of the reactions of imines and crotylboranes (**47**, **96**) depends on the relative rates of crotyl transfer (*e.g.* **95a** → **93**) *versus* imine isomerization that leads to competitive pathways (*e.g.* **94d** → **92**). When R′ is an aryl group, the rate of crotyl transfer is probably faster than competitive imine isomerization. When R′ is an alkyl group, however, the relative rates are probably inverted. The driving force for imine isomerization is probably that complex (**95a**) is not very stable owing to the bulky 9-BBN unit positioned *syn* to R, while the complex of crotyl-9-BBN (**47**) and a (*Z*)-aldimine (*e.g.* **94d**) is probably much more stable. It is conceivable, therefore, that the overall rate of reaction *via* (**94d**) can be much faster than *via* (**95a**) even though the (*Z*)-imine cannot be detected in solution. Additional research is clearly needed to clarify the stereochemical course of these reactions.

### *1.1.2.2.3 Reagents based on silicon*

Stereoselective reactions of crotylsilicates (**97**)–(**100**) and aldehydes have been described (Scheme 17).[28] These reactions readily proceed at room temperature in the absence of a Lewis acid catalyst, and type I diastereoselection is clearly evident. Evidence supporting a cyclic transition state has been provided through studies of optically active crotylsilicates such as (**101**; Scheme 18).[67] The absolute stereochemistry of the products requires that the reaction is suprafacial with respect to the allylsilane moiety, in contrast to the *anti* stereochemical outcome of $S_E'$ reactions of allylsilanes.[68] Cyclic transition states are also implicated in the reactions of the crotyltrifluorosilanes and CsF, but the crotyltrifluorosilane/$Bu_4NF$ reaction apparently proceeds *via* an uncomplexed allyl anion species.[67]

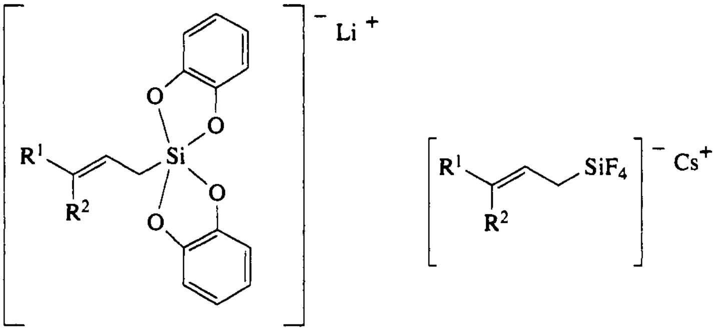

(**97**) $R^1$ = Me, $R^2$ = H    (**99**) $R^1$ = Me, $R^2$ = H

(**98**) $R^1$ = H, $R^2$ = Me    (**100**) $R^1$ = H, $R^2$ = Me

| *RCHO* | *Reagent* | *Isomeric purity* | *Yield (%)* | *(3):(4)* | *Ref.* |
|---|---|---|---|---|---|
| PhCHO | (**97**) | 88:12 | 82 | 88:12 | 28b |
| PhCHO | (**98**) | 21:79 | 91 | 22:78 | 28b |
| PhCHO | (**99**) | 99:1 | 92 | 99:1 | 28d |
| PhCHO | (**100**) | 1:99 | 96 | 1:99 | 28d |
| n-$C_8H_{17}$CHO | (**99**) | 99:1 | 96 | 99:1 | 28d |
| n-$C_8H_{17}$CHO | (**100**) | 1:99 | 89 | 2:98 | 28d |

**Scheme 17**

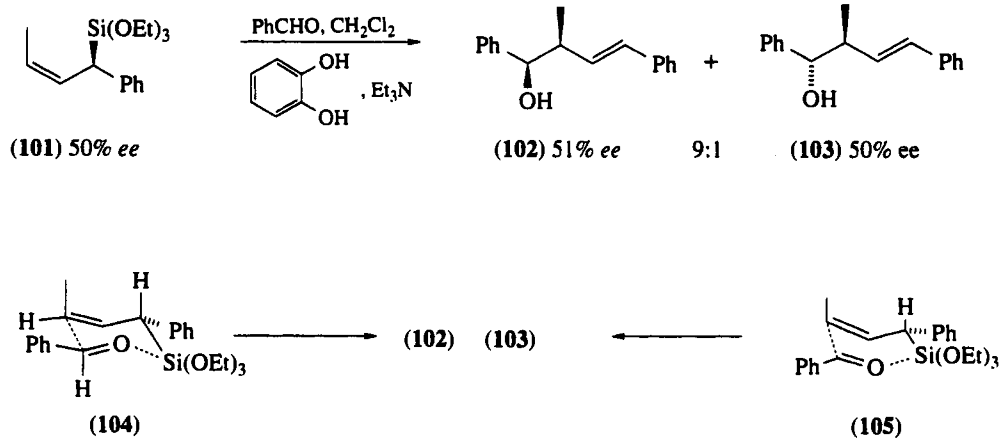

**(101)** 50% *ee* **(102)** 51% *ee* 9:1 **(103)** 50% ee

**(104)** **(105)**

**Scheme 18**

### *1.1.2.2.4 Reagents based on tin*

Type I reactions of aldehydes and trialkylcrotylstannanes have been reported to occur both thermally (20–200 °C) and under high pressure (10 kbar). The first investigation of the thermal reaction was performed with isomerically impure crotyltributylstannanes (**5**; Scheme 19).[8a] A subsequent investigation of the reaction of chloral and isomerically pure (**6**) showed this reaction to be highly selective for the *syn* diastereomer (**4**).[30b]

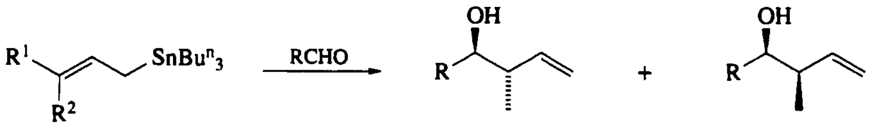

**(5)** R$^1$ = Me, R$^2$ = H
**(6)** R$^1$ = H, R$^2$ = Me

**(3)** **(4)**

| *R* | *Reagent* | *Isomeric purity* | *Temp. (°C)* | (3):(4) |
|---|---|---|---|---|
| CCl$_3$ | **(5)** | 90:10 | 20 | 90:10 |
| CCl$_3$ | **(5)** | 65:35 | 20 | 67:33 |
| CCl$_3$ | **(6)** | 0:100 | 25 | 1:99 |
| Ph | **(5)** | 92:8 | 200 | 87:13 |
| Ph | **(5)** | 60:40 | 200 | 62:38 |

**Scheme 19**

Yamamoto has reported that the reactions of aldehydes less activated than chloral occur at 23 °C using high pressures (10 kbar).[69] The diastereoselectivity of the reactions of (**5**) and aryl aldehydes, however, is only 65–80% in favor of the *anti* diastereomer.

Thomas and coworkers have reported that the readily accessible alkoxy-substituted stannane (**106**) displays excellent *anti* diastereoselectivity in the thermal reactions with a range of aromatic and aliphatic aldehydes.[70] The reaction of benzaldehyde in Scheme 20 is representative. Marshall, however, has reported that the diastereoselectivity of the reactions of Bu$^t$Me$_2$SiO(CH$_2$)$_3$C≡CCHO and (**106**) is only 56:44 in favor of the *anti* diastereomer, and that the reaction with β,β-disubstituted acroleins fails altogether.[71]

The thermal reactivity of the crotylstannanes is strongly influenced by the substituents on tin. The reactions of (crotyl)SnX$_3$ and (crotyl)(butyl)$_n$SnX$_{3-n}$ with aldehydes have been described, but in no cases has high stereoselectivity been clearly demonstrated.[31] Crotylstannanes of the general structure (crotyl)SnX$_n$Y$_{3-n}$ have also been generated *via* the reactions of allyl halides and SnF$_2$,[72] allylic acetates,[73] carbonates,[74] and alcohols[75] with PdCl$_2$(PhCN)$_2$–SnCl$_2$ and allylic phosphates with SnF$_2$–Et$_2$AlCl or

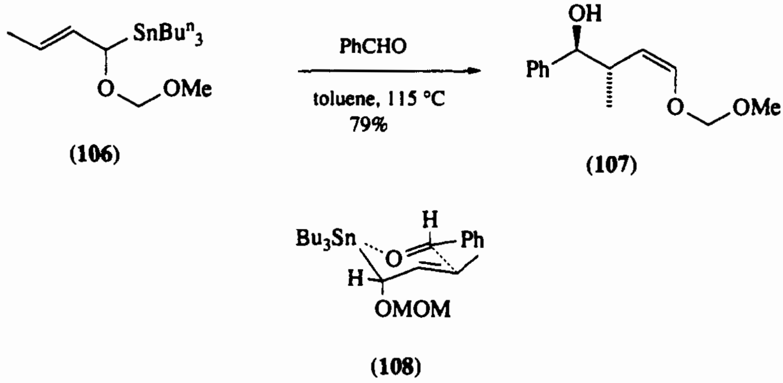
SnBu$^n_3$
OMe
(106)
PhCHO
toluene, 115 °C
79%
OH
Ph
OMe
(107)
Bu$_3$Sn
H
Ph
OMOM
(108)

Scheme 20

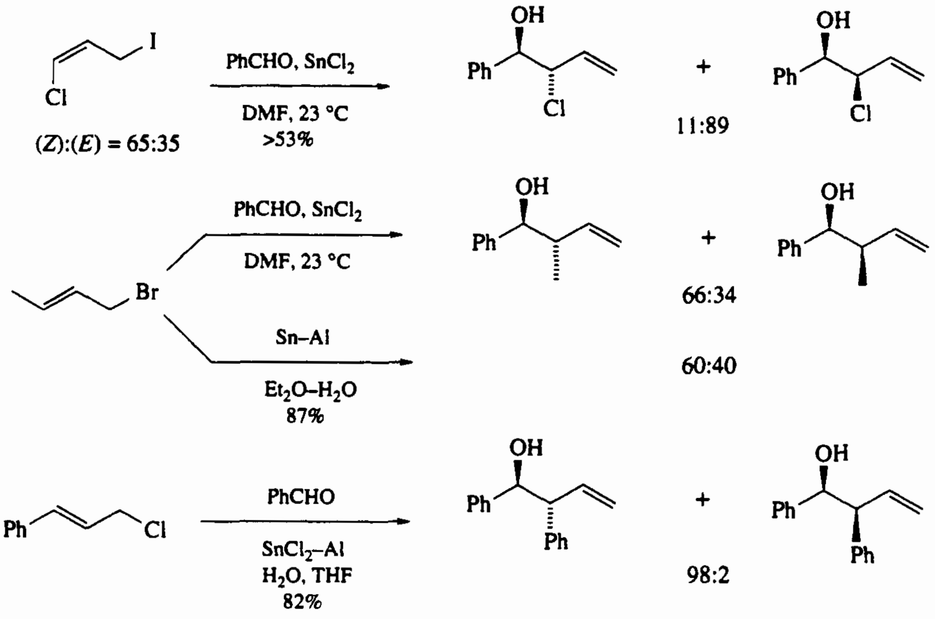
I
Cl
(Z):(E) = 65:35
PhCHO, SnCl$_2$
DMF, 23 °C
>53%
OH
Ph
Cl
+
11:89
Br
PhCHO, SnCl$_2$
DMF, 23 °C
66:34
Sn–Al
Et$_2$O–H$_2$O
87%
60:40
Ph
Cl
PhCHO
SnCl$_2$–Al
H$_2$O, THF
82%
98:2

Scheme 21

Bu$^n_3$SnLi–Et$_2$AlCl.[76] In none of these cases, however, has diastereoselectivity exceeded 75:25. It is probable that these reagents are configurationally unstable, as implied by the results summarized in Scheme 21.[32b,77] It is noteworthy that cinnamyl halides display very high *anti* selectivity with SnCl$_2$–Al[77a] and Sn–Al[77b] in contrast to the poor results obtained with the crotyl systems.[32b,77c]

### 1.1.2.3 Reactions of Type III Crotyl Organometallics with Achiral Aldehydes and Ketones

#### *1.1.2.3.1 Reagents based on chromium*

Crotylchromium reagents (**8**) are among the most selective and most widely applied of the type III crotyl organometallics.[9] Allylchromiums are typically generated by the reduction of an allylic halide using CrCl$_2$ in THF; the diastereoselectivity decreases in other solvents such as DMF.[9b,c] Commercially available CrCl$_2$ is often used, but several cases have been reported where selectivity is substantially better when CrCl$_2$ is generated *via* the LiAlH$_4$ reduction of CrCl$_3$. Other methods of generating CrCl$_2$ *in situ* lead to crotylchromium reagents that show diminished stereoselectivity.[78] Allylchromium reagents containing vinyl or allylic halides,[9c,79] vinyl sulfones[34c] and even carboalkoxy[80] or cyano[81] substituents have been prepared from suitable allyl halide precursors, while γ-alkoxyallylchromiums have been generated by the reduction of acrolein acetals with $CrCl_2$ in the presence of $Me_3SiI$ (Scheme 22).[82] Stereoconvergence has been demonstrated in several instances, indicating that the isomeric purity and geometry of the allylchromium precursor is not a factor that influences diastereoselectivity.[9b,c,80]

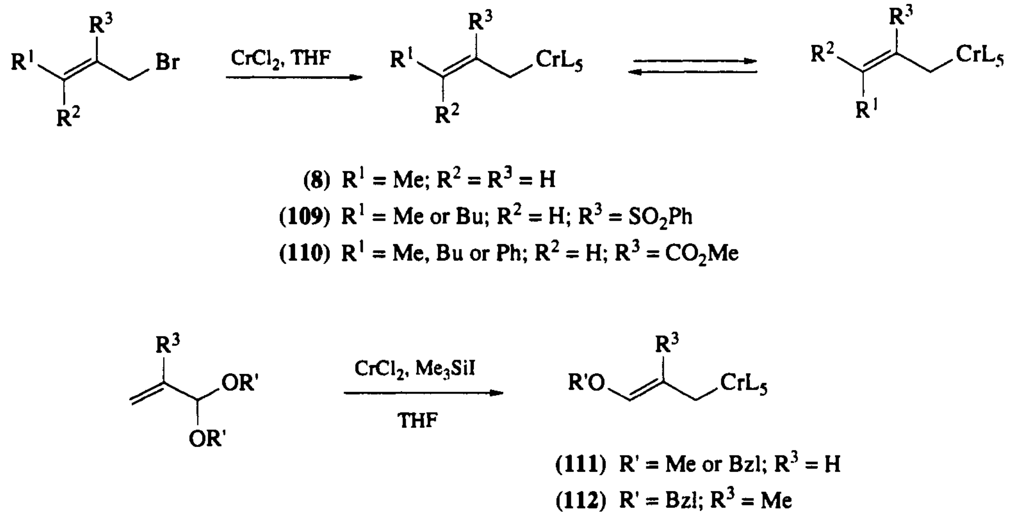

**(8)** $R^1$ = Me; $R^2$ = $R^3$ = H
**(109)** $R^1$ = Me or Bu; $R^2$ = H; $R^3$ = $SO_2Ph$
**(110)** $R^1$ = Me, Bu or Ph; $R^2$ = H; $R^3$ = $CO_2Me$

**(111)** R' = Me or Bzl; $R^3$ = H
**(112)** R' = Bzl; $R^3$ = Me

**Scheme 22**

The reaction of aldehydes and substituted allylchromiums (**8**), (**111**) and (**112**) are generally highly selective for the *anti* product diastereomer (Table 2),[9b,c,82] except for the reactions with pivalaldehyde that provide the *syn* diastereomer with modest selectivity. This result has been attributed to the involvement of a boat transition state (**13**; Scheme 7),[9c] although the same product could also be produced *via* a chair transition state (**12**; $R^1$ = H, $R^2$ = Me) if the (*Z*)-crotylchromium intermediate is more reactive than the (*E*)-isomer. We favor the latter interpretation, since tartrate (*Z*)-crotylboronate (**19**) is more reactive than the (*E*)-crotyl isomer (**18**) towards pivalaldehyde — the only documented case of a (*Z*)-crotyl metal reagent exhibiting greater reactivity than the (*E*)-isomer.[37a] Boat-like transition states with internal coordination of Cr by the (*Z*)-γ-alkoxy substituent have been invoked to rationalize the *anti* diastereoselectivity of the reactions of (**111**),[82] although here again the stereochemistry is consistent with a chair-like transition state (**12**) and an (*E*)-geometry for (**111**).

**Table 2** Diastereoselectivity of the Reactions of Substituted Allylchromiums (**8**) and (**111**) with RCHO[a]

| *RCHO* | *Reagent* | *Yield (%)* | *Diastereoselectivity anti:syn*[b] |
|---|---|---|---|
| PhCHO | (**8**) | 96 | 100:0 |
| PhCHO | (**111**) | 98 | 88:12[c] |
| $Pr^nCHO$ | (**8**) | 59 | 93:7 |
| $n\text{-}C_8H_{17}CHO$ | (**111**) | 95 | 87:13 |
| $Pr^iCHO$ | (**8**) | 81 | 97:3 |
| $c\text{-}C_6H_{11}CHO$ | (**111**) | 93 | 88:12 |
| $Bu^tCHO$ | (**8**) | 64 | 35:65 |
| $Bu^tCHO$ | (**111**) | 91 | 33:67 |

[a] Reactions of (**8**) were performed at 23 °C, while those of (**111**) were performed at –30 °C. Data for (**111**) are for R' = Bzl. [b] Ratio of *anti*:*syn* homoallyl alcohols. [c] Identical selectivity was obtained for (**111**) with R' = Me or Bzl.

In contrast to these results, *syn* diastereoselectivity is observed in the reactions of (**109**) and (**110**) with aldehydes.[34c,80,81] The stereochemistry in these cases leaves little doubt that it is the (*Z*)-allylchromium species that is involved, presumably as a result of a destabilizing interaction between the $R^1$ and bulky $R^3$ substituents in the (*E*)-isomer (Scheme 23). In the case of methallyl derivative (**113**), however, *anti* diastereoselection is realized in this interesting macrocyclization (Scheme 24).[83]

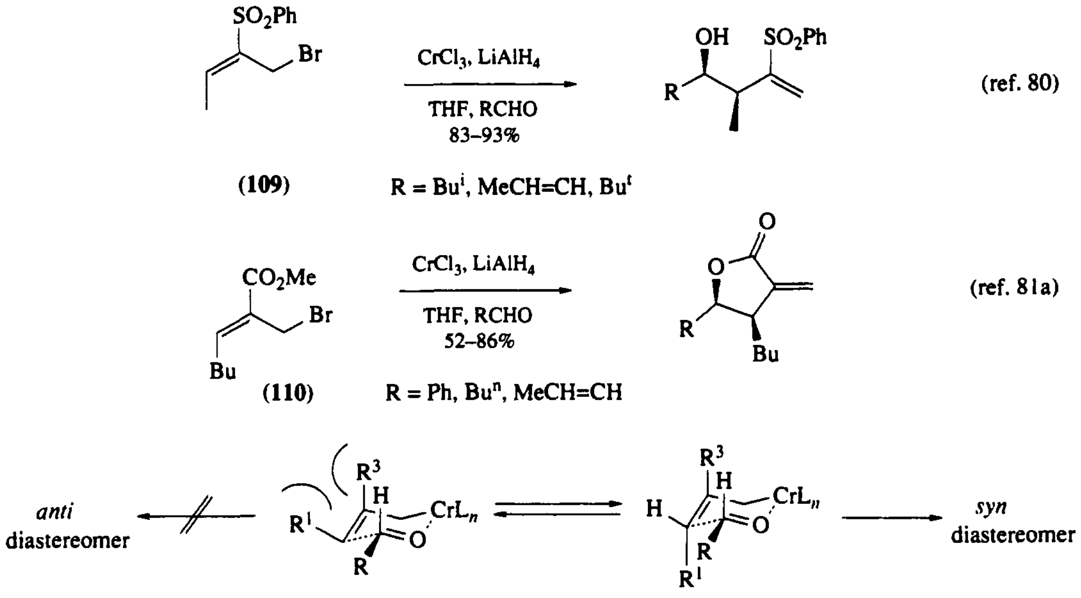
SO2Ph
Br
CrCl3, LiAlH4
THF, RCHO
83–93%
OH
SO2Ph
R
(ref. 80)
(109)
R = Bu^i, MeCH=CH, Bu^t
CO2Me
Br
Bu
CrCl3, LiAlH4
THF, RCHO
52–86%
O
O
R
Bu
(ref. 81a)
(110)
R = Ph, Bu^n, MeCH=CH
anti diastereomer
R3
H
R1
CrLn
O
R
R3
H
H
CrLn
O
R
R1
syn diastereomer

**Scheme 23**

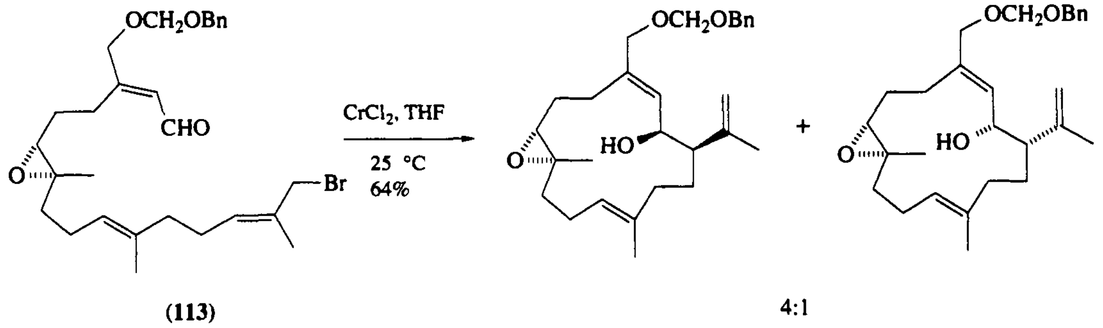
OCH2OBn
CHO
O
Br
CrCl2, THF
25 °C
64%
OCH2OBn
HO
O
+
OCH2OBn
HO
O
(113)
4:1

**Scheme 24**

### *1.1.2.3.2 Reagents based on lithium*

Crotyllithium is configurationally unstable[20] and shows poor regio- and stereo-selectivity in reactions with aldehydes.[6d,84] Regio- and stereo-chemical control has been achieved, however, by using substituted allyllithiums such as (**114**)–(**118**).[34a,b,43b,85] Reagents (**114**)–(**117**) are stabilized by chelation that helps to maintain their isomeric integrity, and type I diastereoselectivity has been demonstrated in reactions with aldehydes.[43b,85] Stereoselectivity is further improved by transmetallation to the corresponding aluminum or titanium reagents (*cf.* Scheme 9).[42,43] Reagent (**118**) reacts preferentially as the (*E*)-crotyl isomer, presumably since the (*Z*)-isomer is destabilized by interactions between Me and an axial S atom in the transition state corresponding to (**12**; Scheme 7, $R^1 = Me$, $R^2 = H$).[34a,b]

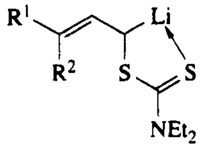
R1
Li
R2
S
S
NEt2

(**114**) $R^1 = Me$; $R^2 = H$
(**115**) $R^1 = H$; $R^2 = Me$

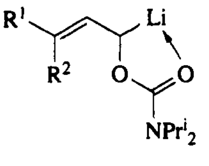
R1
Li
R2
O
O
NPr^i2

(**116**) $R^1 = Me$; $R^2 = H$
(**117**) $R^1 = H$; $R^2 = Me$

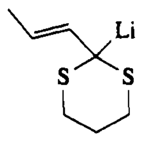

(**118**)

### *1.1.2.3.3 Reagents based on titanium*

$\eta^1$-Crotyltitanium reagents (**119**)–(**121**), prepared by treatment of $Cp_2TiX_2$, $(RO)_3TiCl$ or $(Et_2N)_3TiCl$ with crotylmagnesium halides, react with aldehydes to give the *anti* diastereomer preferentially.[17] Greatest stereoselectivity in reactions with aldehydes has been achieved by using (**119a**) with X = Br. Reagent (**120a**) with R = Ph is more selective than other alkoxy- or amino-substituted titanium derivatives, including (**120b**) and (**121**; Table 3). Ate complexes (**122**) have also been studied,[17e] but seem to have no particular advantage relative to (**119**)–(**121**). Interestingly, however, the ate complex generated by the addition of allylmagnesium bromide to $Ti(NEt_2)_4$ reacts faster with ketones than aldehydes.[86] The reactions of a number of γ-heteroatom-substituted allyltitanium reagents have also been described.[45b,87]

α-Substituted crotyltitanium reagent (**123**) displays exceptional levels of diastereoselectivity, and is much more selective than the corresponding lithium or aluminum derivatives.[42b,43]

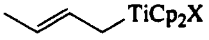

**(119a)** X = Br
**(119b)** X = Cl

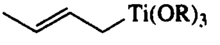

**(120a)** R = Ph
**(120b)** R = Pr$^i$

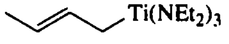

**(121)**

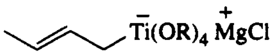

**(122a)** R = Pr$^i$
**(122b)** R = Ph

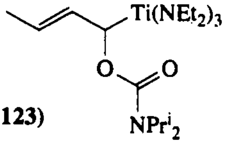

**(123)**

**Table 3** Diastereoselectivity of Aldehyde Addition Reactions of (**119**)–(**121**)

| *Reagent* | *RCHO* | *Diastereoselectivity (3):(4)* | *Ref.* |
|---|---|---|---|
| (**119a**) | PhCHO | 99:1 | 17a |
| (**119b**) | PhCHO | 60:40 | 17a |
| (**119a**) | EtCHO | 96:4 | 17a |
| (**119a**) | Pr$^i$CHO | 99:1 | 17a |
| (**120a**) | PhCHO | 85:15 | 17c |
| (**120a**) | Pr$^i$CHO | 96:4 | 17c |
| (**120b**) | Pr$^i$CHO | 88:12 | 17c |
| (**121**) | PhCHO | 69:31 | 17e |

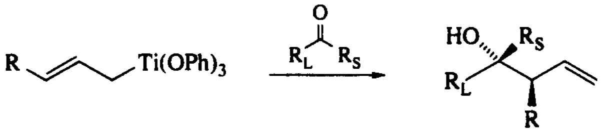

**(120a)** **(124)**

| | | *Diastereoselectivity, R =* | | |
|---|---|---|---|---|
| $R_L$ | $R_S$ | *Me* | *Bu$^n$* | *Pr$^i$* |
| Ph | Me | 88:12 | 87:13 | 87:13 |
| Ph | C≡CMe | 72:28 | 77:23 | 77:23 |
| Bu$^t$ | Me | >98:<2 | | |
| Bu$^t$ | Ph | >98:<2 | | |
| c-$C_6H_{11}$ | Me | 87:13 | | |
| c-$C_6H_{11}$ | Et | 60:40 | | |

**Scheme 25**

Seebach has shown that various 2-alkenyltitanium triphenoxides, including (**120a**), display useful levels of diastereoselectivity with ketones, especially when the size difference between the two carbonyl substituents is pronounced (Scheme 25).[17b,d] The major diastereomer (**124**) presumably arises *via* transition state (**20**).

The reactions of $\eta^3$-crotyltitanium reagents (**125**) and aldehydes have been studied by Sato and coworkers.[19a,88] These reactions proceed in good yield and with high *anti* diastereoselectivity. For example, the reactions of (**125**; R = H) with propionaldehyde and benzaldehyde are 93–95% selective for the *anti*-homoallyl alcohol.[19a] The stereochemical course is consistent with the reaction proceeding by way of the usual chair-like transition state (**126**).

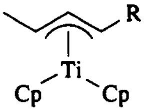

(**125**) R = H, $SiMe_3$, OPh, SPh

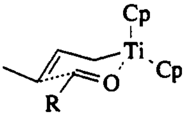

(**126**)

### *1.1.2.3.4 Reagents based on zinc*[89]

Crotylzinc, like crotyllithium, is configurationally unstable and provides a mixture of *syn* and *anti* diastereomers upon reaction with aldehydes.[6d] Stereoselectivity improves, however, as the size of R of RCHO or the steric requirements of R′ of $R'CH{=}CHCH_2ZnX$ increases.[6d,90] For example, cinnamylzinc provides up to 87:13 selectivity for the *anti* diastereomer in reactions with benzaldehyde,[90a] while the silicon-substituted allylzinc (**127**), generated *in situ* from the corresponding allyllithium and $ZnCl_2$, provides *anti* diastereomer (**128**) with excellent selectivity in all cases examined except heptanal (4:1 selectivity).[90b] Oxidation of (**128**) as indicated provides diols (**129**) that are of interest as intermediates in the synthesis of carbohydrates. The allylzinc species generated by treatment of allyllithium (**118**) with $ZnCl_2$ is much more selective than (**118**) in reactions with ethyl pyruvate, a result attributed to the greater ability of the zinc cation to coordinate to the $—CO_2Et$ residue in the transition state.[34a]

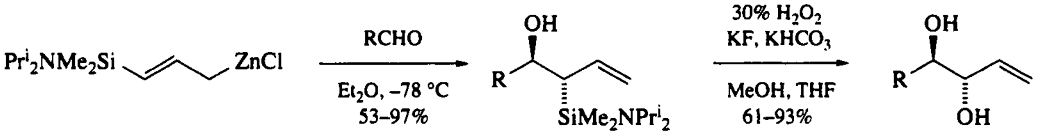

(**127**) (**128**) (**129**)

| | |
|---|---|
| R = n-$C_6H_{13}$ | 4:1 |
| R = c-$C_6H_{11}$ | one isomer |
| R = Ph | one isomer |

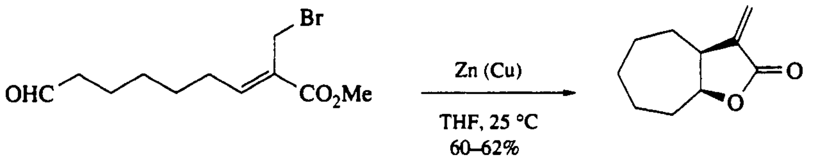

(**130**) (**131**)

The presence of a substituent at C-2 of the allyl unit also influences the stereoselectivity of allylzinc reactions, in the same way that C-2 substituents influence the reactions of allylchromium (**109**) and (**110**) (Schemes 22 and 23). For example, the —ZnBr derivative corresponding to (**109**) displays *syn* diastereoselectivity comparable in the best cases to that realized with (**109**).[34c] The reaction of (**130**) with Zn(Cu) in dilute solution similarly provides (**131**) with *syn* stereochemistry about the new C—C bond. Type III diastereoselectivity has been demonstrated in this series, as the (*E*)-isomer of (**130**) provides a 3.8:1 mixture of (**131**) and the corresponding *trans*-fused lactone.[91]

#### *1.1.2.3.5 Reagents based on zirconium*

Crotylzirconiums (**132**)–(**134**) have been generated *in situ* by the addition of one, two and three equivalents of crotyllithium or crotylmagnesium chloride to $Cp_2ZrCl_2$ in THF, and exhibit a preference for the *anti*-homoallyl alcohol (**3**) in reactions with aldehydes (87–95% yield; Scheme 26).[18] Variable temperature NMR experiments have shown (**133**) to be a 60:40 mixture of (*E*)- and (*Z*)-isomers at 30 °C and an 87:13 mixture at –70 °C.[18a] Reagents (**132**) and (**134**) were similarly determined to be 85:15 and 55:45 mixtures of isomers at –70 °C. Thus, the reaction diastereoselectivity closely parallels the isomeric composition of these crotylzirconium species in solution. Crotylzirconium species of the general structure $(crotyl)Zr(OR)_3$, prepared by the addition of crotylmagnesium chloride and $Zr(OR)_4$, have also been studied, but in general are less diastereoselective than (**132**)–(**134**) or the comparable crotyltitanium complexes (**123**).[18a] The most selective of the alkoxy-substituted zirconium reagents is (**135**).

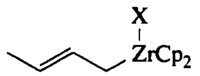

(**132**) X = Cl
(**135**) X = $OC_5H_{11}$

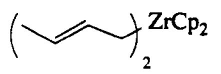

(**133**)

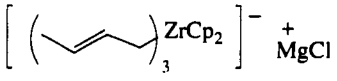

(**134**)

*Diastereoselectivity (3):(4)*

| *Reagent* | *Temp.* (°C) | *PhCHO* | *MeCHO* | *EtCHO* | *Pr$^i$CHO* | *Ref.* |
|---|---|---|---|---|---|---|
| (**132**) | –78 | 86:14 | 73:27 | 86:14 | 88:12 | 18a |
|  | –78 | – | 77:23 | 78:22 | 74:26 | 18b |
| (**133**) | 30 | – | 78:22 | 79:21 | 72:28 | 18a |
|  | 0 | – | 80:20 | 81:19 | 77:23 | 18a |
|  | –78 | 85:15 | 88:12 | 89:11 | 82:18 | 18a |
|  | –110 | – | 91:9 | 92:8 | 86:14 | 18a |
| (**134**) | –78 | – | 58:42 | 66:34 | 55:45 | 18a |
| (**135**) | –78 | – | 90:10 | 90:10 | 89:11 | 18a |

**Scheme 26**

#### *1.1.2.3.6 Other type III crotyl metal reagents*

Crotyl metal reagents based on antimony,[92] bismuth,[93] indium[94] and manganese[95] have also been described. These reagents display moderate preferences for the *syn* diastereomer (**4**) in reactions with aromatic aldehydes (antimony, up to 75:25; bismuth, 85:15; indium, 66:34; manganese, 65:35). Too few examples have yet been reported, however, to fully assess the potential of these systems as reagents for organic synthesis.

## 1.1.3 RELATIVE DIASTEREOSELECTION

### 1.1.3.1 Reactions with Chiral Aldehydes

The stereochemistry of the reactions of chiral carbonyl compounds with nucleophiles has been a topic of considerable theoretical and synthetic interest since the pioneering study by Cram appeared in 1952.[96] The available predictive models focus entirely on the conformational and stereoelectronic demands of the chiral carbonyl substrate, the implicit assumption being that the relative stabilities of the competing transition states are determined only by stereoelectronics and the minimization of nonbonded interactions between the substituents on the chiral center and the nucleophile. These models totally ignore the possibility, however, that the geometric requirements of the nucleophile may also have an effect on reaction diastereoselectivity. Considerable evidence is now available, particularly in the reactions of Type I (*Z*)-crotylboronates and *Z*(*O*)-metal enolates, that the stereochemistry of the nucleophile is indeed an important issue that must be considered when assessing reaction diastereoselectivity.

Consider the reactions of pinacol crotylboronates (**1**) and (**2**) with a chiral aldehyde, RCHMeCHO (Scheme 27). The four diastereomeric products (**136**)–(**139**) arise *via* the indicated transition states (**140**)–(**143**). According either to the Cram rule or the Felkin–Anh paradigm, the 3,4-*anti*-4,5-*syn* diastereomer (**136**) should be favored over *anti,anti*-(**137**) in the reactions of the (*E*)-crotyl isomer (**1**), a result that is in fact observed experimentally.[97,98] The same reasoning leads to the prediction that *syn,syn* diastereomer (**138**) should be the major product of the reactions of (*Z*)-crotylboronate (**2**). In this case, however, it is the 3,4-*syn*-4,5-*anti* diastereomer (**139**) that is produced preferentially.[97,98] The reason that the reactions of (*Z*)-crotylboronates fail to follow the Felkin–Anh paradigm is probably that transition state (**142a**) is destabilized by the indicated 1,5-interaction between methyl groups. Although (**138**) can also arise *via* (**142b**) in which the 1,5-Me–Me interaction of (**142a**) is relieved, this transition state still suffers from a relatively large nonbonded interaction between Me and R. Transition state (**143**), on the other hand, allows for fewer interactions between the crotyl unit and the substituents at C-2 of the chiral aldehyde substrate and consequently is favored even though it corresponds to an 'anti-Felkin' arrangement. Similar 'anti-Felkin' diastereoselectivity has been observed in reactions of various *Z*(*O*)-boron and -lithium enolates with α-methyl chiral aldehydes, undoubtedly for similar reasons.[4a,5,99]

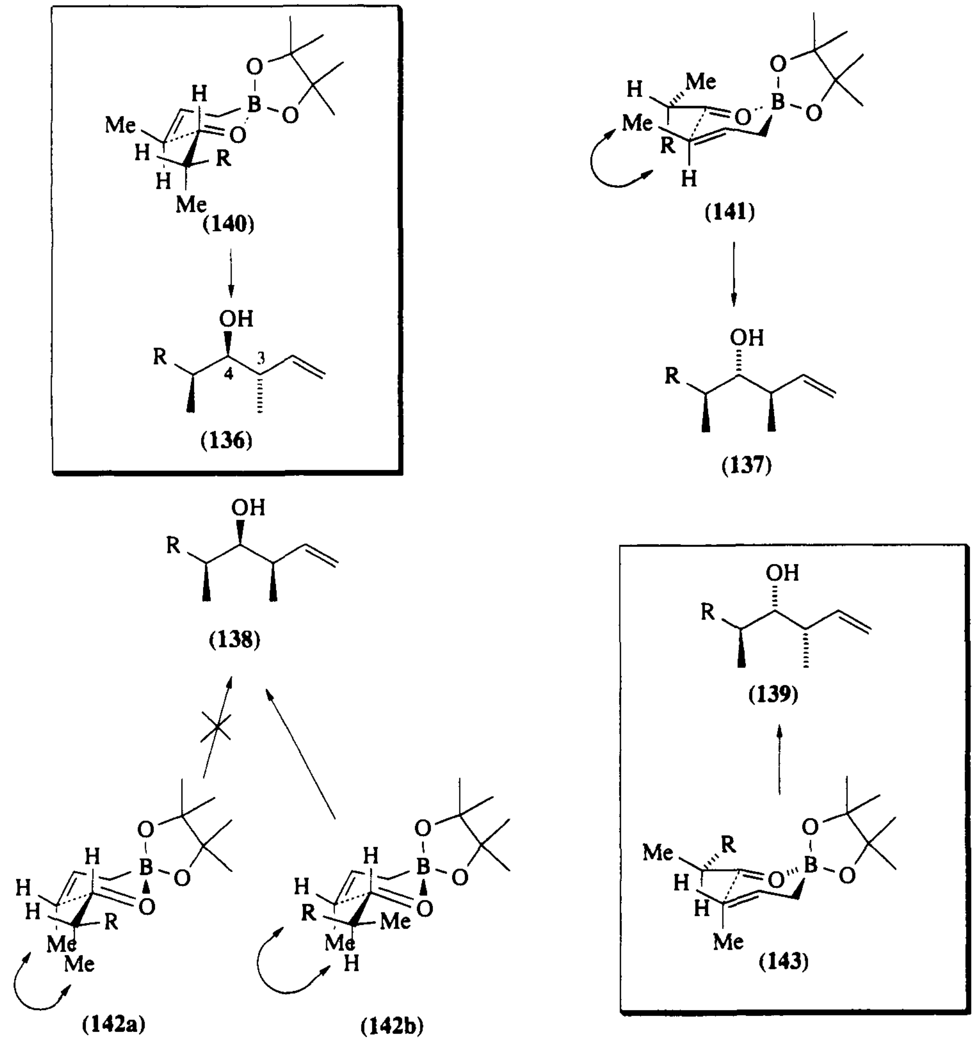

**Scheme 27**

It is to be expected that the extent of relative diastereoselection will depend on the difference in size of the R substituent relative to Me. The examples summarized in Table 4 are generally supportive of this thesis, particularly the reactions of (**1**) with aldehydes (**146**) and (**147**) that are much more selective than with the structurally less complex aldehyde (**145**).[97] The data cited for reactions of pinacol allylboronate

(**144**) and (*Z*)-crotylboronate (**2**), however, also show that diastereoselectivity depends on the stereochemistry at C-3 of (**146**) and (**147**). This can be rationalized by inspecting transition states (**148**) and (**149**) that correspond to (**142b**) of Scheme 27. Aldehyde (**147**) can easily adopt the conformation indicated in (**148**) that minimizes the interactions between C-3 and the crotyl unit. These interactions are only slightly greater than the methyl/methyl interactions in the favored transition state (**143**). With aldehyde (**146**), however, the interactions between the C-3 substituents and the crotyl unit are envisaged to be much more serious due to the conformation indicated in (**149**). The R substituent of (**146**) thus behaves as a more sterically demanding unit than in (**147**), and consequently the diastereoselectivity of the reaction of (**146**) is greater.

**Table 4** Relative Diastereoselection in the Reactions of Allylboronates and α-Methyl Chiral Aldehydes: Ratios of 4,5-*Syn* to 4,5-*Anti* Products[97]

| *Reagent* | 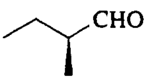 <br>(**145**) | 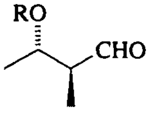 <br>(**146**) | 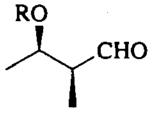 <br>(**147**)[a] |
|---|---|---|---|
| Pinacol (*E*)-crotylboronate (**1**)[b] | 83:17 | 95:5 (R = TBDMS)<br>89:11 (R = MOM) | 98:2 (R = TBDMS)<br>94:6 (R = MOM) |
| Pinacol allylboronate (**144**) | 62:38 | 49:51 (R = TBDMS)<br>61:39 (R = MOM) | 79:21 (R = TBDMS)<br>79:21 (R = MOM) |
| Pinacol (*Z*)-crotylboronate (**2**)[c] | 30:70 | 9:91 (R = TBDMS)<br>22:78 (R = MOM) | 40:60 (R = TBDMS)<br>41:59 (R = MOM) |

[a] The enantiomeric aldehyde was actually used (ref. 97a). [b] 4,5-*Syn* diastereomer (**136**) is the major product. [c] 4,5-*Anti* diastereomer (**139**) is the major product.

(**147**)

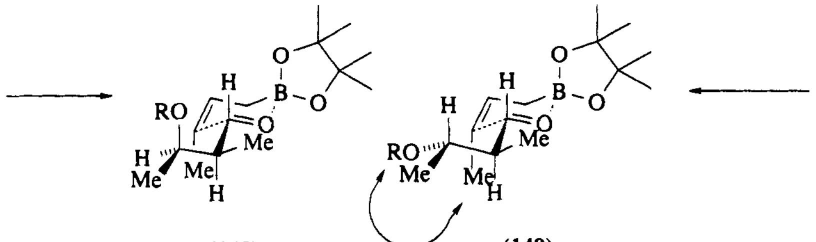

(**146**)

(**148**) (**149**)

A more complete picture of relative diastereoselection in the reactions of allylboronates and chiral aldehydes is given in Table 5; structures of the products in the glyceraldehyde acetonide (**151**) series are given in Scheme 28.[25,100–102] The data for (**150**) and (**151**) reconfirm the conclusion of Table 4 that diastereoselectivity is dependent on the geometry and substitution pattern of the allylboronate. In addition, however, the data in Table 5 also show that diastereoselectivity depends strikingly on the aldehyde, with greater selectivity for the 4,5-*anti* diastereomer being realized as one moves across any row of the table. This is strongly suggestive of an electronic effect, particularly since it is believed, for example, that the reactions of (*Z*)-γ-substituted allylboronates (**2**) and (**74**) proceed preferentially *via* the same transition states: (**143**) for α-methyl chiral aldehydes and (**158**) for the α-oxygenated aldehydes.[25,100a] Transition state (**158**) corresponds to the Cornforth model and the increased diastereoselection in the reactions of (**2**) and (**74**) with oxygenated aldehydes *versus* the reactions of (**2**) with aldehydes like (**145**) has been attributed to the electronic stabilization of (**158**) relative to competitive diastereomeric arrangements.[25] The usually invoked Felkin–Anh arrangement (**159**) is probably not involved in the reactions of (*Z*)-allyl-boronates (**2**) and (**74**) owing to serious steric interactions between R of the allylboronate and the alkyl substituent at C-2 of the chiral aldehyde substrate.

Electronic effects are also clearly operational in the reactions of allylboronate (**144**) since the diastereofacial preference switches upon moving from an α-methyl chiral aldehyde (**145**) to an oxygenated aldehyde such as (**150**) or (**151**). The identity of the major transition state(s) is less clear with (**144**), however, since at least two reasonable possibilities exist in every case (those resembling (**142a**) or (**142b**) in reactions with α-methyl chiral aldehydes and (**158**) or (**159**) with oxygenated aldehydes).

**Table 5** Relative Diastereoselection in the Reactions of Substituted Allyboronates and Chiral Aldehydes (*145*), (*150*) and (*151*): Ratios of 4,5-*Anti* to 4,5-*Syn* Products

| *Reagent* | 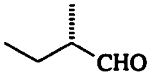 <br>**(145)** | 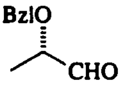 <br>**(150)** | 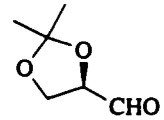 <br>**(151)** |
|---|---|---|---|
| Pinacol (*E*)-crotylboronate (**1**) | 17:83[97] | — | 55:45[25] |
| Pinacol (*E*)-γ-methoxyallylboronate (**73**) | — | 40:60 | — |
| Pinacol allylboronate (**144**) | 38:62[97] | 65:35[100a]<br>(55:45)[25] | 80:20[25,101] |
| Pinacol (*Z*)-crotylboronate (**2**) | 70:30[97] | — | 97:3[25] |
| Pinacol (*Z*)-γ-methoxyallylboronate (**74**) | — | 82:18[100a]<br>(90:10)[100b] | >95:5[25,102] |

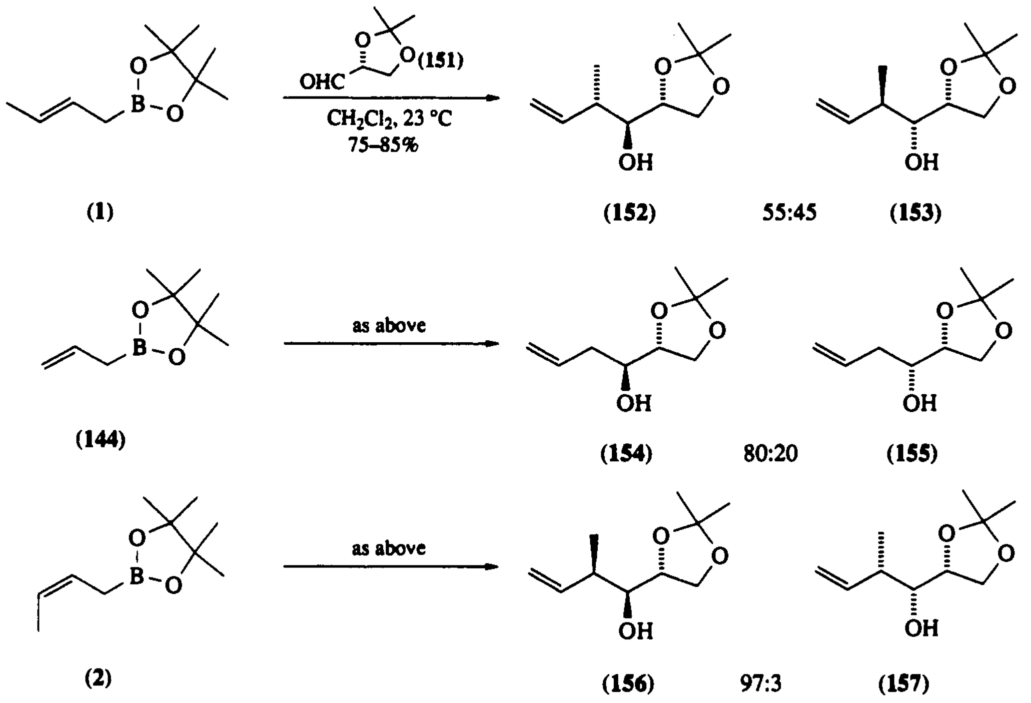
O
B
O
(1)
O
O(151)
OHC
CH₂Cl₂, 23 °C
75–85%
O
O
OH
(152)
55:45
O
O
OH
(153)
O
B
O
(144)
as above
O
O
OH
(154)
80:20
O
O
OH
(155)
O
B
O
(2)
as above
O
O
OH
(156)
97:3
O
O
OH
(157)

**Scheme 28**

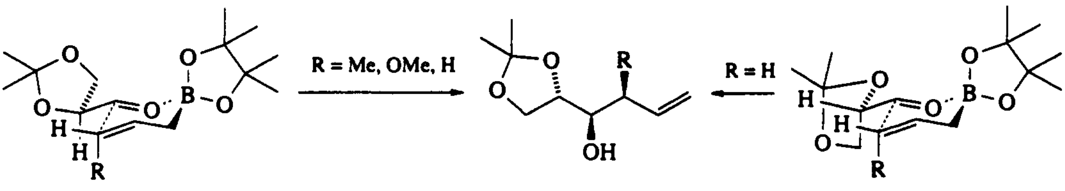
O
O
O
O
B
O
H
H
R
(158)
R = Me, OMe, H
O
O
R
OH
R = H
O
H
H
O
O
O
B
O
R
(159)

Electronic arguments have been presented to rationalize the poor diastereoselectivity of the reactions of (**1**) and (**151**).[25] It may be argued that even though transition state (**160**) has greater nonbonded interactions than (**161**) (which corresponds to (**140**), the major pathway in the reactions with α-methyl chiral aldehydes, Scheme 27), the electronic effect (Felkin activation) is sufficient to lower the energy of (**160**) so that it is slightly more accessible than (**161**). This result probably represents a special case, however, since C-3 of (**151**) is not very sterically demanding in (**160**), owing to the acetonide unit that minimizes

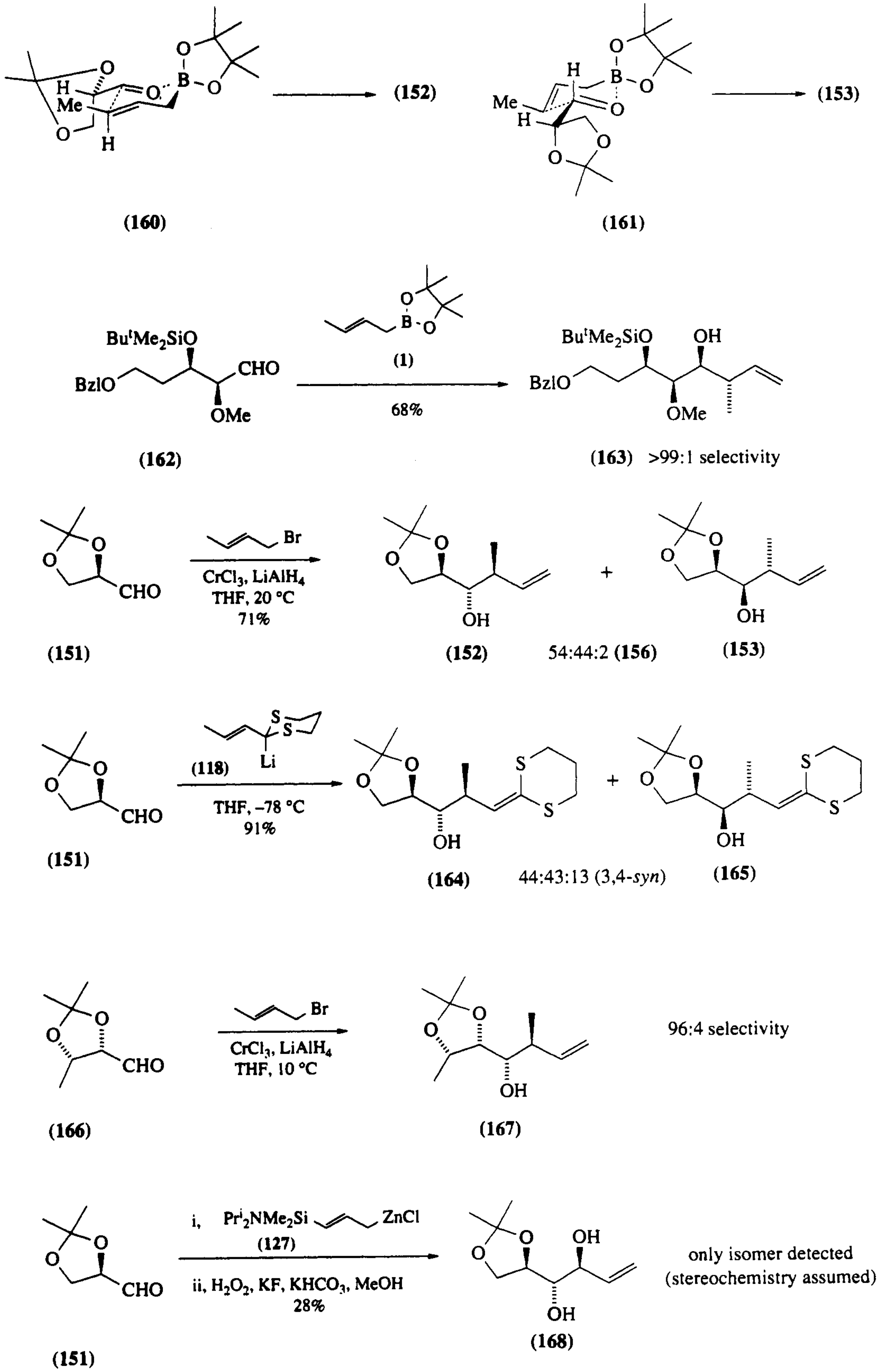
(152)
(153)
(160)
(161)
Bu$^t$Me$_2$SiO
BzlO
CHO
OMe
(1)
68%
OH
(162)
(163) >99:1 selectivity
Br
CrCl$_3$, LiAlH$_4$
THF, 20 °C
71%
(151)
(152)
54:44:2 (156)
(153)
(118)
Li
THF, –78 °C
91%
(164)
44:43:13 (3,4-*syn*)
(165)
CrCl$_3$, LiAlH$_4$
THF, 10 °C
96:4 selectivity
(166)
(167)
i, Pr$^i_2$NMe$_2$Si ZnCl
(127)
ii, H$_2$O$_2$, KF, KHCO$_3$, MeOH
28%
only isomer detected
(stereochemistry assumed)
(168)

Scheme 29

interactions of the C-3 alkoxy group with the crotyl unit. Indeed, the reaction of differentially protected α,β-dialkoxyaldehyde (**162**) and (*E*)-crotylboronate (**1**) provided (**163**) with very high diastereoselectivity *via* a transition state corresponding to (**161**).[103] Thus, increased steric interactions are sufficient to destabilize (**160**) relative to (**161**).

The aldehyde diastereofacial selectivity realized in the reactions of many other type I and III crotyl metal reagents closely parallels the results summarized above for the crotylboronates. For example, the reactions of glyceraldehyde acetonide (**151**) either with the crotylchromium reagent[104] or with allyllithium (**118**; Scheme 29)[34a] provide mixtures of diastereomers strikingly similar to those realized in the reaction of (**151**) and (*E*)-crotylboronate (**1**). Steric effects certainly have an effect on diastereoselectivity, as evidenced by the reaction of (**166**) and crotylchromium (**8**) that provides (**167**) with excellent stereoselectivity.[105] In contrast, however, the reaction of (**151**) and substituted allylzinc reagent (**127**) is reported to provide (**168**), but stereochemistry was not rigorously assigned in this case.[90b]

Reactions of the crotylchromium reagent (**8**) and α-methyl chiral aldehydes are summarized in Scheme 30.[9a,c,106] The results with (**169**)–(**173**) demonstrate that diastereoselectivity *via* a transition state analogous to (**140**) increases as the steric demands of R increase, while the data for (**174**)–(**177**) indicate that diastereoselectivity in these more stereochemically complicated cases depends subtly on the stereochemistry of the centers at C-3 and C-4 relative to C-2. This effect undoubtedly is related to the conformational preferences of the C(2)—C(3) bond, which influences the nonbonded interactions involving the

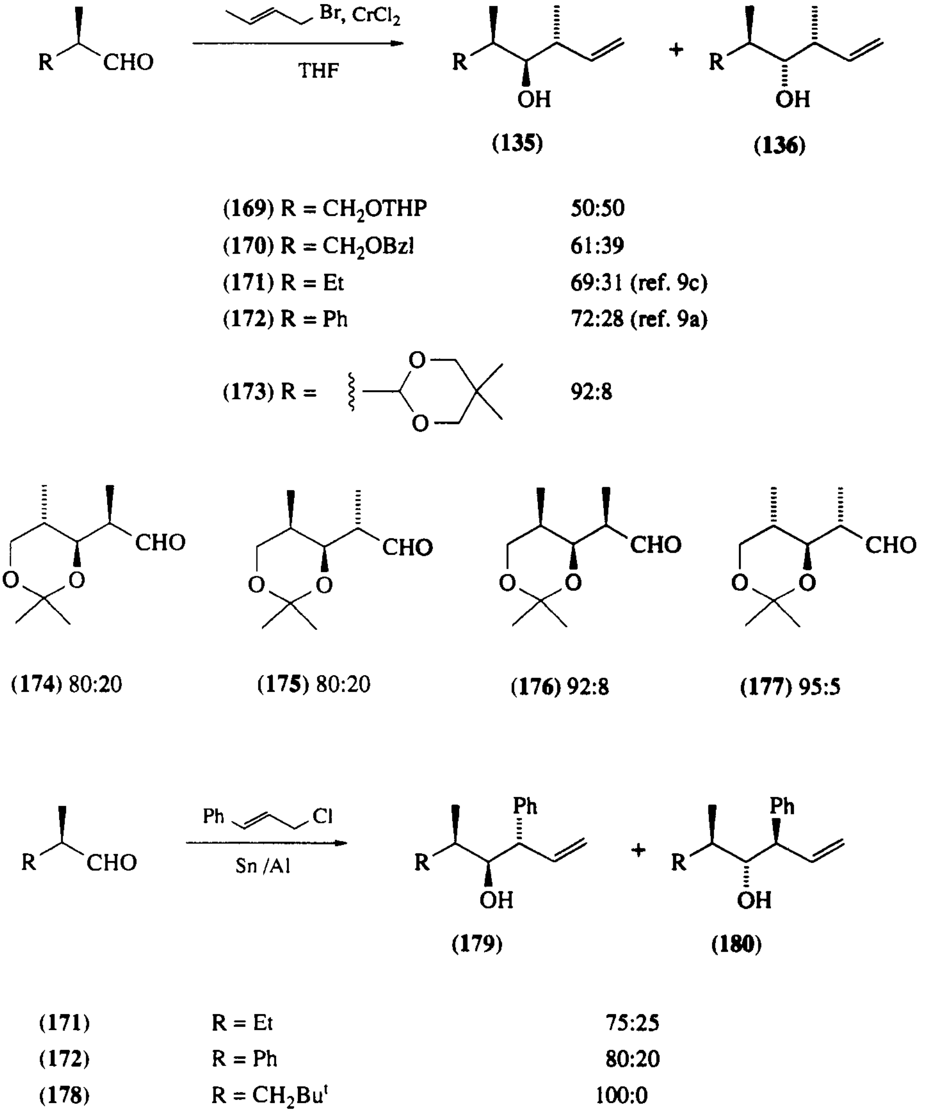

(169) R = $CH_2OTHP$ 50:50
(170) R = $CH_2OBzl$ 61:39
(171) R = Et 69:31 (ref. 9c)
(172) R = Ph 72:28 (ref. 9a)
(173) R = 92:8

(171) R = Et 75:25
(172) R = Ph 80:20
(178) R = $CH_2Bu^t$ 100:0

Scheme 30

bulky R unit in the disfavored transition state (**141**).[106a] Interestingly, the reaction of (*E*)-crotylboronate (**1**) with (**170**) provides (**135**) and (**136**) in a ratio of 68:32,[98] while the reaction of (**172**) and (crotyl)ZrCp$_2$Cl (**132**) provides (**135**) and (**136**) in the ratio of 73:27,[18b,107] diastereoselectivities very

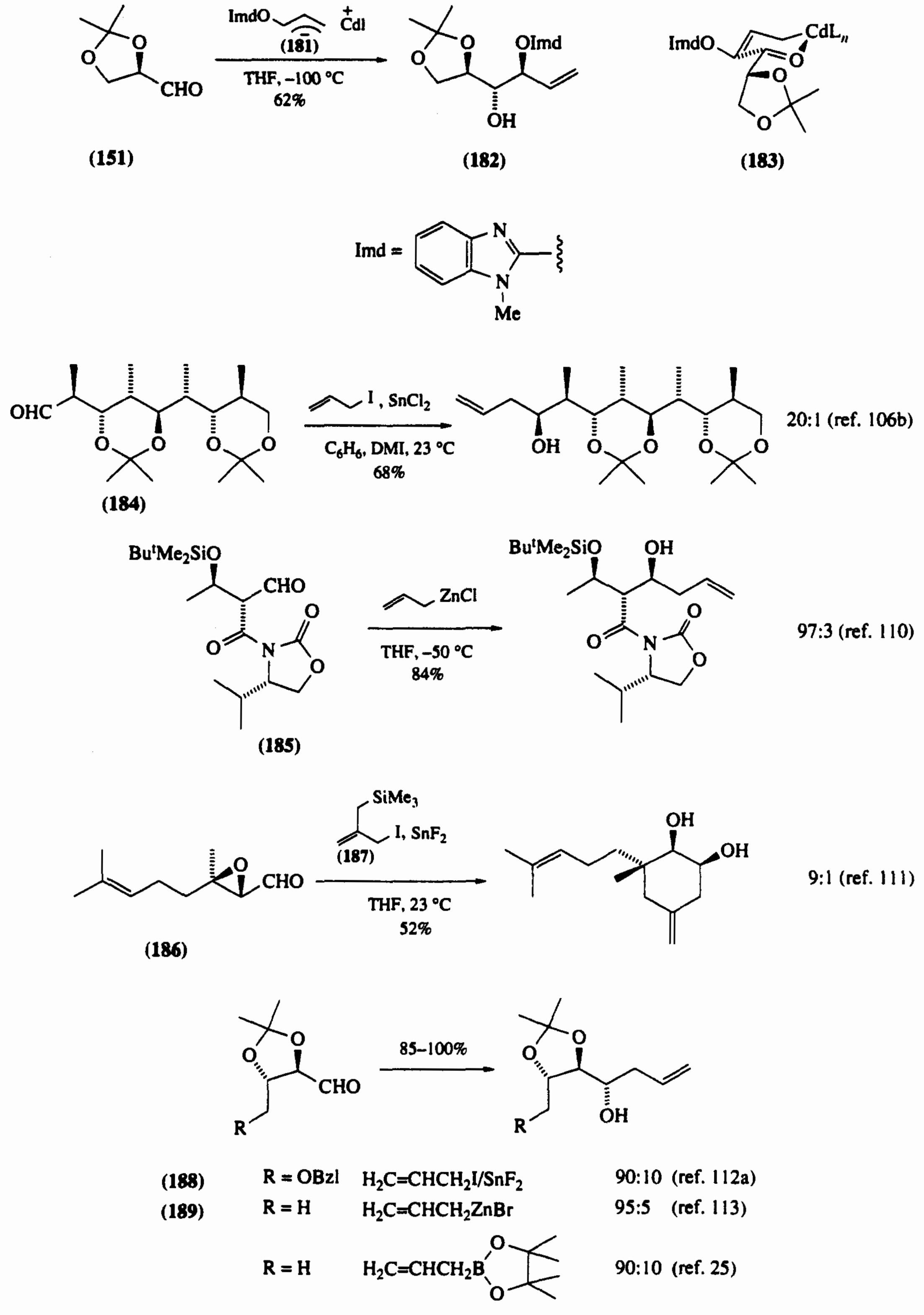

(151)
ImdO
CdI
(181)
THF, –100 °C
62%
OImd
OH
(182)
ImdO
CdL$_n$
(183)
Imd =
N
N
Me
OHC
(184)
I, SnCl$_2$
C$_6$H$_6$, DMI, 23 °C
68%
OH
20:1 (ref. 106b)
Bu$^t$Me$_2$SiO
CHO
(185)
ZnCl
THF, –50 °C
84%
OH
97:3 (ref. 110)
SiMe$_3$
I, SnF$_2$
(187)
CHO
(186)
THF, 23 °C
52%
OH
OH
9:1 (ref. 111)
CHO
85–100%
R
OH

(**188**) R = OBzl H$_2$C=CHCH$_2$I/SnF$_2$ 90:10 (ref. 112a)

(**189**) R = H H$_2$C=CHCH$_2$ZnBr 95:5 (ref. 113)

R = H H$_2$C=CHCH$_2$B 90:10 (ref. 25)

**Scheme 31**

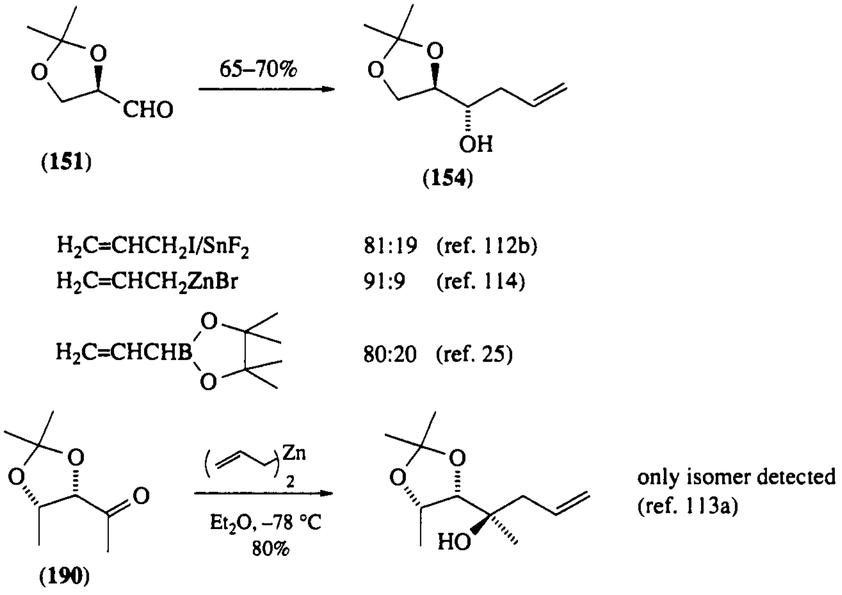
(151)
65–70%
(154)
$H_2C=CHCH_2I/SnF_2$ 81:19 (ref. 112b)
$H_2C=CHCH_2ZnBr$ 91:9 (ref. 114)
$H_2C=CHCHB$ 80:20 (ref. 25)
(190)
$Et_2O$, -78 °C
80%
only isomer detected (ref. 113a)

Scheme 31 *(continued)*

similar to those obtained with the crotylchromium reagent (**8**). The reactions of aldehyde (**171**), (**172**) and (**178**) and the cinnamyltin reagent also proceed *via* a transition state analogous to (**140**), again with diastereoselectivity increasing as the steric requirements of R increase.[77b,106b,108]

Several sets of experimental data have been reported that deviate from the stereochemical picture summarized above. The first involves the reaction of aldehyde (**32**) and (*Z*)-crotyldiethylalane (**31**) that provides *syn,syn* diastereomer (**33**) with 3:1 selectivity (Section 1.1.2.2.1).[39] This is the only example reported to date of a type I (*Z*)-crotyl metal reagent that reacts preferentially through transition states (**142a**) or (**142b**). Perhaps Felkin–Anh stereoelectronic considerations are more significant in this case because of the greater nucleophilicity of (**31**) compared to the (*Z*)-crotylboronates. In addition, the longer C—Al and Al—O bonds relative to the boron reactions may result in a longer developing C—C bond that further minimizes the magnitude of the nonbonded interactions noted in (**142a**) and (**142b**). Further experimentation is necessary, however, to establish the validity of these conclusions.

A second example concerns the reaction of glyceraldehyde acetonide (**151**) and γ-alkoxyallylcadmium reagent (**181**).[109] This reaction apparently proceeds preferentially by way of a Felkin–Anh transition state (**183**) analagous to (**160**) in the reactions of (*E*)-crotylboronates,[25] because of the smaller steric requirements of the γ-alkoxy group in (**181**). Here again, additional experimental data are required to verify this hypothesis. The reaction of (**151**) and allylzine reagent (**127**) appears also to be in disagreement with this stereochemical model (Scheme 29).

Numerous reactions of chiral aldehydes and allyl metal reagents have been reported. Some of the more highly selective examples are summarized in Scheme 31. The stereochemistry of the reaction of (**184**)[106b] and the allyl iodide/$SnCl_2$ reagent are typical of reactions of α-methyl chiral aldehydes: the 4,5-*syn* diastereomer predominates, but usually not with the level of stereoselection seen in this example.[97,98,107] Similar diastereoselection is realized in the reaction of (**185**) and allylzinc chloride, with the exception that in this case it is the imide function that appears to function as the largest substituent.[110,115] The allyltin intermediate generated from (**187**) displays very good levels of *anti* diastereoselectivity in the reactions with epoxy aldehydes such as (**186**),[111] a result in good agreement with those obtained in the addition of various allyl metal derivatives to α,β-dialkoxy aldehydes (**151**), (**188**) and (**189**).[25,112-114] The general agreement of the results with the different allyl metal reagents, especially those involving allylboronate (**144**), suggests that chelated transition states are not involved, as is often assumed by many investigators.[114a,116] Allylzinc chloride and allylmagnesium bromide also add with excellent stereoselectivity to methyl ketone (**190**), one of the rare, highly selective examples of the reaction of a chiral ketone with an allyl metal reagent.[113a]

The reactions of β-alkoxy-α-unsubstituted aldehydes are generally not highly diastereoselective, except in cases where the allyl metal addition occurs *via* a chelated transition state.[107,117] An interesting example along these lines is the reaction of aldol (**191**) and $Zr(allyl)_4$ that evidently proceeds with intra-

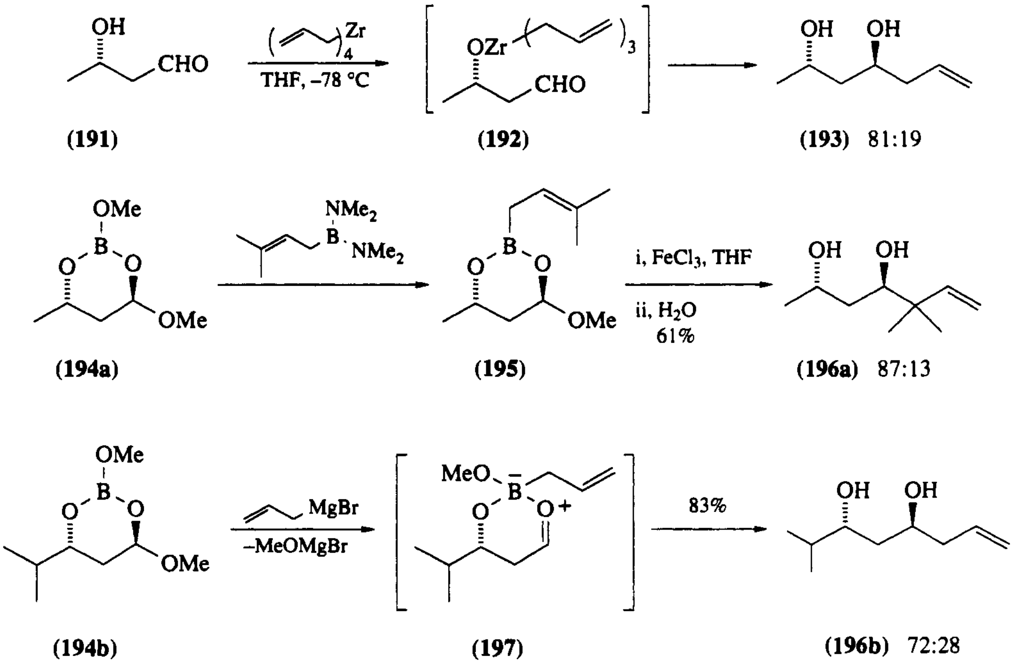

Scheme 32

molecular transfer of an allyl unit *via* intermediate **(192)**, producing **(193)** as the major product of an 81:19 mixture (Scheme 32).[117] A related process involves the reactions of 1,3,2-dioxaborinanes **(194)** with suitable allyl donors that provide *anti* (*threo*)-1,3-diols **(196)** with 70–87% diastereoselectivity *via* intermediates like **(197)**.[118]

### 1.1.3.2 Reactions with Chiral C=N Electrophiles

Diastereoselective reactions of oxime **(198)** and phenylsulfenimines such as **(201)** with allyl metal reagents have been described (Scheme 33). The reaction of **(198)** and allylboronate **(144)** provides **(199)** with modest selectivity,[62a] while excellent diastereoselectivity was realized in the reactions of **(201)** and its C-2 epimer with the allylzinc reagent.[119] The corresponding ketone derivatives, however, gave 70:30 mixtures of **(204)** and **(205)** upon reaction with diallylzinc, while with allyl Grignard, **(205)** is almost the exclusive product.[119b] The latter result is suggestive of a chelated transition state.

Yamamoto and coworkers have studied the reactions of various allyl metal reagents and chiral aldimines.[6a,120] The reactions of **(206)** with allyl-9-BBN and other allyl metal reagents are highly selective for **(207**; Scheme 34).[120a] In contrast, however, the reactions of **(206)** and crotyl metal reagents do not exhibit such outstanding selectivity. Interestingly, the stereochemistry of the reactions of alkoxy-substituted imines **(209)** and **(210)** can be controlled within reasonable limits by selecting the appropriate reagent: the aluminum ate complex apparently reacts by way of chelated transition states, while those of allyl-9-BBN and (allyl)Ti($OPr^i$)$_3$ proceed *via* conventional cyclic transition states.[120b]

Asymmetric induction from a stereocenter in a chiral group bound to N has also been studied, and good to excellent levels of relative diastereoselection have been observed (Scheme 35).[120a] Interestingly, incorporation of a *N*-phenethyl unit of appropriate absolute stereochemistry into **(214)** resulted in substantially improved selectivity for the 1,3-*syn* product diastereomer (compare results with **210**, Scheme 34).[120b] This is an example of double stereodifferentiation, a synthetic strategy that is discussed in Section 1.1.5.

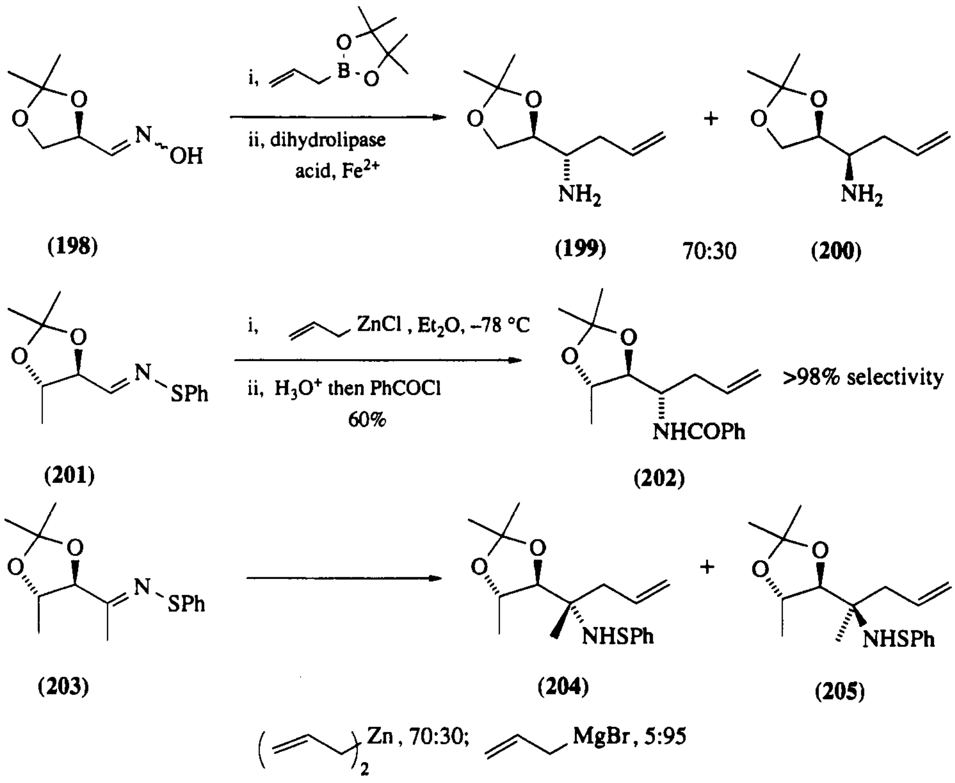

Scheme 33

## 1.1.4 SINGLE ASYMMETRIC SYNTHESIS: REACTIONS OF ACHIRAL ALDEHYDES AND CHIRAL ALLYL ORGANOMETALLICS

A number of highly enantioselective chiral allyl organometallic reagents have been described in the literature. These are of considerable interest both for the asymmetric synthesis of homoallyl alcohols as well as in double asymmetric reactions with chiral C═X electrophiles.[3,5] Two distinct groups of chiral allyl metal reagents can be identified: those with conventional, easily introduced chiral auxiliaries and ones in which the center of chirality is a structural component of the reagent (*e.g.* allyl metal compounds with substituents at C-1). These are discussed separately in the sections that follow.

### 1.1.4.1 Chiral Allyl Organometallics with Conventional Auxiliaries

The most highly enantioselective type I and type III allyl metal reagents that fall into this category are listed in Scheme 36. Reagents (**215**)–(**217**), developed by Hoffmann, are of historical significance since they were the first chiral allyl metal compounds to be studied, and were also among the first chiral reagents of any sort shown to be capable of increasing the stereoselectivity of moderately diastereoselective reactions of chiral aldehydes (*i.e.* matched double asymmetric synthesis).[97b,121] Allyl reagent (**215**) gives 86% *ee* (enantiomeric excess) in the reaction with acetaldehyde at –90 °C, but for most other aldehydes the selectivity is in the range of 36% *ee* (PhCHO) to 72% *ee* (PrCHO) for reactions at –40 °C. The allylborane (**218**) recently described by Reetz is substantially improved and gives 88–96% *ee* with a range of aldehydes at –78 °C.[122] The corresponding crotyl reagent, however, has not yet been described.

The allyldiisopinocampheylboranes (**51**), (**52**), (**219**) and (**220**) developed by Brown give consistently excellent results (83–96% *ee*) in reactions with aldehydes (Scheme 37).[23c,123] The homoallyl alcohols have (*R*) absolute configuration at the carbinol center, assuming that the allyl group transferred has priority over the R substituent of the aldehyde and that the $Ipc_2B$ unit derives from (+)-α-pinene as indicated in Scheme 37. The analogous allylboranes prepared from (+)-3-carene show even greater levels of enantioselectivity.[123] The crotyl-*trans*-2,5-dimethylborolanes (**221**) and (**222**) are among the most highly

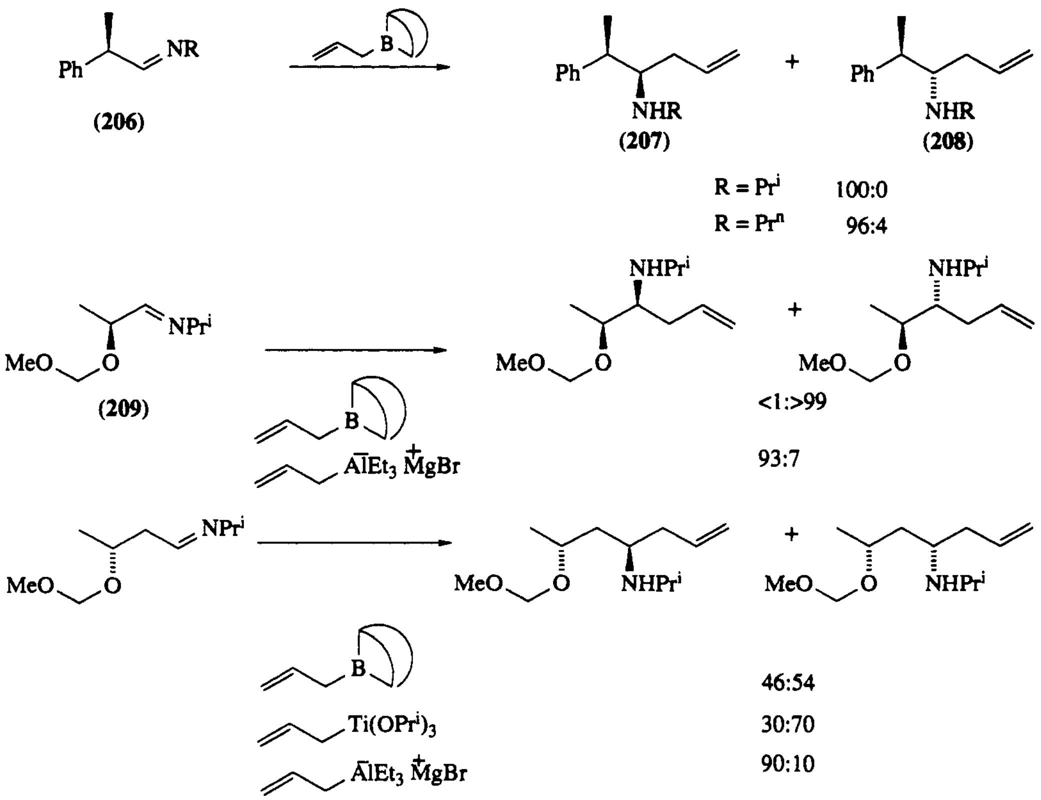
Ph
NR
(206)
B
Ph
NHR
(207)
+
Ph
NHR
(208)
R = Pr$^i$ 100:0
R = Pr$^n$ 96:4
NPr$^i$
MeO
O
(209)
B
AlEt$_3$ MgBr
NHPr$^i$
MeO
O
+
NHPr$^i$
MeO
O
<1:>99
93:7
NPr$^i$
MeO
O
MeO
O
NHPr$^i$
+
MeO
O
NHPr$^i$
B
Ti(OPr$^i$)$_3$
AlEt$_3$ MgBr
46:54
30:70
90:10

**Scheme 34**

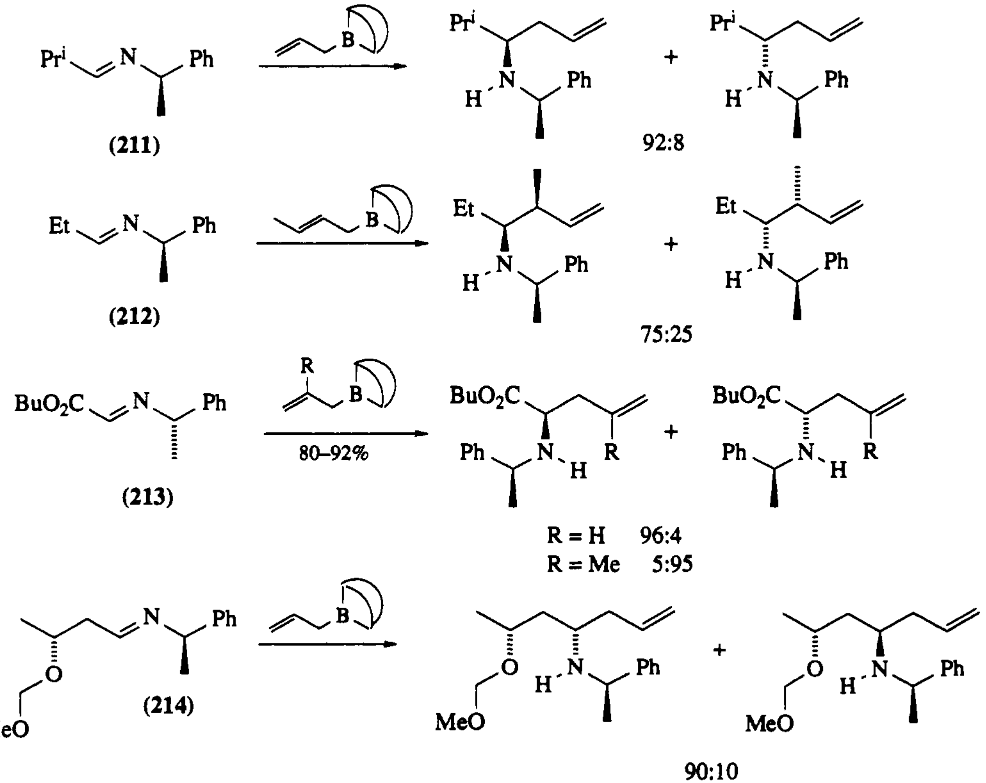
Pr$^i$
N
Ph
(211)
B
Pr$^i$
H
N
Ph
+
Pr$^i$
H
N
Ph
92:8
Et
N
Ph
(212)
B
Et
H
N
Ph
+
Et
H
N
Ph
75:25
BuO$_2$C
N
Ph
(213)
R
B
80–92%
BuO$_2$C
Ph
N
H
R
+
BuO$_2$C
Ph
N
H
R
R = H 96:4
R = Me 5:95
N
Ph
O
MeO
(214)
B
O
MeO
H
N
Ph
+
O
MeO
H
N
Ph
90:10

**Scheme 35**

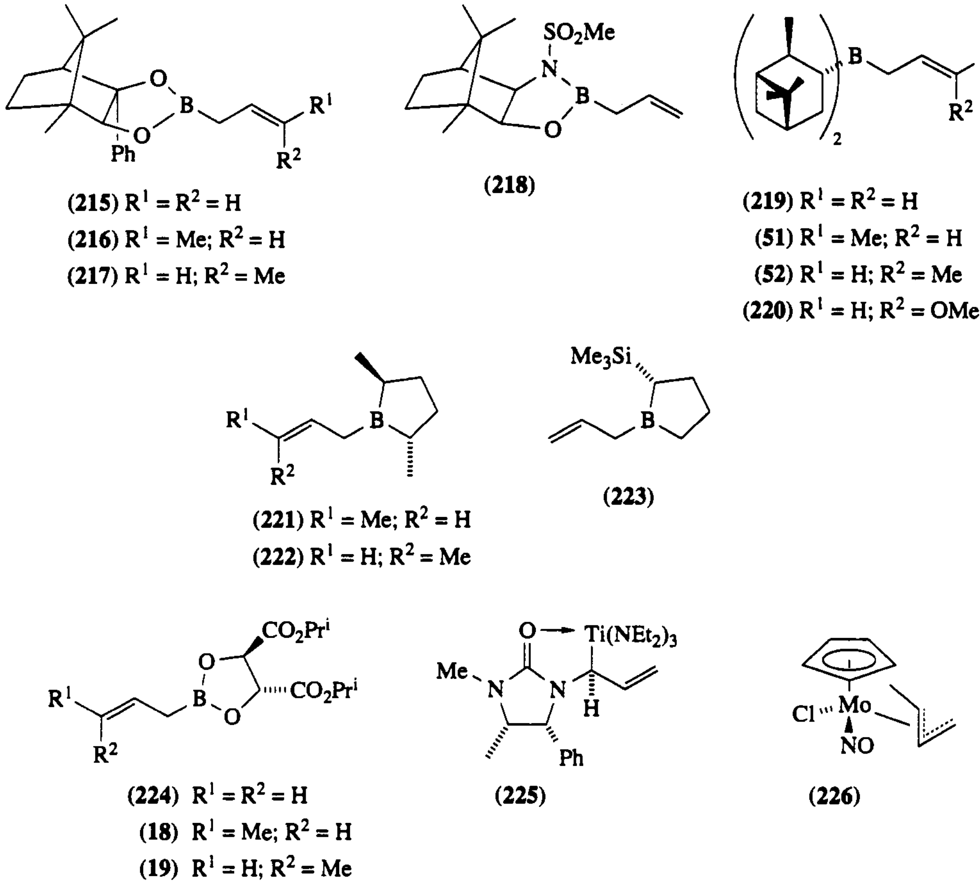

**Scheme 36**

enantioselective crotyl metal reagents yet described: in five of the six examples reported the enantioselectivity is 93–97% *ee* (simple diastereoselectivity is 93–96%).[124a] However, the difficult synthesis of the β-methoxy-2,5-dimethylborolane precursor renders these reagents unattractive for synthetic applications. Allylborane (**223**) has recently been reported to be an exceptionally enantioselective allyl transfer reagent (92–97% *ee*).[124b]

The tartrate ester modified allylboronates (**224**), (**18**) and (**19**) are attractive alternatives to the (allyl)B(Ipc)$_2$ reagents, owing to their ease of preparation and stability to storage.[37,125] In the best cases the tartrate allylboronates are about as enantioselective as Brown's allylboranes (82–88% *ee* with unhindered aliphatic aldehydes), but with hindered aliphatic, aromatic, α,β-unsaturated and most α- and β-alkoxy aldehydes the enantioselectivity falls to a level of 55–75% *ee* (Scheme 38). Enantioselectivity is highly dependent on reaction solvent, with best results being obtained in toluene for all substrates except aromatic ones for which the % *ee* is highest in THF. An electronic origin of asymmetry has been proposed (Scheme 39), and on this basis reagent (**228**) was designed and found to be significantly more enantioselective than the corresponding tartrate ester derivative (**224**; see data in Scheme 38).[126] Allylboronate (**228**), however, is less reactive and less soluble than (**224**), and consequently is less attractive, especially for large-scale work in spite of its enhanced enantioselectivity.

Allyltitanium reagent (**225**) undergoes highly diastereoselective reactions with aldehydes and even a ketone as indicated in Scheme 40.[127] It is interesting that (**225**) possesses a stereocenter at C-1 of the allyl unit, but unlike the other C-1 chiral reagents discussed in the following section this center is introduced in a very simple manner by the metallation of allylurea (**229**). The $\eta^3$-crotylmolybdenum reagent (**226**) undergoes a highly enantio- and diastereo-selective reaction with benzaldehyde (Scheme 41), but the full scope of this methodology has not yet been reported.[33]

Several additional chiral type I and III allyl metal reagents based on boron,[128] chromium,[129] tin[130] and titanium[131] have been reported. The most selective of these are the chiral γ-alkoxyallylboronate (**231**) developed by Wuts for application in a synthesis of (–)-*exo*-brevicomin,[128] and the allyltin reagent gener-

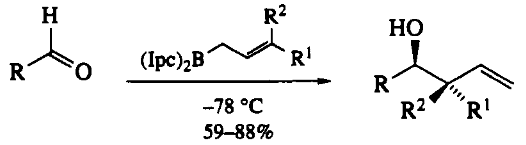
H
R
O
R²
(Ipc)₂B
R¹
–78 °C
59–88%
HO
R
R²
R¹

*Enantioselectivity (% ee)*

| | *(219)* | *(51)** | *(52)** | *(220)** |
|---|---|---|---|---|
| MeCHO | 93 | 90 | 90 | 90 |
| EtCHO | 86 | 90 | 90 | 88 |
| $Pr^iCHO$ | 90 | – | – | 88 |
| $Bu^tCHO$ | 83 | – | – | – |
| $H_2C{=}CHCHO$ | – | 90 | 90 | 88 |
| PhCHO | 96 | 88 | 88 | 90 |

*Simple diastereoselectivity ≥ 98%

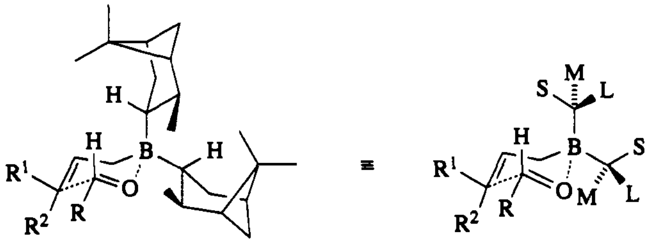
H
H
B
H
R¹
O
R²
R
≡
M
S
L
H
B
S
R¹
O
M
L
R²
R

**Scheme 37**

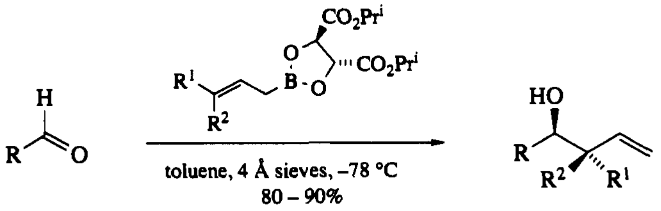
CO₂Prⁱ
O
CO₂Prⁱ
R¹
B
O
H
R
O
R²
toluene, 4 Å sieves, –78 °C
80 – 90%
HO
R
R²
R¹

*Enantioselectivity (% ee)*

| *R* | *(18)** | *(19)** | *(224)* | *(228)* |
|---|---|---|---|---|
| n-$C_9H_{19}$ | 87 | 82 | 86 | – |
| $C_6H_{11}$ | 87 | 86 | 87 | 97 |
| $Bu^tPh_2SiOCH_2CH_2CH_2$ | – | – | 82 | 94 |
| $Bu^tMe_2SiOCH_2CH_2$ | 85 | 72 | 60 | – |
| $BzlOCH_2$ | – | – | 60 | 85 |
| $Bu^t$ | 73 | 70 | 86 | 96 |
| (E)-$C_7H_{15}CH{=}CH$ | 74 | 62 | 60 | – |
| Ph (THF) | 67 | 55 | 72 | 85 |

*Simple diastereoselectivity ≥97%

**Scheme 38**

ated *in situ* from $Sn(OTf)_2$, $H_2C{=}CHCH_2AlBu^i{}_2$ and the chiral diamine (**233**) reported by Mukaiyama (Scheme 42).[130] It is interesting to speculate that asymmetric induction with (**231**) may be a consequence of the *exo* anomeric effect, a stereoelectronically favored conformation that places the aglycone O—C bond antiperiplanar to the pyran C(1)—C(2) bond.[132] Related asymmetric induction has been observed in the reactions of the THP ether corresponding to (**231**).[61]

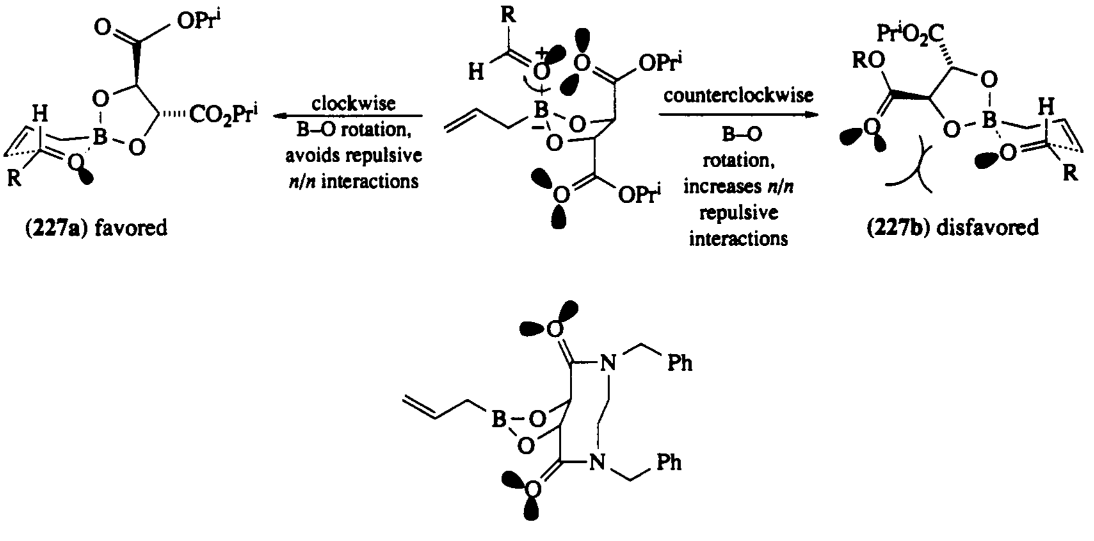
clockwise
B–O rotation,
avoids repulsive
n/n interactions
counterclockwise
B–O
rotation,
increases n/n
repulsive
interactions

**(227a)** favored

**(227b)** disfavored

*(R,R)*-**(228)**

**Scheme 39**

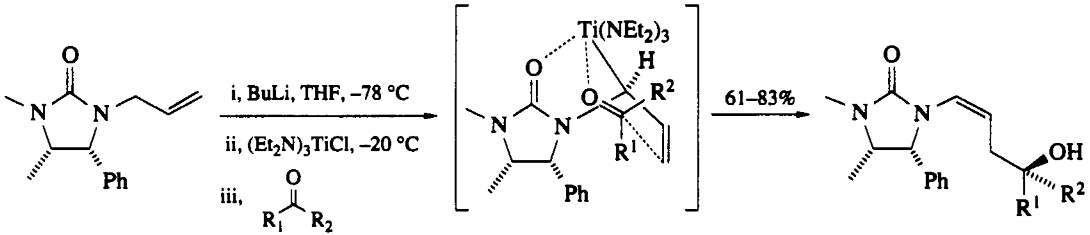
i, BuLi, THF, –78 °C
ii, $(Et_2N)_3TiCl$, –20 °C
iii,
61–83%

**(229)** **(225)** **(230)**

| *$R^1$* | *$R^2$* | *Diastereoselectivity (%)* |
|---|---|---|
| n-$C_8H_7$ | H | 88 |
| Et | H | 92 |
| $Pr^i$ | H | 92 |
| $Pr^i$ | Me | 96 |

**Scheme 40**

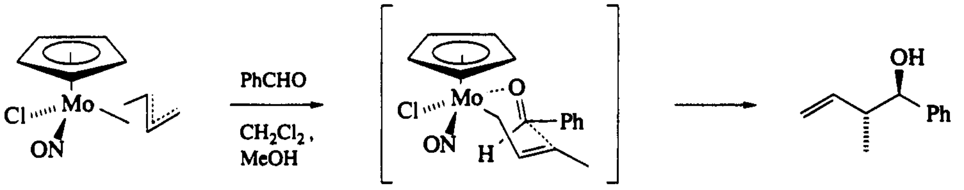
PhCHO
$CH_2Cl_2$,
MeOH

**(226)**

>98% *ee*
(96:4 *anti:syn)*

**Scheme 41**

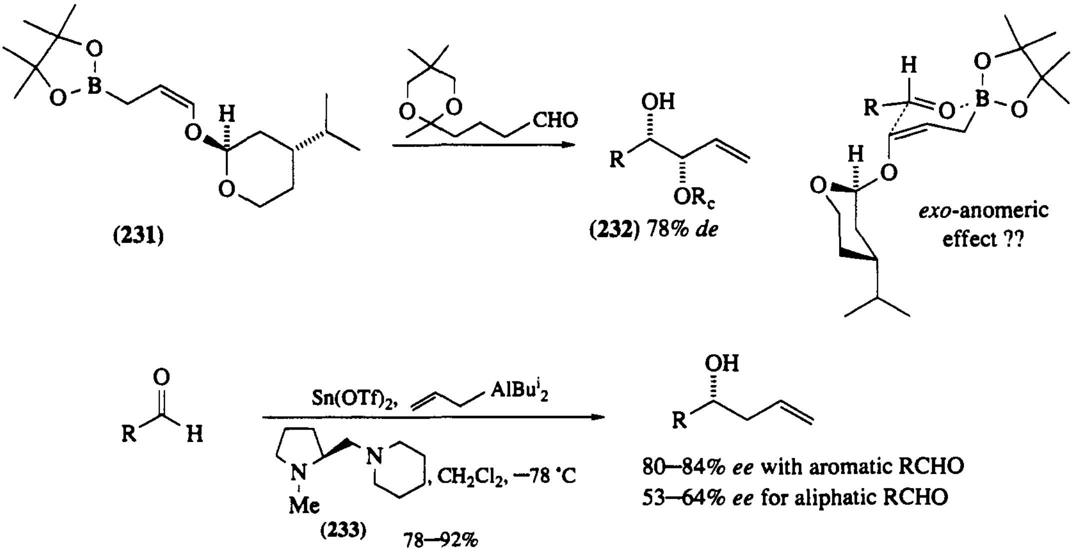
(231)
CHO
OH
R
OR_c
(232) 78% de
H
R
exo-anomeric effect ??
O
R
H
Sn(OTf)_2, AlBu^i_2
N
Me
, CH_2Cl_2, −78 °C
(233)
78–92%
OH
R
80–84% ee with aromatic RCHO
53–64% ee for aliphatic RCHO

Scheme 42

### 1.1.4.2 Chiral Allyl Organometallics with Stereocenters at C-1 or C-4

Allyl organometallics with stereocenters at either C-1 or C-4 of the allyl/crotyl unit have been described. For such compounds to be useful in single or double asymmetric reactions it is necessary that they be accessible with a high degree of enantiomeric purity. Such reagents are frequently less convenient to synthesize than those with conventional auxiliaries, but the trade off is that the reactions with aldehydes often occur with nearly 100% asymmetric induction. Chiral, nonracemic reagents that fall into this category are (**101**; Scheme 18)[67] and (**234–240**; Scheme 43). Of these, (**235**)[133] and (**240**)[134a] provide homoallyl alcohols with the lowest enantiomeric purity, (**235**) because of the method of synthesis and (**240**) presumably due to racemization; examples of their reactions will not be discussed in this chapter. The interesting, easily prepared chiral crotyllithium reagent (**241**), however, undergoes transmetallation

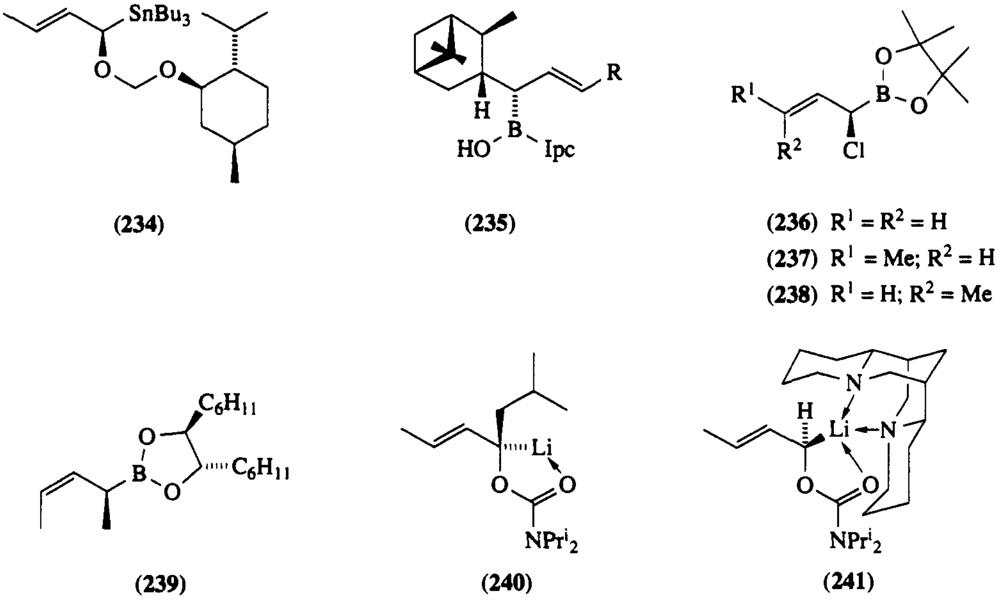
SnBu_3
(234)
R
H
B
HO
Ipc
(235)
R^1
R^2
Cl
(236) R^1 = R^2 = H
(237) R^1 = Me; R^2 = H
(238) R^1 = H; R^2 = Me
C_6H_11
C_6H_11
(239)
Li
NPr^i_2
(240)
H
Li
N
NPr^i_2
(241)

Scheme 43

with Ti(OPr$^i$)$_4$ at –70 °C to give a reagent that reacts with aldehydes with reasonable levels of enantioselectivity (80–84% *ee*).[134b]

Thomas and coworkers have shown that the chiral crotylstannane (**234**) undergoes highly diastereoselective reactions with benzaldehyde, cinnamaldehyde and cyclohexanecarbaldehyde (Scheme 44).[135] These reactions occur by way of transition state (**108**; Scheme 20) with the α-alkoxy unit occupying an axial position so as to avoid nonbonded interactions with the butyl substituents on tin. Reagent (**234**) was prepared by the addition of Bu$_3$SnLi to crotonaldehyde and resolved by the reaction with chloromethyl (–)-menthyl ether. The menthyl unit probably has little to do with the asymmetric induction in aldehyde reactions, since diastereoselection is identical to that obtained with the racemic reagent (**106**; Scheme 20). Consequently, recent reports that α,β-unsaturated acylstannanes undergo highly enantioselective reductions with BINAL-H should provide an alternative preparative route to nonracemic crotylstannanes of this class.[136]

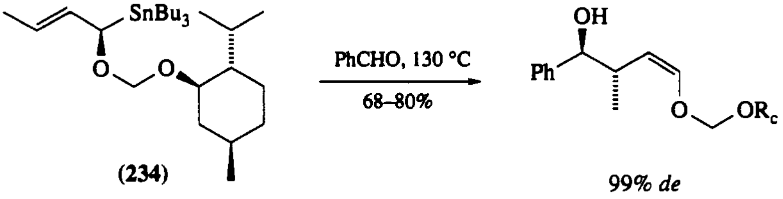

Scheme 44

The α-chiral allyl- and crotyl-boronates (**236**)–(**239**) have been developed and studied extensively by Hoffmann and his coworkers.[137] Reagents (**236**) (92% *ee*) and (**239**) (>95% *ee*) are synthesized by using the Matteson α-haloalkylboronate alkylation procedure,[138] while (**237**) (95–98% *ee*) is prepared by hydroboration of 3-butyn-2-yl trimethylsilyl ether followed by an allylic rearrangement with SOCl$_2$.[139] (*Z*)-α-Chlorocrotylboronate (**238**) has so far been studied only as the racemate.[137b] Allylboronate (**236**)[140] and (*E*)-crotylboronate (**237**) provide roughly 95:5 mixtures of (**242**) and (**243**) in reactions with aldehydes, with the enantiomeric purity of the major isomer (**242**) closely paralleling the enantiomeric purity of the starting materials.[137a,b] (*Z*)-α-Methylcrotylboronate (**239**) also undergoes an exceptionally enanti-

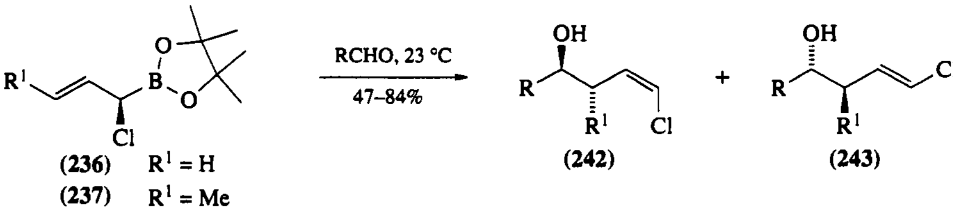

| *R* | *via (236)* (242):(243) | *via (236)* (242) % ee | *via (237)* (242):(243) | *via (237)* (242) % ee |
|---|---|---|---|---|
| Me | 95:5 | 92 | 95:5 | 95 |
| Et | 96:4 | 89 | 95:5 | 96 |
| Pr$^i$ | 95:5 | 92 | 95:5 | 96 |
| Ph | 94:6 | 92 | 95:5 | 98 |

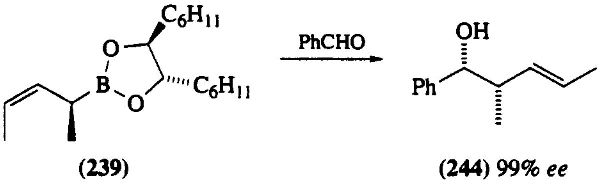

oselective reaction with benzaldehyde.[137c] α-Chloroallyl- and α-chlorocrotyl-boronates (**236**) and (**237**) react preferentially *via* transition state (**245**) with an axial orientation of the chloro substituent that is favored apparently for steric and/or stereoelectronic reasons (Scheme 45).[141] With (**238**) and (**239**), however, the α-substituent prefers an equatorial position as indicated in (**246**) in order to avoid 1,3-interactions with the (*Z*)-Me group.

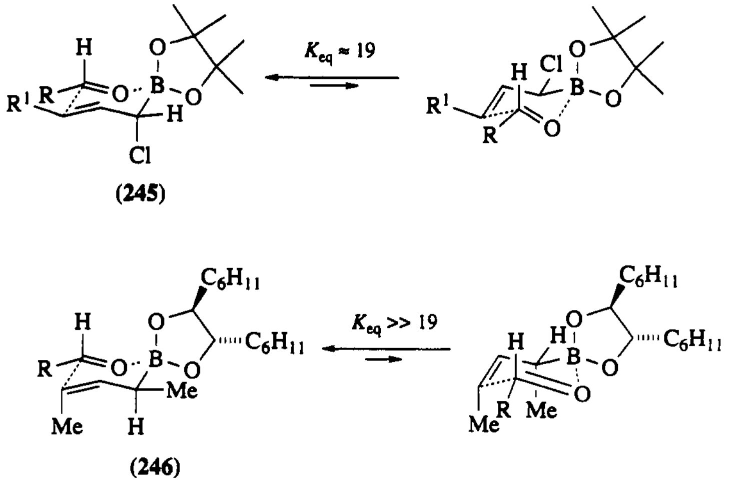

**(245)**

**(246)**

Scheme 45

Finally, Thomas has reported that allylstannanes (**247**) and (**248**) possessing stereocenters at C-4 undergo moderately diastereoselective reactions with *p*-nitrobenzaldehyde (Scheme 46).[142] The origin of asymmetric induction in these cases is probably related to that presented in Section 1.1.3.1 for the reactions of achiral allyl metal compounds and chiral aldehydes (*e.g.* Scheme 27).

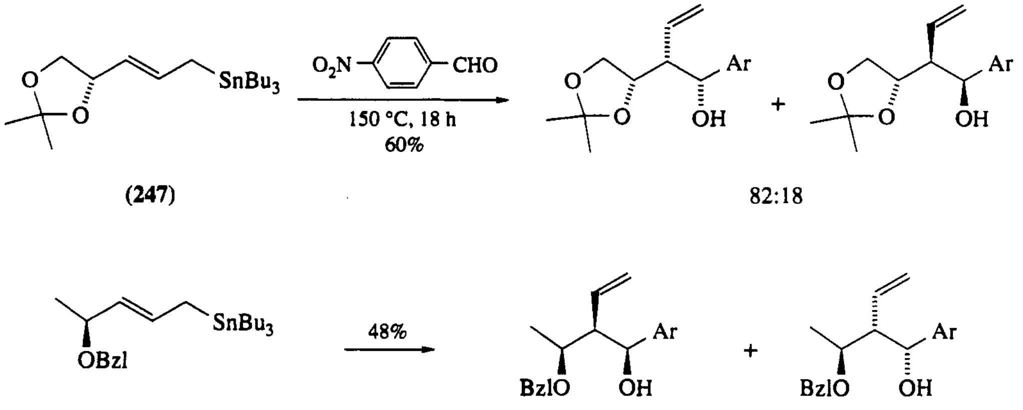

**(247)** 82:18

**(248)** 73:27

Scheme 46

## 1.1.5 DOUBLE ASYMMETRIC SYNTHESIS: REACTIONS OF CHIRAL C=X ELECTROPHILES AND CHIRAL ALLYL ORGANOMETALLICS

We have seen in Section 1.1.3 that reactions of many allyl organometallics and chiral C=X electrophiles proceed with only modest levels of relative diastereoselection. Significant improvement in diastereoselectivity is possible, however, by using double asymmetric synthesis,[5] that is, by using the highly enantioselective allyl metal reagents described in Section 1.1.4 rather than the less diastereoface-selective achiral allyl metal compounds discussed in Section 1.1.3. Double asymmetric synthesis is also referred to as 'double stereodifferentiation'. Two types of double asymmetric reactions are possible: those in which the intrinsic diastereofacial preferences of the C═X electrophile and the chiral allyl metal reagent are cooperative, each favoring the production of the same product diastereomer, 'matched double asymmetric synthesis', and those in which the intrinsic diastereofacial preferences of the two reactants are dissonant, each favoring different stereochemical outcomes, 'mismatched double asymmetric synthesis'. If the chiral reagent has a larger diastereofacial preference than the chiral C═X electrophile, and as long as the transition state of the double asymmetric reaction is similar to that involved in single asymmetric induction experiments, the reagent will dominate the stereochemical course and the otherwise intrinsically disfavored product diastereomer will be formed preferentially. It is almost always more difficult to achieve high diastereoselection in mismatched than in matched double asymmetric reactions since the reagent is always fighting against the intrinsic diastereofacial preference of the C═X electrophile, and the larger that preference the more difficult the goal. Consequently, highly enantioselective reagents should be used, the more selective the better. On the other hand, high levels of diastereoselection are relatively easy to achieve in matched double asymmetric reactions since the intrinsic face selectivity of the substrate reinforces that of the reagent, and in many cases it has been possible to achieve synthetically useful levels of matched diastereoselection by using only moderately enantioselective reagents. Finally, it is worth reminding the reader that both components of double asymmetric reactions need to be chiral and nonracemic in order for the maximum diastereoselectivity to be realized.

Chiral crotylboronates (**216**) and (**217**) were among the first chiral allyl metal reagents to be used in double asymmetric reactions.[97b,121a] The example in Scheme 47, however, shows that (**217**) induces only modest changes in the stereoselectivity of the reactions of (**249**), thus underscoring the need for highly enantioselective chiral reagents.

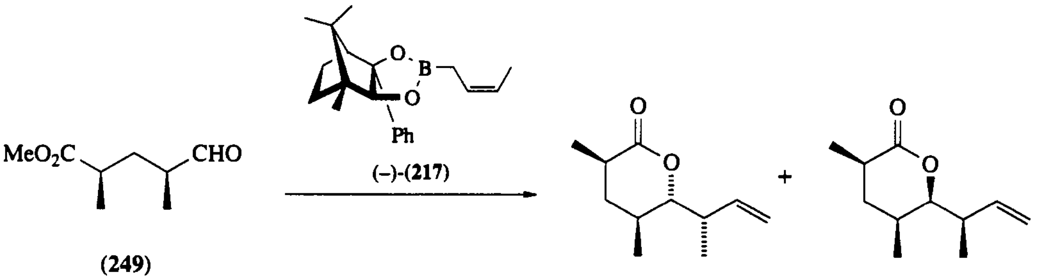

**(249)**

| | |
|---|---|
| (–)-(**217**) | 32:68 |
| (**2**) | 60:40 |
| (+)-(**217**) | 81:19 |

**Scheme 47**

The first examples of highly diastereoselective double asymmetric reactions involving chiral allyl metal reagents were obtained in reactions with D-glyceraldehyde acetonide (**151**; Table 6). Aldehyde (**151**) displays an 80:20 preference for (**154**) in reactions with the achiral pinacol allylboronate (**144**; entry 4),[25,101] and the selectivity for (**154**) improves to 96–98% with reagents (–)-(**215**) and (*R*,*R*)-(**224**).[101,125,143] With (*R*,*R*)-(**228**) the diastereoselectivity is 300:1, which is the highest selectivity yet documented for a reaction of a chiral allyl metal reagent.[126] Tartrate allylboronate (*S*,*S*)-(**224**) undergoes a highly diastereoselective mismatched double asymmetric reaction with D-(**151**), providing the 4,5-*syn* (*threo*) diastereomer (**155**) with 92% selectivity. Here again, diastereoselectivity for (**155**) increases to 98:2 by using the more enantioselective allylboronate (*S*,*S*)-**228**. Matched double diastereoselectivity is

**Table 6** Reactions of D-Glyceraldehyde Acetonide (**151**) and Chiral Allyl Metal Reagents

| *Reagent* | *Yield (%)* | *(154):(155)* | *Ref.* |
|---|---|---|---|
| (*R*,*R*)-(**224**) | 90 | 98:2 | 125 |
| (*R*,*R*)-(**228**) | 81 | 99.7:0.3 | 125 |
| (–)-(**215**) | 87 | 96:4 | 101 |
| (**144**) | 75 | 80:20 | 25,101 |
| (*S*,*S*)-(**224**) | 85 | 8:92 | 125 |
| (*S*,*S*)-(**228**) | 84 | 2:98 | 126 |

also very good (94%) by using α-chloroallylboronate (*R*)-(**236**), but mismatched diastereoselection using (*S*)-(**236**), leading to (**252**), is considerably lower (77%) than that realized with tartrate allylboronate (*S*,*S*)-(**224**) (Scheme 48).[137a]

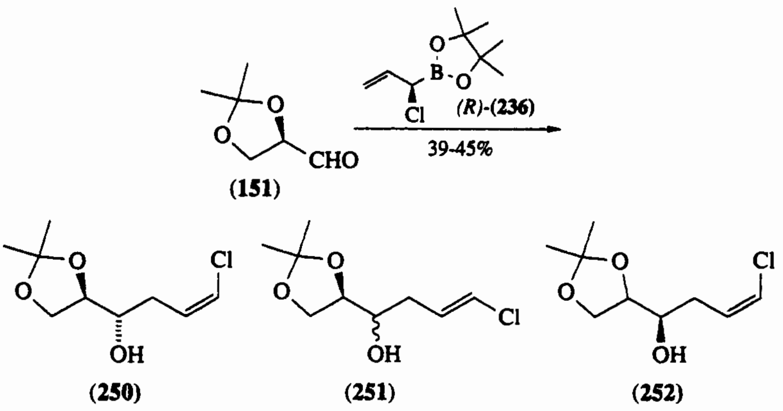

| | |
|---|---|
| (*R*)-(**236**) | 94:2:4 |
| (*S*)-(**236**) | 11:12:77 |

Scheme 48

Excellent double diastereoselection has also been realized in the reactions of (**151**) and chiral crotylboron reagents (Table 7). Interestingly, the best selectivity for diastereomers (**153**) and (**156**) is obtained by using the tartrate crotylboronates (*S*,*S*)-(**18**) and (*R*,*R*)-(**19**), respectively (entries 2 and 3),[144,145] while Masamune's 2,5-dimethylborolane reagents (*R*,*R*)-(**221**) and (*S*,*S*)-(**222**) provide the greatest selectivity for diastereomers (**152**) and (**157**; entries 7 and 10).[124] Comparative data for the diastereoselectivity obtained with the achiral crotylboronates (**1**) and (**2**) appear in the last two entries of Table 7.

**Table 7** Reactions of D-Glyceraldehyde Acetonide (**151**) and Chiral Crotyl Metal Reagents

| *Reagent* | *Yield (%)* | *(152)* | *(153)* | *(156)* | *(157)* | *Ref.* |
|---|---|---|---|---|---|---|
| (*R*,*R*)-(**18**) | 87 | 87 | 9 | 4 | — | 144 |
| (*S*,*S*)-(**18**) | 85 | 2 | 96 | 2 | — | 144 |
| (*R*,*R*)-(**19**) | 84 | 1 | — | 99 | — | 145 |
| (*S*,*S*)-(**19**) | 90 | 7 | 2 | 76 | 15 | 145 |
| (–)-(**216**) | 85 | 72 | 28 | — | — | 101 |
| (–)-(**217**) | 86 | — | — | >98 | <2 | 101 |
| (*R*,*R*)-(**221**) | 71 | 96 | 3 | 1 | — | 124 |
| (*S*,*S*)-(**221**) | 74 | 12 | 86 | — | 2 | 124 |
| (*R*,*R*)-(**222**) | 66 | 4 | 2 | 92 | 2 | 124 |
| (*S*,*S*)-(**222**) | 65 | — | 2 | 16 | 82 | 124 |
| (**1**) | 75 | 52 | 42 | 6 | — | 25 |
| (**2**) | 85 | 5 | 1 | 91 | 5 | 25 |

Results of reactions of chiral α-methyl aldehydes and several chiral crotyl- and allyl-boron reagents are summarized in Tables 8 and 9. It is apparent from these data that the Brown $(Ipc)_2B$(crotyl) and $(Ipc)_2B$(allyl) reagents (**51**), (**52**) and (**219**) consistently give excellent results for the synthesis of each product diastereomer (Table 8, entries 3–6, 11, 16, 20, and 24; Table 9, entries 1, 2, 10 and 18). This is true also for their reactions with chiral α- and β-alkoxy aldehydes (Scheme 49).[146,148–150] The tartrate crotylboronates (**18**) and (**19**) also display excellent selectivity in the synthesis of crotyl diastereomers (**136**), (**137**) and (**139**) (Table 8, entries 7, 10, 13, 17, 25 and 28), but are much less selective for the synthesis of crotyl diastereomer (**138**), especially from β-alkoxy-substituted aldehydes such as (**253**).[98] Tartrate allylboronate (**224**) is also less effective than $(Ipc)_2$Ballyl (**219**) for the synthesis of (**257**) and (**258**) in Table 9,[98] and of (**266**) and (**267**) in Scheme 49.[149] Substantial improvements in selectivity have been realized by using the tartramide-based allylboronate (**228**), and the results with this reagent (Table 9, entries 4, 7, 9, 12, 14, 17, 20 and 22) compare very favorably with those obtained with (**219**).[126] The data

**Table 8** Reactions of α-Methyl Chiral Aldehydes and Chiral Crotylboron Reagents

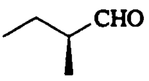

**(145)**

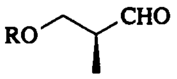

**(253a)** R = $Bu^tMe_2Si$
**(253b)** R = $Bu^tPh_2Si$
**(253c)** R = Bzl

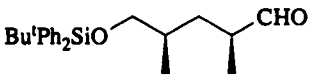

**(254)**

| Entry | RCHO | Reagent[a] | Yield (%) | Reaction products[b,c] | | | | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | | | *(136)* | *(137)* | *(139)* | *(138)* | |
| 1 | **(145)** | (–)-(**216**) | 74 | 92 | 8 | — | — | 97b |
| 2 | **(145)** | (–)-(**217**) | 99 | — | — | 45 | 55 | 97b |
| 3 | **(145)** | (*d*)-(**51**) | 75 | 96 | 4 | — | — | 146 |
| 4 | **(145)** | (*l*)-(**51**) | 70 | 9 | 91 | — | — | 146 |
| 5 | **(145)** | (*d*)-(**52**) | 79 | — | — | 96 | 4 | 146 |
| 6 | **(145)** | (*l*)-(**52**) | 73 | — | — | 18 | 82 | 146 |
| 7 | **(253a)** | (*R*,*R*)-(**18**) | 80 | 97 | 3 | — | — | 98 |
| 8 | **(253b)** | (*R*,*R*)-(**18**) | — | 82 | 15 | 1 | 2 | 98 |
| 9 | **(253b)** | (*R*,*R*)-(**255**) | 26 | 92 | 7 | 1 | — | 147 |
| 10 | **(253c)** | (*R*,*R*)-(**18**) | — | 93 | 5 | 1 | 1 | 98 |
| 11 | **(253c)** | (*d*)-(**51**) | — | 98 | 2 | — | — | 146b |
| 12 | **(253a)** | (*S*,*S*)-(**18**) | — | 16 | 81 | 3 | — | 98 |
| 13 | **(253b)** | (*S*,*S*)-(**18**) | 85 | 10 | 90 | — | — | 98 |
| 14 | **(253b)** | (*S*,*S*)-(**255**) | 27 | 4 | 96 | — | — | 147 |
| 15 | **(253c)** | (*S*,*S*)-(**18**) | — | 14 | 85 | 1 | — | 98 |
| 16 | **(253c)** | (*l*)-(**51**) | — | 5 | 95 | — | — | 146b |
| 17 | **(253a)** | (*S*,*S*)-(**19**) | 71 | — | 4 | 95 | 1 | 98 |
| 18 | **(253b)** | (*S*,*S*)-(**19**) | — | — | 4 | 85 | 12 | 98 |
| 19 | **(253c)** | (*S*,*S*)-(**19**) | — | — | 3 | 88 | 9 | 98 |
| 20 | **(253c)** | (*l*)-(**52**) | — | — | — | 95 | 5 | 146b |
| 21 | **(253a)** | (*R*,*R*)-(**19**) | — | 12 | 2 | 45 | 41 | 98 |
| 22 | **(253b)** | (*R*,*R*)-(**19**) | — | 9 | 3 | 24 | 64 | 98 |
| 23 | **(253c)** | (*R*,*R*)-(**19**) | — | 8 | 2 | 45 | 45 | 98 |
| 24 | **(253c)** | (*d*)-(**52**) | — | — | — | 8 | 92 | 146b |
| 25 | **(254)** | (*R*,*R*)-(**18**) | 56 | >98 | <2 | — | — | 147 |
| 26 | **(254)** | (*S*,*S*)-(**18**) | 55 | 16 | 84 | — | — | 147 |
| 27 | **(254)** | (*S*,*S*)-(**255**) | 51 | 12 | 88 | — | — | 147 |
| 28 | **(254)** | (*S*,*S*)-(**19**) | 63 | — | — | 94 | 6 | 147 |
| 29 | **(254)** | (*R*,*R*)-(**19**) | 55 | 6 | — | 16 | 78 | 147 |

[a] Reagents (–)-(**216**) and (–)-(**217**) are prepared from (1*R*,2*S*,3*S*,4*S*)-3-*endo*-phenyl-bornane-2-*exo*-3-*exo*-diol, whileq (*d*)-(**51**) and (*d*)-(**52**) are prepared from (+)-α-pinene. [b] Refer to Figure 27 for structures. [c] Additional minor diastereomers are produced in the reactions of (**51**), (**52**), (**216**) and (**217**), but only the amounts of the two most predominant products are cited in the original literature.

summarized in entries 9, 14 and 27 of Table 8 (compare entries 8, 13 and 26) also indicate that stereoselectivity may be improved in the crotyl series by using tartramide crotylboronate (**255**).[147]

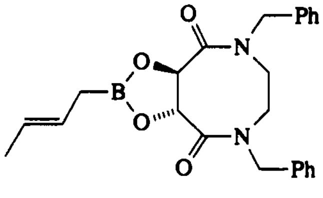

(*R*,*R*)-(**255**)

**Table 9** Reactions of α-Methyl Chiral Aldehydes and Chiral Allylboron Reagents

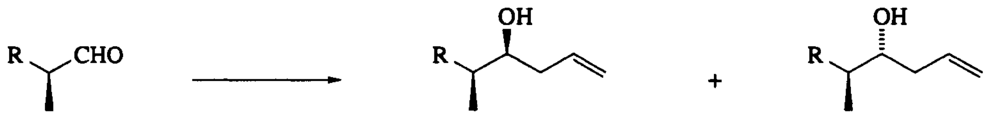

**(257)** **(258)**

| *Entry* | *RCHO* | *Reagent*[a,b] | *Temperature* (°C)[c] | *Yield* (%) | *(257)* | *(258)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | **(145)** | (*d*)-**(219)** | | 81 | 96 | 4 | 146b,c |
| 2 | **(145)** | (*l*)-**(219)** | | — | 5 | 95 | 146b,c |
| 3 | **(253a)** | (*R*,*R*)-**(224)** | | 71 | 89 | 11 | 98 |
| 4 | **(253a)** | (*R*,*R*)-**(228)** | | 46 | 97 | 3 | 126 |
| 5 | **(253a)** | (*R*,*R*)-**(228)** | −50 | 76 | 95 | 5 | 126 |
| 6 | **(253b)** | (*R*,*R*)-**(224)** | | — | 79 | 21 | 98 |
| 7 | **(253b)** | (*R*,*R*)-**(228)** | | 48 | 95 | 5 | 126 |
| 8 | **(253c)** | (*R*,*R*)-**(224)** | | — | 83 | 17 | 98 |
| 9 | **(253c)** | (*R*,*R*)-**(228)** | −50 | 56 | 93 | 7 | 126 |
| 10 | **(253c)** | (*d*)-**(219)** | | — | 95 | 5 | 146b |
| 11 | **(253a)** | (*S*,*S*)-**(224)** | | — | 19 | 81 | 98 |
| 12 | **(253a)** | (*S*,*S*)-**(228)** | | 43 | 3 | 97 | 126 |
| 13 | **(253b)** | (*S*,*S*)-**(224)** | | 72 | 13 | 87 | 98 |
| 14 | **(253b)** | (*S*,*S*)-**(228)** | | 35 | 3 | 97 | 126 |
| 15 | **(253b)** | (*S*,*S*)-**(228)** | −50 | 68 | 4 | 95 | 126 |
| 16 | **(253c)** | (*S*,*S*)-**(224)** | | — | 20 | 80 | 98 |
| 17 | **(253c)** | (*S*,*S*)-**(228)** | −50 | 53 | 7 | 93 | 126 |
| 18 | **(253c)** | (*l*)-**(219)** | | — | 2 | 98 | 146b |
| 19 | **(254)** | (*R*,*R*)-**(224)** | | 91 | 92 | 8 | 147 |
| 20 | **(254)** | (*R*,*R*)-**(228)** | | 82 | 97 | 3 | 147 |
| 21 | **(254)** | (*S*,*S*)-**(224)** | | — | 13 | 87 | 147 |
| 22 | **(254)** | (*S*,*S*)-**(228)** | | 76 | 7 | 93 | 147 |

[a] Allylborane (*d*)-(219) is prepared from (+)-α-pinene. [b] The reactions in entries 4, 5, 7, 9, 12, 14, 15 and 17 involving **(228)** were actually performed with the enantiomers of **(253)** and **(228)** indicated here (ref. 126). The data are presented in the enantiomeric series only for the convenience of the structural representations. [c] All reactions were performed at −78 °C unless indicated otherwise.

Excellent results have also been obtained in double asymmetric reactions by using Hoffmann's α-substituted crotylboronates **(237)**, **(268)** and **(238)** (Scheme 50).[137c,151] Aldehyde **(145)** and reagent (*R*)-**(237)** are a matched pair and react to provide **(269)** with >98:2 selectivity. The mismatched double asymmetric reaction of **(145)** and (*S*)-**(237)** is more difficult, and provides **(271)** with modest levels of selectivity. This reaction is improved, however, by using the α-methoxy-substituted reagent (*S*)-**(268)**, providing **(271)** with *ca.* 95% selectivity.[151a] Evidently, the methoxy group has a much greater preference for an axial orientation in the transition state (refer to Scheme 45), resulting in **(268)** being more selective than **(237)**. Finally, **(249)** and (*S*)-**(238)** are a matched pair and provide **(273)** with >95% selectivity.[137c] It should be noted, however, that even though the results obtained with these chiral α-substituted crotylboronates are excellent, the greater difficulty of their preparation compared to the $(Ipc)_2$crotylboranes **(51)**/**(52)** and the tartrate crotylboronates **(18)**/**(19)** does not warrant their use, especially in matched double asymmetric reactions where **(51)**/**(52)** and **(18)**/**(19)** are comparably selective.

It was noted at the beginning of this section that as the intrinsic diastereofacial selectivity of the chiral aldehyde increases, the ease of accomplishing highly diastereoselective matched double asymmetric reactions increases and, correspondingly, the difficulty of achieving success in the mismatched pair also increases. The intrinsicially favored products of reactions of α-methyl chiral aldehydes and (*E*)- and (*Z*)-crotyl metal reagents are diastereomers **(136)** and **(139)**, respectively (Scheme 27 and Table 4), and it is this pair of diastereomers that will always be easily prepared with very high diastereoselection by using matched double asymmetric reactions (Table 8; see also **269** and **273**, Scheme 50). Diastereomers **(137)**, **(271)** and **(138)**, however, are the intrinsicially disfavored set of products, and it is these that are the most difficult to access with synthetically useful levels of mismatched double diastereoselectivity, especially as the intrinsic diastereofacial selectivity of the aldehyde increases. The examples presented in

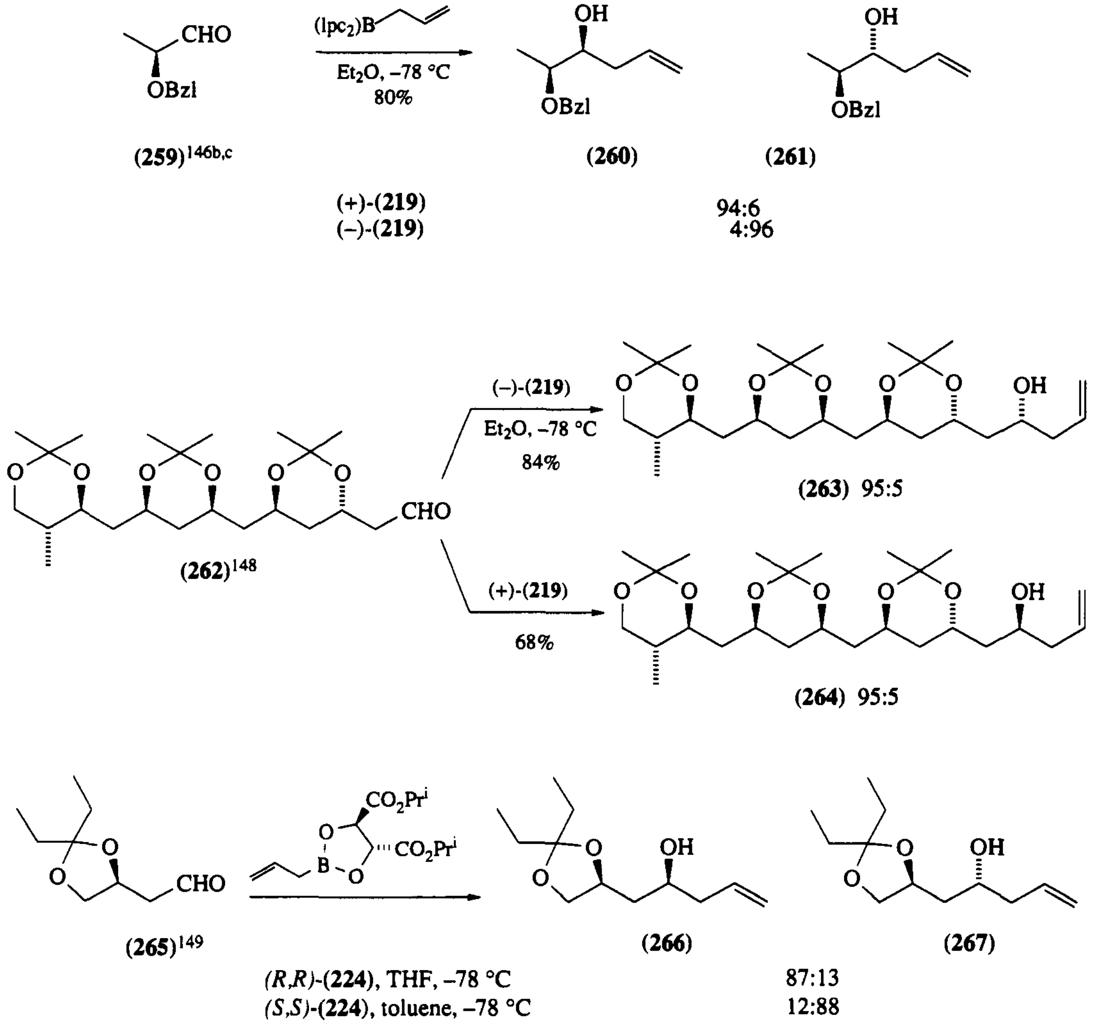
CHO
OBzl
(259)146b,c
(Ipc2)B
Et2O, –78 °C
80%
OH
OBzl
(260)
OH
OBzl
(261)
(+)-(219)
(–)-(219)
94:6
4:96
O
O
CHO
(262)148
(–)-(219)
Et2O, –78 °C
84%
OH
(263) 95:5
(+)-(219)
68%
OH
(264) 95:5
O
O
CHO
(265)149
CO2Pri
CO2Pri
B
(R,R)-(224), THF, –78 °C
(S,S)-(224), toluene, –78 °C
OH
(266)
OH
(267)
87:13
12:88

**Scheme 49**

Scheme 51 illustrate this point.[115] First, the mismatched double asymmetric reaction of (**274**) and (*S*,*S*)-(**18**) provides the 3,4-*anti*-4,5-*anti* diastereomer (**276**) (*cf.*, **137**) with only 73% selectivity. This is a substantial drop in stereoselectivity compared to the mismatched reaction of (*S*,*S*)-(**18**) and (**254**) that provides (**137**) with 84% selectivity (Table 8, entry 26). Substrate (**277**) is even more problematic: diastereomer (**278**) predominates with >95:5 selectivity from the reaction with (*R*,*R*)-(**18**), while (**279**) was the 'expected' product based on the stereochemical preferences of (*R*,*R*)-(**18**). Thus, the intrinsic diastereofacial selectivity of (**277**) totally overwhelmed that of (*R*,*R*)-(**18**) in this attempted mismatched double asymmetric reaction.

Of all the chiral allyl metal reagents reported to date, the one that is most effective in demanding cases of mismatched double diastereoselection is the α-methoxycrotylboronate (**268**) developed by Hoffmann.[151] Two illustrative cases are presented in Scheme 52. First, the reaction of (**280**) and (*R*)-(**268**) provides the 3,4-*anti*-4,5-*anti* diastereomer (**281**) with roughly 84% stereoselectivity. This is remarkable in view of the very high intrinsic diastereofacial selectivity (98:2) for the 3,4-*anti*-4,5-*syn* diastereomer exhibited by the structurally related aldehyde (**147**; Table 4). The second involves (**283**), which with (*S*)-(**268**) provides 3,4-*anti*-4,5-*anti* (**284**) with 73% stereoselection. By way of comparison, the α-chlorocrotylboronate (*S*)-(**237**) is incapable of overriding the intrinsic diastereofacial preference of (**283**), giving 3,4-*anti*-4,5-*syn* diastereomer (**E**)-(**285**) with 92% selectivity (compare also **277**, Scheme 51).

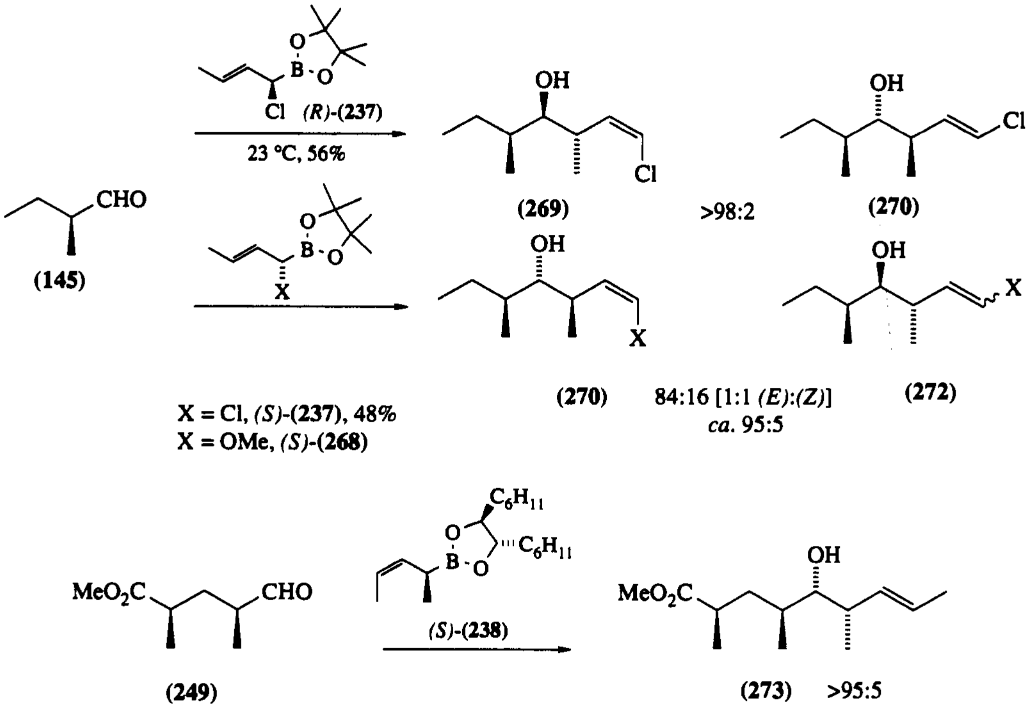

**Scheme 50**

## 1.1.6 SUMMARY

Tremendous progress has been realized in the past decade concerning the stereochemistry of the reactions of type I and type III allyl metal compounds with C═X electrophiles. Numerous reagents exist that provide excellent stereochemical control in reactions with achiral aldehydes and imines (simple diastereoselection, Section 1.1.2), and a clear stereochemical picture has emerged, particularly concerning the reactions with chiral aldehydes (relative diastereoselection, Section 1.1.3). Even more impressive has been the development of highly enantioselective chiral allyl metal reagents (Section 1.1.4) capable of enhancing, or reversing, depending on the absolute configurations of the two reactants, the diastereofacial selectivity of the chiral C═X electrophile *via* the strategy of double asymmetric synthesis (Section 1.1.5). Consequently, it is fair to say that the goal stated at the outset, namely the development of a family of allyl organometallics capable of providing highly selective access to each of the products depicted in Scheme 2, has been achieved. While room for improvement certainly exists, especially in terms of the discovery of allyl metal reagents that are both economical and practical as well as highly enantioselective, the state of the art of allyl organometallic chemistry is now at a sufficiently high level that significant opportunities exist for its application to the highly stereocontrolled synthesis of complex, biologically active molecules.[152]

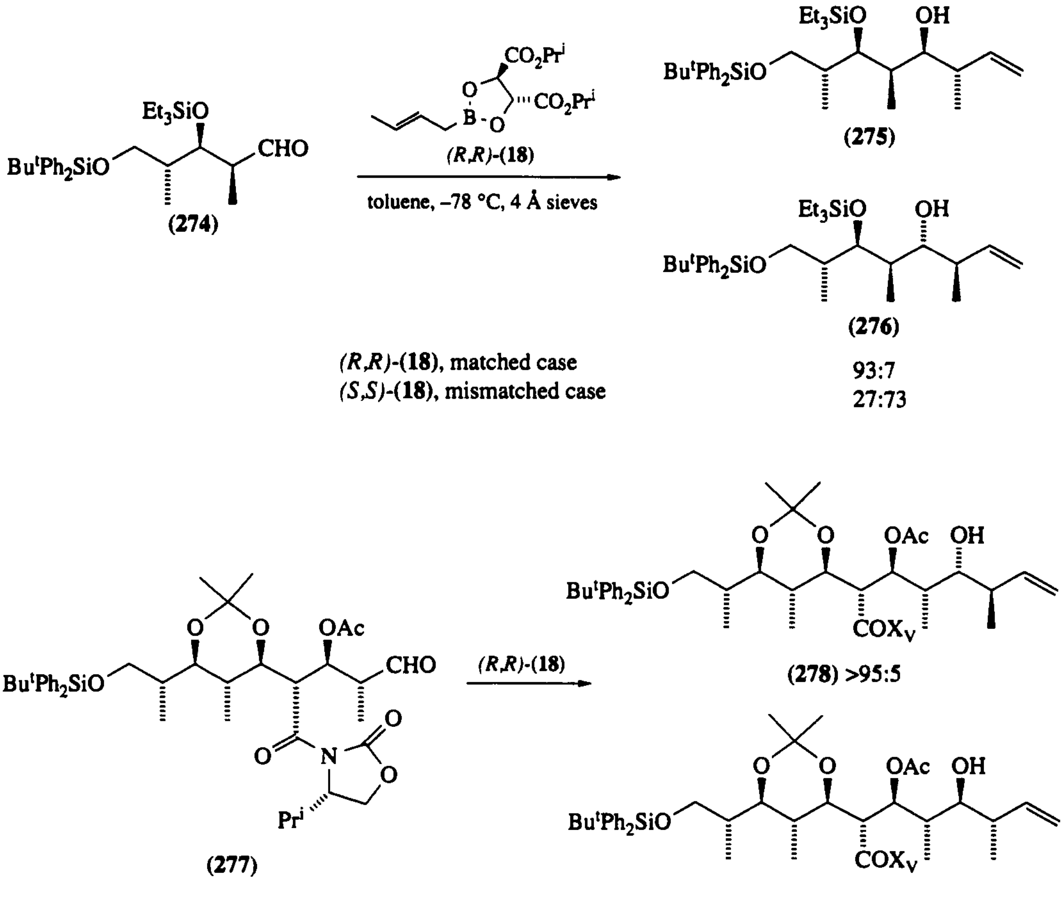

(R,R)-(18), matched case 93:7
(S,S)-(18), mismatched case 27:73

(279) expected product

Scheme 51

## 1.1.7 ADDENDUM

Several highly enantioselective chiral allyl metal reagents have been described in the literature since the original manuscript was submitted. Riediker and Duthaler have reported that the chiral allyltitanium reagent (**287**), prepared as indicated from (**286**), which incorporates two diacetone glucose residues as chiral auxiliaries, undergoes highly enantioselective reactions with aldehydes at −78 °C (Scheme 53).[153] The enantioselectivity ranges from 85 to 94% *ee* for 16 aldehydes that were examined, while lower levels of asymmetric induction are obtained in reactions with ketones (*ca.* 50% *ee*; 80% *ee* with acetophenone). Several substituted allyltitanium reagents were also described (*e.g.* (*E*)-crotyl, (*E*)-cinnamyl and (*E*)-pentadienyl) that provided the corresponding *anti* homoallyl alcohols in 83–90% *ee*.

Corey and coworkers have described the preparation of allylborane (**289**) by the reaction of bromoborane (**288**) and allyltributylstannane and shown that (**289**) undergoes highly stereoselective reactions with both achiral (95–97% *ee*) and chiral aldehydes (Scheme 54).[154] The corresponding methallyl, (*E*)-crotyl and 2-chloro- and 2-bromo-allyl reagents were prepared by similar methods and shown to give excellent results in reactions with achiral aldehydes (84–99% *ee* in most cases).

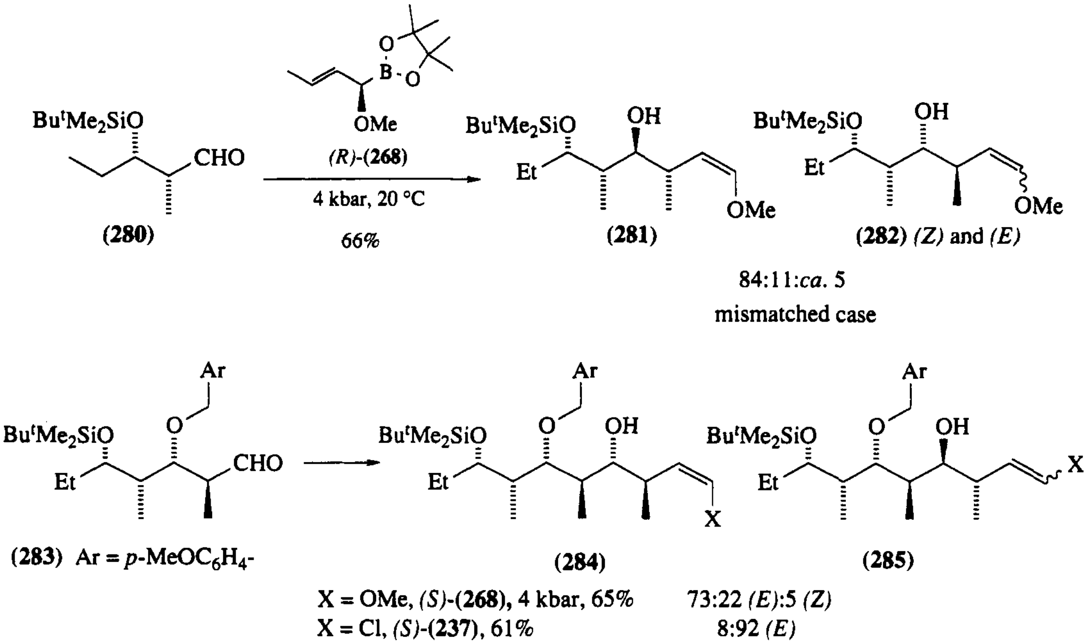
Bu$^t$Me$_2$SiO
CHO
(280)
OMe
(R)-(268)
4 kbar, 20 °C
66%
Bu$^t$Me$_2$SiO
OH
Et
OMe
(281)
(282) (Z) and (E)
Ar
CHO
(283) Ar = p-MeOC$_6$H$_4$-
X
(284)
(285)

84:11:*ca.* 5
mismatched case

X = OMe, (*S*)-(**268**), 4 kbar, 65% 73:22 (*E*):5 (*Z*)
X = Cl, (*S*)-(**237**), 61% 8:92 (*E*)

**Scheme 52**

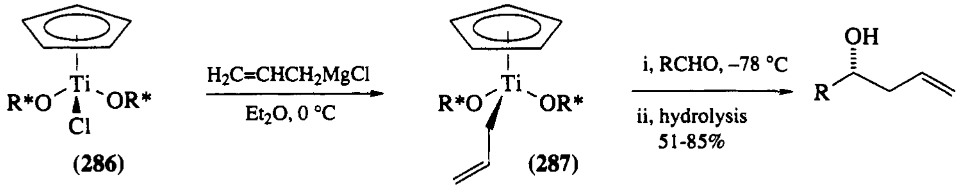
Ti
R*O
OR*
Cl
(286)
H$_2$C=CHCH$_2$MgCl
Et$_2$O, 0 °C
(287)
i, RCHO, -78 °C
ii, hydrolysis
51-85%
OH
R

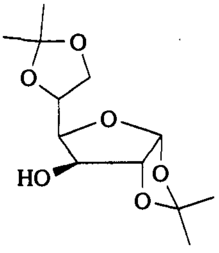

R*OH

| *R* | *ee* (%) |
|---|---|
| Pr$^n$ | 93 |
| Bu$^i$ | 85 |
| Cyclohexyl | 92 |
| Bu$^t$ | 88 |
| Vinyl | 86 |
| Styryl | 90 |
| Ph | 90 |
| 9-Anthryl | 94 |

**Scheme 53**

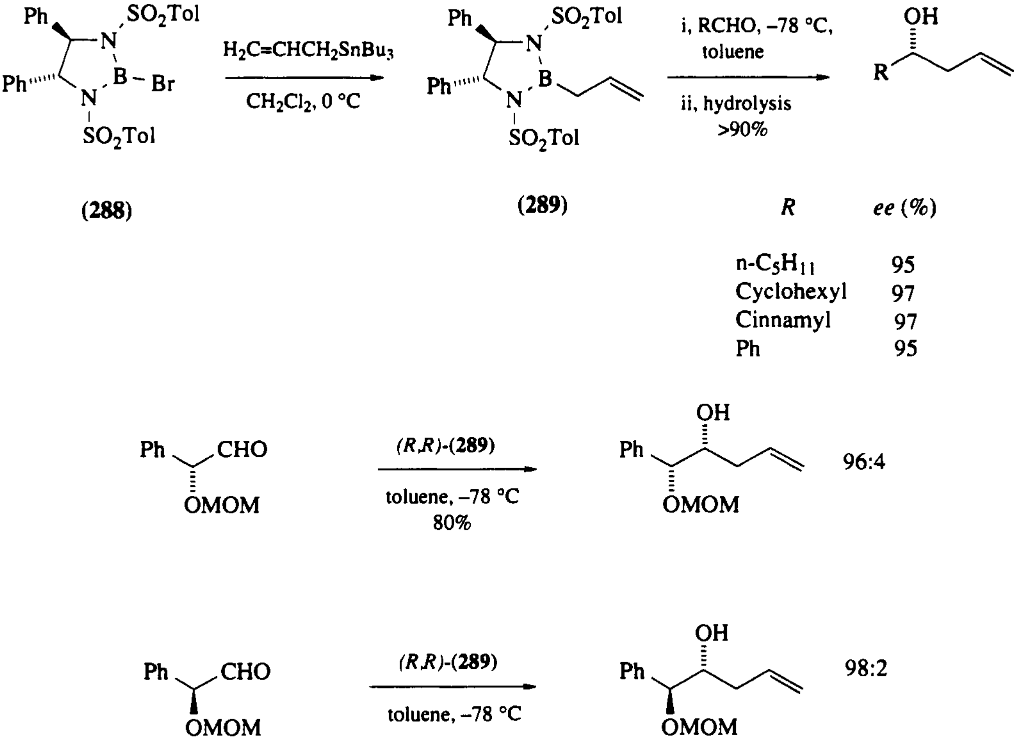

**(288)** **(289)**

| *R* | *ee* (%) |
|---|---|
| n-$C_5H_{11}$ | 95 |
| Cyclohexyl | 97 |
| Cinnamyl | 97 |
| Ph | 95 |

**Scheme 54**

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# 1.2

# Heteroatom-stabilized Allylic Anions

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## 1.2.1 SYNTHETIC UTILITY

Heteroatom-stabilized allylic anions (**1** and **2**; X = Y = heteroatom) can be used as homoenolate anion synthons (**3**) and (**4**) or reversed polarity equivalents (**5**) and (**6**), as shown in Scheme 1. Homoenolates are important synthetic species since they are capable of converting aldehydes or ketones into γ-lactols or γ-lactones (Volume 2, Chapter 1.14). Acyl anion equivalents are also very important in organic synthesis.[1d] Electrophiles may react at either of the termini of allylic anions. A great deal of effort has been exerted to control the regioselectivity (α:γ ratio); regioselective attack at the γ-position of (**1**) leads to homoenolate anion equivalents, whereas the attack at the α-position leads to reversed polarity equivalents. The α/γ-selectivity is dictated by a number of factors, such as the nature of the heteroatom, the substituents attached to the heteroatom, the countercation, the type of electrophile, additives and solvent, reaction temperature, and reaction time.[1] The following rule of thumb is useful for predicting the regioselectivity of an allylic anion like (**1**; R = H, M = Li; Scheme 1),[2] in which lithium and the allylic anion are associated, thus free anions or anions bearing strong electron-withdrawing groups are excluded. When X is an anion-destabilizing substituent, higher electron density would be expected at the γ-position and (**1a**) would be preferred over (**1b**). Accordingly, alkyl halides and protons would react at the γ-position (the site of higher electron density), while carbonyl compounds would react at the α-position *via* a rearrangement process involving lithium. When X is an anion-stabilizing substituent, (**1b**) or (**1c**) would be preferred over (**1a**) and thus complementary regioselectivity would be observed. In fact, allylic anions substituted by anion-destabilizing groups (X = OR, $NR_2$, alkyl) undergo alkylation and protonation preferentially at the γ-position and react with carbonyl compounds predominantly at the α-position. Anions bearing anion-stabilizing groups (X = SR, $BR_2$) react with carbonyl compounds at the γ-position and with alkyl halides and protons at the α-position. However, these tendencies may be modified by a number of factors mentioned above.

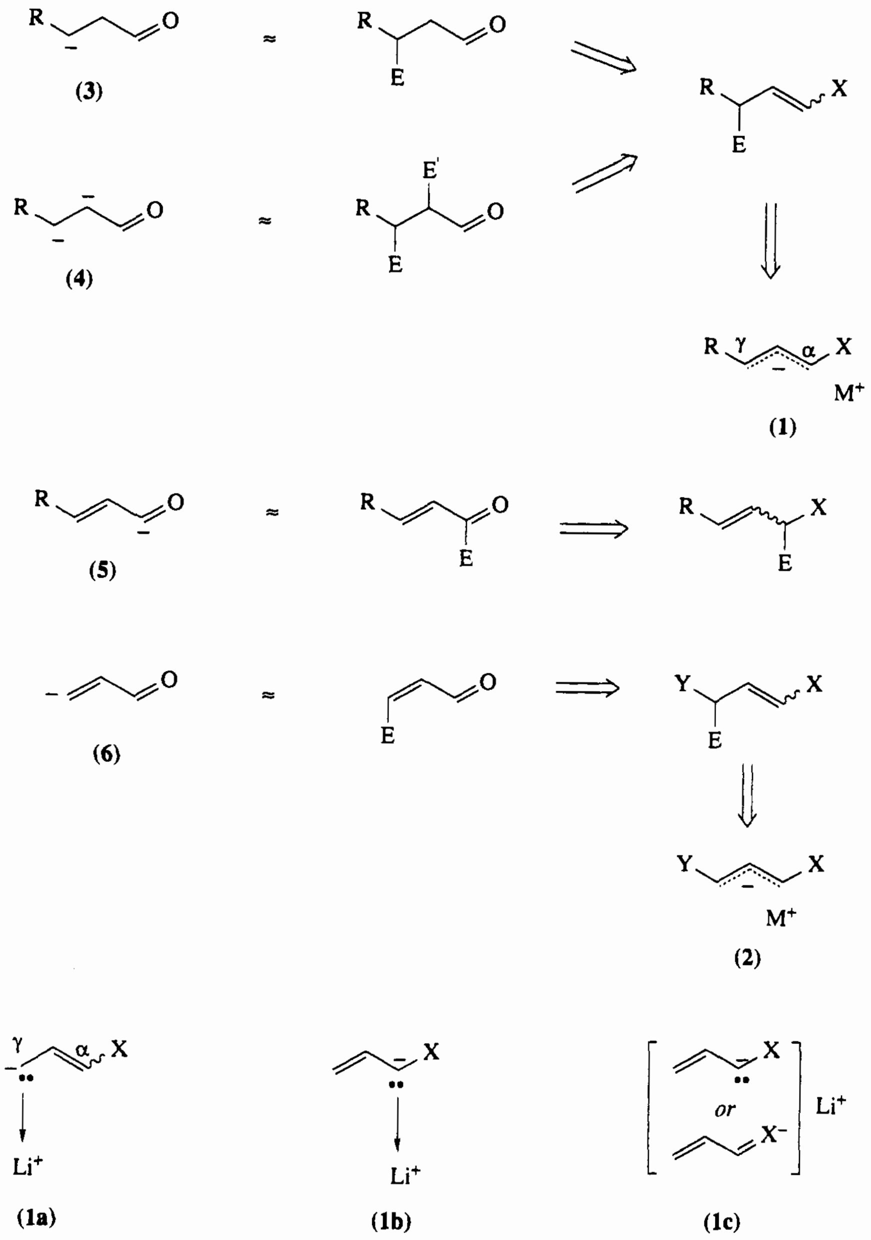

Scheme 1

The allylic anions are normally generated by deprotonation of the corresponding allylic derivatives with *n*-butyl- or *s*-butyl-lithium, often in conjunction with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA). Lithium dialkylamides are also employed. The deprotonation is usually performed in THF or ether at –65 °C or lower because of the high reactivity of both the lithium bases and the resulting allylic anions. Chloro-substituted allylic anions are most efficiently prepared by transmetallation of 3-chloroallyltriphenyllead with *n*-butyllithium.

## 1.2.2 BORON-SUBSTITUTED ALLYLIC ANIONS

Although (**7**) reacts with methyl iodide and water predominantly at the α-carbon and with acetone mainly at the γ-carbon,[3] anion (**8**), which is readily prepared from the corresponding allyldimesitylborane by treatment with mesityllithium or lithium dicyclohexylamide, reacts with both alkyl halides and benzaldehyde exclusively at the γ-position (Scheme 2).[4] The resulting alkenylborane (**9**) can be converted to the three-carbon-homologated aldehyde upon oxidation with $H_2O_2$–NaOH. The reaction of (**8**) with benzaldehyde followed by the usual oxidation gives the γ-lactol in 70% yield. The γ-regioselectivity exhibited by (**8**), regardless of the types of electrophiles, is presumably due to the steric bulkiness of the mesityl group. Unlike other allylic boranes, such as the precursor of (**7**), allyldimesitylborane is readily made from allylmagnesium bromide and fluorodimesitylborane, and is a crystalline compound, m.p. 68 °C, stable enough to be recrystallized from ethanol.

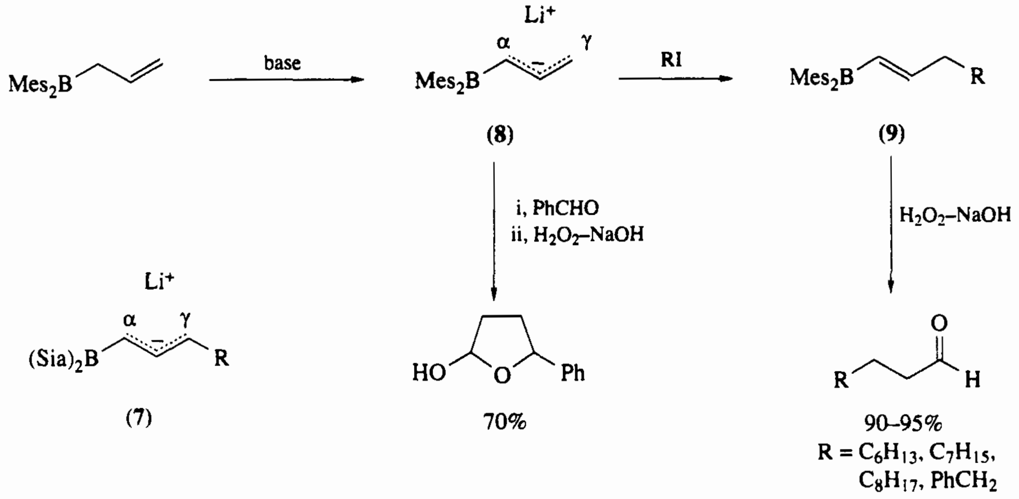
Mes2B
base
Li+
α
γ
Mes2B
RI
Mes2B
R
(8)
(9)
i, PhCHO
ii, H2O2–NaOH
H2O2–NaOH
Li+
α
γ
(Sia)2B
R
(7)
HO
O
Ph
70%
O
R
H
90–95%
R = C6H13, C7H15,
C8H17, PhCH2

**Scheme 2**

Although (**7**) reacts with trimethylsilyl chloride (TMS-Cl) at the γ-position because of the steric bulk of the siamyl group,[3] the 9-borabicyclo[3.3.1]nonyl (9-BBN) derivative (equation 1) gives the α-trimethylsilyl or α-trimethylstannyl allylic-9-BBN upon treatment with TMS-Cl or trimethyltin chloride.[5]

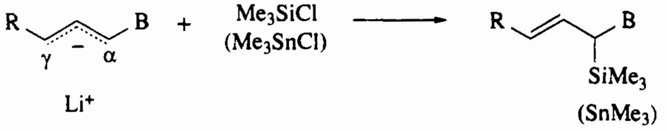
R
B
γ
α
Li+
+
Me3SiCl
(Me3SnCl)
R
B
SiMe3
(SnMe3)

(1)

## 1.2.3 SILICON-SUBSTITUTED ALLYLIC ANIONS

The anion (**10**), prepared from allyltrimethylsilane and *s*-butyllithium in THF–TMEDA at –76 °C, reacts with a variety of aldehydes and ketones to give the γ-adducts (**11**).[6] The resulting vinylsilanes are converted to α,β-epoxysilanes by treatment with *m*-chloroperbenzoic acid (MCPBA). Ring opening with boron trifluoride etherate in methanol affords lactol ethers. Finally, γ-lactones are obtained from the lactols by Jones' reagent (equations 2 and 3). The γ-regioselectivity of carbonyl compounds can be converted to α-selectivity by changing the counterion to magnesium(II),[7] or by addition of triethylaluminum

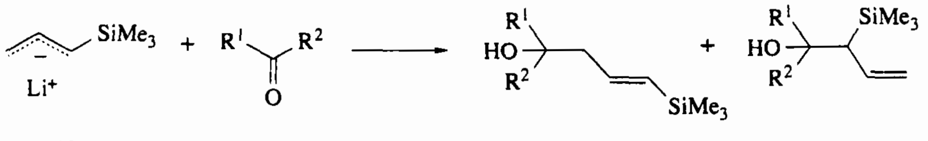
SiMe3
Li+
+
R1
R2
O
R1
HO
R2
SiMe3
+
R1
SiMe3
HO
R2

(2)

**(10)** **(11)** **(12)**

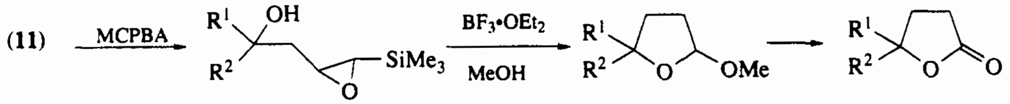
(11)
MCPBA
R1
OH
R2
SiMe3
O
BF3•OEt2
MeOH
R1
R2
O
OMe
R1
R2
O
O

(3)

to form the aluminum ate complex (equation 4).[8] The ate complex of crotyl anion (**13**) reacts with carbon dioxide to give the α-silyl-substituted carboxylic acid (equation 5).[9] Carboxylation without triethylaluminum produces the γ-silylated-β,γ-unsaturated carboxylic acid. Other additives, such as $R_3B$, $R_2BCl$, $RBCl_2$, $RAlCl_2$, and $R_3SnCl$, direct aldehydes to the α-position.[10] Presumably, γ-silyl-substituted organometallics, like the aluminum ate complex, are formed *in situ*, and these reagents react with aldehydes with allylic rearrangement to give (**12**). Boron, aluminum and titanium complexation all induce *anti* selectivity, whereas the use of tin results in a *syn* preference, providing stereocontrolled routes to terminal dienes by Peterson alkenation. The α-adducts (**12**) can undergo the Peterson *syn* elimination of $OSiMe_3$ to give the 1,3-dienes (Scheme 3). Addition of copper(I) cyanide to (**10**) produces the copper complex, which reacts selectively at the γ-position with chloromethyl methyl ether and acetyl chloride to give the corresponding vinylsilanes.[11] Further, the copper complex adds to α,β-unsaturated ketones and esters in a highly regioselective γ-1,4-manner (equation 6). In contrast, α,β-unsaturated aldehydes give the γ-1,2-addition products.

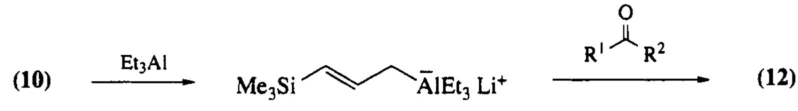

(4)

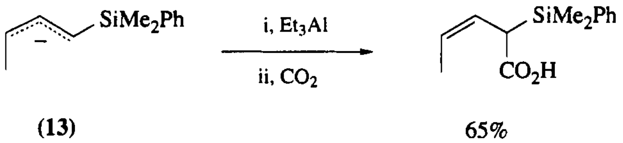

(5)

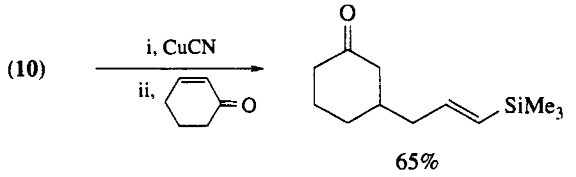

(6)

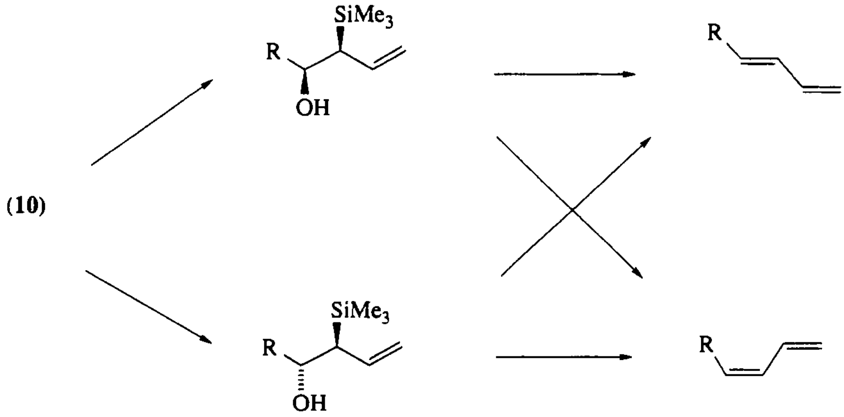

**Scheme 3**

Regiocontrol has been satisfactorily accomplished in cases where carbonyl derivatives are the electrophiles. However, the reaction of (**10**) with simple alkyl halides produces a mixture of the α- and γ-alkylation products. The addition of various metal salts, such as $MgX_2$, $ZnX_2$ and CuX, does not induce appreciable change in the α:γ ratio. However, use of $Bu^tOK/Bu^nLi$ in hexane as the proton-abstracting system enhances γ-selectivity (γ:α > 80:20).[12] A sterically demanding group on silicon such as in (**14a**) can increase the extent of γ-alkylation (γ:α = 80:20–99:1),[13] in which the deprotonation of allyltriisopropylsilane is carried out with the usual base ($Bu^nLi$–TMEDA). Epoxidation of the vinylsilanes, followed by treatment with silica gel affords α-triisopropylsilyl aldehydes (Scheme 4). The reaction of (**10**) with epoxides (equation 7) gives a mixture of (**15**) and (**16**).[14] Ethylene oxide and monosubstituted epoxides produce (**15**) predominantly, while 1,2-di- or 1,1,2-tri-substituted epoxides give (**16**) preferentially. The γ-selectivity can be enhanced by addition of one-half equivalent of $CuBr{\cdot}SMe_2$, which produces the cuprate intermediate. Silicon-substituted allyl anions are normally prepared from 2-alkenylsilanes. Treatment of 1-propenyltriphenylsilane with $Bu^nLi$ in THF–HMPA also produces (**14b**).[15] The triphenylgermyl-substituted allyl anion is produced similarly and exhibits a similar regioselectivity to (**14b**). Treatment of allyl(diethylamino)dimethylsilane with $Bu^nLi$/TMEDA produces (**14c**).[16] Addition of CuCN, followed by treatment with aldehydes gives δ-hydroxy vinylsilanes which can be converted to lactols (Scheme 5). Addition of $ZnCl_2$, $MgBr_2$ or $Ti(OPr^i)_4$ results in almost exclusive α-selectivity. The stereochemistry of the α-adducts is *anti*, and they may be converted to *anti* diols by oxidation of the Si—C bond.

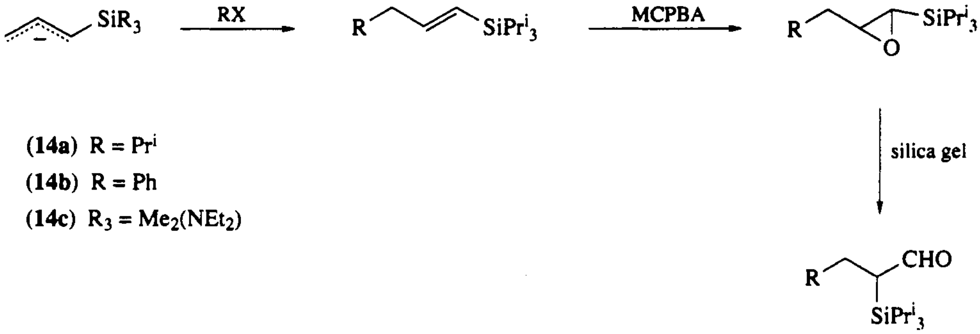
$SiR_3$
RX
$SiPr^i_3$
MCPBA
O
silica gel
CHO

(**14a**) $R = Pr^i$
(**14b**) $R = Ph$
(**14c**) $R_3 = Me_2(NEt_2)$

Scheme 4

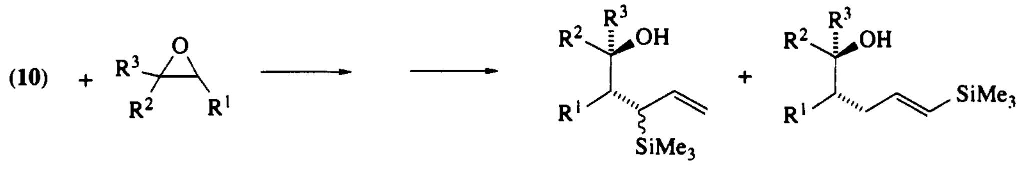
O
$R^3$
$R^2$
$R^1$
OH
$SiMe_3$

(**10**) + … (7)

(**15**) (**16**)

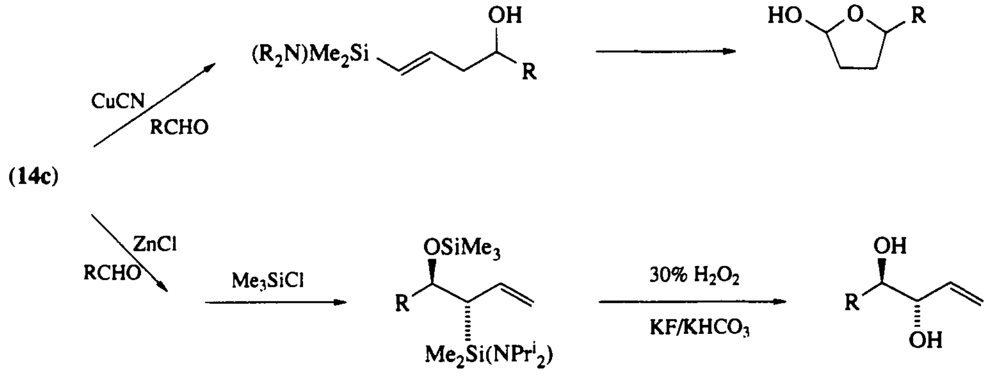
(14c)
CuCN
RCHO
$(R_2N)Me_2Si$
OH
R
HO
O
ZnCl
RCHO
$Me_3SiCl$
$OSiMe_3$
$Me_2Si(NPr^i_2)$
30% $H_2O_2$
$KF/KHCO_3$
OH

Scheme 5

Pentadienylation of simple aliphatic ketones or aldehydes by (**17**; equation 8) proceeds regioselectively at the C-3 position of the pentadienyl moiety, whereas the reaction with (**18**; Scheme 6) leads

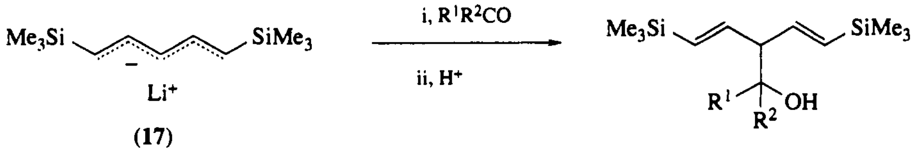
$Me_3Si$
$SiMe_3$
$Li^+$
i, $R^1R^2CO$
ii, $H^+$
$R^1$
$R^2$
OH

(**17**) (8)

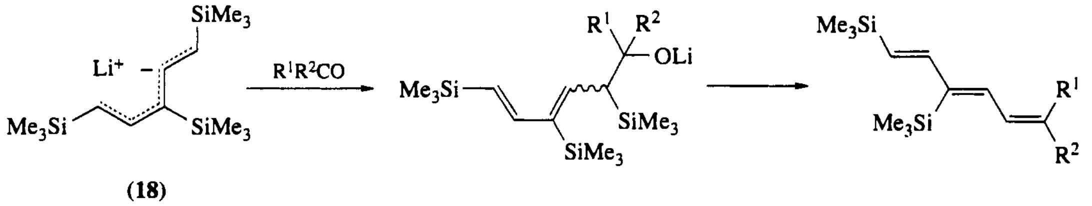
SiMe3
Li+
Me3Si
SiMe3
(18)
R1R2CO
R1
R2
OLi
Me3Si
SiMe3
SiMe3
Me3Si
Me3Si
R1
R2

Scheme 6

to preferential addition at the terminal carbon atom, resulting in conjugated trienes through Peterson elimination.[17] 1-Trimethylsilylpentadienyllithium generally gives a mixture of two regioisomers by competitive attack at the central (C-3) and terminal (C-1) carbons. Pentadienylation of α,β-unsaturated ketones or aldehydes with **(17)** or **(18)** occurs selectively in a 1,4-fashion at the C-3 position.

## 1.2.4 NITROGEN-SUBSTITUTED ALLYLIC ANIONS

Deprotonation of enamines or allylamines with bases such as Bu$^n$Li and Bu$^t$OK–Bu$^t$Li produces nitrogen-substituted allylic anions (**19a**; Scheme 7), which undergo protonation, alkylation, trimethylsilylation and reaction with carbonyl compounds and epoxides either exclusively or predominantly at the γ-position.[18] The resulting enamines can be hydrolyzed by dilute hydrochloric acid to give three-carbon-homologated carbonyl compounds (**20** and **21**). Reactions with carbonyl compounds and epoxides afford the corresponding hydroxy derivatives, which can be isolated as trimethylsilyl ethers. Upon heating, the hydroxy derivatives produce dihydrofurans or dihydropyrans (Scheme 7). Derivatives (**19b**) and (**19c**) also exhibit γ-regioselectivity. Alkylation of (**19c**) followed by hydrolysis produces 2-oxoalkanoic esters. Conjugate addition of (**19b**) to cyclohexenone gives the γ-1,4-adduct, which is converted to the carboxylic acid derivative after hydrolysis (Scheme 8).[18b]

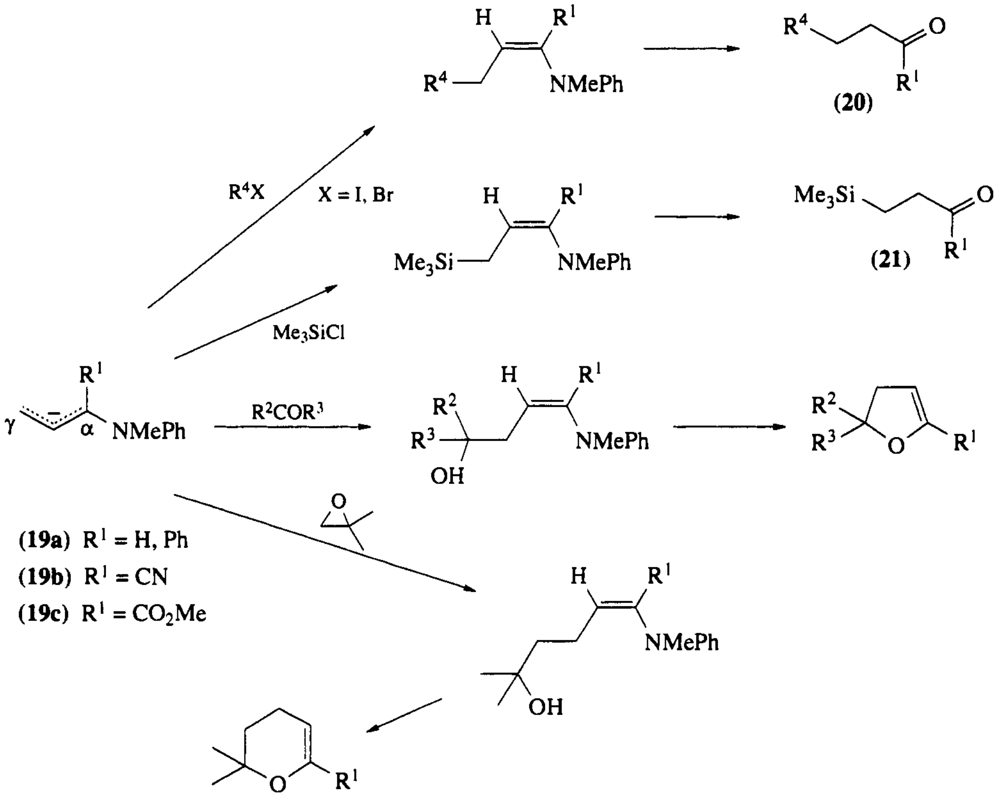
H
R1
R4
NMePh
R4
O
R1
(20)
R4X
X = I, Br
H
R1
Me3Si
NMePh
Me3Si
O
(21)
R1
Me3SiCl
R1
γ
α
NMePh
R2COR3
H
R1
R2
R3
OH
NMePh
R2
R3
O
R1
O
(19a) R1 = H, Ph
(19b) R1 = CN
(19c) R1 = CO2Me
H
R1
NMePh
OH
O
R1

Scheme 7

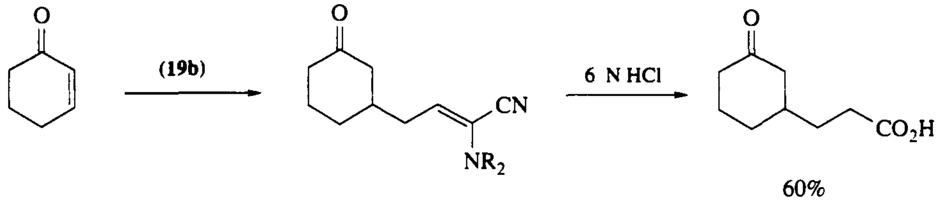

**Scheme 8**

On the other hand, allylic anions (**22**; Scheme 9) undergo alkylation at the α-position either exclusively or predominantly. Hydrolysis of the α-alkylation products gives α,β-unsaturated ketones in fair to good yields.[19] Allylpyrrolidine anion (**23**) and allylcarbazole anion (**24**) are alkylated at the γ-position with high regioselectivity, but additions of carbonyl compounds to (**23**) result in low regioselectivity.[1e] With zinc cations, almost exclusive α-addition of carbonyl compounds to (**23**) is accomplished. Treatment of (**23**) with triethylaluminum followed by addition of TMS-Cl produces the α-silylated allylpyrrolidine, though the direct reaction of (**23**) with TMS-Cl gives the γ-silylated enamine derivative.[8] The allylic anion (**25**; Scheme 10) produces the α-adduct upon treatment with ketones at –78 °C, while it gives the γ-adduct at 0 °C.[20] The γ-adduct can be converted to the three-carbon-annelation product. Thus, (**25**) can serve as either an acyl anion or a β-homoenolate equivalent, depending on the reaction conditions.

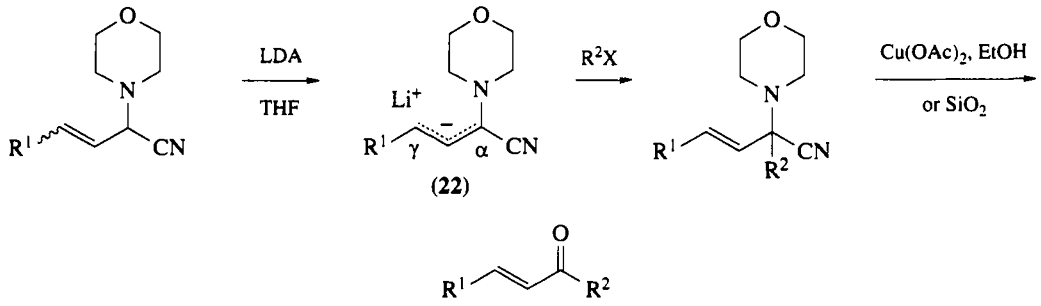

R$^1$ = Me, Ph; R$^2$ = Me, Et, hexyl

**Scheme 9**

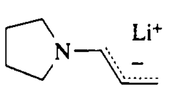

(**23**)

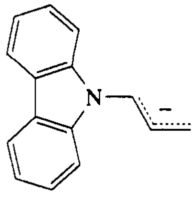

(**24**)

Treatment of *N*-methyl-*N*-allylphosphoramide with Bu$^n$Li at –50 °C, followed by an alkyl halide results in γ-alkylation of the intermediate anion (**26**; Scheme 11). Acid-catalyzed hydrolysis gives the corresponding aldehydes. Although the reaction of (**26**) with benzophenone produces a mixture of the α- and γ-adducts, replacement of the lithium cation by magnesium leads almost exclusively to γ-substitution.[21] Acid hydrolysis affords the lactol almost quantitatively, but such a high yield is not realized with other ketones. The phosphoramide group is a convenient mask, since it is easily introduced to allylic structures and it is easily removed after the reaction. Although (**27a**) gives a mixture of the α- and γ-adducts, (**27b**) produces γ-adducts exclusively upon treatment with alkyl halides or carbonyl compounds. Replacement of lithium by less electropositive metals (Mg, Zn, Cd) leads to increased α-reactivity.[1d] The dilithiated anion (**28**) derived from deprotonation of the corresponding *N*-allylamide with two equivalents of lithium diisopropylamide (LDA) gives the γ-adduct with high regioselectivity.[1e] *N*-Nitroso-*N*-

alkyl-*N*-allyl anions (**29**) show kinetically favored α-addition, but the addition of carbonyl compounds is essentially reversible and thus the γ-adducts become favorable under thermodynamic control.[1e] Metallated chiral allylamines (**30**; M = Li, K) are used as chiral homoenolate equivalents and allow, after alkylation and acid hydrolysis, asymmetric C—C bond formation to β-substituted aldehydes in up to 67% *ee*.[18d]

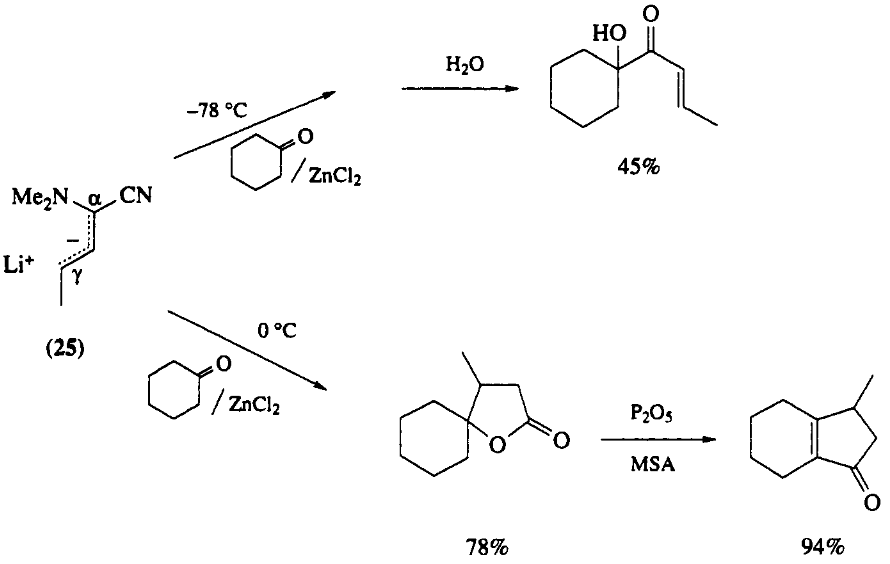
Me$_2$N
α
CN
Li$^+$
γ
(25)
−78 °C
O
/ZnCl$_2$
H$_2$O
HO
O
45%
0 °C
O
/ZnCl$_2$
O
O
78%
P$_2$O$_5$
MSA
O
94%

**Scheme 10**

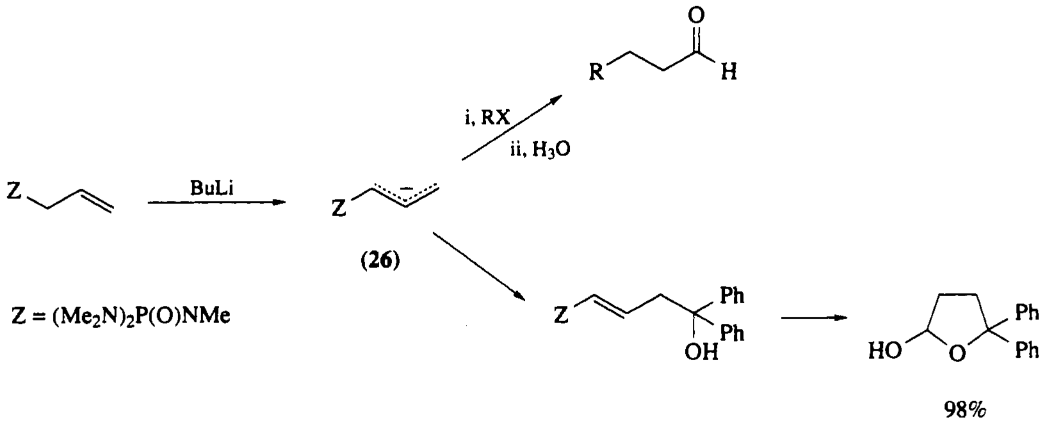
Z
BuLi
Z
(26)
i, RX
ii, H$_3$O
R
O
H
Z
Ph
Ph
OH
HO
O
Ph
Ph
98%
Z = (Me$_2$N)$_2$P(O)NMe

**Scheme 11**

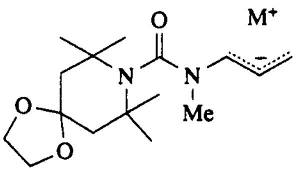

(**27a**) M = Li
(**27b**) M = MgX

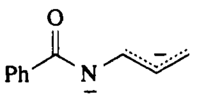

(**28**)

A stereo- and regio-selective synthesis of *trans*-2,5-dialkylpyrroline structures is accomplished *via* the *N*-substituted allylic anion intermediates (Scheme 12).[22a] The α-regioselective alkylation is presumably due to the presence of the electron-withdrawing methoxycarbonyl group. The piperidine ring system

(Scheme 13), the cyclic analog of (**25**), gives α-products upon treatment with alkyl halides, protons or sterically unhindered aldehydes, whereas it affords γ-adducts upon treatment with bulkier electrophiles such as pivaloyl chloride and benzaldehyde.[22b]

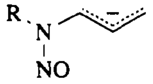

**(29)**

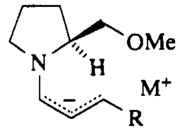

**(30)**

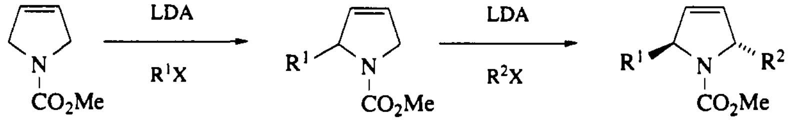
LDA
R¹X
LDA
R²X
CO2Me
R¹
R²

**Scheme 12**

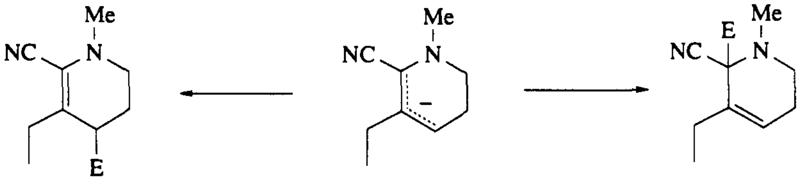

E = MeCO, PhS, PhCH(OH)

E = D, Me, Pr$^i$, Pr$^n$CH(OH), C(O)Me

**Scheme 13**

3-Nitropropene (Scheme 14) undergoes α,α-double-deprotonation to give a dianion that reacts with carbonyl compounds at the α-nitro carbon to form nitro alcohols, whereas 4-nitro-1-butene (Scheme 15) produces an α,β-abstraction product that reacts with alkyl halides and carbonyl compounds to give a mixture of the β- and δ-adducts.[23] The δ-isomer can be separated and converted to an α,β-unsaturated aldehyde by Nef reaction with $TiCl_3$ (equation 9).

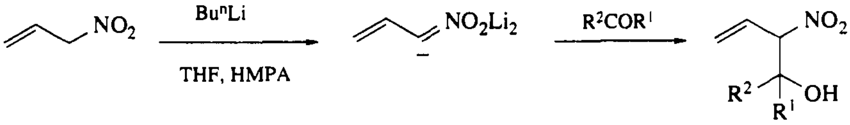
NO2
BunLi
THF, HMPA
NO2Li2
R²COR¹
NO2
R²
R¹
OH

**Scheme 14**

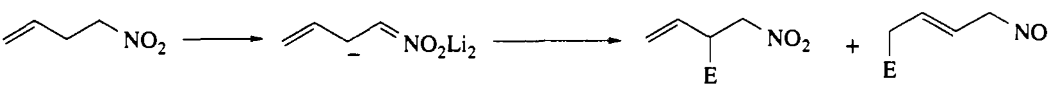
NO2
NO2Li2
NO2
E
+
NO2
E

**Scheme 15**

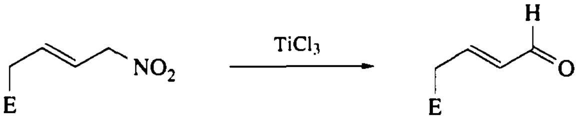
NO2
E
TiCl3
H
O
E

(9)

E = Pr$^i$, Bn

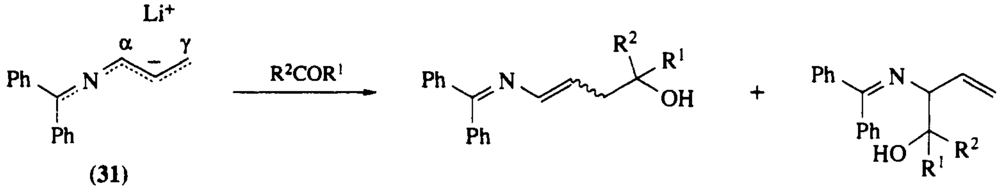
Li+
α
γ
Ph
N
Ph
(31)
R2COR1
R2
R1
OH
+
HO
R1
R2

(10)

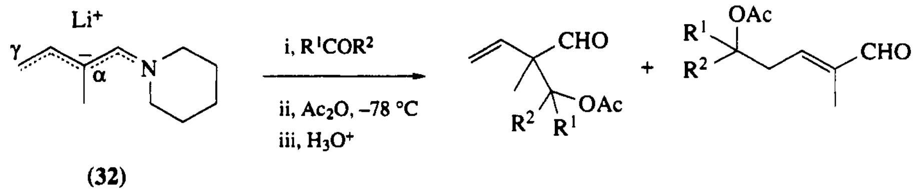
Li+
γ
α
N
(32)
i, R1COR2
ii, Ac2O, -78 °C
iii, H3O+
CHO
OAc
R2
R1
+
OAc
CHO

(11)

2-Azapentadienyl anion (**31**), readily prepared by deprotonation of the *N*-allylimine, reacts with carbonyl compounds at either the α- or the γ-position (equation 10).[24] The regioselectivity depends upon the reaction conditions. 1-Azapentadienyl anion (**32**; equation 11), prepared from the cyclohexylimine of tiglaldehyde and LDA, reacts with aldehydes and ketones to give the γ-capture products in the presence of HMPA or the α-capture products in the absence of HMPA.[25]

## 1.2.5 PHOSPHINE-SUBSTITUTED ALLYLIC ANIONS

Deprotonation of allyl tetramethylphosphorodiamidate, readily prepared from allyl alcohol, induces the migration of phosphorus from oxygen to carbon. A second deprotonation then occurs to give the dianion (**33**; Scheme 16).[26] Alkylation with 1-iodopropane takes place at the γ-position to give hexanoic acid after hydrolysis. Reaction of (**33**) with aldehydes and ketones followed by hydrolysis gives γ-lactones, and a similar sequence with epoxides produces δ-lactones.

1,2-Addition of trivalent phosphorus siloxanes with α,β-unsaturated aldehydes gives high yields of (**34**), which can be easily deprotonated to give (**35**; Scheme 17). Here again, electrophiles react at the γ-position either exclusively or predominantly. The dianion (**33**; R = Ph; equation 12) reacts with excess methyl iodide and subsequent methanolysis affords a mixture of (**36**) and (**37**). Thus, (**36**) most closely approximates the binucleophilic homoenolate synthon (**4**; Scheme 1).[27]

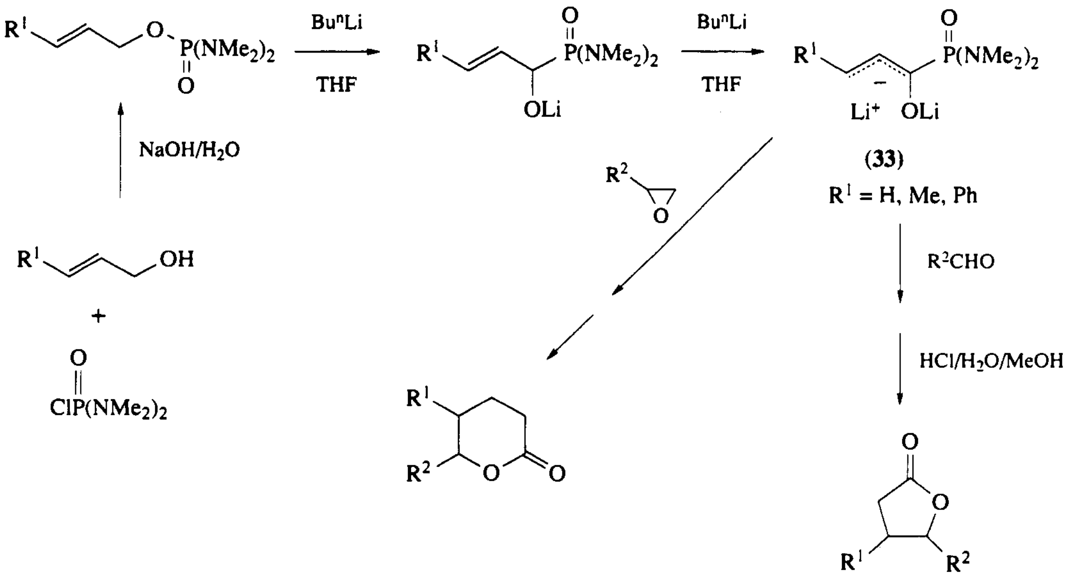
R1
O
P(NMe2)2
O
BunLi
THF
P(NMe2)2
OLi
BunLi
THF
Li+
OLi
(33)
R1 = H, Me, Ph
NaOH/H2O
OH
+
ClP(NMe2)2
R2
R2CHO
HCl/H2O/MeOH

**Scheme 16**

Allyl anions (**38a**),[28] (**38b**)[29] and (**38c**)[30] exhibit a similar regioselectivity toward electrophiles, and thus serve as homoenolate synthons. Addition of titanium tetraisopropoxide to (**39**) followed by condensation with aldehydes gives the *anti* adducts exclusively, which can be converted to the (*Z*)-1,3-dienes upon treatment with methyl iodide (Scheme 18).[31] The (*E*)-1,3-dienes can be prepared from the lithiated allyldiphenylphosphine oxide. The stabilized allylic phosphonate anion (**40**) condenses with carbonyl

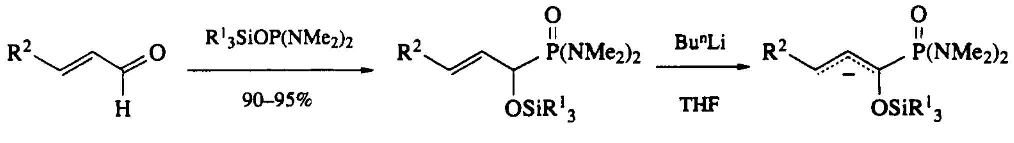
R2
O
H
R'3SiOP(NMe2)2
90–95%
R2
O
P(NMe2)2
OSiR'3
BunLi
THF
R2
O
P(NMe2)2
OSiR'3

(**34**) (**35**)

$R^1$ = Me, Et; $R^2$ = H, Me, Ph

**Scheme 17**

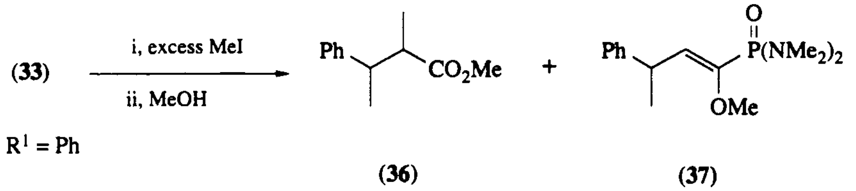
(33)
i, excess MeI
ii, MeOH
R1 = Ph
Ph
CO2Me
+
Ph
O
P(NMe2)2
OMe
(36)
(37)

(12)

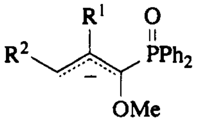
R1
O
R2
PPh2
OMe

(**38a**)

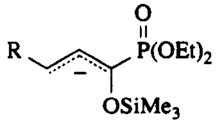
O
R
P(OEt)2
OSiMe3

(**38b**)

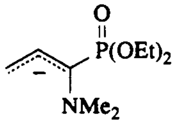
O
P(OEt)2
NMe2

(**38c**)

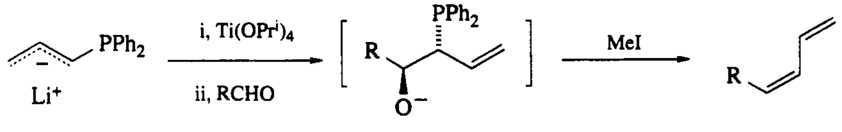
PPh2
Li+
i, Ti(OPri)4
ii, RCHO
PPh2
R
O−
MeI
R

(**39**)

**Scheme 18**

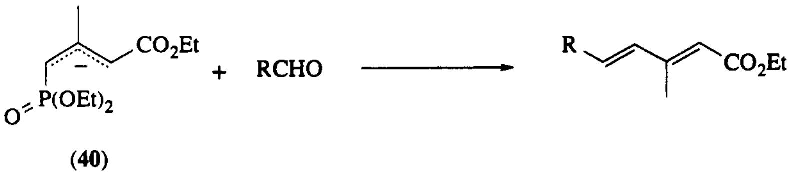
CO2Et
P(OEt)2
O
+ RCHO
R
CO2Et
(40)

(13)

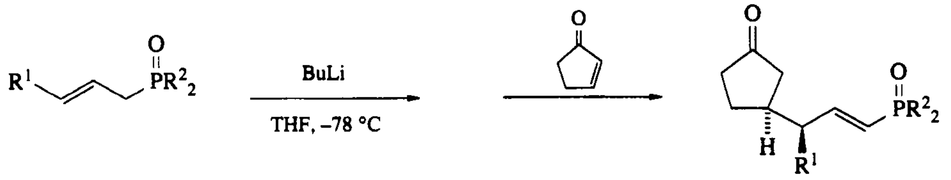
R1
O
PR22
BuLi
THF, -78 °C
O
O
H
R1
O
PR22

R = Ph, OEt

**Scheme 19**

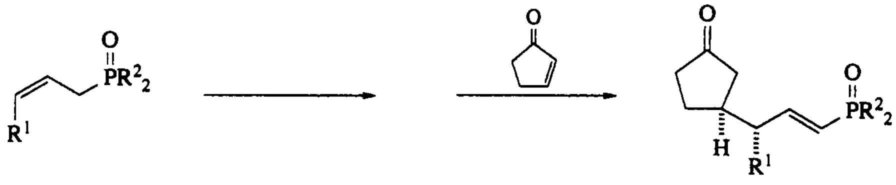

**Scheme 20**

compounds regioselectively at the phosphorus-bearing carbon atom to give stereospecifically the corresponding (2*E*,4*E*)-dienoate (equation 13).[32]

Lithiated (*E*)- and (*Z*)-2-alkenylphosphine oxides and phosphonates react with cyclic enones in a 1,4-conjugate addition manner (Schemes 19 and 20). The (*E*)- and (*Z*)-allylic anions react in highly diastereoselective fashion to deliver respectively *syn* and *anti* vinylic phosphine oxides and phosphonates.[33] Chiral allylphosphonyl anions undergo enantioselective 1,4-addition with cyclic enones of varying size.[34]

## 1.2.6 OXYGEN-SUBSTITUTED ALLYLIC ANIONS

Allyl ethers are readily deprotonated by *s*-butyllithium in THF at –65 °C in essentially quantitative yield (Scheme 21). At these temperatures, the allylic anion (**41a**) exhibits no tendency to undergo Wittig rearrangement, a reaction characteristic of these species at higher temperature. The reaction of (**41a**) with alkyl halides produces mixtures of enol ethers ($\gamma$-attack products) and allyl ethers ($\alpha$-attack products).[35] With *t*-butyl allyl ether (**41a**; $R^1 = Bu^t$), the ratio of $\gamma$:$\alpha$ for $R^2 = n\text{-}C_6H_{13}$ is 89:11. Allyl triethylsilyl ether derivative (**41c**) gives similar results;[36] the ratio of $\gamma$:$\alpha$ for $R^2$ = Me is 97:3. More bulky alkyl halides, such as *s*-propyl iodide and cyclohexyl iodide, give more of the $\alpha$-alkylation product. Five-membered ring chelation (**42**) in the $\gamma$-lithio allylic derivatives (**41a, 41c**) may explain the (*Z*)-stereochemistry of the enol ether product. The importance of chelation is shown in the fact that the allylic anions derived from phenyl allyl ether (Scheme 22) and from phenyl (*Z*)-1-propenyl ether (Scheme 23) give different product ratios upon methylation.[37] The former presumably produces a mixture of (*Z*)-chelated and (*E*)-nonchelated lithium derivatives, while the latter affords an all-(*Z*)-chelated lithium intermediate.

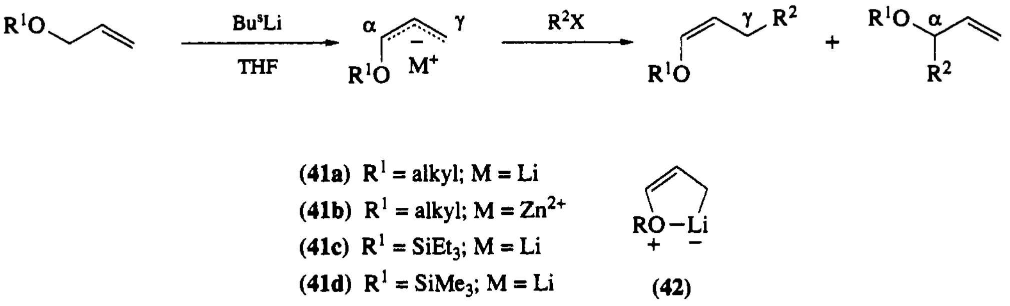

(**41a**) $R^1$ = alkyl; M = Li
(**41b**) $R^1$ = alkyl; M = $Zn^{2+}$
(**41c**) $R^1$ = $SiEt_3$; M = Li
(**41d**) $R^1$ = $SiMe_3$; M = Li

(**42**)

**Scheme 21**

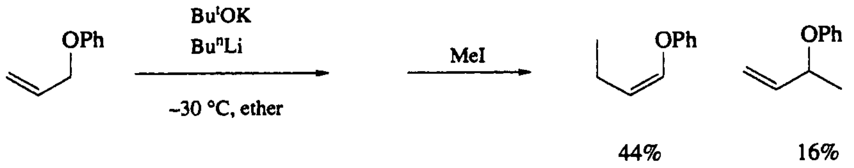

**Scheme 22**

The reaction of carbonyl groups produces the opposite regioselectivity. The reaction of (**41c**) with cyclohexanone gives predominantly the $\alpha$-adduct ($\alpha$:$\gamma$ = 71:29). The lithium salt of the trimethylsilyl derivative (**41d**) in THF–HMPA produces the $\alpha$-adduct in reactions with a variety of aldehydes and ketones (98–100% regioselectivity).[2] Mild acid hydrolysis of the product monosilyl ethers affords 3,4-dihydroxy-

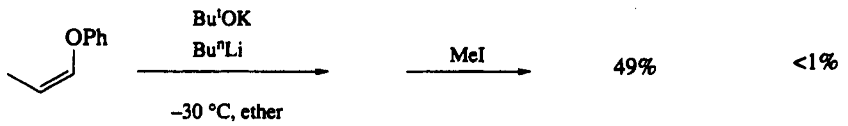
OPh
Bu$^t$OK
Bu$^n$Li
–30 °C, ether
MeI
49%
<1%

Scheme 23

1-alkenes in high yields. Although the butyl ether (**41a**; $R^1$ = Bu$^t$) gives mostly α-adducts, the γ-adducts are predominantly obtained when the smallest group is present in ether (**41a**; $R^1$ = Me; Scheme 24). The corresponding allylzinc reagents (**41b**; Scheme 24) are useful for effecting regiospecific α-attack on ketones.[34] The addition of triethylaluminum to (**41a**) also directs electrophiles to the α-position (Scheme 25).[8,38] Further, *syn* stereospecific condensation is accomplished *via* the aluminum ate complexes. By this method, (±)-*exo*-brevicomin is synthesized stereoselectively.

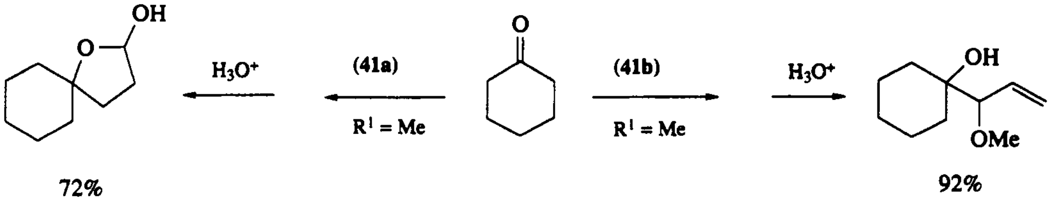
OH
O
$H_3O^+$
(41a)
$R^1$ = Me
O
(41b)
$R^1$ = Me
$H_3O^+$
OH
OMe
72%
92%

Scheme 24

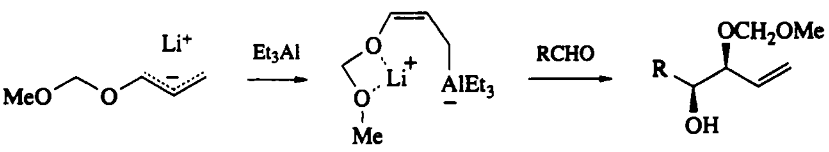
Li$^+$
MeO
O
$Et_3Al$
O
Li$^+$
O
Me
$AlEt_3$
–
RCHO
R
$OCH_2OMe$
OH

Scheme 25

The α-chelating anions (**43**) from allyl *N*,*N*-dialkylcarbamate esters react with carbonyl compounds at the γ-position with very high regioselectivity (in most cases >95%) to afford γ-hydroxyenol carbamates.[1d] Solvolysis gives a lactol which is readily oxidized to a lactone (Scheme 26). The γ-selectivity increases with increasing γ-substitution and with decreasing α-substitution in (**43**), and also with decreasing reactivity of the carbonyl group in the electrophiles. Ketones are better in this regard than aldehydes. In contrast to carbonyl addition, the regiochemistry of alkylation and silylation is largely controlled by the position of the alkyl groups present in the allylic system. The carbamoyl group has very little influence. Thus, the reaction of (**43**) itself with TMS-Cl gives a mixture of the γ- and α-products in the ratio of 41:59.

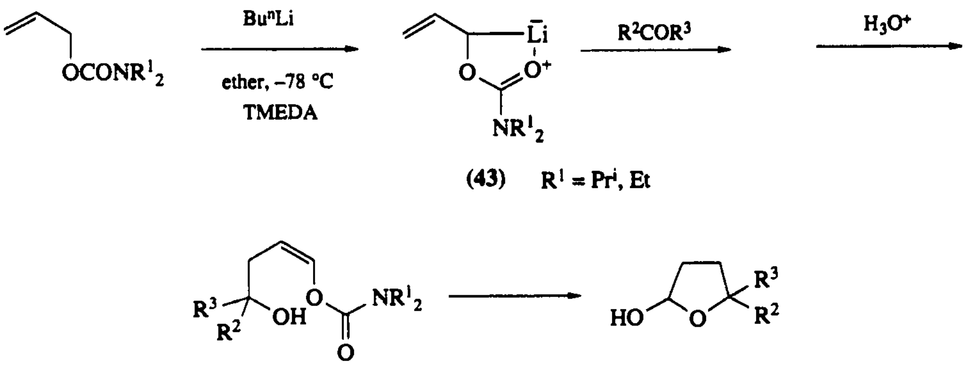
$OCONR^1_2$
Bu$^n$Li
ether, –78 °C
TMEDA
Li
O
O$^+$
$NR^1_2$
$R^2COR^3$
$H_3O^+$
$R^3$
$R^2$
OH
O
$NR^1_2$
O
HO
O
$R^3$
$R^2$

(**43**) $R^1$ = Pr$^i$, Et

Scheme 26

The anions from crotyl carbamates (*E*)-(**44**) and (*Z*)-(**44**) are useful for diastereoselective homoaldol reactions.[1d] Diastereoselection with the lithium reagents (*E*)-(**44**) and (*Z*)-(**44**) is low, as expected from the results on crotyl organometallic condensation reactions.[39] The diastereoselectivity is improved by metal exchange. Addition of tris(dimethylamino)titanium chloride [$(Et_2N)_3TiCl$] to (*E*)-(**44**) gives the (*Z*)-*anti* adduct almost exclusively,[40] and addition of $Bu^i_2AlCl$ produces the (*E*)-*anti* adduct predominantly (Scheme 27). The addition of diisobutylaluminum methanesulfonate ($Bu^i_2AlOMs$) to (*Z*)-(**44**) gives the (*E*)-*syn* adduct with variable selectivity, and in general the derivatives of (*Z*)-(**44**) result in low diastereoselectivity (Scheme 28). The α-chiral anion (**45**) reacts with 2-methylpropanal to give the optically active (*Z*)-(–)-*anti* adduct (24% yield, 52% *ee*) and the (*Z*)-(–)-*syn* isomer (29% yield, ≥25% *ee*). The metal exchange from lithium to titanium by treatment with $(Et_2N)_3TiCl$ followed by addition of the same aldehyde produces only one adduct, the (*Z*)-(+)-*anti* isomer (36% yield, 35% *ee*).[41] Therefore, the lithium–titanium exchange in (**45**) presumably takes place with inversion. Highly optically active 3-phenylalkanals are obtained by the reaction of alkyl halides and the chiral anion (**46**).[42] After exchange of lithium in (**47**) with $Bu^i_2AlOMs$, the addition of an aldehyde proceeds with high *anti* diastereoselectivity, affording (*E*)-(**48**), whereas exchange with tris(dimethylamino)titanium chloride produces (*Z*)-(**48**).[43] Peterson elimination introduces the second double bond either with (3*E*)- or with (3*Z*)-configuration.

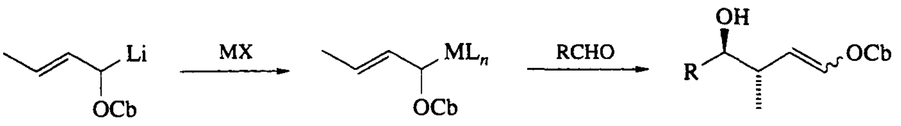

(*E*)-(**44**) M = Al, Ti (*E*)- and (*Z*)-*anti*

**Scheme 27**

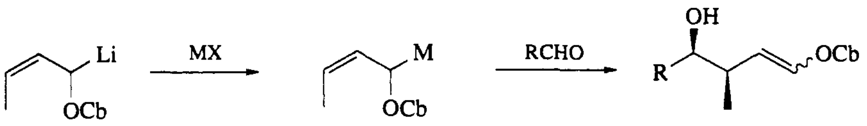

(*Z*)-(**44**) (*E*)- and (*Z*)-*syn* ; Cb = $C(O)NPr^i_2$

**Scheme 28**

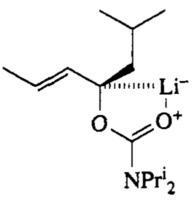

**(45)**

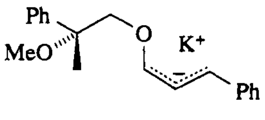

**(46)**

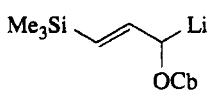

**(47)**

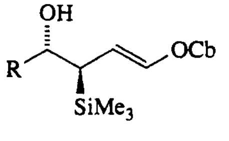

(*E*)-(**48**)

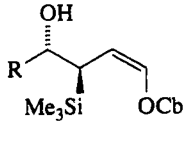

(*Z*)-(**48**)

1-Oxyallyl anions are prone to rearrangement, such as Wittig and Brook rearrangements as well as acyl and phosphoryl migration (equations 14 to 17).[1d] Although allyloxy carbanions (**41**) are in rapid equilibrium with (**49**; equation 15), the alkylation generally proceeds at the γ-position *via* (**41**).[36] Hard electrophiles such as $Me_3SiCl$, chloroformates, diphenyl carbonate and protons react at oxygen either exclusively or predominantly (equation 18).[44] The anion (**50a**, **50b**), prepared by treatment of the cyanohy-

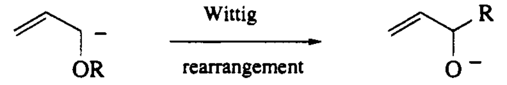
OR
Wittig
rearrangement
R
O⁻

(14)

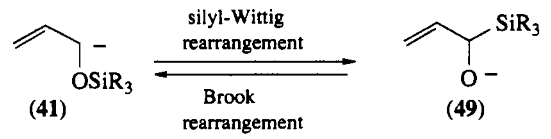
OSiR3
silyl-Wittig
rearrangement
Brook
rearrangement
SiR3
O⁻

(41) (49)

(15)

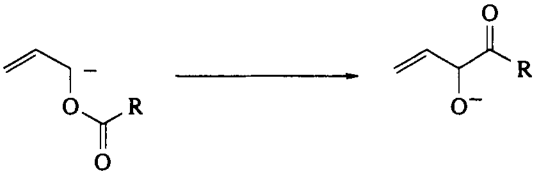

(16)

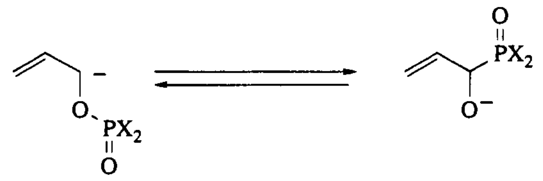
O
PX2
O
O
PX2
O⁻

(17)

drin ethers (**51**) with LDA at −78 °C, undergoes 1,3-silyl migration at −25 °C (Scheme 29).[45] Reactions of (**50**) with alkyl halides at −78 °C give the α-alkylation products.

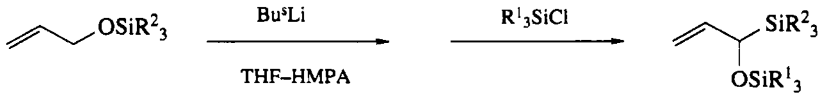
OSiR²3
BusLi
THF–HMPA
R¹3SiCl
SiR²3
OSiR¹3

(18)

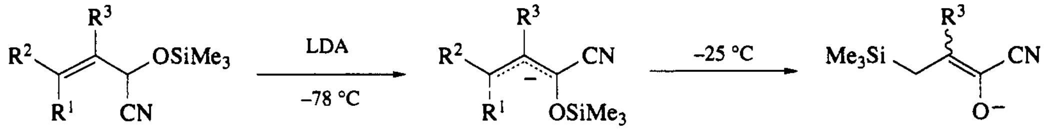
R3
R2
OSiMe3
R1
CN
LDA
-78 °C
R3
R2
CN
R1
OSiMe3
-25 °C
R3
Me3Si
CN
O⁻

(**51**)

(**50a**) $R^1 = R^2 = R^3 = H$

(**50b**) $R^1 = R^2 = H$ ; $R^3 = Me$

(**50c**) $R^1 = R^3 = H$ ; $R^2 = Me$

**Scheme 29**

Reaction of (**50**) with alkyl halides gives exclusive α-alkylation. With aldehydes and ketones, α-addition again takes place to give (**52**) *via* intramolecular silyl transfer with concomitant loss of lithium cyanide (*cf.* **25**; Scheme 30).[46] Treatment of (**52**) with *p*-TsOH·$H_2O$ gives the cyclopentenone annelation product. The allylic cyanohydrin anion (**53**) also gives α-adducts upon treatment with aldehydes and ketones at −78 °C, whereas reaction with electrophiles at 0 °C affords γ-adducts (*cf.* **25**).

Lithium anion (**54**) gives predominantly α-adducts with aldehydes and ketones, whereas alkylation or trialkylsilylation produces γ-adducts preferentially.[47] Here also, the zinc anion leads to exclusive α-attack of carbonyl compounds (*cf.* **41b**). The pentadienyl anion (**55**) reacts with ketones at the terminal (γ) position, and thus serves as a convenient $C_5$ unit.[48] On alkylation, however, the undesired α-attack is competitive. Reaction of (**55**) with dimethyl disulfide produces (**56**) regioselectively. The methylthio substituent of (**56**) not only facilitates deprotonation to (**57**), but also directs the alkylation of (**57**) toward the desired γ-products: the alkylation takes place exclusively at the carbon bearing the sulfur group. The anion (**58**), generated from 4*H*-1,3-dioxin, reacts with various alkyl halides, ketones, aldehydes and ethylene oxide to give (**59**) in good to high yields (Scheme 31).[49] Reflux of (**59**) in toluene produces α,β-

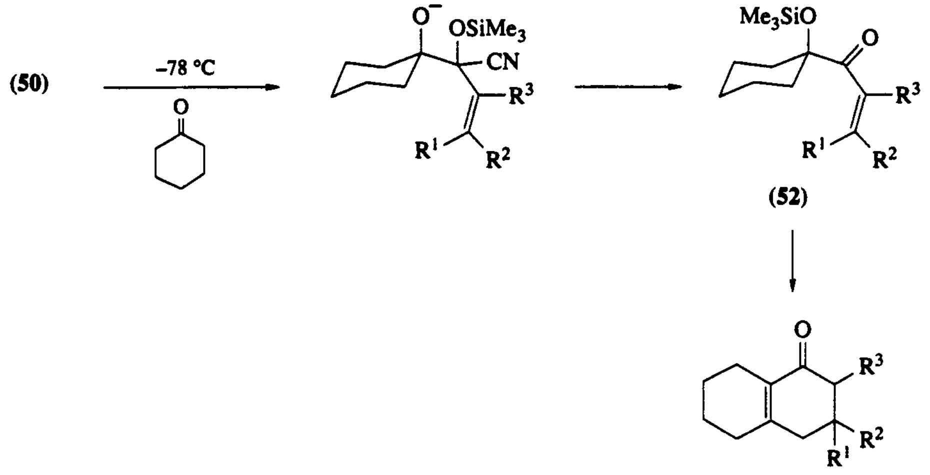
(50)
-78 °C
O
O⁻
OSiMe3
CN
R3
R1
R2
Me3SiO
O
R3
R1
R2
(52)
O
R3
R2
R1

Scheme 30

unsaturated aldehydes, and thus (**58**) serves as a β-acylvinyl anion equivalent (**6**). The reaction of Bu$^s$Li with acrolein dialkyl acetals results in the formation of (**60**), which reacts with organosilicon and organotin chlorides at the γ-position to give the corresponding ketone acetals.[50] Treatment of 6-methoxy-1-indanone with two equivalents of LDA produces the dianion, which reacts with ethyl iodide to give 3-ethyl-1-indanone with very high regioselectivity.[51] Reaction of 2-allyloxybenzimidazoles with butyllithium followed by addition of cadmium iodide generates the metallated allylic ethers, which react with aldehydes to give the α-adducts selectively.[52] The adducts are converted to vinyloxiranes in good yields on treatment with sodium hydride.

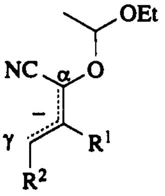
OEt
NC
α
O
γ
R1
R2

(**53**)

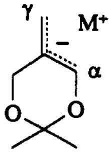

(**54**)

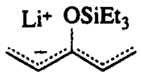

(**55**)

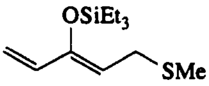

(**56**)

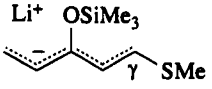
Li+ OSiMe3
γ
SMe

(**57**)

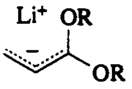

(**60**)

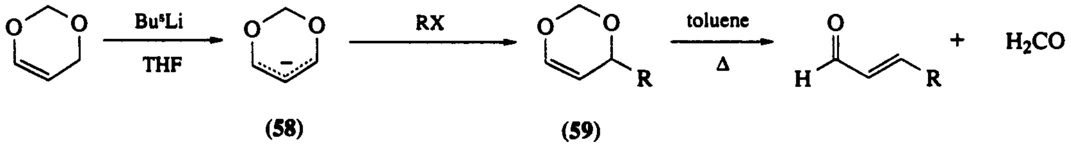
O
O
BusLi
THF
(58)
RX
R
(59)
toluene
Δ
O
H
R
+
H2CO

Scheme 31

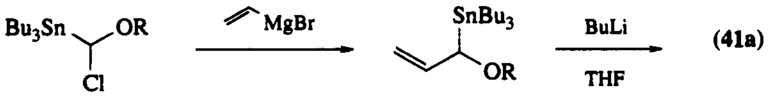
Bu3Sn
OR
Cl
MgBr
SnBu3
OR
BuLi
THF
(41a)

Scheme 32

Normally, anions like (**41**) are prepared by deprotonation of allyl ethers. Another method to generate (**41a**) is transmetallation of a C—Sn bond to a C—Li bond (Scheme 32). Treatment of an α-alkoxyallyltin with *n*-butyllithium gives (**41a**).[53] However, this is an inconvenient method for the preparation of the allyl anions, compared to the ordinary way.

## 1.2.7 SULFUR-SUBSTITUTED ALLYLIC ANIONS

The thioallyl anions (**61**), prepared by treatment of the corresponding sulfides with Bu$^n$Li in THF at –30 °C in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), react with alkyl halides predominantly at the α-position.[1c] Anions (**61b**) and (**61c**), which are more highly substituted at the γ-position, show a higher α-selectivity (85–100%). The reaction of (**61b**) with acetone in THF produces the γ-adduct in 100% yield, while (**61b**) in the presence of cryptand[2.2.2] gives only the α-adduct.[1c] The former reaction involves intimate ion pairs, whereas the latter proceeds through dissociated ion pairs. Carbanions derived from benzyl allyl ethers ($R^1 = CH_2Ph$ in **61**) undergo complex rearrangements and thus are useless in organic synthesis.[54]

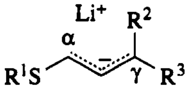

(**61a**) $R^1 = Ar; R^2 = R^3 = H$
(**61b**) $R^1 = Ph; R^2 = R^3 = Me$
(**61c**) $R^1 = Et; R^2 = R^3 = Me$

(**61d**) $R^1 =$ 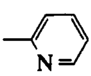; $R^2 = R^3 = H$

(**61e**) $R^1 =$ 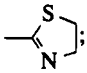; $R^2 = R^3 = H$

(**61f**) $R^1 = Pr^i; R^2 = R^3 = H$
(**61g**) $R^1 = Pr^i; R^2 = H; R^3 = Me$

Intramolecular chelation of the lithium to the heteroaromatic ring may direct electrophiles to the α-position (equation 19). In fact, alkylation of (**61d**) and (**61e**) gives the α-product in the ratio of 99:1.[55]

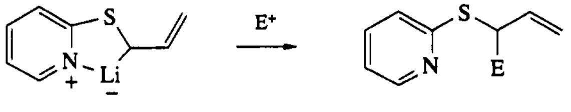

(19)

Addition of triethylaluminum or triethylborane to (**61f**) produces the ate complexes, which react with aldehydes at the α-position.[8] In contrast to the ate complex of the oxygen-substituted anion, the ate complex of (**61f**) produces low diastereoselectivity. Reaction of the boron ate complex with γ,γ-dimethylallyl chloride and bromide occurs at the α-position with inversion of the allyl unit.

The addition of copper iodide to (**61f**), followed by alkylation with allylic halides, gives γ-allylation products with inversion of the allyl unit, whereas reaction with acetone yields predominantly the α-ad-

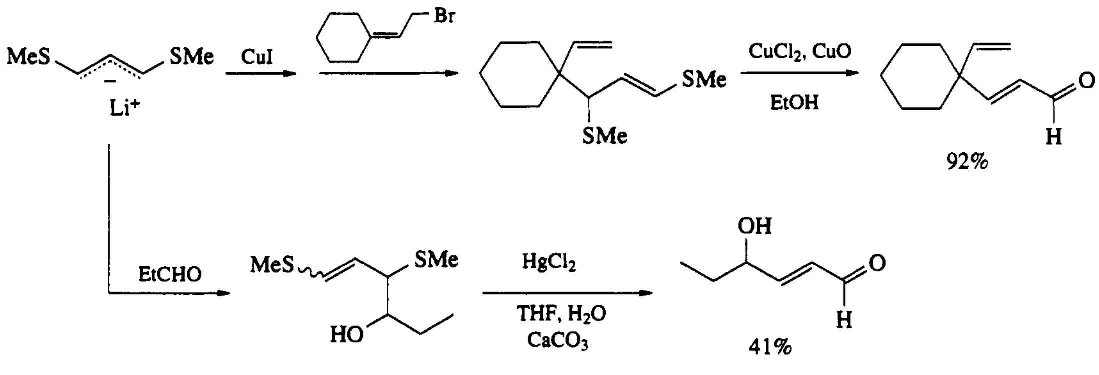

Scheme 33

duct: therefore, selectivity of the copper derivative is opposite to that of the lithio reagent (**61f**).[56] The copper derivative of 1,3-di(methylthio)allyl anion reacts with the allylic bromide with allylic rearrangement (Scheme 33). The hydrolysis and elimination of sulfur may be accomplished with thiophilic metal salts, including silver nitrate, mercury(II) chloride[57] or copper(II) chloride.[56] By using this procedure, α,β-unsaturated aldehydes can be prepared. 3-Alkyl- and 2,4-dialkyl-furans are prepared *via* similar condensation with aldehydes (Scheme 33).[58]

Addition of titanium tetraisopropoxide to the anion (**61**; $R^2 = R^3 = H$) produces a 3-(alkylthio)allyltitanium reagent that condenses with aldehydes to give *anti*-β-hydroxy sulfides in a highly regio- and stereo-selective manner (Scheme 34).[59] *Anti*-β-hydroxy sulfides are transformed stereoselectively to *trans*-vinyloxiranes or 1,3-alkadienes. In contrast, the titanium[59] and lithium[8] reagents from crotyl ethyl sulfide react with aldehydes affording δ-hydroxyvinyl sulfides exclusively.

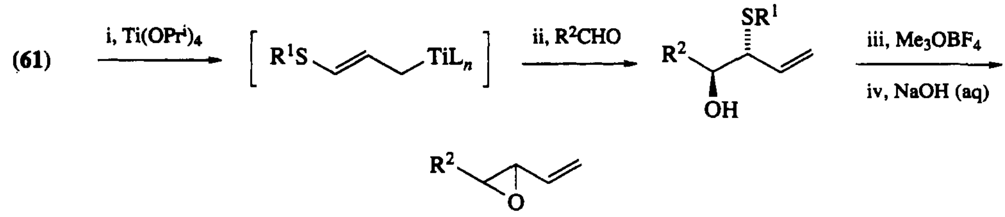

Scheme 34

Substitution on the aromatic ring in (**61a**) has little effect on the α:γ ratio.[60] However, substituents on the allyl group cause dramatic changes in the regioselectivity, as shown in Table 1.

The dianion (**62**; Scheme 35), prepared from alkenethiols, gives good γ-selectivity toward both alkylation and carbonyl addition.[78] The γ-products (enol sulfides) may be converted to dimethylacetals by treatment with mercury(II) chloride in methanol. When (**62**) is associated with magnesium dibromide, the addition of carbonyl compounds produces the α-adducts with regioselectivity greater than 90%. The reaction with methyl vinyl ketone, followed by a Cope rearrangement, results in reattachment at the original γ-position.

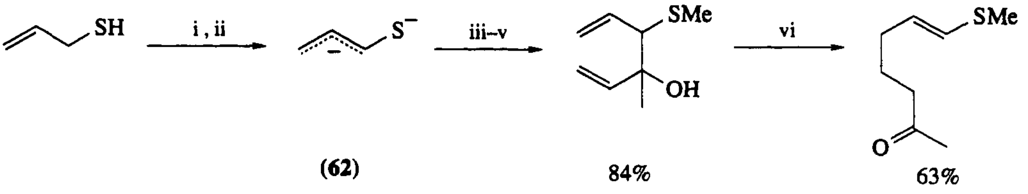

i, Bu$^n$Li, 0 °C, TMEDA–THF; ii, HMPA, –50 °C, Bu$^t$OK; iii, MgBr$_2$; iv, 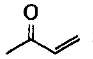; v, MeI; vi, KH, THF, HMPA

Scheme 35

Ketene dithioacetals are deprotonated with LDA–HMPA and complexed with copper(I) iodide (Scheme 36). This reagent reacts with allylic halides exclusively at the γ-position with allylic rearrangement ($S_N2'$).[79] The reaction of the lithium reagent with simple alkylating reagents gives mostly α-attack. Ketene dithioacetals can be converted to esters by aqueous mercury(II) chloride.

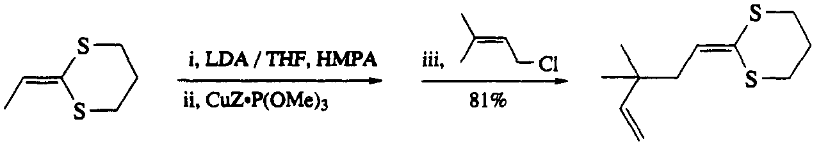

$S_N2'$:$S_N2$ = 80:20

Scheme 36

**Table 1** Reaction of Sulfur-substituted Allylic Anions with Electrophiles

| *Anion* | *Electrophile/reaction conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 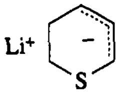 | Me(CH$_2$)$_5$COMe | 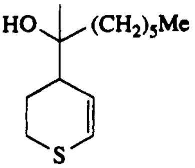 | 73 | 61 |
| 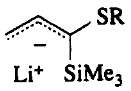 | 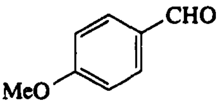 | 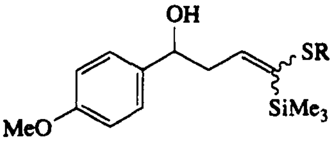 | 72 | 62 |
| 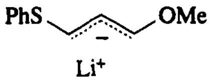 | Bu$^n$I | 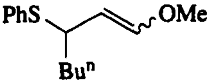 | 80 | 63 |
| 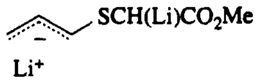 | n-C$_6$H$_{13}$Br | 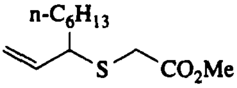 | 75 | 64 |
| 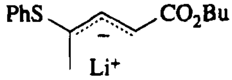 | EtI | 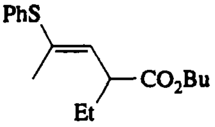<br>*(E)* only | 88 | 65 |
| 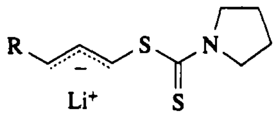 | i, Me$_3$SiCH$_2$I<br>ii, MeI/LiF, Li$_2$CO$_3$ | 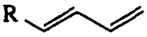 |  | 66 |
| 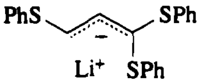 | 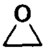 | 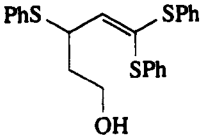 | 72 | 67 |
| 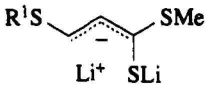 | i, R$^2$X<br>ii, MeI | 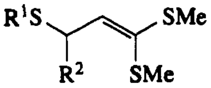 |  | 68 |
| 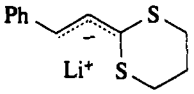 | PhCH$_2$I | 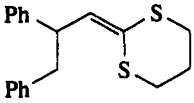 | 60 | 69 |
|  | Me$_2$SO$_4$ | 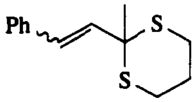 | 55 |  |

**Table 1** *(continued)*

| *Anion* | *Electrophile/reaction conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 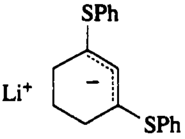 | i, PhCH=CHCOPh<br>ii, $Cu^+$, $H_2O$, MeCN | 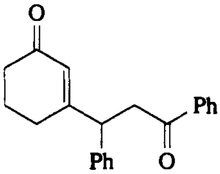 | 59 | 70 |
| 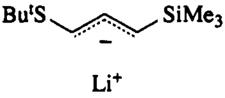 | i, $Ti(OPr^i)_4$<br>ii, 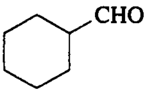 | 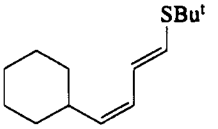 | 62 | 71 |
| 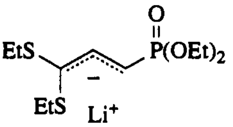 | RCHO | 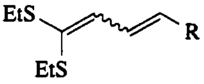 |  | 72 |
| 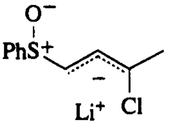 | MeI | 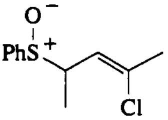 | 65 | 73 |
| 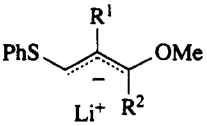 | $R^3CHO$ | 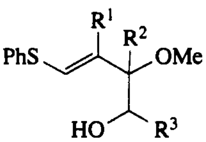 |  | 74 |
| 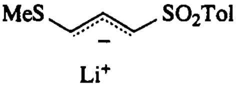 | i, n-$C_{12}H_{25}Br$<br>ii, $TiCl_4$, $CuCl_2$ ($H_2O$)<br>iii, $K_2CO_3$ | 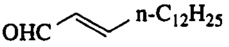 | 73 | 75 |
| 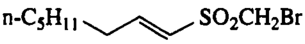 | 2.5 equiv. $Bu^tOK$<br>$Bu^tOH$/THF | 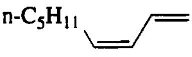<br>*Z*:*E* = 83:17 | 59 | 76 |
| 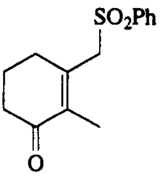 | i, NaH<br>ii, 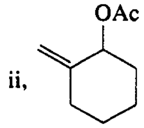<br>$Pd(PPh_3)_4$ (cat.)<br>THF–HMPA<br>iii, DBU, 80 °C | 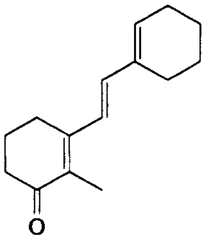 | 77 | 77 |

Anion (**63**), prepared from an allyl sulfoxide and LDA, reacts with alkyl halides at the α-position to give α-alkylated sulfoxides, which undergo rearrangement upon treatment with a thiophile, resulting in formation of allylic alcohols (Scheme 37).[55] This method can be applied to the synthesis of cyclic allylic alcohols (Scheme 38). The reaction of (**63**) with aldehydes produces a mixture of regioisomers and thus it is less synthetically useful.

Although allylic sulfoxides produce allyl anions like (**63**) upon treatment with bases, 1-alkenyl sulfoxides afford α-lithiated derivatives with LDA (Scheme 39).[80] *N*,*N*-Dimethyl-3-(phenylthio)-2-propenylamine also undergoes lithiation at the $sp^2$ carbon next to sulfur.

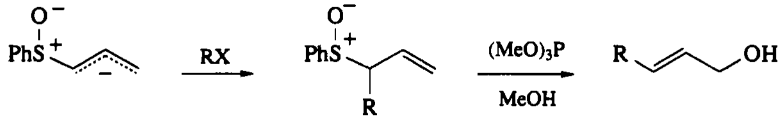

**(63)**

Scheme 37

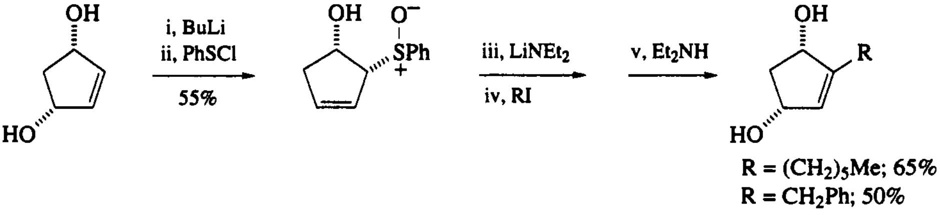

Scheme 38

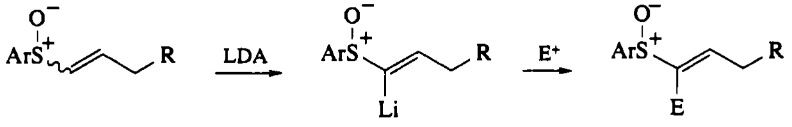

Scheme 39

Treatment of (+)-($R$)-allyl $p$-tolyl sulfoxide with LDA in THF at −78 °C followed by one equivalent each of HMPA and 2-cyclopentenone provides the 1,4-adduct in 90% yield with 96% *ee*.[81] The adduct is converted to (+)-($R$)-3-oxocyclopentaneacetic acid (Scheme 40). Lithiated ($E$)- and ($Z$)-2-alkenyl sulfoxides, derived from the corresponding allylic sulfoxides and LDA, undergo highly diastereoselective conjugate addition to cyclopentenone, producing *syn* and *anti* vinylic sulfoxides respectively (Schemes 41 and 42).[33] Therefore, the addition takes place at C-3 ($C_\gamma$) of the allylic sulfoxide anions. The reaction of lithiated allylic phenyl sulfides with cyclopentenones in THF at −78 °C proceeds with 1,2-addition and gives regioisomeric mixtures of vinylic and allylic sulfides, whereas the reaction in the presence of HMPA in THF at −78 °C involves conjugate addition to afford allylic sulfides arising from reaction at C-1 ($C_\alpha$) of the allylic anions.[82a] Lithiated allylic sulfones react in the same way as lithiated allylic sulfides in that HMPA causes kinetic conjugate addition to give allylic sulfones as mixtures of diastereomers.[82b]

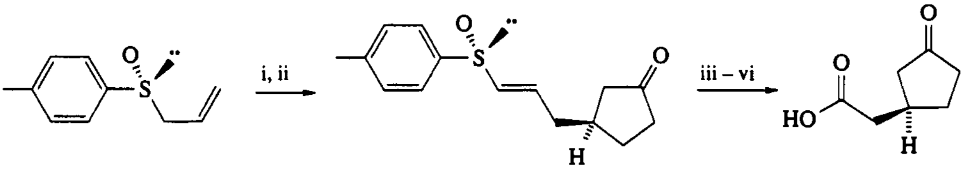

i, LDA; ii, 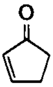 ; iii, Zn–AcOH; iv, HO(CH$_2$)$_2$OH, pyridinium tosylate; v, O$_3$;

vi, Bu$_4$NMnO$_4$, NaHSO$_3$–HCl

Scheme 40

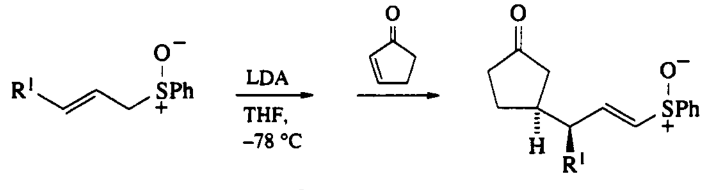

Scheme 41

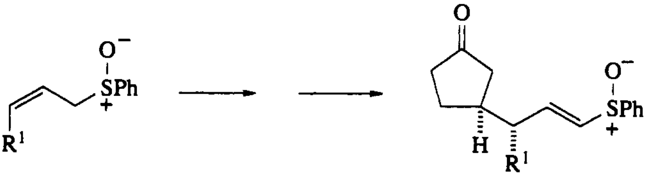

Scheme 42

Allylic sulfonyl carbanions react with electrophiles such as alkyl halides[83a] and aldehydes[83b] at the α-position. Although relatively strong bases like $Bu^nLi$ and LDA are usually used for deprotonation of allylic sulfur compounds, including sulfones, a catalytic two-phase system that consists of a concentrated aqueous NaOH solution and a quaternary ammonium salt can be used to generate allylic sulfonyl carbanions.[83a] 1,1-Dilithiated allyl phenyl sulfone (equation 20) reacts with excess benzaldehyde to afford the 1,3-(*E*)-diadduct, while 1,*ortho*-dilithiated allyl phenyl sulfone gives the 1,*ortho*-diadduct predominantly.[84] Other examples of sulfur-substituted allylic anions are summarized in Table 1.

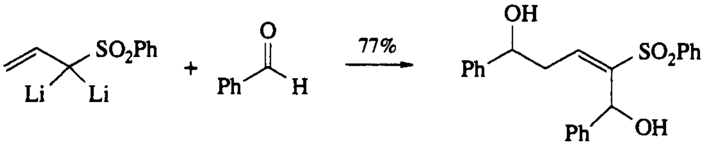

(20)

## 1.2.8 SELENIUM-SUBSTITUTED ALLYLIC ANIONS

Anion (**64**) generally reacts with carbonyl compounds at the γ-position, whereas it reacts with alkyl halides at the α-position. The triethylaluminum ate complex of (**64**) exhibits reversed regioselectivity: propanal and 2-methylpropanal give exclusively the α-adducts.[8] The *anti* isomers are produced predominantly. Organic halides and trimethylsilyl chloride do not react with the aluminum ate complex. 9,11-Dodecadien-1-yl acetate, a pheromone of *Diparopsis castanea*, is prepared by condensation of 9-oxonon-1-yl acetate *via* the ate complex (Scheme 43).

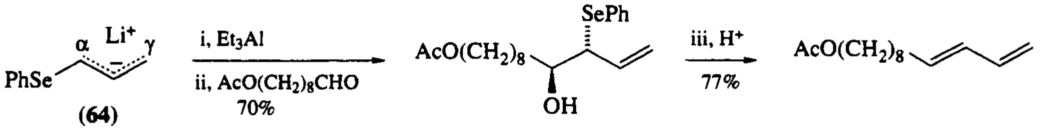

Scheme 43

The regioselectivity of (**64**) depends on the nature of the electrophile:[85] TMS-Cl produces an α:γ ratio of 82:18, but $PhSiMe_2Cl$ gives an α:γ ratio of 41:59. Furthermore, substituents on the allylic unit exert a strong influence on the regioselectivity; α-selectivity increases with substituents at the γ-position.

Although (**64**) is produced by treatment of the corresponding allyl selenide with LDA or lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF, treatment with *n*-butyl- or methyl-lithium leads to rapid transmetallation at −78 °C, giving the allyllithium and alkyl phenyl selenides.[86]

The selenium group can be removed under very mild oxidative conditions (Scheme 44).[87] Treatment of the anion of (**65**) with TMS-Cl gives another reagent that can be deprotonated and used with various electrophiles to prepare vinyl silyl ketones (Scheme 45). Therefore, (**65**) can be used as synthons of (**6**) and (**66**), like the 1,3-di(methylthio)allyl anions.[57]

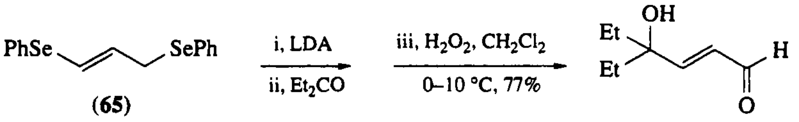

Scheme 44

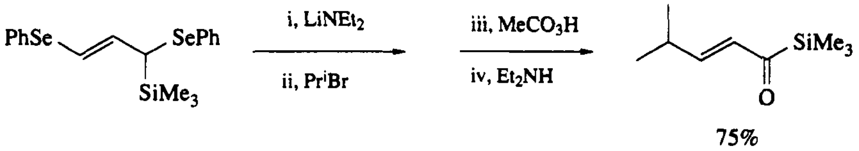
PhSe
SePh
SiMe3
i, LiNEt2
ii, PriBr
iii, MeCO3H
iv, Et2NH
SiMe3
O
75%

**Scheme 45**

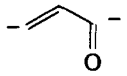

**(66)**

## 1.2.9 HALOGEN-SUBSTITUTED ALLYLIC ANIONS

The anions (**67c**)–(**67e**) are prepared by the low temperature transmetallation reactions of *n*-butyllithium with the corresponding allylic tin or lead compounds. The addition of (**67d**) to aldehydes and ketones proceeds with C—C bond formation at either terminus. Dialkyl ketones give the α-products, while benzaldehydes and benzophenone afford the γ-products. Aliphatic aldehydes, acetophenone and substituted acetophenones give both types of products.[88] The anion (**67e**) is not stable in solution even at –95 °C and cannot be preformed prior to its reaction with the desired substrate; (**67e**) may be generated by Li–Br exchange between *n*-butyllithium and 3,3-difluoro-3-bromopropene at –95 °C. When this preparation is performed in the presence of chlorosilanes, aldehydes, ketones, and esters, the α-products are obtained, often in good yields (Scheme 46).[89] Reactions of (**67c**) with TMS-Cl and benzaldehyde afford γ-adducts, whereas those with methyl iodide, acetophenone and pentanal produce α-adducts predominantly.[90] Anions (**67a**) and (**67b**) give α-alkylation products with aliphatic halides and TMS-Cl, but afford γ-adducts with iminium salts.[91]

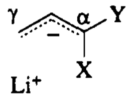

(**67a**) X = Cl, Y = H
(**67b**) X = Cl, Y = Me
(**67c**) X = Cl, Y = SiMe$_3$
(**67d**) X = Y = Cl
(**67e**) X = Y = F

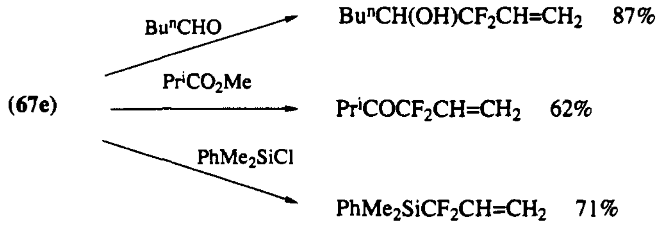
(67e)
BunCHO
PriCO2Me
PhMe2SiCl
BunCH(OH)CF2CH=CH2 87%
PriCOCF2CH=CH2 62%
PhMe2SiCF2CH=CH2 71%

**Scheme 46**

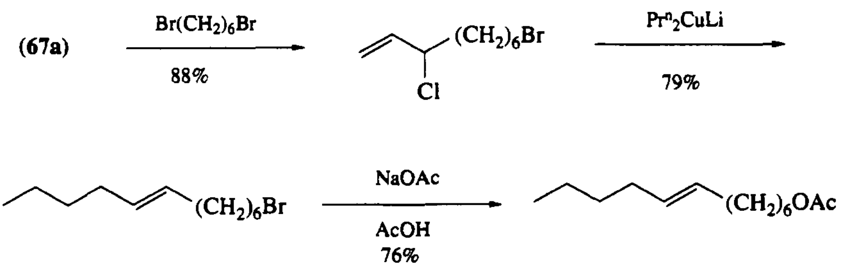
(67a)
Br(CH2)6Br
88%
(CH2)6Br
Cl
Prn2CuLi
79%
(CH2)6Br
NaOAc
AcOH
76%
(CH2)6OAc

**Scheme 47**

Treatment of (**67a**) with 1,6-dibromohexane gives the α-product, which is reacted with di-*n*-propylcuprate, resulting in formation of 7-dodecenyl bromide by $S_N2'$ displacement at the allylic position.[92] Conversion of this bromide into the corresponding acetate completes the synthesis of the *A. leucotreta* sex pheromone (Scheme 47).

## 1.2.10 ADDENDUM

The dithio-substituted cinnamyllithium (**68a**) reacts predominantly at the α-site with aldehydes and ketones in the presence of $BF_3·OEt_2$.[93] No selectivity is found when the reaction is carried out in the absence of $BF_3·OEt_2$. The reactions of (**68a**) and (**68b**) with three- to six-membered cyclic ethers take place exclusively at α-carbons in the presence of $BF_3·OEt_2$.[94]

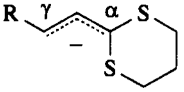

(**68a**) R = Ph
(**68b**) R = Me

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# 1.3

# Propargyl and Allenyl Organometallics

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## 1.3.1 INTRODUCTION

The chemistry of acetylene and allene has seen a phenomenal expansion during the past two decades. The alkynic and allenic intermediates employed in these studies are frequently assembled by the reaction of propargyl and allenyl organometallics.[1] Unfortunately, the utility of this methodology is limited by the tendency of propargylic metal derivatives to combine with carbonyl compounds (and other electrophiles) to produce both allenic and alkynic products. This regiochemical ambiguity arises from the fact that these species generally exist as an equilibrium mixture of allenic and propargylic organometallic derivatives.

## 1.3.2 PREPARATION OF PROPARGYL AND ALLENYL ORGANOMETALLICS

Organometallics of allenic structure are usually prepared by the reactions of metals with propargylic or allenic halides, or by metallation with alkyllithiums of the corresponding hydrocarbons.[1] The first preparation of allenylmagnesium bromide was accomplished by Prevost in 1950.[2,3] Allenylzinc bromide is easily obtained by the direct reaction of the metal with propargyl bromide at –100 °C in anhydrous tetrahydrofuran. The yield is greater than 80%.[4]

## 1.3.3 STRUCTURE AND PHYSICAL PROPERTIES

The structure of the propargyl Grignard reagent has been investigated over a considerable period of time, and it is known to be correctly represented by the allenic structure.[5] NMR studies on the Grignard reagents obtained from various propargylic bromides show in all cases a rapid equilibrium between the allenic and alkynic forms.[1a]

## 1.3.4 REGIOSELECTIVE REACTIONS

Reactions of the allenic Grignard derivative with most electrophiles give mainly or exclusively alkynic products. This behavior is rationalized by attack at the 3-position, which may be interpreted as an *S*E2′ (or *S*E*i*′) reaction of allenyl Grignard compounds. For example, organometallic derivatives combine with carbonyl compounds by the *S*E2′ pathway to afford homopropargylic and allenic alcohols from the corresponding allenyl or propargyl organometallics, respectively (Scheme 1). The product distribution of these reactions is determined by the position of the equilibrium between the two organometallic intermediates and by their relative rates of addition to carbonyl compounds.[1]

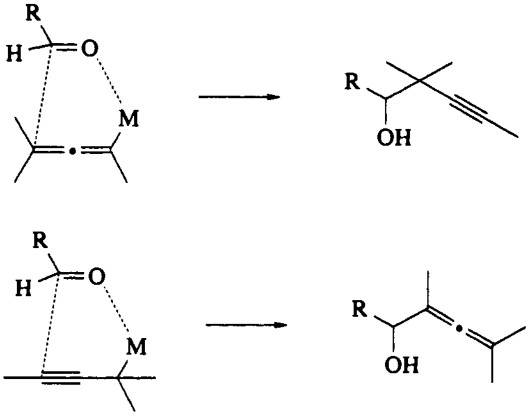

Scheme 1

### 1.3.4.1 Non-heteroatom-substituted Propargyl or Allenyl Organometallics

The organometallic reagent produced by reaction of trimethylsilylpropargyl bromide with aluminum amalgam in anhydrous tetrahydrofuran condenses readily with aldehydes and ketones to give allenic alcohols resulting from coupling α to the trimethylsilyl substituent (Scheme 2). Dramatically divergent behavior is observed with the zinc reagent, which gives the corresponding homopropargylic alcohols.[6]

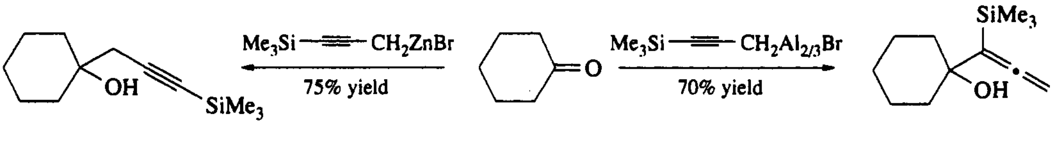

Scheme 2

Propargylic lithium alanates or lithium borates react with allylic halides or with carbonyl compounds in a regioselective manner to furnish 1,1-disubstituted allenes (Scheme 3).[7]

The reaction between alkyl halides and aluminum metal is the basis of the oldest method for the synthesis of organoaluminum compounds. For example, propargylic bromides react with aluminum in ether giving organoaluminum compounds that on treatment with acetals yield solely α-allenic ethers (equation 1).[8] However, the reaction of simple alkyl halides with aluminum metal requires a long reaction time.

Diallenyltin dibromide, prepared by treatment of propargyl bromide with metallic tin in the presence of metallic aluminum in dry tetrahydrofuran, reacts with aldehydes and ketones to afford β-alkynic alcohols selectively (Scheme 4).[9] This result is different from a previous report in which an α-allenic alcohol was found to be a major product from a propargyltin reagent prepared from a tin(II) halide.[10] On the other hand, β-alkynic and α-allenic alcohols were synthesized selectively by the reaction of aldehydes and ketones with bis(trimethylsilylpropargyl)tin diiodide using different solvent systems (Scheme 5).[10]

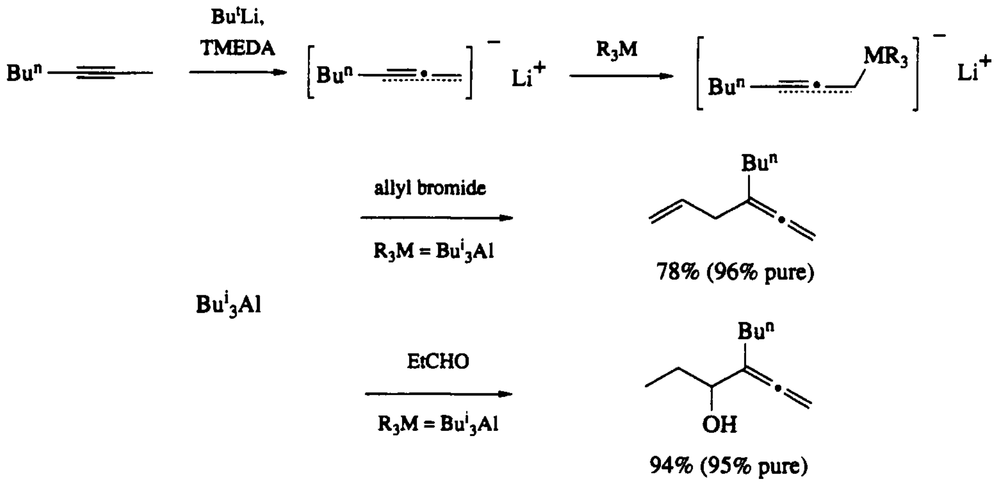
Bu^tLi,
TMEDA
Bu^n
Li^+
R3M
MR3
Li^+
allyl bromide
R3M = Bu^i3Al
Bu^i3Al
EtCHO
R3M = Bu^i3Al
Bu^n
Bu^n
OH
78% (96% pure)
94% (95% pure)

**Scheme 3**

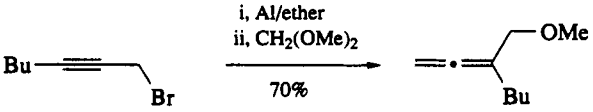
i, Al/ether
ii, CH2(OMe)2
70%
Bu
Br
OMe
Bu

(1)

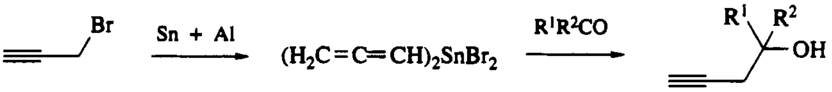
Br
Sn + Al
(H2C=C=CH)2SnBr2
R1R2CO
R1
R2
OH

| | |
|---|---|
| benzaldehyde | 94% |
| heptanal | 77% |
| cyclohexanone | 90% |

**Scheme 4**

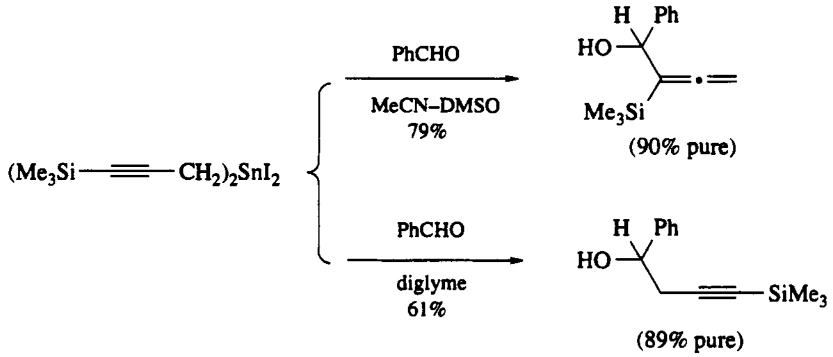
(Me3Si—≡—CH2)2SnI2
PhCHO
MeCN-DMSO
79%
PhCHO
diglyme
61%
H
Ph
HO
Me3Si
(90% pure)
H
Ph
HO
SiMe3
(89% pure)

**Scheme 5**

The ate complex of an organoborane reagent, formed by reaction of a trialkylborane with lithium chloropropargylide at –90 °C, undergoes a spontaneous anionotropic rearrangement in which one alkyl group migrates from boron to the adjacent carbon concomitant with an electron pair shift and loss of chloride to produce the allenic borane. Treatment of the allenic borane with an aldehyde results in an allenic–propargylic rearrangement to give, after oxidative work-up, a homopropargylic alcohol. However, if the allenic borane initially formed is allowed to warm, it rearranges to the thermodynamically more stable propargylic borane. This in turn reacts with the carbonyl group of an aldehyde, with boron transposition, to produce an α-allenic alcohol (Scheme 6).[11]

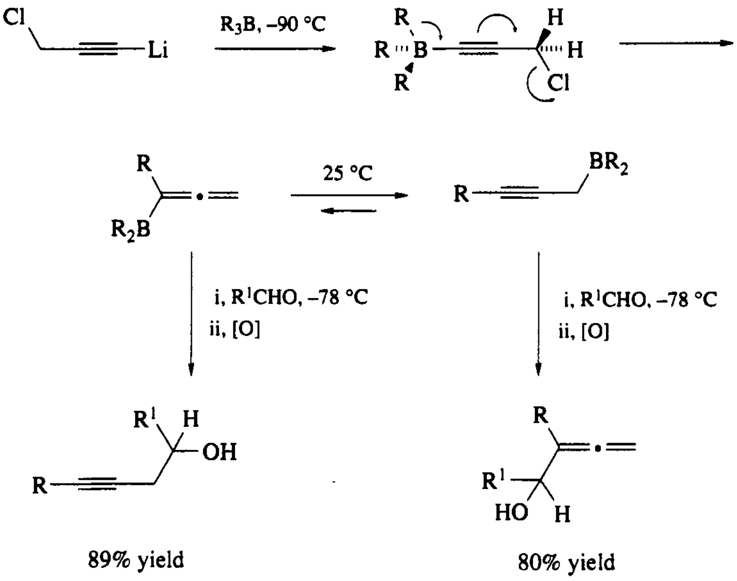

R = cyclopentyl, R$^1$ = ethyl

**Scheme 6**

Propargylic organoboranes derived from the corresponding lithium reagents react with aldehydes and certain ketones with high regioselectivity to give trimethylsilyl-substituted α-allenic alcohols (Scheme 7).[12]

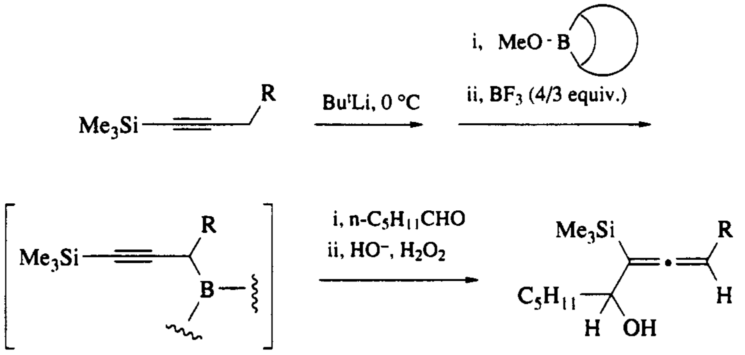

R = H; 82%
R = Pr$^n$; 78%
allene:alkyne = 88:12

**Scheme 7**

The high regioselectivity in the formation of α-allenic alcohols from boron reagents at low temperature is markedly different from that seen with the titanium reagent derived from 1-trimethylsilyl-1-butyne, in which exclusive formation of β-alkynic alcohols is observed.[47] This result was explained by a rapid exchange between the allenic and alkynic structures, as shown in equation (2). The alkynic structure is thermodynamically less stable and kinetically more reactive than that of the allenic form. At lower temperature, the rate of equilibrum becomes faster than the subsequent reaction with aldehydes and thus the alkynic species becomes the major reaction form.

The reaction of trimethylsilylallenes with aldehydes and ketones in the presence of titanium tetrachloride provides a regiocontrolled route to homopropargylic alcohols of a variety of substitution types. Thus, the addition of 1-alkyl-substituted trimethylsilylallenes to carbonyl compounds furnishes the desired alkynes directly, whereas reactions involving allenylsilanes initially produce mixtures of alkynes

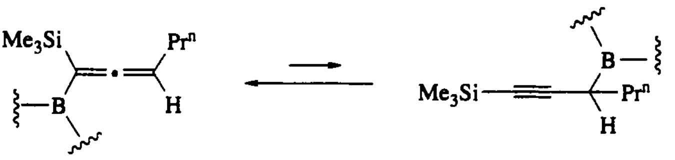

(2)

and trimethylsilylvinyl chloride derivatives. Exposure of these mixtures to the action of potassium fluoride in DMSO generates the desired homopropargylic alcohols (Scheme 8).[13]

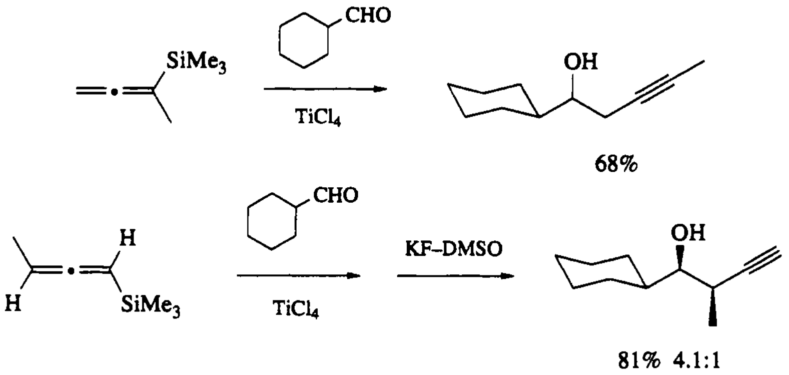

**Scheme 8**

The requisite allenylsilanes are prepared selectively by the method of copper-catalyzed addition or by direct silylation of the lithium derivative of 1,2-butadiene (Scheme 9).[14]

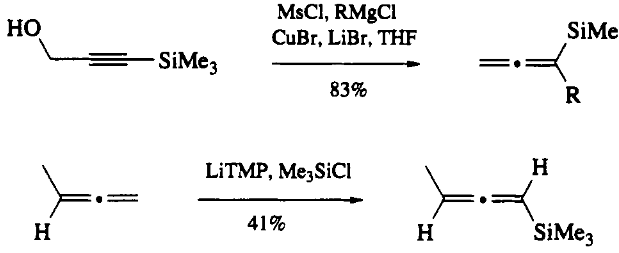

**Scheme 9**

Allenylsilanes combine with electron-deficient alkenes or alkynes regio- and stereo-selectively to afford highly substituted and functionalized cyclopentenes (Scheme 10). The [3 + 2] annulation reaction has been used for heteroannulation approaches to five-membered oxygen and nitrogen heterocycles.[15,16] One particularly useful application of the method is that readily available tropylium salts can function as allenophiles in a general [3 + 2] annulation route to substituted azulenes (equation 3).[17]

The condensation of propargyltrimethylsilane with acyl cyanide gives good yields of γ-allenic acyl cyanides (equation 4).[18]

Allenylsilver(I) compounds are prepared *in situ* by deprotonation of the allenic hydrocarbon with *n*-butyllithium and subsequent treatment with silver bromide (equation 5).[19] Allenylsilver compounds afford allenic derivatives when treated with a variety of electrophiles, without significant isomerization to the propargyl system (equation 6).[19,20] Reaction of the allenylsilver compound with carbon disulfide results in an interesting transformation to β,γ-unsaturated-γ-dithiolactones presumably by way of silver salts (Scheme 11).[19,21]

Convenient methods for the preparation of propargylic and allenic mercurials have been reported and their halogenation affords a route to the corresponding rearranged allenic and propargylic bromides and iodides (Scheme 12).[22] These organomercurials undergo facile acylation with rearrangement to afford the corresponding allenic and propargylic ketones in high yields (Scheme 13).[23]

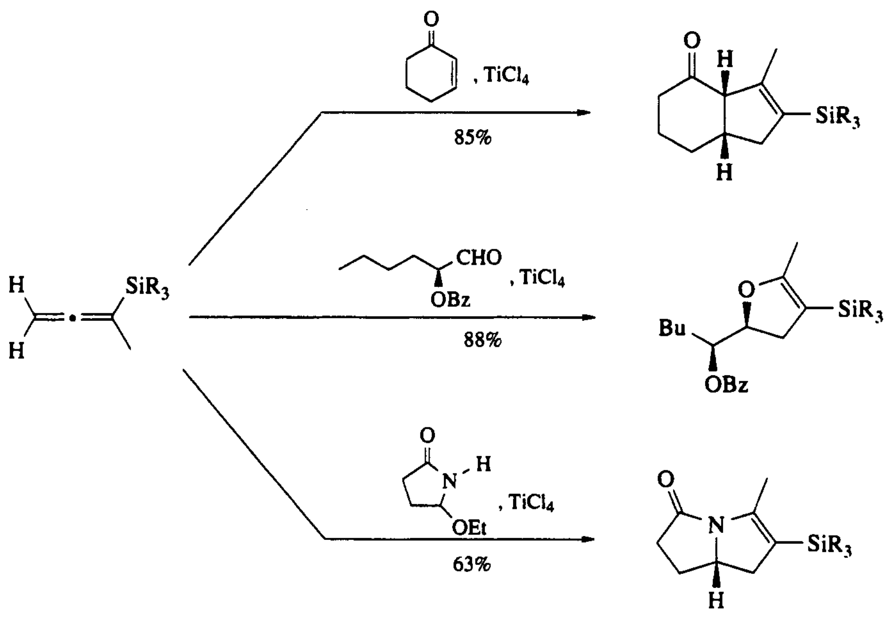

, TiCl4
85%
SiR3
, TiCl4
88%
Bu
OBz
, TiCl4
63%
H

**Scheme 10**

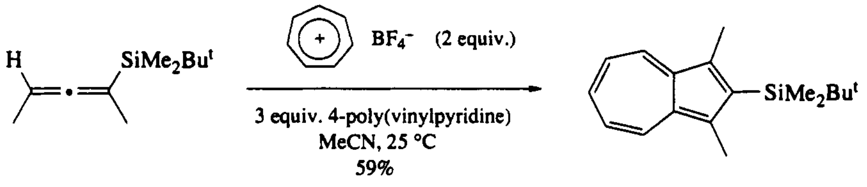

SiMe2Bu'
BF4- (2 equiv.)
3 equiv. 4-poly(vinylpyridine)
MeCN, 25 °C
59%

(3)

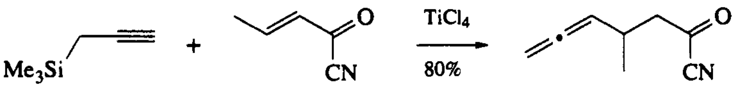

Me3Si
TiCl4
80%
CN

(4)

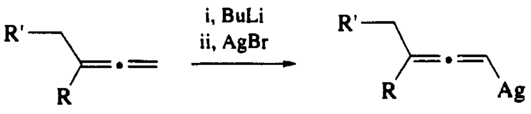

R'
R
i, BuLi
ii, AgBr
Ag

(5)

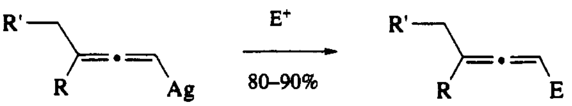

R'
R
Ag
E+
80–90%
E

(6)

| *E* | *Reagent* | *E* | *Reagent* |
|---|---|---|---|
| Br | BrCN | Br | NBS |
| MeS | $MeSSO_2Me$ | Cl | NCS |
| $CH_2{=}CHCH_2$ | Allyl bromide | $CO_2H$ | $CO_2$ |
| $Me_3Si$ | TMS-Cl | | |

Allenyllithium compounds can function as nucleophiles for the synthesis of quinolines. The reaction of 3-methyl-1,2-butadienyllithium with phenyl isothiocyanate in THF at –70 °C produces the allenyl thiocarboximidate, which can be thermally cyclized to 2-methylthioquinoline (Scheme 14).[24]

Reactions of allenyltin reagents with isoquinoline in the presence of chloroformate esters as acylating agents give 2-alkoxycarbonyl-1-(2-alkynyl)-1,2-dihydroisoquinolines in good to excellent yields (equation 7). Similarly, reactions with quinoline give 1-alkoxycarbonyl-2-(2-alkynyl)-1,2-dihydroquinolines exclusively.[25] Quinoxaline when treated with an excess of the allenylmagnesium bromide affords the di-

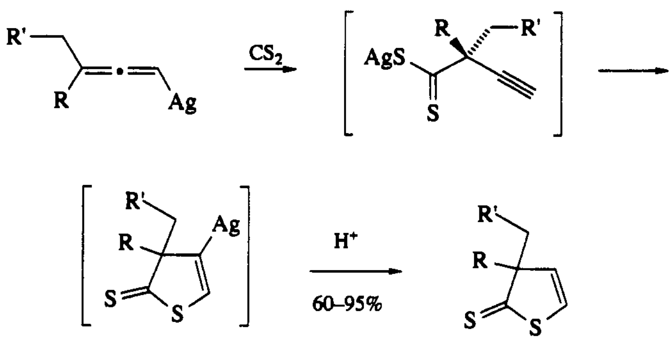
R'
R
Ag
$CS_2$
AgS
S
R
R'
R'
R
Ag
S
S
H⁺
60–95%
R'
R
S
S

**Scheme 11**

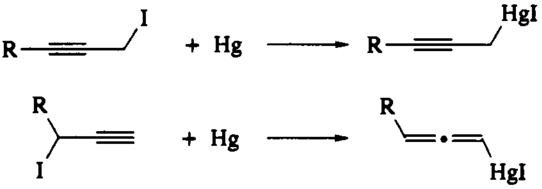
R
I
+ Hg
R
HgI
R
I
+ Hg
R
HgI

**Scheme 12**

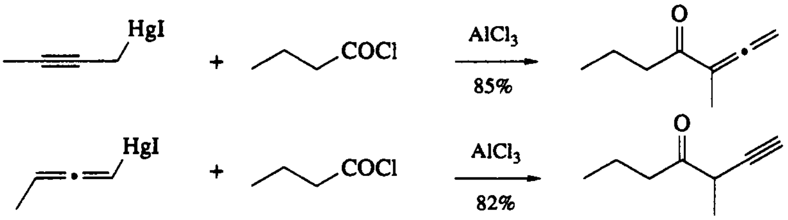
HgI
+
COCl
$AlCl_3$
85%
O
HgI
+
COCl
$AlCl_3$
82%
O

**Scheme 13**

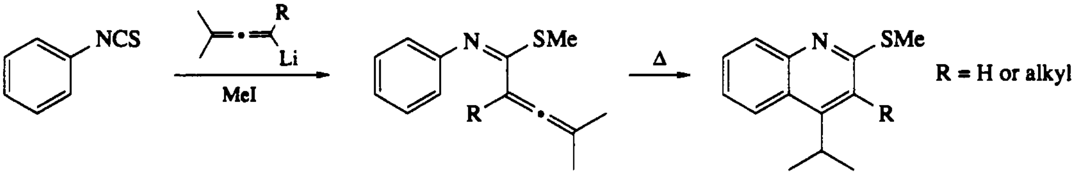
NCS
R
Li
MeI
N
SMe
R
Δ
N
SMe
R
R = H or alkyl

**Scheme 14**

methylpropargyldihydroquinoxaline, accompanied by small amounts of the bis-addition product.[26] Similarly, 2-chlorobenzoxazole reacts rapidly and cleanly with the Grignard reagents from propargyl bromide, 1-methylpropargyl bromide and 1,1-dimethylpropargyl bromide, giving high to excellent yields of 2-allenylbenzoxazole, 2-(1-methylpropargyl)benzoxazole and 2-(1,1-dimethylpropargyl)benzoxazole, respectively. Thus, the substitution pattern influences the allene/alkyne product distribution significantly.[27]

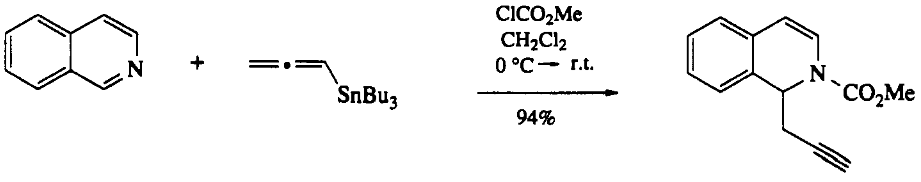
N
+
$SnBu_3$
$ClCO_2Me$
$CH_2Cl_2$
0 °C → r.t.
94%
N
$CO_2Me$

(7)

Nikam and Wang have reported a related boron reagent addition to C=N bonds. Reactions were carried out by adding imines to the organoboranes derived from 1-trimethylsilyl-1-alkynes. After oxidative work-up, the condensation adducts are isolated. The allenic/alkynic distribution is strongly influenced by the structures of both the imine and the organoborane reagent. Since imines are much less reactive toward the boron reagent than aldehydes, the regioselectivity of this reaction is simply determined by the difference of the energy barriers of the two subsequent condensation reaction pathways (Scheme 15).[28]

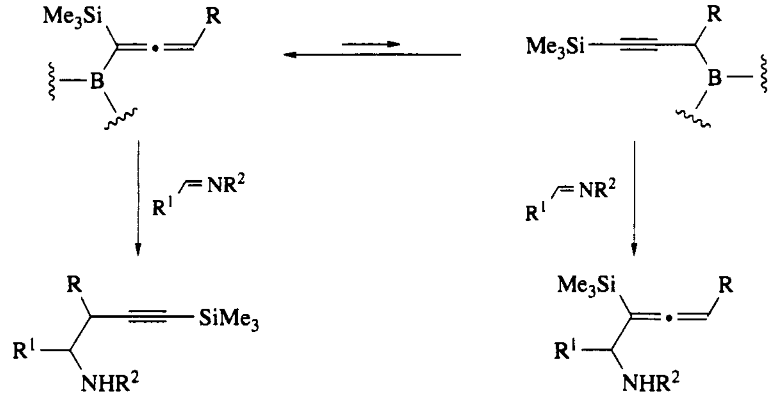

| *R* | *R¹* | *R²* | *Alkyne:allene* |
|---|---|---|---|
| H | Ph | $Pr^n$ | <1:99 |
| $Pr^n$ | Ph | $Pr^n$ | <1:99 |
| $Pr^n$ | Ph | Ph | >99:1 |
| $Pr^n$ | $Pr^i$ | c-Hexyl | >99:1 |

**Scheme 15**

### 1.3.4.2 Heteroatom-substituted Propargyl and Allenyl Organometallics

Heterosubstituted allenes are versatile synthetic intermediates. Direct substitution of a heteroatom on the allene confers upon the system an electronic bias that allows the molecule to be deprotonated easily using an organolithium reagent, and also permits regioselective reaction with carbonyl compounds.

The reaction of α-lithio-α-methoxyallene with cyclopentanone gives an allenic carbinol. Treatment of this material with potassium *t*-butoxide in *t*-butyl alcohol containing 18-crown-6 heated at reflux for 15 h provides the dihydrofuran derivative, which, after acid hydrolysis, gives a spirodihydrofuranone. The method has been utilized as an iterative process for the synthesis of helical molecules (Scheme 16).[29]

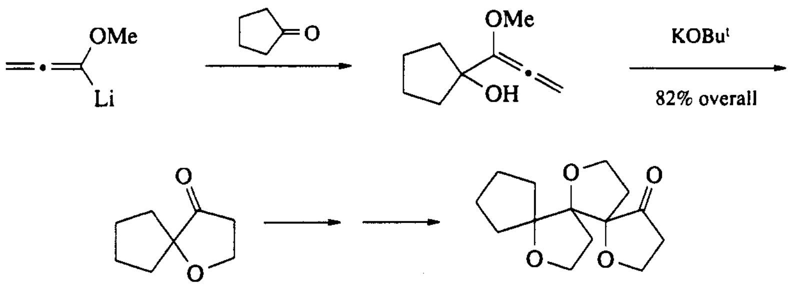

**Scheme 16**

Vinyl silyl ketones have been prepared from alkoxyallenes as shown in Scheme 17. Deprotonation and silylation afford the corresponding allenylsilanes, which are hydrolyzed to vinyl silyl ketones.[30,31,32] The regioisomeric organoaluminum reagents react with aldehydes to give furans after acid hydrolysis (Scheme 18).[33]

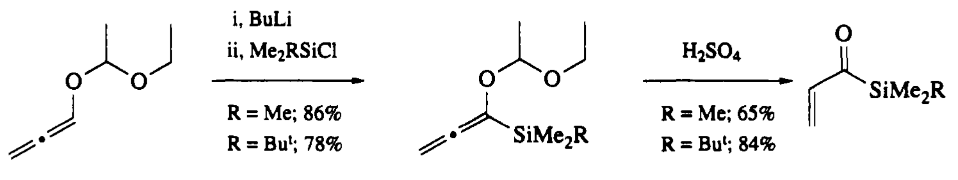

Scheme 17

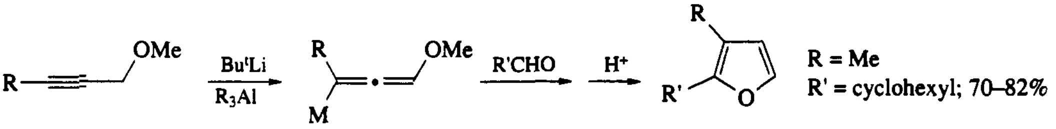

Scheme 18

The alkoxyallene adducts of *O*-trimethylsilyl hydroxymethylene ketones undergo a facile acid-catalyzed cyclization to produce functionalized cyclopentanones. Of various allene ether derivatives, methoxymethoxyallene gave the most satisfactory results (Scheme 19).[34]

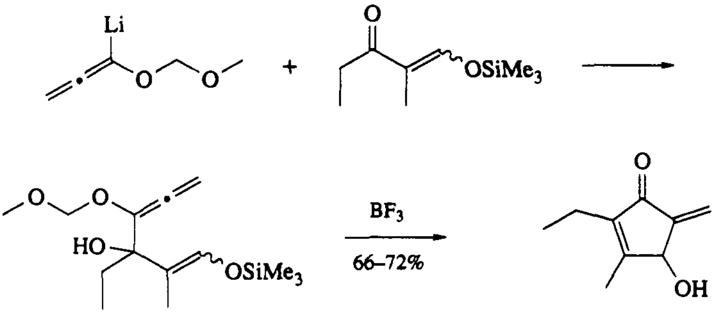

Scheme 19

The intramolecular addition of propargylic silanes to cyclic enones proceeds smoothly under mild conditions, yielding functionalized exocyclic allenes (Scheme 20). This useful process has been reviewed by Schinzer.[35]

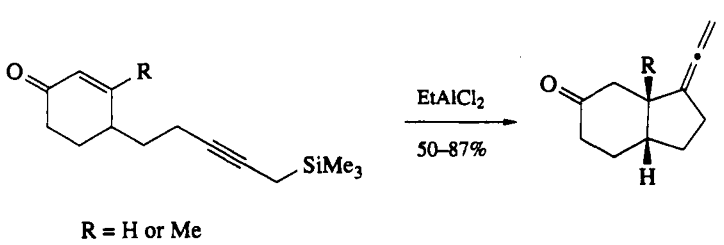

Scheme 20

Reaction of propargyltrimethylsilane with ω-ethoxylactams under the influence of boron trifluoride affords ω-allenyllactams.[36] The intramolecular version of this process gives rise to bridged azabicyclic systems containing the uncommon α-allenic amide functionality (equation 8).[37]

On treatment with LDA, methyl 1-trimethylsilylallenyl ether isomerizes to methyl 3-lithio-1-trimethylsilylpropargyl ether, which can be used efficiently for the preparation of 1-methoxy-1-alken-3-ynes and 2-methoxy-2,5-dihydrofurans. The isomerization in the first step may proceed through a sequence of deprotonation and protonation processes with LDA and diisopropylamine, respectively, since it does not take place under the influence of butyllithium (Scheme 21).[38]

A 3-*t*-butyldimethylsiloxyallenyllithium reagent generated quantitatively from the 1-silylpropargyl alcohol can be used as a synthetic equivalent of an α,β-unsaturated ketone having nucleophilic character at

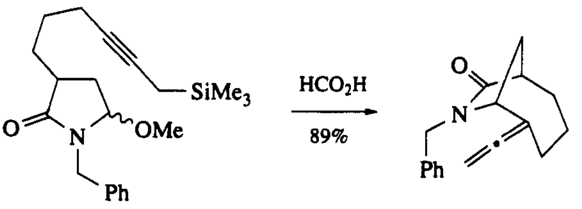
SiMe3
O
N
OMe
Ph
HCO2H
89%
O
N
Ph

(8)

its β-position (Scheme 22). Both alkylation with alkyl halides and addition to carbonyl compounds proceed in good yields.[39]

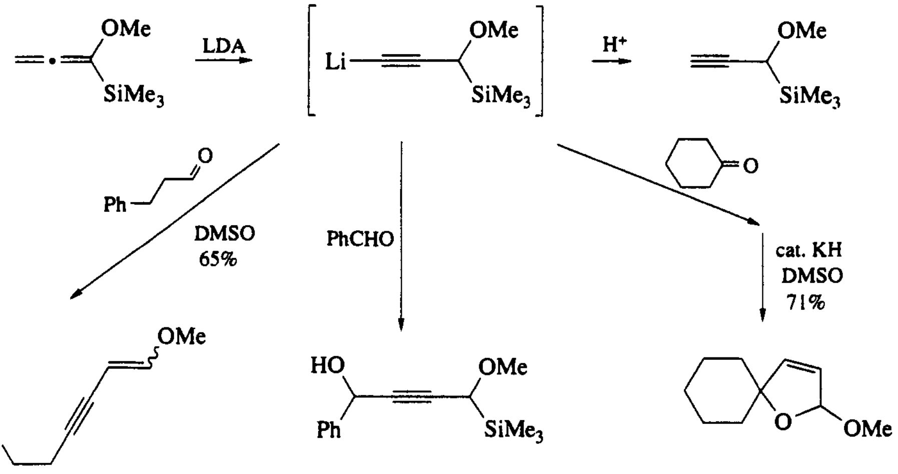
OMe
SiMe3
LDA
Li
OMe
SiMe3
H+
OMe
SiMe3
O
Ph
DMSO
65%
PhCHO
O
cat. KH
DMSO
71%
OMe
Ph
HO
OMe
Ph
SiMe3
O
OMe

Scheme 21

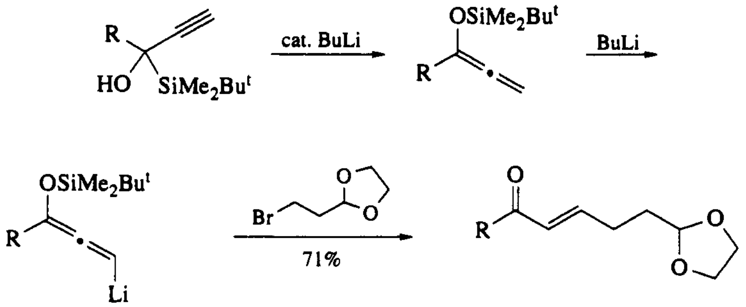
R
HO
SiMe2Bu$^t$
cat. BuLi
OSiMe2Bu$^t$
R
BuLi
OSiMe2Bu$^t$
R
Li
O
Br
O
71%
O
R
O
O

Scheme 22

3,3-Dialkyl-1-lithio-1-phenylthioallenes add efficiently to ketones only on warming to −20 °C or above; the adducts are readily cyclized by acid, or several other electrophiles, to produce highly substituted 2,5-dihydrofurans (Scheme 23).[40]

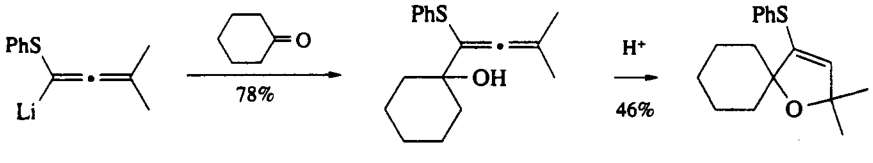
PhS
Li
O
78%
PhS
OH
H+
46%
PhS
O

Scheme 23

2-Ethynyl-1,3-dithiane and several of its silyl and lithio derivatives have been reported (Scheme 24). The α-lithio-γ-silyl derivative is a particularly useful carbon nucleophile giving efficient α-alkylation with a variety of electrophiles ($H_2O$, $D_2O$, $Me_3SiCl$, MeI, allyl chlorides, $R_2CO$ and RCHO).[41]

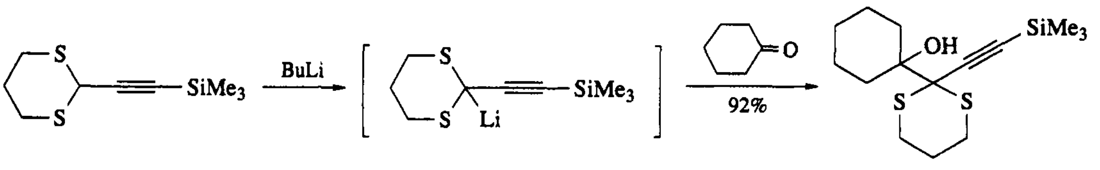

Scheme 24

Treatment of a solution of γ,γ-dimethylallenyl phenyl sulfone with one-half equivalent of *n*-butyllithium at 0 °C results in dimerization of the substrate. However, if the same reaction is carried out at reflux temperature for 6 h, the cyclodimer is obtained (Scheme 25).[42]

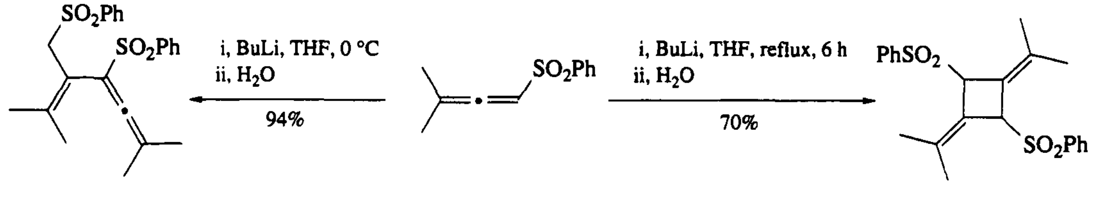

Scheme 25

## 1.3.5 DIASTEREOSELECTIVE REACTIONS

The mechanism of the condensation between allenyl organometallics and carbonyl groups is thought to be a cyclic *S*E*i*′ (or *S*E2′) process. In the reaction of aldehydes with 1,2-butadienylmagnesium halides, the *anti*:*syn* product ratio depends on the size of substituent group of the aldehyde and may be rationalized as shown in (1).[43]

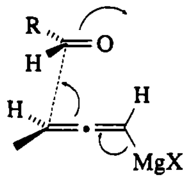

(1)

| *R* | *threo*:*erythro* |
|---|---|
| Me | 76:24 |
| Et | 82:18 |
| Pr$^i$ | 90:10 |
| Bu$^t$ | 95:5 |

The stereoselectivity of the reaction is also sensitive to the metal and to the bulk of the substituent on the allene (Scheme 26). For example, the lithium anion of 1,3-bis(trimethylsilyl)propyne reacts with aliphatic aldehydes and ketones to give a mixture of (*Z*)- and (*E*)-1,3-enynes in a ratio of about 1:3. Use of the anion of 3-*t*-butyldimethylsilyl-1-trimethylsilylpropyne results in a ratio of approximately 8:1. The corresponding allenylmagnesium reagent reacts with aldehydes to give enynes with exclusive formation of the (*Z*)-isomer (50:1).[44] High (*Z*)-selectivity is also observed in reactions of the anion derived from 1,3-bis(triisopropylsilyl)propyne, in which the (Z):(E) ratio is about 20:1.[45] The reagent apparently prefers the allenic structure and reacts *anti* selectively, the adduct undergoing a *syn* stereospecific elimination under the reaction conditions.

Similarly, the corresponding titanium reagents react with aldehydes in a one-pot procedure to provide (*Z*)-isomers exclusively (Scheme 27).[46,47]

Allenylzinc reagents react with aldehydes in a highly regio- and diastereo-selective manner to produce *anti* homopropargylic alcohols with diastereomeric purities of 96–99% (Scheme 28).[48]

Metallation of 1-methoxy-2-butyne with *n*-butyllithium at –78 °C, followed by the addition of one equivalent of zinc chloride, generates the very reactive and unisolable organozinc intermediate. Reaction of this zinc reagent with cyclohexenone affords the alkynic alcohol in 95% yield as a 65:35 mixture of diastereomers. Subsequent reduction of the triple bond provides either the *trans* alkene or the *cis* alkene, depending on the reaction conditions. A modified oxy-Cope rearrangement thus provides the diastereomeric ketones, which have been used for the synthesis of juvabione (Scheme 29).[49]

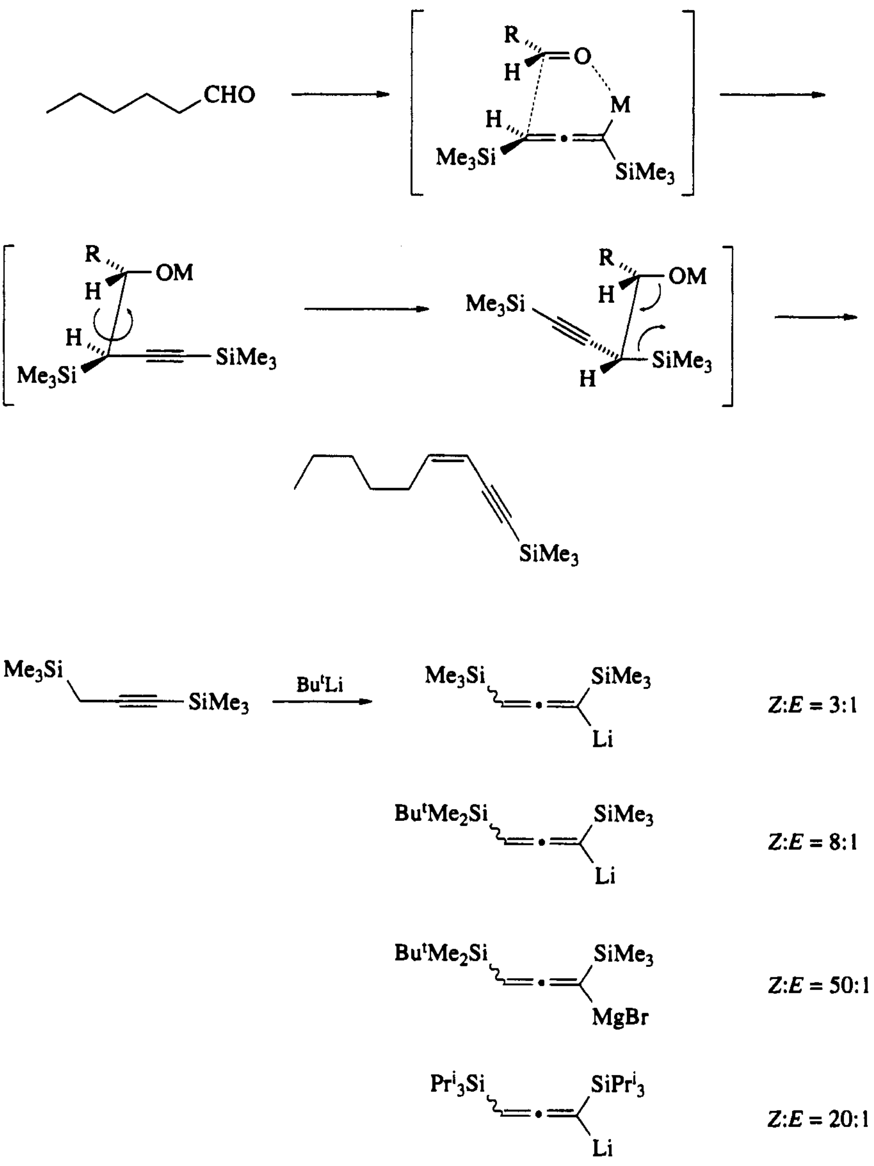
CHO
R
H
O
M
H
Me3Si
SiMe3
OM
SiMe3
Bu^tLi
Li
Z:E = 3:1
Bu^tMe2Si
Z:E = 8:1
MgBr
Z:E = 50:1
Pr^i3Si
SiPr^i3
Z:E = 20:1

**Scheme 26**

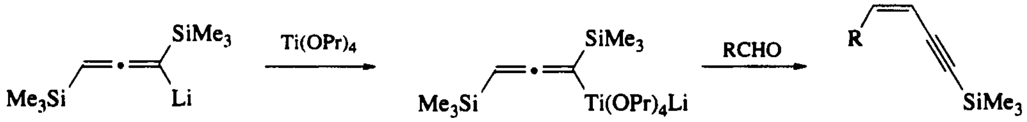
SiMe3
Me3Si
Li
Ti(OPr)4
Ti(OPr)4Li
RCHO
R

**Scheme 27**

The propargyltitanium reagents derived from 2-alkynes condense with aldehydes to give α-allenyl alcohols, whereas the allenyltitanium reagents generated from 3-alkynes give β-alkynic alcohols. In both cases, the reactions proceed with high regioselectivity. The observed site selectivity may be explained as follows. Titanation of the propargylic anion takes place with extremely high regioselectivity to produce allenic or alkynic titanium derivatives, depending on the substitution pattern of the original alkynes. Indeed, the IR spectrum of the titanium reagent in THF derived from 1-trimethylsilyl-1-butyne shows a strong absorption at 1898 $cm^{-1}$, characteristic of the allenic structure, while that of the reagent derived

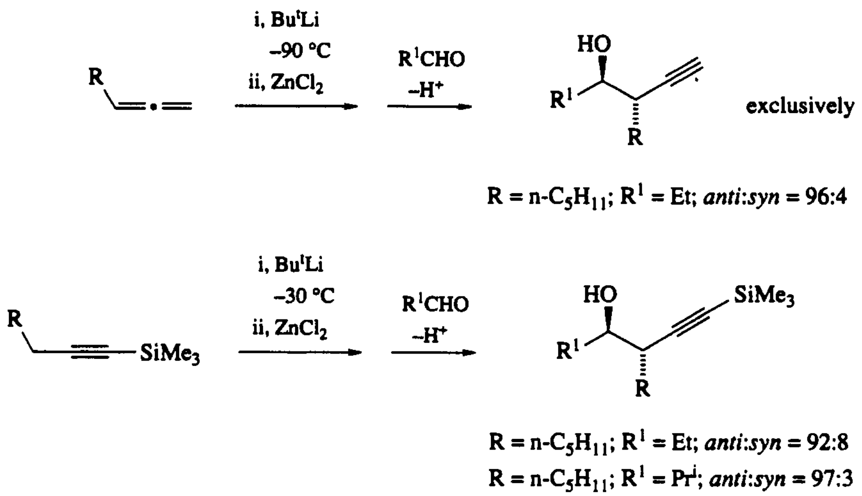
R
i, Bu$^t$Li
−90 °C
ii, ZnCl$_2$
R$^1$CHO
−H$^+$
HO
R$^1$
R
exclusively
R = n-C$_5$H$_{11}$; R$^1$ = Et; *anti*:*syn* = 96:4
R
SiMe$_3$
i, Bu$^t$Li
−30 °C
ii, ZnCl$_2$
R$^1$CHO
−H$^+$
HO
SiMe$_3$
R$^1$
R
R = n-C$_5$H$_{11}$; R$^1$ = Et; *anti*:*syn* = 92:8
R = n-C$_5$H$_{11}$; R$^1$ = Pr$^i$; *anti*:*syn* = 97:3

Scheme 28

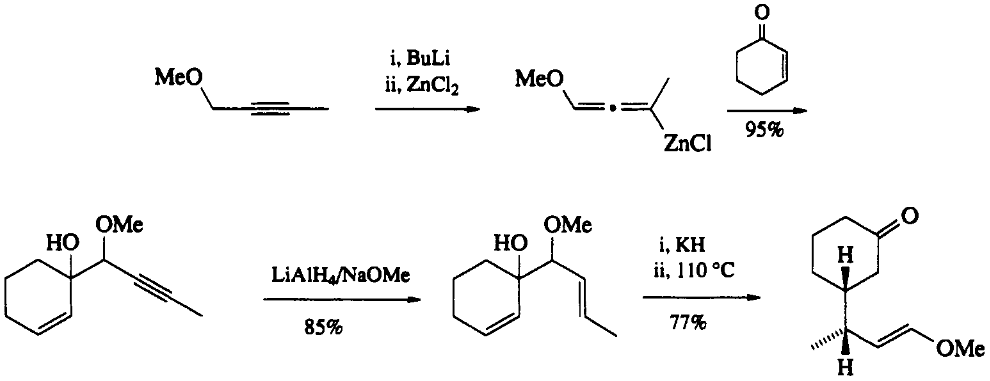
MeO
i, BuLi
ii, ZnCl$_2$
MeO
ZnCl
O
95%
HO
OMe
LiAlH$_4$/NaOMe
85%
HO
OMe
i, KH
ii, 110 °C
77%
O
H
H
OMe

Scheme 29

from 1-trimethylsilylpropyne reveals only alkynic absorption at 2092 cm$^{-1}$, in accord with the foregoing speculation. Subsequent reaction with the electrophile then occurs in the usual $S_Ei'$ (or $S_E2'$) manner (Scheme 30).[46,47]

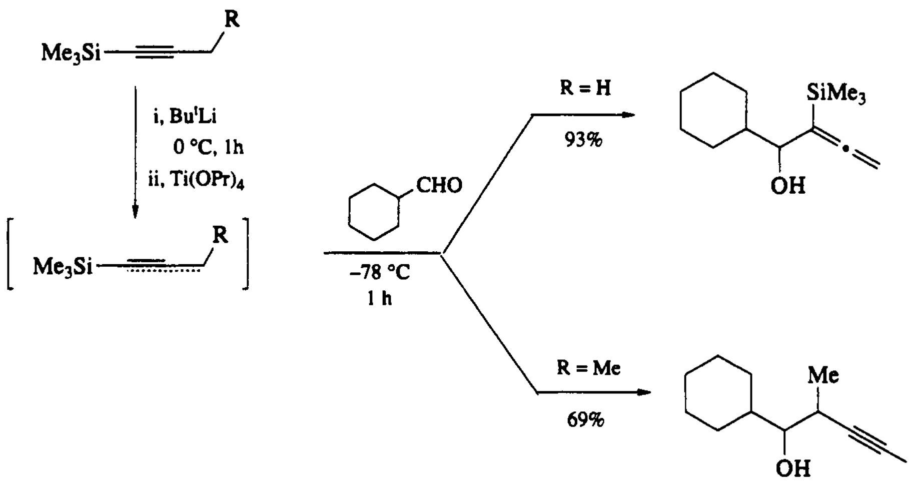
R
Me$_3$Si
i, Bu$^t$Li
0 °C, 1h
ii, Ti(OPr)$_4$
R
Me$_3$Si
CHO
−78 °C
1 h
R = H
93%
SiMe$_3$
OH
R = Me
69%
Me
OH
SiMe$_3$

Scheme 30

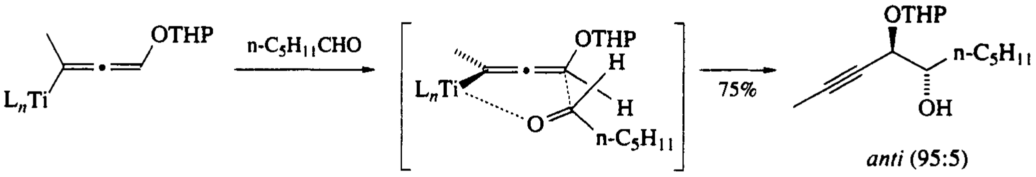

Scheme 31

The titanium reagents add to aldehydes to give *anti* vicinal diols. For example, the allenyltitanium reagent generated from 1-alkyl-1-butyne derivatives gives *anti* β-alkynic alcohols with high diastereoselectivities (Scheme 31). This method has been applied in a stereocontrolled synthesis of (±)-asperlin and related compounds (Scheme 32).[50]

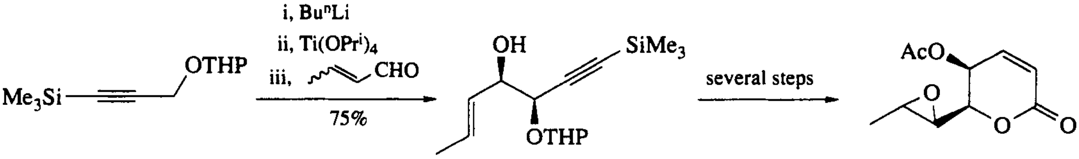

Scheme 32

*N*,*N*-Diisopropyl-2-alkynyl carbamates are deprotonated by *n*-butyllithium to form lithium compounds. After exchange of the cation, the resulting titanium reagents add highly regio- and diastereo-selectively to aldehydes with the formation of *syn* allenyl alcohols (Scheme 33). Thus, in contrast to metallated 2-alkynyl ethers, the titanium reagent exhibits high γ-regioselectivity due to the powerful chelating carbamoyl group.[51]

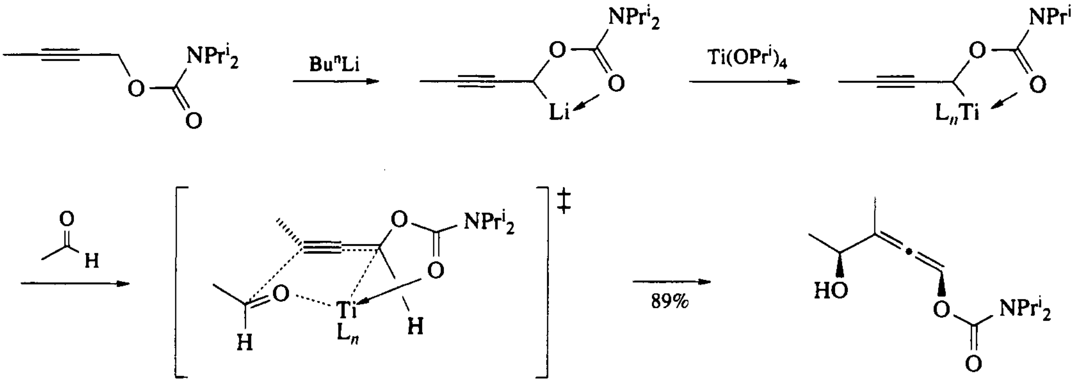

allene:acetylene = >95:5 *syn*:*anti* = >95:5

Scheme 33

The carbamate-stabilized allenyl anion was shown to have moderate configurational stability. Thus, when the 4-benzoate derivative of the allenyl compound is lithiated, 1,4-elimination of lithium benzoate occurs to form the very reactive 3-alken-1-ynyl carbamates stereospecifically (Scheme 34).[52]

Information about the degree of configurational stability of allenyltitanium compounds has been provided by Hoffmann and Hoppe (Scheme 35).[53] Racemic allenyltitanium reagent (**3**) is prepared by sequential treatment of 3-methoxy-1,2-butadiene (**2**) with *n*-butyllithium and titanium tetraisopropoxide. In the reaction of the racemate with one equivalent of (*S*)-(**4**) or its racemate, products (**5**)–(**8**) are formed in 70–90% total yield in the ratios shown in Scheme 35. Since the product ratios from the two experiments are different, the equilibrium between the enantiomers of (**3**) must be slow compared to the rate of reaction of (**3**) with (**4**). Thus, (*S*)-(**3**) leads to (**5**) + (**6**) and (*R*)-(**3**) leads to (**7**) + (**8**) (*i.e.* 51:49). From experiment B, the combinations (*S*)-(**3**) + (*S*)-(**4**) and (*R*)-(**3**) + (*R*)-(**4**) are shown to react considerably more rapidly than that of the (*R*)/(*S*) pairs (mutual kinetic resolution).[54]

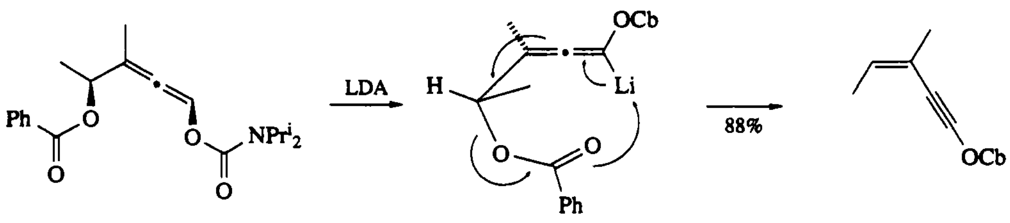
Ph
O
O
O
O
NPr$^i_2$
LDA
H
OCb
Li
O
O
Ph
88%
OCb

**Scheme 34**

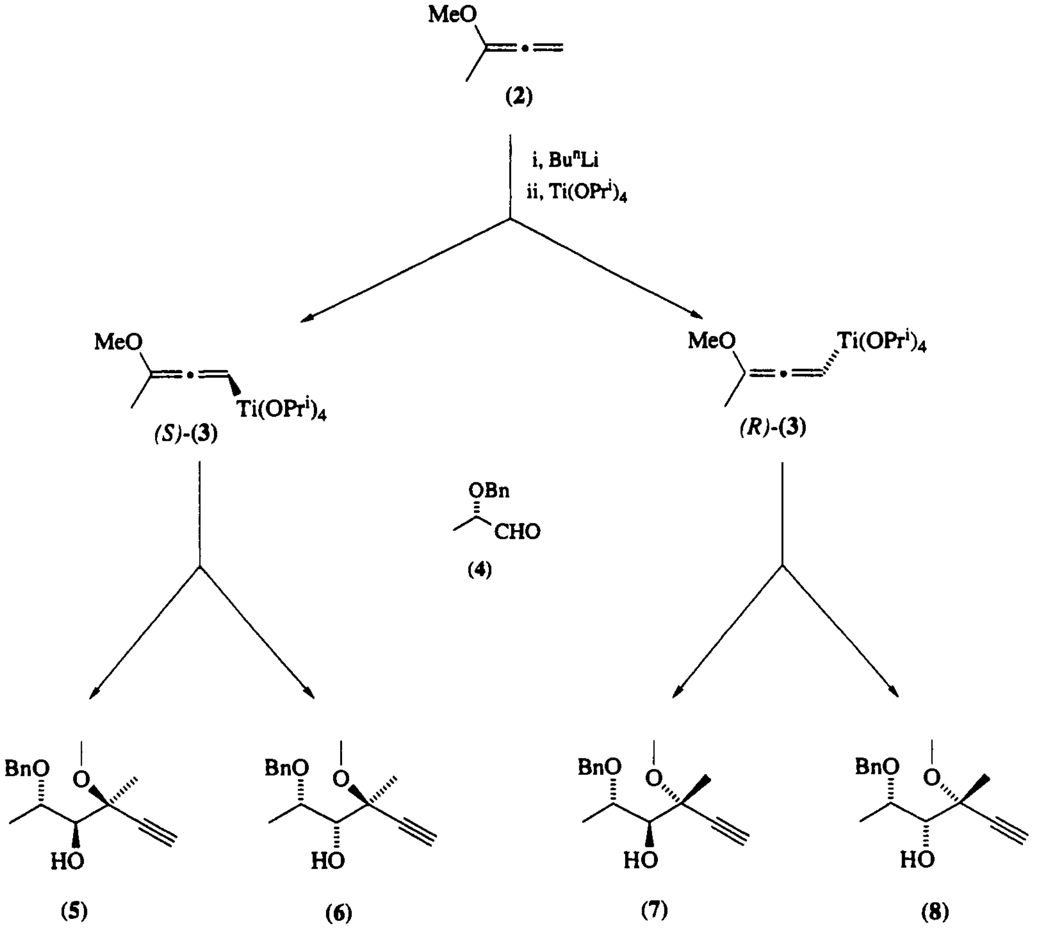
MeO
(2)
i, Bu$^n$Li
ii, Ti(OPr$^i$)$_4$
MeO
Ti(OPr$^i$)$_4$
(S)-(3)
MeO
Ti(OPr$^i$)$_4$
(R)-(3)
OBn
CHO
(4)
BnO
HO
(5)
BnO
HO
(6)
BnO
HO
(7)
BnO
HO
(8)

| A: *(S)*-(4) | (5) | | (6) | | (7) | | (8) |
|---|---|---|---|---|---|---|---|
| | 50 | : | 1 | : | 35 | : | 14 |
| **B**: rac-(4) | *rac*-(5) | | *rac*-(6) | | *rac*-(7) | | *rac*-(8) |
| | 92 | : | < 1 | : | 6 | : | 2 |

**Scheme 35**

The reaction between the imines and allenic titanium reagents give the *anti* adducts with high stereoselectivity (Scheme 36). The observed stereoselectivity can be explained by a cyclic transition state in which the metal coordinates to the lone pair of the nitrogen atoms.[55]

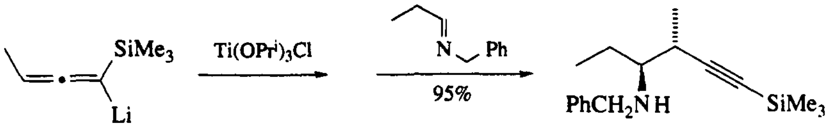
SiMe3
Li
Ti(OPr^i)3Cl
N Ph
95%
PhCH2NH
SiMe3

*anti*:*syn* = >99:1

Scheme 36

## 1.3.6 ENANTIOSELECTIVE REACTIONS

Diastereoselective carbon–carbon bond formation at the α-position to the amine nitrogen may be accomplished as shown in Scheme 37. Propargylamine is converted into the silylated amidine, which is metallated with *n*-butyllithium. After alkylation, the metallation and alkylation are repeated with a second alkyl halide to obtain the fully alkylated derivative. Thus, optically active α-substituted propargylamines and amino acids are obtained by hydrolysis of the amidine function and oxidative cleavage.[56]

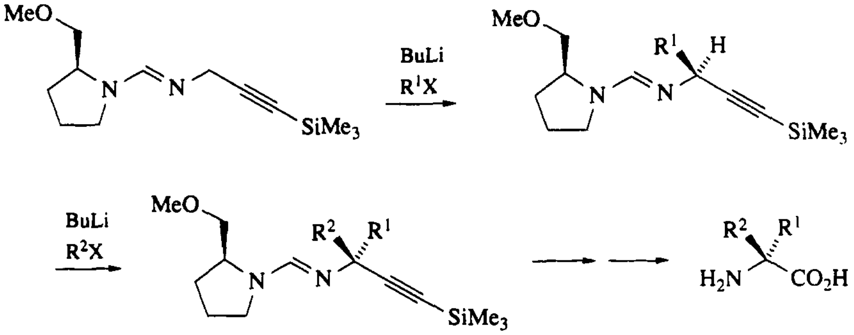
MeO
N
N
SiMe3
BuLi
R1X
MeO
R1
H
SiMe3
BuLi
R2X
MeO
R2
R1
SiMe3
R2
R1
H2N
CO2H

$R^1$ = Me; $R^2$ = $CH_2Ph$; 84% *ee*
$R^1$ = $CH_2Ph$; $R^2$ = Me; 67% *ee*

Scheme 37

Treatment of the propargyl Grignard reagent with trimethyl borate followed by acidic work-up gives the crystalline allenylboronic acid.[1] Reactions of this material with cyclohexanecarbaldehyde in the presence of various tartrate esters gives the homopropargyl alcohols. The greatest enantioselectivity was found with the tartrates of 2,4-dimethyl-3-pentanol or cyclododecanol (Scheme 38).[57,58]

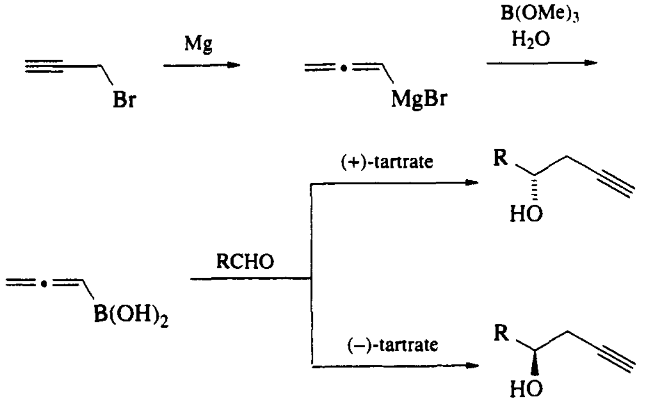
Br
Mg
MgBr
B(OMe)3
H2O
B(OH)2
RCHO
(+)-tartrate
R
HO
(−)-tartrate
R
HO

2,4-dimethyl-3-pentyl tartrate
R = cyclohexyl ⟹ 89% yield; 99% *ee*

Scheme 38

Reaction of allenylboronic acid with β-hydroxy ketones in anhydrous ether at room temperature in the presence of 5A molecular sieves for 20 h, followed by treatment with basic hydrogen peroxide, yields 1,3-diols with high 1,3-asymmetric induction (>99%) (equation 9).[59]

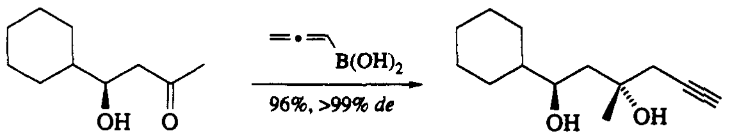

(9)

Reaction of allenylsilanes with the easily accessible iron tricarbonyl complex (**9**) in the presence of $TiCl_4$ at –78 °C gives the homopropargyl alcohol in 65% yield, and leads to only the Ψ-*endo* derivative with the (*R*)-configuration at the secondary alcohol function (Scheme 39). It is noteworthy that $Fe(CO)_3$ acts here as an efficient protecting group.[60]

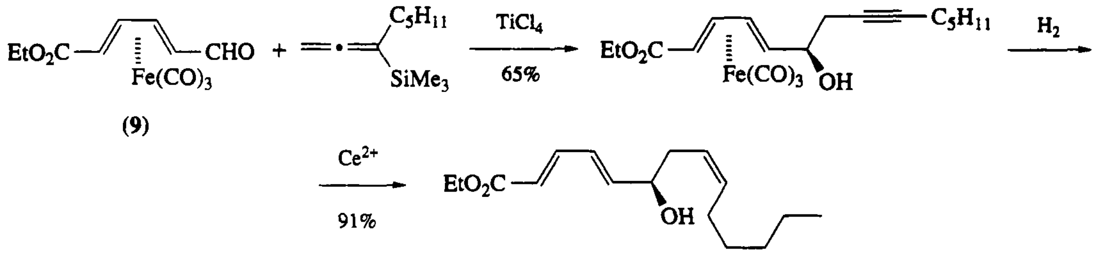

Scheme 39

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# 1.4

# Formation of Enolates

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## 1.4.1 INTRODUCTION

Enolates, or oxyallyl anions, are versatile reagents for the formation of α-substituted carbonyl compounds and are therefore important intermediates for the synthesis of complex molecules. The stereochemical outcome of an enolate reaction often depends on the geometry of the enolate and therefore the selective formation of enolates is a key step in many bond-forming processes.[1]

The counterion of an enolate has a pronounced influence on competing transition states of enolate reactions. The effect is often the result of cation chelation by the carbonyl oxygen atom and one or more additional basic portions of the reactants. For example, alkylation of chiral enolates may lead to more or less diastereomerically pure products and selectivity often depends on the countercation. The importance of the countercation in controlling enolate reaction product distributions requires that the synthetic chemist has at hand stereoselective methods for the preparation of enolate anions with a wide variety of counterions. This chapter is divided into several sections. The 10 following sections describe important current methods for preparing Li, Mg, B, Al, Sn, Ti, Zr, Cu, Zn and other transition metal enolates.

Enolates occur commonly in only two forms: the metal may be found either closer to the oxygen or closer to the carbon atom. Groups I, II and III enolates exist as O–metal tautomers. These strongly electropositive metals bind closely to the oxygen atom. Among transition metal enolates both types of enolates are observed. In a few transition metal enolates the cation is associated with a delocalized enolate anion ($\eta^3$-enolate complexes).

The structures of enolates have been examined through magnetic resonance studies (NMR) and with X-ray crystallography.[2–12] It has been observed that solvated enolates exist as dimers, tetramers or hexamers, depending on the enolate structure, the nature of the cation and the solvent.

The following nomenclature for enolate stereoisomers is adopted throughout this chapter: the (*E*)/(*Z*) nomenclature is used according to the Cahn–Ingold–Prelog rules, with one change. At the carbonyl C-atom, the OM (oxy–metal) group is defined to be of highest priority without regard to the nature of the metal,[1] *e.g.* (**1**) and (**2**). This has the advantage that changing the metal associated with a given enolate does not affect the (*E*)/(*Z*) nomenclature.

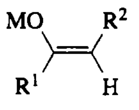

(**1**) *(Z)*

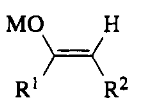

(**2**) *(E)*

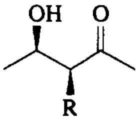

(**3**) *syn/erythro*

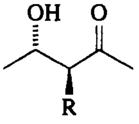

(**4**) *anti/threo*

In the work cited here, the (*E*)/(*Z*) geometry of the enolate is sometimes not known or is not specified by the original authors. When this is the case, a wavy line is used in the representation of the enolate. Unfortunately, despite the importance of enolate geometry, many authors provide little direct information on this point. The exact nature of the countercation is also not always specified or known. Where the counterions are rather obvious but not certainly known, they are included in the formulas but placed in brackets [ ].

For aldol products many types of nomenclature have been proposed. Throughout this chapter the *syn/anti* nomenclature of Masamune[13] is adopted and defined as shown in (**3**) and (**4**).

This chapter is restricted to the formation of metal and metalloid enolates that are more or less anionic and which can react with carbonyl groups without a catalyst. Silicon derivatives are therefore not described.

## 1.4.2 ALKALI METAL ENOLATES

The alkali metal enolates are the most commonly employed and most useful of all enolates. Among alkali elements, lithium enolates are of greatest importance because these can often be formed under kinetic or thermodynamic conditions, as desired, and side reactions can be minimized since lithium is a small, tightly bound cation. Sodium and potassium countercations are more likely to support enolate equilibration, which is sometimes desired, but often undesired. This section is subdivided, based on the different methods of enolate formation.

### 1.4.2.1 Alkali Metal Enolates by Deprotonation of Carbonyl Compounds

Deprotonation of carbonyl compounds by lithium dialkylamide bases is the single most common method of forming alkali enolates. Four excellent reviews have already been published.[1,14–16] Sterically hindered amide bases are employed to retard nucleophilic attack on the carbonyl group. The most common and generally useful bases are: (i) lithium diisopropylamide (LDA; **5**); (ii) lithium isopropylcyclohexylamide (LICA; **6**); (iii) lithium 2,2,6,6-tetramethylpiperidide (LITMP; **7**); (iv) lithium hexamethyldisilylamide (LHMDS; **8**); and (v) lithium tetramethyldiphenyldisilylamide (LTDDS; **9**). Bases that are not amides include sodium hydride, potassium hydride and triphenylmethyllithium.

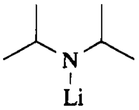

(**5**)

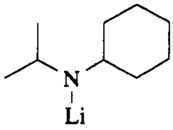

(**6**)

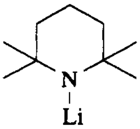

(**7**)

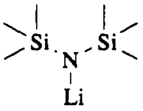

(**8**)

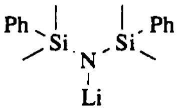

(**9**)

For ketone enolates the question of the regioselectivity of deprotonation arises.[1,17] Under kinetic conditions (low temperature, typically –78 °C, excess base, small cation), the less-substituted enolate is formed. More-hindered bases give higher selectivity. Under conditions designed to provide an equilibrium mixture of product enolates ('higher' temperature, excess ketone, larger cation) the more-substituted enolate is usually formed.

Aldehyde enolates and aldehydes are extremely reactive and therefore, to avoid undesirable side reactions, fast and quantitative conversion of aldehydes to enolates is necessary. Strong bases are needed, *e.g.* potassium amide in liquid ammonia[18] or potassium hydride in THF.[19] Aldehyde enolates are very rarely used in organic synthesis.

Ester enolates are less reactive than aldehyde enolates but rapid and quantitative deprotonation is still necessary because of the possibility of Claisen condensation side reactions.

For all enolates, (*E*)- and (*Z*)-geometry is possible. Much effort has been expended to determine the geometry of enolates and to define rules to predict the outcome of carbonyl group deprotonations.[1,14–16] This knowledge is relevant to the aldol reaction because (*Z*)-enolates tend to give *syn* products, whereas (*E*)-enolates tend to give *anti* products with varying degrees of stereoselectivity.

Under product-equilibrating conditions the (*Z*)-enolate is always the major product (except in smaller ring systems, three to nine membered, where the (*E*)-enolate is favored). Under conditions of kinetic product control, a closer study of reactants and bases is necessary. Reactions of ketones, esters or thioesters with lithium dialkylamides like LDA, LICA or LITMP in THF give predominantly the (*E*)-enolate. Larger, bulkier bases give better (*E*)-selectivity. However, if a bulky group (*e.g. t*-butyl, phenyl) is attached directly to the carbonyl group, the (*Z*)-enolate is preferred. If lithium dialkylamide bases are used in a mixture of THF and HMPA, or if silylamide bases are employed, the (*Z*)-enolates are found to be the major products. Carboxylic acid amides always give (*Z*)-enolates with high selectivity. Ireland *et al.*[20] proposed a cyclic six-membered transition state between the carbonyl and the dialkylamide base to explain these results. Recently, Moreland and Dauben[21] presented theoretical calculations that support this model.

Deprotonation of α-heteroatom-substituted carbonyl compounds (at the carbon bearing the substituent) has been less studied. In several cases it has been observed that, if chelation of the counterion by the enolate is possible, the (*Z*)-enolate is the preferred compound. Garst and coworkers reported two examples in which an α-dialkylamino ketone gives (*E*)-enolates selectively, whereas the corresponding

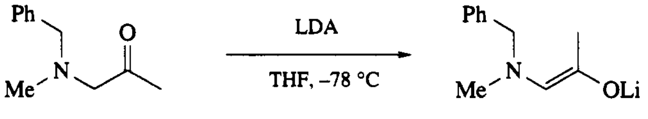

(1)

(*E*):(*Z*) > 98:2

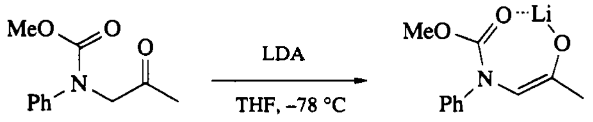

(2)

(*Z*):(*E*) = 80:20

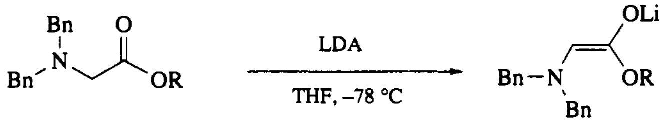

(3)

(*E*):(*Z*) = 58:42

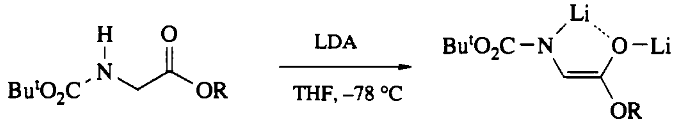

(4)

(*Z*) > 90%

urethane gives predominantly the (*Z*)-enolate (equations 1 and 2).[22] Ireland found a similar effect with α-amino esters (equations 3 and 4).[20]

α-Hydroxy ketones give (*Z*)-enolates (equation 5),[23] but if α-hydroxy esters are deprotonated, the prediction of (*E*)/(*Z*) selectivity is more difficult because both enolates can be stabilized through chelation. For the reaction shown in equation (6),[24] the (*E*):(*Z*) ratio is not known.

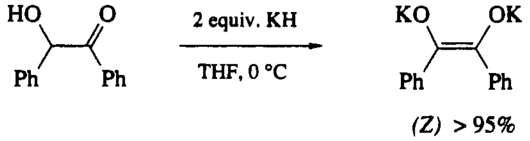
HO
O
Ph
Ph
2 equiv. KH
THF, 0 °C
KO
OK
Ph
Ph
(Z) >95%

(5)

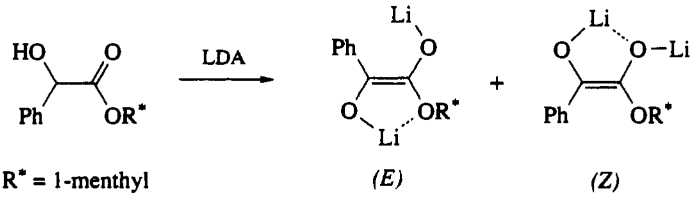
HO
O
Ph
OR*
R* = 1-menthyl
LDA
Li
Ph
O
O
OR*
Li
(E)
+
Li
O
O−Li
Ph
OR*
(Z)

(6)

α-Alkoxy esters would give (*Z*)-enolates if chelation effects dominated but the experimental results are inconsistent. Whitesell and Helbling[25] deprotonated an α-methoxy ester with LDA to get both diastereomers in roughly equal amounts (Scheme 1), but Kallmerten and Gould[26] obtained the chelated (*Z*)-enolate predominantly (Scheme 2). Ireland *et al.*[27] used a cyclic α-alkoxy ester and obtained a 5:1 mixture of enolates with LDA (in favor of the chelated (*Z*)-enolate) and a 1:1 mixture with LDA–HMPA. This latter change in selectivity can be explained by loss of the chelation effect (Scheme 3).

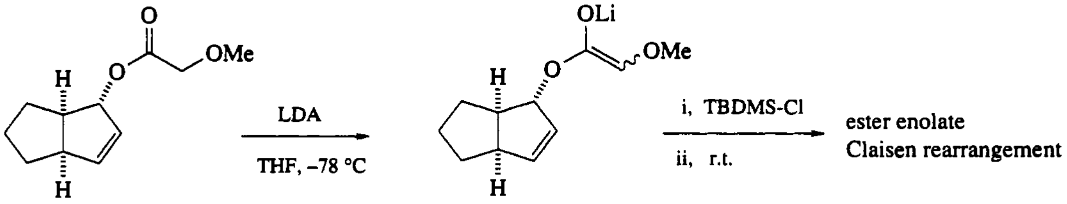
O
OMe
H
O
H
LDA
THF, −78 °C
OLi
OMe
H
O
H
i, TBDMS-Cl
ii, r.t.
ester enolate
Claisen rearrangement

**Scheme 1**

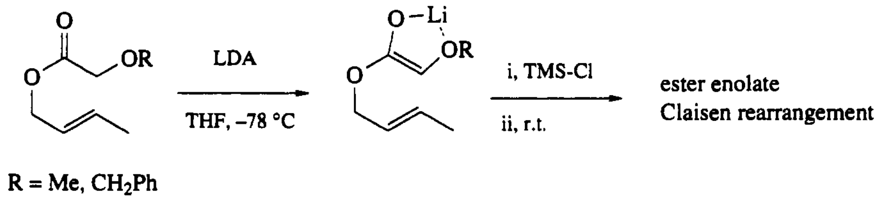
O
OR
O
R = Me, CH₂Ph
LDA
THF, −78 °C
O−Li
OR
O
i, TMS-Cl
ii, r.t.
ester enolate
Claisen rearrangement

**Scheme 2**

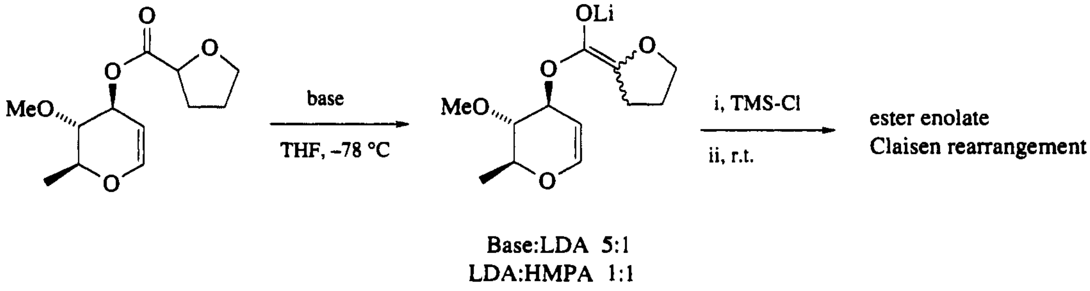
O
O
O
MeO
O
base
THF, −78 °C
OLi
O
O
MeO
O
i, TMS-Cl
ii, r.t.
ester enolate
Claisen rearrangement
Base:LDA 5:1
LDA:HMPA 1:1

**Scheme 3**

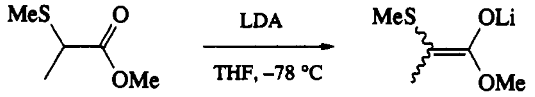
MeS
O
OMe
LDA
THF, -78 °C
MeS
OLi
OMe

75:25 (7)

Deprotonation of one α-methylthio ester is reported to give a 75:25 diastereomer mixture, but it is not known if the (*E*)- or (*Z*)-isomer is the major product (equation 7).[28]

Dianion enolates of succinate diesters show the same stereochemical behavior as simple ester enolates: deprotonation with LITMP in THF gives the (*E*,*E*)-enolate and deprotonation in THF–HMPA gives the (*Z*,*Z*)-enolate (Scheme 4).[29] No mixed enolates are observed. The corresponding diamides seem to give (*Z*,*Z*)-enolates.[1,30]

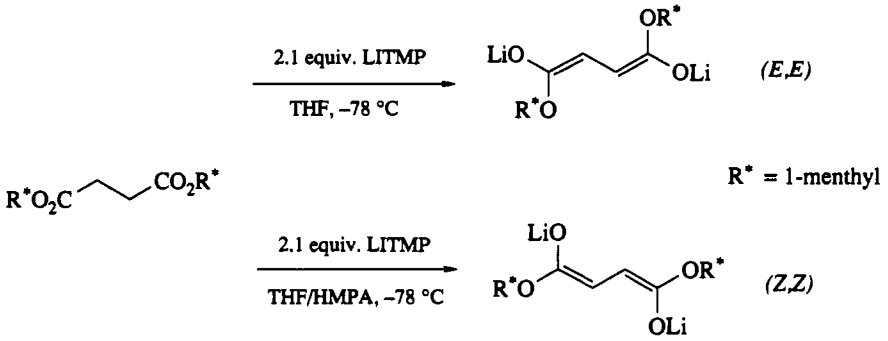
R*O2C
CO2R*
2.1 equiv. LITMP
THF, -78 °C
LiO
R*O
OR*
OLi
(E,E)
R* = 1-menthyl
2.1 equiv. LITMP
THF/HMPA, -78 °C
LiO
R*O
OR*
OLi
(Z,Z)

Scheme 4

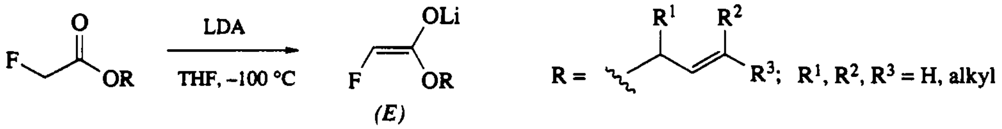
O
F
OR
LDA
THF, -100 °C
OLi
F
OR
(E)
R =
R1
R2
R3; R1, R2, R3 = H, alkyl

Scheme 5

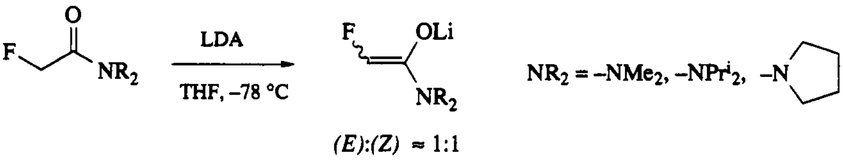
O
F
NR2
LDA
THF, -78 °C
F
OLi
NR2
(E):(Z) ≈ 1:1
NR2 = -NMe2, -NPri2, -N

Scheme 6

Welch *et al.* reported successful generation of α-fluoro enolates.[31,32] Deprotonation of ester enolates in THF gave the (*E*)-enolate as expected (Scheme 5), but no effect of HMPA on the enolate geometry was observed. The α-fluoroamides reacted unselectively (Scheme 6).

A versatile method to generate β-ketophosphonates that cannot be generated through the Arbuzov reaction has been developed: α-phosphonate enolates of cyclic ketones are obtained through sequential treatment of ketones with LDA, diethyl phosphorochloridate and LDA (Scheme 7).[33,34]

Acyclic β-ketophosphonates can also be formed from α-bromo ketones (Scheme 8)[35] and in a similar reaction α-trialkylsilyl enolates can also be obtained (Scheme 9).[35,36]

Kuwajima and Takeda employed the reaction of α-phenylselenylvinyl silyl ethers with lithium and dimethylaminonaphthalene (DMAN) to generate α-silyl enolates (Scheme 10).[37]

In these reactions (Schemes 7, 9 and 10) it is interesting that a strong P—O or Si—O bond is broken to get a less stable P—C or Si—C bond. The effect is apparently more than offset by the fact that a very unstable vinyl anion is converted to a relatively stable enolate anion.

The reaction of esters and γ-lactone enolates with diphenylmethylsilyl chloride is reported to be atypical and to give the *C*-silylated product (Scheme 11).[38]

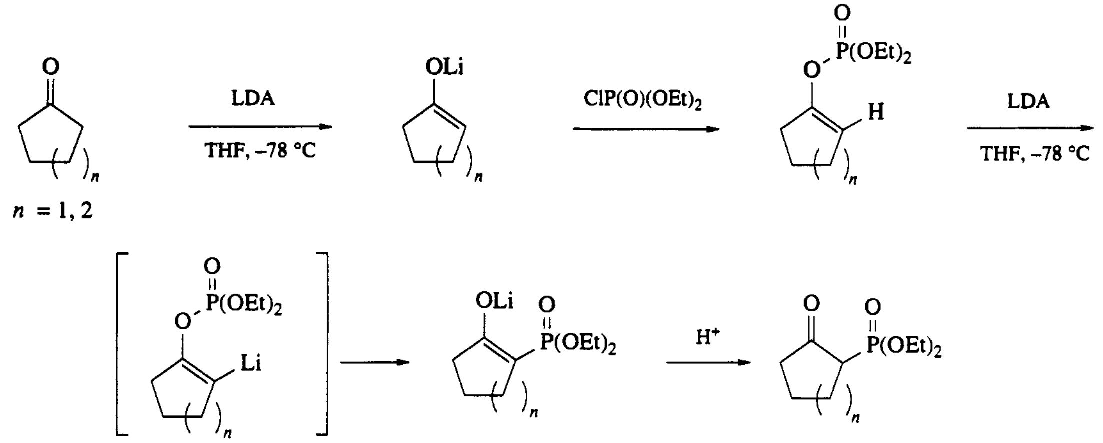
LDA
THF, –78 °C
ClP(O)(OEt)$_2$
LDA
THF, –78 °C
H$^+$
n = 1, 2

**Scheme 7**

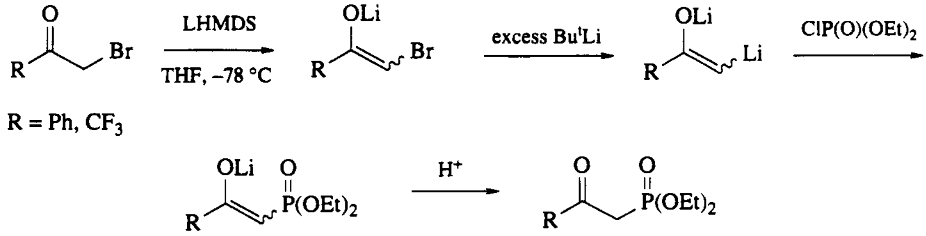
LHMDS
THF, –78 °C
excess Bu$^t$Li
ClP(O)(OEt)$_2$
H$^+$
R = Ph, CF$_3$

**Scheme 8**

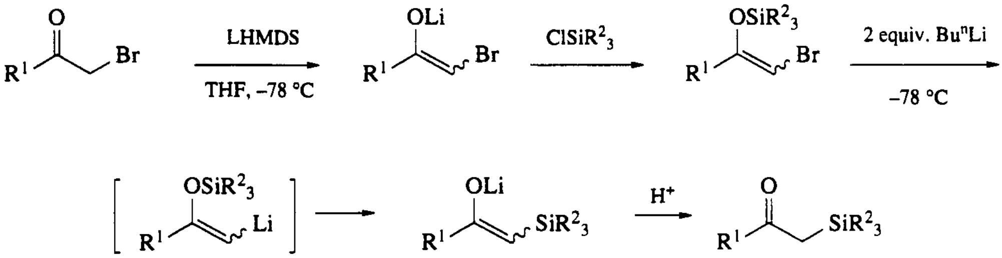
LHMDS
THF, –78 °C
ClSiR$^2_3$
2 equiv. Bu$^n$Li
–78 °C
H$^+$

$R^1 = Bu^t$, Ph; $R^2$ = Me, Et

**Scheme 9**

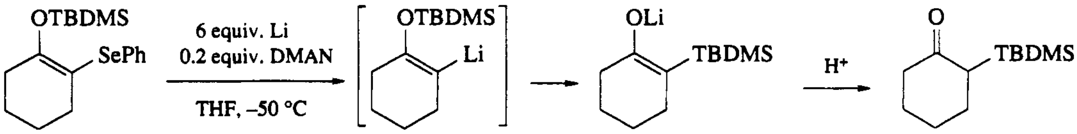
6 equiv. Li
0.2 equiv. DMAN
THF, –50 °C
H$^+$

**Scheme 10**

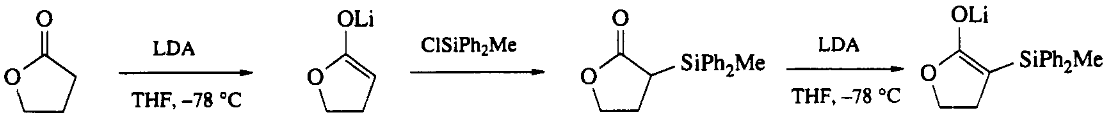
LDA
THF, –78 °C
ClSiPh$_2$Me
LDA
THF, –78 °C

**Scheme 11**

Enantioselective deprotonation by chiral lithium amide bases has been reported. The degree of asymmetric induction depends on the base and on the bulkiness of the alkyl group in the cyclohexanone (Scheme 12).[39]

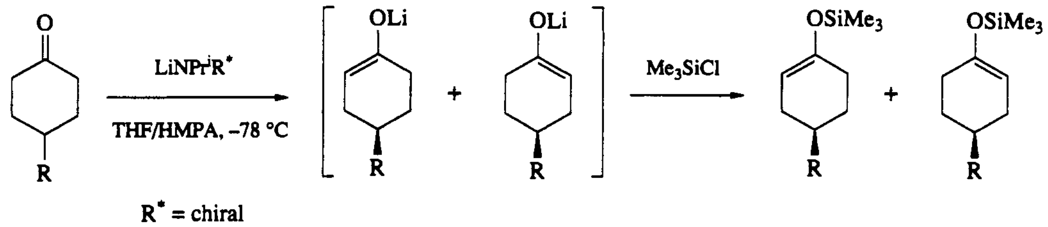
O
R
LiNPr$^i$R*
THF/HMPA, −78 °C
R* = chiral
OLi
OLi
R
R
+
Me$_3$SiCl
OSiMe$_3$
OSiMe$_3$
R
R
+

**Scheme 12**

Very recently, two examples of generating enolates with metallic potassium appeared. In one case potassium was dispersed ultrasonically, in the other 18-crown-6 was added to the potassium metal (equations 8 and 9).[40,41]

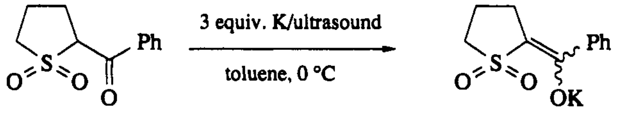
Ph
O
S
O
O
3 equiv. K/ultrasound
toluene, 0 °C
Ph
OK

(8)

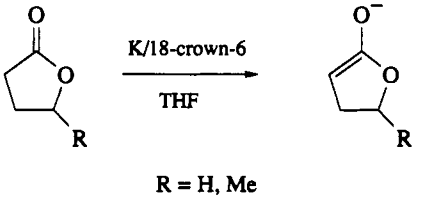
O
O
R
K/18-crown-6
THF
O⁻
O
R
R = H, Me

(9)

Fuchigami and coworkers have formed enolates with electrogenerated bases (equations 10 and 11).[42,43] The basic anions of 2,6-di-*t*-butyl-*p*-cresol and α-pyrrolidone were obtained by cathodic reduction. Countercations with a weak affinity for the fluorine atom (*e.g.* quaternary ammonium, phosphonium or tertiary sulfonium cations) had to be used in the example shown in equation (11) in order to impede defluorination.

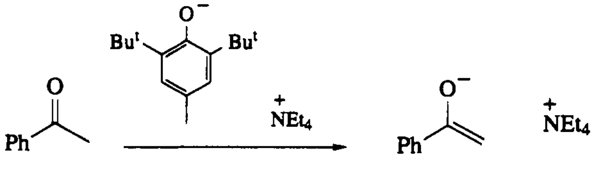
O
Ph
O⁻
Bu$^t$
Bu$^t$
+NEt$_4$
O⁻
Ph
+NEt$_4$

(10)

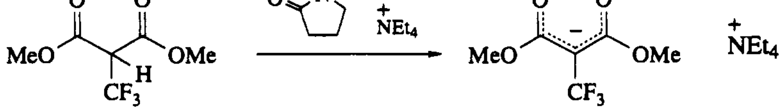
O
O
MeO
OMe
H
CF$_3$
O
N⁻
+NEt$_4$
O
O
MeO
OMe
CF$_3$
+NEt$_4$

(11)

α,β-Unsaturated ketones can be deprotonated in two positions.[17] Under thermodynamic conditions the major product is that afforded by deprotonation at the γ-position, whereas under kinetic conditions the hydrogen in the α′-position is usually abstracted (equations 12 and 13).[44,45]

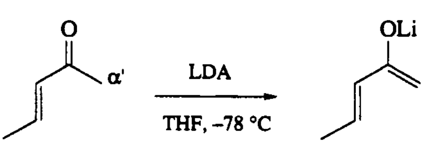
O
α'
LDA
THF, −78 °C
OLi

(12)

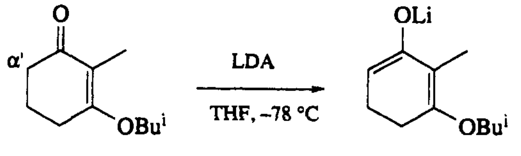
α'
O
OBu$^i$
LDA
THF, −78 °C
OLi
OBu$^i$

(13)

Little is known about the (*E*)/(*Z*) stereoselectivity of the enolate double bond and the newly generated $\Delta^3$ double bond. Two experiments indicate that esters may give preferentially (*Z*)-enolates under kinetic conditions (Schemes 13 and 14).[46,47] If the $\Delta^2$ double bond in an α,β-unsaturated ester has only alkyl ligands, (*Z*)-esters seem to give only enolates with (*E*)-geometry on the $\Delta^3$ double bond and (*E*)-esters afford (*Z*)-$\Delta^3$ double bonds (equation 14).[48,49]

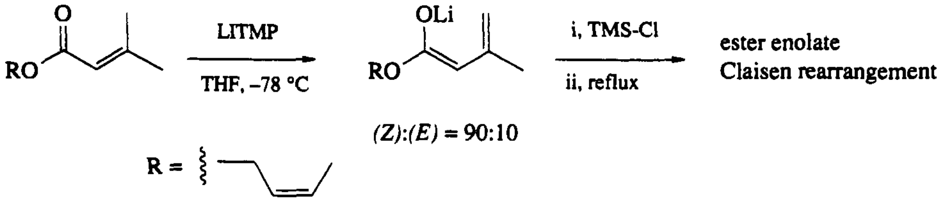
O
RO
LITMP
THF, −78 °C
OLi
RO
i, TMS-Cl
ii, reflux
ester enolate
Claisen rearrangement
(Z):(E) = 90:10
R =

Scheme 13

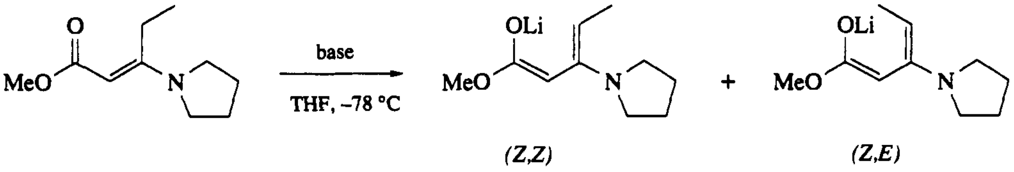
O
MeO
N
base
THF, −78 °C
OLi
MeO
N
+
OLi
MeO
N
(Z,Z)
(Z,E)

| | (Z,Z) | (Z,E) |
|---|---|---|
| LDA | 0 | 100 |
| KDA | 50 | 50 |

Scheme 14

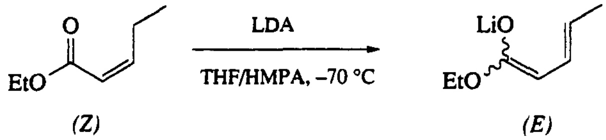
O
EtO
LDA
THF/HMPA, −70 °C
LiO
EtO
(Z)
(E)

(14)

## 1.4.2.2 Alkali Metal Enolates by Addition to α,β-Unsaturated Carbonyl Compounds

The reduction of α,β-unsaturated carbonyls with lithium in ammonia is a versatile reaction of great utility.[17,50–52] The advantage of this method is that regiospecific enolates are obtained that are sometimes not accessible by other routes. This technique finds important applications in steroid-like systems (equation 15).[50]

Chamberlin and Reich investigated hydride additions to α,β-unsaturated ketones and the correlation of conformational preferences in enones with the (*E*)/(*Z*) stereoselectivity in formation of the corresponding enolates. They found that in acyclic systems *s-trans* enones gave enolates A and *s-cis* enones gave enolates B (Scheme 15).[53] The reduction of α,β-unsaturated amides with L-selectride gave the same stereochemical results (Scheme 16).[54]

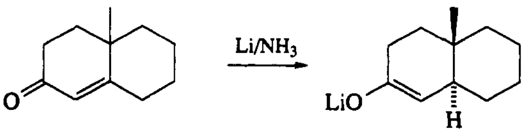
O
Li/NH$_3$
LiO
H

(15)

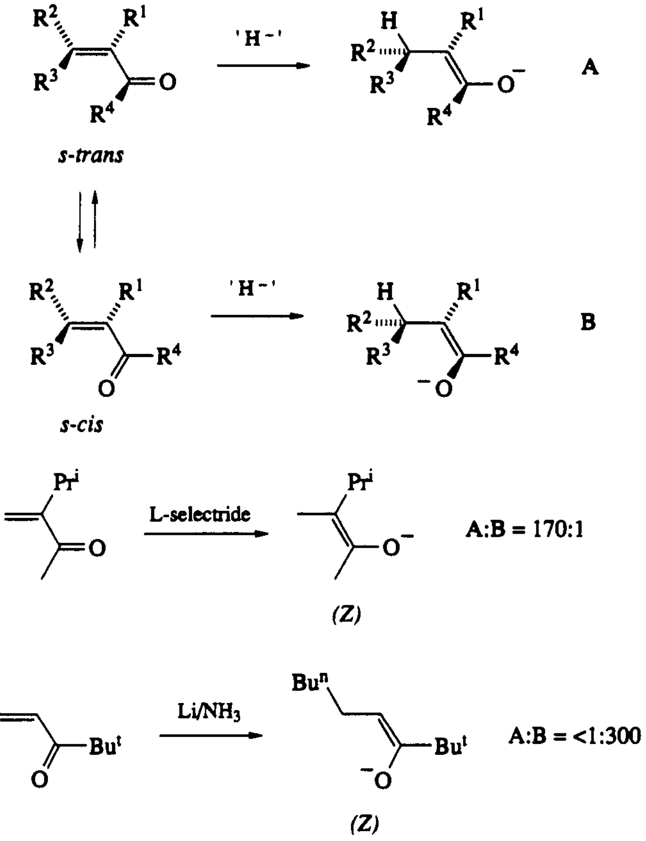
s-trans
'H⁻'
A
s-cis
'H⁻'
B
L-selectride
A:B = 170:1
(Z)
Li/NH3
A:B = <1:300
(Z)

Scheme 15

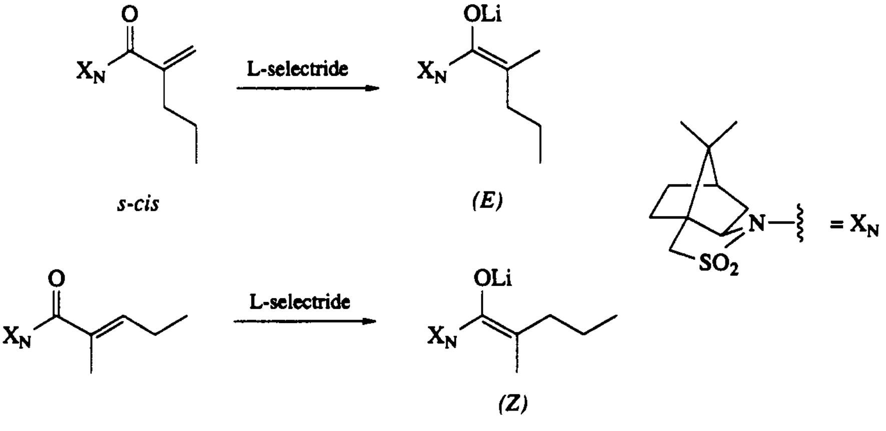
L-selectride
s-cis
(E)
L-selectride
(Z)
= XN

Scheme 16

Alkyllithium reagents normally react with α,β-unsaturated carbonyls in a 1,2-fashion, but with sterically hindered substrates or reagents 1,4-addition is preferred (Scheme 17).[55–57] Of course, the presence of other metals can also affect this preference. Other examples of 1,4-additions will be seen in later sections.

### 1.4.2.3 Alkali Metal Enolates from Ketenes

The formation of enolates from ketenes generates tetrasubstituted enolates regio- and stereo-selectively.[58–61] Deprotonation of the corresponding ketones gives mixtures of enolates. Ketenes are produced from sterically hindered esters, from α-bromoacyl bromides and zinc, or from acid chlorides and triethylamine. Alkyllithium reagents add to the ketenes from the less-hindered side to give only (*Z*)-enolates (Scheme 18).[58,60]

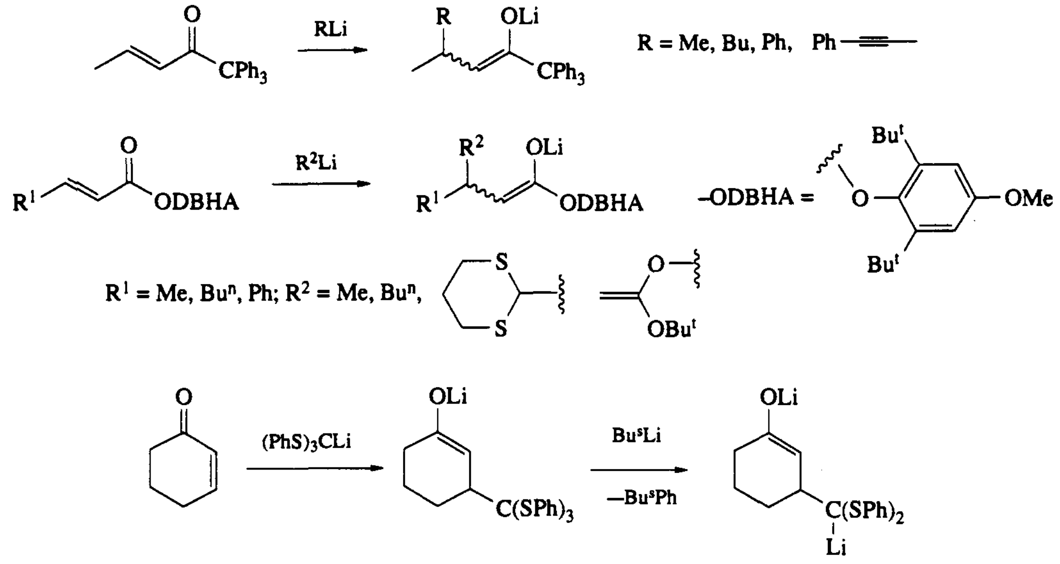
RLi
R
OLi
CPh$_3$
R = Me, Bu, Ph, Ph—≡—
ODBHA
$R^2Li$
$R^1$
$R^2$
-ODBHA =
Bu$^t$
OMe
$R^1$ = Me, Bu$^n$, Ph; $R^2$ = Me, Bu$^n$,
OBu$^t$
(PhS)$_3$CLi
Bu$^s$Li
—Bu$^s$Ph
C(SPh)$_3$
C(SPh)$_2$
Li

Scheme 17

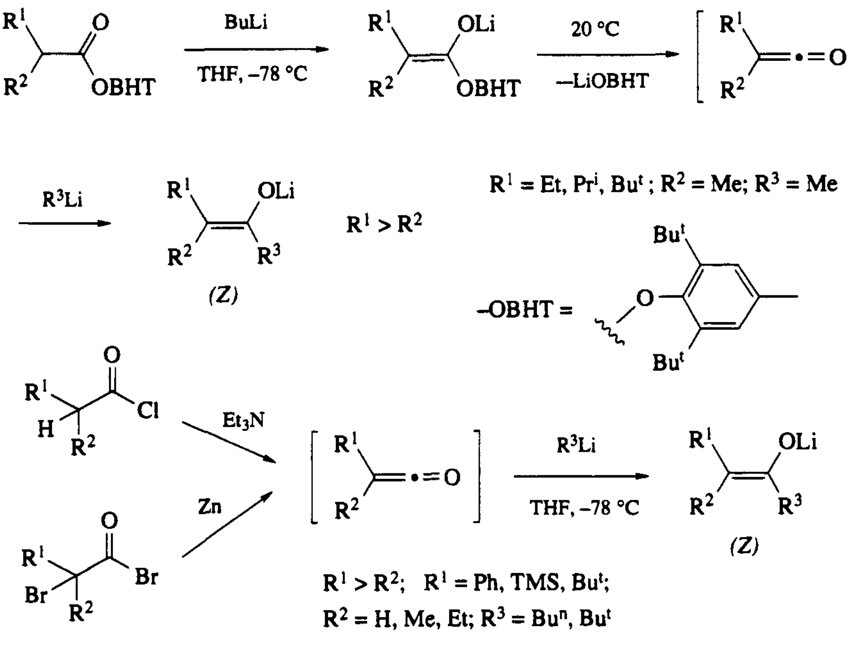
BuLi
THF, −78 °C
OBHT
OLi
20 °C
—LiOBHT
$R^3Li$
(Z)
$R^1 > R^2$
$R^1$ = Et, Pr$^i$, Bu$^t$ ; $R^2$ = Me; $R^3$ = Me
-OBHT =
Bu$^t$
Cl
Et$_3$N
Zn
Br
THF, −78 °C
$R^1 > R^2$; $R^1$ = Ph, TMS, Bu$^t$;
$R^2$ = H, Me, Et; $R^3$ = Bu$^n$, Bu$^t$

Scheme 18

### 1.4.2.4 Alkali Metal Enolates from Enol Acetates and Silyl Enol Ethers

Enol acetates and silyl enol ethers may be prepared from enolates. This is sometimes advantageous because they are stable enolate equivalents.[17] Enol acetates can be cleaved with 2 equiv. of methyllithium

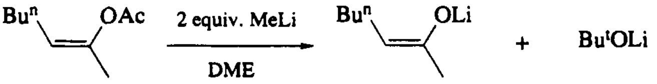
Bu$^n$
OAc
2 equiv. MeLi
DME
Bu$^n$
OLi
+
Bu$^t$OLi

(16)

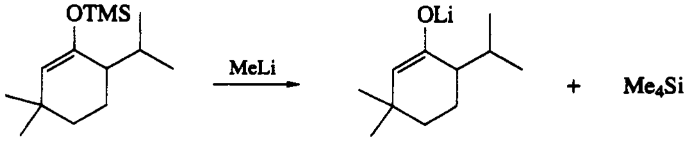
OTMS
MeLi
OLi
+ Me₄Si

(17)

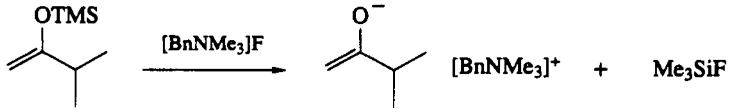
OTMS
[BnNMe₃]F
O⁻
[BnNMe₃]⁺ + Me₃SiF

(18)

(equation 16).[62] Silyl enol ethers can be cleaved with methyllithium (equation 17),[63] with lithium or sodium amide,[64] or with benzyltrimethylammonium fluoride (equation 18).[65] These enolate formations occur without isomerization.

### 1.4.2.5 Alkali Metal Enolates by Miscellaneous Methods

Kowalski *et al.*[66–69] employed dibromomethyllithium (prepared *in situ*) to prepare an α-bromo ketone enolate at low temperatures. At higher temperatures and under extremely basic conditions, this enolate rearranged to give an ynolate. A mixture of 1,3-cyclohexadiene and LITMP transformed the ynolate to an aldehyde (*E*)-enolate (Scheme 19).

Reaction of benzil with (benzenesulfonyl)methylenedilithium gives an enolate by an insertion process (Scheme 20).[70]

Lithium allenolates are obtained from 2,2-dimethyl-4-methylene-1,3-dioxolane and 2 equiv. of *s*-butyllithium. These allenolates can further undergo aldol reactions (Scheme 21).[71]

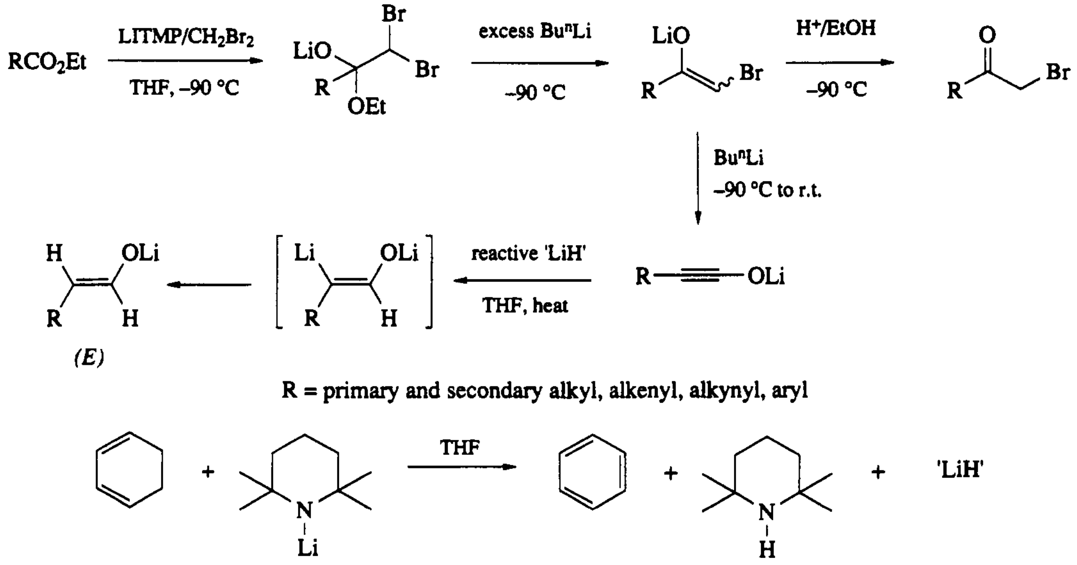
RCO₂Et
LITMP/CH₂Br₂
THF, –90 °C
LiO
Br
Br
R
OEt
excess BuⁿLi
–90 °C
LiO
R
Br
H⁺/EtOH
–90 °C
O
R
Br
BuⁿLi
–90 °C to r.t.
R—≡—OLi
reactive 'LiH'
THF, heat
Li
OLi
R
H
H
OLi
R
H
(E)
+
N
Li
THF
+
N
H
+ 'LiH'

R = primary and secondary alkyl, alkenyl, alkynyl, aryl

**Scheme 19**

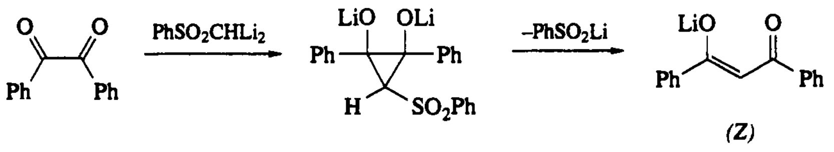
O
O
Ph
Ph
PhSO₂CHLi₂
LiO
OLi
Ph
Ph
H
SO₂Ph
–PhSO₂Li
LiO
O
Ph
Ph
(Z)

**Scheme 20**

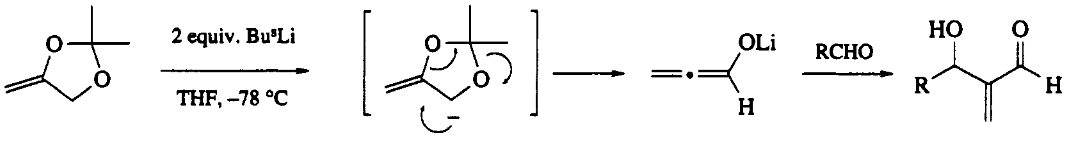
O
O
2 equiv. BusLi
THF, –78 °C
O
O
OLi
H
RCHO
HO
O
R
H

Scheme 21

## 1.4.3 MAGNESIUM ENOLATES

Magnesium enolates are similar to alkali metal enolates. For example, often the same stereoselectivity is observed in their formation and in the aldol reactions of these enolates.

Carbonyl compounds can be deprotonated with magnesium dialkylamides, which are generated from Grignard reagents and are thus free of lithium. Again, the more-substituted enolate is obtained under thermodynamic conditions (equations 19 to 21).[72–74]

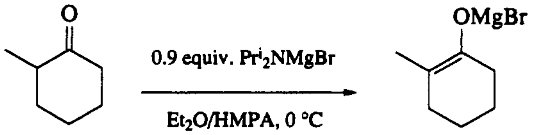
O
0.9 equiv. Pri2NMgBr
Et2O/HMPA, 0 °C
OMgBr

(19)

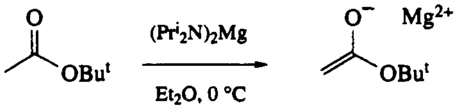
O
OBut
(Pri2N)2Mg
Et2O, 0 °C
O–
Mg2+
OBut

(20)

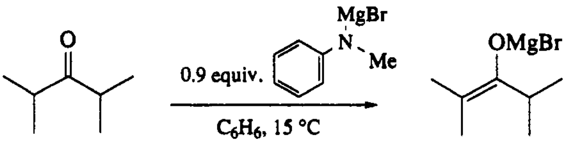
O
MgBr
N
Me
0.9 equiv.
C6H6, 15 °C
OMgBr

(21)

α-Bromocarbonyl compounds react with magnesium to give bromomagnesium enolates (equations 22 and 23),[75,76] and silyl enol ethers can be cleaved with methylmagnesium bromide (equation 24).[63]

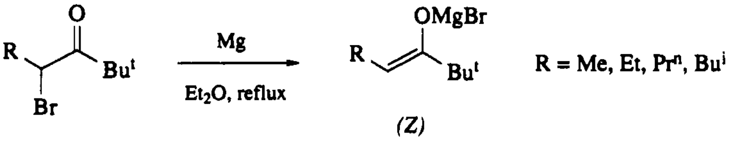
O
R
But
Br
Mg
Et2O, reflux
OMgBr
R
But
(Z)
R = Me, Et, Prn, Bui

(22)

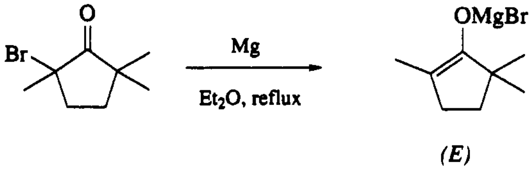
O
Br
Mg
Et2O, reflux
OMgBr
(E)

(23)

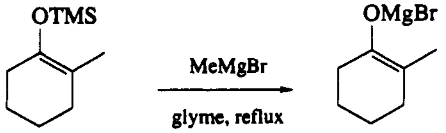
OTMS
MeMgBr
glyme, reflux
OMgBr

(24)

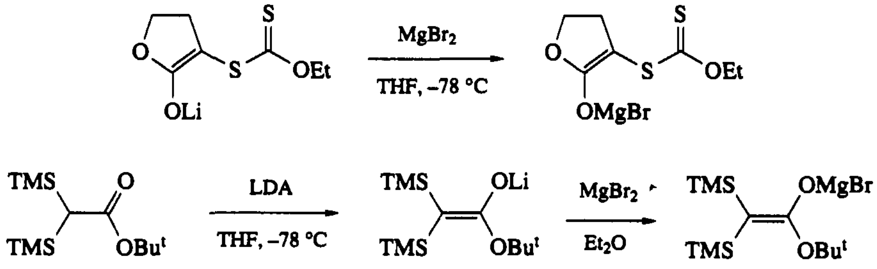

Scheme 22

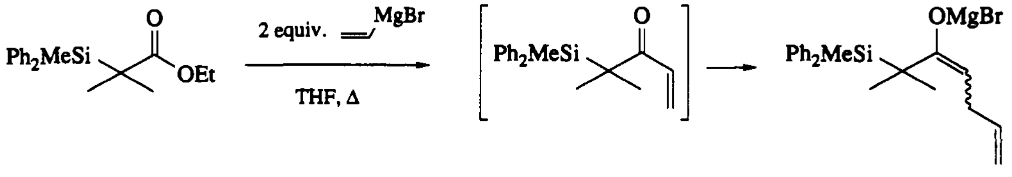

Scheme 23

An important practical route involves the transmetallation reaction between lithium enolates and $MgCl_2$ or $MgBr_2$ (Scheme 22).[77,78] However, in such cases the true nature of the reactant (Li or Mg or both?) is obscured.

A different type of reaction is the addition of two equivalents of vinyl Grignard reagent to an ester. This involves a conjugate addition to a sterically hindered ketone in the second step (Scheme 23).[79]

## 1.4.4 BORON ENOLATES

Boron enolates (other names are vinyloxyboranes, enol borinates, or boron enol ethers) are often employed in the aldol reaction because they show higher stereoselectivity than alkali and magnesium enolates. Extensive developmental work in this area has been carried out by Evans, Masamune and Mukaiyama, and their respective coworkers.[14–16,80,81] The correspondence between enolate geometry and aldol stereochemistry is exceptional: (*Z*)-enolates give *syn*/*erythro* aldol products, whereas (*E*)-enolates give *anti*/*threo* aldol products, albeit with slightly lower selectivity.

Hooz *et al.* produced boron enolates by treating α-diazo ketones with substituted boranes. Tri-*n*-butylborane gave almost exclusively the (*E*)-enolate, which could be isomerized quantitatively to the (*Z*)-enolate by a catalytic amount of pyridine or lithium phenoxide (Scheme 24).[82] This method has the disadvantage that only one of the three alkyl groups is utilized. If boranes with different substituents are employed, the question arises as to which substituent has the highest 'migration aptitude'. It was found that the order is aryl > alkyl > Cl (equation 25).[83] A hydride can be transferred, if a dialkylborane is used. Dicyclohexylborane proved to be the most efficient reagent to synthesize regiospecifically a terminal enolate (equation 26).[84] In a similar reaction, boron enolates can be obtained from α-halogen alkali enolates[85,86] and sulfur ylides.[87]

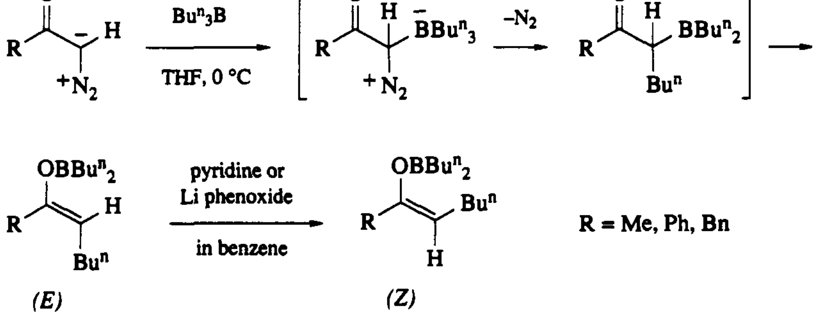

Scheme 24

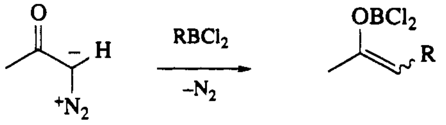

(25)

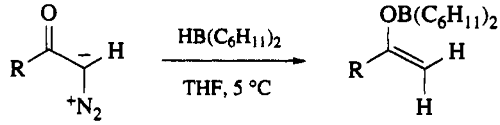

(26)

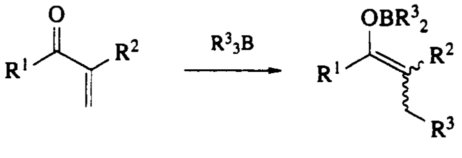

(27)

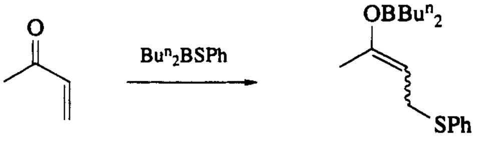

(28)

α,β-Unsaturated carbonyl compounds react with boron reagents solely through conjugate addition (equations 27 and 28).[88-90] The enolate stereochemistry, (*E*) or (*Z*), depends on the enone substituents but without useful trends in stereochemical control.[89]

Boron enolates can be formed with good stereoselectivity by the reaction of ketenes with dibutylthioborinates (equations 29 and 30).[90-92]

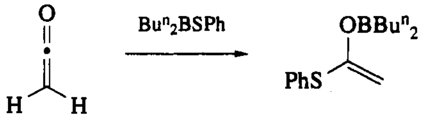

(29)

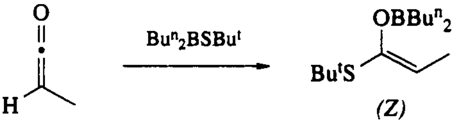

(30)

The most common route to boron enolates uses the method of carbonyl enolization. Köster and coworkers employed triethylborane with diethylboryl pivalate as a catalyst under vigorous conditions, which probably led to the thermodynamic enolates (equation 31).[93,94]

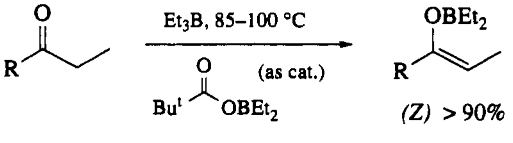

(31)

In an important experiment, Mukaiyama and coworkers enolized carbonyl compounds under much milder conditions (low temperatures) with dialkylboryl triflate and a sterically hindered tertiary amine base such as 2,6-lutidine (2,6-dimethylpyridine) or diisopropylethylamine (DPEA).[95-97] Less-hindered bases led to formation of a stable borane–amide complex (Lewis acid–Lewis base) and prevented the reaction with the carbonyl compound. Masamune *et al.*[98] and Evans *et al.*[99,100] carried out a study to investigate the reasons for the selective enolate formation. They showed that it depends on the boron ligand, base, solvent and the group attached to the carbonyl moiety. Ketones give (*Z*)-enolates with often excellent selectivity, whereas *t*-butyl thiolates give selectively the (*E*)-enolates (equations 32 and 33).[100,101] Evans suggests that reactions with 9-BBN triflate are often under thermodynamic control.[15] In equation

(34), the (*Z*)-enolate could well have arisen by equilibration of the kinetic (*E*)-enolate.[102–104] Recent examples of this type of reaction often employ chiral carbonyl compounds or chiral boranes to get enantioselective aldol products (equations 35 and 36).[105–110]

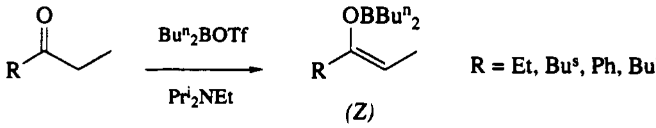
O
R
Bu$^n_2$BOTf
Pr$^i_2$NEt
OBBu$^n_2$
R
(Z)
R = Et, Bu$^s$, Ph, Bu$^t$

(32)

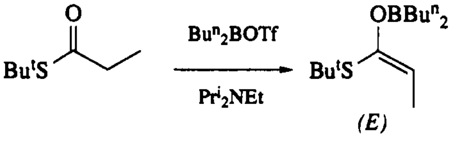
O
Bu$^t$S
Bu$^n_2$BOTf
Pr$^i_2$NEt
OBBu$^n_2$
Bu$^t$S
(E)

(33)

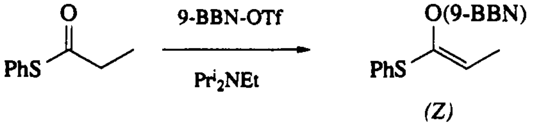
O
PhS
9-BBN-OTf
Pr$^i_2$NEt
O(9-BBN)
PhS
(Z)

(34)

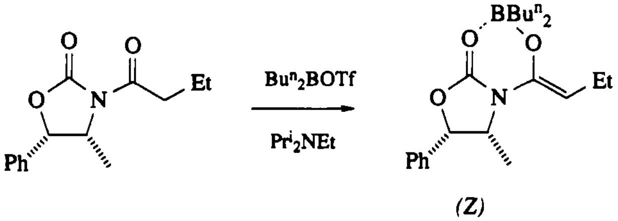
O
O
O
N
Et
Ph
Bu$^n_2$BOTf
Pr$^i_2$NEt
BBu$^n_2$
O
O
O
N
Et
Ph
(Z)

(35)

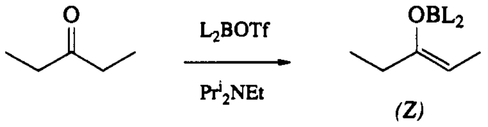
O
L$_2$BOTf
Pr$^i_2$NEt
OBL$_2$
(Z)

L$_2$BOTf = (–)-(Ipc)$_2$BOTf
(+)-(Ipc)$_2$BOTf
Ipc = diisopinocampheyl

(36)

Simple alkyl esters do not react with boryl triflate reagents, but acyloxyboranes give diborane enediolates under these conditions (Scheme 25).[15] These diborane enediolates usually give more *anti* aldol than *syn* aldol product. Because aldol geometry depends on enolate geometry, it can be inferred that (*E*)-boron enolates are somewhat more reactive than the (*Z*)-isomers.

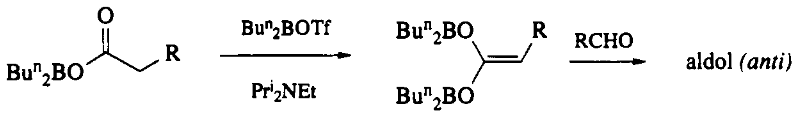
O
Bu$^n_2$BO
R
Bu$^n_2$BOTf
Pr$^i_2$NEt
Bu$^n_2$BO
R
Bu$^n_2$BO
RCHO
aldol (anti)

**Scheme 25**

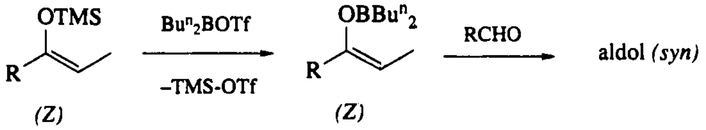
OTMS
R
(Z)
Bu$^n_2$BOTf
-TMS-OTf
OBBu$^n_2$
R
(Z)
RCHO
aldol (syn)

**Scheme 26**

Trimethylsilyl enol ethers react rapidly with boryl triflate reagents (Scheme 26).[111,112] Subsequent aldol reaction occurs with apparent stereospecificity provided that the by-product trimethylsilyl triflate is removed before the addition of the aldehyde. This seems to be a useful reaction for the synthesis of boron enolates that are not accessible by other methods, but the boryl triflate reagents are ineffective with trimethylsilyl enol ethers of amides and esters.

Trichloroborane reacts with ketones to form a complex. Subsequent addition of DPEA leads to a dichloroboron enolate (Scheme 27).[114] If the trichloroborane and DPEA are added at the same time, direct complex formation will preclude reaction of the ketone.

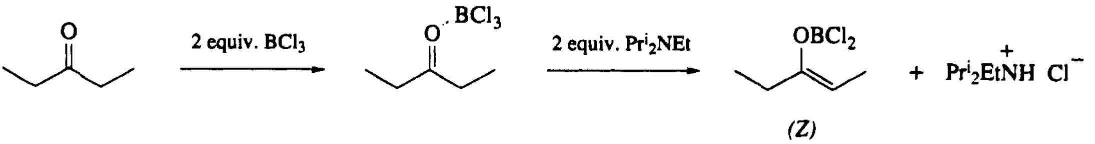
O
2 equiv. BCl3
O
BCl3
2 equiv. Pri2NEt
OBCl2
(Z)
+ Pri2EtNH Cl−

Scheme 27

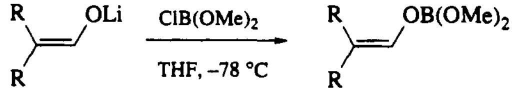
R
OLi
R
ClB(OMe)2
THF, −78 °C
R
OB(OMe)2
R

(37)

Lithium enolates react with chlorodimethoxyborane to give dimethoxyboron enolates (equation 37).[113]

## 1.4.5 ALUMINUM ENOLATES

Aluminum enolates can be formed by conjugate addition with diisobutylaluminum hydride (DIBAL-H) and a catalytic amount of methylcopper in a mixture of THF and HMPA (Scheme 28).[115–117] The role of copper and HMPA is crucial, for without these 1,2-reduction of the carbonyl group takes place. The effect of copper(I) on conjugate addition is not unexpected. In regard to the solvents it is suggested that HMPA functions not as a cosolvent but as an essential ligand. Treatment of an α,β-unsaturated ketone with trimethylaluminum and a catalyst leads to a dimethylaluminum enolate with moderate (*E*)/(*Z*) selectivity. The (*Z*)-enolate reacts with diphenylketene to give another enolate (Scheme 29).[118,119]

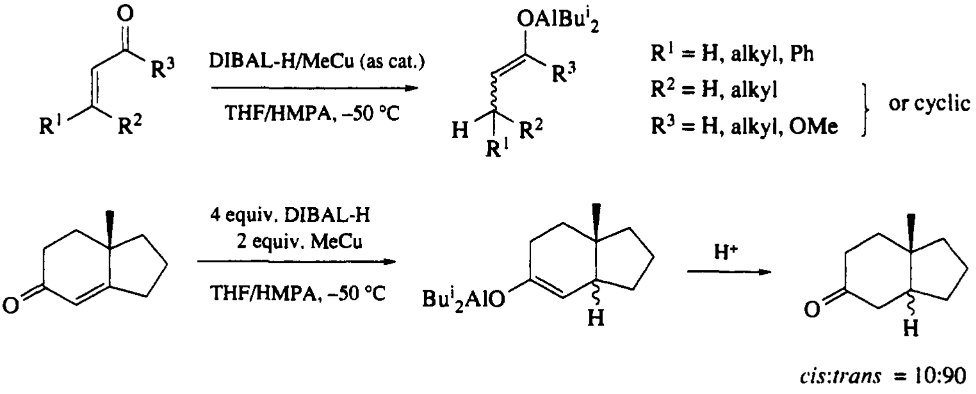
O
R3
R1
R2
DIBAL-H/MeCu (as cat.)
THF/HMPA, −50 °C
OAlBui2
R3
H
R1
R2
R1 = H, alkyl, Ph
R2 = H, alkyl
R3 = H, alkyl, OMe
or cyclic
O
4 equiv. DIBAL-H
2 equiv. MeCu
THF/HMPA, −50 °C
Bui2AlO
H
H+
O
H
cis:trans = 10:90

Scheme 28

Another route to aluminum enolates is through the reaction of ketones with a trialkylaluminum, usually trimethylaluminum (Scheme 30).[120,121]

Aluminum enolates can be obtained also by transmetallation of lithium enolates (Scheme 31).[73]

Diethylaluminum enolates can be produced regiospecifically through reaction of diethylaluminum chloride and zinc dust with α-bromo ketones and esters (Scheme 32).[122] Obviously zinc is involved in this reaction, but the mild conditions are in sharp contrast to the Reformatsky reaction and support the existence of an aluminum enolate in this process. The same type of enolate can be obtained from *t*-butyl acetates and diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), which is generated *in situ* from diethylaluminum chloride and LITMP (Scheme 33).[123]

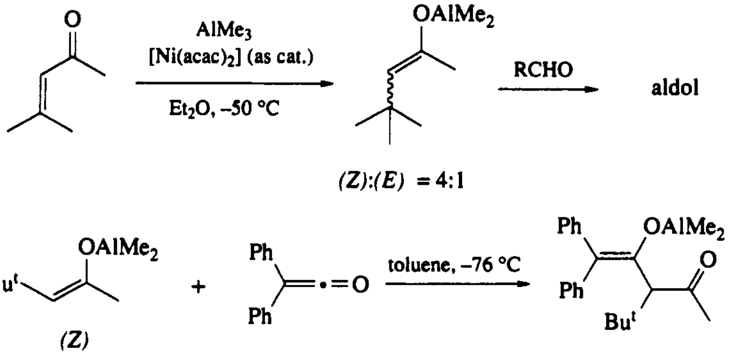
AlMe3
[Ni(acac)2] (as cat.)
Et2O, -50 °C
OAlMe2
RCHO
aldol
(Z):(E) = 4:1
OAlMe2
Bu<sup>t</sup>
(Z)
+
Ph
Ph
toluene, -76 °C
Ph
OAlMe2
O
Ph
Bu<sup>t</sup>

**Scheme 29**

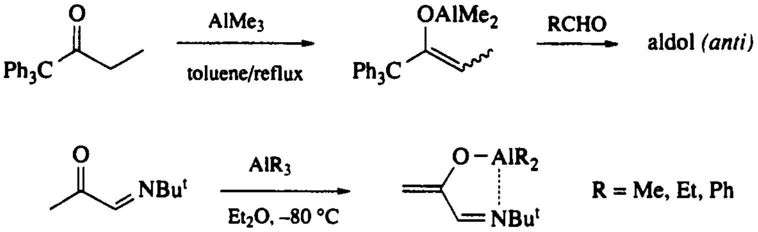
O
Ph3C
AlMe3
toluene/reflux
OAlMe2
Ph3C
RCHO
aldol (anti)
O
NBu<sup>t</sup>
AlR3
Et2O, -80 °C
O-AlR2
NBu<sup>t</sup>
R = Me, Et, Ph

**Scheme 30**

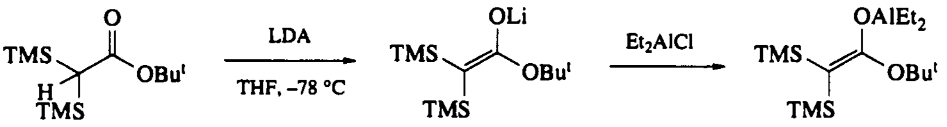
O
TMS
H
TMS
OBu<sup>t</sup>
LDA
THF, -78 °C
OLi
TMS
OBu<sup>t</sup>
TMS
Et2AlCl
OAlEt2
TMS
OBu<sup>t</sup>
TMS

**Scheme 31**

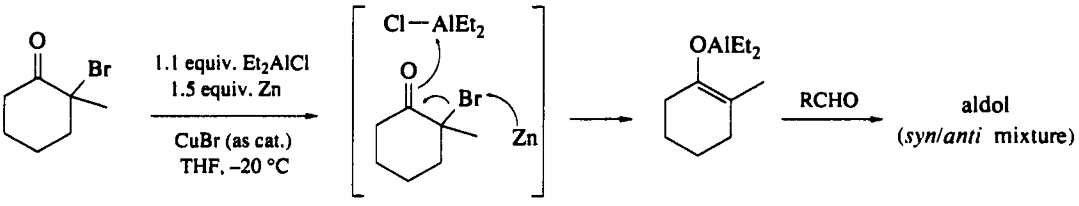
O
Br
1.1 equiv. Et2AlCl
1.5 equiv. Zn
CuBr (as cat.)
THF, -20 °C
Cl—AlEt2
O
Br
Zn
OAlEt2
RCHO
aldol
(syn/anti mixture)

**Scheme 32**

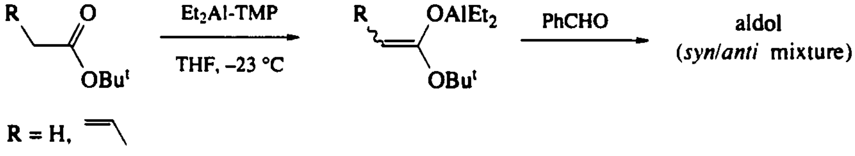
R
O
OBu<sup>t</sup>
Et2Al-TMP
THF, -23 °C
R
OAlEt2
OBu<sup>t</sup>
PhCHO
aldol
(syn/anti mixture)
R = H,

**Scheme 33**

Fluorinated enolates are generally difficult to form. Ishihara and coworkers used fluorovinyl phosphates, which can be prepared from α-fluoro ketones and sodium diethyl phosphite. Reaction of these fluorinated enol phosphates with a reagent prepared from lithium aluminum hydride ($LiAlH_4$) and copper(II) bromide, zinc(II) chloride, tin(II) chloride or bromine afforded the enolate (Scheme 34).[124] The reaction of the enol phosphate with the reagents mentioned above suggests that the metal cation of the enolate is an aluminum species, though its actual structure is not known at present.

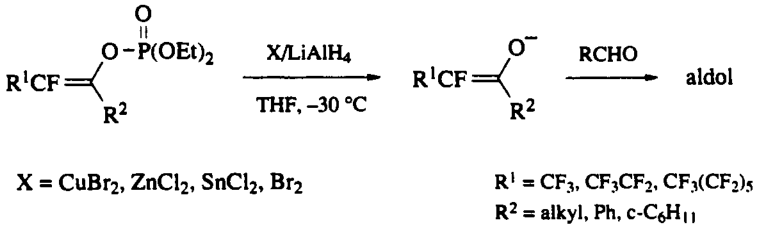
X/LiAlH4
THF, -30 °C
RCHO
aldol
X = CuBr2, ZnCl2, SnCl2, Br2
R1 = CF3, CF3CF2, CF3(CF2)5
R2 = alkyl, Ph, c-C6H11

Scheme 34

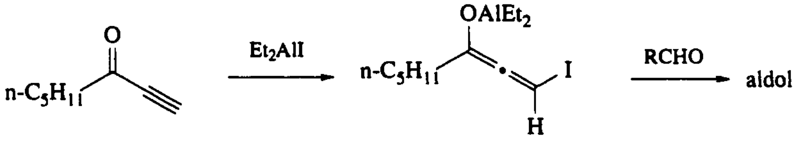
Et2AlI
RCHO
aldol

Scheme 35

The reaction of α,β-alkynic ketones with diethylaluminum iodide gives allenolates by 1,4-addition (Scheme 35).[125] These intermediates can react with aldehydes to give aldol-type products.

## 1.4.6 TIN ENOLATES

Tin(II) enolates can be generated by more than one method (for reviews see refs. 75 and 126). The most common is the method of Mukaiyama:[127–141] ketones and amides react with tin(II) triflate and *N*-ethylpiperidine in methylene chloride at low temperatures to give tin(II) enolates which can have various substituents in the α-position. These divalent tin enolates have either (*Z*) or unknown configuration and produce predominantly the *syn*/*erythro* aldol products (Scheme 36).[127–136]

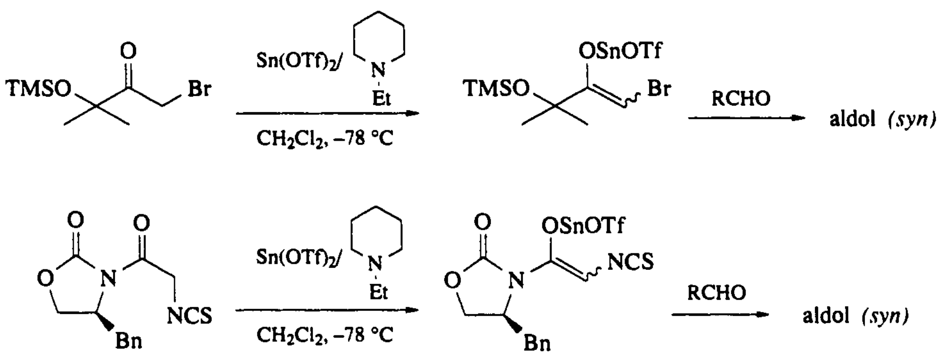
Sn(OTf)2/
CH2Cl2, -78 °C
RCHO
aldol (syn)
Sn(OTf)2/
CH2Cl2, -78 °C
RCHO
aldol (syn)

Scheme 36

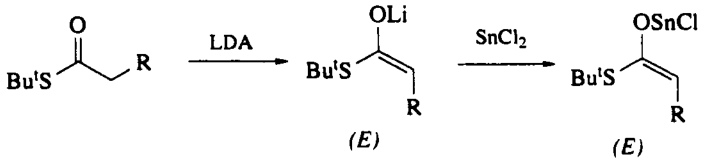
LDA
SnCl2
(E)
(E)

Scheme 37

Another method is the reaction of lithium enolates with tin(II) chloride, tin(II) bromide or tin(II) triflate (Scheme 37).[142,143] During the transmetallation reaction, the geometry of the enolate is believed to be unchanged.[143]

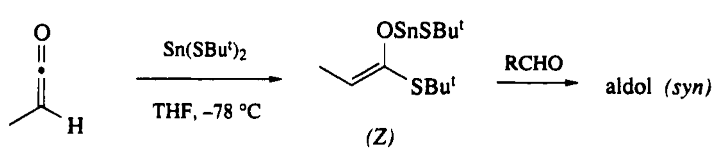
O
H
Sn(SBu$^t$)$_2$
THF, -78 °C
OSnSBu$^t$
SBu$^t$
(Z)
RCHO
aldol (syn)

**Scheme 38**

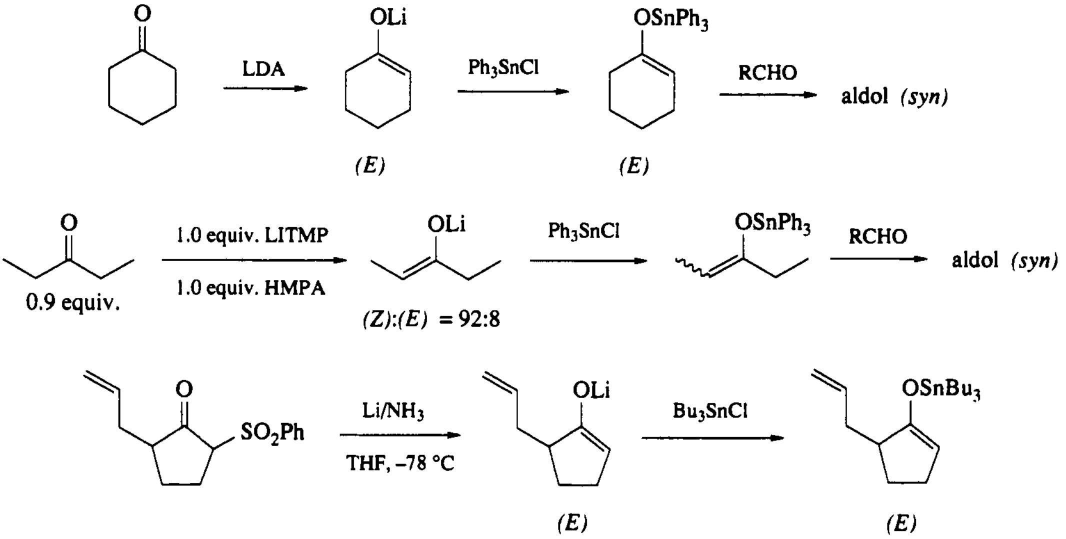
O
LDA
OLi
(E)
Ph$_3$SnCl
OSnPh$_3$
(E)
RCHO
aldol (syn)
O
0.9 equiv.
1.0 equiv. LITMP
1.0 equiv. HMPA
OLi
(Z):(E) = 92:8
Ph$_3$SnCl
OSnPh$_3$
RCHO
aldol (syn)
O
SO$_2$Ph
Li/NH$_3$
THF, -78 °C
OLi
(E)
Bu$_3$SnCl
OSnBu$_3$
(E)

**Scheme 39**

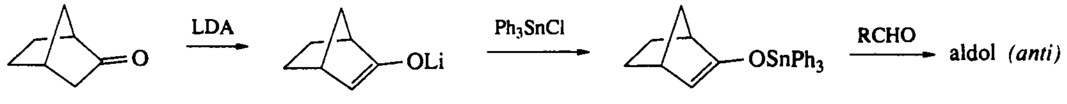
O
LDA
OLi
Ph$_3$SnCl
OSnPh$_3$
RCHO
aldol (anti)

**Scheme 40**

The reaction of ketenes with tin(II) thiolates gives tin(II) thioester enolates with (*Z*)-configuration (Scheme 38).[144,145]

Tin(IV) enolates are generated by the reaction of lithium enolates with trialkyltin chlorides.[77,136,146,147] The best stereoselectivity in the aldol reaction with tin(IV) enolates has been achieved by employing triphenyltin chloride. *Syn/erythro* aldol products were predominantly produced irrespective of the geometry of the starting enolates (Scheme 39).[146,147] However, the aldol condensation *via* the enolate derived from norbornanone gave the *anti/threo* product predominantly (Scheme 40).[146]

## 1.4.7 TITANIUM ENOLATES

The Mukaiyama version of the aldol reaction is well known:[75] a carbonyl–titanium tetrachloride complex reacts with a trimethylsilyl enol ether. Under these conditions there is *no* titanium enolate involved. Another procedure has been reported:[148–150] a trimethylsilyl enol ether reacts with titanium tetrachloride to give the titanium enolate; addition of the carbonyl compound generates the aldol product (although with slightly lower diastereoselectivity than with Mukaiyama's procedure). (*Z*)-Enolsilanes from acyclic ketones react rapidly and stereospecifically with $TiCl_4$ to form (*Z*)-configured $Cl_3Ti$ enolates, while the (*E*)-isomers react slowly to afford low yields of mixtures of (*E*)- and (*Z*)-$Cl_3Ti$ enolates (Scheme 41).[149]

Another way of generating titanium enolates is the reaction of lithium enolates with titanium salts [$ClTi(OPr^i)_3$;[151–154] $ClTi(NEt_2)_3$;[153] $ClTi(NMe_2)_3$[153]]. The ratio of (*E*)- and (*Z*)-enolate remains unchanged in the exchange process (Scheme 42).

Titanium enolates generated with bis(cyclopentadienyl)titanium dichloride show *anti/threo* selectivity (Scheme 43),[155] although the corresponding zirconium enolates (*vide infra*) react *syn* selectively.

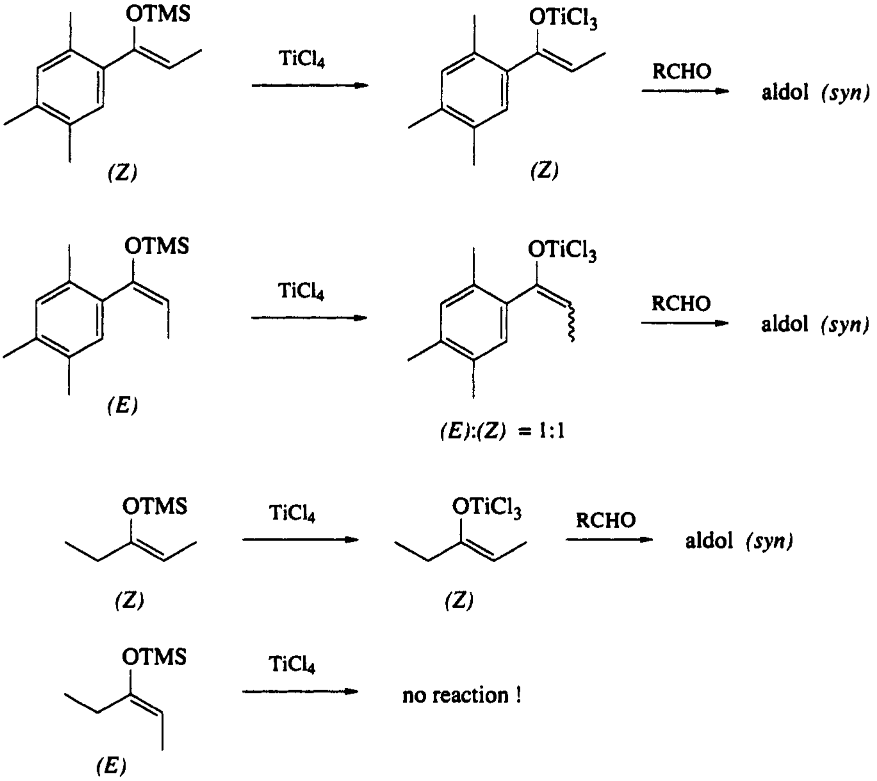
OTMS
(Z)
TiCl4
OTiCl3
(Z)
RCHO
aldol (syn)
OTMS
(E)
TiCl4
OTiCl3
(E):(Z) = 1:1
RCHO
aldol (syn)
OTMS
(Z)
TiCl4
OTiCl3
(Z)
RCHO
aldol (syn)
OTMS
(E)
TiCl4
no reaction !

Scheme 41

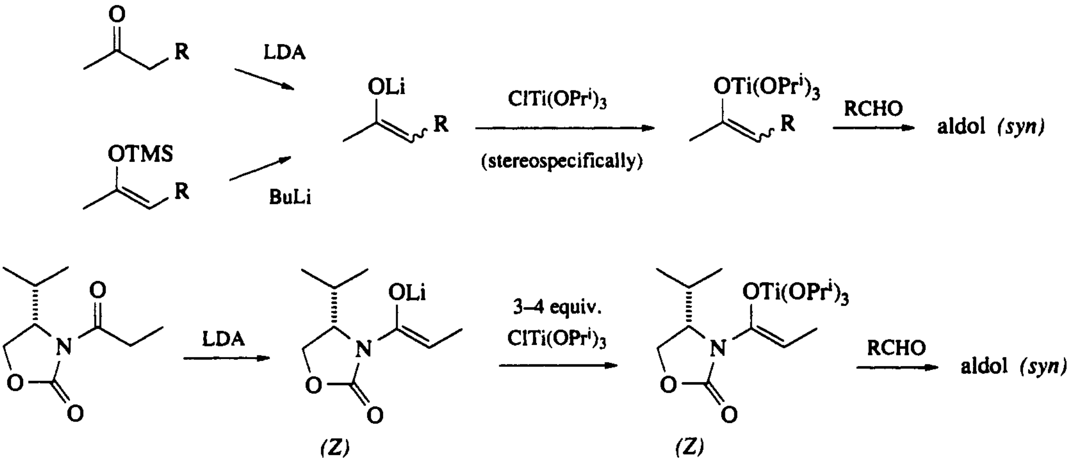
O
R
LDA
OTMS
R
BuLi
OLi
R
ClTi(OPri)3
(stereospecifically)
OTi(OPri)3
R
RCHO
aldol (syn)
O
N
O
O
LDA
OLi
(Z)
3–4 equiv.
ClTi(OPri)3
OTi(OPri)3
(Z)
RCHO
aldol (syn)

Scheme 42

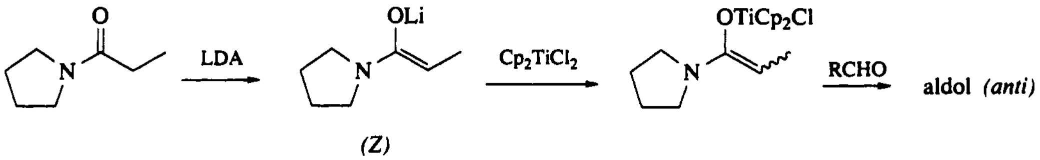
O
N
LDA
OLi
(Z)
Cp2TiCl2
OTiCp2Cl
RCHO
aldol (anti)

Scheme 43

### 1.4.8 ZIRCONIUM ENOLATES

Zirconium enolates are formed by reaction of the corresponding lithium enolates with bis(cyclopentadienyl)zirconium dichloride.[146,156-163] Complete retention of enolate geometry accompanies the metal exchange.[156,157] Both (*E*)- and (*Z*)-zirconium enolates have been shown to undergo selective kinetic aldol condensation to give mainly *syn*/*erythro* products (Scheme 44).[156-160] Again, the enolate derived from norbornanone provides an exception to the rule (Scheme 45).[146]

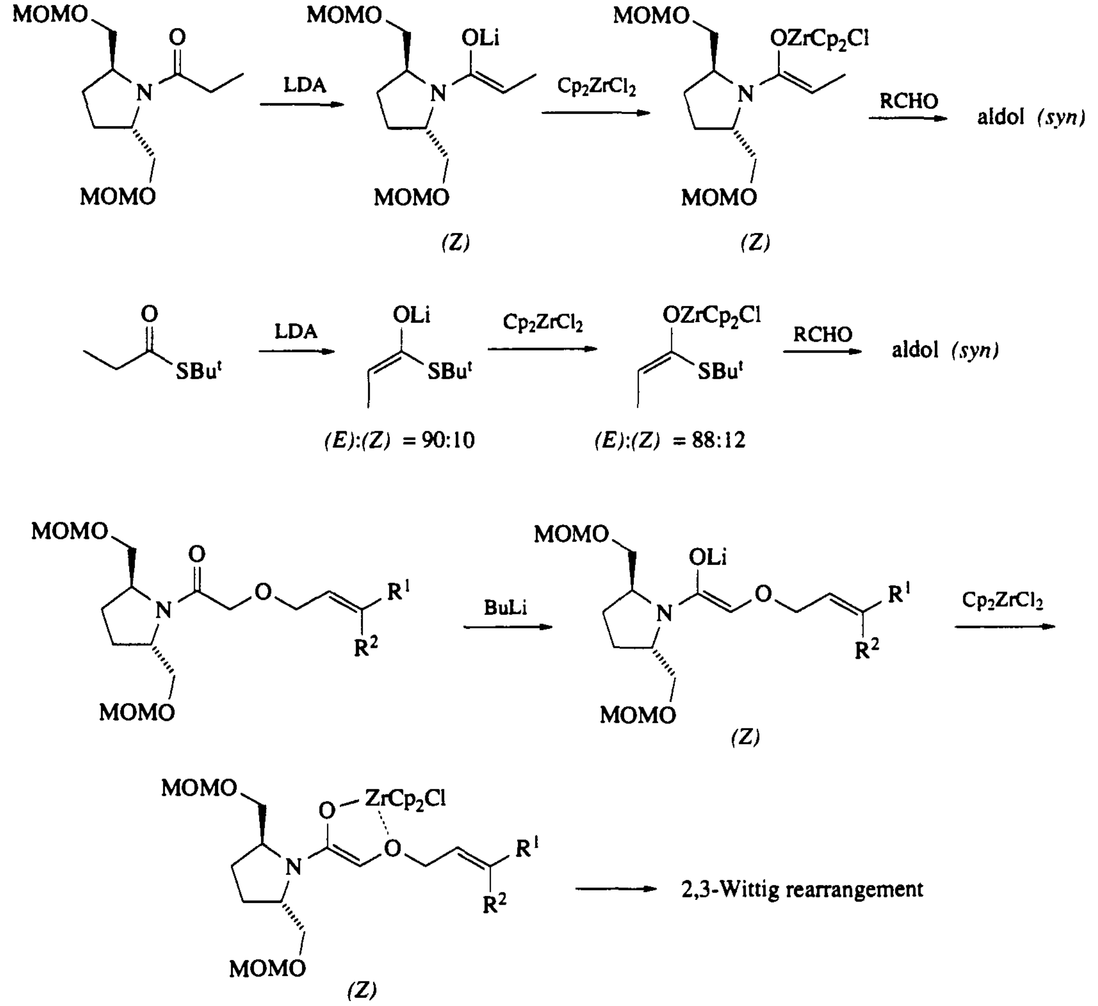
MOMO
O
N
MOMO
LDA
OLi
(Z)
$Cp_2ZrCl_2$
$OZrCp_2Cl$
(Z)
RCHO
aldol (*syn*)
SBu$^t$
(E):(Z) = 90:10
(E):(Z) = 88:12
BuLi
$R^1$
$R^2$
$ZrCp_2Cl$
2,3-Wittig rearrangement

Scheme 44

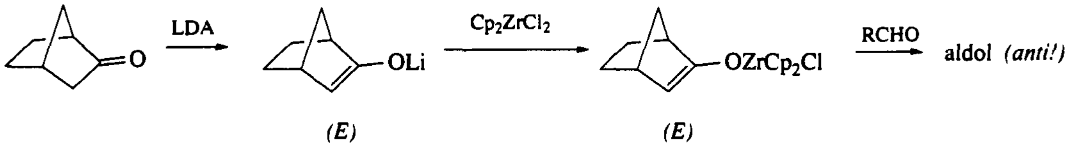
O
LDA
OLi
(E)
$Cp_2ZrCl_2$
$OZrCp_2Cl$
(E)
RCHO
aldol (*anti!*)

Scheme 45

### 1.4.9 COPPER ENOLATES AND ENOLATES FROM CUPRATES

Conjugate addition to an α,β-unsaturated carbonyl compound is achieved routinely by using a lithium organocopper reagent or a copper-catalyzed Grignard reaction.[164-168] It should be noted that in many of these examples, and in particular in the case of lithium diorganocuprates, the resultant enolate has properties most consistent with a lithium enolate, and the reactivity of these enolates is unaffected by soluble copper(I) salts.[169] The chemist who desires to generate authentic copper enolates would better avoid the use of lithium- or magnesium-ion-containing reagents. In this section, however, some discussion of lithiocuprate reagents is included. The reagent $Me_2CuLi$ is often used (Scheme 46).[171,173] There has been considerable work done to reveal the mechanism of this reaction (Scheme 47). Now it seems to be certain that the first intermediate between the α,β-unsaturated carbonyl and the cuprate is a *d,p**-complex (**10**), and this is followed by a copper(III) β-adduct (**11**).[170–174]

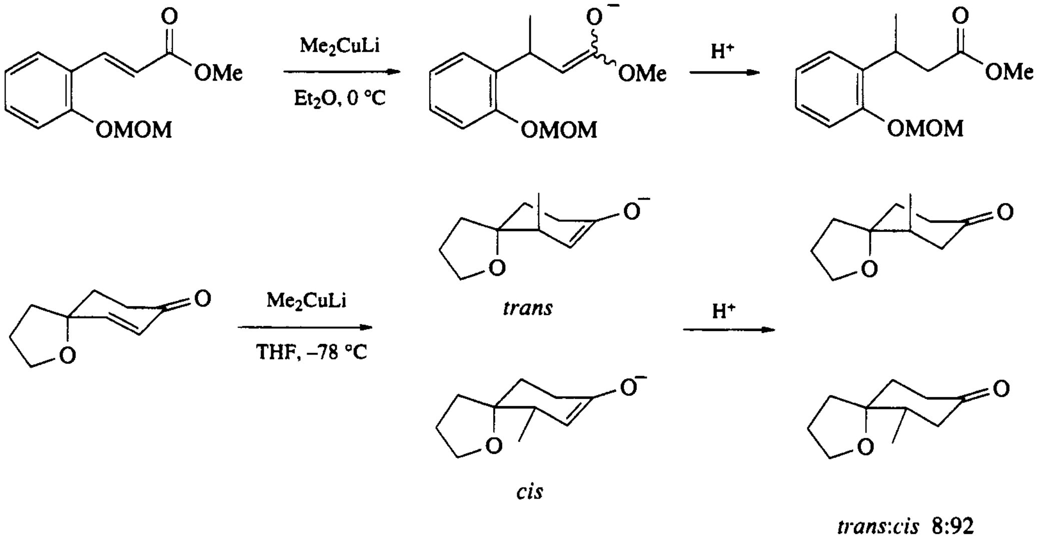

Scheme 46

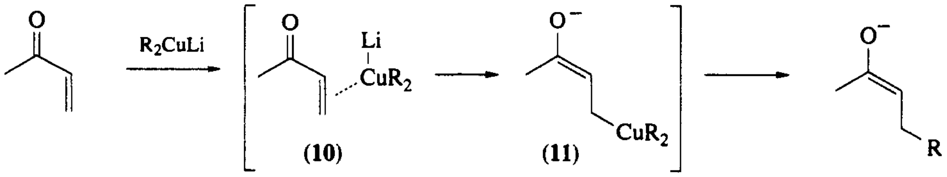

Scheme 47

An authentic copper enolate can be prepared by an alternative route, which involves the conjugate addition of $BuCu(BF_3)$.[175] Experimental results indicate clearly that the intermediate is a copper-bonded enolate (**12**) rather than an α-cupriocarbonyl derivative (**13**).

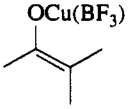

**(12)**

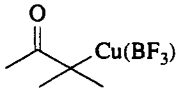

**(13)**

The addition of lithium diallylcuprate to α,β-unsaturated carbonyl compounds is highly substrate dependent. Good yields can only be obtained with doubly activated esters as shown in (**14**) and (**15**).[176,177]

The importance of the conjugate addition has prompted numerous searches for procedures and methods to effect asymmetric induction.[178–182] One recent example is the use of (*S*)-2-(methoxymethyl)pyrrolidine as a chiral copper ligand (Scheme 48).[181]

One of the mildest and most efficient reactions for effecting conjugate addition to α,β-unsaturated ketones is the use of the so-called 'mixed higher order cuprates' $R_2Cu(CN)Li_2$ and $RMeCu(CN)Li_2$. The latter have the advantage that 100% of the alkyl groups can be transferred (Scheme 49).[183–186]

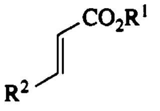

**(14)**

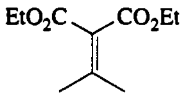
$EtO_2C$
$CO_2Et$

**(15)**

$R^1$ = Me, Et; $R^2$ = $CO_2Me$, Me, Ph,

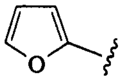

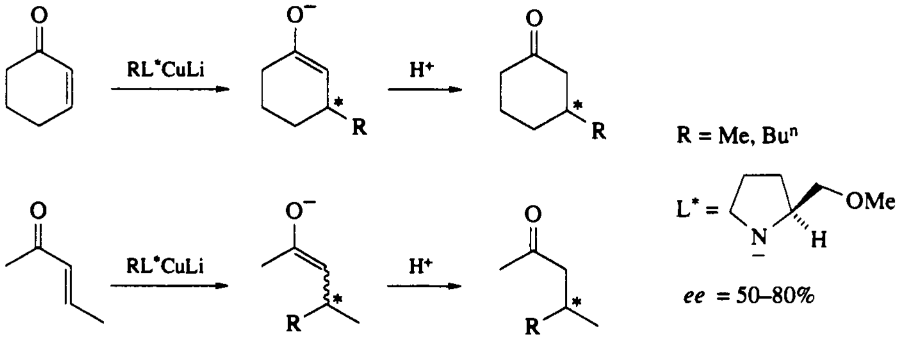
RL*CuLi
H+
R = Me, Bu^n
L* =
OMe
N
H
ee = 50–80%

**Scheme 48**

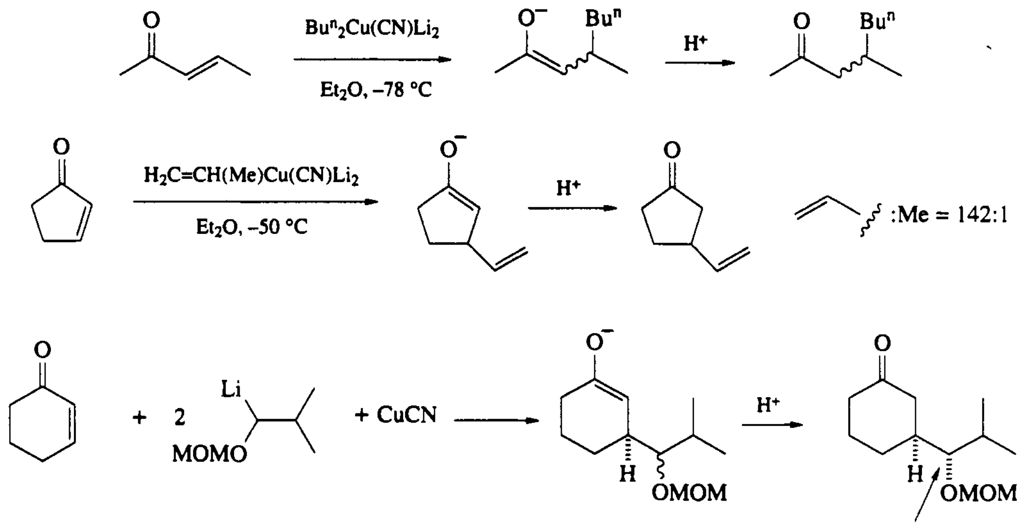
$Bu^n_2Cu(CN)Li_2$
$Et_2O$, –78 °C
H+
$H_2C=CH(Me)Cu(CN)Li_2$
$Et_2O$, –50 °C
:Me = 142:1
+ 2
Li
MOMO
+ CuCN
OMOM

diastereoselectivity 91:9

**Scheme 49**

The use of the mixed lithium phenylthio(alkyl)cuprates, PhSCuRLi, for conjugate addition to α,β-unsaturated carbonyl compounds is well known.[187,188] The reaction of phenylthiocuprates derived from Grignard reagents with cinnamates and crotonates has also been reported (Scheme 50).[189]

Another method to generate copper enolates through conjugate addition is the use of alkyl bromides and highly reactive zerovalent copper prepared by lithium naphthalide reduction of the CuI–$PBu_3$ complex (Scheme 51).[190,191] The activated copper inserts directly into the carbon–halogen bond. The exact nature of the active copper and of the subsequent organocopper species is unknown. The advantage of this method is that the alkyl bromides can contain remote ester, nitrile, or chloride functionalities.

Finally, copper enolates of an α-thio lactone have been generated by the reaction of a lithium enolate with copper iodide (Scheme 52).[77]

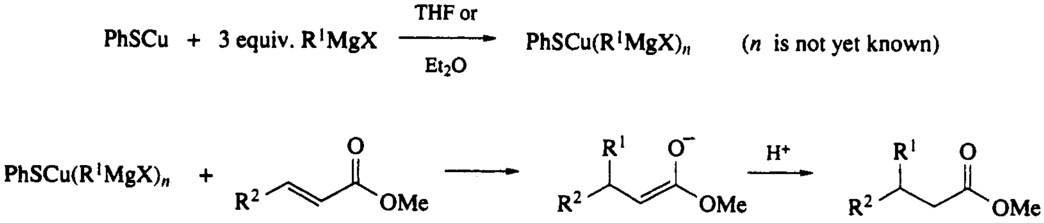

$R^1$ = Me, Et, Pr$^i$, Bu$^t$, vinyl; $R^2$ = Ph, Me

Scheme 50

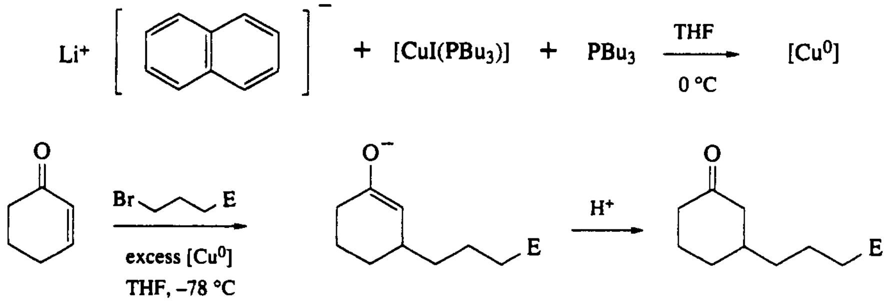

E = $CO_2Et$, CN, Cl

Scheme 51

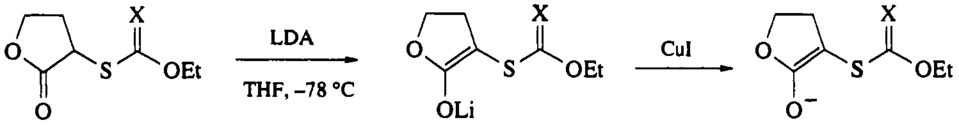

X = O, S

Scheme 52

### 1.4.10 ZINC ENOLATES

The Reformatsky reaction has been known for over 100 years: α-bromo esters, ketones and amides react with activated zinc dust to give zinc enolates, which can react with carbonyl compounds to give aldol-type products.[192-194] Recent examples include the reactions with sterically crowded oxazolidone

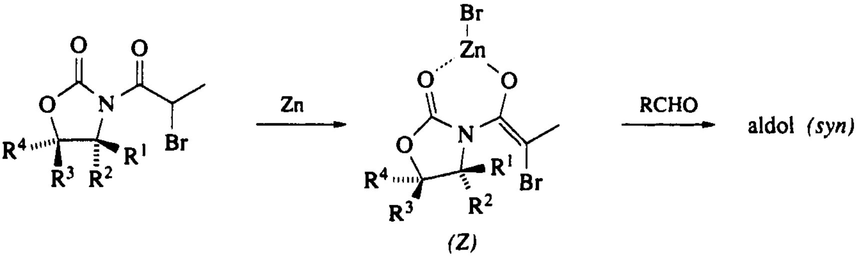

$R^1 = R^2$ = Me; $R^3 = R^4$ = H

$R^1 = R^2$ = Bu; $R^3 = R^4$ = $-(CH_2)_5-$

Scheme 53

derivatives, which give predominantly *syn* aldol products (Scheme 53),[197,198] and an intramolecular reaction (Scheme 54).[199] A zinc ester enolate has been observed to have a dimeric structure containing both Zn—O and Zn—C bonds.[195,196]

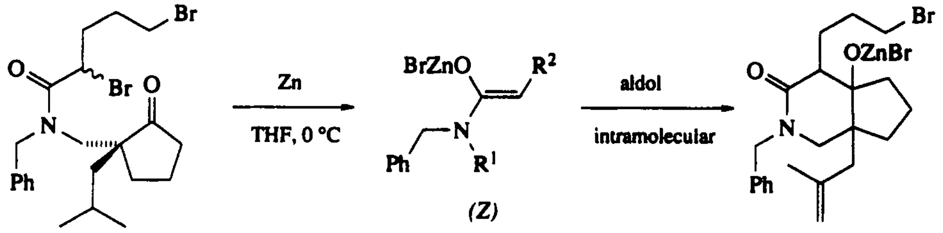
Br
O
Br
O
N
Ph
Zn
THF, 0 °C
BrZnO
R2
N
Ph
R1
(Z)
aldol
intramolecular
Br
OZnBr
O
N
Ph

**Scheme 54**

The reaction of α-bromo ketones with diethylzinc leads to an ethylzinc enolate (equation 38).[200]

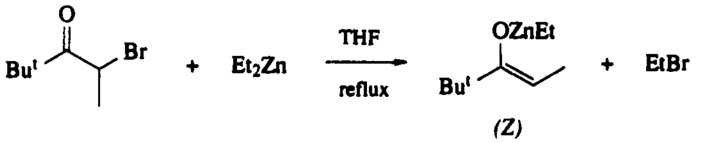 (38)
O
Bu^t
Br
+
Et2Zn
THF
reflux
OZnEt
Bu^t
(Z)
+
EtBr

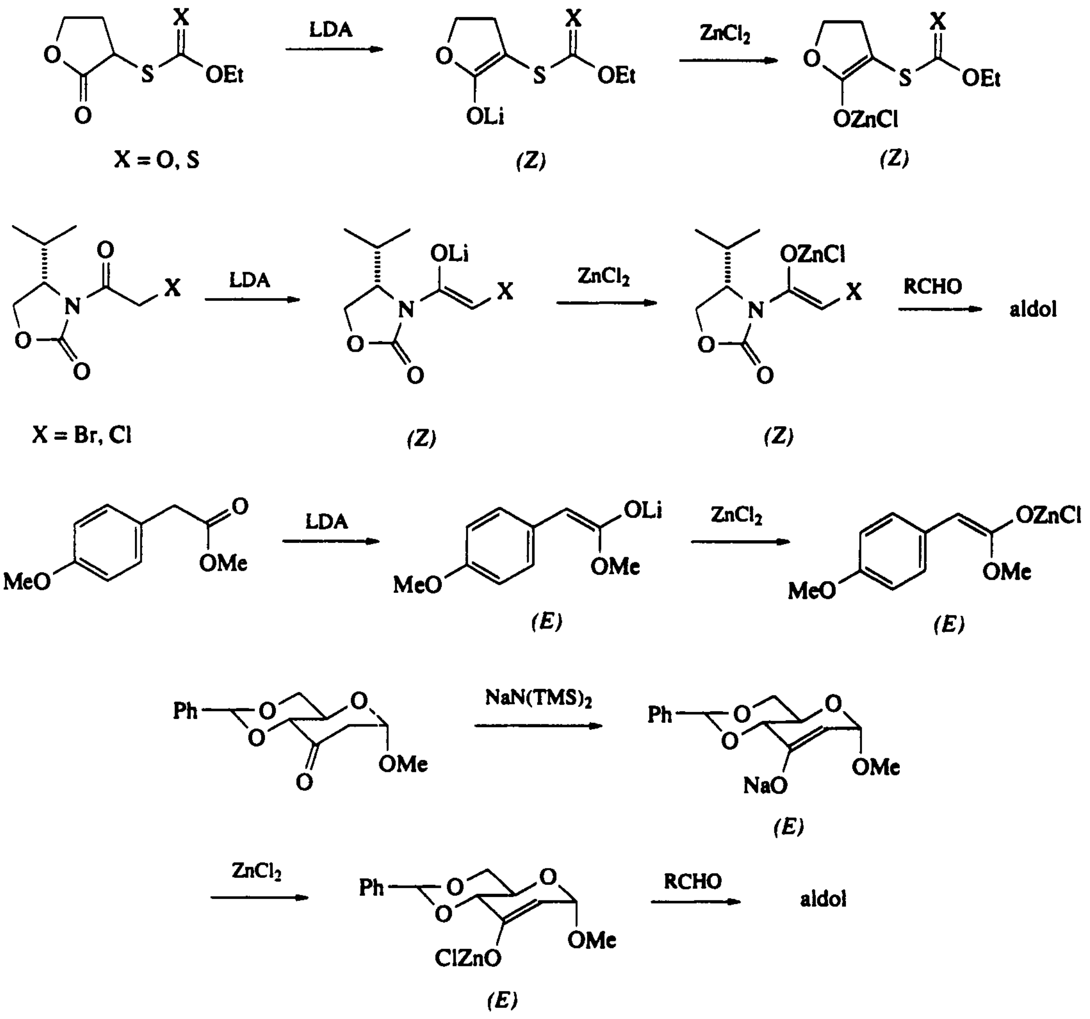
X
O
S
OEt
O
X = O, S
LDA
OLi
(Z)
ZnCl2
OZnCl
(Z)
O
X
N
O
X = Br, Cl
LDA
OLi
(Z)
ZnCl2
OZnCl
(Z)
RCHO
aldol
O
OMe
MeO
LDA
OLi
OMe
MeO
(E)
ZnCl2
OZnCl
OMe
MeO
(E)
Ph
O
O
O
OMe
NaN(TMS)2
NaO
OMe
(E)
ZnCl2
ClZnO
OMe
(E)
RCHO
aldol

**Scheme 55**

A common way to generate zinc enolates, introduced by House,[201] is the reaction of (usually) lithium enolates with zinc chloride or zinc bromide (Scheme 55).[77,136,202,203] Boersma's experiments showed that the second chlorine atom could not be replaced with an excess of lithium enolate.[204]

Lithium triorganozincates, $R_3ZnLi$, are known to effect 1,4-addition of alkyl groups to α,β-unsaturated ketones (Scheme 56).[205–208] They are an attractive alternative to the lithium diorganocuprates because of their solubility and thermal stability. A disadvantage of this method is that only one alkyl ligand can be transferred; the other two are lost. Mixed zincates of the type $R^1R^2_2ZnLi$, where $R^2$ is methyl, are very effective for circumventing this problem.[209] The $R^1$ group undergoes efficient 1,4-addition to α,β-unsaturated ketones, but the methyl groups ($R^2$) remain untransferred. The reactions with ketones (**16**) to (**18**) work well, when the transferring ligand is *n*-butyl or *s*-butyl, but ketones that are disubstituted on the β-carbon (**19**) give no 1,4-adduct. The mixed zincates are generated from methyllithium, zinc chloride and the lithiated transfer group (Scheme 57).[209]

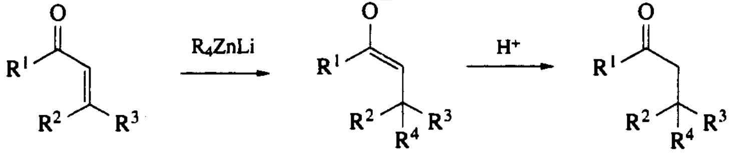

Scheme 56

$$\text{2 equiv. MeLi} \xrightarrow[\text{THF, 0 °C}]{\text{ZnCl}_2\text{/TMEDA}} \text{Me}_2\text{Zn} \xrightarrow{\text{RLi}} \text{RMe}_2\text{ZnLi}$$

Scheme 57

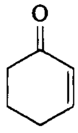
(**16**)

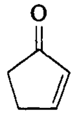
(**17**)

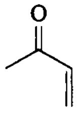
(**18**)

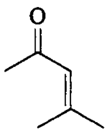
(**19**)

A similar type of reaction has been conducted with $ZnCl_2$–TMEDA and 3 equiv. of a variety of Grignard reagents.[210] The experiments offer no real evidence for the existence of $R_3ZnMgX$ (X = Cl, Br). The formula '$R_3ZnMgX$' denotes only the stoichiometry involved in preparing the solutions used. Reactions of ketones (**16**) to (**18**) with '$R_3ZnMgX$' (R = *n*-butyl, isopropyl, phenyl) give excellent yields of 1,4-adduct and usually less than 3% 1,2-adduct. Ketone (**19**) fails to react here, too (see above). An example with similar reagents to achieve 1,4-addition is shown in equation (39).[211]

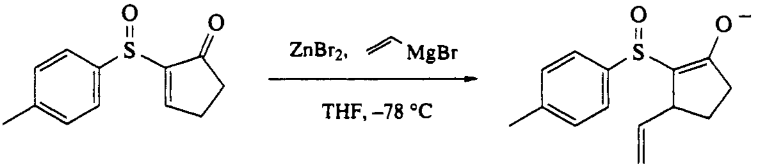

(39)

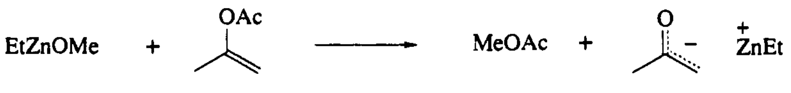

(40)

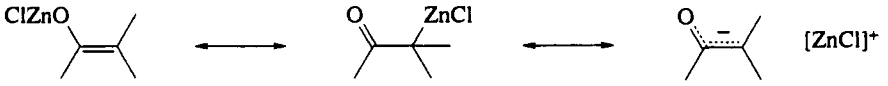

Scheme 58

The exchange reaction between ethylzinc methoxide and enol acetates affords ethylzinc enolates, which decompose by polymerization or by reaction with the methyl acetate produced in the exchange reaction (equation 40).[204]

Although zinc ketone enolates are generally considered to exist with an oxygen-bound rather than a carbon-bound metal, there is still some controversy. Boersma assumes that they contain both zinc–carbon and zinc–oxygen bonds (Scheme 58).[204] One indication that they contain only an oxygen–metal bond in solution is that the $^{13}C$ NMR data for zinc enolates are similar to the data for alkali metal enolates.[200]

## 1.4.11 OTHER TRANSITION METAL ENOLATES

Three different types of transition metal enolates are known:[212,213] metallaenolates (**20**); enolates with *O*-bonded (**21**) metals; and enolates with *C*-bonded (**22**) metals.

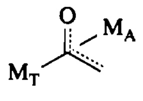

**(20)**

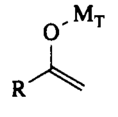

**(21)**

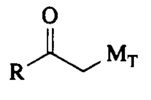

**(22)**

$M_T$ = transition metal
$M_A$ = alkali metal (mostly)

Metal–acyl complexes of iron, cobalt and rhenium have been reported to react with strong bases (BuLi or LDA) to give lithium enolates. Reaction of these enolates with various metal salts generates enolates with different countercations through transmetallation. These enolates are called metallaenolates (**20**). They are somewhat different from the usual enolates:[214–216] (i) they undergo *C*- rather than *O*-silylation; and (ii) very strong bases are needed to generate them, indicating that an ionic resonance form makes a significant contribution to the structure (Scheme 59).

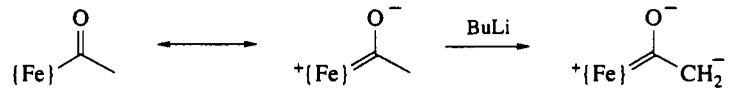

**Scheme 59**

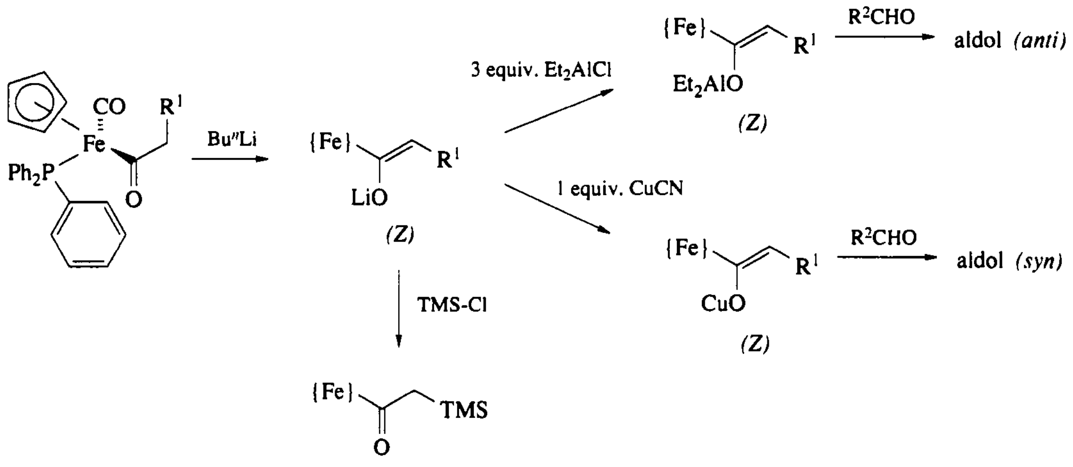

**Scheme 60**

Enolates of iron–acyl complexes have been studied extensively, especially by Davies and Liebeskind and their respective coworkers. The chiral complex [$\eta^5$-CpFe(PPh$_3$)(CO)COCH$_2$R] is usually used; it can be prepared in racemic or optically active form. The enolate usually has the *anti* conformation with regard to CO and $O^-$.[217–223] Copper (*Z*)-enolates give predominantly *syn* aldols, whereas diethylaluminum (*Z*)-enolates produce *anti* aldols (Scheme 60).[224,225] If $R^1$ = H, the terms *syn* and *anti* make no sense

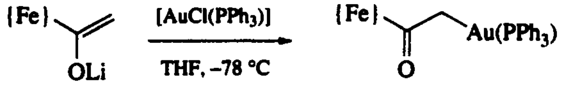
{Fe}
OLi
[AuCl(PPh3)]
THF, -78 °C
{Fe}
Au(PPh3)
O

(41)

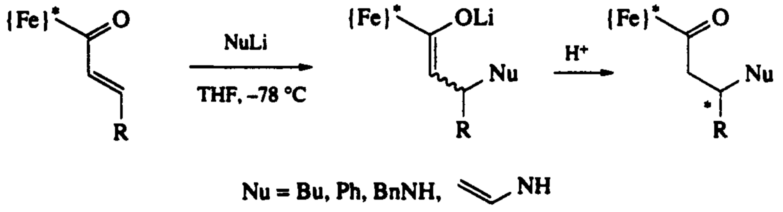
{Fe}*
O
R
NuLi
THF, -78 °C
{Fe}*
OLi
Nu
R
H+
{Fe}*
O
Nu
R
Nu = Bu, Ph, BnNH,
NH

Scheme 61

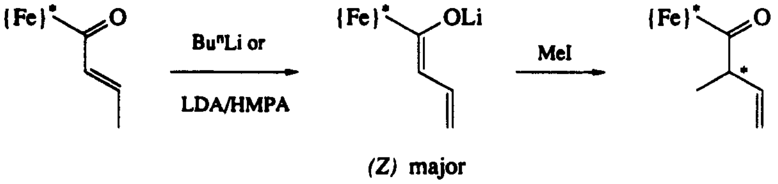
{Fe}*
O
BunLi or
LDA/HMPA
{Fe}*
OLi
MeI
{Fe}*
O
(Z) major

Scheme 62

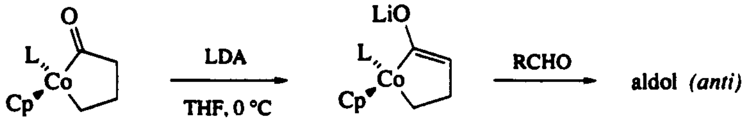
O
L
Co
Cp
LDA
THF, 0 °C
LiO
L
Co
Cp
RCHO
aldol (anti)

Scheme 63

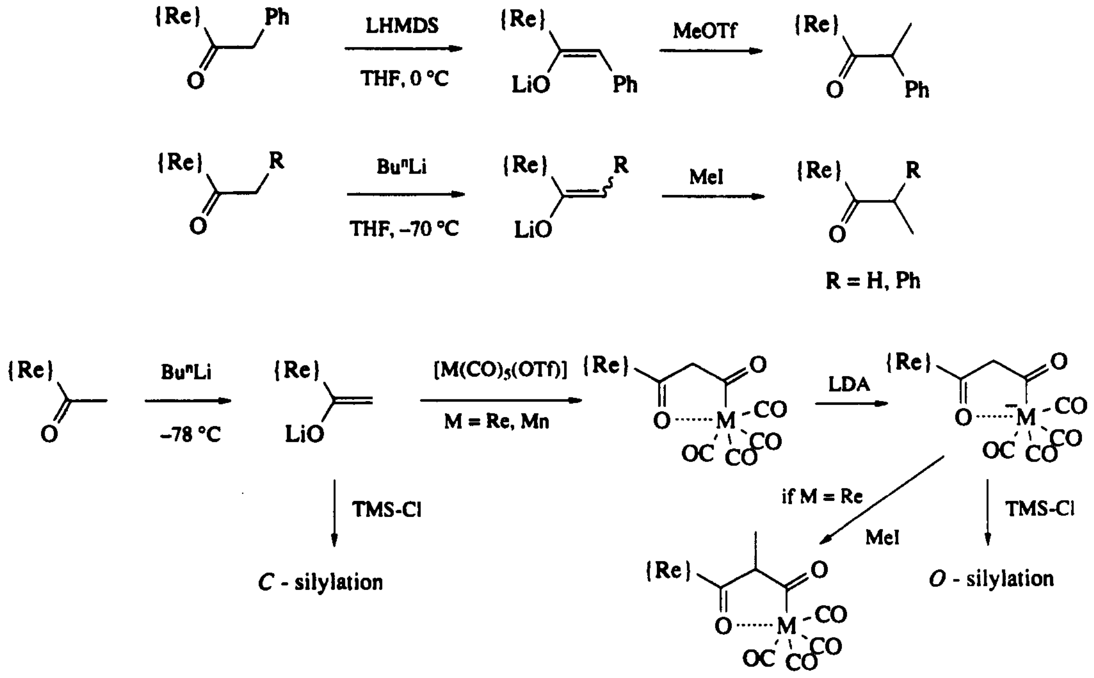
{Re}
Ph
O
LHMDS
THF, 0 °C
{Re}
LiO
Ph
MeOTf
{Re}
O
Ph
{Re}
R
O
BunLi
THF, -70 °C
{Re}
R
LiO
MeI
{Re}
R
O
R = H, Ph
{Re}
O
BunLi
-78 °C
{Re}
LiO
[M(CO)5(OTf)]
M = Re, Mn
{Re}
O
O
M
CO
OC
CO
CO
LDA
{Re}
O
O
M
CO
OC
CO
CO
TMS-Cl
C - silylation
if M = Re
MeI
{Re}
O
O
M
CO
OC
CO
CO
TMS-Cl
O - silylation

Scheme 64

anymore, but two diastereomers are distinguishable.[226-228] $Bu^{i}_2Al$, ClSn and BrSn enolates produce one diastereomer with good selectivity. A *C*-bonded enolate of an iron–acyl complex can be generated with $[AuCl(PPh_3)]$ (equation 41).[229] Another way to these enolates is the diastereoselective conjugate addition of nucleophiles to chiral α,β-unsaturated acyl complexes of $[\eta^5\text{-CpFe(PPh}_3\text{)(CO)}]$ (Scheme 61)[230] or the deprotonation of these with $Bu^nLi$ or LDA–HMPA (Scheme 62).[231,232]

Cyclic cobalt–acyl complexes can be deprotonated, and subsequent reaction of these enolates with aldehydes gives predominantly the *anti/threo* product (Scheme 63).[233] Rhenium–acyl complexes can be deprotonated in the same manner. These lithium enolates can be alkylated or can react with $[M(CO)_5(OTf)]$ (M = Re, Mn) to give the corresponding enolates (Scheme 64).[234,235]

Many transition metal enolates of type (**21**) or (**22**) are known,[212,213,236] but only a few have shown 'normal enolate behavior', *e.g.* aldol reaction, reaction with alkyl halides, *etc.* Particularly useful examples have been developed by Molander. In a process analogous to the Reformatsky reaction, an α-bromo ester may be reduced with $SmI_2$ to provide excellent yields of condensation products (Scheme 65) which are generated through intermediacy of a samarium(III) enolate.[237]

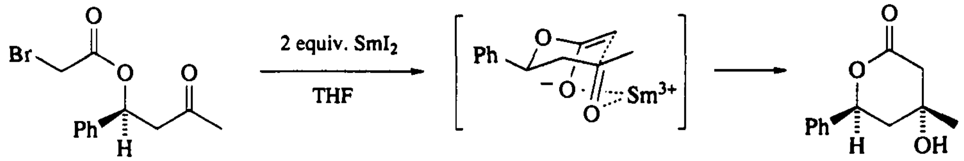

**Scheme 65**

A manganese reagent prepared from RLi or RMgCl and $MnCl_2$ reacts with cyclohexenone in a 1,4-addition (Scheme 66).[238,239] The structure of the reagent is not known and the formula (*e.g.* '$R_2Mn$') is attributed based upon the ratio of the reactants.

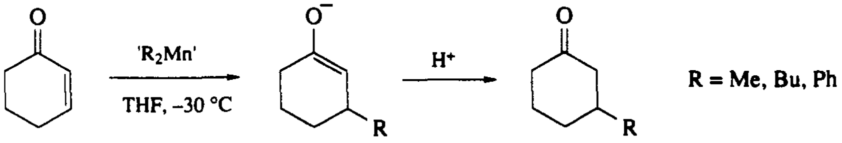

**Scheme 66**

Molybdenum and tungsten *C*-enolates can be generated by reaction of complexes with α-chlorocarbonyls (Scheme 67).[212,213] These 2-oxaallyl($\eta^1$-*C*-enolate) complexes react with aldehydes in a photoreaction to produce aldol products, by way of the $\eta^3$-enolate.

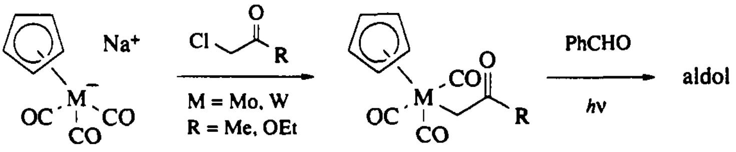

**Scheme 67**

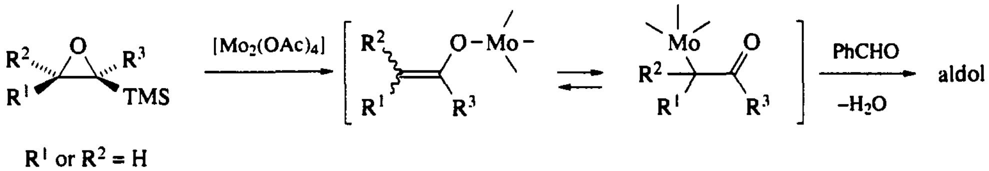

**Scheme 68**

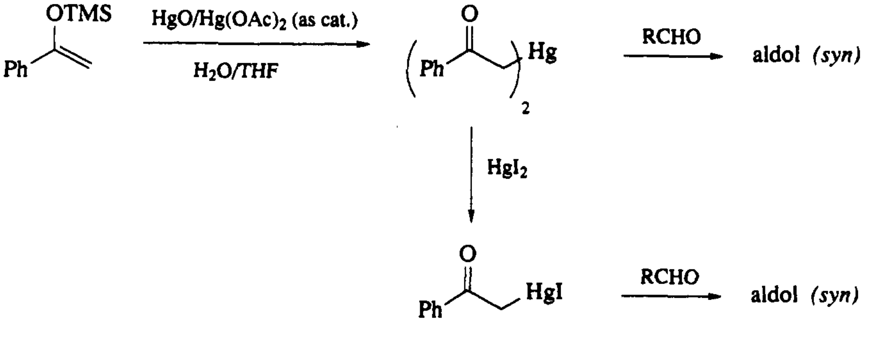

**Scheme 69**

α,β-Epoxysilanes react with molybdenum(II) acetate dimer to give presumably an enolate intermediate, which can subsequently undergo aldol reaction (Scheme 68).[240]

α-Mercurio ketones (*C*-bonded enolates) can be generated by the reaction of trimethylsilyl vinyl ethers with mercury(II) oxide, followed sometimes by further reaction with mercury(II) iodide (Scheme 69).[241,242]

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# 1.5
# The Aldol Reaction: Acid and General Base Catalysis

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## 1.5.1 INTRODUCTION

An 'aldol' reaction is the reaction of one carbonyl compound, acting as a nucleophile in the form of its enol or enolate derivative, with another, acting as an electrophile. The two carbonyl compounds may or may not be the same. The general reaction is subject to either acid or base catalysis. The initial product is a β-hydroxycarbonyl compound. Under some conditions, this primary product undergoes dehydration, resulting in an α,β-unsaturated carbonyl compound. In this chapter, we summarize the aldol reaction from a historical perspective and point out the limitations of the reaction as it was generally used prior to about 15 years ago.[1] Succeeding chapters treat the aldol reaction as it is usually practiced today, in a 'directed' manner, using 'preformed' enolates.[2] As will be seen in the sequel, an understanding of the factors regulating the stereochemistry of the aldol reaction has been largely responsible for the rebirth of this venerable reaction in the last 15 years.[3]

## 1.5.2 BACKGROUND

The trivial name of the reaction was applied by Wurtz in 1872, and stems from the trivial name of the dimer resulting from the acid-catalyzed self-reaction of acetaldehyde (equation 1).[4] In time, the term came to be applied to the analogous self-condensation reactions of ketones, the first known example of which was the acid-mediated dimerization of acetone, discovered in 1838.[5] The first use of a base as a catalyst for the aldol reaction was in the reaction of furfural with acetaldehyde or acetone (equation 2).[6] This example also illustrates the first example of a 'mixed' aldol reaction, a process that came to be known as the Claisen–Schmidt condensation.[7]

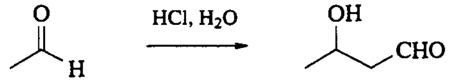

(1)

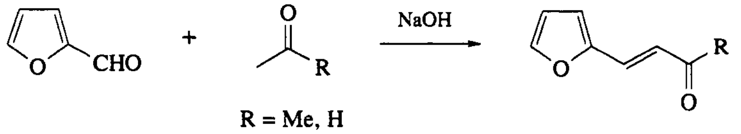

(2)

As implied in equations (1) and (2), the general reaction may give rise to a β-hydroxycarbonyl compound or to its dehydration product, the corresponding α,β-unsaturated carbonyl compound. For the first century after its christening, both processes were generally referred to as the 'aldol condensation'.[1] More recently, the latter term has been reserved for reactions leading to α,β-unsaturated carbonyl products, in keeping with the more general usage of 'condensation'.[8] In this treatise, we use the terms aldol *addition* reaction[9] for processes leading to β-hydroxycarbonyl compounds (*e.g.* equation 1) and the term aldol *condensation* for processes leading to α,β-unsaturated carbonyl compounds (*e.g.* equation 2); the term aldol reactions is used generically to apply to either kind of process.

## 1.5.3 REVERSIBILITY OF THE ALDOL REACTION

One of the most important characteristics of the aldol reaction is its easy reversibility under many conditions. Since this factor has such a generally profound effect, we briefly introduce the topic here. For an aldol addition reaction that is carried out under the influence of a catalytic amount of acid or base in protic medium $\Delta H^\circ$ and $\Delta G^\circ$ can be estimated from thermochemical data. Guthrie has estimated $\Delta H^\circ$ and $\Delta G^\circ$ for the aldol addition depicted in equation (3) to be –9.8 kcal mol$^{-1}$ and –2.4 kcal mol$^{-1}$, respectively (1 cal = 4.18 J).[10] The thermochemical values used in this estimation, and the derived values of $\Delta H^\circ$ and $\Delta G^\circ$, refer to species at equilibrium with the covalently hydrated aldehydes. It is not expected that values for the free aldehydes would be greatly different. The equilibrium constant for equation (3) is 400 M$^{-1}$.

A similar estimate for the dimerization of acetone (equation 4) leads to an estimated $\Delta G^\circ$ of +2 kcal mol$^{-1}$.[11] Other values of $\Delta G^\circ$ for selected aldol equilibria are presented in Table 1.

The data in Table 1 are in qualitative accord with our experience with the aldol addition reaction on two counts: (1) aldol reactions in which aldehydes are receptors are often easily reversible under mild conditions; (2) aldol reactions in which ketones are receptors are invariably more easily reversible than

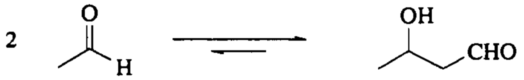

(3)

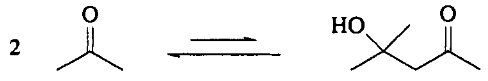

(4)

**Table 1** Equilibrium Constants for Aldol Addition Equilibria[a]

| *Nucleophile* | *Electrophile* | *$\Delta G°$* (kcal mol$^{-1}$) | *K* (M$^{-1}$) |
|---|---|---|---|
| MeCHO | $CH_2O$ | –6.32 | |
| | MeCHO | –3.55 | 400 |
| | PhCHO | –2.18 | |
| | $Me_2CO$ | –0.02 | |
| | PhCOMe | +2.31 | |
| $Me_2CO$ | $CH_2O$ | –4.58 | |
| | MeCHO | –1.75 | |
| | PhCHO | –1.27 | 8.5 |
| | $Me_2CO$ | +1.92 | 0.039 |
| | PhCOMe | +4.08 | |
| PhCOMe | $CH_2O$ | –3.30 | |
| | MeCHO | –0.47 | |
| | PhCHO | +0.16 | 0.76 |
| | $Me_2CO$ | +3.00 | |
| | PhCOMe | +5.37 | |
| $MeCO_2H$ | $CH_2O$ | –9.84 | |
| | MeCHO | –6.94 | |
| | PhCHO | –6.35 | |
| | $Me_2CO$ | –3.39 | |

[a]Values for $\Delta G°$ are mostly calculated from free energies of formation of reactants. Values for $K$ are experimental values. For more details, see ref. 12.

analogous reactions with aldehydes. The available evidence suggests that the aldol addition reaction has only a modest driving force in most cases, and in some is actually endothermic. The main structural factor that favors reversibility is steric compression in the aldol. As seen in the difference between equations (3) and (4), branching at the hydroxy carbon in the aldol results in a less favorable $\Delta H°$. Similarly, branching at the carbon between the hydroxy and carbonyl functions in the aldol promotes reversal.

The foregoing value of $\Delta G°$ for the catalytic aldol addition reaction shows that the strong O—H bond in the product provides a significant fraction of the driving force for the reaction. For example, in equation (3) about 60% of the driving force comes from exchange of one of the acetaldehyde C—H bonds for the aldol O—H bond; this approximation assumes $\Delta H°$ for the C—H and O—H bonds to be 98 kcal mol$^{-1}$ and 104 kcal mol$^{-1}$, respectively. It follows that an aldol addition reaction carried out with a preformed acetaldehyde enolate in nonprotic medium (equation 5) will be less exothermic than the catalytic version by 6 kcal mol$^{-1}$. In addition, one must consider the relative basicities of the two anions (or relative acidities of the corresponding conjugate acids). These are taken to be p$K_a$ 20 for a methyl ketone and p$K_a$ 18 for a secondary alcohol. The difference of 2 p$K$ units contributes an additional –2.7 kcal mol$^{-1}$ to $\Delta H°$ at room temperature. If we take the actual $\Delta G°$ of equation (3) to be –10 kcal mol$^{-1}$, then we can estimate that $\Delta G°$ of equation (5) is of the order of –1 kcal mol$^{-1}$. The preformed enolate version of equation (4) is estimated to be endothermic by about 5 kcal mol$^{-1}$.

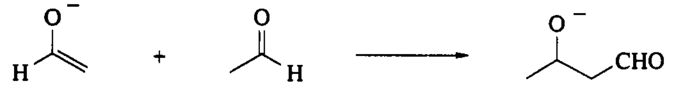

(5)

Of course, under many conditions, the preformed enolate aldol reaction appears to be significantly exothermic. The additional driving force is presumably provided by the enthalpy of coordination of the ambident aldolate ion with a cation. The importance of cation solvation in providing a driving force for the aldol reaction has been elegantly demonstrated by Noyori and coworkers.[12] In this important experiment, the tris(dimethylamino)sulfonium ($TAS^+$) enolate of 1-phenyl-2-propanone was prepared as shown in equation (6). The 'naked enolate' was obtained as a yellow crystalline material, free of trimethylsilyl fluoride, by concentration of the THF solution.

The $TAS^+$ enolate reacts rapidly with acetic anhydride in THF to give the enol acetate, and with methyl iodide to give the *C*-methylated product. However, addition of benzaldehyde to the THF solution

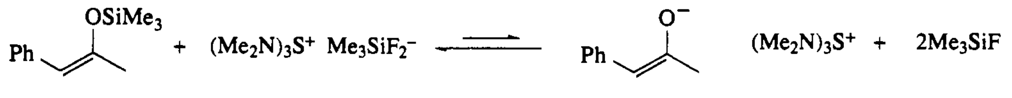

(6)

of the naked enolate, followed by aqueous work-up, gives no aldol! If trimethylsilyl fluoride is added to the enolate + benzaldehyde solution prior to work-up, the silylated aldol is obtained. The most straightforward rationale for these observations is that the aldol addition reaction of the TAS$^+$ enolate is endothermic. The successful reaction in the presence of trimethylsilyl fluoride results from silylation of a small, equilibrium amount of aldolate. The driving force in this case is presumably formation of F$^-$ and the strong Si—O bond in the reaction of the aldolate with $Me_3SiF$. Note that this rationale requires that the aldolate react with $Me_3SiF$ considerably more rapidly than the enolate.

Although we do not know the precise $\Delta G°$ for preformed enolate aldol additions, the available evidence implies that such reactions are only modestly exothermic in many cases, particularly with Group I and Group II cations. As in the catalytic aldol addition, there are a number of structural features that can make the reaction less exothermic. One of these factors, demonstrated vividly in the Noyori experiment, is a weakly coordinated cation. Thus, it is found that sodium and potassium aldolates are more prone to reversal than are their lithium counterparts. Conversely, a strongly coordinated cation provides a greater driving force for reaction; examples are seen in the increased stability of boron and zinc aldolates relative to Group I analogs. Steric compression in the aldolate is another factor that makes the reaction more easily reversible. Use of a more basic enolate results in a more exothermic process, for an obvious reason. Aldolates derived from amide enolates are less prone to reversal than those derived from ketone or ester enolates. Aldol reactions involving preformed enolates are discussed in succeeding chapters in this volume.

For aldol reactions carried out under catalytic conditions, dehydration of the initial aldol may provide an additional driving force, due to formation of water (with two strong O—H bonds) and the enone system. Such reactions are almost always thermodynamically favorable.

After this chapter had been completed, there appeared a paper describing the first determination of the thermochemistry of an aldol reaction of a preformed enolate (E. M. Arnett, F. J. Fisher, M. A. Nichols and A. A. Ribeiro, *J. Am. Chem. Soc.*, 1989, **111**, 748). The enthalpy of reaction of the hexameric lithium enolate of pinacolone with pivalaldehyde in hexane at 25 °C is $-30.19 \pm 0.76$ kcal mol$^{-1}$. With one equivalent of various added ligands, enthalpies of reaction are: $-17.94 \pm 0.36$ kcal mol$^{-1}$ in tetrahydrofuran (THF); $-20.85 \pm 0.72$ kcal mol$^{-1}$ in tetramethylethylenediamine (TMEDA); and $-19.05 \pm 0.44$ kcal mol$^{-1}$ in dimethoxyethane (DME). The product is believed to be a tetrameric lithium aldolate in each case. In view of the discussion given in this section, these reactions are surprisingly exothermic. Note, however, that one equivalent of THF makes the reaction about 10 kcal mol$^{-1}$ *less* exothermic. The enthalpy of reaction in pure THF has yet to be determined experimentally.

## 1.5.4 OVERVIEW: REACTIONS UNDER PROTIC CONDITIONS

Traditionally, aldol reactions were carried out under conditions wherein the enol or enolate is generated reversibly in the presence of the electrophilic carbonyl component. Typical conditions employed sodium hydroxide in aqueous solvents, alkali metal alkoxides in the corresponding alcoholic solvents, or protic acids. Stronger bases (*e.g.* aluminum tri-*t*-butoxide) were sometimes used, but usually in the presence of both the aldol donor and acceptor molecules. When the reaction is carried out under these enol- or enolate-equilibrating conditions, there are several serious limitations, as follows: (1) Because of the modest intrinsic driving force for the reaction, self-addition processes often proceed in low yield. (2) Under enol- or enolate-equilibrating conditions, 'mixed' aldol reactions often give complex mixtures of products. This is especially true if the two reactants have α-hydrogens of comparable acidity and if the two carbonyl groups are of comparable electrophilicity. (3) Dehydration of the initially formed aldol presents a complication, especially with acid catalysis. However, this dehydration provides a significant driving force, and the formation of α,β-unsaturated aldehydes and ketones by the aldol condensation under conditions of catalytic acid or base is often an excellent preparative method.

## 1.5.5 SELF-REACTIONS OF ALDEHYDES

Base-catalyzed self-addition of aldehydes to form β-hydroxy aldehydes is successful under mild conditions, but only with relatively low molecular weight aldehydes; examples are presented in equations (7) and (8).[13,14] The rule of thumb is that aldehydes of up to about six carbons can be dimerized in aqueous and alcoholic medium by such methods.[15] Attempts to force the addition reaction of higher molecular weight aldehydes by using more vigorous conditions result in dehydration of the initial aldols, with formation of the corresponding α,β-unsaturated aldehydes. These products are often available by this method in reasonable yield (*e.g.* equation 9).[16]

2,4,6-Trimethylphenoxymagnesium bromide catalyzes aldol condensation of aliphatic aldehydes to form α,β-unsaturated aldehydes in excellent yield if the reaction is carried out in benzene (Scheme 1).[17] In hexamethylphosphoric triamide (HMPA), the diol monoesters (**1**) and (**2**) are produced, also in nearly quantitative yield. Compounds (**1**) and (**2**) arise from a process known as the 'Tischtschenko reaction' (*vide infra*).

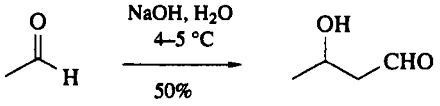
O
H
NaOH, H2O
4–5 °C
50%
OH
CHO

(7)

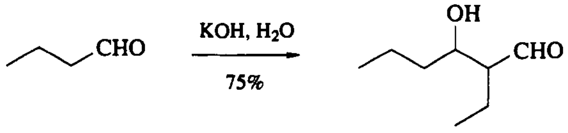
CHO
KOH, H2O
75%
OH
CHO

(8)

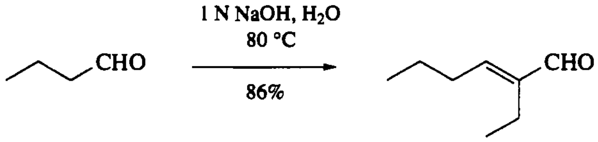
CHO
1 N NaOH, H2O
80 °C
86%
CHO

(9)

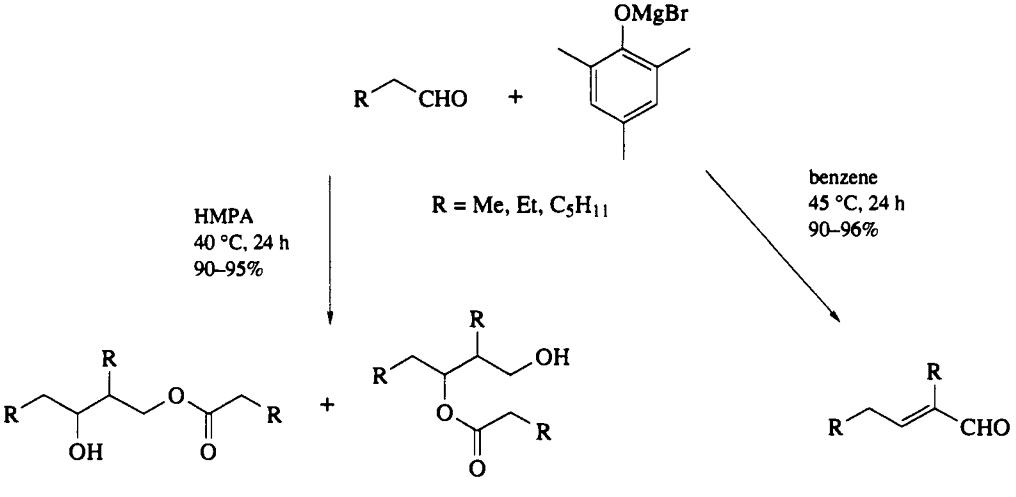
OMgBr
R
CHO
+
R = Me, Et, C5H11
HMPA
40 °C, 24 h
90–95%
benzene
45 °C, 24 h
90–96%
R
R
O
R
OH
O
+
R
R
OH
O
R
O
R
R
CHO

(**1**) (**2**)

**Scheme 1**

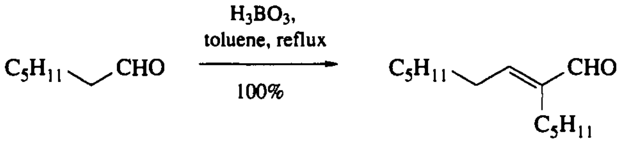
C5H11
CHO
H3BO3,
toluene, reflux
100%
C5H11
CHO
C5H11

(10)

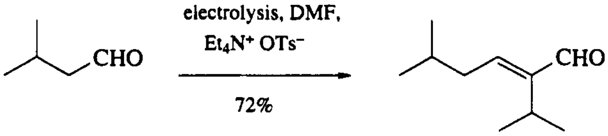
CHO
electrolysis, DMF,
Et4N+ OTs−
72%
CHO

(11)

Offenhauer and Nelsen discovered that boric acid is an excellent catalyst for aldol condensations; treatment of heptanal with boric acid in refluxing toluene under a Dean–Stark trap gives the condensation product in quantitative yield (equation 10).[18] The authors suggested an intermediate enol borate; this was probably the first example of a boron enolate aldol reaction.

Shono and coworkers have shown that aliphatic aldehydes may be condensed electrochemically (equation 11).[19] Current efficiency for the reaction in equation (11) was found to be $0.96 \times 10^4$%.

Aldehydes may be dimerized, either to β-hydroxy aldehydes or to α,β-unsaturated aldehydes, by the use of the anion-exchange resins Amberlite and Dowex.[20]

Catalytic aldol dimerizations of aldehydes sometimes lead to unexpected products. An example is shown in equation (12), where the initial aldol has formed an 'aldoxan' derivative by interacting with a third equivalent of propionaldehyde.[21] Although the aldoxan is dissociated to 1 mol each of the aldol and aldehyde upon distillation, the reaction effectively limits the yield of the aldol addition reaction itself to 66.7%.

A related phenomenon is the easy dimerization of some aldols upon standing; an example is the conversion of aldol itself into paraldol (equation 13).[22] Again, aldol can be regenerated by distillation of the dimer.

A more complex oligomer is obtained by treatment of butanal with KOH or NaOH in aqueous ethanol. This reaction has been shown to produce the tetramers (**3**)–(**5**) and trimer (**6**; equation 14), some in respectable yield, depending on the exact reaction conditions.[23,16] Compound (**3**) is produced as a mixture of four diastereomers and probably arises from dimerization of the initial aldol condensation product, 2-ethylhexenal. Diol (**4**), also obtained as a mixture of four stereoisomers, appears to be a Cannizarro reduction product of (**3**). Lactones (**5**) and (**6**) can reasonably arise by mechanisms involving hydride transfer from a cyclic hemiacetal.

Hydride transfer is also involved in the Tischtschenko reaction, wherein an aliphatic aldehyde is dimerized under the influence of aluminum tri-*t*-butoxide to the corresponding ester (equation 15).[24] Tischtschenko reaction products are sometimes observed as side products in aldol reactions. Under proper conditions, rather complex esters may be prepared in excellent yield (*e.g.* equations 16 and 17).[25]

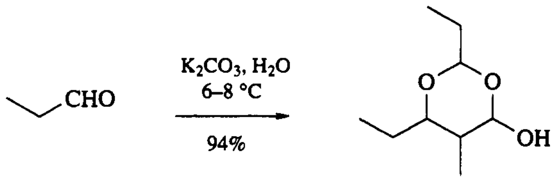

(12)

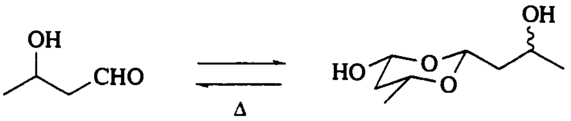

(13)

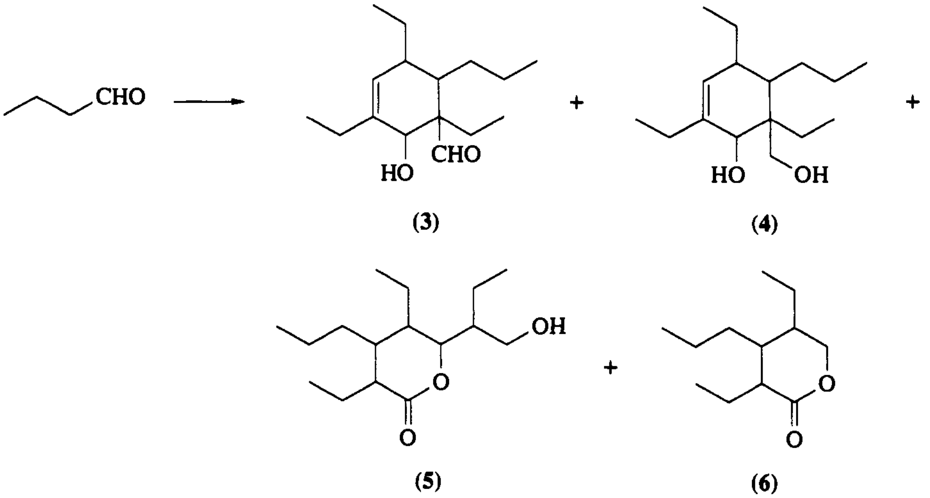

(14)

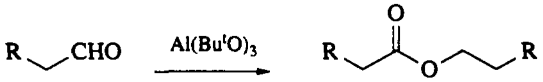

(15)

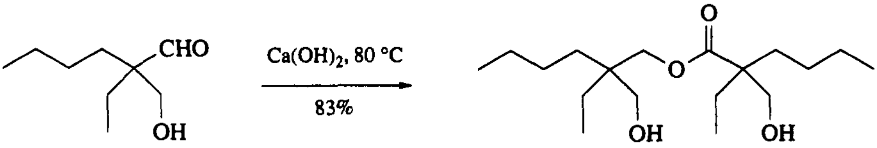

(16)

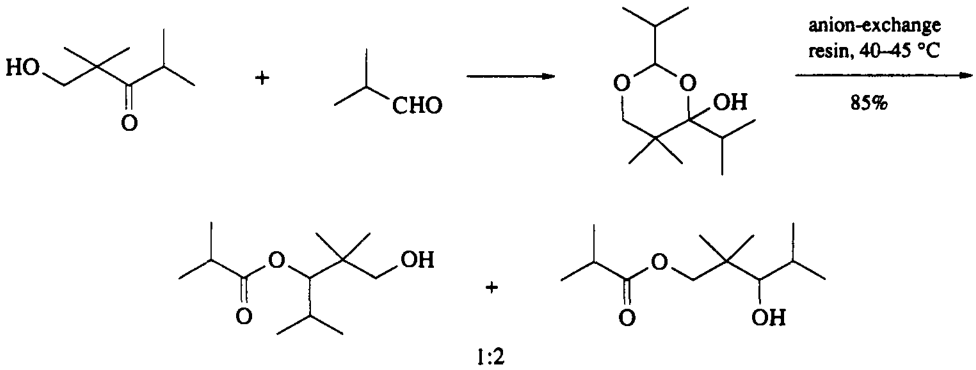

(17)

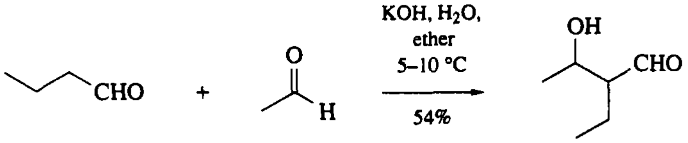

(18)

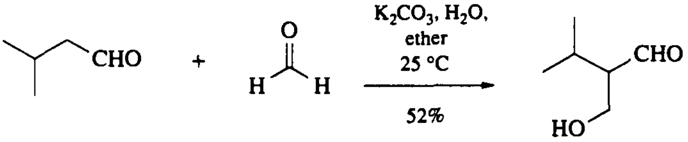

(19)

## 1.5.6 MIXED REACTIONS OF ALDEHYDES

Mixed aldol reactions between two different aldehydes generally give mixtures when each aldehyde can function both as enolate precursor and electrophilic component. In fortunate cases, one of the four possible aldols may predominate. An early generalization (Lieben's rule)[26] stated that the major aldol results from attachment of the carbonyl carbon of the aldehyde with the lesser number of α-substituents to the α-carbon of the aldehyde having the greater number of α-substituents (*e.g.* equation 18).[13]

An extreme case of the foregoing generalization is the reaction of formaldehyde with other aliphatic aldehydes, known as Tollen's reaction.[27] In this reaction it is possible to introduce only one hydroxymethyl group in certain exceptional cases (equation 19).[28] Generally, however, all available α-hydrogens are replaced by hydroxymethyl groups. Unless the reaction conditions are carefully controlled, the aldehyde function of the final aldehyde is reduced by formaldehyde (crossed Cannizzaro reaction), leading to a diol, triol or tetraol (*e.g.* equations 20 and 21).[27a,29] Ho has used this method for a convenient synthesis of branched sugars (equation 22).[30]

The other category of mixed aldehyde reactions that is generally successful is the reaction of an aromatic aldehyde with an aliphatic one. Although the aldol addition products have only rarely been isolated, the method is often acceptable for the preparation of β-aryl-α,β-unsaturated aldehydes (*e.g.* equations 23–25).[31-33]

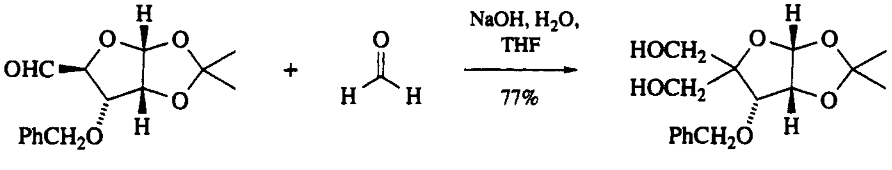

(20)

$$\mathrm{MeCHO} + \mathrm{CH_2O} \xrightarrow[65\%]{\mathrm{Ca(OH)_2,\ H_2O}\ \ 25\ ^\circ\mathrm{C}} \mathrm{C(CH_2OH)_4} \qquad (21)$$

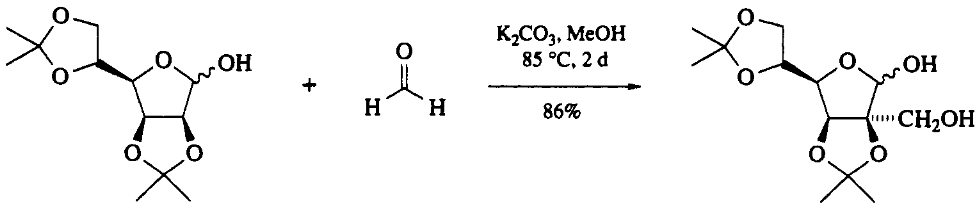

(22)

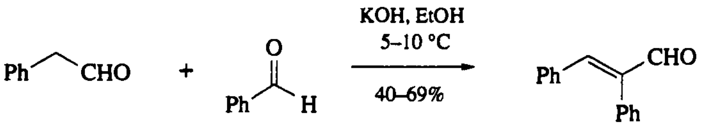

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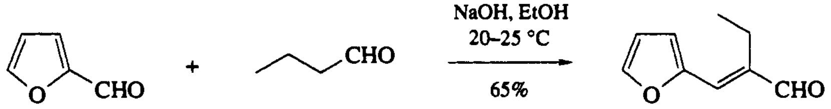

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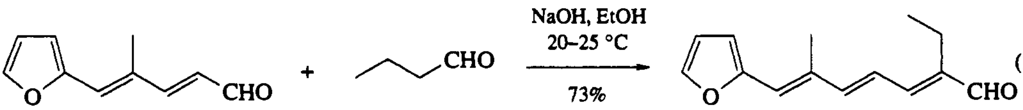

(25)

## 1.5.7 SELF-REACTIONS OF KETONES

Aldol addition reactions of ketones are rarely successful, since they are usually endoergonic. For example, the base-mediated aldolization of acetone provides only a few percent of the aldol, 'diacetone alcohol' (equation 26).[11,34] However, the conversion may be accomplished in 75% yield by refluxing acetone under a Soxhlet extractor containing calcium or barium hydroxide.[13,35] On the other hand, dimethoxyacetone dimerizes under basic conditions to the aldol, with an equilibrium constant significantly greater than unity ($K = 10$ dm$^3$ mol$^{-1}$; equation 27).[36] The difference in equilibrium constants of equations (26) and (27) parallels the equilibrium constants for hydration of the two ketones, and results from the inductive effect of the methoxy groups.

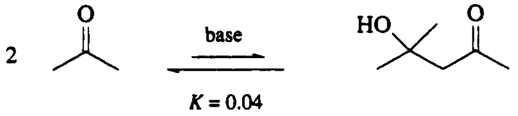

(26)

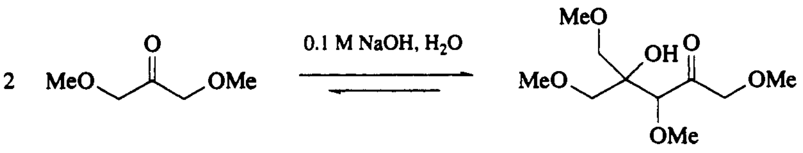

(27)

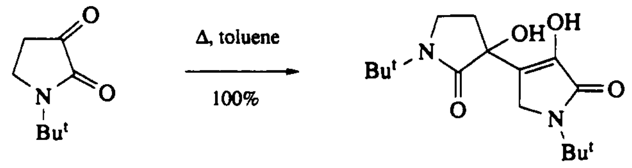

(28)

Cyclic ketones cannot usually be dimerized to the corresponding β-hydroxy ketones under protic conditions. An exception to this generalization is shown in equation (28).[37] The 2,3-dioxopyrrolidine is quantitatively dimerized by being warmed briefly with ethanolic pyridine, or by attempted recrystallization from warm toluene. In this case, as in equation (27), the favorable equilibrium constant is no doubt related to the inductive effect of the amide C═O, which favors hydration and other addition reactions of the ketonic carbonyl.

A number of methods may be used for self-condensation of ketones to give α,β-unsaturated ketones. Cyclic ketones are especially prone to aldol condensation, and the product from cyclopentanone (equation 29)[38] is frequently encountered as a by-product in reactions that involve exposure of cyclopentanone to acid or base. In the example shown in equation (29), the aldol addition reaction is carried out with gaseous HCl, leading to an intermediate β-chloro ketone that is dehydrochlorinated by treatment with base. It has recently been shown that basic alumina is an effective catalyst for the aldol condensation of ketones.[39]

Aldol condensations of monoketones can lead to trimeric products if the reaction is carried out under more vigorous conditions. The prototypical example of this behavior is acetone, which can give rise to mesityl ketone (**7**), phorone (**8**) and isophorone (**9**; equation 30). An example is seen in the treatment of acetone with aluminum tri-*t*-butoxide in toluene (equation 31).[40] Isophorone is frequently obtained as a by-product in base treatment of acetone;[41] it may be formed from the phorone enolate by an electrocyclization mechanism (equation 32).

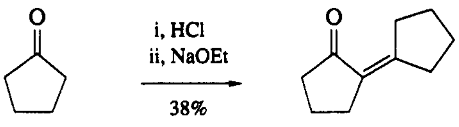

(29)

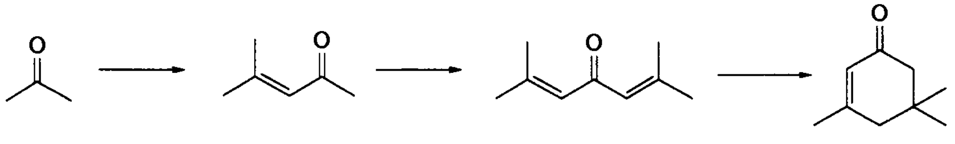

(**7**) (**8**) (**9**)

(30)

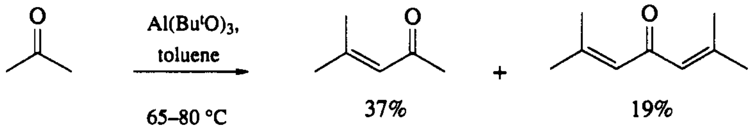

(31)

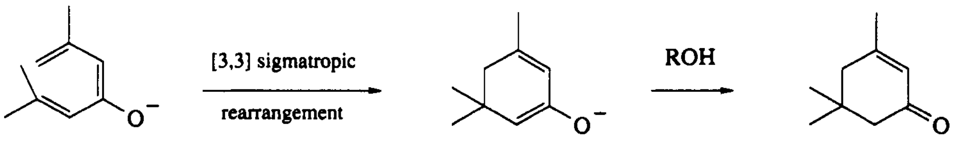

(32)

Acid-catalyzed aldol condensation of ketones can give rise to aromatic products. Examples are the trimerization of acetone to mesitylene (equation 33)[42] and the analogous conversion of 1-indanone to the heptacyclic product (**10**; equation 34).[43]

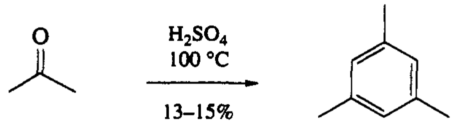

(33)

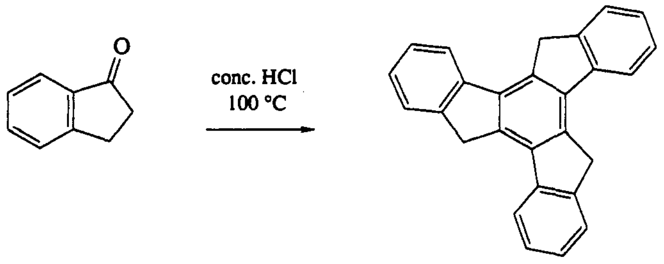

**(10)**

(34)

## 1.5.8 MIXED REACTIONS OF KETONES

Mixed condensations of two ketones are rarely preparatively useful. The factors that determine which of the four possible products will predominate include the relative concentrations and relative acidities of the two ketones, the relative rates of addition of the two carbonyl groups, and the relative rates of dehydration of the intermediate aldols. The examples shown in equations (35)[44] and (36)[45] demonstrate that only minor structural changes can greatly affect the product distribution.

Benzil and its derivatives condense with aliphatic ketones to give 4-hydroxycyclopentenones in good yield (equation 37).[46] Although this reaction is not usually observed with aliphatic diketones, a recent example has been reported.[47] A special version of this reaction involves the use of dibenzyl ketone. In such cases the initial 4-hydroxycyclopentenone dehydrates to form the tetraphenylcyclopentadienone ('tetracyclone'; equation 38).[48]

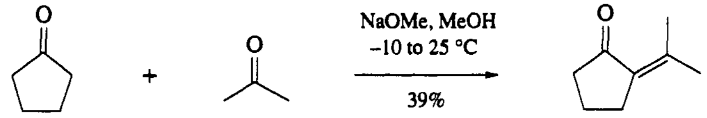

(35)

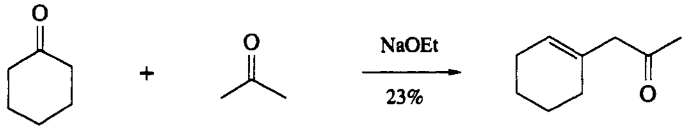

(36)

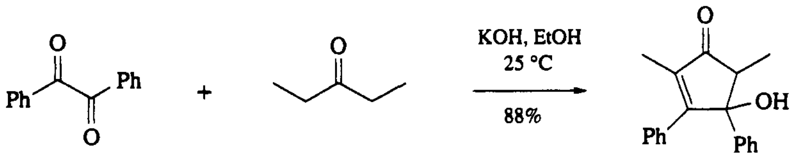

(37)

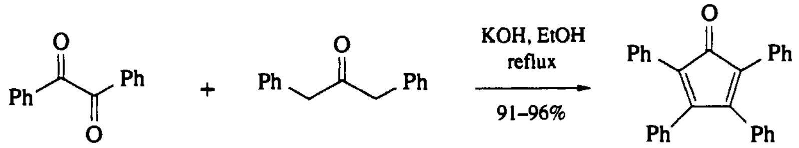

(38)

## 1.5.9 REACTIONS OF KETONES WITH ALDEHYDES

Mixed aldol reactions between ketones and aldehydes are frequently successful because one of the competing side reactions, self-reaction of the ketone, is endothermic. Most commonly, these mixed aldol reactions are carried out under conditions that lead to the α,β-unsaturated ketone product. The principal side reaction is usually aldehyde dimerization.

### 1.5.9.1 Acyclic Ketones

The condensation of aliphatic aldehydes with acetone to give methyl vinyl ketone derivatives is rather common. The reaction can be carried out to the ketol stage (equations 39 and 40),[49,50] or under conditions that lead to the α,β-unsaturated ketone (equations 41 and 42).[51,52] By adjusting the stoichiometry, bis-condensation products can often be obtained in excellent yield (equations 43 and 44).[53,54]

Similar transformations can be obtained in the reactions of acetone with aromatic aldehydes, the classic Claisen–Schmidt reaction. These reactions invariably give the α,β-unsaturated ketone products. Either the mono- or bis-condensation product may be obtained by suitable adjustment of the reaction conditions (equation 45 and 46).[55,56]

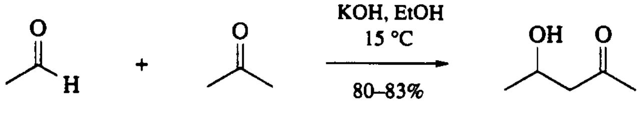
O
H
+
O
KOH, EtOH
15 °C
80–83%
OH
O

(39)

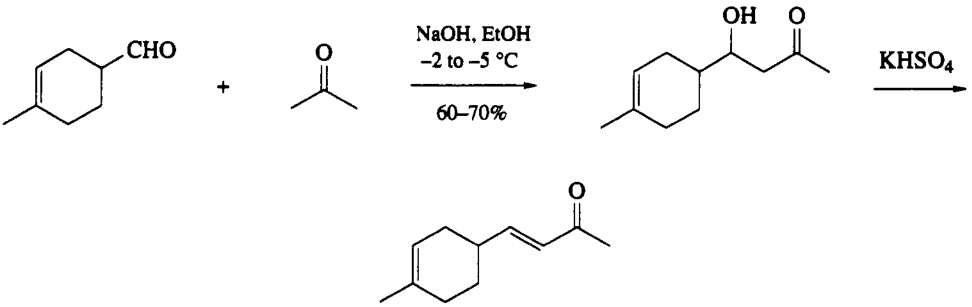
CHO
+
O
NaOH, EtOH
–2 to –5 °C
60–70%
OH
O
KHSO4
O

(40)

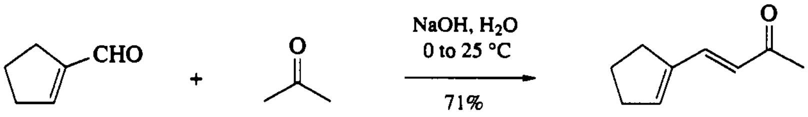
CHO
+
O
NaOH, H2O
0 to 25 °C
71%
O

(41)

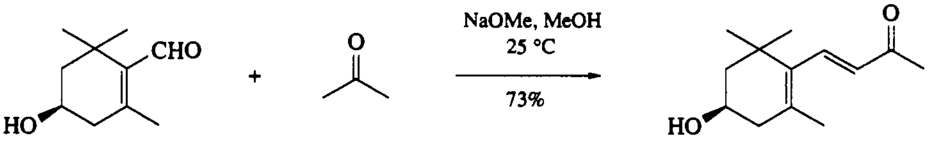
CHO
HO
+
O
NaOMe, MeOH
25 °C
73%
O
HO

(42)

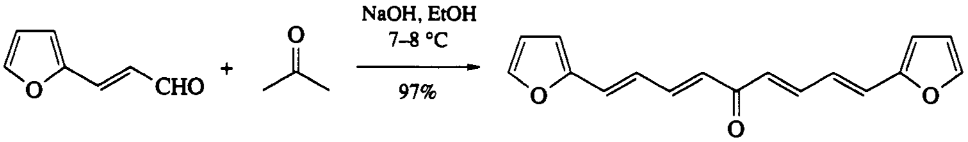
O
CHO
+
O
NaOH, EtOH
7–8 °C
97%
O
O
O

(43)

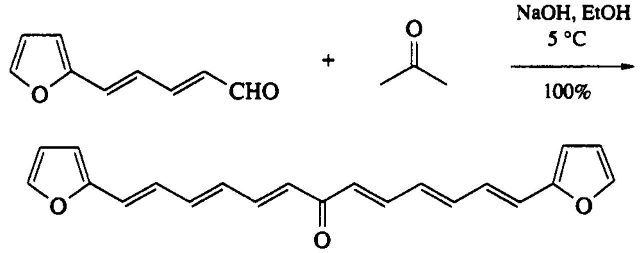
O
CHO
+
O
NaOH, EtOH
5 °C
100%
O
O
O

(44)

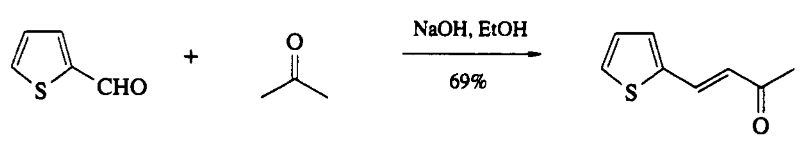

(45)

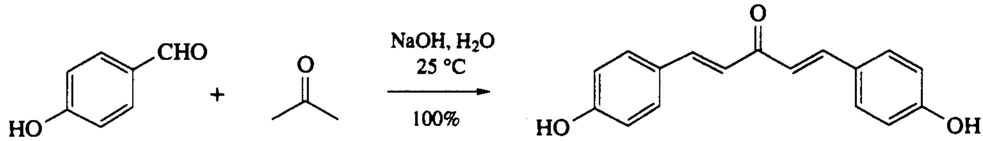

(46)

3-Pentanone is similar to acetone in its behavior, and 1:1 adducts may be obtained from aliphatic aldehydes in good yield (equations 47 and 48).[57,58] 4-Heptanone and higher symmetrical ketones are much less reactive and give very poor yields of aldols with simple aldehydes. However, the reactions of these ketones with *o*-phthalaldehyde often provide benzotropone derivatives in excellent yield (*e.g.* equation 49).[59] Diisopropyl ketone and diisobutyl ketone do not give mixed adducts with aldehydes under the normal protic conditions.

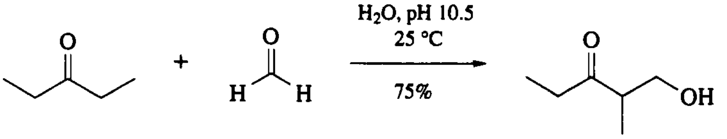

(47)

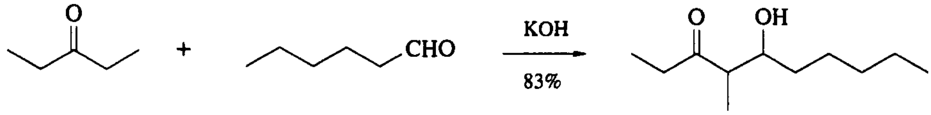

(48)

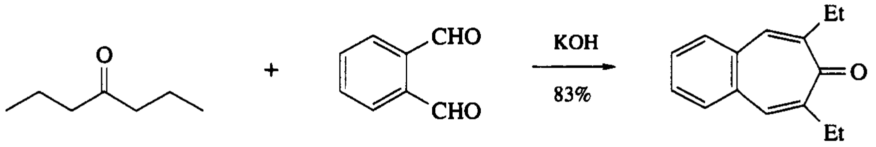

(49)

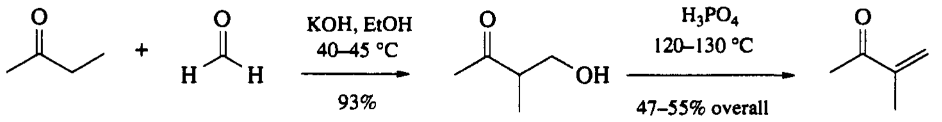

(50)

With unsymmetrical aliphatic ketones there is a regiochemical feature. The situation is complicated, and the actual product obtained seems to depend on catalyst, solvent and the structures of both the aldehyde and ketone. Some representative examples are presented in the following paragraphs.

Butanone reacts with formaldehyde and other aliphatic aldehydes under mildly basic conditions to give monosubstitution products at C-3 (*e.g.* equations 50 and 51).[60,61] The behavior of aromatic aldehydes with this ketone is complex; condensation at both C-1 and C-3 has been reported.

Dubois and Fellmann have studied the kinetic regioselectivity in the base-promoted reactions of 2-butanone and 2-pentanone with a series of aliphatic aldehydes (equation 52);[62] results are summarized in Table 2. The data indicate that steric effects play a subtle role in the determination of aldol regiochemistry in unsymmetrical ketones. Although reaction at C-3 is favored for 2-butanone with all of the aldehydes, pivalaldehyde gives more reaction at C-1 than the other aldehydes studied. Selectivity for reaction at C-3 in 2-pentanone is significantly less with all aldehydes, especially pivalaldehyde.

A similar trend may be seen in a study of the reaction of chloral with unsymmetrical ketones (equation 53; Table 3).[63] Reactions were carried out in glacial acetic acid with or without added sodium acetate as catalyst. Several control experiments showed that the isomer ratios obtained were kinetic. The lack of reversibility in this reaction implies that $\Delta G^\circ$ is much more negative than for the simple aldol reactions discussed previously. This is presumably because of the inductive effect of the chlorines, which is known to favor hydration and other nucleophilic additions to chloral.

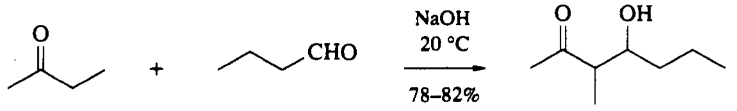

(51)

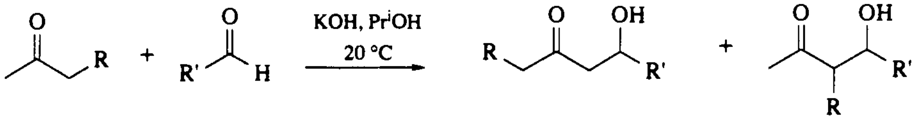

(52)

**Table 2** Regiochemistry of Aldol Reactions with 2-Alkanones (equation 52)

| *Aldehyde R′:* | | | *Percent reaction at C-3 of the ketone* | | | | |
|---|---|---|---|---|---|---|---|
| | *Me* | *Et* | *Pr$^i$* | *Bu$^t$* | *Pr$^n$* | *Bu$^i$* | *neo-Pe* |
| 2-Butanone (R = Me) | 93 | 90 | 86 | 70 | 88 | 90 | 88 |
| 2-Pentanone (R = Et) | 78 | 75 | 56 | 17 | 71 | 71 | 70 |

The data in Tables 2 and 3 show common qualitative trends, although chloral appears to have a greater proclivity for reaction at C-1. This preference for reaction at C-1 is actually enhanced in the reactions conducted without added sodium acetate, in contrast to the normal generalization that methyl alkyl ketones undergo acid-catalyzed reactions preferentially at C-3.[64] Kiehlmann has reported that the rates of deuteration of the ketones shown in equation (53) are much faster than the rates of the aldol reactions, supporting a mechanism in which carbon–carbon bond formation is the rate-limiting step. This is also true in the Dubois study (equation 52; Table 2). The difference is presumably due to the greater steric bulk of chloral, leading to a greater C-1:C-3 ratio.

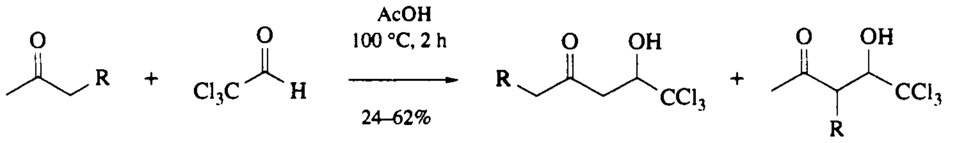

(53)

**Table 3** Regiochemistry of Aldol Reactions of Chloral with 2-Alkanones (equation 53)

| *R* | *Percent reaction at C-3*<br>*NaOAc/HOAc* | *HOAc* |
|---|---|---|
| Me | 56 | 15 |
| Et | 23 | 11 |
| Pr$^n$ | 28 | 15 |
| Bu$^n$ | 22 | 11 |
| Pr$^i$ or Bu$^t$ | 0 | 0 |

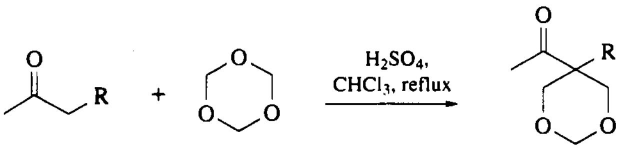

(54)

**Table 4** Regiochemistry of Aldol Reactions of Formaldehyde with 2-Alkanones (equation 54)

| *R* | *Yield (%)* | *C-3:C-1* |
|---|---|---|
| H | 3 | n/a |
| Me | 98 | 100:0 |
| Et | 80 | 100:0 |
| Pr$^n$ | 79 | 100:0 |
| Pr$^i$ | 43 | 86:14 |
| Bu$^t$ | 6 | n/a |

Wesslén has investigated the acid-catalyzed reactions of trioxane with methyl alkyl ketones to give dioxanes; representative data are shown in equation (54) and Table 4.[65] These data show a strong preference for reaction at a more substituted position. Indeed, the examples presented where reaction *must* occur at a methyl group (acetone and pinacolone) give very low yields of product.

Base-promoted reactions of unsymmetrical methyl ketones often give C-1 substituted products in high yield; an example of such a case is shown in equation (55).[66] A clue to the source of this behavior is seen in the two aldol reactions presented in equations (56) and (57). Under the milder set of conditions, benzaldehyde reacts with butanone to give a mixture of aldols resulting from attack at C-1 and C-3 (equation 56).[67] When the reaction is carried out at higher temperature and for a longer period, the C-1 condensation product is obtained in nearly quantitative yield (equation 57).[68]

The indication is that, in basic medium, the aldol addition reaction has a preference for formation of the more-substituted addition product. Under the more forcing conditions that lead to the enone, aldol reversal must occur, and formation of the C-1 condensation product must be favored over formation of the C-3 condensation product. This preference may be the result of more facile dehydration of the C-1 addition product.

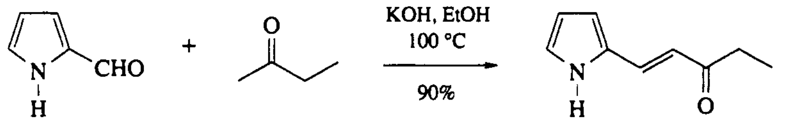

(55)

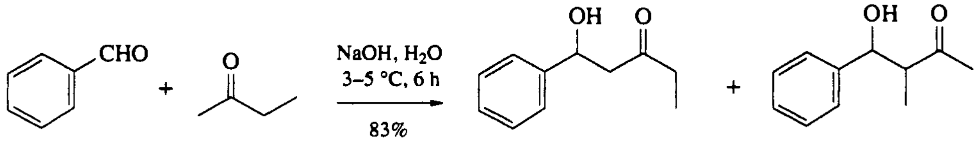

(56)

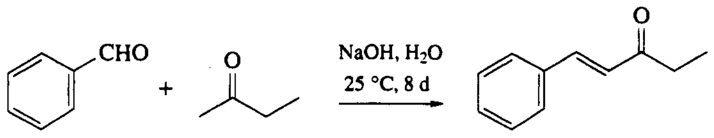

(57)

Under acidic conditions, benzaldehyde reacts with butanone to give exclusively the C-3 condensation product (equation 58).[69] In this example, we are presumably seeing the normal acid-mediated preference for aldol addition at C-3, followed by rapid acid-mediated dehydration. The latter reaction is probably irreversible under the reaction conditions.

Citral undergoes base-catalyzed aldol condensation with 2-butanone to give the methylpseudoionones in excellent yield; the C-3:C-1 ratio is 2:1 (equation 59).[70]

McKervey and coworkers have used lithium iodide as a catalyst for mixed aldol reactions; several examples are shown in equation (60).[71] In all cases studied, 2-butanone reacts solely at C-1. The process is also applicable to other ketones, but they react much more slowly than do methyl ketones. For

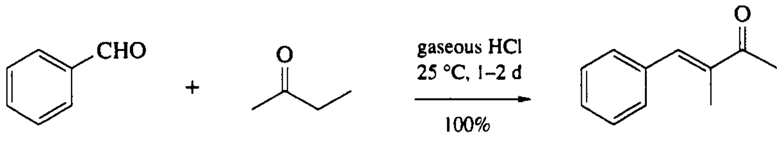

(58)

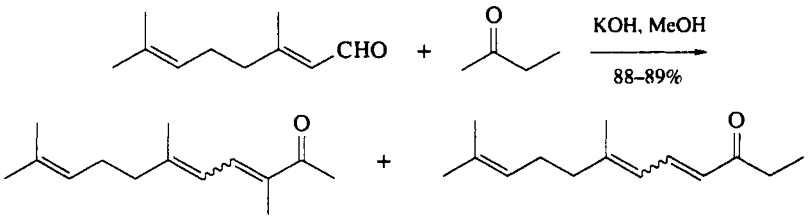

(59)

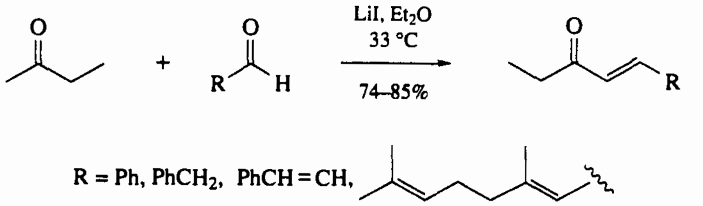

(60)

example, whereas *p*-methoxybenzaldehyde reacts with 2-butanone in 7 h, the comparable reaction with 3-pentanone requires 72 h. Cyclohexanone is comparable to 2-butanone and acetone in reactivity.

In contrast to the foregoing examples, 2-pyridinecarbaldehyde reacts with 4-*N*,*N*-dimethylamino-2-butanone to give only the C-3 substitution product (equation 61).[72] In this case, the inductive effect of the C-4 heteroatom must play a role, perhaps by favoring enolization toward C-3.

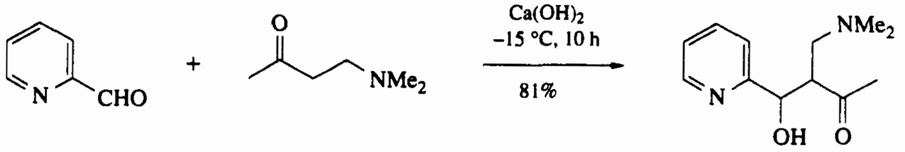

(61)

## 1.5.9.2 Cyclic Ketones

The base-catalyzed aldol addition reaction of cyclic ketones with formaldehyde is limited by the propensity of the initial hydroxymethyl products to undergo subsequent reactions (*e.g.* equations 62 and 63).[73,74] Similar problems occur with enolizable aliphatic aldehydes.

On the other hand, cyclic ketones react well with nonenolizable aldehydes (equations 64–66).[75,76] As shown in equation (65), mild conditions lead to the aldol (as a diastereomeric mixture). More forcing conditions provide the α-benzylidine derivatives (equations 64 and 65). By adjusting the stoichiometry, α,α′-bisarylidine derivatives may be obtained in excellent yield from cyclohexanone or cyclopentanone (*e.g.* equation 66).[77]

With unsymmetrical cyclic ketones, regioisomers may be formed. However, if one of the enolizable positions is substituted, or if other structural features favor enolization in a given direction, good yields of aldol products may be realized. 2-Substituted cycloalkanones undergo condensation reactions at the

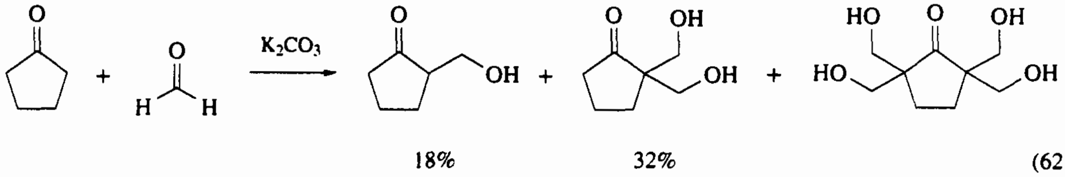

(62)

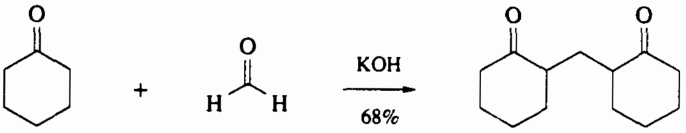

(63)

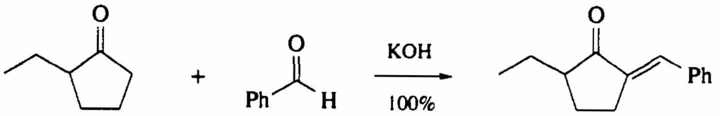

(64)

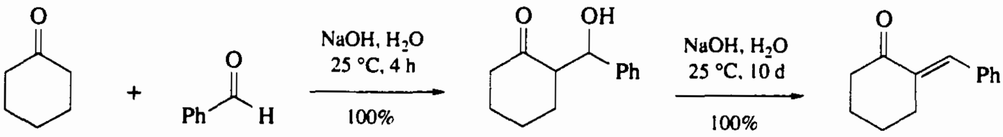

(65)

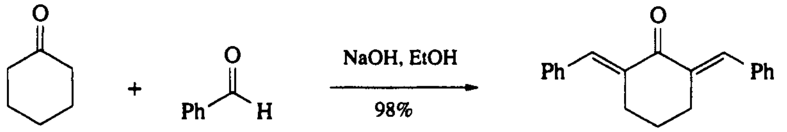
NaOH, EtOH
98%
Ph
H
Ph
Ph

(66)

unsubstituted α-position under dehydrating conditions (equations 64 and 67).[78] The example shown in equation (68) is regioselective, presumably because of steric hindrance to reaction at the neopentyl center.[79]

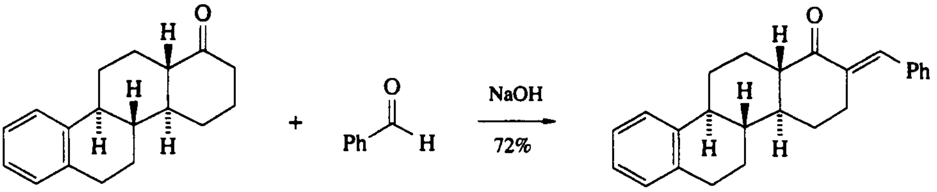
H
H
H
H
Ph
H
NaOH
72%
H
H
H
H
Ph

(67)

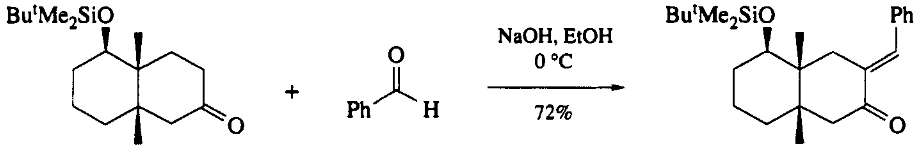
Bu^tMe_2SiO
Ph
H
NaOH, EtOH
0 °C
72%
Bu^tMe_2SiO
Ph

(68)

As shown in many of the foregoing examples, aldol condensation of an aromatic aldehyde with a ketone normally provides the (*E*)-α,β-unsaturated ketone. This stereochemical generalization has been investigated by Hassner and Mead.[80] It was found that even very hindered ketones such as 2,2-diphenylcyclohexanone give the (*E*)-enone under mild conditions (equation 69).[81] The (*Z*)-enone is obtained quantitatively by irradiation in alcoholic solution, but this isomer is easily transformed back to the (*E*)-isomer.

Acid-catalyzed reactions with cyclic ketones sometimes give products of further reactions (*e.g.* equations 70 and 71).[82]

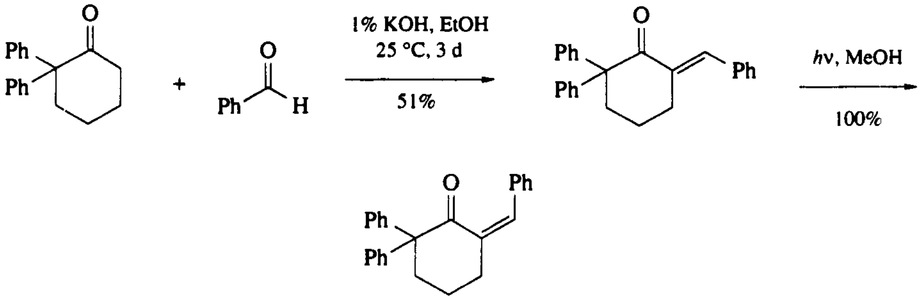
Ph
Ph
Ph
H
1% KOH, EtOH
25 °C, 3 d
51%
Ph
Ph
Ph
hν, MeOH
100%
Ph
Ph
Ph

(69)

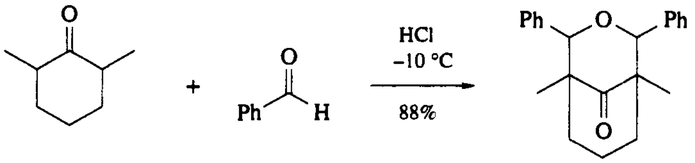
Ph
H
HCl
-10 °C
88%
Ph
Ph

(70)

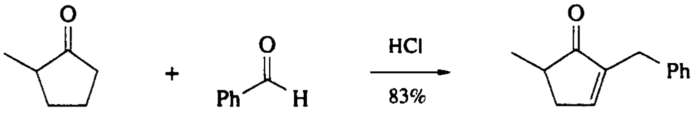
Ph
H
HCl
83%
Ph

(71)

There are an immense number of examples of aldol condensations of aromatic carbocyclic ketones with aromatic aldehydes. These systems usually give excellent yields of aldol condensation products, because the starting ketone can usually enolize in only one direction and because the ketones do not afford

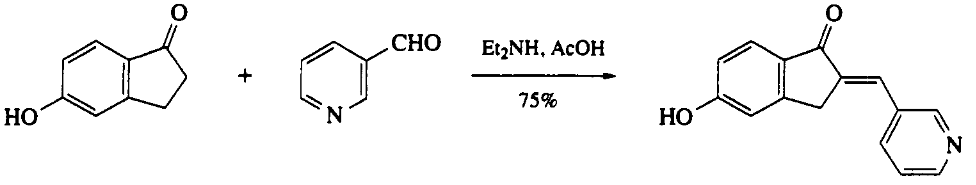
O
HO
CHO
N
Et$_2$NH, AcOH
75%
O
HO
N

(72)

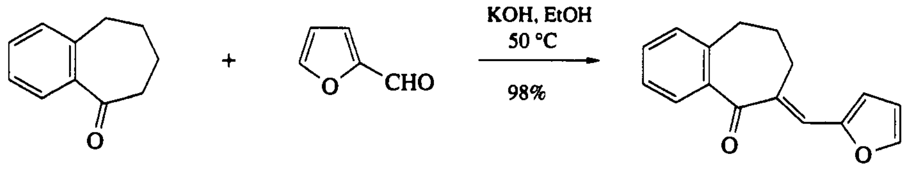
O
O
CHO
KOH, EtOH
50 °C
98%
O
O

(73)

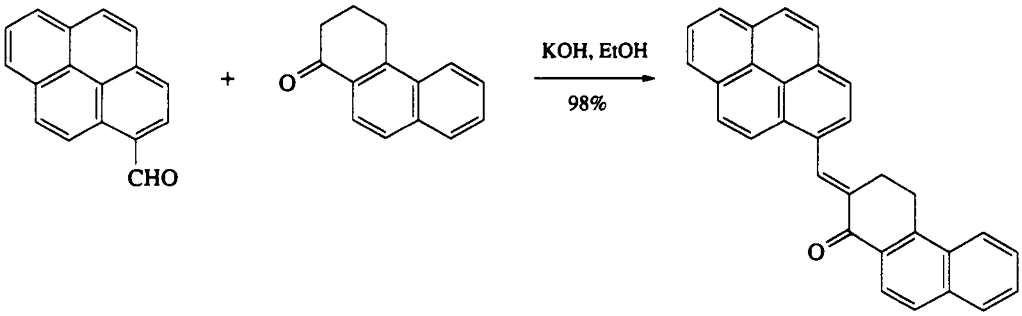
CHO
O
KOH, EtOH
98%
O

(74)

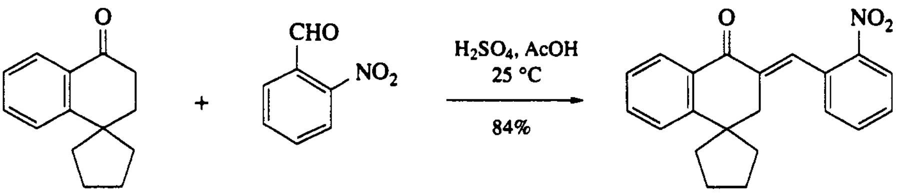
O
CHO
NO$_2$
H$_2$SO$_4$, AcOH
25 °C
84%
O
NO$_2$

(75)

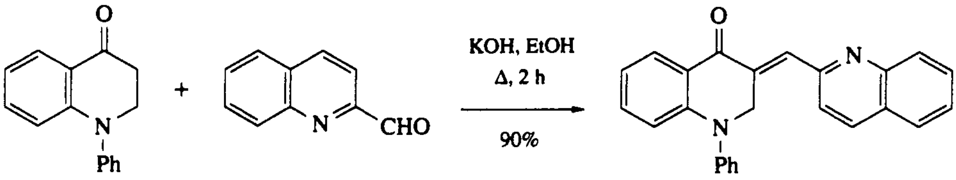
O
N
Ph
N
CHO
KOH, EtOH
Δ, 2 h
90%
O
N
N
Ph

(76)

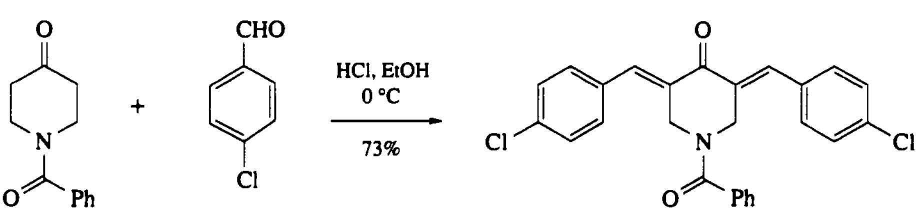
O
N
O
Ph
CHO
Cl
HCl, EtOH
0 °C
73%
O
Cl
N
Cl
O
Ph

(77)

stable self-condensation products. A few high-yielding examples from the older literature are given in equations (72)–(75);[83–86] the reader is directed to the Nielsen–Houlihan review for a a much more extensive compilation of examples.[87]

Saturated heterocyclic ketones are also good substrates for mixed aldol condensations with aromatic aldehydes. Again, a selection of high-yielding examples is presented in equations (76)–(80).[88–92] These

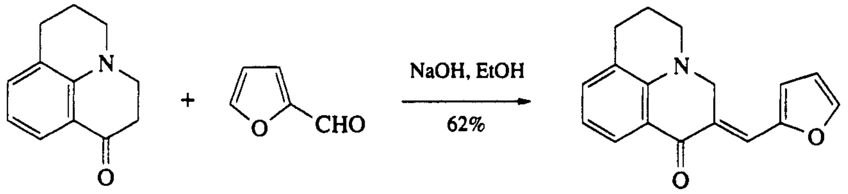

(78)

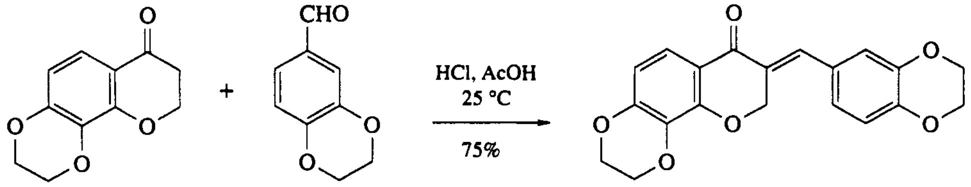

(79)

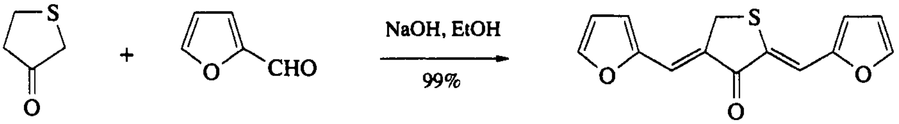

(80)

examples illustrate base catalysis and acid catalysis, and include examples of oxygen, nitrogen and sulfur heterocyclic ketones. Note that in each case β-elimination of the heteroatom might have provided a complication.

### 1.5.9.3 Alkylaryl and Related Ketones

In this section, we discuss a useful version of mixed ketone–aldehyde condensation, the reaction of aromatic methyl ketones with nonenolizable (usually aromatic) aldehydes. The prototype reaction is the condensation of acetophenone with benzaldehyde, leading to 1,3-diphenylprop-2-en-1-one, 'chalcone' (equation 81).[7b] The scope of this reaction is exceedingly broad; the Nielsen–Houlihan review enumerates hundreds of examples comprising almost every imaginable combination of substituted acetophenone and aromatic aldehyde.[93]

It has recently been found that chalcone formation may be carried out under the influence of copper(II) 2,2′-bipyridyl[94] or a complex of cobalt(II) acetate and a 4-vinylpyridine–styrene–divinylbenzene copolymer; chalcone is obtained in high yield and the catalyst may be recovered and reused.[95]

A recently reported procedure calls for addition of sodium hydroxide pellets to a rapidly stirring solution of the ketone and aldehyde in absolute ethanol at room temperature. The crystalline chalcones are isolated by simple filtration. Yields are reported to be in the range 72–99%; an example is shown in equation (82).[96]

Becher and coworkers have studied the aldolization of 3-formyl-2(1*H*)-pyridinethiones.[97] Aldehyde (**11**) reacts with *p*-chloropropiophenone to give a single diastereomeric aldol, shown by X-ray analysis to have the *syn* structure (**12**), in 83% yield (equation 83). Several other examples, all apparently highly

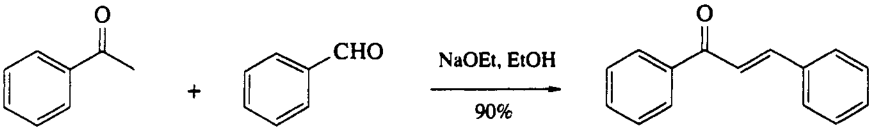

(81)

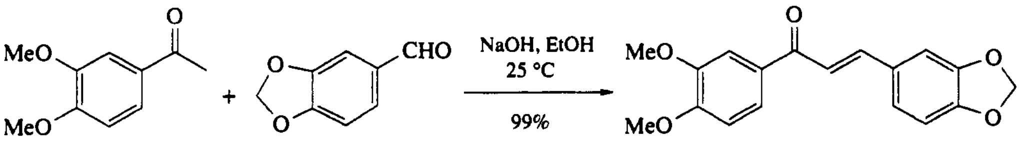

(82)

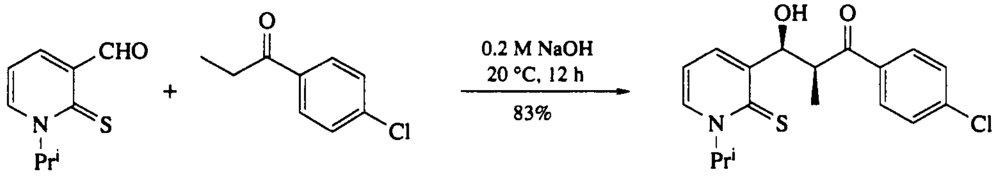
CHO
N
S
Pr$^i$
O
Cl
0.2 M NaOH
20 °C, 12 h
83%
OH
O

**(11)** **(12)**

(83)

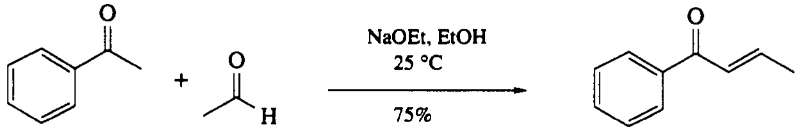
O
H
NaOEt, EtOH
25 °C
75%

(84)

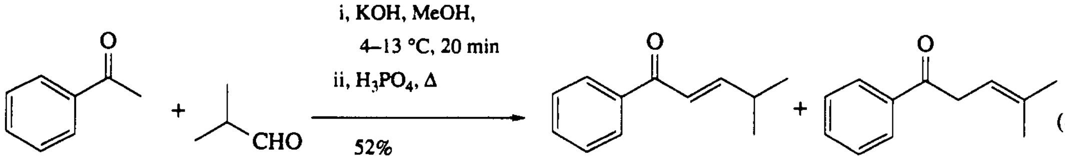
O
CHO
i, KOH, MeOH,
4–13 °C, 20 min
ii, $H_3PO_4$, Δ
52%

73:27

(85)

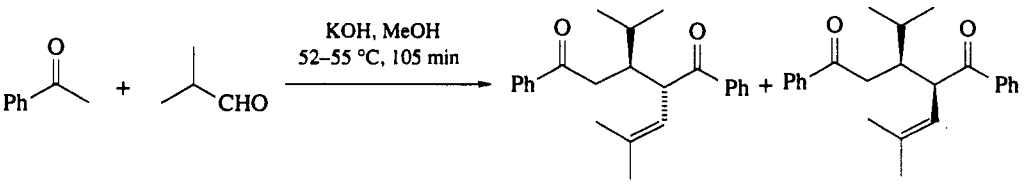
Ph
O
CHO
KOH, MeOH
52–55 °C, 105 min

**(13)** 60% **(14)** 9%

(86)

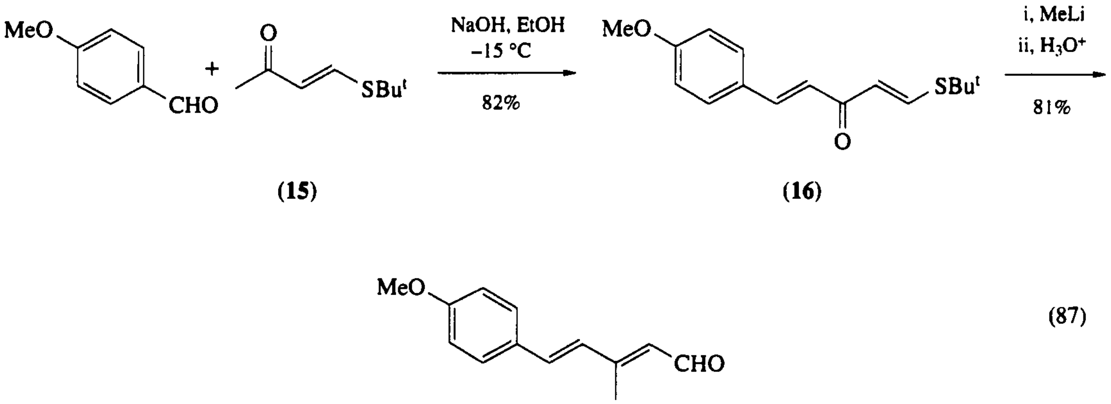
MeO
CHO
O
SBu$^t$
NaOH, EtOH
-15 °C
82%
i, MeLi
ii, $H_3O^+$
81%

**(15)** **(16)** **(17)**

(87)

stereoselective, were reported. Such stereoselective aldol reactions are highly unusual under protic conditions. Oxoamides corresponding to (**11**) were found to give the α,β-unsaturated ketone products.

Condensations of acetophenones with aliphatic aldehydes are often complicated by side reactions, although some simple cases are known to proceed in good yield (*e.g.* equation 84).[96] An example of the kind of complications that may arise in such cases is seen in the reaction of acetophenone with isobutyraldehyde. Base-mediated reaction at low temperature gives a crude aldol that is dehydrated by heating with phosphoric acid to obtain a 3:1 mixture of α,β- and β,γ-unsaturated ketones (equation 85).[98] If the reaction is carried out under more traditional conditions, by heating an alcoholic solution of the reactants with potassium hydroxide, the main products are diones (**13**) and (**14**), resulting from subsequent Michael addition of the initially formed enones (equation 86).[98,99]

Some methyl vinyl ketones behave similarly to acetophenones in aldol condensations, a primary requirement being that the vinyl ketone not be particularly susceptible to Michael addition or base-catalyzed polymerization processes. A recent example utilizes the vinylogous β-keto sulfide (**15**), which undergoes smooth condensation with benzaldehyde and its derivatives (equation 87).[100] The product of this aldol condensation, enone (**16**), may be converted by a straightforward sequence of steps into the dienal (**17**), which is obtained as a 4:1 mixture of (*E*)- and (*Z*)-isomers at the C(2)═C(3) double bond. A number of other examples of this useful process are reported in the primary publication.

An annulenone synthesis that employs aldol condensations in two key steps is outlined in Scheme 2.[101] Condensation of *o*-ethynylcinnamaldehyde (**18**) with acetone provides (**19**), which is condensed with aldehyde (**20**) to obtain ketone (**21**). Intramolecular oxidative coupling of the two alkyne functions affords annulenone (**22**).

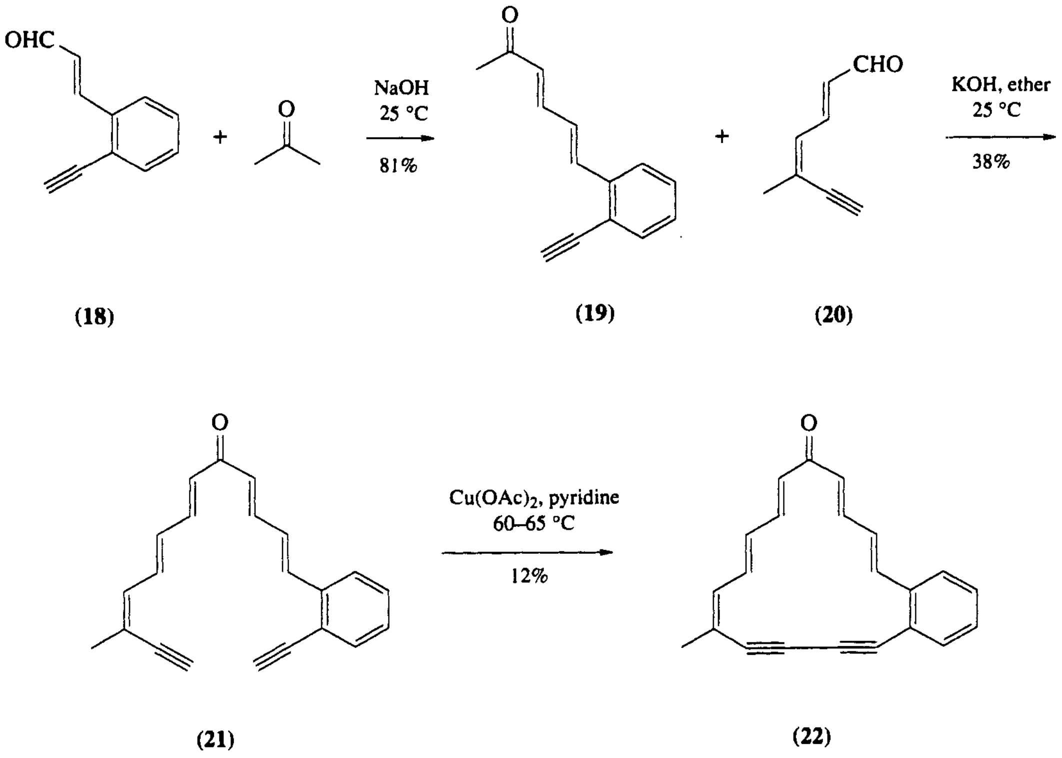

Scheme 2

### 1.5.9.4 Vinylogous Enolates

There have been frequent reports of the condensation of cyclic α,β-unsaturated ketones at the γ-position; an example is seen in equation (88).[102] Other 3-methylcyclohexenones have been reported to undergo similar reactions.[103] Unfortunately, the original literature does not report yields for these transformations. These reactions would bear reinvestigation with modern methods of analysis. Other cyclohexenones have also been found to undergo aldol condensation at the γ-position. For example, carvone condenses with two equivalents of benzaldehyde (equation 89).[104]

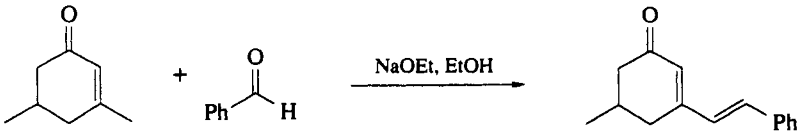

(88)

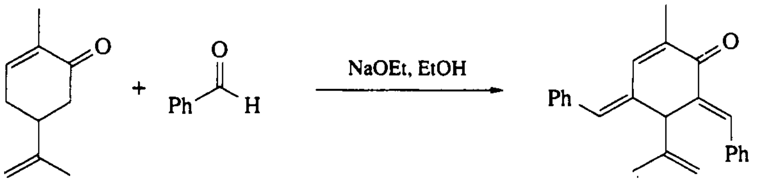

(89)

A similar phenomenon has been reported by Sugiyama and coworkers, who found that the vinylogous amide (**23**) reacts with benzaldehyde to give (**24**) as the sole product (equation 90).[105] When (**23**) is treated with two equivalents of sodium amide in ammonia, followed by treatment with benzaldehyde, aldol (**25**) is formed in 25% yield. Although the authors invoke a dianion in the latter reaction, it is unlikely that one could be formed under the reaction conditions used. Instead, it is likely that deprotonation at the endocyclic α-position is preferred kinetically, and that this leads to the product observed with $NaNH_2/NH_3$ (irreversible enolate formation). Reaction of this enolate must be slow, for steric reasons, as witnessed by the low yield in the aldol reaction. Under conditions of enolate equilibration, the more stable extended dienolate is produced.

Schulze and Oediger have used such a reaction in the synthesis of piperine (**26**), the sharp principle of black pepper. Condensation of piperonal with *N*-crotonylpiperidine in DMSO in the presence of benzyltriethylammonium hydroxide provides piperine in 80% yield (equation 91).[106]

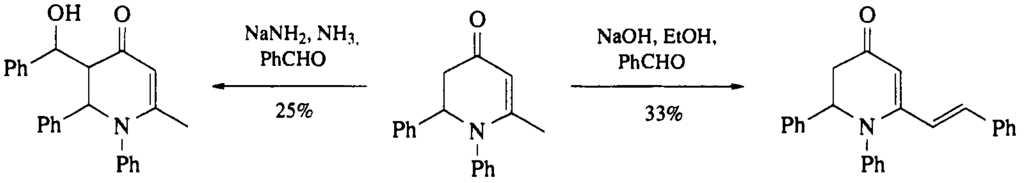

(90)

**(25)** **(23)** **(24)**

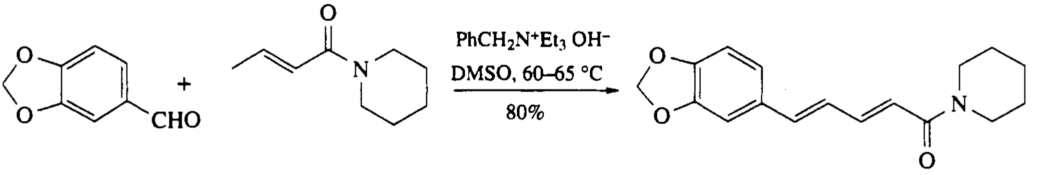

(91)

**(26)**

### 1.5.9.5 Stereochemistry

One of the features of the aldol addition reaction that limited its usefulness prior to the early 1970s was an imperfect understanding of its stereochemistry. Indeed, the methods of analysis prior to the advent of $^1H$ NMR spectroscopy were not especially appropriate for distinguishing diastereomers. Reactions such as those depicted in equations (8), (14), (18), (40), (48), (51), (56), and (65) give mixtures of diastereomers, but this issue was largely ignored because it was not conveniently addressed.

One of the first attempts to study this issue came from Zimmerman and Traxler, in a 1952 paper on the Ivanov reaction. It was observed in this work that the preformed magnesium dianion of phenylacetic acid reacts with benzaldehyde to give the '*threo*' and '*erythro*' β-hydroxy acids (**27**) and (**28**) in a ratio of 3:1 (equation 92).[107] It was proposed that the reaction proceeds through transition state (**29**), in which the magnesium cation is chelated by the benzaldehyde oxygen and one oxygen of the carboxylate. The same proposal was later advanced by Toromanoff in a paper dealing with the general topic of perpendicular attack by nucleophiles on carbonyl groups.[108]

In a 1964 paper, Stiles and coworkers isolated and identified diastereomeric aldols.[109] However, the first person to address the question of aldolization stereochemistry in a serious manner was the French physical organic chemist J.-E. Dubois.[110] His first study was of the KOH-promoted aldolization of cyclopentanone with several aliphatic aldehydes (equation 93);[111] the results are summarized in Table 5. In this discussion of the Dubois work, we use the stereochemical descriptors '*threo*' and '*erythro*' in the same sense that they were employed in the original Dubois papers, in order to avoid confusion for those

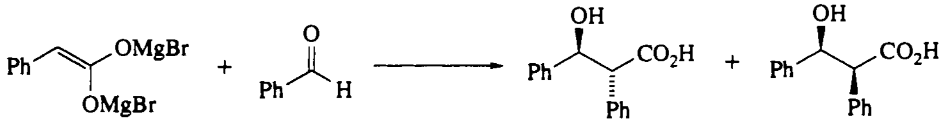

(27) 69% (28) 22%

(92)

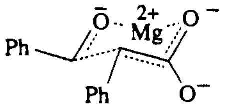

(29)

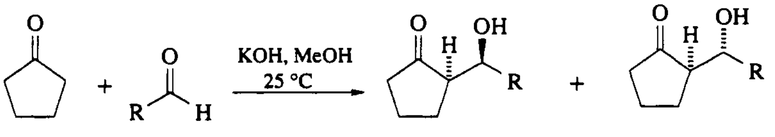

*erythro* *threo*

(93)

**Table 5** Stereochemistry of Aldol Reactions of Cyclopentanone with Aliphatic Aldehydes (equation 93)

| *R* | *Threo* (%) | *Erythro* (%) |
|---|---|---|
| Me | 43 | 57 |
| Et | 38 | 62 |
| $Pr^i$ | 32 | 68 |
| $Bu^t$ | 13 | 87 |
| neo-$C_5H_{11}$ | 35 | 65 |

who wish to consult the original publications for more detail. It was established by appropriate control experiments that the reactions were under thermodynamic control.

In a later series of papers, Dubois and Fort studied the stereochemistry of the reaction of 2,2,5-trimethylcyclopentanone with isovaleraldehyde (equation 94).[112] In this study, it was shown that, whereas the *erythro* diastereomer is thermodynamically preferred, the *threo* isomer is formed more rapidly under certain conditions.

The concentrations of *erythro* and *threo* aldols as a function of time are presented in Figure 1(a) for a relatively nonpolar solvent (90:10 THF–MeOH) and in Figure 1(b) for a polar solvent (pure MeOH). In the nonpolar solvent the *threo* aldol is formed more rapidly than the *erythro* isomer. However, as a result of the reversibility of the system, its concentration peaks and then diminishes to eventually reach an equilibrium value. In pure MeOH, on the other hand, the *erythro:threo* equilibrium composition is maintained throughout the reaction. Thus, the reaction is under thermodynamic control in the polar solvent and under kinetic control in the less polar one.

Dubois defined a quantity called the 'restoring energy', $E_r$, that measures the difference between kinetic and thermodynamic stereoselectivity. The idea in this concept is that, for easily reversible reactions under kinetic control, the reverse reactions, whose rate constant ratio is related to $E_r$, restores the diastereomeric system to its equilibrium composition. This is illustrated with the generic reaction coordinate diagram for equation (94), presented in Figure 2. Figure 2 ignores the deprotonation step, which is common for the two competing reactions, and subsequent protonation of the aldolates. It may be seen in this figure that the reaction of (**30**) and (**31**) is under kinetic control, with formation of the *threo* diastereomer being more rapid. However, because neither of the competing reactions is very exothermic ($\Delta G°$ for these reactions can be estimated to be only a few kcal mol$^{-1}$) the activation energies for the reverse reactions are only slightly greater than those for the forward reactions. In addition, Figure 2 shows that the more rapidly formed *threo* diastereomer will reverse more rapidly than the more slowly formed *erythro* diastereomer. Thus, $E_r = \Delta G^{\ddagger}{}_{-E} - \Delta G^{\ddagger}{}_{-T}$. From the known *threo–erythro* equilibrium constant, and a careful measurement of the activation parameters for the forward reactions, Dubois evaluated the effect of various parameters on $E_r$. For the two conditions depicted in Figure 1, $E_r$ was found to have values of 1.95 kcal mol$^{-1}$ (90:10 THF–MeOH) and 0.01 kcal mol$^{-1}$ (pure MeOH).

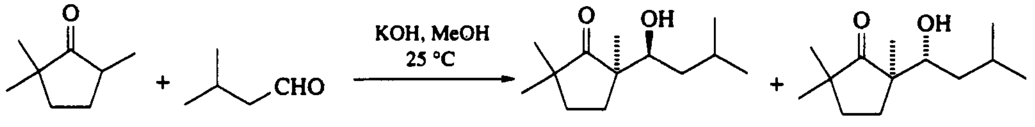

(94)

**(30)** **(31)** *erythro* *threo*

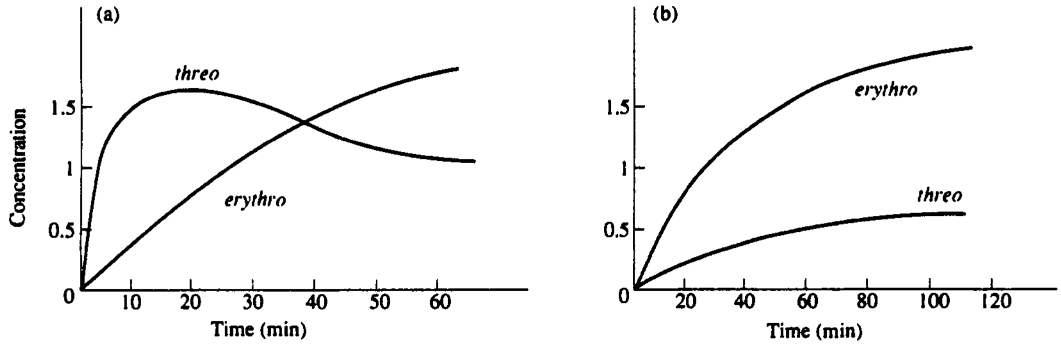

**Figure 1** Concentration of *threo* and *erythro* aldols as a function of time for equation (94). (a) 90:10 THF:MeOH; (b) pure MeOH

For $E_r$ to be zero, as it is in the reaction of (**30**) and (**31**) in methanol, $\Delta G^{\ddagger}{}_{-E}$ must be equal to $\Delta G^{\ddagger}{}_{-T}$, and the reaction is under pure thermodymanic control. It follows that interactions in the transition states and products are similar. This was found to be the case in polar solvents ($H_2O$, MeOH, DMSO) and in less polar solvents (90:10 THF–MeOH) when the cation is highly dissociating ($Me_4N^+$). Dubois postulated that reactions with significant positive $E_r$ proceed through Zimmerman–Traxler transition states, in which the cation is chelated by the two partially negative oxygens (Figure 3). Of these, the *erythro* transition state is presumed to be the less stable, because it brings the aldehyde R group into interaction with the cyclopentanone ring. For reactions with negligible $E_r$, it was proposed that an open transition state

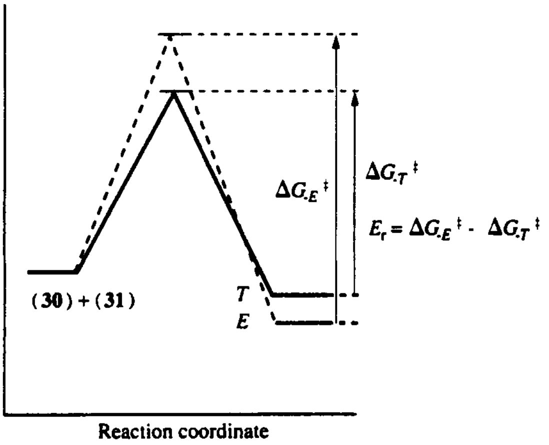
$\Delta G_{-E}^{\ddagger}$
$\Delta G_{-T}^{\ddagger}$
$E_r = \Delta G_{-E}^{\ddagger} - \Delta G_{-T}^{\ddagger}$
(30) + (31)
T
E
Reaction coordinate

**Figure 2** Potential energy diagram for the aold reaction of ketone (**30**) and aldehyde (**31**) (equation 94)

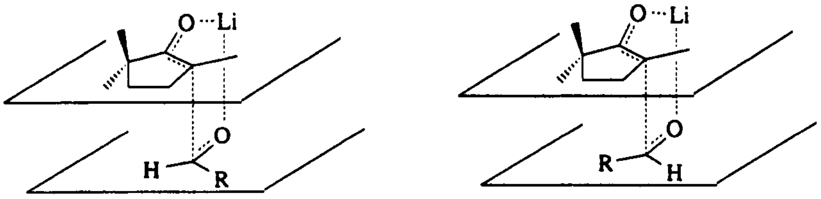

*threo* transition state *erythro* transition state

**Figure 3** Chelated transition states for equation (94)

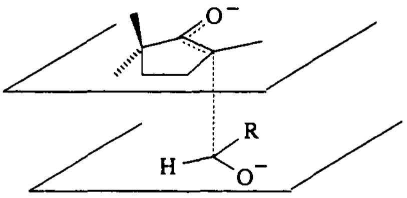

**Figure 4** Open transition states for equation (94)

prevails (Figure 4). In this case, the *threo* and *erythro* transition states would have steric interactions that mirror those found in the aldols themselves. This is the case when the solvent is polar or when the cation is dissociating.

These important papers by Dubois and his coworkers laid the groundwork for an understanding of the factors governing the stereochemistry of the aldol reaction. Further studies were greatly facilitated by the introduction, in the 1970s, of reliable methods for the use of preformed enolates in the aldol reaction. This subject is discussed at length in succeeding chapters in this volume.

## 1.5.10 INTRAMOLECULAR ALDOL REACTIONS

Examples of intramolecular aldol reaction are legion, mainly in the context of the Robinson annelation reaction. Because this process has been the subject of recent reviews,[113] we do not here attempt an exhaustive survey. Emphasis in this chapter is placed on representative examples, to show the scope of the reaction, and questions of regio- and stereo-selectivity.

### 1.5.10.1 Dialdehydes

Intramolecular condensation of alkane dialdehydes gives cycloalkenecarbaldehydes under conditions of acid or base; cyclizations of symmetrical dialdehydes leading to five-, six- and seven-membered rings are depicted in equations (95)–(97).[114–116]

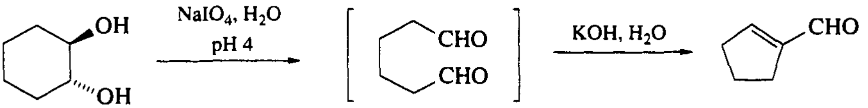

58% overall

(95)

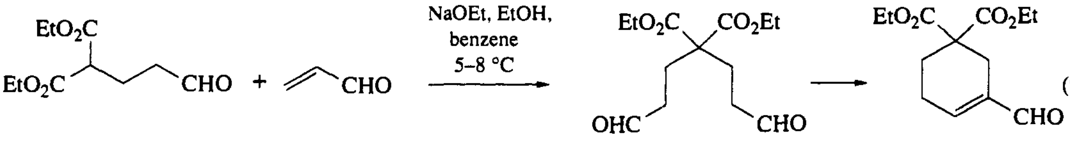

(96)

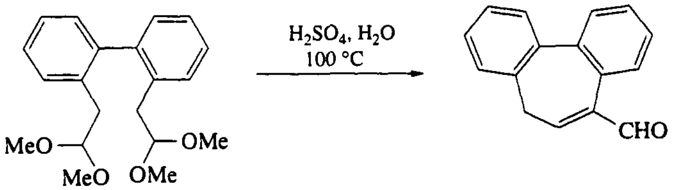

(97)

With unsymmetrical dialdehydes, a regiochemical issue exists. The first study of such a situation came as a part of Woodward's steroid synthesis.[117] Dialdehyde (**32**) is cyclized by piperidinium acetate, *via* an intermediate enamine, to give predominantly the cyclopentenecarbaldehyde (**33**; equation 98). It was proposed that the β-aldehyde (that is, CHO of the C-14 formylmethyl group) is less hindered and therefore more susceptible to intramolecular attack by an enamine derived from the more encumbered aldehyde.

In connection with a total synthesis of gibberellic acid, Corey and coworkers used dibenzylammonium trifluoroacetate to accomplish a regioselective aldol condensation (equation 99).[118] The success of this transformation was rationalized by the authors on the basis of activation of the less hindered formyl group as its enamine by a 'not-too-basic, sterically discriminating secondary amine under almost neutral aprotic conditions'.

Inubushi and coworkers have studied a similar unsymmetrical dialdehyde in the context of their fawcettimine synthesis.[119] Dialdehyde (**34**) cyclizes under various conditions to give a mixture of enals (**35** and **36**; equation 100). Unexpectedly, both the Woodward and Corey methods give the same major product, providing (**35**):(**36**) ratios of 21:1 (80% yield) and 19:1 (62% yield), respectively. The opposite regioselectivity is obtained by using morpholine and camphoric acid in ether–HMPA solvent; under these conditions, the (**35**):(**36**) ratio is 1:25 and the yield is 54%.

Büchi and coworkers have applied the Woodward conditions for the completely regioselective cyclization of dialdehyde (**37**) to (**38**) (equation 101).[120] As in the earlier examples, the cyclization appears to occur by the enamine of the more hindered aldehyde reacting with the less hindered aldehyde.

Nakane and Hutchinson have further shown that the aldol step in this cyclization is stereoselective as well as regioselective. Treatment of (**39**) with Hunig's base, acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP), followed by sodium borohydride reduction of the intermediate β-hydroxy aldehyde, gives diol (**40**) in 48% yield; no diastereomeric diols were detected (equation 102).[121]

An exception to the generalization that the enamine of the more hindered aldehyde acts as the nucleophilic arm in intramolecular aldol reactions of unsymmetrical dialdehydes is seen in equation (103).[122] The regioselectivity of this cyclization is apparently very high; none of the other isomer was detectable by HPLC or NMR; the 57% yield quoted is the overall yield of the alcohol obtained by sodium borohy-

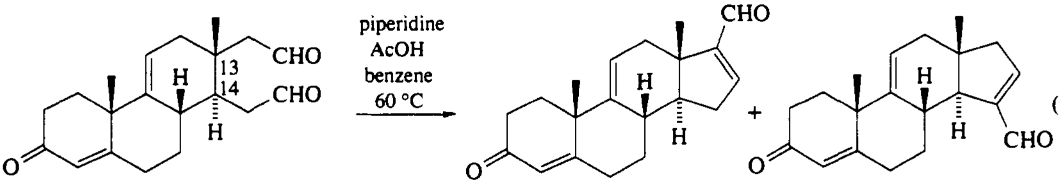

(98)

(**32**) (**33**) 66% very little

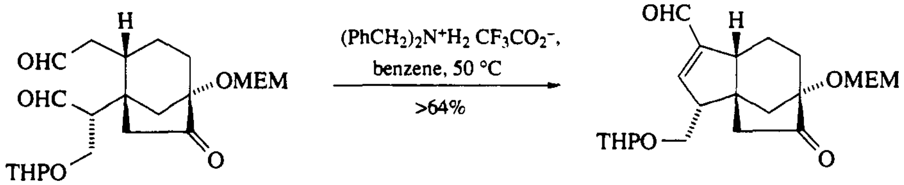

(99)

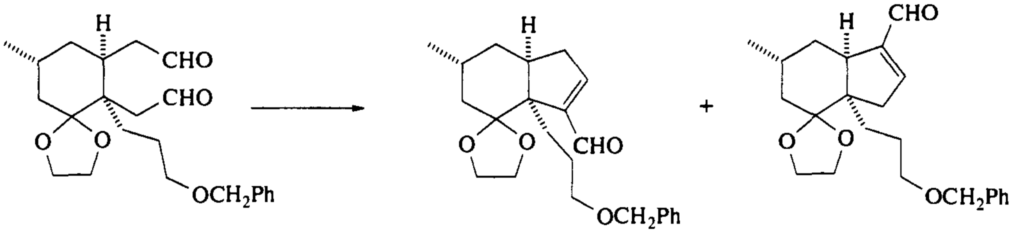

(100)

(**34**) (**35**) (**36**)

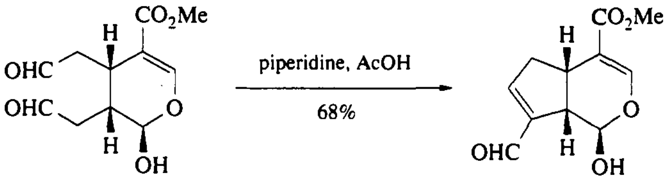

(101)

(**37**) (**38**)

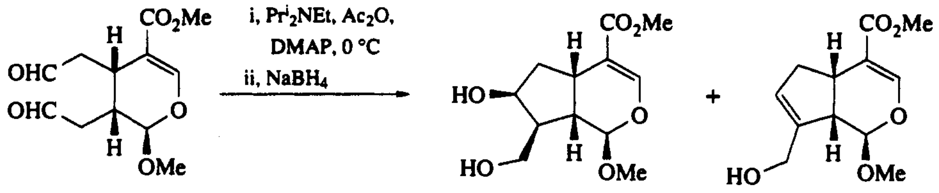

(39) (40) 48% (41) 5%

(102)

dride reduction of (43). The Woodward procedure was also highly regioselective, but gave (43) in low yield (16% of the derived alcohol); the Inubushi method in this case gave the two regioisomeric enals in a 1:1 ratio.

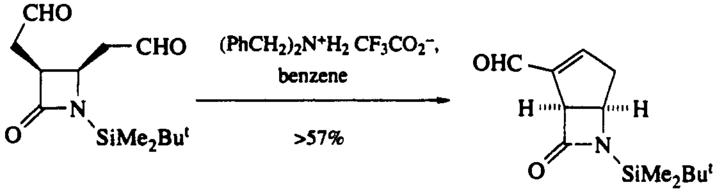

(42) (43)

(103)

## 1.5.10.2 Keto Aldehydes

Keto aldehydes are intrinsically unsymmetrical, and at least two isomeric products are usually possible. Conditions are known in which either the ketone or the aldehyde can function as the nucleophilic component. Aqueous or alcoholic base generally results in addition of the ketone enolate to the aldehyde, as shown in equation (104).[123] This example also illustrates the general preference for formation of an α,β-unsaturated ketone, rather than an isomeric α,β-unsaturated aldehyde under equilibrating conditions.

Aldol cyclization of keto aldehyde intermediates has been used in several steroid syntheses, as part of a strategy for conversion of a six-membered D-ring into a five-membered ring. An example is seen in equation (105), a step in the Sarett steroid synthesis.[124] A similar transformation has been utilized by Johnson and coworkers in a steroid synthesis.[125]

Corey and Nozoe cyclized a keto aldehyde as one step in a total synthesis of helminthosphoral (equation 106).[126] In this case, note that the aldehyde enolate adds to the more hindered ketone carbonyl to form a five-membered ring. The alternative addition of the ketone enolate to the aldehyde would give a seven-membered ring.

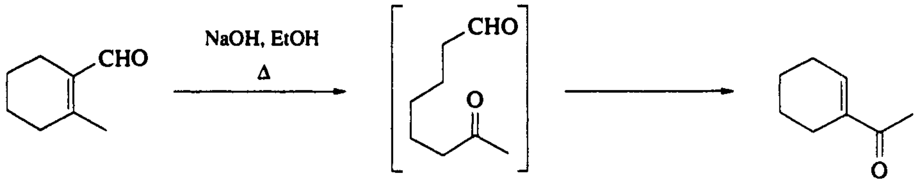

68%

(104)

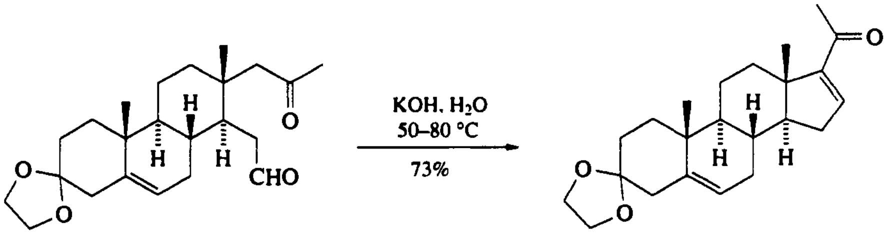

(105)

Lalande and coworkers have studied the regiochemistry of cyclization of keto aldehyde (**44**; equation 107).[127] In this system, aqueous KOH gives exclusively the cyclopentenyl methyl ketone (**45**), while piperidinium acetate leads to cyclopentenecarbaldehyde (**46**). Similar results were obtained by Wolinsky with the isopropenyl analog of (**44**).[128] These examples also demonstrate the preference for formation of a five- over a seven-membered ring.

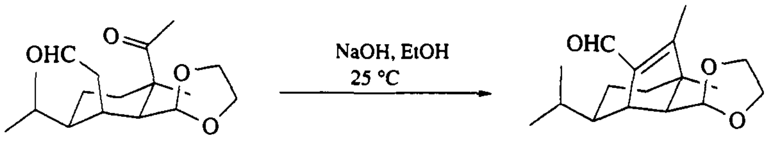

(106)

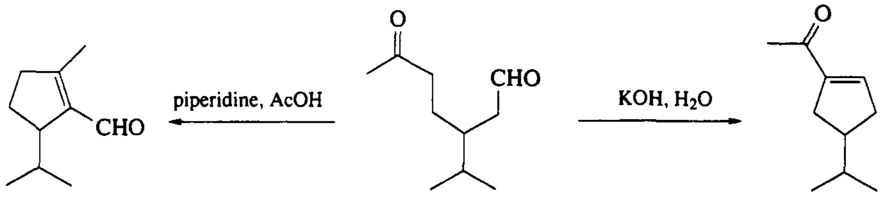

(107)

(**46**) (**44**) (**45**)

The cyclization depicted in equation (108) was a key step in a total synthesis of lycopodine.[129] Oppenauer oxidation of keto alcohol (**47**) gives keto aldehyde (**48**), which is cyclized under the reaction conditions to provide dehydrolycopodine (**49**). The transformation failed with keto diol (**50**). It was reasoned that, in this case, the tertiary hydroxy group acts as a general acid, protonating the nitrogen and allowing the intermediate β-amino aldehyde to undergo elimination. To remove this side reaction, compound (**50**) was deprotonated with KH prior to the Oppenauer reaction. Under these modified conditions, enone (**51**) is obtained in reasonable yield (equation 109).[130]

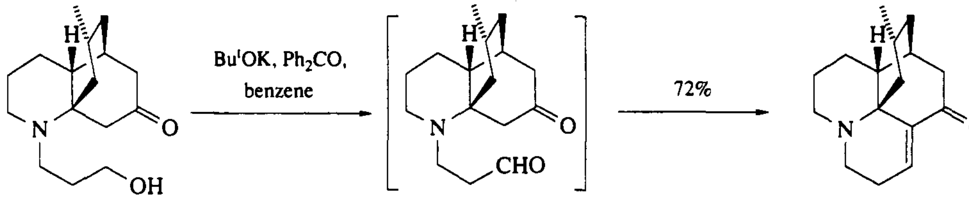

(108)

(**47**) (**48**) (**49**)

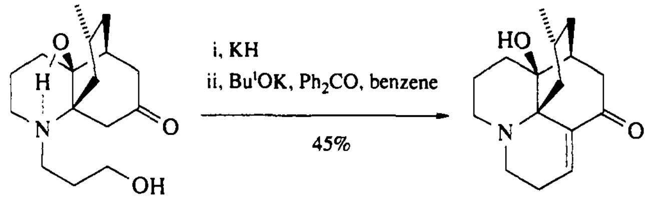

(109)

(**50**) (**51**)

Murai and coworkers carried out the intramolecular aldolization of intermediate (**52**) as one of the key steps in a synthesis of glycinoeclepin A (equation 110).[131] This example is more complicated than it may appear at first glance. There are four functions that may reasonably be deprotonated (two esters, the ketone and the aldehyde). Of these, the aldehyde is probably the most acidic. Although addition of the aldehyde enolate to the ketone is expected to be reversible, it could have undergone acylation by the side chain ester group (five-membered ring) or by the acetoxy group (six-membered ring).

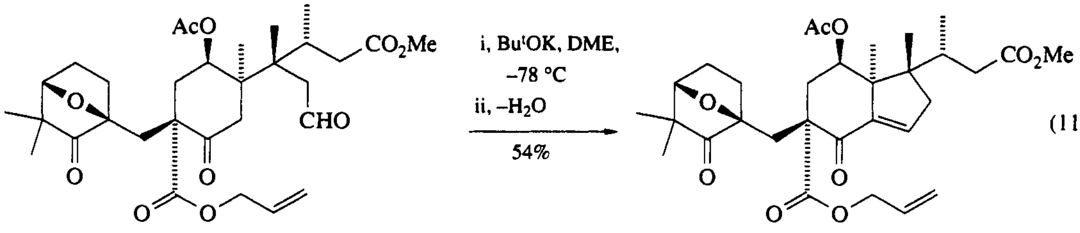
AcO
CO2Me
CHO
O
O
O
O
O
i, ButOK, DME, -78 °C
ii, -H2O
54%
AcO
CO2Me
O
O
O
O
O

(110)

**(52)** **(53)**

When the preferred cyclization of the ketone enolate to the aldehyde is disfavored, the alternate mode of cyclization is observed; an example in which a cyclopentenecarbaldehyde is formed from a 1,6-keto aldehyde is shown in equation (111).[132]

Grieco and coworkers have utilized intramolecular aldolization of keto aldehydes to form seven-membered rings. In a synthesis of (±)-helenalin, keto aldehyde (**54**) was cyclized to aldol (**55**; equation 112).[133] In a later modification of the basic approach, keto aldehyde (**56**) was cyclized to cycloheptenone (**57**; equation 113).[134] The success of these cyclizations is related to the fact that the normally preferred five-membered ring closure would yield a strained *trans*-fused bicyclo[3.3.0]octene system.[135]

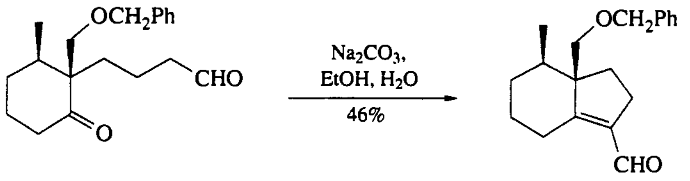
OCH2Ph
CHO
O
Na2CO3, EtOH, H2O
46%
OCH2Ph
CHO

(111)

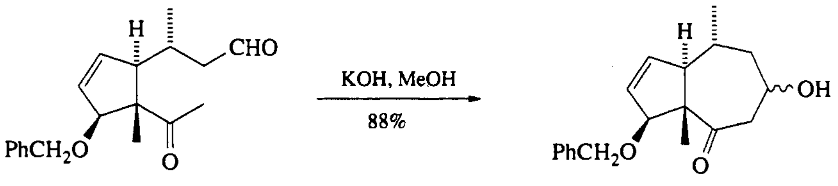
H
CHO
PhCH2O
O
KOH, MeOH
88%
H
OH
PhCH2O
O

(112)

**(54)** **(55)**

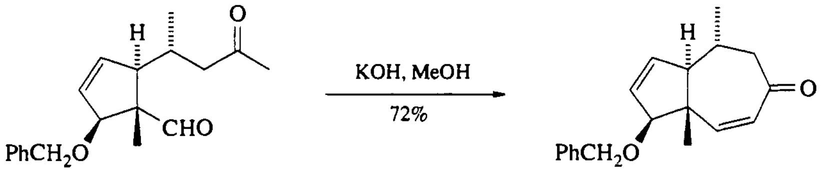
H
O
CHO
PhCH2O
KOH, MeOH
72%
H
O
PhCH2O

(113)

**(56)** **(57)**

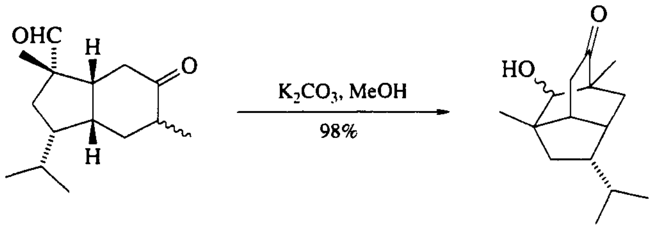
OHC
H
O
H
K2CO3, MeOH
98%
O
HO

(114)

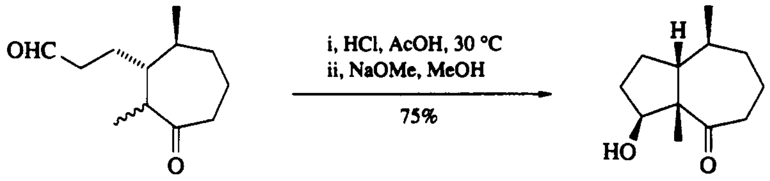

(115)

Keto aldehydes are often observed to cyclize to aldols that cannot undergo dehydration. An example is taken from Corey's synthesis of (±)-2-isocyanopupukeanane (equation 114).[136]

Keto aldehydes may also be cyclized under acidic conditions, as is shown by the transformation in equation (115), a step in the total synthesis of (±)-parthenin.[137] The aldol ester that is produced in the initial reaction is saponified by treatment with methanolic sodium methoxide.

### 1.5.10.3 Diketones

Aldol cyclization of 1,4-diketones yields cyclopentenones. Indeed, this excellent cyclization has been employed dozens of times in syntheses of the perfumery material *cis*-jasmone (**58**; equation 116).[138]

McCurry has investigated the regiochemistry of unsymmetrical 1,4-diketone cyclizations.[139] 2,5-Nonanedione undergoes cyclization under weakly basic conditions to give cyclopentenones (**59**) and (**60**) in a ratio of 94:6 (equation 117). Under the reaction conditions, independently synthesized (**60**) was not converted into (**59**). However, it was found that such trisubstituted alkenes *are* rearranged to the more stable tetrasubstituted isomers under more drastic conditions (equation 118).

Aldol cyclization can be used as a method of annulating a cyclopentenone ring onto another ring, provided the necessary 1,4-diketone is readily available. A pertinent example is seen in equation (119) in the

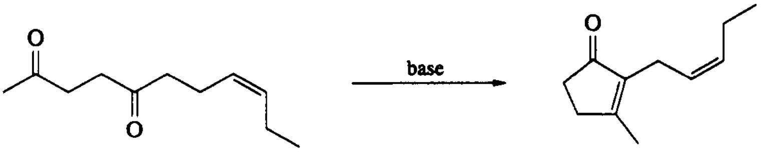

(116)

**(58)**

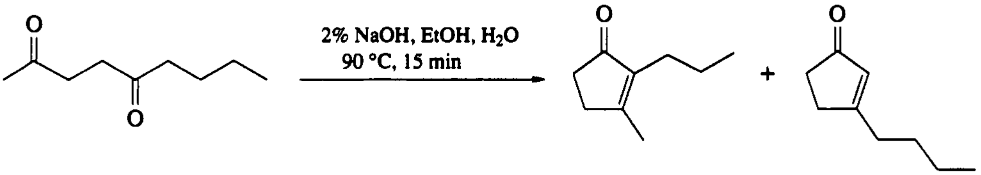

(117)

**(59)** **(60)**

94:6

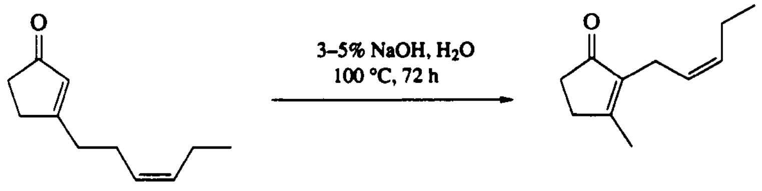

(118)

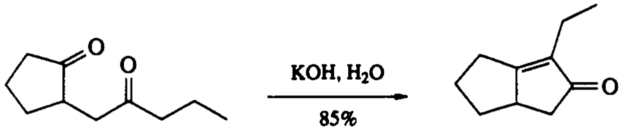

(119)

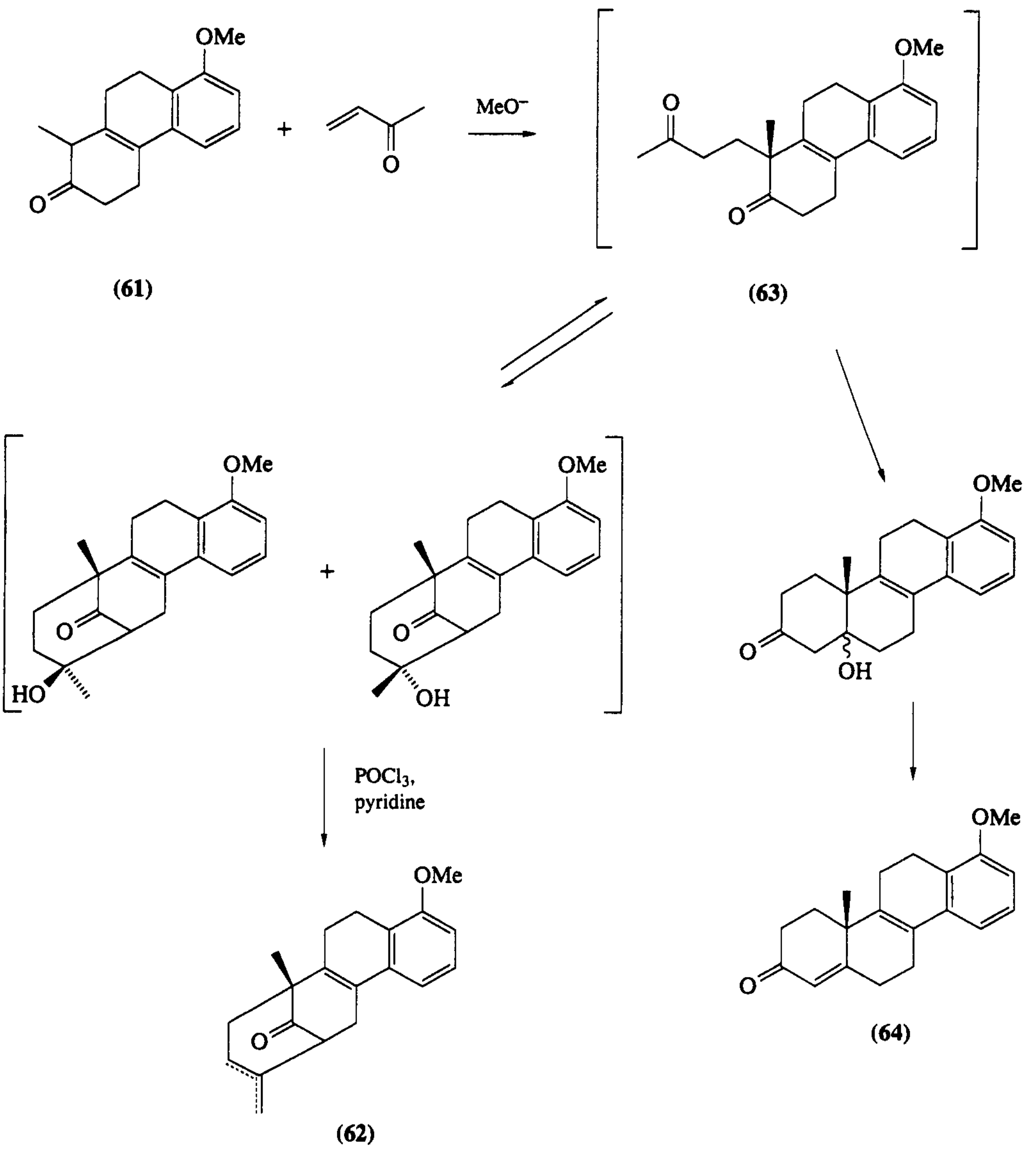

**Scheme 3**

formation of a bicyclo[3.3.0]octenone derivative.[140] However, the unsubstituted bicyclo[3.3.0]octenone cannot be prepared by this straightforward method.[141]

1,5-Diketones condense to give cyclohexenones. There are an enormous number of examples of such cyclizations, as this is one of the two steps in the Robinson annelation reaction.[113] In the annelation of a cyclohexenone onto a preexisting ring, the intermediate 1,5-diketone is unsymmetrical, and there is a question of regiochemistry. This issue was addressed by W. S. Johnson and coworkers in the context of steroid total synthesis.[142] As shown in Scheme 3, Robinson annelation of β,γ-unsaturated ketone (**61**) with methyl vinyl ketone affords a mixture of two bridged ketols. Dehydration of the separated isomers provides a mixture of β,γ-unsaturated ketones (**62**). However, treatment of the original ketol mixture under more vigorous basic conditions leads to the α,β-unsaturated ketone (**64**). Presumably, the kinetically formed ketols are in equilibrium with dione (**63**), which cyclizes, *via* the isomeric ketols, to (**64**).

Similar behavior with the simpler 1,5-diketone (**65**) has been documented by Marshall and Schaeffer.[143] As shown in equation (120), diketone (**65**) cyclizes to octalone (**66**) under basic conditions and to the bicyclo[3.3.1]nonenone (**67**) under acidic conditions. The regiochemistry of ring closure in this system is sensitive to the exact reaction conditions. For example, diketone (**65**), an intermediate in the acid-mediated Robinson annelation process, cyclizes to octalone (**66**; equation 121).[144] In this example, it is possible that enones (**66**) and (**67**) are actually in equilibrium, and that the former is favored on thermodynamic grounds.

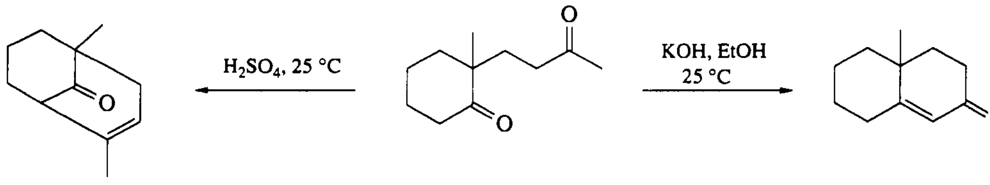

(120)

(**67**) (**65**) (**66**)

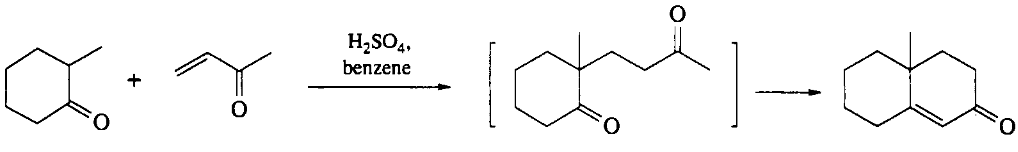

(121)

(**65**) (**66**) 60%

Several groups have examined the regiochemistry of cyclizations of acyclic 1,5-diketones. One of the first investigations was carried out by Plieninger and Suchiro, who studied the regiochemistry of cyclization of diketone (**68**; equation 122).[145] It was found that acidic conditions lead to the cyclohexenone (**69**), a reaction in which the enol of the more hindered ketone has condensed with the less hindered ketone. With piperidine and acetic acid (enamine conditions), the enamine of the less hindered ketone appears to add to the more hindered carbonyl group. This cyclization has been studied in detail by Kreiser and Below, who investigated compound (**68**) and eight of its analogs.[146] The best reagent for cyclization to (**69**) was found to be a mixture of HCl and trimethylsilyl chloride; compound (**69**) and its analogs are obtained in 70–92% yield after 16 h at room temperature. Piperidine and acetic acid in refluxing benzene for 12 h provides (**70**) in 65–94% yield. Similar investigations have been reported by Koga and coworkers[147] and by Frater and coworkers.[148]

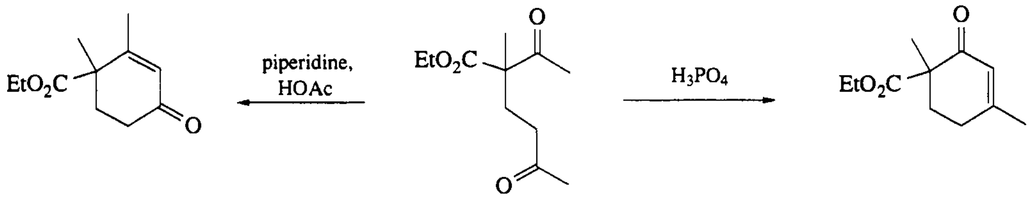

(122)

(**70**) (**68**) (**69**)

Danishefsky examined the regiochemistry of 1,5-diketone cyclization in the context of a steroid synthesis.[149] Diketone (**71**) cyclizes in aqueous ethanolic base to give a mixture of isomeric cyclohexenones (**72**) and (**73**) (equation 123). If the reaction is carried out at room temperature, the (**72**):(**73**) ratio is 77:23; after refluxing for 50 h, the ratio is 21:79. Furthermore, pure (**72**) is converted into (**73**) under the latter reaction conditions. With diketone (**74**), cyclohexenone (**75**) is the only product seen under either conditions (equation 124).

The foregoing work suggests that the 3-substituted cyclohexenones (**72**) and (**75**) are kinetically favored in the cyclization of diketones (**71**) and (**74**), but that sufficiently vigorous conditions might cause isomerization to the 2,3-disubstituted cyclohexenone (*e.g.* **72** → **73**). The fact that (**75**) does not undergo this further isomerization suggests that chain branching might perturb the equilibrium ratio in favor of the 3-substituted isomer. The effect of chain branching was verified in a further investigation.[150] Diketone (**76**) cyclizes at room temperature to give the 3-substituted product (**77**) as the only detected product in 91% yield (equation 125). Under identical conditions, the unbranched diketone (**78**) affords isomers (**79**) and (**80**) in a ratio of 17–19:1 (equation 126). The effect of branching is attenuated when the branch point is moved away from the carbonyl group, as shown in equation (127). The data in this equation suggest that, in the absence of branching, there is no intrinsic preference for formation of either the trisubstituted or tetrasubstituted alkene. Branching near one of the carbonyl groups causes a pref-

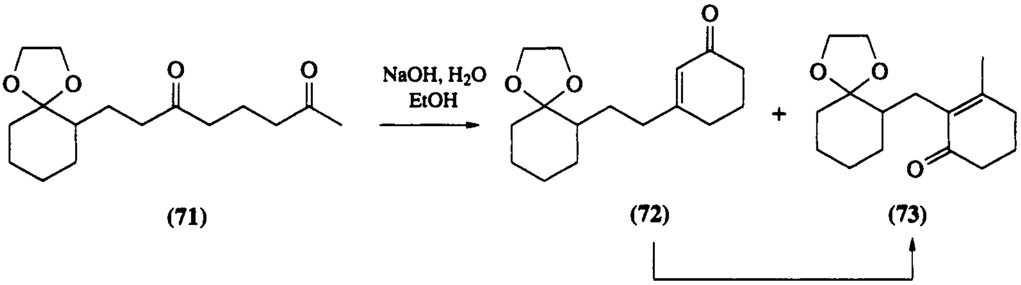
NaOH, H$_2$O
EtOH
+

**(71)** **(72)** **(73)** (123)

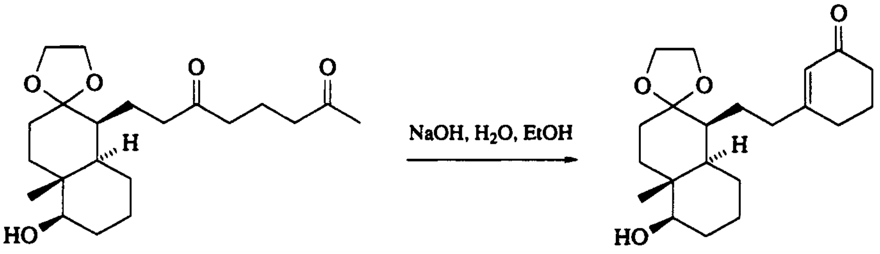
H
H
HO
HO
NaOH, H$_2$O, EtOH

**(74)** **(75)** (124)

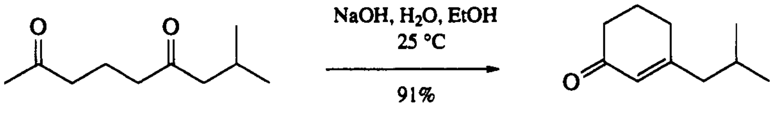
NaOH, H$_2$O, EtOH
25 °C
91%

**(76)** **(77)** (125)

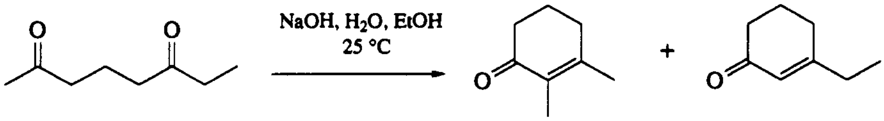
NaOH, H$_2$O, EtOH
25 °C
+

**(78)** **(79)** 79% **(80)** 4.5% (126)

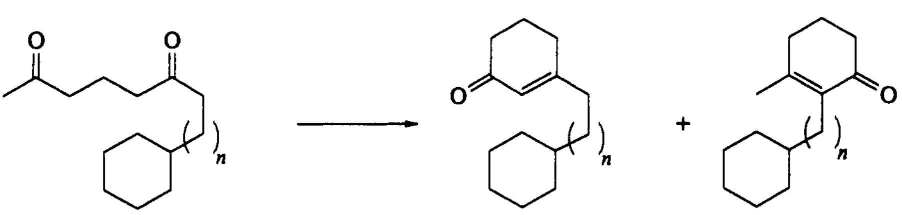

**(81)** **(82)** **(83)** (127)

| *n* | **(82)**:**(83)** |
|---|---|
| 0 | > 30:1 |
| 1 | 8.1:1 |
| 2 | 1.3:1 |
| 3 | 1.3:1 |
| 4 | 1.1:1 |

erence for formation of isomer (**82**), with the effect being stronger the nearer the branch point is to the carbonyl group.

Baldwin and Lusch have studied several triketones that could, in principle, undergo intramolecular aldol condensation to give several different enones.[151] Triketone (**84**), which is both a 1,4- and a 1,5-diketone, reacts under mild basic conditions to give only the corresponding cyclohexenone (**85**); neither of the two possible cyclopentenones are produced (equation 128). Triketone (**86**) is a more complex case, since it embodies 1,4-, 1,5- and 1,6-diketone relationships. In principle, this material can cyclize to five-, six- or seven-membered aldol products, in a total of eight different ways. However, when an aqueous alcoholic basic solution of (**86**) is refluxed, only two of these eight modes of cyclization are observed (equation 129). Cyclohexenones (**87**) and (**88**) are formed in a ratio of 85:15 (*cf.* equation 122), along with smaller amounts of the bicyclic aldols (**89**) and (**90**), shown to be secondary products arising from (**87**) and (**88**). Triketone (**91**) is a somewhat simpler case, in that it may cyclize to a cyclohexenone or to three different cyclopentenones. In the event, (**91**) was found to give only cyclohexenone (**92**; equation 130). This work clearly shows that six-membered rings are formed in preference to five- or seven-membered rings by intramolecular aldolization under condensation conditions.

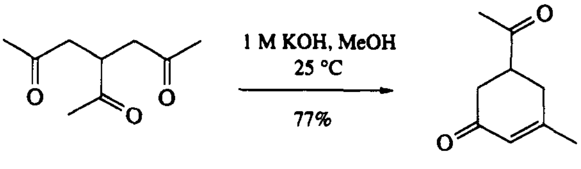

**(84)** **(85)**

(128)

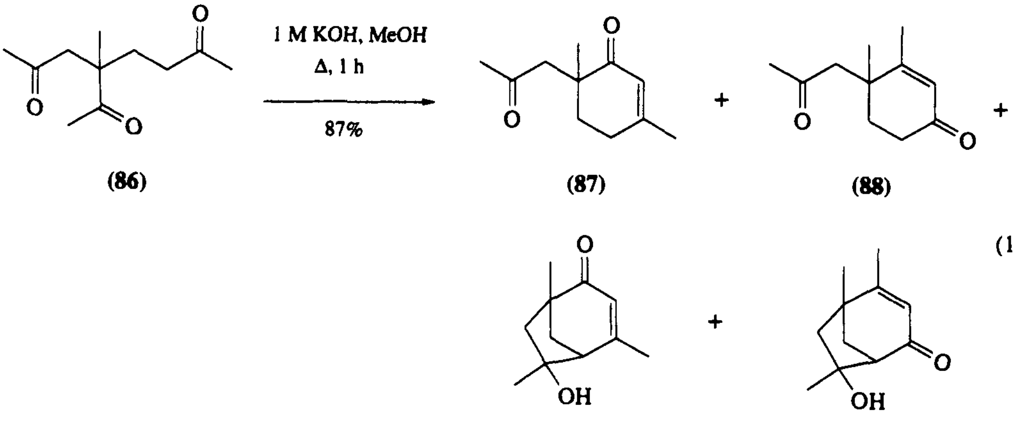

**(86)** **(87)** **(88)** **(89)** **(90)**

(129)

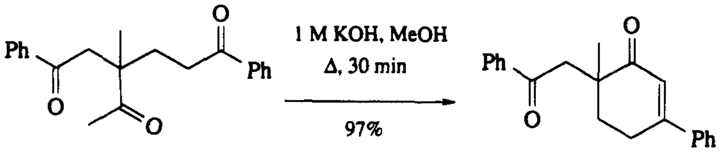

**(91)** **(92)**

(130)

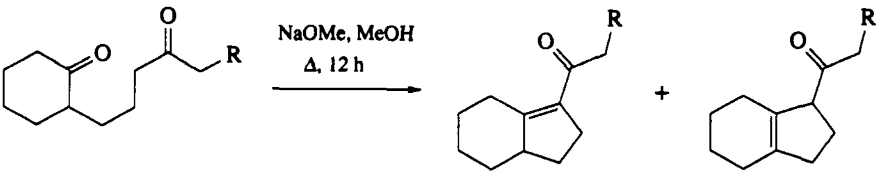

**(93)** **(94)** **(95)**

(131)

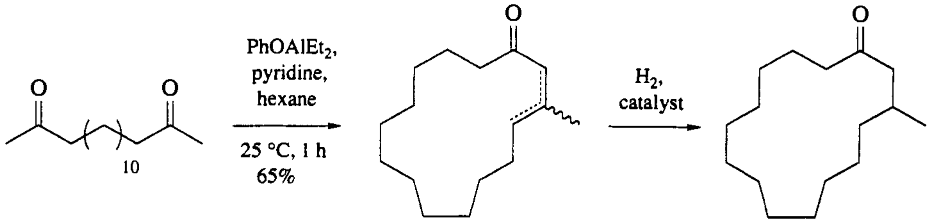

(132)

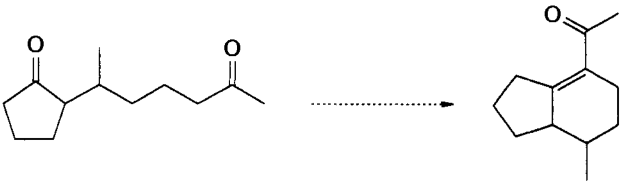

(133)

**(96)** **(97)**

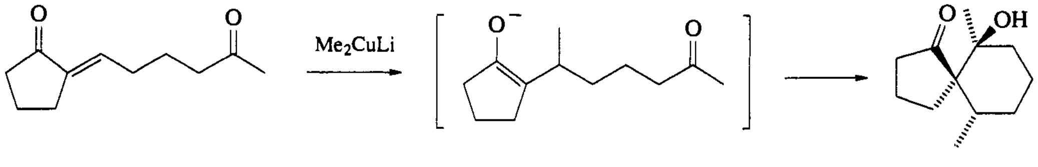

(134)

**(98)** **(99)** **(100)**

Two other research groups have also examined the relative ease of formation of five- and seven-membered aldol condensation products from 1,6-diketones.[152,153] In one study, diketone (**93**; equation 131; R = H) was found to cyclize to give solely (**94**). In another investigation, (**93**; R = Me) was employed and the product was carefully examined for minor amounts of seven-membered ring isomers. None could be detected, although an unspecified amount of the β,γ-unsaturated isomer (**95**) was found.

Tsuji and coworkers have developed diisobutylaluminum phenoxide–pyridine as an effective aldol condensation catalyst and applied it to the macrocyclization of 2,15-hexadecanedione (equation 132).[154] Addition of the diketone at high dilution to a solution of the catalyst in hexane provides a mixture of *cis* and *trans* isomers of the $\Delta^2$ and $\Delta^3$ enones. Catalytic hydrogenation of the mixture affords (±)-muscone. The authors explain the regioselectivity of the process by assuming that the aluminum phenoxide functions as a Lewis acid, coordinating to the carbonyl group. Pyridine functions as a base to remove a proton from the less hindered methyl group.

As will be seen in the following chapter, the use of strong amide bases for preforming enolates allows a considerable measure of control in defining the regiochemistry of aldol reactions. This technique, however, is more often applied in intermolecular aldol additions than in intramolecular ones. Näf and coworkers have reported an interesting way to control regiochemistry.[155] Diketone (**96**) would presumably cyclize under dehydrating conditions to give the acetylcyclohexene (**97**; equation 133). However, if the unsaturated diketone (**98**) is treated with lithium dimethylcopper, enolate (**99**) is formed and cyclizes to give the spirocyclic aldol (**100**; equation 134).

### 1.5.10.4 Stereochemistry of Aldol Cyclizations

There are few cases in which the stereochemistry of cyclic aldol addition reactions has been carefully examined. The situation is complicated by the problem of retro-aldolization and by the propensity of such aldols to dehydrate to the enone. There is a suggestion that under strictly kinetic conditions, aldols in which the carbonyl and hydroxy groups can chelate a metal cation are favored. However, in protic medium, it does not appear that the kinetic product is generally the more stable one. A particularly instructive example is seen in equation (135).[156] The complex keto aldehyde (**101**) was treated with dilute KOH in methanol for 15 min at various temperatures. At –20 °C, +25 °C, and +65 °C, the (**102**):(**103**) ratios were 93:7, 50:50 and 0:100, respectively.

Similar behavior is seen in the cyclization of dialdehyde (**104**), an intermediate in the dimerization of 2-ethyl-2-hexenal; the resulting mixture of aldol products contains 99% of isomer (**105**; equation 136).[23a–b]

Cyclizations that are carried out under equilibrating conditions often give mixtures of stereoisomeric aldols. An example of this behavior is seen in aldolization of keto aldehyde (**106**) with potassium *t*-butoxide in benzene; aldols (**107**) and (**108**) are formed in a ratio of 2:3 (equation 137).[157]

However, other structural features can provide a thermodynamic selection of one stereoisomer. Intramolecular aldolization of 2,2′-*O*-methylene-bis-D-glycerose (**109**) under weakly basic conditions affords only two of the four possible aldols, (**110**) and (**111**) (Scheme 4).[158] The (**110**):(**111**) ratio greatly favors the former, and conditions were found under which only isomer (**110**) is produced. It was proposed that the aldol cyclization is under thermodynamic control, and that the initial products are trapped as their intramolecular hemiacetals (**112**) and (**113**). The other two possible aldols cannot form such hemiacetals. Isomer (**112**) is presumably favored over (**113**) because of the normal equatorial preference of a hydroxy group that is hydrogen-bonded to water.

In 1971, groups at Hoffmann–La Roche and Schering AG reported the exceedingly useful discovery that symmetric triketones such as (**114**), in which the two cyclopentanone carbonyl groups are enantiotropic, undergo aldolization in the presence of L-proline to give aldols (**115**) in high enantiomeric excess (equation 138).[159,160] Using (**114**; R = Me), the aldol is produced in quantitative yield with 93.4% *ee*; with (**114**; R = Et), the aldol is obtained in 70–76% yield with 99.5% *ee*. Dehydration of the aldols provides the synthetically useful hydrindenediones (**116**; R = Me or Et). The method was subsequently extended to the synthesis of enantiomerically homogeneous Wieland–Miescher diketone (**117**; equation 139).[161] Takano and coworkers have used the procedure with an indanedione derivative to prepare the gibbane framework in enantiomerically pure form (equation 140).[162]

Danishefsky and Cain examined several amino acids for asymmetric aldolization of trione (**118**; equation 141).[163] With L-proline, the hydrindenedione (**119**) was obtained in only 27% *ee*. However, L-phenylalanine was more effective, giving (**119**) with 85% *ee*. Other amino acids (tyrosine *O*-methyl ether,

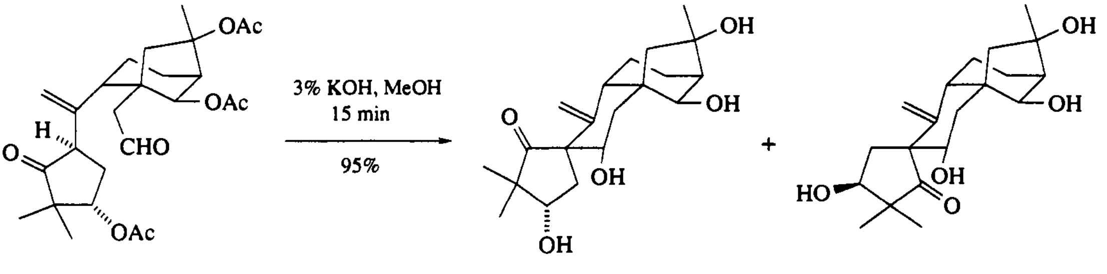

(**101**) (**102**) (**103**) (135)

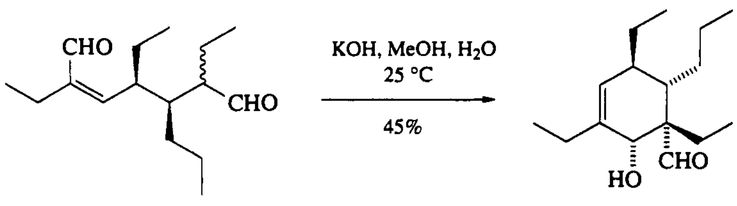

(**104**) (**105**) (136)

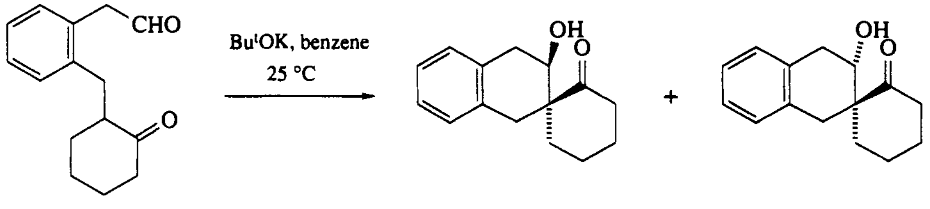

(**106**) (**107**) 21% (**108**) 30% (137)

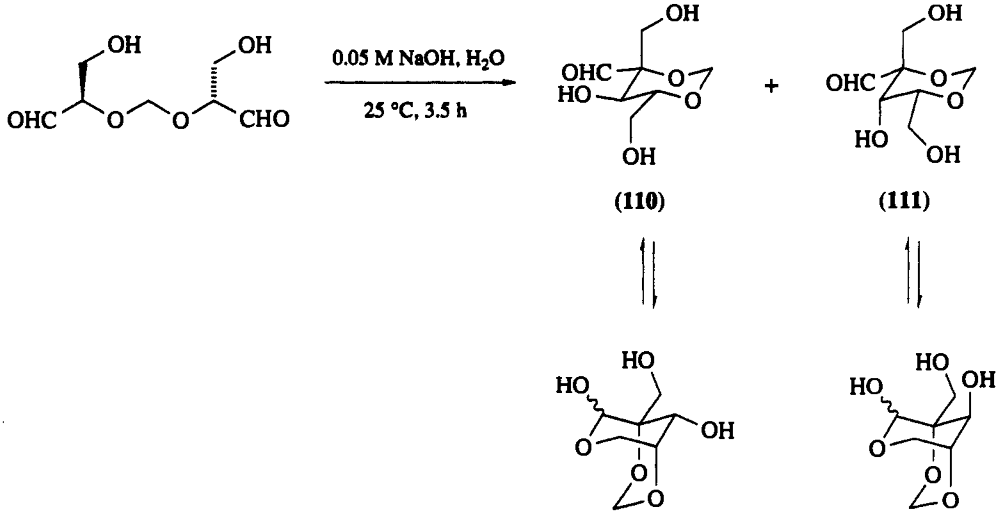
0.05 M NaOH, H2O
25 °C, 3.5 h
+

(110) (111)

(112) (113)

**Scheme 4**

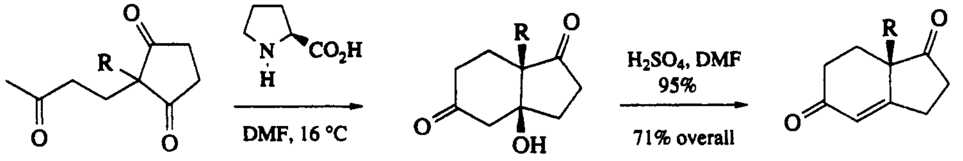
DMF, 16 °C
H2SO4, DMF
95%
71% overall

(138)

(114) R = Me, Et (115) R = Me, Et (116) R = Me, Et

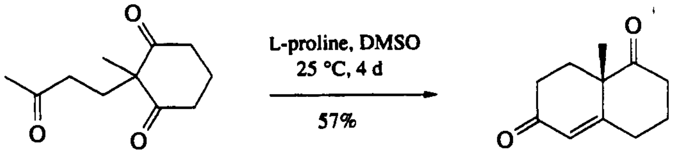
L-proline, DMSO
25 °C, 4 d
57%

(139)

(117)

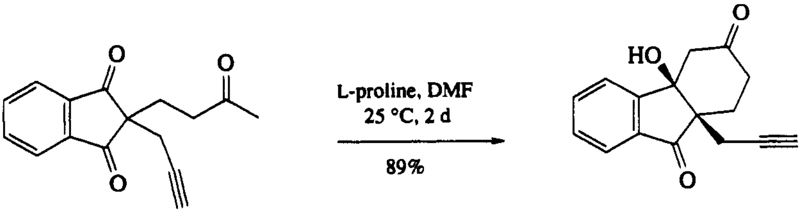
L-proline, DMF
25 °C, 2 d
89%

(140)

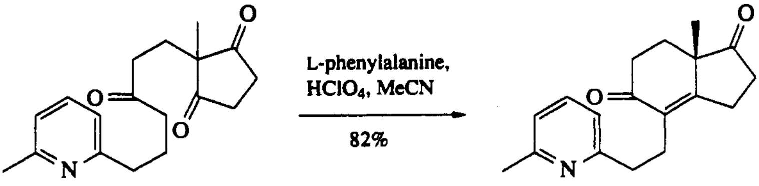
L-phenylalanine,
HClO4, MeCN
82%

(141)

(118) (119) 85% *ee*

tryptophan, serine and valine) also gave cyclized products, with enantiomeric excesses of 84%, 78%, 35% and 21%, respectively.

### 1.5.10.5 Transannular Cyclizations

Macrocyclic diketones can undergo transannular aldol cyclization reactions, giving bicyclic aldols. A representative example is seen in the cyclization of 1,6-cyclodecanedione to the corresponding hydroazulenone (equation 142).[164] Aldolization of the related cyclodecadienedione (**120**) has also been examined; under mildly basic conditions aldols (**121**) and (**122**) are the main products, being formed in a ratio of 1:4 (equation 143).[165] Control experiments with the pure aldols showed that this is the thermodynamic ratio of isomers.

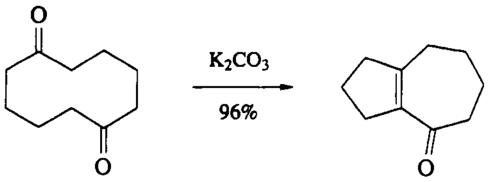

(142)

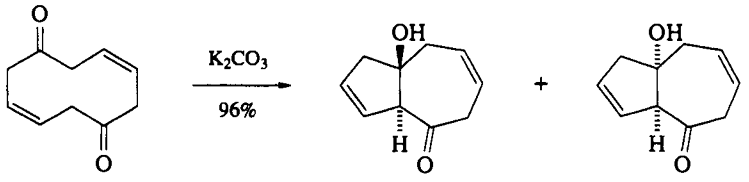

(143)

**(120)** **(121)** **(122)**

Aldolization of 1,7-cyclododecanedione proceeds smoothly to produce a crystalline aldol in 66% yield (equation 144).[166] Although the stereochemistry of this product has not been elucidated, its sharp melting point (70–71 °C) suggests that it may be a single isomer.

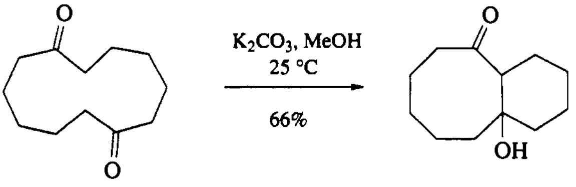

(144)

Related cyclizations are observed in certain bicyclic diketones, converting them into tricyclic aldols. Deslongchamps and coworkers discovered that *cis*-bicyclo[4.4.0]decane-3,9-dione is the minor isomer in equilibrium with its intramolecular aldol, the twistane derivative (**123**; equation 145).[167] The equilibrium could be shifted completely to the aldol by acetylation.

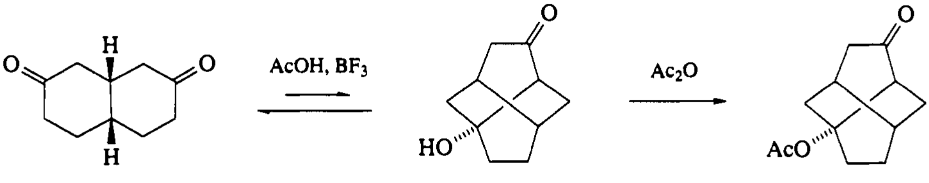

(145)

**(123)** **(124)**

Yordy and Reusch observed a similar intramolecular aldolization in a decalindione. As shown in equation (146), dione (**125**) is in equilibrium with aldol (**126**) under basic conditions ($K = 2.3$).[168] Aldol (**126**) may be obtained as a crystalline substance, but it is easily converted back into dione (**125**) (*e.g.* under

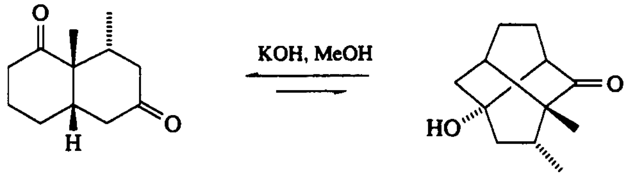

(125) (126)

(146)

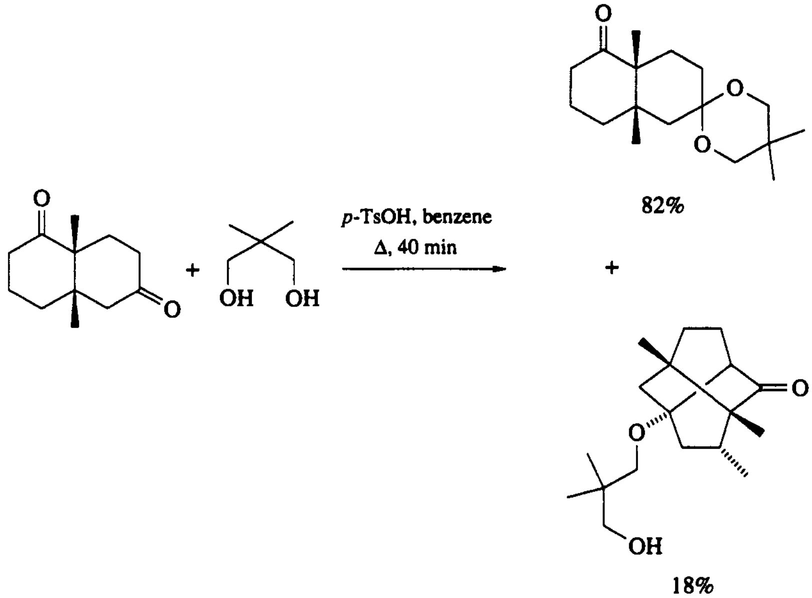

(147)

acidic conditions). Similar intramolecular aldolizations can sometimes give rise to quite unexpected products (equation 147).[169]

### 1.5.10.6 Polyketides

In 1907, Collie showed that dehydroacetic acid is converted into orcinol (**128**) on treatment with base.[170] It was presumed that this transformation proceeds through triketone (**127**; equation 148). On the basis of this reaction, Collie suggested the 'polyacetate' biogenesis of naturally occurring phenolic compounds. In later work, it was shown that trione (**127**) is converted by acid into phenol (**128**).[171,172]

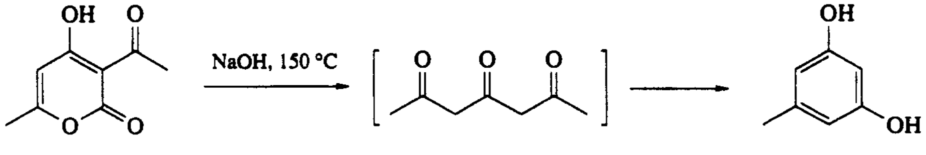

(127) (128)

(148)

Birch and coworkers fully elaborated the polyketide hypothesis and examined possible biomimetic syntheses. In one example, treatment of γ-pyrone (**129**) with base was found to give a mixture of resorcinols (**131**; dihydropinosylvin) and (**132**), presumably from the two modes of intramolecular aldolization of triketone (**130**; equation 149).[173]

Money, Scott and coworkers utilized a similar strategy of protecting the labile polyketone as a pyrone ring. As shown in equation (150), pyranopyrone (**133**) reacts with aqueous base to give orsellinic acid, presumably by way of the intermediate triketo diacid (**134**).[174] The procedure was found to be quite general; equation (151) shows a further application in the synthesis of pinosylvin, (**135**).[175]

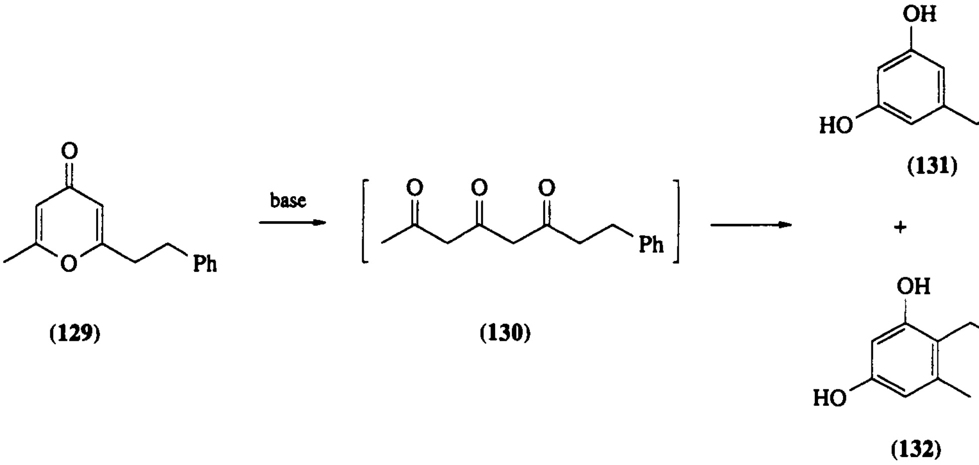

(149)

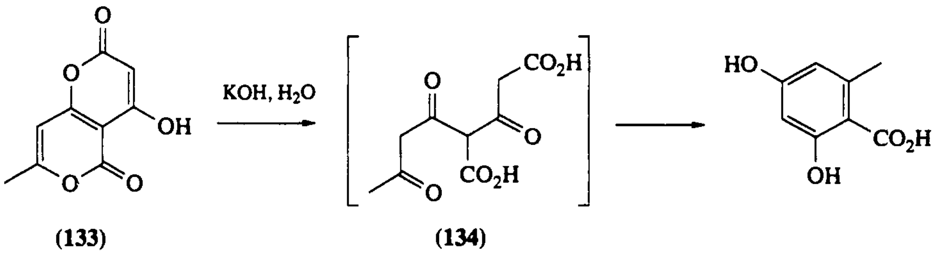

(150)

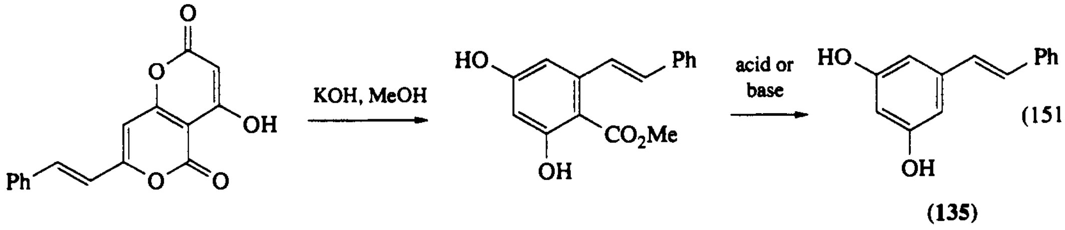

(151)

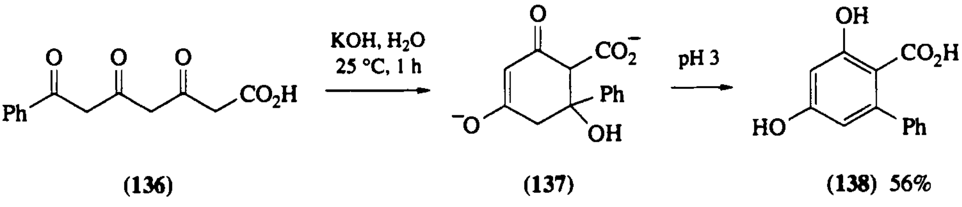

(152)

Harris and coworkers have developed ways to prepare polyketones and have carried out extensive studies on their intramolecular aldol reactions.[176] A simple and representative example of this work is shown in equation (152); treatment of triketo acid (**136**) with aqueous base at room temperature gives (**137**), the dianion of a 1,3-cyclohexanedionecarboxylic acid.[177] Although (**137**) is stable for several days in basic solution, acidification results in rapid dehydration to give the resorcylic acid (**138**).

A more complex substrate is hexaketone (**139**), which has three possible initial aldolization modes (Scheme 5; a, b and c). Treatment of this material with sodium bicarbonate or silica gel provides naphthalene derivative (**140**), the result of mode b aldolization.[178] On the other hand, use of aqueous KOH gives resorcinol derivatives (**141**) and (**142**), resulting from aldolization modes a and c. Further aldolization of (**142**) to (**143**) is achieved by treatment with potassium carbonate.

In extending these biomimetic studies to higher polyketones, one encounters a plethora of possible aldol reactions. For example, 2,4,6,8,10,12,14-pentadecaneheptone can undergo five possible initial cyclizations leading to six-membered rings (**144**). To reduce the number of possible reactions, Harris and Wittek prepared the diketal (**145**). Cyclization of this material occurs mainly by mode b to give (**146**), which further cyclizes on acidification to provide eleutherinol (**147**); equation 153).[179]

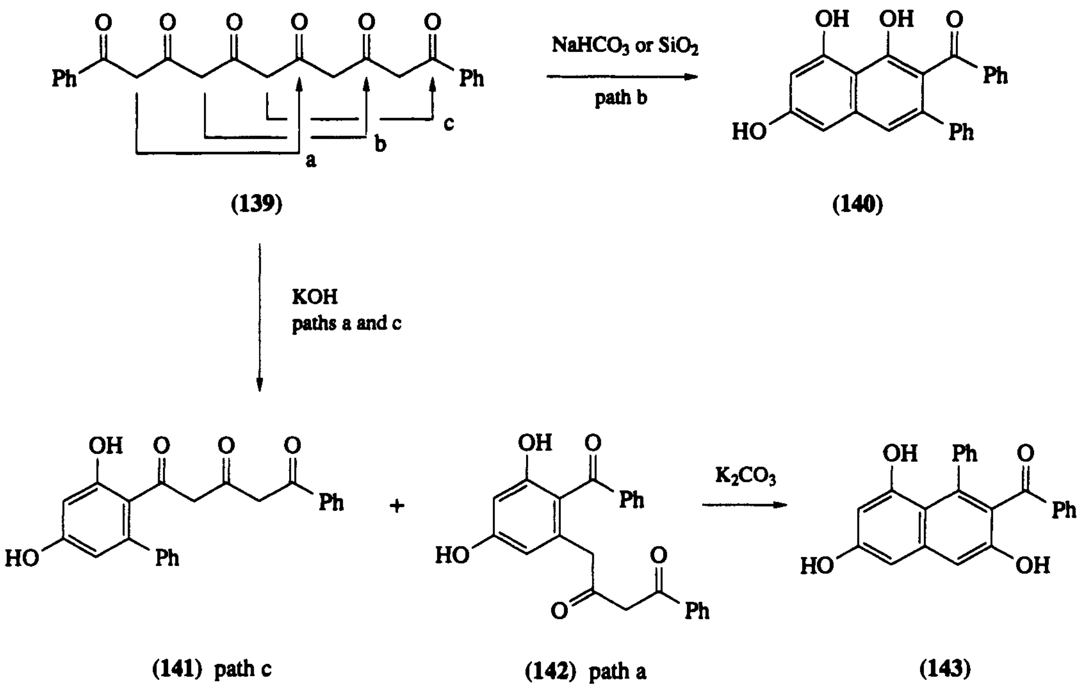
NaHCO3 or SiO2
path b
KOH
paths a and c
$K_2CO_3$
a
b
c
(139)
(140)
(141) path c
(142) path a
(143)

**Scheme 5**

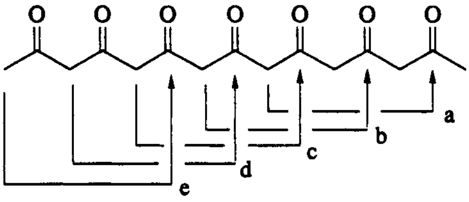

**(144)**

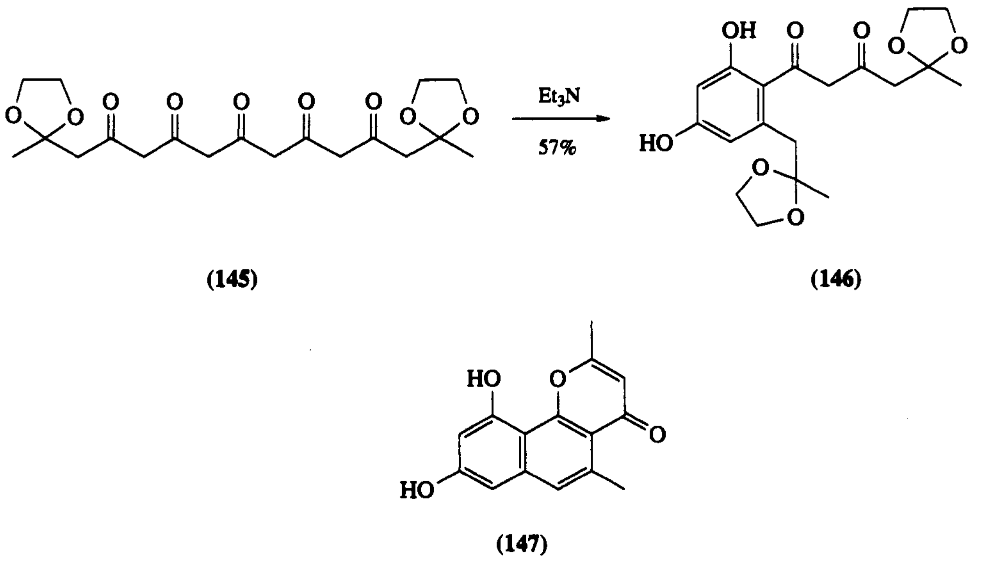
$Et_3N$
57%
$H_3O^+$
(145)
(146)
(147)

(153)

To achieve type c aldolization, the monoprotected heptaketone (**148**) was prepared as shown in Scheme 6.[180] Condensation of the dianion of 2,4-pentanedione with the ethylene ketal of diethyl 3-oxoglutarate presumably affords (**148**). However, the substance eludes isolation or even spectral identification. Instead, naphthalene derivative (**149**) is obtained in 39% yield. Further aldolization, dehydration, and removal of the ethylene glycol moiety provides the naturally occurring anthrone (**150**).

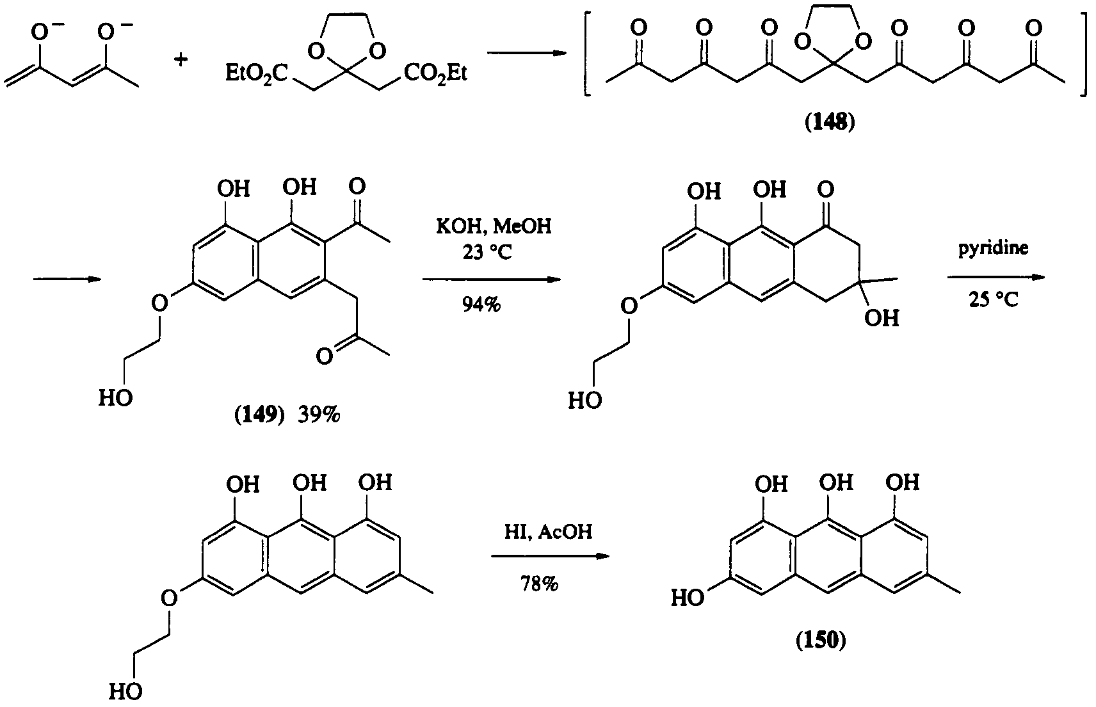

**Scheme 6**

Bringmann has reported a similar cyclization.[181] Reaction of lithiopotassioacetone with the ethylene ketal of dimethyl 3-oxoglutarate provides phenol (**151**) in 19% yield (equation 154). Again, the intermediate tetraketone eludes isolation. A series of transformations serves to convert (**151**) into the isoquinoline (**152**).

One of the most complex molecules yet prepared by these biomimetic approaches is the pretetramid (**158**; Scheme 7).[182] The 3-pyrrolidinoglutaric acid diamide (**153**) is condensed with two equivalents of the dianion of *t*-butyl acetoacetate. The putative intermediate (**154**) undergoes spontaneous cyclization to provide the naphthalene derivative (**155**). This substance is transformed by a sequence of steps into naphthalenopyrone (**156**), which is extended by reaction with an isoxazole dianion. Spontaneous aldolization again occurs, yielding the anthracene derivative (**157**). Closure of the final ring ensues when (**157**) is treated with HI.

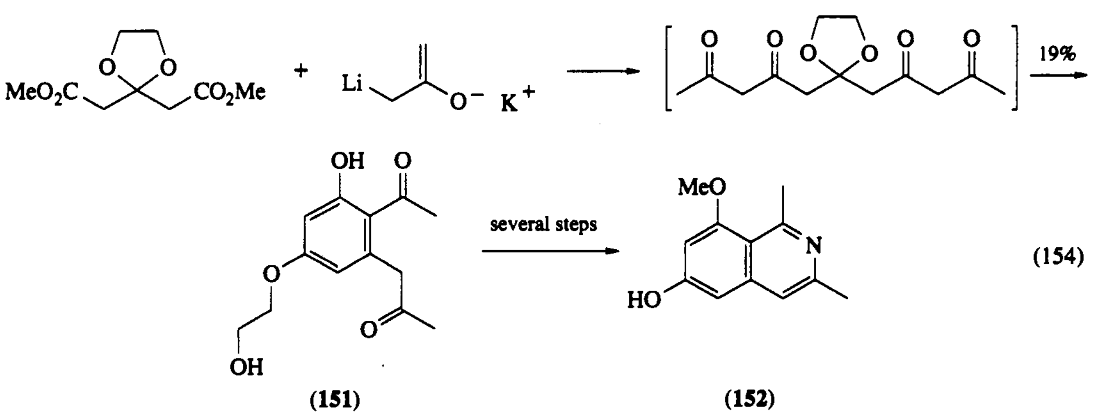

(154)

Yamaguchi has reported the preparation of polyketone compounds by addition of the dianion of methyl acetoacetate to *N,N,N',N'*-tetramethylsuccinamide in the presence of boron trifluoride etherate (equation 155).[183] Treatment of the resulting tetraketo diester with aqueous acid provides the hydrindanone (**159**) in 67% overall yield. *N,N,N',N'*-Tetramethylglutaramide is treated similarly to obtain the tetralone (**160**; equation 156). The homologous tetraketo diester (**161**) fails to undergo the aldolization reaction under the normal conditions. However, cyclization is brought about in 40% yield by manganese acetate in refluxing methanol (equation 157). A metal template effect has been invoked to explain this reaction.

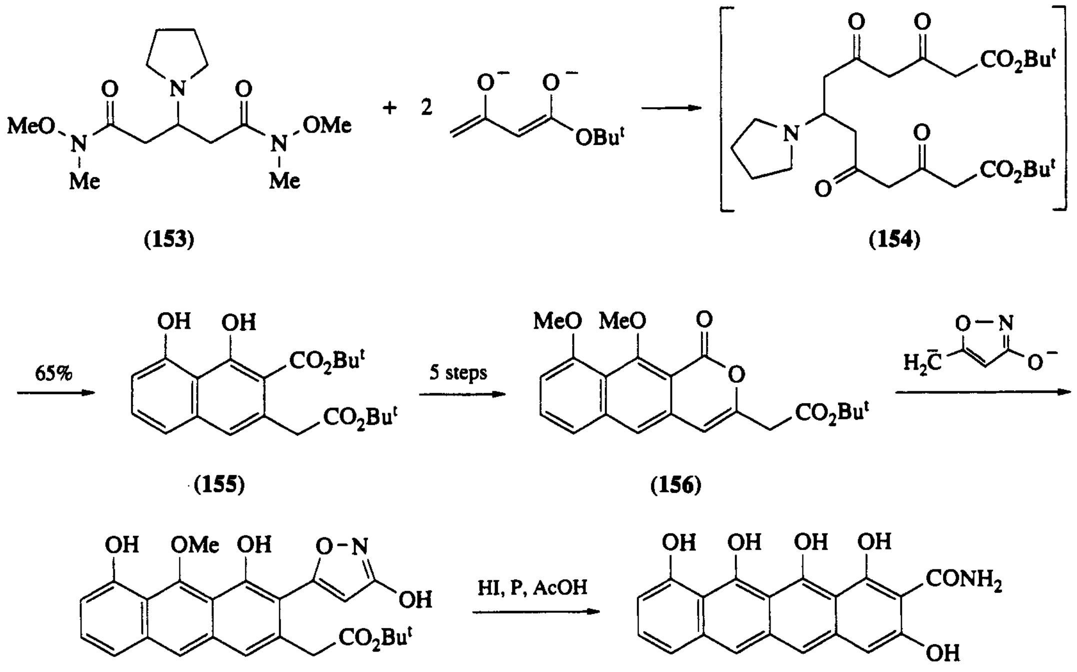

**(153)** **(154)** **(155)** **(156)** **(157)** **(158)**

**Scheme 7**

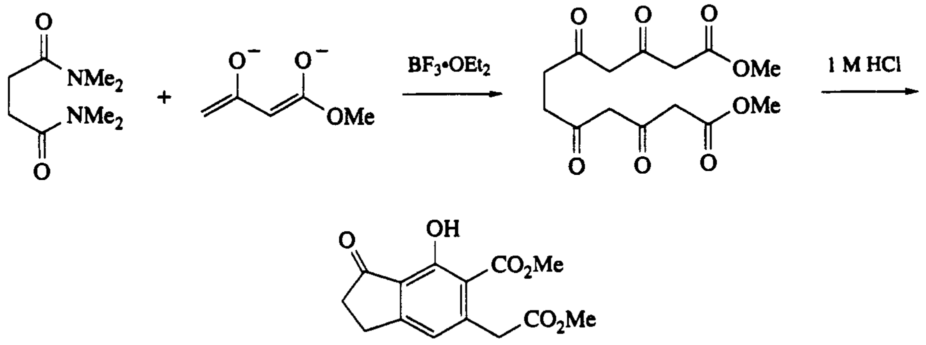

**(159)** 67% overall

(155)

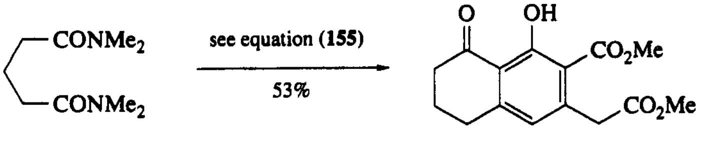

**(160)**

(156)

Starting with a preformed A-ring, in the form of phthalide (**162**), Harris and coworkers assembled the anthracene derivative (**164**) as shown in Scheme 8.[184] The intermediate tetraketo diester (**163**) closes spontaneously under the conditions of its synthesis from (**162**) and the dianion of *t*-butyl acetoacetate.

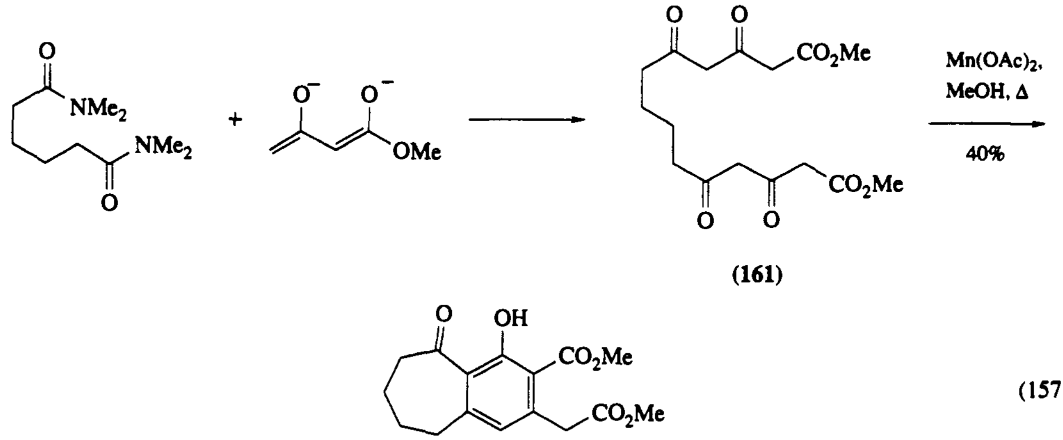
NMe2
NMe2
OMe
CO2Me
CO2Me
Mn(OAc)2, MeOH, Δ
40%
OH
CO2Me
CO2Me

(**161**)

(157)

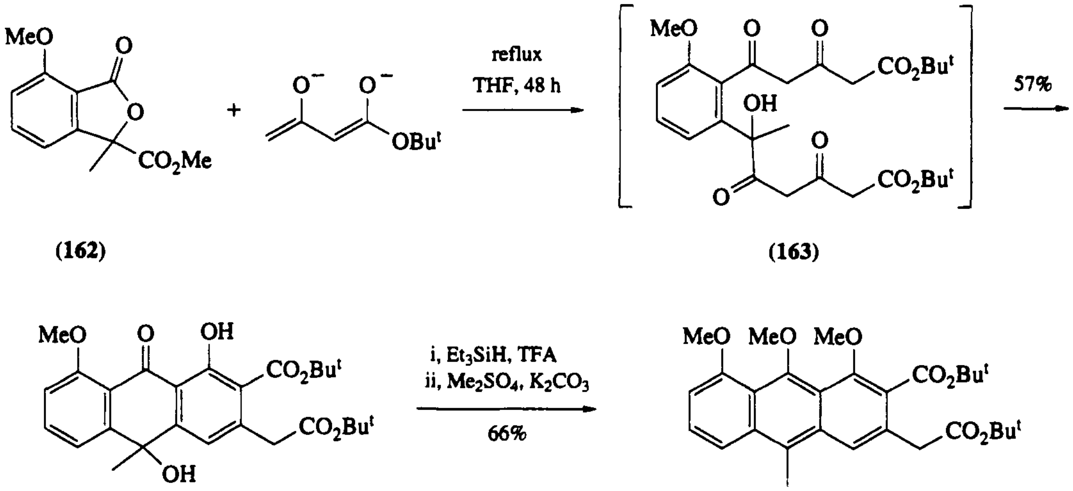
MeO
CO2Me
OBu^t
reflux
THF, 48 h
CO2Bu^t
OH
57%
i, Et3SiH, TFA
ii, Me2SO4, K2CO3
66%
MeO MeO MeO

(**162**)

(**163**)

(**164**)

**Scheme 8**

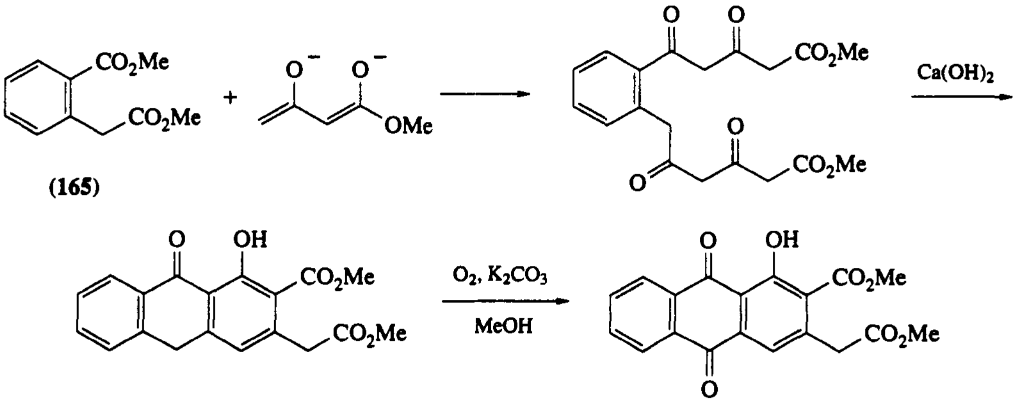
CO2Me
CO2Me
OMe
Ca(OH)2
OH
O2, K2CO3
MeOH

(**165**)

(**166**)

(**167**)

**Scheme 9**

Yamaguchi has reported a related biomimetic synthesis of anthraquinones, summarized in Scheme 9.[185] Reaction of diester (**165**) with methyl acetoacetate dianion provides a tetraketo diester which is cyclized by calcium hydroxide to obtain anthrone (**166**). Air oxidation in basic medium affords the anthraquinone (**167**).

## 1.5.11 REFERENCES

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# 1.6

# The Aldol Reaction: Group I and Group II Enolates

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## 1.6.1 INTRODUCTION

Traditionally, aldol reactions were carried out under protic conditions, such that the enolate was formed reversibly (see Volume 2, Chapter 1.5). An added measure of control is possible if one uses a sufficiently strong base that the enolate may be quantitatively formed prior to addition of the electrophile. The renaissance that has occurred in the aldol reaction in the last two decades has been mainly due to the development of methods for the formation and use of preformed enolates. The simplest enolates to prepare are those associated with lithium and magnesium, and there now exists a considerable literature documenting certain aspects of lithium and magnesium enolate aldol chemistry. This chapter summarizes the aldol chemistry of preformed enolates of these Group I and Group II metals. Other chapters in this volume deal with boron enolates, zinc enolates, transition metal enolates and the related chemistry of silyl and stannyl enol ethers.

## 1.6.2 FORMATION AND ALDOL REACTIONS OF REGIO-DEFINED ENOLATES

The great power of the aldol addition reaction lies in the ability to generate and use structurally defined enolates. In this section, the emphasis is on the formation of regio-defined enolates, and the aldol reactions of these enolates. Stereochemical issues are dealt with in Sections 1.6.2–1.6.4.

### 1.6.2.1 Stoichiometric Deprotonation of Carbonyl Compounds

The first use of preformed enolates for synthesis appears to have been by Hauser and coworkers, who converted *t*-butyl and ethyl acetate into the lithium enolates by reaction with $LiNH_2$ in liquid ammonia; the resulting enolates were found to react with aldehydes and ketones to give β-hydroxy esters (equations 1 and 2).[1]

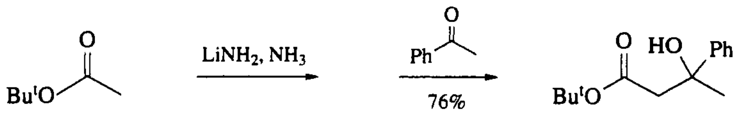

(1)

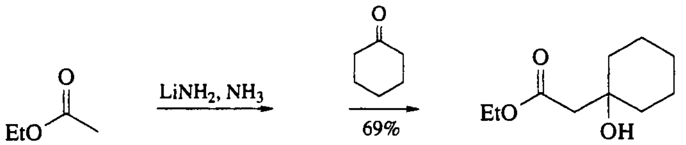

(2)

It was later found that dialkyl- and disilyl-amides have several attractive advantages, relative to the unsubstituted amides. Firstly, because they are relatively hydrophobic, these bases dissolve readily in organic solvents such as ether, tetrahydrofuran (THF), benzene and toluene. Secondly, the steric hindrance of the nitrogen atom reduces the nucleophilicity of the amide, thus ameliorating one of the principal side reactions of $LiNH_2$ and $NaNH_2$ with esters.[2]

One of these important bases, diisopropylaminomagnesium bromide, was first introduced by Frostick and Hauser in 1949 as a catalyst for the Claisen condensation.[3] However, the most generally useful base has turned out to be lithium diisopropylamide (LDA), which was first used by Hamell and Levine for the same purpose in 1950 (equation 3).[4] After the introduction of LDA, it was more than 10 years before it was used by Wittig for the stoichiometric deprotonation of aldimines in what has come to be known as the 'Wittig directed aldol condensation.'[5] In a seminal paper in 1970, Rathke reported that the lithium enolate of ethyl acetate is formed by reaction of the ester with lithium hexamethyldisilazane in THF.[6,7] Rathke found that THF solutions of the lithium enolate are stable indefinitely at –78 °C, and that the enolate reacts smoothly with aldehydes and ketones to give β-hydroxy esters (equation 4).

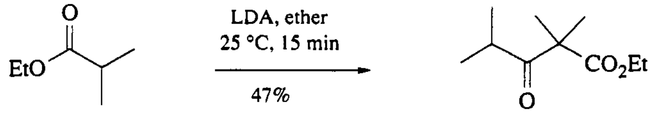

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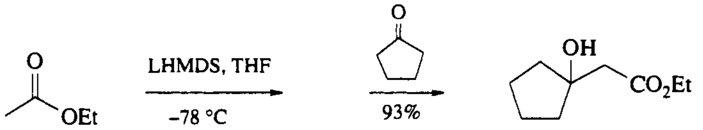

(4)

In a 1971 paper, Rathke and Lindert reported that lithium *N*-isopropylcyclohexylamide (LICA) is a superior reagent for the generation of ester enolates.[8] Subsequent workers, however, have found that LDA works just as well.[9] This base has the added virtue of being derived from a relatively volatile amine (the b.p. of diisopropylamine is 84 °C).

Lithium 2,2,6,6-tetramethylpiperidide (LITMP) was introduced by Olofson and Dougherty in 1973.[10] This base appears to be significantly more hindered than LDA, and is useful for regioselective enolate formation in cases where a very bulky base is desirable.[9c] Another very hindered base is lithium *t*-butyl-*t*-octylamide, introduced by Corey and Gross.[11]

Lithium, sodium and potassium hexamethyldisilazanes are available from the corresponding amine, bis(trimethylsilyl)amine. (This amine has a multitude of traditional common names, the most common of which are 'hexamethyldisilazine' and 'hexamethyldisilazane.' Its conjugate base has been called 'hexamethyldisilazide' and 'hexamethyldisilazane,' among other things. Although these names are somewhat confusing to the uninitiated, they are firmly entrenched in the literature. In this volume, we will use hexamethyldisilazane, abbreviated HMDS.) The lithium base may be formed by treatment of the amine with an alkyllithium in an ether solvent;[12] the sodium and potassium bases are produced by reaction of the amine with $NaNH_2$ or $KNH_2$.[7,13] All three of the hexamethyldisilazanes are also commercially available.

Triphenylmethylpotassium[14] and triphenylmethyllithium[15,16] were once used for stoichiometric deprotonation of ketones, but these bases offer no significant advantages over the foregoing amide bases, and they are rarely used now.

### 1.6.2.2 Regioselective Deprotonation of Ketones

The introduction of the foregoing bases opened the way for the preparation of structurally defined enolates; examples are seen in equations (5) to (7).[16,17] The first examples of the use of these regio-defined enolates in crossed aldol reactions were reported by Stork, Kraus and Garcia in 1974; representative examples are shown in equations (8) and (9).[18,19]

An application of this process is seen in the synthesis of (±)-[6]-gingerol (1; equation 10).[20] In this example, the regioselectivity of deprotonation is 92% at C-1 and 8% at C-3. With the weaker base lithium hexamethyldisilazane, the C-1:C-3 ratio is only 3:1. The method has also been used to prepare nine other (±)-gingerols.

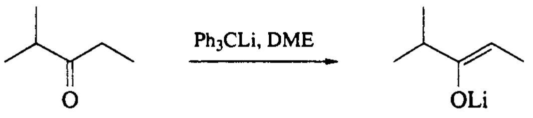

(5)

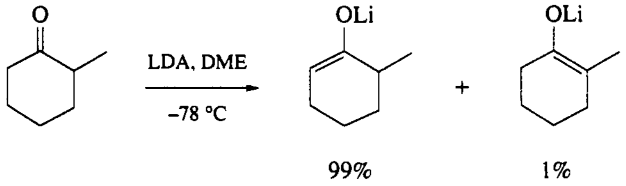

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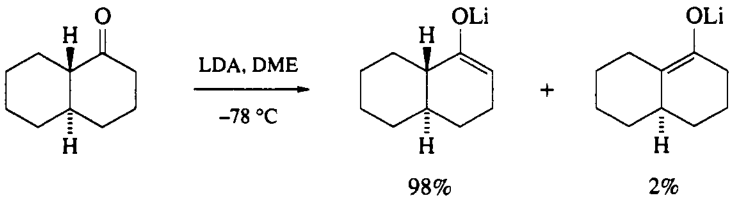

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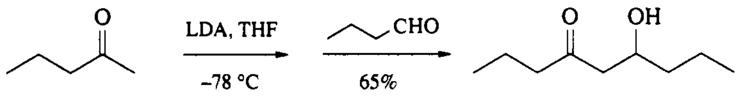

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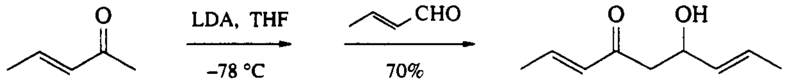

(9)

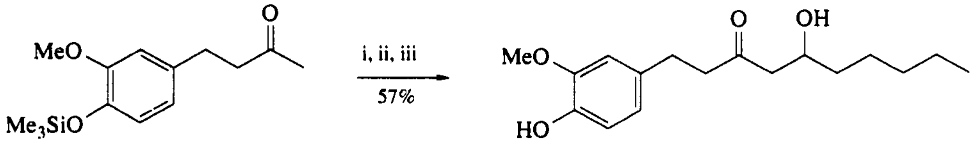

(10)

(1)

i, LDA, DME, -78 °C; ii, $Me(CH_2)_4CHO$; iii, $H_3O^+$

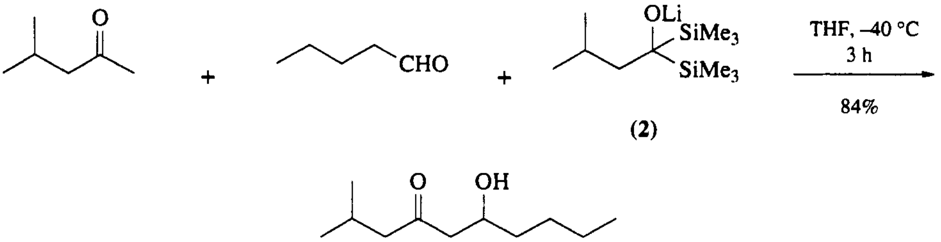

(11)

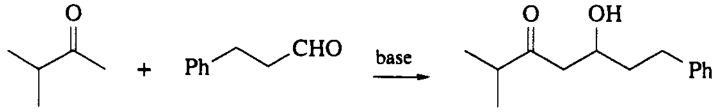

(12)

Kuwajima and coworkers used very hindered bases such as (**2**) to deprotonate methyl alkyl ketones regioselectively *in the presence of enolizable aldehydes.*[21] One example of this amazing process is shown in equation (11); the reaction is reported to work equally well with other methyl ketones, including 2-pentanone. The process was also demonstrated with other bases in the reaction of 3-methyl-2-butanone with dihydrocinnamaldehyde (equation 12). Among the bases that are effective are LDA, lithium hexamethyldisilazane, lithium *t*-butoxide and even lithium ethoxide. However, base (**2**) is superior, giving the aldol in 83% yield.

### 1.6.2.3 Enolates from Enol Esters and Silyl Enol Ethers

Enolates can also be prepared by reaction of enol esters[16,22,23] or silyl enol ethers[16,24] with alkyllithium reagents. House has worked out a protocol wherein these enolates are allowed to react with aldehydes to give the corresponding aldols.[25] Higher yields of aldol products are obtained when the lithium enolate is generated in ether or 1,2-dimethoxyethane (DME) by reaction of an enol acetate with methyllithium. Lower yields are obtained if the enolate is produced by reaction of a silyl enol ether with methyllithium. For the aldol reaction, ether or mixtures of ether and DME are superior to THF. Acceptable yields of aldol adducts are obtained in ether at low temperatures (–20 to –50 °C). In the more polar solvents DME or THF, the addition of anhydrous $ZnCl_2$ or $MgBr_2$ results in higher yields. An example is seen in equation (13).[25b] The stereochemistry of this process is discussed in Section 1.6.5.

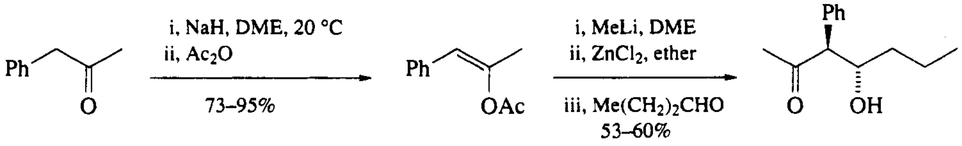

(13)

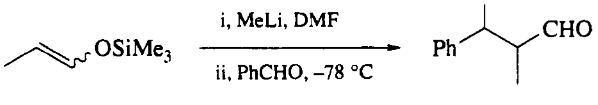

(14)

The enol ester or silyl enol ether route to enolates has advantages over direct deprotonation in certain cases. If direct deprotonation provides a mixture of regio- or stereo-isomers, it is often possible to trap the enolate mixture by esterification or silylation, separate the desired enol ester or silyl enol ether and regenerate the enolate by reaction with methyllithium. It is also useful for preparation of enolates from substances that are so electrophilic that direct deprotonation is complicated by self-aldolization. For example, aldehyde enolates have been prepared in this manner (equation 14).[9c]

### 1.6.2.4 Enolates from Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

A classic method for generating regio-defined enolates is metal–ammonia reduction of an enone.[26] Stork and d'Angelo found that the enolate resulting from lithium–ammonia–*t*-butyl alcohol reduction of octalone (**3**), followed by evaporation of ammonia, suspension of the enolate in ether and treatment with gaseous formaldehyde, provides a mixture of hydroxy ketones (**4**) and (**5**), with the latter predominating (equation 15).[27] Enolate equilibration can be suppressed by use of aniline, rather than *t*-butyl alcohol, as the proton source in the reduction step (equation 15). However, the yield of hydroxymethyl ketone is only 60%. A much better overall yield (90%) is realized by trapping the original enolate as the trimethylsilyl enol ether and regenerating the enolate in the absence of any proton donors (*vide infra*).

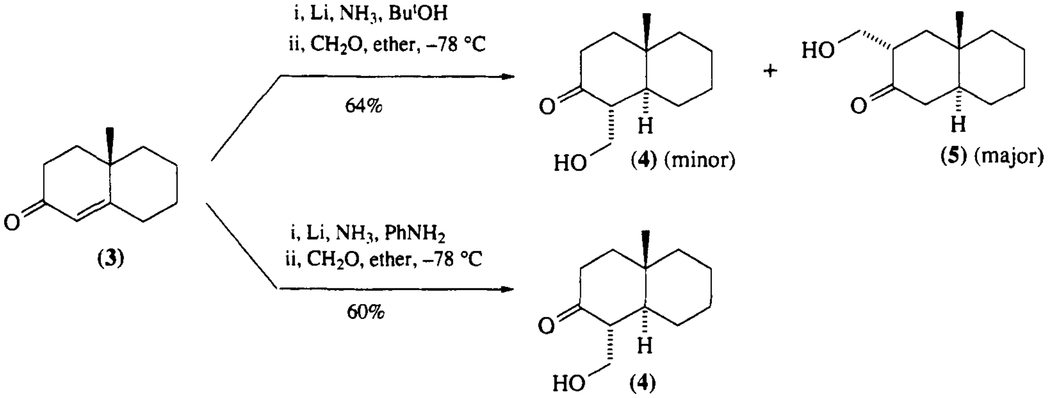

(**3**) (**4**) (minor) (**5**) (major) (**4**)

(15)

As shown in equation (15), the necessary presence of a proton source in the reaction medium that is used to generate specific enolates by metal–ammonia reduction limits the use of these enolates for regio-defined aldol reactions. The enolates resulting from conjugate additions of Grignard reagents or Gilman reagents to α,β-unsaturated carbonyl compounds do not suffer from this limitation, and have frequently been employed for aldol reactions.

Two papers that appeared in 1974 were the first to demonstrate the preparation and aldol reaction of a regio-defined magnesium enolate from copper(I)-mediated conjugate addition of a Grignard reagent to an enone.[27,28] As shown in equation (16), 3-methylcyclohexenone reacts with methylmagnesium iodide to give an enolate that reacts smoothly with crotonaldehyde, producing an aldol as a mixture of diastereomers in excellent yield.

A nice example of the foregoing stratagem is seen in equation (17); enone (**6**) undergoes copper(I)-catalyzed reaction with vinylmagnesium bromide from its less-hindered face to give an enolate that reacts with formaldehyde from the opposite face to provide decalone (**7**), an intermediate in the synthesis of insect antifeedants.[29] Yoshida and coworkers have used this method for the stereospecific generation of tetrasubstituted thioamide enolates, which undergo remarkably stereoselective aldol reactions (equation 18).[30] The stereochemistry of this process is discussed in Section 1.6.3.6.

Heng and Smith found that the regio-defined enolates resulting from conjugate addition of lithium dialkylcuprates to enones undergo acceptable aldol additions under the House conditions.[31] One of the

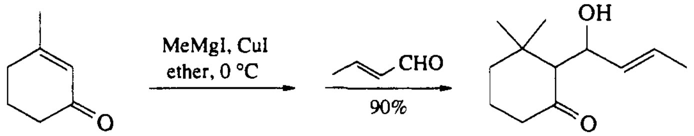

(16)

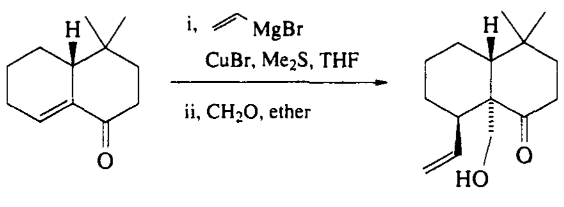

(**6**) (**7**)

(17)

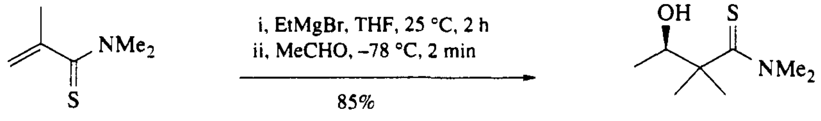

(18)

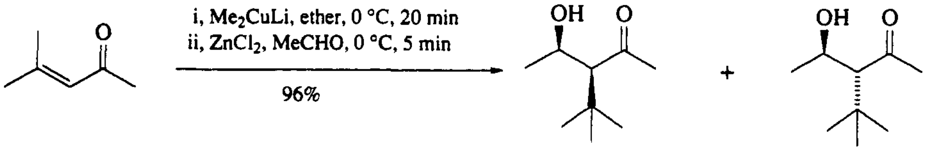
i, Me2CuLi, ether, 0 °C, 20 min
ii, ZnCl2, MeCHO, 0 °C, 5 min
96%
OH
O
+

(19)

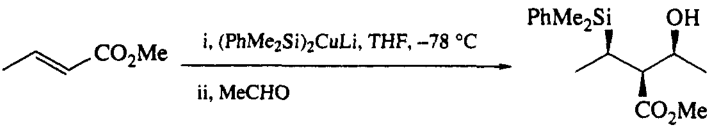

(20)

many examples reported in this investigation is shown in equation (19). The stereochemistry of these reactions is discussed in Section 1.6.3.2.

Fleming has generated enolates by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to α,β-unsaturated esters.[32] The intermediate (*Z*)-enolates undergo stereoselective aldol addition, providing adducts having three contiguous stereocenters; one example of this process is seen in equation (20).[33]

### 1.6.2.5 Enolates from Reduction of α-Heteroatom-substituted Carbonyl Compounds

Several workers have observed aldol reactions with enolates prepared by reductive removal of an α-heteroatom from a carbonyl compound. The classic example is the Reformatsky reaction, which is reviewed in Volume 2, Chapter 1.8. Dubois and coworkers have employed this method for the preparation of magnesium enolates.[34] An important example from this study, which stimulated much of the subsequent work on aldol stereoselectivity, is shown in equation (21).

Clark and coworkers have used a similar process for generation and aldol reactions of a cyclobutanone enolate; one example of many is illustrated in equation (22).[35] Direct formation of the enolate in this case gives aldols in low yield.

Trost has used α,α-disulfenylated lactones as enolate precursors.[36] As shown in equation (23), α,α-di-(phenylthio)-γ-butyrolactone is treated sequentially with ethylmagnesium bromide and acetaldehyde to obtain β-hydroxy lactone (**8**) in virtually quantitative yield. Oxidation of the phenylthio group and subsequent elimination of the resulting sulfoxide provides the unsaturated hydroxy lactone (**9**). The process was employed with more complex lactones in a total synthesis of iridoids. The method fails with α,α-disulfenylated ketones unless a catalytic amount of copper(I) bromide is included in the reaction mixture.

Reaction of γ-butyrolactone with LDA and bis[methoxy(thiocarbonyl)] disulfide in THF at –78 °C provides an enolate that reacts with heptanal to give the (*E*)-α-heptylidine-γ-butyrolactone (**10**), contaminated by only 4% of the (*Z*)-isomer (**11**; equation 24).[37] If the aldol step is carried out in the presence

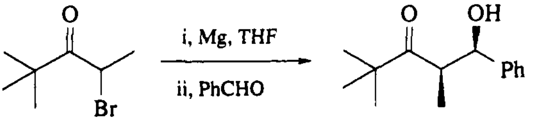

(21)

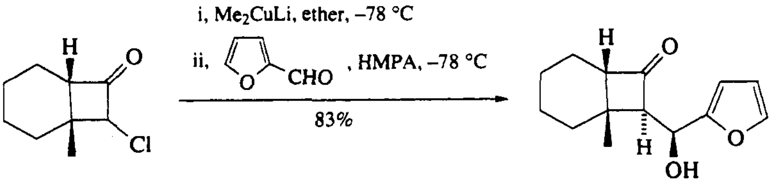

(22)

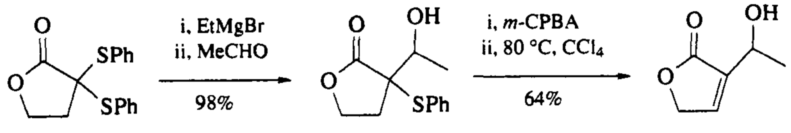

(8) (9)

(23)

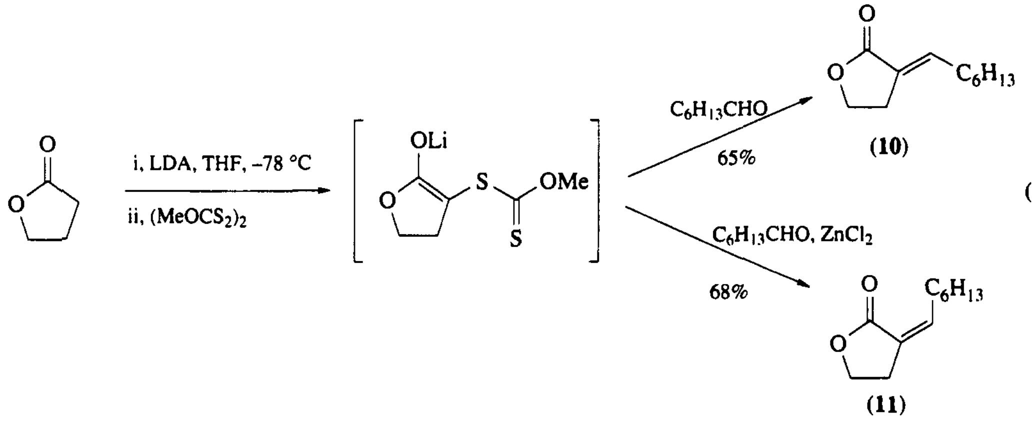

(24)

of $ZnCl_2$, compounds (**11**) and (**10**) are formed in a ratio of 85:15. The reaction apparently proceeds through an intermediate episulfide, and the double-bond geometry is a function of the initial aldol stereochemistry. The process illustrated in equation (24) seems to be quite general; the original reference should be consulted for numerous other examples.

### 1.6.2.6 Enolates of α,β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds can present two regiochemical problems. With ketones that have hydrogens at the γ- and α′-position, there is a regiochemical issue in the deprotonation reaction itself. Stork and Danheiser have shown that α′-deprotonation is favored over γ-deprotonation, and that the resulting enolates may be alkylated without the complication of proton transfer (equation 25).[38] Stork and Kraus extended this method to aldol reactions, as shown in equation (26).[39,40] Although the original

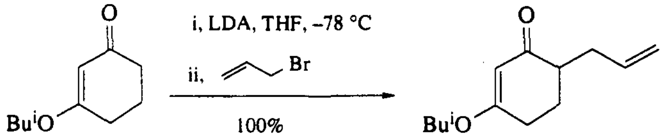

(25)

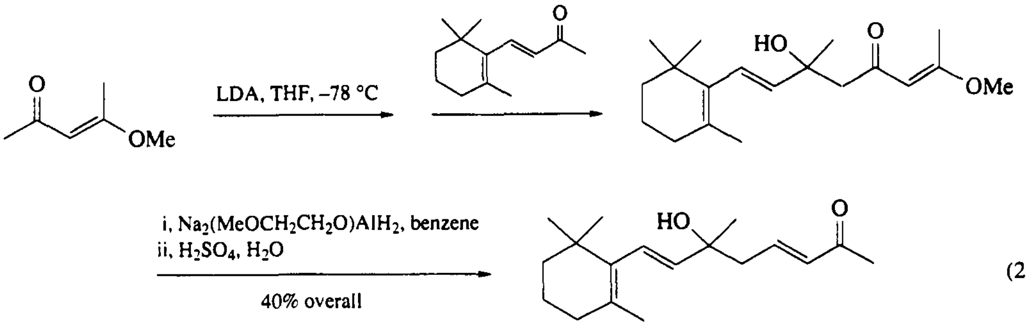

(26)

aldol reaction occurs exclusively at the α′-position of the vinylogous ester, the product after reduction and acid hydrolysis of the initial aldol is the one that would result from aldol reaction at the γ-position of 3-penten-2-one.

α,β-Unsaturated carbonyl compounds that do not have enolizable hydrogens at the α′-position give ambident enolates that can react with electrophiles at two sites—α or γ.[41] Reaction at either position has been observed. Instructive examples are seen in the different behaviors of ethyl 3-methylcrotonate and ethyl 2-methylcrotonate (equations 27 and 28).[42,43] Control experiments showed that both enolates undergo alkylation exclusively at the α-position. It is likely that both also undergo kinetic aldol addition at this position, but that the more substituted α-substituted aldolate from ethyl 2-methylcrotonate equilibrates with the less-congested γ-substituted isomer.

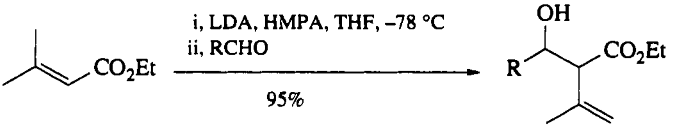

CO2Et
i, LDA, HMPA, THF, -78 °C
ii, RCHO
95%
OH
R
CO2Et

(27)

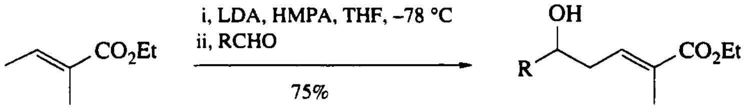

CO2Et
i, LDA, HMPA, THF, -78 °C
ii, RCHO
75%
OH
R
CO2Et

(28)

Heathcock and Dugger examined the enolate derived from methyl 3-methylcrotonate (equation 29).[44] When the aldol reaction with benzaldehyde is carried out at –70 °C and quenched at this temperature, diastereomeric aldols (**12**) and (**13**) are formed in a ratio of 3:2. However, if the aldolate is warmed to 15 °C prior to work-up, lactone (**14**; 80%) and hydroxy ester (**15**; 12%) are produced. These results con-

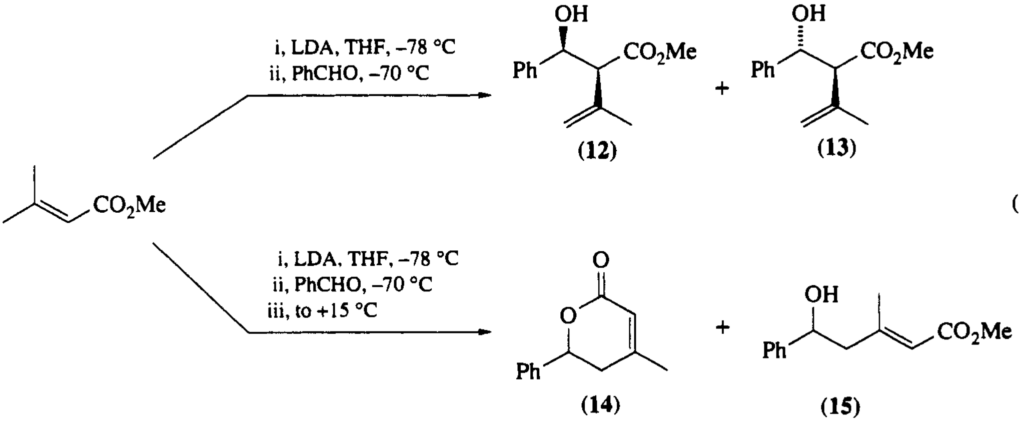

i, LDA, THF, -78 °C
ii, PhCHO, -70 °C
OH
Ph
CO2Me
+
OH
Ph
CO2Me
(12)
(13)
CO2Me
i, LDA, THF, -78 °C
ii, PhCHO, -70 °C
iii, to +15 °C
O
O
Ph
+
OH
Ph
CO2Me
(14)
(15)

(29)

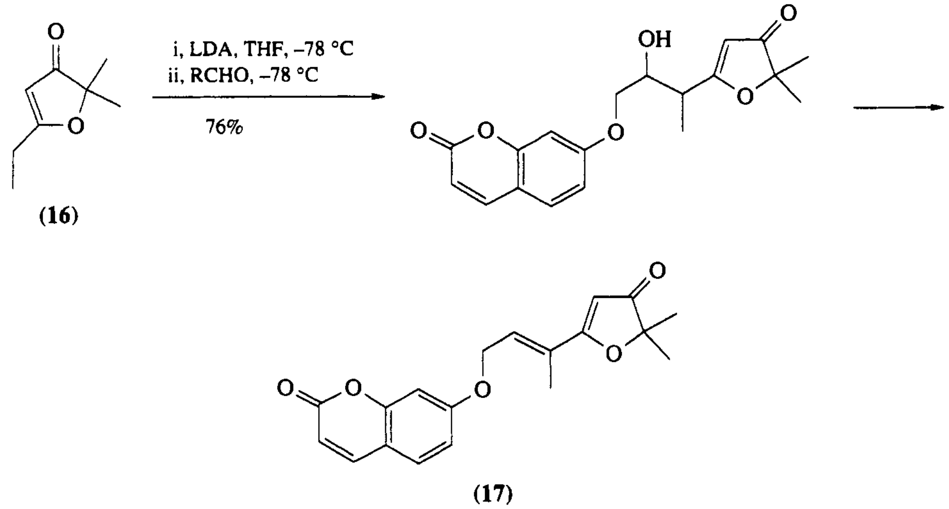

O
O
(16)
i, LDA, THF, -78 °C
ii, RCHO, -78 °C
76%
OH
O
O
O
O
O
O
O
O
O
O
(17)

(30)

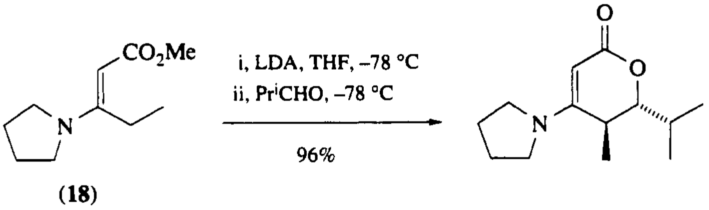

CO2Me
N
(18)
i, LDA, THF, -78 °C
ii, PriCHO, -78 °C
96%
O
O
N

(31)

clusively demonstrate that such dienolates react kinetically at the α-position, and that the initial aldolate isomerizes to the more stable γ-substituted isomer at elevated temperatures.

3(2*H*)-Furanone (**16**) gives a dienolate that shows a proclivity for reaction with electrophiles at the exocyclic γ-position (equation 30).[45] Dehydration of the mixture of diastereomeric aldols gives a 1:1 mixture of geiparvarin (**17**) and its geometric isomer.

Schlessinger and coworkers have studied the aldol reactions of the dienolates derived from the vinylogous carbamate (**18**); in all cases, reaction occurs solely at the γ-position, as shown in equation (31).[46] Various evidence has been adduced that (**18**) reacts kinetically at the γ-position, in contrast to the behavior of crotonate enolates (*vide supra*). The process has been used to synthesize the Prelog–Djerassi lactonic acid and a chiral version of (**18**) has been used to synthesize a fragment of the antibiotic virginiamycin $M_2$ (*vide infra*).[47]

### 1.6.2.7 Dianions of Diketones and Keto Esters

β-Dicarbonyl compounds may be converted into dianions, which react with electrophiles at the more basic site.[48] Huckin and Weiler found that β-keto ester dianions undergo aldol addition reactions at the more basic methyl position (equation 32).[49] The lithium/sodium dianion shows surprisingly weak reactivity, giving the aldol in only 11% yield after 1 h at –78 °C! In contrast, the lithium enolates of simple ketones and esters, which should be much less basic than the β-keto ester dianion, react with aldehydes to give nearly quantitative yields of aldols in THF in seconds at –78 °C.[50] Seebach and Meyer also studied this reaction, and obtained the oxolactone (equation 33).[51] Simple diastereoselection in the reaction of β-keto ester dianions has also been studied (*vide infra*).

Hauser and coworkers have extensively developed the chemistry of 1,3-diketone dianions.[52] In a 1965 paper, it was reported that treatment of a refluxing DME solution of benzoylacetone with NaH and various aromatic aldehydes and ketones gives unsaturated β-diketones in fair yield (equation 34).[53] Although this result suggests the intermediacy of the dianion, control experiments showed that benzoylacetone is converted only into the monoanion under the reaction conditions. Wolfe and coworkers reexamined this reaction with KH and found that, indeed, treatment of a THF solution of benzoylacetone with 4 equiv. of KH at 25 °C gives only 1.1 equiv. of hydrogen, corresponding to the formation of only 10% dianion. However, upon addition of benzophenone to the reaction mixture, the remaining 0.9 equiv. of hydrogen is rapidly evolved. Upon work-up, the aldol is obtained in 66% yield (equation 35).[54] The reason for this unusual behavior is still not clear.

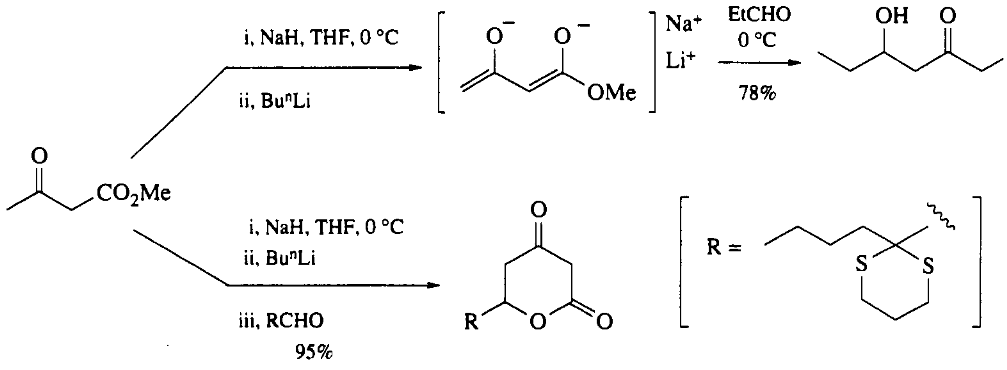

(32)

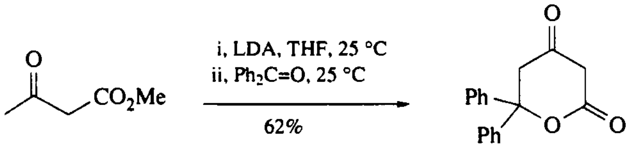

(33)

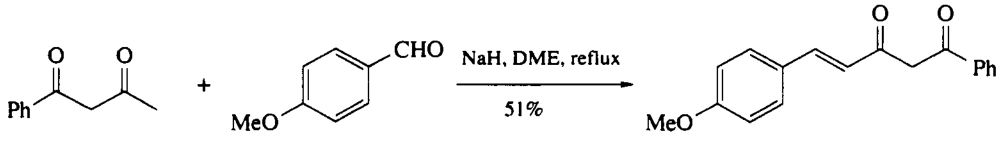

(34)

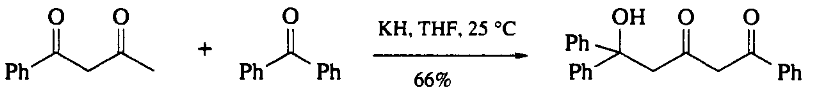

(35)

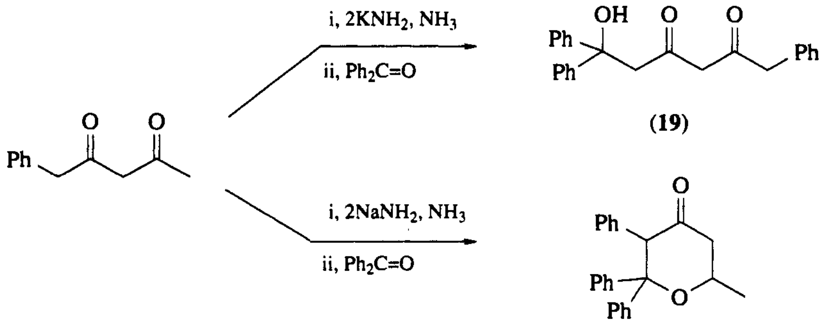

**(19)**

**(20)**

(36)

When 1-phenyl-2,4-pentanedione is doubly deprotonated with potassium amide in ammonia, the ensuing aldol reaction with benzophenone gives the expected aldol (**19**).[55] However, if sodium amide is employed to generate the dianion, the reaction product with benzophenone is the dihydro-γ-pyrone (**20**; equation 36).[56] This result suggests the intermediacy in the latter reaction of a dianion involving the benzylic position. Further study of this interesting reaction is warranted.

## 1.6.3 SIMPLE DIASTEREOSELECTION

### 1.6.3.1 General Overview

The principal factor that was responsible for the rebirth of the venerable aldol reaction as a modern method of synthesis was the discovery that its stereochemistry can be controlled quite effectively through the use of preformed enolates.[57] In this section is discussed 'simple diastereoselection,' reactions between prochiral enolates and prochiral aldehydes (equation 37); the *syn*/*anti* stereochemical notation is employed.[58]

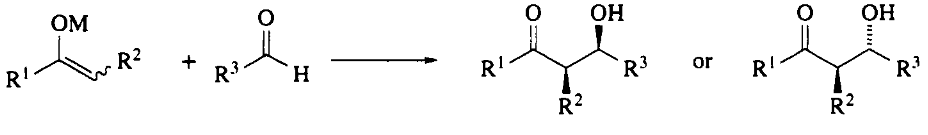

*syn* *anti*

(37)

Before commencing this discussion, it is appropriate to consider briefly the issue of kinetic *versus* thermodynamic control in the reactions of preformed Group I and Group II enolates and to summarize the structure–stereoselectivity generalizations that have emerged to date. It is now well established that preformed lithium, sodium, potassium and magnesium enolates react with aldehydes in ethereal solvents at low temperatures (typically −78 °C) with a very low activation barrier. For example, reactions can often be quenched within seconds of the addition of an aldehyde to a solution of a lithium enolate.[9c]

The kinetic stereoselectivity of the aldol is a function of the enolate stereochemistry *and* its structure. One often reads the over-generalization that '(*Z*)-enolates gives *syn* aldols and (*E*)-enolates give *anti* aldols.' However, the situation is much more complex than this; in addition to enolate geometry, several variables are involved. The following generalizations may be made at this time (refer to equation 37 for definition of $R^1$, $R^2$ and $R^3$).

*(Z)-Enolates.* If $R^1$ is large, (*Z*)-enolates give *syn* aldols; for moderate $R^1$, (*Z*)-enolates are still fairly *syn* selective; but for very small $R^1$, they are stereorandom. Examples are shown in equation (38).[9c] Another apparent structural effect is the size of $R^2$ (equation 37). As this is increased in size, there is a greater propensity for formation of the *anti* aldol; examples are seen in equation (39).[59]

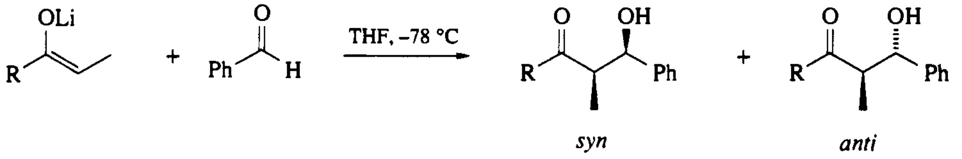

(38)

| *R* | *syn:anti* | *R* | *syn:anti* |
|---|---|---|---|
| $\mathrm{Bu^t}$ | 98.7:1.3 | Et | 90:10 |
| $\mathrm{Pr^i}$ | 90:10 | H | 50:50 |

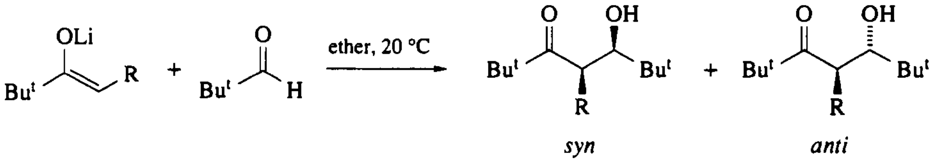

(39)

| *R* | *syn:anti* | *R* | *syn:anti* |
|---|---|---|---|
| Me | 100:0 | $\mathrm{Bu^i}$ | 97:3 |
| Et | 100:0 | $\mathrm{Pr^i}$ | 29:71 |
| $\mathrm{Pr^n}$ | 98:2 | $\mathrm{Bu^t}$ | 0:100 |

*(E)-Enolates.* For large $R^1$, high *anti* selectivity is seen but (*E*)-enolates with medium-sized and small $R^1$ groups are stereorandom (equation 40).[9c] The effect of the size of $R^2$ on (*E*)-enolate stereoselectivity has not been systematically investigated. However, if one extrapolates from the behavior of (*Z*)-enolates, it is likely that the (*E*)-enolate of an ester like ethyl 3,3-dimethylbutanoate might react with aldehydes to give rather high *anti* selectivity (equation 41).

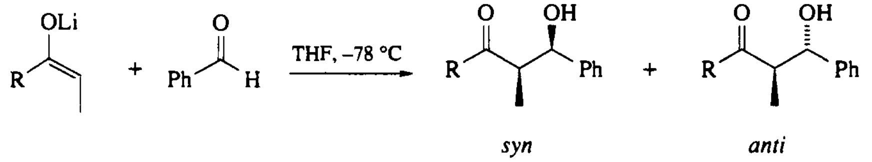

(40)

| *R* | *anti:syn* | *R* | *anti:syn* |
|---|---|---|---|
| 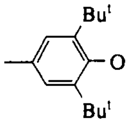 | >98:2 | MeO | 60:40 |
| | | Et | 60:40 |
| | | $\mathrm{Pr^i}$ | 50:50 |
| | | H | 60:40 |

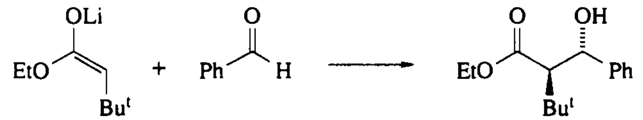

(41)

In addition to the foregoing structural effects, it is clear that the nature of the enolate cation affects aldol stereoselectivity. Since the kinetic stereoselectivity of the aldol reaction seems to result from a rather tightly organized, six-center transition state,[60] cations that are effectively chelated tend to give higher stereoselectivity. Although the question has not yet been carefully investigated, magnesium enolates appear to give somewhat higher stereoselectivity than comparable lithium enolates. As is discussed in Volume 2, Chapter 1.7, boron enolates give even higher simple diastereoselection.

Although most aldol reactions of preformed Group I and Group II enolates are quite rapid, even at −78 °C, the $\Delta G^\circ$ of reaction is not normally very negative. Thus, aldol reversal is possible under relatively mild conditions. In such cases, the observed stereochemistry is governed partially or fully by the thermodynamic properties of the diastereomeric aldolates. Some of the factors that promote aldol reversal are

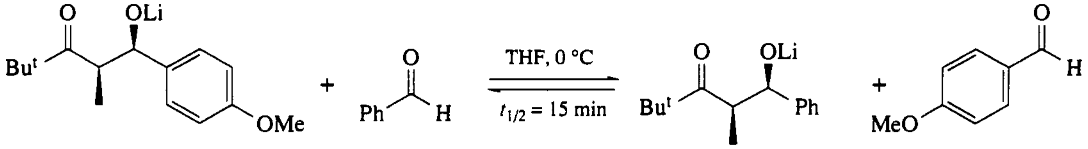

**(21)** **(22)** (42)

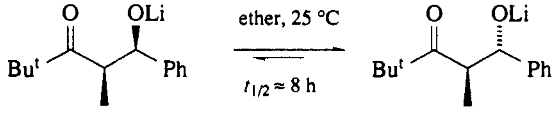

**(22)** **(23)** (43)

discussed in Volume 2, Section 1.5.3. For the purpose of the following discussion, the most important factor is the basicity of the enolate. In general, the more basic the enolate, the less likely is aldol reversal. Amide and ester aldolates show little tendency toward reversal, whereas ketone aldolates often undergo reversal under very mild conditions. Of course, the occurrence of a retroaldol process need not be reflected in rapid erosion of stereochemical homogeneity. For example, the *syn* aldolate (**21**) derived from ethyl *t*-butyl ketone and *p*-anisaldehyde reacts with benzaldehyde to give aldolate (**22**) with a half-life of only 15 min at 0 °C (equation 42). However, aldolate (**22**) equilibrates to its *anti* diastereomer (**23**) in ether with a half-life of approximately 8 h at 25 °C (equation 43).[9c] The reason for this discrepancy is that the (*Z*)-enolate that results from the retroaldol reaction of (**21**) or (**22**) shows a very high kinetic stereoselectivity (*ca.* 80:1). Thus, on average, aldol reversal must occur 80 times in order for one molecule of (**22**) to be converted into one molecule of (**23**).

### 1.6.3.2 Ketone Enolates

Enolates of acyclic ketones can be prepared stereoselectively with a fair amount of control by varying the base that is used for deprotonation. Some representative data are shown in equation (44) and Table 1.[9c] In discussing the stereochemistry of enolates, the (*E*)/(*Z*) notational format suggested by Evans (ref. 2c) is followed. Thus, in naming an enolate derived from an ester $R^2CH_2CO_2R^1$, OM is assigned higher priority than $OR^1$, regardless of the metal. It is clear from this table that there is an intrinsic preference for esters and ketones with small R groups to give the (*E*)-enolate, regardless of base. As R is increased in size an increasing amount of (*Z*)-enolate results. On the other hand, a more bulky base gives relatively more of the (*E*)-enolate (*i.e.* LITMP *versus* LDA).

Masamune and coworkers studied the deprotonation of 3-pentanone and ethyl cyclohexyl ketone with various bases.[61] These workers confirmed that lithium hexamethyldisilazane gives more (*Z*)-isomer than

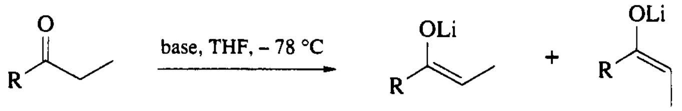

(*Z*) (*E*) (44)

**Table 1** Enolate Stereochemistry (equation 44)

| *R* | *LITMP* | *(Z)-Isomer (%)*<br>*LDA* | *LHMDS* |
|---|---|---|---|
| MeO | — | 5 | — |
| 2,4,6-$Me_3C_6H_2$ | 4 | 8 | 87 |
| Et | 16 | 30 | 66 |
| $Pr^i$ | 32 | 56 | >97 |
| $Pr^i_2N$ | 52 | 81 | — |
| Ph | >97 | >97 | >97 |
| $Bu^t$ | >97 | >97 | >97 |

does LDA and found that other bis(trialkylsilyl)amides are even more (*Z*)-selective. The best base studied was lithium hexamethyldisilazane, which gives >99% (*Z*)-isomer with both ketones.

Certain (*Z*)-ketone enolates react with aldehydes to give *syn* aldols with excellent stereoselectivity. As shown in equation (45), the (*Z*)-enolates of ethyl *t*-butyl ketone, ethyl 1-adamantyl ketone and ethyl mesityl ketone all react with benzaldehyde to give *syn*:*anti* ratios of >50:1.[9c,62] The bulky *t*-butyl, adamantyl and mesityl groups assure that (*Z*)-enolates are formed with high selectivity and organize the transition state so as to maximize formation of the *syn* aldol. To capitalize on this discovery, various ketone reagents have been devised that have bulky alkyl groups that can be removed oxidatively or reductively. One such reagent is the α-trimethylsilyloxy ketone (**27**; equation 46).[9c,63] A related reagent, compound (**28**), also gives high *syn* selectivity in its aldol reactions. The resulting β-hydroxy ketone may be reduced to a diol that is oxidatively cleaved by lead tetraacetate to an aldehyde (equation 47).[64] Trityl ketone (**29**) functions predictably, giving *syn* aldol with excellent stereoselectivity and in high yield (equation 48).[65] These aldols may be reductively cleaved with lithium triethylborohydride, after protection of the secondary alcohol. The (*Z*)-lithium enolate of ketone (**30**), formed with lithium hexamethyl-

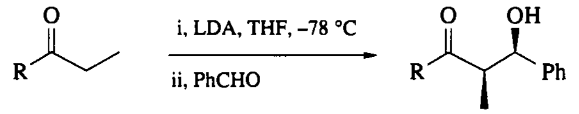
i, LDA, THF, –78 °C
ii, PhCHO
R
O
OH
Ph

(45)

(**24**) R = Bu$^t$
(**25**) R = 1-adamantyl
(**26**) R = 2,4,6-$Me_3C_6H_2$

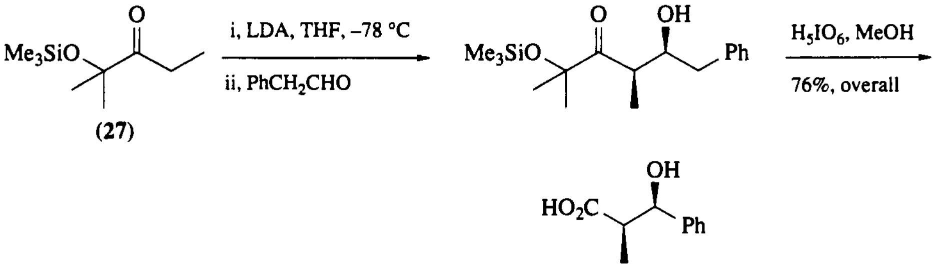
Me3SiO
i, LDA, THF, –78 °C
ii, PhCH2CHO
H5IO6, MeOH
76%, overall
HO2C
OH
Ph

(**27**)

(46)

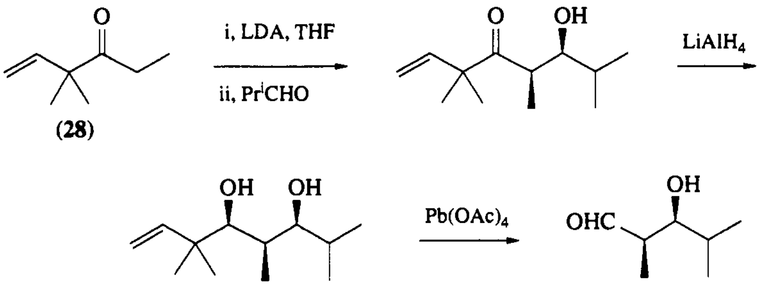
i, LDA, THF
ii, PriCHO
LiAlH4
Pb(OAc)4
OHC
OH

(**28**)

(47)

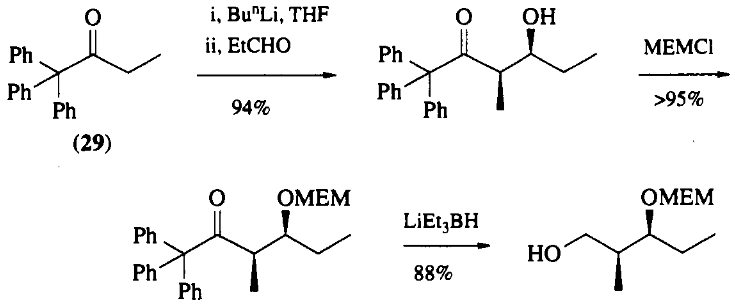
Ph
i, BunLi, THF
ii, EtCHO
94%
MEMCl
>95%
OMEM
LiEt3BH
88%
HO

(**29**)

(48)

disilazane, gives *syn* aldols with several aldehydes. Flash vacuum pyrolysis of the aldol silyl ether expels cyclopentadiene by a retro-Diels–Alder reaction, providing the *syn* aldol of an α,β-unsaturated ketone (equation 49).[66]

Ketone (**27**) and reagents related to it have been used in synthesis. In equation (50) is shown an application of the magnesium enolate in Still's synthesis of monensin; the facial selectivity in this case is 5:1 and the reaction proceeds in 85% yield.[67] The lithium enolate of (**27**) has been employed in a synthesis of the C-1,C-7 segment of erythronolide A (equation 51); the facial selectivity in this case is 6:1.[68] Ketone (**31**) was used in a synthesis of the basic nucleus of crassin acetate (equation 52).[69] The aldol reaction of (**31**) with (**32**), derived from geraniol, occurs in 58% yield to give only one isomer. Four further

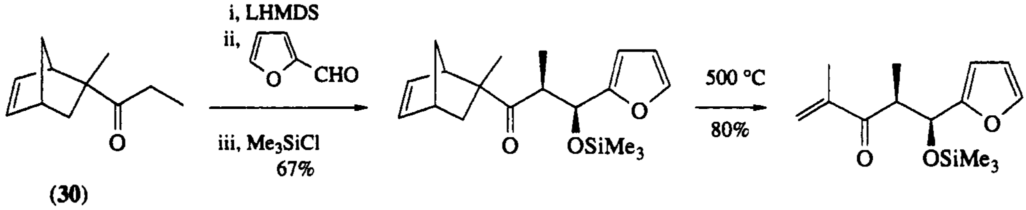
i, LHMDS
ii, CHO
iii, Me3SiCl
67%
O
O
OSiMe3
500 °C
80%
O
O
OSiMe3

(**30**)

(49)

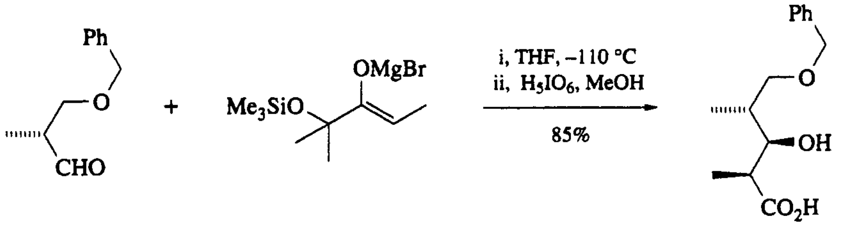
Ph
O
CHO
+
OMgBr
Me3SiO
i, THF, –110 °C
ii, H5IO6, MeOH
85%
Ph
O
OH
CO2H

(50)

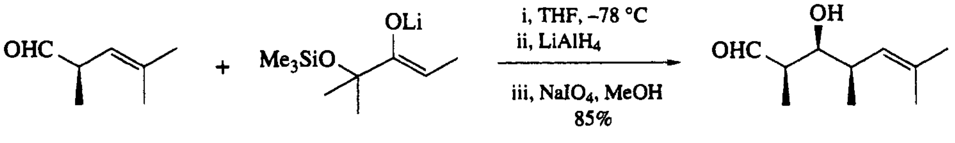
OHC
+
OLi
Me3SiO
i, THF, –78 °C
ii, LiAlH4
iii, NaIO4, MeOH
85%
OH
OHC

(51)

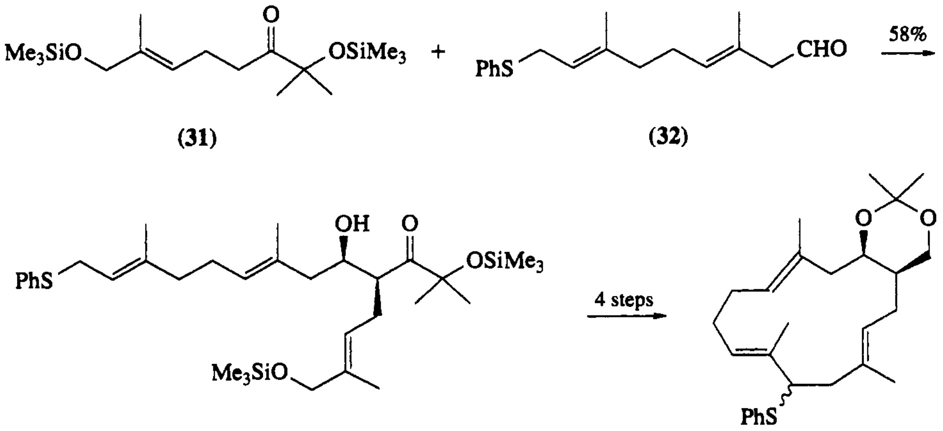
O
Me3SiO
OSiMe3
+
PhS
CHO
58%
(31)
(32)
OH
O
PhS
OSiMe3
Me3SiO
4 steps
O
O
PhS

(52)

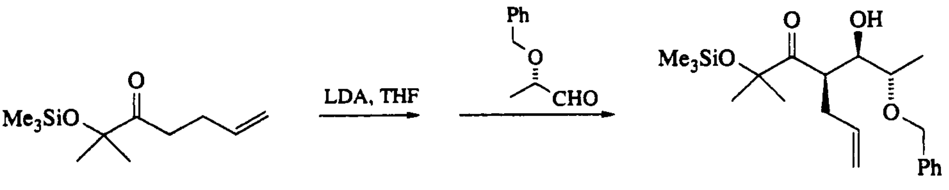
O
Me3SiO
LDA, THF
Ph
O
CHO
O
OH
Me3SiO
O
Ph

(**33**) (**34**)

(53)

steps converted the aldol into the 14-membered crassin ring. (±)-Ristosamine was synthesized starting with ketone (**33**), which adds to (*S*)-*O*-benzyllactaldehyde to give the *syn* aldol (**34**; equation 53); the facial selectivity in this reaction is 4:1 and the total yield is 97%.[70] Ketone (**27**) has been used in a similar manner to prepare the C-29,C-37 fragment of amphotericin B and nyastatin (equation 54).[71]

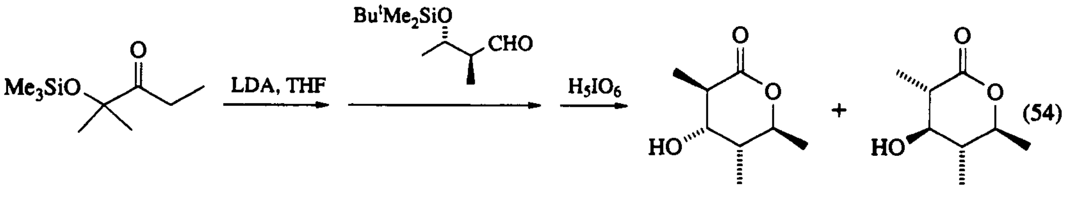

(54)

**(27)**

40% 15%

Reaction of reagent (**27**) with crotonaldehyde provides a *syn* aldol, which is transformed by a four-step sequence including a Claisen rearrangement into (**35**; equation 55).[72] Aldol (**36**), obtained from (**27**) and acrolein, was converted *via* propionate (**37**) into (**38**), a building block for the vitamin E side chain (equation 56).[72b,73] The strategy of parlaying the 1,2 relative stereochemistry obtainable from the aldol reaction into 1,5 relative stereochemistry by use of a Claisen rearrangement has also been used to prepare the $C_{40}$ archaebacterial diol and one of its stereoisomers.[72b,74]

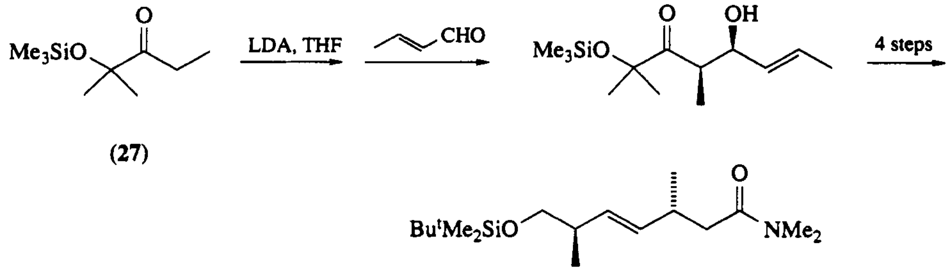

**(27)**

(55)

**(35)**

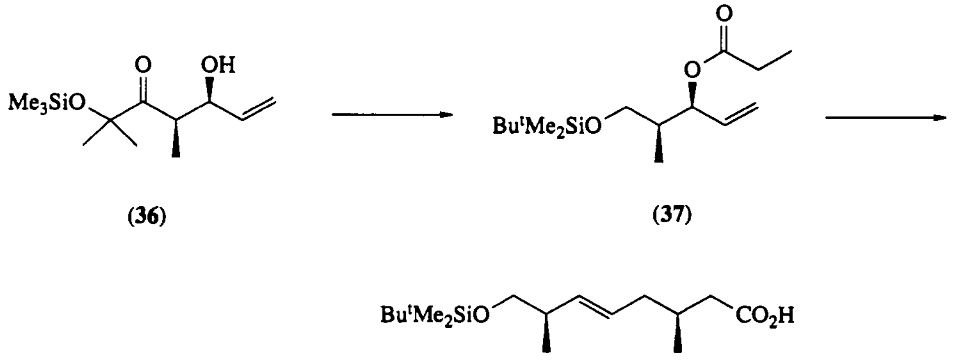

**(36)** **(37)**

(56)

**(38)**

A study of ethyl *t*-butyl ketone (**39**) and its homologs (**40**) to (**42**) (equation 57) revealed several interesting differences.[75] Firstly, there is a significant steric effect on the rate of deprotonation in this series. Whereas ketone (**39**) (0.2 M in THF) is deprotonated completely by LDA in 20 min at –20 °C, ketone (**42**) requires 4 h for deprotonation at this temperature. Aldol reactions of (**39**) to (**42**) with benzaldehyde were compared in THF and in pentane. All four ketones give exclusively the *syn* aldol in THF at –78 °C. In pentane, (**40**) to (**42**) give some *anti* aldol under the normal reaction conditions, with the amount of *anti* product being greater with increasing size of R. With ketone (**42**), reaction for 30 min at room temperature provides aldols with an *anti*:*syn* ratio of >50:1. The formation of *anti* aldols in pentane solution was shown to result from equilibration of the kinetic *syn* product to the more stable *anti* aldolate. Whereas the equilibration of *syn* aldolate (**43**) to *anti* aldolate (**44**) has a half-life in ether solution at 25 °C of approximately 8 h (*vide supra*), this reaction has a half-life in pentane at 25 °C of only 45 min. As expected, steric bulk in the aldolate promotes the retroaldol reaction; the half-life for equilibration of (**45**) to (**46**) in pentane at 25 °C is only 7 min; the *n*-propyl and *n*-butyl aldolates undergo *syn* to *anti* equilibration under the same conditions with a half-life of less than 4 min.

Although a considerable amount of data exists pertaining to simple diastereoselection with trisubstituted enolates, very little is known about reactions of fully substituted enolates, principally because of a dearth of methods for the stereospecific generation of such enolates. (Ester enolates that are substituted at the α-position by heteroatoms constitute a special exception to this generalization; these fully substituted enolates are discussed in Section 1.6.3.3.) Two research groups have recently reported an interesting approach to the generation of such enolates, which is summarized in equation (58).[76] The method is based on the discovery that amine-free enolates of 2,6-di-*t*-butyl-4-methylphenol ('butylated hydroxytoluene', or BHT) decompose by ejection of phenoxide upon being warmed from –78 °C to room temperature (the onset of decomposition is believed to be at about –20 °C). If this decomposition occurs in the presence of an alkyllithium species, the ketene produced is trapped to give a regio-defined enolate. If the ester has two α-substituents of differing size, the enolate produced is also stereochemically defined because the alkyllithium reagent attacks the ketene preferentially *syn* to $R^S$, the smaller of the two substituent groups. Consequently, a (*Z*)-ketone enolate is generated preferentially, the stereoselectivity of the process depending upon the difference in size between $R^S$ and $R^L$. The enolate mixture so generated may

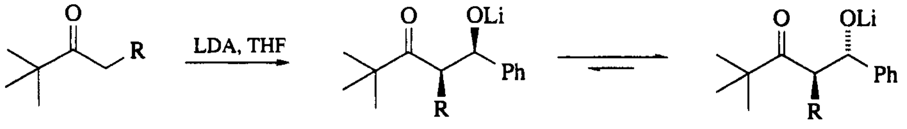

(57)

(**39**) R = Me
(**40**) R = Et
(**41**) R = $\mathrm{Pr^n}$
(**42**) R = $\mathrm{Bu^n}$

(**43**) R = Me
(**45**) R = Et

(**44**) R = Me
(**46**) R = Et

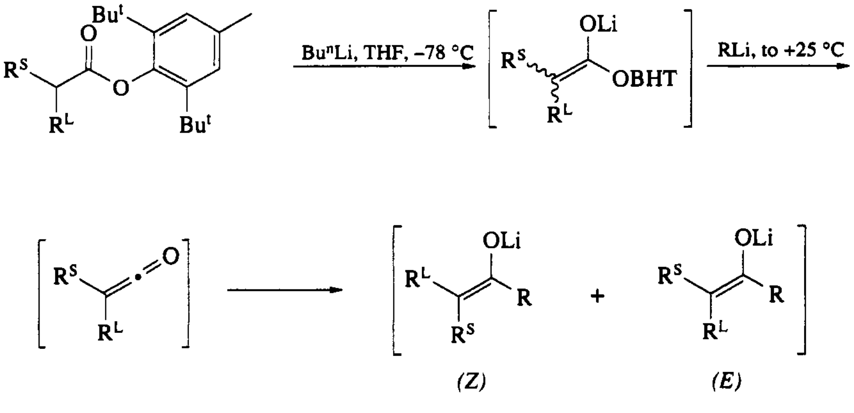

(58)

**Table 2** Enolate Stereochemistry (equation 58)

| $R^S$ | $R^L$ | $R$ | Yield (%)[a] | (Z):(E) |
|---|---|---|---|---|
| Me | Et | Me | | 1.7:1 |
| Me | $\mathrm{Pr^i}$ | Me | | 7:1 |
| Me | $\mathrm{Bu^t}$ | Me | | >99:1 |
| Et | Me3Si | $\mathrm{Bu^n}$ | 77 | >99:1 |
| Me | Ph | $\mathrm{Bu^n}$ | 50 | >99:1 |
| Et | Ph | $\mathrm{Bu^n}$ | 76 | >99:1 |
| H | $\mathrm{Bu^t}$ | $\mathrm{Bu^t}$ | 62 | >99:1 |

[a] Yield of the trimethylsilyl enol ether.

be trapped with trimethylsilyl chloride to give a mixture of stereoisomeric silyl enol ethers, which reflects the stereoselectivity of enolate formation; data for three different esters are summarized in Table 2. As is shown in the table, there is a little stereoselectivity in enolate formation when $R^S$ and $R^L$ are Me and Et, moderate stereoselectivity when the two groups are Me and $Pr^i$, and excellent stereoselectivity with Me and $Bu^t$.

The substituted enolates produced in the foregoing manner may be trapped with aldehydes; one example is shown in equation (59). In this case, the aldol ratio, assigned as shown without rigorous proof, corresponds closely to the enolate ratio (Table 2). A related enolate, in which $R^S$ and $R^L$ are Me and $Bu^t$, gives a sole aldol (equation 60); unexpectedly, this aldol was found to have the indicated structure by X-ray analysis.[77] This result is understood in terms of the Zimmerman–Traxler transition state, if one assumes that the *gauche* interaction between the phenyl of the aldehyde and the bulky *t*-butyl group strongly destabilizes the normal chair-like transition state with phenyl equatorial.[78] [The stereochemical outcome of this reaction is also in accord with the results of Dubois and Fellmann on 2-*t*-butyl-5,5-dimethylcyclopentanone (*vide infra*, equation 67).] In the light of this result, the stereochemical assignment of the aldols shown in equation (59) should probably be regarded as tentative.

The degree of stereoselectivity of aldol reactions of simple cyclohexanone enolates has been a subject of some confusion. For cyclohexanone itself, it has been reported that reaction of the lithium enolate with benzaldehyde gives the two isomeric aldols (Scheme 1) in ratios of 52:48 in THF at –78 °C[9c] and 50:50 in dimethoxyethane at –20 °C.[79] On the other hand, Seebach reports ratios of 79:21 at –78 °C and 85:15 at –150 °C.[80] Hirama and coworkers reinvestigated the reaction of the lithium enolate of cyclohexanone with benzaldehyde (Scheme 1) and found *anti*:*syn* ratios of about 82:18 at –78 °C.[81] The ratio is

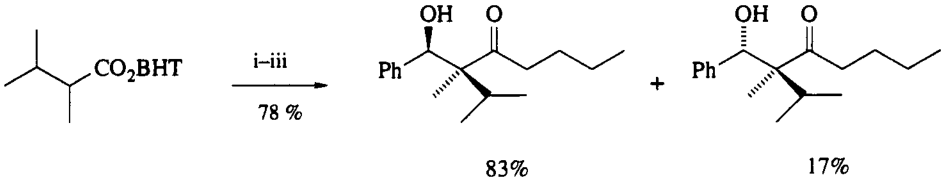

(59)

i, 2 equiv.$Bu^nLi$, THF, –78 °C; ii, warm to +25 °C; iii, PhCHO

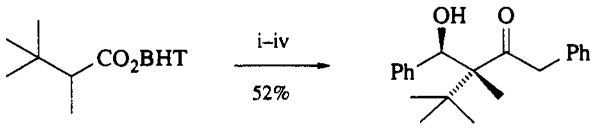

(60)

i, $Bu^nLi$, THF, –78 °C; ii, $PhCH_2Li$; iii, warm to +25 °C; iv, PhCHO

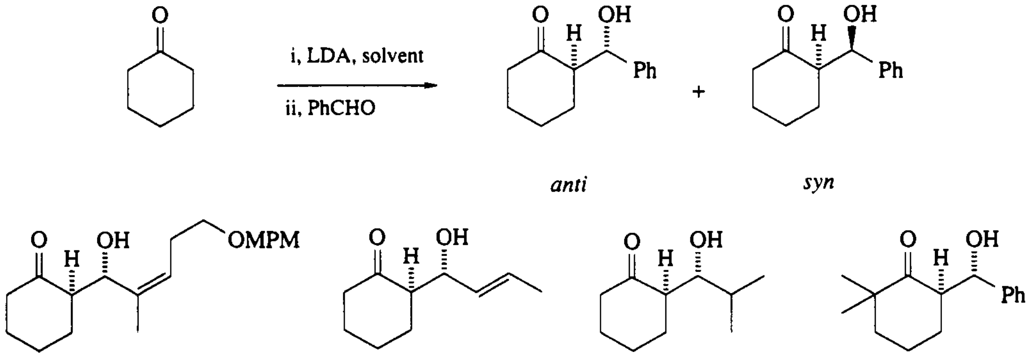

**(49)** **(50)** **(51)** **(52)**

**Scheme 1**

also 82:18 at –50 °C if the reaction is worked up after 3 s, but falls to 60:40 if worked up after 5 min. Careful temperature monitoring showed that there is a significant rise (up to 5 °C) at the moment of addition of benzaldehyde to the enolate solution, even if the aldehyde is precooled. Hirama and coworkers also observed high *anti* selectivity in the preparation from cyclohexanone of aldols (**49**; 100% *anti*),[82] (**50**; 88% *anti*) and (**51**; 96% *anti*). The lithium enolate of 2,2-dimethylcyclohexanone reacts with benzaldehyde to produce aldol (**52**; 88% *anti*).[9c,83]

The lithium enolate of (2*R*,4*R*)-2,4-dimethylcyclohexanone has been condensed with an appropriate aldehyde to prepare several isomers of the antibiotic cycloheximide (equation 61).[84] The major isomer results from reaction on the unsubstituted face of the cyclohexanone ring, and has the same relative stereochemistry at the two new stereocenters as the major isomer in Scheme 1. The second most abundant isomer is also a *syn* aldol, and results from attack on the more-substituted face of the dimethylcyclohexanone.

The α′-enolate of cyclopentenone reacts with aldehydes to give *anti* and *syn* aldols in ratios of 70:30 to 95:5, with the degree of stereoselectivity being related to the size of R (equation 62).[85] Similar yields, with reversed diastereoselectivity, are observed with the corresponding zirconium enolates.

Stotter has reported a study that suggests that the low stereoselectivity sometimes observed in aldol reactions of cyclohexanones results from significant aldolate equilibration.[86] As shown in equation (63), the lithium enolate of 1-azabicyclo[2.2.2]octan-3-one reacts with benzaldehyde to give, after normal

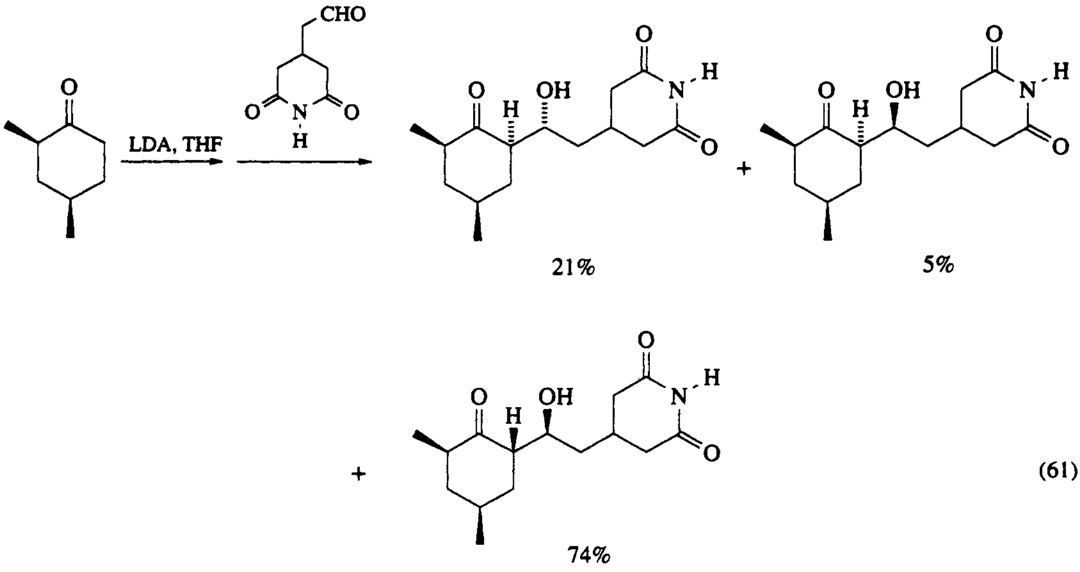

(61)

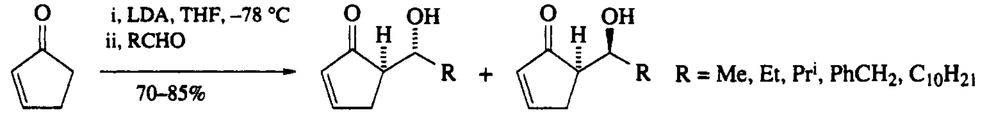

(62)

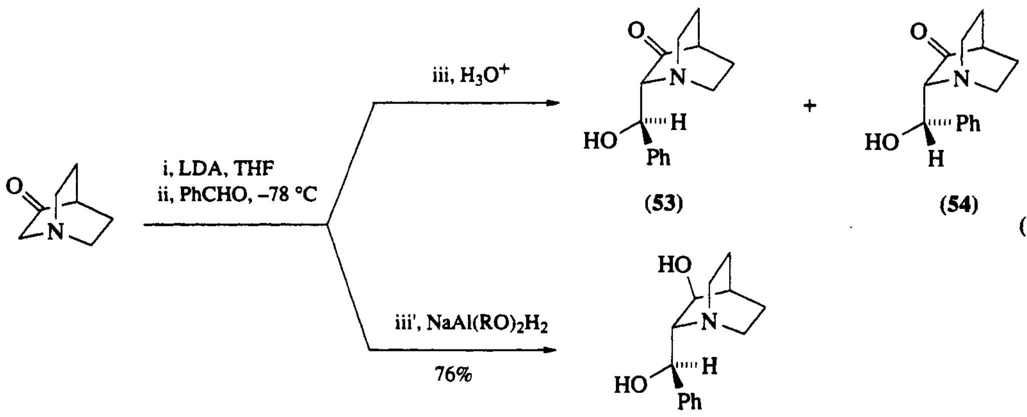

(63)

work-up, aldols (**53**) and (**54**) in a ratio of about 90:10. Aldol (**53**) was found to be exceedingly sensitive with respect to conversion to (**54**), particularly in solution. If the initial aldolate was reduced prior to work-up, a single diol was obtained, suggesting that the aldol reaction itself proceeds with nearly 100% diastereoselectivity.

Dianions derived from 1,2-cyclohexanediones react with aldehydes rather stereoselectively, as shown in equation (64).[87] The *anti*:*syn* ratio of about 8:1 was shown to be kinetic rather than thermodynamic in nature, and was found to be independent of the alkyl group at C-3. The *anti* stereoselectivity is even higher with α-branched aldehydes (*e.g.* >99:1 with isobutyraldehyde).

Dubois and Fellmann have carried out a careful investigation of the reaction of magnesium enolates of substituted cyclopentanones with various aldehydes (Scheme 2).[59] Data from this important study are summarized in Table 3. As shown in entries 1–6, the α-unsubstituted cyclopentanone enolate shows *anti* selectivity, with the magnitude of stereoselectivity increasing with the degree of branching at the α-position of the aldehyde; branching at the β-position of the aldehyde has essentially no effect. Substitution at the enolate carbon has an interesting effect, ***reducing the amount of*** anti ***diastereomer as the size of*** $R^1$ ***increases*** (Table 3, entries 7–11). This study also revealed that the magnesium enolate is somewhat more stereoselective than the corresponding lithium enolate. With the lithium enolate only minor medium-effects are observed.

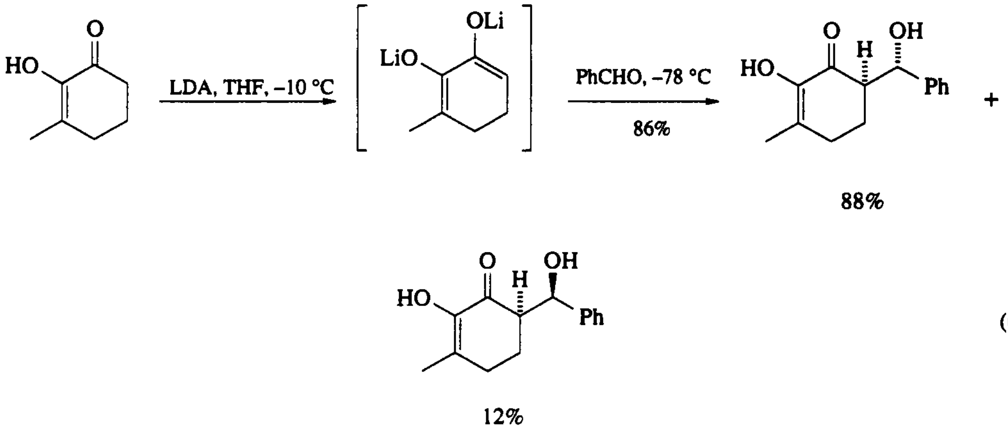

(64)

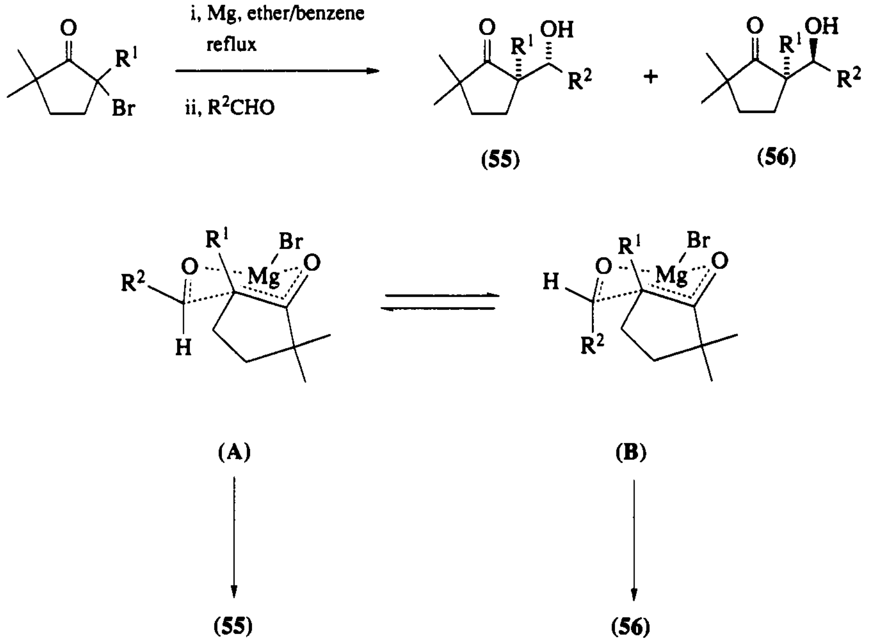

Scheme 2

**Table 3** Aldol Stereochemistry (Scheme 2)

| *Entry* | *R*$^1$ | *R*$^2$ | *(55):(56)* |
|---|---|---|---|
| 1 | H | Me | 93.5:6.5 |
| 2 | H | Et | 94:6 |
| 3 | H | Bu$^i$ | 93.5:6.5 |
| 4 | H | neo-Pe$^a$ | 94:6 |
| 5 | H | Pr$^i$ | 97:3 |
| 6 | H | Bu$^t$ | >99:1 |
| 7 | Me | Me | 93.5:6.5 |
| 8 | Et | Me | 87.5:12.5 |
| 9 | Bu$^i$ | Me | 80:20 |
| 10 | Pr$^i$ | Me | 46:54 |
| 11 | Bu$^t$ | Me | 29:71 |

$^a$neo-Pe = neopentyl.

The foregoing results are in accord with the transition state structures depicted in Scheme 2. The usual Zimmerman–Traxler chelates (**A**) and (**B**) lead to aldols (**55**) and (**56**), respectively. With small R$^1$, (**A**) is favored over (**B**), because the latter transition state brings group R$^2$ into interaction with the cyclopentane ring; this interaction is more serious with larger R$^2$ groups. If group R$^1$ is larger, the *gauche* R$^1$:R$^2$ interaction disfavors (**A**) and leads to more reaction through transition state (**B**). Note that these results are precisely in accord with the observations by Seebach and coworkers with an acyclic (*Z*)-tetrasubstituted enolate (*vide supra*, equation 60).

### 1.6.3.3 Ester and Lactone Enolates

Deprotonation of esters with lithium dialkylamides gives rise to (*E*)-enolates.[9c,88] However, with normal alkyl propionates there is little or no stereoselectivity in additions to aldehydes (equation 65).[9c] It was found by Meyers and Reider that certain esters that contain additional ether oxygens in the alcohol moiety give reasonably high *anti* selectivity (equation 66).[89] Unfortunately, this high selectivity is not general, as is shown by the example in equation (67).[9c]

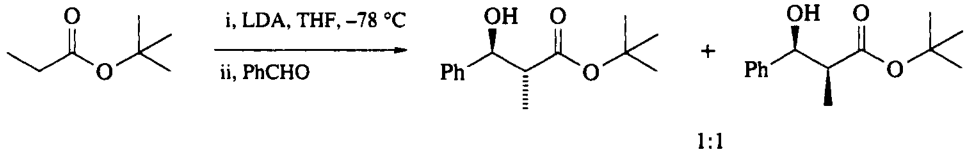

(65)

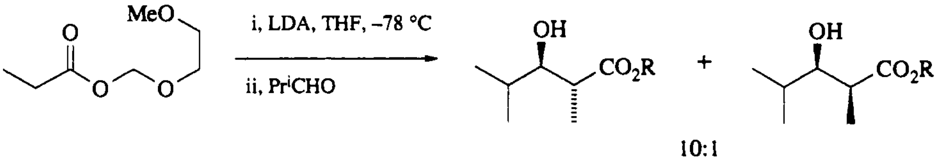

(66)

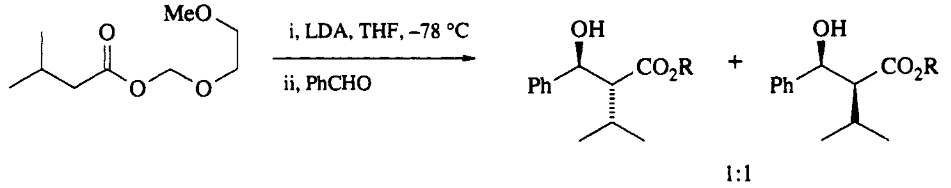

(67)

As shown in Scheme 3, (*Z*)-enolate (**57**), prepared by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to methyl crotonate or methyl cinnamate, reacts with acetaldehyde or benzaldehyde to give a mixture of two diastereomeric aldols, (**58**) and (**59**), with excellent diastereomeric excess favoring (**58**) (ratios of 85:15 to 94:6).[90] On the other hand, deprotonation of ester (**60**) by LDA provides the (*E*)-enolate (**61**), which reacts with the same two aldehydes to give the aldol (**59**) as the major product (ratios of 89:11 to 94:6). Enolates (**57**) and (**61**) both show exceptional diastereofacial preferences, in the same sense. If one assumes enolate homogeneity, the simple diastereoselection observed (6:1 to 16:1) is remarkable. The sense of simple diastereoselection is the same as is observed for other stereoselective enolates [(*Z*)-enolate (**57**) gives the 2,3-*anti* aldol and (*E*)-enolate (**61**) gives the 2,3-*syn* aldol]. This process has been used in a synthesis of the antibiotic thienamycin.[91]

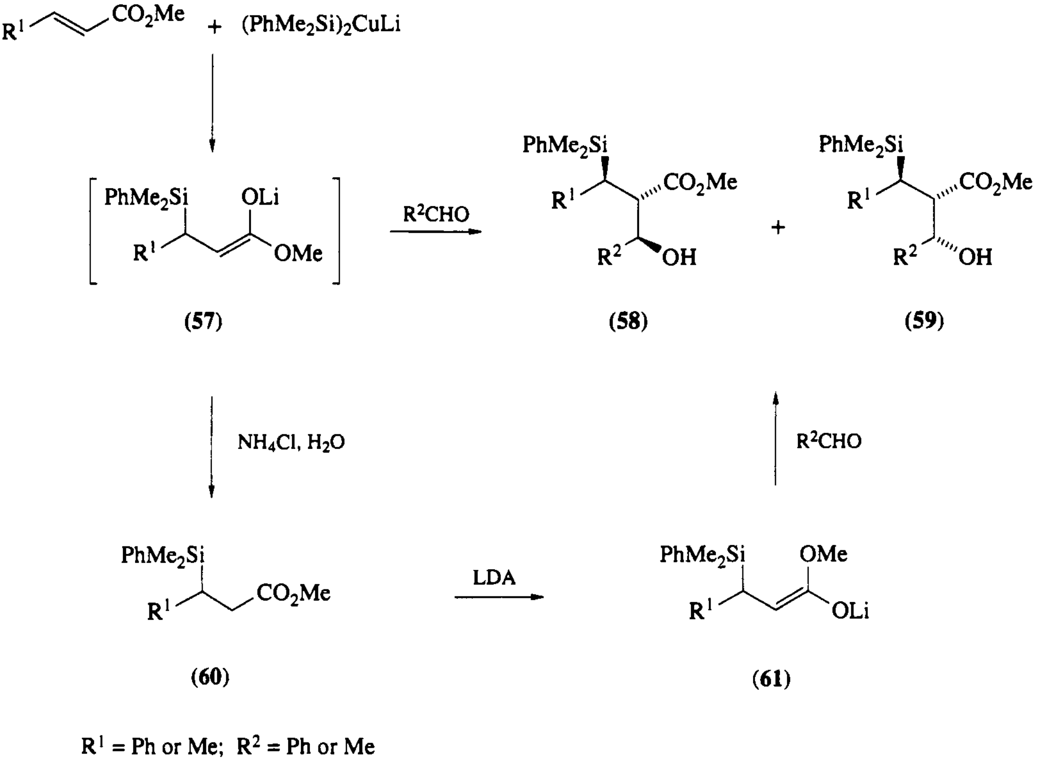

Scheme 3

In connection with the synthesis of podophyllum lignans, ester (**62**) was deprotonated and the resulting enolate condensed with 3,4,5-trimethoxybenzaldehyde to give a 1:1 mixture of diastereomeric aldols (equation 68).[92] The structure of (**63**) was established by X-ray analysis; the other diastereomer was assigned the 2,3-*anti* relative stereochemistry (**64**) on circumstantial evidence. It was suggested that the 1:1 mixture of isomeric products results from a 1:1 mixture of the (*E*)- and (*Z*)-enolate, each of which shows complete simple and diastereofacial selectivity in its reactions with 3,4,5-trimethoxybenzaldehyde. For this to be true, it is also necessary that the (*E*)-enolate reacts through a 'non-Zimmerman', boat-like transition state, whereas the (*Z*)-enolate reacts through the normal chair-like transition state.

The hindered aryl esters (**65**) to (**71**) (Scheme 4) have been shown to be effective reagents for the preparation of 2,3-*anti* aldols.[93] Aldol additions with the enolates of these esters give predominantly 2,3-*anti* aldols (Table 4). The DMP esters (**65**), (**66**) and (**67**) give *anti*:*syn* ratios of 6:1 to 10:1 with aromatic aldehydes and α-unbranched aliphatic aldehydes (Table 4, entries 1, 2, 7 and 8) and pure *anti* products with α-branched aliphatic aldehydes (entries 3–6, 9). The BHT and DBHA esters (**68**) to (**71**) give only *anti* aldols with all aldehydes (Table 4, entries 10–20). The DMP, BHT and DBHA esters are conveniently prepared from commercially available phenols. The DMP aldols may be hydrolyzed to obtain the corresponding β-hydroxy acids. The DMP reagents are limited, however, since high stereoselectivity is only observed with α-branched aldehydes. The BHT reagents do not have this limitation, and have the added virtue that the product aldols are often nicely crystalline solids. However, the BHT aldols may not be hydrolyzed, because of the severe steric hindrance of the carbonyl group. The DBHA reagents show the same high stereoselectivity as their BHT analogs. With this reagent, the DBHA moiety may be removed oxidatively, thus permitting access to the β-hydroxy acid.

The foregoing *anti* selective aldol reagents have been employed for several synthetic purposes. Paterson used reagent (**65**) to convert aldehyde (**72**) into β-hydroxy ester (**73**); the yield in this reaction is 92%

and the diastereomer ratio at –100 °C is 13:1 (equation 69).[94] Aggarwal and Warren employed (**65**) to convert aldehyde (**74**) into aldol (**75**) (equation 70, stereoselectivity = 95:5) and the related acyclic aldehyde (**76**) into aldol (**77**) (equation 71).[95] In the latter example, the aldol stereoselectivity (C-2,C-3) is complete and the diastereofacial selectivity (C-3,C-4) is 10:1.

In the course of a synthesis of davanone, Bartlett and Holmes utilized ester (**68**) to convert aldehyde (**78**) into aldol (**79**); the stereochemical purity of the product is 97.6% (equation 72).[96] Sato and co-

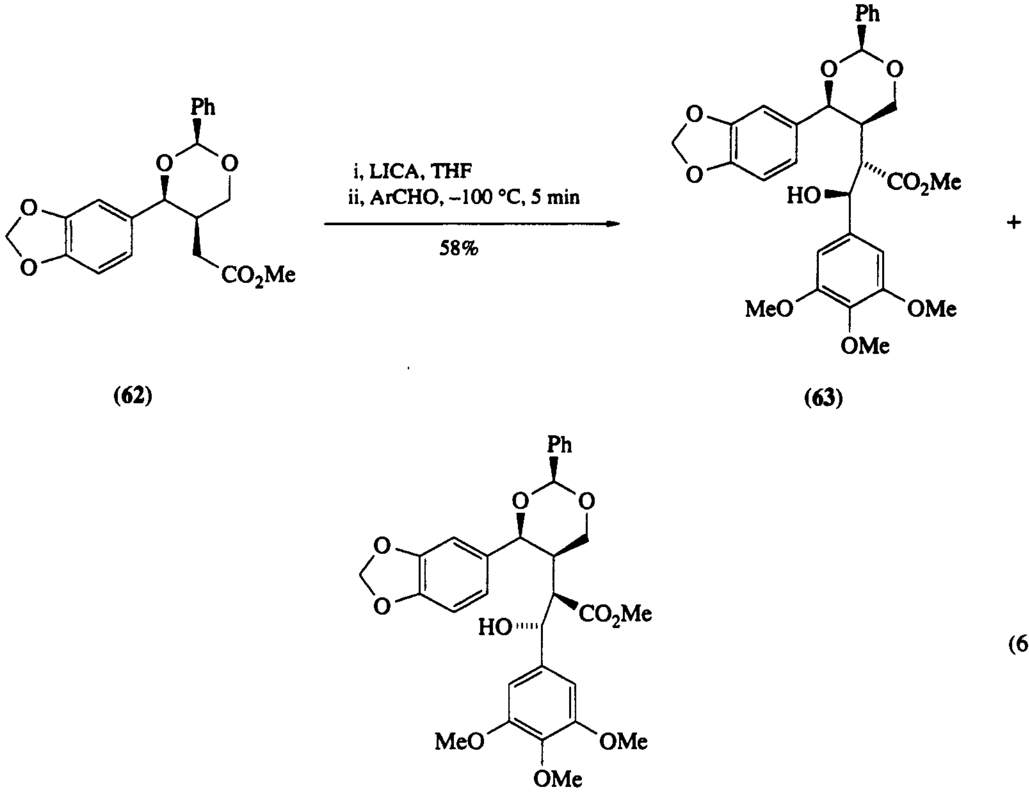

(**62**) (**63**) (**64**)

(68)

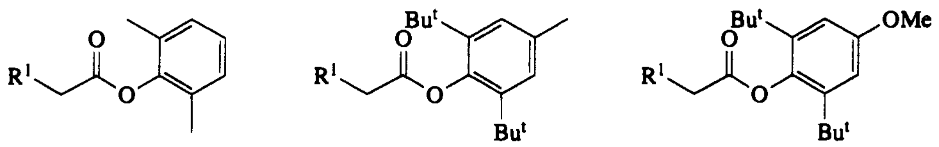

(**65**) $R^1$ = Me
(**66**) $R^1$ = Et
(**67**) $R^1$ = $H_2C{=}CHCH_2$

(**68**) $R^1$ = Me
(**69**) $R^1$ = $H_2C{=}CHCH_2$

(**70**) $R^1$ = Me
(**71**) $R^1$ = Et

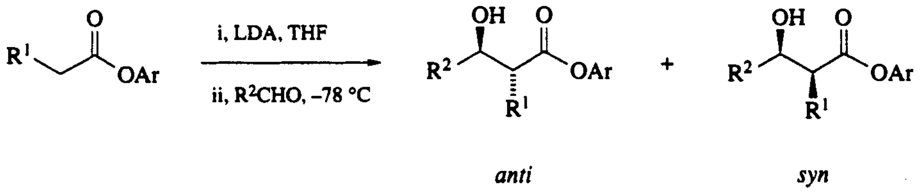

Scheme 4

**Table 4** Aldol Stereochemistry (Scheme 4)

| *Entry* | *Ester* | *Aldehyde* | *Yield* (%) | *Anti:syn* |
|---|---|---|---|---|
| 1 | **(65)** | PhCHO | 72 | 88:12 |
| 2 | **(65)** | n-C$_5$H$_{11}$CHO | 70 | 86:14 |
| 3 | **(65)** | Pr$^i$CHO | 78 | >98:2 |
| 4 | **(65)** | Bu$^t$CHO | 82 | >98:2 |
| 5 | **(65)** | Ph(Me)CHCHO | 81 | >98:2$^a$ |
| 6 | **(66)** | Pr$^i$CHO | 93 | >98:2 |
| 7 | **(67)** | PhCHO | 87 | 91:9 |
| 8 | **(67)** | EtCHO | 67 | 84:16 |
| 9 | **(67)** | Pr$^i$CHO | 77 | >98:2 |
| 10 | **(68)** | PhCHO | 96 | >98:2 |
| 11 | **(68)** | Pr$^i$CHO | 100 | >98:2 |
| 12 | **(68)** | Ph(Me)CHCHO | 100 | >98:2$^a$ |
| 13 | **(69)** | PhCHO | 76 | >94:6 |
| 14 | **(69)** | EtCHO | 81 | >98:2 |
| 15 | **(69)** | Pr$^i$CHO | 60 | >96:4 |
| 16 | **(70)** | EtCHO | 75 | >98:2 |
| 17 | **(70)** | n-C$_5$H$_{11}$CHO | 70 | >98:2 |
| 18 | **(70)** | Pr$^i$CHO | 79 | >98:2 |
| 19 | **(70)** | Bu$^t$CHO | 77 | >98:2 |
| 20 | **(71)** | Pr$^i$CHO | 68 | >98:2 |

$^a$4:1 mixture of C-3,C-4 diastereomers.

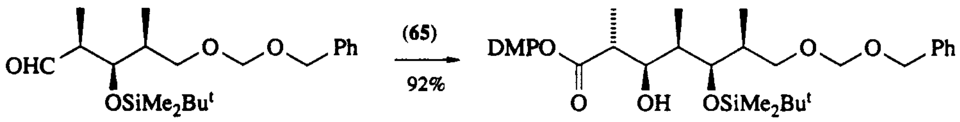
OHC
OSiMe$_2$Bu$^t$
O
O
Ph
(65)
92%
DMPO
O
OH
OSiMe$_2$Bu$^t$
O
O
Ph

**(72)** **(73)** (69)

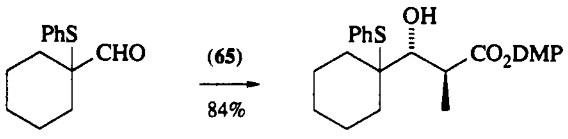
PhS
CHO
(65)
84%
PhS
OH
CO$_2$DMP

**(74)** **(75)** (70)

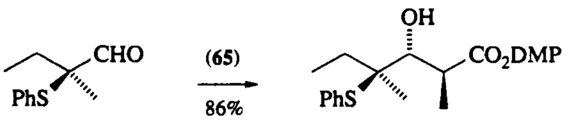
CHO
PhS
(65)
86%
OH
CO$_2$DMP
PhS

**(76)** **(77)** (71)

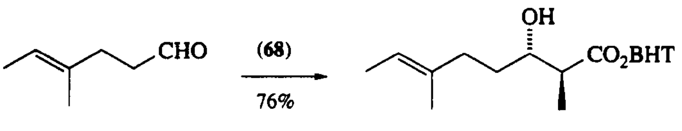
CHO
(68)
76%
OH
CO$_2$BHT

**(78)** **(79)** (72)

workers added (**68**) to the β,γ-unsaturated aldehyde (**80**) to obtain aldol (**81**), of at least 97% stereochemical purity (equation 73).[97]

Lactone enolates typically show poor simple diastereoselection. For example, in connection with a synthesis of (±)-podorhizol, Ziegler and Schwartz added the lithium enolate of butyrolactone (**82**) to 3,4,5-trimethoxybenzaldehyde (equation 74). Although the diastereofacial selectivity of the chiral enolate is complete, aldols (**83**) and (**84**) are formed in a ratio of 50:50 in THF and 25:75 in an equimolar mixture of dimethoxyethane and ether.[98]

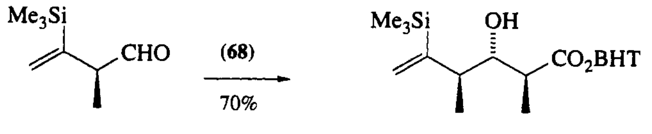

(73)

**(80)** **(81)**

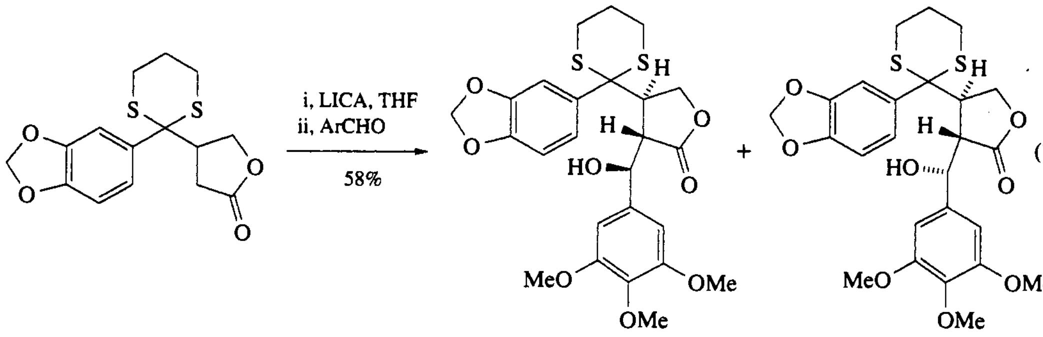

(74)

**(82)** **(83)** **(84)**

Widdowson and coworkers investigated aldol reactions of butyrolactone itself with benzaldehyde (equation 75).[99] The lithium enolate gives diastereomers (**85**) and (**86**) in a ratio of 40:60 to 30:70, depending upon reaction temperature. If 0.5 mol equiv. $ZnCl_2$ is added to the reaction mixture prior to enolate formation, the (**85**):(**86**) ratio is 56:44 to 70:30, depending upon reaction temperature.

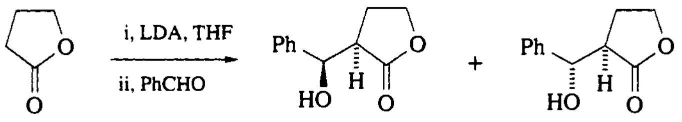

(75)

**(85)** **(86)**

The dianion of the hydroxybutyrolactone (**87**) reacts with aldehydes with high diastereofacial selectivity to give mixtures of dihydroxy lactones (**88**) and (**89**) (equation 76; Table 5).[100] The lithium enolate shows little simple stereoselection with the sterically undemanding aldehydes phenylacetaldehyde and tetradecanal. Significant stereoselectivity is seen in the reaction with benzaldehyde, and pivalaldehyde gives only a single product. Because the aldol relative stereochemistry in the reactions with benzalde-

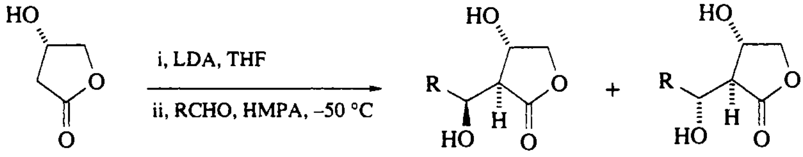

(76)

**(87)** **(88)** **(89)**

**Table 5** Aldol Stereochemistry (equation 76)

| *R* | *Without* $ZnCl_2$ |  | *With* $ZnCl_2$ |  |
|---|---|---|---|---|
|  | *(88):(89)* | *Yield (%)* | *(88):(89)* | *Yield (%)* |
| Ph | 90:10 | 43 | 80:20 | 85 |
| $PhCH_2$ | 57:43 | 45 | 42:58 | 89 |
| $Bu^t$ | >100:1 | 34 | >100:1 | 48 |
| $n\text{-}C_{13}H_{27}$ | 50:50 | 48 | 45:55 | 60 |

hyde and pivalaldehyde is different from that normally observed with (*E*)-enolates, the authors postulate an open transition state to explain the results. As in the previous example, the stereoselectivity is not very much affected by the addition of $ZnCl_2$, although yields are improved significantly.

β-Propiolactone enolates that are substituted at C-2 show excellent simple and diastereofacial selectivity in their reactions with aldehydes.[101] As shown in equation (77) and Table 6, the reaction is quite general; yields are in the range 85–95%. In only one case (Table 6, entry 2) is an isomer detected; in this case the (**90**):(**91**) ratio is 85:15. (The data in Table 6 are taken from the preliminary communication (ref. 101a). In this publication, structures (**90**) and (**91**) were tentatively advanced. In ref. 101b, it is reported that the structure of the major product (**90**) had been determined by X-ray crystallography. This was presumably done on the major product of Table 6, entry 1, although this is not clear from ref. 101b. In addition, in ref. 101b, it is stated that the reactions in equation (77) all proceed with >88% enantioselectivity, presumably referring to the degree of simple diastereoselection. No experimental details for the preparation of aldol (**90**) were given in this full paper.)

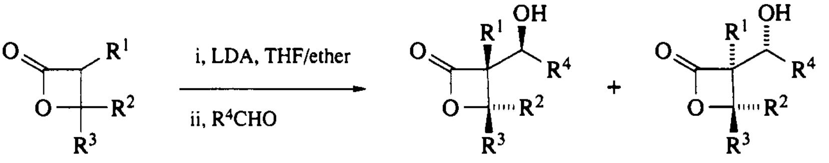

(77)

(**90**) (**91**)

**Table 6** Aldol Stereochemistry (equation 77)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *Isomer ratio* |
|---|---|---|---|---|---|
| 1 | $Bu^t$ | H | Ph | Ph | Only one |
| 2 | $Bu^t$ | H | Ph | Me | 85:15 |
| 3 | $Bu^t$ | H | Ph | H | Only one |
| 4 | $Pr^i$ | H | Ph | Ph | Only one |
| 5 | $Pr^i$ | H | Ph | Me | Only one |
| 6 | $Pr^i$ | H | Ph | H | Only one |
| 7 | $Pr^i$ | H | H | H | Only one |
| 8 | $(CH_2)_4$ |  | Ph | Ph | Only one |
| 9 | $(CH_2)_4$ |  | Ph | Me | Only one |
| 10 | $Bu^t$ | H | Me | Ph | Only one |

An extensive study of the aldol reactions of α-alkoxypropionate esters has been carried out.[102] The results of this investigation are summarized in Scheme 5 and Table 7. The trend that emerges from an examination of the data in Table 7 is that aldols of structure (**99**) are favored by small $R^2$, while aldols of structure (**100**) are favored by large $R^2$. The size of $R^3$, the aldehyde ligand, is also important; the larger this group, the more aldol of structure (**100**) is produced (compare entries 13–17, 18–19 and 20–23, Table 7). The ethers of methyl lactate (**92**) to (**94**) show only modest preferences for aldol structure (**99**). An exception to this generalization is seen in the reaction of methyl *O*-methyllactate (**92**), which gives a single isomer in its reactions with α-branched aliphatic aldehydes (Table 7, entries 2 and 3). The excellent complementary stereoselectivity observed with this reagent and the corresponding BHT ester (**97**) is striking (entries 24–26). It is also noteworthy that 2-phenylpropanal shows perfect diastereofacial selectivity in its reaction with the latter reagent.

Reagent (**98**) has been employed in syntheses of the C-1,C-7 and C-8,C-15 segments of erythronolide A.[103,104] Reaction of the lithium enolate of (**98**) with aldehyde (**101**) provides aldols (**102**) and (**103**) in a

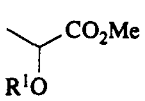

**(92)** $R^1$ = Me

**(93)** $R^1$ = $PhCH_2$

**(94)** $R^1$ = $MeOCH_2CH_2OCH_2$

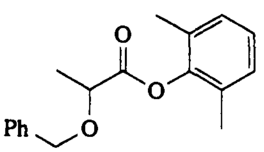

**(95)**

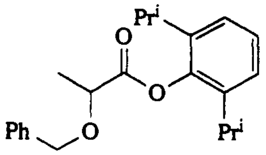

**(96)**

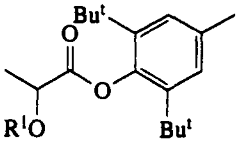

**(97)** $R^1$ = Me

**(98)** $R^1$ = $PhCH_2$

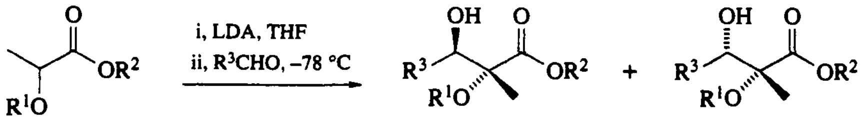

**(99)** **(100)**

Scheme 5

**Table 7** Aldol Stereochemistry (Scheme 5)

| *Entry* | *Ester* | *Aldehyde* | *Yield (%)* | ***(99):(100)*** |
|---|---|---|---|---|
| 1 | **(92)** | EtCHO | 99 | 70:30 |
| 2 | **(92)** | Pr$^i$CHO | 98 | >97:3 |
| 3 | **(92)** | Bu$^t$CHO | 84 | >97:3 |
| 4 | **(92)** | PhCHO | 85 | >75:25 |
| 5 | **(93)** | EtCHO | 87 | 70:30 |
| 6 | **(93)** | Pr$^i$CHO | 85 | 70:30 |
| 7 | **(93)** | Bu$^t$CHO | 80 | 70:30 |
| 8 | **(93)** | PhCHO | 100 | 70:30 |
| 9 | **(94)** | EtCHO | 60 | 82:18 |
| 10 | **(94)** | Pr$^i$CHO | 83 | 85:15 |
| 11 | **(94)** | Bu$^t$CHO | 73 | 88:12 |
| 12 | **(94)** | PhCHO | 95 | 85:15 |
| 13 | **(95)** | $CH_2$=CHCHO | 65 | 64:36 |
| 14 | **(95)** | EtCHO | 50 | 78:22 |
| 15 | **(95)** | Pr$^i$CHO | 77 | 83:17 |
| 16 | **(95)** | Bu$^t$CHO | 30 | <3:97 |
| 17 | **(95)** | PhCHO | 65 | 25:75 |
| 18 | **(96)** | Pr$^i$CHO | 73 | 33:67 |
| 19 | **(96)** | PhCHO | 73 | 10:90 |
| 20 | **(98)** | EtCHO | 57 | 17:83 |
| 21 | **(98)** | Pr$^i$CHO | 89 | <3:97 |
| 22 | **(98)** | Bu$^t$CHO | 0 | — |
| 23 | **(98)** | PhCHO | 62 | <3:97 |
| 24 | **(97)** | Pr$^i$CHO | 84 | <3:97 |
| 25 | **(97)** | PhCHO | 91 | <3:97 |
| 26 | **(97)** | Ph(Me)CHCHO | 59 | <3:97[a] |

[a] A single diastereofacial isomer is produced in this reaction.

ratio of 85:15 (equation 78).[103] With the β,γ-unsaturated aldehyde (**104**), ester (**98**) gives a single aldol (equation 79).[104]

The enolate of α,β-dialkoxy ester (**105**) reacts with acetone to give (**106**) in good yield (equation 80); the product has been converted into (+)-viridifloric acid.[105]

The enolates of dioxolanones (**107**) react with aldehydes to give aldols (**108**) and (**109**) with, at most, a 3:1 preference for the former (equation 81).[102b] This modest preference is of the same magnitude, and in the same sense, as the preference seen with the lithium enolate of butyrolactone (equation 75, *vide supra*). However, Seebach and coworkers have carried out aldol reactions with chiral dioxolanone (**110**) and have observed high diastereofacial preference, as well as high simple diastereoselection in some cases (equation 82, Table 8).[106] The enolate of (**110**) also adds, in excellent yield and with essentially perfect diastereofacial selectivity, to ketones (cyclohexanone, acetone, acetophenone and benzophenone).

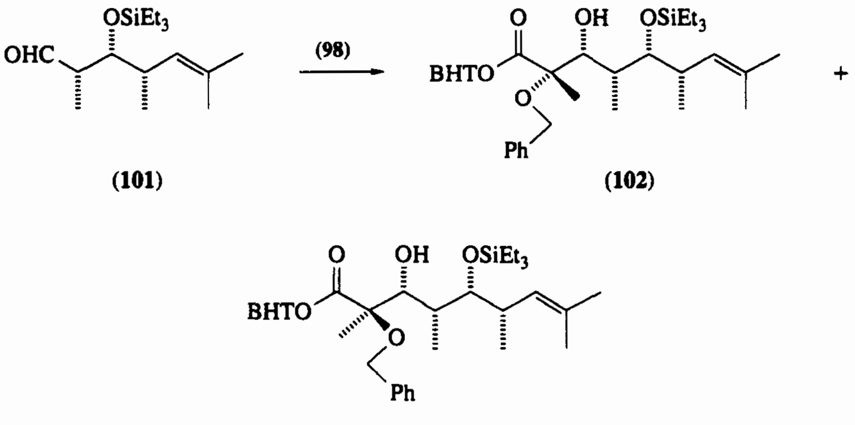
OSiEt3
OHC
(98)
O
OH
OSiEt3
BHTO
O
Ph
+
O
OH
OSiEt3
BHTO
O
Ph

**(101)** **(102)** **(103)**

(78)

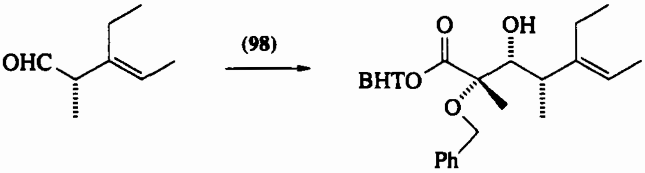
OHC
(98)
O
OH
BHTO
O
Ph

**(104)**

(79)

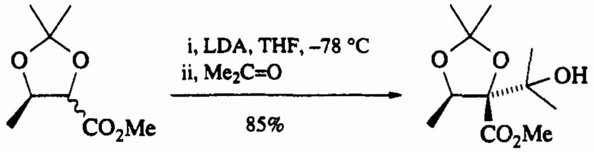
O
O
CO2Me
i, LDA, THF, –78 °C
ii, Me2C=O
85%
O
O
OH
CO2Me

**(105)** **(106)**

(80)

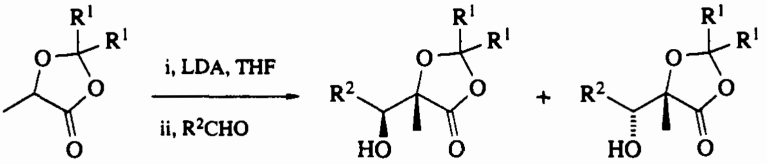
R1
R1
O
O
O
i, LDA, THF
ii, R2CHO
R2
HO
O
+
R2
HO
O

**(107)** **(108)** **(109)**

(81)

$R^1$ = H, Me; $R^2$ = Et, $Pr^i$, $Bu^t$, Ph

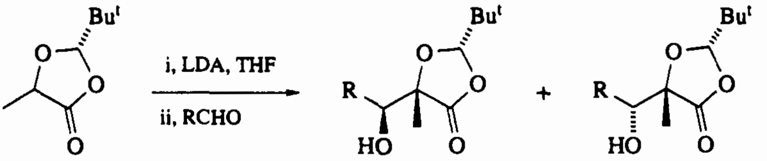
Bu^t
O
O
O
i, LDA, THF
ii, RCHO
R
HO
O
+
R
HO
O

**(110)** **(111)** **(112)**

(82)

**Table 8** Aldol Stereochemistry (equation 82)

| *Entry* | *R* | *Yield (%)* | *(111):(112)* |
|---|---|---|---|
| 1 | Me | 84 | 82:18 |
| 2 | Et | 80 | 85:15 |
| 3 | Bu$^t$ | 83 | 53:47 |
| 4 | Ph | 85 | 84:16 |
| 5 | 2,4,6-$Me_3C_6H_2$ | 65 | 78:22 |
| 6 | CH=CHPh | 66 | 64:40 |

Aldol reactions of chiral dioxolanones (**113**) and (**114**) are summarized in Scheme 6 and Table 9.[107] With both (**113**) and (**114**), essentially perfect diasterofacial selectivity is observed. The simple diastereoselection is modest to good, and is dependent on the enolate counterion. For the lithium and magnesium enolates, the sense of simple diastereoselection is the same as is observed with the achiral dioxolanone (**107**) and the chiral dioxolanone (**110**). Use of the zirconium enolate generally reverses the sense of simple diastereoselection, although the isomer ratios are not very high in some cases.

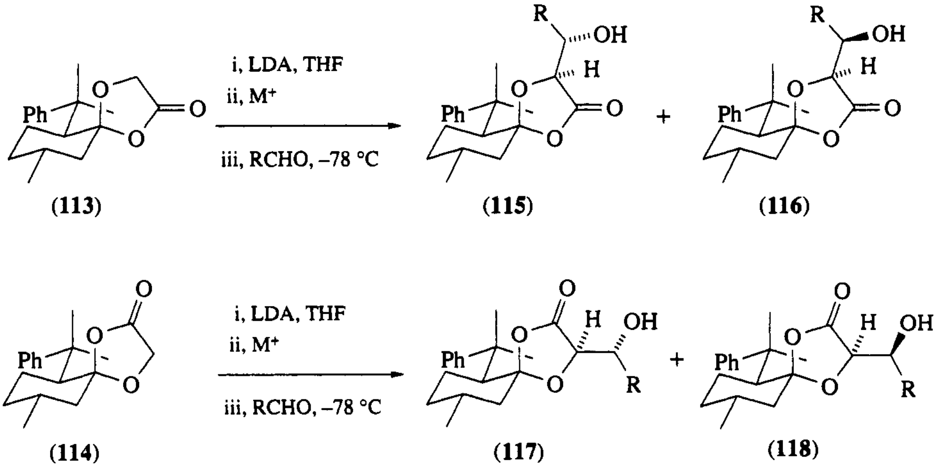

**Scheme 6**

**Table 9** Aldol Stereochemistry (Scheme 6)

| *Entry* | *Dioxolanone* | *M$^{+a}$* | *R* | *Yield (%)* | *(115):(116)* | *(117):(118)* |
|---|---|---|---|---|---|---|
| 1 | (113) | Li$^+$ | Ph | 92 | 68:32 | — |
| 2 | (113) | Mg$^{2+}$ | Ph | 92 | 83:17 | — |
| 3 | (113) | Zr$^{4+}$ | Ph | 95 | 19:81 | — |
| 4 | (113) | Li$^+$ | Pr$^n$ | 93 | 96:4 | — |
| 5 | (113) | Mg$^{2+}$ | Pr$^n$ | 86 | 90:10 | — |
| 6 | (113) | Zr$^{4+}$ | Pr$^n$ | 97 | 45:55 | — |
| 7 | (113) | Li$^+$ | Pr$^i$ | 85 | 90:10 | — |
| 8 | (113) | Mg$^{2+}$ | Pr$^i$ | 86 | 73:27 | — |
| 9 | (113) | Zr$^{4+}$ | Pr$^i$ | 91 | 24:76 | — |
| 10 | (114) | Li$^+$ | Ph | 99 | — | 68:32 |
| 11 | (114) | Mg$^{2+}$ | Ph | 89 | — | 75:25 |
| 12 | (114) | Zr$^{4+}$ | Ph | 91 | — | 18:82 |
| 13 | (114) | Li$^+$ | Pr$^n$ | 96 | — | 88:12 |
| 14 | (114) | Mg$^{2+}$ | Pr$^n$ | 92 | — | 74:26 |
| 15 | (114) | Zr$^{4+}$ | Pr$^n$ | 91 | — | 37:63 |
| 16 | (114) | Li$^+$ | Pr$^i$ | 86 | — | 96:4 |
| 17 | (114) | Mg$^{2+}$ | Pr$^i$ | 89 | — | 89:11 |
| 18 | (114) | Zr$^{4+}$ | Pr$^i$ | 89 | — | 17:83 |

[a] For M$^+$ = Li$^+$, no extra salt was used; for M$^+$ = Mg$^{2+}$ or Zr$^{4+}$, 1.0 equiv. of $MgBr_2$ or $Cp_2ZrCl_2$ was added.

Ethyl fluoroacetate gives a 1:1 mixture of the (*E*)- and (*Z*)-enolate, which reacts with aldehydes and ketones to give mixtures of *syn* and *anti* aldols (equation 83).[108] Stereoselectivity is generally low, the *syn*:*anti* ratio ranging from 50:50 for 2-butanone to 4:1 for ethyl *t*-butyl ketone. However, since a mixture of enolates was employed in this study, there remains the possibility that one of the enolates is highly stereoselective, whereas the other one is stereorandom.

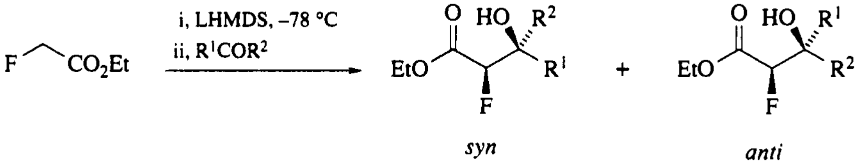

(83)

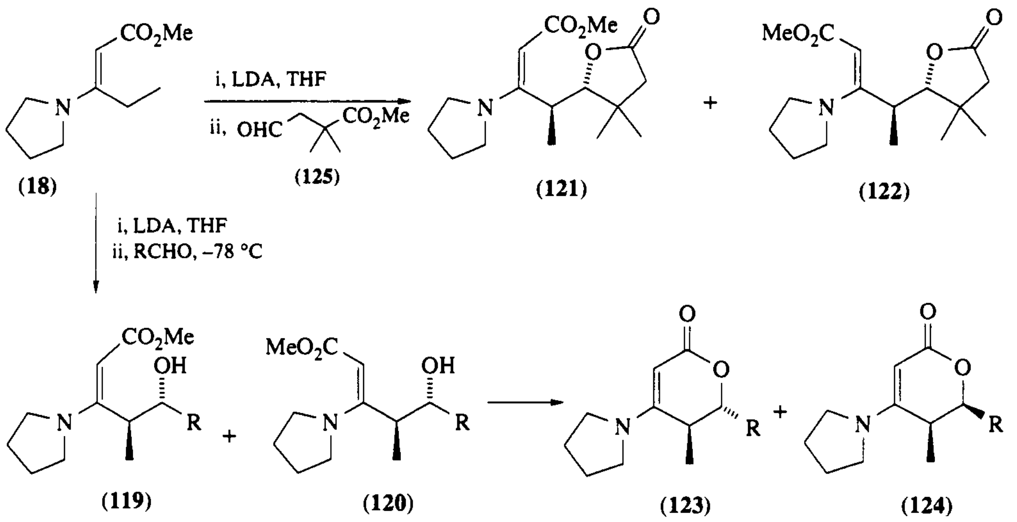

Scheme 7

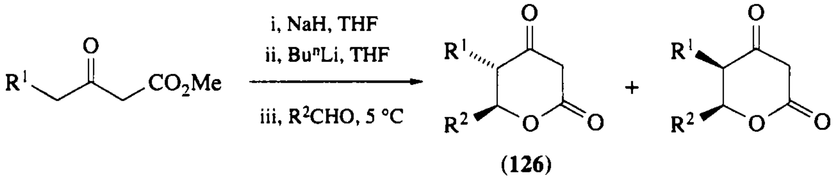

(84)

Schlessinger and coworkers have investigated vinylogous ester enolates derived from enamino ester (**18**).[46] As shown in Scheme 7, the lithium enolate of (**18**) reacts with isobutyraldehyde or pivalaldehyde at –78 °C to give two adducts, (**119**) and (**120**), that both have the *anti* relative configuration at the new stereocenters. If the initial aldolate solution from the reaction of (**18**) with isobutyraldehyde is kept for an extended period of time at –78 °C, or warmed to 0 °C for 5 min, cyclization occurs, providing lactones (**123**) and (**124**) in a ratio of 20:1 under both conditions. However, the pivalaldehyde adduct gives (**123**) and (**124**) in a ratio of 18:1 at –78 °C or 7.8:1 at 0 °C. If the enolate of (**18**) is treated with aldehyde (**125**), the only products obtained are lactones (**121**) and (**122**), both having the *anti* relative configuration at the new stereocenters. The foregoing evidence is taken to indicate that the enolate of (**18**) reacts kinetically at C-4, in contrast to simple crotonate esters, which undergo aldolization at C-2. Cyclization of the original aldolate must involve geometric isomerization of the double bond, and may be complicated by reverse aldolization, particularly with the pivalaldehyde adduct at 0 °C.

The foregoing reactions bear a resemblance to the reactions of β-keto ester dianions (*vide supra*, equation 32), in that reaction occurs at C-4 instead of C-2. The only study of simple diastereoselection in the aldol reactions of β-keto ester dianions shows a stereochemical similarity as well. As shown in equation (84), the dianions of a series of β-keto esters react with aldehydes to give largely the *trans* lactone (**126**); data are summarized in Table 10.[109]

**Table 10** Aldol Stereochemistry (equation 84)

| *Entry* | $R^1$ | $R^{2a}$ | *Yield (%)* | *(125):(126)* |
|---|---|---|---|---|
| 1 | $PhCH_2$ | Me | 94 | 100:0$^b$ |
| 2 | $PhCH_2$ | n-$C_3H_7$ | 96 | 100:0$^b$ |
| 3 | $PhCH_2$ | n-$C_7H_{15}$ | 82 | 100:0 |
| 4 | $PhCH_2$ | c-$C_6H_{11}$ | 91 | 100:0 |
| 5 | $PhCH_2$ | c-$C_8H_{15}$ | 85 | 89:11 |
| 6 | $PhCH_2$ | Ph | 78 | 87:13 |
| 7 | *m*-$MeOC_6H_4CH_2$ | c-$C_6H_{11}$ | 21 | 100:0 |
| 8 | *p*-$MeC_6H_4CH_2$ | n-$C_3H_7$ | 26 | 100:0$^b$ |
| 9 | $CH_2{=}CHCH_2$ | c-$C_6H_{11}$ | 84 | 79:21 |
| 10 | $CH_2{=}C(CH_3)CH_2$ | c-$C_6H_{11}$ | 94 | 100:0$^b$ |
| 11 | Bu | Ph | 83 | 63:37 |

[a] c-$C_6H_{11}$ = cyclohexyl; c-$C_8H_{15}$ = cyclooctyl. [b] Although a single diastereomer was obtained, the NMR spectra did not allow definite stereochemical assignment.

### 1.6.3.4 Carboxylic Acid Dianions (Ivanov Reaction)

The Ivanov reaction is the preparation of a β-hydroxy acid by reaction of the magnesium dianion of a carboxylic acid with an aldehyde or ketone.[110] In a seminal paper, Zimmerman and Traxler investigated the Ivanov reaction of phenylacetic acid and benzaldehyde and obtained *anti* and *syn* β-hydroxy acids (**127**) and (**128**) in 69% and 22% yields, respectively (equation 85).[111] The observed stereochemistry was rationalized with a cyclic, chair-like transition state in which a magnesium cation is chelated by one oxygen each of the carboxylate enolate and the aldehyde (the 'Zimmerman–Traxler transition state').

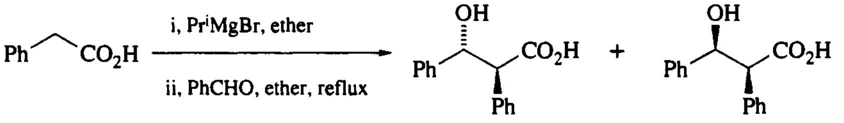

(**127**) 69% (**128**) 22%

(85)

**Table 11** Aldol Stereochemistry (equation 86)

| *Entry* | $R^1$ | $R^2$ | *Method A*$^a$ *Yield (%)* | *Method A*$^a$ *(129):(130)* | *Method B*$^b$ *Yield (%)* | *Method B*$^b$ *(129):(130)* |
|---|---|---|---|---|---|---|
| 1 | Me | Bu$^t$ | 70 | 50:50 | 68 | 50:50 |
| 2 | Me | Ph | 75 | 55:45 | 75 | 55:45 |
| 3 | Et | Ph | 73 | 52:48 | 75 | 55:45 |
| 4 | Pr$^i$ | Ph | 80 | 55:45 | 73 | 58:42 |
| 5 | Bu$^t$ | Pr$^i$ | 78 | 79:21 | 75 | 90:10 |
| 6 | Bu$^t$ | $PhCH_2CH_2$ | 70 | 67:33 | 65 | 67:33 |
| 7 | Bu$^t$ | Bu$^t$ | 85 | 80:20 | 83 | >98:2 |
| 8 | Bu$^t$ | Ph | 73 | 60:40 | 70 | 88:12 |
| 9 | Ph | Ph | 88 | 71:29 | 90 | 92:8 |
| 10 | Ph | 1-Naphthyl | 85 | 73:27 | 80 | 92:8 |
| 11 | Ph | 2-Thienyl | 75 | 70:30 | 68 | 91:9 |
| 12 | Ph | 2-Furyl | 68 | 71:29 | 60 | 92:8 |
| 13 | Ph | $PhCH{=}CH$ | 88 | 71:29 | 79 | 92:8 |
| 14 | Bu$^t$ | Mesityl | 68 | 64:36 | 60 | 93:7 |
| 15 | Mesityl | Mesityl | 95 | 91:9 | 85 | >98:2 |
| 16 | 1-Adamantyl | Bu$^t$ | 80 | >95:5 | 77 | >95:5 |
| 17 | Ph | Bu$^t$ | 95 | 66:34 | 90 | >98:2 |
| 18 | Ph | Pr$^i$ | 83 | 66:34 | 77 | 93:7 |
| 19 | Ph | Et | 70 | 58:42 | 70 | 64:36 |
| 20 | Ph | Me | 65 | 58:42 | 60 | 64:36 |

[a] Method A: –50 °C, 10 min. [b] Method B: 50 °C, 3 d.

Blagoy *et al.* examined the effect of the counterion on the stereochemistry of this reaction.[112] With the bis(bromomagnesium) salt, a (**127**):(**128**) ratio of about 60:40, similar to that observed by Zimmerman and Traxler, is obtained. With the disodium salt, the sole isomer obtained (in 40% yield) is (**127**).

Mulzer and coworkers have examined the reactions of dilithium salts of carboxylic acids (equation 86, Table 11).[113] Products were assayed under kinetic conditions (10 min at –50 °C), and after 3 d at 50 °C. The compounds studied fall into two categories. For one set of reactions (*e.g.* Table 11, entries 1–4), the diastereomer ratios under the two conditions are essentially the same, showing that there is no equilibration after prolonged reaction time at elevated temperature. On the other hand, if the combined steric bulk of $R^1$ and $R^2$ is great enough, there is significant equilibration to isomer (**129**) under the more vigorous reaction conditions (*e.g.* Table 11, entries 7–15).

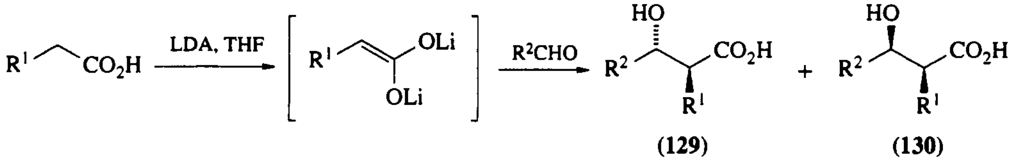

(86)

## 1.6.3.5 Amide and Lactam Enolates

Simple amide enolates give poor stereoselection as shown by the examples in equation (87).[9c,114,115] This low degree of simple stereoselection appears to result from differences in the diastereomeric transition states, since *N*-propionylpyrrolidine gives a single enolate.[114] Welch found that the lithium enolates of fluoroacetamides give mixtures of *syn* and *anti* aldols, and that the lack of stereoselectivity is due to the fact that enolate mixtures are obtained; a typical example is shown in equation (88).[116] On the other hand, *N*-acyl derivatives of 2,3-dihydro-4*H*-1,4-benzothiazine and phenothiazine react with a variety of aldehydes to give *syn*-β-hydroxy amides (equations 89–90).[117]

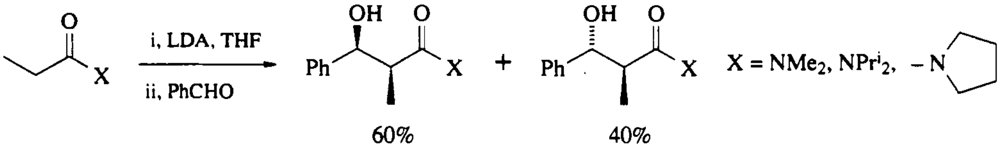

(87)

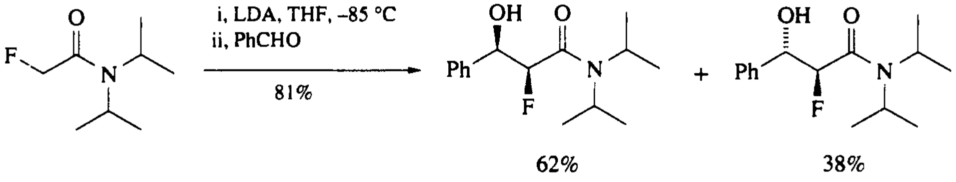

(88)

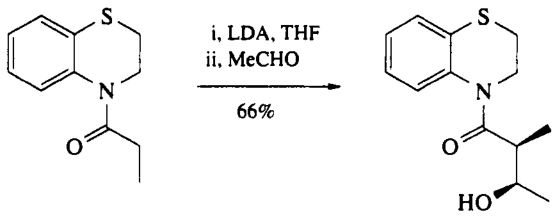

(89)

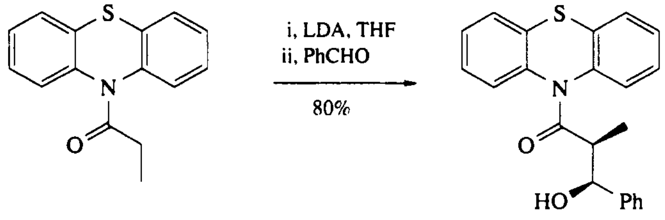

(90)

The antibiotic thienamycin has stimulated considerable interest in aldol reactions of β-lactams. In one of the first papers on this subject, DiNinno and coworkers examined various versions of this aldol reaction, one of which is shown in equation (91).[118] The magnesium enolate of the β-lactam, prepared by metallation of the 6-iodo derivative in THF, gives isomers (**131**) to (**133**) in a ratio of 24:49:27. In this reaction, the facial preference of the chiral β-lactam and the simple diastereoselection (*anti*:*syn*) are both modest (3:1). If metallation is carried out with *n*-butyllithium in ether, the ratio of the three isomers is 47:35:18, corresponding to a facial preference of 4:1 and an *anti*:*syn* ratio of 1:1. The stereochemistry of aldol reactions of the 6-bromopenam enolate derived from metallation of 6,6-dibromopenams has also been studied.[118,119] If the metallation is carried out in THF, either with *n*-butyllithium or methylmagnesium bromide, there is a surprising preference for reaction on the more congested concave face of the β-lactam; with the magnesium enolate, aldol (**134**) is isolated in 67% yield (equation 92). Metallation of the dibromo-β-lactam (**135**) with methylmagnesium bromide, followed by reaction of the magnesium enolate with acetaldehyde, gives aldol (**136**) as a single isomer in excellent yield (equation 93).[120] Again, the aldehyde attacks the concave face of the bicyclic system.

Several groups have studied aldol reactions of simpler β-lactam enolates. Diarylazetidinones such as (**137**) react as their lithium enolates to give completely or largely one of the four possible stereoisomers (**138**); a typical reaction is shown in equation (94).[121] [The interpretation of this paper is complicated by

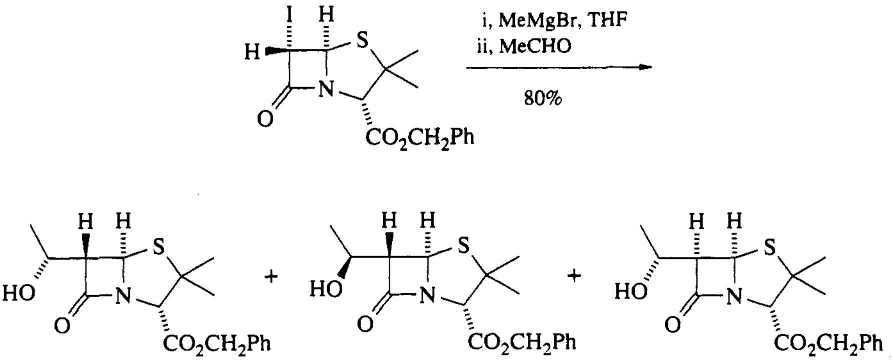

(**131**) (**132**) (**133**)

(91)

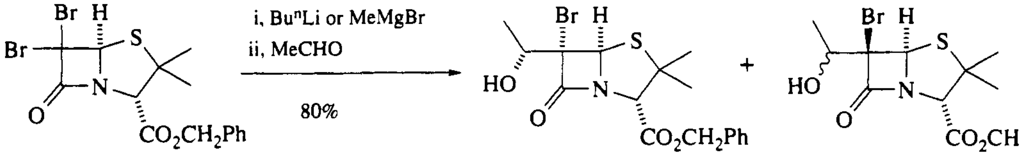

(92)

(**134**)

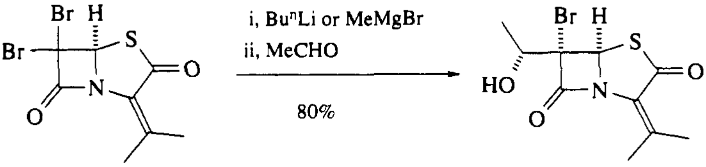

(93)

(**135**) (**136**)

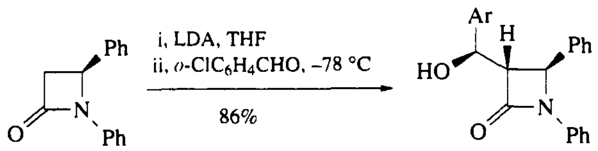

(94)

(**137**) (**138**)

an error in nomenclature; product (**92**) and a number of structural analogs are incorrectly designated as ($\alpha S^*,3S^*,4R^*$), rather than as ($\alpha R^*,3S^*,4S^*$) or ($\alpha S^*,3R^*,4R^*$).] The aldol product has the *anti* configuration at the two new stereocenters, as expected for an (*E*)-enolate. In a few cases, minor amounts of the *syn* product were isolated.

On the other hand, it has been found that β-lactams having other substituents at C-1 and C-4 give complex isomer mixtures.[122–124] A typical example is shown in equation (95); *anti* and *syn* aldols (**139**) and (**140**) are formed in excellent yield, but in a ratio of 1:1.[122] Another example is seen in the reaction of β-lactam (**141**; R = SPh); aldols (**142**) to (**145**) are produced in a ratio of 34:27:11:23 (equation 96).[125] Similar results are obtained with the 4-trityl derivative (**141**; R = $CPh_3$); aldols (**142**) to (**145**) are formed in a ratio of 32:39:12:17.[126] However, the lithium enolate of β-lactam (**146**) reacts with acetaldehyde to give a single aldol (**147**) in 80% yield (equation 97)! The implication from these results is that the methoxymethyl group in (**146**) effects the stereoselectivity, both facial and simple, by coordination of the lithium cation. Again, (**147**) has *anti* aldol stereochemistry, as is expected for an (*E*)-enolate.

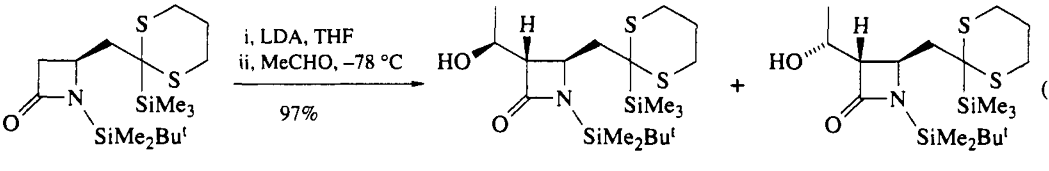

**(139)** **(140)** (95)

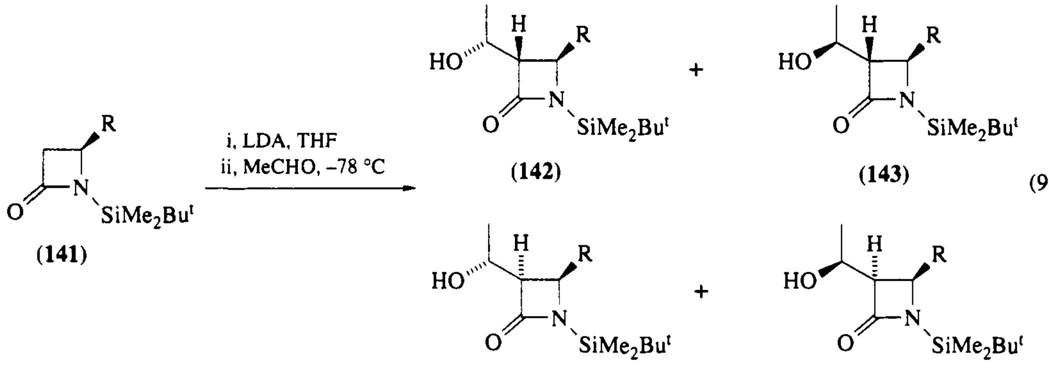

**(141)** **(142)** **(143)** **(144)** **(145)** (96)

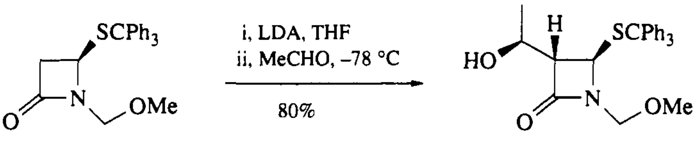

**(146)** **(147)** (97)

The lithium enolate of lactam (**148**; R = Me) reacts with aromatic aldehydes to give the diastereomeric aldols (**149**) and (**150**) in ratios of 6:1 to 9:1 (equation 98); stereoselectivity is reduced with (**148**; R = H), and with aliphatic aldehydes.[127]

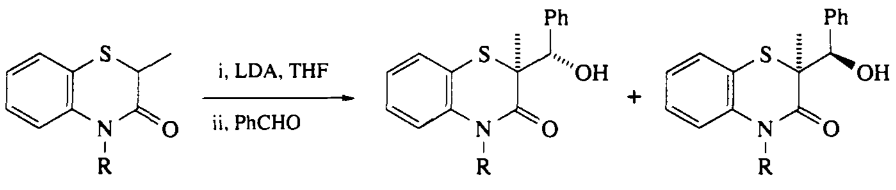

**(148)** **(149)** **(150)** (98)

### 1.6.3.6 Thioester and Thioamide Enolates

In the Woodward erythromycin synthesis, the lithium enolate of *t*-butyl thiopropionate[128] was added to aldehyde (**151**); aldol (**152**) was obtained in 85% yield (equation 99).[129] The remarkable diastereofacial selectivity observed in this reaction may be a general property of thioester enolates (*vide infra*).

Dithiopropionate esters are deprotonated by LDA in THF to give mixtures of the (*Z*)- and (*E*)-enolate, favoring the former.[130] [As with ester enolates, the Evans (*E*)/(*Z*) notational format (ref. 2c) is followed. Thus, in naming an enolate derived from a dithioester $R^2CH_2CS_2R^1$, SM is assigned higher priority than $SR^1$, regardless of the metal.] The reactions of these enolate mixtures with aldehydes have been studied (equation 100; Table 12).[131,132] The data in Table 12 suggest a relationship between enolate geometry and aldol stereochemistry, at least for (*Z*)-enolates of dithioesters with moderately large $R^1$ groups. The simple diastereoselection seen with the sterically encumbered aldehydes 2-phenylpropanal and 2-cyclohexylpropanal (Table 12, entries 3 and 4) is exceptional in light of the fact that the enolate ratio is

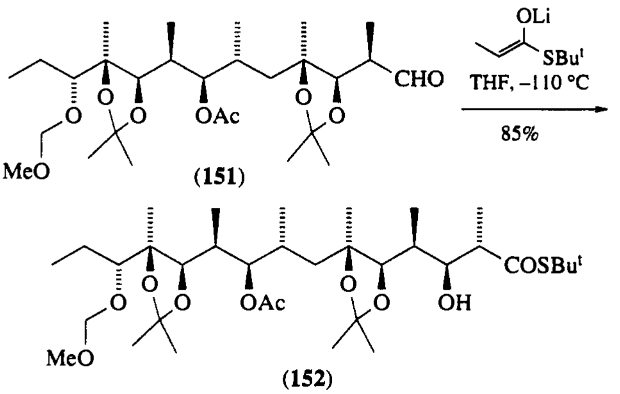

**(151)**

**(152)**

(99)

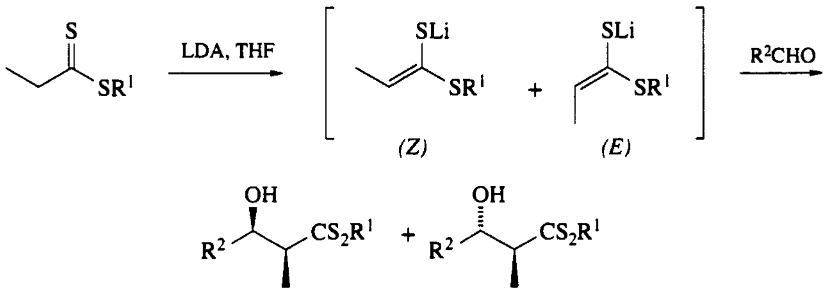

(100)

**Table 12** Aldol Stereochemistry (equation 100)

| *Entry* | $R^1$ | *(Z):(E)*[a] | $R^2$ | *Temperature* (°C) | *Yield* (%)[d] | *Syn:anti* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Me | 75:25 | Ph | –78 | 84 | 57:43 | 131 |
| 2 | Et | b | Ph | –120 | 50–60 | 46:54 | 132 |
| 3 | Et | b | Ph(Me)CH | –120 | 50–60 | 95:5 | 132 |
| 4 | Et | b | c-$C_6H_{13}$(Me)CH | –120 | 50–60 | 84:16 | 132 |
| 5 | Pr$^i$ | 81:19 | Et | –78 | 85[e] | 82:18 | 131 |
| 6 | Pr$^i$ | 81:19 | Pr$^i$ | –78 | 50[f] | 83:17 | 131 |
| 7 | Bu$^t$ | 84:16 | Ph | –78 | 40 | 77:23 | 131 |
| 8 | Bu$^t$ | 84:16 | Et | –78 | 60 | 76:24 | 131 |
| 9 | $CH_2OMe$ | 86:14 | Et | –78 | 50 | 77:23 | 131 |
| 10 | Ph | 87:13 | Ph | –78 | 35 | 74:26 | 131 |
| 11 | Ph | 87:13 | Et | –78 | 15[f] | 81:19 | 131 |
| 12 | Pr$^i$ | 44:56[c] | Ph | –78 | 60 | 64:36 | 131 |

[a] Enolate ratio obtained with LDA in THF at –78 °C. [b] The enolate ratio was not determined in this study. [c] Enolate ratio obtained with LHMDS or LITMP. [d] Yield after 10 s reaction time, unless stated. [e] Reaction time 30 s; yield after 10 s was 47%. [f] Reaction time 2 min.

probably of the order of 75:25. This high stereoselectivity, apparently independent of enolate geometry, has been interpreted by Meyers and Walkup as indicative of an open transition state.

Thioamides of secondary amines give (*Z*)-enolates that react with aldehydes to give *syn* aldols with good stereoselectivity (equation 101; Table 13).[115,133] The stereoselectivity is slightly greater with the magnesium enolate than with the lithium enolate (Table 13, entries 2 and 3) and is strongly influenced by conditions (entries 6 and 7). The poor stereoselectivity observed with the thioamide of valeric acid (Table 13, entries 10 and 11) is attributed to the formation of a mixture of enolate geometric isomers.

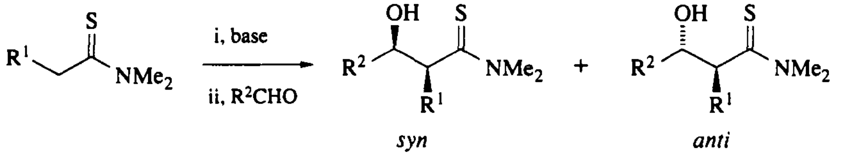

(101)

**Table 13** Aldol Stereochemistry (equation 101)

| *Entry* | *R*$^1$ | *R*$^2$ | *Base* | *Temperature* (°C) | *Time* (min) | *Syn:anti*[a] | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Me | Pr$^i$ | Pr$^i$MgBr | −78 | 30 | 95:5 | 115 |
| 2 | Me | Ph | Pr$^i$MgBr | −78 | 2 | 93:7 | 115 |
| 3 | Me | Ph | Bu$^n$Li | −78 | 2 | 87:13 | 115 |
| 4 | Me | Et | Bu$^n$Li | −78 | 10 | 90:10 | 115 |
| 5 | Me | $CH_2{=}CH$ | Pr$^i$MgBr | −78 | 30 | 89:11 | 115 |
| 6 | Ph | Pr$^i$ | Pr$^i$MgBr | −78 | 2 | 72:28 | 115 |
| 7 | Ph | Pr$^i$ | Pr$^i$MgBr | +25 | 60 | 3:97 | 115 |
| 8 | Ph | $CH_2{=}CMe$ | Pr$^i$MgBr | −78 | 10 | 73:27 | 115 |
| 9 | PhS | Pr$^i$ | Pr$^i$MgBr | −78 | 10 | 66:34 | 115 |
| 10 | Pr$^i$ | Ph | Pr$^i$MgBr | −78 | 2 | 34:66 | 133 |
| 11 | Pr$^i$ | $PhCH_2CH_2$ | Bu$^n$Li | −78 | 2 | 32:68 | 133 |

[a] Combined isolated yields = 85–100%.

Thioamides of primary amines react with two equivalents of *n*-butyllithium or isopropylmagnesium bromide to give dianions that have been shown to have the (*Z*)-configuration. These species react with aldehydes to afford predominantly *anti* aldols (equation 102; Table 14).[134] Again, the magnesium dianions generally show superior stereoselectivity. In certain cases, the degree of stereoselectivity is excellent. This procedure provides a convenient complement to the *syn* selectivity obtained with thioamides of secondary amines.

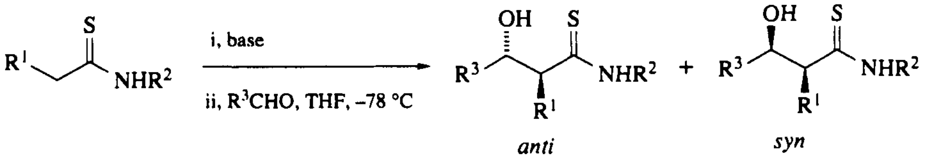

(102)

**Table 14** Aldol Stereochemistry (equation 102)

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *Base* | *Anti:syn*[a] |
|---|---|---|---|---|---|
| 1 | Me | Ph | Me | Bu$^n$Li | 69:31 |
| 2 | Me | Ph | Pr$^i$ | Bu$^n$Li | 88:12 |
| 3 | Me | Ph | Ph | Bu$^n$Li | 62:38 |
| 4 | Pr$^i$ | Ph | Pr$^i$ | Bu$^n$Li | 93:7 |
| 5 | Pr$^i$ | Ph | Ph | Bu$^n$Li | 69:31 |
| 6 | Ph | Me | Pr$^i$ | Bu$^n$Li | 78:22 |
| 7 | Ph | Me | Pr$^i$ | Pr$^i$MgBr | 98:2 |
| 8 | Ph | Me | Ph | Bu$^n$Li | 71:29 |
| 9 | Ph | Me | Ph | Pr$^i$MgBr | 94:6 |
| 10 | Ph | $CH_2CH_2OMe$ | Ph | Bu$^n$Li | 94:6 |
| 11 | Ph | $CH_2CH_2OMe$ | Ph | Pr$^i$MgBr | 97:3 |

[a] Combined isolated yields = 75–99%.

Thioamide enolates may be prepared by conjugate addition of organometallics to α,β-unsaturated thioamides. Reaction of these enolates with aldehydes affords *anti* aldols, often in excellent diastereomeric excess (equation 103; Table 15).[133] It is believed that the conjugate addition reactions provide (*Z*)-enolates, *via* a cyclic, six-centered transition state.[135] The *anti* stereochemistry observed in the aldol reactions of these (*Z*)-enolates would result from a boat-like, chelated transition state. The transition state has boat-like character to avoid a serious *gauche* interaction between $R^3$ and the bulky secondary alkyl group in the thioamide enolate. Several of the intermediate enolates in this study (*e.g.* Table 15,

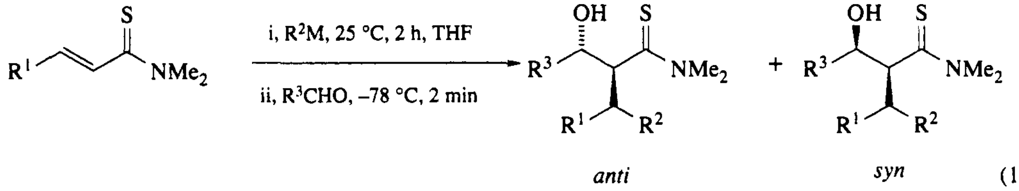

(103)

**Table 15** Aldol Stereochemistry (equation 103)

| *Entry* | *R*$^1$ | *R*$^2$*-Metal* | *R*$^3$ | *Anti:syn*$^a$ |
|---|---|---|---|---|
| 1 | Me | MeMgI | Me | 96:4 |
| 2 | Me | MeLi | Me | 90:10 |
| 3 | Me | MeMgI | $\mathrm{Pr^i}$ | >99:1 |
| 4 | Me | MeMgI | Ph | 94:6 |
| 5 | Me | EtMgBr | Ph | 85:15 |
| 6 | Me | $\mathrm{Bu^nLi}$ | Ph | 87:13 |
| 7 | Me | $\mathrm{Pr^iMgBr}$ | Me | 74:26 |
| 8 | Me | $\mathrm{Pr^iMgBr}$ | $\mathrm{Pr^i}$ | >99:1 |
| 9 | MeCH═CH | MeMgI | $\mathrm{Pr^i}$ | >99:1 |
| 12 | MeCH═CH | $\mathrm{Pr^iMgBr}$ | Me | 89:11 |
| 13 | MeCH═CH | $\mathrm{Pr^iMgBr}$ | $\mathrm{Pr^i}$ | >99:1 |
| 14 | Ph | $\mathrm{Pr^iMgBr}$ | Me | 82:18 |

[a] Combined isolated yields = 70–88%.

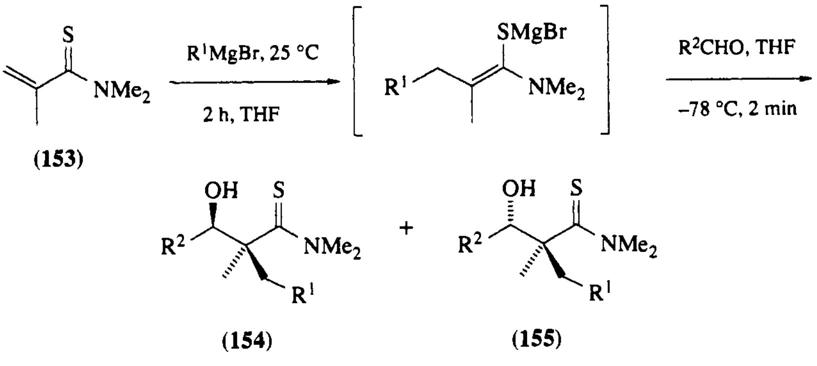

(153)

(154)

(155)

(104)

**Table 16** Aldol Stereochemistry (equation 104)

| *Entry* | *R*$^1$ | *R*$^2$ | *Temperature* (°C) | *Time* (min) | *(154):(155)* | *Yield* (%) |
|---|---|---|---|---|---|---|
| 1 | Et | Me | –78 | 2 | >99:1 | 85 |
| 2 | Et | $\mathrm{Pr^i}$ | –78 | 2 | >99:1 | 86 |
| 3 | $\mathrm{Pr^i}$ | Me | –78 | 2 | >99:1 | 95 |
| 4 | $\mathrm{Pr^i}$ | Et | –78 | 2 | >99:1 | 86 |
| 5 | Ph | Me | –78 | 2 | >99:1 | 24 |
| 6 | Ph | MeCH═CH | –78 | 2 | >99:1 | 25 |
| 7 | Ph | PhCH═CH | –78 | 2 | >99:1 | 48 |
| 8 | Et | Ph | –78 | 2 | 41:59 | 80 |
| 9 | Et | Ph | +25 | 1080 | 8:92 | 80 |
| 10 | $\mathrm{Pr^i}$ | Ph | –78 | 2 | 33:67 | 83 |
| 11 | Ph | Ph | –78 | 2 | 17:83 | 81 |

entries 5–8, 12–14) are chiral. However, no information pertaining to the diastereofacial selectivity, if any, has been provided.

Conjugate addition to thioamide (**153**) gives tetrasubstituted enolates, presumably having the (*Z*)-configuration.[30] Reaction of these enolates with aliphatic aldehydes gives aldols of high stereochemical purity (equation 104; Table 16).[136] This is a relatively uncommon example of a stereoselective aldol reaction involving a tetrasubstituted enolate. Note that the use of benzaldehyde as the electrophile leads to stereochemical reversal, which is strongest under conditions of thermodynamic control (Table 16, entries 8–11).

## 1.6.4 DIASTEREOFACIAL SELECTIVITY

In this section are treated aldol reactions of preformed lithium and magnesium enolates in which one or both of the reaction partners are chiral.

### 1.6.4.1 Chiral Substrates

The two faces of a chiral aldehyde are diastereotopic, and reaction with an achiral enolate can therefore give two diastereomeric products. Qualitatively, the major and minor products of such a reaction are determined by the intrinsic diastereofacial preference of the chiral aldehyde, which may be evaluated by the use of Cram's rule or one of its more modern derivatives.[137] Quantitatively, the diastereomeric ratio in such a reaction is a function of the enolate. An example is seen in Scheme 8. 2-Phenylpropanal reacts with the lithium enolates of acetone, pinacolone, methyl acetate and *N*,*N*-dimethylacetamide to give 3,4-*syn* and 3,4-*anti* diastereomers in ratios of 3:1 to 4:1.[138] With ethyl ketones and propionate esters, the diastereofacial ratio is approximately 6:1,[9c] and with methyl isobutyrate only a single isomeric product is produced.[139] This tendency of more bulky nucleophiles to give higher diastereofacial ratios in reactions

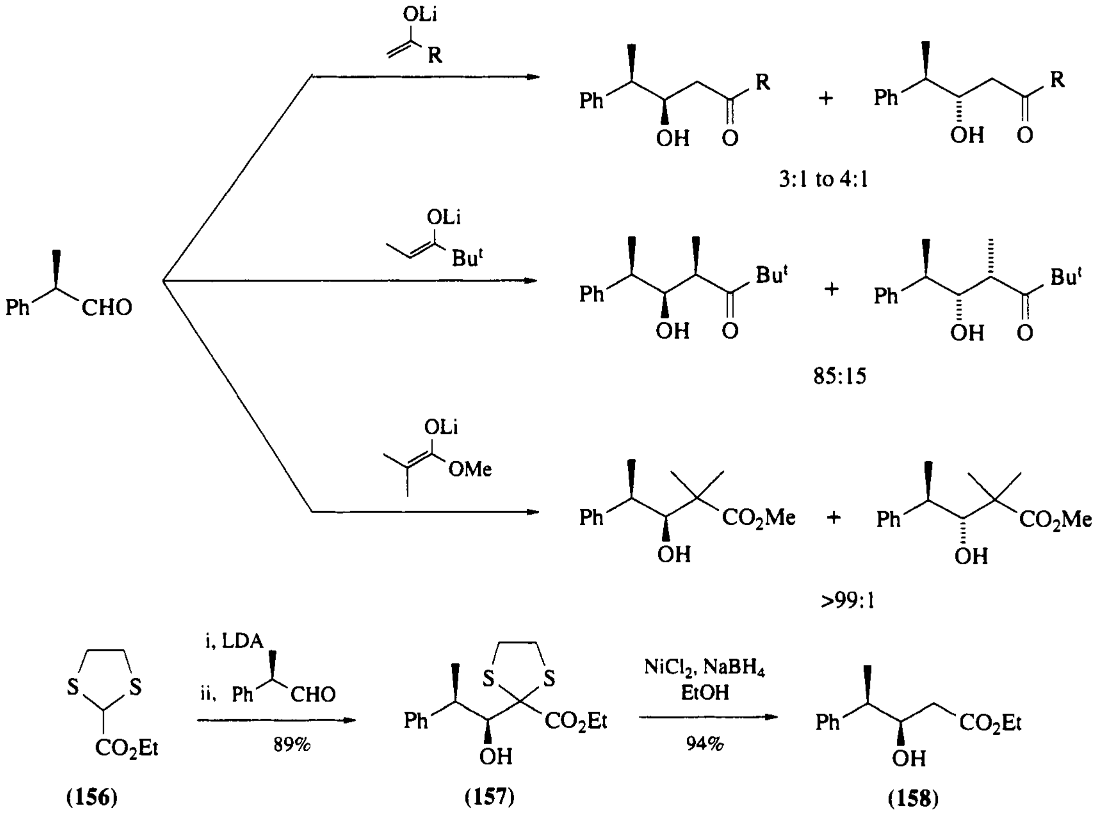

**Scheme 8**

with chiral aldehydes has been exploited as shown in Scheme 8; addition of the enolate of ester (**156**) to 2-phenylpropanal gives a single adduct (**157**), which is desulfurized to obtain β-hydroxy ester (**158**).[140]

Data for the addition of the lithium enolate of pinacolone to a variety of α-chiral aldehydes are presented in equation (105) and Table 17.[141] The results in the table show that the diastereofacial preference of a chiral aldehyde is a function of the steric bulk and the electronic nature of the groups attached to the stereocenter. In a purely empirical manner, the major isomer may be correctly predicted by the

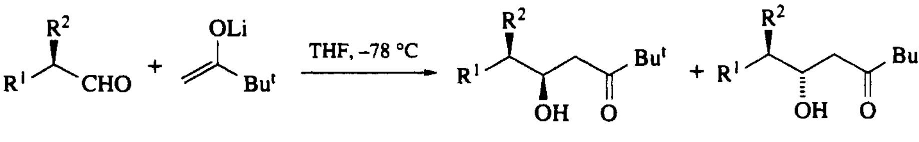
R$^2$
R$^1$
CHO
OLi
Bu$^t$
THF, –78 °C
R$^2$
R$^1$
Bu$^t$
OH
O
R$^2$
R$^1$
Bu$^t$
OH
O

**(159)** **(160)** (105)

**Table 17** Aldol Stereochemistry (equation 105)

| *Entry* | *R*$^1$ | *R*$^2$ | *(159):(160)*$^a$ |
|---|---|---|---|
| 1 | Ph | Me | 78:22 |
| 2 | Ph | Et | 86:14 |
| 3 | Ph | Pr$^i$ | 70:30 |
| 4 | Ph | Bu$^t$ | 37:63 |
| 5 | Ph | OMe | 17:83 |
| 6 | Me | OMe | 42:58 |
| 7 | Et | OMe | 24:76 |
| 8 | Pr$^i$ | OMe | 8:92 |
| 9 | Bu$^t$ | OMe | 7:93 |

$^a$Each ratio is the average of three independent determinations.

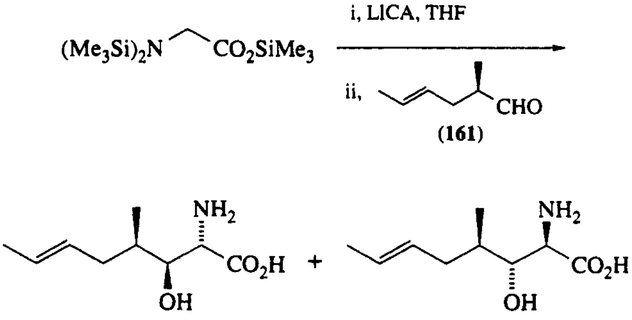
(Me$_3$Si)$_2$N
CO$_2$SiMe$_3$
i, LICA, THF
ii,
CHO
NH$_2$
CO$_2$H
OH
NH$_2$
CO$_2$H
OH

**(161)**

3:1 (106)

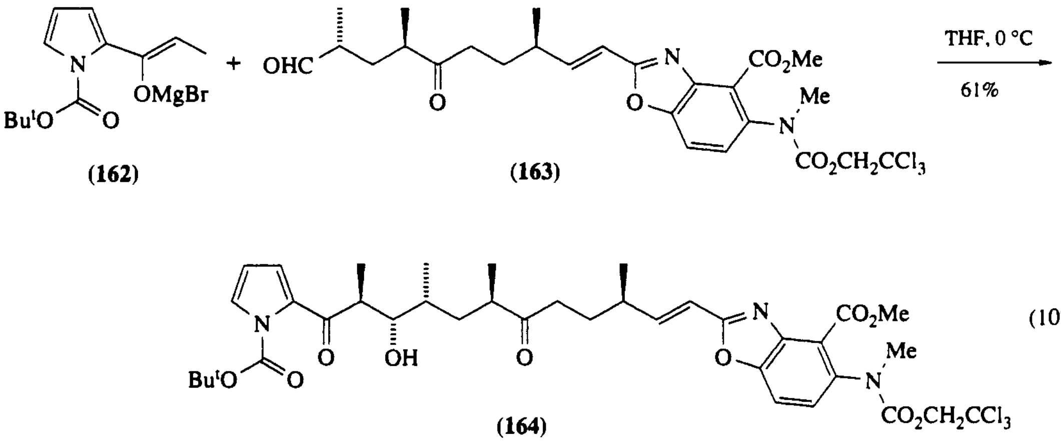
N
Bu$^t$O
O
OMgBr
OHC
O
N
O
CO$_2$Me
Me
N
CO$_2$CH$_2$CCl$_3$
THF, 0 °C
61%
N
Bu$^t$O
O
O
OH
O
N
O
CO$_2$Me
Me
N
CO$_2$CH$_2$CCl$_3$

**(162)** **(163)**

**(164)** (107)

Felkin model for asymmetric induction if one uses the order of ligand preferences for the *anti* position: MeO > Bu$^t$ > Ph > Pr$^i$ > Et > Me > H. Note that the major isomers produced in reactions of the α-methoxy aldehydes (Table 17, entries 5–9) are not those expected from a chelation-controlled process.

It is often necessary in a synthetic project to carry out an aldol addition on a chiral aldehyde in which the α-ligands are hydrogen, methyl and an alkyl group. In the synthesis of MeBMT, the characteristic amino acid of the antibiotic cyclosporin, the lithium enolate of *N,N,O*-tris(trimethylsilyl)glycine is added to aldehyde (**161**) to give, after deprotection, two hydroxy amino acids in a ratio of 3:1 (equation 106).[142] One step in a total synthesis of the polyether antibiotic A23187 (calcimycin) is the aldol reaction of the magnesium enolate (**162**) with aldehyde (**163**); β-hydroxy ketone (**164**) is obtained in 61% yield, along with 16% of a stereoisomer (equation 107).[143] For other examples of such reactions, see equations (50) and (51), (69), (73) and (78) and (79).

Reagent (**27**) has been used in a synthesis of the C-1,C-7 segment of erythronolide A, as shown in equation (108).[144] Addition of the lithium enolate of (**27**) to chiral aldehyde (**165**) provides aldols (**166**) and (**167**) in a ratio of approximately 6:1. [The initial report that this aldol reaction gives a stereoisomer ratio of approximately 15:1 was subsequently found to be in error (ref. 144b).]

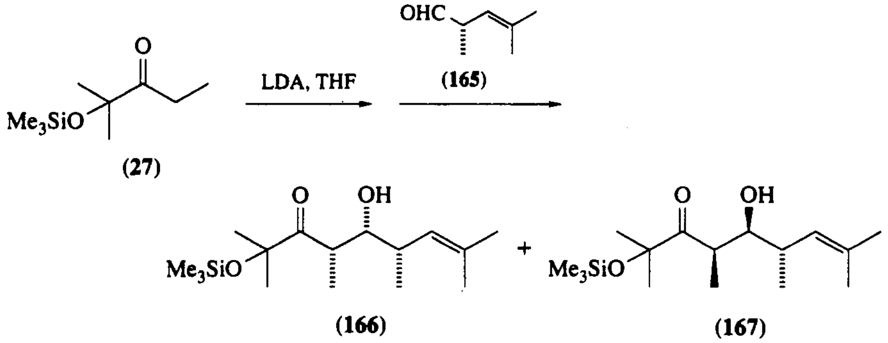

(108)

The major and minor products obtained in aldol reactions of chiral aldehyde (**168**; equation 109) are not those predicted by Cram's rule, presumably because the lithium cation is chelated by the alkoxy and aldehyde oxygens, leading to a rigid six-membered intermediate that undergoes attack primarily from its unsubstituted face.[68] Similar behavior, with somewhat higher diastereofacial selectivity (5:1), is seen with the magnesium enolate (equation 50).

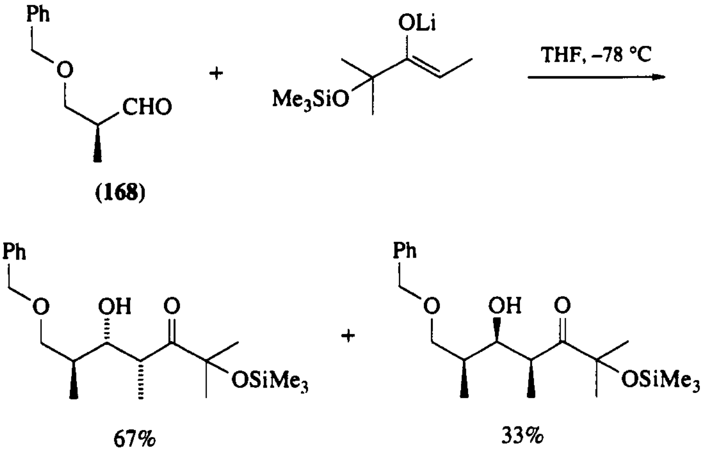

(109)

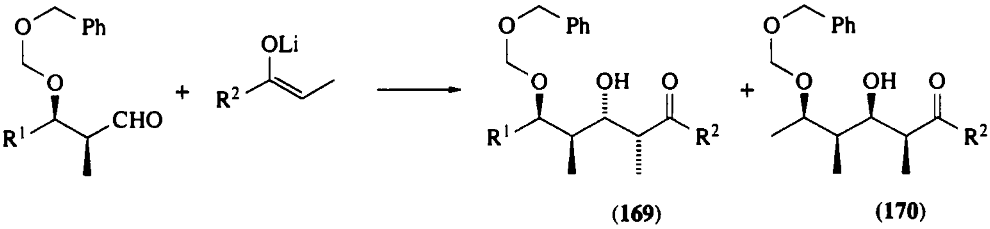

(110)

**Table 18** Aldol Stereochemistry (equation 110)

| $R^1$ | $R^2$ | (169):(170) | Yield (%) |
|---|---|---|---|
| H | Et | 80:20 | 87 |
| H | Cy[a] | 78:22 | 79 |
| Et | Et | 83:17 | 81 |
| Et | Cy | 90:10 | 79 |
| $PhCD_2$ | Et | 85:15 | 71 |
| $PhCD_2$ | Cy | 90:10 | 70 |
| $Pr^i$ | Et | 87:13 | 75 |
| $Pr^i$ | Cy | 92:8 | 68 |
| $Bu^tMe_2SiOCH_2CH_2$ | Et | 93:7 | 82 |
| $Bu^tMe_2SiOCH_2CH_2$ | Cy | 95:5 | 79 |

[a] Cy = cyclohexyl.

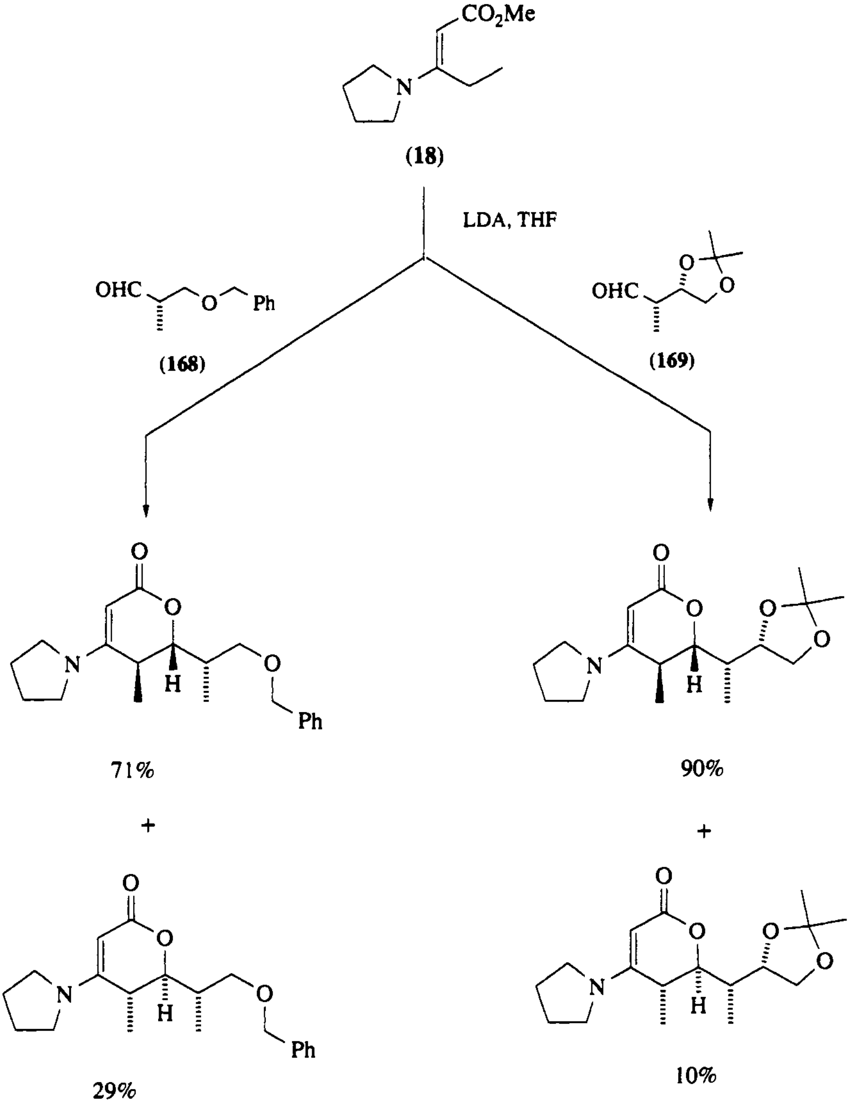
CO2Me
N
(18)
LDA, THF
OHC
O
Ph
(168)
OHC
O
O
(169)
O
O
N
H
O
Ph
71%
+
O
O
N
H
O
Ph
29%
O
O
N
H
O
O
90%
+
O
O
N
H
O
O
10%

**Scheme 9**

Masamune and coworkers have examined the facial selectivity of the (*Z*)-lithium enolates of 3-pentanone and ethyl cyclohexyl ketone with a series of β-alkoxy aldehydes having stereocenters at both the α- and β-position (equation 110; Table 18).[61] In the six-membered chelate, the methyl and $R^1$ groups are on the same side of the ring, and it may be seen from the data in Table 18 that the nature of $R^1$ influences the facial preference of the chiral aldehyde. Another example of this effect is seen in equation (54).

However, such chelation effects are not always observed. For example, in the Woodward erythromycin A synthesis (equation 99), the facial preference of aldehyde (**151**) is that predicted by application of Cram's rule, even though there is an alkoxy group at the β-position. Addition to a chelated carbonyl group in this case would amount to a choice between addition to the convex or concave face of a bicyclo[4.3.0]nonane structure (equation 111).

Other cases in which chelation control is not involved in addition to a chiral β-alkoxy aldehyde are shown in equations (69) and (78); in these cases, it might be argued that the *t*-butyldimethylsilyloxy and triethylsilyloxy groups are not good ligands for steric reasons. Yet other examples are seen in the two reactions summarized in Scheme 9.[46a] Here, the lithium enolate of the vinylogous ester (**18**) adds to aldehyde (**168**) to give predominantly the Cram-predicted isomer; with aldehyde (**169**), the Cram diastereofacial preference is even greater.

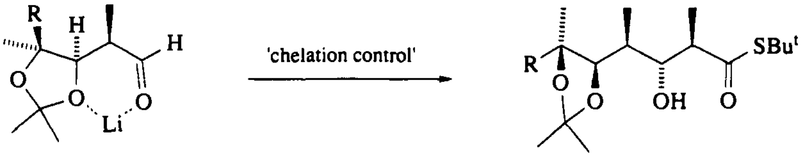

**(151)**

(111)

Additions to chiral aldehydes in which the stereocenter ligands are H, methyl and alkoxy are also relatively common. With lithium enolates, these aldehydes show diastereofacial preferences that suggest that the major product does not involve addition to an intermediate chelate (*vide supra*). However, diastereomer ratios are often rather low. For example, in equation (112) the diastereofacial preference with reagent (**27**) is 65:35,[145] and that with reagent (**33**) is 78:22.[70]

A detailed study has been carried out with the lithium enolates of methyl and *t*-butyl *N*,*N*-dimethylglycinate (equation 113).[146] Selected data from this study are presented in Table 19. The data show that the

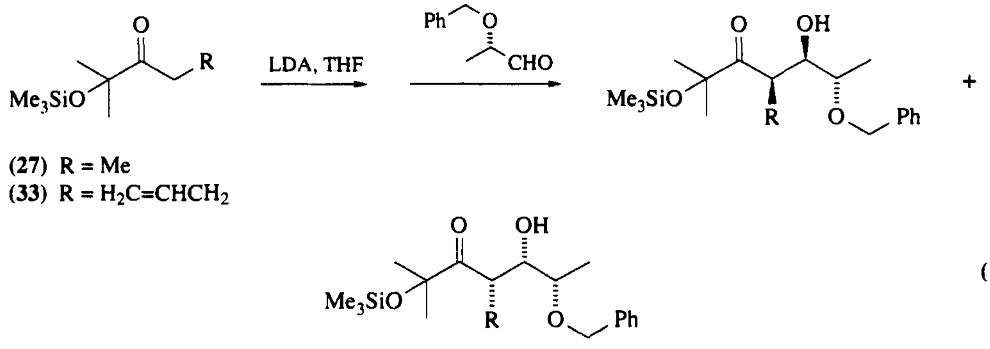

(**27**) R = Me
(**33**) R = $H_2C{=}CHCH_2$

(112)

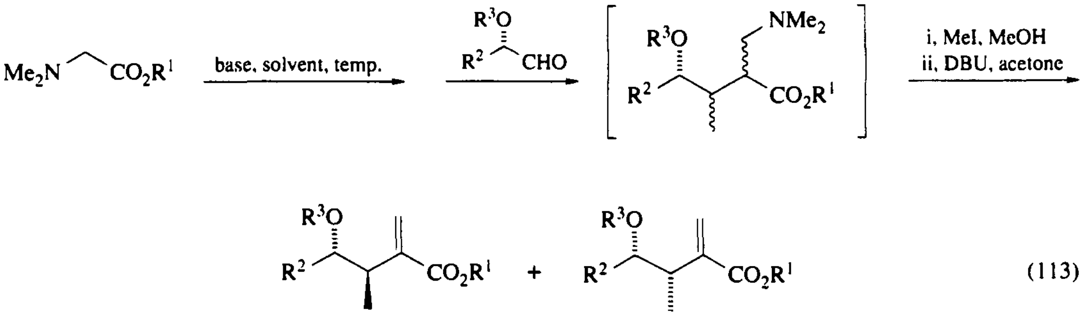

**(170)** **(171)**

(113)

size of $R^1$ has a significant effect, whereas that of $R^2$ or $R^3$ is not very important. The solvent, temperature and period of metallation strongly affect the diastereomer ratio, suggesting that enolate equilibration may be occurring. This was confirmed by trapping the enolate as its *t*-butyldimethylsilyl enol ether. Deprotonation at –78 °C with LDA in THF gives two enolates in a ratio of 67:33, whereas the use of LDA in ether at 0 °C for 4 h leads to a ratio of 14:86.

**Table 19** Aldol Stereochemistry (equation 113)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *Solvent* | *Metallation temperature* (°C)[a] | *Yield* (%) | *Anti:syn* |
|---|---|---|---|---|---|---|---|
| 1 | Me | Me | $PhCH_2OCH_2$ | THF | –78 | 55 | 65:35 |
| 2 | $Bu^t$ | Me | $PhCH_2OCH_2$ | THF | –78 | 68 | 80:20 |
| 3 | Me | Me | $MeOCH_2$ | THF | –78 | 42 | 77:23 |
| 4 | $Bu^t$ | Me | $MeOCH_2$ | THF | –78 | 47 | 83:17 |
| 5 | Me | Me | $MeOCH_2CH_2OCH_2$ | THF | –78 | 52 | 65:35 |
| 6 | $Bu^t$ | n-$C_6H_{13}$ | $PhCH_2OCH_2$ | THF | –78 | 72 | 79:21 |
| 7 | Me | n-$C_6H_{13}$ | $MeOCH_2$ | THF | –78 | 60 | 73:27 |
| 8 | $Bu^t$ | n-$C_6H_{13}$ | $MeOCH_2$ | THF | –78 | 69 | 82:18 |
| 9 | $Bu^t$ | n-$C_6H_{13}$ | $MeOCH_2$ | THF/HMPA | –78 | —[c] | 63:37 |
| 10 | $Bu^t$ | n-$C_6H_{13}$ | Me | THF | –78 | 71 | 80:20 |
| 11 | $Bu^t$ | n-$C_6H_{13}$ | Me | THF | –30 | —[c] | 87:13 |
| 12 | $Bu^t$ | n-$C_6H_{13}$ | Me | THF | 0 | —[c] | 88:12 |
| 13 | $Bu^t$ | n-$C_6H_{13}$ | Me | Ether | –30 | —[c] | 92:8 |
| 14 | $Bu^t$ | n-$C_6H_{13}$ | Me | Ether | 0 | —[c] | 93:7 |
| 15 | $Bu^t$ | n-$C_6H_{13}$ | Me | Ether | 0[b] | —[c] | 96:4 |

[a] Metallation was carried out at the indicated temperature for 1 h, unless otherwise noted. [b] Metallation was carried out for 4 h in this case. [c] Yields were not given for these cases.

Scheme 10 summarizes what appears to be a highly stereoselective addition to an α-methoxy aldehyde.[147] The (*Z*)-lithium enolate (**173**), formed from the enone by reaction with lithium hexamethyldisilazane, reacts with benzaldehyde to give *syn* and *anti* aldols in a ratio of 8:1. Reaction of (**173**) with

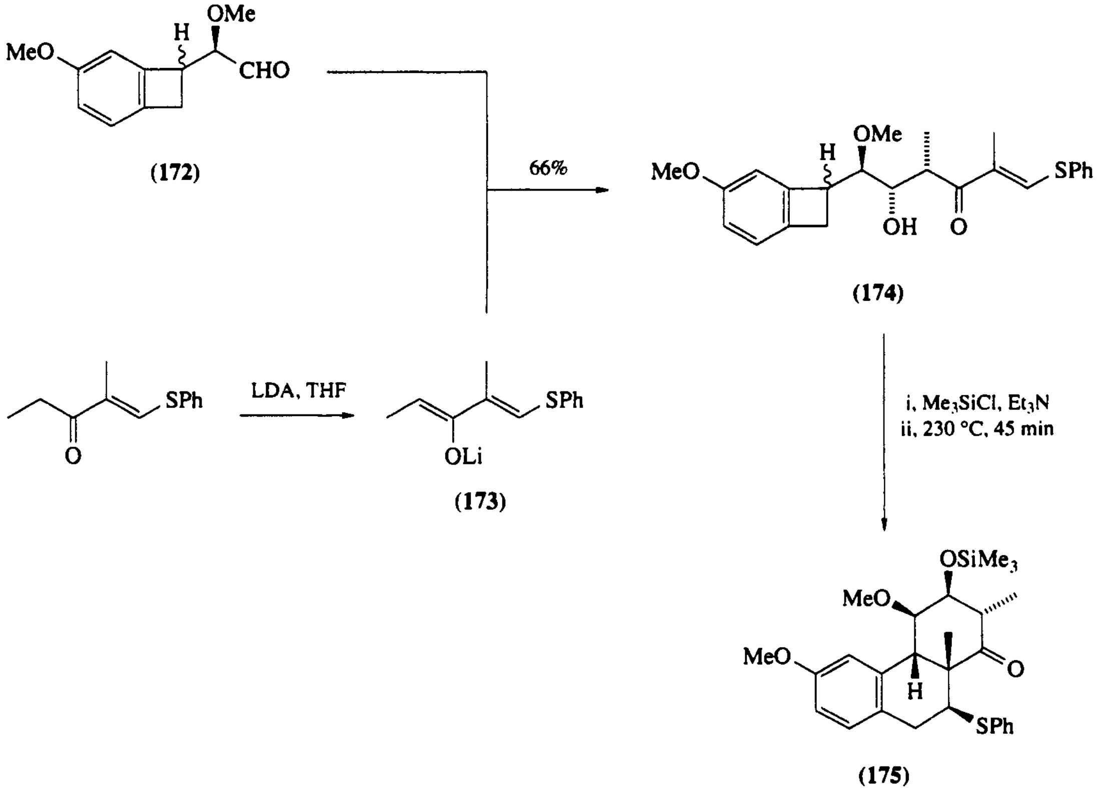

**Scheme 10**

aldehyde (**172**), a diastereomeric mixture, gives diastereomeric aldols (**174**). These isomers must have the same relative stereochemistry at $C_\alpha$, $C_\beta$ and $C_\gamma$ because the intramolecular Diels–Alder reaction that occurs upon heating the trimethylsilyl ethers of (**174**) gives a single product, (**175**).

Much less is known about aldol additions to chiral aldehydes that have heteroatoms other than oxygen at the α-stereocenter. In connection with a synthesis of statine analogs, α-amino aldehyde (**176**) was allowed to react with ethyl lithioacetate to obtain (**177**) and (**178**) in a ratio of 60:40 (equation 114).[148]

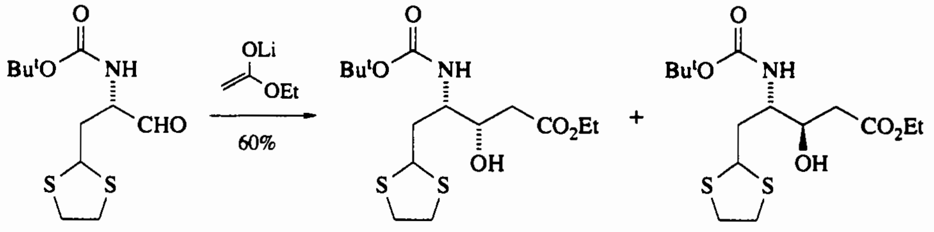

(114)

**(176)** **(177)** **(178)**

### 1.6.4.2 Chiral Enolates

In this section are discussed aldol reactions of achiral aldehydes with chiral enolates. In previous sections, many such examples have already been given for enolates derived from rigid cyclic ketones, lactones and lactams. The emphasis here is on reactions of the enolates of conformationally flexible, achiral ketones, esters and amides.

In one of the first such examples, the lithium enolate of (*S*)-3-methyl-2-pentanone was allowed to react with several aldehydes; in the case of propanal, the two products are formed in 15% diastereomeric excess, favoring (**179**; equation 115).[149] The di-*n*-butylboron enolate of this ketone has been studied and found to give (**179**) and (**180**) in a ratio of 63:37 in $CH_2Cl_2$ and 64:36 in pentane.[150]

In the interest of asymmetric synthesis, there has been a considerable effort to develop chiral ketones, esters and amides that will undergo aldol reactions with high diastereofacial preference. One such reagent is ketone (**181**), available in three steps from (*S*)-*t*-butylglycine.[151] [For a discussion of the use of the racemic version of ketone (**181**) for aldol reactions, see ref. 57d, pp. 181–184.] Aldol reactions of several different enolates of (**181**) have been studied with benzaldehyde (Scheme 11; Table 20).[150c,d] The

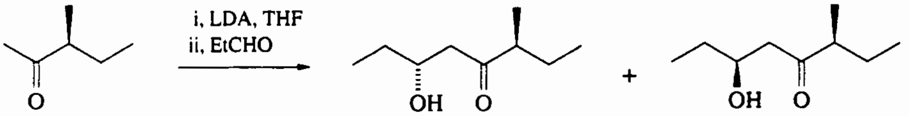

(115)

**(179)** **(180)**

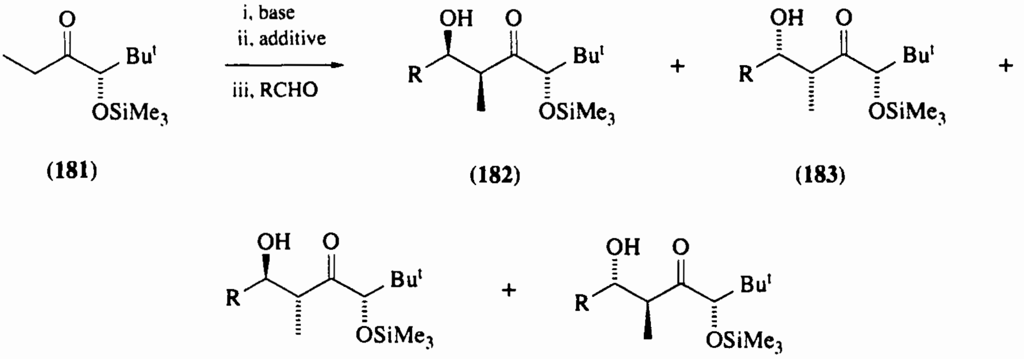

**(181)** **(182)** **(183)**

**(184)** **(185)**

Scheme 11

**Table 20** Aldol Stereochemistry (Scheme 11)

| *Entry* | *Enolization Conditions* | *Enolate (Z):(E)* | *R* | *(182)* | *(183)* | *(184)* | *(185)* | *Yield (%)* |
|---|---|---|---|---|---|---|---|---|
| 1 | LDA, THF, -78 °C | >98:2 | Ph | >95 | <5 | 0 | 0 | 80 |
| 2 | LDA, THF, -78 °C | >98:2 | $Pr^i$ | >95 | <5 | 0 | 0 | 70 |
| 3 | $Bu_2BOTf$, $R_3N$, $CH_2Cl_2$ | >98:2 | Ph | <5 | >95 | 0 | 0 | 85 |
| 4 | $Bu_2BOTf$, $R_3N$, $CH_2Cl_2$ | >98:2 | $Pr^i$ | <5 | >95 | 0 | 0 | 70 |
| 5 | $Pr^i_2NMgBr$, THF, -78 °C | <4:96 | Ph | 0 | 0 | 95 | 5 | 80 |
| 6 | $Pr^i_2NMgBr$, THF, -78 °C | <4:96 | Pr | 0 | 0 | 95 | 5 | 75 |
| 7 | i, $Pr^i_2NMgBr$, THF, -78 °C,<br>ii, $(Pr^iO)_3TiCl$, sonicate | <4:96 | Ph | 0 | 0 | 20 | 80 | 80 |
| 8 | i, $Pr^i_2NMgBr$, THF, -78 °C,<br>ii, $(Pr^iO)_3TiCl$, sonicate | <4:96 | Ph | 0 | 0 | <5 | >95 | 80 |

lithium and di-*n*-butylboron enolates both have the (*Z*)-configuration. However, they have opposite diastereofacial preferences because lithium can be coordinated by three oxygens in the aldol transition state, whereas boron cannot. Deprotonation of (**181**) with bromomagnesium diisopropylamide gives the (*E*)-enolate, which has the same diastereofacial preference as the lithium enolate. Finally, treatment of the (*E*)-bromomagnesium enolate with tris(isopropoxy)titanium chloride[152] affords the (*E*)-titanium enolate, which reacts with the same diastereofacial preference as does the (*Z*)-boron enolate, leading predominantly to isomer (**185**). Thus, by appropriate choice of reaction conditions, all four stereoisomeric aldols can be obtained from the same chiral reactant.

A related reagent (**186**) is prepared in three steps from (*S*)-atrolactic acid.[153] The lithium enolate of (**186**) reacts with phenylacetaldehyde to give two aldols in a ratio of 94:6 (Scheme 12). [The full relative stereochemistry of aldols (**187**) and (**188**) was not rigorously determined, but may be deduced from the stereochemistry of (**190**). It is surprising that the lithium enolate of (**186**) has a diastereofacial preference that is *opposite* that of the related ketone (**181**).] Compound (**186**) has been used in a synthesis of the Prelog–Djerassi lactonic acid (**191**), as shown in Scheme 12. Reagents related to (**181**) and (**186**) have been used as their boron enolates for other synthetic purposes (see Chapter 1.7, this volume).

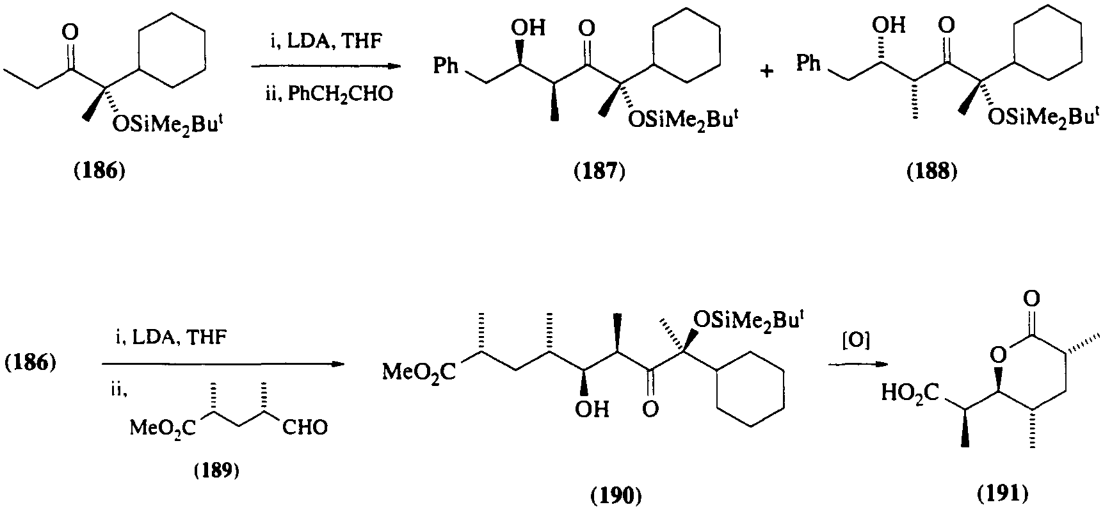

**Scheme 12**

The diastereofacial preferences of keto ethers (**192**) are summarized in equation (116) and Table 21. The (*Z*)-lithium enolate of (**192**), prepared by reaction of the keto ether with lithium hexamethyldisilazane, reacts with isobutyraldehyde to give *syn* aldols (**193**) and (**194**), along with small amounts of an *anti* aldol of undefined stereochemistry (**195**).[154] The results of this investigation demonstrate that the facial preference of a chiral β-hydroxy ketone can be affected to some extent by the hydroxy-protecting group.

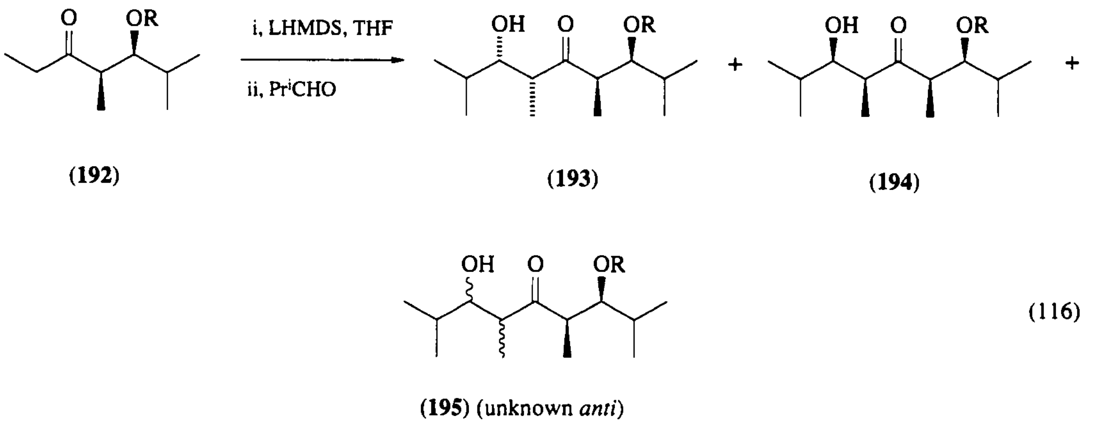

**(192)** **(193)** **(194)**

**(195)** (unknown *anti*)

(116)

**Table 21** Aldol Stereochemistry (equation 116)

| *Entry* | *R* | *(193)* | *(194)* | *(195)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | H | 26 | 54 | 20 | 75 |
| 2 | $PhCH_2$ | 52 | 48 | 0 | 79 |
| 3 | $MeOCH_2CH_2OCH_2$ | 56 | 40 | 4 | 73 |
| 4 | $PhCH_2OCH_2$ | 63 | 31 | 6 | 81 |
| 5 | $Bu^tMe_2Si$ | 76 | 17 | 7 | 85 |
| 6 | $Me_3Si$ | 78 | 13 | 9 | 66 |
| 7 | $Et_3Si$ | 78 | 12 | 10 | 74 |

Although alkylation of β-hydroxy ester dianions occurs with high diastereofacial selectivity, the aldol reaction of the dianion obtained from methyl 3-hydroxybutanoate with benzaldehyde gives all four diastereomeric aldols in a ratio of 43:34:14:9 (equation 117).[155] On the other hand, dianions of δ-hydroxy esters show rather good diastereofacial preferences under the proper conditions. Deprotonation of *t*-butyl-5-hydroxyhexanoate with lithium diethylamide in the presence of lithium triflate gives an enolate that reacts with benzaldehyde to give aldols (**196**) and (**197**) in a ratio of 91:9 (equation 118).[156] Use of the *t*-butyldimethylsilyl ether instead of the alcohol resulted in no facial preference.

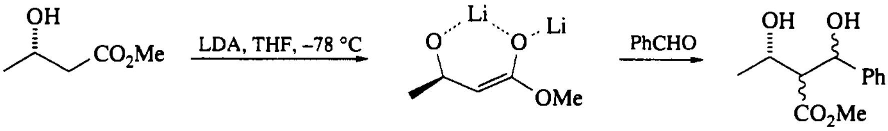

(117)

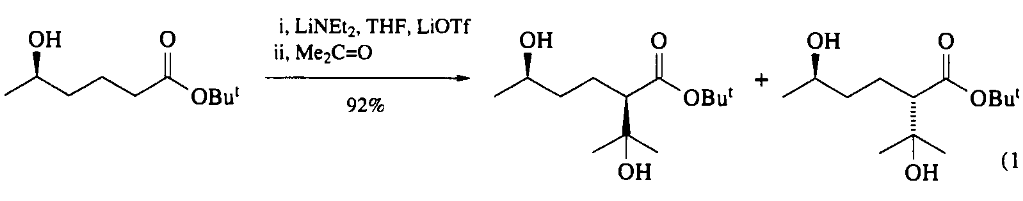

(118)

**(196)** **(197)**

The chiral β-amino thiol ester (**198**) gives a lithium enolate that shows excellent diastereofacial preference in its reactions with α,β-unsaturated and aryl aldehydes (equation 119; Table 22).[154] The stereochemistry of the major isomer (**199**) is consistent with attack of the aldehyde on a relatively rigid enolate chelate.

In an early attempt to achieve useful levels of asymmetric induction in aldol reactions of chiral esters, Solladié and coworkers examined the reaction of menthyl acetate with several aryl ketones in the presence of bromomagnesium diethylamide (equation 120).[157] After hydrolytic removal of the chiral au-

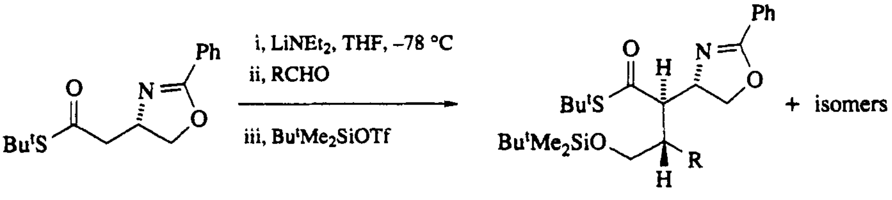

(198) (199)

(119)

**Table 22** Aldol Stereochemistry (equation 119)

| *Entry* | *RCHO* | *Yield (%)* | *(199):(isomers)*[a] |
|---|---|---|---|
| 1 | EtCHO | 70 | 77:(18:5) |
| 2 | $Bu^tMe_2SiOCH_2CH_2CHO$ | 67 | 79:(21) |
| 3 | PhCHO | 89 | >50:(1) |
| 4 | $3,4,5\text{-}(MeO)_3C_6H_2CHO$ | 99 | 87:(13) |
| 5 | $4\text{-}NO_2C_6H_4CHO$ | 92 | 95:(3:1:1) |
| 6 | $CH_2{=}CHCHO$ | 95 | >50:(1) |
| 7 | (*E*)-PhSCH=CHCHO | >40 | 84:(13:3) |
| 8 | (*E*)-$Me_3SiCH{=}CHCHO$ | 91 | 20:(1) |

[a] Ratio of isomer (199) and other detectable isomers.

xiliary and methylation of the resulting β-hydroxy acid, the β-hydroxy esters are obtained in 48–58% enantiomeric excess, favoring enantiomer (**200a**).

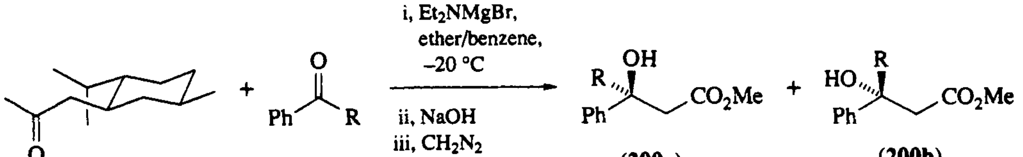

(**200a**) (**200b**)

R = Me, Et, Pr$^i$, Bu$^t$

(120)

A number of ethyl ketones and propionate esters derived from carbohydrates have been investigated in the aldol reaction.[158] None of the compounds studied give useful levels of stereoselection. The most selective compound from this study is ketone (**201**; equation 121); *syn* aldols (**202**) and (**203**) are produced in a ratio of 79:21.

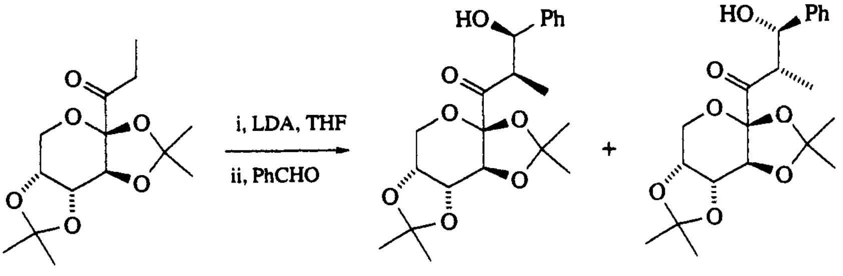

(**201**) (**202**) (**203**)

(121)

Chiral acetate (**204**) shows excellent diastereofacial selectivity and has obvious utility as a reagent for asymmetric aldol reactions.[159] As shown in equation (122), reaction of (**204**) with benzaldehyde provides diastereomers (**205**) and (**206**). As shown in Table 23, entry 1, the diastereoselectivity is 83% if the lithium enolate is formed in the conventional manner and the aldol reaction is carried out in THF at –78 °C. A significant improvement is obtained by using the magnesium enolate (Table 23, entry 5), and diastereoselectivity of up to 98% is obtained by the use of very low reaction temperatures (Table 23, entries 10–13).

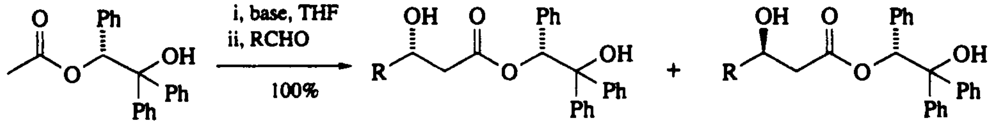

(122)

**(204)** **(205)** **(206)**

**Table 23** Aldol Stereochemistry (equation 122)

| *Entry* | *Temperature* (°C) | *Solvent* | *Base* | *Additive* | *(205):(206)* |
|---|---|---|---|---|---|
| 1 | -78 | THF | LDA | None | 83:17 |
| 2 | -78 | THF | $Me_3SiCH_2K$ | None | 59:41 |
| 3 | 0 | THF | LDA | $ZnCl_2$ | 60:40 |
| 4 | -78 | THF | LDA | $(Pr^iO)_3TiCl$ | 85:15 |
| 5 | -78 | THF | LDA | $MgBr_2$ | 88:12 |
| 6 | -78 | DME | LDA | $MgBr_2$ | 84:16 |
| 7 | -78 | Ether | LDA | $MgBr_2$ | 59:41 |
| 8 | -150 | 2-MeTHF | LDA | $MgBr_2$ | 55:45 |
| 9 | -78 | THF | $Pr^i_2NMgBr$ | None | 60:40 |
| 10 | -135 | THF/$Me_2O$ | LDA | $MgCl_2$ | 94:6 |
| 11 | -135 | THF/$Me_2O$ | LDA | $MgCl_2$ | 96:4 |
| 12 | -130 | THF/2-methylbutane | LDA | $MgBr_2$ | 97:3 |
| 13 | -135 | THF/$Me_2O$ | LDA | $MgI_2$ | 98:2 |

One of the virtues of the Braun reagent is that both enantiomers are available, since the chiral diol is made by reaction of phenylmagnesium bromide with (*R*)- or (*S*)-methylmandelate. An application of the (*S*)-enantiomer is shown in equation (123).[160] The initial aldol reaction was carried out with the magnesium enolate in THF at -78 °C to give the diastereomeric aldols in a ratio of 97:3. Transesterification with methanol gives β-hydroxy ester (**207**) in 94% enantiomeric excess.

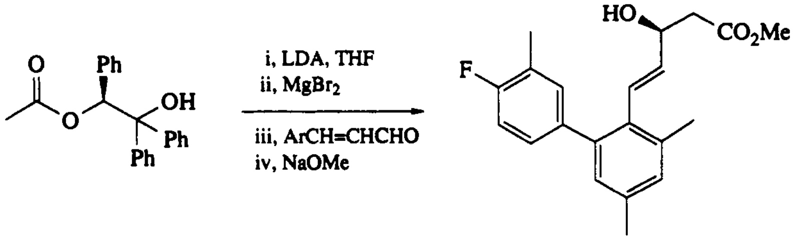

(123)

**(207)**

Aldol reactions of the lithium enolates of chiral α-alkoxy esters have also been studied. Ester (**208**) reacts with acetone to give diastereomers (**209**) and (**210**) in a ratio of 85:15 in THF at -120 °C (equation 124); the ratio is only 64:36 in THF at -78 °C.[161] Even higher facial selectivity is obtained with the mesityl analog of (**208**); the lithium enolate of this ester reacts with acetone in THF at -120 °C to give the aldols corresponding to (**209**) and (**210**) in a ratio of 94:6. The Seebach and Pearson methods to accomplish this same goal have already been discussed (*vide supra*, Schemes 6 and 7).

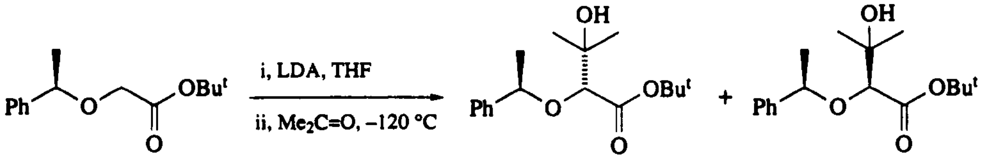

(124)

**(208)** **(209)** **(210)**

Solladié has introduced α-sulfinyl acetates as reagents for asymmetric aldol reactions.[162] Compound (**211**) is prepared in good optical purity from the menthyl ester of *p*-tolylsulfinic acid. The magnesium enolate of (**211**), prepared by reaction of the sulfinyl ester with *t*-butylmagnesium bromide, reacts with aldehydes and ketones to give diastereomeric mixtures of α-sulfinyl-β-hydroxy esters (Scheme 13). No condensation results if *t*-butyllithium or sodium hydride is used as the base for formation of the enolate ion. Reductive removal of the chiral auxiliary provides the corresponding β-hydroxy esters (**213a**) and (**213b**): data are summarized in Table 24. The diastereofacial selectivity is excellent with aldehydes and with some ketones. The full stereochemistry of the intermediate α-sulfinyl-β-hydroxy ester was found to be as shown in (**212**) for the reaction with benzaldehyde. A transition state (**214**) in which the magnesium cation is chelated by three oxygens was invoked to explain the observed facial and simple stereoselectivity. Several applications of the Solladié reagent in synthesis have been reported.[163,164]

Attempts to extend this methodology to α-sulfinyl derivatives of other esters have been only moderately successful.[165] As shown in Scheme 14, ester (**215**) may be deprotonated by *t*-butylmagnesium bromide and added to aldehydes, although not to ketones. The intermediate β-hydroxy-α-sulfinyl esters, in each case a mixture of diastereomers, are reduced to obtain diastereomeric mixtures of β-hydroxy esters. The diastereomeric ratio of these materials does not reveal the degree of asymmetric induction in the original aldol reactions, because of the unknown stereochemistry of the desulfurization step. Aldols (**216**) were converted by a three-step process into secondary alcohols (**217**), which were found to have isomeric purities of 33.5% enantiomeric excess for R = Ph and 80% enantiomeric excess for R = *n*-heptyl.

The Solladié method has been extended to *N*,*N*-dimethylacetamide derivatives with good success (equation 125; Table 25).[166,167] The lithium enolate of (**218**) gives low overall stereoselectivity (Table

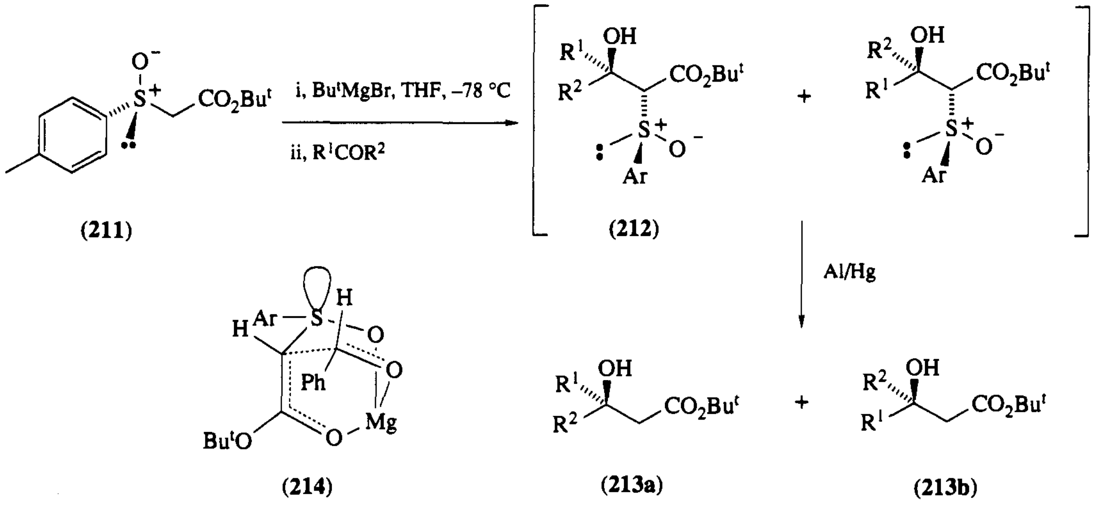

Scheme 13

Table 24 Aldol Stereochemistry (Scheme 13)

| *Entry* | *R*$^1$ | *R*$^2$ | *Yield* (%) | *(213a):(213b)* |
|---|---|---|---|---|
| 1 | Ph | H | 85 | 95:5 |
| 2 | Ph | Me | 75 | 84:16 |
| 3 | Ph | $CF_3$ | 75 | 64:40 |
| 4 | n-$C_7H_{15}$ | H | 80 | 93:7 |
| 5 | $Pr^nCH{=}CH$ | H | 65 | 85:15 |
| 6 | n-$C_{11}H_{23}$ | H | 74 | 90:10 |
| 7 | n-$C_8H_{17}$ | H | 80 | 92:8 |
| 8 | c-$C_6H_{11}$ | Me | 88 | 98:2 |
| 9 | $CO_2Et$ | Me | 80 | 54:46 |
| 10 | $CH(OMe)_2$ | Me | 80 | 55:45 |
| 11 | $CH_2CH(OMe)_2$ | Me | 57 | 54:46 |
| 12 | $CH_2CH_2OAc$ | Me | 90 | (70:30) |
| 13 | $CH_2CH_2CO_2Me$ | Me | 63 | 75:25 |
| 14 | $CH_2CH_2CH_2CO_2Me$ | H | 76 | 80:20 |
| 15 | $CH_2NMe_2$ | Me | 0 | — |
| 16 | $PhC{\equiv}C$ | H | 75 | >95:5 |
| 17 | $Pr^nC{\equiv}C$ | H | 73 | 95:5 |
| 18 | n-$C_6H_{13}C{\equiv}C$ | H | 53 | 95:5 |
| 19 | $Bu^tC{\equiv}C$ | H | 64 | 92:8 |

25, entries 1–9). The stereoisomer ratios observed seem to be kinetic, rather than thermodynamic, since the same yield and enantiomeric excess are observed at reaction times of 3 or 60 min (Table 25, entries 3 and 4). Stereoselectivity decreases as the size of R$^2$ increases (entries 1, 2, 3 and 6). Addition of HMPA has a deleterious effect on stereoselectivity. The magnesium enolate shows excellent diastereoselectivity. Again, stereoselectivity diminishes as the size of R$^2$ increases (Table 25, entries 10, 11, 14 and 16) and HMPA has a detrimental effect (entry 18). The analogous thioamide was prepared and studied, but it appears to offer no advantage over the oxoamide.[168]

Schneider and Simon prepared the α-sulfinyl ketones (**220**) and studied their aldol reactions with several aldehydes (equation 126).[169] In seven cases examined, the chiral secondary alcohols (**221**) were obtained in reasonable overall yield (40–67%), but with only modest stereoselectivity (54–78% *ee*).

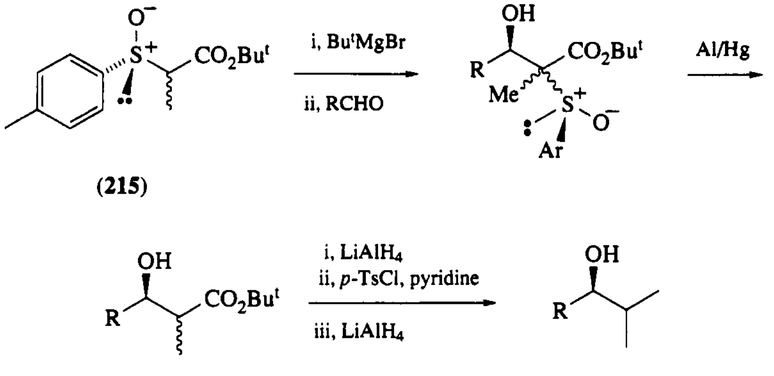

**(215)** **(216)** **(217)**

R = Ph, n-C$_7$H$_{15}$

**Scheme 14**

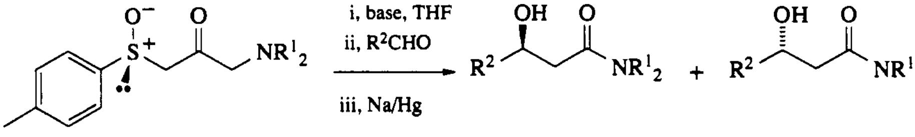 (125)

**(218)** **(219a)** **(219b)**

**Table 25** Aldol Stereochemistry (equation 125)

| *Entry* | *R*$^1$ | *Base, mol equiv.* | *Reaction Time* (min) | *R*$^2$ | *Yield* (%) | *(219a):(219b)* |
|---|---|---|---|---|---|---|
| 1 | Me | Bu$^n$Li, 1.1 | 3 | Me | 65 | 74:26 |
| 2 | Me | Bu$^n$Li, 1.1 | 3 | Bu$^i$ | 77 | 73:27 |
| 3 | Me | Bu$^n$Li, 1.1 | 3 | Pr$^i$ | 77 | 67:33 |
| 4 | Me | Bu$^n$Li, 1.1 | 60 | Pr$^i$ | 78 | 66:34 |
| 5 | Me | Bu$^n$Li, 2.0 | 3 | Pr$^i$ | 40 | 59:41 |
| 6 | Me | Bu$^n$Li, 1.1 | 3 | Bu$^t$ | 20 | 54:26 |
| 7 | Me | Bu$^n$Li, 1.1 | 3 | Pr$^i$ | 78 | 60:40[a] |
| 8 | Me | Bu$^n$Li, 0.55 | 60 | Pr$^i$ | 74 | 64:36 |
| 9 | Me | LDA, 1.1 | 60 | Pr$^i$ | 70 | 67:33 |
| 10 | Me | Bu$^t$MgBr, 0.55 | 60 | Me | 68 | >99:1 |
| 11 | Me | Bu$^t$MgBr, 0.55 | 60 | Bu$^i$ | 71 | 99:1 |
| 12 | Me | Bu$^t$MgBr, 1.1 | 3 | Bu$^i$ | 73 | 95:5 |
| 13 | Me | Bu$^t$MgBr, 0.55 | 3 | Pr$^i$ | 62 | 93:7 |
| 14 | Me | Bu$^t$MgBr, 0.55 | 60 | Pr$^i$ | 66 | 98:2 |
| 15 | Me | Bu$^t$MgBr, 1.1 | 3 | Pr$^i$ | 63 | 85:15 |
| 16 | Me | Bu$^t$MgBr, 0.55 | 60 | Bu$^t$ | 56 | 95:5 |
| 17 | Me | Bu$^t$MgBr, 0.1 | 60 | Pr$^i$ | 31 | 64:40 |
| 18 | Me | Bu$^t$MgBr, 0.55 | 60 | Pr$^i$ | 31 | 76:24[a] |

[a] In the presence of 3 mol equiv. of HMPA.

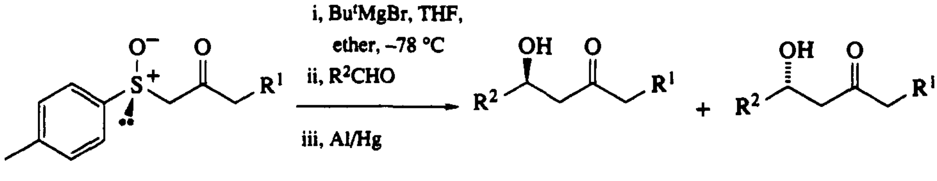
i, Bu$^t$MgBr, THF, ether, –78 °C
ii, R$^2$CHO
iii, Al/Hg

(126)

**(220)** **(221a)** **(221b)**

R$^1$ = H, Me; R$^2$ = Et, c-$C_6H_{11}$, Ph, $PhCH_2CH_2$

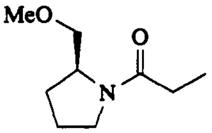

**(222)**

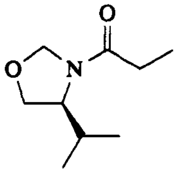

**(223)**

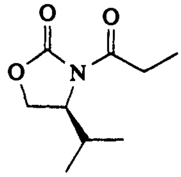

**(224)**

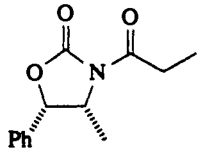

**(225)**

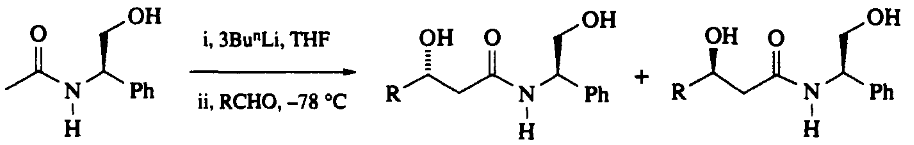
i, 3Bu$^n$Li, THF
ii, RCHO, –78 °C

(127)

**(226)** **(227)** **(228)**

**Table 26** Aldol Stereochemistry (equation 127)

| *Entry* | *R* | *Yield (%)* | *(227):(228)* | *Yield (%)*[a] |
|---|---|---|---|---|
| 1 | Ph | 96 | 80:20 | 43 |
| 2 | Bu$^t$ | 98 | 85:15 | 35 |
| 3 | Pr$^i$ | 82 | 77:23 | 24 |
| 4 | Pr$^n$ | 93 | 78:22 | 25 |

[a] Yield of pure (227) after recrystallization.

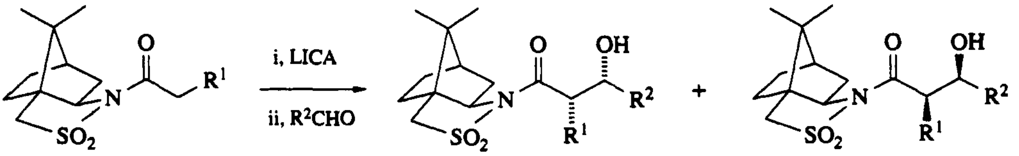
i, LICA
ii, R$^2$CHO

(128)

**(229)** **(230)** **(231)**

**Table 27** Aldol Stereochemistry (equation 128)

| *Entry* | *R*$^1$ | *R*$^2$ | *(230):(231):other* | *Major product*[a] *Yield (%)* | *de (%)* |
|---|---|---|---|---|---|
| 1 | Me | Ph | 8:85:(7) | 72 | >99 |
| 2 | Me | Pr$^i$ | 6:86:(8) | 70 | >95 |
| 3 | Et | Ph | 9:88:(3) | 51 | >95 |
| 4 | Me | Bu$^t$ | 7:88:(5) | 51 | >95 |

[a] Yield and purity of (231) after recrystallization or chromatography.

Chiral amides (**222**) and (**223**) and imides (**224**) and (**225**) have also been studied as reagents for asymmetric aldol reactions. These reagents show excellent diastereofacial preferences as their boron and zirconium enolates, but generally show poor selectivity as their lithium enolates. The reader is referred to other chapters in this volume for a discussion of these and related reagents.

The lithium enolate of amide (**226**) shows reasonable diastereofacial selectivity in its reactions with several aldehydes (equation 127; Table 26).[170] The hydroxymethyl group is important, as *N*-acetylphenethylamine has almost no diastereofacial preference.[171]

One of the more useful chiral auxiliaries that has been developed is illustrated in equation (128).[172] The lithium enolates of imides (**229**) react with aldehydes to give mainly the *syn* diastereomer (**230**), along with (**231**) and an *anti* isomer (Table 27). After purification, the major *syn* isomer is obtained in good yield and in good stereochemical purity. The results shown in Table 27 nicely complement the results obtained using the boron enolate. In this case, no *anti* products are observed and the (**231**):(**230**) ratio is >95:5 in all cases. Thus, acylsultam (**229**), like α-alkoxy ketone (**181**; Scheme 11), has opposite diastereofacial preference as its lithium and boron enolates.

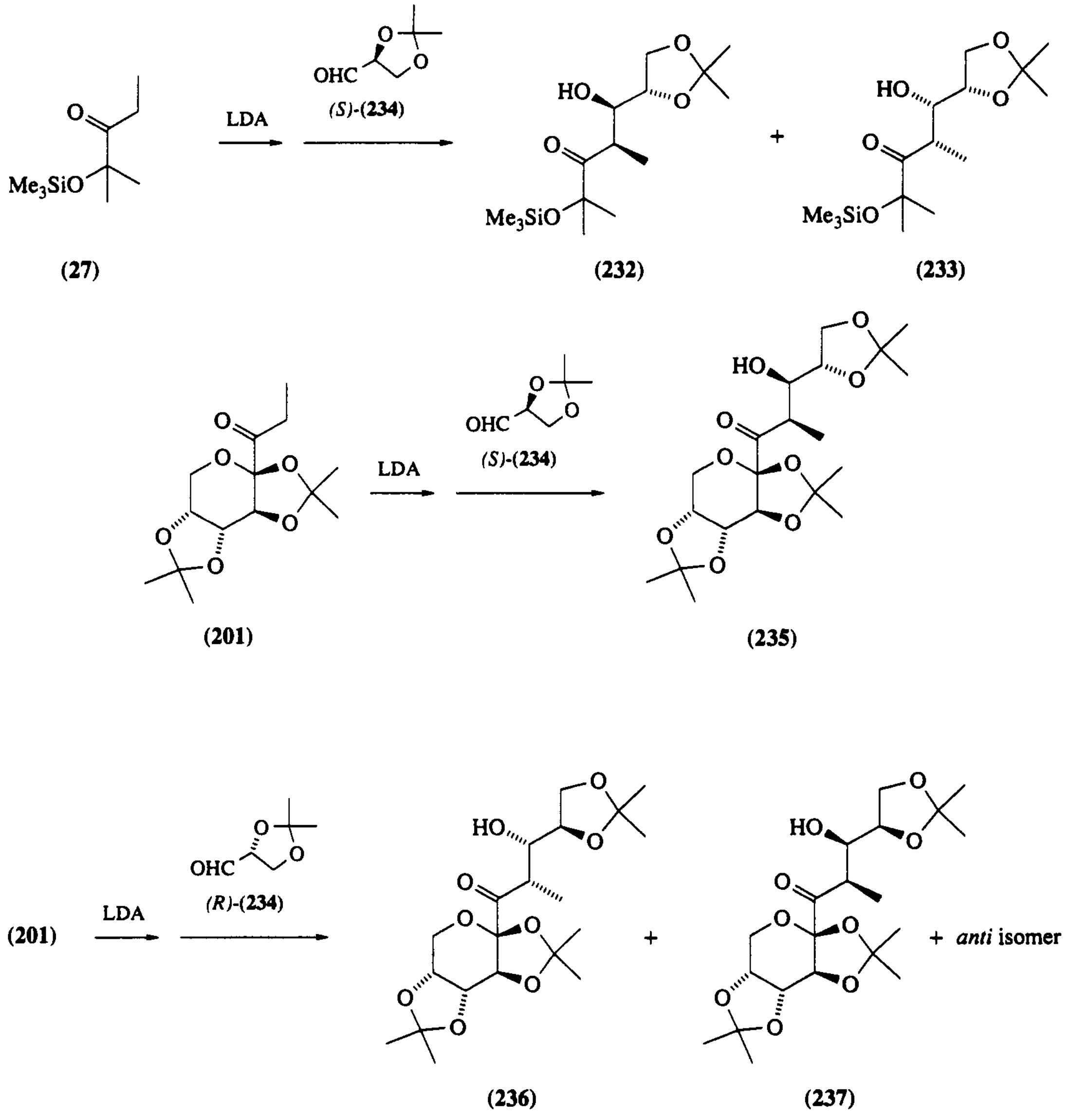

**Scheme 15**

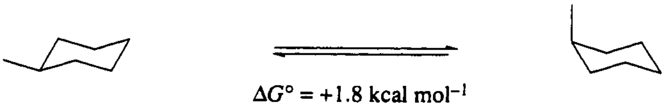

(129)

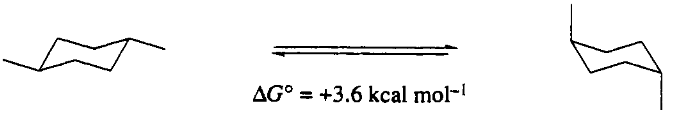

(130)

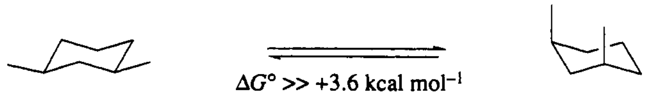

(131)

### 1.6.4.3 Double Diastereoselection

In this section is discussed the phenomenon of double diastereoselection (double asymmetric synthesis). If both partners in a reaction are chiral, each has its own intrinsic diastereofacial preference. New stereocenters that are created in such a process are, therefore, formed under the influence of both chiral reactants.[173–177] To a first approximation, one can think of the effects of the two stereodifferentiating reactants as being additive.[152,157,178] For example, as shown in equation (121) (*vide supra*), chiral ketone (**201**) reacts with benzaldehyde, a representative achiral aldehyde, to give aldols (**202**) and (**203**) in a ratio of 4:1. As shown in Scheme 15, chiral aldehyde (*S*)-(**234**) reacts with achiral ketone (**27**) to give aldols (**232**) and (**233**) in a ratio of 4.3:1. The two double stereodifferentiation experiments are also shown in Scheme 15. Reaction of ketone (**201**) with (*S*)-(**234**) gives a single aldol (**235**), whereas reaction of (**201**) with (*R*)-(**234**) gives *syn* aldols (**236**) and (**237**) and an *anti* aldol in a ratio of 5.5:2.5:1.[157] Similar experiments have been reported by several other workers.[152,169a,179] Double stereodifferentiation experiments such as those illustrated in Scheme 15 have been referred to as 'consonant' and 'dissonant' and as 'matched' and 'mismatched' pairs. If one of the reactants has an exceedingly high diastereofacial preference, it will totally dominate the situation and solely determine the stereochemistry at the new stereocenters.[180]

However, one should not always expect to see additivity in such double stereodifferentiation experiments, as is illustrated by the following logic.[181] For equation (129), $\Delta G^\circ = +1.8$ kcal mol$^{-1}$ (1 cal = 4.18 J); that is, an axial methyl group disfavors the conformation on the right by 1.8 kcal mol$^{-1}$. In equation (130), the effects of two axial methyl groups are additive, and $\Delta G^\circ = 3.6$ kcal mol$^{-1}$. However, in equation (131), the effects of the two axial methyl groups are not additive, and $\Delta G^\circ \gg 3.6$ kcal mol$^{-1}$. Thus, we should expect that there will be cases in which the ideas of 'consonant' and 'dissonant' double stereodifferentiation will break down.[176,182]

### 1.6.4.4 Chiral Auxiliaries

Some of the chiral reagents discussed in earlier sections have proven useful for preparation of enantiomerically pure aldols. From a practical viewpoint, the first level of asymmetric induction is that in which the chiral auxiliary is stoichiometrically consumed in the overall process. An example of this kind of 'first order' asymmetric induction is illustrated in equation (132).[183] Mandelic acid is converted by a three-step procedure into the enantiomerically homogeneous α-silyloxy ketone (**238**). The boron enolate of the latter substance shows excellent diastereofacial preference in reactions with aldehydes, giving aldol (**239**) in high purity (diastereoselectivity = 100:1). Desilylation of (**239**) and periodic acid cleavage of the resulting α,β-dihydroxy ketone provides the corresponding β-hydroxy acid (**240**) and cyclohexanecarbaldehyde. In this process, the chiral auxiliary is mandelic acid and at least 1 mol of this material is expended for each mole of hydroxy acid prepared. Other examples of this kind of 'immolative' process are the Solladié reagent (**211**) and the related amide (**218**) (*vide supra*).

A more efficient process is one in which the chiral auxiliary, although still used stoichiometrically, can be recovered and reused. A notable example of a 'second order' chiral reagent is ester (**204**; equation 122). In this process, methyl mandelate is converted into chiral ester (**204**). After the aldol reaction, the product (**205**) is saponified and the chiral auxiliary may, in principle, be fully recovered and recycled. However, in practice, yields are never quantitative and the overall efficiency of auxiliary recovery is usually of the order of 50%.

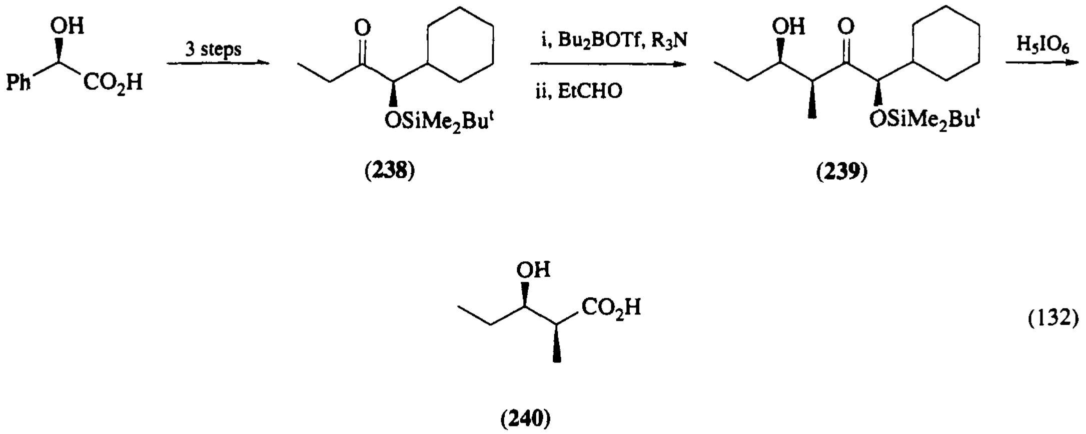

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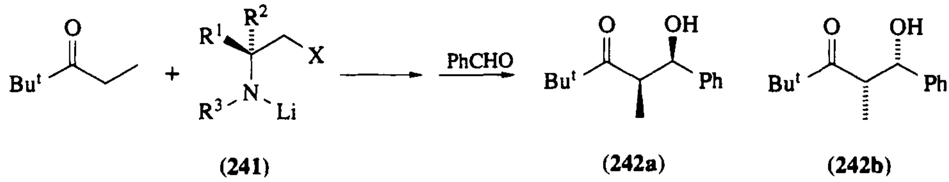

(133)

**Table 28** Aldol Stereochemistry (equation 133)

| *Entry* | *Ketone* | *Reagent ratios* *(241)* | *Bu$^n$Li* | *Pr$^i_2$NH* | *Temp.* (°C) | *Yield* (%) | *(242a):(242b)* |
|---|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.2 | 0.6 | | −10 | 89 | 49:51 |
| 2 | 1.0 | 1.2 | 1.2 | | −10 | 90 | 59:41 |
| 3 | 1.0 | 1.2 | 1.8 | | −10 | 52 | 79:21 |
| 4 | 1.0 | 1.2 | 2.2 | | −10 | 29 | 86:14 |
| 5 | 1.0 | 1.2 | 2.4 | 1.2 | 25 | 92 | 74:26 |
| 6 | 1.0 | 1.2 | 2.4 | 1.2 | −10 | 93 | 84:16 |
| 7 | 1.0 | 1.2 | 2.4 | 1.2 | −40 | 91 | 84:16 |
| 8 | 1.0 | 1.2 | 2.4 | 1.2 | −70 | 88 | 67:33 |

The most efficient kind of asymmetric induction is one in which the chiral auxiliary is used catalytically. An outstanding example of such a process is the Monsanto procedure for enantioselective catalytic hydrogenation of dehydro amino acids.[184] So far, there has been no report of a highly efficient catalytic asymmetric aldol reaction of Group I or Group II enolates. There is one report of good asymmetric induction involving a noncovalently bound chiral auxiliary in an aldol reaction of a tin(II) enolate.[185] However, there is to date only one example of a truly *catalytic* asymmetric aldol addition reaction, the Ito–Hiyashi carbomethoxyisoxazoline synthesis, which proceeds through a gold(I) enolate.[186]

A number of chiral amines, diamines and amino ethers have been investigated, but only low degrees of asymmetric induction have been observed with lithium or magnesium enolates.[187,188] Recently, however, progress has been made.[189] The aldol reaction employed in this study was that between the lithium enolate of ethyl *t*-butyl ketone and benzaldehyde (equation 133); *syn* aldols (**242a**) and (**242b**) are produced in various ratios if the enolate is formed with a lithium amide derived from the chiral secondary amine (**241**). One of these amines ($R^1$ = Pr$^i$, $R^2$ = H, $R^3$ = Me and X = OMe) was utilized to optimize the reaction conditions; results are presented in Table 28. The data reveal a pronounced effect on stereoselectivity of the *amount of base*. Thus, when 1.2 equiv. of base are employed, the aldol yield is excellent, but the product is obtained in only 18% *ee* (Table 28, entry 2). If more base is used, enantioselectivity improves at the expense of yield (entries 3–4). These results suggest that the lithium amide derived from (**241**) is a more effective chiral auxiliary than the amine itself. In fact, if the reaction is carried out with excess *n*-butyllithium, along with a corresponding amount of the achiral diisopropylamine, the yield is excellent and the diastereomeric excess is a very respectable 68% (Table 28, entry 6). It is interesting to observe that the stereoselectivity diminishes, both at higher and lower temperatures (entries 5 and 8).

**Table 29** Aldol Stereochemistry (equation 133)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *X* | *Yield (%)* | *(242a):(242b)* |
|---|---|---|---|---|---|---|
| 1 | Me | H | $Pr^i$ | MeO | 85 | 73:27 |
| 2 | $Pr^i$ | H | Me | MeO | 77 | 53:47 |
| 3 | $Pr^i$ | H | $Pr^i$ | MeO | 93 | 84:16 |
| 4 | $Pr^i$ | H | $Et_2CH$ | MeO | 90 | 68:32 |
| 5 | $Pr^i$ | H | c-$C_6H_{11}$ | MeO | 89 | 79:21 |
| 6 | $Pr^i$ | H | $Bu^tCH_2$ | MeO | 93 | 56:44 |
| 7 | H | Ph | $Pr^i$ | H | 80 | 17:83 |
| 8 | H | Ph | $Pr^i$ | MeO | 92 | 16:84 |
| 9 | H | Ph | $Pr^i$ | $Bu^tO$ | 85 | 23:77 |
| 10 | H | Ph | $Pr^i$ | $Me_2N$ | 87 | 36:64 |
| 11 | H | Ph | $Pr^i$ | $(CH_2)_5N$ | 84 | 35:65 |
| 12 | $PhCH_2$ | H | $Pr^i$ | MeO | 80 | 72:28 |

Using the optimum conditions (Table 28, entry 6), a variety of chiral secondary amines have been investigated. The results are shown in Table 29. The most effective auxiliary for preparation of the enantiomeric aldol (**242b**) is the phenylglycine-derived amine (Table 29, entry 8).

The foregoing results clearly constitute an encouraging lead, and represent the best that has yet been done with chiral auxiliaries for lithium enolate aldol reactions. Although the chiral auxiliary is not covalently attached to either reactant, it is still used stoichiometrically. Furthermore, the process has only been demonstrated with the aldol reaction in equation (133). It will be interesting to see if the efficacy of this method will extend to other enolates and aldehydes.

## 1.6.5 EQUILIBRATION; THERMODYNAMIC CONTROL

The bulk of this chapter has dealt with kinetically controlled aldol addition processes. However, one of the characteristics of aldol reactions involving Group I and Group II enolates is that they are frequently subject to ready reversibility (see Volume 2, Chapter 1.5). Under appropriate conditions, aldol reactions can be carried out under conditions of thermodynamic control. Furthermore, it is usually found that the stereoisomer ratio formed under equilibrating conditions is quite different from the kinetic isomer mixture.

In most cases, aldolate equilibration is to be avoided, since the result is usually to degrade the kinetically established stereoisomer ratio. A good example is seen in the reaction of the lithium enolate of cyclohexanone with benzaldehyde (Scheme 1, *vide supra*). If this reaction is carried out at –50 °C and worked up after 3 s, the diastereomer ratio is 82:18. If the reaction mixture is worked up after 5 min, however, the ratio is only 60:40.

In some cases, however, there is a significant bias in favor of the more stable aldolate. For example, the kinetic product mixture in the reaction of the bromomagnesium enolate of ethyl *t*-butyl ketone and

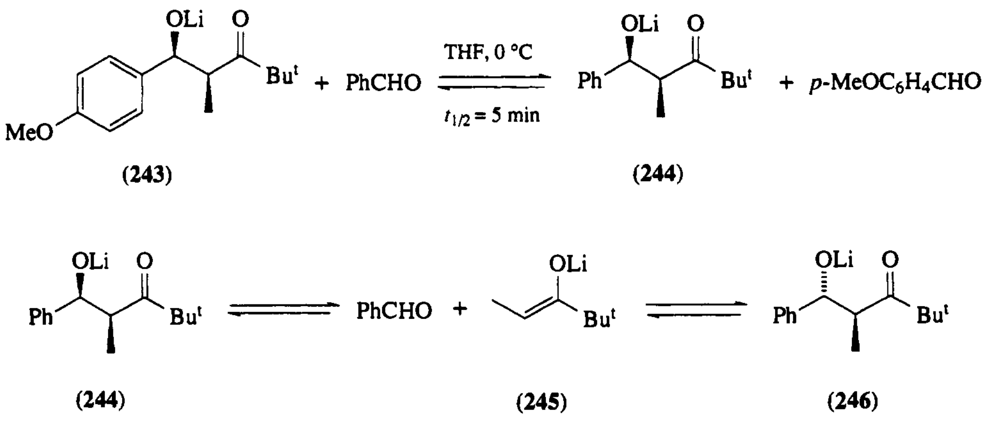

Scheme 16

benzaldehyde is *syn:anti* >95:5 (equation 21, *vide supra*).[34] However, under conditions of thermodynamic control the *anti:syn* ratio is >95:5.

Even when the retroaldol reaction is fairly facile, stereoisomer equilibration can be slow.[9c] This phenomenon is illustrated in Scheme 16. A solution of the lithium aldolate (**243**) and benzaldehyde equilibrates to (**244**) and *p*-anisaldehyde with a half-life of 15 min at 0 °C. However, the *syn* lithium aldolate (**244**) equilibrates with its *anti* diastereomer (**246**) with a half-life of approximately 8 h at room temperature. The reason for this apparent dichotomy is that enolate (**245**) is so stereoselective in its reactions with aldehydes. Since the kinetic *syn:anti* ratio is 98.7:1.3,[9c] the *syn* aldolate must dissociate approximately 75 times in order for one *syn* aldolate molecule to be converted into one *anti* aldolate molecule. Of course, for less stereoselective enolates, such as the cyclohexanone enolate referred to above, stereochemical isomerization will more nearly parallel the rate of actual aldol reversal.

The classic case of effective stereocontrol under equilibrating conditions is the House method, wherein the aldol reaction of the preformed lithium enolate is carried out in the presence of coordinating divalent metal ions, such as magnesium and zinc.[190] An example is seen in equation (134). The enolate of phenylacetone reacts with propionaldehyde to give 86–90% *anti* aldol, regardless of the original enolate geometry. Further discussion on zinc endates is found in Volume 2, Chapter 1.8.

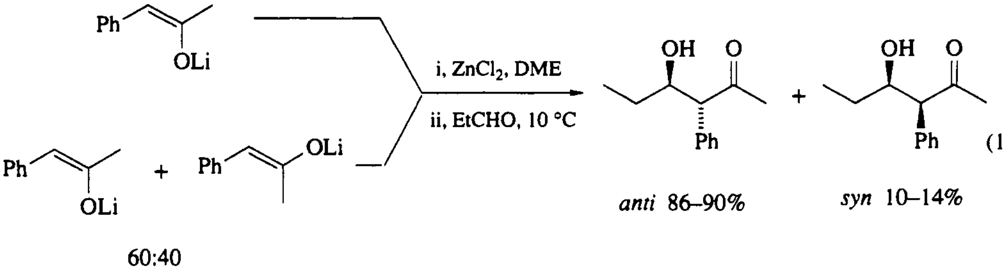

(134)

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# 1.7

# The Aldol Reaction: Group III Enolates

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## 1.7.1 INTRODUCTION

Over the past two decades the chemistry of boron-mediated aldol reactions has been the subject of intense studies and a wealth of information essential for mechanistic elucidation and synthetic applications is now available. Some general comments which highlight the differences between boron- and lithium-mediated aldol reactions are appropriate at the outset of this chapter. (i) The reacting boryl (boron) enolate species in solution appears to be homogeneous and uncomplicated in terms of aggregation, while the lithium counterparts exist in dimeric, tetrameric and hexameric forms. Characterization of the lithium species involved in product formation for some reaction systems is still required.[1] (ii) The B—O and B—C bonds are significantly shorter than the Li—O and Li—C bonds,[2] respectively, and the nucleophilicity of boryl enolates is generally less pronounced than that of the lithium enolates. These characteristics would predict a comparatively tight and organized transition state for the boron-mediated aldol reaction and, in fact, the stereochemical information embedded in the boryl enolates is 'faithfully' expressed in the aldol products on many occasions. These findings have provided incentive to explore the boron aldol methodology for the total synthesis of polyketide-type natural products such as macrolide and ionophore antibiotics. Many successful examples are recorded in the recent literature.

The only main Group III metal, other than boron, that has been utilized in the aldol reaction is aluminum, the enolates of which behave rather capriciously in terms of stereochemistry. The Al—C bond is relatively weak. However, aldol reactions with aluminum enolates derived from chiral acyl–iron complexes proceed with high asymmetric induction.

There are a number of excellent review articles on the subject of boron-mediated aldol reactions and related reactions.[2–7]

## 1.7.2 BORON-MEDIATED ALDOL REACTION

The chemistry of boron-mediated aldol reactions has developed in several stages. A variety of inorganic acids and bases, including boric acid and boron oxide, have long been known to catalyze aldol condensations of aldehydes and ketones.[8] An alkenyloxyborane was presumed to be involved as a reactive intermediate in the aldol reaction when boric acid was used as a catalyst.[9] In 1973 alkenyloxyboranes were recognized by Mukaiyama[10] as useful enolate reagents for the directed aldol reaction. Since then extensive studies have revealed that the (*E*)- or (*Z*)-stereochemistry of alkenyloxyboranes is directly reflected in the stereochemical outcome of the aldol reaction.[11] In the early 1980s, enantiomerically pure (homochiral) alkenyloxyboranes with significant facial selectivity were prepared for use in the aldol reaction. Thus boron-mediated aldol methodology has now become one of the most efficient methods for diastereoselective and enantioselective C—C bond formation.

Alkenyloxyboranes formulated as $R^1R^2C{=}CR^3OBXY$ are perhaps more conventionally called boryl enolates and both terms are used in this article. Alkenyloxyboranes may be categorized as alkenyloxydialkylboranes, alkenyloxyalkylalkoxyboranes and alkenyloxydialkoxyboranes. To avoid confusion the terms 'borinyl', 'boronyl' and 'borate' are not used.[12] Although the majority of the stereoselective aldol reactions reported involve alkenyloxydialkylboranes, alkenyloxydialkoxyboranes have also been utilized. The stereochemical course of the latter aldol reaction has been evaluated both experimentally and computationally and is discussed separately in Section 1.7.2.4.

Before beginning the mechanistic discussion of aldol reactions involving boryl enolates, brief comments are in order on the stereochemical descriptors used below. The two possible stereoisomers derived by deprotonation of a carbonyl compound, *e.g.* (**1**) and (**2**) from (**3**) (Scheme 1), are designated *Z*(*O*) and *E*(*O*),[13] instead of the usual (*Z*) and (*E*), so that enolates that have an identical stereochemical relationship between the C(2) and C(1)—OM substituents may be grouped together. According to this system, the OM substituent on C(1) always takes the higher priority regardless of the Cahn–Ingold–Prelog priority of the R group (consider the case when R = $SiR'_3$).

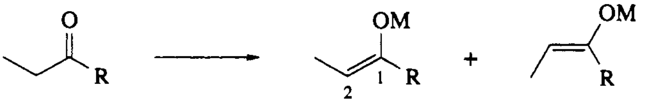

(**3**) (**1**) *Z*(*O*) (**2**) *E*(*O*)

**Scheme 1**

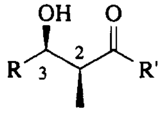

(**4**) 2,3-*syn*

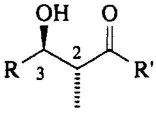

(**5**) 2,3-*anti*

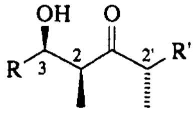

(**6**) 2,3-*syn*, 2,2'-*anti*, 2',3-*anti*

To describe the stereochemistry of the aldol products, the terms *syn* and *anti* are used to express the relative stereochemistry of the substituents attached to a main chain, whenever the chain is unambiguously identified and expressed in a zigzag fashion: *syn* describes two substituents on the same side of the plane defined by the chain (**4**), and *anti* is used when they are on opposite sides (**5**). The relative stereochemistry of distant stereogenic centers can also be described using this notation (**6**).

### 1.7.2.1 Preparation of Alkenyloxydialkylboranes

A variety of methods are now known for the preparation of alkenyloxydialkylboranes and are enumerated below more or less in chronological order. Stereochemical problems associated with dialkylboryl enolate formation and subsequent aldol reaction are discussed in the following two sections (1.7.2.2 and 1.7.2.3). It is interesting to note that most of the methods initially developed (before 1975) do not use direct enolization procedures.

The products (**8**) that result from the reaction of trialkylboranes with α,β-unsaturated carbonyl compounds followed by hydrolysis (Scheme 2),[14] provided the first strong evidence to permit assignment of the alkenyloxyborane structure to the precursors (**7**).

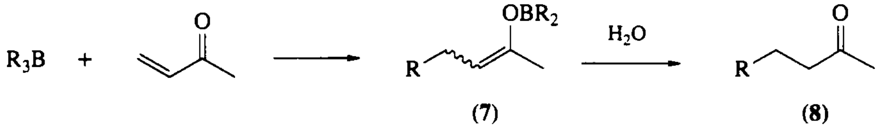
R3B
OBR2
H2O
(7)
(8)

**Scheme 2**

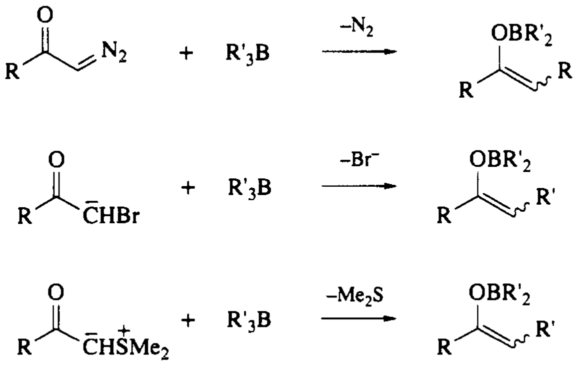
-N2
R'3B
OBR'2
-Br⁻
CHBr
-Me2S
CHSMe2

**Scheme 3**

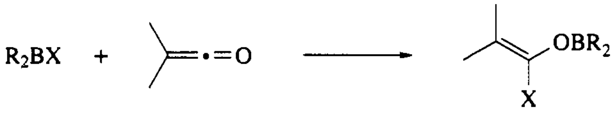

**Scheme 4**

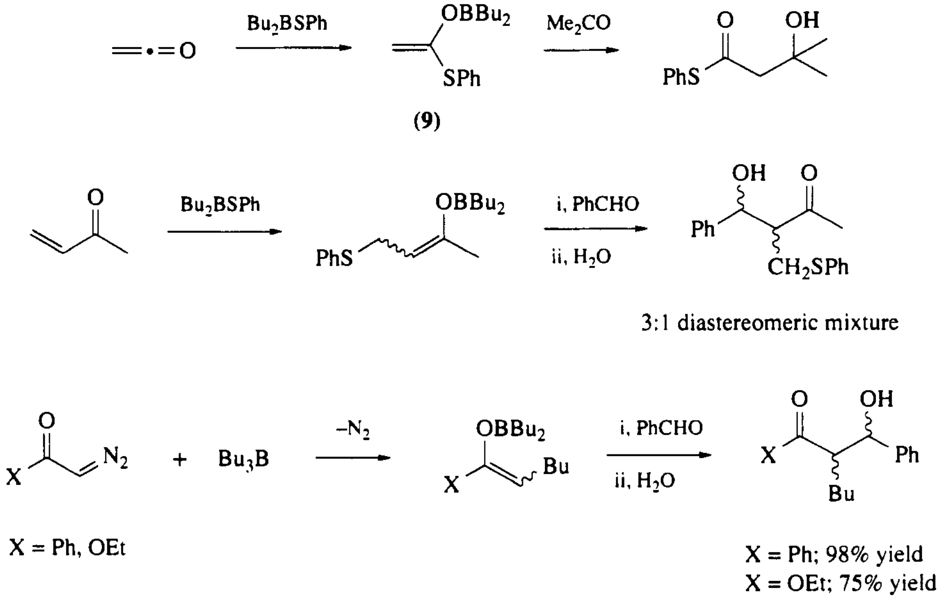
Bu2BSPh
OBBu2
SPh
Me2CO
PhS
(9)
i, PhCHO
ii, H2O
CH2SPh
3:1 diastereomeric mixture
-N2
Bu3B
Bu
X = Ph, OEt
X = Ph; 98% yield
X = OEt; 75% yield

**Scheme 5**

Reactions of α-diazocarbonyl compounds,[15] halogen-substituted enolates[14b,16] and sulfur ylides[17] *with* trialkylboranes were subsequently recorded and represent alternative methods of preparation (Scheme 3).

Addition of boron reagents ($R_2BX$; X = halogen, —SR′, *etc.*) across the C═O bond of ketenes also produces alkenyloxyboranes (Scheme 4).[18]

Mukaiyama *et al.* prepared boryl enolates from thiol esters in this way and unambiguously demonstrated that enolate (**9**) is capable of effecting directed aldol reactions.[10] Similarly, alkenyloxyboranes prepared in the two other ways mentioned above afford the expected aldol products, as shown in Scheme 5, confirming that alkenyloxyboranes are responsible for the directed aldol reactions.

A boryl enolate of an ester can be generated *in situ* by treatment of ethoxyacetylene with diphenylhydroxyborane in the presence of mercury(II) acetate, as shown in Scheme 6.[19]

Direct enolization of carbonyl compounds using dialkylboryl trifluoromethanesulfonate (dialkylboryl triflate; $R_2BOTf$) in the presence of a tertiary amine base is versatile and advantageous in many ways compared with the foregoing indirect methods (see Sections 1.7.2.3 and 1.7.2.4).[20] The resulting boryl enolates, *e.g.* (**10**), react cleanly with various aldehydes to provide high yields of crossed aldol products (Scheme 7).

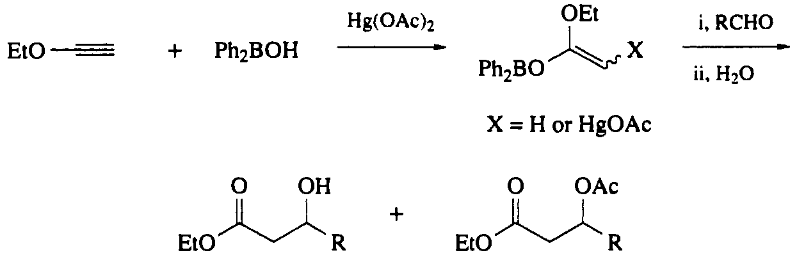
EtO
+ Ph2BOH
Hg(OAc)2
OEt
Ph2BO
X
i, RCHO
ii, H2O
X = H or HgOAc
O
OH
EtO
R
+
O
OAc
EtO
R

**Scheme 6**

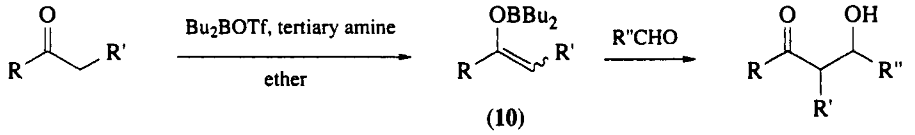
O
R
R'
Bu2BOTf, tertiary amine
ether
OBBu2
R
R'
(10)
R''CHO
O
OH
R
R''
R'

**Scheme 7**

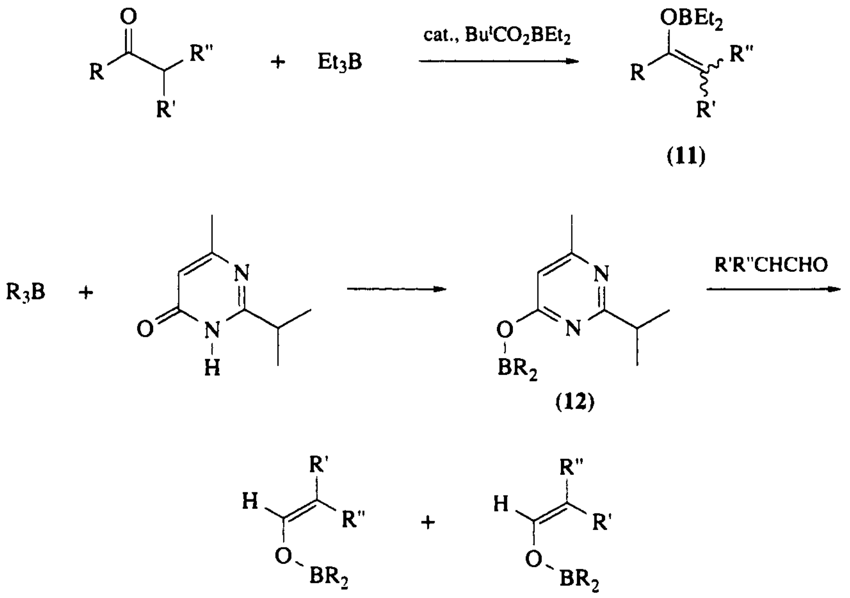
O
R
R''
R'
+ Et3B
cat., ButCO2BEt2
OBEt2
R
R''
R'
(11)
R3B +
N
O
N
H
N
O
N
BR2
(12)
R'R''CHCHO
R'
H
R''
O
BR2
+
R''
H
R'
O
BR2

**Scheme 8**

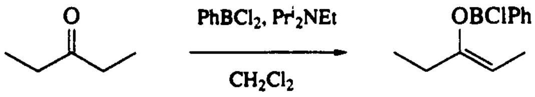
O
PhBCl$_2$, Pr$^i_2$NEt
CH$_2$Cl$_2$
OBClPh

**Scheme 9**

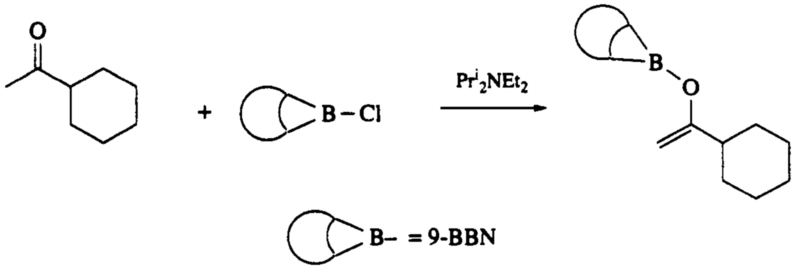
O
+
B–Cl
Pr$^i_2$NEt$_2$
B
O
B– = 9-BBN

**Scheme 10**

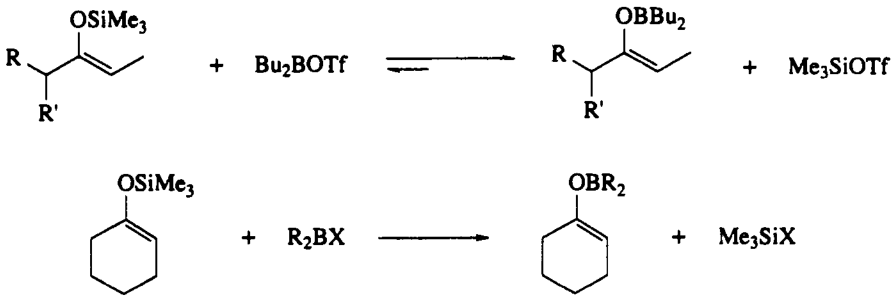
OSiMe$_3$
R
R'
+ Bu$_2$BOTf
OBBu$_2$
R
R'
+ Me$_3$SiOTf
OSiMe$_3$
+ R$_2$BX
OBR$_2$
+ Me$_3$SiX

X = OTf, Br, Cl

**Scheme 11**

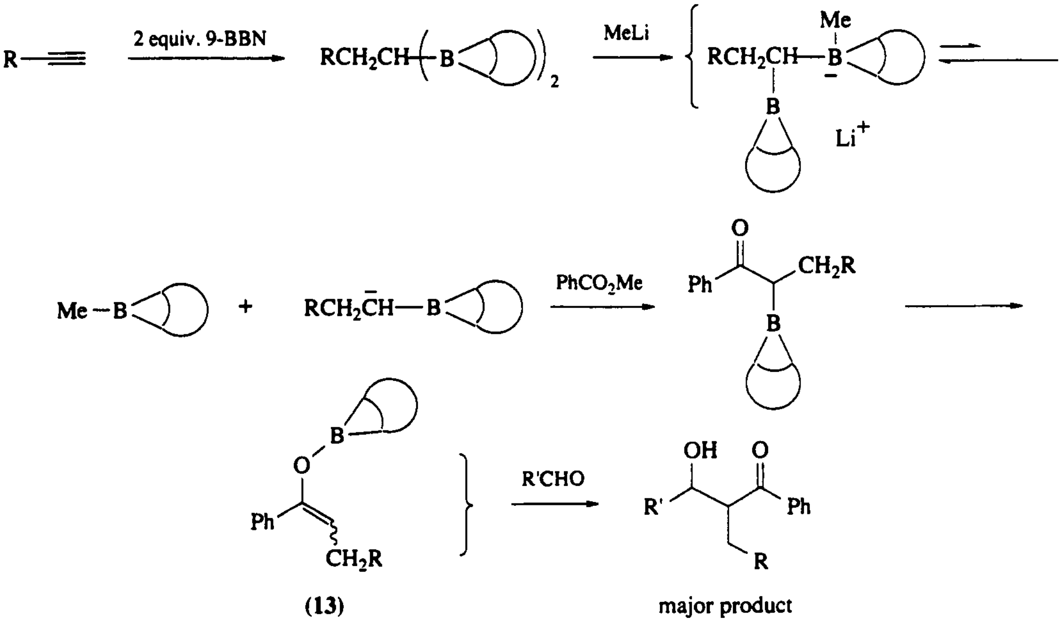
R
2 equiv. 9-BBN
RCH$_2$CH(B)$_2$
MeLi
Me
RCH$_2$CH—B
B
Li$^+$
Me–B
+
RCH$_2\bar{C}$H—B
PhCO$_2$Me
O
Ph
CH$_2$R
B
B
O
Ph
CH$_2$R
(13)
R'CHO
OH
O
R'
Ph
R
major product

**Scheme 12**

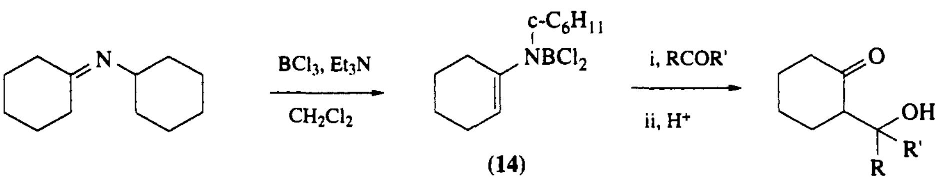

(14)

Scheme 13

The reaction of triethylborane with a ketone in the presence of a catalytic amount of diethylboryl pivalate provides another direct route to the corresponding boryl enolate (**11**; Scheme 8).[11,21] This is probably the first time that the alkenyloxyborane was isolated and fully characterized.[21] Unfortunately this method requires rather vigorous reaction conditions and has not been used frequently. The stereochemistry of the resulting boryl enolates is probably controlled thermodynamically. 4-Dialkylboryloxy-2-isopropyl-6-methylpyrimidine (**12**) may be used specifically for the preparation of boryl enolates from aldehydes.[22]

Ethyl ketones have been enolized by Hamana *et al.* using dichlorophenylborane in the presence of a tertiary amine (Scheme 9).[23] Recently Chow and Seebach found that, under carefully controlled conditions, trichloroborane can also be used to prepare the corresponding alkenyloxydichloroboranes.[24]

Dialkylchloroboranes instead of dialkylboryl triflates can also be successfully utilized for the generation of alkenyloxyboranes, as exemplified in Scheme 10.[25] Dialkylchloroboranes are more easily manipulated than the corresponding triflates, offering an advantage as reagents for enolization. However, enolization using a dialkylchloroborane proceeds more slowly, resulting in self-condensation of certain unhindered methyl ketones (up to 30%).[26]

An exchange reaction of trimethylsilyl enolates with dialkylboryl triflates will provide the corresponding boron enolates (Scheme 11) after removal of trimethylsilyl triflate.[27]

C(1)-Phenyl-substituted alkenyloxyboranes (**13**) may be prepared by the acylation of boron-stabilized carbanions with methyl benzoate (Scheme 12).[28]

Alkenylaminoboranes (**14**), though not in the category of alkenyloxyboranes, also undergo aldol reactions with carbonyl compounds (Scheme 13). Pure alkenylaminoboranes can be isolated from the reaction of a ketimine, boron trichloride and triethylamine in dichloromethane.[29]

### 1.7.2.2 Diastereoselective Aldol Reactions (2,3-Stereochemistry)

In 1975 Fenzl and Köster made some important observations which eventually led to the development of highly diastereoselective aldol reactions using alkenyloxyboranes.[11] The *Z*(*O*) and *E*(*O*) ratios of alkenyloxyboranes prepared from various ketones according to Scheme 8 in Section 1.7.2.1 apparently correspond to the diastereoselectivities of subsequent aldol reactions with aldehydes (Scheme 14).[11] Thus, the pure *Z*(*O*)-enolate (**15**) derived from propiophenone provides exclusively the *syn* aldol product (**16**) upon treatment with propanal. Although the enolates of only a few ketones were examined, the results strongly suggested a direct stereochemical correlation between alkenyloxyborane configuration and aldol product stereochemistry. Compound (**16**) and all other aldol products shown in this section are racemic.

A study on stereodefined boryl enolates that employed both pure (*Z*)- and (*E*)-dialkylboryl enolates has been carried out by Masamune *et al.*[30] Hooz' reaction involving α-diazocarbonyl compounds (Scheme 3) and a trialkylborane provides exclusively *E*(*O*)-alkenyloxyboranes, which can be isomerized cleanly to the corresponding *Z*(*O*)-isomers.[30] The *Z*(*O*)-dibutylboryl enolates (**17**) react with various aldehydes exhibiting uniformly high *syn* selectivities (*syn*:*anti* > 95:5), while the corresponding *E*(*O*)-isomers (**18**) are converted into the *anti* aldol products with somewhat lower selectivities (Scheme 15).

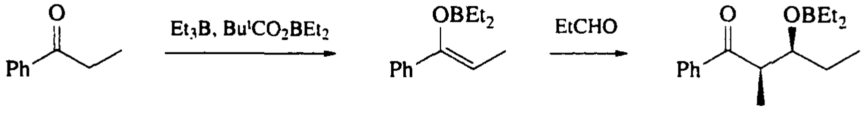

(**15**) 100% *Z*(*O*) (**16**)

Scheme 14

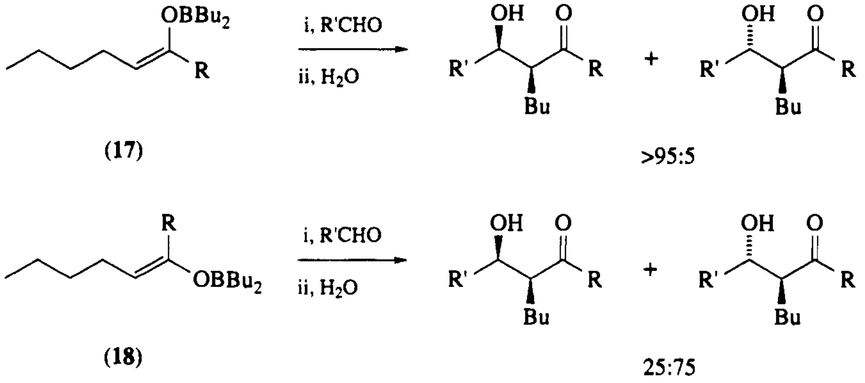

**Scheme 15**

Diastereoselective addition of a propionate unit to an achiral aldehyde is an important process in organic synthesis (see Section 1.7.2.3 for the reaction with chiral aldehydes). This process can be achieved with full control by the judicious choice of a thiol ester and a dialkylboryl triflate.[18b,20d] As shown in Scheme 16, the *E*(*O*)-enolate (**19**) generated from *S*-*t*-butyl propanethioate, dicyclopentylboryl triflate and diisopropylethylamine furnishes, upon reaction with an aldehyde, the *anti* aldol product (**20**). The *syn* product (**21**) is obtained from the *Z*(*O*)-enolate (**22**) derived from the reaction of *S*-phenyl propanethioate with 9-borabicyclo[3.3.1]non-9-yl triflate (9-BBNOTf).

Van Horn and Masamune have shown that it is possible to prepare either boryl enolate stereoisomer from the same ketone by changing the steric demand of the dialkylboryl triflate (Scheme 17).[20e]

Evans *et al.* also carried out independent studies on the stereochemical course of these aldol reactions and demonstrated that dialkylboryl enolates were kinetically stable even at elevated temperatures.[20f,31] The results obtained from the Evans group also established that exceptionally high levels of aldol diastereoselection are governed by the stereochemistry of the dialkylboryl enolates (Table 1).

It has been shown by Evans *et al.* that the aldol reaction of diboryl enediolates (**23**), with one exception, exhibit varying degrees of *anti* stereoselection[31,32] (Scheme 18). This implies that (**23**) reacts more effectively as an *E*(*O*)-boryl enolate than as a *Z*(*O*)-enolate.[33]

When dichlorophenylborane in the presence of diisopropylethylamine is used to enolize ethyl ketones (see Scheme 9), excellent *syn* diastereoselectivity (>94:6) is observed (Scheme 19).[23] Similar *syn* selectivity ranging from 90 to 99% depending on the aldehyde employed is recorded by Chow and Seebach[24] when trichloroborane is used.

A metal exchange reaction between an alkenyloxysilane (silyl enolate) and a dialkylboryl triflate has already been described (Scheme 11).[27] When a mixture of a silyl enolate and dibutylboryl triflate is allowed to react with an aldehyde, aldol product diastereoselectivity is negligible, presumably because trimethylsilyl triflate promotes an aldol reaction of the silyl enolate. When trimethylsilyl triflate is com-

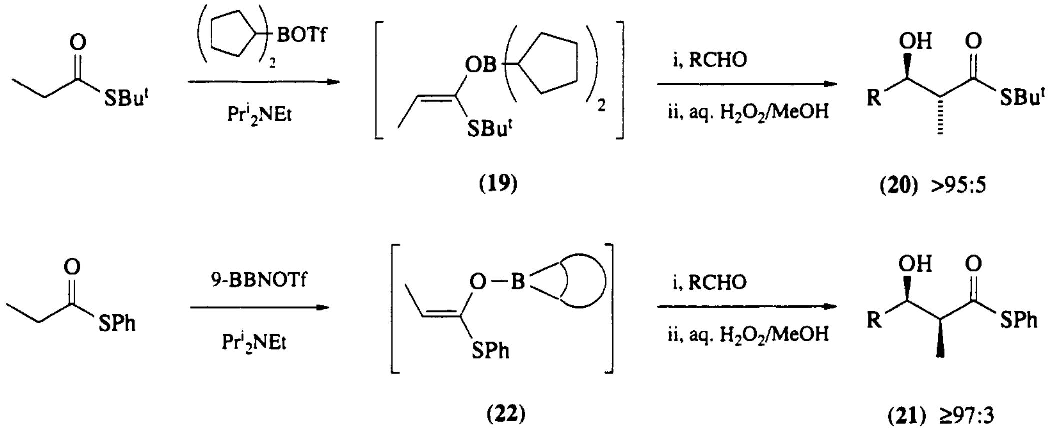

**Scheme 16**

pletely removed from the reaction mixture, the aldol reaction proceeds with high stereoselectivity to provide a 95:5 ratio of *syn*:*anti* aldol products from a 96:4 ratio of *Z*(*O*)-/*E*(*O*)-silyl enolates (Scheme 20).

Systematic studies by Evans *et al.*[31] and Masamune and coworkers,[18b,20d,20e,34] including experimental results discussed above, reveal several factors affecting the kinetic enolization involving boron reagents. At low temperature (–78 to 0°C) enolization is thought to be completely kinetically controlled. The struc-

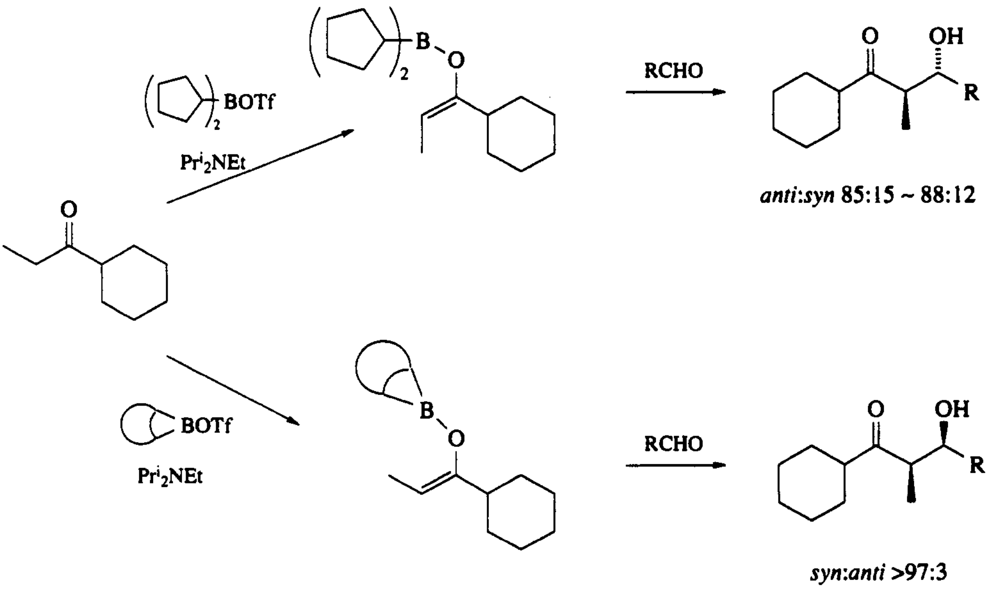
BOTf
$Pr^i_2NEt$
B
O
RCHO
O
OH
R
BOTf
$Pr^i_2NEt$
B
O
RCHO
O
OH
R

*anti*:*syn* 85:15 ~ 88:12

*syn*:*anti* >97:3

**Scheme 17**

**Table 1**[20f,31] Kinetic Boron-mediated Aldol Reactions of Various Ketones with Representative Aldehydes[a]

| *Entry* | *Carbonyl compound* | *Aldehyde* | *L in $L_2BOTf$* | *Z(O):E(O) ratio* | *Syn:anti ratio of aldol products* |
|---|---|---|---|---|---|
| 1 | EtCOEt | PhCHO | $Bu^n$ | >97:3 | >97:3 |
| 2 | EtCOEt | $Pr^iCHO$ | $Bu^n$ | >97:3 | >97:3 |
| 3 | $Pr^iCOEt$ | PhCHO | $Bu^n$ | 45:55 | 44:56 |
| 4 | $Pr^iCOEt$ | PhCHO | c-$C_5H_9$ | 19:81 | 18:82 |
| 5 | $EtC(O)SBu^t$ | $Pr^nCHO$ | $Bu^n$ | ≤5:95 | 10:90 |
| 6 | $EtC(O)SBu^t$ | $Pr^iCHO$ | $Bu^n$ | ≤5:95 | 9:91 |

[a] Enolization was carried out at –78 °C (entries 1–3) or at 0 °C (entries 4–6). In all cases $Pr^i_2NEt$ was used as the base.

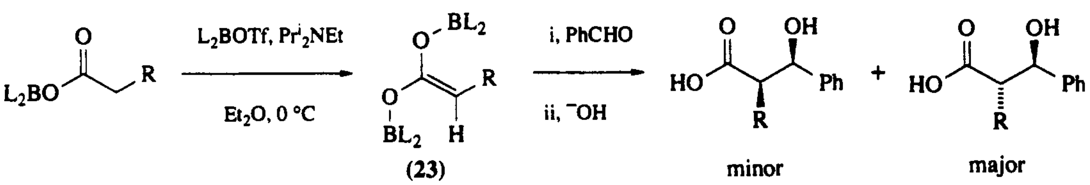
O
$L_2BO$
R
$L_2BOTf$, $Pr^i_2NEt$
$Et_2O$, 0 °C
O
$BL_2$
O
R
$BL_2$
H
i, PhCHO
ii, $^-OH$
O
OH
HO
Ph
R
+
O
OH
HO
Ph
R

(23)

minor

major

**Scheme 18**

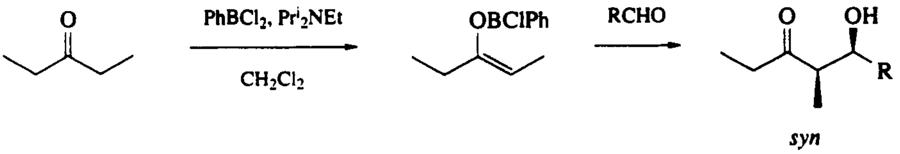
O
$PhBCl_2$, $Pr^i_2NEt$
$CH_2Cl_2$
OBClPh
RCHO
O
OH
R

*syn*

**Scheme 19**

tural features of the carbonyl compound, tertiary amine and boryl triflate, individually contribute to the observed enolate stereoselection. Recently both experimental and computational studies by Reetz *et al.*[35] have shown that $BF_3$ forms an adduct with benzaldehyde such that the Lewis acid is placed *anti* to the phenyl ring. Thus, all four atoms of the C—C=O—B complex lie in a common plane. This Lewis acid complexation of the carbonyl group may be extrapolated into the discussion of the kinetic enolization, which utilizes a strongly Lewis acidic boron reagent. The discussion can be summarized as follows (Scheme 21): (i) *Z*(*O*)- and *E*(*O*)-enolates are derived from the deprotonation of two complexes (**A**) and (**B**), respectively. (ii) With all other factors equal, kinetic stereoselection is maximized with increased steric hindrance of the amine base.[20e,31,34] (iii) Several factors are involved in the kinetic enolization of a carbonyl compound using a boryl triflate. With a given base, when the steric interaction between R and the boron ligands is relatively small (see **22** in Scheme 16), complex (**A**) is preferred, leading to the formation of the *Z*(*O*)-enolate. However, if the steric interaction between R and the boron moiety becomes severe (see **19** in Scheme 16 and **91** in Section 1.7.2.3.1 iii), *E*(*O*)-enolate formation prevails through complex (**B**). If the interaction between R and Me becomes unendurably large with an extremely bulky R group (see **29** in Scheme 23 and **37** in Scheme 25), the boron reagent can only be complexed *syn* to R (complex **A**), resulting in the formation of the *Z*(*O*)-enolate. When both interactions between R and Me and R and the boron ligands are large, the enolate formation becomes sluggish (see Table 2).

An improvement in aldol diastereoselection for a given boron ligand is obtained when less polar solvents are employed, presumably due to 'transition state compression' in nonpolar solvents. This solvent effect is also significant in enolate chirality transfer in asymmetric aldol reactions.

Selective formation of either *Z*(*O*)- or *E*(*O*)-enolates from ethyl ketones has been accomplished by Brown *et al.*[82] by employing dialkylchloroborane as well as dialkylboryl triflate. The results of enolization with propiophenone and diethyl ketone are summarized in Table 1a. It is of note that *anti* aldol pro-

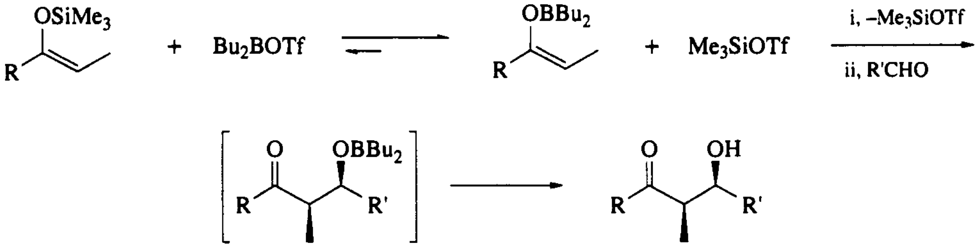

Scheme 20

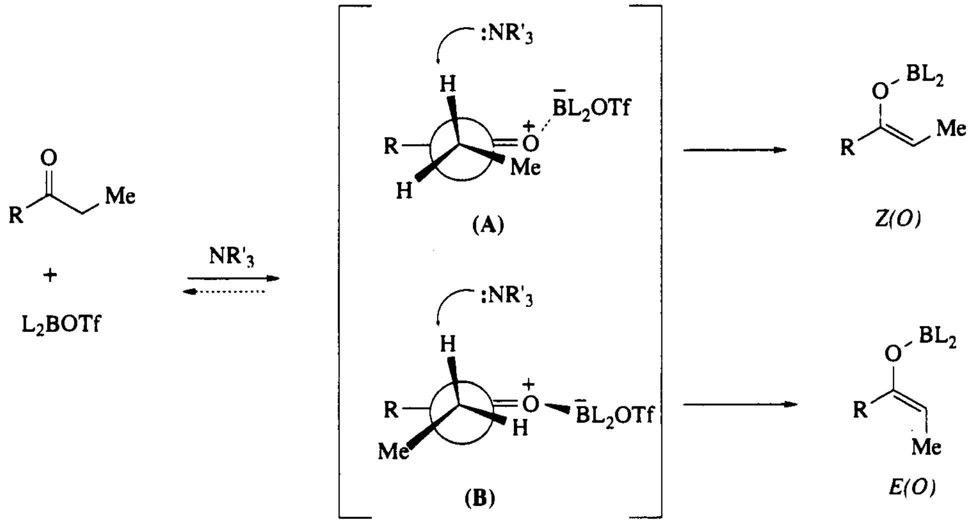

Scheme 21

**Table 1a** Enolization of Propiophenone and Diethyl Ketone in the Presence of $R_2BX$ and Amines at 0 °C

| *Reagent $R_2BX$* | *Amine $R_3N$* | *Syn/anti ratio* | |
|---|---|---|---|
| | | *Propiophenone* | *Diethyl ketone* |
| B-Cl-9-BBN | $Et_3N$ | 60:40 | >99:1 |
| | $Pr^i_2EtN$ | 95:5 | >99:1 |
| B-OTf-9-BBN | $Et_3N$ | 93:7 | >99:1 |
| | $Pr^i_2EtN$ | 95:5 | >99:1 |
| c-$Hex_2BCl$ | $Et_3N$ | 5:95 | 21:79 |
| | $Pr^i_2EtN$ | 51:49[a] | 72:28 |
| c-$Hex_2BOTf$ | $Et_3N$ | 67:33[a] | 80:20 |
| | $Pr^i_2EtN$ | 98:2 | 93:7 |

[a] Ratios of enolates determined by $^1H$ NMR analysis.

ducts of high diastereomeric purity (79–99%) can be obtained by the use of a combination of dicyclohexylchloroborane and triethylamine.

### 1.7.2.3 Aldol Reactions Using Enantiomerically Homogeneous Alkenyloxydialkylboranes (3,4-Stereochemistry)

The reaction of a chiral aldehyde with an achiral enolate leads to the formation of two diastereomeric isomers in a proportion which largely reflects the facial selectivity inherent to the aldehyde. This proportion is often referred to as the Cram/anti-Cram ratio. The ratio is normally small for acyclic chiral aldehydes (ranging 1:1 ~ 1:5) and is often unpredictable, as exemplified below for the aldol reaction involving an achiral boron enolate (**22**) and the chiral aldehyde (**24**; Scheme 22).[3a,5b]

The observed 2,3-*syn* stereoselectivity of the products (**25**) and (**26**) reflects the *Z*(*O*)-configuration of the enolate (**22**), and the predominant product (**25**) is the anti-Cram product, indicated by the *anti* orientation of the C-3 and C-4 substituents. The control of the 3,4-stereoselectivity of the aldol reaction is a problem more generally associated with the apparent facial selectivity of a substrate in any reaction and has been a major challenge in organic synthesis of acyclic systems. As a solution to this problem a new strategy emerged based on the rule of double asymmetric synthesis.[5b] In the reaction of an enantiomerically pure aldehyde with an enantiomerically pure reagent, the use of an (*S*)- or (*R*)-reagent with a *large* facial selectivity either enhances the apparent facial selectivity of the substrate when the facial selectivities of both reactants are acting in concert (matched pair reaction), or overrides it when they are counteracting each other (mismatched pair reaction). In this way the stereochemical course of the reaction is controlled by the reagent. This reagent-controlled organic synthesis requires the design and preparation of reagents with exceedingly high enantioselectivities (>50:1), a term normally defined as the ratio of two enantiomers that result from the reaction of an achiral substrate with a chiral reagent (after removal of the chiral auxiliary group from the products), and a term synonymous with diastereofacial stereoselectivity (*DS*)[5b] of a chiral reactant. Such reagents (and catalysts) are now available for many organic reactions including boron-mediated aldol reactions.

Over the past decade the enantio- and diastereo-selective aldol methodology has been developed mainly with the purpose of synthesizing polyketide-type natural products such as macrolides and ionophore antibiotics. These natural products have the basic structural units that result from propionate and acetate addition: α-methyl-β-hydroxycarbonyl (**27a–d**) and β-hydroxycarbonyl (**28a** and **28b**). Discussions on the construction of these units will be followed by comments on the stereoselective assembly

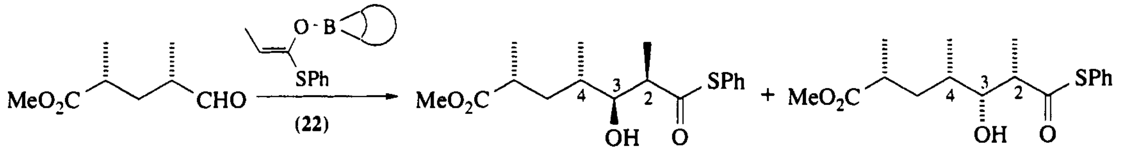

**(24)** **(25)** **(26)**

(**25**):(**26**) = 3:2

Scheme 22

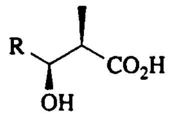

**(27a)**

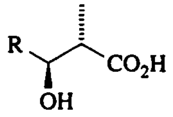

**(27c)**

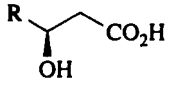

**(28a)**

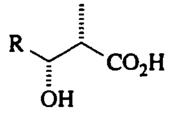

**(27b)**

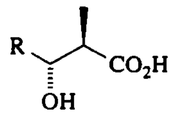

**(27d)**

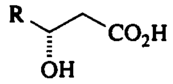

**(28b)**

R = achiral or chiral

of two enantiomerically pure fragments by an aldol reaction. Some references pertinent to this section can be found in ref. 84.

### *1.7.2.3.1 Construction of α-methyl-β-hydroxycarbonyl units*

*(i) Syn-selective aldol reactions*

The first highly enantioselective construction of α-methyl-β-hydroxycarbonyl units, described by Masamune *et al.*, used alkenyloxyboranes (**29**) prepared by enolization of ethyl ketone (**30**) derived in three steps from enantiomerically pure mandelic acid.[36] Various dialkylboryl triflates are used with diisopropylethylamine for enolization. The alkenyloxyboranes (**29**) exhibit striking stereoselectivity as chiral reagents in reactions with representative aldehydes. With judicious choice of the alkyl ligands on the

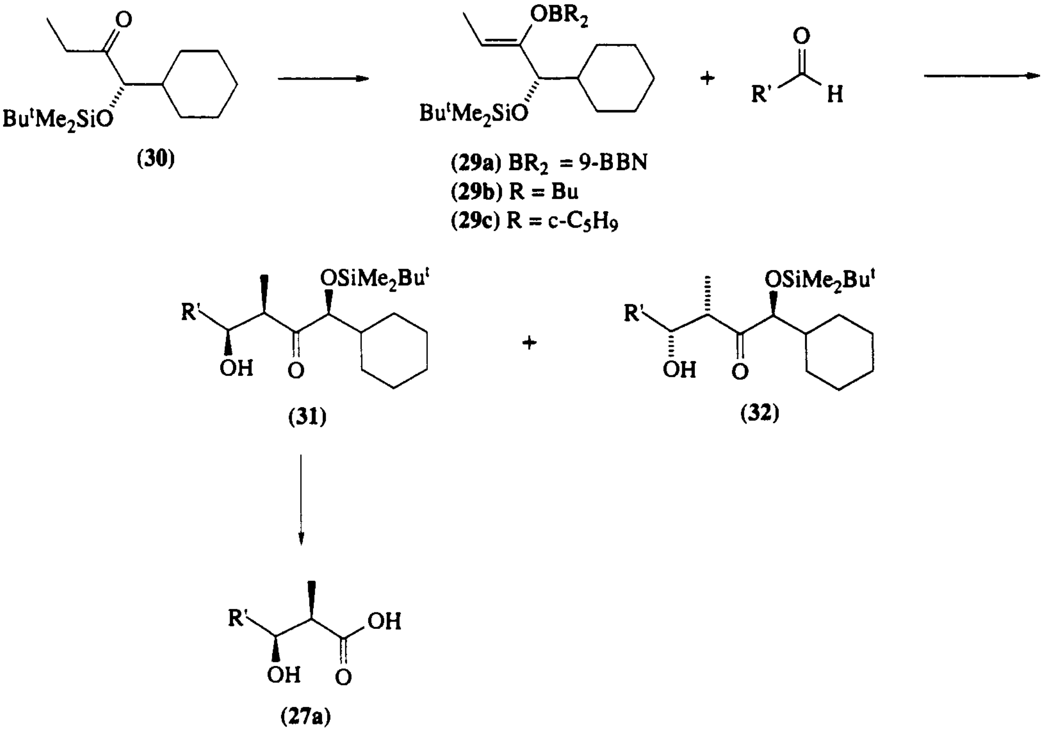

Scheme 23

boron atom, diastereoselectivities (ratio of **31** to **32** in Scheme 23) exceed 100:1. Removal of the TBDMS group from the aldol products followed by $NaIO_4$ treatment provides the corresponding α-methyl-β-hydroxycarboxylic acids (**27a**) with enantiomeric excesses exceeding 98% (Table 2). This highly stereoselective aldol reaction can be rationalized by the Zimmerman–Traxler[37] six-membered chair-like transition state as shown in (**C**).

**Table 2** Reaction of Aldehydes with Boron Enolate (**29**)

| *Aldehyde* | *Boron enolate* | *Ratio of (31):(32)* |
|---|---|---|
| $BnOCH_2CH_2CHO$ | (**29a**) | 16:1 |
| | (**29b**) | 28:1 |
| | (**29c**) | 100:1 |
| $Pr^iCHO$ | (**29a**) | >100:1 |
| | (**29b**) | >100:1 |
| | (**29c**) | No reaction |

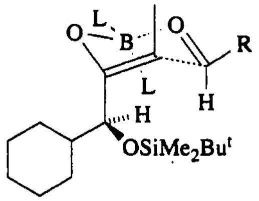

**(C)**

Since the stereochemical outcome of the aldol reaction with these enolates is predictable from the above results, selection of either (*S*)-(**29b**) or (*R*)-(**29b**) for a matched or mismatched pair can easily be made. Thus, in the reaction of chiral aldehyde (**24**) with (*S*)-(**29b**) (matched) the product ratio exceeds 100:1, favoring formation of (**33**), whereas when reagent (*R*)-(**29b**) is used, (**34**) becomes the predominant product with a respectable stereoselection (mismatched) (Scheme 24). Compared to the ratios observed for the reaction with an achiral enolate (Scheme 22), it is clear that the facial selectivity of the enolates dictates the 3,4-stereochemistry of the aldol reaction and either the 2,3-*syn*-3,4-*anti* or 2,3-*syn*-3,4-*syn* units can be constructed in a predictable manner.

Independent work on asymmetric aldol reactions by Evans *et al.* led to the development of alternative chiral boron enolates that exhibit >100:1 facial selectivity.[38] A pair of chiral *N*-acyl-2-oxazolidones (**35**)

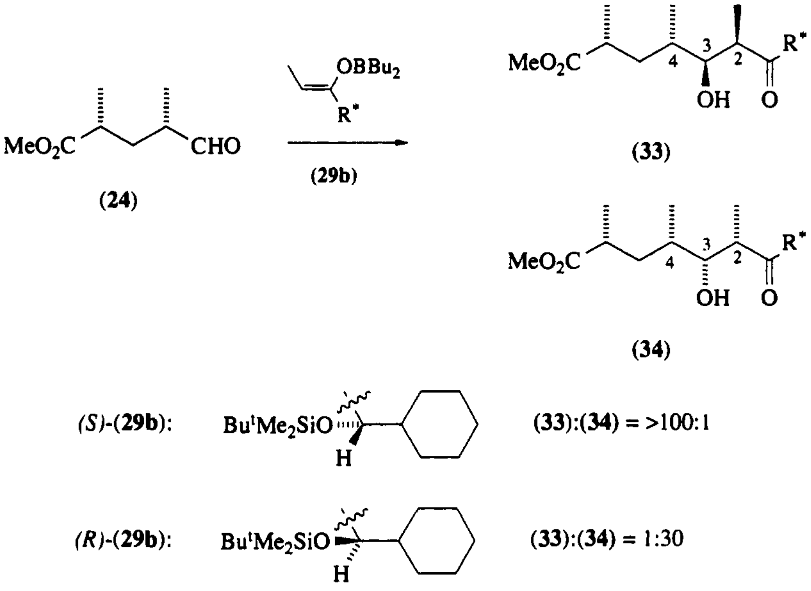

**Scheme 24**

and (**36**), derived from (*S*)-valine and (1*S*,2*R*)-norephedrine, can be converted under standard (Mukaiyama) conditions into the corresponding boron enolates (**37**) and (**38**), respectively. Reaction of either (**37**) or (**38**) with a set of aldehydes provides a single 2,3-*syn* diastereomeric aldol product showing that both the enolate formation and the aldol reaction proceed with near perfect stereoselection (Table 3), as shown in Scheme 25. Treatment of the aldol products (**39**) and (**40**) with sodium methoxide (molar ratio 1:1) in methanol leads to the corresponding methyl esters (**41**) and (**42**) with >99% optical purity and opposite absolute stereochemistry. As in the case of enantiomerically homogeneous boryl enolates (**29**), the observed stereoselection can be explained by the Zimmerman–Traxler transition state model (**D**).

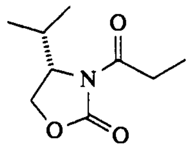

**(35)**

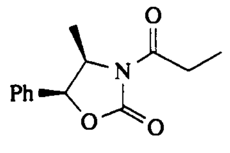

**(36)**

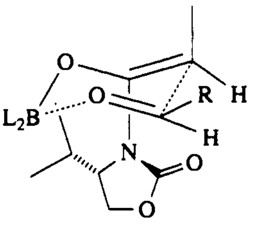

**(D)**

**Table 3** Aldol Reactions of (**37**) and (**38**) with Representative Aldehydes (Scheme 25)[38]

| *Entry* | *Boron enolate* | *Aldehyde* | *Ratio of syn diastereomers*[a] | *Aldol product* | *Yield (%)* | *Overall product* | *Overall Yield (%)* |
|---|---|---|---|---|---|---|---|
| 1 | (**37**) | $Pr^iCHO$ | 497:1 | (**39**) | 78 | (**41**) | 69 |
| 2 | (**38**) | $Pr^iCHO$ | <1:500 | (**40**) | 91 | (**42**) | 78 |
| 3 | (**37**) | $Bu^nCHO$ | 141:1 | (**39**) | 75 | (**41**) | 68 |
| 4 | (**38**) | $Bu^nCHO$ | <1:500 | (**40**) | 95 | (**42**) | 71 |
| 5 | (**37**) | PhCHO | >500:1 | (**39**) | 88 | (**41**) | 81 |
| 6 | (**38**) | PhCHO | <1:500 | (**40**) | 89 | (**42**) | 60 |

[a] In all cases the *anti* aldol adducts constituted <1% of the total reaction mixture.

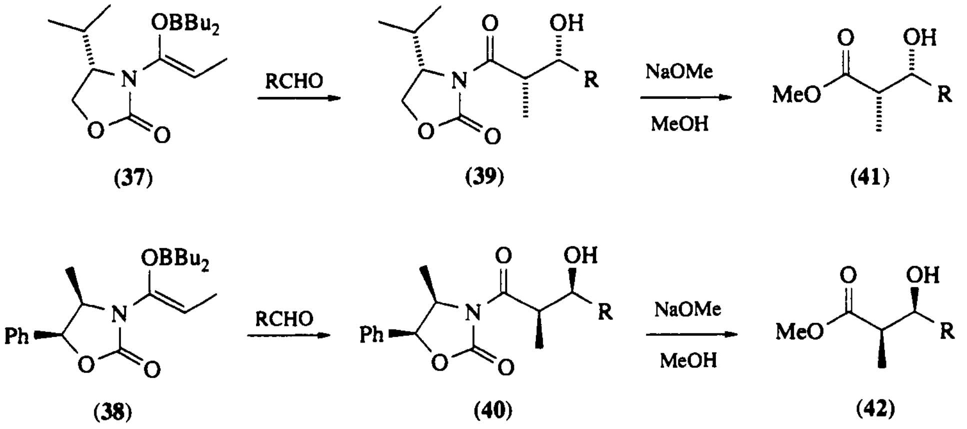

**Scheme 25**

The reactions of chiral aldehyde (**43**) with reagents (**37**) and (**38**) represent a typical example of double asymmetric synthesis.[39] As shown in Scheme 26, the reactions provide exclusively (**44**) and (**47**), with stereoselection of 660:1 and 400:1, respectively.

The facial selectivity of (**43**) was found to be 1.75:1 from the ratio of aldol products (**48**) and (**49**) obtained by the reaction with the achiral boron enolate (**50**). The latter is structurally similar to reagents (**37**) and (**38**). These experiments confirm again the validity of the rule of double asymmetric synthesis. The product (**44**) can be further converted through a sequence of reactions to provide (+)-Prelog–Djerassi lactonic acid (**51**; Scheme 27): (i) trimethylsilylation; (ii) hydroboration with thexylborane (single asymmetric induction with a 5.7:1 ratio in favor of the diastereomer (**52**), see C-6), followed by oxidative work-up; (iii) acid hydrolysis to remove the trimethylsilyl group of (**52**); (iv) ruthenium-catalyzed oxidation of the primary hydroxy group; and finally (v) hydrolytic removal of the chiral auxiliary.

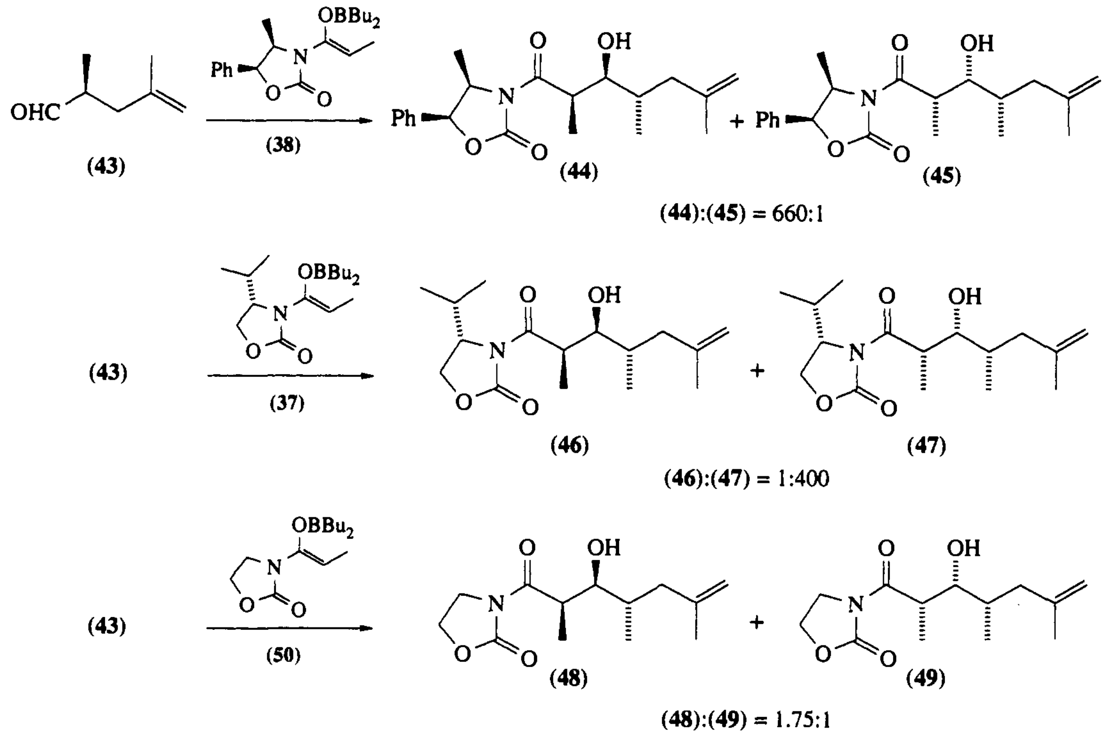

OHC
(43)
OBBu2
Ph
N
O
O
(38)
O
OH
(44)
+ Ph
(45)
(44):(45) = 660:1
(43)
(37)
(46)
+
(47)
(46):(47) = 1:400
(43)
(50)
(48)
(49)
(48):(49) = 1.75:1

Scheme 26

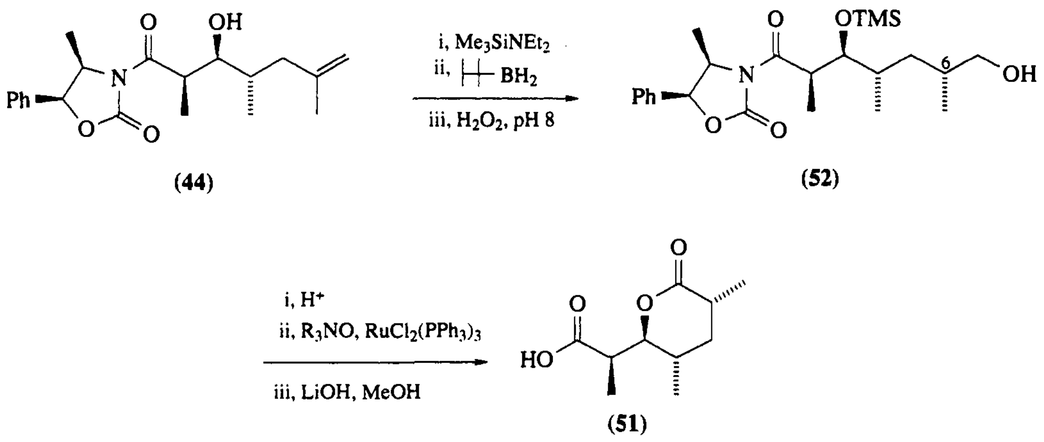

O
OH
Ph
N
(44)
i, Me3SiNEt2
ii, BH2
iii, H2O2, pH 8
OTMS
6
OH
(52)
i, H+
ii, R3NO, RuCl2(PPh3)3
iii, LiOH, MeOH
HO
(51)

Scheme 27

Meyers *et al.*[40] reported the use of boron azaenolate (**53**), derived from enantiomerically homogeneous oxazoline (**54**) and 9-BBN triflate, for the preparation of 2,3-*syn* aldol units (**55**), as shown in Scheme 28. The resulting *syn*-3-hydroxy-2-methyl esters (**56**) are obtained with very high (95–98%) *syn* diastereoselectivities but modest enantiomeric excesses (29–71% *ee*).

An interesting asymmetric aldol reaction utilizing enantiomerically homogeneous bornane sultam derived boron enolates has recently been reported by Oppolzer *et al.*[41] The reaction of aldehydes with boron enolates (**57**), generated from acyl sultams (**58**) under standard enolization conditions ($Pr^i_2NEt/Bu_2BOTf$/0 °C), provides *syn* aldol products (**59**) with extremely high ratios of (**59**) to (**60**) as shown in Scheme 29. Results from the aldol reactions with representative aldehydes are summarized in

Table 4. It is interesting to note that the tin enolate corresponding to (**57**), upon reaction with aldehydes, also provides *syn* aldol products (**60**), diastereomeric to (**59**), with high diastereoselection. This opposite sense of asymmetric induction is believed to be due to coordination of the sultam oxygen to the metal (Sn) in the transition state, which is absent in the boron counterpart. Notably, the products can be easily purified by flash chromatography and/or crystallized to nearly perfect (>99% *de*) diastereomeric purity.

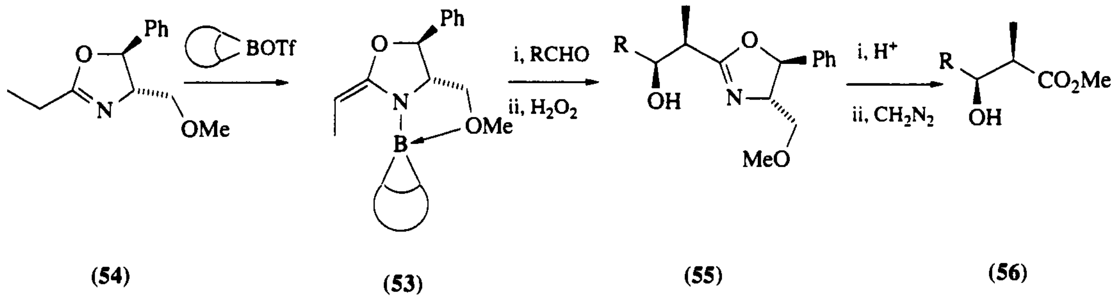

Scheme 28

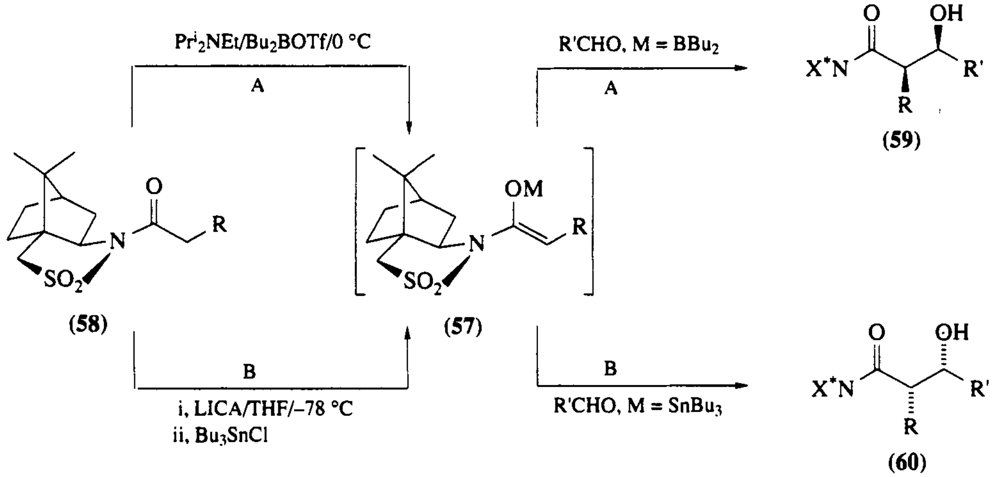

Scheme 29

**Table 4** Aldol Reactions of Boron Enolates Derived from Enantiomerically Pure Acyl Sultam (**58**)[41]

| *R* | *R'* | *Yield of the major product (%)* | *Product ratio*[a] *(**59**):(**60**)* | *After purification (**59**):(**60**)* |
|---|---|---|---|---|
| Me | Ph | 78 | >95:<5 | >200:1 |
| Me | Pr$^i$ | 48 | >99:<1 | >200:1 |
| Me | Me (–100 °C) | 48 | >99:<1 | >200:1 |
| Et | Me (–100 °C) | 69 | >95:<5 | >40:1 |
| Et | Ph | 63 | >95:<5 | >40:1 |
| Et | Pr$^i$ | 72 | >95:<5 | >40:1 |

[a] No *anti* aldol products were obtained.

### *(ii) Application of the* syn*-selective propionate aldol methodology to natural product synthesis*

The synthesis of 6-deoxyerythronolide B (**61**), accomplished by Masamune *et al.*[42] in 1981, was the first successful demonstration of double asymmetric synthesis applied to the construction of molecules of this stereochemical complexity, and manifests clearly the power of this new strategy using enantiomerically homogeneous reagents to control stereochemistry. The macrolide (**61**) is the lactone derived from 13-hydroxypentadecanoic acid (**62**), which consists of seven propionate building blocks (Scheme 30). Retrosynthetic analysis of the seco-acid (**62**) into fragments (**63**) and (**64**) immediately suggests the order of the aldol reactions to be used in the synthesis. Aldol reaction I (involving propanal and its enolate equivalent **65**) produces (**63**), while aldol reactions II (**65** and **66**) and III (**67** and **65′**; an enolate equivalent of propanethioate) complete the synthesis of fragment B. Finally, both fragments are combined *via* aldol reaction IV. Note that aldol reactions I, II, and III all concern the creation of 2,3-*syn* stereochemistry, a task that can be readily achieved with the *Z*(*O*)-enolates (**29**) described above.

In practice, eight stereogenic centers out of the 10 embedded in the target molecule have been created with remarkable efficiency and stereoselection *via* the aldol reactions I–III using (**29**). The overall yield was 30% and overall stereoselectivity approximately 90%. Many other natural product syntheses using the strategy outlined above are now on record.

Evans *et al.* utilized the chiral oxazolidones to prepare optically pure β-hydroxy-α-amino acids,[43] important constituents of peptides and β-lactams. As shown in Scheme 31, an asymmetric aldol reaction using the boron enolate derived from the *N*-(α-haloacyl)oxazolidone (**68**) provides the *syn*-β-hydroxy-α-halocarbonyl derivative (**69**), which is converted to the *anti*-β-hydroxy-α-azidocarbonyl derivative (**70**)

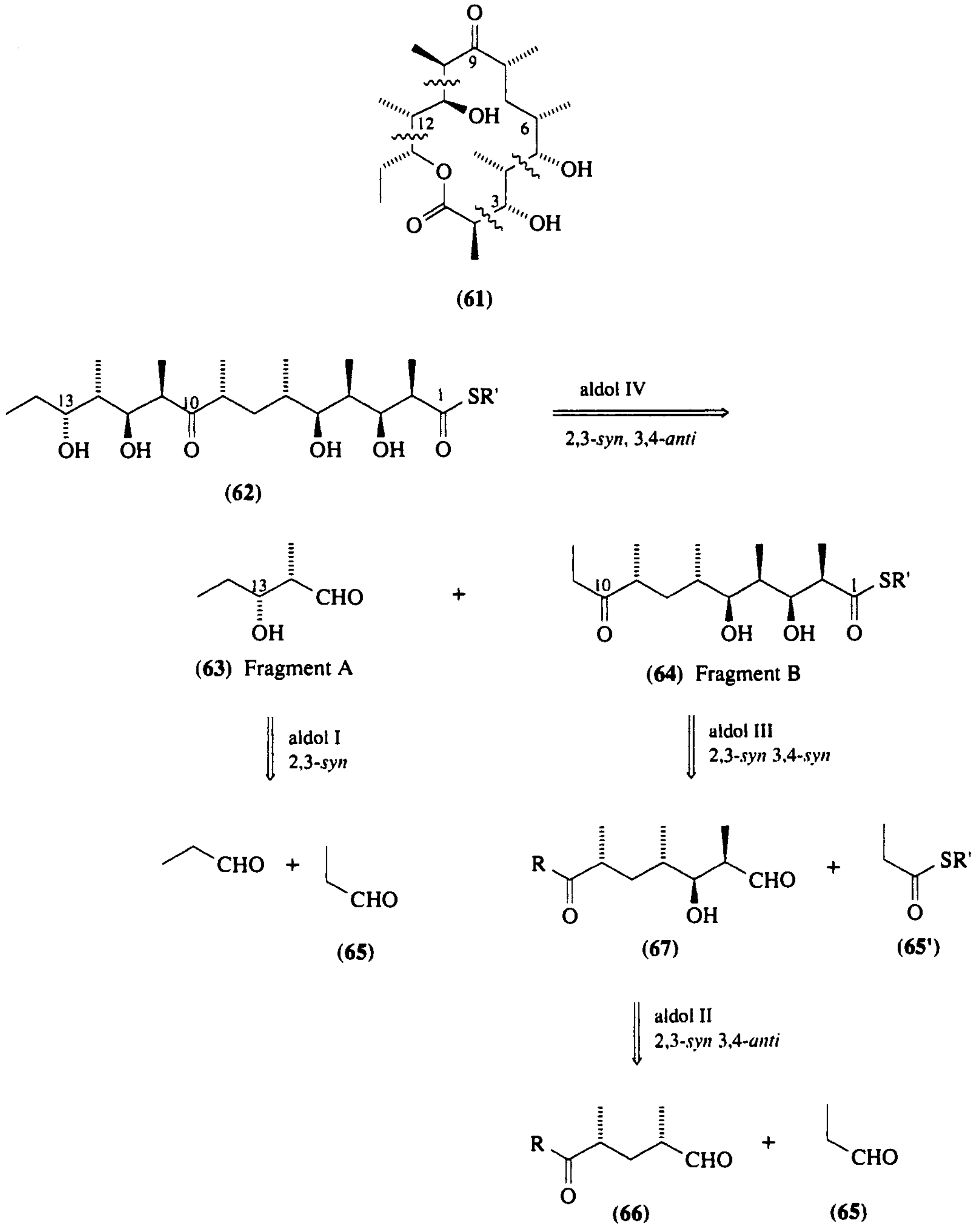
O
9
OH
12
6
OH
O
3
OH
O
(61)
13
10
1
SR'
OH OH O OH OH O
(62)
aldol IV
2,3-syn, 3,4-anti
13
CHO
OH
(63) Fragment A
+
10
1
SR'
O OH OH O
(64) Fragment B
aldol I
2,3-syn
aldol III
2,3-syn 3,4-syn
CHO
+
CHO
(65)
R
CHO
O OH
(67)
+
SR'
O
(65')
aldol II
2,3-syn 3,4-anti
R
CHO
O
(66)
+
CHO
(65)

**Scheme 30**

by an $S_N2$ displacement. Further synthetic transformations of (**70**) provide routes to β-hydroxy-α-amino acids (**71**) and β-lactams (**72**). Notably *syn*-β-hydroxy-α-amino acids (**73**) can be obtained by reaction of the tin enolate derived from (**74**) as shown in Scheme 32.[44]

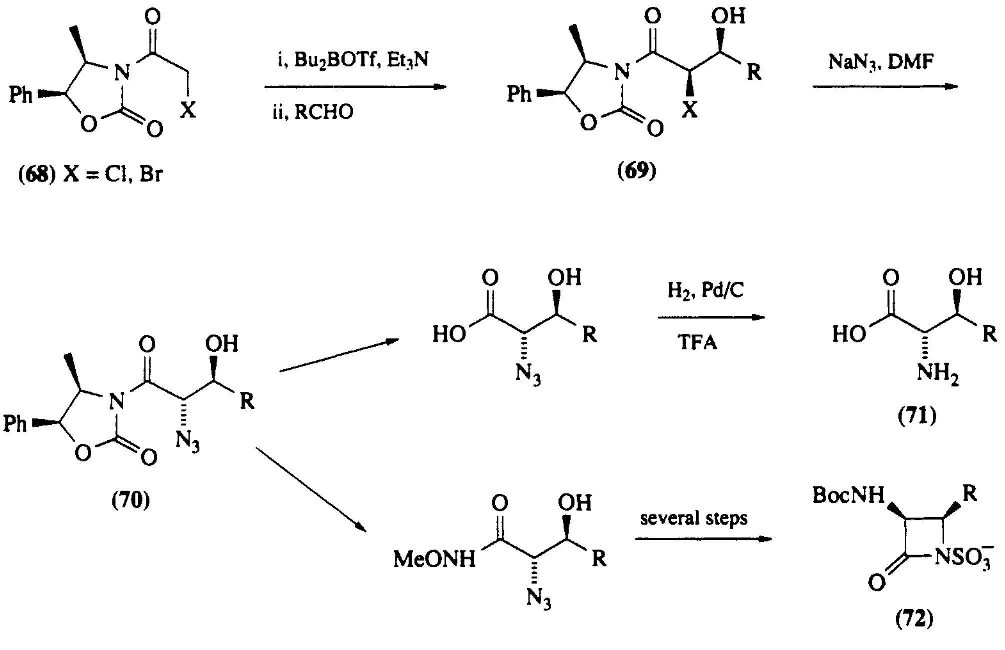
(68) X = Cl, Br
i, Bu2BOTf, Et3N
ii, RCHO
(69)
NaN3, DMF
(70)
H2, Pd/C
TFA
(71)
several steps
(72)
Ph
N
O
OH
R
X
N3
NH2
HO
MeONH
BocNH
NSO3−

**Scheme 31**

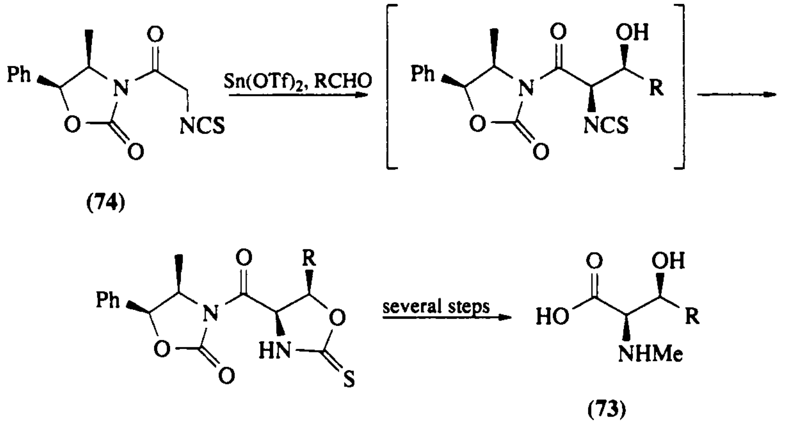
(74)
Sn(OTf)2, RCHO
several steps
(73)
Ph
NCS
HN
S
HO
NHMe
OH
R

**Scheme 32**

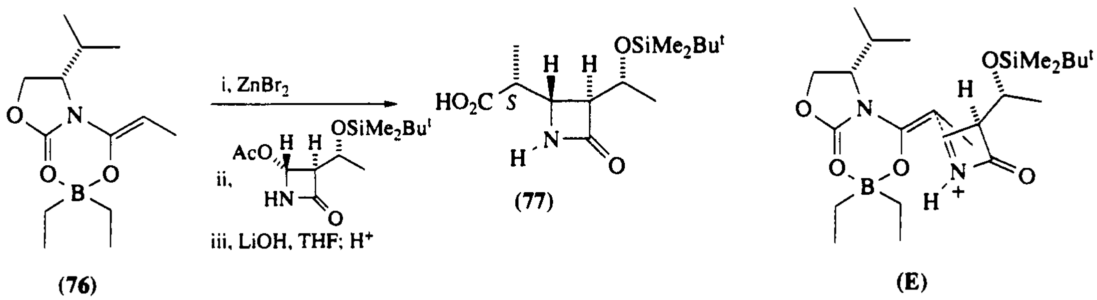
(76)
i, ZnBr2
ii,
iii, LiOH, THF; H+
AcO
HN
OSiMe2Bu^t
HO2C
S
(77)
(E)
H
N
O
B

*S*:*R* ≥ 99:1

**Scheme 33**

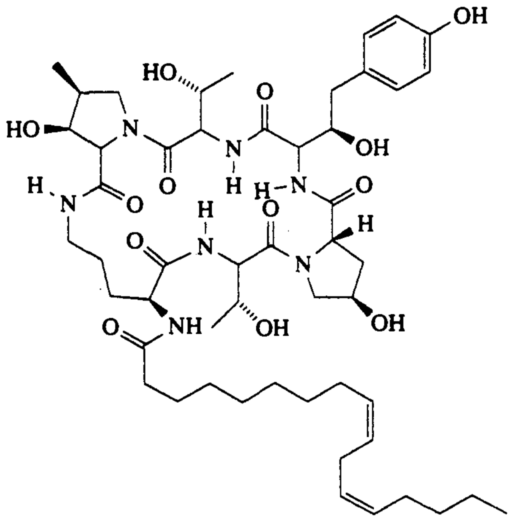

(**75**) Echinocandin D

The cyclic hexapeptide echinocandin D (**75**) has been successfully synthesized with the aid of the foregoing methods for the preparation of *syn*- and *anti*-β-hydroxy-α-amino acid units.[45]

Fuentes *et al.*[46] have also used boron-mediated aldol reactions to prepare enantiomerically homogeneous β-lactam moieties. In the presence of a Lewis acid ($ZnBr_2$), enantiomerically homogeneous boryl enolate (**76**) provides adduct (**77**) with high diastereoselectivity (see acyclic transition state E; Scheme 33).

### *(iii)* Anti-*selective aldol reactions*

*(a) Earlier methods.* Since *E*(*O*)-boron enolates with acceptably high facial selectivities were not available before 1985, the enantio- and diastereo-selective construction of 2,3-*anti*-α-methyl-β-hydroxycarbonyl units had to rely on indirect, circuitous approaches. Depicted in Scheme 34 is a typical example of such an approach.[13,47] The *Z*(*O*)-enolate (**78**) prepared from (*Z*)-enone (**79**) adds to an aldehyde in the expected manner (diastereoselection > 100:1) to provide the *syn* aldol product (**80**), which is converted into ester (**81**). Straightforward manipulation of the ester followed by ozonolysis of

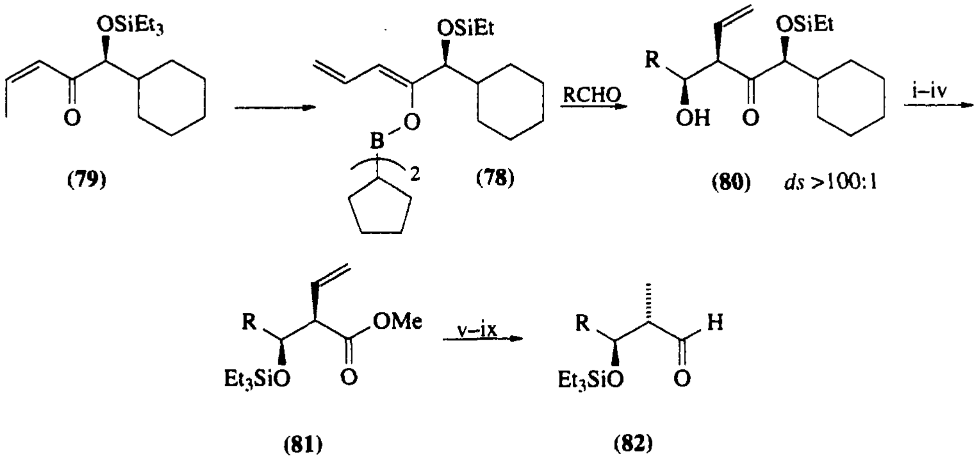

i, HF; ii, $NaIO_4$; iii, $CH_2N_2$; iv, $Et_3SiOTf$; v, DIBAL; vi, *p*-TsCl; vii, NaI; viii, $NaBH_3CN$; ix, $O_3$

**Scheme 34**

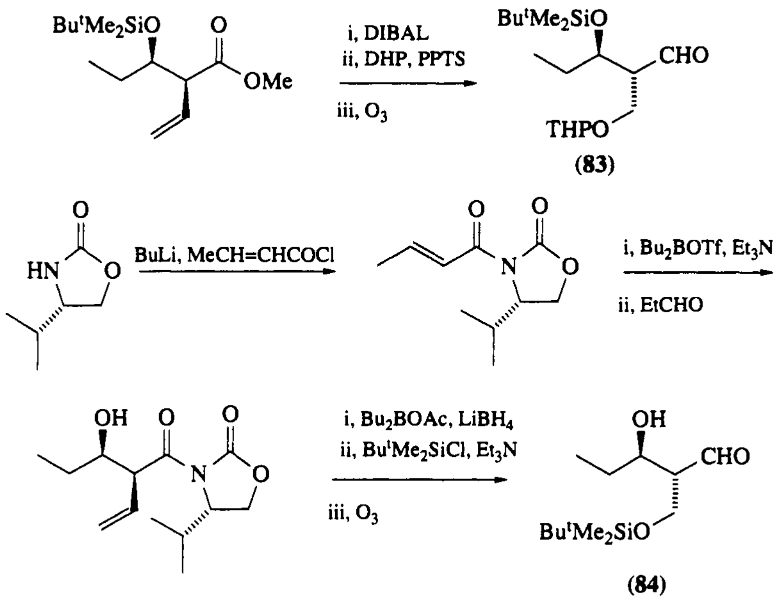
Bu$^t$Me$_2$SiO
OMe
i, DIBAL
ii, DHP, PPTS
iii, O$_3$
Bu$^t$Me$_2$SiO
CHO
THPO
(83)
HN
BuLi, MeCH=CHCOCl
i, Bu$_2$BOTf, Et$_3$N
ii, EtCHO
OH
i, Bu$_2$BOAc, LiBH$_4$
ii, Bu$^t$Me$_2$SiCl, Et$_3$N
iii, O$_3$
OH
CHO
Bu$^t$Me$_2$SiO
(84)

Scheme 35

the double bond furnishes the *anti* unit (**82**). This methodology was applied to the construction of β-hydroxy-α-(hydroxymethyl)carbonyl units (**83**) and (**84**) in Masamune's[13b,47] and Evans'[4a] tylonolide syntheses, respectively (Scheme 35).

*(b) Preparation of anti-α-methyl-β-hydroxy units using external reagents.* The aldol reactions with each of the synthetically useful enantiomerically homogeneous boron reagents discussed above (**29**, **37**, **38** and **57**) provide almost exclusively a single diastereoisomer in which the chiral auxiliary of the reagent is covalently attached to the remainder of the molecule. Reagents of this type are designated internal as opposed to external (chiral) reagents, where the auxiliary is detached from the product after usual work-up. The advantages of the external reagent over the internal are obvious and the crucial role of the external reagent becomes evident in the process of assembling two chiral fragments *via* an aldol reaction, as will be discussed in Section 1.7.2.3.4.

In 1981 Meyers and Yamamoto[40] reported the use of an external reagent in the construction of a 2,3-*anti* unit. The boron azaenolate (**85**), prepared from the chiral boron reagent (**86**; diisopinocampheylboryl triflate; Ipc$_2$BOTf) and the achiral oxazoline derivative (**87**), reacts with aldehydes in ether at –78 °C (Scheme 36). The direct products (**88**) are converted, after hydrolysis and esterification, to the corresponding α-methyl-β-hydroxycarboxyl derivatives (**89**), which are rich in the *anti* isomer (*anti*:*syn*

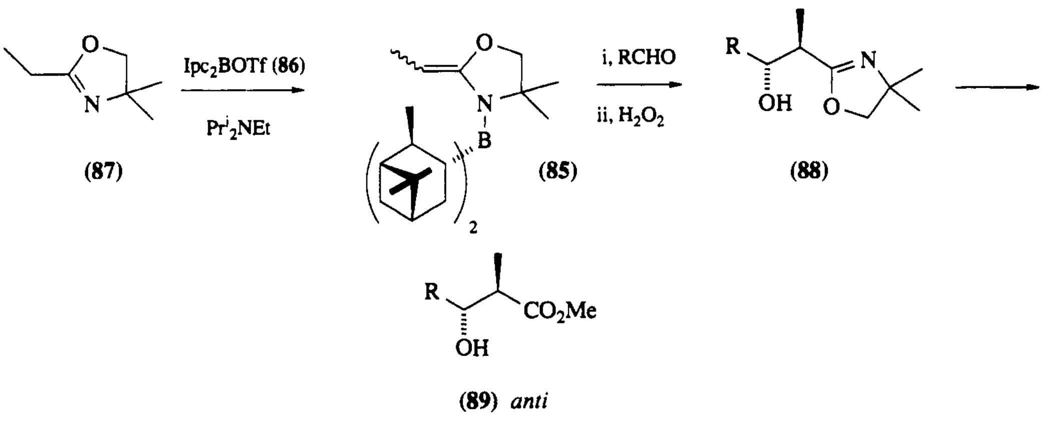
(87)
Ipc$_2$BOTf (86)
Pr$^i_2$NEt
N
B
2
(85)
i, RCHO
ii, H$_2$O$_2$
R
OH
(88)
R
CO$_2$Me
OH
(89) anti

Scheme 36

ratio, 9:1–19:1) and have significant enantiomeric purity (77–85% *ee*). Unfortunately the overall conversion proceeds in low yield (22–36%), probably due to the rather harsh conditions (3 N sulfuric acid, 12 h) used to hydrolyze the oxazoline moiety.

Masamune and coworkers[48] designed a set of chiral *trans*-2,5-dimethylborolane-based reagents that show remarkable enantioselectivities in hydroboration,[49] ketone reduction[50] and crotyl addition to aldehydes.[51] The chirality transfer also turns out to be highly efficient in the aldol reaction. Initial experiments were aimed at defining the structural parameters which affect the *E*(*O*):*Z*(*O*) ratios of the enolates prepared from various alkanethioates with 2,5-dimethylborolanyl triflate (**90**) under standard conditions

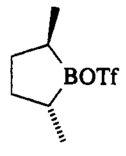

(2*R*,5*R*)-(**90**)

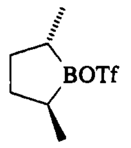

(2*S*,5*S*)-(**90**)

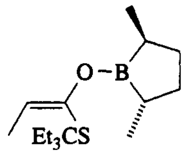

(2*S*,5*S*)-(**91**)

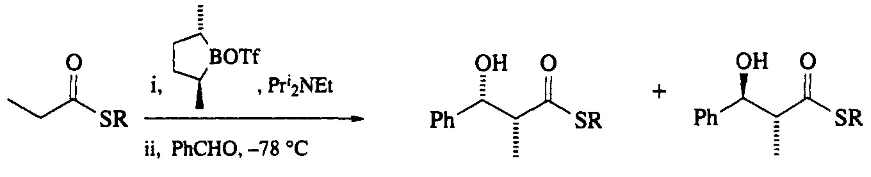

**Scheme 37**

**Table 5** *Anti/Syn* Selectivity of the Aldol Reaction using (2*S*,5*S*)-(**90**)

| *Entry* | *R in thiol esters* | *Combined yield (%)* | *Anti:syn ratio* |
|---|---|---|---|
| 1 | $Pr^i$ | 85 | 78:22 |
| 2 | $Bu^t$ | 100 | 91:9 |
| 3 | 3-(3-Ethyl)pentyl | 75 | 97:3 |
| 4 | Ph | 87 | 7:93 |
| 5 | 2-Naphthyl | 83 | 5:95 |

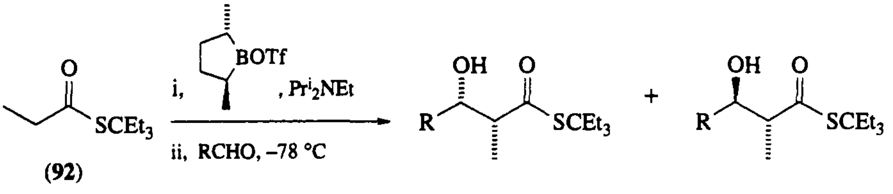

**Scheme 38**

**Table 6** Aldol Reaction of Thioate (**92**) using (2*S*,5*S*)-(**90**) with Representative Aldehydes

| *Entry* | *Aldehyde* | *Yield (%)* | *Anti:syn ratio* | *ee of Anti product (%)* | *Configuration* |
|---|---|---|---|---|---|
| 1 | $Pr^nCHO$ | 91 | 33:1 | 97.9 | (2*R*,3*R*) |
| 2 | $Pr^iCHO$ | 85 | 30:1 | 99.5 | (2*R*,3*R*) |
| 3 | $Bu^tCHO$ | 95 | 30:1 | 99.9 | (2*R*,3*S*) |
| 4 | c-$C_6H_{11}CHO$ | 87 | 32:1 | 98.0 | (2*R*,3*R*) |
| 5 | PhCHO | 71 | 33:1 | 99.8 | (2*R*,3*S*) |
| 6 | $BnO(CH_2)_2CHO$ | 93 | 30:1 | >97.1 | (2*R*,3*R*) |

(Scheme 37). It is clear from Table 5 that the *E*(*O*):*Z*(*O*) ratio increases with the size of the alkanethiol moiety, whereas formation of the *Z*(*O*)-enolate prevails with *S*-aryl thioates.

The *E*(*O*)-reagent (**91**) is formed almost exclusively from *S*-3-(3-ethyl)pentyl propanethioate (**92**) and borolanyl triflate (**90**). Despite its apparent steric demand, (**91**) still retains a high degree of reactivity towards aldehydes (in Scheme 21 the interaction between R and Me is not exceedingly large). Summarized in Table 6 are the results obtained from aldol reactions of representative aldehydes with (**91**; Scheme 38). All reactions proceed smoothly at −78 °C and the major products have the 2,3-*anti* stereochemistry (*anti*:*syn* > 30:1). With (2*S*,5*S*)-(**90**) the aldehydes examined provide, in most cases, the (2*R*) aldol products with more than 98% *ee*. It is important to note that the external chiral moiety can be recovered as its 2,2-dimethylaminoethanol complex, and that the aldol products are equipped with a versatile thioate functionality for further synthetic transformation.

The boron enolates prepared from propanethioate (**92**) and borolanyl triflate (**90**) were examined in reactions with enantiomerically homogeneous aldehydes and proved to follow the rule of double asymmetric synthesis (Scheme 39).[52] As shown in Table 7, the results obtained from a set of lactonization experiments are fully consistent with the approximate multiplicativity rule for double asymmetric synthesis.

The two other aldol products that can be derived *via* propionate addition to (**24**) are the Prelog–Djerassi lactonic acid diastereomers, both of which were prepared successfully with the internal chiral boron enolates discussed earlier in this section. Thus this work completes a set of chiral reagents that can control the relative stereochemistry at the 2, 3 and 4 positions of aldol products.

Another $C_2$ symmetric chiral borane reagent has been utilized by Corey *et al.*[83] for the construction of *syn* aldol products in a highly enantioselective manner. When an enolate prepared from *S*-phenyl pro-

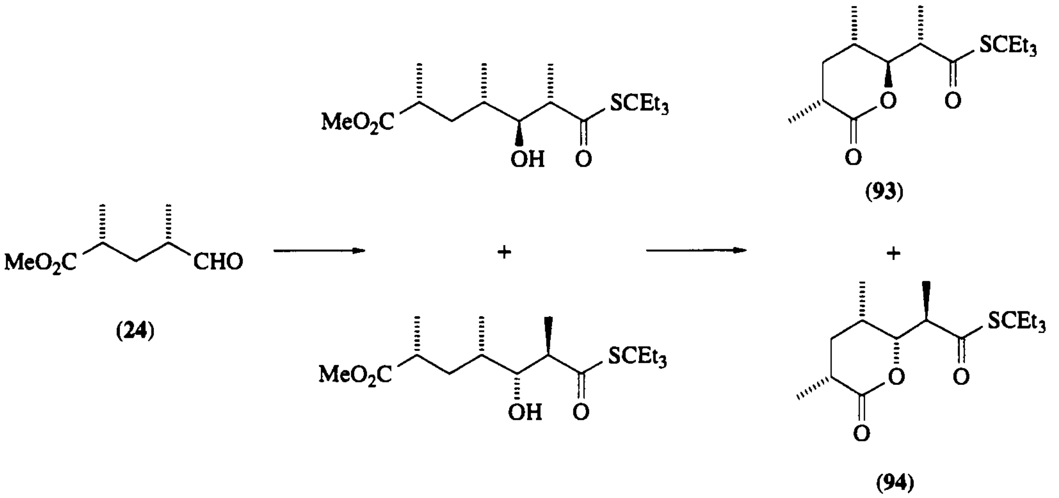

(**24**)

(**93**)

(**94**)

**Scheme 39**

**Table 7** Aldol Reactions of (**24**) and Ent-(**24**) with Enolate (**91**) Followed by Lactonization

| *Entry* | *Aldehyde* | *Products after lactonization*<br>*3,4-anti* |  <br>*3,4-syn* | *3,4-Anti:syn ratio (corrected)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | (**24**) | (**93**) | (**94**) | 200:1 | 90 |
| 2 | Ent-(**24**) | Ent-(**93**) | Ent-(**94**) | 1:55 | 83 |

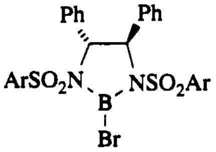

*(R,R)*-(**i**)

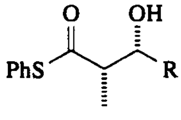

(**ii**)

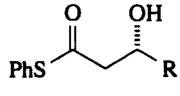

(**iii**)

panethioate and the chiral borane reagent (*R*,*R*)-(**i**) in the presence of $Pr^i_2EtN$ is allowed to react with benzaldehyde or isobutyraldehyde, highly *syn* selective aldol products (**ii**) (*syn*/*anti* 95:5 and 98:2, respectively) are obtained with very high enatioselectivities (95 and 97% *ee*, respectively). Likewise, the aldol reaction of acetate derivatives using a similar chiral borane reagent proved to be very enantioselective. The enolate prepared from phenyl thioacetate and the chiral borane reagent in the presence of triethylamine provided, upon reaction with benzaldehyde or isobutyraldehyde at –90 °C, the aldol products (**iii**) of 91% and 83% *ee*, respectively.

### 1.7.2.3.2 Construction of α-unsubstituted-β-hydroxycarbonyl units

The synthesis of enantiomerically homogeneous α-unsubstituted-β-hydroxycarbonyl compounds by the aldol reaction has been a difficult challenge. Nor analogs of the chiral boron enolates developed for the highly *syn* selective propionate aldol reaction have given disappointingly low degrees of stereoselection with representative aldehydes. Several attempts have been made to overcome this problem. These efforts include aldol reactions of boron enolates which incorporate at the α-position a 'dummy' group which is removed after the reaction. Using this technique high levels of asymmetric induction have been recorded as shown in Scheme 40.[5e,38]

Various other methods not involving boron enolates have been developed to achieve high asymmetric induction in acetate addition and are discussed elsewhere in this volume.

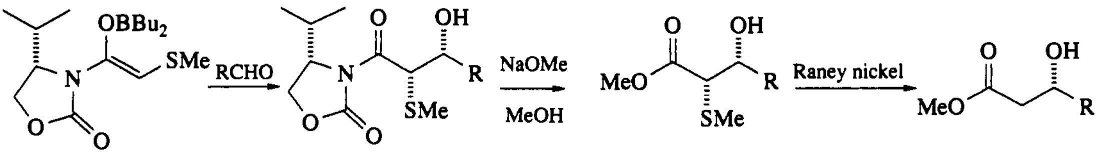

**Scheme 40**

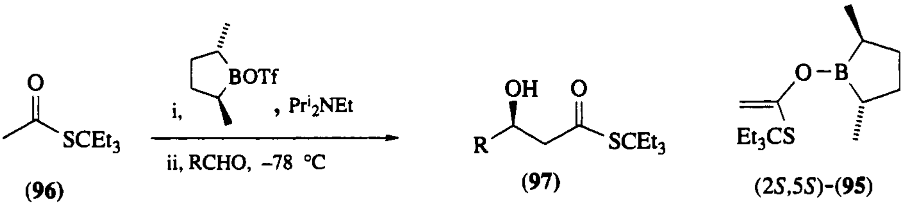

**Scheme 41**

**Table 8** Synthesis of 3-Hydroxy Thioesters (**97**)

| *Entry* | *Aldehyde* | *Yield (%)* | *Corrected ee (%)* | *Configuration* |
|---|---|---|---|---|
| 1 | $Pr^nCHO$ | 82 | 91.2 | (*R*) |
| 2 | $Bu^iCHO$ | 81 | 91.5 | (*S*) |
| 3 | $Bu^tCHO$ | 71 | 98.4 | (*S*) |
| 4 | c-$C_6H_{11}CHO$ | 95 | 90.1 | (*S*) |
| 5 | PhCHO | 78 | 92.2 | (*S*) |
| 6 | $BnO(CH_2)_2CHO$ | 93 | 89.1 | (*R*) |

**Table 9** Aldol Reactions of (**24**) and Ent-(**24**) with Enolate (**95**) Followed by Lactonization

| *Entry* | *Aldehyde* | *Products after lactonization* | | *3,4-Anti:syn ratio (corrected)* | *Yield (%)* |
|---|---|---|---|---|---|
| | | *3,4-anti* | *3,4-syn* | | |
| 1 | (**24**) | (**98**) | (**99**) | 13:1 | 81 |
| 2 | Ent-(**24**) | Ent-(**98**) | Ent-(**99**) | 1:7 | 83 |

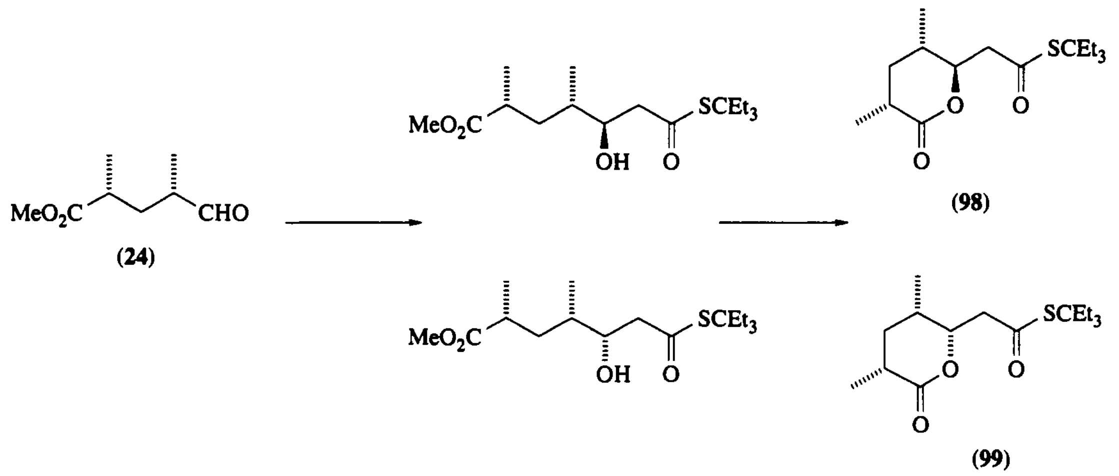

Scheme 42

In contrast to all known chiral boron enolates, the external reagent (**95**) derived from ethanethioate (**96**) and 2,5-dimethylborolanyl triflate (2*S*,5*S*)-(**90**) effects asymmetric induction in the aldol reaction to provide β-hydroxy thioesters of approximately 90% *ee* for most aldehydes (Scheme 41; Table 8).[48]

The 10% decrease in enantiomeric excess compared with that observed for the propionate enolate (**91**) is reflected in the double asymmetric synthesis outlined in Scheme 42 and Table 9 (see Table 7 for comparison).[52]

### *1.7.2.3.3 Comments on the facial selectivities of the chiral alkenyloxydialkylboranes*

For many aldol reactions, a Zimmerman–Traxler model[37] is most conveniently used to rationalize the stereochemical outcome of these reactions. It may be used here again to explain the higher enantioselectivities exhibited by (**91**) compared to (**95**). In transition state (**F**) for the reaction of an aldehyde with re-

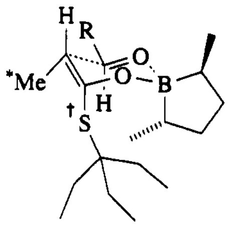

(**F**)

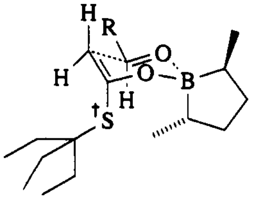

(**G**)

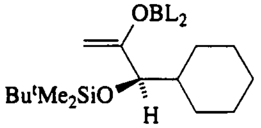

(**100**)

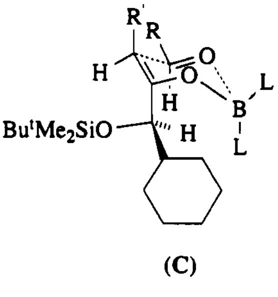

(**C**)

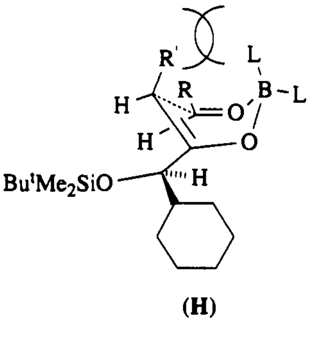

(**H**)

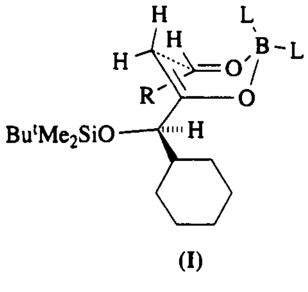

(**I**)

agent (**91**), the asterisked methyl group steers the 3-ethyl-3-pentanethiol group toward the borolane moiety, effectively transferring the chirality. In the absence of this 'steering effect', as may be the case for transition state (**G**), depicting the reaction of reagent (**95**), the enantioselection of the reaction decreases. The supposition that both reactions proceed through a chair-form transition state is of great interest in that both (**91**) and (**95**) have no *Z*(*O*)-methyl substituent. The nor analog (**100**) of reagent (**29**), previously discussed in Section 1.7.2.3.1, provides an approximately 1:1 mixture of two diastereomeric aldol products.[53]

While the preferred transition state for reaction with (**29**) is (**C**) (rather than (**H**) where the steric hindrance between the *Z*(*O*)-methyl group (R′) and the ligand (L) attached to the boron atom is prohibitively severe), the reaction with (**100**) may well proceed through the boat-form transition states (**H**; R′ = H) and/or (**I**). Transition states (**H**) and (**I**) would be expected to be of approximately equal energy, differing only in the orientation of the reacting aldehyde with respect to (**100**), as shown. The reaction thus proceeds stereorandomly. In contrast, the 3-ethyl-3-pentanethiol group in (**F**) and (**G**), despite its steric bulk, is conformationally more flexible and free to rotate about the axis of the carbon–sulfur bond, indicated by the dagger. (Note: the carbon–sulfur bond is long.) Thus, this large group can be accommodated within the chair-form framework.

### *1.7.2.3.4 External chiral reagents for the aldol reaction of ketones*

#### *(i) Aldol reactions of ethyl ketones*

The aldol reaction has been recognized as a useful reaction for assembling two large fragments with concomitant creation of a stereogenic center or centers in the convergent synthesis of many natural products. Stereocenters embedded in the fragments necessarily correspond to those of a target molecule, and the stereoselectivity of the coupling reaction heavily depends on the diastereoselectivities of the two reactants, *e.g.* an enolate and an aldehyde, derived from the two fragments, if an aldol reaction is used. Diastereofacial selectivities are predetermined but are normally unpredictable in both magnitude and

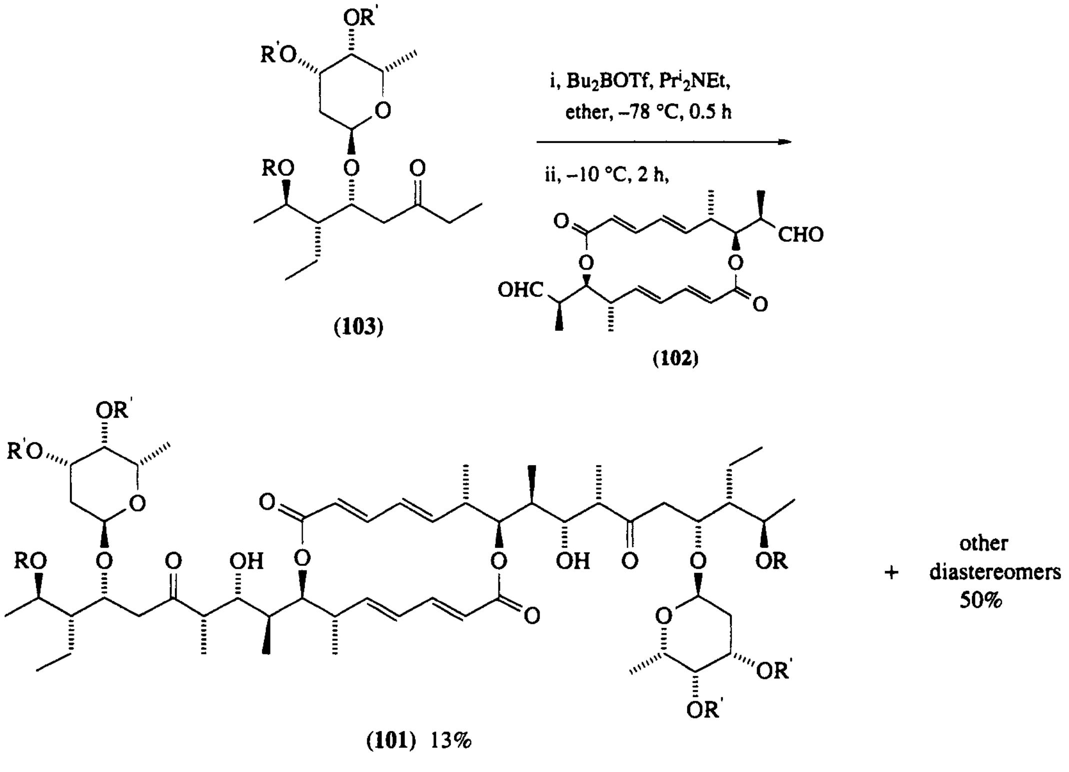

**Scheme 43**

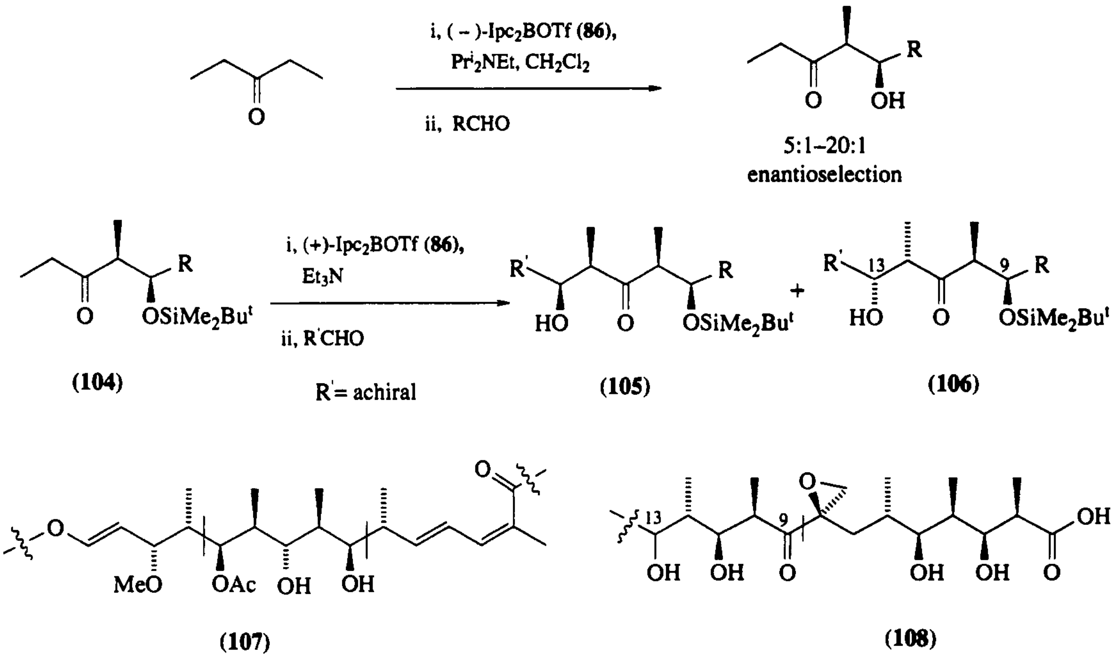
i, (–)-Ipc2BOTf (86), Pri2NEt, CH2Cl2
ii, RCHO
5:1–20:1 enantioselection
i, (+)-Ipc2BOTf (86), Et3N
ii, R'CHO
R' = achiral
(104)
(105)
(106)
(107)
(108)
13
9
R
R'
O
OH
OSiMe2But
HO
MeO
OAc

**Scheme 44**

sense. The coupling often constitutes the least stereoselective step in the total synthesis unless the two reactants fall into a matched pair favoring the formation of the desired stereochemistry.

Depicted in Scheme 43 is an example of an apparently mismatched, but otherwise highly convergent, set of two simultaneous coupling reactions used by Kinoshita and coworkers[54] in their synthesis of elaiophylin (azalomycin B; **101**; R = R′ = H), a C(2)-symmetrical 16-membered macrodiolide. When the aldehyde (**102**) is treated with the dibutylboryl enolate of (**103**), generated in a standard fashion, the desired diastereomer (**101**) is obtained in 13% yield. This crucial closing stage of the total synthesis is enfeebled by a 2:1 preponderance of the unwanted ‘Cram’ product over the desired ‘anti-Cram’ product (**101**). The latter upon removal of the protecting groups R and R′ provides azalomycin B. A similar situation where the selectivity is solely dependent upon the inherent facial selectivity of two coupling substrates has arisen in the final stage of a recent total synthesis of ionophore X-206 by Evans.[55]

How can we gain stereocontrol over aldol reactions used for coupling? One solution is to alter, or ideally overpower, the diastereofacial selectivities of the enolates derived from chiral ketones by using an external chiral boron reagent, *e.g.* $Ipc_2BOTf$ (**86**) and 2,5-*trans*-dimethylborolanyl triflate (**90**), instead of the achiral reagent ($Bu_2BOTf$) exemplified above in the azalomycin B synthesis. In this way, the stereochemical course of the coupling reaction may be analyzed in terms of three diastereofacial selectivities, that of the chiral ligands attached to the boron reagent and those of the two chiral fragments. The boron reagent can be designed, selected and serve as a controlling component.

Paterson *et al.*[56] have prepared the enolate of 3-pentanone, an achiral ketone, with (+)- or (–)-$Ipc_2BOTf$ and have found that its aldol reactions with various aldehydes proceed with high *syn:anti* ratios (>9:1) and respectable enantioselectivities (5:1–20:1) (Scheme 44). High degrees of asymmetric induction are noted with unhindered aldehydes. The combination of the chiral ethyl ketone (**104**) and (+)-$Ipc_2BOTf$ constitutes a matched pair, which enhances the diastereofacial selectivity of the resulting enolate (compared to that obtained with an achiral boron reagent), and provides *via* aldol reactions high

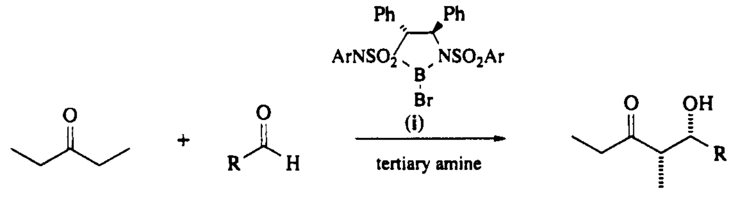

**Scheme A**

ratios (30:1–47:1) of the products (**105**) and (**106**). The product (**105**) is an intermediate that can be converted to the ansa chain (**107**) of rifamycin S.[57] Attempts to prepare (**106**) as the major product were made for the purpose of preparing (**108**), the seco-acid of oleandomycin. The use of (–)-(**86**) and (**104**) (mismatched pair) results in a decrease of the (**105**):(**106**) ratio to 3:1 but not in the predominant formation of (**106**). Apparently the diastereofacial selectivity of (+)- or (–)-$Ipc_2BOTf$ is smaller than that intrinsic to (**104**).

Highly enantioselective aldol reactions of diethyl ketone have been recorded with the use of the chiral borane reagent (**i**).[83] As shown in Scheme A, *syn* aldol products of 95–98% *ee* have been obtained upon reaction with various aldehydes with 94–98% diastereoselectivities.

### *(ii) Aldol reactions of methyl ketones*

Achievement of high asymmetric induction in boron-mediated aldol reactions of methyl ketones turns out to be an exceedingly challenging task, and chiral reagents capable of meeting this challenge are yet to be designed and synthesized. This section briefly summarizes the endeavors of the Masamune group toward this aim, with the hope that the data shown below are of some use for the future development of this methodology.

Diastereofacial selectivities have been examined for a set of external chiral boron reagents using a standard sequence of processes: (i) preparation of the enolates of methyl cyclohexyl ketone, pinacolone and methyl neopentyl ketone with the boron reagents, (ii) aldol reactions with isobutyraldehyde and (iii) determinations of enantiomer ratios. Selected examples are shown in Table 10. The diastereofacial selectivities (or enantioselectivities) of (**86**), (2*S*,5*S*)-(**90**), (2*R*,5*R*)-(**90a**), (**109**) and (**110**) are not significantly high; mostly in the range of 3:1–8:1 (50–70% *ee*), except for that shown in entry 6. These results suggest that use of the foregoing chiral reagents in the assembly of two chiral fragments will effectively enhance the stereoselectivity of the reaction in a matched case, but will not reverse its stereochemical course. Several trends are predictable: (i) when $Ipc_2BOTf$ (**86**; entries 4 and 6) is used, the aldol reactions must be carried out at an elevated temperature (0 °C instead of –78 °C) to provide reasonable yields of products; and (ii) for a given boron reagent, *e.g.* (**86**) and (**90**), the more highly hindered ketone (pinacolone) undergoes aldol reactions with lower asymmetric inductions (compare entries 1 and 5, and 4 and 6).

Application of the external chiral boron reagent (**90**) in the total synthesis of bryostatin, a natural product, is shown in Scheme 45.[58] The convergent approach adopted involves coupling of the boron enolate derived from (**111**) with aldehyde (**112**). The reaction mediated by an achiral boron reagent ($Et_2BOTf$) provides only a 2:1 preference for the formation of the desired isomer (11*S*) in adduct (**113**). The use of chiral (2*R*,5*R*)-dimethylborolanyl triflate in this reaction increases the selectivity to a 6:1 preference as

$Ipc_2BOTf$

(**86**)

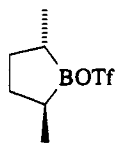

(2*S*,5*S*)-(**90**)

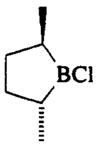

(2*R*,5*R*)-(**90a**)

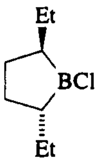

(**109**)

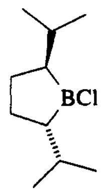

(**110**)

**Table 10** Asymmetric Aldol Reaction of Ketones with Various Boron Reagents[a]

| *Entry* | *Ketone* | *Boron reagent* | *Solvent* | *Reaction conditions* | *Isolated yield (%)* | *Configuration* | *Ee (%)* |
|---|---|---|---|---|---|---|---|
| 1 | $MeCOc\text{-}C_6H_{11}$ | (*S,S*)-(**90**) | Pentane | –78 °C, 2 h | 68 | (*S*) | 60 |
| 2 | $MeCOc\text{-}C_6H_{11}$ | (*R,R*)-(**110**) | Pentane | –78 to –65 °C, 7 h | 76 | (*R*) | 56 |
| 3 | $MeCOc\text{-}C_6H_{11}$ | (*R,R*)-(**109**) | Pentane | –78 °C, 4.5 h | 72 | (*R*) | 61 |
| 4 | $MeCOc\text{-}C_6H_{11}$ | (**86**)[b] | Pentane | 0 °C, 2 h | 54 | (*R*) | 77 |
| 5 | $MeCOBu^t$ | (*S,S*)-(**90**) | Pentane | –78 °C, 4 h | 91 | (*S*) | 50 |
| 6 | $MeCOBu^t$ | (**86**)[b] | $CH_2Cl_2$ | 0 °C, 2 h | 66 | (*R*) | 23 |
| 7 | $MeCOCH_2Bu^t$ | (*R,R*)-(**90a**) | $CH_2Cl_2$ | –78 °C, 3 h | 86 | (*R*) | 64 |

[a] Unless otherwise noted, the enolates are prepared by adding the boron reagent (1.2 equiv.) to a mixture of the ketone (1.0 equiv., 0.15–0.20 M) and $Pr^i_2NEt$ (1.2 equiv.), isobutyraldehyde (1.5 equiv.) is then added to the enolate. [b] Prepared from (α)-(+)-pinene.

predicted for this matched reaction. In contrast, the mismatched reaction using the (2*S*,5*S*)-dimethylborolanyl triflate produces a 1:2 preference for the formation of the (11*R*) isomer.

The stereochemical outcome for the assembly of the C(1)–C(16) fragment of bryostatin outlined above is consistent with the rule of double asymmetric synthesis. This suggests that the approximate multiplicativity of *ds* values may even apply to a reaction system involving three chiral components (triple asymmetric synthesis). To examine this possibility, Masamune *et al.*[59] have selected an aldol reaction involving (–)-aldehyde (**24**) and ketone (**114**) (enolate precursor), both of which are 3,4-*anti* selective, and each has a *ds* of *ca.* 2:1. As expected, the reaction with achiral diethylboryl triflate provides the aldol products (**115**) with a 7:1 *anti*:*syn* selection (Scheme 46). The chiral reagent (2*R*,5*R*)-(**90**) is matched with both (**24**) and (**114**) and its utilization in the aldol reaction enhances the above selection to 25:1, whereas the mismatched reaction of (2*S*,5*S*)-(**90**) leads to a 1:1 ratio of diastereomers. These results also support the approximate multiplicativity rule for triple asymmetric synthesis and assure that the fragment assembly can be stereocontrolled to secure either isomer with an external chiral reagent possessing a higher *ds*. The *ds* of (**90**) is approximated to be 5:1 in aldol reactions using methyl ketone enolates.

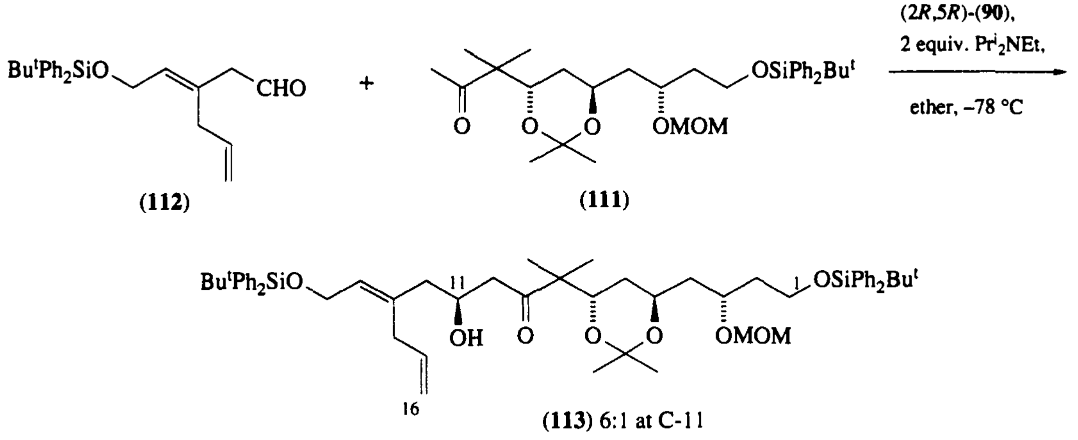
Bu<sup>t</sup>Ph₂SiO
CHO
+
O
O
O
OMOM
OSiPh₂Bu<sup>t</sup>
(2R,5R)-(90),
2 equiv. Pr<sup>i</sup>₂NEt,
ether, –78 °C
(112)
(111)
Bu<sup>t</sup>Ph₂SiO
11
OH
O
O
O
OMOM
1
OSiPh₂Bu<sup>t</sup>
16
(113) 6:1 at C-11

**Scheme 45**

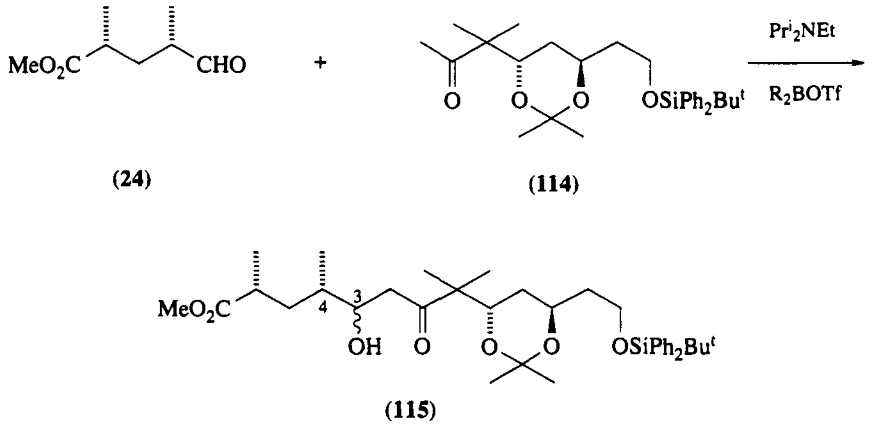
MeO₂C
CHO
+
O
O
O
OSiPh₂Bu<sup>t</sup>
Pr<sup>i</sup>₂NEt
R₂BOTf
(24)
(114)
MeO₂C
4
3
OH
O
O
O
OSiPh₂Bu<sup>t</sup>
(115)

| | *3,4-anti*:*3,4-syn* |
|---|---|
| $R_2BOTf = Et_2BOTf$ | 7:1 |
| (2*R*,5*R*)-(**90**) | 25:1 |
| (2*S*,5*S*)-(**90**) | 1:1 |

**Scheme 46**

### 1.7.2.4 Aldol Reactions Mediated by Alkenyloxydialkoxyboranes

The high degree of stereoselectivity achieved with alkenyloxydialkylboranes due to the tightness of the six-membered transition states has been amply discussed in an earlier section of this chapter. Hoffmann and Ditrich[60] investigated aldol reactions of alkenyloxydialkoxyboranes with the assumption that a decrease in the Lewis acidity of these reactants may lead to an even tighter transition state at a later stage of the reaction pathway. Either of the two stereoisomeric enolates can be prepared using different routes. The *Z*(*O*)-enolate (**116**) can be derived from (*Z*)-2-bromo-2-butene *via* a Grignard reaction as shown in Scheme 47. The preparation of *E*(*O*)-enolate (**117**) is achieved through a sequence of reactions involving hydroboration of 2-butyne with catecholborane, transesterification of the dialkoxyborane with pinacol and oxidation to (**117**). Aldol reactions of aldehydes with *Z*(*O*)-enolate (**116**) proceed very slowly (10–75 h at 25 °C) compared to those with typical alkenyloxydialkylboranes (several hours at –78 °C). The *Z*(*O*)-enolate (**116**) as expected yields *syn* products with aldehydes after work-up with triethanolamine (Table 11, entries 1–3). Unexpectedly, the *E*(*O*)-enolate (**117**) also provides *syn* diastereomers with a much enhanced rate ($t_{1/2} \approx$ 20 min at –60 °C) as shown in entries 4–6. Thus, aldol reactions with (**116**) and (**117**) are stereoconvergent.

Alkenyloxydialkoxyboranes can also be generated from the corresponding silyl enolates, either directly or *via* the lithium enolates.[60] The slow reaction of *Z*(*O*)-enolate (**116**) with aldehydes can be accelerated with the aid of a catalytic amount (10–20 mol %) of trimethoxyborane.[60] This acceleration is presumably due to a facile transesterification that converts (**116**) into the more reactive alkenyloxydimethoxyborane.

Several reports by Gennari *et al.*[61] describe the generation of enolates directly from carbonyl compounds by using ethylenedioxychloroborane (*B*-chloro-2,5-dioxaborolane; **118**) in the presence of diisopropylethylamine. Reactions of these enolates, derived from ketones and thiol esters, with aldehydes provide good yields (60–85%) of aldol adducts, whereas esters give unsatisfactory yields (~30%). When ethyl ketones or propanethioates are employed, *Z*(*O*)-enolates (**119**) can be formed exclusively using specific reaction conditions,[62] and excellent *syn* selectivities (92:8 to 99:1) are observed (Scheme 48).

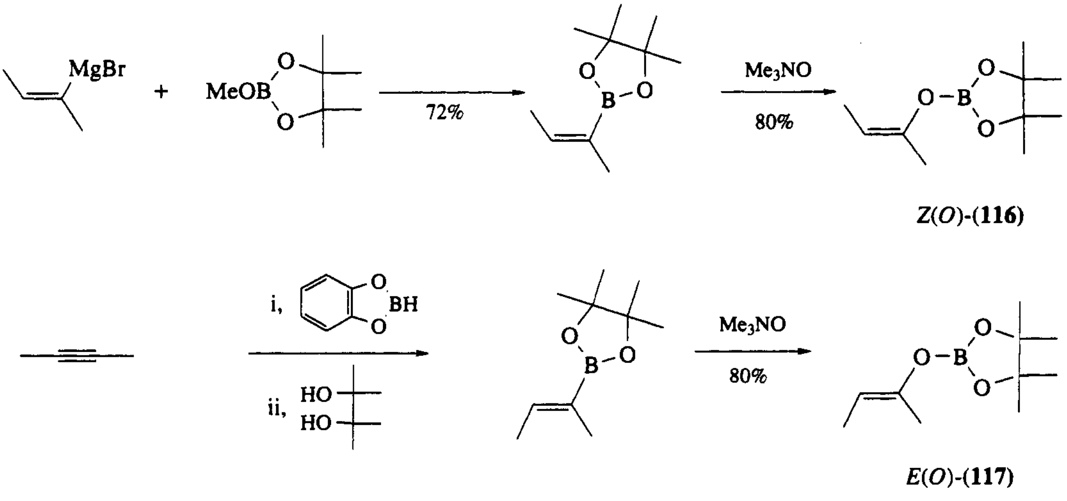

**Scheme 47**

**Table 11** *Syn*:*Anti* Ratios of Aldol Products From the Reaction of *Z*(*O*)- and *E*(*O*)-Alkenyloxydialkoxyboranes with Representative Aldehydes

| *Entry* | *Dialkoxyboryl enolate* | *Aldehyde* | *Yield (%)* | *Syn:anti ratio* |
|---|---|---|---|---|
| 1 | *Z*(*O*)-(**116**) | PhCHO | 89 | >95:5 |
| 2 | *Z*(*O*)-(**116**) | Pr$^i$CHO | 85 | 91:9 |
| 3 | *Z*(*O*)-(**116**) | EtCHO | 88 | 88:12 |
| 4 | *E*(*O*)-(**117**) | PhCHO | 79 | 95:5 |
| 5 | *E*(*O*)-(**117**) | Pr$^i$CHO | 86 | 90:10 |
| 6 | *E*(*O*)-(**117**) | EtCHO | 82 | 90:10 |

*Z*(*O*)-Enolates are readily equilibrated to the corresponding *E*(*O*)-isomers in the presence of a protonated amine.

To explain the *syn* selectivity for the reactions of both *Z*(*O*)- and *E*(*O*)-enolates derived from (**118**), Gennari *et al.* suggested a chair-like transition state (**J**) for *Z*(*O*)-enolates and a boat-like transition state (**K**) for *E*(*O*)-enolates (Scheme 49).[62,63] Computational studies undertaken later by the same group[64] on aldol reactions using enolates (**120**) and (**121**), as well as dialkylboryl enolates, provided a set of data that was consistent with the experimental results and further corroborated the proposed mechanism. Thus: (i) The ground-state conformations of the enolates are important in determining the different reactivities of *Z*(*O*)-enolates (**120**) and *E*(*O*)-enolates (**121**), the latter are much more reactive than the former. (ii) The energy requirements for the reactions with aldehydes indicate that *Z*(*O*)-enolates prefer half-chair transition states, while *E*(*O*)-enolates favor half-boat transition states. Both transition states lead to the formation of *syn* aldol products. (iii) In contrast, when dialkylboryl enolates are used, bulky substituents on the boron atom disfavor the twist-boat for both *E*(*O*)- and *Z*(*O*)-enolates, resulting in the formation of *anti* and *syn* isomers, respectively (Section 1.7.2.2).

An attempt to accomplish asymmetric induction using a dialkoxyboryl enolate has been made by Chow and Seebach.[24] Reaction of the alkenyloxydialkoxyborane (**122**) derived from (–)-(*S*)-1,1′-bi-2-

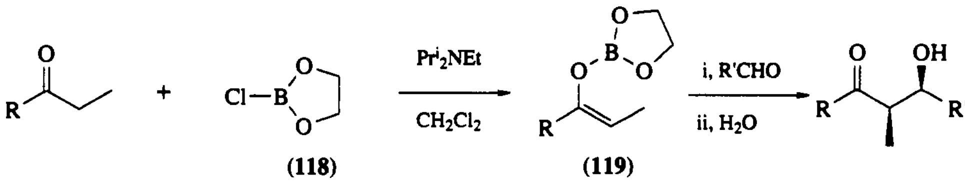

Scheme 48

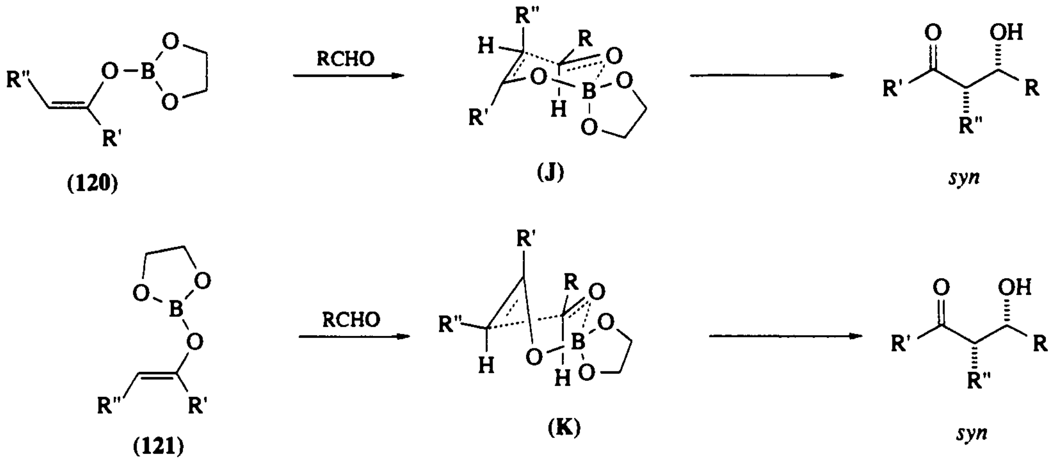

Scheme 49

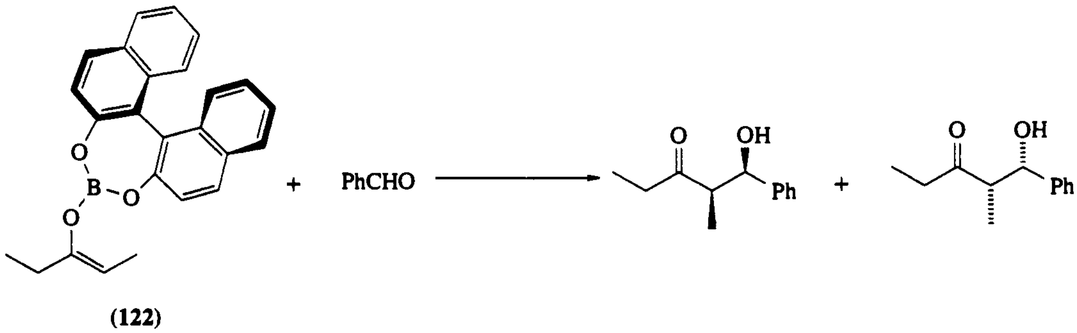

Scheme 50

naphthol with benzaldehyde provides the *syn* aldol product in 47% *ee* (Scheme 50). The absolute configuration of this product is not recorded.

## 1.7.3 ALUMINUM-MEDIATED ALDOL REACTION

### 1.7.3.1 Preparation of Alkenyloxyalanes and Subsequent Aldol Reactions

Aluminum oxide has been one of the most frequently used reagents for self-condensation of ketones and aldehydes.[65] However applications of aluminum-mediated aldol reactions to cross-coupling have appeared only recently in the literature. Aluminum reagents, in common with other Lewis acids, form aldol product chelates so that unwanted side reactions such as dehydration or secondary condensation may be avoided.[66]

In 1974, Jeffery *et al.* reported the first use of well-defined dimeric or trimeric aluminum enolates in the aldol reaction.[67,68] Reaction of dimethyl-*Z*(*O*)-4,4-dimethylpent-2-en-2-oxyalane (**123**) with acetaldehyde or benzaldehyde provides the *anti* aldol products (**124**) as chelated dimers involving five-coordinate aluminum atoms, as shown in Scheme 51. However, the corresponding *E*(*O*)-enolate (**125**) gives dimeric products of *syn* configuration which undergo isomerization, if not hydrolyzed immediately, to provide the same *anti* products.[69] This *syn–anti* isomerization is much more facile with benzaldehyde, and is in sharp contrast to aldol reactions mediated by boron.

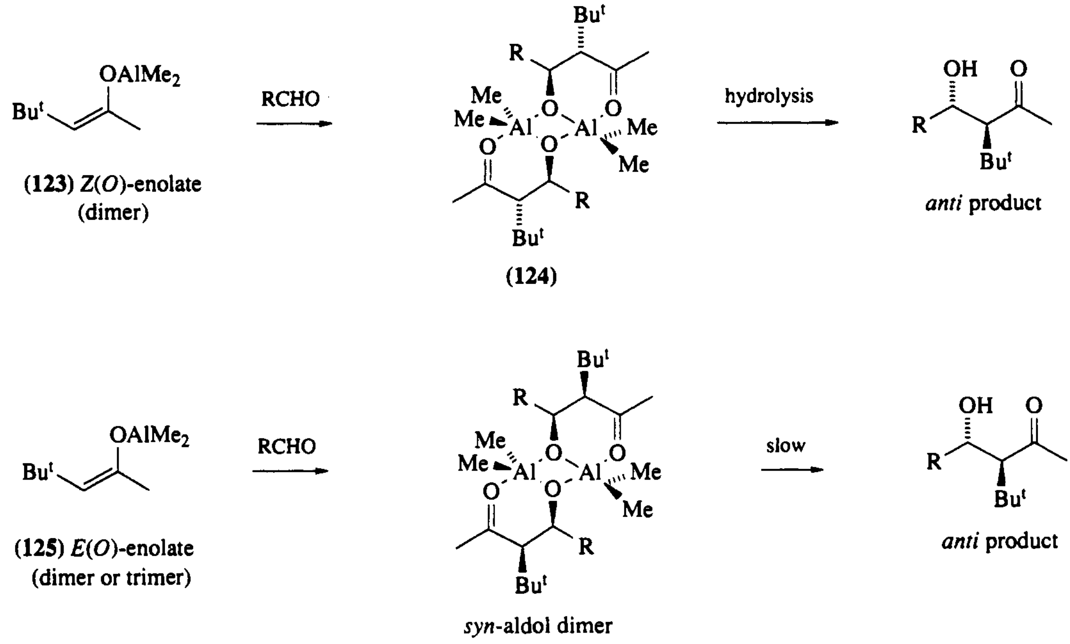

(**123**) *Z*(*O*)-enolate (dimer)

(**124**)

*anti* product

(**125**) *E*(*O*)-enolate (dimer or trimer)

*syn*-aldol dimer

*anti* product

Scheme 51

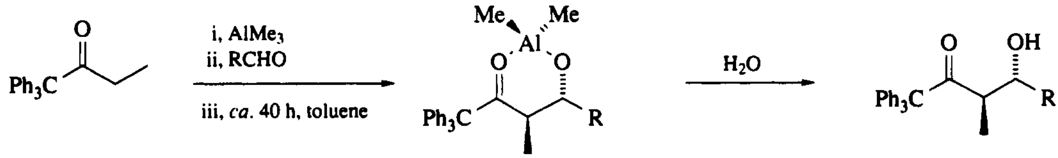

Scheme 52

Ertas and Seebach[70] have studied the *syn–anti* isomerization of aldol adducts chelated to aluminum for the reaction of ethyl trityl ketone with aldehydes in the presence of trimethylaluminum (Scheme 52).

Aldol reactions involving aluminum species are considered to be of less synthetic value because of the ambiguous isomerization of the aldol products, under the influence of the Lewis-acidic aluminum species. Efforts have been made to generate an aluminum enolate in a regiospecific manner. Addition of dialkylchloroalane and zinc to a mixture of an α-halo ketone (**126**) and an aldehyde leads to the formation of enolate (**127**), which subsequently reacts with the aldehyde, as shown in Scheme 53.[71] This method is applicable to the construction of medium to large rings by intramolecular aldol cyclization of various α-bromocarboxylates of ω-hydroxy aldehydes (*e.g.* $BrCHRCO_2(CH_2)_nCHO$ where $n = 9$, 11 or 12 and R = H or Me). The macrolactonization proceeds in reasonable yield, as shown in Scheme 53.

A new procedure for the preparation of β-trimethylsilyloxy ketones and esters from silyl enolates (**128**) and silyl ketene acetals (**128a**; $R^1 = OPr^i$) has been developed by Yamamoto *et al.* (Scheme 54).[72] Good to excellent yields of protected aldol products are obtained using a catalytic amount (0.05–0.1 equiv.) of dimethylaluminum chloride. However, only a small degree of diastereoselectivity is obtained even when silyl enolates of high stereochemical purity are used.

In a manner analogous to the earlier boron work (Section 1.7.2.1), an effort has been made to generate alkenyloxyalanes from α,β-unsaturated carbonyl compounds by 1,4-addition of aluminum reagents.[73] The addition of $Me_2AlSPh$ or $Me_2AlSeMe$ to an α,β-unsaturated carbonyl compound produces a 3-substituted alkenyloxyalane derivative, which upon reaction with an aldehyde gives a crossed aldol product,

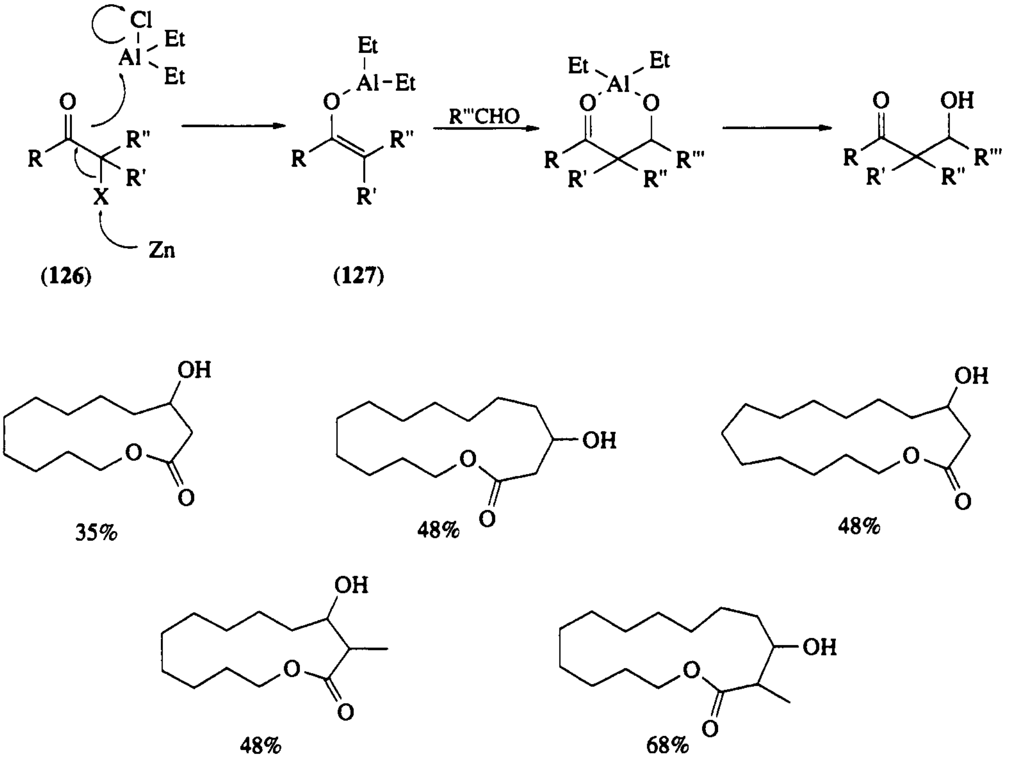

(**126**) (**127**)

Scheme 53

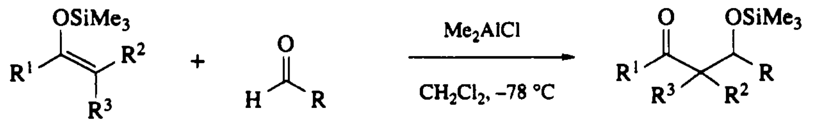

(**128**) or (**128a**)

Scheme 54

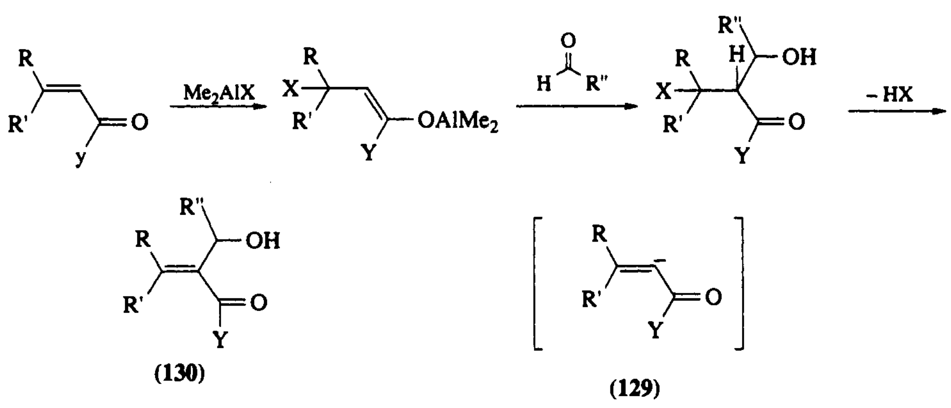
Me2AlX
OAlMe2
- HX
OH
R R' R'' X Y

(130) (129)

Scheme 55

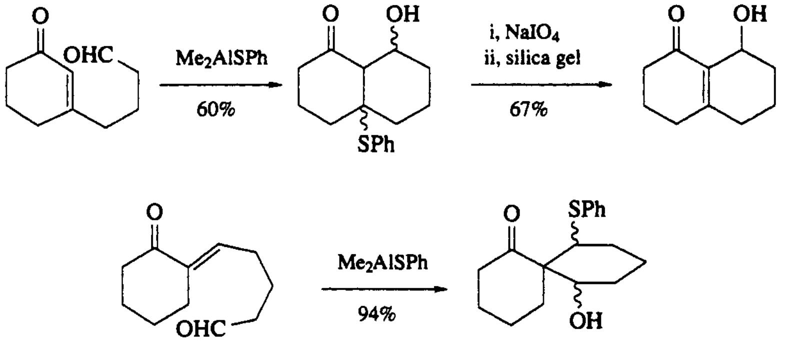
OHC
Me2AlSPh
60%
SPh
OH
i, NaIO4
ii, silica gel
67%
Me2AlSPh
94%

Scheme 56

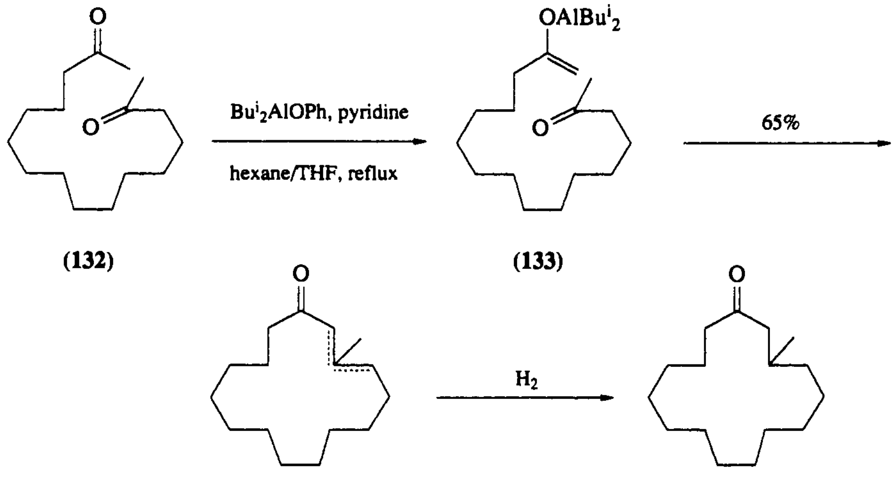
Bui2AlOPh, pyridine
hexane/THF, reflux
OAlBui2
65%
H2

(132) (133) (131)

Scheme 57

as shown in Scheme 55. The overall transformation is viewed as addition of the acylethenyl anion (**129**) to the aldehyde to form (**130**). The application of this method is exemplified in Scheme 56.

Regioselective aldol reactions can be achieved with organoaluminum reagents, and a good example of this application is in the synthesis of muscone (**131**; Scheme 57).[74] The key step involves macrocycli-

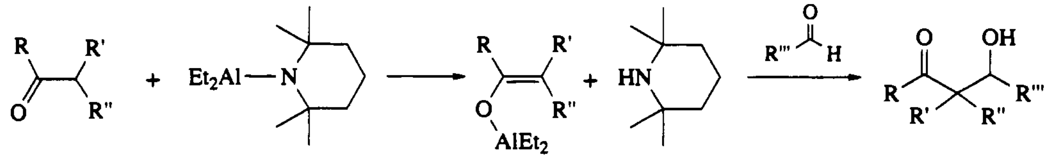
R
R'
O
R''
Et$_2$Al—N
AlEt$_2$
HN
R''' H
OH
R'''

55–92% yields

**Scheme 58**

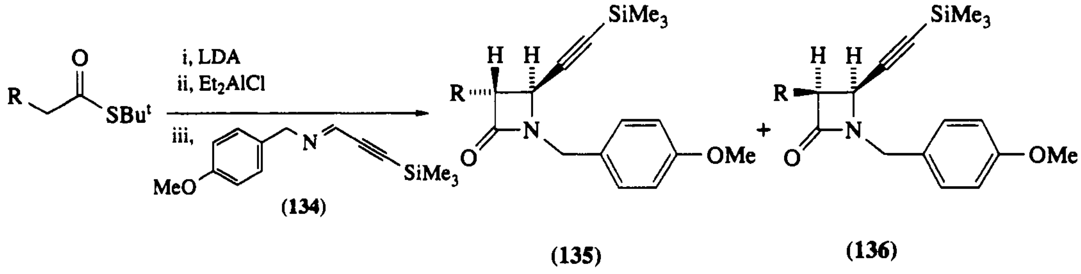
i, LDA
ii, Et$_2$AlCl
iii,
SBu$^t$
MeO
SiMe$_3$
(134)
H H
OMe
(135)
(136)

*anti*:*syn* 3:1 ~ 4:1

**Scheme 59**

zation of the diketone (**132**), which uses diisobutylphenoxyalane and pyridine to furnish the kinetic enolate (**133**). The desired intramolecular aldol reaction of (**132**) is difficult to achieve by other methods.

A similar method for the formation of enolates derived from esters and ketones uses diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), as shown in Scheme 58.[75]

Reaction of an alkenyloxydiethylalane with an imine has been reported by Iwasaki and Shibasaki (Scheme 59).[76] The diethylaluminum enolate derived from *S*-*t*-butyl alkanethioate, upon reaction with imine (**134**), furnishes β-lactams (**135**) and (**136**) in an *anti* selective manner.

### 1.7.3.2 Aldol Reactions Using Enantiomerically Homogeneous Alkenyloxydialkylalanes

Davies[77] and Liebeskind[78] independently prepared chiral aluminum enolates from enantiomerically homogeneous acyl–iron complexes (**137**) and recorded the first aluminum-mediated asymmetric aldol reactions. Although the lithium enolate of the chiral iron complex (CHIRAC) provides aldol products with

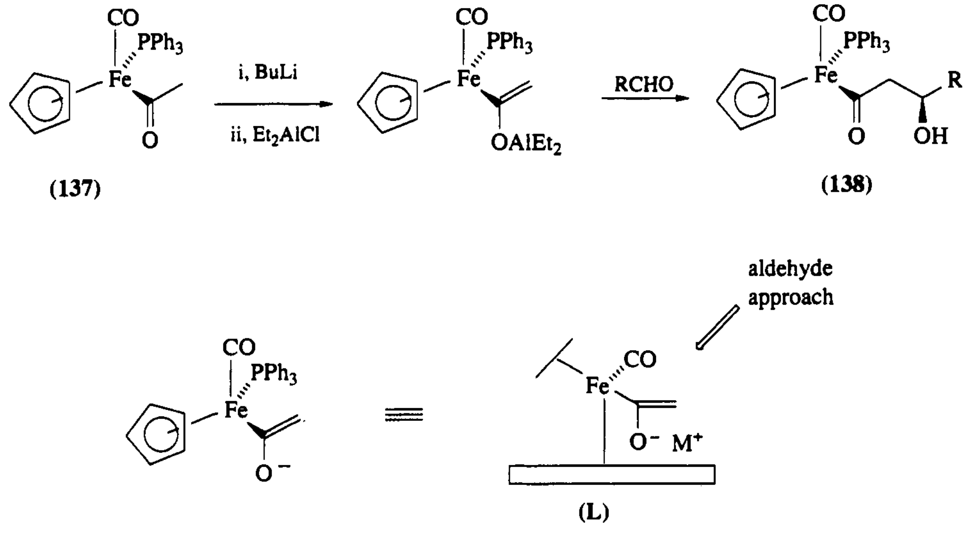
CO
PPh$_3$
Fe
O
(137)
i, BuLi
ii, Et$_2$AlCl
OAlEt$_2$
RCHO
R
OH
(138)
aldehyde approach
O$^-$
O$^-$ M$^+$
(L)

**Scheme 60**

low diastereoselectivity, the corresponding aluminum enolate species prepared by adding chlorodiethylalane to the lithium enolate gives aldol products (**138**) with high selectivity (~20:1 to 100:1). A rationale for the observed high selectivity is based on the facial selectivity of the enolate of the enantiomerically homogeneous iron complex as shown in Scheme 60 (conformation **L**).

This facial selectivity can also be utilized in alkylation reactions of the β-hydroxy aldol products (**138**), so that overall a chiral propionate aldol unit is formed, as shown in Scheme 61.[77,79] The final products are *syn*-α-methyl-β-hydroxycarboxylic acids (**139**).

Asymmetric aldol reactions are also possible with chiral propanoyl–iron complexes, as shown in Scheme 62.[80] Good to excellent stereoselectivities for *anti* aldol products (**140**) are obtained when the lithium enolate of the propanoyl–iron complex is treated with 3 equiv. of $Et_2AlCl$ at –40 °C, followed by an aldehyde at –100 °C. Interestingly the same reaction using CuCN instead of $Et_2AlCl$ provides exclusively *syn* aldol products (**141**).

Recently Ojima and Kwon[81] reported aldol reactions of a chiral iron–acyl complex possessing a pentafluorophenyl group on the phosphine ligand. In contrast with the CHIRAC complex, this newer complex, $[(C_6F_5)Ph_2P](CO)CpFeCOMe$ (PFCHIRAC) provides, upon reaction with aldehydes, product (**142**) with high stereoselectivity (89–99% *de*) regardless of the metal enolate species (Scheme 63). Furthermore, while an aluminum enolate prepared by direct metal exchange exhibits moderate selectivity (8:1) in the aldol reaction with benzaldehyde, addition of the lithium enolate to a mixture of an aldehyde and chlorodiethylalane greatly enhances the diastereoselectivity of the reaction.

A variable temperature NMR ($^1$H, $^{19}$F and $^{31}$P) study on the dynamic behavior of PFCHIRAC has allowed a rationalization of the unique stereodifferentiation and opposite sense of asymmetric induction observed with this complex, compared to the CHIRAC complex. Thus, a highly selective generation of the *endo* (or *syn*) enolate (**143**) in the PFCHIRAC system is suggested to be due to an electron donor–

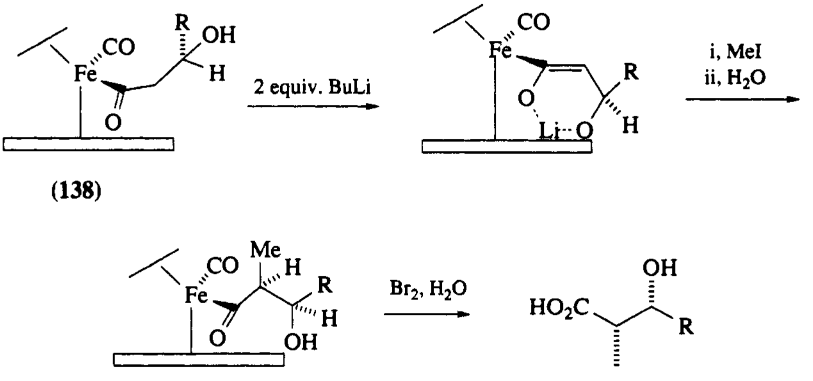

**(138)**

**(139)**

Scheme 61

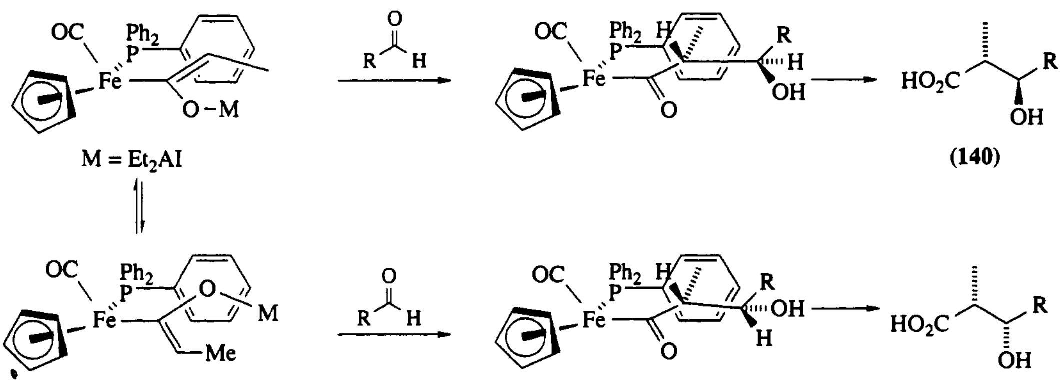

**(140)**

**(141)**

Scheme 62

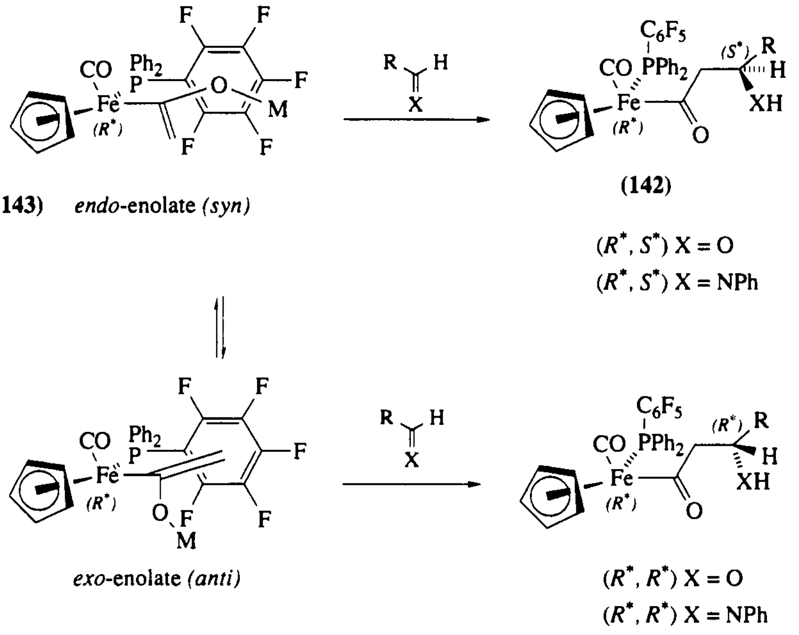

**Scheme 63**

acceptor type attractive interaction between the pentafluorophenyl moiety (electron acceptor) and the enolate oxygen (electron donor).

## 1.7.4 REFERENCES

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# 1.8

# Zinc Enolates: the Reformatsky and Blaise Reactions

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## 1.8.1 INTRODUCTION

The Reformatsky reaction is the reaction of an α-halo ester with an aldehyde or ketone in the presence of zinc metal as shown in Scheme 1. The usual product of the reaction is a β-hydroxy ester, which may be dehydrated in subsequent steps to give an unsaturated ester. A zinc ester enolate (**1**), the so-called Reformatsky reagent, is an intermediate in the reaction and the sequence is thus classified as an aldol condensation. Compared to the usual base-promoted aldol procedures, the distinguishing features of the Reformatsky reaction are the use of a metal–halogen redox reaction rather than an acid–base reaction to form the enolate, and the fact that the counterion of the enolate is zinc.

Assuming ready availability of the α-halo ester component, the Reformatsky reaction is often a convenient and economical alternative to base-promoted aldol procedures. Since its discovery in 1887,[1] over 500 research articles and six reviews[2–7] of the reaction have been published. Heathcock has recently reviewed the stereochemistry of the reaction of a variety of zinc enolates with aldehydes and ketones.[8]

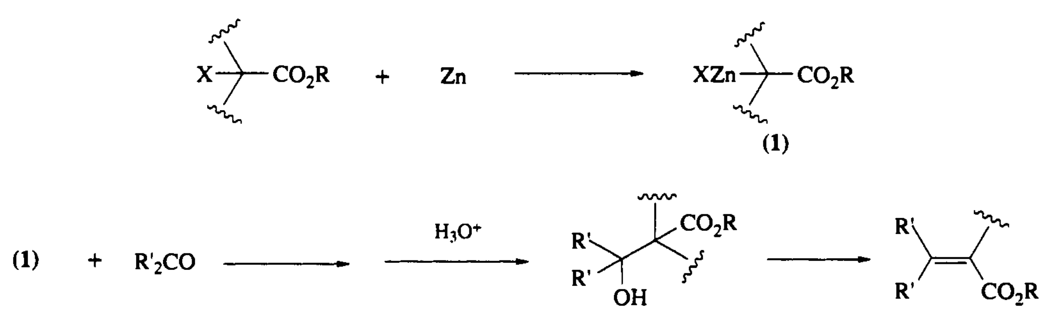

Scheme 1

This chapter summarizes studies on the nature of the Reformatsky reagent as well as other, related, zinc enolates and outlines the synthetic aspects of the reaction with aldehydes and ketones. In addition, reactions of the Reformatsky reagent with imines and nitriles (the Blaise reaction) are described.

## 1.8.2 NATURE OF THE REFORMATSKY REAGENT

### 1.8.2.1 Isolation and Stability of Zinc Enolates

The Reformatsky reaction is most commonly conducted in a single step by addition of a mixture of α-halo ester and carbonyl substrate to a suspension of zinc in a suitable solvent. This one-stage procedure clearly minimizes any problems due to instability of the Reformatsky reagent. Since 1953,[9] solutions of the reagent have occasionally been prepared, with varying degrees of success, by reaction of the α-halo ester with zinc in an initial separate step of a two-stage procedure.

The first detailed examination of a Reformatsky reagent was described in 1965 by Vaughan and coworkers,[10] who prepared a solution of the reagent from ethyl α-bromoisobutyrate. Hydrolysis of the freshly prepared solution gave ethyl isobutyrate (from the Reformatsky reagent) and the so-called 'condensed ester', ethyl isobutrylisobutyrate (**2**; equation 1). Refluxing the reaction mixture for longer periods prior to hydrolysis gave a gradual decrease in ethyl isobutyrate and a corresponding increase in (**2**). Vaughan[11] proposed that the zinc ester enolate decomposed by loss of EtOZnBr to form a ketene intermediate, which subsequently formed condensed ester (Scheme 2). A similar formation of ketenes from

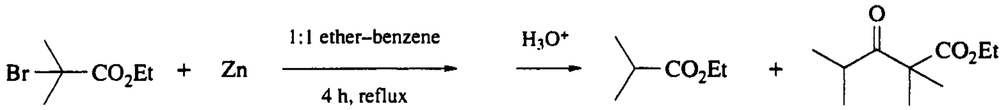

(1)

(2)

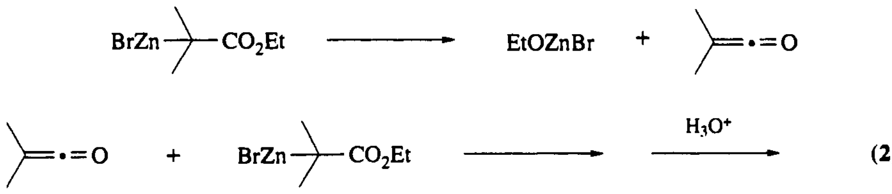

Scheme 2

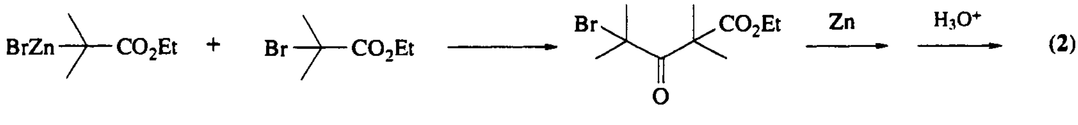

Scheme 3

lithium ester enolates has been well documented.[12,13] It is also possible that at least some of the condensed ester is produced by a direct condensation as suggested earlier by Newman and Hussey (Scheme 3).[14]

According to Gaudemar and Curé,[5,15] dimethoxymethane is an especially useful solvent for two-stage reactions and they report yields of 70–80% for the Reformatsky reagents derived from a variety of α-bromo esters (equation 2); however, the procedure was unsatisfactory with ethyl α-bromopropionate, methyl α-bromophenylacetate and phenyl α-bromoisobutyrate. The zinc enolates were generally used shortly after preparation and no data on their stability in this solvent were reported.

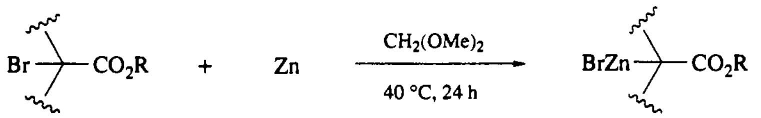
Br
CO2R
+
Zn
CH2(OMe)2
40 °C, 24 h
BrZn
CO2R

(2)

Orsini and coworkers[16,17] obtained $BrZnCH_2CO_2Bu^t{\cdot}THF$ in 80% yield as a colorless crystalline solid by reaction in THF at 25–35 °C. They described the reagent as mostly unchanged after 4–6 d in a number of solvents, with a slow hydrolysis to *t*-butyl acetate and a gradual formation of $Bu^tOZnBr$. Using the same procedure, $BrZnCHMeCO_2Bu^t$ and $BrZnCMe_2CO_2Bu^t$ were isolated as THF complexes. They were described as stable in THF for a few hours and in pyridine and in DMSO for about 10–15 min, after which time an abundant precipitate of $BrZnOBu^t$ was present.

Orsini and coworkers[16] obtained primarily 'condensed ester' from the reaction of methyl α-bromopropionate with zinc in a variety of solvents; however, Johnson and Zitsman[18] evidently obtained the reagent from ethyl α-bromopropionate in good yield by conducting the reaction at a lower temperature in ether (equation 3).

It seems likely that many simple α-bromo esters can be reacted with zinc to produce the Reformatsky reagent nearly quantitatively, and that the reagent forms condensed ester primarily in a subsequent step. A successful synthesis of a Reformatsky reagent should then depend strongly on the time and temperature required for the preparation. Recently, a number of methods, including ultrasound promotion[19] and the use of highly active forms of zinc,[20] have allowed completion of the Reformatsky sequence in

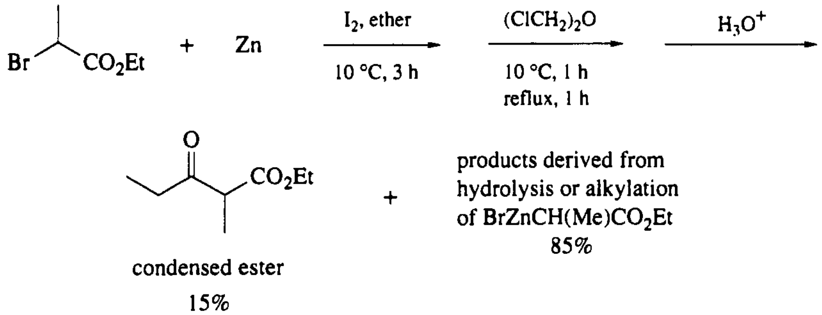
Br
CO2Et
+
Zn
I2, ether
10 °C, 3 h
(ClCH2)2O
10 °C, 1 h
reflux, 1 h
H3O+
O
CO2Et
condensed ester
15%
+
products derived from
hydrolysis or alkylation
of BrZnCH(Me)CO2Et
85%

(3)

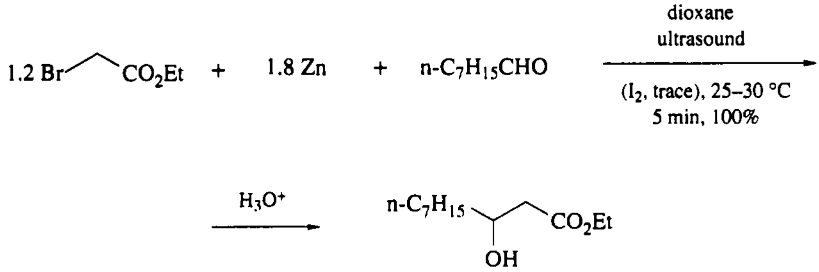
1.2 Br
CO2Et
+
1.8 Zn
+
n-C7H15CHO
dioxane
ultrasound
(I2, trace), 25–30 °C
5 min, 100%
H3O+
n-C7H15
CO2Et
OH

(4)

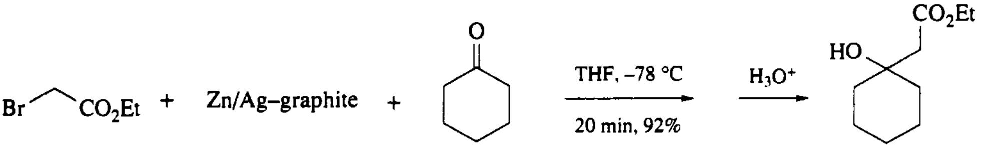
Br
CO2Et
+
Zn/Ag–graphite
+
O
THF, −78 °C
20 min, 92%
H3O+
HO
CO2Et

(5)

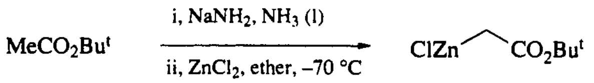

(6)

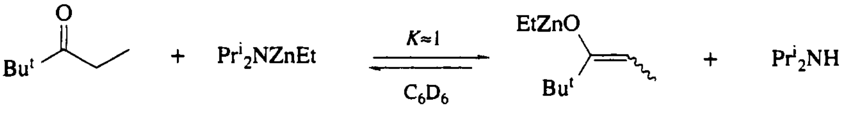

(7)

remarkably short times and at low temperatures. However, these methods have so far been applied only to one-stage procedures (equations 4[19] and 5[21]).

Zinc ester enolates may also be obtained by the addition of $ZnX_2$ to lithium or sodium enolates as first described by Hauser and Puterbaugh (equation 6).[22] This approach has so far received little attention but similar reactions have been used to obtain zinc ketone enolates.[22,23] In this regard, it should be noted that Heathcock and coworkers[24] have shown that deprotonation reactions of ketones with zinc dialkylamide bases reach equilibrium at only about 50% conversion (equation 7). This result implies that attempts to prepare zinc enolates from solutions of amide-generated lithium enolates will be successful only when the lithium enolate is made amine-free.

### 1.8.2.2 Structure of Zinc Enolates

Metal enolates may have structures with either a metal–oxygen (**3**) or a metal–carbon (**4**) bond. Lithium enolates typically have oxygen-bonded structures,[25] while mercury enolates are usually assumed to have carbon-bonded structures.[26]

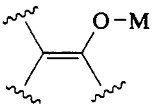

**(3)**

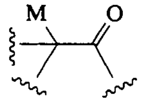

**(4)**

From a crystallographic study of the Reformatsky reagent obtained from *t*-butyl α-bromoacetate, Boersma and coworkers[27] reported the carbon-bonded dimeric structure (**5**). Based on ebulliometric and cryoscopic molecular weight measurements, the dimeric structure persists in solvents of medium coordinating power (THF, DME, dioxane, dimethoxymethane and pyridine), but the reagent is monomeric in strongly coordinating solvents (HMPA and DMSO). Spectral data[16] are also consistent with a carbon-bonded structure for the reagent in solution (Table 1). The spectral differences observed between the solvents THF and DMSO are consistent with the presence (THF solution) or absence (DMSO solution) of zinc coordination to the carbonyl oxygen of a carbon-bonded structure, as first suggested by Gaudemar and Martin.[28] In strongly coordinating solvents, the carbonyl frequency of a variety of Reformatsky reagents appears just below 1700 cm$^{-1}$, close to the normal value for ester carbonyls.[28] It is interesting to note that a dimeric structure (**6**) completely analogous to (**5**) was considered in 1970 for the Reformatsky reagent obtained from ethyl α-bromoisobutyrate and discarded, based on the failure of the reagent to react with Grignard reagents.[11] Clearly, with sufficient ionic character to the metal bonds, the reactivity of a carbon-bonded enolate to any reagent must approach that of the corresponding oxygen-bonded enolate.

No crystallographic structure has been reported for zinc ketone enolates. Although carbon-bonded structures analogous to (**5**) have been proposed,[27] spectral data obtained for the bromozinc and ethylzinc

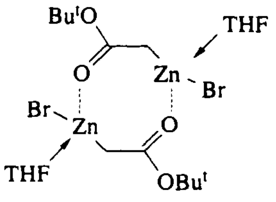

**(5)**

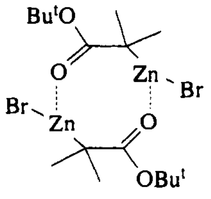

**(6)**

**Table 1** Spectral Data for $BrZnCH_2CO_2Bu^t$

| *Spectrum* | *Solvent* | *Signal (assignment)* |
|---|---|---|
| $^1H$ NMR<br>$BrZnCH_2CO_2C(CH_3)_3$<br>A B | THF | p.p.m. relative to $Me_4Si$<br>1.88 (A), 1.40 (B) |
| | DMSO | 1.04 (A), 1.30 (B) |
| $^{13}C$ NMR<br>$BrZnCH_2CO_2C(CH_3)_3$<br>A B C D | THF | p.p.m. relative to $Me_4Si$<br>22.7 (A), 186.2 (B),<br>80.4 (C), 27.6 (D),<br>$J(C_1—H_\alpha)$ 132 Hz |
| | DMSO | 20.8 (A), 177.4 (B),<br>75.3 (C), 28.6 (D)<br>$J(C_1—H_\alpha)$ 128.6 Hz |
| IR | | $cm^{-1}$ |
| | THF | 1580 (C=O) |
| | DMSO | 1660 (C=O) |

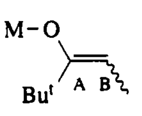

(7)

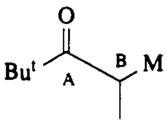

(8)

**Table 2** NMR Spectral Data for Enolates (7) and (8)

| *M* | *Solvent* | *Chemical shifts (p.p.m.)* $C_A$ | $C_B$ | $H_\alpha$ | $J(C_B—H_\alpha)$ *(Hz)* | *Ref.* |
|---|---|---|---|---|---|---|
| ZnEt | THF-$d_8$ | 165.5 | 93.0 | 4.41 | 155 | 24 |
| ZnBr | THF | 164.7 | 96.6 | — | — | 29 |
| MgBr | Ether | 162.4 | 95.5 | 4.54 | 154 | 30 |
| Li | Benzene | 169 | 84 | — | — | 31 |
| HgBr | Benzene | 213 | 51 | — | 140 | 31 |

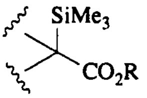

(9)

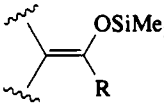

(10)

enolates of 2,2-dimethyl-3-pentanone seem most consistent with oxygen-bonded (7) rather than carbon-bonded (8) structures. The chemical shifts and C—H coupling constants are close to the oxygen-bonded lithium or magnesium enolates and not to the presumably carbon-bonded mercury enolates (Table 2).[24]

The preference of zinc ester enolates for carbon-bonded structures and zinc ketone enolates for oxygen-bonded structures is reminiscent of the situation with silicon. A carbon-bonded structure (9) is the thermodynamically more stable form for the trimethylsilyl derivatives of esters, while the oxygen-bonded structure (10) is the more stable form for ketone derivatives. This has been attributed to the greater resonance stability of ester compared to ketone carbonyls.[32]

## 1.8.3 REACTION WITH ALDEHYDE AND KETONE SUBSTRATES

### 1.8.3.1 Scope and Procedures

Reformatsky reactions of more than 500 different aldehydes and ketones have been tabulated.[2,5,7] One of the significant features of the Reformatsky reaction is that it succeeds even with highly hindered ketones (equation 8).[33] It is one of the few successful methods[34] for the addition of carbon nucleophiles to the readily enolized cyclopentanone ring system (equation 9).[35]

Because the Reformatsky sequence allows the generation of an ester enolate in the presence of an enolizable aldehyde or ketone, it is uniquely suited for intramolecular aldol reactions.[36–40] The transformation shown in equation (10) would be difficult to accomplish by conventional base-promoted aldol methods.[40]

Single-stage procedures are most commonly used for the Reformatsky reaction with aldehydes and ketones. A mixture of α-halo ester and carbonyl substrate is added to a suspension of zinc at a rate sufficient to maintain the reaction. In the original procedure of Reformatsky,[1] no solvent was used but modern practice is to use benzene or an ether solvent such as diethyl ether, THF, glyme or dimethoxymethane. The reaction is often conducted at reflux temperature, probably to avoid surges from the highly exothermic nature of the reaction. However, in a comparison with a number of aldehydes and ketones, much higher yields were obtained at room temperature than at reflux in benzene (equation 11).[41]

The zinc metal is typically activated before use and methods for accomplishing this have been reviewed.[20] The use of highly reactive forms of zinc (Reike powders), obtained by reduction of zinc salts with an alkali metal, detracts from the convenience of the classical procedure but much higher yields have been obtained, at least with the simple substrates that have so far been examined. One of the most convenient preparations of a Reike powder uses sodium naphthalide, as shown in Scheme 4.[42] Reactive zinc powders also allow the use of α-chloro esters which are unsatisfactory with the usual forms of zinc.[20]

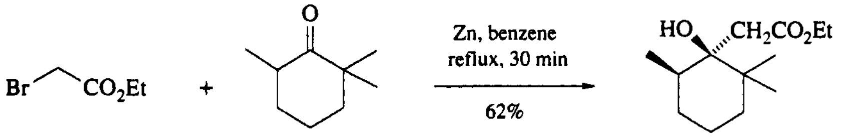
Br
CO2Et
+
O
Zn, benzene
reflux, 30 min
62%
HO
CH2CO2Et

(8)

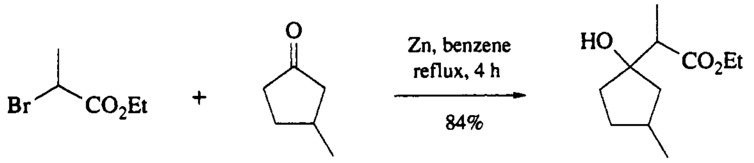
Br
CO2Et
+
O
Zn, benzene
reflux, 4 h
84%
HO
CO2Et

(9)

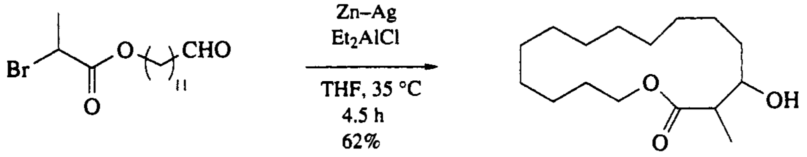
Br
O
CHO
O
11
Zn–Ag
Et2AlCl
THF, 35 °C
4.5 h
62%
O
OH
O

(10)

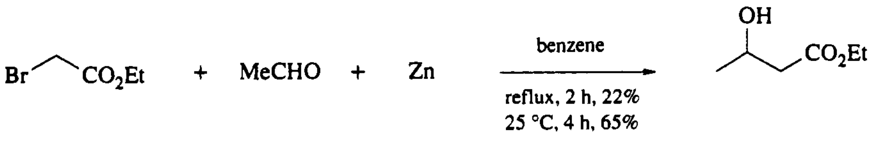
Br
CO2Et
+ MeCHO + Zn
benzene
reflux, 2 h, 22%
25 °C, 4 h, 65%
OH
CO2Et

(11)

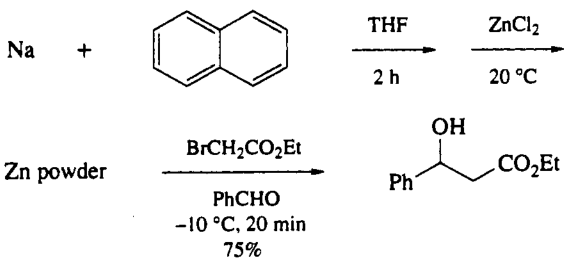
Na +
THF
2 h
ZnCl2
20 °C
Zn powder
BrCH2CO2Et
PhCHO
-10 °C, 20 min
75%
OH
Ph
CO2Et

**Scheme 4**

### 1.8.3.2 Chemoselectivity

In addition to aldehydes and ketones, organic compounds which are known to react with Reformatsky reagents include: esters,[43] nitriles,[44] acid chlorides,[43] organic halides,[17,45] epoxides,[46] nitrones,[47] azirenes[48] and imines.[49] This section describes the selectivity reported for Reformatsky reactions with functionally substituted aldehydes or ketones.

Symmetrical diketones react normally with either one (equation 12)[50] or two (equation 13)[51] equivalents of the Reformatsky reagent. There are no reports of selective reaction at a single carbonyl of an unsymmetrical substrate, although this has been accomplished by selective acetal protection (Scheme 5).[52]

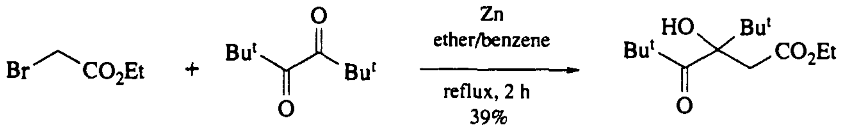
Br CO2Et
+
Bu^t
O
O
Zn
ether/benzene
reflux, 2 h
39%
HO
CO2Et

(12)

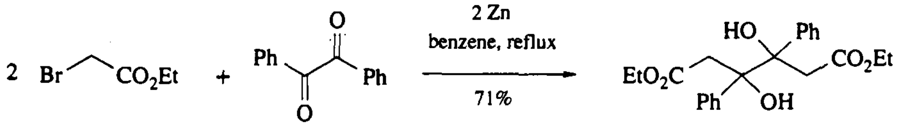
2 Br CO2Et
+
Ph
O
2 Zn
benzene, reflux
71%
HO
EtO2C
CO2Et
OH

(13)

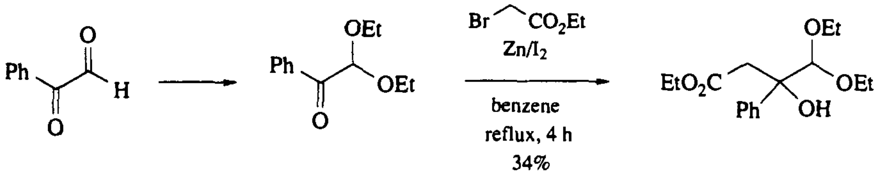
Ph
O
H
OEt
Br CO2Et
Zn/I2
benzene
reflux, 4 h
34%
EtO2C
OH

Scheme 5

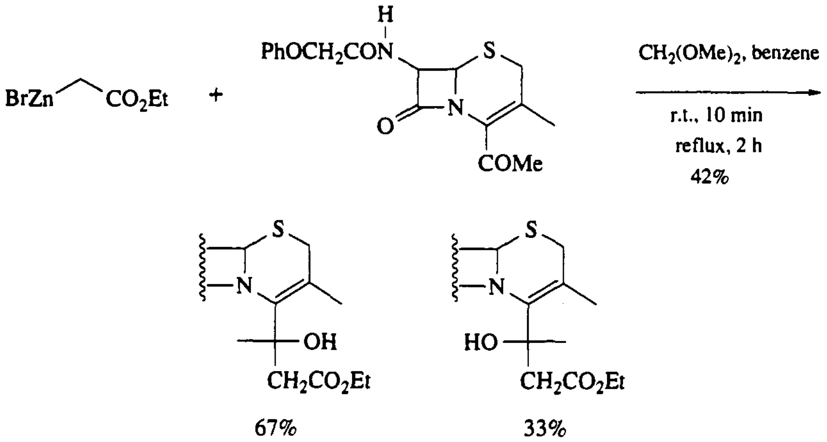
H
PhOCH2CON
S
N
O
COMe
BrZn CO2Et
+
CH2(OMe)2, benzene
r.t., 10 min
reflux, 2 h
42%
OH
HO
CH2CO2Et
67%
33%

(14)

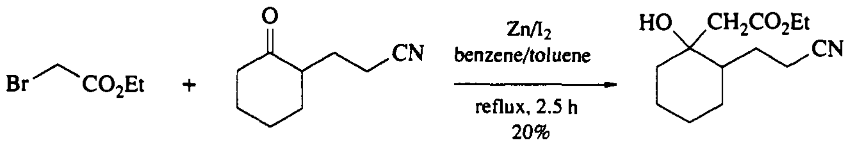
Br CO2Et
+
O
CN
Zn/I2
benzene/toluene
reflux, 2.5 h
20%
HO
CH2CO2Et

(15)

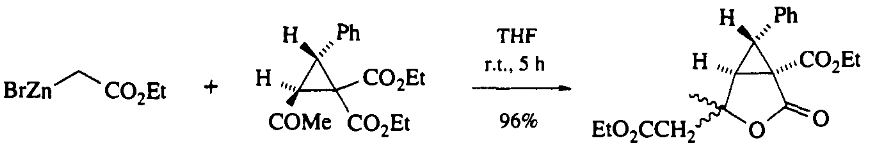
BrZn CO2Et
+
H
Ph
CO2Et
COMe
THF
r.t., 5 h
96%
EtO2CCH2
O

(16)

Ketoamides,[53] ketonitriles[54] and keto esters[55] may all be reacted selectively at the ketone function (equations 14–16). In fact, esterification was found to be the best of several hydroxy-protecting methods for the transformation shown in Scheme 6.[56]

Ethyl acetoacetate gave only low yields in a Reformatsky reaction[57] but even this is remarkable considering its acidic nature (equation 17). β-Keto esters that lack acidic hydrogens react in good yield (equation 18).[58]

Halogen can be tolerated either in the carbonyl substrate or in the bromo ester component of the Reformatsky reaction. It is noteworthy that the intermediate zinc aldolate (**11**) does not internally substitute halogen until HMPA is added (Scheme 7).[39] For reactions with α-halo ketone substrates in a Δ[1]-buten-

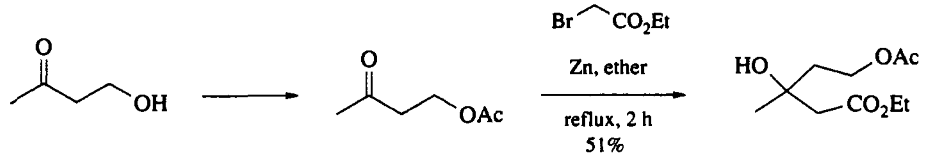

OH
OAc
Br⌒CO2Et
Zn, ether
reflux, 2 h
51%
HO
OAc
CO2Et

**Scheme 6**

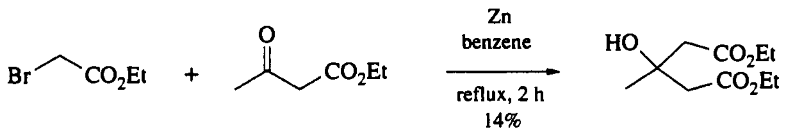

Br
CO2Et
+
CO2Et
Zn
benzene
reflux, 2 h
14%
HO
CO2Et
CO2Et

(17)

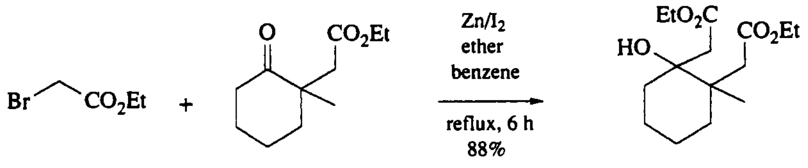

Br
CO2Et
+
O
CO2Et
Zn/I2
ether
benzene
reflux, 6 h
88%
EtO2C
HO
CO2Et

(18)

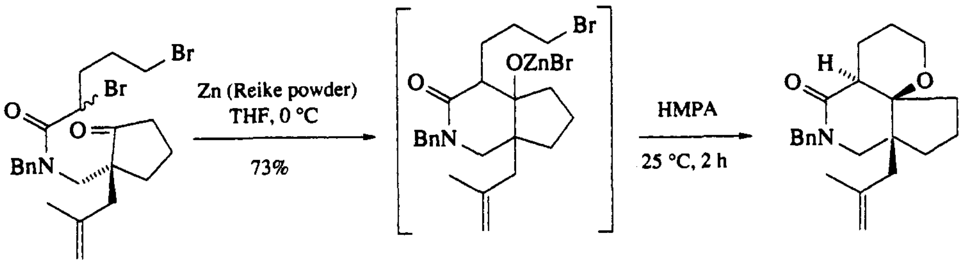

Br
Br
O
O
BnN
Zn (Reike powder)
THF, 0 °C
73%
Br
OZnBr
O
BnN
HMPA
25 °C, 2 h
H
O
O
BnN

**(11)**

**Scheme 7**

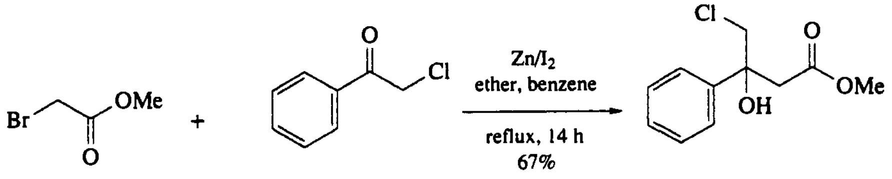

Br
OMe
O
+
O
Cl
Zn/I2
ether, benzene
reflux, 14 h
67%
Cl
O
OH
OMe

(19)

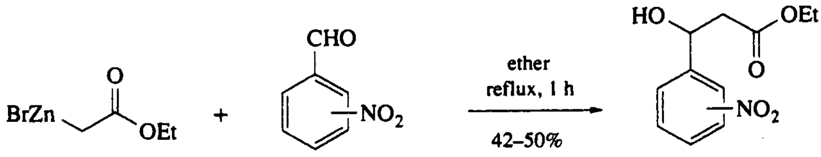

BrZn
O
OEt
+
CHO
NO2
ether
reflux, 1 h
42–50%
HO
OEt
O
NO2

(20)

olide synthesis,[59] the use of α-chloro rather than α-bromo ketones was recommended to avoid formation of a zinc ketone enolate (equation 19).

The two-stage Reformatsky procedure was originally devised to avoid the reduction of quinone substrates by zinc, which was observed in a single-stage sequence.[9] A two-stage sequence also allows successful reaction with nitrobenzaldehydes (equation 20),[60] although in this case the problem is a marked inhibition of the reaction of zinc with the bromo ester by nitro aromatics.

## 1.8.3.3 Regioselectivity

### *1.8.3.3.1 Reaction of zinc ester enolates with conjugated enones*

Reaction of zinc ester enolates with a conjugated enone can give either β-hydroxy esters (**12**) from 1,2-addition, or δ-keto esters (**13**) from 1,4-addition, as shown in Scheme 8. Cyclization of the 1,4-product to the corresponding δ-lactone (**14**) is occasionally observed.

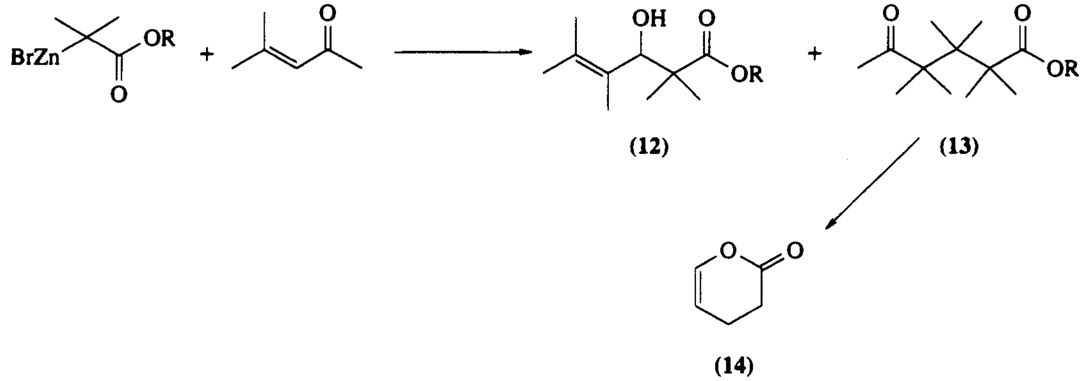
BrZn
OR
O
+
O
OH O
OR
+
O
O
OR
(12)
(13)
O
O
(14)

Scheme 8

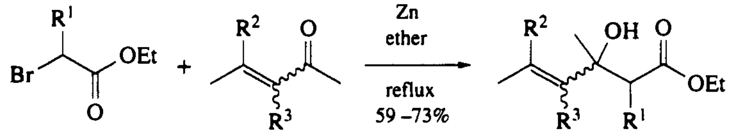
R1
Br
OEt
O
+
R2
O
R3
Zn
ether
reflux
59–73%
R2
OH
O
OEt
R3
R1

(21)

$R^1$ = H, Me, Et; $R^2$ = H, Me; $R^3$ = H, Me

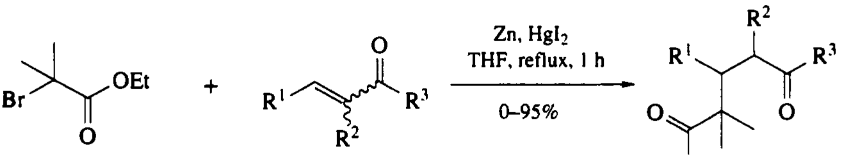
Br
OEt
O
+
O
R1
R3
R2
Zn, HgI2
THF, reflux, 1 h
0–95%
R2
R1
R3
O
O
OEt

(22)

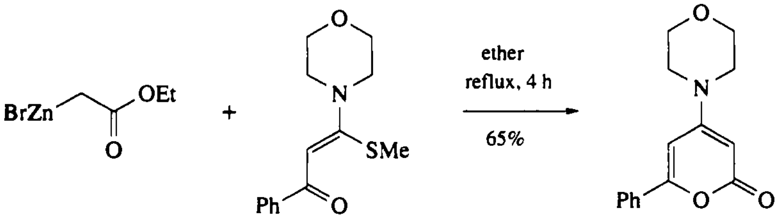
BrZn
OEt
O
+
O
N
SMe
Ph
O
ether
reflux, 4 h
65%
O
N
Ph
O
O

(23)

Reaction of a variety of unsaturated methyl ketones with relatively unhindered bromo esters in refluxing ether gave only 1,2-addition products (equation 21).[61] A similar study in refluxing THF with the more hindered ethyl α-bromoisobutyrate gave exclusively 1,4-addition products; however, the conditions of work-up were such that 1,2-addition products would not have been isolated (equation 22).[62]

There has been no systematic study of the Reformatsky reaction of conjugated enones under conditions where both 1,2- and 1,4-products could be determined. In general, only 1,2-addition products are obtained with α-bromoacetates. However, in one favorable case, exclusive 1,4-addition was observed (equation 23).[63] Reactions with α-bromoisobutyrates commonly give 1,4-addition products. It is not known whether these are the result of a kinetically or thermodynamically controlled process. Low temperature reactions of conjugated enones with preformed Reformatsky reagents of α-bromoisobutyrates, conditions most favorable for a kinetically controlled process, have apparently never been reported.

### *1.8.3.3.2 Reaction of zinc ester dienolates with simple aldehydes and ketones*

The Reformatsky reaction of 4-bromocrotonate esters can give either α- or γ-products as shown in equation (24). Hudlicky and coworkers[64] have suggested that the high γ-selectivity usually observed for the reaction may be due to the instability of the α-products to isolation procedures. They examined the reaction of ethyl 4-bromocrotonate with 10 carbonyl substrates and defined conditions for obtaining either α- or γ-products with generally good selectivity (Scheme 9). In at least one case, these results were shown[34] to be the result of a selection between kinetic control, leading to α-product, and thermodynamic control, leading to γ-product (equation 25).

In a similar study of the reaction of trimethylsilyl esters of 4-bromocrotonic and 4-bromosenecioic acids with benzaldehyde, low temperatures favored α-products, while higher temperatures or longer reaction times favored γ-products (equation 26).[65]

It seems reasonable to conclude that, as originally proposed by Gaudemar,[66] one-stage Reformatsky reactions of zinc ester dienolates will produce mainly α-products in kinetically controlled processes, and

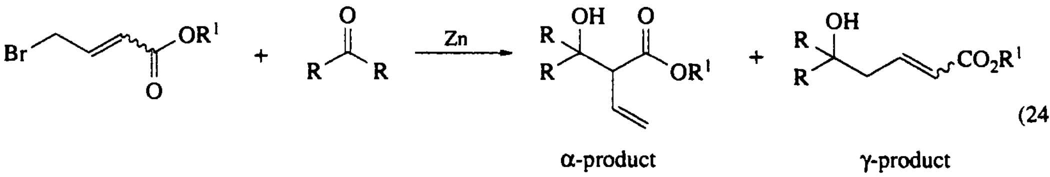

(24)

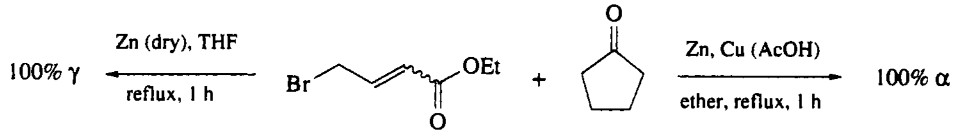

**Scheme 9**

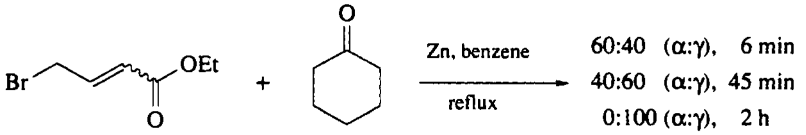

(25)

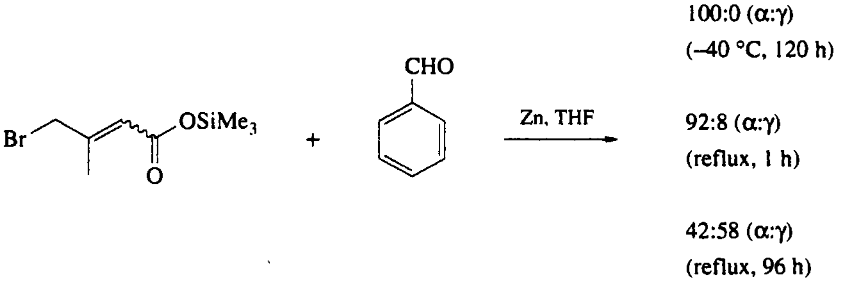

(26)

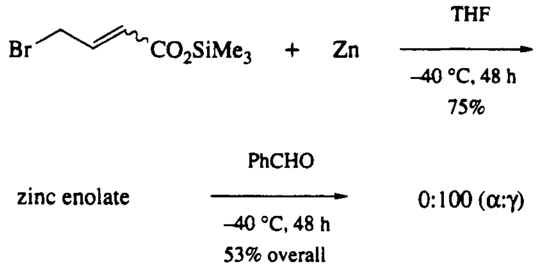
Br
CO2SiMe3
+ Zn
THF
–40 °C, 48 h
75%
zinc enolate
PhCHO
–40 °C, 48 h
53% overall
0:100 (α:γ)

**Scheme 10**

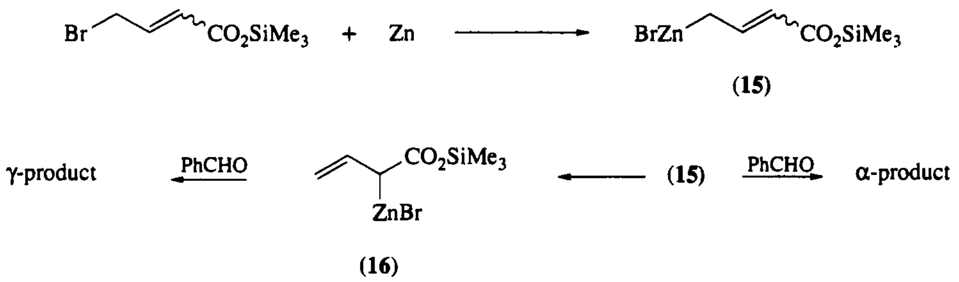
Br
CO2SiMe3
+ Zn
BrZn
CO2SiMe3
(15)
γ-product
PhCHO
CO2SiMe3
ZnBr
(16)
(15)
PhCHO
α-product

**Scheme 11**

mainly γ-products in thermodynamically controlled processes. Similar conclusions were reached for the corresponding reactions of lithium ester dienolates.[67] It is therefore surprising that two-stage Reformatsky reactions, completed under conditions where the α-product is stable, gave exclusively γ-products (Scheme 10).[65] The existence of two different zinc dienolates was proposed to explain these results, as shown in Scheme 11. In one-stage reactions, the initially formed enolate (**15**) is trapped to give α-products. In two-stage reactions, (**15**) rearranges to a second enolate (**16**), which then reacts to give γ-products.

### *1.8.3.3.3 Reaction of zinc ester dienolates with conjugated enones*

The Reformatsky reaction of 4-bromocrotonate esters with conjugated enones can conceivably give four regioisomers, as shown in equation (27). Several workers have applied such reactions to the synthesis of vitamin A and related compounds.[7] In most cases, δ-lactones derived from 1,2-γ-adducts were obtained, as exemplified by results with β-cyclocitral (equation 28).[68]

In a study of the reaction of ethyl 4-bromocrotonate with a variety of conjugated enones, Hudlicky and coworkers[34] observed almost exclusive formation of 1,2-α-products at very short reaction times in

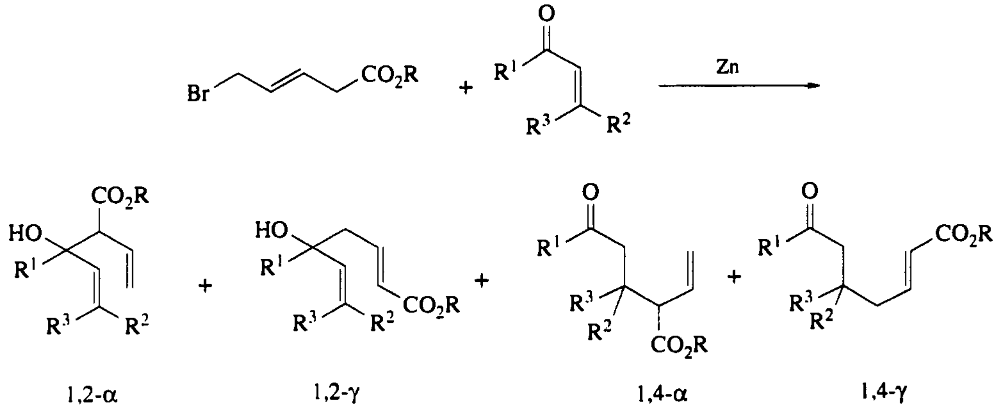
Br
CO2R
+
O
R1
R3
R2
Zn
CO2R
HO
R1
R3
R2
+
HO
R1
R3
R2
CO2R
+
O
R1
R3
R2
CO2R
+
O
R1
CO2R
R3
R2
1,2-α
1,2-γ
1,4-α
1,4-γ

(27)

refluxing ether. Longer reaction times produced increasing amounts of 1,2-γ- and 1,4-γ-products. Reaction for several hours in refluxing THF gave, with ketones, exclusively the 1,4-γ-product and, with the single aldehyde examined, exclusively the 1,2-γ-product. Selected data are shown in Table 3. Interestingly, the lithium enolate of ethyl crotonate gave primarily the 1,4-α-product with cyclohexenone (entry 7), a regioisomer not observed with any of the Reformatsky reactions of Table 3.

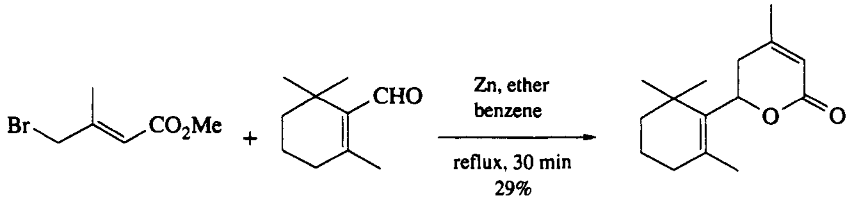

(28)

**Table 3** Regioselectivity in the Reformatsky Reaction (equation 27)

| *Unsaturated carbonyl compound* | *Reaction conditions* | *Product distribution (%)* | | | |
|---|---|---|---|---|---|
| | | *1,2α* | *1,2γ* | *1,4α* | *1,4γ* |
| 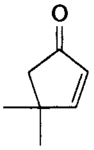 | Zn/Cu (HOAc)/$Et_2O$, 3 min | >95 | | | |
| | Zn/Cu (HOAc)/$Et_2O$, 1 h | 28 | 26 | | 46 |
| | Zn, THF, 4 h | 10 | | | 90 |
| 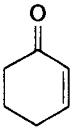 | Zn/Cu (HOAc)/$Et_2O$, <1 min | >90 | | | <10 |
| | Zn/Cu (HOAc)/$Et_2O$, 45 min | 53 | 17 | | 30 |
| | Zn, THF, 6 h | | | | >90 |
| | LDA, –78 °C, THF, $MeCHCHCO_2Et$ | | | 75 | 25 |
| 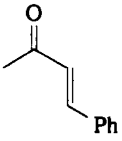 | Zn/Cu (HOAc)/$Et_2O$, 1 min | 100 | | | |
| | Zn/Cu (HOAc)/$Et_2O$, 1 h | 16 | 26 | | 58 |
| | Zn, THF, 4 h | | | | >90 |
| 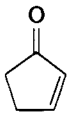 | Zn/Cu (HOAc)/$Et_2O$, 3 min | >96 | | | |
| | Zn, THF, 2 h | 15 | | | 85 |
| 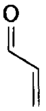 | Zn/Cu (HOAc)/$Et_2O$, 30 s | 100 | | | |
| | Zn/Cu (HOAc)/$Et_2O$, 1 h | 41 | 59 | | |
| | Zn, THF, 2 h | | 100 | | |
| 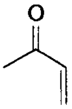 | Zn/Cu (HOAc)/$Et_2O$ | 35 | 55 | | <10 |

### 1.8.3.4 Stereoselectivity

#### *1.8.3.4.1 Introduction*

Reaction of an α-substituted enolate with an aldehyde or ketone can give two pairs of aldol diastereomers, which are conveniently designated as the *syn* form (**17**) and the *anti* form (**18**), where $R^2$ is part of the parent chain in IUPAC nomenclature (equation 29). For simplicity, only one enantiomer of each pair will usually be shown throughout this section. The *syn*/*anti* notation for aldol diastereomers has been described in detail by Heathcock.[8]

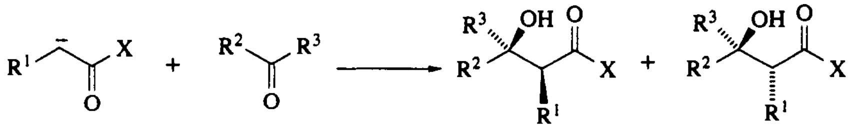

(29)

(**17**) *syn*-aldol (**18**) *anti*-aldol

#### *1.8.3.4.2 Thermodynamic stereoselection*

Aldol condensations of zinc enolates under conditions of thermodynamic control are reasonably discussed in terms of the relative stability of the two chelated aldolates; (**19**), which leads to the *syn* aldol, and (**20**), which leads to the *anti* aldol. If $R^2$ is larger than $R^3$, the *anti* chelate, with $R^1$ and $R^2$ *trans* in a six-atom ring, is expected to be the more stable form. Heathcock[8] has noted that the most common mechanism for equilibration of aldolate stereochemistry is reverse aldolization (reversal of equation 29). Aldolates obtained by reaction of an enolate with ketone substrates are expected to undergo reverse aldolization at a faster rate than those obtained with aldehyde substrates, in part for steric reasons. Similarly, aldolates derived from ketone enolates are expected to undergo reverse aldolization at a faster rate than those derived from the more basic ester or amide enolates.

Chelated structures analogous to (**19**) and (**20**) were first proposed by House and coworkers[23] to explain the increased *anti* selectivity observed for lithium ketone enolates following addition of $ZnCl_2$ (equation 30). Heathcock and coworkers[69] determined the rate of equilibration as well as the equilibrium composition for a number of aldolates derived from benzaldehyde and zinc ketone enolates (equation 31). Again, the preference for *anti* aldolates is in accord with zinc-chelated structures.

Jacques and coworkers[70] examined the Reformatsky reaction of a series of α-alkyl-substituted bromo esters. In refluxing benzene, the zinc aldolates derived from aromatic ketones, but not from aromatic

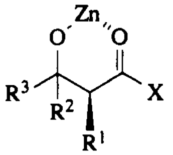

(**19**) *syn*-chelate

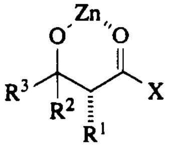

(**20**) *anti*-chelate

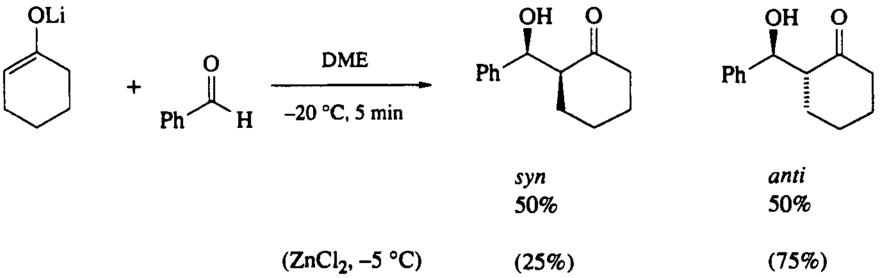

(30)

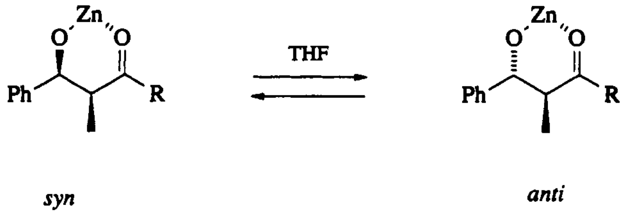
THF
syn
anti

(31)

| | | | |
|---|---|---|---|
| 25% | $T_{1/2} = 4$ min, –10 °C | 75% | R = Ph |
| 9% | $T_{1/2} = 0.5$ min, –78 °C | 91% | R = mesityl |
| — | $T_{1/2} = 210$ min, 25 °C | — | R = Bu$^t$ |

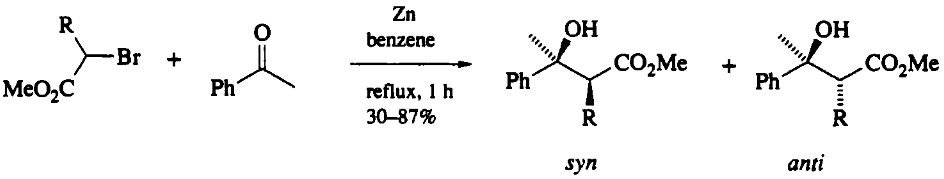
Zn
benzene
reflux, 1 h
30–87%
syn
anti

(32)

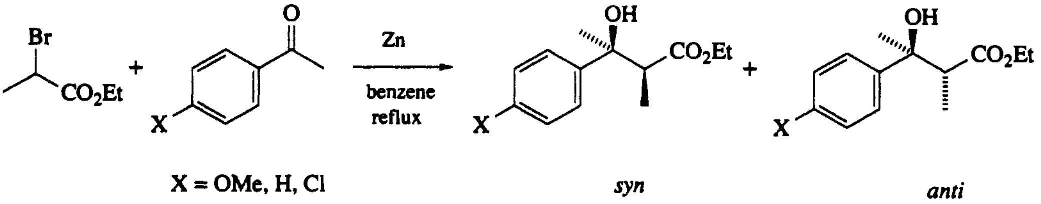
Zn
benzene
reflux
X = OMe, H, Cl
syn
anti

(33)

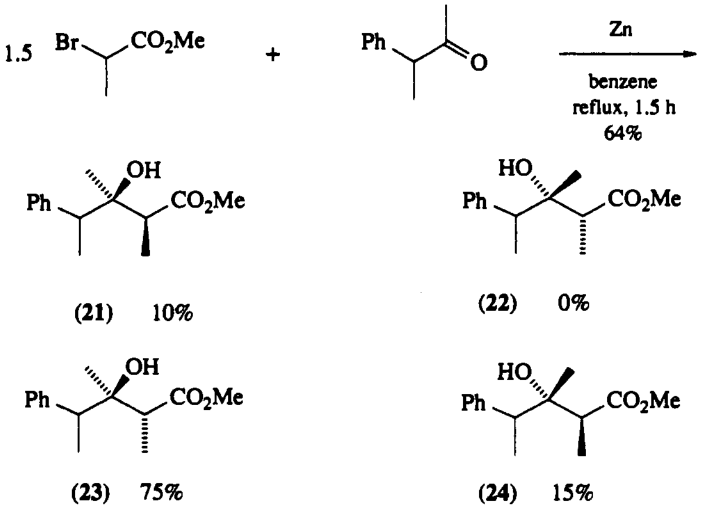
1.5
Zn
benzene
reflux, 1.5 h
64%
(21) 10%
(22) 0%
(23) 75%
(24) 15%

(34)

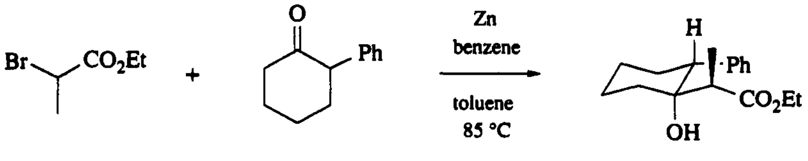
Zn
benzene
toluene
85 °C

(25)

(35)

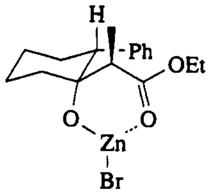

**(26)**

aldehydes, were found to equilibrate. *Syn:anti* ratios increased with increasing size of R and ranged from 30:67 (R = Me) to 17:83 (R = Pr$^i$) (equation 32). Balsamo and coworkers[71] observed a similar equilibration in the reaction of ethyl α-bromopropionate with substituted acetophenones in refluxing benzene (equation 33). Equilibration of stereochemistry was fastest with X = OMe (complete equilibration in 1 h) and slowest with X = Cl (complete equilibration in 5 h). All three substrates gave approximately the same equilibrium *syn:anti* ratio of 30:70.

Other studies of the Reformatsky reaction in refluxing benzene with ketone substrates are readily explained in terms of equilibrated zinc aldolates, although direct evidence for equilibration was not obtained. Matsumoto and coworkers[72] examined the reaction of 3-phenyl-2-butanone with methyl α-bromopropionate and observed a net *syn:anti* ratio [(**21** + **22**):(**23** + **24**)] of 10:90, in harmony with equilibrated zinc aldolates (equation 34).

Thomas and coworkers[73] examined the reaction of 2-phenylcyclohexanone with a number of nucleophiles. The highest stereoselectivity was observed with a Reformatsky reaction of ethyl α-bromopropionate (equation 35). The exclusive product (**25**) corresponds to that expected from the most stable zinc aldolate (**26**) with the α-methyl away from the phenyl group.

### *1.8.3.4.3 Kinetic stereoselection*

Because of conflicting reports or inadequate controls, the question of kinetic or thermodynamic control of stereochemistry for reported Reformatsky reactions often has no satisfactory answer. Jacques and coworkers[70] have concluded that Reformatsky reactions of benzaldehyde in refluxing benzene can be completed with kinetic stereoselection. The relatively high *syn:anti* ratios they observed, at least with small R groups (equation 36 and Table 4), are not those expected for equilibrated zinc chelates.

Matsumoto and coworkers[74] observed a similar high *syn:anti* ratio for the Reformatsky reaction of a chiral aldehyde in refluxing benzene [*syn:anti* = (**27** + **28**):(**29** + **30**) = 71:29] (equation 37).

The optimum approach to kinetic stereoselection in the Reformatsky reaction would appear to be the use of two-stage procedures, which allows the zinc aldolates to be formed at the lowest possible temperature. Gaudemar-Bardone and Gaudemar[75] prepared a variety of zinc ester enolates in dimethoxymethane at 40 °C which were then reacted at lower temperatures with benzaldehyde or with acetophenone (equation 38). Selected data from their study are shown in Table 5. If these data are the result of total kinetic control, as concluded by the authors, it is clear that the reactions exhibit only a modest kinetic stereoselectivity.

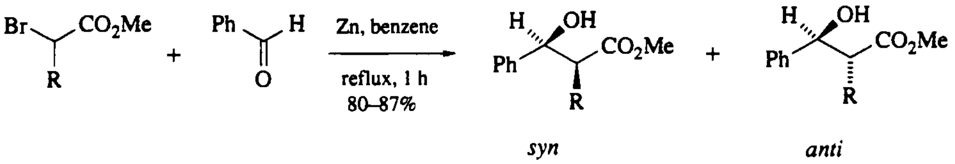

(36)

Table 4 *Syn:Anti* Ratios (equation 36)

| *R* | *Syn:anti* | *R* | *Syn:anti* |
|---|---|---|---|
| Me | 63:37 | c-C$_6$H$_{11}$ | 50:50 |
| Et | 54:46 | Bu$^t$ | 31:69 |
| Pr$^i$ | 47:53 | Ph | 24:76 |

Gaudemar and Curé[76] examined a two-stage procedure for condensing α-bromoamides with aldehydes and ketones. Again, no significant stereoselectivity was observed (*syn:anti* ratios ranged from 52:48, R = Me, to 72:28, R = Pr$^i$; Scheme 12).

Ito and Terashima[77] obtained good *syn* selectivity for a two-stage condensation of 3-(2-bromopropionyl)-2-oxazolidone derivatives and zinc dust with aldehydes (Scheme 13). *Syn:anti* ratios as high as 98:2 were obtained.

Although zinc–carbon bonded structures have been established for zinc ester enolates, it is conceivable that the alternate zinc–oxygen bonded structure is the reactive form in aldol condensations. Two research groups[78,79] have observed a modest degree of optical activity in the products from reaction of benzalde-

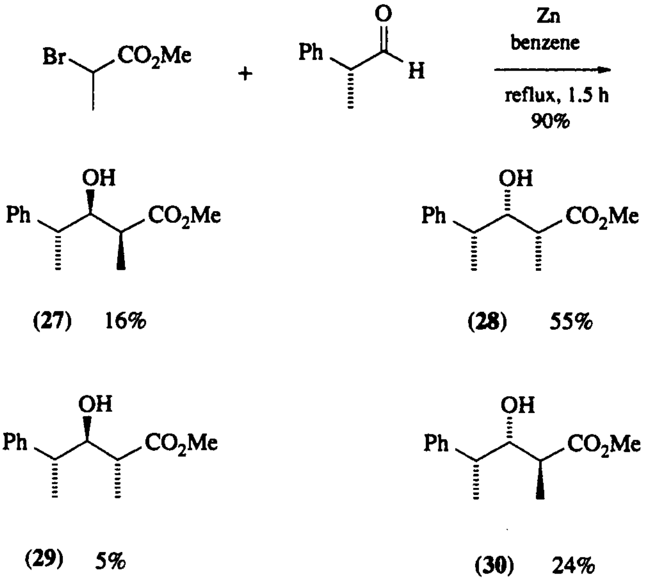
Br
CO2Me
+
Ph
O
H
Zn
benzene
reflux, 1.5 h
90%
OH
Ph
CO2Me
OH
Ph
CO2Me
OH
Ph
CO2Me
OH
Ph
CO2Me

(27) 16%

(28) 55%

(29) 5%

(30) 24%

(37)

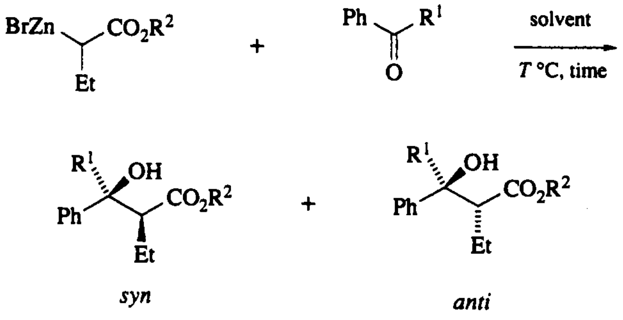
BrZn
CO2R2
Et
+
Ph
R1
O
solvent
T °C, time
R1
OH
Ph
CO2R2
Et
+
R1
OH
Ph
CO2R2
Et
syn
anti

(38)

**Table 5** Syn:Anti Ratios (equation 38)

| *$R^1$* | *$R^2$* | | *Syn:anti* | |
|---|---|---|---|---|
| | | *Dimethoxymethane (−75 °C, 24 h)* | *Dimethoxymethane (−10 °C, 0.5 h)* | *DMSO (−10 °C, 0.5 h)* |
| Me | Me | 62:38 | 29:71 | 60:40 |
| Me | Et | 50:50 | 25:75 | 52:48 |
| Me | Pr$^i$ | 30:70 | 21:79 | 50:50 |
| Me | Bu$^t$ | 15:85 | 15:85 | 40:60 |
| H | Me | 50:50 | 50:50 | 68:32 |
| H | Et | 44:56 | 51:49 | 66:34 |
| H | Pr$^i$ | 38:62 | 42:58 | 68:32 |
| H | Bu$^t$ | 47:53 | 44:56 | 68:32 |

hyde with optically active methyl α-bromopropionate (equation 39), and this result is most simply explained by reaction of a zinc–carbon bonded enolate.

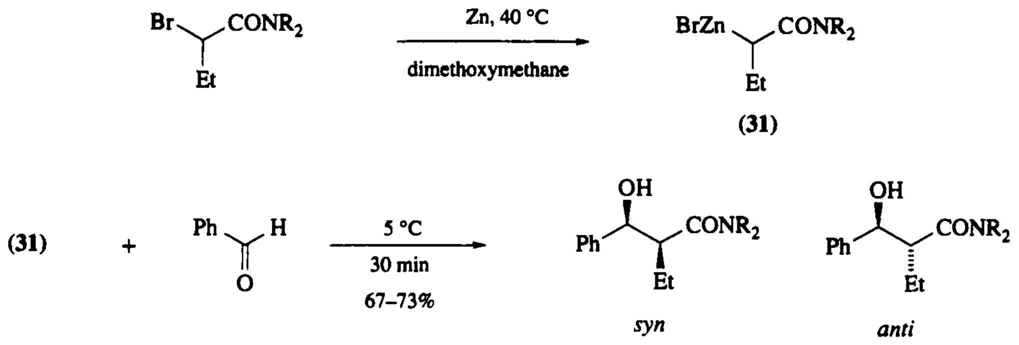
Br
CONR2
Et
Zn, 40 °C
dimethoxymethane
BrZn
CONR2
Et
(31)
(31)
+
Ph
H
O
5 °C
30 min
67–73%
OH
Ph
CONR2
Et
syn
OH
Ph
CONR2
Et
anti

**Scheme 12**

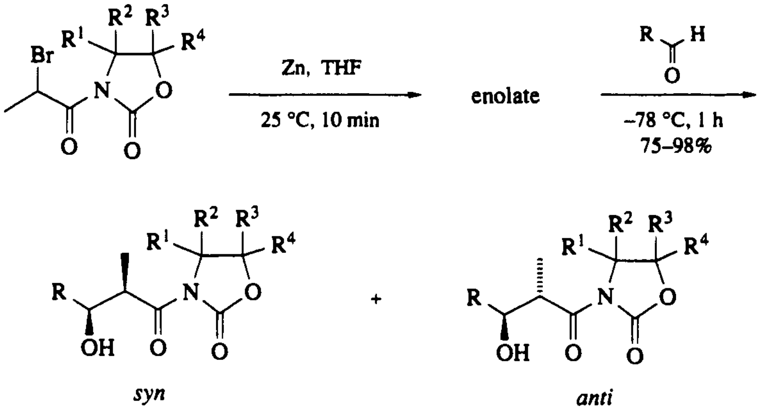
Br
R1
R2
R3
R4
N
O
O
O
Zn, THF
25 °C, 10 min
enolate
R
H
O
–78 °C, 1 h
75–98%
R
OH
O
O
syn
+
anti

**Scheme 13**

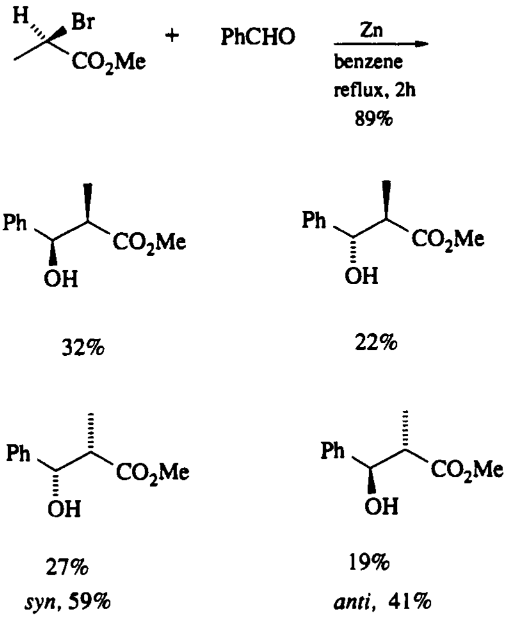
H
Br
CO2Me
+
PhCHO
Zn
benzene
reflux, 2h
89%
Ph
CO2Me
OH
32%
22%
27%
syn, 59%
19%
anti, 41%

(39)

### 1.8.3.5 Preparation of Unsaturated Esters

Dehydration of the aldol products of a Reformatsky reaction does not normally occur under the usual reaction conditions but is often accomplished in a separate step to prepare unsaturated esters. Acid-promoted dehydration of β-hydroxy esters can give significant amounts of nonconjugated unsaturated esters by either kinetic or thermodynamic control.[2] Mirrington and coworkers[80] found that acetates can be prepared directly from Reformatsky reaction mixtures by addition of acetyl chloride. Base-promoted elimination of the acetates produced conjugated esters in high yield. For the reaction shown in Scheme 14, the thermodynamic ratio of products (**32**):(**33**) is 40:60 and four different acid-promoted dehydration procedures gave at best a 68:32 ratio of products.[2]

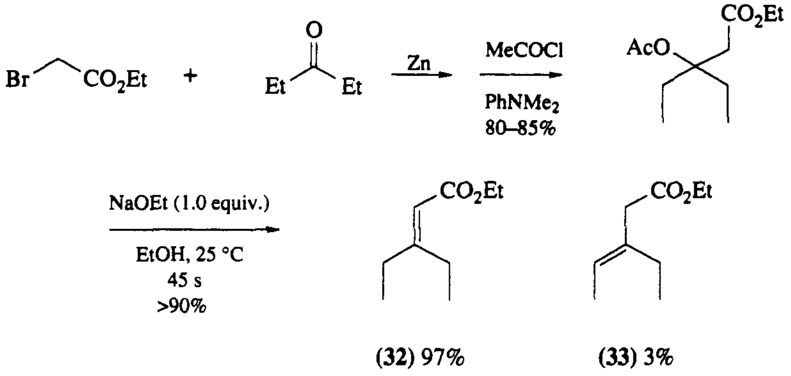
Br
CO2Et
+
O
Et
Et
Zn
MeCOCl
PhNMe2
80–85%
AcO
CO2Et
NaOEt (1.0 equiv.)
EtOH, 25 °C
45 s
>90%
CO2Et
CO2Et
(32) 97%
(33) 3%

Scheme 14

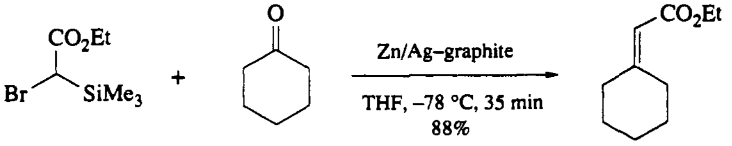
CO2Et
Br
SiMe3
+
O
Zn/Ag–graphite
THF, –78 °C, 35 min
88%
CO2Et

(40)

Reformatsky reactions of α-trimethylsilyl esters have been used to obtain α,β-unsaturated esters directly from carbonyl substrates in a Peterson-type alkenation,[81] as shown in equation (40).

## 1.8.4 REACTION WITH IMINES

The reaction of imines with Reformatsky reagents was first examined by Gilman and Speeter[82] in 1943 with benzalaniline. The product of the reaction was a β-lactam, formed by cyclization of an intermediate zinc salt (Scheme 15). The stereoselectivity of the reaction of α-alkyl-substituted bromo esters with a variety of benzalanilines was examined by both Luche and Kagan,[83] and Gaudemar and coworkers.[84] Condensations conducted at reflux temperatures gave a mixture of *cis* and *trans* β-lactams (equation 41).

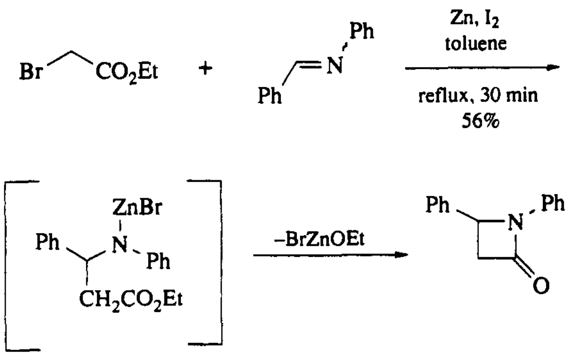
Br
CO2Et
+
Ph
N
Ph
Zn, I2
toluene
reflux, 30 min
56%
ZnBr
Ph
N
Ph
CH2CO2Et
–BrZnOEt
Ph
N
Ph
O

Scheme 15

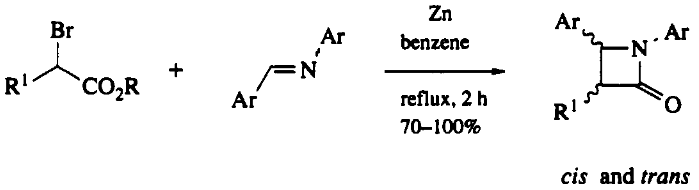
Br
R1
CO2R
+
Ar
N
Ar
Zn
benzene
reflux, 2 h
70–100%
Ar
N
Ar
R1
O
cis and trans

(41)

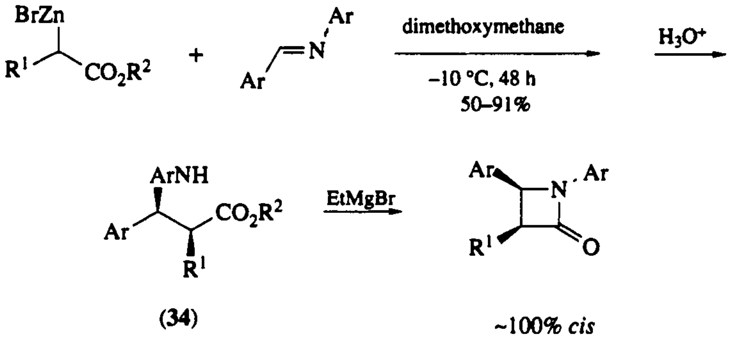
BrZn
R1
CO2R2
+
Ar
N
Ar
dimethoxymethane
−10 °C, 48 h
50–91%
H3O+
ArNH
Ar
CO2R2
R1
(34)
EtMgBr
Ar
N
Ar
R1
O
~100% cis

Scheme 16

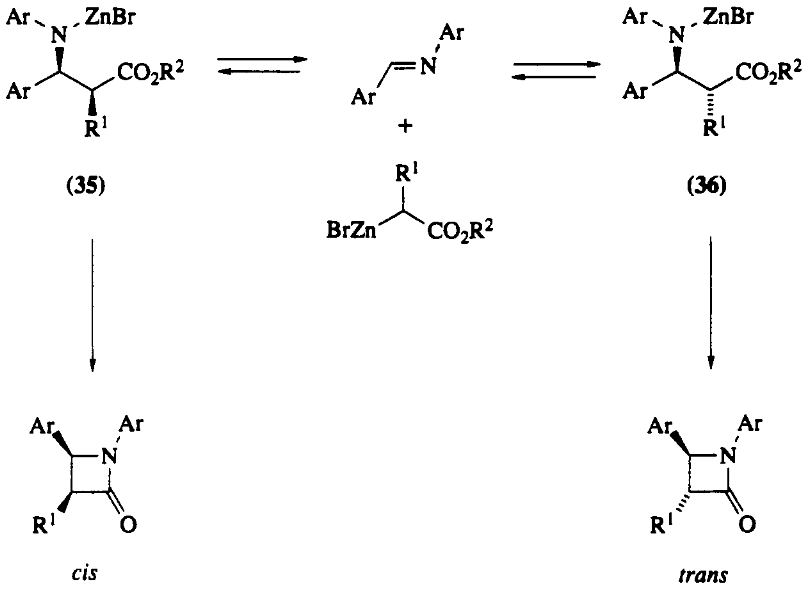
Ar
N
ZnBr
Ar
CO2R2
R1
(35)
Ar
N
Ar
+
R1
BrZn
CO2R2
Ar
N
ZnBr
Ar
CO2R2
R1
(36)
Ar
N
Ar
R1
O
cis
Ar
N
Ar
R1
O
trans

Scheme 17

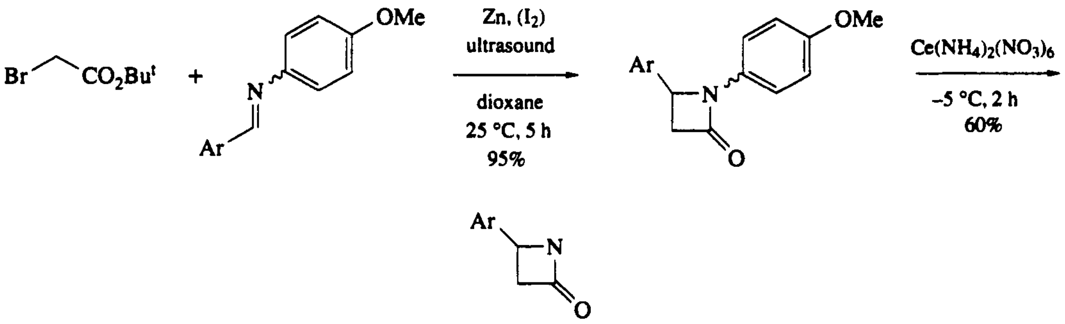
Br
CO2But
+
OMe
N
Ar
Zn, (I2)
ultrasound
dioxane
25 °C, 5 h
95%
Ar
N
OMe
O
Ce(NH4)2(NO3)6
−5 °C, 2 h
60%
Ar
N
O

Scheme 18

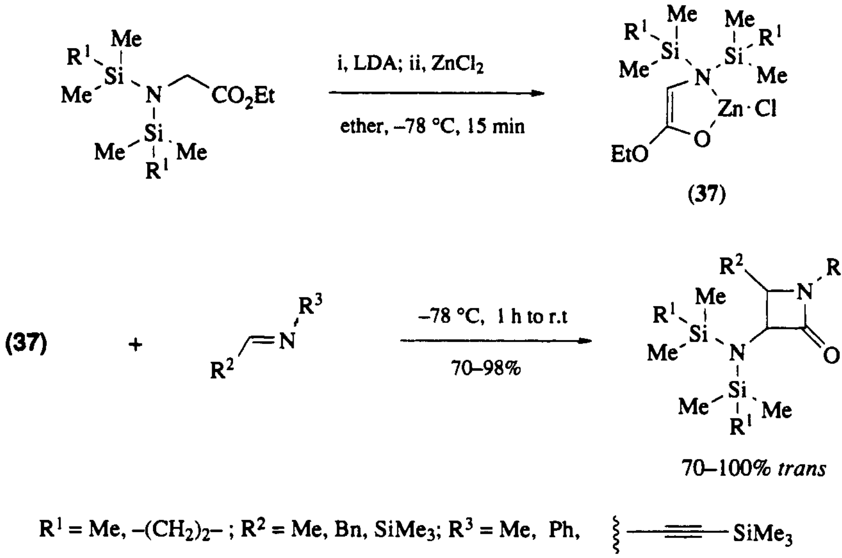
i, LDA; ii, ZnCl2
ether, –78 °C, 15 min
(37)
–78 °C, 1 h to r.t
70–98%
70–100% trans
R1 = Me, –(CH2)2– ; R2 = Me, Bn, SiMe3; R3 = Me, Ph,
SiMe3

**Scheme 19**

Condensations conducted at low temperatures using preformed Reformatsky reagents gave β-amino esters that have almost exclusively the *syn* configuration (**34**; Scheme 16). These may be cyclized by forming the magnesium salt to give the pure *cis*-β-lactam. It was concluded that the first step of the reaction is reversible at reflux temperature and equilibration of *syn* and *anti* zinc salts, (**35**) and (**36**), is competitive with irreversible cyclization, as shown in Scheme 17.[84]

Bose and coworkers[85] have reported that the condensation of ethyl bromoacetate with a variety of imines can be completed in a few hours at room temperature by means of ultrasound activation. Oxidative removal of a *N*-(*p*-methoxyphenyl) group gave *N*-unsubstituted β-lactams, which are useful intermediates in the preparation of β-lactam antibiotics (Scheme 18).

Van Koten and coworkers[86] prepared zinc ester enolates of *N*-protected α-amino esters from the corresponding lithium enolates and allowed them to react with imines at low temperature to obtain *trans*-3-amino-β-lactams, often with high stereoselectivity as shown in Scheme 19. Interestingly, the authors interpreted their results in terms of an internally chelated zinc–oxygen bonded enolate (**37**).

## 1.8.5 REACTION WITH ACYLATING AGENTS

### 1.8.5.1 Reaction with Esters and Acid Chlorides

Reactions of Reformatsky reagents with esters or with acid chlorides generally give only low yields of β-keto esters.[2] Hauser reported that ethyl α-bromoisobutyrate could be acylated in reasonable yields with either the acid chlorides[43] or the phenyl esters[87] of aromatic acids, but the reaction fails with acylating

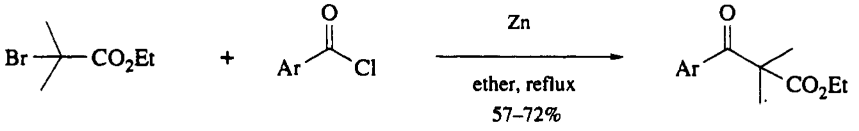
Br
CO2Et
+
Ar
Cl
Zn
ether, reflux
57–72%
Ar
CO2Et

(42)

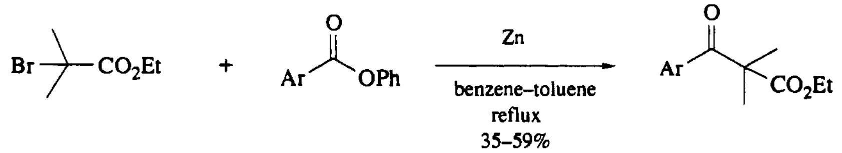
Br
CO2Et
+
Ar
OPh
Zn
benzene–toluene
reflux
35–59%
Ar
CO2Et

(43)

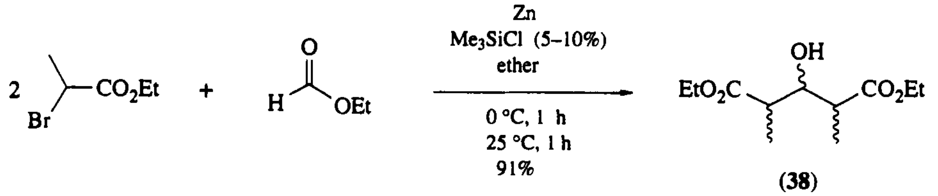
2
Br
CO2Et
+
O
H
OEt
Zn
Me3SiCl (5–10%)
ether
0 °C, 1 h
25 °C, 1 h
91%
OH
EtO2C
CO2Et

(38) (44)

agents or with bromo esters which possess α-hydrogens (equations 42 and 43). It is interesting to note that Reformatsky himself[88] reported a reasonably successful synthesis (41% yield) of the tandem aldol product (**38**) by reaction of ethyl formate with two equivalents of ethyl α-bromopropionate. Recently, with zinc metal activated with $Me_3SiCl$,[89] the same product was obtained in 91% yield (equation 44).

### 1.8.5.2 Reaction with Nitriles, the Blaise Reaction

The most successful acylations of Reformatsky reagents have been obtained with nitriles. This reaction, first reported in 1901 by Blaise,[90] was little used until Kagan and Suen[91] reported that slow addition of a benzene solution of α-bromo esters to a refluxing mixture of zinc and the nitrile gave good yields (70–83%) of α,α-disubstituted β-keto esters. Hannick and Kishi[92] reported that a similar proce-

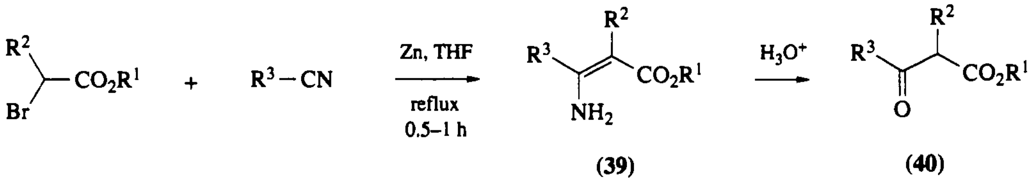
R2
Br
CO2R1
+
R3—CN
Zn, THF
reflux
0.5–1 h
R3
R2
CO2R1
NH2
H3O+
R3
R2
CO2R1
O

(39) (40)

Scheme 20

Table 6 Yield of Enamino Esters (**39**) or β-Keto Esters (**40**) (Scheme 20)

| $R^1$ | $R^2$ | $R^3$ | *(38) (%)* | *(39) (%)* |
|---|---|---|---|---|
| Me | H | $(CH_2)_4Cl$ | 95 | 85 |
| $Bu^t$ | H | $(CH_2)_4Cl$ | 87 | 83 |
| Me | H | $C(CH_3)_2(CH_2)_2Cl$ | 70 | 62 |
| Me | H | Ph | 88 | 82 |
| Me | Me | Ph | 84 | 79 |
| Me | Me | $(CH_2)_4Cl$ | 54 | 84 |

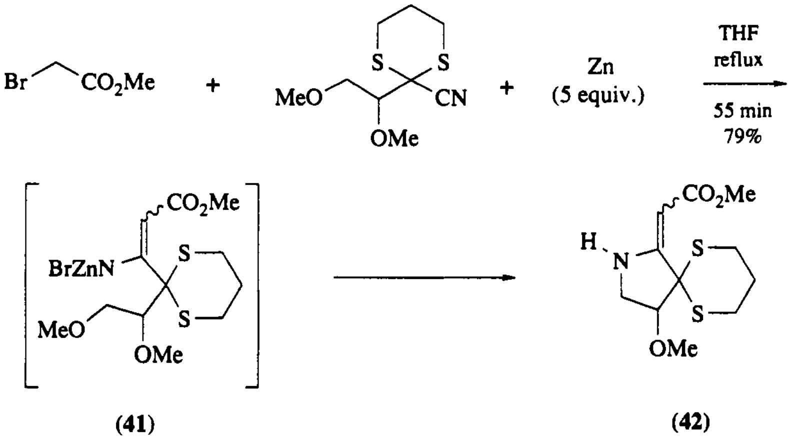
Br
CO2Me
+
S
S
MeO
CN
OMe
+
Zn
(5 equiv.)
THF
reflux
55 min
79%
CO2Me
BrZnN
S
S
MeO
OMe
CO2Me
H
N
S
S
OMe

(41) (42)

Scheme 21

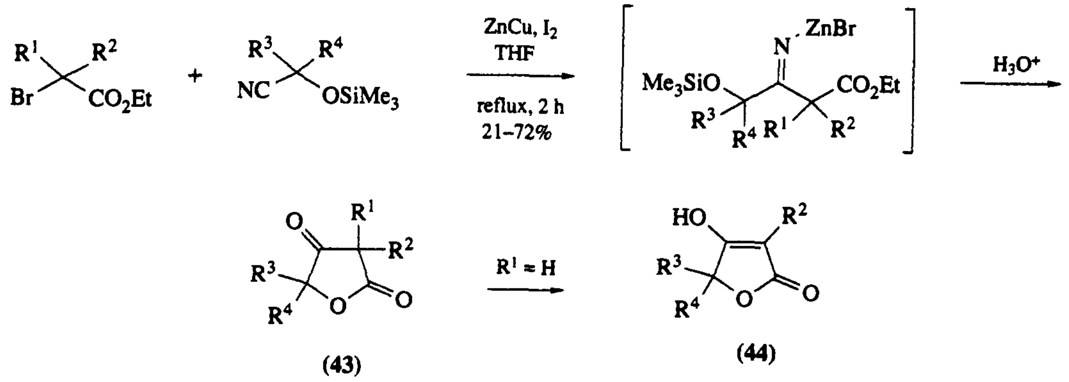

Scheme 22

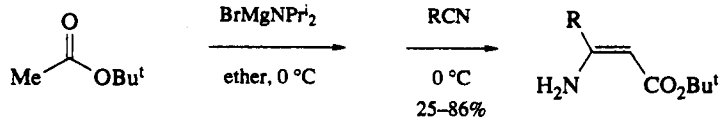

Scheme 23

dure using activated zinc dust in refluxing THF was substantially better for the preparation of both α-monosubstituted or α-unsubstituted β-keto esters (Scheme 20 and Table 6).

Hannick and Kishi[92] cyclized an intermediate bromozinc enamino ester (**41**; Scheme 21) to obtain the heterocycle (**42**), used for the synthesis of saxitoxins. The Kishi procedure for the Blaise reaction has been applied[44] to a facile synthesis of β-keto-δ-butyrolactones (**43**), or tetronic acids (**44**; Scheme 22).

It is useful to note that Hiyama and Kobayashi[93] have reported successful reactions of nitriles with a magnesium ester enolate (Scheme 23), whereas the corresponding lithium ester enolate failed to react.

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# 1.9
# The Aldol Reaction: Transition Metal Enolates

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## 1.9.1 INTRODUCTION

The application of transition metal and lanthanide metal enolates to the aldol reaction is a recent development. There are significant potential advantages to be gained in selectivity over the aldol addition reactions of their main group counterparts: the use of less electropositive metals leads to reduced enolate basicity; stabilization of the aldolate by transition metal coordination can lead to improved conversion and avoidance of retroaldolization, thus ensuring kinetic control of reaction; greater stereochemical control arising from sterically demanding transition metal centers; moreover, enantioselective aldol reactions are possible by the introduction of chiral ligands on the metal or a chiral metal center. Correspondingly, the aldol reactions of specific transition metal enolates, where a marked improvement in selectivity over the main group reactions has been realized in practice, will be emphasized here. While mercury with a $d^{10}$ electronic configuration is not normally considered as a transition metal, it is convenient to deal with its aldol chemistry in this section. The aldol reactions of the enolates of acyl–transition metal complexes are also included in this section, even though their reactivity is largely governed by the enolate counterion and not the transition metal itself.

To facilitate an analysis of enolate reactivity and as an aid to the rationalization of the stereochemical outcome of the aldol reaction, a consideration of the enolate structure is necessary.[1] For convenience, the following classification of transition metal and lanthanide metal enolates will be used here: $\eta^1$-*O*-bound metal enolates (**1**) of carbonyl compounds; $\eta^1$-*C*-bound metal enolates (**2**) and $\eta^3$-metal enolates (**3**) of

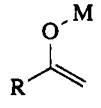

**(1)**

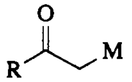

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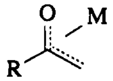

**(3)**

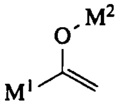

**(4)**

carbonyl compounds; main group metal enolates of acyl–transition metal complexes (**4**). Other important considerations include: the metal oxidation state; the nature of the ligands; type of ligand–metal coordination; and ligand- and metal-centered chirality.

## 1.9.2 ALDOL REACTIONS OF $\eta^1$-*O*-BOUND METAL ENOLATES

### 1.9.2.1 Zirconium

The aldol reactions mediated by the early transition metals zirconium and titanium are characterized by high *syn* stereoselectivity and good yields. They usually involve formation of the required enolate intermediate by a transmetallation reaction of a preformed lithium enolate with the appropriate transition metal halide. An important feature is that, unlike the situation with lithium and boron enolates, high *syn* stereoselectivity in additions to aldehydes is generally obtained for acyclic carbonyl compounds regardless of enolate geometry. The enolate geometry, therefore, does not need to be controlled at the enolization stage to ensure useful levels of stereocontrol in the aldol step. For example, the di(cyclopentadienyl)chlorozirconium enolates (**5**) of ethyl ketones, propionate esters and thioesters, and propionamides, prepared by transmetallation of the preformed lithium enolates with $Cp_2ZrCl_2$, undergo aldol additions to aldehydes in THF at −78 °C with moderate to high levels of diastereoselectivity favoring the *syn* adduct (**6**; Scheme 1 for $R^2$ = Me and Table 1, entries 1–14).[2,3] In contrast, the corresponding lithium enolate precursors usually show much lower levels of stereoselectivity even when a single enolate geometry is involved (Volume 2, Chapter 1.5). Evans and McGee have demonstrated that these zirconium-mediated aldol reactions proceed under kinetic control, and, to explain the stereochemical convergency operating, propose that the (*Z*)-enolates favor reaction with the aldehyde *via* a chair-like transition state (**7**) to give (**6**), whereas the (*E*)-enolates favor reaction *via* a boat-like transition state (**8**) to also give (**6**).[2] Acyclic transition states have also been proposed for these reactions.[3] Either way, the steric effect of the ligands on the metal plays a significant role in controlling the stereochemistry. Cyclic ketones (Table 1, entries 15 and 16), which can only give the (*E*)-enolate, also produce the *syn* aldols *via* the zirconium enolate in moderate selectivity.[3] Here the lithium enolates lead to mainly *anti* aldol pro-

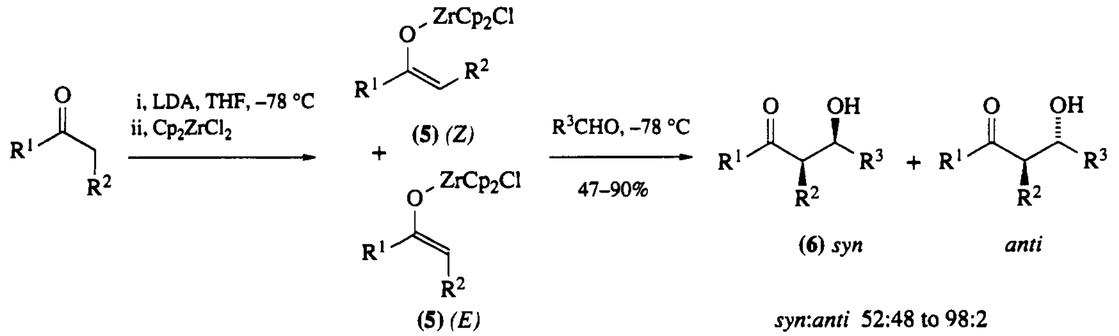

**Scheme 1**

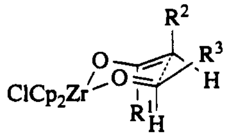

**(7)**

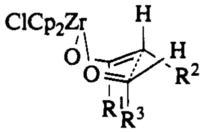

**(8)**

**Table 1** *Syn:Anti* Selectivity in the Aldol Reactions of Di(cyclopentadienyl)chlorozirconium Enolates (Scheme 1)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(Z):(E)* | *Syn:Anti* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | $Bu^tS$ | Me | Ph | 10:90 | 93:7 | 70 | 2 |
| 2 | MeO | Me | Ph | 5:95 | 87:13 | 80 | 2 |
| 3 | $Bu^tO$ | Me | Ph | 5:95 | 72:28 | — | 2 |
| 4 | Ph | Me | Ph | >98:2 | 90:10 | 62 | 2 |
| 5 | Et | Me | Ph | 92:8 | 67:33 | 86 | 3 |
| 6 | Et | Me | Ph | 14:86 | 88:12 | 70 | 3 |
| 7 | $Pr^i_2N$ | Me | Ph | 81:19 | >98:2 | 87 | 2 |
| 8 | $Pr^i_2N$ | Me | $Pr^n$ | 81:19 | 98:2 | 80–90 | 2 |
| 9 | $Pr^i_2N$ | Me | $Pr^i$ | 81:19 | 97:3 | 80–90 | 2 |
| 10 | $Pr^i_2N$ | Me | $H_2C{=}CMe$ | 81:19 | 95:5 | 80–90 | 2 |
| 11 | $c\text{-}(CH_2)_4N^a$ | Me | Ph | >95:5 | 95:5 | 80 | 2 |
| 12 | $c\text{-}(CH_2)_4N$ | Me | $Pr^n$ | >95:5 | 94:6 | 80–90 | 2 |
| 13 | $c\text{-}(CH_2)_4N$ | Me | $Pr^i$ | >95:5 | 95:5 | 80–90 | 2 |
| 14 | $c\text{-}(CH_2)_4N$ | Me | $H_2C{=}CMe$ | >95:5 | 90:10 | 80–90 | 2 |
| 15 | $—(CH_2)_3—$ | | Ph | 0:100 | 74:26 | 82 | 3 |
| 16 | $—(CH_2)_4—$ | | Ph | 0:100 | 64:36 | 75 | 3 |
| 17 | $—CH{=}CH(CH_2)_2—$ | | Ph | 0:100 | 75:25 | 65 | 4 |
| 18 | $—CH{=}CH(CH_2)_2—$ | | $Bu^n$ | 0:100 | 52:48 | 55 | 4 |
| 19 | $—CH{=}CHCH_2—$ | | Ph | 0:100 | 85:15 | 65 | 4 |
| 20 | $—CH{=}CHCH_2—$ | | $Bu^n$ | 0:100 | 57:43 | 47 | 4 |

[a] $c\text{-}(CH_2)_4N$ = 1-pyrrolidinyl.

ducts. Moderate levels of *syn* selectivity have also been found in the aldol reactions of the zirconium dienolates derived from 2-cyclohexenone and 2-cyclopentenone (Table 1, entries 17–20).[4]

The high *syn* stereoselectivity attained in zirconium enolate aldol reactions has proved useful in complex natural product synthesis. The zirconium-mediated aldol reaction of the chiral ethyl ketone (**9**) with a chiral aldehyde has been used by Masamune *et al.* to give selectively adduct (**10**), which was further elaborated into the ansa chain of rifamycin S (equation 1).[5] Good enolate diastereofacial selectivity is also obtained here and leads to a predominance of one of the two possible *syn* adducts. A zirconium enolate aldol reaction also features in the Deslongchamps formal total synthesis of erythromycin A, where the di(cyclopentadienyl)chlorozirconium enolate from methyl propionate adds with high levels of Cram selectivity to the chiral aldehyde (**11**) to give the *syn* adduct (**12**; equation 2).[6] A further example is

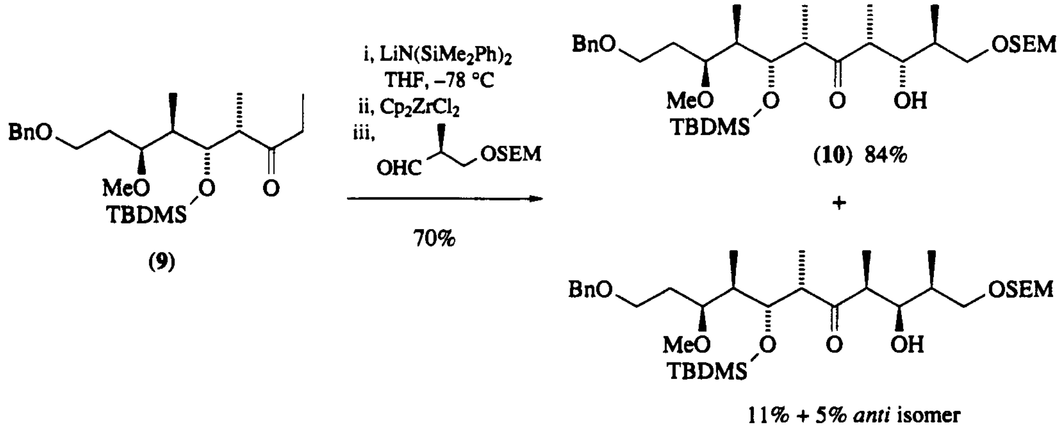

(1)

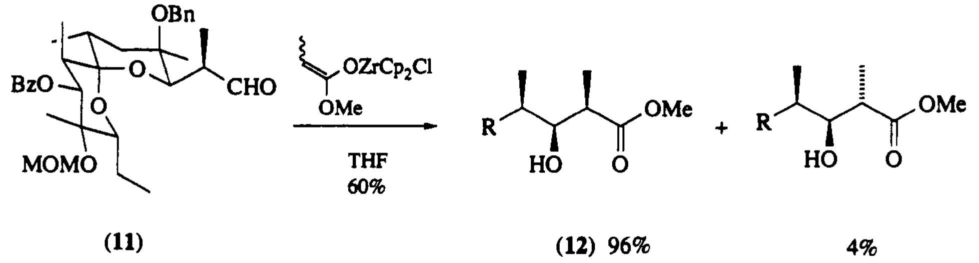

(2)

the aldol reaction of the β-lactam (**13**), which sets up the stereochemistry in the *syn* adduct (**14**), as required for a projected thienamycin synthesis (equation 3).[7]

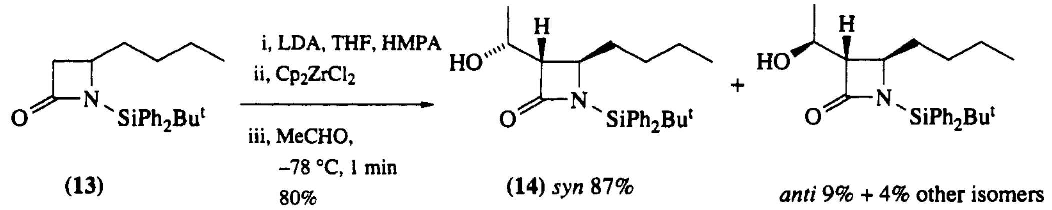
SiPh₂Buᵗ
(13)
i, LDA, THF, HMPA
ii, Cp₂ZrCl₂
iii, MeCHO,
-78 °C, 1 min
80%
HO
H
SiPh₂Buᵗ
(14) syn 87%
+
anti 9% + 4% other isomers

(3)

Highly stereoselective aldol reactions have been developed using the zirconium enolates (**15**) to (**18**), which now have a chiral auxiliary attached to the enolate.[8,9] Evans and McGee have described the use of the amino acid derived zirconium enolates (**15**) and (**16**) for stereoregulated aldol reactions, which proceed to give the *syn* isomers (**19**) and (**20**) respectively in >96% diastereoselectivity for $R^1$ = Me (Scheme 2 and Table 2, entries 1–8).[8] The overall result, after auxiliary removal to give the *syn*-α-methyl-β-hydroxycarboxylic acid, is equivalent to an enantioselective aldol reaction of a propionate enolate. Note that a (*Z*)-substituent in the enolate is a prerequisite for good diastereofacial selection as the analogous acetate enolates show virtually no selectivity. A preferred chair-like transition state (**21**) for the reaction has been proposed based on minimizing steric interactions between the enolate substituents and the bulky cyclopentadienyl ligands on the metal.

The diastereofacial selectivities of these enolates are greatly superior to those of most chiral aldehydes, such that the reaction can also be used to control the aldol addition to a chiral aldehyde (Table 2, entries

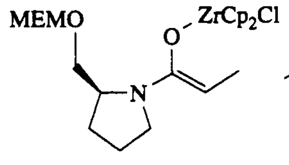
MEMO
ZrCp₂Cl

**(15)**

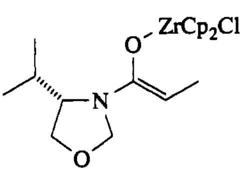

**(16)**

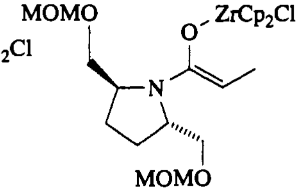
MOMO
ZrCp₂Cl
MOMO

**(17)**

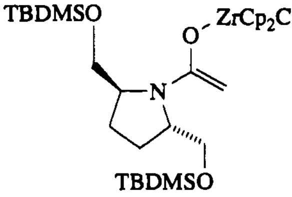
TBDMSO
ZrCp₂Cl
TBDMSO

**(18)**

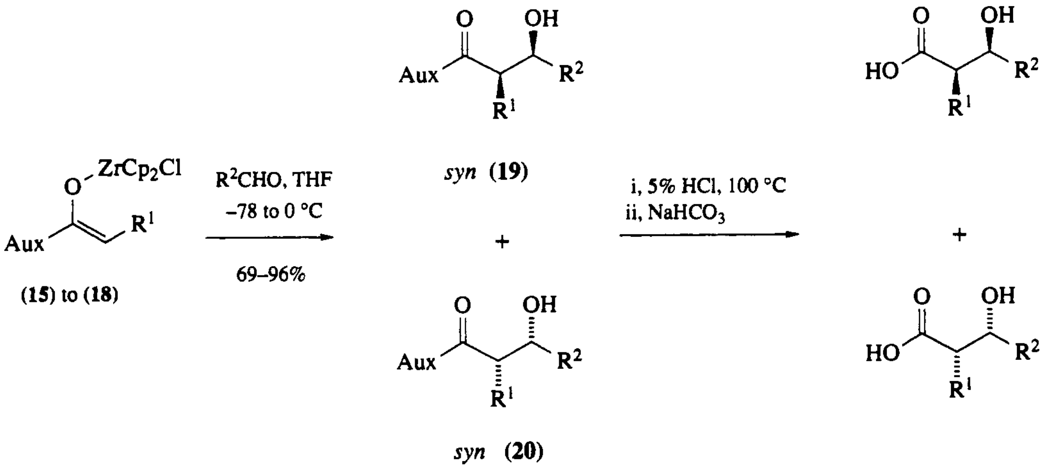
ZrCp₂Cl
Aux
R¹
(15) to (18)
R²CHO, THF
-78 to 0 °C
69–96%
Aux
R²
R¹
syn (19)
+
syn (20)
i, 5% HCl, 100 °C
ii, NaHCO₃
HO
R²
R¹
+

(**19**):(**20**) ≥ 96:4 for (**15**) or (**17**), $R^1$ = Me
(**20**):(**19**) ≥ 96:4 for (**16**), $R^1$ = Me
(**19**):(**20**) ≥ 89:11 for (**18**), $R^1$ = H

**Scheme 2**

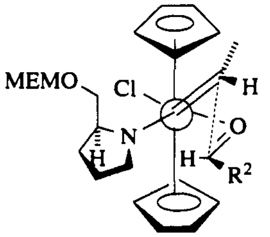

(**21**)

**Table 2** Stereoselectivity in the Aldol Reactions of Chiral Di(cyclopentadienyl)chlorozirconium Enolates (Scheme 2)

| *Entry* | *Enolate* | *R*$^1$ | *R*$^2$ | *Syn* (**19**) (%) | *Syn* (**20**) (%) | *Anti* (%) | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | (**15**) | Me | Bu$^n$ | 96 | 2 | 2 | 69 | 8 |
| 2 | (**16**) | Me | Bu$^n$ | 1 | 97 | 2 | 96 | 8 |
| 3 | (**15**) | Me | Pr$^i$ | 96 | 2 | 2 | 77 | 8 |
| 4 | (**16**) | Me | Pr$^i$ | 0.5 | 97.5 | 2 | 77 | 8 |
| 5 | (**15**) | Me | Ph | 96 | 1 | 3 | 71 | 8 |
| 6 | (**16**) | Me | Ph | 1.5 | 94.5 | 4 | 71 | 8 |
| 7 | (**16**) | Me | 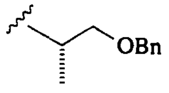 OBn | 0.9 | 98.7 | 0.4 | — | 8 |
| 8 | (**16**) | Me | 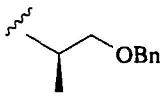 OBn | 1.7 | 94.5 | 3.8 | — | 8 |
| 9 | (**17**) | Me | Pr$^i$ | >99 | <1 | | 85 | 9 |
| 10 | (**17**) | Me | Et | >99 | <1 | | 92 | 9 |
| 11 | (**18**) + Et$_2$NH | H | Ph | 84 | 16 | | 62 | 9 |
| 12 | (**18**) + BuNH$_2$ | H | Ph | 89.5 | 10.5 | | 20 | 9 |

7 and 8). For acid-stable adducts, amide hydrolysis by boiling in 5% hydrochloric acid leads to the corresponding β-hydroxycarboxylic acid without appreciable epimerization. However, such conditions for auxiliary removal are probably incompatible with application to the synthesis of complex acid-sensitive structures. Similar results have been obtained by Katsuki and Yamaguchi for the zirconium enolate (**17**), which gives the aldol product (**19**) with both high diastereofacial selectivity and *syn* diastereoselectivity (Table 2, entries 9 and 10).[9] Again, acid hydrolysis is required for auxiliary removal, which restricts its application to acid-tolerant aldol products. This chemistry can also be extended to some extent to give a chiral acetate enolate equivalent (**18**; Table 2, entries 11 and 12), but much better reagents are available.[10]

## 1.9.2.2 Titanium

The aldol reactions of titanium enolates have been the best studied of all the transition metal enolates.[11,12] In many cases they show higher stereoselectivity and chemoselectivity in their reactions than lithium enolates and are easily prepared using inexpensive reagents. They also promote high levels of diastereofacial selectivity in reactions of chiral reactants. The Lewis acidity of the titanium metal center can be easily manipulated by variation of the ligands (chloro, alkoxy, amino, cyclopentadienyl, *etc.*) attached to titanium, which leads to enhanced selectivity in appropriate cases. Moreover, the incorporation of chiral ligands on titanium makes possible efficient enantioselective aldol reactions.

Titanium enolates of cyclic and acyclic ketones, like their zirconium counterparts, usually give rise to *syn* aldol products irrespective of enolate geometry. Tri(alkoxy)- or tri(dialkylamino)-titanium enolates

(**22**) are prepared (Scheme 3) from lithium enolates by an exchange reaction with $ClTi(OPr^i)_3$ or $BrTi(NEt_2)_3$ in THF at −78 °C and can be isolated by evaporating the solvent at room temperature.[13] The subsequent aldol reactions are carried out in pentane at −78 °C or −120 °C. Useful levels of diastereoselectivity towards the *syn* adduct (**23**) are usually obtained in the aldol reactions of acyclic ketones and cyclohexanone using these titanium enolates (Table 3, entries 1–16).[13] Poorer selectivities are obtained in only a few cases (Table 3, entries 17 and 18). This is probably the best method available for obtaining high *syn* selectivity in the aldol reactions of five- to seven-membered cyclic ketones (Table 3 entries 11–

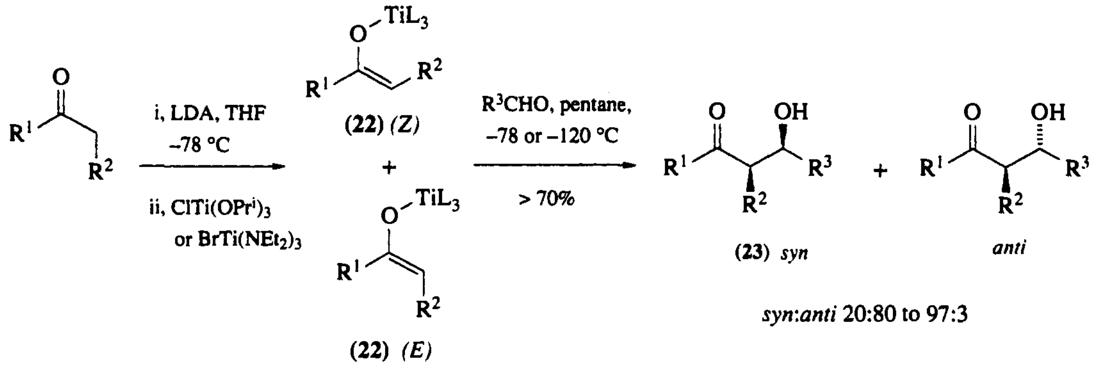

**Scheme 3**

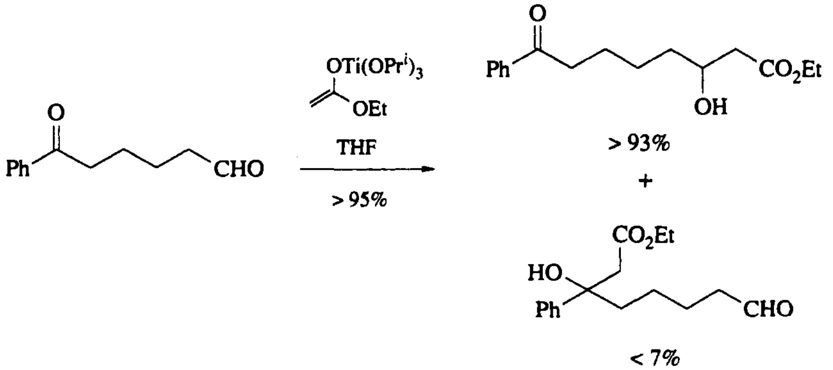

(4)

**Table 3** *Syn:Anti* Selectivity in the Aldol Reactions of Tri(isopropoxy)- and Tri(diethylamino)-titanium Enolates (Scheme 3)[13]

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *L* | *Temperature (°C)* | *(Z):(E)* | *Syn:Anti* |
|---|---|---|---|---|---|---|---|
| 1 | Et | Me | Ph | $Pr^iO$ | −120 | 36:64 | 89:11 |
| 2 | Et | Me | Ph | $Pr^iO$ | −120 | 92:8 | 88:12 |
| 3 | Et | Me | Ph | $Et_2N$ | −78 | 36:64 | 76:24 |
| 4 | Me | Me | Ph | $Et_2N$ | −78 | 5:95 | 74:26 |
| 5 | Et | Me | $c\text{-}C_6H_{11}$ | $Pr^iO$ | −120 | 36:64 | 77:23 |
| 6 | Et | Me | $Bu^t$ | $Pr^iO$ | −120 | 36:64 | 81:19 |
| 7 | $Bu^t$ | Me | Ph | $Pr^iO$ | −120 | >98:2 | 87:13 |
| 8 | Ph | Me | Ph | $Pr^iO$ | −120 | >98:2 | 87:13 |
| 9 | Ph | Me | Et | $Pr^iO$ | −120 | >98:2 | 89:11 |
| 10 | Mesityl | Me | Ph | $Pr^iO$ | −120 | 87:13 | 90:10 |
| 11 | $-(CH_2)_3-$ |  | Ph | $Et_2N$ | −78 | 0:100 | 85:15 |
| 12 | $-(CH_2)_4-$ |  | Ph | $Et_2N$ | −78 | 0:100 | 97:3 |
| 13 | $-(CH_2)_4-$ |  | Ph | $Pr^iO$ | −120 | 0:100 | 86:14 |
| 14 | $-(CH_2)_4-$ |  | $Pr^i$ | $Pr^iO$ | −120 | 0:100 | 96:4 |
| 15 | $-(CH_2)_5-$ |  | Ph | $Et_2N$ | −78 | 0:100 | 97:3 |
| 16 | $-(CH_2)_5-$ |  | Ph | $Pr^iO$ | −120 | 0:100 | 91:9 |
| 17 | Mesityl | Me | Ph | $Pr^iO$ | −120 | 5:95 | 20:80 |
| 18 | Et | Me | Ph | $Et_2N$ | −78 | 92:8 | 41:59 |

16). A similar chair and boat dual transition state model to that for zirconium enolates has been used by Reetz and Peter to explain the *syn* stereoselectivity, although acyclic transition states may also be operative.

These tri(alkoxy)titanium enolates, which have low Lewis acidity, are known to react chemoselectively with an aldehyde group in the presence of a ketone (equation 4).[14] Other uses described by Reetz *et al.* include the diastereofacially selective additions of ketone and ester enolates to chiral α-alkoxy aldehydes with nonchelation control.[15,16] For example, aldol addition of the tri(isopropoxy)titanium enolate of propiophenone to the aldehyde (**24**) leads to only the two *syn* diastereomers, with the nonchelation adduct (**25**) favored (equation 5); *i.e.* Felkin–Anh selectivity is operating. In the case of aldol addition of *t*-butyl propionate to the same aldehyde (equation 6), highest stereoselectivity for the isomer (**26**) is obtained using the tri(diethylamino)titanium enolate.[17] Very high levels of nonchelation stereoselectivity can also be obtained in the aldol addition to chiral α-siloxy or α-benzyloxy ketones if a titanium enolate of low Lewis acidity is employed, as in equation (7).[18]

In some cases titanium enolates give as good, if not better, stereoselectivity as the corresponding boron enolate aldol reactions (Volume 2, Chapter 1.7). For example, the tri(isopropoxy)titanium enolate of the chiral ethyl ketone (**27**) has been found to undergo aldol reactions with aldehydes with very high dia-

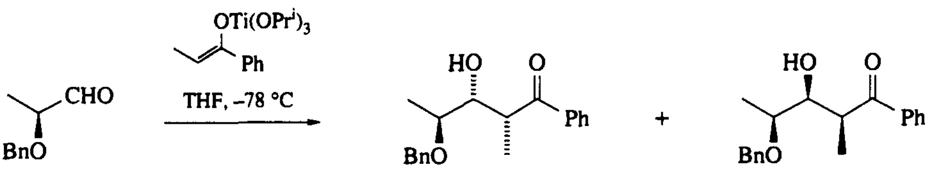

OTi(OPr$^i$)$_3$
Ph
THF, -78 °C
CHO
BnO
HO O
Ph
BnO
+
HO O
Ph
BnO

(**24**) (**25**) 87% 13% (5)

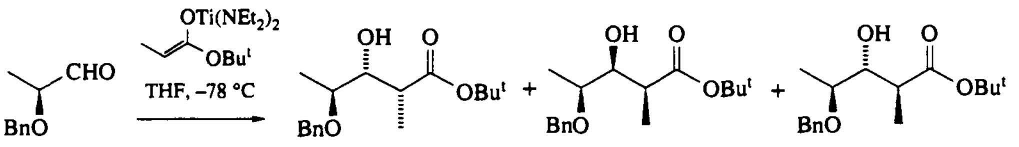

OTi(NEt$_2$)$_2$
OBu$^t$
THF, -78 °C
CHO
BnO
OH O
OBu$^t$
BnO
+
OH O
OBu$^t$
BnO
+
OH O
OBu$^t$
BnO

(**24**) (**26**) 85% 7% 8% (6)

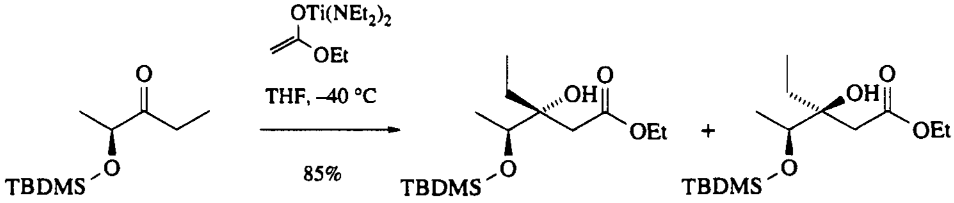

OTi(NEt$_2$)$_2$
OEt
THF, –40 °C
85%
O
TBDMS O
O
OH
OEt
TBDMS O
+
O
OH
OEt
TBDMS O

> 99% < 1% (7)

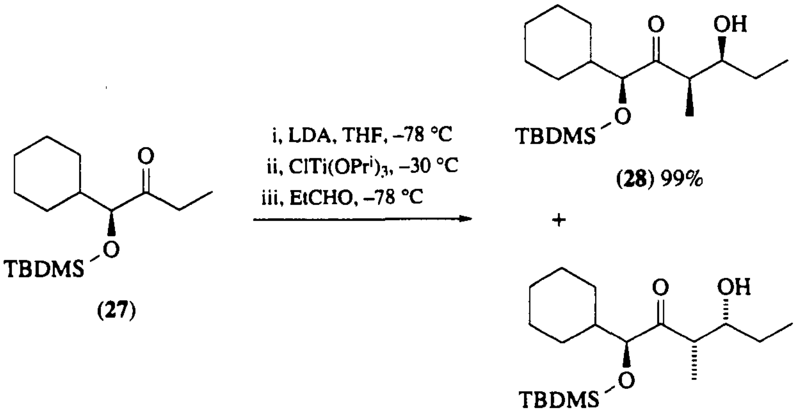

O
TBDMS O
i, LDA, THF, -78 °C
ii, ClTi(OPr$^i$)$_3$, -30 °C
iii, EtCHO, -78 °C
O OH
TBDMS O
+
O OH
TBDMS O

(**27**) (**28**) 99% 1% (8)

stereofacial selectivity at the 99% level (equation 8).[19] The titanium enolate is easily prepared in THF from the preformed lithium enolate. Highest selectivity requires the use of three equivalents of $ClTi(OPr^i)_3$, presumably ensuring complete Li → Ti exchange in the enolate, and produces the same major *syn* isomer (**28**) as that from the corresponding boron enolate reaction. The aldol products may be oxidatively converted into *syn*-α-methyl-β-hydroxycarboxylic acids in optically pure form.[20] An advantage of the use of titanium with this chiral propionate enolate equivalent is that the reagent is inexpensive and no oxidative work-up is now needed compared to the boron reaction described by Masamune *et al.*[20] Nerz-Stormes and Thornton have reported a similar study for the aldol reactions of the Evans chiral imide reagent (**29**; equation 9).[21] However, this time the diastereofacial selectivity is poorer for titanium than boron; but of more interest, it is in the opposite direction, which has been explained by invoking a chelated chair transition state.

An important development is the use of D-glucose-derived alkoxy ligands on titanium in cyclopentadienyldi(alkoxy)titanium enolates, which undergo efficient enantioselective aldol reactions with aldehydes. The chiral titanium reagent (**30**), prepared from reaction of cyclopentadienyltitanium trichloride with two equivalents of (1,2;5,6)-di-*O*-isopropylidene-α-D-glucofuranose,[22] can be used to transmetallate the lithium enolate of *t*-butyl acetate in ether solution (equation 10).[23] The titanium enolate generated is then

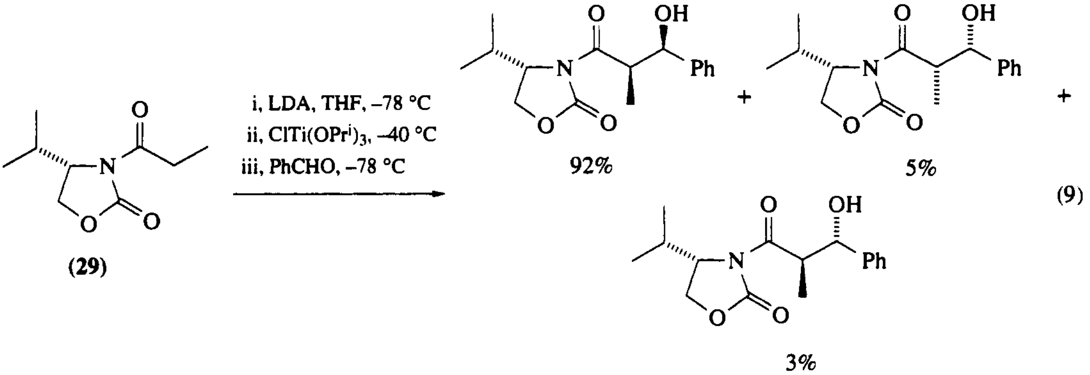
O
N
O
O
i, LDA, THF, –78 °C
ii, $ClTi(OPr^i)_3$, –40 °C
iii, PhCHO, –78 °C
O
OH
Ph
N
O
O
92%
+
5%
+
3%

**(29)**

(9)

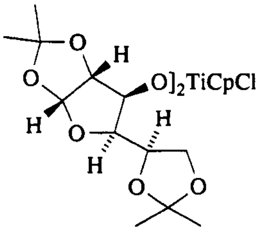
O
H
$O]_2TiCpCl$
O
H
O
H
H
O
O

**(30)**

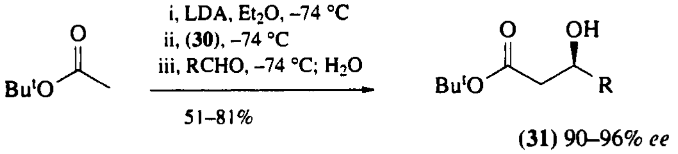
O
$Bu^tO$
i, LDA, $Et_2O$, –74 °C
ii, (**30**), –74 °C
iii, RCHO, –74 °C; $H_2O$
51–81%
O
OH
$Bu^tO$
R

(**31**) 90–96% *ee*

(10)

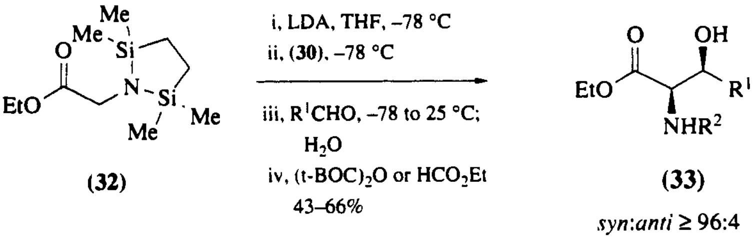
Me
Me
Si
O
N
Si
EtO
Me
Me
i, LDA, THF, –78 °C
ii, (**30**), –78 °C
iii, $R^1CHO$, –78 to 25 °C; $H_2O$
iv, $(t\text{-BOC})_2O$ or $HCO_2Et$
43–66%
O
OH
EtO
$R^1$
$NHR^2$

**(32)**

**(33)**

*syn*:*anti* ≥ 96:4
87–98% *ee*

(11)

reacted at −74 °C with an aldehyde *in situ*, which after hydrolytic work-up gives the β-hydroxy ester adduct (**31**) in 90–96% *ee*. Duthaler *et al.* have shown that the reaction is applicable to a wide range of aldehydes (Table 4) and that the carbohydrate ligand can be recycled.[23] The use of other ligands should make available the enantiomeric adducts, while application of this method to the enantioselective aldol reactions of other carbonyl compounds should also be feasible. For instance, the method has also been applied to the enantioselective synthesis of *N*-protected *syn*-β-hydroxy-α-amino acids (**33**) by aldol reaction of the titanium enolate of the glycine derivative (**32**; equation 11).[24] Here high *syn* diastereoselectivity is obtained as expected from titanium, while the attached chiral ligands induce a high level of enolate π-face selectivity in addition to aldehydes (Table 5).

**Table 4** Enantioselective Aldol Reactions of the Chiral Titanium Enolate of *t*-Butyl Acetate with Aldehydes (equation 10)[23]

| *Entry* | *R* | *Ee (%)* | *Yield (%)* |
|---|---|---|---|
| 1 | $Pr^n$ | 94 | 51 |
| 2 | $Me(CH_2)_{11}$ | 94 | 70 |
| 3 | $Bu^i$ | 94 | 81 |
| 4 | $Pr^i$ | 95 | 66 |
| 5 | $c\text{-}C_6H_{11}$ | 92 | 70 |
| 6 | $Bu^t$ | 91 | 80 |
| 7 | (*E*)-$Pr^nCH{=}CH$ | 91 | 81 |
| 8 | (*E*)-$MeCH{=}CH$ | 92 | 58 |
| 9 | $H_2C{=}CMe$ | 96 | 81 |
| 10 | Ph | 95 | 69 |
| 11 | 2-Furyl | 90 | 62 |

**Table 5** Enantioselective Aldol Reactions of the Chiral Titanium Enolate Derived from (**32**) with Aldehydes (equation 11)[24]

| *Entry* | *$R^1$* | *$R^2$* | *Syn:Anti* | *Ee (%)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Me | BOC | ≥98:2 | 97 | 53 |
| 2 | $Pr^n$ | BOC | ≥98:2 | 98 | 66 |
| 3 | $Bu^t$ | BOC | ≥96:4 | 96 | 43 |
| 4 | $H_2C{=}CH$ | BOC | ≥97:3 | 97 | 48 |
| 5 | $H_2C{=}CMe$ | BOC | 99:1 | 98 | 57 |
| 6 | Ph | BOC | ≥96:4 | 97 | 60 |
| 7 | $Bu^tO_2C$ | CHO | ≥96:4 | 87 | 66 |

The formation and aldol reactions of di(cyclopentadienyl)chlorotitanium enolates have also been studied. The aldol reaction of *N*-propionylpyrrolidine proceeds with *anti* selectivity (equation 12) by using the di(cyclopentadienyl)chlorotitanium enolate prepared from the lithium enolate and $Cp_2TiCl_2$.[25] Procter and coworkers have found that high selectivity for the *anti* isomer (**34**) requires ageing of the titanocene enolate solution in THF at room temperature, which probably facilitates some enolate equilibration process, followed by addition of the aldehyde and quenching of the aldol reaction at −78 °C. This result further illustrates the fine tuning which is possible in transition metal mediated aldol reactions, since the corresponding di(cyclopentadienyl)chloro*zirconium* enolate (**5**) gives the reverse diastereoselectivity favoring the formation of the *syn* adduct (Table 1, entries 11–14). Rationalization of these contrasting results, however, is hampered by the lack of detailed information on the enolate structures. Other methods for the formation of titanocene enolates are also available. The di(cyclopentadienyl)chlorotitanium enolates of methyl ketones, *e.g.* (**35**), can be formed regiospecifically by reaction of an acid chloride with the di(cyclopentadienyl)titanocene methylene complex (Scheme 4).[26] These titanium enolates are regiostable and undergo aldol addition exclusively at the methyl position.

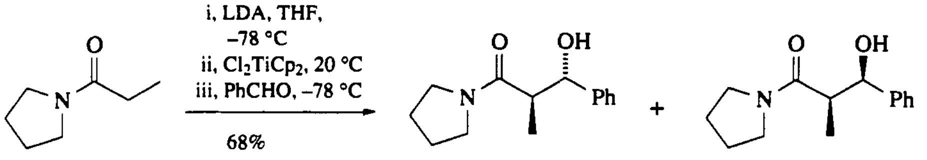

(12)

(**34**) *anti* 98%    *syn* 2%

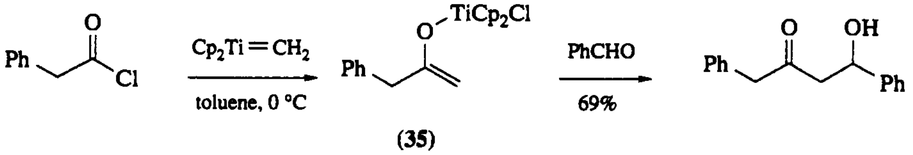

Scheme 4

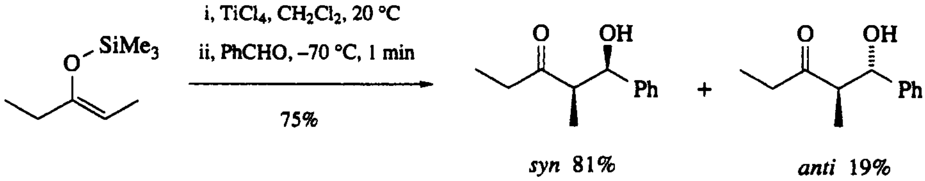

(13)

Trichlorotitanium enolates are formed in variable yield from trimethylsilyl enol ethers and an equivalent of $TiCl_4$ in dichloromethane at 20–35 °C.[27] These highly Lewis acidic preformed enolates then undergo aldol reactions at –70 °C to give moderate levels of *syn* selectivity, as in equation (13).[28] Trichlorotitanium enolates have also been used by Reetz *et al.* in their studies on diastereofacially selective aldol additions to α-alkoxy aldehydes.[15,16] Trichlorotitanium enolates are formed *in situ* in the aldol reaction of aromatic ketones and aldehydes using $TiCl_4$ and $Et_3N$.[29]

### 1.9.2.3 Rhodium

The aldol reactions of rhodium enolates have limited synthetic utility when employed stoichiometrically. *O*-Bound rhodium enolates of ketones, *e.g.* (**36**), have been prepared in high yield by reaction of preformed potassium enolates with carbonyldi(trimethylphosphine)rhodium(I) chloride or fluoride.[30] However, the basic nature of these particular enolates restricts their aldol reactions to nonenolizable aldehydes.

If rhodium enolates are used in a catalytic cycle they can promote aldol reactions under reasonably mild conditions. For example, the aldol reactions of trimethylsilyl enol ethers and ketene silyl acetals (**37**) with aldehydes can be catalyzed by various rhodium(I) complexes, under essentially neutral conditions, to give β-trimethylsiloxy ketones and esters (**38**; equation 14 and Table 6).[31,32] The study of Matsuda and coworkers[31] suggests that use of the rhodium complex $Rh_4(CO)_{12}$ (**39**; at 2 mol %) in benzene at 100 °C gives best results for the formation of adduct (**38**; Table 6, entries 1–7). There is negligible diastereoselectivity in most cases. Various cationic rhodium complexes such as (**40**) also catalyze the reaction. Reetz and Vougioukas have found that this aldol reaction proceeds well with the more reactive ketene silyl acetals, (**37**) for $R^1$ = OMe or OEt, in $CH_2Cl_2$ at room temperature (Table 6, entries 8–13).[32] The intermediacy of an $\eta^1$-*O*-bound rhodium enolate, such as (**41**), in the catalytic cycle is like-

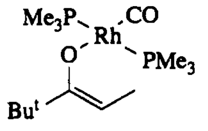

**(36)**

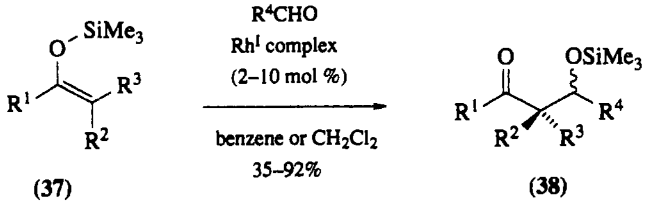

(14)

**Table 6** $Rh^I$-catalyzed Aldol Reactions of Enol Silanes with Aldehydes (equation 14)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *Catalyst* | *Temperature (°C)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | n-$C_5H_{11}$ | **(39)** | 100 | 71 | 31 |
| 2 | Me | H | H | c-$C_6H_{11}$ | **(39)** | 100 | 35 | 31 |
| 3 | Me | H | H | Ph | **(39)** | 100 | 61 | 31 |
| 4 | —$(CH_2)_4$— | | H | n-$C_5H_{11}$ | **(39)** | 100 | 71 | 31 |
| 5 | —$(CH_2)_4$— | | H | c-$C_6H_{11}$ | **(39)** | 100 | 52 | 31 |
| 6 | —$(CH_2)_4$— | | H | Ph | **(39)** | 100 | 83 | 31 |
| 7 | Et | Me | H | Ph | **(39)** | 100 | 54 | 31 |
| 8 | MeO | Me | Me | Ph | **(40)** | 22 | 75 | 32 |
| 9 | MeO | Me | Me | n-$C_6H_{13}$ | **(40)** | 22 | 71 | 32 |
| 10 | EtO | $OSiMe_3$ | OEt | Ph | **(40)** | 22 | 92 | 32 |
| 11 | EtO | $OSiMe_3$ | OEt | $Pr^n$ | **(40)** | 22 | 91 | 32 |
| 12 | EtO | $OSiMe_3$ | OEt | n-$C_6H_{13}$ | **(40)** | 22 | 82 | 32 |
| 13 | EtO | $OSiMe_3$ | OEt | $CH_2{=}CH(CH_2)_8$ | **(40)** | 22 | 74 | 32 |
| 14 | Et | Ph | H | H | **(40)** | 22 | 35 | 32 |

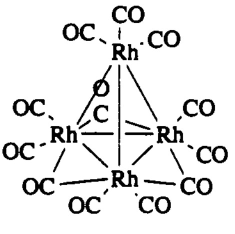

**(39)**

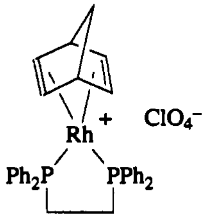

**(40)**

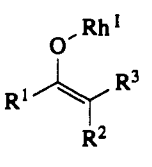

**(41)**

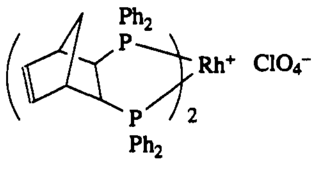

**(42)**

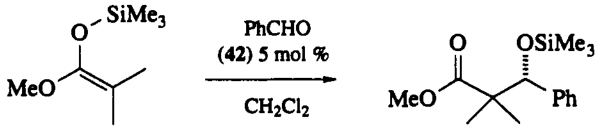

**(43)** 12% *ee*

(15)

ly in these reactions. Support for this comes from the related work of Slough, Bergman and Heathcock, who have also developed a rhodium-catalyzed aldol reaction with benzaldehyde involving silyl enol ethers and ketene silyl acetals.[30]

Preliminary examples of catalytic enantioselective aldol additions using rhodium complexes with chiral phosphine ligands attached, *e.g.* **(42)**, have been disclosed by Reetz and Vougioukas (equation 15);[32] although the low level of asymmetric induction so far obtained in the silylated aldol adduct **(43)** requires substantial enhancement before this reaction has any synthetic value. However, there is ample scope for future improvement by the use of more effective chiral diphosphine–rhodium complexes.

### 1.9.2.4 Cerium

The use of lanthanide metal enolates in the aldol reaction has, to date, only been developed to a synthetically useful level in the case of cerium (Scheme 5 and Table 7). Stereoselectivities are no better than those of lithium enolates, but the cerium enolates of ketones work well in crossed aldol additions to ketones (Table 7, entries 1–7) and sterically hindered aldehydes (Table 7, entries 9 and 10). Such crossed aldol reactions do not often work well with lithium enolates as enolate equilibration, retroaldolization and steric retardation of addition occur. Imamoto *et al.* have shown that cerium enolates **(44)**, formed from anhydrous $CeCl_3$ (1.2 equiv.) and the preformed lithium enolates of ketones in THF at –78 °C, undergo such aldol reactions to give the corresponding β-hydroxy ketones **(46)**, usually in high yield.[33] The cerium suppresses the retroaldol reaction by efficient chelation of the aldolate **(45)**. A similar effect is known for zinc halide mediated aldol reactions (Volume 2, Chapter 1.8).[34] The stereoselectivity of the

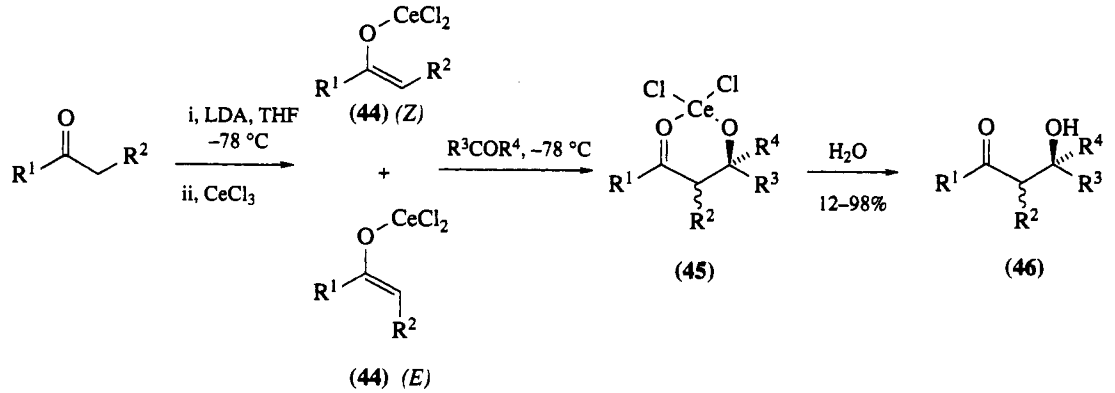

Scheme 5

Table 7 Aldol Reactions of Ketone Cerium Enolates with Aldehydes and Ketones (Scheme 5)[33]

| *Entry* | *R¹* | *R²* | *R³* | *R⁴* | *Diastereoselectivity* | *Yield (%)* |
|---|---|---|---|---|---|---|
| 1 | Ph | Me | —(CH2)5— | | | 79 |
| 2 | Ph | Me | —(CH2)4— | | | 45 |
| 3 | Ph | Me | Me | Et | 40:60 | 62 |
| 4 | Mesityl | Me | —(CH2)5— | | | 56 |
| 5 | Mesityl | Me | —(CH2)4— | | | 12 |
| 6 | Ph | H | $p$-ClC$_6$H$_4$ | Me | | 60 |
| 7 | Ph | Br | —(CH2)5— | | | 75 |
| 8 | Ph | Me | Ph | H | 18:82 | 98 |
| 9 | Ph | Me | Mesityl | H | 20:80 | 93 |
| 10 | Mesityl | Me | Mesityl | H | 7:93 | 91 |
| 11 | Mesityl | Me | Ph | H | 9:91 | 94 |
| 12 | —(CH2)4— | | Ph | H | 50:50 | 95 |
| 13 | Ph | Br | Ph | H | | 74 |

cerium enolate addition parallels that of the lithium enolate and, therefore, can be rationalized by the conventional chair-like transition state.

Cerium enolates may also be generated reductively in THF from α-iodo or α-bromo esters in the presence of an aldehyde or ketone using cerium metal turnings and catalytic HgCl$_2$ (or cerium amalgam).[35] This leads to a Reformatsky-type reaction (Volume 2, Chapter 1.7) producing the β-hydroxy ester (**47**) as a mixture of diastereomers (equation 16).

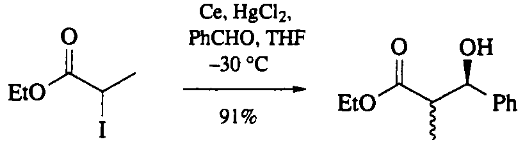

(16)

(**47**) *syn* : *anti* 50 : 50

## 1.9.3 ALDOL REACTIONS OF η¹-*C*-BOUND METAL ENOLATES AND η³-METAL ENOLATES

### 1.9.3.1 Tungsten, Molybdenum and Rhenium

The enolates (**48**) and (**49**) of the transition metals tungsten, rhenium and molybdenum can be successfully prepared by the nucleophilic displacement of α-chloro ketones and α-chloro esters with the appropriate transition metal anion (Scheme 6). They are isolated as *C*-bound enolate derivatives and, except for the rhenium enolate (**49**), do not undergo thermal aldol additions to benzaldehyde. However, Bergman and Heathcock *et al.* have found that an aldol reaction of complex (**48**) with benzaldehyde can occur on irradiation *via* the rearranged η³-oxaallyl derivative (**50**), where the metal aldolate (**51**) can then be

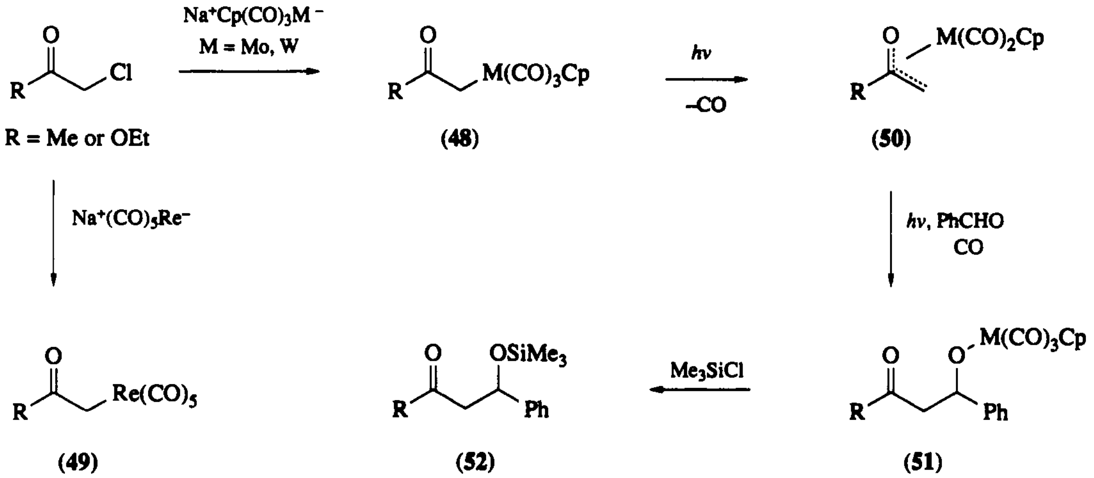

**Scheme 6**

converted *in situ* into the β-trimethylsiloxy ketone or ester (**52**).[36] These reactions have no real synthetic value at present; however, if it is possible to establish viable catalytic cycles in such photochemical transition metal enolate aldol reactions, then catalytic enantioselective aldol reactions might become accessible by using chiral phosphine ligands on the metal.[37] Some success has already been reported in this area using rhodium enolates (Section 1.9.2.3).

**Table 8** *Syn*:*Anti* Selectivity in the $BF_3{\cdot}OEt_2$-catalyzed Aldol Reactions of α-Mercurio Ketones with Aldehydes (equation 17)[38]

| *Entry* | *Substrate* | $R^3$ | *Solvent* | *Temperature (°C)* | *Time* | *Syn*:*Anti* | *Yield (%)* |
|---|---|---|---|---|---|---|---|
| 1 | 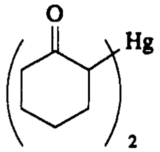 | Ph | THF | r.t.[a] | 2 h | 80:20 | 85 |
| 2 | 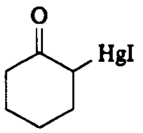 | Ph | THF | r.t. | 7 h | 90:10 | 60 |
| 3 | | Ph | $CH_2Cl_2$ | 0 | 2 min | >98:2 | 35 |
| 4 | 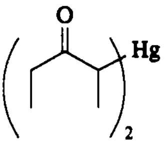 | Ph | THF | r.t. | 10 min | 74:26 | 82 |
| 5 | | Ph | THF | r.t. | 13 h | 74:26 | 85 |
| 6 | | Ph | $CH_2Cl_2$ | 0 | 1 min | 96:4 | 56 |
| 7 | | Ph | $CH_2Cl_2$ | 0 | 2 h | 89:11 | 87 |
| 8 | | $Bu^n$ | THF | r.t. | 2 h | 72:28 | 75 |
| 9 | | $Bu^n$ | $CH_2Cl_2$ | 0 | 2 min | 73:27 | 70 |
| 10 | 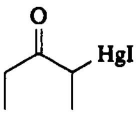 | Ph | THF | r.t. | 2 h | 90:10 | 40 |

[a] r.t. = room temperature.

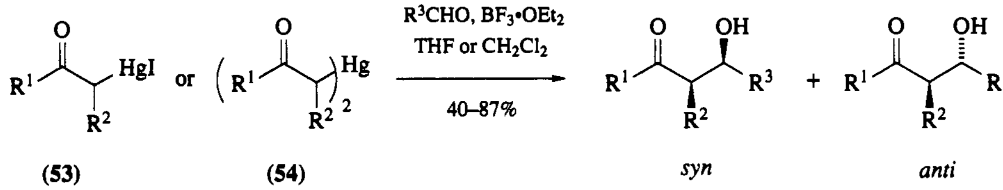

**(53)** **(54)**

(17)

*syn*:*anti* 72:28 to > 98:2

### 1.9.3.2 Mercury

The aldol reactions of *C*-bound mercury enolates (**53** or **54**; *i.e.* α-mercurio ketones) with aldehydes take place with *syn* selectivity in CH$_2$Cl$_2$ or THF under Lewis acid catalysis (equation 17 and Table 8).[38] The level of diastereoselectivity compares well with that obtained for zirconium and titanium enolates, but their preparation is more involved and so they are unlikely to be as useful in synthesis. Yamamoto and Maruyama have found that an equivalent of the Lewis acid BF$_3$·OEt$_2$ is required to promote the reaction, although this has no apparent effect on the stereoselectivity (*i.e.* Hg → B exchange is assumed not to be operating). *Syn*:*anti* ratios are very high for short reaction times in CH$_2$Cl$_2$ (Table 8, entries 3 and 6), but some equilibration towards the thermodynamic *anti* isomer takes place on longer reaction times (Table 8, entry 7). The very high *syn* selectivity of >98% recorded for the kinetic aldol reaction between α-iodomercuriocyclohexanone and benzaldehyde (Table 8, entry 3) is comparable to that found for the corresponding titanium-mediated reaction of cyclohexanone (Table 3, entry 13). An acyclic transition state model involving an $S_E$-type reaction of the C—Hg bond has been proposed to account for this selectivity.

## 1.9.4 ALDOL REACTIONS OF METAL ENOLATES OF ACYL–TRANSITION METAL COMPLEXES

### 1.9.4.1 Cobalt

Organotransition metal acyls (**55**) are readily prepared by acylation of transition metal anions, migratory insertion in alkyl metal–carbonyl complexes or by attack of carbanions at metal-bound carbon monoxide. Their conversion into reactive lithium enolates (**56**) by deprotonation by strong base (LDA or Bu$^n$Li in THF) has been demonstrated for various cobalt– and iron–acyl complexes (equation 18). These lithium enolates, like simple ester enolates, undergo aldol reactions with aldehydes and ketones. The important attribute of these systems is that transition metal centered chirality can be introduced to exert high levels of diastereofacial selectivity in aldehyde or ketone attack on the enolate. The transition metal group can then function as a removable chiral auxiliary giving rise to chiral enolate equivalents. For example, Bergman and coworkers have shown that the optically pure lithium enolate (**58**), derived from the resolved acyl–cobalt complex (**57**), undergoes an aldol addition with pivaldehyde to give the *anti* adduct (**59**) as a single isomer (Scheme 7).[39] The very high stereoselectivity in this reaction is explained by the large steric bias for electrophilic attack on the face of the metallocyclopentanone enolate (**58**) opposite the bulky phosphine ligand and the operation of a chair-like aldol transition state, *viz.* (*E*)-enolate → *anti* aldol. The chiral auxiliary may then be removed oxidatively by FeCl$_3$ treatment to give the cyclobutanone (**60**) in enantiomerically pure form. Other less sterically demanding aldehydes give more modest *anti*:*syn* ratios using the simpler system (**61**; equation 19). However, conversion of the lithium enolate into a different metal enolate derivative might enhance this selectivity further.

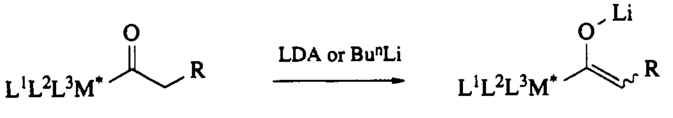

**(55)** **(56)**

(18)

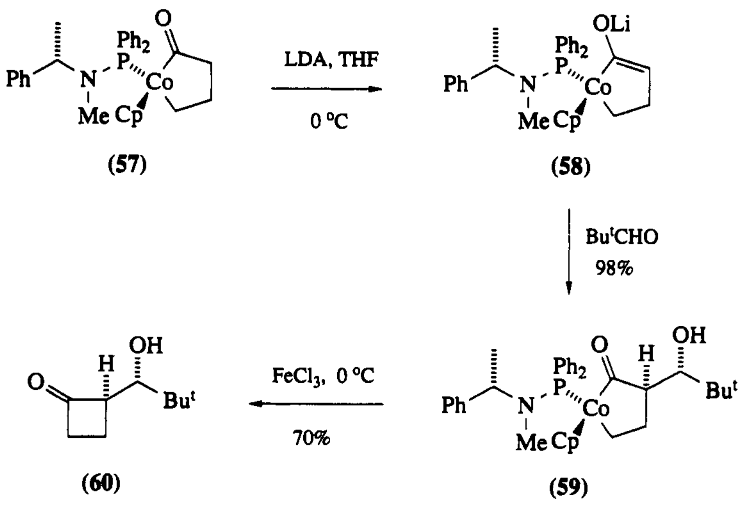

Scheme 7

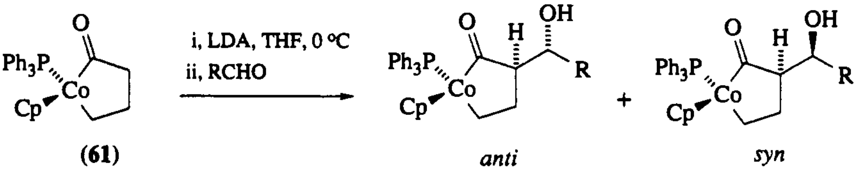

(19)

R = Bu$^t$ *anti:syn* 100:0

R = Me *anti:syn* 78:12

R = Pr$^i$ *anti:syn* 75:25

### 1.9.4.2 Iron

Related aldol chemistry has been developed independently by the groups of Liebeskind and Davies based on acyclic chiral acyl–iron complexes,[40–46] which can be prepared in optically pure form. In the case of the acetyl system (**62**), the derived lithium enolate shows negligible diastereofacial selectivity in additions to aldehydes (equation 20 and Table 9, entry 1).[40–42] However, >97% diastereofacial selectivity is possible *via* the diethylaluminum enolate under carefully controlled conditions, *i.e.* when 2 equiv. of Bu$^n$Li are first used to generate the lithium enolate and an excess of $Et_2AlCl$ (5 equiv.) is then added before addition of the aldehyde at ≤–95 °C (Table 9, entries 6–12).[42,43] Small changes in stoichiometry in this reaction lead to much poorer selectivity for isomer (**63**),[43] such that the $Et_2AlCl$ may also be functioning as a Lewis acid for the aldehyde. Oxidative removal of the iron group then gives the β-hydroxy ester in high *ee*, if enantiomerically pure iron complex (**62**) is used. Note, however, that the results in Table 9 were obtained for the racemic complex (**62**). In principle, this method provides a highly selective chiral acetate enolate equivalent for aldol additions. The enolate face selectivity can also be reversed to produce adduct (**64**) as the major diastereomer if the corresponding tin(II) enolate is used (Table 9, entry 2).[41,43] Moreover, Ojima and Kwon[47] have subsequently shown that high aldol stereoselectivities (98:2 for benzaldehyde) can easily be obtained using the lithium enolate itself if one of the phenyl groups is replaced by a pentafluorophenyl group, as in the iron–acyl complex (**65**). The sense of the stereoselectivity

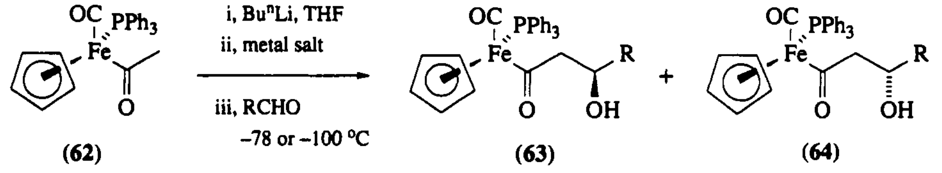

(20)

is now unaffected by variation of the metal counterion. This high π-face selection has been interpreted by the preferred formation and reaction of the enolate *via* conformation (**66**), which is favored by a stabilizing electrostatic interaction between the enolate oxygen and the electron-deficient pentafluorophenyl group.[47]

**Table 9** Diastereofacial Selectivity in the Aldol Reactions of Chiral Acetyliron Enolates (equation 20)

| *Entry* | *Metal salt* | *R* | *Temperature (°C)* | *Stereoselectivity* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | None | $Pr^i$ | −78 | 58:42 | — | 42 |
| 2 | $SnCl_2$ | $Pr^i$ | −78 | 8:92 | 74 | 41, 43 |
| 3 | CuCN | Et | −100 | 45:55 | — | 42 |
| 4 | $(Pr^iO)_3TiCl$ | Et | −100 | 87:13 | — | 42 |
| 5 | $Bu^i_2AlCl$ | $Pr^i$ | −78 | 89:11 | 76 | 41, 43 |
| 6 | $Et_2AlCl$ | $Pr^i$ | −100 | >99:1 | 86–90 | 42 |
| 7 | $Et_2AlCl$ | $Pr^i$ | −95 | 97:3 | 85 | 43 |
| 8 | $Et_2AlCl$ | Me | −100 | 96:4 | 86–90 | 42 |
| 9 | $Et_2AlCl$ | Et | −100 | >99:1 | 86–90 | 42 |
| 10 | $Et_2AlCl$ | $PhCH_2$ | −100 | >95:5 | 86–90 | 42 |
| 11 | $Et_2AlCl$ | $Bu^t$ | −100 | >99:1 | 86–90 | 42 |
| 12 | $Et_2AlCl$ | Ph | −100 | >95:5 | 86–90 | 42 |

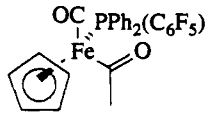

(**65**)

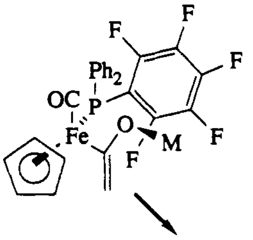

(**66**)

The corresponding chiral propionate enolate from (**67**) can be used to produce *anti* adducts (**68**) with high selectivity by this aluminum-mediated aldol reaction (equation 21 and Table 10, entries 1–4).[44] Again, carefully controlled experimental conditions are probably required for optimum selectivity. Using optically active reagents, this reaction has been applied by Davies and coworkers to the enantiocontrolled synthesis of (**72**), a degradation product of the marine norterpene sigmosceptrellin.[45] If the lithium enolate is converted instead into the copper(I) enolate by reaction with copper cyanide in THF at −40 °C, the major product in the aldol reaction with aldehydes is the *syn* isomer (**69**; Table 10, entries 5–9).[44] When this copper(I) enolate is reacted with symmetrical cyclic ketones, the aldol adduct (**73**) is obtained with high stereoselectivity (≥95:5).[46] A working model for this selectivity is suggested by consideration of structure (**74**) as the reacting conformation of the enolate. The important feature of these reactions is that the enolate reacts with the aldehyde, *via* a chair or boat transition state, on its π-face opposite the sterically demanding $PPh_3$ group.

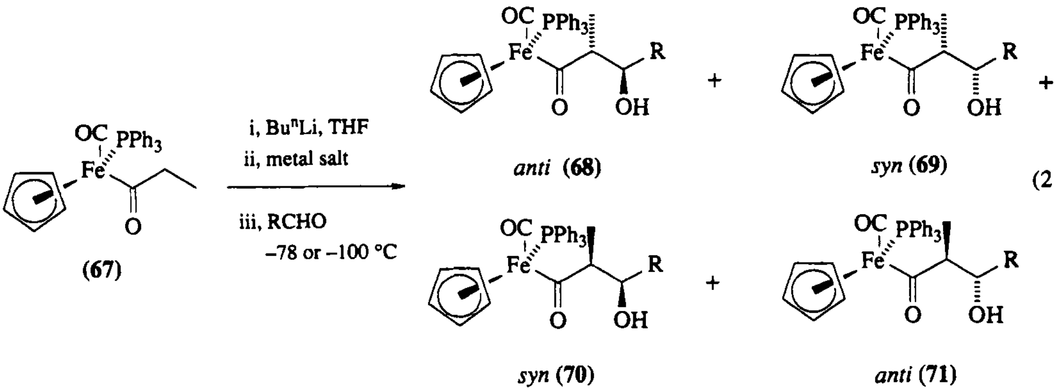

(21)

**Table 10** Stereoselectivity in the Aldol Reactions of Chiral Propionyliron Enolates (equation 21)[44]

| *Entry* | *Metal salt* | *R* | *Temperature (°C)* | *Anti* (**68**) | *Syn* (**69**) | *Syn* (**70**) | *Anti* (**71**) |
|---|---|---|---|---|---|---|---|
| 1 | $Et_2AlCl$ | Me | −100 | 91 | 0 | 6 | 3 |
| 2 | $Et_2AlCl$ | Et | −100 | 88 | 0 | 12 | 0 |
| 3 | $Et_2AlCl$ | $Pr^i$ | −100 | 90 | 0 | 9 | <1 |
| 4 | $Et_2AlCl$ | $Bu^t$ | −100 | 100 | 0 | 0 | 0 |
| 5 | CuCN | Me | −78 | 12 | 87 | <1 | 0 |
| 6 | CuCN | Et | −78 | 9 | 90 | <1 | 0 |
| 7 | CuCN | $Pr^i$ | −78 | 6 | 93 | <1 | 0 |
| 8 | CuCN | $Bu^t$ | −78 | 4 | 96 | 0 | 0 |
| 9 | CuCN | Ph | −78 | 4 | 95 | <1 | 0 |

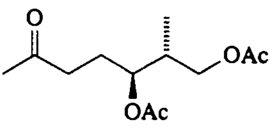

**(72)**

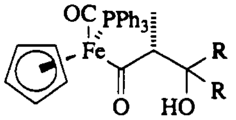

**(73)**

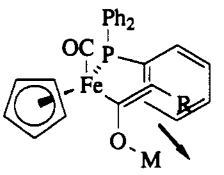

**(74)**

## 1.9.5 OTHER ASYMMETRIC ALDOL REACTIONS INVOLVING TRANSITION METALS

A significant advance in the development of catalytic enantioselective aldol reactions has been made by the use of rationally designed chiral ferrocenylphosphine ligands like (**75**) and (**76**) in the presence of the cationic gold(I) complex (**77**).[48,49] Ito *et al.* have found that the gold-catalyzed aldol reaction of methyl isocyanoacetate with aldehydes, using 1 mol % of ligands (**75**) or (**76**) in $CH_2Cl_2$ at 25 °C, leads to *trans* oxazolines (**78**) in up to 96% *ee* with high diastereoselectivity (equation 22 and Table 11). Acid hydrolysis of the oxazoline aldol product gives *syn*-α-amino-β-hydroxycarboxylic acids like L-threonine (Table 11, entry 2 and equation 23).[49] Overall, this reaction then corresponds to the enantioselective aldol reaction of a glycine enolate equivalent and gives comparable selectivity to that obtained using chiral titanium enolates (Section 1.9.2.2). The impressive selectivity in this aldol reaction has been interpreted by coordination of the ammonium enolate of the isocyanoacetate and aldehyde to the gold in the preferred transition state (**79**). Other metals, as well as other chiral phosphine ligands, are found to give

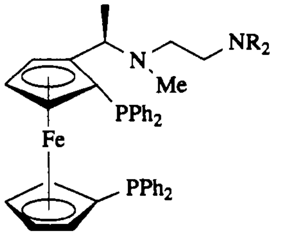

(**75**) $NR_2 = NEt_2$ (**76**) $NR_2$ = 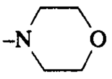

$[Au(c\text{-}C_6H_{11}NC)_2]^+ BF_4^-$

**(77)**

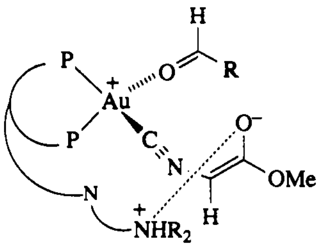

**(79)**

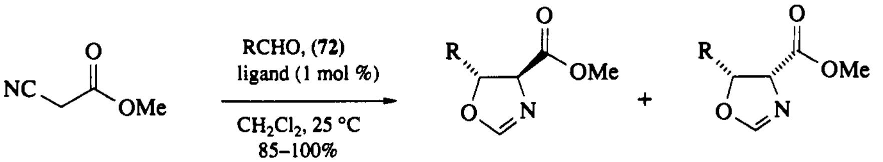

(22)

*trans* (**78**) *cis*

72–97% *ee*

*trans:cis* 84:16 to 100:0

**Table 11** Enantioselectivity and Diastereoselectivity in the Aldol Reactions of Methyl Isocyanoacetate Under Catalysis by Chiral Ferrocenylphosphine–Gold Complexes (equation 22)

| *Entry* | *Phosphine* | *R* | *Trans:Cis* | *Ee/trans (%)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | (**75**) | Me | 84:16 | 72 | 100 | 48 |
| 2 | (**76**) | Me | 89:11 | 89 | 99 | 49 |
| 3 | (**75**) | $Pr^i$ | 98:2 | 90 | 99 | 48, 49 |
| 4 | (**76**) | $Pr^i$ | 99:1 | 92 | 100 | 48 |
| 5 | (**76**) | (*E*)-$Pr^nCH{=}CH_2$ | 87:13 | 92 | 85 | 48 |
| 6 | (**75**) | Ph | 89:11 | 93 | 98 | 48 |
| 7 | (**76**) | Ph | 95:5 | 95 | 93 | 48 |
| 8 | (**75**) | c-$C_6H_{13}$ | 97:3 | 95 | 90 | 48 |
| 9 | (**75**) | $Bu^i$ | 100:0 | 97 | 100 | 48 |

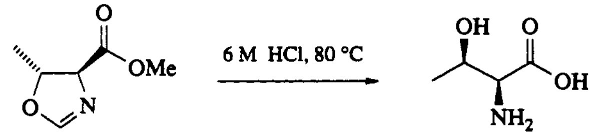

(23)

much lower selectivity. The nature of the terminal amine, as well as the length of the connecting chain to the ferrocene nucleus, is also critical.

Future significant developments in the catalytic enantioselective and diastereoselective aldol reactions of a wide range of carbonyl compounds are anticipated by the design of other new and efficient chiral transition metal reagents.

## 1.9.6 ADDENDUM

A highly effective method for the direct generation of trichlorotitanium enolates from acyclic ketones has been developed by the Evans group,[50] which relies on precomplexing with $TiCl_4$ followed by enolization with diisopropylethylamine at -10 °C in dichloromethane. The (*Z*)-enolates produced in this way then undergo a *syn* selective aldol reaction on addition of aldehydes (*c.f.* Scheme 3). The stereochemical control is comparable to that using boron enolates, which indicates that this simple titanium-mediated aldol reaction will have wide utility. Furthermore, high levels of diastereofacial selectivity can be obtained using α-chiral ethyl ketones.

The titanium carbohydrate complex (**30**) has been used to transmetallate the (*E*) lithium enolate of 2,6-dimethylphenyl propionate to aldol addition to aldehydes.[51] This provides access to either *syn* aldols in 91-97 % *ee* (reaction at -78 °C throughout) or *anti* aldols in 94–98% *ee* (warming the enolate to -30 °C) with good diasteroselectivity in many cases. This highly unusual situation, that is that the kinetically generated (*E*)-enolate → *syn* adduct and the isomerized (*Z*)-enolate → *anti* adduct, has been rationalized by Duthaler and coworkers by invoking boat transition states for both reactions. Together with the earlier aldol reactions described using D-glucose-derived titanium enolates (equations 10 and 11), these additions all lead to attack at the *re*-face of the aldehyde. This method is clearly useful for enantioselective ester–aldehyde aldol reactions in many situations. Moreover, it suggests that boat transition states may be more important in titanium aldol reactions than previously recognized.

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# 1.10

# The Henry (Nitroaldol) Reaction

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## 1.10.1 INTRODUCTION

The utilization of carbanions stabilized by various electron-withdrawing groups to effect carbon–carbon bond formation occupies a central position in organic synthesis. This chapter focuses on the reactions of nitro-stabilized carbanions (nitronate anions or their equivalents) with aldehydes and ketones. This route for the coupling of a carbonyl and a nitroalkane component, leading to vicinal nitro alcohols, was discovered in 1895 by Henry[1] and is currently known as the Henry or nitroaldol reaction.

At the end of the 19th century, nitroalkanes were the center of very important achievements made by organic chemists. During 1872, Victor Meyer[2] produced the first mononitroalkane and a few months later Kolbe[3] prepared nitromethane from sodium nitrite and chloroacetate. It was 23 years later that Louis Henry discovered his reaction, and within the next year J. U. Nef prepared the first nitronic ester and discovered the conversion of nitro group to carbonyl group,[4] one of the most important transformations of nitroalkanes, which now bears his name. Since the original work of Henry, shortly before the turn of the century, the nitroaldol reaction has been depicted as a classical chain-lengthening reaction and, in common with a number of other classical reactions, there is a vast literature. The vigorous development of organic chemistry over the past decades reveals an ever-increasing interest in the utilization of nitroalkanes in synthesis; the Henry reaction and some of its recent improvements have found numerous applications in assembling carbon atoms and functional groups to build natural product structures with high chemo- and regio-selectivity.

There are several important general reviews on the utility of nitro aliphatic compounds and the Henry reaction in organic synthesis.[5–19] Several of these are quite recent reviews and give further evidence for renewed interest in this area of chemistry.

## 1.10.2 GENERAL CONSIDERATIONS ON THE NITROALDOL REACTION AND ITS UTILITY IN ORGANIC SYNTHESIS

The Henry reaction (nitroaldol addition) is one of the classical C—C bond-forming processes by which diastereomeric mixtures of 2-nitro alcohols are formed on treatment of primary and secondary nitroalkanes and carbonyl derivatives (more frequently aldehydes) with a base. It is clear that the Henry reaction (Scheme 1) is an aldol-type reaction and the deprotonation of primary and secondary nitroalkanes with a whole range of different bases for generating the corresponding nitronate monoanions constitutes the first step of the sequence. The nitro group is particularly effective in stabilizing a negative charge on the adjacent carbon. Nitroalkanes (**1**) have p$K_a$ values of approximately 9–10; the corresponding nitronic acids (**2**), or *aci*-nitro compounds, resemble carboxylic acids in their acid strength (p$K_a$ 2–6), and thus they are readily deprotonated to give a nitronate salt. Then the nitro and *aci*-nitro forms, related by the nitro–*aci*-nitro tautomerism, share a common anion (**3**). These stabilized carbanions are ambident nucleophiles as implied in the canonical forms of (**3**). Since oxygen is the more electronegative 'end' of the delocalized system, such ions might have been expected to undergo *O*-alkylation rather than the exclusive *C*-alkylation. The fact is that these reagents are rather poor C-nucleophiles and normally they undergo predominant *O*-alkylation with electrophiles.

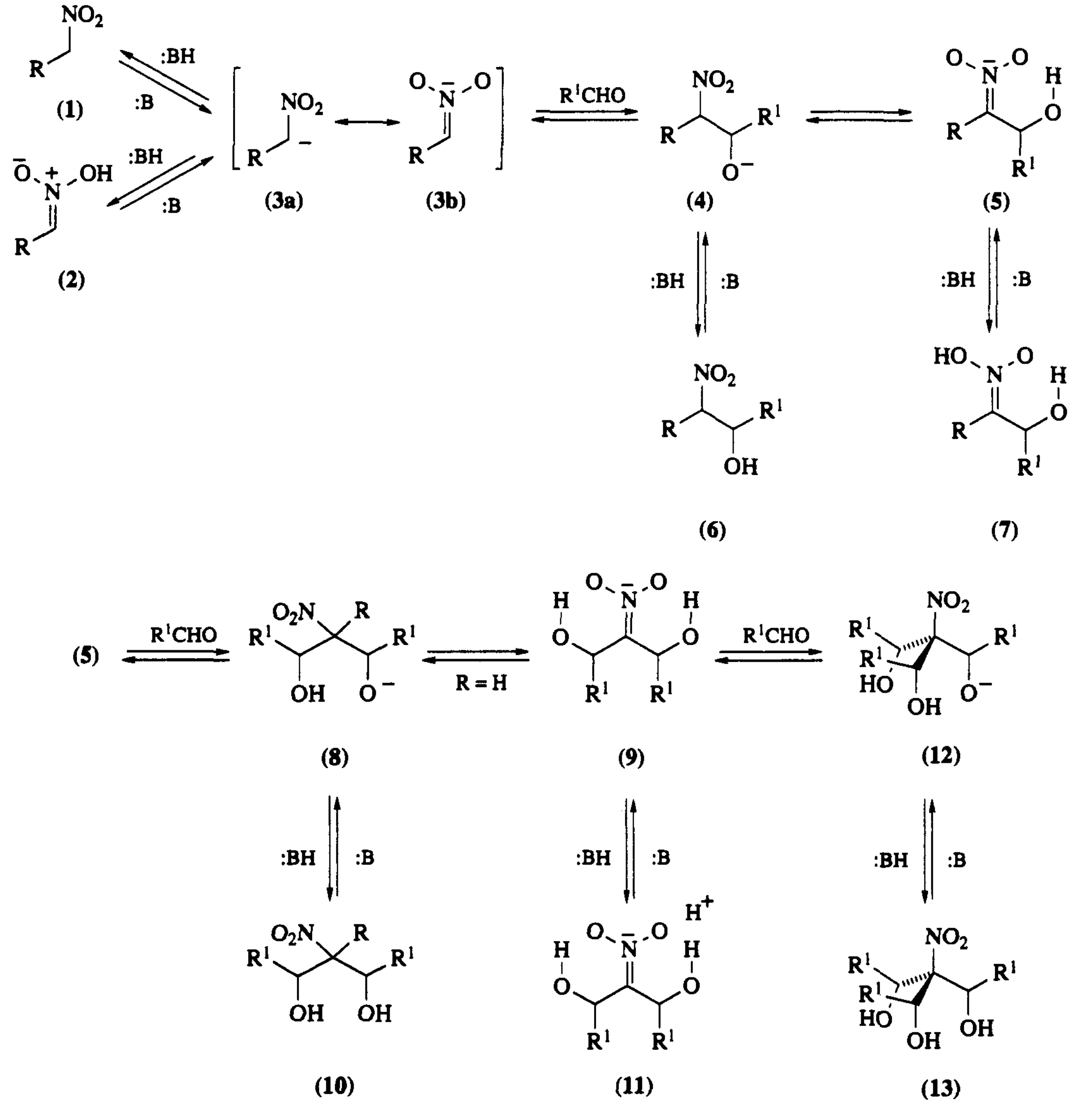

**Scheme 1**

Scheme 1 illustrates the equilibria involved in a base-catalyzed nitroaldol reaction consisting of: deprotonation of a nitroalkane to give the anion (**3**); nucleophilic attack at the carbonyl group leading to the formation of the hydroxyalkylated nitroalkane anion (**4**), as well as its corresponding α-hydroxy nitronate (**5**); and protonation of these latter systems to give a diastereomeric mixture of the 2-nitro alcohol (**6**), its α-hydroxynitronic acid (**7**) and the regenerated free base. However, in the case of primary nitroalkanes and nitromethane the product of this reaction sequence still contains an acidic hydrogen, and the process may thus be repeated giving the dihydroxyalkyl derivatives (**8**) and (**9**) of the starting nitroalkane. The second hydroxyalkylation may be more difficult than the first because the first hydroxyalkyl substituent introduced, being electron repulsive, will reduce the acidity of the adjacent hydrogen, and the corresponding carbanion will, in any case, be more sterically hindered than its parent analog. Trihydroxyalkylation is a peculiar reaction of nitromethane with aldehydes.

It is well known[20] that the tautomerization of a nitronic acid to its parent nitroalkane through a nitronate anion proceeds essentially to completion for most simple nitroalkanes because of the relatively weaker acidity of a nitroalkane compared to its corresponding nitronic acid or *aci* form. Inductive effects exhibit predictable behavior in relation to ionization constants, which affect tautomerization rates. Electron-withdrawing groups (*e.g.* halogen and nitro groups) increase the strength of nitronic acids and the tautomerization rate, while electron-releasing groups such as methyl decrease both acidity and tautomerization rate. Slow tautomerization of nitronic acids to the nitro forms has been observed when resonance-stabilized nitronate anions (*e.g.* fluorene-9-nitronic acid is very stable) are involved. These findings reveal[20] the relatively slow *C*-protonation of resonance-stabilized nitronic acids. However, it is worth noting that tautomerization may be slowed down by the hydrogen-bonded stabilization of the nitronate intermediate in spite of the enhanced acidity. This effect is of great importance in the Henry reaction where vicinal nitro alcohols are formed. This stabilizing effect increases with the number of hydrogen-bonding groups and significantly influences the equilibria of Scheme 1 involving compounds (**6**), (**7**), (**10**), (**11**) and (**13**) as products of mono-, di- and tri-hydroxyalkylation reactions. For example, 2-*aci*-nitropropane-1,3-diol (**11**; R′ = H), where two hydroxy groups are available, has been isolated in 73% yield from nitromethane and paraformaldehyde in a 1:2 ratio under fluoride ion catalysis.[21]

It will become apparent in the subsequent discussion that the success of most of the preparatively useful reactions involving the Henry reaction is attributable to the selection of appropriate reaction conditions to avoid concomitant or further transformations of the initial 2-nitro alcohol product.

By examining Scheme 1 it is possible to verify the key role of the base as catalyst for the overall process and to justify the lack of stereoselectivity which, in general, has been observed in nitroaldol additions. In fact, the reversibility of the nitroaldol process, as well as the difficulty of a stereoselective protonation of the stereogenic center of the nitronate intermediates, leads to a mixture of diastereomeric 2-nitro alcohols.

The potential utility of the Henry reaction as a chain-lengthening tool can be illustrated by the great importance of 2-nitro alcohols as pivotal synthetic intermediates in synthesis (Scheme 2). They can be converted into 2-amino alcohols by reduction of the nitro group with lithium aluminum hydride,[22] aluminum amalgam,[23] hydrogen and palladium on carbon,[24,25] hydrogen and platinum[7] or by using Raney nickel.[7,26–30] This route to such useful compounds is in addition to a number of different synthetic procedures[31,32] including, *inter alia*, reduction of α-amino ketones, ring-opening of epoxides with amines or amine precursors, oxyamination of alkenes and other methods. Vicinal amino alcohols have a broad significance in organic chemistry and their biological relevance can be seen in the structures of epinephrine (adrenalin) and related mediators of the sympathetic nervous system,[33] as well as in the chemistry and biochemistry of sphingolipids[34] and in the structures of some carbohydrate components of a group of biologically important anthracycline antibiotics. L-Daunosamine, L-ristosamine, L-acosamine and L-vancosamine are typical compounds of this family of amino sugars.[28–30,35]

2-Nitro alcohols can be oxidized to give the corresponding 2-nitro ketones. In the past, this kind of reaction has been performed with strong oxidizing agents and in strong acidic media.[36,37] However, more recently, several very mild and efficient procedures have been devised to effect this conversion. Pyridinium chlorochromate[38] in dichloromethane, and chromium reagents under phase-transfer conditions[39] were shown to be sufficiently mild and also gave good results with substrates which are acid or base sensitive. The utility of linear α-nitro ketones has been increased recently by the discovery of some direct[17] and indirect[19] procedures to effect the replacement of the nitro group by hydrogen. These reductive denitration reactions have opened up new routes to nitroalkanes. In fact, one synthetic utility of such a transformation consists in the possibility of using primary nitroalkanes as synthons for alkyl anions. Several functionalized nitroalkanes have been reported to be useful functionalized alkyl anion synthons in the synthesis of natural products *via* 2-nitro alcohol and α-nitro ketone intermediates.[17,19] In some cases it has also been possible to effect a direct reductive denitration of the 2-nitro alcohol itself to obtain the

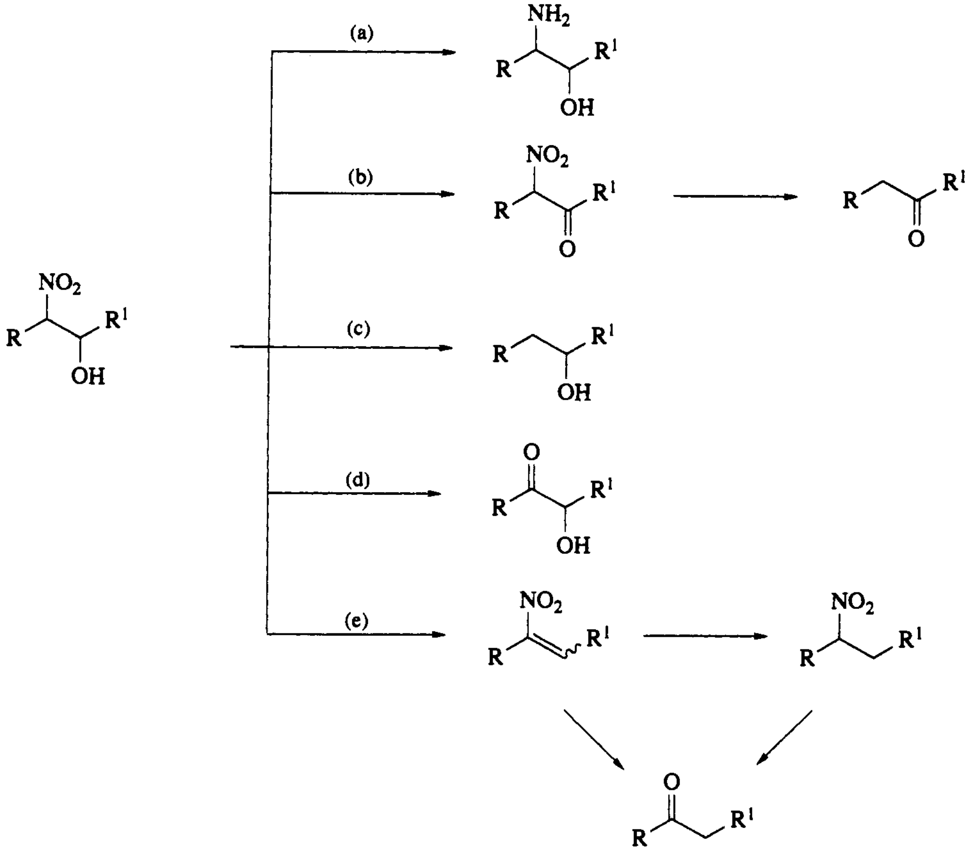

Scheme 2

corresponding alcohol.[40] However, the conversion of 2-nitro alcohols into conjugate nitroalkenes can be considered by far the most important. This reaction can be accomplished by dehydration with several reagents including dicyclohexylcarbodiimide, methanesulfonyl chloride, pivaloyl chloride and acetic or phthalic anhydride. Conjugated nitroalkenes are intermediates of a certain importance; there are a wide range of efficient methods for their transformations into other functionalities. Among them, the selective reduction to nitroalkanes[18] and the conversion of the latter into their corresponding ketones by the Nef reaction[4,19] play a very important role. This key reaction, which effectively reverses the polarity of the neighboring carbon from a potentially nucleophilic to an electrophilic one, is of great strategic importance, and can also be performed by working on the α-nitroalkene itself.[18] The wide range of new methods for carrying out the Nef reaction, together with the nitroaldol reaction, has led synthetic chemists to consider primary nitroalkanes as useful and convenient reagents for acyl anion synthons.[12,19] This double possibility for using primary nitroalkanes as versatile starting material and reagents for alkyl anion synthons (equation 1), as reported before, and for acyl anion synthons (equation 2) has significantly increased the synthetic potential of nitroalkane derivatives in the building of organic structures in a predictable way. In any case, both these possibilities stem from the central role of the Henry reaction in C—C bond formation.

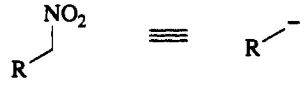

(1)

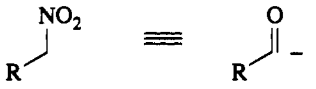

(2)

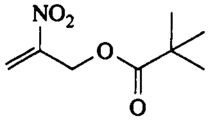

**(14)**

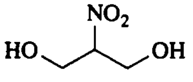

**(15)**

The vast preparative potential of nitroalkenes has been the subject of recent excellent reviews,[8,14–16,18] some of them highly focused on synthetic aspects. It is worthy of note that conjugate nitroalkenes, being good activated alkenes, are also very efficient dienophiles in Diels–Alder reactions[15] and their use, in some cases, can be considered complementary to that of other classical dienophiles in the regiochemistry of cyclization. In addition, they are very good acceptors of C-nucleophiles as well as S-, O- and N-nucleophiles[9,15] and a number of heteroatom-substituted nitro compounds have been reported,[14] in particular, the condensation reactions of conjugated nitroalkenes with enol silanes,[14,15] carboxylic acid dianions, ester enolates and monoanions derived from β-dicarbonyl compounds to give 1,4-dicarbonyl derivatives.[15]

Reactions of metal-activated nucleophiles with conjugated nitroalkenes, dialkylcuprates, Grignard reagents and alkyllithium derivatives gave unsatisfactory yields of alkylated products, owing to both the high reactivity and the basic properties of these organometallic reagents. Nevertheless, more recently it was reported that triorganoallanes ($AlR_3$, $AlR_2R'$) and the corresponding etherate complexes are very effective reagents in conjugate alkyl, aryl, alkenyl and alkynyl group transfer to α-nitroalkenes.[41,42]

Finally, it has been shown that the pivalate of 2-nitro-2-propen-1-ol (**14**; NPP),[43] a nitroalkene with an allylic leaving group, can be used as a versatile *multiple coupling reagent* by selective sequential reactions with several nucleophiles as varied as anilines, indoles, enolates and organolithium compounds. The preparation of NPP has been reported on a 50 g scale from nitromethane and formaldehyde through the nitropropanediol (**15**), deriving from two consecutive nitroaldol reactions. Due to the multitude of conversions of the nitro group, NPP[43] and its analogs[44,45] provide access to a great variety of structures without $NO_2$ and constitute very important multiple coupling reagents for convergent syntheses.

## 1.10.3 CLASSICAL NITROALDOL PROCEDURES AND THEIR LIMITATIONS

The Henry reaction is routinely performed in the presence of only catalytic quantities of a base. Several base catalysts including alkali metal hydroxides, carbonates, bicarbonates, alkoxides, calcium and barium hydroxides and magnesium and aluminum ethoxides have been used. Anion-exchange resins and, among organic bases, primary and tertiary amines and ammonium acetate and fluoride have proven to be

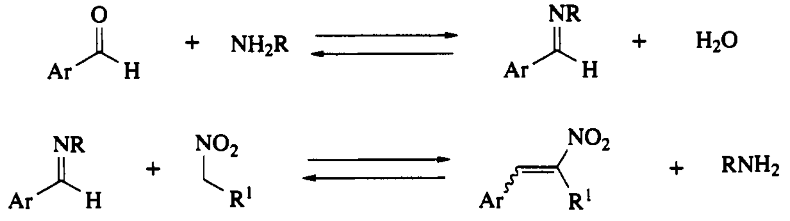

**Scheme 3**

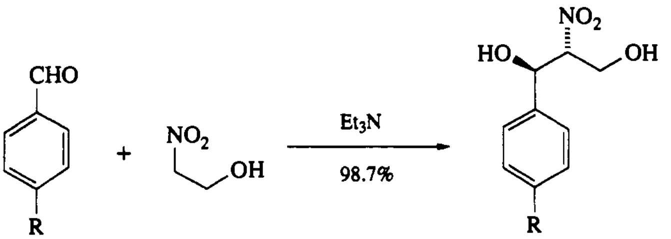

(3)

**(16)** R = H
**(17)** R = $NO_2$

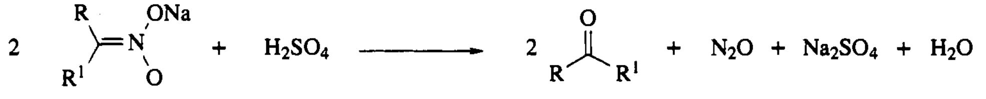

(4)

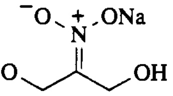

**(18)**

useful. Since basic reagents are also catalysts for the aldol condensation and for the Cannizzaro reaction when aldehydes are used as carbonyl sources, it is necessary to adopt experimental conditions to suppress these competitive reactions.[5-9] To obtain better yields of 2-nitro alcohols, it is necessary to carefully control the basicity of the reaction medium. The concentration of carbonyl component also has to be kept to a minimum for a sufficient rate of reaction avoiding aldol condensation and the Cannizzaro reaction. Furthermore, 2-nitro alcohols formed in the Henry reaction may undergo base-catalyzed elimination of water to give α-nitroalkenes which readily polymerize. This elimination is difficult to avoid when aryl aldehydes and ketones are used. The use of primary amines as base catalysts improves yields of β-nitrostyrenes, presumably *via* the formation of an imine intermediate (Scheme 3).[6,9] However, when benzaldehyde was treated with 2-nitroethanol in the presence of triethylamine as catalyst DL-*threo*-1-phenyl-2-nitropropane-1,3-diol (**16**; equation 3) was obtained in 98.7% yield with >95% *ds*; compound (**17**) is important as an intermediate in an industrial synthesis of the antibiotic chloroamphenicol.[12,46] It was found that inorganic bases, such as sodium and potassium hydroxides and sodium alkoxides could be used with some success in the preparation of 1-aryl-1-hydroxy-2-nitroalkanes if their alkali salts are acidified with acetic acid or by slow addition of mineral acids. In the presence of strong acids, a fast, acid-catalyzed dehydration occurs, giving β-nitrostyrene derivatives in high yields.

In general, it would be better to remove the base catalyst before working up the reaction mixture. This operation must be done with sufficient care to avoid, if this is not desired, the Nef reaction (equation 4) on the salt of the *aci* tautomer of the product as well as of the starting nitroalkane present at the equilibrium. Anyway, since base-catalyzed aerobic oxidation of nitroalkanes can give products formed by a free radical chain reaction, it is necessary to keep the temperature of the nitroaldol reaction at a practical minimum. Aliphatic aldehydes, and formaldehyde in particular, are more prone than ketones to undergo the Henry reaction. Nitromethane reacts more easily to give multiple addition products (**10**), (**11**) and (**13**). Primary nitroalkanes also may react with two equivalents of formaldehyde but, in general, the reaction tends to stop with only one aldehyde condensed when homologs of nitromethane and formaldehyde are used and when the ratio of reagents has been chosen with care. Secondary nitroalkanes react more sluggishly than primary ones, while tertiary nitroalkanes obviously do not react at all.

In some cases, a stoichiometric amount of the base was employed to facilitate isolation of the product by precipitation of its salt. For instance, the sodium salt of 2-*aci*-nitropropane-1,3-diol (**18**) was prepared in >95% yield of isolated product starting from nitromethane and paraformaldehyde in a 1:2 ratio by using 1.2 equiv. of sodium methoxide in methanol. The successive protonation of (**18**) was achieved in 75% yield by quick addition of salicylic acid in *t*-butyl methyl ether. These highly satisfying results in preparing 2-nitropropane-1,3-diol (**15**),[43] key intermediate for NPP synthesis, stem also from adequate control of temperatures and reaction times, dilution of the reaction mixtures and choice of solvents.

### 1.10.3.1 Nitroaldol Reactions with Dialdehydes

Reaction of nitromethane in aqueous sodium carbonate with glyoxal led to cyclization (equation 5).[7] A substance soon precipitated (72% yield), to which was assigned the structure of 1,4-dideoxy-1,4-dinitro-

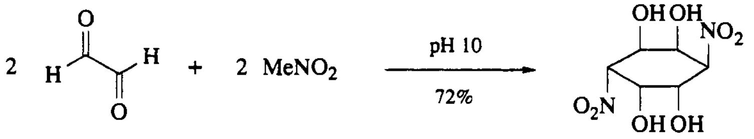

(5)

**(19)**

neo-inositol (**19**), one of the 14 theoretically possible configurations. 3-Nitrolactaldehyde (**20**) was demonstrated to be a key intermediate, probably together with (**21**), in the cyclization of glyoxal with nitromethane.

Two consecutive nitroaldol reactions were observed when nitromethane, or one of its higher homologs, was treated with 1,4-, 1,5- and 1,6-dialdehydes in the presence of catalytic or stoichiometric amounts of a base. This sequence consists of a cyclization process where a faster intramolecular nitroaldol reaction follows the first intermolecular one and the methyl group of the nitromethane is incorporated into the ring. This reaction leads to five-, six- and seven-membered rings and is equally applicable to aliphatic, aromatic and sugar dialdehydes.[7,9] Three-atom tethers offer the best results. In the case of glutaraldehyde and nitromethane, nitrodiol (**22**; equation 6) was readily obtained as a single *trans,trans* diastereomer. This compound represented a useful system for model studies of synthetic and stereochemical problems implicated in the more complex chemistry of nitro sugars. The pioneering studies of Fisher and Lichtenthaler were useful to Seebach and coworkers[45] in the preparation of enantiomerically pure derivatives of cyclic 2-nitroallylic alcohols, which are important chiral multiple coupling reagents. *trans,trans*-2-Nitrocyclohexane-1,3-diol (**23a**), 3,4,5,6-tetrahydro-4-nitro-2*H*-pyran-3,5-diol (**23b**), 4-nitrothiane-3,5-diol (**23c**) and some of their derivatives (Scheme 4) were easily prepared from methanolic solutions of the starting dialdehydes and nitromethane or nitroethane (1.5 equiv.) in the presence of cata-

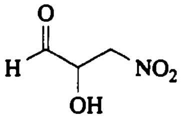

**(20)**

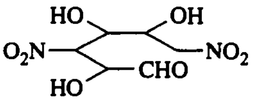
HO
OH
O2N
NO2
CHO
HO

**(21)**

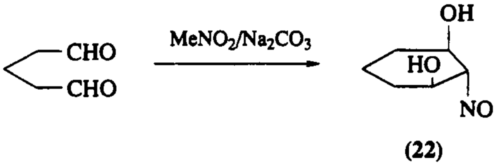
CHO
CHO
MeNO2/Na2CO3
OH
HO
NO2
(22)

(6)

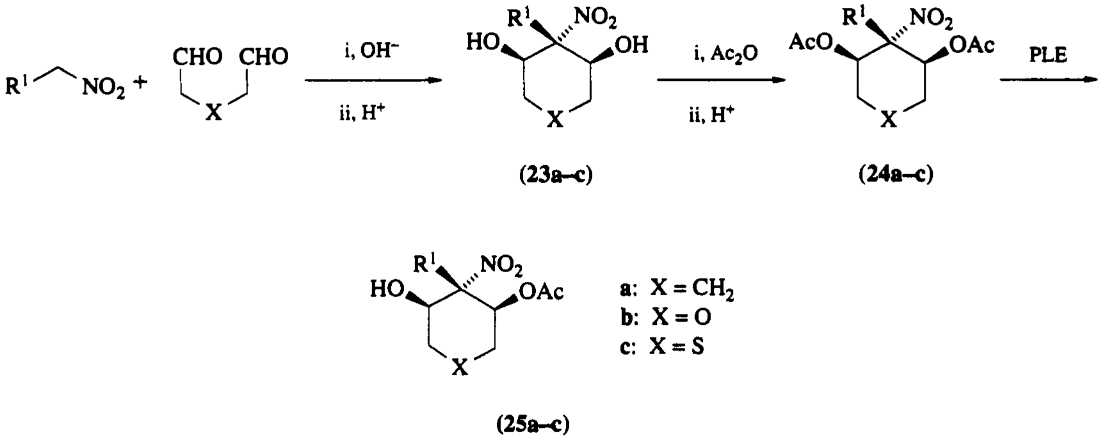
R1
NO2
+
CHO CHO
X
i, OH-
ii, H+
R1
NO2
HO
OH
X
(23a–c)
i, Ac2O
ii, H+
R1
NO2
AcO
OAc
X
(24a–c)
PLE
R1
NO2
HO
OAc
X
a: X = CH2
b: X = O
c: X = S
(25a–c)

**Scheme 4**

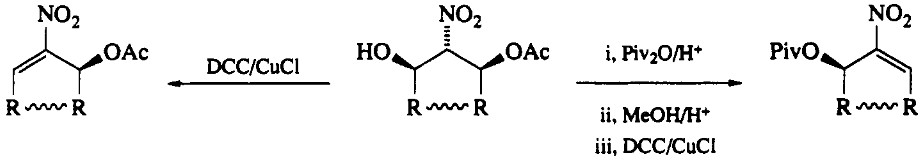
NO2
OAc
R R
DCC/CuCl
NO2
HO
OAc
R R
i, Piv2O/H+
ii, MeOH/H+
iii, DCC/CuCl
NO2
PivO
R R

**Scheme 5**

lytic amounts of 2 M NaOH and then converted into the corresponding diacetates (**24a–c**). The reproducible enantioselective saponification of the corresponding diacetates with pig liver esterase (PLE) gave monoacetates (**25a–c**) of >95% *ee*. The *pro-(R)* enantiotopic acetate group appeared to be saponified preferentially and the open chain diacetate of *meso*-2-nitropropane-1,3-diols also gave satisfying results. Enantiomerically pure derivatives of nitroallylic alcohols were obtained by elimination of water or acetic acid from the hydroxy acetates (Scheme 5). The cyclization reaction of nitromethane with aldehydic diglycol derivatives of monosaccharides formed by periodate oxidation, 'sugar dialdehydes', has been depicted as an excellent procedure to synthesize 3-amino sugars.[7,9] 'Sugar dialdehydes' (**26**) to (**34**) are the most used in cyclization reactions with nitromethane to prepare 3-amino-3-deoxy derivatives of, *inter*

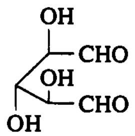

**(26)**

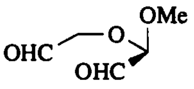

**(27)**

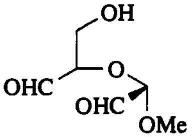

**(28)**

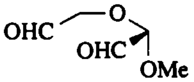

**(29)**

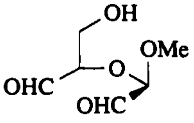

**(30)**

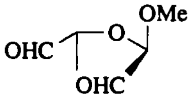

**(31)**

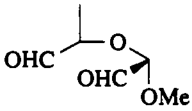

**(32)**

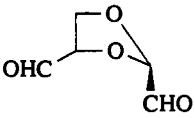

**(33)**

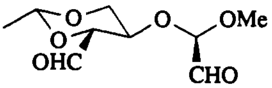

**(34)**

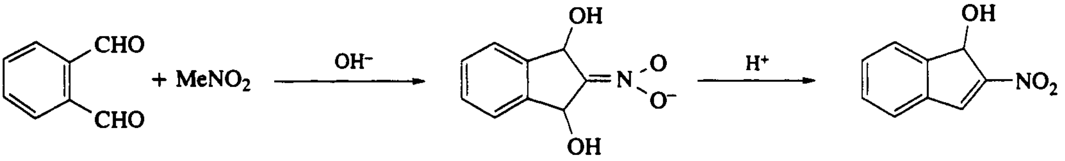

(35)

**Scheme 6**

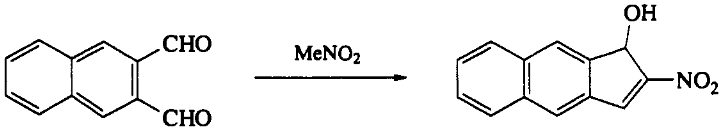

(7)

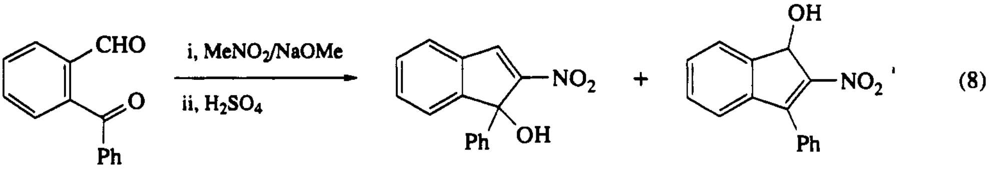

(36) (37) (8)

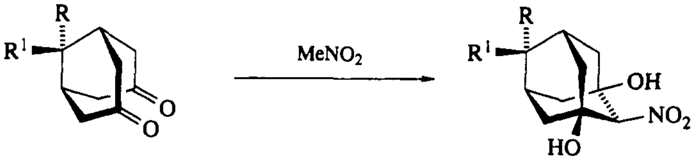

(9)

*alia*, glucose, mannose, talose, 3-amino-3,6-dideoxyglucosides of the D and L series and 3-amino derivatives of 3-deoxyheptopyranoses.

In the case of aromatic dialdehydes, the cyclization is frequently accompanied by dehydration.[7,9] Thus, *o*-phthalaldehyde cyclizes when treated with nitromethane in the presence of alcoholic potassium hydroxide (Scheme 6) to give the *aci*-nitro salt that undergoes dehydration by acidification with mineral acid to form 2-nitroinden-1-ol (**35**). This reaction was discovered in 1910 by Thiele and Weitz and can be considered the first demonstrated example of the cyclization of a dialdehyde with nitromethane. Like *o*-phthalaldehyde, naphthalene-2,3-dicarbaldehyde and *o*-benzoylbenzaldehyde[47] undergo ready cyclization with nitromethane under similar reaction conditions to form respectively, 2-nitrobenzinden-1-ol (equation 7) and two isomeric *o*-nitrohydroxyindenes (**36**) and (**37**) (equation 8) upon acidification with mineral acid. The cyclization with nitromethane also works well with suitable diketones such as bicyclo[3.3.1]nonane-3,7-diones where the carbonyl groups are favorably oriented for cyclization: on treatment with nitromethane and sodium methoxide the corresponding 2-nitroadamantane-1,3-diols (equation 9) are obtained in fair to good yields.

### 1.10.3.2 Nitroaldol Reactions with Ketones

It has been observed that 'the nitroaldol reaction becomes less and less satisfactory as more substituents are attached to the C atoms to be linked together'.[48]

The Henry reaction of ketones is sensitive to steric factors and yields of 2-nitro alcohols normally are very low except for those reactions involving nitromethane.[9–12] For instance, nitromethane reacts with cyclohexanone and its 3- and 4-methyl derivatives, with sodium ethoxide as the catalyst, to form the corresponding 1-nitromethylcyclohexan-1-ols in, respectively, 33.7% (36 h), 29% (79 h) and 42% (one week) yields after reaction times indicated in parentheses. Nevertheless, under the same reaction conditions, nitroethane and 1-nitropropane did not react when sodium ethoxide was used but, with piperidine as the catalyst, reacted with 3- and 4-methylcyclohexanone to give the corresponding 2-nitroalkylcyclohexanols in 5–13% yield after two weeks at room temperature. 2-Methylcyclohexanone, a more sterically hindered ketone, did not react at all by using these procedures. Moreover, when nitromethane and alicyclic ketones of five to eight carbons in the ring were treated in refluxing solution in the presence of piperidine or secondary aliphatic amines, oximes of azadispiro ketocyclic hydroxamic acids (**38** for cyclohexanone) were obtained as by-products.[49] However, yields were observed ranging from low to good with significant effect due to the amount and type of amine catalyst used.

More recently, the use of high pressure with tetra-*n*-butylammonium fluoride as catalyst allowed these reactions to be accomplished with cyclic ketones.[50] Thus, the Henry reaction of nitroalkanes with 3- and 4-methylcyclohexanones in THF at 30 °C and 9 kbar (1 bar = 100 kPa) afforded fair to high yields (60–90% after 4 d) of the corresponding nitro alcohols, while with 2-methylcyclohexanones it was possible to obtain addition products, although in moderate yields. These facts explain the modest utility of the Henry reaction as a chain-lengthening reaction when the carbonyl component is a ketone, but also show the difference in reactivity of aldehyde and ketone C=O groups with respect to nitromethane, primary and secondary nitroalkanes in the presence of a base as catalyst. Such a difference in reactivity can be considered as the most evident chemoselectivity of this reaction.

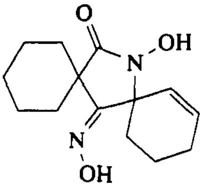

(**38**)

### 1.10.3.3 Nitroaldol Reactions by Heterogeneous Phase Methods

Recently, several improved methods have been devised to overcome many drawbacks of Henry reactions by increasing their chemo-, regio- and, in some specific cases, stereo-selectivity. The Henry reaction performed by using commercial chromatographic alumina in the absence of solvent gave[51] mixtures of diastereomeric 2-nitro alcohols in fair to high yields after 24 h of reaction at room temperature (equation 10). This heterogeneous, solvent-free method is mild and convenient. Good results could also be obtained with substrates which are acid- or base-sensitive and the method was shown to be useful in multistep syntheses of natural products.[19] A very important application of the alumina procedure concerns the total synthesis of biologically important aminodeoxy sugars *via* the nitroaldol reaction. Treatment of *O*-benzyl-D-lactaldehyde with methyl 3-nitropropionate (equation 11) in the presence of chromatographic alumina without solvent[30] led to a mixture of three nitroaldol products from which the predominant crystalline D-*ribo* isomer (**39**) was formed and easily isolated as the major component (*ribo*:*xylo*:*arabino* = 15.0:1.5:1). Stereoselectivity was much lower when the nitroaldol reaction was performed by using catalytic amounts of potassium *t*-butoxide in THF at 0 °C or with stoichiometric quantities of potassium *t*-butoxide in THF at 0 °C in the presence of various salts of divalent metals.

The preparation of 2-nitro alcohols was also achieved by reaction of equimolar amounts of nitroalkanes and aldehydes in the presence of alumina-supported potassium fluoride without solvent (equation 12).[52] A peculiar feature of this method were reactions performed with aromatic aldehydes, such as benzaldehyde and furaldehyde, which allowed preparation of the corresponding 2-nitro alcohols without dehydration of these into nitroalkenes, as observed when nitroaldol reactions were performed with organic bases in homogeneous medium or with alumina alone.

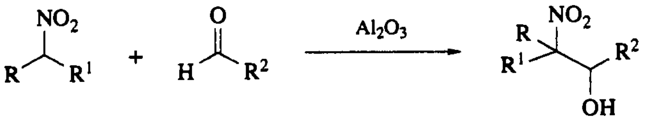

(10)

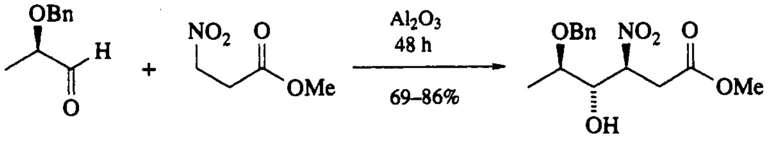

(11)

(**39**) major isomer

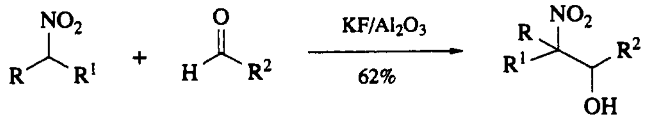

(12)

### 1.10.3.4 Regio- and Stereo-selectivity in the Nitroaldol Reaction with α,β-Unsaturated Aldehydes and Ketones

Another kind of reaction competes with the nitroaldol reaction when primary and secondary nitroalkanes, as well as α-nitroalkanones, undergo base-catalyzed reaction with α,β-unsaturated aldehydes and ketones. The reaction of these latter systems with a stabilized carbanion (nitronate anion) will be expected to give either a 1,4-addition to the conjugate system (Michael reaction) or 1,2-addition to the carbonyl group (Henry reaction). The Michael reaction is another classic C—C bond-forming reaction of primary and secondary nitroalkanes with several conjugate systems such as aldehydes, ketones, nitriles, esters, sulfones and sulfoxides. These reactions are typically run in homogeneous systems using organic bases such as tetramethylguanidine (TMG), diisopropylamine, tri-*n*-butylphosphine, triphenylphosphine, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetra-*n*-butylammonium fluoride and potassium *t*-butoxide, as well as inorganic bases such as potassium fluoride/18-crown-6, sodium hydroxide/18-crown-6 and, more recently, chromatographic alumina under solvent-free conditions.[17,19] Several applications of the conjugate addition of nitroalkanes to α,β-unsaturated compounds have concerned, *inter alia*, the synthesis of prostaglandins, monomerine I and quercus lactone, the preparation of α,β-unsaturated aldehydes, 1,4-dicarbonyl compounds and jasmonoids, 1,5-dicarbonyl derivatives, 2-substituted-2-nitrocycloalkanones and spiroacetal pheromones.[19]

Of the two types of reactions (equations 13 and 14), nitroaldol reaction and conjugate addition at the β-position, the latter is prevalent especially with β-substituted-α,β-unsaturated ketones. In the case of α,β-unsaturated aldehydes the Michael addition seems to proceed better but the selective conditions of these two reaction pathways have not been well established.

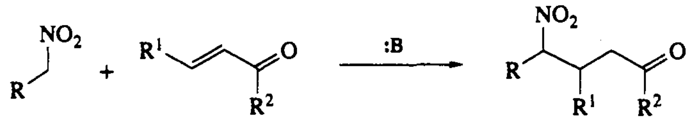

(13)

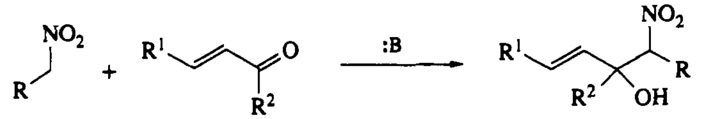

(14)

A recent paper, however, revealed a successful attempt to control the regioselectivity of the reaction to prepare racemic *erythro*-sphingosine and ceramids. Hino *et al.*[23] reported that the reaction of (*E*)-hexadec-2-enal with 2-nitroethanol in triethylamine at room temperature gave a diastereomeric mixture of 1,2-addition products (**40**) and (**41**) in 70% overall yield, while the reaction in methanol–potassium carbonate gave a mixture of compounds (**42**; 50%) and (**43**; 12%). Both these compounds are derived from a Michael adduct intermediate (Scheme 7). Previously, it was observed[53] that the reaction of hexadec-2-ynal with 2-nitroethanol (equation 15) in methanol in the presence of potassium carbonate at room temperature gave a mixture of diastereomeric nitrodiols (**44**) and (**45**) in 80% yield.

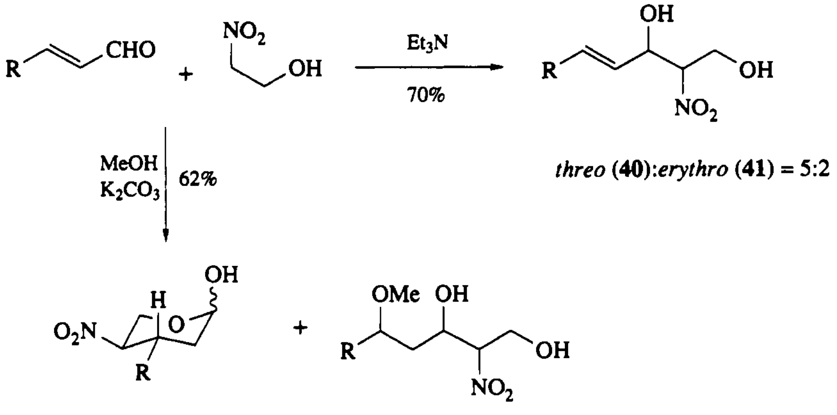

(**42**) 50% (**43**) 12%

R = $Me(CH_2)_{12}$

**Scheme 7**

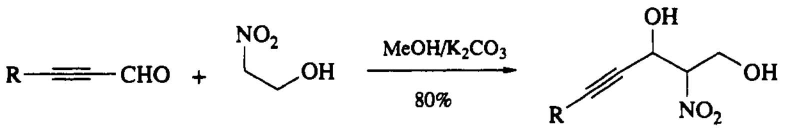

(15)

R = $Me(CH_2)_{12}$

*threo* (**44**):*erythro* (**45**) = 1:1

### 1.10.3.5 Significant Functionalized Nitroalkanes Used in Nitroaldol Reactions

Although the Henry reaction has been known for over 90 years and is considered as a classic carbon–carbon bond-forming process, its utilization has so far been limited to simple nitroalkanes and the more

**Table 1** Significant Functionalized Nitroalkanes Used in Nitroaldol Reactions

| *Nitroalkane* | | *Ref.* |
|---|---|---|
| $BrCH_2NO_2$ | | 54 |
| $CF_3CH_2NO_2$ | | 55 |
| $CHF_2CH_2NO_2$ | | 55 |
| $ArSO_2CH_2NO_2$ | | 56 |
| $PhSCH_2NO_2$ | | 57 |
| $RO(CH_2)_2NO_2$ | R = H | 23, 46, 53, 58 |
| | R = 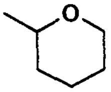 | 51, 58, 59 |
| | R = –CH(Me)OBu$^n$ | 51 |
| $MeCH(OH)(CH_2)_2NO_2$ | | 51 |
| 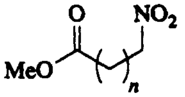 | $n = 1$<br>$n = 2$<br>$n = 6$ | 30, 60, 61<br>51<br>19 |
| $R(NO_2)CHCO_2Et$ | R = H<br>R = Me<br>R = Et<br>R = Pr$^n$<br>R = Pr$^i$<br>R = Bu$^n$ | 62<br>63<br>63<br>63<br>63<br>63 |
| 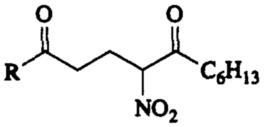 | R = Me<br>R = OMe | 63<br>63 |
| 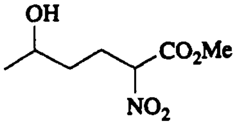 | | 63 |
| 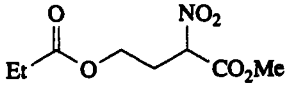 | | 63 |
| 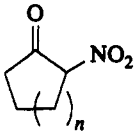 | $n = 1$<br>$n = 2$<br>$n = 3$ | 63<br>63<br>63 |
| 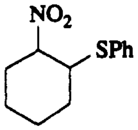 | | 64 |
| 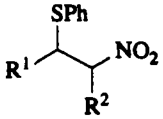 | $R^1$ $R^2$ $R^1$ $R^2$<br>H Me Et Me<br>H Et Pr$^i$ Me<br>H Bu$^n$ Me Ph<br>H n-$C_7H_{13}$ Ph H<br>Ph Me Me H | 64 |

**Table 1** *(continued)*

| *Nitroalkane* | | *Ref.* |
|---|---|---|
| 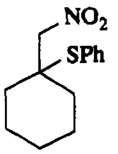 | | 64 |
| 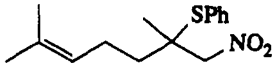 | | 64 |
| 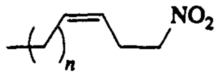 | *n* = 1<br>*n* = 4 | 19<br>19 |
| 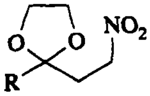 | R = H<br>R = Me | 19, 25<br>19, 51 |
| 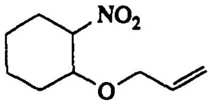 | | 65 |
| 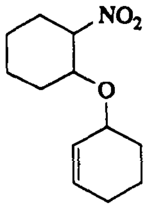 | | 65 |
| 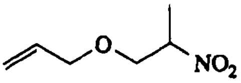 | | 65 |
| 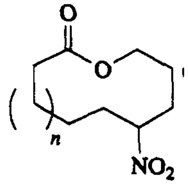 | *n* = 1<br>*n* = 7 | 66<br>66 |
| 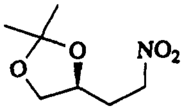 | | 28 |
| 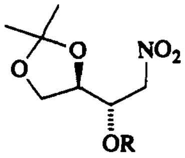 | R = H<br>R = THP | 58<br>58 |

**Table 1** *(continued)*

| *Nitroalkane* | *Ref.* |
|---|---|
| 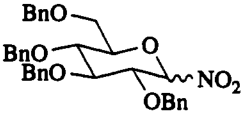 | 40, 67 |
| 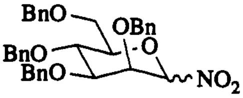 | 40 |
| 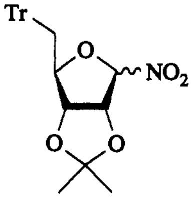 | 40 |

common carbonyl compounds. Because recent studies have developed new methodologies and disclosed the use of new catalysts to improve regio-, chemo- and stereo-selectivity of nitroaldol reactions, an ever-increasing utilization of the reaction has been observed. During the last few decades, functionalized nitroalkanes have been used more as building blocks in organic syntheses by nitroaldol reactions. Among them, the compounds in Table 1 are the most important. α-Nitroalkenes are also good substrates for nitroaldol reactions when they have at least one allylic hydrogen.[68] In fact, treatment of α,β-unsaturated nitro compounds with base results in the formation of allylic carbanions that react with aldehydes regioselectively at the position α to the nitro group (equation 16). The choice of base is important in this reaction, which is useful for preparing γ,δ-unsaturated-β-nitro alcohols. When $R^2$ is not hydrogen, the reaction is limited to formaldehyde.

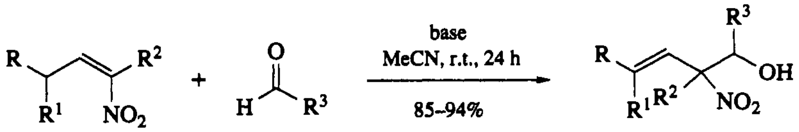

(16)

base = $NEt_3$, $NPr^{i}Et_2$, 1,4-diazabicyclo[2.2.0]octane (DABCO)

Intramolecular nitroaldol reactions of 6-nitro-1,3-dicarbonyl compounds (**46**) have been the focus of attention for their peculiar aspects. Seebach *et al.*[69,70] reported the cyclization of these (equation 17), yielding highly functionalized and substituted six-membered rings in diastereomerically pure form. Cyclization of the corresponding 5-nitro-1,3-dicarbonyl compounds (equation 18) has been performed by adding a tetrahydrofuran solution of them and diisopropylamine to hydrochloric acid/borate buffer solution. Compounds (**47**) and (**48**), certainly formed as intermediates in all these reactions as one stereoisomer, were not very stable and an easy elimination of nitrous acid from (**47**) gave (**48**), which completely rearranged to the more stable isomer (**49**).

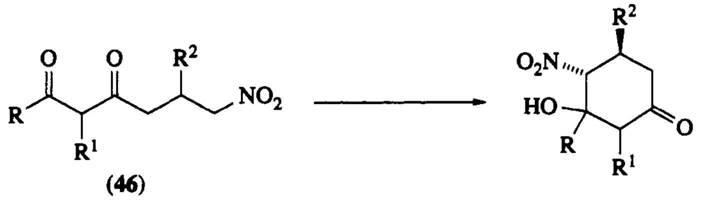

(**46**)

(17)

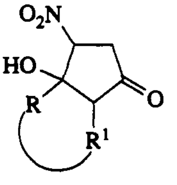

(47)

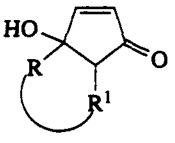

(48)

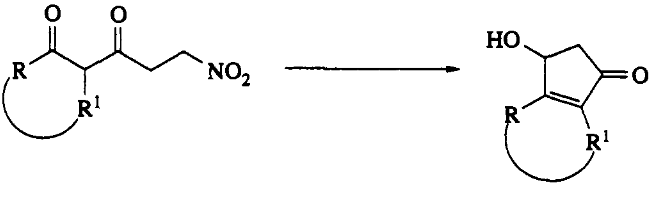

(49)

(18)

## 1.10.4 NITROALDOL REACTIONS WITH SILYL NITRONATES AND WITH α,α DOUBLY DEPROTONATED NITROALKANES

Significant improvements to the Henry reaction have been achieved by using silyl nitronates[71] and catalytic amounts of fluoride ion or, alternatively, α,α doubly deprotonated primary nitroalkanes.[48] Both of these procedures, discovered by the Seebach group, have proved to be useful for the stereoselective preparation of vicinal amino alcohols.

Trialkylsilyl nitronates can be prepared in good yields from primary nitroalkanes by consecutive treatment at −78 °C in THF with lithium diisopropylamide and trimethylsilyl or *t*-butyldimethylsilyl chloride. Again at −78 °C in THF, and in the presence of catalytic amounts of tetra-*n*-butylammonium fluoride (TBAF), the reaction between (**50**) and a wide range of aliphatic and aromatic aldehydes gave the trialkylsilyl ethers of 2-nitro alcohols in fair to excellent yields (equation 19). Highly pure *erythro* nitro ethers (**51**; >98% *ds*) are obtained in yields of about 60% from aliphatic aldehydes if the *t*-butyldimethylsilyl nitronates are used.[26] Among the most important factors to ensure reproducible diastereoselectivity are the use of tetrabutylammonium fluoride freshly dried over molecular sieves in a THF solution, careful control of the reaction temperature at low enough values and avoiding reaction mixtures being kept too long at room temperature before work-up. With aromatic aldehydes reduced diastereoselectivity (≈80% *ds*) is observed.

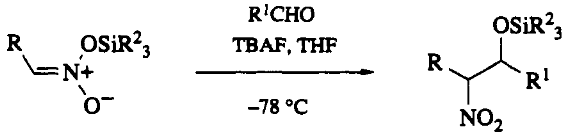

(50)

(19)

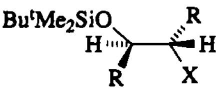

(51) $X = NO_2$
(52) $X = NH_2$

Secondary nitroalkanes are converted into the corresponding silyl nitronates in lower yields and only those with *t*-butyldimethylsilyl groups are sufficiently stable to be available for the next reaction. However, their fluoride-catalyzed *O*-silylnitroaldol addition gives only free nitro alcohols which can be subsequently silylated.

*O*-*t*-Butyldimethylsilylnitroaldols show a peculiar reactivity with respect to the corresponding free vicinal nitro alcohols and play a central role in the synthesis of *erythro*-1,2-amino alcohols (**52**). In fact, the diastereomeric enrichment of (**51**) can be preserved during reduction by Raney nickel. Thus, almost pure (*RS*,*SR*) diastereomers of *O*-protected β-amino alcohols can be prepared with retention of configurational purity. The ensuing deprotection by $LiAlH_4$ in diethyl ether or TBAF in tetrahydrofuran or aqueous HF occurs again with retention of configuration giving (*RS*,*SR*)-β-amino alcohols. On the contrary, direct reductive treatment of (**53**) with $LiAlH_4$ produces free β-amino alcohols but stereochemical integrity is lost.

Diastereomeric mixtures of vicinal nitro alcohols obtained by a classical Henry reaction with low diastereoselectivity can be easily silylated to give the corresponding mixture of *O*-*t*-butyldimethylsilyl ethers.[26] The latter undergoes an enrichment of the *erythro* isomer (**54**; up to >95:5) by treatment with LDA and successive protonation of the corresponding lithium salts (Scheme 8), which occurs with high diastereoselectivity.

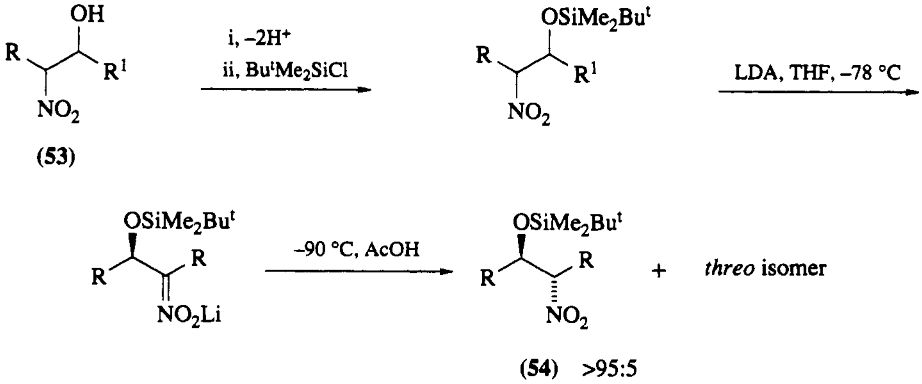

**Scheme 8**

A stereoselective Henry reaction has also been observed between bicyclic trimethylsilyl nitronates and benzaldehyde with fluoride ion as the catalyst. The reaction results in the formation in high yield of a cyclic hemiacetal (equation 20) and is highly diastereoselective (95% *ds*).[72]

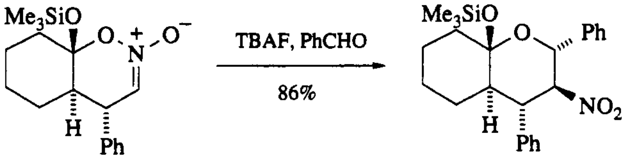

(20)

Ketones do not undergo fluoride-mediated reactions with silyl nitronates. However, enhancement of the C-nucleophilicity of nitronates has been achieved by double deprotonation at –90 °C with *n*-butyllithium in THF in the presence of at least 2 equiv. of HMPA (equation 21). Under these conditions, the residual proton of the monolithium salt, the acidity of which has been indicated to be in the same range as that of diisopropylamine, is metallated to give the dianion.

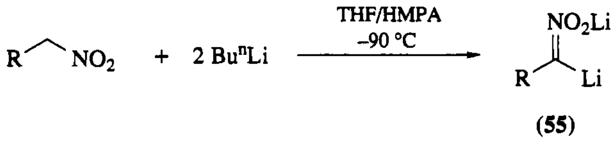

(21)

(**55**)

α,α Doubly deprotonated primary nitroalkanes show enhanced C-nucleophilicity with respect to that of the corresponding nitronate monoanions. They undergo acylation with carboxylic acid esters, anhydrides and acyl chlorides; *C*-alkylation with alkyl bromides and iodides; and hydroxyalkylation with aldehydes and ketones (Scheme 9).[48] This variant of the nitroaldol reaction proceeds in better yields than classical Henry procedures, especially in cases with steric hindrance. Benzophenone reacts with (**55**) and the stability of the dianion (**56**), greater than that of the corresponding monoanion, suppresses the reversibility of the addition process. Clean reactions and satisfactory yields depend on careful control of the temperature of these reactions at –90 °C. Under these conditions, the addition of α,α doubly deprotonated primary nitroalkanes to aromatic and aliphatic aldehydes leads to a *threo*-enriched product. The de-

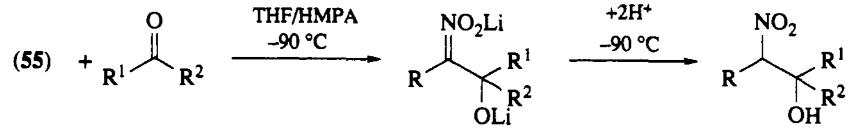

**(56)**

**Scheme 9**

gree of stereoselectivity depends strongly upon the presence of HMPA and is highest in the case of nitroaldols from aromatic aldehydes. When a diastereomeric mixture of nitroaldols is obtained by classical Henry procedures, with low or no stereoselectivity, double deprotonation under the foregoing reaction conditions gives the same dilithio derivative as that formed by addition of (**55**) to an aldehyde. Subsequent double protonation in the presence of HMPA furnishes *threo* nitro alcohols in ≈50% yields and good to high stereoselectivity (75% to 94%). This procedure also avoids the easy epimerization at the nitro-substituted C-atom. (Scheme 10).

Using the simple trick devised by Seebach *et al.*, all nitro alcohol derivatives can be prepared diastereoselectively in a complementary fashion, and even β-amino alcohols, which cannot be prepared by oxyamination of alkenes, are accessible.

Tetrahydropyranyl-protected nitroethanol and other protected vicinal nitro alcohols can be doubly deprotonated to lithium lithionitronates without β-elimination of the pyranyloxy group.

The double deprotonation of 2-arylnitroethanes followed by treatment with electrophiles led to 2-substituted-2-arylnitroethanes.[73] This fact suggested that the strong base sequentially abstracted α- and then β-protons of these substrates giving α,β-dianions (**57**). The same behavior has been observed with primary nitroalkanes having a vinyl or carbonyl group on the β-carbon. If there is only one α-nitro CH as in open-chain and cyclic secondary nitroalkanes, bis(lithioxy)enamines (**58**) and (**59**) (dianion derivatives of α-nitroalkenes, also called super enamines) are generated and exclusively those with a terminal double bond in the case of 2-nitroalkanes (equations 22 and 23). These dianion derivatives react with aromatic and aliphatic aldehydes as well as ketones to give 1,3-difunctional derivatives. In contrast to the lack of

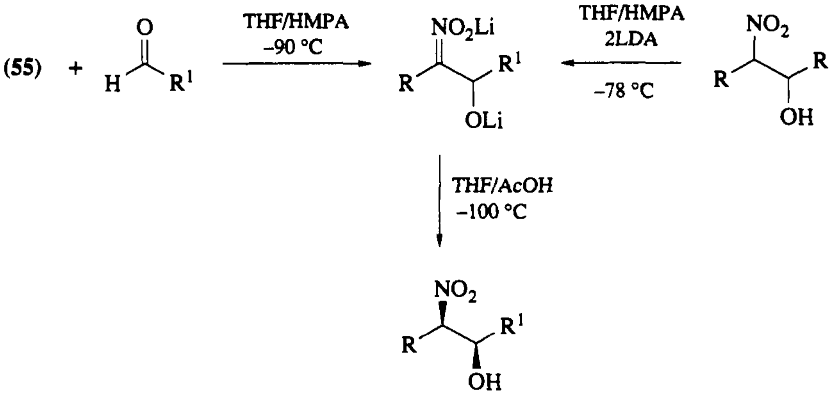

**Scheme 10**

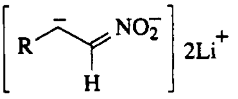

(**57**) R = Ph, vinyl, COR$^1$

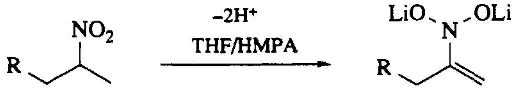

(22)

**(58)**

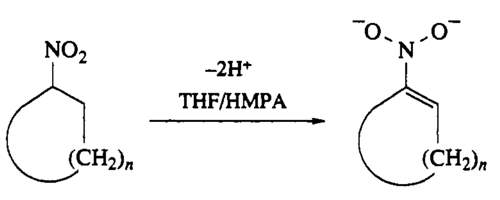

(59)

(23)

stereoselectivity observed in reactions between secondary open-chain nitroalkanes, 'super-enamines' of cyclic secondary nitroalkanes produce stereoselectively (60% to more than 95% *ds*) derivatives with three newly formed centers of chirality.[74]

## 1.10.5 ADDENDUM

Stereochemical control in nitroaldol reactions continues to be a challenge for organic chemists. Barrett and coworkers recently have discovered an experimentally simple procedure for stereoselective preparation of *erythro*-2-nitroalkanols.[75] The procedure consists of the treatment of alkyl nitronates formed by the action of *n*-butyllithium on nitroalkanes in THF solution with aldehydes in the presence of isopropoxytitanium trichloride at room temperature. The method works well in the case of electron-deficient aromatic aldehydes but is less efficient with aliphatic aldehydes. Another interesting reaction uses alumina without a solvent. In the course of studies of the synthesis of polyhydroxylated α-amino acids it was discovered[76] that equimolar mixtures of 2,3-epoxy aldehydes and ethyl nitroacetate furnished 3-ethoxycarbonyl-4-hydroxy-5-(1-hydroxyalkyl)-2-isoxazoline 2-oxides when absorbed with commercial chromatographic alumina without solvent at room tempeature for 2 to 24 h. The reaction was depicted as a base-catalyzed tandem nitroaldol addition–cyclization in which the carbon–carbon bond forming step affords a 2-nitroalkanol and/or the corresponding *aci*-nitro form as a transient species that undergoes a fast epoxide ring-opening cyclization (Scheme 11). The method is of particular interest in that 3-*trans*-monosubstituted substrates gave C(4),C(5)-*trans* and *cis* isomers (*dr* = 1.5) with C(5),C(6)-*anti* configuration (equation 24), whereas 3-*cis*-monosubstituted 2,3-epoxy aldehydes give C(4),C(5)-*trans* and *cis* derivatives with a much higher diastereoselectivity (*dr* = 20) and C(5),C(6)-*syn* configuration (equation 25). 5-*Exo* cyclization rather than the 6-*endo* one has been observed even though the cyclization to 2-isoxazoline 2-oxides involves intramolecular nucleophilic attack to the more substituted end of the oxirane. Since homochiral 2,3-epoxy aldehydes are easily available from the corresponding (*E*)- and (*Z*)-allylic alcohols by a Sharpless asymmetric epoxidation–oxidation sequence[77] and 2-isoxazoline 2-oxides can be converted into 2-isoxazolines, which are central intermediates in organic synthesis,[78] this stereoselective reaction can be considered as a useful tool in the construction of polyhydroxylated linear structures in a controlled and predictable way.

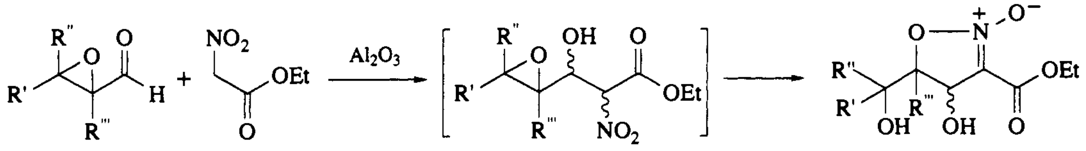

Scheme 11

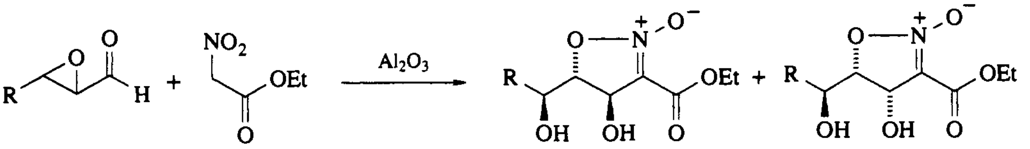

(24)

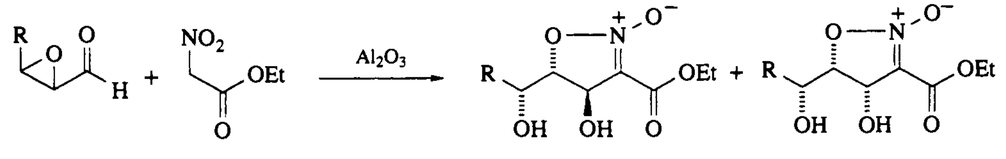

(25)

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# 1.11
# The Knoevenagel Reaction

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## 1.11.1 INTRODUCTION

In 1894 Knoevenagel published a paper in the journal *Chemische Berichte* on the reaction of formaldehyde and diethyl malonate in the presence of diethylamine as catalyst.[1] He obtained the bis adduct (**1**).

Two years later he was able to show that the reaction of benzaldehyde and ethyl acetoacetate in the presence of piperidine gives the bis adduct (**2**) at room temperature and at 0 °C the benzylidene-1,3-dicarbonyl (**3**; Scheme 1).[2]

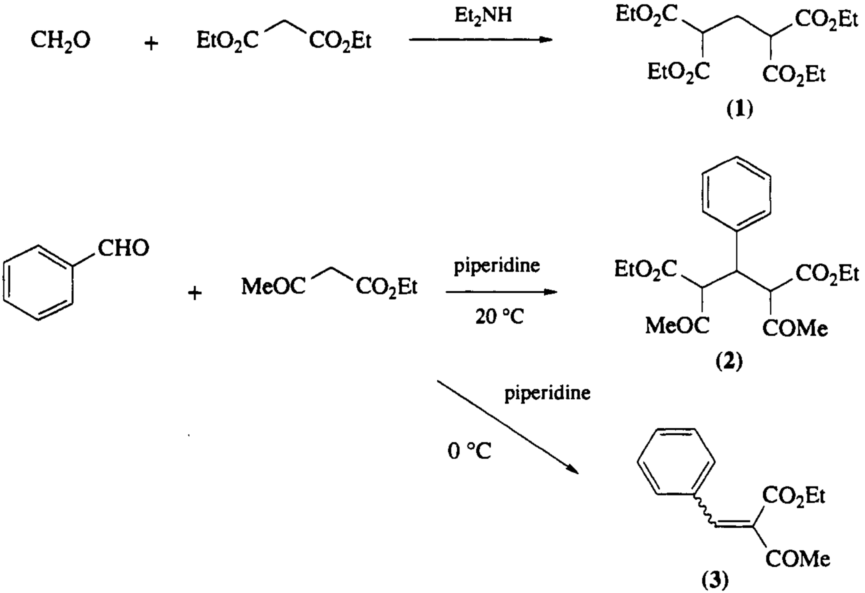

**Scheme 1**

The Knoevenagel condensation[3–7] covers reactions of aldehydes and ketones with active methylene compounds in the presence of a weak base, *e.g.* an amine, to give alkylidene- or benzylidene-dicarbonyls or analogous compounds (Knoevenagel products). Usually methylene groups activated by two electron-withdrawing moieties are employed; the reaction of an aldehyde or a ketone with nitroalkanes in the presence of a weak base is, however, also considered a variant of the Knoevenagel condensation. This reaction (the Henry reaction) is treated elsewhere in this volume (Chapter 1.9). The active methylene compounds used most often are acyclic 1,3-dicarbonyls and analogous substances such as malonates, acetoacetates, acetonitriles, acetylacetone and malonodinitrile, though cyclic compounds like 1,3-cyclohexanediones, Meldrum's acid, barbituric acids, oxazepanediones and 4-hydroxycoumarins are also frequently employed (Scheme 2). With the latter compounds, it is often difficult to isolate the Knoevenagel product, since a fast Michael addition with a second molecule of the methylene component to give a bis adduct takes place. It should also be noted that isomerization of the initial α,β-unsaturated dicarbonyl to a β,γ-unsaturated system frequently takes place. In the case of unsymmetrical 1,3-dicarbonyls and analogous compounds two diastereomeric products can be formed and some of these transformations show a pronounced stereoselectivity.

The aldehydes used in the reaction can be varied over a wide range; chiral compounds such as sugar aldehydes have been employed to some extent. The use of ketones is limited due to their lower reactivity.

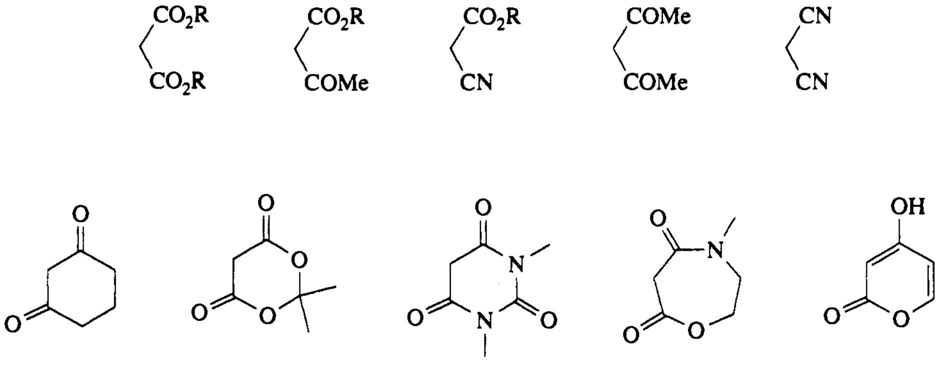

**Scheme 2**

On the other hand the catalyst is of great importance; primary, secondary or tertiary amines or their corresponding ammonium salts are usually used, but many other catalysts such as phase transfer catalysts, Lewis acids or potassium fluoride can also be applied. The most widely employed catalysts are pyridine, with or without added piperidine, and ammonium salts, such as ammonium or piperidinium acetate. Condensations that employ strong bases or preformed metal salts of the methylene component are not covered here since transformations under these conditions are not usually considered to be Knoevenagel reactions.

Several mechanisms may operate. In some cases there is probably first a reaction between the aldehyde and the amine to give an imine or an iminium salt, which, rather than the free aldehyde, reacts with the anion derived from the active methylene compound.

## 1.11.2 GENERAL ASPECTS

### 1.11.2.1 Reaction Conditions

The Knoevenagel condensation is effected by treating a carbonyl compound with an active methylene compound in the presence of at least catalytic amounts of a base and an acid. It is appropriate in these reactions to remove the water formed either azeotropically or by addition of molecular sieves or sodium sulfate. As the methylene compounds are more acidic than the aldehydes and ketones used in the aldol reaction, the bases employed as catalysts are usually weaker than those needed to effect the aldol condensation. Ammonia, primary, secondary and tertiary amines, as the free bases or their salts, are effective catalysts.[3] The condensation of aliphatic and heterocyclic aldehydes with ethyl cyanoacetate can be brought about by secondary amines like piperidine or diethylamine.[8] Another possibility is the use of ammonium salts or amines of organic acids, such as ammonium acetate, ethylenediammonium diacetate or piperidinium acetate, usually in an acetic acid solution or in other organic solvents like dioxane, dichloromethane or benzene. Acetamide, which is usually contaminated with ammonium acetate, can also be used. The condensation of ketones with ethyl cyanoacetate can be performed under similar conditions.[9] Piperidinium acetate has become one of the most popular catalysts in Knoevenagel condensations. $\varepsilon$-Aminocaproic acid, $\alpha$-aminophenylacetic acid, $\beta$-alanine and *p*-aminophenol are also very efficient catalysts for the condensation of various ketones with malonodinitrile and ethyl cyanoacetate.[10] Alkali metal fluorides have found wide application in base-catalyzed reactions.[11,12] In particular, potassium fluoride is a useful catalyst for the Knoevenagel reaction because of its adequate basicity, its high affinity to water and its low cost. A comparison of the activity of the various alkali metal fluorides in the Knoevenagel condensation of benzaldehyde and cyclohexanone with malonodinitrile, ethyl cyanoacetate and ethyl malonate has shown that potassium fluoride, in less than equivalent amounts, is an effective catalyst and that rubidium and cesium fluoride are even better, while lithium fluoride and sodium fluoride are ineffective. This is probably due to an increase in solubility from LiF to CsF in polar solvents. It can be assumed that the fluoride anion acts as a base to promote the deprotonation of the methylene compound.[13]

As a new generally applicable catalyst for the Knoevenagel condensation, a mixture of titanium tetrachloride and a tertiary organic base in solvents like tetrahydrofuran or dioxane was introduced by Lehnert.[14] The procedure is often superior to standard methods in reactions of sensitive compounds because it can be performed at low temperature. As an example, the reaction of the aldehyde (**4**) with malonate or cyanoacetate in the presence of titanium tetrachloride and pyridine gives the desired products (**5**) in high yield, whereas the classical method using piperidine acetate fails (Scheme 3).[15]

In recent years the use of inorganic solids and solid supports as reagents or reaction media has rapidly increased as these reactions often involve milder conditions, easier workup and higher selectivity than

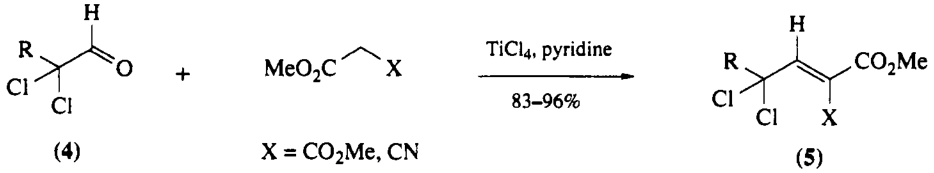

**Scheme 3**

similar reactions in solution. Foucaud *et al.* found that Knoevenagel condensations can be achieved in the presence of dry alumina without organic solvents under mild conditions. Condensations with aldehydes are generally very fast, but reactions with ketones are more difficult to accomplish.[16,17] Knoevena-

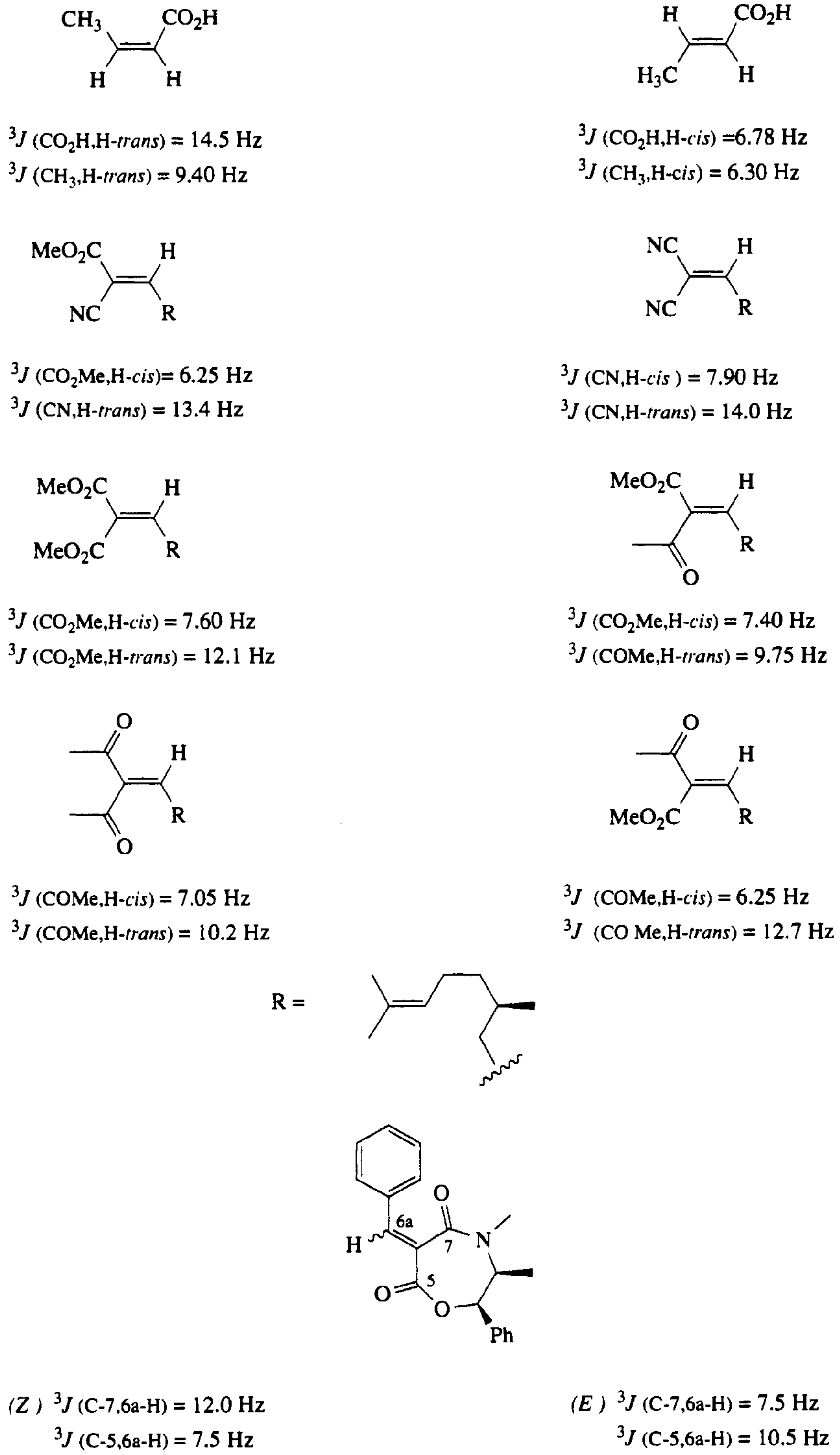
CH3
CO2H
H
H
H
CO2H
H3C
H
MeO2C
H
NC
R
NC
H
NC
R
MeO2C
H
MeO2C
R
MeO2C
H
R
O
O
H
R
O
O
H
MeO2C
R
R =
H
6a
O
7
N
5
O
O
Ph

$^3J$ (CO$_2$H,H-*trans*) = 14.5 Hz
$^3J$ (CH$_3$,H-*trans*) = 9.40 Hz

$^3J$ (CO$_2$H,H-*cis*) =6.78 Hz
$^3J$ (CH$_3$,H-*cis*) = 6.30 Hz

$^3J$ (CO$_2$Me,H-*cis*)= 6.25 Hz
$^3J$ (CN,H-*trans*) = 13.4 Hz

$^3J$ (CN,H-*cis* ) = 7.90 Hz
$^3J$ (CN,H-*trans*) = 14.0 Hz

$^3J$ (CO$_2$Me,H-*cis*) = 7.60 Hz
$^3J$ (CO$_2$Me,H-*trans*) = 12.1 Hz

$^3J$ (CO$_2$Me,H-*cis*) = 7.40 Hz
$^3J$ (COMe,H-*trans*) = 9.75 Hz

$^3J$ (COMe,H-*cis*) = 7.05 Hz
$^3J$ (COMe,H-*trans*) = 10.2 Hz

$^3J$ (COMe,H-*cis*) = 6.25 Hz
$^3J$ (CO Me,H-*trans*) = 12.7 Hz

(*Z* ) $^3J$ (C-7,6a-H) = 12.0 Hz
$^3J$ (C-5,6a-H) = 7.5 Hz

(*E* ) $^3J$ (C-7,6a-H) = 7.5 Hz
$^3J$ (C-5,6a-H) = 10.5 Hz

**Scheme 4**

gel condensations in solid–liquid systems with magnesium oxide or zinc oxide as catalyst occur at room temperature.[17] Another inorganic catalyst that can be used in the absence of a solvent is aluminum phosphate/aluminum oxide. It was established that the reaction mechanism under these conditions is the same as that in solution.[18] Knoevenagel condensations can also be achieved employing catalytic amounts of xonotlite, or xonotlite doped with potassium *t*-butoxide at ambient temperature.[19] Recently, silica gel functionalized with amino groups has found application as a catalyst.[20] In addition, successful catalysis by ion-exchange resins has been known for a long time.[21,22] The use of dibenzo-18-crown-6 supported on a polymer in condensations of aromatic aldehydes has been studied recently.[23] Copper(II) chloride catalyzes the Knoevenagel condensation of aldehydes or their tosylhydrazones with 2,4-pentanedione under neutral conditions at room temperature;[24] zinc acetate in the presence of defined quantities of water can be also used.[25]

The Knoevenagel reaction is strongly solvent-dependent. The first step, the formation of the enolate from the 1,3-dicarbonyl and its addition to the carbonyl (or imine) is facilitated in solvents of high polarity and the second step, 1,2-elimination, is inhibited by protic solvents. Thus, dipolar aprotic solvents such as dimethylformamide are especially useful in Knoevenagel condensations.[26,27]

It must be emphasized that the scope and limitations of many of the new Knoevenagel catalysts have not been explored sufficiently. From the practising chemist's point of view the situation is somewhat confusing and the search for the appropriate reaction conditions is still largely a process of trial and error.

### 1.11.2.2 Spectroscopy and Physical Properties

NMR spectroscopy is the most widely used method to investigate both the configuration and conformation of Knoevenagel products. The configuration of acrylic or cinnamic acids obtained by condensation of aldehydes with malonic acid and other 1,2-disubstituted alkenes can be determined from the value of the vicinal coupling constant $^3J_{\mathrm{H,H}}$ (between the protons of the double bond) on the basis of the relationship $^3J_{\mathrm{H,H}\text{-}trans} > {^3J_{\mathrm{H,H}\text{-}cis}}$. If only one isomer is available, the electronegativity of the substituents has to be considered.[28] This method, however, is not applicable to 1,2-disubstituted alkenes where the chemical shifts of the alkenic protons are similar, or to tri- and tetra-substituted alkenes. Allylic and homoallylic coupling constants ($^4J_{\mathrm{H,H}}$ and $^5J_{\mathrm{H,H}}$) have been used to determine the geometry of alkenes, but they are less reliable than the vicinal coupling constants for this purpose.[28,29]

Analysis of $^3J_{\mathrm{C,H}}$ coupling constants is a powerful, generally applicable tool for establishing double bond configuration in di- and tri-substituted Knoevenagel products.[30–32] It is even possible to apply this method without separating mixtures of isomers. Examples of $^3J_{\mathrm{C,H}}$ coupling constants in di- and tri-substituted Knoevenagel products are given in Scheme 4.[30,33,34] The analysis of vicinal coupling constants is not restricted to H,H and C,H couplings, but can also be applied to couplings between vinylic protons and other nuclei having a magnetic moment. The values of $^3J_{\mathrm{P,H}}$ coupling constants for trisubstituted Knoevenagel products obtained from phosphonatoacetates have been determined.[35]

Since the chemical shift of an alkenic proton or carbon depends on the nature and position of the other alkenic substituents, this property can be used for configurational assignment. It can be evaluated by the empirical relation shown in equation (1), which is based on additive shielding increments (*Z*) that have been extracted from a large number of alkenes.[28,36,37] This 'differential shielding method' is especially useful for the determination of configuration in alkenes containing highly anisotropic substituents like carbonyl groups.[28,38] The method has been applied successfully to elucidate the double bond configuration of Knoevenagel products between aldehydes or ketones and cyanoacetates. The β-vinylic proton and the protons of β-substituents are more deshielded when they are *cis* to the ester group (Scheme 5).[39–42]

$$\delta_{\mathrm{H}}\ (\text{p.p.m.}) = 5.28 + Z_{cis} + Z_{trans} + Z_{gem} \qquad (1)$$

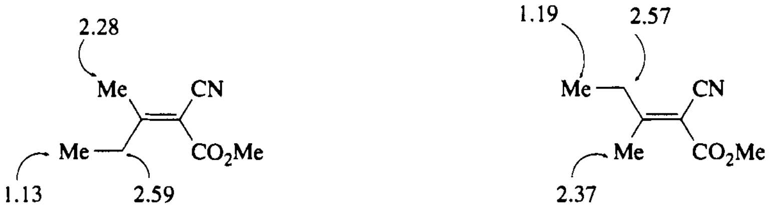

**Scheme 5**

From the data shown it is clear that both isomers must be available to allow unambiguous stereochemical assignments.

There is also a correlation of $^{13}C$ NMR chemical shifts of the α- and β-carbons of di- and tri-substituted α,β-unsaturated acids, represented by the empirical relation in equations (2a) and (2b), which relies on the additive shielding increments $Z_i$.[28,43] Another method used for the determination of double bond configuration makes use of effects induced by benzene or other aromatic solvents on the chemical shifts of double bond substituents; preferential shielding of protons or alkyl groups *trans* to the polar groups is usually observed. An example of the use of this method is the determination of the stereochemistry of the double bond in (*Z*)- and (*E*)-geranic acids (**6** and **7**; Scheme 6).[44]

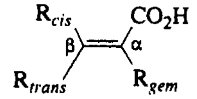

$$\delta_\alpha = -64 + \sum_i Z_i^\alpha \text{ (p.p.m.)} \tag{2a}$$

$$\delta_\beta = -60 + \sum_i Z_i^\beta \text{ (p.p.m.)} \tag{2b}$$

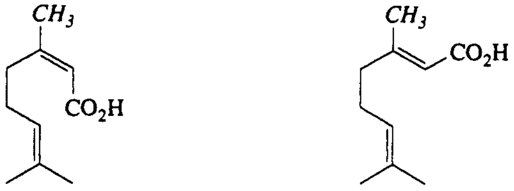

(**6**)

δ ($CCl_4$) = 1.96 p.p.m.
Δ ($C_6H_6/CCl_4$) = 0.45 p.p.m.

(**7**)

δ ($CCl_4$) = 2.18 p.p.m.
Δ ($C_6H_6/CCl_4$) = 0.13 p.p.m.

**Scheme 6**

Spectroscopic methods have also been used to characterize the conformational properties of Knoevenagel products from acyclic[39,45] and cyclic[46,47] active methylene compounds.

Knoevenagel products display interesting physical properties, the most striking of which is their Lewis acidity.[48] The strength of these neutral organic Lewis acids increases with increasing strength of the electron-withdrawing groups and with increasing planarity of the system. Thus, the Lewis acidity of the nearly coplanar methylene derivatives of Meldrum's acid (**8**) exceeds that of the corresponding methylenemalonates (**9**), in which one ester group is probably out of the general plane of the conjugated system.

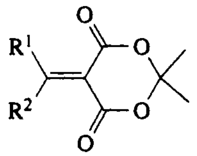

(**8**)

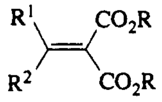

(**9**)

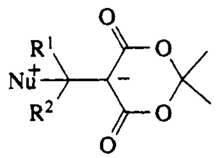

(**10**)

The acidity of these products cannot be determined by means of direct pH determination. However, the virtual acidity constant, $K'_L$, is accessible from optical and electrochemical measurements. Comparison of the p$K'_L$ values of selected Knoevenagel products and the p$K$ values of some typical carboxylic acids in methanol establishes that they exhibit comparable acidity (Scheme 7). Using the $\sigma^+$-values, the p$K'_L$ values of benzylidene derivatives of Meldrum's acid are in good accordance with the Hammett equation. The Lewis acidity of Knoevenagel products is due to the formation of labile pseudobase adducts, the so-called anbadons (**10**), upon reaction with nucleophiles. Structures of the anbadons have

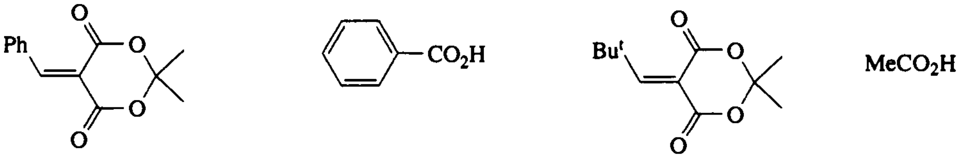

p$K'_L$ = 9.2 p$K$ = 9.4 p$K'_L$ = 8.4 p$K$ = 9.65

**Scheme 7**

been established by means of NMR and UV spectroscopy as well as by chemical methods. The alkenic protons of the Knoevenagel products in question absorb in the range δ = 7–9 in different solvents like $CD_3OD$, $CCl_4$ or $CDCl_3$. The signal for this proton disappears on addition of $CD_3ONa$ and a new absorption appears in the range δ = 3.8–5.5.[48]

### 1.11.2.3 Mechanism

The Knoevenagel reaction belongs to the general class of base-catalyzed aldol-type condensations, where a carbanion adds to a carbonyl or heterocarbonyl group. Two different mechanisms, mainly depending on the base used, have been proposed for the reaction of (**11**) and (**12**) to give (**14**; Scheme 8). In the Hann–Lapworth[49] mechanism the intermediacy of a β-hydroxydicarbonyl compound (**13**) is assumed; this certainly holds true when using tertiary amines such as pyridines by reaction of (**12**). (**13**) is also formed as an intermediate with the sodium salt of (**11**); however, this transformation is not classified as a Knoevenagel reaction. Employing secondary and primary amines as catalysts, Knoevenagel[50] has shown that a condensation of the aldehyde (**12**) and the amine (**15**) takes place to give an iminium salt (**16**), which then forms the alkylidene- or benzylidene-1,3-dicarbonyl product (**14**). Since an elimination step is involved in both mechanisms, the final product would be the same. Kinetics of several

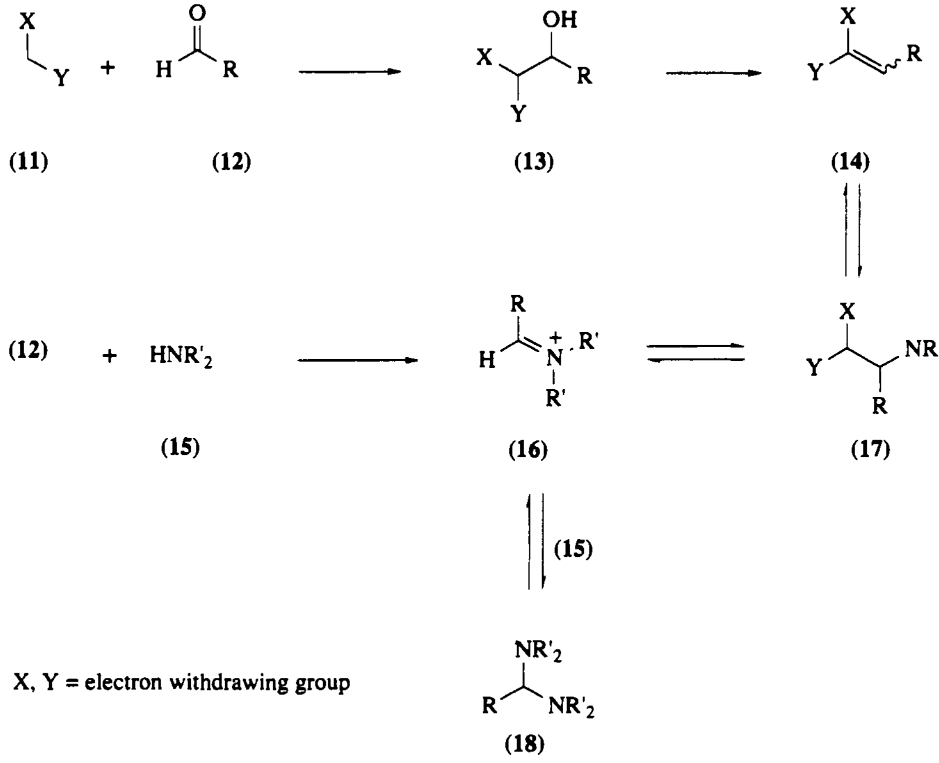

X, Y = electron withdrawing group

**Scheme 8**

Knoevenagel reactions have been measured. Patai *et al.* and others have studied the effect the catalyst has on the reaction mechanism.[51–53] For the reaction of malonodinitrile and 3-methylcyclohexanone in benzene with triethylamine or piperidine, the rate of the reaction was found to be first order in amine, ketone and nitrile[54] and was interpreted in terms of basic catalysis by the amine. Using a mixture of triethylamine or piperidine and an acid like acetic acid or benzoic acid, general acid catalysis was observed, but its effect on the overall rate of the reaction was small since the acid lowers the concentration of free amine. With mixtures of primary amines like hexylamine and acetic acid in the reaction of 3-methylcyclohexanone with malonodinitrile the rate is zero order in malonodinitrile. It was argued that in the rate-determining acid-catalyzed step hexylamine forms an imine with cyclohexanone. This imine then reacts rapidly with malonodinitrile. When employing hexylamine without acid, a complex rate law indicates that hexylamine acts mainly as a basic catalyst and the reaction proceeds according to the Hann–Lapworth mechanism.[54] Furthermore, it has been shown that weak bases producing solutions having a pH of 7.5–8.0 are most efficient. With β-alanine the energy of activation is 7.6 kcal $mol^{-1}$, compared to 11 kcal $mol^{-1}$ for the uncatalyzed reaction.[55] Although stronger bases such as KF or piperidine cause even more rapid condensation, the yield is lower because of telomerization of malonodinitrile.

Various aromatic aldehydes react with active methylene compounds in the presence of piperidine to give the corresponding dipiperidines (**18**), which are in equilibrium with the iminium ion (**16**) under the reaction conditions (Scheme 8). In addition, the primary reaction products (**17**) of iminium ions (**16**) with the active methylene compound (**11**) can also be isolated.[56] In the reaction of *N*,*N*-dimethylbarbituric acid and citronellal using catalytic amounts of ethylenediammonium diacetate, the β-hydroxy-1,3-dicarbonyl has been identified by NMR spectroscopy.[57]

In a valuable variation of the Knoevenagel reaction, malonic, cyanoacetic and acetoacetic acids are used as active methylene compounds. The reaction is accompanied by decarboxylation to give α,β-unsaturated esters, nitriles or ketones. The transformation could either proceed *via* β-hydroxy or β-amino intermediates followed by decarboxylation and elimination or *vice versa*. To elucidate this mechanism, Knoevenagel reactions of *p*-nitrobenzaldehyde with methylmalonic acid in the presence of a secondary or a tertiary amine have been carried out with NMR observation.[58–60] In the presence of pyridine the concentration of the β-hydroxy intermediate (**19**) reaches a maximum in about 3.5 h and the decarboxylation product (**20**) begins to appear after 24 h.[58] It seems clear that the reaction between the starting materials and intermediate (**19**) is reversible.[61] The α,β-unsaturated acid (**21**) was not observed. In contrast, in the presence of piperidine, depending on the concentration of the amine, compounds (**19**)–(**21**) are obtained. Since (**21**) is not formed *via* (**19**) or (**20**), another pathway, namely the Knoevenagel mechanism, is implicated. Here, a bisdialkylamino derivative and an iminium salt are formed. It is of interest that the formation of the bisdialkylamino derivative depends on the type of secondary base. Thus, with piperidine and morpholine the formation of (**21**) *via* the Knoevenagel mechanism is preferred, whereas with diethylamine and dicyclohexylamine mainly (**20**) *via* the Hann–Lapworth mechanism is formed.[58]

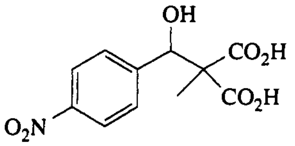

(**19**)

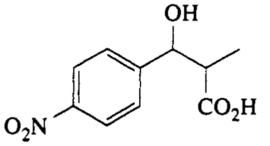

(**20**)

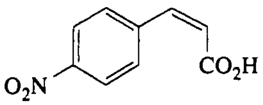

(**21**)

The generalization can be made that in the presence of tertiary amines, with and without acids, the Knoevenagel reaction always proceeds according to the Hann–Lapworth mechanism through a β-hydroxy intermediate. With secondary and primary amines, the Hann–Lapworth and Knoevenagel mechanisms can compete. The formation of an imine intermediate mainly depends on the bulkiness of the amine and the carbonyl compound. With ketones and piperidine as catalyst, with or without acid, normal basic catalysis is found, whereas with hexylamine in the presence of an acid, an intermediate imine is formed. With aldehydes and piperidine, an intermediate imine is observed, whereas with diisopropylamine, the chief intermediate is the β-hydroxy adduct. However, using only catalytic amounts of secondary or primary bases the β-hydroxy compound is clearly the intermediate.[58] In some cases β-hydroxy-1,3-dicarbonyls have been isolated in the Knoevenagel reaction.[62,63] Crystalline adduct (**24**) is obtained by condensation of *o*-nitrobenzaldehyde (**23**) and aminocrotononitrile (**22**) in basic or neutral media; the structure was elucidated by X-ray crystallography. In ethanolic hydrochloric acid the corresponding ketonitrile (**25**) is formed (Scheme 9).[64] The influence of pressure on the Knoevenagel reaction has also been investigated. As expected, pressure increases the reaction rate.[65]

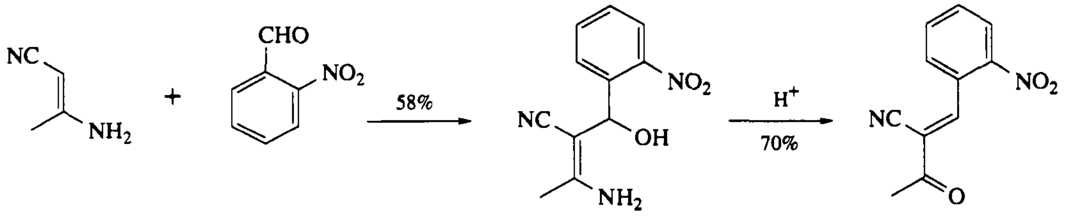
NC
NH2
CHO
NO2
58%
NC
NO2
OH
NH2
H+
70%
NC
NO2
O

**(22)** **(23)** **(24)** **(25)**

**Scheme 9**

### 1.11.2.4 The Retro-Knoevenagel Reaction

The rate of the hydrolytic cleavage of Knoevenagel products (retro-Knoevenagel reaction)[5] strongly depends on the pH of the aqueous solution[66,67] as well as on cosolvents such as DMSO[68] and additional nucleophiles such as amines.[69] The hydrolysis of these alkenes to $CH_2XY$ can be presented by equation (3) at pH < $pK_a^{CH_2XY}$ and by equation (4) at pH > $pK_a^{CH_2XY}$. Although the kinetics are related to the nature of Y and X, the mechanism is basically the same for all Knoevenagel products. Detailed studies have been performed for the hydrolysis of benzylidene-Meldrum's acid, benzylidenemalonodinitrile, benzylidene-1,3-indandione, benzylideneacetylacetone and 1,1-dinitro-2,2-diphenylethylene. Below pH 3 an aqueous solution of benzylidene-Meldrum's acid is relatively stable (half-life ≈ 35 min). With increasing pH the decomposition increases rapidly and shows a rate maximum near pH 6 (half-life ≈ 2 min). The hydrolysis rate decreases above pH 6 with a minimum around pH 8–9 (half-life at pH 8 ≈ 60 min). Above pH 9 cleavage takes place due to attack of hydroxide ion at one of the carbonyl groups. The different cleavage rates can easily be explained by assuming four consecutive steps (Scheme 10).[67–69]

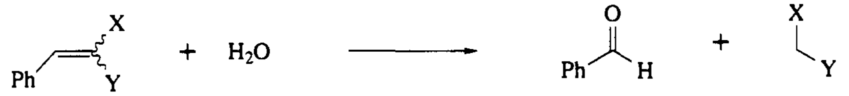
X
Ph
Y
+ H2O
O
Ph
H
+
X
Y

(3)

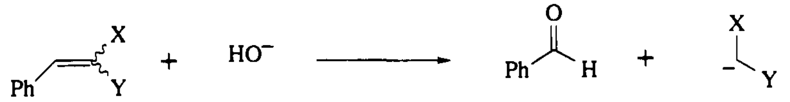
X
Ph
Y
+ HO−
O
Ph
H
+
X
−
Y

(4)

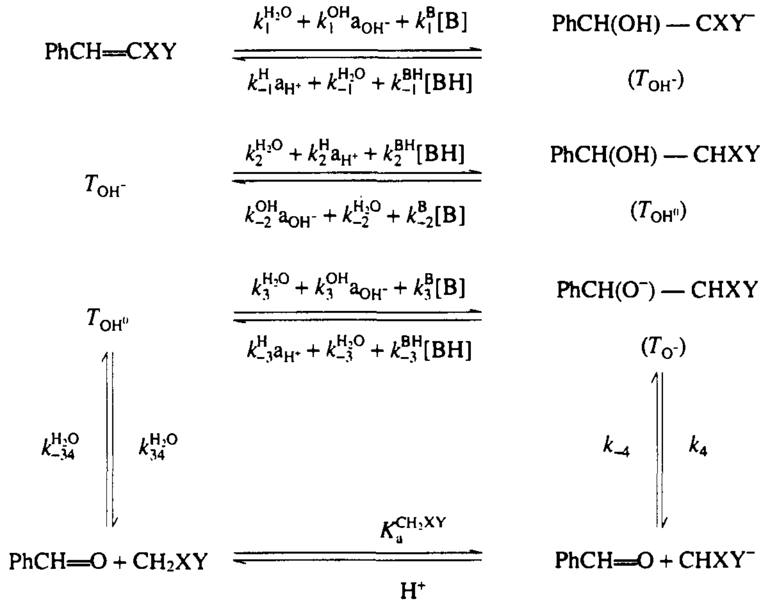
PhCH=CXY
k1H2O + k1OH aOH− + k1B[B]
k−1H aH+ + k−1H2O + k−1BH[BH]
PhCH(OH)—CXY−
(TOH−)
TOH−
k2H2O + k2H aH+ + k2BH[BH]
k−2OH aOH− + k−2H2O + k−2B[B]
PhCH(OH)—CHXY
(TOH0)
TOH0
k3H2O + k3OH aOH− + k3B[B]
k−3H aH+ + k−3H2O + k−3BH[BH]
PhCH(O−)—CHXY
(TO−)
k−34H2O
k34H2O
k−4
k4
PhCH=O + CH2XY
KaCH2XY
H+
PhCH=O + CHXY−

**Scheme 10**

(i) Attack of water or $OH^-$ at the β-carbon to form an adduct ($T_{\mathrm{OH}}^-$) subject to a weak general base catalysis; (ii) protonation of the α-carbon of $T_{\mathrm{OH}}^-$ to form $T_{\mathrm{OH}}^0$; (iii) deprotonation of the OH group of $T_{\mathrm{OH}}^0$ to form the tetrahedral intermediate $T_{\mathrm{O}}^-$; and (iv) breakdown of $T_{\mathrm{O}}^-$ into the aldehyde and the anion of the 1,3-dicarbonyl compound.

At high pH (pH > 6) protonation of $T_{\mathrm{OH}}^-$ is rate limiting, whereas at low pH (pH ≤ 6) deprotonation of the OH group in the neutral adduct $T_{\mathrm{OH}}^0$ is rate limiting. The breakdown of the tetrahedral intermediate $T_{\mathrm{O}}^-$ must be at least in the order of $10^{10}$ $s^{-1}$. Since carbanions are generally considered to be sluggish nucleofuges, the high rate for the last step is astounding.

### 1.11.2.5 Stereochemistry

Geometrical isomers can be obtained in the Knoevenagel reactions of compounds (**11**) when X and Y are different. The selectivity in these reactions is mainly governed by steric effects. Condensations of cyanoacetate with aliphatic and aromatic aldehydes give (*E*)-products almost exclusively.[40,70] Thus, reaction of methyl cyanoacetate and aldehyde (**26**) in the presence of piperidinium acetate in $CH_2Cl_2$ affords the (*E*)-isomer (**27**) in 82% yield after chromatography.[71] With (**28**) as the methylene component (*E*)-alkenes (**29**) are obtained, in which the β-substituent is *anti* to the more bulky methanesulfonyl group.[72] If the electron-withdrawing groups X and Y in (**11**) are of similar size, a mixture of the two diastereomeric Knoevenagel products is formed. Thus, condensation of methyl acetoacetate with an aliphatic aldehyde like 7-methyl-6-octenal (**26**) gives (*E*)-(**30**) and (*Z*)-(**30**) in a 40:60 ratio. Although the diastereomers can be separated by chromatography, they isomerize slowly at 0 °C.[71] It is noteworthy that 1,3-dicarbonyl compounds in which one group is COPh undergo highly stereoselective Knoevenagel reactions. Thus, condensation of benzaldehyde with (**31**) and (**32**) gives the products (**33**) and (**34**), respectively, in which the phenyl group derived from benzaldehyde is *trans* to the COPh group (99:1).[73]

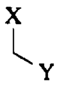

(**11**)

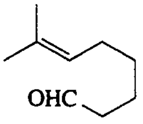

(**26**)

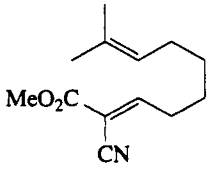

(**27**)

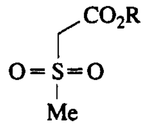

(**28**)

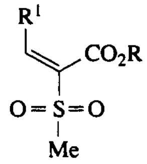

(**29**)

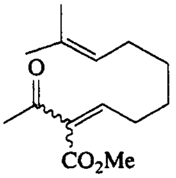

(*E*/*Z*)-(**30**)

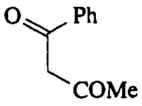

(**31**)

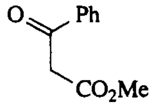

(**32**)

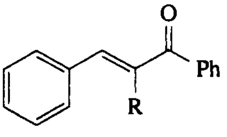

(**33**) R = COMe
(**34**) R = $CO_2Me$

The stereochemical course of the Knoevenagel reaction of methyl arene-sulfinylacetate (**35**) with aliphatic and aromatic aldehydes has been investigated in detail.[74] In the presence of catalytic amounts of piperidine, methyl (*E*)-3-alkyl- and methyl (*E*)-3-arene-sulfinylalk-2-enoates (*E*)-(**36**) are formed exclusively. It is of interest that the sodium and lithium enolates of (**35**) do not react with aldehydes. However, using the magnesium or zinc salts it is possible to drive the equilibrium towards the condensation products.[75-77] Primary and tertiary amines are not effective as catalysts either. This is a strong hint that an iminium salt (**37**) is an intermediate in this reaction. Also, (**39**), which is an adduct of the proposed iminium salt (**37**) and methyl arenesulfinylacetate (**35**), can be obtained in crystalline form either from (**38**) and (**35**) or from the aldehyde and (**35**); (Scheme 11). The *erythro*/*threo* ratio of (**39**) depends on the secondary amine used ($R^1$ = phenyl; *threo*/*erythro* ratio for dimethylamine is 0:100; for pyrrolidine is 0:100; and for 2-methylpiperidine is 30:70). The ratio is clearly related to the relative bulkiness of the groups $CO_2Me$, SOAr, $R^1$ and $NR^2_2$. In acetic acid a stereospecific *anti* elimination is found to give (*E*)-(**36**) from *threo*-(**39**) and (*Z*)-(**36**) from *erythro*-(**39**). However, a different mechanism operates under Knoevenagel conditions, where the thermodynamically more stable alkene (*E*)-(**36**) is obtained from both diastereomers (**39**) *via* an intermediate carbanion.[74] One has always to keep in mind though, that isomerization of the Knoevenagel product is possible.

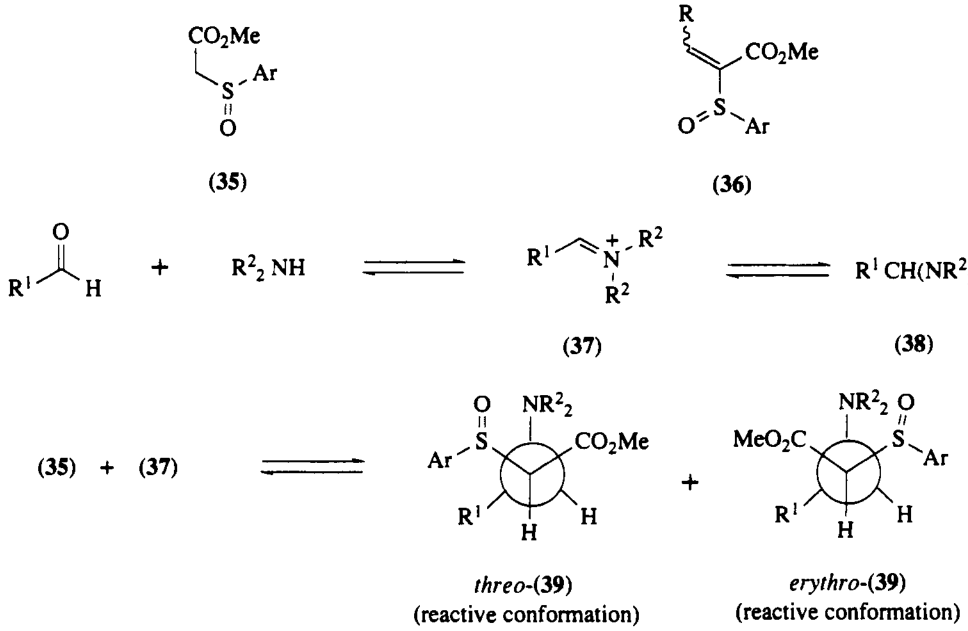

Scheme 11

In the Knoevenagel reaction, the thermodynamically more stable compounds are usually formed. However, a closely related transformation provides access to compounds of opposite stereochemistry. Condensation of phosphonoacetate (**40**) with aliphatic and aromatic aldehydes in the presence of *N*-methylmorpholine/$TiCl_4$ yields product (**41**) with the thermodynamically more stable (*E*)-configuration.[78] In contrast, titanated (**40**), obtained from the reaction of the sodium salt of (**40**) with $ClTi(OCHMe_2)_3$ reacts with aldehydes to give preferentially the thermodynamically less stable (*Z*)-isomer (**42**).[35]

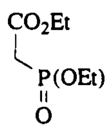
(**40**)

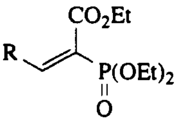
(**41**)

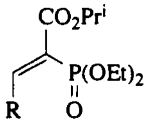
(**42**)

Unsymmetrical cyclic active methylenes such as pyrazolones, isoxazolones and oxazepane-5,7-diones can also undergo stereoselective condensation with aldehydes. Benzylidenepyrazolones (**43**) with a hydrogen at C-5 are more stable in the (*E*)-configuration, whereas the corresponding compounds (**44**) with an alkyl or aryl substituent at C-5 have the (*Z*)-configuration.[79–81] Knoevenagel condensation of benzaldehyde with oxazepane-5,7-diones in the presence of $TiCl_4$, ethylenediammonium diacetate or piperidine/acetic acid leads mainly to the Knoevenagel product (**45**) with a (*Z*)-configuration,[34] contrary to earlier descriptions in the literature.[82] The pronounced selectivity is rationalized by the pseudo-boat conformation of the seven-membered ring with an upwards flexion of the lactone carbonyl of 57.4° and of the amide carbonyl of 31.5°. Thus, the benzylidene compound with the (*Z*)-configuration should be sterically less hindered.[34]

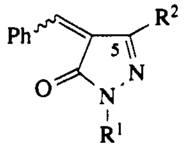
(**43**) $R^2 = H$
(**44**) $R^2 =$ alkyl, Ph

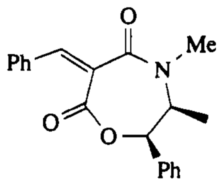
(**45**)

Condensation of unsymmetrical ketones with methyl cyanoacetate usually gives a mixture of (*E*)- and (*Z*)-isomers in which the isomer with a *trans* relationship between the bulkier substituent and the carboalkoxy group predominates. Thus, condensation of alkyl 2-furyl ketones (**46**) and (**47**) affords a mixture of (*E*)- and (*Z*)-isomers of (**48**) and (**49**) with the (*E*)-isomer predominating (Scheme 12).[39]

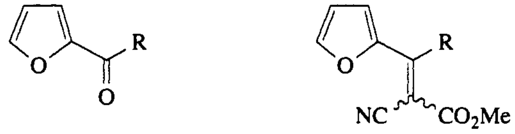

(**46**) R = Me
(**47**) R = Pr$^i$

(**48**) R = Me (*E*):(*Z*) = 5:1
(**49**) R = Pr$^i$ (*E*):(*Z*) = 1.1:1

**Scheme 12**

Knoevenagel products of cyclic ketones such as cyclohexanone show a pronounced preference in adopting a chair conformation with an axial orientation of substituents in the α-position. Condensation of *trans*-2,5-dimethylcyclohexanone (**50**) with malonodinitrile under neutral or weakly basic conditions leads, as expected, to (**51**); under the same conditions the *cis*-2,5-dimethylcyclohexanone (**52**) affords (**53**). It is remarkable that the *cis* product (**53**) is thermodynamically more stable than (**51**), whereas the ketone (**50**) with *trans* orientated methyl groups is more stable than (**52**). The unexpected difference in stability is due to the necessity of the α-substituent in the Knoevenagel products (**51**) and (**53**) to adopt an axial orientation. In the conformation with an equatorial α-methyl group a severe steric interaction would occur because of a coplanar arrangement of the methyl and the dicyanomethylene moiety.[83]

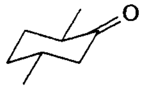

(**50**)

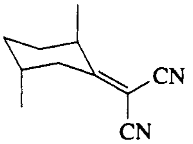

(**51**)

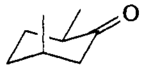

(**52**)

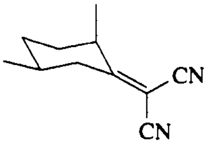

(**53**)

Instead of α,β-unsaturated acids, (*E*)-β,γ-unsaturated acids can be obtained in the Knoevenagel condensation if the reaction is performed in boiling xylene with an excess of malonic acid.[84]

### 1.11.2.6 Competitive Reactions

The main problem inherent in the application of the Knoevenagel condensation for synthesis is the undesired formation of the so-called bis adduct or Michael adduct, resulting from the Michael addition of a second molecule of the active methylene compound to the initial Knoevenagel product.[3,5,85] In the reaction of α,β-unsaturated ketones and malonodinitrile it has been found that the ratio of Knoevenagel and Michael products depends on steric factors. As an example, in the reaction of mesityl oxide (**54**), Knoevenagel condensation is followed by conjugate addition and finally by intramolecular condensation to yield the trinitrile (**55**; equation 5).[86] Whereas the reaction of barbituric acid (**56**) and *N*,*N*-dimethylbarbituric acid (**57**) yield Knoevenagel products with nearly every type of aldehyde,[3,87,88] Meldrum's acid (**58**) and its derivatives give Knoevenagel products only with aromatic aldehydes and ketones and with hindered aliphatic aldehydes, but yield Michael products upon reaction with simple aliphatic aldehydes.[89] An unusual Michael product (**60**) is formed by the reaction of Meldrum's acid with *n*-butanal.[90] Finally, dimedone (**59**) and similar cyclic 1,3-diketones yield Michael adducts exclusively with every type of aldehyde.[3,91,92] This property of dimedone (**59**) has been used traditionally in analytical chemistry for the qualitative and quantitative determination of aldehydes (see Section 1.11.2.7).[93] The different be-

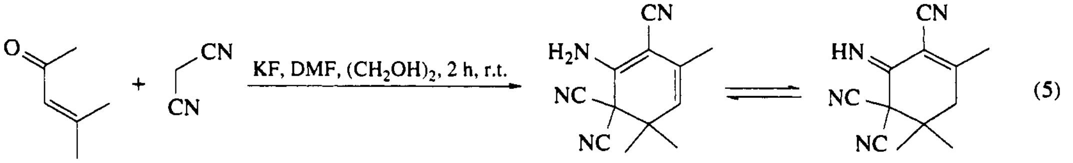

(**54**) (**55**) (5)

havior of various Knoevenagel products upon reaction with active methylenes has been correlated with their calculated Lewis acid strength.[48]

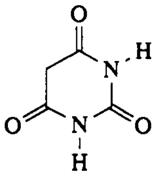

**(56)**

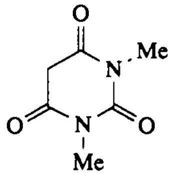

**(57)**

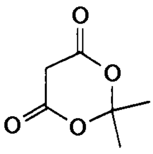

**(58)**

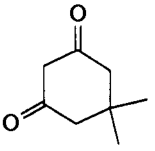

**(59)**

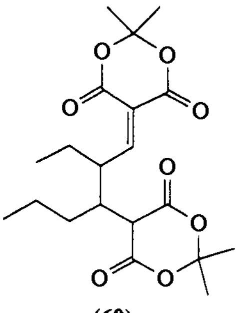

**(60)**

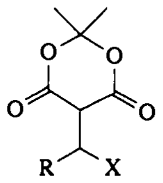

**(61)** X = OR$^-$
**(62)** X = NR$_2$
**(63)** X = SPh

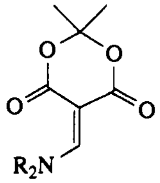

**(64)**

Formation of the undesired Michael adducts can be avoided by trapping the Knoevenagel product with methoxide,[94] secondary amines,[95] or thiols[90] to give the 3-heterosubstituted alkyl-1,3-dicarbonyls (**61**), (**62**) and (**63**), respectively, from which the alkene may be generated by acid or in the case of the thio compound by an oxidative base-catalyzed hydrolysis. In some cases the adduct (**63**) shows a reactivity similar to the alkylidene-Meldrum's acid, *e.g.* yielding the corresponding epoxide with $H_2O_2$.[90] Alkylidene-Meldrum's acid can also be prepared by addition of metal organic reagents[96] to the easily available aminomethylidene-Meldrum's acids (**64**),[97] or by oxidative elimination of selenoalkylated Meldrum's acid.[98] A novel method for preparation of the highly reactive methylidenemalonates on a multigram level involves trapping them as Diels–Alder adducts with anthracene and their liberation by a subsequent retro-Diels–Alder thermolysis.[99] Thus, heating symmetric or unsymmetric malonates with paraformaldehyde, copper(II) acetate and anthracene in a mixture of xylene and acetic acid affords the crystalline Diels–Alder adducts (**66**), which generate the alkenic material (**65**) by thermolysis at 200–250 °C in the presence of maleic anhydride (Scheme 13).[99] In contrast, di-*t*-butyl methylenemalonate, a stable clear liquid, can be prepared by normal Knoevenagel condensation of di-*t*-butyl malonate and paraformaldehyde in acetic acid in the presence of potassium acetate and copper(II) acetate.[100]

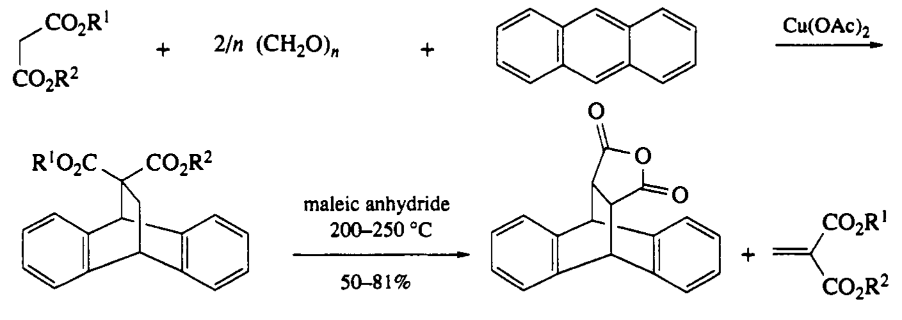

**(66)** **(65)**

**Scheme 13**

With some methylene active compounds ($NCCH_2PO(OEt)_2$) competition between Knoevenagel and Wittig–Horner reactions has been observed; the ratio of Knoevenagel and Wittig–Horner products is dependent upon the reaction conditions.[16,17]

Another non-trivial problem with Knoevenagel compounds that contain a γ-hydrogen atom is their tendency to undergo isomerization to β,γ-unsaturated products.[101,102] It has been observed that the ratio of α,β- and β,γ-isomers is dependent upon the nature of the amine catalyst used. Separation of α,β- and β,γ-isomers is usually difficult, but has been achieved in a few cases.[71,103]

### 1.11.2.7 Analytical Applications

The Knoevenagel condensation with 1,3-dicarbonyls followed by a Michael reaction of a second molecule of the methylene compound, with or without addition of an amine or ammonia, may be used for the qualitative and quantitative determination of aldehydes even in the presence of ketones. Thus, cyclic β-diketones such as dimedone (**59**) react with aldehydes but not with ketones in the absence of a catalyst. For the characterization the bis(2,6-dioxo-4,4-dimethylcyclohexyl)methanes (**67**) or the 4,6-dioxo-2,2,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-9*H*-xanthene (**68**) may be used.[93,104,105]

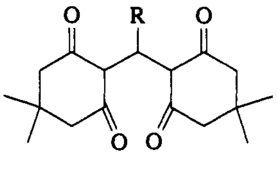

**(67)**

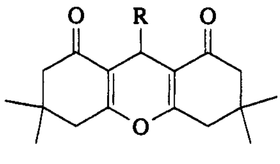

**(68)**

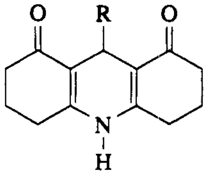

**(69)**

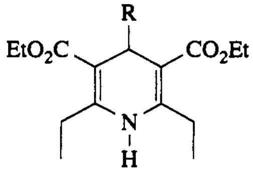

**(70)**

For fluorimetric measurements aldehydes are transformed to 9-substituted-1,8-dioxodecahydroacridines (**69**) by reaction with 1,3-cyclohexanedione and ammonia in aqueous acetic acid.[106] The acridine derivative (**69**) obtained from acetaldehyde absorbs at $\lambda_{max}$ = 360 nm and emits at 470 nm in acidic medium, allowing the detection of as little as 0.2 μg of aldehyde. Finally, aldehydes can also be selectively determined in the presence of ketones by reaction with diethyl 3-oxoglutarate and ammonia to give dihydropyridines (**70**), which show a strong absorption at $\lambda_{max}$ = 340 nm.[107] The difference in reactivity of ketones and aldehydes in the Knoevenagel reaction can be used to purify ketones. This process has some economical relevance and has been used to separate a mixture of glucose and fructose obtained by hydrolysis of sucrose over a cation exchanger. Stirring of the mixture with ethyl acetoacetate in the presence of $CaCl_2$ gives a solid glucose adduct; fructose can be obtained as a syrup of >95% purity.[108]

## 1.11.3 SCOPE AND LIMITATION

### 1.11.3.1 Variation of the Active Methylene Compound

The active methylene compounds $XCH_2Y$ can be divided into cyclic and acyclic, into symmetrical and unsymmetrical compounds and into compounds that contain either carbon or heteroatoms at positions 1 and 3. The groups X and Y can be $CO_2R$, $CONR_2$, COR, CN, $CNNR_2$, Ar, $NO_2$,[109] $PO(OR)_2$, $SO_2OR$, $SO_2NR_2$, $SO_2R$, SOR, SR and $SiR_3$ or similar functional groups (R = H, alkyl, aryl). General overviews on the variation of active methylene compounds[3] and on malonodinitrile[110,111] have appeared.

#### *1.11.3.1.1 Malonic esters*

Most aldehydes easily undergo Knoevenagel condensation using secondary amines or their salts as a catalyst.[3] Under standard conditions, reaction of simple unbranched aliphatic aldehydes and of most ketones is difficult. However, the use of $TiCl_4$/amine allows reaction even of refractory aldehydes and a multitude of ketones in good to very good yields.[112,113] For example, the synthesis of Knoevenagel adducts (**72**) from 5-formyl-octaethylporphyrin (**71**) and different malonic esters in the presence of $TiCl_4$/pyridine at 0 °C has been achieved in 75–94% yield.[114]

Usually the Knoevenagel condensation yields the unsaturated product, but, with appropriate aldehydes, β-hydroxymalonates can be isolated.[62] The unusual formation of an α-naphthol (**74**) has been reported from the reaction of diphenylacetaldehyde (**73**) with diethyl malonate under Knoevenagel conditions.[115] Condensation of salicylaldehydes and other aromatic *o*-hydroxy aldehydes with malonates is still in use for the synthesis of the corresponding coumarin-3-carboxylic esters (**75**).[3,116–118] Reduction of several coumarins (**75**) to yield 3-substituted-3,4-dihydrocoumarin-3-carboxylic esters has been achieved using boranes.[118] Steroidal α-pyrones (**77**) have been obtained in one step from α-ketohydroxymethylene compounds (**76**) in a $TiCl_4$-mediated Knoevenagel condensation with dimethyl malonate followed by intramolecular cyclization.[119]

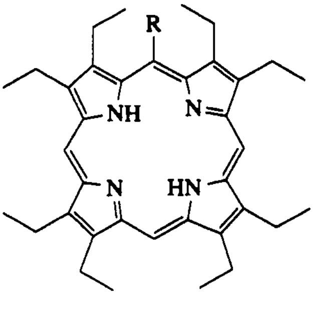

(**71**) R = CHO

(**72**) R = $HC{=}C(CO_2R^1)_2$

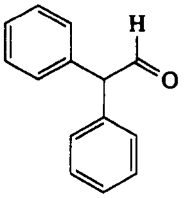

(**73**)

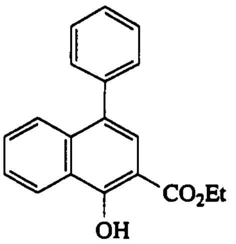

(**74**)

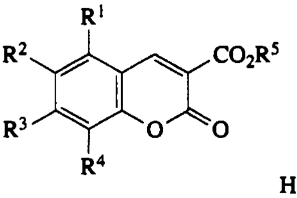
R1
R2
CO2R5
R3
O
O
R4

(**75**)

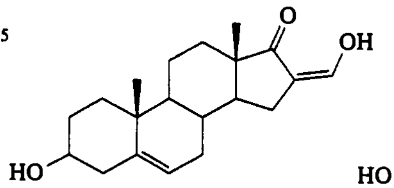

(**76**)

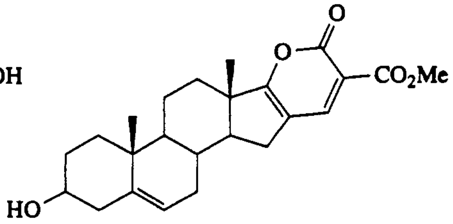

(**77**)

### *1.11.3.1.2 Meldrum's acid and derivatives*

Meldrum's acid undergoes standard Knoevenagel condensations with aromatic and heteroaromatic aldehydes,[120,121] with hindered aliphatic aldehydes $R^1R^2R^3CCHO$[48] and with reactive, simple aliphatic ketones.[121–123] Condensation with less reactive ketones can be performed in the presence of $TiCl_4$/amine[124,125] or by prior conversion of the ketone into the corresponding ketimine.[48] The reaction with simple aliphatic aldehydes under standard conditions usually gives the corresponding Michael products as described in Section 1.11.2.6. Knoevenagel condensations of some other cyclic esters of malonic acid have also been reported.[126,127]

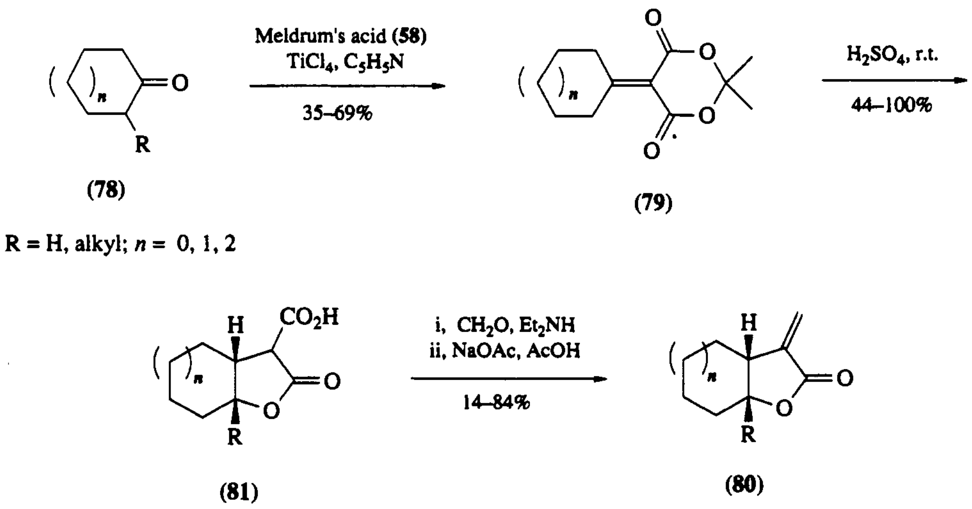
O
R
(78)
R = H, alkyl; n = 0, 1, 2
Meldrum's acid (58)
TiCl4, C5H5N
35–69%
O
O
O
O
(79)
H2SO4, r.t.
44–100%
H
CO2H
O
O
R
(81)
i, CH2O, Et2NH
ii, NaOAc, AcOH
14–84%
H
O
O
R
(80)

**Scheme 14**

The 1,4-addition of nucleophiles to Knoevenagel products of Meldrum's acid has been widely used synthetically. The products of the addition of Grignard reagents can be degraded to yield monocarboxylic acids and monocarboxylic esters, respectively.[128] Although hydrolysis of Knoevenagel products in aqueous methanol yields Meldrum's acid and the corresponding aldehyde or ketone, with a trace of hydrochloric acid in ethanol half-esters of 2-methylenemalonates are obtained.[66,120]

An interesting route to α-carboxy-δ-lactones (**81**) and α-methylenelactones (**80**), based on hydrolysis of Knoevenagel products (**79**) of Meldrum's acid with cyclic aliphatic ketones (**78**), has been developed (Scheme 14).[129] Reduction of 5-methylene derivatives of Meldrum's acid has been performed catalytically[130] or by use of LAH.[48] Imidoylation reaction of Meldrum's acid and subsequent solvolysis of the resulting (**82**) yields β-enamino esters (**83**) in good yields.[131,132] Flash vacuum pyrolysis of alkylidene derivatives of Meldrum's acid can be used to prepare methylene ketenes (**84**), a class of compounds difficult to prepare by conventional methods. By this procedure, methylene ketenes are obtained from aromatic aldehydes and ketones and from aliphatic ketones in only two steps.[133,134] Intramolecular trapping of the methylene ketene obtained from the ketone (**85**) has been used successfully in the synthesis of the naphthol (**86**).[133]

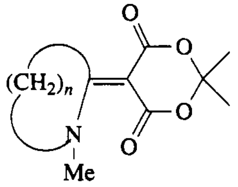

**(82)**

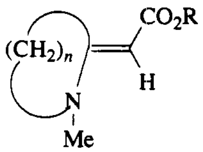

**(83)**

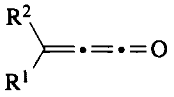

**(84)**

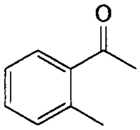

**(85)**

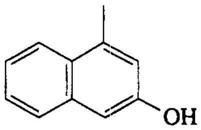

**(86)**

### 1.11.3.1.3 Malonic acid

Malonic acid undergoes Knoevenagel condensations with nearly every type of aldehyde and with very reactive ketones.[3] If condensations with malonic acid are performed in ethanolic ammonia below 70 °C, the methylenemalonic acids are usually obtained. If, however, the condensations are performed in pyridine (Doebner modification), decarboxylation normally takes place and the acrylic or cinnamic acid is

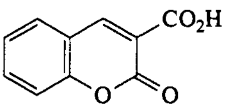

**(87)**

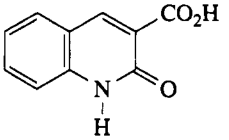

**(88)**

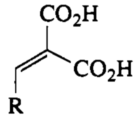

**(89)**

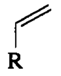

**(90)**

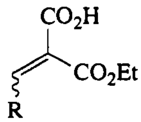

**(91)**

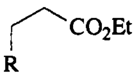

**(92)**

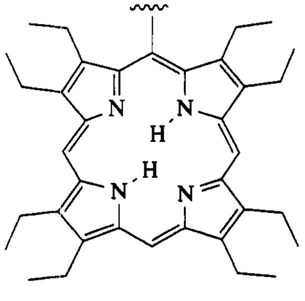

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formed (see also Section 1.11.2.3). In these reactions the double bond isomer with the carboxyl group *trans* to the larger substituent is usually obtained (see also Section 1.11.2.5).[3,135,136] A problem with condensations of malonic acid is the isomerization of the α,β-isomer to the β,γ-isomer.[3,84] Coumarin-3-carboxylic acid (**87**) and related compounds are obtained in the reaction of salicylaldehyde and other 3-hydroxy aldehydes with malonic acid.[3,26,117] Finally, reaction of *o*-aminobenzaldehyde with malonic acid yields 2(1*H*)-quinolone (**88**).[3] The condensation of aldehydes with 2-alkylmalonic acids is of limited synthetic value as the reaction is susceptible to steric hindrance.[3] In these cases the β-hydroxy acids instead of α-alkyl-α,β-unsaturated acids can be obtained, depending on the reaction conditions.[58,60,137] An example from the porphyrin field illustrates the problem of prediction in chemical reactivity. Condensation of 5-formyloctaethylporphyrin with malonic acid delivers compound (**89**) which is double decarboxylated under conditions of catalytic hydrogenation to give (**90**). The desired compound (**92**), however, is obtained by hydrogenation of half-ester (**91**).[114] Monoalkyl malonates, obtained by partial hydrolysis of dialkyl malonates, show a reactivity similar to malonic acid. The Knoevenagel reaction is usually accompanied by decarboxylation, giving a cinnamic ester.[138,139] Addition of halogen to the double bond with subsequent dehydrohalogenation is a method for the preparation of alkynic acid esters.[140]

### *1.11.3.1.4 Mono- and di-amides of 1,3-diacids*

Malonomonoamides can be condensed with aldehydes to give acrylamides or cinnanamides, but condensation with malonodiamides is of only minor importance.[3] In contrast to Meldrum's acid (**58**), Knoevenagel reactions of barbituric acid (**56**) and *N*,*N*-dimethylbarbituric acid have been less explored. However, several aliphatic, aromatic and heteroaromatic aldehydes are known to react easily and with high yields in most cases.[57,87,88] Reactions of 1,2-dimethyl-3,5-pyrazolidinedione (**93**) with several aliphatic and aromatic aldehydes using standard conditions yield Knoevenagel products in good yield.[141] A similar reactivity is observed with 2-phenyl-3,5-dioxoisoxazolidine (**94**)[142] and oxazepanediones (**45**; see Section 1.11.2.5).[34,82] Recently, the oxidations of alcohols to carbonyl compounds and thiols to disulfides with 5-arylidene-1,3-dimethylbarbituric acids (**95**) have been described. Mechanistically (**95**) mimics enzymic oxidation by flavin adenine dinucletide (FAD).[143]

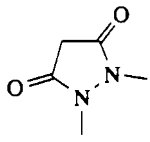

**(93)**

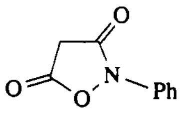

**(94)**

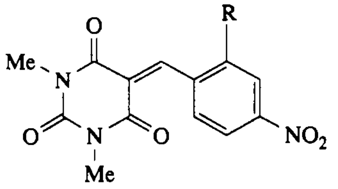

**(95)** R = H, $NO_2$

### *1.11.3.1.5 1,3-Diketones*

Aromatic aldehydes condense with acyclic 1,3-diketones to yield the α,β-unsaturated Knoevenagel products exclusively.[3,144–148] With aliphatic aldehydes, particularly those that are α-branched, the situation is somewhat more complex as the α,β-unsaturated Knoevenagel products (**96**) tend to isomerize to enolic β,γ-unsaturated products (**97**) that are stabilized by intramolecular chelation.[3,14,71,102,103,145] At higher temperatures or with prolonged reaction times Michael addition products are formed.[3] However, to bring about Knoevenagel condensations with 1,3-diphenyl-1,3-propanedione and similar compounds, higher temperatures must usually be employed.[146] In the reaction of the ethyl acylpyruvate (**98**) with benzaldehyde γ-lactone (**100**) is obtained, probably *via* intermediate (**99**).[149] The condensation of 1,1,1-trifluoroacetylacetone with aromatic aldehydes using piperidine/AcOH is a relatively slow reaction, and gives not only the expected product (**101**), but (**102**) as well.[150]

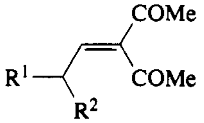

**(96)**

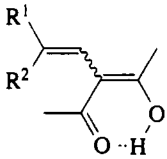

**(97)**

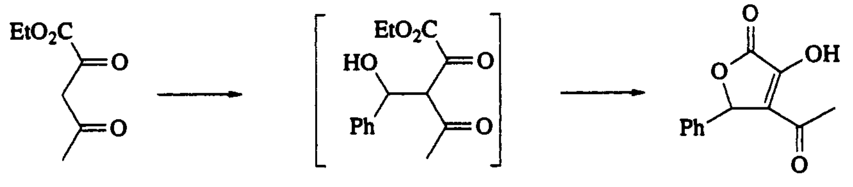

**(98)** **(99)** **(100)**

Hydrogenation of Knoevenagel products of 2,4-alkanediones over Raney nickel provides a simple route to 3-substituted 2,4-diones.[145] Alternatively, reductive deacetylation can be accomplished using tetracarbonylhydridoferrate(0) in ethanol to prepare alkyl ketones. If the reaction is carried out in THF or acetone, exclusive reduction of the α,β-unsaturated double bond is observed.[146,151] Reactions of aldehydes with cyclic 1,3-diketones generally lead to the formation of Michael adducts under standard conditions.[91] Indane-1,3-dione (**103**) yields Knoevenagel products with different aldehydes, ketones and ketimines, whereas perinaphthindane-1,3-dione (**104**) gives the Michael adducts.[48]

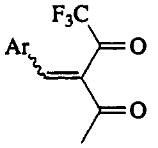

**(101)**

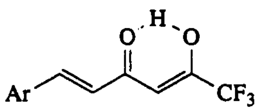

**(102)**

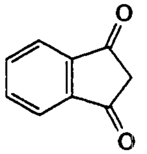

**(103)**

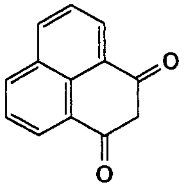

**(104)**

### *1.11.3.1.6 Malondialdehyde*

Stable and isolable derivatives of methylene malondialdehydes are not accessible using standard Knoevenagel methodology.[152] However, they have been prepared *in situ* in the synthesis of cephalosporin C,[153] iridoids and secoiridoids.[154,155] Arnold *et al.* have recently succeeded in the synthesis, isolation and characterization of methylenemalondialdehydes (**106**) by exploitation of the reactivity of polymethinium salts (**105**) toward electrophilic reagents as shown in Scheme 15. Detailed studies have revealed that reaction takes place with aromatic, heteroaromatic, aliphatic unsaturated aldehydes and different types of dialdehydes. The method has also been used for the synthesis of diarylmethylene aldehydes. The reactivity of these compounds is governed by the strongly electron-deficient β-carbon atom. Michael additions with a series of CH-acidic compounds, amines, phosphines and different inorganic anions such as $CN^-$, $CNO^-$ and $N_3^-$, have been studied.[156,157]

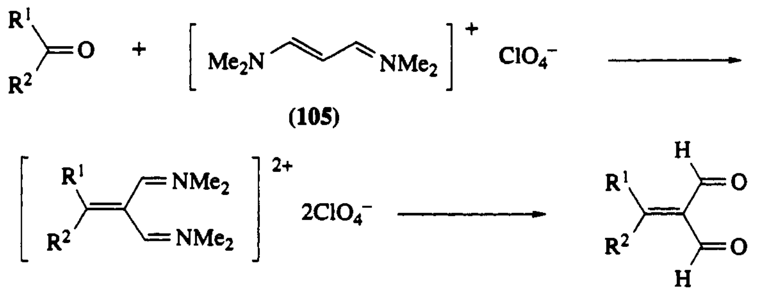

**(105)**

**(106)**

Scheme 15

### *1.11.3.1.7 Malonodinitrile*

Syntheses with malonodinitrile, including Knoevenagel condensations, have been reviewed extensively[3,110,111] Malonodinitrile is one of the most reactive methylene compounds employed in the Knoevenagel condensation and alkylidene and arylidene malonodinitriles are readily available. In many cases the condensation proceeds satisfactorily without any added catalyst, although it is efficiently catalyzed by weak bases like ammonium acetate and piperidinium acetate or amino acids like β-alanine.[10] Several other catalysts, including potassium fluoride[11,12], aluminum oxide,[16] aluminum phosphate/aluminum oxide[18] and xonotlite–potassium *t*-butoxide,[19] have also been used. Recently, ylidene malonodinitriles have been prepared by reaction of an organometallic reagent (**107**) with a nitrile (**108**) to produce a metal ketimate intermediate (**109**), which gives the desired ylidene malonodinitrile (**110**) upon treatment with 2 equiv. of malonodinitrile (Scheme 16).[158] The Knoevenagel condensation of malonodinitrile with aldehydes and ketones followed by cyclization has been used widely for the synthesis of a multitude of carbocycles and heterocyclic compounds (see Section 1.11.5.1).[110,111]

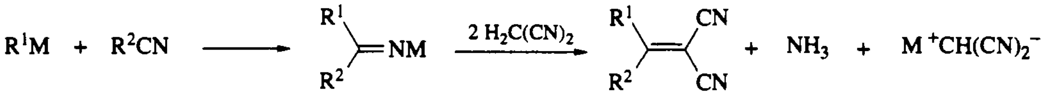

**(107)** **(108)** **(109)** **(110)**

**Scheme 16**

Ylidene malonodinitriles are known to undergo 1,4-addition reactions with a wide range of nucleophiles.[3,110,111,159] Reduction of the double bond can be performed by the Meerwein–Ponndorf–Verley reaction, $NaBH_4$, $LiBH_4$ or *N*-alkyl-1,4-dihydronicotinamides, to give the corresponding substituted malonodinitriles.[3,159] Conjugate addition of Grignard reagents to methylidenemalonodinitriles gives 2-substituted malonodinitriles.[160] Reaction at the δ-position of alkylidene malonodinitriles can be accomplished with secondary amines and orthoformates to provide access to 4-amino-1,1-dicyano-1,3-butadienes in moderate to good yields.[161]

### *1.11.3.1.8 β-Keto esters and β-keto acids*

A wide range of catalysts and reaction conditions have been developed to bring about Knoevenagel condensations of β-keto esters.[3,162] A useful procedure involves the use of $TiCl_4$/pyridine in THF at low temperatures, which allows formation of methyleneacetoacetates from aliphatic, aromatic and heteroaromatic aldehydes.[162] Knoevenagel reactions of β-keto esters with hydroxy aldehydes and ketones are followed by ring closure to give 3-acylcoumarins (**111**), acylfuranones (**112**) and dihydropyranones (**113**).[3] Similar reactions have been reported with *o*-aminobenzaldehydes.[3] The tendency of the alkylidene-β-keto esters to form Michael adducts with carbonyl compounds at elevated temperatures has been widely exploited in the synthesis of 1,5-diketones (**114**) that can cyclize to give cyclohexenones (Scheme 17).[163] Reaction between aromatic aldehydes and 4-hydroxy-6-methyl-2-pyrone (**116**) affords the Knoevenagel product only as an intermediate that reacts with a second molecule of (**116**) or added thiols to yield the corresponding Michael adducts (**117**) or (**118**).[164] In contrast to β-keto esters, the corresponding β-keto acids have received little attention with respect to the Knoevenagel condensation. However, the reaction of β-keto acids with aliphatic aldehydes is a good method for the stereoselective preparation of (*E*)-α,β-

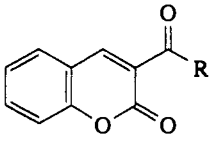

**(111)**

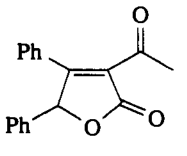

**(112)**

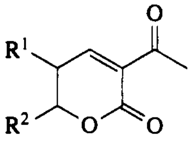

**(113)**

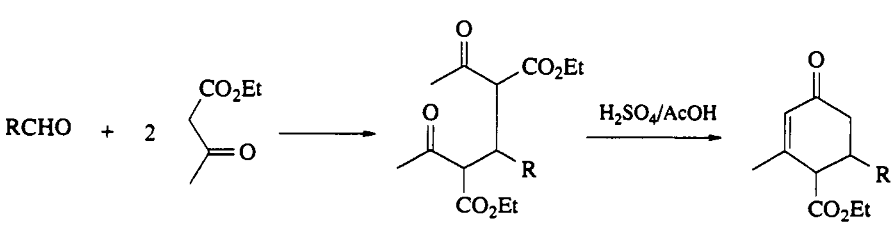

**(114)** **(115)**

**Scheme 17**

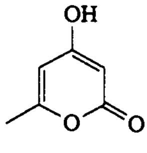

**(116)**

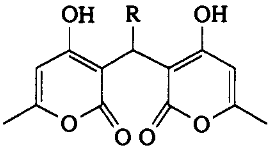

**(117)**

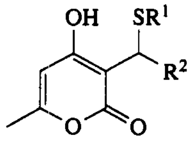

**(118)**

unsaturated ketones. Aromatic aldehydes are less reactive and give β-ketols in some cases.[165a] Formyl acetate can not be used for Knoevenagel reactions because of its instability. However, 4,4,4-trichloro-3-oxobutanal may be employed as an equivalent.[165b]

### *1.11.3.1.9 Cyanoacetic esters, cyanoacetic acid and isocyanoacetic esters*

Like malonodinitrile, cyanoacetic esters are sufficiently reactive to undergo Knoevenagel condensation with a wide variety of aldehydes and ketones. In contrast to the reaction with malonodinitrile, only the Knoevenagel products and usually no Michael adducts are obtained under standard conditions. Nearly all known Knoevenagel catalysts can be successfully employed.

Condensations with aldehydes are stereoselective, yielding the stereoisomer in which the β-alkyl or β-aryl group is *cis* to the smaller cyano function (see Section 1.11.2.5). Some side products that originate from the reaction of benzaldehydes with ethyl cyanoacetate are formed.[166] Reaction of *o*-hydroxybenzaldehyde with ethyl cyanoacetate affords (**119**), arising from attack of the phenol oxygen at the cyano group. The imino lactone (**119**) thus obtained can be hydrolyzed to yield lactone (**120**).[16,18] The synthesis of substituted dihydrothiophenes has been accomplished starting with the unsaturated (*Z*)-aldehyde (*Z*)-(**121**). Michael addition of a second molecule of cyanoacetate to the initially formed Knoevenagel product (*Z*)-(**122**), followed by elimination of HCN, yields (**123**). With the (*E*)-aldehyde (*E*)-(**121**) the reaction stops at (*E*)-(**122**).[167] Stereoselective cyclopropane formation is accomplished by reaction of the α-anions of compounds containing allylic or benzylic nitro groups with alkylidene and benzylidene cyanoacetates (Scheme 18).[168] α-Naphthols are formed by heating the Knoevenagel products of ethyl cyanoacetate and benzyl ketones.[3,169] Mixtures of stereoisomers of α,β-unsaturated nitriles are obtained under Krapcho conditions from alkylidene cyanoacetates.[170] Reduction of the methylene cyanoacetates has been performed by using $NaBH_4$[171] and by catalytic hydrogenation[171,172] to yield substituted cyanoacetates or by LAH to yield amino alcohols.[173] The conversion of Knoevenagel products from steroidal ketones and ethyl cyanoacetate to the corresponding α-keto esters is possible.[171]

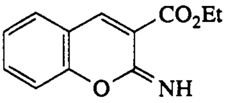

**(119)**

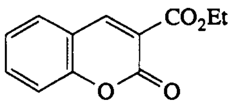

**(120)**

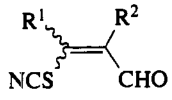

**(121)**

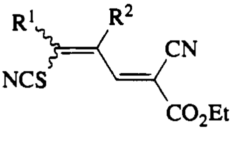

**(122)**

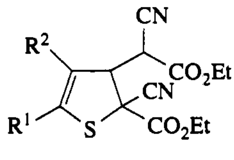

**(123)**

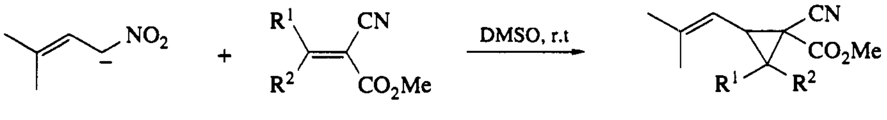

**Scheme 18**

No substantial developments on Knoevenagel condensations with cyanoacetic acid have emerged in the last few years. As in the reaction with cyanoacetates, Knoevenagel products can be obtained from aldehydes and different ketones using ammonia and ammonium salts, primary and secondary amines and their salts, amino acids and ion-exchange resins as catalysts. α,β-Unsaturated nitriles are obtained when pyridine or pyridine/piperidine is used as the catalyst at a higher temperature.[3] The isocyanide group also has an activating effect on the α-methylene group. Thus, isocyanoacetates react with aldehydes or ketones in the presence of bases such as DBU or Bu$^t$OK. Instead of the normal Knoevenagel products, α-formylaminoacrylates are formed (Scheme 19).[174,175]

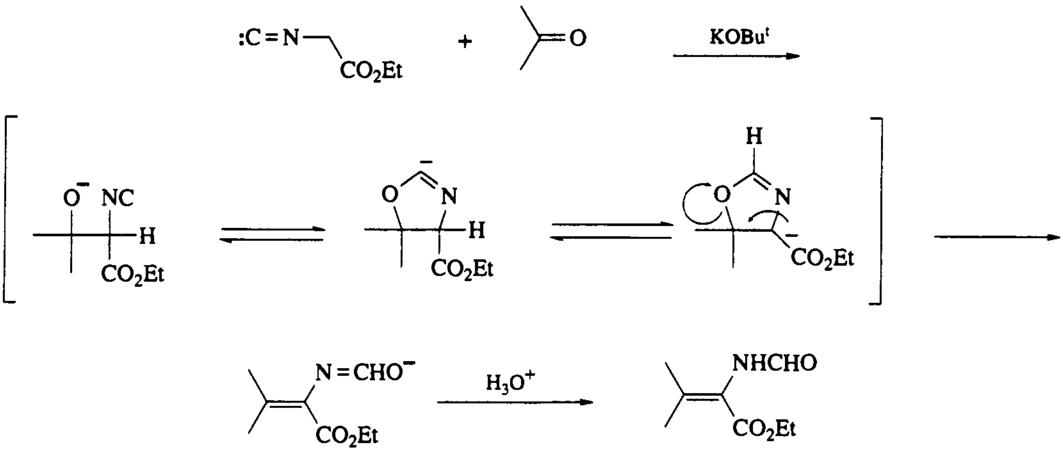

Scheme 19

### 1.11.3.1.10 Cyanoacetamides, thiocyanoacetamides and β-keto nitriles

Cyanoacetamides yield α-cyanoacrylamides (**124**) stereoselectively upon reaction with aldehydes and nonselectively with ketones under standard Knoevenagel conditions.[3] α-Cyanoacrylamides (**124**) are also obtained by partial hydrolysis of methylenemalonodinitriles.[158] With 1,3-diketones, *e.g.* acetylacetone, pyridones like (**125**) are formed upon reaction with cyanoacetamides.[176] Base-catalyzed dimerization of α-cyanoacrylamides (**124**) yields piperidones.[176]

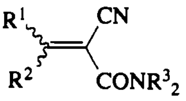

**(124)**

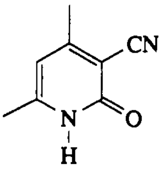

**(125)**

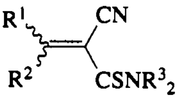

**(126)**

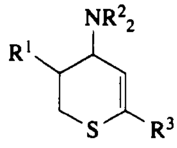

**(127)**

The Knoevenagel reaction of aromatic and heteroaromatic aldehydes with cyanothioacetamides affords α-cyanothioacrylamides (**126**), which easily undergo thermal dimerization to 3,4-dihydro-2*H*-thiopyrans (**127**).[177] α-Keto-substituted acrylonitriles are synthesized by condensation of β-keto nitriles with aldehydes or ketones.[3,178] Benzoylacetonitrile self-condenses to afford (**128**), which can be transformed

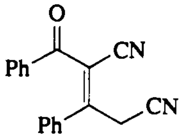

**(128)**

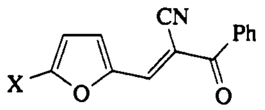

**(129)** X = $NO_2$, Br, PhS, $PhSO_2$

to different heterocycles such as pyrazoles and pyridazines.[179] Substituted furancarbaldehydes react with benzoylacetonitrile and other activated acetonitriles to give Knoevenagel products (**129**) in good yield.[180]

### *1.11.3.1.11 Derivatives of arylacetic acid*

Condensations of arylacetic acids, arylacetates and arylacetonitriles with aromatic aldehydes and ketones proceed under standard Knoevenagel conditions, providing access to stilbenes or substituted stilbenes.[3,59,181–184] Thus 3-nitrobenzaldehyde and 4-nitrophenylacetic acid react in the presence of different amines to give (**130**), (**131**) and (**132**). The ratio of the products varies greatly with the amine used. (**131**) and (**132**) could easily be transformed into (**130**) in high yield.[59] Reaction of arylacetates with *o*-hydroxybenzaldehydes yields the corresponding coumarins.[3] The condensation of 2-hydroxy-4-methoxybenzaldehyde (**133**) with pyridylacetates like (**134**) yields 7-methoxy-3-pyridylcoumarins like (**135**); (Scheme 20).[184]

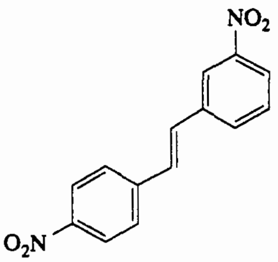

**(130)**

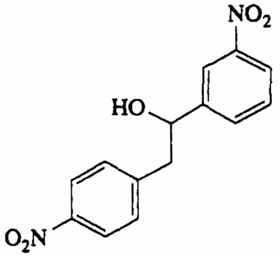

**(131)**

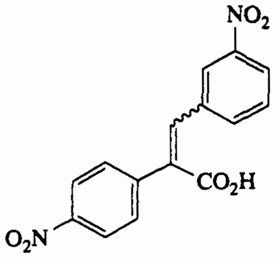

**(132)**

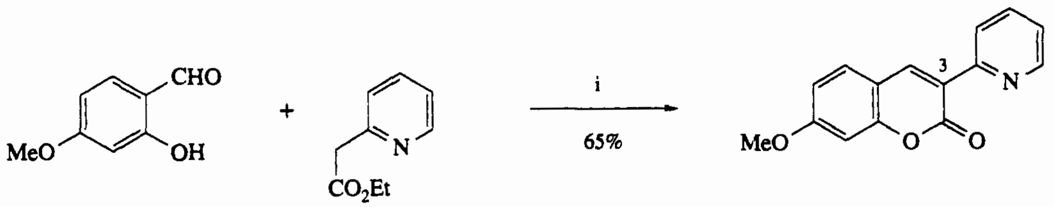

**(133)** **(134)** **(135)**

i, pyridine, isopropyl alcohol, reflux, 8 h

Scheme 20

### *1.11.3.1.12 Methylenes activated by sulfur-containing functional groups*

Knoevenagel condensations with methylenes activated by sulfur-containing functionalities have been less explored than reactions with typical 1,3-dicarbonyl compounds. Mostly sulfones and sulfoxides, but also sulfonic acid derivatives, have been used.[185] Aliphatic and aromatic aldehydes react with sulfonylacetates (**136**) to give α-sulfonyl-α,β-unsaturated esters in good yields using piperidine as catalyst.[56,186] The (*E*)-configuration of the products has been proven (see Section 1.11.2.5). Dealkoxycarbonylation of Knoevenagel products (**138**) with LiI in DMF provides a useful route to (*E*)-α,β-unsaturated sulfones

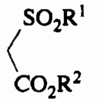

(**136**) $R^2$ = alkyl
(**137**) $R^2$ = H

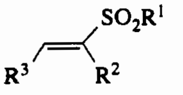

(**138**) $R^2 = CO_2R$
(**139**) $R^2$ = H

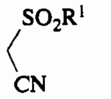

**(140)**

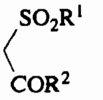

**(141)**

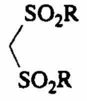

**(142)**

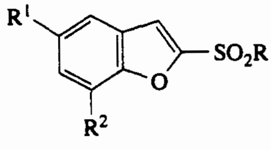

**(143)**

(**139**), which cannot be obtained in reasonable yield by direct condensation with sulfonylacetic acid (**137**).[72]

Knoevenagel condensations have also been performed with unsymmetrical active methylenes like (**140**), (**141**)[56,186,187] and symmetrical compounds (**142**).[188,189] Reaction of (**142**) with aliphatic aldehydes affords only the β,γ-unsaturated condensation products.[188] Reaction of (**142**) with salicylaldehydes in the presence of piperidine followed by acidification yields 2-alkylsulfonylbenzofurans (**143**).[189]

The condensation of aromatic and aliphatic aldehydes with sulfoxide-activated methylenes like phenylsulfinylacetonitriles and phenylsulfinylacetates selectively forms α-sulfinyl-α,β-unsaturated carbonyl compounds (**144**) with the alkyl or aryl group *trans* to the sulfinyl group (see Section 1.11.2.5).[52,73,186,187] Oxidations of (**144**) with *m*-chloroperbenzoic acid yield the unsaturated (*E*)-sulfones (**138**) and reductions with $NaI/(CF_3CO)_2O$ give (*E*)-α-phenylthioacrylates (**145**).[56] With cyclic sulfoxides (**146**) and (**147**), however, benzylidene products with (*Z*)-configurated double bonds are obtained on reaction with aromatic aldehydes.[190] α-Phenylsulfinylacrylates (**148**) undergo acid-induced vinylogous Pummerer rearrangement yielding γ-oxygen-functionalized products (**149**).[191] Michael reactions involving enantiomerically pure α-sulfinyl-α,β-unsaturated carbonyl compounds are of particular interest, as they provide access to optically active addition products. This approach has been applied for the preparation of enantiomerically pure β-substituted cyclopentanones, β-alkylcarboxylic acids and other useful intermediates for the synthesis of natural products. However, it must be pointed out that optically active α,β-ethylenic sulfoxides have not been prepared by the Knoevenagel condensation.[192]

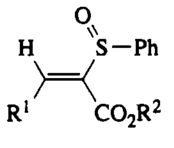

(**144**)

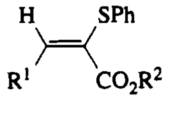

(**145**)

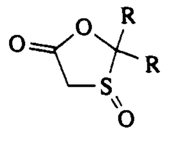

(**146**)

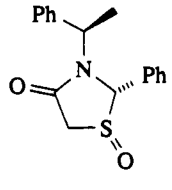

(**147**)

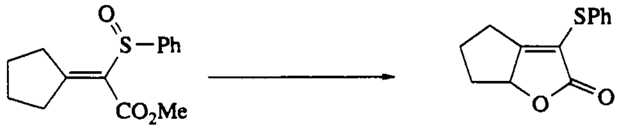

(**148**) (**149**)

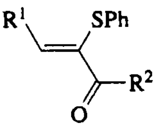

(**150**)

Knoevenagel condensations of β-carbonyl aryl sulfides and similar compounds have been little studied.[186,193,194] β-Cyano aryl sulfides undergo condensation with a number of aromatic aldehydes and ketones in modest yield, but β-ethoxycarbonyl aryl sulfides fail to form Knoevenagel products.[186,193] In contrast to the results obtained with sulfonyl- and sulfinyl-containing active methylenes, condensations with β-keto sulfides yield α-sulfenyl-α,β-unsaturated compounds (**150**) with the (*Z*)-configuration at the double bond, that is, with the alkyl group *cis* to the sulfinyl moiety.[56] Oxidation of these compounds gives access to unsaturated sulfines and sulfones with the (*Z*)-configuration.[56]

### *1.11.3.1.13 Phosphonates*

The anions of cyanophosphonates and alkoxycarbonylphosphonates are generally used for Wittig–Horner alkenation. However, under appropriate conditions, Knoevenagel condensations can be observed.[16,17] Reactions of triethylphosphonoacetic acid with aliphatic aldehydes, aromatic aldehydes, or aromatic ketones in the presence of $TiCl_4$/*N*-methylmorpholine yield Knoevenagel condensation products with the thermodynamically more stable (*E*)-configuration (**41**).[78] The corresponding (*Z*)-configured products (**42**) can be obtained using titanated triethylphosphonoacetate (**38**) (see Section 1.11.2.5).[35] In an intramolecular Knoevenagel condensation phosphonate (**151**) affords cyclopentenone (**152**).[195] Vinylic phosphonates undergo a variety of reactions.[8,196–200] Tetraalkyl alkylidene- and benzylidene-diphosphonates (**153**) can be prepared from tetraalkyl diphosphonates and aromatic or α-substituted aliphatic aldehydes using $TiCl_4$/amine as the condensing reagent.[78] A preparation of methylidenediphosphonates has also been reported.[201]

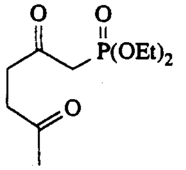

**(151)**

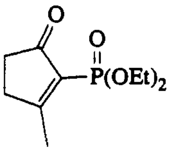

**(152)**

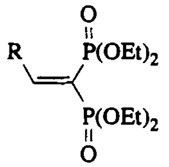

**(153)**

### 1.11.3.1.14 *Methylenes activated by nitro groups*

Reactions of carbonyl compounds with nitroalkanes like nitromethane (Henry reaction) are described in Volume 2, Chapter 1.10. The doubly activated ethyl nitroacetate readily reacts with aliphatic, aromatic and heteroaromatic aldehydes to give $\alpha,\beta$-unsaturated-$\alpha$-nitrocarboxylic acid esters in the presence of $TiCl_4$/*N*-methylmorpholine as mixtures of *cis* and *trans* isomers.[162]

### 1.11.3.1.15 *Pyrazolones and isoxazolones*

Pyrazolones (**154**) and isoxazolones (**155**) can also be used in the Knoevenagel reaction. Thus condensations with aliphatic aldehydes, aromatic aldehydes and ketones in the presence of ethylenediammonium diacetate or other typical catalysts provide the corresponding alkylidene and benzylidene compounds in good yields (for stereochemistry see Section 1.11.2.5).[79–81,202,203] A new method involves the use of dicyclohexylcarbodiimide at 20 °C without an additional catalyst.[204]

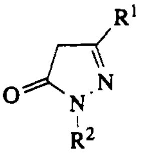

**(154)**

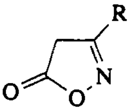

**(155)**

### 1.11.3.1.16 *Methylenes activated by heterocycles*

Certain heteroaromatic compounds that have acidic methyl groups are effective in the Knoevenagel condensation. 6-Methyl-1,3,5-triazine (**156**), 2-methylpyridine *N*-oxides (**157**), quinolines and pyrimidines all condense with aromatic aldehydes in the presence of the usual catalysts. An example of a doubly activated methylene compound in which one activation group is a heterocycle is the 2-oxopropylthiazole (**158**), which condenses with a number of aldehydes.[205–207]

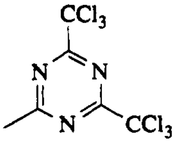

**(156)**

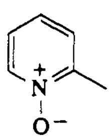

**(157)**

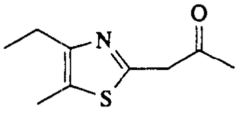

**(158)**

## 1.11.3.2 Variation of the Carbonyl Compound

There is almost no restriction in the choice of an appropriate electrophile in the Knoevenagel reaction. Aldehydes, ketones, thioketones, imines, enamines, acetals and orthoesters have been used. With less reactive methylene groups, however, drastic reaction conditions may be necessary. Steric effects have a significant influence on the rate and unexpected compounds are often obtained as a result of secondary reactions. Reaction of 1,3-dicarbonyl compounds with carbon disulfide followed by dialkylation with an alkyl halide give diacylketene-*S*,*S*-acetals (**159**). However, even with highly acidic dicarbonyl compounds, strong bases such as sodium hydride in DMF must be used for this reaction (Scheme 21).[208–210] The reactivity of the electrophilic reactant decreases in the order aldimine > aldehyde > ketimine > enamine > ketone. Branched compounds are generally less reactive than the unbranched analogs. In accord with the second-order kinetics observed for the reaction of malonodinitrile with benzaldehyde in alcohol, the reaction rate decreases in the order *p*-nitrobenzaldehyde > benzaldehyde > 4-methoxybenzaldehyde.[211] Similar results are obtained with ethyl cyanoacetate in boiling ethanolic triethylamine.[212] As mentioned already, using highly reactive 1,3-dicarbonyl compounds such as Meldrum's acid, the main deleterious side reaction is Michael addition. However, condensation of Meldrum's acid with aliphatic aldehydes having less than two hydrogens at the α-position with piperidine or pyridine and a small amount of acetic acid gives excellent yields of condensation products. Similarly, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups and a variety of heteroaromatic aldehydes (furan, pyrrole, indole, pyridine) readily react with Meldrum's acid. Even ferrocenylcarbaldehyde (**160**) gives 91% yield of the desired product. In contrast, α-unbranched aldehydes do not afford the Knoevenagel products (see Section 1.11.2.6).[48]

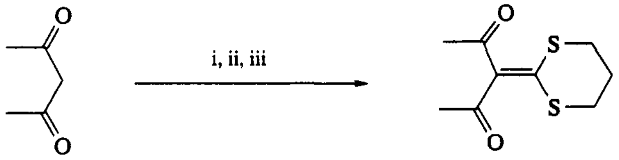

**(159)**

i, NaH; ii, $CS_2$; iii, $Br(CH_2)_3Br$

**Scheme 21**

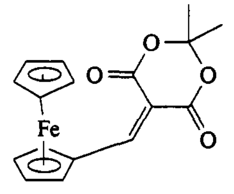

**(160)**

α,β-Unsaturated aldehydes react with 1,3-dicarbonyl compounds in the presence of piperidine or triethylamine to give the Knoevenagel adducts in only modest yield (42–74%).[213–215] Crotonaldehyde reacts with malonic acid in acetic acid to give the expected alkylidenemalonic acid, but if the reaction is carried out in pyridine hexadienoic acid is formed in 30% yield.[95] Alkynic aldehydes such as trimethylsilyl-2-propynal can also be used.[214] Aromatic aldehydes with electron-donating or electron-withdrawing groups give good yields in most Knoevenagel condensations. Many reactions of this type are known and the procedure is widely used for the construction of heterocyclic systems (see Section 1.11.5.1). The reactions of aldehydes with nitroalkanes to give nitro alcohols are usually rapid, but elimination of water to give nitroalkenes takes place only upon acidification of the reaction mixture or azeotropic removal of water in the presence of piperidine. By the latter method 1-nitromethylcycloheptene (**161**) has been prepared in 60% yield from cycloheptanone and nitromethane (Scheme 22).[215,216] With $ZnCl_2$ as catalyst, aromatic and heteroaromatic aldehydes can be transformed directly to β-nitrostyrene derivatives. Thus, benzaldehyde and nitromethane at 160 °C give 56% of β-nitrostyrene.[217] Dialdehydes may also be used

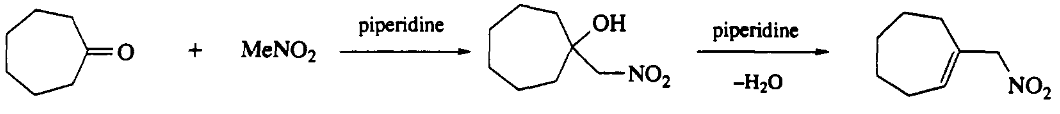

**(161)**

**Scheme 22**

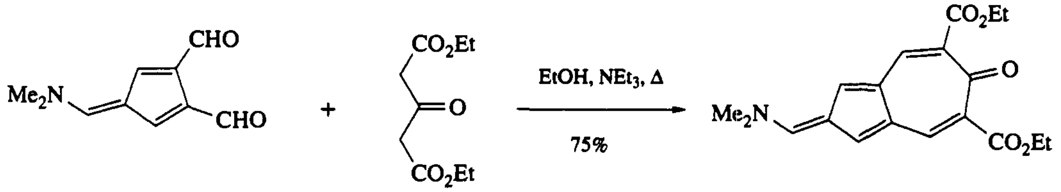

**(162)** **(163)** **(164)**

**Scheme 23**

in the Knoevenagel condensation. An interesting example is the reaction of 2,3-diformyl-6-dimethylaminofulvene (**162**) with diethyl 3-ketoglutarate (**163**) to give 2-methylene-6-oxo-2,6-dihydroazulene (**164**; Scheme 23). If the reaction is carried out at room temperature with piperidine as catalyst the bis-Knoevenagel product is produced.[218]

Simple aliphatic ketones react with unhindered 1,3-dicarbonyl compounds and analogous compounds to give good yields of the condensation products in most cases. Thus, with cyanoacetate in the presence of piperidine, piperidinium acetate or zinc chloride in acetic anhydride, alkylidenecyanoacetates are obtained nonstereoselectively (Scheme 24). However, with branched ketones the yields decrease dramatically and camphor does not react at all.[219,220] Condensations of the less reactive malonates with ketones except acetone, cyclohexanone or similar compounds give low yields or do not proceed. Electron-deficient ketones such as hexafluoroacetone give best results with malonodinitrile in the presence of zinc chloride. In this case the reaction stops at the stage of the β-hydroxydinitrile, which can be transformed in a second step employing $P_4O_{10}$ to afford the corresponding alkylidene.[221]

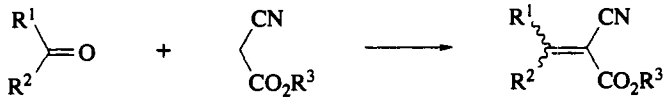

**Scheme 24**

It is of interest that a methyl group in compounds bonded to a 1,2-dicarbonyl moiety, such as in pyruvaldehyde (2-oxopropanal), displays the same reactivity as the methyl group in acetaldehyde; however,

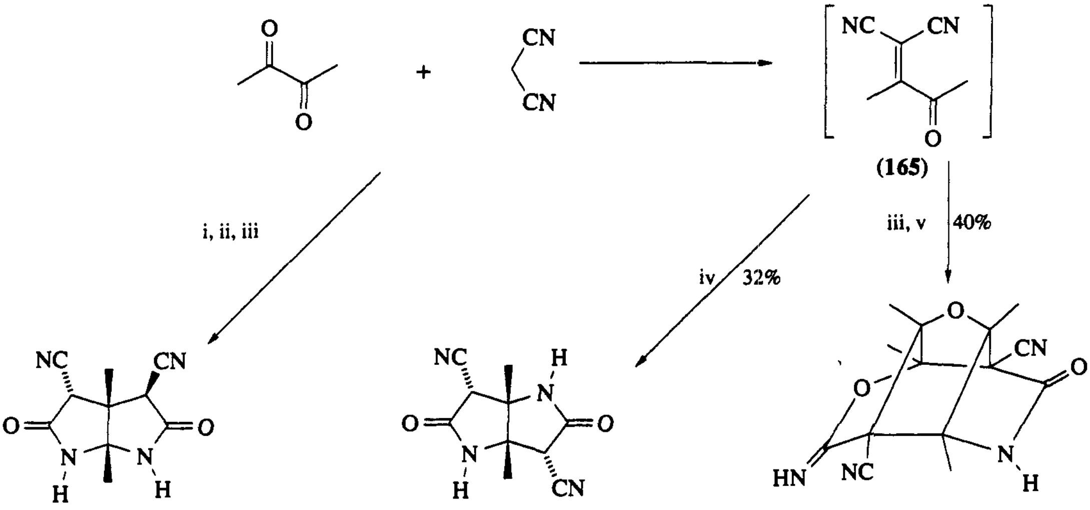

**(166)** **(167)** **(168)**

i, NaOEt/EtOH, 0 °C, 4 h; ii, HCl; iii, $CH_2(CN)_2$; iv, $H_2O$, $CH_2(CN)_2$; v, MeCOCOMe

**Scheme 25**

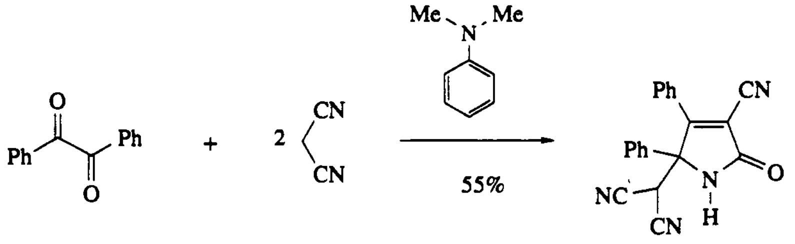

**(169)**

Scheme 26

the reactivity of the formyl group is enhanced.[222] Aliphatic and aromatic 1,2-diketones are reactive carbonyl components in the Knoevenagel reaction with malonodinitrile. Depending on the 1,2-diketone, the catalyst used and the ratio of the reagents, one gets either simple Knoevenagel products or substituted γ-lactams. Reaction of 2,3-butanedione with malonodinitrile in the presence of piperidine leads to a complex mixture of 32% of the bislactam (**167**) and 40% of the bridged compound (**168**), whereas with sodium methoxide bislactam (**166**) is obtained. Compounds (**167**) and (**168**) are presumably formed *via* the alkylidenemalonodinitrile (**165**; Scheme 25).[223] With benzil the mono-Knoevenagel product is obtained using *N,N*-dimethylaniline or *N,N*-diethylaniline as catalyst.[224,225] However, by increasing the proportion of the amine, a γ-lactam (**169**) is formed in 55% yield (Scheme 26).[226]

In some cases it is appropriate to use an imine[48,227–229] instead of a carbonyl compound. Thus, benzalaniline reacts with activated methylenes in the presence of carbocyclic acid anhydrides to give the corresponding Knoevenagel products (Scheme 27).[229] Similarly, the enamine (**170**) reacts with cyanoacetic acid in ethyl acetate[230] or dimethylformamide[231] to afford the cyclohexylidene compound (**171**; Scheme 28). Acetals may be employed instead of the free ketones. An example is the reaction of fluorenone cyclic acetal (**172**) with malonodinitrile, which occurs in butanol without added catalyst to af-

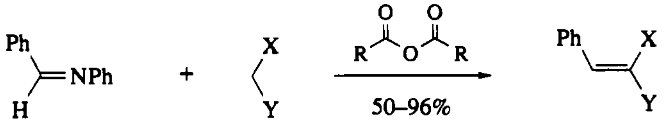

X, Y = $CO_2H$, $CO_2Et$, CN, COMe, $NO_2$, $SO_2Ph$

Scheme 27

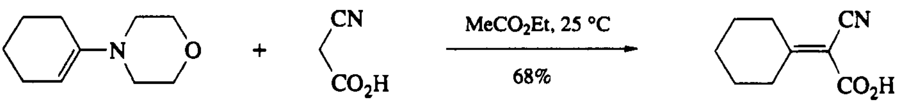

**(170)** **(171)**

Scheme 28

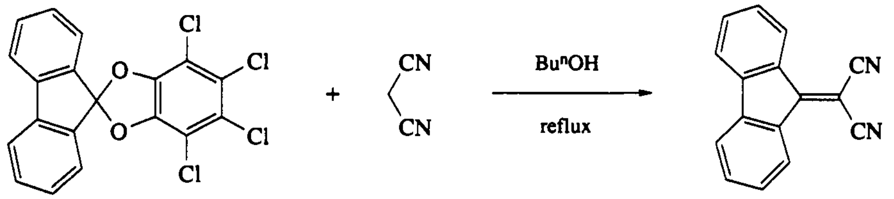

**(172)** **(173)**

Scheme 29

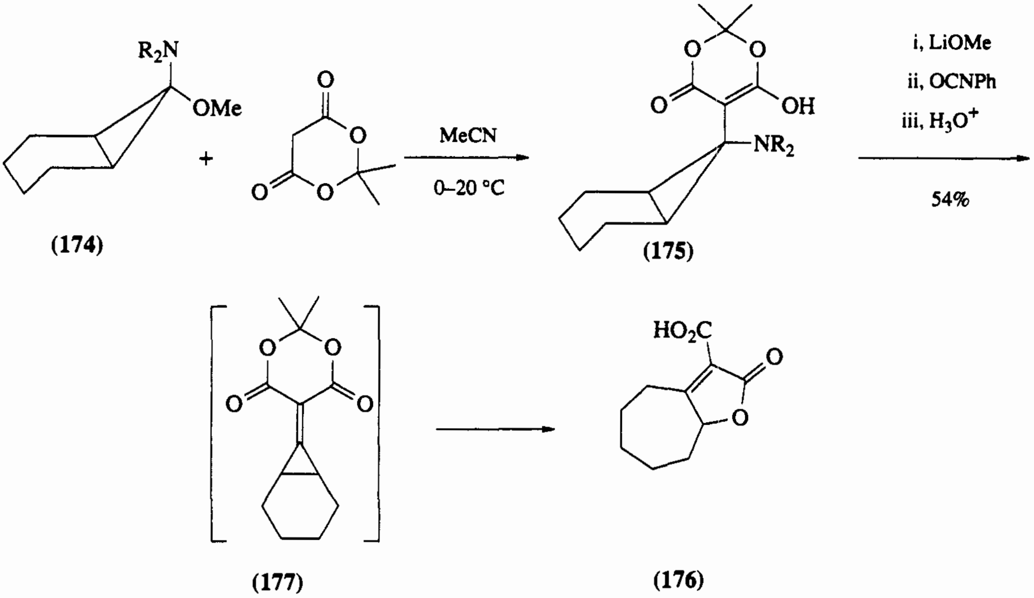

**Scheme 30**

ford (**173**; Scheme 29).[232] α-Amino ethers derived from bicyclo[4.1.0]heptanone and bicyclo[5.1.0]octanone react with Meldrum's acid and dimedone. Reaction of (**174**) with Meldrum's acid gives adduct (**175**), which is dehydrated to give the unsaturated lactone (**176**) *via* the unstable methylenecyclopropane derivative (**177**; Scheme 30).[233]

Orthoesters and carbonic acid derivatives can be employed in lieu of carbonyl compounds.[234–239] For example, 2,2-diethoxy-2*H*-chromene (**178**) and methyl cyanoacetate give the 2*H*-chromene derivative (**179**; Scheme 31).[234] (Methylthio)alkylideniminium salts (**180**) react with active methylene compounds under basic conditions ($K_2CO_3$ or $Et_3N$) to give the corresponding condensation products (**181**; Scheme 32).[240] This method is an alternative to the Eschenmoser procedure[241] for synthesizing vinylogous lactams and urethanes. *N*-Alkyl and *N*-acylpyridinium salts can also serve as electrophiles in the Knoevenagel condensation with activated methylenes.[242–244] Suitably activated nitriles ($R^1CN$) such as trichloroacetonitrile or ethyl cyanoformate react with various 1,3-dicarbonyl compounds to afford (**182**) in the presence of catalytic amounts of metal acetylacetonates [M(acac)$_n$]. In the presence of $TiCl_4$ non-

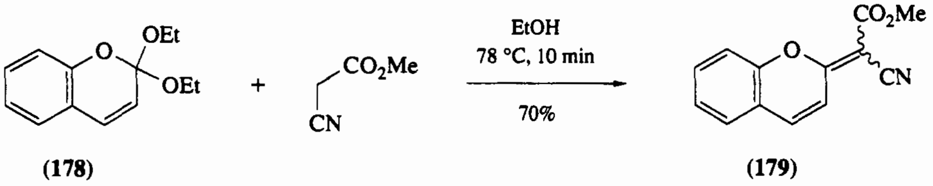

**Scheme 31**

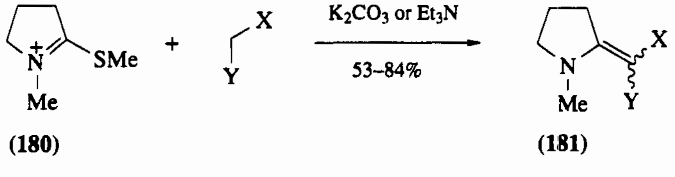

X, Y = H, $NO_2$; $CO_2Me$, $CO_2Me$; $CO_2Et$, $CO_2Et$; COMe, $CO_2Bu^t$; $CO_2Et$, CN; $CO_2Et$, COMe; COMe, COMe

**Scheme 32**

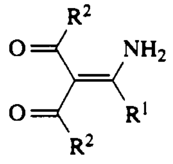

**(182)**

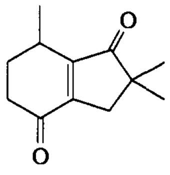

**(183)**

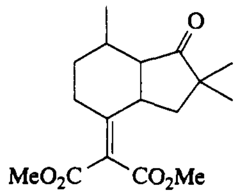

**(184)**

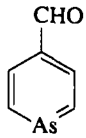

**(185)**

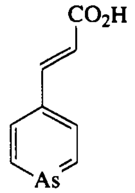

**(186)**

activated nitriles give the corresponding enamines (**182**) with a few 1,3-dicarbonyl compounds, including dimethyl malonate.[245]

As has been mentioned already, steric effects have a great influence on the rate of Knoevenagel reactions. Thus, a selective condensation of the less sterically congested carbonyl group in (**183**) with dimethyl malonate using $TiCl_4$/pyridine as catalyst affords the alkylidene product (**184**) in 74% yield.[246] If the carbonyl group of an α,β-unsaturated ketone is hindered, preferential formation of the Michael product is observed. On the other hand, compounds with an unhindered α,β-unsaturated carbonyl tend to undergo an initial Knoevenagel reaction that may or may not be followed by further reaction (Scheme 33).[86,247] Interesting chemoselectivity is observed in the Knoevenagel reaction of arsabenzaldehyde (**185**), which yields exclusively the (*E*)-arsacinnamic acid (**186**) upon reaction with malonic acid in pyridine. In contrast, with PhMgBr addition at the C=As bond occurs.[248] Finally, an alternative route to α,β-unsaturated acids[249] and cyanides[250] is the reaction with trimethylsilylacetic acid or trimethylsilylacetonitrile[250] and derivatives.[251] Addition of the dianion (**187**) to aldehydes gives trimethylsilylalkoxides, which undergo Peterson elimination to give the α,β-unsaturated acids (**188**).[249]

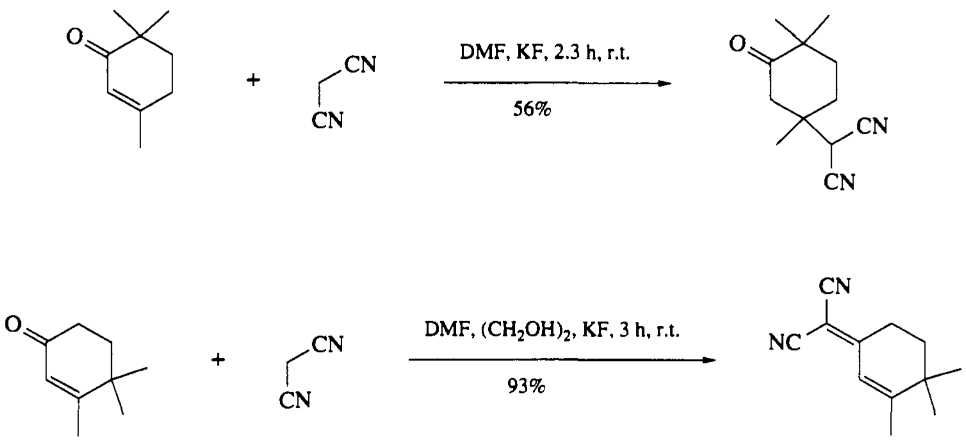

**Scheme 33**

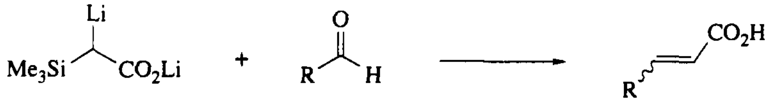

**(187)** **(188)**

## 1.11.4 SEQUENTIAL REACTIONS

Knoevenagel products are highly reactive compounds because of their low energy LUMO. They can act as dienophiles in the normal Diels–Alder reaction,[48,252] as heterodienes in the hetero Diels–Alder reaction with inverse electron demand,[253] as dipolarophiles in 1,3-dipolar cycloadditions,[48,254] as enophiles in the ene reaction[255a] and as acceptors for the addition of allylsilanes.[255b] Sigmatropic rearrangements and photochemical reactions have been described.

The Knoevenagel product (**189**), obtained from the reaction of ethyl pyruvate and malonodinitrile in the presence of β-alanine, undergoes a normal Diels–Alder reaction with 1-(*p*-methoxyphenyl)butadiene (**190**) to give cycloadduct (**191**), which has been transformed into (**192**), a promising precursor for the synthesis of $C_{19}$-gibberellins (plant-growth hormones; Scheme 34).[256,257] In a similar way, (**195**), obtained in 48% overall yield from Meldrum's acid and the ketone (**193**) *via* (**194**), reacts with diene (**196**) to give regioisomers (**197**) and (**198**) as a 3:2 mixture (Scheme 35).[258] δ-Damascone (**201**) has been synthesized by a Knoevenagel condensation of Meldrum's acid and acetone to give (**199**), followed by a Diels–Alder reaction with 1,3-pentanediene. Treatment of adduct (**200**) with allyllithium and isomerization of the double bond with $NH_4Cl$ affords δ-damascone (**201**) in 18% overall yield (Scheme 36).[259] An intramolecular cycloaddition was accomplished by condensation of the aldehyde (**202**) with different 1,3-dicarbonyl compounds. Thus, reaction of (**202**) with dimethyl malonate affords the corresponding Knoevenagel product, which cyclizes upon heating at 150 °C to the *trans*-hydrindene (**203**).[260]

The Knoevenagel products of sufficiently reactive acyclic as well as cyclic 1,3-dicarbonyls can act as oxadienes in hetero Diels–Alder reactions with enol ethers and enamines. Alkenes may be used as dienophiles if the reaction is performed in an intramolecular mode.[253] The cycloadditions of ethyl vinyl ether

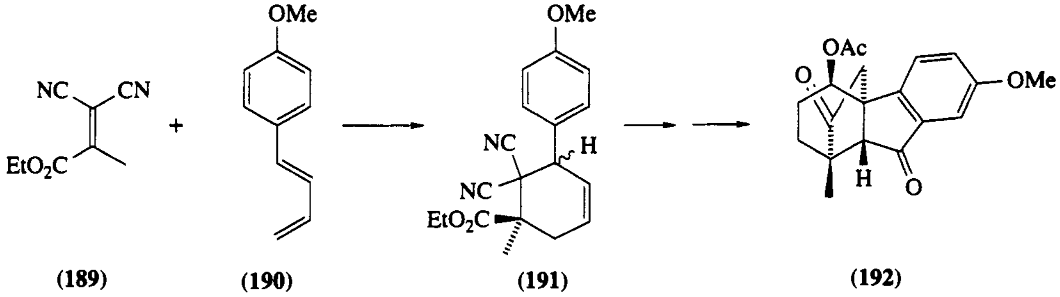

Scheme 34

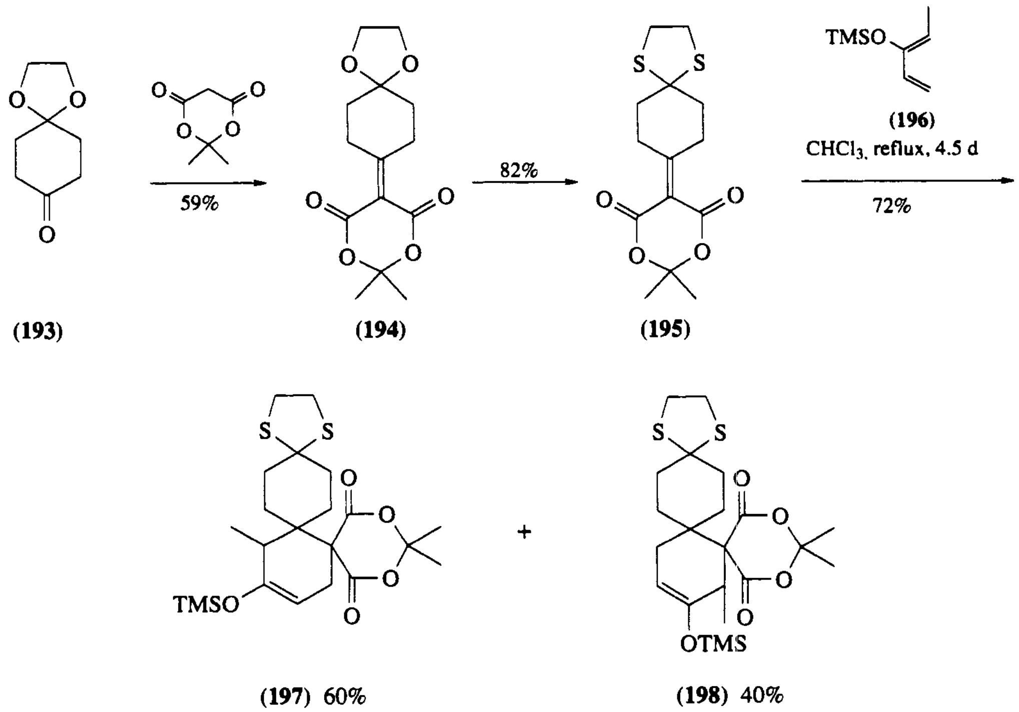

Scheme 35

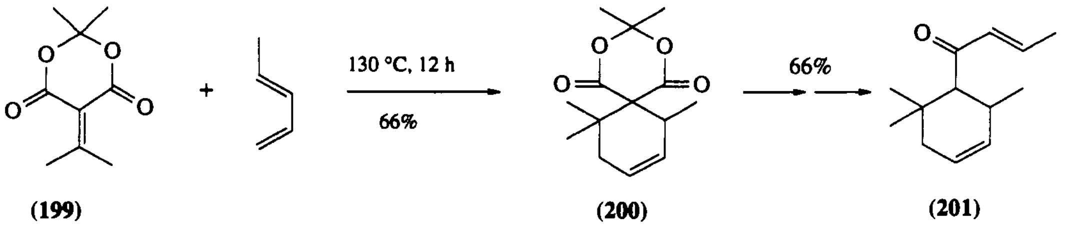

Scheme 36

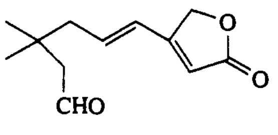

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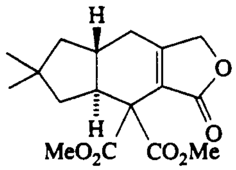

(203)

and the alkylidene or benzylidene compounds (**204**) give adducts (**205**) as mixtures of diastereomers in good yields (Scheme 37).[261] The Knoevenagel products of Meldrum's acid are even more reactive. The tandem-Knoevenagel–hetero-Diels–Alder reaction, first introduced in 1980, is especially useful.[262] Here, the initial alkylidene or benzylidene compound is not isolated but is directly transformed into the cycloadducts. The reaction can be carried out as a two- or three-component transformation (Scheme 38).[253] An example of a three-component reaction is the condensation of malondialdehyde, a monoprotected malondialdehyde and an enol ether to give a dihydropyran ring system with the skeleton and relative configuration of secologanin.[154,155] In the two-component transformation using aldehydes that contain a dienophile moiety a high induced and noninduced diastereoselectivity is observed in the final intramolecular cycloaddition step. Thus, the sequential reaction of citronellal (**206**) leads nearly exclusively to the cycloadduct (**207**) as one of four possible stereoisomers (Scheme 39).[57,263] The *cis* annulated compounds are obtained exclusively by using appropriate aromatic aldehydes[264] and asymmetric induction with *de* >99% is found by employing enantiomerically pure 1,3-dicarbonyls such as oxazepanediones derived from ephedrine.[34] In addition to the six-membered ring systems, cyclopentane and cycloheptane derivatives as well as novel heterocycles have been synthesized by the tandem-Knoevenagel–hetero-Diels–Alder reaction.[264,265]

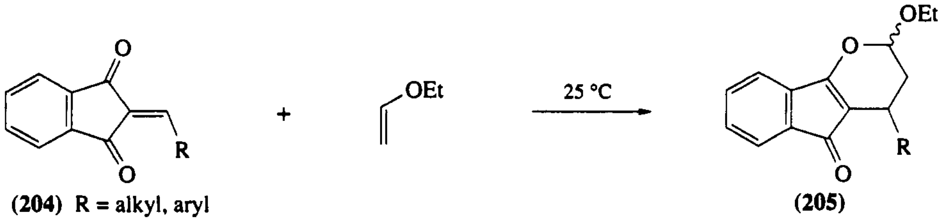

Scheme 37

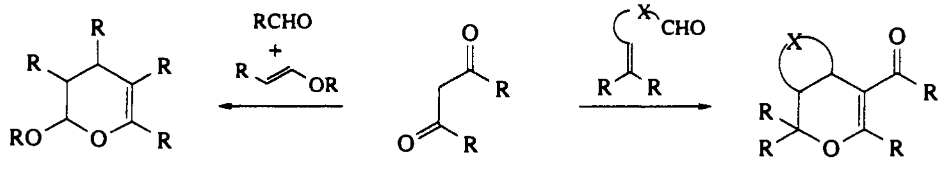

Scheme 38

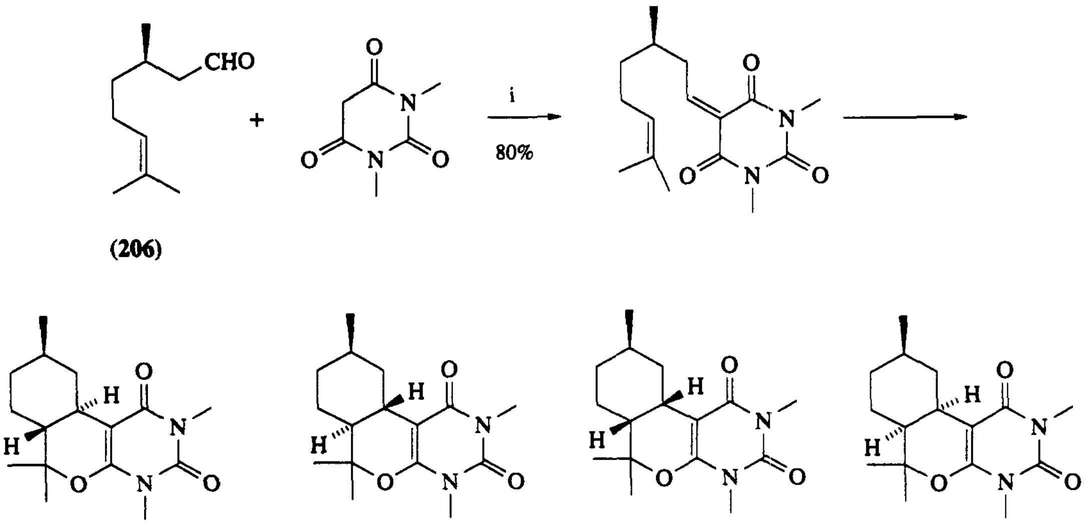

(206)

(207) 95.2%

3.6%

0.7%

0.5%

i, ethylenediammonium diacetate, acetonitrile, 3 h, 20 °C

Scheme 39

Several natural products such as cannabinoids,[253] iridoids,[266] indole alkaloids,[267-269] furofuran lignans[270] and other compounds[271] have been synthesized using this methodology. Deoxyloganin (**210**) was obtained by condensation of the enantiomerically pure aldehyde (**208**) with Meldrum's acid in the presence of ethylenediammonium diacetate to give the Knoevenagel product (**209**), which cyclizes immediately, yielding the cycloadducts (**211**) and (**212**) in a 10:1 ratio (Scheme 40).[266] (–)-Ajmalicine

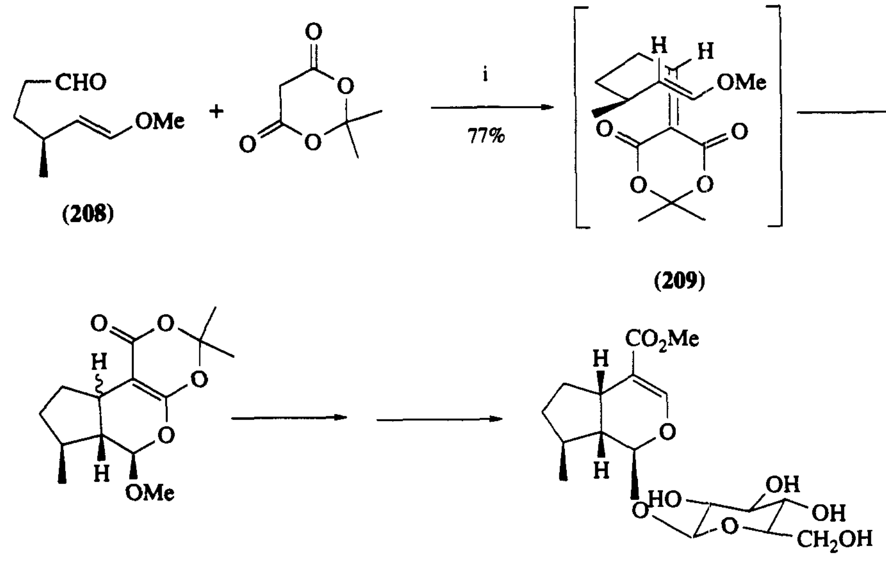

(208)

(209)

(211) β-H

(212) α-H

(210)

i, ethylenediammonium diacetate, toluene, $Na_2SO_4$, 20 °C, 2 h

Scheme 40

(**215**) and (–)-tetrahydroalstonine (**216**), which possess *trans*- and *cis*-fused D/E ring systems, respectively, have been synthesized from the single cycloadduct (**217**), which is obtained by a Knoevenagel condensation of the enantiomerically pure aldehyde (**213**) with Meldrum's acid followed by a hetero-Diels–Alder reaction of the intermediate (**214**; Scheme 41).[267,268] By a similar sequence the furofuran lignans (–)-sesamolin, (–)-sesamine and (–)-acuminatolide (**219**) have been prepared from aldehyde (**218**) and Meldrum's acid (Scheme 42).[270] A novel synthetic entry to indole alkaloids along a biosynthetic pathway has been developed using strictosidine derivatives (**221**). These compounds were constructed by a three-component tandem-Knoevenagel–hetero-Diels–Alder reaction of aldehyde (**220**), dimethylbarbituric acid and an enol ether (Scheme 43).[269]

The alkylidene-1,3-dicarbonyl moiety is also a highly reactive enophile. Thus, the Knoevenagel adduct (**223**) obtained from aldehyde (**222**) and dimethyl malonate in the presence of piperidinium acetate, cyclizes by treatment with Lewis acids such as $FeCl_3$ on $Al_2O_3$ exclusively to the *trans*-substituted cyclohexane (**224**; *trans*:*cis* > 99.5:0.5; Scheme 44).[71,103,272] The sesquiterpene veticadinol (**225**) has been synthesized in enantiomerically pure form by this method.[273] Contrary to the expectation, *trans*-substituted cyclopentanes can also be obtained with excellent induced and noninduced diastereoselectivities.[274] Similarly, aldehydes containing an allylsilane moiety[274] can be used for a highly stereoselective formation of *trans*-1,2-disubstituted cyclopentanes and cyclohexanes by a Knoevenagel

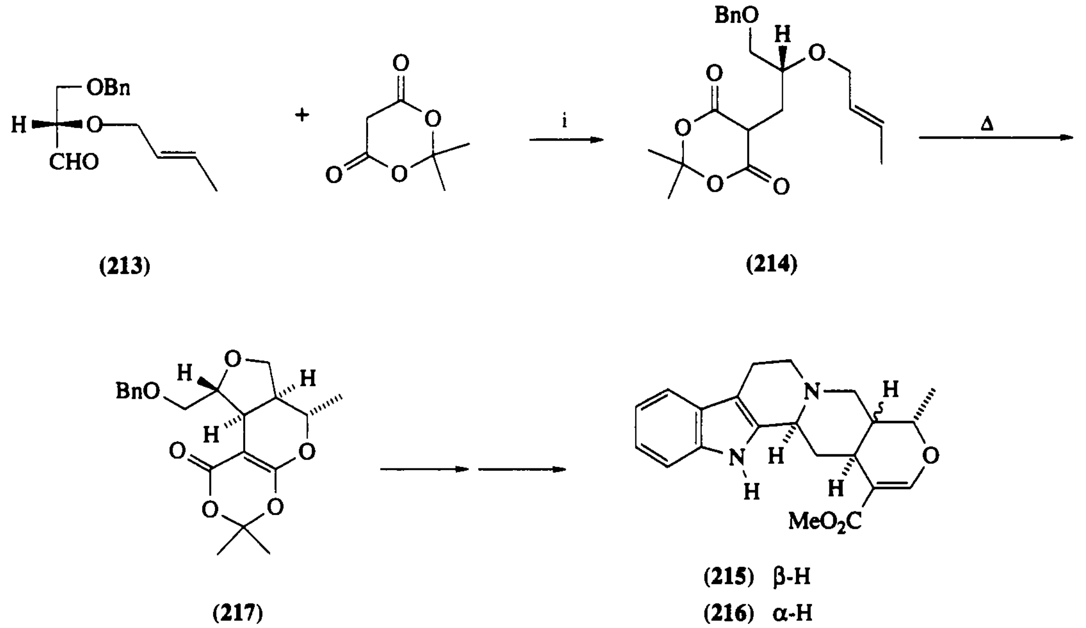

(**213**)

(**214**)

(**217**)

(**215**) β-H

(**216**) α-H

i, ethylenediammonium diacetate, MeOH, 0–20 °C

Scheme 41

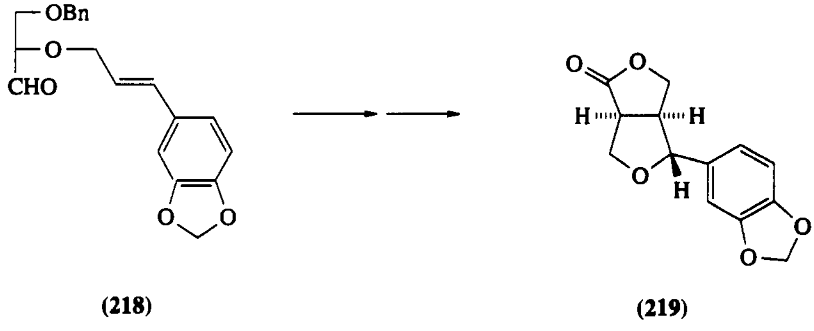

(**218**)

(**219**)

Scheme 42

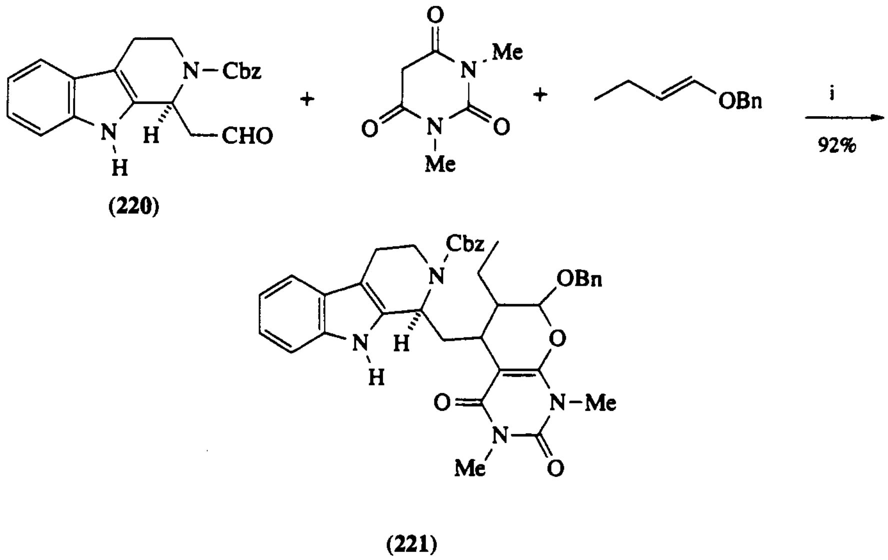

i, ethylenediammonium diacetate, ultrasound, 50–60 °C, 4 h

Scheme 43

condensation with 1,3-dicarbonyl compounds, followed by a Lewis acid promoted cyclization.[255b] An interesting transformation is the tandem-Knoevenagel [2,3] sigmatropic rearrangement, which leads to γ-hydroxy-α,β-unsaturated acid derivatives (**230**; Scheme 45).[275,276] Knoevenagel condensation of the sulfoxides (**226**) yields the (*E*)-condensation products (**227**), which can be converted, *via* (**228**) and (**229**), into the allyl alcohols (**230**) by treatment with piperidine. The reaction can also be carried out with enantiomerically pure sulfoxides.[276,277]

Knoevenagel products of aliphatic aldehydes do not undergo photochemically induced [2 + 2] cycloaddition with alkenes, but are isomerized instead to the β,γ-unsaturated isomers. On the other hand, benzylidene-Meldrum's acids give two isomeric cycloadducts upon irradiation in the presence of cyclohexene.[48] Unsymmetrical Knoevenagel products such as the benzylidenepyrazolones undergo *cis*/*trans* isomerization on irradiation. The photostationary state of (**231**) is (*E*):(*Z*) = 2:1, whereas the thermo-

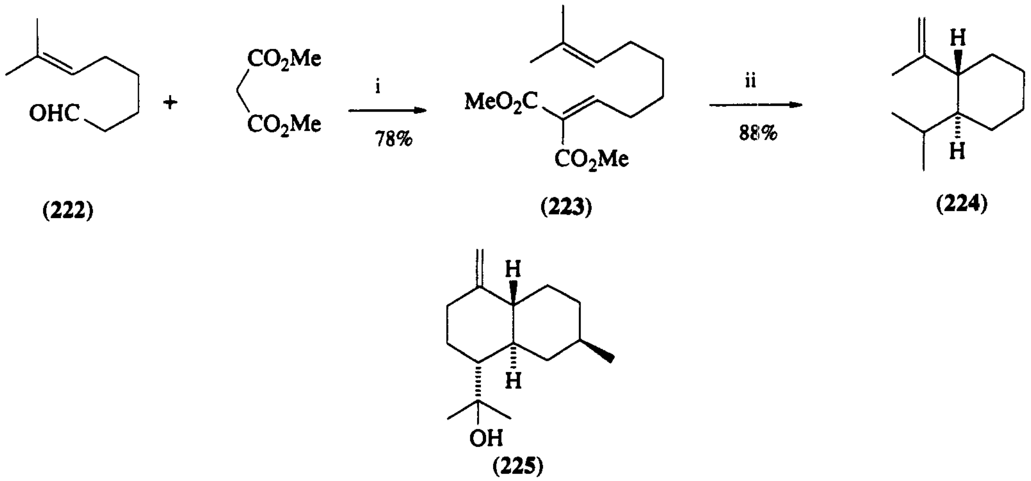

i, piperidinium acetate, $CH_2Cl_2$, 20 °C, 1 h; ii, $ZnBr_2$, $CH_2Cl_2$, 20 °C, 30 min

Scheme 44

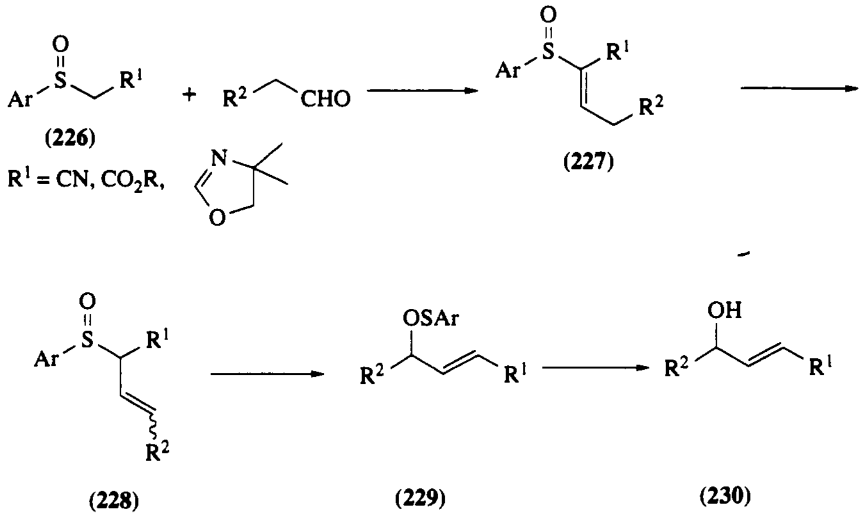

Scheme 45

dynamic equilibrium is (*E*):(*Z*) = 10:1.[81] An interesting new aspect in the photochemistry of Knoevenagel products is the interconversion of pairs of compounds with photochromic behavior. Irradiation of the dihydroazulene (**232**) with visible light affords the vinylheptafulvene (**233**), which can be thermically reconverted to (**232**). Compound (**233**) is synthesized by a Knoevenagel condensation of malonodinitrile and the ketone (**234**) in the presence of ammonium acetate/acetic acid followed by oxidation with DDQ or hydride abstraction with triphenylmethyl tetrafluoroborate (Scheme 46).[278]

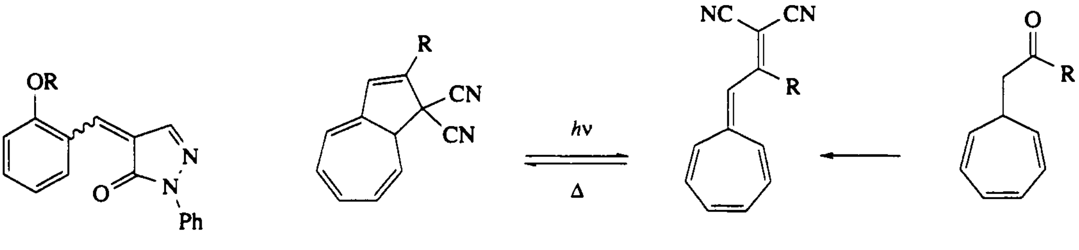

Scheme 46

## 1.11.5 SYNTHETIC APPLICATIONS

The Knoevenagel reaction is a synthetic method with a broad scope. The educts are simple and cheap, reaction conditions are mild, and a wide variety of solvents can be used. In addition, the Knoevenagel products are reactive compounds and may be employed in sequential transformations (see also Section 1.1.1.4). This is why the Knoevenagel reaction is widely employed, especially in the formation of heterocycles. The most used active methylene in these reactions is malonodinitrile. In many syntheses of natural products, drugs, dyes and other compounds, the condensation of a carbonyl group with an activated methylene compound is found. It is beyond the scope of this review to discuss all examples described in the literature, so only a few recent examples are given in this section.

### 1.11.5.1 Carbocycles and Heterocycles

An interesting approach to the substituted 6,8-bisdehydro[13]annulenone (**238**) includes a double Knoevenagel reaction of the mixed acetonedicarboxylic ester (**235**) with aldehyde (**236**) in the presence of piperidine to give (**237**). Oxidative coupling of the acetylene moieties in (**237**) with $Cu(OAc)_2$ in pyridine affords (**238**) in 10% yield (Scheme 47).[279] α,β-Unsaturated malonodinitriles are suitable intermediates for the synthesis of a variety of carbocyclic systems. Cyclization of the benzylidene malonodinitrile (**239**) to form a five-membered carbocyclic ring (**240**) can be achieved upon treatment with acid and subsequent hydrolysis (Scheme 48).[158] A similar cyclization of (**241**) affords six-membered carbocyclic ring systems.[158,169]

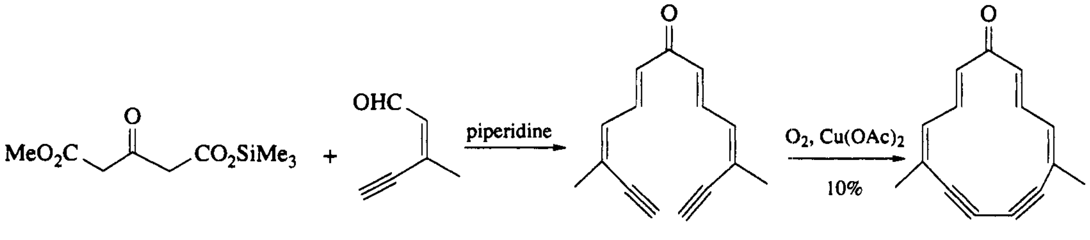

**(235)** **(236)** **(237)** **(238)**

Scheme 47

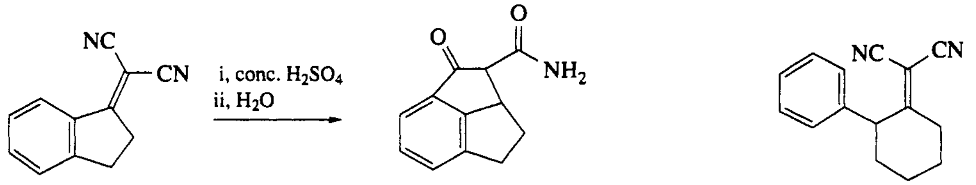

**(239)** **(240)** **(241)**

Scheme 48

Knoevenagel reactions are used in the synthesis of a wide variety of O- and N-heterocycles. In the typical Knorr pyrrole synthesis, a 1,3-dicarbonyl compound is condensed with an oximino- or azimino-1,3-dicarbonyl compound followed by reductive cyclization. Thus, catalytic hydrogenation of benzyl acetoacetate (**243**) and diethyl oximinoacetonedicarboxylate (**242**) affords pyrrole (**244**), which is transformed to (**245**) by another Knoevenagel reaction (Scheme 49). A rational synthesis of all four uroporphyrines has been achieved by cyclization of appropriate pyrroles such as (**245**).[280] Another typical preparation of a heterocycle that involves a Knoevenagel condensation is the Hantzsch 1,4-dihydropyridine synthesis. Here, an aldehyde and two molecules of a 1,3-dicarbonyl compound react in the

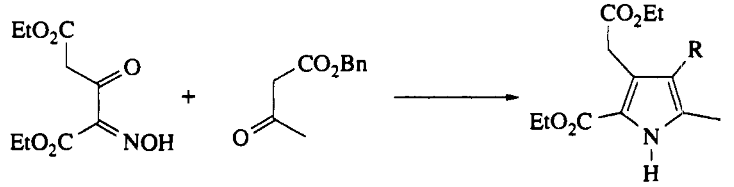

**(242)** **(243)**

**(244)** R = $CO_2H$
**(245)** R = $CH_2CH_2CO_2Et$

Scheme 49

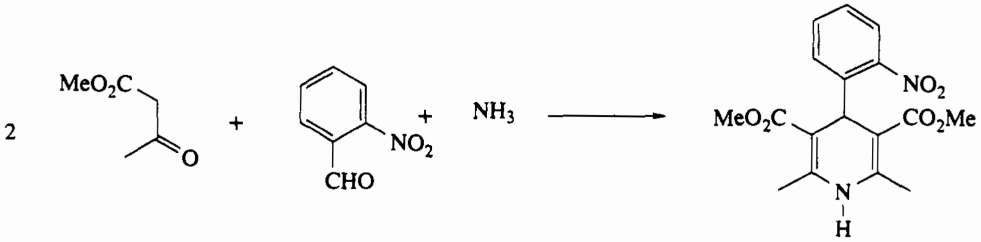

**(246)**

**Scheme 50**

presence of ammonia or an amine. Newer methods use the condensation of an aldehyde, a 1,3-dicarbonyl compound and an enamine of a second 1,3-dicarbonyl compound. The reaction is used in the preparation of the important calcium antagonist nifedepin (**246**; Scheme 50).[281,282]

Compound (**248**), a relative of [14] annulene containing a hydrazine bridge, has been synthesized by a Knoevenagel condensation of the [1,1′-bipyrrole]-2,2′-dicarbaldehyde (**247**) and *t*-butyl cyanoacetate, followed by reduction of the *exo* double bond with diisobutylhaluminum hydride, acid-catalyzed cyclization, and decarboxylation.[283]

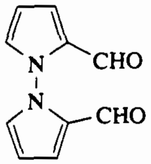

**(247)**

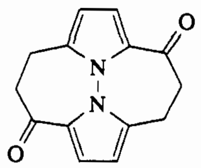

**(248)**

As part of a project to synthesize stable analogs of the indole-2,3-quinodimethane system, the 2,4-dihydropyrrolo[3,4]indole (**251**) has been prepared from formylindole (**249**). Knoevenagel condensation with ethyl malonate followed by bromination and nucleophilic substitution of the bromide with azide yields (**250**), which immediately undergoes intramolecular 1,3-dipolar cycloaddition to give the triazoline (**252**). Treatment of (**252**) with toluene-*p*-sulfonic acid affords diethyl diazomalonate and (**251**;

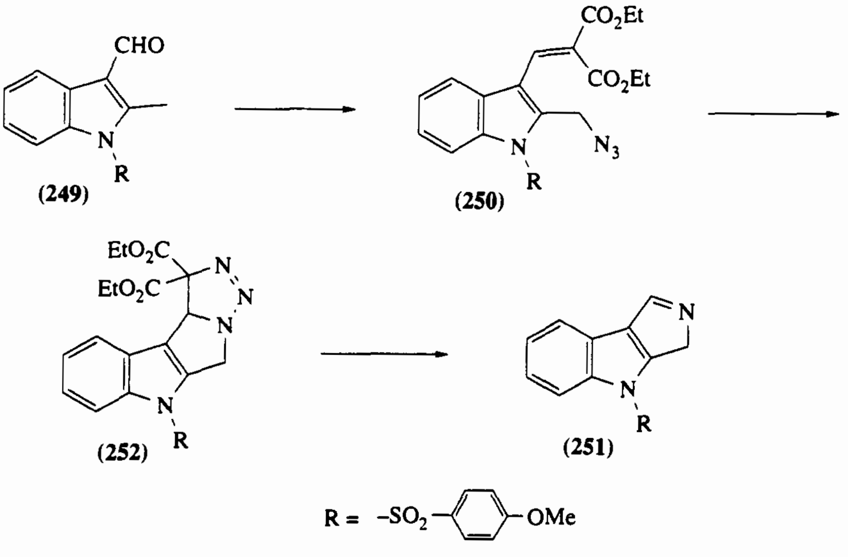

**(249)** **(250)** **(252)** **(251)**

**Scheme 51**

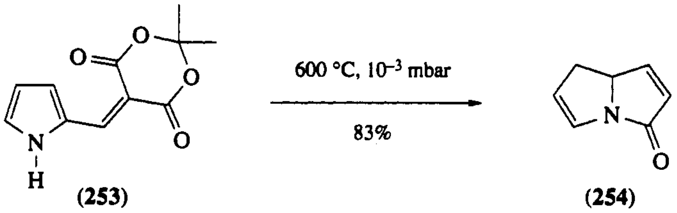

(6)

Scheme 51).[284] The annulated dihydropyrrole (**254**) is formed by gas phase pyrolysis of the Knoevenagel product (**253**; equation 6).[285]

Another interesting transformation starting from 3-methylthiophene-2-carbaldehyde yields 5*H*-thieno [2,3-*c*]pyrrole *via* a Knoevenagel reaction with malonate and a Staudinger reaction.[286]

For the synthesis of pyridine derivatives, the Knoevenagel condensation with malonodinitrile, cyanoacetamide or cyanoacetates followed by an intramolecular addition of an amino function to a C≡N triple bond has found wide application. Hence, the formation of 2-hydroxypyridines like (**257**) is accomplished by Knoevenagel reaction of 1,3-diketones with cyanoacetamide, cyanoacetate and malonodinitrile, and that of 2,6-dihydroxypyridines like (**258**) by reaction with β-keto esters and cyanoacetamide followed by direct cyclization. With malonodinitrile, the reaction with β-keto esters usually stops at the Knoevenagel stage (**255**). However, with a mixture of ammonium acetate and acetic acid as catalyst, the 6-alkoxy-2-hydroxypyridines (**259**) are formed exclusively.[287–291] Pyran (**256**) is an intermediate in the latter process.[287] Enamines of 1,3-dicarbonyl compounds and their thio analogs may also be used in this transformation. Thus, reaction of (**260**) with malonodinitrile gives thiopyran (**262**) at room temperature and thiopyridone (**263**) at 80 °C, presumably *via* the Knoevenagel adduct (**261**; Scheme 52).[292] Knoevenagel condensation of phthalic anhydride with ethyl cyanoacetate in the presence of triethylamine in toluene yields highly reactive benzofulvene (**265**), which can be transformed into the indenopyridine-1,3-dione (**266**) with base or into indenopyridazine-3,9-diones and indenopyran-1,9-diones

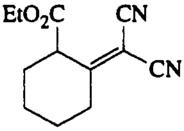

**(255)**

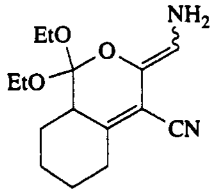

**(256)**

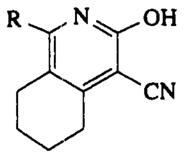

**(257)** R = alkyl
**(258)** R = OH
**(259)** R = *O*-alkyl

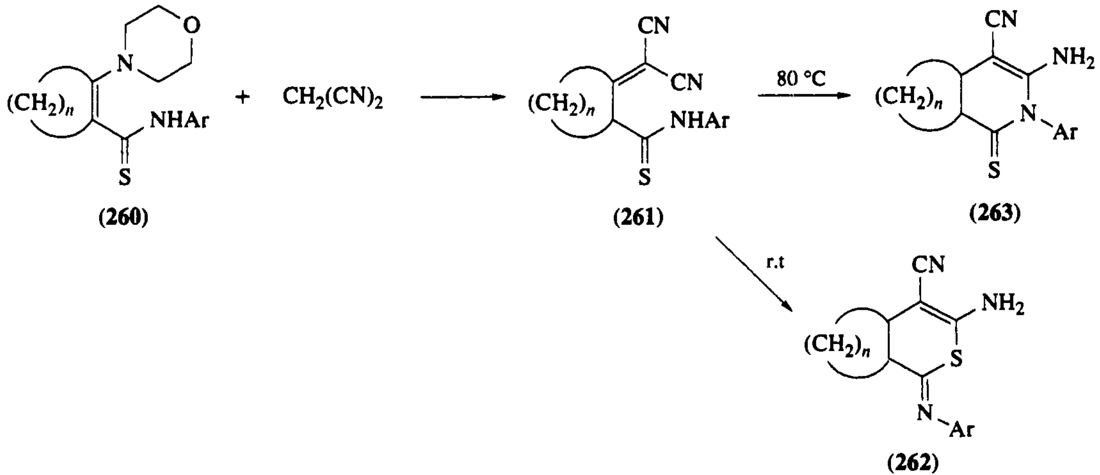

**Scheme 52**

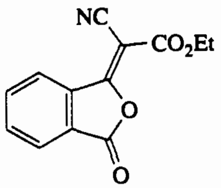

**(264)**

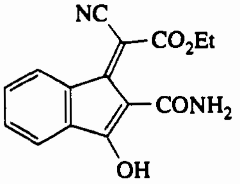

**(265)**

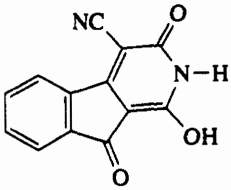

**(266)**

under other conditions. Knoevenagel product (**264**) is not formed if an amine is used as catalyst, whereas with sodium 9% of (**264**) can be isolated.[293]

Pyrido[4,3-*b*]carbazole (**269**), an intermediate for the synthesis of ellipticine analogs, has been prepared by a Knoevenagel condensation of the aldehydes (**267**) with malonic acid to give (**268**). The derived acyl azides are thermolyzed to obtain (**269**).[294] An interesting synthesis of hexahydropyrazino[1,2-*a*]quinolines (**273**) is summarized in Scheme 53.[295] The transformation involves a Knoevenagel reaction of aldehyde (**270**) with malonodinitrile to yield (**271**) ↔ (**272**), which cyclizes in refluxing 1-butanol after a [1,5] H shift to give (**273**). The Knoevenagel self-condensation product of benzoylacetonitrile (**275**) can be transformed into a variety of heterocyclic compounds, such as pyridazine (**274**), pyran (**276**), benzene derivative (**277**), or pyrazole (**278**) by treatment with benzenediazonium chloride, malonodinitrile or acetoacetate, benzoylacetonitrile, or hydrazine, respectively (Scheme 54).[296] Condensation of 1,4-diketones with malonodinitrile using ammonium acetate/acetic acid as catalyst affords the cyclopentadiene derivatives (**279**) *via* the intermediate bis-Knoevenagel products. Acid-catalyzed cyclization of (**279**) yields the pentalenes (**280**), whereas in basic medium the pyridines (**281**) are formed. With succindialdehyde, however, a bicyclo[3.2.1]octene is obtained exclusively.[297]

4-Flavones and their thia anologs (**282**) undergo Knoevenagel condensation with malonodinitrile to give the corresponding 4,4-dicyanomethylene derivatives (**283**). These compounds give ready access to

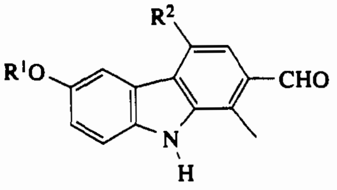

**(267)**

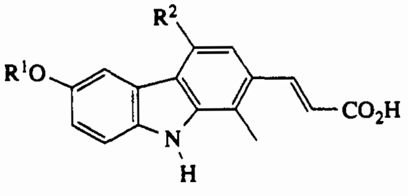

**(268)**

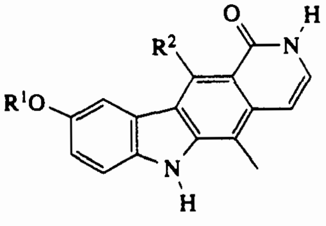

**(269)**

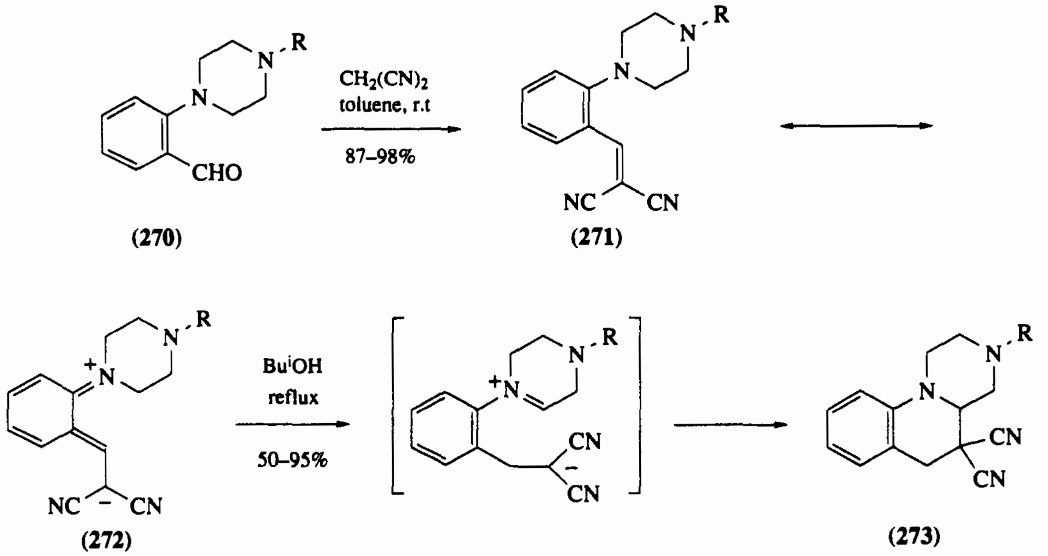

**Scheme 53**

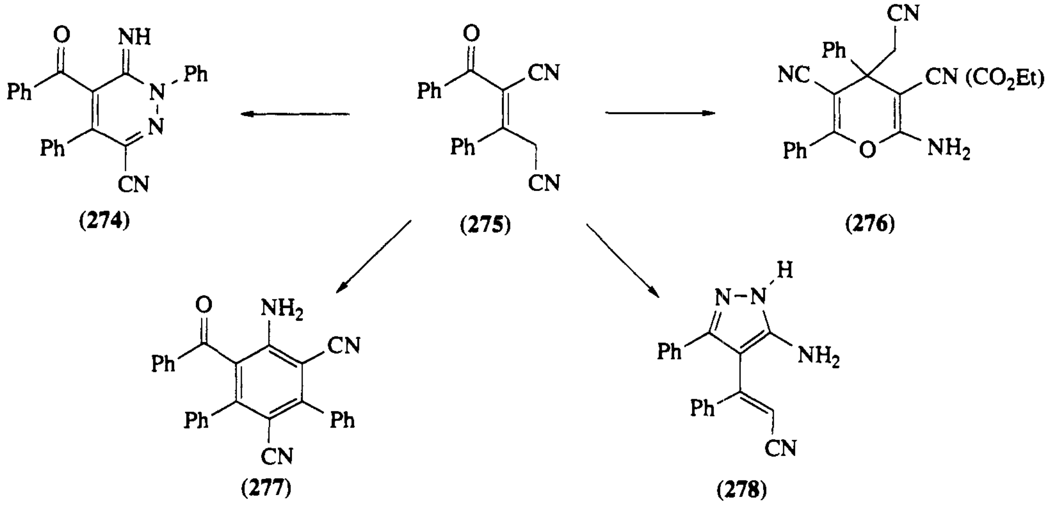

Scheme 54

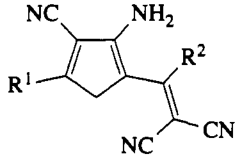

**(279)**

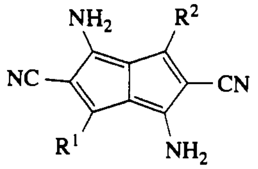

**(280)**

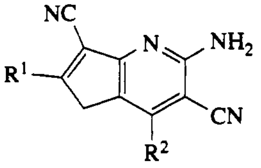

**(281)**

pyranonaphthyridine (**284**; X = O) and its thia analog (**284**; X = S) by condensation with a second equivalent of malonodinitrile (Scheme 55).[298]

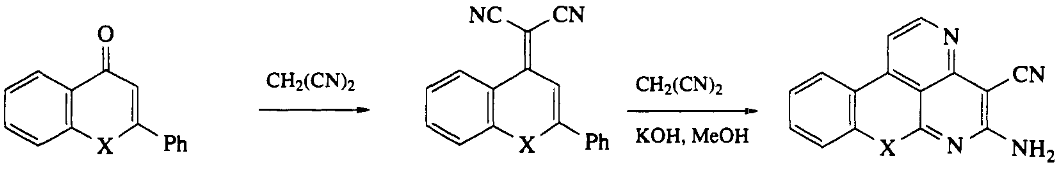

Scheme 55

Pyrano[2,3-*b*]pyridines (**286**) are obtained in a one-pot procedure from the Knoevenagel product (**285**) and malonodinitrile.[299]

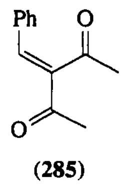

**(285)**

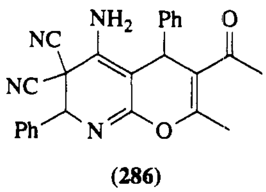

**(286)**

O-Heterocycles such as furan and pyran derivatives can easily be constructed from Knoevenagel products either after double bond isomerization or functionalization at the γ- or δ-position. Hence, acid-catalyzed ring closure of (**287**) affords the 4,5-dihydrofurans (**289**), presumably *via* the double bond isomer (**288**; Scheme 56).[102] Knoevenagel condensation of acrolein and malonic acid in the presence of pyridine gives 70% of (*E*)-pentadienoic acid which, after formation of the bromohydrin (**290**), undergoes photochemically mediated isomerization and acid-catalyzed cyclization to give the substituted α,β-butenolide (**291**; equation 7).[300]

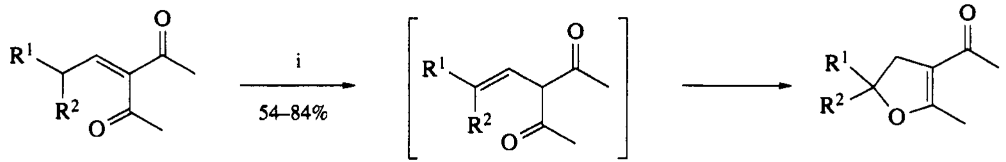

**(287)** **(288)** **(289)**

i, conc. $H_2SO_4$, 20 °C, 12 h; or HCl, DMF, 140 °C, 24 h; or *p*-TsOH, xylene, 140 °C, 12 h

**Scheme 56**

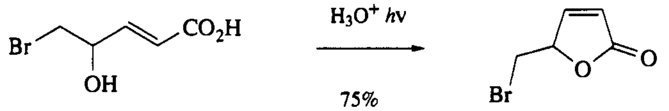

**(290)** **(291)** (7)

Unsaturated δ-lactones are biologically active structural elements in many natural products. The synthesis of this heterocyclic moiety can be achieved by a Knoevenagel condensation of 3-hydroxy aldehydes with active methylene in the presence of $TiCl_4$/pyridine or under standard conditions.[301–303]

## 1.11.5.2 Natural Products and Biologically Active Compounds

In nature, the intramolecular condensation of a 1,3-dicarbonyl moiety with a keto group in polyketides is an important step in the biosynthesis of aromatic compounds. Biomimetic transformations of this type have been intensively investigated by Harris.[303] (For a discussion, see Chapter 1.5, this volume.) In the following, the synthesis of some natural products and biologically active compounds using the Knoevenagel reaction will be described.

An efficient and short synthesis of (*E*)-10-hydroxy-2-decenoic acid (**293**), the major component of the royal jelly of the common honey bee (*Apis mellifera*) uses the Knoevenagel condensation of aldehyde (**292**) with malonic acid in the presence of pyridine to give 61% of (**293**).[304] For the synthesis of stable prostacyclin analogs (**297**), the hemiacetal (**294**) is condensed with active methylenes containing one sulfenyl or sulfinyl group to give adducts (**295**) and (**296**), respectively. Thermal elimination of the sulfoxides (**296**), either obtained directly or by oxidation of the sulfides (**295**), affords (**297**; Scheme 57).[305] A simple process that yields carbocyclic analogs of prostacyclines starts with a sequential Knoevenagel–Michael reaction of 2 equiv. of dimethyl acetonedicarboxylate and 1 equiv. of glyoxal with sodium hydroxide in methanol to give the bicyclo[3.3.0]octadiene (**298**).[306,307] This compound can be transformed into (**299**), which is a starting material for the highly active prostacyclin analogs iloprost and cicaprost.[308]

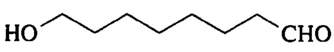

**(292)**

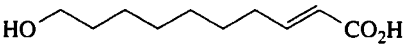

**(293)**

A synthesis of cyclobutane derivative (**301**), which may be a useful substrate in an approach to podophyllotoxin, involves Knoevenagel reaction of an aromatic aldehyde with cyanoacetate to give (**300**) followed by a Michael addition, demethylcarbonylation, intramolecular alkylation and exchange of a cyano group with acetate.[309]

In connection with a synthesis of the hydroazulenic sesquiterpene kessanol (**304**), Knoevenagel condensation of photocitral-A (**302**) with ethyl cyanoacetate was found to give (**303**) as a single isomer. The following sequence includes an intramolecular Prins reaction initiated with $SnCl_4$.[310] In Isobe's synthesis of vernolepin (**307**) the two carbons of the γ-lactone are introduced by a Knoevenagel condensation. Reaction of ketone (**305**) with di-*t*-butyl malonate followed by treatment with DBU affords (**306**), which is transformed to the α,α′-dihydroxy compound (**308**). Hydrolysis of the esters followed by decarboxylation, formation of the γ-lactone, Mannich reaction and elimination yields vernolepin (**307**; Scheme 58).[311]

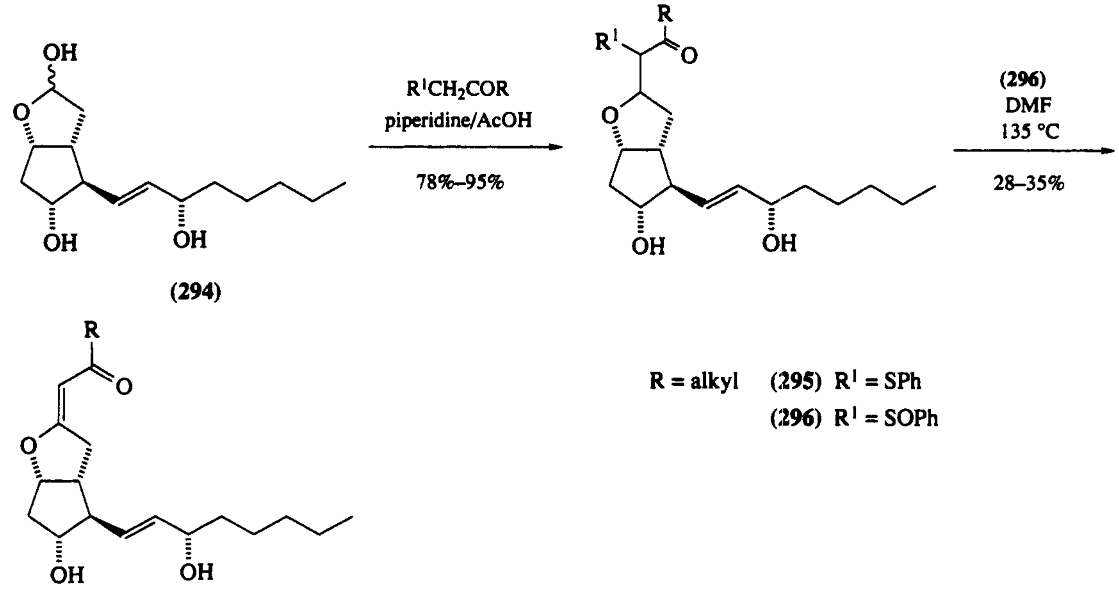
R¹CH₂COR
piperidine/AcOH
78%–95%
(296)
DMF
135 °C
28–35%
OH
O
R
R¹
R = alkyl

(294)

(295) $R^1$ = SPh

(296) $R^1$ = SOPh

(297)

Scheme 57

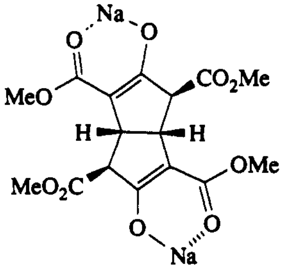
Na
O
MeO
CO₂Me
H
OMe
MeO₂C

(298)

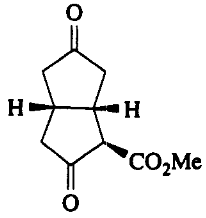

(299)

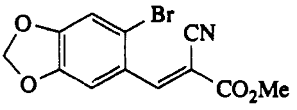
O
Br
CN
CO₂Me

(300)

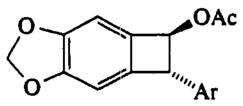

(301)

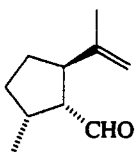

(302)

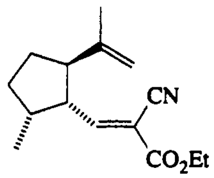

(303)

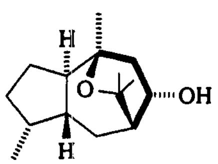

(304)

Steroidal ketones have been used extensively in the Knoevenagel reaction.[312–315] Thus, the transformation of 17-oxoandrostane derivatives (**309**), which are readily available by microbiological degradation of sitosterin, are employed for the synthesis of enantiomerically pure cardiotonic steroids such as bufadienolide and cardenolide (**311**). In both syntheses the substitutent at C-17 is introduced by a Knoevenagel reaction of the 17-oxoandrostane derivative (**309**) with ethyl cyanoacetate in the presence of ammonium acetate to give the cyano ester (**310**), presumably as a mixture of the (*E*)- and (*Z*)-isomers, in 89% yield.[315]

The Knoevenagel reaction has also been used in the synthesis of alkaloids. In a preparation of yohimbane derivatives, 2-cyano-4′-methoxycinnamic acid, the Knoevenagel product of *p*-anisaldehyde and

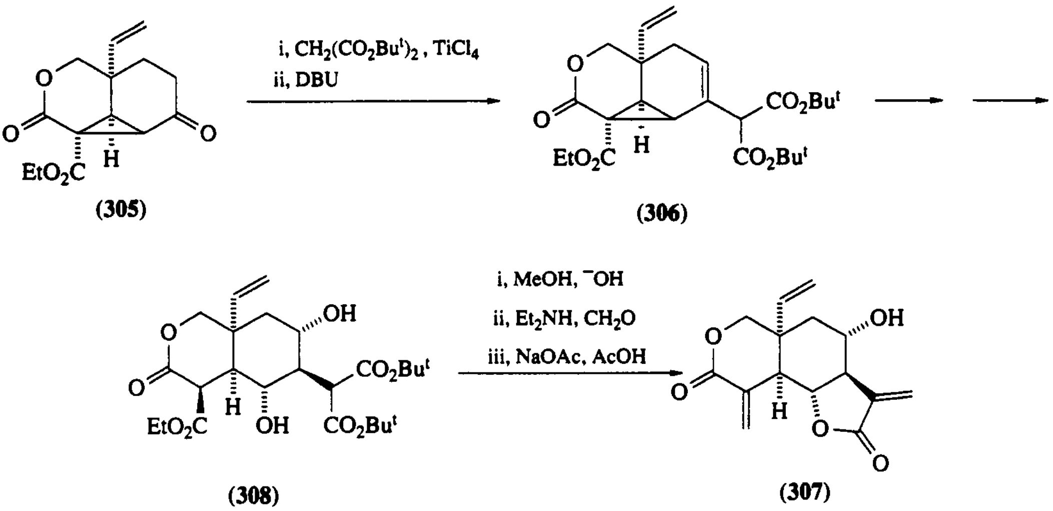
i, $CH_2(CO_2Bu^t)_2$, $TiCl_4$
ii, DBU
i, MeOH, $^-OH$
ii, $Et_2NH$, $CH_2O$
iii, NaOAc, AcOH
(305)
(306)
(308)
(307)

Scheme 58

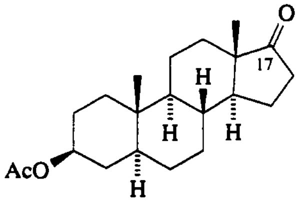

(309)

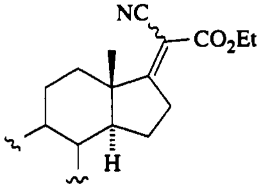

(310)

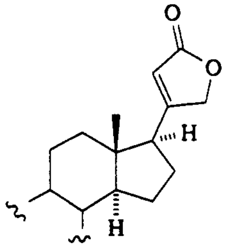

(311)

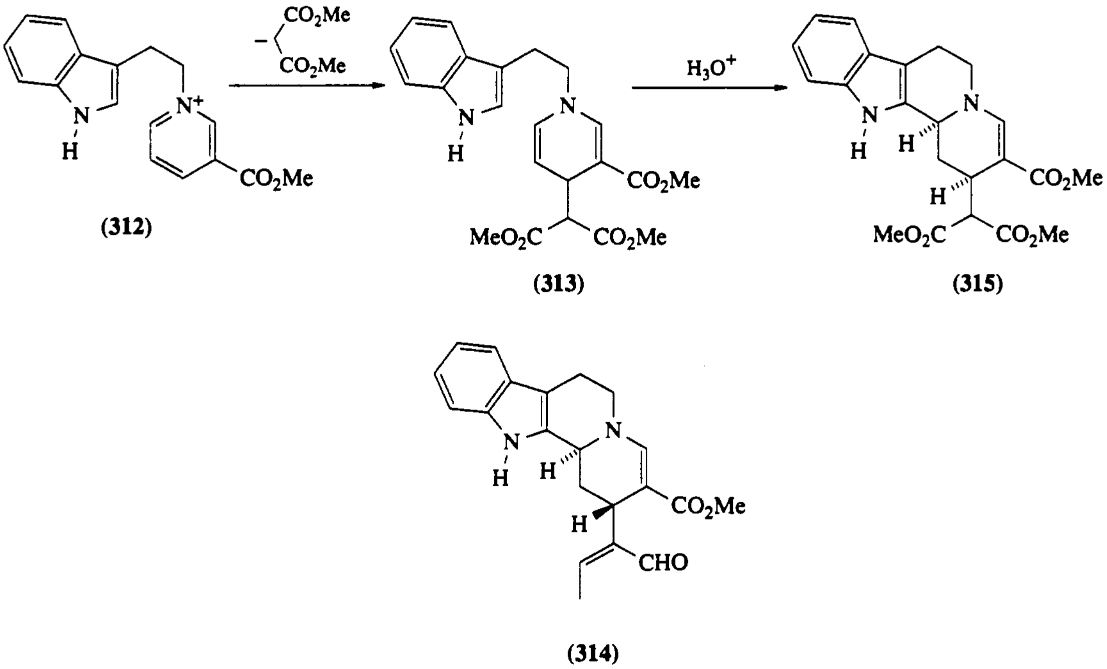
$H_3O^+$
(312)
(313)
(315)
(314)

Scheme 59

cyanoacetic acid, was employed as the starting material.[316] A new synthesis of indole alkaloids involves sequential addition of a carbanion such as the sodium salt of dimethyl malonate to a tryptophylpyridinium salt (**312**), followed by hydronium ion catalyzed cyclization of the product (**313**), to give the β-carboline (**315**) in 28% yield (Scheme 59).[317] It has recently been shown in the synthesis of the indole alkaloid vallesiachotamine (**314**) that the yield can be improved by using the lithium salt of ethyl trimethylsilylacetate as the active methylene component.[318]

Surugatoxin (**319**), with its unique spirooxindole moiety connected to a tetrahydropteridine ring, is an interesting marine natural product. Inoue *et al.* have synthesized the pentacyclic ring system (**318**) of surugatoxin in 10 steps from the oxindole derivative (**317**), which is obtained in 79% yield by a Knoevenagel condensation of isatin (**316**) and 4-phthalimidoacetoacetate.[319]

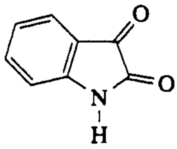

**(316)**

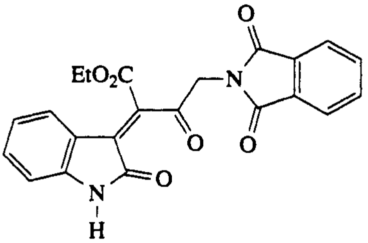

**(317)**

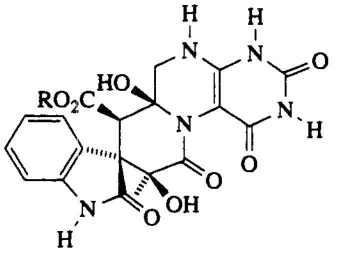

**(318)** R = Et

**(319)** R =

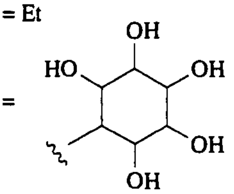

In addition to natural products, a multitude of biologically active unnatural compounds have also been synthesized using the Knoevenagel condensation. A few recent examples are given here. In an attempt to obtain enantiomerically pure 1,4-dihydropyridines as calcium channel antagonists,[281] (*R*)-sulfinylpropanone (**320**) was condensed with 2-chlorobenzaldehyde in acetonitrile with piperidine as catalyst to provide exclusively the (*E*)-benzylidene compound (**321**). Formation of the (*S*)-1,4-dihydropyridine (**323**) as a

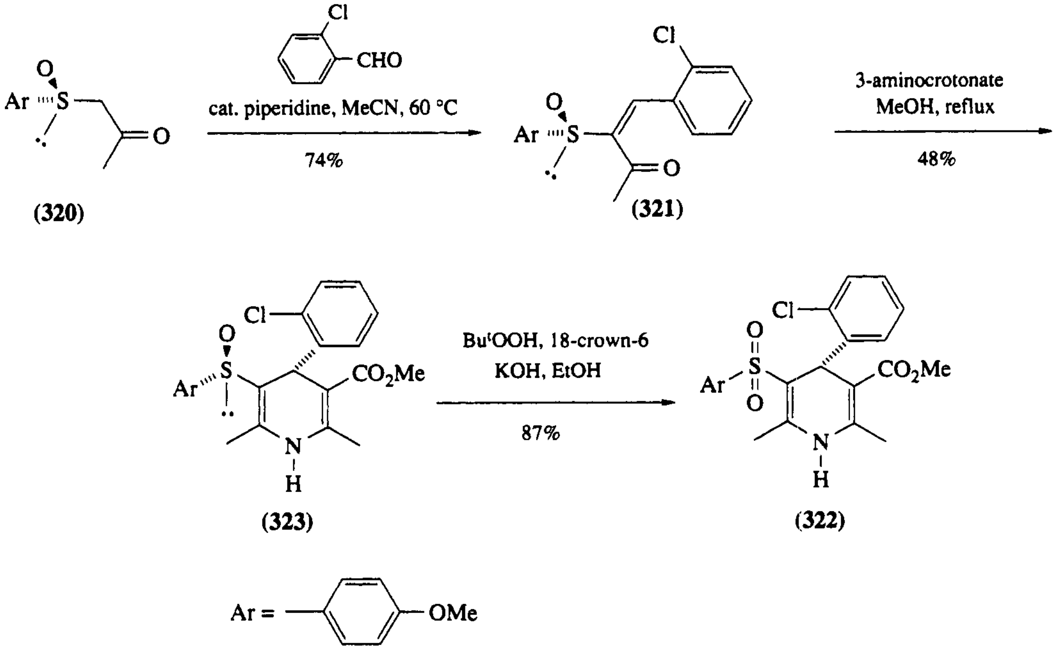

**Scheme 60**

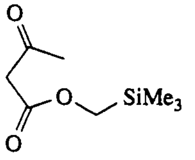

**(324)**

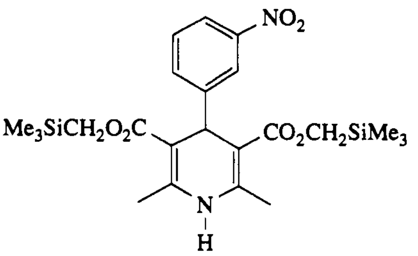

**(325)**

single diastereomer as a result of an asymmetrically induced Michael addition has been achieved by reaction with methyl 3-aminocrotonate according to Hantzsch (Scheme 60).[320] A sila-substituted nifedipine-like 1,4-dihydropyridine (**325**) has been synthesized by condensation of the Knoevenagel product obtained from 3-nitrobenzaldehyde and β-keto ester (**324**) with the β-aminocrotonic ester derived from (**324**).[321]

Compound (**329**), a potent inhibitor of dihydrofolate reductase, was synthesized by a Knoevenagel condensation of the ketone (**326**) with ethyl cyanoacetate to afford (**327**) in 28–81% yield. Catalytic hydrogenation of (**327**) over Pd/C gave almost exclusively the undesired *endo* isomer, whereas with lithium in liquid ammonia and phenol as proton donor the desired *exo* compound (**328**) was obtained in 71% yield.[322] Knoevenagel condensation of benzaldehydes with malonodinitrile in the presence of a base leads to benzylidenemalonodinitriles. These compounds, especially the 2-chlorobenzylidenemalonodinitrile (CS, **330**), are used as riot-control agents (sneeze and tear gas).[323,324]

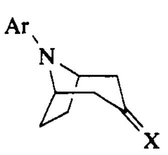

**(326)** X = O

**(327)** X =

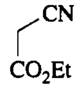

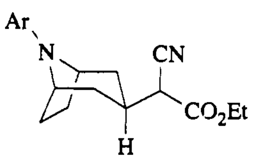

**(328)**

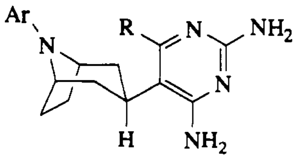

**(329)**

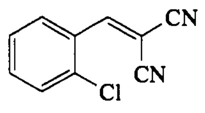

**(330)**

### 1.11.5.3 Transformation of Sugars

The Knoevenagel condensation of sugar aldehydes with different 1,3-dicarbonyl compounds is a useful method for chain elongation of carbohydrates. Thus, condensation of isopropylidene-2-arabinose (**331**) with alkyl hydrogen malonates in the presence of pyridine (Knoevenagel–Doebner modification) stereoselectively yields alkyl (*E*)-3-polyhydroxyalkylacrylates (**332**).[325–328] It is noteworthy that the Wittig reaction of (**331**) gives a mixture of (*E*)- and (*Z*)-acrylates. Compound (**332**) can be hydroxylated and reduced to give heptoses. Hexuloses, deoxyhexuloses and branched-chain sugars have been synthesized in a similar manner. For the latter reaction, monoethyl methylmalonate and α-methylacetoacetic acid are used. As an example, the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde gives the corresponding alkylidene compounds with cyanoacetate, benzoylacetate and benzoylacetone using piperidine as catalyst.[328] With the 2,5-anhydroarabinose derivative (**333**) and methyl acetoacetate, the β,γ isomer (**335**; mixture of 1,3-dicarbonyl and enol form) is obtained in addition to the Knoevenagel product (**334**). Treatment of (**335**) with acid results in the formation of a mixture of the spiro derivatives (**336**) and

(**337**), leading to the thermodynamically more stable compound (**337**) after prolonged reaction time.[329] In the Knoevenagel reaction of the 2,3-*O*-isopropylidene derivatives of D-ribofuranose (**338**) with monomethyl malonate, using pyridine as catalyst, the epimer with the *threo* arrangement at C-4 and C-5 (**339**) is obtained, due to the stronger reaction conditions. The isomerization takes place either in the starting material or in an intermediate, since the compound with the *erythro* configuration shows no tendency to epimerize.[330] An interesting example of a sugar transformation involving the Knoevenagel reaction is the synthesis of pseudopyranoses with a cyclohexane skeleton (**342**) from D-ribose *via* (**343**). One of the key steps is condensation of (**340**) and dimethyl malonate to give (**341**) using pyridine and acetic anhydride (Scheme 61).[331]

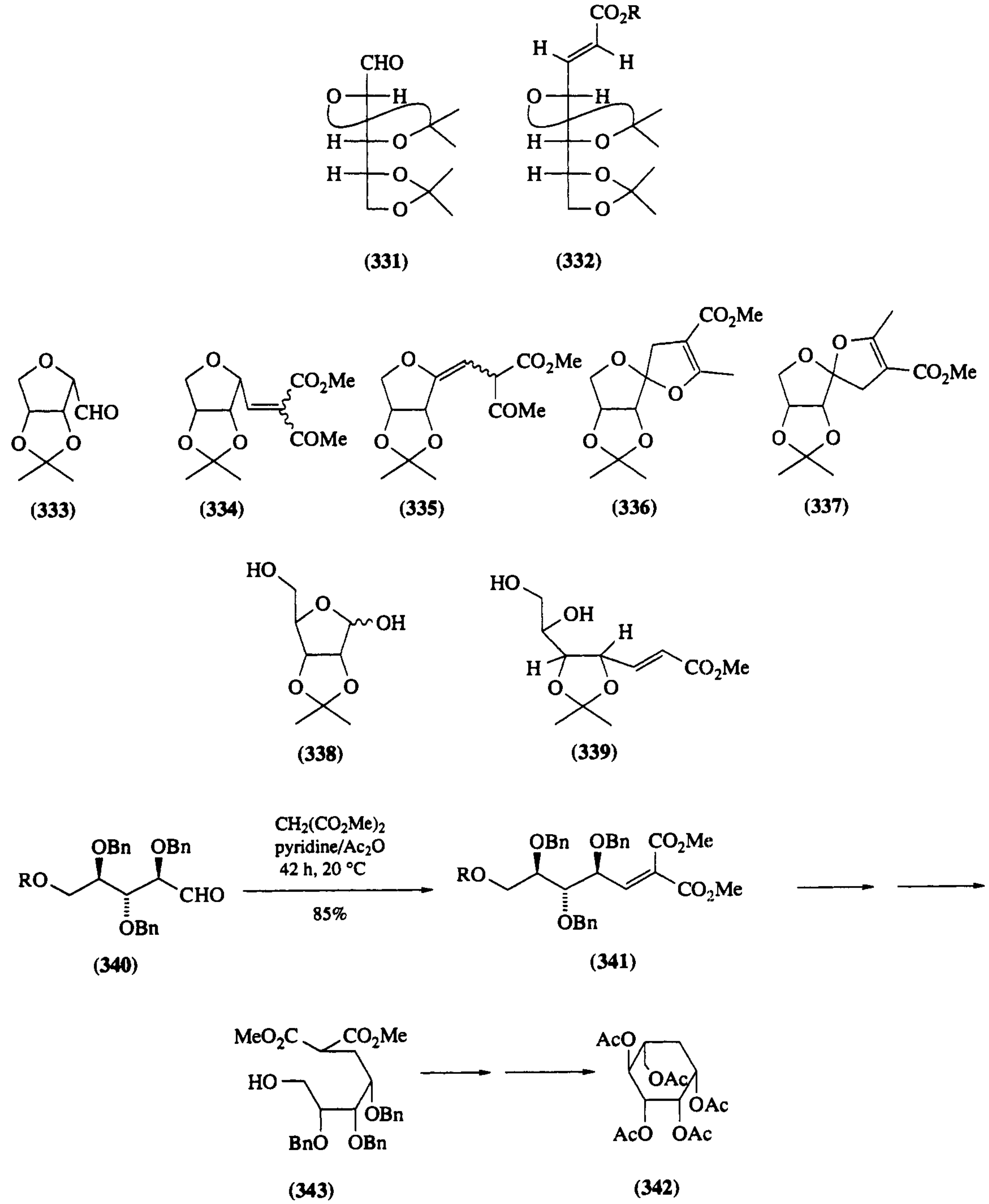

Scheme 61

### 1.11.5.4 Dyes and Polymers

The Knoevenagel condensation has been used in the synthesis of different types of dyes. Thiophene derivatives (**345**), which may be useful for dyeing synthetic fibers or plastic, have been prepared by condensation of the azo aldehydes (**344**) with a variety of methylene compounds.[332] Dyes (**347**) exhibiting positive solvatochromatical and negative thermochromatical properties are prepared by Knoevenagel reaction of isophorone (**346**) and malonodinitrile followed by an aldol condensation with substituted benzaldehydes (Scheme 62). Similar reactions have been performed using *N*,*N*-diethylthiobarbituric acid as the active methylene compound.[27] In the course of investigations directed at the preparation of synthetic oxygen carriers, tetraphenylporphyrins (**349**) containing a long chain alkylimidazole moiety were synthesized. A step in this approach was the Knoevenagel condensation of the aldehyde (**348**) with malonic acid.[333]

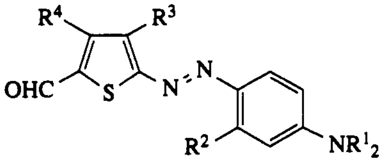

**(344)**

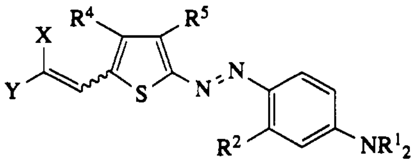

**(345)**

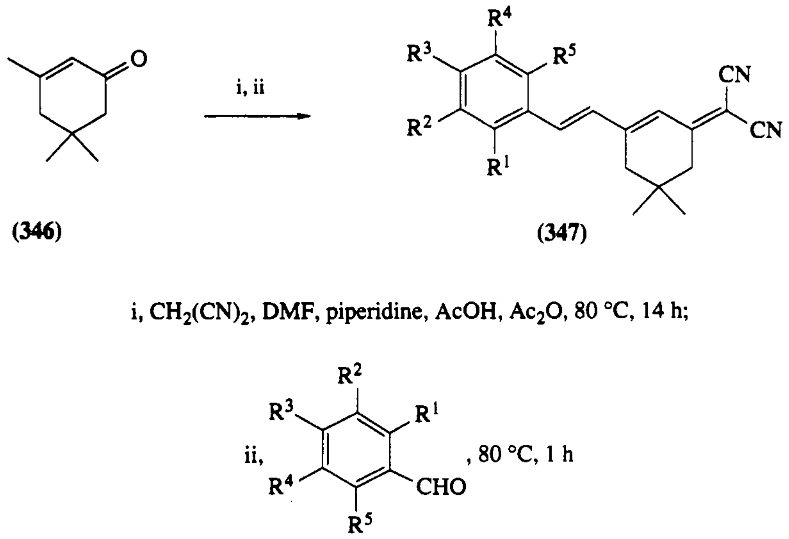

**(346)** **(347)**

i, $CH_2(CN)_2$, DMF, piperidine, AcOH, $Ac_2O$, 80 °C, 14 h;

ii, , 80 °C, 1 h

**Scheme 62**

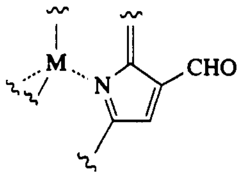

**(348)**

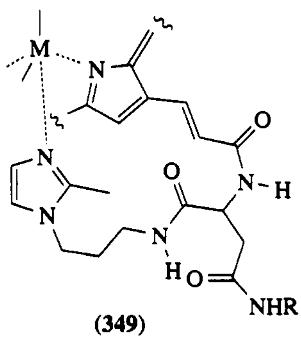

**(349)**

With respect to the formation of polymers, the Knoevenagel condensation is usually employed to prepare the monomers.[334–337] Thus, 4-(*N*,*N*-dimethylamino)cinnamaldehyde is condensed with methyl cyanoacetate to give the corresponding Knoevenagel product (**350**), which is copolymerized with terephthalate and ethylene glycol to give a brilliant yellow polyester.[337] On the other hand, the Knoevenagel reaction has been successfully used to perform the polycondensation step itself. Hence, poly(arylenalkenylene)s and poly(heteroarylenalkenylene)s have been synthesized by a Knoevenagel condensation of bifunctional active methylene compounds like (**351**) and bifunctional aldehydes such as (**352**).[338,339]

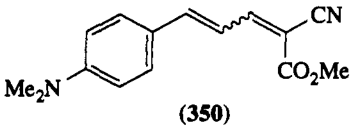

**(350)**

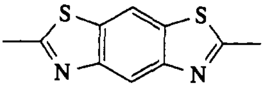

**(351)**

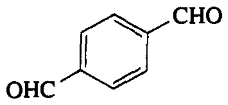

**(352)**

## 1.11.6 SYNTHETIC ALTERNATIVES

The Knoevenagel condensation is the method of choice for the preparation of α,β-unsaturated dicarbonyl compounds and related compounds and only a few alternative methods have been developed. However, with the traditional Knoevenagel condensation there are problems with the reactivity of ketones, with the competitive Michael addition occuring in the reaction of some active methylene compounds. There is also a problem with stereocontrol in the synthesis of Knoevenagel products from unsymmetrical 1,3-dicarbonyl compounds. An alternative method is the addition of Grignard reagents to vinylogous carbamates (see Section 11.2.6).[96] Another possibility is the reaction of a metal ketimate with malonodinitrile to yield ylidenemalonodinitriles (see Section 11.3.1.7).[158]

A way to synthesize enantiomerically pure α,β-unsaturated-α-sulfinylcarboxylic esters (**354**) is based on reaction of the lithiated enantiomerically pure α,β-unsaturated sulfoxide (**353**) with carbon dioxide, followed by esterification (Scheme 63).[192] Similarly, procedures involving α-vinyl anions are known for the synthesis of α,β-unsaturated α-keto esters and α,β-unsaturated-α-formylcarboxylic acids.[340]

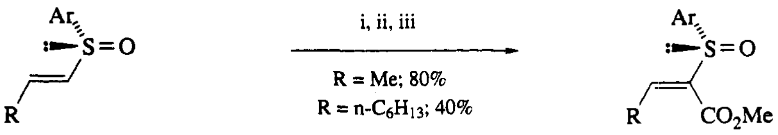

**(353)** **(354)**

i, $Pr^i_2NLi$, THF, −78 °C; ii, $CO_2$, −78 °C; iii, MeI, HMPA

**Scheme 63**

A general alternative to obtain Knoevenagel products is the dehydrogenation of β-dicarbonyl and related compounds. In practice, however, the yields using classical dehydrogenation protocols like DDQ oxidation or α-halogenation/dehydrohalogenation are usually modest.[341] Sulfinyl compounds with at least one β-hydrogen are known to undergo *syn* elimination on pyrolysis to yield alkenes. By using this method α,β-unsaturated dicarbonyl compounds can be obtained by pyrolysis of 1,3-dicarbonyl-2-phenylsulfinyls.[342–344] Similarly, α-selenodicarbonyl compounds easily undergo oxidative *syn* elimination to afford the α,β-unsaturated-1,3-dicarbonyls. Several methods have been developed to synthesize the α-selenodicarbonyls.[345]

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# 1.12
# The Perkin Reaction

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## 1.12.1 INTRODUCTION

The Perkin reaction involves the condensation of a carboxylic acid anhydride and an aldehyde in the presence of a weak base, often the sodium or potassium salt of the acid or triethylamine, to give unsaturated carboxylic acids (equation 1).[1] The first example of this reaction was described by Perkin in 1868 and involves a synthesis of coumarin by heating the sodium salt of salicylaldehyde with acetic anhydride (equation 2).[2] The reaction is generally applicable only to aromatic aldehydes and is particularly useful for the preparation of substituted cinnamic acids, as illustrated by equation (3).[3]

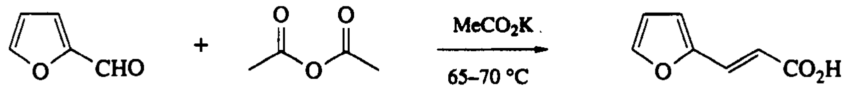

(1)

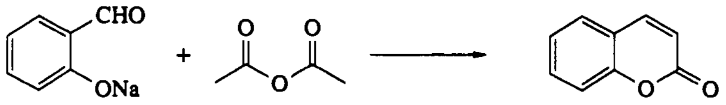

(2)

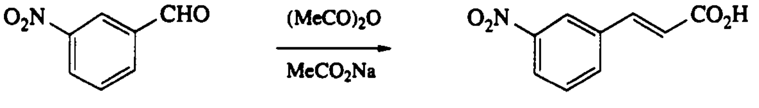

(3)

In 1883, an important variation of the reaction was reported by Plöchl, involving the condensation of benzaldehyde and hippuric acid in the presence of acetic anhydride.[4] It was Erlenmeyer, however, who determined the azalactone structure of the product (equation 4) and extended its scope to include other

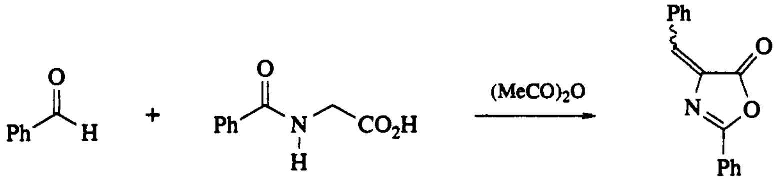

(4)

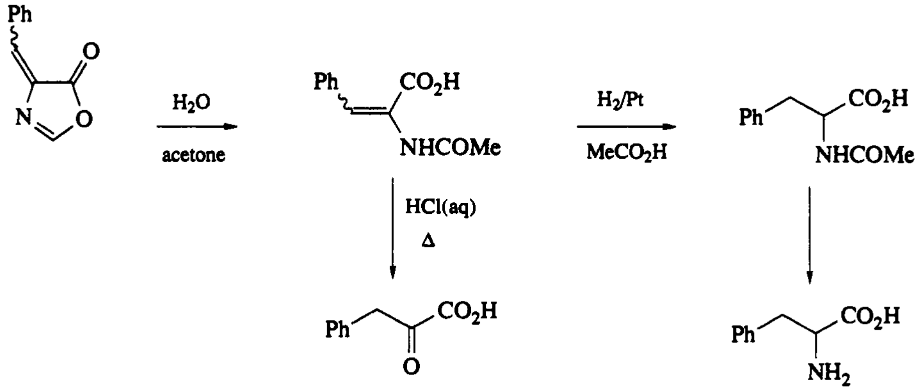

Scheme 1

aldehydes; this modification of the reaction, utilizing acylglycine derivatives, is usually referred to as the Erlenmeyer azalactone synthesis.[5,6] Azalactones (also referred to as oxazolones) serve as important intermediates for the synthesis of α-amino acids and α-keto acids (Scheme 1).[7] Interestingly, penicillin was initially assigned an incorrect thiazolidine–oxazolone structure, and much information regarding the chemistry and properties of azalactones was developed from penicillin research during the Second World War.[8] In this chapter, the scope of the Perkin condensation is examined with an emphasis on modifications that have extended its utility beyond the synthesis of cinnamic acids.

## 1.12.2 MECHANISTIC CONSIDERATIONS

The generally accepted mechanism for the Perkin reaction is shown in Scheme 2. Much of the early work leading to this view, which was the result of numerous investigations spanning a period of greater than 50 years, has been reviewed in some detail.[1] Formation of the anhydride enolate (**1**) and aldol-type condensation generates the alkoxide anhydride (**2**). Intramolecular acylation provides an acetoxycarboxylate (**3**), which forms a mixed anhydride; elimination of acetic acid and hydrolysis affords the unsatu-

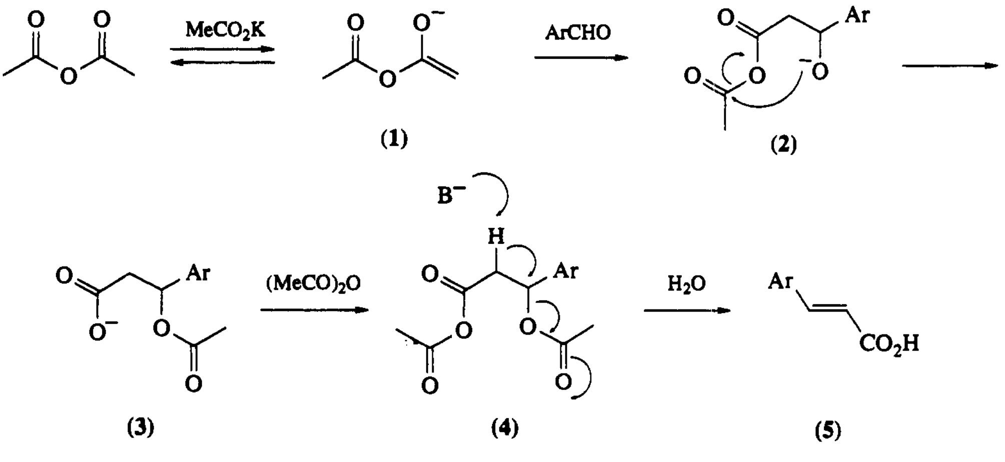

Scheme 2

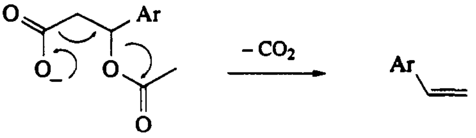

(3)

(5)

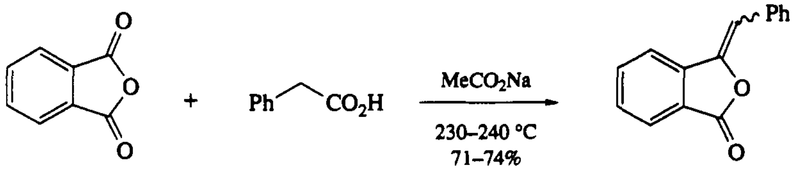

(6)

rated acid (**5**). A potential side reaction involves decarboxylative elimination of (**3**) to form an alkene (equation 5). This side reaction is generally minor, although higher temperatures and/or activating substituents may facilitate this pathway (equation 6;[9] compare this reaction to conditions and outcome shown in equation 12).

The Perkin reaction of an aromatic aldehyde with phenylacetic acid affords preferentially the α-phenylcinnamic acid stereoisomer in which the phenyl groups are in a *cis* relationship (equation 7).[10] This product was also shown to be favored thermodynamically; heating α-phenyl-*cis*-cinnamic acid in a dilute solution of acetic anhydride–triethylamine affords an equilibrium mixture containing 81% of the (*E*)-cinnamic acid and 19% of the (*Z*) isomer (equation 8). Zimmerman and Ahramjian studied this reaction in some detail, and through a series of elegant experiments found evidence indicating that the condensation step of the sequence is not reversible.[10] The lack of reversibility is suggested to result from rapid acetylation of the β-alkoxide substituent in the intermediate analogous to (**2**; Scheme 2). Furthermore, the elimination of each of the diastereomeric 3-hydroxy-2,3-diphenylpropionic acids (**6**) and (**7**) under Perkin conditions (acetic anhydride, $Et_3N$, reflux, 35 min), affords products consisting of 99 ± 2% of α-phenyl-*trans*-cinnamic acid (**8**; Scheme 3); under the same relatively mild conditions, the Perkin condensation of benzaldehyde and phenylacetic acid affords products consisting of 96% of (**8**). Thus, a significantly greater proportion of the stable isomer is obtained than is accountable on simply a thermodynamic basis. The observed product ratios apparently reflect a kinetic preference. The authors postulate that the stere-

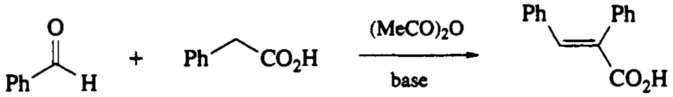

(7)

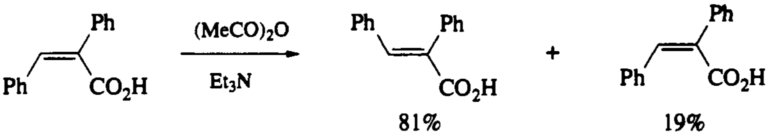

(8)

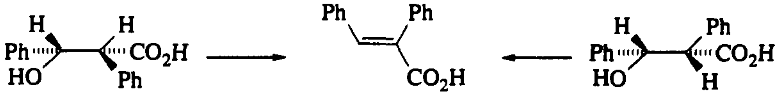

(6) (8) (7)

Scheme 3

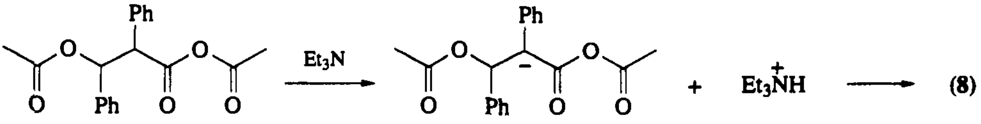

*erythro* or *threo* (**9**)

Scheme 4

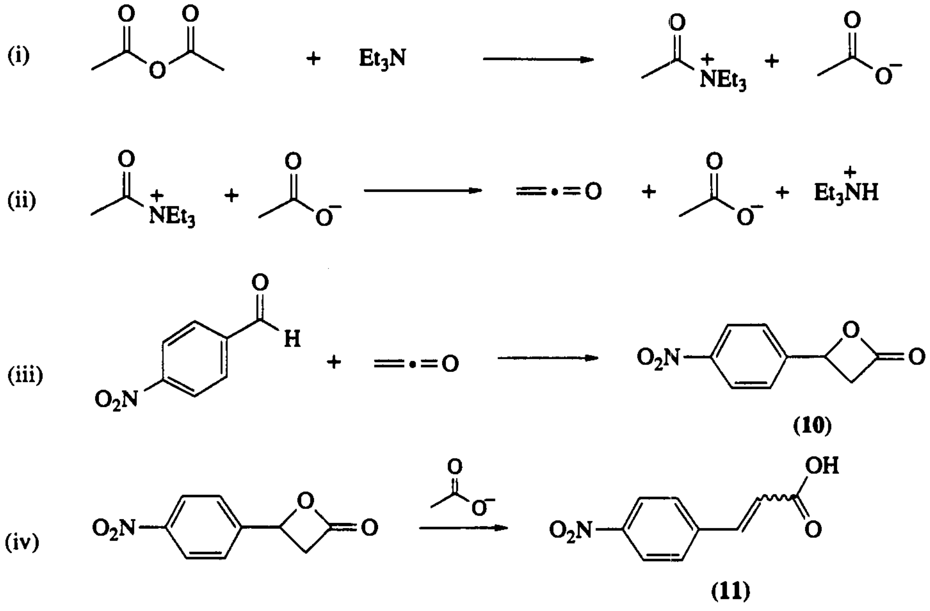

Scheme 5

ochemical outcome of the reaction is determined by the conformations of the presumed intermediates (**9**) that allow maximum conjugation between the carboxyl group, the double bond being formed and the β-phenyl substituent in the transition state leading to (**8**) (overlap control; Scheme 4).[11] Applying this underlying driving force, the authors present a series of arguments explaining the preference of both diastereomers (**9**) to afford a single geometric isomer (**8**). Kinetic data, concluding that the condensation step is the slowest step in the Perkin reaction, have also been reported.[12]

More recently, results have been published indicating that the initial condensation, at least in the presence of triethylamine, may not be only of the aldol type but also include a pathway involving the formation and subsequent cycloaddition of ketene to form a β-lactone intermediate that cleaves to provide

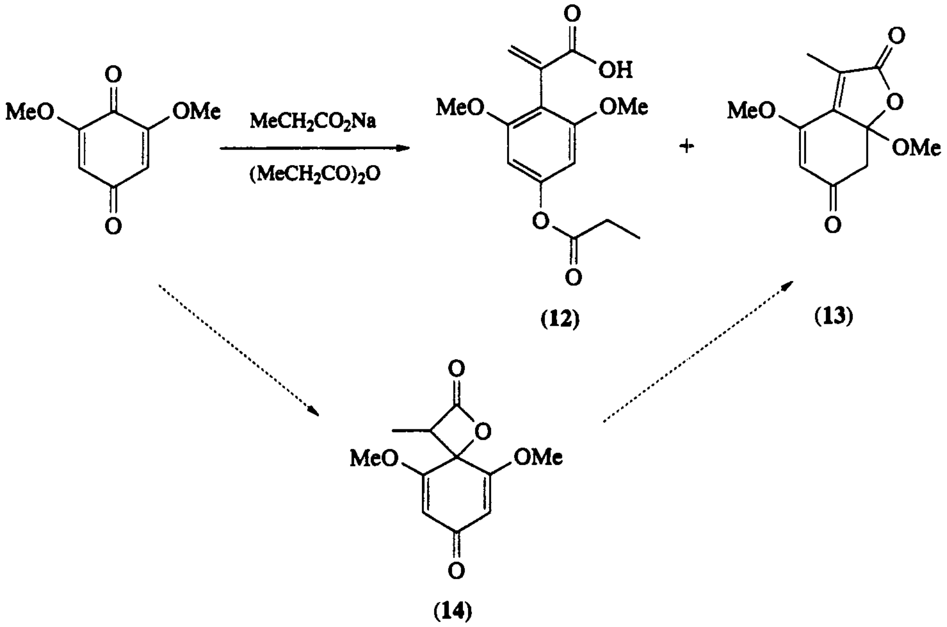

Scheme 6

the cinnamic acid (**11**; Scheme 5).[13] Spectroscopic (IR, NMR) evidence is provided for the formation of a β-lactone intermediate (as suggested in 1936 by Hurd and Williams) in the reaction of *p*-nitrobenzaldehyde with ketene to afford the Perkin product, cinnamic acid. Subsequently, the reaction between *p*-nitrobenzaldehyde, acetic anhydride and triethylamine was investigated, and the β-lactone (**10**) was observed by IR spectroscopy under these conditions. Furthermore, it was shown that independently prepared (**10**) treated with acetic anhydride and triethylamine affords *p*-nitrocinnamic acid (**11**). It was also found that decomposition of (**10**) in dioxane to afford (**11**) is catalyzed by acetate ion, while amine catalyzes the decomposition of (**10**) to a series of minor products rather than (**11**), leading the authors to propose the mechanism shown in Scheme 5.

Analogous results were reported earlier concerning the Perkin reaction of quinones.[14] Treatment of 2,6-dimethoxy-*p*-benzoquinone with propionic anhydride in the presence of sodium propionate affords a mixture of condensation-derived products (**12**) and (**13**) (Scheme 6). However, when the reaction is carried out under milder conditions, among the products isolated is the β-lactone (**14**). Compound (**14**) can be converted under Perkin conditions to (**12**) and (**13**). It is noted that (**14**) could be in equilibrium with dimethoxybenzoquinone and methylketene; its isolation does not prove with certainty its intermediacy in the formation of (**12**) and (**13**). Thus, the actual mechanism of this condensation is not necessarily as simple as indicated in Scheme 2 and may involve more than one distinct pathway, depending on the exact nature of the particular substrate or base employed.

## 1.12.3 REACTION SCOPE

### 1.12.3.1 Preparation of Cinnamic Acids and Related Aromatic Derivatives

The Perkin condensation is a primary method for the synthesis of substituted cinnamic acids (equation 9), and several examples are illustrated in Table 1.[1,15,16] Interestingly, 2,6-dimethylbenzaldehyde (entry i) fails to react under the conditions employed, while 2,6-dichlorobenzaldehyde (entry j; similar steric situation) affords the corresponding cinnamic acid in excellent yield, illustrating the activating effect of the electron-withdrawing chloro substituents. The reaction is limited to acetic acid and monosubstituted acetic acids, as two α-hydrogen atoms must necessarily be eliminated to form the α,β-unsaturation. The reaction typically requires relatively high temperatures (>150 °C). The aromatic dialdehydes phthalaldehyde,[17] isophthalaldehyde[18] and terephthaldehyde[19] also undergo the transformation, affording the corresponding benzenediacrylic acids in 20–80% yields. Heteroaromatic aldehydes such as furfural[20] (equation 1) and 2-thiophenecarbaldehyde[21] also take part in the reaction. 2-Pyridinecarbaldehyde, on the other hand, does not afford the Perkin product, 3-(2-pyridyl)acrylic acid.[22] Instead, it gives a mixture of indolizine derivatives as shown in equation (10). Detailed mechanistic discussions for these and related transformations are found in the original work. Cinnamaldehyde affords β-styrylacrylic acid under Perkin conditions (equation 11).[23] An extensive list of cinnamic acids formed in this reaction is found in ref. 1.

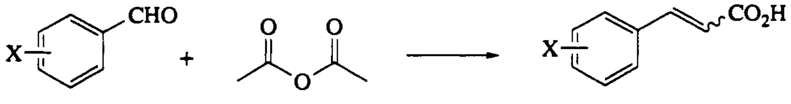

(9)

Table 1 Preparation of Cinnamic Acids from Substituted Benzaldehydes[1,15,16]

| *Entry* | *Substituent* | *Yield of cinnamic acid (%)* |
|---|---|---|
| a | H | 70–75 |
| b | 4-Me | 33 |
| c | 2-Cl | 71 |
| d | 4-Cl | 52 |
| e | 2-MeO | 55 |
| f | 4-MeO | 30 |
| g | $2\text{-}NO_2$ | 75 |
| h | $4\text{-}NO_2$ | 82 |
| i | $2,6\text{-}Me_2$ | 0 |
| j | $2,6\text{-}Cl_2$ | 82 |

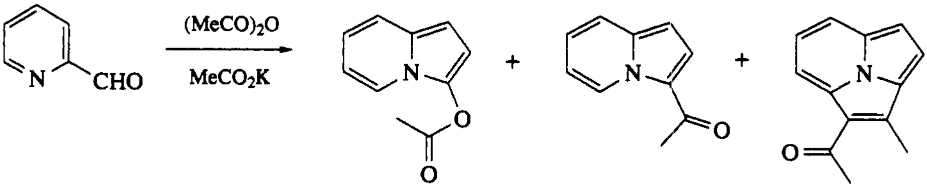

(10)

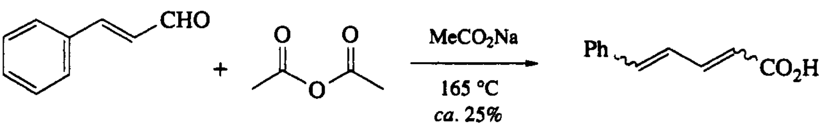

(11)

Phthalic anhydride, when used as the carbonyl component in the Perkin reaction, affords, on treatment with acetic anhydride and potassium acetate, phthalylacetic acid (**15**; equation 12).[24] α-Arylacetic acids also react with aromatic aldehydes to afford α-arylcinnamic acids (Ogliaro modification of the Perkin condensation, equation 7);[1] this type of reaction presumably involves the formation of the mixed anhydride of phenylacetic acid and acetic acid and/or phenylacetic anhydride. This modification is also illustrative of the equilibrium that is established between acid, acid salt and acid anhydrides under the conditions of the reaction.

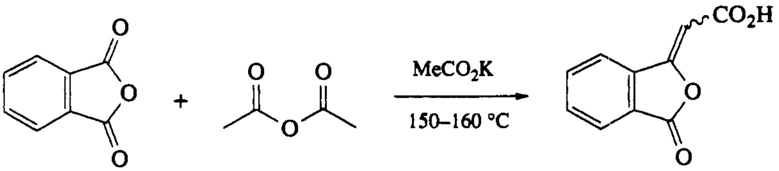

**(15)**

(12)

## 1.12.3.2 Aliphatic Aldehydes and Ketones

Simple aliphatic or aromatic ketones are not suitable substrates in the Perkin transformation. Similarly, aliphatic aldehydes are not generally acceptable components in this reaction. This long-known limitation was studied by Crawford and Little.[25] They demonstrated that many aliphatic aldehydes give diacetates and enol acetates when heated with acetic anhydride, with or without sodium acetate, suggesting this side reaction causes the typical Perkin process to fail. Semmeler had previously obtained similar results.[26] They did show, however, that several short chain aldehydes, as well as *trans*-citral (**16**), undergo the Perkin condensation with *p*-nitrophenylacetic anhydride; the *p*-nitrophenyl substituent activates the anhy-

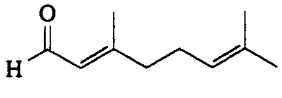

**(16)**

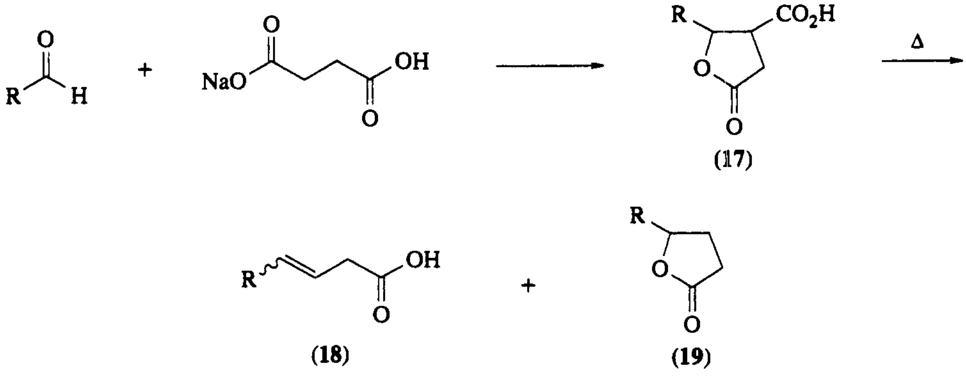

**Scheme 7**

dride, and these reactions are carried out at 35–55 °C. Higher aldehydes and *cis*-citral do not give Perkin products under these conditions, presumably because of increased hindrance due to the side chain sterically interfering with the reactivity of the carbonyl group. It is also suggested that a principal factor in the decreased reactivity of aliphatic aldehydes is the reduced rate in the elimination step relative to the aromatic systems in which this process is facilitated by conjugation of the newly forming double bond and the aromatic π-system in the transition state. Thus, from a practical standpoint, the Perkin condensation remains limited in scope to the use of aromatic aldehydes.

Related condensations involving the replacement of the anhydride component with succinic acid (Fittig synthesis)[27] or with malonic acid (Knoevenagel condensation, see Volume 2, Chapter 1.11) provide complementary preparative methods which are useful for both aromatic and aliphatic systems. The Fittig extension of the Perkin transformation involves heating an aliphatic or aromatic aldehyde with sodium succinate and acetic anhydride to give the condensation products (**17**), which lose carbon dioxide to afford β,γ-unsaturated carboxylic acids (**18**), accompanied by small amounts of the corresponding γ-butyrolactones (**19**; Scheme 7).[27]

### 1.12.3.3 Preparation of Coumarins

As exemplified by equation (2), the Perkin condensation of *o*-hydroxybenzaldehydes is an important method for the synthesis of substituted coumarins. An interesting variation on this procedure has been reported recently.[28] Heating a mixture of *o*-fluorobenzaldehyde, 2-thiopheneacetic acid, acetic anhydride and triethylamine affords directly the coumarin (**20**; equation 13) instead of the expected cinnamic acid (**21**). The reaction proceeds similarly with several arylacetic acids. The reaction presumably proceeds through the cinnamic acids (**21**). The observed product can conceivably arise by direct nucleophilic displacement involving the carboxylate or by an elimination/addition (benzyne) mechanism. The authors note that when 2-fluorobenzaldehyde is replaced by its 2-bromo analog in this reaction, the substituted cinnamic acid (**22**) is the major product and the corresponding coumarin (**20**) is obtained only in low yield. It is suggested that since it is known that fluoride is displaced more rapidly in nucleophilic aromatic substitution reactions, while bromo aromatic compounds form benzynes more rapidly, this result is consistent with a nucleophilic displacement mechanism.

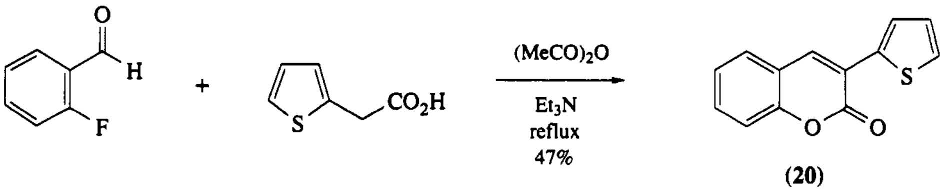

**(20)**

(13)

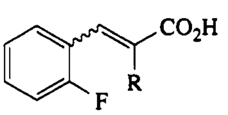

**(21)** R = 2-thienyl

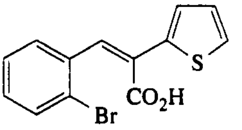

**(22)**

Analogous to the preparation of coumarins (equation 2), treatment of 2-methyl-3-formyl-4-hydroxyquinoline (**23**) with acetic anhydride and triethylamine affords the pyranoquinoline (**24**; equation 14).[29] When sodium acetate was employed as the base, instead of triethylamine, no pure (**24**) could be isolated.

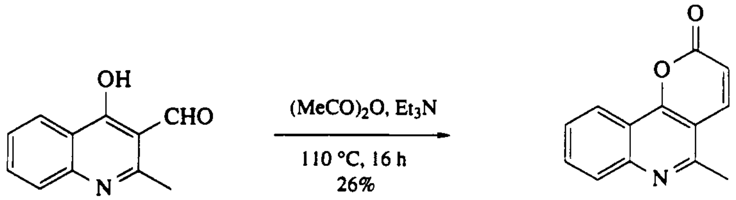

**(23)** **(24)**

(14)

Recently, it has been reported that significantly higher yields are obtained and shorter reaction times required in the Perkin synthesis of cinnamic acids when sodium acetate is replaced by cesium acetate.[30]

## 1.12.4 ERLENMEYER AZALACTONE SYNTHESIS

### 1.12.4.1 General and Mechanistic Considerations

An important variation of the Perkin reaction is the Erlenmeyer azalactone synthesis exemplified by equation (4), involving condensation of an aldehyde and an *N*-acylglycine derivative in the presence of acetic anhydride and sodium acetate.[6] Although this reaction, analogous to the classical Perkin condensation, was initially limited to the use of aromatic aldehydes, Baltazzi and Robinson reported[31] that the use of lead acetate and THF allowed the preparation of several azalactones derived from aliphatic aldehydes (equation 15). The results for the condensation of several aldehydes and ketones with hippuric acid (**28**) under these conditions are shown in Table 2. The reaction proceeds through the intermediate (**26**) (intramolecular condensation of **25**), which reacts with the aldehyde in Perkin fashion to provide the so-called azalactone product (Scheme 8). It is the formation of such oxazolones from acylamino acids which is be-

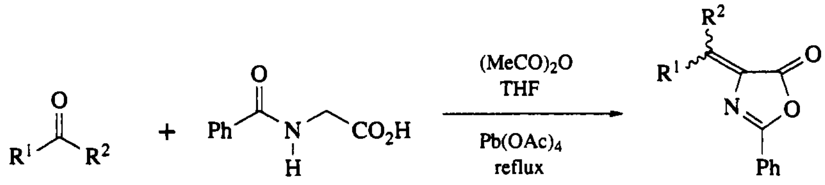

(**28**) (**29**)

(15)

Table 2 Erlenmeyer Reaction in the Presence of $Pb(OAc)_4$[31]

| $R^1R^2CO$ | *Reflux time* (h) | *Yield of (**29**)* (%) |
|---|---|---|
| Propanal | 4 | 55 |
| Isobutyraldehyde | 4 | 61 |
| Cinnamaldehyde | 4.5 | 78 |
| Cyclohexanone | 22 | 70 |
| 2-Methylcyclohexanone | 22 | 5–6 |
| Fluorenone | 22 | 71 |

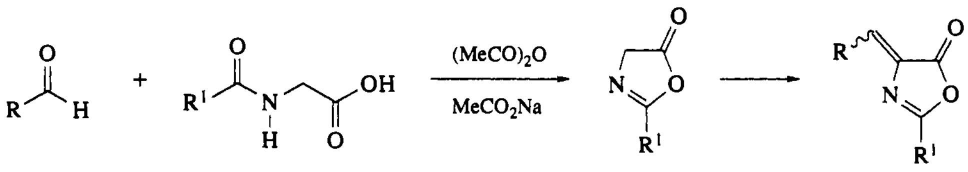

(**25**) (**26**)

**Scheme 8**

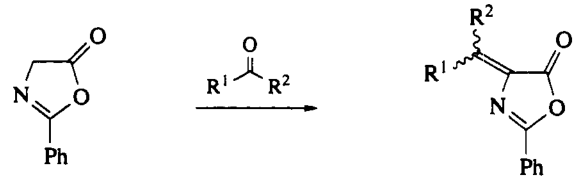

(**26**) (**30**)

(16)

lieved to be primarily responsible for racemization during peptide synthesis using activated esters.[32] Crawford and Little, in a key mechanistic study, demonstrated that independently prepared 2-phenyloxazol-5-one (**26**) reacts with aldehydes in the absence of both acetic anhydride and sodium acetate to provide Perkin products (**30**; equation 16).[33]

The oxazolone (**26**) is highly activated and acts as the equivalent of the anhydride reagent in the normal Perkin condensation. Compound (**26**) may be thought of as the anhydride of the parent α-acylamino acid and may be generated from acylamino acids using cyclodehydrating agents other than acetic anhydride such as carbodiimides[34] or ethyl chloroformate.[35] Yields in the condensation of (**26**) and carbonyl compounds are improved by the addition of lead acetate or acetic anhydride, perhaps facilitating the elimination step. The results for the reaction of (**26**) with several carbonyl compounds are shown in Table 3.[33] Aromatic aldehydes (entries a–d) react quite well and afford (**30**) in good yields. Lower aldehydes (entries e–g) give moderate to good yields of product, particularly in the presence of lead acetate; heptanal, octanal, 2-methylpropanal and 2-ethylbutanal fail to provide (**30**) under these conditions. Acetone and cyclohexanone also afford condensation products in this reaction. Thus, the similarity between the Perkin condensation and the Erlenmeyer reaction lies in the analogy between the role of the acid anhydride in the former case and the intermediate oxazolone (**26**) in the latter, each condensing with aldehydes to generate a new carbon–carbon double bond. It should be noted that there has been significant effort directed toward the synthesis of saturated azalactones of the general structure (**31**), including the development of methodology for the preparation of compounds possessing high enantiomeric purity at C-2,[36] this center being highly prone to racemization, as well as the development of alternative methods for the synthesis of this heterocyclic system; the reader is referred to earlier reviews in these areas.[6,37]

**Table 3** Condensation of 2-Phenyloxazol-5-one with Aldehydes and Ketones[33]

| *Entry* | *Carbonyl compound* | *Yield of (30) (%)* |
|---|---|---|
| a | Benzaldehyde | 63[a] |
| b | Anisaldehyde | 55[a] |
| c | Furfuraldehyde | 82[a] |
| d | Cinnamaldehyde | 72[a] |
| e | Ethanal | 58[b] |
| f | Propanal | 55[b] |
| g | Butanal | 34[b] |
| h | Acetone | 35[b] |
| i | Cyclohexanone | 74[b] |

[a] Based on equimolar quantities of the reactants. Much higher yields can be obtained by using an excess of either component.
[b] Reaction carried out in the presence of lead acetate.

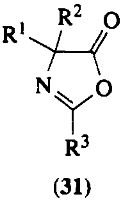

(**31**)

## 1.12.4.2 Geometric Isomers of Oxazolone Products

The Erlenmeyer azalactone synthesis generally affords predominantly, and often exclusively, (*Z*) isomers (**32**).[38] However, a simple method for the synthesis of (*E*) isomers (**33**), obtained previously by separation of isomeric mixtures or isomerization procedures, has been reported.[39] Aromatic aldehydes condense with hippuric acid when heated in polyphosphoric acid (PPA) to afford (**33**) in 80–90% yields (equation 17; Table 4). Alternatively, the (*Z*) isomers may be heated in PPA to afford the corresponding (*E*) isomers in excellent yield. The authors note that hippuric acid is not converted to (**26**) in PPA, the generally accepted intermediate in the Erlenmeyer synthesis. Furthermore, both isomers of 2-(benzamidoyl)cinnamic acid, (**34**) and (**35**), obtained by the alkaline hydrolysis of (**32**; R = H, Ar = Ph) and (**33**; R = H, Ar = Ph), respectively are converted to (**33**; R = H, Ar = Ph) in PPA (Scheme 9). The authors therefore suggest a mechanism involving condensation, first of the aldehyde and hippuric acid followed by

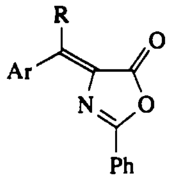
(32)

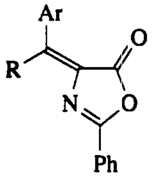
(33)

cyclodehydration. However, it is not clear what factors control the interesting stereochemical outcome of the overall transformation. It should be noted that it is also possible that (26) is indeed formed in this reaction, however under these conditions it exists only in low steady-state concentrations (in equilibrium with hippuric acid) and is therefore still a potential intermediate. The (*E*) isomers are converted to the (*Z*) isomers by heating with pyridine.[6c] A report has also appeared describing the use of ion-exchange resins in the Erlenmeyer synthesis to obtain (*E*) isomers of the product azalactones.[40]

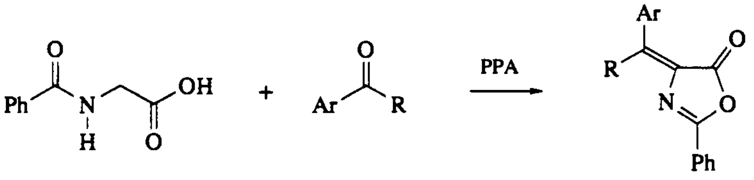

(33) (17)

Table 4 Preparation of (*E*)-4-Arylmethylene-2-oxazolin-5-ones (*33*)[39]

| *Ar* | *R* | *Yield of (33) (%)* |
|---|---|---|
| 4-$ClC_6H_4$ | H | 85 |
| 4-$MeOC_6H_4$ | H | 90 |
| 4-$MeC_6H_4$ | H | 80 |
| 3,4-$(MeO)_2C_6H_3$ | H | 82 |
| 4-$HOC_6H_4$ | H | 80 |
| 2-$HOC_6H_4$ | H | 70 |
| Ph | Me | 80 |
| 4-$ClC_6H_4$ | Me | 52 |
| 4-$MeOC_6H_4$ | Me | 50 |
| 4-$NO_2C_6H_4$ | Me | 88 |
| 4-$MeC_6H_4$ | Me | 70 |

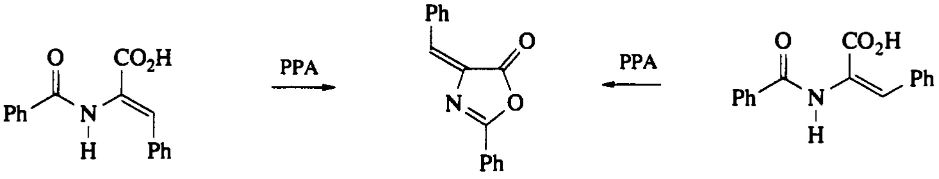

(34) (33) Ar = Ph; R = H (35)

Scheme 9

### 1.12.4.3 Imines as Substrates

The condensation is also reported to proceed with aromatic Schiff bases, as shown in equation (18).[41] In a more recent publication, the condensation of 2-substituted oxazolones with imines was compared to the corresponding reaction with the parent aldehydes and ketones.[42] When aldehydes are employed in place of imines, better or comparable yields of condensation product (36) are obtained. Two ketones, acetophenone and cyclohexanone, were investigated in this study. In both of these cases, significantly improved yields of (**36**) are obtained with the corresponding ketone imine (equation 19; Table 5). The authors also note that in the ring cleavage of (**36**) with aniline, the products maintain the stereochemistry of the carbon–carbon double bond (equation 20). The same authors have also published work describing the preparation and conversion of several azalactones of the general structure (**36**), by 1,5-bond cleavage with amines, hydroxide and alkoxides, to afford *N*-substituted 2-acylamino-2-alkenamides (**37**)[43] or 2-acylamino-2-alkenoic acids (or esters) (**38**),[44] respectively (Scheme 10); these cleavage reactions afford alkenes that maintain the initial (*Z*) stereochemistry of the oxazolones (**36**). From a practical standpoint, it has been suggested that α-acetamido compounds are preferable to the corresponding α-benzamido derivatives when the ultimate target (such as in the case of the preparation of amino acids) requires

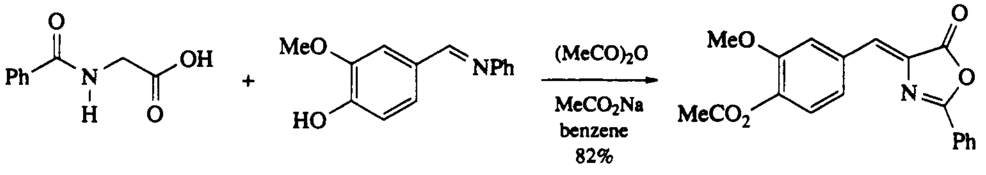
Ph
N
H
O
OH
O
+
MeO
HO
NPh
(MeCO)2O
MeCO2Na
benzene
82%
MeO
MeCO2
O
O
N
Ph

(18)

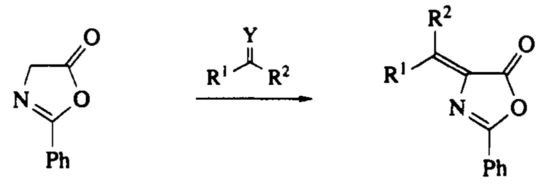
O
N
O
Ph
Y
R1
R2
R2
R1
O
N
O
Ph

(**36**)

(19)

**Table 5** Condensation of Oxazolones with Carbonyl Compounds and Their Corresponding Imines[42]

| *R¹* | *R²* | *Y* | *Yield of (36) (%)*[a] |
|---|---|---|---|
| Ph | H | O | 77 |
| Ph | H | *N*-Ph | 60 |
| Ph | Me | O | 0 |
| Ph | Me | *N*-Ph | 42 |
| —(CH$_2$)$_5$— | | O | 8.4[b], 25[c] |
| —(CH$_2$)$_5$— | | *N*-Ph | 50 |

[a] Reaction mixtures heated on water bath for *ca.* 10 min. [b] Reaction mixture heated for 20 h. [c] Reaction mixture heated with *p*-TsOH (catalyst) for 20 h.

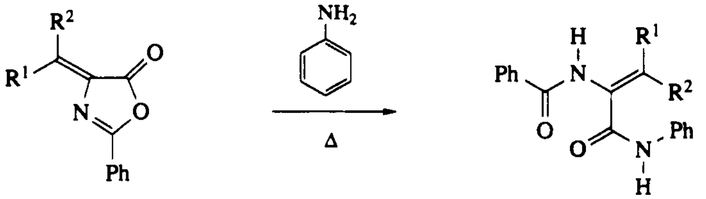
R2
R1
O
N
O
Ph
NH2
Δ
H
R1
Ph
N
R2
O
O
N
Ph
H

(**36**)

(20)

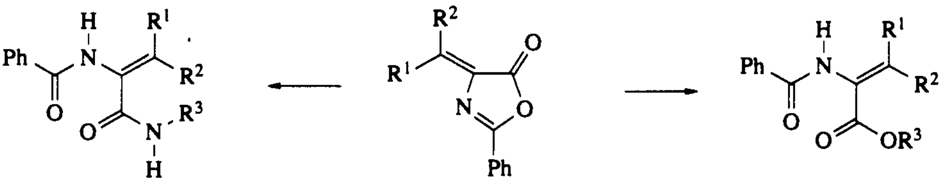
H
R1
Ph
N
R2
O
O
N
R3
H
R2
R1
O
N
O
Ph
H
R1
Ph
N
R2
O
O
OR3

(**37**) (**36**) (**38**)

**Scheme 10**

cleavage of this moiety, since they are more readily hydrolyzed;[1] it is also suggested that it is generally simpler to separate the hydrolysis products from acetic acid than from benzoic acid.[6b] Meléndez and coworkers have also reported related work on the cleavage of oxazolones to give stereospecifically (*Z*) and (*E*) isomers of dehydroacylamino acids and amides.[45] The mechanism of the hydrolysis of (*Z*)-4-benzylidene-2-methyloxazolin-5-one and (*Z*)-4-benzylidene-2-phenyloxazolin-5-one derivatives has been investigated, and the results indicate that under alkaline conditions hydrolysis occurs through nucleophilic attack at the carbonyl carbon of the substrate, while acidic hydrolysis involves attack at the imine carbon.[46]

Dehydroamino acids are important synthetic intermediates in that their reduction provides a route to α-amino acids. There has been a large volume of research examining the hydrogenation of such compounds, mediated by asymmetric homogeneous catalysts, to provide amino acids with varying degrees of optical purity.[47] For example, a key step in an industrial procedure for the manufacture of L-DOPA is reported to involve the hydrogenation of (**39**) in the presence of the bisphosphine rhodium catalyst (**40**) to provide (**41**) in 94% optical yield (equation 21).

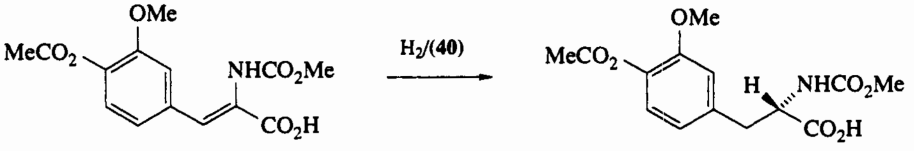

(**39**) (**41**) (21)

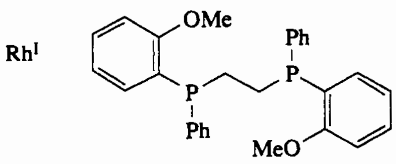

(**40**)

### 1.12.4.4 Rhodanine and Hydantoin Derivatives

The condensation of rhodanine (**42**) with aldehydes is an important reaction closely related to the Erlenmeyer azalactone synthesis (equation 22);[48] the resulting condensation products are particularly useful intermediates for the preparation of various functionalized arylacetic acids and derivatives *via* standard manipulations of the nitrile (**43**), which is available as illustrated in Scheme 11.[48] Similarly, aldehydes

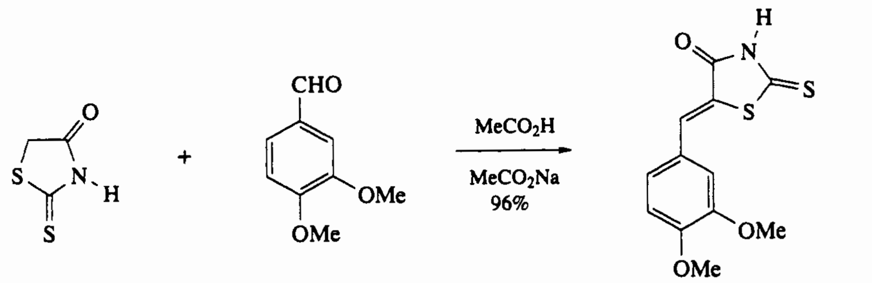

(22)

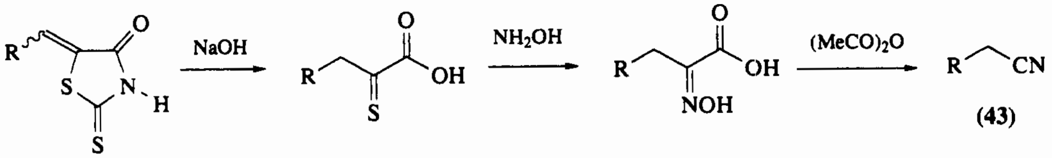

**Scheme 11**

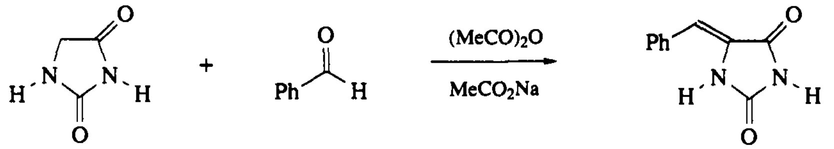

(23)

condense with hydantoin under Perkin conditions (equation 23);[49] these condensation products, analogous to azalactones, may be converted to α-amino acids.

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# 1.13

# Darzens Glycidic Ester Condensation

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## 1.13.1 INTRODUCTION

The Darzens glycidic ester condensation involves the condensation of an aldehyde or ketone with an α-halo ester, in the presence of a base, to afford an α,β-epoxy ester (a 'glycidic ester'). The first synthesis of a glycidic ester was reported by Erlenmeyer in 1892 and is illustrative of the general reaction, as shown in equation (1).[1] The reaction was subsequently developed and generalized by Darzens.[2] Glycidic esters, in addition to undergoing transformations normally associated with epoxides, afford upon hydrolysis glycidic acids, which subsequently decompose to provide aldehydes or ketones (Scheme 1).[3] The reaction is thus pivotal in a general method for the one-carbon homologation of aldehydes and ketones.[4] An illustration of the classic reaction is found in one of the major industrial achievements of the 1940s, the commercial synthesis of vitamin A.[5] A key step in this process involves the Darzens condensation of methyl chloroacetate and β-ionone to give the corresponding glycidic ester, which upon sequential hydrolysis, decarboxylation and basic treatment affords the thermodynamically favored α,β-unsaturated aldehyde, subsequently converted to vitamin A (Scheme 2). The mechanism and stereochemical course of the reaction have been studied extensively and have been the subject of some controversy;[2,6] the scope of its applicability has been broadened beyond the use of α-halo esters to include α-halo compounds that are activated by a variety of electron-withdrawing substituents.

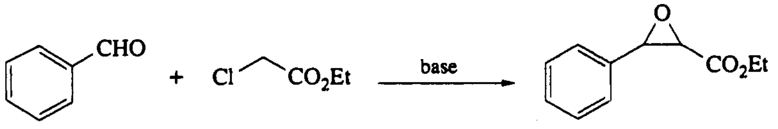

(1)

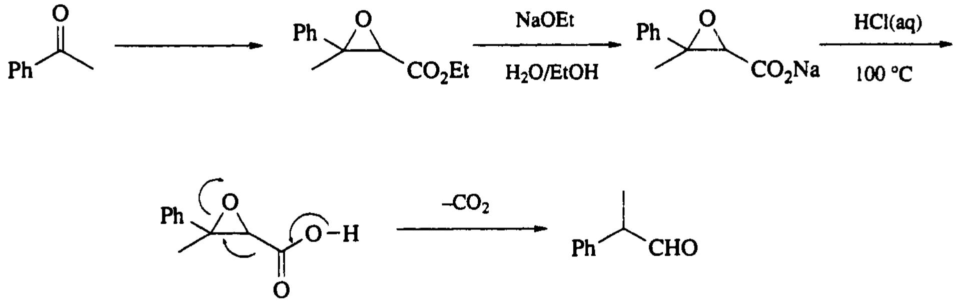

Scheme 1

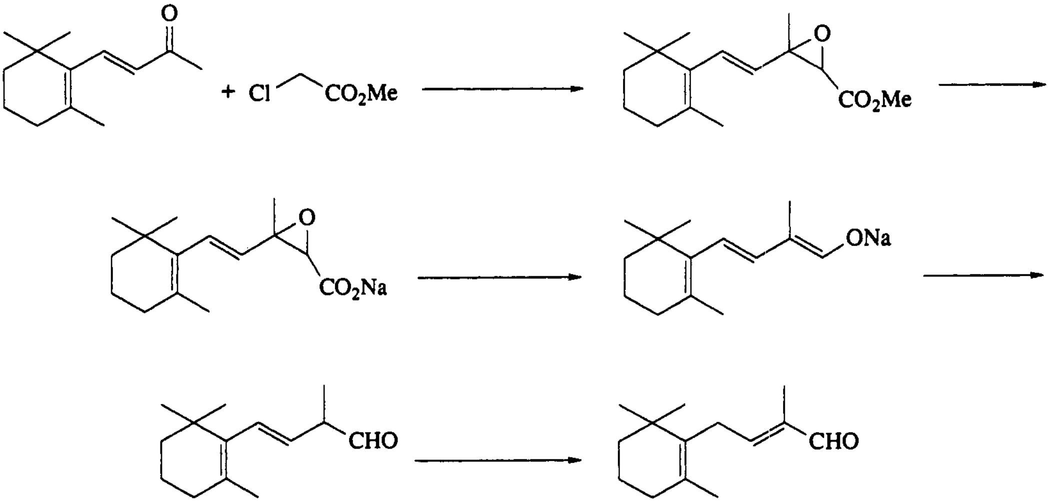

Scheme 2

In this chapter, key studies which have led to the current understanding of the mechanism of this transformation will be discussed, as a basis for dealing with issues of selectivity and choice of experimental variables in subsequent sections. Since the initial development of this reaction, it has evolved in scope to become a primary method for the stereoselective synthesis of epoxides to which an electronegative substituent is directly attached. Several recent variations on the initial protocol which afford functionally diverse molecules are the subject of Section 1.13.3. Section 1.13.5 examines related reactions that afford substituted aziridines instead of epoxides, and Section 1.13.6 examines some recent variants of the reaction using multiphase systems. This section also discusses Darzens condensations involving α,β-unsaturated carbonyl systems and an extension of the reaction that provides methodology for the synthesis of substituted cyclopropanes. Section 1.13.7 is concerned with several studies aimed at developing enantioselective variants of the reaction.

## 1.13.2 GENERAL AND MECHANISTIC CONSIDERATIONS

The mechanism of the Darzens condensation has been studied extensively; for discussions of early mechanistic proposals, some of which have been ruled out, reference is made to previous reviews.[2,6] The generally accepted mechanism for this transformation is shown in Scheme 3.

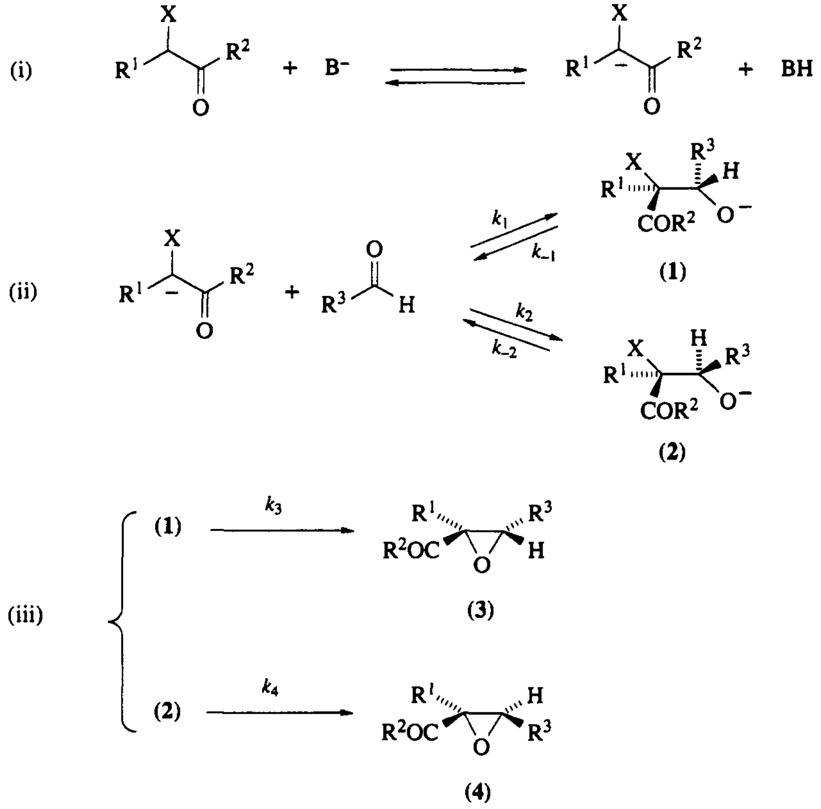

Scheme 3

The reaction involves generation of the carbanion of an activated halide (step i) and subsequent addition to an aldehyde or ketone to generate the diastereomeric aldolates (**1** and **2**; step ii), which cyclize (internal $S_N2$) to afford the stereoisomeric epoxides (**3** and **4**), respectively (step iii). The α-halo aldolates (**1**) and (**2**), or the related halohydrins, are not normally isolated, although this has been done with α-fluoro esters[7] as well as with α-chloro esters.[8] The isolation of these products is amongst the evidence which rules out carbene intermediates, which were invoked in earlier mechanistic proposals.

The ratio of diastereomers (**3**) and (**4**) can vary greatly, depending on the structures of the reactants, the solvent and the base. The stereochemistry of the product epoxide is determined by the configuration of the intermediate α-halo aldolate (step ii), and its control may be the result of kinetic or thermodynamic factors, depending on the relative rates of cyclization ($k_3$ and $k_4$) and retroaddition ($k_{-1}$ and $k_{-2}$). Either step (ii) or step (iii) can be the rate-determining step. For example, treatment of the isolated halohydrin (**5**), derived from the reaction of benzaldehyde and phenacyl chloride, with hydroxide in the presence of *p*-nitrobenzaldehyde affords the epoxy ketone (**6**) in 98% yield (equation 2).[2b] This result has been interpreted as indicating that aldolization (step ii), in this case, is the rate-determining step and that cyclization (step iii) is fast. If cyclization was the slow step, the aldol–retroaldol preequilibrium would generate

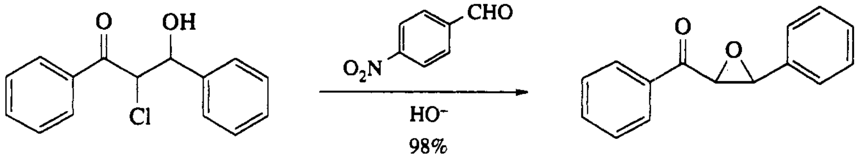

**(5)** **(6)**

(2)

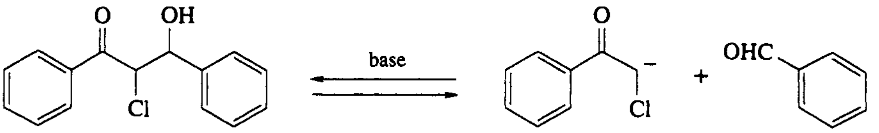

**(7)**

(3)

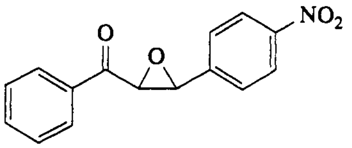

**(8)**

the carbanion (**7**; equation 3), which would be expected to condense with the highly reactive aldehyde acceptor *p*-nitrobenzaldehyde to afford the epoxy ketone (**8**), which is not observed.

In contrast to this result, Zimmerman and Ahramjian have reported that treatment of the halohydrin (**9**; a single diastereomer, unknown relative stereochemistry) with potassium *t*-butoxide in the presence of *m*-nitrobenzaldehyde affords only the glycidic ester (**10**; equation 4), indicating that in this case the rate-limiting step is cyclization.[9]

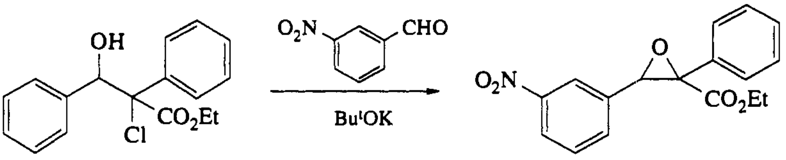

**(9)** **(10)**

(4)

In a similar trapping experiment, Bachelor and Bansal identified a Darzens condensation in which the rates for the aldol–retroaldol preequilibrium and cyclization steps are similar.[10] Treatment of the diastereomeric mixture of halohydrins, derived from acetophenone and *t*-butyl chloroacetate, with potassium *t*-butoxide in the presence of *p*-nitrobenzaldehyde gives a mixture of products consisting of 87% from direct cyclization (**11**) and 13% from condensation with *p*-nitrobenzaldehyde (**12**; equation 5).

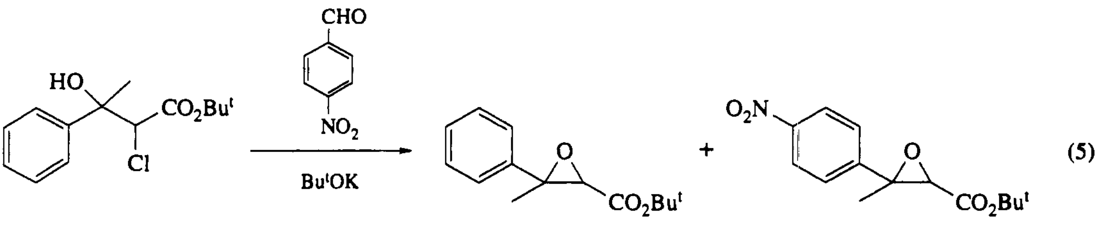

**(11)** 87% GLC **(12)** 13%

(5)

Thus far, this discussion has neglected the issue of stereochemistry and its control, and implications concerning mechanism. However, the stereochemical outcome of the Darzens condensation has been central to mechanistic studies. As part of a key mechanistic study, it was shown that treatment of each of the diastereomeric halohydrins (**13**) and (**14**) with potassium *t*-butoxide furnishes ethyl *cis*-2,3-diphenyl-2,3-epoxypropionate (**15**) as the only isolable product (Scheme 4); this stereoisomer is also the product obtained from the Darzens condensation itself.[9] Earlier mechanistic proposals do not explain this experimental observation.[11,12] Based on the reasonable assumption that the intramolecular displacement must occur with inversion, the result is interpreted to indicate a rapid aldol–retroaldol preequilibrium (interconverting **13** and **14**), followed by a rate-limiting cyclization (Scheme 5); furthermore, the transition state barrier for the cyclization of the alkoxide of (**13**) must be of lower energy than that for the cyclization of the alkoxide of (**14**) which would lead to the *trans*-epoxide. Simple steric arguments do not explain the observed product. In order to achieve an antiperiplanar relationship for displacement to afford (**15**), the two phenyl substituents must experience a van der Waals repulsive interaction, whereas this interaction is not present in the analogous transition state leading to the *trans* isomer. The driving force advanced to explain the stereochemical outcome is overlap control; that is, stabilization of the transition state occurs by delocalization of electrons from the relatively electron rich *p*-orbital on C-2 to the ester carbonyl $\pi$-orbital (Figure 1). This overlap is possible only when the newly forming carbon–oxygen bond and the breaking carbon–chlorine bond are both perpendicular to the plane of the ester function. Such a conformation is easily attainable in the transition state leading to the *cis* product, as the carboethoxy group is unhindered. Models indicate that the proper conformation for such overlap is less easily obtainable in the transition state leading to the *trans* isomer due to steric interactions between the ester and phenyl substituents. Thus, this mechanism predicts that for condensations in which the rate-limiting step is cyclization, the major isomer is that in which the carbonyl group is *trans* to the larger group on the epoxide. It should be noted that this type of orbital overlap has been invoked as an influencing factor in determining a favored transition state for other transformations, such as the base-catalyzed dehydration of aldol products.

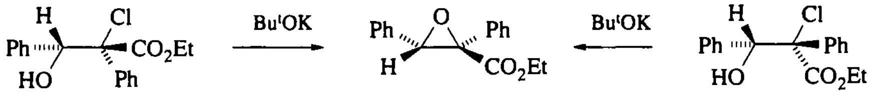

(**13**) (**15**) (**14**)

**Scheme 4**

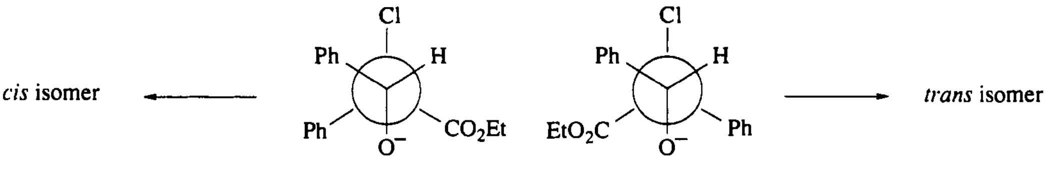

alkoxide of (**13**) alkoxide of (**14**)

**Scheme 5**

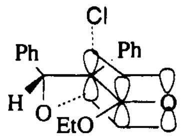

**Figure 1** Overlap control as an explanation for the stereochemical control of the Darzens condensation

Bachelor and Bansal observed that in the condensation between acetophenone and *t*-butyl chloroacetate, the major product is that in which the carboalkoxy group is *cis* to the phenyl group, in contrast to the results predicted by the previous mechanism.[10] A series of glycidic esters was prepared using benzaldehyde, acetophenone and butyrophenone as the carbonyl component and the methyl, ethyl, isopropyl and *t*-butyl esters of chloroacetic acid as the carbanion source (equation 6). Potassium *t*-butoxide/*t*-butyl alcohol was used as the base/solvent system. The results are shown in Table 1. Two general trends are apparent. As the size of $R^1$ or $R^2$ increases, the *cis:trans* isomer ratio increases. Furthermore, epimerization of the glycidic esters was ruled out as a controlling factor. Based on these results, it is concluded that in this series, the stereochemistry of the final product is fixed by the aldol step. A primary consideration in this premise involves the consideration of the preferred conformations of the α-chloro aldolates required for cyclization (**16** and **17**; Scheme 6). It is proposed that since increasing the size of $R^2$ enhances the predominance of *cis*-epoxide (*via* **17**), cyclization must be rapid compared with the aldol step. The authors postulate an interesting controlling factor in this step, involving optimal overlap of the developing oxyanion and the π-orbital of the ester carbonyl which requires an eclipsed conformation (**18**) in the transition state. Increasing the size of $R^1$ or $R^2$ increases the repulsive energy of the eclipsed groups, and when this energy exceeds that gained by overlap, the favored conformation for attack becomes (**19**), in which the partial negative charge on the ester carbonyl oxygen and the developing alkoxide are as far apart as possible (*trans* coplanar); conformation (**19**) leads to the *cis*-epoxide after cyclization.

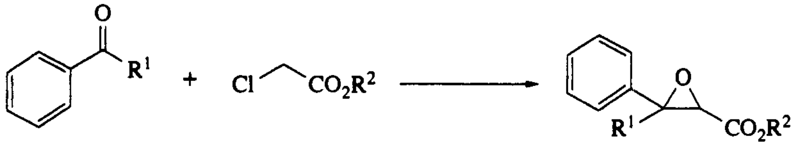

(6)

**Table 1** *Cis:Trans* Isomer Ratios from Darzens Condensations[10]

| $R^1$ | $R^2$ | *Cis* (%) | *Trans* (%) |
|---|---|---|---|
| H | Me | 21 | 79 |
| | Et | 26 | 74 |
| | $Pr^i$ | 33 | 67 |
| | $Bu^t$ | 54 | 46 |
| Me | Me | 43 | 57 |
| | Et | 49 | 51 |
| | $Pr^i$ | 60 | 40 |
| | $Bu^t$ | 62 | 38 |
| $Pr^i$ | Me | 73 | 27 |
| | Et | 75 | 25 |
| | $Pr^i$ | 79 | 21 |
| | $Bu^t$ | 75 | 25 |

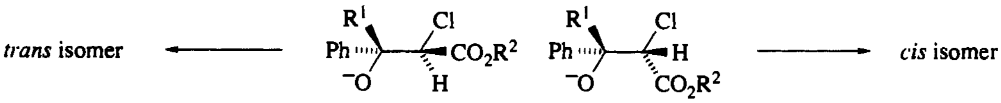

(**16**) (**17**)

**Scheme 6**

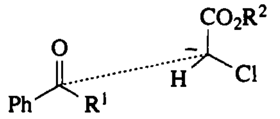

(**18**)

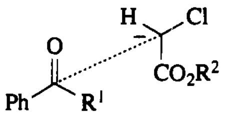

(**19**)

These stereochemical results obtained by Bachelor and Bansal, using *t*-butyl alcohol as solvent, differ from those observed in a study using hexamethylphosphoramide (HMPA).[13] In a subsequent paper, it is suggested that the differences must be attributed to differences in the degree of reversibility of the aldol step in the two solvents; when irreversible aldolization is ensured (by appropriate modification of reaction conditions), the stereochemical results obtained in HMPA, ether and *t*-butyl alcohol/ether are essentially the same.[14,15] In HMPA, it was found that this condition is reached at ambient temperature, however in *t*-butanol/ether the aldol step has a significant component of reversibility above –40 °C. Similar observations have been reported by Villieras and Combret in a study of the condensation of isobutyraldehyde with alkyl chloroacetates (equation 7).[16] The results of this study are summarized in Table 2. The results at room temperature are similar to those shown in Table 1; the ratio of *cis*-epoxide increases as the size of the ester substituent increases. However, at low temperature the corresponding ratios of isomeric adducts (encompassing varying amounts of epoxide and the related uncyclized halohydrin) are essentially constant, independent of the size of R. Thus, it appears that the products obtained at room temperature do not accurately represent the kinetic steric course of the reaction, and the data indicate that the rate-limiting step for the ethyl and isopropyl ester cases is cyclization. In addition the data shown in Table 1, also at room temperature, may not reflect kinetic control and, as noted previously,[6] the subsequent mechanistic implications must be taken with caution. Indeed, it is clear that much of the early work attempting to define the factors influencing the stereochemical outcome of the Darzens condensation must be viewed similarly, as many of these experiments were carried out at room temperature. Although the work described thus far has increased the knowledge base concerning the mechanism of the Darzens reaction, a unifying interpretation of its steric course is still lacking. Additional mechanistic information and proposals are discussed subsequently, in the context of the specific studies involved in the more recent evolution of this reaction.

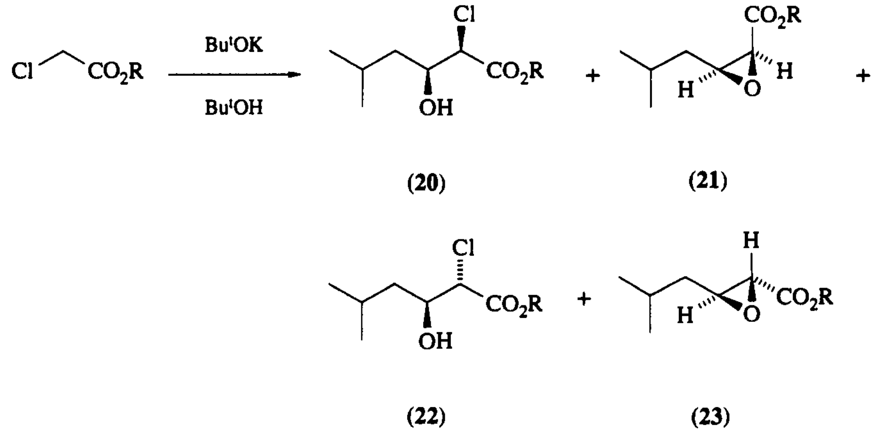

(7)

Table 2 Temperature Dependence of *Cis:Trans* Isomer Ratio in the Darzens Condensation[16]

| *R* | *Composition at room temperature (%)* | | *Composition at –78 °C (%)* | |
|---|---|---|---|---|
| | *(21);cis* | *(23);trans* | *(20) + (21)* | *(22) + (23)* |
| Et | 16 | 84 | 72 | 28 |
| Prⁱ | 20 | 80 | 73 | 27 |
| Buᵗ | 70 | 30 | 70 | 30 |

It will be recognized by the reader that the aldol reaction has been one of the most intensely studied reactions (see Volume 2, Chapters 1.5–1.7) in contemporary organic chemistry, in terms of mechanism, stereochemical outcome and practical application, and therefore this work is relevant in the context of the Darzens condensation. Very recently, this technology has been applied to the Darzens condensation, making available a new asymmetric stereocontrolled epoxide synthesis, and this work is discussed in Section 1.13.7.2.

## 1.13.3 CONDENSATIONS EMPLOYING ANIONS STABILIZED BY SUBSTITUENTS OTHER THAN SIMPLE ESTERS

### 1.13.3.1 Sulfur-containing Groups

#### *1.13.3.1.1 Sulfones*

A large amount of effort has been devoted to studying Darzens condensations employing anions stabilized by substituents other than ester groups. Several sulfur-containing functional groups have been investigated. Chloro- and bromo-methyl *p*-tolyl sulfone condense with a variety of aldehydes and ketones in the presence of potassium *t*-butoxide to afford α,β-epoxy sulfones (**24**) in good to excellent yield (equation 8; Table 3).[17] These reactions afford exclusively epoxides in which the sulfone group is *trans* to the larger group of the electrophile. It is postulated that the cyclization step is rate-determining (initial nucleophilic attack on aldehyde or ketone being rapidly reversible), and that the transition state (**25**) leading to the observed *trans* products is of lower energy than (**26**) for steric reasons. It is suggested that solvation of the highly polarized sulfonyl group also may be a contributing factor, pointing the *p*-tolyl group toward the *cis* substituent on the adjacent carbon atom and thereby enhancing the negative steric interaction in (**26**; Figure 2).

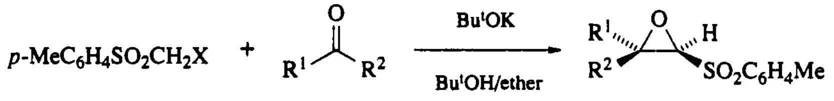

(8)

(**24**)

**Table 3** Preparation of α,β-Epoxy Sulfones by the Darzens Condensation (equation 8)[17]

| *Halo sulfone* | *Carbonyl compound* | *Yield of epoxy sulfone (**24**) (%)* |
|---|---|---|
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl | Benzaldehyde | 95 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl | Acetaldehyde | 53 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl | Acetone | 80 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl | Benzophenone | 57 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl | Cyclohexanone | 77 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Br | Benzaldehyde | 92 |
| $p$-MeC$_6$H$_4$SO$_2$CH$_2$Br | Benzaldehyde | 91 |
| $p$-MeC$_6$H$_4$SO$_2$CHClMe | Acetone | 77 |

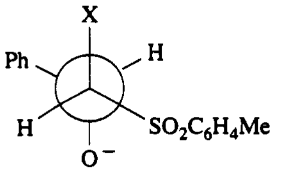

(**25**)

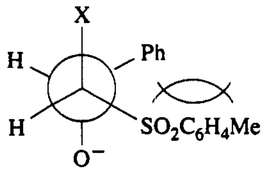

(**26**)

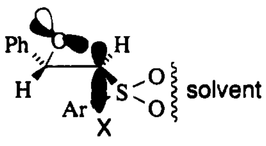

**Figure 2** Solvation of the sulfonyl group, enhancing the negative steric interaction in (**26**)

### 1.13.3.1.2 Sulfoxides

Generation of the sulfinyl carbanion of chloromethylphenyl sulfoxide (Bu$^n$Li/THF, −78 °C), followed by treatment with cyclohexanone, acetone or benzophenone, affords the corresponding chlorohydrin (**27**) in good yield (68–79%).[18] Treatment of the cyclohexanone or acetone adducts with methanolic KOH provides the α,β-epoxy sulfoxides in yields of greater than 90% (Scheme 7). Each of the halohydrin products appeared to be a single diastereomer, although the relative stereochemistry was not assigned.

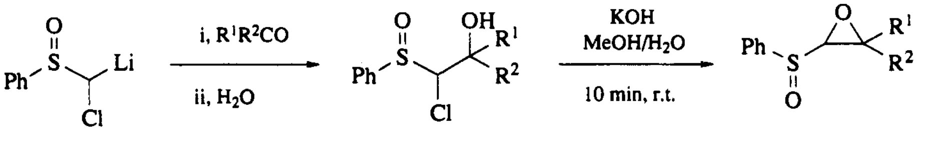

(**27**) (**28**)

**Scheme 7**

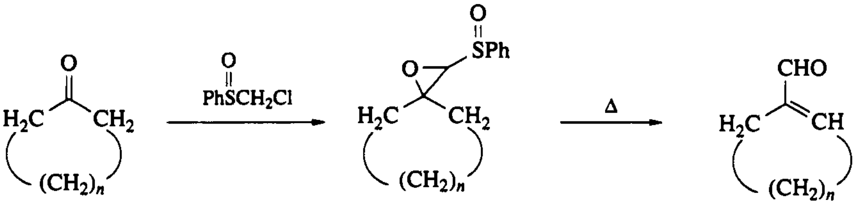

Scheme 8

The α,β-epoxy sulfoxides available using this protocol are important intermediates for several synthetic methodologies.[19] For example, they give upon thermal rearrangement α,β-unsaturated aldehydes and thus represent the pivotal intermediate in a two-step procedure for the one-carbon homologation of carbonyl compounds (Scheme 8).[20]

### *1.13.3.1.3 Sulfides*

In an attempt to further extend the foregoing methodology to include the preparation of α,β-epoxy sulfides, the condensation of chloromethyl *p*-tolyl sulfide and benzaldehyde using a protocol similar to that employed successfully in the sulfone case (Bu$^t$OK) gave only poor conversion to the desired epoxide.[21] However, addition of the hindered amine base 1,4-diazabicyclo[2.2.2]octane (DABCO) results in the formation of the isomeric expoxides (**29**) in good yield (equation 9). In the case of benzaldehyde, the *cis*-epoxide predominates over the *trans*-epoxide (**29b**; 82% *versus* 18%), while in the corresponding condensation with pivalaldehyde, the only epoxy sulfide obtained is the *cis* isomer (**29c**). Several attempts to effect an analogous reaction with ketones were unsuccessful; formation of (**30**) (displacement–elimination) becomes the favored process (equation 10).

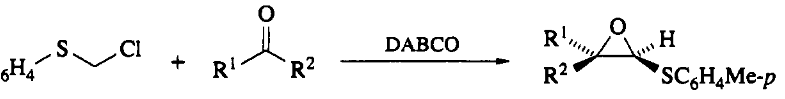

(9)

(**29a**) R$^1$ = Ph; R$^2$ = H

(**29b**) R$^1$ = H; R$^2$ = Ph

(**29c**) R$^1$ = H; R$^2$ = Bu$^t$

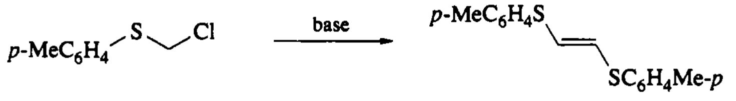

(10)

(**30**)

### *1.13.3.1.4 Sulfoximines*

The α-halo sulfoximine (**31**) reacts with benzaldehyde and several ketones to afford epoxy sulfoximines (equation 11; Table 4).[22] The products (**32a**), (**32b**) and (**32c**) are each mixtures of two diastereomers due to the contiguous stereocenters at sulfur and the α-carbon atom. Product (**32c**) is a diastereomeric mixture in which the *t*-butyl and sulfoximino groups are predominantly (90%) *cis*. The epoxy sulfoximines (**32**) were viewed as potential intermediates in a homologation sequence for alde-

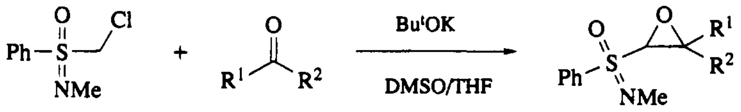

(11)

(**31**) (**32**)

**Table 4** Condensations of (31) with Carbonyl Compounds Giving Epoxy Sulfoximines[22]

| *$R^1$* | *$R^2$* | *Product* | *Yield (%)* |
|---|---|---|---|
| Me | Me | **(32a)** | 81 |
| $—(CH_2)_5—$ | | **(32b)** | 75 |
| $—(CH_2)_2CHBu^t(CH_2)_2—$ | | **(32c)** | 50 |
| H | Ph | **(32d)** | 75 |

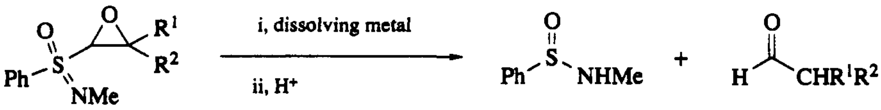

(12)

hydes and ketones (equation 12). Several attempts to achieve this transformation, however, were unsuccessful.

### *1.13.3.1.5 Thiol esters*

α-Halo thiol esters also undergo Darzens condensations, providing a method for the synthesis of *S*-alkyl glycidic thiol esters (equation 13).[23] In the formation of glycidic thiol esters, it is important to use nonnucleophilic bases such as NaH or lithium hexamethyldisilylamide (LHMDS) and polar aprotic solvents such as THF or DMF. It is also noted that α-bromo thiol ester reactants are usually preferable to

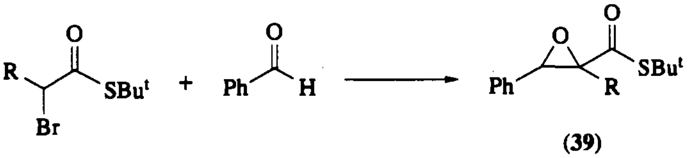

**(39)**

(13)

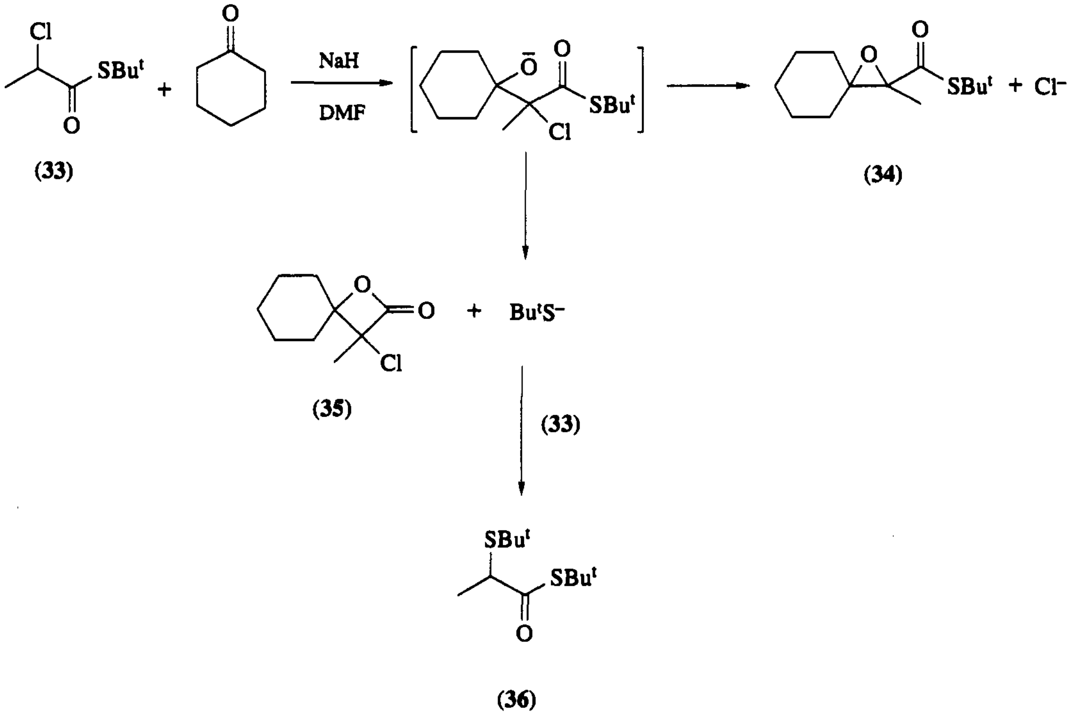

**Scheme 9**

the corresponding α-chloro thiol esters. In the reaction of cyclohexanone with *S*-*t*-butyl 2-chloropropanethioate (**33**) in NaH/DMF, the thioglycidate (**34**) is obtained in a yield of only 15% along with the two by-products (**35** and **36**; Scheme 9). The formation of the β-lactone (**35**) suggests that an intramolecular nucleophilic acyl substitution reaction is competitive with epoxide formation; the liberated thiolate anion is trapped by the starting substrate (**33**), resulting in the formation of (**36**). Replacing (**33**) with the corresponding α-bromo derivative results in an improved yield (60%) of the thioglycidate (**34**). Presumably, the enhanced leaving group ability of the bromide substituent enhances epoxide formation in the intermediate halo alkoxide relative to alternative reaction pathways. The competing intramolecular displacement of thiolate to afford a β-lactone, which is not a problem in the formation of glycidic (oxygen) esters, is a manifestation of the improved leaving group ability of thiolate relative to alkoxide.

Another potential side reaction in the thiol ester version of this condensation may be more likely than in the simple ester analogy, due to the greater acidity of the α-protons in the thiol ester. The reaction of benzaldehyde with *S*-*t*-butyl 2-chloroethanethioate in NaH/THF gives several products, including 2-chlorocinnamic acid and a diastereomeric mixture of (**38**); (**38**) presumably arises from the elimination product (**37**). A competing elimination process may also explain the result that no thioglycidate (**39**) was obtained in the attempted condensation of benzaldehyde with *S*-*t*-butyl 2-chloroethanethioate using NaH/DMF (Scheme 10). In contrast, replacing 2-chloroethanethioate with the corresponding bromide affords the thioglycidate (**39**) in 67% yield (70:30, *cis*:*trans*; equation 14). Again, bromide presumably facilitates the epoxide-forming intramolecular cyclization at the expense of competing intermolecular side reactions.

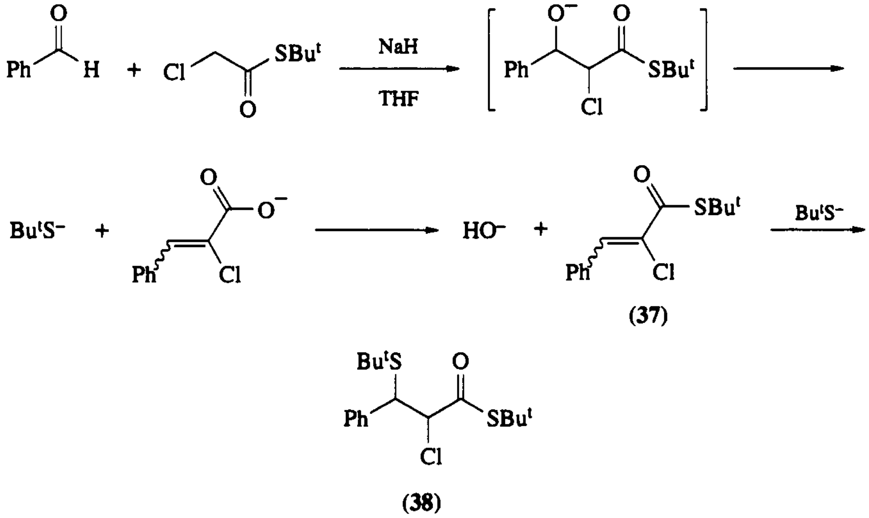

**Scheme 10**

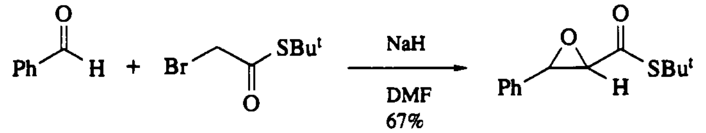

(14)

(39)

## 1.13.3.2 Nitriles

The Darzens condensation, as a source of glycidonitriles,$^{24}$ is a pivotal step in a method for the one-carbon homologation of ketones to afford carboxylic acids (Scheme 11).$^{25}$ Treatment of a ketone with chloroacetonitrile in the presence of sodium *t*-amyl oxide affords the corresponding glycidonitrile in excellent yield (greater than 95% after distillation). Crude β-arylglycidonitriles (**40**) are converted to α-ketonitriles upon treatment with lithium perchlorate; subsequent basic hydrolysis provides the acid (**42**; method A). Alternatively, heating (**41**) with an amine provides the corresponding amide. A less direct route is employed for aliphatic ketones. Exposure of the glycidonitrile (**43**) to dry HCl gives an α-hydroxy-β-chloronitrile which is acetylated and dehydrohalogenated to provide an α-acetoxyacrylonitrile (**44**). Basic hydrolysis affords the desired carboxylic acid (**45**; method B); the α-acetoxyacrylonitriles

(**44**) may also be converted to α-keto carboxylic acids (**46**) upon treatment with cold mineral acid. The results for several ketones are shown in Table 5. In contrast to the clean addition of HCl to glycidonitriles, it was found that treatment of glycidic esters with HCl affords a mixture of α-hydroxy-β,γ-unsaturated esters and α-hydroxy-β-chloro esters (equation 15). It is suggested that this propensity for glycidic esters to form elimination products may be due to intramolecular deprotonation of the incipient tertiary carbonium ion by the carboalkoxy group.

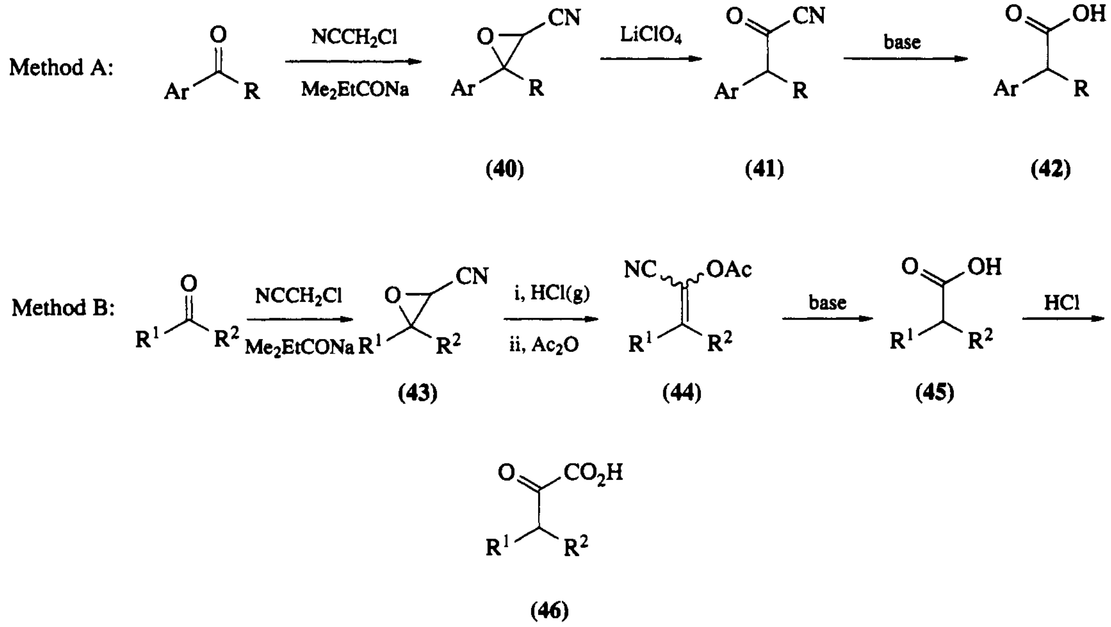

**Scheme 11**

**Table 5** Carboxylic Acids Prepared from Ketones[25]

| *Ketone* | *Product* | *Yield (%)* *Method A* | *Yield (%)* *Method B* |
|---|---|---|---|
| *p*-Isobutylacetophenone | 2-(*p*-Isobutylphenyl)propionic acid | 72 | 73 |
| α-Tetralone | 1,2,3,4-Tetrahydro-1-naphthoic acid | 47 | 68 |
| Cyclohexanone | Cyclohexanecarboxylic acid | | 57 |
| Cyclopentanone | Cyclopentanecarboxylic acid | | 51 |
| 2-Pentanone | 2-Methylpentanoic acid | | 57 |

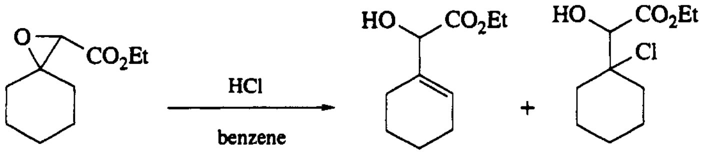

(15)

### 1.13.3.3 Lactones

The Darzens condensation of aldehydes with α-halo lactones has been investigated as a method for a homologation of the type $\mathrm{ArCHO \rightarrow ArCH_2COCH_2COMe}$.[26] Addition of an equimolar mixture of 3,5-dimethoxybenzaldehyde and α-bromo-γ-valerolactone (mixture of *cis* and *trans* isomers) to a solution of $\mathrm{Bu^tOK}$ affords the epimeric mixture of lactones (**47**) in 78% yield with high stereoselectivity (addition to the carbonyl). Saponification followed by irradiation affords the decarboxylated β-hydroxy ketone (**49**) in 62% yield, accompanied by the secondary photolysis product (**51**).[27] Oxidation of (**49**) with Jones' reagent affords the diketone (**50**), characterized as its copper(II) chelate (Scheme 12). Methodology has been described for the preparation of tetrasubstituted epoxy lactones (**52**) involving the Darzens reaction of α-bromobutyrolactone and ketones (equation 16).[28]

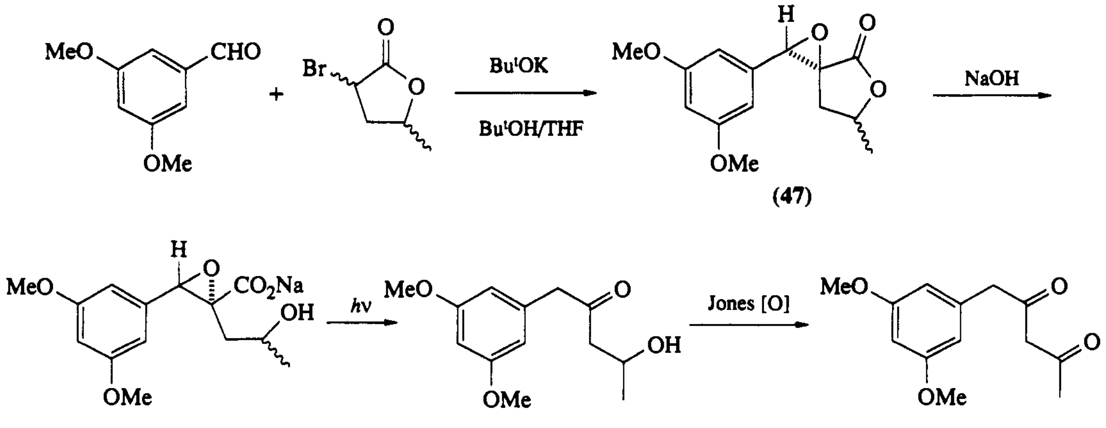

(**47**)

(**48**) (**49**) (**50**)

**Scheme 12**

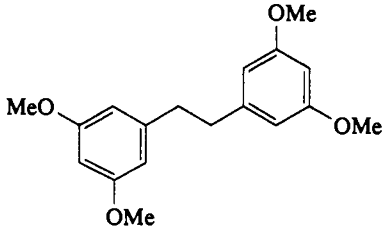

(**51**)

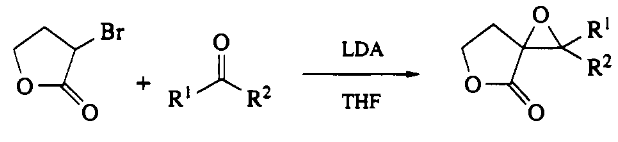

(**52**) (16)

### 1.13.3.4 Vinylogous Esters

A vinylogous Darzens condensation has been reported.[29] Treatment of benzaldehyde and methyl 4-bromocrotonate with $Bu^tOK/Bu^tOH$ (0 °C, 40 min) affords a mixture of the *cis*- and *trans*-epoxides (**53**) and (**54**) in 70% yield (equation 17). It is noted that compounds (**53**) and (**54**) could have been formed either by γ-alkylation of (**52**) or by α-alkylation followed by rearrangement. However, it is suggested that the lack of formation of the dihydrofuran derivatives (**55** and **56**; Scheme 13), as well as the prolonged reaction times and/or elevated temperature generally required to induce rearrangement, argue against the α-alkylation–rearrangement mechanism.

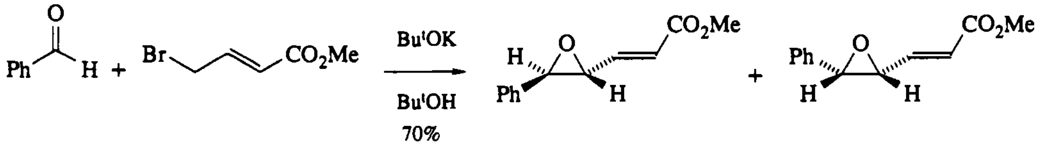

(**52**) (**54**) 70% (**53**) 30% (17)

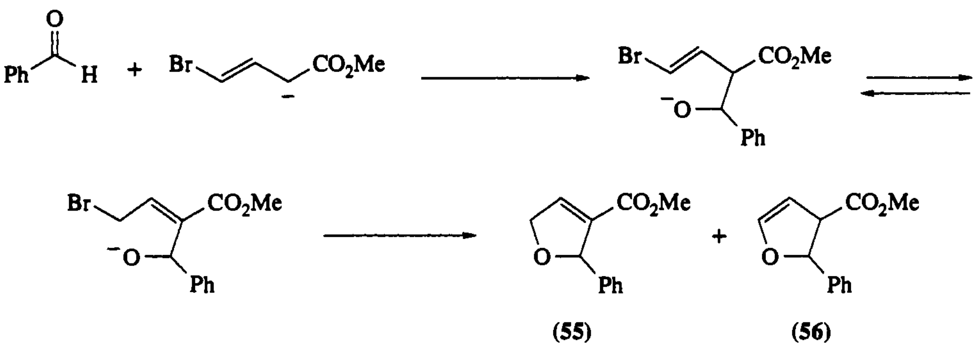

Scheme 13

### 1.13.3.5 Diazo Ketones

The condensation of 1-chloro-3-diazopropanone (**57**) with aldehydes provides epoxy diazo ketones (equation 18).[30] Treatment of a methanolic solution of (**57**) and benzaldehyde, in a stoichiometric ratio, with aqueous sodium hydroxide furnishes 1-diazo-3,4-epoxy-4-phenyl-2-butanone (**59a**) in 69% yield; the *trans*-epoxide is obtained stereoselectively, analogous to the Darzens condensation of benzaldehyde and chloroacetone.[31] The reaction is reported to proceed to give also the diazo ketones (**59b–59e**), and the epoxides obtained are exclusively of the *trans* configuration.[30]

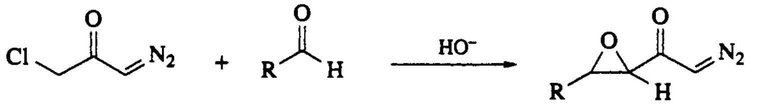

(18)

(**57**) (**58**)

(**59a**) R = Ph

(**59b**) R = $p$-$NO_2C_6H_4$

(**59c**) R = $p$-$MeOC_6H_4$

(**59d**) R = PhCH $\overset{t}{=}$ CH

(**59e**) R = 2-thienyl

### 1.13.3.6 Imines

In general, α-halogenated ketones are poor substrates in the Darzens condensation, except when they lack α′-hydrogen atoms (for example, phenacyl halides). The unsuitability of α-halo ketones is due to their propensity to undergo undesirable side reactions such as the Favorskii rearrangement (*via* 1,3-dehydrohalogenation), elimination (1,2-dehydrohalogenation) or nucleophilic substitution under basic conditions. In an effort to circumvent these problems, *N*-alkyl-α-haloimines, which have been previously shown to be useful as masked α-halocarbonyl compounds,[32] were investigated for their utility in the Darzens condensation.[33] α-Chloroimines (**60**), prepared by condensation of the corresponding α-chloro ketones with a primary amine in the presence of titanium tetrachloride,[34] are converted into 1-aza-3-chloroallylic anions upon treatment with LDA.[32] These anions react cleanly with ketones and aldehydes, generating 2-imidoyloxiranes (**61**) in high yield (Scheme 14; Table 6); the intermediate noncyclized

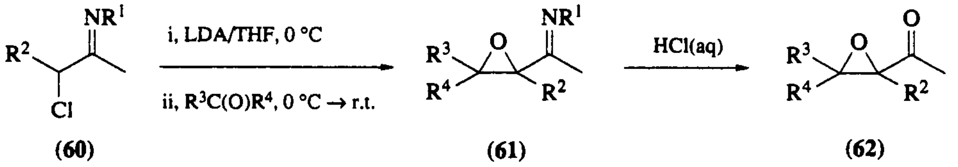

Scheme 14

**Table 6** Preparation of 2-Imidoyloxiranes (**61**)[33]

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *Yield* (%) |
|---|---|---|---|---|---|
| (**61a**) | Pr$^i$ | Me | Me | Me | 80 |
| (**61b**) | Pr$^i$ | Me | Ph | H | 81 |
| (**61c**) | Pr$^i$ | Me | Ph | Ph | 80–90$^a$ |
| (**61d**) | Pr$^i$ | Ph | Me | Me | 92 |
| (**61e**) | Pr$^i$ | Ph | Me | Et | 95$^b$ |
| (**61f**) | $C_6H_{11}$ | Me | Ph | Ph | 92 |

[a] In the presence of HMPA and greater than 100 mol % of LDA, compound (**63**) was also isolated. [b] A mixture (7:3) of *cis* and *trans* isomers is formed; isomeric assignments were not determined.

chloroimines could not be isolated. Treatment of the imidoyloxiranes with aqueous hydrochloric acid (2M HCl, r.t., 1 d) provides the corresponding 2-acyloxiranes (**62**).

Formation of oxiranes (**61**) proceeds smoothly when aliphatic ketones or benzaldehyde are employed as the carbonyl substrates. When greater than 100 mol % of LDA is used for the deprotonation of (**60**; R$^1$ = Pr$^i$; R$^2$ = Me) in the presence of HMPA and 200 mol % of benzophenone is added to the resulting anion, the oxirane (**61c**; Table 6) is formed in 80% yield accompanied by the unsaturated amide (**63**), obtained in 15% yield (equation 19). Rearranged amides, such as (**63**), are formed only when benzophenones are used as the electrophiles; if only 100 mol % of LDA is employed in the deprotonation step, (**61c**) is obtained exclusively. When 200 mol % of LDA is utilized in this step, unsaturated amides, analogous to (**63**), are obtained in 26–65% yield; these butenamides are isolated in significant yield only if HMPA is present in the reaction medium. The geminal diphenyloxirane (**61g**) was shown to be a probable intermediate in the formation of the corresponding rearrangement product (**64**). Treatment of (**61g**) with LDA in HMPA/THF affords butenamide (**64**) in 25% yield as the only isolable product (equation 20).

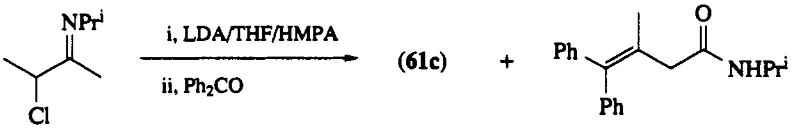

(**60**) (**63**) (19)

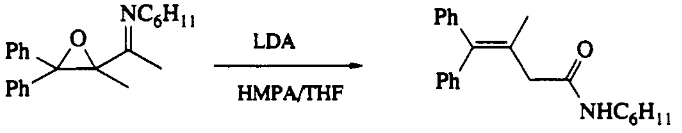

(**61g**) (**64**) (20)

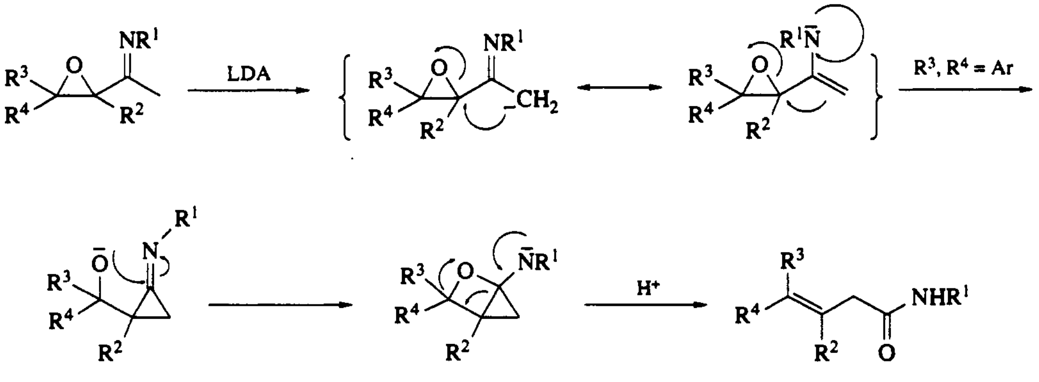

**Scheme 15**

A mechanistic rationale for the formation of the butenamides is shown in Scheme 15. Apparently, base-induced intramolecular cleavage of the oxirane does not occur in alkyl-substituted epoxides (**61**). However, this pathway becomes important for activated diaryl derivatives. The proposed process is somewhat analogous to the Favorskii rearrangement of α-halo ketones, in this case the geminal diaryl activated epoxide leaving group being analogous to the halogen leaving group. It is noted that α-halo imines[35] as well as α,β-epoxy ketones[36] have been shown to undergo base-induced Favorskii rearrangements.

### 1.13.3.7 Ketones

*trans*-β-Substituted-α,β-epoxy ketones are obtained with reasonable facility by hydrogen peroxide epoxidation of α,β-unsaturated ketones; however, *cis*-β-substituted-α,β-epoxy ketones cannot be prepared by this procedure. Mukaiyama and coworkers have developed a two-step procedure for the synthesis of such *cis*-epoxides involving a tin-mediated aldol reaction between α-bromo ketones and aldehydes, followed by treatment of the adduct with KF/dicyclohexyl-18-crown-6 to effect cyclization (Scheme 16).[37]

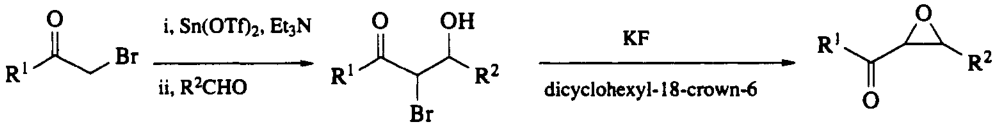

**Scheme 16**

The stereoselectivity of the aldol reaction was initially investigated using bromoacetone and benzaldehyde, and it was found that THF is the best solvent for obtaining an optimum *syn*:*anti* ratio; the *syn*-bromohydrin (**65**; precursor to *cis*-epoxide) predominates in a ratio of 81:19. When the 81:19 mixture of (**65**) and (**66**) was treated with triethylamine, the *trans*-epoxide (**68**) was obtained exclusively in nearly quantitative yield (equation 21). After exploring several sets of reaction conditions aimed at avoiding the facile isomerization of (**65**) to the thermodynamically favored *anti* isomer (**66**), it was found that KF/dicyclohexyl-18-crown-6 induces cyclization with a minimum amount of isomerization. The overall results for the process of Scheme 16 for several reactants are shown in Table 7. It was found that, in each case, *cis*-epoxy ketones are obtained with moderate to high stereoselectivity.

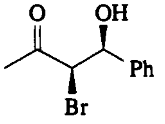

**(65)**

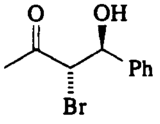

**(66)**

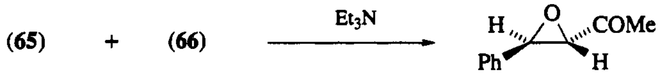

**(68)**

(21)

**Table 7** Synthesis of α,β-Epoxy Ketones *via* Divalent Tin Enolates[37]

| *α-Bromo ketone* | *Aldehyde* | *Yield of epoxy ketone (67) (%)* | *Cis (%)* | *Trans (%)* |
|---|---|---|---|---|
| $MeCOCH_2Br$ | $PhCHO$ | 72 | 70 | 30 |
| $MeCOCH_2Br$ | $Ph(CH_2)_2CHO$ | 65 | 73 | 27 |
| $PhCOCH_2Br$ | $Ph(CH_2)_2CHO$ | 80 | 66 | 34 |
| $PhCOCH_2Br$ | $Me_2CHCHO$ | 80 | 65 | 35 |
| $Bu^tCOCH_2Br$ | $PhCHO$ | 64 | >95 | <5 |
| $Bu^tCOCH_2Br$ | $Ph(CH_2)_2CHO$ | 48 | >95 | <5 |
| $Bu^tCOCH_2Br$ | $Me_2CHCHO$ | 47 | >95 | <5 |

### 1.13.3.8 Carboxylic Acids

A major complication in the use of glycidic esters as precursors to aldehydes (homologation sequence shown in Scheme 17) involves premature epoxide cleavage during ester hydrolysis. In an effort to obviate this complication, the use of dianions of α-halocarboxylic acids in place of monoanions of esters was investigated. This procedure produces glycidic acids directly, avoiding the potential problems associated with the ester hydrolysis.[38] The dianions (**69**)–(**71**), generated using LDA in THF at –80 °C, were studied in condensation reactions with aldehydes and ketones. The results for the addition of (**70**) to several carbonyl compounds (equation 22) are shown in Table 8. The yields of product (**72**) shown are those for the isolation of the corresponding methyl glycidates obtained by treatment of (**72**) with diazomethane. The glycidic acids are difficult to isolate and purify; when used in a homologation sequence, they are decarboxylated directly with as little handling as possible. Dianion (**70**) reacts quite efficiently with acetophenone to afford, after methylation, methyl glycidate in 93% yield. If the reaction mixture, at –80 °C, is poured into aqueous acid 30 s after the addition of acetophenone, the only product isolated after work-up and methylation is the uncyclized α-chloro-β-hydroxy methyl ester (2:3 diastereomeric mixture, 90% yield). The alkoxide does not close to the epoxide at –80 °C, even after 4 h. When the reaction mixture is allowed to warm, epoxide begins to appear at *ca.* –15 °C, and almost complete conversion occurs by the time the reaction mixture reaches 25 °C. To assess steric effects, the condensations of (**70**) with diisopropyl ketone and di-*t*-butyl ketone were evaluated. Addition to diisopropyl ketone occurs reasonably efficiently, furnishing the corresponding methyl glycidate in 77% yield, after treatment with diazomethane. This yield is somewhat lower than that obtained with methyl ethyl ketone (96%), suggesting a steric effect. Di-*t*-butyl ketone fails to react. The yields (37–79%) obtained with the dianion (**71**) are consistently lower than those obtained with (**70**), perhaps reflecting the increased bulk of (**71**). Significantly lower yields (38–59%) are obtained with the dianion (**69**) relative to both (**70**) and (**71**). The decreased yields are due to an enhanced propensity for condensation of the dianion with the monoanion of α-chloroacetic acid as compared with the analogous reactions for (**70**) and (**71**).

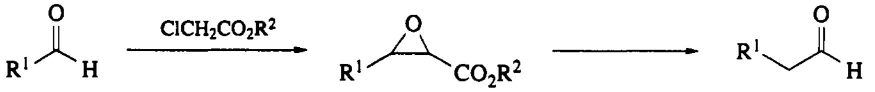

**Scheme 17**

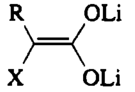

(**69**) R = H; X = Cl
(**70**) R = Me; X = Cl
(**71**) R = Pr$^i$; X = Br

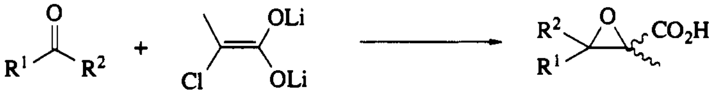 (22)

(**70**) (**72**)

**Table 8** Addition of Dianion (**70**) to Carbonyl Compounds[38]

| *Carbonyl compound* *R*$^1$ | *R*$^2$ | *Yield of methyl glycidate (%)* | *Cis (%)* | *Trans (%)* |
|---|---|---|---|---|
| Ph | Me | 93 | 65 | 35 |
| Ph | Ph | 76 | | |
| Et | Me | 96 | 50 | 50 |
| —($C_5H_{10}$)— | | 74 | | |
| —($C_4H_8$)— | | 47 | | |
| Pr$^i$ | Pr$^i$ | 77 | | |
| Bu$^t$ | Bu$^t$ | 0 | | |
| Ph | H | 90 | 4 | 96 |
| Et | H | 34 | 33 | 67 |

The decarboxylation of the glycidic acids obtained in this study was studied under various pyrolytic and catalytic conditions; although moderate to good yields of product could be obtained, the overall synthetic potential of the homologation sequence shown in Scheme 17 remains limited due to the lack of a general method for mild and rapid decarboxylation.

### 1.13.3.9 Silicon

A very useful methodology that accomplishes the overall transformation envisaged in Scheme 17 involves the addition of an α-chloro-α-trimethylsilyl carbanion to carbonyl compounds in a Darzens-type condensation, followed by hydrolysis of the resulting α,β-epoxysilane (Scheme 18).[39] The anion (73) is generated by treatment of chloromethyltrimethylsilane with *s*-butyllithium in THF containing 100 mol % of TMEDA. Table 9 shows the results of the reaction of several carbonyl compounds with (73) to give epoxysilanes. If the reaction of (73) and benzaldehyde is quenched at –55 °C, a mixture of the chlorohydrins (76) and (77) is isolated (equation 23). The *threo* isomer (77) is the major component of this mixture; treatment of (77) with sodium hydride (THF, 50 °C) affords only the *cis*-epoxide (79). Elimination of trimethylsilanol, to afford vinyl chlorides, is not observed. Warming the mixture of (73) and benzaldehyde from –55 °C to 20 °C causes the initially formed chlorohydrins (76) and (77) to cyclize to the corresponding *trans*- and *cis*-epoxides (78) and (79), respectively (equation 24). The *threo*-chlorohydrin (77) is converted more slowly to the *cis*-epoxide (79) than the *erythro* isomer (76) is converted to the *trans*-

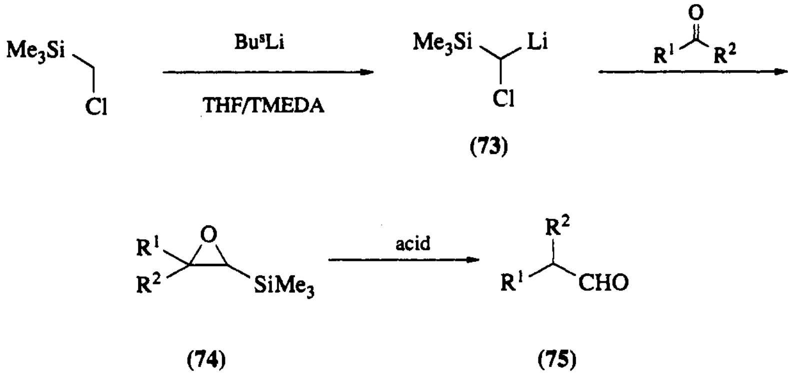

Scheme 18

Table 9 Epoxysilanes from the Condensation of α-Chloro-α-trimethylsilyl carbanion (73) and Carbonyl Compounds[39]

| *Carbonyl substrate* | *Yield of epoxysilane (74) (%)* | *Carbonyl substrate* | *Yield of epoxysilane (74) (%)* |
|---|---|---|---|
| Benzaldehyde | ≥95 | Butanal | ≥75 |
| Benzophenone | ≥95 | 9-Fluorenone | ≥60 |
| Cyclohexanone | ≥95 | Cyclodocecanone | ≥70 |
| 4-*t*-Butylcyclohexanone | ≥95 | 2-Adamantanone | ≥90 |
| Cholestanone | ≥95 | Cyclohex-2-enone | ≥80 |
| | | Cyclopentanone | ≥90 |
| 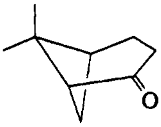 | ≈40 | | |
| 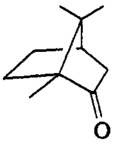 | ≥20 | | |

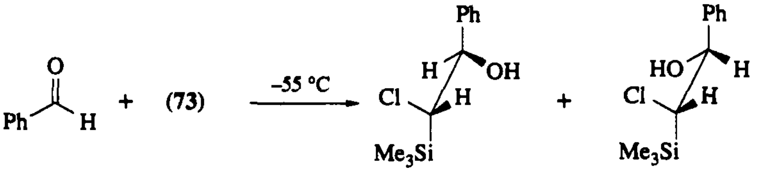

(76) (77)

(23)

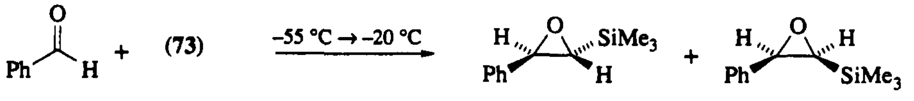

(78) 29% (79) 71%

(24)

epoxide (**78**). All of the substrates shown in Table 9 react rapidly and cleanly with the anion (**73**) to give the corresponding α,β-epoxysilanes. The only limitations noted are that sterically hindered or easily enolizable carbonyl groups cause decreased yields. In all cases, hydrolysis of the α,β-epoxysilanes affords a clean rapid conversion to the corresponding aldehydes (**75**; Scheme 18), thus providing a simple and versatile homologation sequence.

## 1.13.4 MISCELLANEOUS MODIFICATIONS

Early attempts to utilize acetaldehyde and monosubstituted acetaldehyde derivatives in the Darzens reaction were unsuccessful, presumably due to competitive base-catalyzed self-condensations of the aldehydes. It was subsequently reported that generation of the requisite bromo ester enolates with LHMDS at –78 °C provides a species which reacts with a variety of aldehydes and ketones to afford glycidic esters in good to excellent isolated yields (equation 25).[40]

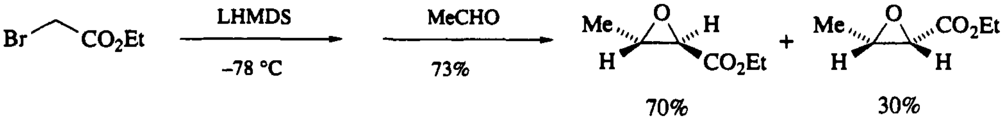

(25)

An interesting alternative procedure for the generation of Darzens intermediates is illustrated in equation (26).[41] In this method such anions are generated by the conjugate addition of a nucleophile to an activated alkene. In the presence of a carbonyl compound, an epoxide is formed. This process has been developed as an annulation procedure.

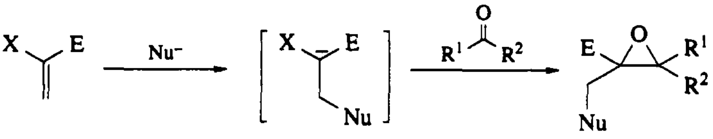

(26)

It has also been reported that diethyl 1-chloro-1-lithioalkanephosphonates react with carbonyl compounds in the presence of HMPA to give diethyl 1,2-epoxyalkanephosphonates (equation 27).[42]

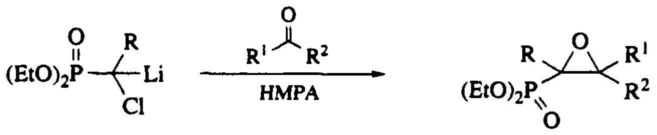

(27)

An intramolecular variant of the Darzens reaction affords 2,7-dioxabicyclo[4.1.0]heptanes (equation 28).[43] Similar results are reported for nitrile, acetyl and sulfoxide derivatives.

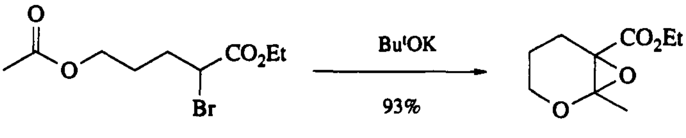

(28)

Studies on Darzens condensations involving substituted cyclohexanones have also been described.[44]

## 1.13.5 PREPARATION OF AZIRIDINES

A procedure has been developed which extends the Darzens synthesis to the preparation of aziridine esters and amides (equation 29).[45] Reaction of benzalaniline (**80**) and ethyl chloroacetate (in Bu$^t$OK/DME) results in the formation of the *trans*-aziridine (**82a**) in 29% yield; analysis of the crude reaction mixture showed no more than 10% of the isomeric *cis* adduct (**83a**). Similarly, condensation of 2-chloro-*N*,*N*-diethylacetamide and (**80**) affords aziridines (**82b**) and (**83b**) in 65% yield. However, in this case the *cis* isomer predominates (≈90:10, *cis*:*trans*). The formation of (**83a**; R = OEt) as the major product is consistent with the overlap control model suggested by Zimmerman. Apparently, the decreased stability of the amide (**81b**) enolate relative to the ester (**81a**) enolate causes $k_2$ (cyclization) to become greater than $k_1$ (addition; Scheme 19); it follows that the stereochemical outcome is determined in the initial aldol step, and steric arguments are advanced to explain this outcome.

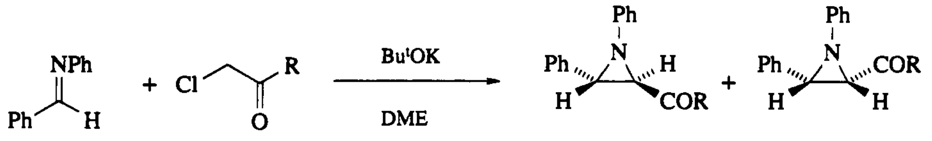

(29)

**(80)** **(81)** **(82)** **(83)**

a: R = OEt
b: R = $NEt_2$

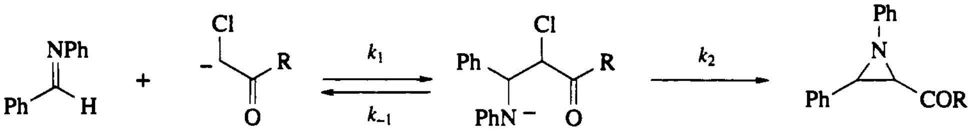

**Scheme 19**

In a subsequent investigation, *t*-butyl esters were utilized to reduce competition from Claisen condensation; the more reactive *m*-chlorobenzalaniline was found to give slightly better yields of product than benzalaniline.[46] The reaction was also extended to the synthesis of nitrile derivatives (equation 30; Table 10). The stereochemical outcome of the reaction appears to be affected by the base (or corresponding cation) employed, depending on the X and R substituents. In the ester examples, when $R^1$ = H, only the

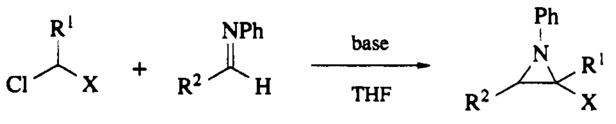

(30)

**(84)**

**Table 10** Substituted Aziridines from Darzens Condensations[46]

| $R^1$ | $R^2$ | X | t (°C) | Yield (%) | Cis:trans ratio ($R^2$ and X substituents) Bu$^t$OK | $(Me_3Si)_2NLi$ |
|---|---|---|---|---|---|---|
| H | Ph | $CO_2Bu^t$ | -50 | 85 | 30:70 | >95:5 |
| H | *m*-$ClC_6H_4$ | $CO_2Bu^t$ | -50 | 90 | 35:65 | >95:5 |
| Me | Ph | $CO_2Bu^t$ | -15 | 60 | 30:70 | 30:70 |
| Me | *m*-$ClC_6H_4$ | $CO_2Bu^t$ | -15 | 75 | 30:70 | 30:70 |
| H | Ph | CN | -80 | 50 | ≈100% *cis* | 80:20 |
| H | *m*-$ClC_6H_4$ | CN | -80 | 70 | ≈100% *cis* | 80:20 |
| Me | Ph | CN | -80 | 75 | 15:85 | 20:80 |
| Me | *m*-$ClC_6H_4$ | CN | -80 | 90 | 15:85 | 15:85 |

*cis* isomer is obtained with LHMDS, while the *trans* isomer predominates with Bu$^t$OK. In the nitrile examples, when $R_1$ = H, the *cis* isomer is formed exclusively with Bu$^t$OK and it is also predominant when LHMDS is the base. When $R^1$ = Me, the *trans* isomer is the major product in all examples, and the ratio is independent of the base. The mechanistic ramifications of these stereochemical results are not clear.

The reactions of aromatic imines with alkyl dichloroacetates in a protic medium afford highly functionalized 1,3-diarylaziridines (equation 31).[47] Excellent yields (65–96%) of 2-aziridine-2-chlorocarboxylic acid isopropyl esters (**87**; $R^2$ = Ph, $R^3$ = Pr$^i$, X = Cl) are obtained. However, the reaction is limited to aromatic imines in which both $R^1$ and $R^2$ are aryl substituents.

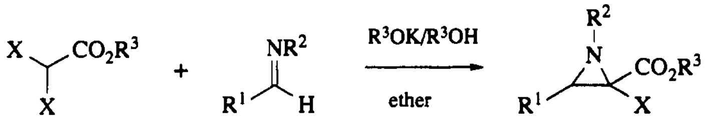

**(87)** (31)

A method for the synthesis of *cis*-*N*-arylaziridines involves sequential condensation of a substituted chloro *p*-tolyl sulfoxide and an aromatic imine, cyclization with Bu$^t$OK and desulfinylation with ethylmagnesium bromide (Scheme 20).[48] Treatment of 1-chloroundecanyl *p*-tolyl sulfoxide with LDA (–40 °C) followed by benzalaniline (**89**; $Ar^1$ = $Ar^2$ = Ph) affords the corresponding crystalline adduct (**90**) as a single diastereomer (94% yield). Cyclization provides the sulfinylaziridine (**91**) in 87% yield; desulfinylation (–55 to –35 °C, 2 h) provides stereospecifically (retention) the *cis*-aziridine (**92**) in 95% yield. Several related examples are provided in which products are obtained stereospecifically in similar yields.

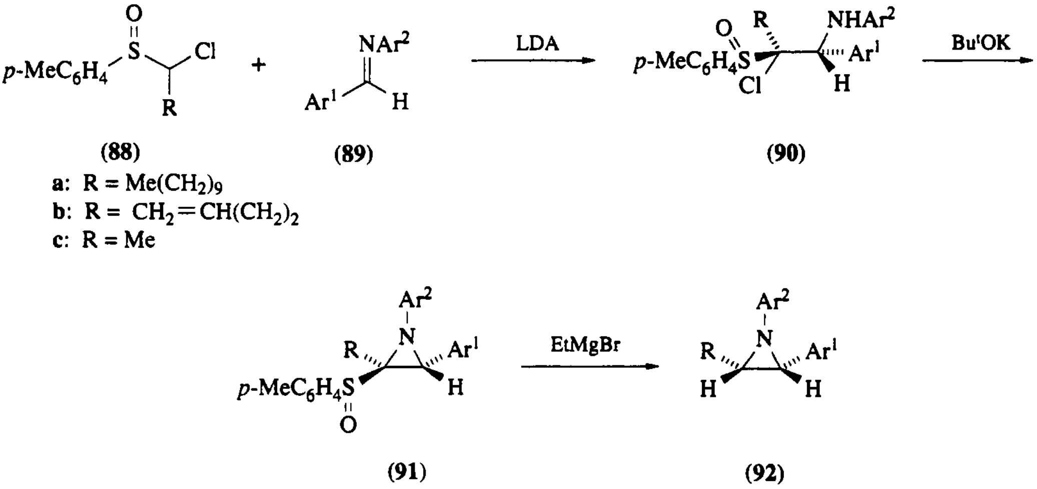

Scheme 20

## 1.13.6 CONDENSATIONS UNDER MULTIPHASE CONDITIONS

### 1.13.6.1 Phase-transfer Conditions

### *1.13.6.1.1 Esters, nitriles, sulfones and sulfonamides*

Darzens condensation of chloroacetonitrile and carbonyl compounds to give glycidic nitriles can be carried out in the presence of aqueous sodium hydroxide and a quaternary ammonium catalyst, such as triethylbenzylammonium chloride (TEBA; equation 32).[49] In a subsequent study, interesting stereochemical control was obtained in an interfacial Darzens condensation.[50] Condensation of α-chlorophenylacetonitrile (**93**) with benzaldehyde, conducted in benzene in the presence of 50% aqueous sodium hydroxide and TEBA as a phase transfer catalyst, affords predominantly the *trans*-glycidonitrile (**94**) accompanied by the corresponding *cis* isomer (**95**; equation 33). Similar results are obtained when catalytic dibenzo-18-crown-6 is employed instead of TEBA. In contrast, when the reaction is carried out without a quaternary ammonium salt, the *cis*- and *trans*-epoxides (**95**) and (**94**) are obtained in a ratio of approximately 1:1. The underlying rationale suggested for the observed stereoselectivity is shown in Scheme 21. It is proposed that the transition state (**96**) leading to the observed major *cis* product is stabilized to a larger extent relative to the corresponding transition state (**97**), leading to *trans*-epoxide at the phase boundary through interactions of the O$^-$, Cl and CN substituents located at the surface of the aqueous phase. This interpretation requires that the cyclization step is the rate-determining step for the reaction; the authors also note that in the two-phase condensation of chloroacetonitrile or α-chloropropionitrile with carbonyl compounds, in which the cyclization step is reportedly[51] the rapid step (under single-phase conditions), enhanced selectivity is not observed. It should be noted that one can also draw a transition state structure (**98**), leading to *trans* product (**94**), which appears to have stabilizing interactions similar to (**96**). However, (**98**) necessitates an interaction of a lipophilic phenyl substituent with the aqueous phase, perhaps destabilizing (**98**) relative to (**96**).

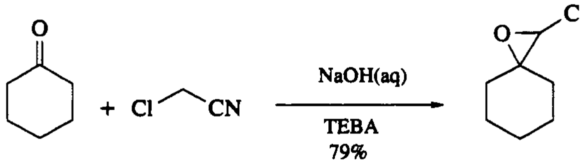

(32)

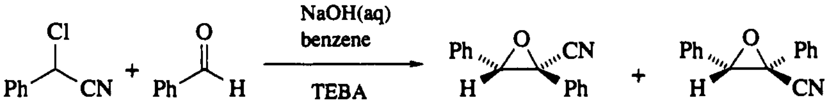

(33)

(**93**) (**94**) 90% (**95**) 10%

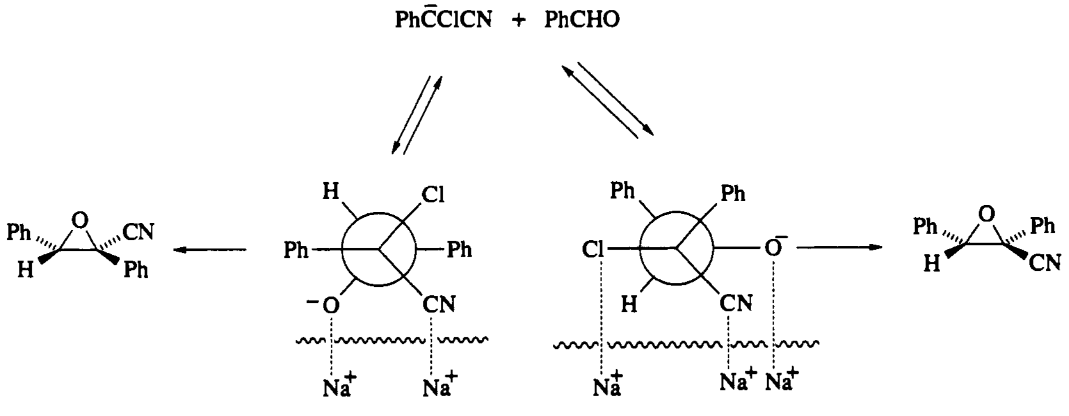

(**97**) (**96**)

**Scheme 21**

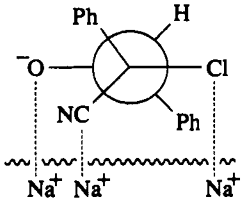

(**98**)

α-Halo sulfones react with aldehydes and ketones under catalytic two-phase conditions (equation 34; Table 11) to give glycidic sulfones.[52a,53] For the aldehyde substrates employed, only *trans*-epoxides are isolated. The sulfonamide (**100**) has also been shown to react in a highly stereoselective manner with aldehydes under phase-transfer conditions;[52b] only *trans*-1,2-epoxyalkanesulfonamides are obtained (equation 35).

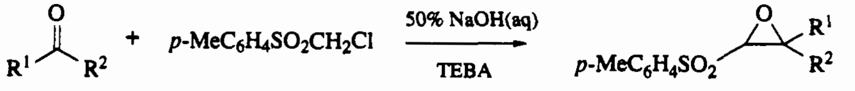

+
$p$-MeC$_6$H$_4$SO$_2$CH$_2$Cl
50% NaOH(aq)
TEBA
$p$-MeC$_6$H$_4$SO$_2$
R$^1$
R$^2$

(34)

**(99)**

**Table 11** Epoxy Sulfones (99) Obtained Under Phase-transfer Conditions[52a]

| *R*$^1$ | *R*$^2$ | *Yield of (99) (%)* |
|---|---|---|
| Ph | Ph | 90 |
| Me | Me | 91 |
| Ph | H | 60 |
| Pr$^i$ | H | 65 |
| —(CH$_2$)$_5$— | | 90 |

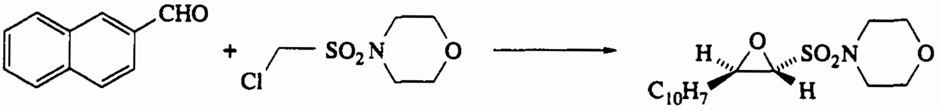

CHO
+
Cl
SO$_2$N
O
H
C$_{10}$H$_7$
SO$_2$N
H

(35)

**(100)** **(101)**

### *1.13.6.1.2 Conjugated enones—preparation of cyclopropanes*

When conjugated enones are employed in Darzens-type condensations, three product types are possible, as shown in Scheme 22, depending on the initial site of addition as well as the mode of intra-

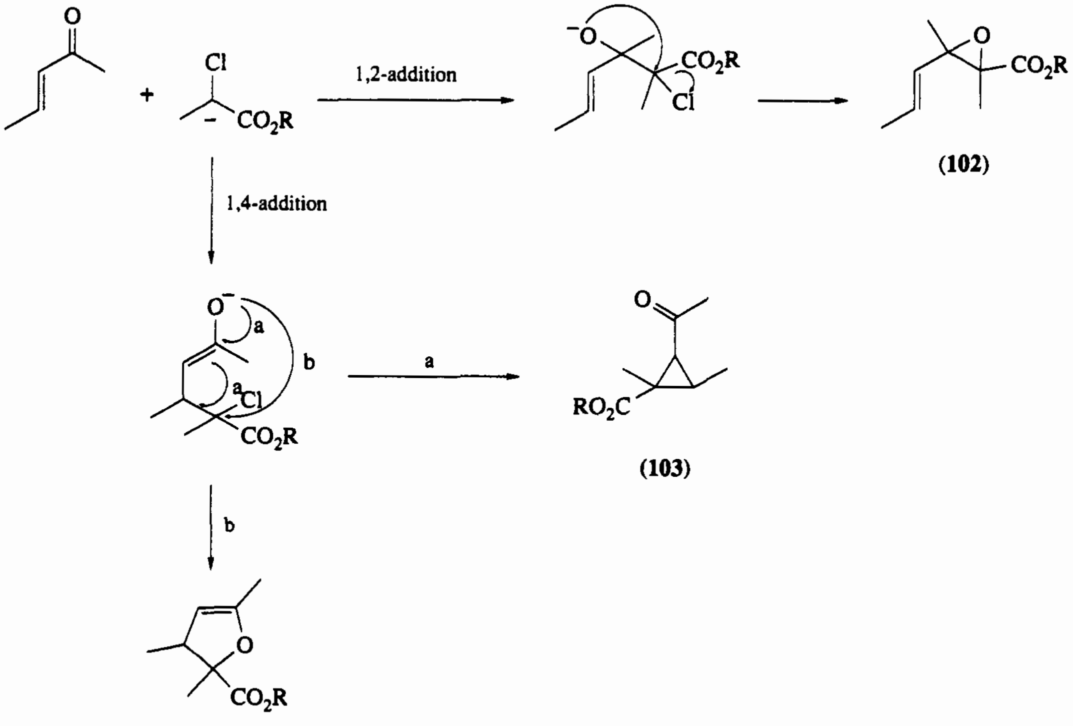

O
+
Cl
CO$_2$R
1,2-addition
$^-$O
CO$_2$R
Cl
O
CO$_2$R
1,4-addition
O$^-$
a
b
a
Cl
CO$_2$R
a
O
RO$_2$C
b
O
CO$_2$R

**(102)**

**(103)**

**(104)**

**Scheme 22**

molecular displacement.[54] In an early systematic investigation on this type of reaction,[55] it was found that under homogeneous conditions, simple α-halo esters afford cyclopropanes analogous to (**103**; equation 36). The reaction was demonstrated to give synthetically useful yields of substituted cyclopropanes from several electrophiles and a variety of α-halo esters. Subsequently, the reaction of electrophilic alkenes with α-chloronitriles and esters was investigated under phase-transfer catalytic conditions (equation 37).[56,57] The results are shown in Table 12. The cyclopropane derivatives are formed in good yield with a slight to moderate predominance of *trans* product. Normally, the Michael adducts cannot be isolated, because cyclization of the incipient carbanions is so rapid. However, phenyl vinyl sulfone and α-chloropropionitrile react under these conditions to afford primarily (**106**; 86% yield). The sulfone can be cyclized under more vigorous conditions.

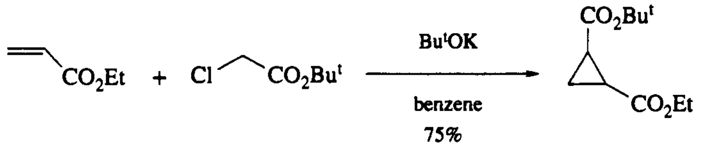

(36)

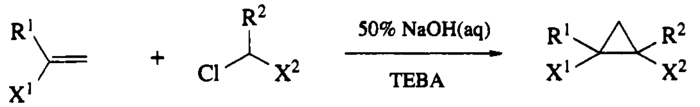

(37)

**(105)**

**Table 12** Preparation of Cyclopropanes (*105*)[56]

| *R*[1] | *R*[2] | *X*[1] | *X*[2] | *Yield of (105) (%)* | *Product ratio*<br>*Cis (%)* | <br>*Trans (%)* |
|---|---|---|---|---|---|---|
| H | H | CN | $CO_2Bu^t$ | 45 | 29 | 71 |
| H | Me | CN | CN | 75 | 46 | 54 |
| H | Me | $CO_2Ph$ | CN | 67 | 24 | 76 |
| H | Me | $SO_2Ph$ | CN | 7 | 32 | 68 |
| Me | Me | CN | CN | 75 | 45 | 55 |

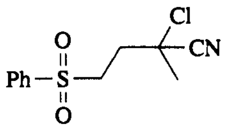

**(106)**

The issue of 1,2- *versus* 1,4-addition, as shown in Scheme 22, in the phase transfer catalyzed (benzyltriethylammonium chloride; TEBA) version of this cyclopropanation reaction, was addressed in a more recent publication.[54] Simple α-halo esters do not react with acrolein, methyl vinyl ketone or 2-chloroacrylonitrile under the conditions examined. However several electrophilic alkenes do react with diethyl bromomalonate to give good yields of substituted cyclopropanes (equation 38; Table 13). The only side

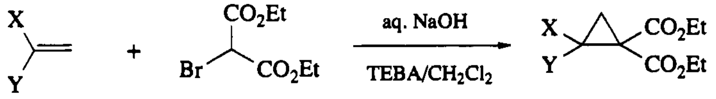

(38)

**(107)**

**Table 13** Substituted Cyclopropanes from Diethyl Bromomalonate and Electrophilic Alkenes[54]

| *X* | *Y* | *Yield of (107) (%)* |
|---|---|---|
| CHO | H | 100 |
| COMe | H | 97 |
| Cl | CN | 75 |
| $Ph_3P^+$ | H | 70 |
| $(EtO)_2P(O)$ | $CO_2Me$ | 65 |

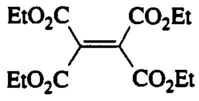
EtO2C
CO2Et
EtO2C
CO2Et

**(108)**

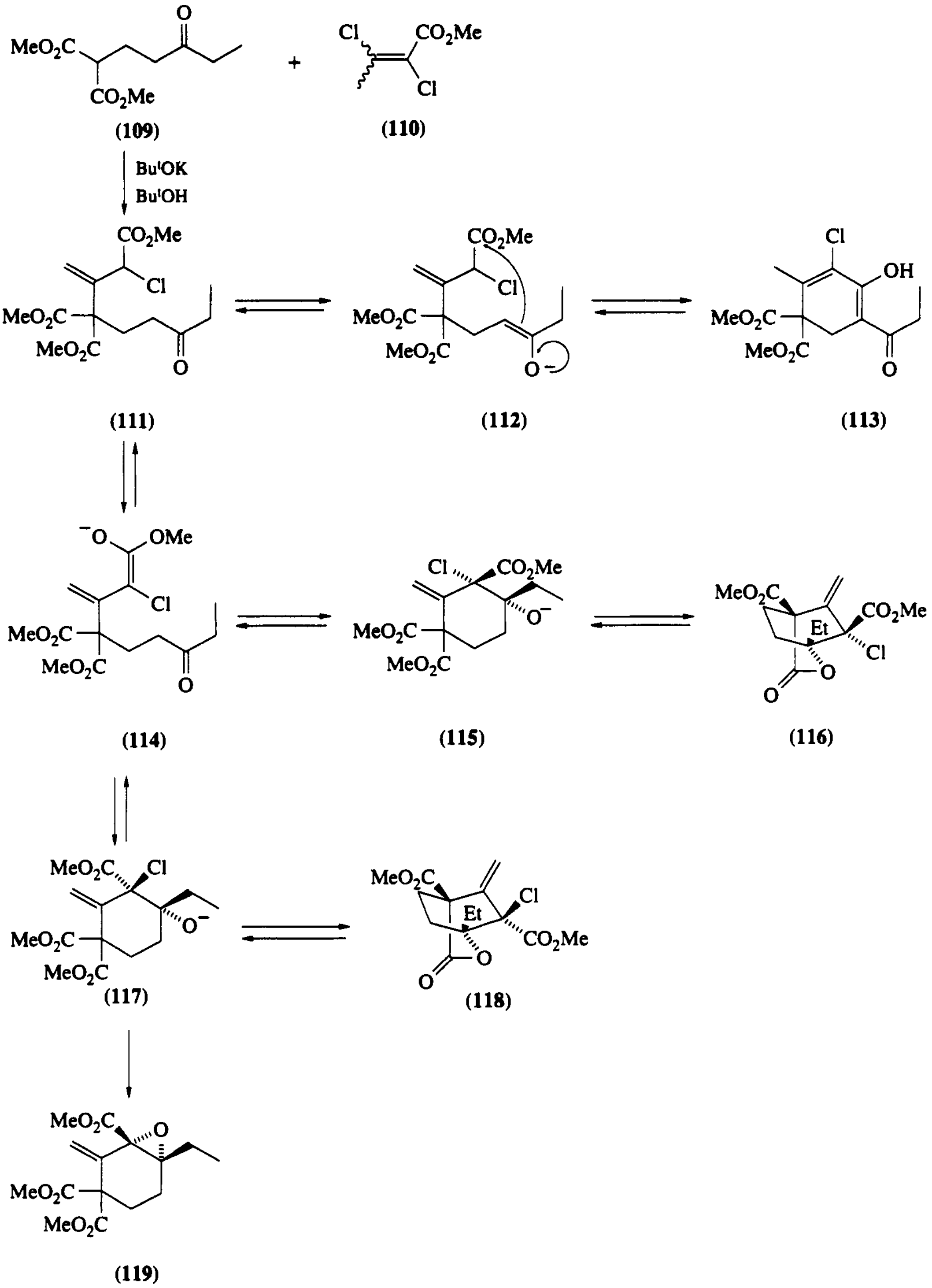
MeO2C
O
CO2Me
(109)
+
Cl
CO2Me
Cl
(110)
Bu^tOK
Bu^tOH
CO2Me
Cl
MeO2C
MeO2C
O
(111)
CO2Me
Cl
MeO2C
MeO2C
O−
(112)
Cl
OH
MeO2C
MeO2C
O
(113)
−O
OMe
Cl
MeO2C
MeO2C
O
(114)
Cl
CO2Me
O−
MeO2C
MeO2C
(115)
MeO2C
CO2Me
Et
Cl
O
O
(116)
MeO2C
Cl
O−
MeO2C
MeO2C
(117)
MeO2C
Cl
Et
CO2Me
O
O
(118)
MeO2C
O
MeO2C
MeO2C
(119)

**Scheme 23**

product observed in these condensations is (**108**), derived from self-condensation of diethyl bromomalonate and subsequent dehydrobromination. Activated alkenes substituted at the β-position do not afford the desired cyclopropane products. Thus, this method, although useful for the preparation of certain substituted cyclopropanes, is somewhat limited due to lack of generality.

Another situation involving multiple electrophilic sites, although investigated under homogeneous conditions, emerged during the course of studies directed toward the synthesis of aklavinone, the aglycone of the potent antitumor antibiotic aclacinomycin.[58] The cyclohexadiene monoepoxide (**119**) was prepared as a potential synthon for the A ring of this natural product. The preparation of (**119**) utilized an intramolecular Darzens condensation as a key step and like the situation portrayed in Scheme 22, several viable regiochemical outcomes could be envisioned. The reaction (Scheme 23) was studied under several conditions, and its course was found to be highly dependent on the exact nature of the variables involved. Despite the complexities, the desired epoxide (**119**) is obtained efficiently under appropriate conditions. The Darzens reaction precursor (**111**) is obtained by condensation of the dichlorocrotonate (**110**) and ketomalonate (**109**) with potassium *t*-butoxide (70% yield). The solvent plays a critical role in determining the subsequent fate of this adduct. In the presence of methanol (**113**) is obtained as the major product; it is postulated that this outcome is due to stabilization of the ketone enolate (**112**) relative to the more delocalized ester dienolate (**114**) by the protic hydrogen-bonding solvent. Although the less-hindered enolate (**112a**) would also be predicted to be similarly stabilized under these conditions, no products derived from this species are observed, most likely because the malonate ester groups, six carbon atoms removed, are too sterically hindered. In polar aprotic solvents, such as DMF or DMSO which strongly solvate the counterion, the delocalized ester (**114**) is more stable than (**112**) or (**112a**). Steric factors thus determine the conformation of (**114**) and the transition states leading to (**115**) or (**117**). Molecular models indicate that steric interactions are minimized when (**114**) exists in the (*Z*)-(*S*)-*cis* conformation as shown in Figure 3a. In less polar solvents, such as diethyl ether or THF, the dienolate (**114**) is postulated to exist as a tight ion pair with the sodium cation, such that chelation of the cation by the ketone and ester carbonyl groups overcomes steric hindrance associated with the (*Z*)-(*S*)-*trans* dienolate. This chelation also controls the transition state conformation in the aldol addition (Figure 3b) leading to (**117**) in a boat conformation. Since the alkoxide and chloro substituents are not antiperiplanar, epoxide formation is precluded, and the lactone (**118**) is the major product. Chelation has a relatively lesser stabilizing effect on the transition states leading to (**116**) or (**119**), and only small quantities of these products are observed.

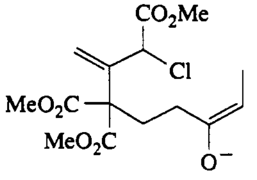

**(112a)**

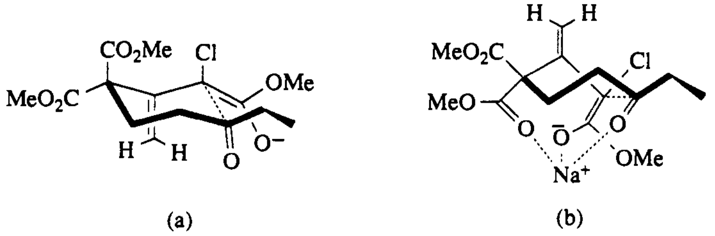

(a) (b)

**Figure 3** (a) Transition state for (**114**) in polar solvents, leading to epoxide (**119**) through the chair conformation; (b) transition state for (**114**) in less-polar solvents, leading to lactone (**118**) through the boat conformation

### 1.13.6.2 Solid–Liquid Systems

Normally, the Darzens reaction of simple α-halo esters is carried out under anhydrous conditions, since in aqueous media or under phase-transfer catalysis conditions the esters are prone to hydrolysis. Saponification can be largely prevented by using *t*-butyl esters, but this strategy also poses potential problems, as hydrolysis of the resulting glycidic ester is often the next stage of a synthetic process. Recently, a procedure has been developed in which α-chloro esters are deprotonated by treatment with potassium carbonate suspended in DMF in the presence of catalytic tetraalkylammonium salts.[59] Under these conditions, the α-halo esters are not hydrolyzed, and the derived carbanions react smoothly with aromatic aldehydes to give the corresponding glycidic esters in high yields (equation 39). The yields of glycidic esters are reduced in the case of aliphatic substrates, due to competitive self-condensation of the aldehydes. Aldehydes possessing only one α-hydrogen afford the oxirane derivatives in satisfactory yield. The conversion of ketones to glycidic esters under these conditions occurs less readily.

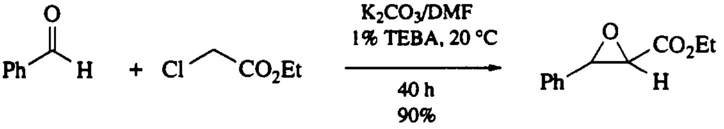

(39)

## 1.13.7 ASYMMETRIC VARIANTS OF THE DARZENS CONDENSATION

### 1.13.7.1 Asymmetric Catalysis

Until recently, little success had been achieved in developing a highly enantioselective version of the Darzens reaction. Several investigations of chiral phase-transfer catalysts for this condensation, in which low or modest asymmetric induction is obtained, have been reported. These include the use of *N*-alkyl-*N*-methylephedrinium halides,[60] the quinine-derived salt (**120**),[61] and polyamino acids.[62] A related study has examined the use of achiral phase-transfer catalysts in the condensations of carbonyl compounds and the asymmetric chloromethylsulfonate ester (**121**).[63a] The same group of researchers subsequently reported similar studies employing the sulfonamides (**122**)–(**124**).[63b]

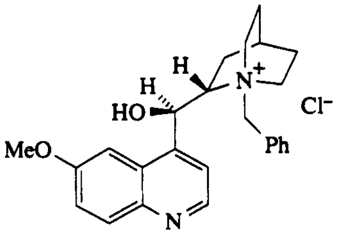

**(120)**

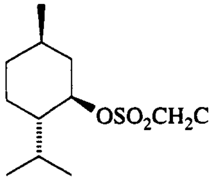

**(121)**

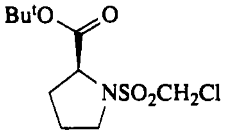

**(122)**

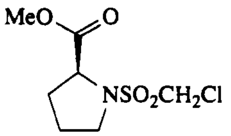

**(123)**

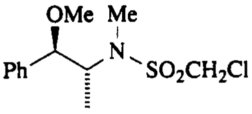

**(124)**

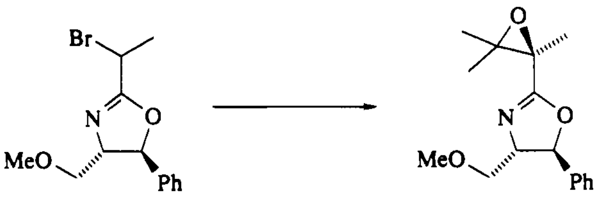

**(125)** **(126)**

(40)

The condensation of the asymmetric oxazoline (**125**) and 2-propanone is reported to give the adduct (**126**; equation 40).[64] The Darzens condensation of aromatic aldehydes with phenacyl halides in the presence of catalytic bovine serum albumin affords epoxy ketones in optical yields as high as 62% *ee*.[65]

### 1.13.7.2 Condensations Employing Asymmetric *N*-(α-Haloacetyl)oxazolidinones

A comprehensive study involving a modified Darzens procedure which employs the aldol reaction of α-haloimides with aldehydes to afford ultimately enantiomerically pure benzyl *cis*-α,β-epoxycarboxylates has been carried out.[66] The research was based on the premise that since the initial phase of the Darzens condensation entails an aldol-type reaction, an asymmetric variant could be developed utilizing technology employed for enantioselective aldol condensations (see Volume 2, Chapters 1.5–1.7). In particular, the work was aimed at using the protocol developed by Evans[67] involving enolates of *N*-acyloxazolidinones, in this case requiring the use of enantiomerically homogeneous α-haloacyloxazolidinones in aldol-like reactions with aldehydes and cyclization of the derived halohydrins to give the desired epoxides. Initially, the effect of enolate countercations in affecting the stereochemical course of the reaction was investigated. The requisite *N*-(α-haloacetyl)oxazolidinones (**127**) are prepared from the corresponding α-haloacetyl halides (**128**) and (4*S*)-4-isopropyl-2-oxazolidinone (**129**; equation 41). Generation of the lithium enolate of (**127a**; LDA, –78 °C) and subsequent trapping with *t*-butyldimethylsilyl chloride affords the enol ether (**130**) as predominantly (>40:1) a single isomer (equation 42). Zn and $Sn^{IV}$ enolates were obtained from lithium enolates by addition of ethereal solutions of $ZnCl_2$ or $SnBu^n{}_3Cl$, respectively. $Sn^{II}$ enolates were obtained by treatment of lithium enolates with a THF solution of tin(II) triflate or by the procedure of Mukaiyama.[68] Boryl enolates were prepared by the method of Evans.[67] In all cases, the aldehyde was added to the enolate solution at –78 °C except for the Zn enolates; in these cases, the addition was done at –20 °C or at 0 °C. The general reaction is shown in equation (43). The diastereoselectivity of this transformation is consistent with earlier findings;[67] *syn* products (**131**) and (**132**) are obtained predominantly. The selectivity is generally moderate (2–3:1) for lithium enolates where X = Cl and somewhat better (3–19:1) for zinc and tin enolates. The boron enolates, however, exhibit exceptionally high diastereoselection (>50:1); no *anti* isomers are detected. Consistently, over the range of aldehydes studied, diastereoselectivity for zinc enolates is improved by a decreased molar ratio of zinc chloride (50 mol % *versus* 100 mol %). It is postulated that the enhanced selectivity is due to the capa-

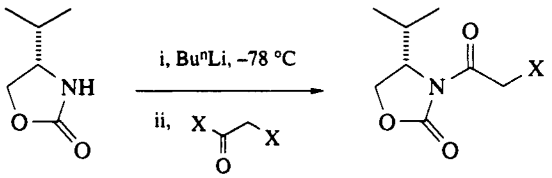

(**129**) (**128**)

(**127a**) X = Cl
(**127b**) X = Br

(41)

(**127a**)

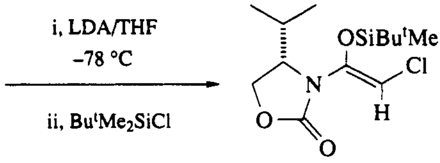

(**130**)

(42)

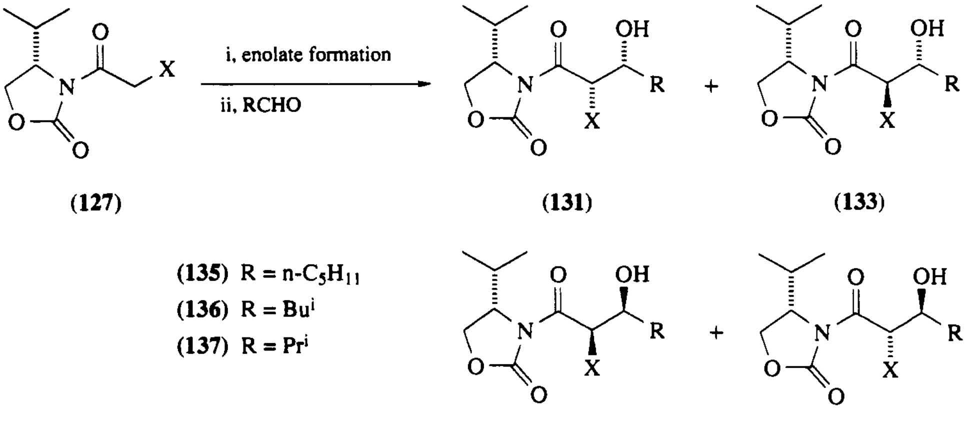

(**127**) (**131**) (**133**) (43)

(**135**) $R = n\text{-}C_5H_{11}$
(**136**) $R = Bu^i$
(**137**) $R = Pr^i$

(**132**) (**134**)

bility of the zinc cation to bind intermolecularly two enolate molecules, thereby producing greater steric demand in the transition state. Diastereoselectivity in the tin(II) triflate-mediated reactions is dependent on the method used to generate the enolate. The α-chloro enolates generated by the Mukaiyama method [$Sn(OTf)_2$, tertiary amine, $CH_2Cl_2$, 0 °C][68] afford modest levels (3–4:1) of diastereoselectivity; in contrast, this selectivity is improved (6–13:1) by generating the lithium enolate prior to adding a THF solution of tin(II) triflate to the system (–78 °C). Generally, α-bromo enolates show enhanced selectivity relative to the corresponding chloro derivatives. Selectivity generally improves with increasing bulk in the aldehyde (**135** → **136** → **137**), although, as noted previously, the boron enolates afford only *syn* products regardless of the other variables investigated.

In addition to the excellent diastereofacial selectivity observed with the boron enolate, an unusual result was obtained concerning the absolute stereochemistry of the *syn* products (ratio of **131**:**132**). Interestingly, the stereochemistry of the newly formed chiral centers in the major products derived from tin(II) and boron enolates (**131**) is reversed from that obtained from lithium, tin(IV) and zinc enolates. Several examples of the reaction are shown in Table 14.

**Table 14** Condensations of *N*-(α-Bromoacetyl)oxazolidinone Enolates and Aldehydes[66b]

| *Aldehyde* | *Metal* | *Yield (%)* | *Diastereoselection* *Syn (%)* *(131) and (132)* | *Diastereoselection* *Anti (%)* *(133) and (134)* | *Enantioselection* *(131) (%)* | *Enantioselection* *(132) (%)* |
|---|---|---|---|---|---|---|
| n-$C_5H_{11}$CHO | B | 55 | >98 | <2 | >98 | <2 |
| n-$C_5H_{11}$CHO | Zn[a] | 65 | 89 | 11 | 12 | 88 |
| Bu$^t$CHO | B | 48 | >98 | <2 | >98 | <2 |
| Bu$^t$CHO | Zn[a] | 72 | 91 | 9 | 17 | 83 |
| Pr$^i$CHO | B | 51 | >98 | <2 | >98 | <2 |
| Pr$^i$CHO | Zn[a] | 79 | 98 | 2 | 11 | 89 |

[a] 50 mol %.

The origin of the cation dependence concerning the sense of enantioselectivity is not completely understood, although a possible explanation has been advanced. In this model (Scheme 24), it is postulated that a major stereocontrolling factor is the difference in orientation as represented by transition states T¹ and T²; enantioselectivity is controlled through direction of attack of the enolate on the aldehyde, which is dependent upon, to a large extent, the orientation of the enolate face with respect to the oxazolidinone ring. Steric constraints cause the aldehyde to approach the enolate from the face remote to the ring isopropyl substituent. The enolate orientation in T¹ (*E,Z*), in which the ring carbonyl is *anti* to the enolate carbonyl leads to (**131**), the observed major product in the B- and Sn$^{II}$-mediated reactions. The alternative transition state T² (*Z,Z*) leads to (**132**), the observed major product in the Li-, Zn- and

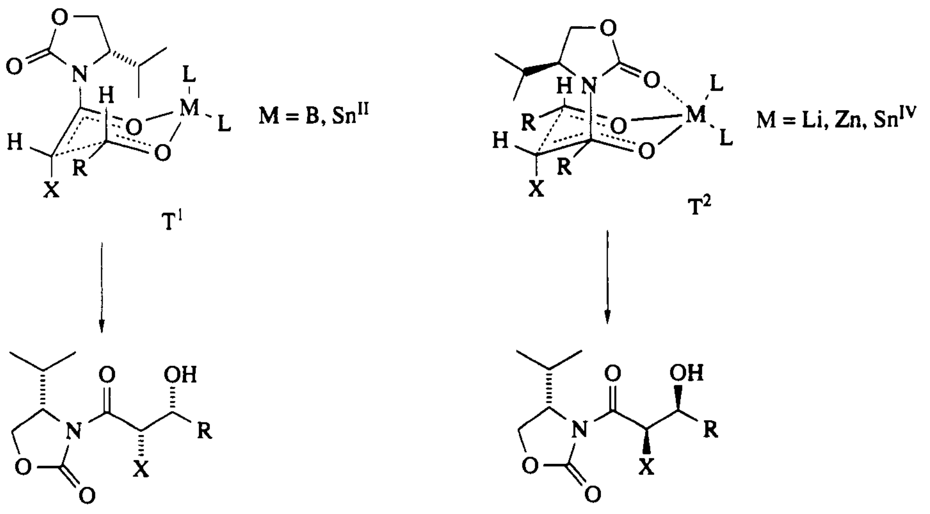

**Scheme 24**

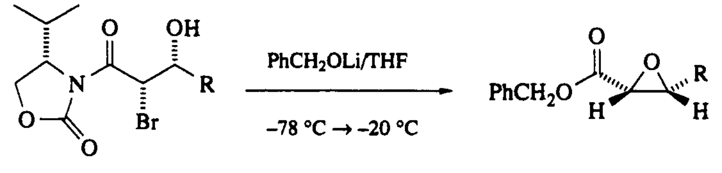

(44)

**(131)**

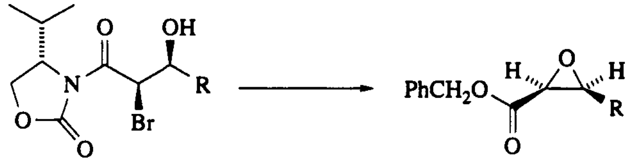

(45)

**(132)**

Sn$^{IV}$-mediated reactions. Apparently, Li, Zn and Sn$^{IV}$ overcome thermodynamic dipolar forces which favor[69a] the (*E,Z*)-orientation through chelation[69b] involving the enolate and both carbonyl groups. Without loss of ligand (L), boron or Sn$^{II}$ cannot bind simultaneously the three oxygen atoms from the enolate and the two carbonyls; in these cases, the reaction proceeds primarily through a template similar to T$^1$ with the (*E,Z*)-orientation to provide predominantly (**131**).

*syn*-Bromohydrins (**131**) and (**132**) afford stereospecifically *cis*-benzyl-α,β-epoxy esters, in 70–74% yield, upon treatment with lithium benzyloxide,[70] with no evidence of epimerization to *trans*-epoxides (equations 44 and 45). Thus, the methodology provides overall a route to both enantiomers of α,β-epoxy esters from the same α-haloimide.

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# 1.14

# Metal Homoenolates

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## 1.14.1 INTRODUCTION

This chapter describes the chemistry of carbanionic species having a carbonyl function at the β-position, relative newcomers among synthetically useful carbanionic species. The chemistry of homoenolates is complicated by the problem of tautomerism between oxyanionic and carbanionic isomers through a process that formally involves homoconjugation.[1] The synthetic problem caused by this tautomerism is much more severe in homoenolate chemistry (Scheme 1) than in enolate chemistry (Scheme 2), which also has a similar problem, since the carbanionic tautomer (**1**; Scheme 1) once formed often undergoes rapid and irreversible cyclization to the oxyanionic tautomer (**2**), and rarely acts as a carbon nucleophile. Until recently, therefore, chemists have not been able to make use of carbanionic homoenolates for organic syntheses.[2-4] However, a large number of useful homoenolate reactions have recently been discovered, and are described in this chapter.

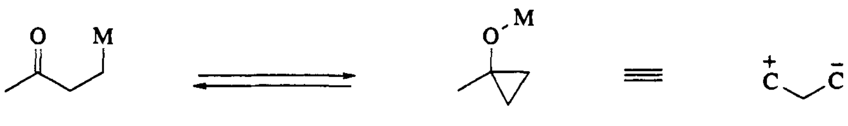

(1) (2)

Scheme 1

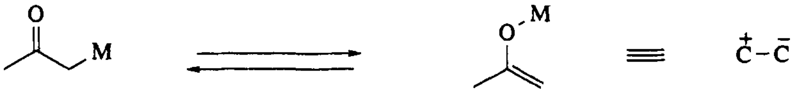

Scheme 2

Because of the convenience of the terminology, the term homoenolate has been used to describe the carbanionic tautomer (**1**). By using this term, trivial names such as homoenolate anion, zinc homoenolate and ester homoenolate may be used, along with more strict terms such as ethyl 3-lithiopropionate, *etc.*

The synthetic value of homoenolates, in exact analogy to that of enolates, stems from their amphoteric nature (equations 1 and 2). In addition, homoenolates represent archetypal synthons in the concept of 'umpolung',[5–7] acting as inverse polarity nucleophilic synthons of Michael acceptors.

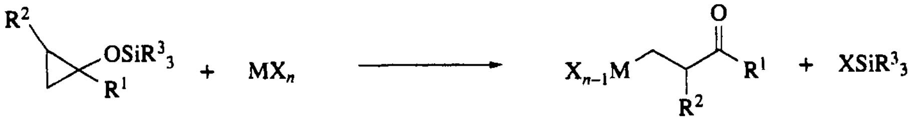

(1)

$R^1$ = hydrogen, alkyl, aryl, alkoxy

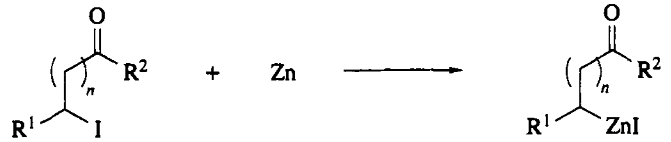

(2)

Because of the lack of appropriate synthetic entries to true homoenolates, many 'homoenolate equivalents' appeared in the early 1970s, and their prototypes are shown in formulae (**3**) to (**5**). Protection of the carbonyl group either as a ketal (**3**) or an enol derivative, *e.g.* (**4**) and (**5**), constitutes the main concept for the design of such synthetic equivalents.[7]

Dianions (**6**)[8] and (**7**)[9] illustrate the concept of *in situ* protection of the carbonyl group, representing another class of synthetic protocol. 3-Lithiated β-ketophosphonates, carboxamides and carboxylic acids have been generated and allowed to react with some electrophiles.

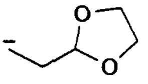

(**3**)

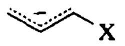

(**4**)

X = OR, NR$_2$, *etc.*

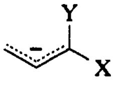

(**5**)

X, Y = OR, P(O)X$_2$, *etc.*

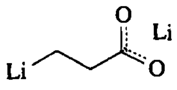

(**6**)

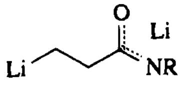

(**7**)

Since the mid-1970s, advances in organometallic chemistry have permitted the preparation and synthetic use of homoenolates. Major efforts have been expended for the exploration of a silyloxycyclopropane route,[10,11] in which silyloxycyclopropanes are cleaved by polyvalent metal salts to obtain reactive metal homoenolates (equation 1). Through such a route, a host of reactive ester,[10,12] ketone[11] and aldehyde homoenolates have been generated.

Reduction of 3-iodocarbonyl compounds (equation 2, $n = 1$) with a low-valent metal,[13,14] such as metallic zinc, generates homoenolates of esters, nitriles and ketones, and represents a convenient new entry to homoenolates. This reductive method also allows the preparation of higher homologs ($n > 2$).

## 1.14.2 ELIMINATION

Palladium homoenolates readily undergo β-elimination to give α,β-unsaturated carbonyl compounds. Treatment of a mercurio ketone with a catalytic amount of palladium(II) in the presence of $CuCl_2$ results in the formation of an enone *via* a 3-palladio ketone (Scheme 3).[15] Treatment of a silyloxycyclopropane (**8**) with $PdCl_2$ also generates *in situ* a palladium homoenolate which then undergoes β-elimination (Scheme 3). Heating a mixture of a 3-trichlorostannyl ketone[16] or aldehyde with DMSO results in the formation of an enone or an enal in excellent yield (Scheme 4).[17]

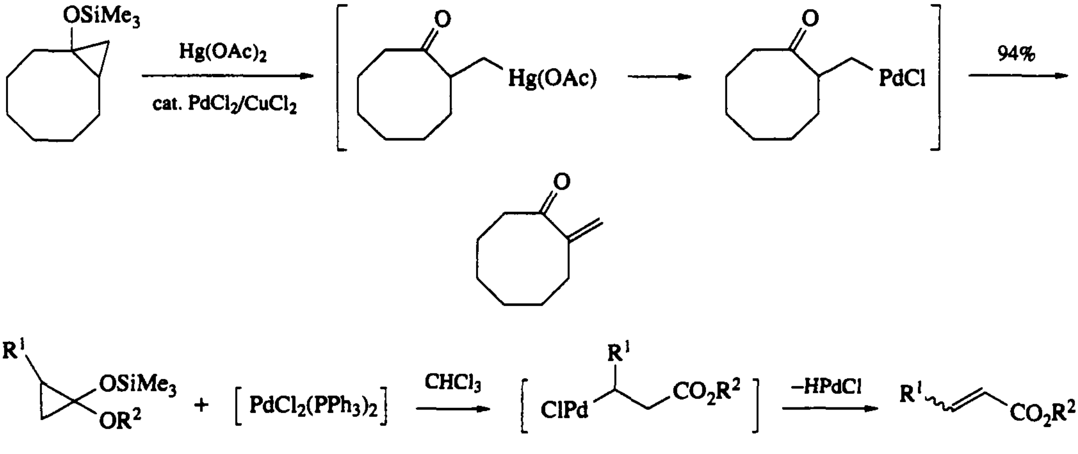

(**8**) $R^1 = H$

Scheme 3

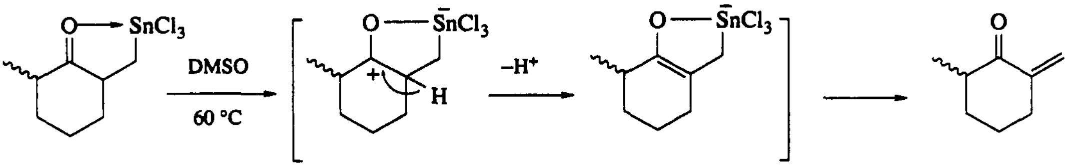

Scheme 4

## 1.14.3 FORMATION AND CLEAVAGE OF CYCLOPROPANE RINGS

### 1.14.3.1 Cyclopropane Ring Formation

Internal nucleophilic cyclization is one of the most typical reactions of reactive metal homoenolates (equation 3 and Scheme 5),[1,2] and provides a convenient route to silyloxycyclopropanes (*e.g.* **8**) through cyclization of 3-halo esters.[18] Zinc homoenolates (**9**) also cyclize to cyclopropanes under suitable conditions. Treatment of the zinc homoenolate in $CHCl_3$ with an acid chloride at room temperature gives an *O*-acylation product (Scheme 6), instead of a 4-keto ester (see Section 1.14.7.1).[19] The reaction of the zinc homoenolate with $Me_3SiCl$ in a polar solvent gives a silyloxycyclopropane (Scheme 6), providing a very mild route to silyloxycyclopropanes.[19]

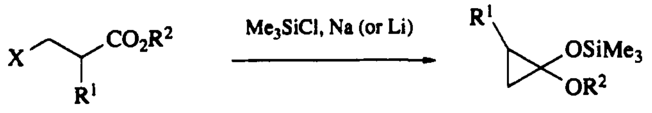

(3)

$R^1$ = H, alkyl; X = halogen (**8**)

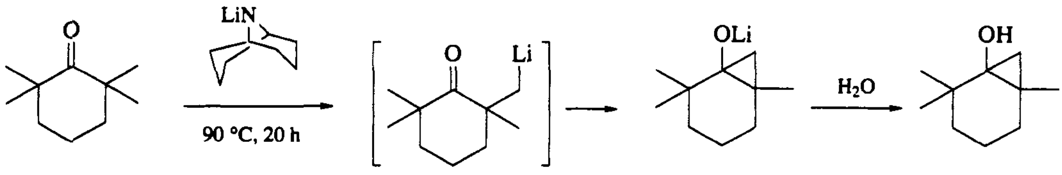
LiN
90 °C, 20 h
O
Li
OLi
H2O
OH

Scheme 5

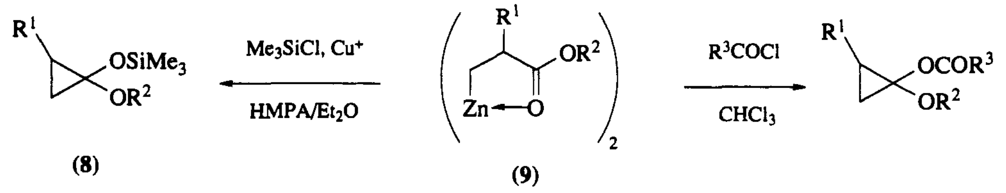
R1
OSiMe3
OR2
(8)
Me3SiCl, Cu+
HMPA/Et2O
R1
OR2
Zn
O
2
(9)
R3COCl
CHCl3
R1
OCOR3
OR2

Scheme 6

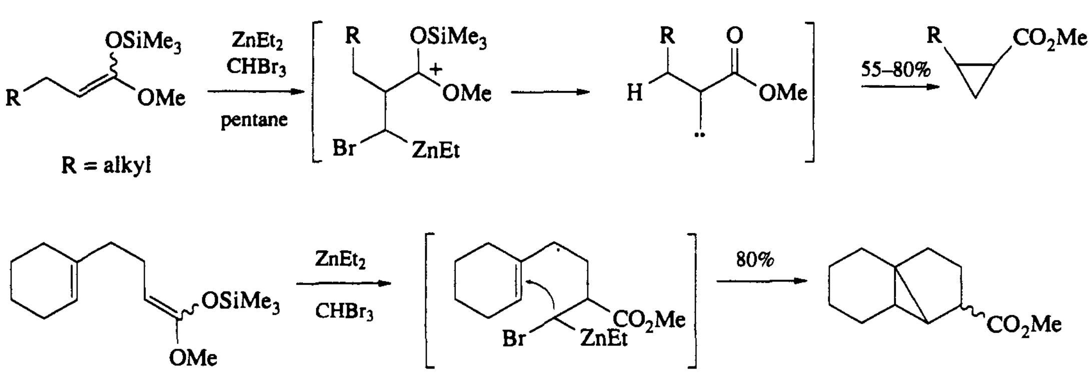
OSiMe3
R
OMe
R = alkyl
ZnEt2
CHBr3
pentane
R
OSiMe3
+
OMe
Br
ZnEt
R
O
H
OMe
55–80%
R
CO2Me
OSiMe3
OMe
ZnEt2
CHBr3
CO2Me
Br
ZnEt
80%
CO2Me

Scheme 7

Two types of cyclization reaction take place when a ketene silyl acetal is treated with a carbenoid generated from $CHBr_3$ and $ZnEt_2$.[20] When the substrate is aliphatic (Scheme 7), a cyclopropylcarboxylate is formed due to a CH insertion reaction of an intermediate zinc carbenoid. With substrates having an alkene in the vicinity of the carbenoid (Scheme 7), in particular those derived from δ,ε-unsaturated esters, internal cyclopropanation takes place.

### 1.14.3.2 Cyclopropane Ring Cleavage

In most of the ring cleavage reactions of silyloxycyclopropanes described in this chapter, the reaction takes place in such a direction that the less alkyl-substituted bond directed to the silyloxy group is cleaved to give the more stable anionic species. Chlorination of a silyloxycyclopropane with $FeCl_3$ in DMF, however, provides a unique case of the cleavage in an opposite direction (Scheme 8).[21,22] Treatment of a silyloxycyclopropane having a bicyclo[*n*.1.0]alkane structure with $FeCl_3$ in DMF produces a 3-

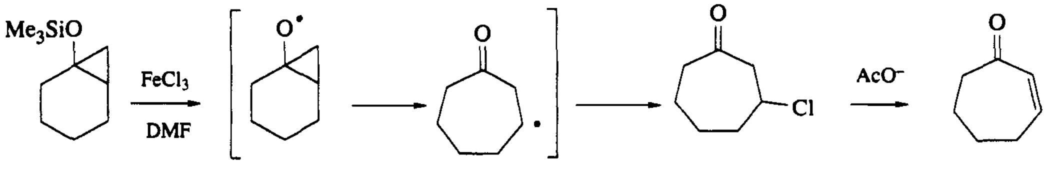
Me3SiO
FeCl3
DMF
O•
O
O
Cl
AcO−
O

Scheme 8

chloro ketone with cleavage of the internal bridging bond. Such regiochemistry is believed to be due to the radical character of the reaction, and it is presently unclear if a metal homoenolate is involved. The overall sequence of cyclopropanation, chlorination and elimination of HCl represents a useful one-carbon ring expansion method.

Fragmentation of a 1-silyloxybicyclo[*n*.1.0]alkane with $Pb(OAc)_4$ in acetic acid leads to two-bond cleavage to yield an alkenoic acid (Scheme 9).[23] The reaction involves fission of the two bonds connected to the carbon bearing a silyloxy group. The reaction is considered to involve prior conversion of the silyloxycyclopropane to the corresponding cyclopropanol. In fact, treatment of a silyloxycyclopropane under strictly aprotic conditions gives a product due to one-bond cleavage (Scheme 9).

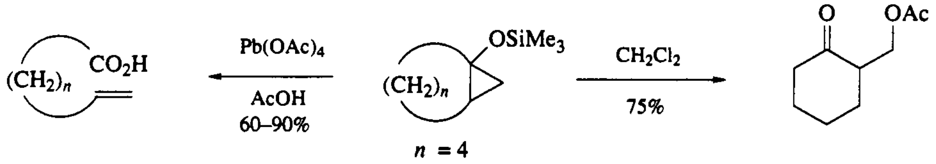

Scheme 9

## 1.14.4 SYMMETRICAL COUPLING

Reaction of a silyloxycyclopropane and $Cu(BF_4)_2$ in ether results in symmetrical coupling of two homoenolate moieties (Scheme 10).[24] This reaction provides a convenient route to 1,6-diketones. Intermediacy of a copper(II) homoenolate has been suggested. $AgBF_4$ and $CuF_2$ effect the same reaction, albeit in lower yield.[25]

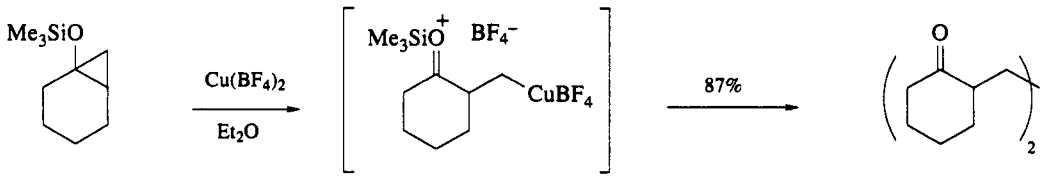

Scheme 10

## 1.14.5 CARBONYL ADDITION

Addition of a homoenolate to a carbonyl compound, which may be called a ‘homoaldol reaction’,[26] provides a straightforward route to 4-hydroxy esters and γ-lactones. Only two classes of well-characterized homoenolates that undergo nucleophilic addition to carbonyl compounds are known, namely titanium and zinc homoenolates of esters.

### 1.14.5.1 Titanium Homoenolates

Trichlorotitanium homoenolates[27,28] (**10**), which can be generated by the reaction of 1-alkoxy-1-silyloxycyclopropanes (**8**) with $TiCl_4$,[10] smoothly add to aldehydes at 0 °C (Scheme 11). They are not, however, sufficiently reactive to add to ketones.

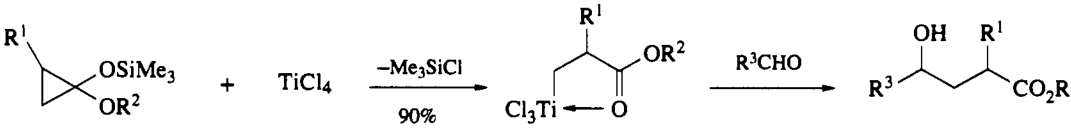

(**8**) (**10**)

Scheme 11

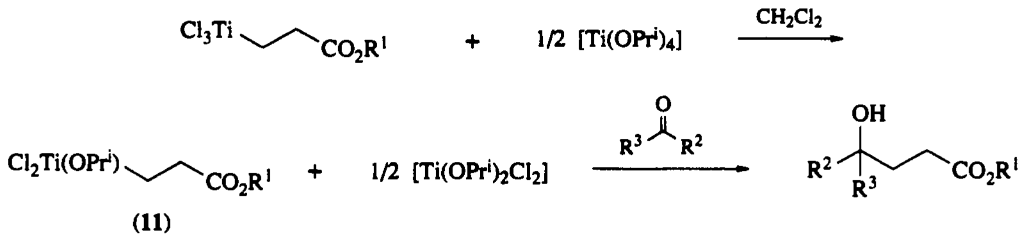
$Cl_3Ti$
$CO_2R^1$
+
1/2 [Ti(OPr$^i$)$_4$]
$CH_2Cl_2$
$Cl_2Ti(OPr^i)$
$CO_2R^1$
+
1/2 [Ti(OPr$^i$)$_2$Cl$_2$]
O
$R^3$
$R^2$
OH
$R^2$
$R^3$
$CO_2R^1$
(11)

**Scheme 12**

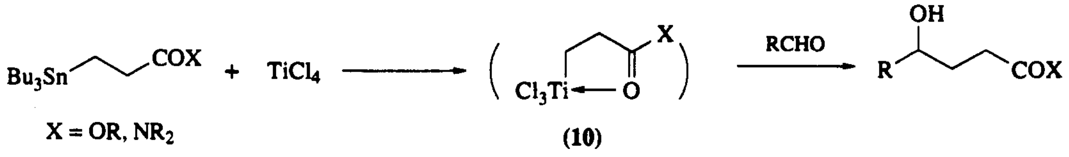
$Bu_3Sn$
COX
+ $TiCl_4$
X = OR, NR$_2$
X
$Cl_3Ti$
O
(10)
RCHO
OH
R
COX

**Scheme 13**

Addition of 0.5 equiv. of Ti(OPr$^i$)$_4$ or Ti(OBu$^t$)$_4$ to the trichlorotitanium homoenolate (**10**) produces an alkoxytitanium species (**11**; Scheme 12) which readily adds to ketones.[28] The basic trend of the chemical behavior, stereo- and chemo-selectivities of (**11**) is similar to that of simple titanium alkyls.[29]

Titanium homoenolates can be prepared by transmetallation of 3-stannyl esters with TiCl$_4$ (Scheme 13).[30,31] The trichlorotitanium species (**10**), shows reactivity very similar to that obtained by the silyloxycyclopropane route.

An attractive alternative to the chemistry of titanium homoenolates is the use of highly nucleophilic lanthanide homoenolates, which can be prepared by reduction of 3-halopropionates (Scheme 14).[32]

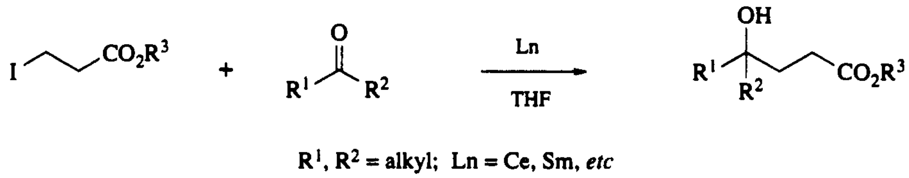
I
$CO_2R^3$
+
O
$R^1$
$R^2$
Ln
THF
OH
$R^1$
$R^2$
$CO_2R^3$
R$^1$, R$^2$ = alkyl; Ln = Ce, Sm, *etc*

**Scheme 14**

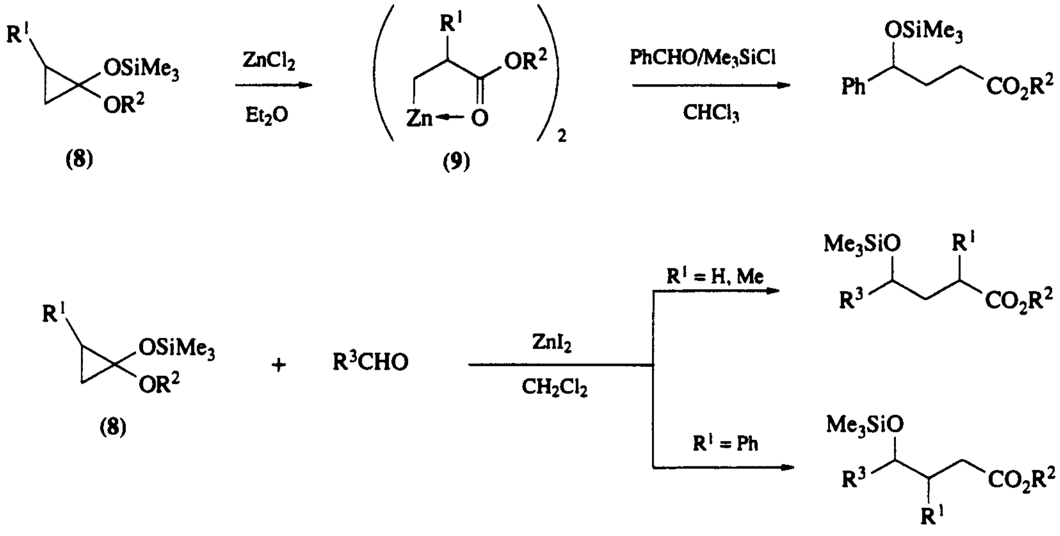
$R^1$
$OSiMe_3$
$OR^2$
(8)
$ZnCl_2$
$Et_2O$
$R^1$
$OR^2$
Zn
O
2
(9)
PhCHO/Me$_3$SiCl
$CHCl_3$
$OSiMe_3$
Ph
$CO_2R^2$
$R^1$
$OSiMe_3$
$OR^2$
(8)
+
$R^3CHO$
$ZnI_2$
$CH_2Cl_2$
R$^1$ = H, Me
$Me_3SiO$
$R^1$
$R^3$
$CO_2R^2$
R$^1$ = Ph
$Me_3SiO$
$R^3$
$CO_2R^2$
$R^1$

**Scheme 15**

### 1.14.5.2 Zinc Homoenolates

In line with the chemistry of dialkylzincs, pure zinc homoenolates (**9**),[12] which can be generated by the reaction of a silyloxycyclopropane (**8**) with $ZnCl_2$, are inert to carbonyl compounds in ethereal solvents. By contrast, when the reaction is conducted in halomethanes in the presence of $Me_3SiCl$, rapid addition occurs.[19] The accelerating effect of the chlorosilane disappears in ethereal solvents (Scheme 15).[19]

A silyloxycyclopropane (**8**) and an aldehyde have been coupled directly in the presence of a catalytic amount of $ZnI_2$.[19] The reaction proceeds with regioselective cleavage of the cyclopropane ring (Scheme 15).

### 1.14.5.3 Other Metal Homoenolates

The preparation of a 3-lithiated propionic acid derivative was reported in 1978.[8] The carbonyl function was protected by prior conversion to the lithium carboxylate. Thus, treatment of the lithium 3-bromopropionate with lithium naphthalenide produces the desired dilithiated propionic acid (**6**), which reacts in moderate yield with carbonyl compounds (Scheme 16).

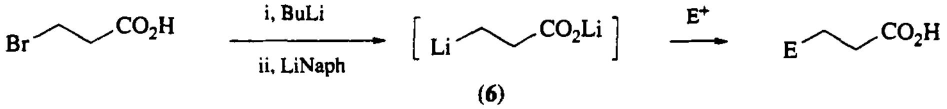
Br
CO2H
i, BuLi
ii, LiNaph
Li
CO2Li
(6)
E+
E
CO2H

$E^+$ = carbonyl compound

Scheme 16

Treatment of a 3-stannylpropionamide with 2 equiv. of $Bu^nLi$ at low temperature gives a dianionic homoenolate (**7**) which reacts with standard electrophiles (Scheme 17).[9,33] It is interesting to note that the tin–carbon bond to the propionate moiety, rather than one to a butyl group, is selectively cleaved during the tin–lithium exchange.

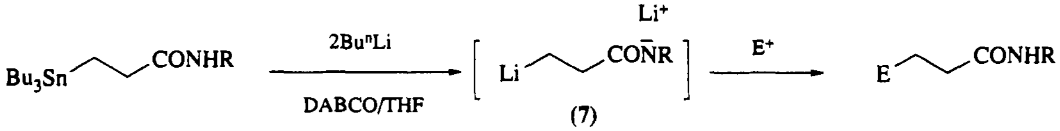
Bu3Sn
CONHR
2BunLi
DABCO/THF
Li+
Li
CONR
(7)
E+
E
CONHR

R = Ph

$E^+$ = alkyl halide, $Me_3SiCl$, ketone

Scheme 17

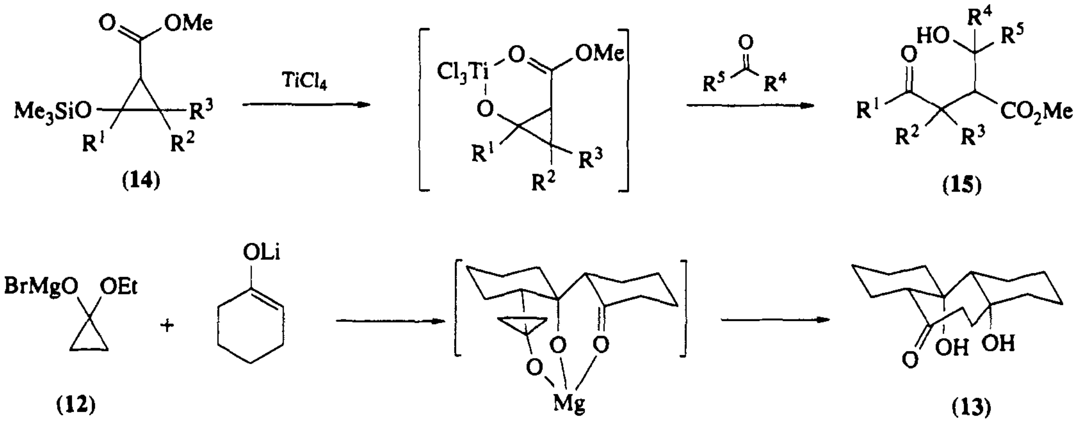
O
OMe
Me3SiO
R1
R2
R3
(14)
TiCl4
Cl3Ti
O
OMe
O
R1
R2
R3
O
R5
R4
HO
R4
R5
O
R1
R2
R3
CO2Me
(15)
BrMgO
OEt
(12)
OLi
+
O
O
O
Mg
O
OH
OH
(13)

Scheme 18

In the presence of a Lewis acid, alkyl 2-silyloxycyclopropanecarboxylates (**14**) react with a wide range of carbonyl compounds to give a diester (**15**), which has been converted to a variety of furan derivatives (Scheme 18).[34,35] An interesting use of the oxyanionic tautomer of a homoenolate involves the reaction of a magnesium cyclopropanolate (**12**) with the lithium enolate of cyclohexanone, from which a tricyclic ring containing a functionalized cycloheptanone (**13**) is formed in a single step (Scheme 18).[36]

## 1.14.6 CONJUGATE ADDITION

### 1.14.6.1 Homoenolate Radicals

The reaction of a mercurio ketone with $NaBH_4$ produces a radical species which can be trapped *in situ* by a reactive acceptor such as a vinyl ketone.[37,38] Treatment of a mixture of a mercurio ketone and an electron-deficient terminal alkene (or fumarate) in $CH_2Cl_2$ with concentrated aqueous $NaBH_4$ gives a conjugate adduct (Scheme 19). Isomerization of such a homoenolate radical, presumably *via* an intermediate cyclopropanoxy radical, has been observed in the reaction of a mercurio aldehyde (Scheme 20).[37,38] The direction of the isomerization is opposite to that observed in the reactions of anionic homoenolates. Such a rearrangement has been used for a ring expansion reaction.[39]

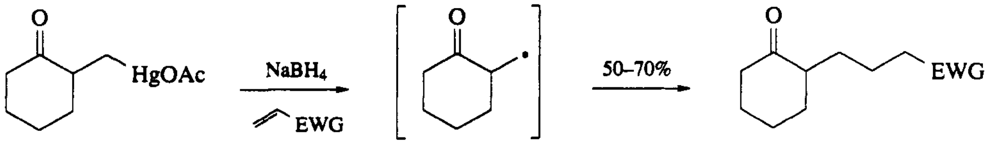

EWG = $CO_2Et$, CN, Ac

Scheme 19

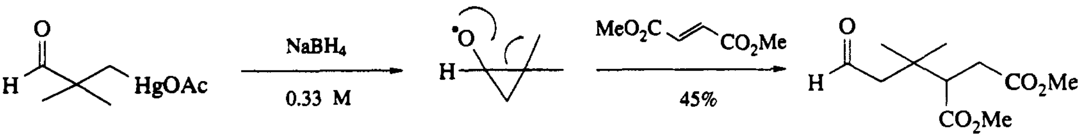

Scheme 20

### 1.14.6.2 Zinc Homoenolates

The copper(I)-catalyzed reaction of a zinc homoenolate (**9**) with a Michael acceptor provides a reliable method for the synthesis of 1,6-keto esters.[40,41] Successive addition of an enone, copper catalyst and HMPA to an ethereal solution of the zinc homoenolate (**9**) containing $Me_3SiCl$ results in quantitative formation of a conjugate adduct as an enol silyl ether (Scheme 21).[19] $Me_3SiCl$ strongly accelerates conjugate addition of the intermediate organocopper species.[42–46] $BF_3{\cdot}OEt_2$ also enhances the reaction rate, but the use of this catalyst may influence the stereochemistry of the reaction.[47] The conjugate addition also takes place with alkynic esters and ketones.

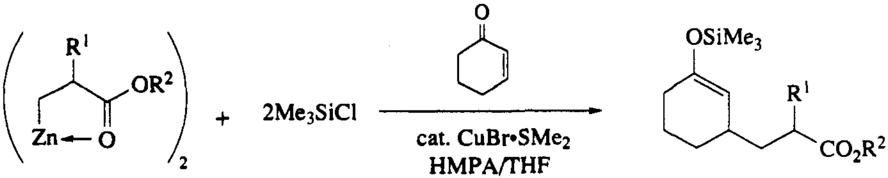

(9)

Scheme 21

### 1.14.6.3 Copper Homeonolates

Divalent copper has been found to be a good catalyst for the direct coupling of silyloxycyclopropanes with highly electron deficient alkynes. If a silyloxycyclopropane and copper(II) are allowed to react in the presence of dimethyl acetylenedicarboxylate or propynyl sulfone in wet $CH_2Cl_2$, a conjugate adduct is obtained in good yield (Scheme 22).[3] Strictly dry conditions lead to oxidative coupling products.

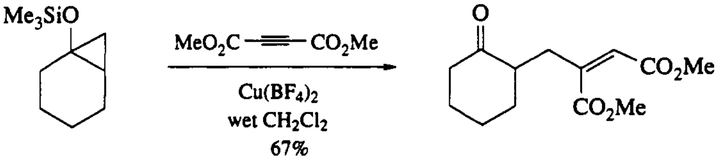

Scheme 22

## 1.14.7 SUBSTITUTION REACTIONS

Copper(I) and metals of the nickel triad have been used to effect allylation, arylation, vinylation and acylation reactions of zinc homoenolates. Transient homoenolates generated under Pd catalysis and Ag catalysis have also been used for direct arylation and acylation of silyloxycyclopropanes.

### 1.14.7.1 Zinc Homoenolates

Zinc homoenolates (**9**) react with allyl halides and diene monoepoxides under copper catalysis.[19,48] Treatment of a zinc homoenolate (**9**) with a catalytic amount of copper(I) in a polar solvent (*e.g.* DMA) generates a copper species which undergoes $S_N2'$ allylation (Scheme 23). Polar solvents accelerate the reaction and greatly improve the $S_N2'$ selectivity. Copper-catalyzed reaction with the acetal of an unsaturated aldehyde proceeds without allylic isomerization (Scheme 23).[19]

Substitution reactions of $sp^2$ halides have been achieved with the aid of a palladium catalyst (Scheme 23).[14,19] A variety of aryl bromides and iodides serve as electrophiles. Reactions with vinyl halides are stereospecific. Vinyl trifluoromethanesulfonates (triflates) also react rapidly with homoenolates.

Zinc homoenolates (**9**) react rapidly with acid chlorides in ethereal solvents containing a dipolar aprotic solvent to give 1,4-keto esters in high yield (Scheme 23).[13,19] A palladium catalyst[49] (or, less effective, a copper catalyst)[40] accelerates the reaction, in contrast to cyclopropane formation in halomethane solvents (see Section 1.14.3.1).

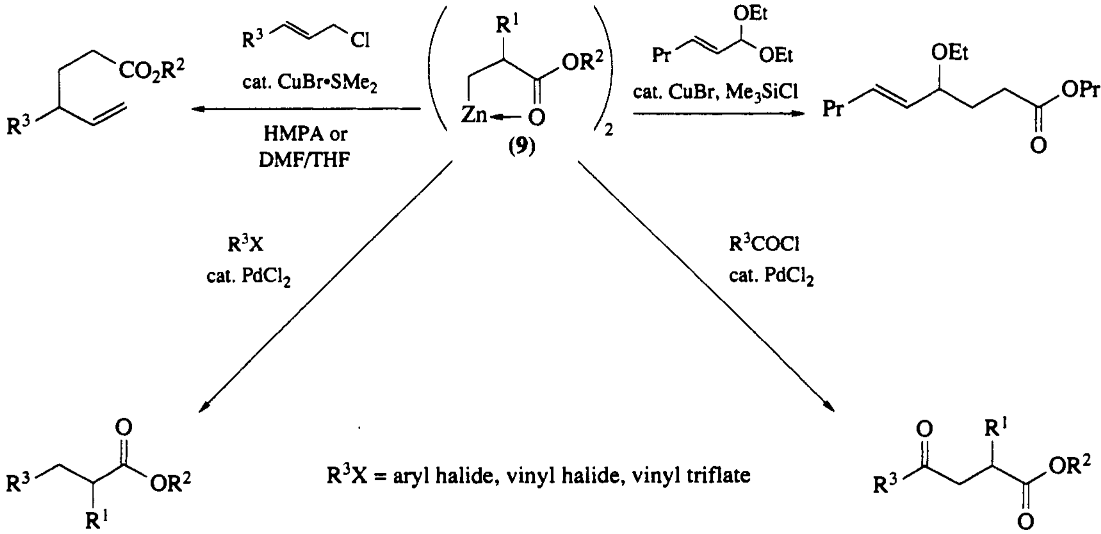

R³X = aryl halide, vinyl halide, vinyl triflate

Scheme 23

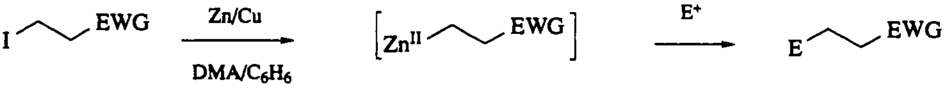

EWG = $CO_2R$, acyl, CN

**Scheme 24**

Reduction of 3-iodocarbonyl compounds with a zinc/copper couple in polar solvents (*e.g.* DMF, DMA)[13,14] generates homoenolates of esters, nitriles and ketones[50,51] (Scheme 24). These species are not well defined, but they appear to be very similar to those obtained by the silyloxycyclopropane route.

### 1.14.7.2 Palladium Homoenolates Generated *In Situ*

Silyloxycyclopropanes react with a $PdCl_2$–phosphine complex to give a transient complex which undergoes β-elimination (see Section 1.14.2.2). However, if the cyclopropane is treated with an $RPd^{II}X$ complex, where R is either aryl or acyl and X is a suitable electron-withdrawing heteroatom, the intermediate palladium homoenolate undergoes reductive elimination to produce a carbonyl compound having the R group at its 3-position (Scheme 25). Thus, heating a mixture of a cyclopropane and an aryl triflate in the presence of a palladium catalyst gives a 3-arylpropionate.[52] Silyloxycyclopropanes corresponding to ketone and aldehyde homoenolates (*e.g.* 3) also undergo reaction with aryl triflates to give arylated products (Scheme 25). Diazonium salts also serve as arylating reagents.[52]

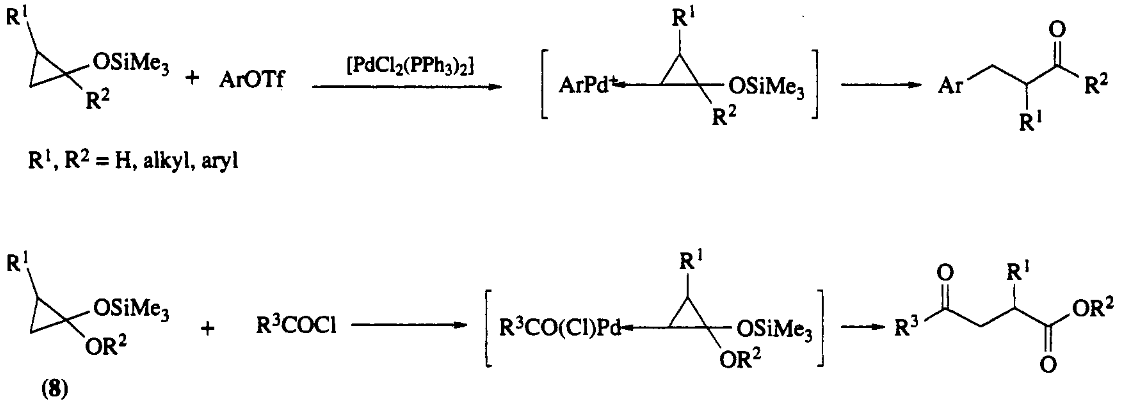

**Scheme 25**

Reaction of a silyloxycyclopropane (**8**) with an acid chloride in the presence of a palladium catalyst also proceeds cleanly to give 1,4-keto esters in high yield (Scheme 25).[53] A mechanism involving the interaction of (**8**) and an acylpalladium chloride complex in the rate-limiting step has been proposed on the basis of kinetic studies.

### 1.14.7.3 Silver Homoenolates

Silyloxycyclopropanes react with allyl chlorides in the presence of AgF in aqueous ethanol to give allylated products (equation 4).[54] The reaction is considered to involve cyclopropanols as initial intermediates.

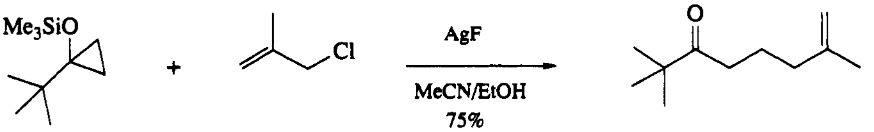

(4)

## 1.14.8 CARBONYLATION

The reaction of a mercurio ketone and carbon monoxide in the presence of a palladium catalyst in methanol (Scheme 26) results in the formation of a 1,4-keto ester with incorporation of one molecule of carbon monoxide.[15] Treatment of a mercurio ketone with [$Ni(CO)_4$] results in symmetrical coupling with incorporation of one molecule of carbon monoxide to give a triketone, presumably *via* a 3-nickel-substituted ketone (Scheme 27).[55] Such symmetrical coupling reactions are general for alkylmercury compounds. If silyloxycyclopropane (**8**) is heated in $CHCl_3$ in the presence of a catalytic amount of a palladium–phosphine complex under CO, symmetrical coupling with incorporation of one molecule of CO takes place to give a 4-ketopimelate (Scheme 27).[56]

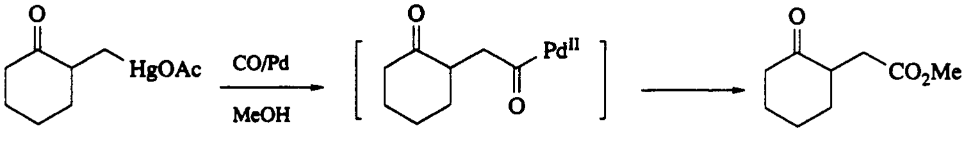

HgOAc
CO/Pd
MeOH
Pd^II
CO₂Me

**Scheme 26**

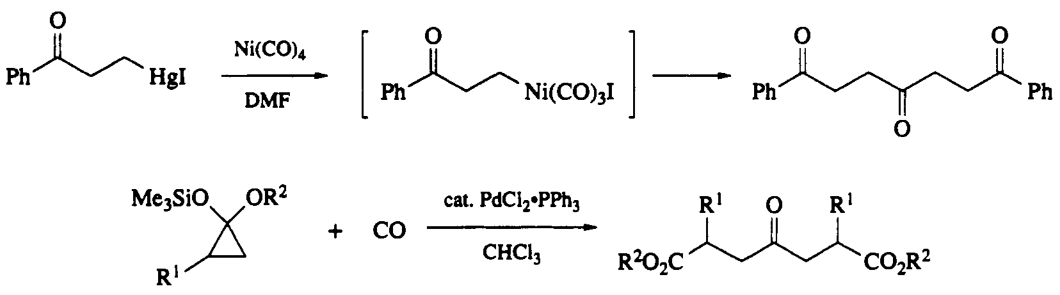

Ph
HgI
Ni(CO)₄
DMF
Ni(CO)₃I
Me₃SiO
OR²
R¹
+ CO
cat. PdCl₂•PPh₃
CHCl₃
R²O₂C
CO₂R²

(**8**)

**Scheme 27**

## 1.14.9 SYNTHETIC APPLICATIONS

As shown in the preceding paragraphs, metal homoenolates represent a very useful nucleophilic species, and their chemistry provides a model for the design of various other functionalized nucleophilic species. Currently this chemistry is still in its infancy, and only a few examples of applications to total syntheses have been reported. However, the diversity of the reactions of metal homoenolates promises the appearance of many more applications.

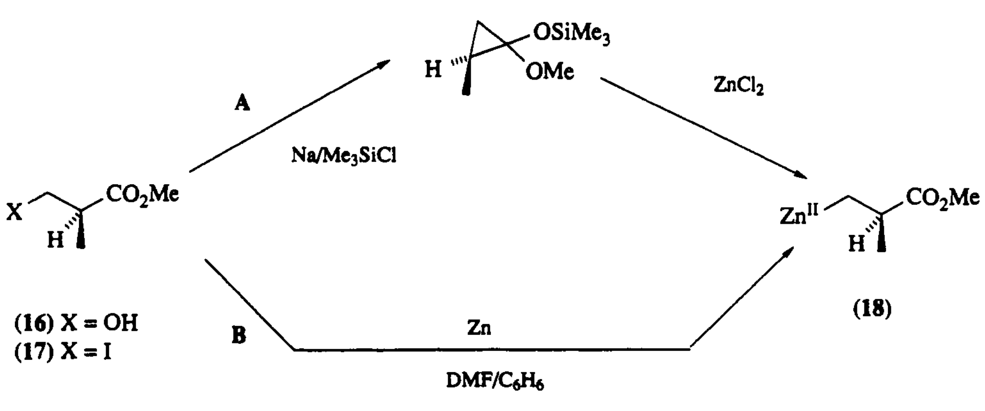

OSiMe₃
H
OMe
A
Na/Me₃SiCl
ZnCl₂
X
CO₂Me
H
Zn^II
CO₂Me
H
B
Zn
DMF/C₆H₆

(**16**) X = OH
(**17**) X = I

(**18**)

**Scheme 28**

### 1.14.9.1 Chiral Ester Homoenolates

Commercially available methyl β-hydroxyisobutyrate (**16**) has been converted to the corresponding halide (**17**), then either *via* the silyloxycyclopropane route (A) or *via* the reductive route (B) to the chiral zinc homoenolate (**18**; Scheme 28). It is optically stable in ether and has been used for several standard carbon–carbon bond-forming reactions, *e.g.* carbonyl addition, arylation and acylation.[57]

### 1.14.9.2 Carbonyl Addition

Synthesis of a marine sterol, depresosterol (**25**), illustrates the utility of the homoenolate as a multifunctional, three-carbon building block.[58] Homo-Reformatsky reaction between an alkoxytitanium homoenolate (**11**; Section 1.14.5.1) and an aldehyde (**19**) afforded the undesired Cram product (**20**) in a ratio of >6:1 (Scheme 29). Inversion of the stereochemistry at the sterically hindered C-22 position was achieved through internal solvolysis by taking advantage of the terminal ester function. Stereoselective hydroxymethylation of the lactone (**22**) followed by introduction of the C-26 and C-27 methyl groups to (**23**) afforded depresosterol (**25**).

Treatment of the mesylate (**21**) with non-nucleophilic *t*-butoxide gives the cyclopropane (**24**), which serves as precursor to a marine sterol, demethylgorgosterol.

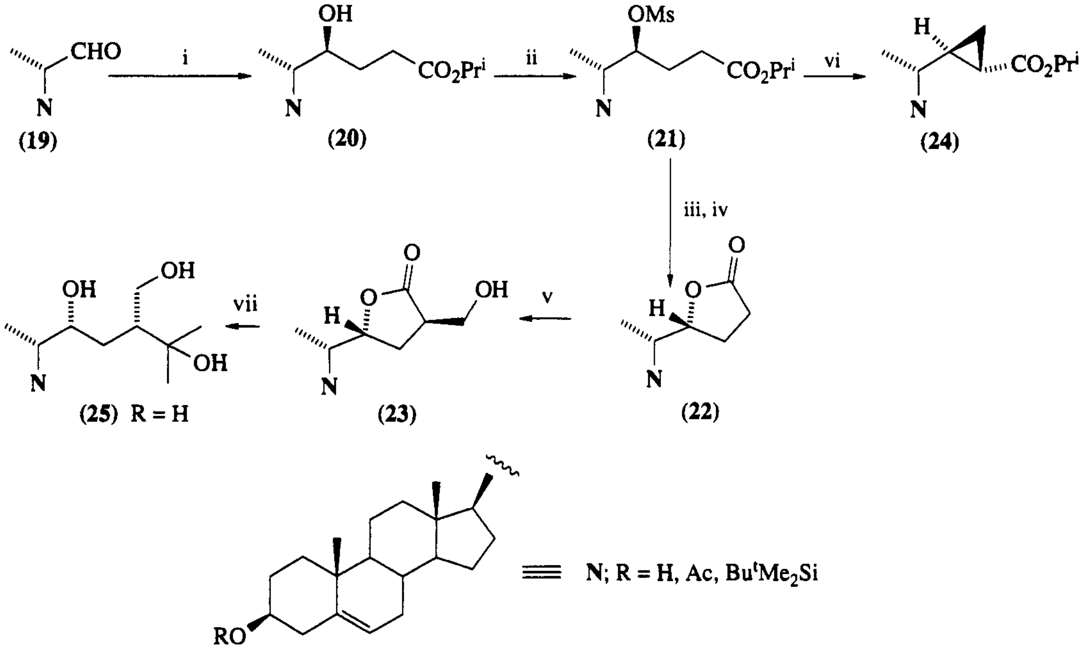

i, (**11**); ii, MsCl; iii, KOH; iv, *p*-TsOH; v, MeMgBr; vi, KOBu$^t$; vii, MeLi

Scheme 29

### 1.14.9.3 Conjugate Addition

Conjugate addition of a catalytically generated copper homoenolate (Section 1.14.6.2) has been used for one stage in the stereoselective synthesis of (±)-cortisone (Scheme 30).[47] $BF_3\cdot OEt_2$-assisted conjugate addition of the copper homoenolate generated *in situ* from the zinc precursor gave the desired conjugate adduct (**26**) in greater than 95% α-selectivity at the newly created stereocenter, C-8.

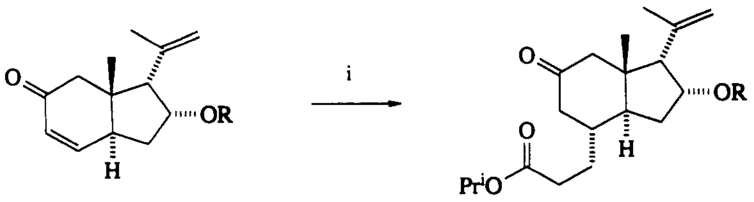

R = Ac, $Bu^tMe_2Si$ (26)

i, $Zn(CH_2CH_2CO_2Pr^i)_2$, cat. $CuBr\cdot SMe_2$, $BF_3\cdot OEt_2$, HMPA/THF

**Scheme 30**

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# 1.15

# Use of Enzymatic Aldol Reactions in Synthesis

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## 1.15.1 INTRODUCTION

The development of methods for the stereoselective formation of carbon–carbon bonds using the aldol reaction is a current topic of interest in organic synthesis.[1–6] Many successful strategies rely on chiral auxiliaries[7–15] and a few employ nonbiological catalysts.[16] Zinc(II) complexes of amino acid esters, for example, catalyze the reaction of *p*-nitrobenzaldehyde with acetone.[17] $\mathrm{Eu(DPPM)_3}$ catalyzes the condensation of ketene silyl acetals with benzaldehyde.[18] A chirotopic ferrocenyl phosphine–gold(I) complex catalyzes the reaction of isocyanoacetate with a number of simple aldehydes such as benzaldehyde, acetaldehyde and pivaldehyde.[19] These latter reactions show fair to good enantiofacial and diastereofacial selectivity, with the chiral gold complex giving the best results: 72–97% diastereomeric and enantiomeric excess.

Enzymes often provide products with still higher enantiomeric purity.[20,21] Their usefulness in organic synthesis is, however, only now being explored. This chapter discusses the utility of readily available carbon–carbon bond-forming enzymes as catalysts for the asymmetric aldol reaction.

## 1.15.2 ENZYMES AS CATALYSTS

Enzymes have been employed as catalysts in organic synthesis for many years, primarily for the construction of small chiral molecules.[22–27] Most synthetic chemists, however, perceive enzymes as being absolutely specific for their natural substrates and thus limited in their application to organic synthesis. The use of enzymes is also plagued by concerns of enzyme stability and requirements for the use of cofactors. Developments in biotechnology have, however, solved many of the problems associated with cofactor regeneration and enzyme stability.

Many enzymes do accept a wide range of substrates.[20–21] Although the reaction of unnatural substrates may be slower than that of the natural substrate, the specificity of many enzymes is broad enough to allow a wide range of compounds to be utilized at an acceptable rate. Lipase,[28] chymotrypsin,[29] lactate dehydrogenase,[30,31] acyclase I,[32] and aldolase[33,34] are only a few examples of enzymes useful in synthetic applications because of their broad substrate specificity. The development of techniques such as enzyme immobilization,[27,35–37] hollow-fiber reactors[38] and the use of membranes[39] allows increased stability, recovery and reuse of enzymes. Deactivation of enzymes by oxidation can also be avoided through the use of reducing agents.

Several groups of enzymes do require cofactors. In many cases these cofactors are too expensive to use stoichiometrically and this was a major limitation for the use of enzymes in organic synthesis. This problem has now been solved through the development of regenerating systems, which allow for the use of catalytic amounts of cofactor. These systems have been extensively reviewed elsewhere.[40,41]

### 1.15.2.1 Enzymes That Form Carbon–Carbon Bonds

Three general types of enzymes have been applied for the formation of carbon–carbon bonds in organic synthesis: aldolases, synthetases and transketolases. Aldolases are a class of enzymes that catalyze the stereoselective construction and degradation of carbon–carbon bonds in monosaccharides.[42–46] Synthetases catalyze an irreversible aldol reaction of activated enols such as phosphoenol pyruvate (PEP) with aldoses to form complex monosaccharides;[47] transketolases catalyze the transfer of a hydroxyketo group of a keto sugar to an aldose.[48] These enzymes are discussed individually below with an outline of their use in organic synthesis.

## 1.15.3 D-FRUCTOSE-1,6-DIPHOSPHATE ALDOLASE

D-Fructose-1,6-diphosphate (FDP) aldolase (E.C. 4.1.2.13) from rabbit muscle, catalyzes the equilibrium condensation of dihydroxyacetone phosphate (**1**; DHAP) with D-glyceraldehyde 3-phosphate (**2**; G-3-P) to form D-fructose 1,6-diphosphate (**3**; FDP; Scheme 1).[42–44] The equilibrium constant for this reaction is $K = 10^4\ M^{-1}$ in favor of the formation of FDP. The stereoselectivity of the reaction is absolute; the configuration of the vicinal diols at C-3 and C-4 is always *threo* (*i.e.* D-*glycero*). Although there is a significant discrimination (20:1) between the antipodes of the natural substrate (*i.e.* D- and L-G-3-P), this selectivity extends to only a few unnatural substrates.[33]

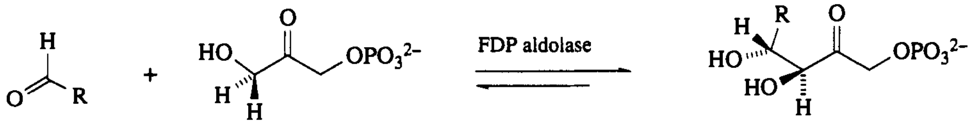

Scheme 1

### 1.15.3.1 Substrate Specificity

FDP aldolase accepts a wide range of aldehydes in place of its natural substrate, G-3-P,[33] thus permitting for the synthesis of carbohydrates such as nitrogen-containing sugars,[34,49] deoxy sugars,[50,51] fluoro sugars[51] and $C_8/C_9$ sugars.[52] More than 75 aldehydes have been identified as substrates based on enzymatic assay and many of the aldol adducts have been isolated and characterized.[53–77] In general, unhindered aliphatic, α-heteroatom-substituted and differentially protected alkoxy aldehydes are substrates; severely hindered aliphatic aldehydes such as pivaldehyde do not react with FDP aldolase, nor do α,β-unsaturated aldehydes, although these compounds do not inhibit the enzyme. Aromatic aldehydes are either poor substrates or unreactive. Some examples are summarized in Table 1.

**Table 1** Products Synthesized by Reacting the Substrate with Dihydroxyacetone Phosphate in the Presence of FDP Aldolase

| *Substrate* | *Product* | *Ref.* |
|---|---|---|
| 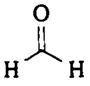 | 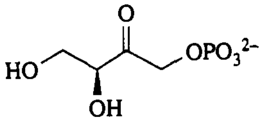 | 33 |
| 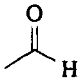 | 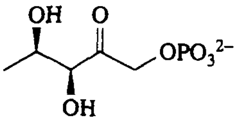 | 60, 69 |
| 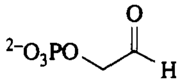 | 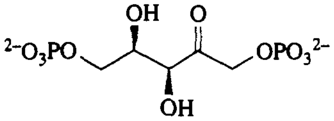 | 59, 70 |
| 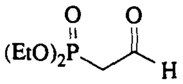 | 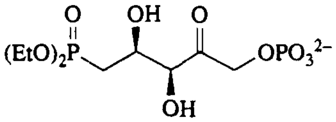 | 66 |
| 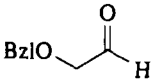 | 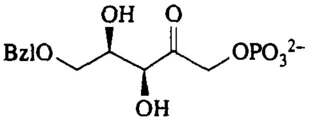 | 33 |
| 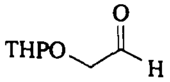 | 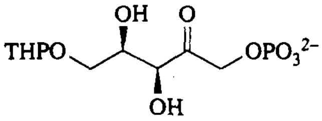 | 33 |
| 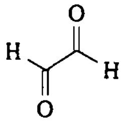 | 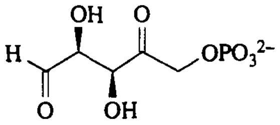 | 66 |
| 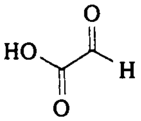 | 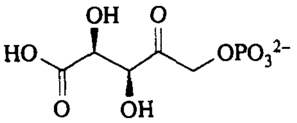 | 66 |
| 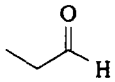 | 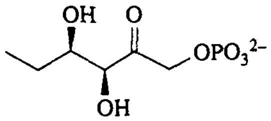 | 33, 61, 72 |
| D-Threose | 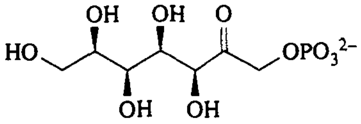 | 60 |
| L-Threose | 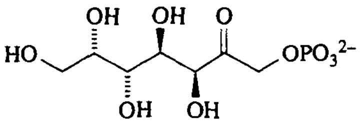 | 55 |

**Table 1** *(continued)*

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| D-Erythrose | 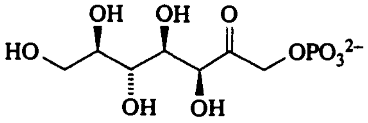 | 33, 59, 62, 65 |
| D-Erythrose-4-P | 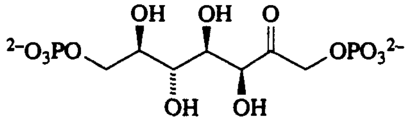 | 71, 73 |
| L-Erythrose | 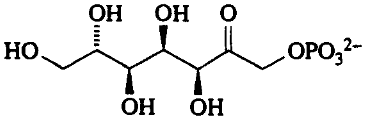 | 62 |
| D-Ribose | 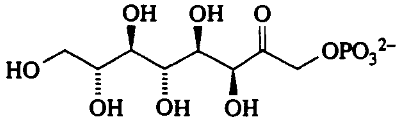 | 53, 57 |
| D-Ribose-5-P | 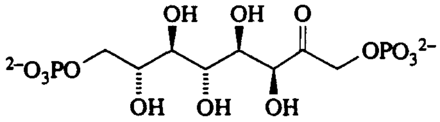 | 52, 58, 59, 63 |
| 2-Deoxy-D-ribose-5-P | 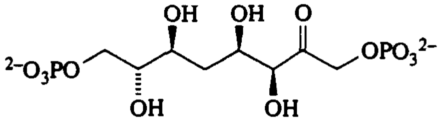 | 52 |
| L-Arabinose | 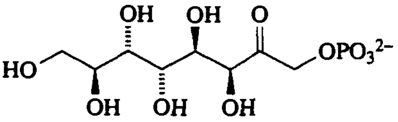 | 53 |
| D-Arabinose-5-P | 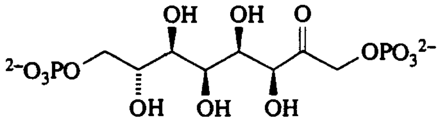 | 52, 58, 63 |
| D-Lyxose | 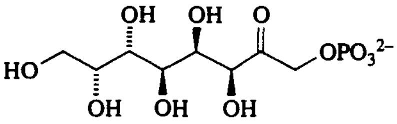 | 53 |
| D-Xylose | 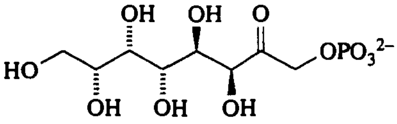 | 53 |
| D-Glucose-6-P | 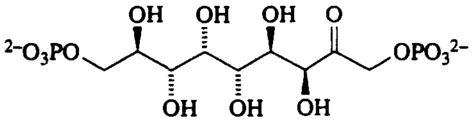 | 52 |

**Table 1** *(continued)*

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| 2-Deoxy-D-glucose-6-P | 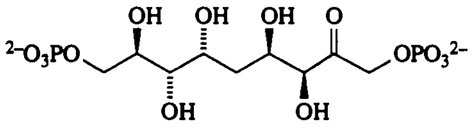 | 52 |
| D-Glucosamine-6-P | 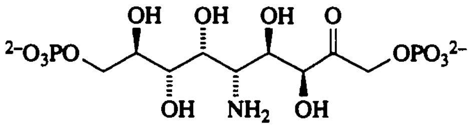 | 52 |
| D-Galactose-6-P | 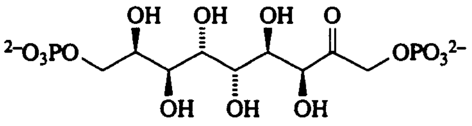 | 52 |
| D-Mannose-6-P | 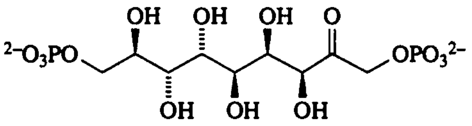 | 52 |
| 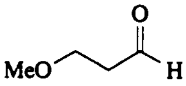 | 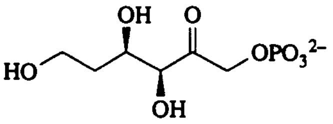 | 33 |
| 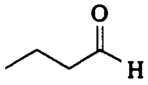 | 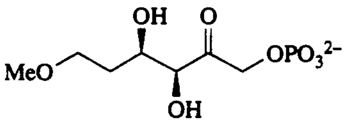 | 72 |
| 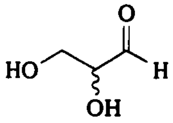 | 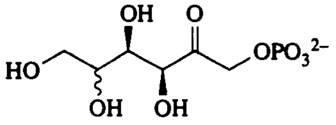 | 50 |
| 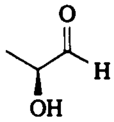 | 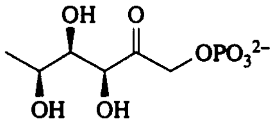 | 33 |
| 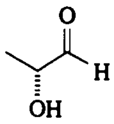 | 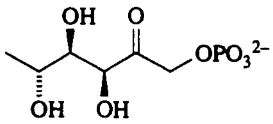 | 33 |
| 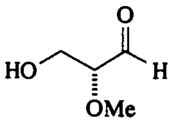 | 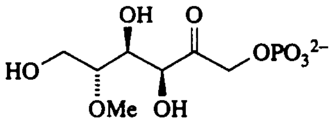 | 33 |
| 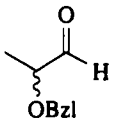 | 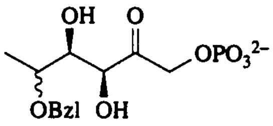 | 33 |

**Table 1** *(continued)*

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| 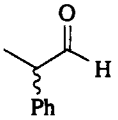 | 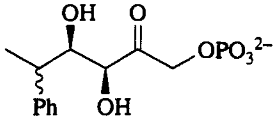 | 33 |
| 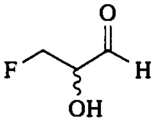 | 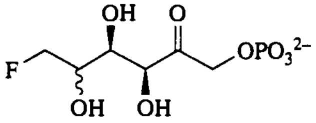 | 51 |
| 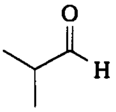 | 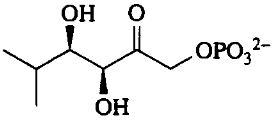 | 66 |
| 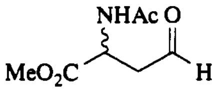 | 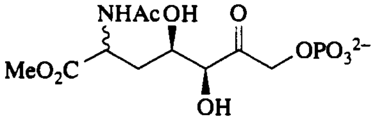 | 66 |
| 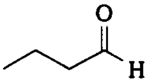 | 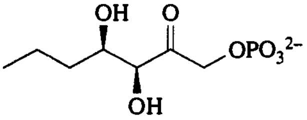 | 66, 33 |
| 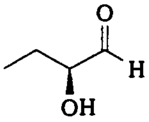 | 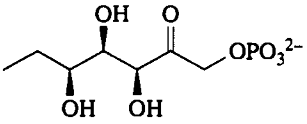 | 51, 49, 68, 69 |
| 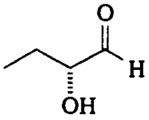 | 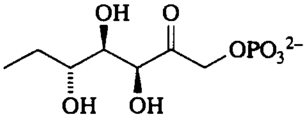 | 49, 51, 68, 69 |
| 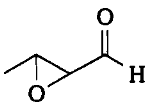 | 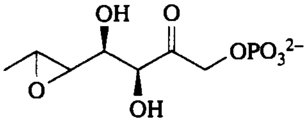 | 66 |
| 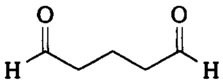 | 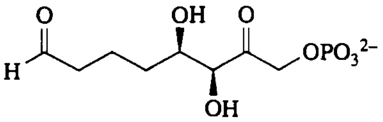 | 66 |
| 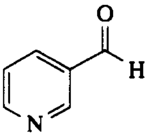 | 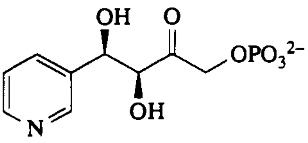 | 33, 66 |
| 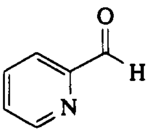 | 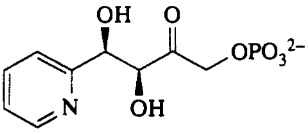 | 33, 66 |

**Table 1** *(continued)*

| *Substrate* | *Product* | *Ref.* |
|---|---|---|
| 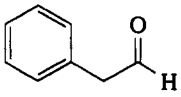 | 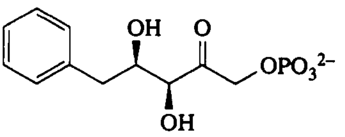 | 33, 66 |

The requirement for the electrophilic component (DHAP) is much more stringent than for the nucleophilic component; so far investigations have demonstrated that only 1,3-dihydroxy-2-butanone 3-phosphate and 1,4-dihydroxy-3-butanone 1-phosphonate are substrates (Table 2).[33]

**Table 2** Relative Rates of DHAP Analogs in FDP Aldolase Catalyzed Reactions using G-3-P as the Aldehyde Substrate

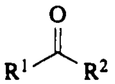

| $R^1$ | $R^2$ | $V_{rel}$ |
|---|---|---|
| $HOCH_2$ | $CH_2OPO_3^{2-}$ | 100 |
| $HOCH_2$ | $CHMeOPO_3^{2-}$ | 10 |
| $HOCH_2$ | $CH_2CH_2PO_3^{2-}$ | 10 |
| $HOCH_2$ | $CH_2SO_3H$ | <0.1 |
| $HOCH_2$ | $CH_2OH$ | <0.1 |
| Me | $CH_2OPO_3^{2-}$ | <0.1 |
| $N_3CH_2$ | $CH_2OPO_3^{2-}$ | <0.1 |
| $AcNHCH_2$ | $CH_2OPO_3^{2-}$ | <0.1 |
| $HOCH_2$ | $CH_2OPO_3^{2-}$ | <0.1 |
| $ClCH_2$ | $CH_2OPO_3^{2-}$ | 0 |
| $BrCH_2$ | $CH_2OPO_3^{2-}$ | 0 |

### 1.15.3.2 Preparation of DHAP

DHAP is an essential substrate of aldolase-catalyzed reactions and a simple preparation of this compound is essential for developing the use of this enzyme in asymetric synthesis. DHAP may be generated by three procedures: (i) *in situ* from fructose 1,6-diphosphate with the enzymes aldolase and triosephosphate isomerase (E.C. 5.3.1.1);[33] (ii) from the dimer of dihydroxyacetone by chemical phosphorylation with $POCl_3$;[33,66] and (iii) from dihydroxyacetone by enzymatic phosphorylation using PEP and glycerol kinase (E.C. 2.7.1.30).[33,50,76] The *in situ* generation of DHAP from FDP is the most convenient method. This reaction does not, however, go to completion and the presence of excess FDP can complicate the isolation of products that are negatively charged. In these cases the chemical synthesis of DHAP is the method of choice.

A mixture of dihydroxyacetone and inorganic arsenate may replace DHAP[49] and this mixture has been used in syntheses by Wong and coworkers. A dihydroxyacetone arsenate monoester probably forms in the rate-determining step, and is consumed in a fast, irreversible aldol reaction. The irreversibility imposed by this method may be useful with slowly reacting substrates, but the toxicity of arsenate limits its usefulness. Vanadate does not operate as a phosphate mimic in FDP aldolase catalyzed reactions.[49]

The phosphate group (derived from DHAP) of the aldol adducts facilitates the purification of aldol products by ion-exchange chromatography or by precipitation as their barium or silver salts. Either enzymatic methods using acid or alkaline phosphatase or chemical methods using acid or base also allow cleavage of this group.[33]

### 1.15.3.3 Enzyme Characteristics

Several characteristics of FDP aldolase make it a useful enzyme for use in synthesis. Commercial preparations of the enzyme are inexpensive (it costs \$0.04 to produce 1 mmol of product per minute, *i.e.* \$0.04 $unit^{-1}$ and it has a reasonable specific activity (60 unit $mg^{-1}$ of protein). FDP aldolase requires no metal ions or cofactors and it is stable in the presence of oxygen and added organic cosolvents, and is not inhibited to a significant extent by the natural product (*i.e.* FDP). The enzyme has been used in soluble or immobilized forms, or enclosed within a dialysis membrane.[33]

### 1.15.3.4 Examples of FDP Aldolase in Organic Synthesis

The biologically active monosaccharide 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (**8**; DAHP) is an important intermediate in the biosynthesis of aromatic amino acids in plants (the shikimate pathway). As shown in Scheme 2, this compound has been produced in a combined chemical and enzymatic synthesis from racemic *N*-acetylaspartate β-semialdehyde (**4**) and DHAP (**1**).[67] The four-step synthesis proceeds in an overall yield of 13% (37% for the aldolase reaction). The enzymatic step generates the required, enantiomerically pure, *syn* aldol adduct compound (**5**). In view of the broad range of substrates tolerated by FDP aldolase, this method may be applicable to the production of analogs of DAHP.

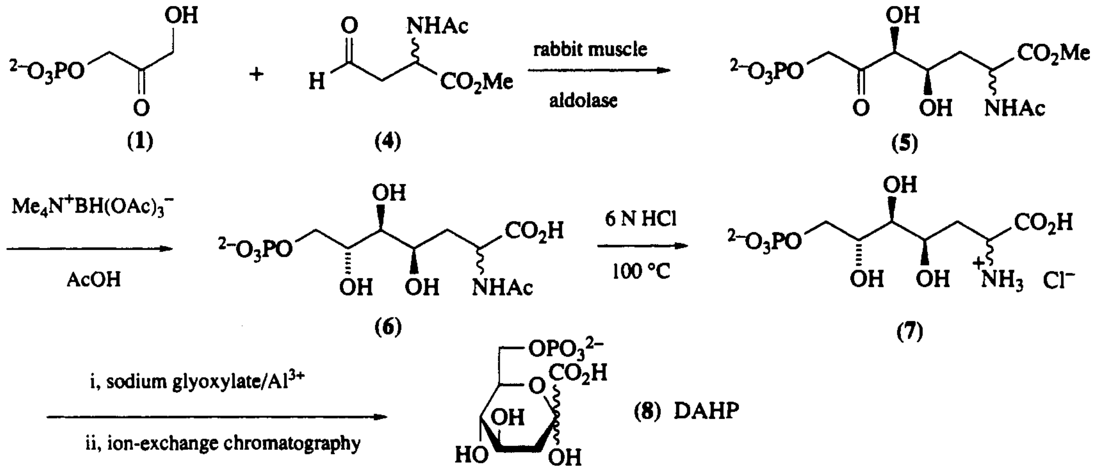
(1)
(4)
rabbit muscle
aldolase
(5)
Me4N+BH(OAc)3−
AcOH
(6)
6 N HCl
100 °C
(7)
i, sodium glyoxylate/Al3+
ii, ion-exchange chromatography
(8) DAHP

**Scheme 2**

Other monosaccharide derivatives have also been synthesized using FDP aldolase as a catalyst. Deoxyfructose derivatives such as compound (**10**) were, for example synthesized using FDP aldolase catalyzed addition of DHAP to lactaldehyde (**9**). The aldol adduct (**10**) was chemically converted to furaneol (**11**), an important flavoring agent (Scheme 3).[50] Other deoxy sugars such as 2-deoxy-L-idose (**15**) are also available using FDP aldolase. The condensation of aldehyde (**12**) with DHAP gives (**13**), which upon dephosphorylation, reduction and deprotection yields the deoxyidose (**15**; Scheme 4).[50,51] Two

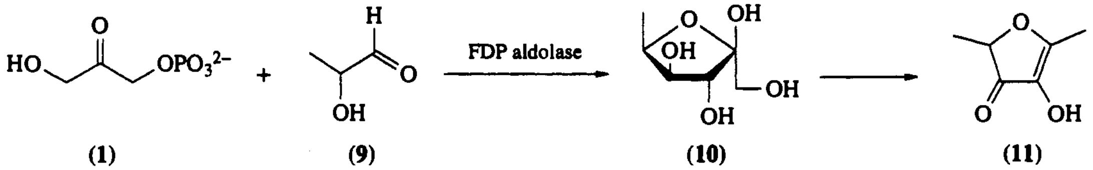
(1)
(9)
FDP aldolase
(10)
(11)

**Scheme 3**

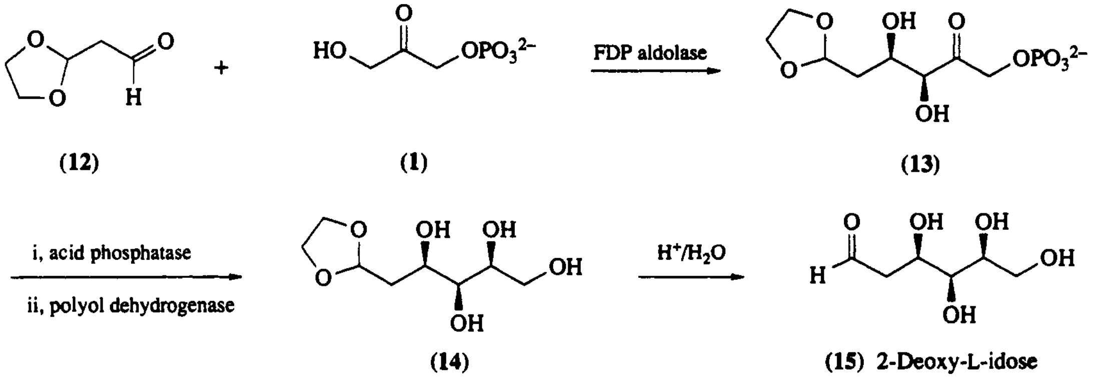
(12)
(1)
FDP aldolase
(13)
i, acid phosphatase
ii, polyol dehydrogenase
(14)
H+/H2O
(15) 2-Deoxy-L-idose

**Scheme 4**

groups have also used aldolase to synthesize alkaloids.[34,78] Aldehyde (**16**) was condensed with DHAP (**1**) using aldolase as a catalyst to give (**17**) and (**18**) respectively (Scheme 5). These compounds were chemically converted into deoxynojirimycin (**19**) and deoxymannonojimycin (**20**) as shown in Scheme 5.[79]

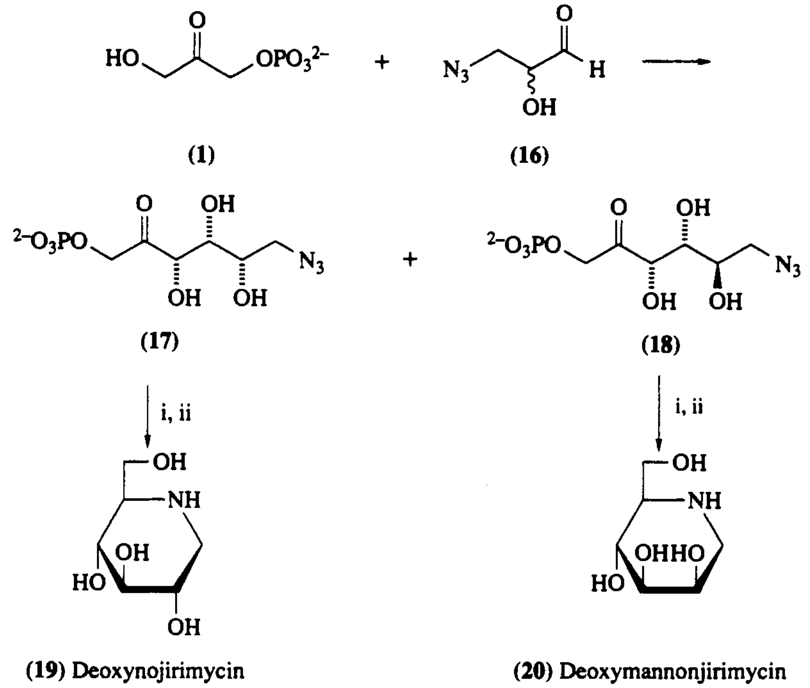

i, phosphatase (or $H^+$); ii, $H_2$/Pd

Scheme 5

## 1.15.4 *N*-ACETYLNEURAMINIC ACID ALDOLASE (E.C. 4.1.3.3)

*N*-Acetylneuraminic acid aldolase catalyzes the reversible aldol condensation of pyruvate (**23**) and *N*-acetylmannosamine (**22**; ManNAc) to form *N*-acetylneuraminic acid (**24**; NeuAc; *N*-acetyl-5-amino-3,5-dideoxy-D-glycerogalacto-2-nonulopyronic acid; Scheme 6).[80–83] *In vivo* the enzyme has a catabolic function and the equilibrium for this reaction is near unity; the presence of excess pyruvate can shift this equilibrium. NeuAc and other derivatives of neuraminic acid are termed sialic acids. These compounds are found at the termini of mammalian glycoconjugates and play an important role in cellular recognition.[84–89] The production of analogs of NeuAc is a point of great interest to synthetic and medicinal chemists. The enzymatic approach has not been fully explored but it may be a practical alternative to the chemical synthesis of certain sialic acids.[89]

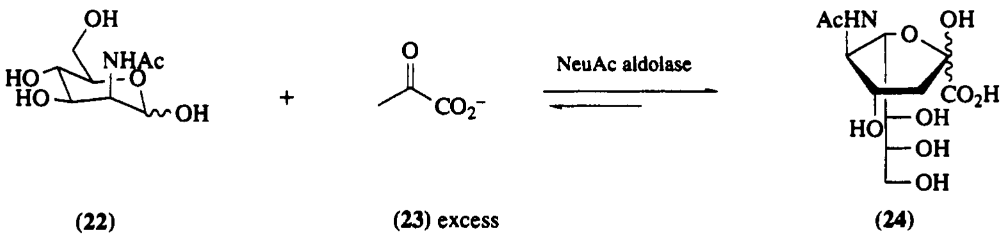

Scheme 6

Reactions catalyzed by NeuAc aldolase have produced several grams of NeuAc after purification by ion-exchange chromatography.[90–92] Although the specificity for pyruvate appears to be absolute, the results of enzymatic assays suggest that NeuAc aldolase accepts a range of substrates in place of ManNAc.[80,81,90–97] Several groups have taken advantage of this observation to synthesize and isolate derivatives of NeuAc. General observations from these syntheses and from assay results suggest that NeuAc aldolase will be useful in synthesis. Substitution at C-2 and C-6 is tolerated, and the enzyme exhibits only a slight preference for defined stereochemistry at other centers (Table 3).

**Table 3** Sialic Acids Synthesized by Condensation of Pyruvate with Analogs of ManNAc in the Presence of NeuAc Aldosase

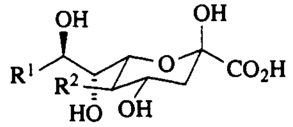

| *R*$^1$ | *R*$^2$ | *Ref.* |
|---|---|---|
| CH$_2$OAc | NHAc | 91 |
| CH$_2$N$_3$ | NHAc | 97 |
| CH$_2$OH | OH | 95a,b |
| CH$_2$OH | H | 95a,b |
| H | OH | 95a,b |
| CH$_2$OH | N$_3$ | 96 |
| CH$_2$OH | NHCOCH$_2$OH | 95b |
| CH$_2$OMe | NHAc | 95b |
| CH$_2$OCOCH(OH)Me | NHAc | 95b |
| CH$_2$OAc | NHCOCH$_2$OH | 95b |
| CH$_2$OH | N$_3$ | 95b |
| CH$_2$OH | NHCOCH$_2$OCOMe | 95b |

In addition to its acceptance of unnatural substrates, several other characteristics make NeuAc aldolase a useful synthesis catalyst. The cloning of the enzyme has reduced its cost and offers the potential to produce large quantities of new proteins with improved stability or with altered stereoselectivity.[98] This approach could be used to extend the chain of a variety of aldoses by two carbon units. Although the optimal pH for activity of NeuAc aldolase is near pH 7.5 at 37 °C, the enzyme is active at pH 7–9.[82,83] The protein is stable in the presence of oxygen and does not require added cofactors.[82,83] One drawback is that an excess of pyruvate (the less expensive reagent) must be used in synthetic reactions to shift the equilibrium towards the formation of product; approximately 7 equiv. of pyruvate are needed to attain 90% conversion of ManNAc to NeuAc at equilibrium. It may be possible to avoid the need for an excess of pyruvate by coupling the synthesis of NeuAc to a more thermodynamically favored process.

An advantage of the enzymatic route compared with the chemical route is that purification of NeuAc or its derivatives may be avoided. For example, an unpurified solution of NeuAc generated enzymatically from an unpurified solution of ManNAc was used in the enzymatic synthesis of cytidine 5′-monophospho-NeuAc (CMP-NeuAc).[89] The unpurified preparation of ManNAc was derived from base-catalyzed epimerization of the much less expensive starting material GlcNAc.

## 1.15.5 TRANSKETOLASE

This enzyme catalyzes the reversible transfer of the hydroxyketo group of a ketose phosphate to an aldose phosphate.[99,100] The cofactor thiamine pyrophosphate (TPP) is associated with the enzyme and activates the ketose (Scheme 7). Most known donor ketoses (xylulose 5-phosphate, sedoheptulose 7-phosphate, fructose 6-phosphate, L-erythrose) have a *trans* arrangement of hydroxy groups at C-3 and C-4; hydroxypyruvate is an exception.[101] A range of aldehydes (such as D-glyceraldehyde 3-phosphate, D-ribose 5-phosphate, D-erythrose 4-phosphate, glycoaldehyde) are acceptors.[102] Transketolase has been

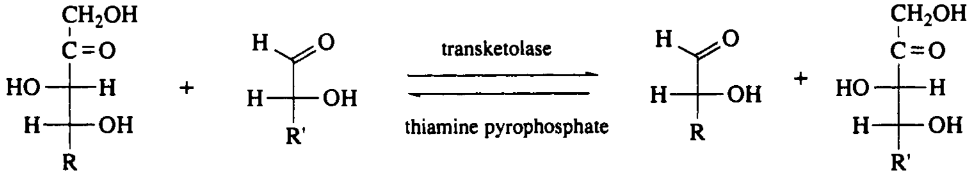

**Scheme 7**

used in synthesis with its natural substrates and has been used to prepare $^{14}$C-labeled intermediates of the pentose pathway.[103,104]

Although the substrate specificity of transketolase has not been thoroughly explored, it appears to be a promising catalyst for use in synthesis. The 2-hydroxypyruvate (**26**) can replace the ketose (**25**), providing a reactive hydroxyketo group after decarboxylation of hydroxypyruvate. This group is transferred to the acceptor aldehyde in an irreversible reaction (Scheme 8) to give (**27**).[102] This method has allowed the synthesis of a number of monosaccharides on scales of 2–5 mmol with yields ranging from 24 to 85% (Table 4).[102–104] The enzyme is commercially available and has also been immobilized.[102]

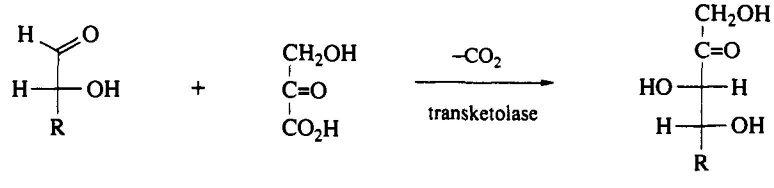

**(25)** **(26)** **(27)**

**Scheme 8**

**Table 4** Products Synthesized Using Transketolase as a Catalyst and Hydroxypyruvate as a Donor

| *Substrate* | *Product* | *Ref.* |
|---|---|---|
| 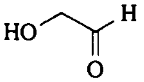 | 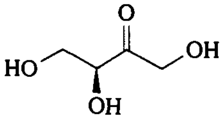 | 102 |
| 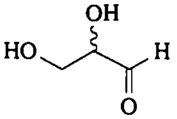 | 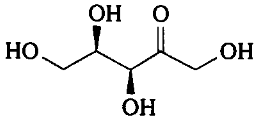 | 102 |
| 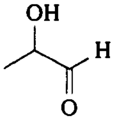 | 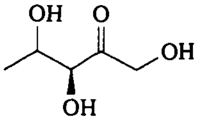 | 102 |
| 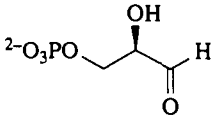 | 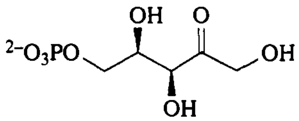 | 103 |
| 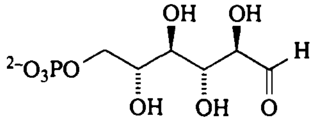 | 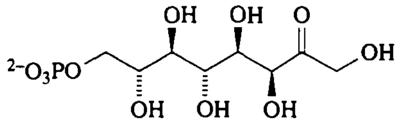 | 104 |
| 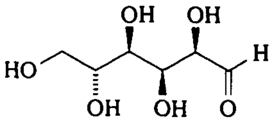 | 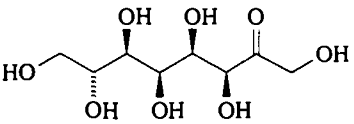 | 104 |

## 1.15.6 KDO SYNTHETASE

KDO synthetase catalyzes the reaction of arabinose 5-phosphate (**29**; Ara-5-P) and phosphoenol pyruvate (PEP) to form KDO-8-P (**30**; Scheme 9).[105] KDO synthetase is not commercially available but has been isolated from *E. coli* and used in the synthesis of KDO-8-P (63% from Ara-5-P, 38 mmol).[106] KDO-8-P is a key intermediate in the synthesis of the lipopolysaccharide region of Gram-negative bacteria (LPS). Inhibitors of LPS biosynthesis are targets for the design of antimicrobial drugs.[107,108]

The substrate specificity of this enzyme has not been thoroughly examined for synthetic application. In the example given below the expensive arabinose 5-phosphate was generated from arabinose by hexokinase-catalyzed phosphorylation (Scheme 9).

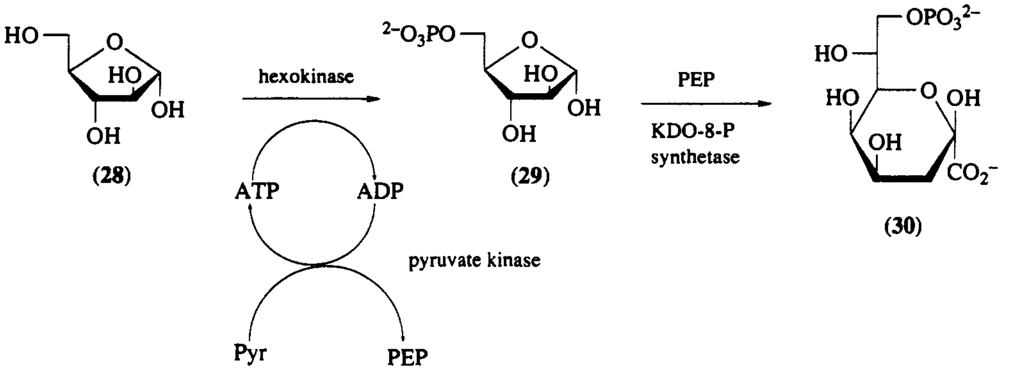
HO
HO
OH
OH
(28)
hexokinase
ATP
ADP
pyruvate kinase
Pyr
PEP
$^{2-}O_3PO$
HO
OH
OH
(29)
PEP
KDO-8-P
synthetase
$OPO_3^{2-}$
HO
HO
O
OH
OH
$CO_2^-$
(30)

**Scheme 9**

## 1.15.7 DAHP SYNTHETASE

This enzyme produces 3-deoxy-D-*arabino*-heptulsonic acid 7-phosphate (**32**; DAHP) from D-erythrose 4-phosphate (**31**). The enzyme was used by Frost[109,110] to synthesize DAHP as an intermediate in the chemical synthesis of its phosphonate analog, 3-deoxy-D-*arabino*-heptulsonic acid 7-phosphonate (DAH phosphonate), a potential inhibitor of the shikimate pathway (Scheme 10).

## 1.15.8 CONCLUSION AND FUTURE PERSPECTIVES

A large number of other aldolases have been isolated and characterized (Table 5).[33,42,43,111–127] Limited explorations of substrate specificity have been made in many cases but these enzymes have not yet been used in synthetic organic chemistry. In terms of potential utility as catalysts, the aldolases of bacterial origin may be of more use than the enzymes from plant or animal sources because the former are more easily cloned and altered by genetic engineering than the latter. The alterations should prove to be useful for controlling the substrate specificity of these enzymes.

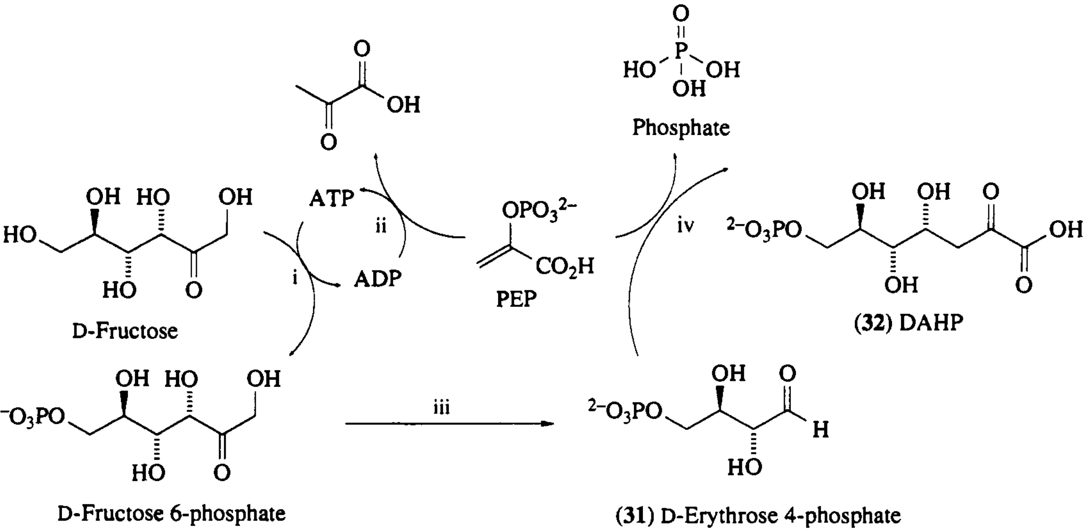
O
OH
O
O
HO P OH
OH
Phosphate
OH HO OH
HO
HO O
D-Fructose
ATP
ii
i
ADP
$OPO_3^{2-}$
$CO_2H$
PEP
iv
$^{2-}O_3PO$
OH OH O
OH
OH O
(32) DAHP
OH HO OH
$^{2-}O_3PO$
HO O
D-Fructose 6-phosphate
iii
OH O
$^{2-}O_3PO$
H
HO
(31) D-Erythrose 4-phosphate

Enzymes: i, hexokinase; ii, pyruvate; iii, transketolase; iv, DAHP synthetase

**Scheme 10**

**Table 5** Summary of the Different Aldolases Available for Use in Asymmetric Organic Synthesis

| *Nucleophile* | *Electrophile* | *Enzyme* | *Product* | *Ref.* |
|---|---|---|---|---|
| 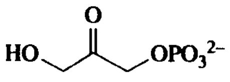 | 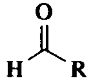 | Fructose-1,5-diphosphate aldolase (E.C. 4.1.2.7) | 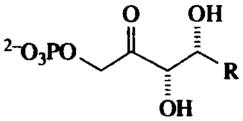  O<br>OH<br>$^{2-}$O$_3$PO<br>R<br>OH | 42, 43, 111 |
|  |  | Fuculose-1-phosphate aldolase (E.C. 4.1.2.17) | 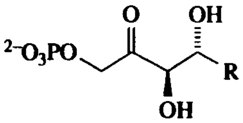  O<br>OH<br>$^{2-}$O$_3$PO<br>R<br>OH | 112 |
|  |  | Rhamulose-1-phosphate aldolase (E.C. 4.1.2.19) | 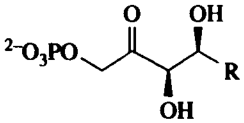  O<br>OH<br>$^{2-}$O$_3$PO<br>R<br>OH | 113 |
|  | 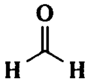 | Erythulose-1-phosphate aldolase (E.C. 4.1.2.2) | 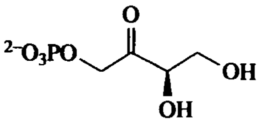  O<br>$^{2-}$O$_3$PO<br>OH<br>OH | 114 |
| 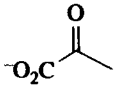 | 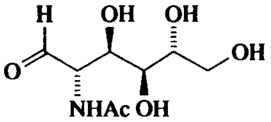  H<br>OH<br>OH<br>O<br>OH<br>NHAc<br>OH | Neuraminic acid aldolase (E.C. 4.1.3.3) | 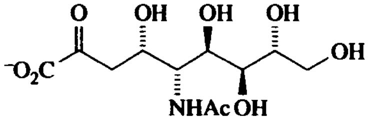  O<br>OH<br>OH<br>OH<br>$^{-}$O$_2$C<br>OH<br>NHAc<br>OH | 90, 115 |
|  | 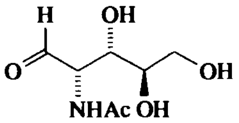  H<br>OH<br>O<br>OH<br>NHAc<br>OH | 2-Keto-3-deoxyoctanoate aldolase (E.C. 4.1.2.23) | 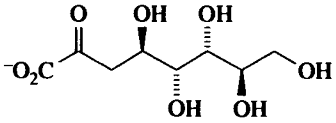  O<br>OH<br>OH<br>$^{-}$O$_2$C<br>OH<br>OH<br>OH | 116 |

**Table 5** *(continued)*

| *Nucleophile* | *Electrophile* | *Enzyme* | *Product* | *Ref.* |
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| 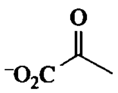 | 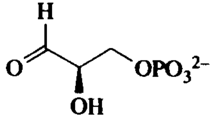 | 2-Keto-3-deoxy-6-phosphogluconate aldolase (E.C. 4.1.2.14) | 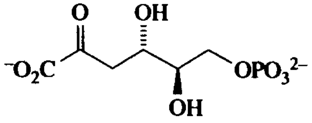 | 117 |
| | 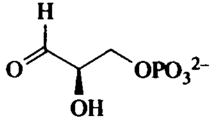 | 2-Keto-3-deoxy-6-phosphogalactonate aldolase (E.C. 4.1.2.21) | 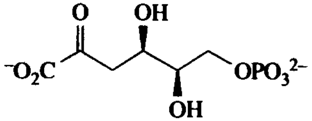 | 117 |
| | 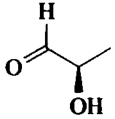 | 2-Keto-3-deoxy-L-arabinoate aldolase (E.C. 4.1.2.18) | 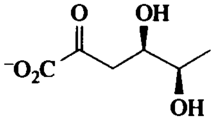 | 117 |
| | 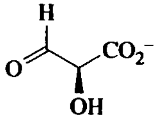 | 2-Keto-3-deoxy-D-glucoarate aldolase (E.C. 4.1.2.20) | 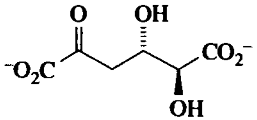 | 117 |
| | 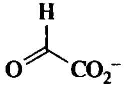 | 2-Keto-4-hydroxyglutarate aldolase (E.C. 4.1.2.31) | 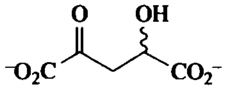 | 117 |
| | 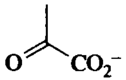 | 4-Methyl-4-hydroxy-2-ketoglutarate aldolase | 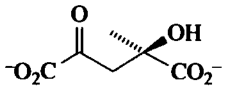 | 117 |
| | 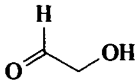 | 2-Keto-3-deoxy-L-arabinate aldolase (E.C. 4.1.2.18) | 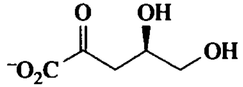 | 117 |

**Table 5** *(continued)*

| *Nucleophile* | *Electrophile* | *Enzyme* | *Product* | *Ref.* |
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| 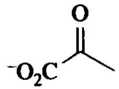 | 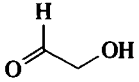 | 2-Keto-3-deoxy-D-pentanoate aldolase (E.C. 4.1.2.28) | 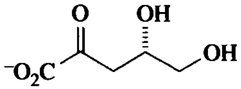 | 118 |
| | 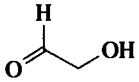 | Hydroxybutyrate aldolase (E.C. 4.2.1.1) | 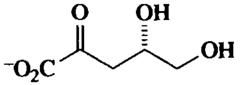 | 119 |
| 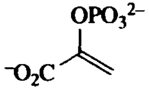 | 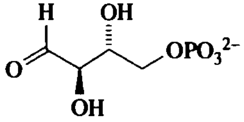 | Phosphono-2-keto-3-deoxyheptanoate aldolase (E.C. 4.2.1.15) | 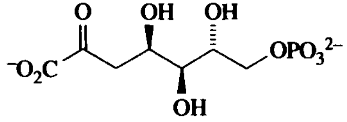 | 120 |
| | 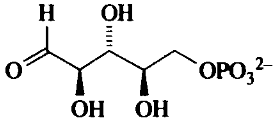 | Phosphono-2-keto-3-deoxyoctanoate aldolase (E.C. 4.2.1.16) | 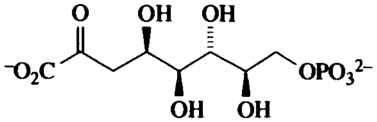 | 121 |
| 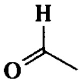 | 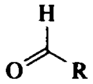 | Deoxyribose aldolase (E.C. 4.1.2.4) | 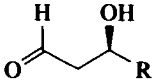 | 122 |
| 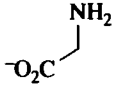 | 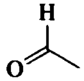 | Threonine aldolase (E.C. 4.1.2.5) | 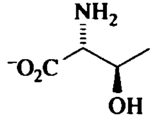 | 123 |
| 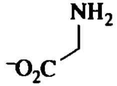 | 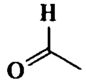 | Serine hydroxymethyl transferase (allothreonine aldolase) (E.C. 4.1.2.6) | 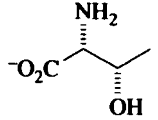 | 124 |

**Table 5** *(continued)*

| *Nucleophile* | *Electrophile* | *Enzyme* | *Product* | *Ref.* |
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| 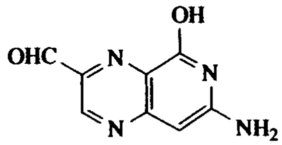 | 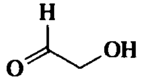 | Dihyroneopterin aldolase (E.C. 4.1.2.25) | 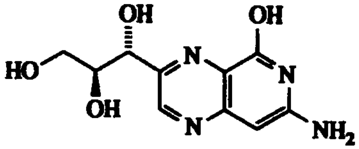 | 125 |
| 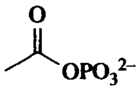 | 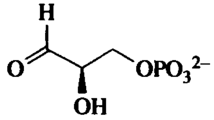 | Phosphoketolase (E.C. 4.1.2.9) | 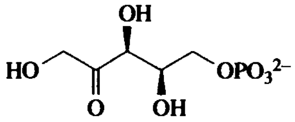 | 126 |
|  | 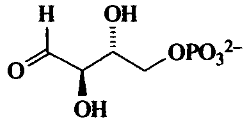 | Fructose-6-phosphate phosphoketolase (E.C. 4.1.2.22) | 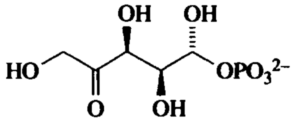 | 127 |

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# 1.16

# Metalloenamines

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## 1.16.1 INTRODUCTION

The β-hydroxycarbonyl and α,β-unsaturated carbonyl functional arrays constitute important structural subunits present in a variety of synthetic targets of natural or unnatural origin and in key intermediates leading thereto. The aldol and related reactions stand as highly useful, classical methods for constructing such bifunctional moieties (Scheme 1).[1] One important variant of this reaction features the refunctionalization of the carbonyl group of the aldehyde or ketone (**1**) to the corresponding imine (**2**). Subsequent regioselective deprotonation of this imine with a suitable, nonnucleophilic base followed by the reaction of the intermediate imine anion (metalloenamine; **3**) with a carbonyl partner yields a β-hydroxyimine (**4**), which may be transformed by hydrolysis into the corresponding β-hydroxy aldehyde or ketone (**5**) or by hydrolysis and dehydration into the corresponding α,β-unsaturated carbonyl compound (**6**).[2] This overall process results in the two-carbon homologation[3] of the carbonyl group of the electrophilic partner $R^4R^5CO$ to provide a structurally more complex product that may be further elaborated. Although an extra step is required for the conversion of the carbonyl function of the starting material into the corresponding imine, the enhanced nucleophilicity coupled with a low propensity to suffer proton transfer of the resulting imine anions relative to the corresponding enolates often justifies the additional steps required. Moreover, the low electrophilicity of the azomethine group ensures that there will be no side reactions involving nucleophilic additions of the intermediate imine anions to either starting or product imines.

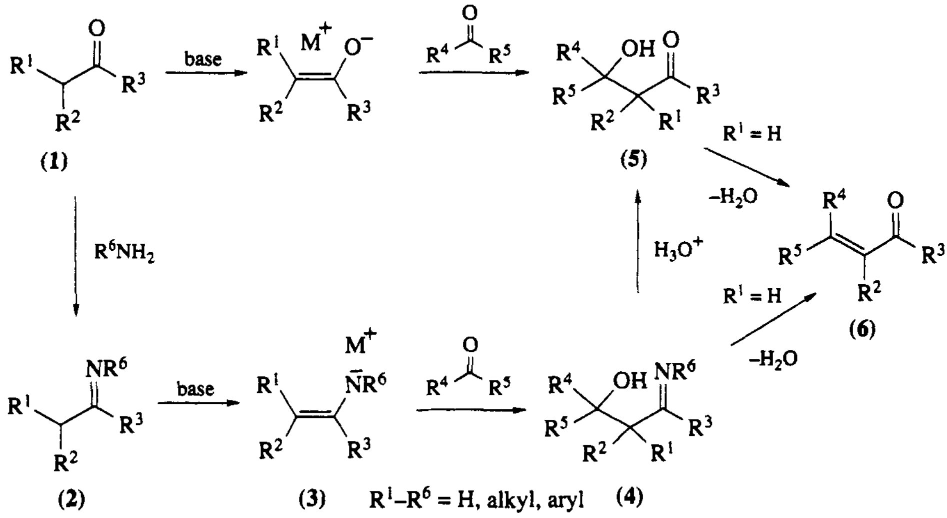

Scheme 1

The metallation of aldimines (**2**; $R^3$ = H) may be readily achieved using lithium dialkylamides and Grignard reagents as bases; alkyllithium reagents are not generally useful because of competing addition to the carbon–nitrogen double bond. Depending upon the experimental conditions (*e.g.* solvent, temperature and base) and the nature of the *N*-substituent, deprotonation of the unsymmetrical ketimines (**2**; $R^3$ = alkyl) may lead to either the less-substituted or more-substituted imine anion; these regiochemical issues have been previously examined in some detail.[4]

Interestingly, the discovery of imine anions as potentially useful synthetic intermediates was made serendipitously by Wittig approximately 30 years ago.[5] Acting upon an earlier discovery that lithium diethylamide may serve as a hydride donor to benzyne, Wittig examined the reaction of lithium diethylamide with benzophenone to ascertain whether the latter might also serve as a hydride acceptor. Surprisingly, the products observed from this reaction were benzhydrol (**7**) and the β-hydroxy aldimine (**8**) rather than the expected oxidation product (**9**). The sequence of reactions depicted in Scheme 2 was then proposed to account for this unexpected transformation. The initially produced aldimine (**9**) undergoes deprotonation with a second equivalent of lithium diethylamide to provide the imine anion (**10**),

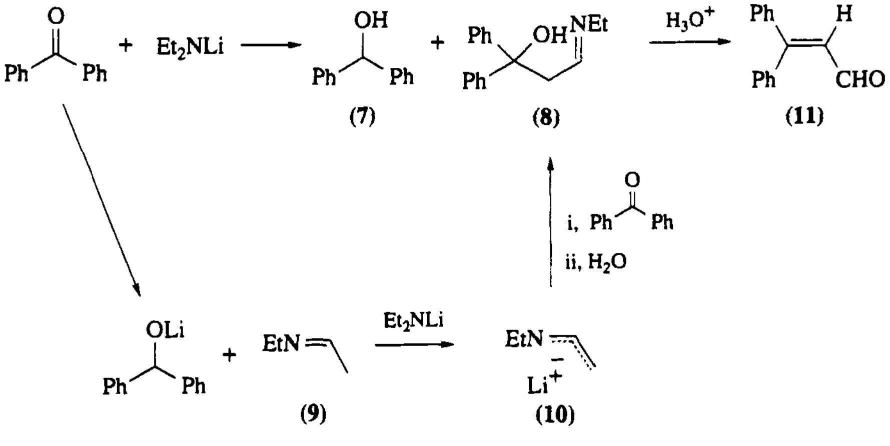

Scheme 2

which adds to benzophenone to provide (**8**); hydrolysis and dehydration of (**8**) furnishes (**11**). The net result of this unexpected process is a 'directed aldol reaction' of acetaldehyde with benzophenone, a transformation that cannot otherwise be easily achieved.

## 1.16.2 DIRECTED ALDOL REACTIONS OF IMINE ANIONS

### 1.16.2.1 Reactions of Imine Anions Derived from Aldimines

Following this exciting discovery Wittig, and subsequently others,[6–12] then explored the scope and limitations of this process, and the development of a highly useful directed aldol reaction evolved for the preparation of α,β-unsaturated aldehydes (**13**; Scheme 3); some representative results are collected in

**Table 1** Directed Aldol Reactions of Metallated Aldimines with Carbonyl Compounds (Scheme 3)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | *Yield of (12) (%)* | *Yield of (13) (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| H | H | c-$C_6H_{11}$ | Ph | Me | 80 | 65 | 6 |
| H | H | c-$C_6H_{11}$ | Ph | H | 94 | 77 | 6 |
| H | H | c-$C_6H_{11}$ |  | —$(CH_2)_5$— | 92 | 58 | 6 |
| H | H | c-$C_6H_{11}$ | $Pr^n$ | H | Not isolated | 65 | 7 |
| H | H | c-$C_6H_{11}$ | 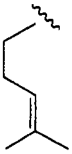 | Me | 76 | 64 | 7 |
| H | H | c-$C_6H_{11}$ | Ph | Ph | 92 | 100 | 7 |
| H | Me | c-$C_6H_{11}$ | Ph | Ph | 91 |  | 7 |
| H | Et | c-$C_6H_{11}$ | Ph | Ph | 71 |  | 7 |
| Me | Me | c-$C_6H_{11}$ | Ph | Ph | 29 |  | 7 |
| Et | Et | c-$C_6H_{11}$ | Ph | Ph | 0 |  | 7 |
| H | Me | $Bu^t$ | 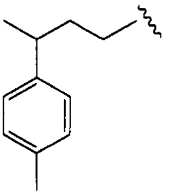 | H | — | 83[a] | 8 |
| H | Me | $Bu^t$ | 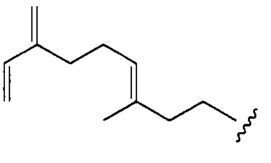 | H |  | 60 | 9 |
| H | H | $Bu^t$ | 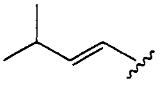 | H |  | 50 | 10 |
| H | H | c-$C_6H_{11}$ |  | —$(CH_2)_2CH{=}CMe$— | 75 | 55[b] | 11 |
| H | H | c-$C_6H_{11}$ |  | —$(CH_2)_2CMe{=}CH$— |  | 57[c] | 11 |
| H | H | c-$C_6H_{11}$ | 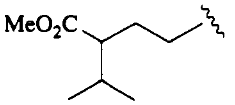 | Me |  | 44[c,d] | 12 |

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[a] (*E*)-isomer only. [b] (*E*):(*Z*)=9:1. [c] (*E*):(*Z*)=3:2. [d] Hydroxy aldehyde isolated in 77% yield and dehydration accompanied by retroaldol.

Table 1, examination of which provides ample support for the generality of the process. It is noteworthy that increased branching at the carbon α to the imine function leads to decreased yields of the desired adducts (**12**); the reason for this failure has not been addressed, but reversion by retroaldolization is one likely possibility. The base that was typically employed to effect the deprotonation of the intermediate aldimines was lithium diisopropylamide, since alkyllithiums were found to add to the carbon–nitrogen double bond of the aldimines. Wittig observed in a number of instances that the overall yields of α,β-unsaturated carbonyl compounds obtained according to this procedure were better than by the corresponding classical Wittig reaction.[7] Interestingly, the anion derived from the *t*-butylimine of isobutyraldehyde reacts with selected α,β-unsaturated ketones to give 1,4-adducts, whereas the corresponding hydrazone anions add to such ketones to provide the 1,2-adducts.[13]

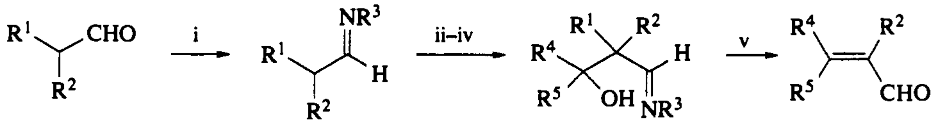

**(12)** **(13)**

i, $R^3NH_2$, $-H_2O$; ii, base; iii, $R^4R^5CO$; iv, $H_2O$; v, $H_3O^+$, $-H_2O$ with $R^1 = H$

**Scheme 3**

Anions derived from the aldimine of tiglaldehyde (**14**) react with carbonyl compounds preferentially at the α-position under conditions of kinetic control to give adducts (**15**), but products (**16**) derived from γ-attack are obtained under equilibrating conditions (Scheme 4).[14] Addition of HMPA to the reaction or adduct mixture is required to promote isomerization of the initially formed α-adduct to the γ-product. There is also an increasing preference for γ-capture of the unsaturated imine anion as the degree of substitution α to the carbonyl function increases as in α-branched aldehydes and ketones (Table 2). Efforts to isomerize the initial α-adduct formed from reaction of the aldimine derived from crotonaldehyde with cyclohexanecarbaldehyde gave complicated mixtures.

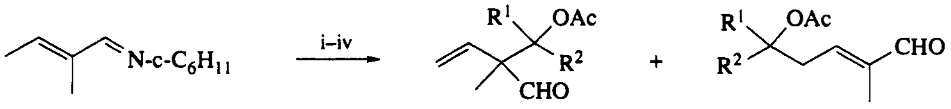

**(14)** **(15)** **(16)**

i, LDA, THF, 0 °C; ii, $R^1R^2CO$, HMPA, –78 °C; iii, $Ac_2O$, –78 °C; iv, $H_3O^+$

**Scheme 4**

**Table 2** Additions of Metallated (**14**) to Carbonyl Compounds (Scheme 4)

| $R^1$ | $R^2$ | *(15)* (%) | *(16)* (%) |
|---|---|---|---|
| c-$C_6H_{11}$ | H | $36^a$ ($6^b$) | $24^a$ ($73^b$) |
| Ph | H | $71^a$ ($<3^b$) | $<3^a$ ($70^b$) |
| $Pr^n$ | H | $71^a$ ($<3^b$) | $11^a$ ($70^b$) |
| $PhCH_2CH_2$ | H | $54^a$ ($15^b$) | $3^a$ ($66^b$) |
| —$(CH_2)_5$— |  | $<3^a$ | $70^{a,c}$ |

[b]In the absence of HMPA. [c]In the presence of HMPA. [d]Isolated free alcohol rather than acetate.

An interesting variant of the original reaction discovered by Wittig has been reported in which carbonyl compounds undergo reactions with vinylaminodichloroboranes (**17**) derived from ketimines to give, upon hydrolytic work-up, the expected aldol adducts (**18**; Scheme 5).[15] The reactions proceed in fair to good overall yields but with relatively poor diastereoselectivity (Table 3). The extension of this reaction

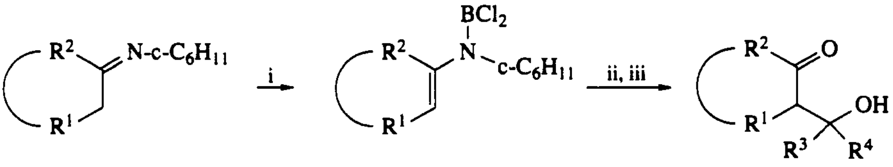

(17) (18)

i, $BCl_3$, $Et_3N$, $CH_2Cl_2$, Δ; ii, $R^3R^4CO$, Δ; iii, $H_3O^+$

**Scheme 5**

**Table 3** Directed Aldol Reactions of Vinylaminodichloroboranes (**17**) with Carbonyl Compounds (Scheme 5)

| *R*¹ | *R*² | *R*³ | *R*⁴ | *Yield of (18) %* | *erythro:threo* |
|---|---|---|---|---|---|
| $—(CH_2)_4—$ | | Ph | H | $71^a$ | 2 |
| $—(CH_2)_4—$ | | $PhCH2CH_2$ | H | $52^a(39^b)$ | 1 |
| $—(CH_2)_4—$ | | Me | Me | $31^a$ | |
| $—(CH_2)_4—$ | | $—(CH2)_5—$ | | $28^a$ | |
| Me | Et | $p\text{-}O_2NC_6H_4$ | H | $59^a$ | 3 |
| $—(CH_2)_3CH(Me)—$ | | Ph | H | $37^b$ | |
| H | Ph | $p\text{-}O_2NC_6H_4$ | H | $46^b$ | |

[a] Overall yield based on carbonyl compound for two-step procedure with isolation of intermediate vinylaminodichloroborane.
[b] Isolated yield of aldol adduct according to one-pot procedure.

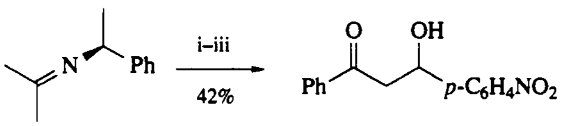

(19) 35% *ee*

i, $BCl_3$, $Et_3N$; ii, $p\text{-}O_2NC_6H_4CHO$; iii, $H_3O^+$

**Scheme 6**

to the asymmetric synthesis of β-hydroxy ketones through the use of a chiral auxiliary on nitrogen has also been reported as illustrated in Scheme 6; however, these reactions proceeded with only modest chemical yields (30–42%) and enantioselectivity (35–48%).[16] The additions of the corresponding magnesium and lithium imine anions derived from (**19**) to *p*-nitrobenzaldehyde proceeded with even lower yields (6–15%) and enantiomeric excesses (19–7%).

### 1.16.2.2 Reactions of Imine Anions Derived from 2-Azadienes

Historically, imine anions have been typically prepared by deprotonation of the corresponding imines, but a highly useful alternative route to these reactive intermediates features the regioselective 1,2-addition of alkyllithium reagents to 2-azadienes (**21**).[17–19] Although the requisite 2-azadienes may be prepared by isomerization of either *N*-allylimines or the imines of α,β-unsaturated ketones,[19] one particularly useful procedure has been devised that involves alkenation of carbonyl compounds with the aminoalkylphosphonate reagent (**20**; Scheme 7).[17] Sequential reaction of the 2-azadienes (**21**) thus produced with *n*-butyllithium and an aldehyde affords intermediate adducts that may be trapped with methyl chloroformate to furnish protected β-hydroxycarbonyl compounds in very good overall yields (Table 4). This novel procedure for effecting the net geminal acylation/hydroxyalkylation of a carbonyl group has been nicely exploited for the formation of quaternary carbons bearing differentially functionalized alkyl appendages.

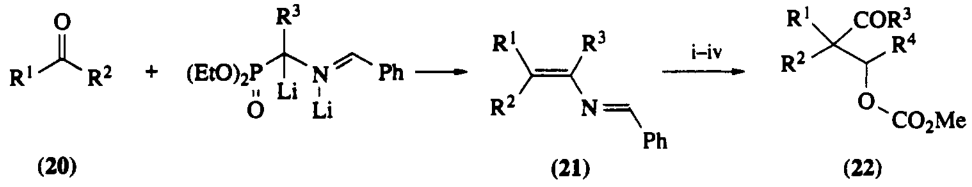

i, Bu$^n$Li; ii, R$^4$CHO; iii, MeO$_2$CCl; iv, H$_3$O$^+$

**Scheme 7**

**Table 4** Geminal Acylation/Hydroxyalkylation of Carbonyl Compounds (Scheme 7)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *Overall yield of (22) (%)* |
|---|---|---|---|---|
| Pr$^n$ | Pr$^n$ | H | Ph | 56 |
| —(CH$_2$)$_5$— | | H | Pr$^n$ | 45 |
| —(CH$_2$)$_5$— | | H | Ph | 47 |
| 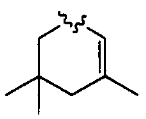 | | H | Ph | 59$^a$ |
| Ph | Me | H | Pr$^n$ | 49$^a$ |
| Ph | Me | H | Ph | 62$^a$ |
| Ph | Me | Me | Ph | 51$^a$ |

$^a$Obtained as mixture of diastereomers 45:55–40:60.

The general utility of this method is nicely illustrated by its application to the synthesis of the cyclohexenone (**24**), a key synthetic intermediate in the synthesis of several of the *Amaryllidaceae* alkaloids, in 51% overall yield from (**23**) as a mixture (1.5:1) of diastereomers (Scheme 8).[18]

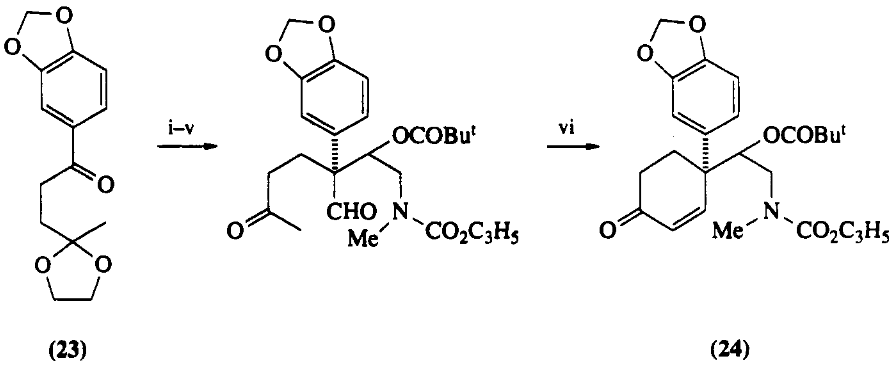

i, (EtO)$_2$P(O)CH(Li)N=CHPh; ii, Bu$^n$Li, ZnCl$_2$; iii, CH$_2$=CHCH$_2$OCON(Me)CH$_2$CHO; iv, Bu$^t$COCl; v, H$_3$O$^+$;

vi, 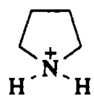 AcO$^-$, MeOH (aq)

**Scheme 8**

### 1.16.2.3 Reactions of Endocyclic Imine Anions Derived from Unsaturated Heterocycles

Imine anions obtained by isomerization of heterocyclic, secondary allylic amines[19] with *n*-butyllithium add to benzophenone (Schemes 9 and 10).[20] However, the generality of this process with respect to the allylamine starting material and the carbonyl partner remains to be established.

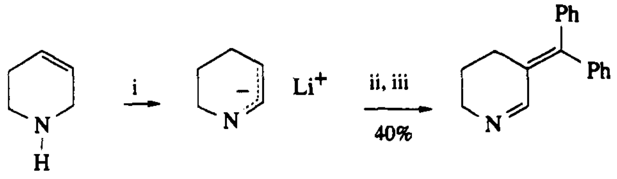
i
Li+
ii, iii
40%
N
H
Ph
Ph

i, $Bu^nLi$, THF, r.t.; ii, $Ph_2CO$; iii, $H_2O$

**Scheme 9**

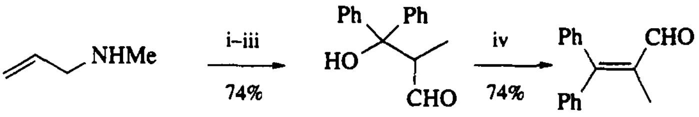
NHMe
i–iii
74%
Ph
Ph
HO
CHO
iv
74%
Ph
CHO
Ph

i, BuLi, THF, r.t.; ii, $Ph_2CO$; iii, $H_3O^+$; iv, $-H_2O$, Δ

**Scheme 10**

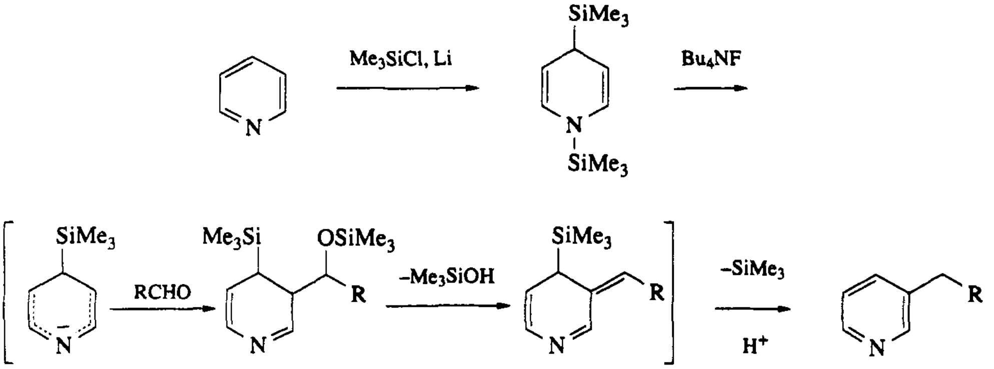
N
Me3SiCl, Li
SiMe3
N
SiMe3
Bu4NF
SiMe3
N
RCHO
Me3Si
OSiMe3
R
N
-Me3SiOH
SiMe3
R
N
-SiMe3
H+
R
N

**(25)**

**Scheme 11**

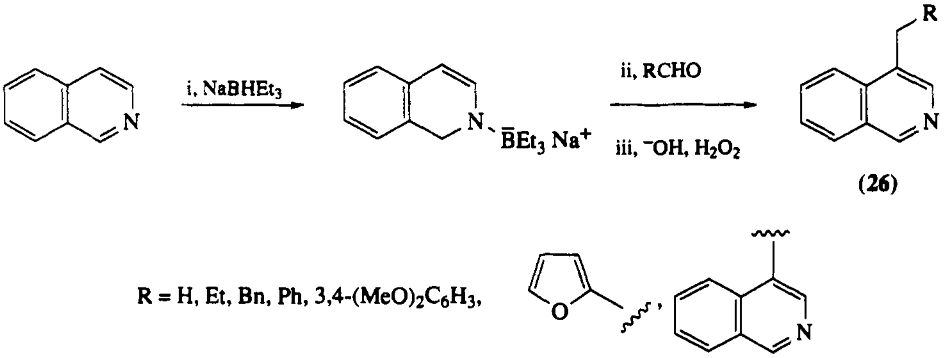
N
i, NaBHEt3
N
BEt3 Na+
ii, RCHO
iii, -OH, H2O2
R
N
O
N

**(26)**

R = H, Et, Bn, Ph, 3,4-$(MeO)_2C_6H_3$,

**Scheme 12**

Several routes to substituted heterocyclic systems have been devised that feature the reactions of unsaturated imine anions formed by reduction of the corresponding aromatic nitrogen heterocycles (Schemes 11 and 12).[21,22] Dehydration of the intermediate adducts gives the alkyl-substituted aromatic heterocycles. These procedures provide useful entries to 3-alkylpyridines (**25**; 15–77% overall yields)[21] and 4-alkylisoquinolines (**26**; 25–65% overall yields).[22]

## 1.16.3 ADDITION REACTIONS OF HETEROATOM-STABILIZED IMINE ANIONS

### 1.16.3.1 Phosphorus- and Silicon-stabilized Imine Anions

The discovery that imine anions (**29**) bearing either phosphorus- or silicon-derived anion-stabilizing groups α to the imine function also serve as nucleophilic partners in reactions with carbonyl compounds has led to the development of several useful synthetic methods for the preparation of α,β-unsaturated carbonyl compounds (Scheme 13). There is an equilibrium, which is a function of the substituent Z, between the imino and enamino tautomers, (**27**) and (**28**) respectively, of the starting material; when Z = $(EtO)_2P(O)$, the major isomer present in solution is (**28**). The starting imines or enamines for the formation of the anions (**29**) may be readily prepared upon condensation of the corresponding carbonyl compound with a suitable amine[23,24] or by nucleophilic addition of a primary amine to the corresponding alkynyl-1-phosphorus compounds.[25,28,29] Recently, however, more expeditious routes for the preparation of lithiated enamino alkylphosphonates [**29**; Z = $(EtO)_2P(O)$] have been devised.[26,27] The intermediate adducts formed upon the reaction of anions generated upon metallation of (**27**) or (**28**) with aldehydes and ketones typically undergo spontaneous elimination to provide α,β-unsaturated imines that may then be hydrolyzed to furnish α,β-unsaturated carbonyl compounds (**30**). The overall process results in the efficient two-carbon homologation of the carbonyl function of the electrophilic partner $R^4R^5CO$.

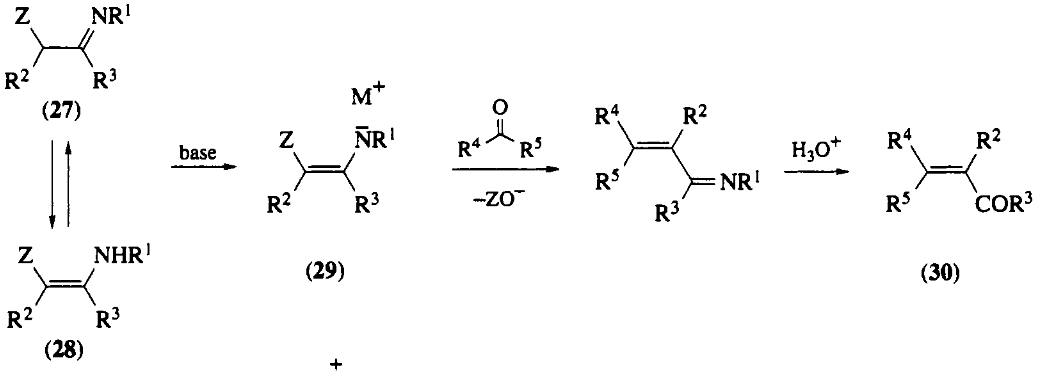

$Z = Ph_3\overset{+}{P}, (EtO)_2PO, Ph_2PO, (EtO)_2PS, SiMe_3, SiEt_3,$ *etc.*

**Scheme 13**

Representative examples of this transformation are collected in Table 5. Examination of these results reveals that these processes generally proceed in good to very good overall yields, and a variety of aldehydes and ketones may be employed as the electrophiles. The overall yields are often best when the more nucleophilic anions derived from the phosphonates [**27**/**28**; Z = $(EtO)_2P(O)$] are employed rather than the anions of the phosphoranes (**27**/**28**; Z = $Ph_3P^+$). Indeed the phosphonate-derived reagents (**27**/**28**; Z = $(EtO)_2P(O)$; $R^3$ = H) are vastly superior to the phosphorane $Ph_3P{=}CHCHO$ for the conversion of aldehydes and ketones to α,β-unsaturated aldehydes.[24]

A useful alternative to the Wittig-type reactions of carbonyl compounds with the phosphorus-stabilized imine anions [**29**; Z = $Ph_3P^+$, $(EtO)_2P(O)$, $Ph_2P(O)$ and $(EtO)_2P(S)$] has been developed which features a variant of the Peterson alkenation.[31–37] This process involves the condensation of the related α-silyl anions (**29**; Z = $R_3Si$) with carbonyl partners. The reaction was originally developed using the α-trimethylsilyl analogs (**29**; Z = $Me_3Si$),[31–34] but there now appears to be a preference for the use of the corresponding α-triethylsilyl derivative (**29**; Z = $Et_3Si$).[36,37] Although reaction times using the latter reagents are somewhat longer than required for the corresponding trimethylsilyl analog, the starting α-triethylsilylimines are more readily available in pure form.[36] As may be seen from examination of Table 6, the overall yields of new α,β-unsaturated aldehydes and ketones prepared by this procedure are generally very good to excellent, often better than the corresponding Wittig process. The one apparent drawback that is evident from early work in this area is that the (*E*):(*Z*) ratios were typically poor, ranging from 1:1 to 3:1. However, recently it has been discovered that treatment of (*E*)/(*Z*) mixtures of the intermediate α-methyl-α,β-unsaturated imines with anhydrous acid followed by hydrolysis affords the corresponding α,β-unsaturated aldehydes in ≥100:1 (*E*):(*Z*) ratios.[37]

**Table 5** Reaction of α-Phosphorus-stabilized Imine Anions with Carbonyl Compounds (Scheme 13)

| *Z* | *R*¹ | *R*² | *R*³ | *R*⁴ | *R*⁵ | *Overall yield of (30) (%)*[a] | *Ref.* |
|---|---|---|---|---|---|---|---|
| $Ph_3P^+$ | c-$C_6H_{11}$ | H | H | Ph | H | 36[b] | 23 |
| | $p$-$Me_2NC_6H_4$ | H | H | Ph | H | 61[b] | |
| | $p$-$Me_2NC_6H_4$ | H | H | PhCH=CH | H | 20[b] | |
| | $p$-$Me_2NC_6H_4$ | H | H | 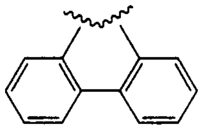 | | 25[b] | |
| $(EtO)_2P(O)$ | c-$C_6H_{11}$ | H | H | —$(CH_2)_5$— | | 86 | 24 |
| | | Me | H | —$(CH_2)_5$— | | 66 | |
| | | Bn | H | —$(CH_2)_5$— | | 63 | |
| | | H | H | Ph | H | 77 | |
| | | H | $Pr^n$ | Ph | H | 55 | 25 |
| | | H | Ph | $p$-$MeOC_6H_4$ | H | 53 | |
| | | H | Me | Ph | Me | 46 | |
| | $Bu^n$ | H | $Bu^n$ | Ph | H | 65 | |
| | | H | $Bu^n$ | —$(CH_2)_5$— | | 67 | |
| | $Bu^t$ | H | H | Ph | H | 70 | 26 |
| | | | | $Ph(CH_2)_2$ | H | 73 | |
| | | | | c-$C_6H_{11}$ | H | 76 | |
| | | | | PhCH=CH— | H | 67 | |
| | | | | —$(CH_2)_5$— | | 94 | |
| | | | | $Pr^n$ | $Pr^n$ | 53 | |
| | | | | Ph | Ph | 71 | |
| | | | | $Pr^i$ | Me | 72 | |
| $(EtO)_2P(O)$ | Ph | Me | H | Ph | H | 71 | 27 |
| | | $Pr^n$ | H | Ph | H | 66 | |
| | | Et | H | $p$-$MeC_6H_4$ | H | 68 | |
| | | Me | H | 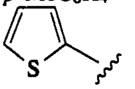 | H | 47 | |
| | | Me | H | PhCH=CH— | H | 45 | |
| | | Me | H | Et | H | 42 | |
| | | Me | H | $Pr^i$ | H | 60 | |
| | | Me | H | 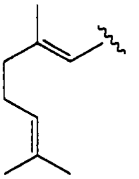 | H | 32 | |
| $Ph_2P(O)$ | $Bu^n$ | H | $Bu^t$ | $p$-$MeOC_6H_4$ | H | 66 | 28 |
| | | | Ph | Ph | H | 57 | |
| | | | $Bu^t$ | Ph | H | 61 | |
| | | | $Pr^n$ | Ph | H | 63 | |
| | | | c-$C_5H_9$ | Ph | H | 59 | |
| | | | c-$C_6H_{11}$ | Ph | H | 70 | |
| | | | Ph | Ph | Ph | 62 | |
| | Bn | H | Ph | —$(CH_2)_5$— | | 53 | |
| $(EtO)_2P(S)$ | $Bu^n$ | H | n-$C_6H_{13}$ | Ph | H | 37 | 29 |

[a] Unless otherwise indicated, isolated as α,β-unsaturated carbonyl compound. [b] Isolated as α,β-unsaturated imine.

**Table 6** Reactions of α-Trialkylsilyl-stabilized Imine Anions with Carbonyl Compounds (Scheme 13)

| *Z* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *R*$^5$ | *Overall yield of (30) (%)*[a] | *(E):(Z)*[b,c] | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| Me$_3$Si | Bu$^t$ | H | H | n-C$_5$H$_{11}$ | H | 94 | | 31 |
| | | | | | —(CH$_2$)$_5$— | 90 | | |
| | | Me | H | Pr$^n$ | H | 88 | | |
| | | | | | —(CH$_2$)$_5$— | 90 | | |
| | | | | Ph | H | 90 | 1:1[b] | |
| | | | | 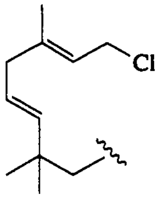 | H | 79 | 3:1[b] | 32 |
| | | H | H | 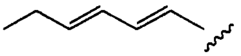 | H | 45 | 12:1[b] | 33 |
| | | | | 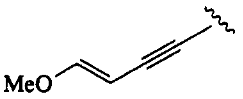 | H | 60 | | 34 |
| | | | | 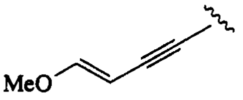 | Me | 80 | | |
| | | H | Me | 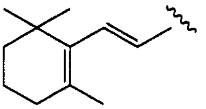 | Me | 59 | 47:53[b] | 35 |
| | | Me | Me | 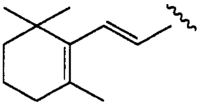 | Me | 52 | 17:83[b] | |
| | | H | Me | 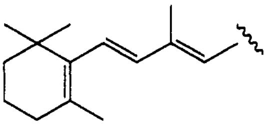 | H | 65 | 62:38[b] | |
| | Bu$^t$ | Me | Me | 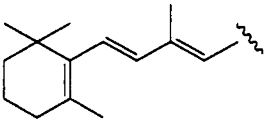 | H | 53 | 41:59[b] | |
| | | H | Me | Ph | Me | 58 | 59:41[b] | |
| | | Me | Me | Ph | Me | <10 | | |
| | | H | Me | Ph | H | 81 | | |
| Et$_3$Si | Bu$^t$ | Me | H | 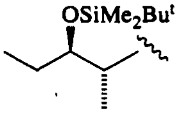 | H | 77 | | 36 |

**Table 6** (*continued*)

| *Z* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *R*$^5$ | *Overall yield of* (**30**) (%)[a] | (*E*):(*Z*)[b,c] | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| $Et_3Si$ | c-$C_6H_{11}$ | Me | H | 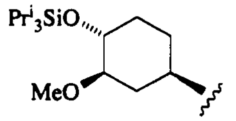 | H | 84<br>85 | 100:1[c]<br>2:1[b] | 37 |
| | | | | Ph | H | 91 | >100:1[c] | |
| | | | | *n*-$C_7H_{15}$ | H | 82 | >100:1[c] | |
| | | | | | | 83 | 6:1[b] | |
| | | | | 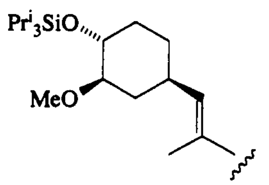 | H | 68 | >100:1[c] | |

[a] Overall yield of α,β-unsaturated carbonyl compound. [b] Hydrolytic workup with aqueous acid. [c] Anhydrous isomerization with trifluoroacetic acid followed by hydrolytic work-up with aqueous acid.

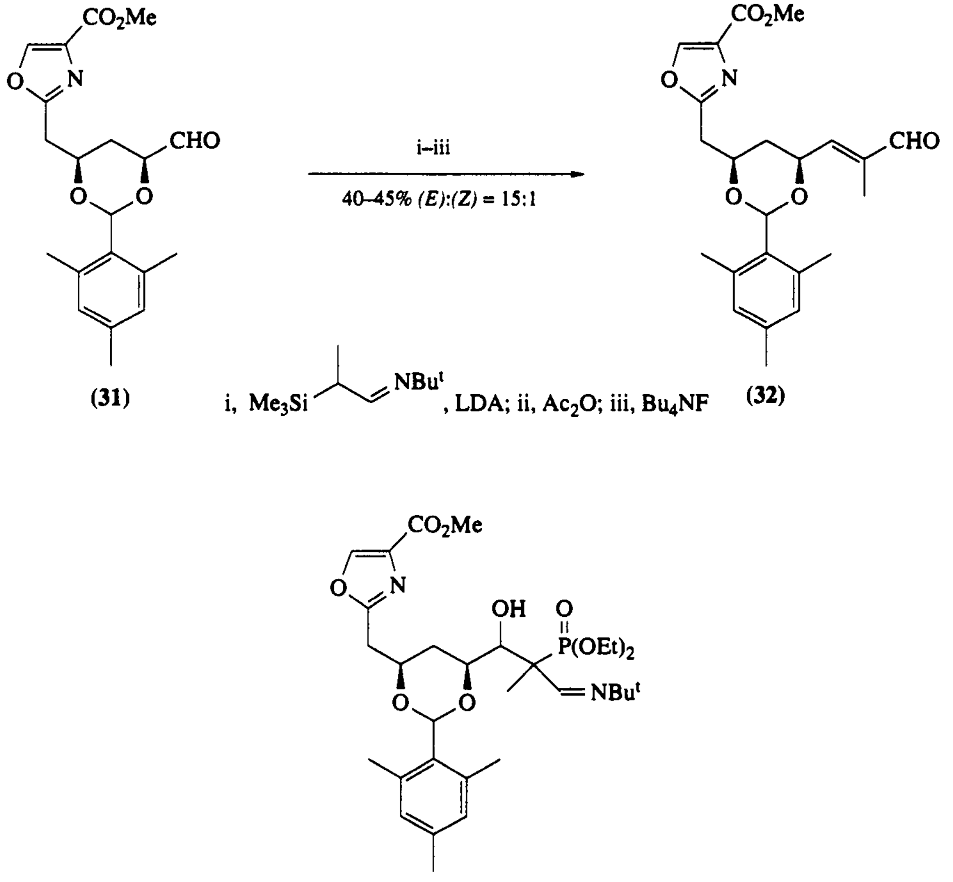
CO2Me
O
N
CHO
O
O
i–iii
40–45% (E):(Z) = 15:1
CO2Me
O
N
CHO
O
O
CO2Me
O
N
OH
O
P(OEt)2
NBu'
O
O

(31) i, $Me_3Si$ NBu$^t$, LDA; ii, $Ac_2O$; iii, $Bu_4NF$ (32)

(33)

Scheme 14

The transformation outlined in Scheme 14 nicely illustrates some of the advantages associated with the Peterson alkenation relative to the Horner–Emmons reaction for the conversion of the aldehyde (**31**) into the α,β-unsaturated aldehyde (**32**). When the corresponding phosphonate reagent is used, only the β-hydroxy phosphonate (**33**) is isolated; elimination to form the α,β-unsaturated imine from (**33**) could not be induced under a variety of conditions.[30]

## 1.16.4 ADDITION REACTIONS OF METALLATED OXIME DERIVATIVES

### 1.16.4.1 Acyclic and Cyclic Oxime Anions

The dianions of (*Z*)-oximes react with aldehydes and ketones to give β-hydroxy oximes in good to very good yields (Scheme 15);[38,39] no dianion formation occurs with (*E*)-aldoximes.

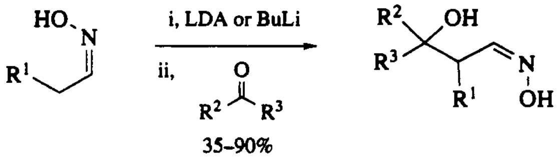

**Scheme 15**

Deprotonation of the chiral 1,2-oxazine (**34**) by *n*-butyllithium proceeds with a high degree of stereoselectivity *cis* to the C-6 substituent; subsequent capture of this carbanion with carbonyl compounds also proceeds *syn* to the C-6 substituent, so that the overall process occurs with retention of configuration at C-4 (Scheme 16).[40] Although the related 1,2-oxazine (**35**) has not been condensed with carbonyl compounds, it is useful to note that the regioselectivity of its deprotonation can be easily controlled by the size of the base employed. Bulky amide bases preferentially abstract the proton at the exocyclic methyl group, whereas small amide bases such as lithium dimethylamide preferentially abstract a proton at C-4.[41]

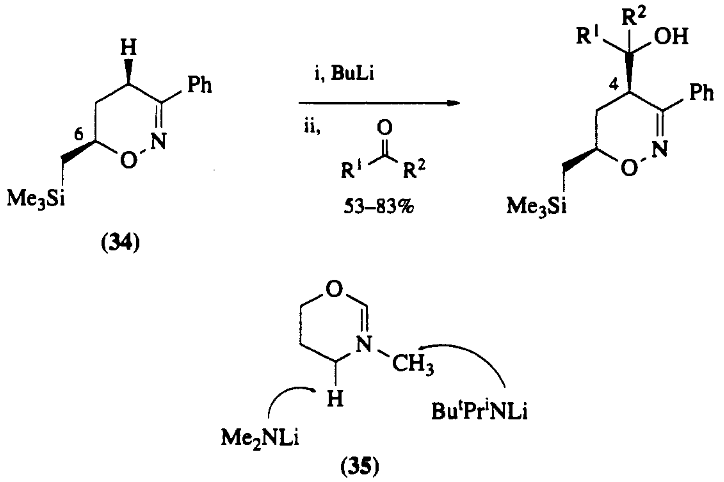

(**34**)

(**35**)

**Scheme 16**

### 1.16.4.2 Stabilized Oxime Anions

A useful protocol for effecting the stereoselective synthesis of masked β,β′-dihydroxy ketones and compounds derived therefrom has recently been developed (Schemes 17 and 18).[42] The process features the metallation of enantiomerically pure 3-*p*-tolylsulfinylmethyl-4,5-dihydroisoxazoles such as (**36**), followed by reaction with an aldehyde to give the intermediate adducts (**37**). The diastereomeric ratio of the adducts obtained varies with the nature of the base used to deprotonate the starting arylsulfinylisoxazole (**36**). For example, when *t*-butylmagnesium bromide is the base, the diastereomeric ratio of the adducts (**37**) is 8:1, whereas when lithium diisopropylamide is the base, the ratio is 1.1:1; other bases give intermediate ratios of products. At least in the specific case illustrated in Scheme 17, the new stereocenter α to the sulfoxide group appears to be formed with a high degree of stereoselectivity, and the adducts are epimeric only at the hydroxy-bearing carbon. Based on other results (*vide infra*, Scheme 18), the major product obtained upon reductive removal of the sulfinyl group of diastereoisomers is (**38**). Subsequent reduction of (**38**) with lithium aluminum hydride gives the aminodiol (**40**) with >50:1 stereoselectivity.

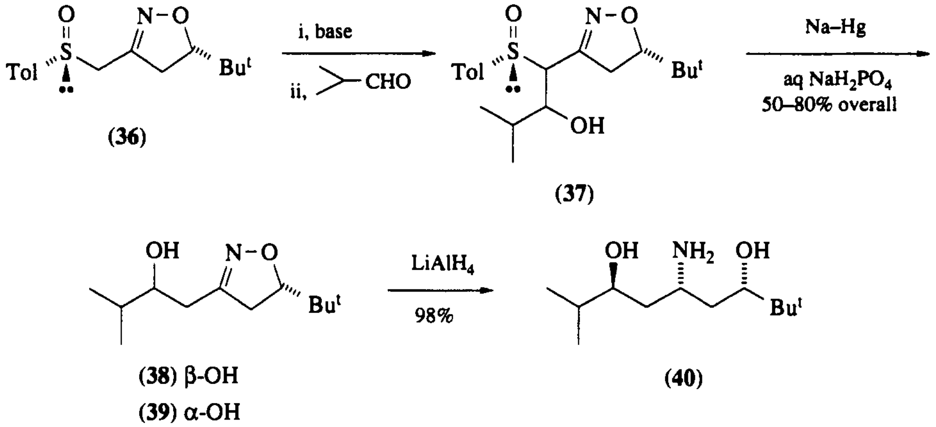

Scheme 17

The adducts obtained upon reaction of enantiomerically pure, metallated sulfinyl-4,5-dihydroisoxazoles with aldehydes can be converted into β,β′-dihydroxy ketones in what is the equivalent of a regiospecific double aldol condensation of a ketone with two different aldehydes (Scheme 18). For example, metallation of (**41**) with *t*-butylmagnesium bromide followed by quenching the intermediate anion with

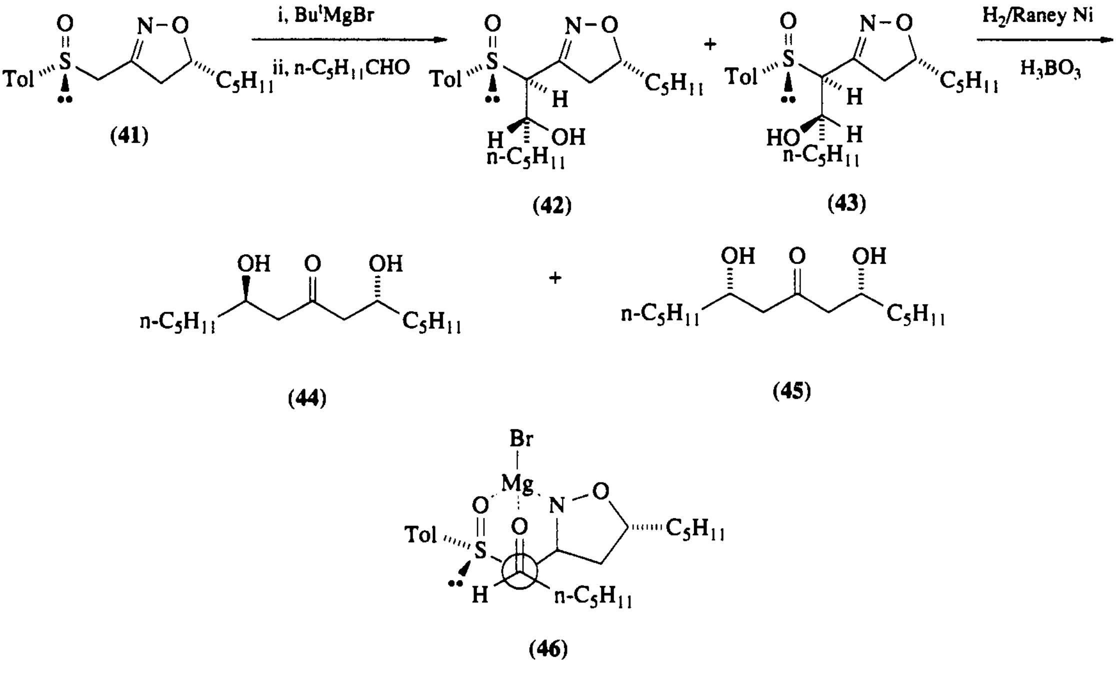

Scheme 18

*n*-hexanal gives a mixture (3:1) of diastereomers (**42**) and (**43**); hydrogenolysis and hydrolysis of the isoxazoline ring leads to a mixture (3:1) of the optically active dihydroxy ketone (**44**) and the *meso*-dihydroxy ketone (**45**). Based on the results of this experiment, a transition state was proposed for additions of metallated derivatives of (**36**) to aldehydes in which the aldehyde approaches the chiral azaenolate according to (**46**).

## 1.16.5 ADDITIONS OF METALLATED DERIVATIVES OF IMIDATES

### 1.16.5.1 Acyclic Imidates

Metallation of the acyclic imidate salt (**47**) followed by reaction of the intermediate dianion with aldehydes leads to the production of the oxazoles (**48**; Scheme 19).$^{30}$ This procedure constitutes a useful modification of the Cornforth oxazole synthesis.

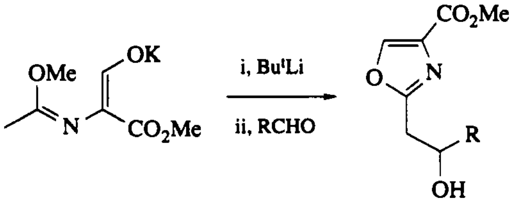

**(47)** **(48)**

**Scheme 19**

Metallation of the arylsulfinyl-*N*-methoxyacetimidate (**49**), which may be prepared in two steps from commercially available *N*-hydroxyacetimidate, followed by reaction with aldehydes provides adducts that after sequential desulfurization and hydrolysis may be converted into β-hydroxy esters with ≥80% enantiomeric excess (Scheme 20).$^{43}$ Thus, under kinetic conditions the reaction of the anion derived from (**49**) with aldehydes gives mixtures of the *syn* and *anti* products, (**50**) and (**51**) respectively, in nearly equal amounts. Under thermodynamic conditions, however, the more stable *anti* adducts (**51**) dominate, and after desulfurization and hydrolysis the β-hydroxy esters (**53**) are obtained in 75–94% enantiomeric excess. When the zinc enolate derived from (**49**) is condensed with aldehydes, the *anti* adducts (**51**) are again the major products and the β-hydroxy esters (**53**) can be isolated in 76–86% enantiomeric excess. On the other hand, the reaction of the zirconium enolate of (**49**), which is obtained by the addition of $Cp_2ZrCl_2$ to the corresponding lithium enolate, with aldehydes followed by desulfurization gives β-hy-

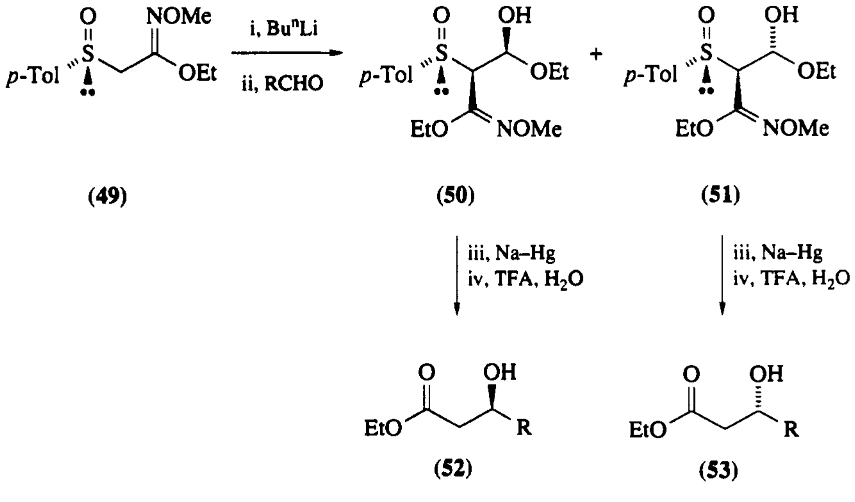

**Scheme 20**

droxy esters (**52**) in 79–88% enantiomeric excess. The only drawback to the use of zirconium enolates is the lower chemical yields in the condensation reaction.

### 1.16.5.2 Metallated 2-Methyloxazolines

The reactions of metallated 2-methyloxazolines with carbonyl compounds to provide adducts constitute the key step in a general procedure for the conversion of carbonyl compounds into β-hydroxy carboxylic acids and esters or their α,β-unsaturated counterparts (Schemes 21–26).[44–50] For example, reaction of the lithiated derivative of (**54**) with carbonyl compounds provides the adducts (**55**) in high yield (Scheme 21). Subsequent acid-catalyzed hydrolysis provides the unsaturated carboxylic acids (**56**); depending upon the severity of the reaction conditions, acid-induced ethanolysis can be performed on the adducts (**55**) to provide either the unsaturated esters (**57**) or the β-hydroxy esters (**58**) in good yields (Table 7).[45] The main limitation of the method is that extensive retroaldolization occurs upon attempts to hydrolyze adducts (**55**; $R^1$ = alkyl), so α-alkyl-β-hydroxy esters and acids do not appear to be accessible.

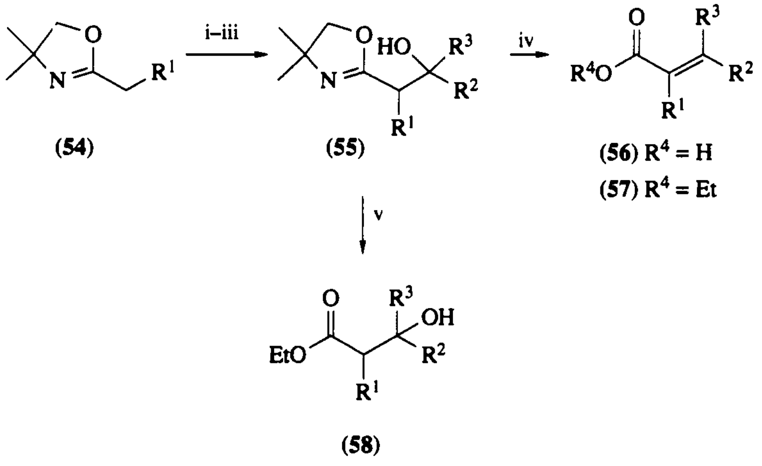

i, BuLi; ii, $R_2R_3CO$; iii, $H_2O$; iv, $R_4OH$, $H^+$; v, EtOH, $H^+$

**Scheme 21**

**Table 7** Reactions of Metallated Achiral 2-Alkyloxazolines (**54**) with Carbonyl Compounds (Scheme 21)[45]

| *$R^1$* | *$R^2$* | *$R^3$* | *(56) (%)* | *(57) (%)* | *(58) (%)* |
|---|---|---|---|---|---|
| H | Me | Me | | | 55 |
| H | $Pr^n$ | $Pr^n$ | | 80[a] | 91 |
| H | $-(CH_2)_5-$ | | 84 | 88 | |
| H | $-(CH_2)_6-$ | | 90[b] | 69[c] | 80 |
| H | 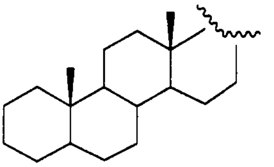 | | 96 | | |
| Me | $-(CH_2)_6-$ | | 88[d] | | |
| Et | $-(CH_2)_5-$ | | e | | |
| Et | Ph | H | e | | |

[a] Contained 54% of the β,γ-unsaturated isomer. [b] Contained 60–70% of the β,γ-unsaturated isomer. [c] Contained 78% of the β,γ-unsaturated isomer. [d] Contained 79% of the β,γ-unsaturated isomer. [e] Although initial 1,2-adduct formed in good yield, there was extensive reversion upon attempted acid-catalyzed hydrolysis of the oxazoline; only retroaldol under alkaline conditions.

After the lithiated chiral oxazoline (**59**) is allowed to react with different aldehydes, the adducts thus obtained can be hydrolyzed to provide optically enriched β-hydroxy acids (**60**), albeit with only poor enantiomeric excesses (18–25%; Scheme 22). When ketones are used as carbonyl partners, the β-hydroxy acids obtained are essentially racemic.[46]

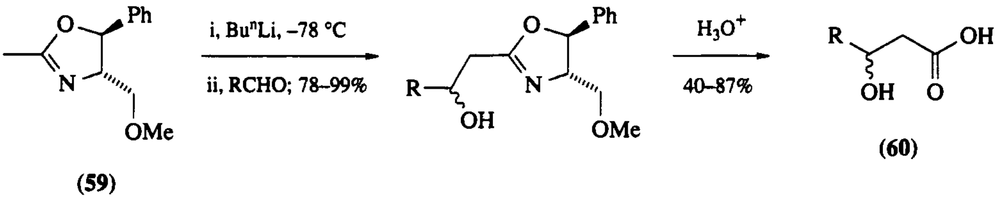

R = Me, Et, Bu$^t$, n-$C_6H_{13}$, c-$C_6H_{11}$, Ph

Scheme 22

In a related process, reaction of the metallated derivatives of the 2-ethyloxazolines (**61a–c**) with isobutyraldehyde produces the diastereomeric adducts (**62a–c**) and (**63a–c**) (Scheme 23).[47] Although reaction of the anion derived from (**61a**) with isobutyraldehyde proceeds with low (56:44) *anti*:*syn* selectivity, the reaction of racemic (**61b**) with isobutyraldehyde proceeds with an acceptable level of *anti*:*syn* selectivity to give a mixture (9:1) of the adducts (**62b**) and (**63b**). When the enantiomerically pure oxazoline (**61c**) is lithiated and treated with isobutyraldehyde, four diastereomers are produced in a ratio of 18.3:1:2.4:2.2; the *anti*:*syn* ratio observed in this reaction is thus 82:18.

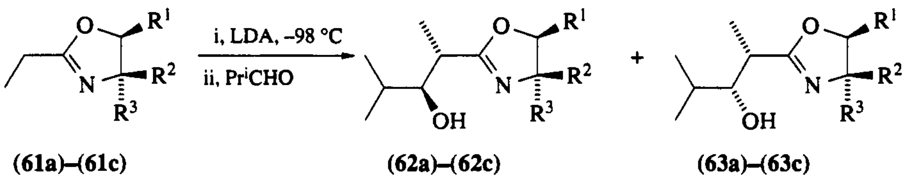

Series a: R$^1$ = H; R$^2$ = R$^3$ = Me
Series b: R$^1$ = R$^2$ = H; R$^3$ = $CH_2OMe$
Series c: R$^1$ = Ph; R$^2$ = H; R$^3$ = $CH_2OMe$

Scheme 23

The diastereoselectivity observed during the addition of (**61c**) to isobutyraldehyde stands in marked contrast to the significantly lower selectivity (1.5:1) that was previously observed when the chiral 2-methyloxazoline (**59**) was used as the nucleophilic partner (*vide supra*). The enhanced diastereoselection in the reaction involving (**61c**) is presumably a consequence of internal lithium chelation, which enhances both the selectivity in the deprotonation step as well as the diastereofacial selectivity in the nucleophilic addition to the aldehyde. For example, in separate experiments it was determined that metallation of (**61c**) proceeded with a (*Z*):(*E*) diastereoselectivity of >9:1.[48] Subsequent reaction of this (*Z*)-azaenolate with isobutyraldehyde *via* the chelated, chair-like transition state depicted in (**64**; R = Me), in which steric interactions between the reacting residues are minimized, would lead preferentially to the *anti* isomer (**62c**).[47] For the additions involving (**59**), examination of the related transition state (**64**; R = H) clearly reveals that the facial selectivity should be somewhat less.

By judicious choice of chiral auxiliary–reagent pairs, it has been possible to extend this chemistry to the enantioselective synthesis of β-hydroxy-α-methyl-carboxylic acid derivatives having either *anti* or *syn* stereochemistry (Schemes 24 and 25).[49] For example, the boron azaenolate obtained upon reaction of (**65**) with diisopinocamphenylboryl triflate reacts with a series of aldehydes to provide adducts that are readily converted to the *anti* methyl esters (**66**) in good overall yields (Scheme 24). The *anti*:*syn* ratios for these reactions are typically >9:1, and the percentage enantiomeric excesses for the *anti* adducts are in the range of 77–85%. On the other hand, the boron azaenolate derived from oxazoline (**61c**) and 9-borabicyclononane triflate reacts with aldehydes to give adducts that can be converted into the methyl esters of the *syn*-carboxylic acids (**67**; Scheme 25). The *syn*:*anti* ratios in these reactions are typically

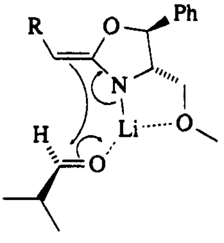

**(64)** R = H, Me

>97:3, but the percentage enantiomeric excesses for the *syn* isomer are only 40–60%. Although it appears that a single boron enolate is formed in the first step of each of these sequences, its geometry is not known. Furthermore, there is not a high correlation between the geometry of the intermediate boron azaenolates that are formed *in situ* and the enantioselectivity of the reaction. Further studies of this process are required to provide the necessary insights.

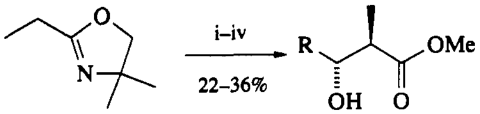

**(65)** **(66)**

i, $Ipc_2BOTf$; ii, RCHO; iii, $H_3O^+$, Δ; iv, $CH_2N_2$

R = Et, $Pr^n$, n-$C_5H_{11}$, $Pr^i$, c-$C_6H_{11}$, $Bu^t$

Scheme 24

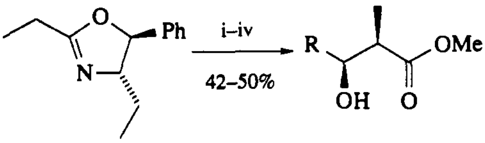

**(61c)** **(67)**

i, 9-BBN-OTf; ii, RCHO; iii, $H_3O^+$, Δ; iv, $CH_2N_2$

Scheme 25

The oxazolines (**68**) and (**69**) are useful synthetic intermediates for the preparation of α,β-unsaturated oxazolines (**70**; Scheme 26),[50] but the phosphonate-derived reagent (**69**) gives higher yields (80–93% *vs.* 37–65%) of (**70**) with higher (*E*):(*Z*) ratios (100:1 *vs.* 80:20 to 100:1). The subsequent nucleophilic addition of organolithium reagents to the chiral oxazolines (**70**) followed by hydrolysis of the intermediate adducts furnishes 3-substituted alkanoic acids (**71**) in >90% enantiomeric excess. By simply reversing the order of the introduction of the alkyl groups, the enantiomers of (**71**) can also be obtained. The high optical yields obtained by this process more than compensate for the modest chemical efficiency (overall

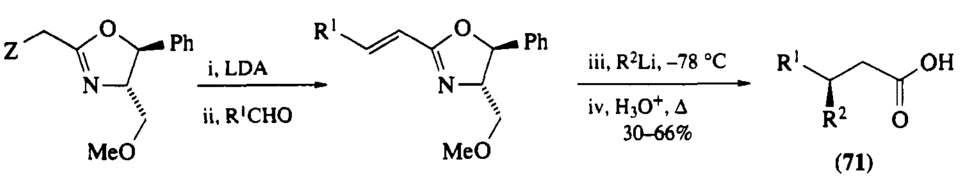

**(71)**

**(68)** Z = H

**(69)** Z = $(Pr^iO)_2P(O)$

**(70)** $R^1$ = Me, Et, Ph; $R^2$ = Et, $Bu^n$, Ph

Scheme 26

yields 30–66%). Lower yields are generally observed in the 1,4-addition to (**70**) whenever $R^1$ is alkyl, because of competing deprotonation of the allylic hydrogen of the starting material.

The nucleophilic addition of anions derived from the enantiomerically pure 2-methyloxazoline (**73**) to the *N*-methoxycarbonylimines generated *in situ* from (**72**) provides adducts that may be readily converted into β-amino acid derivatives (**74**) in good overall chemical yield (40–65%) and 72–90% enantiomeric excess (Scheme 27).[51] This transformation has been featured as a key step in the enantioselective synthesis of carbapenem antibiotics.

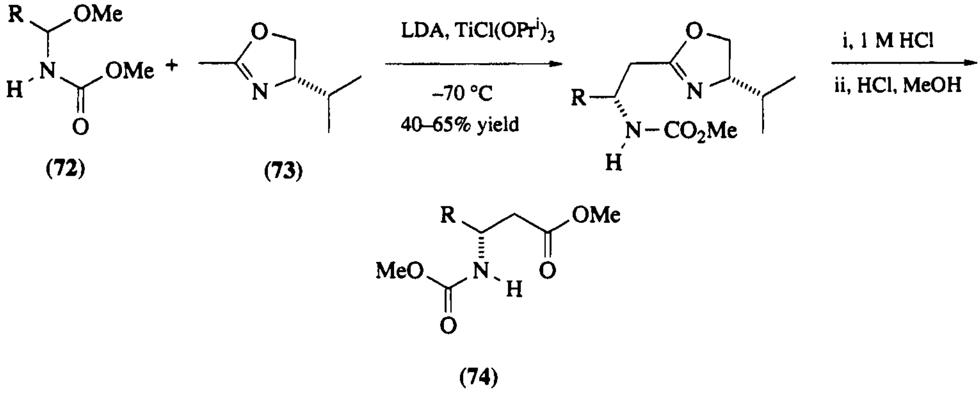

R = Pr$^i$, Me, $-CH_2CH=CH_2$, $-CH_2CH_2OSiMe_2Bu^t$

**Scheme 27**

The reaction of simple aliphatic aldehydes with the lithiated derivative of the enantiomerically pure arylsulfinylmethyloxazoline (**75**) provides adducts which can be converted by sequential desulfurization and hydrolysis into the β-hydroxy acids (**76**) in 60–85% overall chemical yield, but with only modest (26–53%) enantiomeric excess (Scheme 28).[52]

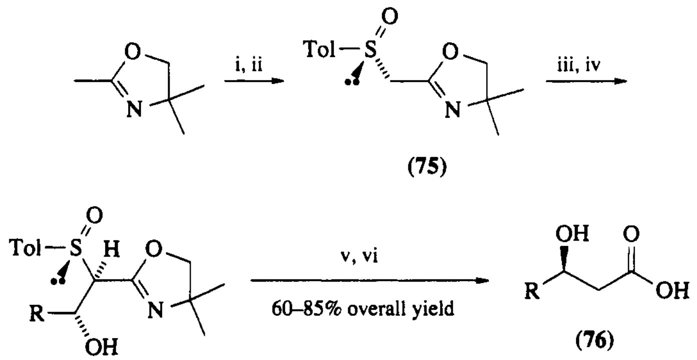

i, Bu$^n$Li; ii, (−)-(*S*)-menthyl-*p*-toluenesulfinate; iii, Bu$^n$Li, −90 °C; iv, RCHO;
v, Na–Hg (MeOH–aq. $NaH_2PO_4$); vi, aq. $H_2SO_4$

R = Me, Pr$^n$, Bu$^i$, Pr$^i$, Bu$^t$

**Scheme 28**

### 1.16.5.3 Metallated 2-Methyldihydro-1,3-oxazines

The anions derived from dihydro-1,3-oxazines have been nicely exploited as reagents to effect the two-carbon homologation of carbonyl compounds to provide α,β-unsaturated aldehydes, ketones and carboxylic acid derivatives.[53,54] For example, metallation of (**77**) followed by reaction with a wide variety of aldehydes and ketones provides adducts (**78**; Scheme 29). Although attempts to purify these adducts have been unsuccessful owing to facile retroaldolization, sequential reduction of (**78**) with sodium borohydride followed by hydrolysis of the intermediate tetrahydro-1,3-oxazines provides the α,β-unsaturated aldehydes (**79**) in generally good overall yields (Table 8).[53]

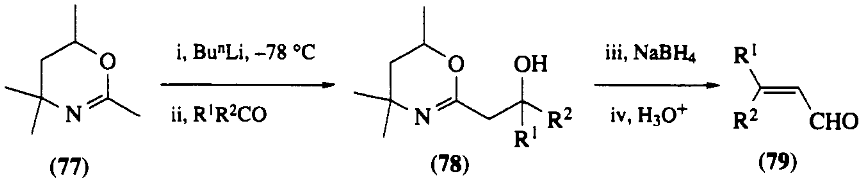

**Scheme 29**

**Table 8** Two-carbon Homologation of Carbonyl Compounds to α,β-Unsaturated Aldehydes Using Dihydro-1,3-oxazines (**77**) (Scheme 29)[53]

| *R*$^1$ | *R*$^2$ | *Overall yield of (79) (%)* |
|---|---|---|
| Me | Me | 50 |
| Et | Et | 62 |
| —(CH$_2$)$_4$— | | 63 |
| —(CH$_2$)$_5$— | | 53 |
| Ph | Ph | 60 |
| Ph | Me | 49[a] |
| Ph | H | 64 |
| Pr$^n$ | H | 61 |
| 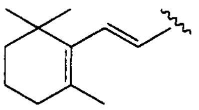 | Me | 28[b] |
| 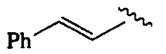 | H | 61 |

[a] *Cis:trans* ratio = 2:3. [b] Isolated in 54% yield as 2,4-DNPH derivative.

Although it is not possible to prepare α,β-unsaturated dihydro-1,3-oxazines (**84**) by mere dehydration of the adducts (**78**), these alkenes can be prepared in good overall yields by Wittig-type reactions of carbonyl compounds with the phosphorus-substituted dihydro-1,3-oxazines (**80**–**83**; Scheme 30).[54] Generally, better yields of (**84**) are obtained when aldehydes are employed as the reaction partners for the phosphoranes (**80**) and (**81**) and ketones are the reactants for the phosphonates (**82**) and (**83**). The α,β-unsaturated dihydrooxazines (**84**) are highly useful intermediates since they can be converted into α,β-unsaturated aldehydes (Scheme 30) as well as α,β-unsaturated ketones and carboxylic acids (Scheme 31).[54]

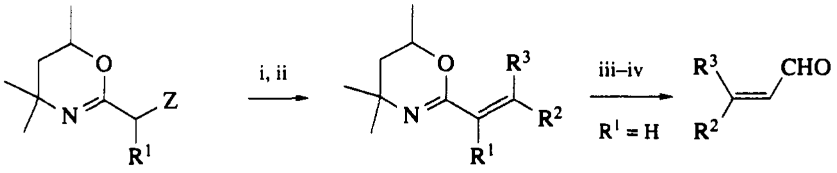

(**80**) R$^1$ = H; Z = $\overset{+}{P}Ph_3$

(**81**) R$^1$ = Me; Z = $\overset{+}{P}Ph_3$

(**82**) R$^1$ = H; Z = P(O)(OEt)$_2$

(**83**) R$^1$ = Me; Z = P(O)(OEt)$_2$

(**84**)

R$^2$ = Me, Et, n-C$_6$H$_{13}$, Ph, 2-Py;
R$^3$ = H, Me, Ph; R$^2$, R$^3$ = (CH$_2$)$_4$

i, KOBu$^t$ or NaH; ii, R$^2$R$^3$CO; iii, MeI or Me$_3$OBF$_4$; iv, NaBH$_4$; v, H$_3$O$^+$

**Scheme 30**

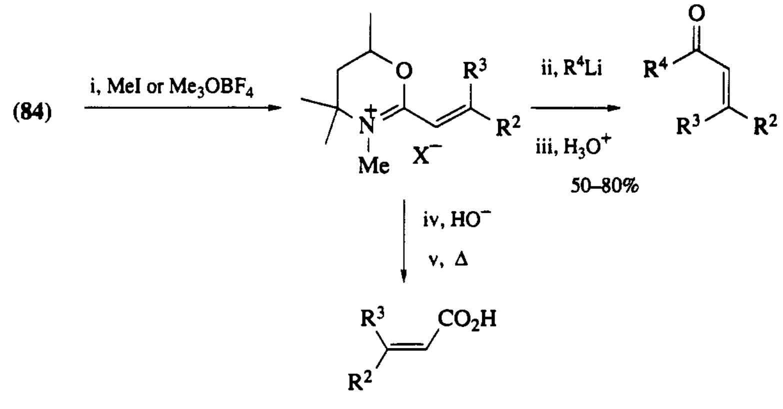

$R^2$ = Ph; $R^3$ = H
$R^2$ = $R^3$ = Me
$R^2$, $R^3$ = $(CH_2)_4$

Scheme 31

### 1.16.5.4 Metallated 2-Methylthiazolines

On a related front, the reactions of carbonyl compounds with metallated derivatives of 2-methylthiazoline furnish adducts (**85**). Although the initial nucleophilic addition occurs smoothly with a wide variety of aldehydes and ketones, the intermediate β-hydroxythiazolines (**85**) suffer thermal reversion upon attempted purification by distillation. Moreover, attempted cleavage of the corresponding β-hydroxythiazolidines, which are readily produced from (**85**) upon dissolving metal reduction (Al–Hg), leads to the formation of β-hydroxy aldehydes only in simple systems; numerous complications arising from dimerization, dehydration and retroaldol processes of the products usually intervene. Consequently it is necessary to protect the initial 1,2-adducts (**85**; $R^2$ = H) as the corresponding *O*-methoxymethyl ether derivatives (**86**; $R^2$ = MOM), which can then be easily transformed into protected β-hydroxy aldehydes by sequential reduction and hydrolysis (Scheme 32).[55]

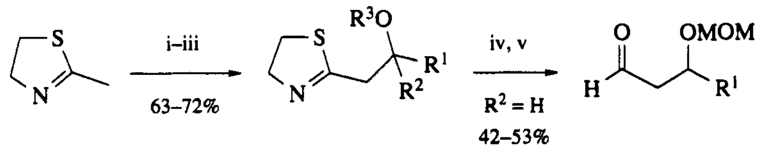

(**85**) $R^3$ = H
(**86**) $R^3$ = MOM

i, $Bu^nLi$, −78 °C; ii, $R^1R^2CO$; iii, $MeOCH_2Cl$; iv, Al–Hg; v, $HgCl_2$

Scheme 32

### 1.16.5.5 Metallated 2-Methylimidazolines

Similarly, the lithiated derivative of the 2-methylimidazoline (**87**) undergoes smooth addition to carbonyl compounds to provide the adducts (**88**; Scheme 33).[56] However, these substances undergo rapid reversal upon standing or heating; trapping with trimethylsilyl chloride is successful only when $R^1$ = $R^2$ = Me. On the other hand, the derived phosphonate reagent, which is prepared *in situ* from (**81**), reacts readily with aldehydes and ketones to give 2-alkenyl-2-imidazolines (**89**); subsequent reaction of these intermediates with alkyllithium reagents gives 2-alkylimidazolines (**90**), which may be converted into β-substituted carboxylic acids and ketones by known methods.[57]

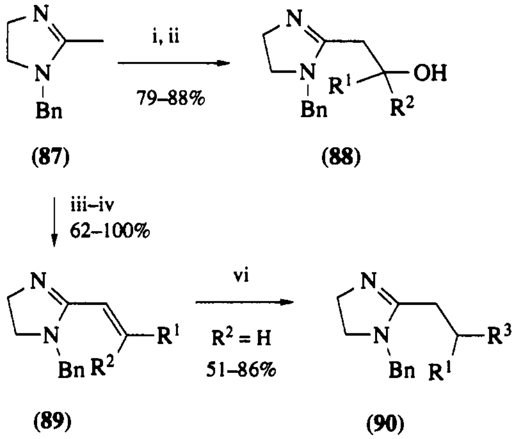

i, BuLi, –78 °C; ii, $R^1R^2CO$; iii, 2LDA; iv, $(EtO)_2P(O)Cl$; v, $R^1R^2CO$, r.t.; vi, $R^3Li$

Scheme 33

## 1.16.6. OTHER METALLATED AZOMETHINE DERIVATIVES

### 1.16.6.1 2-Methyl Azaheteroaromatic Compounds

Alkyl groups on the carbon atom adjacent to the ring nitrogen atom in nitrogen heteroaromatic compounds (**91**) are activated by the carbon–nitrogen double bond, and aldol-type reactions of such substances have been known for years. Indeed, the process outlined in Scheme 34 is one of the classical methods for preparing alkenyl-substituted heterocycles.[58–61] These condensations are typically catalyzed by $ZnCl_2$, $Ac_2O/HOAc$, KOMe, *etc.* Although the intermediate hydroxy compounds (**92**) may occasionally be isolated, dehydration normally proceeds spontaneously to give the alkenic products (**93**).

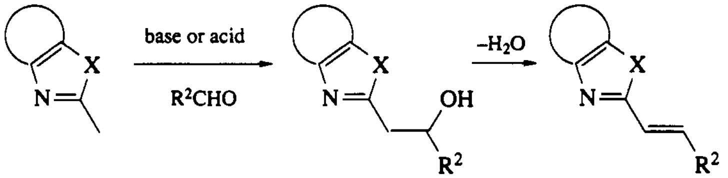

(**91**) (**92**) (**93**)

X = CH=CH, O, S, $NR^1$

Scheme 34

More recently, it has been discovered that metallation of the alkyl heterocycle with a strong base such as $Bu^nLi$ followed by reaction of the intermediate anion with carbonyl compounds leads to the formation in high yields of adducts, which may either be isolated or subjected to chemical transformations (Schemes 35–37).[62–65]

Because of the ease with which the heterocyclic ring of benzothiazoles may be further elaborated into carbonyl compounds and carboxylic acid derivatives,[63,66] there has been considerable interest in the reactions of metallated 2-alkylbenzothiazoles (**94**) with aldehydes and ketones to give the adducts (**95**) and (**96**) (Scheme 36). As may be seen upon examination of the representative results in Table 9, the yields in these reactions are generally excellent when either aldehydes or ketones are employed as the electrophilic partners. When lithium is the counterion, the diastereoselection in the addition of (**94**; $R^1$ = alkyl) is only modest, giving mixtures of the *erythro* and *threo* adducts (**95**) and (**96**), with the latter predominating. However, the corresponding organotin reagents add to aldehydes with significant *erythro* selectivity.[64] When allyl anions are the nucleophilic reaction partners, the α-adduct is typically formed under the conditions of kinetic control with *erythro*:*threo* diastereoselectivity varying from 2:1 to 9:1.[65] When these adducts are allowed to warm to room temperature prior to quenching, the γ-adducts are produced together with other by-products.[65]

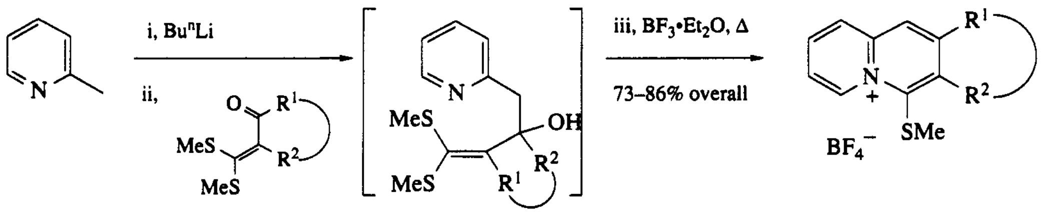
i, Bu$^n$Li
ii,
O
R$^1$
MeS
R$^2$
MeS
MeS
N
OH
MeS
R$^2$
R$^1$
iii, BF$_3$•Et$_2$O, Δ
73–86% overall
R$^1$
N
+
R$^2$
BF$_4^-$
SMe

Scheme 35[62]

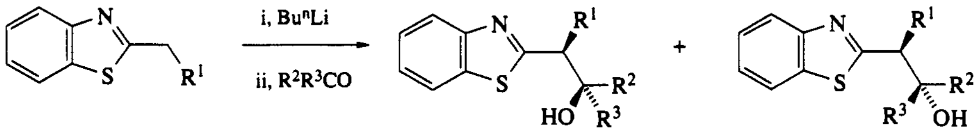
N
S
R$^1$
i, Bu$^n$Li
ii, R$^2$R$^3$CO
N
S
R$^1$
R$^2$
HO
R$^3$
+
N
S
R$^1$
R$^2$
R$^3$
OH

**(94)** **(95)** **(96)**

Scheme 36

Table 9 Reactions of Metallated 2-Alkylbenzothiazoles (**94**) with Carbonyl Compounds (Scheme 36)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *(95):(96)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| H | Et | H | — | 98 | 63 |
| H | Pr$^i$ | H | — | 98 | |
| H | Bu$^t$ | H | — | 99 | |
| H | Ph | H | — | 95 | |
| H | Ph | Me | — | 98 | |
| H | Bu$^n$ | Bu$^n$ | — | 96 | |
| H | CH═CH$_2$ | Me | — | 96 | |
| Me | Ph | H | 42:58$^a$ | 88 | 64 |
| Me | Ph | H | 19:81$^b$ | 90 | |
| Me | Ph | H | 72:28$^c$ | 58 | |
| Me | Pr$^i$ | H | 38:62$^a$ | 62 | |
| Et | Ph | H | 43:57$^a$ | 83 | |
| Et | Ph | H | 28:72$^b$ | 68 | |
| Et | Ph | H | 80:20$^c$ | 89 | |
| Et | *p*-ClC$_6$H$_4$ | H | >98$^c$ | 84 | |
| CH═CH$_2$ | Ph | H | 67:33$^d$ | 95 | 65 |
| CH═CH$_2$ | Me | H | *ca.* 100:0$^d$ | 95 | |

$^a$Bu$^n$Li used as base in lithiation step. $^b$LDA used as base in lithiation step. $^c$From 2-trichlorostannane derivative. $^d$α-Adduct obtained when reaction quenched at −78 °C.

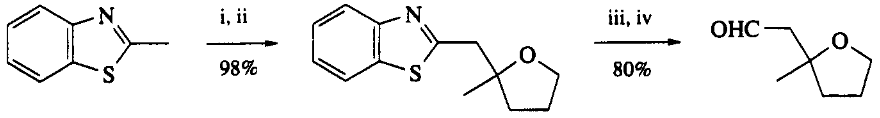
N
S
i, ii
98%
N
S
O
iii, iv
80%
OHC
O

i, Bu$^n$Li; ii, MeCO(CH$_2$)$_3$Cl; iii, MeI, DMF, Δ; iv, NaBH$_4$; v, AgNO$_3$ (aq), MeCN

Scheme 37[63]

Although the adducts (**95**) and (**96**) can be dehydrated under a variety of conditions to provide the corresponding alkenes, the alternative application of the Peterson[66] (Scheme 38) or the Wittig and Horner–Emmons[67–69] (Schemes 39–41) reactions to the preparation of alkenyl heterocycles may often be preferred because of the mildness of the reaction conditions required. For example, such an alkenation

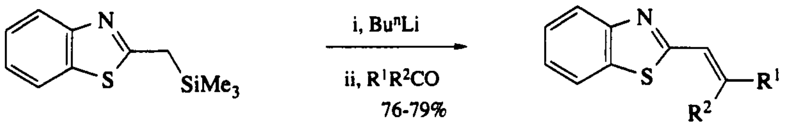
i, $Bu^nLi$
ii, $R^1R^2CO$
76-79%
SiMe₃
N
S
R¹
R²

**(97)**

$R^1$ = alkyl, aryl; $R^2$ = H, alkyl

Scheme 38

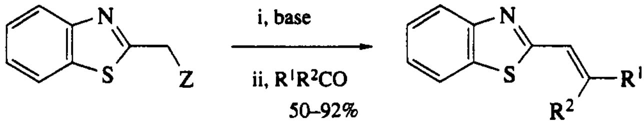
i, base
ii, $R^1R^2CO$
50–92%
N
S
Z
R¹
R²

$Z = Br, \overset{+}{P}Ph_3, P(O)(OEt)_2$

Scheme 39[67]

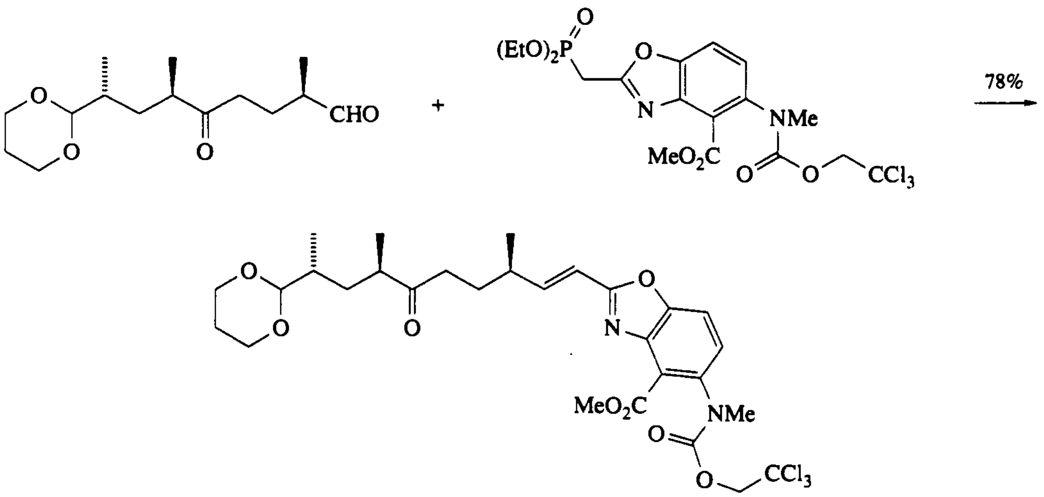
78%
CHO
+
(EtO)₂P
MeO₂C
NMe
CCl₃

Scheme 40

was recently used as the key step in the total synthesis of the polyether antibiotic calcimycin (Scheme 40).[68] The vinylbenzothiazoles (**97**) are useful synthetic intermediates since the thiazole ring may be unmasked to provide carbonyl derivatives by straightforward synthetic transformations.[66]

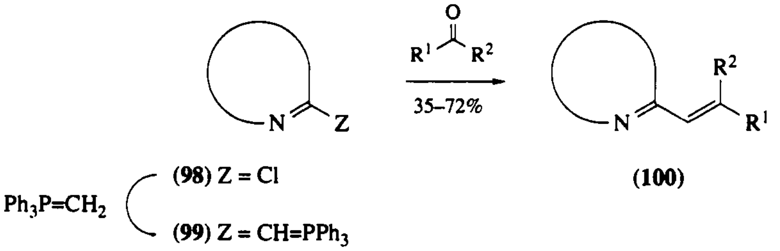
R¹
R²
35–72%
N
Z
Ph₃P=CH₂
(98) Z = Cl
(99) Z = CH=PPh₃
(100)

$R^1$ = Me, $Pr^n$, Ph; $R^2$ = H, Me, Ph

Scheme 41

A highly useful alternative entry to Wittig reagents of the general type (**99**) has been developed that features displacement of a chloride leaving group from the readily available chloroaza heterocycle (**98**) by an alkylidenephosphorane.[69] The intermediate phosphonium salt then undergoes transylidation with a second equivalent of the Wittig reagent to produce the heterocyclic ylide (**99**) which may be treated with a variety of carbonyl partners to furnish alkenyl-substituted heterocycles in good overall yields (Scheme 41). The process is applicable to a number of five- and six-membered systems as well as to monocyclic and polycyclic heterocyclic frameworks including pyridines, pyrazines, quinolines, isoquinolines, quinazolines, quinoxalines and benzoxazoles.

## 1.16.7 ADDITIONS OF METALLATED BIS-LACTIM ETHERS OF 2,5-DIKETOPIPERAZINES

### 1.16.7.1 Asymmetric Synthesis of Amino Acids

Over the past decade Schöllkopf and coworkers have worked toward the development of a general procedure for the synthesis of optically active, nonproteinogenic amino acids. The strategy underlying the approach is based upon the observation that metallated derivatives of bislactim ethers of 2,5-diketopiperazines, such as (**102**), undergo reactions with electrophiles at C-3 with a high degree of stereoselectivity from the face of the delocalized anion opposite to the isopropyl group at C-6.[70–79] This has proven to be a highly useful synthetic method for the asymmetric synthesis of amino acids. During the course of these investigations, Schöllkopf has demonstrated that carbonyl compounds admirably serve as electrophilic partners in reactions with (**102**) to give the adducts (**103**; Scheme 42), and some representative results are collected in Table 10.

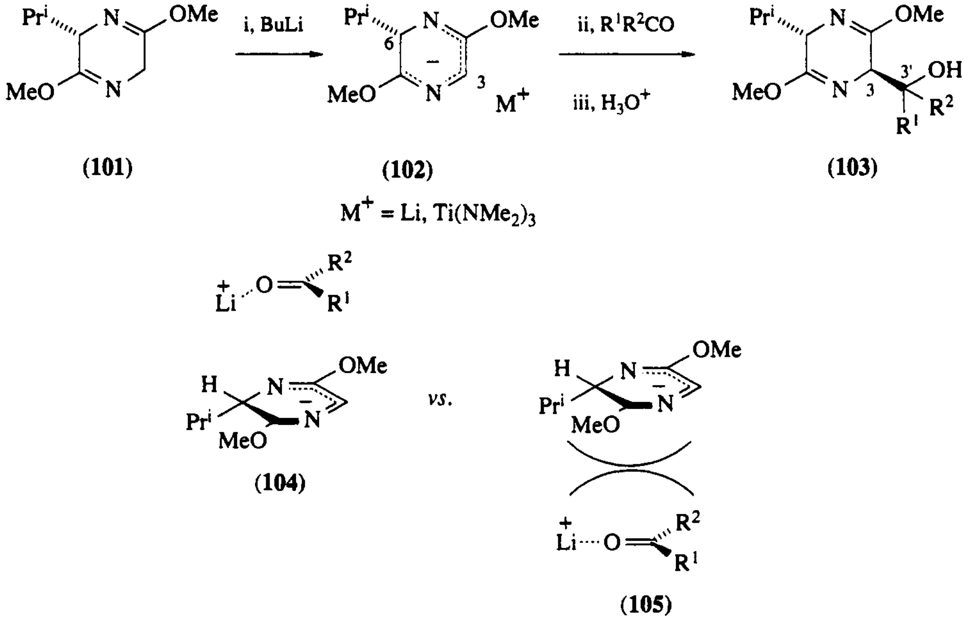

M$^+$ = Li, Ti(NMe$_2$)$_3$

Scheme 42

The diastereoselection at C-3 of (**103**) is uniformly high, generally exceeding 98%. The extent of asymmetric induction at this center does not depend very much upon the size of the alkyl groups R$^1$ and R$^2$. Clearly these groups must not play a decisive role in the transition state, and the primary factor determining the stereochemical course of these reactions would seem to involve the interactions between the isopropyl group at C-6 of the piperazine ring and the carbonyl oxygen in the two possible transition states (**104**) and (**105**). The stereoselectivity at C-3′ is generally somewhat less. However, it has been recently observed that the titanium derivative of the anion (**102**; M = Ti(NMe$_2$)$_3$) adds to aldehydes with very high (>95%) diastereoselectivity at both C-3 and C-3′.[75] Presumably, the titanium enforces a tighter transition state, which then results in increased diastereoselection in the addition.

**Table 10** Diastereoselective Reactions of Metallated Piperazines (**102**) with Aldehydes and Ketones (Scheme 42)

| *R*[1] | *R*[2] | *de (C-3) (%)* | *de (C-3') (%)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| Me | Me | >95 | | 98 | 71 |
| Ph | Me | >95 | 38 | 91 | |
| H | H | 80 | | | |
| Ph | H | 86 | 4 | 97 | |
| $PhCH_2$ | H | 89 | 66 | 77 | |
| $Bu^t$ | H | 92 | 56 | 96 | |
| $Pr^i$ | H | 94 | 70 | 96 | |
| Me | H | 85 | 60 | 95 | |
| Me | H | 98[a] | 97[a] | 79 | 72 |
| 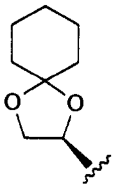 | H | 66 | 5 | 69 | 73 |
| | | 95[a] | 87[a] | 73 | |
| $CH_2SiMe_2Bu^t$ | H | >95 | 58 | 76 | 74 |
| $CH(Me)SiMe_2Bu^t$ | H | >95 | 0 | 80 | |
| $C(Me)_2SiMe_2Bu^t$ | H | >95 | 25 | 70 | |
| 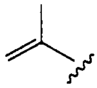 | H | 94 | 51 | | 75 |
| | | 96[a] | >98[a] | 85 | |
| 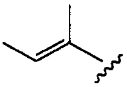 | H | 99[a] | 99[a] | 82 | |
| 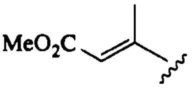 | H | 96[a] | 95[a] | 80 | |

[a] Lithium anion was treated with $TiCl(NMe_2)_3$ prior to reaction with the aldehyde.

Of particular synthetic importance are the subsequent transformations of the initially formed adducts (**103**) and analogs thereof. For example, hydrolysis of (**106**) provides the β-hydroxy-α-amino acid ester (**107**) together with Val-OMe (Scheme 43).[76] On the other hand, dehydration of (**108**) with thionyl chloride in the presence of 2,6-lutidine furnishes a mixture (4:1) of (**109**) and (**110**); hydrolysis of the former led to the unsaturated amino acid (**111**; Scheme 44).[71] α-Alkenylglycine methyl esters may be also prepared from the silyl derivatives (**112**; Scheme 45).[74] An alternative route to α-alkenylglycines features the addition of the metallated derivative of (**101**) to thioketones followed by *S*-methylation to provide adducts (**113**), which undergo elimination of methanethiol upon reaction with Raney nickel (Scheme 46).[74]

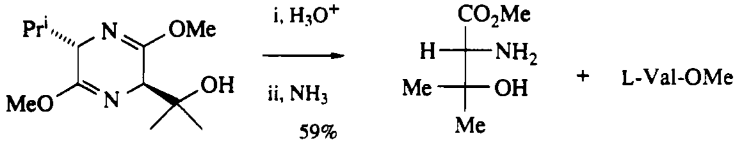

(**106**) (**107**)

**Scheme 43**

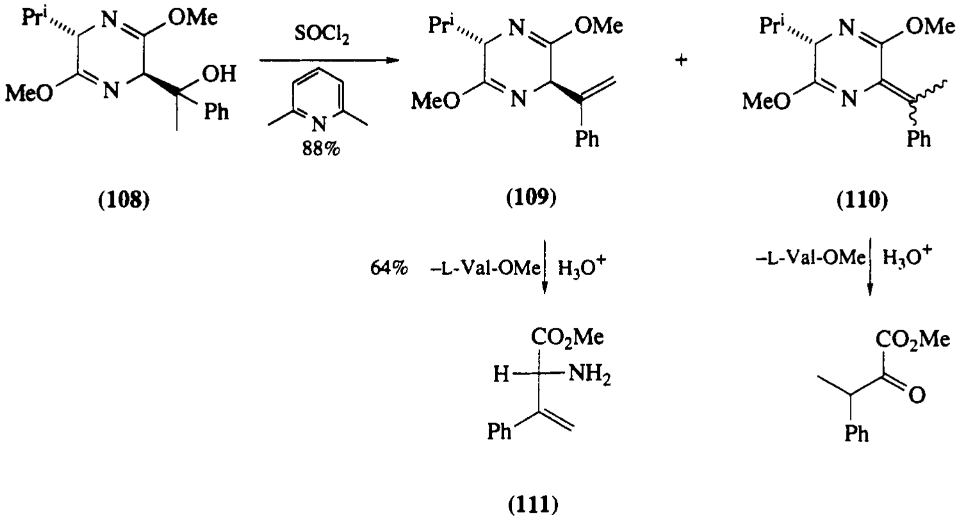
SOCl₂
88%
+
(108)
(109)
(110)
64% –L-Val-OMe H₃O⁺
–L-Val-OMe H₃O⁺
(111)

Scheme 44

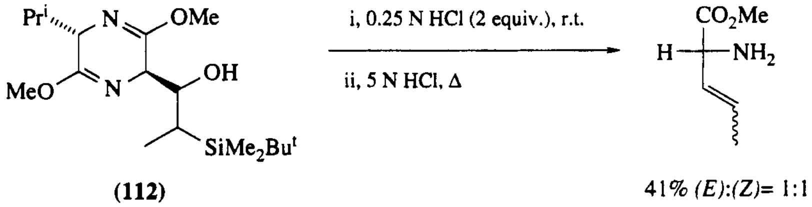
i, 0.25 N HCl (2 equiv.), r.t.
ii, 5 N HCl, Δ
(112)
41% (E):(Z)= 1:1

Scheme 45

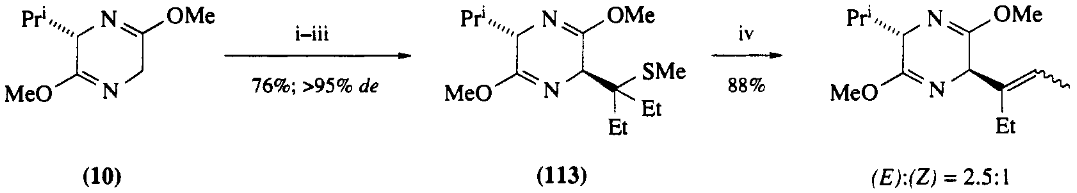
i–iii
76%; >95% de
iv
88%
(10)
(113)
(E):(Z) = 2.5:1

i, $Bu^nLi$; ii, EtC(S)Et; iii, MeI; iv, Raney Ni, EtOH, Δ

Scheme 46

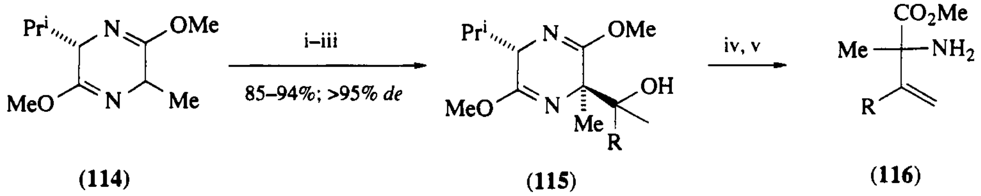
i–iii
85–94%; >95% de
iv, v
(114)
(115)
(116)

R = H, Me, Ph

i, $Bu^nLi$; ii, MeCOR; iii, $H^+$, iv, $SOCl_2$, Py; v, $H_3O^+$

Scheme 47

When the bislactim ether of the diketopiperazine (**114**) is metallated with $Bu^nLi$, deprotonation occurs exclusively α to the methyl substituent to provide an anion that undergoes highly selective reaction with aldehydes and ketones to generate adducts of the general type (**115**). As before, these adducts undergo dehydration to form α-methyl-α-alkenylglycines (**116**; Scheme 47),[78] but attempted hydrolysis of these adducts gives a mixture of products because of preferential retroaldol reactions.

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# 1.17

# Hydrazone Anions

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## 1.17.1 INTRODUCTION

Carbanions derived from hydrazones are primarily used as equivalents of carbanions derived from ketones and aldehydes. Reactions that ultimately lead to electrophilically substituted carbonyl derivatives through hydrazone anions proceed through four separate steps. First, the hydrazone has to be prepared from the starting carbonyl compound. In most cases, this requires a simple, facile condensation reaction between a hydrazine derivative and a ketone or aldehyde. Second, the neutral hydrazone has to be converted into a nucleophile; typically this involves deprotonation with a strong base. Both regiochemical and stereochemical considerations affect this step. Third, the nucleophilic anion so formed undergoes electrophilic substitution. Various electrophiles can be used; the most common are $sp^3$-hybridized carbon electrophiles (*e.g.* alkyl halides) and $sp^2$-hybridized carbon electrophiles (*e.g.* carbonyl compounds). This chapter will concentrate on the latter reactions, introducing alkylations only when appropriate for discussions of regiochemistry and stereochemistry in anion generation. Finally, the product hydrazones produced in these electrophilic substitution reactions have to be converted back into carbonyl compounds, as hydrazones are rarely if ever the desired final product. In a few instances, one or both nitrogens of the hydrazone can be used for heterocycle formation. In such instances, the last step then becomes a more efficient convergent step in an overall synthetic strategy.

Since hydrazone anion chemistry is complementary to more conventional deprotonation–electrophilic substitutions effected with carbonyl derivatives such as ketones and aldehydes, and since hydrazone chemistry involves two additional synthetic operations, the use of hydrazones has to have some additional advantages. Compensating for the additional synthetic effort required to prepare and hydrolyze the hydrazone derivatives is the greater synthetic utility of these intermediates. The reactivity of the intermediate azaallyl anions, the control over stereochemistry of the electrophilic substitution step afforded by the nitrogen substituent, and the considerable control of regiochemistry which can be attained using hydrazones, make them especially useful.

## 1.17.2 PREPARATION OF HYDRAZONES FROM ALDEHYDES AND KETONES

Formation of *N*,*N*-dialkylhydrazones from ketones and aldehydes is generally a facile reaction. In the case of most aldehydes, all that is required is stirring of the unsymmetrical *N*,*N*-dialkylhydrazine with the aldehyde in the presence of a drying agent. In some cases, these reactions can be carried out at room temperature. Ketones react similarly but can require more vigorous conditions. In the case of less-reactive carbonyl substrates, acid catalysts like *p*-toluenesulfonic acid or azeotropic distillation are commonly used to promote hydrazone formation. Formation of the aldehyde and ketone dimethylhydrazones and of the chiral hydrazone in equations (1)–(4) are examples of typical procedures.[1–4] Monosubstituted hydrazones such as (**6**) are prepared in a similar manner (equation 5).[5] These reactions often proceed in near-quantitative yield.

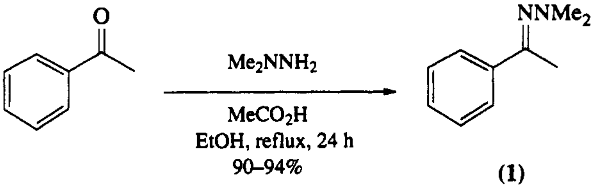
O
$Me_2NNH_2$
$MeCO_2H$
EtOH, reflux, 24 h
90–94%
$NNMe_2$

(**1**) (1)

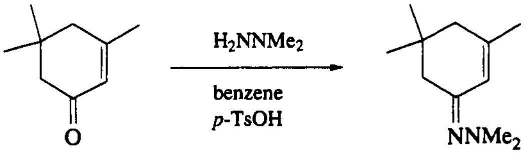
O
$H_2NNMe_2$
benzene
*p*-TsOH
$NNMe_2$

(**2**) (2)

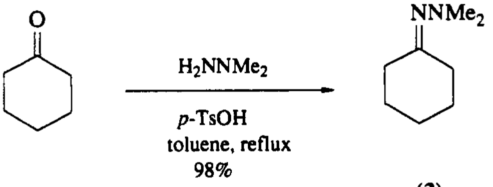
O
$H_2NNMe_2$
*p*-TsOH
toluene, reflux
98%
$NNMe_2$

(**3**) (3)

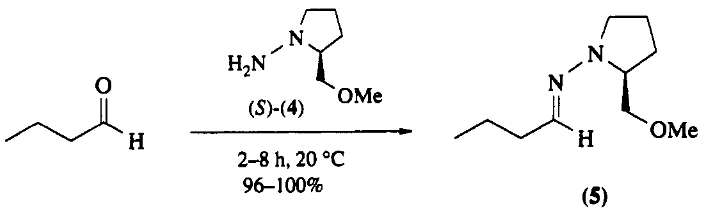
O
H
$H_2N$
N
OMe
(*S*)-(**4**)
2–8 h, 20 °C
96–100%
N
N
H
OMe

(**5**) (4)

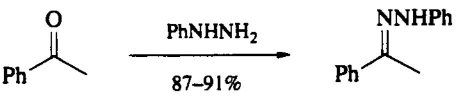
O
Ph
$PhNHNH_2$
87–91%
NNHPh
Ph

(**6**) (5)

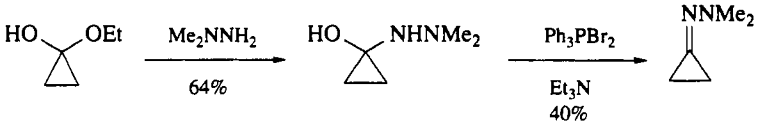

(7) (8) (6)

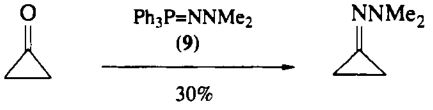

(8) (7)

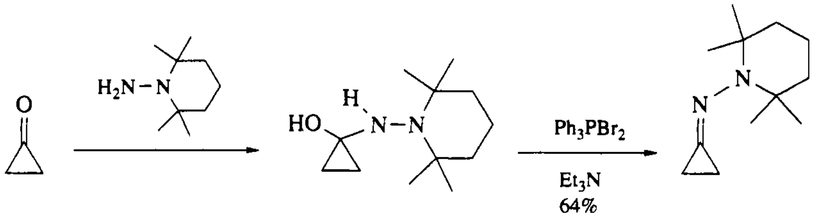

(10) (8)

Cyclopropanone *N*,*N*-dialkylhydrazones such as (**8**) and (**10**) are examples of *N*,*N*-dialkylhydrazones that are formed with some difficulty,[6] as the high reactivity of cyclopropanone makes its use problematic. However, the *N*,*N*-dimethylhydrazone (**8**) can be prepared using one of two routes starting either with the ethyl acetal of cyclopropanone or cyclopropanone itself. Starting with the ethylacetal, the initial product is a hemiaminal (**7**; equation 6). This intermediate which normally could be converted to the hydrazone by acid catalysis instead undergoes ring opening with acid. However, dehydration to yield the hydrazone is still possible using triphenylphosphine dibromide. An interesting alternative route to the *N*,*N*-dimethylhydrazone (**8**) uses cyclopropanone and the nitrogen ylide (**9**; equation 7).[7] These procedures are also effective in preparation of the still more hindered *N*,*N*-dialkylhydrazone (**10**; equation 8).

In some cases, *N*,*N*-dimethylhydrazones (or other dialkylhydrazones) can be most easily prepared from simpler *N*,*N*-dimethylhydrazones by alkylation. Such reactions can be especially useful in controlling regiochemistry or stereochemistry at positions α to the carbonyl carbon. For example, Yamashita has emphasized the desirability of using acetone dimethylhydrazone as a precursor of unsymmetrical ketone dimethylhydrazones.[8] This strategy has been used successfully in various syntheses including Schreiber's synthesis of an ionomycin fragment precursor (**13**; equation 9) and a recent synthesis of (−)-gloeosporone.[9,10] Isotopically labeled hydrazones, *e.g.* (**14**; equation 10), are also conveniently available in this same manner.[11,12] Other examples using this strategy to prepare hydrazones of relatively unavailable ketones, that can then be used in addition reactions to $sp^2$-hybridized electrophiles, are included in some of the syntheses discussed below. Finally, α-functionalized aldehyde and ketone hydrazones can also be prepared *via* an intermediate azaallyllithium reagent (as an alternative to synthesis from the car-

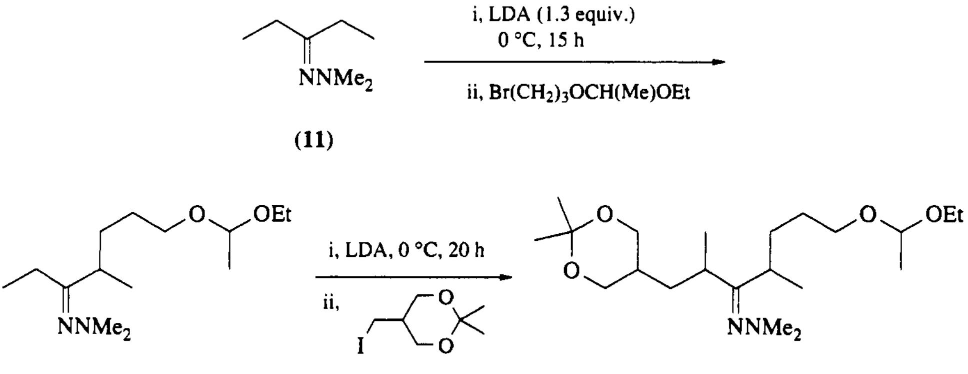

(11)

(12) (13) (9)

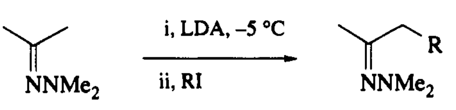

(10)

**(14a)** R = $^{13}CH_3$

**(14b)** R = $C^2H_3$

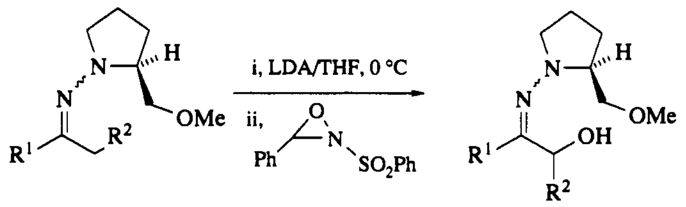

(11)

$R^1$ = H, Me, Ph;

$R^2$ = Me, Ph, $C_6H_{13}$, $PhCH_2$

**(15)**

bonyl compound). This is illustrated in equation (11) by the asymmetric synthesis of α-hydroxy ketone and aldehyde hydrazones (**15**) by oxidation of a chiral hydrazone-derived azaallyllithium reagent.[13] Yields in equation (11) range from 60 to 85%. An additional advantage of this synthesis, like alkylation of similar chiral hydrazones, is that a new stereocenter is produced with very high enantioselectivity (*ee* > 93% in most cases).

## 1.17.3 FORMATION OF AZAALLYL METAL REAGENTS FROM HYDRAZONES

Once formed, dialkylhydrazones can be converted into nucleophilic anions using a number of strong bases. In one of the earliest examples of this chemistry, Stork and Benaim deprotonated α,β-unsaturated ketone dimethylhydrazones such as (**2**) with sodium hydride in THF in the presence of 10% HMPA.[2] A second α,β-unsaturated *N*,*N*-dimethylhydrazone derived from $\Delta^4$-cholestenone was lithiated using *n*-butyllithium. In both cases, the deprotonation occurred regioselectively to yield the linearly conjugated anion (*e.g.* **16**). The final product in these cases was a new α,β-unsaturated carbonyl compound in which overall replacement of the α-vinyl proton by an alkyl group had occurred. Isomerization of the double bond back into conjugation presumably occurred during hydrazone hydrolysis (equation 12).

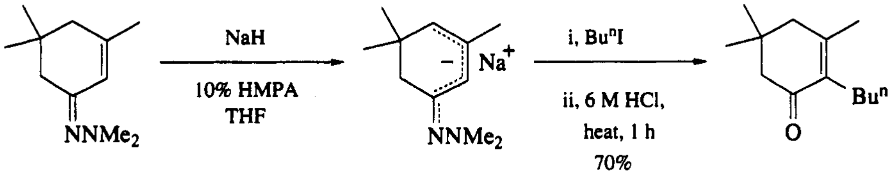

(12)

**(2)** **(16)**

Formation of nucleophilic carbanions from *N*,*N*-dialkylhydrazones is more often accomplished using LDA or alkyllithium reagents including both $Bu^nLi$ and $Bu^tLi$.[14,15] The intermediate azaallyllithium reagents so formed are sometimes soluble in THF, the solvent most commonly used. In other cases such as with simple aldehyde dimethylhydrazones, the intermediate azaallyllithium reagents are insoluble unless a cosolvent like HMPA is added. Formation of dianions from monosubstituted hydrazones such as tosylhydrazones is accomplished most commonly through the use of $Bu^nLi$.[16] In each case, the azaallyllithium reagents generated are not isolated but are used immediately in synthesis.

Potassium diisopropylamide (KDA) has been advocated as an alternative to alkyllithium reagents and LDA as a means to form anions from *N*,*N*-dimethylhydrazones.[17] The KDA for this purpose is prepared most conveniently *in situ* from $Bu^nLi$, $Bu^tOK$ and diisopropylamine. The principal advantage of KDA over lithium reagents is reportedly that its use produces anions from any hydrazone and generates them more rapidly.

Potassium salts of hydrazones are also available by other procedures. Potassium amide has been used to generate potassium salts of monoaryl ketone hydrazones.[18] The reactive intermediate generated in these cases is a dianion. Highly dispersed forms of potassium have also been reported to generate potassium salts from *N,N*-dimethylhydrazones at –60 °C.[19] The use of $K/Al_2O_3$ in metalation of aldehyde hydrazone anions produces modest yields of alkylated products in THF suspension. In hexane suspension, side reactions believed to include nitrile formation lead to lower synthetic yields of hydrazone products.

Potassium and sodium salts of hydrazone anions in which a second methoxycarbonyl or nitrile group stabilizes the anion have been prepared by metalation with potassium hydride and sodium hexamethyldisilazane, respectively.[20] Use of these bases affords clean solutions suitable for NMR structural studies. Other azaallyl metal derivatives of hydrazones, including copper(I) and magnesium derivatives, have been used in synthesis and are discussed below. These reagents are generally prepared from an azaallyllithium reagent by transmetalation with copper(I) iodide or with magnesium bromide.[21,22] Transmetalation starting with a lithium salt of a cyclohexanone dimethylhydrazone and chlorotitanium triisopropoxide, bromotitanium tris(diethylamine) or titanium tetraisopropoxide has been similarly used by Reetz to make azaallyltitanium reagents from hydrazones.[23]

Silylation of azaallyllithium reagents derived from hydrazones unlike silylation of enolates seems to occur mainly on carbon. While chiral (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) aldehyde hydrazones (*cf.* equation 4) alkylate to a greater extent on nitrogen to form an azaallylsilyl reagent, ketones give predominant *C*-silylation. In the case of chiral ketone hydrazones derived from (*S*)-(**4**), α-silylated ketone hydrazones are produced in these reactions with consistently high *ee* (≥96%).[24]

Side reactions can occur in formation of hydrazone anions and limit the thermal stability of these anions. Most commonly these side reactions involve addition at the carbonyl carbon or elimination of a dialkylamide anion and nitrile formation.[25] Normant has described both problems and has suggested that nitrile formation also occurs slowly in cases where HMPA has been added to azaallyllithium reagents derived from *N,N*-dimethylhydrazones. These problems are exacerbated in the case of aldehyde hydrazones when there is branching at the carbon α or β to the carbonyl carbon.

## 1.17.4 STRUCTURES OF AZAALLYL METAL REAGENTS DERIVED FROM HYDRAZONES

The structure of the intermediate azaallyllithium reagents typically used in hydrazone anion chemistry has been a subject of considerable speculation. Interest in the structure of these intermediates parallels related studies on other delocalized anions and has been sparked by advances in asymmetric syntheses that employ enolates and related species. Collum and Clardy have recently reported two X-ray structures of lithiated cyclohexanone dimethylhydrazone and lithiated 2-methoxycarbonylcyclohexanone dimethylhydrazone.[26,27] In the case of the simple lithiated cyclohexanone dimethylhydrazone (**17**), the azaallyllithium reagent was in the form of a polymer with an extended array of dimethylcyclohexanone anions and lithium in alternating $\eta^1$- and $\eta^4$-coordination. The $\eta^4$-coordination in this structure is unusual and serves to differentiate it from enolate structures described by others.[28] The C—C—N—N group coordinated to lithium is planar and the lithium is 1.64 Å from this plane. This same lithium is coordinated to the central anionic nitrogen of another C—C—N—N group in an $\eta^1$-fashion with a Li—N distance of 0.5 Å. The two C—C—N—N planes of alternating lithiated cyclohexanone dimethylhydrazones were disposed at an angle of 111° to one another. Collum and Clardy speculated that the $\eta^4$-coordination in this azaallyllithium reagent could be responsible both for the pronounced stereoselectivity in electrophilic alkylations and for the known preference for *syn* structures in these anions (*vide infra*).

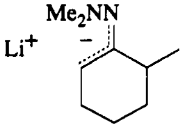

(**17**)

In the case of (**17**), Collum and Clardy were able to obtain some osmometric data about aggregation in solution. They found that (**17**) in THF had an apparent molecular weight of 515, which corresponds to a 3.5 degree of aggregation. Based on these results, and the independence of axial alkylation stereoselectivity with respect to the concentration of (**17**) or the nature of the metal ion and solvent, Collum and Clardy suggested that solvent free tetramers of (**17**) may be the predominant species in solution. Studies with models also suggested that cyclic tetramers with alternating $\eta^4$–$\eta^1$ Li–CCNN coordination are both plausible and that such an arrangement would have two sterically different faces for each anionic cyclohexanone dimethylhydrazone subunit.

Collum and Clardy have also described the X-ray crystal structure of (**18**).[27] Unlike (**17**), no C–Li interactions were present in the chelated structure (**18**). No definitive evidence of C–Li interactions was obtained with [$^6$Li]-labeled (**18**) either. Solution molecular weight studies with (**18**) showed that extensive dissociation occurred at high dilution. This dissociation could be due to dimer–monomer exchange (which would have to be fast to account for the temperature invariant NMR spectra) or could be due to solvent dissociation from (**18**). NMR studies with 3.0 equiv. of added THF in toluene-$d_8$ showed that exchange of free and coordinated THF was fast at all temperatures.

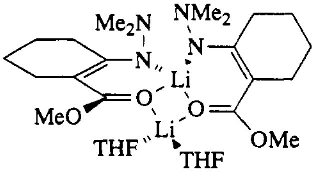

(**18**)

More recently, Enders' group has described the X-ray crystal structure of the chiral hydrazone anion (**19**).[29] This internally chelated chiral hydrazone crystallizes as the bis(tetrahydrofuran) monomeric adduct. The lithium in this structure is 17° out of the C—C—N plane and is predominantly associated with the anionic nitrogen (and the chelating methoxy group). Interactions with the $=CH_2$ carbon are minimal. Earlier studies by Bauer and Seebach had examined the association behavior of (**19**). They found that in THF this azaallyllithium reagent was monomeric.[30] While there is no $\eta^3$- or $\eta^4$-interaction with the azaallyl anion, the lithium in this structure is tetracoordinate and prochiral. Preferential coordination of lithium to an electrophile such as a carbonyl oxygen with selective replacement of one THF moiety could be involved in some of the asymmetric aldol reactions discussed below.

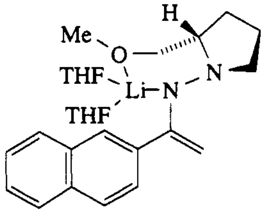

(**19**)

It is clear from these X-ray structures of dimethylhydrazone anions and from related studies carried out by a variety of other groups on related enolate and enolate-like species[28,30,31] that a variety of metal coordination and aggregation phenomena can be expected for these organometallic reagents. Simple monomeric species that do not include metal interactions are implausible and are not likely to be the species responsible for the chemistry seen with these reagents. However, identifying the major species present *in solution* and the major species of kinetic importance remains an especially challenging problem, both in enolate chemistry generally and for reactions of lithium dimethylhydrazone anions in particular. For example, detailed studies by Wanat and Collum have suggested that aggregation of cyclohexanone dimethylhydrazone lithio anions does occur, but that dissociation to a monomer may precede rate-determining alkylation.[32] In more recent work, Collum has carried out $^6$Li and $^{23}$Na NMR

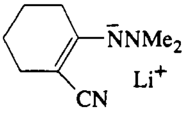

(**20**)

$[\,(\text{hydrazone}^-)_2\ \text{M}^+\,]\ \text{M}^+$ cryptand

(**21**)

spectroscopic studies of (**17**), (**18**) and (**20**).[20] In these studies, ion triplets of general structure (**21**) were observed. Based on these results, it is equally possible that aggregated azaallyllithium reagents derived from hydrazones alkylate *via* ion triplets. Distinguishing between such ion triplets and the aforementioned tetramer–monomer dissociation in determining the true intermediates in alkylations would be difficult and was not attempted. In the case of stabilized hydrazone anions, the effects of cryptate lithium complexing agents suggest that alkylation stereoselectivities are not necessarily dependent on the metal counterion present. Extensions of these studies to the potentially more complicated case of additions to $sp^2$-hybridized electrophiles have not been reported.

These X-ray structures and detailed multinuclear studies of hydrazone anions are the most recent structural details available about these anions. While they are likely to prove invaluable in understanding the mechanistic basis of hydrazone selectivity in electrophilic substitution reactions, other questions of stereochemistry and regiochemistry in anion generation are of more immediate synthetic interest. Both questions have received considerable study within the last 10 years.

## 1.17.5 REGIOCHEMICAL AND STEREOCHEMICAL CONTROL IN HYDRAZONE DEPROTONATION

Regiochemical questions in hydrazone anion formation from ketone hydrazones center on two issues. First, if the starting hydrazone has two different types of acidic α-hydrogens, selectivity in proton removal is an important consideration if a synthetic sequence is to produce a single product. In the case of hydrazones, deprotonation regioselectivity of this sort is typically both high and predictable. For example, in the case of (**22**)–(**25**) the deprotonation occurs selectively at the circled carbon to produce alkylated products. In general, deprotonation occurs at the less-substituted carbon unless there is an anion stabilizing group present.[3,33] Hydrazones (**24**) and (**25**) are examples of this latter case.

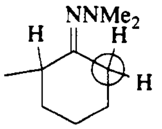

(**22**)

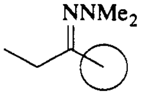

(**23**)

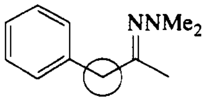

(**24**)

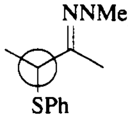

(**25**)

A second question concerns the regio- or stereo-selectivity of deprotonation of ketone hydrazones that contain two α-$CH_2$ groups. This question has been studied for several sorts of compounds. In an early report of the use of hydrazone anions,[2] Stork described deprotonation of α,β-unsaturated hydrazones such as (**2**). In this case, deprotonation could have occurred at either the α-$CH_2$ or the $CH_2$ group adjacent to the conjugated double bond. Based on the results of the alkylation shown in equation (12), the linearly conjugated anion evidently formed. It was not established whether these regioselective γ-deprotonations of α,β-unsaturated ketone hydrazones were the result of kinetic or thermodynamic factors, or whether the additional methyl groups on the ring affected the deprotonation regiochemistry. In subsequent work, the dimethylhydrazone of cyclohexenone and a chiral hydrazone of cyclohexenone were deprotonated regiospecifically so as to form anions (**26**) and (**27**).[3,34] However, regioselectivity like that noted by Stork was again seen in deprotonation and in electrophilic substitution to prepare (**28**; equation 13), a precursor in the total synthesis of picrotoxinin.[35] Based on these results it is evident that the substituents on the

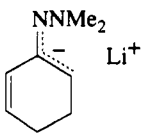

(**26**)

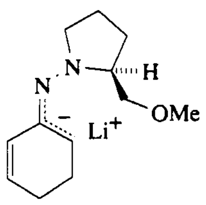

(**27**)

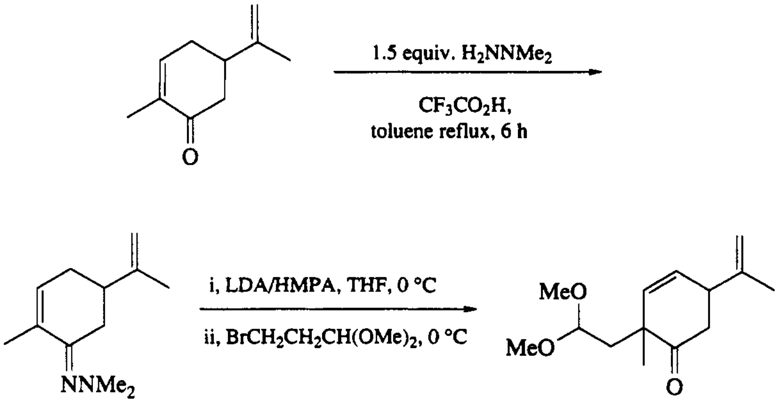

(13)

(28)

cyclohexyl ring can significantly influence deprotonation regioselectivity of cyclic α,β-unsaturated ketones.

The kinetic selectivity of deprotonation in ketone dimethylhydrazones containing two —$CH_2$ groups differing only in their stereochemistry relative to the nitrogen —$NMe_2$ group is low. While there was some initial confusion in the literature, NMR studies using diastereomerically pure $^{13}CH_3$-labeled 3-pentanone dimethylhydrazone showed that deprotonation occurred at both —$CH_2$ groups.[11] Earlier reports had suggested that deprotonation occurred *anti* to the dimethylamino group.[36] A subsequent study further established that this lack of preference for deprotonation *syn* or *anti* to the dimethylamino group was not due to equilibration of the starting isomerically pure hydrazone through proton transfer reactions as suggested by others.[12,37] This resistance of hydrazones to proton transfer between a neutral ketone or aldehyde hydrazone and an azaallyllithium reagent is such that the half life of such equilibrations is of the order of 2 to >8 h. In contrast, deprotonations are typically complete within 30 min. In fact, this resistance to proton transfer (and subsequent formation of disubstituted products) is one of the major advantages of hydrazones in alkylation reactions.

Studies of deprotonation regioselectivity in mono-*N*-substituted ketone hydrazones have mainly dealt with the regiochemistry of ketone tosylhydrazone deprotonations. Deprotonation of these tosylhydrazones, as well as deprotonation of mono-*N*-alkyl- or mono-*N*-aryl-hydrazones, proceeds predominantly *syn* to the starting —NHR group.[16] This regioselectivity is plausibly similar to that reported for oxime and imine deprotonations.[38,39]

The stereochemistry of the intermediate azaallyl anions formed in ketone and aldehyde hydrazone deprotonation has been studied and is of interest, especially in the context of asymmetric synthesis. The first study of this sort demonstrated that the azaallyllithium reagents derived from hydrazones did not undergo rapid isomerization about the carbon–carbon bond of the C—C—N anion.[40,41] This study further established that the stereoselectivity of this deprotonation reaction could be varied, with an $(E)_{C-C}$ anion formed with LDA in THF, while a $(Z)_{C-C}$ anion formed using LDA in THF in the presence of 2 equiv. of HMPA. Subsequent $^1H$ NMR studies have shown that SAMP aldehyde hydrazones deprotonate with LDA to yield $(E)_{C-C},(Z)_{C-N}$ anions and that deprotonation stereoselectivity is also altered by the addition of 2 equiv. of HMPA to become predominantly $(Z)_{C-C},(E)_{C-N}$.[42] This latter study showed that use of these stereoisomeric intermediate azaallyllithium reagents produced enantiomeric products in alkylation reactions. Several groups have speculated that the same factors responsible for stereoselective enolate formation[43] are responsible for stereoselective hydrazone anion formation, though the explanations offered to explain HMPA's effects with ketones and esters cannot be valid in the case of aldehyde *N*,*N*-dialkylhydrazones.[40]

The stereospecificity of deprotonation of ketone *N*,*N*-dialkylhydrazones is less defined because of the problem of making unambiguous stereochemical assignments. However, based on the observed stereoselectivity of electrophilic substitutions on these anions, on $^{13}C$ chemical shift data and on analogies to enolate chemistry, it appears that $(E)_{C-C}$ stereochemistry again predominates, at least with LDA deprotonations.[44]

## 1.17.6 1,2-ADDITIONS TO ALDEHYDES AND KETONES

Dialkylhydrazone lithio anions readily react with aldehydes and ketones to generate aldol-like products. Depending on the procedures used, β-hydroxycarbonyl products or α,β-unsaturated carbonyls can be obtained. The regioselective control over dimethylhydrazone anion formation and the stereoselectivity afforded these anions by use of chiral nitrogen substituents are advantages of this alternative strategy for aldol reactions.

Corey, Enders and Bock were among the first to describe the utility of lithium dimethylhydrazone anions for crossed aldol reactions.[45] In the reaction shown in equation (14), an azaallyllithium reagent derived from an aldehyde dimethylhydrazone was first silylated with trimethylsilyl chloride to yield a silyl aldehyde dimethylhydrazone. Subsequent lithiation using lithium diethylamide at –20 °C for 1 h generated the silylated azaallyllithium reagent (**29**). Subsequent addition of one equivalent of an aldehyde or ketone at –78 °C and warming to –20 °C then yielded the product α,β-unsaturated aldehyde dimethylhydrazone in yields of 85–95%. Hydrolysis produced the unsaturated aldehyde in 75% overall yield.

The 1,2-addition of simple azaallyllithium reagents derived from ketone and aldehyde dimethylhydrazones to aldehydes and ketones was also first described by Corey and Enders.[14,21] Regioselective deprotonation of 2-pentanone dimethylhydrazone with $Bu^nLi$ followed by addition of an aldehyde or

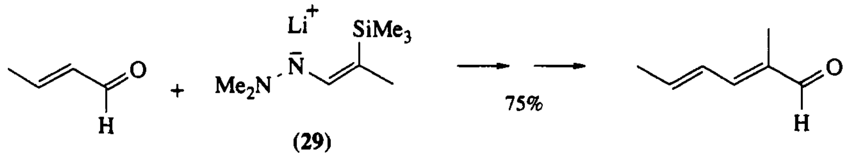
O
H
+
$Li^+$
$SiMe_3$
$Me_2N$
N
(29)
75%
O
H

(14)

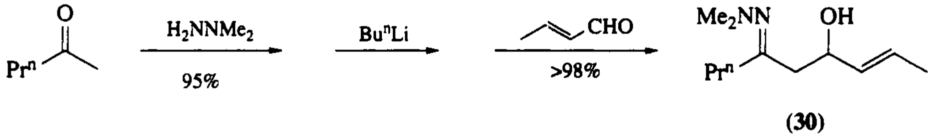
O
$Pr^n$
$H_2NNMe_2$
95%
$Bu^nLi$
CHO
>98%
$Me_2NN$
OH
$Pr^n$
(30)

(15)

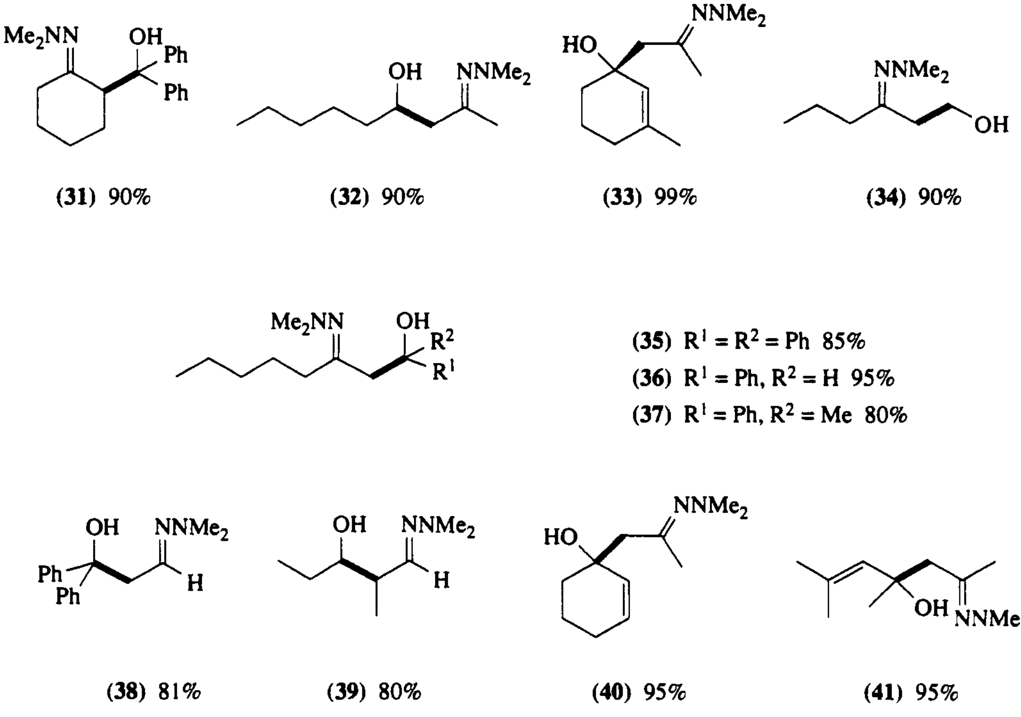
$Me_2NN$
OH
Ph
Ph
(31) 90%
OH
$NNMe_2$
(32) 90%
HO
$NNMe_2$
(33) 99%
$NNMe_2$
OH
(34) 90%
$Me_2NN$
OH
$R^2$
$R^1$
OH
$NNMe_2$
Ph
Ph
H
(38) 81%
OH
$NNMe_2$
H
(39) 80%
HO
$NNMe_2$
(40) 95%
OH
$NNMe_2$
(41) 95%

(35) $R^1 = R^2 = Ph$ 85%
(36) $R^1 = Ph, R^2 = H$ 95%
(37) $R^1 = Ph, R^2 = Me$ 80%

**Scheme 1**

ketone yielded a β-hydroxy dimethylhydrazone in high yield. Oxidative cleavage of the dimethylhydrazone group using sodium periodate in methanol at pH 7 yielded the final product (equation 15). Examples of β-hydroxycarbonyl compounds prepared in this manner, together with yields, are shown in Scheme 1, with the carbon–carbon bond formed by the aldol addition highlighted. In each case, hydrolysis to the carbonyl derivative was effected without dehydration.

The azadienyllithium reagent derived from the *N*,*N*-dimethylhydrazone of crotonaldehyde when allowed to react with simple ketones yielded α,β-unsaturated-δ-hydroxy-*N*,*N*-dimethylhydrazone products, resulting from 1,2-addition at the γ-carbon. This is in contrast to alkylation which occurs at the α-carbon (*cf.* equation 13) and to the reactivity of (**42**; equation 16) with cyclohexenone which led to mixtures of Michael adducts arising from electrophilic substitution at both the α- and γ-carbons.[21]

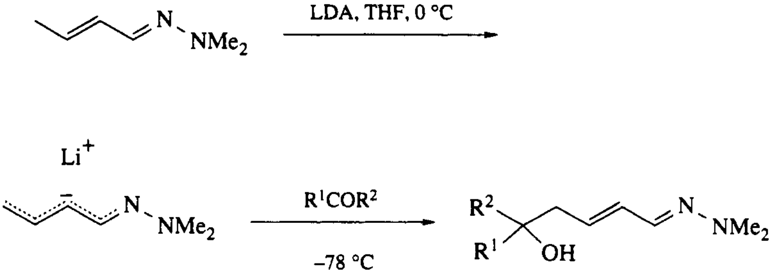

(16)

(**42**)

(**43a**) $R^1 = R^2 = Me$ (90%)

(**43b**) $R^1 = R^2 = -(CH_2)_5-$ (40%)

(**43c**) $R^1 = Bu^t, R^2 = Me$ (30%)

Aldol-type reactions are also feasible using trianions derived from simple hydrazones.[46] Thus, the hydrazone from acetophenone can be generated using Bu$^n$Li and added to benzophenone or 4-methylbenzophenone to yield an aldol product in modest yield. However, it does not appear that this method has any special advantages over the procedures using *N*,*N*-dimethylhydrazones described by Corey and Enders.

*Syn* selective aldol additions of titanated aldehyde hydrazones and ketone hydrazones have been reported by Reetz.[23] The observed *syn* selectivity parallels the *syn* selectivity seen in titanium ketone enolates,[47] and the intermediate titanium aldehyde hydrazone derivatives were seen to have (*E*)$_{C—C}$ geometry (equation 17).

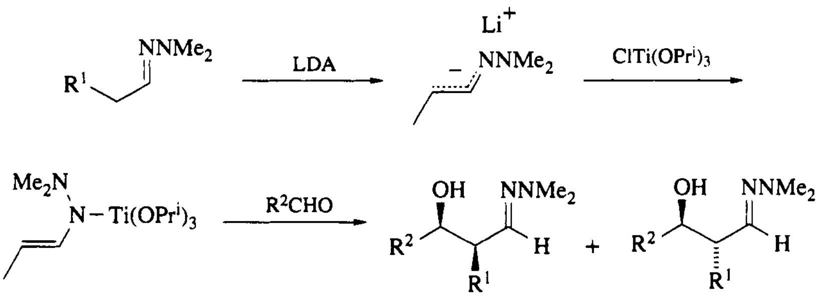

*syn* *anti*

(17)

| *R$^1$* | *R$^2$* | *syn*:*anti* |
|---|---|---|
| Me | Ph | 91:9 |
| Ph | *p*-NO$_2$C$_6$H$_4$ | 98:2 |
| Ph | Pr$^i$ | 98:2 |
| Pr$^i$ | Ph | 94:6 |
| Me | Me | 95:5 |
| Me | Bu$^t$ | 93:7 |

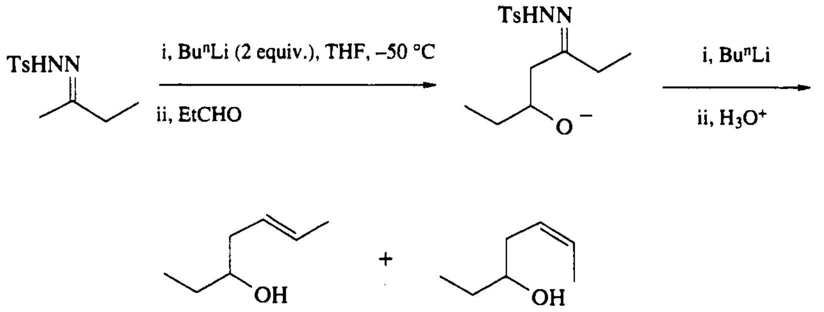
TsHNN
i, Bu^nLi (2 equiv.), THF, -50 °C
ii, EtCHO
TsHNN
O⁻
i, Bu^nLi
ii, H₃O⁺
+
OH
OH

(18)

Aldol reactions between dilithio tosylhydrazone dianions and aldehydes and ketones afford good yields of β-hydroxy tosylhydrazones.[16] However, attempts to regenerate the ketone group from the tosylhydrazone either led to no reaction (basic conditions) or retro-aldol reactions (acidic conditions). While this potentially regioselective route to aldol products *via* tosylhydrazones was frustrated, the β-hydroxy tosylhydrazones could be converted in good yield into homoallylic alcohols using the Shapiro reaction, thus making use of the intermediate aldol product in equation (18). Tosylhydrazone dianions also react readily with chloroformates to yield ethyl esters. Thus, using a procedure analogous to that in equation (18) the dianion formed from the tosylhydrazone of cyclopentanone can be trapped with ethyl chloroformate to yield 73% of 2-ethoxycarbonylcyclopentanone tosylhydrazone.

β-Hydroxy tosylhydrazones, which are the products of a conventional aldol reaction between a dilithiated tosylhydrazone reagent and an aldehyde, can also be prepared by alternative routes. For example, Stork and Ponaras have described a procedure whereby an epoxy ketone is converted into an epoxy hydrazone. Subsequent addition of an alkyl- or aryl-magnesium bromide followed by hydrolysis yields either an α-alkylated- or α-arylated-β-hydroxy ketone or an α,β-unsaturated ketone. Since the attack of the Grignard reagent on the epoxide occurs with inversion at the α-carbon, this reaction can be used to

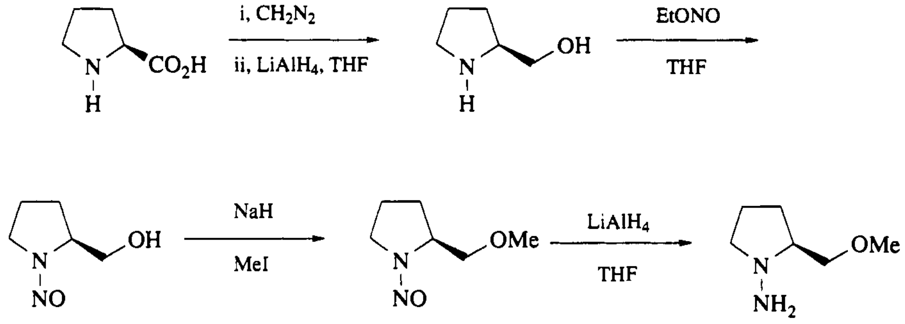
N
H
CO₂H
i, CH₂N₂
ii, LiAlH₄, THF
N
H
OH
EtONO
THF
N
NO
OH
NaH
MeI
N
NO
OMe
LiAlH₄
THF
N
NH₂
OMe

(*S*)-(4) SAMP

**Scheme 2**

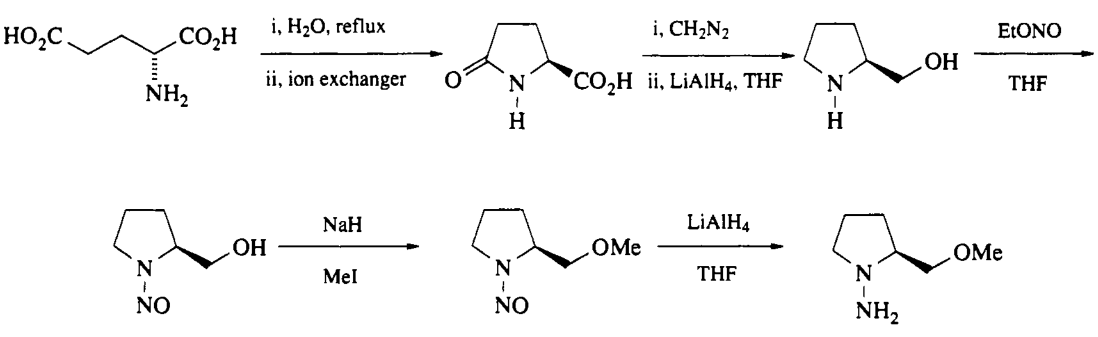
HO₂C
CO₂H
NH₂
i, H₂O, reflux
ii, ion exchanger
O
N
H
CO₂H
i, CH₂N₂
ii, LiAlH₄, THF
N
H
OH
EtONO
THF
N
NO
OH
NaH
MeI
N
NO
OMe
LiAlH₄
THF
N
NH₂
OMe

(*R*)-(4) RAMP

**Scheme 3**

prepare a single diastereomer of a β-hydroxy hydrazone.[48] Similar reactions can also be carried out with α,β-epoxy tosylhydrazones and organocopper reagents.[49]

An advantage of using azaallyllithium reagents derived from aldehyde and ketone hydrazones is the potential for asymmetric synthesis. Enders' group has provided many elegant demonstrations of the practicality of this approach.[50] Enders' work in this area has relied on the use of (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine as a replacement for *N*,*N*-dimethylhydrazine. This chiral auxiliary is available commercially and can be prepared in the (*S*)-form starting with proline or in the (*R*)-form starting with glutamic acid (Scheme 2 and Scheme 3). These two chiral auxiliaries are often referred to as SAMP and RAMP respectively. Hydrazone formation with either enantiomer of this hydrazine follows the general procedures discussed above. These chiral hydrazines can be recycled when the product hydrazones are cleaved oxidatively and the resulting SAMP nitrosoamine is recovered. Large scale synthesis of chiral hydrazines including analogs of (*S*)-(**4**) in which the —$CH_2OMe$ group is changed into more hindered groups such as —$CMe_2OMe$ have recently been discussed by Enders and coworkers.[51]

Initial applications of SAMP and RAMP hydrazones in regio- and enantio-specific aldol reactions were first reported by Enders' group.[52] In these initial studies, several methyl ketones were converted into SAMP hydrazones, deprotonated with $Bu^nLi$ and then allowed to react with various aldehydes and methyl ketones. The diastereomeric hydrazone products of these reactions were then cleaved to form β-ketols in good chemical yields and with enantiomeric excesses of 31–62%.

Enders used SAMP and RAMP hydrazones in enantioselective aldol reactions leading to an efficient enantioselective synthesis of (+)-(*S*)-[6]-gingerol (**46**), the major pungent constituent of ginger.[53] Using the scheme shown in equation (19), the chiral acetone hydrazone prepared using RAMP was deprotonated and alkylated. A second regiospecific deprotonation followed by addition of *n*-hexanal at –100 °C yielded a hydroxy hydrazone which was protected with trimethylsilyl chloride. Oxidative hydrolysis followed by hydrogenolysis of the benzylic protecting group yielded the product (*S*)-(**46**). Through the use of azaallyllithium reagents derived from acetone RAMP hydrazone, acetone SAMP hydrazone and acetone dimethylhydrazone, it was possible similarly to prepare samples of both enantiomers of (**46**) as well as of racemic (**46**).

Stereospecific aldol syntheses can also be accomplished using chiral α-sulfinylhydrazones such as (**47**).[54] These reagents are prepared from dimethylhydrazone anions using (–)-(*S*)-methyl *p*-toluenesulfinate as an electrophile according to equation (20). The enantiomeric excess of the chiral sulfoxide so prepared can be measured by $^1H$ NMR using chiral shift reagents. The absolute configuration at sulfur was assigned as shown based on the assumption that the nucleophilic substitution at sulfur proceeds with inversion of configuration. Hydrolysis of these hydrazones yielded known 2-oxoalkyl sulfoxides and con-

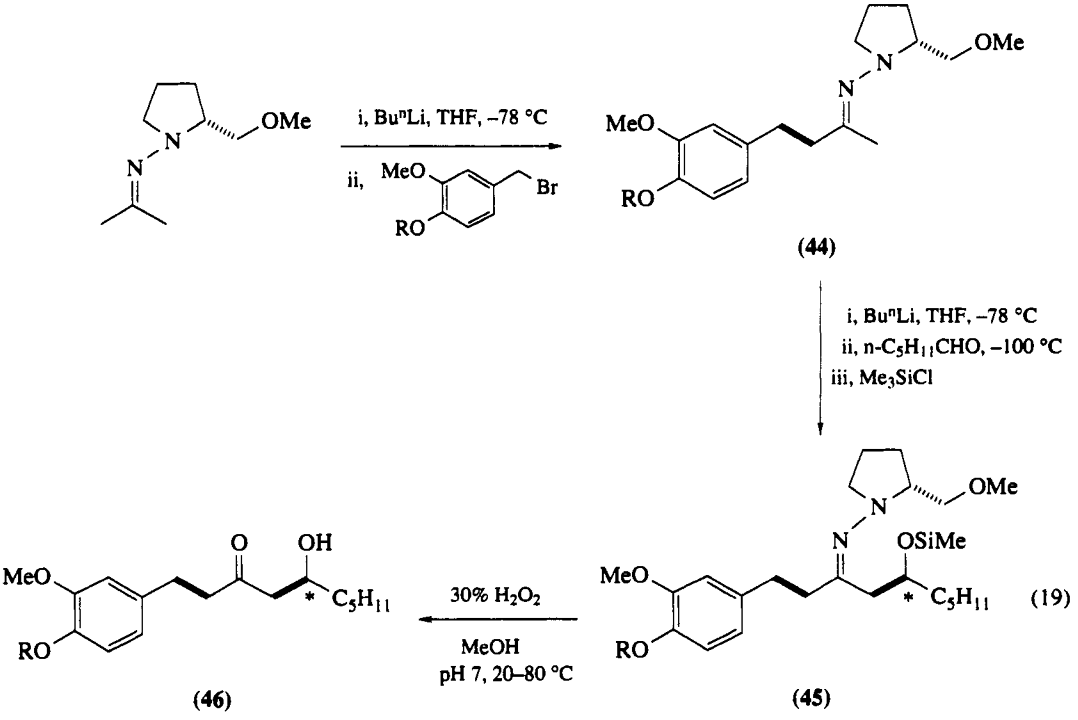

(**44**)

(**45**)

(**46**)

(19)

firmed the stereochemical assignments. Hydrolyses were, however, accompanied by some racemization and were unsuccessful in the case of aldehyde dimethylhydrazones. Unlike SAMP or RAMP hydrazones, the chirality of these hydrazones derives from the chirality at the attached sulfur atom.

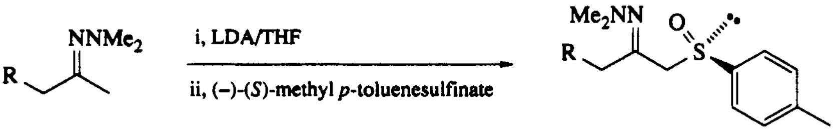
NNMe2
R
i, LDA/THF
ii, (–)-(S)-methyl p-toluenesulfinate
Me2NN
O
S
R

(47)

(20)

Chiral α-sulfinyl dimethylhydrazones form stabilized carbanions that can be used in enantioselective aldol reactions. A typical example is shown in equation (21).[55,56] Removal of the chiral sulfur auxiliary is accomplished by reductive desulfurization. Under these conditions recovery and reuse of the sulfur moiety is impossible. Synthetic and optical yields reported for these aldol reactions are modest in most cases. However, in a direct comparison to the SAMP/RAMP methodology, Annunziata has prepared (–)-(*R*)-[6]-gingerol in 60% *ee*.[57] Enders' prior synthesis had yielded this aldol product in 36% *ee*.[53]

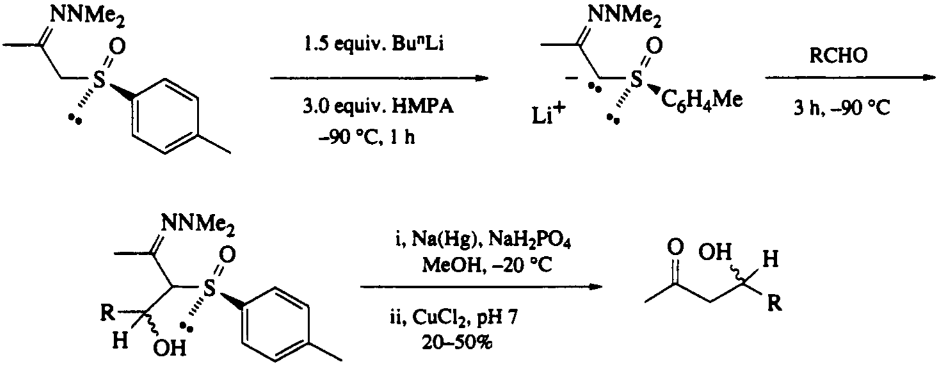
NNMe2
O
S
1.5 equiv. BunLi
3.0 equiv. HMPA
–90 °C, 1 h
NNMe2
O
S
Li+
C6H4Me
RCHO
3 h, –90 °C
NNMe2
O
S
R
H
OH
i, Na(Hg), NaH2PO4
MeOH, –20 °C
ii, CuCl2, pH 7
20–50%
O
OH
H
R

(48) (49)

(21)

The effect of metalation conditions and the conditions under which 1,2-addition of sulfinylhydrazones occurs on the overall stereoselectivity of processes like that in equation (21) have been studied.[56] Optimi-

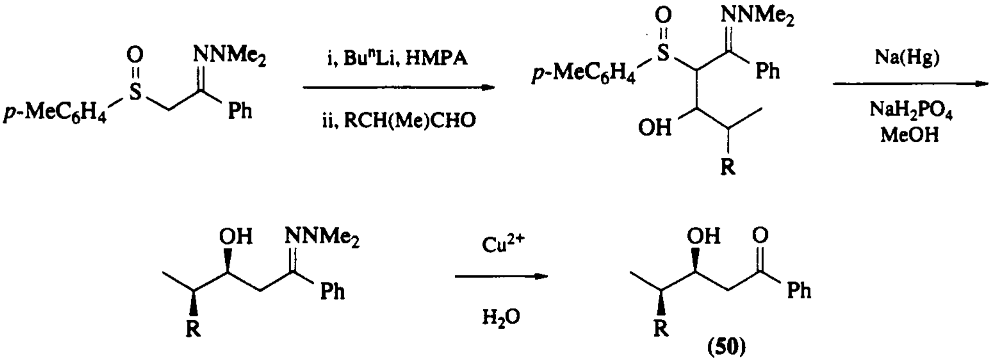
O
NNMe2
S
p-MeC6H4
Ph
i, BunLi, HMPA
ii, RCH(Me)CHO
O
NNMe2
p-MeC6H4
S
Ph
OH
R
Na(Hg)
NaH2PO4
MeOH
OH
NNMe2
Ph
R
Cu2+
H2O
OH
O
Ph
R

(50)

(22)

| *Ketol* | *Yield (%)* | *Diastereoselectivity (%)* | *Enantioselectivity (%)* |
|---|---|---|---|
| **(50a)** R = Et | 40 | 10 | ≥80 |
| **(50b)** R = $Pr^i$ | 40 | 50 | 60 |
| **(50c)** R = $Pr^i$ | 42 | 91 | 50 |
| **(50d)** R = $PhCH_2$ | 46 | 10 | ≥90 |
| **(50e)** R = $Me(CH_2)_4CH_2$ | 38 | 100 | 100 |

zation of these experimental variables produced enantiomeric excesses as high as 88% in one instance. However, the *ee* values were more generally in the range of 30–50%.

The reaction of anions derived from chiral α-sulfinyl hydrazones with chiral racemic aldehydes proceeds with both high diastereoselectivity and high enantioselectivity in certain cases.[58] The overall stereoselectivity of the reaction sequence in equation (22) was determined by HPLC and/or $^1H$ NMR analysis of the ratio of diastereomers and by the application of chiral shift reagents. The results seen both in equation (22) and with similar reactions employing α-alkyl- or α-aryl-α-alkoxy aldehydes show that the diastereoselectivity of these reactions is dependent on the size of the α-alkyl or α-aryl group. The enantioselectivity varied but again was highest with the most-hindered α-sulfinyl dimethylhydrazone, 2-phenylpropanal. Application of this chemistry led to a synthesis of manicone, (4*E*)-4,6-dimethyloct-4-en-3-one, an alarm pheromone of *Manica mutica* and *Manica bradleyi* in 11% *ee*.

While the configuration of the predominant stereoisomer formed in reactions of α-alkoxy aldehydes with these azaallyllithio anions was not determined, $^1H$ NMR analysis was successful at assigning the configuration of the ketols in equation (22). Based on coupling constants, the predominant isomer formed was the *syn* isomer.

## 1.17.7 1,2-ADDITIONS TO CARBOXYLIC ACID DERIVATIVES

In additions to aldehydes and ketones, carboxylic acids and carboxylic acid derivatives also react with hydrazone anions in synthetically useful ways. In analogy to the Claisen reaction of ketone enolates and carboxylic acid derivatives, lithium dimethylhydrazone ketone anions can be used as nucleophiles in reactions with acid chlorides (equations 23 and 24).[59] LDA at 0 °C could also be used in place of Bu$^n$Li in these metalations. The resulting lithium dimethylhydrazone anion then reacted in a regiospecific manner with an acid chloride to afford on hydrolysis a 1,3-diketone. Overall yields in these reactions with various methyl ketone dimethylhydrazones ranged from 53 to 60%. Yields with 2-methylcyclopentanone and 2- or 3-methylcyclohexanone dimethylhydrazones ranged from 67 to 83%. With the exception of (**53**), all these reactions yielded products with overall substitution at the less-substituted α-carbon. Hydrolysis of the product hydrazone in these reactions only worked with acidic methanol and was a limiting step in the overall reaction scheme. Alternative dimethylhydrazone hydrolyses using 30% hydrogen peroxide, sodium metaperiodate and copper(II) chloride were not successful. Similar acylations using anhydrides, isocyanates, nitrile and carbon disulfide were also reported to work. However, specific examples were not reported.

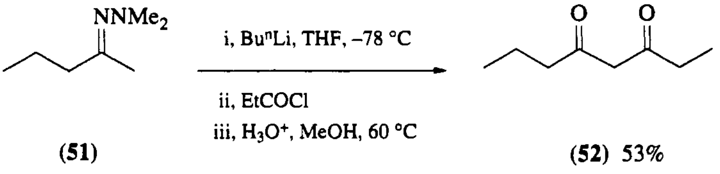

(23)

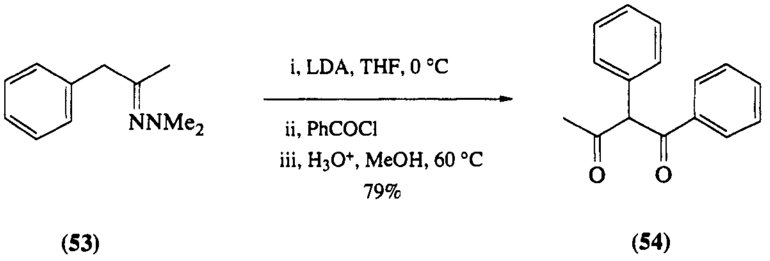

(24)

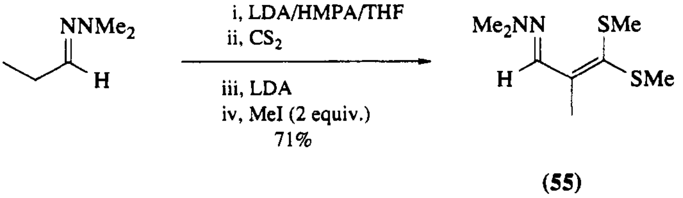

(25)

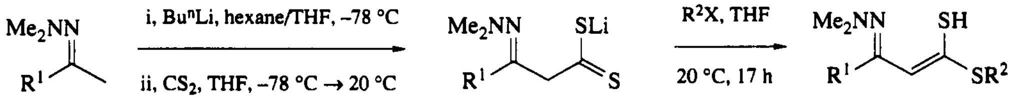

**(56)** **(57)**

(26)

R$^1$ = Me, Ph; R$^2$ = Me, Et, Pr$^n$ or PhCH$_2$

Conjugated ketene thioacetals have been successfully prepared starting with aldehyde dimethylhydrazones.[60] In these reactions, the first-formed azaallyllithium reagent was allowed to react with carbon disulfide to form an intermediate lithium 3-dimethylhydrazonoalkanedithiolate. A second deprotonation of this dithiolate with a second equivalent of LDA then generated a dianion that was successfully alkylated with two equivalents of methyl iodide to yield the ketene thioacetal (*e.g.* **55**; equation 25). This two step sequence avoided competing formation of a methyl dithiocarbamate by addition of LDA to carbon disulfide.

Examples of the reaction of carbon disulfide with lithium dimethylhydrazone anions derived from ketones were reported by Oliva and Delgado.[61] In these reactions, the initial lithium dimethylhydrazonoalkanedithioate (**56**) was not isolated but was instead alkylated to yield an alkyl dithiolate (**57**; equation 26). High yields of products were obtained using various alkyl iodides. Hydrolysis of the product hydrazone was not described.

## 1.17.8 1,4-CONJUGATE ADDITIONS TO α,β-UNSATURATED CARBONYL DERIVATIVES

Addition of lithium dimethylhydrazone anions in a Michael fashion to α,β-unsaturated carbonyl compounds can be used in a variety of ways in synthesis. In their original paper describing 1,2-carbonyl additions of azaallyllithium reagents derived from *N*,*N*-dimethylhydrazones, Corey and Enders described the use of organocopper derivatives of dimethylhydrazones for conjugate additions.[21] In this chemistry, an azaallyllithium reagent derived from the dimethylhydrazone of 2-methylcyclohexanone was transmetalated with 0.5 equiv. of copper iodide/isopropyl sulfide at –78 °C for 1 h and then allowed to react with methyl vinyl ketone at –30 °C with gradual warming to 0 °C over 12 h to yield a Michael adduct. Oxidative hydrolysis to cleave the dimethylhydrazone yielded the octalone precursor (**59**) in 90–95% yield (equation 27). In a like manner, the 1,5-dicarbonyl compounds (**60**)–(**62**) were prepared from azaallylcopper reagents prepared from hydrazones *via* azaallyllithium reagents.

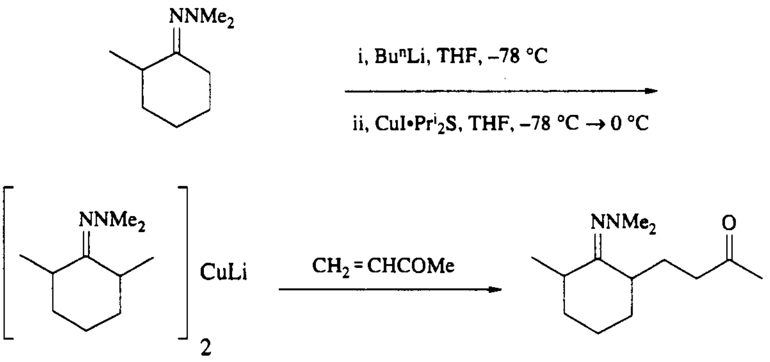

(27)

**(58)** **(59)**

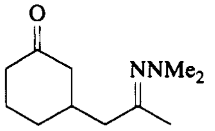

**(60)**

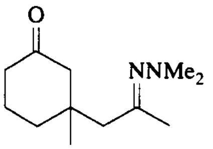

**(61)**

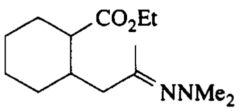

**(62)**

Homocuprates like (**58**) were used by Heathcock in the course of a total synthesis of lycopodine.[62] In this case, the cuprate derived from acetone dimethylhydrazone (**63**) was added to the cyano enone (**64**). In this example, the hydrazone-derived azaallylcuprate was about as effective as lithium dimethylallylcuprate addition followed by ozonolysis, and gave a lower overall yield than the Sakurai method using methallyltrimethylsilane and titanium tetrachloride. The product (**65**) was formed as a mixture of isomers (equation 28).

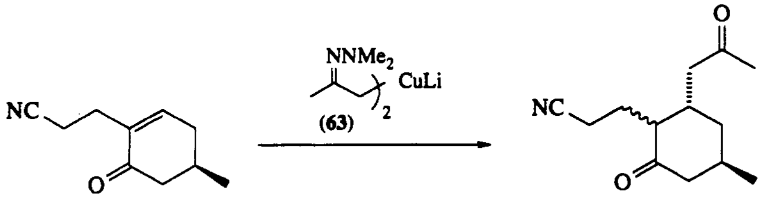

(**64**) (**65**)

(28)

Mixed cuprates derived from deprotonation and transmetalation of ketone dimethylhydrazones, using copper(I) thiophenoxide as the copper(I) source, are effective as enolate equivalents in 1,4-conjugate additions to α,β-unsaturated esters.[63] The mixed phenylthio cuprate was found to exhibit approximately the same selectivity and reactivity in these reactions as a similar homocuprate (**63**) prepared from the azaallyllithium reagents and copper(I) iodide (equation 29).

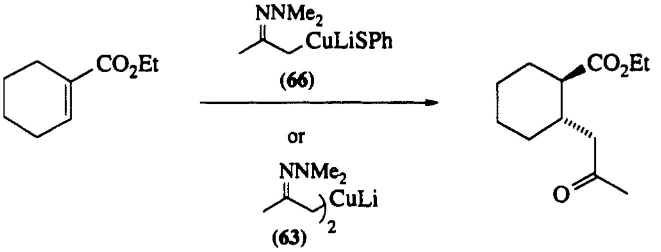

(29)

Regiospecific alkylation of dimethylhydrazone anions with the masked acrolein equivalent, 3-bromopropionaldehyde dimethyl acetal, has been used as an alternative to a conventional Michael reaction in Corey's total synthesis of picrotoxinin (*cf.* equation 13).[35] Azaallyllithium reagents derived from aldehyde and ketone hydrazones, unlike enolates, yield monoalkylation products with control of both regiochemistry and stereochemistry. In appropriate cases, alkylation followed by deprotection to form a dicarbonyl product can be a very effective synthetic strategy.

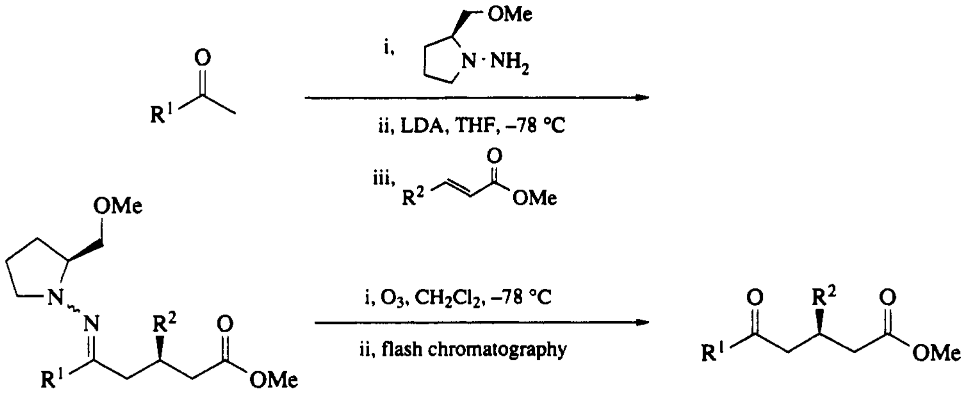

(**67**)

(30)

(**68**) 96–100% *ee*
45–62% yield

$R^1$ = Me, Et, $Pr^n$, $Pr^i$, n-$C_5H_{11}$, Ph; $R^2$ = Me, Ph

Asymmetric 1,4-conjugate additions can be carried out with SAMP and RAMP hydrazones without the need for added copper. This three-step reaction (equation 30) sequence yielded δ-keto esters in very high enantiomeric excesses ranging from 96 to 100%. Chemical yields ranged from 45 to 62%.[64]

Enders has used these asymmetric Michael additions as the key steps in the enantioselective synthesis of various esters and alcohols (**69–73**) which are chiral volatile ant pheromones. In these syntheses, asymmetric Michael additions of the lithio salt of the SAMP hydrazone of propanal to methyl 2-butenoate and methyl 2-pentenoate were used to establish the chiral centers. Subsequent hydrolysis and reduction of the aldehyde or carboxylic acid ester by conventional procedures afforded the pheromones.[65]

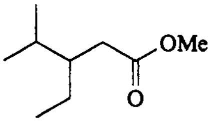

**(69)**

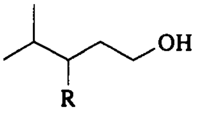

**(70)** R = Me
**(71)** R = Et

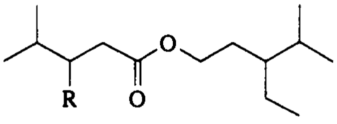

**(72)** R = Me
**(73)** R = Et

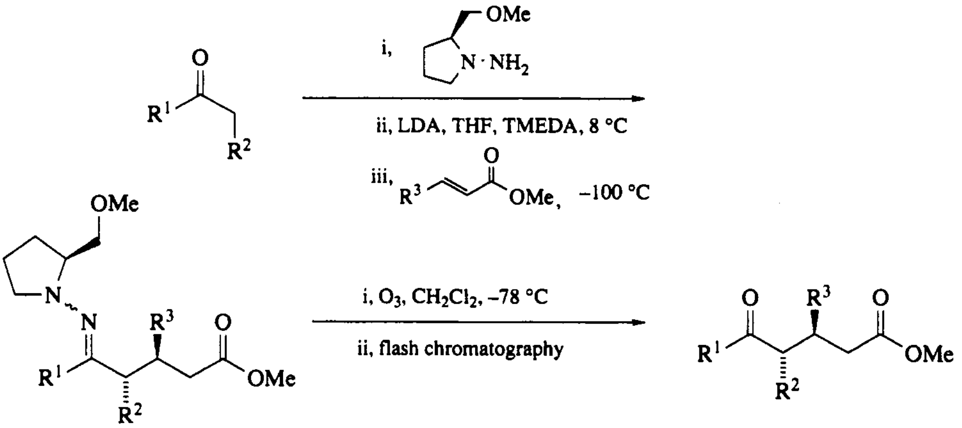
O
R1
R2
i,
OMe
N·NH2
ii, LDA, THF, TMEDA, 8 °C
iii,
O
R3
OMe, −100 °C
OMe
N
N
R3
O
R1
OMe
R2
i, O3, CH2Cl2, −78 °C
ii, flash chromatography
O
R3
O
R1
OMe
R2

(31)

**(74)**

**(75)** 92–100% *ee*
90–100% *de*

$R^1$ = H, Et, Bu$^n$, Ph; $R^2$ = Me, Et, PhCH$_2$, Pr$^n$; $R^3$ = Me, Et, Ph

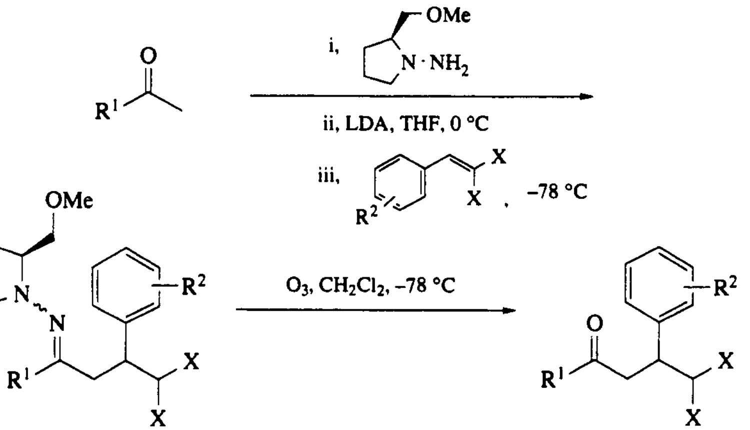
O
R1
i,
OMe
N·NH2
ii, LDA, THF, 0 °C
iii,
X
X
R2
, −78 °C
OMe
N
N
R2
R1
X
X
O3, CH2Cl2, −78 °C
R2
O
R1
X
X

(32)

**(76)**

**(77)**

$R^1$ = Me, Et, Ph; $R^2$ = H, 3-OMe, 4-OCH$_2$Ph, 4-OMe; X = CO$_2$Me, CN

Extensions of the 1,4-conjugate addition methodology shown in equation (30) were recently described by Enders.[66] In this work, azaallyl metal reagents derived from aldehyde and ketone SAMP hydrazones were added to 2-alkenoates. Unlike the reactions leading to (**69**)–(**73**) in which the aldehyde carbonyl group was chemically reduced to form a methyl group, the aldehyde or ketone group was kept to yield chiral 3,4-disubstituted-5-oxoalkanoates. Both the diastereomeric excess and enantiomeric excess in these reactions were very high, with typical stereoselectivity exceeding 96% *de* and 96% *ee*. The overall chemical yields were also good and generally between 40 and 60%. The (*S*,*S*)-stereochemistry of the product shown in equation (31) was determined by X-ray analysis of the intermediate hydrazone (**74**; $R^1$ = Ph, $R^2$ = Me, $R^3$ = Me; equation 31). Substitution of RAMP for SAMP in this synthesis produced the (*R*,*R*)-enantiomer.

By coupling the asymmetric Michael additions of a SAMP or RAMP acetaldehyde hydrazone like those shown in equation (30) with hydrolysis and reduction of the chiral β-substituted δ-oxopentanoates, Enders was able to prepare chiral δ-lactones with control of stereochemistry at C-3 of the lactone ring.[67] As would be expected based on the results shown above, the enantioselectivity in this overall process was high (90–96%) and good chemical yields were obtained.

Recently Enders has shown that the asymmetric 1,4-conjugate addition methodology illustrated above will also work in enantioselective 1,4-additions of azaallyllithium derivatives of SAMP and RAMP methyl ketones to Knoevenagel acceptors like dimethyl benzylidenemalonates and benzylidenemalonitriles.[68] Oxidative cleavage of the SAMP (or RAMP) group leads to 2-aryl-4-oxo diesters and 2-aryl-4-oxodinitriles in overall yields of 50–82% with enantioselectivity exceeding 95%. The absolute stereochemistry of the products was shown to be (*R*) based on chemical correlation of (**77**) with methyl (*R*)-5-oxo-3-phenylhexanoate (equation 32).

## 1.17.9 HETEROCYCLE SYNTHESES *VIA* 1,2- AND 1,4-ADDITIONS OF HYDRAZONE ANIONS TO CARBONYL COMPOUNDS AND α,β-UNSATURATED CARBONYL COMPOUNDS

Extensions of the chemistry described in equation (32) have led to an enantioselective method for annulation of cyclic 1,3-diketones leading to tetrahydro-2,5(1*H*,3*H*)-quinolinediones.[69] As was true for the other 1,4-conjugate additions described above, these reactions proceed with exceptionally good enantioselectivity (>98%) and good chemical yields (50–60% overall). The absolute configuration of the products is as shown, and was confirmed by X-ray crystallographic analysis of (**80**; R* = SAMP, R = Me and Ar = Ph; equation 33).

By substituting (*S*)-(–)-1-amino-2-(dimethylmethoxymethyl)pyrrolidine (*S*)-(**83**) for (*S*)-(**4**), Enders has developed an efficient and enantioselective Hantzsch synthesis (Scheme 4). In this synthesis, the more-hindered hydrazone formed from (**83**) was condensed with an acetoacetic acid ester. Deprotonation of the hydrazone so-formed (the major tautomer present was an enehydrazine) followed by addition of an arylidene malonate derivative yielded (**85**), which could be closed with mild acid to yield optically active

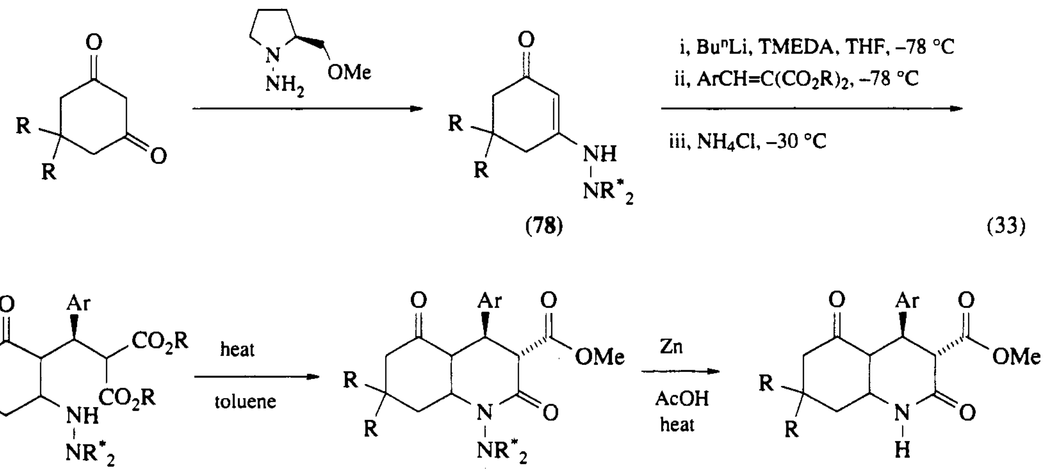

(**78**) (33)

(**79**) (**80**) *ee* ≥ 98%; overall yield 50–60%

dihydropyridines. In the ring closure step, the pyrrolidine precursor to the chiral auxiliary (**83**) was regenerated and recoverable. Overall yields in this synthesis were very good and ranged from 64 to 72%. Enantioselectivities ranged from 84 to >96% with most reactions proceeding with >90% *ee*. Substituents on the aryl ring could be varied and examples with pyridyl, methyl and alkoxy groups were described.[70]

An earlier application of 1,4-conjugate additions employing azaallyllithium reagents formed from ketone dimethylhydrazones is Kelly's hydrazone version of the classical Knoevenagel route to substituted pyridine derivatives.[71] In this chemistry, a mixed cuprate derived from a dimethylhydrazone lithio anion and copper thiophenoxide was first allowed to react with an α,β-unsaturated ketone. The product enolate can then be acylated or protonated to yield either a diketo hydrazone or a keto hydrazone. Addition of

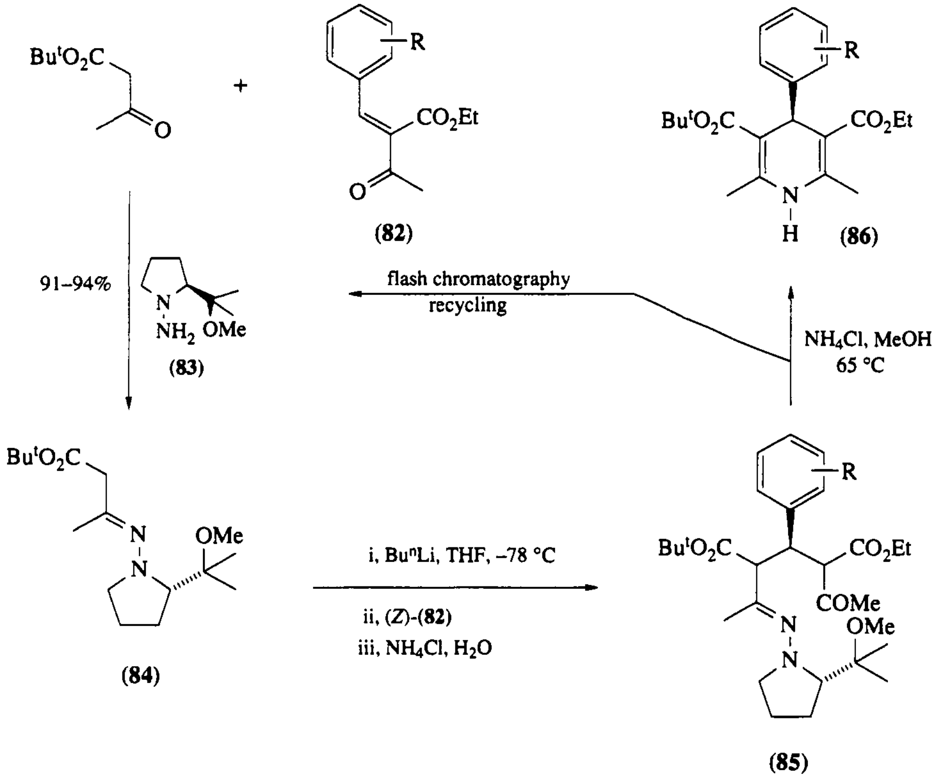

$Bu^tO_2C$
O
+
R
$CO_2Et$
O
(82)
R
$Bu^tO_2C$
$CO_2Et$
N
H
(86)
91–94%
N
$NH_2$
OMe
(83)
flash chromatography
recycling
$NH_4Cl$, MeOH
65 °C
$Bu^tO_2C$
N
OMe
N
(84)
i, $Bu^nLi$, THF, –78 °C
ii, (*Z*)-(82)
iii, $NH_4Cl$, $H_2O$
R
$Bu^tO_2C$
$CO_2Et$
COMe
N
OMe
N
(85)

**Scheme 4**

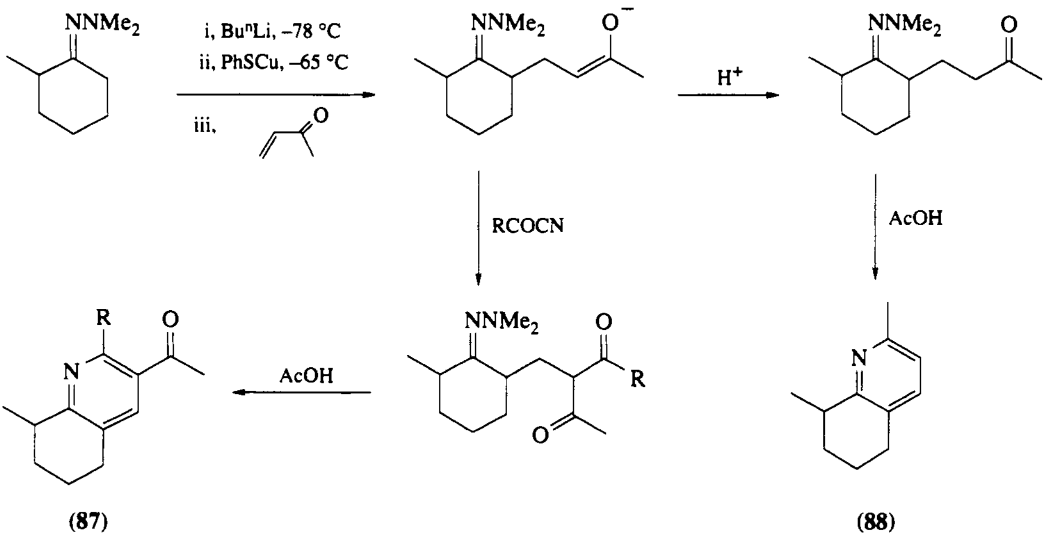

$NNMe_2$
i, $Bu^nLi$, –78 °C
ii, PhSCu, –65 °C
iii,
O
$NNMe_2$
$O^-$
$H^+$
$NNMe_2$
O
RCOCN
AcOH
R
O
N
AcOH
$NNMe_2$
O
R
O
N
(87)
(88)

**Scheme 5**

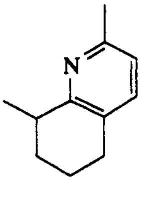

**(89)**

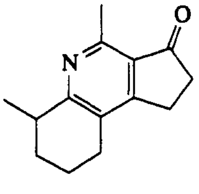

**(90)**

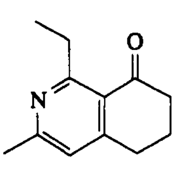

**(91)**

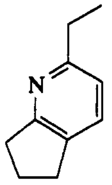

**(92)**

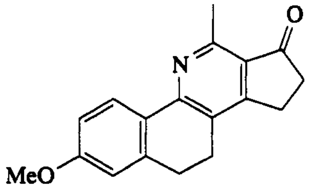

**(93)**

acetic acid then leads to cyclization. Unlike some other examples, hydrazone hydrolysis is not required in this synthesis. Instead, the hydrazone nitrogen is used for heterocycle formation. Overall, this one-pot sequence (Scheme 5) represents a very efficient and direct route to substituted pyridines like (**87**)–(**93**).

The 1,2-addition of hydrazone anions to carbonyl compounds has also been used to advantage in other heterocycle syntheses. The synthesis of heterocyclic compounds including pyrazoles and pyridazones using hydrazone anions are examples of this chemistry. Foote, Beam and Hauser first described application of this reaction for the synthesis of 1,3,5-trisubstituted aryl pyrazoles as shown in equation (34).[72] In this initial report, they found that various *p*-chloro and *p*-methoxy phenyl groups could be placed in predetermined and unambiguous positions on the product pyrazole ring. These reactions proceed by initial formation of a dianion from a starting *N*-arylhydrazone. In such cases, a strong base like Bu$^n$Li is used to deprotonate both the N—H and the α-Me of the starting ketone *N*-arylhydrazone. After addition of the ester, a transient β-keto *N*-phenylhydrazone anion is formed. Condensation of the anionic nitrogen with the new ketone carbon then closes the heterocycle. Loss of water at this point or during work-up then yields the product pyrazole. This pyrazole synthesis has the advantage of forming unambiguously a single isomeric triarylpyrazole in yields typically exceeding 80%.

The pyrazole synthesis described in equation (34) has been extended in a number of ways by Beam's group. Starting with unsubstituted hydrazones of various acetophenone and propiophenone derivatives, deprotonation with 3 equiv. of Bu$^n$Li leads to trianions that can be condensed with an ester and subsequently cyclized with acid to yield pyrazoles containing N—H groups (as opposed to N—Ar groups in

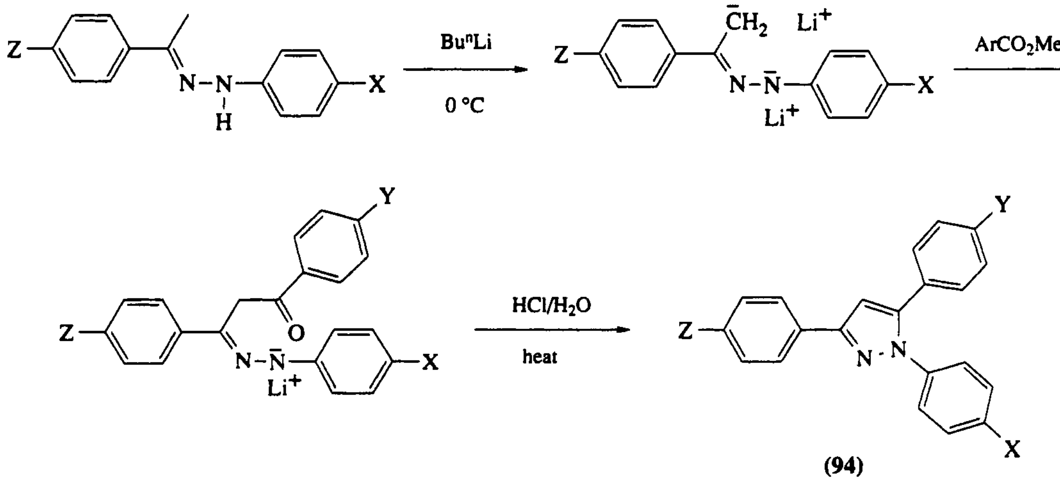

(94)

X,Y and Z = H, Cl, OMe

(34)

equation 34).[73] Substitution of an aroyl chloride for the aryl ester in equation (34) yields 4-acylpyrazoles.[74] More recently Beam's group has shown that *N*-phenylhydrazones of acetophenone can be doubly deprotonated with LDA to yield dianions which react with diethyl carbonate. The intermediate formed in this reaction is in effect the same as that prepared from a β-keto ester and phenylhydrazine, and can likewise cyclize to 2-pyrazolin-5-one derivatives.

## 1.17.10 HYDRAZONE ANIONS AS ACYL ANION EQUIVALENTS

Lithium salts of *t*-butylhydrazones of aldehydes have been shown to be useful acyl anion equivalents.[75] Treatment of an aldehyde *t*-butylhydrazone with an alkyllithium reagent or LDA gives the ambident nucleophile (**95**), which reacts with both aldehydes and ketones to give carbon-substituted products as shown in equation (35). The condensation works best with nonenolizable carbonyl derivatives. Extension of this chemistry to the reaction of (**95**) with α,β-unsaturated carbonyl compounds met with mixed success. While good yields of Michael products were seen in the addition of (**95**) to methyl crotonate, other α,β-unsaturated electrophiles such as methyl acrylate, acrylonitrile and methyl β,β-dimethylacrylate gave negligible yields of carbon-substituted products.

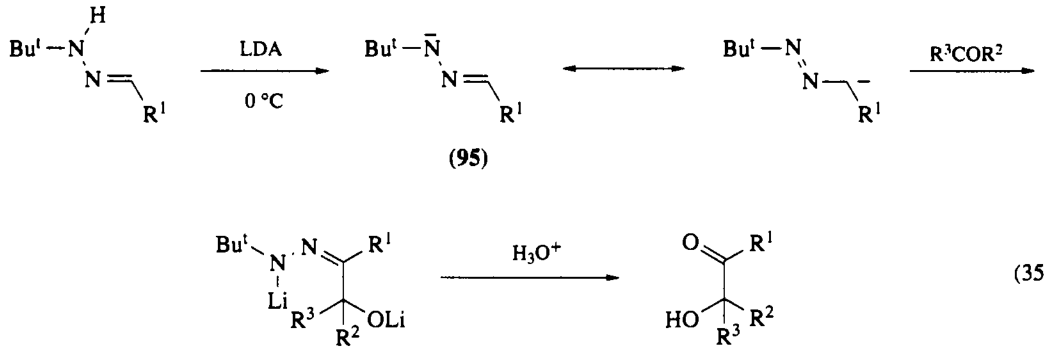

(**95**)

(35)

## 1.17.11 CLEAVAGE OF HYDRAZONES TO REGENERATE CARBONYL GROUPS

In cases other than the aforementioned heterocycle syntheses (see Section 1.17.9), the final step of a synthetic sequence employing azaallyl metal reagents derived from hydrazones is removal of the hydrazone group. This can be accomplished by several methods listed in Table 1 without affecting other functional groups in the molecule. The potential effects of oxidation, strong acid and racemization at any

**Table 1** Reagents for Regeneration of Carbonyl Compounds from Ketone and Aldehyde Hydrazones

| *Reagents/Comments* | *Ref.* |
|---|---|
| Aqueous $NaIO_4$ 2.2 equiv., pH 7, 20–25 °C | 79 |
| suitable for ketone hydrazones, β-hydroxy groups are not affected | |
| $H_5IO_6$ 1 equiv., pH 4.5 buffer, 1:1 THF/$H_2O$, 20–25 °C, 2–3 h | 79 |
| specific for aliphatic aldehydes | |
| $BF_3{\cdot}Et_2O$ | 13 |
| does not attack enol acetate groups | |
| *N*-Bromosuccinimide in acetone/water | 85 |
| not compatible with carbon–carbon double bonds | |
| Nitronium or nitrosonium tetrafluoroborate | 86 |
| Clay-supported iron(III) nitrate | 87 |
| Molybdenyl chloride ($MoOCl_3$) in THF/$H_2O$ | 88 |
| Molybdenum(VI) fluoride ($MoF_6$) in Freon 113 | 88 |
| Tungsten(VI) fluoride ($WF_6$) in water | 89 |
| Cobalt(III) trifluoride in $CHCl_3$ with heat | 90 |
| Silica | 91 |
| Cerium(IV) ammonium nitrate in methanol/water | 84 |
| Tin(II) fluoride, pH 7 buffer, methanol/water | 84 |

newly formed stereocenters are commonly subjects of concern in this regard. Three methods seem to be most generally useful: oxidative cleavage by ozonolysis at low temperature; *N*-methylation of the hydrazone using methyl iodide followed by hydrolysis in a biphasic HCl–pentane system; and copper-catalyzed hydrolysis.

The classical method is hydrolysis of a hydrazone using 1–6 M HCl.[2,76] However, this method is generally too harsh. In some cases, milder acids such as acetic acid and oxalic acid have successfully been used in place of HCl.[77,78]

Regeneration by ozonolysis is most commonly used by Enders and coworkers for SAMP/RAMP hydrazones primarily because it allows almost complete recycling of the chiral auxiliary.[50] The method gives almost quantitative chemical yields with only a small degree of racemization in a few cases. Other advantages of this method are the neutral conditions, short reaction times (15–30 min) and the ease in detecting the endpoint *via* the development of a green color due to the presence of yellow nitrosamine and blue ozone.[50] However, the method cannot be used if there are other ozone-sensitive groups such as alkenes in the molecule.

Earlier, it was noted by Levisalles[79] that conversion of *N*,*N*-dimethylhydrazones to the corresponding trimethylhydrazonium iodides facilitated hydrolysis even under mild conditions. The reaction was carried out in quantitative yield by reacting the hydrazone with excess methyl iodide at 60 °C. Hydrolysis may be achieved using refluxing 95% ethanol, mineral acid or dilute sodium bicarbonate solution. In cases where aqueous sodium bicarbonate is used to hydrolyze aldehyde trimethylhydrazonium iodides, nitrile formation is also observed. However, keeping the pH below 2 by using mineral acid eliminates this problem.[80] A subsequent modification of this method by Enders[81] utilized a biphasic *n*-pentane/3–4 M HCl system to effect hydrolysis in good chemical yields and short reaction times (15–60 min). Yields seemed to be lower than those for ozonolytic cleavage. No racemization was observed with this biphasic method, presumably because the carbonyl compounds were rapidly transferred to the pentane phase by stirring. A partial recycling of the chiral auxiliary was also achieved.[50]

Still another powerful method for the regeneration of carbonyl compounds from dialkylhydrazones is copper-catalyzed hydrolysis. The reagents that have been tested for this purpose are 2% aqueous copper(II) acetate solution at pH 4,[53] copper(II) chloride in 0.05M phosphate buffer and 75% tetrahydrofuran/water,[53] and copper(II) sulfate pentahydrate[82,83]. Under the conditions of the hydrolysis, no reaction is observed in the absence of the copper(II) ion. Typical yields are 85–100%. Other functional groups like α-dicarbonyl, α-tricarbonyl, acetal and aldehydic formyl groups were not affected by this hydrolysis procedure. Nitrile formation in the case of aldehyde dimethylhydrazones was not a significant side reaction. However, reaction times ranged from 1 to 15 h. The reaction is believed to be nonoxidative in nature; rather, the copper is believed to activate the C═N bond and catalyze hydrolysis. The dimethylhydrazine produced during hydrolysis also complexes irreversibly with the copper(II) ion to drive the reaction to completion.

A new method for cleavage was recently reported by Enders.[84] Treatment of the hydrazone with three equivalents of sodium perborate regenerated the carbonyl compound in 70–95% yield according to equation (36). This oxidative cleavage was chemoselective and left carbon–carbon double bonds intact. This chemoselectivity plus the neutral hydrolytic conditions and the low cost of the oxidant make this method quite attractive. The main disadvantage of this method is the relatively long reaction time required, ranging from 4–24 h for aliphatic ketone hydrazones to 2–3 d for aromatic ketone hydrazones.

Many other reagents have been used to cleave hydrazones and to regenerate carbonyl groups. Table 1 lists some of these other examples of procedures to regenerate carbonyl compounds from their *N*,*N*-dialkylhydrazones.

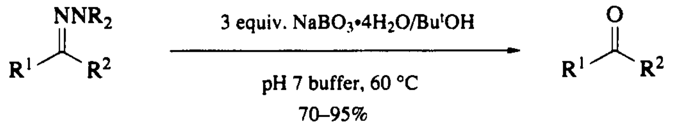

(36)

$NR_2 = NMe_2$, SAMP/RAMP

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# 2.1

# The Prins and Carbonyl Ene Reactions

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## 2.1.1 INTRODUCTION

The addition of aldehydes and ketones to alkenes in the presence of Brønsted acids is usually called the Prins reaction.[1,2] Addition of the protonated carbonyl compound to the alkene gives a β-hydroxy carbocation which reacts with a nucleophile such as chloride, water or acetate to give (**1**), adds to a second molecule of aldehyde to give (**2**) or loses a proton to give homoallylic alcohol (**3**; Scheme 1). Formaldehyde and electron-deficient carbonyl compounds undergo concerted thermal ene reactions with alkenes at temperatures ranging from 100 to 200 °C to give homoallylic alcohols (equation 1; $R^1$ = H, $CCl_3$, or $CO_2R$).[3–7] A wide variety of carbonyl compounds undergo Lewis acid catalyzed reactions with alkenes to give homoallylic alcohol ene adducts in excellent yield with high selectivity, although in some cases γ-chloro alcohols are formed as by-products.[8,9] Recent investigations suggest that at least some of these

Lewis acid catalyzed ene reactions are stepwise, rather than concerted, but that the intermediate bears more resemblance to a π-complex than to the open carbocation intermediate in the Prins reaction.[10–13]

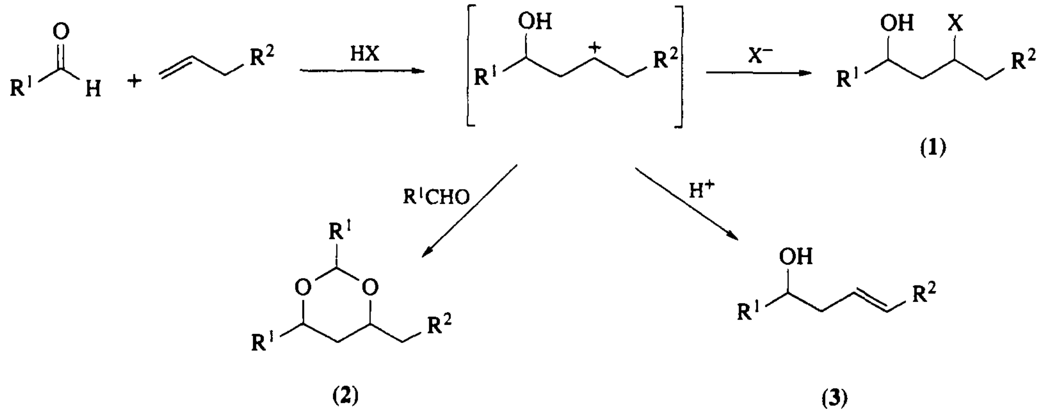

Scheme 1

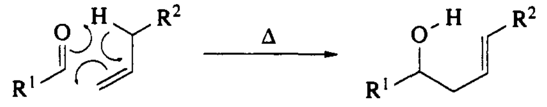

(1)

The ene and Prins reactions are not mechanistically distinct. Coverage will therefore be organized by the nature of the carbonyl compound, with intermolecular reactions presented first, followed by intramolecular reactions. The emphasis will be on material published since the field has been reviewed[1–9] and on examples demonstrating the stereo-, regio- and chemo-selectivity of these reactions. Coverage is restricted to the addition of carbonyl and thiocarbonyl compounds to simple alkenes. Addition of carbonyl compounds to vinylsilanes, allylsilanes and enol ethers is covered in the following chapters. Addition of imines and iminium compounds to alkenes is presented in Part 4 of this volume. Ene reactions with alkenes and alkynes as enophiles are covered in Volume 5, Chapter 1.1. Use of aldehydes and acetals as initiators for polyene cyclizations is covered in Volume 3, Chapter 1.6.

## 2.1.2 INTERMOLECULAR REACTIONS

### 2.1.2.1 Formaldehyde

### *2.1.2.1.1 Prins reactions*

The reaction of formaldehyde with alkenes is of industrial interest and has been extensively studied.[1,2] Reaction of excess formaldehyde as formalin with an alkene and aqueous acid gives 1,3-dioxanes (**2**) in 40–90% yield. Reaction of 2-butenes with paraformaldehyde and hydrogen chloride at –65 °C gives a mixture of diastereomeric γ-chloro alcohols rich in the isomer formed by *trans* addition to the alkenyl double bond.[14] For example *trans*-2-butene gives an 85:15 mixture of *erythro*- and *threo*-3-chloro-2-methyl-1-butanol (equation 2). Reaction of 1-alkenes under similar conditions gives 3-alkyl-4-chlorotetrahydropyrans (**5**) in 50–80% yield (Scheme 2).[15] Initial reaction occurs *via* addition of formaldehyde to the terminal carbon of the double bond, followed by loss of a proton to give the 3-alken-1-ol. Reaction of

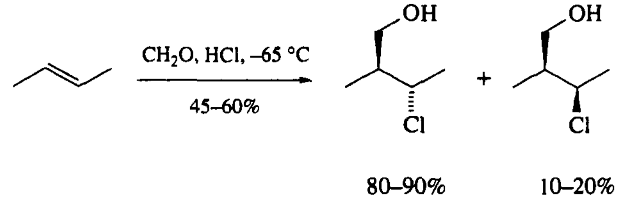

(2)

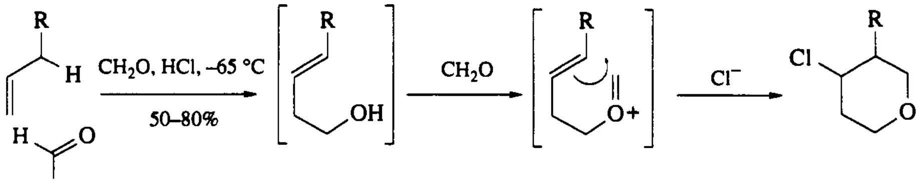

(4) (5)

Scheme 2

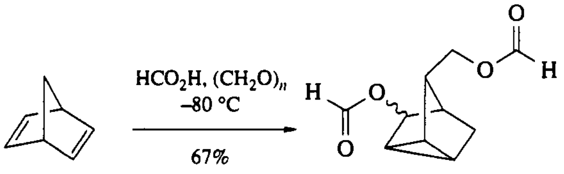

(6)

(3)

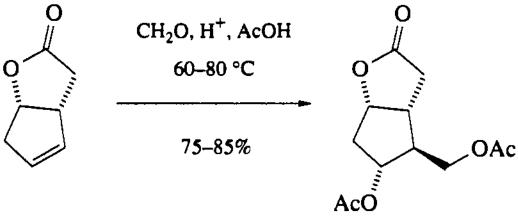

(7) (8)

(4)

the 3-alken-1-ol with formaldehyde followed by loss of water gives (**4**), which undergoes an intramolecular Prins reaction followed by chloride attack on the cation to give (**5**).

Prins reactions with formaldehyde have been used to prepare prostaglandin intermediates. Reaction of norbornadiene with paraformaldehyde and formic acid at –80 °C gives (**6**) in 67% yield (equation 3).[16] Reaction of unsaturated lactone (**7**) with formaldehyde in acetic acid at 60–80 °C gives prostaglandin intermediate (**8**) in 75–85% yield (equation 4).[17] Addition of protonated formaldehyde occurs from the less-hindered face of the double bond followed by *trans* addition of acetate to the carbocation.

### *2.1.2.1.2 Thermal ene reactions*

Formaldehyde undergoes thermal ene reactions with reactive 1,1-disubstituted and trisubstituted alkenes at 180–220 °C. β-Pinene, a particularly reactive ene component, reacts with formaldehyde at 180 °C to give nopol in 95% yield (equation 5).[18] Methylenecyclohexane reacts similarly.[19] Blomquist extended the scope of these reactions by using acetic acid–acetic anhydride as solvent at 180–190 °C.[20]

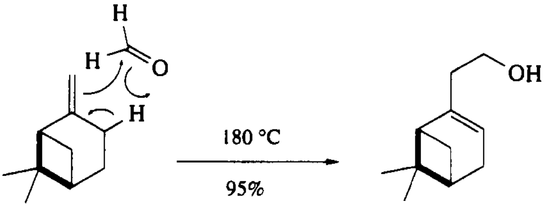

(5)

### *2.1.2.1.3 Lewis acid catalyzed ene reactions*

Excellent yields of ene adducts can be obtained from $BF_3 \cdot Et_2O$- or $SnCl_4$- catalyzed addition of formaldehyde to alkenes that can give a tertiary carbocation.[21] Limonene reacts selectively at the 1,1-disubstituted double bond to give ene adduct (**9**) in 80% yield (equation 6). $SnCl_4$- catalyzed addition of formaldehyde to 2,6-dimethyl-2,5-heptadiene gives lavandulol (**10**) in 55% yield (equation 7).[22] $BF_3 \cdot Et_2O$-catalyzed ene reaction of formaldehyde with (**11**) occurs exclusively from the less-hindered α-face to give ene adduct (**12**) with the correct stereochemistry at C-20 and functionality suitable for construction of the vitamin D side chain (equation 8).[23]

A problem with Lewis acid catalyzed ene reactions of aldehydes is that the alcohol–Lewis acid complex produced in the reaction is susceptible to solvolysis and is a strong protic acid capable of protonating the double bond of the ene adduct or alkene starting material. $Me_2AlCl$ in equivalent or greater

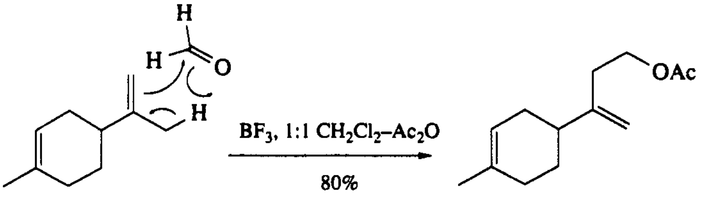
H
H
O
H
BF₃, 1:1 CH₂Cl₂–Ac₂O
80%
OAc

**(9)**

(6)

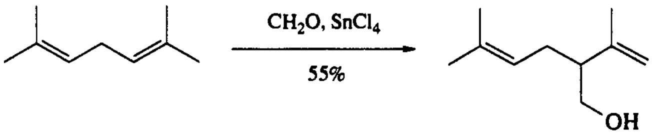
CH₂O, SnCl₄
55%
OH

**(10)**

(7)

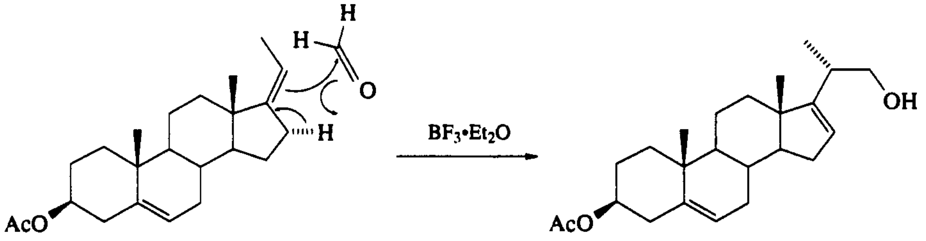
H
H
O
H
AcO
BF₃•Et₂O
OH
AcO

**(11)** **(12)**

(8)

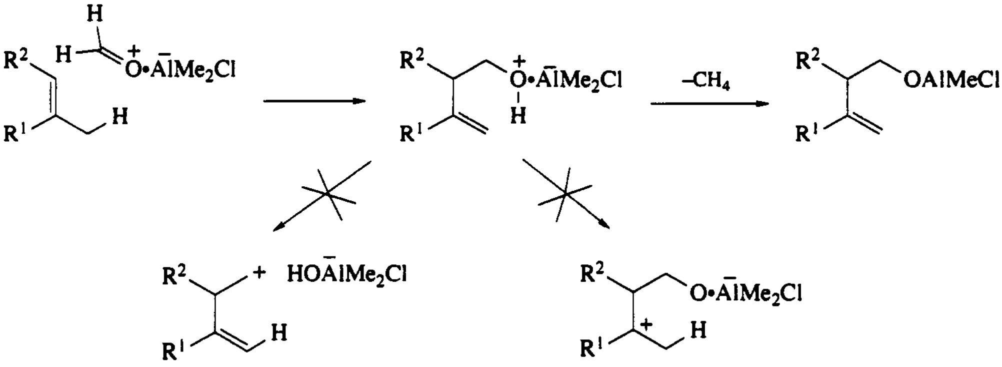
H
R²
H
+
O•AlMe₂Cl
R¹
H
R²
+
O•AlMe₂Cl
H
R¹
–CH₄
R²
OAlMeCl
R¹
R²
+
HOAlMe₂Cl
R¹
H
R²
O•AlMe₂Cl
R¹
+
H

**Scheme 3**

amounts is a useful catalyst for these reactions.[24] The alcohol–$Me_2AlCl$ complex formed in the reaction decomposes rapidly to give methane and a nonbasic aluminum alkoxide which does not undergo these side reactions (Scheme 3). With this Lewis acid, ene adducts are obtained in good yield from formaldehyde and mono- and 1,2-disubstituted alkenes as well as those that can give a tertiary carbocation.

These reactions involve a zwitterionic intermediate or π-complex that selectively undergoes a [1,5] proton shift to give the ene adduct–$Me_2AlCl$ complex, which loses methane. With 1 equiv. of $Me_2AlCl$, a γ-chloro alcohol is formed as a by-product when the carbocation is secondary. With 1.5–2 equiv. of $Me_2AlCl$, γ-chloro alcohols are formed as transient intermediates. Those derived from acyclic alkenes give ene adducts. Those derived from cyclohexene and cyclopentene give complex mixtures of products. The chloro alcohols formed from 1,2-disubstituted alkenes result from the stereospecifically *cis* addition of the hydroxymethyl group and the chloride to the double bond (Scheme 4). Formaldehyde undergoes $Me_2AlCl$-induced reactions with terminal alkynes to give a 2:3 mixture of the ene adduct (**13**) and the (*Z*)-chloro alcohol (**14**) in 50–75% yield (equation 9).[25]

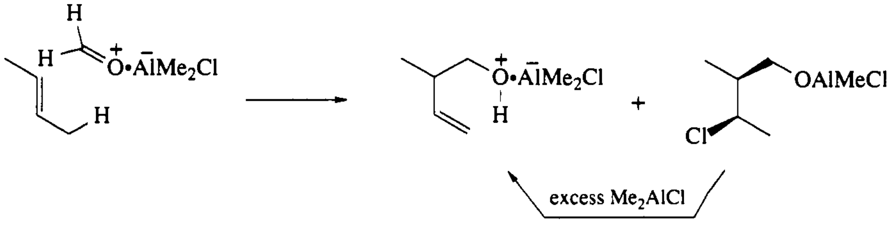

**Scheme 4**

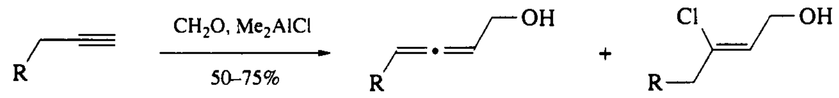

(**13**) 40% (**14**) 60% (9)

These $Me_2AlCl$-catalyzed reactions of formaldehyde are successful because the Lewis acid is a Brønsted base as well as a strong Lewis acid.[26] Unfortunately, the methyl group of $Me_2AlCl$ can also act as a nucleophile. Formaldehyde undergoes $Me_2AlCl$-induced reactions with all simple alkenes. However, many functionalized alkenes are not nucleophilic enough to react with the formaldehyde–$Me_2AlCl$ complex. Reaction of 5-hexenyl acetate with formaldehyde and $Me_2AlCl$ gives only ethanol from addition of a methyl group to the aldehyde. The acetate group is more basic than formaldehyde so $Me_2AlCl$ preferentially complexes to it. Furthermore, the acetate–Lewis acid complex is electron withdrawing and decreases the nucleophilicity of the double bond relative to that of the methyl group of $Me_2AlCl$. Therefore, no ene reaction occurs even if a second equivalent of $Me_2AlCl$ is used. Fortunately, use of 2 equiv. of $EtAlCl_2$, a stronger Lewis acid with a less nucleophilic alkyl group, gives (**15**) as a 3:1 (*E*):(*Z*) mixture in 70% yield (equation 10).[27]

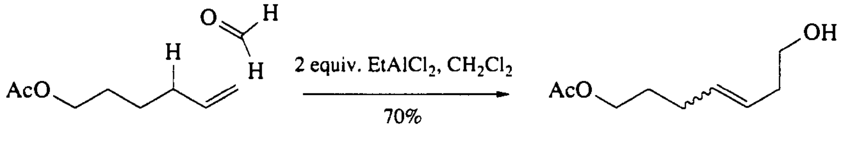

(**15**) (10)

A formal synthesis of pseudomonic acids A and C has been carried out using two ene reactions and a Diels–Alder reaction starting with 1,5-hexadiene and three molecules of formaldehyde to give the key intermediate (**22**) in only three steps (Scheme 5).[28] $Me_2AlCl$-catalyzed reaction of formaldehyde with 1,5-hexadiene gives (**16**) as an 8:1 mixture of (*E*)- and (*Z*)-isomers in 81% yield. Only traces of 2:1 adducts are obtained in the ene reaction, even when excess formaldehyde and $Me_2AlCl$ are used, since the aluminum alkoxide inductively deactivates the double bond of (**16**). Treatment of acetate (**17**) with 3 equiv. of paraformaldehyde and 4.5 equiv. of $EtAlCl_2$ in 1:1 $CH_2Cl_2$:nitromethane for 12 h at 25 °C gives a 16:1 mixture of (**22**) and (**23**) in 37% yield. The acetate of (**17**) is more basic than formaldehyde and complexes to $EtAlCl_2$. This complex reacts selectively with formaldehyde·$EtAlCl_2$ at the less deactivated terminal double bond to give ene adduct (**18**), which loses ethane to give (**19**). Complexation of (**19**) with formaldehyde gives (**20**), which undergoes a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction to give (**21**). Aqueous work-up gives (**22**). The regiochemistry of the Diels–Alder reaction is controlled by the Lewis acid, which is bound to the diene and complexed to the dienophile, giving rise to a quasi-intramolecular Diels–Alder reaction.

In most cases the ene adduct formed from Lewis acid induced addition of formaldehyde to an alkene does not react with a second equivalent of aldehyde due to the inductive effects of the aluminum alkox-

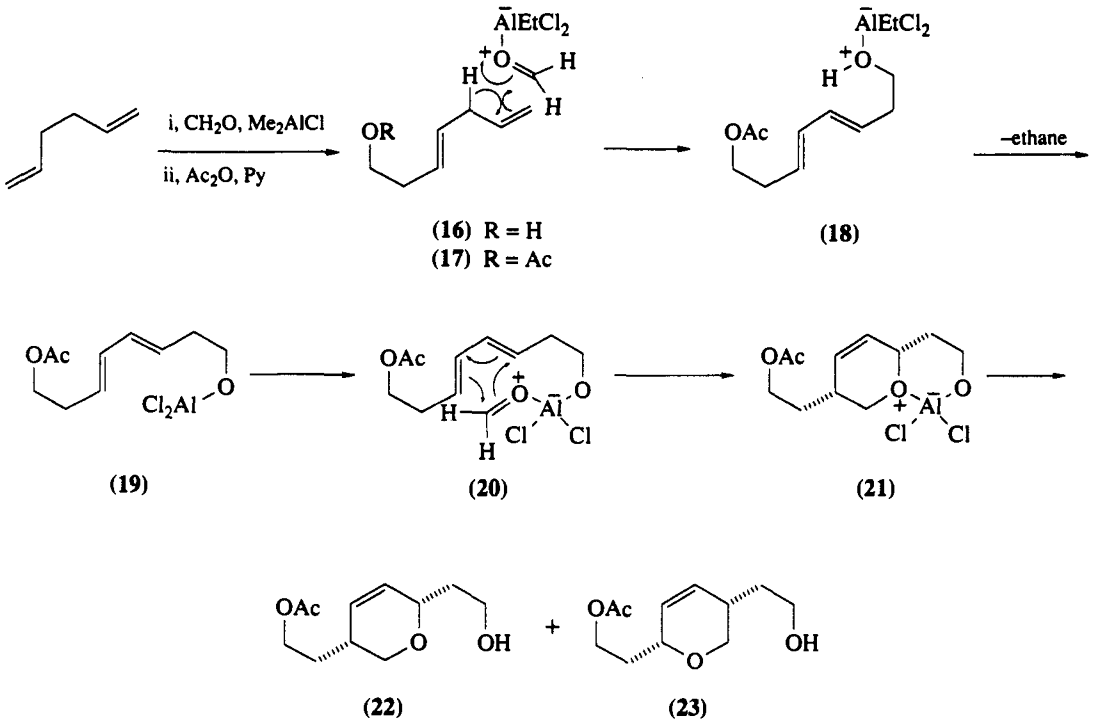
i, CH2O, Me2AlCl
ii, Ac2O, Py
AlEtCl2
OR
(16) R = H
(17) R = Ac
AlEtCl2
OAc
(18)
–ethane
OAc
Cl2Al
(19)
OAc
Cl
Cl
(20)
OAc
Cl
Cl
(21)
OAc
OH
+
OAc
OH
(22)
(23)

Scheme 5

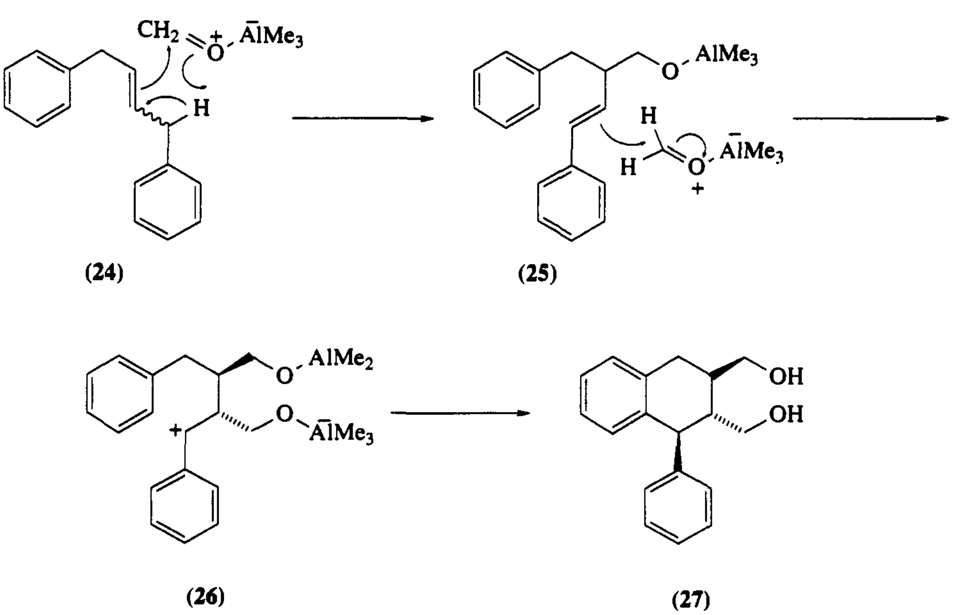
CH2
AlMe3
H
(24)
AlMe3
H
H
AlMe3
(25)
AlMe2
AlMe3
(26)
OH
OH
(27)

Scheme 6

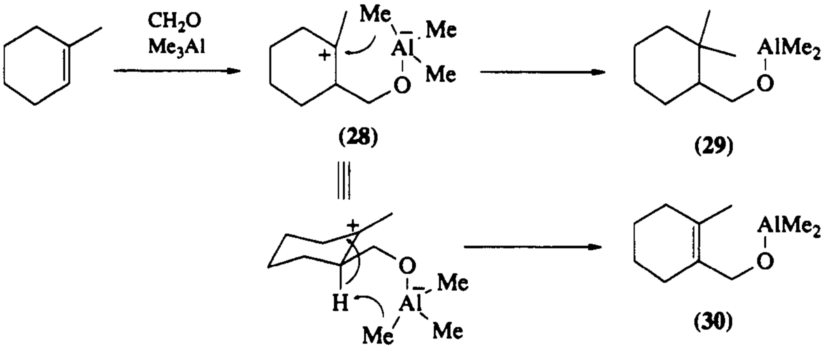

Scheme 7

ide, which deactivates the double bond of the homoallylic alcohol ene adduct. In special cases, the double bond of the product is more nucleophilic than the starting alkene so that 2:1 adducts are formed. As shown in Scheme 6, a one-pot synthesis of the aryltetralin lignan skeleton was carried out by reaction of (*E*)- or (*Z*)-(**24**) with 6 equiv. of paraformaldehdye and methylaluminum sesquichloride to give a 40–50% yield of (**27**) as the only characterizable product.[29] Ene reaction occurs as expected to give the ene adduct (**25**). The styrene double bond of (**25**) is much more nucleophilic than the 1,2-disubstituted double bond of (**24**), so (**25**) reacts with formaldehyde to give benzylic cation (**26**), which undergoes a Friedel–Crafts reaction to give (**27**) as the *trans,trans* isomer.

The reaction of formaldehyde and $Me_3Al$ with 1-methylcyclohexene gives only 5% of the expected ene adducts, the exclusive products from formaldehyde and $Me_2AlCl$.[24] The major products are the alcohol derived from (**29**), resulting from *cis* addition of the hydroxymethyl and methyl groups to the double bond and the allylic alcohol derived from (**30**; Scheme 7).[30] The enhanced basicity and nucleophilicity of the methyl groups of intermediate (**28**), as compared to the intermediate obtained with $Me_2AlCl$, are apparently responsible for the difference between these reactions. The yields in these reactions are acceptable only with 1,1-di- and tri-substituted alkenes, since competing addition of a methyl group to formaldehyde is a significant side reaction with these substrates and the only reaction with less nucleophilic alkenes.

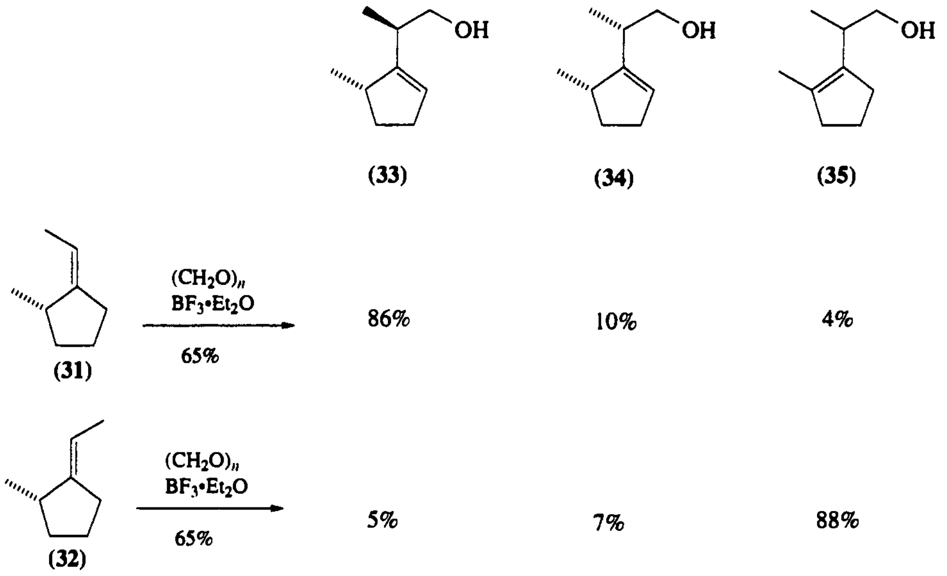

Scheme 8

#### *2.1.2.1.4 Regioselectivity of Lewis acid catalyzed ene reactions*

After correction for statistical factors a methylene hydrogen is twice as reactive as a methyl or methine hydrogen.[25] 1,2-Disubstituted double bonds are formed ≈90% (*E*) with $Me_2AlCl$ and ≈75% (*E*) with $EtAlCl_2$. Trisubstituted double bonds are formed ≈70% (*E*). In the ene reactions of formaldehyde with trisubstituted double bonds, there is a preference for transfer of a hydrogen from the alkyl group *syn* to the vinylic hydrogen. In most cases this selectivity is modest,[25] although one highly selective example has been reported (Scheme 8).[31] The major product (**33**), obtained from (**31**), was converted to Prelog–Djerassi lactone. The regioselectivity is most likely due to steric interaction between the formaldehyde–$BF_3$ complex and the alkenyl methyl group in the transition state for proton abstraction from the carbon *anti* to the vinylic hydrogen. Reaction occurs with high facial selectivity from the less hindered β-face of (**31**) to give an 86:10 mixture of (**33**):(**34**). Reaction with (**32**) shows little facial selectivity.

### 2.1.2.2 Electron-deficient Aldehydes

The thermal and Lewis acid catalyzed reactions of electron-deficient aldehydes such as chloral, glyoxylate esters and phenylglyoxal have been extensively studied. The reactions with glyoxylate esters are particularly intriguing, since use of a chiral ester group has permitted these reactions to be carried out with excellent asymmetric induction.

#### *2.1.2.2.1 Chloral*

Pioneering studies on the $AlCl_3$- and $SnCl_4$-catalyzed addition of chloral to alkenes were carried out by Colonge and Perrot, and Klimova and Arbuzov.[32] Recent studies by Gill and coworkers have provided a more complete understanding of this reaction.[33–36] The general trend in reactivity with alkenes is as follows: 1,1-di- > tri- > mono- > *cis*-1,2- > alkynes > *trans*-1,2-disubstituted.[33] Thermal reactions can be carried out at 90–130 °C with 1,1-di- and tri-substituted alkenes. Lewis acid catalyzed reactions are best carried out with 2% $AlCl_3$ in $CH_2Cl_2$ or $CCl_4$ for reactive alkenes and 6–20% $AlCl_3$ for less reactive alkenes. All products result from addition of the carbonyl group to the less-substituted end of the double bond. The ene adduct (**36**) is usually the major product (equation 11). Chloro ketones (**37**) are formed in significant amounts from mono- and 1,2-disubstituted alkenes. Prins type products (**38**) are occasionally isolated, particularly with less reactive alkenes. Bromal is less reactive than chloral in these reactions.

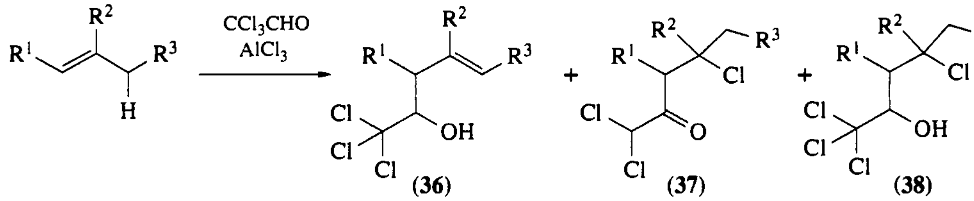

(11)

The *endo*/*exo* and regioselectivity of these reactions was carefully examined.[34] *Endo*/*exo* selectivity appears to be determined largely by steric interactions rather than electronic effects. Thermal reaction of β-pinene with chloral at 95 °C gives an 83:17 mixture of (**40**; equation 12) and (**42**; equation 13). The major product is formed *via* transition state (**39**) with the trichloromethyl group *endo* (under the π-system) to avoid steric interactions with the one-carbon bridge. Lewis acid catalyzed reactions of chloral with β-pinene provide mixtures rich in (**42**). Optimal results were obtained with $TiCl_4$, which gives exclusively (**42**). The Lewis acid complexes to the lone pair of the carbonyl group *trans* to the trichloromethyl group. Reaction occurs selectively from transition state (**41**) with the trichloromethyl group *exo* and the $TiCl_4$ *endo*, which minimizes steric interactions of the bulky Lewis acid with β-pinene.

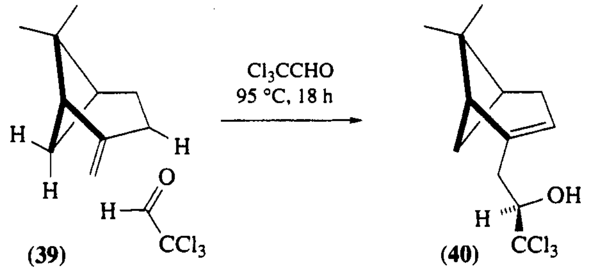

(12)

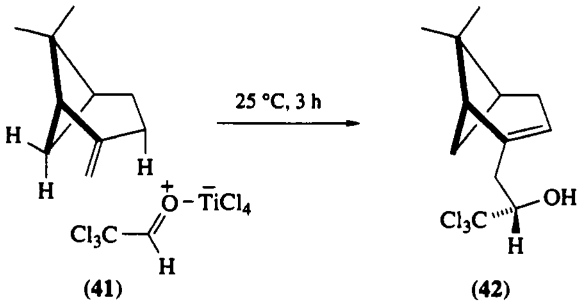

(13)

$AlCl_3$-catalyzed reaction of C-5 through C-8 cycloalkenes affords ≈90:10 mixtures of diastereomers. The major isomers were shown to be (**44**), formed from transition state (**43**) with the trichloromethyl group *endo* and the Lewis acid *exo*. Formation of the minor isomers (**46**) proceeds through transition state (**45**), with severe steric interactions between the *exo* trichloromethyl group and the ring carbons. Reactions with trisubstituted alkenes are more complex since the hydrogen can be transferred from two different sites. Reaction occurs with some preference for the alkyl group *anti* to the vinylic hydrogen. 2-Methyl-2-butene gives an 85:15 mixture of isomers with the major isomer (**48**) apparently formed *via* transition state (**47**; Scheme 9).[34]

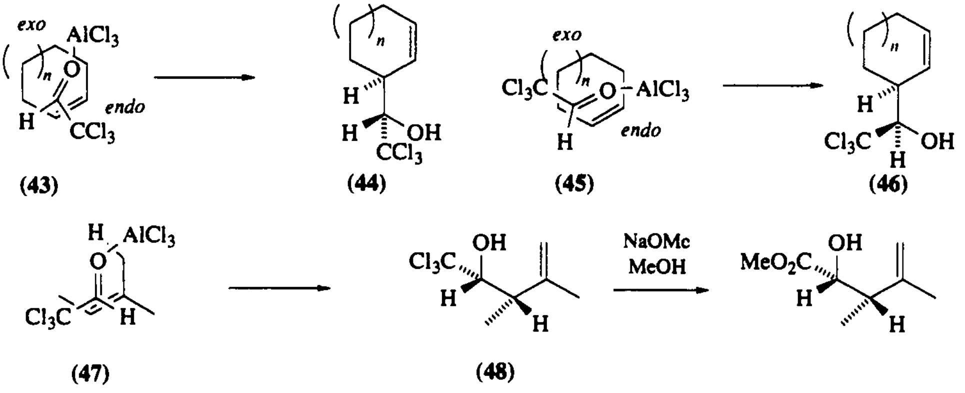

**Scheme 9**

The synthetic utility of the chloral ene adducts has been extensively explored.[35] Reaction with NaOR in ROH gives the α-alkoxy ester with inversion of configuration.[37] Reaction of the corresponding tosylate with sodium ethoxide in ethanol affords ethyl alka-2,4-dienoates (Scheme 9).

### *2.1.2.2.2 Glyoxylate esters*

Klimova and Arbuzov demonstrated that $SnCl_4$- and $AlCl_3$-catalyzed ene reactions of glyoxylate esters with cyclohexene, 1-alkenes, β-pinene and isobutene occur at 25–45 °C and that thermal ene reactions with this enophile occur at 150 °C.[38] Snider and van Straten determined the *endo*/*exo* stereochemistry of the thermal and $FeCl_3$-catalyzed ene reactions of methyl glyoxylate with *cis*- and *trans*-2-butene, cyclohexene, 2-methyl-2-butene and 1-methylcyclohexene.[39] Reaction of *cis*-2-butene with methyl glyoxylate for 60 h at 200 °C gives a 7.4:1 mixture of (**50**) and (**53**) in 54% yield. Similar reaction of *trans*-2-butene gives a 0.57:1 mixture of (**50**) and (**53**) in 20% yield. In both cases the *endo* transition states (**49**) and (**54**) are preferred due to minimized steric interactions between the ester and methyl groups (Scheme 10). Better selectivity and yields are obtained with *cis*-2-butene. Lewis acid catalyzed reactions show little selectivity and give chloro alcohols from a Prins reaction as significant by-product. $FeCl_3$-catalyzed ene reaction of methyl glyoxylate with cyclohexene affords a 4.4:1 mixture of ene adducts favoring the *endo* isomer.

Achmatowicz examined asymmetric induction in the ene reactions of (–)-menthyl glyoxylate with 1-pentene and found modest asymmetric induction of 5–30%.[40] The configuration of the new center in the adducts was (*S*) with $SnCl_4$, $BF_3$ and $TiCl_4$ and (*R*) with $AlCl_3$. In marked contrast to these results, Whitesell found that excellent asymmetric induction is obtained with 8-phenylmenthyl and *trans*-2-phenylcyclohexyl glyoxylate esters.[41–48]

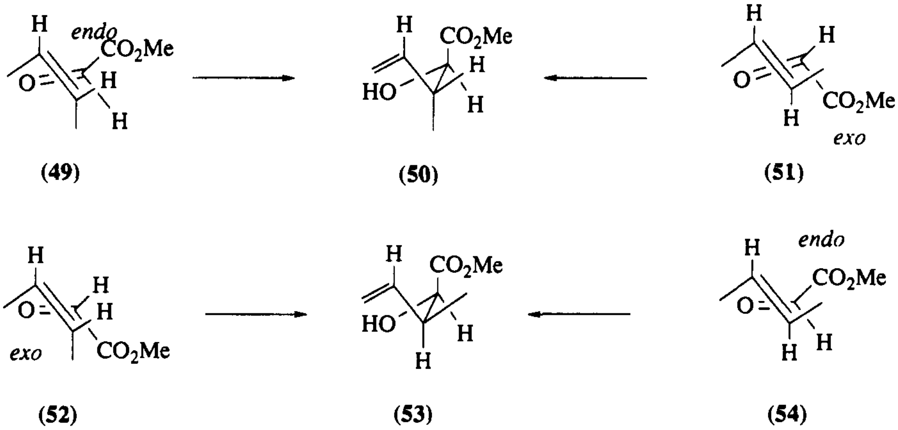

**Scheme 10**

Ene reaction of 8-phenylmenthyl glyoxylate (**55**) with 1-alkenes occurs rapidly at –78 °C in $CH_2Cl_2$ with 1 equiv. of $SnCl_4$ to give (**56**) in ≈90% yield with >97% enantiomeric excess.[41,44] The phenyl group, which clearly plays a major role in asymmetric induction, may form a π-complex with the aldehyde–Lewis acid complex forcing addition to occur from the other face. The newly formed double bond is 94% *trans*. Similar facial selectivity occurs in the ene reactions of (**55**) with methylenecyclohexane. Excellent asymmetric induction has also been obtained in $SnCl_4$-catalyzed ene reactions of the glyoxylate ester of 2-*epi*,*ent*-8-phenylmenthol, obtained as an impurity in the preparation of 8-phenylmenthol.[46] A detailed study of the effect of auxiliary structure on asymmetric induction in the ene reaction of chiral glyoxylates with 1-hexene demonstrated that an aromatic group is necessary.[47]

Reaction of (**55**) with *trans*-2-butene also proceeds with excellent asymmetric induction to give a 15:1 mixture of (**58**) and the diastereomer at C-3 in 85% yield. The stereochemistry at C-2 is the same in both isomers. Mixtures of isomers are produced since *endo* and *exo* transition states give different products with an internal alkene. The major isomer (**58**) is formed *via* the less-hindered *exo* transition state (**57**). These reactions are stepwise, rather than concerted, since *cis*-2-butene is isomerized to *trans*-2-butene under the reaction conditions. $SnCl_4$-catalyzed addition of (**55**) to *cis*-4-methyl-2-pentene results in isomerization of the alkene to the *trans* isomer, which reacts exclusively at C-3 giving (**59**) in 86% yield (Scheme 11).

$SnCl_4$-catalyzed ene reactions of *trans*-2-phenylcyclohexyl glyoxylate (**60**) also proceed with very high asymmetric induction.[43] Since both enantiomers of *trans*-2-phenylcyclohexanol are readily available, this chiral auxiliary has practical advantages. $SnCl_4$-catalyzed reaction of (**60**) with diene (**61**) gives

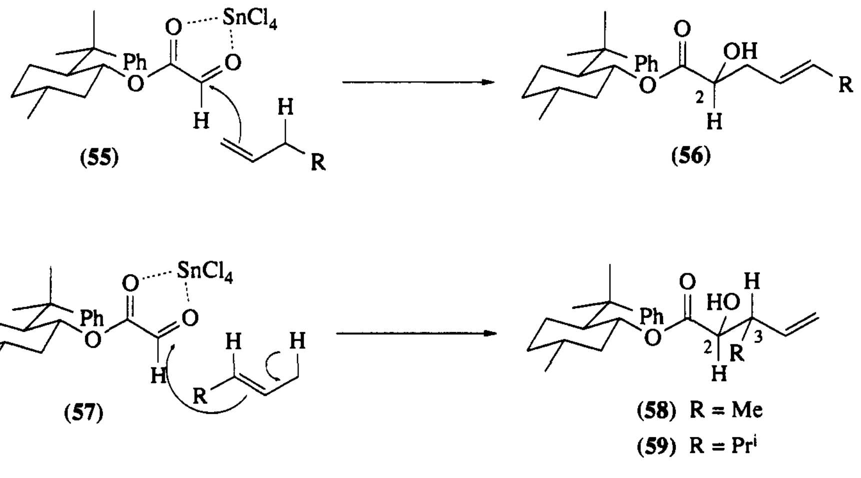

**Scheme 11**

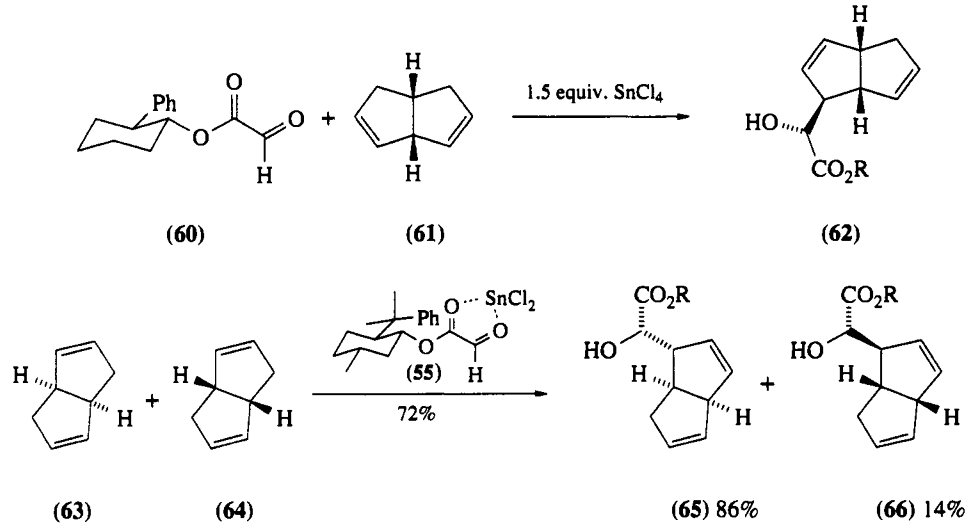

**Scheme 12**

(**62**) in 81% yield.[42,48] Reaction occurs exclusively from the less-hindered β-face of diene (**61**) and only at the double bond that can react through the less-hindered *endo* transition state. For reasons which are not clear, the stereochemistry at C-2 of (**62**) is opposite to that obtained from diene (**61**) and glyoxylate (**55**) with the same three-dimensional orientation of groups. Ene adduct (**62**) has been converted to (–)-specionin.[48]

$SnCl_4$-catalyzed reaction of (**55**) with an excess of a mixture of racemates (**63**) and (**64**) gives a 72% yield of an 8:1 mixture of (**65**) and (**66**).[45] Reaction occurs exclusively from the less-hindered face of the diene and the face of the glyoxylate opposite the phenyl group. The double bonds of (**63**) and (**64**) are symmetrical; identical products are obtained from reaction at either site. Reaction with either double bond of (**63**) occurs through an unhindered *endo* transition state to give (**65**). Reaction with either double bond of (**64**) must occur through a hindered *exo* transition state to give (**66**). Reaction therefore occurs selectively with (**63**), giving (**65**), resulting in a kinetic resolution (Scheme 12). Adduct (**65**) has been converted to the secoiridoid (–)-xylomollin.[45]

Lewis acid catalyzed ene reactions of ethyl glyoxylate with allylglycine derivatives have been described as a route to highly functionalized unsaturated amino acids.[49] $SnCl_4$-catalyzed ene reactions of phenylglyoxal with alkenes occur in 40–78% yield. Treatment of the adducts obtained from monosubstituted alkenes with periodate gives 3-alkenals in 50–70% yield.[50]

### 2.1.2.3 Aliphatic and Aromatic Aldehydes

Normal aliphatic and aromatic aldehydes, *e.g.* acetaldehyde and benzaldehyde, are much less reactive than formaldehyde and electron-deficient aldehydes in ene and Prins reactions. Prins reactions of these aldehydes lead to even more complex mixtures of products than Prins reactions of formaldehyde, due to the additional stereocenter introduced in the reaction. Thermal ene reactions of these aldehydes cannot be carried out successfully. Snider and coworkers have found that moderate to good yields of adducts can be obtained from $Me_2AlCl$-catalyzed ene reactions of these aldehydes and 1,1-di-, tri- and tetra-substituted alkenes (equation 14).[24] Use of a stoichiometric amount of $Me_2AlCl$ is necessary since the

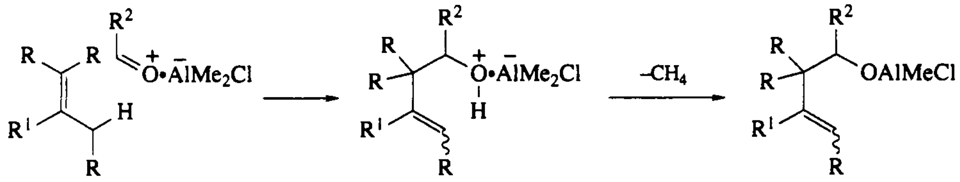

(14)

R = H, alkyl; R$^1$ = alkyl; R$^2$ = alkyl or aryl adduct–$Me_2AlCl$ complex loses methane, preventing Brønsted acid catalyzed isomerization of the ene adduct or starting alkene (Scheme 3). Addition of a methyl group to the aldehyde is a significant side reaction in all cases and is more severe with sterically hindered aldehydes and alkenes. Mono- and 1,2-disubstituted alkenes are not nucleophilic enough to react with these aldehyde–$Me_2AlCl$ complexes. Reaction with limonene occurs selectively on the 1,1-disubstituted double bond. Reaction of isovaleraldehyde with isoprene gives ene adduct ipsenol (**67**) in 16% yield and Diels–Alder adduct (**68**) in 60% yield (Scheme 13). Reaction of a series of aldehydes with (*E*)- and (*Z*)-3-methyl-2-pentene gives a complex mixture of *erythro* and *threo* isomers and double bond position isomers.[51] Ene reaction of 2-phenylpropionaldehyde with methylenecyclohexane affords a 1.5:1 mixture of diastereomers.

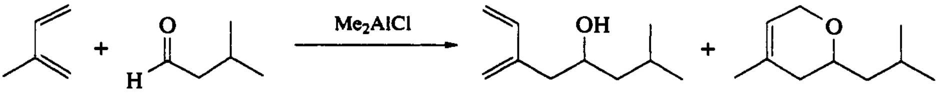

**(67)** **(68)**

**Scheme 13**

$EtAlCl_2$, a stronger Lewis acid than $Me_2AlCl$, with a less nucleophilic alkyl group, successfully catalyzes the ene reactions of aliphatic aldehydes with terminal alkenes. Reaction of an aliphatic aldehyde with a terminal alkene and $EtAlCl_2$ in $CH_2Cl_2$ for a few minutes at 0 °C gives the ene adduct as a 4:1 (*E*):(*Z*) mixture in 50–60% yield. Reaction of 9-decenoic acid with 1 equiv. of acetaldehyde and 2.2 equiv. of $EtAlCl_2$ affords (**69**) as a 4:1 (*E*):(*Z*) mixture in 66% yield.[27] Lactonization of the (*E*)-isomer provides recifeiolide. Reaction of 10-undecenoic acid with 1 equiv. of heptanal and 2.2 equiv. of $EtAlCl_2$ provides a 4:1 mixture of ricinelaidic acid (*E*)-(**70**) and ricinoleic acid (*Z*)-(**70**) in 41% yield (Scheme 14).[27]

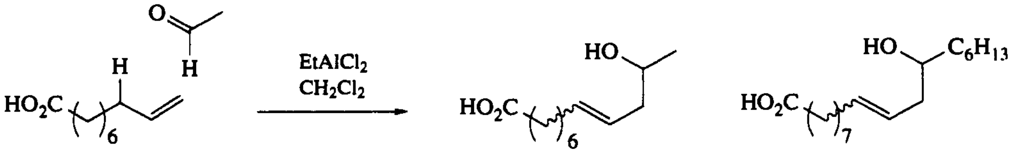

**(69)** **(70)**

**Scheme 14**

### 2.1.2.4 Ketones

Ketones are less electrophilic than aldehydes and the ene adducts are tertiary alcohols that are much less acid stable than the secondary alcohols produced from aldehydes. Ene adducts can be isolated from the $EtAlCl_2$-catalyzed reactions of cycloalkanones and reactive ene components, *i.e.* 1,1-disubstituted alkenes with one end of the double bond sterically accessible and the other end capable of stabilizing a positive charge in an intermediate.[52] The yields are moderate at best (6–55%), but the reaction does provide an extremely simple route to homoallylic tertiary alcohols.

#### *2.1.2.4.1 Electron-deficient ketones*

Thermal and Lewis acid catalyzed ene reactions of electron-deficient ketones proceed in good yield. Dialkyl oxomalonate esters[53–57] and pyruvate esters[58–60] have been most extensively studied. 1,2,3-Triketones,[61] methyl phenylglyoxylate,[62] carbonyl sulfide,[63] carbonyl cyanide,[64] hexafluoroacetone,[65,66] hexafluorocyclobutanone[67] and 1,1,1-trifluoromethyl ketones[68] have also been developed as enophiles.

Thermal and $SnCl_4$-catalyzed ene reactions of diethyl dioxomalonate have been extensively explored by Salomon.[56] The use of clay as a catalyst for this reaction has also been reported.[57] Mono-, 1,1-di-, 1,2-di- and tri-substituted alkenes afford ene adducts upon heating with 1 equiv. of diethyl oxomalonate at 80–185 °C for 1–340 h. Ene adducts can also be obtained in comparable yield with $SnCl_4$ at 0 °C. The enophile approaches the alkene from the less-hindered face. *Endo*/*exo* stereoisomerism is not possible

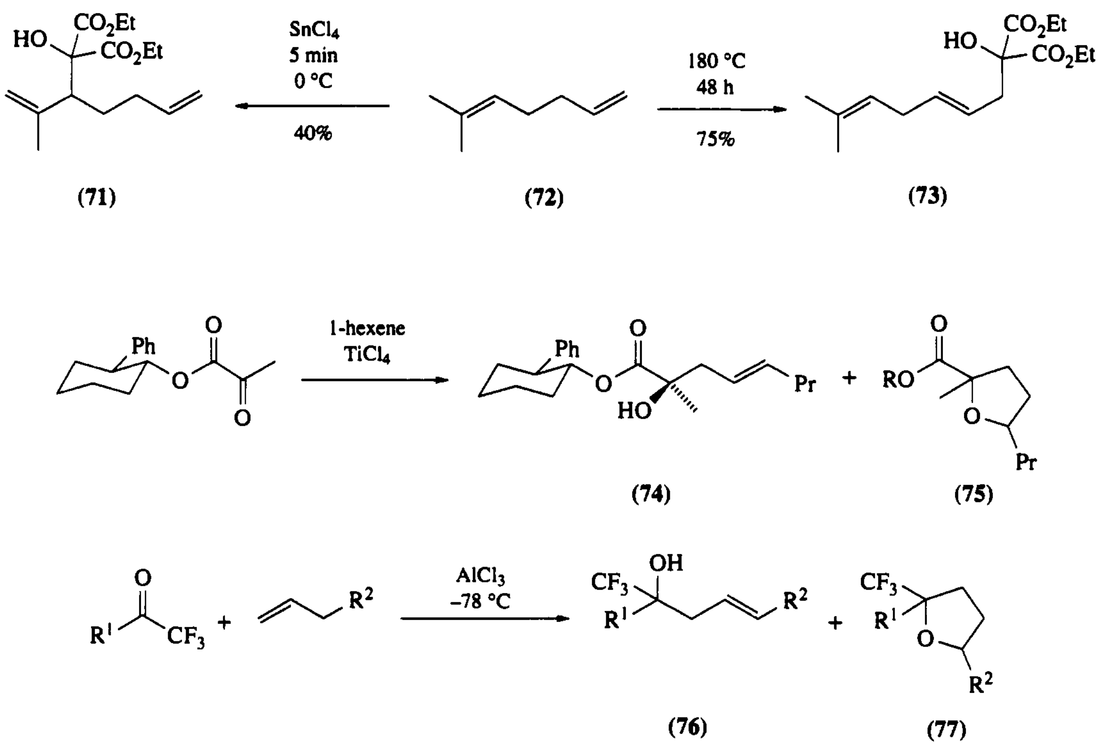

**Scheme 15**

with this symmetrical enophile. The regio- and stereo-chemistry of the double bond produced in the ene adduct was determined in several cases.[56]

Mechanistic differences between the thermal and Lewis acid catalyzed reactions were carefully examined. Thermal ene reaction with a series of 1-arylcyclopentenes show only a small rate enhancement with electron-donating substituents ($\rho = -1.2$). $SnCl_4$-catalyzed ene reactions show a strong rate enhancement with electron-donating substituents ($\rho = -3.9$). $SnCl_4$-catalyzed ene reaction with diene (**72**) occurs only at the more nucleophilic trisubstituted double bond to give (**71**) in 40% yield. Thermal ene reaction with (**72**) occurs mainly at the less-hindered terminal double bond to give an 11:1 ratio of (**73**) to (**71**) in 75% yield (Scheme 15).

Oxidation of the hydroxymalonic acid ene adducts with cerium(IV) ammonium nitrate in aqueous acetonitrile or sodium periodate results in oxidative didecarboxylation to give an allylcarboxylic acid.[55] The two step process ene reaction with diethyl oxomalonate and oxidative didecarboxylation provides a general procedure for the conversion of alkenes to allylcarboxylic acids.

Thermal ene reaction of β-pinene with methyl pyruvate provides a 1:1 mixture of *endo* and *exo* ene adducts.[58] This reaction can also be carried out in quantitative yield at 40 kbar for 17 h at 25 °C.[59] Contrary to a published report 8-phenylmenthyl pyruvate does not undergo a Lewis acid catalyzed ene reaction with 1-hexene.[60] However, reaction of *trans*-2-phenylcyclohexyl pyruvate with 1-hexene and 2 equiv. of $TiCl_4$ for 15 min at 0 °C affords a 15:1 mixture in 85% yield of ene adduct (**74**) in 86% diastereomeric excess and tetrahydrofuran (**75**) derived from (**74**) by protonation of the double bond and cyclization.

Thermal ene reaction of 1,2,3-indanetrione with β-pinene, 1-hexene and cyclohexene occurs in quantitative yield on heating at 80 °C for 0.3–58 h. The ene adducts can be converted to allylcarboxylic acids by oxidative didecarboxylation with periodate.[61] Heating β-pinene with methyl phenylglyoxylate for 120 h at 165 °C gives the ene adduct resulting from hydrogen abstraction from the less-hindered α-face.[62] Ene reaction of hexafluoroacetone and hexafluorocyclobutanone occurs readily with most classes of alkenes under very mild conditions.[65–67] 1,1,1-Trifluoromethyl ketones undergo $AlCl_3$-catalyzed ene reactions with terminal alkenes at –78 °C to give ene adducts (**76**) in good yield and small quantities of tetrahydrofurans (**77**) derived from (**76**) by protonation of the double bond and cyclization (Scheme 15).[68]

## 2.1.3 INTRAMOLECULAR REACTIONS

Intramolecular ene and Prins reactions have been divided into three classes depending on the connectivity pattern of the carbonyl and alkene.[5] In type I reactions the carbonyl group forms a bond to the internal carbon of the double bond. Concerted or stepwise ene reaction occurs to give (**79**). Prins reactions give products derived from cation (**78**), which may include ene type adducts (equation 15). Type I ene reactions are restricted to the formation of five- and six-membered rings. In type II reactions the carbonyl group forms a bond to the terminal carbon of the double bond. Concerted or stepwise ene reaction occurs to give (**81**). Prins reaction occurs to give products derived from (**80**; equation 16). Type II ene reactions are restricted to the formation of six- and seven-membered rings. Type II Prins reactions can form five-membered rings. In type III reactions the alkene-bearing side chain is attached to the carbonyl oxygen (**82**). These reactions are Prins reactions which give rise to cyclic ethers derived from cations (**83**) or (**84**; equation 17).

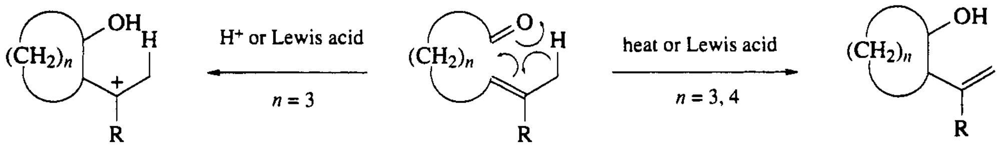

(15)

**(78)** **(79)**

**Type I**

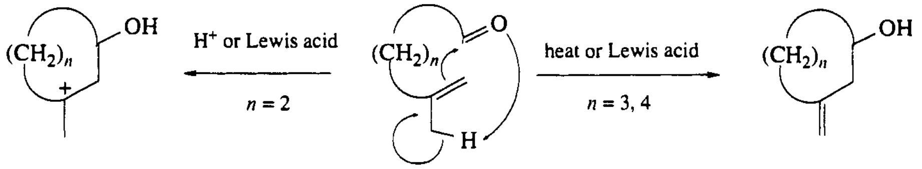

(16)

**(80)** **(81)**

**Type II**

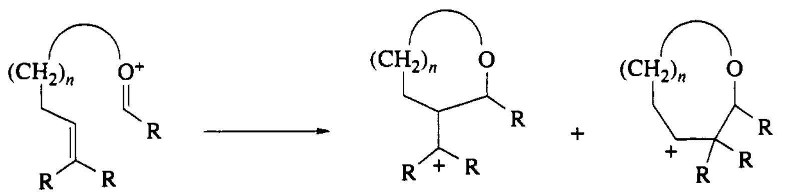

(17)

**(82)** **(83)** **(84)**

**Type III**

### 2.1.3.1 Type I Reactions

### *2.1.3.1.1 Formation of cyclohexanols*

Thermal cyclization of citronellal (**85**) to give mixtures of the four ene adducts (**86**)–(**89**) is the prototypical type I ene reaction. The thermal cyclization at 180 °C gives a 49:16:4:12 mixture of adducts.[69] Zinc bromide was shown to be an optimal Lewis acid catalyst giving a 66:4:0:0 mixture of adducts.[70] Use of Wilkinson's catalyst gives a 14:41:0:0 mixture of products, although the reasons for this stereocontrol are not understood.[71] Oxidation of citronellol with PCC gives (**85**), which undergoes an acid or Lewis acid catalyzed cyclization to (**86**)–(**89**). Further oxidation by PCC and conjugation of the double bond gives pulegone.[72] The scope and limitations of this oxidative cyclization have been determined.[72] Thermal ene reactions of citral have been investigated.[73]

Yamamoto has shown that the zinc phenoxide (**93**; 6 equiv.) catalyzes the ene reaction of (**90**) to give (**94**) in 91% yield in 90% enantiomeric excess.[74] The ene reaction of (**85**) is also catalyzed by (**93**) to give exclusively (**86**). However, the absolute stereochemistry of the adduct (**86**) is controlled by the methyl group of (**85**) rather than the stereochemistry of the catalyst (**93**). Zinc phenoxide (**93**) catalyzes the ene reaction of 7-methyl-6-octenal, lacking a methyl group at C-3, to provide racemic adduct in only 31% yield. These results indicate that the *gem* dimethyl group of (**90**) is necessary for asymmetric induction and that the buttressing effect of the methyl groups facilitates the cycloaddition.

Yamamoto has also shown that the hydrogen is selectively removed from the *trans* alkyl group.[74] Ene reaction of (**91**) catalyzed by (**93**) gives (**95**) in 89% yield in 91% enantiomeric excess. Similar cyclization of (**92**) gives (**96**) in 83% yield in 32% enantiomeric excess. The ene reactions of (**85**), (**90**), (**91**) and (**92**) indicate that *trans*-2-alkenylcyclohexanols are produced selectively in type I reactions (Scheme 16).

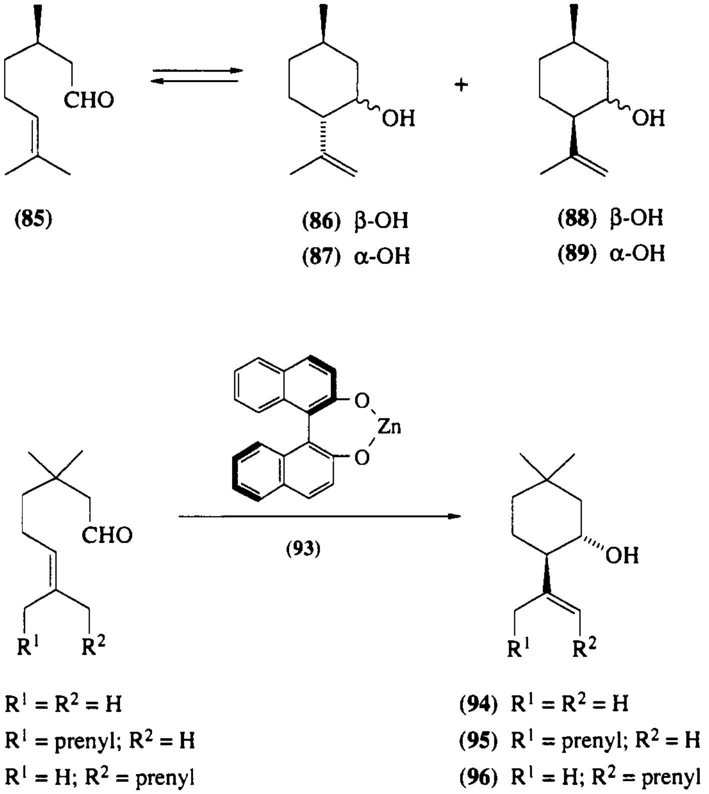

(**85**)

(**86**) β-OH
(**87**) α-OH

(**88**) β-OH
(**89**) α-OH

(**90**) $R^1 = R^2 = H$
(**91**) $R^1$ = prenyl; $R^2 = H$
(**92**) $R^1 = H$; $R^2$ = prenyl

(**94**) $R^1 = R^2 = H$
(**95**) $R^1$ = prenyl; $R^2 = H$
(**96**) $R^1 = H$; $R^2$ = prenyl

**Scheme 16**

Type I ene reactions with less nucleophilic 1,2-disubstituted double bonds have been more problematic.[75] Ene reaction has been achieved using 1 equiv. of $Me_2AlCl$ as catalyst at 0 °C.[76] Cyclization of the (*Z*)-aldehyde (**97**) gives exclusively the *cis* cyclohexanol (**99**), due to geometrical constraints on the transition state which preclude the formation of (**100**) and (**101**). Cyclization of the (*E*)-aldehyde (**98**) gives mainly the *trans* cyclohexanols (**100**) and (**101**). Smith has used this reaction as a key step in the synthesis of phyllanthoside.[77] $Me_2AlCl$-catalyzed reaction of (**102**) gives (**103**) in 83% yield along with 5% of several stereoisomers. Not only are the hydroxy and alkenyl groups *cis* as expected from the cyclization of a (*Z*)-alkene, but they are introduced on the face opposite the benzyloxymethyl group. $Me_2AlCl$ also catalyzes the ene reaction of ketone (**104**) giving a 4.5:1 mixture of tertiary alcohols (**105a**) and (**105b**) in 58% yield (Scheme 17).[76]

Type I ene reactions have been applied with good success to form polycyclic intermediates in total synthesis. $SnCl_4$-catalyzed cyclization of aldehyde (**106**) affords (**107**) as a mixture of isomers, one of which was converted to junenol.[78] Similar mixtures were obtained in the *cis* series. Cyclization of (**108**) with 0.002 M HCl in $CHCl_3$ provides (**109**), apparently as the *cis* isomer.[79] Cyclization of (**110**) with zinc iodide in $CH_2Cl_2$ gives a quantitative yield of a 1:3 mixture of (**111**) and (**112**).[80] It is possible that (**112**) is not a primary product since it can be formed by the acid-catalyzed isomerization of (**111**). Oxi-

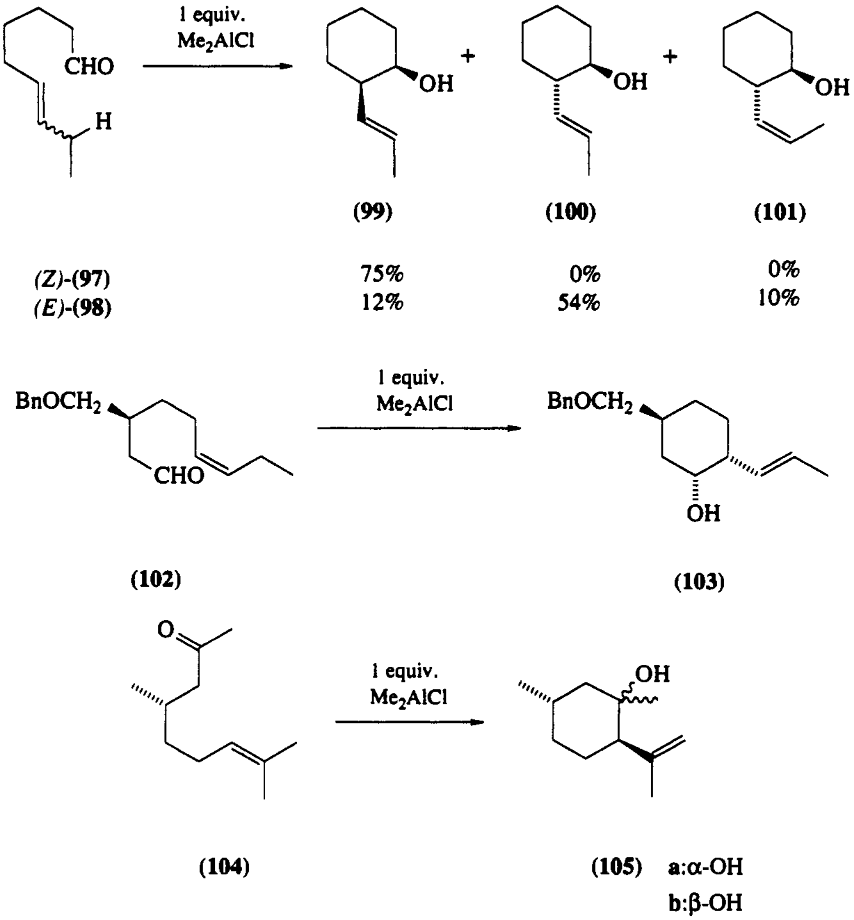

Scheme 17

dative Prins cyclization[72] of alcohol (**113**) with PCC gives (**114**) in 67% yield, which was converted to seychellene, isocycloseychellene and isoseychellene.[81] Periodate oxidation of diol (**115**) generated the aldehyde, which spontaneously cyclized to give (**116**) as a 3:1 mixture of diastereomers in 77% yield, which were converted to seychellene and cycloseychellene.[82] Treatment of β-keto ester (**117**) with $Me_2AlCl$ gives (**118**) in 33% yield and (**119**) in 19% yield.[52] No ene adducts can be isolated from treatment of the corresponding cycloalkanone lacking the carboethoxy group (Scheme 18).

Excellent yields of ene adducts have been obtained in Lewis acid catalyzed intramolecular ene reactions of homoallylic glyoxylates. Treatment of (**120**) with $SnCl_4$ in nitromethane provides (**121**) in 85% yield.[83] Similar treatment of (**122**) gives (**123**) in 50–60% yield, which was converted to actinobolin.[84] Allylic glyoxylates decompose in the presence of Lewis acids but give modest yields of ene adducts in thermal reactions (Scheme 19).[40]

### *2.1.3.1.2 Formation of cyclopentanols*

Intramolecular ene reactions of 1,6-dienes to give vinylcyclopentanes are much faster than intramolecular ene reactions of 1,7-dienes to give vinylcyclohexanes due to the less negative $\Delta S^{\ddagger}$ for formation of five-membered rings (see Volume 5, Section 1). Both reactions are thermodynamically favored even at elevated temperatures. Intramolecular ene reactions of unsaturated aldehydes are much faster than those of dienes due to the polarity of the carbonyl double bond. However, the ene reactions of carbonyl compounds are less exothermic than those of all carbon systems due to the greater bond strength of the carbonyl double bond. In type I intramolecular ene reactions, formation of cyclohexanols is both faster and more exothermic than formation of cyclopentanols due to the greater ring strain of cyclopentanols. Type I ene reactions to give cyclopentanols are reversible in unconstrained systems, which permits Lewis acid catalyzed stepwise reactions to compete effectively.

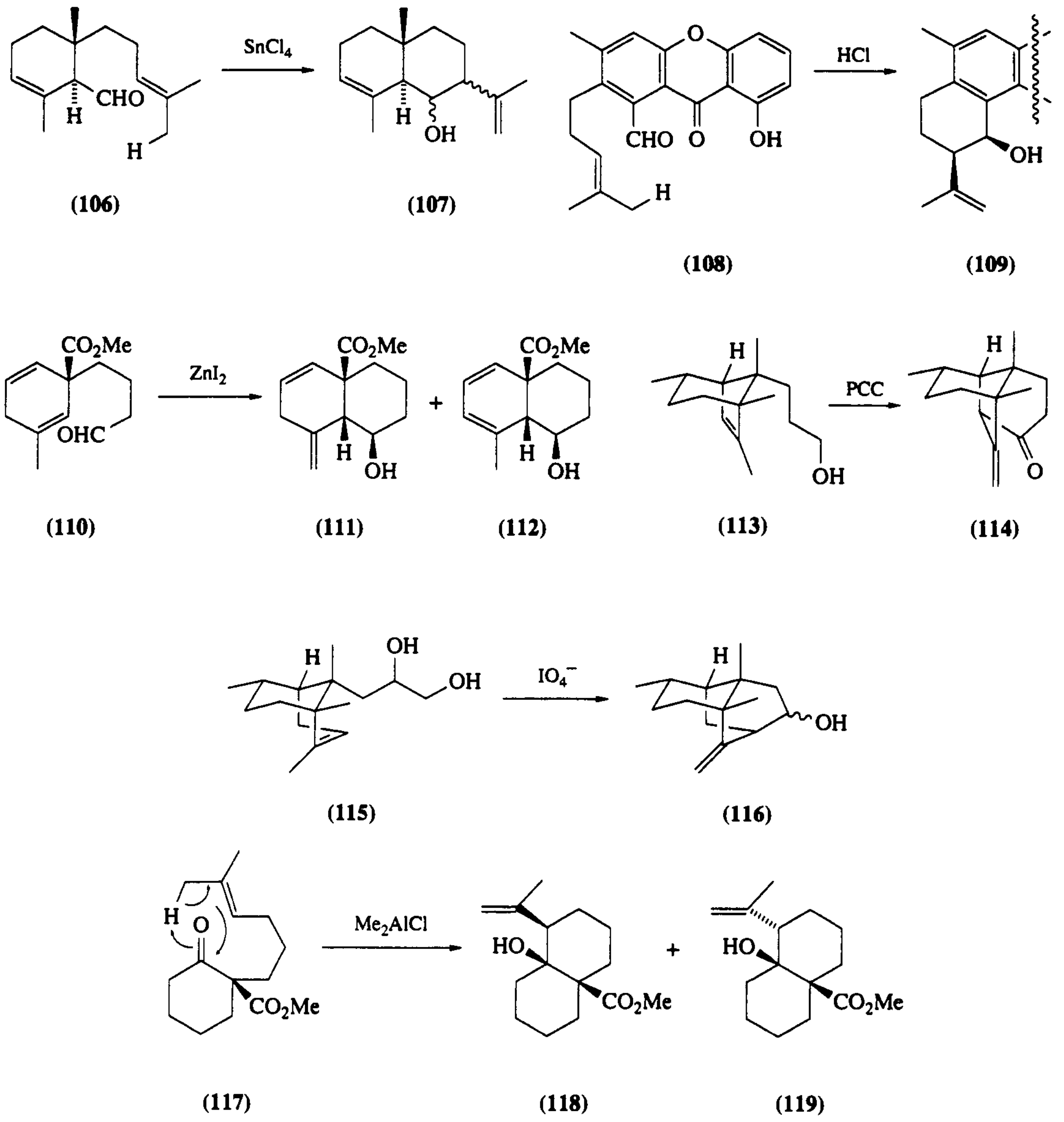
SnCl$_4$
HCl
ZnI$_2$
+
PCC
IO$_4^-$
Me$_2$AlCl
+
CHO
H
OH
CO$_2$Me
OHC
O
(106)
(107)
(108)
(109)
(110)
(111)
(112)
(113)
(114)
(115)
(116)
(117)
(118)
(119)

Scheme 18

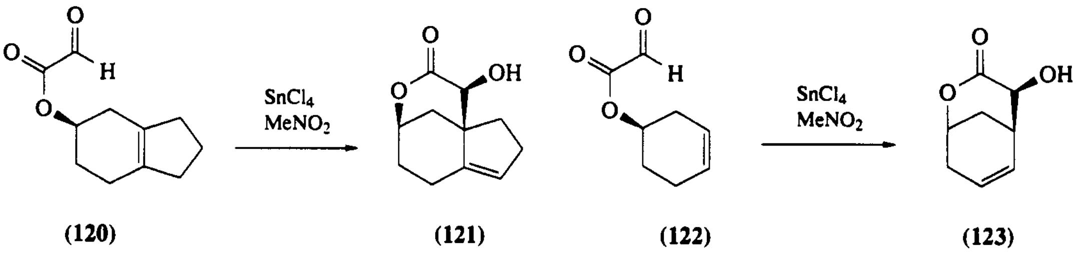
SnCl$_4$
MeNO$_2$
SnCl$_4$
MeNO$_2$
O
H
OH
(120)
(121)
(122)
(123)

Scheme 19

Treatment of (**124**) with 0.1 equiv. of $SnCl_4$ for <15 min at 0 °C gives ene adduct (**125**) in 85% yield as an 80:20 *cis:trans* mixture.[85] On the other hand, treatment of (**126**) with 2.9 equiv. of $BF_3{\cdot}Et_2O$ for 1 h at 25 °C gives cyclopentanone (**127**; Scheme 20).[86] Examination of the reactions of (**126**) with various alkylaluminum halides indicates that the nature of the reaction can be controlled by variation of the strength and amount of Lewis acid.[76] Treatment of (**126**) with 1 equiv. of $Me_2AlCl$ at –78 °C gives primarily (**128**) as a 4:1 mixture of α-methyl and β-methyl isomers. (In the text (**126**)–(**134**) refer to the alcohol or carbonyl compound obtained after workup). Alcohol (**128**) is probably formed by a concerted ene reaction or a π-complex rather than a zwitterionic intermediate, since concerted thermal ene reactions of 1,6-dienes give mainly *cis*-substituted cyclopentanes.[5]

Treatment of (**126**) with 2 equiv. of $Me_2AlCl$ gives the more electrophilic aldehyde–$(Me_2AlCl)_2$ complex or a species stoichiometrically equivalent to it. This complex reacts rapidly at –78 °C to give zwitterion (**129**). At –78 °C an irreversible [1,5] chloride shift to give chloro alkoxide (**132**) is the major process. At 0 °C, the [1,5] chloride shift is apparently reversible, so the products obtained from (**129**) by three competing processes are obtained. A [1,5] methyl shift gives (**130**) in 30% yield, a reversible [1,5]

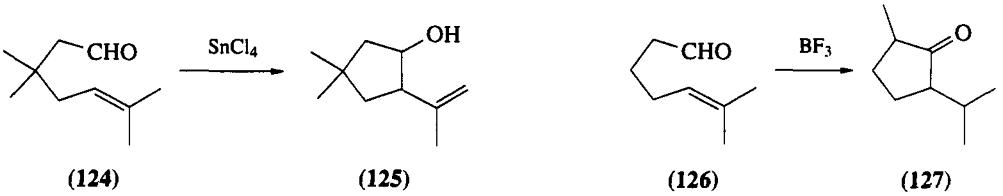
CHO
SnCl4
OH
CHO
BF3
O
(124)
(125)
(126)
(127)

Scheme 20

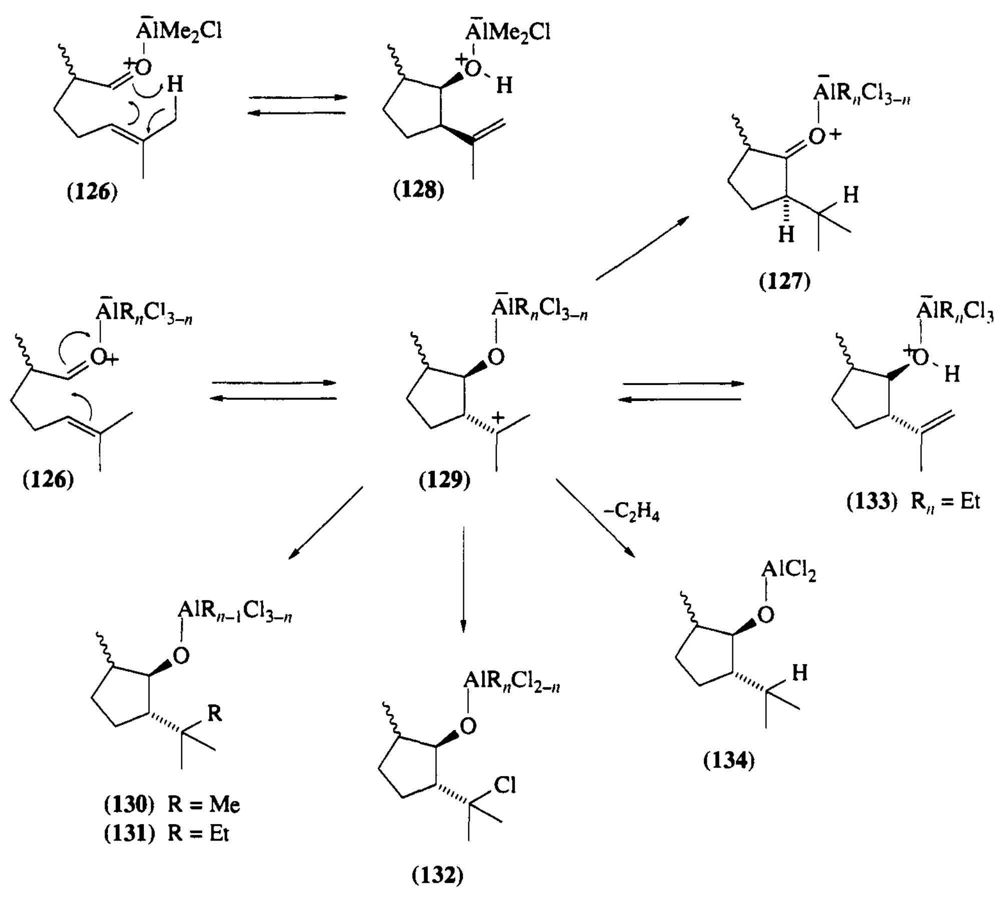
AlMe2Cl
+O
H
(126)
AlMe2Cl
+O
H
(128)
AlRnCl3–n
O+
H
H
(127)
AlRnCl3–n
O+
(126)
AlRnCl3–n
O
+
(129)
AlRnCl3–n
+O
H
(133) Rn = Et
–C2H4
AlRn–1Cl3–n
O
R
(130) R = Me
(131) R = Et
AlRnCl2–n
O
Cl
(132)
AlCl2
O
H
(134)

Scheme 21

proton shift followed by an irreversible loss of methane gives (**133**) in 45% yield and two [1,2] hydride shifts give (**127**) in 22% yield (Scheme 21). The formation of *trans* ene adduct (**133**) by a stepwise ene reaction confirms that the *cis* adduct (**128**) is not formed from an open zwitterion intermediate. The reactions of (**126**)–$(Me_2AlCl)_2$ are consistent with the general observation that enhancing the electrophilicity of a carbonyl compound accelerates stepwise reactions more than concerted reactions.

Treatment of (**126**) with 2 equiv. of $MeAlCl_2$ at –78 °C gives mainly (**127**). The greater Lewis acidity of $MeAlCl_2$ leads to a faster cyclization, makes (**132**) unstable, even at –78 °C, and makes the oxygen of (**129**) less basic, decreasing the rate of [1,5] proton shift, which gives (**133**). The methyl group of $MeAlCl_2$ is less basic than those of $Me_2AlCl$ so the [1,5] methyl shift to give (**130**) is slower. Addition of 2 equiv. of $EtAlCl_2$ to (**126**) at –78 °C gives mainly the reductive cyclization product (**134**; Scheme 21). The vastly different reactions with $EtAlCl_2$ and $MeAlCl_2$ were not anticipated. However, ethylaluminum compounds are much more nucleophilic than methylaluminum compounds and β-hydride delivery to the electrophilic site can be the major reaction of ethylaluminum compounds.[26]

Excellent yields of cyclopentanols are obtained in type I intramolecular ene reactions if the aldehyde and alkene are held in close proximity by a cyclic system. This not only accelerates the cyclization by decreasing $\Delta S^{\ddagger}$ for the ene reaction, but also stabilizes the product relative to the starting material by removing repulsive steric interactions in the starting material. Thermolysis of (**135a**) for 16 h in toluene at reflux yields 94% of ene adduct (**136**), which was converted to 2-deoxystemodione.[87] A mixture of products was obtained from (**135a**) in Lewis acid catalyzed reactions. The presence of the hydroxy group is significant, since no ene adduct could be obtained from (**135b**) under thermal or Lewis acid catalyzed conditions. Hydrolysis of the acetal of (**137**) with aqueous acetic acid gives aldehyde (**138**) in 62% yield

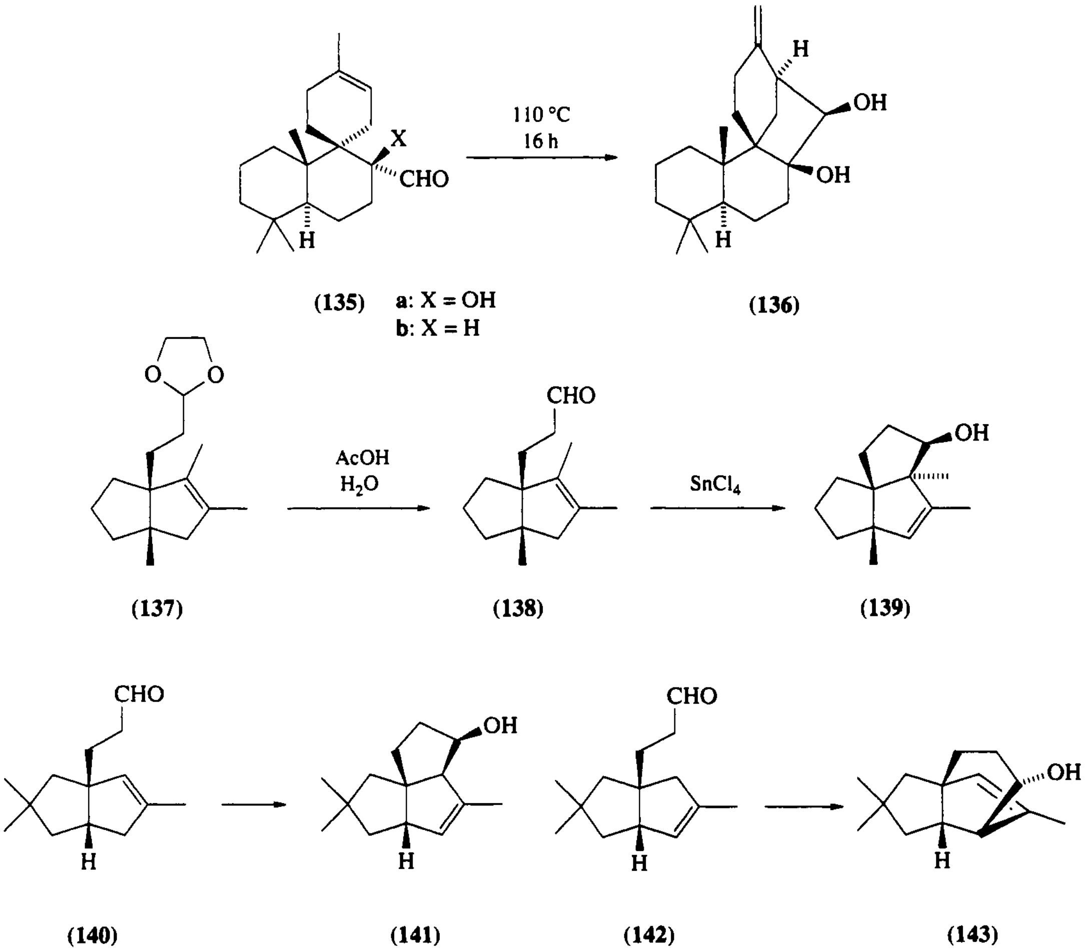

Scheme 22

and ene adduct (**139**) derived from it in 19% yield.[88] Cyclization of (**138**) with $SnCl_4$ in benzene at 5 °C gives (**139**) in 95% yield, an intermediate in the synthesis of isocomene. Cyclization of aldehydes (**140**) and (**142**) with $SnCl_4$ in benzene gives ene adducts (**141**) and (**143**), which are intermediates in the synthesis of pentalenene, in excellent yield (Scheme 22).[89]

Ketones cannot be used as enophiles in simple systems since products analogous to (**127**) are formed.[76] Success has been achieved in special cases. Treatment of keto epoxide (**144**) with $SnCl_4$ in $CH_2Cl_2$ at −78 °C gives ketol (**146**) in 96% yield *via* the intermediacy of ene adduct (**145**).[90] $EtAlCl_2$-catalyzed intramolecular ene reaction of the electron-deficient trifluoromethyl ketone (**147**) gives (**148**) in quantitative yield.[91] Diels–Alder adduct (**149**) undergoes a remarkable ene reaction with a ketone eno-

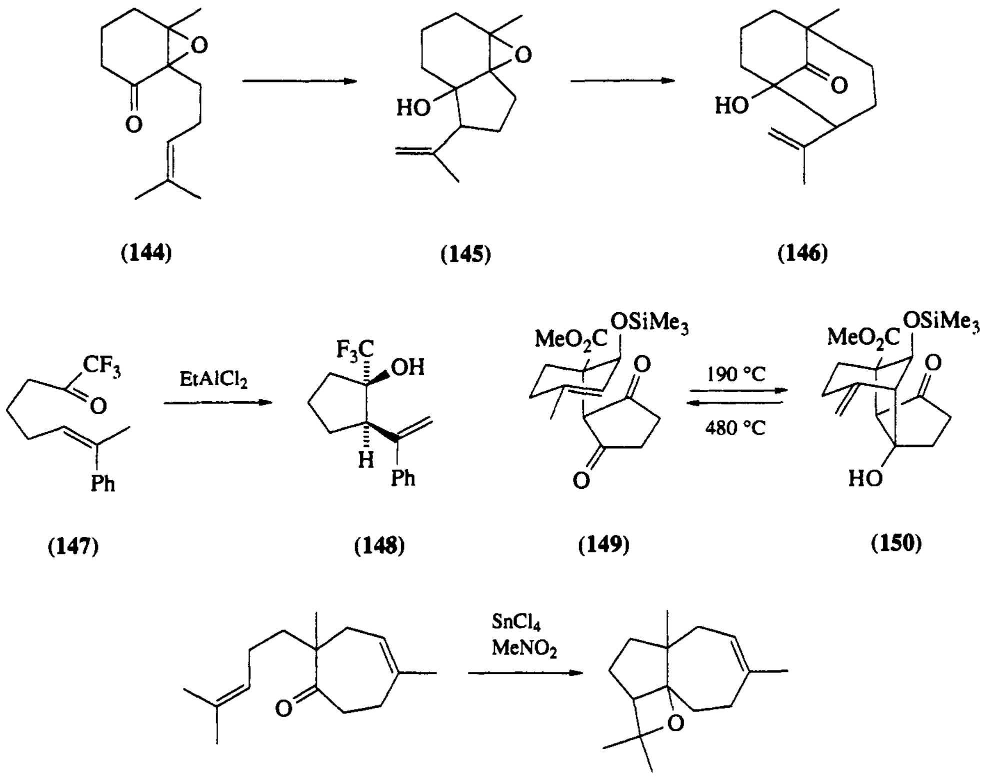
O
O
HO
O
HO
O
CF3
O
Ph
EtAlCl2
F3C
OH
H
Ph
MeO2C
OSiMe3
O
O
190 °C
480 °C
MeO2C
OSiMe3
O
HO
SnCl4
MeNO2
O
O

(**144**) (**145**) (**146**)

(**147**) (**148**) (**149**) (**150**)

(**151**) (**152**)

Scheme 23

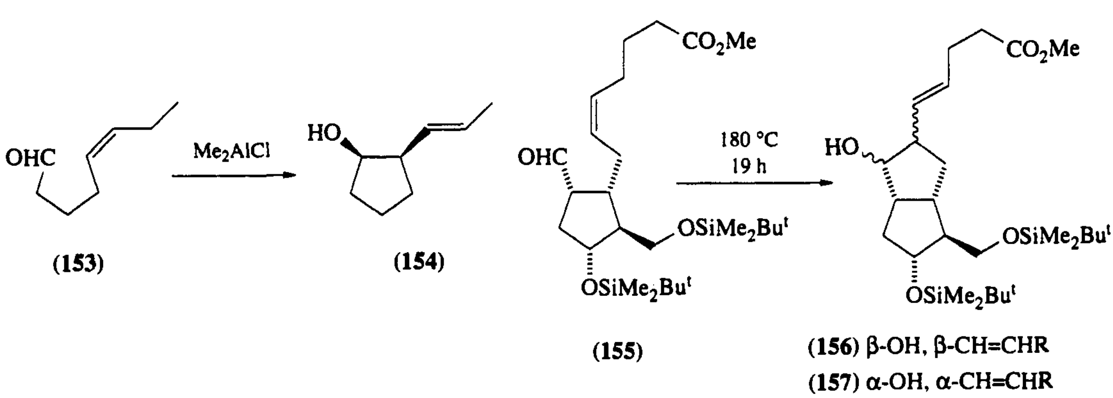
OHC
Me2AlCl
HO
CO2Me
OHC
OSiMe2Bu^t
OSiMe2Bu^t
180 °C
19 h
CO2Me
HO
OSiMe2Bu^t
OSiMe2Bu^t

(**153**) (**154**) (**155**)

(**156**) β-OH, β-CH=CHR

(**157**) α-OH, α-CH=CHR

Scheme 24

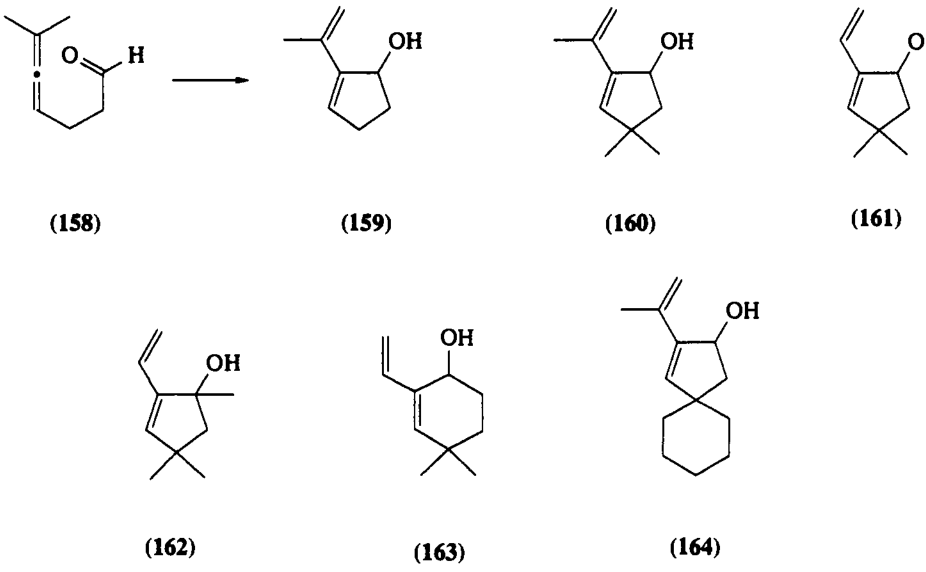

(158) (159) (160) (161)

(162) (163) (164)

Scheme 25

phile to give ene adduct (**150**), which was converted to verrucarol.[92] Treatment of (**151**) with $SnCl_4$ in nitromethane affords oxetane (**152**) in 58% yield.[93] Geometric constraints in (**151**) apparently preclude an ene reaction (Scheme 23).

Type I ene reactions of aldehydes with less nucleophilic 1,2-disubstituted double bonds have not been extensively explored. Treatment of (**153**) with 0.9 equiv. of $Me_2AlCl$ at 25 °C at high dilution gives (**154**) in 66% yield.[76] Pyrolysis of (**155**) in toluene for 19 h at 180 °C affords a 5:3 mixture of (**156**) and (**157**) in 87% yield.[94] The exclusive formation of *cis*-2-alkenylcyclopentanols in both of these cases is noteworthy (Scheme 24).

French workers have extensively explored type I intramolecular ene reactions of allenic aldehydes which give dienols.[95] Thermolysis of aldehydes and ketones such as (**158**) affords ene adducts (**159**; 42%, 150 °C, 30 min), (**160**; 75%, 150 °C, 60 min), (**161**; 70%, 200 °C, 15 min), (**162**; 52%, 200 °C, 60 min), (**163**; 65%, 230 °C, 60 min) and (**164**). Lewis acid catalysis was investigated with limited success (Scheme 25). Comparison of yields and reaction times indicates that buttressing *gem* methyl groups and trisubstituted allenes facilitate the reaction, while use of ketones and formation of six- rather than five-membered rings retard it.

### 2.1.3.2 Type II Reactions

Type II intramolecular ene reactions of unsaturated aldehydes and ketones have been extensively investigated. Ene reactions occur thermally or with Lewis acid catalysis to give 3-methylenecyclohexanols[52,96–109] or 3-methylenecycloheptanols.[110–114] 3-Methylenecyclopentanols cannot be formed in type II reactions. However, Lewis or Brønsted acid induced cyclization of $\gamma,\delta$-unsaturated aldehydes and ketones gives zwitterionic intermediates that lose a proton to give unsaturated cyclopentanols[85,122] or rearrange to cyclopentanones.[115–121]

### *2.1.3.2.1 Formation of cyclohexanols*

Treatment of (**165**) with $SnCl_4$ gives exclusively (**166**).[96] The selective formation of an axial alcohol and exocyclic double bond, a general characteristic of type II ene reactions, is required by either a concerted reaction or a stepwise reaction with an intramolecular proton transfer. Similar treatment of (**167**), as a mixture of isomers, gives the less stable isomer (**168**) with an axial alcohol and an equatorial methyl group, since the alcohol must be formed axial and the methyl group prefers to be equatorial in the transition state (Scheme 26).[97]

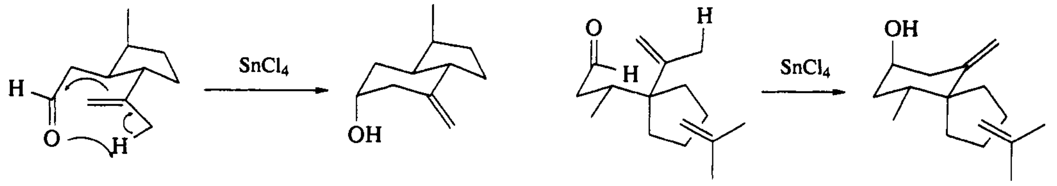

**(165)** **(166)** **(167)** **(168)**

Scheme 26

Reaction of alkylidenecyclohexanes with acrolein derivatives and $Me_2AlCl$ generates unsaturated aldehydes (**169**; $R^1$ = H), which cannot be isolated but undergo type II intramolecular ene reactions to give (**170**). Reaction of alkylidenecyclohexanes with methyl vinyl ketone derivatives gives (**169**; $R^1$ = Me), which can be isolated if the reaction is carried out at –20 °C but cyclize at 25 °C to give (**170**; Scheme 27).[88,99] The alcohol group is formed exclusively in the axial orientation. Alkyl substituents at $R^3$ and $R^2$ are formed preferentially equatorial. On the other hand, a bromo substituent at $R^2$ is formed preferentially axial. Similar results have been obtained with alkylidenecyclopentanes[98] and 2- and 3-substituted methylenecycloalkanes.[99] Wovkulich, Uskokovic and coworkers have used an ene reaction as a key step in the total synthesis of mevinolin and an angular methyl regioisomer of compactin (equation 18).[100] The aldehyde approaches from the less hindered α-face of the cyclohexene despite the fact that this forces the methyl and hydroxy groups into a 1,3-diaxial relationship.

Aldehydes can also serve to initiate cation–alkene cyclizations (Scheme 28).[101] Cyclization of aldehyde (**171**) with $SnCl_4$ in $CH_2Cl_2$/ethylene carbonate for 3 min at 0 °C gives alcohol (**172**) in 68% yield.[102] Similar cyclization of (**173**) for 20 s at –30 °C affords a 4:1 mixture of tetracycle (**175**) and tri-

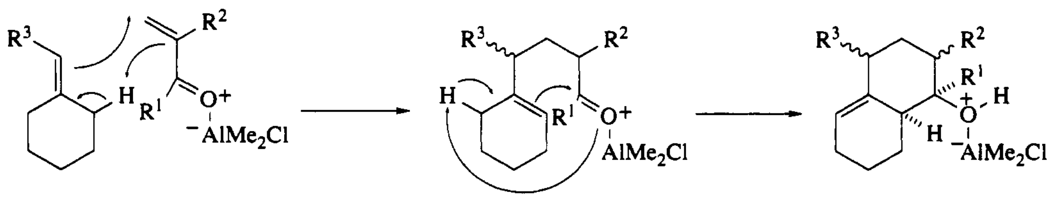

**(169)** **(170)**

Scheme 27

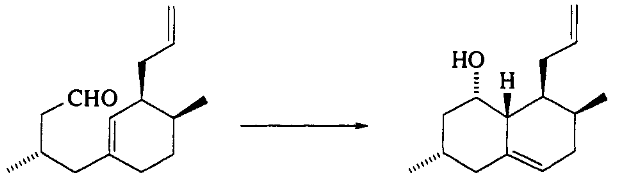

(18)

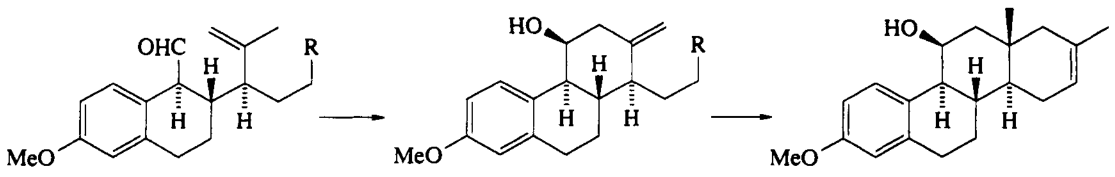

**(171)** R = C≡CMe

**(173)** R = $C(CH_2)Me$

**(172)** R = C≡CMe

**(174)** R = $C(CH_2)Me$

**(175)**

Scheme 28

cycle (**174**), which cyclized to (**175**) on further treatment with $SnCl_4$. This suggests that ene reaction of (**173**) to give (**174**) is the first step in the cation–alkene cyclization that gives (**175**; Scheme 28).

Treatment of (**176**) with $SnCl_4$ in $CH_2Cl_2$ for 3 min at 0 °C results in cyclization and cleavage of the ketal to give axial alcohol (**177**) in 70% yield as the sole product.[103] The alcohol is exclusively axial as required by the ene reaction despite severe steric interactions with adjacent axial substituents. Cyclization of (**178**) with $SnCl_4{\cdot}5H_2O$ in $CH_2Cl_2$ gives (**179**) in 93% yield, which was converted to citromycinone.[104] Lewis acid induced cyclization of (**180**), with a methyl group on carbon 2, 3 or 4, gives

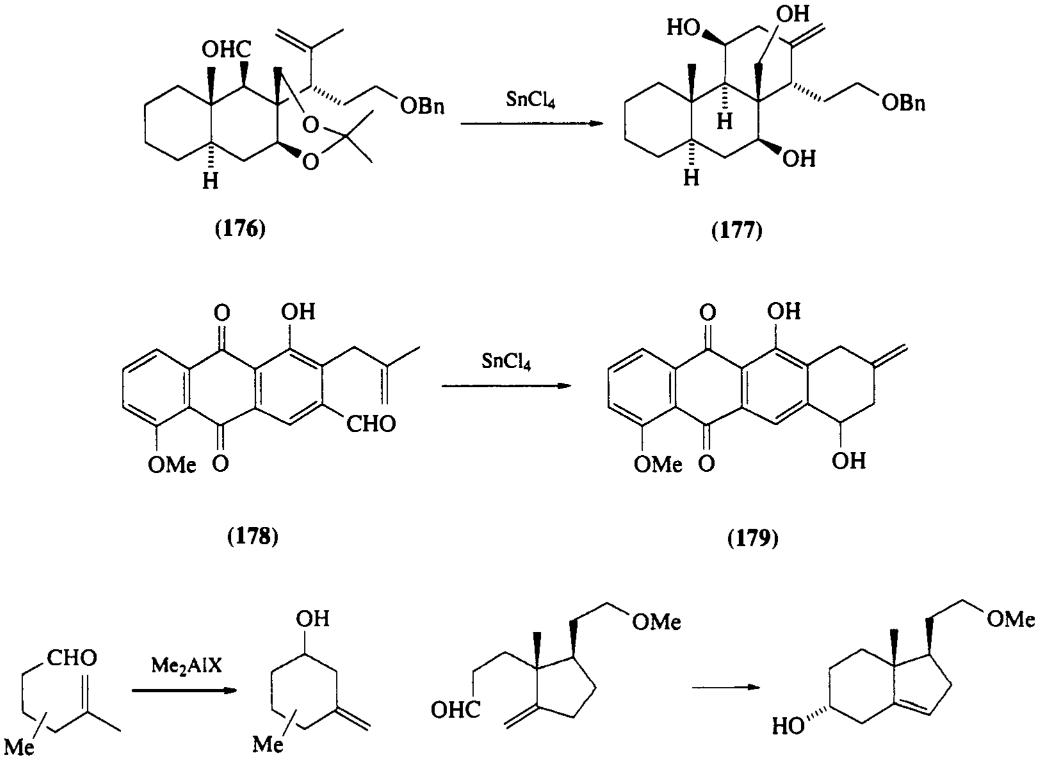
OHC
OBn
O
O
H
SnCl4
HO
OH
OBn
H
OH
H
O
OH
CHO
OMe
O
SnCl4
O
OH
OMe
O
OH
CHO
Me2AlX
Me
OH
Me
OMe
OHC
OMe
HO

(**176**) (**177**)

(**178**) (**179**)

(**180**) (**181**) (**182**) (**183**)

**Scheme 29**

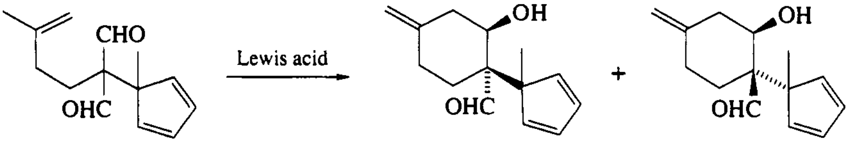
CHO
OHC
Lewis acid
OH
OHC
+
OH
OHC

(**184**) (**185**) (**186**)

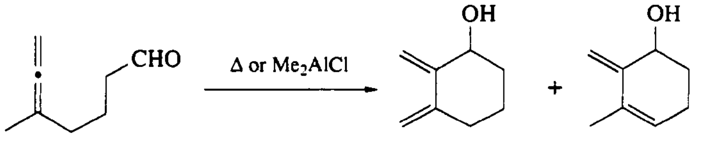
CHO
Δ or Me2AlCl
OH
+
OH

(19)

**Scheme 30**

selectively *cis*-6-methyl-3-methylenecyclohexanol, *trans*-5-methyl-3-methylenecyclohexanol and *cis*-4-methyl-3-methylenecyclohexanol (**181**) resulting from the methyl group adopting an equatorial conformation in the transition state.[105] Intramolecular ene reaction of (**182**) gives (**183**), which will be used for an enantiospecific route to the CD-ring system of steroids (Scheme 29).[106]

Intramolecular type II ene reaction of prochiral aldehyde (**184**) can give four adducts: both enantiomers of (**185**) and (**186**).[107] Cyclization on silica gel gives a 1:1 mixture. Cyclization with purified Eu(fod)$_3$ as Lewis acid catalyst for one week in $CH_2Cl_2$ gives an 8:1 mixture of (**185**), a potential intermediate for the synthesis of anguidine and (**186**). Use of Eu(hfc)$_3$, (+)-Eu(DPPM)$_3$ or (*S*)-1,1′-bi-2-naphthol/TiCl$_2$ as Lewis acid catalyst affords (**185**), with 20–38% enantiomeric excess.

Thermal or Lewis acid catalyzed type II ene reactions of allenic aldehydes give mixtures of dienols (equation 19; Scheme 30).[105]

Tertiary cyclohexanols such as (**170**; $R^1$ = Me) are formed in the ene reaction of ketones.[98] Treatment of acetal (**187**) with 2 M HCl in THF for 24 h at 25 °C gives the ketone, which cyclizes to α-ambrinol (**188**; 77%) and β-ambrinol (**189**; 6%). The selective formation of (**188**) with an axial alcohol suggests that this may be an ene rather than a Prins reaction.[108] Cyclization of unsaturated ketone (**190**) with 2 equiv. of AlCl$_3$ for 1.5 h at 25 °C gives a 3:1 mixture of (**191**) and (**192**) in 91% yield.[109] This cyclization, which leads to analogs of pumilotoxin A, is noteworthy for several reasons. The presence of the amine in (**193**) is remarkable. Two equivalents of catalyst are used; the first equivalent complexes with the amine, the second catalyzes the reaction. This is also the first example in which exocyclic trisubstituted double bonds were produced in a type II ene reaction. In simpler systems the opposite double bond stereoisomer predominates. An 88:12 mixture of (*E*)- and (*Z*)-3-ethylidenecyclohexanol (**194**) and (**195**) are produced in the cyclization of (**193**).[105] In both cases the major isomer results from the alkyl group adopting the less-hindered position in the transition state (Scheme 31).

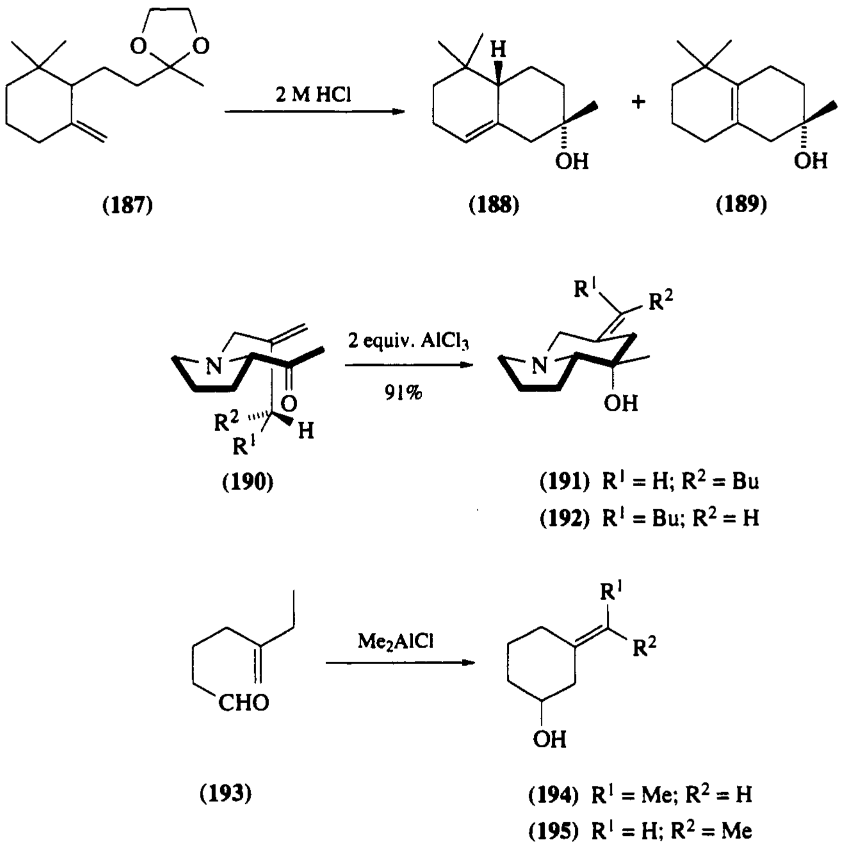
2 M HCl
(187)
(188)
(189)
2 equiv. AlCl$_3$
91%
(190)
(191) $R^1$ = H; $R^2$ = Bu
(192) $R^1$ = Bu; $R^2$ = H
$Me_2AlCl$
CHO
(193)
(194) $R^1$ = Me; $R^2$ = H
(195) $R^1$ = H; $R^2$ = Me

**Scheme 31**

### *2.1.3.2.2 Formation of cycloheptanols*

The first examples of type II cyclizations of unsaturated aldehydes are due to Marshall, who showed that these reactions are well suited to hydroazulene synthesis.[96,110,111] Treatment of (**196**) with $SnCl_4$ in benzene gives an 88:12 mixture of (**198**) and (**199**) in 94% yield.[110] Cyclization of (**197**) on silica gel provides (**200**) with a trace of the regioisomer. Cyclization of (**201**) with $SnCl_4$ in $CH_2Cl_2$ gives a 26:1 ratio of (**202**) and (**203**).[111] Cyclization of acetals or acylals derived from (**201**) is less selective, giving significant amounts of (**203**).[96] $SnCl_4$-catalyzed cyclization of (**204**) gives (**205**) as a mixture of isomers, which were used for the synthesis of kessanol.[112] Cyclization of (**206**) with $Me_2AlCl$ gives a 1.7:1 mixture of (**207**) and (**208**) in 62% yield, which were both converted to (+)-confertin.[113] Similar cyclization of aldehyde (**209**) gives (**210**) in 35% yield.[114] The stereochemistry of the methyl group controls the stereochemistry of the two new centers. The aldehyde adds to the double bond from the less hindered α-face; intramolecular proton transfer can only occur with an α-hydroxy group. These results indicate that the synthesis of cycloheptanols is general. Mixtures of isomers at the alcohol carbon are often obtained (Scheme 32).

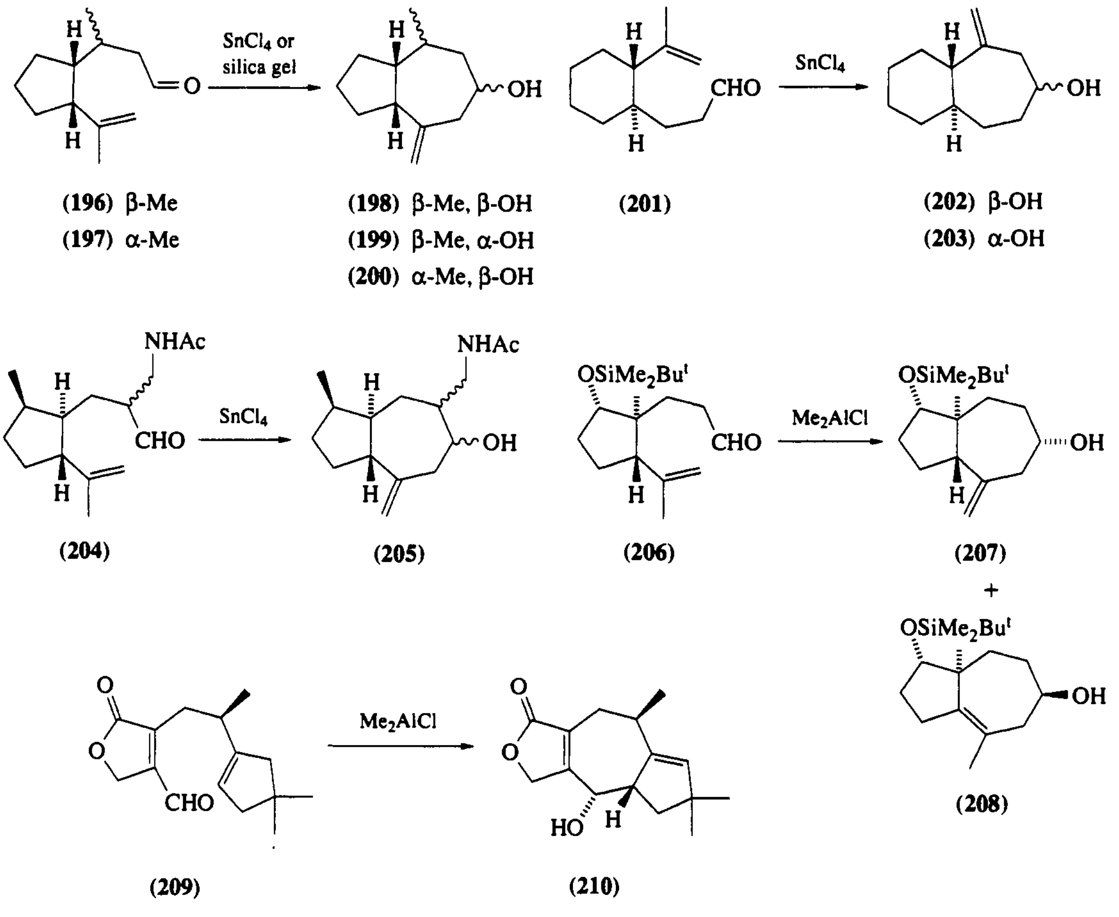

Scheme 32

### *2.1.3.2.3 Formation of cyclopentanols and cyclopentanones*

3-Methylenecyclopentanols cannot be formed by intramolecular ene reactions of γ,δ-unsaturated aldehydes, since the two-carbon tether makes the transition state for an ene reaction too strained. Cyclization to a zwitterionic intermediate does occur readily. Cyclization of (**211**) gives zwitterion (**212**), which undergoes two [1,2] hydride shifts to give cyclopentanone (**213**).[115–117] Using $MeAlCl_2$ as a catalyst, this process can be extended to methyl ketones.[118–121] Treatment of (**214**) with 1.1 equiv. of $MeAlCl_2$ in $CH_2Cl_2$ in a sealed tube at 90 °C for 2 h gives steroid intermediate (**216**) in 50% yield.[119] Similar cyclization of (**217**) provides a 9:1 mixture of *trans*- and *cis*-fused hydroazulenones (**218**) and (**219**) in 85% yield.[120] Cyclization of (**220**) gives androstane-2,17-dione (**221**) in 31% yield (Scheme 33).[121]

Cyclopentanol ene type products have been obtained in stepwise reactions. Treatment of (**223**) with $SnCl_4$ gives (**222**) in 42% yield. Cyclization with $TiCl_4$ affords chloro alcohol (**224**) in 80–90% yield.[85] Treatment of (**225**) with formic acid at 45 °C results in loss of methanol to give the unsaturated ketone, followed by transannular Prins reaction and loss of a proton to give, after hydrolysis of formate esters,

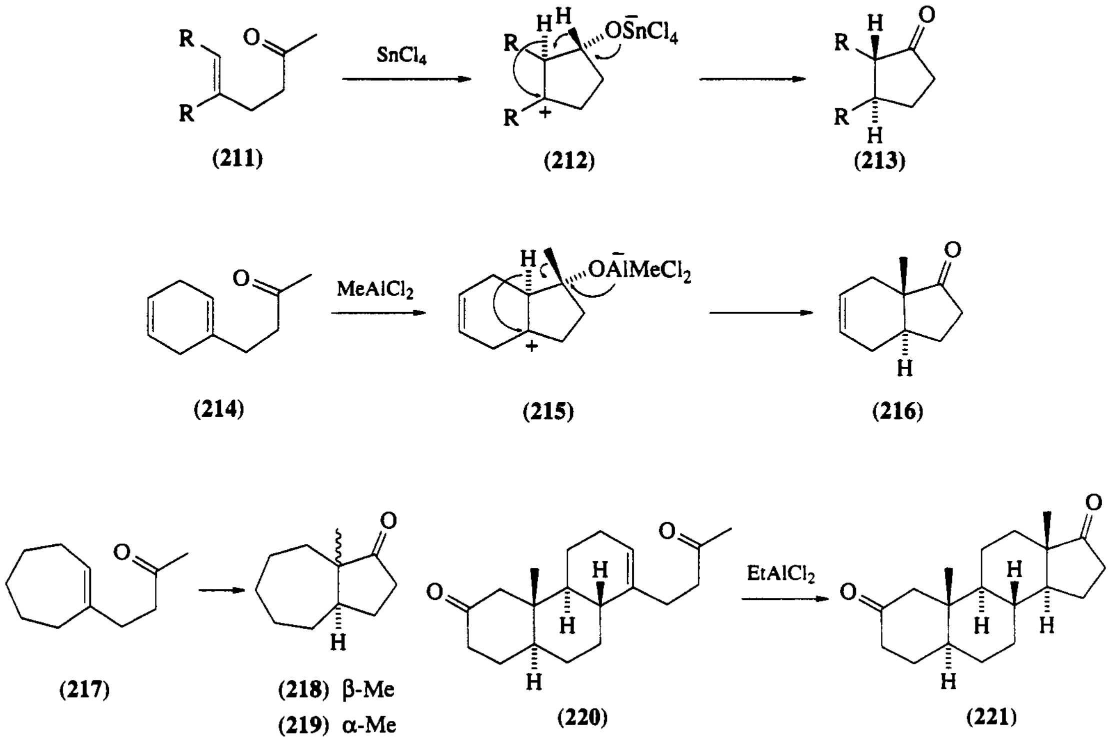

R
O
R
(211)
SnCl4
H
H
OSnCl4
R
R
+
(212)
H
O
R
R
H
(213)
O
(214)
MeAlCl2
H
OAlMeCl2
+
(215)
O
H
(216)
O
(217)
O
H
(218) β-Me
(219) α-Me
O
O
H
H
H
(220)
EtAlCl2
O
O
H
H
H
H
(221)

**Scheme 33**

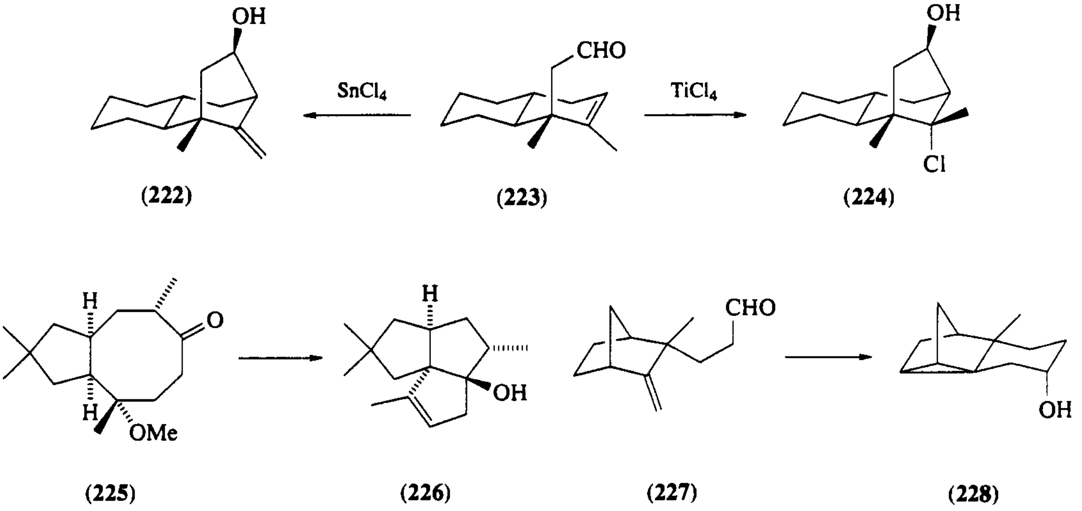

OH
(222)
SnCl4
CHO
(223)
TiCl4
OH
Cl
(224)
H
O
H
OMe
(225)
H
OH
(226)
CHO
(227)
OH
(228)

**Scheme 34**

(**226**) in 67% yield, an intermediate in the synthesis of pentalenolactones E and F.[122] $BF_3{\cdot}Et_2O$-induced cyclization of aldehyde (**227**), which cannot undergo an ene reaction, gives cyclopropane carbinol (**228**) in 67% yield (Scheme 34).[123]

### 2.1.3.3 Transannular Ene Reactions

Transannular ene reactions provide an effective route to bicyclic systems from medium-sized rings. Cyclization of preisocalamendiol (**229**) with $AlCl_3$ in ether for 10 min at 0 °C gives dienol (**230**) in 54% yield *via* a transannular ene reaction. A thermal ene reaction at 180 °C for 90 min gives (**230**) in 86% yield. Photolysis of cyclohexenones and methyl 1-cyclobutenecarboxylate gives tricyclo[6.2.0.0$^{2,7}$]decanes such as (**231**). Pyrolysis of (**231**) at 180–200 °C results in ring cleavage to give cyclodecadienone (**232**), which undergoes a transannular ene reaction to give decalin (**233**) in 92% yield.[124–127] This reaction has been used in the synthesis of calameon[125] and isocalamendiol.[126] Hydroazulenes can be obtained from transannular ene reactions of 5-cyclodecenones, if the substitution pattern of the double bond is different. Thermolysis of (**234**) in toluene for 16 h provides ene adduct (**235**) in 45% yield.[128] Treatment of dictyodial (**236**) with silica gel as catalyst in $CH_2Cl_2$ for 12 h at 25 °C gives sanadaol (**237**; Scheme 35).[129]

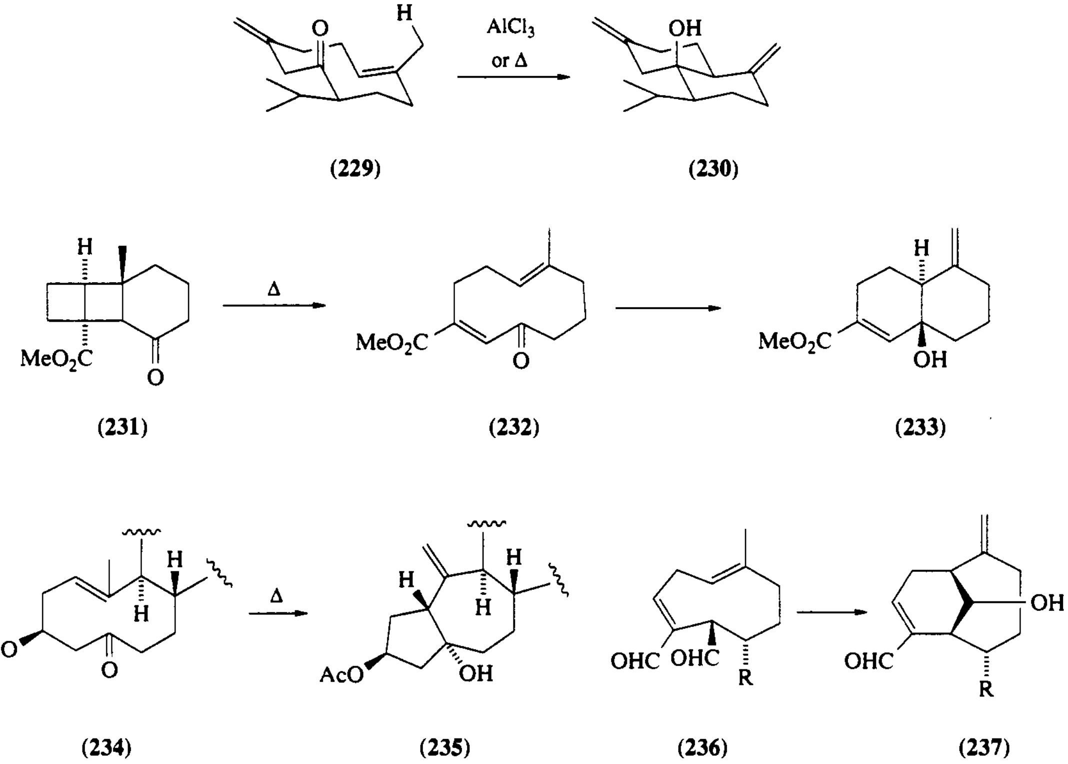

Scheme 35

### 2.1.3.4 Type III Reactions and other Reactions of Acetals

In type III reactions an acetal, hemiacetal or enol ether is converted to a cation (**82**), which cyclizes to (**83**) or (**84**) depending on the substitution pattern of the double bond (equation 17). If the internal end of the double bond is more highly substituted, cyclization occurs in an endocyclic mode to give (**84**). This reaction has been extensively explored for the formation of 4-chlorotetrahydropyrans (**5**; Scheme 2).[1,2,15,130–132] Cyclization of acetal (**238**) with $TiCl_4$ at –45 °C gives (**239**) in 95% yield as a single isomer in which both new ring substituents are equatorial.[131] Similar cyclization of the homopropargyl acetal (**240**) gives (**241**) in 70% yield as a single isomer. Reaction of alkoxyallylsilanes (**242**) with aldehydes and $AlCl_3$, $SnCl_4$ or $TiCl_4$ gives all *cis*-2,6-dialkyl-4-chlorotetrahydropyrans (**244**). The last step is probably the cyclization of (**243**), followed by trapping with chloride.[132]

Cyclization of tetrahydropyranyl ether (**245**) with $BF_3{\cdot}Et_2O$ in trichloroethanol gives (**246**) in 61% yield.[130] Similar cyclizations can be carried out on acylal derivatives.[133] Acid-catalyzed cyclization of 1-cyclohexeneacetic acid (**247**) with formaldehyde gives (**249**) *via* the presumed intermediacy of (**248**). If the terminal end of the double bond is more highly substituted, cyclization occurs in an exocyclic mode to give (**83**). Treatment of (**250**) with methanesulfonic acid gives (**251**), which cyclizes to give (**252**) after loss of a proton (Scheme 36).[134]

Overman has shown that treatment of cyclic acetals such as (**253**) with $SnCl_4$ results in cleavage to give (**254**), which undergoes an intramolecular Prins addition to give (**255**), which undergoes a pinacol rearrangement, providing (**256**; Scheme 37).[135] The stereochemistry of the methyl group results from a preference for equatorial substituents in a chair transition state for the Prins cyclization.

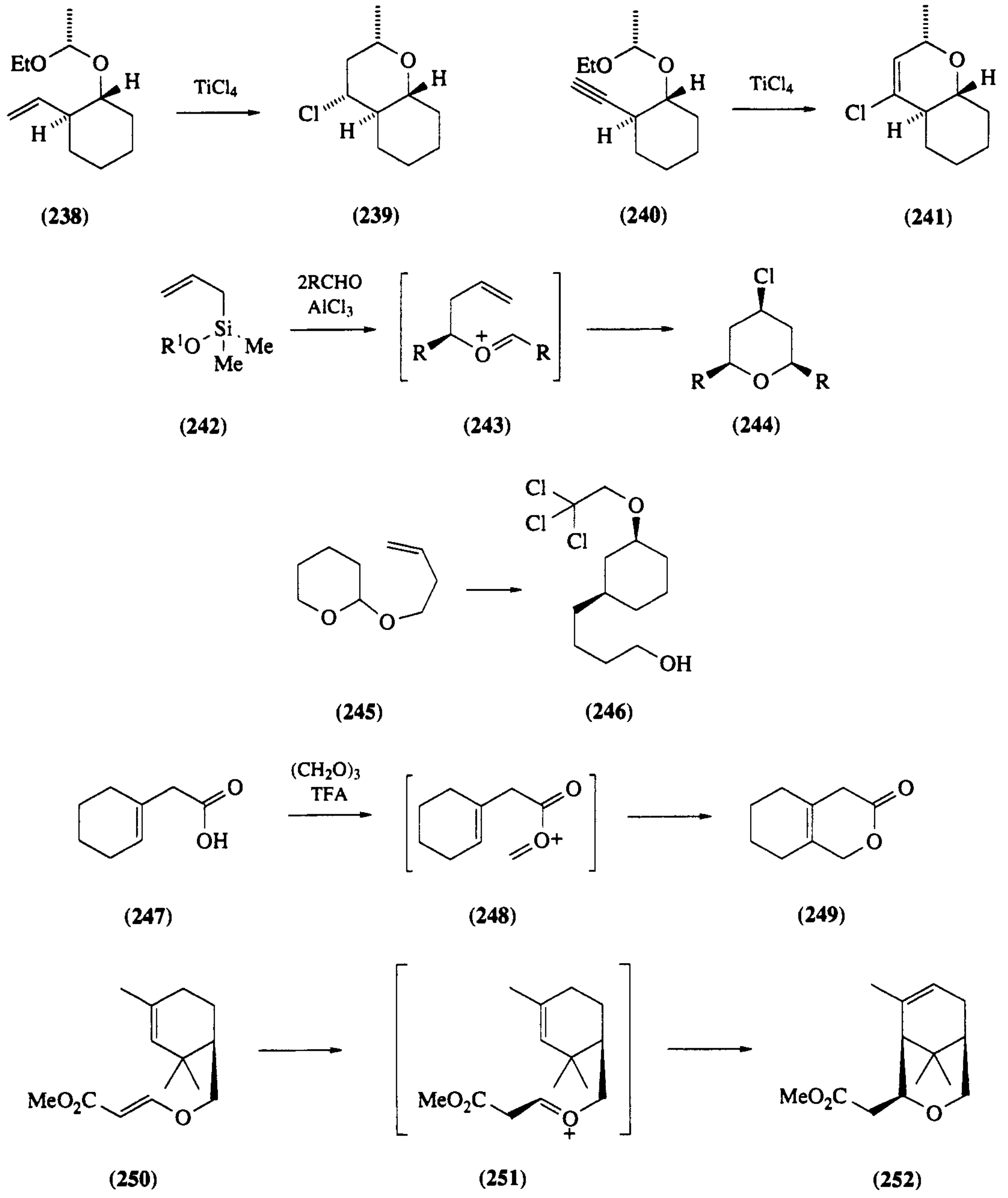

**Scheme 36**

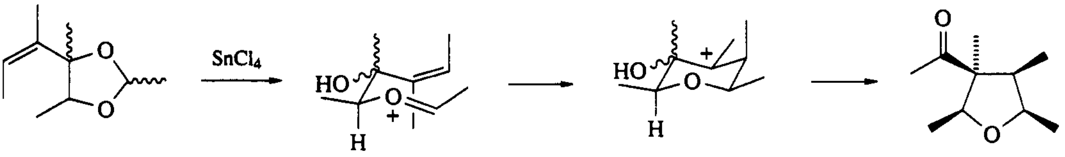

(253) (254) (255) (256)

Scheme 37

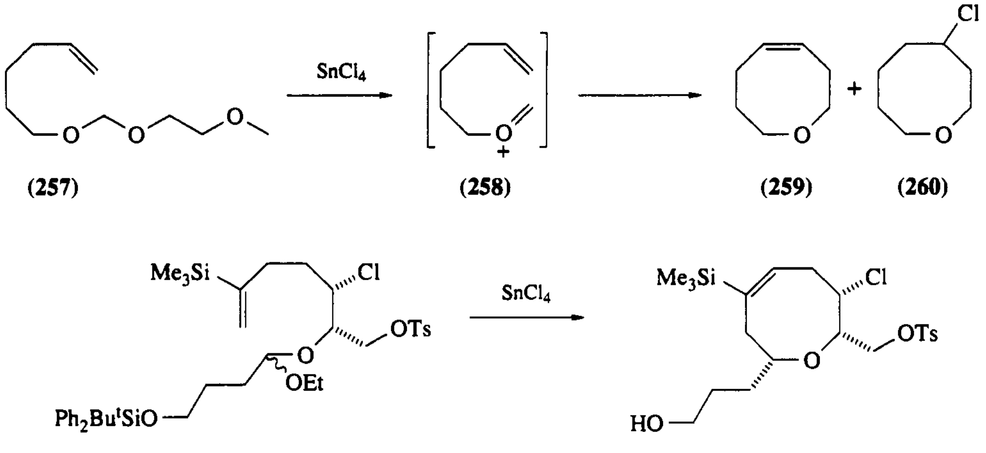

(257) (258) (259) (260)

(261) (262)

Scheme 38

Overman has also shown that eight- and nine-membered cyclic ethers can be prepared by type III cyclizations.[136] Treatment of (**257**) with 2 equiv. of $SnCl_4$ for 13 h at –20 °C gives (**258**), which cyclizes to give a 2:1 mixture of (**259**) and (**260**) in 83% yield.[137] Cleaner reaction mixtures have been obtained using vinylsilanes, as in the synthesis of laurenyne.[138] $SnCl_4$-mediated cyclization of acetal (**261**) in $CH_2Cl_2$ at 0 °C, followed by *O*-desilylation produces oxocene (**262**) in 37% yield as the sole cyclic ether (Scheme 38).

Aside from the type III cyclizations described above, acetals have seen limited use in intermolecular Prins reactions[138–141] and extensive use as initiators for cation–alkene cyclizations.[142,143] Only limited success has been achieved in Lewis acid catalyzed addition of acetals to alkenes.[138,139] Better success has been achieved in the synthesis of *C*-glycosides by Lewis acid catalyzed addition of glycosyl acetates[140] or glycals to alkenes.[141] Johnson has extensively developed the use of acetals as initiators for cation–alkene cyclizations.[142] Recent studies have shown that excellent asymmetric induction can be obtained using chiral acetals derived from optically active 2,3-butanediol or 2,4-pentanediol.[143]

## 2.1.4 THIOCARBONYL COMPOUNDS

Electron-deficient thiocarbonyl compounds such as hexafluorothioacetone,[144] methyl cyanodithioformate[145] and thioglyoxylate esters[146] are particularly reactive enophiles. Since these compounds react primarily or exclusively by pathway (b) to give allylic sulfides (**264**), rather than by pathway (a) to give homoallylic thiols (**263**), they are outside the scope of this chapter (Scheme 39). Thiobenzaldehyde, generated *in situ*, reacts with β-pinene to give thiol in 38% yield and sulfide in 19% yield.[147]

Intramolecular type I ene reactions of thiocarbonyl compounds do give homoallylic thiols. Pyrolysis of (**265**) for 10 min at 176 °C generates the thioaldehyde (**266**), which undergoes an ene reaction to give (**267**) in 60% yield.[148] Thioaldehyde (**268**), generated *in situ* by a retro Diels–Alder reaction of the anthracene adduct of the thiocarbonyl group in toluene at reflux, gives (**271**) and (**269**) gives (**272**). The (*E*)-isomer (**270**) does not give any ene adduct.[149] The selective abstraction of a proton from the allylic site *cis* to the thioaldehyde and the formation of cyclopentanes with *cis* thiol and alkenyl groups suggests that these are concerted ene reactions. Preparation of (**273**) by a retro Diels–alder reaction from the cy-

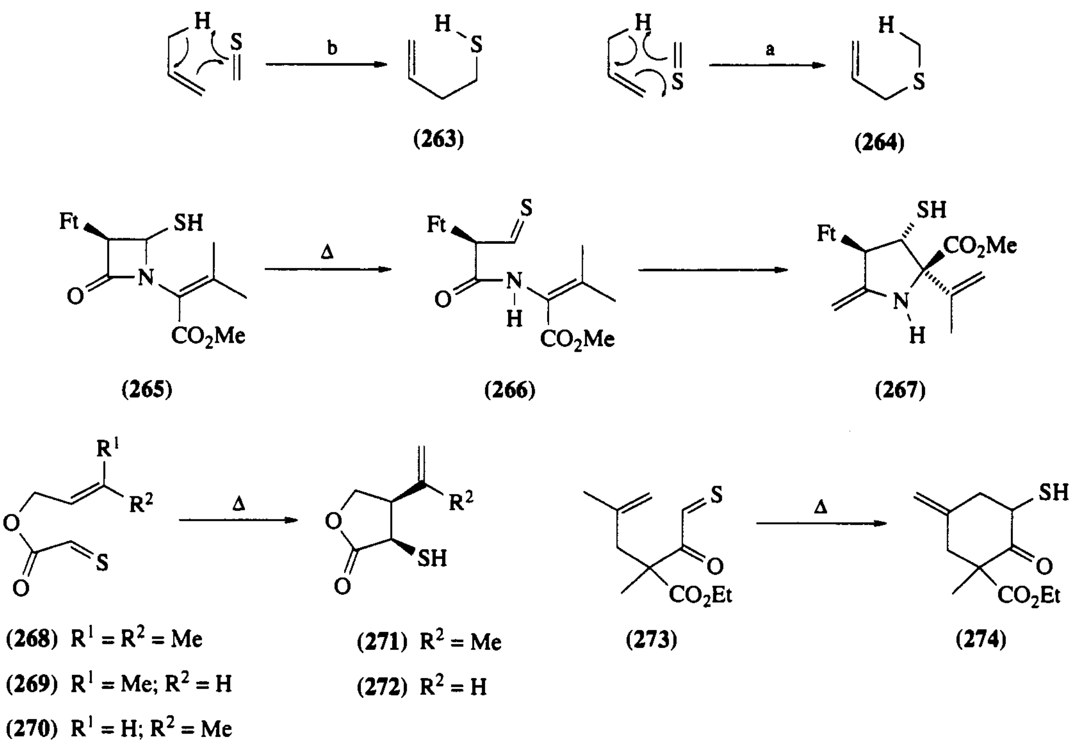

Scheme 39

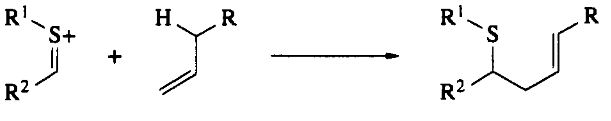

(20)

clopentadiene adduct at 140 °C leads to the type II intramolecular ene adduct (**274**) as mixture of stereoisomers in 62% yield (Scheme 39).[150]

Alkylated thioaldehydes, generated by Pummerer rearrangements or treatment of α-chloro sulfides with $SnCl_4$, undergo ene type reactions with terminal alkenes to give homoallylic sulfides in 50–70% yield (equation 20).[151–153]

## 2.1.5 ADDENDUM

*Lewis Acid Catalyzed Ene Reactions.* Johnson and coworkers have used the $BF_3{\cdot}Et_2O$ catalyzed ene reaction of formaldehyde shown in equation (8) to prepare the Inhoffen–Lythgoe diol.[154]

*Chloral.* Yamamoto has found that the organoaluminum reagent prepared from $Me_3Al$ and (*R*)-(+)-3,3′-bis(triphenylsilyl)binaphthol catalyzes the ene reaction of chloral and pentafluorobenzaldehyde with 1,1-disubstituted alkenes at −78 °C, giving the expected ene adducts in 40–90% yield and 60–90% enantiomeric excess.[155] Use of the sterically hindered chiral auxiliary is necessary. Low yields of racemic products are obtained with 3,3′-diphenylbinaphthol.

*Glyoxylate Esters.* Nakai and coworkers found that the reagent prepared from optically pure binaphthol and $(Pr^iO)_2TiX_2$ in the presence of molecular sieves catalyzes the ene reaction of methyl glyoxylate with 1,1-disubstituted alkenes at −30 °C to give ene adducts in 70–90% yield and 50–98% enantiomeric excess.[156] Nakai and coworkers found that the stereochemistry of ene reactions of glyoxylate esters with 2-butene could be controlled by choice of Lewis acid.[157] $SnCl_4$-catalyzed reaction of methyl glyoxylate with either (*E*)- or (*Z*)-2-butene at −78 °C gives a 4:1 mixture of *threo* adduct (**50**) and *erythro* adduct (**53**) in quantitative yield. Similar reactions catalyzed by $Me_2AlOTf$ give mixtures rich in the *erythro* adduct (**53**) in 30–60% yield. Very low yields are obtained with $Me_2AlCl$.

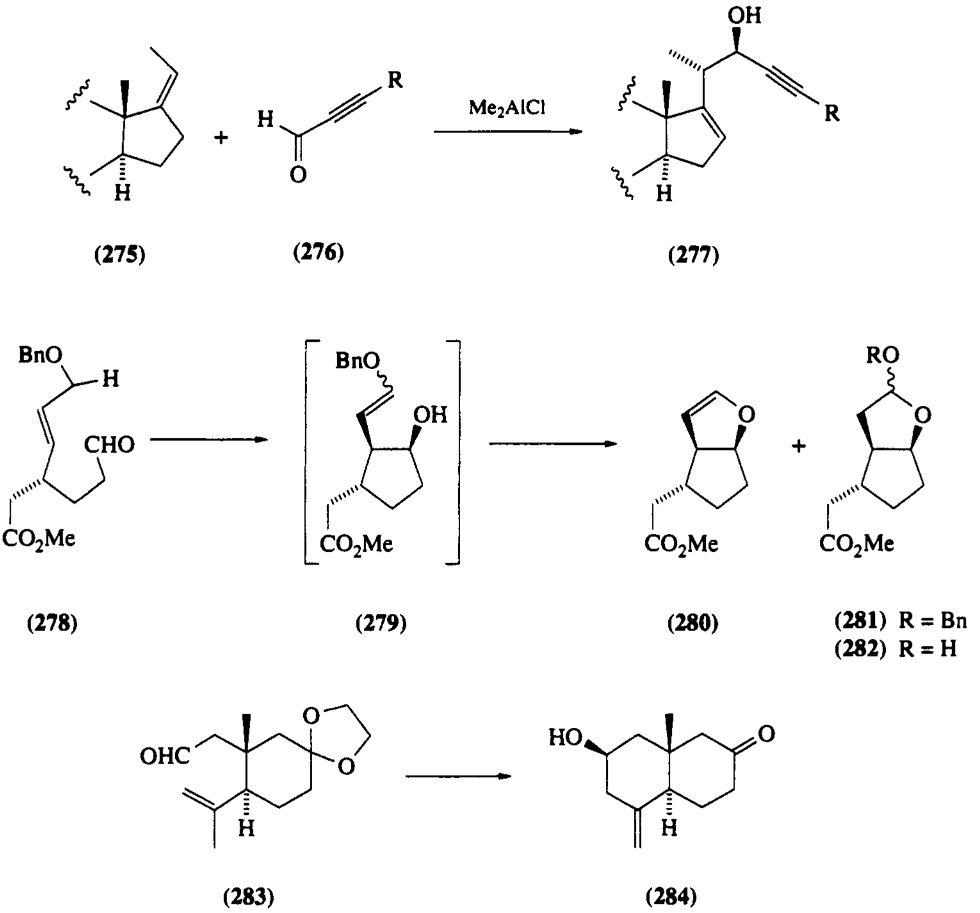
Me2AlCl
OH
R
H
O
(275)
(276)
(277)
BnO
CHO
CO2Me
OH
O
RO
(278)
(279)
(280)
(281) R = Bn
(282) R = H
OHC
HO
(283)
(284)

Scheme 40

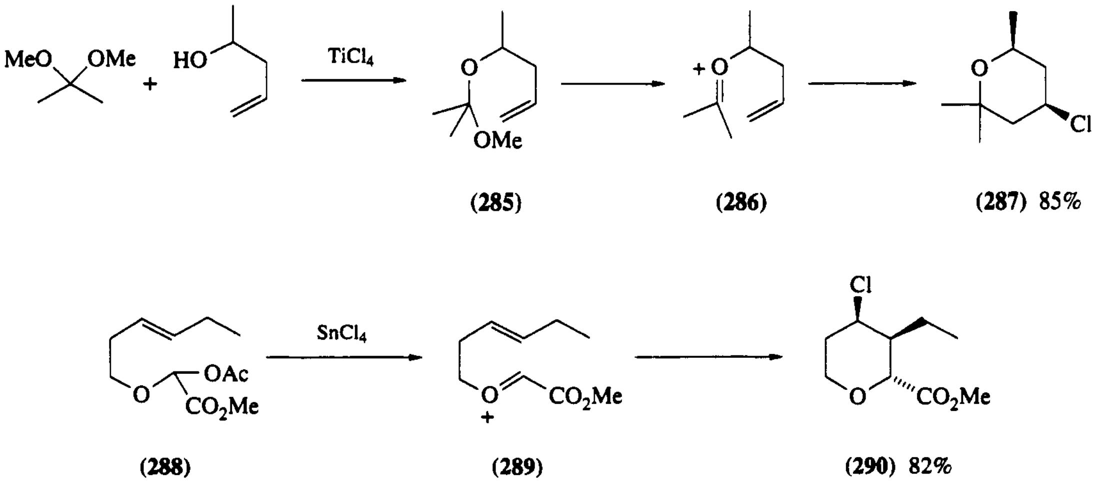
MeO
OMe
HO
TiCl4
O
OMe
+O
Cl
(285)
(286)
(287) 85%
OAc
CO2Me
SnCl4
O
+
Cl
(288)
(289)
(290) 82%

Scheme 41

*Aliphatic and Aromatic Aldehydes.* Reaction of (*Z*)-$\Delta^{17,20}$-steroidal alkene (**275**) with alkynic aldehydes (**276**; R = Me, $SiMe_3$ or = $Pr^i$; R ≠ H) in the presence of $Me_2AlCl$ produces a 9:1 mixture of the (20*S*,22*R*)-alcohol (**277**) and the (20*S*,22*S*)-alcohol.[158]

*Formation of Cyclopentanols.* Pyrolysis of unsaturated aldehyde (**278**) at 220 °C leads to ene adduct (**279**), which reacts further to give a mixture of enol ether (**280**) and acetal (**281**).[159] Hydrolysis of the mixture with hydrochloric acid gives hemiacetal (**282**) in 44% yield from (**278**).

*Formation of Cyclohexanols.* Tomioka and Koga used a type II ene reaction as a key step in the synthesis of the sesquiterpene (+)-ivalin.[160] Ene reaction and concomitant deprotection of the ketal occur on treatment of aldehyde (**283**) with $SnCl_4$ in $CH_2Cl_2$ at –10 to 25 °C to give 65% of adduct (**284**) with an axial hydroxy group.

*Type III Reactions and Other Reactions of Acetals.* Treatment of symmetric acetals with alkenols or alkynols in the presence of $TiCl_4$ results in transacetalization to give mixed acetals such as (**285**) which react further *via* cation (**286**) to give cyclic products such as (**287**) in 50–99% yield.[161] In this one-pot procedure the alkenic acetal need not be isolated. Acetoxyalkoxyacetic esters, such as (**288**), prepared in two steps from methyl glyoxylate and unsaturated alcohols, cyclize under the influence of $SnCl_4$ in $CH_2Cl_2$ to give oxacyclic carboxylic esters such as (**290**).[162] These reactions proceed through the intermediacy of methoxycarbonylcarbonium ion (**289**).

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# 2.2

# Allylsilanes, Allylstannanes and Related Systems

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## 2.2.1 INTRODUCTION

The carbon–carbon bond forming step of the Prins reaction, the reaction of an alkene with a carbonyl group (**1**) → (**2**), is, in one sense, the most fundamental reaction of synthetic organic chemistry: at one extreme it is the base-catalyzed aldol reaction, where the alkene component is an enolate ion and the carbonyl group is unprotonated, and at the other extreme it is the Friedel–Crafts reaction. It is a paradigm for a fast organic reaction: both bonds involved in the key step are π-bonds, which are simultaneously more reactive than σ-bonds and more susceptible to modification in reactivity by the presence or absence of substituents on either or both components. It is no wonder that, in one form or another, it is the most frequently used of all carbon–carbon bond forming reactions.

The problem with the Prins reaction itself, and the reason that it plays such an inconspicuous part in organic synthesis, is the difficulty in controlling the outcome: the cation (**2**) can, and usually does, suffer

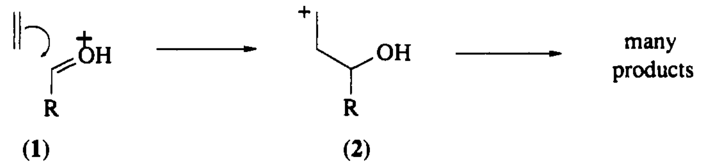

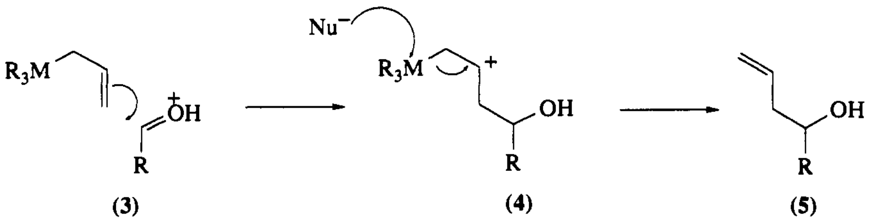

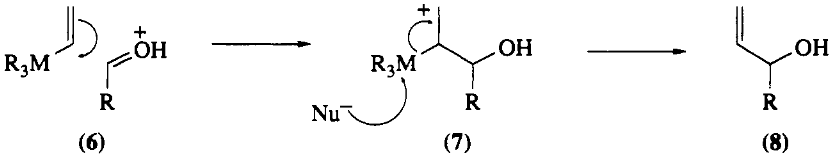

several different fates. Recently, cationic reactions of this type have been controlled by incorporating a silyl[1] or stannyl[2] group into the nucleophilic component of the reaction. Silyl or stannyl groups placed in the allylic (**3**) or the vinyl (**6**) position encourage the formation specifically of the cations (**4**) and (**7**), respectively, because these cations are *thermodynamically* stabilized by hyperconjugation of the adjacent carbon–metal bond. Furthermore, cations like these are *kinetically* unstable with respect to the loss of the metal group giving specifically the homoallylic alcohol (**5**) and the allylic alcohol (**8**). There is, of course, a continuity of behavior between that invoked here for silicon and tin and that of the more electropositive metals like lithium and magnesium, but it is necessary in the organization of books like this to make somewhat artificial separations of one group of reactions from another.

In this chapter, the carbon nucleophiles discussed will include allyl, vinyl, ethynyl, propargyl and allenyl silicon and tin systems, with most emphasis on the allyl, and the carbon electrophiles will be those at the oxidation level of aldehydes and ketones, including acetals, alkoxyalkyl halides and the corresponding sulfur derivatives. However, it does not include iminium ions, since these are covered in Chapter 4.3.

There is an extensive review of the electrophilic substitution reactions of allylsilanes and vinylsilanes in *Organic Reactions*[3] and the reactions of allylstannanes have been reviewed briefly.[4] The major books on synthetic organosilicon[5] and organotin chemistry[6] also cover the types of reaction discussed here.

## 2.2.2 MECHANISM

The very general picture of the mechanism given in the introduction needs to be modified somewhat. It is fairly clear that allylsilanes react in the manner illustrated as (**3**) → (**5**), except that the acid catalyst is almost invariably a Lewis acid not a proton. Protic acid is apt to induce protodesilylation in competition with carbon–carbon bond formation, but Lewis acids are less likely to attack the carbon–carbon double bond. The intervention of a cationic intermediate (**4**) has not been proved for this type of reaction, but there is good circumstantial evidence that cations are involved: by analogy with protodesilylation,[7] from the occasional formation of oxepins, without loss of the silyl group,[8] and from the stereochemistry of the reaction.

With allylstannanes, however, the mechanistic picture is less clear: some Lewis acids, especially tin(IV) chloride, react very fast with allylstannanes, inducing an exchange of the trialkyltin group for the metal of the Lewis acid. The actual carbon nucleophile taking part in the carbon–carbon bond forming step, therefore, may not always be the original allylstannane.[9] Furthermore, tin is more electropositive and more powerful as a Lewis acid than silicon, so that it is possible, with a cyclic intermediate (**9**), for allylstannanes to react with aldehydes in the absence of any external acid catalysis. All that is needed to induce this behavior is heat,[2] pressure,[10] or electron-withdrawing ligands on the tin to increase its Lewis acidity.[11] These reactions are potentially, and sometimes actually, reversible, as in the conversion of the homoallylic alcohol derivative (**10**) into the homoallylic alcohol derivative (**11**).[12] Finally, some

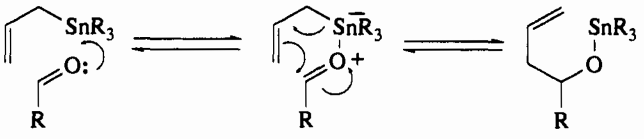
SnR3
O:
R
SnR3
O+
R
SnR3
O
R

(9)

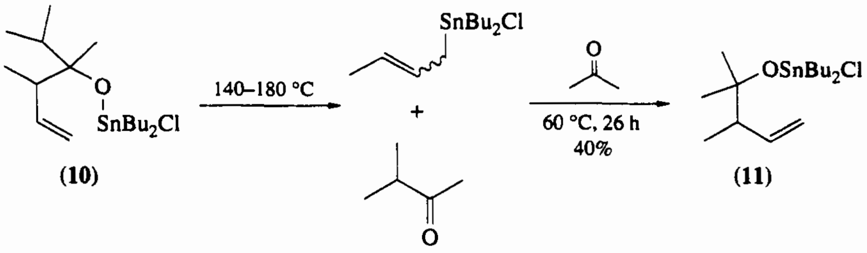
O
SnBu2Cl
140–180 °C
SnBu2Cl
+
O
O
60 °C, 26 h
40%
OSnBu2Cl

(10) (11)

allylstannane reactions may take place in the tin(II) oxidation state, where the allylstannane is generated *in situ*.[13]

A different set of mechanistic possibilities comes into play when nucleophilic catalysis is used in place of the electrophilic catalysis induced by Lewis acids. The most common form of this reaction is fluoride ion catalysis of allylsilane reactions, where the carbon nucleophile is probably a hypervalent allylsilane (**12**), with the fluoride ion coordinated to the silicon, making the allylsilane unit nucleophilic enough to react with aldehydes without acid catalysis.[14]

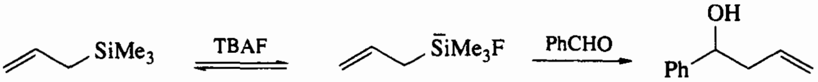
SiMe3
TBAF
SiMe3F
PhCHO
OH
Ph

(12)

Allylsilanes are very stable thermally with respect to allylic shift of the silyl group[15] and regioisomeric allylsilanes are therefore very reliable in the regiospecificity of their Lewis acid catalyzed reactions (Scheme 1), the electrophile always bonding to the terminus of the allyl unit remote from the silyl group.[16] In contrast, fluoride-catalyzed reactions are not regiospecific (Scheme 2),[14] probably because

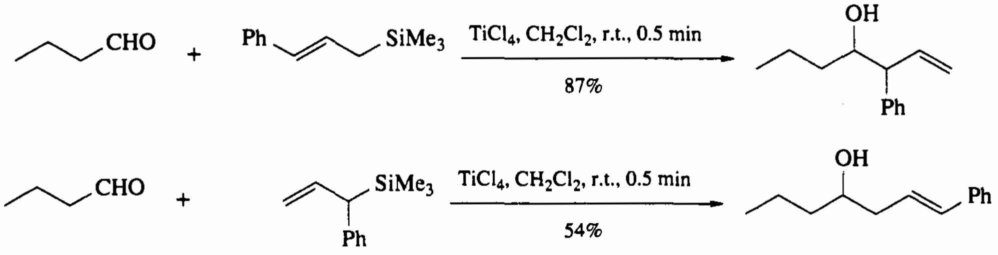
CHO
+
Ph
SiMe3
TiCl4, CH2Cl2, r.t., 0.5 min
87%
OH
Ph
CHO
+
SiMe3
Ph
TiCl4, CH2Cl2, r.t., 0.5 min
54%
OH
Ph

Scheme 1

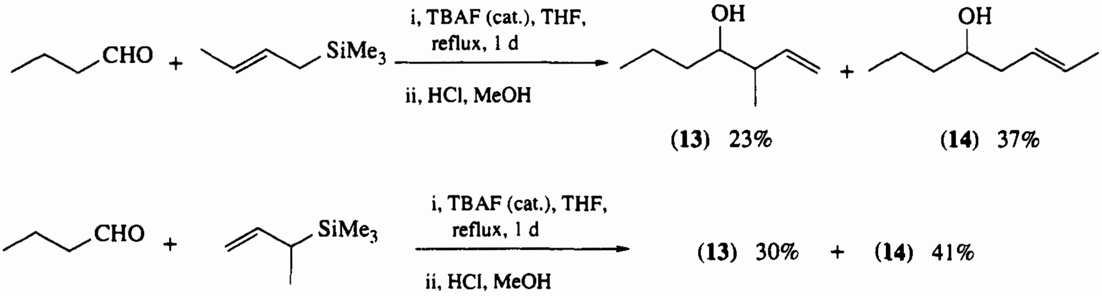
CHO
+
SiMe3
i, TBAF (cat.), THF, reflux, 1 d
ii, HCl, MeOH
OH
+
OH
(13) 23%
(14) 37%
CHO
+
SiMe3
i, TBAF (cat.), THF, reflux, 1 d
ii, HCl, MeOH
(13) 30% + (14) 41%

Scheme 2

the hypervalent intermediate is no longer stable with respect to [1,3] sigmatropic shift of the silyl group.[17] Allylstannanes are less stable than allylsilanes in this respect, but they can react regiospecifically both in Lewis acid catalyzed reactions (Scheme 3)[18] and in thermal reactions (Scheme 4).[19] However, allylstannane reactions are not reliably regiospecific in this sense when other Lewis acids are used. They can even be regioselective in the opposite sense (Scheme 5).[20] The tributylstannyl group in the crotylstannane (**15**) is replaced by the chlorostannyl group from the Lewis acid, as already mentioned; the new allyl–metal species (**16**), which can be detected as an intermediate, is regioisomeric with that of the original allylstannane, and reacts in the normal way, with a second allylic transposition, to give the homoallylic alcohol (**17**), regioisomeric with that expected from the normal reaction. However, since the halogenated allylstannane is allylically unstable, this type of selectivity is rarely reliable. Furthermore, allyltrialkylstannanes themselves are allylically stable only in nonpolar solvents, and there is a risk of allylic interconversion even before the electrophile is introduced.

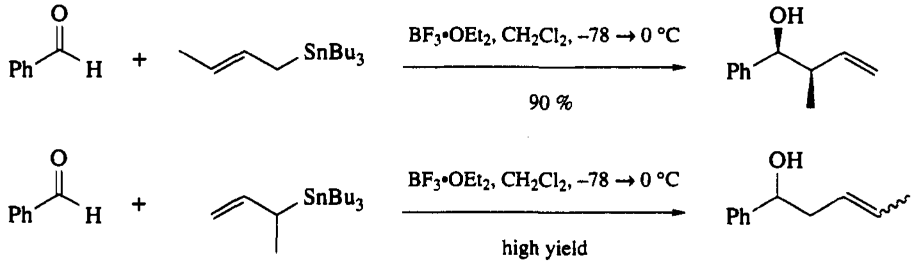

**Scheme 3**

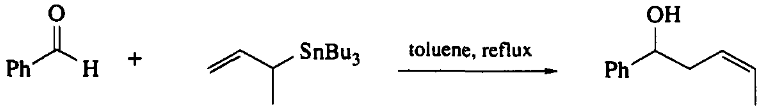

**Scheme 4**

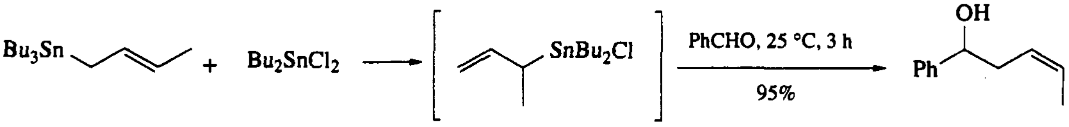

(**15**) (**16**) (**17**)

**Scheme 5**

The mechanism of the reactions of the other types of silanes and stannanes to be discussed in this chapter has hardly been studied, but the general outline given in the introduction is likely to be an adequate framework for thinking about these reactions. Fluoride-catalyzed reactions of vinylsilanes only work when there are anion-stabilizing groups present, which implies that there is substantial anionic character on carbon in the intermediate nucleophile, but this does not identify it as a carbanion; it could still be a hypervalent silyl species.

In general, the unreacting substituents on the silyl and stannyl groups make comparatively little difference. In the silicon series the trimethylsilyl group is much the most common, with phenyldimethylsilyl the next, because of the ease with which it can be introduced using the silyl–cuprate reagent. These two groups can usually be regarded as imparting similar reactivity, with the former perhaps about five times more reactive.[21] If larger groups are placed on the silicon, reactivity increases a little, but there is a serious risk that the silyl group is no longer capable of controlling the outcome: a proton may be lost in competition with the loss of the silyl group. In the tin series, tributylstannyl groups are the most common, for economic reasons, but trimethylstannyl occasionally shows some advantage, and halostannyl groups do significantly increase the reactivity by providing a built-in Lewis acid. Attempts to transfer chiral information from chiral substituents on the silyl[22] and stannyl[23] groups show some promise.

## 2.2.3 ALDEHYDES AND KETONES

### 2.2.3.1 Allylsilanes

In the absence of Lewis acids, allylsilanes react only with very electrophilic ketones like hexafluoroacetone, when they undergo 'ene' reactions rather than electrophilic replacement of the silyl group.[24] In the presence of Lewis acids, allylsilanes react with aldehydes and ketones with clean allylic transposition (Scheme 1) and the formation of homoallylic alcohols. The range of Lewis acids used is wide, but titanium tetrachloride and boron trifluoride etherate are the most common. Typically, reaction takes place somewhere between –78 °C and 0 °C in dichloromethane solution, and a molar proportion of Lewis acid is used.

Sometimes, the reaction does not stop at the homoallylic alcohol. Thus ketones are more troublesome than aldehydes, since the product alcohols are tertiary and apt to react further.[25] Another problem arises when the alkene group of the product reacts with the electrophile (Scheme 6),[26] but further reaction is usually avoidable, because the double bond of the allylsilane, activated to a significant extent by the silyl group, is usually more nucleophilic than the double bond in the first-formed product. Occasionally, the product may be unavoidably more reactive than the allylsilane. This is chiefly a problem when the allylsilane has the silyl group at the more substituted end of the allyl group (Scheme 7),[27] in which the first-formed product (**19**) is a trisubstituted alkene, more nucleophilic than the monosubstituted double bond of the allylsilane (**18**), and consequently it reacts further, giving substantial amounts of the chloride (**20**). This sort of problem is less evident when acetals are used in place of aldehydes (Scheme 37). Another kind of reaction in which the first-formed product reacts further is less troublesome: a suitably placed ester group may lactonize onto the hydroxy group of the homoallylic alcohol (Scheme 8), where again the corresponding acetal reacts without this complication.[28]

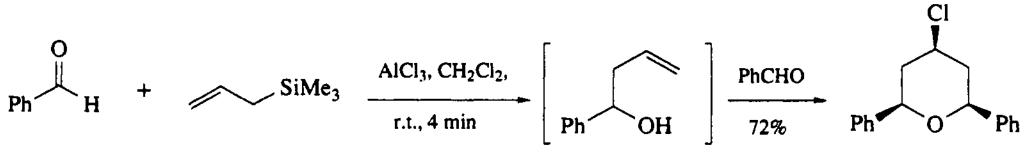

Scheme 6

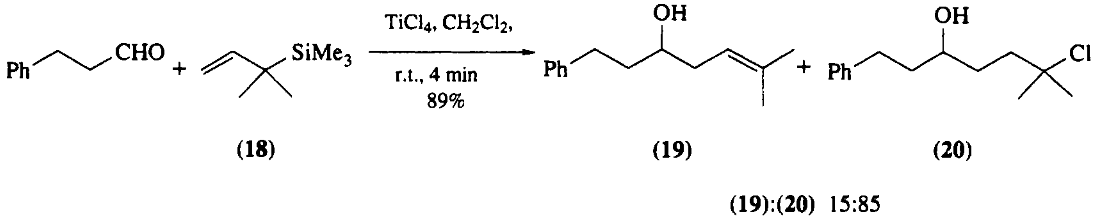

Scheme 7

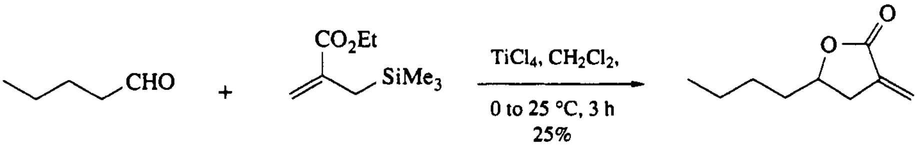

Scheme 8

When the allylsilane has an extra double bond extending the conjugation, reaction takes place at the terminus of the diene system remote from the silyl group (Scheme 9).[29]

Intramolecular reactions work well (Scheme 10) giving bicyclic, spirocyclic and tricyclic homoallylic alcohols in these examples.[30]

Allylsilanes, monosubstituted at C-3, react with aldehydes to give more of the *syn* (= *erythro*) product than the *anti* (Scheme 11); the (*E*)-allylsilane (**21**) is very clean in this respect, especially with the more heavily substituted aldehydes, but the (*Z*)-allylsilane (**22**) is not very selective.[31] Antiperiplanar transition

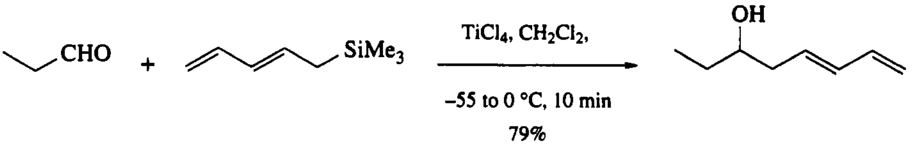
CHO
SiMe3
TiCl4, CH2Cl2,
-55 to 0 °C, 10 min
79%
OH

**Scheme 9**

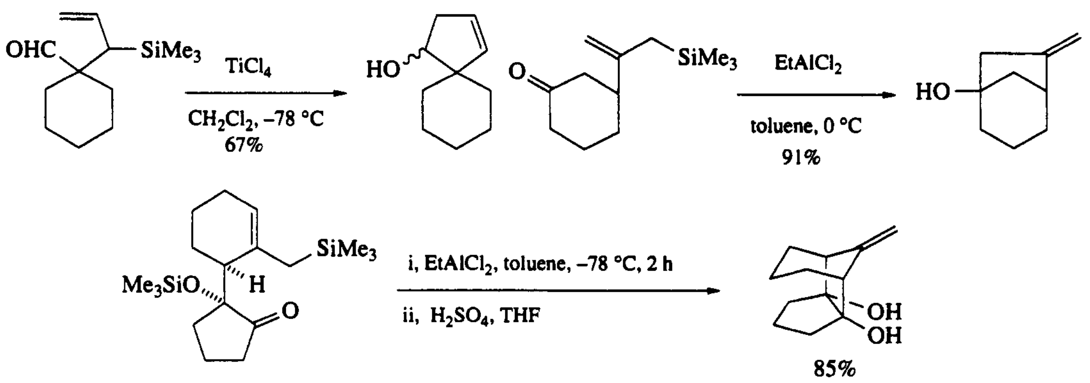
OHC
SiMe3
TiCl4
CH2Cl2, -78 °C
67%
HO
O
SiMe3
EtAlCl2
toluene, 0 °C
91%
HO
Me3SiO
H
SiMe3
O
i, EtAlCl2, toluene, -78 °C, 2 h
ii, H2SO4, THF
OH
OH
85%

**Scheme 10**

states (**23**) and (**24**) have been invoked to explain the preference for the formation of the *syn* products, the alternative arrangements placing the methyl group unfavorably between the R group of the aldehyde and the carbonyl oxygen. However, synclinal transition states, such as (**25**) and (**26**), in which the size of the Lewis acid attached to the oxygen atom helps to determine the most favorable transition state geometry, have also been suggested. In the only test designed to probe this point (Scheme 12), the Lewis acid was found to influence the proportion of reaction taking place from the synclinal (**27**) and antiperiplanar (**29**) arrangements, with the former in general the more important.[32]

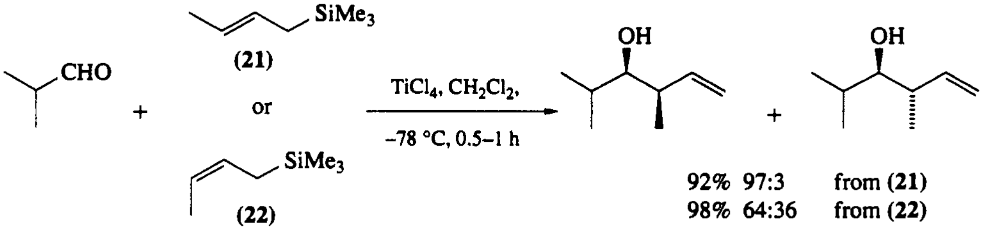
CHO
SiMe3
(21)
or
SiMe3
(22)
TiCl4, CH2Cl2,
-78 °C, 0.5–1 h
OH
OH
92% 97:3 from (21)
98% 64:36 from (22)

**Scheme 11**

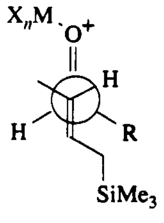
XnM
O+
H
H
R
SiMe3

**(23)**

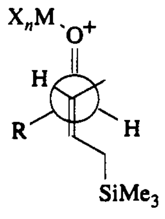
XnM
O+
H
R
H
SiMe3

**(24)**

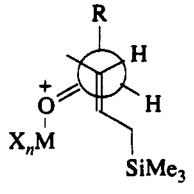
R
H
+
O
H
XnM
SiMe3

**(25)**

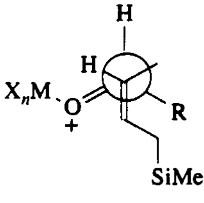
H
H
XnM
O
+
R
SiMe3

**(26)**

Chiral allylsilanes react antarafacially; the incoming electrophile attacks the double bond on the surface opposite to the silyl group (Scheme 13) and the major products are *syn*, in this case even from the (*Z*)-allylsilane.[33] The overall *anti* stereospecific reaction (*anti* to the extent of 90:10) in favor of product (**32**) having the substituents on the carbon chain *syn* to the extent of about 80:20 is still found with the (*Z,E*)-silane (**31**) in an $S_E2''$ reaction (Scheme 14), even though the new stereocenters are five and six

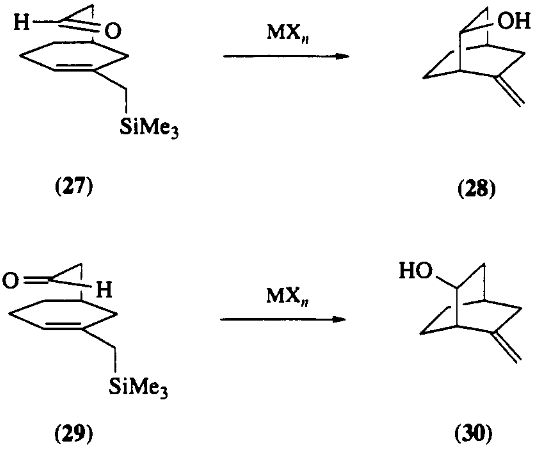

MX$_n$
MX$_n$
SiMe$_3$
SiMe$_3$
OH
HO
(27)
(28)
(29)
(30)

| MX$_n$ | (28):(30) |
|---|---|
| $BF_3•OEt_2$ | 80:20 |
| $FeCl_3$ | 70:30 |
| $Et_2AlCl$ | 66:34 |
| $SnCl_4$ | 49:51 |

Scheme 12

atoms from the original stereocenter.[34] In the intramolecular reaction in Scheme 15, both the (*R*,*E*)-allylsilane (**33**) and the (*S*,*Z*)-allylsilane (**34**) react antarafacially to the silyl group, the former with a synclinal transition state and the latter with an antiperiplanar transition state, to give the same diastereoisomer and enantiomer (**35**).[35]

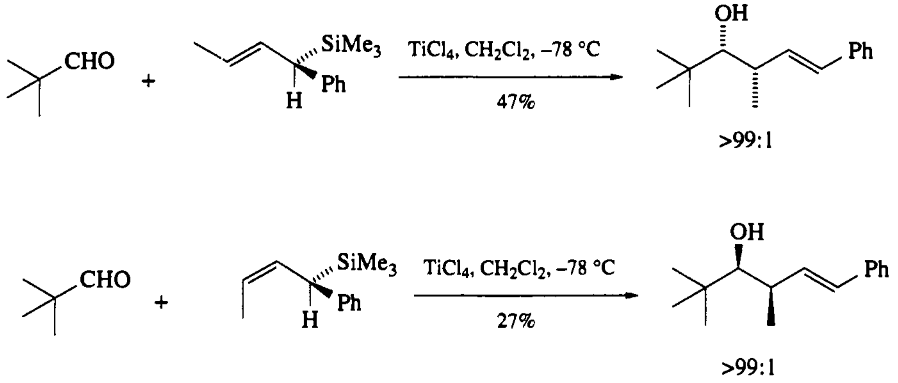

CHO
+
SiMe$_3$
Ph
H
$TiCl_4$, $CH_2Cl_2$, –78 °C
47%
OH
Ph
>99:1
CHO
+
SiMe$_3$
Ph
H
$TiCl_4$, $CH_2Cl_2$, –78 °C
27%
OH
Ph
>99:1

Scheme 13

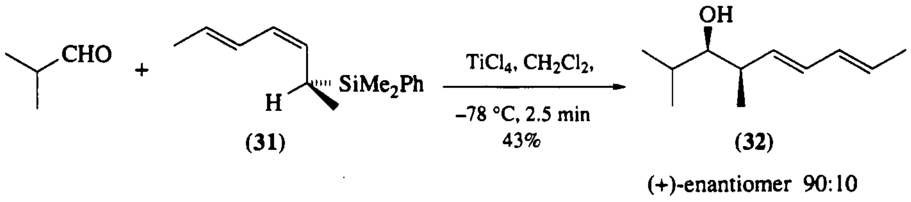

CHO
+
SiMe$_2$Ph
H
(31)
$TiCl_4$, $CH_2Cl_2$,
–78 °C, 2.5 min
43%
OH
(32)
(+)-enantiomer 90:10

Scheme 14

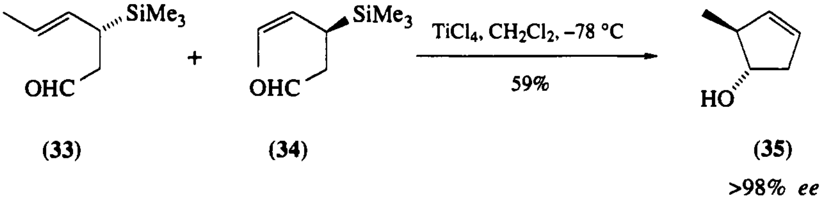

SiMe$_3$
OHC
(33)
+
SiMe$_3$
OHC
(34)
$TiCl_4$, $CH_2Cl_2$, –78 °C
59%
HO
(35)
>98% ee

Scheme 15

When the aldehyde or ketone contains a stereocenter, diastereofacial selectivity on the carbonyl group is possible. 2-Phenylpropionaldehyde is moderately Cram-selective to an extent (up to 76% *de*) common with several other carbon nucleophiles.[36] However, when the stereocenter has an ether group α or β to the carbonyl group, very high diastereoselectivity is observed (Scheme 16), consistent with attack by the allylsilane from the less hindered side of a ring made up by chelation of the Lewis acid between the ether oxygen and the carbonyl oxygen.[36,37] Lewis acids like boron trifluoride, with only one coordination site, have different and usually rather lower diastereoselectivities. The choice of Lewis acid can invert the selectivity in favorable cases (Scheme 17), with titanium tetrachloride giving the product (**36**) of chelation control and boron trifluoride the product (**37**) in the normal Cram sense.[38]

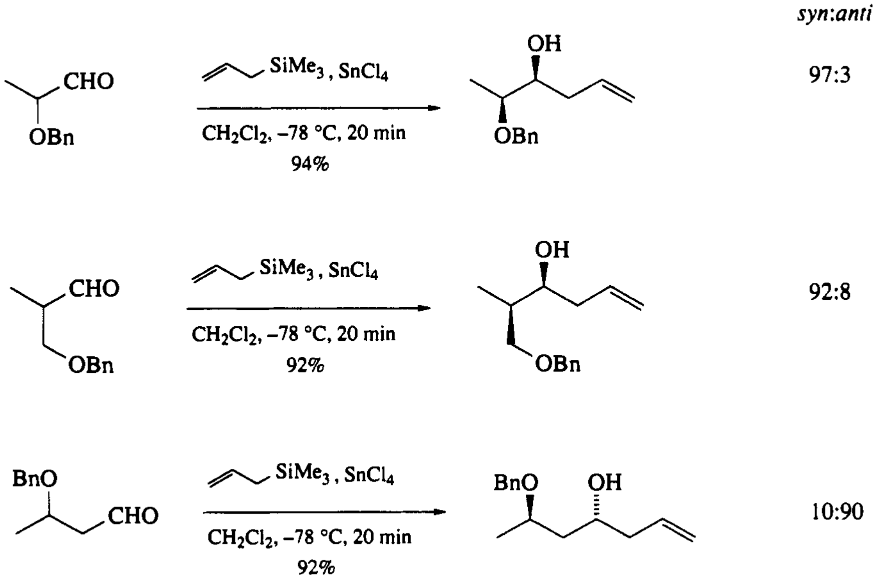
syn:anti
CHO
OBn
SiMe3, SnCl4
CH2Cl2, -78 °C, 20 min
94%
OH
OBn
97:3
CHO
OBn
SiMe3, SnCl4
CH2Cl2, -78 °C, 20 min
92%
OH
OBn
92:8
BnO
CHO
SiMe3, SnCl4
CH2Cl2, -78 °C, 20 min
92%
BnO
OH
10:90

**Scheme 16**

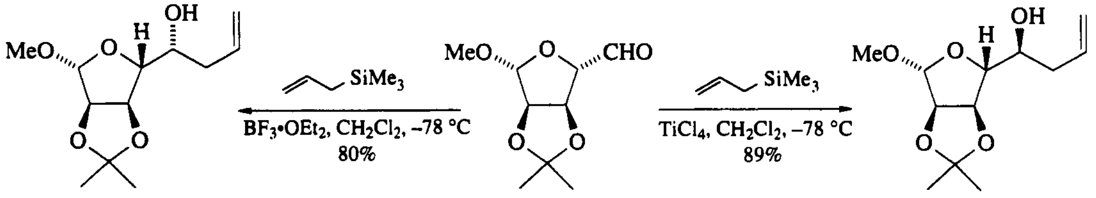
MeO
O
H
OH
O
O
SiMe3
BF3•OEt2, CH2Cl2, -78 °C
80%
MeO
O
CHO
O
O
SiMe3
TiCl4, CH2Cl2, -78 °C
89%
MeO
O
H
OH
O
O

(**37**) (**36**)

(**37**):(**36**) 99:1 (**36**):(**37**) 95:5

**Scheme 17**

When both the allylsilane and the aldehyde are chiral, double stereodifferentiation becomes possible. This has not yet been used in synthesis, probably because enantiomerically pure allylsilanes have only recently become available, but it appears likely to lead to very high levels of stereoselection: the racemic aldehyde (**38**) and the racemic allylsilane (**39**) combine (Scheme 18) to give largely (>90:10) one dia-

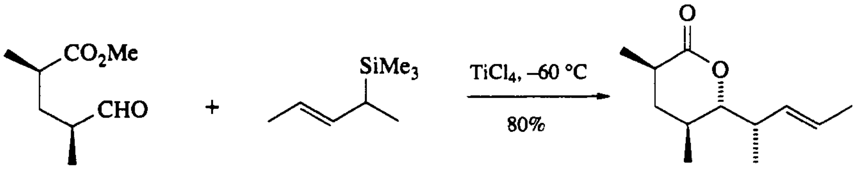
CO2Me
CHO
+
SiMe3
TiCl4, -60 °C
80%
O
O

(**38**) (**39**) (**40**)

**Scheme 18**

stereoisomer, namely the racemic lactone (**40**), which implies that each enantiomer of the two reagents is finding its partner with considerable selectivity and reacting in the *anti*-Cram sense as a result of chelation to the ester group.[39]

In fluoride ion catalyzed reactions of allylsilanes, aldehydes are the only carbon electrophiles that work well; protodesilylation is unavoidable with most other electrophiles, even in the most rigorously dried media. The most commonly used fluoride ion source, which only needs to be present in catalytic amounts, is TBAF in THF at room temperature or under reflux, benzyltrimethylammonium fluoride may be better, and cesium fluoride in DMF, potassium fluoride with 18-crown-6 in THF, and TASF in polar

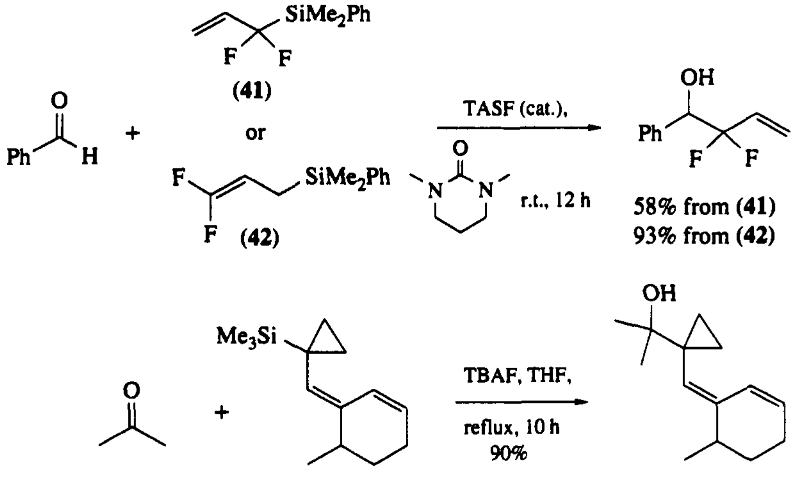
SiMe2Ph
F F
(41)
or
SiMe2Ph
(42)
Ph H
TASF (cat.),
r.t., 12 h
OH
Ph
58% from (41)
93% from (42)
Me3Si
TBAF, THF,
reflux, 10 h
90%
OH

**Scheme 19**

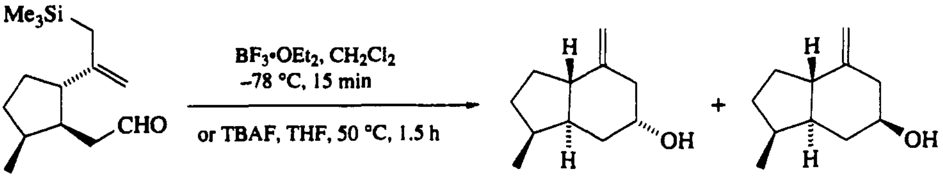
Me3Si
CHO
BF3•OEt2, CH2Cl2
-78 °C, 15 min
or TBAF, THF, 50 °C, 1.5 h
H
H
OH
OH

85:15 with $BF_3{\cdot}OEt_2$
18:82 with TBAF

**Scheme 20**

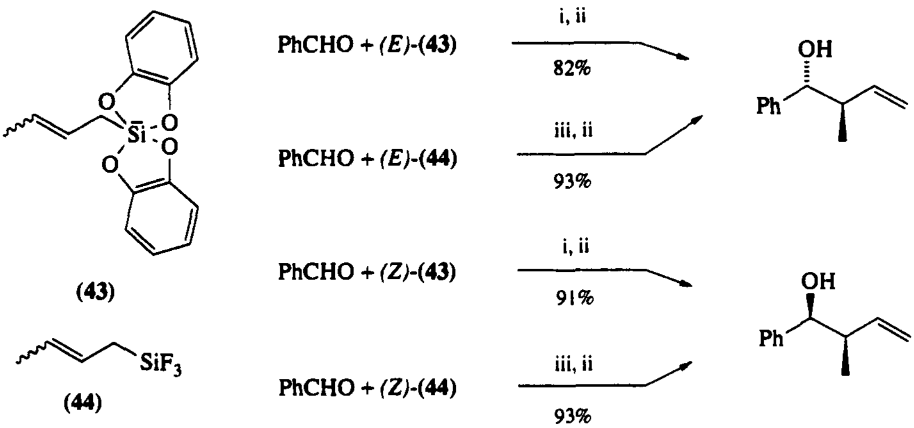
(43)
SiF3
(44)
PhCHO + (E)-(43)
i, ii
82%
PhCHO + (E)-(44)
iii, ii
93%
PhCHO + (Z)-(43)
i, ii
91%
PhCHO + (Z)-(44)
iii, ii
93%
OH
Ph
OH
Ph

i, THF, reflux, 90 h; ii, HCl, $H_2O$; iii, CsF, THF, r.t., 16 h

**Scheme 21**

aprotic solvents have all been used. The first-formed product is the silyl ether, which is usually hydrolyzed in the workup. The reaction may not be regiospecific (Scheme 2), but it can be regioselective (Scheme 19), depending upon the ambident character of the intermediate anion.[40,41] The stereoselectivity can be different from the corresponding Lewis acid catalyzed reactions (Scheme 20).[42] The nucleophile does not have to be fluoride, nor do the substituents on the silicon need to be alkyl groups: hypervalent silyl systems like (**43**) and (**44**) in the presence of fluoride ion are nucleophilic enough to react directly with aldehydes.[43] The stereochemistry observed (Scheme 21), namely *anti* with respect to the disposition of the substituents on the carbon chain,[44] and *syn* with respect to the electrophilic substitution process,[45] is that expected for a cyclic transition state, implying that the aldehyde oxygen becomes one of the ligands on the silicon in the transition state.

### 2.2.3.2 Allylstannanes

Unlike allylsilanes, allylstannanes react directly with aldehydes on heating, transferring the stannyl group to oxygen (Scheme 22).[2] Haloallylstannanes, where a Lewis acid is built into the reagent, are generally more reactive. They show little basic character, reacting in water, for example, where they can be generated *in situ* (Scheme 23).[13,46] They also react easily with ketones (Scheme 24).[47,48]

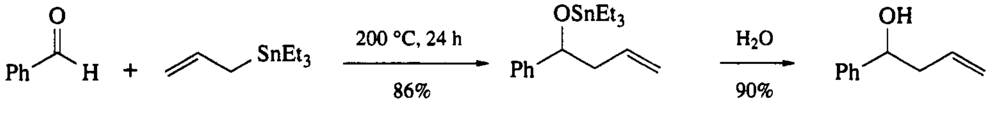
O
Ph
H
+
SnEt3
200 °C, 24 h
86%
OSnEt3
Ph
H2O
90%
OH
Ph

Scheme 22

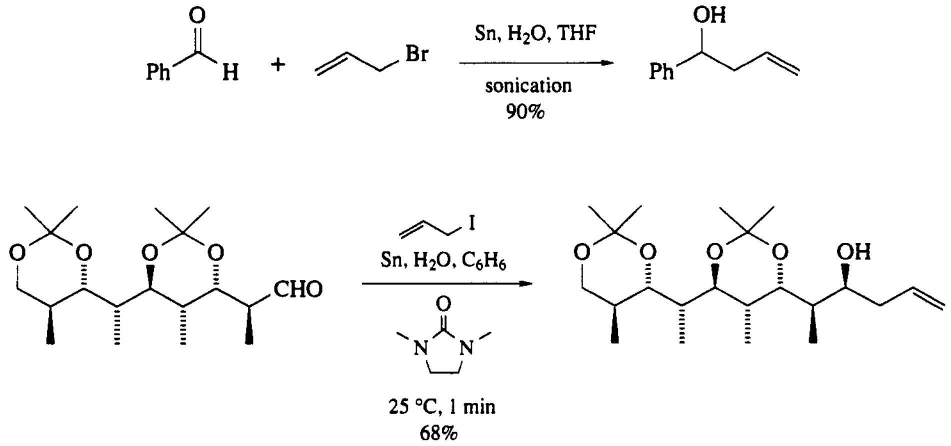
O
Ph
H
+
Br
Sn, H2O, THF
sonication
90%
OH
Ph
O
O
O
O
CHO
I
Sn, H2O, C6H6
O
N
N
25 °C, 1 min
68%
O
O
O
O
OH

Scheme 23

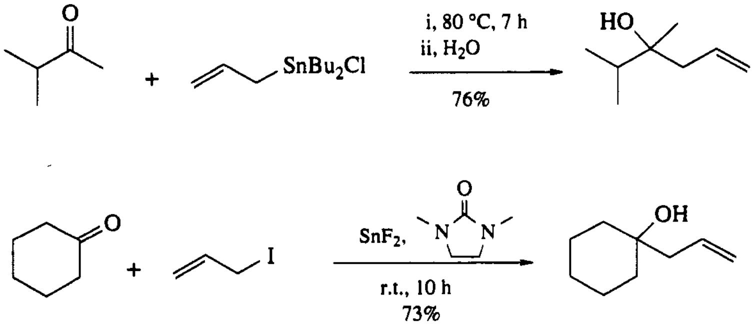
O
+
SnBu2Cl
i, 80 °C, 7 h
ii, H2O
76%
HO
O
+
I
SnF2,
O
N
N
r.t., 10 h
73%
OH

Scheme 24

Boron trifluoride etherate is much the most commonly used Lewis acid in allyltrialkylstannane reactions. The preference for synclinal transition states is more marked with the stannane equivalent of the system illustrated in Scheme 12 than with the silyl system: the preference for the transition state (**27**) over (**29**) is 87:13 with boron trifluoride as the Lewis acid and a tributylstannyl group in place of the trimethylsilyl, and 99:1 using a proton.[49] As with allylsilanes, there is a preference, in the Lewis acid catalyzed reactions, for the formation of the product with the substituents *syn* on the carbon chain (Scheme 3), but with allylstannanes the (*Z*)-isomer is as effective as the (*E*).[18] However, the preference for the *syn* arrangement on the carbon chain is not always observed, even with Lewis acids like boron trifluoride: with a phenyl group on the double bond in place of the methyl, the product has the *anti* arrangement of the phenyl and hydroxy groups.[50] In reactions involving cyclic transition states, the *anti* arrangement of the substituents on the carbon chain is that expected from (*E*)-allylstannanes, and the *syn* is that expected from (*Z*)-allylstannanes.[51,52] For this reason, the order of mixing of an allylstannane and the Lewis acid can be important, because it affects the extent to which the Lewis acid replaces the stannyl group before reaction with the aldehyde takes place (Scheme 25).[53] Presumably an allyltitanium intermediate uses a cyclic transition state (**47**) and hence gives rise to the *anti* product.

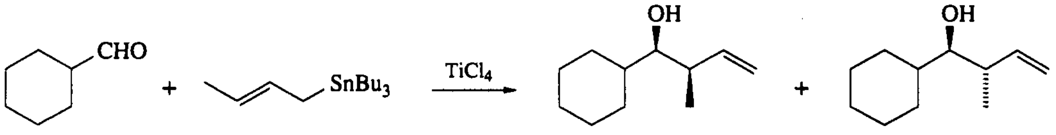

(**45**) (**46**)

Conditions: i, 93:7
Conditions: ii, 5:95

i, add (**46**) to a mixture of (**45**) and $TiCl_4$; ii, add (**45**) to a mixture of 2 equiv. of $TiCl_4$ and (**46**)

**Scheme 25**

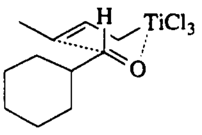

(**47**)

Chelation and Cram selectivity can also be controlled by taking advantage of the differing abilities of Lewis acids to accept chelation (Scheme 26). The *anti* product (**48**) is that expected from an open-chain transition state and Felkin–Anh effects, and the *syn* product (**49**) is that from chelation control. The former is the major product with boron trifluoride, especially when the oxygen function is protected with a TBDMS group, and the latter with titanium tetrachloride or magnesium bromide.[54] Normally, allylstannanes give higher levels of Cram control than other carbon nucleophiles,[55] but high *anti*-Cram selectivity is observed in a synthesis of the Prelog–Djerassi lactone[55] resembling the allylsilane reaction in Scheme 18. Chelation by the ester group to the Lewis acid, even though the Lewis acid is boron trifluoride, appears to be involved.[56]

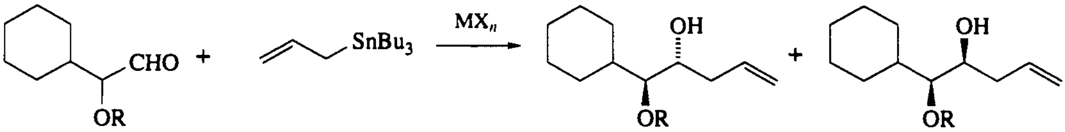

(**48**) (**49**)

| *R* | *$MX_n$* | | |
|---|---|---|---|
| $Bu^tMe_2Si$ | $BF_3{\bullet}OEt_2$ | 83% | 95:5 |
| Bn | $MgBr_2$ | 85% | 1:>250 |

**Scheme 26**

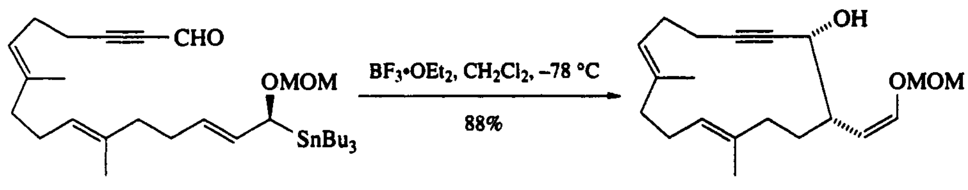

CHO
OMOM
SnBu$_3$
BF$_3$•OEt$_2$, CH$_2$Cl$_2$, –78 °C
88%
OH
OMOM

**Scheme 27**

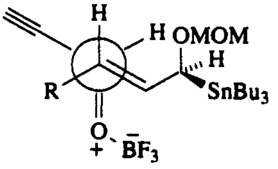

H
H
OMOM
H
R
SnBu$_3$
O
+
–
BF$_3$

**(50)**

The overall electrophilic substitution reaction in the Lewis acid catalyzed reaction is *anti* (Scheme 27), with reaction probably taking place in the synclinal transition state (**50**).[57]

In the absence of Lewis acids, stereoselectivity is strongly dependent upon the geometry of the double bond in the allylstannane, both in simple thermal reactions (Scheme 28)[58] and in pressure-induced reactions,[18] as expected for a cyclic transition state. As well as being selective for the formation of the *anti* arrangement of substituents on the carbon chain, the overall electrophilic substitution in the thermal reaction of an (*E*)-allylstannane, is stereospecifically *syn* (Scheme 29),[59] with a cyclic transition state (**51**),

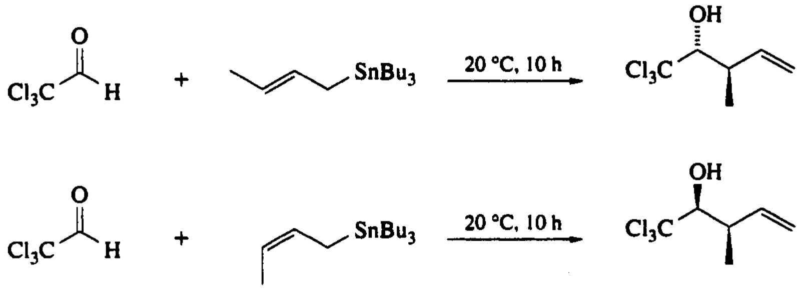

O
Cl$_3$C
H
+
SnBu$_3$
20 °C, 10 h
OH
Cl$_3$C
O
Cl$_3$C
H
+
SnBu$_3$
20 °C, 10 h
OH
Cl$_3$C

**Scheme 28**

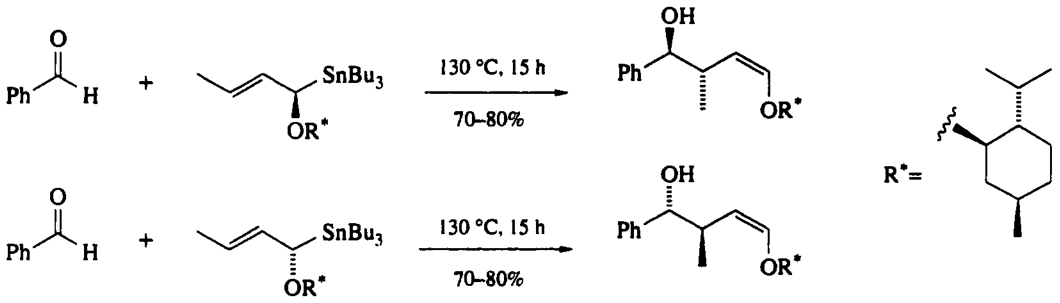

O
Ph
H
+
SnBu$_3$
OR*
130 °C, 15 h
70–80%
OH
Ph
OR*
O
Ph
H
+
SnBu$_3$
OR*
130 °C, 15 h
70–80%
OH
Ph
OR*
R*=

**Scheme 29**

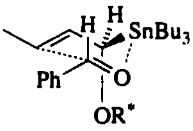

H
H
SnBu$_3$
Ph
O
OR*

**(51)**

in contrast to the Lewis acid catalyzed reaction with the open chain transition state (**50**). In both cases it is the oxygen substituent that eclipses (or partly eclipses) the double bond in the allylstannane, causing the double bond in the product to have the (*Z*)-geometry, just as it has when the substituent on the stereocenter is methyl (Scheme 4).[19,51]

Dienylmethylstannanes react with aldehydes in the presence of Lewis acids equally at the $\gamma$ and the $\varepsilon$ position,[50] in contrast to the allylsilane reactions in Schemes 9 and 14.

### 2.2.3.3 Allenyl-, Propargyl-, Vinyl- and Ethynyl-silanes and -stannanes

Allenylsilanes react with aldehydes in the presence of Lewis acids (Scheme 30).[60] This reaction is also capable of being subverted: a [3 + 2] annulation takes place, forming a 3-silyldihydrofuran, when the silyl group is the TBDMS group, which is more reluctant to leave than the trimethylsilyl.[61] Propargylsilanes also react regiospecifically in the presence of Lewis acids, complementing the behavior of the corresponding allenylsilanes, but they react with loss of regiocontrol in the presence of fluoride ion (Scheme 31).[62]

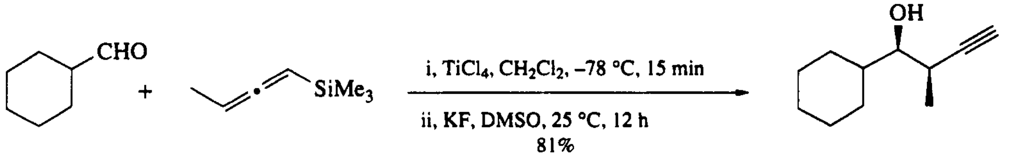

Scheme 30

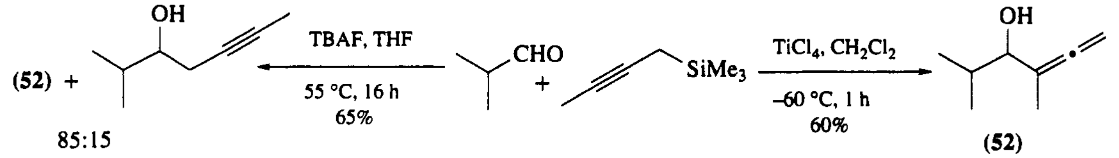

Scheme 31

Allenylsilanes and propargylsilanes are interconvertible only at high temperatures,[15] but allenylstannanes and propargylstannanes interconvert fast enough that product mixtures are sometimes seen when either reacts with an aldehyde or ketone,[63] just as with regioisomeric allylstannanes. Thus, when the reagent is generated *in situ* from tin and a propargyl iodide in dipolar aprotic solvents, the major product is the allene, but in diglyme the major product is the alkyne.[64] Simple thermal reactions appear to be more straightforward (Scheme 32), where the propargylstannane is 6.5 times more reactive than the allenylstannane.[63]

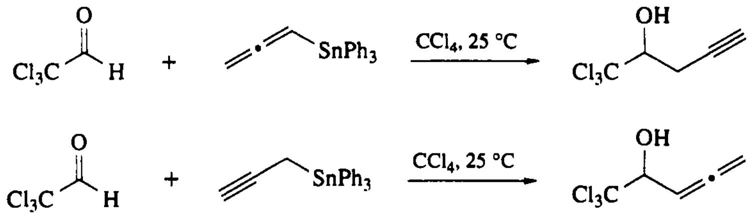

Scheme 32

Vinylsilanes react with chloral in the presence of Lewis acids (Scheme 33),[65] but this type of reaction is little used, probably because the products are allylic alcohols, which are apt to undergo ionization in the presence of Lewis acids to give allyl cations, and hence further reaction. Reactions employing nucleophilic catalysis, although free of this problem, are also limited, only anion-stabilized systems undergoing reaction (Scheme 34).[66,67] On the other hand, there is less of a problem with $\beta$-elimination of a halide ion, as there would be with most metals $\beta$ to a halogen.[40]

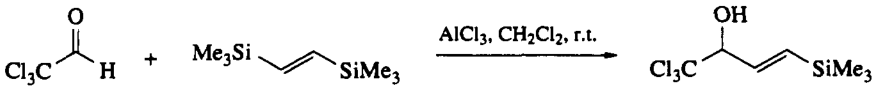

Scheme 33

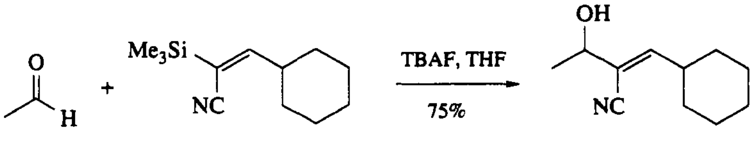

Scheme 34

Vinylstannanes might reasonably be expected to react with aldehydes and ketones. In practice this is not done: instead the stannyl group is replaced by lithium, using butyllithium, before any reaction with the aldehyde or ketone. Vinylstannanes are also effective carbon nucleophiles in a number of transition metal mediated reactions outside the scope of this chapter.[68]

Ethynylsilanes react with aldehydes and ketones in the presence of Lewis acids[65] or fluoride ion (Scheme 35).[69] Ethynylstannanes react in the presence of Lewis acids (Scheme 36),[2,70] showing higher Cram selectivity than other ethynyl nucleophiles.

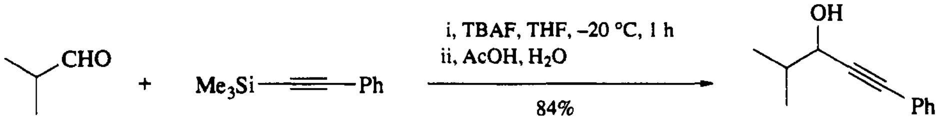

Scheme 35

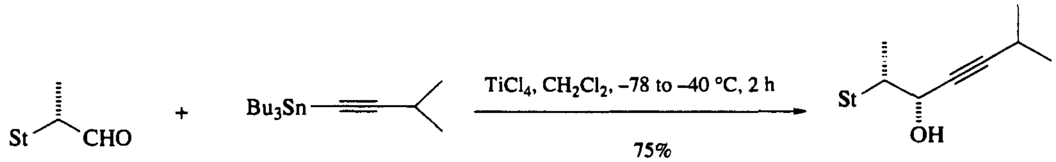

St = steroid

Cram:*anti*-Cram 90:10

Scheme 36

## 2.2.4 ACETALS AND KETALS

### 2.2.4.1 Allylsilanes

Acetals and ketals are exceptionally good electrophiles for allylsilanes,[71] often giving better yields than the corresponding aldehyde or ketone, because the products are less prone to further reaction. Typically the reactions are catalyzed by stoichiometric amounts of titanium tetrachloride in dichloromethane at –78 °C, and the regiospecific reaction is complete in a few minutes (Scheme 37).[27,72] Other Lewis acids used are boron trifluoride etherate, tin(IV) chloride and, in catalytic amounts, trimethylsilyl triflate,[73] trityl perchlorate[74] and montmorillonite clays.[75] With the unsymmetrical acetal (**53**), the methoxyethoxy group departs selectively (Scheme 38), presumably because it chelates the Lewis acid.[76]

As in the reactions with aldehydes and ketones, intramolecular reactions are easy (Scheme 39),[77,78] and the reaction is selective for the formation of the product with the substituents *syn* on the carbon chain, whatever the geometry of the double bond in the allylsilane (Scheme 40).[79] However, this clean stereoselectivity is not seen with the acetals of aromatic aldehydes, where the choice of Lewis acid and the nature of *para* substituents affect the proportion of the diastereoisomers.

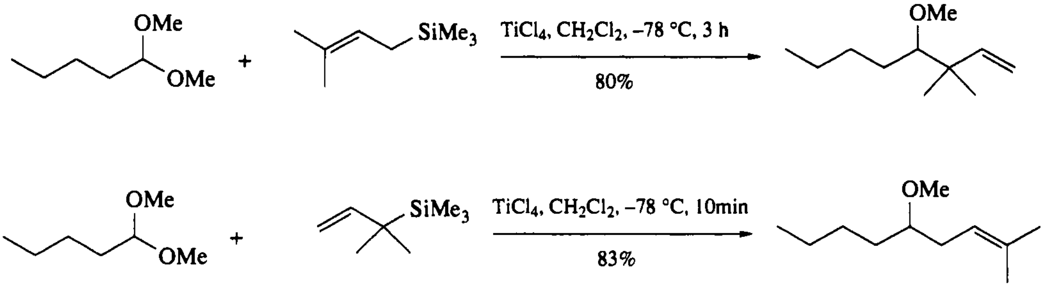
OMe
OMe
SiMe3
TiCl4, CH2Cl2, -78 °C, 3 h
80%
OMe
OMe
OMe
SiMe3
TiCl4, CH2Cl2, -78 °C, 10min
83%
OMe

**Scheme 37**

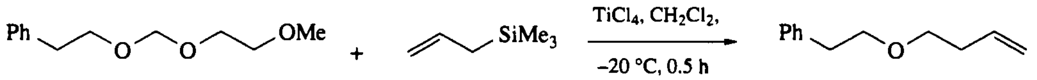
Ph
O
O
OMe
SiMe3
TiCl4, CH2Cl2,
-20 °C, 0.5 h
Ph
O

**Scheme 38**

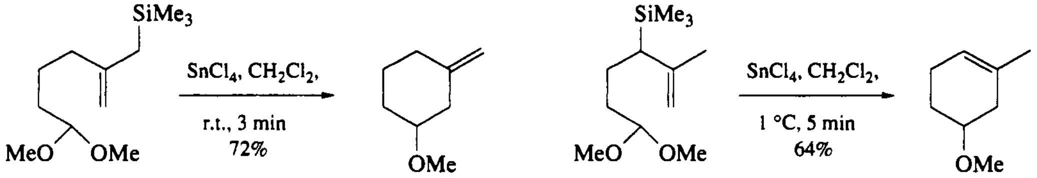
SiMe3
MeO
OMe
SnCl4, CH2Cl2,
r.t., 3 min
72%
OMe
SiMe3
MeO
OMe
SnCl4, CH2Cl2,
1 °C, 5 min
64%
OMe

**Scheme 39**

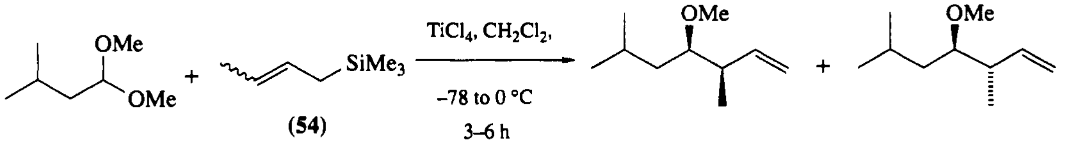
OMe
OMe
SiMe3
(54)
TiCl4, CH2Cl2,
-78 to 0 °C
3–6 h
OMe
OMe

| | | |
|---|---|---|
| 99% | 91:9 | from (*E*)-(**54**) |
| 90% | 91:9 | from (*Z*)-(**54**) |

**Scheme 40**

Allylsilanes attack cyclohexanone ketals axially (93:7)[73] and attack 2-phenylpropionaldehyde acetal with a degree of Cram selectivity that is influenced by the choice of Lewis acid, tin(IV) chloride giving the highest ratio (3.5:1).[80] With β-alkoxyacetals, chelation control is not possible as it is with the corresponding aldehydes; stereoselectivity is not high, it is in the opposite sense (Scheme 41, compare Scheme 16), and it depends upon the choice of Lewis acid.[80]

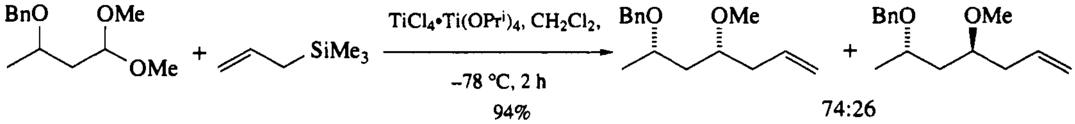
BnO
OMe
OMe
SiMe3
TiCl4•Ti(OPr$^i$)4, CH2Cl2,
-78 °C, 2 h
94%
BnO
OMe
BnO
OMe
74:26

**Scheme 41**

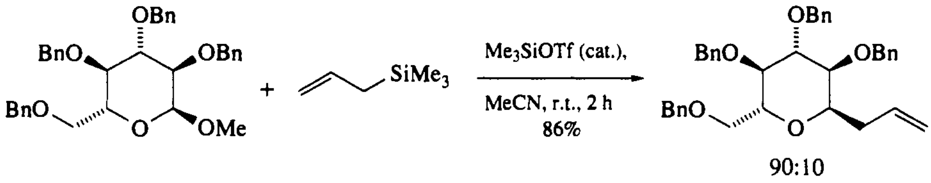
OBn
BnO
OBn
BnO
O
OMe
SiMe3
Me3SiOTf (cat.),
MeCN, r.t., 2 h
86%
OBn
BnO
OBn
BnO
O
90:10

**Scheme 42**

Sugar acetals and acetates react with α-axial attack on the ring (Scheme 42),[81] but the corresponding halides react somewhat faster and need less catalyst. It appears that the better the leaving group, the more polar the solvent and the more powerful the Lewis acid, the better the stereoselectivity, the combination of *p*-nitrobenzoate and boron trifluoride etherate being notably effective. A closely similar reaction takes place with vinylogous acetals,[82,83] where the example (Scheme 43) from Danishefsky's synthesis of avermectin A-1a is further notable in that the stereochemistry at the methyl-bearing carbon was determined by the geometry of the double bond in the allylsilane,[84] in contrast to the results in Scheme 40.

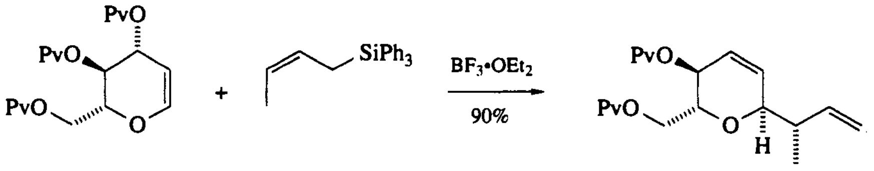
PvO
PvO
PvO
O
+
SiPh3
BF3•OEt2
90%
PvO
PvO
O
H

Pv = pivaloyl

Scheme 43

The acetals of optically active 1,2- and 1,3-glycols show striking stereoselectivity, giving homoallylic ethers in high diastereoisomeric excess, especially when titanium tetrachloride–titanium tetraisopropoxide mixtures are used as the Lewis acid (Scheme 44).[85] Even non-cyclic acetals made from aldehydes and enantiomerically pure 1-phenylethanol give homoallylic ethers with high diastereoselectivity.[86]

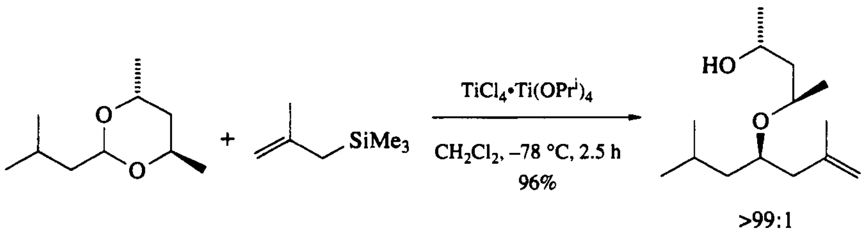
O
O
+
SiMe3
TiCl4•Ti(OPr^i)4
CH2Cl2, –78 °C, 2.5 h
96%
HO
O
>99:1

Scheme 44

### 2.2.4.2 Allylstannanes

Allylstannanes react with acetals in the presence of bis(diethylaluminum) sulfate (Scheme 45)[87] and the reaction has been used in a synthesis of lavandulol (Scheme 46). However, the allylstannane (**55**) was not necessary in this reaction, for the mixture of dienes (**56**) worked just as well in the presence of tin(IV) chloride. It is conceivable that in the latter reaction the tin(IV) chloride combines with the diene to make an allylstannane *in situ*.[88]

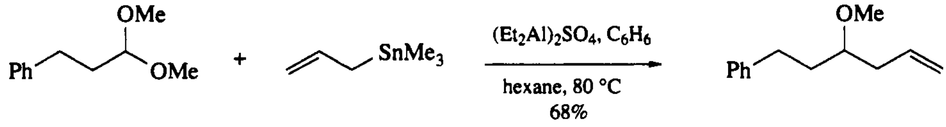
OMe
Ph
OMe
+
SnMe3
(Et2Al)2SO4, C6H6
hexane, 80 °C
68%
OMe
Ph

Scheme 45

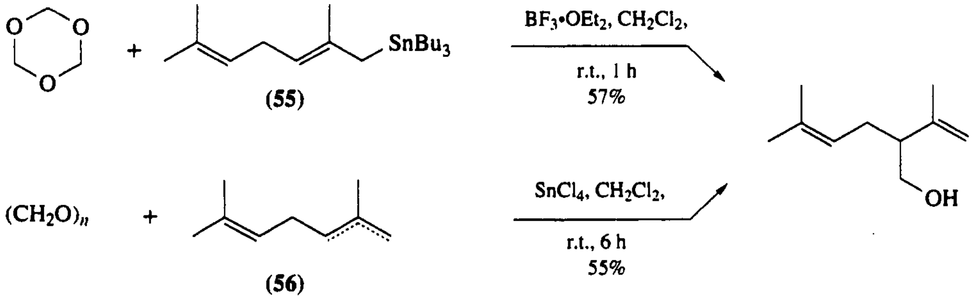
O
O
O
+
SnBu3
(55)
BF3•OEt2, CH2Cl2,
r.t., 1 h
57%
(CH2O)n
+
(56)
SnCl4, CH2Cl2,
r.t., 6 h
55%
OH

Scheme 46

In the reaction in Scheme 47, the allylstannane gave the isomer (**58**) as the major product, whereas the corresponding allylsilane gave the isomer (**57**). The product (**57**) is that expected from Cram's rule and (**58**) is that expected by analogy with the reaction in Scheme 44. The explanation suggested is that the allylstannane, as the more nucleophilic species, has an early transition state, and the allylsilane a late transition state.[89] Of course, when the chiral centers in the acetal ring are inverted, the two influences support each other and very high diastereocontrol for the formation of the steroidal C-22 configuration of (**57**) is possible with both allyl–metal reagents. The controlling influence of an acetal of this type is similarly overridden by what appears to be a chelation effect to an oxygen substituent in a 1,3-relationship to the acetal oxygens.[90]

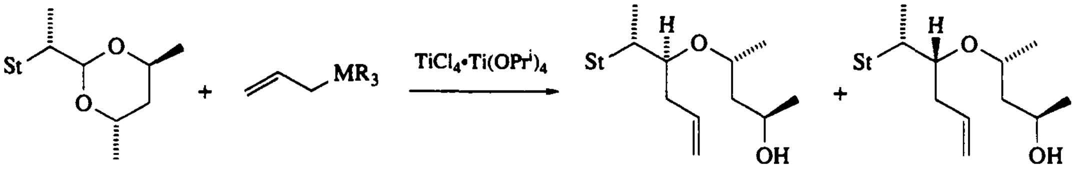

(**57**) (**58**)

St = steroid MR$_3$ = SiMe$_3$ 93% 90:10
MR$_3$ = SnBu$_3$ 84% 30:70

**Scheme 47**

### 2.2.4.3 Allenyl-, Propargyl-, Vinyl- and Ethynyl-silanes

Allenylsilanes react with acetals, as they do with aldehydes, by addition, but a simple elimination step completes the substitution reaction (Scheme 48).[91] Propargylsilanes likewise react with acetals in the presence of Lewis acids (Scheme 49).[92] The reaction has been used intramolecularly (Scheme 50),[93] where the first step is likely to be acetal or hemiacetal formation followed by ring closure, and in reactions at the anomeric position of sugars with high levels of axial attack giving allenes.[94]

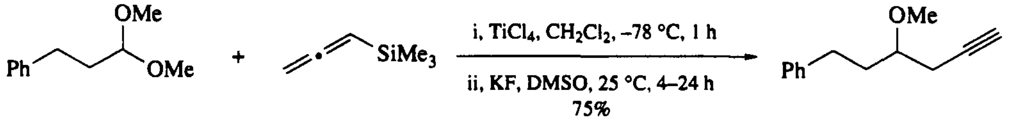

**Scheme 48**

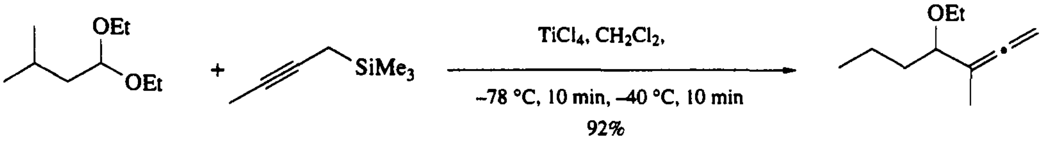

**Scheme 49**

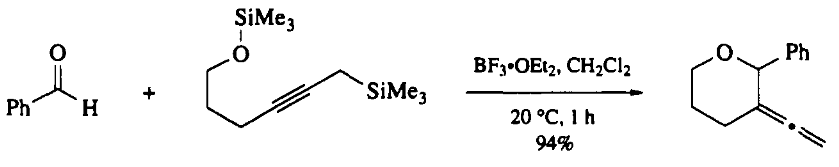

**Scheme 50**

Vinylsilanes react with acetals in the presence of Lewis acids to give allylic ethers, which go on to react further.[95] Intramolecular reactions are less susceptible to this difficulty[78] and provide an opportunity for controlling the configuration of exocyclic double bonds (Scheme 51). As usual with vinylsilanes, the vinylsilane (**59**) reacts stereospecifically with retention of configuration; the (*E*)-stereoisomer of (**59**) gives the (*E*)-product corresponding to (**60**).[96]

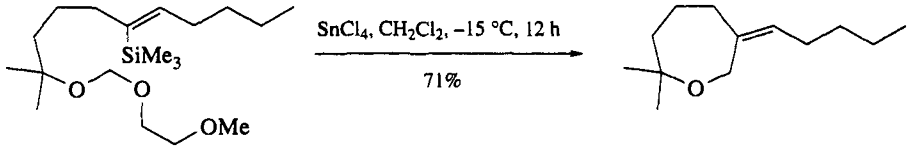
SiMe3
O
O
OMe
SnCl4, CH2Cl2, -15 °C, 12 h
71%
O

**(59)** **(60)**

Scheme 51

Ethynylsilanes react with the chiral acetal in Scheme 52 with good diastereoselection,[97] providing a route to enantiomerically enriched alcohols to rival the Midland method.

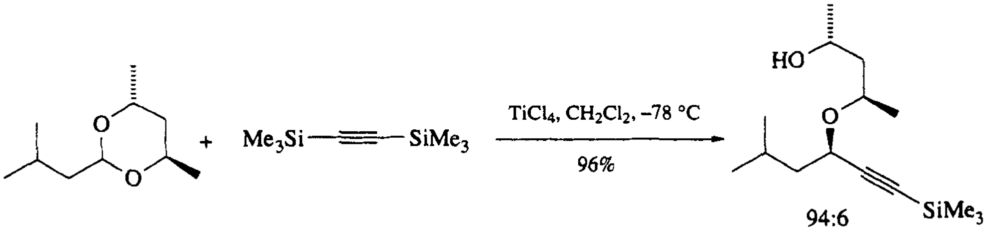
O
O
+
Me3Si——SiMe3
TiCl4, CH2Cl2, -78 °C
96%
HO
O
94:6
SiMe3

Scheme 52

## 2.2.5 OTHER SUBSTRATES AT THE OXIDATION LEVEL OF ALDEHYDES AND KETONES

### 2.2.5.1 Allylsilanes and Allylstannanes

Allylsilanes react with alkoxymethyl and phenylthiomethyl chlorides in the presence of Lewis acids (Scheme 53),[98,99] and dithioacetals, similarly, where substantial stereoselection can be achieved with large aryl groups on the sulfur atoms (Scheme 54).[100] Monothioacetals react selectively with cleavage of the carbon–sulfur bond when tin(IV) chloride is used as the Lewis acid (Scheme 55).[101]

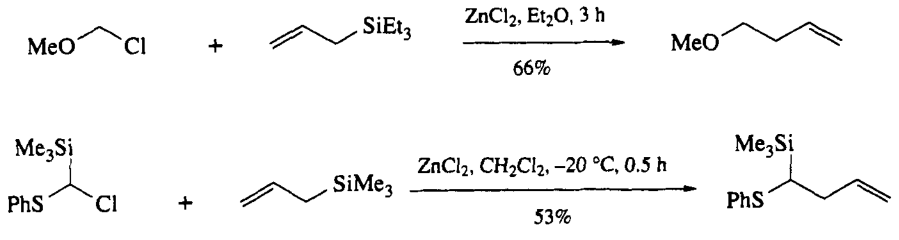
MeO
Cl
+
SiEt3
ZnCl2, Et2O, 3 h
66%
MeO
Me3Si
PhS
Cl
+
SiMe3
ZnCl2, CH2Cl2, -20 °C, 0.5 h
53%
Me3Si
PhS

Scheme 53

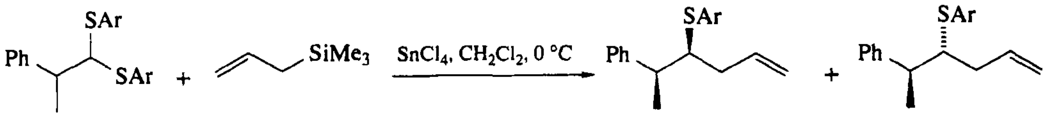
SAr
Ph
SAr
+
SiMe3
SnCl4, CH2Cl2, 0 °C
SAr
Ph
+
SAr
Ph

| | | |
|---|---|---|
| Ar = Ph | 56% | 75:25 |
| Ar = 2,4,6-trimethylphenyl | 74% | >97:3 |

Scheme 54

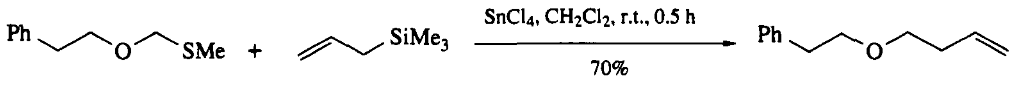
Ph
O
SMe
+
SiMe3
SnCl4, CH2Cl2, r.t., 0.5 h
70%
Ph
O

**Scheme 55**

Allylstannanes are much better nucleophiles for dithioacetals than allylsilanes, and dimethyl(methylthio)sulfonium fluoroborate is a particularly good catalyst in this reaction. The reaction has been used tellingly in a macrocyclization (Scheme 56).[102] Monothioacetals also react with allylstannanes, with cleavage of either the carbon–oxygen or the carbon–sulfur bond, depending upon the choice of Lewis acid (Scheme 57).[103] Sugar thioacetals react in the same way (Scheme 58), but with the opposite anomeric stereoselectivity from that of the corresponding radical chain substitution.[104]

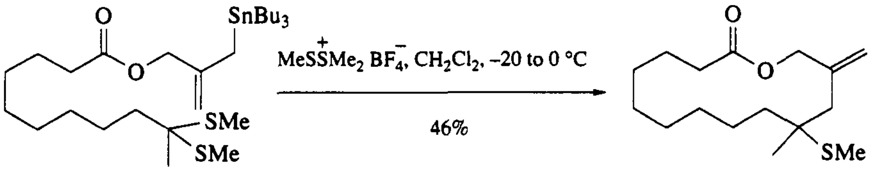
O
SnBu3
O
SMe
SMe
MeSSMe2 BF4, CH2Cl2, –20 to 0 °C
46%
O
O
SMe

**Scheme 56**

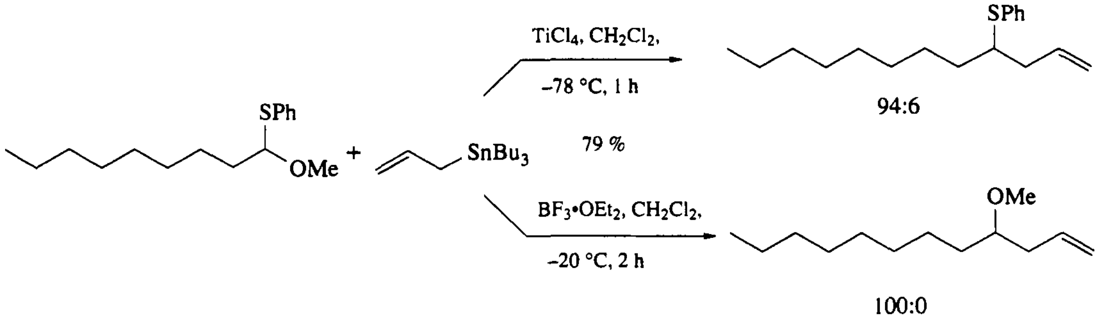
SPh
OMe
+
SnBu3
TiCl4, CH2Cl2,
–78 °C, 1 h
79 %
BF3•OEt2, CH2Cl2,
–20 °C, 2 h
SPh
94:6
OMe
100:0

**Scheme 57**

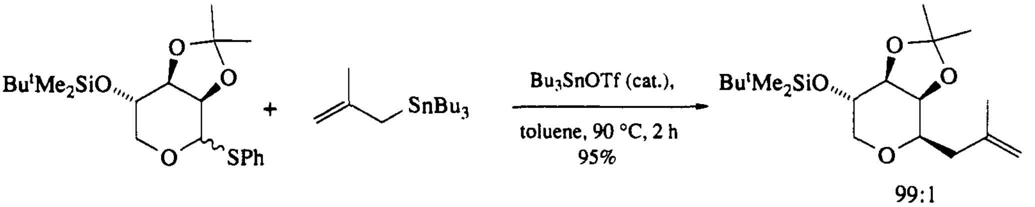
Bu^tMe2SiO
O
O
O
SPh
+
SnBu3
Bu3SnOTf (cat.),
toluene, 90 °C, 2 h
95%
Bu^tMe2SiO
O
O
O
99:1

**Scheme 58**

### 2.2.5.2 Vinylsilanes and Ethynylstannanes

Vinylsilanes react with methoxymethyl chloride,[98] and with monothioacetals, cleaving the carbon–oxygen bond when molybdenum chloride is used as the catalyst.[105] Vinylsilanes also react intramolecu-

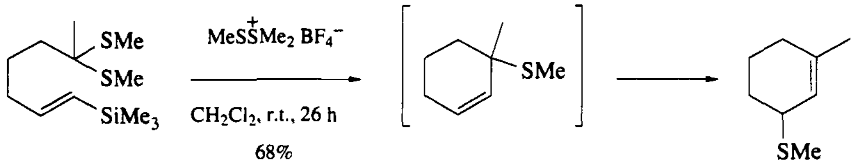
SMe
SMe
SiMe3
MeSSMe2 BF4–
CH2Cl2, r.t., 26 h
68%
SMe
SMe

**Scheme 59**

larly with dithioacetals uniquely using dimethyl(methylthio)sulfonium fluoroborate as the Lewis acid, although the first-formed product suffers an allylic shift of the sulfur group (Scheme 59).[106]

Ethynylstannanes react with anomeric sugar bromides, and similar alkoxymethyl and alkylthiomethyl halides, to give propargyl ethers (Scheme 60).[107]

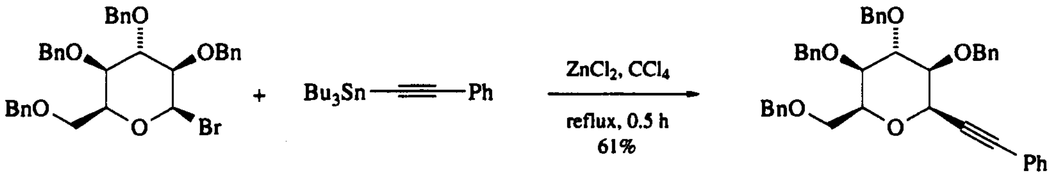

Scheme 60

## 2.2.6 SYNTHESES OF THE SILANES AND STANNANES

The methods described in this section are far from being a complete list. The growing importance of silylated and stannylated synthons in organic chemistry has led to the development of a great many syntheses, both controlled and uncontrolled, of which only a selection can be presented here to illustrate the range and the problems involved.

### 2.2.6.1 Allylsilanes

The methods to be summarized here can be divided into four main classes depending upon which bond (A–D) in the general structures (**61**) and (**62**) is made in the key step.

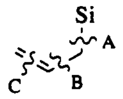

(**61**)

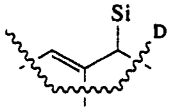

(**62**)

#### 2.2.6.1.1 *Syntheses based on disconnection A*

The most simple and direct route is the silylation of an allyl–metal reagent such as a Grignard or lithium reagent, a method that is also amenable to being carried out in the manner of a Wurtz reaction by treating an allyl halide and trimethylsilyl chloride with sodium.[77] The problem with this approach is that regiocontrol is not always possible. Thus the prenylsilanes (**63**) and (**64**) can be prepared selectively (Scheme 61),[27,108] but when the difference in the degree of substitution at the ends of the allyl system is less extreme, mixtures of regioisomers are usually produced (Scheme 62).[15,109]

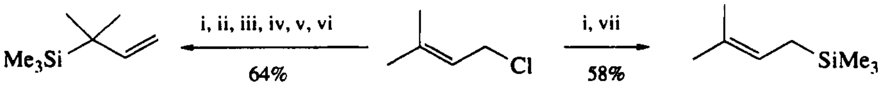

(**63**) (**64**)

i, Mg; ii, $HSiCl_3$; iii, MeMgBr; iv, EtOH, $H_2PtCl_6$; v, $HBF_4$; vi, MeLi; vii, $Me_3SiCl$

Scheme 61

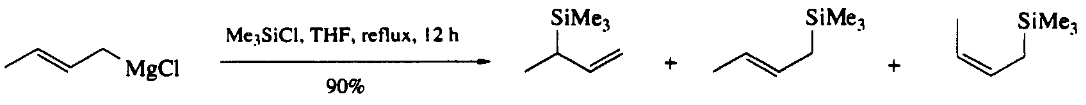

75:10:15

Scheme 62

The umpolung version of this disconnection gives more regiocontrol, together with high levels of stereocontrol and a greater degree of compatibility with other functional groups that may be present. Allyl chlorides react with silyl–metal reagents with good regiocontrol when the allyl system is at the end of a chain (Scheme 63) to place the silyl group either at the more- (**65**) or at the less-substituted end (**66**) of the allyl system.[110,111] Silyl–cuprate reagents react with tertiary allylic acetates (Scheme 64) with complete regioselectivity to place the silyl group at the less-substituted terminus of the allyl system and with complete *anti* stereospecificity.[112] When the allyl ester is secondary at both ends (Scheme 65), the reaction (**67**) → (**68**) + (**69**) is still stereospecifically *anti*, and regioselectivity is moderately good when the double bond is *cis*, as it is in (**67**).[113] However, the regioselectivity is improved, and the stereospecificity changed to *syn* (**70**) → (**71**), when the corresponding urethane is used. Substituted allenes also react with the silyl cuprate reagent to give allylsilanes (Scheme 66).[114] When stereocontrol is not important and the silyl group is wanted at the less-substituted end of the allyl system, a simple method uses the allylic alcohol as its lithium alkoxide and hexamethyldisilane as the source of the nucleophilic silyl group (Scheme 67).[115]

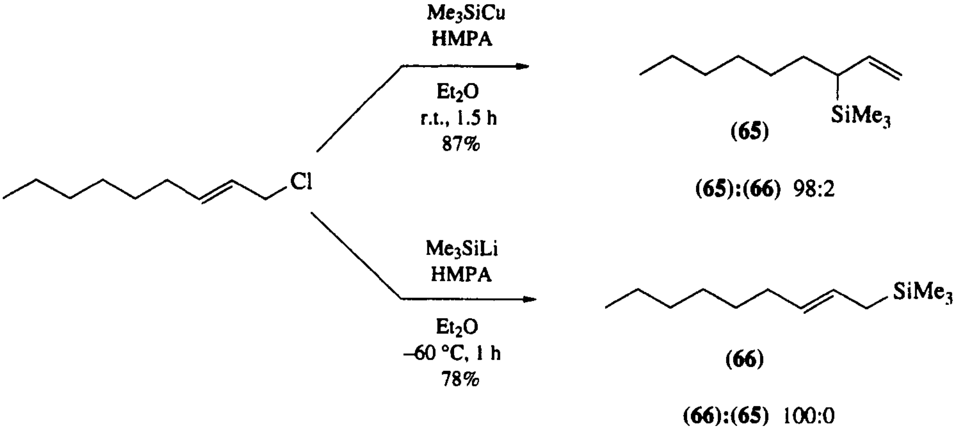
Cl
Me3SiCu
HMPA
Et2O
r.t., 1.5 h
87%
SiMe3
(65)
(65):(66) 98:2
Me3SiLi
HMPA
Et2O
–60 °C, 1 h
78%
SiMe3
(66)
(66):(65) 100:0

**Scheme 63**

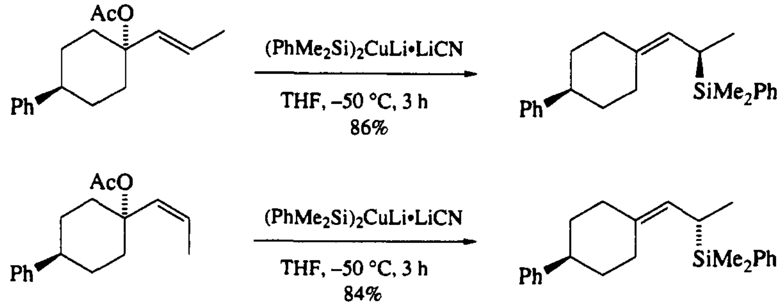
AcO
Ph
(PhMe2Si)2CuLi•LiCN
THF, -50 °C, 3 h
86%
Ph
SiMe2Ph
AcO
Ph
(PhMe2Si)2CuLi•LiCN
THF, -50 °C, 3 h
84%
Ph
SiMe2Ph

**Scheme 64**

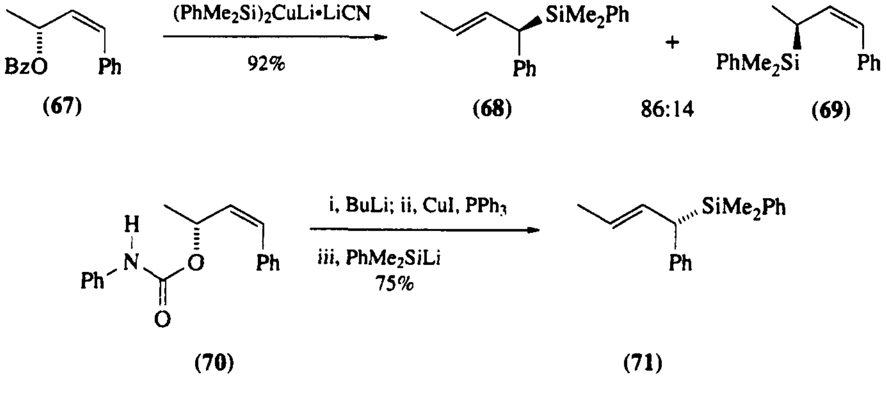
BzO
Ph
(67)
(PhMe2Si)2CuLi•LiCN
92%
SiMe2Ph
Ph
(68)
+
86:14
PhMe2Si
Ph
(69)
H
N
Ph
O
O
Ph
(70)
i, BuLi; ii, CuI, PPh3
iii, PhMe2SiLi
75%
SiMe2Ph
Ph
(71)

**Scheme 65**

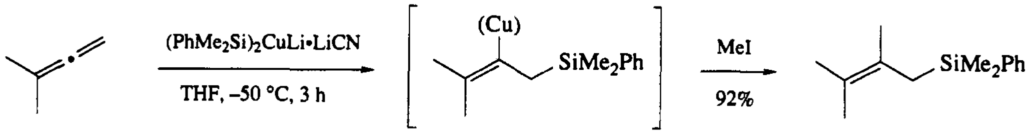
(PhMe₂Si)₂CuLi•LiCN
THF, -50 °C, 3 h
(Cu)
SiMe₂Ph
MeI
92%
SiMe₂Ph

Scheme 66

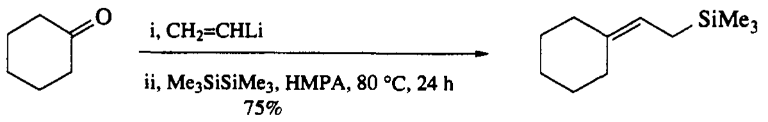
O
i, CH₂=CHLi
ii, Me₃SiSiMe₃, HMPA, 80 °C, 24 h
75%
SiMe₃

Scheme 67

Other versions of disconnection A are (i) the sila-Birch reduction of aromatic rings and dienes (Scheme 68);[116] (ii) an impractical but intriguing [2,3] sigmatropic rearrangement following the interaction of a silylene with an allylic ether;[117] (iii) the hydrosilylation of dienes, a reaction that can be made enantiocontrolled using a chiral, enantiomerically enriched catalyst (Scheme 69);[118] and (iv) the reduction and dehydration of β-silyl esters, in a sequence that guarantees that the silyl group is placed at the more-substituted end of the allyl system (Scheme 70).[119]

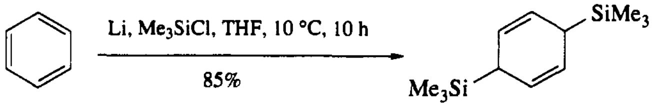
Li, Me₃SiCl, THF, 10 °C, 10 h
85%
SiMe₃
Me₃Si

Scheme 68

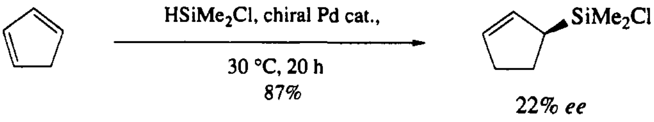
HSiMe₂Cl, chiral Pd cat.,
30 °C, 20 h
87%
SiMe₂Cl
22% ee

Scheme 69

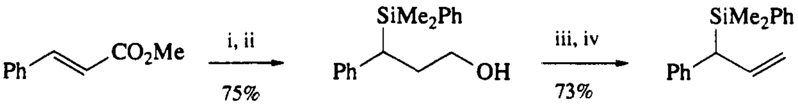
Ph
CO₂Me
i, ii
75%
SiMe₂Ph
Ph
OH
iii, iv
73%
SiMe₂Ph
Ph

i, $(PhMe_2Si)_2CuLi{\bullet}LiCN$; ii, $LiAlH_4$; iii, $o$-$O_2NC_6H_4SeCN$, $Bu_3P$; iv, $H_2O_2$

Scheme 70

### 2.2.6.1.2 *Syntheses based on disconnection B*

The most common version of this approach is the catalyzed reaction between the trimethylsilylmethyl Grignard reagent and various substrates, such as esters, enol derivatives, or vinyl halides (Scheme 71).[120–123] The same approach can be used to prepare enantiomerically pure allylsilanes using an appropriate catalyst (Scheme 72).[124] Trimethylsilylmethyl cuprate reagents react with alkynes by *syn* carbocupration and the products can be treated further with electrophiles (Scheme 73).[125] A quite different approach starting with an alkyne is to use a rearrangement set off by hydroalumination (Scheme 74).[126]

### 2.2.6.1.3 *Syntheses based on disconnection C*

The most simple of this category of syntheses is that based on the Wittig reaction (Scheme 75).[127] This method is limited by the difficulty of synthesizing phosphoranes substituted on the silicon-bearing carbon, by the low yields obtained when the phosphorus-bearing carbon is substituted, by the low yields ob-

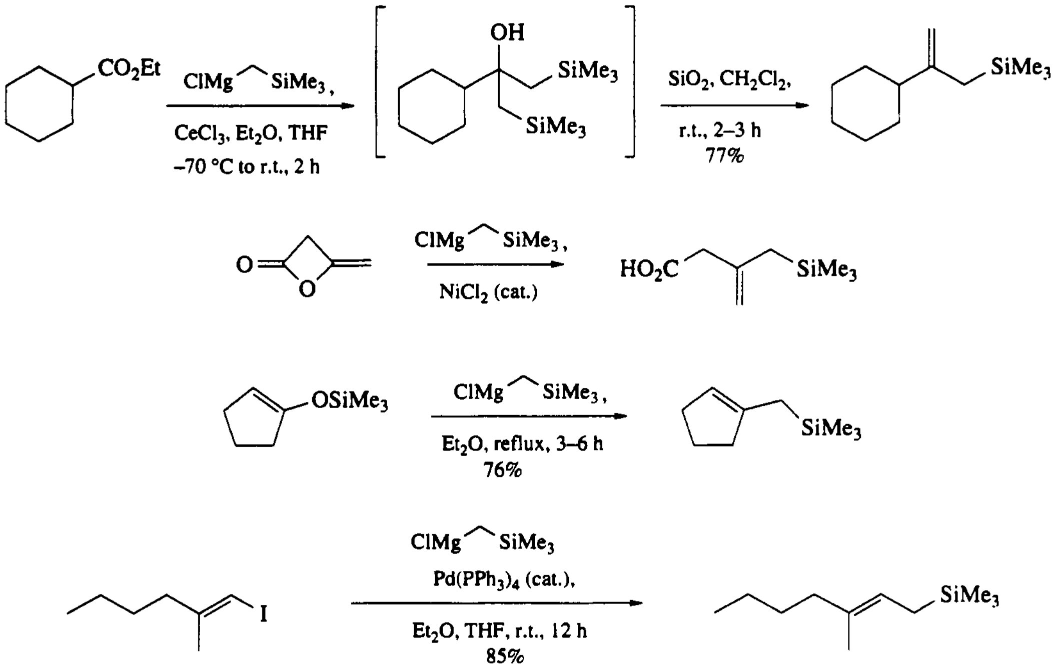
CO2Et
ClMg SiMe3,
CeCl3, Et2O, THF
-70 °C to r.t., 2 h
OH
SiMe3
SiMe3
SiO2, CH2Cl2,
r.t., 2–3 h
77%
SiMe3
O
O
ClMg SiMe3,
NiCl2 (cat.)
HO2C
SiMe3
OSiMe3
ClMg SiMe3,
Et2O, reflux, 3–6 h
76%
SiMe3
I
ClMg SiMe3
Pd(PPh3)4 (cat.),
Et2O, THF, r.t., 12 h
85%
SiMe3

**Scheme 71**

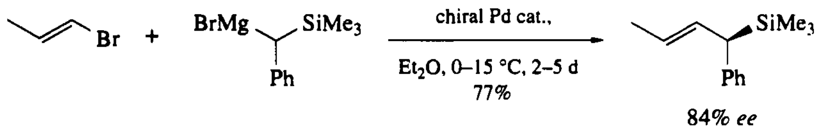
Br
+
BrMg
SiMe3
Ph
chiral Pd cat.,
Et2O, 0–15 °C, 2–5 d
77%
SiMe3
Ph
84% ee

**Scheme 72**

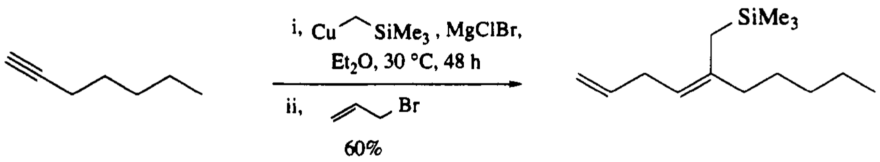
i, Cu SiMe3, MgClBr,
Et2O, 30 °C, 48 h
ii, Br
60%
SiMe3

**Scheme 73**

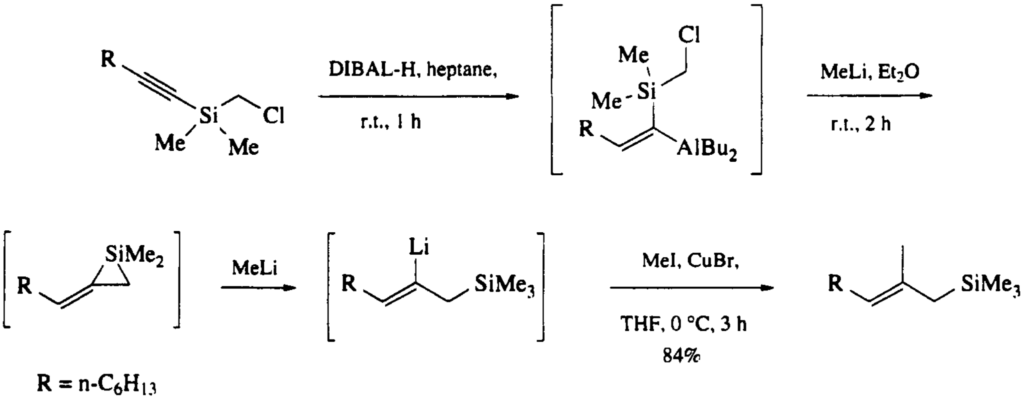
R
Si
Cl
Me
Me
DIBAL-H, heptane,
r.t., 1 h
Cl
Me
Me
Si
R
AlBu2
MeLi, Et2O
r.t., 2 h
SiMe2
R
MeLi
Li
R
SiMe3
MeI, CuBr,
THF, 0 °C, 3 h
84%
R
SiMe3
R = n-C6H13

**Scheme 74**

tained with certain ketones such as cyclopentanones, and by an alternative reaction taking place in some cases to give the silyl ether of an allylic alcohol.[128] The reaction with aldehydes however can be very useful and it is possible to make it highly selective for the (*Z*)-allylsilane.[129]

Methods for overcoming these difficulties include the reaction in Scheme 64 and the corresponding Julia (Scheme 76)[130] or Krief–Reich[131] alkene syntheses, which are all selective for the synthesis of (*E*)-allylsilanes. These methods use phosphorus, sulfur or selenium as the electrofugal group; another possibility is to use electrofugal carbon in a decarboxylative elimination, which can be carried out stereospecifically either *anti* or *syn* (Scheme 77).[132]

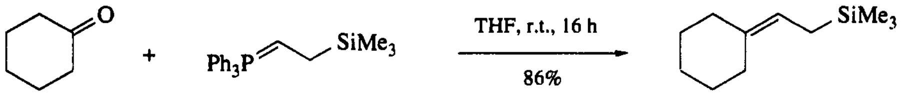
O
+
Ph3P
SiMe3
THF, r.t., 16 h
86%
SiMe3

**Scheme 75**

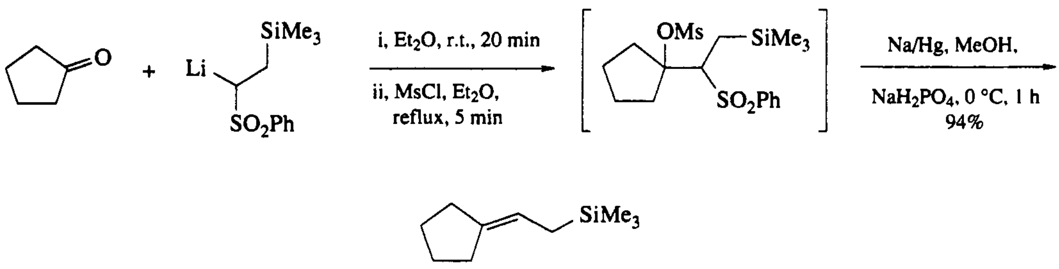
O
+
Li
SiMe3
SO2Ph
i, Et2O, r.t., 20 min
ii, MsCl, Et2O, reflux, 5 min
OMs
SiMe3
SO2Ph
Na/Hg, MeOH,
NaH2PO4, 0 °C, 1 h
94%
SiMe3

**Scheme 76**

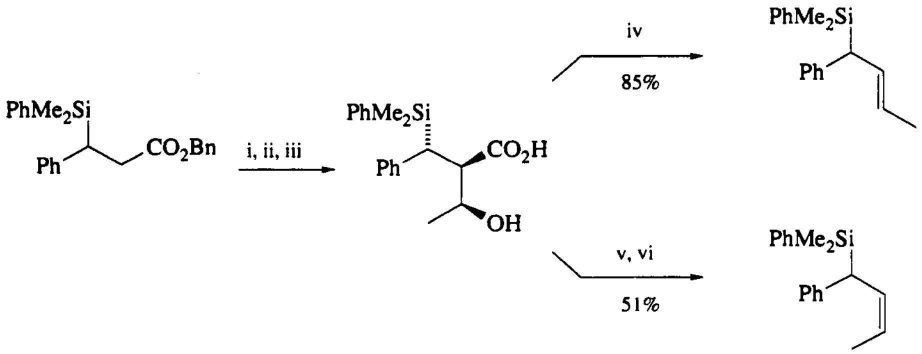
PhMe2Si
Ph
CO2Bn
i, ii, iii
PhMe2Si
Ph
CO2H
OH
iv
85%
PhMe2Si
Ph
v, vi
51%
PhMe2Si
Ph

i, LDA, THF; ii, MeCHO; iii, $H_2$, Pd; iv, $Me_2NCH(OMe)_2$, reflux; v, $PhSO_2Cl$, Py; vi, collidine, reflux

**Scheme 77**

### *2.2.6.1.4 Syntheses based on disconnection D*

A different approach is to add substituents to or manipulate substituents on an existing allyl- or propargyl-silane system. Thus propargyltrimethylsilane itself can be alkylated at the terminus and the triple bond reduced with Brown's nickel catalyst[133] or by hydroalumination–protonation,[134] both of which give the (*Z*)-allylsilane. Alternatively, zirconium-catalyzed carboalumination of propargylsilanes introduces more substituents onto the allyl framework.[123] Allylsilane anions show some selectivity for alkylation α to the silyl group, and the geometry of the double bond can be controlled by using either the kinetic or the thermodynamic allyllithium intermediate (Scheme 78).[135]

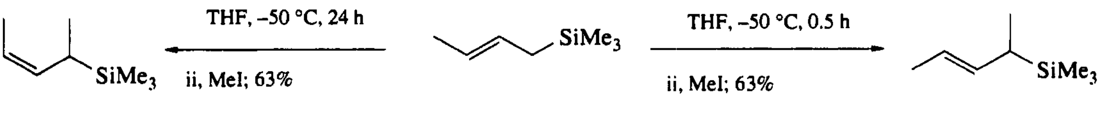
SiMe3
i, BuLi, KOBu$^t$,
THF, -50 °C, 24 h
ii, MeI; 63%
SiMe3
i, BuLi, KOBu$^t$,
THF, -50 °C, 0.5 h
ii, MeI; 63%
SiMe3

*(Z):(E)* 90:10

**Scheme 78**

Another approach is to move the double bond into the allylic position from somewhere else in the molecule. Thus, transition metal catalyzed isomerization of alkenes containing a remote silyl group brings a double bond into the allylic position and largely causes it to stop there (Scheme 79).[136] Presumably retrohydrometallation is slow when the hydrogen is adjacent to the silyl group, causing the allylsilane to accumulate. Diels–Alder reactions on butadienylsilanes give 3-silylcyclohexenes,[137] and allylic rearrangements convert some silicon-containing allylic alcohols into (*E*)-allylsilanes (Scheme 80).[138,139]

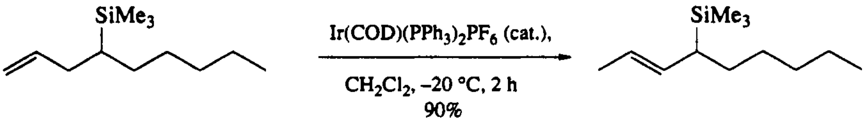

**Scheme 79**

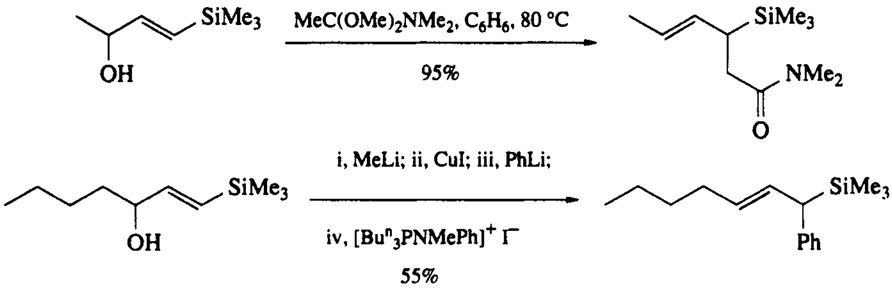

**Scheme 80**

### 2.2.6.2 Allylstannanes

Allylstannanes are made by very similar methods to those used for allylsilanes, where the same problems arise when unsymmetrical allyl nucleophiles are treated with tin halides.[24,110] To solve this problem, there are tin equivalents of the reactions in Schemes 63, 65,[110,140] 69,[141] 70,[142] 75[143] and 77.[144] Specific to allylstannanes is a radical-chain sequence (Scheme 81).[88]

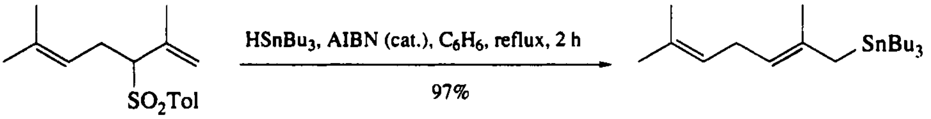

**Scheme 81**

### 2.2.6.3 Allenyl- and Propargyl-silanes and -stannanes

The synthesis of allenyl- and propargyl-silanes and -stannanes is generally carried out by silylation or stannylation of the appropriate lithium or Grignard reagent. This method naturally runs into the same problem as in the regiocontrolled synthesis of allylsilanes, namely the control of which end of the conjugated system the silyl or stannyl group attaches itself to. In this case one regioisomer is the allenyl system and the other the propargyl. For terminal propargylsilanes, one simple solution to this problem is to use the commercially available parent propargyltrimethylsilane and to join it on to the rest of the molecule.[133] For propargylsilanes substituted on the silicon-bearing carbon, the starting material can be prepared by regioselective silylation of a terminal alkyne (Scheme 82), in which very little allenylsilane is formed, followed by desilylation.[145] For allenylsilanes, the standard synthesis is to start from a silylated propargyl alcohol and to introduce a second carbon group using cuprate chemistry (Scheme 83).[146] Allenylstannanes can be prepared using a similar reaction (Scheme 84)[147] and there are also syntheses based on silyl- and stannyl-cuprate reagents reacting with propargyl alcohol derivatives.[112,148] For terminal allenylsilanes, there is a good route from silylated ethynyl ketones (Scheme 85).[91]

A radical chain reaction is again available in the tin series but not in the silyl, and it has been used in the synthesis of the parent allenylstannane (Scheme 86).[149]

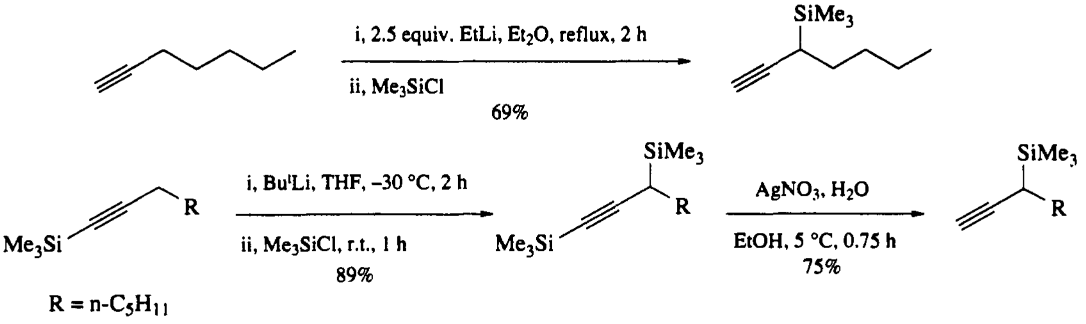
i, 2.5 equiv. EtLi, Et2O, reflux, 2 h
ii, Me3SiCl
69%
SiMe3
Me3Si
R
i, BuᵗLi, THF, -30 °C, 2 h
ii, Me3SiCl, r.t., 1 h
89%
AgNO3, H2O
EtOH, 5 °C, 0.75 h
75%
R = n-C5H11

Scheme 82

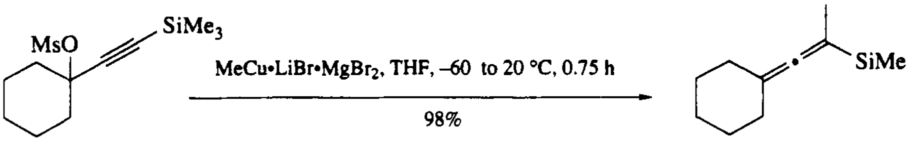
MsO
SiMe3
MeCu•LiBr•MgBr2, THF, -60 to 20 °C, 0.75 h
98%

Scheme 83

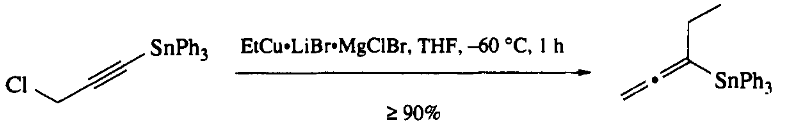
Cl
SnPh3
EtCu•LiBr•MgClBr, THF, -60 °C, 1 h
≥ 90%

Scheme 84

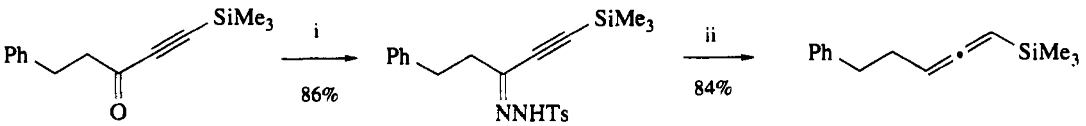
Ph
SiMe3
O
i
86%
NNHTs
ii
84%

i, $TsNHNH_2$; ii, 8 equiv. $NaBH_3CN$, DMF, cyclohexane, pH 1–2, 40–90 °C

Scheme 85

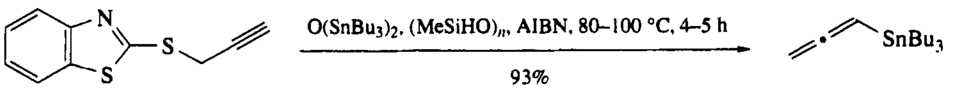
N
S
S
O(SnBu3)2, (MeSiHO)n, AIBN, 80–100 °C, 4–5 h
93%
SnBu3

Scheme 86

### 2.2.6.4 Vinyl-silanes and -stannanes

Vinyl-silanes and -stannanes can most easily be made from the corresponding vinyllithium or vinyl Grignard reagents by treating them with a silyl or tin(IV) chloride, but there is usually little point in exchanging the strongly electropositive metals, lithium or magnesium, for the much less electropositive metals, silicon or tin, when aldehydes or ketones are the electrophiles. However, this method is useful when it provides an opportunity for purification, as when the vinyllithium species are made by a Shapiro reaction (Scheme 87).[150] An umpolung version of this route to vinylstannanes is the combination of the enol triflate of the ketone reacting with a trimethyltin–magnesium reagent.[151]

Entirely different in concept are several useful methods based on alkynes. Hydrosilylation of alkynes, generally catalyzed by chloroplatinic acid and hydrostannation, generally in a radical chain process, give vinylsilanes and vinylstannanes (Scheme 88).[152] Catalyzed hydrosilylation is stereoselectively *syn*, but radical chain hydrostannylation is stereoselectively *anti* only when under kinetic control. Under thermodynamic control, as when there is a small excess of tin hydride present, the reaction is often stereoselectively *syn*. Alternatively, the silyl or stannyl groups can be introduced using the corresponding cuprate

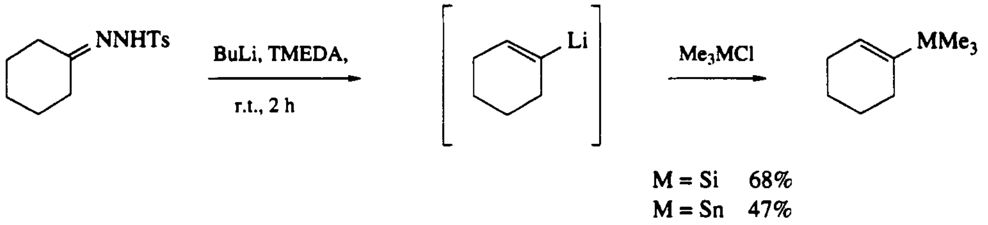
NNHTs
BuLi, TMEDA,
r.t., 2 h
Li
Me3MCl
MMe3
M = Si 68%
M = Sn 47%

Scheme 87

reagents in reactions that are usually stereoselectively *syn* (Scheme 89).[153] Similar reactions, both for silicon[154] and tin,[151] can be carried out using catalytic quantities of transition metals in place of the stoichiometric use of copper(I). A silyl group can be attached to a terminal alkyne and the other groups added to the triple bond using such methods as hydroalumination (Scheme 90)[155] or hydroboration.[156] The alkyl group can be attached by rearranging it from boron in an alkynylborate, either with the silyl group already in the molecule (**72**)[157] or with a silyl halide as the electrophile initiating the rearrangement (**74**) → (**75**) (Scheme 91),[158] the two methods being stereochemically complementary. The boron atom in the vinylboranes (**73**) and (**75**) can be replaced by a proton or by other groups.

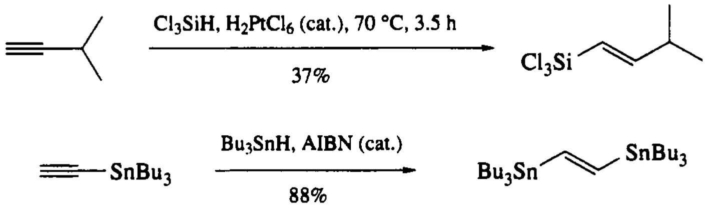
Cl3SiH, H2PtCl6 (cat.), 70 °C, 3.5 h
37%
Cl3Si
SnBu3
Bu3SnH, AIBN (cat.)
88%
Bu3Sn
SnBu3

Scheme 88

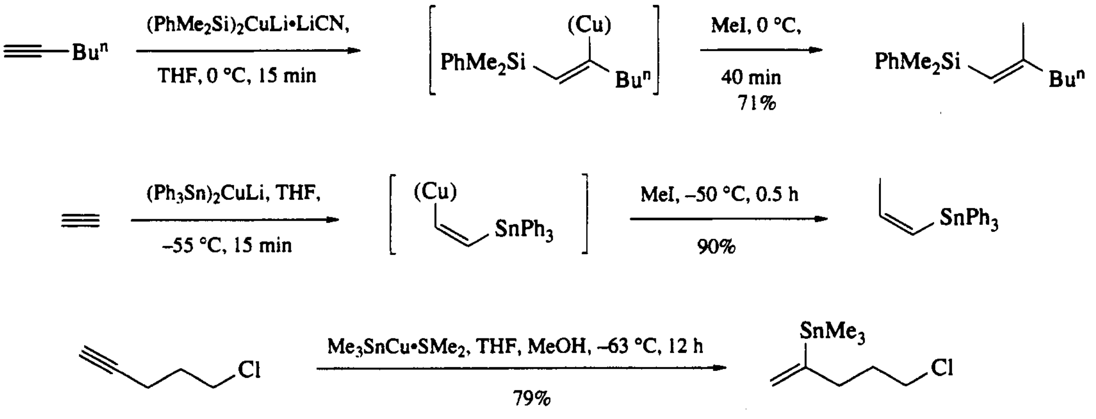
Bun
(PhMe2Si)2CuLi•LiCN,
THF, 0 °C, 15 min
(Cu)
PhMe2Si
Bun
MeI, 0 °C,
40 min
71%
PhMe2Si
Bun
(Ph3Sn)2CuLi, THF,
-55 °C, 15 min
(Cu)
SnPh3
MeI, -50 °C, 0.5 h
90%
SnPh3
Cl
Me3SnCu•SMe2, THF, MeOH, -63 °C, 12 h
79%
SnMe3
Cl

Scheme 89

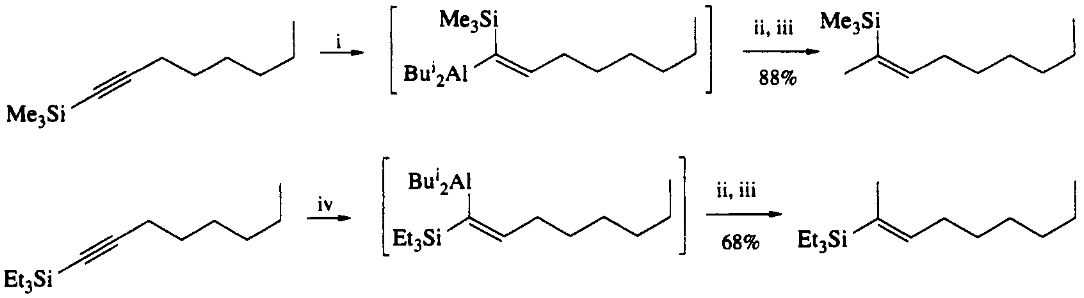
Me3Si
i
Me3Si
Bui2Al
ii, iii
88%
Me3Si
Et3Si
iv
Bui2Al
Et3Si
ii, iii
68%
Et3Si

i, DIBAL-H, heptane, ether, r.t., 17 h; ii, MeLi; iii, MeI, r.t., 20 h; iv, DIBAL-H, heptane, r.t., 20 h

Scheme 90

Another pair of stereochemically complementary routes to mid-chain vinylsilanes starts from the allylic alcohol (**76**) made by combining the α-trimethylsilylvinyllithium reagent with the appropriate aldehyde. Cuprate chemistry allows the other chain to be attached with either stereochemical outcome (Scheme 92) and the route is also amenable to the synthesis of tetrasubstituted vinylsilanes, simply by starting with a ketone in place of the aldehyde.[159]

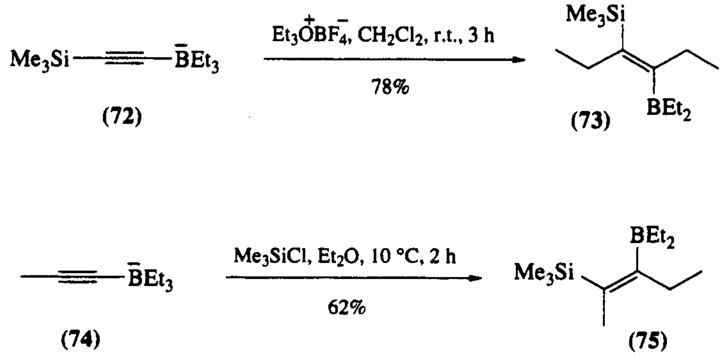

Scheme 91

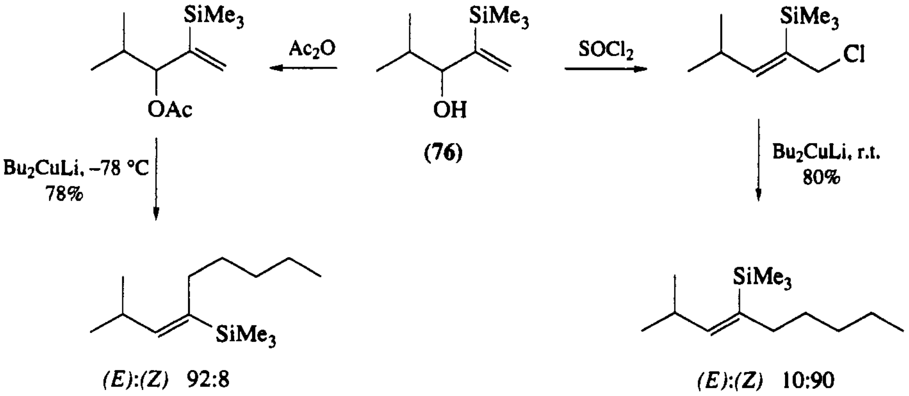

Scheme 92

## 2.2.7 REFERENCES

1. First example: R. Calas, J. Dunoguès, G. Déléris and F. Pisciotti, *J. Organomet. Chem.*, 1974, **69**, C15.
2. First example: K. König and W. P. Neumann, *Tetrahedron Lett.*, 1967, 495.
3. I. Fleming, J. Dunoguès and R. H. Smithers, *Org. React.*, 1989, **37**, 57.
4. Y. Yamamoto, *Acc. Chem. Res.*, 1987, **20**, 243; *Aldrichimica Acta*, 1987, **20**, 45.
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# 2.3
# Formation and Addition Reactions of Enol Ethers

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## 2.3.1 INTRODUCTION

This chapter is concerned with the reactions of enol ethers with carbonyl compounds as illustrated in Scheme 1. The enol ethers considered include alkyl, silyl, germyl and stannyl ethers, and to a small extent enol esters. The carbonyl compounds encompass aldehydes, ketones, esters and their functional equivalents. Overall, the reaction depicted in Scheme 1 is similar to the classical aldol and related condensations discussed in Part 1 of this volume. However, in contrast to the basic conditions inherent in

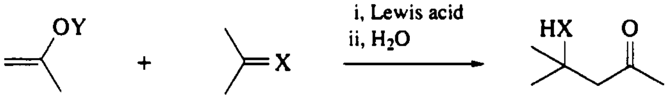

Y = alkyl, acyl, silyl, germyl or stannyl; X = O or equivalent

**Scheme 1**

enolate anion chemistry, the reactions of enol ethers with carbonyl compounds are usually carried out under neutral or acidic conditions. Their chemistry, and consequently their synthetic utilities, often complement each other.

## 2.3.2 PREPARATION OF ENOL ETHERS

### 2.3.2.1 Formation of Alkyl Enol Ethers and Enol Esters

Alkyl enol ethers can be conveniently prepared by the alkylation of α-methoxyvinyllithium and related metallated enol ethers.[1] In a typical example, methyl vinyl ether (**1**) is converted by *t*-butyllithium to give α-methoxyvinyllithium (**2**). Reaction of (**2**) with octyl iodide gives the enol ether (**3**). Metallation of methyl propenyl ether (**4**) and methyl allenyl ether (**5**) can be similarly executed.[2]

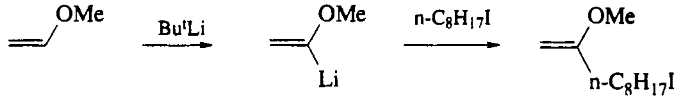

(**1**) (**2**) (**3**)

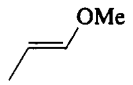

(**4**)

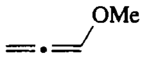

(**5**)

Carbometallation of alkynic ethers with organocopper reagents can also give enol ethers.[3] Even though the triple bond in (**6**) is unsymmetrically substituted, carbometallation occurs regioselectively to give compound (**7**), presumably due to the directing effect of the ethoxy group. Regioselection is lost when the other carbon of the alkyne bears an alkyl group.

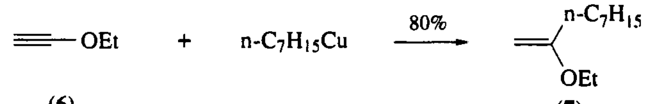

(**6**) (**7**)

Alkenation of carbonyl compounds can be used as a general method for the synthesis of enol ethers. The Horner–Wittig reaction of the phosphorus-stabilized carbanion (**8**) with aldehydes or ketones gives the adducts (**9**), which on heating eliminate to give the enol ethers (**10**) as a mixture of (*E*)- and (*Z*)-isomers. Since the two diastereomeric adducts (**9**) can be separated and the elimination reaction is stereospecific, this method can be used to prepare the individual geometrical isomers[4] of (**10**) according to Scheme 2.

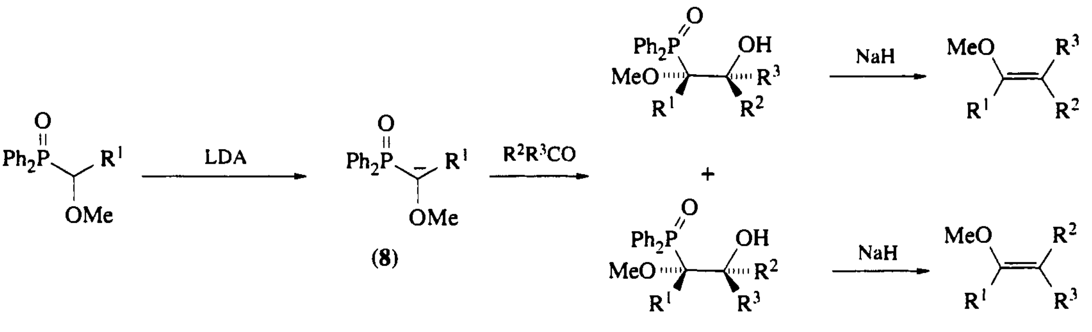

(**8**) (**9**) (**10**)

**Scheme 2**

Alternatively, Horner–Wittig reaction of diazomethylphosphonate (**11**) with carbonyl compounds gives, presumably, the diazoalkenes (**12**). Replacement of the diazo group *in situ* by an alkoxy group gives the enol ethers (**13**; Scheme 3).[5]

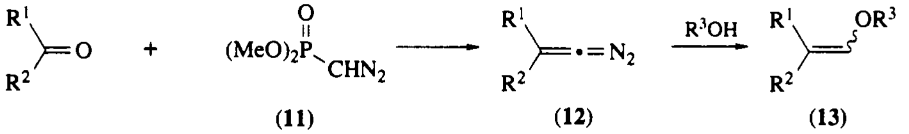

Scheme 3

Peterson alkenation of carbonyl compounds with trimethylsilylmethoxymethyl carbanion (**14**) can also give enol ethers.[6,7] An example is the reaction of (**14**) with adamantanone. Another method of alkene synthesis is the elimination of $CO_2$ and $H_2O$ from a β-hydroxycarboxylic acid. If the carboxylic acid is substituted by an α-alkoxy group, the reaction can be used for the synthesis of enol ethers, as illustrated in Scheme 4.[8]

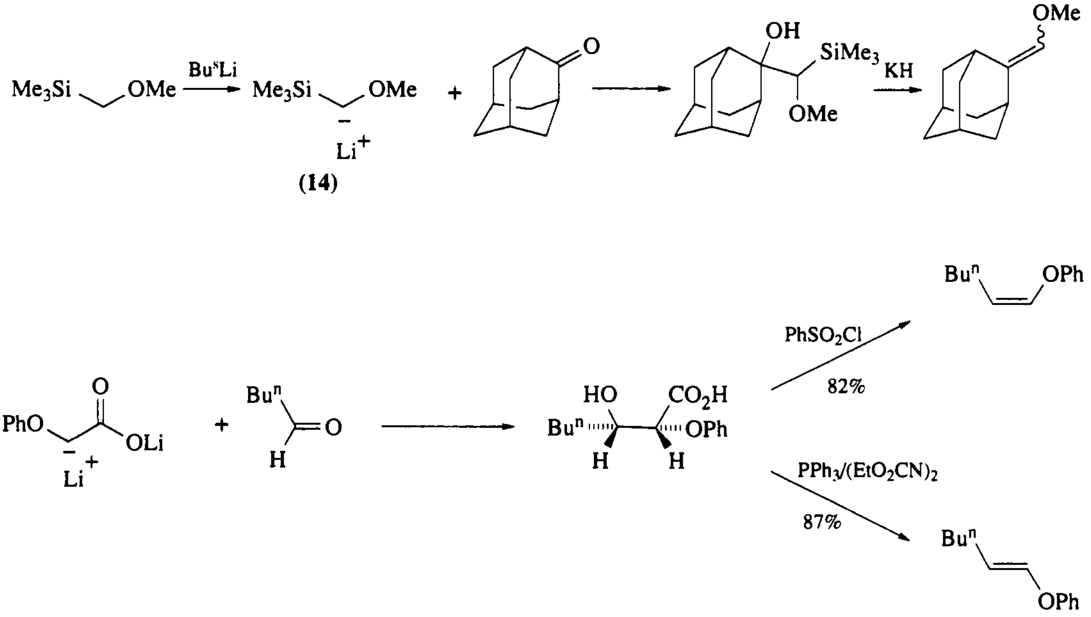

Scheme 4

The carbonyl group of an ester function can be converted to the corresponding methylene compound using Tebbe's reagent. The reaction can thus be considered as a general method of enol ether synthesis.[9] An example of this reaction is given in Scheme 5.[96] The same conversion can be achieved by reagents prepared from the reduction of 1,1-dibromoalkanes with zinc and $TiCl_4$ in the presence of TMEDA.[10]

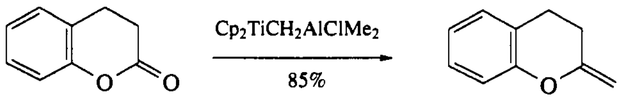

Scheme 5

Alkylation of enolate anions usually gives *C*-alkylation and is therefore not suitable for the preparation of enol ethers. The exception is when triethyloxonium tetrafluoroborate is used as the alkylating agent in a dipolar aprotic solvent.[11] *O*-Alkylation can be regioselectively achieved if the enolate anion is derived from acetoacetate or a similar compound. On the other hand, *O*-acylation of enols or enolate anions is quite common. Enol esters can therefore be prepared readily from the parent carbonyl compounds. For example, cyclooctanone (**15**) is converted by heating with acetic anhydride and *p*-toluenesulfonic acid to cyclooctenyl acetate (**16**).[12]

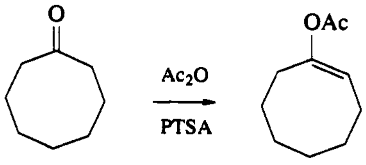
O
OAc
$Ac_2O$
PTSA

**(15)** **(16)**

Conversion of aldehydes and ketones to the corresponding acetals followed by elimination of an alcohol moiety is a general method to prepare enol ethers.[13] The elimination is usually conducted under mildly acid-catalyzed conditions as in the preparation of (**18**) from (**17**). When the ketone is unsymmetrically substituted, good regiocontrol of the enol ether formed is difficult to achieve (Scheme 6).[14]

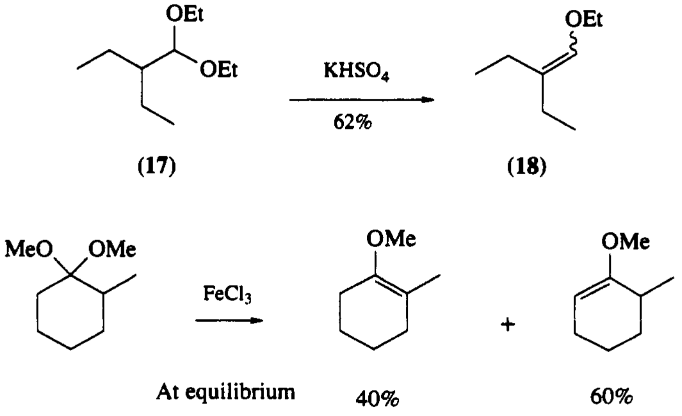
OEt
OEt
$KHSO_4$
62%
OEt
(17)
(18)
MeO
OMe
$FeCl_3$
OMe
+
OMe
At equilibrium
40%
60%

**Scheme 6**

Addition of an alcohol to a triple bond is another way to obtain an enol ether. An example is the conversion of *m*-ethynylpyridine (**19**) to β-methoxyvinylpyridine (**20**). Addition, in this particular case, is stereoselective to give the (*Z*)-isomer.[15]

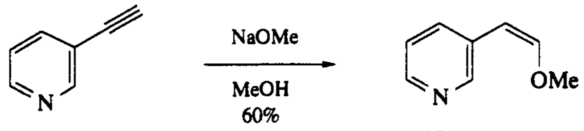
N
NaOMe
MeOH
60%
N
OMe

**(19)** **(20)**

Oxytelluration of terminal alkenes followed by elimination of the tellurium moiety gives enol ethers as shown in Scheme 7.[16]

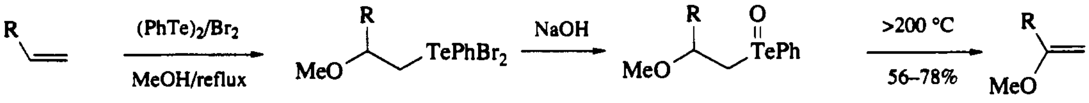
R
$(PhTe)_2/Br_2$
MeOH/reflux
R
MeO
$TePhBr_2$
NaOH
R
O
MeO
TePh
>200 °C
56–78%
R
MeO

R = Ph or n-$C_8H_{17}$

**Scheme 7**

A very useful method to prepare carbocyclic enol ethers is the Birch reduction of aryl ethers.[17] In the simplest example, metal ammonia reduction of methoxybenzene gives methoxycyclohexadiene (**21**). The reaction has been applied to numerous aryl ethers of complex structures.

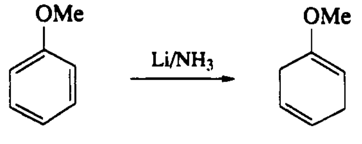

(21)

The isomerization of allyl ethers with a transition metal catalyst, though normally used as a method of deprotection of the allyl group,$^{18,19}$ can be considered as a convenient method of enol ether synthesis. The conversion of (22) to the propenyl ether (23) serves as an example.$^{20}$

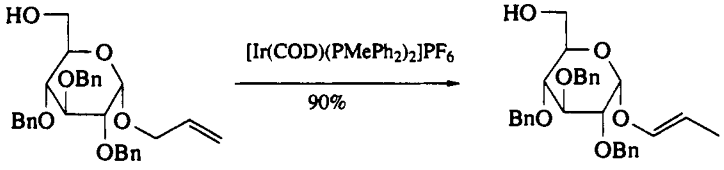

(22) (23)

### 2.3.2.2 Formation of Enol Silyl Ethers and Silyl Ketene Acetals

Enol silyl ethers and silyl ketene acetals have become important synthetic reagents in organic synthesis. Their chemistry has been the subject of a number of recent reviews.$^{21}$

#### *2.3.2.2.1 Enol silyl ethers of aldehydes and ketones*

Enol silyl ethers can be prepared readily from the parent carbonyl compounds by silylation of the corresponding enolate anions.$^{22}$ Particularly useful is the observation$^{23}$ that with unsymmetrical ketones it is often possible to generate the less-substituted enol silyl ether under conditions of kinetic control, and the more-substituted enol silyl ether by equilibration, giving thermodynamic control. Using 2-methylcyclohexanone (24) as an example, generation of the enolate anion with LDA followed by quenching with trimethylchlorosilane gives the kinetic enol silyl ether (25), whereas treatment of (24) with triethylamine/trimethylchlorosilane in DMF at 130 °C for 66 h gives the more stable enol silyl ether (26; Scheme 8).

Regiospecific synthesis of enol silyl ethers can also be achieved from enones either by reductive silylation or by 1,4-addition of the conjugated system. Thus, Li/NH$_3$ reduction of the decalone (27) and silylation give the enol silyl ether (28).$^{24}$ Similarly, addition of lithium dimethylcuprate to cyclohexenone$^{25}$ followed by silylation gives the enol silyl ether (29). Trimethylsilyl cyanide (30) normally adds 1,2 to conjugated ketones (*e.g.* carvone, 31). However, in the presence of trialkylaluminum, 1,4-addition takes place to give the enol silyl ether (32; Scheme 9). The same overall transformation can be accomplished by diethylaluminum cyanide and trimethylchlorosilane.$^{26}$

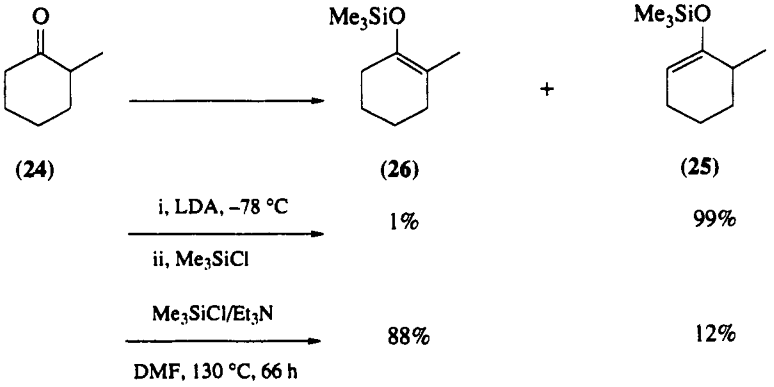

Scheme 8

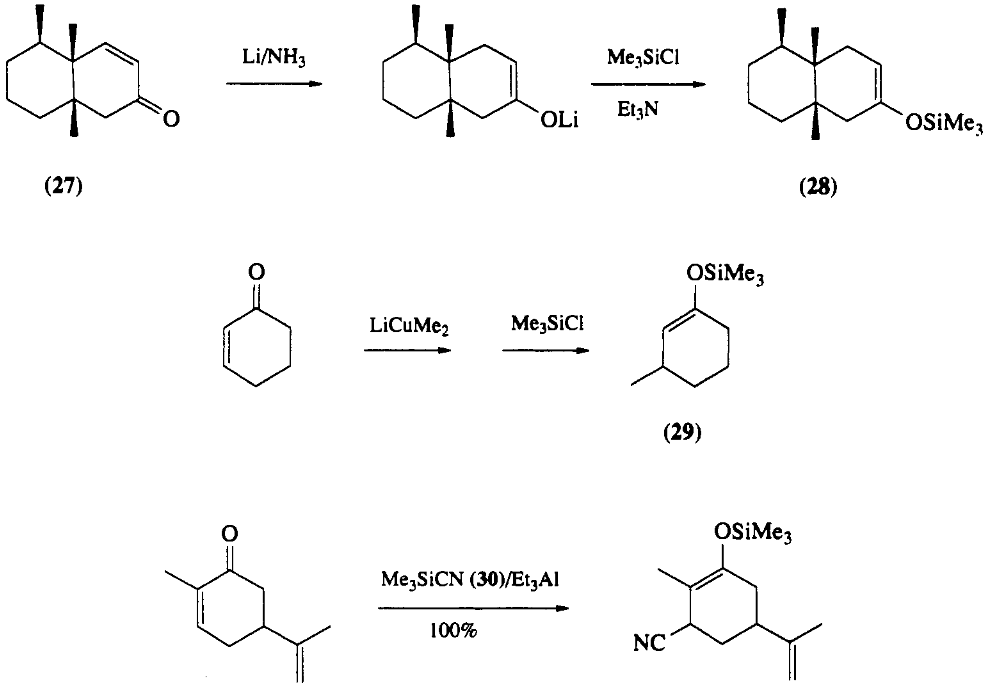
Li/NH3
OLi
Me3SiCl
Et3N
OSiMe3
LiCuMe2
Me3SiCl
OSiMe3
Me3SiCN (30)/Et3Al
100%
OSiMe3
NC

(27) (28)

(29)

(31) (32)

**Scheme 9**

Reductive silylation of α-halo ketones is synthetically useful if the halo ketone can be obtained regiochemically pure to begin with. An example is the zinc/TMS-Cl reaction with (33).[27]

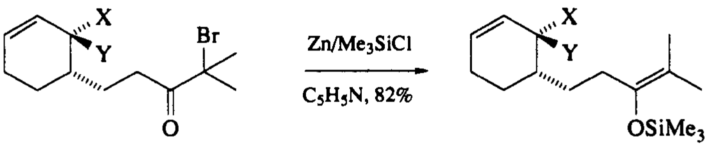
X
Y
Br
O
Zn/Me3SiCl
C5H5N, 82%
X
Y
OSiMe3

(33) X = H; Y = OAc
X = OAc; Y = H

Conversion of aldehydes into the corresponding enol silyl ethers can be accomplished with a number of enolization–silylation reagents: KH/DME–TMS-Cl/$Et_3N$,[28] TMS triflate with amines[29] or bis(trimethylsilyl)acetamide[30] among them. In the specific case of siloxyethylene, it has been prepared by the fragmentation of tetrahydrofuran with butyllithium and silylation of the resulting enolate anion (Scheme 10).[31]

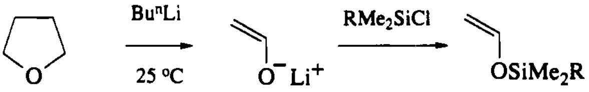
O
Bu^nLi
25 °C
O⁻ Li⁺
RMe2SiCl
OSiMe2R

**Scheme 10**

Generation of enol silyl ethers from acyclic ketone precursors can be accomplished using the same kind of reagents. Depending on the reaction conditions, stereoselective formation of either the (*E*)- or the (*Z*)-isomer of the enol silyl ethers has been reported (Scheme 11).[32] An *in situ* method of generating the enolate anion with lithium dialkylamides in the presence of trimethylchlorosilane leads to enhanced selection for the kinetically preferred enol silyl ether (*e.g.* **34a**).[33] Lithium *t*-octyl-*t*-butylamide (LOBA) is

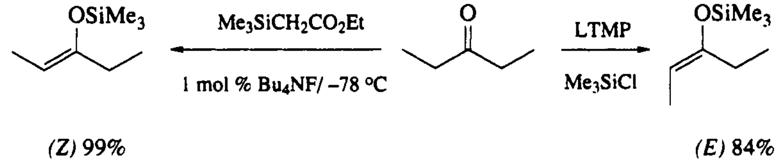

OSiMe3
Me3SiCH2CO2Et
1 mol % Bu4NF/ -78 °C
O
LTMP
Me3SiCl
OSiMe3
(Z) 99%
(E) 84%

**Scheme 11**

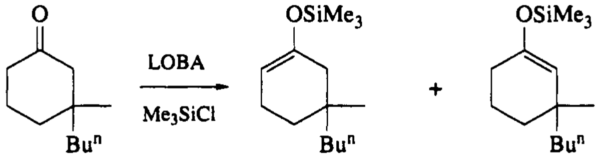

O
Bu<sup>n</sup>
LOBA
Me3SiCl
OSiMe3
Bu<sup>n</sup>
+
OSiMe3
Bu<sup>n</sup>

**(34a)** 97% 3%

shown to be superior to LDA in the regioselective generation of enolates and in the stereoselective formation of (*E*)-enolates in this *in situ* method.

Rearrangement of the α-silyl ketone (**35**) has been used to prepare the halo-substituted enol silyl ether (**36**; Scheme 12).[34] Normal enolization of α-halo ketones would have given the other regioisomers.

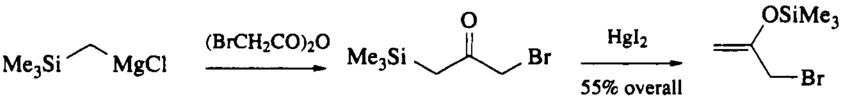

Me3Si MgCl
(BrCH2CO)2O
Me3Si
O
Br
HgI2
55% overall
OSiMe3
Br

**(35)** **(36)**

**Scheme 12**

Rearrangement of acylsilanes under pyrolytic or photolytic conditions can give enol silyl ethers, presumably *via* α-siloxycarbenes (Scheme 13).[35] Reactions of acylsilanes with vinyl or alkynyl carbanions give the adduct α-silylcarbinols (**37**). Treatment of (**37**) with Bu$^n$Li gives the oxyanions (**38**), which can undergo the Brook rearrangement to give the siloxycarbanions (**39**). Quenching of (**39**) with electrophiles leads eventually to the enol silyl ethers (**40**; Scheme 14).[36] The same siloxycarbanions (**39**) can be generated from allyloxysilanes (**41**).[37] The enol silyl ethers (**40**) formed have the (*Z*)-stereochemistry be-

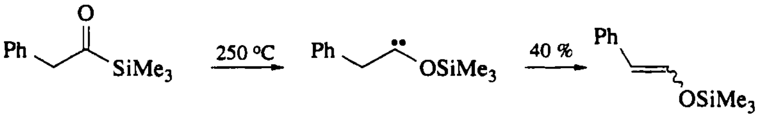

O
Ph
SiMe3
250 °C
Ph
OSiMe3
40 %
Ph
OSiMe3

**Scheme 13**

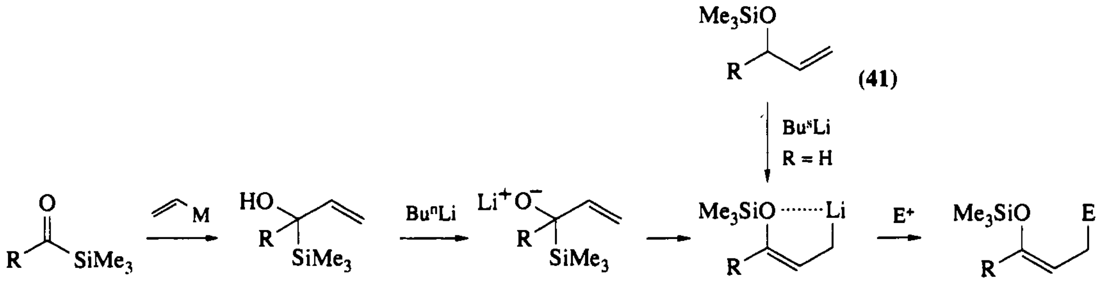

Me3SiO
R
(41)
Bu<sup>s</sup>Li
R = H
O
R
SiMe3
M
HO
R
SiMe3
Bu<sup>n</sup>Li
Li<sup>+</sup>O<sup>-</sup>
R
SiMe3
Me3SiO·······Li
R
E<sup>+</sup>
Me3SiO
E
R

**(37)** **(38)** **(39)** **(40)**

**Scheme 14**

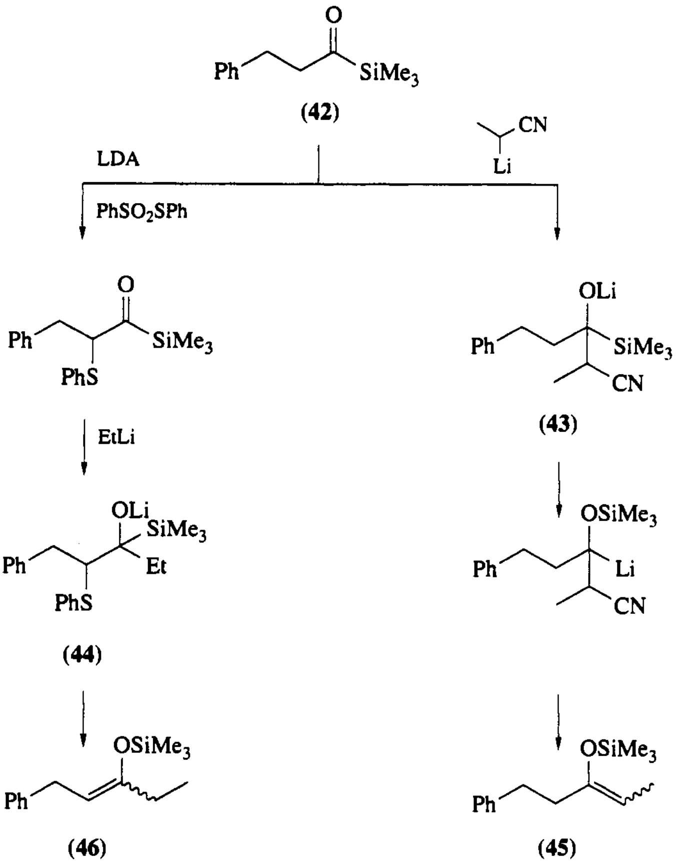

**Scheme 15**

cause of the internal chelation present in (**39**). Alternatively, acylsilane (**42**) can be converted to the silyloxyanions (**43**) and (**44**). Similar rearrangement followed by elimination reaction gives regioselectively the enol silyl ethers (**45**) and (**46**) respectively as illustrated in Scheme 15. In these cases, the stereochemistry of the double bond is not controlled and a mixture of geometric isomers is formed.[38]

Epoxysilanes, which can be obtained by epoxidation of vinylsilanes or other methods, can rearrange to enol silyl ethers as shown in Scheme 16.[39]

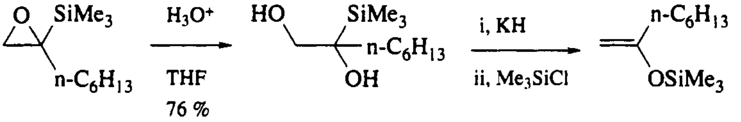

**Scheme 16**

Acyloin condensations of esters conducted with TMS-Cl and sodium in toluene give 1,2-bis(trimethylsilyloxy)alkenes.[40] In general, the silylacyloin reaction provides higher yields than the conventional acyloin reaction and is particularly useful for the preparation of cyclic enol silyl ethers.[41] The synthesis of compound (**47**) serves as an illustration.

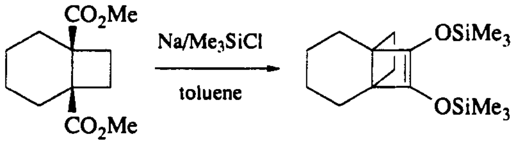

(**47**)

Alkylidenation of the carbonyl group of silyl esters with a reagent derived from the reduction of 1,1-dibromoalkanes with zinc/$TiCl_4$ gives (*Z*)-silyl enol ethers in good yield (*e.g.* **48**).[42]

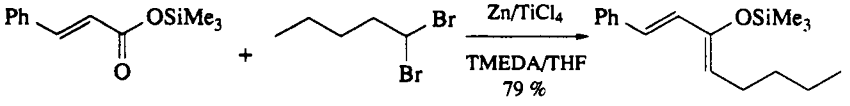
Ph
OSiMe3
O
+
Br
Br
Zn/TiCl4
TMEDA/THF
79 %
Ph
OSiMe3

**(48)**

Silanes normally reduce aldehydes or ketones under catalytic conditions to the silyl ethers. However, with certain catalysts such as nickel sulfide,[43] $Co_2(CO)_8$,[44] or $(Ph_3P)_3RhCl$,[45] carbonyl compounds react with silanes to yield an equilibrium mixture of enol silyl ethers (Scheme 17). In a similar vein, the silylhydroformylation reaction of cycloalkenes with CO and silanes may be a practical way to prepare enol silyl ethers.[46] An example is the preparation of compound (**49**). Catalytic 1,4-hydrosilation of α,β-unsaturated ketones or aldehydes gives the corresponding enol silyl ethers. The reaction is similar to the reductive silylation referred to previously, but the reaction conditions are neutral and milder. The formation of the enol silyl ether (**50**) is outlined below.[47]

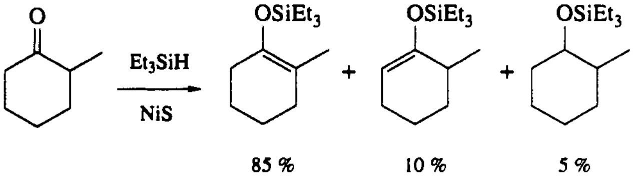
O
Et3SiH
NiS
OSiEt3
+
OSiEt3
+
OSiEt3
85 %
10 %
5 %

**Scheme 17**

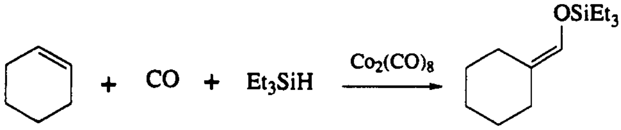
+
CO
+
Et3SiH
Co2(CO)8
OSiEt3

**(49)**

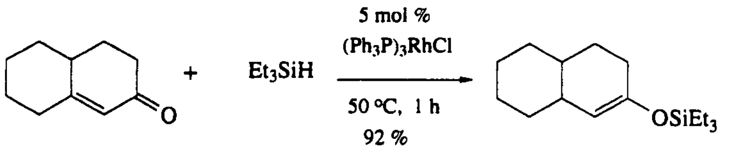
+
Et3SiH
O
5 mol %
(Ph3P)3RhCl
50 °C, 1 h
92 %
OSiEt3

**(50)**

Oxidation of (*E*)- or (*Z*)-vinyllithium with silyl peroxide (**51**) at −110 °C affords enol silyl ethers in modest to good yield.[48] The reaction proceeds with retention of stereochemistry at the double bond.

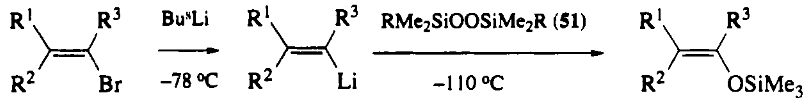
R1
R3
R2
Br
BunLi
-78 °C
R1
R3
R2
Li
RMe2SiOOSiMe2R (51)
-110 °C
R1
R3
R2
OSiMe3

R = Me or Bu$^t$

Recently, enol silyl ethers that bear chloro, alkoxy or amino groups on the silicon have been prepared (Scheme 18).[49]

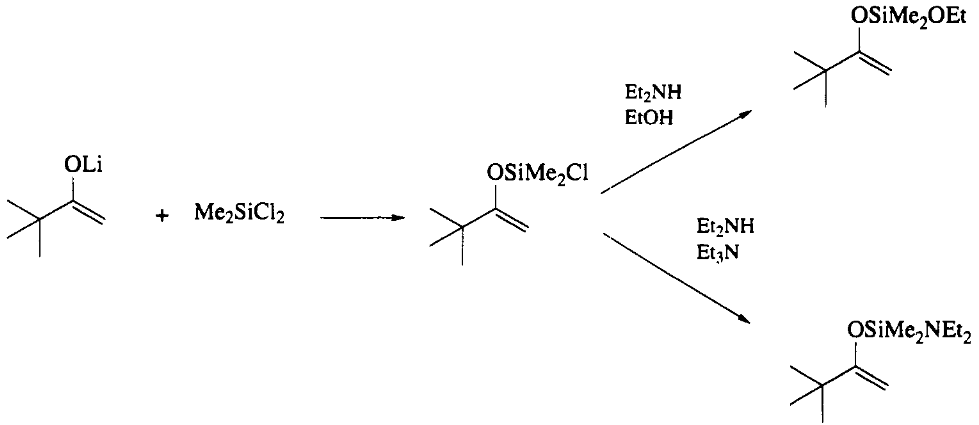

**Scheme 18**

### 2.3.2.2.2 Silyl ketene acetals and related compounds

In principle, silyl ketene acetals can be prepared from the parent ester compounds using the same reagents as discussed above for the synthesis of enol silyl ethers. An important difference is the fact that *C*-silylation can be an effective competition in the silylation of the ester enolate anion (Scheme 19). The extent of *O*- *versus* *C*-silylation depends on the nature of the ester R group, the substitutent in the α-carbon, the structure of the silylating agent and the reaction conditions.[50] With TMS-Cl, silylation of the lithium ester enolates of methyl or ethyl acetate gives predominantly *O*-silylation. Ethyl esters of higher acids give almost exclusively *O*-silylation as well. *t*-Butyl esters, on the other hand, give better yields of the *C*-silylated products. For example, *t*-butyl acetate gives only *C*-silylation and *t*-butyl butanoate gives 60% *C*- and 40% *O*-silylation. It seems that substitution in the alcohol part favors *C*-silylation and substitution at the α-carbon favors *O*-silylation.[51] The extent of *O*-silylation depends also on the nature of the counterion. Zinc enolates are to be avoided since a Reformatsky-type reaction[52] of ethyl bromoacetate and TMS-Cl with zinc gives the *C*-silylated product (**52**). On the other hand, quenching of the Reformatsky reagent iododifluoroacetate–Zn with TMS-Cl is reported to give the corresponding silyl ketene acetal.[53] Another variable is the nature of the silylating agent. For example, reaction of methyl acetate with lithium cyclohexylisopropylamide followed by TMS-Cl yields methyl trimethylsilyl ketene acetal (65%) and methyl trimethylsilylacetate (35%). Higher selectivity for *O*-silylation can be achieved by the use of *t*-butyldimethylchlorosilane.[51] The polarity of the solvent can also play a significant role. The reaction of methyldiphenylchlorosilane with lithium ester enolate gives *C*-silylation in THF and *O*-silylation in THF–HMPA.[54]

Geometric isomers of silyl ketene acetals can be prepared from the acyclic ester precursors, depending on the solvent used.[55] Treatment of ethyl propanoate with LDA in THF, followed by reaction with TMS-

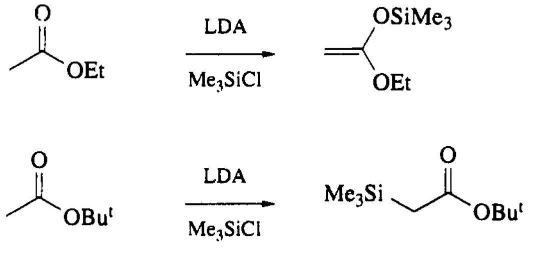

**Scheme 19**

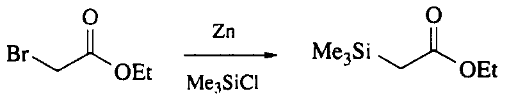

**(52)**

Cl, gives predominantly the (*E*)-isomer of (**53**), but addition of HMPA causes exclusive formation of the (*Z*)-isomer (Scheme 20).[56]

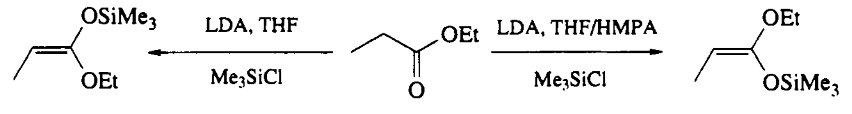
OSiMe3
OEt
LDA, THF
Me3SiCl
OEt
O
LDA, THF/HMPA
Me3SiCl
OEt
OSiMe3

(**53**) *(E):(Z)* = 85:15

(**53**) *(E):(Z)* = 0:100

Scheme 20

In the case of compound (**54**) where there is an SMe group at the β-position, the usual reaction with LDA leads to β-elimination. The silyl ketene acetal (**55**) is prepared by the *in situ* method[33] of adding (**54**) to a solution of LDA and TMS-Cl at –90 °C.[57]

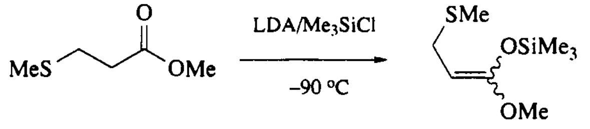
O
MeS
OMe
LDA/Me3SiCl
–90 °C
SMe
OSiMe3
OMe

(**54**)

(**55**)

Thiol esters can be converted to the corresponding *O*-silyl ketene thioacetals.[58] The thiol ester (**56**), under different silylating conditions, can be converted stereoselectively into either the (*E*)- or the (*Z*)-isomers of (**57**).[59]

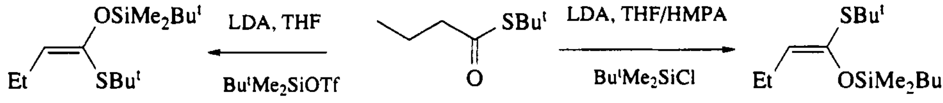
OSiMe2Bu^t
Et
SBu^t
LDA, THF
Bu^tMe2SiOTf
SBu^t
O
LDA, THF/HMPA
Bu^tMe2SiCl
SBu^t
Et
OSiMe2Bu^t

(**57**) *(Z):(E)* > 95:5

(**56**)

(**57**) *(E):(Z)* > 95:5

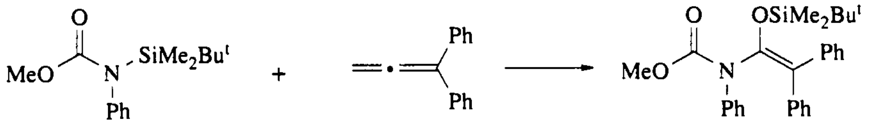
O
MeO
N
SiMe2Bu^t
Ph
+
Ph
Ph
O
OSiMe2Bu^t
MeO
N
Ph
Ph
Ph

Scheme 21

Tertiary amides can also be silylated by LDA/TMS-Cl, but a mixture of *C*- and *O*-silylated products results.[60] An alternative approach may be through the reaction of ketenes with silylamines as illustrated in Scheme 21.[61]

Lactones can be converted to the corresponding silyl ketene acetals in an unexceptional manner.[62]

### 2.3.2.2.3 *Di- and poly-silyl enol ethers and ketene acetals*

In contrast to metal enolates, enol silyl ethers are covalent compounds. It is easier to accommodate two or more enol silyl ether structures within the same molecule, whereas it would be more difficult to generate the corresponding enolate structures because of their strongly basic and reactive characters. 2,3-Butanedione has been converted to 2,3-bis(trimethylsiloxy)butadiene by a number of methods; the best appears to be TMS triflate and $Et_3N$ in benzene.[63] Likewise, 1,3-diketones have been converted to the

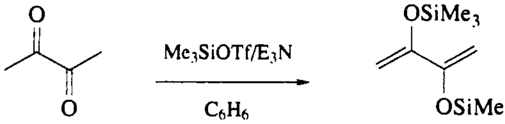
O
O
Me3SiOTf/Et3N
C6H6
OSiMe3
OSiMe3

corresponding 1,3-bis(trimethylsiloxy)butadienes (*e.g.* **58**; Scheme 22).[64] With 1,4-diketones, two regioisomers of the dienol silyl ethers are usually formed, the proportions depending on the reagents used (Scheme 23).[65]

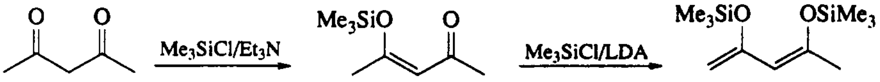
Me3SiCl/Et3N
Me3SiO
Me3SiCl/LDA
Me3SiO
OSiMe3

**(58)**

**Scheme 22**

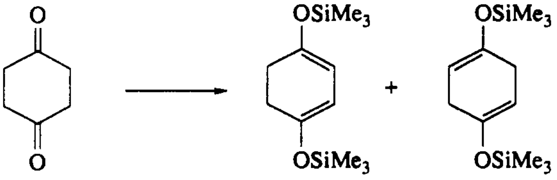
OSiMe3
OSiMe3
OSiMe3
OSiMe3

| | | |
|---|---|---|
| $Me_3SiOTf/C_6H_6$ | 31% | 51% |
| $Me_3SiCl/Et_3N/ZnCl_2/C_6H_6$ | 80% | 20% |

**Scheme 23**

The question of regiochemistry does not arise in the case of diesters. Diethyl succinate has been converted to the disilyl ketene acetal (**59**) in good yield.[66] A number of glutarate esters (**60**) have been similarly transformed to (**61**).[67]

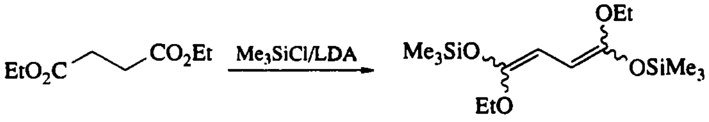
EtO2C
CO2Et
Me3SiCl/LDA
Me3SiO
OEt
OSiMe3
EtO

**(59)**

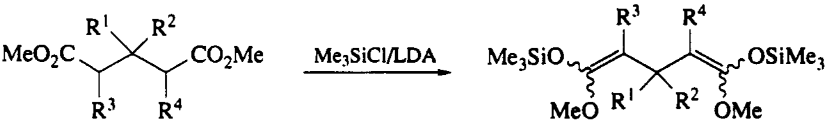
R1
R2
MeO2C
CO2Me
R3
R4
Me3SiCl/LDA
R3
R4
Me3SiO
OSiMe3
MeO
R1
R2
OMe

**(60)** a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
c: $R^1 = R^2 = Me$; $R^3 = R^4 = H$
d: $R^1 = R^2 = R^4 = H$; $R^3 = Me$
e: $R^1 = R^2 = H$; $R^3 = R^4 = Me$

**(61)**

Mixed enol silyl ethers and silyl ketene acetals can be derived from keto esters. Methyl acetoacetate is first converted to a monoenol silyl ether (**62**), which is further silylated by LDA/TMS-Cl to the dienol silyl ether (**63**; Scheme 24).[68,69]

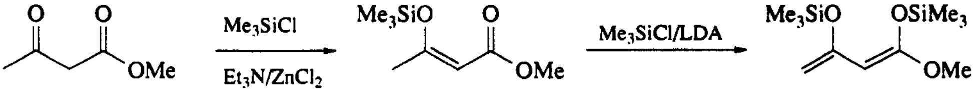
OMe
Me3SiCl
Et3N/ZnCl2
Me3SiO
OMe
Me3SiCl/LDA
Me3SiO
OSiMe3
OMe

**(62)** **(63)**

**Scheme 24**

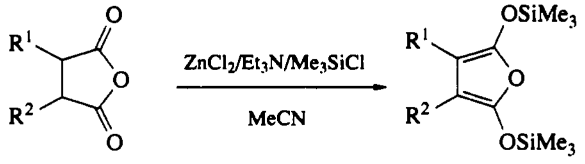
R1
R2
O
O
O
ZnCl2/Et3N/Me3SiCl
MeCN
OSiMe3
O
OSiMe3

**(64)** a: $R^1 = R^2 = H$

b: $R^1 = H$; $R^2 = Me$

c: $R^1 = R^2 = Me$

d: $R^1, R^2 = (CH_2)$

e: $R^1, R^2 = CH_2CH{=}CHCH_2$

**(65)**

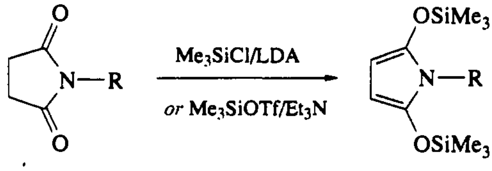
O
N—R
O
Me3SiCl/LDA
or Me3SiOTf/Et3N
OSiMe3
N—R
OSiMe3

**(66)** a: R = Me

b: $R = PhCH_2$

**(67)**

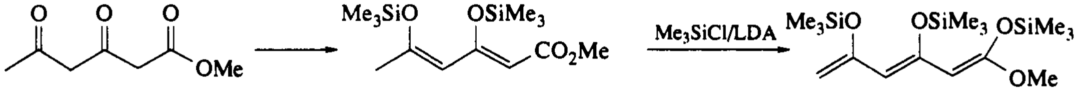
O
O
O
OMe
Me3SiO
OSiMe3
CO2Me
Me3SiCl/LDA
Me3SiO
OSiMe3
OSiMe3
OMe

**(68)** **(69)** **(70)**

Treating succinic anhydrides (**64**) with triethylamine, zinc chloride and trimethylchlorosilane in acetonitrile gives 2,5-bis(trimethylsiloxy)furans (**65**).[70] The relative ease of silylation in these cases demonstrates one of the differences between enol silyl ether chemistry and classical enolate anion chemistry. It would have been quite difficult to generate the dianion of succinic anhydride.

Succinimides (**66**) have been similarly converted to the corresponding 2,5-bis(trimethylsiloxy)pyrroles (**67**).[71,72]

Methyl 3,5-dioxohexanoate (**68**) has been converted first to the dienol silyl ether (**69**) and then to the trisilyl ether (**70**). Compound (**70**) can be considered as the equivalent of the trianion of (**68**).[73]

### 2.3.2.3 Formation of Enol Stannyl Ethers

Enol stannyl ethers have recently been used as synthetic equivalents of enolate anions.[74] However, organotin enol ethers usually exist as mixtures of *C*- and *O*-metallated species, irrespective of the methods of preparation.[75,76] Nevertheless, the two tautomers (**71**) and (**72**) often show similar reactivity and can be considered collectively as 'tin enolates'.

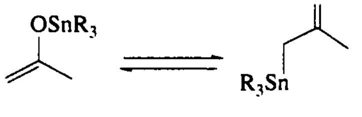
OSnR3
O
R3Sn

**(71)** **(72)**

### *2.3.2.3.1 Organotin(IV) enol ethers*

These compounds have been synthesized by several methods. A convenient method is by the interaction of trialkylmethoxytin compounds with enol acetates.[77] For example, reaction of triethylmethoxytin (**73**) with isopropenyl acetate (**74**) gives the tin(IV) enolates as a mixture of *O*- and *C*-isomers (**75**) and (**76**) (Scheme 25).[75] The exchange reaction appears to maintain the regiochemistry of the starting enol ester. Thus, reaction of 2-methyl-1-acetoxycyclohexene with tributylmethoxytin[77] gives compound (**77**). On the other hand, the regioisomer (**78**) has been generated *in situ* by treatment of the precursor lithium enolate with tri-*n*-butylstannyl chloride (Scheme 26).[78]

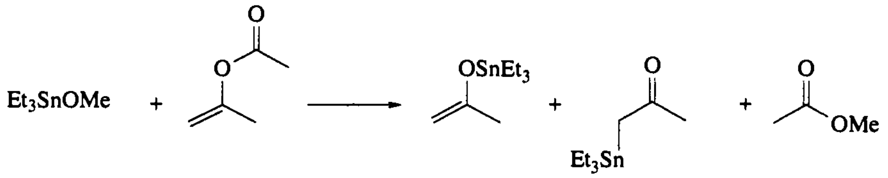
Et3SnOMe
+
O
O
OSnEt3
+
O
Et3Sn
+
O
OMe

(**73**) (**74**) (**75**) 10% (**76**) 90%

**Scheme 25**

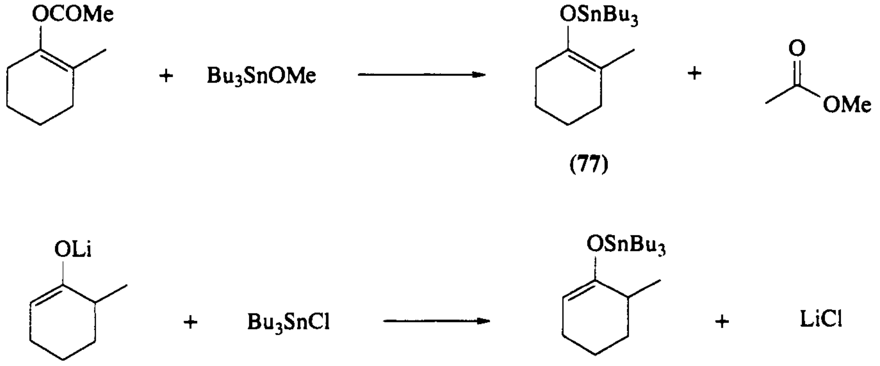
OCOMe
+ Bu3SnOMe
OSnBu3
+
O
OMe
OLi
+ Bu3SnCl
OSnBu3
+ LiCl

(**77**)

(**78**)

**Scheme 26**

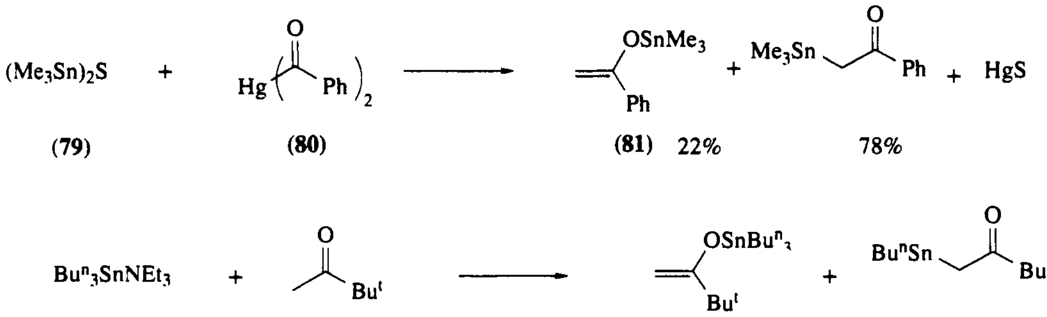
(Me3Sn)2S +
O
Hg
Ph
2
OSnMe3
Ph
+ Me3Sn
O
Ph
+ HgS
Bun3SnNEt3 +
O
But
OSnBun3
But
+ BunSn
O
But

(**79**) (**80**) (**81**) 22% 78%

(**82**) 33% 66%

**Scheme 27**

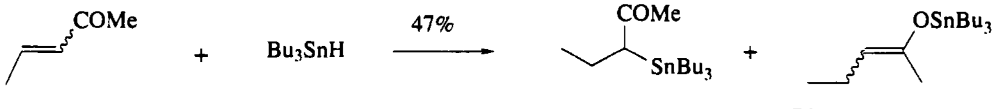
COMe
+ Bu3SnH
47%
COMe
SnBu3
+
OSnBu3

25% 75% (a mixture of 8% *cis* and 67% *trans*)

**Scheme 28**

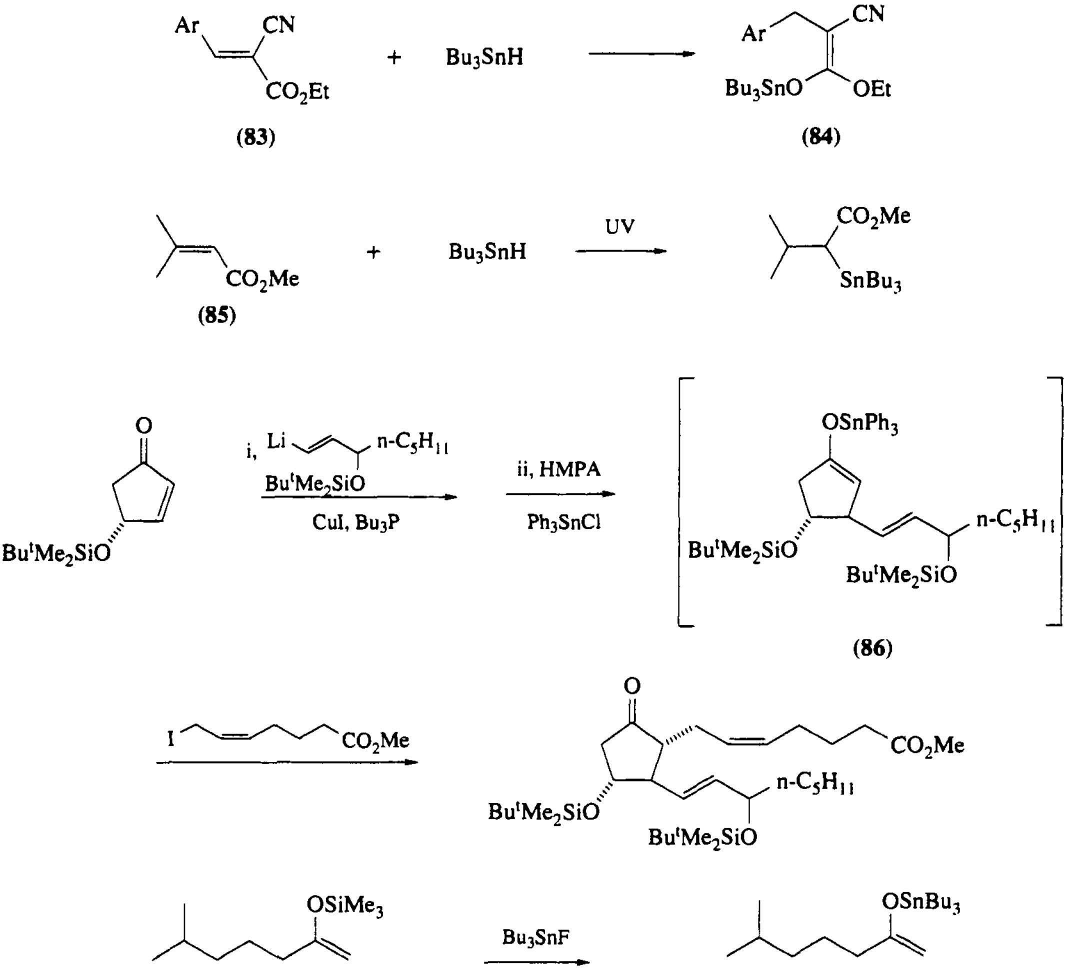
Ar
CN
$CO_2Et$
+
$Bu_3SnH$
Ar
CN
$Bu_3SnO$
OEt
+
$Bu_3SnH$
UV
$CO_2Me$
$CO_2Me$
$SnBu_3$
O
$Bu^tMe_2SiO$
i, Li
n-$C_5H_{11}$
$Bu^tMe_2SiO$
CuI, $Bu_3P$
ii, HMPA
$Ph_3SnCl$
$OSnPh_3$
$Bu^tMe_2SiO$
n-$C_5H_{11}$
$Bu^tMe_2SiO$
I
$CO_2Me$
O
$CO_2Me$
n-$C_5H_{11}$
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$
$OSiMe_3$
$Bu_3SnF$
$OSnBu_3$

**(83)** **(84)** **(85)** **(86)**

**Scheme 29**

Exchange reaction can also be carried out by treating bis(trimethylstannyl) sulfide (**79**) with the α-mercurated ketone (**80**) to yield the enol stannyl ether (**81**) and its *C*-isomer.[76,79] Direct reaction of carbonyl compounds with trialkylstannylamines can also give enol stannyl ethers. An example is the preparation of compound (**82**; Scheme 27).[80]

1,4-Addition of tin hydride to α,β-unsaturated carbonyl compounds is a general method of obtaining enol stannyl ethers. With triphenyltin hydride, the resulting tin enolate cannot be isolated and the reaction leads to the saturated carbonyl compounds.[81] With tributyltin hydride, a mixture of *O*- and *C*-stannylated adducts is obtained (Scheme 28).

With the substrate (**83**), the *O*-stannyl ketene acetal (**84**) can be made by 1,4-hydrostannation.[82] Normally, addition of tin hydride to alkenic esters gives the *C*-stannylated compounds. An example is the reaction of (**85**) with tri-*n*-butyltin hydride.[83]

The enol stannyl ether (**86**), formed by conjugate addition to the precursor cyclopentenone and then stannylation, is implicated as an intermediate in a short and efficient synthesis of prostaglandins.[84]

Finally, a method of generating enol stannyl ethers *in situ* is to start from enol silyl ethers by an exchange reaction with tributyltin fluoride.[85] An example is given in Scheme 29.[86] It has been reported that this process occurs preferentially at the less-substituted enol silyl ether site if several are available.[87]

### 2.3.2.3.2 *Tin(II) enol ethers*

Strictly speaking, tin(II) enol ethers should be considered more as metal enolates. However, their chemistry resembles that of tin(IV) enol ethers in reactions with C—X π-bonds.

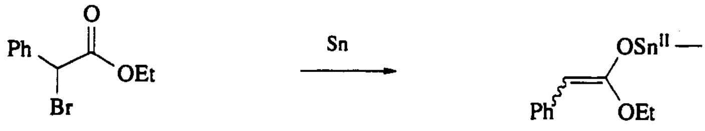

**(87)**

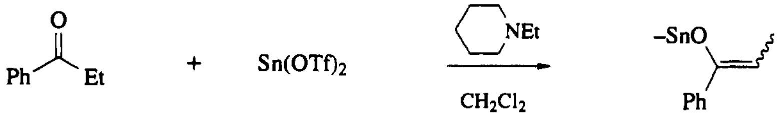

**(88)**

Tin(II) enolates can be generated from the reactions of α-bromo ketones with tin(0).[88] The activated metallic tin is typically prepared by the reduction of tin(II) chloride with lithium aluminum hydride.

A tin(II) ester enolate is also the presumed intermediate in the reaction of α-halo ester (**87**) with metallic tin in a Reformatsky-type reaction.[89]

More conveniently, tin(II) enolates can be generated by reaction of ketones and $Sn(OTf)_2$ in the presence of a tertiary amine. The choice of the amine is critical. For example, pyridine and DBU fail to promote the reaction, whereas *N*-ethylpiperidine gives excellent results.[90,91] Thus, the divalent tin enolate (**88**) of propiophenone has been generated by treating propiophenone with tin(II) triflate and *N*-ethylpiperidine in dichloromethane.[92]

Under similar reaction conditions, tin(II) ester enolates derived from 3-acyl-1,3-thiazolidine-2-thiones have been prepared.[93,94] An example is given in Scheme 30.[95]

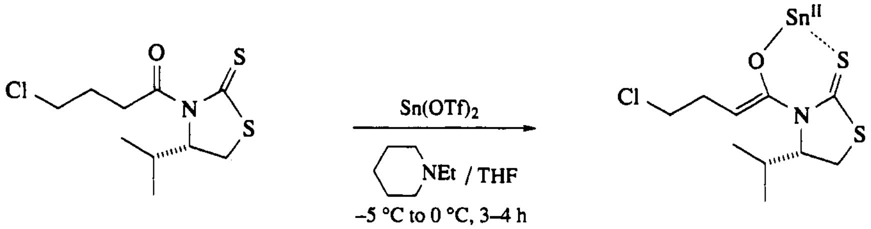

**Scheme 30**

### 2.3.2.4 Other Enol Ethers

Enol germyl ethers are known to equilibrate slowly with the *C*-isomers at room temperature.[96] They can be prepared by the reaction of lithium enolates of ketones with chlorotrimethylgermane as a mixture of the *O*- and *C*-germyl isomers (*e.g.* **89**).[97]

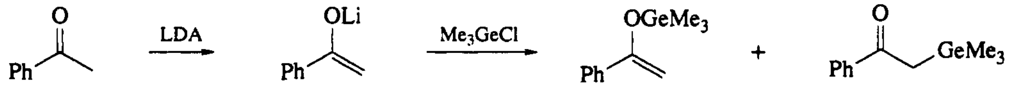

7% **(89)** 93%

Enol phosphates have been suggested as enol equivalents.[98] Their use in synthesis seems to have been supplanted by enol silyl ethers.

Various enol boron derivatives have found extensive applications in synthesis. They form the subject matter of discussion elsewhere in Part 1 of this volume.

## 2.3.3 REACTIONS WITH C—X π-BONDS AND EQUIVALENTS

### 2.3.3.1 Uncatalyzed Aldol and Related Condensations

In the direct reaction of various enol ethers with carbonyl compounds in the absence of any catalyst to give the aldol condensation products according to Scheme 1, the reaction depends critically on the nature of the enol ethers. Enol stannyl ethers, being most similar to metal enolates, react readily. For example, 1-cyclohexenyloxytributyltin reacts with benzaldehyde at –78 °C in the absence of catalyst to give high yield of the aldol condensation product (**90**).[99] The reactivity of the organotin(IV) reagents is sensitive to the particular structure. Thus, although acetonyltributyltin (**91**) reacts spontaneously with aldehydes at –78 °C, the reaction of ethyl tributylstannylacetate (**92**) with benzaldehyde proceeds only at 80 °C.[99]

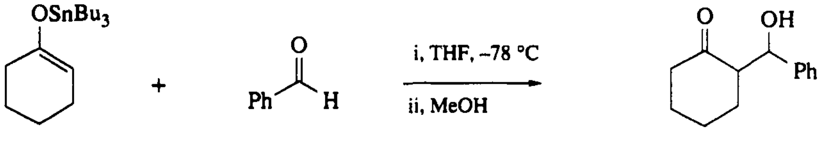

**(90)**

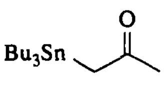

**(91)**

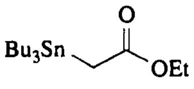

**(92)**

The crossed aldol reaction between two different ketones is a difficult reaction under the classical metal enolate conditions.[100] By employing divalent tin enol ethers, directed aldol reaction between ketones is easily achievable.[92] An example is given in Scheme 31.

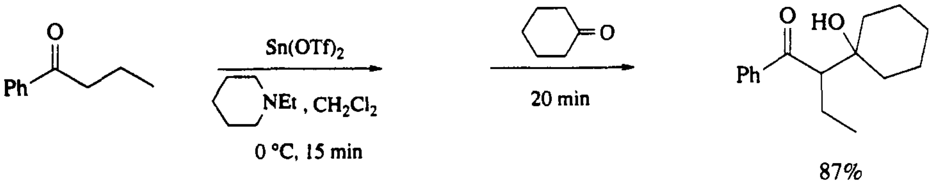

Scheme 31

The aldol-type condensation can be extended to carbonyl equivalents such as the 4-acetoxy-2-azetidinone (**93**)[94] or similar α-acetoxylactams.[95] The condensation of (**93**) with the chiral tin(II) enol ether (**94**) has been used in a highly diastereoselective synthesis of chiral carbapenems.

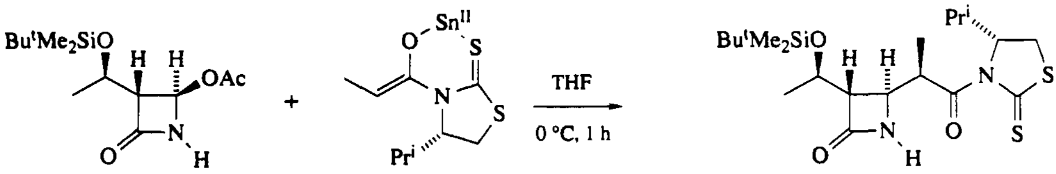

**(93)** **(94)**

The condensation of an enol silyl ether with an aldehyde or ketone usually requires Lewis acid catalyzed conditions (*vide infra*). However, under high pressure, the reaction can be induced to proceed in the absence of catalyst (Scheme 32).[101] Silyl ketene acetals, on the other hand, can react with aldehydes to give the aldol products by heating in the absence of Lewis acid.[102]

Enol ethers are insufficiently nucleophilic to react with C—X π-bonds under uncatalyzed conditions.

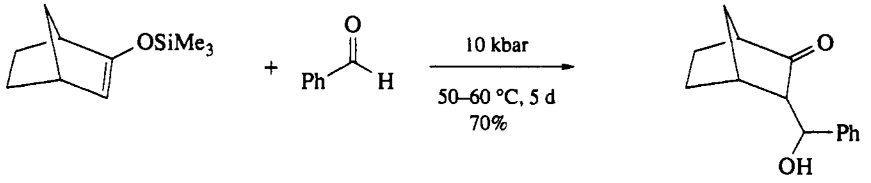

**Scheme 32**

### 2.3.3.2 Catalyzed Addition to C—X π-Bonds and Equivalents

The catalyzed reaction of enol ethers with carbonyl compounds (Scheme 1) has become an important reaction in synthesis. Compared to the metal enolate reactions (Part 1, Volume 2), the catalyzed enol ether reactions offer the following distinct differences. Enol ethers are often isolable, stable covalent compounds, whereas the metal enolates are usually generated and used *in situ*. Under Lewis acid catalyzed conditions, a number of functional equivalents such as acetals, orthoesters, thioacetals, α-halo ethers and sulfides can participate as the electrophilic components, whereas many of them are normally unreactive towards metal enolates. In synthesis, enol ether reactions now rival and complement the enolate reactions in usefulness. Enol silyl ethers are particularly useful because of their ease of preparation, their reasonable reactivity and the mildness of the desilylation process.

#### *2.3.3.2.1 Reactions of enol ethers*

Enol ethers react with acetals or ketals, promoted by Lewis acids, to give aldol-type adducts.[103,104] It has been used, for example, in a synthesis of carotene (Scheme 33).[105]

In the condensation of the ketal (**95**) with ethyl vinyl ether, montmorillonite clay 10 was found to be an effective catalyst and superior to the previously reported Lewis acid.[106] In this reaction, the work-up is simplified to filtration of the catalyst.

The relative reactivities of acetals and orthoesters in Lewis acid catalyzed reactions with enol ethers have been investigated. For $BF_3{\cdot}OEt_2$-catalyzed reactions with methyl vinyl ether, the following order has been found; saturated acetals < methyl orthoformate < benzaldehyde acetals < α,β-unsaturated acetals.[107]

Enol esters, like enol ethers, can also react with various acetals and aldehydes in the presence of Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_4$, $ZnCl_2$, and $BF_3{\cdot}OEt_2$ to afford the corresponding aldol-type addition products.[108] A typical example is the reaction of isopropenyl acetate and γ-phenylpropionaldehyde acetal

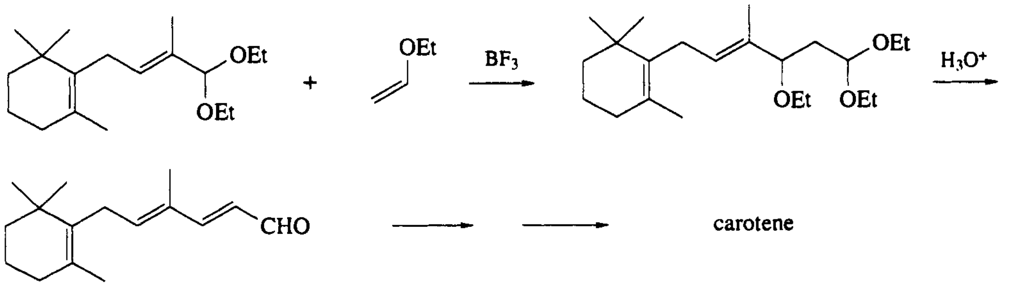

**Scheme 33**

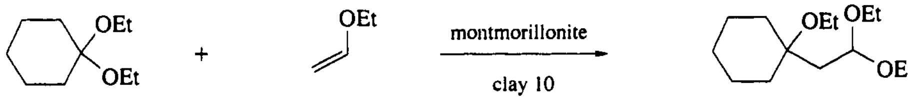

(**95**)

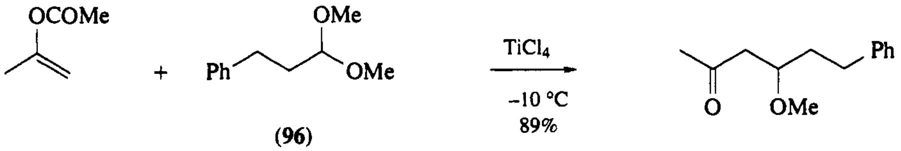

(**96**)

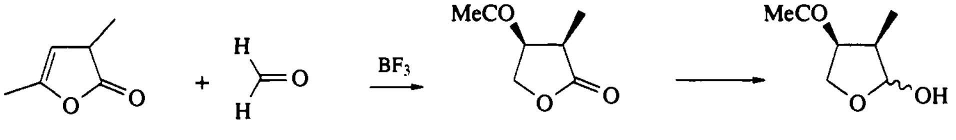
H
H
O
BF$_3$
MeCO
O
O
MeCO
O
OH

**(97)**

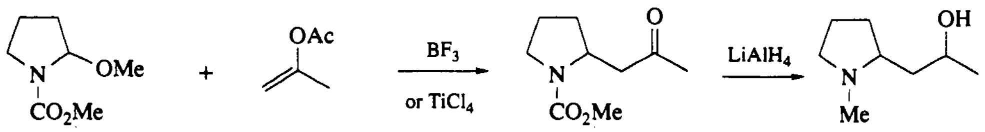
N
OMe
CO$_2$Me
OAc
BF$_3$
or TiCl$_4$
O
N
CO$_2$Me
LiAlH$_4$
OH
N
Me

**(98)**

(**96**).[109] The reaction has been used in a convenient synthesis of the antibiotic and antileukemic agent botryodiplodin (**97**).[110]

Aminohemiacetals (*e.g.* **98**) can also condense with enol ethers or enol esters to give the cross-aldol products.[111] A number of piperidine and pyrrolidine alkaloids have been synthesized by this approach.

The disadvantage of the acid-catalyzed reaction of enol ethers or esters is that there are often undesirable side reactions. On the other hand, the reaction may be a useful industrial process because of the relatively inexpensive nature of the starting materials.

### *2.3.3.2.2 Reactions of enol silyl ethers*

In 1974, Mukaiyama and his coworkers reported on the Lewis acid promoted condensation of enol silyl ethers with carbonyl compounds to give the cross-aldol products.[112] The reaction usually proceeds with retention of the regiochemical integrity of the starting enol silyl ethers as shown by those illustrated in Scheme 34. However, occasional examples of loss of regiointegrity of the starting enol silyl ethers have been noted in the literature.[113]

In addition to aldehydes and ketones, acetals, ketals, orthoesters,[112] α-halo ethers, α-halo sulfides, amino acetals[114] and their equivalents also react with enol silyl ethers in the presence of Lewis acid to af-

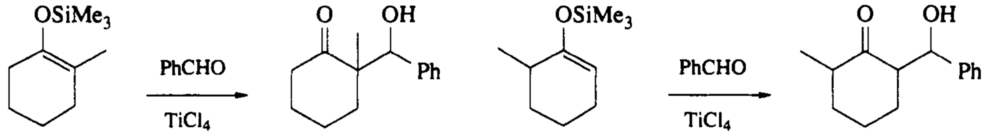
OSiMe$_3$
PhCHO
TiCl$_4$
O
OH
Ph
OSiMe$_3$
PhCHO
TiCl$_4$
O
OH
Ph

**Scheme 34**

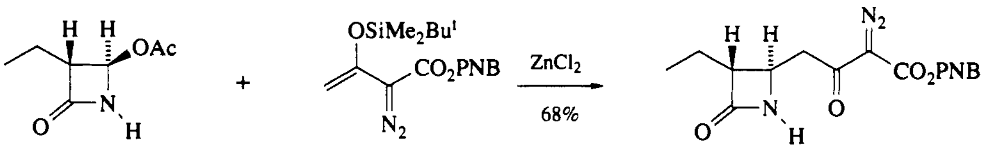
H
H
OAc
O
N
H
OSiMe$_2$Bu$^t$
CO$_2$PNB
N$_2$
ZnCl$_2$
68%
H
H
N$_2$
CO$_2$PNB
O
N
O
H

**Scheme 35**

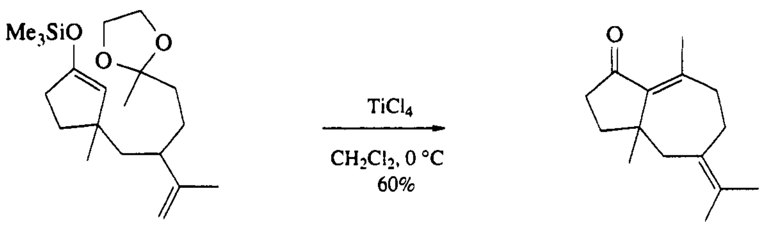
Me$_3$SiO
O
O
TiCl$_4$
CH$_2$Cl$_2$, 0 °C
60%
O

**(99)**

ford the corresponding condensation products in high yields.[115] An example is given in Scheme 35. Intramolecular reactions of this type can be used to synthesize cyclic compounds, for example in the construction of the pseudoquaiane system (**99**).[116]

### *(i) Choice of catalyst*

A variety of Lewis acids have been used for the catalyzed reaction of enol silyl ethers with carbonyl compounds. Very often, these Lewis acids have to be used in stoichiometric amounts to promote the reaction. However, excess Lewis acid can sometimes lead to further transformations.[117] There have been no systematic studies on comparing the efficacy of the various catalysts. In general, for simple aldehydes and ketones, Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnCl_2$ and so on have been used. Among these acids, $TiCl_4$ is most commonly used and is usually superior to the other Lewis acids with respect to yields.[112] Occasionally, $TiCl_2(OR)_2$, generated by mixing equivalent amounts of $TiCl_4$ and $Ti(OR)_4$, is found to be better than $TiCl_4$ in promoting the reaction.[112] On the other hand, in the reaction of (*S*)-*O*-benzyllactaldehyde with the silyl ketene acetal (**100**), the best results come from $SnCl_4$ or $MgBr_2$. $TiCl_4$ fails to promote the reaction (Scheme 36).[57]

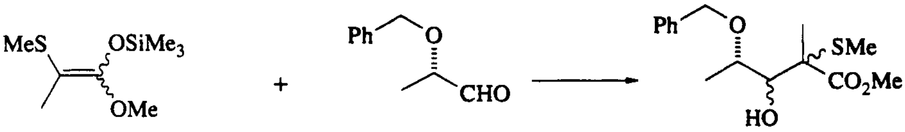

**(100)**

| *Lewis acid* | *Temp* (°C) | *Yield* (%) |
|---|---|---|
| $TiCl_4$ | −78 to 0 | 0 |
| $SnCl_4$ | −78 | 65 |
| $ZnCl_2$ | −40 | 45 |
| $MgBr_2$ | −40 | 60 |

**Scheme 36**

In the reaction of enol silyl ethers with α-chloro sulfides (*e.g.* **101**), $TiCl_4$ or $ZnX_2$ appears to be the Lewis acid of choice.[118] When dithioacetals[119] are used as the electrophiles, $FeCl_3$ or dimethyl(methylthio)sulfonium fluoroborate (DMTSF; **102**) have been used successfully as the initiator for the condensations with enol silyl ethers. For example, the intramolecular reactions of (**103**) induced by 1 equiv. of DMTSF lead to good yields of the cyclization products.[120]

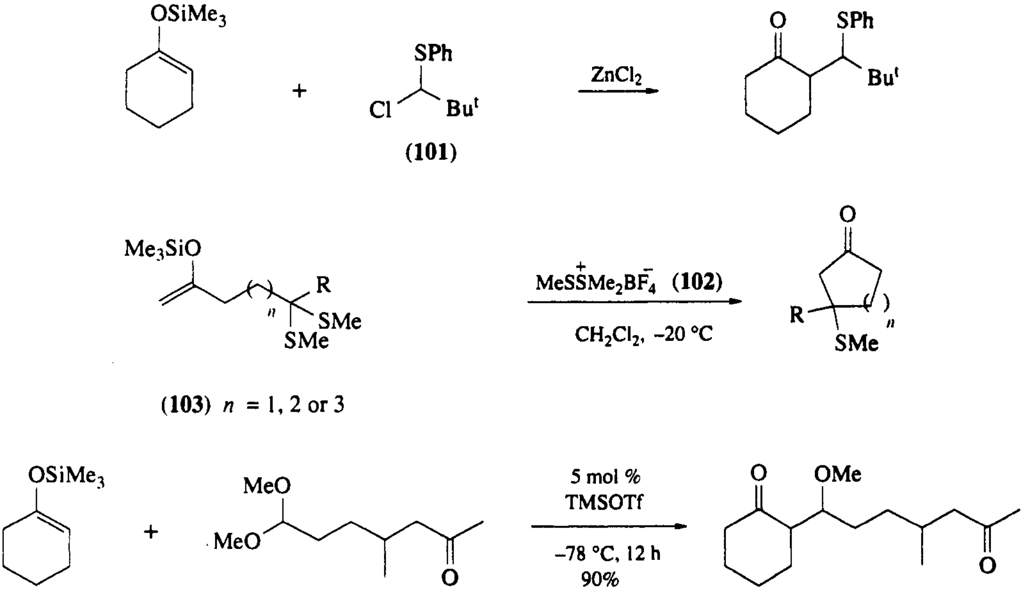

**(101)**

**(103)** *n* = 1, 2 or 3

**Scheme 37**

Aldol-type condensation of enol silyl ethers and acetals or orthoesters can be accomplished by the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[121] In these reactions, TMSOTf acts as a true catalyst and is required in 1–5 mol %. The reactions show interesting chemoselectivity in that acetals are highly reactive receptors of enol silyl ethers but the parent aldehydes and ketones do not react under these conditions (Scheme 37). Similarly, trityl perchlorate is found to be an efficient catalyst to promote the reaction between enol silyl ethers and acetals.[122,123]

Crossed aldol reactions of enol silyl ethers with aldehydes have been successfuly performed with the aid of catalytic amounts of the rhodium complex $[(COD)Rh(DPPB)]^+X^-$ ($X = PF_6$ or $ClO_4$) or $Rh_4(CO)_{12}$. Although the intermediacy of rhodium enolate has been suggested for these reactions,[124] the fact that the same rhodium catalysts can promote the condensations of acetals as well (Scheme 38) tends to indicate that the reactive species may not be a metal enolate.[125]

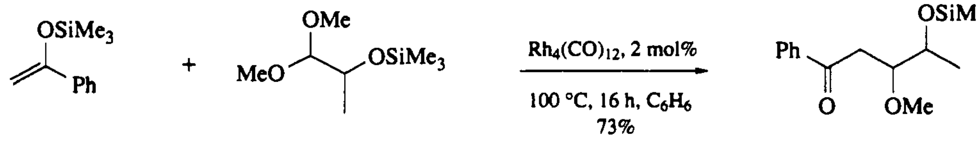

Scheme 38

A number of organoaluminum reagents, especially $Me_2AlCl$, have been found to be effective catalysts for reactions of enol silyl ethers with aldehydes.[126] It is possible that in these reactions, aluminum enolates may be involved as the intermediates. Similarly, bismuth trichloride has been reported to be an efficient catalyst.[127] Since $BiCl_3$ is considered to be a weak Lewis acid, the involvement of a bismuth enolate is perhaps implicated. Enolate intermediates are definitely generated when tetraalkylammonium fluorides[128] or tris(dialkylamino)sulfonium (TAS) difluorotrimethylsiliconates (**104**)[129] are used as reagents to promote the reactions of enol silyl ethers. Their chemistry will therefore not be discussed in this chapter.

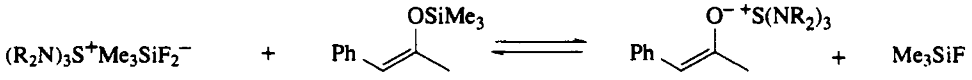

**(104)**

Heterogeneous catalysts such as cation-exchanged montmorillonite clay or Nafion also catalyze the aldol reaction of enol silyl ethers with aldehydes and acetals.[130]

### *(ii) Chemoselectivity*

It is clear from the foregoing discussion that different kinds of carbonyl functions will react differently with enol silyl ethers depending on the choice of catalyst. Under the same reaction conditions, chemose-

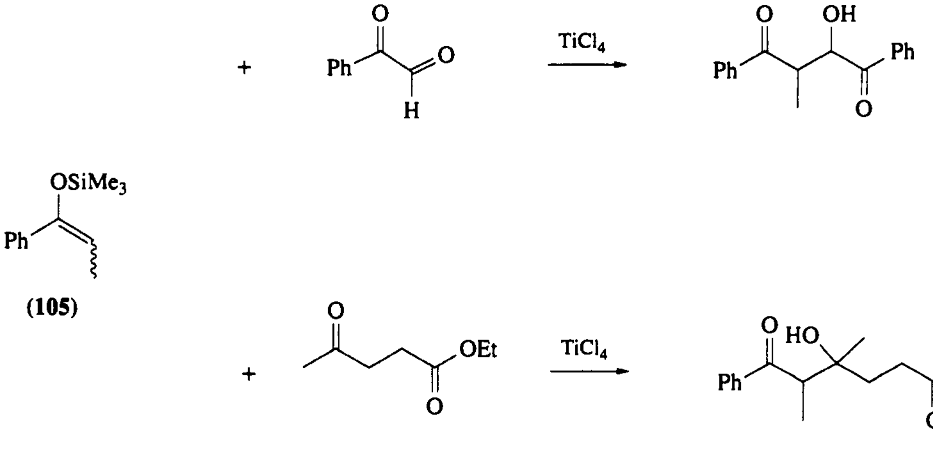

**(105)**

Scheme 39

lectivity is observed with acceptors having two or more different kinds of carbonyl electrophilic sites in the same molecule. In general, with $TiCl_4$ as the Lewis acid, aldehydes are more reactive than ketones, which are in turn more reactive than esters. This is demonstrated in Scheme 39 where the enol silyl ether (**105**) is allowed to react with phenylglyoxal or with ethyl levulinate.[131] In another study, using the enol silyl ether (**63**) in a series of competitive experiments under $TiCl_4$ conditions, it is possible to establish qualitatively the following order of reactivity: aldehyde > conjugated position of β-oxy-α,β-unsaturated ketone ≈ isolated ketone > carbonyl position of β-oxy-α,β-unsaturated ketone > acetal or monothioacetal > conjugate position of β-oxy-α,β-unsaturated ester ≈ ester carbonyl.[132] The order may well be changed when other catalysts or enol silyl ethers are used.

### *(iii) Regioselectivity*

Although enol silyl ethers are ambident species capable of reacting either at carbon or at oxygen, nearly all the aldol-type condensations occur at carbon. The exception is in the reaction with acylating agents, where either the *O*- or the *C*-acylated products can be obtained depending on the reaction conditions (*e.g.* Scheme 40).[133,134] On the other hand, the more reactive silyl ketene acetals react with acid chlorides without a catalyst to give β-keto esters, the *C*-acylation products.[135,136] Another exception is the reaction of the enol silyl ether (**106**) with iodomethyl methyl ether. A mixture of *C*- and *O*-alkylation products (**107**) is obtained.[137] This has been attributed to the tendency of cyclobutanone to undergo *O*-alkylation.[138]

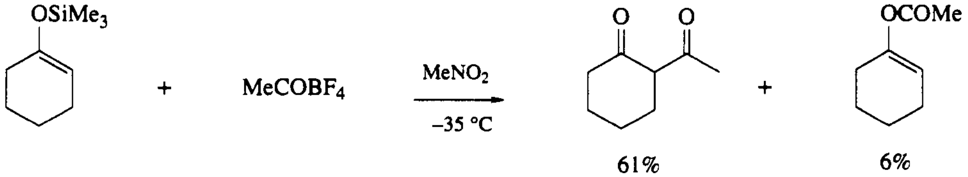

Scheme 40

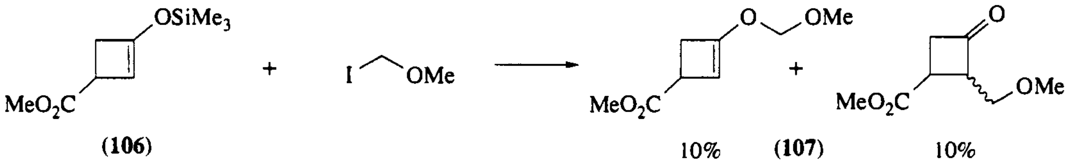

A question of regiochemistry arises with *O*-silylated dienolates derived from α,β-unsaturated aldehydes, ketones and esters. The silylated dienolates of crotonaldehyde and its 3-methyl derivative (**108**) react with acetals in Lewis acid catalyzed conditions at the γ-position. This high regioselectivity has been used in the synthesis of vitamin A acetate (Scheme 41).[139]

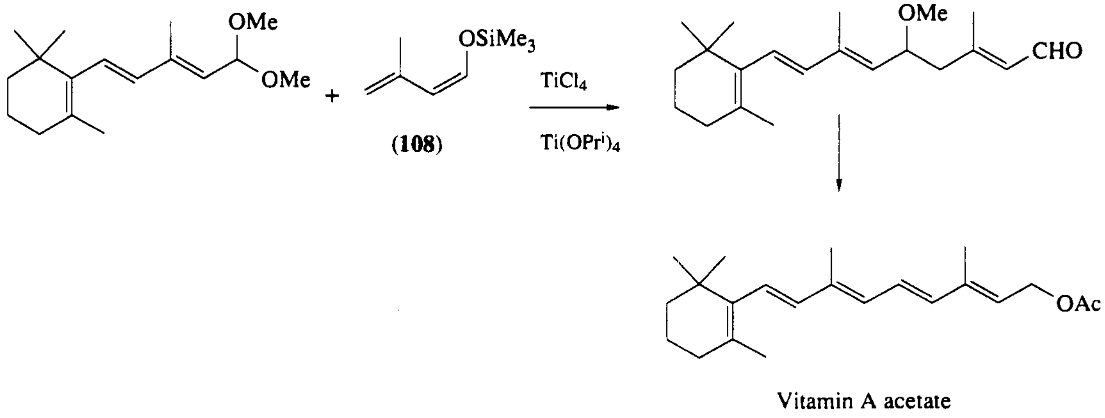

Scheme 41

The regioselectivity depends very much on the nature of the electrophile and on the structure of the siloxydiene.[140] For example, the silyl ketene acetal (**109**) reacts with chloromethyl phenyl sulfide (**110**) to give nearly equal amounts of the α- and γ-products, whereas the compound (**111**) is phenylthiobutylated with essentially complete γ-selectivity (Scheme 42).[141] Changing the substituents on the silyl group has the most dramatic effect. Using the reaction of the siloxydiene (**112**) with compound (**110**) as the standard reaction, it has been found that the *t*-butyldimethylsilyl group gives the highest proportion of the α-product (**113**), and the *m*-chlorophenyldiphenylsilyl group gives exclusively the γ-product (**114**).[142]

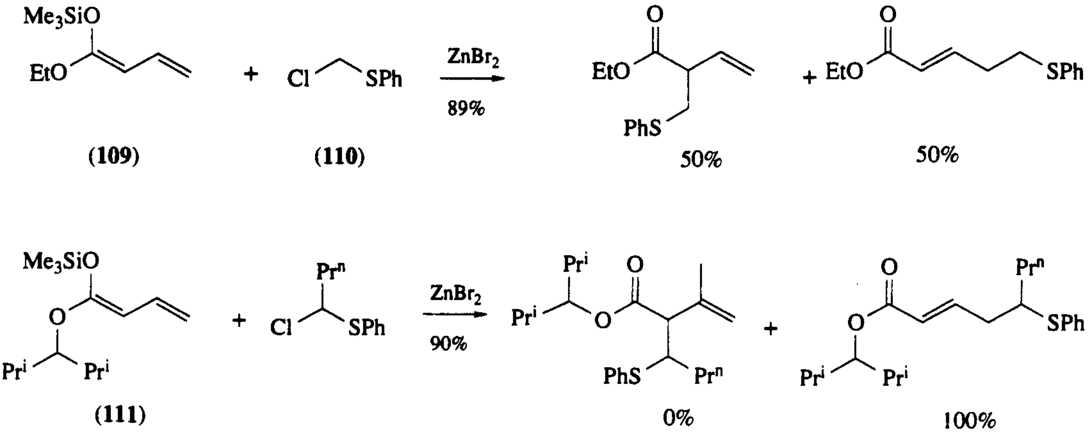
Me$_3$SiO
EtO
+
Cl
SPh
ZnBr$_2$
89%
O
EtO
PhS
50%
+ EtO
O
SPh
50%
(109)
(110)
Me$_3$SiO
O
Pr$^i$
Pr$^i$
+
Pr$^n$
Cl
SPh
ZnBr$_2$
90%
Pr$^i$
O
Pr$^i$
O
PhS
Pr$^n$
0%
+
O
O
Pr$^n$
SPh
Pr$^i$
Pr$^i$
100%
(111)

**Scheme 42**

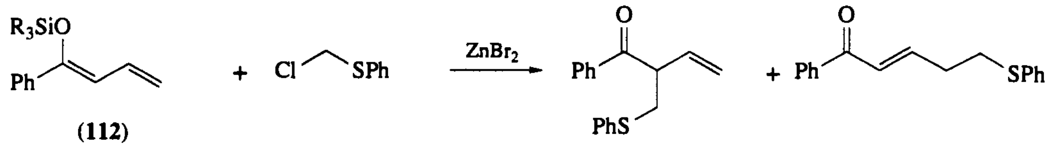
R$_3$SiO
Ph
+
Cl
SPh
ZnBr$_2$
O
Ph
PhS
+ Ph
O
SPh
(112)

| | *Yield* (%) | (**113**) (%) | (**114**) (%) |
|---|---|---|---|
| $R_3 = Me_2Bu^t$ | 62 | 77 | 23 |
| $R_3 = Me_3$ | 58 | 55 | 45 |
| $R_3 = Ph_3$ | 93 | 15 | 85 |
| $R_3 = m\text{-}ClC_6H_4Ph_2$ | 58 | 0 | 100 |

Similar γ-regioselectivity has been observed[143] in the reaction of the steroidal siloxydiene (**115**) with the Eschenmoser's salt (**116**) to give the Mannich adduct (**117**).

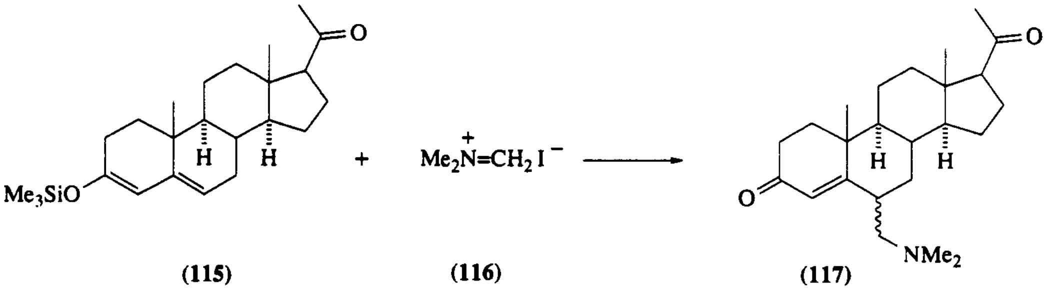
O
H
H
Me$_3$SiO
+
$\overset{+}{\text{Me}_2\text{N}}\text{=CH}_2\text{ I}^-$
O
H
H
O
NMe$_2$

**(115)** **(116)** **(117)**

2-Trimethylsiloxyfuran (**118**) reacts with various aldehydes, ketones and acetals in the presence of tin(IV) chloride to give the corresponding γ-adducts (**119**).[144] On the other hand, 2,5-bis(trimethylsiloxy)furan (**65**) reacts with aldehydes and ketones under activation of titanium tetrachloride to give the 3,7-dioxabicyclo[3.3.0]octane system (**120**) by reaction at the α-positions.[145] However, with increasing

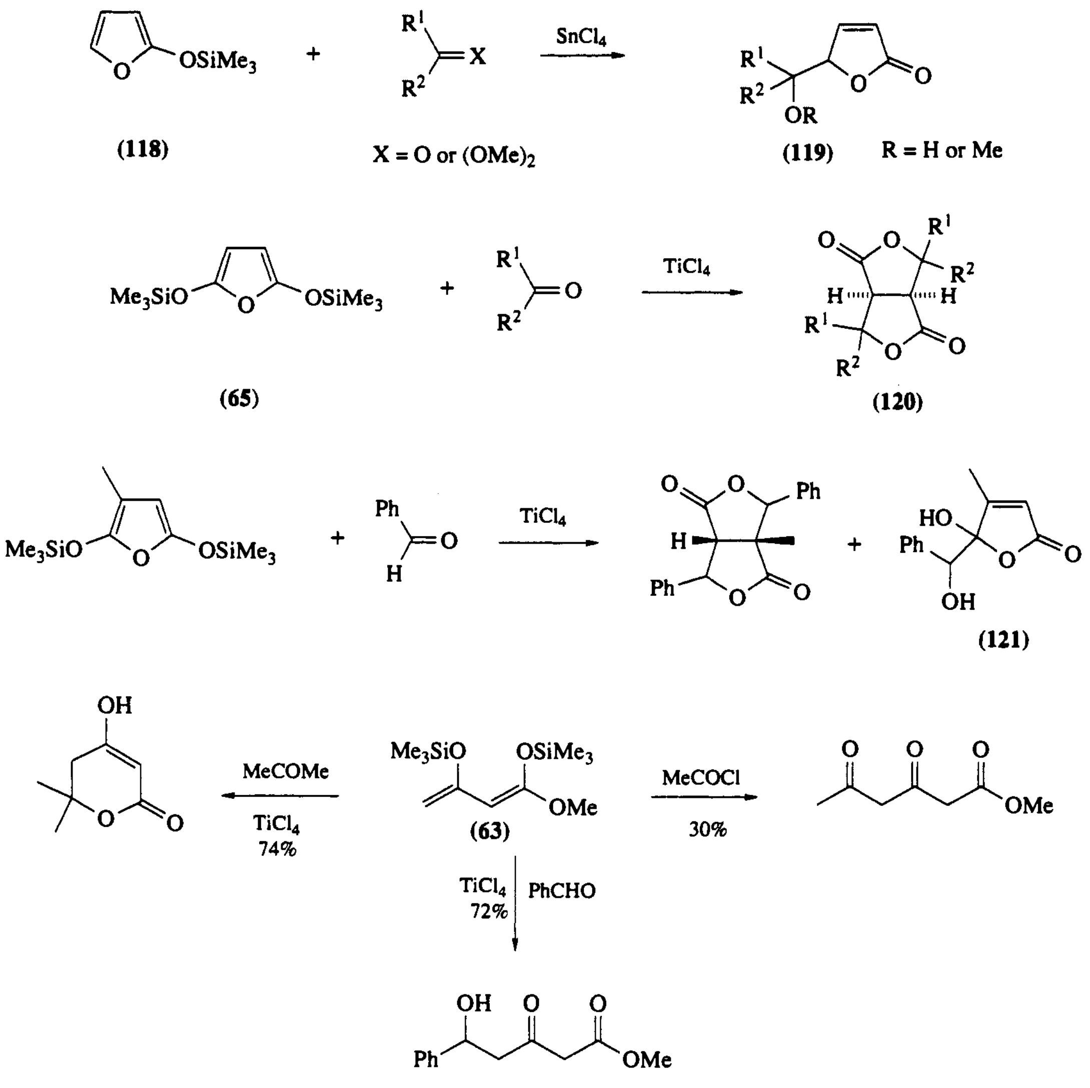
OSiMe3
(118)
R1
R2
X
X = O or (OMe)2
SnCl4
R1
R2
OR
O
(119)
R = H or Me
Me3SiO
OSiMe3
(65)
TiCl4
(120)
Me3SiO
OSiMe3
Ph
H
TiCl4
Ph
H
HO
OH
(121)
OH
MeCOMe
TiCl4
74%
Me3SiO
OSiMe3
OMe
(63)
MeCOCl
30%
OMe
TiCl4
72%
PhCHO
OH
Ph
OMe

Scheme 43

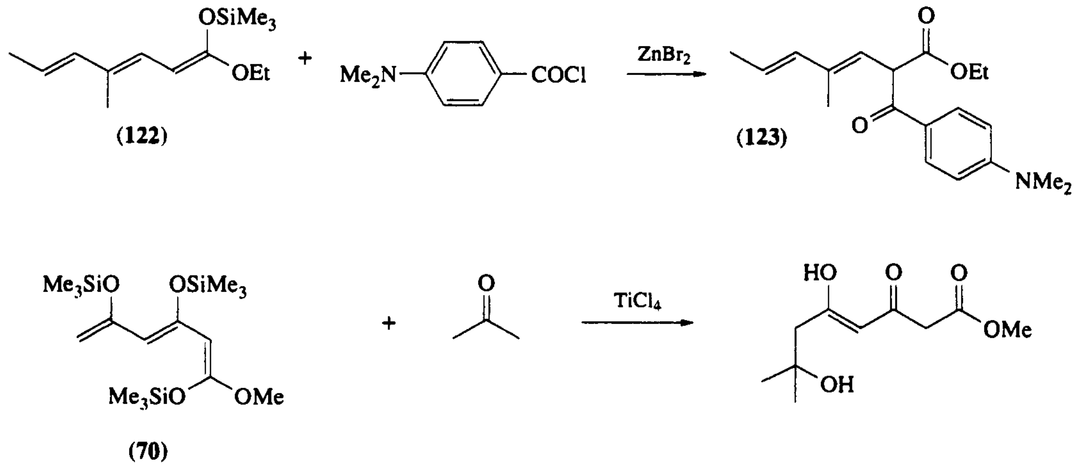
OSiMe3
OEt
(122)
Me2N
COCl
ZnBr2
OEt
(123)
NMe2
Me3SiO
OSiMe3
Me3SiO
OMe
(70)
TiCl4
HO
OMe
OH

Scheme 44

alkyl substitution in (**65**), addition of the carbonyl compound occurs at the γ-position to give the butenolides (**121**).[146]

In the dienol silyl ether (**63**), where the γ-selectivity of the siloxy diene is enhanced by the second siloxy substituent, reactions with electrophiles occur exclusively in the γ-position as illustrated in Scheme 43.[68,132] The same γ-selectivity is observed for the siloxydiene (**58**) derived from a 1,3-diketone.[64]

The trienol silyl ether (**70**) reacts with carbon electrophiles at the ε-position as illustrated in Scheme 44.[73,147] Unexpectedly, the trienyl silyl ketene acetal (**122**) reacts with *p*-dimethylaminobenzoyl chloride and zinc bromide at the α-position to give the ester (**123**) as the only isolable product.[134] It is not known at this time whether such α-selectivity is general for other aldol-type reactions of (**122**) or limited to acylations.[148]

### *(iv) Aldol condensation cascade as a general synthesis of cyclic compounds*

Aldol-type condensation of β-polyketides is an important pathway in nature to form cyclic compounds.[149] Based on these biogenetic considerations, the controlled aldol condensations of enolate anions have been extensively studied.[150] In view of the selective nature of the catalyzed condensation of enol silyl ethers with carbonyl compounds, the reaction has been used with some success for the synthesis of cyclic compounds. The general strategy is based on the condensation of two fragments: one fragment (**124**) containing two nucleophilic sites in the form of enol silyl ethers (represented as N), and the other fragment (**125**) containing two electrophilic sites in the form of carbonyl groups or their equivalents (represented as E). For compounds where the two enol silyl ethers are not of identical structure, their reactivities may be sufficiently different so that a reactivity order can be assigned (say, $N_1$ more reactive than $N_2$). Similarly, the two electrophilic sites may also have reactivity difference (say, $E_1$ more reactive than $E_2$) according to the order discussed in Section 2.3.3.2.2.ii. The regiochemistry of the cyclization reaction can then be controlled by the differential reactivities of these sites as shown in Scheme 45.

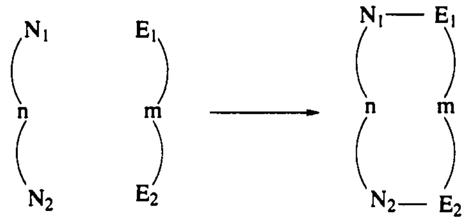

**(124)** **(125)**

**Scheme 45**

*(a) Formation of four-membered rings.* The dienol silyl ketene acetals (**61a–e**) derived from dimethyl glutarates can be considered as 1,3-dinucleophiles. They react with carbon electrophiles preferentially at only one site. For example, (**61b**) on reaction with benzaldehyde dimethyl acetal (**126**) and $TiCl_4$ gives the methoxy diester (**127**) as the only product in the form of a mixture of diastereoisomers in 69% yield.[67] When acetic anhydride is used as the electrophile, the cyclobutane compound (**128**) is obtained (Scheme 46). The reaction is apparently highly stereoselective in that only one stereoisomer (**128**) is detected and isolated.

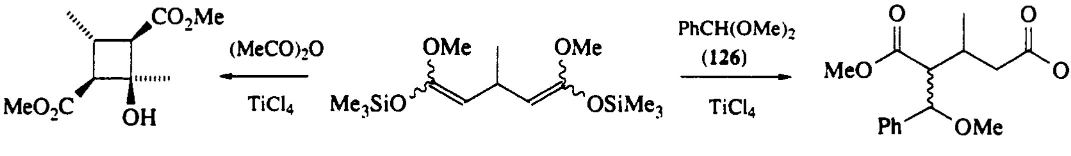

**(128)** **(61b)** **(127)**

**Scheme 46**

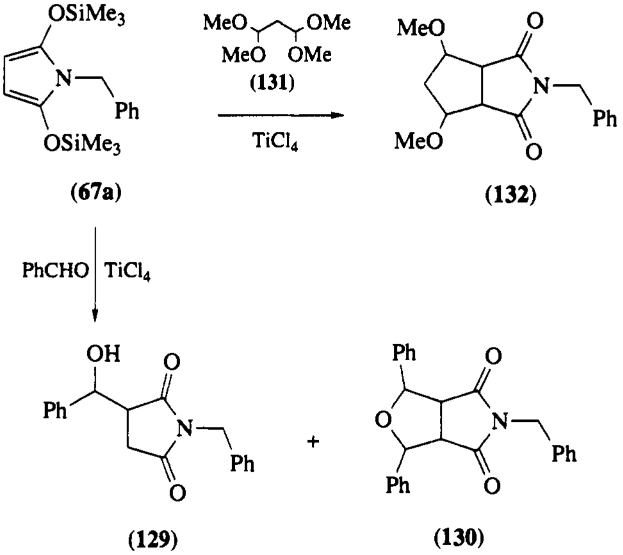
OSiMe3
N
Ph
OSiMe3
(67a)
MeO OMe
MeO OMe
(131)
TiCl4
MeO
O
N
Ph
MeO
O
(132)
PhCHO
TiCl4
OH
O
Ph
N
Ph
O
(129)
+
Ph
O
O
N
Ph
Ph
O
(130)

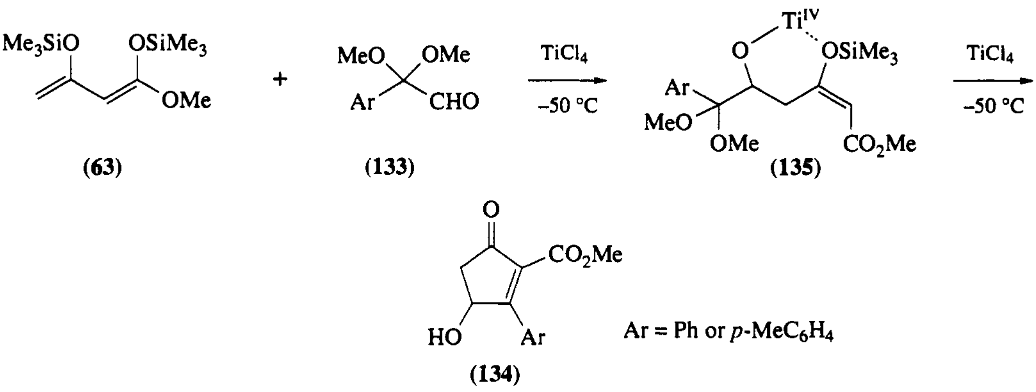
Me3SiO
OSiMe3
OMe
(63)
+
MeO
OMe
Ar
CHO
(133)
TiCl4
-50 °C
Ti^IV
O
OSiMe3
Ar
MeO
OMe
CO2Me
(135)
TiCl4
-50 °C
O
CO2Me
HO
Ar
(134)
Ar = Ph or p-MeC6H4

*(b) Formation of five-membered rings.* As mentioned previously, compound (**65**) behaves as a 1,2-dinucleophile in that it reacts with aldehydes and ketones under activation of $TiCl_4$ to give reactions at the α-positions, but the adducts rearrange to give dilactones (**120**). However, 2,5-bis(trimethylsiloxy)pyrrole (**67a**) reacts with aldehydes or ketones to give the substituted succinimides (**129**) and (**130**) without rearrangement. When a 1,3-dielectrophile such as (**131**) is used, condensation with (**67a**) gives the bicyclic compound (**132**).[72]

Alternatively, five-membered ring formation can be achieved by the condensation between a 1,3-dinucleophile and a 1,2-dielectrophile. This is demonstrated by the reaction of (**63**) with 2-aryl-2,2-dimethoxyethanal (**133**) to give the cyclopentenone product (**134**). The cyclization process is regioselective. INEPT $^{29}Si$ NMR has been used to follow the reaction,[151] which shows that the first condensation is between the more reactive nucleophilic site at C-4 of (**63**) with the more reactive electrophilic site at C-1 of (**133**) to give the intermediate (**135**).

*(c) Formation of six-membered rings.* Using the enol silyl ether chemistry, sequential aldol-type condensation between a 1,3-dinucleophile and a 1,3-dielectrophile has been developed as a general method of synthesis for functionalized benzenoid compounds.[152]

The approach is illustrated by the reactions of (**63**) with the two 1,3-dielectrophiles (**136**) and (**137**) under identical reaction conditions to form regioselectively the two isomeric aromatic compounds (**138**) and (**139**) respectively (Scheme 47). The regiochemistry of the condensation is governed by the differential reactivity of the two sites in (**63**; C-4 > C-2) and in the electrophiles (conjugate position > ketone > acetal).

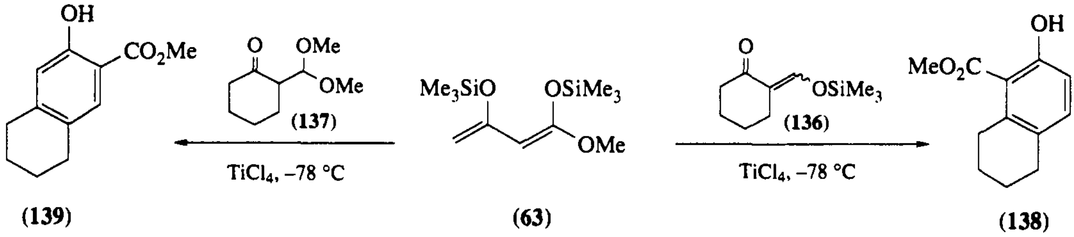
OH
CO2Me
O
OMe
OMe
(137)
TiCl4, -78 °C
Me3SiO
OSiMe3
OMe
O
OSiMe3
(136)
TiCl4, -78 °C
OH
MeO2C
(139)
(63)
(138)

Scheme 47

Methyl olivetolate (**140**) and its regioisomer (**141**) have been prepared in a regiocontrolled manner by the condensation of (**63**) with the two 1,3-electrophiles (**142**) and (**143**) respectively (Scheme 48).[153] In these cases, the reactivity order in the electrophilic components is acid chloride > acetal > ester. This reaction has been used in a biomimetic synthesis of (–)-$\Delta^1$-tetrahydrocannabinol (**144**).

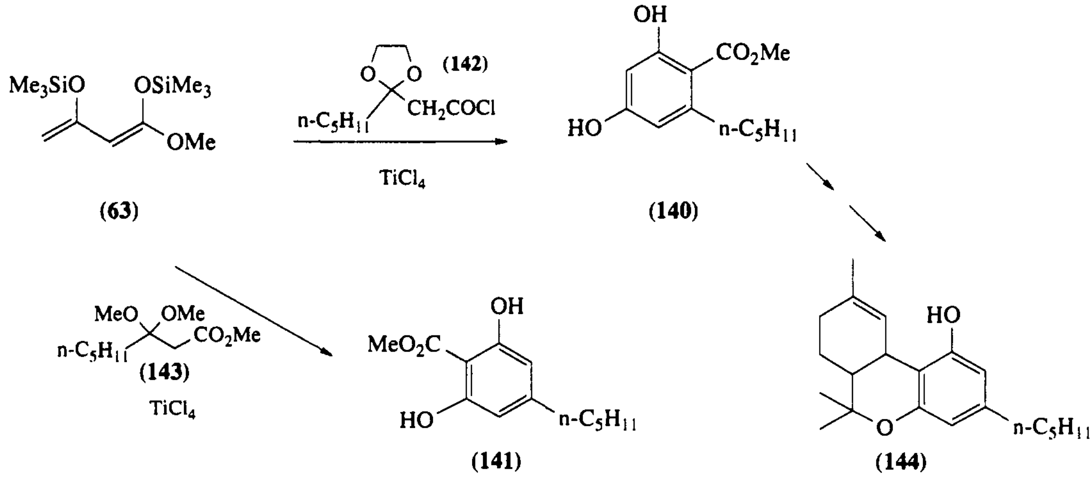
Me3SiO
OSiMe3
OMe
(63)
O
O
(142)
n-C5H11
CH2COCl
TiCl4
OH
CO2Me
HO
n-C5H11
(140)
MeO
OMe
n-C5H11
CO2Me
(143)
TiCl4
OH
MeO2C
HO
n-C5H11
(141)
HO
O
n-C5H11
(144)

Scheme 48

The hexasubstituted benzenoid compound (**145**) is synthesized in one step by the condensation of 2 mol of the dienol silyl ether (**146**) with 1 mol of methyl orthoacetate and $TiCl_4$. The reaction is believed to proceed through the intermediate (**147**). Compound (**147**) can be considered as a potential 1,3,5-trielectrophile. The more reactive sites in (**147**) are at C-5 and at C-3 respectively. Condensation of (**147**) with a second mole of (**146**) gives therefore regioselectively the aromatic compound (**145**). By this method, the plant growth substance sclerin (**148**) can easily be prepared.[132,154]

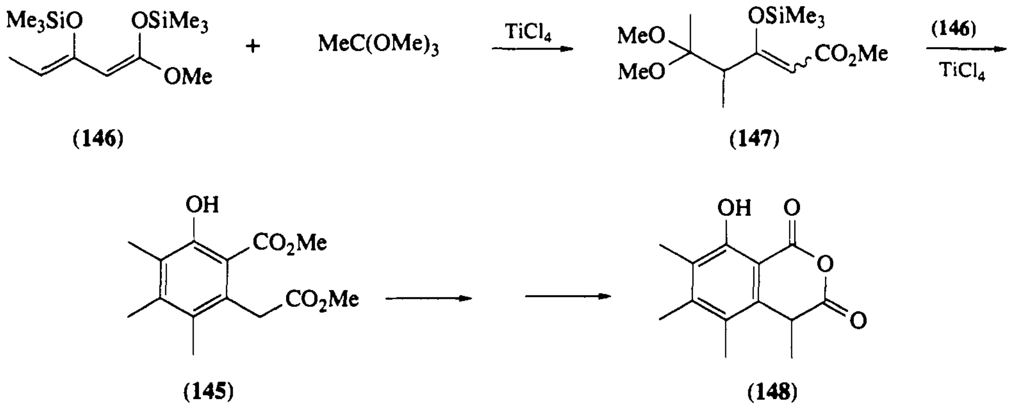
Me3SiO
OSiMe3
OMe
(146)
+
MeC(OMe)3
TiCl4
MeO
MeO
OSiMe3
CO2Me
(147)
(146)
TiCl4
OH
CO2Me
CO2Me
(145)
OH
O
O
O
(148)

A similar cycloaromatization reaction has been used as a key step in the synthesis of (–)-pseudopterosin A (**149**), a marine natural product with analgesic activity.[155]

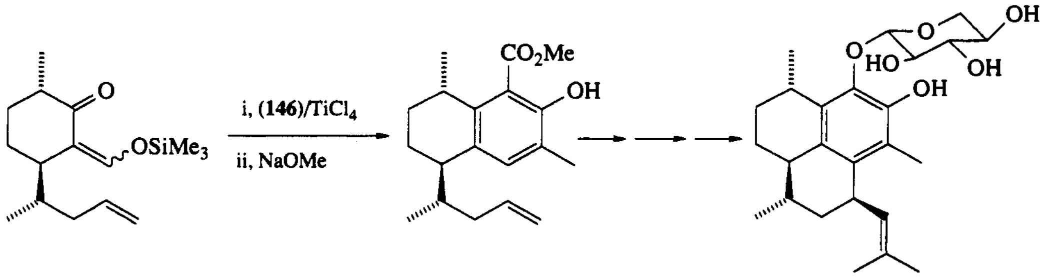
O
OSiMe3
i, (146)/TiCl4
ii, NaOMe
CO2Me
OH
O
HO
OH
OH
OH

**(149)**

When the 1,3-dielectrophile is part of a macrocycle, the cycloaromatization reaction can be used as a synthesis of *m*-cyclophanes as illustrated in Scheme 49.[156]

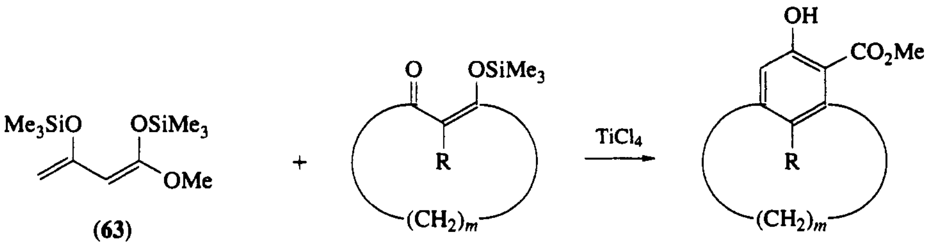
Me3SiO
OSiMe3
OMe
(63)
O
OSiMe3
R
(CH2)m
TiCl4
OH
CO2Me
R
(CH2)m

$m$ = 11 or 14
R = H, Me or $PhCH_2$

Scheme 49

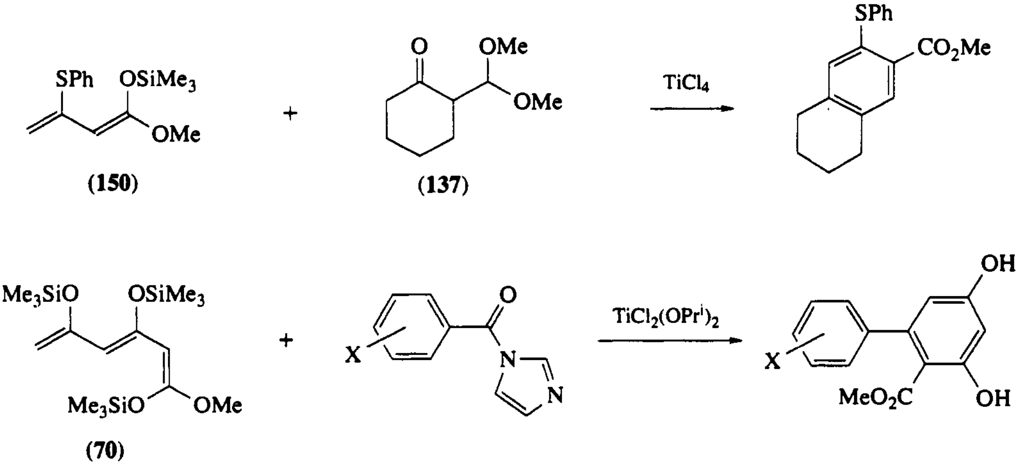
SPh
OSiMe3
OMe
(150)
O
OMe
OMe
(137)
TiCl4
SPh
CO2Me
Me3SiO
OSiMe3
Me3SiO
OMe
(70)
X
O
N
N
TiCl2(OPri)2
OH
X
MeO2C
OH

Scheme 50

Aryl sulfides can be synthesized from acyclic precursors by the same cycloaromatization reaction starting from the thio-substituted compound (**150**). Compound (**150**) reacts with the 1,3-dielectrophile (**137**) selectively at the γ-position first, followed by an intramolecular condensation at the α-position and then aromatization (Scheme 50).[157] The regiochemistry of the condensation is governed by the same reactivity difference in (**137**) as the example in Scheme 47.

An alternative way to construct a six-membered ring is through the condensation of a five-carbon dinucleophilic unit and a one-carbon electrophilic unit, *i.e.* a [5 + 1] condensation.[73] This is demonstrated by the reaction of (**70**) with an acid chloride, an imidazolide or an orthoester in the presence of $TiCl_2(OPr^i)_2$. The reaction provides an easy route to unsymmetrical biphenyls (Scheme 50).[147]

*(d) Formation of seven- and eight-membered rings.* Reaction of (**63**) with 1,4-dielectrophiles such as the cyclic acetal (**151**) gives the 8-oxabicyclo[3.2.1]octyl system (**152**), which has been converted to the oxygen analog of cocaine.[158,159] 2,5-Hexanedione reacts in a similar fashion.

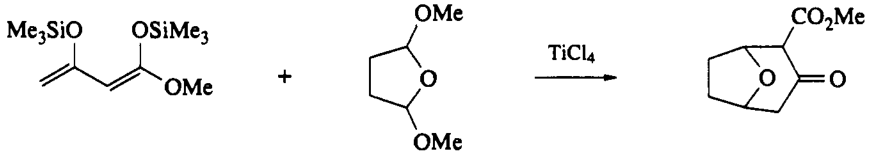

(**63**) (**151**) (**152**)

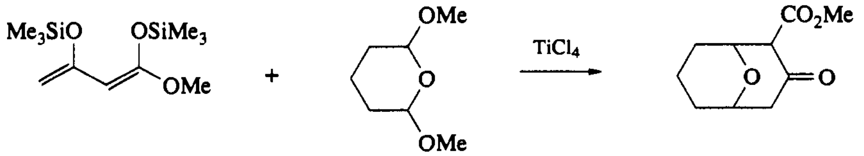

(**63**) (**153**) (**154**)

Using the acetal (**153**), the higher homolog 9-oxabicyclo[3.3.1]nonyl system (**154**) can be prepared by the same type of condensation.[158]

*(e) Bicycloaromatization.* Conceptually, the approach outlined in Scheme 45 for the construction of cyclic compounds can be extended into a general strategy for the formation of polycyclic compounds according to Scheme 51. It is not a trivial task to reduce the concept into practice experimentally. It requires the ability to assemble the appropriate precursors, (**155**) and (**156**), with the proper nucleophilic and electrophilic sites in the necessary order of reactivity.

Examples of a bicycloaromatization reaction have recently been demonstrated by the reactions of a 1,3,5-trinucleophile (**70**) with several 1,3,5-trielectrophiles (**157**) as illustrated in Scheme 52.[160] The regiochemistry of the reaction appears to be controlled by the first aldol condensation, which is initiated at the ε-position of (**70**) and the ketal position of (**157**).

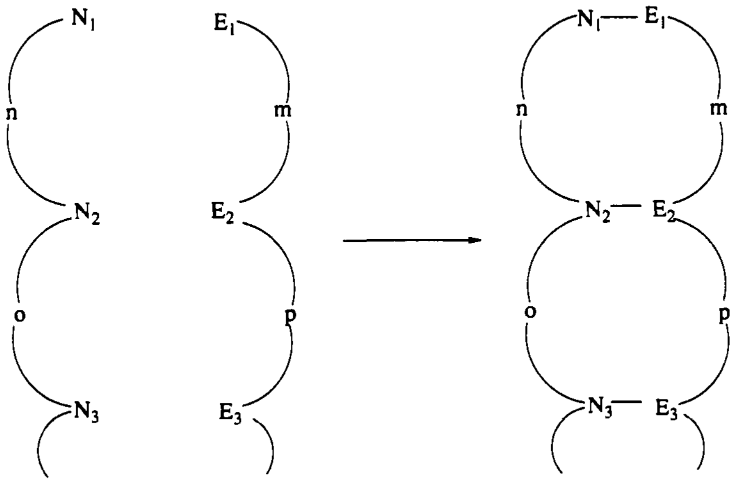

(**155**) (**156**)

**Scheme 51**

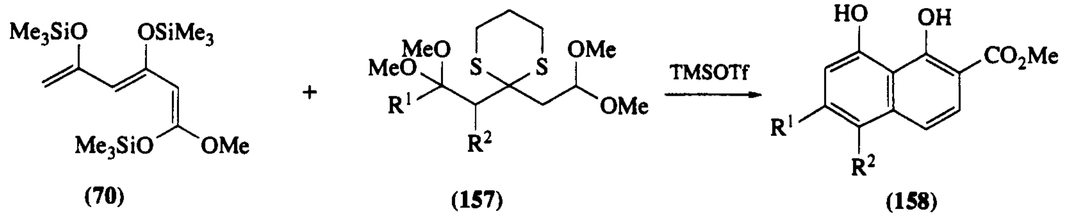
Me3SiO
OSiMe3
Me3SiO
OMe
(70)
+
MeO
MeO
R1
S
S
OMe
OMe
R2
(157)
TMSOTf
HO
OH
CO2Me
R1
R2
(158)

a : $R^1$ = Me, $R^2$ = H
b : $R^1$ = Et, $R^2$ = H
c : $R^1$ = Bu, $R^2$ = H
d : $R^1$ = Oct, $R^2$ = H
e : $R^1$ = $R^2$ = Me

Scheme 52

### *2.3.3.2.3 Reactions of enol germyl and stannyl ethers*

As discussed in Section 2.3.3.1, enol stannyl ethers react with carbonyl compounds readily without the need for catalysts. However, catalytic amounts of $AgBF_4$ and $I_2$ have been found[161] to improve considerably the yield of the condensation of the tin(II) enol ether (**159**) with the azetidinone (**93**). The use of a catalytic amount of $PdCl_2[P(o\text{-}MeC_6H_4)_3]_2$ improves the yield of the reactions between enol stannyl(IV) ethers and aldehydes.[86]

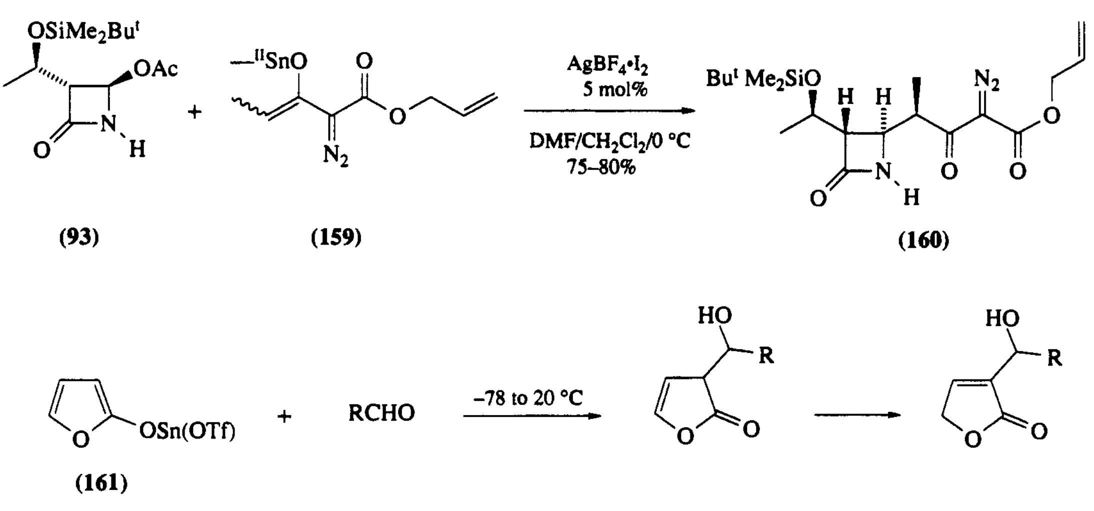
OSiMe2Bu^t
OAc
N
H
O
(93)
+
—IISnO
O
O
N2
(159)
AgBF4•I2
5 mol%
DMF/CH2Cl2/0 °C
75–80%
Bu^t Me2SiO
H
H
N2
O
N
H
O
O
O
(160)
OSn(OTf)
O
(161)
+
RCHO
–78 to 20 °C
HO
R
O
O
HO
R
O
O

Scheme 53

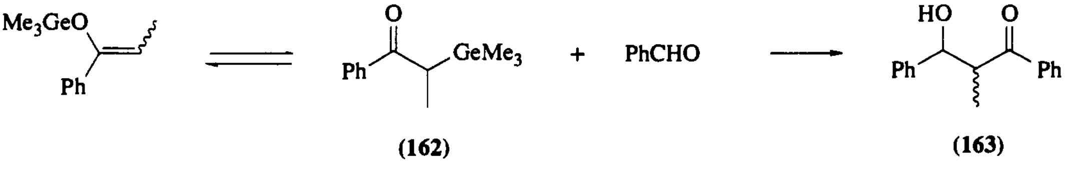
Me3GeO
Ph
O
Ph
GeMe3
(162)
+
PhCHO
HO
O
Ph
Ph
(163)

| *Additive* | *Temp* (°C) | *Yield* (%) |
|---|---|---|
| none | –78 to –40 | 27 |
| $BF_3 \cdot OEt_2$ | –78 | 58 |
| LiBr | –78 to –40 | 82 |

Scheme 54

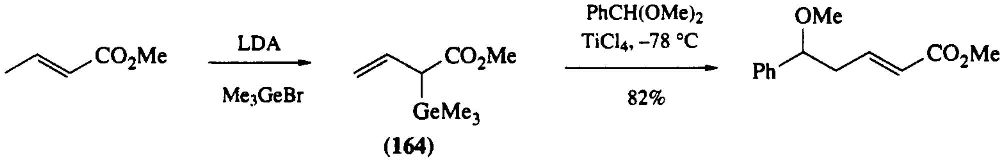

Scheme 55

As mentioned previously, 1-trimethylsiloxyfuran (**118**) undergoes aldol reactions at the γ-position. The corresponding tin(II) furanolate (**161**) reacts with aldehydes regioselectively at the α-position to give the 2-substituted butenolides (Scheme 53).[162]

Enol germyl ethers are expected to be more stable than the corresponding enol stannyl ethers, but more reactive than the enol silyl ethers. A recent study[163] shows that enol germyl ethers derived from a number of ketones (*e.g.* **162**) condense with benzaldehyde at –78 to –40 °C without the need for a catalyst. However, the yield of the product (**163**) appears to be improved by the addition of $BF_3{\cdot}OEt_2$. Interestingly, the presence of lithium halide also affects the reaction (Scheme 54).

The α-germylated ester (**164**) reacts with a number of aldehydes and acetals in the presence of Lewis acid to give, regioselectively, the γ-products (Scheme 55).[164] In that sense the germanium-masked dienolate behaves like the siloxy dienes in their regioselection.

## 2.3.4 CONCLUSION

It is clear that the addition reactions of enol ethers to C—X π-bonds are useful transformations in organic synthesis. Selectivity can be exercised with a range of enol ethers, with the proper choice of catalysts, and with a range of carbon electrophiles. The question of stereoselectivity of these reactions will be discussed in the next chapter. In the future, we can expect more new developments in this area including a better understanding of the structural[61] and mechanistic details of these reactions.[165]

## ACKNOWLEDGEMENT

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# 2.4
# Asymmetric Synthesis with Enol Ethers

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## 2.4.1 INTRODUCTION

The Lewis acid mediated aldol-type reaction of nucleophilic alkenes (alkyl enol ethers, enol esters) has been investigated since 1939 and is well documented in the literature.[1] The first breakthrough in this field was in 1973–74 when Mukaiyama and coworkers found that silyl enol ethers are much more effective than alkyl enol ethers in Lewis acid mediated additions to carbonyl compounds.[2] This is related to the fact that silicon is markedly more electropositive than carbon (1.8 *versus* 2.5), resulting in a stronger polarization of Si—O bonds and in a stronger tendency for nucleophilic attack at silicon with consequent Si—O bond heterolysis.[3] Since then the 'Mukaiyama reaction' has become a useful chemo- and regio-selective synthetic method. During the 1980s several researchers made a second breakthrough by succeeding in making this reaction diastereo- and enantio-selective. These stereochemical aspects are the subject of the present review. The reader should be aware that progress in this area is still rapid and that some of the tentative conclusions drawn in this review are likely to change. Because of the mass of data that has accrued in this field, this chapter is selective and critical rather than exhaustive. The reader is referred to earlier reviews for further discussion of individual points.[3,4]

## 2.4.2 PROCHIRAL NUCLEOPHILES AND ELECTROPHILES (SIMPLE STEREOSELECTION)

Although the mechanism of the 'Mukaiyama reaction' is not yet fully understood, several points have now been firmly established: (a) a Lewis acid enolate is not involved; (b) the Lewis acid activates the carbonyl group for the nucleophilic addition; and (c) the Si—O bond is cleaved by nucleophilic attack of the anionic species, generally halide, on silicon. Point (a) has been established by the use of INEPT–$^{29}$Si NMR spectroscopy.[5] Moreover, trichlorotitanium enolates have been synthesized, characterized and shown to give a completely different stereochemical outcome than the $TiCl_4$-mediated reactions of silyl enol ethers.[6] Complexes between Lewis acids and carbonyl compounds have been isolated and characterized by X-ray crystallography[7] and recently by NMR spectrometry.[8] On the basis of these observations 'closed' transition structures will not be considered here; 'open' transition structures with no intimate involvement between the silyl enol ether and the Lewis acid offer the best rationale for the 'after the fact' interpretation of the stereochemical results and the best model for stereochemical predictions.

If a prochiral silyl enol ether reacts with a prochiral C═X compound, a pair of racemic diastereoisomers results (equation 1). A reaction that gives an excess of one of these diastereoisomers is said to exhibit simple stereoselection.[4a] In this section we discuss the factors that govern the stereochemistry of this process. Diastereoisomers such as (**1**) and (**2**) will be called *syn* (**1**) and *anti* (**2**) in accord with the convention first proposed by Masamune *et al.*[9] Although only one enantiomer is depicted in each case, all structures in this section represent racemates.

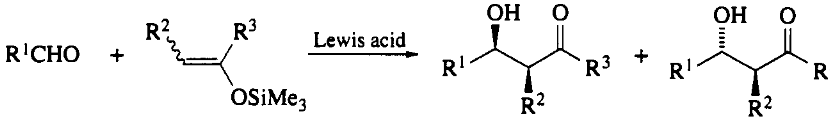

(**1**) *syn* (**2**) *anti*

(1)

### 2.4.2.1 Lewis Acid Mediated Additions to Aldehydes

Silyl enol ethers and silyl ketene acetals add to aldehydes in the presence of a stoichiometric amount of a Lewis acid (generally titanium tetrachloride, boron trifluoride etherate, tin(IV) chloride) with low levels or a complete lack of simple stereoselection. The *anti*:*syn* ratios usually range from 25:75 to 80:20, depending on the particular aldehyde, Lewis acid, enol ether and on the double bond stereochem-

**Table 1** Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Enol Silanes with Aldehydes (equation 1)[a]

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(Z)/(E)* | *Lewis acid* | *(Anti)/(syn)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | $Me_2CH$ | Me | OEt | 15/85 | $TiCl_4$ | 93/7 | 75 | 11 |
| 2 | Ph | Me | OEt | 25/75[b] | $TiCl_4 \cdot PPh_3$ | 91/9 | 79 | 19 |
| 3 | Et(Me)CH | Me | Et | c | $TiCl_4$ | 98/2 | 92 | 20 |
| 4 | $Me_2CH$ | Me | $Bu^t$ | 100/0 | $BF_3 \cdot OEt_2$ | >95/5 | 84 | 10 |
| 5 | Ph | Me | $Bu^t$ | 100/0 | $BF_3 \cdot OEt_2$ | >95/5 | 95 | 10 |
| 6 | Ph | Me | $C(Me_2)OTMS$ | 100/0 | $TiCl_4$ | 90/10 | 77 | 10 |
| 7 | Ph | Me | $SBu^t$ | <5/95[b,d] | $BF_3 \cdot OEt_2$ | 96/4 | 93 | 21 |
| 8 | $n\text{-}C_5H_{11}$ | Me | $SBu^t$ | 90/10[d] | $BF_3 \cdot OEt_2$ | 92/8 | 95 | 21 |
| 9 | $Me_2CH$ | Me | $SBu^t$ | <5/95[b,d] | $BF_3 \cdot OEt_2$ | 91/9 | 93 | 21 |
| 10 | $C_6H_{11}$ | Me | $SBu^t$ | 90/10[d] | $BF_3 \cdot OEt_2$ | 91/9 | 95 | 21 |
| 11 | PhCH═CH | Me | $SBu^t$ | <5/95[b,d] | $BF_3 \cdot OEt_2$ | 93/7 | 85 | 21 |
| 12 | Ph(Me)CH | Me | $SBu^t$ | <5/95[b,d] | $BF_3 \cdot OEt_2$ | 93/7 | 75 | 21 |
| 13 | Ph | Me | $NMe_2$[e] | 100/0 | $ZnBr_2$[f] | 90/10 | 75 | 22 |
| 14 | Ph | TMS | OMe | 25/75 | $TiCl_4$ | <5/95 | 91 | 23 |
| 15 | $n\text{-}C_8H_{17}$ | TMS | OMe | 95/5 | $TiCl_4$ | 5/95 | 90 | 23 |
| 16 | Ph | $Bu^t$ | OEt | 76/24 | $TiCl_4$ | <8/92 | c | 24 |
| 17 | Ph | $Bu^t$ | OEt | <5/95 | $TiCl_4$ | <8/92 | c | 24 |

[a] $CH_2Cl_2$ solvent. [b] $OSiMe_2Bu^t$ ether. [c] Not specified. [d] Note that silyl ketene acetals derived from thiol esters have opposite (*Z*)/(*E*) descriptors compared to esters due to change of sequence rule priority associated with the sulfur atom. [e] STMS ether. [f] Catalytic amount.

istry.[2,10–18] By judiciously choosing substrates and reaction conditions, preparatively useful ratios of the *anti* diastereoisomers (>90%) have been obtained in several cases (equation 1): significant results are summarized in Table 1.[10,11,19–24] When $R^2$ is small (Me), as in the case of ethyl ketones or propionate derivatives (Table 1; entries 1–13), the most general way to obtain good *anti* selectivities, independent of the double bond stereochemistry, is to have a bulky $R^3$ group, as with sterically demanding ketones (entries 4–6) and thiol esters (entries 7–12). Esters usually give poor stereoselectivity except for isolated cases (entries 1 and 2). Thiol esters, which are electronically more similar to ketones than esters because of the weak overlap of the C(2*p*) and S(3*p*) orbitals, can undergo a wide variety of further synthetic transformations and are therefore attractive reagents.[21]

The staggered transition structures for the Lewis acid mediated reaction of a (*Z*)-silyl enol ether with an aldehyde are summarized in Figure 1. It is assumed that the Lewis acid occupies a coordination site on the carbonyl oxygen that is *cis* to the aldehydic hydrogen.[7,10] We can immediately rule out $A_2$ (steric interaction between $R^3$ and the Lewis acid), $A_3$ (nonbonded interaction between $R^1$ and $R^3$ plus unfavorable dipole–dipole interaction of the two carbon–oxygen bonds) and $S_2$ (unfavorable dipole–dipole interaction of the two carbon–oxygen bonds). When $R^3$ is large (Bu$^t$, SBu$^t$) and $R^2$ is small (Me) both $S_1$ (nonbonded interaction between $R^1$ and $R^3$) and $S_3$ (nonbonded interaction between oxygen and $R^3$) are disfavored compared to $A_1$, destabilized only by the *gauche* interaction between $R^1$ and $R^2$, and the *anti*

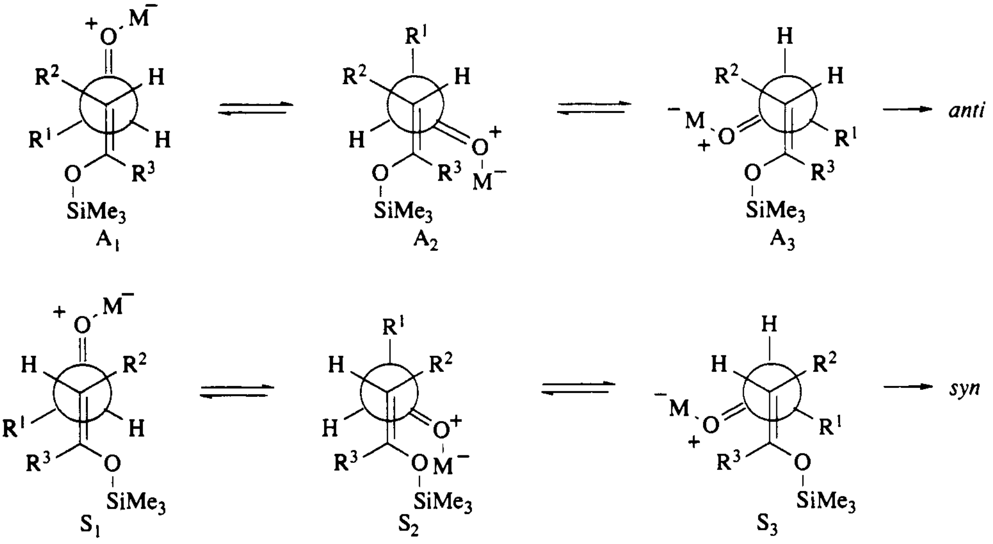

**Figure 1**

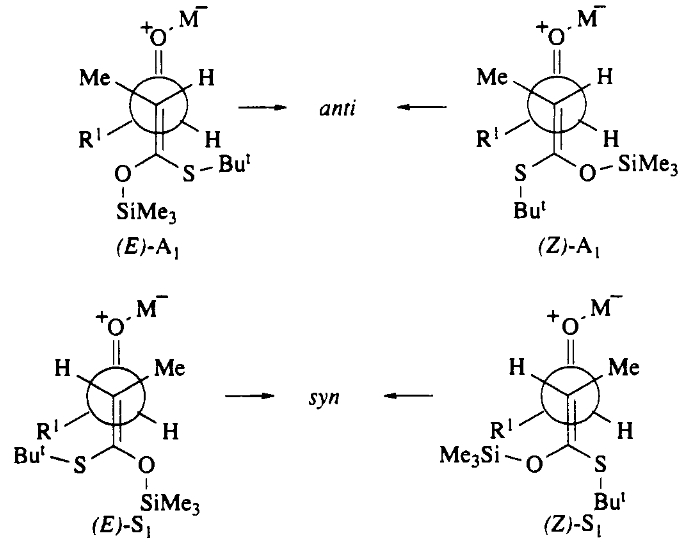

**Figure 2**

isomers are obtained. In the case of thiol esters the particular 'pinwheel' conformation$^{21}$ is probably responsible for the enhanced *anti* selectivity irrespective of the double bond geometry because of the greater effective transmission of the steric hindrance (Figure 2, (*E*) S$_1$ and (*Z*) S$_1$ destabilized by R$^1$/Bu$^t$ and R$^1$/TMS interactions).

When R$^3$ is replaced by a smaller group, and R$^2$ is large (TMS, Bu$^t$), then both A$_1$ and S$_3$ (*gauche* interaction between R$^1$ and R$^2$) are disfavored compared to S$_1$, and the *syn* isomers are obtained (Table 1; entries 14–17). The same analysis applies to several other cases: ketene bis(trimethylsilyl) acetals (R$^3$ = OTMS) are *anti* selective when R$^2$ is Me (*anti* 86–89%) and *syn* selective when R$^2$ is Bu$^t$ (*syn* 70–89%);$^{24}$ silyl ketene acetal (**3**) derived from butyrolactone is *anti (R*,R*)* selective when R = H (*anti* 70%) and *syn (R*,S*)* selective when R = TMS (single isomer, equation 2);$^{25a-c}$ *S*-trimethylsilyl *S,N*-acetals (**4**) are *anti* selective when R = Me (*anti* 60–87%) and *syn* selective when R = Pr$^i$ (*syn* 60%, equation 3).$^{22}$ Cyclic enol silanes usually show poor selectivity,$^{2,10,26}$ apart from isolated cases where good *anti*:*syn* ratios were obtained by carefully choosing reagents and Lewis acids. Fair *anti* preferences were observed with the cyclopentenone-derived silyl enol ether and TiCl$_4$ (equation 4; R = Pr$^i$, Bn; *anti (R*,R*)*:*syn(R*,S*)* >90:10)$^{27}$ and with 2-trimethylsilyloxyfuran (**5**; equation 5; *anti (R*,R*)*:*syn(R*,S*)* 76–88:24–12).$^{17,27}$

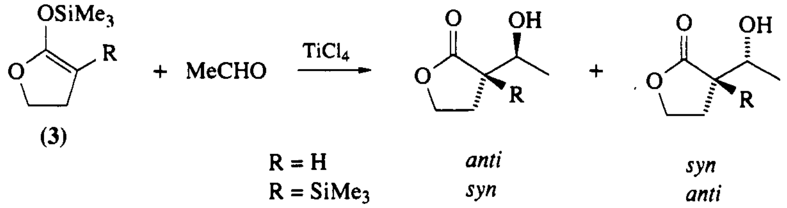

(2)

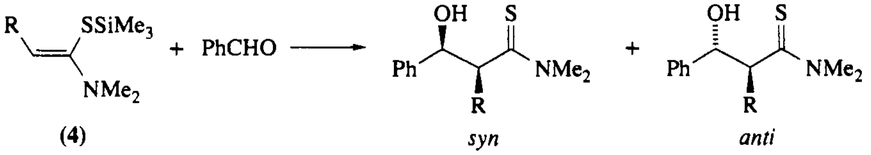

(3)

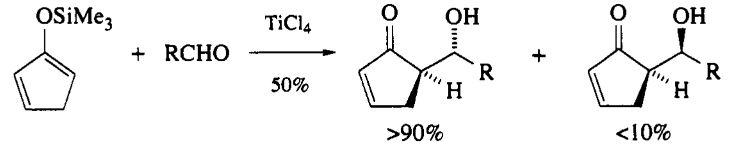

(4)

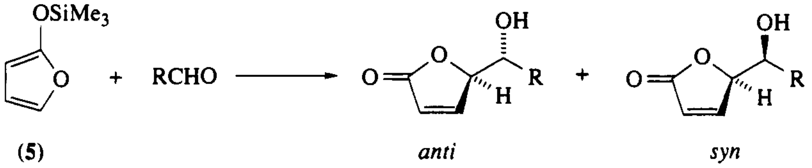

(5)

Similar to all the reactions with a negative activation volume $\Delta V^\ddagger$, the silyl enol ether aldol addition is accelerated by using high pressure (10 kbar)$^{28a}$ or the hydrophobic effect (water and sonication);$^{28b}$ under these conditions the reaction can be conducted without catalyst to give good yields of products with a stereoselectivity that is the reverse of that seen in the acid-catalyzed reaction. With TiCl$_4$ enol silane (**6**) gives the *anti* isomer predominantly (75:25), while under neutral conditions the *syn* isomer is preferred (75:25; equation 6). These studies show unambiguously that $\Delta V^\ddagger$ is smaller for the *syn* isomer transition structure, and that the Lewis acid not only acts as carbonyl group activator but also plays an important role for controlling the reaction stereoselectivity.

Recently Mukaiyama and coworkers introduced the use of trityl salts as efficient catalysts for the aldol reaction. Using a catalytic amount of trityl perchlorate (5 mol %) and *t*-butyldimethylsilyl enol ethers, the *anti* aldols were preferentially obtained (*anti* 73–84%) regardless of the double bond geometry.$^{29a}$ With trityl triflate (5 mol %) and dimethylphenylsilyl enol ethers, the *syn* isomers are produced predominantly (*syn* 63–79%; Scheme 1).$^{29b}$ Several variations of the catalyst system have been developed. Trityl

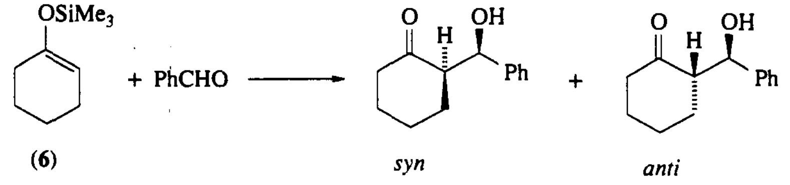
OSiMe3
+ PhCHO
O
OH
H
Ph
+
(6)
syn
anti

(6)

perchlorate can be supported on a polymer.[30] The combined use of catalytic amounts of trityl chloride and tin(II) chloride (*anti* 69–82%)[31] or of trimethylsilyl chloride and tin(II) chloride[32] is a mild and effective procedure. Trityl perchlorate can also be used to catalyze the tandem Michael–aldol reaction with good yields and excellent stereoselectivity (Scheme 2).[33a] The aldol product is obtained as a single isomer (*syn*), in agreement with the foregoing discussion (Figure 1, transition structure $S_I$) when $R^3$ is small and $R^2$ is a large group. Analogously, a single aldol isomer (100% *syn*) is obtained in the $Ph_3CSbCl_6$-catalyzed tandem Michael–aldol reaction on cyclohexenone.[33b]

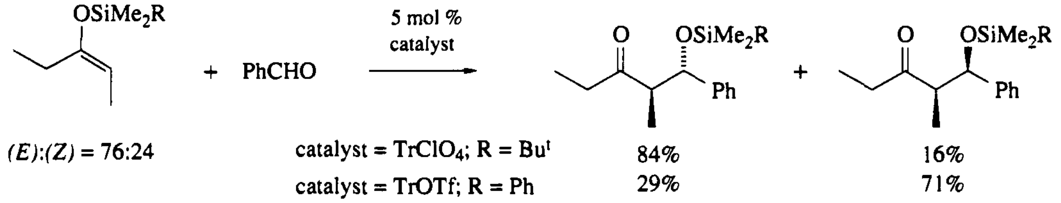
OSiMe2R
+ PhCHO
5 mol %
catalyst
O
OSiMe2R
Ph
+
(E):(Z) = 76:24
catalyst = TrClO4; R = Bu^t
catalyst = TrOTf; R = Ph
84%
29%
16%
71%

**Scheme 1**

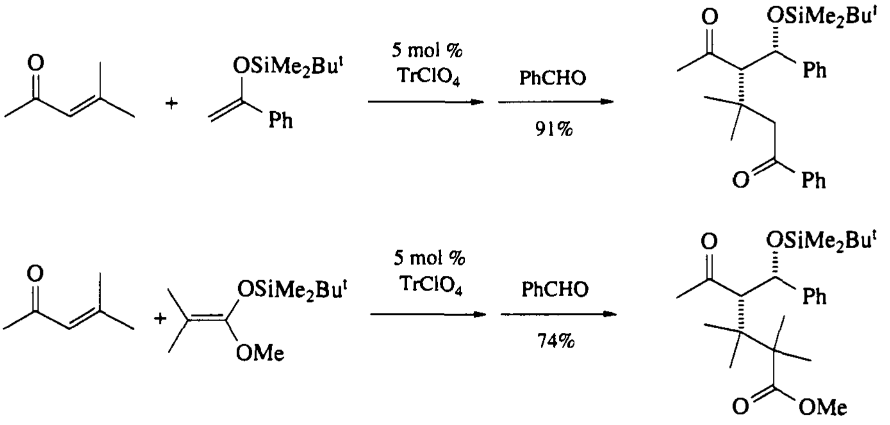
O
+
OSiMe2Bu^t
Ph
5 mol %
TrClO4
PhCHO
91%
O
OSiMe2Bu^t
Ph
O
Ph
O
+
OSiMe2Bu^t
OMe
5 mol %
TrClO4
PhCHO
74%
O
OSiMe2Bu^t
Ph
O
OMe

**Scheme 2**

### 2.4.2.2 Fluoride Ion Mediated Additions to Aldehydes

In 1976 Kuwajima, Nakamura and coworkers found that fluoride ion catalyzes the reaction of enol silanes with aldehydes.[34a] The efficacy of fluoride in such reactions reflects the high homolytic dissociation energy of the Si—F bond (807 kJ $mol^{-1}$).[3] The mechanism and stereoselectivity of this reaction have been examined by several groups, and the subject has been recently reviewed.[3,4a,6a] The aldol coupling is effected smoothly at low temperatures with about 0.1 equiv. of tetrabutylammonium fluoride (TBAF) in THF. The process appears to proceed through a catalytic cycle involving several reversible steps (Scheme 3). The principal features are the following: (a) TMSF is essential for trapping the unstable aldolate (**9**) and driving the reaction forward; (b) TMSF probably also acts as an activator of the carbonyl group; (c) the reactive species is probably the metal-free enolate anion (**8**) and not the anionic hypervalent silyl enol ether (**7**);[34b] and (d) the equilibration between enolate (**8**) and aldolate (**9**) is much more facile than the fluoride-mediated retrograde reaction of the aldol silyl ether (**10**). Usually the kinetic products are the *syn* isomers; however, longer reaction times and higher temperatures lead to product mixtures approximating the thermodynamic ratio of *syn* and *anti* isomers. For example, the *syn*:*anti* diastereomeric ratio in the reaction of (**6**) with TBAF and benzaldehyde changed gradually from 65:35 (5 min) to final equilibrium of 54:46 (8 h).[35] With the (*Z*)-silyl enol ether derived from ethyl *t*-butyl ketone, TBAF and benzaldehyde, the *syn*:*anti* ratio varied from 100:0 (–70 °C, 1 h) to 20:80 (room temperature).[36] Added extra TMSF proved advantageous for both stereoselectivity and yield: reaction of the cyclopentanone-derived trimethylsilyl enol ether with isobutyraldehyde gave, in the presence of catalytic TBAF and 2 equiv. of TMSF, the *syn* isomer exclusively.[35] *Syn* selectivity was also obtained with ketene bis(trimethylsilyl) acetals (equation 7; Table 2, entries 1 and 2),[37] thiol ester silyl ketene acetals (entries 3 and 4),[21] 2-trimethylsilyloxyfuran (**5**), catalytic TBAF and various aldehydes (equation 5; *syn* 78–92%),[17] *S*-trimethylsilyl *S*,*N*-acetals (**4**; R = Me, $Pr^i$), catalytic TBAF and benzaldehyde (equation 3; *syn* 81–96%).[22] Preparatively useful ratios of the *syn* isomers, regardless of silyl enol ether geometry, are obtained using catalytic amounts of tris(dimethylamino)sulfonium (TAS) difluorotrimethylsiliconate as fluoride ion source.[38] For example the silyl enol ethers derived from both cyclopentanone and cyclohexanone give with isobutyraldehyde the *syn* isomers exclusively. The reaction has also been studied with several acyclic enol silanes (equation 7): *syn* selectivity ranged from moderate, when $R^3$ is a small alkyl group (Table 2, entries 5–7), to good when $R^3$ is aryl (entries 8 and 9).

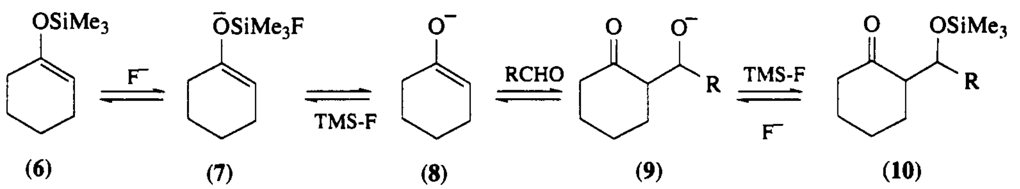

**Scheme 3**

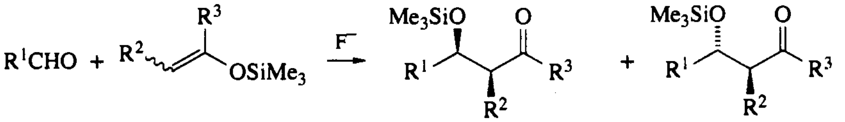

(7)

**Table 2** Ratio of Diastereoisomers in the Fluoride Ion Catalyzed Reactions of Enol Silanes with Aldehydes (equation 7)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(Z)/(E)* | *Catalyst* | *(Syn)/(anti)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | OTMS | — | TBAF | 79/21 | 75 | 37 |
| 2 | Ph | Et | OTMS | — | CsF | 78/22 | 78 | 37 |
| 3 | Ph | Me | $SBu^t$ | 7/93[a] | TBAF | 95/5 | 91 | 21 |
| 4 | Ph | Me | $SBu^t$ | 90/10[a] | TBAF | 57/43 | 42 | 21 |
| 5 | Ph | Me | Et | 100/0 | $TASTMSF_2$ | 86/14 | 89 | 38 |
| 6 | Ph | Me | Et | 30/70 | $TASTMSF_2$ | 63/37 | 84 | 38 |
| 7 | Ph | Et | $Pr^n$ | 100/0 | $TASTMSF_2$ | 86/14 | 65 | 38 |
| 8 | Ph | Me | Ph | 99/1 | $TASTMSF_2$ | 95/5 | 75 | 38 |
| 9 | Ph | Me | Ph | 9/91 | $TASTMSF_2$ | 94/6 | 78 | 38 |

[a] See footnote d of Table 1.

Nakamura, Kuwajima and coworkers have recently shown that TBAF and TAS difluorotrimethylsiliconate-catalyzed reactions give identical sense and degree of stereoselection.[34b] As the stereoselectivity of the fluoride-catalyzed aldol reaction is independent of the countercation and of the type of silyl group,[34b] the 'open' transition structures **A** (extended) and **B** (skew) have been proposed to account for the observed dependence of the *syn*:*anti* ratios on the steric hindrance of $R^1$, $R^2$ and $R^3$ (Figure 3).[34b,38]

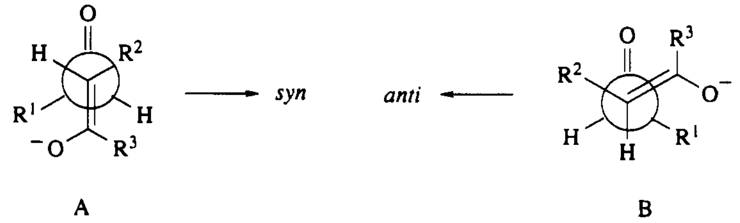

**Figure 3**

### 2.4.2.3 Lewis Acid Mediated Additions to Acetals

The $TiCl_4$-mediated reaction of enol silanes with acetals (equation 8) was reported by Mukaiyama and coworkers in 1974.[1] More recently various catalysts (1–10 mol %), *i.e.* trimethylsilyl trifluoromethanesulfonate (TMSOTf),[39,40] trityl perchlorate ($TrClO_4$),[41,42] polymer-supported trityl perchlorate,[30] clay montmorillonite,[14] trimethylsilyl iodide (TMSI)[43] and rhodium complexes,[44] have been used to promote the addition to give good yields of the aldol products. The reaction is usually *syn* stereoselective; significant results are reported in Table 3. Moderate to good *syn*:*anti* ratios were obtained with silyl enol ethers derived from cyclic ketones (entries 1–5), acyclic ketones when $R^3$ is aryl or a bulky alkyl group regardless of the enol ether geometry (entries 6–8), and thiol esters (entry 9). When $R^3$ is OMe or Et the selectivity is lost (entries 10 and 11). The mechanism of the TMSOTf-catalyzed reaction was recently studied in detail by $^1H$ and $^{13}C$ NMR spectroscopy and shown to proceed through carboxonium triflate ion pairs.[39c] 'Open' extended transition structures, similar to the ones proposed for the fluoride-catalyzed reactions (Figure 3, structure A) have been used to rationalize the *syn* selectivity irrespective of the double bond geometry.[39c]

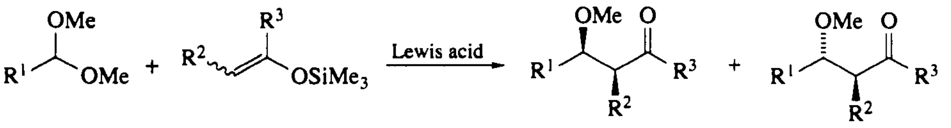

(8)

**Table 3** Ratio of Diastereoisomers in the Lewis Acid Catalyzed Reactions of Enol Silanes with Dimethyl Acetals (equation 8)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *(Z)/(E)* | *Catalyst* | *(Syn)/(anti)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | $—(CH_2)_4—$ | | 0/100 | TMSI | 95/5 | 89 | 43 |
| 2 | $Pr^n$ | $—(CH_2)_4—$ | | 0/100 | TMSOTf | 89/11 | 91 | 39 |
| 3 | $Pr^i$ | $—(CH_2)_4—$ | | 0/100 | $TrClO_4$ | 80/20 | 90 | 41 |
| 4 | Ph | $—(CH_2)_3—$ | | 0/100 | TMSI | 99/1 | 87 | 43 |
| 5 | PhCH═CH | $—(CH_2)_3—$ | | 0/100 | TMSI | 80/20 | 82 | 43 |
| 6 | Ph | Me | Ph | 0/100 | TMSOTf | 71/29 | 83 | 39 |
| 7 | Ph | Me | Ph | 100/0 | TMSOTf | 84/16 | 97 | 39 |
| 8 | Ph | Me | $Bu^t$ | 100/0 | TMSOTf | 95/5[a] | 94 | 39 |
| 9 | Ph | Me | $SBu^t$ | 0/100 | TMSOTf | 78/22 | 92 | 39 |
| 10 | Ph | Me | OMe | 0/100[b] | TMSOTf | 50/50 | 74 | 39 |
| 11 | Ph | Me | Et | 79/21 | TMSI | 57/43 | 84 | 43 |

[a] This stereochemical assignment was questioned (ref. 4a). [b] (*Z*)/(*E*) = 100/0 gave (*syn*)/(*anti*) = 55/45 (ref. 39c).

### 2.4.2.4 Lewis Acid Mediated Additions to Imines

The $TiCl_4$-mediated reaction of enol silanes with imines was first introduced by Ojima and coworkers in 1977.[45] The reaction was then extended to several similar substrates, *i.e.* nitrones,[46] α-methoxycarbamates,[47] aminals,[48] 4-acetoxyazetidin-2-one,[49,50] and to different Lewis acids, *i.e.* $SnCl_4$,[51] $TiCl_2(OPr^i)_2$,[51] catalytic $ZnX_2$,[49,51] catalytic TMSOTf,[50] to give good yields of the addition products with low levels (≤80:20) or a complete lack of simple stereoselection. Moderate to good *anti* selectivities were reported in the addition of silyl ketene acetals to imines under particular reaction conditions (equation 9); significant results are summarized in Table 4.

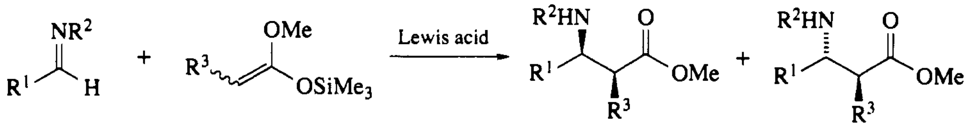

(9)

Table 4 Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Silyl Ketene Acetals with Imines (equation 9)

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *(Z)/(E)* | *Lewis acid* | *(Anti)/(syn)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | TMS | Et | 0/100 | $ZnI_2$ | 90/10 | 61 | 52 |
| 2 | TMSC≡C | TMS | Ph | 0/100 | $ZnI_2$ | 92/8 | 53 | 52 |
| 3 | Ph | Ph | Ph | 64/36 | TMSOTf$^a$ | 86/14 | 85 | 53 |
| 4 | PhCH═CH | *p*-$MeOC_6H_4$ | Ph | 64/36 | TMSOTf$^a$ | 85/15 | 78 | 53 |
| 5 | Ph | Ph | Me | 25/75 | TMSOTf$^a$ | 100/0 | 85 | 53 |

[a] Catalytic amount (10 mol %).

## 2.4.3 CHIRAL NUCLEOPHILES

Chiral silyl ketene acetals (**11**)–(**20**) were recently introduced for diastereoselective aldol-type additions. Camphor derivatives (**11**)–(**16**) are conformationally rigid with one diastereotopic face of the enol silane sterically shielded.[54,55] *N*-Methylephedrine derivatives (**17**)–(**20**) are likely to bind to $TiCl_4$ through the $NMe_2$ group with consequent dramatic conformational constraint.[19,56,57] As a result the Lewis acid mediated additions to C═X occur in a highly stereoselective way. The chiral auxiliaries can then be removed (and recycled) by reduction, saponification or displacement with various nucleophiles to give useful synthetic intermediates.

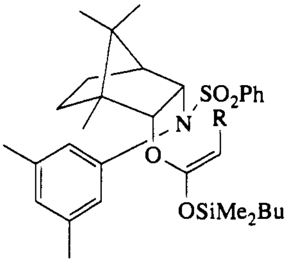

(**11**) R = H
(**12**) R = Me

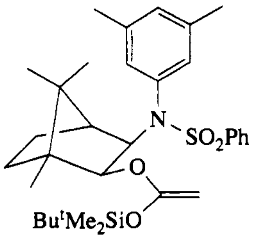

(**13**)

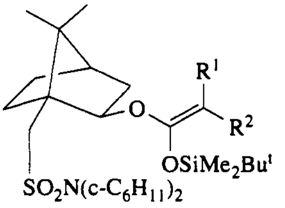

(**14**) R¹ = R² = H
(**15**) R¹ = Me; R² = H
(**16**) R¹ = H; R² = Me

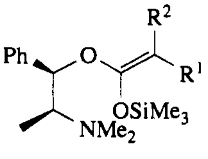

(**17**) R¹ = H; R² = Me
(**18**) R¹ = Me; R² = H

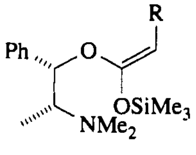

(**19**) R = Me
(**20**) R = Et

### 2.4.3.1 Diastereoselective Aldol Additions of Chiral Silyl Ketene Acetals and Chiral Silyl Enol Ethers

Acetate-derived silyl ketene acetals (**11**, **13** and **14**) react with aldehydes with good stereoselectivity (equation 10); significant results are reported in Table 5. Removal of the auxiliary, with methanolic KOH, gave the corresponding β-hydroxy acids in good enantiomeric excess (*ee*). The asymmetric variants of the Mukaiyama reaction also helped to solve the long-standing problem of an efficient *anti* selective chiral propionate equivalent (equation 11);[4a] significant results are reported in Table 6. It is interesting to observe that with the camphor derivatives changing the double bond geometry gives rise to reversal of stereochemistry in the product aldol (entries 7 and 8), whereas with the *N*-methylephedrine derivatives the results are more or less the same (entries 8 and 10). It is therefore probable that these reactions, although appearing similar, have different mechanisms; transition structure hypotheses[54,55,57] are also likely to be *ad hoc* rather than general. The adducts (**23**) and (**24**) were reduced (using $LiAlH_4$) to diols,[54,55] saponified to hydroxy acids (LiOH; NaOH),[55–57] or converted to hydroxamates ($RONH_2 \cdot HCl$, $Et_3Al$) for β-lactam synthesis,[58] without detectable epimerization. It is worth noting that with the *N*-methylephedrine derivatives both the major *anti* (**23**) and the major *syn* (not shown) stereoisomers have the same absolute configuration (*S*) at C-2. This shows that, while the aldehyde π-facial selectivity is only moderate, the silyl ketene acetal π-facial selectivity is very high. Indeed, using trimethyl orthoformate (**25**) as electrophile, adduct (**26**) was obtained in 65% yield with good selectivity (≥95.5:4.5; Scheme 4). By simple functional group modifications (**26**) was converted in high yield to aldehyde (**27**; 91% *ee*).[59]

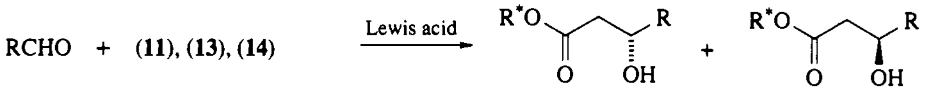

(**21**) (**22**)

(10)

**Table 5** Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Chiral Silyl Ketene Acetals with Aldehydes (equation 10)

| *Entry* | *Reagent* | *R* | *Lewis acid* | *(**21**)/(**22**)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | (**11**) | Et | $TiCl_4$ | 93/7 | 67 | 54 |
| 2 | (**11**) | $n\text{-}C_7H_{15}$ | $TiCl_4$ | 93/7 | 59 | 54 |
| 3 | (**11**) | $Pr^i$ | $TiCl_4$ | 97/3 | 51 | 54 |
| 4 | (**13**) | $Pr^i$ | $TiCl_4$ | 5/95 | 62 | 54 |
| 5 | (**13**) | Ph | $TiCl_4$ | 6/94 | 69 | 54 |
| 6 | (**14**) | Ph | $TiCl_4$ | 92/8 | 56 | 55 |
| 7 | (**14**) | $Pr^i$ | $TiCl_4$ | 99/1 | 47 | 55 |
| 8 | (**14**) | $Pr^n$ | $TiCl_4$ | 92/8 | 48 | 55 |
| 9 | (**14**) | $n\text{-}C_8H_{17}$ | $TiCl_4$ | 92/8 | 51 | 55 |
| 10 | (**14**) | Ph | $BF_3 \cdot OEt_2$ | 92/8 | 30 | 55 |
| 11 | (**14**) | $Pr^i$ | $BF_3 \cdot OEt_2$ | 95/5 | 44 | 55 |

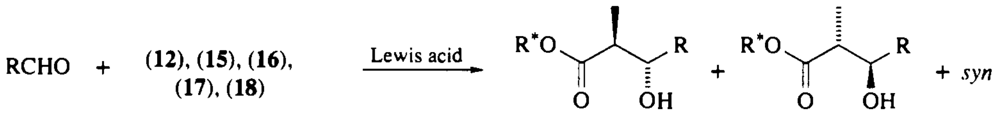

(**23**) (**24**)

(11)

**Table 6** Ratio of Diastereoisomers in the Lewis Acid Mediated Reactions of Chiral Silyl Ketene Acetals with Aldehydes (equation 11)

| *Entry* | *Reagent* | *R* | *Lewis acid* | *(Anti)/(syn)* | *(**23**)/(**24**)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | (**12**) | $Pr^i$ | $TiCl_4$ | 93.5/6.5 | 2/98 | 66 | 54 |
| 2 | (**15**) | Ph | $TiCl_4$ | 81/19 | 5/95 | 44 | 55 |
| 3 | (**15**) | Et | $TiCl_4$ | 100/0 | 16/84 | 30 | 55 |
| 4 | (**15**) | $Pr^n$ | $TiCl_4$ | 94/6 | 7/93 | 50 | 55 |
| 5 | (**15**) | $Pr^i$ | $TiCl_4$ | 98.2/1.8 | 7.5/92.5 | 60 | 55 |
| 6 | (**15**) | $Pr^i$ | $BF_3 \cdot OEt_2$ | 73/27 | 3/97 | 58 | 55 |
| 7 | (**16**) | $Pr^i$ | $BF_3 \cdot OEt_2$ | 93.5/6.5 | 93.5/6.5 | 57 | 55 |
| 8 | (**17**) | Ph | $TiCl_4$ | 85/15 | 97/3 | 80 | 56 |
| 9 | (**17**) | Ph | $TiCl_4 \cdot PPh_3$ | 97/3 | 97/3 | 90 | 19 |
| 10 | (**18**) | Ph | $TiCl_4$ | 80/20 | 95.5/4.5 | 65 | 56, 57 |
| 11 | (**17**) | (*E*)-PhCH═CH | $TiCl_4$ | 85/15 | 95.5/4.5 | 60 | 56 |
| 12 | (**17**) | (*E*)-PhCH═CH | $TiCl_4 \cdot PPh_3$ | 93.7/6.3 | 93/7 | 50 | 19 |
| 13 | (**17**) | (*E*)-MeCH═CH | $TiCl_4$ | 80/20 | 95.5/4.5 | 78 | 56 |
| 14 | (**17**) | $Pr^n$ | $TiCl_4$ | 80/20 | 95.5/4.5 | 88 | 56 |
| 15 | (**17**) | $n\text{-}C_5H_{11}$ | $TiCl_4$ | 75/25 | 96.5/3.5 | 60 | 56 |

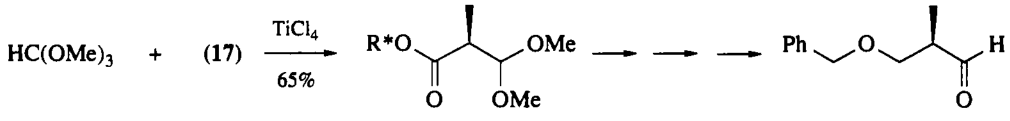

**(25)** **(26)** **(27)** 91% *ee*

**Scheme 4**

Equation (12) illustrates the following general principle: 'electrophiles able to form a chelated complex with the Lewis acid (*e.g.* **28**) control (usually invert) the simple stereoselection of the reaction'. The major isomer (**29**) is, in fact, *syn*. Adducts (**29**) and (**30**) were then transformed, by simple functional group chemistry, into (+)-PS-5, a carbapenem antibiotic.[60] Transition structure models for this process are discussed in detail in Section 2.4.4.1.

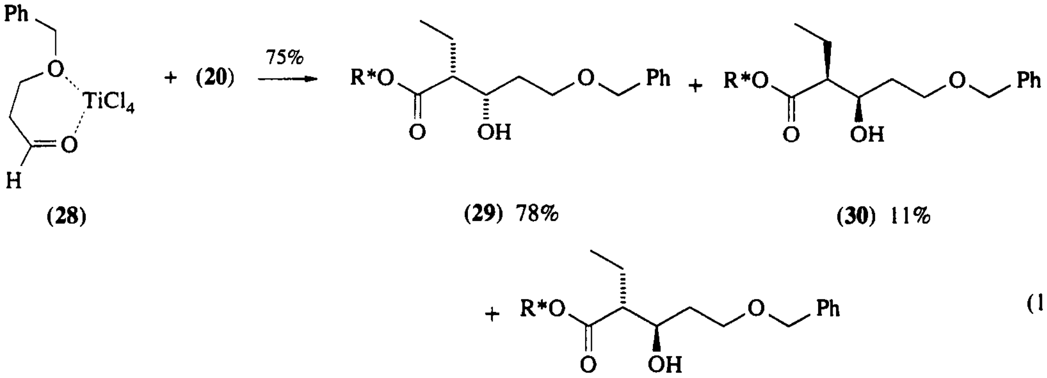

**(28)** **(29)** 78% **(30)** 11% **(31)** 11% (12)

Chiral butyrolactone derivatives (**32**) and (**33**) react with aldehydes to give the condensation products (**34**)–(**36**) as single stereoisomers in high yield (equation 13);[25b,c] both simple stereoselection (TMS and OH *syn*, see Section 2.4.2.1) and diastereofacial selection are 100%. Another example where a substituent on a cyclic silyl enol ether causes 100% diastereofacial selection is shown in equation (14).[61]

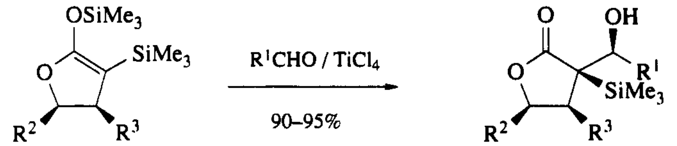

(13)

**(32)** $R^2$ = Me; $R^3$ = H

**(33)** $R^2$ = H; $R^3$ = Me

**(34)** $R^1$ = Me; $R^2$ = Me; $R^3$ = H

**(35)** $R^1$ = $Pr^i$; $R^2$ = Me; $R^3$ = H

**(36)** $R^1$ = Me; $R^2$ = H; $R^3$ = Me

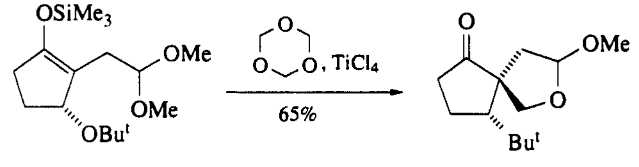

(14)

### 2.4.3.2 Diastereoselective Additions of Chiral Silyl Ketene Acetals to Imines

*N*-Methylephedrine-derived silyl ketene acetals react with imines in the presence of 2 mol equiv. of $TiCl_4$ to give β-amino esters (equation 15); significant results are summarized in Table 7. With benzylideneaniline the reaction is *anti* selective (entry 1), while with imino esters that chelate $TiCl_4$ to give complexes such as (**41**), the reaction is *syn* selective (entries 2 and 3), in agreement with the general principle described in the preceding section. Adducts (**37**)–(**40**) have been transformed into optically active *trans* and *cis* β-lactams.[58,62]

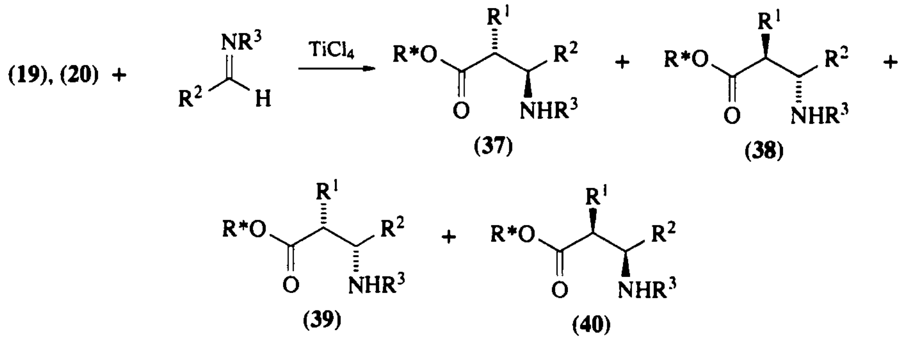
(19), (20) +
NR3
R2
H
TiCl4
R*O
R1
R2
O
NHR3
(37)
(38)
(39)
(40)

(15)

**Table 7** Ratio of Diastereoisomers in the $TiCl_4$-mediated Reactions of Chiral Silyl Ketene Acetals with Imines (equation 15)

| *Entry* | *Reagent* | *$R^1$* | *$R^2$* | *$R^3$* | *(37) + (38)/(39) + (40)* | *(37)/(38)* | *(39)/(40)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (**19**) | Me | Ph | Ph | 91.5/8.5 | 97.5/2.5 | — | 75 | 58, 62 |
| 2 | (**20**) | Et | $CO_2Et$ | $CH_2Ph$ | 11.1/88.9 | — | 75/25 | 53 | 58 |
| 3 | (**20**) | Et | $CO_2Et$ | *p*-$MeOC_6H_4$ | 12.5/87.5 | — | 87.5/12.5 | 70 | 58 |

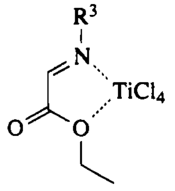
R3
N
TiCl4
O
O

(**41**)

Another case where simple stereoselection is reversed by the use of particular reagents is shown in Scheme 5; (**42**) was obtained as a single isomer (*syn*),[63] in contrast with the *anti* selectivity shown by achiral silyl ketene acetals with the same catalyst (Table 4, entries 3–5).

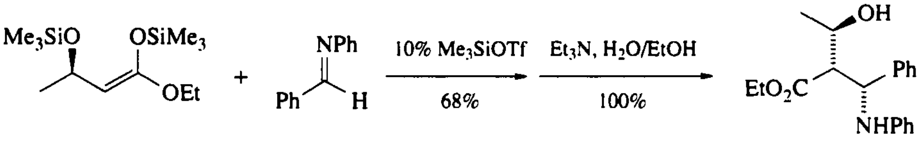
Me3SiO
OSiMe3
OEt
+
NPh
Ph
H
10% Me3SiOTf
68%
Et3N, H2O/EtOH
100%
OH
Ph
EtO2C
NHPh

(**42**)

Scheme 5

## 2.4.4 CHIRAL ELECTROPHILES

When the electrophile is chiral, besides simple stereoselection a second type of diastereoselectivity, termed 'diastereofacial selectivity', is possible. This sort of diastereofacial preference, qualitatively predictable by Cram's rule for asymmetric induction or one of its more modern descendants,[4a] is typical for additions to chiral aldehydes.

### 2.4.4.1 Diastereoselective Additions to Chiral Carbonyl Compounds

Chiral α-methyl aldehydes (**43**) show exceptional diastereofacial preferences in their Lewis acid mediated reactions with enol silanes (equation 16);[21,25c,26–64] selected data are reported in Table 8. The reason for this selectivity may be due to an approach trajectory of the nucleophile closer to the stereocenter when the carbonyl group is bound to the Lewis acid.[64] Additions to chiral α-alkoxy aldehyde (**48**) were studied with both nonstereogenic (equation 17; Table 9) and stereogenic enol silanes (equation 18; Table 10). (Stereogenic and nonstereogenic are defined according to Mislow and Siegel.)[170]

With nonstereogenic enol silanes (Table 9) usually (not always, see entry 2) a single isomer was obtained using tin(IV) chloride or titanium chloride as a promoter (entries 3, 5, 7 and 9). This high facial

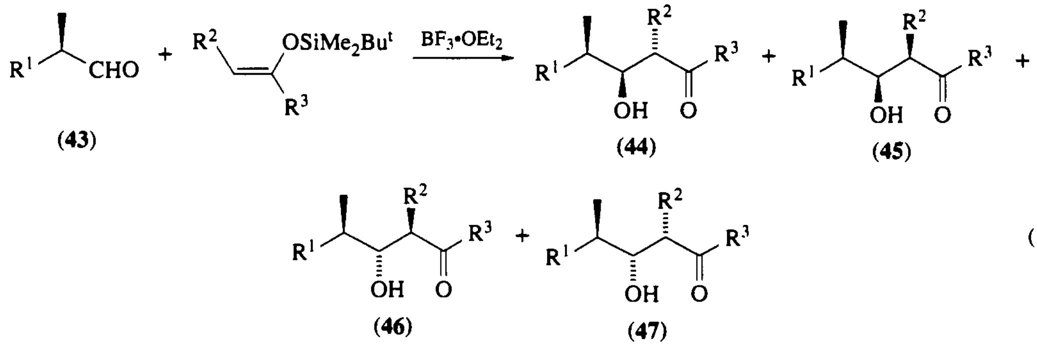

(16)

**Table 8** Ratio of Diastereoisomers in the $BF_3·OEt_2$-mediated Reactions of Enol Silanes with Chiral α-Methyl Aldehydes (equation 16)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *Yield (%)* | *(44)* | *(45)* | *(46)* | *(47)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | H | Me | 75 | 91 | — | 9 | — | 64 |
| 2 | Ph | H | $Bu^t$ | 74 | 96 | — | 4 | — | 64 |
| 3 | Ph | H | OMe | 81 | 94 | — | 6 | — | 64 |
| 4 | Ph | H | $OBu^t$ | 81 | 97 | — | 3 | — | 64 |
| 5 | Ph | Me | $SBu^t$ | 75 | 91 | 7 | 2 | 0 | 21 |
| 6 | $PhCH_2$ | H | $OBu^t$ | 88 | 72 | — | 28 | — | 64 |
| 7 | $Me_2C{=}CH$ | H | $OBu^t$ | 68 | 96 | — | 4 | — | 64 |
| 8 | $c\text{-}C_6H_{11}$ | H | $OBu^t$ | 77 | 94 | — | 6 | — | 64 |

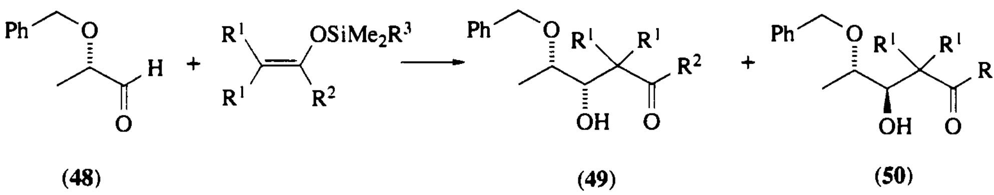

(17)

**Table 9** Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Aldehyde (**48**; equation 17)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *Promoter* | *Yield (%)* | *(49)* | *(50)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | H | OMe | $Bu^t$ | $BF_3·OEt_2$ | 48 | 60 | 40 | 10 |
| 2 | H | $OBu^t$ | $Bu^t$ | $SnCl_4$ | 65 | 65 | 35 | 10 |
| 3 | H | $SBu^t$ | $Bu^t$ | $SnCl_4$ | 50 | >98 | <2 | 80 |
| 4 | H | $Bu^t$ | Me | $BF_3$(gas) | 85 | 10 | 90 | 65a |
| 5 | H | $Bu^t$ | Me | $SnCl_4$ or $TiCl_4$ | 86 | >99 | <1 | 10, 66 |
| 6 | H | $Bu^t$ | Me | $BF_3·OEt_2$ | a | 50 | 50 | 67 |
| 7 | H | Ph | Me | $SnCl_4$ or $TiCl_4$ | 70 | >99 | <1 | 10, 68 |
| 8 | H | Ph | Me | $BF_3·OEt_2$ | a | 35 | 65 | 68 |
| 9 | Me | OMe | Me | $SnCl_4$ or $TiCl_4$ | 85 | >97 | <3 | 66 |
| 10 | Me | OMe | Me | $BF_3·OEt_2$ | 85 | 35 | 65 | 66 |
| 11 | Me | OMe | Me | $BF_3$(gas) | 85 | 16 | 84 | 65a |

[a] Not reported.

selectivity is due to the formation of a chelated complex between the aldehyde and the Lewis acid (*e.g.* **55**) and addition of the nucleophile to the less-encumbered face of the complex (to give **49**). A further remarkable example of this chelation control, taken from the synthesis of pestalotin, is shown in equation (19).[72]

The lack of facial selectivity in $BF_3{\cdot}OEt_2$-mediated reactions (entries 1, 6, 8 and 10) is not surprising as this Lewis acid is incapable of bis-ligation. Using an excess of gaseous $BF_3$ a conformationally rigid

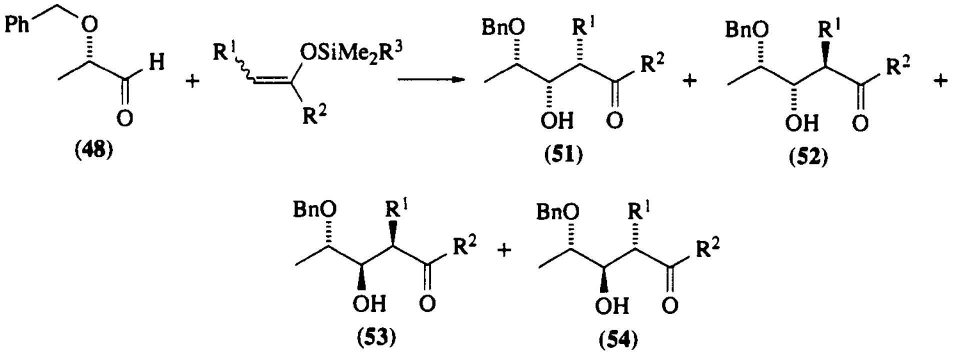

(18)

**Table 10** Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Aldehyde (**48**; equation 18)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(E)/(Z)* | *Promoter* | *Yield (%)* | *(**51**)* | *(**52**)* | *(**53**)* | *(**54**)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | Et | Me | 0/100 | $TiCl_4$ | a | 18 | 82 | 0 | 0 | 69a |
| 2 | Me | Et | Me | 34/66 | $TiCl_4$ | a | 44 | 56 | 0 | 0 | 69a |
| 3 | Me | $Pr^i$ | Me | 0/100 | $TiCl_4$ | 75 | 50 | 50 | 0 | 0 | 10 |
| 4 | Me | $Pr^i$ | Me | 100/0 | $TiCl_4$ | 73 | 88 | 12 | 0 | 0 | 10 |
| 5 | Me | $Bu^t$ | Me | 0/100 | $SnCl_4$ | 66 | 59 | 41 | 0 | 0 | 10, 70 |
| 6 | Me | $Bu^t$ | $Bu^t$ | 0/100 | $TiCl_4$ | 80 | 39 | 61 | 0 | 0 | 70 |
| 7 | Me | Ph | Me | 0/100 | $SnCl_4$ or $TiCl_4$ | 80 | 95 | 5 | 0 | 0 | 10, 68 |
| 8 | Me | Ph | Me | 100/0 | $TiCl_4$ | 73 | 85 | 15 | 0 | 0 | 10, 70 |
| 9 | Me | Ph | Me | 0/100 | TBAF | 60 | 18 | 0 | 82 | 0 | 65a |
| 10 | Me | $C(Me_2)OTMS$ | Me | 0/100 | $SnCl_4$ | 65 | 100 | 0 | 0 | 0 | 70 |
| 11 | Me | OMe | Me | 83/17 | $TiCl_4$ | 75 | 77 | 23 | 0 | 0 | 69, 70 |
| 12 | Me | OMe | Me | 83/17 | $SnCl_4$ | 75 | 80 | 20 | 0 | 0 | 69, 70 |
| 13 | Me | $OBu^t$ | Me | 0/100 | $TiCl_4$ or $SnCl_4$ | a | 58 | 31 | 7 | 4 | 69a |
| 14 | Me | $SBu^t$ | Me | 93/7[b] | $SnCl_4$ | 90 | 95 | 5 | 0 | 0 | 21, 71 |
| 15 | Me | $SBu^t$ | Me | 10/90[b] | $SnCl_4$ | 87 | 85 | 15 | 0 | 0 | 21, 71 |
| 16 | Me | $SBu^t$ | $Bu^t$ | >95/5[b] | $SnCl_4$ | 89 | 97 | 3 | 0 | 0 | 21, 71 |
| 17 | Me | $SBu^t$ | $Bu^t$ | <5/95[b] | $SnCl_4$ | 90 | 76 | 24 | 0 | 0 | 21, 71 |
| 18 | Me | $SBu^t$ | Me | 93/7[b] | $TiCl_4$ | 85 | 94 | 6 | 0 | 0 | 21 |
| 19 | Me | $SBu^t$ | Me | 10/90[b] | $TiCl_4$ | 82 | 83 | 17 | 0 | 0 | 21 |
| 20 | Me | $SBu^t$ | Me | 93/7[b] | TBAF | 72 | 16 | 3 | 73 | 8 | 21, 71 |
| 21 | Me | $SBu^t$ | Me | 10/90[b] | TBAF | 68 | 13 | 3 | 72 | 12 | 21, 71 |
| 22 | Me | $SBu^t$ | Me | 93/7[b] | $BF_3{\cdot}OEt_2$ | 57 | 6 | 22 | 12 | 60 | 21 |

[a] Not reported. [b] See footnote d of Table 1.

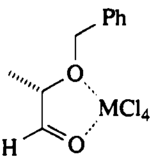

**(55)**

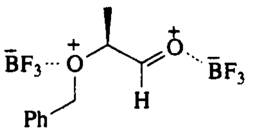

**(56)**

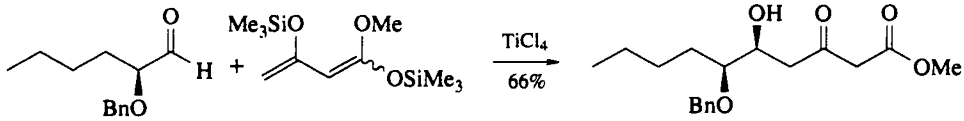

(19)

*syn*:*anti* = 99:1

complex such as (**56**) is likely to form due to electrostatic repulsion.[65a] Addition of the nucleophile to the less encumbered face of complex (**56**) gives the opposite stereoisomer (**50**; entries 4 and 11). With stereogenic enol silanes (Table 10) usually two (**51** and **52**) of the four possible diastereoisomers were obtained using tin(IV) chloride or titanium chloride. In particular cases [propiophenone silyl enol ethers (entries 7 and 8), Heathcock's reagent (entry 10), thiol ester silyl ketene acetals (entries 14–19)] mainly one (**51**) of the four possible isomers was obtained. The predominant isomer (**51**) is the result of *syn* simple stereoselection (at C-2, C-3), in agreement with the general principle that chelation controls (usually inverts) simple stereoselection (the same enol silanes are *anti* selective in their reactions with aldehydes incapable of chelation, see Table 1, entries 6–12). To rationalize these results the four staggered transition structures shown in Figure 4 were proposed.[10,21,71] The other eight possible staggered transition structures (not shown) were discarded because of steric interactions between the ligands of the chelated metal and $R^1$, Me or OTMS. For (*E*)-isomers the size of the $R^1$ group should not affect stereochemistry since $R^1$ interacts only with the aldehydic hydrogen in both $S_l$ and $A_l$. $S_l$ is favored over $A_l$ because of the unfavorable dipole–dipole interactions between the two C—O bonds. As a result, the (*E*)-isomers are C-2,C-3 *syn* selective and in about the same degree (Table 10, entries 4, 8, 15, 17 and 19). For the (*Z*)-isomers the $R^1$ group interacts with C-2 in transition structure $S_l$ and with the metal ligands in transition structure $A_l$. As a result the C-2,C-3 *syn*:*anti* ratios are related in some manner to the steric demand of $R^1$ (entries 1, 3 and 5) and are excellent only in particular cases (entries 7, 10, 14, 16 and 18). Fluoride ion catalyzed reactions (Table 10, entries 9, 20 and 21) gave (**53**) as the major stereoisomer, as a result of *syn* simple stereoselection (see Table 2), and diastereofacial selection predicted by the Felkin–Anh model.[4a] Note that silyl ketene acetals derived from thiol esters have opposite (*E*)/(*Z*) descriptors compared to esters and ketones due to change of sequence rule priority associated with the sulfur atom.

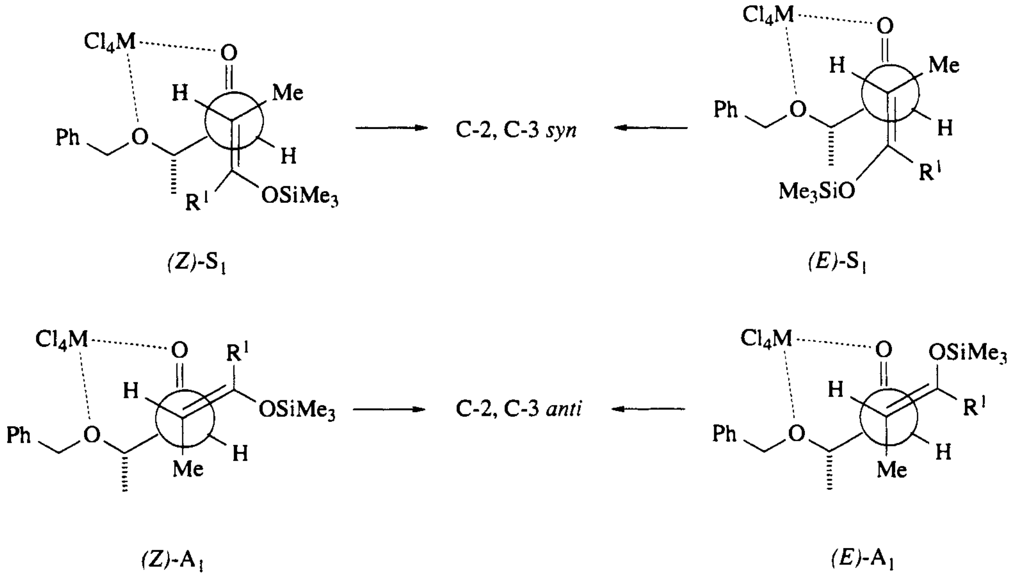

**Figure 4**

Additions of heteroatom-substituted enol silanes to aldehyde (**48**) were studied by several groups (equations 18 and 20);[73–78] significant results are reported in Tables 11 and 12. High facial selectivity (chelation control) was obtained in most cases using magnesium bromide as Lewis acid, whereas tin or titanium tetrachloride generally gave worse results. Simple stereoselection was found to be dependent on the Lewis acid (Table 12; entries 3–5) and on the type of heteroatom (Table 12; entries 6, 7 and 9). It is clear that the heteroatom can interfere with the formation of the aldehyde–Lewis acid chelated complex (**55**) causing different stereochemical outcomes when the metal in such a complex is coordinatively saturated (Sn, Ti) or unsaturated (Mg, Zn). Complete ratios are not available for the methylthio derivatives as the adducts were desulfurized by reduction (Raney Ni)[76] or elimination ($NaIO_4$; heat)[73,74] to give acetate or acrylate derivatives.

Additions to α,β-dialkoxy aldehydes (protected glyceraldehydes) are complicated by the possibility of chelation involving either the α or β alkoxy group. With 2,3-*O*-isopropylideneglyceraldehyde (**62**; equations 21 and 22) and $ZnI_2$ as catalyst, a preponderance of the β-chelated complex (**63**) was obtained with consequent formation of the C-3,C-4 *anti* compounds as major isomers (Table 13, entries 1–3; Table 14,

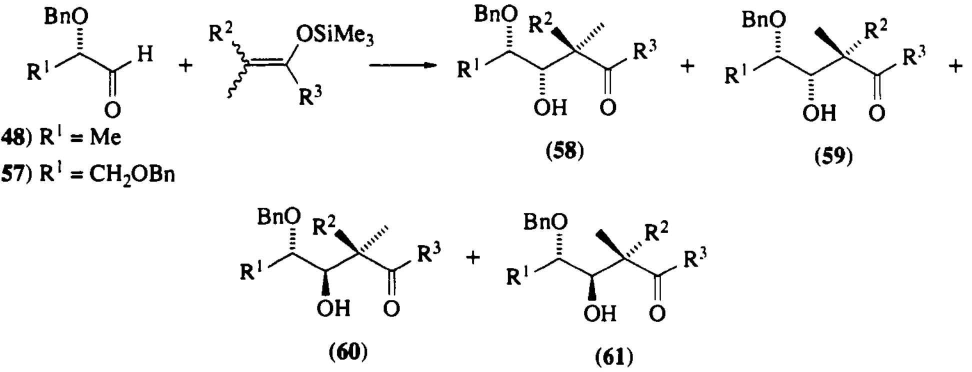
(48) $R^1$ = Me
(57) $R^1$ = $CH_2OBn$
(58) (59) (60) (61)
(20)

**Table 11** Ratio of Diastereoisomers in the Reactions of Heteroatom-substituted Enol Silanes with Chiral α-Alkoxy Aldehydes (equation 20)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(E)/(Z)* | *Promoter* | *Yield (%)* | **(58)** | **(59)** | **(60)** | **(61)** | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | SMe | OMe | a | $MgBr_2$ | 50 | ( 95 | ) | ( 5 | ) | 73, 74 |
| 2 | Me | OMe | OTMS | — | $SnCl_4$ | a | 95 | 5 | | 0 | 75 |
| 3 | $CH_2OCH_2Ph$ | SMe | OMe | a | $MgBr_2$ | 45 | ( 95 | ) | ( 5 | ) | 73, 74 |
| 4 | $CH_2OCH_2Ph$ | SMe | OMe | a | $SnCl_4$ | 50 | ( 25 | ) | ( 75 | ) | 74 |

[a] Not reported.

**Table 12** Ratio of Diastereoisomers in the Reactions of Heteroatom-substituted Enol Silanes with Aldehyde (**48**; equation 18)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(E)/(Z)* | *Promoter* | *Yield (%)* | **(51)** | **(52)** | **(53)** | **(54)** | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | SMe | Me | Me | 80/20 | $MgBr_2$ | 70 | ( 99 | ) | ( 1 | ) | 76 |
| 2 | SMe | $OBu^t$ | Me | a | $MgBr_2$ | 55 | ( 96 | ) | ( 4 | ) | 76 |
| 3 | $OCH_2Ph$ | OTMS | Me | — | $MgBr_2$ | 28 | 80 | 19 | 1 | 0 | 77 |
| 4 | $OCH_2Ph$ | OTMS | Me | — | $ZnCl_2$ | 54 | 39 | 61 | 0 | 0 | 77 |
| 5 | $OCH_2Ph$ | OTMS | Me | — | $Eu(fod)_3$ | 53 | 9 | 80 | 11 | 0 | 77 |
| 6 | $N(CH_2Ph)_2$ | $OBu^t$ | Me | a | $MgBr_2$ | 40 | 1.5 | 97 | 0 | 1.5 | 78 |
| 7 | $N(CH_2Ph)_2$ | $OBu^t$ | Me | a | $SnCl_4$ | 50 | 16 | 82.5 | 0 | 1.5 | 78 |
| 8 | $CH_2SMe$ | OMe | Me | a | $MgBr_2$ | 78 | ( 99 | ) | ( 1 | ) | 73 |
| 9 | $CH_2OCH_2Ph$ | OMe | Me | a | $MgBr_2$ | 81 | 75 | 25 | 0 | 0 | 73 |

[a] Not reported.

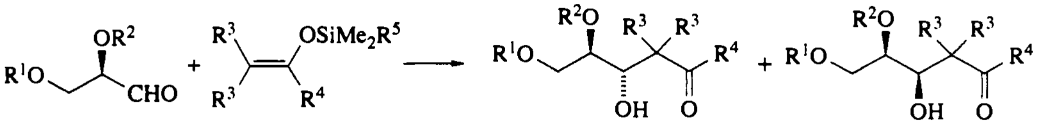
(62) $R^1$, $R^2$ = $-CMe_2-$
(66) $R^1$ = $Bu^tMe_2Si$; $R^2$ = Bn
(64) (65)
(21)

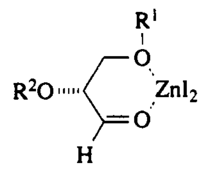
(63) $R^1$,$R^2$ = $-CMe_2-$

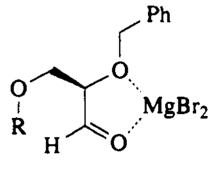
(69)

entries 1–4).[79] With protected glyceraldehydes (**57**, **66** and **67**; equations 20–22) the α-chelated complex (**69**) can effectively compete, with consequent formation of the C-3,C-4 *syn* compounds as major isomers (Table 11, entry 3; Table 13, entry 4; Table 14, entries 5–7). Additions of nonstereogenic enol silanes to α-methyl-β-alkoxy aldehyde (**74**; equation 23) are reported in Table 15. High selectivity (che-

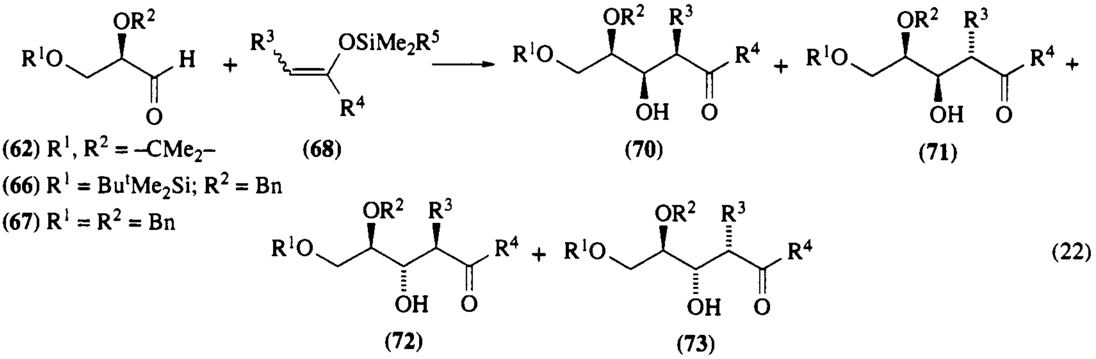
**(62)** $R^1, R^2 = -CMe_2-$ **(68)** **(70)** **(71)**

**(66)** $R^1 = Bu^tMe_2Si$; $R^2 = Bn$

**(67)** $R^1 = R^2 = Bn$

**(72)** **(73)** (22)

**Table 13** Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Chiral α,β-Dialkoxy Aldehydes (equation 21)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *$R^5$* | *Promoter* | *Yield (%)* | *(64)* | *(65)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | —$CMe_2$— | | H | OMe | $Bu^t$ | $ZnI_2$[a] | 67 | 96 | 4 | 79a |
| 2 | —$CMe_2$— | | Me | OMe | Me | $ZnI_2$[a] | 70 | 91 | 9 | 79a |
| 3 | —$CMe_2$— | | F | OMe | $Bu^t$ | $ZnI_2$ | 66 | 94.5 | 5.5 | 79b |
| 4 | TBDMS | Bn | H | OMe | Me | $SnCl_4$ | 90 | <2 | >98 | 65b, 69b |

[a] Catalytic amount.

**Table 14** Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Chiral α,β-Dialkoxy Aldehydes (equation 22)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *$R^5$* | *(E)/(Z)* | *Promoter* | *Yield (%)* | *(70)* | *(71)* | *(72)* | *(73)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | —$CMe_2$— | | Me | OMe | Me | 100/0 | $ZnI_2$[a] | 50 | ( 12 ) | | 64 | 24 | 79a |
| 2 | —$CMe_2$— | | Me | OMe | $Bu^t$ | 0/100 | $ZnI_2$[a] | 65 | ( 10 ) | | 76 | 14 | 79a |
| 3 | —$CMe_2$— | | Et | OMe | $Bu^t$ | 0/100 | $ZnI_2$[a] | 45 | ( 6 ) | | 84 | 10 | 79a |
| 4 | —$CMe_2$— | | Et | OMe | $Bu^t$ | 100/0 | $ZnI_2$[a] | 57 | ( 8 ) | | 83 | 9 | 79a |
| 5 | TBDMS | $CH_2Ph$ | Me | Ph | Me | 0/100 | $SnCl_4$ | 90 | 94 | 0 | 0 | 6 | 65b |
| 6 | $CH_2Ph$ | $CH_2Ph$ | Me | $SBu^t$ | $Bu^t$ | >95/5 | $SnCl_4$ | 75 | >95 | <5 | 0 | 0 | 21 |
| 7 | $CH_2Ph$ | $CH_2Ph$ | $CH_2SMe$ | OMe | Me | b | $MgBr_2$ | 67 | ( 98 ) | | ( 2 ) | | 73 |

[a] Catalytic amount, [b] Not reported.

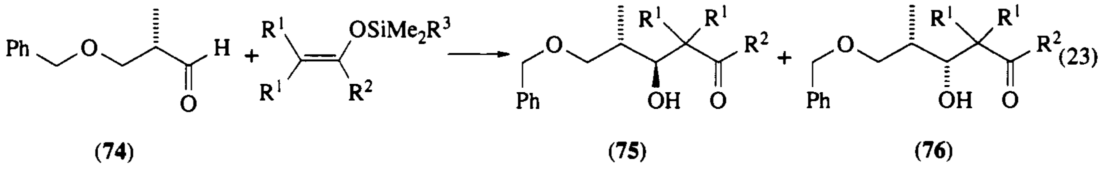
**(74)** **(75)** **(76)** (23)

**Table 15** Ratio of Diastereoisomers in the Reactions of Nonstereogenic Enol Silanes with Aldehyde (**74**; equation 23)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *Promoter* | *Yield (%)* | *(75)* | *(76)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | H | $Bu^t$ | Me | $TiCl_4$ | a | 95 | 5 | 65a, 69a |
| 2 | Me | OMe | Me | $TiCl_4$ | a | >97 | <3 | 65a, 69a, 69b |
| 3 | H | $SBu^t$ | $Bu^t$ | $TiCl_4$ | 80 | ≥97 | ≤3 | 80 |
| 4 | H | $OBu^t$ | $Bu^t$ | $TiCl_4$ | 45 | 50 | 50 | 80 |
| 5 | H | $Bu^t$ | Me | $BF_3$(gas) | a | 12 | 88 | 65a, 69a |
| 6 | Me | OMe | Me | $BF_3$(gas) | a | 55 | 45 | 65a |
| 7 | H | $Bu^t$ | Me | $BF_3 \cdot OEt_2$ | a | 23 | 77 | 65a |

[a] Not reported.

lation control) was obtained with $TiCl_4$ (entries 1–3) due to the formation of the 1:1 complex (**77**), which was shown to be quite rigid and essentially conformationally locked.[8a,b] The other stereoisomer was obtained with $BF_3$ *via* the 1:2 complex (**79**; entries 5–7). Additions of stereogenic enol silanes to aldehyde (**74**; equation 24) are reported in Table 16. Excellent ratios were obtained with thiol ester silyl ketene

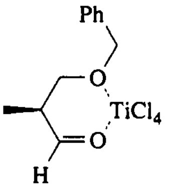

**(77)**

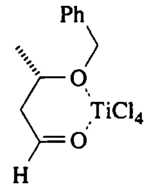

**(78)**

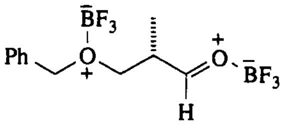

**(79)**

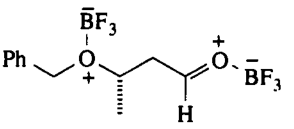

**(80)**

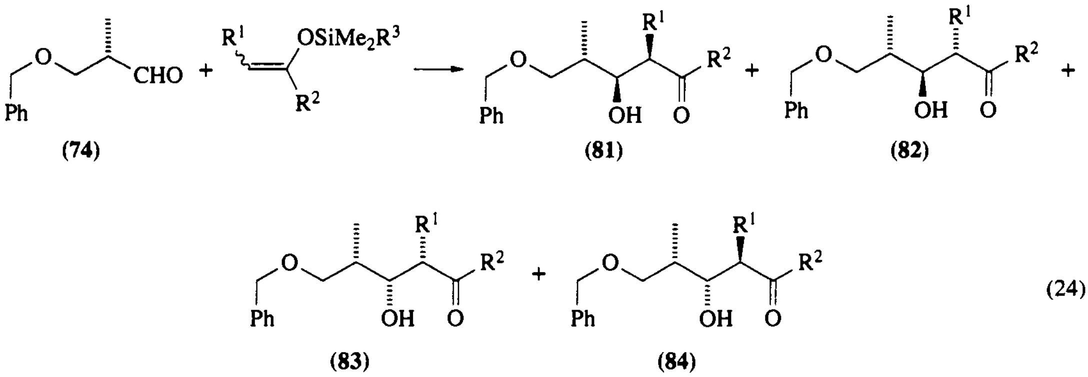
(74)
(81)
(82)
(83)
(84)

(24)

Table 16 Ratio of Diastereoisomers in the Reactions of Stereogenic Enol Silanes with Aldehyde (**74**; equation 24)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(E)/(Z)* | *Promoter* | *Yield (%)* | *(**81**)* | *(**82**)* | *(**83**)* | *(**84**)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | Ph | Me | 0/100 | $TiCl_4$ | >90 | 91 | 9 | 0 | 0 | 69a |
| 2 | Me | Et | Me | 0/100 | $TiCl_4$ | a | 50 | 50 | 0 | 0 | 69a |
| 3 | Me | $SBu^t$ | $Bu^t$ | >95/5[b] | $TiCl_4$ | 67 | >99 | <1 | 0 | 0 | 21, 59 |
| 4 | Me | $SBu^t$ | $Bu^t$ | <5/95[b] | $TiCl_4$ | 65 | >99 | <1 | 0 | 0 | 21, 59 |
| 5 | Me | $SBu^t$ | Me | 93/7[b] | $SnCl_4$ | 65 | 97 | 3 | 0 | 0 | 21 |
| 6 | Me | $SBu^t$ | Me | 10/90[b] | $SnCl_4$ | 69 | 46 | 3 | 0 | 51 | 21 |
| 7 | Me | $SBu^t$ | $Bu^t$ | >95/5[b] | $BF_3 \cdot OEt_2$[c] | 75 | 0 | 9 | 14 | 77 | 21, 59 |
| 8 | Me | $SBu^t$ | $Bu^t$ | <5/95[b] | $BF_3 \cdot OEt_2$[c] | 71 | 0 | 7 | 16 | 77 | 21, 59 |
| 9 | Et | $SBu^t$ | $Bu^t$ | <5/95[b] | $TiCl_4$ | 75 | 96 | ( | 4 | ) | 60 |
| 10 | Et | $SBu^t$ | $Bu^t$ | >95/5[b] | $TiCl_4$ | 80 | 99 | ( | 1 | ) | 60 |

[a] Not reported. [b] See footnote d of Table 1. [c] 2 mol. equiv.

acetals and $TiCl_4$ (entries 3, 4, 9 and 10) as a result of chelation control (C-3,C-4 *anti*) and *syn* simple stereoselection (C-2,C-3 *syn*). Staggered transition structures, analogous to the ones reported in Figure 4 for α-alkoxy aldehydes, were suggested in order to rationalize the high selectivity irrespective of the double bond geometry.[21,59] It is possible to obtain complete nonchelation control by changing the protecting group of the β-alkoxy aldehyde from benzyl to $Et_3Si$ or $Me_2Bu^tSi$;[8b] two examples taken from total syntheses of natural products are shown in Scheme 6[81] and Scheme 7.[82]

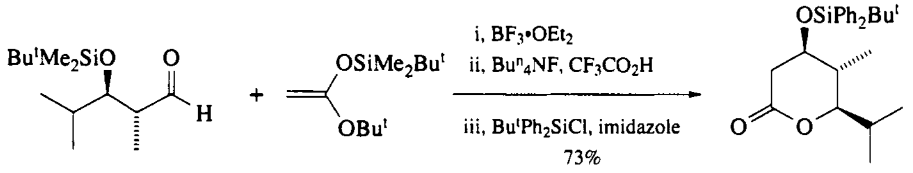
$Bu^tMe_2SiO$
O
H
+
$OSiMe_2Bu^t$
$OBu^t$
i, $BF_3 \cdot OEt_2$
ii, $Bu^n{}_4NF$, $CF_3CO_2H$
iii, $Bu^tPh_2SiCl$, imidazole
73%
$OSiPh_2Bu^t$
O
O

**Scheme 6**

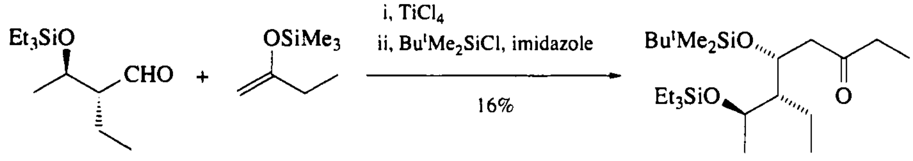
$Et_3SiO$
CHO
+
$OSiMe_3$
i, $TiCl_4$
ii, $Bu^tMe_2SiCl$, imidazole
16%
$Bu^tMe_2SiO$
$Et_3SiO$
O

**Scheme 7**

Additions of enol silanes to β-alkoxy aldehyde (**85**; equation 25) are reported in Table 17. High selectivity (chelation control) was obtained with $TiCl_4$ *via* complex (**78**; entries 1, 2).[8a,b] The same preference for isomers (**86**) and (**87**) was obtained with $BF_3$ *via* complex (**80**), which simulates chelation.[65a,66] The influence of chelation on simple stereoselection is also evident in the reactions of achiral aldehydes (**90**) and (**92**) with silyl enol ethers (*Z*)-(**91**) and (*E*)-(**93**), which are usually moderately *anti* selective in their reactions with aldehydes incapable of chelation;[10] high *syn* selectivity was obtained irrespective of the enol ether geometry (equations 26 and 27).[69,70]

$TiCl_4$-mediated addition of silyl enol ether (**95**) to chiral α-amino aldehyde (**94**) was reported to proceed with good chelation control, albeit in poor yield (equation 28).[84] Effective chelation control was also reported in the $TiCl_4$-mediated reactions of chiral α-alkoxy and β-alkoxy acyl cyanides (**96**) and (**97**) with silyl enol ether (**95**; equations 29 and 30).[69b,85] Reaction of acyl cyanide (**97**) with the (*E*)-silyl enol ether (**93**) gave a single stereoisomer as a result of complete chelation control and *syn* simple stereoselection (equation 31).[85] Additions of silyl enol ethers and silyl ketene acetals to (–)-menthyl phenylglyoxylate and pyruvate were reported to proceed with moderate facial selectivity; the best result (84:16) is shown in equation (32).[86]

**Table 17** Ratio of Diastereoisomers in the Reactions of Enol Silanes with Aldehyde (**85**; equation 25)

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *(E)/(Z)* | *Promoter* | *Yield (%)* | *(**86**)* | *(**87**)* | *(**88**)* | *(**89**)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | Ph | Me | — | $TiCl_4$ | 95 | 92 | — | 8 | — | 69b, 83 |
| 2 | Me | Ph | Me | 0/100 | $TiCl_4$ | 95 | 92 | ( | 8 | ) | 70, 83 |
| 3 | H | Ph | Me | — | $BF_3$(gas) | 82 | 85 | — | 15 | — | 66 |
| 4 | Me | Ph | Me | 0/100 | $BF_3$(gas) | a | 55 | 27 | 12 | 6 | 66 |

[a] Not reported.

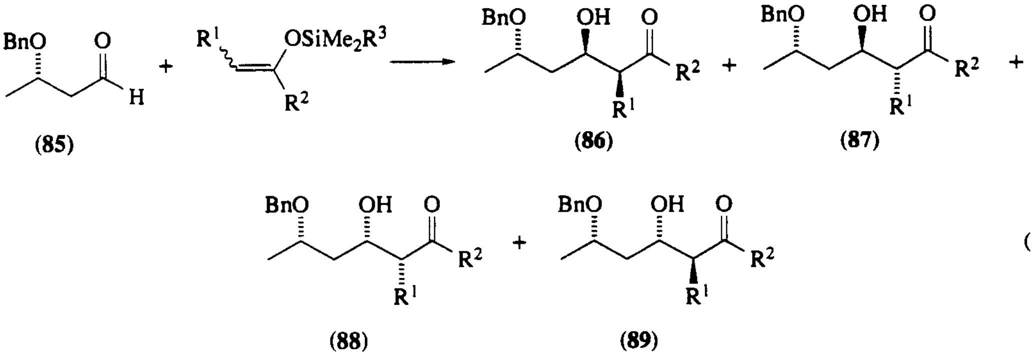
BnO
O
H
R1
OSiMe2R3
R2
BnO OH O
R2
R1
BnO OH O
R2
R1
BnO OH O
R2
R1
BnO OH O
R2
R1
(85)
(86)
(87)
(88)
(89)

(25)

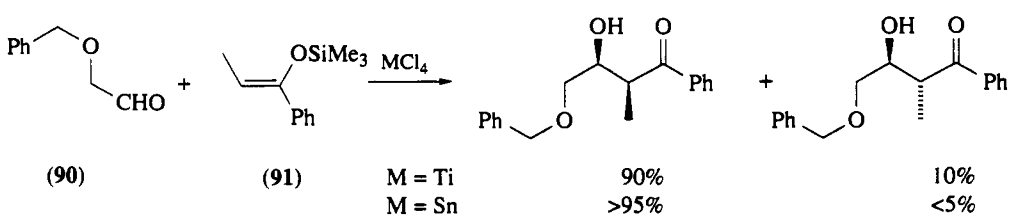
Ph
O
CHO
OSiMe3
Ph
MCl4
OH O
Ph
Ph
O
OH O
Ph
Ph
O
(90)
(91)
M = Ti
M = Sn
90%
>95%
10%
<5%

(26)

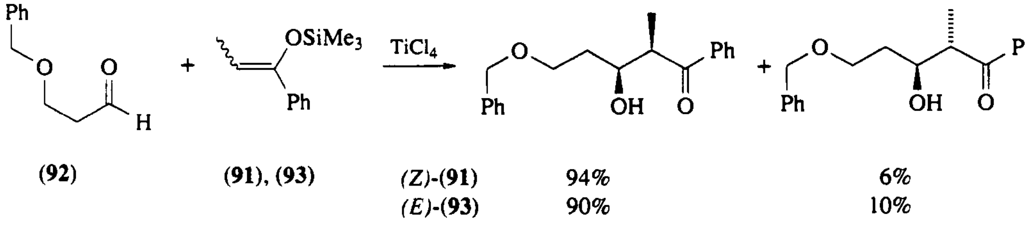
Ph
O
O
H
OSiMe3
Ph
TiCl4
O
Ph
Ph
OH O
O
Ph
Ph
OH O
(92)
(91), (93)
(Z)-(91)
(E)-(93)
94%
90%
6%
10%

(27)

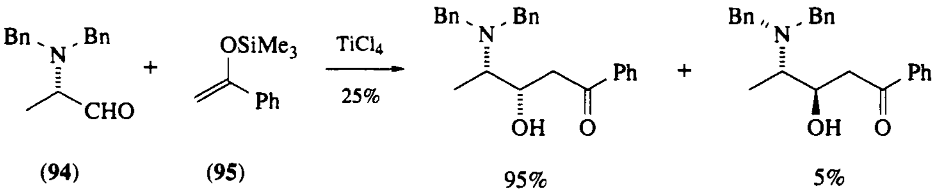
Bn
N
Bn
CHO
+
OSiMe3
Ph
TiCl4
25%
Bn
N
Bn
Ph
OH
O
+
Bn
N
Bn
Ph
OH
O
(94)
(95)
95%
5%

(28)

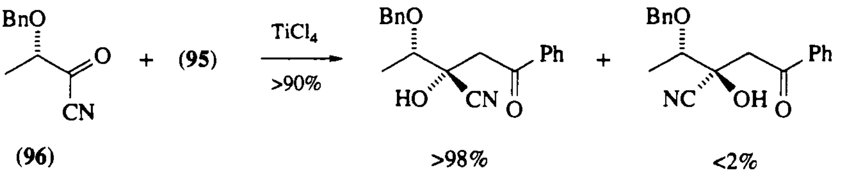
BnO
O
CN
+
(95)
TiCl4
>90%
BnO
Ph
HO
CN
O
+
BnO
Ph
NC
OH
O
(96)
>98%
<2%

(29)

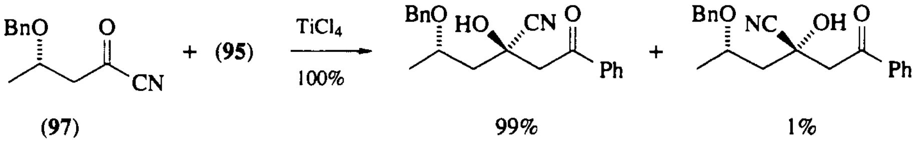
BnO
O
CN
+
(95)
TiCl4
100%
BnO
HO
CN
O
Ph
+
BnO
NC
OH
O
Ph
(97)
99%
1%

(30)

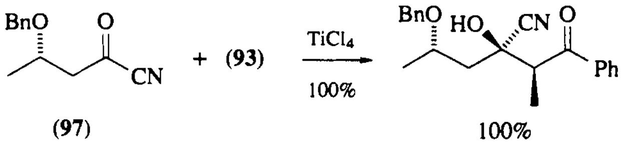
BnO
O
CN
+
(93)
TiCl4
100%
BnO
HO
CN
O
Ph
(97)
100%

(31)

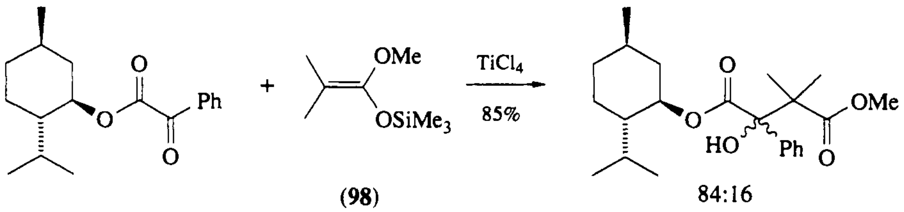
O
Ph
O
O
+
OMe
OSiMe3
TiCl4
85%
O
O
OMe
HO
Ph
O
(98)
84:16

(32)

### 2.4.4.2 Diastereoselective Addition to Chiral Imines, Nitrones and 4-Acetoxyazetidin-2-ones

$TiCl_4$-mediated additions of silyl ketene acetal (**98**) to chiral imines (**99**) and (**100**) (R = Et, $Pr^n$, $Bu^n$, $Bu^i$) are described in equations (33) and (34); good diastereoisomeric ratios were obtained using imines (**100**), derived from (*S*)-valine methyl ester, which form with $TiCl_4$ the chelated complex (**101**).[87] $ZnI_2$-catalyzed additions of acetate-derived silyl ketene acetals to chiral α,β-dialkoxy nitrones (**102**; $R^1$ = H) were reported to proceed with good yield (86–100%) and high diastereofacial selectivity (*ca.* 90:10) in favor of the *anti* isomer (**103**; $R^1$ = H, $R^2$ = $CHPh_2$, $R^3$ = $Bu^t$) or of the *syn* isomer (**104**; $R^1$ = H, $R^2$ = $CH_2Ph$, $R^3$ = Me) depending on the steric hindrance of $R^2$ and $R^3$ (Scheme 8).[88a] Addition to nitrone (**102**; $R^1$ = Me) gave the *anti* isomer (**103**; $R^1$ = Me, $R^2$ = CHMePh, $R^3$ = Me) in quantitative yield and 100% diastereofacial selectivity. This material was further elaborated to *N*-benzoyl-L-daunosamine (Scheme 8).[88b]

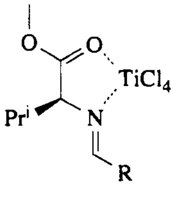
O
O
TiCl4
Pri
N
R

(**101**)

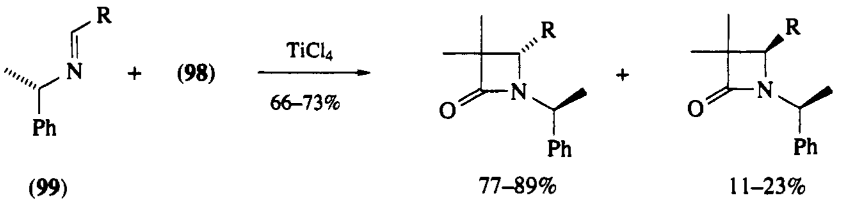
(98)
TiCl4
66–73%
(99)
77–89%
11–23%

(33)

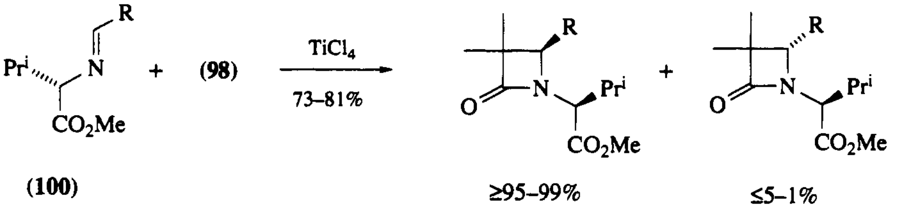
(98)
TiCl4
73–81%
(100)
≥95–99%
≤5–1%

(34)

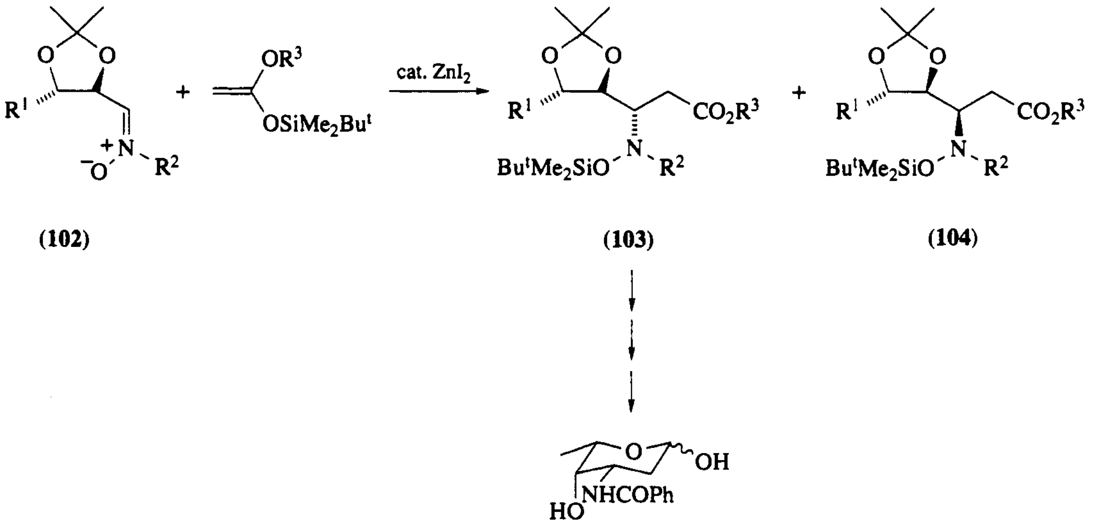
cat. ZnI2
(102)
(103)
(104)

**Scheme 8**

Lewis acid mediated additions to chiral 4-acetoxyazetidin-2-ones (**105**) have been shown to proceed through azetinones (**106**) by trapping this reactive intermediate with silyloxydienes.[89,90] Enol silane additions to (**105**) were reported to give good yields of 100% *trans*-azetidinones (**107**; equation 35); results relevant for the synthesis of carbapenem antibiotics (PS-5, thienamycin and analogs) are shown in Table 18 (entries 1–8).[91–97a] Reactions with stereogenic enol silanes (equation 36) gave mixtures of the β-isomer (**108**) and the undesired α-isomer (**109**; Table 19, entries 1–5).[96,97c,98]

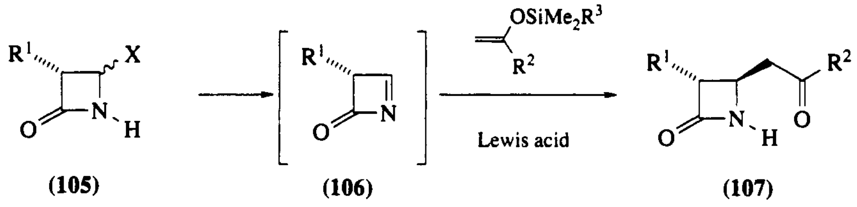
Lewis acid
(105)
(106)
(107)

(35)

**Table 18** Lewis Acid Mediated Reactions of Enol Silanes with Chiral Azetinones (**106**) and (**111**) (equations 35 and 37)

| *Entry* | *X* | *R* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *Lewis acid* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | OAc | — | (*R*)-MeCH(OH) | C(N$_2$)CO$_2$Bn | Me | ZnI$_2$ | 81 | 91 |
| 2 | OAc | — | (*R*)-MeCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Bu$^t$ | ZnCl$_2$ | 84 | 92 |
| 3 | OAc | — | (*S*)-MeCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Bu$^t$ | ZnCl$_2$ | 83 | 93 |
| 4 | OAc | — | Et | C(N$_2$)CO$_2$Bn | Bu$^t$ | ZnCl$_2$ | 63–83 | 94, 95 |
| 5 | OAc | — | Et | C(N$_2$)CO$_2$Bn | Me | TMSOTf$^a$ | 55 | 96 |
| 6 | OAc | — | (*R*)-MeCH(OBz) | OEt | Me | ZnI$_2$ | 60 | 96 |
| 7 | Cl | — | (*R*)-MeCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Bu$^t$ | AgBF$_4$ | 64 | 97a |
| 8 | OAc | — | (*R*)-MeCH(OTBDMS) | CH═CHPh | Bu$^t$ | ZnCl$_2$ | 72 | 89 |
| 9 | OAc | TMS | (*S*)-MeO$_2$CCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Me | TMSOTf$^a$ | 64 | 99 |
| 10 | OAc | TMS | (*R*)-MeCH(OCO$_2$Bn) | SPh | Me | TMSOTf$^a$ | 93 | 100 |
| 11 | OAc | TMS | (*R*)-MeCH(OTBDMS) | OBn | Me | TMSOTf$^a$ | 91 | 100 |
| 12 | OAc | TMS | (*R*)-MeCH(OBz) | C(N$_2$)CO$_2$Bn | Me | TMSOTf$^a$ | 90 | 96 |
| 13 | Cl | TBDMS | (*R*)-MeCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Me | AgBF$_4$ | 70 | 97b |
| 14 | OAc | TMS | (*R*)-MeCH(OTBDMS) | SPh | Me | TMSOTf$^a$ | 83 | 100, 101 |
| 15 | OAc | CH$_2$TMS | PhthN | Tol | Me | TMSOTf$^a$ | 70 | 102 |

$^a$ Catalytic amount.

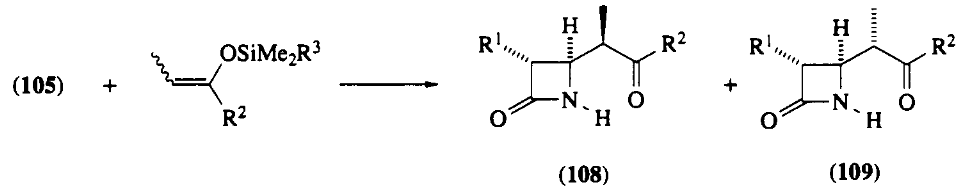

(36)

**Table 19** Lewis Acid Mediated Reactions of Stereogenic Enol Silanes with Chiral Azetinones (**106**) and (**111**) (equations 36 and 37)

| *Entry* | *X* | *R* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *Promoter* | (**108**)/(**109**) | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | OAc | — | (*R*)-MeCH(OTBDMS) | C(N$_2$)CO$_2$Bn | Bu$^t$ | TMSOTf$^a$ | 33/67 | 85 | 98 |
| 2 | OAc | — | (*R*)-MeCH(OTBDMS) | OMe | Me | TMSOTf$^a$ | 48/52 | 75 | 98 |
| 3 | OAc | — | (*R*)-MeCH(OTBDMS) | SPh | Me | TMSOTf$^a$ | 5/95 | 87 | 98 |
| 4 | OAc | — | (*R*)-MeCH(OTBDMS) | OMe | Me | ZnI$_2$ | 50/50 | b | 96 |
| 5 | OAc | — | (*R*)-MeCH(OTBDMS) | CH$_2$CO$_2$Me | Me | SnCl$_2$ | 69/31 | 70 | 97c |
| 6 | OAc | TMS | (*R*)-MeCH(OTBDMS) | OMe | Me | TMSOTf$^a$ | 28/72 | 94 | 103 |
| 7 | OAc | TMS | (*R*)-MeCH(OTBDMS) | SPh | Me | TMSOTf$^a$ | 62/38 | 81 | 103 |

$^a$ Catalytic amount. $^b$ Not reported.

### 2.4.4.3 Diastereoselective Additions to Chiral Iminium, Oxonium and Thionium Ions

When the nitrogen of 4-acetoxyazetidin-2-ones is protected (**110**; R = TMS, TBDMS, CH$_2$TMS), the Lewis acid catalyzed condensation occurs through the corresponding iminium salt (**111**; equation 37); illustrative examples of this process yielding 100% *trans*-azetidinones are reported in Table 18 (entries 9–15) and Table 19 (entries 6 and 7). Iminium ions have also been invoked as intermediates in enol silane additions to chiral bromides (**112**; equation 38); predominant attack from the less encumbered α-face gives the *anti* adduct (**113**) as the major stereoisomer (93.5:6.5).[104] Additions to thionium ions[105] have been shown to proceed with excellent diastereofacial selectivity (equation 39); the product predicted by the Felkin–Anh model (**114**) was obtained as the major isomer not only when R is Ph or cyclohexyl (>98:2) but also when it is benzyl (97:3) or Et (83:17).[106] This behavior is consistent with an approach trajectory of the nucleophile very close to the stereocenter, in analogy with the Lewis acid mediated additions to chiral α-methyl aldehydes (see Section 2.4.4.1 and Table 8).[64,106] Highest selectivity required the use of bulky mesitylthio derivatives, while with phenyl-substituted thionium ions ratios were lower (80:20). The addition of a silyl enol ether to an α-chiral phenyl-substituted thionium ion was applied (ZnBr$_2$ as catalyst) in a macrolide total synthesis and reported to proceed with 100% facial selectivity in favor of the 'Felkin–Anh stereoisomer';[107] the very high facial selectivity in this reaction is probably due to use of a more-substituted silyl enol ether combined with a more sterically biased substrate.

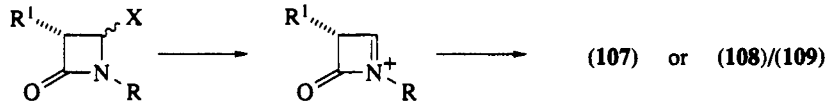

R¹
X
O
N
R
R¹
N+
O
R
(107) or (108)/(109)

**(110)** **(111)**

(37)

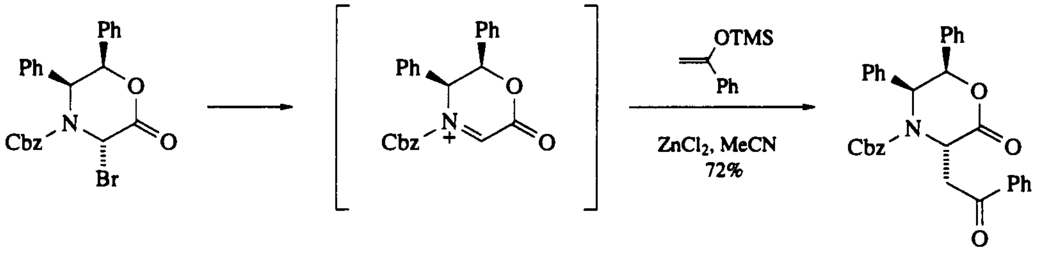

Ph
Ph
O
Cbz
N
O
Br
Ph
Ph
O
Cbz
N
+
O
OTMS
Ph
ZnCl2, MeCN
72%
Ph
Ph
O
Cbz
N
O
Ph
O

**(112)** **(113)**

(38)

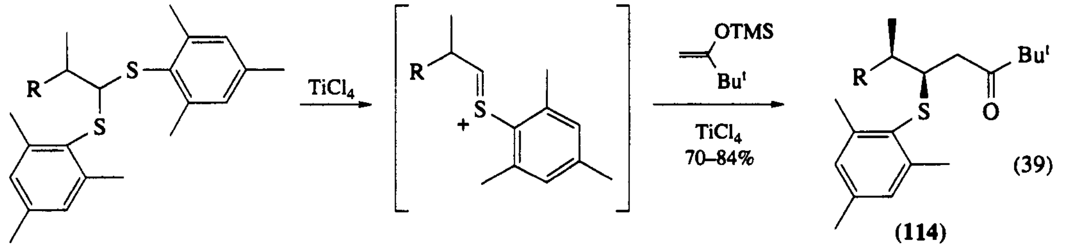

R
S
S
TiCl4
R
S
+
OTMS
Bu^t
TiCl4
70–84%
R
Bu^t
S
O

**(114)**

(39)

Enol silane additions to chiral oxonium ions have been shown to proceed with good stereoselectivity.[39c,d] In the field of *C*-glycoside synthesis, selective β-glycosylation was realized *via* neighboring group participation of a 2α-acyl group.[108] In the case of 2-deoxy sugars the neighboring participation of a group at the 3α-position was exploited for selective formation of the β-anomer (**115**; β:α = 91:9; equation 40).[109]

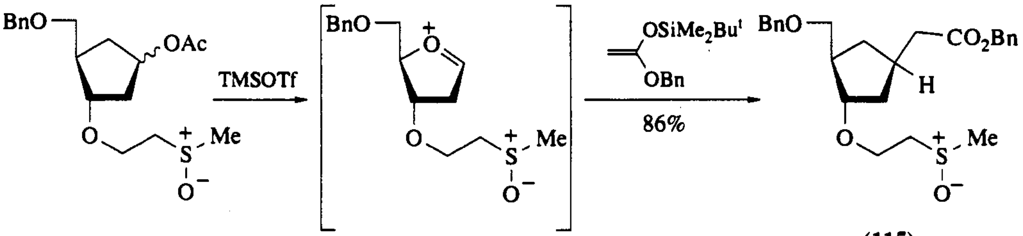

BnO
OAc
O
S
Me
O
TMSOTf
BnO
O
+
O
S
Me
O
OSiMe2Bu^t
OBn
86%
BnO
CO2Bn
H
O
S
Me
O

**(115)**

(40)

### 2.4.4.4 Diastereoselective Additions to Chiral Acetals

Six-membered chiral acetals, derived from aliphatic aldehydes, undergo aldol-type coupling reactions with α-silyl ketones, silyl enol ethers,[110] and with silyl ketene acetals[111] in the presence of titanium tetrachloride with high diastereoselectivities (equation 41); significant results are reported in Table 20. This procedure, in combination with oxidative destructive elimination of the chiral auxiliary, has been applied

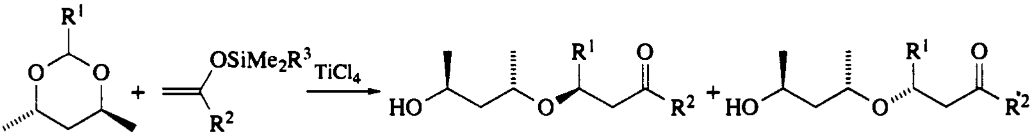

R¹
O
O
+
OSiMe2R³
R²
TiCl4
HO
O
R¹
O
R²
+
HO
O
R¹
O
R²

**(116)** **(117)**

(41)

**Table 20** Ratio of Diastereoisomers in the $TiCl_4$-mediated reactions of Enol Silanes with Chiral Acetals (equation 41)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *(116)/(117)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | $(CH_2)_2CH{=}CH_2$ | Me | Me | 97/3 | 89 | 110 |
| 2 | $Pr^i$ | Et | Me | 96/4 | 84 | 110 |
| 3 | $n\text{-}C_8H_{17}$ | Et | Me | 97/3 | 95 | 110 |
| 4 | $n\text{-}C_8H_{17}$ | $Bu^t$ | Me | 96/4 | 96 | 110 |
| 5 | $c\text{-}C_6H_{11}$ | $OBu^t$ | $Bu^t$ | 97/3 | 98 | 111a |
| 6 | $n\text{-}C_8H_{17}$ | $OBu^t$ | $Bu^t$ | 98/2 | 98 | 111a |
| 7 | $(CH_2)_4CO_2Pr^i$ | $OBu^t$ | $Bu^t$ | 98/2 | 93 | 111a |

to the preparation of (*R*)-(+)-α-lipoic acid,[111a] of mevinolin analogs,[111b] and of a key intermediate for the synthesis of nonactic acid.[110]

Lewis acid catalyzed aldol coupling of silyl enol ethers with substituted cyclohexanone acetals showed an excellent preference for equatorial attack (95–100%).[112] In accord with this general rule, additions of a silyl enol ether to equatorially or axially substituted chiral spiroketals derived from -menthone gave 100% equatorial attack and formation of a single one of the four possible diastereoisomers (Scheme 9).[113,114] This methodology, followed by protection of the hydroxy group (X = OTHP, $OCPh_3$) and alkaline removal of the chiral auxiliary was used for the synthesis of several natural products.[114]

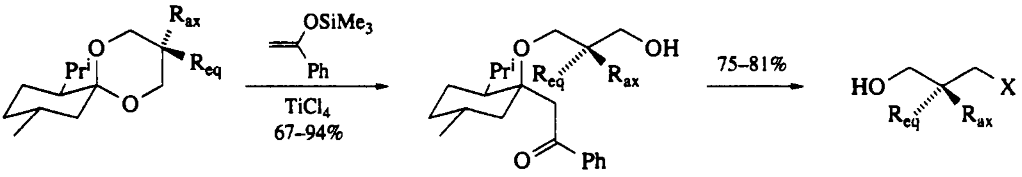

Scheme 9

### 2.4.4.5 Intramolecular Diasteroselective Aldol-type Additions

Lewis acid mediated cleavage of an acetal to a trigonal oxonium ion followed by intramolecular capture of the oxonium ion by a trigonal enol silane proved a useful process for the stereoselective synthesis of five-,[115] six-,[116–119] seven-,[118–121] eight-[118,119] and eleven-membered rings.[122] The rapid formation of eight-membered rings by direct aldol reaction without the need for high dilution conditions is noteworthy since eight-membered rings are usually difficult to construct by any method of ring closure (equation 42). Compound (**118**) was obtained as a single diastereoisomer (*trans*), along with polymeric by-products.[119] In the six-membered ring case (equation 43) only the *cis*-tetrahydropyran-4-one (**119**) was obtained starting from either *cis*- or *trans*-dioxolanes.[118,119] Stereoselective cyclopentane annulations were realized (equation 44) using a TMSOTf-catalyzed addition to trimethyl orthoesters; compounds (**120**) were obtained as single stereoisomers with *cis* ring fusion and the phenylsulfonyl substituent *exo*.[115a]

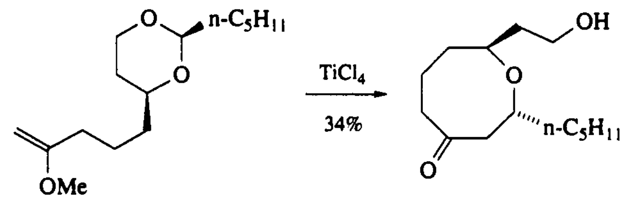

(42)

**(118)**

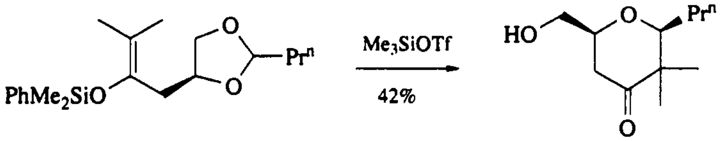

(43)

**(119)**

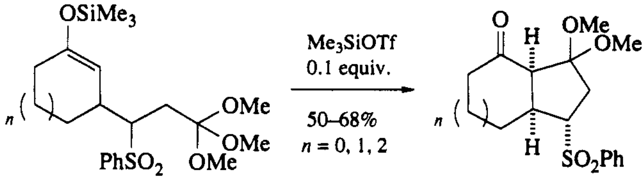

**(120)**

(44)

Highly stereoselective intramolecular reactions of a silyl enol ether ($BF_3 \cdot OEt_2$)[123a] and a vinyl sulfide ($HgCl_2$, CSA)[123b] with *N*-acyliminium ions have recently been accomplished.

## 2.4.5 CHIRAL NUCLEOPHILES AND ELECTROPHILES

When both the enol silane and the electrophile are chiral, the inherent diastereofacial preferences of the two reactants may reinforce one another (matched pair) or oppose one another (mismatched pair).[4a,124] If the chiral enol silane shows sufficiently high diastereoface preference, it can completely override the modest diastereoface preference of particular electrophiles, and the sense of chirality of the new stereocenters is determined almost solely by the sense of chirality of the enol silane (reagent control).[4a,124] Reagent (**121**), for example, is able to override the preference of the chiral 4-acetoxyazetidin-2-one (**122**) for formation of the α-isomer with achiral enol silanes (see Section 2.4.4.2 and Table 19), although the net β-preference is still only moderate (equation 45).[125]

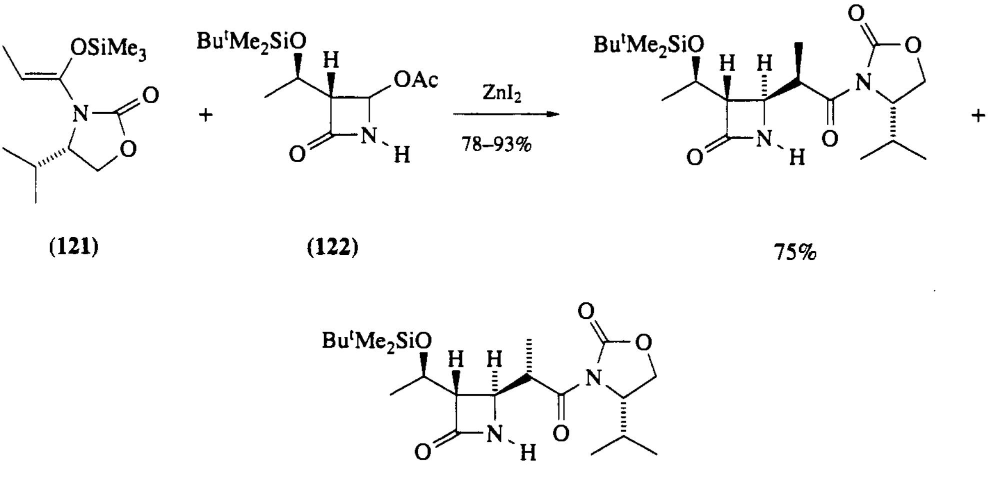

(45)

### 2.4.5.1 Diastereoselective Additions of Chiral Silyl Ketene Acetals to Chiral Aldehydes

In the total synthesis of zincophorin, *N*-methylephedrine-derived silyl ketene acetal (**17**) gave with chiral aldehyde (**123**) the desired adduct (**124**) as the major stereoisomer (*anti*:*syn* = 89:11; facial selectivity > 95:5) in the presence of a (likely) modest diastereofacial guidance from the remote stereocenter at C-4 (Scheme 10).[126] In the synthesis of tetrahydrolipstatin, *N*-methylephedrine-derived silyl ketene acetal (**125**) gave with chiral aldehyde (**126**) the desired adduct (**127**) as the major stereoisomer (C-2,C-3 *anti*:C-2,C-3 *syn* = 75:25; facial selectivity > 95:5; equation 46).[127] This result is particularly noteworthy as the reagent is able to override the strong preference of β-alkoxy aldehydes (*e.g.* **85**, equation 25 and Table 17) for chelation control and C-2,C-3 *syn* simple stereoselection. In the synthesis of the carbapenem antibiotic 1-β-methyl-PS-5, *N*-methylephedrine-derived silyl ketene acetal (**20**) gave with aldehyde (*S*)-(**128**), prepared in 91% *ee* according to Scheme 4,[59] the aldol addition product (**129**) in 70% yield as a single isomer out of the eight possible isomers (Scheme 11).[60] The explanation for this excellent selectivity is the following; both the (1*S*,2*R*)-*N*-methylephedrine-derived silyl ketene acetal (**20**) and (*S*)-(**128**) have an intrinsic preference for establishing a (2*R*,3*S*) absolute configuration at C-2,C-3, as is evident from the reaction of (**20**) with the achiral aldehyde (**28**) (see Section 2.4.3.1, equation 12) and from the reaction of (*S*)-(**128**) with the achiral thiol ester derived silyl ketene acetals (see Section 2.4.4.1, equation 24, Table 16 entries 3, 4, 9, and 10). As (**20**) and the (*S*)-aldehyde form a matched pair (they cooperate to realize the same stereochemical result), while (**20**) and the (*R*)-aldehyde form a mismatched pair, only the (*S*)-enantiomer of the starting 95.5/4.5 = (*S*)/(*R*) mixture of aldehyde (**128**) reacts with (**20**), and the reaction occurs with concomitant kinetic resolution. The relative configuration of the three contiguous stereocenters is a result of chelation control (C-3,C-4 *anti*) and *syn* simple stereoselection (C-2,C-3 *syn*) in agreement with the transition structure model (Figure 5A).[57,60] An analogous matched pair condensation between enantiomerically pure aldehyde (*S*)-(**128**) and silyl ketene acetal (*R*)-(**130**) was reported to give the aldol product (**131**), in ≥ 97% diastereoisomeric purity, which was further elaborated to 1-β-methylthienamycin (Scheme 12).[128]

An example of the mismatched pair is shown in Scheme 13;[57] here the (1*R*,2*S*)-*N*-methylephedrine-derived silyl ketene acetal (**17**) reacts with (*S*)-(**128**) (91% *ee*) to give a mixture of adducts (**132**) and (**133**) in poor yield. Compound (**132**) was obtained in 100% *ee* through transition structure (Figure 5**B**), which is against the aldehyde preference (Me inside the titanium-containing ring), while (**133**) was obtained in 65% *ee* through transition structure (Figure 5C), which is against the silyl ketene acetal preference. It is also interesting to observe that, while (**132**) is enantiomerically pure, the *ee* of (**133**) is only 65%. This means that, as the starting aldehyde is a 95.5/4.5 (*S*)/(*R*) mixture, almost all the minor (*R*)-en-

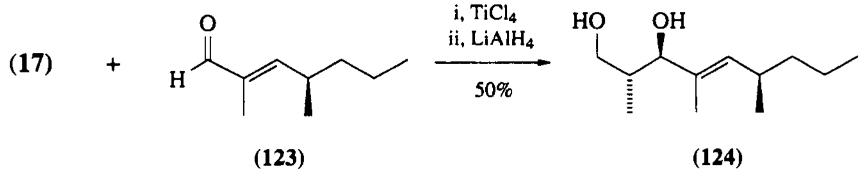
(17)
+
O
H
i, TiCl4
ii, LiAlH4
50%
HO
OH
(123)
(124)

**Scheme 10**

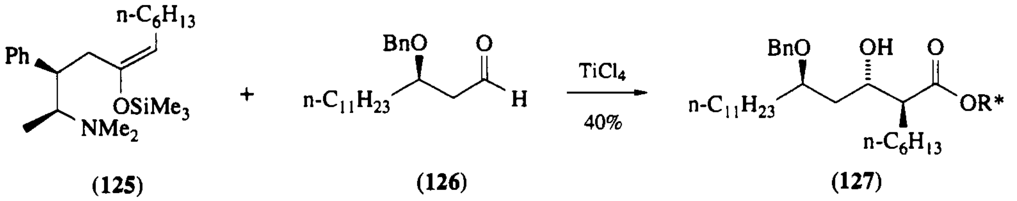
n-C6H13
Ph
OSiMe3
NMe2
+
BnO
O
n-C11H23
H
TiCl4
40%
BnO
OH
O
n-C11H23
OR*
n-C6H13
(125)
(126)
(127)

(46)

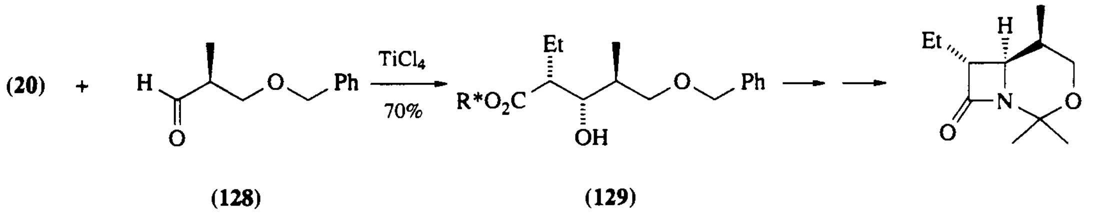
(20)
+
H
O
O
Ph
TiCl4
70%
Et
R*O2C
O
Ph
OH
Et
H
O
N
O
O
(128)
(129)

**Scheme 11**

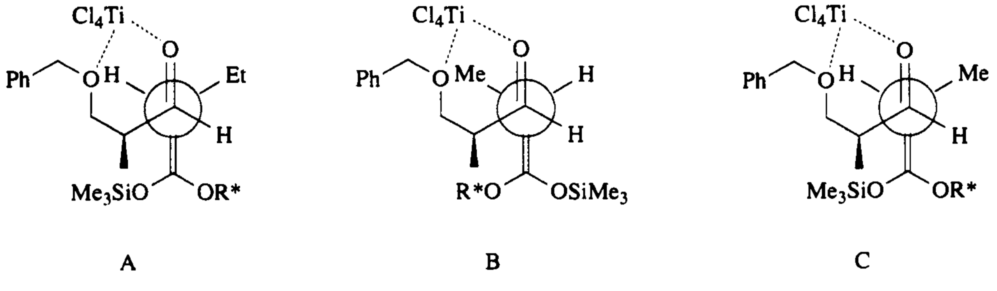
Cl4Ti
O
Ph
O
H
Et
H
Me3SiO
OR*
A
Cl4Ti
O
Ph
O
Me
H
H
R*O
OSiMe3
B
Cl4Ti
O
Ph
O
H
Me
H
Me3SiO
OR*
C

**Figure 5**

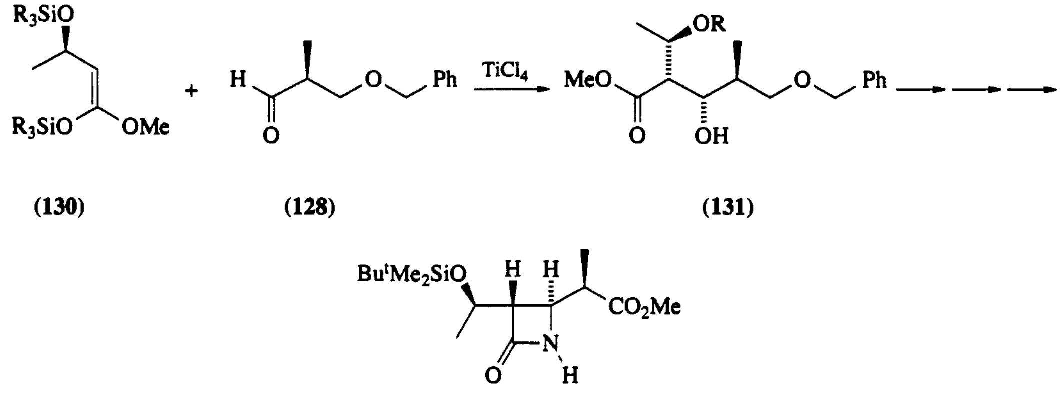
R3SiO
R3SiO
OMe
H
O
O
Ph
TiCl4
MeO
OR
OH
Ph
(130)
(128)
(131)
ButMe2SiO
H
H
CO2Me
N
H

Scheme 12

antiomer was consumed to produce the enantiomer of (**133**), through a process of kinetic resolution opposite to the one described above. A process of mutual kinetic resolution is shown in equation (47); chiral enol silane (**32**) gave with 2-phenylpropanal (**134**) the aldol product as a 99:1 mixture of stereoisomers (**135**) and (**136**).[25c] As (**3**; R = TMS), the achiral analog of (**32**), gives with aldehyde (**134**) a 90:10 mixture, it is evident that the inherent diastereoselectivity of (**134**) was enhanced by a factor of 10 by advantageous face matching.[25c]

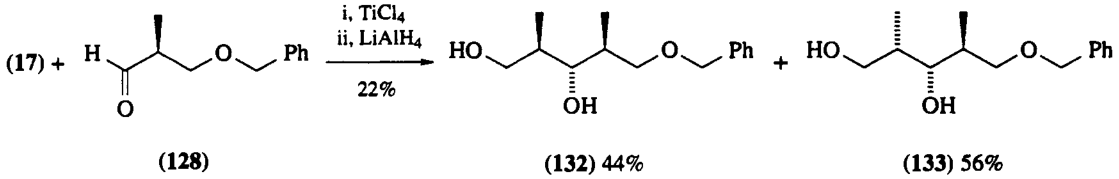
(17) +
H
O
O
Ph
i, TiCl4
ii, LiAlH4
22%
HO
OH
Ph
+
(128)
(132) 44%
(133) 56%

Scheme 13

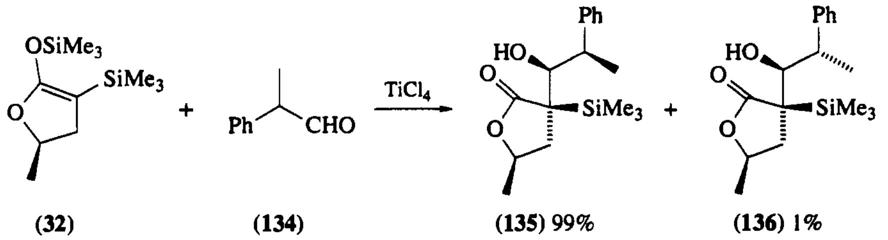
OSiMe3
SiMe3
O
+
Ph
CHO
TiCl4
HO
O
Ph
SiMe3
+
(32)
(134)
(135) 99%
(136) 1%

(47)

## 2.4.6 CHIRAL LEWIS ACIDS

The use of chiral Lewis acids for enantioselective Diels–Alder and hetero Diels–Alder reactions and for other processes of C—C bond formation has recently received great attention. Reetz and coworkers reported that a stoichiometric amount of the chiral Lewis acid (**137**) effectively promotes the reaction of silyl ketene acetal (**98**) to give the aldol product in 57% yield and 90% *ee* (equation 48, R = $Me_2CHCH_2$—).[129] When a catalytic amount (5 mol %) of the chiral rhodium perchlorate (**138**) is used, the aldol product is obtained in >75% yield and 12% *ee* (equation 48; R = Ph).[130] Both reactions probably proceed through the corresponding metal enolates.[129,130] The development of new efficient chiral catalysts for the Mukaiyama reaction is certainly one of the challenges of the 1990s.

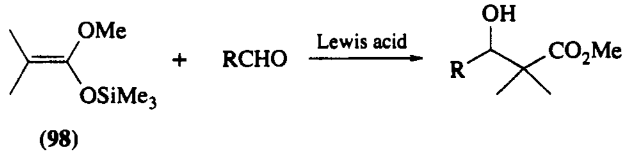
OMe
OSiMe3
+
RCHO
Lewis acid
OH
R
CO2Me
(98)

(48)

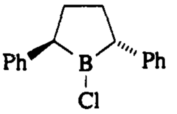

**(137)**

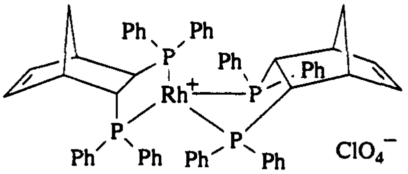

**(138)**

## ACKNOWLEDGEMENTS

I thank Professor Franco Cozzi for reading the manuscript and for helpful discussions. It is also a pleasure to thank my student Pier Giorgio Cozzi for his enthusiastic cooperation and for most of the unpublished results of the present review.

## 2.4.7 ADDENDUM

Since the submission of this chapter, a number of important contributions to this field have appeared in the literature.

### *Section 2.4.2*

The 'pinwheel' shape of a *t*-butyl propionate derived silylketene acetal (see Section 2.4.2.1) was revealed by a single-crystal X-ray diffraction analysis.[131] Several different catalysts were reported to promote the aldol-type condensation of alkyl enol ethers[132,133,134a] and silyl enol ethers[134b–144] with aldehydes, acetals and various other electrophiles. In some cases the reaction proceeded with high simple stereoselection.[133–136] The mechanism of the Lewis acid mediated additions to acetals (see Section 2.4.2.3) was investigated in detail,[145] as well as the uncatalyzed aldol reaction of silyl enol ethers with aldehydes promoted by the hydrophobic effect[146] (see Section 2.4.2.1).

### *Section 2.4.3*

In the field of chiral silyl enol ethers, the enolsilane derived from camphor was reported to give highly *exo* selective additions to iminium ions[147] and acetals;[148] the stereoselectivity at the acetal stereocenter was found to be strongly dependent on the acetal structure.[148] The optically active (*E*) enol ethers shown in Scheme 14 were reported to undergo highly diastereoselective reactions with a variety of aliphatic and aromatic acetals.[149] *Syn–anti* ratios ranged from 90:10 to 99:1 and enantiomeric excesses of the major *syn* isomer from 60 to 94%, depending on the various substituents. It is interesting to note that the reaction with benzaldehyde gave a 7:93 *syn–anti* ratio, in analogy with the reversal of stereoselectivity observed in the reaction of silyl enol ethers with acetals (*cf.* Section 2.4.2.3) and aldehydes (*cf.* Section 2.4.2.1).

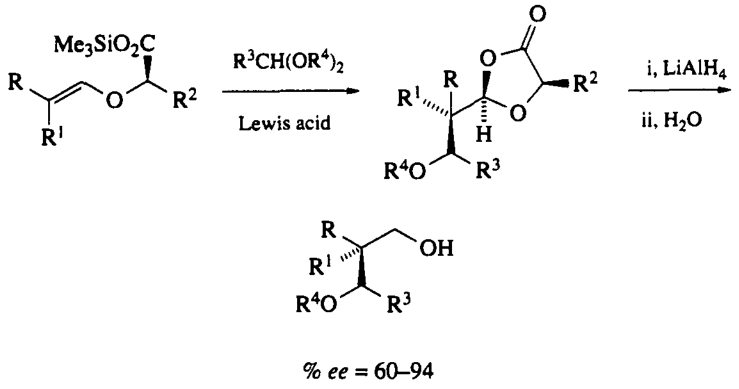

Scheme 14

The addition of a sugar-derived enol ether (glycal) to a dimethyl acetal was reported to proceed with good stereoselectivity.[134a] Danishefsky and coworkers reported the highly stereoselective additions of chiral silyl enol ethers to aldehydes in the total synthesis of prostaglandins[150] and compactin[151] (Schemes 15 and 16). In both cases the aldol product shown was obtained as the only diastereoisomer.

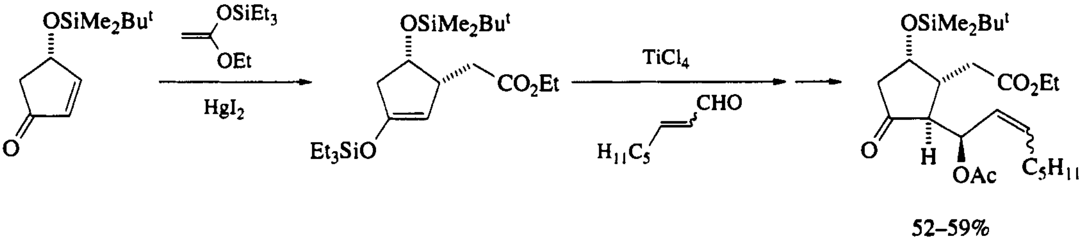
OSiMe2Bu^t
OSiEt3
OEt
HgI2
Et3SiO
CO2Et
TiCl4
CHO
H11C5
OAc
C5H11
H
O
52–59%

**Scheme 15**

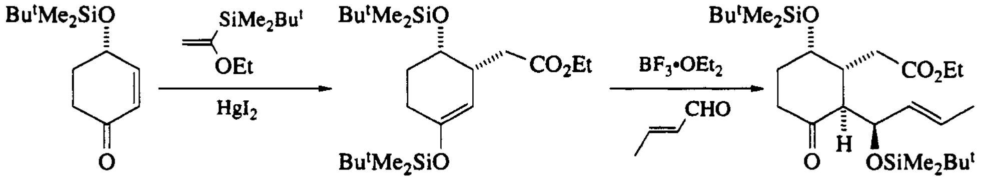
Bu^tMe2SiO
SiMe2Bu^t
OEt
HgI2
CO2Et
BF3•OEt2
CHO
H
O
OSiMe2Bu^t

**Scheme 16**

*Section 2.4.4*

In the field of chiral electrophiles, diastereoselective additions of enolsilanes to chiral α-fluoro-α-methyl-β-alkoxy aldehydes,[152] α-methyl aldehydes,[137] α-alkoxy aldehydes,[137] α,β-dialkoxy aldehydes[138] and α-methyl-β-alkoxy aldehydes[153] were reported to proceed with good stereocontrol following Felkin–Anh or chelation models (*cf.* Section 2.4.4.1). Very good selectivities were reported in the addition of enolsilanes to chiral imines,[154–156] particularly those derived from carbohydrates (Scheme 17 and 18).[155,156]

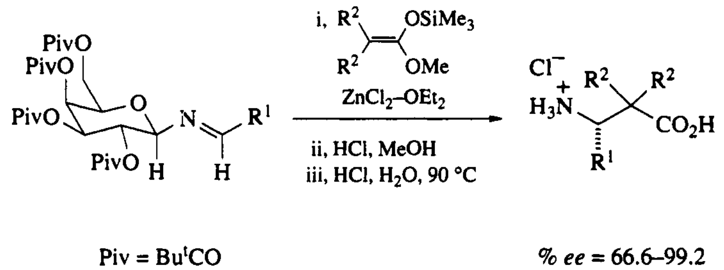
PivO
O
N
R1
H
i, R2 OSiMe3
R2 OMe
ZnCl2–OEt2
ii, HCl, MeOH
iii, HCl, H2O, 90 °C
Cl−
H3N
R2
CO2H
R1
Piv = Bu^tCO
% ee = 66.6–99.2

**Scheme 17**

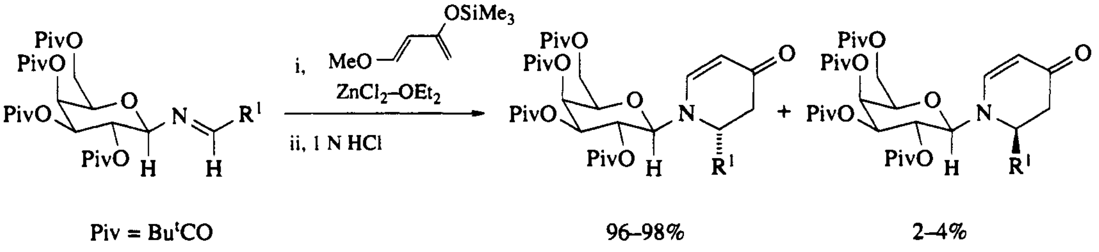
PivO
O
N
R1
H
OSiMe3
i, MeO
ZnCl2–OEt2
ii, 1 N HCl
+
Piv = Bu^tCO
96–98%
2–4%

**Scheme 18**

In the addition to chiral 4-acetoxyazetidin-2-ones[157–159] (*cf.* Section 2.4.4.2) it is noteworthy that the desired β-isomer (**108**; equation 36) could now be obtained as a single diastereoisomer (>98%) in 85–90% yield by the use of $ZnCl_2$ and the silylketene acetal derived from 2-picolyl thiopropionate[158,159] (*cf.* Table 19, entries 1–5). *N*-Acyliminium ions (see Section 2.4.4.3) with chiral *N*-acyl substituents were reported to undergo $TiCl_4$-mediated addition of silyl enol ethers with diastereomeric ratios up to 95:5.[160] $TiCl_4$-mediated addition of a silyl enol ether to a sugar-derived sulfonium ion (see Section 2.4.4.3) was reported to proceed with 70% yield and 4:1 diastereomeric ratio.[138] In the field of *C*-glycosides synthesis (see Section 2.4.4.3), selective α-[161a,b] or β-[161b] glycosylation was realized, depending on substrate and Lewis acid, by enolsilane addition to chiral oxonium ions (*cf.* equation 40). Oxonium ions are also probably involved in the diastereoselective $AlCl_3$-mediated additions of enolsilanes to chiral 2-benzenesulfonyl cyclic ethers.[162] In the diastereoselective additions to chiral acetals[163,164] (see Section 2.4.4.4), an extension of the methodology shown in Scheme 9 to the enantio differentiation of *meso* 1,2- and 1,4-diols was reported.[164] An intramolecular Mukaiyama acetal–aldol reaction (see Section 2.4.4.5) was reported as the key step to construct the 11-membered ring of hydroxyjatrophone A and B.[165]

### *Section 2.4.5*

In the diastereoselective additions of chiral silylketene acetals to chiral aldehydes (see Section 2.4.5.1), details on the chemistry involved in Scheme 12 were published.[166]

### *Section 2.4.6*

Spectacular results were reported by Mukaiyama and coworkers[167,168] in the field of chiral Lewis acids. Reaction of thiol ester derived silylketene acetals with aldehydes promoted by the combined use of a chiral diamine coordinated with tin(II) triflate and tributyltin fluoride gave excellent yields of aldol products in very high enantiomeric excess (Scheme 19).

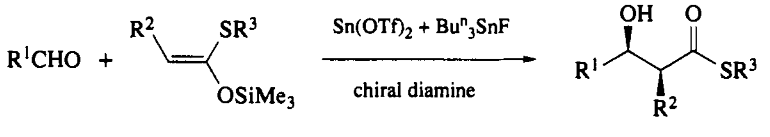

$R^2$ = H; % *ee* = 78–95

$R^2$ = Me; % *ee* >98

**Scheme 19**

An interesting result (17–35% *ee*) was reported in the TMSOTf-catalyzed condensation of benzaldehyde dimethyl acetal with a cyclohexanone silyl enol ether bearing an optically pure binaphthylic derivative at silicon.[169]

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# 2.5

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## 2.5.1 INTRODUCTION

The reaction of activated dienes with aldehydes is emerging as a powerful tool in the synthesis of natural products.[1–4] This chapter reviews the major contributions that have led to the discovery and use of this reaction in organic synthesis. The first part of the chapter discusses the mechanism of the reaction, the second part describes the use of chiral aldehydes, chiral dienes and chiral catalysts in controlling stereochemistry, and the last section outlines applications in the synthesis of natural products.

### 2.5.1.1 Activated Dienes and Their Use in the Diels–Alder Reaction

Dienes that contain electron-donating groups (activated dienes) are more reactive in Diels–Alder reactions than unsubstituted or electron-deficient dienes.[5–8] In molecular orbital formalism, the substituents on the diene perturb the π-electron density to cause an increase in the energy of the highest occupied molecular orbital (HOMO; Figure 1).[9] In a normal-demand Diels–Alder reaction this results in an increase in the interaction between the HOMO of the diene and the LUMO (lowest unoccupied molecular orbital) of the dienophile. This interaction, in turn, lowers the transition state energy of the reaction.[10] Similar arguments have also been used to explain the increased reactivity of activated dienes towards heterodienophiles such as aldehydes.[10]

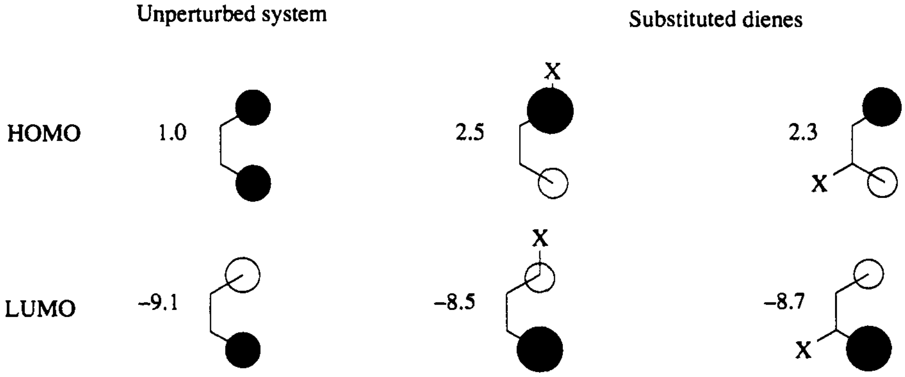

**Figure 1** Orbital energies in eV are given for substituted and unsubstituted dienes. The size of the circles give relative indication of orbital coefficients. X = electron-donating substituents (*e.g.* OMe, $NR_2$)[9]

Activated dienes are also highly regioselective. This is due to the unsymmetrical polarization of the HOMO that is caused by the placement of substituents on the diene. The use of activated dienes is well documented in classical Diels–Alder reactions. They provide for high reactivity, good regioselectivity and introduce useful functionality into the cycloadducts.[11]

### 2.5.1.2 Aldehydes as Dienophiles

In 1951 Gresham and Steadman reported that formaldehyde can be used as a dienophile in Diels–Alder reactions (hetero Diels–Alder reaction).[12] This report led to the investigation of several dienes and aldehydes under thermal reaction conditions.[13–20] These studies revealed that the reaction is restricted to the use of formaldehyde or aldehydes that contain strong electron-withdrawing groups (such as glyoxaldehyde) as dienophiles (Scheme 1).

In an effort to cause unreactive aldehydes to react in the hetero Diels–Alder reaction Kubler introduced the use of the activated, electron-rich 1-alkoxy-1,3-butadiene.[21] This diene shows increased reactivity and high regioselectivity but only with activated aldehydes. In 1971 Scheeren showed that the potent diene 1,1-dimethoxy-3-silyloxy-1,3-butadiene also reacts with aldehydes.[22] The high reactivity of

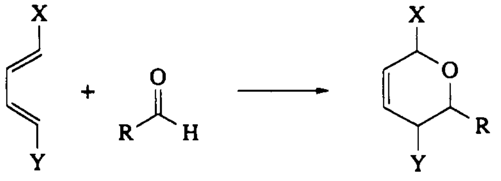

(1) (2) (3)

R = H or an electron-withdrawing group (*e.g.* $CO_2Me$)
X and Y are electron-withdrawing groups

**Scheme 1**

this diene allows the use of heterodienophiles at lower temperatures but the diene does not react with unactivated aldehydes. More recently, Jankowski and coworkers reported on the thermal cycloaddition reaction of trimethylsilyloxy dienes with mesoxylate $[(RO_2C)_2CO]$.[20] This symmetrical dienophile shows only moderate regioselectivity and did not allow for the critical evaluation of the stereoselectivity; despite limitations and problems with *endo* to *exo* specificity David and coworkers applied this methodology to the synthesis of the human trisaccharide blood group antigens (this synthesis is discussed in more detail in Section 2.5.4.1).[23]

An important development in the hetero Diels–Alder reaction came when Jurczak used high pressure to help improve the reactivity of dienes with aldehydes. 1-Methoxybutadiene, for example, was shown to react at 15–25 kbar (1 bar = 100 kPa) with a variety of unactivated aldehydes.[24,25] These reactions give predominantly *endo* adducts and allow for the use of simple alkyl and aromatic aldehydes as dienophiles. Jurczak also realized the importance of this reaction in the synthesis of carbohydrates and applied it to the construction of simple monosaccharide derivatives (see Section 2.5.2.1).[26–28]

### 2.5.1.3 Lewis Acid Catalysis

Lewis acid catalysts increase the reactivity of dienophiles in Diels–Alder reactions by complexing to basic sites on the dienophile.[10] The Lewis acid lowers the LUMO of the adjacent π-system, which strengthens the overlap between the LUMO of the dienophile and the HOMO of the diene. In 1979 Scheeren reported that $ZnCl_2$ catalyzes the cyclocondensation reaction of unactivated aldehydes with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene.[22] Experimental details of this reaction, however, were not fully documented. In 1982 Scheeren also reported the use of aluminum alkoxydichlorides as catalysts

**Table 1**

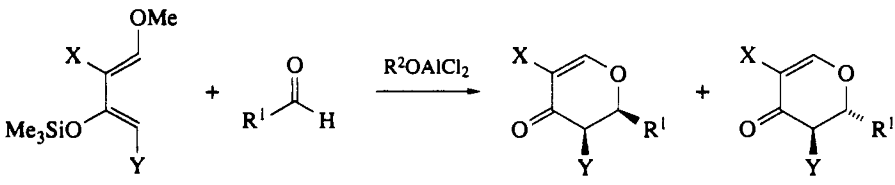

(4) (5) (6) *syn* (7) *anti*

| *Diene* | *X* | *Y* | *Aldehyde* | *$R^1$* | *Adduct* | *Yield (%)* |
|---|---|---|---|---|---|---|
| **(4a)** | H | H | **(5a)** | H | **(6a)** | 50 |
| **(4a)** | H | H | **(5b)** | $Pr^i$ | **(6b)** | 65 |
| **(4a)** | H | H | **(5c)** | $CH_2{=}CH$ | **(6c)** | 60 |
| **(4a)** | H | H | **(5d)** | $MeCH{=}CH$ | **(6d)** | 60 |
| **(4a)** | H | H | **(5e)** | Ph | **(6e)** | 70 |
| **(4b)** | H | Et | **(5b)** | $Pr^i$ | **(6f:7f)** | 35 (**6f:7f**; 3:1) |
| **(4c)** | Et | H | **(5e)** | Ph | **(6g)** | 60 |
| **(4d)** | H | OEt | **(5b)** | $Pr^i$ | **(6h:7h)** | 45 (**6h:7h**; not reported) |
| **(4e)** | OEt | H | **(5e)** | Ph | **(6i)** | 45 |

$R^2$ = bornyl, propyl, isopropyl.

using diene (**4**) and unactivated aldehydes (**5**; Table 1).[29] The reaction using the aluminum catalyst was thought to be general but no critical investigation into the mechanism and stereochemistry was reported.

The major development in the Lewis acid catalyzed reaction came in 1981 when Danishefsky and coworkers reported that $ZnCl_2$ and $BF_3{\cdot}OEt_2$ catalyze the cyclocondensation of silyloxy dienes with unactivated aldehydes.[30] The use of these Lewis acid catalysts permits a variety of simple aldehydes to be used in the reaction (Table 2). Danishefsky also critically evaluated the mechanism and stereochemistry of the cyclocondensation reaction with a series of dienes, aldehydes and catalysts. These studies resulted in conditions to control the relative and absolute stereochemistry of the reaction and allowed the use of this chemistry in natural product synthesis.

**Table 2**

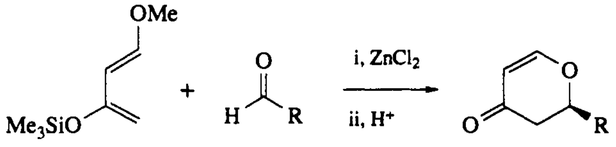

**(8)** **(9)** **(10)**

| *Aldehyde* | *R* | *Adduct* | *Yield (%)* |
|---|---|---|---|
| **(9a)** | $CH_2OCH_2Ph$ | **(10a)** | 87 |
| **(9b)** | $CH_2SPh$ | **(10b)** | 70 |
| **(9c)** | CHNHCbz | **(10c)** | 80 |
| **(5e)** | Ph | **(10d)** | 65 |
| **(9d)** | *p*-$NO_2C_6H_4$ | **(10e)** | 58 |
| **(9e)** | *o*-$OMeC_6H_4$ | **(10f)** | 58 |
| **(9f)** | Me | **(10g)** | 17 |
| **(9g)** | Et | **(10h)** | 48 |
| **(5b)** | $Pr^i$ | **(10i)** | 43 |
| **(9h)** | $Bu^i$ | **(10j)** | 37 |

## 2.5.2 MECHANISM

### 2.5.2.1 Thermal and High-pressure Reactions

Initial investigations focused on the use of thermal and high-pressure conditions to perform reactions between aldehydes and dienes.[13–28] Under these conditions the only products observed are those which

**Table 3**

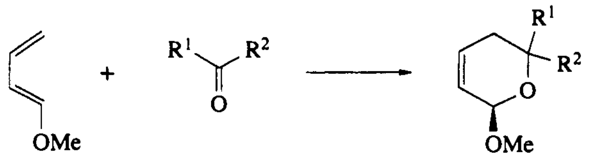

**(11)** **(12)** **(13)**

| *Aldehyde* | $R^1$ | $R^2$ | *Adduct* | *Pressure* (kbar) | *Temperature* (°C) | *Yield* (%) | *Isomer ratio endo* ($R^2$ *cis to* OMe)*:exo* ($R^2$ *trans to* OMe) |
|---|---|---|---|---|---|---|---|
| **(12a)** | Me | $CO_2C_{10}H_{21}$ | **(13a)** | 25.0 | 20 | 79 | 79:21 |
| **(12b)** | Me | $CO_2Me$ | **(13b)** | 20.0 | 50 | 85 | 70:30 |
| **(12c)** | Me | Ph | **(13c)** | 19.5 | 20 | 81 | 64:36 |
| **(5e)** | H | Ph | **(13d)** | 19.5 | 50 | 80 | 75:25 |
| **(12d)** | H | 2-Furyl | **(13e)** | 19.5 | 50 | 73 | 73:27 |
| **(9f)** | H | Me | **(13f)** | 20.0 | 65 | 62 | 70:30 |
| **(12e)** | H | n-$C_5H_{11}$ | **(13g)** | 23.5 | 20 | 16 | 78:22 |

seem to be derived from a classical Diels–Alder reaction. The high-pressure reactions reported by Jurczak give, for example, product ratios and rate accelerations which are similar to those observed for carbon–carbon bond-forming cycloaddition reactions.[25] The *endo* to *exo* ratios also reflect those expected for a Diels–Alder process (Table 3).

### 2.5.2.2 Lewis Acid Catalyzed Reactions

#### *2.5.2.2.1 Zinc chloride and boron trifluoride etherate*

The Lewis acid catalyzed reaction has two distinct mechanistic pathways. The first set of rigorous mechanistic investigations was performed by Danishefsky and coworkers. As previously mentioned only highly activated aldehydes bearing electron-withdrawing groups α to the carbonyl group participate in the thermal cycloaddition reaction. In 1982 Danishefsky, Kerwin and Kobayashi reported an important improvement that allows oxygenated dienes to react with simple aldehydes by using zinc chloride ($ZnCl_2$) as a catalyst.[30]

In further studies by Larson and Danishefsky it was shown that boron trifluoride etherate ($BF_3{\cdot}OEt_2$) also catalyzes the reaction but with a dramatically different stereochemical outcome.[31] When $ZnCl_2$ is used as a catalyst the reaction between benzaldehyde and diene (**14**) gives predominately the *cis* dihydropyrone (**16**). Under $BF_3{\cdot}OEt_2$ catalysis, however, the *trans* dihydropyrone (**17**) is the major product (Table 4).

**Table 4** Comparison of the Ratio of *Cis* to *Trans* Products in the $ZnCl_2$- and $BF_3$-catalyzed Cyclocondensation Reactions

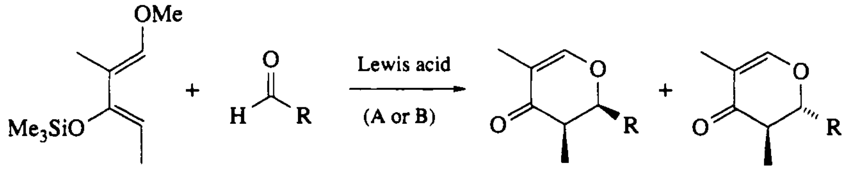

(**14**) (**15**) (**16**) *cis* (**17**) *trans*

| *Aldehyde* | *R* | *Method* | *(**16**) Yield (%)* | *(**17**) Yield (%)* |
|---|---|---|---|---|
| (**12e**) | $C_5H_{11}$ | A ($BF_3$–$CH_2Cl_2$, –78 °C; TFA) | 21 | 69 |
| | | B ($ZnCl_2$–THF, 25 °C; $NaHCO_3$; TFA) | 91 | 2 |
| (**5e**) | Ph | A | 23 | 68 |
| | | B | 78 | 2 |
| (**15a**) | $PH(CH_2)_3$ | A | 17 | 64 |
| | | B | 83 | 2 |
| (**9a**) | $BnOCH_2$ | A | 17 | 68 |
| | | B | 66 | 24 |

The $ZnCl_2$ reaction seems to pass through a pericylic mechanistic pathway while the $BF_3{\cdot}OEt_2$-catalyzed reaction resembles a Mukaiyama aldol reaction.[32] Danishefsky described the process in which an activated diene is condensed with an aldehyde as a cyclocondensation reaction, thus avoiding the implication of a concerted reaction pathway in cases where aldol products are unambiguously isolated (Scheme 2).

To account for the stereoselectivity in the pericylic manifold it was proposed that the Lewis acid binds to the aldehyde so that it is *syn* to the hydrogen. If the steric demand of the catalyst solvent array exceeds that of the side chain on the aldehyde, *endo* selectivity is observed, yielding the *cis* cycloadduct (Scheme 3). The primary cycloadduct is either decomposed by the catalyst, or by the addition of acid, into dihydropyrones (**16**) and (**17**).

The $BF_3{\cdot}OEt_2$-catalyzed reaction, on the other hand, is characterized by the isolation of the β-hydroxy- or β-silyloxy-methoxy enones. These compounds upon treatment with acid cyclize into dihydropyrones (**16**) and (**17**). The mechanistic nature of the aldol process allows for high *anti (trans)* stereoselectivity on the dihydropyrone, but is dependent on the diene employed in the reaction.[33]

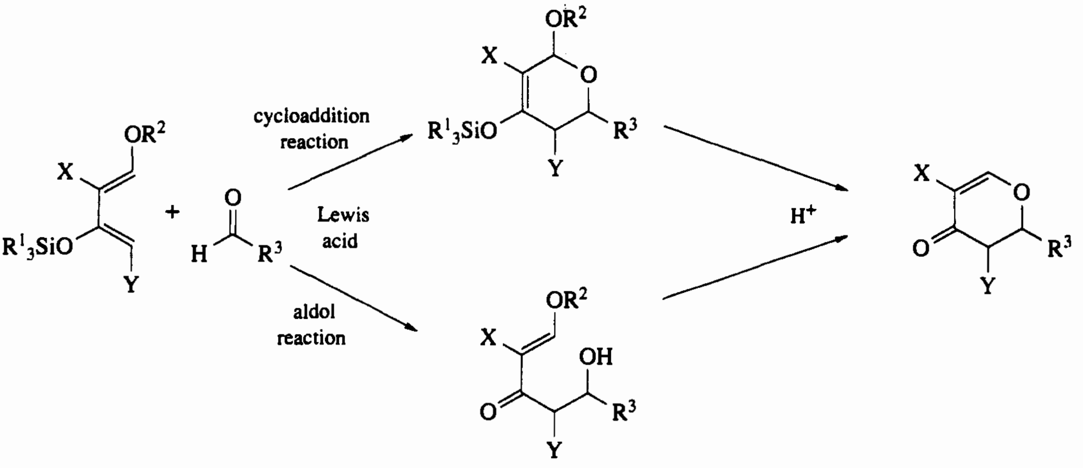
cycloaddition reaction
Lewis acid
aldol reaction
H+
OR2
X
R13SiO
Y
R3
OH

Scheme 2

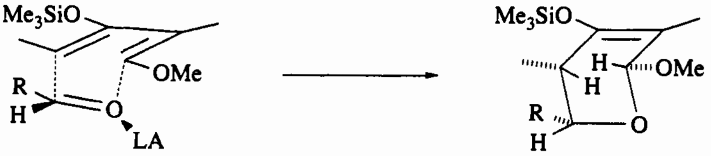
Me3SiO
OMe
R
H
O
LA

Scheme 3

Initial investigations of chiral aldehydes by Danishefsky[34,35] demonstrated that both $ZnCl_2$ and $BF_3{\cdot}OEt_2$ exhibited high Cram,[36] Felkin–Ahn (CF)[37,38] stereoselectivity.[39] The cyclocondensation reaction of diene (**14**) with aldehyde (**18**) (2-phenylpropanal) under $BF_3{\cdot}OEt_2$ catalysis was found to give a 4.3:1 mixture of the *trans*-CF dihydropyrone (**19**) and the *cis*-CF dihydropyrone (**20**). Only traces of anti Cram–Felkin (ACF) products are isolated. Under $ZnCl_2$ catalysis, however, an 8:1 mixture of the *cis*-CF product (**20**) and the *cis*-ACF product (**21**) is obtained (Scheme 4). A detailed analysis of these stereochemical issues is given later in Section 2.5.3.1.

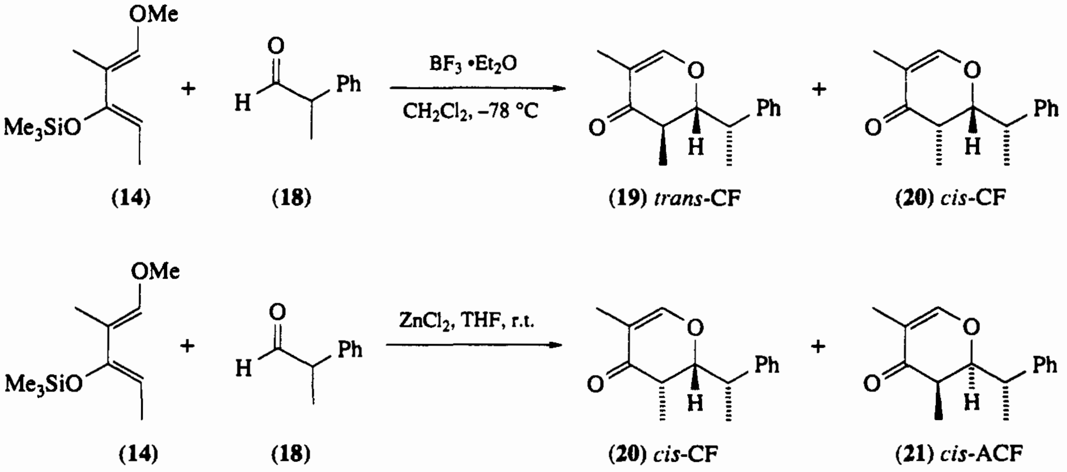
$BF_3{\cdot}Et_2O$
$CH_2Cl_2$, −78 °C
$ZnCl_2$, THF, r.t.
OMe
Me3SiO
Ph
H
O

(**14**) (**18**) (**19**) *trans*-CF (**20**) *cis*-CF

(**14**) (**18**) (**20**) *cis*-CF (**21**) *cis*-ACF

Scheme 4

### 2.5.2.2.2 Magnesium bromide and titanium tetrachloride

Since the investigations which used $ZnCl_2$ and $BF_3{\cdot}OEt_2$ as catalysts, other Lewis acids have been shown to catalyze the cyclocondensation reaction. $MgBr_2$, for example, was used by Pearson and Danishefsky[40] to add the power of chelation control to the reaction. When chiral α-alkoxy aldehydes are condensed with dienes under the influence of $MgBr_2$, products derived from an ACF transition state predominate. The chelation of the metal by the α-alkoxy group of the aldehyde forces the aldehyde side chain to occupy the same side of the aldehyde as the metal. The diene, therefore, can attack the aldehyde from the least hindered *exo* face giving rise to the *trans*-ACF product (Scheme 5). When an aldehyde is used that cannot form a chelate to the metal (such as benzaldehyde) *syn* (*endo*) selectivity is observed.

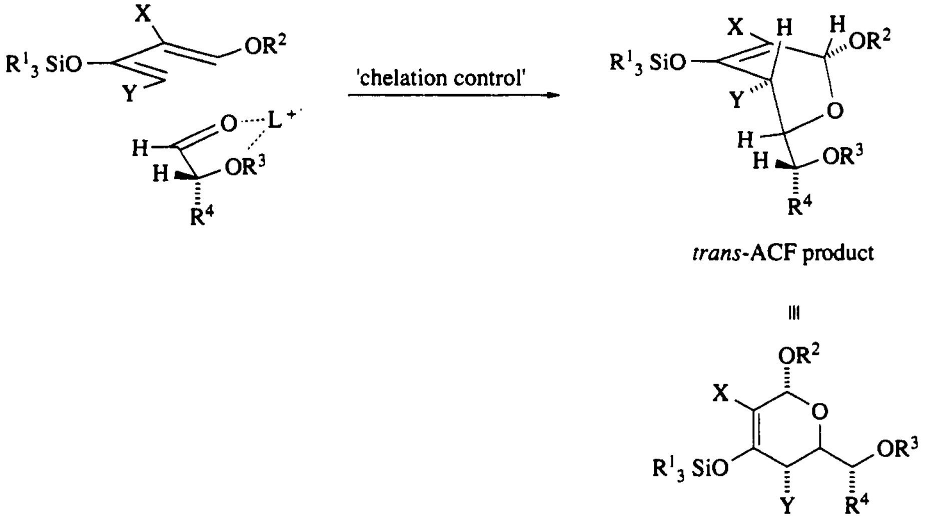

Scheme 5

Other strongly chelating Lewis acids were investigated by Danishefsky, Pearson and Harvey.[41,42] When α-alkoxy aldehydes are used under $TiCl_4$ catalysis, *cis*-ACF products such as compound (**22**) are the major products (Scheme 6). The *cis* dihydropyrone stereochemistry is opposite to that obtained in the $MgBr_2$-mediated reaction. When using nonchelating aldehydes, however, the *trans* dihydropyrone (**23**) is the major product of the reaction. The $TiCl_4$-catalyzed reaction is thought to proceed through an aldol mechanism and the observed stereochemistry is consistent with studies by Mukaiyama and Reetz.[43,44] The stereochemistry with the $TiCl_4$ catalyst is, therefore, highly dependent on the aldehyde and diene employed in the reaction. We address the mechanistic details of this and other catalytic systems in Section 2.5.2.3. A summary of initial investigations of these catalysts is given in Table 5.

**Table 5** General Consequences of some Commonly Used Catalysts in the Diene–Aldehyde Cyclocondensation Reaction

| *Catalyst/solvent* | *Topology and stereochemistry* |
|---|---|
| $ZnCl_2$/THF[a] | Pericyclic/nonchelating with α-alkoxy aldehydes: *cis* Cram products with both chelatable and nonchelatable aldehydes |
| $MgBr_2$/THF[a] | Pericyclic/chelating with α-alkoxy aldehydes: *trans* anti-Cram products with chelatable aldehydes, *cis* Cram products with nonchelatable aldehydes |
| $BF_3{\cdot}Et_2O/Et_2O$[b] | Aldol/nonchelating with α-alkoxy aldehydes: *trans* Cram products with both chelatable and nonchelatable aldehydes |
| $TiCl_4$/THF[b] | Aldol/chelating with α- and β-alkoxy aldehydes: *cis* anti-Cram products with chelatable aldehydes, *trans* Cram products with nonchelatable aldehydes |

[a] Nonpolar solvents (*e.g.* benzene) have also led to aldol products. [b] Topology and stereochemistry can be a function of aldehyde and diene used in the reaction (*vide infra*).

### 2.5.2.2.3 Lanthanide catalysts

Despite the effort put forth in developing catalytic systems, no general method existed for the production and preservation of the sensitive, highly functionalized primary cycloadducts. The only case in

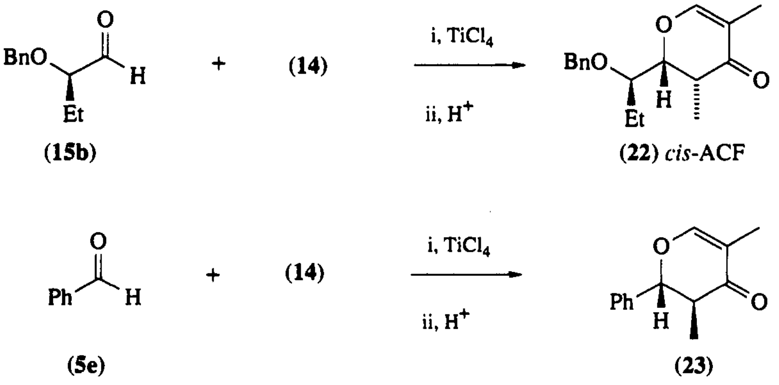
BnO
H
Et
+
i, $TiCl_4$
ii, $H^+$
BnO
O
H
Et
O
Ph
H
O
Ph
H

**(15b)** + **(14)** → **(22)** *cis*-ACF

**(5e)** + **(14)** → **(23)**

Scheme 6

which one of these intermediates had previously been isolated and fully characterized was in the reaction of benzaldehyde with diene (**24**) under $ZnCl_2$ catalysis (Scheme 7). Even in this case, however, the yield of (**25**) was low (40%) and the reaction mixture also contained significant amounts of pyrones (**16b**) and (**17b**).[31,32]

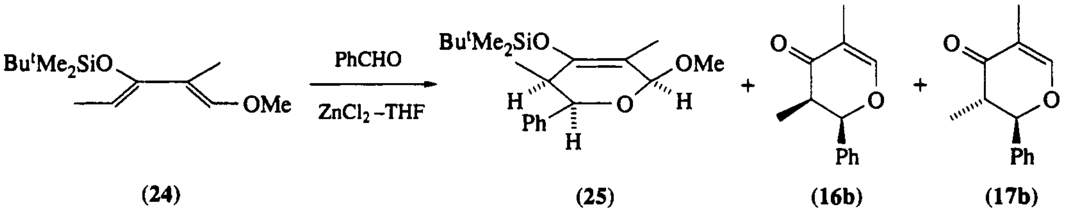
Bu$^t$Me$_2$SiO
OMe
PhCHO
$ZnCl_2$-THF
Bu$^t$Me$_2$SiO
OMe
H
Ph
H
O
H
+
O
O
Ph
+
O
O
Ph

**(24)** **(25)** **(16b)** **(17b)**

Scheme 7

**Table 6** The Lanthanide-catalyzed Hetero Diels–Alder Reaction using Eu(fod)$_3$

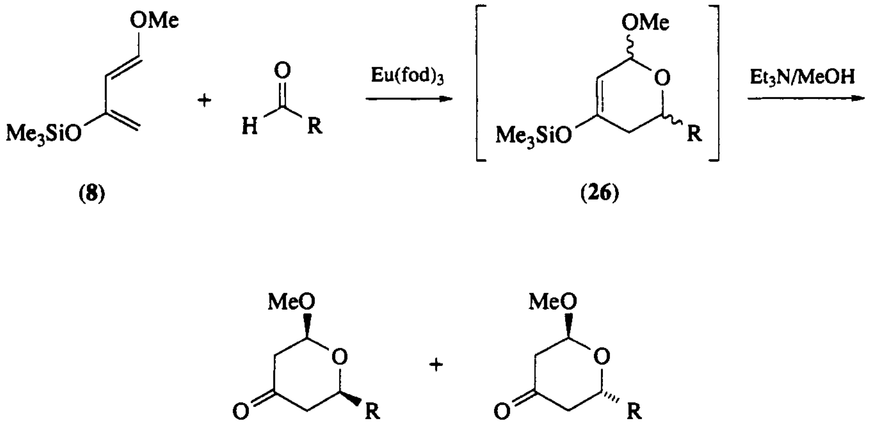
OMe
Me$_3$SiO
+
O
H
R
Eu(fod)$_3$
OMe
O
Me$_3$SiO
R
$Et_3N$/MeOH
MeO
O
O
R
+
MeO
O
O
R

**(8)** **(26)**

**(27)** *endo (cis)* **(28)** *exo (trans)*

| *Aldehyde* | *R* | *(27)* | : | *(28)* |
|---|---|---|---|---|
| **(5e)** | Ph | 12 | | 1 |
| **(12d)** | 2-Furyl | 6 | | 1 |
| **(15c)** | *trans*-Styryl | 8 | | 1 |
| **(9f)** | Me | 2.8 | | 1 |
| **(12e)** | n-$C_5H_{11}$ | 1.2 | | 1 |
| **(5b)** | Pr$^i$ | 1.5 | | 1 |

In 1984 Danishefsky and Bednarski demonstrated that lanthanide(III) complexes catalyze the cycloaddition of activated dienes with aldehydes.[45] The stereoselectivity increases dramatically when using these catalysts. When diene (**8**), for example, reacts with a variety of aldehydes with Eu(fod)$_3$ as catalyst virtually complete *cis (endo)* selectivity is observed (Table 6). The aldehydes that function as dienophiles can be aliphatic (acetaldehyde and hexanal) or aromatic (benzaldehyde and furfural).

The predominance of *cis* products is consistent with the model previously described for *endo* addition: the Lewis acid complexes to the lone pair of the aldehyde *anti* to the R group, driving the R group *endo* in the transition state. In the case of lanthanide catalysts, however, the large steric bulk of the lanthanide metal–ligand complex causes the *cis* selectivity to increase (Scheme 8).

LA = lanthanide(III) ion, $ZnCl_2$ or $MgBr_2$, where R cannot chelate to the metal

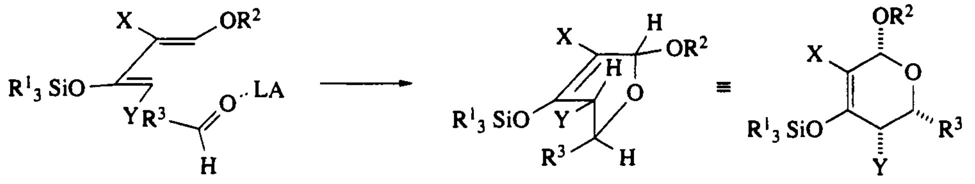

$R^3$ < LA–aldehyde complex gives *cis (endo)* addition products

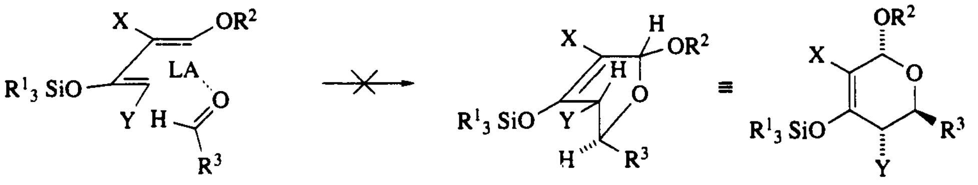

Steric interactions between the lanthanide metal and the diene disfavor the *exo* transition state.

$R^3$ > LA–aldehyde complex gives *trans (exo)* addition products

Scheme 8

The high *endo* selectivity of aromatic aldehydes is also a result of their capability to participate in secondary orbital interactions.[10] The mixing of the LUMO of benzaldehyde with the HOMO of the diene can form secondary orbital overlap which lowers the energy of the *endo* transition state. The electron-withdrawing effect of the catalyst [*e.g.* Eu(fod)$_3$] on the aldehyde further enhances secondary orbital overlap with aromatic aldehydes by an additional reduction of the LUMO energy (Figure 2). Similar arguments have been made to rationalize the increase in *endo* selectivity of homo Diels–Alder reactions when Lewis acids are used as catalysts.[10] Secondary orbital interactions are, however, absent when the dienophile is an aliphatic aldehyde; in such reactions the *cis (endo)* stereoselectivity is based solely on steric interactions.

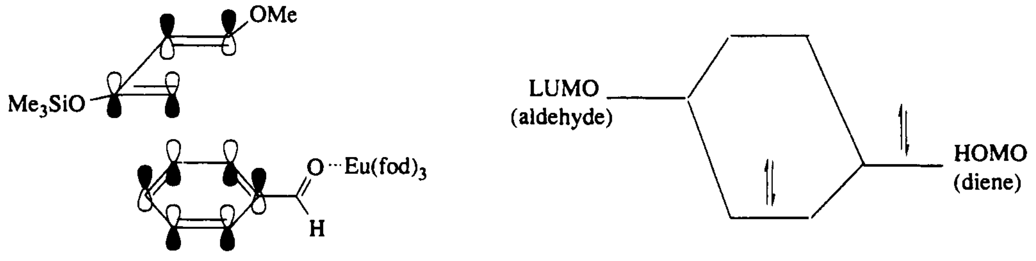

Figure 2

Virtually complete *endo* selectivity is maintained in the reaction of substituted dienes with both aromatic and aliphatic aldehydes. The 2,4-dimethyl diene (**14**), for example, reacts with benzaldehyde, acetaldehyde, or heptanal to give only the *syn* (*endo*) stereoisomers (**29a–c**; Scheme 9). Three stereocenters are established in this suprafacial *endo* cycloaddition process and a fourth stereocenter can be introduced by axial protonation of the silyl enol ether, giving methoxy ketones (**30a–c**). Alternatively, treatment of enol ethers (**30a–c**) with trifluroacetic acid (TFA) yields the *cis* dihydropyrones (**31a–c**; Scheme 10).[45]

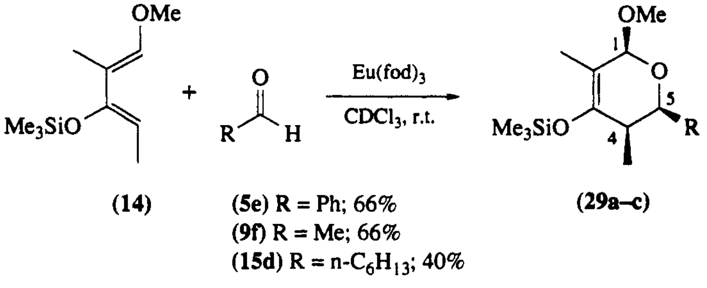

**(14)** (**5e**) R = Ph; 66%
(**9f**) R = Me; 66%
(**15d**) R = n-$C_6H_{13}$; 40%
**(29a–c)**

**Scheme 9**

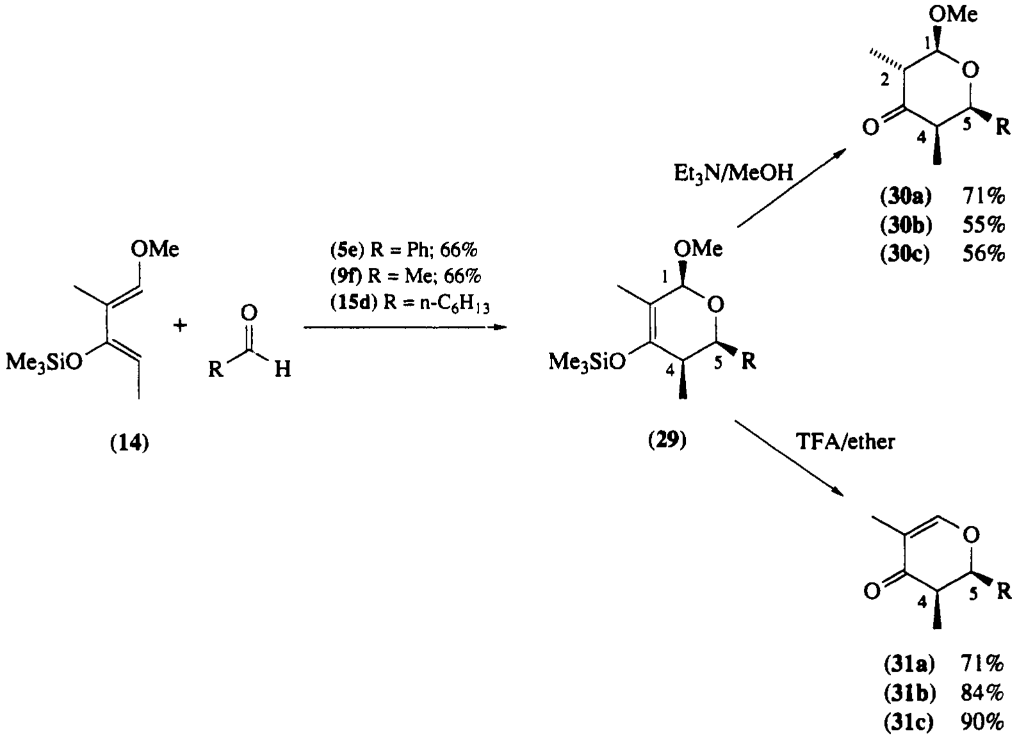

**(14)** **(29)**

| | |
|---|---|
| **(30a)** | 71% |
| **(30b)** | 55% |
| **(30c)** | 56% |

| | |
|---|---|
| **(31a)** | 71% |
| **(31b)** | 84% |
| **(31c)** | 90% |

**Scheme 10**

The high degree of *endo* topography observed for the substituted diene (**14**) may be due to the inherent increase in steric demands of 1,3-disubstituted dienes. The proposed *endo* and *exo* transition states between an aldehyde and the 2,4-dimethyl diene (**14**) are shown in Figure 3. Strong steric interactions can develop between the methyl group of the diene and the lanthanide–aldehyde complex in the *exo* transition state. This interaction, which is not present in the *endo* transition state, strongly disfavors the *exo* mode of addition. It will be shown later that other substitution patterns on the diene are a sufficient perturbation to cause high *endo* selectivity, leading to *syn* products.[46]

The use of the lanthanide catalyst was also investigated with sensitive highly oxygenated dienes.[47] The cycloaddition of furfural with diene (**32**) occurs at room temperature using 0.5 mol % Eu(fod)$_3$ as catalyst (Scheme 11). Treatment of the crude cycloadducts (**33**) with triethylamine and methanol, cleaves the silyl enol ether, while maintaining the sensitive dimethoxyketene acetal to yield compound (**34a**). Reduction of compound (**34a**) with L-selectride gives a 6:1 mixture of axial and equatorial alcohols, which

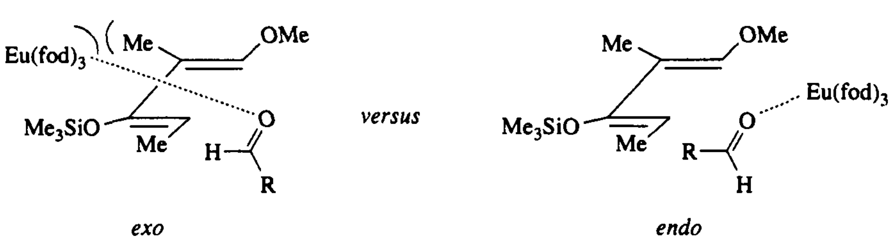
Eu(fod)3
Me
OMe
Me3SiO
Me
O
H
R
versus
Me
OMe
Eu(fod)3
Me3SiO
Me
O
R
H
exo
endo

**Figure 3**

were protected and characterized as the acetate (**35**; Scheme 12). These acetals serve as useful intermediates in synthesis.

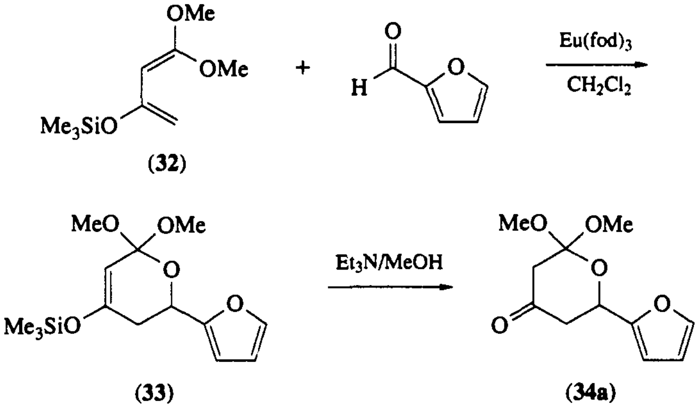
OMe
OMe
Me3SiO
(32)
+
O
H
O
Eu(fod)3
CH2Cl2
MeO
OMe
O
Me3SiO
O
(33)
Et3N/MeOH
MeO
OMe
O
O
O
(34a)

**Scheme 11**

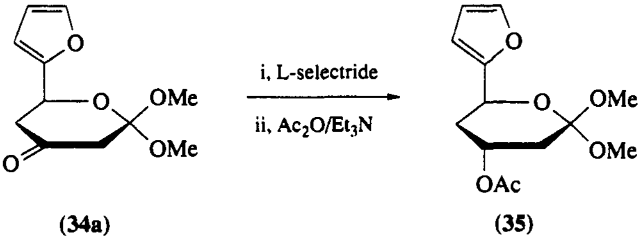
O
O
OMe
OMe
O
(34a)
i, L-selectride
ii, Ac2O/Et3N
O
O
OMe
OMe
OAc
(35)

**Scheme 12**

Castellino and Sims have also used Eu(fod)$_3$ to catalyze the hetero Diels–Alder reaction between a variety of aldehydes and the highly nucleophilic dienes such as (**32**).[49] The resulting dihydropyrones (**36a–d**) are also useful building blocks for natural product synthesis (Table 7).

Observations first made by Danishefsky and later confirmed by Sims and coworkers[48] showed that nucleophilic dienes such as (**32**) react with $\alpha,\beta$-unsaturated aldehydes exclusively at the aldehyde functional group. Sims and coworkers have exploited this observation by condensing cinnamaldehyde (**15d**) with diene (**32**) to produce (**37**), an $\alpha$-pyrone isolated from the kava plant (Scheme 13).[50]

Danishefsky has also reported investigations on the cycloadditions of highly oxygenated dienes such as (**32**) and (**38**) under lanthanide catalysis.[48] This methodology has proven to be a rapid and general route to various dihydropyrone derivatives, including *C*-glycoside units (**39a, b**). These results are summarized in Scheme 14.

Jurczak has reported that Eu(fod)$_3$ can be used to improve conditions for the hetero Diels–Alder reaction of 1-methoxy-1,3-butadiene (**11**) with aldehydes under pressure; yields for this process range from 10 to 80% (Scheme 15). The attempted use of other Lewis acids such as ZnCl$_2$ or BF$_3$·OEt$_2$ failed to give any products and led primarily to polymerization of the diene.[51]

**Table 7** Lanthanide-catalyzed Hetero Diels–Alder Reaction of Highly Activated Dienes with Unactivated and α,β-Unsaturated Aldehydes

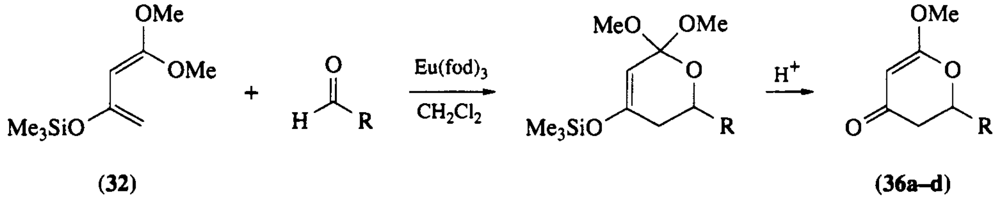
OMe
OMe
Me3SiO
(32)
+
O
H
R
Eu(fod)3
CH2Cl2
MeO
OMe
O
Me3SiO
R
H+
OMe
O
O
R
(36a–d)

| *Aldehyde* | *R* | *Yield (%)* |
|---|---|---|
| (**5e**) | Ph | 85 |
| (**5b**) | $Pr^i$ | 69 |
| (**5d**) | 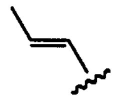 | 70 |
| (**15e**) | 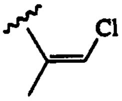 | 87 |
| (**15f**) | CO2Me | 73 |

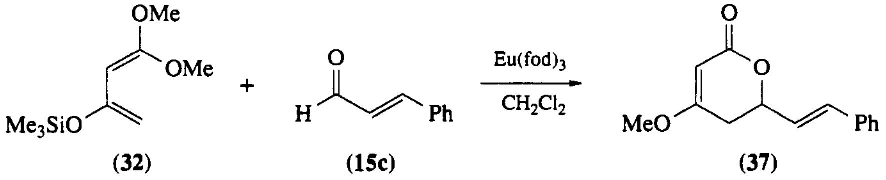
OMe
OMe
Me3SiO
(32)
+
O
H
Ph
(15c)
Eu(fod)3
CH2Cl2
O
O
MeO
Ph
(37)

**Scheme 13**

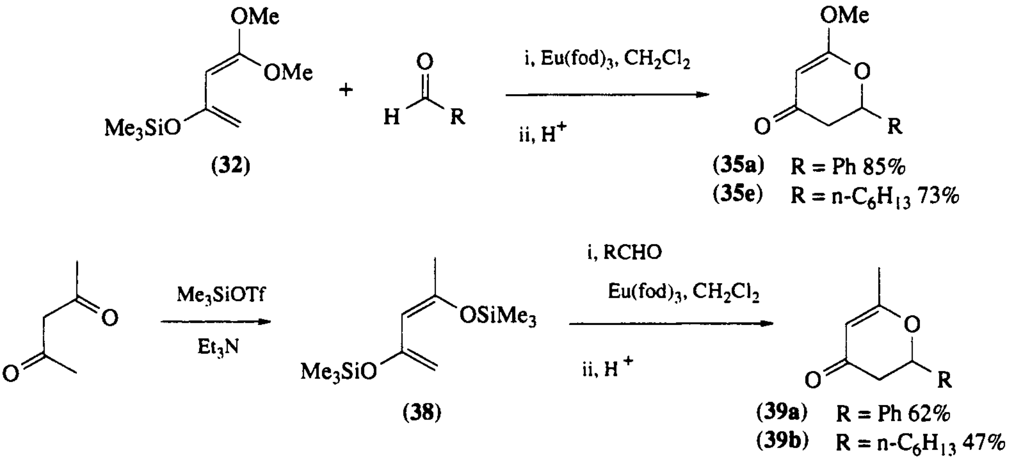
OMe
OMe
Me3SiO
(32)
+
O
H
R
i, Eu(fod)3, CH2Cl2
ii, H+
OMe
O
O
R
(35a) R = Ph 85%
(35e) R = n-C6H13 73%
O
O
Me3SiOTf
Et3N
OSiMe3
Me3SiO
(38)
i, RCHO
Eu(fod)3, CH2Cl2
ii, H+
O
O
R
(39a) R = Ph 62%
(39b) R = n-C6H13 47%

**Scheme 14**

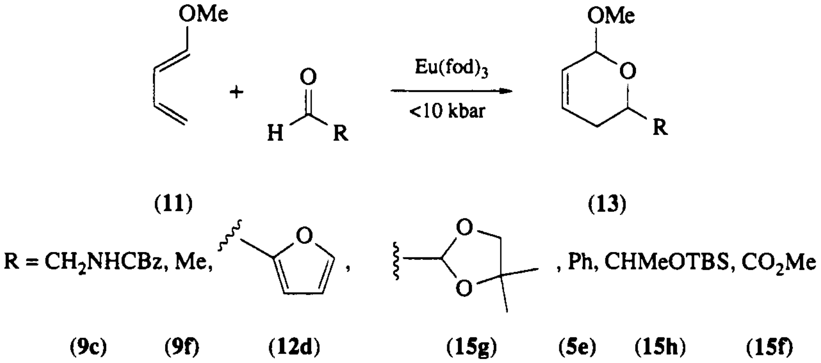
OMe
O
H
R
Eu(fod)3
<10 kbar
OMe
O
R
(11)
(13)
R = CH2NHCBz, Me,
O
O
O
, Ph, CHMeOTBS, CO2Me
(9c)
(9f)
(12d)
(15g)
(5e)
(15h)
(15f)

Scheme 15

### 2.5.2.3 Comparison of Lewis Acid Catalysis: Analysis of Reaction Conditions

Further investigations of the use of Lewis acids with different dienes and under various solvent conditions and temperature expanded the control of stereochemistry in the cyclocondensation reaction. A summary of the results for $ZnCl_2$ in THF is given in Table 8. In general, high *endo* selectivity is observed with this catalyst–solvent system.[33] The modest *endo* selectivity observed for (**9a**) in Table 8, can be explained by a competing β-chelation complex. The benzyloxy group on the aldehyde can complex to the metal, thus restraining the R group to be *syn* to the Lewis acid and forcing an *exo* mode of addition for the diene. There exists, therefore, a competition between chelated and nonchelated dienophiles in cycloadditions of α-alkoxy aldehydes, resulting in decreased *endo* selectivity (Figure 4).[32,33]

**Table 8** Summary of the Stereochemical Results using $ZnCl_2$ in THF as a Catalytic System

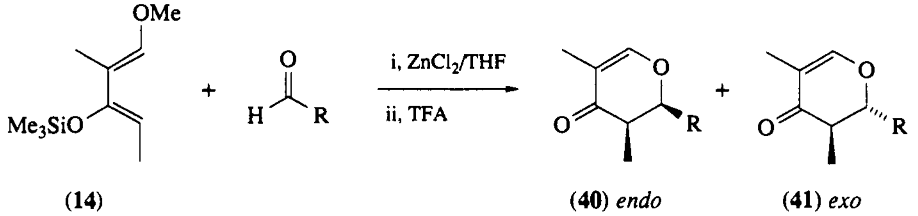
OMe
Me3SiO
O
H
R
i, ZnCl2/THF
ii, TFA
O
O
R
O
O
R
(14)
(40) endo
(41) exo

| *Aldehyde* | *R* | *Yield* (**40**) (%) | *Yield* (**41**) (%) |
|---|---|---|---|
| (**12e**) | n-$C_5H_{11}$ | 91 | 2 |
| (**5e**) | Ph | 78 | <2 |
| (**18**) | PhCHMe | 91 | <2 |
| (**15a**) | $Ph(CH_2)_3$ | 83 | <2 |
| (**9a**) | $PhCH_2OCH_2$ | 66 | 24 |

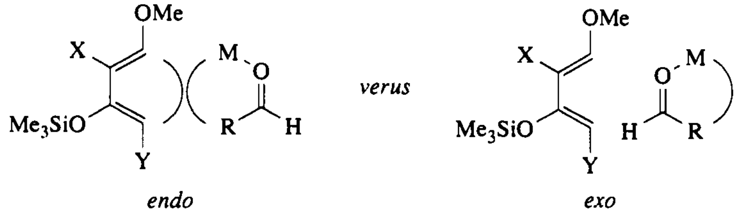
OMe
X
M
O
Me3SiO
R
H
Y
endo
verus
OMe
X
O
M
Me3SiO
H
R
Y
exo

**Figure 4** Steric interactions between metal, aldehyde and the diene disfavor the *endo* transition state. Chelation control should prefer the *exo* transition state in the Diels–Alder cycloaddition pathway

When $MgBr_2$ in THF is used as the Lewis acid catalyst both dienes (**8**) and (**14**) show a high *endo* preference with benzaldehyde (Table 9).[40] As in the case of $Eu(fod)_3$ catalysis, the dimethyl diene (**14**) exhibited a much higher *endo* selectivity than did the unsubstituted diene (**8**). In the case of aldehydes

(**19a**) and (**42**) the *exo (trans)* product is observed. As mentioned previously, magnesium is believed to form chelates with α-alkoxy aldehydes which, in turn, give products derived from *exo* transition states.[40–42]

**Table 9** The Stereoselectivity of $MgBr_2$-catalyzed Cyclocondensation Reaction

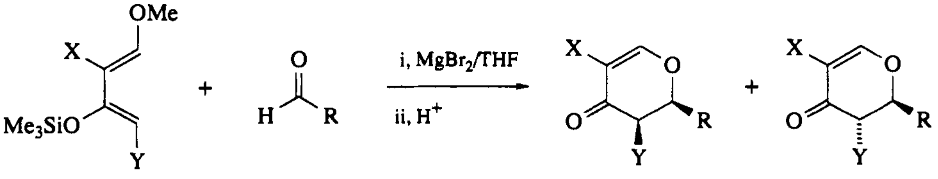

(**8**) or (**14**) *endo (cis)* *exo (trans)*

| *Diene* | *X* | *Y* | *Aldehyde* | *R* | *Endo (cis)* | | *Exo (trans)* |
|---|---|---|---|---|---|---|---|
| (**8**) | H | H | (**5e**) | Ph | 3.6 | : | 1 |
| (**14**) | Me | Me | (**5e**) | Ph | 38 | : | 1 |
| (**14**) | Me | Me | (**9a**) | $BnOCH_2$ | <1 | : | >99 |
| (**14**) | Me | Me | (**42**) | BnOCHMe | <1 | : | >99 |

Diene (**14**) reacted with a series of aldehydes under $BF_3{\cdot}OEt_2$ catalysis in $CH_2Cl_2$ to give predominantly *trans* products (Table 10).[31,32] Aldol-type products, such as β-hydroxy enones, are isolated (along with dihydropyrones) from the reaction mixtures. Using TFA as a catalyst, the β-hydroxy enones are, as previously described, converted into dihydropyrones. The stereoselectivity of these reactions is consistent with a Mukaiyama–aldol reaction rather than a Diels–Alder cycloaddition. The stereochemistry of the β-hydroxy enones is also consistent with the observation that the (*Z*)-alkoxysilane reacts with the aldehyde in an extended transition state to give *anti (threo)* aldol products (Scheme 16). In the cases using $ZnCl_2$ or lanthanide ions as catalysts aldol products have not been detected.

**Table 10** Stereochemistry of $BF_3{\cdot}OEt_2$-catalyzed Aldol Reactions with 2,4-Dimethyl-substituted Diene (**14**)

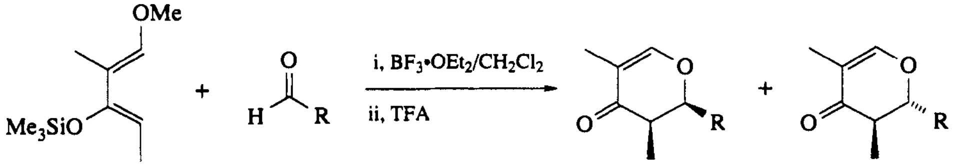

(**14**) (**43**) *endo (cis)* (**44**) *exo (trans)*

| *Aldehyde* | *R* | *Yield (43) (%)* | *Yield (44) (%)* |
|---|---|---|---|
| (**12e**) | n-$C_5H_{11}$ | 21 | 69 |
| (**5e**) | Ph | 23 | 68 |
| (**18**) | PhCHMe | 17 | 73 |
| (**15a**) | $Ph(CH_2)_3$ | 17 | 64 |
| (**9a**) | $PhCH_2OCH_2$ | 17 | 68 |

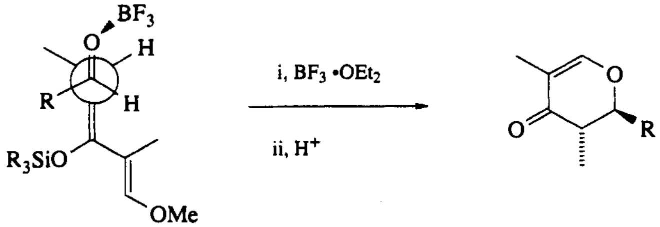

**Scheme 16**

When the monomethylated diene (**45a**) or the benzyloxy diene (**45b**) react under $BF_3{\cdot}OEt_2$ catalysis with benzaldehyde (**5e**) the *cis* pyrones (**46**) are the major products (Table 11).[33,35] This change in diastereoselectivity is consistent with a cycloaddition-type mechanism and not with the previously described aldol pathway.[35] A possible explanation for this change in stereochemistry is that the *s-cis* conformation of the diene that is necessary for a pericyclic reaction is more easily accessible in dienes (**45a**) and (**45b**) than in diene (**14**). An additional substituent (X) at C-2 of the diene causes severe steric interactions with the silyl group when the diene is in an *s-cis* conformation, raising the transition state energy for the cycloaddition pathway for 2,4-disubstituted dienes (Scheme 17). The aldol reaction, on the other hand, operates through an *s-trans* conformation, and this is now the lower energy path. The sense of the topographical diastereoselectivity in the $BF_3{\cdot}OEt_2$-catalyzed reaction is also dependent upon the solvent. When toluene is substituted for $CH_2Cl_2$ a dramatic reversal in diastereoselectivity is observed.[52] It has been suggested that in toluene the Diels–Alder reaction becomes a competitive (and even the dominant) reaction pathway, compared to the aldol process (Table 12). Interestingly, the magnitude of the diastereoselectivity is also dependent upon the silyloxy ligands.[52] The trimethylsilyl protecting group (compared to the *t*-butyldimethylsilyl group) would cause less steric hindrance to occur in the *s-cis* configuration (Table 13). This, in turn, could cause the reaction to proceed through the cycloaddition pathway as previously discussed.

When $TiCl_4$ is used as a catalyst with substituted dienes such as (**14**), a predominant route is the Mukaiyama aldol process.[40–42] When diene (**14**) reacts with benzaldehyde the *trans (anti)* product is observed. When compound (**42**) is used as the aldehyde, one observes exclusive formation of the *(erythro)* aldol products (Table 14). These stereochemical results can be rationalized by using a Zimmerman–Traxler transition state (Scheme 18).[53] Chelation by the metal of the aldehyde α-alkoxy group causes it to be placed in a pseudo axial position in the transition state structure. This results in a stereochemical relationship that gives *syn* aldol products.[54]

In summary, $ZnCl_2$ and the lanthanide catalysts give products derived from a classical [4 + 2] cycloaddition reaction. The side chain on the aldehyde occupies an *endo* position in the transition state, leading to *cis (endo)* products. This is probably due to the large steric bulk of the solvated metal complex, which binds *anti* to the aldehyde side chain. In addition, vinylogous ortho ester products, which are the expected products for a cycloaddition process, can be isolated when using these catalysts. $MgBr_2$ also

**Table 11** The Stereochemistry of the $BF_3$-catalyzed Cyclocondensation Reaction with the C(4)-substituted Diene (**45**)

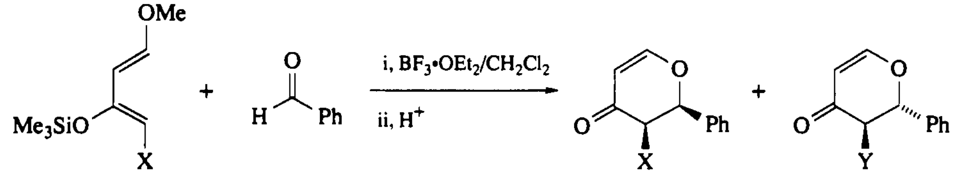

(**45**) (**5e**) (**46**) *cis* (**47**) *trans*

| *Diene* | *X* | *(46)* | *:* | *(47)* |
|---|---|---|---|---|
| (**45a**) | Me | 8.5 | | 1 |
| (**45b**) | OBz | 11 | | 1 |

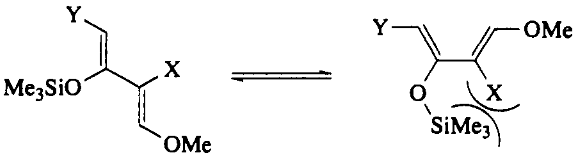

The *s-trans* conformation is favored when X = Me. When X = H however the diene can adopt the *s-cis* conformation. The population of this conformation may be responsible for the change in stereoselectivity in these dienes

**Scheme 17**

Table 12 Solvent Dependence in the Cyclocondensation Reaction using $BF_3$ as a Catalyst

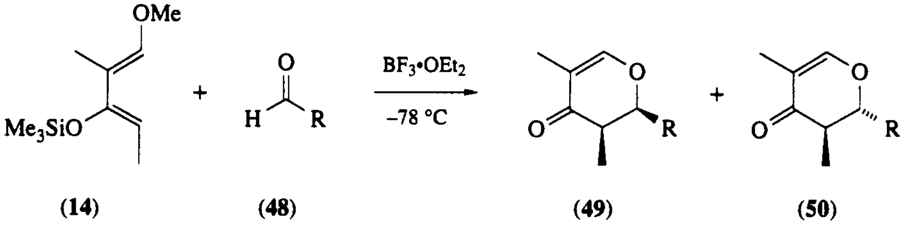

| Aldehyde | R | Solvent | (49) | : | (50) |
|---|---|---|---|---|---|
| (48a) | Ph | $CH_2Cl_2$<br>Toluene | 1<br>7 | | 2.3<br>1 |
| (48b) | PhCHMe | $CH_2Cl_2$<br>Toluene | 1<br>10 | | 2.0<br>1 |
| (48c) | $BnOCH_2$ | $CH_2Cl_2$<br>Toluene | 1<br>1 | | 4.5<br>1.7 |

Table 13 The Dependency of the Silyl Protecting Group on the Stereoselectivity of the Cyclocondensation Reaction using $BF_3$ as a Catalyst

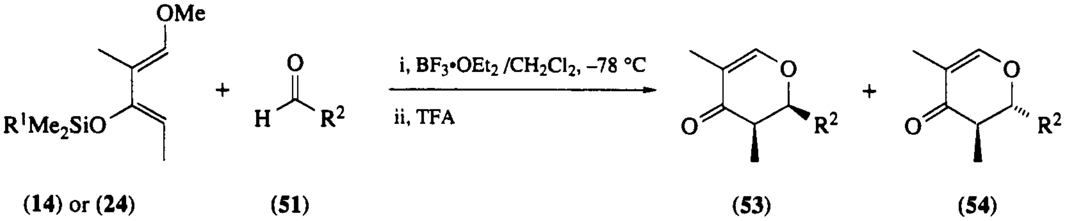

| Diene | Aldehyde | Solvent | (53) | : | (54) |
|---|---|---|---|---|---|
| (14) $R^1$ = Me<br>(24) $R^1$ = $Bu^t$ | (51a) R = Ph<br>(51a) | $CH_2Cl_2$<br>$CH_2Cl_2$ | 1<br>1 | | 2.3<br>4.6 |
| (14)<br>(24) | (51b) R = PhCHMe<br>(51b) | $CH_2Cl_2$<br>$CH_2Cl_2$ | 1<br>1 | | 2.0<br>6.5 |
| (14)<br>(24) | (51a)<br>(51a) | Toluene<br>Toluene | 7<br>2.2 | | 1<br>1 |
| (14)<br>(24) | (51b)<br>(51b) | Toluene<br>Toluene | 10<br>3.7 | | 1<br>1 |

seems to operate through the cycloaddition pathway. The advantage of this catalyst is its capability to form chelates with α-alkoxy aldehydes, resulting in an *exo* transition state that gives *trans (anti)* products. In general, $BF_3{\cdot}OEt_2$ operates through an aldol mechanism. *Syn* pyrones predominate with dienes that have substitution only at C-4. When the diene is substituted at both C-2 and C-4, the *trans* pyrone is the major product. The $BF_3{\cdot}OEt_2$ catalytic system is also very sensitive to solvent conditions. When toluene is substituted for $CH_2Cl_2$ the *syn* pyrone dominates even when using disubstituted dienes such as (**14**). This is probably due to a change in mechanism from the aldol process to the Diels–Alder pathway.

$TiCl_4$ also operates through an aldol reaction mechanism. Unlike $BF_3{\cdot}OEt_2$, however, $TiCl_4$ can form an ordered Zimmerman–Traxler transition state and is also able to chelate α-alkoxy aldehydes. This forces the production of *syn* pyrones from the reaction with aldehydes that contain groups that are able to chelate to the metal; aldehydes that cannot coordinate give *trans* aldol products. Primary [4 + 2] cycloaddition products (*i.e.* vinylogous ortho esters) have not been isolated in the $TiCl_4$-catalyzed reactions.

**Table 14** The Stereochemistry of the Cyclocondensation Reaction using $TiCl_4$ as a Catalyst

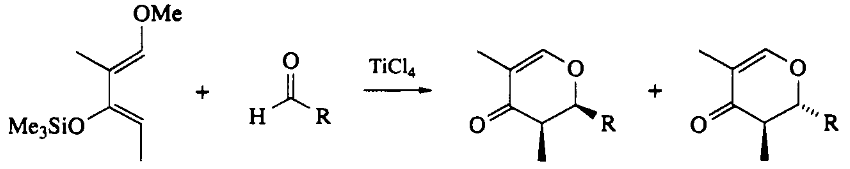
OMe
Me3SiO
+
O
H
R
TiCl4
O
O
R
+
O
O
R

**(14)** *cis (syn)* *trans (anti)*

| *Aldehyde* | *R* | *Cis (syn)/trans (anti)* | | *Cis (syn)/trans (anti)* |
|---|---|---|---|---|
| **(5e)** | Ph | 1 | : | 8 |
| **(42)** | CH(Me)OBn | >99 | : | <1 |

*Non chelation model*

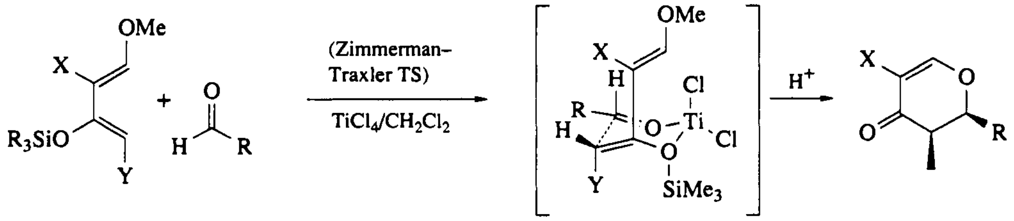
OMe
X
R3SiO
Y
+
O
H
R
(Zimmerman–Traxler TS)
TiCl4/CH2Cl2
OMe
X
H
R
H
Cl
O
Ti
Cl
O
Y
SiMe3
H+
X
O
O
R

**(48)**

*Chelation model*

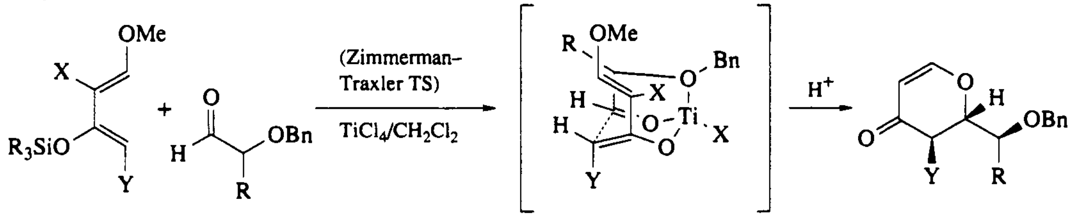
OMe
X
R3SiO
Y
+
O
H
OBn
R
(Zimmerman–Traxler TS)
TiCl4/CH2Cl2
R
OMe
Bn
O
H
X
H
O
Ti
X
O
Y
H+
O
H
OBn
O
Y
R

**(49)**

**Scheme 18**

## 2.5.3 DIASTEREOFACIAL SELECTIVITY

### 2.5.3.1 Cram–Felkin and Anti Cram–Felkin Stereochemical Control

Another major contribution put forth by the Danishefsky group was the realization and exploitation of the stereochemical control available through the use of chiral aldehydes in the cyclocondensation reaction. Scheme 19 shows the possible products that can be produced when a chiral aldehyde is condensed with a substituted diene. $R_L$ represents a group that is the most sterically demanding or has the most electron-withdrawing characteristics; $R_M$ represents a medium-sized group which, in most cases, will be a methyl substituent; X is a group that can chelate to a metal such as a benzyloxy substituent. A chiral aldehyde has two possible faces of attack, which we will denote as Cram–Felkin (CF) or anti Cram–Felkin (ACF) following the nomenclature adopted in the literature for this type of diastereofacial selectivity.[36–38,55] In addition, the pyranose ring can have a *cis (syn)* orientation (*i.e.* products derived from an *endo* pericylic reaction or *syn* aldol) or *trans (anti)* orientation (*i.e.* products derived from an *exo* pericylic reaction or *anti* aldol), which represents the stereochemistry of the aldehyde side chain relative to the substituent on the diene. The simple diastereofacial selectivity for the cyclocondensation reaction (*i.e. endo versus exo* products) was described in the previous section. The terms *cis* and *trans* will be used synonymously with *syn* and *anti* as descriptors of the dihydropyrone stereochemistry because this nomenclature can be used to directly relate the stereochemistry of the products obtained from the cyclocondensation reaction with products derived from the aldol reaction.[55] In the past several years methods have been developed to control the relative stereochemistry (*syn versus anti* and CF *versus* ACF) and the absolute stereochemistry of products obtained from the reaction of activated dienes with aldehydes. These methods are discussed in the following sections.

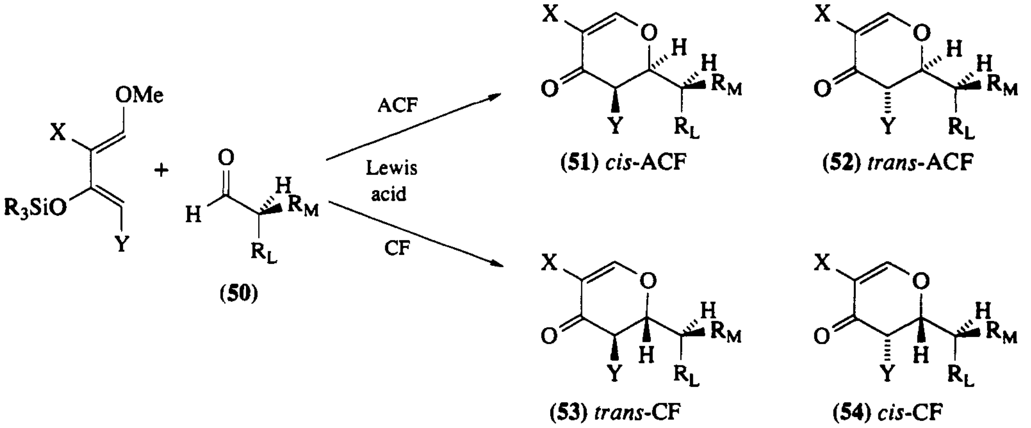

(50)

(51) *cis*-ACF

(52) *trans*-ACF

(53) *trans*-CF

(54) *cis*-CF

Scheme 19

### 2.5.3.2 The Effect of Lewis Acids on Diastereofacial Selectivity

As previously discussed two modes of addition (*endo* and *exo*) are possible for the orientation of the diene with respect to the aldehyde. In addition to these orientations are preferences for a particular diastereofacial selectivity (CF, ACF) for reactions with chiral aldehydes. A summary of these relationships and how the diastereofacial selectivity can be controlled by use of different Lewis acid catalysts is given in Table 15 and Scheme 19.

**Table 15** The Topography and Diastereoselectivity of Different Lewis Acids with Chiral Aldehydes that *cannot* Chelate to the Metal

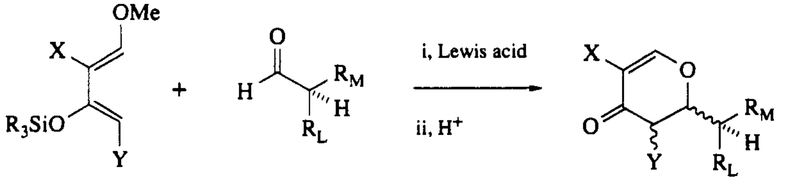

| | *Topography* | | *Diastereofacial selectivity* | | |
|---|---|---|---|---|---|
| *Catalyst* | *Cis/syn (endo)* | *Trans/anti (exo)* | *CF* | *ACF* | *Product* |
| $ZnCl_2$ | + | 0 | + | 0 | **(54)** |
| $BF_3·OEt_2$ (X = H; Y = Me or OBz) | + | 0 | + | 0 | **(54)** |
| $BF_3·OEt_2$ (X = Y = Me) | 0 | + | + | 0 | **(53)** |
| $Eu(fod)_3$ or $Eu(hfc)_3$ | + | 0 | + | 0 | **(54)** |
| $MgBr_2$ | + | 0 | NA | NA | NA |
| $TiCl_4$ | + | 0 | NA | NA | NA |

Table 15 shows the stereochemistry of the cyclocondensation products with chiral aldehydes that contain side chains that do not chelate to the catalyst. Table 16 summarizes the results for chiral aldehydes that are able to chelate the metal. The '+' implies that, in general, compounds from that particular transition state can be expected to be the major product of the reaction. The '0' implies that compounds arising from this transition state are usually minor products. 'NA' indicates the information on this reaction is not available. These catalysts are discussed individually below.

**Table 16** The Topography and Diastereofacial Selectivity of Different Lewis Acids with Chiral Aldehydes that *can* Chelate to the Metal

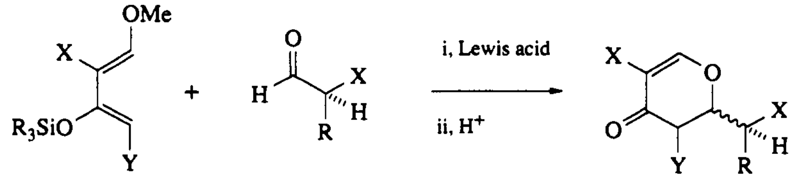

| Catalyst | Topography<br>*Cis/syn (endo)* | <br>*Trans/anti (exo)* | *Diastereofacial selectivity*<br>*CF* | <br>*ACF* |
|---|---|---|---|---|
| $ZnCl_2$ | + | 0 | + | 0 |
| $BF_3·OEt_2$ (X = H; Y = Me or OBz) | + | 0 | + | 0 |
| $BF_3·OEt_2$ (X = Y = Me) | 0 | + | + | 0 |
| $Eu(fod)_3$ or $Eu(hfc)_3$[a] | + | NA | + | + |
| $MgBr_2$ | 0 | + | 0 | + |
| $TiCl_4$ | + | 0 | 0 | + |

[a] One case of chelation controlled has been reported by Midland.

### 2.5.3.2.1 *Zinc chloride and lanthanide complexes*

The use of $ZnCl_2$ and β-diketonate complexes of lanthanide metals give predominately *endo*-type addition products and CF diastereofacial selectivity. The CF stereoselectivity seems to prevail in cases using $ZnCl_2$ as a catalyst and chiral aldehydes that contain groups that do not chelate to the metal. The selectivity clearly decreases when aldehydes that can form chelates are used. The lanthanide catalysts also exhibit strong CF-type selectivity with nonchelating chiral aldehydes. This trend seems to hold with most chelating aldehydes; however, ACF products have been reported when α-alkoxy aldehydes are used in the reaction.[56] The stereochemical consequences of using lanthanide catalysts with α-alkoxy aldehydes are therefore not predictable.

### 2.5.3.2.2 *Boron trifluoride*

$BF_3·OEt_2$ also shows strong CF selectivity, but the topography of the reaction depends on the substitution pattern of the diene. *Endo* products are observed when the diene is substituted at C-4 with a methyl or benzoyloxy group (*e.g.* dienes **45a** and **45b**). *Exo* products, however, dominate when C-2 and C-4 of the diene are substituted with methyl groups (*e.g.* diene **14**). This change in topography of the reaction could be due to a change in mechanism. In the case of dienes (**45a**) and (**45b**) a [4 + 2] cycloaddition process might dominate over the aldol reaction, as previously discussed.

### 2.5.3.2.3 *Magnesium bromide and titanium tetrachloride*

$MgBr_2$ and $TiCl_4$ give ACF products with chiral aldehydes that contain groups that can chelate with the metal. The use of $MgBr_2$ results in an almost exclusive preference for *exo* products, resulting from chelation control in the cycloaddition mechanism; *endo* products are observed for aldehydes that do not form chelates. However, $TiCl_4$ leads to products derived from *endo* topography while retaining the ACF diastereofacial selectivity. This change in diastereofacial selectivity is believed to represent a change in mechanism in which $TiCl_4$ causes an aldol-type reaction to give acyclic products that subsequently cyclize to dihydropyrones. Chelation models using a Zimmerman–Traxler transition state can be used to account for the change in topography while retaining the ACF stereoselectivity.

### *2.5.3.2.4 Summary*

In summary, ACF products are available only through the use of chiral aldehydes with groups that are able to strongly chelate $MgBr_2$ or $TiCl_4$. The *endo* and *exo* topography is tunable by changing the metal: $MgBr_2$ gives *exo (trans* or *anti)* products while $TiCl_4$ gives *endo (cis* or *syn)* products. This allows the construction of both *syn*-ACF and *anti*-ACF products with chiral aldehydes that can form a chelate to the catalyst. Lanthanide catalysts such as $Eu(fod)_3$ and $ZnCl_2$ give *syn*-CF products with chiral aldehydes that do not have groups available for chelation. The stereochemistry when using aldehydes that can form chelates is not predictable for either $ZnCl_2$ or lanthanide catalysts. *Syn*-CF products can, therefore, be obtained with a variety of chiral aldehydes containing nonchelatable groups. To obtain *anti*-CF products the stereochemistry of the diene must be altered. This can be accomplished by synthesizing the (*E*)-alkene (*trans* alkene) on the diene, which, in conjunction with the *endo* topography, can give the *anti* relationship on the resulting dihydropyrone (Scheme 20). Despite the difficulty in obtaining these dienes the ability to obtain the *anti*-CF stereochemistry justifies the effort in many cases (*e.g.* Scheme 53). In summary, by choosing the appropriate catalyst, aldehyde and diene all possible combinations of stereochemistry (*syn*-CF, *anti*-CF, *syn*-ACF and *anti*-ACF) are available.

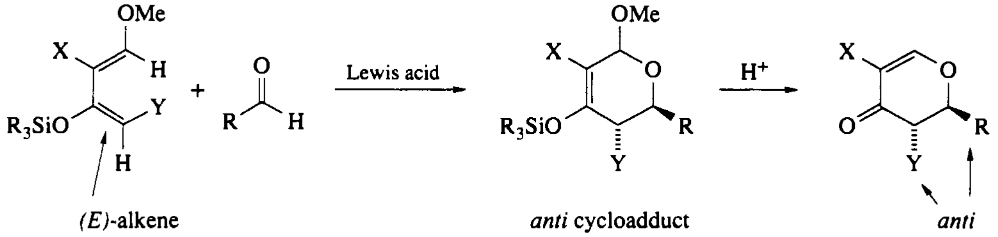

**Scheme 20**

## 2.5.4 METHODS TO CONTROL ABSOLUTE STEREOCHEMISTRY

Methods to control the absolute stereochemistry of the products obtained from the cyclocondensation reaction have also been developed. The use of both chiral auxiliary based methods and chiral catalysts have been investigated. The first and most straightforward method of controlling absolute stereochemistry is the use of a chiral and optically pure aldehyde. All of the methodology developed for the control of relative stereochemistry can then be directly applied to give optically pure cyclocondensation products. In many cases, however, the synthesis of optically pure aldehydes is difficult (if not impossible) due to their tendency to undergo racemization under the reaction conditions. This method also suffers from the fact that only chiral aldehydes can be used in the cyclocondensation reaction to get optically pure products; simple and readily available achiral aldehydes can not be used.

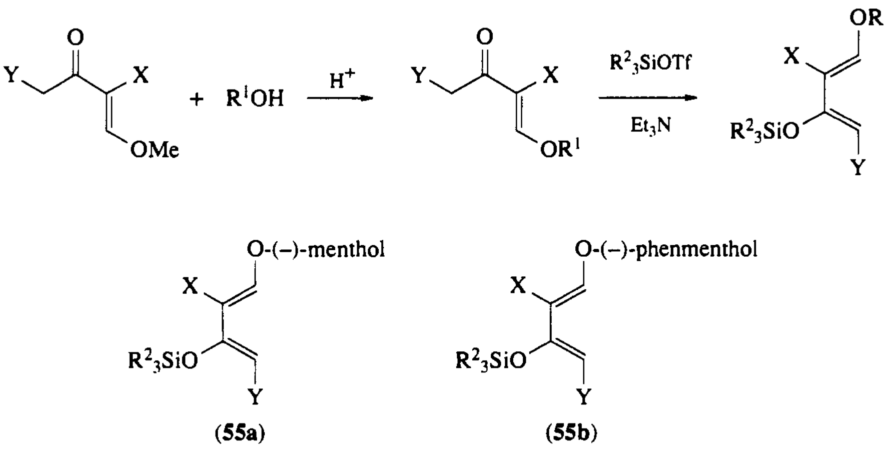

**Scheme 21**

### 2.5.4.1 Chiral Auxiliary Based Methods

The first approach to this problem was to attach the chiral auxiliary to the diene by a vinylogous trans-esterification reaction of chiral alcohols with the β-alkoxy enones (Scheme 21).[57] This reaction was used to construct a variety of chiral dienes including the menthol and phenmenthol dienes (**55a**) and (**55b**) by transesterification followed by enol silylation using the Simchen procedure ($R_3SiOTf/Et_3N$).[58] However, these dienes exhibit poor diastereofacial selectivity despite the precedent for high stereochemical control in homo Diels–Alder reactions by the use of similar auxiliaries on α,β-unsaturated enones.[59–61]

High diastereofacial selectivities, but poor *endo:exo* preferences were observed in the use of chiral dienes (**60**)–(**63**) under thermal reaction conditions with activated aldehydes (Table 17).[62] Despite the low stereoselectivity David used this methodology to synthesize the ABX blood antigen oligosaccharides.

**Table 17** The Topography and Diastereoselectivity of the Hetero Diels–Alder Reaction of Chiral Dienes with Activated Aldehydes

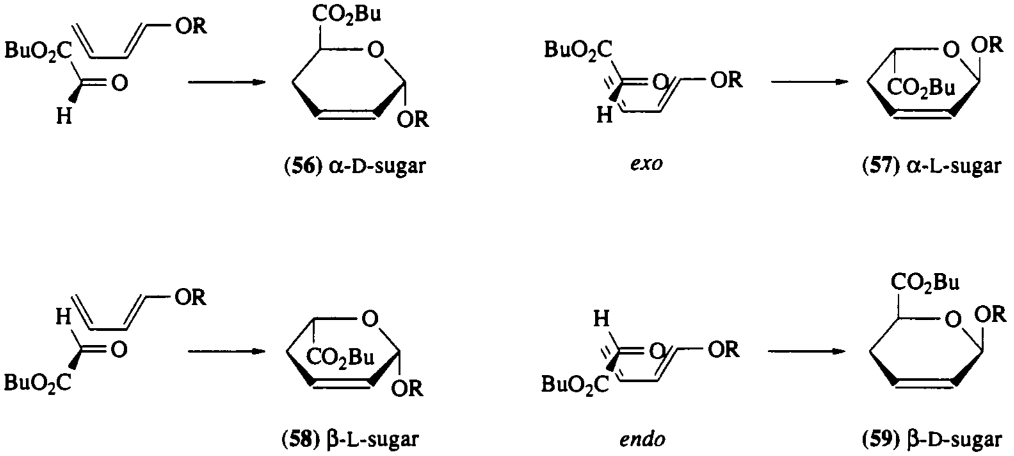

| Diene | (56) α-D (%) | (59) β-D (%) | (57) α-L (%) | (58) β-L (%) |
|---|---|---|---|---|
| (**60**) | 13 | 18 | 9 | 60 |
| (**61**) | 44 | 4 | 0 | 52 |
| (**62**) | 48 | 18 | 0 | 34 |
| (**63**) | 1 | 50 | 47 | 2 |

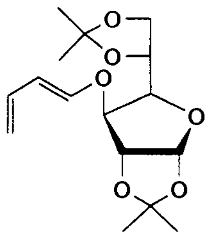

(**60**)

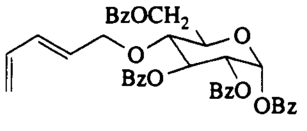

(**61**)

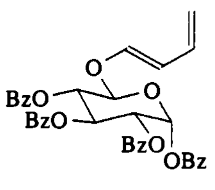

(**62**)

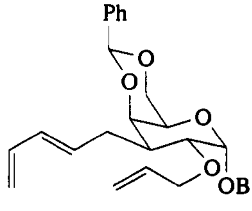

(**63**)

### 2.5.4.2 Chiral Catalysts

With the achievement of high stereochemical control resulting from nearly exclusive *endo* topography in the Lewis acid catalyzed reactions interest next turned to the effect of chiral Lewis acid complexes on the enantiofacial selectivity of the cyclocondensation reaction. For example, consider the cycloaddition of benzaldehyde to diene (**8**) under the influence of a chiral catalyst. Assuming a pericyclic reaction mode and high *endo* selectivity, a mixture of two possible products can result. Compound (**64**) is designated as a D-pyranose and compound (**65**) as an L-pyranose, based on carbohydrate nomenclature (compounds **64** and **65** are, of course, enantiomers). A simple and practical method to synthesize compounds such as (**64**) and (**65**) in either enantiomeric form and in high optical purity is of synthetic value (Scheme 22).

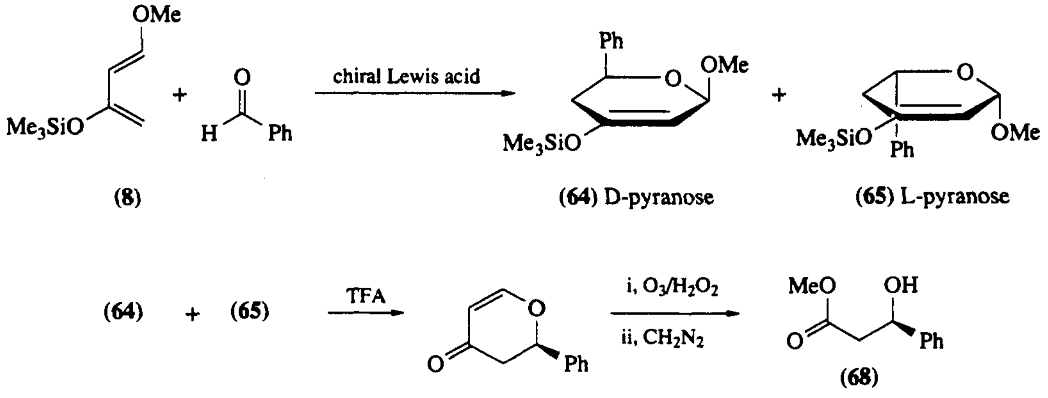
OMe
Me3SiO
+
O
H
Ph
chiral Lewis acid
Ph
O
OMe
Me3SiO
+
O
Me3SiO
Ph
OMe
(8)
(64) D-pyranose
(65) L-pyranose
(64) + (65)
TFA
O
O
Ph
i, O3/H2O2
ii, CH2N2
MeO
OH
O
Ph
(68)

Scheme 22

### 2.5.4.2.1 *Optical induction in the Eu(hfc)$_3$-catalyzed reaction*

The first catalyst to be evaluated was the commercially available chiral lanthanide β-diketonate complex Eu(hfc)$_3$.[63] The reaction of benzaldehyde with diene (**8**) was chosen as the system to screen various catalysts for their enantiofacial selectivity. A simple method to assess the extent and sense of the optical induction was also developed.[63,64] This was accomplished by optical and NMR measurements on compound (**68**), obtained from (**64**) and (**65**) by a previously described protocol (Scheme 22).[30–33] The enantioselectivity with diene (**8**) and benzaldehyde is 18%.[64]

Attempts to improve the asymmetric induction by varying the substituents on the diene was explored (Scheme 23). Substitution at either C-2 or C-4 of the diene seemed to increase the optical induction. By using the 2,4-dimethyl diene (**14**), for example, the *ee* is increased to 36%.[64] Interestingly, both the 2-methyl diene (**66a**) and 2-acetoxy diene (**66b**) show no significant improvement in facial selectivity over the parent diene (**8**).

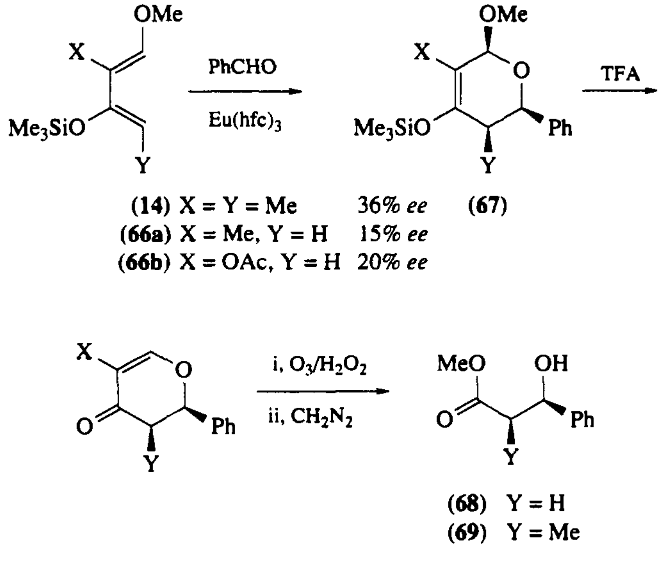
OMe
X
Me3SiO
Y
PhCHO
Eu(hfc)3
OMe
X
O
Me3SiO
Ph
Y
TFA
(14) X = Y = Me 36% ee
(66a) X = Me, Y = H 15% ee
(66b) X = OAc, Y = H 20% ee
(67)
X
O
O
Ph
Y
i, O3/H2O2
ii, CH2N2
MeO
OH
O
Ph
Y
(68) Y = H
(69) Y = Me

Scheme 23

To help improve the optical induction in the chiral lanthanide catalyzed reaction the C-1 alkoxy group on the diene was also varied systematically. The previously described transesterification reaction provides an easy method to install different alkoxy groups at the C-1 position of the diene by conducting an exchange reaction of various enones (**70**) with alcohols ($R^3OH$) in refluxing benzene (Scheme 24). Pyridinium *p*-toluenesulfonate (PPTS) is an effective acid catalyst for this reaction, since it is sufficiently mild to allow survival of sensitive functionality in both the alcohol and enone components. With inexpensive volatile alcohols such as $Bu^tOH$, $R^3OH$ is used in excess. When the alcohol is less readily available, nearly equivalent molar ratios can be employed. In some instances, a 3:1 excess of enone was helpful in driving the exchange reaction to completion. In this fashion, readily available β-methoxy enones (**73a**), (**74a**) and (**74d**) have been converted in the indicated yields to enones (**73b–f**) and (**74b, c, e–g**), respectively (Table 18). The resulting exchanged enones can be converted to dienes by the previous described enolsilylation procedure.[58]

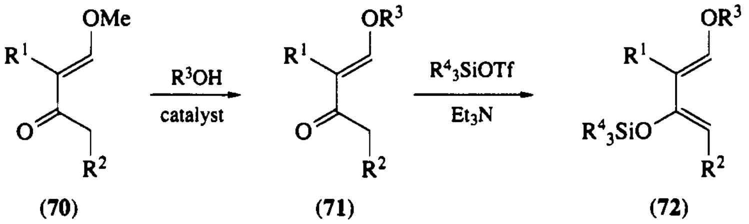

Scheme 24

Table 18 β-Alkoxy Enones Available Through the Vinylogous Transesterification Reaction

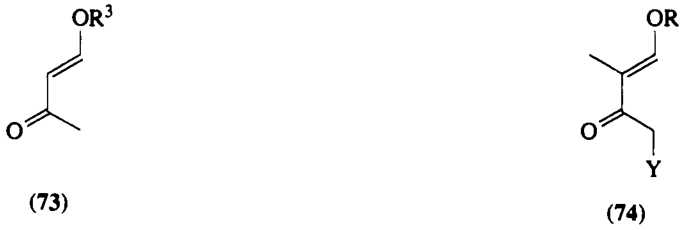

| *Enone* | $R^3$ | *Yield (%)* | *Enone* | $R^3$ | *Y* |
|---|---|---|---|---|---|
| (**73a**) | Me | | (**74a**) | Me | H |
| (**73b**) | $Bu^t$ | 55 | (**74b**) | $Bu^t$ | H |
| (**73c**) | (+)- or (−)-menthyl | 80 | (**74c**) | (−)-Menthyl | H |
| (**73d**) | (−)-8-Phenmenthyl | 94 | (**74d**) | Me | Me |
| (**73e**) | (+)- or (−)-Phenethyl | 72 | (**74e**) | (−)-Menthyl | Me |
| (**73f**) | 3-Cholestanyl | 92 | (**74f**) | (−)-Phenmenthyl | Me |
| | | | (**74g**) | (+)- or (−)-Phenethyl | Me |

With the ability to change the C-1 functionality of the diene, investigations focused on the effects these changes had on the optical induction in the chiral lanthanide catalyzed cycloaddition reaction. The presence of large achiral alkoxy groups at C-1 of the diene results in a significant increase in facial selectivity (**75a,b**; Scheme 25).[64] In the case of the 2-methyl diene (**66a**) and the 2,4-dimethyl diene (**14**), changing the C-1 methoxy to a *t*-butoxy group increases the *ee* from 15% to 39% in the former and from 36% to 42% in the latter (Scheme 26). When using the 2-acetoxy diene (**77a**) and the corresponding 2-siloxy diene (**77b**), substantial increases in *ee* from 29% and 18% to 33% and 42%, respectively, occurred by replacing the methoxy group with the *t*-butoxy group (Scheme 27).

Finally, with two of the dienes the induction was maximized by modifying the experimental conditions. By conducting the reactions of dienes (**76a**) and (**76b**) in the absence of solvent and at reduced temperatures up to 55% and 58% *ee*, respectively, could be obtained.[64]

While the exact causes of the induction are not clearly understood, there seem to be some important general conclusions to be drawn from these experiments. First, chiral lanthanide complexes that are the most effective NMR shift reagents [*e.g.* $Eu(hfc)_3$] seem to give the best optical induction. Interestingly, $Eu(hfc)_3$ is also known to be one of the most acidic shift reagents since it carries the greatest number of

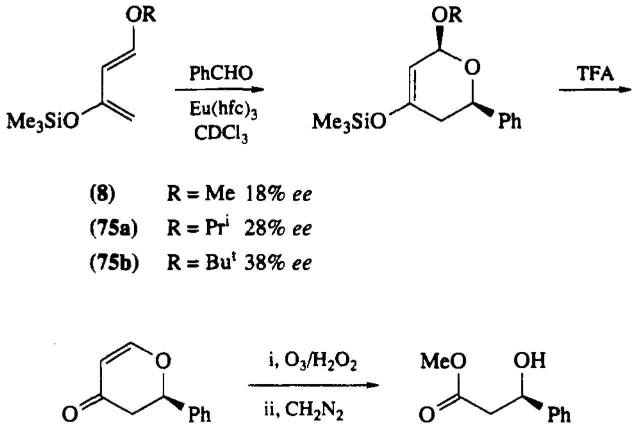
OR
Me3SiO
PhCHO
Eu(hfc)3
CDCl3
O
Ph
TFA
i, O3/H2O2
ii, CH2N2
MeO
OH

**(8)** R = Me 18% *ee*
**(75a)** R = $Pr^i$ 28% *ee*
**(75b)** R = $Bu^t$ 38% *ee*

Scheme 25

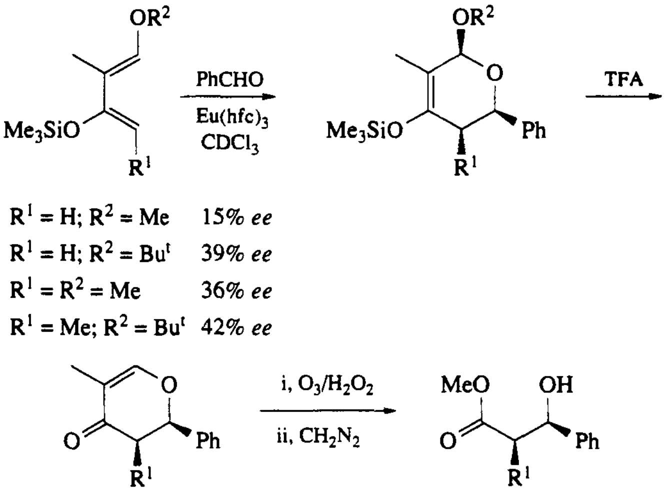
OR2
Me3SiO
R1
PhCHO
Eu(hfc)3
CDCl3
O
Ph
TFA
i, O3/H2O2
ii, CH2N2
MeO
OH

**(66a)** $R^1$ = H; $R^2$ = Me 15% *ee*
**(76a)** $R^1$ = H; $R^2$ = $Bu^t$ 39% *ee*
**(14)** $R^1$ = $R^2$ = Me 36% *ee*
**(76b)** $R^1$ = Me; $R^2$ = $Bu^t$ 42% *ee*

Scheme 26

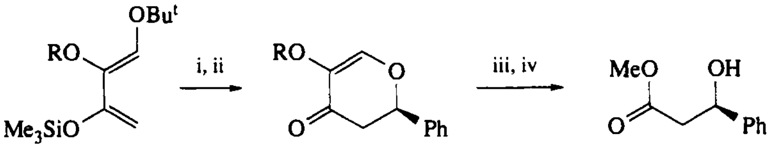
OBut
RO
Me3SiO
i, ii
RO
O
Ph
iii, iv
MeO
OH

**(77a)** R = Ac 33% *ee*
**(77b)** R = $Me_3Si$ 42% *ee*
**(78a)** R = Ac
**(78b)** R = $Me_3Si$

i, PhCHO, Eu(hfc)$_3$, $CDCl_3$, r.t.; ii, TFA; iii, $O_3/H_2O_2$; iv, $CH_2N_2$

Scheme 27

electron-withdrawing fluorine atoms on its ligands.[65] Secondly, conducting the reactions in nonpolar aprotic solvents or in the absence of any solvent and at reduced temperatures also helps increase the extent of optical induction. Finally, and most importantly, changing the substituents on the diene can dramatically affect the facial selectivity. Especially important in this respect is the C-1 position. It will be shown later that with the correct choice of alkoxy group a stereofacial selectivity of greater than 90% can be obtained (*e.g.* Table 25).

Major progress has recently been made in developing chiral catalysts for the cyclocondensation reaction. Initial investigations using chiral lanthanide complex Eu(hfc)$_3$ showed promising results. A study by Jankowski and coworkers has recently surveyed the use of a variety of chiral catalysts in the cyclocondensation reaction of chiral dienes with aldehydes.[66] A summary of these results is given in Table 19. The lanthanide catalyst Eu(hfc)$_3$ gave the highest (albeit modest) enantiofacial selectivity at 64% *ee*.

**Table 19** Asymmetric Diels–Alder Reactions using Chiral Catalysts: Comparison of Eu(hfc)$_3$ with Menthol Aluminum Dichloride (Men*OAlCl$_2$)

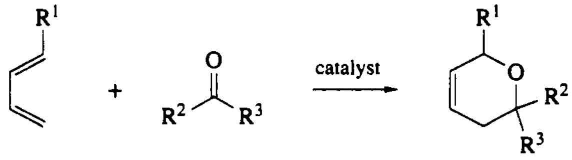

| *Diene* | *Dieneophile* | *Catalyst* | *Yield (%)* | *ee (%)* |
|---|---|---|---|---|
| $R^1$ = OMe | $R^2 = R^3 = CO_2Et$ | Men*OAlCl$_2$ | 30 | 9 |
| | | Eu(hfc)$_3$ | 100 | 15 |
| $R^1$ = Me | $R^2 = R^3 = CO_2Et$ | Men*OAlCl$_2$ | 15 | 4 |
| | | Eu(hfc)$_3$ | $>1$ | — |
| $R^1$ = OMe | $R^2 = H_2$; $R^3 = CO_2Bu$ | Men*OAlCl$_2$ | *cis* : 17 | 16 |
| | | | *trans* : 9 | 3 |
| | | Eu(hfc)$_3$ | *cis* : 19 | 64 |
| | | | *trans* : 79 | 39 |
| $R^1$ = Me | $R^2 = H_2$; $R^3 = CO_2Bu$ | Men*OAlCl$_2$ | *trans* : 25 | $<1$ |
| | | | *cis* : 6 | 5 |
| | | Eu(hfc)$_3$ | *trans* : 6 | 5 |
| | | | *cis* : trace | |

### 2.5.4.2.2 *Optical induction using a chiral aluminum catalyst*

Yamamoto and coworkers have recently found a chiral aluminum catalyst (**79**) that catalyzes the hetero cyclocondensation reaction (Scheme 28).[67] In the reaction of benzaldehyde with diene (**14**) an enantiofacial selectivity of up to 95% *ee* was observed. A summary of substituted aldehydes and dienes used in this study is given in Table 20. As with the Eu(hfc)$_3$ catalyst, the more substituted dienes give higher enantiofacial selectivity. Aromatic aldehydes are the best substrates and xylyl groups give the most efficient catalysts. The aluminum catalyst has also been extended to other simple aldehydes (Table 21) and has recently been used for the resolution of racemic dienophiles.[67]

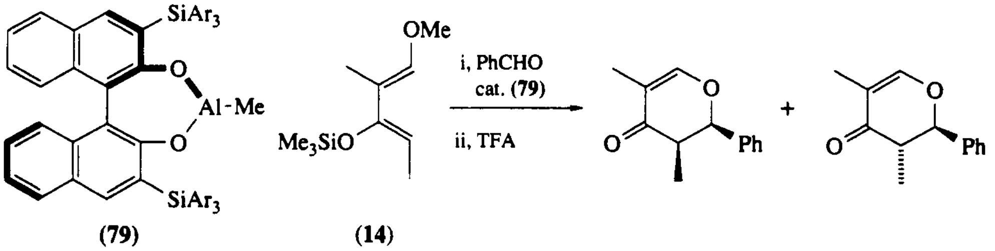

(**79**) (**14**)

**Scheme 28**

**Table 20** The Enantiofacial Selectivity of Various Chiral Aluminum Catalysts with Benzaldehyde

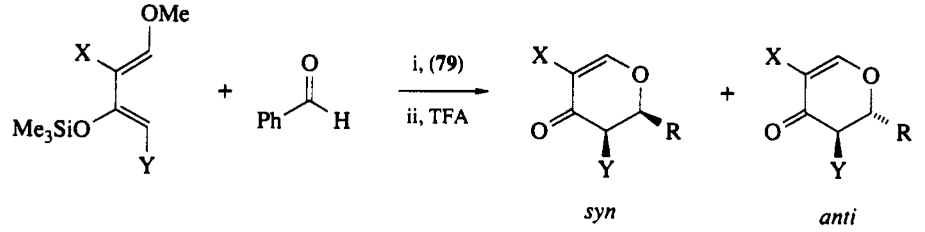

| *Diene* | *Catalyst (79)* | *Temperature (°C)* | *Yields syn:anti* | *ee (%)* |
|---|---|---|---|---|
| X = Y = Me | Ar = Ph | 0 | 89:7 | 92 (2*R*,3*R*) |
| X = Y = Me | Ar = Ph | –20 | 77:7 | 95 (2*R*,3*R*) |
| X = Y = Me | Ar = Ph | –78 | 75:7 | 95 (2*R*,3*R*) |
| X = Y = Me | Ar = 3,5-Xylyl | 0 | 90:3 | 97 (2*R*,3*R*) |
| X = Y = H | Ar = Ph | –20 | 71 | 67 (*R*) |
| X = Y = H | Ar = 3,5-Xylyl | –20 | 81 | 81 (*R*) |
| X = Y = H | Ar = 3,5-Xylyl | –78 | 88 | 85 (*R*) |
| X = H; Y = Me | Ar = Ph | –20 | 91:5 | 95 (2*R*,3*R*) |
| X = OAc; Y = H | Ar = 3,5-Xylyl | –20 | 83 | 90 (2*S*,3*R*) |

**Table 21** The Enantiofacial Selectivity of Various Aldehydes with Chiral Aluminum Catalysts

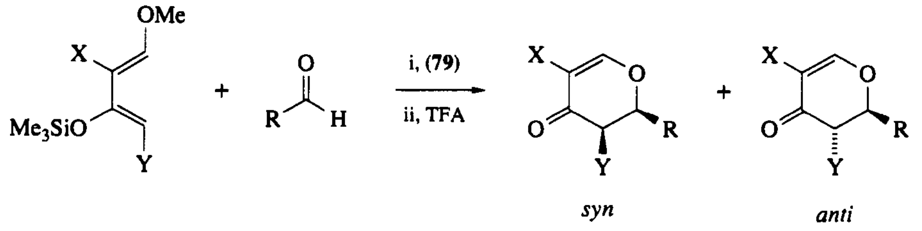

| *Diene* | *Aldehyde* | *Catalyst* | *Temperature (°C)* | *Yields syn:anti* | *ee (%)* |
|---|---|---|---|---|---|
| X = Y = Me | R = PhCH═CH (*E*) | Ar= Ph | -20 | 89:10 | 90(*S*,3*R*) |
| X = Y = Me | R = PhCHCH (E) | Ar = 3,5-Xyly | 0 | 93:2 | 96 (2*S*,3*R*) |
| X = Y = Me | R = $C_6H_{11}$ | Ar = Ph | –20 | 65 | 91 (2*S*,3*R*) |
| X = H; Y = Me | R = $C_6H_{11}$ | Ar = Ph | –20 | 76:9 | 93 (2*S*,3*R*) |
| X = Y = Me | R = $Bu^n$ | Ar = Ph | –20 | 62:18 | 86 (2*S*,3*R*) |

### *2.5.4.2.3 Double diastereofacial selectivity*

To achieve high stereoselectivity applicable to any aldehyde in the cyclocondensation reaction the use of double diastereofacial selectivity has been investigated. These studies revealed an interesting relationship between the chiral catalyst used in the reaction and the chiral auxiliary. Contrary to the notion that the selectivity of a chiral diene and chiral dienophile are enhanced only in a matched pair,[68] the interactivity of a chiral catalyst with a chiral diene where the two individual components have an opposite facial preference seems to give a high degree of asymmetric induction in the cyclocondensation reaction.[63]

Dienes (**80**) and (**81**) were synthesized by previously described methods. The inherent facial selectivities of these dienes in their reactions with benzaldehyde under achiral [Eu(fod)$_3$] catalysis were determined (Scheme 29). In line with previous precedents, these reactions are highly *endo* specific, thus giving rise to a two-component mixture of (**82**) and (**83**). The extent and sense of the facial inductions were ascertained by conversion of this mixture to (**68**) and (**69**). The optical purities of compounds (**68**) and (**69**) were determined by NMR methods using chiral shift reagents.[63,64] The data shown in Scheme

29 for the reactions starting with the (+)-menthyloxy dienes reveals a modest bias in favor of the 'D-pyranose' products (**82**), over their L-facial isomers (**83**).[63]

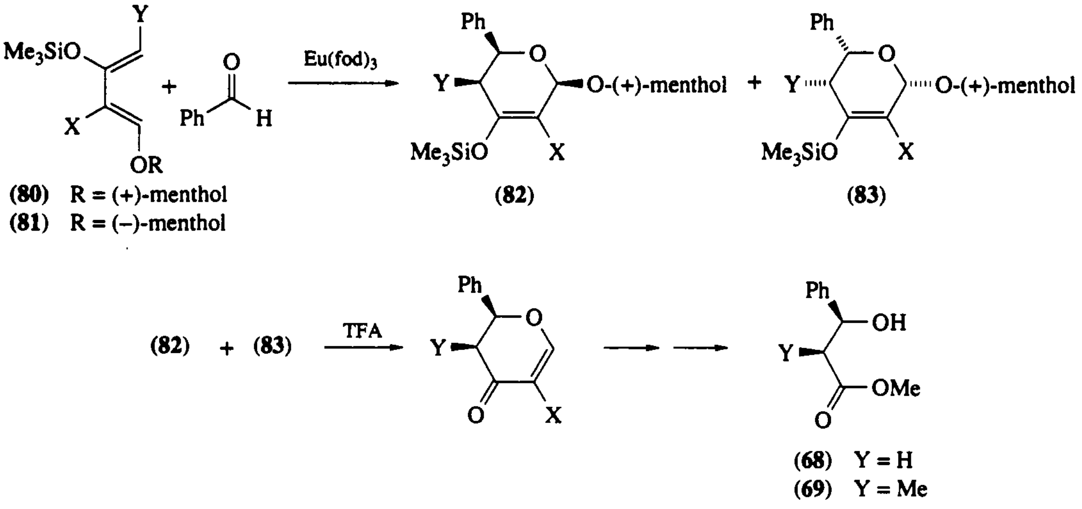

(**80**) R = (+)-menthol
(**81**) R = (–)-menthol

(**82**) (**83**)

(**68**) Y = H
(**69**) Y = Me

| | | |
|---|---|---|
| (**80a**) | X = Y = H | 27% *ee* |
| (**80b**) | X = Me; Y = H | 10% *ee* |
| (**80c**) | X = OAc; Y = H | 10% *ee* |
| (**80d**) | X = Y = Me | 2% *ee* |

**Scheme 29**

The cyclocondensation reactions of these chiral dienes with benzaldehyde, under the influence of the chiral catalyst Eu(hfc)$_3$ were then examined.[71] The data are provided in Table 22. The inherent facial selectivity data for the Eu(fod)$_3$ reactions of the same dienes with benzaldehyde are given in parentheses.

**Table 22** The Results of Mixing Matched and Mismatched Pairs of (+)- and (–)-Menthyloxy Dienes with Eu(hfc)$_3$

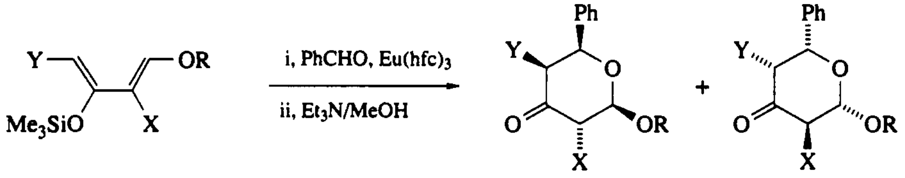

(**80**) R = (+)-menthol
(**81**) R = (–)-menthol

(**84**) (**85**)
(**86**) (**87**)

| *Diene* | *X* | *Y* | *(84) (%)* | *(85) (%)* | *Diene* | *X* | *Y* | *(86) (%)* | *(87) (%)* |
|---|---|---|---|---|---|---|---|---|---|
| (**80a**) | H | H | 37 (37) | 63 (63) | (**81a**) | H | H | 25 (63) | 75 (37) |
| (**80b**) | Me | H | 41 (45) | 59 (55) | (**81b**) | Me | H | 8 (55) | 92 (45) |
| (**80c**) | OAc | H | 41 (45) | 59 (55) | (**81c**) | OAc | H | 7 (55) | 93 (45) |
| (**80d**) | Me | Me | 49 (49) | 51 (51) | (**81d**) | Me | Me | 13 (51) | 87 (49) |
| (**80e**)[a] | H | Me | 34 (37) | 66 (63) | (**81e**)[a] | H | Me | 14 (63) | 86 (37) |

[a] TBDMSO diene used instead of the TMSO diene.

Recall that the intrinsic enantiotopic preference of the Eu(hfc)$_3$ catalyst with achiral alkoxy groups and benzaldehyde as the heterodienophile is in the 'L-pyranose' direction. Comparison of the Eu(hfc)$_3$ and Eu(fod)$_3$ diastereoselectivities in the case of (+)-menthyloxy diene (**80**) reveals essentially no cooperativity of the chiral elements. The situation is strikingly different in the case of the Eu(hfc)$_3$-catalyzed reactions of the (–)-menthyloxy diene (**81**). These reactions, upon similar work-up, afford facial isomers (**86**) and (**87**), which are processed in the same way as (**84**) and (**85**).

The highest degree of diastereoselectivity is between the mismatched pairs. The normal low diastereoselectivity of the (–)-menthyloxy diene is completely reversed and enhanced by using the chiral catalyst with opposite enantiofacial selectivity. Since the primary cycloadducts also contain the chiral auxiliary, the major stereoisomers can be purified and subsequently eliminated to give optically pure dihydropyrones. This method can, therefore, be used as a general method for synthesis of a variety of optically pure dihydropyrones.

The (–)-phenmenthol parent diene (**88**) and (+)-$Eu(hfc)_3$ combination can also be used with a variety of aldehydes to produce optically pure cycloadducts (**90a–d**) with high diastereofacial selectivity (Table 23).[69] Separation of minor isomers can be easily accomplished by flash chromatography or crystallization at the stage of the cycloadducts. Treatment of the optically pure cycloadducts with TFA gives good yields of the L-pyranosides (**90a–d**). In many cases the less elaborate (–)-menthol diene can be used in place of the (–)-phenmenthol diene, as shown in Table 24 for benzaldehyde and furfural. Despite the lower diastereofacial selectivity the convenience of the menthol auxiliary can, in many cases, outweigh this disadvantage. As with the phenmenthol dienes, the cycloadducts can be obtained in optically pure form by chromatography or crystallization. A summary of the highest diastereofacial selective reactions using a combination of a chiral diene and catalyst is given in Table 25.

A variety of methods are now available to control the relative and absolute stereochemistry of the cyclocondensation reaction of activated dienes with aldehydes. Chiral aldehydes that posses a high degree of diastereofacial selectivity with a variety of dienes can be used and the stereoselectivity controlled by the choice of diene, aldehyde and catalyst. Chiral dienes in combination with chiral catalysts can also be used in an unusual process of double diastereofacial selectivity. The resulting adducts can be purified and eliminated to give optically pure dihydropyrones. The chiral auxiliary can be isolated and reused if

**Table 23** The Use of the (–)-Phenmenthol Diene and $Eu(hfc)_3$ Catalyst in the Process of Double Asymmetric Induction

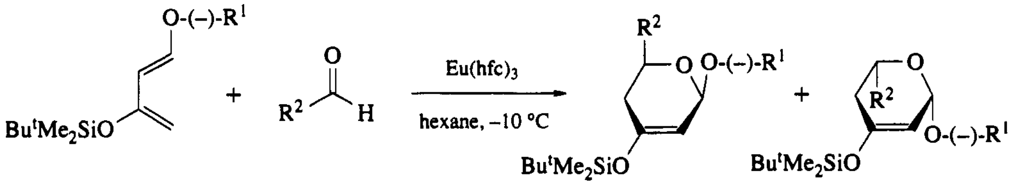

(**88**) R$^1$ = phenmenthol (**89**) D-pyranoside (**90**) L-pyranoside

| *Aldehyde* | *R²* | *(89)* | *(90)* |
|---|---|---|---|
| (**5e**) | Ph | 1 | 25 |
| (**5d**) | MeCH═CH (*E*) | 1 | 6.4 |
| (**12d**) | 2-Furyl | 1 | 22 |
| (**9f**) | Me | 1 | 5.6 |

**Table 24** The Practical Use of the (–)-Menthol Diene in the Process of Double Asymmetric Induction

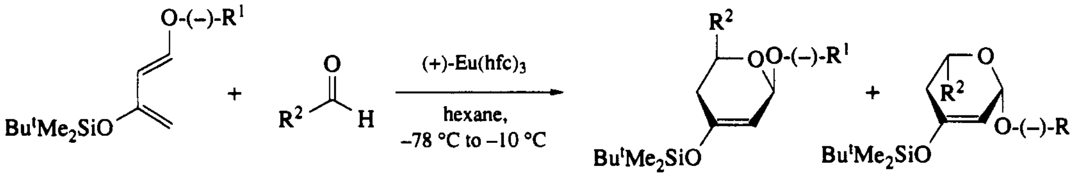

(**91**) R$^1$ = menthol (**92**) D-pyranoside (**93**) L-pyranoside

| *Aldehyde* | *R²* | *(92)* | *(93)* |
|---|---|---|---|
| (**5e**) | Ph | 1 | 7.2 |
| (**12d**) | 2-Furyl | 1 | 5.8 |

**Table 25** A Comparison of Chiral Dienes in the Process of Double Asymmetric Induction

*Chiral interactivity: (–)-menthol*

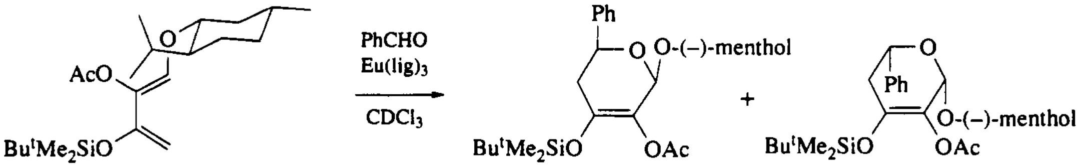
AcO
$Bu^tMe_2SiO$
O
PhCHO
$Eu(lig)_3$
$CDCl_3$
Ph
O
O-(–)-menthol
$Bu^tMe_2SiO$
OAc
+
O
Ph
O-(–)-menthol
$Bu^tMe_2SiO$
OAc

**(94)** **(95)** D-sugar **(96)** L-sugar

| *Diene (**94**)* | *Catalyst* | *$Eu(lig)_3$* | *(**95**)* | *(**96**)* |
|---|---|---|---|---|
| D-Selective | Achiral | $Eu(fod)_3$ | 1.22 | 1 |
| D-Selective | D-Selective | $(-)$-$Eu(hfc)_3$ | 1.44 | 1 |
| D-Selective | L-Selective | $(+)$-$Eu(hfc)_3$ | 1 | 13.3 |

*Chiral interactivity: (–)-phenmenthol*

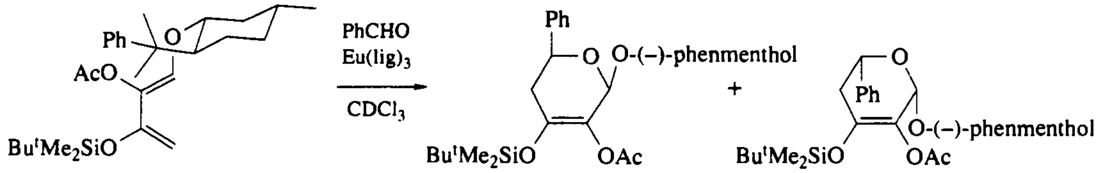
Ph
O
AcO
$Bu^tMe_2SiO$
PhCHO
$Eu(lig)_3$
$CDCl_3$
Ph
O
O-(–)-phenmenthol
$Bu^tMe_2SiO$
OAc
+
O
Ph
O-(–)-phenmenthol
$Bu^tMe_2SiO$
OAc

**(97)** **(98)** D-sugar **(99)** L-sugar

| *Diene (**97**)* | *Catalyst* | *$Eu(lig)_3$* | *(**98**)* | *(**99**)* |
|---|---|---|---|---|
| D-Selective | Achiral | $Eu(fod)_3$ | 1.50 | 1 |
| D-Selective | D-Selective | $(-)$-$Eu(hfc)_3$ | 2.07 | 1 |
| D-Selective | L-Selective | $(+)$-$Eu(hfc)_3$ | 1 | 25 |

necessary. Finally, chiral catalysts such as the aluminum–binaphthalene complexes are available which give high enantiofacial selectivity.

## 2.5.5 APPLICATIONS IN ORGANIC SYNTHESIS

### 2.5.5.1 Simple Monosaccharides

The most straightforward application of the cyclocondensation reactions of aldehydes with activated dienes is in the synthesis of simple monosaccharides.[30] Condensation of diene (**100**) with benzyloxyacetaldehyde (**9a**) using $BF_3{\cdot}EtO_2$ as a catalyst, followed by treatment with TFA, gives the dihydropyrone (**102**). Reduction of (**102**) using DIBAL-H followed by hydroxylation of the glycal gives, after deprotection, talose (**103**; Scheme 30).

More complex monosaccharides such as daunosamine and fucose are assembled using a similar strategy (Scheme 31).[33] Cyclocondensation of diene (**104**) with acetaldehyde (**9f**) using the lanthanide catalyst $Eu(hfc)_3$ gives the *syn* cycloadduct (**105**). Treatment of (**105**) with TFA followed by oxymercuration [$Hg(OAc)_2$–$NaCNBH_4$] and reductive amination of the oxime acetate (derived from the ketone) gives daunosamine (**108**). Fucose (**107**) is prepared from compound (**106**) by reduction of the ketone and treatment of the glycal with MCPBA in methanol.

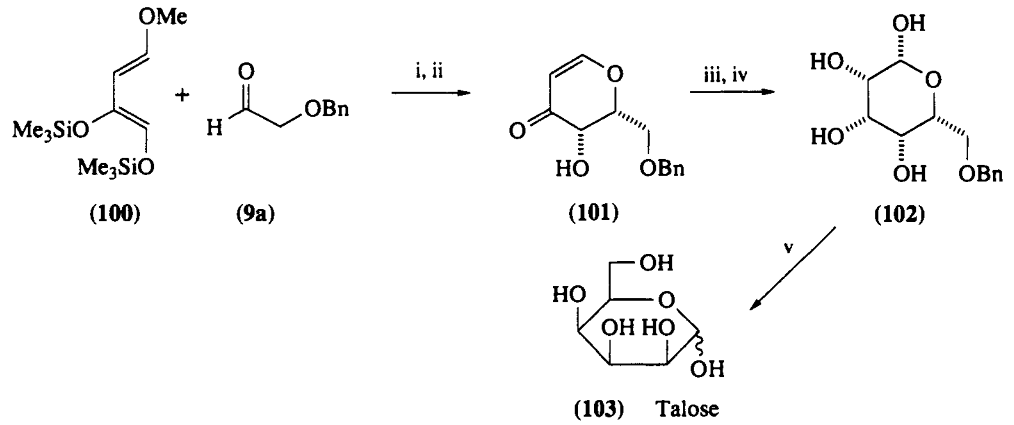
OMe
Me3SiO
Me3SiO
+
O
H
OBn
(100)
(9a)
i, ii
O
O
HO
OBn
(101)
iii, iv
OH
HO
O
HO
OH
OBn
(102)
v
OH
HO
O
OH HO
OH
(103) Talose

i, $BF_3{\bullet}OEt_2$; ii, TFA; iii, DIBAL; iv, hydroxylation; v, deprotection

Scheme 30

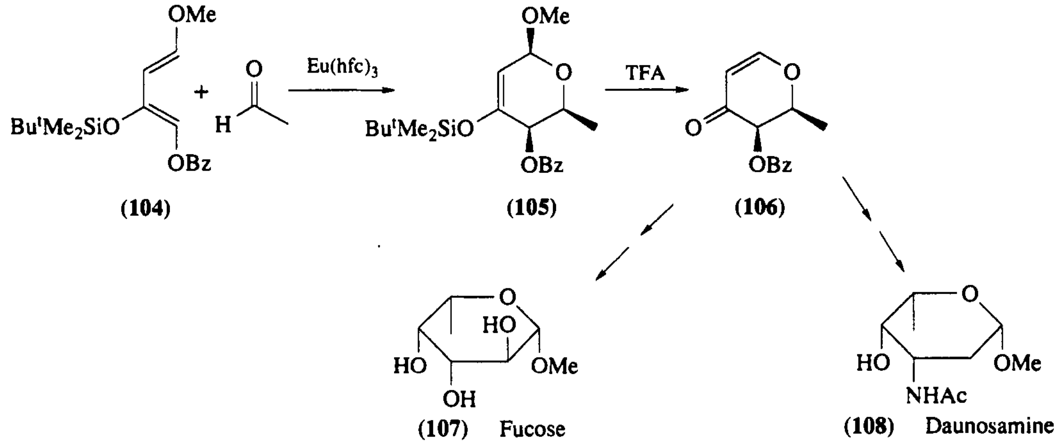
OMe
Bu$^t$Me2SiO
OBz
+
O
H
(104)
Eu(hfc)3
OMe
O
Bu$^t$Me2SiO
OBz
(105)
TFA
O
O
OBz
(106)
O
HO
HO
OMe
OH
(107) Fucose
O
HO
OMe
NHAc
(108) Daunosamine

Scheme 31

The cyclocondensation reaction was expanded by Danishefsky and coworkers to synthesize any simple monosaccharide.[1,2] The key to this approach is a method to construct both the *syn* pyrone (**109**) and the *anti* pyrone (**110**; Scheme 32). From compounds (**109**) and (**110**) all possible sugars could be synthesized by controlling the stereochemistry of the reduction (axial and equatorial hydride delivery) and oxidation of the glycals (*syn* and *anti* to the C-3 hydroxy group). This strategy was demonstrated by the synthesis of glucose (**112**) and galactose (**111**) from their corresponding pyrones. The use of chiral catalysts in conjunction with chiral dienes were used to construct L-glucose in optically pure form to demonstrate the use of this chemistry to construct optically pure monosaccharides.

The synthesis of L-glucose (and a variety of L-glucal derivatives) begins with the hetero Diels–Alder reaction of the phenmenthol diene in hexane at -10 °C under (+)-Eu(hfc)$_3$ catalysis (Scheme 33). This reaction is *endo* specific and gives high diastereofacial selectivity resulting in a 25:1 mixture of the L-pyranoside (**113b**) to the D-pyranoside (**113a**). Chromatography and crystallization gives L-pyranoside (**113b**) in 78% yield. Treatment of (**113b**) with TFA unravels the enol ether to give the optically pure dihydropyrone (**114**) in 86% yield. Compound (**114**) is converted into L-glucose (and various L-glucose derivatives) by first introducing the acetoxy group at C-4 using manganese triacetate, Mn(OAc)$_3$,[70] followed by reduction of the ketone, osmylation of the glucal, oxidation of the aromatic group and reduction of glucuronic acid.[71] This chemistry has been demonstrated for a variety of side chains as shown in Table 26.

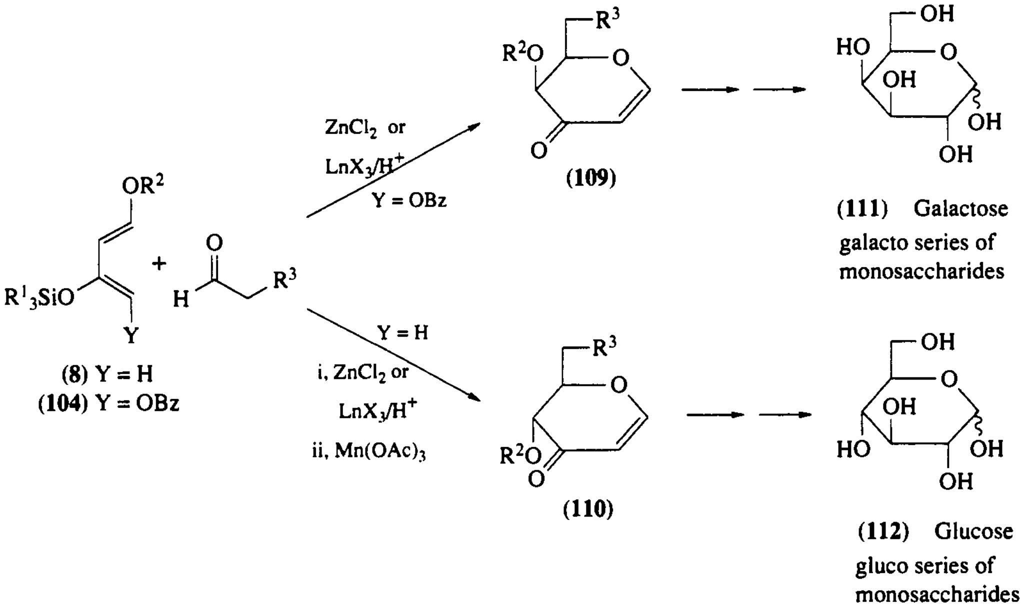

$OR^2$
$R^1{}_3SiO$
Y
+
O
H
$R^3$
(8) Y = H
(104) Y = OBz
$ZnCl_2$ or
$LnX_3/H^+$
Y = OBz
Y = H
i, $ZnCl_2$ or
$LnX_3/H^+$
ii, $Mn(OAc)_3$
$R^3$
$R^2O$
O
(109)
(110)
OH
HO
OH
(111) Galactose
galacto series of
monosaccharides
(112) Glucose
gluco series of
monosaccharides

Scheme 32

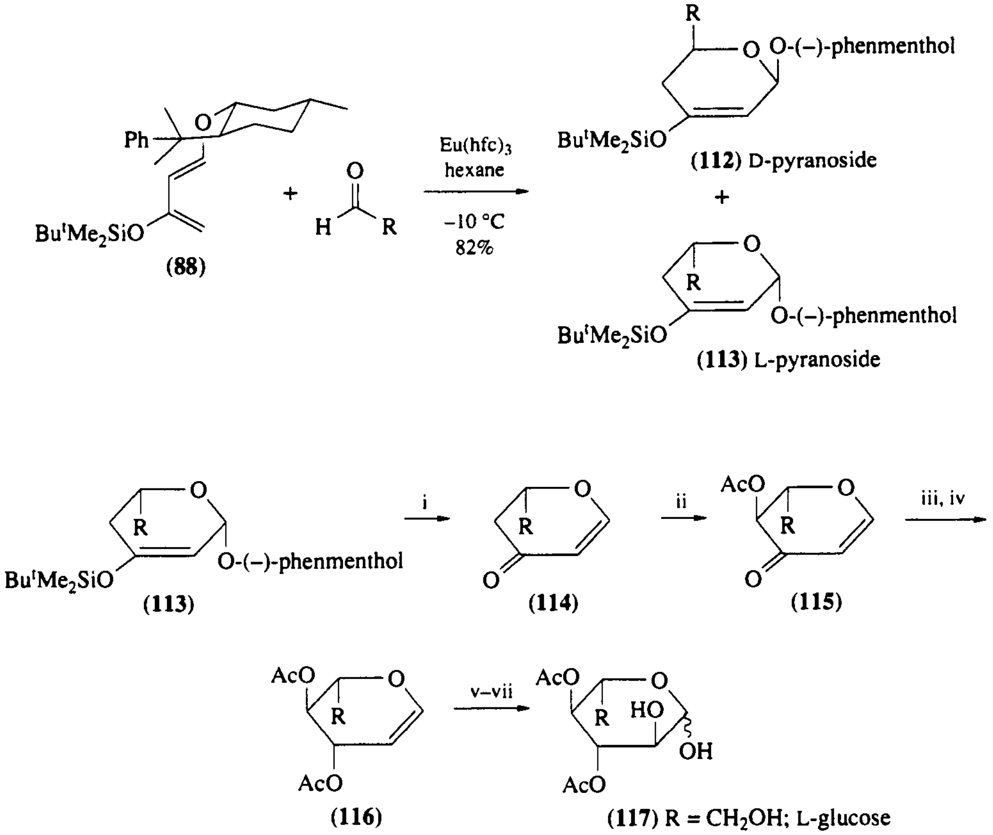

Ph
O
$Bu^tMe_2SiO$
(88)
+
O
H
R
$Eu(hfc)_3$
hexane
−10 °C
82%
R
O
O-(−)-phenmenthol
$Bu^tMe_2SiO$
(112) D-pyranoside
+
(113) L-pyranoside
i
ii
iii, iv
v–vii
AcO
HO
OH
(113)
(114)
(115)
(116)
(117) R = $CH_2OH$; L-glucose

i, TFA; ii, $Mn(OAc)_3$; iii, $NaBH_4/CeCl_3$; iv, $Ac_2O/Et_3N$; v, $OsO_4/AcOH$; vi, $O_3/H_2O_2$; vii, $B_2H_6/NaOMe$

Scheme 33

**Table 26** Acetoxylation of Chiral Glycals

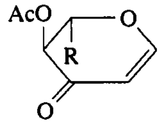

**(115)**

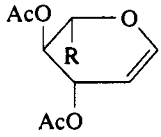

**(116)**

| *Dihydropyrone* | *R* | *Yield (115) (%)* | *Yield (116) (%)* |
|---|---|---|---|
| **(114a)** | Ph | 64 | 89 |
| **(114b)** | Furyl | 53 | 78 |
| **(114c)** | Crotyl | 51 | 83 |
| **(114d)** | Me | 44 | 78 |

Various L-monosaccharide derivatives, including glycolipids, can be synthesized by simply varying the aldehyde, diene or catalyst used in the cycloaddition reaction. For example, 4-deoxy-L-glucose derivatives are synthesized by using the 2-acetoxy diene (**118**; Scheme 34). Cyclocondensation of (**118**) with furfural under (+)-Eu(hfc)$_3$ catalysis gives a cycloadduct which is worked up with Et$_3$N/MeOH (axial protonation) to give the optically pure ketone (**119**).[69] Reduction of this ketone with K-selectride followed by acetylation provides diacetate (**120**). Ozonolysis of the furan ring in (**120**) affords the 4-deoxyglucuronic acid derivative (**121**), characterized as its methyl ester (**122**). Reduction of (**121**) with borane–THF followed by acetylation affords the β-4-deoxy-L-glycoside of (–)-menthol (**123**), formally a glycolipid.

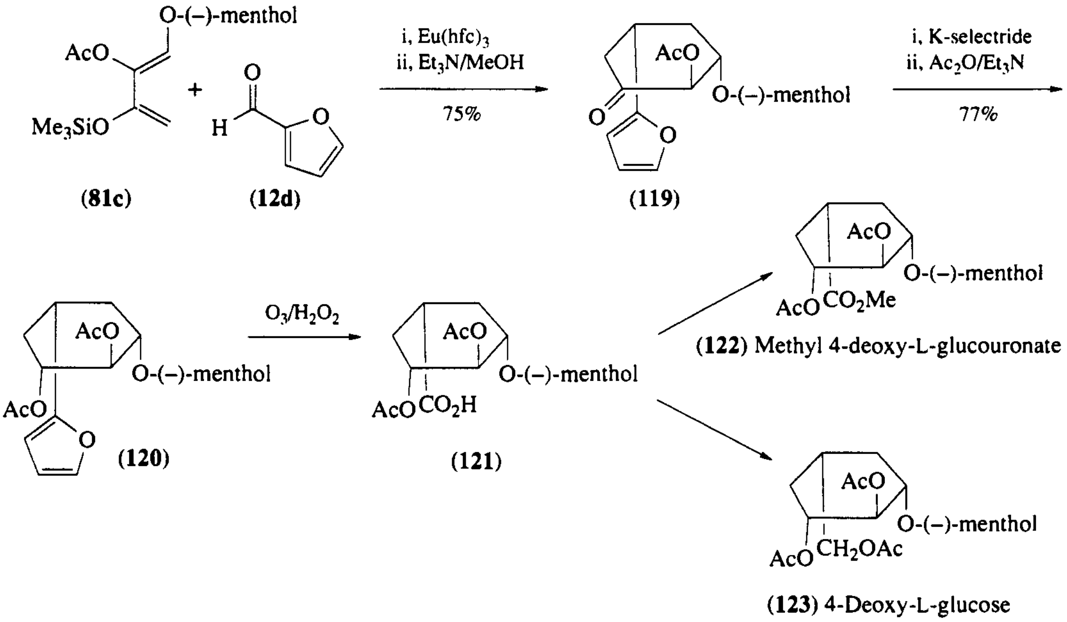
O-(–)-menthol
AcO
Me$_3$SiO
+
O
H
O
(81c)
(12d)
i, Eu(hfc)$_3$
ii, Et$_3$N/MeOH
75%
AcO
O-(–)-menthol
O
O
(119)
i, K-selectride
ii, Ac$_2$O/Et$_3$N
77%
AcO
O-(–)-menthol
AcO
O
(120)
O$_3$/H$_2$O$_2$
AcO
O-(–)-menthol
AcO CO$_2$H
(121)
AcO
O-(–)-menthol
AcO CO$_2$Me
(122) Methyl 4-deoxy-L-glucouronate
AcO
O-(–)-menthol
AcO CH$_2$OAc
(123) 4-Deoxy-L-glucose

Scheme 34

### 2.5.5.2 3-Deoxy-D-manno-2-octulopyranosate (KDO)

The synthesis of more complex monosaccharides requires the construction of more complex and highly functionalized dienes and aldehydes. Furyl diene (**124**) serves as an important starting material in syntheses of KDO and NeuAc. This diene is easily synthesized from the condensation of benzoyloxy acetyl chloride with acetylfuran, followed by treatment with diazomethane.[72] Cyclocondensation of diene (**124**) with chiral aldehyde (**125a**) using BF$_3$·OEt$_2$ as a catalyst gives the CF-type products (**126**) in a 5:1 ratio of *syn* and *anti* isomers (**126a** and **126b**). Aldehyde (**125**) is also available in optically pure form from

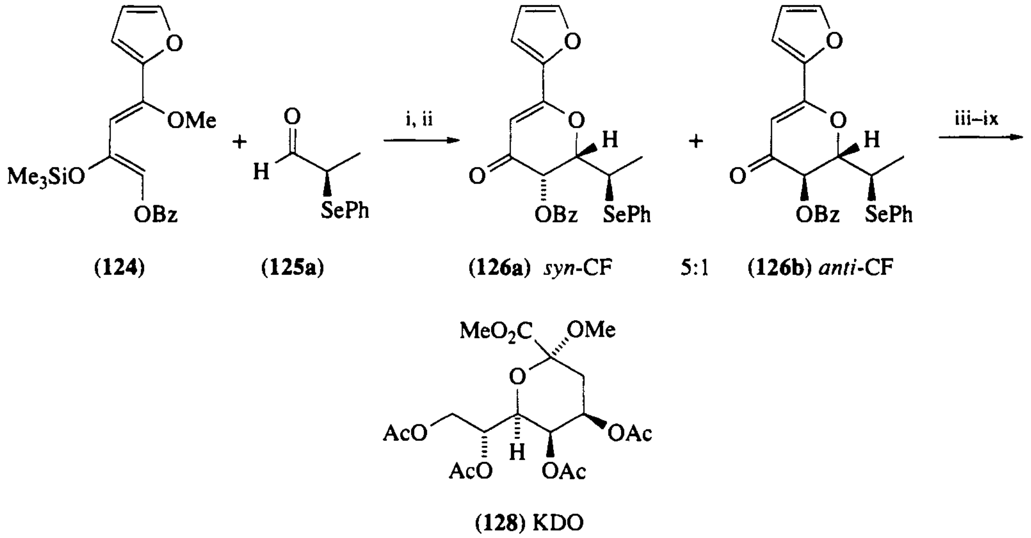
(124)
(125a)
i, ii
(126a) *syn*-CF
5:1
(126b) *anti*-CF
iii–ix
(128) KDO

i, $BF_3•OEt_2$; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, TMSOTf, 2,6-lutidine, $CH_2Cl_2$; v, $K_2CO_3/MeOH$; vi, DMAP, $Ac_2O$, Py; vii, $H_2O_2$, $H_2O$; viii, $OsO_4/NMO$; ix, $Ac_2O$, Py, DMAP; x, $RuO_2•H_2O/NaIO_4$; xi, $CH_2N_2$; xii, $H_2$, Pd/C, EtOH; xiii, $Ac_2O$, Py, DMAP

**Scheme 35**

methyl lactate, which allows chiral synthesis of (**126**).[73] The *cis* isomer is transformed into KDO (**128**) by the standard transformations outlined in Scheme 35.

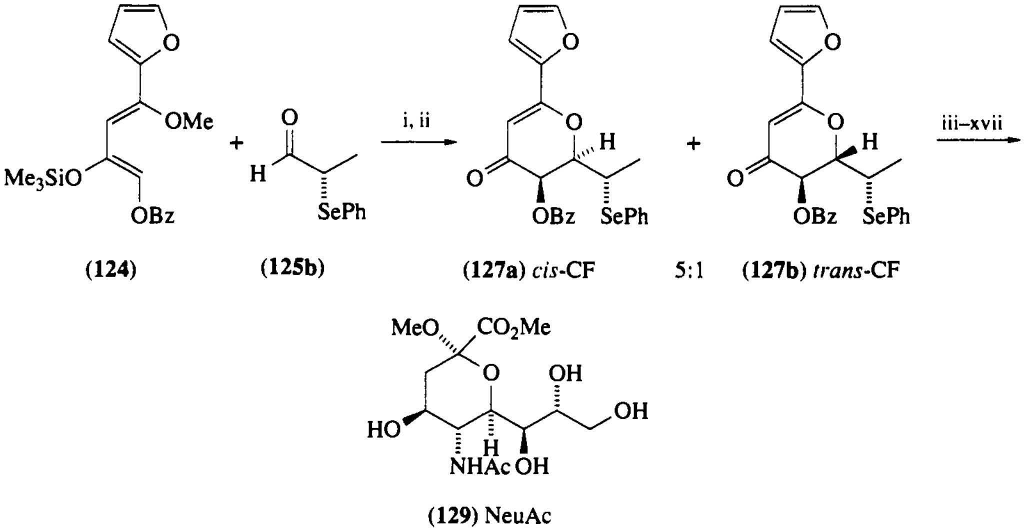
(124)
(125b)
i, ii
(127a) *cis*-CF
5:1
(127b) *trans*-CF
iii–xvii
(129) NeuAc

i, $BF_3•OEt_2$; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, CSA/MeOH; v, $Bu^tMe_2SiOTf$, 2,6-lutidine; vi, $H_2O_2/Py$; $OsO_4/NMO$; viii, $Pb(OAc)_4$; ix, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$/ KHMDS/18-crown-6; x, $OsO_4$; xi, $LiEt_3BH$; xii, BzCl/DMAP; xiii, $RuO_2•H_2O/NaIO_4$, $CH_2N_2$; xiv, HF/MeOH; xv, $Bu_4N^+N_3^-$; xvi, $Pd/CaCO_3$ (Lindlar), $Ac_2O/DMAP$; xvii, 4:1 THF/1M NaOH, $H^+$, $CH_2N_2$

**Scheme 36**

### 2.5.5.3 *N*-Acetylneuraminic Acid (NeuAc)

Using a similar strategy diene (**124**) has also been used to synthesize *N*-acetylneuraminic acid (**129**) *via* cycloadduct (**126**; Scheme 36).[74] In contrast to the scheme used for KDO, the alkene resulting from the selenoxide elimination is oxidized to the aldehyde and the NeuAc side chain is installed by a modification of the Horner–Emmons reaction. Osmylation and reduction of the side chain followed by deprotection provides NeuAc (**129**).

### 2.5.5.4 Lincosamine

The synthesis of lincosamine employs a slightly different strategy than that used for NeuAc and KDO.[75] By using aldehyde (**130**) a precursor to the sugar side chain was installed directly in the cyclocondensation reaction (Scheme 37). Reduction of the carbonyl group of pyrone (**131**) under Luche conditions, epoxidation of the glycal, and a series of manipulations on the alkene side chain to install the amino alcohol portion gives lincosamine (**132**).

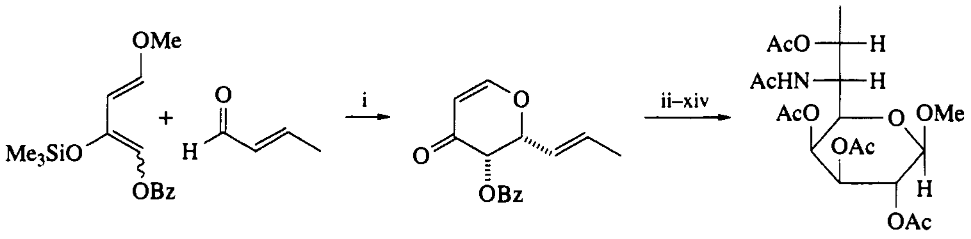

(**130**) (**131**) *syn*; 67% (**132**) Lincosamine

i, $BF_3$•$OEt_2$; ii, $NaBH_4/CeCl_3$•$7H_2O/MeOH$, DMAP, $Et_3N$, BzCl; iii, MCPBA/MeOH, BzCl/DMAP/$Et_3N$; iv, NBS/AcOH/$H_2O$; v, DBN; vi, $Bu^n{}_4N^+N_3^-/Me_3SiN_3$; vii, TFA/MeOH; viii, $Et_3N/MeSO_2Cl$; ix, $P(OMe)_3$, NaH; x, $K_2CO_3/MeOH$; xi, CDI; xii, AcOH; xiii, $K_2CO_3/MeOH$; xiv, $Py/Ac_2O$

Scheme 37

### 2.5.5.5 Hikosamine

The synthesis of more complex carbohydrates employs a strategy of pyrone annulation that involves the cyclocondensation of activated dienes with the C-5 and C-6 aldehydes of simple carbohydrates. These aldehydes function as excellent heterodienophiles in the cyclocondensation reaction. The synthesis of hikosamine begins with the lanthanide-catalyzed condensation of furfural and benzoxyloxy diene (**135**; Scheme 38).[76] The Diels–Alder reaction using the lanthanide catalyst gives exclusively the *syn (endo)* cycloadduct which is cleaved to compound (**133**) using TFA. Conversion of (**133**) into a galactose derivative, followed by homolgation of the side chain provides aldehyde (**134**). Cycloaddition of (**134**) with diene (**135**) using $MgBr_2$ as a catalyst affords (**136**). The stereochemistry of this reaction can be described as an *anti*-ACF (*trans*-ACF) addition, which is expected for a chelation-controlled process using $MgBr_2$ as a catalyst. Luche reduction followed by a Henbest epoxidation (introduction of the amine) and acetylation gives hikosamine (**137**) in its peracetylated form.

Jurczak and coworkers have also used this strategy in the synthesis of annulated pyranosides.[77] The C-6 aldehyde of galactose (**138**) reacts with diene (**11**) under high pressure to give predominately *syn*-ACF product (**139**; Scheme 39). It is interesting to note the unusual stereochemistry of the high-pressure reaction compared to the Lewis acid catalyzed process; *syn*-ACF products are only available through the use of $TiCl_4$. Nevertheless, these products could represent an important class of starting materials for the synthesis of more complex carbohydrates.

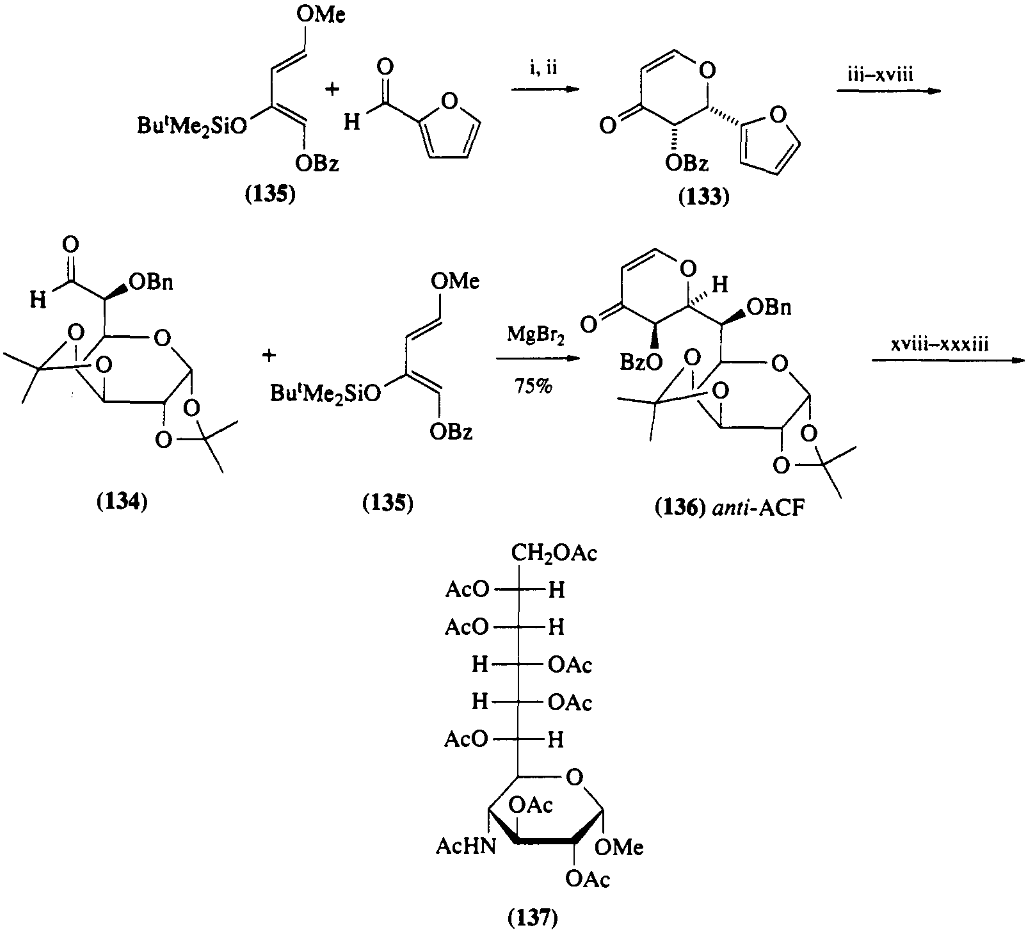
OMe
Bu'Me2SiO
OBz
(135)
H
O
i, ii
(133)
OBz
iii–xviii
(134)
OBn
(135)
MgBr2
75%
(136) anti-ACF
BzO
xviii–xxxiii
CH2OAc
AcO
H
OAc
AcHN
OMe
(137)

i, $Eu(fod)_3$; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, BzCl/Py; v, $OsO_4$, NMO; vi, $Me_2CO$, $H_2SO_4$; vii, $K_2CO_3/MeOH$; viii, $Me_2CO$, $H_2SO_4$; ix, $O_3/CH_2Cl_2/MeOH$, –78 °C; x, $BH_3{\bullet}THF$; xi, [O]; xii, $BF_3{\bullet}OEt_2$, acylation; xiii, BnBr/NaH/DMF; xiv, $O_3/CH_2Cl_2$, –78 °C; xv, Zn, AcOH; xvi, $Ac_2O/Et_3N$, $DMAP/CH_2Cl_2$; xvii, $O_3/CH_2Cl_2$, –78 °C; xviii, Zn, AcOH; xix, $NaBH_4/CeCl_3$; xx, Henbest epoxidation; xxi, $K_2CO_3/MeOH$; xxii, $LiBH_4/THF$, reflux; xxiii, BnBr, NaH/DMF; xxiv, HCl/MeOH; xxv, BzCl/Py; xxvi, MsCl/Py; xxvii, $Bu^n{}_4N^+N_3^-$; xxviii, $K_2CO_3/MeOH$; xxix, acetylation; xxx; $PPh_3$; xxxi, acetylation of amino group; xxxii, $H_2/Pd(OH)_2$; xxxiii, $Ac_2O$

Scheme 38

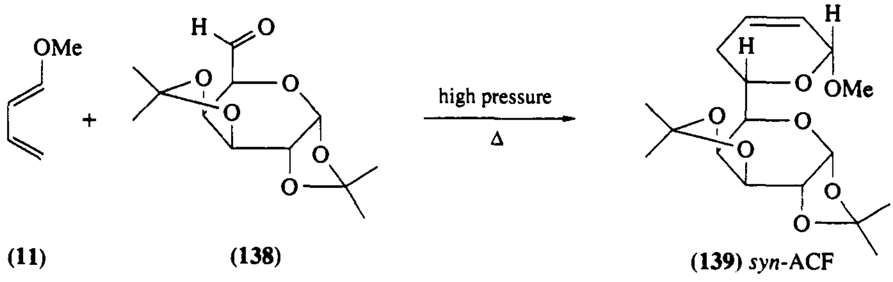
OMe
(11)
H
O
(138)
high pressure
Δ
H
OMe
(139) syn-ACF

Scheme 39

### 2.5.5.6 Octosyl Acid A

Danishefsky and coworkers have used a similar sequence of reactions to synthesize octosyl acid A (**144**; Scheme 40).[78] Aldehyde (**140**)[79] readily undergoes a hetero cyclocondensation reaction with diene (**8**), catalyzed by $ZnCl_2$, to give the CF pyrone (**141**). Reduction of the ketone followed by osmylation, oxidation and introduction of the mesylate gives compound (**142**). Introduction of the pyrimidine glycoside, followed by an intramolecular displacement of the mesylate through the tin complex (**143**), gives an intermediate that is converted to octosyl acid A (**144**) by a series of standard manipulations.

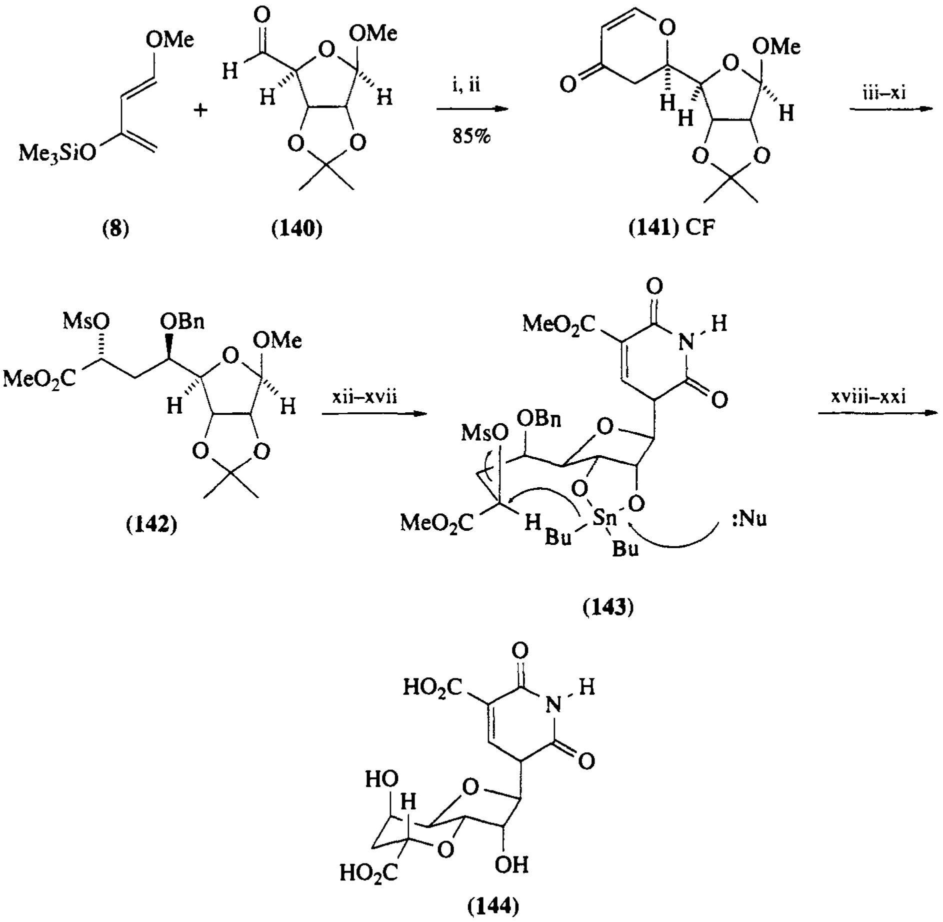
OMe
Me3SiO
+
(8)
O
H
OMe
O
H
H
O
O
(140)
i, ii
85%
O
O
OMe
O
H
H
H
O
O
(141) CF
iii–xi
MsO
OBn
OMe
MeO2C
O
H
H
O
O
(142)
xii–xvii
MeO2C
O
N
H
O
MsO
OBn
O
O
O
Sn
MeO2C
H
Bu
Bu
:Nu
(143)
xviii–xxi
HO2C
O
N
H
O
HO
H
O
O
HO2C
OH
(144)

i, $ZnCl_2$/THF; ii, TFA; iii, $NaBH_4/CeCl_3$; iv, NaH, *p*-methoxybenzyl chloride; v, $OsO_4$, $NaIO_4$; vi, $K_2CO_3$/MeOH; vii, $Ag_2CO_3$/Celite/xylene, Δ; viii, $LiOH{\bullet}H_2O$/THF; ix, NaH/BnBr/DMF; x, $CH_2N_2$, DDQ; xi, MsCl/$Et_3N/CH_2Cl_2$; xii, HCl/MeOH; xiii, acetylation; xiv, $Ac_2O$/AcOH, $CH_2Cl_2/H_2SO_4$; xv, 2,4-bis(trimethylsilyloxy)-5-carbomethoxypyrimidine/$Me_3SiOTf$; xvi, NaOMe/MeOH, xvii, $Bu_2SnO$/MeOH; xviii, CsF/DMF/60 °C; xix, $Pd(OH)_2$; xx, $LiOH{\bullet}H_2O/H_2O$/THF; xxi, $H^+$

**Scheme 40**

### 2.5.5.7 Spectinomycin Analogs

In the synthesis of analogs of the antibiotic spectinomycin, Danishefsky and coworkers used the hetero Diels–Alder reaction to construct a precursor to install the stereochemistry on the tricyclic ring system.[80] Trimethylsilyl diene (**145**) reacts with acetaldehyde and a catalytic amount of $Eu(fod)_3$ to give a 5.7:1

ratio of *cis (syn)* cycloadduct (**146**) and the *trans (anti)* epimer (**147**; Scheme 41). These compounds can be separated and treated sequentially with MCPBA and HF to yield the ring-closed products, of which (**148**) is the major product.

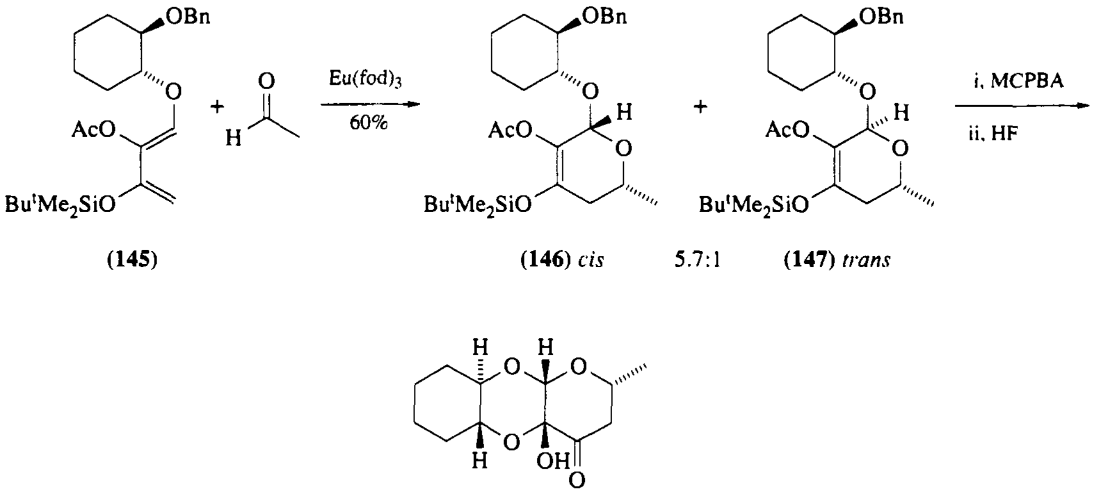

**Scheme 41**

Diene (**149**) reacts with acetaldehyde in the presence of 10% Eu(fod)$_3$ to give cycloadduct (**150**); only minor amounts of the *trans* compound are observed. Treatment of (**150**) with MCPBA, Pd(OH)$_2$ and HF gives (**151**), an analog of spectinomycin (Scheme 42).

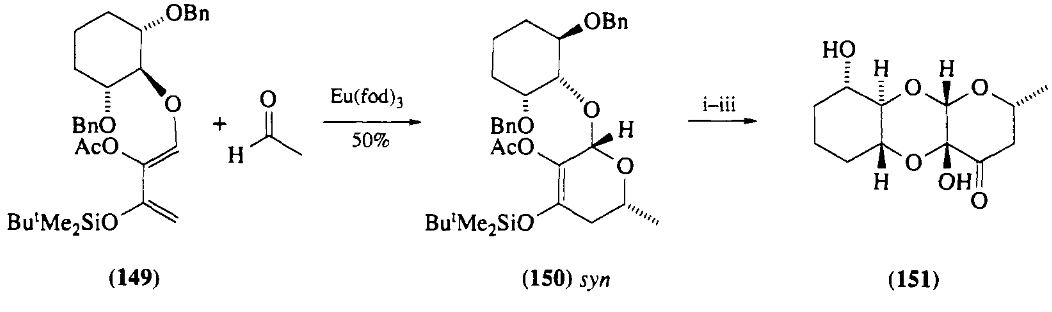

i, MCPBA; ii, Pd(OH)$_2$/H$_2$/EtOAc; iii, HF

**Scheme 42**

### 2.5.5.8 Tunicaminyluracil

In 1985 Danishefsky and Barbachyn reported the total synthesis of the glycosidase inhibitor tunicaminyluracil (Scheme 43).[81] The crucial parts of this synthesis involve a cyclocondensation reaction between diene (**152**) and chiral aldehyde (**153**). Using Ce(OAc)$_3$–BF$_3$·OEt$_2$ as a catalyst in toluene a 45% yield of a single dihydropyrone (**154**; the *syn*-ACF stereoisomer) was obtained. No explanation was offered for the high diastereofacial selectivity observed with this aldehyde. In similar systems other catalysts gave two (of the four possible) dihydropyrones in varying ratios. Compound (**154**) is transformed into tunicaminyluracil (**155**) by a series of reactions outlined in Scheme 43.

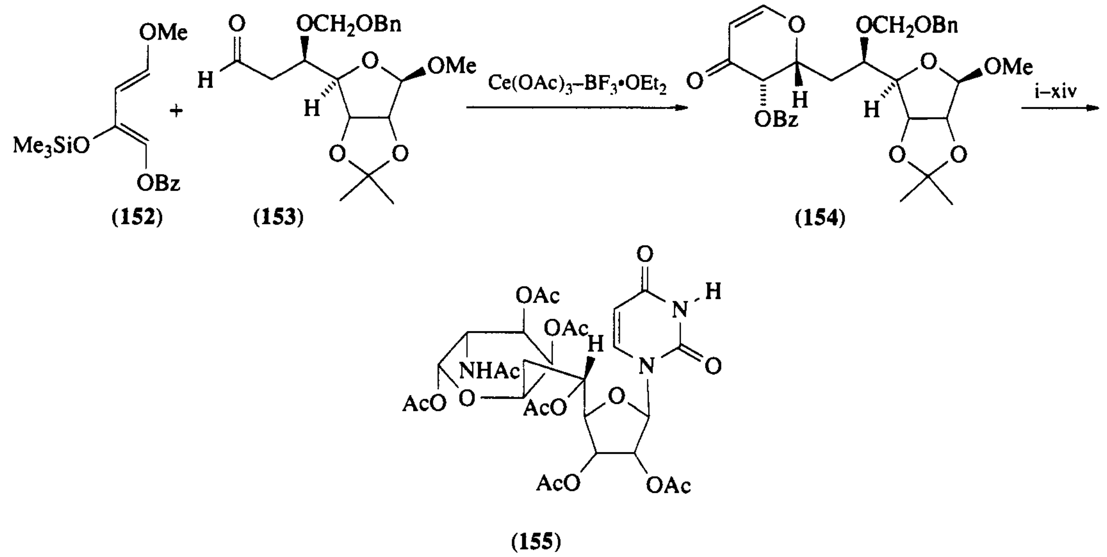
(152)
(153)
Ce(OAc)$_3$–BF$_3$•OEt$_2$
(154)
i–xiv
(155)

i, NaBH$_4$/CeCl$_3$; ii, benzoylation; iii, azidonitration; iv, LiBr/MeCN; v, AgOTf, (Me$_2$N)$_2$CO, THF; vi, PPh$_3$/THF; vii, Ac$_2$O, Py; viii, H$_2$, Pd(OH)$_2$/C, MeOH; ix, K$_2$CO$_3$/MeOH; x, Ac$_2$O/Et$_3$N/DMAP; xi, MeOH/HCl; xii, acetylation; xiii, AcOH/Ac$_2$O/H$_2$SO$_4$/CH$_2$Cl$_2$; xiv, 2,4-bis[(trimethylsilyl)oxy]pyrimidine/Me$_3$SiOTf/MeCN

Scheme 43

### 2.5.5.9 Vineomycinone B$_2$

The total synthesis of the methyl ester of the anthracycline antibiotic vineomycinone B$_2$ is summarized in Scheme 44.[82] The key step of this synthesis is introduction of the pyranose side chain by means of a

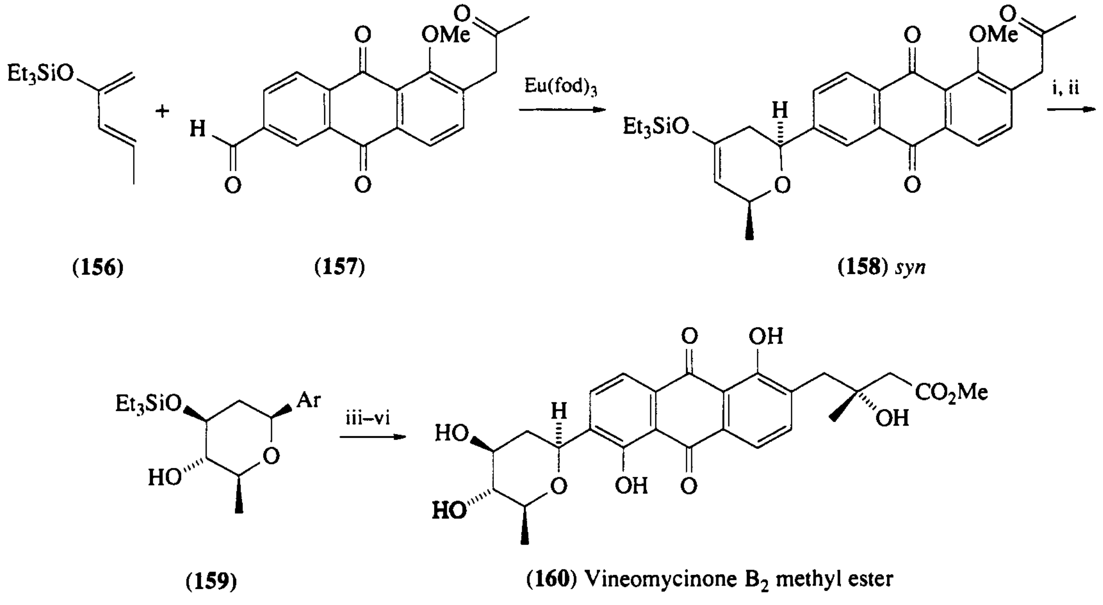
(156)
(157)
Eu(fod)$_3$
(158) syn
i, ii
(159)
iii–vi
(160) Vineomycinone B$_2$ methyl ester

i, BH$_3$•DMS; ii, H$_2$O$_2$; iii, BH$_3$•DMS/H$_2$O$_2$; iv, BBr$_3$/CH$_2$Cl$_2$/–78 °C; v, BrMgCH$_2$COmenthyl; vi, K$_2$CO$_3$/MeOH (resolved via (–)-menthoxy esters)

Scheme 44

hetero Diels–Alder reaction between triethylsilyloxy diene (**156**) and keto aldehyde (**157**). The reaction is catalyzed by 5% $Eu(fod)_3$ in $CHCl_3$ giving a 95% yield of the *endo (syn)* product (**158**); no *anti (exo)* product is produced. The silyl enol ether (**158**) is hydroborated and oxidized to give the monosilyl-protected *trans* diol (**159**). The sense of the hydroboration is exclusively *trans* to the methyl group and aromatic side chain on the pyranose ring. After demethylation with $BBr_3$, reaction of the methyl ketone with the reagent derived from magnesium and (–)-menthyl bromoacetate results in a diastereomeric mixture. The diastereomers are separated by HPLC and deprotected to give optically active (**160**). This approach demonstrates the usefulness of the cyclocondensation reaction in the construction of *C*-glycosides.

### 2.5.5.10 Pstelotin

Midland has used the cyclocondensation reaction with activated dienes to synthesize pstelotin A (**165**; Scheme 45)[56]. The key step in the Midland synthesis is the ACF addition of diene (**162**) with aldehyde (**161**) to give (**164**), using $Eu(hfc)_3$ as catalyst. Deprotection of the benzyl group gave the target molecule (**165**).

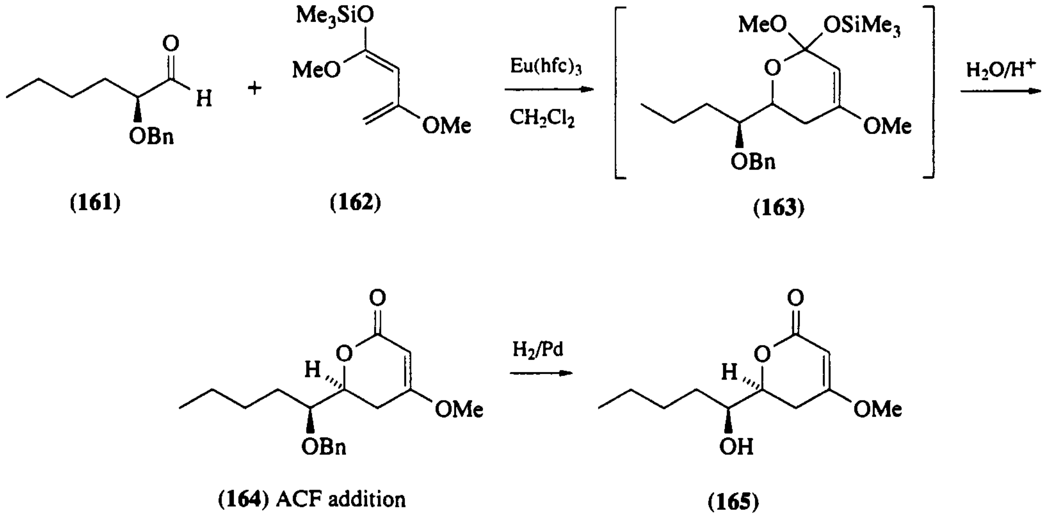

**(161)** **(162)** **(163)**

**(164)** ACF addition **(165)**

**Scheme 45**

### 2.5.5.11 Lantin

Garner has used the cyclocondensation reaction of chiral α-alkoxy aldehydes with $ZnCl_2$ and $Eu(fod)_3$ as catalysts (Scheme 46).[83] In this case, however, the CF product (**166**) dominated the reaction. A variety of catalysts were surveyed; the lanthanide complex and $ZnCl_2$ gave similar results. Compound (**166**) was converted into lantin (**167**) by standard manipulations.

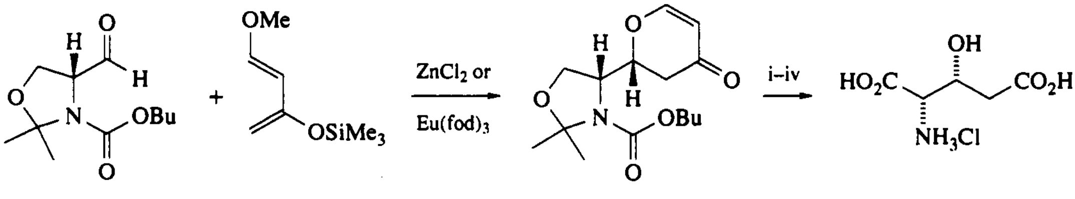

**(166)** **(167)** *threo*-β-Hydroxy-L-glutamic acid

i, $NaIO_4$, $RuO_2$, $CH_2N_2$; ii, $Et_2NSiMe_3$; iii, MeOH/TsOH; iv, $KMnO_4$

**Scheme 46**

### 2.5.5.12 Prelog–Djerassi Lactone

Application of the diene–aldehyde cyclocondensation reaction to polypropionate synthesis has also been investigated. The 2,4-dimethyl diene (**14**) plays a major role in this chemistry. Danishefsky and coworkers have carried out an efficient synthesis of the Prelog–Djerassi lactone using this diene (Scheme 47).[34,35] The cyclocondensation reaction between trimethylsilyloxy diene (**14**) and chiral aldehyde (**168**), catalyzed by $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ gives the *anti*-CF pyrone (**169**) in an overall yield of 95% with a 4.3:1 ratio (*anti* to *syn*). Each pyrone is derived from a CF-type addition of the diene to the chiral aldehyde. The *anti* pyrone is purified and treated with DIBAL-H in toluene to give a mixture of epimeric alcohols, which is subjected to a Ferrier-type rearrangement with $Pr^iOH$ in the presence of *p*-toluenesulfonic acid (*p*TsOH), followed by reduction of the glycal and ozonolysis to give the Prelog–Djerassi lactone (**170**).

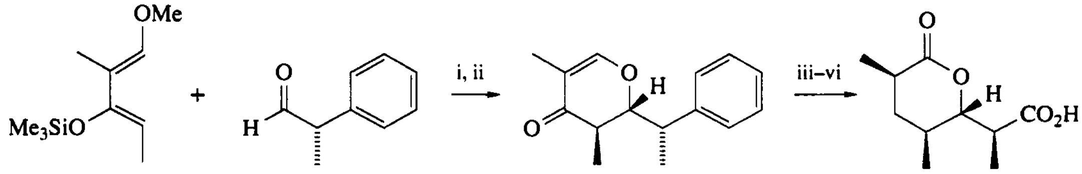

**(14)** **(168)** **(169)** 4.3:1 *anti*-CF:*syn*-CF **(170)**

i, $BF_3$; ii, TFA; iii, DIBAL; iv, $Pr^iOH$/*p*-TsOH; v, $H_2$/Pd–alumina/EtOAc; vi, $O_3$/AcOH/$H_2O$/TFA; $H_2O_2$/AcOH/$H_2O$

Scheme 47

### 2.5.5.13 6-Deoxyerythronolide B

Lactone (**170**) is reduced to aldehyde (**171**) and used as a heterodienophile in a Diels–Alder reaction with diene (**14**), with $ZnCl_2$ in THF as a catalyst, to give (**172**; Scheme 48).[34,35] The major product of this cycloaddition is the *syn* pyrone derived from a Cram–Felkin attack (*syn*-CF); 27% of the *syn*-ACF product is also produced. The *syn*-CF pyrone (**172**) is ozonized and subjected to an oxidative work-up fol-

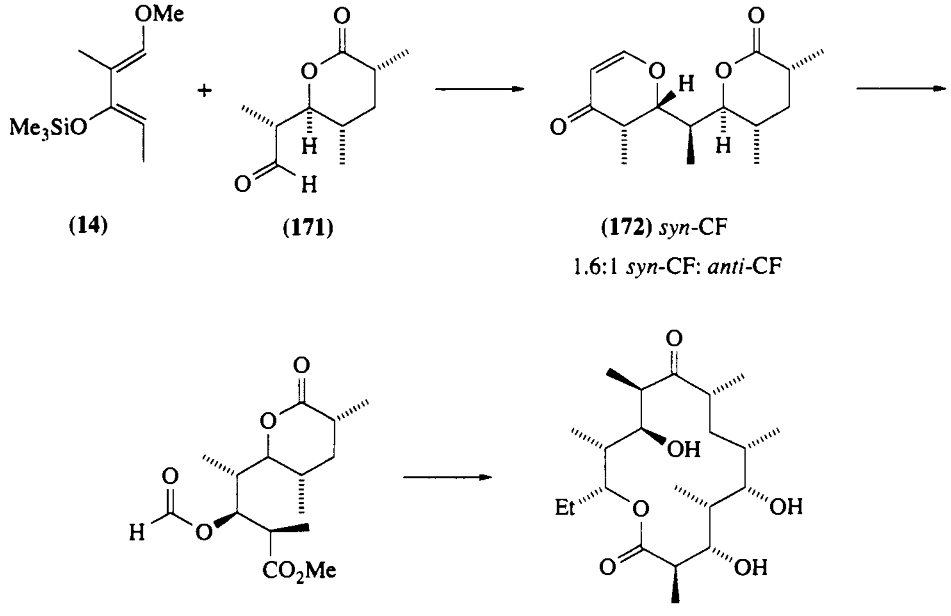

**(14)** **(171)** **(172)** *syn*-CF

1.6:1 *syn*-CF: *anti*-CF

**(173)** **(174)**

Scheme 48

lowed by methylation of the resulting acid with diazomethane to give intermediate (**173**). Compound (**173**) has been used by Masamune to synthesize 6-deoxyerythronolide B (**174**).

### 2.5.5.14 Avermectin

Danishefsky and coworkers have synthesized the algylcon of avermectin based on a hetero Diels–Alder reaction between trimethylsilyloxy diene (**8**) and chiral aldehyde (**175**; Scheme 49).[84] The pyrone must come from an anti Cram–Felkin addition, so $MgBr_2$ is used as the catalyst in this reaction. The cycloaddition reaction gives the expected product (**176**) and the CF diastereomer in a ratio of 3:1. The target compound (**178**) is obtained after a series of reactions outlined in Scheme 49.[85]

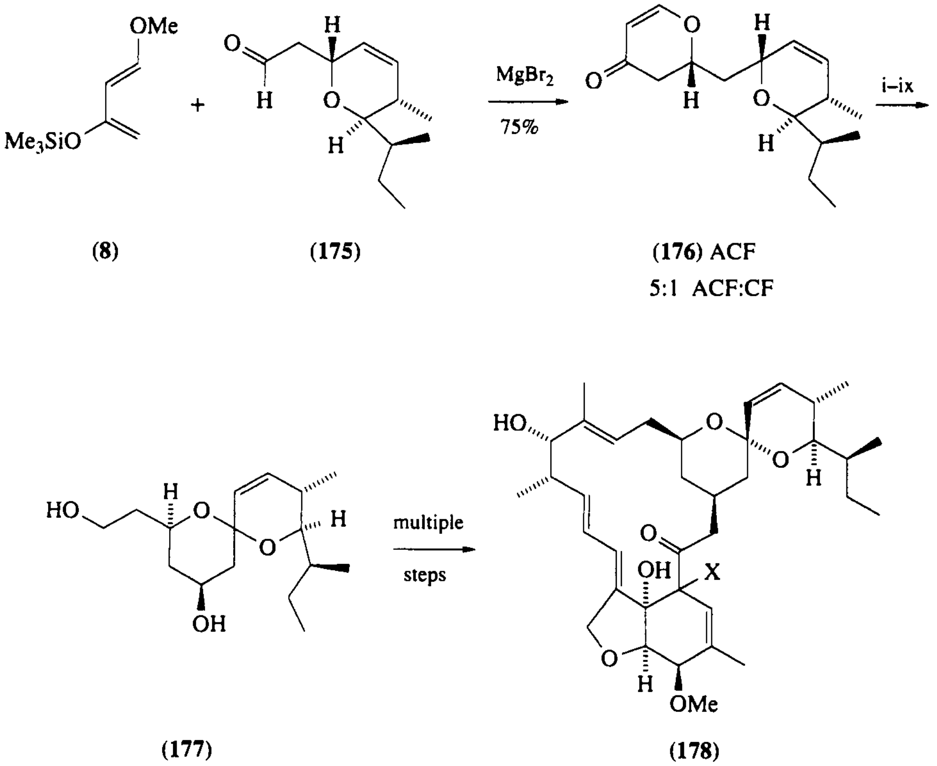

(**8**) (**175**) (**176**) ACF

5:1 ACF:CF

(**177**) (**178**)

i, $NaBH_4$–$CeCl_3$; ii, TBSOTf; iii, NBS•$H_2O$/THF; iv, $Bu_3SnH$, PhMe, AIBN; v, $LiBH_4$, THF; vi, pivaloyl chloride/Py, DMAP/$CH_2Cl_2$; vii, HF/MeCN; viii, HgO–$I_2$, $CCl_4$; ix, LiOH/MeOH/THF/$H_2O$

**Scheme 49**

### 2.5.5.15 Monensin Lactone

A total synthesis of the monensin lactone is summarized in Scheme 50.[86] The crucial point of this synthesis is the hetero Diels–Alder reaction of triethylsilyloxy diene (**179**) with aldehyde (**180**), carried out with 10 mol % of Yb(fod)$_3$ to give the *syn* Diels–Alder cycloadduct (**181**) as the only isomer. Compound (**181**) is treated with HF in pyridine and MeOH to obtain ketone (**182**), which is converted into the monensin lactone (**183**).

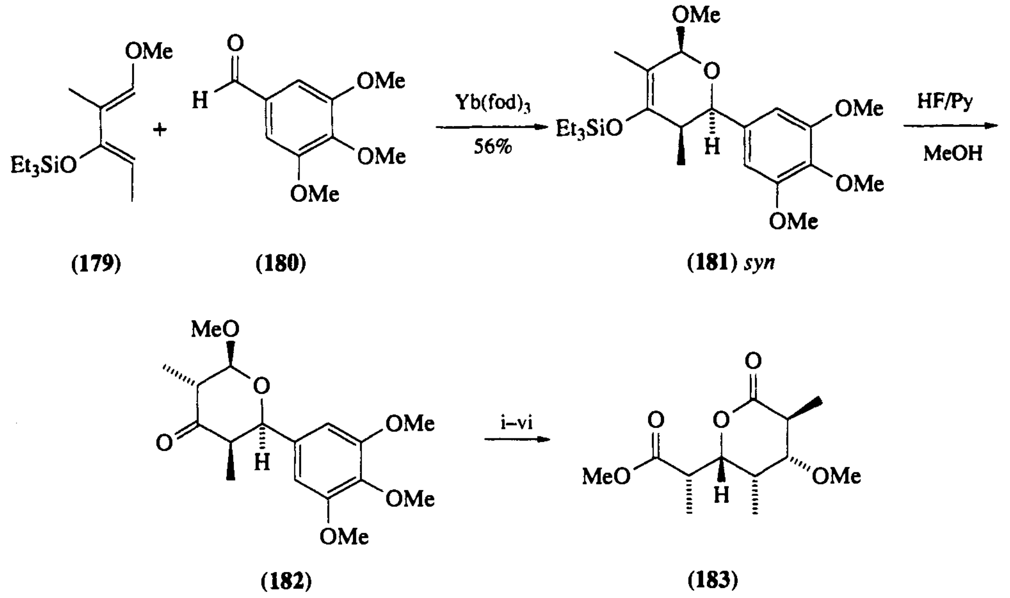

i, HF/pyridine/MeOH; ii, $NaBH_4$–MeOH/THF; iii, NaH (MeI/DMF); iv, HCl–THF, v, $RuO_2$–$NaIO_4$; vi, $CH_2N_2$/ether

Scheme 50

### 2.5.5.16 Tirandamycin

Danishefsky and Harvey have reported the synthesis of an important subunit in the construction of tirandamycin (Scheme 51).[86] Trimethylsilyl diene (**14**) reacts with 4,5-dimethylfuran-2-carbaldehyde (**184**) followed by a brief treatment with TFA to give exclusively the *syn* pyrone (**185**). Pyrone (**185**) is reduced using LAH and subjected to a Ferrier-like rearrangement using benzyl alcohol in the presence of

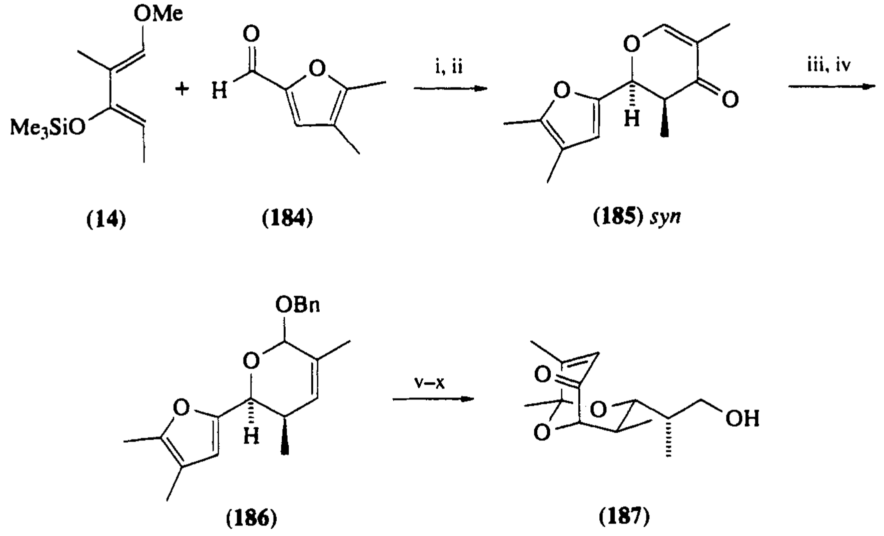

i, Yb(fod)$_3$, $CHCl_3$; ii, TFA; iii, $LiAlH_4$; iv, BnOH/TsOH; v, $B_2H_6$–THF, $H_2O_2/OH^-$; vi, Swern oxidation; vii, $NaBH_4$; viii, TBDMSOTf/$Et_3N$; ix, Na, $NH_3$, $Et_2O$, −33 °C, 1 h; x, MCPBA, HF–MeCN

Scheme 51

*p*-toluenesulfonic acid to give (**186**). Hydroboration followed by a Swern oxidation and reduction with sodium borohydride establishes the proper stereochemistry at C-3. The alcohol is then protected as its *t*-butyldimethylsilyl ether and the pyrone ring is opened and reduced. Treatment with MCPBA followed by HF in acetonitrile provides (**187**), a subunit of triandamycin.

### 2.5.5.17 Rifamycin S

Danishefsky and coworkers employed two hetero Diels–Alder reactions in a total synthesis of the ansa bridge of rifamycin S (Scheme 52)[87] The first cyclocondensation reaction uses the trimethylsilyloxy diene (**14**) and a preincubated solution of 3-(benzoyloxy)-2-methyl-1-propanal (**188**) with an excess of $TiCl_4$ in $CHCl_2$. The product is exclusively the *syn*-ACF pyrone (**189**). Through a Ferrier rearrangement and a sequence of oxidation–reduction steps followed by functional group manipulations aldehyde (**190**) is obtained.

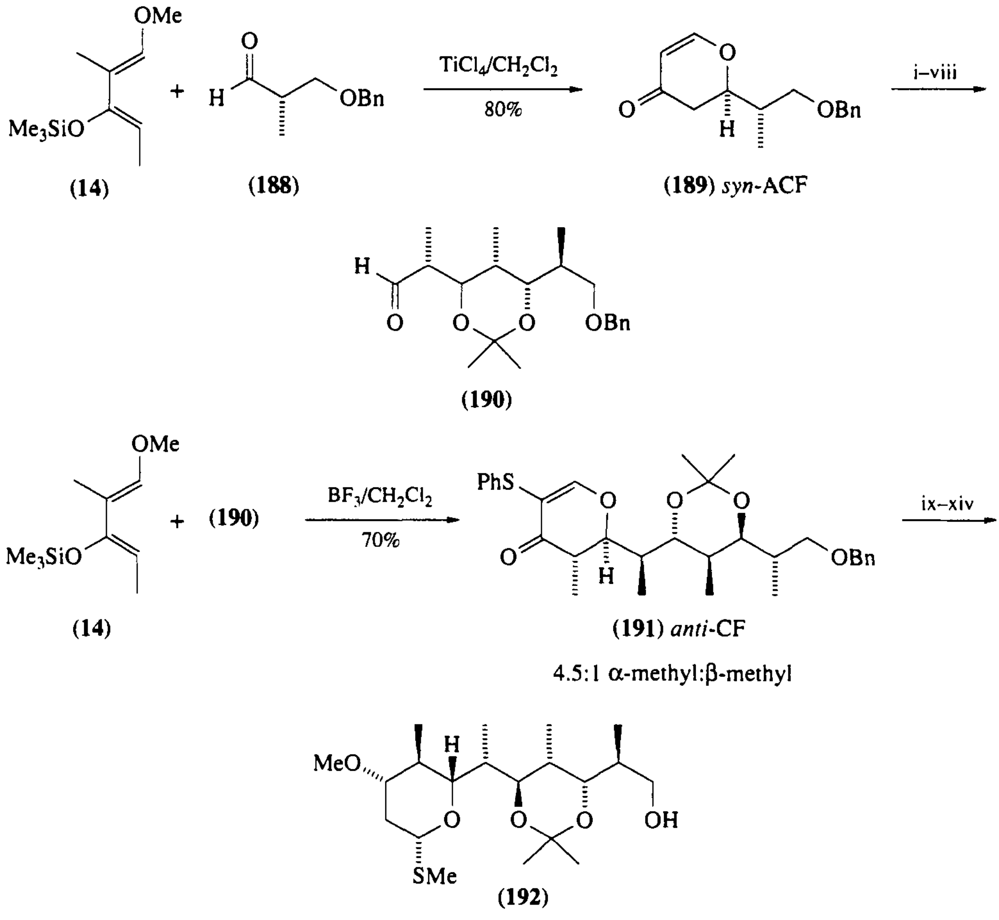

i, $LiAlH_4$; ii, Ferrier, MeOH, TsOH; iii, $BH_3 \cdot THF$, $OH^-$, $H_2O_2$; iv, Swern (oxalyl chloride/DMSO); v, $NaBH_4$/MeOH; vi, 1,3-propanedithiol/$BF_3 \cdot OEt_2$; vii, 2,2-dimethoxypropane/ CSA; viii, NBS/acetone, $H_2O$; ix, L-selectride; x, MCPBA, Δ; xi, MeSH/$Bu^n_4N^+$ $F^-$/THF; xii, $NaBH_4$, MeOH; xiii, NaH, MeI; xiv, Na, $NH_3$

**Scheme 52**

In the second hetero Diels–Alder reaction an *anti* pyrone derived from Cram–Felkin addition was needed, so trimethylsilyloxy diene (**14**) was allowed to react with aldehyde (**190**) in $CH_2Cl_2$ using $BF_3 \cdot OEt_2$ as the catalyst. Under these conditions, *anti*-CF pyrone (**191**) is obtained in 57% yield, accompanied by 13% of the *syn*-CF pyrone. Through further manipulations compound (**192**), a key intermediate in the Kishi synthesis of the ansa bridge of rifamycin S, was obtained.

### 2.5.5.18 Zincophorin

In the synthesis of zincophorin,[88] two cyclocondensation reactions are also used. In the first cyclocondensation reaction, trimethylsilyloxy diene (**14**) reacts with aldehyde (**193**) using anhydrous $MgBr_2$ as the catalyst to give the *anti*-ACF pyrone (**194**) in 80% yield (Scheme 53). The *syn:anti* ratio in this reaction is 7:1. After a series of standard manipulations aldehyde (**196**) is obtained. In the second cyclocondensation reaction, *anti*-CF pyrone (**197**) results from reaction of the (4*E*)-*t*-butyldimethylsilyloxy diene (**195**) with aldehyde (**196**) under $BF_3 \cdot OEt_2$ catalysis; (**197**) and its *syn*-CF isomers are obtained in a ratio of 4:1 and overall yield of 68%. The *anti*-CF aldol product is purified and cyclized to *anti*-CF pyrone (**197**) in benzene using pyridinium *p*-toluenesulfonate as a catalyst. Pyrone (**197**) converted into zincophorin (**198**) by a sequence of steps shown in Scheme 52.

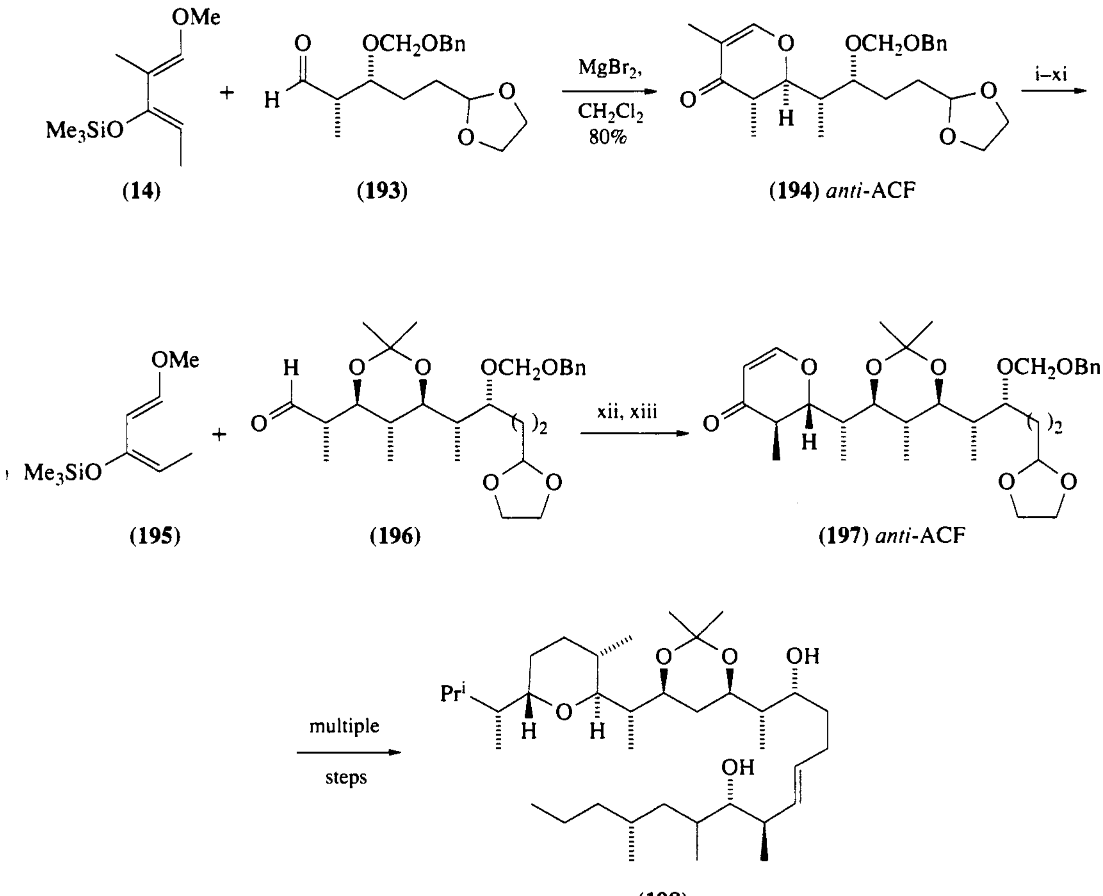
OMe
$Me_3SiO$
(14)
+
O
H
$OCH_2OBn$
O
O
(193)
$MgBr_2$,
$CH_2Cl_2$
80%
O
O
$OCH_2OBn$
H
O
O
i–xi
(194) *anti*-ACF
OMe
$Me_3SiO$
(195)
+
H
O
O
O
$OCH_2OBn$
$)_2$
O
O
(196)
xii, xiii
O
O
O
O
H
$OCH_2OBn$
$)_2$
O
O
(197) *anti*-ACF
multiple
steps
$Pr^i$
O
H
H
O
O
OH
OH
(198)

i, $NaBH_4$–$CeCl_3$; ii, Ferrier rearrangement (3,4-dimethoxybenzyl alcohol), *p*-TsOH, benzene; iii, $BH_3$–DMS, $H_2O_2$–NaOH; iv, Swern; v, L-selectride; vi, DDQ; vii, $LiBH_4$; viii, $Bu^tPh_2SiCl$/DMF/imidazole; ix, dimethoxypropane, PPTS; x, $Bu^n_4NF$; xi, Swern; xii, $BF_3 \cdot Et_2O$; xiii, PPTS, benzene

**Scheme 53**

In summary, the condensation of activated dienes with aldehydes is a versatile tool in organic synthesis. The reaction is applicable to both complex and simple aldehydes and dienes; a list of the dienes which were used in cyclocondensation reactions is given in Figure 5. The high degree of stereoselectivity also makes the cyclocondensation of activated dienes with aldehydes a useful synthetic tool.

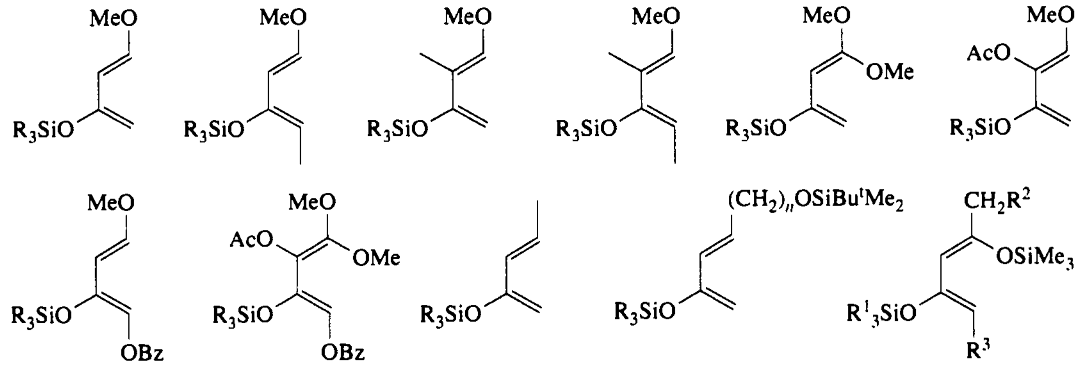

**Figure 5**

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# 3.1

# The Aliphatic Friedel–Crafts Reaction

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## 3.1.1 INTRODUCTION

The Friedel–Crafts acylation reaction is one of the oldest reactions for the preparation of ketones by carbon–carbon bond formation, and is one of the major methods used for the preparation of aromatic ketones.[1] However, acylation by an acid chloride in the presence of a Lewis acid is also applicable to nonaromatic substrates. Whilst it has been known for almost as long as its better-known relative, the aliphatic Friedel–Crafts reaction has not been used as often. Nevertheless, two reviews of early aliphatic Friedel–Crafts acylations do summarize the reaction's history and a considerable body of information.[2,3]

By comparison with the reactions with aromatic substrates, the absence of the driving force of rearomatization by proton loss in electrophilic acylations of alkenes leads to competition between alternative pathways for the carbocation intermediate. In particular, capture of halide to form β-halo ketones can become dominant. Hence, the aliphatic Friedel–Crafts acylation reaction need not necessarily result in substitution of an acyl residue for a hydrogen atom in an alkene, nor in the formation of unsaturated ketones. Indeed, within this broader scope, acylations of alkynes and some classes of alkanes can be synthetically useful.

Recently, considerable progress has been made in extending the acylation to new substrates, particularly silanes, providing a far greater degree of chemo- and regio-selectivity.

## 3.1.2 GENERAL ASPECTS OF ALIPHATIC FRIEDEL–CRAFTS ACYLATIONS

### 3.1.2.1 Mechanistic Aspects

The course of the Friedel–Crafts reaction of alkenes is commonly considered to proceed by reaction of the alkene with the reactive acylating agent to form the β-ketocarbenium ion, which can then either react with a nucleophile (usually halide) to give overall addition to the double bond, or eliminate a proton, forming unsaturated products (Scheme 1).

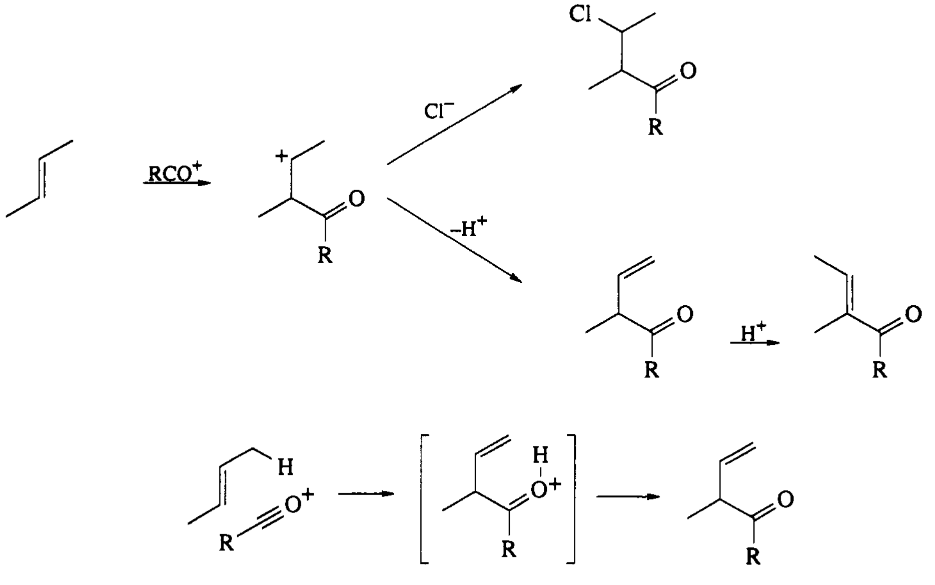

Scheme 1

A number of factors influence the nature of the unsaturated products formed. Under nonequilibrating workup conditions, β,γ-unsaturated ketones tend to predominate, an observation attributed to [1,5] hydrogen shifts in the intermediate β-ketocarbenium ion. Equilibration readily leads to the more thermodynamically stable conjugated enone, particularly under the influence of the released acid. The intermediacy of the β-ketocarbenium ion opens further pathways for rearrangements *via* hydride migration and carbon–carbon bond cleavage depending on substrate structure.[3] However, the lack of rearrangement observed in acylations by preformed acylium ions and the clean formation of β,γ-unsaturated ketones suggest that reactions can occur mechanistically *via* an ene reaction (Scheme 1).[4] Reactions with acylium salts give highest conversions to β,γ-unsaturated ketones when the reaction is performed in the presence of a base to neutralize and hence prevent the build up of released acid. Non-nucleophilic bases such as ethyldiisopropylamine or dicyclohexylethylamine are most effective, but even weak bases such as tetramethylurea can suppress the formation of the conjugated enone.

Ene reactions of electron-deficient nitriles and trisubstituted alkenes in the presence of boron trichloride offer related routes to β,γ-unsaturated ketones.[5]

### 3.1.2.2 Catalysts

Aluminum chloride is the most frequently used Lewis acid in aliphatic Friedel–Crafts acylations, and is one of the strongest. Its complexes with acyl halides are strong, producing very active acylating species. Titanium and tin tetrachlorides also find use as catalysts, and are powerful enough to induce reaction at low temperatures.

With anhydrides, aluminum chloride reacts to form the acid chloride complex. Zinc chloride is more commonly used with acid anhydrides, although this is restricted practically to acetic and other simple anhydrides that can be used as the reaction solvent. This nevertheless remains a useful reagent for acylations, giving predominantly nonconjugated products.[6] Active zinc compounds prepared from a zinc–copper couple and alkyl halides also promote the acylation of alkenes by acyl chlorides at room temperature.[7]

Ethylaluminum dichloride has been described as a catalyst for acylation of alkenes by acyl chlorides, giving nonconjugated enones together with the chloroketone.[8] This is interpreted as a result of the deprotonation by $EtAlCl_3^-$ rendering the [1,5] proton shift irreversible. This catalyst has not been utilized to any great extent at present, but should offer advantages in that acylium salts do not need to be prepared.

The use of protic acids is discussed in Section 3.1.3.3.

### 3.1.2.3 Reaction Temperatures

The ease with which alkenes undergo electrophilic addition is demonstrated by the ready reaction with acylating reagents at low temperatures. Indeed, the propensity for alkenes to polymerize under the influence of acid catalysts means that temperatures should be kept as low as possible. In addition, the stability of acyl chlorides in the presence of Lewis acids in general, and aluminum chloride in particular, supports the use of low temperatures. Decarbonylation can occur readily if the resulting carbenium ion is tertiary, and elimination of proton from acylium ions leads to ketenes, which can themselves be acylated in a Friedel–Crafts reaction. The high reactivity of both acylating agent and substrate combine to give reaction times that are short, and reaction temperatures that are low.

### 3.1.2.4 Stability of Acylating Reagents

Acyl halides bearing α-hydrogen atoms, and acetyl chloride in particular, have limited stability in the presence of strong Lewis acids. Elimination of proton from the acylium ion leads to the ketene. This intermediate undergoes ready Friedel–Crafts acylation, acetyl chloride eventually forming the diacetylacetylium ion,[9,10] which is a poor acylating agent. For this reason, excessive reaction temperatures and times should be avoided in Friedel–Crafts acetylations.

## 3.1.3 ACYLATIONS OF ALKENES

### 3.1.3.1 Intermolecular Acylations

The regioselectivity of Friedel–Crafts acylations of unsymmetrical alkenes can often be predicted simply by consideration of the alternative carbenium ions formed in an initial electrophilic attack. Pathways *via* tertiary carbocations are generally preferred over those involving secondary ions. It is the subsequent fate of the initially generated ion that determines the products formed. As has been indicated already, elimination of a proton completes a substitution, although there is a predominance of nonconjugated unsaturated ketone formed, and treatment with base is required to form the conjugated product.[11]

Capture of a nucleophile, usually halide, represents a second major pathway, leading to overall addition to the alkene double bond. Acylations of ethylene (conveniently by automatic gasimetric techniques)[12] and simple alkenes often give mainly the chloroethyl ketones.[13,14] Nucleophile capture has been used to advantage in the preparation of β-amido ketones by using nitriles as the reaction solvent (equation 1).[15]

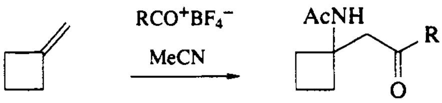

(1)

Further pathways that may be followed include hydride transfer, leading to the possibility of more remote functionalization of the carbon skeleton, and carbon migration, leading to a rearranged skeleton. This is more common when there is a quaternary center next to the carbenium carbon,[16] or in polycyclic systems, as observed in the acetylation of cedrene.[17]

The rich chemistry of carbenium ions that may be accessed by the Friedel–Crafts acylation means that careful consideration must be given to any particular reaction planned, especially with regard to competing pathways.[3] Nevertheless, the method remains an important, if relatively infrequently used, route to aliphatic ketones.

Acylations by α,β-unsaturated acyl halides provide routes to α,β,α′,β′-unsaturated ketones.[18] Care must be taken in choice of reaction conditions, since Lewis acids are excellent catalysts for Nazarov cyclizations[19] to cyclopentenones (Scheme 2). Indeed, this can be exploited as a synthesis of the five-membered ketones without isolation of the intermediate divinylic ketones.[20] Cyclizations are also observed after acylations of cyclohexenes with vinylacetyl chloride derivatives (equation 2).[21,22] The acylation–cycloalkylation sequence provides a complement for the Robinson annelation, since the carbonyl function is located adjacent to the bridgehead position. This potential has been realized in natural product syntheses.[23]

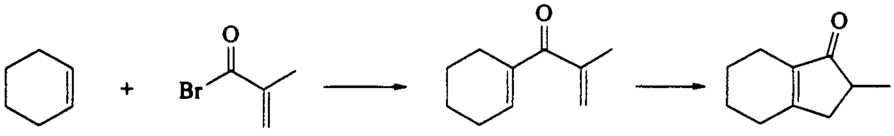

Scheme 2

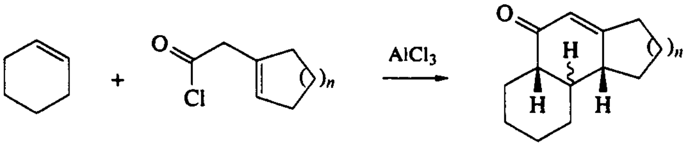

(2)

### 3.1.3.2 The Formation of Cyclic Ketones

Intramolecular Friedel–Crafts acylation provides a useful synthetic approach to cyclic ketones.[2] The cyclization is well-suited to the preparation of six- and particularly five-membered rings, as used in key steps in routes to methyl dihydrojasmonate (equation 3),[24] and precursors to some marine sesquiterpenes (equation 4)[25] and the theoretically interesting spiro[4.4]nonatetraene (equation 5).[26] Extension to cycloheptanones has been achieved,[27,28] but tars were formed on attempting to prepare cyclooctanones.[27]

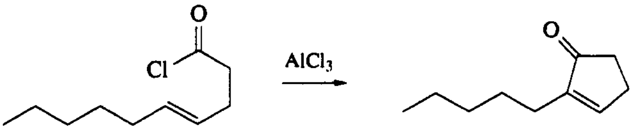

(3)

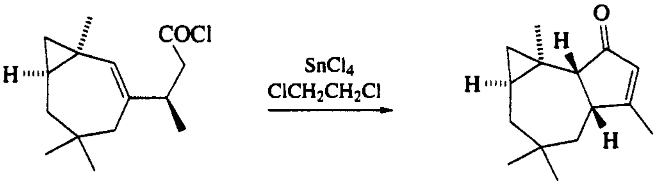

(4)

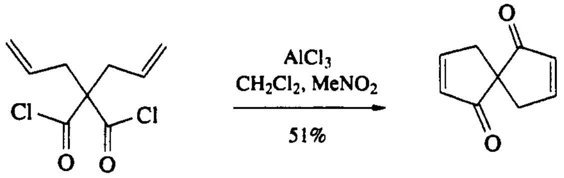

(5)

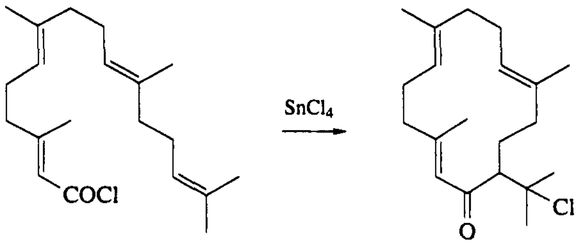

(6)

However, high dilution techniques were successful for the cyclization of geranylgeranic acid chloride to the cembrene skeleton (equation 6).[29]

Intramolecular cyclizations offer a versatile method for the preparation of bicyclic and polycyclic ketones. Indeed, in favorable cases, reaction can ensue on simply heating the acyl halide[30] as well as on treatment with a Lewis acid,[31] offering control of the product isolated (Scheme 3). However, the structural constraints imposed in detailed examination of specific ring systems in which the stereochemistry of cyclization can be determined[31–34] may well preclude the deduction of more general conclusions about stereochemical control.

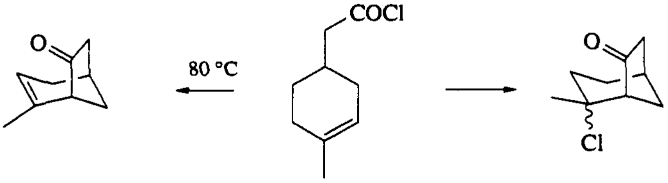

Scheme 3

### 3.1.3.3 The Use of Protic Acid

Protic acids can be used in acylations of alkenes by carboxylic acids and their derivatives. Polyphosphoric acid is the protic acid most frequently used, but suffers from several well-known disadvantages, particularly on scale-up. Its extreme viscosity requires that reactions be carried out at elevated temperatures to permit stirring, and it is a poor solvent for organic substrates. Hydrolysis during work-up is often tedious. Phosphorus pentoxide in methanesulfonic acid is a more convenient reagent for dehydrative cyclization of lactones and unsaturated carboxylic acids, being a mobile liquid with good solvent properties. In comparison with polyphosphoric acid, yields were also higher with the methanesulfonic acid derived reagent.[35] The reagent, which was superior to that based on trifluoromethanesulfonic acid, was developed for cyclizations of dilactones (equation 7),[36] and has found application for the cyclopentannelation of six- to twelve-membered rings.[37] Ester groups do not interfere with such cyclizations.[38]

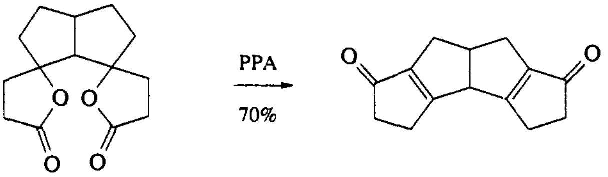

(7)

Acylations with carboxylic acids and anhydrides have been carried out with sulfuric acid as both solvent and catalyst, the reactive acylating agents from acyl halides probably being haloacyloxonium ions. Trifluoroacetic anhydride offers a rather milder reagent for reactions of carboxylic acids, with mixed anhydrides being likely intermediates. However, polyphosphoric acid remains the most widely used dehydrating agent for acylations by carboxylic acids.

Such reactions are particularly well suited to intramolecular dehydrative acylations for the formation of cyclic ketones.[2] One advantage of this procedure is the fact that acid chloride need not be preformed, a process that often causes problems with unsaturated acids. Polyphosphoric acid is again the most commonly used reagent for the necessary dehydration and cyclization.

Substrate structure plays a greater role than double bond location, in determining the ring size of the cyclization product, since under the strongly acidic reaction conditions migration of the site of unsaturation can occur prior to ring closure. In simple cases, five-membered rings are preferred, but substitution patterns can control the site of reaction, by stabilization of the intermediate carbonium ion.[39]

The reaction can be extended to substrates that can form unsaturated acids under the acidic reaction conditions, the most important being lactones, as cited previously (*e.g.* equation 7).

### 3.1.3.4 Di- and Poly-acylation

The acylation of alkenes gives rise to unsaturated ketones, which themselves may be further acylated under the same reaction conditions. This is particularly the case with the nonconjugated products that often are formed preferentially. The diacyl derivatives readily cyclize to form pyrylium salts when this can be accommodated, and the sequence represents one of the best strategies for the formation of pyrylium salts symmetrically substituted at the 2- and 6-positions. Friedel–Crafts acylation as a route to pyrylium salts has been reviewed, and compared with other synthetic strategies.[40]

In diacylations of alkenes, the Perrier procedure, where the alkene is added to the complex of the Lewis acid and acyl halide, has been used most frequently. Precursors of alkenes, for example *t*-butyl chloride or the alcohol, can also be used, relying on the presence of the Lewis acid, usually aluminum chloride, to form the acylation substrate, in these cases isobutene.

Yields of pyrylium salts are often higher in diacylations of alkenes than in the acylation of an equilibrium mixture of unsaturated ketones. This may be attributed to the preferential formation of the nonconjugated isomer in the first acylation, whereas isomerization of the (usually) thermodynamically more stable isomer is required before an α,β-unsaturated ketone may acylate.

Di- and poly-acylated products are often water soluble, and so require care in isolation. Low recoveries of desired products from aliphatic Friedel–Crafts monoacylations may suggest that over reaction is leading to water-soluble products that have not been recognized, and therefore lost during work up.

## 3.1.4 ACYLATIONS OF SILANES

### 3.1.4.1 Introduction

The well-established stabilization of a positive charge on carbon β to silicon[41,42] has been utilized in very versatile methods for the control of aliphatic Friedel–Crafts reactions. The specificity of this stabilization lies behind the utility of both alkenyl- and allyl-silanes as substrates for electrophilic substitutions, and acylations in particular. These classes offer complementary regiospecificities in controlling both the site of acylation and the location of the double bond. This promotion of simple substitution is one of the most significant advances in aliphatic Friedel–Crafts acylations of recent times, and has recently been the subject of an exhaustive review.[43]

### 3.1.4.2 Alkenylsilanes

The β-effect of silicon tends to direct the site of electrophilic attack on alkenylsilanes to the carbon bearing the silicon atom (Scheme 4). In comparison with a proton, the greater ease with which the trimethylsilyl group is displaced from carbon leads more often to the formation of substitution products rather than those of addition. Thus vinyltrimethylsilane (b.p. 55 °C) is a convenient equivalent for ethylene in Friedel–Crafts acylations. The alkenyl ketone is formed directly, in contrast to the β-chloroethyl ketone formed in the acylation of ethylene.

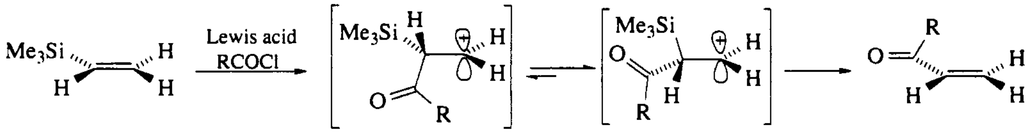

Scheme 4

Alkenylsilane acylation has been employed for the synthesis of two furano monoterpenes, dehydroelsholzione (**1**) and isoegomaketone (**2**; Scheme 5).[44] Acylation of isobutene with 3-methyl-2-furoyl chloride gave dehydroelsholzione in poor yield with a variety of Lewis acid catalysts ($SnCl_4$, $AlCl_3$, $TiCl_4$), but using the equivalent silane substrate, the ketone was obtained in 55% overall yield. Probably as a result of work-up conditions, the initial reaction gave a mixture of three products, the conjugated and deconjugated ketones, together with the chloro ketone addition product. Isomerization and dehydrochlorination were effected with a tertiary amine base to maximize the yield of the desired product.

Friedel–Crafts acetylation of a cyclobutenylsilane has been used in a short synthesis of grandisol (**3**; Scheme 6).[45]

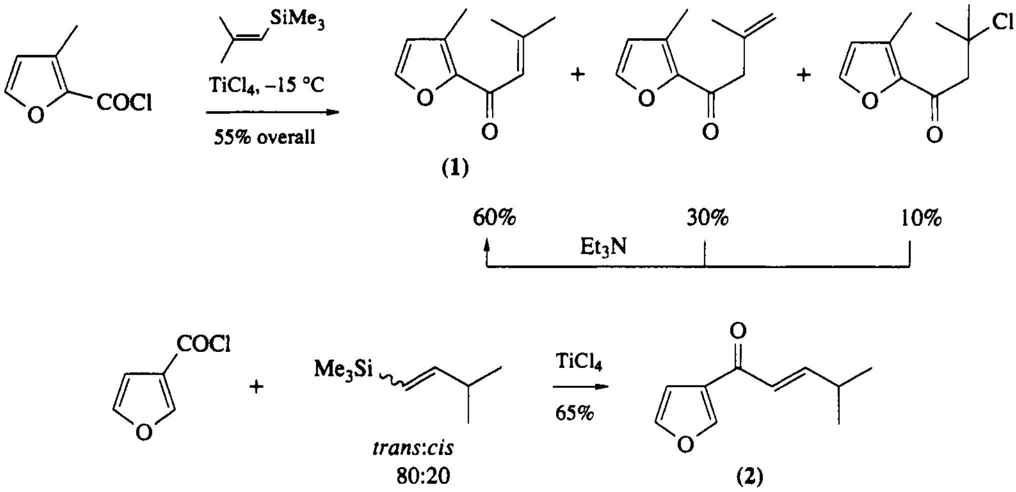

**Scheme 5**

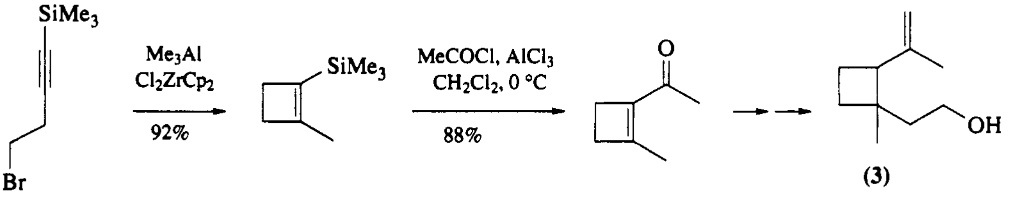

**Scheme 6**

Acylations of alkenylsilanes with α,β-unsaturated acid chlorides lead to dienones in good yield. These may undergo Nazarov-type cyclization to the cyclopentenone, synthetically useful yields in particular being realized when fused ring systems are formed. This leads to two strategies for cyclopentenone annulation. Dienones may be synthesized from either a cyclic α,β-unsaturated acid chloride and a simple alkenylsilane,[46] or from an acrylic acid derivative and a cyclic alkenylsilane (Scheme 7).[47] The regiospecificity of acylation of the silane results in regiocontrol in the annulation.[47] In the former strategy, tin(IV) chloride has been used for both the Friedel–Crafts acylation at *ca.* –30 °C and the cyclization at room temperature in a one-pot reaction. In the second, the two steps were carried out separately, using aluminum chloride at low temperature for the acylation, with tin(IV) chloride or boron trifluoride for the cyclization. In the acylation of vinyltrimethylsilane with acyclic α,β-unsaturated acyl chlorides using aluminum chloride as the catalyst at *ca.* –10 °C, the use of 1,2-dichloroethylene as cosolvent with the usual chlorinated hydrocarbons in some instances reduced the addition of hydrogen chloride to the product.[48] Cyclization to the simple cyclopentenone was observed at higher temperatures with this catalyst. It is therefore apparent that solvent, catalyst and reaction temperature, as well as mode of addition and work-up conditions, are all factors of importance in maximizing yields in these acylation reactions.

The β-stabilization of positive charge by silicon requires that the carbon–silicon bond be in the same plane as the *p*-orbital carrying the positive charge. As the electrophile approaches, the principle of least motion generates a further characteristic of the initial reaction with acylating agents. The substitution usually takes place with retention of geometrical configuration of the alkene.[49] However, under the conditions of both reaction and work-up, isomerization to any thermodynamically more stable enone may occur.

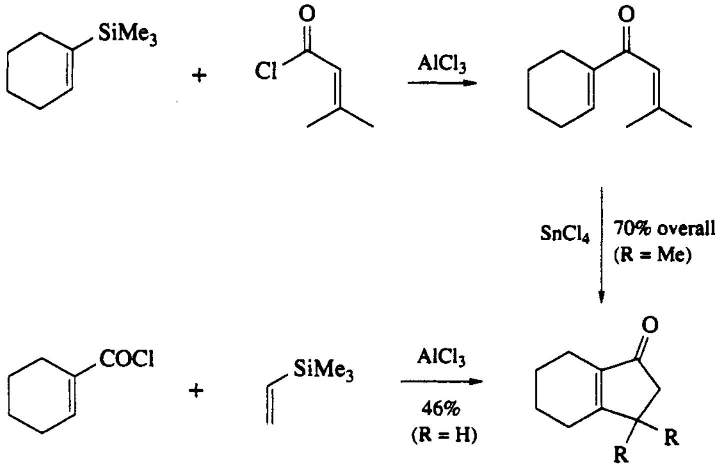

**Scheme 7**

Intramolecular acylations proceed with greater success for alkenylsilanes than the simple alkenyl substrates. In several cases, (*E*)-silyl substrates have been cyclized to enones, ring size constraints precluding reaction with retention of alkene geometry (equation 8).[50,51] The cyclization approach can be used to prepare enones where the double bond lies exocylic to the ring.[52] In the example shown, retention of configuration is also evident, although the product was easily isomerized under acidic conditions (equation 9).

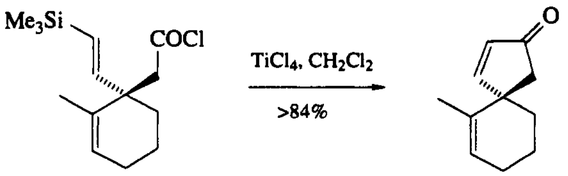

(8)

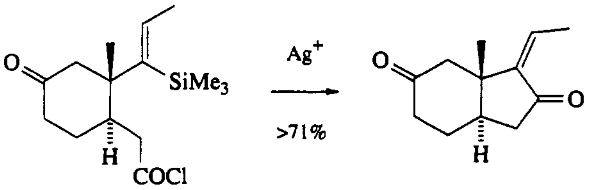

(9)

Initiation of polyalkene cyclization by an acid chloride and termination by an alkenylsilane have been combined in a synthesis of an octahydronaphthalene as part of studies towards the synthesis of dihydrocompactin, where the silane can be viewed as controlling the Friedel–Crafts acylation of the disubstituted double bond (equation 10).[53] In this case, antimony pentachloride gave superior yields compared to a wide variety of commonly used Lewis acid catalysts.

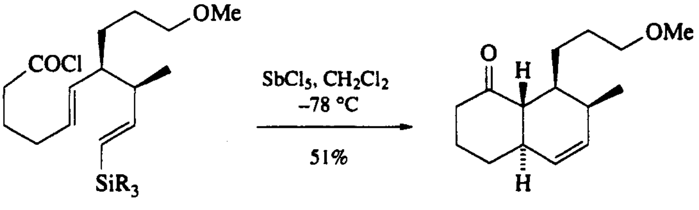

(10)

Although the silyl group confers a site selectivity on the acylation reaction, other structural factors may be sufficient to override the β-effect. This is demonstrated by comparison of acylations of the alkenylsilanes (4) and (5) (Scheme 8).[54] In the former, both the aromatic and silyl substituents direct the electrophile to the same carbon site, and acylation proceeds in high yield. However, in the latter substrate, where the substituents are in opposition, the aromatic group dominates the site of acylation, and the initial product retains the silicon substituent. Nevertheless, elimination of hydrogen halide followed by protodesilylation gives the substitution product in a higher overall yield than in the 'direct' acylation of the nonsilylated dihydronaphthalene. Similarly, cyclizations to form indenones are preferred, not only for electronic reasons, but also from ring strain considerations (equation 11).[55] A β-acylation is also the major pathway for the $AlCl_3$-induced cyclization of (**6**; *n* = 1), with the 'normal' α-acylation less favored as a result of the increased strain in forming the four-membered ring. In addition, cyclization reactions have demonstrated the limits of the β-effect's control of the regioselectivity of acylation.[56] Whilst the substrate (**6**; *n* = 2) cyclizes in very high yield to the methylenecyclopentanone anticipated from consideration of the β-effect, the isomeric silane (**7**) gives the cyclohexenone from β-acylation and rearrangement (Scheme 9). In order to rationalize such reactions, consideration must be given to the relative stability of the incipient potential cations. In the cyclization of (**7**), the tertiary α-silyl cation predominates over the primary β-silyl intermediate.

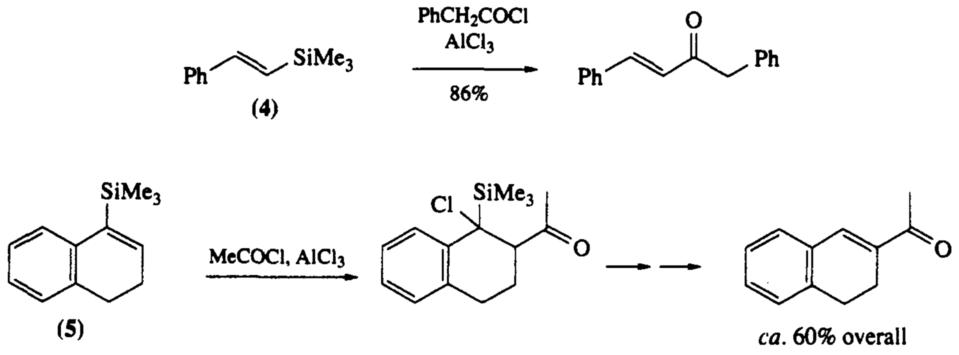
Ph
SiMe3
(4)
PhCH2COCl
AlCl3
86%
O
Ph
Ph
SiMe3
(5)
MeCOCl, AlCl3
Cl
SiMe3
O
O
ca. 60% overall

**Scheme 8**

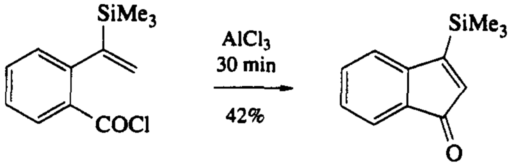
SiMe3
COCl
AlCl3
30 min
42%
SiMe3
O

(11)

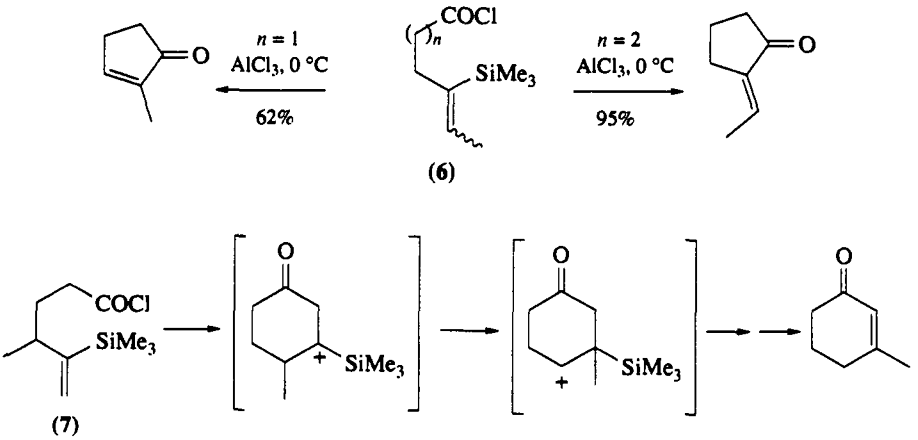
O
n = 1
AlCl3, 0 °C
62%
COCl
( )n
SiMe3
(6)
n = 2
AlCl3, 0 °C
95%
O
COCl
SiMe3
(7)
O
+
SiMe3
O
+
SiMe3
O

**Scheme 9**

Other substituents on the alkene are tolerated, but may influence the regiochemical outcome. The silyl group is replaced in the acylation of 1-halo-2-trimethylsilylethylenes, although Lewis acids catalyzed the

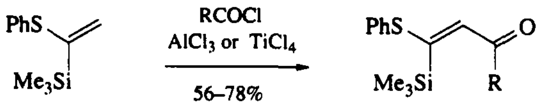
PhS
Me3Si
RCOCl
AlCl3 or TiCl4
56–78%
PhS
O
Me3Si
R

(12)

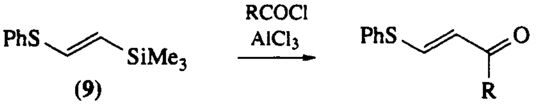

(13)

isomerization of *cis* products to the more stable *trans* isomers.[57] Sulfur substituents on a double bond dominate over silicon,[58,59] as shown by comparison of the alkenes (**8**; equation 12) and (**9**; equation 13).

### 3.1.4.3 Allylsilanes

The silyl group in allylsilanes exerts a strong influence on the regioselectivity of reactions with a variety of electrophiles, and acylating agents in particular.

The stabilization of intermediates and transition states with β-carbenium character by silicon may be explained as a σ–π-conjugative interaction between the silicon–carbon bond and the π-system. This requires an overlap that can occur far earlier along the reaction coordinate for allylsilanes than with alkenylsilanes, where the orbitals are initially orthogonal. This earlier stabilization accounts for the observations that acylations of allylic silanes are regiochemically reliable. In common with reactions with other electrophiles, acylation reaction occurs with allylic rearrangement to give β,γ-unsaturated ketones (equation 14). Even γ,γ-disubstituted allylsilanes readily react at the more-hindered site with acyl chlorides in the presence of a Lewis acid at low temperature to give tertiary alkyl ketones,[60] a reaction used in a short high-yielding synthesis of the monoterpene artemesia ketone (equation 15).[61] Allylsilanes are therefore efficient precursors for the construction of quaternary carbon centers.

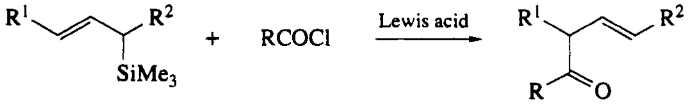

(14)

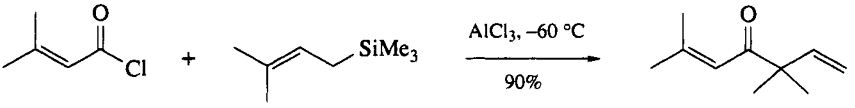

(15)

β,γ-Unsaturated ketones derived from α-substituted allylsilanes have disubstituted double bonds with predominantly (*E*)-configuration, and reactions of optically active examples have shown a high *anti* selectivity with the product ketone retaining a stereochemical relation to the precursor.[62] This is consistent with a reaction geometry of the form shown in (**10**), where the electrophile approaches the double bond selectively *anti* to the leaving trimethylsilyl group, and the product stereochemistry reflects the configuration of the disubstituted double bond in the substrate (Scheme 10). Stereochemical transfer is also pronounced in the high-yielding acylations of fluorodimethylsilyl derivatives, but in reactions of trifluorosilyl substrates yields appear low, and products racemic.[63]

Unusual circumstances in allyl substrates can lead to unusual acylation products. Extremely hindered allylsilanes have been noted to react without allylic rearrangement (equation 16),[64] and steric arguments may account for acylations that take place with apparent overall *syn* addition (equation 17).[65]

Lewis acids used for acylation of allylsilanes with acid chlorides include titanium and tin tetrachlorides, aluminum, gallium and indium trichlorides and zinc dichloride, and boron trifluoride for reactions with acid anhydrides. Although gallium and indium chlorides have been used successfully in catalytic (*ca.* 2 mol %) amounts,[66] most frequently aluminum chloride has been used as catalyst, with titanium tetrachloride also commonly employed, both in molar quantities. With these catalysts, acylations can often be carried out at low temperatures, and with short reaction times.

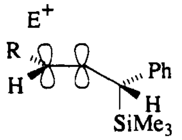

**(10)**

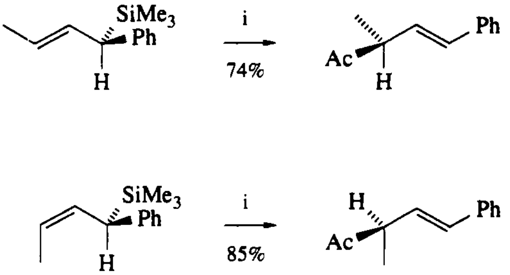
SiMe3
Ph
H
i
74%
Ac
H
Ph
SiMe3
Ph
H
i
85%
H
Ac
Ph

i, AcCl, $AlCl_3$, $CH_2Cl_2$, –78 °C, 5 min

**Scheme 10**

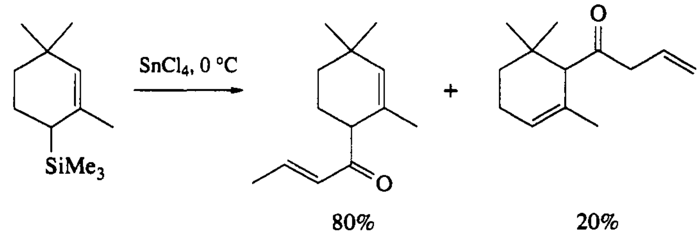
SiMe3
SnCl4, 0 °C
O
+
O
80%
20%

(16)

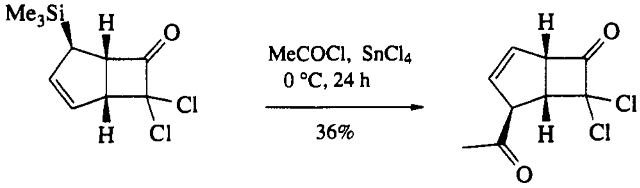
Me3Si
H
O
Cl
H
Cl
MeCOCl, SnCl4
0 °C, 24 h
36%
H
O
Cl
H
Cl
O

(17)

The regiochemical reliability of the Friedel–Crafts acylation of allylsilanes extends to a wide variety of substrates, including cycloalkenylsilanes,[67] and 1-trimethylsilylmethylcyclohexenes.[68] The mild conditions necessary for acylation are demonstrated in the reactions of 7-trimethylsilyl-α-pinene, where the acid sensitive pinene carbon skeleton survives without rearrangement (equation 18). The formation of methylenecyclohexanes from silylmethylcyclohexenes should be contrasted with Friedel–Crafts acylations of the simple methyl derivatives, which lead to cyclohexenyl products.

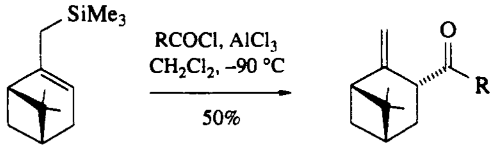
SiMe3
RCOCl, AlCl3
CH2Cl2, -90 °C
50%
O
R

(18)

Thus the double bond may be either cyclic or exocyclic to a ring, and the silyl group on a ring substituent or on a ring. Silacyclopentene derivatives also may be acetylated, either with acetyl chloride/aluminum chloride or acetic anhydride/boron trifluoride, with retention of the silyl group (equation 19).[69]

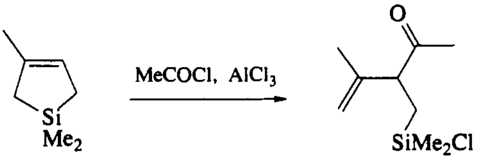
Si
Me2
MeCOCl, AlCl3
O
SiMe2Cl

(19)

1,4-Disilylcyclohexa-2,5-dienes, obtained by reductive silylation of benzene derivatives, undergo regiospecific diacylation giving, after aerial oxidation, *p*-diacylated arenes.[70] The aliphatic Friedel–Crafts reaction can thus be used to prepare benzenoid compounds difficult to obtain by classical aromatic chemistry (Scheme 11).

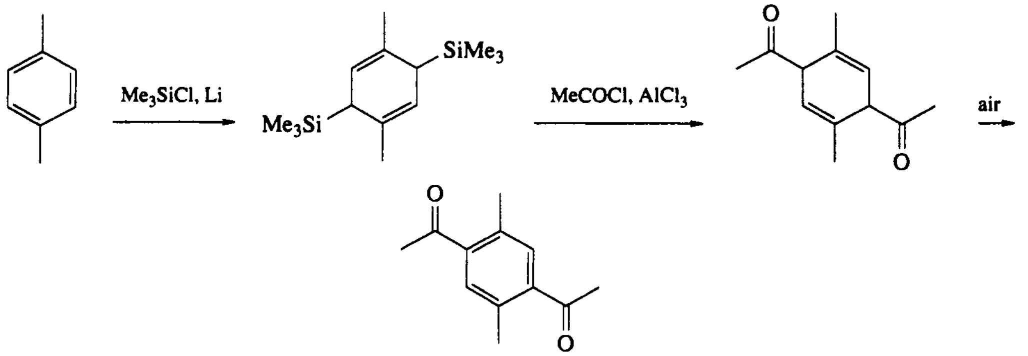
Me3SiCl, Li
SiMe3
Me3Si
MeCOCl, AlCl3
O
O
air
O
O

**Scheme 11**

Unsymmetrically substituted 1,4-disilyl-2-butenes undergo selective acylation, with the trimethylsilyl group being replaced in preference to triphenylsilyl (equation 20).[71]

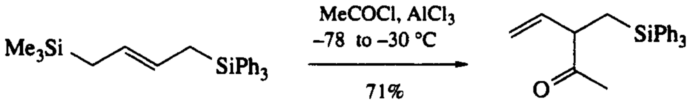
Me3Si
SiPh3
MeCOCl, AlCl3
–78 to –30 °C
71%
SiPh3
O

(20)

1,1-Disilylalkenes provide an access to acylated (*E*)-vinylsilanes. 1,3-Disilylpropenes tend to behave as 3-silylpropenes towards acylation, because of the lability of the α-silyl ketone formed initially.[72] Divinyl ketones are isolated from reactions with unsaturated acid chlorides.[73] Since these are cyclized under the reaction conditions, they are presumably formed during work up, possibly from silyl dienolate intermediates (Scheme 12).

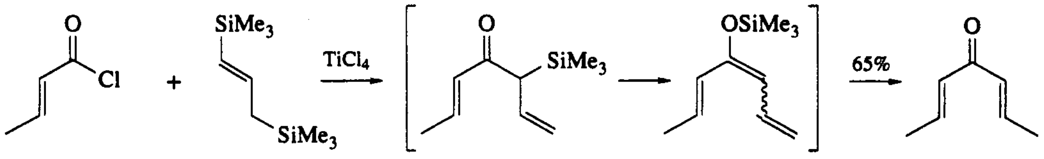
O
Cl
+
SiMe3
SiMe3
TiCl4
O
SiMe3
OSiMe3
65%
O

**Scheme 12**

The greater reactivity of allyl- compared to vinyl-silanes is shown in the acylation of 2,3-disilylalkenes, giving rearranged alkenylsilanes.[74] Interestingly, this acylation offers a route to the *trans*-cyclononene skeleton (equation 21).[75]

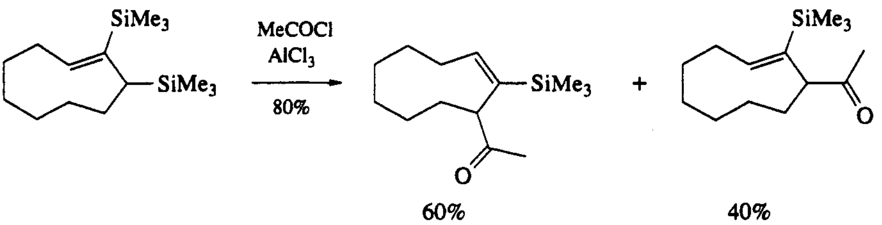
SiMe3
SiMe3
MeCOCl
AlCl3
80%
SiMe3
O
+
SiMe3
O
60%
40%

(21)

Many functional groups are tolerated during the Friedel–Crafts acylation of allylsilanes, giving rise to a wide variety of functionalized ketones, some of which are shown in Scheme 13.[76–81] The stability of a sulfone group under conditions required for acylation has potential for the formation of dienones, as demonstrated in the synthesis of (*E*)- and (*Z*)-tagetones (**11**) shown in Scheme 13.[79]

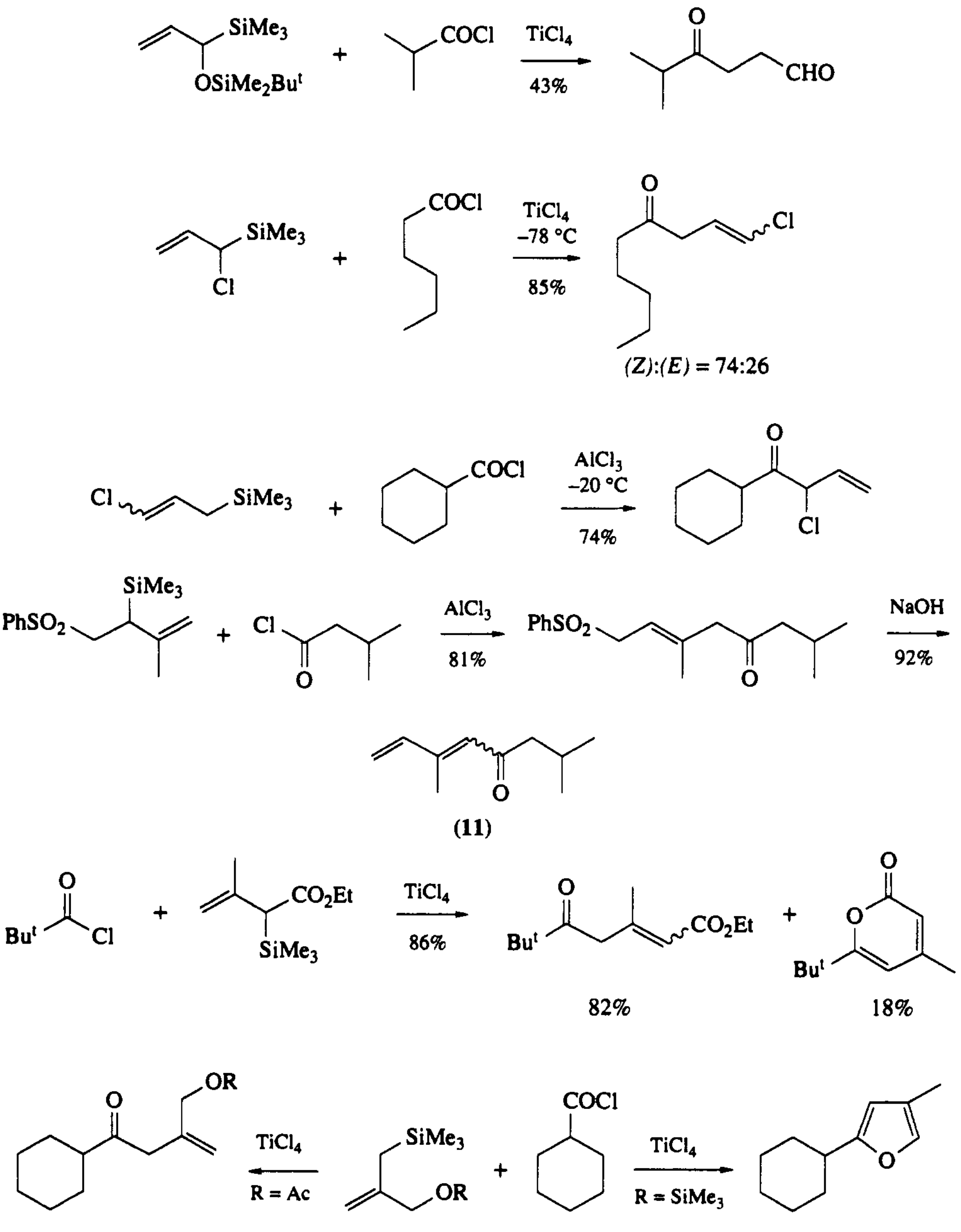
SiMe3
OSiMe2Bu^t
COCl
TiCl4
43%
CHO
SiMe3
Cl
COCl
TiCl4
–78 °C
85%
Cl
(Z):(E) = 74:26
SiMe3
COCl
AlCl3
–20 °C
74%
Cl
SiMe3
PhSO2
Cl
AlCl3
81%
PhSO2
NaOH
92%
(11)
Bu^t
Cl
CO2Et
SiMe3
TiCl4
86%
Bu^t
CO2Et
82%
Bu^t
18%
OR
TiCl4
R = Ac
SiMe3
OR
COCl
TiCl4
R = SiMe3

**Scheme 13**

### 3.1.4.4 Acylations of Other Unsaturated Silanes

Three types of products have been observed in intermolecular acylations of homoallylic silanes, the major one being cyclopropylmethyl ketones, along with minor amounts of 3-butenyl ketones and β-chloro ketones.[82] It is likely that all derive from the carbenium ion formed by acylation of the double bond, which then undergoes cyclodesilylation or hydride transfer followed by β-elimination (Scheme 14). The former leads to the cyclopropane, which can ring open to give the chloro products. The latter pathway gives the butenyl ketone, and is supported by location of substituent positions on methylated substrates. However, the direct acylation of the carbon–silicon bond should not necessarily be excluded in consideration of more general cases. Titanium tetrachloride seems the preferred catalyst in these cyclodesilylations, and low temperatures minimize the formation of the chloro by-products. Intramolecular versions

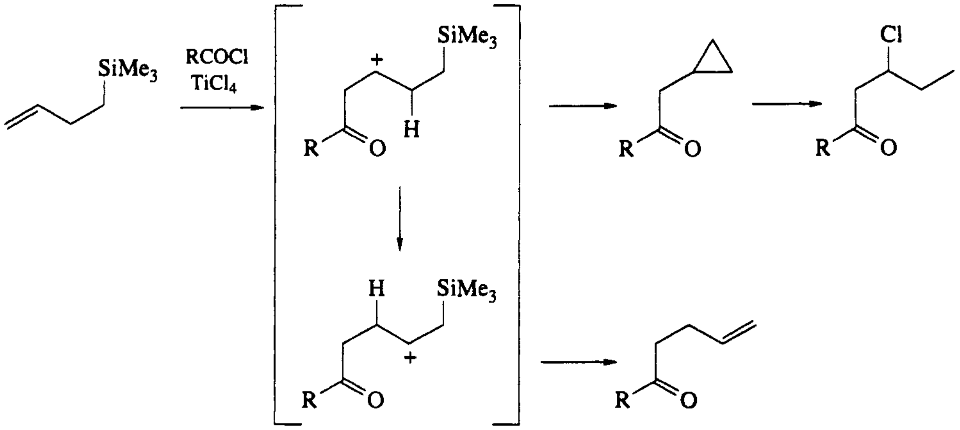

**Scheme 14**

of the reaction are also successful, leading to 2-cyclopropylcycloalkanones, particularly when forming five-, six- and seven-membered ring ketones.[52,83] Moving the silyl group further from the double bond removes its influence, and simple cyclic ketones retaining the silicon are formed.

## 3.1.5 ACYLATIONS OF CONJUGATED DIENES

### 3.1.5.1 Simple Dienes

Early reviews indicate that few conjugated dienes had been successfully acylated under Friedel–Crafts conditions. This probably results from the sensitivity of such substrates to the strongly acidic reaction conditions, leading to polymerization. However, provided reaction temperatures are low enough, synthetically useful yields of acylated products can be obtained. Butadiene itself is acylated at the terminal position in the presence of aluminum chloride at dry ice temperatures to give the *trans*-dienone.[84] In the presence of the more mild Lewis acid tin(IV) chloride, propionylation occurred at slightly higher temperatures (*ca.* –40 °C), although the yield of 42% quoted was after prolonged treatment with calcium carbonate, presumably to effect dehydrochlorination.[85]

Chloro ketones have been observed in tin(IV) chloride catalyzed acylations of isoprene as part of high-yielding synthetic approaches to tagetones (**12**) and ocimenones (**13**; Scheme 15).[86] Typically, it was not necessary to isolate these, dehydrohalogenation to mixtures of *cis*- and *trans*-dienones being accomplished using lithium fluoride and lithium carbonate in DMF.

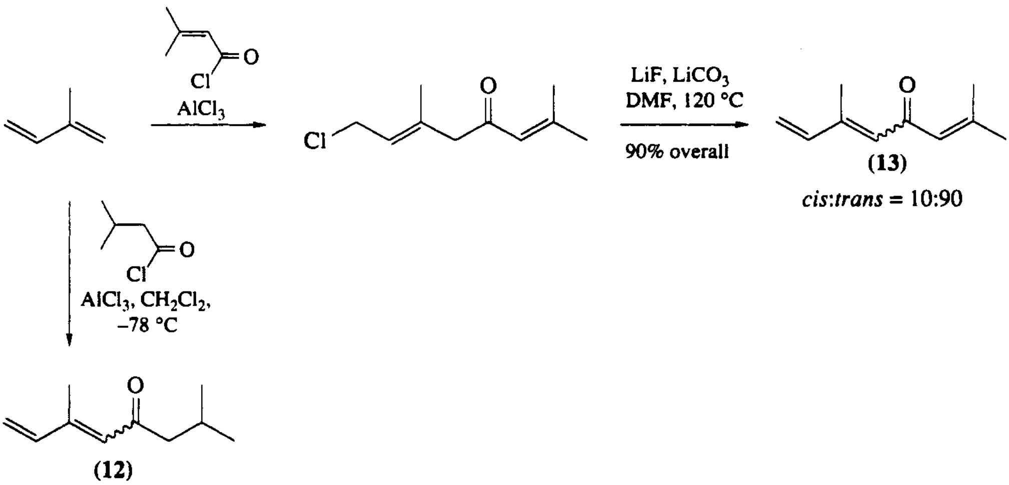

**Scheme 15**

Silicon has also been used to control the acylation of 1,3-dienes in a manner analogous to the situation with alkenes. Isoprenylation with 2-trimethylsilylmethylbuta-1,3-diene follows the course expected of acylation of the allylic silane. In these very rapid reactions, titanium tetrachloride seems to be one of the more efficient catalysts, as is aluminum chloride. The method was used in synthetic approaches to the terpenes ipsenol (**14**) and ipsdienol (**15**; Scheme 16).[87] Of particular interest is the comparison of this isoprenylating agent with isoprene itself. The examples of Friedel–Crafts acylations cited show the regiocontrol that can be achieved by suitable choice of substrate.

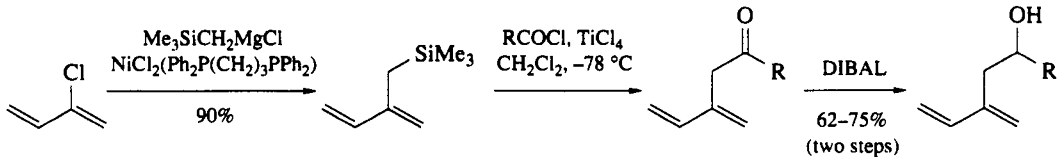

Cl
Me3SiCH2MgCl
NiCl2(Ph2P(CH2)3PPh2)
90%
SiMe3
RCOCl, TiCl4
CH2Cl2, -78 °C
O
R
DIBAL
62–75%
(two steps)
OH
R

(**14**) R = $Bu^i$

(**15**) R = $CH{=}CMe_2$

**Scheme 16**

(Pentadienyl)trimethylsilane, in its reaction with pivaloyl chloride in the presence of titanium tetrachloride, acylates to give a mixture of products, chiefly derived from reaction at the ε-carbon, with γ-acylation also observed (equation 22).[88] The latter mode of reaction is more prevalent if the ε-carbon is further substituted, presumably because of steric hindrance. This electrophile showed lower selectivity for the ε-carbon than other electrophiles, including aldehydes and acetals.

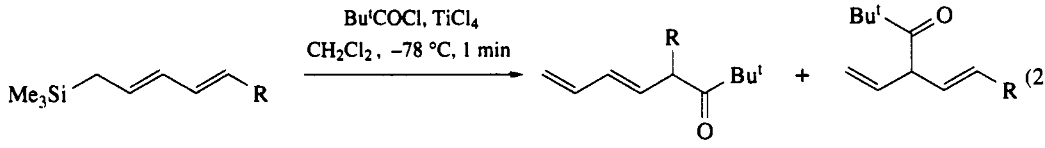

Me3Si
R
Bu^tCOCl, TiCl4
CH2Cl2, -78 °C, 1 min
R
Bu^t
O
+
Bu^t
O
R

(22)

| | | | | |
|---|---|---|---|---|
| R = H | 59% | 58% | : | 42% |
| R = Me | 55% | 22% | : | 78% |

Relatively little work has been reported on the acylation of 1-trialkylsilyl-1,3-butadienes. As is observed with vinylic substrates, the regioselectivity of reaction can be controlled by substituents other than the silyl group. For example, acylations of 3-alkyl derivatives are controlled by the relative stability of the tertiary carbenium ion following attack of the electrophile at the C-4 terminus (Scheme 17). Silicon is retained in both the immediate chloride addition product, and the diene formed by subsequent base-catalyzed eliminations.[89]

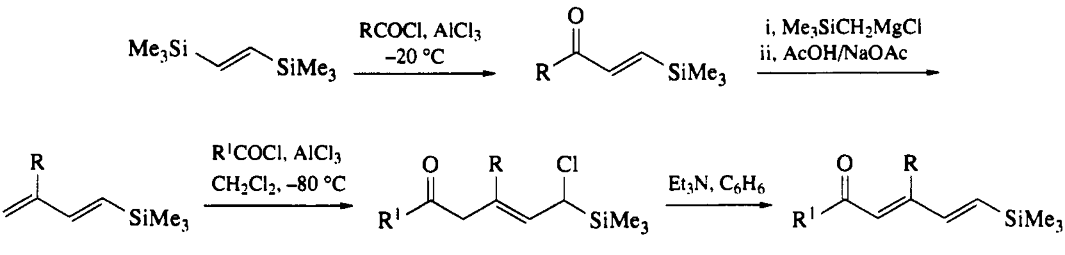

Me3Si
SiMe3
RCOCl, AlCl3
-20 °C
O
R
SiMe3
i, Me3SiCH2MgCl
ii, AcOH/NaOAc
R
SiMe3
R1COCl, AlCl3
CH2Cl2, -80 °C
O
R
Cl
R1
SiMe3
Et3N, C6H6
O
R
R1
SiMe3

**Scheme 17**

### 3.1.5.2 Diene Complexes

Although few examples of acylations of 1,3-butadienes have been described, Friedel–Crafts acylations of diene complexes, in particular iron tricarbonyl derivatives, can give synthetically useful yields. In acylations of iron tricarbonyl complexes with the Perrier reagent from acetyl chloride and aluminum chloride, acylation occurs only at unsubstituted terminal carbons (Scheme 18).[90] The primary product is the *cis*-dienone complex, although the intermediate σ-complex (**16**) has on occasion been isolated,[91] X-ray structure determination showing that under Friedel–Crafts conditions the complex undergoes stereospecific *endo* attack.[92] In order to isolate the primary *cis* product, the reaction should be quenched with cold aqueous ammonia.[93] Isomerization to the more stable *trans*-dienone complex takes place under more strongly acidic or basic conditions. Methanolic sodium methoxide is recommended for preparative isomerization.[94]

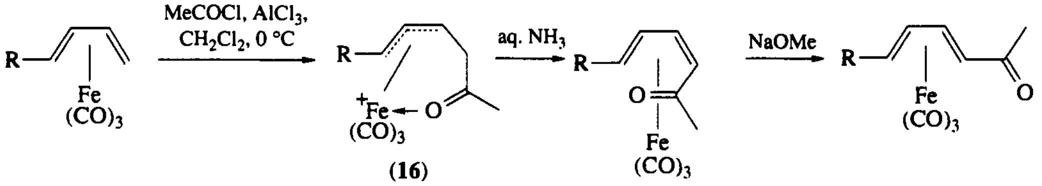
MeCOCl, AlCl3, CH2Cl2, 0 °C
aq. NH3
NaOMe
R
Fe (CO)3
+Fe
O
(16)

Scheme 18

The value of the metal complexation results from control of the reaction, rather than any activation, Lewis acids being excellent catalysts for diene polymerization. Friedel–Crafts acylations of diene complexes have been used for the preparation of dienes, with decomplexation following carbonyl reduction.[95] Decomplexation to afford dienones has been less explored. The intermediate cationic σ-complex on treatment with triethyl phosphite or triphenylphosphine affords metal-free β,γ-unsaturated phosphonates or phosphonium salts (Scheme 19).[96] The initial *s-cis* conformation of the diene fragment of the

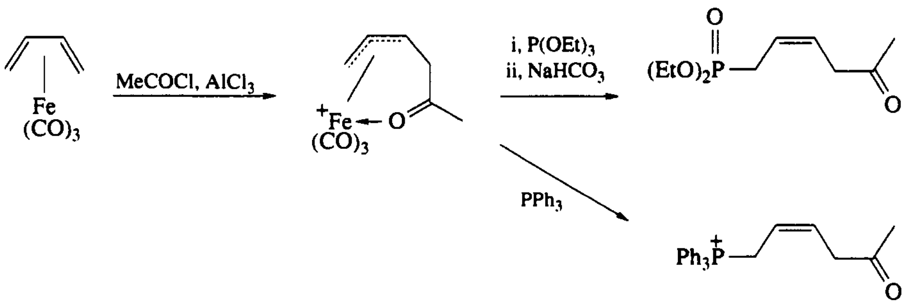
MeCOCl, AlCl3
i, P(OEt)3
ii, NaHCO3
PPh3
Fe (CO)3
+Fe
(EtO)2P
Ph3P+
O

Scheme 19

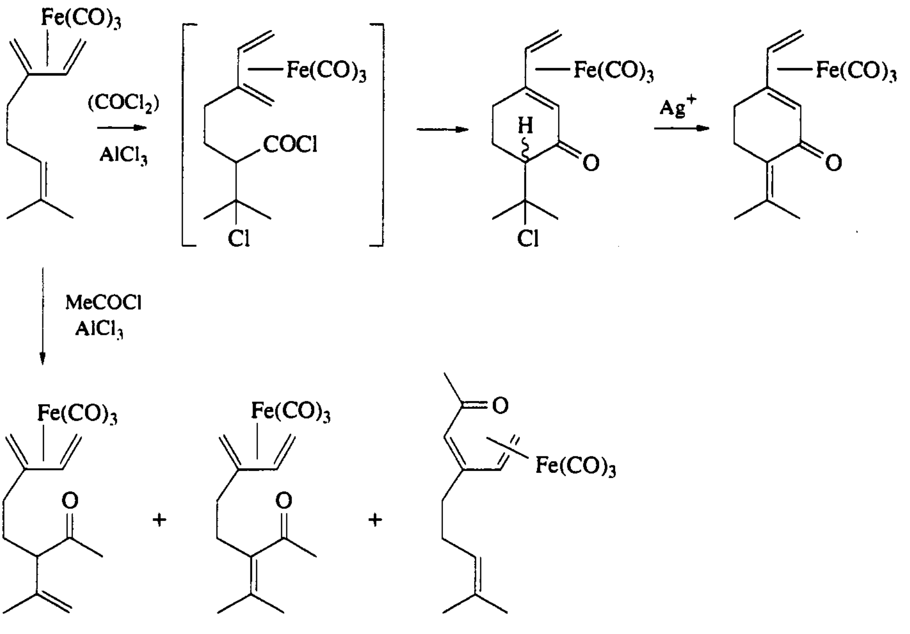
Fe(CO)3
(COCl2)
AlCl3
COCl
Cl
H
O
Ag+
MeCOCl
AlCl3
+

Scheme 20

complex is retained, and leads stereospecifically to functionalized (*Z*)-alkenes with considerable synthetic potential.

2-Trialkylsilylated butadienyliron tricarbonyl complexes acylate to give solely terminal *cis*-dienone complexes, reacting preferentially at the 4-position.[97]

The iron tricarbonyl unit has been described as a protecting group for a 1,3-diene, as in the acetylation of the complex of myrcene at low temperature (Scheme 20). The usual combinations of α,β- and β,γ-unsaturated ketones were formed. At higher temperatures, some acylation at the terminus of the diene complex was also observed. In an interesting extension, reaction of the complex with oxalyl chloride resulted in cyclization of the acid chloride initially formed by reaction at the alkene.[98]

A terminal acyl group is not totally deactivating towards further acylation of dienone–iron complexes derived from isoprene and 2,3-dimethylbutadiene,[99] and 2-trialkylsilylbutadienes,[97] provided the acyl group lies in the *exo* configuration (Scheme 21). The required isomerization may be carried out using acetyl chloride. With excess acetylating agent, *trans*-dienone complexes acylate slowly to give the *cis–trans*-dienedione complexes. Partial isomerization to the *trans–trans* isomers was noted. These interesting dienediones could be released (although with further isomerization) from their complexes by cleavage with hydrogen peroxide in methanolic sodium hydroxide. Other cleavage methods proved unsuitable.[99]

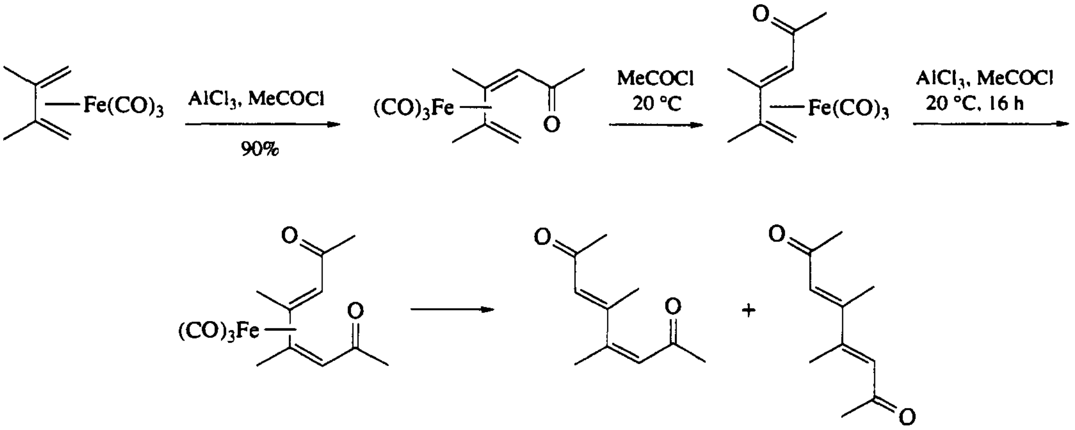

Scheme 21

## 3.1.6 ACYLATION OF ALKYNES

### 3.1.6.1 Simple Alkynes

The Friedel–Crafts acylation of alkynes is an extremely rapid reaction, and usually leads to the formation of the *trans*-β-chlorovinyl ketone (equation 23). Reaction temperatures can be as low as –70 °C. The reaction proceeds *via* reaction of the acyl halide–Lewis acid complex with the alkyne, and whilst the implied vinyl cation has not been observed directly, the reaction products can be understood in terms of reaction of such an intermediate with nucleophiles, usually halide ion. Whilst the *trans*-chlorovinyl ketone has been described as the sole product of the reaction by some workers, others have reported the formation of mixtures of the *cis* and *trans* forms, under conditions that did not appear to lead to isomerization.[100]

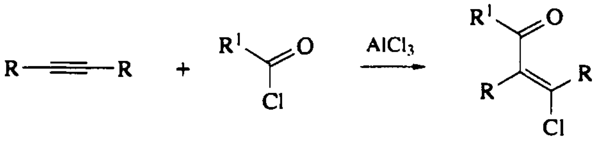

(23)

Other nucleophilic species can be present in the reaction medium to trap the cationic 'intermediate'. The rate of acylation of an alkyne is indicated by reaction in the presence of an aromatic compound, leading to arylated products (equation 24).[101] This reaction can take place at low temperatures where the

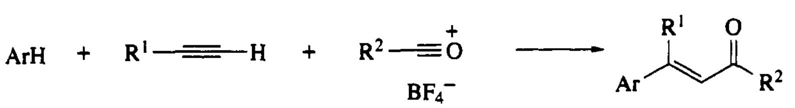
ArH
+
R¹—≡—H
+
R²—≡O⁺
BF₄⁻
R¹
O
Ar
R²

(24)

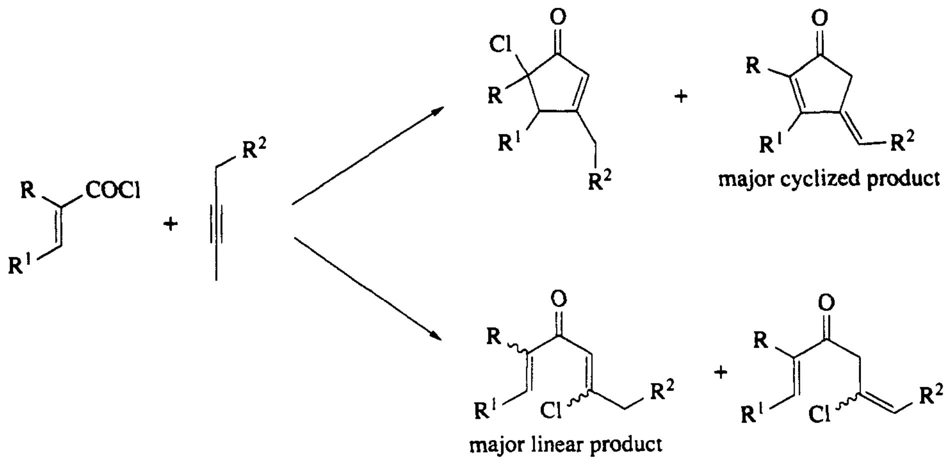
R
COCl
R¹
+
R²
O
Cl
R
R¹
R²
+
O
R
R¹
R²
major cyclized product
O
R
R¹
Cl
R²
major linear product
+
O
R
R¹
Cl
R²

Scheme 22

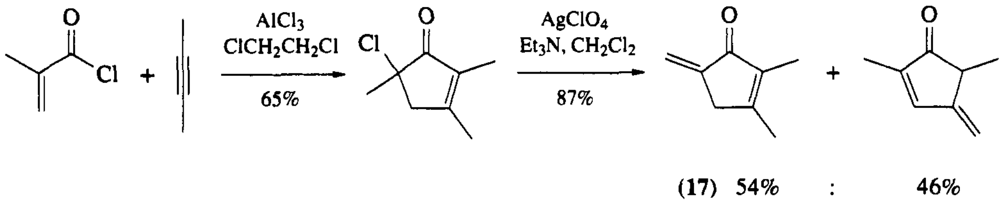
O
Cl
+
AlCl₃
ClCH₂CH₂Cl
65%
Cl
O
AgClO₄
Et₃N, CH₂Cl₂
87%
O
+
O
(17) 54%
:
46%

Scheme 23

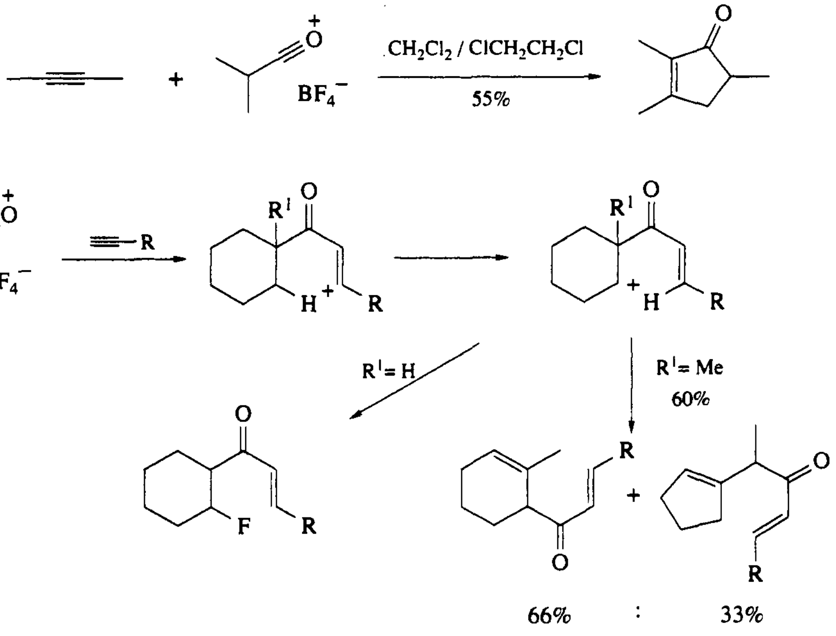
+
O⁺
BF₄⁻
CH₂Cl₂ / ClCH₂CH₂Cl
55%
O
R¹
O⁺
BF₄⁻
≡—R
R¹
O
H
+
R
R¹
O
+
H
R
R¹= H
R¹= Me
60%
O
F
R
R
O
+
O
R
66%
:
33%

Scheme 24

rate of arene acylation is essentially zero, although a limiting factor to this reaction is probably the reactivity of the arene used. Halogenated and alkylated arenes have been used successfully.

Unsaturated acyl chlorides react with substituted alkynes to give mixtures of linear and cyclopentenyl products, the latter being formed in greater yield at higher temperatures (Scheme 22).[102] This offers a convenient access to a variety of 5-chlorocyclopentenones bearing substituents at the 4- and 5-positions, with control over the location of the double bond.[103–105] Application of this method includes a short synthesis of the antibiotic methylenomycin B (**17**; Scheme 23).[106]

Hydride transfers are implicated in several acylations of alkynes by saturated acyl chlorides leading to cyclopentenes.[107] Intramolecular [1,5] hydride shifts have been shown to be a common feature in silver-assisted reactions of cyclohexanylcarbonyl chloride with alkynes.[108,109] The nature of the final product depends on the structure of the resulting cation. Capture of fluoride ion, ring contraction and acyl or alkyl migrations of axial substituents have been observed (Scheme 24).

In a related transformation, acylation of terminal alkynes catalyzed by copper(I) iodide and bis(triphenylphosphine)dichloropalladium(II) leads directly to alkynic ketones.[110]

### 3.1.6.2 Alkynylsilanes

Only rarely is proton loss observed from the 'intermediate' cation derived from acylation of a terminal alkyne. In contrast, acylation of alkynylsilanes provides an excellent strategy for the synthesis of alkynyl ketones.[111] Here, it is apparent that elimination of the silyl substituent competes very effectively with capture of a nucleophile. Acylation of bis(trimethylsilyl)ethyne[111] provides a convenient route to terminal alkynic ketones, particularly since desilylation can be carried out using bases as weak as dilute aqueous borax, conditions mild enough to prevent the ready hydration of the triple bond (Scheme 25).[112] Silylated diynes are also excellent substrates for Friedel–Crafts acylation.[112–114]

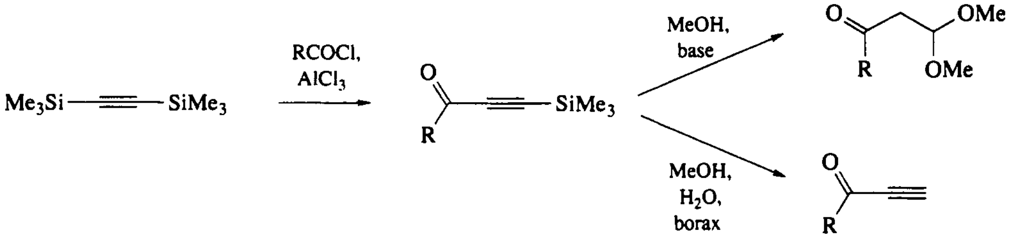

**Scheme 25**

Acylations have generally been carried out using aluminum chloride as catalyst, although on occasions no catalyst was required.[115] Titanium tetrachloride proved superior to aluminum, tin(IV) and zinc chlorides in reactions of 4-substituted-1-trimethylsilylbuta-1,3-diynes and the derived (*Z*)-enynes.[114] The most frequently used solvents are chlorinated hydrocarbons,[116,117] in preference to carbon disulfide and nitrobenzene.[111]

Both acid chlorides, including ethylsuccinyl chloride,[118] and acid anhydrides[111,119] have been used as acylating agents, as have carbamoyl chlorides.[120] Silver-assisted reactions of anhydrides of α-bromotoluic acid also lead to alkynic ketones, probably *via* an intermediate acyloxyalkyloxycarbenium salt (Scheme 26).[121]

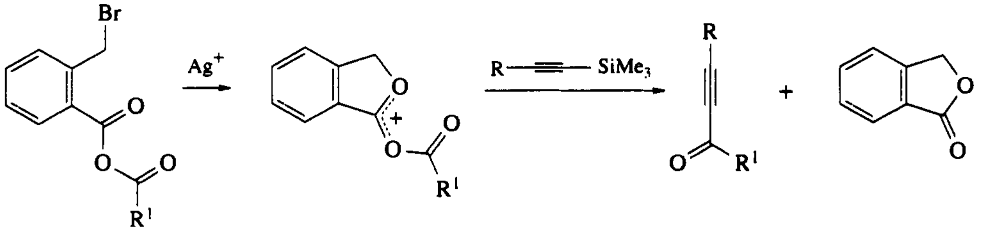

**Scheme 26**

With chloroacetyl chloride and aluminum chloride,[111] addition of chloride gave the β-chloro-α-silyl enone in addition to the alkynic ketone. Addition of halide has also been observed in alkynations of 2-alkoxy-1-trimethylsilylethynes.[122]

ω-Trimethylsilylethynylalkanoyl chlorides cyclize under high dilution conditions to form large (11–15-membered) ring ynones, exemplified by syntheses of (±)- and (*R*)-muscone (Scheme 27).[123] Extension of the cycloacylation to smaller ring systems provides products of chloride addition to the intermediate vinyl cation, rather than desilylation to form strained alkynes.

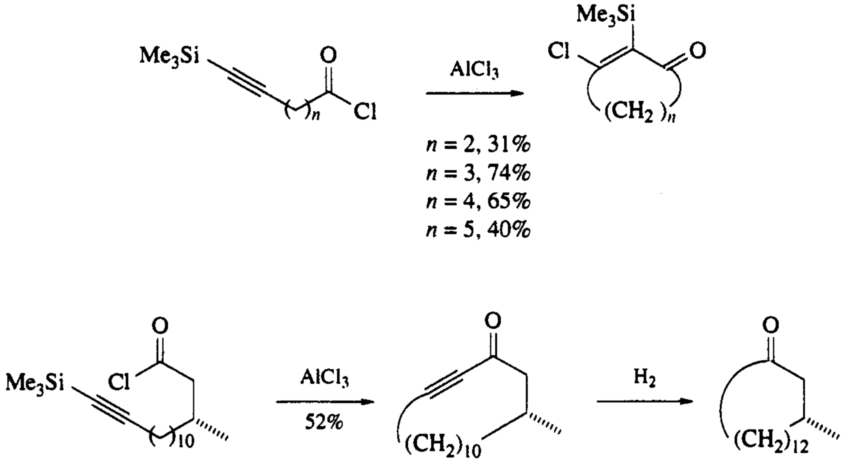

Scheme 27

Propargylsilanes react with acyl halides to afford α-allenic ketones by rearrangement (equation 25).[124]

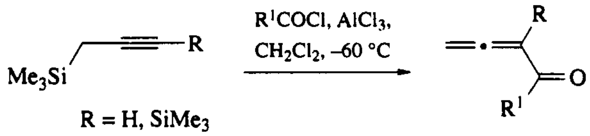

(25)

## 3.1.7 ACYLATION OF TIN SUBSTRATES

### 3.1.7.1 Lewis Acid Catalyzed Acylations of Stannanes

The similarities between organic tin and silicon compounds, particularly their abilities to stabilize positive charge on a β-carbon atom,[125] suggest that vinylic and allylic tin compounds should be useful substrates for Friedel–Crafts acylation reactions. However, very few examples of the acylation of stannanes under the action of Lewis acids have been reported, and this remains a field of Friedel–Crafts reactions not yet fully exploited. The acylation of 1,2-bis(tri-*n*-butylstannyl)ethylene in the presence of aluminum chloride offers a moderately yielding route to tributylstannyl-substituted enones, useful as precursors to 4,5-dialkylcyclopent-2-enones.[126]

Allylchlorostannanes react with acyl chlorides in the absence of any added catalyst, the chlorostannane having sufficient Lewis acid character to promote acylation with allylic rearrangement (equation 26).[127] Similarly, no added catalyst appears necessary for acylations of alkynylstannanes, although the trialkylchlorostannane formed in the thermal acylation may exert a catalytic influence on the reaction.

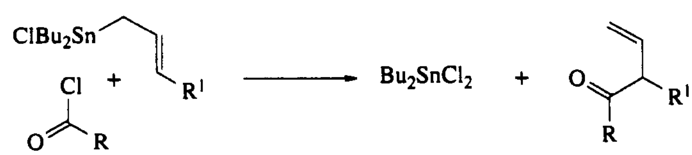

(26)

### 3.1.7.2 Alternatives to Lewis Acids for the Acylation of Stannanes

Despite the lack of examples of Friedel–Crafts acylations catalyzed by Lewis acids,[128] reactions of stannanes with acyl halides catalyzed by palladium species have found considerable use for the preparation of ketones.[129] Since alkyl groups are only transferred slowly from tin, more rapid transfer to the acyl chloride is observed for alkynyl, alkenyl and allyl, as well as aryl and benzyl, groups. This leads to a versatile synthesis of ketones.[130] Acylations of alkenylstannanes are both regio- and stereo-specific.

This alternative to the Friedel–Crafts reaction, extensively developed by Stille and coworkers, is particularly important, since the reaction conditions are essentially neutral, and so provides a method for acylation of compounds containing an acid-sensitive functionality which would preclude the use of the Friedel–Crafts reaction. Reaction temperatures are often below 100 °C, and high (1000-fold) turnovers of the catalyst have been achieved. Solvents employed include chloroform, toluene, and, on occasions, HMPA. Some reactions have been carried out under an atmosphere of carbon monoxide to prevent excessive decarbonylation of the acyl palladium intermediate. Indeed, carbonylative coupling of alkenylstannanes with allyl halides in the presence of carbon monoxide (*ca.* 3 atm or greater; 1 atm = 101 kPa) offers an alternative to the Friedel–Crafts acylation, ketones being formed by the reaction of the stannane with the acyl species formed by carbon monoxide insertion into the allyl palladium intermediate.[131]

Aromatic, aliphatic and heterocyclic acid chlorides all give high yields of ketones, [1,4] addition not being observed with α,β-unsaturated acid chlorides. This leads to a potentially very useful synthesis of divinyl ketones since, in contrast to Lewis acid catalyzed acylations of alkenes, under the neutral reaction conditions for the acylation of alkenylstannanes, cyclizations to cyclopentenones do not occur.[132]

Rhodium has also been found to catalyze regioselective acylations of allylic tin derivatives, with chlorotris(triphenylphosphine)rhodium(I) being particularly efficient in the terpenoid field.[133] Again, the use of nonacidic conditions for stannanes offers advantages over classical conditions both in the elimination of skeletal rearrangement and in the observance of altered regioselectivity by comparison with acylations of silyl substrates (Scheme 28). However, it has not yet been firmly established that rhodium-catalyzed acylations always proceed without rearrangement.

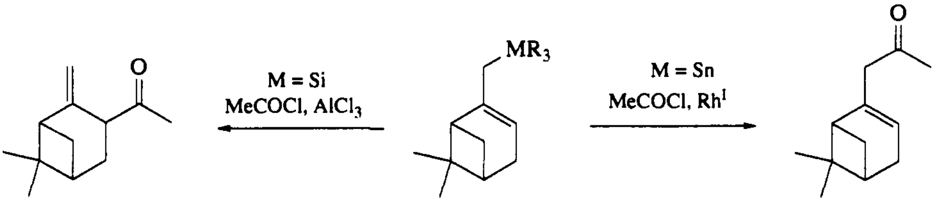

Scheme 28

Palladium-catalyzed acylations offer a useful chemoselectivity. Since alkenylsilanes do not react, this allows the formation of silyl-substituted ketones which could not readily be made by classical aliphatic Friedel–Crafts acylations (equation 27).[134]

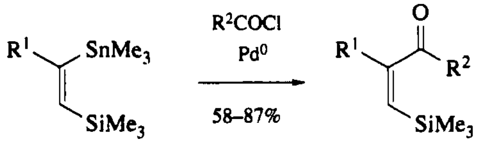

(27)

## 3.1.8 ACYLATIONS OF ALKANES

The acylation of alkanes has also been known for a long time,[2] but for synthetic purposes is limited to simple substrates. The initial step is hydride abstraction by an acylium ion, a process well established in the presence of a powerful Lewis acid, most commonly an aluminum halide, or strong protic acid.[135] The carbocation so formed can then undergo elimination, possibly after hydride or alkyl migration, to give an alkene which is then acylated. In the presence of excess alkane, saturated ketones are formed by a further intermolecular hydride transfer, whereas with an excess of acyl halide, the product is the (conjugated) unsaturated ketone.[136] The synthetic potential is obviously likely to be limited to simple substrates, which undergo specific initial hydride transfer. One such example is the preparation of 1-acetyl-2-methylcyclopentene by acetylation of cyclohexane.[137]

Whilst acylation of alkanes requires initial hydride abstraction, and has limited application, the weakly polarized carbon–silicon bond in tetraalkylsilanes can be cleaved by electrophilic attack. Since silanes are generally relatively stable, strong Lewis acids are required to induce reaction. In the limited studies to date, aluminum chloride is the only reagent described as effective in acylation of silanes. This acylation offers potential for conversion of acid halides to simple (methyl, ethyl) ketones, primarily because of the availability of the necessary tetraalkylsilanes, and the fact that only one alkyl group is transferred.[138] Unsymmetrical silanes have not been studied, except for intramolecular reactions leading to cylcopentanones.[139] Here the selectivity for cyclization is high, with no methyl ketones observed. Even *s*-alkyltrimethylsilanes cyclize in good yield (equation 28). However it is unlikely that this selectivity will apply to intermolecular acylations. Of greater potential is the use of cyclopropylsilanes, which acylate readily to form cyclopropyl ketones,[140] provided there are no further substituents on the three-membered ring. Acylations of 1-trimethylsilyl-2-methylcyclopropanes are both regio- and stereo-specific, the *trans* isomer giving the (*Z*)-β,γ-unsaturated ketone and the *cis*-cyclopropane the (*E*)-isomer (equation 29).[141]

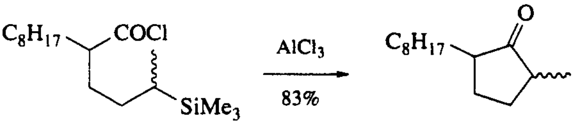

(28)

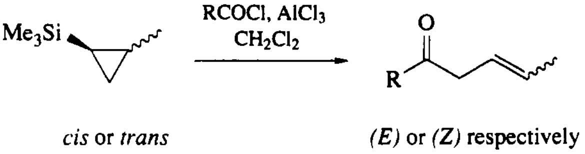

(29)

## 3.1.9 ALIPHATIC FORMYLATION

Direct formylation of alkenes has rarely proved a satisfactory route to unsaturated aldehydes. The classical Gatterman–Koch formylation with carbon monoxide, hydrogen chloride and aluminum chloride gives ketonic and acidic products, whilst formylation under Gatterman conditions using hydrogen cyanide in place of carbon monoxide generally leads to *N*-formylamino compounds by addition to the double bond.[142] Although outside the scope of reactions related to aliphatic Friedel–Crafts acylations, hydroformylation reactions of alkenes do provide well-established routes to (saturated) aldehydes.

More-controlled formylation can be achieved by the use of silylated substrates. The familiar use of the titanium tetrachloride catalyzed formylation of aromatic substrates by dichloromethyl methyl ether can be extended to the formylation of alkenylsilanes.[49,143] As with the aromatic case, the reaction proceeds by initial chloromethoxylation, followed by hydrolysis to the aldehyde. The formylation is also applicable to 1-silyl-1,3-dienes, leading to 2,4-dienals.[144] The anticipated regioselectivity is observed, with substitution of the silyl group to give the α,β-unsaturated aldehyde, but unlike the acylation of alkenylsilanes where substitution occurs with retention of geometry about the double bond, the (*E*)-configuration is observed in the product irrespective of the configuration of the starting alkene.[145] This is likely to be a result of isomerization of the allylic chloride intermediate in the presence of the Lewis acid. The formylating species shows lower steric requirements than acylating agents, since formylation has been observed of substrates which failed to acetylate (equation 30).[146]

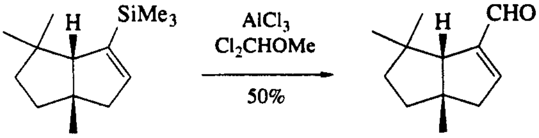

(30)

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# 3.2

# The Bimolecular Aromatic Friedel–Crafts Reaction

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## 3.2.1 INTRODUCTION

This chapter is concerned with intermolecular reactions that lead, either directly or indirectly, to the acylation of an aromatic system. A series of books is available[1] and Friedel–Crafts chemistry has also been updated in a single volume that covers the literature to mid-1972.[2] By comparison with the acylation of amino and hydroxy groups, the acylation of aromatic carbon requires, in the majority of cases, a considerable increase in the electrophilicity of the reagent. An electrophilic catalyst is thus normally required in addition to the aromatic substrate and the acylating reagent. Although acyl halides and carboxylic anhydrides are the most frequently used sources of the acyl group, we will consider a number of others. For many benzenoid derivatives a strongly electrophilic Lewis acid such as aluminum chloride is used, while for nucleophilic heterocycles such as furan, a milder reagent such as zinc chloride may well suffice. Many acylation reactions of very nucleophilic heterocycles such as pyrrole can be carried out in the absence of a catalyst. We will also discuss the use of a number of acyl cation equivalents but we will exclude certain formylation procedures that are the subjects of other chapters. There are a number of reasons why this method of carbon–carbon bond formation is widely investigated. The importance of the introduction of an acyl residue into an aromatic system relates to a number of important transformations that can be easily carried out, as well as to the inherent importance of aromatic ketones themselves. The conversion of acetophenone derivatives into amines *via* the Beckmann rearrangement[3] and into phenols *via* the Baeyer–Villiger rearrangement is well known.[4] An acyl group can also be converted, using a number of reductive methods, in dihydro-deoxo-disubstitution reactions, into the related hydrocarbon residue.[5]

The acylation of an aromatic system can therefore serve as a valuable alternative to direct alkylation even though extra steps are required. Acylating agents are generally more reactive than alkylating agents in Friedel–Crafts reactions. The lower energy of alkyl cation equivalents makes them more accessible and results in alkylation occurring in preference to acylation, for example when using lactones as Friedel–Crafts precursors. The alkyl-substituted aromatic compounds are more nucleophilic than their precursors and so over-alkylation is often a problem. In addition, where alkylation proceeds by way of a carbocation, rearrangement of the alkyl residue is not unusual. On the other hand, the aromatic ketones are less nucleophilic than their precursors. It is usually difficult to introduce more than one acyl group into an aromatic ring and over-acylation is not normally a major problem. Mesitylene is an exception; diacetylmesitylene is formed easily, presumably because the methyl groups prevent the first-formed ketone complex from being coplanar with the ring. In addition no rearrangement of the carbon chain of the acylating agent is observed. The only problem that is observed occurs when the product of the reaction is soluble in the reaction medium. Under those conditions deprotonation of the ketone–Lewis acid complex can lead to side chain acylation, and hence to the formation of β-diketones *via* an enol complex.

## 3.2.2 MECHANISMS

We will consider the mechanisms that may operate in Friedel–Crafts acylations; the mechanisms of other reaction types that are included in this chapter will be considered in the appropriate subsections along with their chemistry. One can, in principle, envisage two extreme mechanistic pathways for acylation reactions. The interaction of an acyl halide with a Lewis acid can give rise to two donor–acceptor complexes that can be in equilibrium with an acylium ion, as shown in equation (1). Which species is the acylating agent will depend on the structure of the acyl halide, the Lewis acid and the solvent. The interaction of the aromatic substrate with a donor–acceptor complex can lead to a product *via* a transition state that resembles that of an $S_N1$ reaction of an alkyl halide. Reaction involving an acylium ion may be compared with an $S_N1$ reaction involving a carbenium ion. It is possible that in between the two extremes reactions proceed that involve tight ion pairs. The effect of an electron-releasing substituent will normally lead, in a benzene derivative, to substitution *ortho* and/or *para* to the group. It is clear that the former transition state will be more sterically demanding than the latter transition state and so differing regioselectivities may be expected to arise from the two mechanistic extremes. A donor–acceptor complex will be expected to afford mainly, and in some cases exclusively, the *para* derivative in reactions of aromatic compounds that contain electron-releasing substituents. There are a small number of exceptional cases where mixtures of *meta* and *para* isomers are obtained. The acetylation of ethyl phenylacetate with acetyl chloride and aluminum chloride in carbon disulfide is one such case.[6]

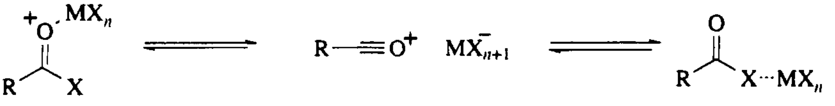

(1)

A considerable amount of research has been concerned with the nature of the electrophiles that are involved in Friedel–Crafts acylation reactions. We will summarize the main points. Acyl halides and carboxylic acid anhydrides have been known, for many years, to form stable complexes with a variety of acid catalysts. A well-defined product is formed between acetyl fluoride and boron trifluoride at low temperatures. Analytical and conductivity data characterized the material as acetylium tetrafluoroborate,[7] and this was further confirmed by IR measurements.[8] In the system acetyl chloride–aluminum chloride the acetylium ion can be differentiated from the donor–acceptor complex involving the carbonyl group by means of their IR carbonyl stetching frequencies.[9] A number of other acyl fluorides have been shown to form well-defined acylium salts by interaction with a number of metal fluorides. Acylium salts can also be prepared from acyl chlorides by means of metathetical reactions involving anhydrous salts such as silver hexafluoroantimonate. As well as characterization by means of IR spectroscopy, acylium salts have been studied in non-nucleophilic solvents by NMR spectroscopy. The $^{13}$C NMR data for the benzoylium ion[10] show why that ion is relatively stable. Considerable delocalization of the positive charge to the *ortho* and *para* positions and away from the *ipso* position, which has some ketene-like character, is indicated by the chemical shifts ($\delta_C$ = 87.7 (C-1), 141.3 (C-2), 132.9 (C-3), 149.9 (C-4), and 154.8 (C═O) p.p.m.).

Kinetic studies of acylation reactions are somewhat limited by the insolubility of the acyl halide–Lewis acid complexes in many of the solvent systems that are used. However, useful results have been obtained and, as far as we are concerned, relative rates of reactions are of greater importance than absolute values. In any case it is not possible to distinguish between the two mechanistic extremes on the basis of the observed kinetics.[11] Friedel–Crafts acylations are generally characterized by high substrate selectivity and frequently by high positional selectivity. Relative rate data show, as expected, that toluene is more reactive than benzene and that *m*-xylene is the most reactive of the dimethylbenzenes. Values, relative to benzene, for benzoylation catalyzed by aluminum chloride were: *t*-butylbenzene (72), toluene ($1.1 \times 10^2$), *p*-xylene ($1.4 \times 10^2$), *o*-xylene ($1.12 \times 10^3$), and *m*-xylene ($3.94 \times 10^3$). Competition data for the trifluoroacetylation of a number of heterocycles using trifluoroacetic anhydride at 75 °C gave the relative rates: thiophene (1.0), furan ($1.4 \times 10^2$), 2-methylfuran ($1.2 \times 10^5$) and pyrrole ($5.3 \times 10^7$).[12]

## 3.2.3 REAGENT SYSTEMS

### 3.2.3.1 Catalysts

It is normally assumed that anhydrous conditions are required in order to carry out Friedel–Crafts reactions. However, it is very difficult to obtain a Lewis acid in a completely anhydrous state. In fact, traces of moisture are found to accelerate the reactions that are catalyzed by some Lewis acids, such as aluminum chloride. Water functions as a cocatalyst. The effectiveness of a catalyst depends on its purity and it is not unusual for what is apparently the same catalyst to give different yields of products when the catalyst is purchased from different suppliers. It is impossible to establish a scale for the effectiveness of Lewis acids for all Friedel–Crafts acylation reactions. An indication of the range and relative reactivity of some Lewis acids is given by the relative efficiency of the following metal chlorides in catalyzing the reaction between acetyl chloride and toluene: $ZnCl_2 < BiCl_3 < TeCl_4 < TiCl_4 < SnCl_4 < TeCl_2 < FeCl_3 < SbCl_5 < AlCl_3$.[13] In spite of the foregoing reservations about establishing a generally applicable sequence, aluminum chloride and aluminum bromide are the most effective catalysts. We will exemplify the use of aluminum halides when we consider the acylating reagent in more detail.

We have mentioned the use of boron trifluoride as a reagent together with an acyl fluoride. Good regioselectivity has been reported for a number of reactions that give mixtures of products when using aluminum chloride as the catalyst. The reaction of isobutyryl fluoride with 2-methylnaphthalene gives an 83% yield of the product shown in equation (2).[14] Boron trichloride has also been used as a catalyst in the benzoylation of *m*-methoxyphenol in high yield *ortho* to the hydroxy group.[15] This type of catalyst can, however, give rise to problems associated with side chain acylation as exemplified by the reaction of mesitylene with acetic anhydride in the presence of boron trifluoride (equation 3).[16] Carboxylic acids have also been used in reactions of phenols[17] and aryl ethers[18] (equation 4) together with boron trifluoride. Dealkylation of an ether residue *ortho* to the introduced acyl group is commonly observed. Advantage was taken of this method in the synthesis of the naturally occurring phenol aurentiacin as shown in equation (5).[19]

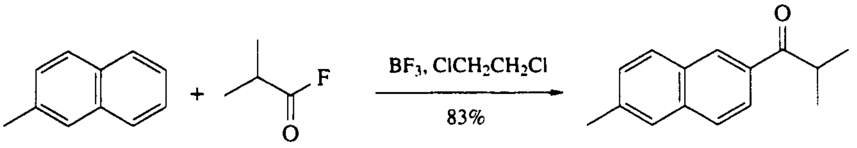

(2)

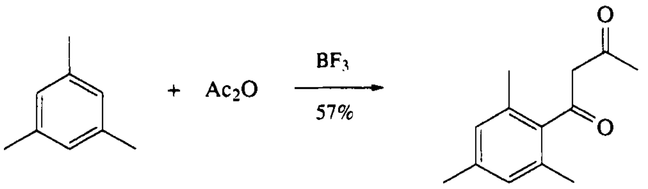

(3)

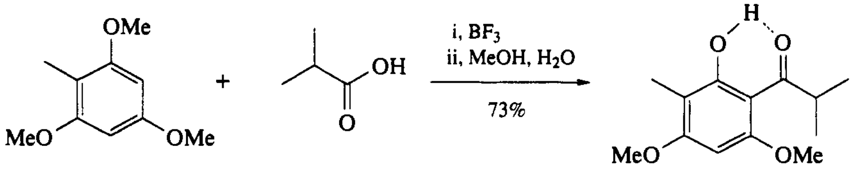
OMe
MeO
OMe
+
OH
O
i, BF$_3$
ii, MeOH, H$_2$O
73%
H
O
O
MeO
OMe

(4)

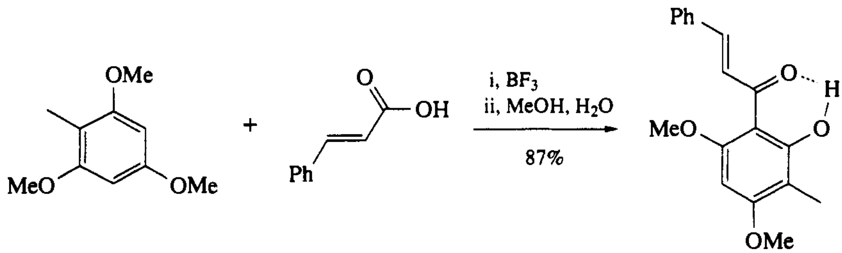
OMe
MeO
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+
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OH
Ph
i, BF$_3$
ii, MeOH, H$_2$O
87%
Ph
O
H
O
MeO
OMe

(5)

A number of protic acids have been used to catalyze acylation reactions. It is assumed that the reactions involve the generation of acylium ions. Polymeric reagents such as Nafion-H have been used; for example 2-fluorobenzoyl chloride and toluene give the benzophenone derivatives with an *ortho:para* ratio of 4:81.[20] A zeolite-catalyzed acylation (equation 6) has been reported to afford 4-dodecenoyltoluene in 96% yield but the yields are low with short chain carboxylic acids.[21] Early examples of the use of trifluoroacetic[22] and perchloric[23] acids reported good yields of products. Some more recent examples are shown in equations (7) to (9). Phosphoric[27] and polyphosphoric acids[28] have been used together with carboxylic acids (equation 10),[29] anhydrides and acylureas (equation 11).[30]

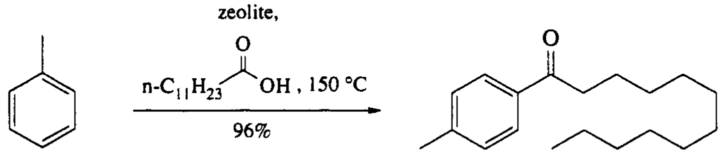
zeolite,
O
n-C$_{11}$H$_{23}$
OH, 150 °C
96%
O

(6)

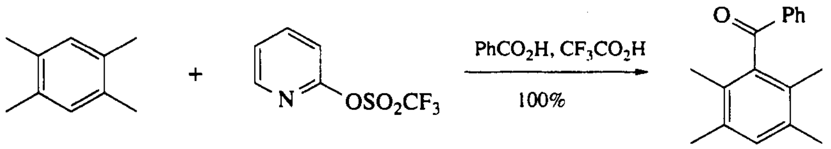
+
N
OSO$_2$CF$_3$
PhCO$_2$H, CF$_3$CO$_2$H
100%
O
Ph

(7)[24]

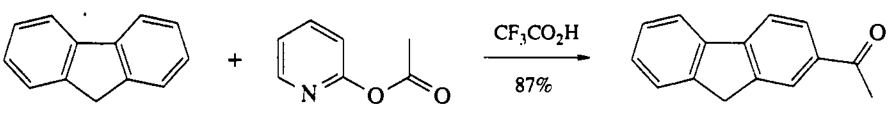
+
N
O
O
CF$_3$CO$_2$H
87%
O

(8)[25]

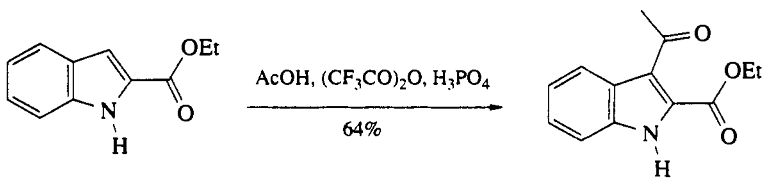
OEt
N
H
O
AcOH, (CF$_3$CO)$_2$O, H$_3$PO$_4$
64%
O
OEt
N
H
O

(9)[26]

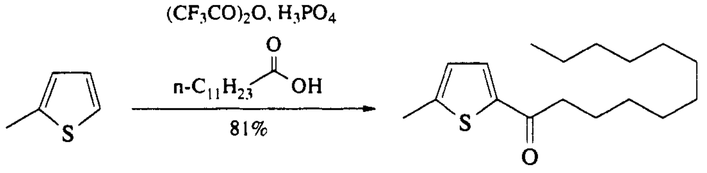
(CF$_3$CO)$_2$O, H$_3$PO$_4$
O
n-C$_{11}$H$_{23}$
OH
81%
S
S
O

(10)

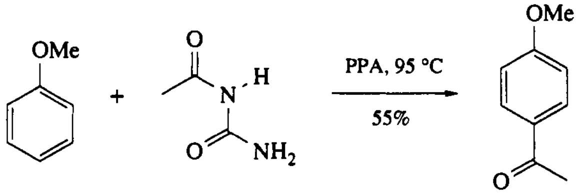
OMe
O
H
N
O
NH2
PPA, 95 °C
55%
OMe
O

(11)

Other metallic salts and metalloidal compounds have been recommended and in many cases excellent yields are indicated. Thiophene, when heated under reflux with acetic anhydride in the presence of magnesium perchlorate, was reported to give 2-acetylthiophene in 90% yield.[31] 1-Dimethylaminopyrrole is acylated in the 2-position as shown in equation (12) using a thiol ester and magnesium bromide.[32] Veratrole is acylated in the 4-position in high yield by *o*-chlorobenzoyl chloride[33] and 2-benzoylthiophene is obtained in a 90% yield[34] using iodine as the catalyst. Included among the transition metal species that have been used are the chromium(III) chloride–DMSO complex,[35] molybdenum pentachloride[36] and a zirconium catalyst.[37] One of the most interesting recent developments involves the use of selenol esters in reactions catalyzed by copper(I) triflate (equations 13 and 14).[38] 2-Substituted-1,3-benzoxathiolium salts react with electron-rich aromatic species to afford very high yields of ketones in a two-step process.[39] It is interesting to compare the acylations of 1-methylindole shown in equations (13) and (15). *O*-Acetyldiethyloxonium hexachloroantimonate acetylates anisole as shown in equation (16).[40]

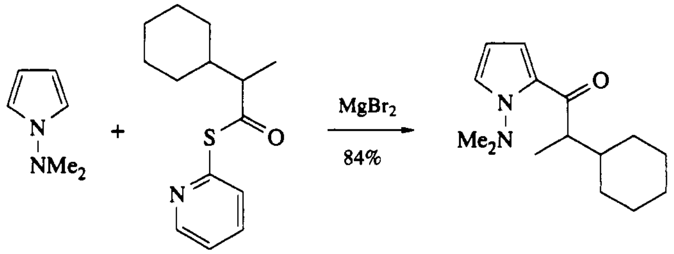
N
NMe2
S
O
N
MgBr2
84%
O
N
Me2N

(12)

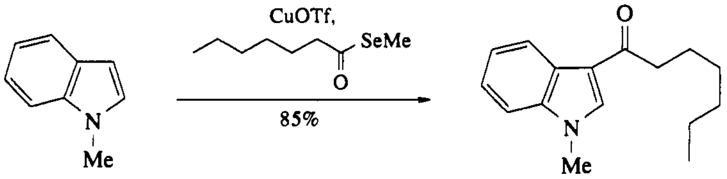
N
Me
CuOTf,
SeMe
O
85%
O
N
Me

(13)

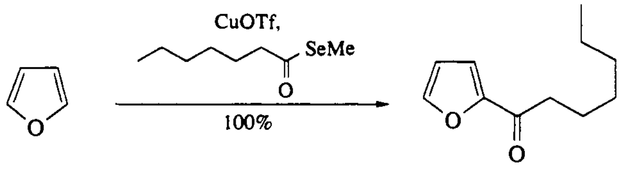
O
CuOTf,
SeMe
O
100%
O
O

(14)

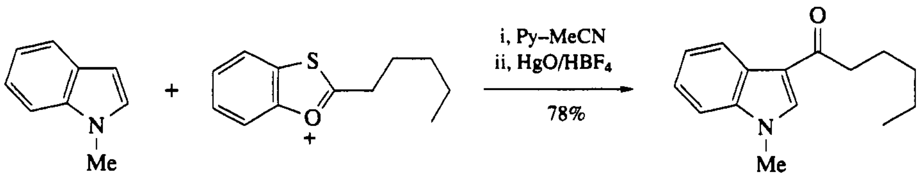
N
Me
S
O
+
i, Py–MeCN
ii, HgO/HBF4
78%
O
N
Me

(15)[39]

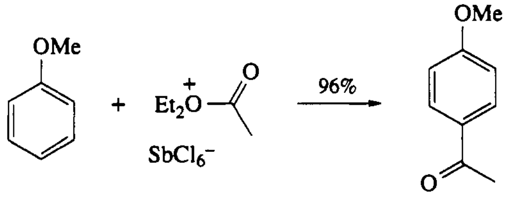
OMe
Et2O
+
O
SbCl6−
96%
OMe
O

(16)

### 3.2.3.2 Solvents

The choice of solvent for a Friedel–Crafts acylation reaction is very important. When the substance to be acylated is a cheap liquid, it is frequently convenient to carry out the reaction in an excess of the substrate. This is the case, for example, in the preparation of acetophenone or β-benzoylpropionic acid from benzene. Hydrocarbons are poor solvents for many Lewis acid catalysts and so only act as diluents in two-phase reactions. The possibility of Lewis acid catalyzed protodealkylation or rearrangement of alkyl-substituted benzenes may render them unsuitable for use both as substrate and solvent. The acetylation of *p*-xylene at high temperatures in the absence of another solvent leads to the formation of 2,4-dimethylacetophenone. It is also sensible not to leave reaction mixtures in solution for prolonged periods before the product is isolated. For example, if a reaction mixture containing 2,4-diisopropylacetophenone and aluminum chloride in carbon disulfide is kept at room temperature for several hours, rearrangement and disproportionation reactions take place. Carbon disulfide is one of the best solvents even though reaction rates may be lower than in some other solvents. Other solvents that are frequently used include dichloromethane and 1,2-dichloroethane, although for slow reactions they may themselves function as alkylating agents. Although aluminum chloride is essentially insoluble in these chlorinated hydrocarbons, they do dissolve many of the complexes that are formed between acyl halides and aluminum chloride.

Nitrobenzene and nitroalkanes are good solvents for Friedel–Crafts acylation reactions. As well as being good solvents they also form addition complexes with Lewis acids such as aluminum chloride. The formation of the complex appears to reduce disproportionation and rearrangement reactions and thus allow acylation to be achieved under mild conditions. The acetylation of toluene in nitrobenzene affords more 4-methylacetophenone than when the reaction is conducted in carbon disulfide. These results evidently reflect a lower steric demand in the reaction carried out in carbon disulfide. The reaction shown in equation (17) when carried out in nitrobenzene leads to the formation of the products (**1**) and (**2**) in good yield. However, when the solvent was changed to nitroethane, an improved yield (82%) was obtained and the ratio of (**1**):(**2**) changed from 44:1 to 61:1.[41]

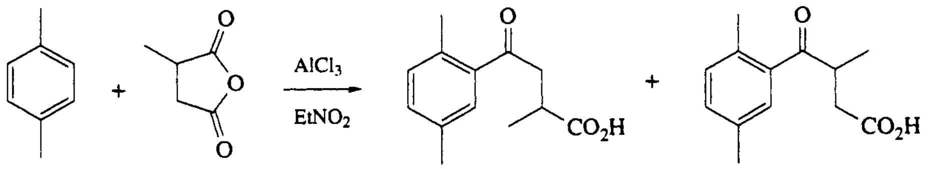

(17)

(**1**) (**2**)

### 3.2.3.3 The Sequence of Addition of the Reagents

In spite of the impression that may have been gained from the earlier part of this chapter, reactions involving the use of aluminum halides, and especially aluminum chloride, constitute the majority of Friedel–Crafts acylation reactions. The interaction of the three components, *i.e.* the acyl halide, the aromatic substrate and the aluminum halide, results in the formation of hydrogen halide and a complex of the aromatic ketone with aluminum halide from which the ketone is liberated after hydrolysis. There are a number of sequences in which the three components can be mixed.

The least satisfactory method involves the addition of an acyl halide to a mixture of the aluminum halide and the aromatic compound (the Bouveault procedure). The problem with this sequence relates to the presence of hydrogen halide, which may be present as a result of the reaction of moisture with the aluminum halide or which will be present in increasing amounts as the reaction proceeds. The hydrogen halide can result in isomerization or disproportionation of, for example, alkylbenzenes.

The most widely used sequence is that developed by Elbs. It is a modification of the method used by Friedel and Crafts in which the catalyst is added as the last reactant.

The prior formation of the reactive species, for example by mixing an acyl halide with aluminum halide, which is then allowed to react with the aromatic substrate, is known as the Perrier procedure. It is normally carried out in a solvent, such as carbon disulfide or dichloromethane, that allows the 1:1 complex to be separated from excess aluminum halide. The main advantage of this method is the solubility of the addition complex in the solvent, but it is frequently observed that the complex of the acylation product and catalyst is insoluble in carbon disulfide and may be separated from soluble by-products. The prior formation of acylium salts mentioned earlier[7–10,42] and their use in the preparation of aromatic ketones can be regarded as a modification of the Perrier procedure.

#### 3.2.3.4 Stoichiometry and the Catalyst

The alkylation of aromatic compounds using alkyl halides and a Lewis acid only requires a small amount of catalyst. Because Lewis acids form complexes with carbonyl compounds, the Lewis acids are effectively removed from the reagent system to the extent that product is formed. Although an equilibrium exists between the product complex and free Lewis acid, there is an apparent inhibition of formation of the acylating species. The net effect is that the amount of the ketone that is formed is normally proportional to the molar quantity of catalyst added. In reactions using acyl halides, completion occurs when slightly more than 1 mol of catalyst is used. When using a carboxylic anhydride, an excess over 2 mol of catalyst will usually be required because the other product, a carboxylic acid, will also complex with the Lewis acid.

### 3.2.4 ACYLATION REACTIONS

#### 3.2.4.1 Reactions Carried Out in the Absence of Catalysts

Very electron-rich aromatic systems interact with acid chlorides and anhydrides in the absence of a catalyst to afford good yields of ketones. Reactions of pyrrole[43a] and substituted pyrroles[43b] exemplify these reactions. The oxalylation shown in equation (18)[44] was part of the synthesis of a complex, highly functionalized antitumor agent. Use of the triisopropylsilyl group to direct reaction to the 3-position (equation 19) is noteworthy.[45]

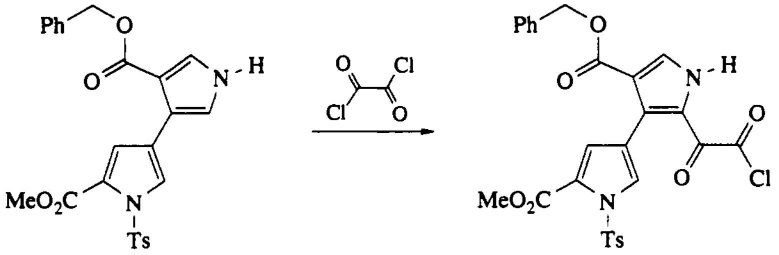

(18)

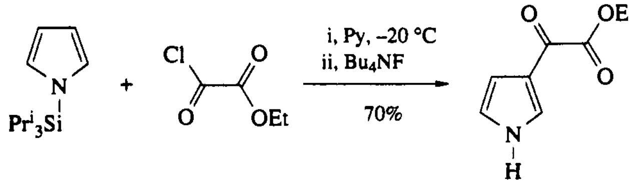

(19)

The use of heptafluorobutanoyl chloride[46] in a reaction with *N*,*N*-diethylaniline pointed the way towards the development of mixed anhydrides that have a very good leaving group. The formation of 2-acetylthiophene in 69% yield using acetylmethanesulfonic anhydride[47] and of 2-acetylfuran in 96% yield using acetyltoluene-*p*-sulfonic anhydride[48] exemplify this principle. The addition of 1% trifluoromethanesulfonic acid (triflic acid) to solutions of acyl chlorides in a number of benzene derivatives led to the formation of ketones in good yields.[49] For example, *p*-xylene and benzoyl chloride gave 2,5-dimethylbenzophenone in 82% yield (equation 20). Similar results have been obtained using nonafluorobutanesulfonic acid.[50] The mixed anhydrides formed between carboxylic acids and triflic acid have also been shown to be very powerful acylating agents (equation 21)[51] and the triflic acid can be recovered almost quantitatively as the barium salt. Kinetic studies of reactions of carboxylic acids in triflic acid suggest

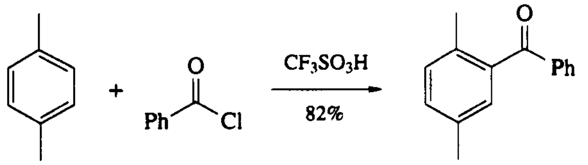

(20)

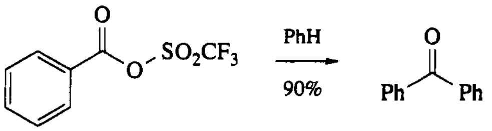

(21)

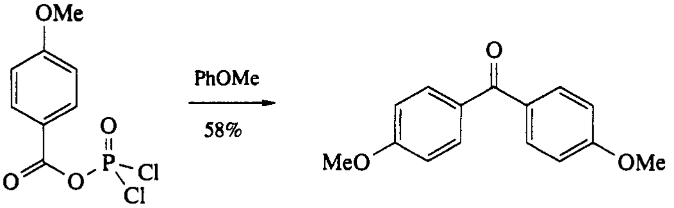

(22)

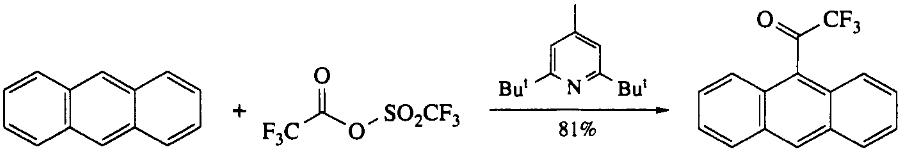

(23)

that protonated mixed anhydrides are the probable precursors to the electrophiles involved in the acylation reactions.[52] Aryl ketones may also be prepared from alkyl and aryl carboxylic dichlorophosphoric anhydrides in reactions with electron-rich compounds such as anisole (equation 22).[53] Trifluoroacetyl trifluoromethanesulfonate is capable of the uncatalyzed trifluoroacetylation of a variety of aromatic rings (equation 23).[54]

### 3.2.4.2 Reactions Using Lewis Acid Catalysts

#### *3.2.4.2.1 Reactions using acyl halides*

The use of an acyl chloride in the presence of aluminum chloride constitutes the most frequently used type of Friedel–Crafts ketone synthesis. Many examples from the earlier literature are reported in the reviews mentioned at the beginning of this chapter.[1,2] The reactivity of acyl halides in reactions of acyl halides with aluminum halides decreases in the order I > Br > Cl > F, but a different order was reported for reactions catalyzed by boron halides. In the latter case the order was acyl fluoride > acyl bromide > acyl chloride. We shall concentrate our attention on recently reported examples.

A very wide range of acyl chlorides interact with aluminum chloride to afford good to excellent yields with both carbocyclic and heterocyclic aromatic compounds. The use of aluminum chloride is implied in the examples quoted in this section. Acetophenone was formed in 97% yield in a reaction of benzene with acetyl chloride carried out at 15–20 °C in which air was passed through the reaction mixture to remove hydrogen chloride.[55] Propionyl chloride reacts with 2-bromonaphthalene and results in substitution at the 6-position[56] and veratrole affords 3,4-dimethoxyacetophenone.[57] Isobutyryl chloride[58] reacts with 4-bromoanisole at the 2-position and pivaloyl chloride reacts *para* to the methyl group with *o*-cresol methyl ether.[59] It is not unusual for decarbonylation to occur with the latter acyl chloride and *t*-butylation of the aromatic substrate is then a problem. Likewise protio-de-*t*-butylation does sometimes occur. For example, the benzoylation of 4-*t*-butylanisole results in the formation of 2-hydroxybenzophenone.[60] The presence of halogens in the alkyl residue of the acyl halide[61] may cause no significant problem and may prove useful as shown in equations (24) and (25). Other types of functionality can be tolerated in both the aromatic compound (for example tyrosine)[62] and in the acylating agent. The use of *N*-(trifluoroacetyl)-α-amino acid chlorides has been reported in the preparation of α-arylalkylamines,[63a] and in a synthesis of (*S*)-(+)-tylophorine the reaction of (*S*)-*N*-(trifluoroacetyl)prolyl chloride to yield the ketone shown in equation (26) is the key step.[63b] Protection of the amino function with the trifluoroacetyl group gives much better results than those obtained with other acyl and sulfonyl groups that have been investigated. Decarbonylation occurs rapidly at room temperature with a number of tertiary amino acid chlorides and *N*-sulfonylated acid chlorides in the presence of Lewis acids.

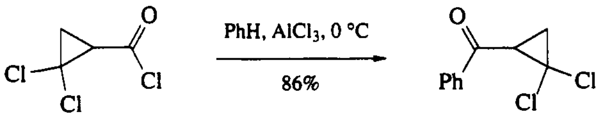

(24)[61c]

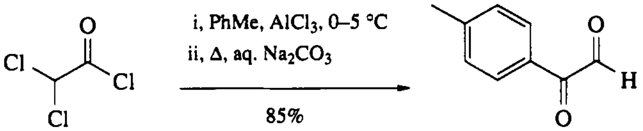

(25)[61d]

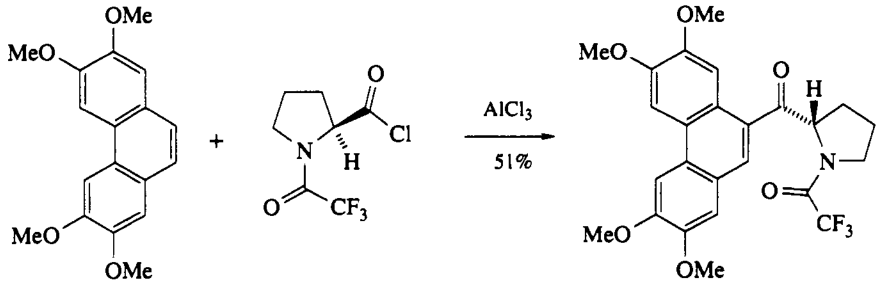

(26)

The acylation of aryl ethers and sulfides is widely used. The acylation of phenyl methyl sulfide[64] using 100 mol % of aluminum chloride gives the maximum yield and *para* selectivity.[64b] It has also been shown that acylation of a number of aryl alkyl ethers proceeds rapidly and in high yield with 100 mol % of catalyst but that reaction is arrested with a large excess of catalyst.[65] The reactions were studied using aluminum bromide because that catalyst allowed a more precise control of the stoichiometry than would be the case with aluminum chloride. The reactions using acetyl chloride in *o*-dichlorobenzene were almost quantitative using 100 mol % aluminum bromide, but the inhibiting effect of an excess of the catalyst was so great that the solvent then became the reactant. In a competition reaction an equimolar mixture of benzene and veratrole was allowed to react at room temperature with 200 mol % of acetyl chloride and 400 mol % of aluminum bromide in *o*-dichlorobenzene. After 1 h more than 95% of the benzene had been consumed and acetophenone was the only product detected by gas chromatography. Methylenedioxybenzene and benzene gave similar results. The ketal formed between catechol and 2,4-dimethylpentan-3-one is acylated particularly easily and does not suffer the inhibition effect. The inhibition is evidently due to coordination of the Lewis acid with the methyl ether and methylenedioxy functions. Acylation with some half-ester half-acid chlorides and some diacid chlorides proceeds satisfactorily. Ethyl oxalyl chloride gives a good yield of the expected product using phenetole (equation 27),[66] and adipoyl chloride gave a reasonable yield using catechol (equation 28).[67] It is not unusual to

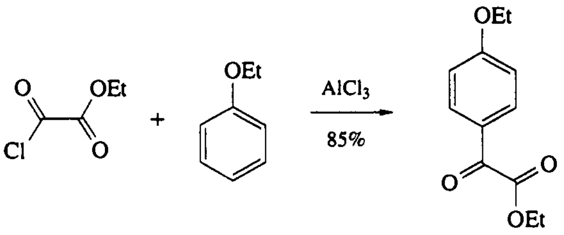

(27)

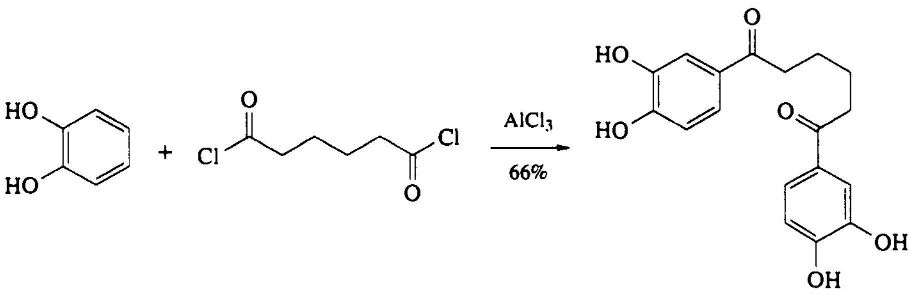

(28)

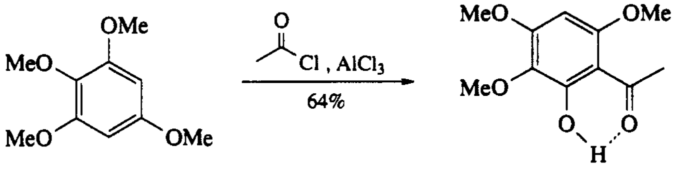

(29)

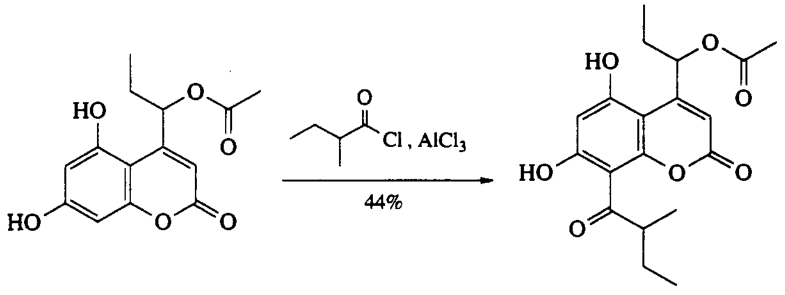

(30)

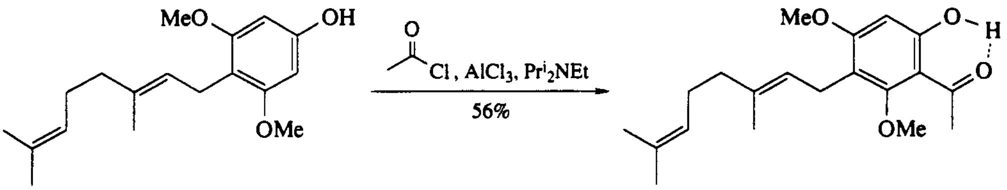

(31)

find that dealkylation of an ether function occurs when an *o*-acyl group is introduced. This effect is exemplified in equation (29).[68] Difficulties are sometimes experienced with highly functionalized compounds. The product shown in equation (30) was obtained in 44% yield,[69] and a 56% yield of the product shown in equation (31) was obtained after sonication.[70]

Problems have been observed when attempting to carry out reactions with either diacid chlorides or half-ester half-acid chlorides when the two carbonyl functions are separated by either two or three carbon atoms. Rearrangement reactions occur with those compounds and so Friedel–Crafts acylation reactions may yield mixtures of products.[71] Optically active methyl 3-methylglutarate was shown to racemize easily.[72] Suggested explanations of these effects include the involvement of alkyl diacyloxonium and acyloxy–alkoxycarbenium ions. $^{13}C$ NMR studies have shown that the half methyl ester–half acid chloride from phthalic acid forms the acyloxy–alkoxycarbenium ion very easily,[73] and that the related ions derived from succinic and glutaric acids can also be generated under stable ion conditions.[74]

The Friedel–Crafts acylation reactions of simple indoles and pyrroles leads to the formation of 3- and 2-substituted products, respectively. Ketones can be prepared from sodium salts of carboxylic acids in a 'one pot' process. Sodium pyridine-3-carboxylate reacts with phosphoryl chloride/DMF and then with aluminum chloride at low temperature in the presence of 2-isopropylindole to afford the 3-substituted indolyl ketone in 81% yield.[75] A particularly mild method for the introduction of a 3-acyl residue into *N*-methylindole involves electrophilic desilylation as shown in equation (32).[76] The *ipso* replacement of a silyl group is particularly useful for controlling the position of entry when using strong electrophiles. 1-Acetyl-4-trimethylsilylindole reacts with 3-chloropropanoyl chloride as shown in equation (33).[77] The replacement of the silyl residue is finely balanced *versus* attack at the 3-position. Deactivation of the heterocyclic ring is necessary if *ipso* replacement is required. It is also of interest to compare the reactivity of an acylating agent with that of a Mannich reagent (Volume 2, Chapter 4.2). The replacement of the silyl residue would not occur in a Mannich reaction. It is worth noting at this point that the replacement

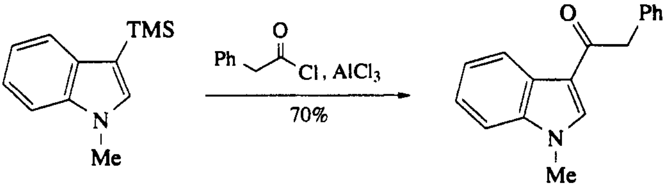

(32)

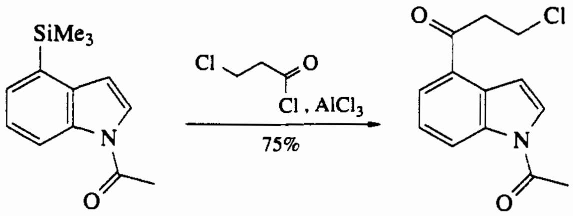

(33)

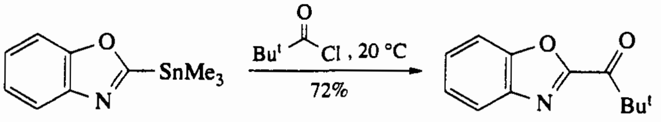

(34)

of a stannyl residue can be effected even more easily.[78] 2-Trimethylstannyl-pyridine and -quinoline and 1-trimethylstannylisoquinoline react with acyl chlorides in the absence of a catalyst,[79] and the benzoxazole shown in equation (34) reacts with pivaloyl chloride to give the expected ketone in 72% yield.[80]

Although reactions of indoles with electrophiles normally take place at the 3-position, the use of a strong electrophile and the presence of an electron-withdrawing group in the heterocyclic ring can lead to substitution at the 5-position. This effect is demonstrated as shown in equations (35) and (36).

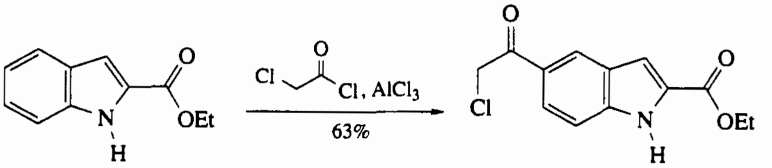

(35)[81]

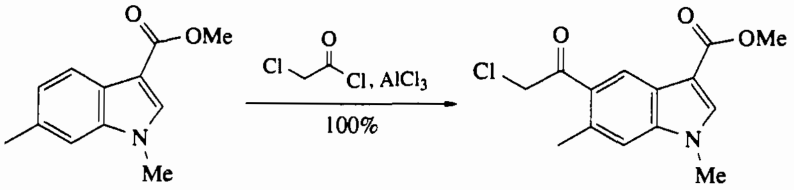

(36)[82]

The introduction of substituents at the 3-position in pyrrole is a desirable objective that has been addressed recently. The method that is mostly used depends on a steric effect being caused by *N*-substitution. The reaction of *N*-methylpyrrole with pivaloyl chloride and tin(IV) chloride rather surprisingly was reported to give 3-*N*-methylpyrryl *t*-butyl ketone in 33% yield.[83] 1-Benzenesulfonylpyrrole is deactivated towards electrophilic attack as well as being to some extent sterically hindered; eneamine-like reactivity may be anticipated. In a reaction with benzoyl chloride and aluminum chloride no 2-acylation was observed.[84] In the reaction of 1-TBDMS-pyrrole (equation 37)[85] with phenylacetyl chloride the effect is presumably exclusively steric in origin. In the case of heavily substituted pyrroles, ester functions (equation 38) do not reduce the reactivity enough to prevent reaction at the 3-position.[86] In the case of pyrroles that are substituted with an electron-withdrawing group at the 2-position, further substitution will be directed to the 4-position which, after removal of the directing group, then effectively becomes the 3-position, as shown in equation (39).[87]

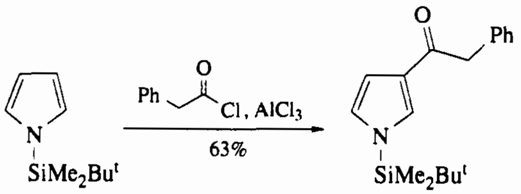

(37)

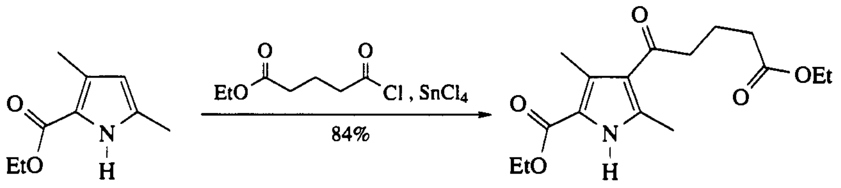

(38)

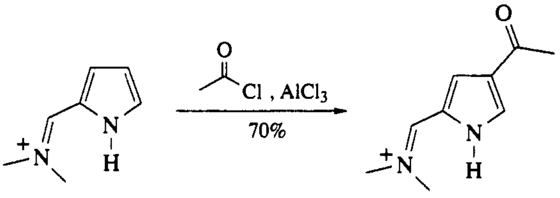

(39)

Other derivatives of carboxylic acids and some unusual catalyst systems have found favor. Diarylboryl hexachloroantimonates activate acyl chlorides, carboxylic anhydrides and acyl enolates.[88] A number of metal oxides have been successfully employed.[89] It is worth noting at this point that the chloroacetylium and bromoacetylium ions, which can be prepared in either Freon 113 or sulfur dioxide, are more stable than the acetylium ion and have been shown to give high yields of ketones at low temperatures.[90]

### *3.2.4.2.2 Reactions using other derivatives of carboxylic acids*

We have already considered the use of mixed anhydrides and so in this section we shall be concerned with homocarboxylic anhydrides. The use of anhydrides constitutes the most frequently reported method after the use of an acyl chloride and aluminum chloride. Anhydrides from monocarboxylic acids yield ketones, and cyclic anhydrides derived from dicarboxylic acids afford keto acids. Very nucleophilic aromatic compounds react with trifluoroacetic anhydride in the absence of a catalyst. The confirmation of aromatic character invariably involves establishing reactivity towards a range of electrophiles. Trifluoroacetic anhydride reacts with homoazulene in the presence of an excess of triethylamine to afford 1-trifluoroacetylhomoazulene in 91–95% yield.[91] The preparations of 3-aroylpropanoic acids from succinic anhydride and 4-aroylbutanoic acids from glutaric anhydride have been known for many years.[92] Maleic anhydride can be used in a similar way to prepare 3-aroylacrylic acids. We will now concentrate our attention on more recent examples.

Acetic anhydride and aluminum chloride in carbon disulfide gives a high yield of the *para*-acylated product with thioanisole,[93] and in dichloromethane the same reagents give an almost quantitative yield of 3-acetyl-1-benzenesulfonylindole.[94] Acylation of more nucleophilic heterocycles can be achieved using milder catalysts, such as zinc chloride. It has been known for some time that furan can be acylated very efficiently using acetic anhydride and zinc chloride. The Paal–Knorr furan synthesis (1,4-diketone, acetic anhydride and zinc chloride) can sometimes result in acylation as well as cyclization (equation 40).[95] Equations (41) and (42) further exemplify the acylation of furan derivatives that have been used in the synthesis of cytotoxic furanonaphthoquinones.

1-Acetylpyrazole has been used in high-boiling petrol together with aluminum chloride in the *C*-acetylation of phenol[98] and the use of oxazolones (equation 43) results in the formation of acylamino ketones.[99] Enol lactones have been used in the preparation of 1,4-diketones.[100]

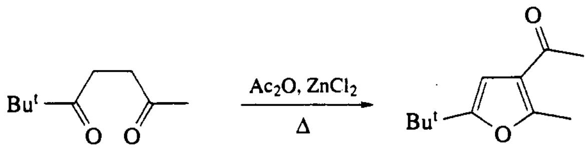

(40)

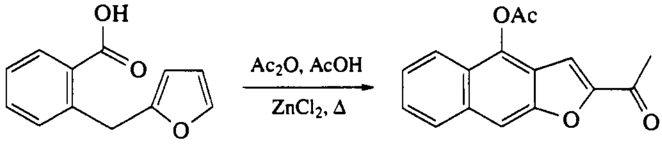

(41)[96]

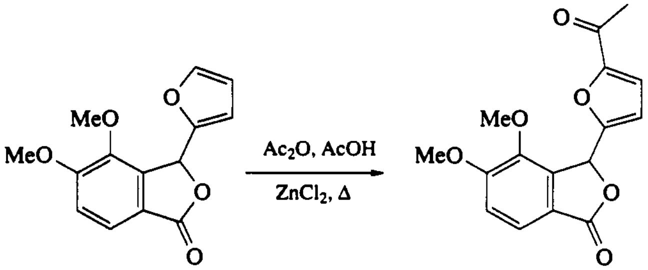

(42)[97]

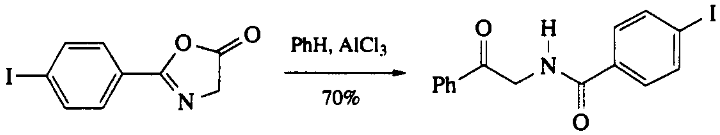

(43)[99]

### 3.2.4.2.3 *Rearrangement and transacylation reactions*

We have mentioned previously the possibility of rearrangement of the substrate; for example, the rearrangement of 2,4,6-trimethylacetophenone to afford the 2,4,5 and 3,4,5 isomers. There is also the possibility, especially with highly substituted compounds, that the acylation reaction may be reversible. The reaction of acetyldurene with aluminum chloride that results in the formation of diacetyldurene and durene was the first reported example.[101] Protiodeacylation–reacylation is evidently involved. A number of hindered ketones interact with a variety of Lewis acids in transacylation reactions. Acetyldurene and mesitylene undergo transacylation in the presence of 2 mol equiv. of aluminum chloride[102] and 2,3,5,6-tetramethylacetophenone interacts with aluminum chloride and anisole to give 4-methoxyacetophenone and durene.[103] Examples are also known in which heterocyclic ketones rearrange. For example, 2-acetyl-1-methylpyrrole gives the 3-isomer in 80% yield on treatment with trifluoroacetic acid, and 2-(4′-chlorobenzoyl)-1,3,5-trimethylpyrrole rearranges slowly in trifluoroacetic acid to 3-(4′-chlorobenzoyl)-1,2,4-trimethylpyrrole.[104] Protiodeacetylation has been studied using Nafion-H but no acetyl transfer was observed.[105] The method may prove to be useful as a method of temporarily protecting a specific position in an aromatic compound that has a number of electron-releasing substituents. The kinetics of acetyl exchange in acetylmesitylene and deuterium labeling has shown that *ipso* acetyl exchange is important.[106]

## 3.2.5 FRIES REACTIONS

Acid-catalyzed reactions of the phenol esters resulting in the formation of phenolic ketones are known as Fries rearrangements. Aluminum chloride was the first catalyst used but other Lewis acids are also effective. Examples from the recent literature are shown in equations (44) to (48). A nitrogen analog, that is the rearrangement of an acyl derivative of an arylamine, is shown in equation (49). Photo–Fries rearrangement reactions have also been studied in detail and are exemplified in equations (50) to (55).

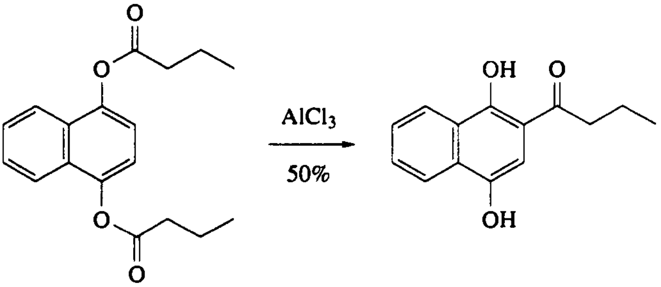

(44)[107]

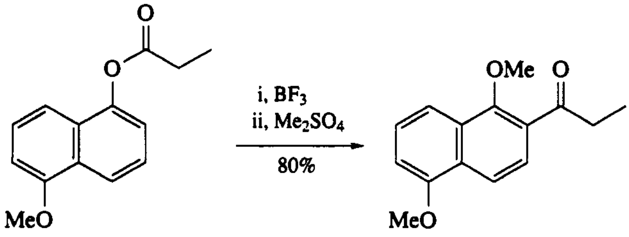

O
O
MeO
i, BF$_3$
ii, Me$_2$SO$_4$
80%
OMe
O
MeO

(45)[108]

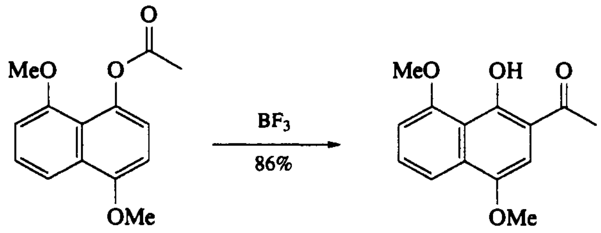

O
MeO
O
OMe
BF$_3$
86%
MeO
OH
O
OMe

(46)[109]

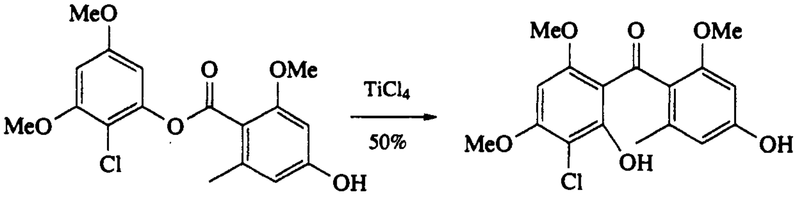

MeO
MeO
Cl
O
O
OMe
OH
TiCl$_4$
50%
MeO
O
OMe
MeO
Cl
OH
OH

(47)[110]

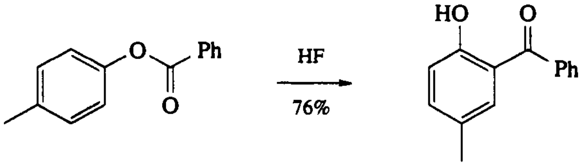

O
Ph
O
HF
76%
HO
O
Ph

(48)[111]

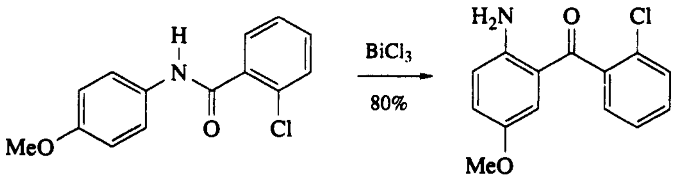

H
N
MeO
O
Cl
BiCl$_3$
80%
H$_2$N
O
Cl
MeO

(49)[112]

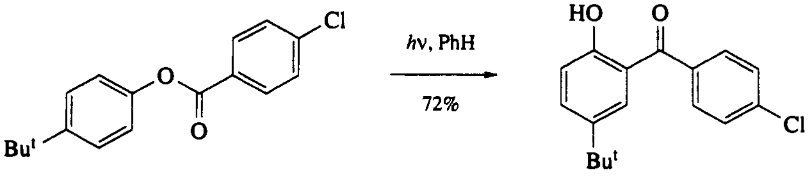

Cl
O
O
Bu$^t$
hν, PhH
72%
HO
O
Cl
Bu$^t$

(50)[113]

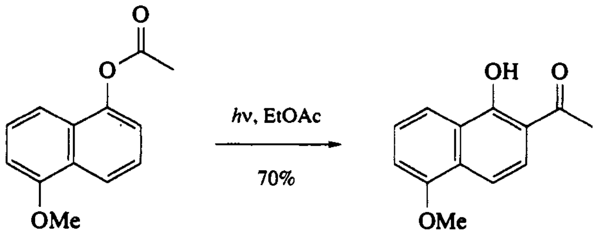

O
O
OMe
hν, EtOAc
70%
OH
O
OMe

(51)[114]

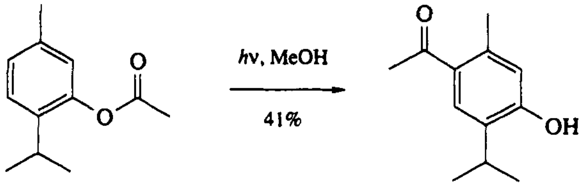
O
O
hν, MeOH
41%
O
OH

(52)[115]

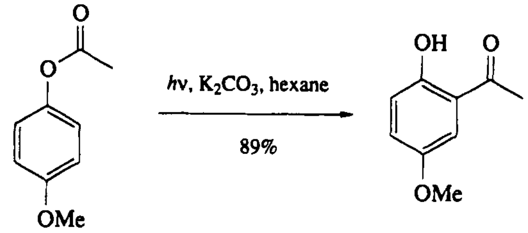
O
O
OMe
hν, K₂CO₃, hexane
89%
OH O
OMe

(53)[116]

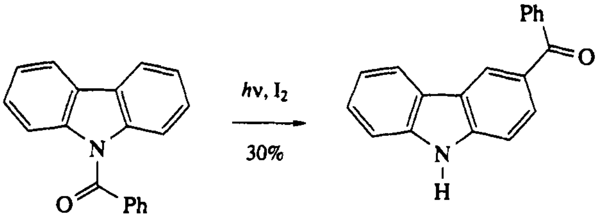
N
O
Ph
hν, I₂
30%
Ph
O
N
H

(54)[117]

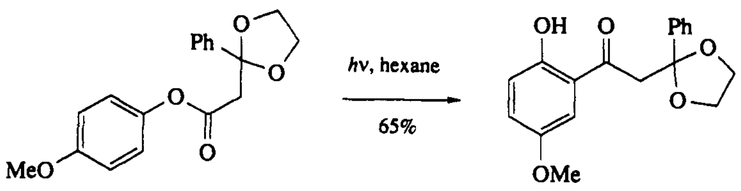
Ph
O
O
O
O
MeO
hν, hexane
65%
OH O Ph
O
O
OMe

(55)[118]

## 3.2.6 REACTIONS USING NITRILES — THE HOUBEN-HOESCH SYNTHESIS

The acylation of aromatic compounds can be achieved by a modification of the Gattermann reaction in which an alkyl or an aryl cyanide replaces hydrogen cyanide.[119] Although zinc chloride was originally the most frequently used catalyst, boron trichloride has often been used in recent studies. The initially formed ketiminium salt is hydrolyzed to give the ketone. In reactions of benzenoid derivatives that lack strong electron-releasing substituents the nitrile must contain an electron-attracting group that increases the electrophilicity of the reactive species. The catalyst is presumed to coordinate with the nitrile function to generate the electrophile. Benzene, for example, reacts with dichloroacetonitrile and aluminum chloride to afford ω,ω-dichloroacetophenone. An interesting intramolecular Houben–Hoesch reaction

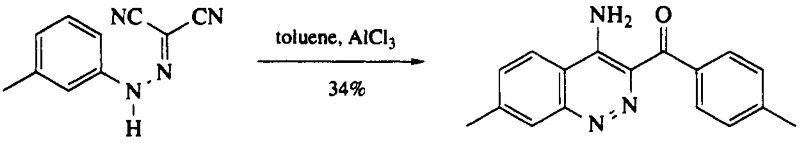
NC
CN
N
N
H
toluene, AlCl₃
34%
NH₂ O
N
N

(56)

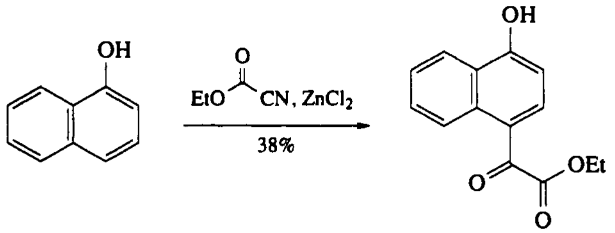
OH
O
EtO CN, ZnCl₂
38%
OH
O
OEt
O

(57)[121]

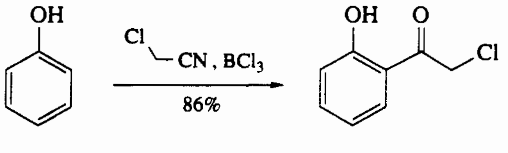

(58)[122]

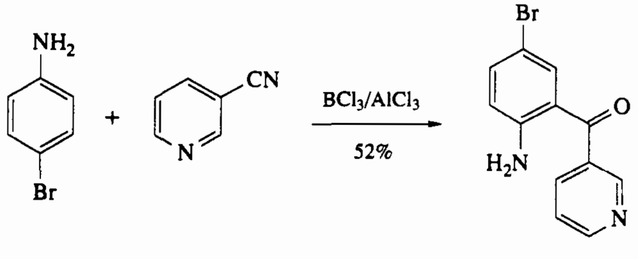

(59)[123]

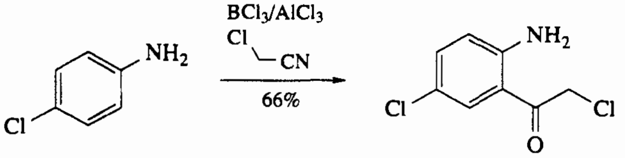

(60)

followed by an intermolecular version is shown in equation (56).[120] The method works well with phenols and arylamines as shown in equations (57) to (59), and has been developed into a new indole synthesis by modification of the type of product shown in equation (60).[124]

The possibility of using *N*-alkylnitrilium salts as acyl cation equivalents has been investigated by allowing nitriles to react with methyl triflate and a nucleophilic aromatic derivative such as 1,3-dimethoxybenzene.[125] *N*-Methylnitrilium salts have also been made by warming nitriles with trimethyloxonium fluoroborate. Subsequent reactions with pyrroles and indoles gave the expected iminium salts in excellent yields, as shown in equation (61).[126]

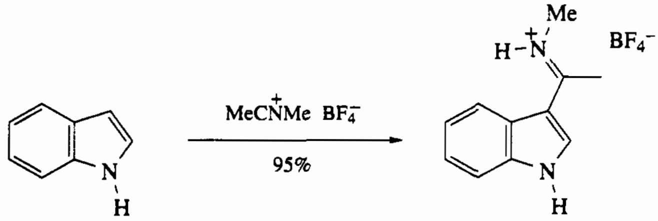

(61)

## 3.2.7 VILSMEIER AND RELATED KETONE SYNTHESES

The relationship between the formylation reactions carried out with formamide derivatives and the formation of ketones when using amides of other carboxylic acids has been pointed out.[127] The method has not been as widely exploited as one might have expected. *N*-Methylacetamide and *N*,*N*-dimethylacetamide both give substituted acetophenones when they are allowed to interact with phosphoryl chloride in the presence of nucleophilic benzene derivatives. The initial product has to be hydrolyzed. Similarly, benzamide derivatives give substituted benzophenones as exemplified in equation (62).[128]

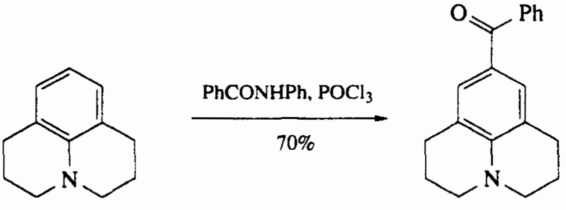

(62)

1,1-Dihaloalkylamines are dehalogenated by Lewis acids and react in a manner that is reminiscent of the Vilsmeier reaction. We show an example in equation (63).[129] The Lewis acid catalyzed dihaloalkylation reactions of, for example, phenyltrichloromethane can be regarded as a further extension.[130]

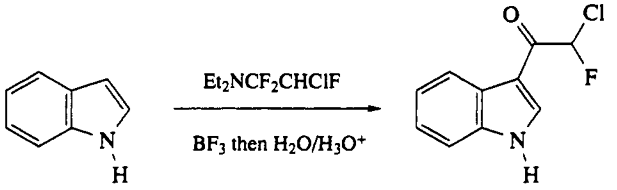

(63)

## 3.2.8 PALLADIUM-MEDIATED KETONE SYNTHESES

A number of *ortho*-palladated *N,N*-dialkylbenzylamines have been shown to react with acetyl or benzoyl chloride to form *o*-dialkylaminomethylaryl ketones.[131] The yields reported were in the range 60–90%. The example shown in equation (64) is representative. Other examples have extended the scope of the reaction.[132]

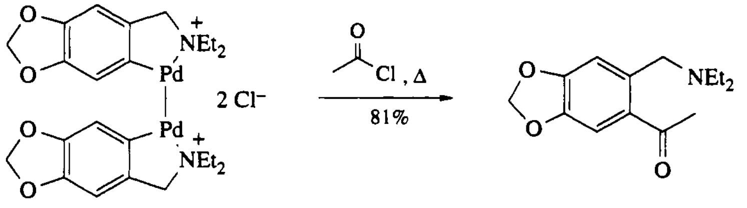

(64)

Acid chlorides couple with arylstannanes to form ketones in HMPA solution in the presence of chlorobis(triphenylphosphinebenzyl)palladium.[133] The same methodology has been used as part of a very efficient synthesis of manoalide and its *seco* derivative.[134] The coupling of aroyl chlorides with benzylzinc bromides also produces arylbenzyl ketones under palladium catalysis.[135] The benzylzinc bromides are formed '*in situ*'.

## 3.2.9 GATTERMANN AND RELATED FORMYLATION REACTIONS

We include in this section formylation reactions involving carbon monoxide, hydrogen cyanide, formyl fluoride and dichloromethyl alkyl ethers.[119] The Vilsmeier and Reimer–Tiemann formylation reactions are the subjects of other chapters (Volume 2, Chapters 3.4 and 3.5).

Formylation of benzene and simple alkylbenzenes can be achieved in good yields using carbon monoxide, hydrogen chloride and aluminum chloride at high pressures ($1–2.5 \times 10^7$ Pa). The reactions can be carried out at atmospheric pressure in the presence of copper(I) chloride, which apparently provides a high local concentration of carbon monoxide by coordination. This is known as the Gattermann–Koch reaction. The reaction functions as if formyl chloride ionizes to give the formylium ion and this is the presumed electrophile. However, the high yields of 4-formylalkylbenzenes suggests that a bulkier electrophile is involved. The reagent mixture is conveniently generated by the action of chlorosulfuric acid on formic acid. Formyl chloride is known to be very unstable; it may be generated from *N*-formylimidazole by reaction with hydrogen chloride in dichloromethane at –65 °C.

Benzene and toluene afford benzaldehyde and *p*-tolualdehyde in 90% and 85% yield respectively using the atmospheric pressure methods, and biphenyl has been converted into 4-formylbiphenyl in yields as high as 73%. With some alkylbenzenes there is, however, a tendency for dealkylation or transalkylation reactions to occur during the course of the reactions. Thus *p*-xylene gives 2,4-dimethylbenzaldehyde and triisopropylbenzene gives only diisopropylbenzaldehydes. Naphthalene appears not to give a naphthaldehyde.

A useful modification of this reaction involves the use of formyl fluoride, which is prepared by the reaction of the mixed anhydride of formic and acetic acids with anhydrous hydrogen fluoride. The formyl fluoride is continuously removed (b.p. –29 °C) as it is formed. Formyl fluoride and boron trifluoride do react with naphthalene to give 1-naphthaldehyde in 73% yield (equation 65).[136]

Formylation using zinc(II) cyanide and hydrogen chloride is known as the Gattermann reaction. Whereas the Gattermann–Koch method fails with phenols and aryl ethers, this method does give good

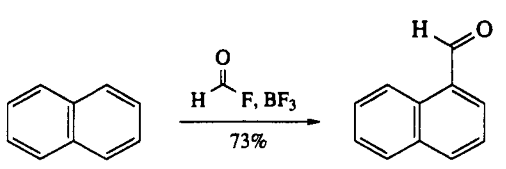

(65)

yields. The original method used hydrogen cyanide, hydrogen chloride and a Lewis acid such as zinc(II) chloride. The reaction shown in equation (66) is typical. The mechanism of the Gattermann reaction is obscure but aldiminium salts are the initial products and are then hydrolyzed to give the aldehydes. The electrophile may be a formimidium complex with the Lewis acid catalyst.

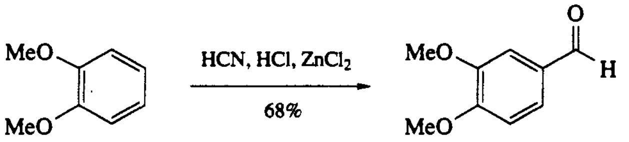

(66)

Arenes such as benzene, biphenyl and naphthalene are formylated using dichloromethyl alkyl ethers in the presence of a Lewis acid. The dichloromethyl alkyl ethers are easily prepared by the reaction of phosphorus pentachloride with alkyl formates. The most frequently used Lewis acids are titanium(IV) chloride and tin(IV) chloride. It is presumed that the electrophiles involved are alkoxychlorocarbenium ions.

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# 3.3

# The Intramolecular Aromatic Friedel–Crafts Reaction

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## 3.3.1 INTRODUCTION

Most of the general features of the intermolecular Friedel–Crafts acylations that are the subject of Volume 2, Chapter 3.2 also apply to the intramolecular versions. The present chapter should be regarded as an extension to the earlier one. The intramolecular Friedel–Crafts reaction has been reviewed previously,[1] including reactions specifically involving the use of polyphosphoric acid.[1c] We will concentrate our attention on more recent examples in order to exemplify the general principles that were also described in those reviews. There is no reason to suppose that the mechanistic considerations that we considered in the earlier chapter do not also apply in the present case. The thermodynamic problems associated with intermolecular reactions result in some important changes to those general features when we consider the intramolecular versions. The enthalpy effect relates to any ring or steric strain that may be present in the transition state leading to cyclization and the entropy effect relates to the ease or difficulty of making the two ends of the reacting system meet. As is the case with the majority of nonradical cyclization reactions, six-membered rings are formed most easily, followed by five- and seven-membered systems. Medium-sized rings are not easily obtained[2] and large-sized rings are only obtained in reasonable yields using high dilution techniques. Thus the conversion of 6-phenylhexanoic acid into the acid chloride and cyclization using aluminum chloride in dichloromethane gave the benzocyclooctenone in only 38% yield (equation 1).[2b] Other reactions leading to the formation of, for example, an eight-membered heterocyclic ring (a benzazocinone),[2c] have also been reported using a procedure[2d] that involves the use of 3 equiv. of aluminum chloride. A reaction of 16-phenylhexadecanoyl chloride with aluminum bromide gave the 20-membered ring product shown in equation (2) in 70% yield using a high dilution procedure.[3] In analogous reactions leading to the formation of 18-, 15- and 13-membered rings the products were obtained in 57%, 30% and 5% yields respectively. Rather surprisingly the cyclization of *o*-β-phenethylphenylacetic acid using polyphosphoric acid gave 2,3,6,7-dibenzocyclooctanone in 93% yield.[4] Presumably this results from the presence of the four $sp^3$ carbon atoms, which impart significant rigidity to the molecule and hence increase the chance that the two ends of the reacting system will meet. We will classify the remaining parts of this chapter according to the size of ring produced.

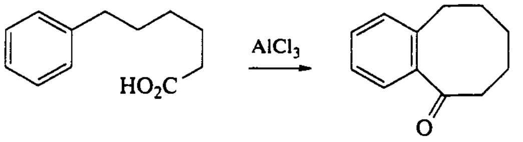

(1)

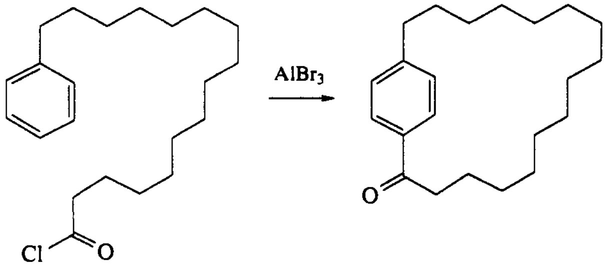

(2)

The most striking difference, by comparison with bimolecular Friedel–Crafts acylation reactions, is that the presence of an acyl group does not necessarily completely inactivate the substrate. Additionally, milder catalysts than were required in the intermolecular reactions may well be more appropriate. The generation of an acylium ion from a carboxylic acid, if it is to be observed at all, normally requires a very strong protic acid. In many intramolecular Friedel–Crafts reactions polyphosphoric or sulfuric acid can be used. The known involvement of mixed anhydrides in intermolecular acylation reactions suggests that a number of the well-known procedures probably also involve the intermediacy of mixed anhydrides. The use of, for example, mixtures of zinc chloride, acetic anhydride and acetic acid represents one such system. Another system that has been investigated involves the use of trifluoroacetic anhydride.[5] The mixed anhydrides that are effective in intermolecular Friedel–Crafts acylation reactions suggest that anhydrides involving other strong acids, such as trifluoromethanesulfonic acid and dichlorophosphoric acid, may well provide additional methodology. It is useful to consider the preparation of the starting materials that are required for intramolecular Friedel–Crafts acylation reactions. Intermolecular acylation using a cyclic anhydride will afford a product that can be cyclized, sometimes after reduction of the ketone function. We will observe, however, that in the case of products obtained from phthalic anhydride and its derivatives, the direct conversion into anthraquinones can be achieved. As was seen in Volume 2, Chapter 3.2, there may be examples when products are obtained that indicate that rearrangement of a reactant or a product has occurred. Examples which are particularly important involve the use of acid chlorides derived from dicarboxylic acids. Thus, phthaloyl chloride reacts with aluminum chloride to afford *pseudo*-phthaloyl chloride and so does not afford a derivative of benzophenone on reaction with benzene. The use of a combination of alkylation followed by intramolecular acylation is a particularly useful strategy that can be effected using lactones as the initial coreactant. The well-known Haworth method for the synthesis of polycyclic hydrocarbons involves succinoylation, reduction of the ketone function and an intramolecular acylation followed by aromatization. We will return to this synthesis in the concluding section. Attention was drawn in the earlier reviews to the variation in yields obtained and their dependence on the purity of the starting materials and the control of the amount of water in the reaction. It is worth reminding ourselves of these factors.

## 3.3.2 ELECTRON DENSITY CONSIDERATIONS

Electron-releasing substituents have their normal effects on intramolecular acylation reactions. Where cyclization could occur to afford a mixture of products, the one that is formed involves reaction with the more electron-rich ring. The indan-1-one shown in equation (3) was formed in 75% yield, and was the only ketone detected. The strongly electron-releasing methoxy group normally directs substitution to the *para* position as indicated in equation (4). There are, however, examples where coordination of a Lewis acid with methoxy groups results in deactivation of an aryl residue towards intramolecular Friedel–Crafts acylation reactions as was mentioned in Volume 2, Chapter 3.2. Except when using polyphosphoric acid, there is no firm evidence that intramolecular acylation reactions can be reversible and so the cyclization reactions of 2-naphthyl-3′-propanoic and -4′-butanoic acids, as illustrated in equation (5), lead to angularly substituted products by way of the anticipated lower energy transition states. We will return to the question of reversibility in the concluding section.

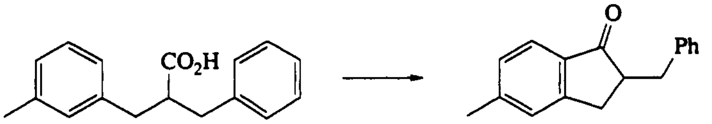

(3)

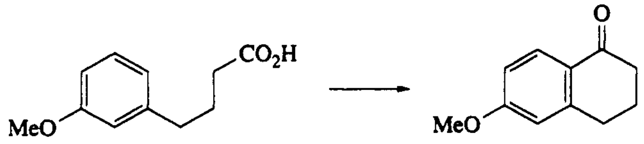

(4)

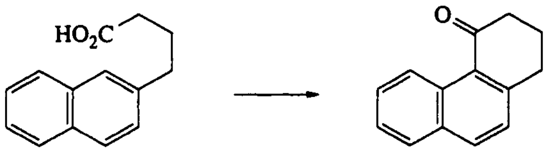

(5)

The presence of strongly electron-withdrawing substituents, such as the nitro group, inhibits cyclization when positioned *ortho* or *para*, but, remarkably, the presence of a carbonyl group has less influence and double cyclizations of dicarboxylic acids are not uncommon, as exemplified in equation (6).

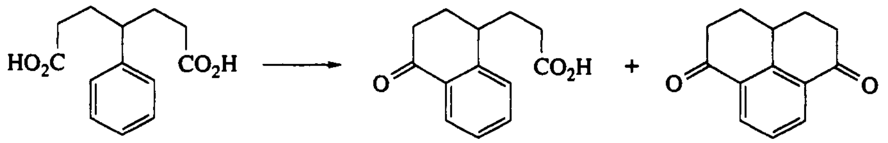

(6)

### 3.3.3 THE SIZE OF THE RING

Qualitative indications concerning the ease of formation of various ring sizes have been indicated in the Introduction. Early studies using substrates that could give mixtures of products with various ring sizes showed that six-membered ring formation is always preferred over the formation of five- and seven-membered rings (equations 7–9). The examples shown in equations (10) and (11) indicate that indan-1-ones are formed more easily than benzosuberones.

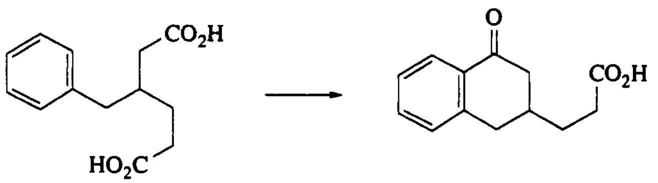

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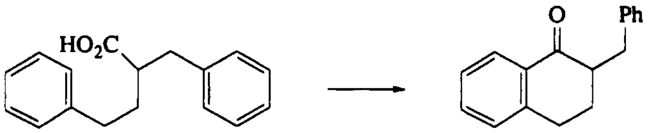

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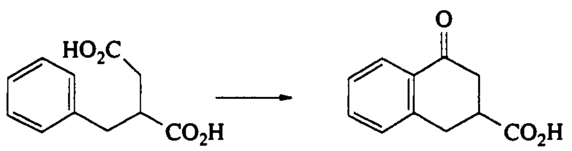

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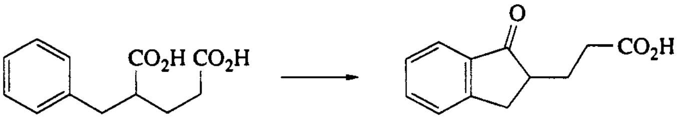

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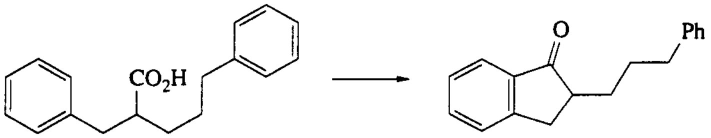

(11)

### 3.3.3.1 Reactions Leading to the Formation of Five-membered Rings

A wide variety of cyclopentanone derivatives have been reported and we will restrict ourselves to a general overview. One of the more important earlier papers[6] reported the cyclization of β-phenylpropanoic acid derivatives that contain electron-withdrawing substituents, using a mixture of aluminum chloride and sodium chloride at relatively high temperatures. The catalyst, which may be regarded as sodium tetrachloroaluminate, is more potent than aluminum chloride alone. In the example shown in equation (12), 4-carboxy-β-phenylpropanoic acid was heated at 180 °C with sodium chloride–aluminum chloride and gave indan-1-one-6-carboxylic acid. A detailed study[7] of a number of procedures for the formation of indanones from β-phenylpropanoyl chlorides concluded that the best method involved the portionwise addition of the acid chloride and aluminum chloride to a large volume of dichloromethane. The amount of aluminum chloride was specified precisely. Other procedures, for example using benzene as the solvent, resulted in attack on the solvent. Intermolecular acylation, including the formation of a cyclic tetramer, was also observed. It was concluded that coordination of excess aluminum chloride with the methoxy function deactivates the ring to intramolecular reaction. This effect is also mentioned in Volume 2, Chapter 3.2. Even when using the optimized conditions, 2-methoxy-β-phenylpropanoyl chloride only gave polymeric material. On the other hand, 4-methoxy-β-phenylpropanoyl chloride gave 6-methoxyindan-1-one in 77.5% yield.[7b] The product shown in equation (13) was obtained in 94% yield.[7a] Cyclization reactions of *N*-methoxycarbonyl-protected phenylalanine derivatives have been studied (an example is shown in equation 14), and enantiomeric excesses better than 96% can be achieved.[8] The retention of chirality was found to be dependent on the use of the *N*-methoxycarbonyl protecting group. Attempts to use *N*-benzyloxycarbonyl protection were unsuccessful, presumably due to the ease of formation of a benzyl cation under the reaction conditions. The synthesis of α-amino ketones *via* azlactones works well for the formation of five-, six- or seven-membered rings. However, their known rapid racemization due to the high acidity of the hydrogen at C-5 invalidates their use in the synthesis of enantiomerically pure α-amino ketones. Mention was made in the Introduction of the use of an alkylation–acylation sequence for building rings. In an interesting variation to the use of lactones, ethyl cyclopropanecarboxylate has

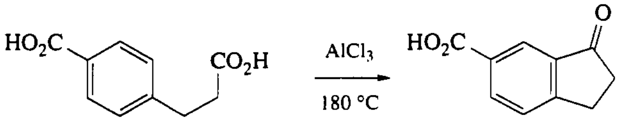

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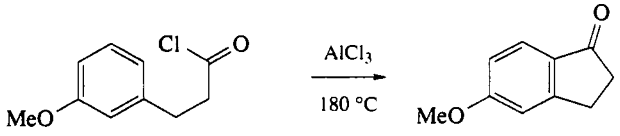

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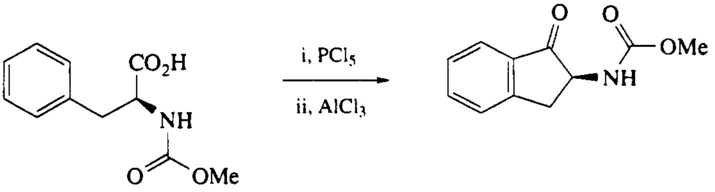

(14)

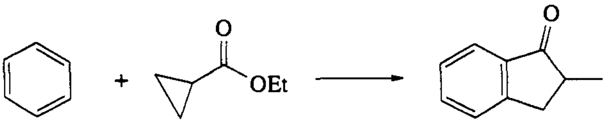

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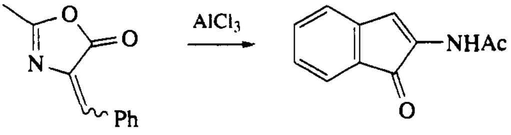

(16)

been shown (equation 15) to give 2-methylindan-1-one in 93% yield.[9] The reaction is assumed to proceed in the normal manner, that is that alkylation precedes acylation. In support of this suggested mechanism, toluene reacts to afford 2,6-dimethylindan-1-one in 67% yield.

The cyclization of what are effectively *cis*-cinnamic acid derivatives to yield indenones can be carried out using azlactones, which are themselves readily available from arylcarbaldehydes and an *N*-acylglycine. The product obtained from *N*-acetylglycine and benzaldehyde gave 2-acetylaminoinden-1-one (equation 16) in 73% yield.[10] The preparation of fluorenones and their benzo analogs by the cyclization of biaryl-2-carboxylic acid derivatives has been studied over a long period of time. Fluorenone-4-carboxylic acid was obtained in quantitative yield when diphenic anhydride was heated with tin(IV) chloride for 7 h at 130 °C.[11] Sulfuric acid has also been used.[12] In a more recent study[13] the cyclizations of biphenyl-2-carboxylic acid using polyphosphoric acid and sodium tetrachloroaluminate have been compared. In the case of the latter reagent, fused sodium tetrachloroaluminate was used both as reagent and solvent and a quantitative yield of fluorenone was obtained when the reagents were heated together for 20 min. The cyclization of 2,2′-binaphthyl-3,3′-dicarboxylic acid occurs readily in sulfuric acid by attack at one of the α-positions (equation 17).[14] Similarly, the cyclization of 2,4-dimethoxy-6,2′-naphthylbenzoic acid proceeds to give the expected product (equation 18) in quantitative yield using trifluoroacetic anhydride in chloroform at room temperature.[15] Other cyclizations, for example using 1-phenanthrylacetyl chloride[16] and 5,6,7,8-tetrahydro-2-phenanthryl-3′-butanoic acid,[17] have been carried out to give acceptable yields of the anticipated polycyclic ketones. In the former case attempted cyclization reactions of the acid failed, using a number of different reagents. The cleavage of benzo[*c*]fluorenone by heating with potassium hydroxide in toluene affords *o*-(2-naphthyl)benzoic acid. This acid was reclosed using polyphosphoric acid to afford the isomeric benzofluorenone in 70% yield.[18] A number of cyclization reactions of half-oxalyl esters to afford coumaran-2,3-diones have been reported. Esterification of 2,5-di-*t*-butylphenol with oxalyl chloride gave the half-ester half-acid chloride and the resulting crude acid chloride gave 4,7-di-*t*-butylcoumaran-2,3-dione in 90% yield on treatment with aluminum chloride in 1,2-dichloroethane.[19]

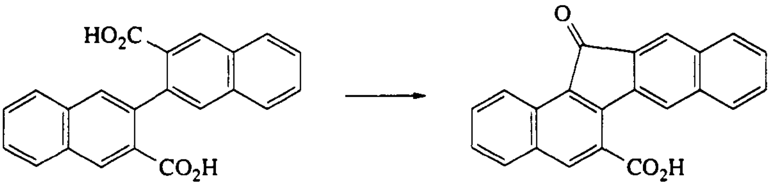

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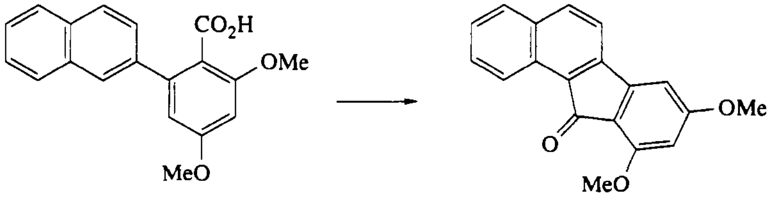

(18)

The reactions of acids and acid chlorides derived from a number of different heterocyclic systems have been studied. Cyclizations either onto a benzene ring or onto a π-excessive heterocycle have been reported. Reactions of 2-phenylquinoline-3-carbonyl chlorides give good yields of the expected products.[20] The product shown in equation (19) was obtained in 90% yield. It was found that the cyclization of pyrrole 1-aspartates proceeds more efficiently using phosphoric anhydride (equation 20) than was the case using polyphosphoric acid.[21] A number of derivatives of indeno[2,1-*b*]thiophen-8-one have been prepared by cyclizations using the trifluoroacetic anhydride–sulfuric acid[22a] and aluminum chloride[22b] methods. Reactions of 2-[23a] and 3-substituted[23b] thienyl-β-propanoyl chlorides give cyclic thienyl ketones as exemplified in equation (21).

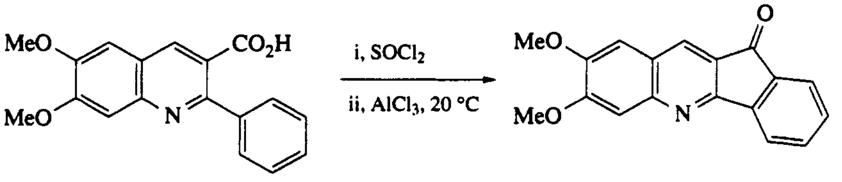

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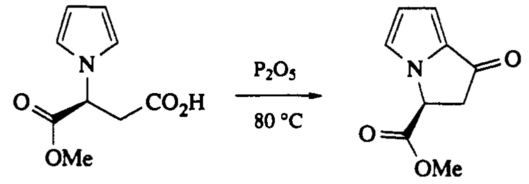

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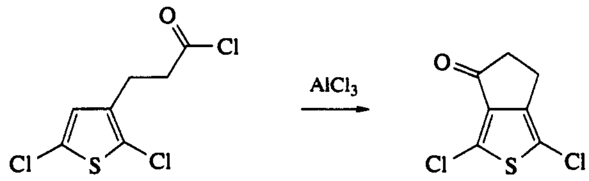

(21)

### 3.3.3.2 Reactions Leading to the Formation of Six-membered Rings

As is expected, the majority of the work carried out on intramolecular Friedel–Crafts acylation reactions has been concerned with the formation of six-membered rings. Examples where double cyclizations have been effected in a single operation include that shown in equation (22).[24] As well as the use of the reactions in carbocyclic ring formation there are cases where cyclization results in the formation of a heterocyclic ring. For example chromanones are obtained from 3-aryloxyacryloyl chlorides and xanthones from 2-aryloxybenzoyl chlorides. The intramolecular version of the Houben–Hoesch synthesis has also been studied. Equation (23), in which the nitrile group functions as a precursor to an acyl cation equivalent, shows one of the steps in a synthesis of the schistosomicidal agent hycanthone.[25] The intermediate imine was hydrolyzed to the product shown without isolation. The aluminum chloride catalyzed cyclization of the phenyl hydrazone derived from ethyl cyanoacetate gives the expected 3-cyanocinnolone. In other examples lacking the ester function, cyclization involving attack at the nitrile group results in aromatization of the intermediate imine to afford a 4-aminocinnoline rather than hydrolysis, as exemplified in equation (24).[26]

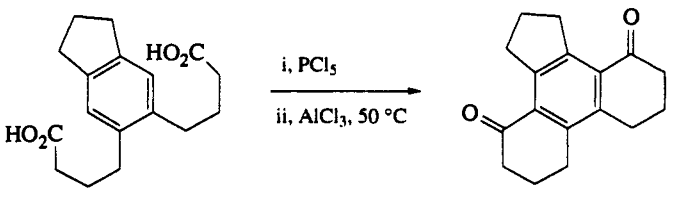

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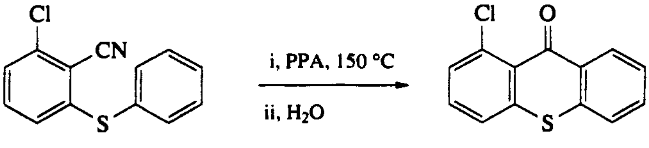

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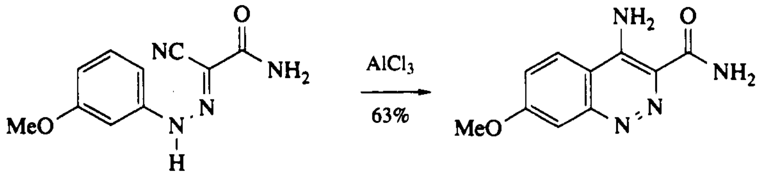

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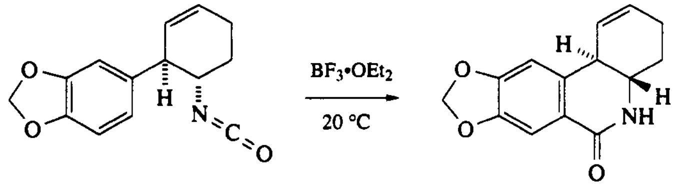

(25)

Isocyanates[27] and isothiocyanates[28] have been used as precursors to formamidyl and thioformamidyl cation equivalents. The reaction shown in equation (25), catalyzed by boron trifluoride etherate, was used in a synthesis of the alkaloid lycoricidine, and proceeded in 89% yield.[27] This type of reaction also works efficiently using other β-phenethyl isocyanates.

The ring-closure reactions of derivatives of γ-arylbutanoic acids proceed in high yields under very mild conditions when the aryl residue is electron rich. This is particularly the case when the aryl residue is a π-excessive heterocycle. Both 2- and 3-furyl-γ-butanoyl chlorides (equation 26) afford the 3,4-dihydro-1(2*H*)-ones in good yields at 0 °C using tin(IV) chloride as the catalyst, though, as expected, the yield is better when the cyclization proceeds by attack at the 2-position on the furan ring.[29] Reactions that have been investigated in the thiophene series include those shown in equations (27)[30] and (28).[31] A number of isomers of the product shown in equation (28) were also prepared. It is of interest to note that the cyclization of the acid chloride derived from 3,3′-dithienylmethane-2-carboxylic acid when reacted with tin(IV) chloride in the presence of acetic anhydride gave the enol acetate in 77% yield. Attempts to form seven-membered rings under conditions similar to those shown in equation (27) were not successful.

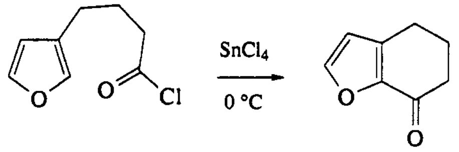

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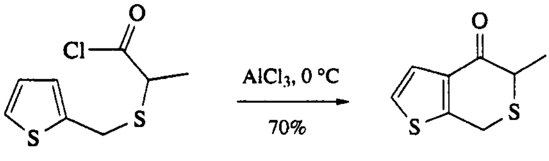

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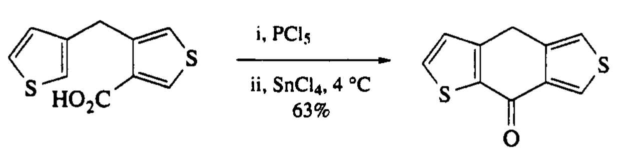

(28)

Many examples of intramolecular Friedel–Crafts acylation reactions that lead to the formation of benzo six-membered heterocyclic systems have been reported over a long period of time. Early examples involved the formation of thiochromanones.[32] The cyclization of 2-phenoxybenzoic acid using sodium tetrachloroaluminate gave chromanone in 99% yield.[13] The synthesis of 1-pyrido[3,2,1-*kl*]phenothiazine[33] *via* the organocadmium compound proceeds in 69% yield, whereas the more conventional treatment of the acid chloride with tin(IV) chloride gave the product in a reduced yield. Other syntheses include acridonecarboxylic acids from *N*-arylaminoisophthalic acids[34a] and diphenylamine-2,2′-dicarboxylic acids,[34b] dibenzochroman-4-ones[35] and thio analogs (equations 29 and 30),[36] and azaanthranols.[37] *N*-(3-Trifluoromethylphenyl)anthranilic acid gave the acridone in 95% yield using polyphosphoric acid as the reagent.[35] The cyclization of *N*-4-quinolylmethylglycine derivatives has been reported using polyphosphoric acid or sulfuric acid.[38] Reactions using sulfuric acid were more successful at lower temperatures than those employing the former reagent system. When reactions were carried out using phosphoryl chloride, the initial product was converted into a chloro derivative, as illustrated in equation (31). The use of an excess of oxalyl chloride in the synthesis of dihydro-*O*-methylsterigmatocystin as shown in equation (32)[39] is interesting and may involve the cyclization of a mixed anhydride type reagent where the driving force for the cyclization is derived from the loss of carbon dioxide and carbon monoxide as chloride ion departs.

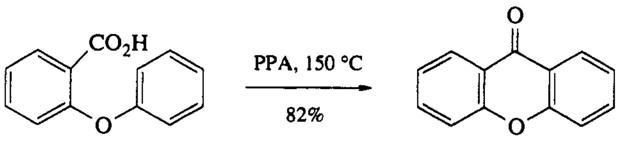

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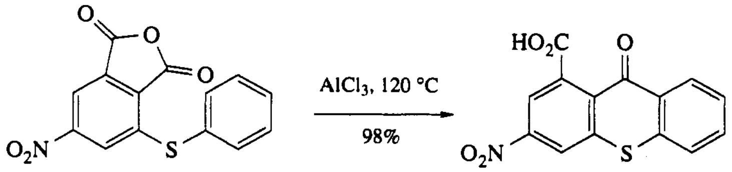

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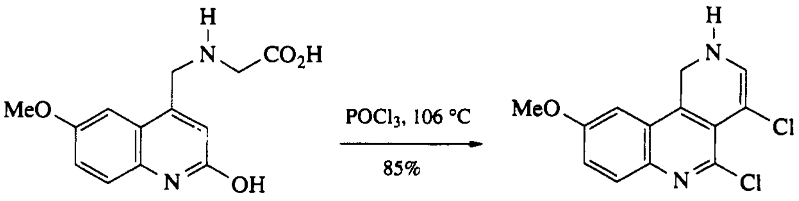

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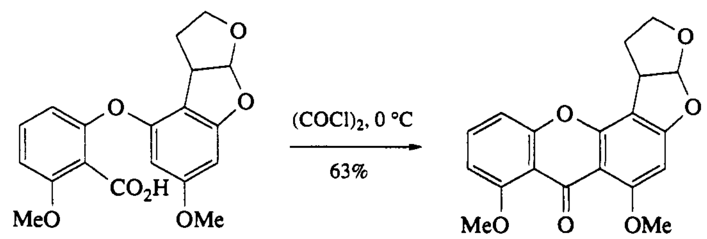

(32)

As is expected, the majority of the papers published on cyclization reactions that result in the formation of six-membered rings involve the synthesis of fully carbocyclic systems. We discussed the use of sodium tetrachloroaluminate in connection with the formation of indanones that have electron-withdrawing groups on the benzene ring.[6] 7-Acetyl-3,4-dihydronaphthalen-1(2*H*)-one was obtained from *p*-acetyl-4-phenylbutanoic acid in 70% yield by that procedure. In the modified Haworth naphthalene synthesis using $\gamma$-valerolactone and *p*-xylene, the acid [4-(2,5-dimethylphenyl)pentanoic acid] was cyclized in high yield using polyphosphoric acid. Wide variations have been reported in both the cyclization conditions and in the reagents used. Polyphosphoric acid is widely recommended for the cyclization of $\gamma$-arylbutanoic acid derivatives. In the example shown in equation (33)[40] it was found that the use of polyphosphoric acid was preferable to the use of aluminum chloride. Phosphoric acid[41] has been used with acid chlorides and sulfuric acid (equation 34) with some activated substrates.[42] The use of pyridinium fluoride in the reaction shown in equation (35) results in cyclization with a reduced tendency to *O*-demethylation.[43] In the synthesis of aurentiacin,[44] which was mentioned in Volume 2, Chapter 3.2, advantage was taken of the fact that Lewis acids frequently cause *O*-demethylation *ortho* to an introduced acyl group. The cyclohexannelation of polycyclic aromatic hydrocarbons can frequently be achieved using mild Lewis acids such as tin(IV) chloride. An example is shown in equation (36).[45] The cyclization of a number of 3-arylidenelevulinic acid derivatives using acetic anhydride has been shown to proceed reasonably efficiently (equation 37) even when electron-withdrawing groups are present.[46] The resulting cyclohexadienone undergoes the expected dienone–phenol rearrangement to the $\alpha$-naphthol under the reaction conditions. A number of *o*-aroylbenzoic acid derivatives have been subjected to reductive cyclization using hydriodic acid[47] as shown in equation (38), or hydriodic acid–red phosphorus. In the case of reactions carried out using hydriodic acid–red phosphorus, cyclization and reduction proceeded eventually to the 9,14-dihydro derivative. The reductive cyclization of a number of *o*-benzoylbenzoic acid derivatives to 9,10-dihydroanthracenes proceed in very high yields.[48]

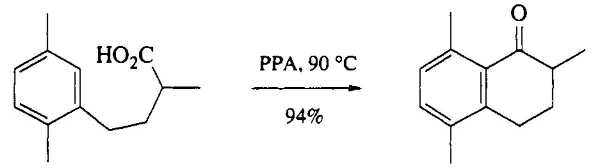

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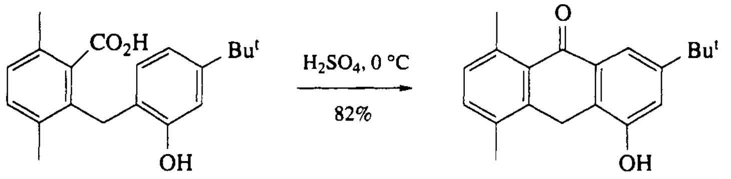

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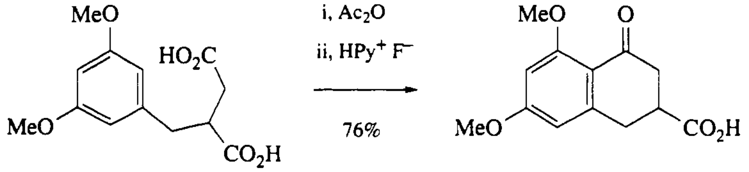

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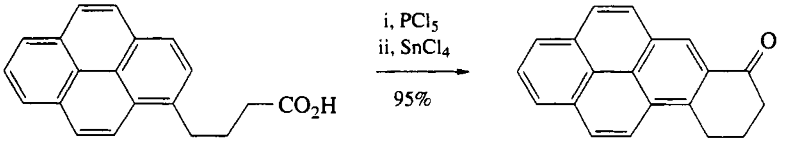

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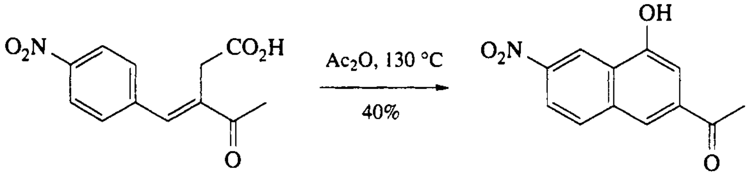

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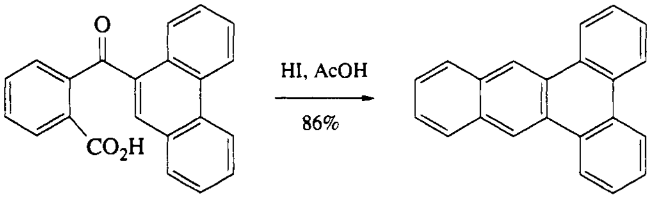

(38)

Ring-closure reactions of alkyl-substituted *o*-benzoylbenzoic acids that are carried out using aluminum chloride are often accompanied by rearrangement of alkyl groups to give the thermodynamically most favoured orientation. 2,5-Diethylbenzoylbenzoic acid gives the anthraquinone that is expected to be formed by the cyclization of the 2,4-diethyl isomer. Once again this mirrors effects that were noted in bimolecular Friedel–Crafts acylation reactions. The cyclization of *o*-benzylbenzoic acids can lead to the formation of anthrones which in some cases are unstable and then afford anthraquinones after oxidation. The example shown in equation (39) is such a case where the 4,6-dimethoxy-2-(4′-methoxybenzyl)benzoic acid does afford an unstable anthrone.[49] The possibility of using masked *o*-benzoylbenzoic acids in connection with anthracycline synthesis is exemplified in equation (40). An overall yield of 75% was obtained in the sequence which included the demethylation steps shown.[50]

The most important applications are involved in the synthesis of polycyclic systems. The cyclization reactions of suitably substituted 2-naphthylcyclopentylacetic acids have been investigated in connection with syntheses of A,B aromatic ring steroids but the traditional Friedel–Crafts procedures proved disappointing.[51] On the other hand, the cyclization shown in equation (41), which used hydrofluoric acid as the electrophile, gave a significant improvement in the yield.[52] It was observed that attempted cyclization of the related but unprotected ketone gave a very poor yield of the expected product. Polyphosphoric acid and polyphosphoric acid containing phosphoryl chloride sometimes give improved yields. It may be in the latter case that, as well as reducing the viscosity of the polyphosphoric acid, the phosphoryl chloride converts the acid into the acyl chloride.

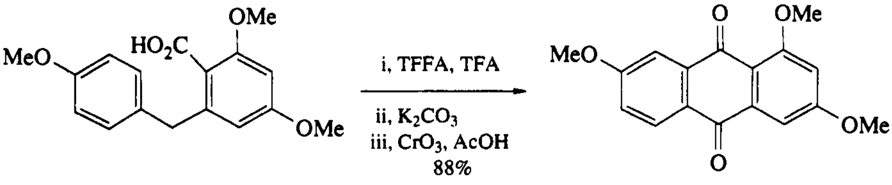

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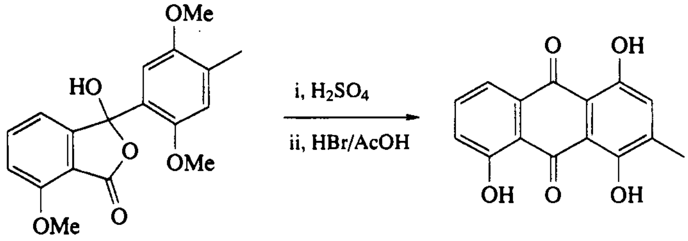

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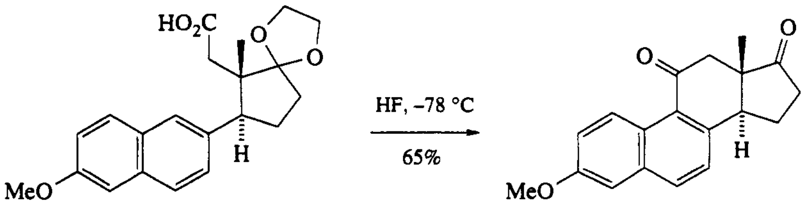

(41)

Many of the more recent applications of intramolecular Friedel–Crafts acylation reactions have involved the synthesis of biologically active tetracycline derivatives. In the synthesis of aclacinomycin[53] the acid shown in equation (42) was cyclized efficiently to the anthrone using trifluoroacetic anhydride in dichloromethane and then converted immediately into the anthraquinone shown.

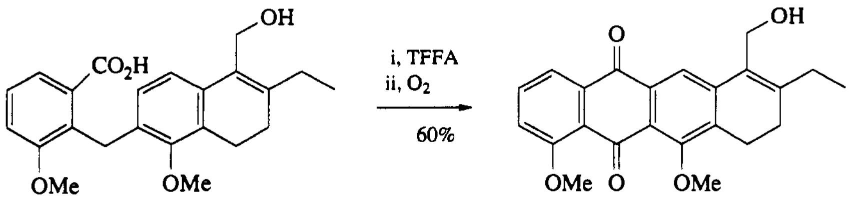

(42)

Considerable attention has been given to the synthesis of the aglycone portions of the antitumor anthracyclines.[54] In one of the seminal procedures[55] the construction of rings A and B (using the Brockmann nomenclature) and the joining together of the two remaining rings were both achieved using Friedel–Crafts methodology. The cyclization of the 2,5-dimethoxyphenylbutanoic acid derivative containing the acetyl group, suitably placed so that it would eventually appear at the 9-position, was achieved using hydrofluoric acid as shown in equation (43). It is of interest to note that similar attempted cyclizations of a 1,4-dihydroxy-5-methoxy-9,10-anthraquinone failed using a variety of acids. An unsaturated lactone (a 2,5-dihydrofuranone) was the major product.[56] On the other hand the cyclization of phthalic anhydride with 2-methyl-1,4-dihydroxybenzene to the anthraquinone was achieved in 79% yield using the sodium tetrachloroaluminate procedure.[56] In a related series of investigations[57] the fusion of the (*R*)-(–)-5,8-dimethoxytetralin derivative (equation 44) gave the (–)-enantiomer of the tetracyclinone shown. The earlier synthesis[55] was continued as shown in equation (45) in which the mixture of methyl hydrogenphthalate and the 5,8-dimethoxytetralin was treated sequentially with trifluoroacetic anhydride and then hydrogen fluoride. We mentioned previously the instability of a trimethoxyanthrone.[49] On the other hand, there have been a number of reports[58] of the successful cyclization reactions involving the formation and isolation of anthrone derivatives in high yields as exemplified in equation (46). The construction of a suitably substituted 5,8-dimethoxy-3,4-dihydronaphthalen-1-(2*H*)one, shown in equation (47), was achieved by using tin(IV) chloride as the catalyst.[59] The acid can be cyclized directly in high yield using polyphosphoric acid to give mainly the 8-hydroxy derivative. In a rather different approach to the synthesis of the tetracyclinone ring system, illustrated in equation (48), the intramolecular Friedel–Crafts acylation was carried out with trifluoroacetic anhydride.[60] The protective group that was required was, of course, removed during the cyclization reaction and had to be reintroduced.

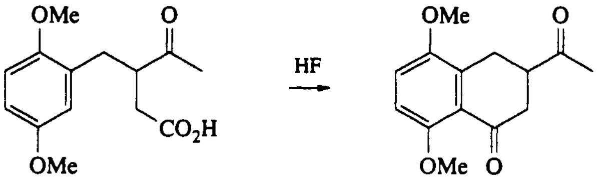
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HF
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O
OMe O

(43)

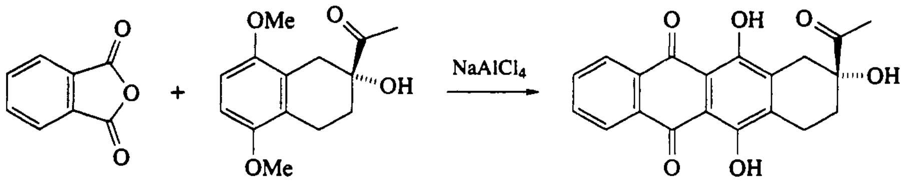
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OH

(44)

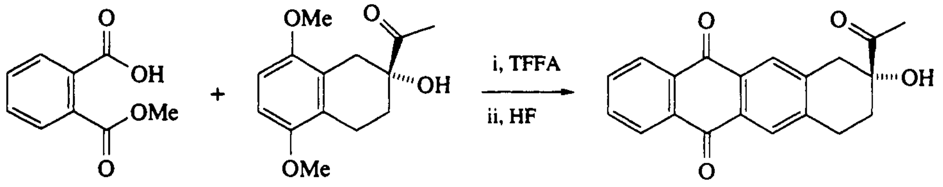
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ii, HF
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OH
O

(45)

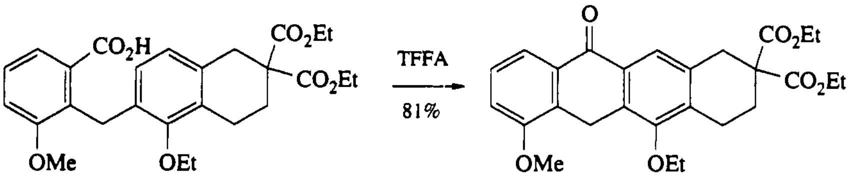
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CO₂Et
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OMe
OEt

(46)

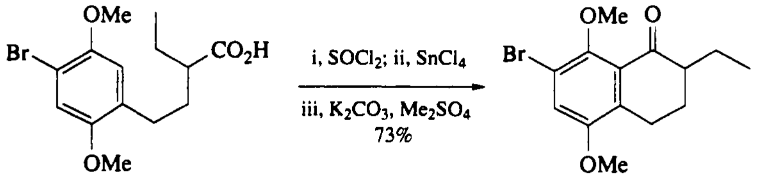
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Br
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(47)

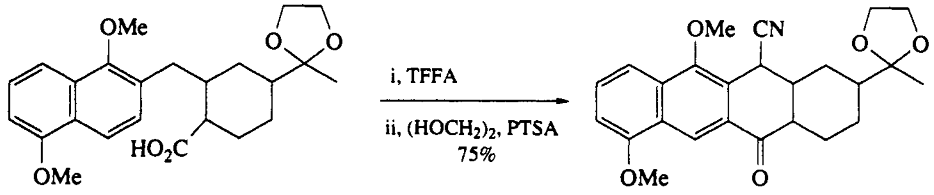
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ii, (HOCH₂)₂, PTSA
75%
OMe CN
O
O
OMe
O

(48)

### 3.3.3.3 Reactions Leading to the Formation of Seven-membered Rings

One of the early examples of the use of sodium tetrachloroaluminate in intramolecular Friedel–Crafts acylation reactions involved the reaction shown in equation (49), in which β-(3-acenaphthoyl)propanoic acid was converted into perisuccinoylacenaphthene.[61] The formation of the benzosuberanone ring system is particularly easy when electron-releasing substituents are present on the benzene ring. Under those circumstances mild reaction conditions may be used. In reactions that are carried out using polyphosphoric acid it is normal to use an unspecified excess of the acid.[62] However, in the example shown in equation (50) the yield of the benzosuberone was found to vary with the amount of acid used. The yield changed from 50% to 79% on doubling the amount of polyphosphoric acid used.[63] The cyclization of 5-(2,3-dimethoxyphenyl)valeric acid proceeds to give the expected product in 78% yield when it is stirred in polyphosphoric acid at 40 °C for 40 h.[64] The same authors reported that 5-(2-acetoxy-3-methoxyphenyl)valeryl chloride was reacted with tin(IV) chloride and gave the product shown in equation (51) in 85% yield. It is noteworthy that the relatively labile acetoxy group survives those reaction conditions. Efficient cyclization reactions of arylalkanoic acids have been carried out using hydrofluoric acid in polythene apparatus.[65] 5-(4-Isopropylphenyl)valeric acid was converted into the expected benzosuberanone in virtually quantitative yield and was isolated in 85% yield after purification. Pyridine hydrochloride has been used with some malonic acid derivatives.[66] The reaction apparently only succeeds with malonic acid derivatives that have a suitably positioned aryl residue, specifically having a *meta* methoxy group and a free *para* position. Demethylation was also observed in this last reaction.

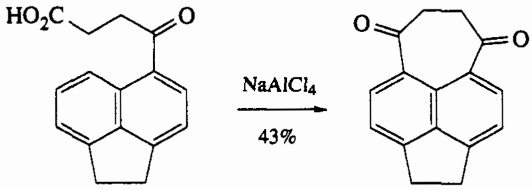
HO$_2$C
O
NaAlCl$_4$
43%
O
O

(49)

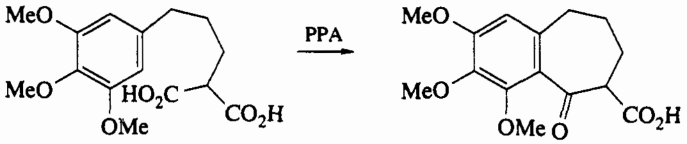
MeO
MeO
OMe
HO$_2$C
CO$_2$H
PPA
MeO
MeO
OMe
O
CO$_2$H

(50)

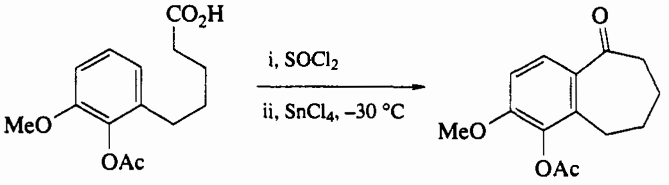
CO$_2$H
MeO
OAc
i, SOCl$_2$
ii, SnCl$_4$, –30 °C
O
MeO
OAc

(51)

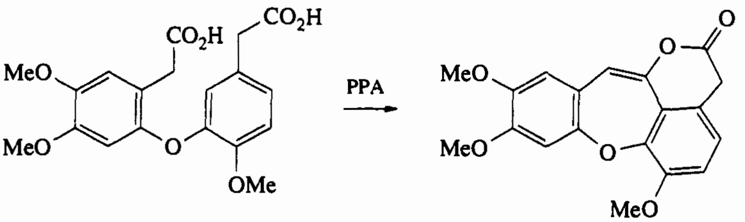
CO$_2$H
CO$_2$H
MeO
MeO
O
OMe
PPA
MeO
MeO
O
O
O
MeO

(52)

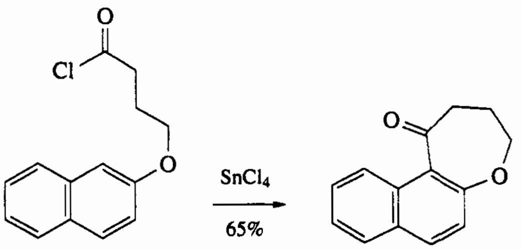
O
Cl
O
SnCl$_4$
65%
O
O

(53)

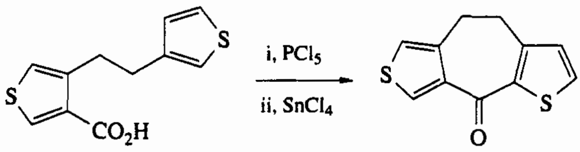
S
S
CO$_2$H
i, PCl$_5$
ii, SnCl$_4$
S
S
O

(54)

The construction of the pyranooxepin system shown in equation (52) proceeds by way of a dibenzoxepinone acetic acid, followed by intramolecular enol ester formation.[67] The regioselective cyclization of 4-(2-naphthyloxy)butanoyl chloride proceeds as expected (equation 53) using tin(IV) chloride as the catalyst, but a mixture of products was obtained when the related carboxylic acid was treated with polyphosphoric acid.[68] The preparation of a thieno[*b*]suberanone in 40% yield has been achieved by the interaction of tin(IV) chloride with 5-(2-thienyl)valeryl chloride.[69] Once again, the expected increase in yield is obtained when cyclization occurs to the 2-position in thiophene. The product shown in equation (54) was isolated in 81% yield.[70] Other intramolecular reactions involving thiophenes have been reported.[71]

Cyclization reactions resulting in the formation of indolo- and indolizino-suberenones are exemplified by equation (55)[72] and a range of benzo-[73] and thieno-[*b*]azepinones[74] have been prepared from glycine derivatives. The example shown in equation (56) showed platelet antiaggregating activity. The cyclization of a 5-(1-indolyl)valeric acid[75] and 3-(3,4-dimethoxyphenyl)propyl isothiocyanate[76] using polyphosphoric acid led to an indoloazepinone and a benzoazepinethione respectively. In the case of the isothiocyanate it appears that the electrophile involved is not very reactive. The yield of the cyclized product dropped to 30% in the absence of the methoxy groups. In the example shown in equation (57) a 1:1 mixture of diastereoisomers was obtained from which the *cis* isomer was isolated by fractional crystallization.[77]

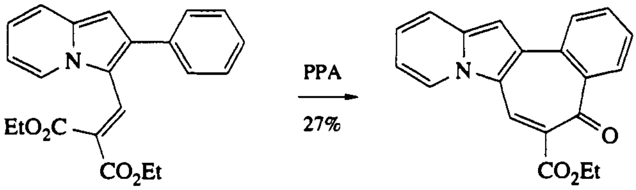

(55)

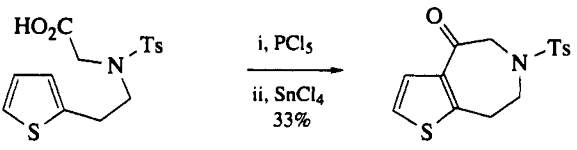

(56)

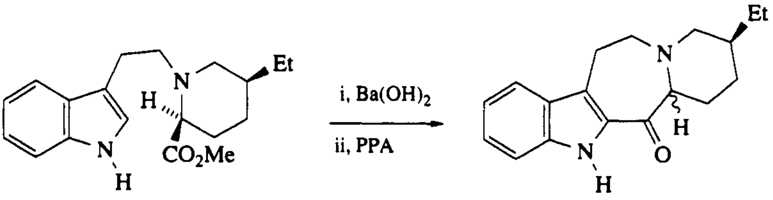

(57)

A wide range of benzo- and dibenzo-thiepinones has been prepared by cyclizing both the free carboxylic acids using polyphosphoric acid,[78] and by using Lewis acids after conversion into the acyl chlorides.[79] In the example shown in equation (58) the *trans* product was obtained in 50% yield while the *cis* isomer gave a slightly improved yield of the *cis* product.[80] Cyclization reactions of 4-(2-thionaphthoxy)butanoyl chloride using aluminum chloride[81] and tin(IV) chloride[82] proceed as expected by reaction at the 1-position in the naphthalene ring. The latter reaction, shown in equation (59), gives the better yield. When the 4-(2-thionaphthoxy)butanoic acid was reacted in polyphosphoric acid, both possible regioisomeric naphthothiepinones were obtained as a 1:1 mixture. This result is similar to the result that was obtained using the naphthoxybutanoic acid.[68]

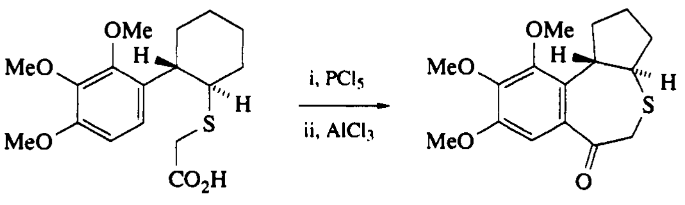

(58)

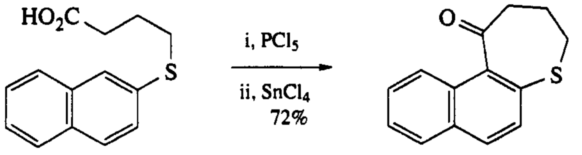

(59)

## 3.3.4 CONCLUSION

We have seen that the intramolecular version of the Friedel–Crafts acylation reaction is wide-ranging and that reaction conditions can normally be devised to allow the synthesis of a large number of different ring sizes. Cyclizations can also be carried out when the aryl residues have widely differing electron densities. The reaction is subject to fewer anomalies than is the case with the intermolecular version. There have been examples reported where unexpected products have been obtained, but a careful choice of reaction conditions will normally allow these problems to be avoided. To quote just one example, cinnamoyl chloride (the *trans* isomer) would not be expected to give a cyclized product, and a reaction with toluene using aluminum chloride as the catalyst leads to the expected intermolecular reaction product. A reaction carried out in benzene solution, however, gave rise to a mixture of 3-phenylindan-1-one and 1,3,3-triphenylpropanone.

It was assumed for many years that the Haworth polycyclic aromatic hydrocarbon synthesis only allowed access to angularly annelated systems. The realization[83] that the benzoylation of naphthalene using benzoic acid in polyphosphoric acid was reversible led to an investigation of potential rearrangements in intramolecular acylation reactions. Although the intramolecular acylation of a 2-substituted naphthalene proceeds under kinetic control to afford the angularly annelated product, heating that compound in polyphosphoric acid has been shown to result in rearrangement to the linearly annelated ketone.[84] In the example shown in equation (60) the linearly annelated ketone is obtained as the predominant product, isolated in a ratio of 4:1, when the angularly annelated ketone is heated in polyphosphoric acid at 115 °C for 10 h. Interestingly, the other possible isomer was shown to be present in only trace amounts. The rearrangement of 3,4-dihydrophenanthren-1-(2*H*)one to 3,4-dihydroanthracen-1-(2*H*)one also proceeds efficiently under thermodynamic reaction conditions.[85]

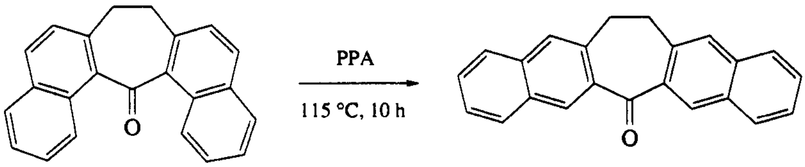

(60)

The origin of the thermodynamic difference is presumably that the ketone is protonated in polyphosphoric acid and interaction with a *peri*-hydrogen causes tilting of the protonated carbonyl group out of the plane of the aromatic system.[86] This effect would reduce the conjugation of the carbonyl group with the aromatic residue. The destabilizing effect is greater for an angular (kinetic) product than for the linearly annelated ketone because a *peri*-hydrogen is closer in the former case. Under thermodynamic reaction conditions of higher temperatures, the rearrangement to the linear ketone is favored.

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# 3.4
# The Reimer–Tiemann Reaction

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## 3.4.1 INTRODUCTION

The Reimer–Tiemann reaction, an aromatic substitution reaction that occurs under basic conditions, is in many respects a unique reaction. It is one of the few organic reactions whose industrial importance seems to increase yearly, notwithstanding the environmental hazards associated with the use of chloroform, while academic interest remains considerable. In addition to the fact that the 'normal' reaction continues to intrigue chemists, the so-called 'abnormal' Reimer–Tiemann reaction that furnishes substituted cyclohexadienes remains of considerable interest. Several previous surveys of the Reimer–Tiemann reaction have been published.[1] Consequently, we focus here on recent developments.

## 3.4.2 THE NORMAL REACTION

It is convenient to discuss the Reimer–Tiemann reaction in terms of its normal and abnormal versions. The normal reaction, discovered in 1876[2] by Reimer, consists of the treatment of a phenol or naphthol with chloroform in the presence of an alkali metal hydroxide solution (see equations 1 and 2), and results

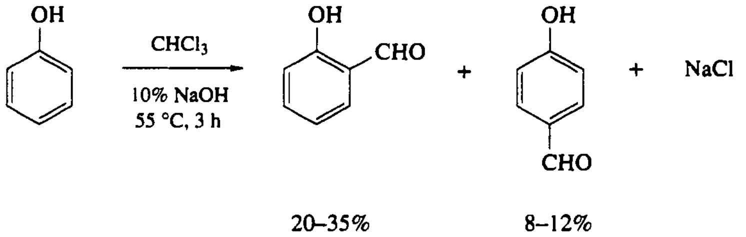

(1)

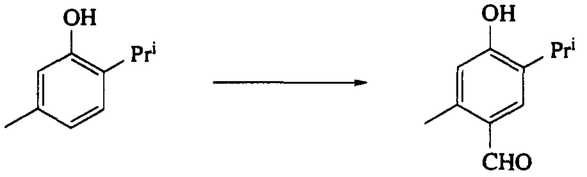

(2)

in the formation of phenolic aldehydes. Depending on the substituents, the products may be mixtures of *o*- and *p*-hydroxy aldehydes[1–5] or pure hydroxy aldehydes.[6–8]

In a recent paper, Rocke and Ihde[9] question the attribution of the name Reimer, citing evidence that the wrong Reimer has been credited with the reaction.

In addition to mono- and poly-hydric phenols and naphthols, several heterocyclic compounds also yield aldehydes upon treatment with chloroform and aqueous base. Thus, we find that hydroxypyridines, hydroxyquinolines and hydroxypyrimidines can be formylated. Even the nonhydroxylated pyrrole yields pyrrole-2-carbaldehyde in fair yield (see equations 3 and 4).[1,7,10]

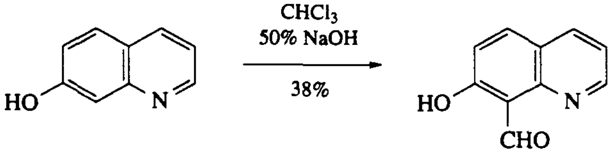

(3)

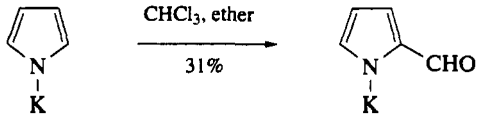

(4)

### 3.4.3 SCOPE AND LIMITATIONS

In addition to phenols, naphthols, their alkyl derivatives and the heterocyclic compounds mentioned above, a large variety of substituted monocyclic as well as condensed phenols have been subjected to the Reimer–Tiemann reaction. Although with a few exceptions the yields are only moderate, the facile reaction conditions, at least on a laboratory scale, have assured the reaction a permanent place among the variety of methods by which an aldehyde group can be attached to an aromatic nucleus. For example, phenolphthalein (1) has been formylated under standard Reimer–Tiemann conditions by van Kampen to yield the *o*-hydroxy aldehyde in 59% yield (equation 5).[11]

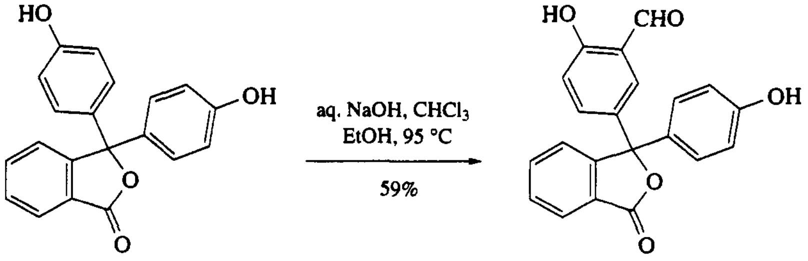

(1)

(5)

In addition to phenolphthalein, other carboxy-substituted phenols have been subjected to the Reimer–Tiemann reaction. Mixtures of compounds, some lacking the carboxyl group, result (equation 6).[1] Even though the nature of the reaction (*i.e.* the attack by the electrophilic dichlorocarbene on the nucleophilic

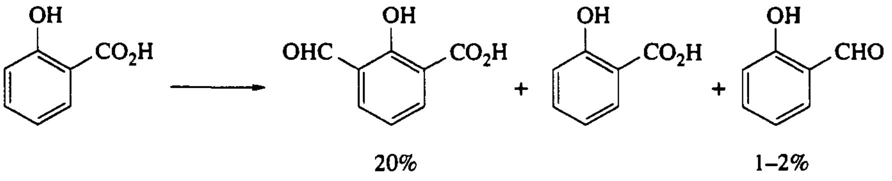

(6)

phenolate carbanion) would seem to preclude successful substitution on phenols carrying such negative substituents as carboxyl and sulfonic acid groups, reports of such substitution can be found, albeit mostly in the patent literature.[1]

A recent careful examination of the substitution pattern of a series of pyrrole-2-carboxylates established that loss of the carboxyl group occurs with simultaneous entry of the formyl group (equation 7).[10]

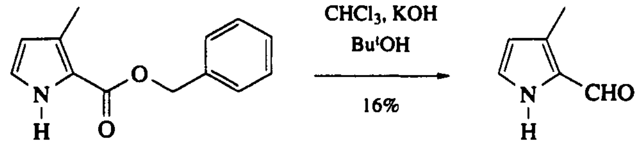

(7)

Another unusual observation concerns the replacement of a methoxy group by a formyl group under Reimer–Tiemann reaction conditions. The mechanism proposed by the authors (Scheme 1) seems reasonable[12] and supposes two consecutive replacements. First, the methoxy substitutent is replaced by the dichlorocarbene to give an *o*-quinone methide. The latter is hydrolyzed to a carboxyl group by a mechanism involving conjugate addition of hydroxide. A second replacement occurs, the carboxyl group being displaced by the formyl (*via* the carbene) group. All-in-all, this is a strange, unsubstantiated, but not unreasonable sequence of events.

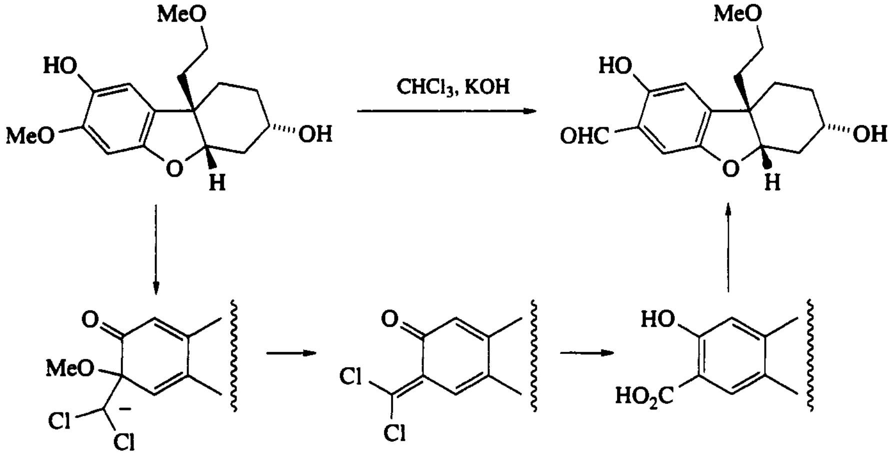

Scheme 1

## 3.4.4 RECENT DEVELOPMENTS

Since several recent reviews of the Reimer–Tiemann reaction are readily available, the last one dating from 1982,[1] it is perhaps most useful to summarize recent developments.

### 3.4.4.1 Regioselectivity

Since the Reimer–Tiemann reaction always yields a mixture of *ortho*- and *para*-substituted phenols whenever the two positions are unsubstituted (and sometimes even when the positions are substituted, see carboxy-substituted phenols), it is not surprising that attempts have been made to increase the regioselectivity. Earlier attempts (for details, see reviews) emphasized the nature of the cation, the solvent, or used phase-transfer catalysis. Recent studies have concentrated on the use of cyclodextrins as base-stable host compounds, permitting exclusive *para* substitution. Attaching the cyclodextrins to a solid support has also been attempted, a natural step in view of the high cost of the cyclodextrins and the need for cheap product (*i.e.* *p*-hydroxybenzaldehyde). *p*-Hydroxybenzaldehyde has been prepared in 59–65% yield using β-cyclodextrin that has been immobilized with epichlorohydrin.[13] The catalyst is easily recovered and can be reused without appreciable loss of activity.

Increased selectivity has also been obtained using polyethylene glycol as complexing agent.[14] Using toluene as solvent, the authors report a 1:10 *para*:*ortho* ratio in the formylation of phenol.

Greater *ortho* selectivity has also been observed under conditions that the authors call a photo Reimer–Tiemann reaction. Since the original paper[15] was not available for perusal, no judgment can be made about the validity of the interesting report. It is worthwhile to recall that the acidity of the phenol changes several orders of magnitude in the excited state. If substitution indeed takes place while phenol is in the excited state, a change in the substitution pattern might well occur.

### 3.4.4.2 Industrial Applications

Even though chloroform as industrial solvent or reagent does not seem to have a bright future, emphasis on the industrially viable Reimer–Tiemann processes continue to appear in the literature, especially from countries such as India and China.[16] This author is familiar with some of the conditions prevailing in these countries from personal experience. It is evident that processes, long ago abandoned by western countries because of environmental hazards or uneconomical procedures, are still finding their way into the industries of developing countries, an interesting but disturbing phenomenon. However, even western companies appear to find the Reimer–Tiemann reaction still of sufficient importance to spend money on research and patents. Thus, a Dow Chemical Company patent[17] describes the use of high pressure and temperatures to accelerate the reaction, with yields reported as high as 52% (Scheme 2).

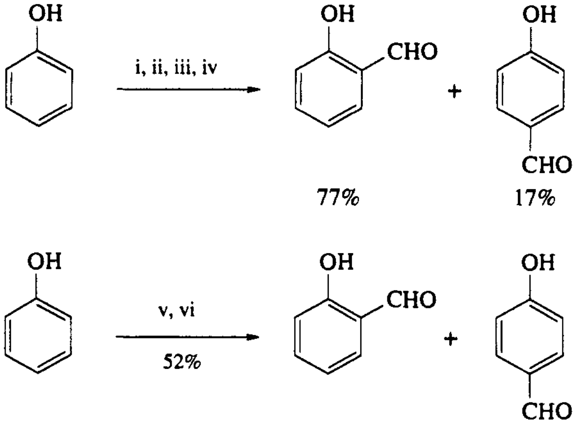

i, 9.4 g phenol, 20 g NaOH; ii, 100 mL $CHCl_3$, 3.6 mL $H_2O$; iii, 58 °C, 1 h;
iv, 12 g NaOH, 2 h; v, 27 g phenol, 25 g NaOH, 100 g $H_2O$, 11 g $CHCl_3$;
vi, 80–88 °C, 100 atm, 12 min

**Scheme 2**

Intriguing but confusing information is available in two *Chemical Abstracts* references to Chinese publications. A 1988 abstract[18] reports the behavior of phenol under Reimer–Tiemann reaction conditions with the addition of tertiary amines. The authors claim that the *para*:*ortho* ratio is reversed from that normally observed and 60% yield of *p*-hydroxybenzaldehyde, 7% yield of *o*-hydroxybenzaldehyde and only 1% tars are obtained when phenol is subjected to the new conditions. One year later[19] a report appeared in which it is claimed that the use of tertiary amines under phase-transfer conditions increases the yield of *ortho* product. The authors report a yield of 79% of salicylaldehyde from phenol using 0.37% catalyst (the nature of the catalyst is not mentioned in the abstract and the Chinese publication is not available to this author), and 35% sodium hydroxide at 55–60 °C for 90 min. Surely, these results (or the translation) warrant checking.

Greater reliance can be placed on a recent report of the effect of ultrasonic irradiation on the Reimer–Tiemann reaction.[20] The authors report 'significant improvement in Reimer–Tiemann yields through ultrasonic irradiation of the reaction system. The effects of ultrasonic intensity and reactor design are discussed.'

### 3.4.5 THE 'ABNORMAL' REIMER–TIEMANN REACTION

It is interesting to compare early experimental work with the facilities available in a modern laboratory. Von Auwers was the first to separate the chloro ketones from the normal phenolic aldehydes of the Reimer–Tiemann reaction.[21] Identification and structure proof by chemical means followed. It is a tribute to von Auwers' skill and insight that his identification procedures have withstood the onslaught of modern spectroscopic means. Although the chloro ketones (equations 8–10) have been called the abnormal products of the reaction, in cases where the *ortho* and *para* positions are occupied (see equation 10) only ketonic material is obtained.[1,22] In fact, the presence of the dichloro ketones provides one of the better arguments for the intermediacy of dichlorocarbene in the reaction mechanism.[23]

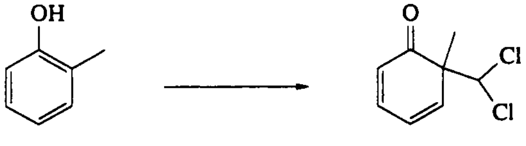

(8)

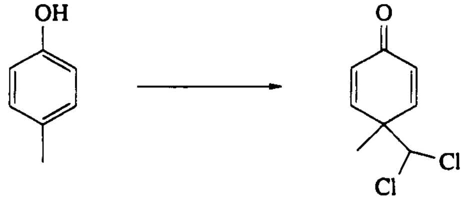

(9)

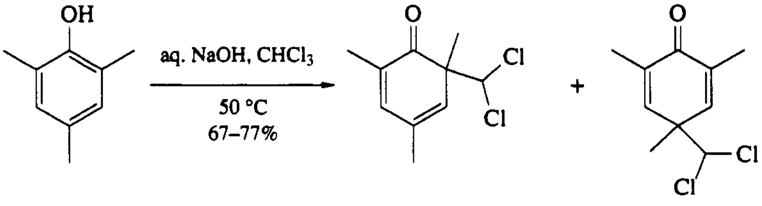

(10)

Although at first these ketonic by-products were mere curiosities, their potential value was noted by Woodward, who used the abnormal Reimer–Tiemann reaction for a synthesis of *trans*-10-methyldecalone from β-(*ar*)-tetralol (equation 11).[24] This author applied this principle for the preparation of a 9-methyldecalone from an α-(*ar*)-tertralol (equation 12).[25]

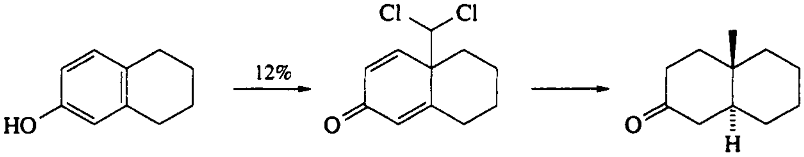

(11)

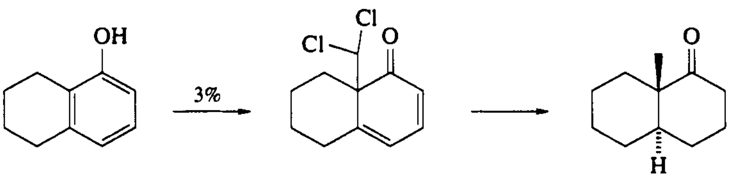

(12)

As is the case with the normal reaction, the abnormal reaction can also be influenced by the use of β-cyclodextrin to give higher selectivity for the *para* position. Australian chemists have carried out a careful product analysis of the normal, abnormal and ring-expansion products resulting from the Reimer–Tiemann reaction with a series of 4-alkylguaiacols.[26]

Ring expansion during Reimer–Tiemann reaction conditions on pyrroles and indoles to furnish pyridines and quinolines was observed by Ciamician in 1881 (equations 13 and 14).[27] Although a preparative reaction of little use due to the low yield, this transformation stimulated others to carry out ring expansion attempts on nonphenolic substrates with considerable success.[28]

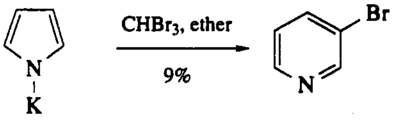
K
N
CHBr3, ether
9%
Br
N

(13)

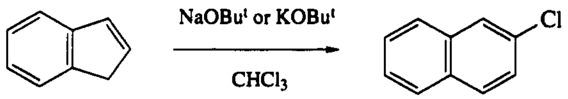
NaOBu^t or KOBu^t
CHCl3
Cl

(14)

## 3.4.6 THE MECHANISM OF THE REACTION

The formation of all of the reaction products, phenolic aldehydes, dichloro ketones and ring-expansion products, can be explained satisfactorily by postulating the carbene intermediate originally proposed by Hine (Scheme 3).[23] The only products that might be thought of as resulting from direct nucleophilic displacement of phenolate anion on chloroform are the orthoformic esters (*e.g.* **2**) formed in low yields in most Reimer–Tiemann reactions (and rarely isolated or identified). However, even these can result from a version of the Hine mechanism.

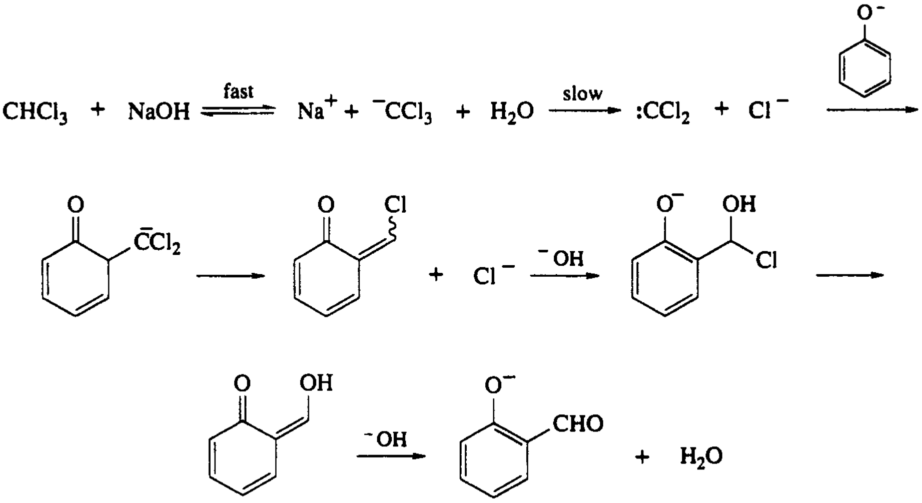
CHCl3 + NaOH
fast
Na+ + −CCl3 + H2O
slow
:CCl2 + Cl−
O−
O
C̄Cl2
O
Cl
+ Cl−
−OH
O−
OH
Cl
O
OH
−OH
O−
CHO
+ H2O

**Scheme 3**

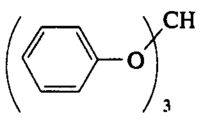

**(2)**

Even less structural information is available on the 'leucarins' or triphenylmethane type dyes, which are a natural result of the condensation of aldehydes with phenols. It is clear that the products of the Reimer–Tiemann reaction can react further with themselves as well as with the starting phenol to yield a delightful variety of colored materials, erroneously called 'tars' by some (*e.g.* **3**).

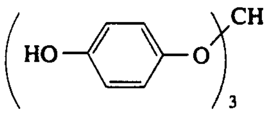

**(3)**

Finally, it should be mentioned that hot alkaline solutions in the presence of air cause oxidation of the sensitive phenols and phenolic aldehydes. Thus, the isolation of traces of acids is not unexpected.

## 3.4.7 CONCLUSIONS

Since 1876, approximately 240 publications have appeared in which the Reimer–Tiemann reaction plays a prominent role. Two publications per year does not seem to be an overwhelming number of publications or interest in a carbon–carbon bond-forming reaction. But quantity may not be the best criterion for explaining the continued interest in this reaction. Certainly, the products of the normal reaction, the hydroxybenzaldehydes, are not only among the most important intermediates in the synthesis of aromatic compounds, their occurrence in nature, naturally not in the free form, but as obvious parts of complex structures (see, for example the vast variety of flavones), also attests to their importance. Undoubtedly, it would be rather extreme to presume that a biochemical/biosynthetic equivalent to the Reimer–Tiemann reaction exists in nature. After all, another certainly more important carbon–carbon bond-forming reaction such as the Michael reaction (with approximately 10 times as many references in the literature as the Reimer–Tiemann reaction) does not seem to have a biochemical equivalent either. Nevertheless, in the absence of strong evidence to the contrary, it can be argued that carbene formation under physiological conditions is eminently feasible, since chloroform is readily identified in (Dutch) waters, and mildly basic conditions would certainly lead to the formation of carbene. Phenols, oxidative degradation products of aromatics, are also obvious organic compounds in our environment, setting the stage for the Reimer–Tiemann reaction under biological circumstances.

An improved synthesis of salicylaldehyde, using solid sodium hydroxide and little water, has recently been reported.[29]

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# 3.5

# The Vilsmeier–Haack Reaction

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and
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## 3.5.1 INTRODUCTION

The classical Vilsmeier–Haack reaction[1,2] involves electrophilic substitution of a suitable carbon nucleophile with a chloromethyleneiminium salt, for example salt (**1**). Suitable carbon nucleophiles are generally electron-rich aromatic compounds such as *N*,*N*-dimethylaniline (**2**), alkene derivatives such as styrene (**3**) or activated methyl or methylene compounds such as 2,4,6-trinitrotoluene (**4**; Scheme 1). These compounds (**2–4**) react with salt (**1**) giving, after loss of hydrogen chloride, the corresponding iminium salts (**5–7**). Hydrolysis of iminium salt (**5**) affords aldehyde derivative (**8**) and this transformation (Ar—H → Ar—CHO) is the well-known Vilsmeier–Haack formylation reaction. Hydrolysis of iminium salt (**6**) similarly yields the formylated product (**9**). Compounds that possess activated methyl or methylene groups such as 2,4,6-trinitrotoluene (**4**) react with salt (**1**) giving iminium salts like (**7**). Proton loss from iminium salt (**7**) affords the enamine derivative (**10**), which can participate in a further electrophilic substitution reaction with salt (**1**) giving vinylamidinium salt (**11**). Hydrolysis of this salt (**11**) yields the malondialdehyde derivative (**12**).

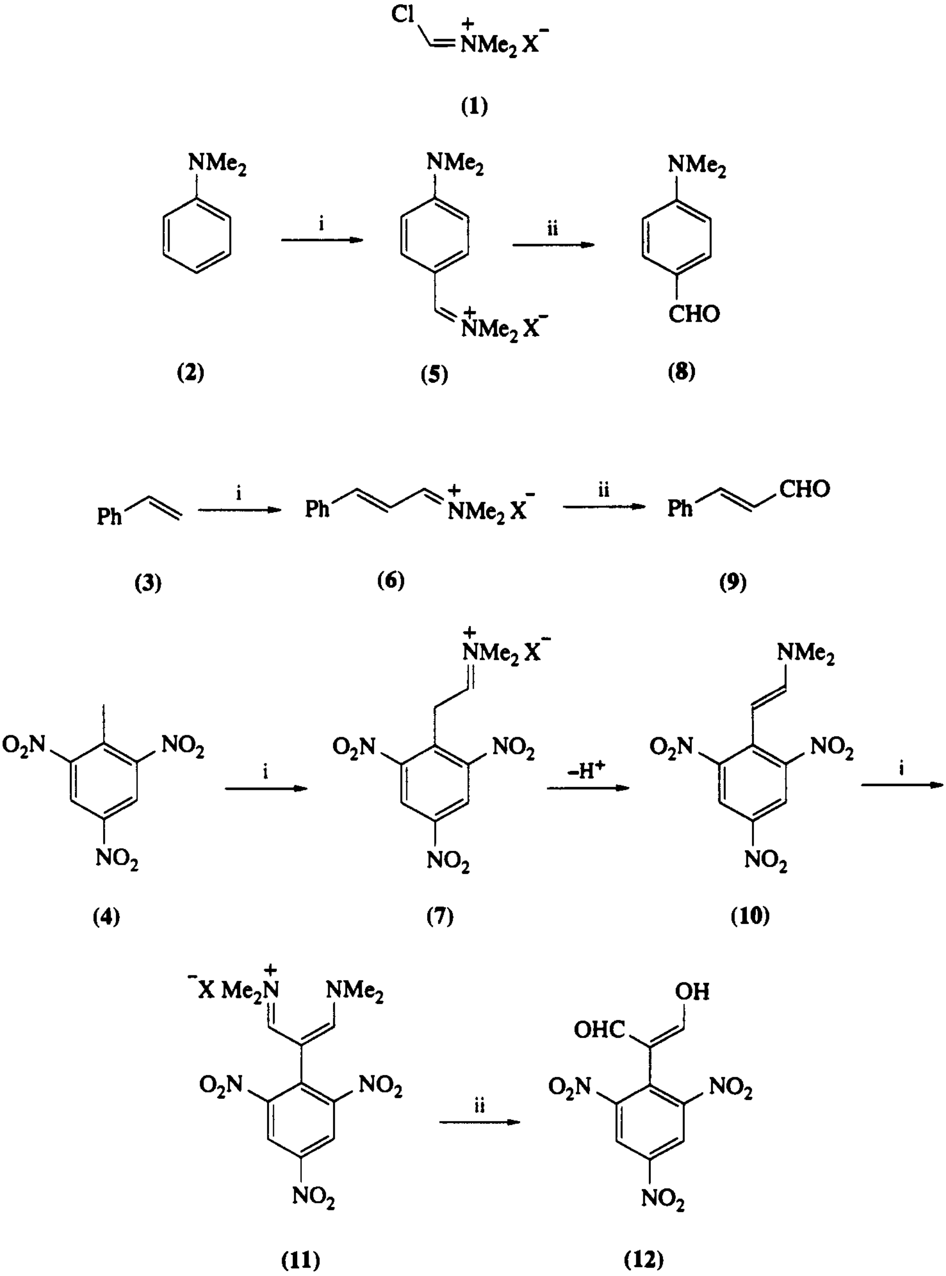

i, salt (**1**); ii, hydrolysis

**Scheme 1**

The Vilsmeier–Haack reaction, as depicted in Scheme 1, is an important method for synthesizing aldehyde derivatives. Numerous other transformations of iminium salts into products other than aldehydes have been achieved, and these additional transformations add considerable scope and versatility to the Vilsmeier–Haack reaction. The Vilsmeier–Haack reaction is not restricted to carbon nucleophiles: oxygen and nitrogen nucleophiles also react with chloromethyleneiminium salts.

## 3.5.2 FORMATION OF CHLOROMETHYLENEIMINIUM SALTS

Chloromethyleneiminium salt (**1**) is formed by treating dimethylformamide (DMF) with an acid chloride.[1] A large number of other chloromethyleneiminium salts (**13**) are available from formamide derivatives $HCONR^1R^2$, but DMF is used most frequently. Formamide derivatives $HCONR^1R^2$ that have been employed in the Vilsmeier–Haack reaction include *N*-methylformanilide, *N*-formylpiperidine and *N*-formylmorpholine. Vilsmeier and Haack originally discovered[3] that *N*-methylformanilide formylated aniline derivatives in the presence of $POCl_3$. The chloromethyleneiminium salt (**13**; $R^1$ = Me, $R^2$ = Ph) was the electrophile in this reaction. Vinylogous formamide derivatives (**14**) give the corresponding vinylogous chloromethyleneiminium salts (**15**), which also participate in the Vilsmeier–Haack reaction.[1,4]

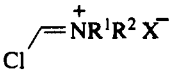
**(13)**

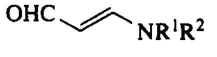
**(14)**

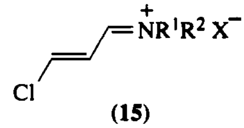
**(15)**

Formamide derivatives can sometimes be replaced with other amides, and examples include *N*,*N*-dimethylacetamide (DMA), *N*-methylpyrrolidone and *N*,*N*-dimethylbenzamide. The resulting chloromethyleneiminium salts react with suitable nucleophiles yielding iminium salts, but self-condensation reactions are frequently encountered when proton loss from the iminium salt can occur. This is illustrated in Scheme 2 for DMA.

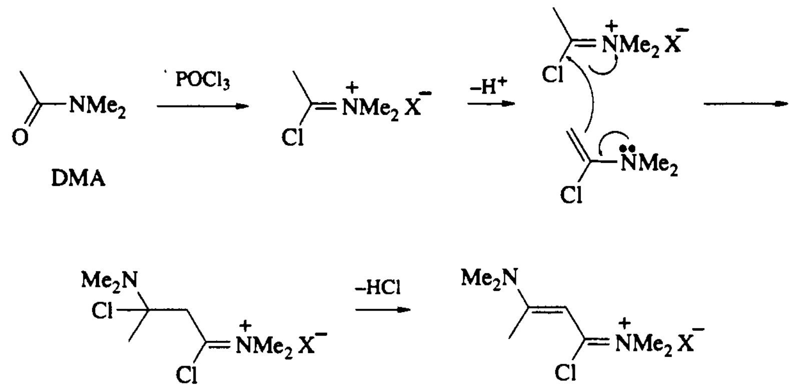

**Scheme 2**

A large number of acid chlorides have been used to convert formamide derivatives into their corresponding chloromethyleneiminium salts (**13**). These include $POCl_3$ (the most popular), $SOCl_2$, phosgene, oxalyl chloride and many others.

Solvents for the Vilsmeier–Haack reaction include DMF (the most common), $POCl_3$ and chlorinated alkanes such as dichloromethane, chloroform and tetrachloromethane. The choice of solvent and conditions is often an important consideration in Vilsmeier–Haack reactions when both mono- and di-substituted products can be formed.

## 3.5.3 REACTIONS OF AROMATIC COMPOUNDS WITH CHLOROMETHYLENIMINIUM SALTS

### 3.5.3.1 Carbocyclic Compounds

The Vilsmeier–Haack reaction of electron-rich carbocyclic aromatic compounds (Ar—H) with chloromethyleneiminium salt (**1**) gives aldehyde derivatives (Ar—CHO), generally in good yield.[1] The intermediate iminium salt (*cf.* salt **5**; Scheme 1) can be treated with hydroxylamine to obtain nitrile derivatives (Ar—CN).[5] Benzene and naphthalene are not sufficiently electron rich to participate in the Vilsmeier–Haack reaction, but polycyclic hydrocarbons, such as anthracene, do react. Benzene and naphthalene derivatives that possess an electron-releasing substituent (—OMe,—SMe,—$NMe_2$, *etc.*) afford aldehyde derivatives. Electrophilic substitution is sometimes followed by intramolecular cyclization. This is exemplified by the synthesis of several 2-substituted benzo[*b*]furan derivatives that were prepared by treating compound (**16**; Y = one or more electron-releasing substituents; R = acetal group, CN, COPh) with salt (**1**).[6] In this reaction the intermediate iminium salt (**17**) cyclizes, and, after loss of dimethylamine, compounds (**18**; R = CHO, CN, COPh; 3–78%) are isolated. Ring-formylated products are also produced in these reactions.

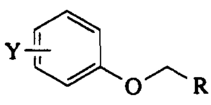

(**16**)

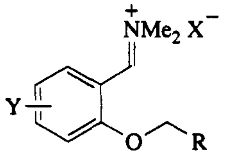

(**17**)

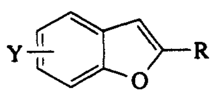

(**18**)

Y = electron-releasing group

Nonbenzenoid carbocyclic compounds also participate in the Vilsmeier–Haack reaction yielding aldehyde derivatives. Examples include azulene[7] and the cyclopentadienyl anion.[8]

### 3.5.3.2 Heterocyclic Compounds

Pyrrole,[4,9] furan, thiophene and selenophene derivatives (**19**) yield aldehyde derivatives (**20**) in the Vilsmeier–Haack reaction with salt (**1**).[1] Yields are generally good. Substitution usually occurs at positions 2 or 5 unless there are suitably located blocking groups or electron-releasing groups that direct substitution to other positions. These heterocycles (**19**) are so reactive towards electrophilic substitution that deactivating groups (*e.g.* halogen, ester) do not preclude substitution. Benzo derivatives of heterocycles (**19**) also participate in the Vilsmeier–Haack reaction.[1,10] Pyrrole derivatives (**19**)[11] and indole derivatives (**21**)[12] afford ketones (**22**) and (**23**) respectively, when allowed to react with appropriate chloromethyleneiminium salts, for example salt (**24**). Numerous other electron-rich heterocycles give aldehyde derivatives under Vilsmeier–Haack conditions, and examples include 1-substituted pyrazoles and indolizines.

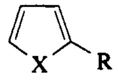

(**19**) R = H; X = NH, O, S, Se
(**20**) R = CHO; X = NH, O, S, Se
(**22**) R = COPh; X = NH, O, S, Se

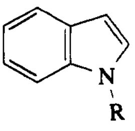

(**21**)

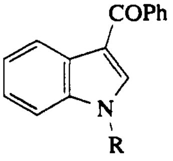

(**23**)

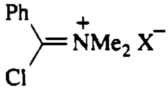

(**24**)

Electrophilic substitution is often followed by intramolecular cyclization,[2] as exemplified by the reaction of 3-cyanomethylthiophene (**25**) with (**1**) yielding the thienopyridine derivative (**26**) *via* the intermediate iminium salt (**27**).[13]

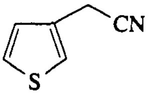

(**25**)

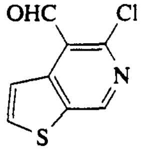

(**26**)

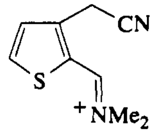

(**27**)

Several porphyrin derivatives participate in the Vilsmeier–Haack reaction giving products of substitution in either the pyrrole ring or at the methylene bridge position.[14]

## 3.5.4 REACTIONS OF ALKENE DERIVATIVES WITH CHLOROMETHYLENEIMINIUM SALTS

### 3.5.4.1 Alkene Derivatives without Electron-releasing Substituents

The reactions of alkene derivatives that do not possess electron-releasing substituents with chloromethyleneiminium salt (**1**) are illustrated for some representative examples in Scheme 3.[1] Electrophilic

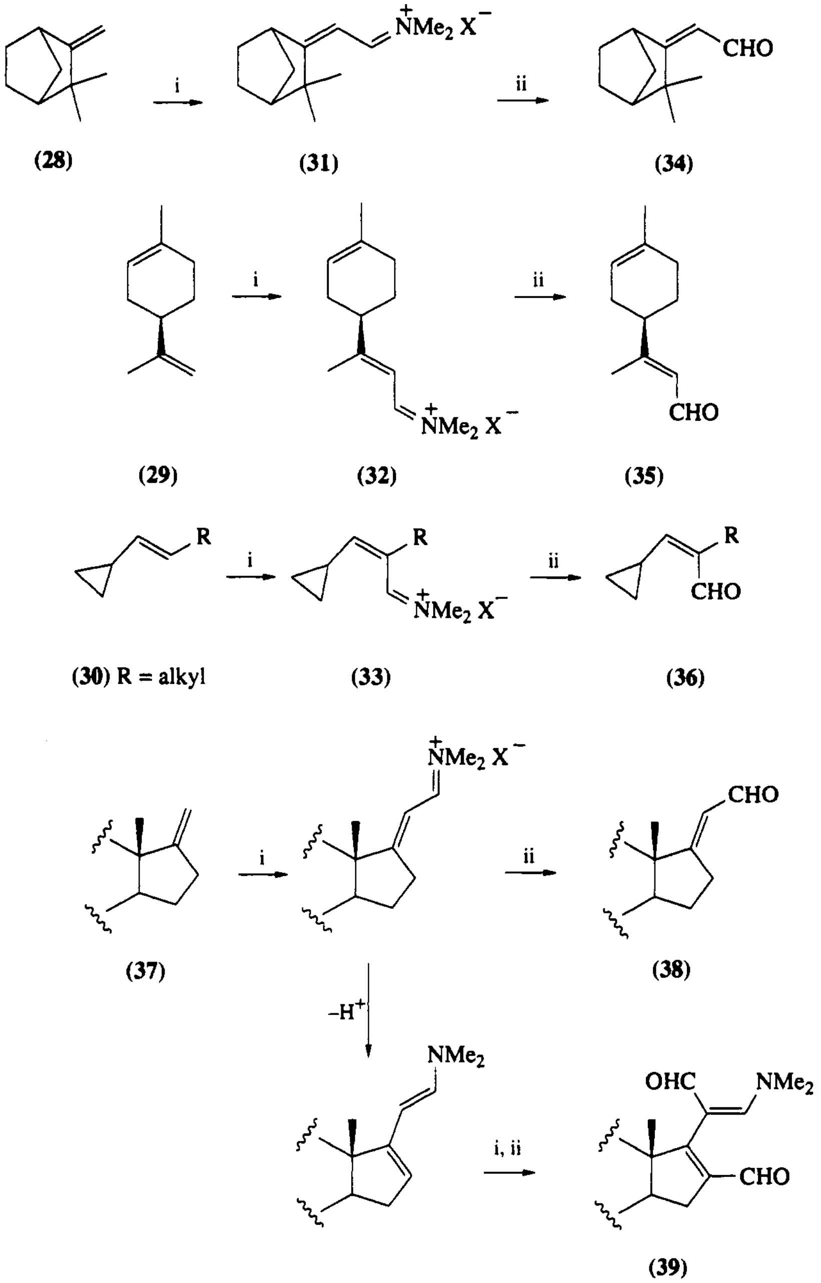

(28)
(31)
(34)
(29)
(32)
(35)
(30) R = alkyl
(33)
(36)
(37)
(38)
(39)
i
ii
i, ii
-H+
NMe2 X−
CHO
R
NMe2
OHC

i, salt (**1**); ii, hydrolysis

**Scheme 3**

substitution of camphene (**28**),[15] limonene (**29**)[16] and vinylcyclopropane derivatives (**30**)[17] by salt (**1**) affords, after loss of hydrogen chloride, the corresponding vinyliminium salts (**31–33**) which can be hydrolyzed giving the α,β-unsaturated aldehydes (**34**; 81%), (**35**; 40%) and (**36**; good yield), respectively. When proton abstraction from a vinyliminium salt can occur giving an enamine, further reaction with salt (**1**) usually occurs, eventually yielding products of polysubstitution. One illustrative example (Scheme 3) is the reaction of steroid derivative (**37**), which affords the monosubstituted product (**38**; 40%) under mild conditions (DMF:$POCl_3$, 1:1.5; 1 d) and product (**39**; 50%) of polysubstitution under forcing conditions (DMF:$POCl_3$, 1:15; 15 d).[18]

1,3-Dienes participate in the Vilsmeier–Haack reaction as illustrated by formation of aldehydes (**40**) and (**41**) from steroid derivatives (**42**) and (**43**) respectively.[19] Carbon–carbon bond migration also occurs in these two reactions and the corresponding aldehydes (**44**) and (**45**) are produced as by-products. 1,3,5-Trienes also yield aldehyde derivatives in the Vilsmeier–Haack reaction.[20,21]

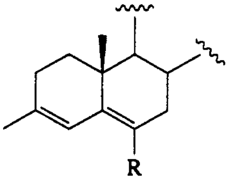

(**40**) R = CHO
(**42**) R = H

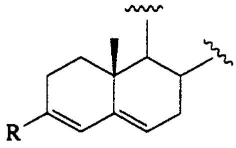

(**41**) R = CHO
(**43**) R = H

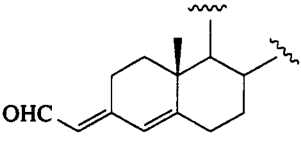

(**44**)

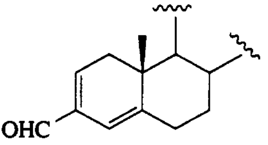

(**45**)

Numerous styrene derivatives (**46**),[22] including 1,2-dihydronaphthalene[23] and chromene[24] derivatives, react with salt (**1**) giving iminium salts (**47**) after loss of hydrogen chloride. Hydrolysis of iminium salts (**47**) gives cinnamaldehyde derivatives (**48**) and treatment with hydroxylamine affords nitriles (**49**),[25] generally in good yield. Iminium salts (**47**) can be conveniently prepared from alcohols (**50**) and related compounds if an excess of salt (**1**) is employed to promote initial dehydration of the alcohols (**50**) to the styrenes (**46**). If the aryl group in styrene derivatives (**46**) possesses a sufficient number of electron-releasing substituents then intramolecular electrophilic substitution of the iminium salt (**47**) can occur under forcing conditions, resulting in the formation of 1-dimethylaminoindene derivatives (**51**; 10–29%). Under mild conditions the corresponding cinnamaldehyde derivatives (**48**; 46–56%) are isolated.[26]

The formylation of styrene derivatives has been extended to several related alkene derivatives: indene (**52**) gives 2-formylindene (**53**; 20%),[27] polyenes (**54**)[28] and (**55**)[29] afford aldehydes (**56**; 92%) and (**57**; 29–65%), and fulvene derivative (**58**)[30] yields (**59**). In several cases, the products of monosubstitution described above are accompanied by products of polysubstitution, particularly under forcing conditions. For example, 2-phenylpropene reacts with salt (**1**) to give 4-phenylpyridine-3-carbaldehyde (**60**) after treatment with aqueous ammonium chloride solution.[31] A useful synthesis of biphenyls (**61**; 30–98%) from alcohol derivatives (**62**) and salt (**1**) has recently been reported.[32]

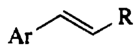

(**46**) R = H
(**47**) R = CH=$\overset{+}{\mathrm{N}}\mathrm{Me}_2$ X$^-$
(**48**) R = CHO
(**49**) R = CN

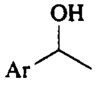

(**50**)

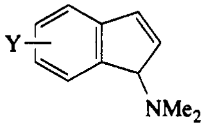

(**51**) Y = electron-releasing group

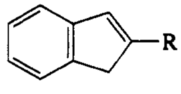

(**52**) R = H
(**53**) R = CHO

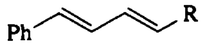

(**54**) R = H
(**56**) R = CHO

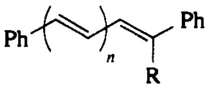

*n* = 1, 2, 3 (**55**) R = H
(**57**) R = CHO

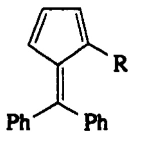

**(58)** R = H
**(59)** R = CHO

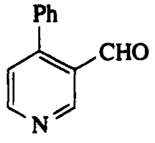

**(60)**

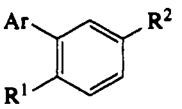

**(61)**

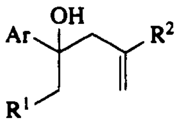

**(62)**

### 3.5.4.2 Alkene Derivatives with Electron-releasing Substituents and their Equivalents

Numerous alkene derivatives that possess one electron-releasing substituent have been found to react with salt (**1**).[1] These include enamines, enamides, enecarbamates, enol ethers and enol acetates. Electrophilic substitution of these alkene derivatives occurs readily, yielding iminium salts that have found substantial use in synthesis.

Enamine derivatives (**63**) give salts (**64**) when treated with salt (**1**) and these salts (**64**) form pyrazole derivatives (**65**; 18–64%) when treated with hydrazine (Scheme 4).[33]

The dienamines (**66**)[34] and (**67**)[35] afford the corresponding iminium salts (**68**) and (**69**) resulting from disubstitution. Hydrolysis of these salts gives the dialdehyde derivatives (**70**; 35%) and (**71**; 36%) respectively. Salt (**68**) forms pyridine-3-carbaldehyde (97%) when treated with aqueous ammonium chloride solution.

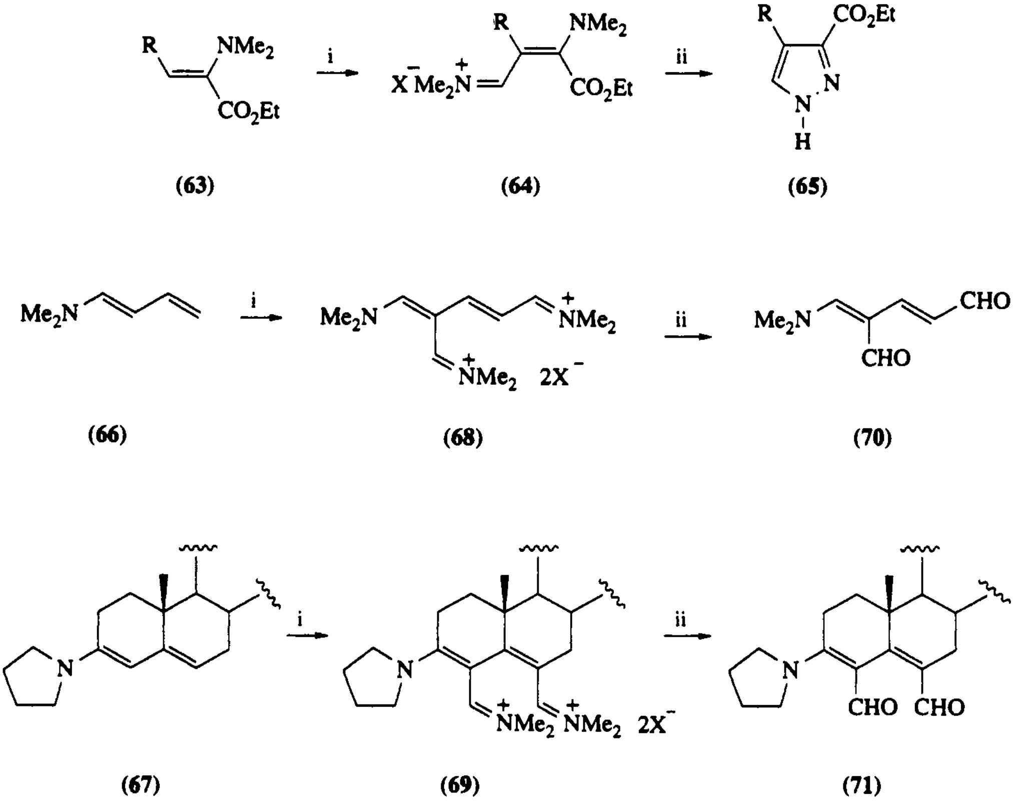
R
NMe2
CO2Et
i
R
NMe2
X⁻ Me2N⁺
CO2Et
ii
R
CO2Et
N
N
H
(63)
(64)
(65)
Me2N
i
Me2N
NMe2⁺
NMe2⁺ 2X⁻
ii
Me2N
CHO
CHO
(66)
(68)
(70)
N
i
N
NMe2⁺ NMe2⁺ 2X⁻
ii
N
CHO CHO
(67)
(69)
(71)

i, salt (**1**); ii, hydrolysis

**Scheme 4**

Several enamides, for example compound (**72**; Scheme 5), have been used as precursors to 1-substituted-2-pyridone derivatives (**73**) and pyridine-3-carbaldehyde derivatives (**74**; 14–69%).[36] Salt (**1**) promotes dehydration of tautomers (**75b**) of 2-acetylbenzamide derivatives (**75a**) to give enamides (**76**), which are converted by further reaction with salt (**1**) into iminium salts (**77**). Hydrolysis of these salts yields aldehydes (**78**; 81–99%; Scheme 5).[37] Enecarbamates, such as (**79**), give formylation products (**80**; 26–94%) in the Vilsmeier–Haack reaction (Scheme 5).[38]

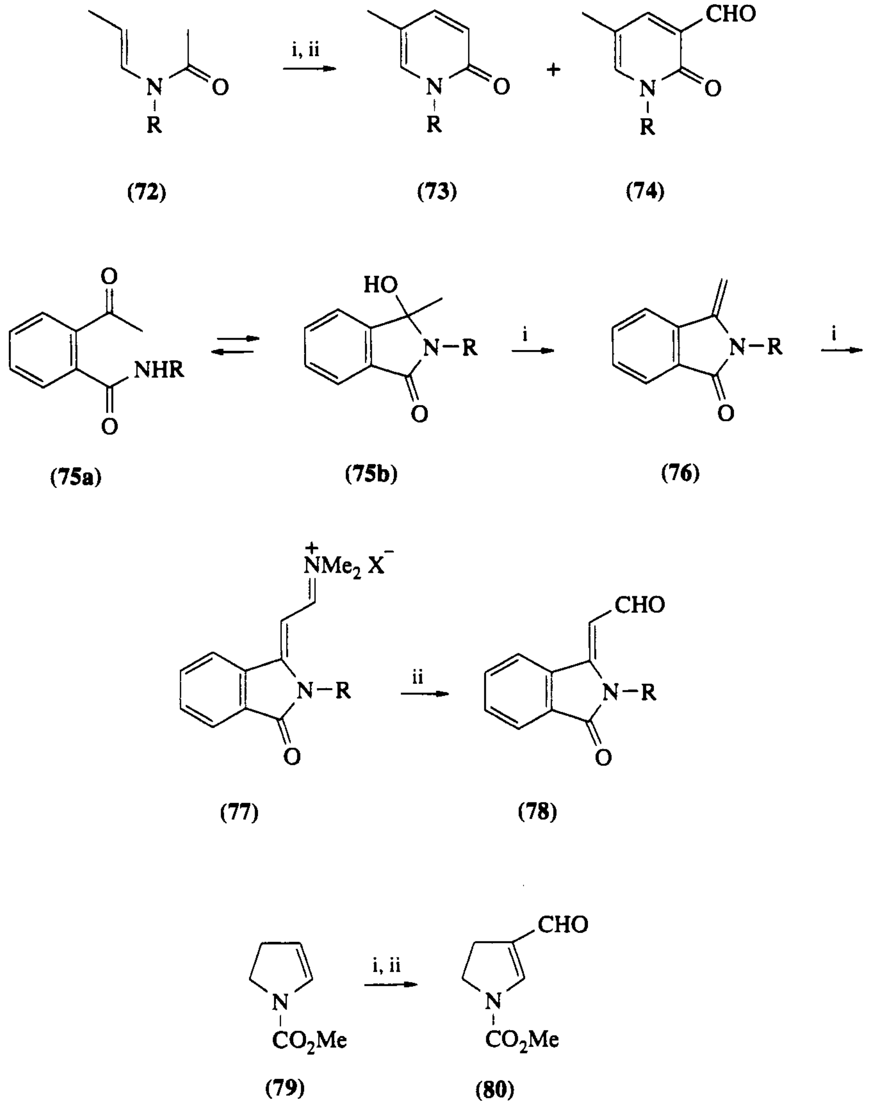

i, salt (**1**); ii, hydrolysis

**Scheme 5**

Enol ethers represented by the general structure (**81**; Scheme 6) and their vinylogs react with salt (**1**) to give iminium salts (**82**).[39a] Enol ethers (**81**) are often prepared *in situ* by treating acetals or ketals (**83**) with salt (**1**). Acetals (**83**) react with an excess of chloromethyleniminium salt (**1**) to provide iminium salts (**82**; $R^1$ = H, $R^2$ = alkyl or phenyl) that are hydrolyzed under basic conditions to afford β-dimethylaminoacrolein derivatives (**84**; 48–89%).[39b] Synthetically useful vinylamidinium salts (**85**; $R^1$ = H)[40] can be prepared by *O*-methylation of compounds (**84**) followed by treatment with dimethylamine. Ketals (**83**; $R^3$ = Et) similarly yield iminium salts (**82**; $R^3$ = Et, $R^1$ = alkyl or phenyl, $R^2$ = alkyl) from which either β-ethoxyacrolein derivatives (**86**; $R^3$ = Et; 59–92%) are isolated after basic hydrolysis or vinylamidinium salts (**85**; 49–56%) are produced after treatment with dimethylamine.[39c] An interesting reaction of 1-methoxycyclohexa-3,6-diene (**87**) and derivatives has recently been reported: this compound gives chlorobenzene-2,4,6-tricarbaldehyde (**88**; 44%) in the Vilsmeier–Haack reaction.[41]

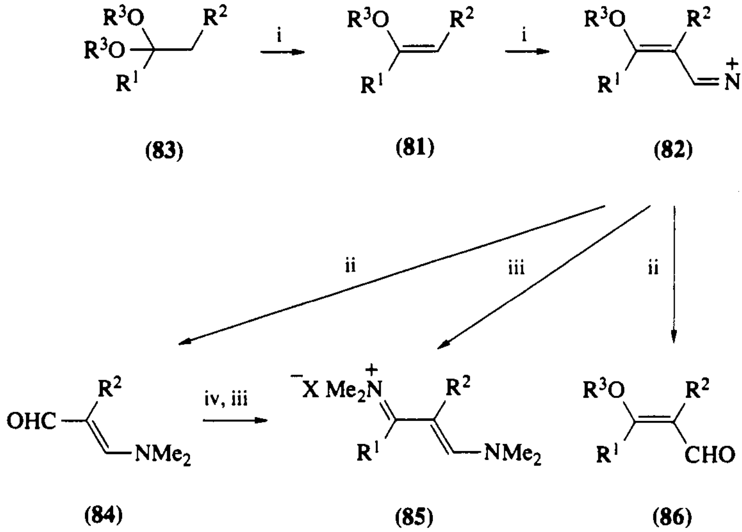

i, salt (**1**); ii, hydrolysis; iii, $Me_2NH$; iv, *O*-methylation

**Scheme 6**

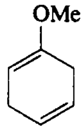

**(87)**

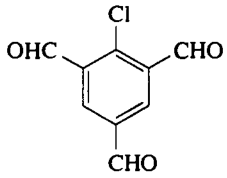

**(88)**

## 3.5.5 REACTIONS OF ACTIVATED METHYL AND METHYLENE GROUPS WITH CHLOROMETHYLENEIMINIUM SALTS

### 3.5.5.1 Aldehydes and Ketones

The reaction of ketone derivatives (**89**) with chloromethyleneiminium salt (**1**) gives iminium salts (**90**) which yield, after hydrolysis, β-chloroacrolein derivatives (**91**; Scheme 7).[42] Numerous β-chloroacrolein derivatives have been prepared by this method and yields are generally moderate to good. β-Chloroacrylonitrile derivatives (**92**) are also available in good yield from iminium salts (**90**; $R^2$ = H) by treatment with hydroxylamine.[43] Ketals (**93**) can be prepared from iminium salts (**90**) by treatment with the monosodium salt of ethylene glycol followed by hydrolysis under basic conditions (32–69%).[44] If the group $R^1$ in ketone (**89**) is aromatic and electron rich, then intramolecular electrophilic substitution of iminium salt (**90**) can occur giving a 1-dimethylamino-3-chloroindene derivative (**94**). The general reaction (**89**) → (**91**) depicted in Scheme 7 has been extended to vinylogs of aldehydes and ketones (**89**).[45]

Ketones that possess active methyl or methylene groups at both α-positions can undergo polysubstitution reactions as exemplified by the Vilsmeier–Haack reaction of dibenzyl ketone (**95**), which affords 3,5-diphenylpyrone (**96**; 35%).[46] Products of polysubstitution are also observed in the Vilsmeier–Haack reaction of 1,3-diketones: a useful synthesis of 2,4-dichlorobenzaldehyde derivatives from 1,3-diketones has recently been reported.[47] Cyclohexenone derivatives similarly yield products of polysubstitution.[48]

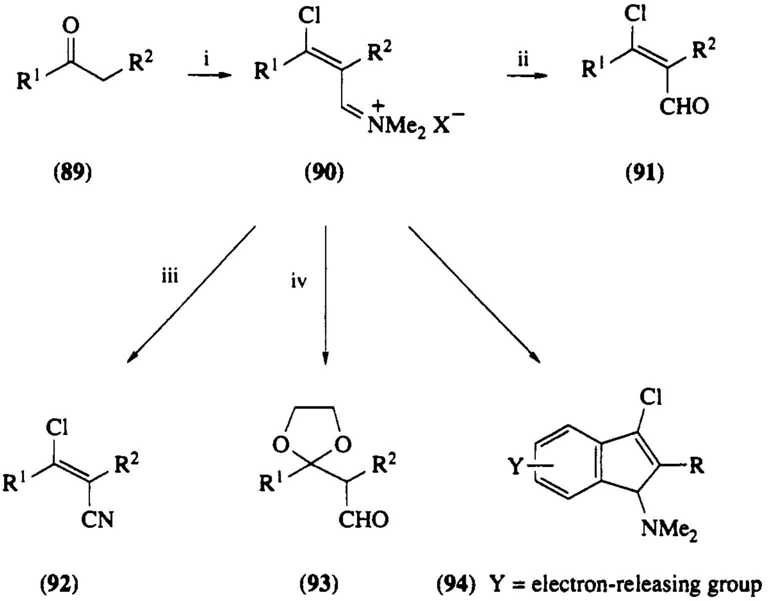

i, salt (**1**); ii, hydrolysis; iii, $NH_2OH$; iv, $NaOCH_2CH_2OH$

Scheme 7

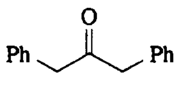

**(95)**

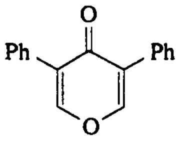

**(96)**

### 3.5.5.2 Carboxylic Acids

Arylacetic acid derivatives (**97**) react with salt (**1**) to give vinylamidinium salts (**98**; R = Ar; Scheme 8). Carbon dioxide is evolved during this reaction. The corresponding vinylamidinium salts (**98**; R = alkyl) are not available from acetic acid derivatives, but can be readily obtained by treating malonic acid derivatives (**99**; R = alkyl) with salt (**1**). Cyanoacetic acid (**100**) affords vinylamidinium salt (**101**) and glycine hydrochloride (**102**) gives salt (**103**) with salt (**1**). In the latter reaction, *N*-substitution also occurs (see Section 3.5.6.2). Bromoacetic acid (**104**) does not give amidinium salt (**105**) but instead yields salt (**106**; Scheme 8), which can also be prepared from malonic acid and salt (**1**). The vinylamidinium salts (**98**), (**101**) and (**103**) are useful precursors of malondialdehyde derivatives (**107**; R = alkyl or aryl, R = CN, R = $NH_3^+Cl^-$) and salt (**106**) is a precursor of triformylmethane (**108**).[1] The acid chloride of cyclohexa-2,6-dienecarboxylic acid yields 1,3,5-triformylbenzene (62%) when treated with salt (**1**).[49]

### 3.5.5.3 Amides, Lactams and Lactones

Amides, for example *N*,*N*-dimethylcarboxamides, represented by the general formula (**109**), react with salt (**1**) to yield chloroiminium salts (**110**; Scheme 9). Hydrolysis of these salts affords 2-dimethylaminomethylene amide derivatives (**111**). If group R in salt (**110**) is hydrogen, further reaction with salt (**1**) is possible, giving chloroiminium salts (**112**). Hydrolysis of these salts (**112**) affords aldehydes (**113**).

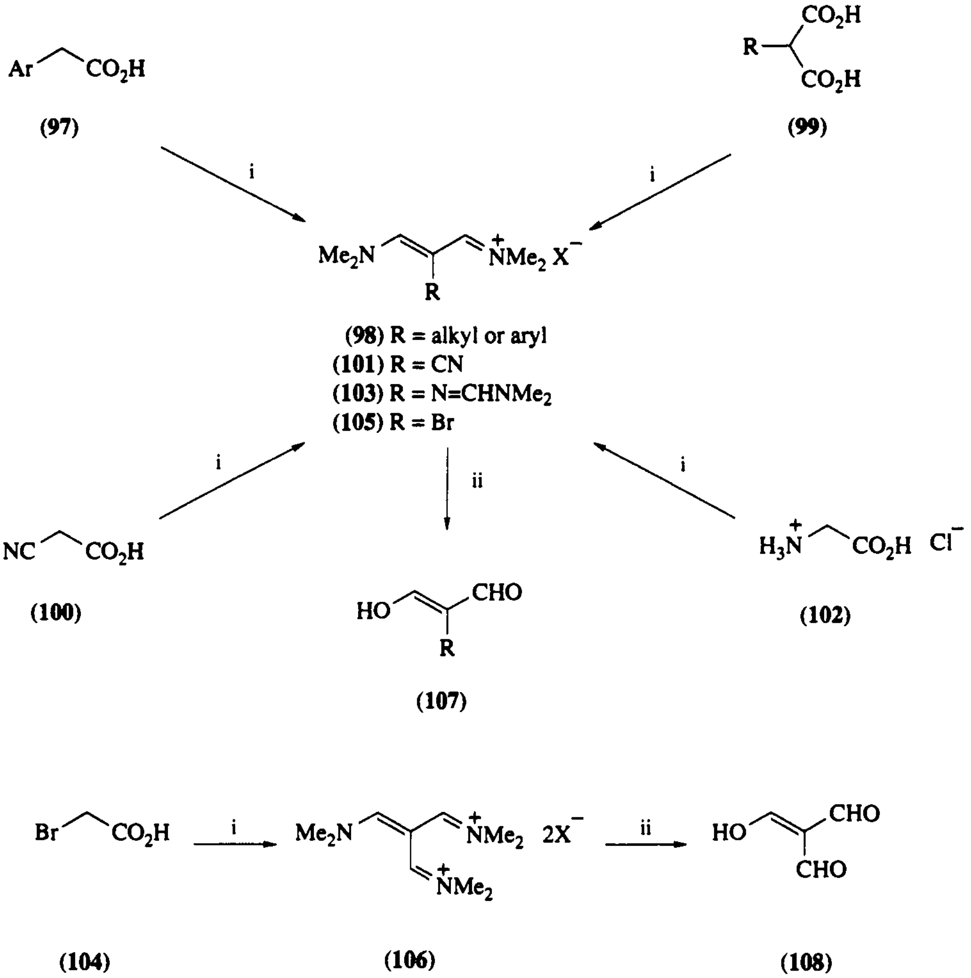

i, salt (**1**); ii, hydrolysis

**Scheme 8**

An excellent method for preparing quinolines from acetanilide derivatives (**114**) and salt (**1**) has been reported.[50] Acetanilide derivatives (**114**) are generally disubstituted (*cf.* Scheme 9) yielding the corresponding chloroiminium salts (**115**). These salts (**115**) undergo an intramolecular electrophilic substitution giving, after loss of dimethylamine, iminium salts (**116**). Hydrolysis of salts (**116**) gives aldehydes (**117**; 0–78%). Propionanilides give 3-substituted-2-chloroquinoline derivatives (28–95%) in an analogous reaction. Acetyl derivatives of aminothiophenes and aminopyrazoles similarly yield thienopyridine and pyrazolopyridine derivatives, respectively. 2-Quinolone derivatives (**118**) are available from *N*-substituted acetanilides (**119**) and related compounds.[51]

Lactams represented by the general formula (**120**), including 2-oxyindole derivatives, yield 2-dimethylaminomethylene derivatives (**121**; *cf.* Scheme 9) or chloroaldehyde derivatives (**122**; *cf.* Scheme 7) when treated with salt (**1**).[52] Lactams (**120**; R = H) react with formamide/$POCl_3$ complex to give pyrimidine derivatives (**123**). $\Delta^3$-Pyrrolidin-2-ones (**124**) behave as vinylogous amides and react with salt (**1**) or DMF/$POBr_3$ to provide iminium salts (**125**; Y = Cl, Br), which yield pyrrole-2-carbaldehydes (**126**; Y = Cl, Br) after hydrolysis. Lactone derivatives (**127**) generally behave analogously to lactam derivatives: products (**128**) and/or (**129**) are formed.[1,53]

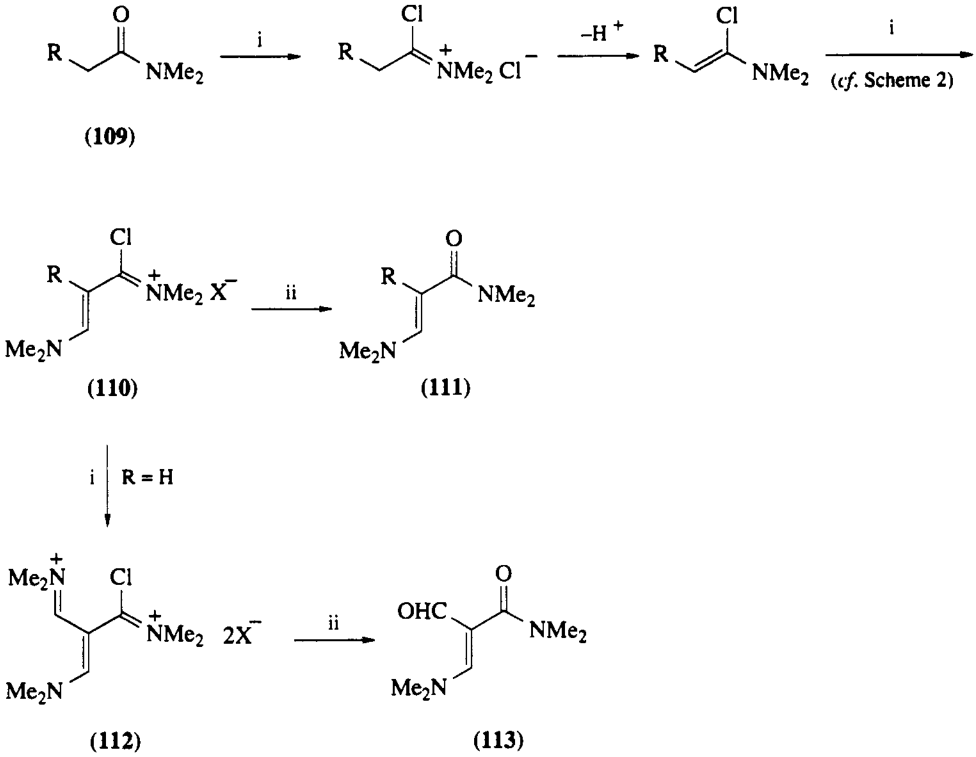
(109)
i
$-H^+$
i
(cf. Scheme 2)
(110)
ii
(111)
i
R = H
(112)
ii
(113)

i, salt (**1**); ii, hydrolysis

**Scheme 9**

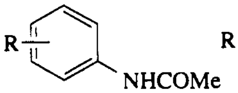

**(114)**

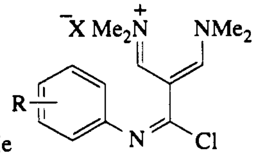

**(115)**

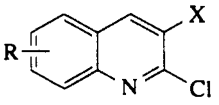

**(116)** X = CH=$\overset{+}{N}Me_2$ $X^-$

**(117)** X = CHO

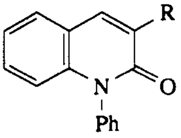

**(118)**

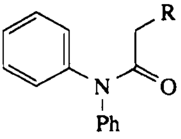

**(119)**

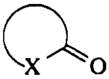

**(120)** X = NR

**(127)** X = O

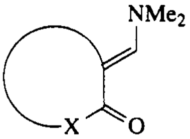

**(121)** X = NR

**(128)** X = O

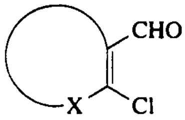

**(122)** X = NR

**(129)** X = O

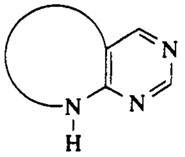

**(123)**

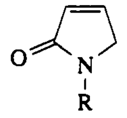

**(124)**

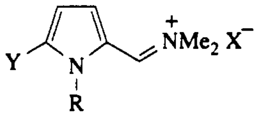

**(125)** Y = Cl, Br

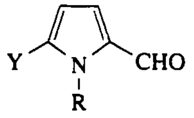

**(126)** Y = Cl, Br

### 3.5.5.4 Nitriles

Acetonitrile (**130**) and malononitrile (**131**) both react with salt (**1**) to yield products of disubstitution (Scheme 10). The monosubstituted intermediates (**132**) and (**133**) react at carbon and nitrogen, giving, after hydrolysis, products (**134**) and (**135**), respectively. Salt (**135**) affords the heterocycle (**136**) when treated with ammonia.[1,54]

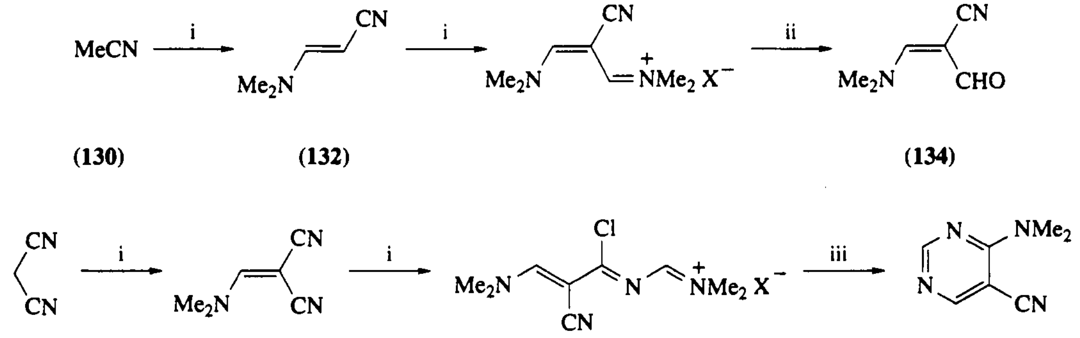

i, salt (**1**); ii, hydrolysis; iii, NH$_3$

**Scheme 10**

### 3.5.5.5 Benzylic Methyl and Methylene Groups

Benzylic methyl groups in nitrogen-containing aromatic compounds represented by general formula (**137**) and salt (**1**) afford products of monosubstitution (**138**) or products of disubstitution (**139**; *cf.* Scheme 1). Hydrolysis of salt (**139**) affords malondialdehyde derivatives (**140**) and this represents an important method of synthesizing these aldehyde derivatives (**140**).[1,55] Benzylic methylene groups behave similarly, yielding the corresponding products of monosubstitution.[1,56] Representative heterocycles that participate in this reaction include 4-methylpyridine and 6-methylpyrimidine. Several nitrogen-containing heterocycles that posses appositely located methyl and amine groups, for example pyrazine derivative (**141**), react with salt (**1**) giving, after loss of hydrogen chloride, amidinium salts like (**142**). After reaction of a second molecule of salt (**1**) at the methyl group in salt (**142**), giving salt (**143**), cyclization and loss of dimethylamine occur, yielding iminium salt (**144**). Hydrolysis of this salt gives aldehyde (**145**). Heterocyclic iminium salts (**146**) react with salt (**1**) giving, after loss of hydrogen chloride, monosubstituted (**147**) or disubstituted (**148**) products. Oxonium salts react similarly.[1] 2,4,6-Trinitrotoluene (**4**) and related compounds react with salt (**1**) to give iminium salts (**11**), which can be converted into aldehyde derivatives (**12**) by hydrolysis (Scheme 1).[1]

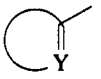

**(137)** Y = N

**(146)** Y = $\overset{+}{N}R$

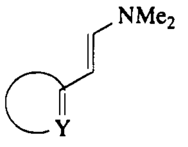

**(138)** Y = N

**(147)** Y = $\overset{+}{N}R$

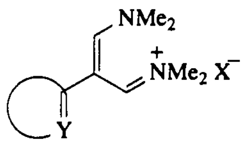

**(139)** Y = N

**(148)** Y = $\overset{+}{N}R$

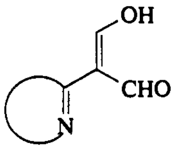

**(140)**

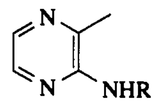

**(141)**

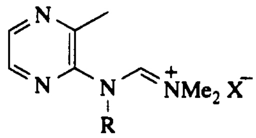

**(142)**

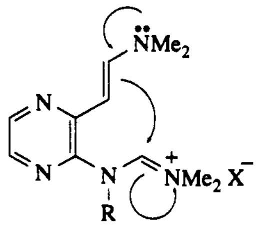

**(143)**

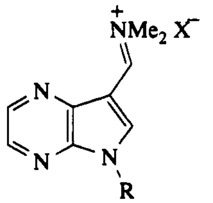

**(144)**

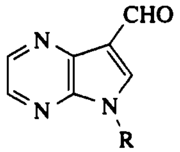

**(145)**

## 3.5.6 REACTIONS OF NONCARBON NUCLEOPHILES WITH CHLOROMETHYLENE IMINIUM SALTS

### 3.5.6.1 Oxygen Nucleophiles

Formates have been prepared by the reaction of chloromethyleneiminium salts with derivatives of alcohols and phenols. Yields are generally good.[57]

The synthesis of several oxygen-containing heterocycles from phenolic precursors using the Vilsmeier–Haack reaction has been achieved (Schemes 11 and 12). Salicylaldehyde (**149**) and chloromethyleneiminium salt (**150**) afford, after treatment with perchloric acid, the benzopyrylium salt (**151**) which yields coumarin (**152**) when treated with aqueous base.[58] Umbelliferone (**153**) has been prepared (62%) by treating DMF with DMA in the presence of POCl3 and condensing the resulting iminium salt (**154**) with resorcinol (**155**).[59] 2,4-Dihydroxydeoxybenzoin (**156**) and chloromethyleneiminium salt (**1**) give isoflavone (**157**), presumably by cyclization of the intermediate (**158**) and loss of dimethylamine. 2-Hydroxyacetophenone (**159**) and related compounds afford aldehyde derivatives (**160**) in the Vilsmeier–

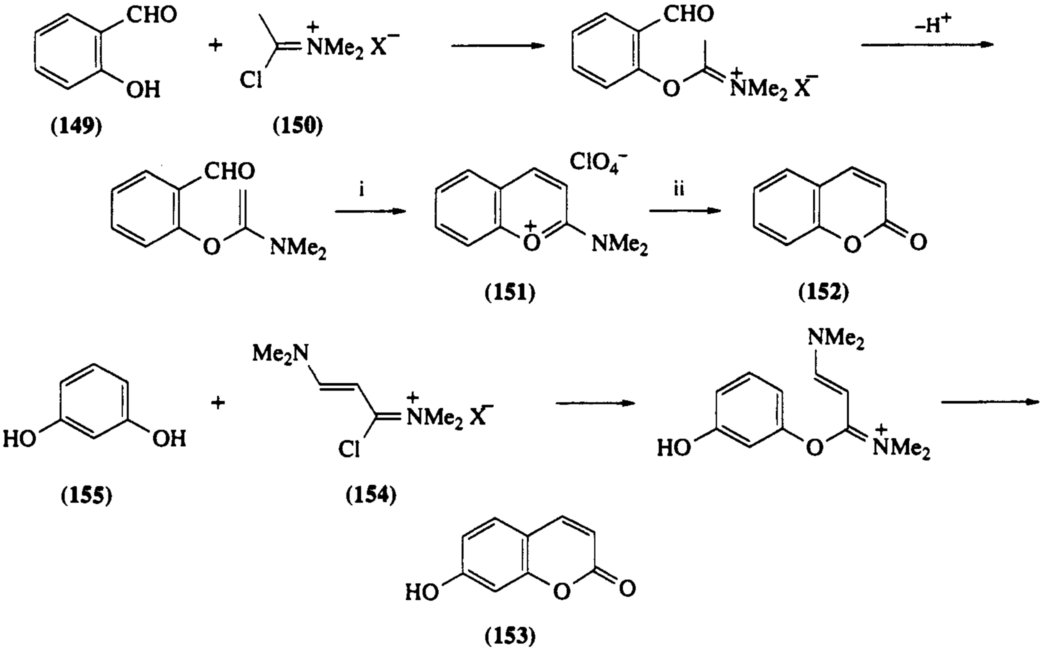

**Scheme 11**

Haack reaction in good yield. In this reaction, the intermediate salt (**161**) cyclizes with loss of dimethylamine giving chromenone (**162**), which then undergoes formylation, yielding product (**160**).

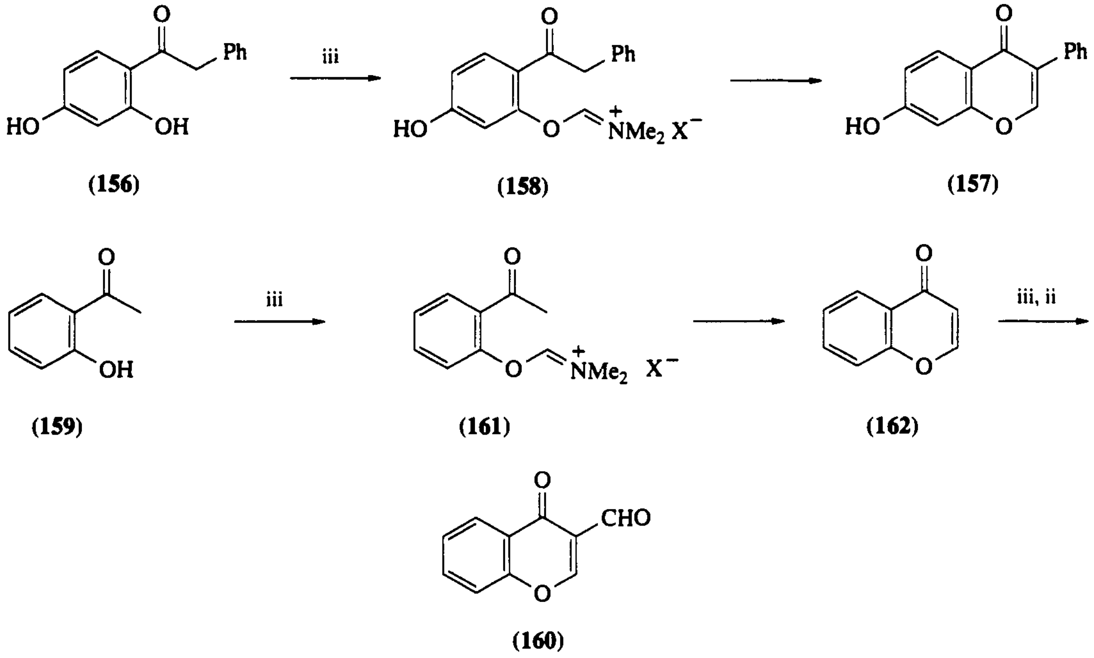

i, HClO$_4$; ii, hydrolysis; iii, salt (**1**)

Scheme 12

### 3.5.6.2 Nitrogen Nucleophiles

Primary amines (R$^1$NH$_2$) react with salt (**1**) to give, after loss of hydrogen chloride, amidine derivatives (**163**).[1] Salts (**164**) derived from urea derivatives react similarly, giving guanidines (**165**).[60]

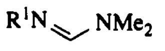

**(163)**

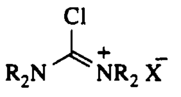

**(164)**

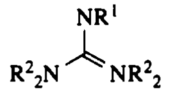

**(165)**

Lactams represented by the general structure (**120**; R = H) are *N*-formylated to give products (**120**; R = CHO) in the Vilsmeier–Haack reaction unless the amide has an available α-hydrogen atom in which case products (**121**) and (**122**) are formed (see Section 3.5.5.3).[1]

## 3.5.7 MISCELLANEOUS REACTIONS OF CHLOROMETHYLENEIMINIUM SALTS

### 3.5.7.1 Hydrazones and Semicarbazones

Hydrazones (**166**) react with chloromethyleneiminium salt (**1**) giving, after hydrolysis, aldehydes (**167**; Scheme 12). In this transformation the hydrazones (**166**) are clearly behaving as aza–enamines.[1,61] Hydrazones (**168**) and (**169**) react with chloromethyleneiminium salt (**1**) at both the methyl group and at nitrogen to yield the corresponding iminium salts (**170**) and (**171**), which cyclize with loss of dimethylamine to provide iminium salts (**172**) and (**173**), respectively. Hydrolysis of these salts (**172**) and (**173**) affords pyrazole-4-carbaldehyde derivatives (**174**) and (**175**; 72–96%; Scheme 13).[1] Product (**174**) can also be prepared from semicarbazone (**176**).

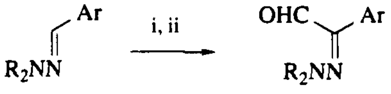

**(166)** **(167)**

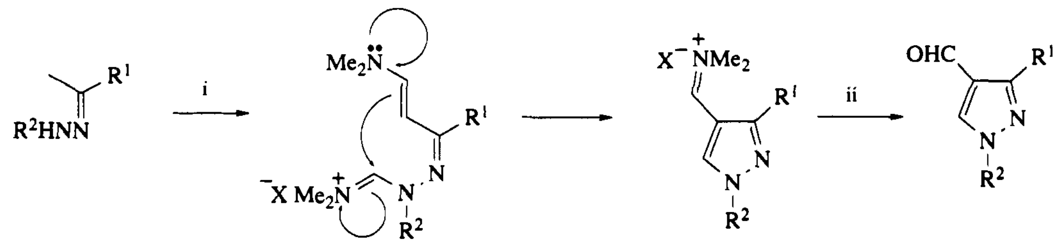

**(168)** $R^2 = H$
**(169)** $R^2 = Ph$
**(176)** $R^2 = NHCONH_2$

**(170)** $R^2 = H$
**(171)** $R^2 = Ph$

**(172)** $R^2 = H$
**(173)** $R^2 = Ph$

**(174)** $R^2 = H$
**(175)** $R^2 = Ph$

i, salt (**1**); ii, hydrolysis

**Scheme 13**

### 3.5.7.2 Enamidines

Enamidine derivatives (**177**) afford pyridinimines (**178**; 31–75%) in the Vilsmeier–Haack Reaction.[62]

### 3.5.7.3 Other Groups

Other groups[1] that react with chloromethyleneiminium salts include hydroxylamines,[63] hydrazines,[64] oximes,[65] imines, azines, anhydrides,[66] imides[67] and ketene *O*-alkyl-*O*′-silyl acetal derivatives;[68] however, reactions with these compounds have been relatively infrequent.

Heterocycles represented by the general structure (**179**) afford ring-expanded products (**180**) in the Vilsmeier–Haack reaction[53,69] with chloromethyleneiminium salt (**13**).

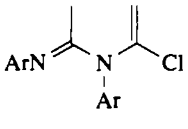

**(177)**

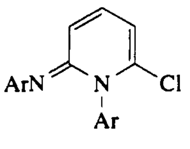

**(178)**

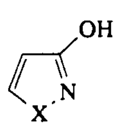

**(179)** X = O, S

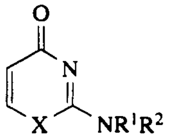

**(180)** X = O, S

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# 3.6

# Acylation of Esters, Ketones and Nitriles

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## 3.6.1 INTRODUCTION

In 1887, Claisen and Lowman[1] reported that the condensation of 2 mol of an ester, such as ethyl acetate, in the presence of base gave the β-keto ester, ethyl acetoacetate (ethyl 3-oxobutanoate; equation 1). The intramolecular equivalent was recognized by Dieckmann in 1894.[2] He found that heating an adipic acid ester with sodium and a trace of alcohol led to cyclization, with the formation of a cyclopentanone (equation 2). The reaction was, at an early stage, extended to the acylation of ketones. Claisen himself reported the base-catalyzed reaction of acetophenone and ethyl benzoate to give dibenzoylmethane in 1887.[3] This reaction, too, has an intramolecular parallel. The acylation of ketones with esters and other acid derivatives is sometimes called a Claisen condensation, although this usage is criticized by some writers and avoided by others. A widely used example of ketone acylation is the synthesis of α-formyl (hydroxymethylene) ketones (equation 3). Intramolecular variants of this reaction include the classical synthesis of dimedone (Scheme 1).

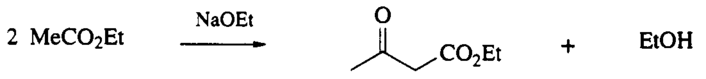

(1)

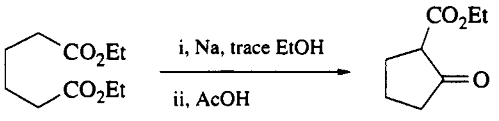

(2)

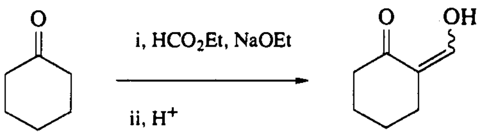

(3)

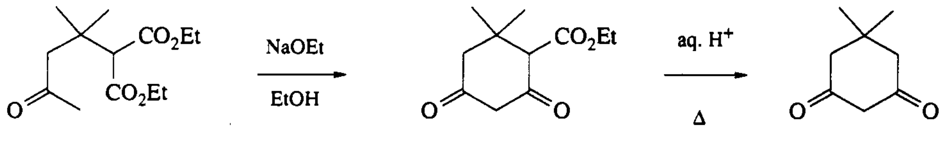

**Scheme 1**

Ketones can be acylated in the presence of acid catalysts such as boron trifluoride, polyphosphoric acid and other proton acids; acid anhydrides are typically used as acylating agents (equation 4). Other anion-stabilizing groups, such as nitrile, have been used in the carbon–carbon bond-forming step. These reactions are also described after their discoverers as the Thorpe and Thorpe–Ziegler reactions (equation 5).

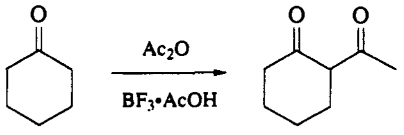

(4)

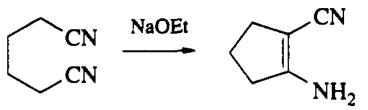

(5)

Modern synthetic practice frequently requires the use of methods more specific than those outlined above. Much attention has been focused on the 'mixed' Claisen or Dieckmann reaction, *i.e.* the acylation of one ester by another, or its intramolecular equivalent, the regioselective cyclization of an unsymmetrical diester. A similar problem arises with the acylation of unsymmetrical ketones. This chapter thus describes the inter- and intra-molecular carbon–carbon bond-forming reactions in which a delocalized enolate anion (or close equivalent) reacts at an $sp^2$ carbon atom in an addition–elimination sequence, as well as the acid-catalyzed equivalent employing an enol. In Table 1 we list the potential nucleophiles and the electrophiles that have been employed in these reactions, although not every possible combination has been reduced to synthetic practice. Table 2 gives details of acid-catalyzed acylations (see Section 3.6.4.3).

**Table 1** Reactions Involving an Enolate Anion or Equivalent

| *Potential nucleophiles* | *Electrophiles* |
|---|---|
| Esters | Esters |
| Carboxylic acids | Nitriles |
| Nitriles | Acyl chlorides |
| Ketones | Acid anhydrides |
| Amides | Acyl cyanides |
| | Carbon dioxide |
| | Alkyl dialkoxyphosphinyl formate |
| | Acyl imidazoles |
| | Thiol esters |
| | Thio esters |

**Table 2** Acid-catalyzed Acylations

| *Nucleophiles* | *Electrophiles* |
|---|---|
| Ketones | Acid anhydrides |
| | Acyl chlorides |
| | Carboxylic acids |

The reactions have been comprehensively reviewed in *Organic Reactions*; the acylation of esters in Volume 1 (1942),[4] the acylation of ketones in Volume 8 (1954)[5] and the Dieckmann and Thorpe–Ziegler reactions in Volume 15 (1967).[6] More recent reviews are provided by House[7] and in a book on carbon–carbon bond-forming reactions.[8] Specific examples of many of these reactions are given in '*Organic Syntheses*'.

## 3.6.2 MECHANISM

The condensation of one ester with another under basic conditions is generally thought to proceed by an ionic mechanism involving anionic species and the transfer of electron pairs.[4] Substantial evidence supports this view, but recent work does indicate the possibility of a single electron transfer (SET) process in some cases.

For an ester with two hydrogens on the α-carbon atom, the accepted mechanism, using sodium ethoxide as catalyst, is shown in Scheme 2. With bases such as sodium ethoxide, with $pK_a \approx 18$, each of the steps leading to the conjugate base of the keto ester is reversible and the initial equilibrium with the ester ($\mathrm{p}K_a \approx 25$) is not favored. However, the overall process is driven towards the product by the formation of the anion of the β-keto ester ($\mathrm{p}K_a \approx 11$) in the final step. For typical aliphatic esters, the equilibrium constant for the overall reaction shown in equation (6) is approximately 1. Thus, the equilibrium can be moved to the right by the use of excess ester or by the removal of ethanol.

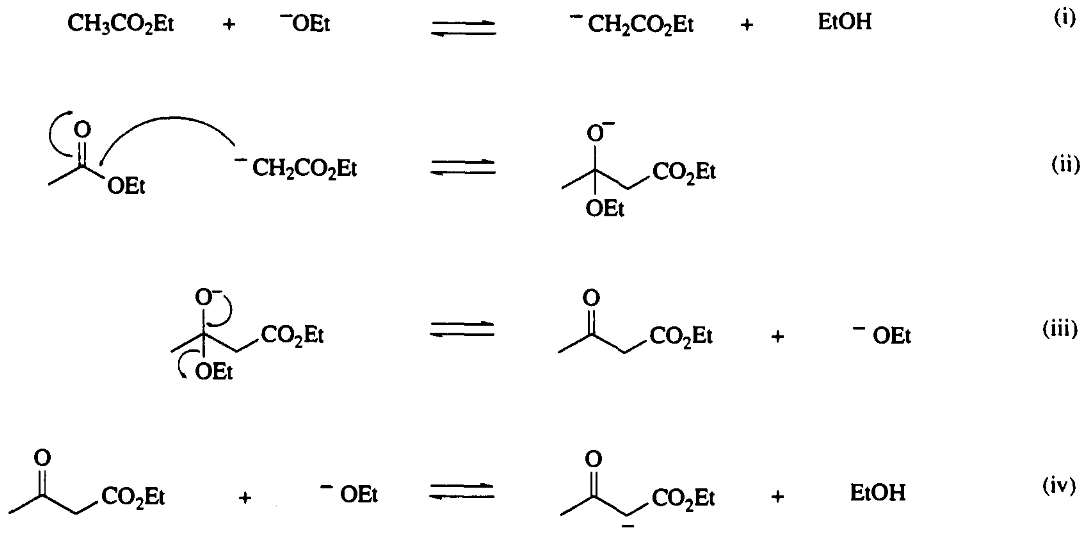

CH3CO2Et + −OEt ⇌ −CH2CO2Et + EtOH (i)
O OEt −CH2CO2Et ⇌ O− CO2Et OEt (ii)
O− CO2Et OEt ⇌ O CO2Et + −OEt (iii)
O CO2Et + −OEt ⇌ O CO2Et − + EtOH (iv)

**Scheme 2**

$$2\ \text{ester} + \text{EtO}^- \rightleftharpoons \text{keto ester anion} + \text{EtOH} \qquad (6)$$

In cases where the starting ester contains only one α-hydrogen, *e.g.* ethyl 2-methylpropanoate, the procedure leads to a β-keto ester disubstituted on the α-carbon atom, $Me_2CHCOCMe_2CO_2Et$. Such reactions are not effected by the use of ethoxide ion, which is not a strong enough base to form the conjugate base of the keto ester product. Strong bases, such as sodium hydride, are sufficient to deprotonate the starting ester, the β-keto ester product and ethanol. In the overall equilibrium, the latter two reactions favor products, while the first favors reactants. On balance, the equilibrium favors products and good yields are obtained. A discussion of the equilibria involved is contained in ref. 9.

Processes occurring in the acid-catalyzed acylation of ketones are discussed in Section 3.6.4.

Work by Ashby *et al.* has established the intermediacy of radicals in a variety of processes previously thought to be purely ionic. The Claisen condensation of ethyl *p*-nitrobenzoate with the lithium enolate of pinacolone gave an EPR-active species whose rate of formation and decay indicated that it was on the pathway to the product.[10] The postulated mechanism is shown in Scheme 3. However, this was the only example of SET observed by this group for this reaction and the intermediacy of the radical anion of the ester in this case is plausible but not proved.[11]

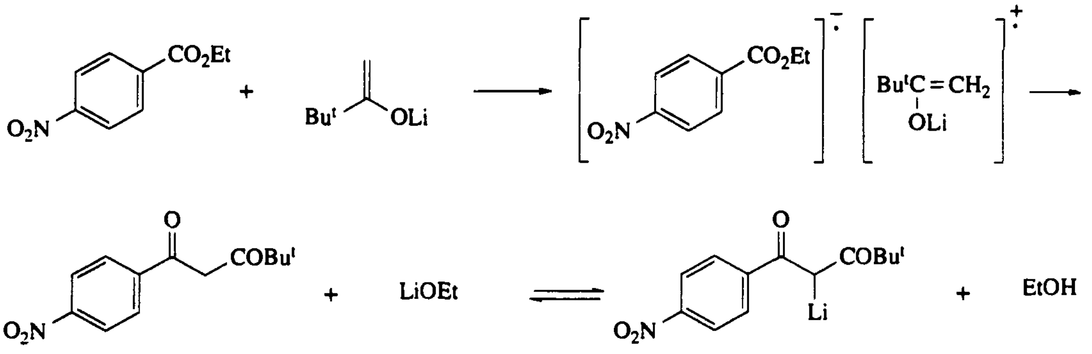

**Scheme 3**

## 3.6.3 THE ACYLATION OF ESTERS

### 3.6.3.1 Introduction

The classic acetoacetic ester condensation, named after Claisen but modeled closely on the conditions reported by Geuther in 1863,[12] employed sodium ethoxide as a base in the self-condensation of ethyl acetate. Yields may be increased by removal of the ethanol formed in the reaction and also by the use of stronger bases, including sodium, sodium amide, bromomagnesium diisopropylamide, sodium hydride or potassium hydride, dimsyl sodium in dimethyl sulfoxide, or various lithium dialkylamide bases (for leading references see ref. 13). Sodium hydride may be used with a catalytic amount of ethanol; the alkoxide is continuously replenished as the reaction proceeds and effects the condensation. The reaction has been performed in a variety of aprotic solvents, such as toluene or THF. α,α-Disubstituted esters do not undergo efficient Claisen condensation using sodium ethoxide, as described above. Very similar procedures are used for the intramolecular variant of the reaction, the Dieckmann cyclization, particularly in the formation of five- and six-membered rings.

### 3.6.3.2 Mixed Esters and Unsymmetrical Diesters

As a reaction of synthetic utility the simple Claisen condensation is limited to the self-condensation of esters possessing one or, more usually, two hydrogen atoms α to the ester carbonyl group. Likewise the original Dieckmann reaction is of most use with symmetrical diesters. However, on many occasions a more complex or less symmetrical β-keto ester is required and the literature continues to provide examples of the synthetic art, where the problem of mixed esters is overcome. A simple condensation of two esters, $R^1CH_2CO_2Et$ and $R^2CH_2CO_2Et$ with base may provide a mixture of four β-keto esters. These are not all formed in the same yield, as the product of reaction between the least hindered carbanion and the least hindered carbonyl group is likely to predominate. However, the reaction is of little synthetic utility today and a number of modifications to the original procedure have allowed considerable scope in developing the synthesis of specific β-keto esters.

#### *3.6.3.2.1 One ester has no α-hydrogen*

One effective technique for selective reaction is to employ one ester which possesses no α-hydrogen atoms. Simple aliphatic esters such as ethyl formate, diethyl oxalate and diethyl carbonate are commonly used while, among the aromatic esters, benzoic, substituted benzoic and furoic esters are commonly employed. Self-condensation of the ester providing the carbanion is not a major problem. Examples of this reaction are given in Scheme 4; further examples are listed in the reviews. Diethyl oxalate and ethyl formate react readily in this way, although forcing conditions are often necessary with diethyl carbonate and aromatic esters.

#### *3.6.3.2.2 Preformed enolates*

In the reactions as originally described, the enolate anion of one ester is generated in the presence of another ester and, with weaker bases such as sodium ethoxide, is not generated quantitatively, leading to the possibility of mixed products. The opportunity exists, therefore, that a preformed enolate, widely used in aldol chemistry, might be employed in the condensation of two different esters, both possessing α-hydrogen atoms. Rathke and Deitch[18] formed the lithium enolates of ethyl acetate, hexanoate and isobutyrate, using LICA. Treatment of these enolates with a variety of acid chlorides gave the corresponding β-keto ester in isolated yields from 51 to 81%. To prevent attack of the enolate on the ketone function of the product, a second mole of base was used to convert the product into its enolate anion. In a similar manner, Logue[19] reacted *t*-butyl α-lithioisobutyrate with a number of substituted benzoyl chlorides; yields of the derived β-keto esters were generally in the range 55–88%. The *t*-butyl group could be removed readily by brief treatment with trifluoroacetic acid at room temperature; decarboxylation occurred at reflux temperatures. Couffignal and Moreau[20] acylated a number of saturated and unsaturated esters with a carboxylic carbonic anhydride ($RCO_2CO_2Et$) to obtain yields of β-keto ester in the range 40–70%. This synthesis was also applied to ketone enolates, producing β-diketones. Cowan

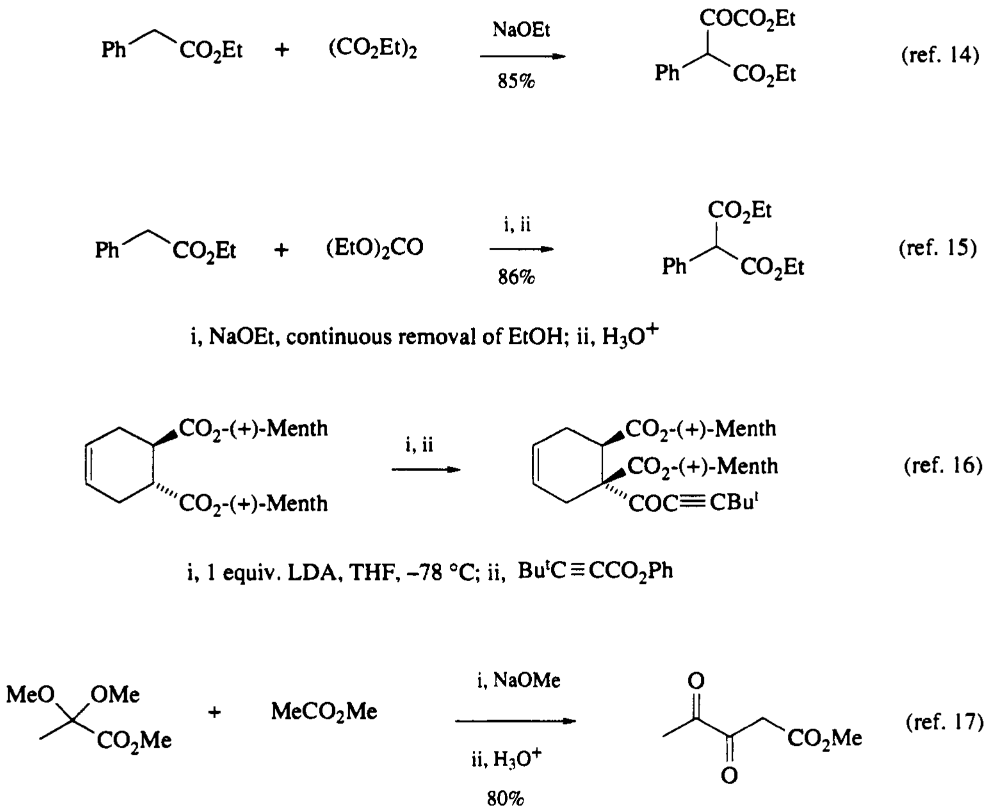

NaOEt
85%
(ref. 14)
i, ii
86%
(ref. 15)
i, ii
(ref. 16)
i, NaOMe
ii, $H_3O^+$
80%
(ref. 17)

i, NaOEt, continuous removal of EtOH; ii, $H_3O^+$

i, 1 equiv. LDA, THF, –78 °C; ii, $Bu^tC\equiv CCO_2Ph$

**Scheme 4**

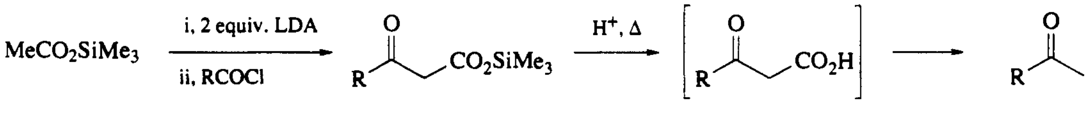

i, 2 equiv. LDA
ii, RCOCl
H+, Δ

R = Ph, *o*-Tol, $Bu^t$, $Pr^i$, $Pr^n$

**Scheme 5**

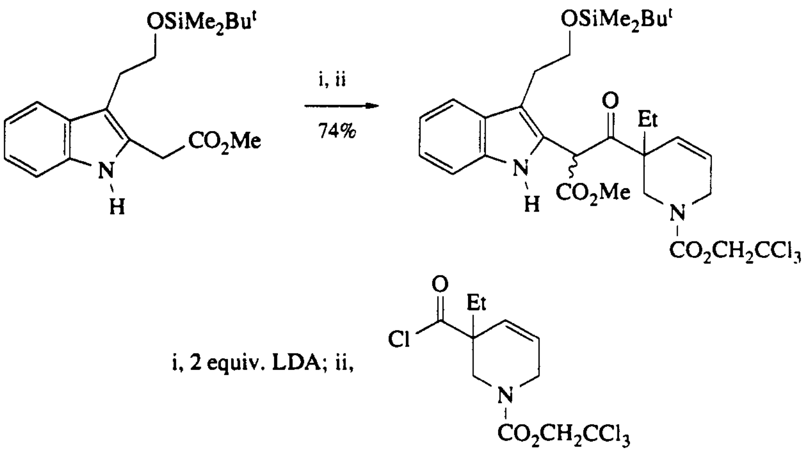

(7)

i, 2 equiv. LDA; ii,

and Rathke[21] utilized the acylation of the lithium enolate of trimethylsilyl acetate as a route to β-keto acids and thus methyl ketones (Scheme 5).[21] Preformed enolates were chosen to synthesize some long chain β-hydroxy acids related to mycolic acid. Acylation with a suitable acid chloride gave the desired β-keto ester in high yield.[22]

The use of preformed enolates continues to provide a valuable route for performing mixed Claisen condensations. Reaction of a 2-indolylacetic ester with 2 mol of LDA and treatment of the product with an α-trisubstituted acid chloride gave the corresponding keto ester as a diastereomeric mixture in 74% yield (equation 7).[23]

In another example, 2 mol of base were used in the production of the enolate; the resulting enolate product was then trapped as the diazo ketone (Scheme 6).[24] A comparative study was provided by the work of Kurihara *et al.* in their approaches to the total synthesis of lysergic acid (equation 8).[25]

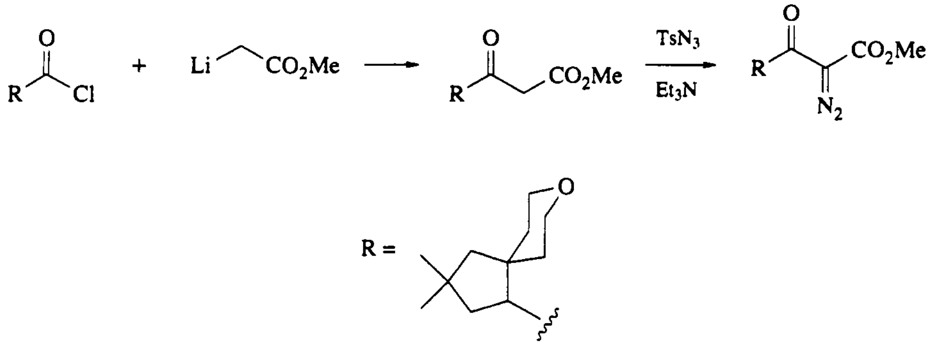

**Scheme 6**

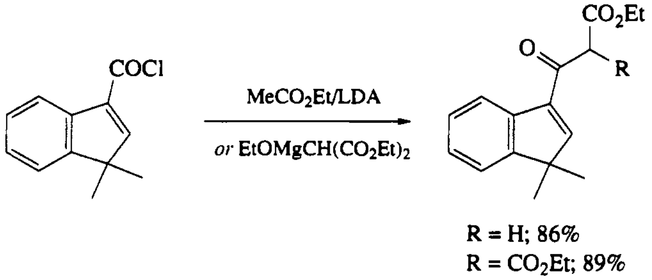

(8)

### 3.6.3.2.3 *One ester is more acidic*

In a mixed Claisen ester condensation, employing two simple monoesters, the acidity of the two sets of α-hydrogen atoms is unlikely to differ greatly and can lead to mixed products. The chemoselectivity can be greatly improved by employing one ester whose α-hydrogen atoms are considerably more acidic, *e.g.* a malonic ester derivative or a β-keto ester.[26] In practice, an anion from diethyl malonate is most often acylated with an acid chloride or acid anhydride. Magnesium enolates have found particular use here, as illustrated in Scheme 7. Acyl cyanides[29] and 1-acyl imidazoles[30] have also been used in this way (Scheme 8). Masamune and coworkers[31] showed that the neutral magnesium salt of a malonic or methyl malonic half ester or half thiol ester reacted with an acylimidazolide to give β-keto esters in excellent yield (equation 9). The reaction appeared to be a substantial improvement on the use of the basic magnesium enolate and has been used by other workers. Useful applications of Masamune's work are illustrated in Scheme 9. A variant allows the direct *C*-acylation of malonic acid derivatives with carboxylic acids themselves, using diethyl phosphorocyanidate and triethylamine (equation 10).[34] Yields varied from good to quantitative, using a number of simple carboxylic acids. Other workers have acylated the dianion of monoethyl malonate to give β-keto esters in over 90% yield,[35] while β-keto acids have been obtained by acylation and hydrolysis of the lithium anion of bis(trimethylsilyl)malonate.[36] With these reactions may be classed the acylation of Meldrum's acid with acyl chlorides.[37] Various β-keto esters were obtained in good yield under mild conditions (Scheme 10).

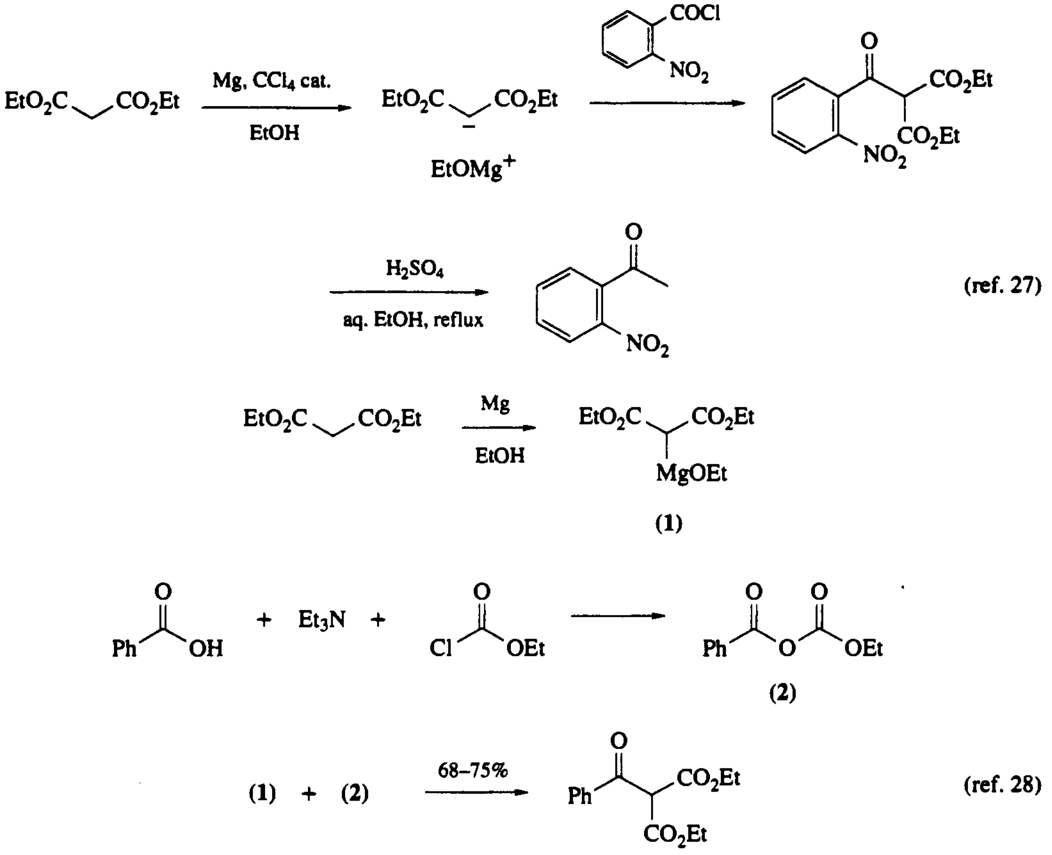
Mg, CCl4 cat.
EtOH
EtOMg+
COCl
NO2
CO2Et
CO2Et
NO2
H2SO4
aq. EtOH, reflux
NO2
(ref. 27)
Mg
EtOH
MgOEt
(1)
Ph
OH
Et3N
Cl
OEt
(2)
(1) + (2)
68–75%
CO2Et
(ref. 28)

**Scheme 7**

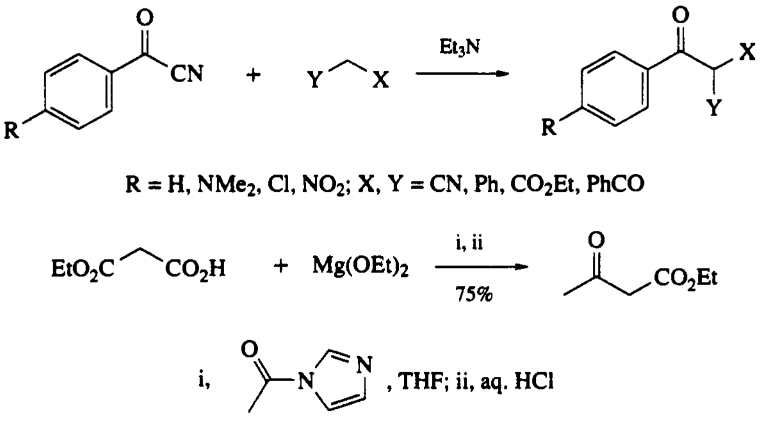
CN
Y
X
Et3N
R
R = H, NMe2, Cl, NO2; X, Y = CN, Ph, CO2Et, PhCO
EtO2C
CO2H
+ Mg(OEt)2
i, ii
75%
CO2Et
i,
, THF; ii, aq. HCl

**Scheme 8**

### 3.6.3.2.4 *Coordination by titanium(IV) bistriflate*

A potentially valuable example of a crossed Claisen condensation was described by Tanabe and Mukaiyama in 1986.[38] It arose from their earlier work on titanium(IV) ditriflate [dichlorobis(trifluoromethanesulfonato)titanium(IV)] and triethylamine as a catalytic promoter of the simple Claisen reaction. The reaction was run in the presence of benzaldehyde, added to observe the aldol reaction, but the propionate anion added to the carbonyl group of another ester molecule in preference (equation 11). The same result was observed in a Dieckmann reaction; dimethyl adipate, $TiCl_2(OTf)_2$ (1.5 equiv.) and triethylamine

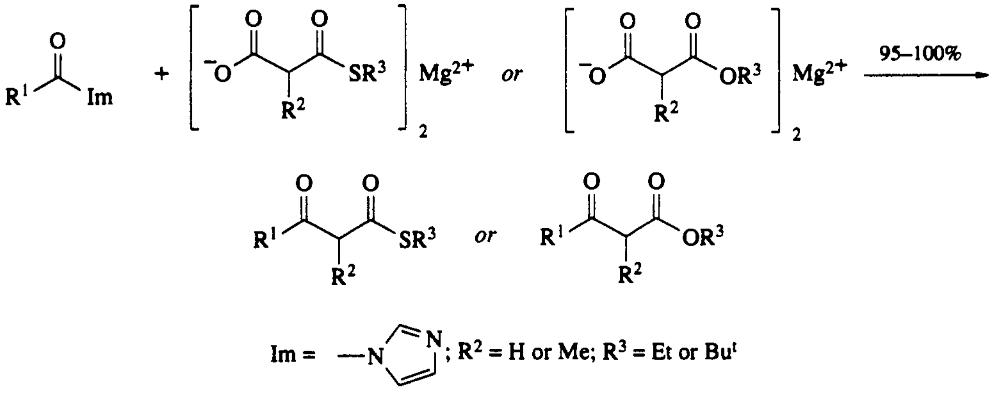

Im = ; $R^2$ = H or Me; $R^3$ = Et or $Bu^t$

(9)

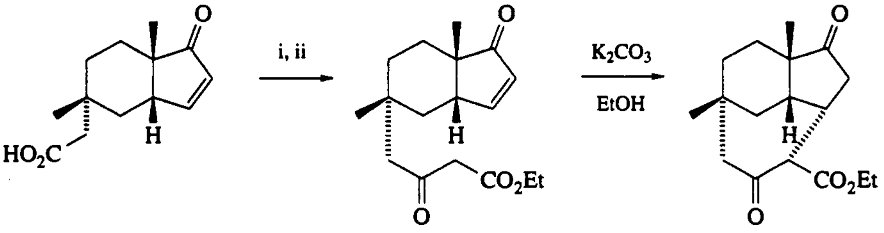

(ref. 32)

i, carbonyl diimidazole, ii, $(EtO_2CCH_2CO_2)_2Mg$

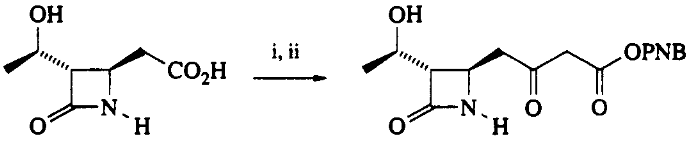

i, carbonyl diimidazole, MeCN, DMF; ii, 1.2 equiv. $Mg(O_2CCH_2CO_2PNB)_2$, r.t., 16 h

PNB = $p$-$O_2NC_6H_4$ (ref. 33)

**Scheme 9**

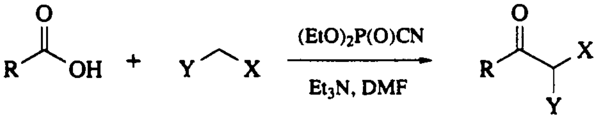

(10)

X, Y = EWG; R = Ph, $Ph(CH_2)_2$, n-$C_5H_{11}$, $MeCO(CH_2)_2$

gave, in the presence of molecular sieves, an 80% yield of the cyclic keto ester. This led on to a successful crossed Claisen ester condensation between a methyl ester and a methoxymethyl ester (equation 12). The titanium ditriflate coordinates strongly with the methoxymethyl ester allowing the tertiary amine base to remove the α-proton from that ester and permit it to undergo acylation by the methyl ester. An intramolecular version was equally successful; methoxymethyl methyl adipate gave, almost exclusively, the cyclic methoxymethyl ester (equation 13).

### *3.6.3.2.5 Silyl ketene acetals*

Silyl alkyl ketene acetals, as ester enolate equivalents, are capable of regioselective acylation by acid chlorides. Rathke and Sullivan[39] showed that a variety of acid chlorides reacted with the acetal (3) to give protected β-keto esters (Scheme 11). Acid hydrolysis of the silylated products gave the free β-keto ester. The reaction was successful with a variety of acyl chlorides, including acetic, butanoic, (2*E*)-buten-

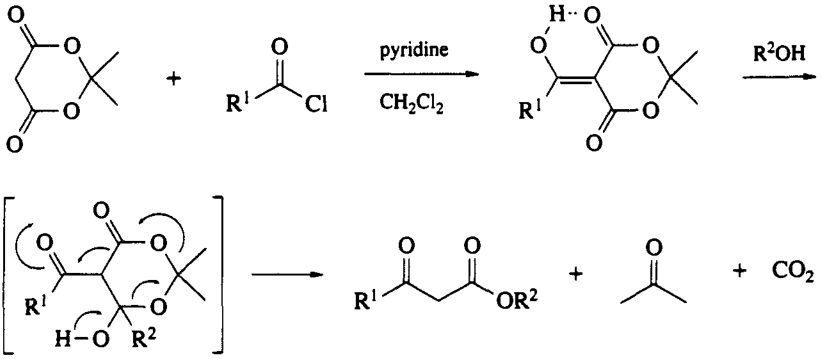

$R^1$ = Et, $Pr^i$, Bu, n-$C_5H_{11}$, n-$C_6H_{13}$, n-$C_7H_{15}$, n-$C_8H_{17}$, $CH_2$=$CH(CH_2)_8$, $PhCH_2$, $MeCOCH_2CH_2$
$EtOCH_2CH_2$; $R^2$ = Me, Et, $PhCH_2$,$Bu^t$

Scheme 10

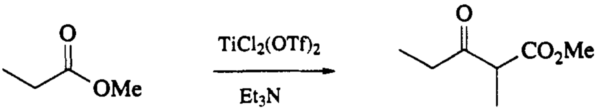

(11)

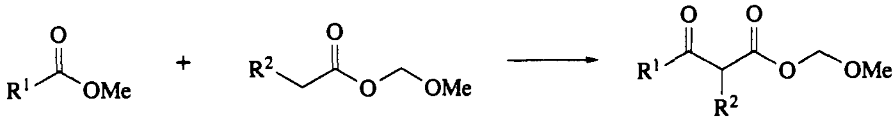

(12)

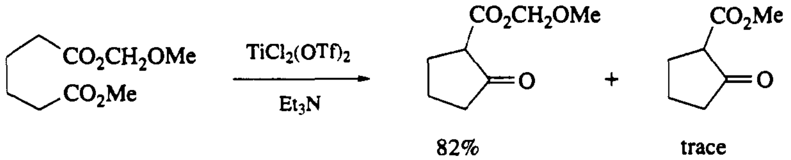

(13)

oic, pivalic and benzoic. In those acids possessing an α-hydrogen atom, the reaction is thought to proceed through a ketene intermediate. Similar results were reported by a Russian group.[40]

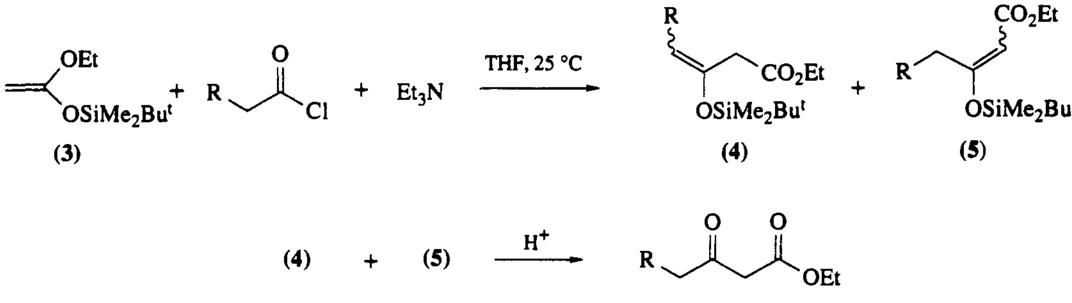

Scheme 11

More recently, Rousseau and Blanco[41] reacted 3-methylbut-2-enoyl chloride with a number of silyl ketene acetals to produce γ,δ-ethylenic β-keto esters, with yields in the range 62–80%; neither but-2-enoyl chloride nor propenoyl chloride reacted under these conditions. They employed this reaction in a new synthesis of (±)-turmerone (**6**; Scheme 12).

1,3-Dioxolan-2-ylium cations (**7**), derived from aldehyde ethylene acetals by hydride abstraction, react with silyl ketene acetals to give β-keto esters, selectively monoprotected at the ketone carbonyl (equation 14).[42]

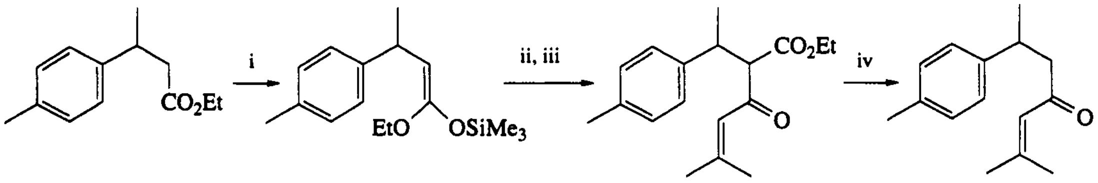

**(6)**

i, LDA, Me$_3$SiCl, THF; ii, 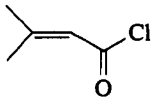 , MeCN, 1 equiv. Et$_3$N; iii, aq. HCl, THF; iv, aq. HCl, Δ

**Scheme 12**

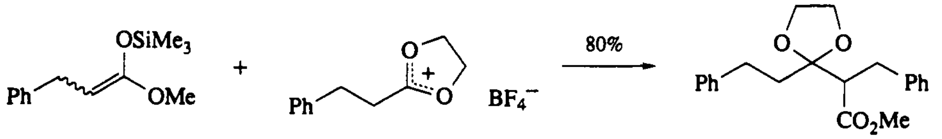

(7)

(14)

### 3.6.3.2.6 *Acylation of oxazolines*

Tohda *et al.*[43] reported on the use of 2-primary alkyl 4,4-dimethyl-2-oxazolines in a crossed Claisen condensation (equation 15). The 2-primary alkyl oxazoline was treated with an acid anhydride in the presence of aluminum chloride and triethylamine in acetonitrile to give moderate yields (typically 50–65%) of the oxazoline derivative of a β-keto acid. The product can be monoalkylated selectively on the carbon adjacent to the heterocyclic ring, while the 2-oxazoline group can be converted into a variety of functional groups.

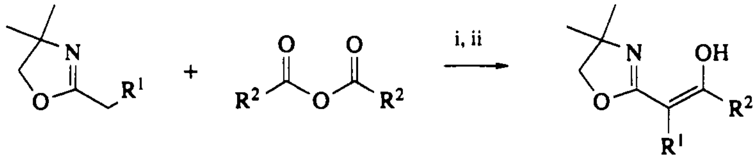

(15)

i, AlCl$_3$–Et$_3$N, MeCN; ii, KOH, r.t., MeOH

### 3.6.3.2.7 *Thiol esters*

Thiol esters readily undergo both Claisen (equation 16) and Dieckmann condensations. The sulfur atom renders the α-protons more acidic and makes the thioalkoxide a better leaving group than alkoxide, properties recognized in the biosynthesis of fatty acids. In mixed Claisen condensations with oxy esters, the thiol ester acts both as nucleophile and electrophile. Reaction of a mixture of thioethyl acetate and ethyl propanoate with isopropylmagnesium chloride gave thioethyl 3-oxobutanoate as the main product (equation 17). When the same catalyst was used with a mixture of thioethyl propanoate and ethyl acetate, the sole product detected was thioethyl 2-methyl-3-oxopentanoate (equation 18).[44] Another group reporting on the value of thiol esters as acylating agents reacted *t*-butyl lithioacetate with various thiomethyl α-hydroxy esters to give β-keto esters in good yield (equation 19).[45]

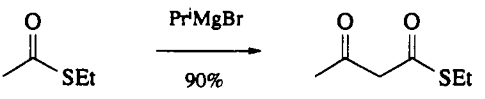

(16)

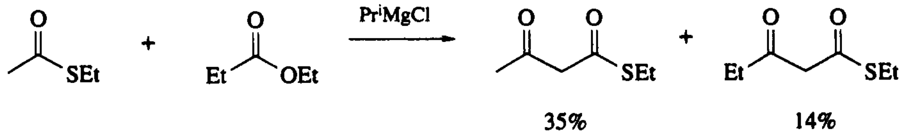

(17)

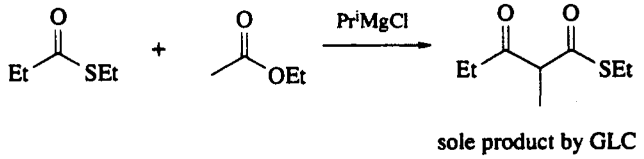

(18)

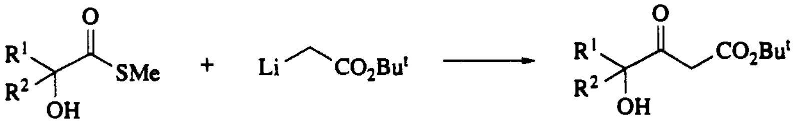

(19)

### 3.6.3.3 The Dieckmann Reaction

The Dieckmann, Thorpe and Thorpe–Ziegler reactions all involve intramolecular cyclization of a stabilized anion to form a cyclic ketone. The Dieckmann reaction is the intramolecular equivalent of the Claisen condensation and yields cyclic 2-alkoxycarbonyl ketones as primary products, whereas the primary products of the Thorpe reaction are 2-cyanoenamines (Scheme 13). Subsequent hydrolysis affords cyclic ketones but the primary products, particularly those from the Dieckmann reaction, have a useful synthetic role (see Section 3.6.3.5.1).

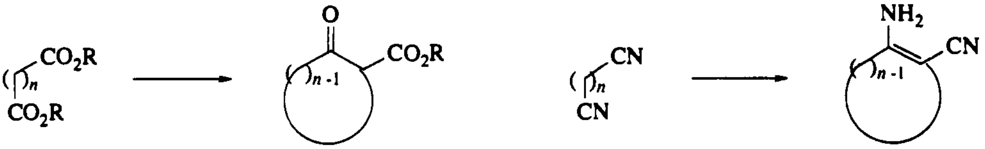

Scheme 13

The Dieckmann reaction is of major importance for the synthesis of five- and six-membered ring compounds. The present account will review the earlier work where necessary, but will concentrate on important developments since the review in *Organic Reactions*.[6]

#### *3.6.3.3.1 Mechanism of the reaction*

The classical Dieckmann reaction occurs under equilibrium conditions, the initial step involving the base-catalyzed formation of the ester enolate anion. The rate-determining step is ring closure, the subsequent loss of the alkoxide being rapid (Scheme 14).[6]

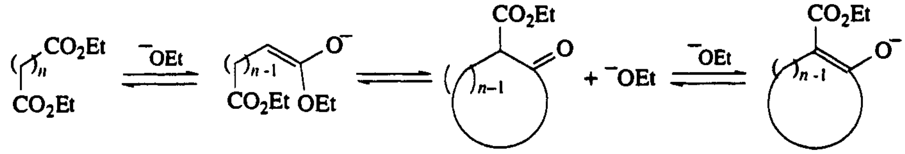

Scheme 14

The reversibility of the process means that cyclic 2-alkoxycarbonyl ketones can be cleaved by alkoxide in the retro-Dieckmann reaction, a process of synthetic significance (see Section 3.6.9.1). More recently, nonequilibrium conditions have been employed in the reaction and this may lead to a change in regioselectivity (see Section 3.6.3.3.3).

The Dieckmann reaction is an *n*-(enolexo)-exo-trig cyclization in Baldwin's terminology,[46] and is a favored reaction (Scheme 15). Kodpinid and Thebtaranonth[47] have extended this to the vinylogous reaction, and have shown (for the substrates chosen) that the 4-(enolendo)-exo-trig mode is disfavored and does not occur to give the desired 4-alkoxycarbonylcyclo-3-pentenones, whereas the 6-(enolendo)-exo-trig mode is favored and does give the desired 4-alkoxycarbonylcyclo-3-hexenones (Scheme 16). However, other workers[48] have reported a successful 5-(enolendo)-exo-trig cyclization. The difference in behavior is probably due both to the presence of the ethanethiol group and the greater flexibility of the cyclizing molecule.

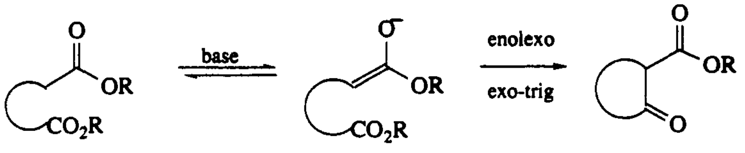
O
OR
CO$_2$R
base
O$^-$
OR
CO$_2$R
enolexo
exo-trig
O
OR
O

Scheme 15

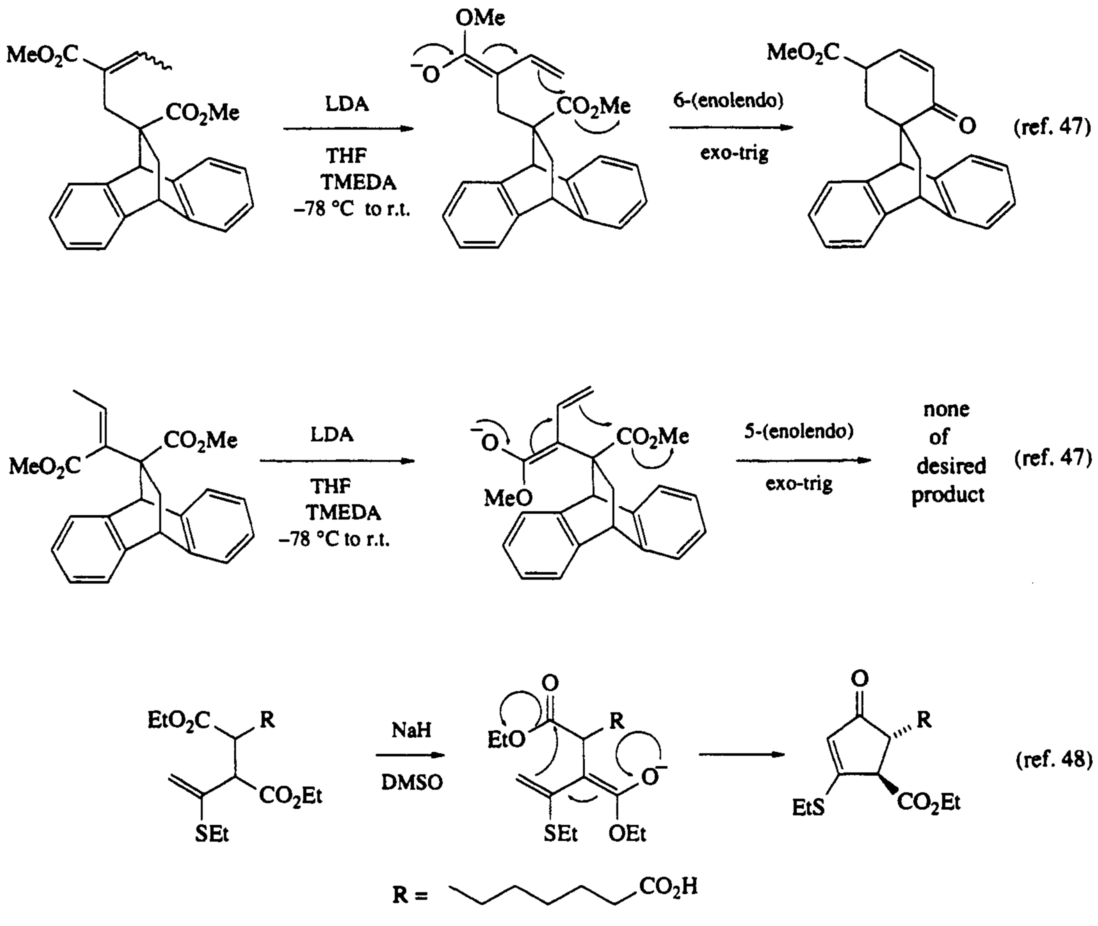
MeO$_2$C
CO$_2$Me
LDA
THF
TMEDA
–78 °C to r.t.
OMe
$^-$O
CO$_2$Me
6-(enolendo)
exo-trig
MeO$_2$C
O
(ref. 47)
MeO$_2$C
CO$_2$Me
LDA
THF
TMEDA
–78 °C to r.t.
$^-$O
MeO
CO$_2$Me
5-(enolendo)
exo-trig
none of desired product
(ref. 47)
EtO$_2$C
R
CO$_2$Et
SEt
NaH
DMSO
O
EtO
R
O$^-$
SEt
OEt
O
R
EtS
CO$_2$Et
(ref. 48)
R =
CO$_2$H

Scheme 16

The mechanism in solution and in the gas phase appears to be the same,[49] except that an alkyl substituent stabilizes the anion in the gas phase and destabilizes it in solution. The mass spectral decomposition of diethyl 2-methylheptanedioate under negative chemical ionization (NCI) conditions shows formation of the methyl-substituted enolate, ring closure and then loss of ethyl methyl ether.

### *3.6.3.3.2 Ring size*

The Dieckmann reaction is usually used to prepare five- or six-membered rings. A variety of substituents can be tolerated on the intervening atoms, although these may influence the regioselectivity of the reaction (see Section 3.6.3.3.3), and some of the intervening atoms need not be carbon. In competition between five- or six-membered ring formation, ambiguous results have been obtained depending on the substrate and conditions. Thus diethyl 3-ethoxycarbonylheptanedioate (**8**) gives the six-membered ring product (**9**) with sodium hydride in benzene and the five-membered ring product (**10**) with sodium ethoxide in ethanol (Scheme 17). This appears to be an example of kinetic *versus* equilibrium control, but other experiments suggest that the five-membered product is formed first and equilibrates to the six-membered. The corresponding 5-methyl-5-aza derivative (**11**) gives the six-membered ring derivative (**12**) with sodium hydride in benzene and mainly the five-membered derivative (**13**) with Bu$^t$OK in toluene at –25 °C.[50]

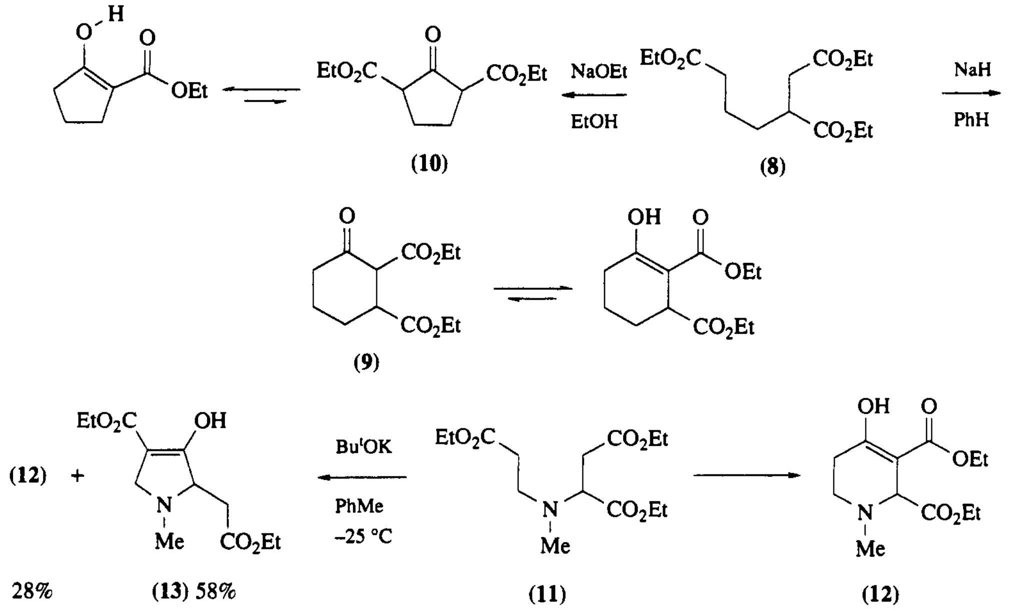

Scheme 17

Examples of five- and six-membered ring formation are illustrated by the following reactions (Scheme 18).

Seven-membered and larger rings can be prepared by this method and the yields can often be satisfactory. Carefully controlled nonequilibrium conditions and high dilution techniques are often required. Medium rings (9–12) are either not formed, or formed in low yield, a combination of a Claisen condensation followed by a Dieckmann reaction giving macrocyclic diketones.[6] The conformational energies of the linear precursor influences ring closure.[69] Examples are illustrated in Scheme 19.

The reaction does not work well for three- or four-membered rings. A small number of examples of four-membered ring formation have been reported but in very low yield (usually <1%).[6]

### *3.6.3.3.3 Regioselectivity*

If the two ester groups are not equivalent then, providing both ester groups have α-carbon atoms bearing protons, two products can result from the ring closure. The two resultant cyclic β-keto esters can often be decarboxylated to the same cyclic ketone and if this is the desired product then nonregioselective ring closure is acceptable. If the β-keto ester is the desired product, or if the two products of ring closure cannot be converted to a common substance, then methods of controlling the regioselectivity must be employed.

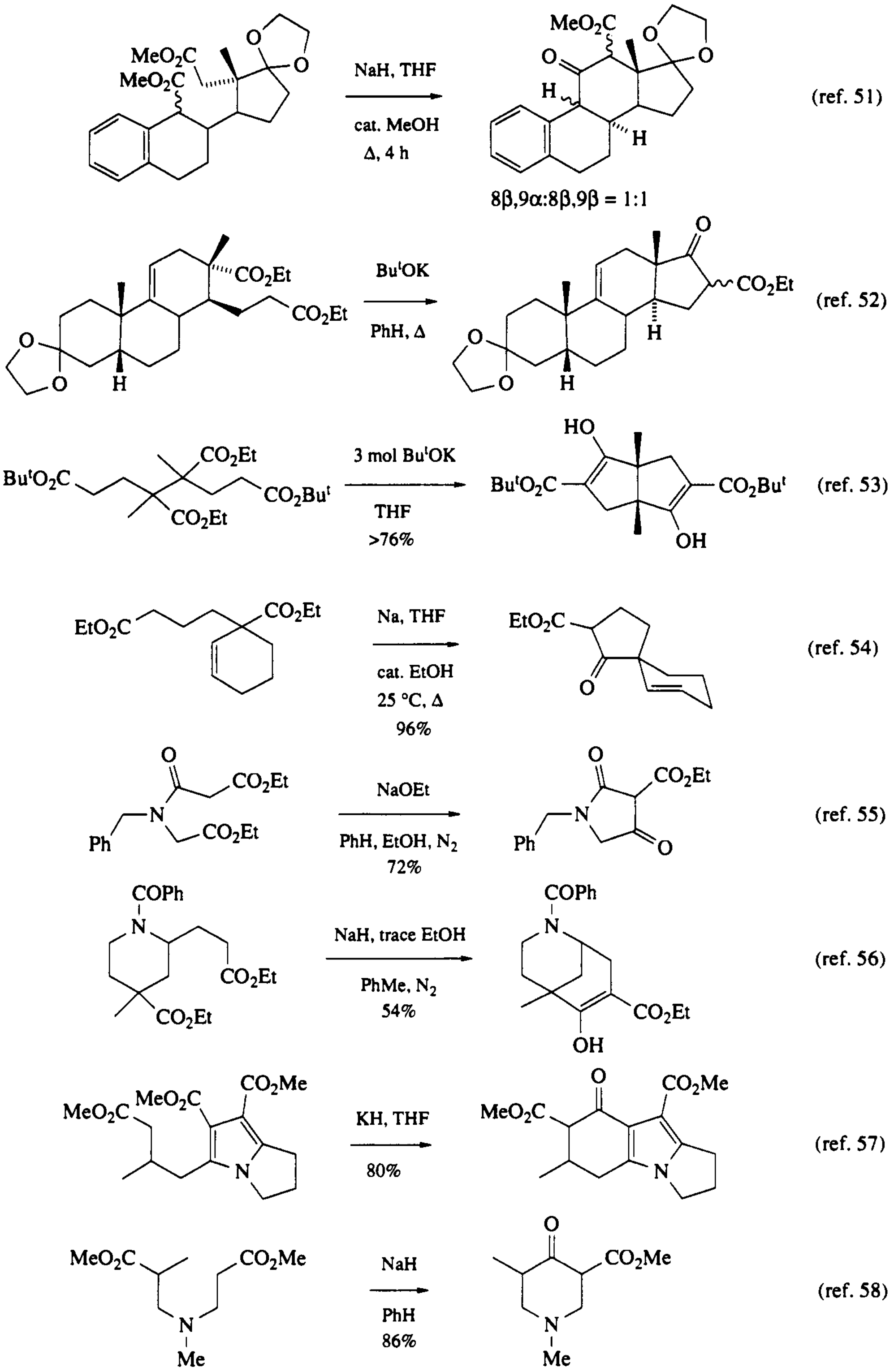
MeO2C
MeO2C
O
O
NaH, THF
cat. MeOH
Δ, 4 h
H
H
8β,9α:8β,9β = 1:1
(ref. 51)
CO2Et
CO2Et
O
O
H
Bu^tOK
PhH, Δ
(ref. 52)
Bu^tO2C
CO2Bu^t
3 mol Bu^tOK
THF
>76%
HO
OH
(ref. 53)
EtO2C
Na, THF
cat. EtOH
25 °C, Δ
96%
(ref. 54)
N
Ph
NaOEt
PhH, EtOH, N2
72%
(ref. 55)
COPh
NaH, trace EtOH
PhMe, N2
54%
(ref. 56)
CO2Me
KH, THF
80%
(ref. 57)
NaH
PhH
86%
Me
(ref. 58)

**Scheme 18**

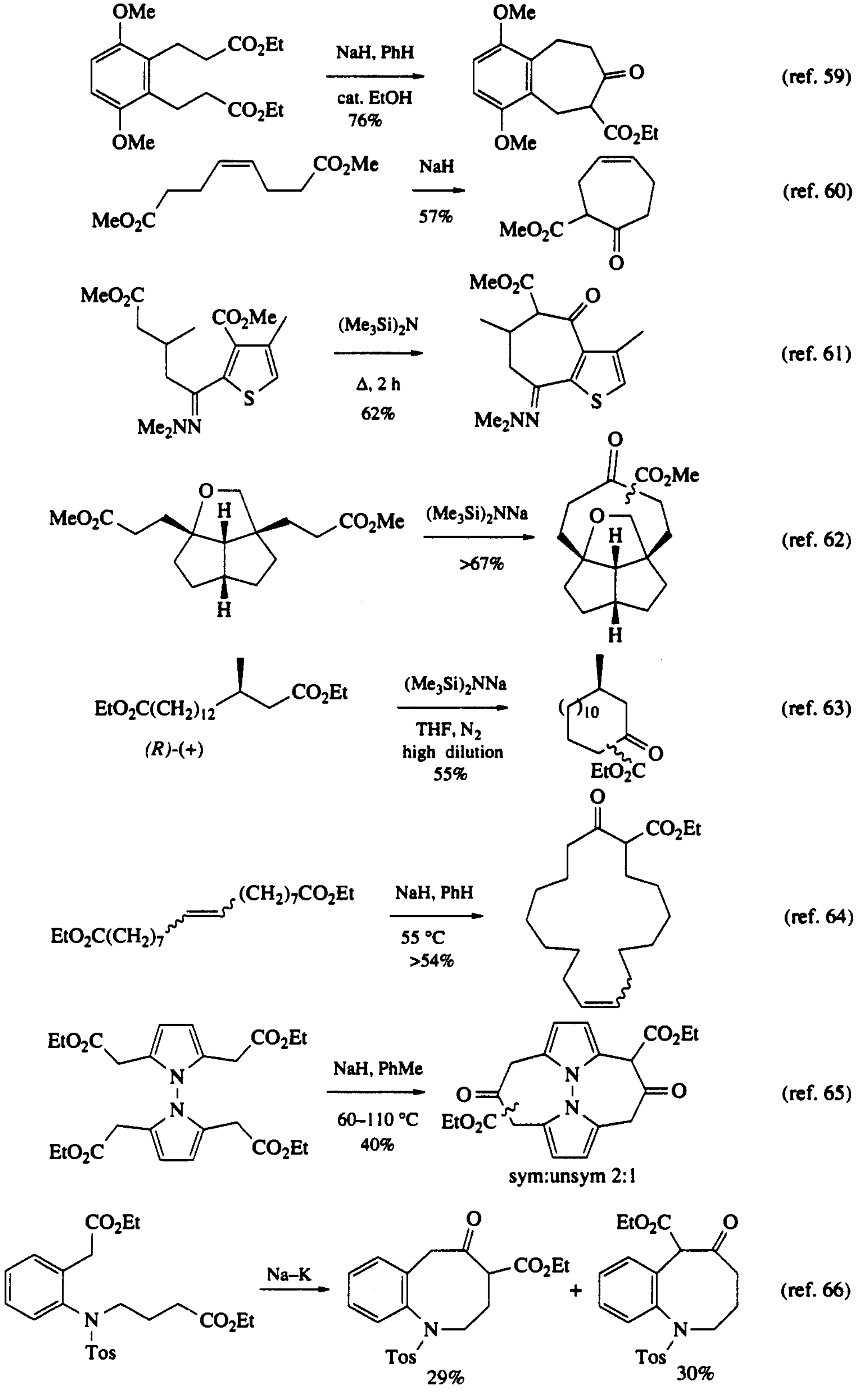
NaH, PhH
cat. EtOH
76%
(ref. 59)
NaH
57%
(ref. 60)
(Me3Si)2N
Δ, 2 h
62%
(ref. 61)
(Me3Si)2NNa
>67%
(ref. 62)
(R)-(+)
(Me3Si)2NNa
THF, N2
high dilution
55%
(ref. 63)
NaH, PhH
55 °C
>54%
(ref. 64)
NaH, PhMe
60–110 °C
40%
sym:unsym 2:1
(ref. 65)
Na–K
29%
30%
(ref. 66)

**Scheme 19**

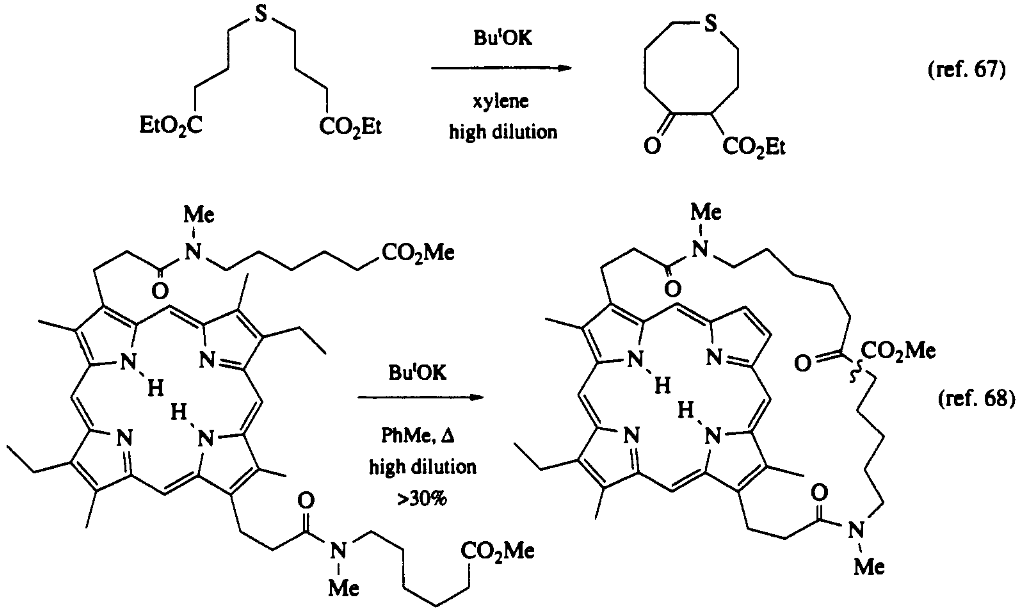

Scheme 19 *(continued)*

### *(i) Substituents at the α-carbon atom*

The stability of the initially formed enolates has a crucial bearing on the direction of ring closure. α-Alkyl substituents destabilize the enolate in solution and the nonsubstituted enolate is favored. Diethyl 2-methylheptanedioate (**14**) cyclizes preferentially through the unsubstituted enolate (**15a**) rather than the substituted enolate (**15b**) to give (**16**) rather than (**17**).[70] This is also the thermodynamic preference since the enolate (**16b**) is more stable than the enolate (**17b**) (Scheme 20).

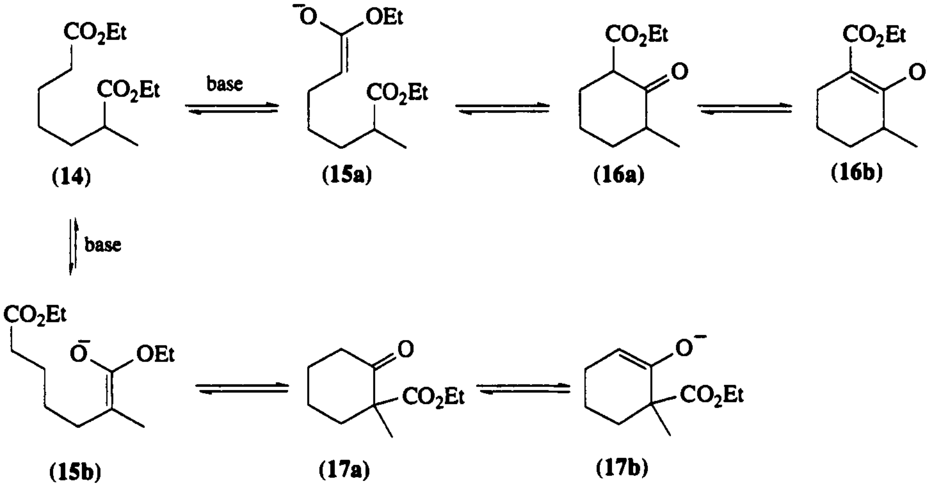

Scheme 20

Similarly, dimethyl 2,4-dimethyl-4-azaheptanedioate gives *N*-methyl-3-methoxycarbonyl-5-methyl-4-oxopiperidine (**18**).[58]

It also follows that primary ester enolates should cyclize preferentially to secondary ester enolates, as is illustrated in the reaction of (**19**).[71] The conformational requirement of the ring closure gives a single diastereomer (**20a** and **20b**) from each diastereomeric ester (**19a** and **19b**; Scheme 21).

If the substituent is electron withdrawing then the enolate is stabilized and the direction of cyclization reversed. Under equilibrium conditions, however, the enolate of the unsymmetrically disubstituted ke-

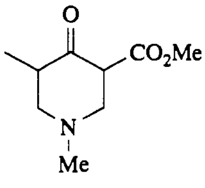

**(18)**

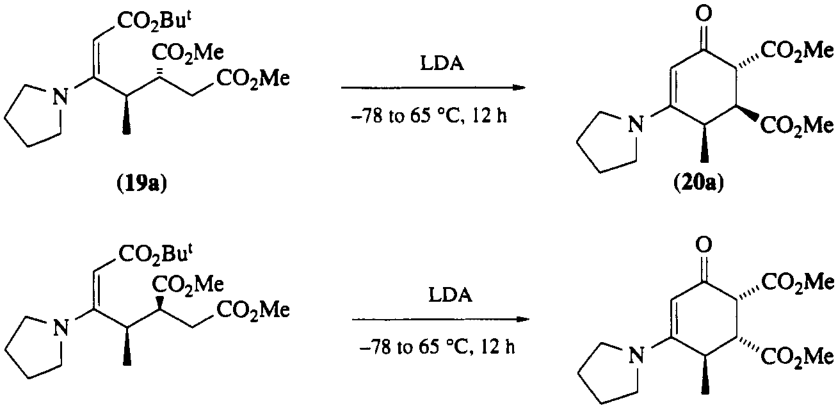

**(19a)** **(20a)** **(19b)** **(20b)**

Scheme 21

tone may be less stable than that of the symmetrically substituted ketone and the final product then results from addition of the unsubstituted enolate.

*(ii) β-Heteroatoms*

The presence of a heteroatom at a β-position to one of the ester groups stabilizes that enolate. Under nonequilibrating conditions, ring closure should be regioselective. Thus the ester (**21**) undergoes cyclization under nonequilibrium conditions to give (**22**), whereas under equilibrium conditions (**23**) is formed, presumably because of the greater stability of the enolate of the cyclized product (Scheme 22).[72]

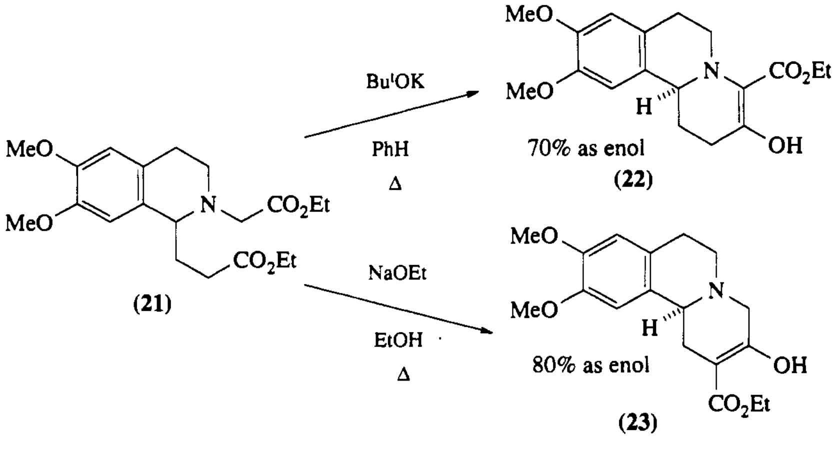

Scheme 22

Cyclization of (**24**) regioselectivity gives (**25**).[73] The conditions are nonequilibrating, which suggests that the destabilizing effect of the alkyl group is greater than the stabilizing effect of the sulfur atom on the enolate. However, the enolate of (**25**) is also more stable than that of the alternative cyclized product. The combination of substituent effects with equilibrium or nonequilibrium conditions has been examined for diethyl 3-thiohexanedioate (**26**) and derivatives.[74] Under nonequilibrium conditions (**26**) gives (**27**), whereas with sodium ethoxide at 0 °C it gives (**28**). Alkylation at C-5 gives products of type (**27**), while substitution at C-4 can lead to both products, the one obtained depending on the reaction conditions. Under nonequilibrium conditions with LDA, the (*R*)-amino ester (**29**) forms the enolate of the secondary α-C, sulfur-stabilized ester, which ring-closes to (**30**) and transfers $Me_3Si$ to give (*R*)-(**31**) as an 8:1 mixture of diastereomers.[75] Some of the substituted ethyl acrylate (**32**) is also formed from the *N*-substituted enolate by elimination of the α-thio ester (Scheme 23).

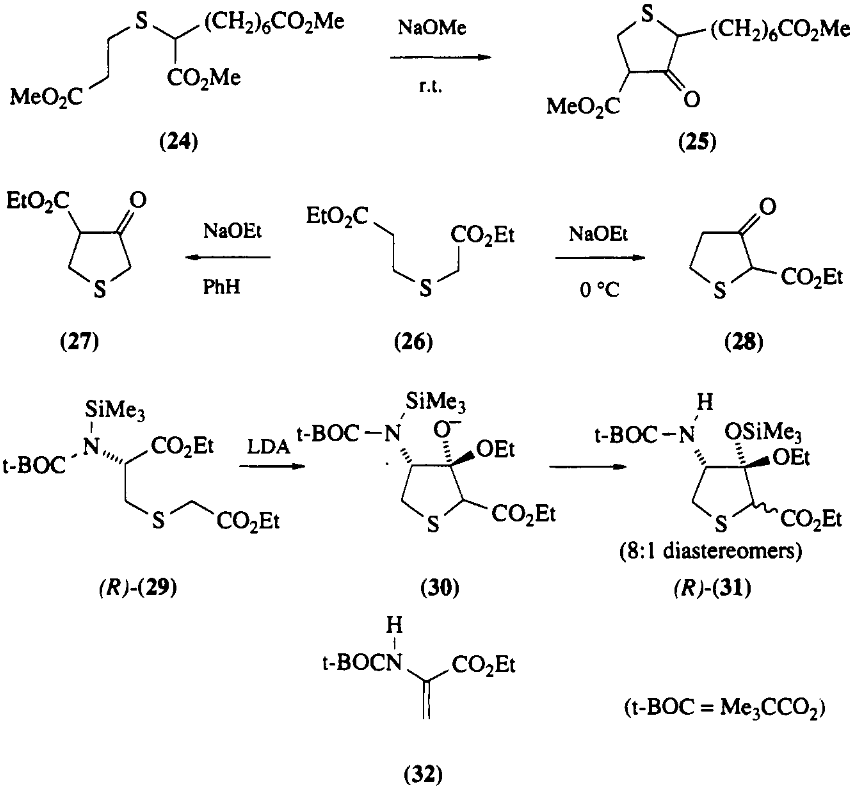
(CH2)6CO2Me
CO2Me
MeO2C
NaOMe
r.t.
(CH2)6CO2Me
MeO2C
O
(24)
(25)
EtO2C
O
NaOEt
PhH
EtO2C
CO2Et
NaOEt
0 °C
O
CO2Et
(27)
(26)
(28)
SiMe3
t-BOC
CO2Et
CO2Et
LDA
t-BOC—N
SiMe3
O⁻
OEt
CO2Et
H
t-BOC—N
OSiMe3
OEt
CO2Et
(8:1 diastereomers)
(R)-(29)
(30)
(R)-(31)
H
t-BOCN
CO2Et
(t-BOC = Me3CCO2)
(32)

**Scheme 23**

### (iii) *Substitution at the β-carbon atom*

With a β-alkyl substituent, cyclization occurs through the least hindered enolate to give the least hindered ketone. Diethyl 3-methylhexanedioate (**33**) cyclizes to give mainly (**34**; >80%), not (**35**), and the triester (**36**) cyclizes to the substituted cyclohexanone (**37**; Scheme 24).[6,70]

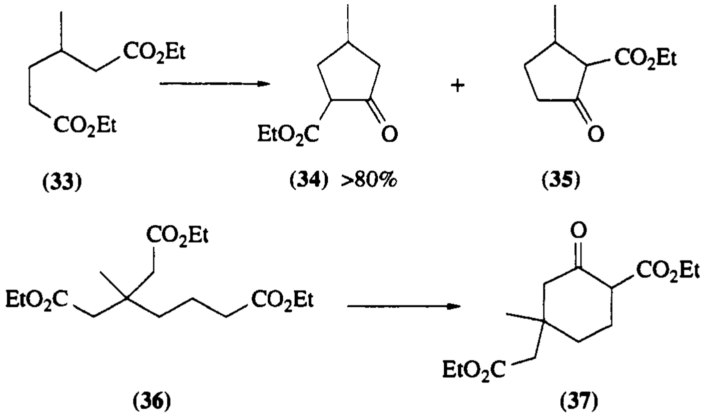
CO2Et
CO2Et
EtO2C
O
+
CO2Et
O
(33)
(34) >80%
(35)
CO2Et
EtO2C
CO2Et
O
CO2Et
EtO2C
(36)
(37)

**Scheme 24**

Where the β-substituent is an ester, cyclization occurs at the hindered, but electronically stabilized, enolate. The triester (**38**) thus gives (**39**) as the major product with lesser amounts of (**40**), the actual proportions depending on the reaction conditions (equation 20).[6,70]

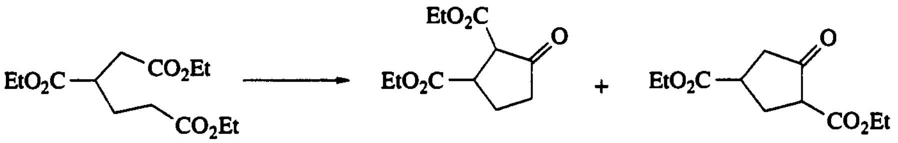

EtO2C
CO2Et
CO2Et
EtO2C
O
EtO2C
+
EtO2C
O
CO2Et

(**38**) (**39**) major (**40**) minor (20)

With both alkyl and ester β-substituents, cyclization occurs on the least hindered side, steric effects or the stability of the product enolates being product determining. Steric effects also dominate the cyclization of the substituted cyclohexadienes (**41**) and (**43**) to the spiroketones (**42**) and (**44**),[76] the cyclization of (**45**) to (**46**) *en route* to gascardic acid,[77] and the cyclization of (**47**) to the norsteroid (**48**; Scheme 25).[78]

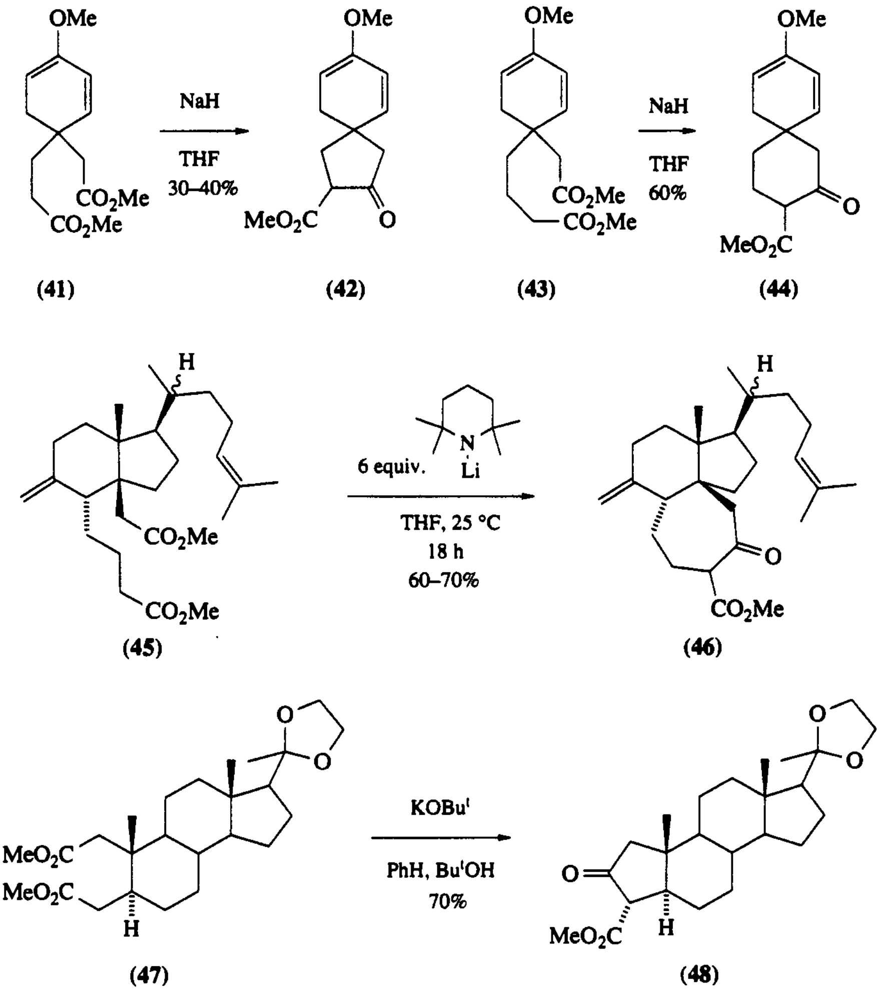

OMe
CO2Me
CO2Me
NaH
THF
30–40%
OMe
MeO2C
O
OMe
CO2Me
CO2Me
NaH
THF
60%
OMe
O
MeO2C
(41)
(42)
(43)
(44)
H
CO2Me
CO2Me
N
Li
6 equiv.
THF, 25 °C
18 h
60–70%
H
O
CO2Me
(45)
(46)
O
O
MeO2C
MeO2C
H
KOBu^t
PhH, Bu^tOH
70%
O
O
O
MeO2C
H
(47)
(48)

Scheme 25

A β-vinyl substituent appears to give a balance between the steric and electronic effect, almost equal amounts of the two products being obtained.[79,80] A reinforcing combination of α- and β-substituents directs ring closure exclusively in one direction, as in the conversion of (**49**) to (**50**) with retention of the stereochemistry at C-3 (equation 21).[81]

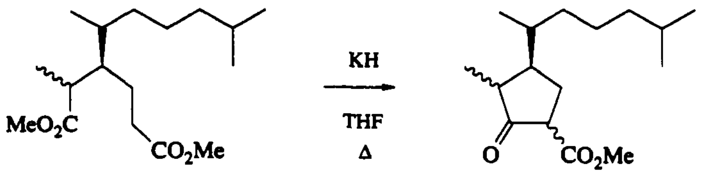
MeO2C
CO2Me
KH
THF
Δ
> 83%
O
CO2Me

**(49)** **(50)** (21)

### *(iv) Variation of the ester group*

Crowley and Rapoport[82] have made a detailed investigation, including labeling studies, of the reaction, both with one carboxylic function attached to a resin, and in solution with the carboxylic functions esterified by different alcohols. Cyclization of the resin-attached methyl (**51**; R = Me) or *t*-butyl ester (**51**; R = Bu$^t$) with Bu$^t$OK gave the methyl (**52**; R = Me) or *t*-butyl 2-oxocarboxylates (**52**; R = Bu$^t$) as the exclusive autocleaved product. Similar results were obtained with the half-benzyl esters in solution but the products were less readily isolated (equation 22).

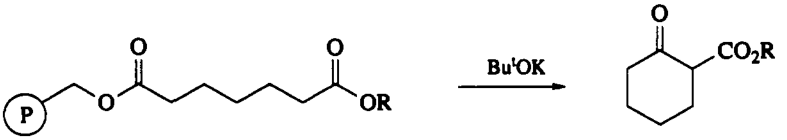
O
O
P
O
OR
Bu$^t$OK
O
CO2R

**(51)** **(52)** (22)

Another way of differentiating the cyclizing groups is to change one of the ester groups to another functional group, for example to a thiol ester (Scheme 26). The thiol ester acts as a good activating group for the Dieckmann reaction and five- and six-membered ring compounds can be prepared from dithiol esters.[44] Substrates with one thiol ester and one ester group can cyclize regioselectively, the direction of cyclization depending on the reaction conditions. Thus (**53**) with sodium hydride gives a 1.6:1 mixture of

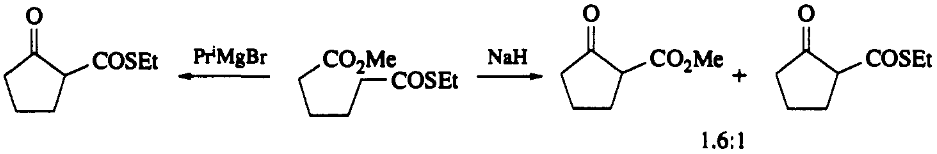
O
COSEt
Pr$^i$MgBr
CO2Me
COSEt
NaH
O
CO2Me
+
O
COSEt
1.6:1

**(55)** **(53)** **(54)** **(55)**

**Scheme 26**

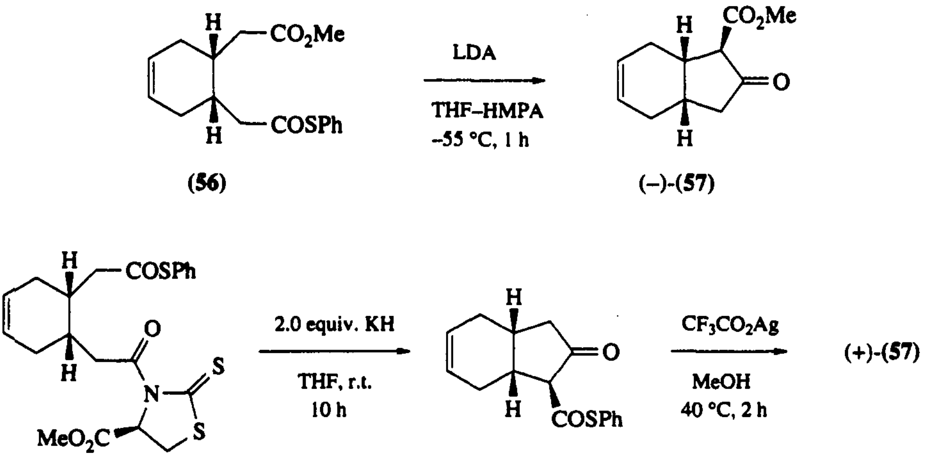
H
CO2Me
COSPh
H
(56)
LDA
THF–HMPA
-55 °C, 1 h
H
CO2Me
O
H
(−)-(57)
H
COSPh
O
H
N
S
MeO2C
S
(58)
2.0 equiv. KH
THF, r.t.
10 h
H
O
H
COSPh
(59)
CF3CO2Ag
MeOH
40 °C, 2 h
(+)-(57)

**Scheme 27**

(**54**) and (**55**), whereas with 2-propylmagnesium bromide it gives only (**55**; Scheme 32). An elegant use of this method has been employed for the cyclization of the 4-cyclohexene (**56**).[83] Reaction of (**56**) with LDA in THF–HMPA at –55 °C gave the enantiomer (–)-(**57**) in 57% yield with >98% optical purity. Dimsyl sodium or dimsyl potassium gave mixtures of enantiomers. With (**58**) cyclization onto the thiol ester group occurs to give (**59**), displacement of the chiral amine group by $PhS^-$ having subsequently occurred. Replacement of the thiophenol group by methoxide occurs when (**59**) is treated with silver trifluoroacetate in methanol and the other enantiomer (+)-(**57**) is obtained (Scheme 27).

Substitution of one of the ester groups for another functional group may also allow one mode of cyclization to occur. Where cyanide replaces one of the esters, cyclization occurs from the cyano-stabilized anion.[84,85] Seven-membered (*e.g.* **60**) and heterocyclic (*e.g.* **61**) rings[84,85] can be prepared regioselectively.[85] In competition between an ester and the $PhSO_2$-stabilized anion the latter cyclizes even where it is secondary and the ester is primary, (**62**) to (**63**), presumably in part a reflection on the electrophilicity of the two groups and the stabilities of the products.[86] The ester lactone (**64**) cyclizes to the keto ester (**65**) involving the enolate of the lactone, but cyclization in the opposite sense is sterically unlikely (Scheme 28).[87]

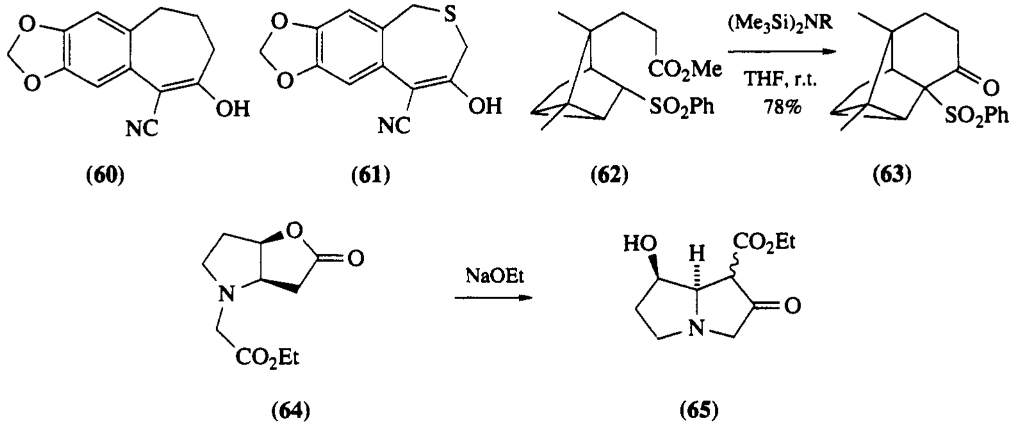

(**60**) (**61**) (**62**) (**63**)

(**64**) (**65**)

Scheme 28

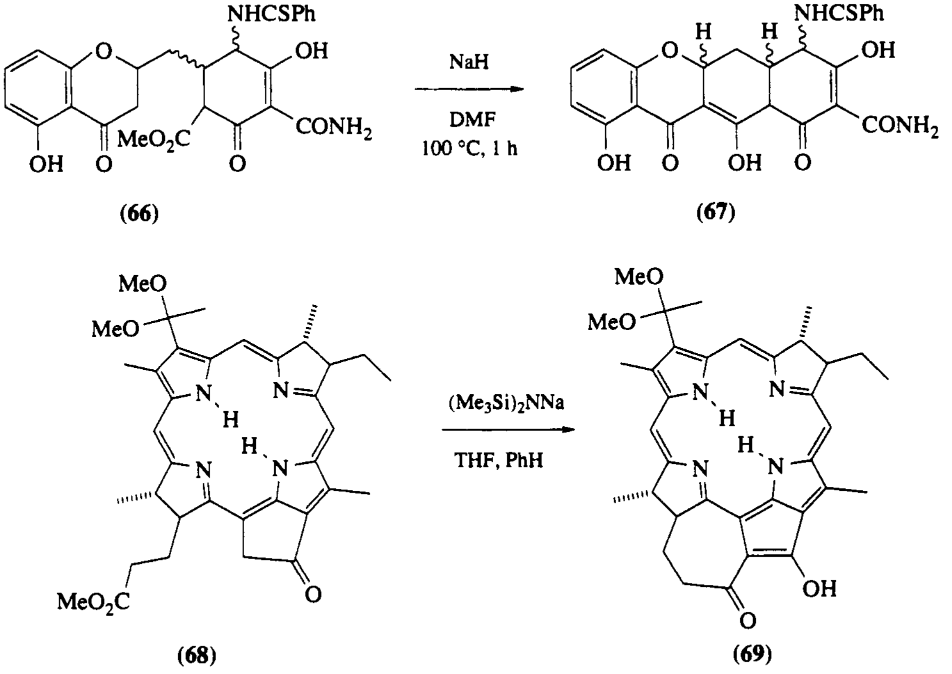

(**66**) (**67**)

(**68**) (**69**)

Scheme 29

With the replacement of one ester grouping by a ketone, the ketone enolate acts as the nucleophile. Thus (**66**) cyclizes regioselectively to (**67**) and (**68**) cyclizes to (**69**; Scheme 29).[88,89] This reaction is described more fully in Section 3.6.4.

### *(v) α,β-Unsaturated esters*

The enolate of an α,β-ester cyclizes preferentially to an alkyl ester enolate, ring closure occurring at the α-carbon. Treatment of (**70**) with either sodium methoxide or potassium *t*-butoxide gives (**71**), *via* the enolate of the α,β-unsaturated ester.[90] Similarly, (**72**) cyclizes to (**73**) with potassium *t*-butoxide.[91] Cyclization of (**74**) occurs, however, from the saturated rather than unsaturated enolate to give (**75**).[92] This may reflect the stabilizing effect of sulfur on the enolate or the greater stability of the enolate of (**75**) relative to that of the alternative product (Scheme 30).

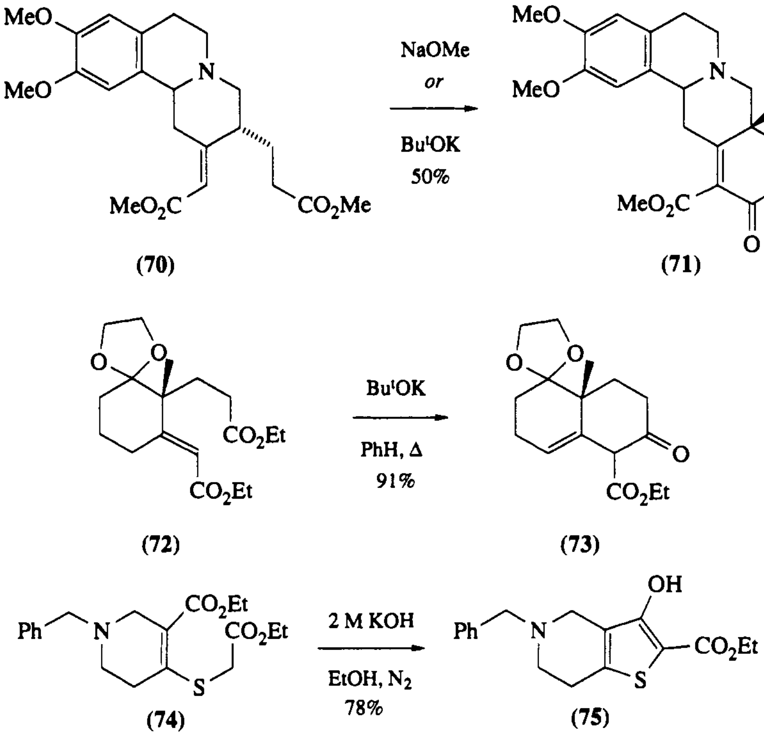

**Scheme 30**

### 3.6.3.4 Application to Synthesis

### *3.6.3.4.1 β-Keto ester as a synthon*

The β-keto esters formed in the Claisen and Dieckmann condensations can act as synthons for a variety of groups. If the α-carbon bears a proton then this is acidic and can be replaced by another electrophile. Alkylation and acylation are important synthetic reactions and can be carried out sequentially or, since the cyclizing reactions are basic, consecutively in one pot. Examples are illustrated in Scheme 31.

*O*-Alkylation of the enolate may compete with *C*-alkylation. The benzoselenophene (**76**) gives a 3:1 mixture of *C*-alkylation (**77**) and *O*-alkylation (**78**) with methyl iodide in methanol but a 1:3 mixture with dimethyl sulfate in water (equation 23).[95]

The most frequent operation carried out on the β-keto esters, particularly those resulting from intramolecular cyclization, is decarboxylation, since in many cases the two products resulting from the two different modes of cyclization give the same ketone. This means that the initial cyclization need not be regioselective and allows mixed products to be carried through the sequence and one-pot procedures to be used. Alkylation or acylation may precede decarboxylation, the ester group then controlling the nucleophilic site. As shown in Scheme 32, 2-ethyl-4-methoxycarbonylcyclohexanone (**82**) has been made

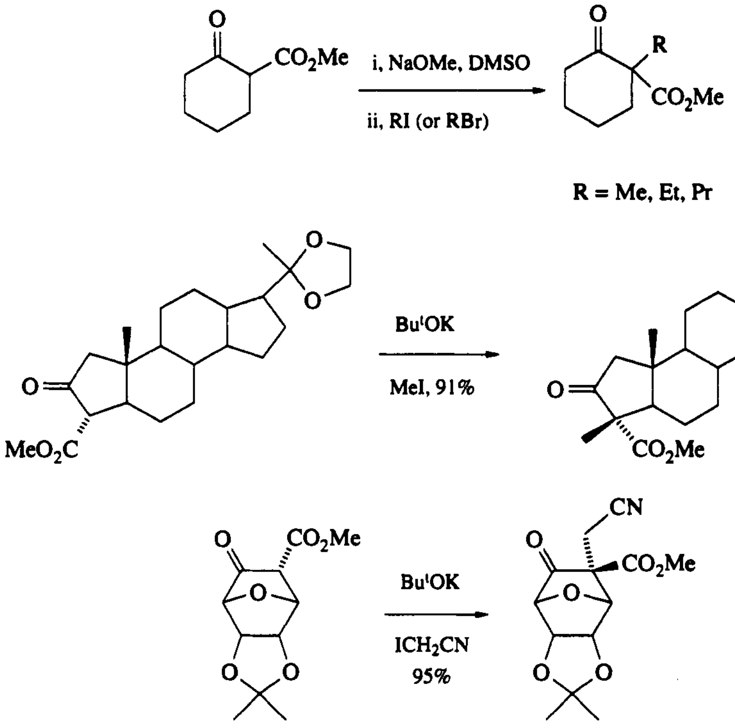
CO2Me
i, NaOMe, DMSO
ii, RI (or RBr)
R
CO2Me
R = Me, Et, Pr
O
MeO2C
Bu'OK
MeI, 91%
CO2Me
CO2Me
Bu'OK
ICH2CN
95%
CN
CO2Me

(ref. 93)

(ref. 78)

(ref. 94)

**Scheme 31**

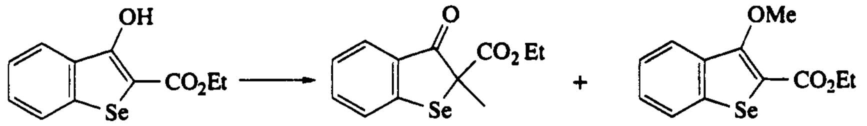
OH
CO2Et
Se
O
CO2 Et
Se
+
OMe
CO2Et
Se

(23)

| | **(76)** | **(77)** | **(78)** |
|---|---|---|---|
| MeI, MeOH | | 60% | 20% |
| $Me_2SO_4$, $H_2O$ | | 20% | 60% |

in a one-pot preparation by cyclization of dimethyl 4-methoxycarbonylheptanedioate (**79**), alkylation with iodoethane, hydrolysis and decarboxylation.[96]

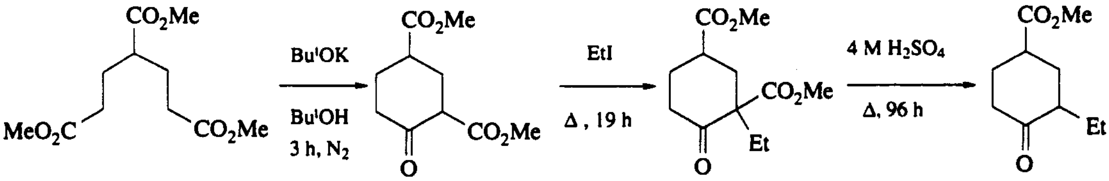
CO2Me
MeO2C
CO2Me
Bu'OK
Bu'OH
3 h, N2
CO2Me
CO2Me
O
EtI
Δ, 19 h
CO2Me
CO2Me
Et
O
4 M H2SO4
Δ, 96 h
CO2Me
Et
O

**(79)** **(80)** **(81)** **(82)** *trans:cis* 1:2

**Scheme 32**

Besides the classical method of ester hydrolysis followed by decarboxylation under acidic conditions, a variety of other methods can be carried out in basic or neutral media. The availability of these routes is important if the compound has acid-labile groups and also for hindered esters that are difficult to hydrolyze. A selection of methods is illustrated in Scheme 33.

Reduction or removal of the ketone function leads to β-hydroxy esters or to esters, respectively. If decarboxylation is carried out first, the alcohol or hydrocarbon results. The Merrell Dow group[75] desilyl-

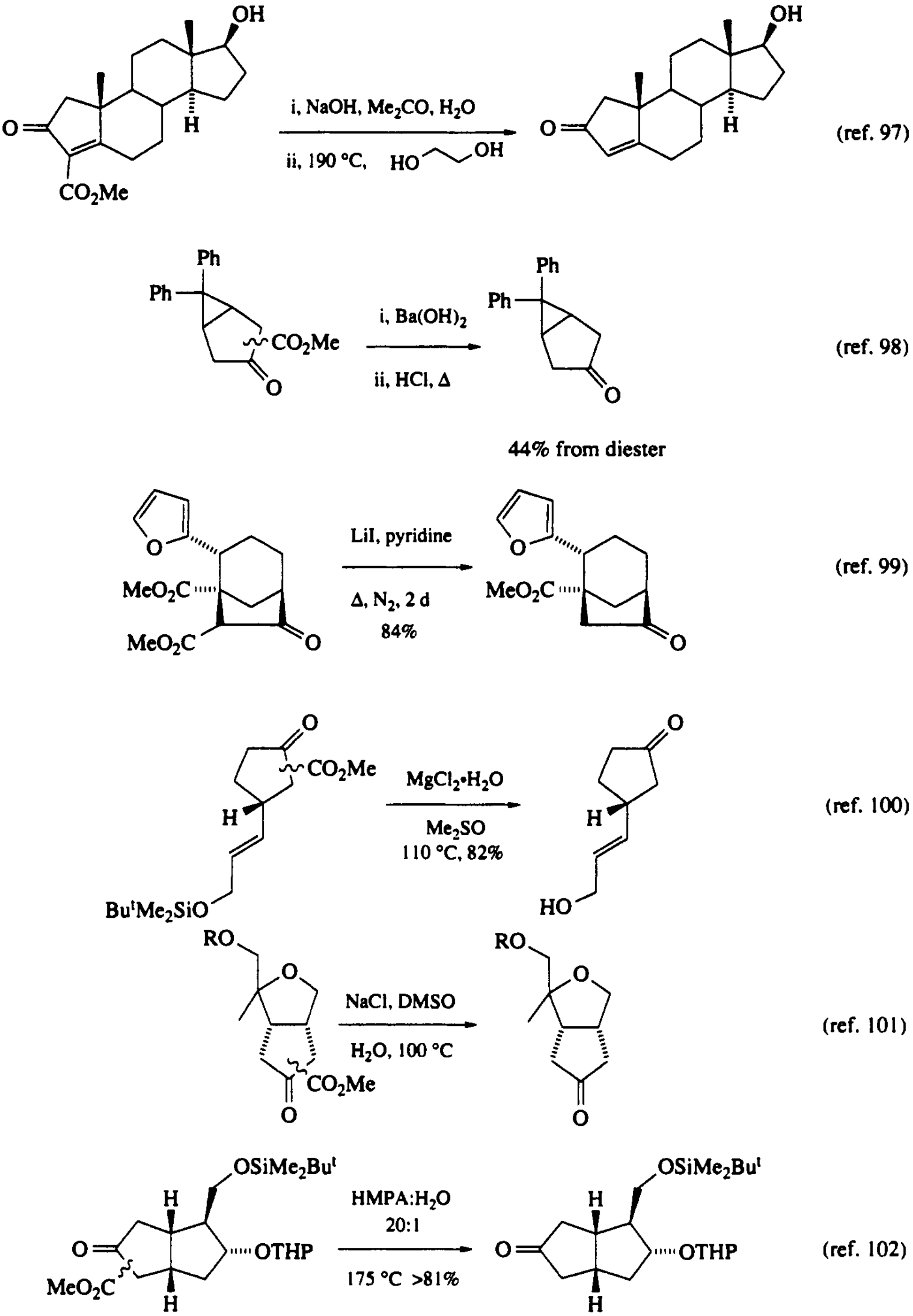

OH
O
H
CO2Me
i, NaOH, Me2CO, H2O
ii, 190 °C, HO OH
(ref. 97)
Ph
Ph
CO2Me
O
i, Ba(OH)2
ii, HCl, Δ
44% from diester
(ref. 98)
O
MeO2C
MeO2C
LiI, pyridine
Δ, N2, 2 d
84%
(ref. 99)
CO2Me
H
ButMe2SiO
MgCl2•H2O
Me2SO
110 °C, 82%
HO
(ref. 100)
RO
CO2Me
NaCl, DMSO
H2O, 100 °C
(ref. 101)
OSiMe2But
OTHP
MeO2C
HMPA:H2O
20:1
175 °C >81%
(ref. 102)

**Scheme 33**

ated the acetal (**83**) with $Bu^n_4NF$ and HF and reduced the resulting ketone, without isolation, with sodium borohydride to (**84**). Elimination then gave (*R*)-(**85**), an inhibitor of GABA-T (Scheme 34).

Bosch and Bonjoch[56] used a reaction combination of Dieckmann reaction, alkylation, ketone removal, a second Dieckmann reaction and finally decarboxylation to prepare functionalized 2-azabicyclo-[3.3.1]nonanes (Scheme 35).

Decarboxylation of the product from (**86**) followed by Wolff–Kishner reduction of the ketone gave (**87**; equation 24).[103]

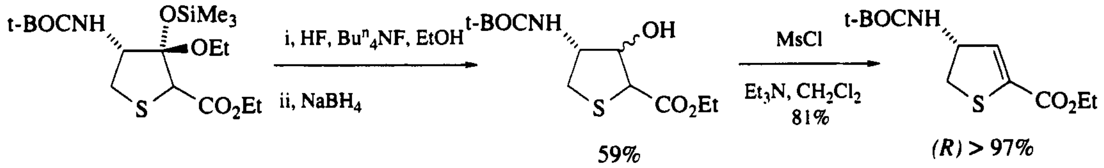
t-BOCNH
OSiMe3
OEt
S
CO2Et
i, HF, Bun4NF, EtOH
ii, NaBH4
t-BOCNH
OH
S
CO2Et
59%
MsCl
Et3N, CH2Cl2
81%
t-BOCNH
S
CO2Et
(R) > 97%

**(83)** **(84)** **(85)**

**Scheme 34**

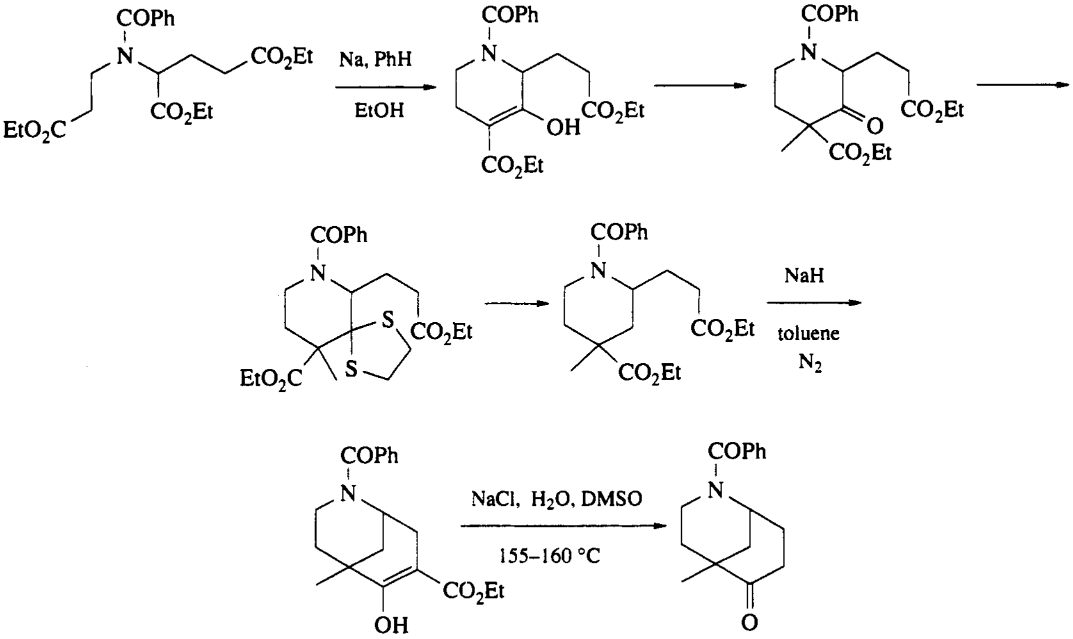
COPh
N
CO2Et
EtO2C
CO2Et
Na, PhH
EtOH
COPh
N
CO2Et
OH
CO2Et
COPh
N
O
CO2Et
CO2Et
COPh
N
S
CO2Et
EtO2C
S
COPh
N
CO2Et
CO2Et
NaH
toluene
N2
COPh
N
CO2Et
OH
NaCl, H2O, DMSO
155–160 °C
COPh
N
O

**Scheme 35**

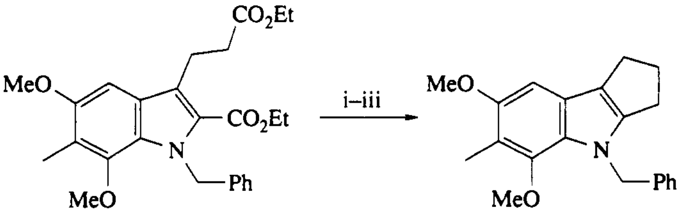
CO2Et
MeO
CO2Et
N
Ph
MeO
i–iii
MeO
N
Ph
MeO

(24)

**(86)** **(87)**

i, NaH, PhH, Δ, 16 h; ii, 10% $H_2SO_4$, EtOH, Δ, 8 h; iii, $NH_2NH_2$, $HOCH_2CH_2OH$, KOH, 180–190 °C

### *3.6.3.4.2 Use of the Claisen condensation in synthesis*

The Claisen condensation has been widely used as a means of C—C bond formation, the reaction having a biological counterpart in the formation of β-keto esters *via* acetylcoenzyme A. The value of the reaction is greatly enhanced if it can be made regioselective. This can be accomplished simply if one of the esters has no available α-hydrogen, otherwise the means must be found for distinguishing the nucleophilicity (and electrophilicity) of the reacting species. One possibility is to preform the enolate of one component. The lithium enolate of *t*-butyl acetate (**89**) reacts regioselectively with (**88**) to give the keto ester (**90**; equation 25).[104]

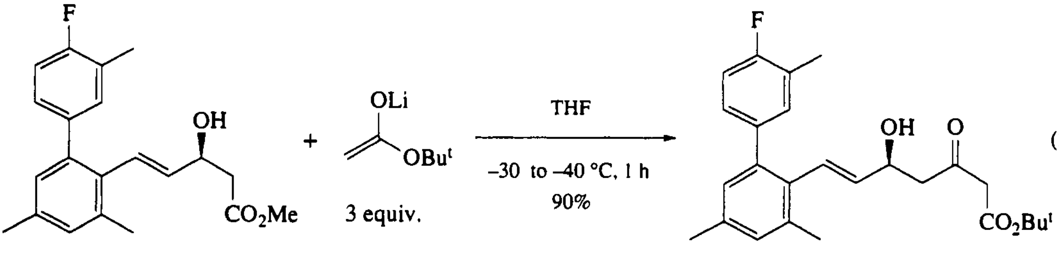
F
OH
CO2Me
+
OLi
OBu^t
3 equiv.
THF
-30 to -40 °C, 1 h
90%
F
OH
O
CO2Bu^t

(25)

(**88**) (**89**) (**90**)

The indole esters (**91**) are not readily enolized and reaction with the lactones (**92**) regioselectively gives (**93**; equation 26).[105] Similarly, the ester function of the oxazole (**94**) acts as the electrophile with ethyl acetate giving (**95**)[106] rather than (**96**) as was originally thought (equation 27).

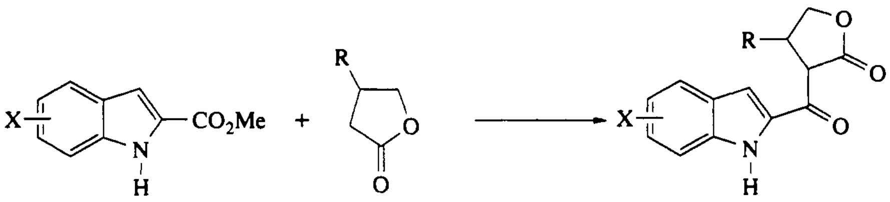
X
CO2Me
N
H
+
R
O
O
X
N
H
R
O
O
O

(26)

(**91**) (**92**) (**93**)

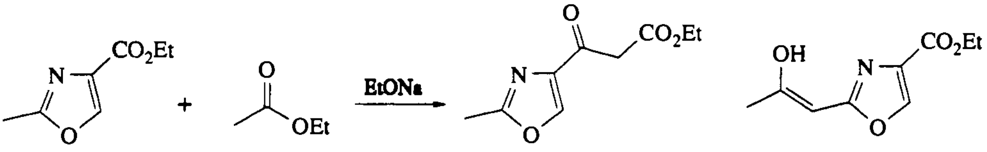
CO2Et
N
O
+
O
OEt
EtONa
O
CO2Et
N
O
OH
N
CO2Et
O

(27)

(**94**) (**95**) (**96**)

The dianion of pentane-2,4-dione (**97**) reacts as the nucleophile with the enolate of dimethyl malonate to give the labile (**98**), which cyclizes to methyl 2,4-dihydroxy-6-methylbenzoate (**99**) at pH 5 (Scheme 36).[107]

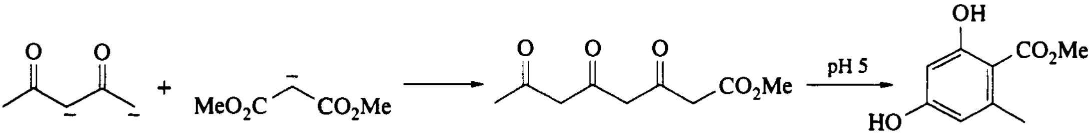
O
O
+
MeO2C
CO2Me
O
O
O
CO2Me
pH 5
OH
CO2Me
HO

(**97**) (**98**) (**99**)

**Scheme 36**

Weedon and coworkers used the condensation of the methyl ketone (**100**) with polyene ester (**101**) to form the enolic β-diketone portion (**102**) of the carotenoids mytloxanthin and trikentriorhodin (equation 28).[108] A similar condensation was used to form the β-diketone (**105**) of all-(*E*)-wallemia C by reaction of (**103**) with the methyl ketone (**104**; equation 29).[109]

Self-condensation reactions, as in the original Claisen reaction, are still synthetically valuable. The ester (**106**) was self-condensed with isopropylmagnesium bromide as the base and this product used in spherand formation (equation 30).[110]

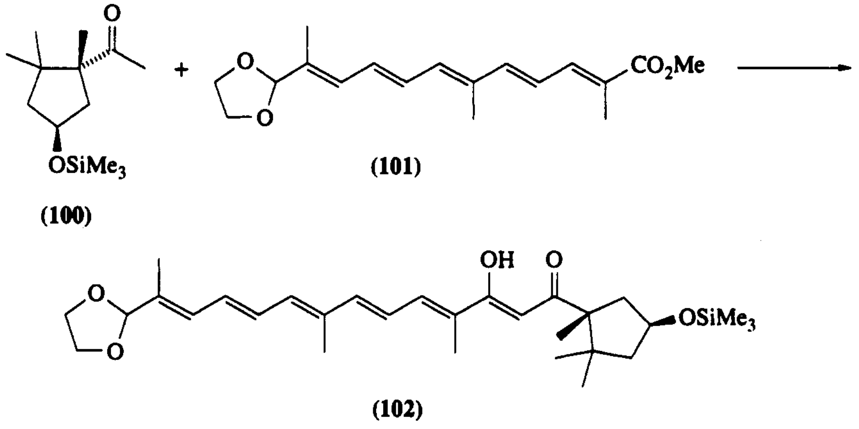
O
OSiMe3
+
O
O
CO2Me
OH
O
OSiMe3

**(100)** **(101)** **(102)**

(28)

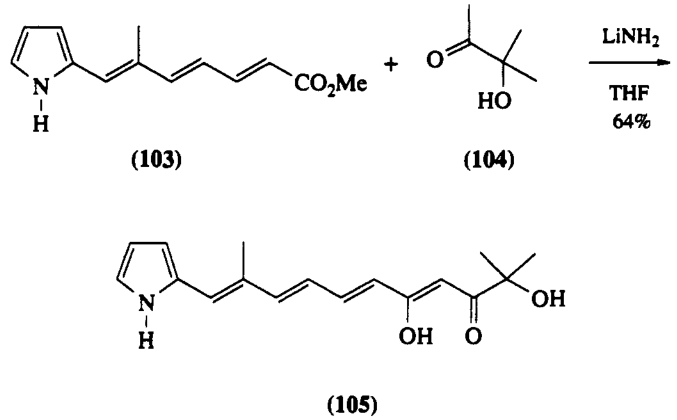
N
H
CO2Me
+
O
HO
LiNH2
THF
64%
OH
OH
O

**(103)** **(104)** **(105)**

(29)

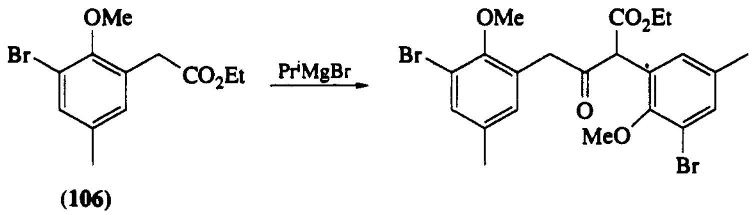
OMe
Br
CO2Et
PriMgBr
OMe
CO2Et
Br
O
MeO
Br

**(106)**

(30)

An interesting double vinylogous Claisen condensation was used in a total synthesis of (±)-secologanin aglycone.[111] Potassium methoxide-catalyzed condensation of methyl 2-hexenoate with dimethyl oxalate gave the tricyclic derivative (**107**; equation 31).

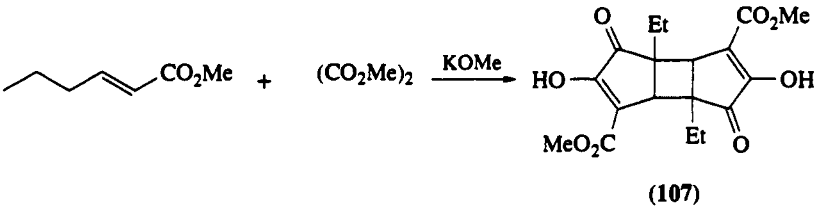
CO2Me
+
(CO2Me)2
KOMe
O
Et
CO2Me
HO
OH
MeO2C
Et
O

**(107)**

(31)

### *3.6.3.4.3 Use of the Dieckmann reaction in synthesis*

The synthetic value of the Dieckmann reaction has been demonstrated in Section 3.6.3.3. It has been used as a major synthetic tool for the preparation of a great variety of natural and nonnatural products. A large measure of its value lies in the range of functional groups that can be tolerated and the variety of reaction conditions that can be used to effect the cyclization. The reaction is more often used at an early stage in the synthetic route, but that is not necessarily always the case.

### *(i) Steroids*

The reaction has been used to prepare both five- and six-membered steroidal rings (Scheme 37). Both the six-membered C-ring[51] and the five-membered D-ring[52,112] have been prepared from the corresponding diesters. Ring A norsteroids are readily prepared by oxidative cleavage of ring A and cyclization of the resulting diacid as the diester (**47**) to (**48**; Scheme 25).[78,97,113,114] The C-10 methyl group (steroid numbering) controls the direction of cyclization, further emphasized in the case of the α,β-unsaturated ester.[97] Subsequent alkylation and decarboxylation gave the 3-methyl-2-ketonorsteroid.[78]

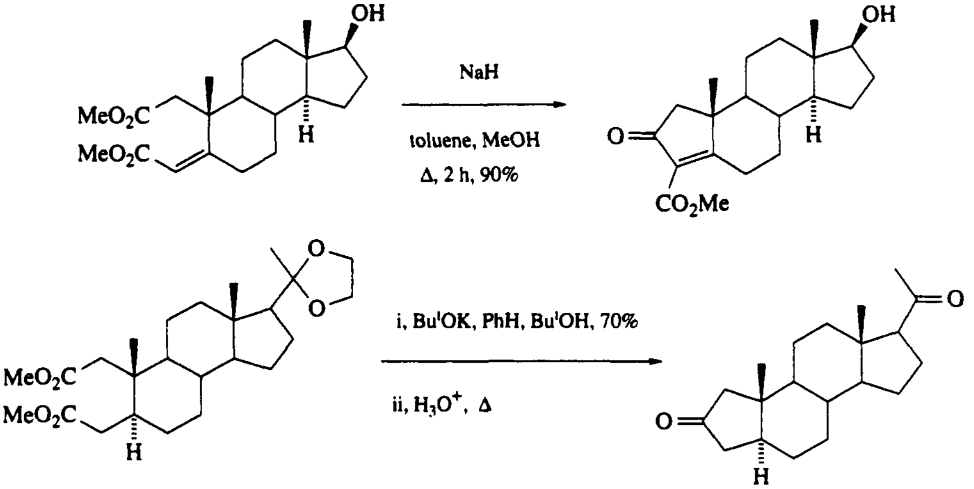
OH
$MeO_2C$
$MeO_2C$
H
NaH
toluene, MeOH
Δ, 2 h, 90%
OH
O
H
$CO_2Me$
O
O
$MeO_2C$
$MeO_2C$
H
i, $Bu^tOK$, PhH, $Bu^tOH$, 70%
ii, $H_3O^+$, Δ
O
O
H

**(47)**

Scheme 37

### *(ii) Prostaglandins*

The diester enantiomer (**108**) derived from ribonolactone, has been cyclized and decarboxylated to the bicyclic ketone (**109**) in 83% overall yield for the two steps (Scheme 38).[115] Similarly, the cyclopentanol diester (**110**) has been cyclized and decarboxylated to (**111**), separation of the two diastereomers being effected on the deprotected alcohols (Scheme 39).[116] Cyclization of (**112**) occurs regioselectively as expected to give (**113**) in 81% yield (equation 32).[117] The 9-azaprostaglandin skeleton has been formed through a combination of Michael and Dieckmann reactions.[118]

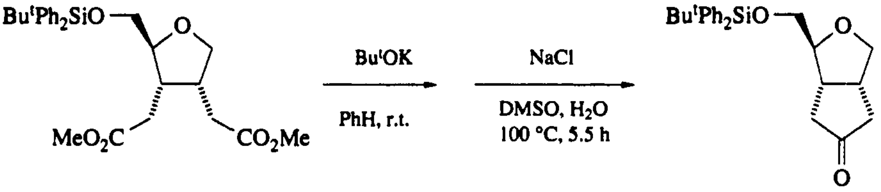
$Bu^tPh_2SiO$
O
$MeO_2C$
$CO_2Me$
$Bu^tOK$
PhH, r.t.
NaCl
DMSO, $H_2O$
100 °C, 5.5 h
$Bu^tPh_2SiO$
O
O

**(108)** **(109)**

Scheme 38

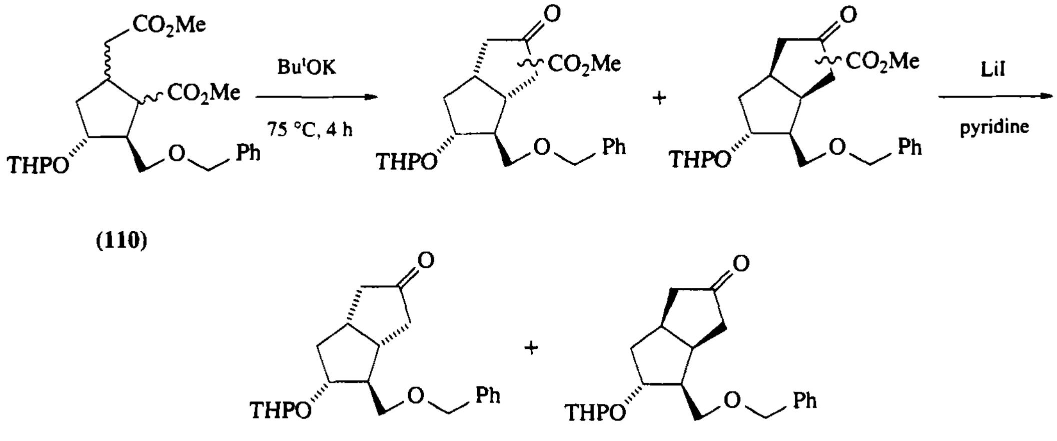
CO2Me
CO2Me
THPO
O
Ph
Bu'OK
75 °C, 4 h
+
LiI
pyridine
+

**(110)**

**(111a)** **(111b)**

Scheme 39

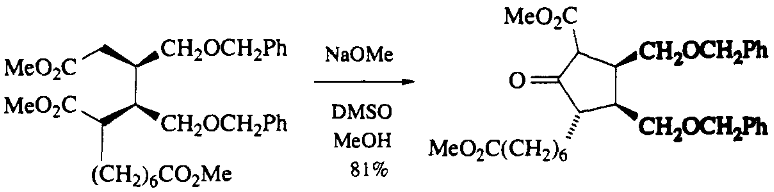
MeO2C
MeO2C
CH2OCH2Ph
CH2OCH2Ph
(CH2)6CO2Me
NaOMe
DMSO
MeOH
81%
MeO2C
O
MeO2C(CH2)6

**(112)** **(113)** (32)

*(iii) Terpenoids*

A variety of terpenoid syntheses have employed the Dieckmann condensation in ring formation. Corey *et al.*[54] constructed the five-membered ring of the 5,6-spiro system of (±)-perhydrohistrionicotoxin in this way and one of the five-membered rings of the sesterterpenes ceroplastol and ophiobolin was similarly formed (equation 33).[119] Cyclization and decarboxylation of the diester (**114**) gave the single enantiomer (**115**), equilibration of the methyl group into the favorable thermodynamic *trans* configuration having occurred under the reaction conditions.[81] The enantiomer (**117**) was prepared from (**116**) in a similar manner (Scheme 40).[100] The seven-membered rings of gascardic acid[71] and (±)-gnididone[61] and the 15-membered ring of optically active muscone[63] were formed in the same way, the salts of hindered bases being used to effect these condensations with high dilution conditions for the macrocyclic ring.

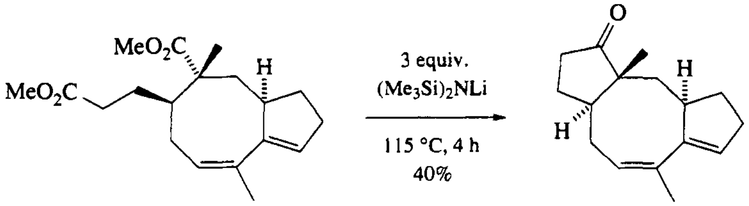
MeO2C
MeO2C
H
3 equiv.
(Me3Si)2NLi
115 °C, 4 h
40%
O
H
H

(33)

*(iv) Anthracycline antibiotics*

Regioselective cyclization of (**118**) *via* the ketone enolate occurs to give (**119**).[120] Zinc is necessary for a reasonable yield, and longer heating rearranges (**119**) to (**120**). Similarly, but under standard conditions, the 4-ketopyran (**121**) cyclizes regioselectively to (**122**)[88] and the anthraquinone (**123**) cyclizes to (**124**; Scheme 41).[121]

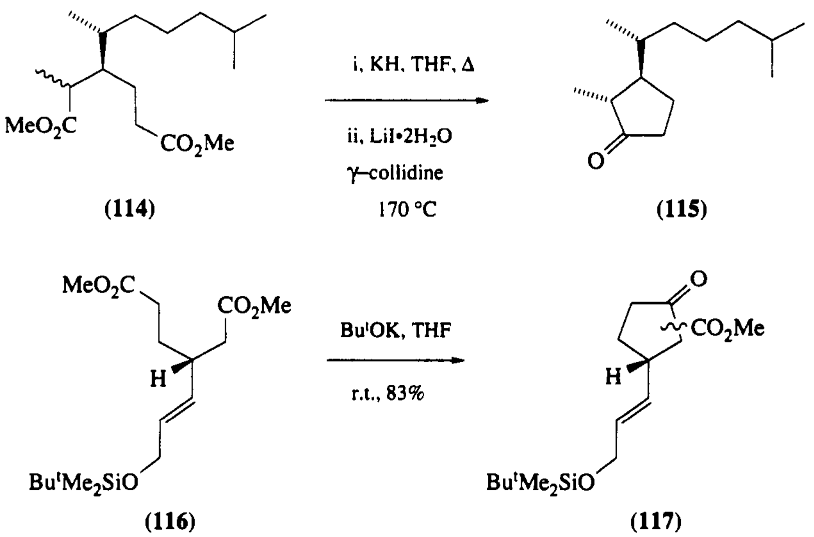
(114)
i, KH, THF, Δ
ii, LiI•2H₂O
γ-collidine
170 °C
(115)
(116)
Bu^tOK, THF
r.t., 83%
(117)

**Scheme 40**

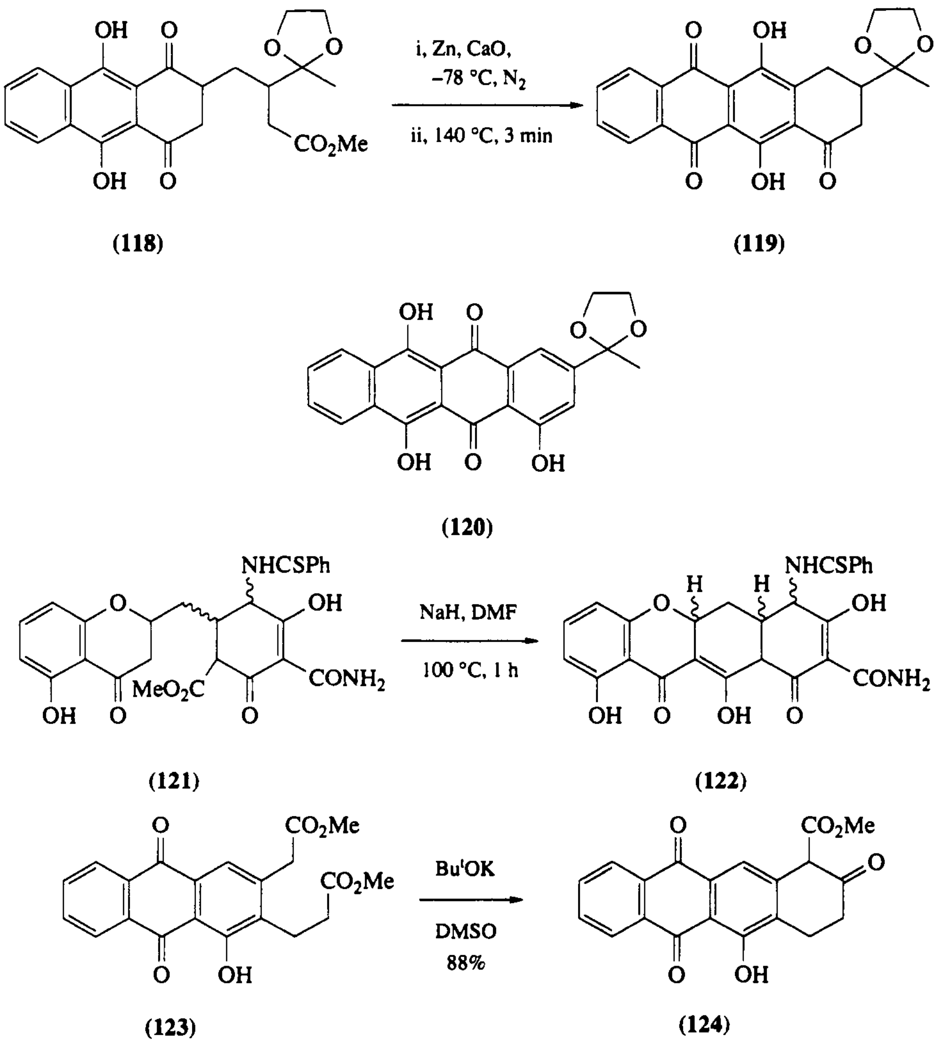
(118)
i, Zn, CaO,
−78 °C, N₂
ii, 140 °C, 3 min
(119)
(120)
(121)
NaH, DMF
100 °C, 1 h
(122)
(123)
Bu^tOK
DMSO
88%
(124)

**Scheme 41**

### *(v) Penicillin antibiotics*

Remarkably, cyclization of a five- or six-membered ring onto the already strained β-lactam can be effected under mild conditions and in high yield (Scheme 42). Regioselective control has been effected by use of a thiol ester, as illustrated in the conversion of (**125**) into (**126**)[122] and of the two diastereomers of (**127**) into the diastereomers of (**128**).[123] In order to facilitate reaction under mild conditions, one of the groups can be made more electrophilic by conversion to an acid chloride. Reaction of (**129**) with lithium hexamethyldisilazane at –78 °C gave (**130**). The ketone group in (**130**) could be reduced selectively with $NaBH_4$ at –60 °C to give (**131**).[124]

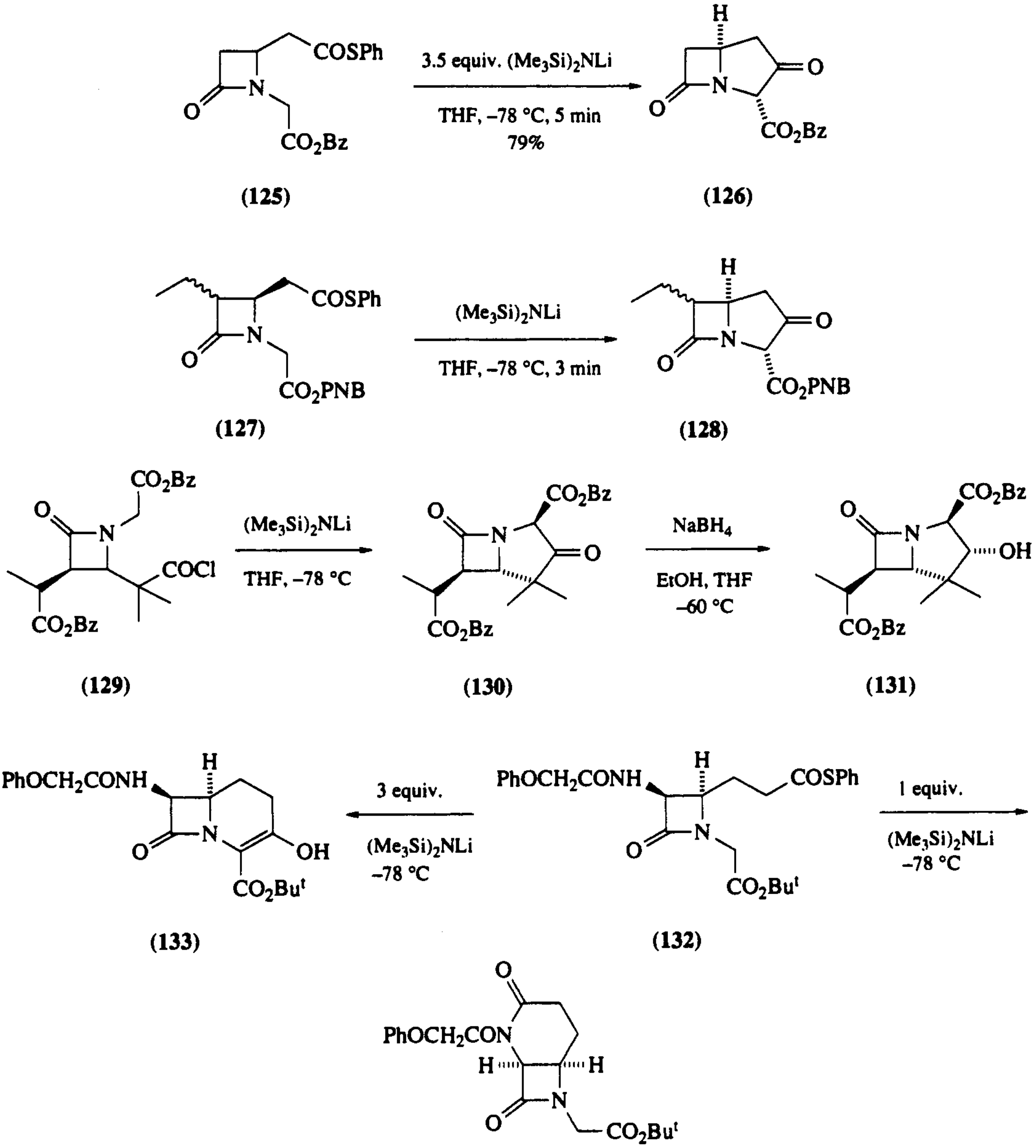
COSPh
N
O
CO2Bz
3.5 equiv. (Me3Si)2NLi
THF, –78 °C, 5 min
79%
H
O
N
O
CO2Bz
(125)
(126)
COSPh
CO2PNB
(Me3Si)2NLi
THF, –78 °C, 3 min
CO2PNB
(127)
(128)
CO2Bz
COCl
CO2Bz
(Me3Si)2NLi
THF, –78 °C
CO2Bz
O
CO2Bz
NaBH4
EtOH, THF
–60 °C
CO2Bz
OH
CO2Bz
(129)
(130)
(131)
PhOCH2CONH
H
OH
CO2Bu^t
3 equiv.
(Me3Si)2NLi
–78 °C
PhOCH2CONH
H
COSPh
CO2Bu^t
1 equiv.
(Me3Si)2NLi
–78 °C
(133)
(132)
O
PhOCH2CON
H
H
N
CO2Bu^t

**(134)**

**Scheme 42**

In their synthesis of the 1-carbacephem derivatives, Hatanaka and Ishimaru observed that the β-lactam (**132**) cyclized to the desired carbacephem skeleton (**133**) with 3 equiv. of lithium hexamethyldisilazane (Scheme 42), but cyclized through the amine nitrogen to give (**134**) with 1 equiv.[125] Presumably deprotonation of the amine occurs with the first equivalent of base.

### *(vi) Carbohydrates*

Carbohydrates, which have recently been used extensively as chiral components in syntheses, have been transformed into diesters that, on cyclization, lead to precursors of polycyclic natural products. The tetrahydrofuran diester (**135**) was cyclized with potassium *t*-butoxide to an isomeric mixture (**136**) that was decarboxylated to (**137**).[126] The related diester (**138**) was cyclized to a mixture (8:1) of (**139**) and (**140**), whereas the lactone (**141**) cyclized regioselectively to (**142**) and this was in turn methylated with iodomethane to the *trans-syn-cis* isomer (**143**; Scheme 43).[127]

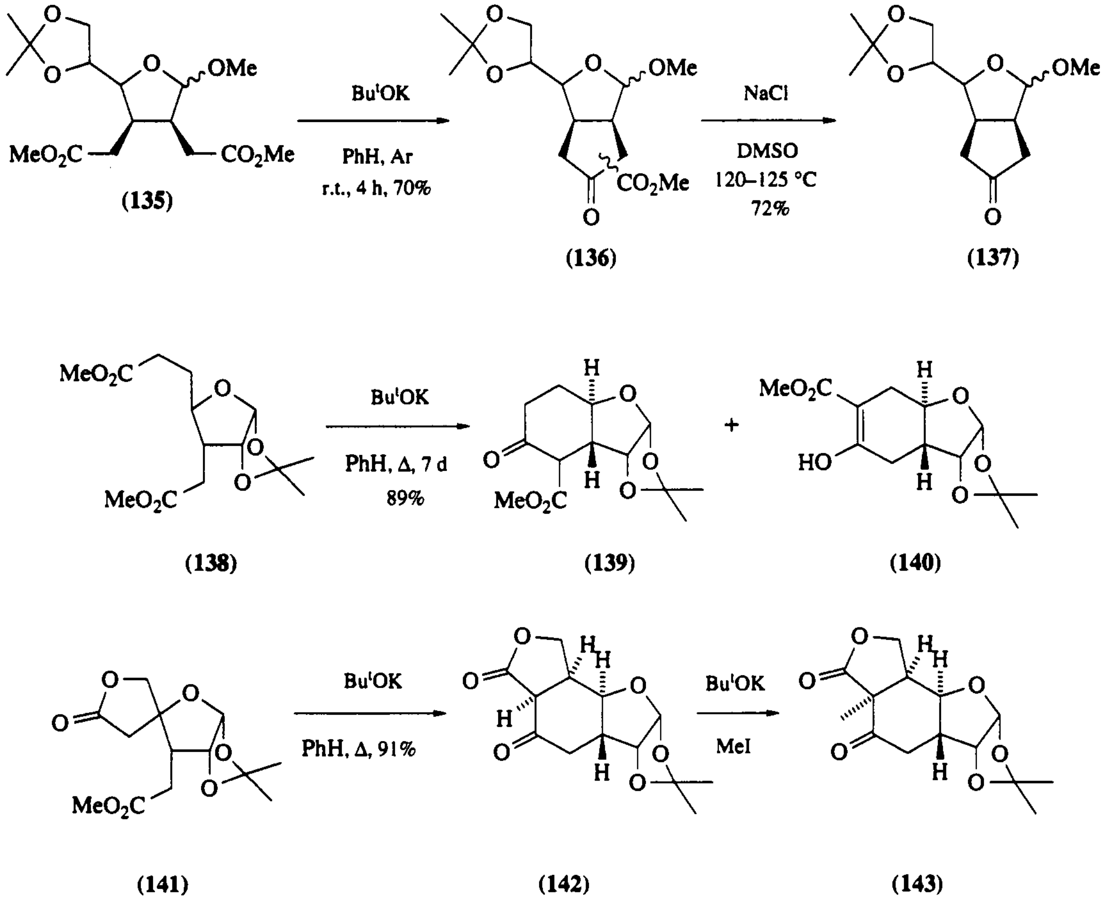
OMe
MeO2C
CO2Me
(135)
Bu'OK
PhH, Ar
r.t., 4 h, 70%
CO2Me
(136)
NaCl
DMSO
120–125 °C
72%
(137)
MeO2C
MeO2C
(138)
Bu'OK
PhH, Δ, 7 d
89%
H
MeO2C
(139)
+
HO
(140)
(141)
Bu'OK
PhH, Δ, 91%
(142)
Bu'OK
MeI
(143)

**Scheme 43**

The dimethyl tartrate derivative (**144**) forms the dilithium salt (**145**) with excess lithium hexamethyldisilazane and this smoothly transforms into the butenolide (**146**), which is obtained crystalline in 78% yield.[128] Lithiation of the hydroxy group prevents 1,2-elimination (Scheme 44).

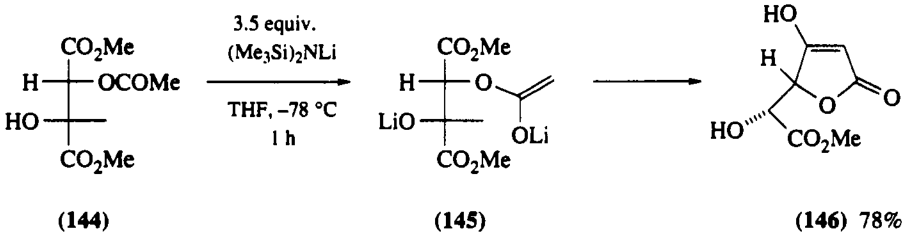
CO2Me
H
OCOMe
HO
CO2Me
(144)
3.5 equiv.
(Me3Si)2NLi
THF, -78 °C
1 h
CO2Me
H
O
LiO
OLi
CO2Me
(145)
HO
H
O
O
HO
CO2Me
(146) 78%

**Scheme 44**

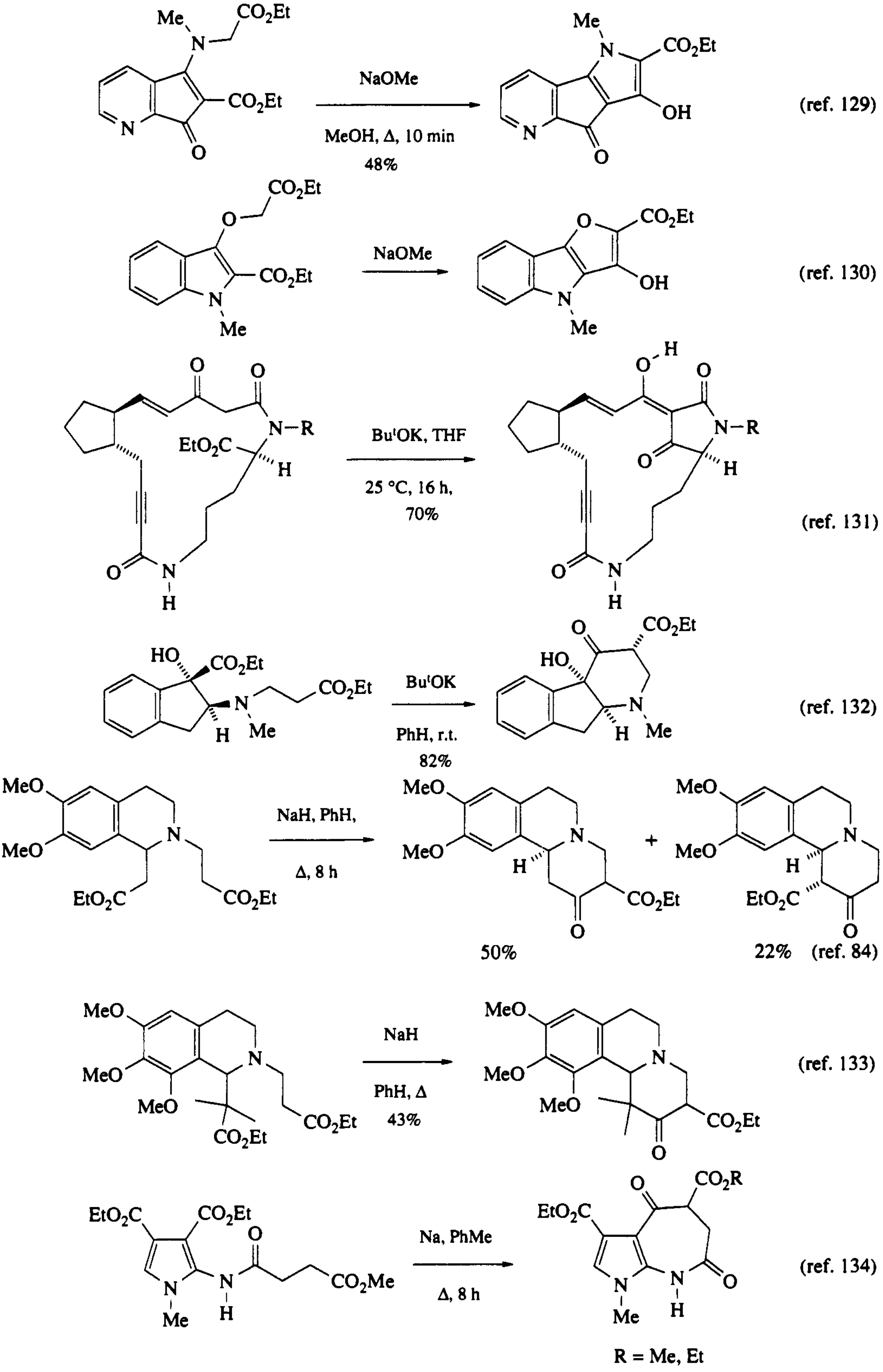
NaOMe
MeOH, Δ, 10 min
48%
(ref. 129)
NaOMe
(ref. 130)
Bu<sup>t</sup>OK, THF
25 °C, 16 h,
70%
(ref. 131)
Bu<sup>t</sup>OK
PhH, r.t.
82%
(ref. 132)
NaH, PhH,
Δ, 8 h
+
50%
22% (ref. 84)
NaH
PhH, Δ
43%
(ref. 133)
Na, PhMe
Δ, 8 h
(ref. 134)
R = Me, Et

**Scheme 45**

### *(vii) Heterocycles and alkaloids*

The ability of the Dieckmann reaction to tolerate heteroatoms in the ring-forming sequence of atoms has led to its extensive use in heterocyclic synthesis. Many complex systems containing heterocyclic rings have been prepared by routes that include this reaction, and both aromatic and alicyclic rings have been constructed. A variety of bases and solvents have been employed and representative examples are illustrated in Scheme 45.

### *(viii) Fenestranes*

A number of routes to the fenestranes have involved Dieckmann reactions (Scheme 46). The ester (**147**)[62] was decarboxylated and the resulting ketone converted into the tosylhydrazone (**148**). Irradiation of the potassium salt gave the [5.5.5.5]fenestrane derivative (**149**) *via* carbene insertion. The bicyclo[2.2.0]hexane diester (**150**) was cyclized with sodium hydride in THF containing a little methanol and the product decarboxylated to give (**151**).[135] The diester (**152a**), however, underwent the Dieckmann reaction in >5% yield, whereas the corresponding dinitrile (**152b**) underwent a Thorpe–Ziegler cyclization in 59% yield.[136]

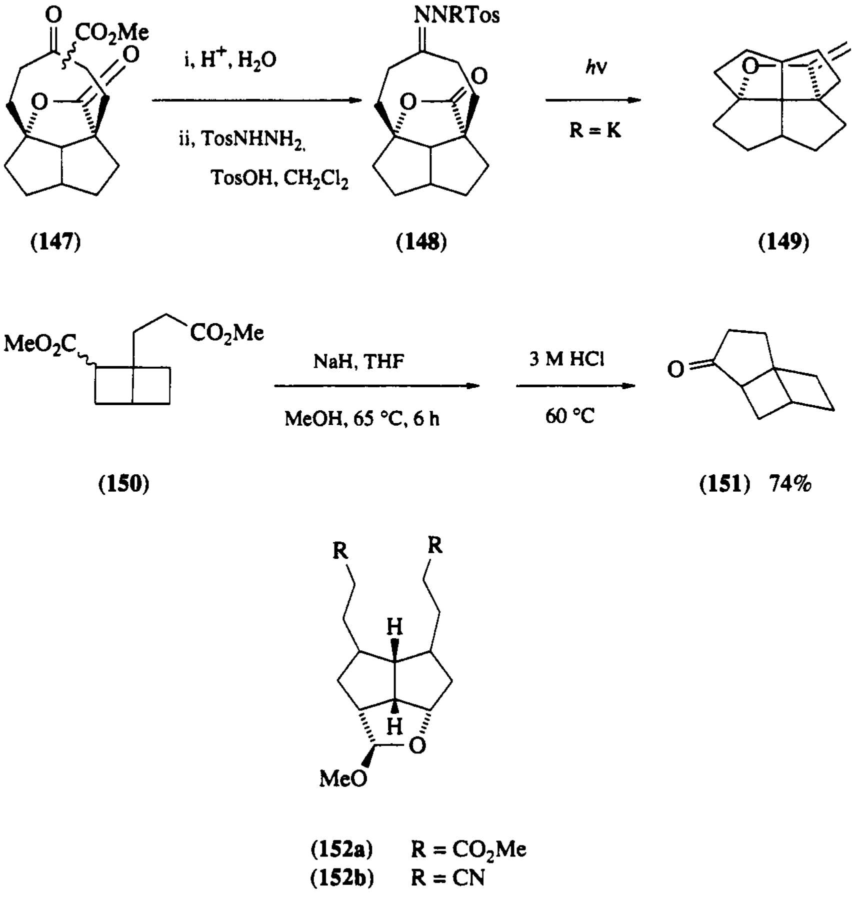

**Scheme 46**

## 3.6.4 ACYLATION OF KETONES BY ESTERS AND OTHER ACID DERIVATIVES

### 3.6.4.1 Introduction

The acylation of ketones by esters and other acid derivatives is a well-established route to β-diketones and β-keto aldehydes. The reaction has been reviewed with extensive coverage to 1949 in *Organic Reactions*[5] and more recently by House[7] and by Caine.[8] The reaction may be effected either with basic or acidic catalysts. With base, a four-step ionic mechanism, similar to that described for the acylation of esters, is involved. Side reactions, such as an aldol reaction of the ketone or a self-condensation of the ester, are also observed but may be minimized by suitable choice of substrate, base and conditions.

## 3.6.4.2 Generation and Use of Enolates and Enol Ethers

### *3.6.4.2.1 Enolate generation in situ*

For acylations with reactive esters, such as formate or oxalate (see Section 3.6.4.5), sodium alkoxides are still the bases of choice, but sodium hydride, dimsyl sodium, sodium or potassium amide or sodium metal have all been used for the *in situ* generation of the enolate anion. A typical example is shown in Scheme 47.[137] Acylation by esters results in the production of 1 equiv. of the alkoxide ion, along with the β-dicarbonyl compound; proton transfer then results in the production of the conjugate base of the dicarbonyl compound. This process normally leads to the more stable anion in the acylation of an unsymmetrical ketone. The acyl group thus becomes attached to the less-substituted α-position of the ketone. The less stable *O*-acylated products are normally not observed in such reversible base-catalyzed reactions. Methyl alkyl ketones are normally acylated on the methyl group; where both α-carbons are substituted to the same extent, acylation occurs at the less-hindered site. Acylation is observed only rarely at a methine carbon as the more stable β-diketone enolate cannot be formed.

$$XC_6H_4COMe \quad + \quad MeO_2CC_6H_4Y \xrightarrow[76\text{–}87\%]{\text{i, ii}} XC_6H_4COCH_2COC_6H_4Y$$

$X = H, Y = H; X = p\text{-MeO}, Y = p\text{-MeO}; X = p\text{-MeO}, Y = H$

i, NaH, DMSO, <15 °C; ii, $H_3O^+$, 0 °C

Scheme 47

### *3.6.4.2.2 Preformed enolates and enol ethers*

Preformed metal enolates and enol ethers, well-established intermediates in aldol chemistry and in the acylation of esters (see Section 3.6.3.2) have also been widely used in the acylation of ketones. The use of enamines for the acylation of ketones is covered elsewhere in this volume. A significant problem in the acylation of enolates is the reaction of the newly formed diketone with the enolate (Scheme 48). Addition of 1 equiv. of acid chloride to 2 equiv. of enolate gives fair to good yields of diketone, calculated from the acylating reagent, but with a theoretical yield of only 50% with respect to the enolate. Further, the diisopropylamine produced if LDA is used as the base may itself undergo acylation. A number of strategies have been developed to overcome this problem. Emphasis in the examples has been on establishing the methodology with simple systems; the extension to more complex systems is less common. The use of mesityllithium[138] avoided the presence of free diisopropylamine and employed a 1:1 ratio of ketone and acid chloride (Scheme 49). The use of dimethylhydrazones[139] avoided *O*-acylation, giving regiospecific *C*-acylation with a 1:1 ratio of reagents (Scheme 50). Acyl cyanides have again proved their value, either with lithium enolates[140] or trimethylsilyl enol ethers (Scheme 51).[141] The latter derivatives were also acylated using acid chlorides with Lewis acids catalysis (equation 34).[142] The less familiar boroxazine intermediates allowed for regioselective acylation in good yield (Scheme 52),[143] a result also achieved using α-chloroacyltrimethylsilanes followed by an intramolecular rearrangement (Scheme 53).[144] Dialkyl acylphosphonates have also been used to acylate a lithium enolate (equation 35).[145]

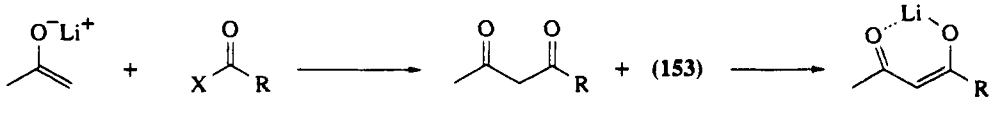

(153)

Scheme 48

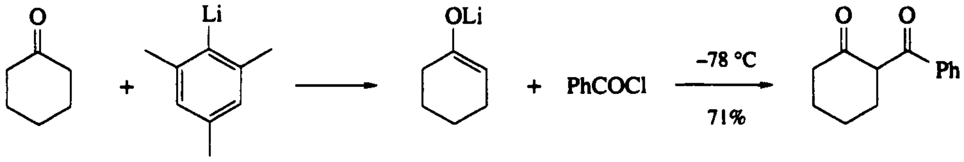
O
Li
OLi
PhCOCl
–78 °C
71%
O
O
Ph

**Scheme 49**

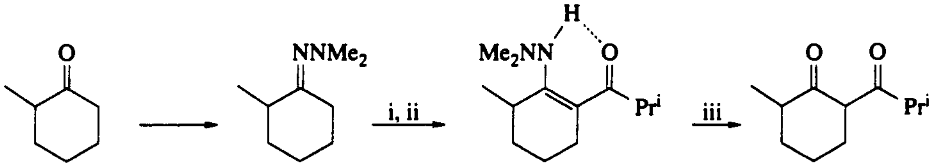
O
NNMe2
i, ii
H
Me2NN
O
Pri
iii
O
O
Pri

i, BuLi, THF, -78 °C *or* LDA, THF, 0 °C 67% overall; ii, $Pr^iCOCl$; iii, $H_3O^+$, MeOH

**Scheme 50**

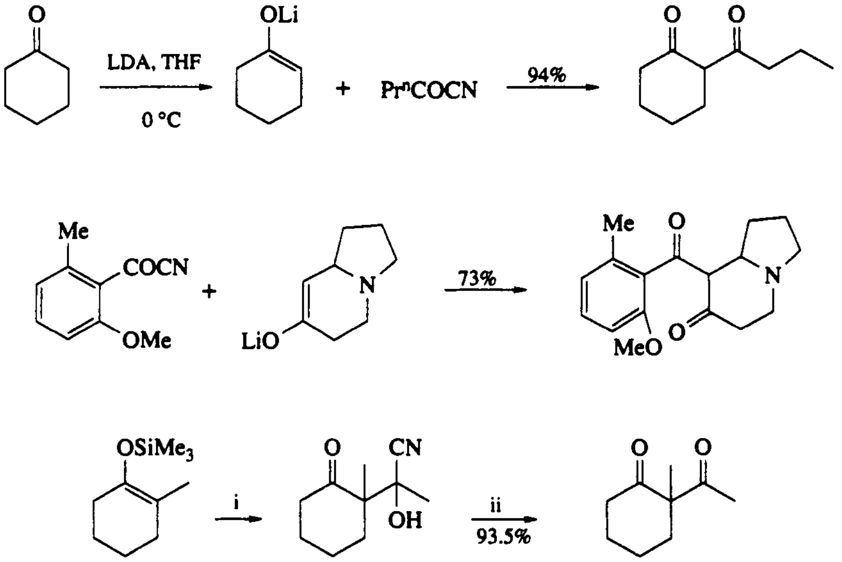
O
LDA, THF
0 °C
OLi
PrnCOCN
94%
O
O
Me
COCN
OMe
LiO
N
73%
Me
O
N
MeO
O
OSiMe3
i
O
CN
OH
ii
93.5%
O
O

i, MeCOCN, $TiCl_4$, $CH_2Cl_2$, -78 °C; ii, cold aq. $OH^-$

**Scheme 51**

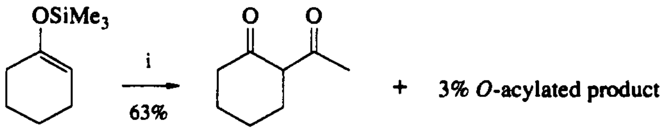
OSiMe3
i
63%
O
O
+ 3% O-acylated product

(34)

i, MeCOCl, $ZnCl_2$, $CH_2Cl_2$, 0 °C ($SbCl_3$ also used)

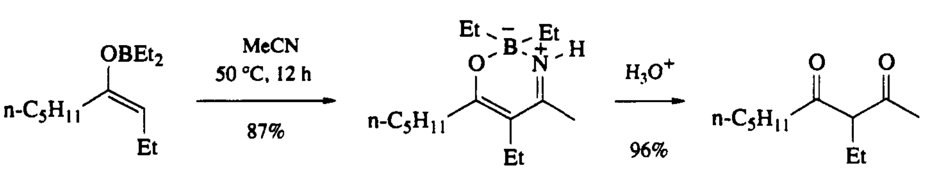

**Scheme 52**

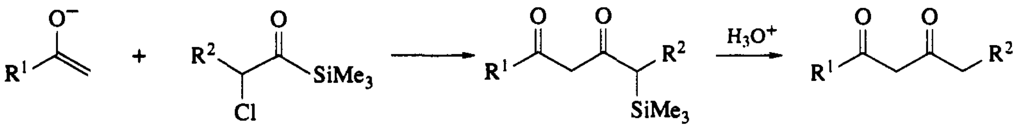

**Scheme 53**

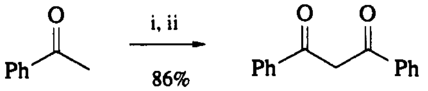

(35)

i, LiN(SiMe$_3$)$_2$; ii, PhCOPO(OEt)$_2$, -78 °C, 30 min

### *3.6.4.2.3 Trapped enolates, organocopper conjugate addition*

Enolates formed by organocopper conjugate addition may be acylated cleanly by acid chlorides to give β-diketones.[146] Although *O*- and *C*-acylation are both possible, the latter is favored by the use of acid chlorides rather than anhydrides and by the use of diethyl ether as solvent, rather than DME. Good yields of β-diketones have been obtained by acylation of the anions derived from both acyclic and cyclic unsaturated ketones with cuprates, or in copper-catalyzed Grignard reactions. Some synthetic applications are given in Scheme 54.

### *3.6.4.2.4 Dianions γ-acylation*

Dianions of β-keto esters undergo γ-acylation when reacted with esters to produce diketo esters in fair yield (Scheme 55). As the monoanion of the product has a more acidic proton than the monoanion of the starting β-keto ester, proton transfer from the monoanion of the diketo ester to the dianion of the starting material should occur and the maximum conversion of β-keto ester to product would be 50% in this reaction. The problem has been overcome, as shown in Scheme 55, by adding 0.5 equiv. of the ester to the dianion and regenerating the quenched dianion by the addition of more base before adding further ester; in this way yields of about 70% were obtained.[151] The reaction has been put to good use in the synthesis of poly-β-diketones which, on cyclization with base, produce polyketides in a biomimetic synthesis. Yamaguchi *et al.*[152] reacted a number of substituted glutarate esters with the dianion of methyl acetoacetate (Scheme 56), while another group[153] reacted the dianion of pentane-2,4-dione with the ethylene ketal of diethyl 3-oxoglutarate to produce, eventually, the anthraquinone emodin (Scheme 57).

### 3.6.4.3 Ketones as Enols: Acid Catalysis of Acylation

Complementary to the acylation of enolate anions is the acid-catalyzed acylation of the corresponding enols, where the regiochemistry of acylation can vary from that observed in base-catalyzed reactions. Although the reaction has been studied extensively in simple systems, it has not been widely used in the synthesis of complex molecules. The catalysts most frequently employed are boron trifluoride, aluminum chloride and some proton acids, and acid anhydrides are the most frequently used acylating agents. Reaction is thought to involve electrophilic attack on the enol of the ketone by a Lewis acid complex of the anhydride (Scheme 58). In the presence of a proton acid, the enol ester is probably the reactive nucleophile. In either case, the first formed 1,3-dicarbonyl compound is converted into its borofluoride complex, which may be decomposed to give the β-diketone, sometimes isolated as its copper complex.[154]

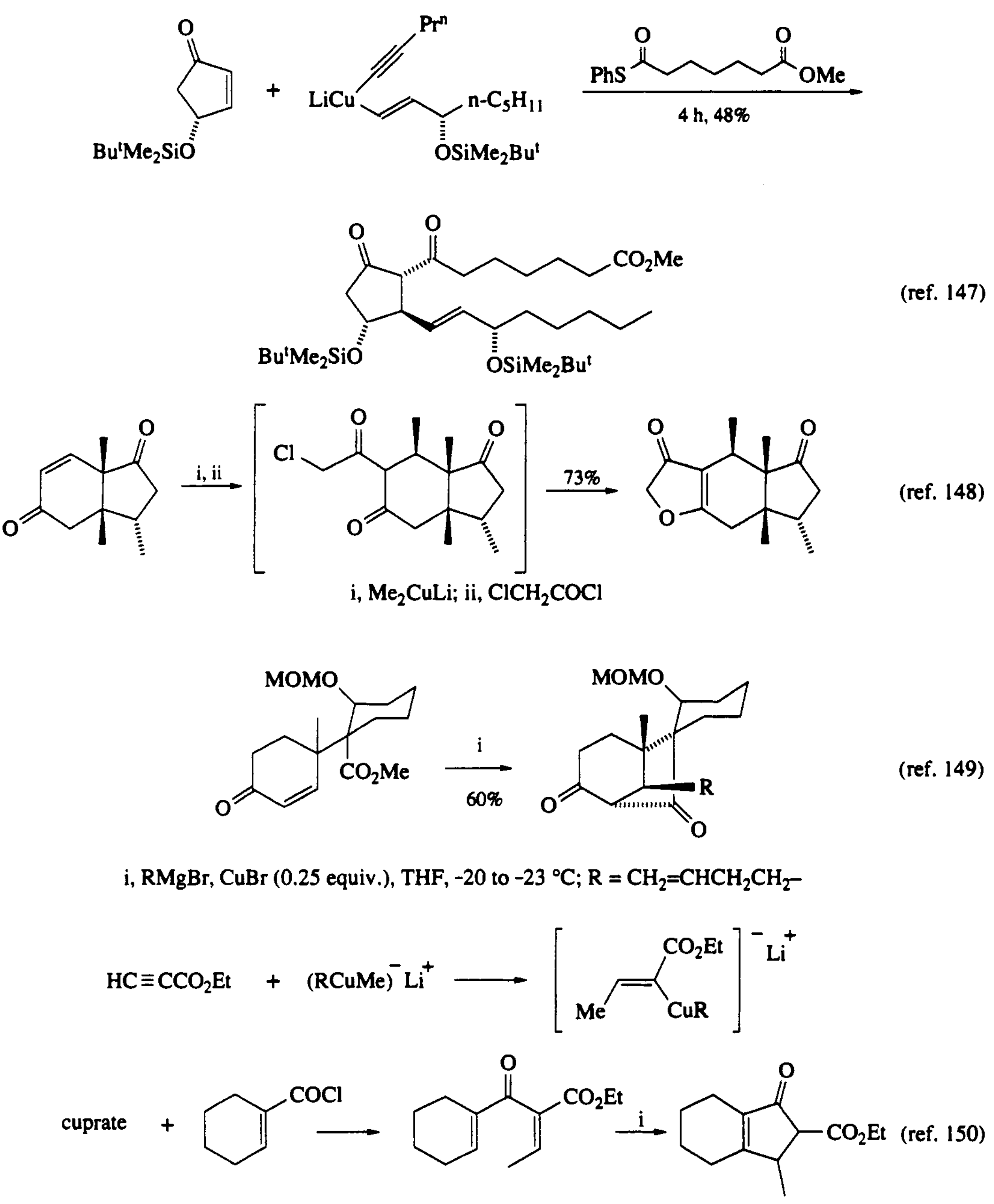
Bu$^t$Me$_2$SiO
LiCu
Pr$^n$
n-C$_5$H$_{11}$
OSiMe$_2$Bu$^t$
PhS
OMe
4 h, 48%
CO$_2$Me
(ref. 147)
Cl
i, ii
73%
(ref. 148)
MOMO
CO$_2$Me
i
60%
R
(ref. 149)
HC≡CCO$_2$Et + (RCuMe)$^-$ Li$^+$
CO$_2$Et
Me
CuR
Li$^+$
cuprate +
COCl
CO$_2$Et
i
(ref. 150)

i, Me$_2$CuLi; ii, ClCH$_2$COCl

i, RMgBr, CuBr (0.25 equiv.), THF, -20 to -23 °C; R = CH$_2$=CHCH$_2$CH$_2$–

i, TMS-I, CCl$_4$, 24 h, r.t.

Scheme 54

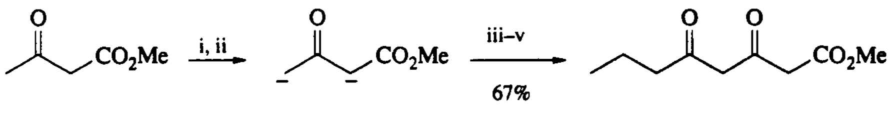
CO$_2$Me
i, ii
iii–v
67%

i, NaH, 1 equiv.; ii, Bu$^n$Li, 1 equiv.; iii, methyl butanoate, 0.5 equiv.; iv, Bu$^n$Li, 1 equiv.; v, methyl butanoate, 0.5 equiv.

Scheme 55

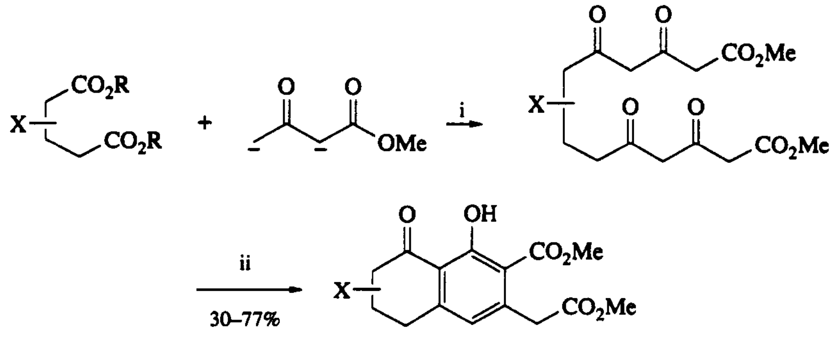

i, THF, r.t., 2 h; ii, Ca(OAc)$_2$, MeOH, reflux, 2 h

**Scheme 56**

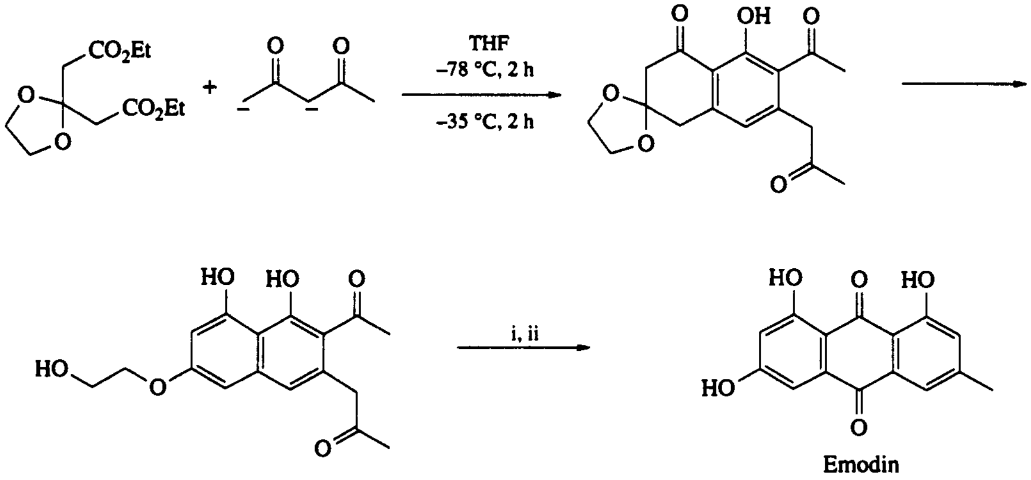

i, aldol; ii, oxidation

**Scheme 57**

Boron trifluoride has been used in gaseous form, or as its complex with acetic acid or diethyl ether. Unsymmetrical ketones may be acylated to produce either of the two possible diketones. In general, the use of gaseous boron trifluoride, in the absence of a proton acid, favors acylation of the kinetic enol and thus leads to substitution at the less highly substituted α-carbon. By contrast, if the reaction is performed in the presence of a proton acid, using one of the boron trifluoride acid complexes, the thermodynamically more stable enol is formed, thus leading to reaction at the more highly substituted carbon atom. A number of simple acyclic and cyclic ketones were acylated in the presence of the boron trifluoride–acetic acid complex to produce diketones in good yield (Scheme 59).[155] The acetylation of 3-methyl-2-buta-

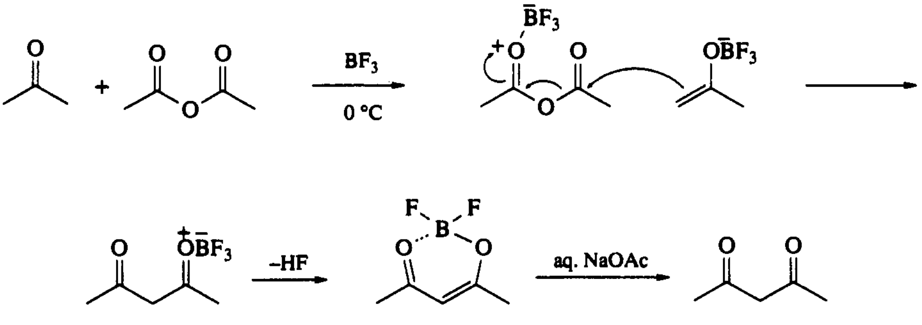

**Scheme 58**

none to give only 3,3-dimethylpentane-2,4-dione (40–47%) indicates that nonenolizable diketones may be synthesized by this method. α,β-Unsaturated ketones may be acylated on the γ-carbon *via* the dienol acetate (Scheme 60);[156] this reaction has been extended to the acylation of cyclohexane-1,3-dione enol ethers.[157]

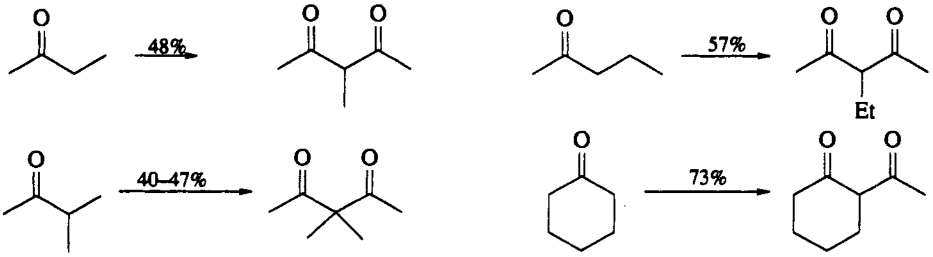

**Scheme 59** Acetylation with acetic anhydride and boron trifluoride–acetic acid complex

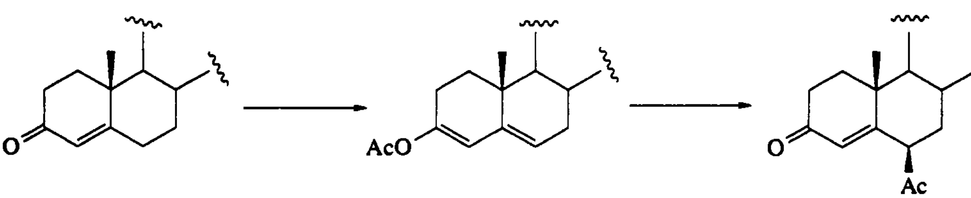

**Scheme 60**

### 3.6.4.4 Regiochemistry of Acylation

#### *3.6.4.4.1* O- versus *C-acylation*

The regiochemistry of acylation of enolate anions, enols and enol ethers has been extensively studied and reviewed.[7,8] In the base-catalyzed acylation of ketones by esters 1 equiv. of alkoxide ion is produced, along with the β-dicarbonyl compound. The reactions are thus reversible and usually proceed to the more stable anion. Although *O*-acyl products may be formed initially, they are not isolated in the final product. However, when ketone enolates are reacted with other acid derivatives in an irreversible reaction, the regiochemistry of acylation becomes critical. *C*-Acylation is favored by tight ion-pairs, rather than solvent-separated ions; this condition is favored by less polar solvents such as diethyl ether or THF, rather than DME, and by cations such as $Mg^{2+}/2$ or $MgBr^+$ rather than the alkali metal ions, $Li^+$, $Na^+$ and $K^+$, and by some divalent ions such as $Zn^{2+}$. *C*-Acylation is also favored by using acyl chlorides or acyl cyanides, rather than acid anhydrides, and by low temperatures. Inverse addition, which ensures the presence of the acylating agent in high concentration, also favors *C*-acylation. In geometrically isomeric enolates, *C*-acylation is favored when the larger β-substituent is *trans* to the alkoxide ion. The evidence points to an intramolecular electrophilic catalysis favoring *C*-acylation (equation 36).[158] When the cation is more firmly bound to the oxygen, such intramolecular catalysis is more readily effected; also the formation of metal chlorides or cyanides should be more favorable than the formation of the metal acetate. The correlation of a high covalent character for the enolate with *C*-acylation is supported by the fact that silyl enol ethers undergo almost exclusive *C*-acylation. In a recent paper[159] 4-(dimethylamino)pyridine has been shown to be an effective catalyst in promoting exclusive *C*-acylation in a benzofuranone. The

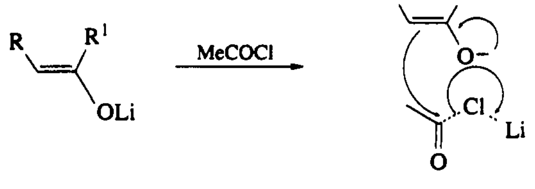

(36)

kinetically favored *O*-acyl compound is converted into the thermodynamically more stable *C*-acyl derivative, as shown in Scheme 61.

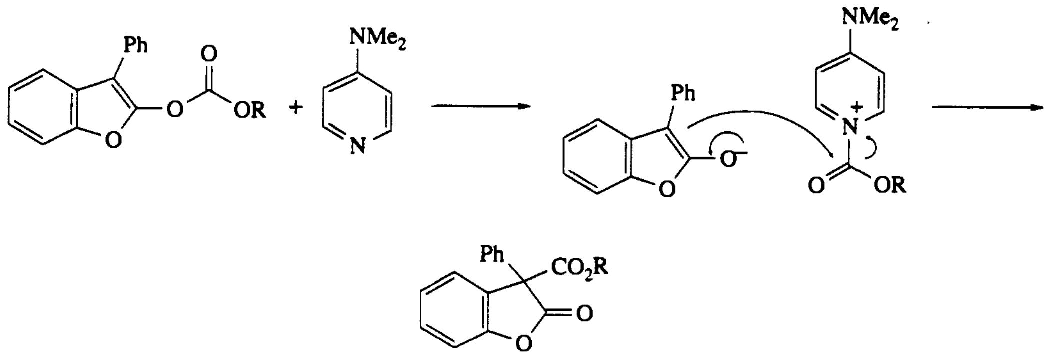
Ph
O
O
OR
+
NMe2
N
Ph
O−
NMe2
N+
O
OR
Ph
CO2R
O
O

**Scheme 61**

Another route to *C*-acylation is illustrated in Scheme 62.[160] The benzofuranone (**154**) on reaction with methyl chloroformate in the presence of LDA gave the *O*-acylated product (**155**) in 88% yield. With methyl cyanoformate, the *C*-acylated product (**156**) was obtained in 94% yield. However, the larger scale use of this reagent was unsatisfactory, so an alternative strategy was devised. The ketone (**154**) was treated with carbon disulfide, dimethyl sulfate and base in DMSO to give the bis(methylthio) ketene acetal. Aqueous base yielded the *C*-acylated product (**156**) in 83% overall yield.

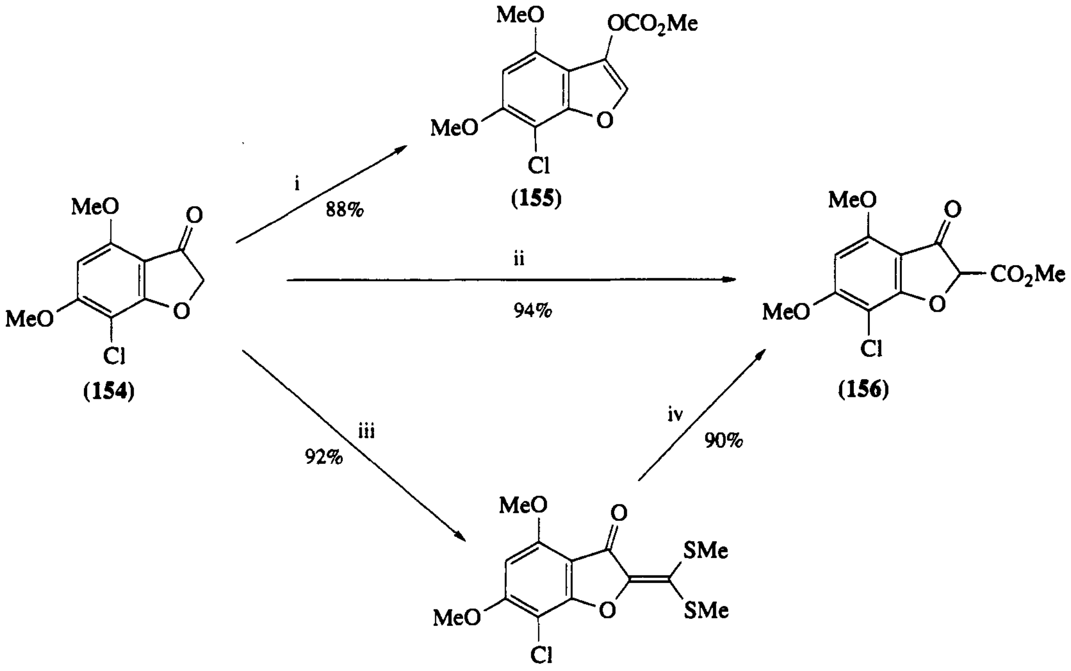
MeO
OCO2Me
MeO
O
Cl
(155)
i
88%
MeO
O
MeO
O
Cl
(154)
ii
94%
MeO
O
CO2Me
MeO
O
Cl
(156)
iii
92%
iv
90%
MeO
O
SMe
SMe
MeO
O
Cl

i, $ClCO_2Me$, LDA, THF, −78 °C; ii, $NCCO_2Me$, LDA, THF, −78 °C; iii, $CS_2$, $Me_2SO_4$, NaOH, DMSO, 5 °C; iv, MeOH, NaOH, THF, 50 °C

**Scheme 62**

### 3.6.4.5 Synthetic Applications of Intermolecular Acylation of Ketones

#### 3.6.4.5.1 Formylation

One of the reactions used most extensively to acylate ketones employs formate esters to produce α-formyl or hydroxymethylene ketones. Earlier work has been reviewed;[5,7] this section summarizes the important reactions of these products, particularly in alicyclic chemistry. As an illustration, the conversion of 2-methylcyclohexanone (**157**) into its 6-hydroxymethylene derivative and the subsequent chemistry of that compound are shown in Scheme 63. Such ketones normally undergo formylation at the less

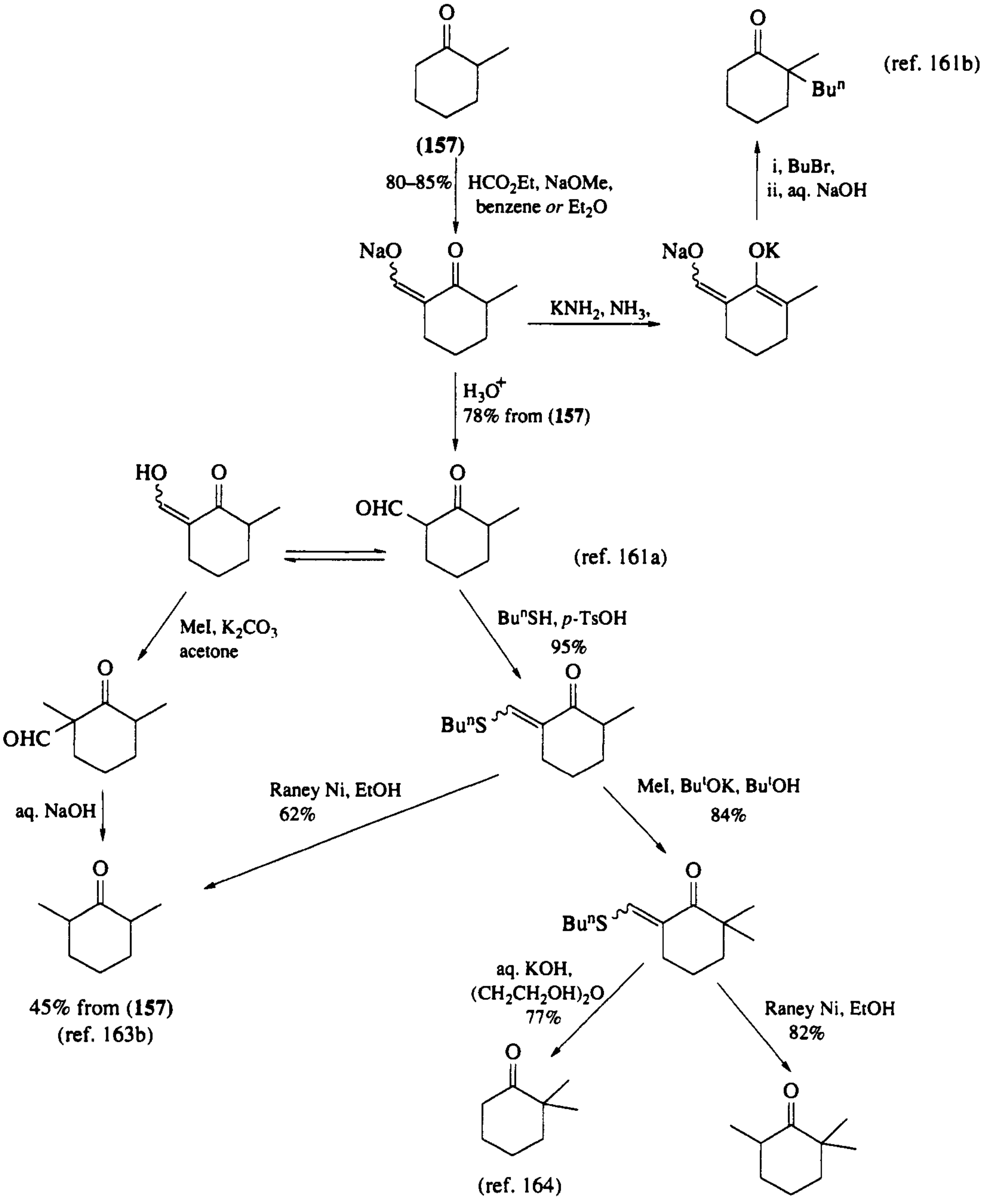

(157)
80–85%
HCO$_2$Et, NaOMe, benzene or Et$_2$O
NaO
O
KNH$_2$, NH$_3$,
OK
i, BuBr, ii, aq. NaOH
Bu$^n$
(ref. 161b)
H$_3$O$^+$
78% from (157)
HO
OHC
(ref. 161a)
MeI, K$_2$CO$_3$ acetone
Bu$^n$SH, p-TsOH
95%
Bu$^n$S
aq. NaOH
Raney Ni, EtOH
62%
MeI, Bu$^t$OK, Bu$^t$OH
84%
45% from (157)
(ref. 163b)
aq. KOH, (CH$_2$CH$_2$OH)$_2$O
77%
Raney Ni, EtOH
82%
(ref. 164)

**Scheme 63**

substituted carbon atom, with the product existing mainly in the enolic form.[161] Acyclic methyl *n*-alkyl ketones give mixtures of acylated products, but reaction at the methyl group is generally favored.[162] The hydroxymethylene group may serve to activate to alkylation the carbon atom to which it is attached.[163] The formyl group can be readily removed by the use of aqueous base. The same function also serves as a precursor of the *n*-butylthiomethylene group,[164] the most widely used removable blocking group for ketone alkylation. The corresponding enamine[165] or enol ether[166] are now rarely used. The extensive chemistry of β-alkylthio-α,β-unsaturated enones has been reviewed.[167] Some examples of its use as a blocking group are described;[168] a recent and testing example of its blocking function is given in Scheme 64.[169] Hydroxymethylene ketones may serve as intermediates to α-formyl α,β-unsaturated ketones (equation 37),[170] to α-methylene ketones in a crossed Cannizzarro reaction followed by dehydration (equation 38),[171] and may be reduced to hydroxymethyl ketones by a variety of reagents (Scheme 65).

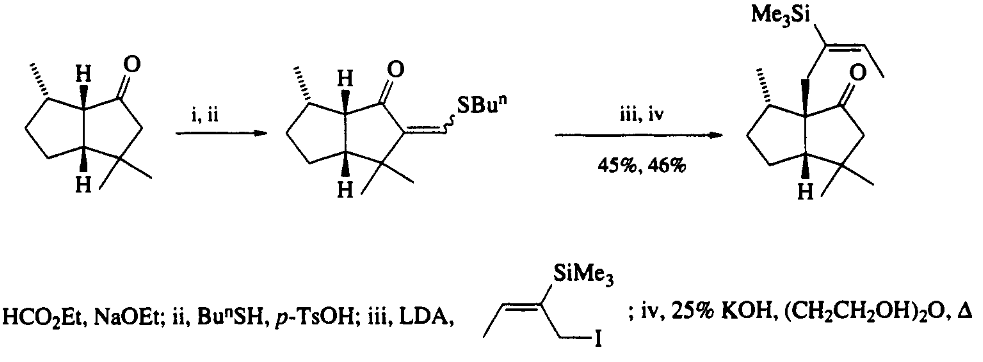

i, $HCO_2Et$, NaOEt; ii, Bu$^n$SH, *p*-TsOH; iii, LDA, ; iv, 25% KOH, $(CH_2CH_2OH)_2O$, Δ

Scheme 64

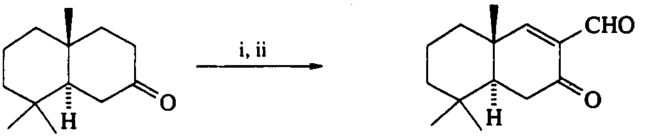

(37)

i, NaH, $HCO_2Et$; ii, PhSeCl, Py, $H_2O_2$

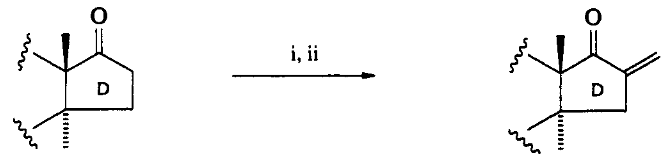

(38)

Various steriods

i, $HCO_2Et$, NaOMe, PhH, 70–96%; ii, HCHO, EtOH, $K_2CO_3$, 68–80%

### 3.6.4.5.2 Oxalylation

The reaction of diethyl oxalate with ketones in the presence of sodium ethoxide, or other bases, has been used extensively; examples are given in Scheme 66. Reaction may occur with ester:ketone ratios of 1:1, 2:1, or 1:2, but only the 1:1 case finds substantial use in modern synthetic practice. Frequently the α-oxalyl ketone is thermally decarbonylated to give the β-keto ester.[174] An early example of this was provided by Bachmann's synthesis of equilenin.[175] The mechanism of this reaction has been examined;[176] labeling studies showed that it was the ester carbonyl that was eliminated. The intact oxalyl group has been used as a directing group in steroid methylation[177] while, more recently, 2-oxalylcyclohexanone has provided a route to (*R*)-(–)-hexahydromandelic acid (Scheme 67).[178] The products of acylation of suitable acyclic ketones can cyclize to form (enolic) cyclopentane-1,2,4-triones (equation 39).[179]

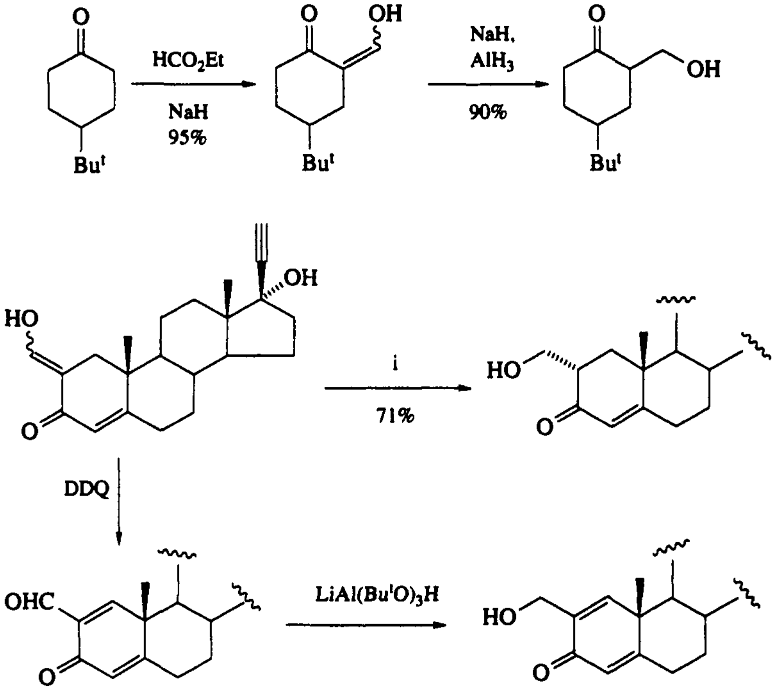
HCO2Et
NaH
95%
NaH,
AlH3
90%
OH
Bu^t
i
71%
DDQ
LiAl(Bu^tO)3H
HO
OHC
O

(ref. 172)

(ref. 173)

i, *Streptomyces roseochromogenus*

**Scheme 65**

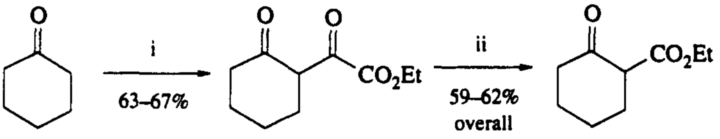
i
63–67%
CO2Et
ii
59–62%
overall
O

(ref. 174)

i, $(CO_2Et)_2$, NaOEt; ii, powdered glass, 165–170 °C

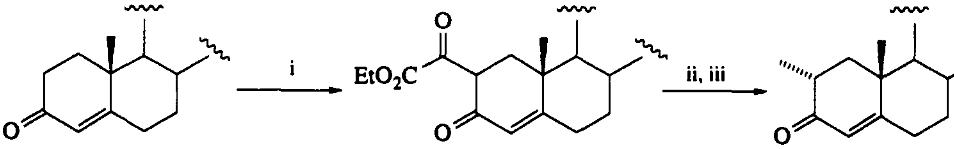
i
EtO2C
ii, iii
O

(ref. 177)

i, $(CO_2Et)_2$, NaH; ii, MeI, $K_2CO_3$, $Me_2CO$; iii, NaOEt

**Scheme 66**

### *3.6.4.5.3 Alkoxycarbonylation*

A variety of reagents will effect the conversion $COCH_2 \rightarrow COCHCO_2R$; the decarbonylation of glyoxalate esters was described above. The most recently described reagent, methyl cyanoformate, reported by Mander and Sethi in 1983,[180] allows the conversion of a preformed lithium enolate to the β-keto ester in high yield (Scheme 68). Diethyl dicarbonate with potassium hydride in benzene effects the same reaction with symmetrical ketones, and with lithium dicyclohexylamide in ether introduces the ethoxycarbonyl group into the α′-position of α,β-unsaturated ketones (Scheme 69).[181] Diethyl carbon-

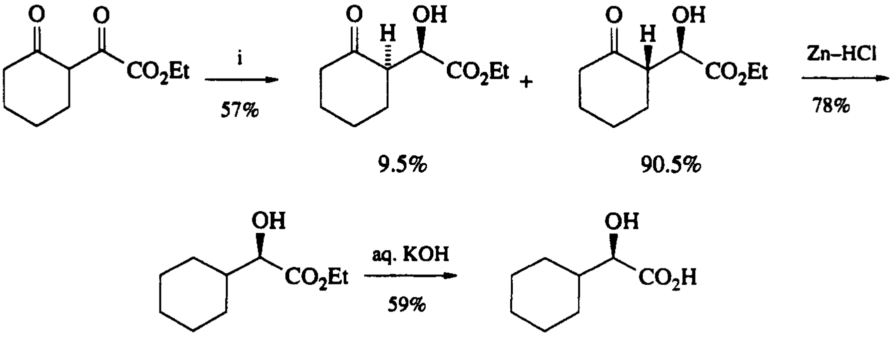

i
57%
9.5%
90.5%
Zn–HCl
78%
aq. KOH
59%

i, Baker's yeast

**Scheme 67**

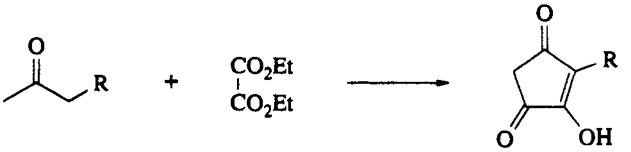

(39)

ate$^{182}$ and EtOCOPO(OEt)$_2$ (Scheme 70)$^{183}$ also introduce the ethoxycarbonyl group, while thioesters were prepared by reaction of ketones with *O,O*-diethyl trithiodicarbonate, using sodium hydride as base (Scheme 71). Ultrasonication of the reaction mixture gave the thioester in 93% yield based on the ester used.$^{184}$ In general, these reactions do not give control of regiochemistry. Thus the examples cited$^{181-184}$

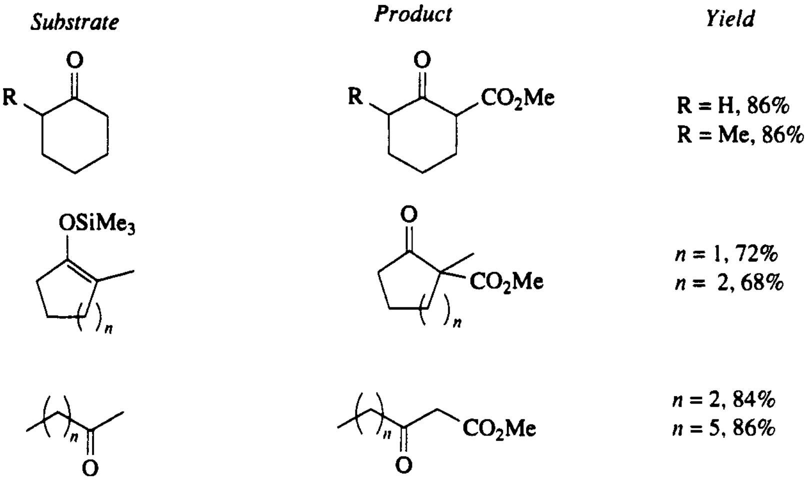

Substrate
Product
Yield
R = H, 86%
R = Me, 86%
n = 1, 72%
n = 2, 68%
n = 2, 84%
n = 5, 86%

**Scheme 68**

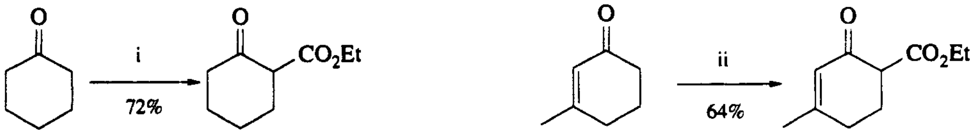

i, KH, EtOCO$_2$CO$_2$Et, PhH, 80 °C; ii, EtOCO$_2$CO$_2$Et, LiN(c-C$_6$H$_{11}$)$_2$

**Scheme 69**

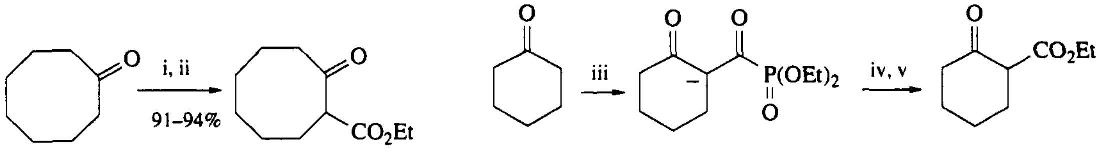

i, $(EtO)_2CO$, NaH, PhH; ii, AcOH, $H_2O$; iii, $EtOCOPO(OEt)_2$, NaH, $Bu^n{}_2O$, 30–60 °C; iv, EtOH, $H_2SO_4$, 50–55 °C; v, $H_2O$

**Scheme 70**

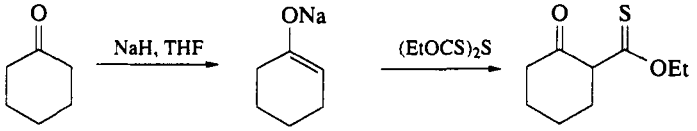

**Scheme 71**

include only symmetrical ketones or methyl *n*-alkyl ketones, where the ethoxycarbonyl group is introduced on the methyl group. The use of methyl magnesium carbonate (Stiles' reagent), where the isolated product is often a β-keto ester, is described in the next section.

### 3.6.4.5.4 Carboxylation

Ketones may be converted into the corresponding β-keto acid, sometimes isolated as its ester, by direct carbonation of the enolate anion or by the use of methylmagnesium carbonate (Stiles' reagent, MMC). Three examples of the former process are shown in Scheme 72; the first[185] involves the generation of the enolate with base while in the second[186] it is formed by reduction of an α,β-unsaturated ketone. In the third example,[187] the dianion of a β-diketone was, as expected, carboxylated on the most basic carbon atom. The more widely used processes for carboxylation employ Stiles' reagent,[188] formed by bubbling carbon dioxide into magnesium methoxide in dimethyl formamide. The reaction mixture is heated to 120 °C and methanol removed by distillation. The pertinent equilibria are shown in Scheme 73. The reagent as normally employed is probably represented by (**158a**), although some of the species (**158b**) may also be present. Typical examples of its use are shown in Scheme 74, which also illustrates the regiochemistry of the reaction; the 2-tetralone gave the 3-carboxylic acid while 4-oxopentanoic acid was carboxylated exclusively on the methyl group. Bis-carboxylation is illustrated in the fourth example.

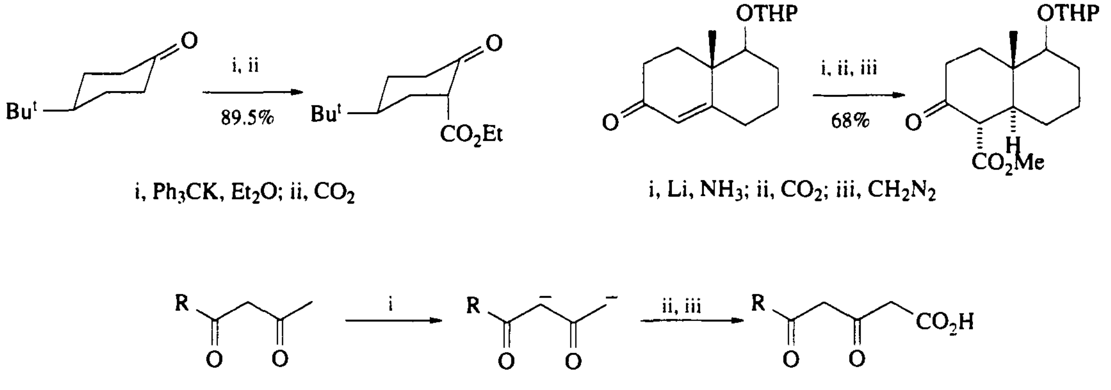

i, $Ph_3CK$, $Et_2O$; ii, $CO_2$

i, Li, $NH_3$; ii, $CO_2$; iii, $CH_2N_2$

i, $NaNH_2$, $NH_3$; ii, $CO_2$, $Et_2O$; iii, $H_3O^+$

**Scheme 72**

$$\underset{}{\mathrm{Mg(OMe)_2 + CO_2}} \rightleftharpoons \underset{\textbf{(158a)}}{\mathrm{MeOMgOCO_2Me{\cdot}}x\mathrm{CO_2}} \rightleftharpoons \underset{\textbf{(158b)}}{\mathrm{(MeOCO_2)_2Mg}}$$

**Scheme 73**

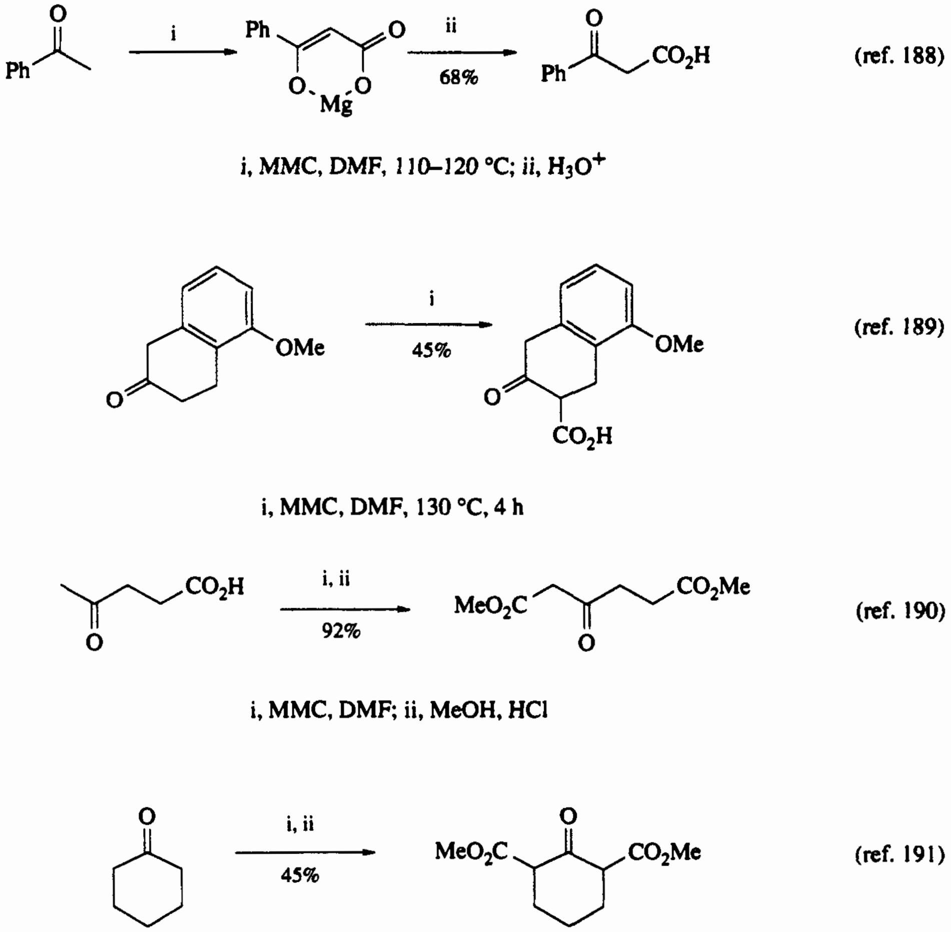
Ph
O
i
Ph
O
O
O
Mg
ii
68%
O
Ph
CO2H
(ref. 188)
OMe
i
45%
O
OMe
O
CO2H
(ref. 189)
CO2H
O
i, ii
92%
MeO2C
CO2Me
O
(ref. 190)
O
i, ii
45%
MeO2C
O
CO2Me
(ref. 191)

i, MMC, DMF, 110–120 °C; ii, $H_3O^+$

i, MMC, DMF, 130 °C, 4 h

i, MMC, DMF; ii, MeOH, HCl

i, MMC, DMF; ii, MeOH, HCl

**Scheme 74**

More recently Rathke and coworkers[192] have described a procedure involving the carboxylation of a ketone in the presence of magnesium halide and triethylamine in acetonitrile with an optimal ratio of amine:halide:ketone of 4:2:1. Advantages included a lower reaction temperature and a solvent more readily removed (equation 40). The reaction showed little regioselectivity, as 2-butanone was carboxylated on the methyl and methylene groups in a ratio of 55:45. The same group reacted a magnesium enolate with butenone in the initial Michael step of a Robinson annelation.[193]

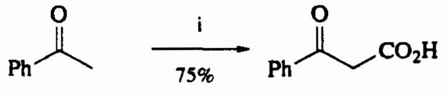
O
Ph
i
75%
O
Ph
CO2H

(40)

i, $Et_3N$, $CO_2$, MeCN, '$MgI_2$' ($MgCl_2$ + 2NaI)

### 3.6.4.6 Intramolecular Acylation of Ketones

The synthesis of alicyclic 1,3-diketones from γ- or δ-keto esters is a well-established reaction. Over 50 examples are tabulated in the 1954 chapter in *Organic Reactions*,[5] and a similar number are tabulated as involving a Michael addition of a diester or keto ester to an unsaturated ketone followed by a Claisen condensation. These latter reactions involve such well-known syntheses as that of dimedone (5,5-dimethylcyclohexane-1,3-dione; Scheme 75).

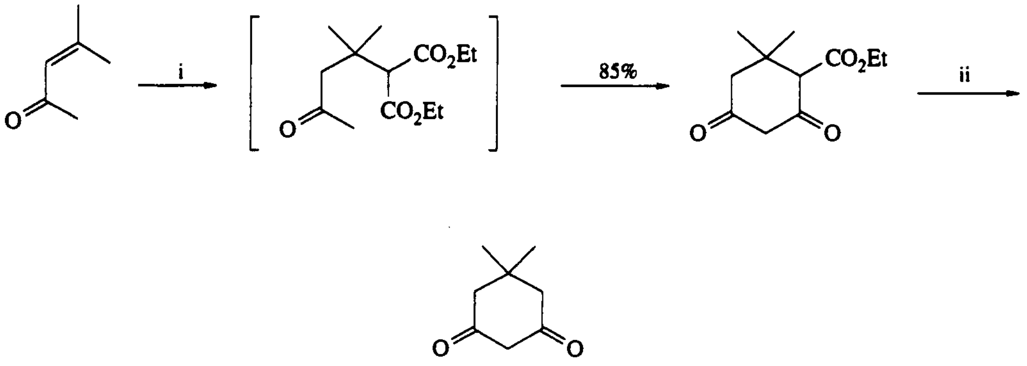
i
CO2Et
CO2Et
85%
CO2Et
ii
O
O
O
O
O

i, $CH_2(CO_2Et)_2$, NaOEt; ii, aq. HCl, Δ

**Scheme 75**

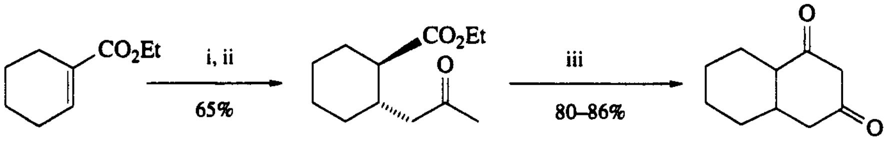
CO2Et
i, ii
65%
CO2Et
O
iii
80–86%
O
O

(ref. 194)

i, 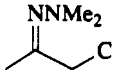 Cu(Li)SPh ; ii, $CuCl_2$, pH 7, THF, $H_2O$; iii, NaH (2–2.2 equiv.), PhH, trace MeOH

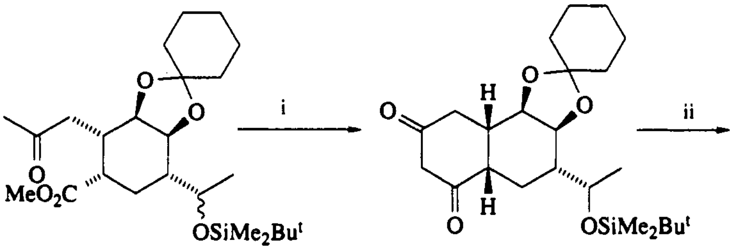
O
O
O
MeO2C
OSiMe2Bu^t
i
H
O
O
O
H
O
OSiMe2Bu^t
ii

mixture of
enol ethers
89% overall

(ref. 195)

i, $KOBu^t$ (3.3 equiv.), PhH, 25 °C, 20 min; ii, $CH_2N_2$, $Et_2O$, 0 °C, 10 min

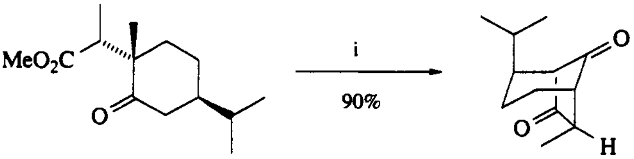
MeO2C
O
i
90%
O
O
H

(ref. 196)

i, $(Me_3Si)_2NNa$, DME

**Scheme 76**

Such reactions are normally base catalyzed, Scheme 76 illustrates the use of this reaction to provide both fused and bridged rings. Other techniques for synthesizing the keto ester from trimethylsilyl ethers are shown in Scheme 77. The diketones shown were usually isolated as a mixture of enols or enol ethers. Acid-catalyzed acylation also provides a route to diketones not readily obtained by other routes (Scheme 78). The acid catalysts included polyphosphoric acid and naphthalene-2-sulfonic acid. In the latter example continuous removal of water facilitated the reaction. A related reaction involved treatment of an acid chloride with silver perchlorate in nitromethane (equation 41), although the yield of diketone was low.[201]

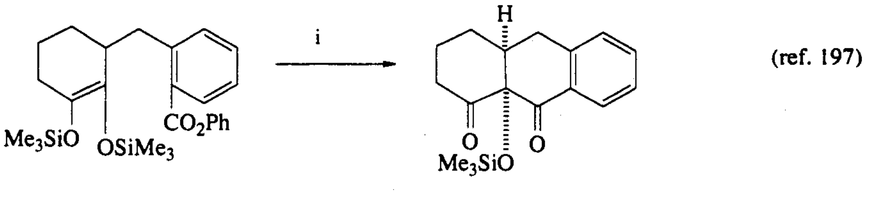
Me$_3$SiO
OSiMe$_3$
CO$_2$Ph
i
H
O
Me$_3$SiO
O
(ref. 197)

i, Bu$^n_4$NF, THF, –78 °C

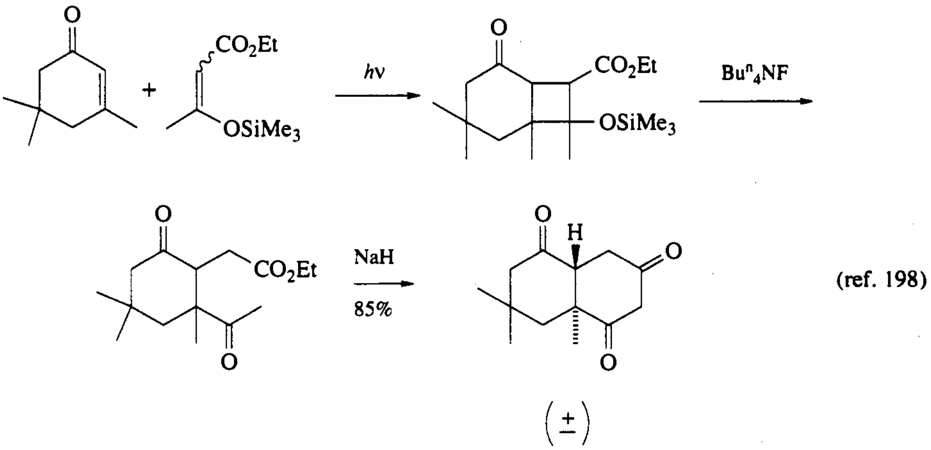
O
CO$_2$Et
+
OSiMe$_3$
hν
O
CO$_2$Et
OSiMe$_3$
Bu$^n_4$NF
O
CO$_2$Et
O
NaH
85%
O
H
O
O
(ref. 198)
(±)

**Scheme 77**

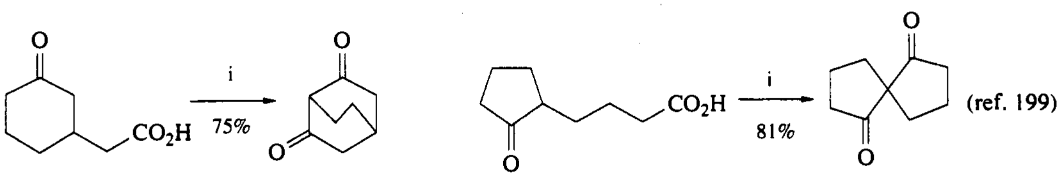
O
CO$_2$H
i
75%
O
O
CO$_2$H
O
i
81%
O
O
(ref. 199)

i, PPA, AcOH

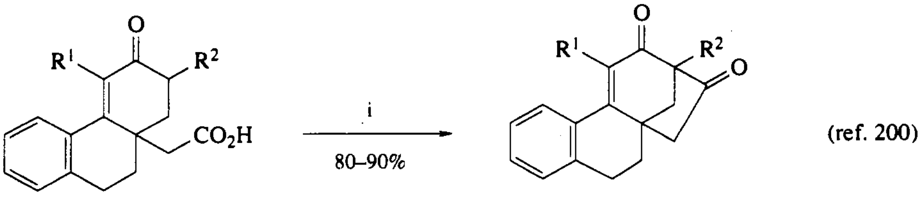
O
R$^1$
R$^2$
CO$_2$H
i
80–90%
O
R$^1$
R$^2$
O
(ref. 200)

R$^1$ = R$^2$ = H; R$^1$ = H, R$^2$ = Me; R$^1$ = Me, R$^2$ = H

i, naphthalene-2-sulfonic acid, toluene, water removal

**Scheme 78**

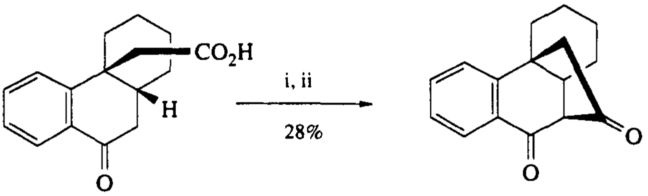

(41)

i, $(COCl)_2$; ii, $AgClO_4$, $MeNO_2$

### 3.6.4.7 Intramolecular Acyl Transfer

Aromatic *o*-acyloxy ketones of general formula (**159**) undergo an intramolecular acyl transfer in the presence of base to give *o*-hydroxyaryl β-diketones (**160**; Scheme 79).[5] In one variant, the 'Baker–Venkataraman' synthesis, the rearrangement is effected with bases such as NaH or KOH in pyridine. Acid catalysis facilitates transformation into a flavone (**161**). In the closely related 'Kostanecki' reaction, the *o*-hydroxyacetophenone is heated with an acid anhydride in the presence of the sodium or potassium salt of the corresponding acid to give the flavone directly (equation 42). The reactions have, for the most part, involved the transfer of an aromatic or heteroaromatic group and the reactions have been widely employed in flavone chemistry. More recently, examples of the transfer of aliphatic acyl groups have

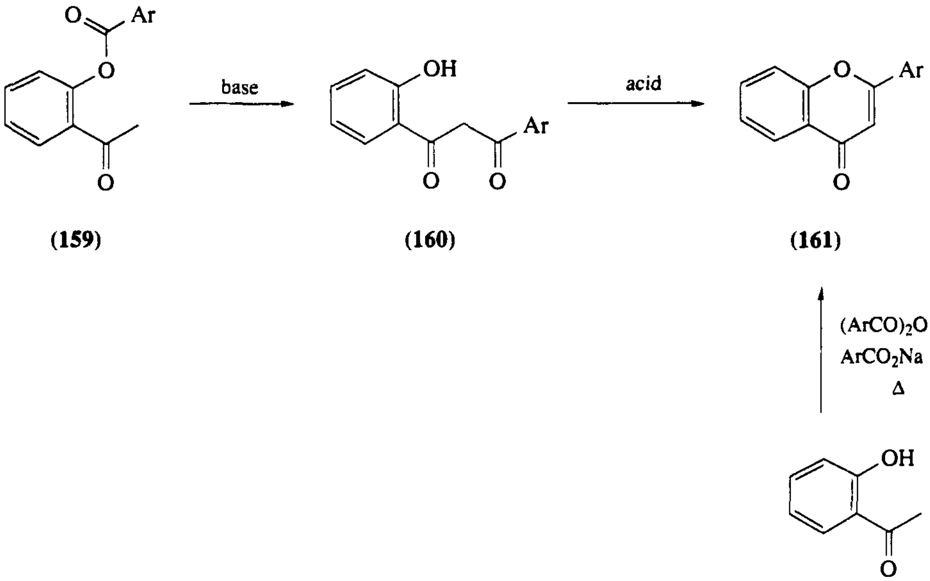

Scheme 79

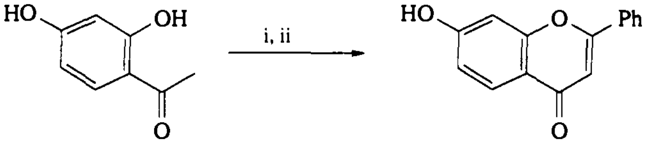

(42)

i, $(PhCO)_2O$, $PhCO_2Na$, 185 °C, 4 h; ii, KOH, EtOH, reflux 30 min

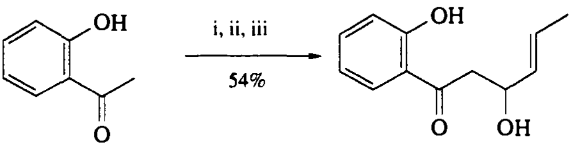

(43)

i, NaH; ii, MeCH=CHCOCl; iii, $KOBu^t$, $Bu^tOH$

been reported (equation 43).[202] Satisfactory yields were obtained with crotonyl and related esters, but transfer of an acetyl group was effected in only 28% yield.

## 3.6.5 STEREOCHEMISTRY

### 3.6.5.1 Chiral β-Dicarbonyl Synthons

A new stereocenter is established in the Claisen condensation whenever the carbanionic carbon center that is undergoing acylation bears two different groups. Normally, however, the basic conditions of the reaction result in the formation of the enolate of the β-dicarbonyl system and the loss of stereochemical integrity. Two groups have now reported the asymmetric acylation of optically active imide enolates.

Evans *et al.*[203] acylated the oxazolidine imides (**162**) and (**163**) with a number of acid chlorides to produce the β-dicarbonyl systems (**164**) and (**165**) in high chemical yield and diastereoselection at the 95% level (Scheme 80). Purification of the reaction products readily afforded material that was diastereomerically pure (≥99%). The surprisingly low kinetic acidity of the β-keto imide system was ascribed to the fact that the bond to the acidic proton is nearly orthogonal to the π-system of the adjacent carbonyl functions. Movement to align the two systems would result in increased $A^{1,3}$ strain. The difficulty in removing a proton in a similar situation was noted, in alkylation studies, by a Japanese group,[204] who also provided the second example of an asymmetric acylation.[205] They showed (Scheme 81) that *C*-acylation of the propionamide derivatives of *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine with a number of acid chlorides produced good to excellent yields of β-keto amides with a *de* of around 98%. The ketonic products were reduced with $Zn(BH_4)_2$ to give the *syn* aldol compound.

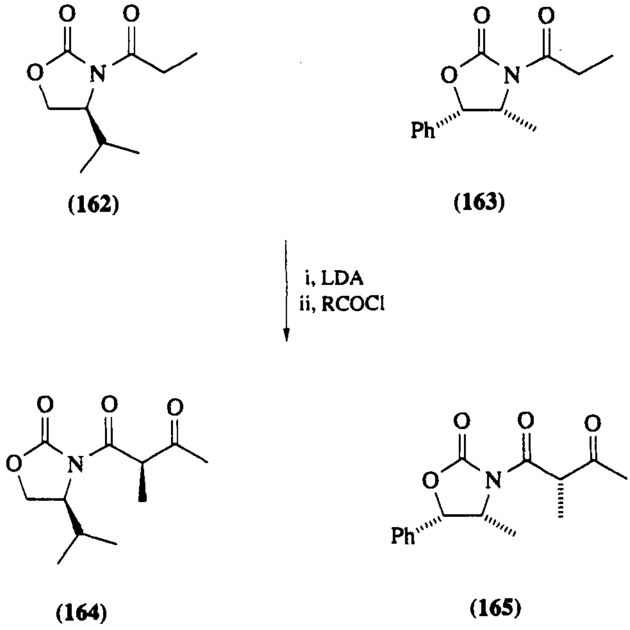

Scheme 80

The availability of these chiral β-dicarbonyl synthons has been put to good use by Evans and Di Mare[206] in an asymmetric synthesis of premonensin (**166**) and by a Japanese group[207] in the synthesis of (+)-pederin (**167**).

When a quaternary carbon atom is produced in the acylation process, racemization is not possible and the stereochemical outcome can be affected by the presence of an adjacent stereocenter. Treatment of the chiral lactone (**168**) with LDA and acetyl cyanide gave the diastereomeric products (**169**) and (**170**) in the ratio 60:1 (equation 44).[208]

Studies pertinent to the acylation of chiral ketones were reported by Seebach and Ehrig (Scheme 82).[209] Acylation of the enolate (**172**) of the optically active (but not optically pure) ketone (**171**) gave

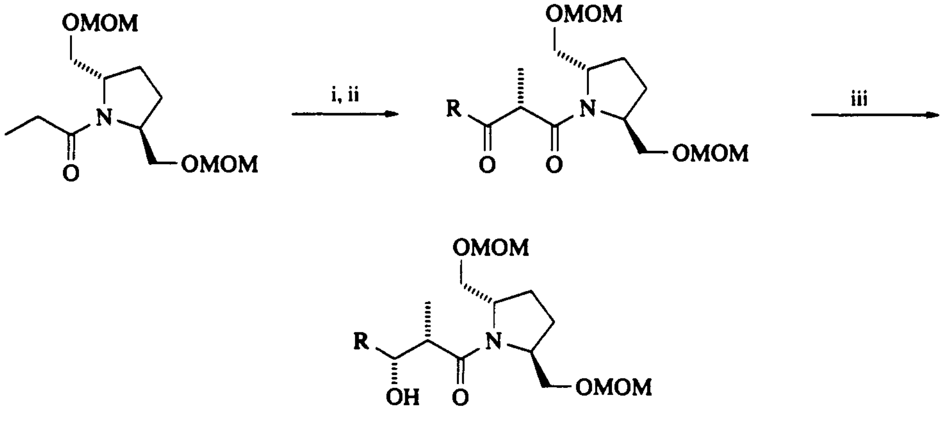

i, BuLi; ii, RCOCl; iii, $Zn(BH_4)_2$

**Scheme 81**

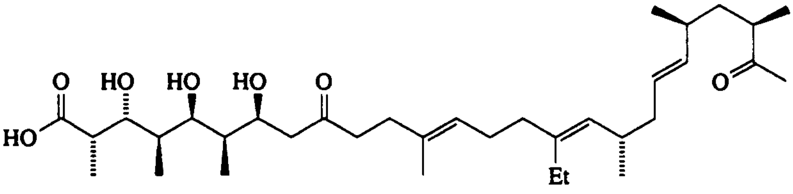

**(166)**

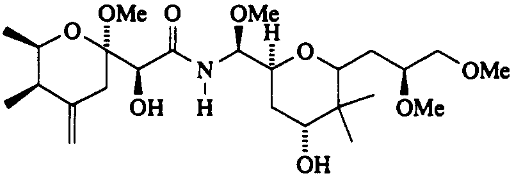

**(167)**

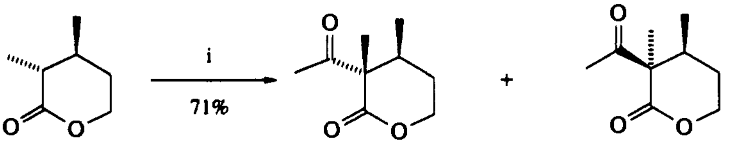

**(168)** **(169)** **(170)** (44)

i, LDA–THF, MeCOCN, –78 °C

the diketone (**173**) with minimal racemization. A similar result was obtained when the acid chloride (**174**) was reacted with the lithium enolate of pinacolone to give the same diketone.

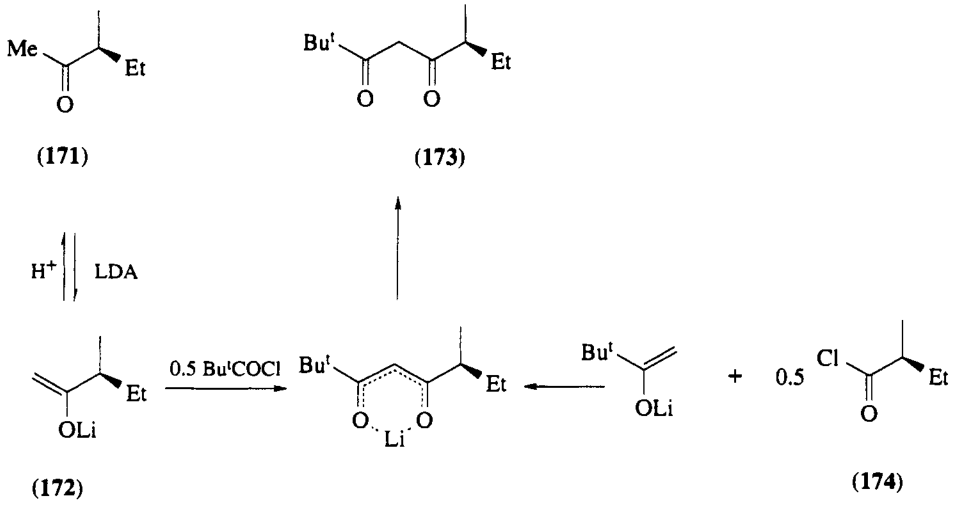

Scheme 82

## 3.6.6 THORPE AND THORPE–ZIEGLER REACTIONS

Thorpe originally investigated the condensation of alkyl cyanides to give 3-iminoalkyl cyanides by analogy with the Claisen and aldol reactions.[6,210] Moore and Thorpe then applied this reaction to a bisnitrile and showed that the intramolecular version of the reaction proceeded to give the cyclic product.[211] The use of Thorpe as a named reaction has usually indicated the cyclic version, the simple condensation not having found great use because of problems with its application to crossed reactions, but it should strictly apply to either. The Ziegler modification of the Thorpe reaction allowed it to be used for the preparation of macrocyclic ring systems, but the term Thorpe–Ziegler reaction is quite often used for intramolecular reactions to form standard rings in which neither of Ziegler's modifications, a soluble base and high dilution conditions, are used. We will not distinguish between the Thorpe and Thorpe–Ziegler reactions and will also include the few examples of the intermolecular condensation in our discussion. A number of intramolecular reactions in systems containing an ester and a nitrile have been considered under the Dieckmann reaction; others will be considered here. The separation is somewhat arbitrary and the reactions have been described in the literature by both names.

### 3.6.6.1 Mechanism

The mechanism of this reaction is closely similar to that described for the Claisen and Dieckmann reactions. The α-protons are acidic, the resulting anion being stabilized by conjugation to the cyanide, and the anion can then act as a nucleophile towards a second molecule of the cyanide. The resulting imine can then rearrange to the enamine and this results in the reaction being driven towards completion (Scheme 83).

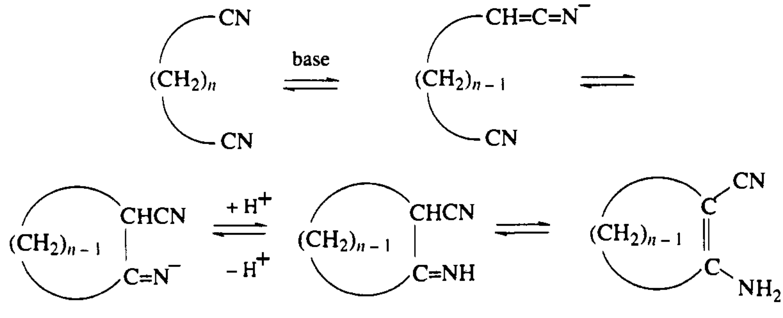

Scheme 83

### 3.6.6.2 Reaction Conditions

The original Thorpe conditions involved a catalytic amount of base, as the mechanism would imply. Later workers[6] found that in certain reactions equivalent amounts of base were required or that catalytic and equivalent amounts of base gave different products. As shown in Scheme 84, the Michael dimer (**177**) is the major product when adiponitrile (**175**) is cyclized with a trace of sodium *t*-butoxide in *t*-butyl alcohol, whereas an equivalent of this base in toluene gave the monomer (**176**).

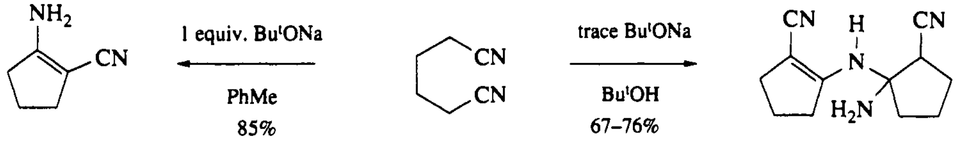

(**176**) (**175**) (**177**)

**Scheme 84**

Ziegler and his coworkers modified the reaction conditions by conducting the reaction under high dilution conditions and using a soluble base in ether as the solvent. Sodium methylanilide was reported to be the best base[6] but an example has been reported in which this gave unexpected products.[212] A variety of other bases have been used more recently and a comparison of LDA, $LiNEt_2$ and $NaN(SiMe_3)_2$ has been made.[213]

### 3.6.6.3 Scope of the Reaction

The reaction has found much less general use than the Dieckmann reaction for a variety of reasons. Dinitriles are less readily available than diesters and the resulting cyanoenamines are both more difficult to hydrolyze and less versatile in their transformation into other groups. Virtually no use has been made of the acyclic reaction but the recent description of a method for cross-coupling may stimulate interest. If the anion of one component of the intermolecular crossed reaction is pregenerated good yields of the desired product can be obtained when the reaction is run at –78 °C in THF.[214] Acetonitrile has usually acted as the nucleophile, being lithiated with butyllithium, and a range of cyanides have acted as the electrophile (Scheme 85). In most cases a mixture of (*Z,E*)-cyanoenamines was obtained but in some cases only the (*Z*)-isomer was isolated, presumably because of steric effects.

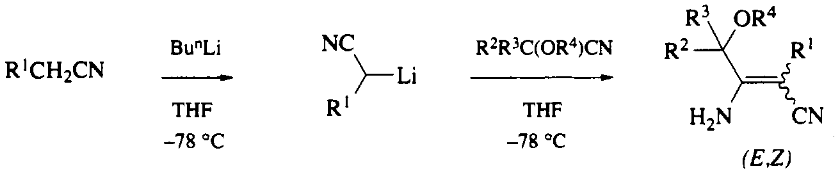

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|---|
| H | H | Me | Et | 83 |
| H | H | Me | 1-EE[a] | 87 |
| H | Me | Me | 1-EE | 78 |
| Et | H | Me | 1-EE | 51 |

[a] 1-EE = 1-ethoxyethyl

**Scheme 85**

The intramolecular reaction has led to cyclic compounds with both standard and macrocyclic rings, but small rings are not readily prepared. An attempt to cyclize (**178**), containing a nitrile and an ester function, gave the cyclic amide (**179**) rather than the desired cyanocyclobutenone (**180**).[215] One disadvantage of the reaction is that if the cyclic ketone is the desired product then the cyanoenamine is often hydrolyzed much less readily than the β-keto esters generated from the Dieckmann reaction. In certain cases, however, the Dieckmann reaction does not occur, whereas the Thorpe–Ziegler does, and hydrolysis and oxidation give the ketone.[216] Cyclization of (**181**) with LiHMDS in THF at reflux gave the cyanoenamine (**182**) in 59% yield, whereas the Dieckmann reaction gave <5% of the equivalent β-keto ester.[216] Hydrolysis, decarboxylation and oxidation of (**182**) gave the cyclooctanone (**183**; Scheme 86). Like the Dieckmann reaction, the Thorpe–Ziegler reaction can readily accommodate heteroatoms and unsaturation in the cyclizing chain and a variety of heterocycles have been prepared. Many of these involve cyano esters and cyano ketones, and examples are given in Scheme 87.

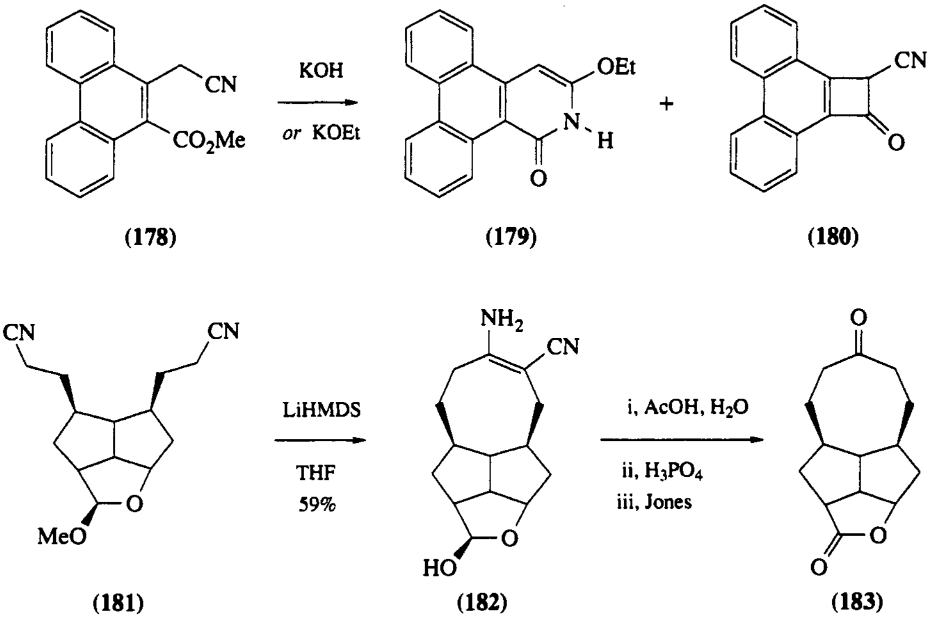
CN
CO2Me
KOH
or KOEt
OEt
N
H
O
+
CN
O
(178)
(179)
(180)
CN
CN
MeO
O
LiHMDS
THF
59%
NH2
CN
HO
O
i, AcOH, H2O
ii, H3PO4
iii, Jones
O
O
O
(181)
(182)
(183)

**Scheme 86**

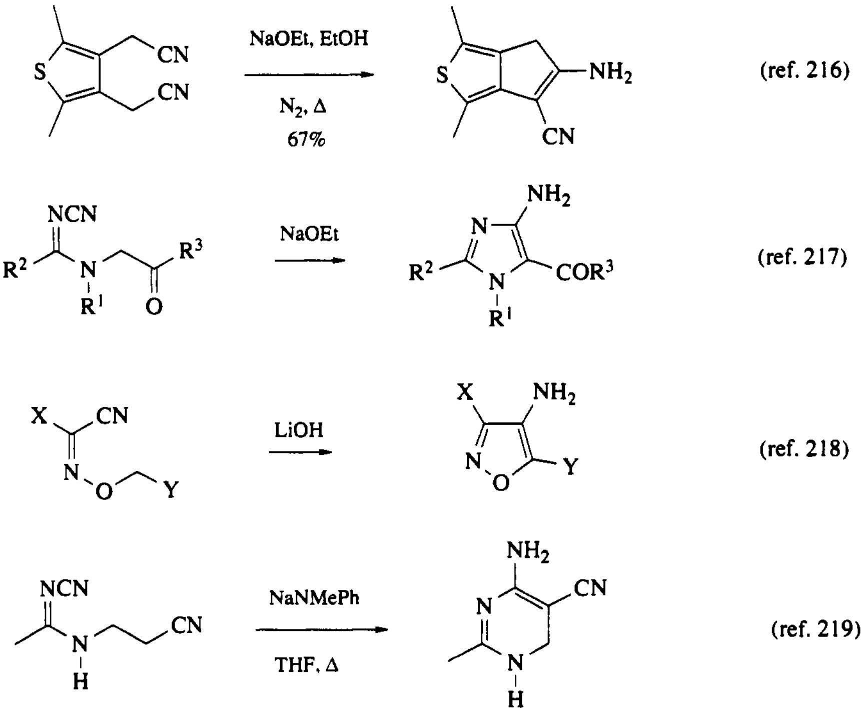
CN
CN
S
NaOEt, EtOH
N2, Δ
67%
NH2
CN
(ref. 216)
NCN
R2
N
R1
O
R3
NaOEt
NH2
N
R2
N
R1
COR3
(ref. 217)
X
CN
N
O
Y
LiOH
X
NH2
N
O
Y
(ref. 218)
NCN
N
H
CN
NaNMePh
THF, Δ
NH2
CN
N
N
H
(ref. 219)

**Scheme 87**

### 3.6.6.4 Regioselectivity

The Thorpe–Ziegler reaction has been little studied with regard to its regioselectivity. As mentioned in Section 3.6.3.3.3.iv, cyclization of mixed cyano esters occur with the ester as electrophile and the cyano-stabilized anion as nucleophile. In many of the known examples cyclization occurs on the cyanide because this is at a tertiary center. One would expect that the control of regioselectivity in the reactions of dicyanides would closely parallel the effects observed in the Dieckmann reaction. Treatment of the dicyanide (**184**) with sodium hydride in DMSO gives, however, the cyclized product (**185**) resulting from the more hindered anion,[220] a finding at variance with that usually observed in the Dieckmann reaction (Section 3.6.3.3.3.iii). It appears that the enamine with the double bond adjacent to the bridgehead methyl is more stable than the alternative isomer (**186**) and it is this that controls the product formation. This may also apply to the final enolate in the cyclization of the equivalent diester, although this would lead to the less stable β-keto ester. A related diester has been cyclized but only the ketone was isolated after decarboxylation, while a steroidal diester analog cyclizes as expected with the ester at the hindered position as electrophile (equation 45).[221]

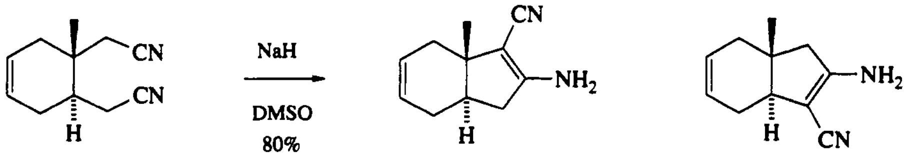

(**184**) (**185**) (**186**)

(45)

### 3.6.6.5 Application to Synthesis

In contrast to the Dieckmann reaction, very few examples of dicyanides being used in synthetic schemes have been reported. Rather, more examples of cyano esters or cyano ketones are known, often taking advantage of the lesser electrophilicity of the cyano group; some examples are shown in Scheme 88. Kametani *et al.* employed the cyclization of the cyano ester (**187**) to (**188**) with sodium hydride in a total synthesis of (±)-yohimbine.[222] A similar advantage was taken in the cyclization of the cyano ester (**189**) to the cyano ketone (**190**) with potassium *t*-butoxide in benzene,[223] and of the regioselectivity of closure of the cyano ester (**191**) to give the cyano ketone (**192**), which was not isolated but converted to the cyanoenamine (**193**) with ammonium formate.[224] The dihydropyrroles were converted to 2,4-diaminopyrrolpyrimidines by condensation with guanidine. Another example is the cyclization of the cyano ester (**194**) to the azocinone (**195**) in 46% yield, cyclization of the corresponding diester going in higher yield but with low regioselectivity.[66] The dicyanide (**196**) cyclizes with the primary cyanide as the electrophile to give (**197**) in 90% yield. This material was hydrolyzed with a phosphoric acid/acetic acid mixture to give the desired ketone in 80% yield.[225]

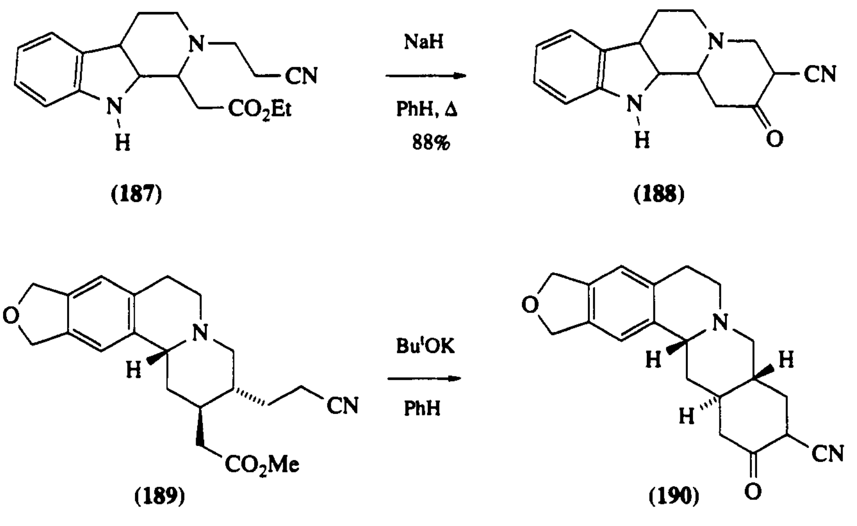

**Scheme 88**

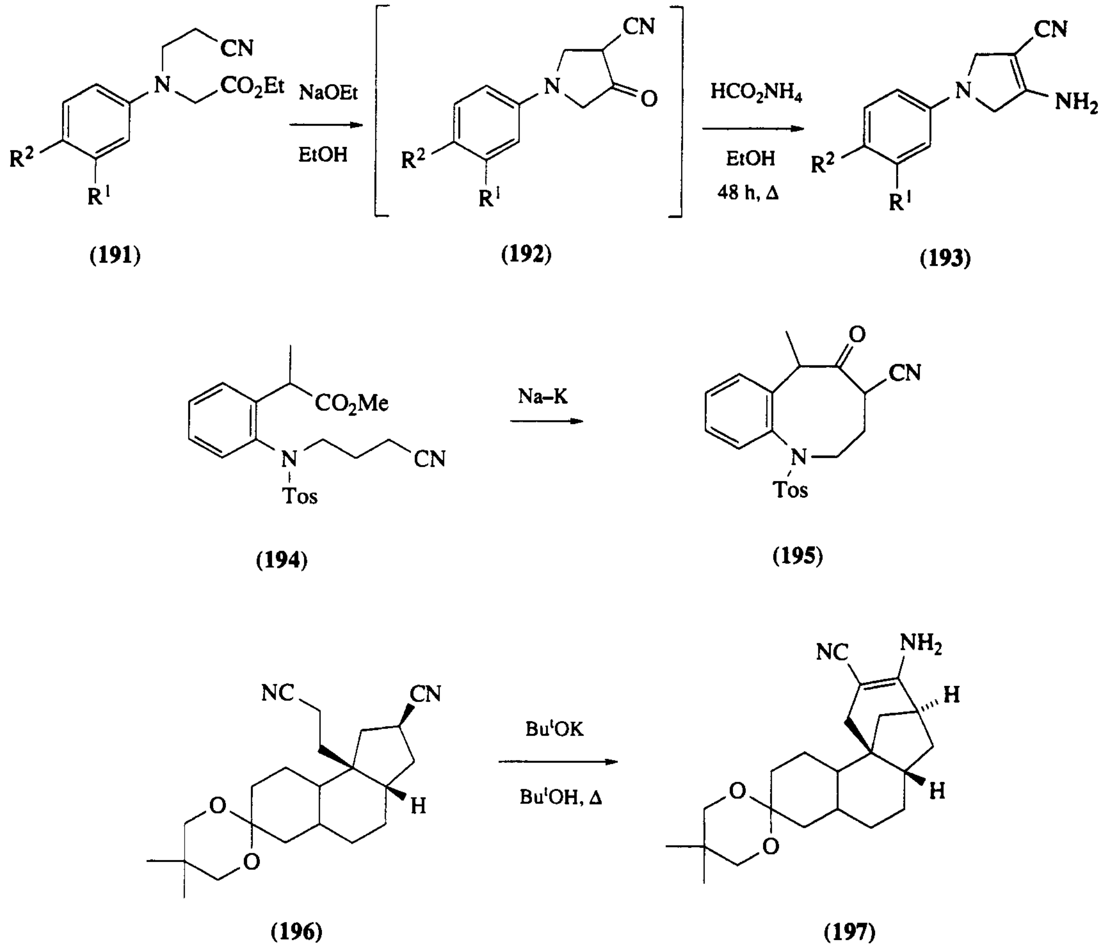

**(191)** **(192)** **(193)**

**(194)** **(195)**

**(196)** **(197)**

**Scheme 88** ***(continued)***

## 3.6.7 TANDEM REACTIONS

The cyclization reactions described in this chapter and, occasionally, even the acyclic condensation reactions, can often be prefaced by a different type of process such as a Michael reaction. We shall term such a sequence a tandem reaction and a number of these have already been described. Others will be collected here to illustrate the types of processes that have been observed. The cycloenones (**198**), when treated with a nucleophile (**199**) under basic conditions, react in a Michael fashion to give the intermediates (**200**), which then undergo the Dieckmann reaction to give the bicyclic dione (**201**).[226] Similarly, methyl cinnamate (**202**) reacts with the nucleophile (**203**) in the same tandem sequence to give the cyclopentanone (**204**) as a diastereomeric mixture (Scheme 89).[227]

Other examples of this tandem sequence are illustrated by the reactions shown in Scheme 90.

Dimethyl oxalate (**205**) reacts with (**206**)[233] and with α,ω-diesters (**207**)[234] in a Claisen–Dieckmann tandem reaction to give cyclopentadienes (**208**) and (**209**), the former spontaneously dimerizing to give (**210**; Scheme 91).

An aldol–Claisen tandem sequence is illustrated by the reaction of the cinnamaldehyde (**211**) with the chiral acetate (**212**) to give (**88**) followed by treatment with the lithium enolate (**89**) to give (**90**; equation 46; see equation 25, Section 3.6.3.4.2).[104]

There are a number of examples of Michael–Thorpe tandem reactions, closely related to the Michael–Dieckmann described above. Some of these are illustrated in Scheme 92.

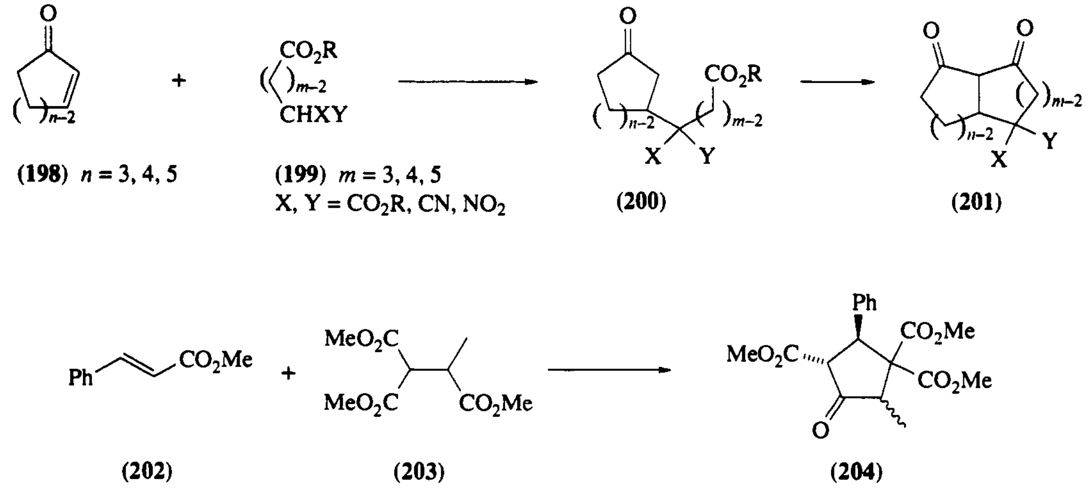
(198) $n = 3, 4, 5$
(199) $m = 3, 4, 5$
X, Y = $CO_2R$, CN, $NO_2$
(200)
(201)
(202)
(203)
(204)

Scheme 89

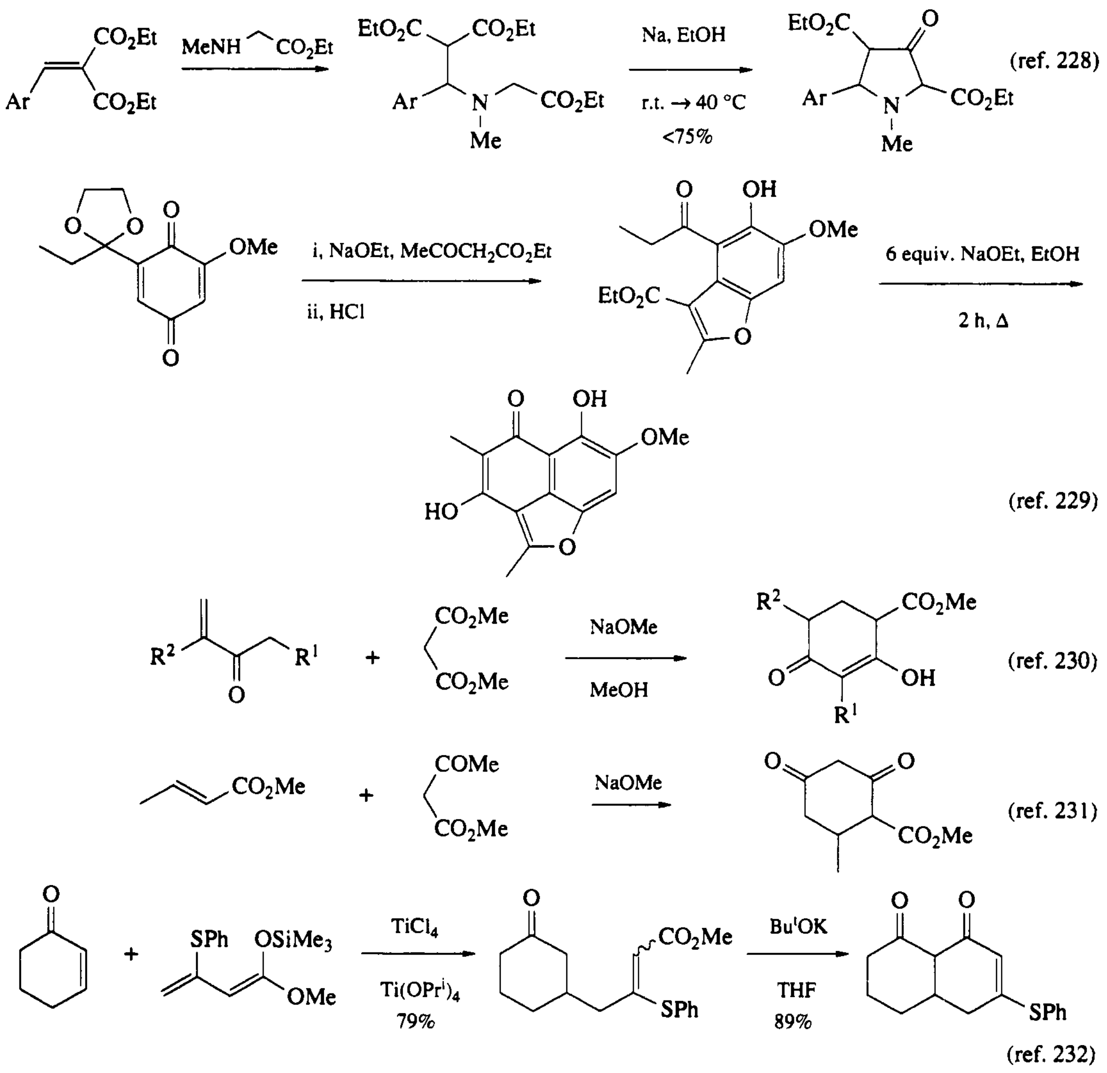
MeNH⌒$CO_2Et$
Na, EtOH
r.t. → 40 °C
<75%
(ref. 228)
i, NaOEt, $MeCOCH_2CO_2Et$
ii, HCl
6 equiv. NaOEt, EtOH
2 h, Δ
(ref. 229)
NaOMe
MeOH
(ref. 230)
NaOMe
(ref. 231)
$TiCl_4$
$Ti(OPr^i)_4$
79%
$Bu^tOK$
THF
89%
(ref. 232)

Scheme 90

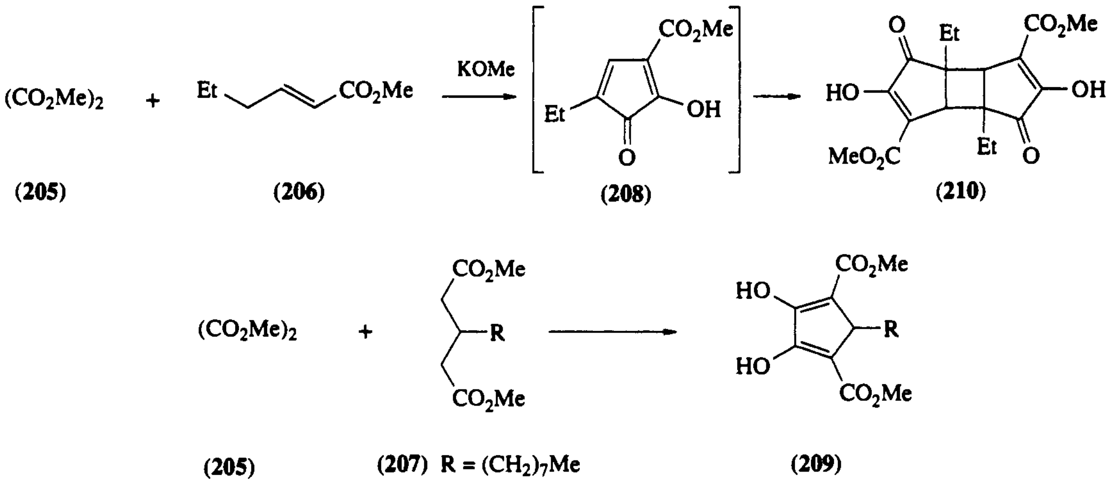
(CO2Me)2
Et
CO2Me
KOMe
CO2Me
Et
OH
O
O
Et
CO2Me
HO
OH
MeO2C
Et
O
(205)
(206)
(208)
(210)
(CO2Me)2
CO2Me
R
CO2Me
HO
CO2Me
R
HO
CO2Me
(205)
(207) R = (CH2)7Me
(209)

**Scheme 91**

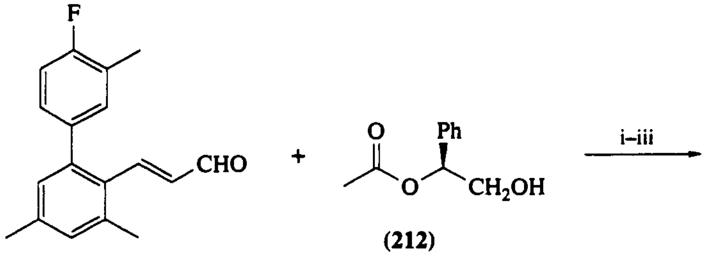
F
CHO
O
Ph
O
CH2OH
i–iii

(211) (212) (88) (46)

i, LDA; ii, MgBr; iii, NaOMe

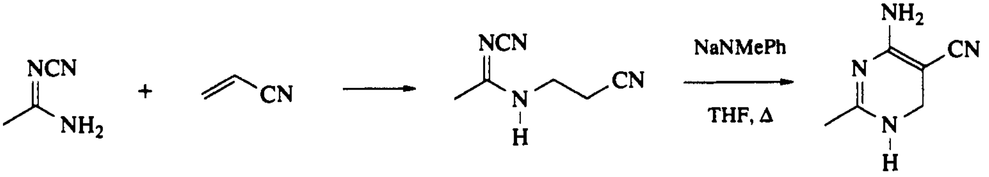
NCN
NH2
CN
NCN
N
H
CN
NaNMePh
THF, Δ
NH2
CN
N
N
H

(ref. 219)

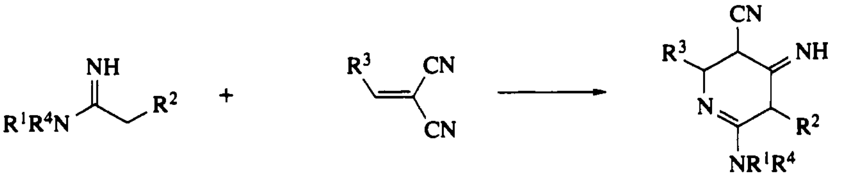
NH
R1R4N
R2
R3
CN
CN
CN
R3
NH
N
R2
NR1R4

(ref. 235)

| *R¹* | *R²* | *R³* | *R⁴* | *Yield* (%) |
|---|---|---|---|---|
| Ph | Ph | Ph | Et | 63 |
| Ph | Ph | Ph | Me | 68 |
| 2-MeC$_6$H$_4$ | Ph | 2-EtC$_6$H$_4$ | Et | 77 |

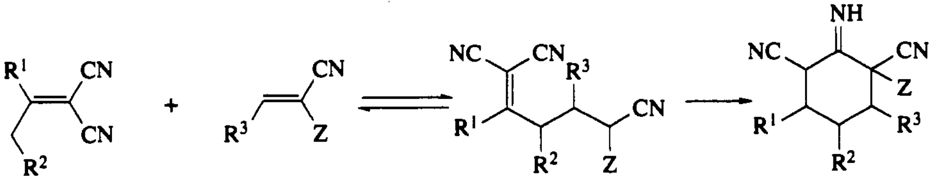
R1
CN
CN
R2
CN
R3
Z
NC
CN
R3
R1
CN
R2
Z
NH
NC
CN
Z
R1
R3
R2

(ref. 236)

**Scheme 92**

## 3.6.8 RETRO-REACTIONS

The equilibrium character of the reactions described in this chapter means that the reverse processes also occur. The retro-Claisen, retro-Dieckmann and retro-Thorpe–Ziegler reactions are all known and can be synthetically useful. In some cases the substrate may have been formed by the same or similar forward reaction, whereas in others the substrate has to be formed by another process since the equilibrium lies completely on the side of the retro-reaction product. As in the case of the forward reaction, tandem reaction sequences can be constructed, often with the same types of preceding reaction as were described for the forward sequence.

### 3.6.8.1 Cleavage of β-Keto Esters

Both simple retro-reactions and complex sequences involving retro-reactions of this type are known. Treatment of (**213**) with NaOH at room temperature for a few minutes gives (**214**), both a retro-Claisen and saponification having occurred.[237] The reaction was not successful with more complex derivatives such as (**215**). Treatment of (**216**) with sodium acetate in EtOH gave ethyl acetate and ethyl dichloroacetate, the facile cleavage resulting from further stabilization of the leaving anion by the chlorines (Scheme 93).[238]

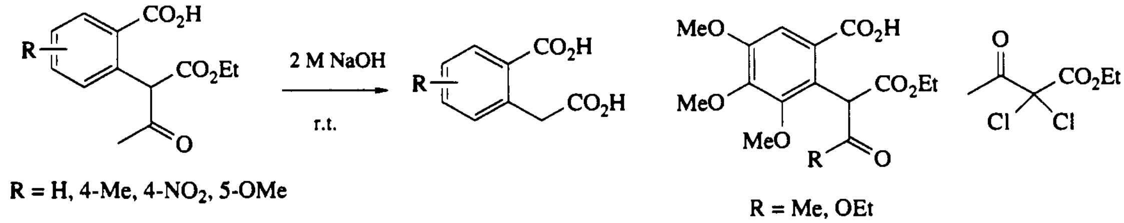

**(213)** **(214)** **(215)** **(216)**

Scheme 93

The bicyclic β-keto ester (**217**) undergoes cleavage to (**218**) with pyridine and water.[239] This reaction was used in a more complex sequence leading to the *C*-nucleoside (±)-showdomycin, compound (**217**) first being alkylated with iodoacetonitrile and the product (**219**) being cleaved with $NaHCO_3$ in THF (Scheme 94). The diterpene derivative (**220**) underwent a similarly facile retro-Dieckmann reaction to (**221**) with potassium carbonate in 80% methanol at room temperature over 3 d.[240] The 2-alkyl-2-methoxycarbonylcyclohexanones (**223**), derived by alkylation of (**222**), undergo ready retro-Dieckmann cleavage followed by reclosure to give the 6-alkyl derivative (**224**; Scheme 95).[93] Lithium methylcuprate addition to 5-methylcyclohex-2-enone (**225**) occurs stereospecifically to give *trans*-3,5-dimethylcyclohexanone (**226**) in 54% yield. This material can then be methoxycarbonylated to (**227**; Scheme 96).[241] Treatment of (**227**) with sodium methoxide in methanol followed by saponification with KOH gives (±)-3,5-dimethylpimelic acid (**228**), in which the relative stereochemistry of the two stereocenters is retained. 3-Oxocarbapenam esters can be readily cleaved to the corresponding β-lactam diester derivatives (equation 47).[242]

Alkylation of 2-methoxycarbonylcyclopentanone followed by treatment with sodium methoxide in methanol led to the ring-opened product, which was then cyclized to the 5-alkyl derivative (Scheme 97).[243] The retro-Claisen competes with transesterification in the reaction of the β-keto ester (**229**) with alkoxide (Scheme 98).[244]

### 3.6.8.2 Cleavage of β-Diketones

This is the reverse of the addition of ketone to an ester and has again found considerable synthetic application. Mahajan[245] found that 1,3-cyclohexanediones substituted at the 2-position with a group with an alcohol function at the terminal position (**230**) when treated with sodium hydride in benzene gave the macrocyclic lactones (**231**). The reaction may occur by nucleophilic addition to give the intermediate (**232**) followed by ring cleavage, the alkoxide acting as the intramolecular nucleophile, or the ketene (**233**) may be formed by proton abstraction and nucleophilic addition then follows. Mahajan has extensively explored this method[246,247] and has described a modification[248] in which the hemiacetal (**234**) is

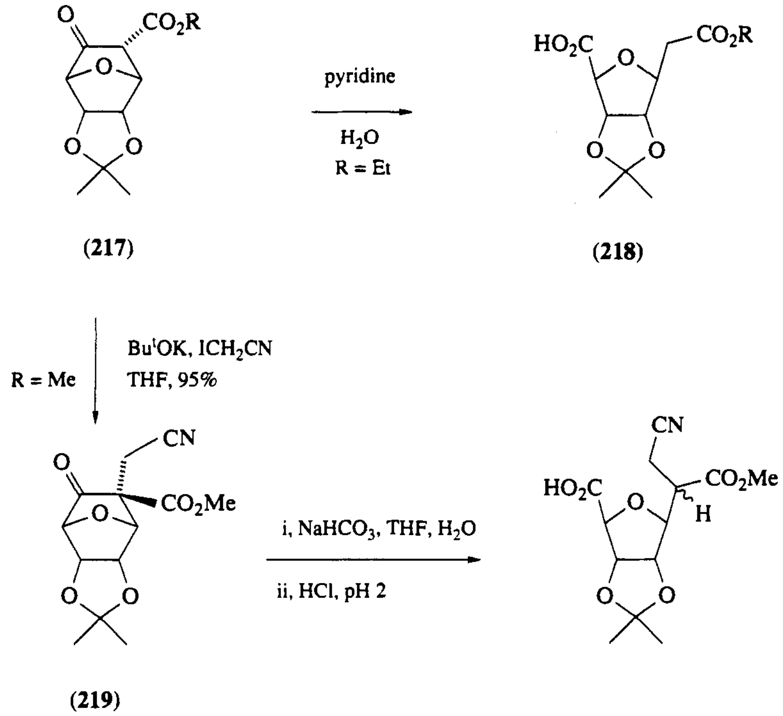
CO2R
pyridine
H2O
R = Et
HO2C
CO2R
(217)
(218)
R = Me
Bu<sup>t</sup>OK, ICH2CN
THF, 95%
CN
CO2Me
i, NaHCO3, THF, H2O
ii, HCl, pH 2
CN
HO2C
CO2Me
H
(219)

Scheme 94

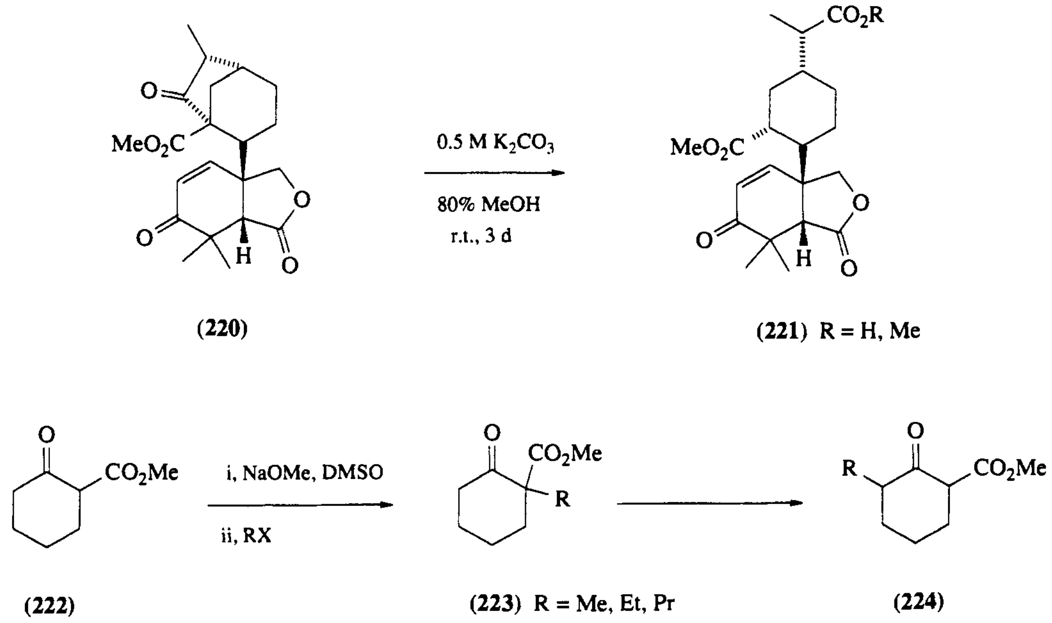
CO2R
MeO2C
H
0.5 M K2CO3
80% MeOH
r.t., 3 d
MeO2C
H
(220)
(221) R = H, Me
CO2Me
i, NaOMe, DMSO
ii, RX
CO2Me
R
R
CO2Me
(222)
(223) R = Me, Et, Pr
(224)

Scheme 95

ring opened in a fragmentation reaction. Others[250] have changed the solvent to THF and obtained good yields of macrocyclic lactones (**235**) together with some dimer (**236**), the formation of the latter supporting the ketene mechanism (Scheme 99).[248]

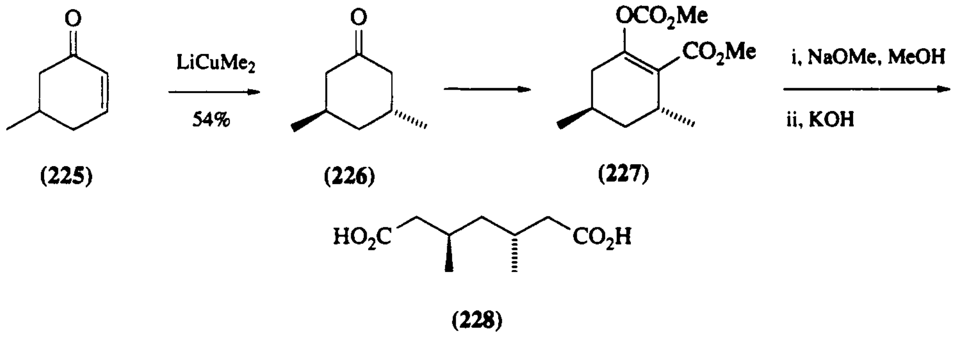
LiCuMe2
54%
OCO2Me
CO2Me
i, NaOMe, MeOH
ii, KOH
HO2C
CO2H
(225)
(226)
(227)
(228)

**Scheme 96**

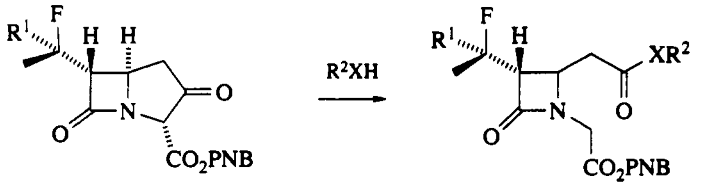
F
R1
H
H
O
N
O
CO2PNB
R2XH
XR2

(47)

$R^1 = Me, XR^2 = HNCH_2Ph; R^1 = H, XR^2 = HNCH_2Ph; R^1 = H, XR^2 = CH_2NO_2$

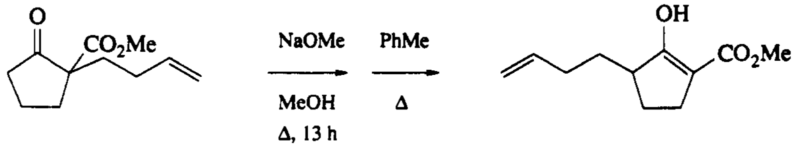
O
CO2Me
NaOMe
MeOH
Δ, 13 h
PhMe
Δ
OH
CO2Me

**Scheme 97**

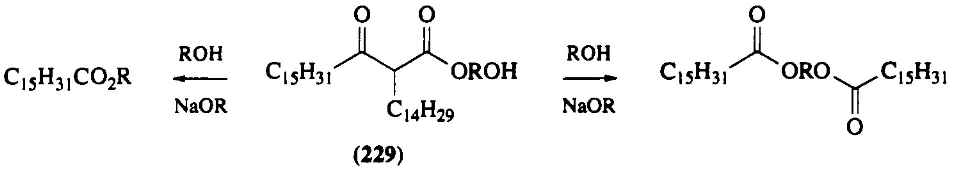
C15H31CO2R
ROH
NaOR
C15H31
OROH
C14H29
(229)
ROH
NaOR
C15H31
ORO
C15H31

**Scheme 98**

An acid-catalyzed retro-Dieckmann reaction converts the β-keto ketal (**237**) into (**238a**), which can be transesterified to the methyl ester (**238b**).[250] No racemization occurs at the noncleaving ring junction, both enantiomers of (**237**) proceeding with retention of configuration (Scheme 100).

### 3.6.8.3 Cleavage of 2-Cyanoenamines

As with the forward reaction, the retro-Thorpe–Ziegler reaction has found much less use than the retro-Dieckmann reaction. A Thorpe–Ziegler, retro-Thorpe–Ziegler sequence has been used to α-tetramethylate the bisnitrile (**239**; Scheme 101).[251]

## 3.6.9 CONCLUSIONS

The Claisen and Dieckmann reactions and their modifications are major synthetic methods for the formation of acyclic and cyclic systems. The resulting β-keto esters, or analogous systems, can undergo a variety of synthetic modifications allowing entry into a range of derivatives. The reactions can be con-

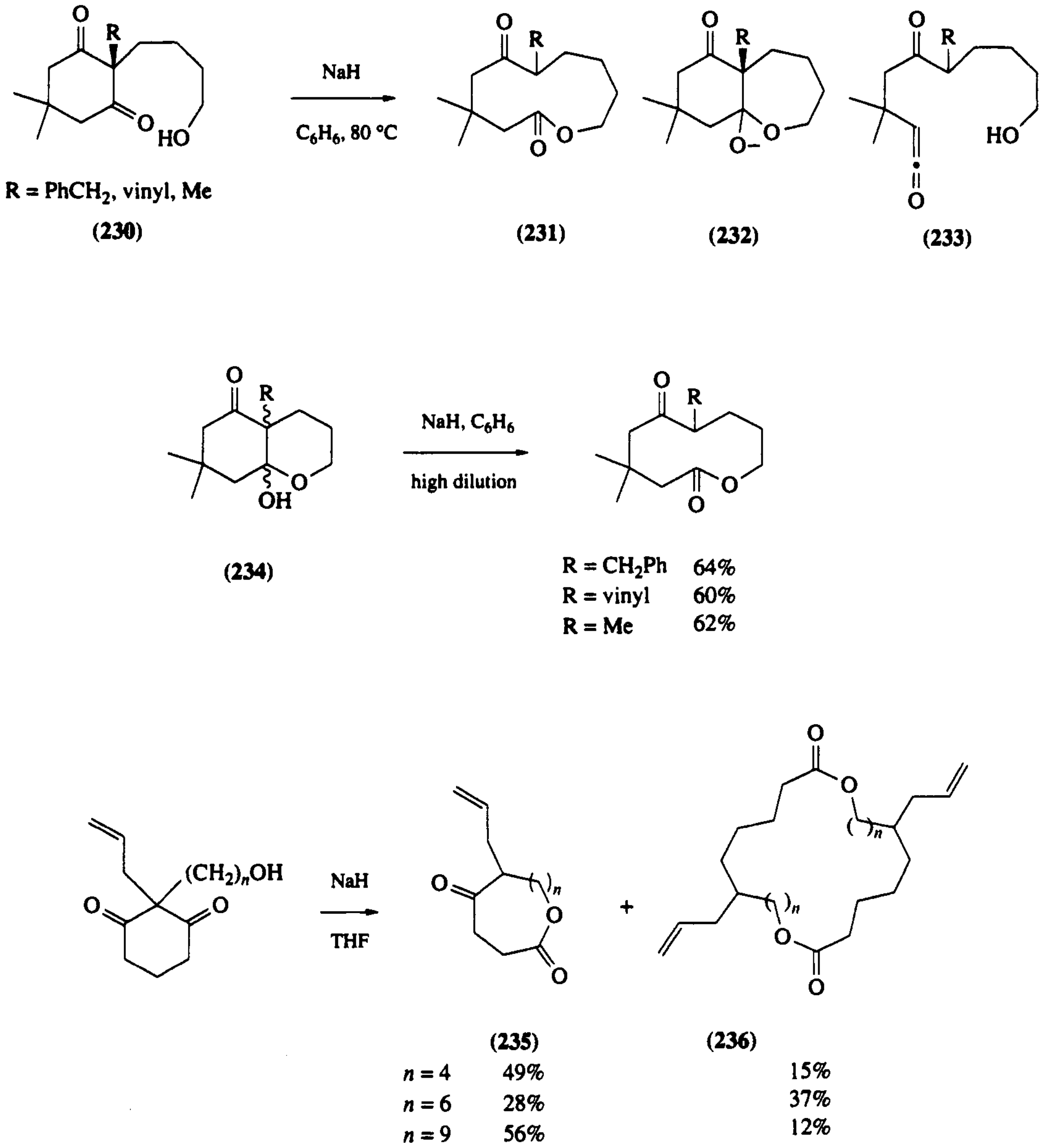
NaH
C6H6, 80 °C
R = PhCH2, vinyl, Me
(230)
(231)
(232)
(233)
NaH, C6H6
high dilution
(234)
R = CH2Ph 64%
R = vinyl 60%
R = Me 62%
NaH
THF
(235)
(236)
n = 4 49% 15%
n = 6 28% 37%
n = 9 56% 12%

**Scheme 99**

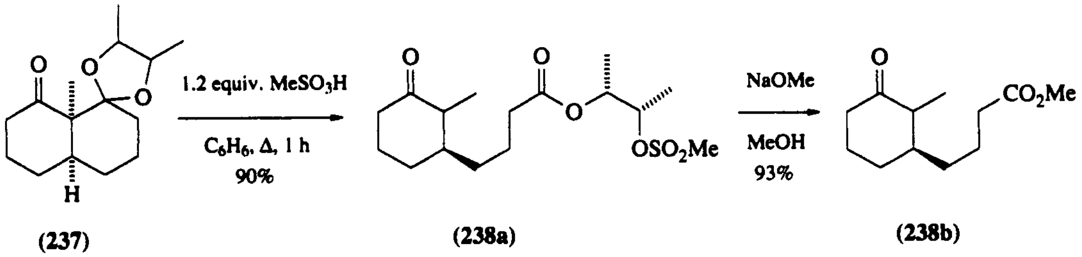
1.2 equiv. MeSO3H
C6H6, Δ, 1 h
90%
NaOMe
MeOH
93%
(237)
(238a)
(238b)

**Scheme 100**

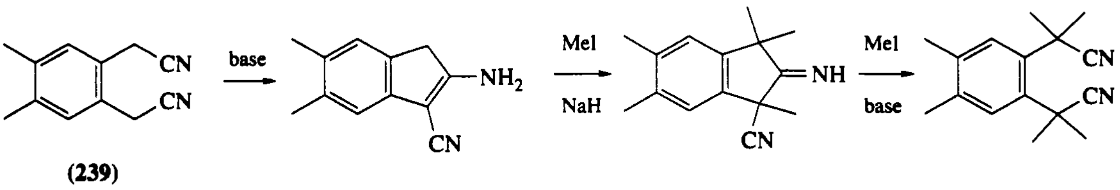

Scheme 101

trolled in a number of ways to give regioselective products but, in the case of the Dieckmann reaction, regioselectivity is not important if the cyclic ketone, derived by decarboxylation, is required. Examples of highly enantioselective Claisen acylations and Dieckmann reactions have recently been described.[252] The reactions are generally successful and tolerate a wide range of other functional groups, and non-carbon atoms in the chain are generally acceptable. Occasionally the Thorpe–Ziegler reaction gives better yields than the Dieckmann reaction and there is at least one reported case of an exhaustive examination of the latter reaction which did not give any product.[253] The Dieckmann is an excellent method for the preparation of five- and six-membered rings and has been applied successfully to the preparation of larger systems. The Thorpe–Ziegler reaction has also been used for the preparation of five- and six-membered rings, particularly heterocycles, and it was a method, in Ziegler's high-dilution procedure, for the synthesis of large rings, although it does not appear to have a great current use in this way.

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# 3.7

# The Eschenmoser Coupling Reaction

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## 3.7.1 INTRODUCTION

The Eschenmoser coupling reaction represents a versatile and efficient method to prepare vinylogous amides and urethanes by alkylation of a secondary or tertiary thioamide with an appropriate electrophilic component followed by elimination of sulfur (equation 1). This coupling, which in essence condenses an enolizable carbon with an amide carbonyl, can be formally considered a variant of the Claisen condensation. An extension of this process through alkylation of thiocarboxylic acids leads to direct synthesis of 1,3-dicarbonyl compounds (equation 2). Vinylogous amides and carbamates along with their hydrolysis products, the 1,3-dicarbonyl compounds, are important synthetic intermediates; their value is attested by the numerous methods available for their synthesis.[1,2] The Eschenmoser reaction provides an alternative approach to prepare these compounds that offers several distinct advantages. The unambiguous formation of a particular vinylogous amide or carbamate or a substituted 1,3-dicarbonyl compound can be achieved. Since the reaction conditions are sufficiently mild, incorporation of various functional groups and preservation of base-sensitive stereocenters are possible. The reacting centers also are relatively insensitive to the steric environment. In addition, the range of applications now available to the reaction has been broadened significantly through modifications and extensions on the original studies.

The coupling reaction is referred to commonly as the 'sulfide-contraction' or 'sulfur-extrusion' reaction. However, this reaction is distinct from other sulfur-eliminating, carbon–carbon bond-forming

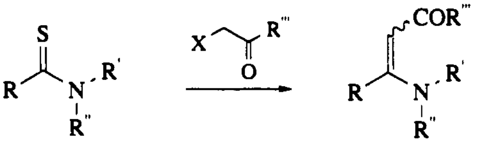

(1)

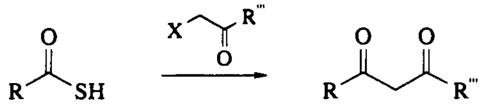

(2)

processes that also are designated as 'sulfur-extrusion' reactions. Several examples of these alternative contractions *via* extrusion methods include the thermal elimination of elemental sulfur in prearomatic systems[3] and the photolytic expulsion of sulfur to form carbon–carbon bonds.[4,5]

The novel method of effecting carbon–carbon bond formation *via* alkylative coupling followed by sulfide contraction was first described by Knott[6] during an investigation of various sulfur-containing chromophores. Knott observed that attempts to enolize the benzothiazolium salt (**1**) with triethylamine did not yield the anticipated salt (**2**; Scheme 1). Rather, a compound was isolated for which compositional data indicated loss of a sulfur atom. Further studies eventually identified the product as the conjugated ketone (**4**). A mechanism proceeding through an episulfide intermediate (**3**) followed by expulsion of sulfur was proposed to explain these observations.

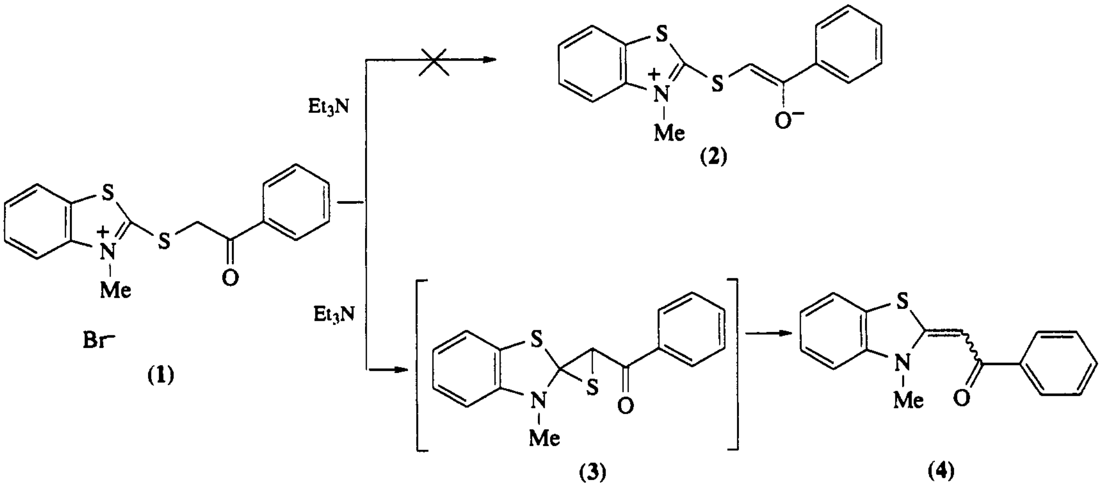

**Scheme 1**

These findings lay dormant in the literature for a number of years until Eschenmoser developed the general synthetic utility of this sulfide-contraction process.[7] This development stemmed from investigation of a related method that was critical in constructing the corrinoid structure involved in the synthesis of vitamin $B_{12}$.[8,9] Eschenmoser demonstrated the versatility and efficiency of this novel reaction by condensing thiopyrrolidinone with bromo ketones and esters to produce vinylogous amides and urethanes (**6**), respectively (equation 3; Table 1). The reagents and reaction conditions necessary to conduct the condensation were determined as well. Similar studies were performed on a set of thiocarboxylic acids, allowing preparation of the complementary β-dicarbonyl compounds. Based on this initial investigation, along with modifications and extensions that have since evolved, the Eschenmoser coupling reaction has proved to be a useful synthetic method that has found wide applications in numerous synthetic endeavors.

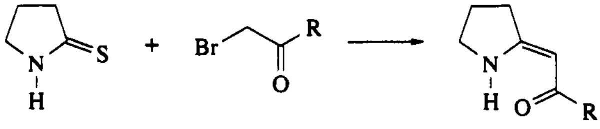

(3)

(**5**) (**6**)

**Table 1** Preparation of Vinylogous Amides and Urethanes *via* Sulfide-contraction (equation 3)[7]

| *R* | *Yield* (%) | *R* | *Yield* (%) |
|---|---|---|---|
| 4-$BrC_6H_4$ | 90[a] | $C(Me)_2CH_2CO_2Me$ | 56[c] |
| Me | 70[b] | *O*-Bu[t] | 75[d] |
| $CH_2CH_2CO_2Me$ | 85[c] | | |

[a] i, Diisopropylaminomethyl–polystyrene; ii, $Ph_3P$, 60 °C. [b] i, $KHCO_3$, $CH_2Cl_2$; ii, $Ph_3P$, Bu[t]OK, benzene (reflux). [c] $Ph_3P$, $CHCl_3$, 60 °C. [d] i, $KHCO_3$, $CH_2Cl_2$; ii, $Ph_3P$, Bu[t]OK, xylene (reflux).

## 3.7.2 MECHANISM

The Eschenmoser coupling reaction is composed of two distinct steps. First, a thioamide (**7**) is alkylated selectively on the sulfur with an electrophile to form an intermediate α-thioiminium salt (**8**; Scheme 2). In the second step, addition of a base and a sulfur scavenger (thiophile) promotes the extrusion of sulfur with concomitant formation of an alkenic bond. According to the accepted mechanism through which the second step of the reaction is believed to proceed, the base abstracts an α-proton in the appended side chain of the α-thioiminium salt (**8**). The anion (**9**) thus generated is then captured by the iminium species (or an imine, depending on the nature of the thioamide) to form a proposed episulfide (**10**). This intermediate then collapses with, or in some cases without, the assistance of a thiophile through elimination of sulfur to produce the unsaturated product (**11**). Although this mechanistic pathway is widely accepted, actual isolation and characterization of the proposed episulfide intermediate (**10**) have not been achieved. In most applications, the intermediate α-thioiminium salt (**8**) is not isolated but is subjected directly to the reagents that promote the second step of the reaction. In doing so, the entire coupling process can be conducted as a one-pot procedure.

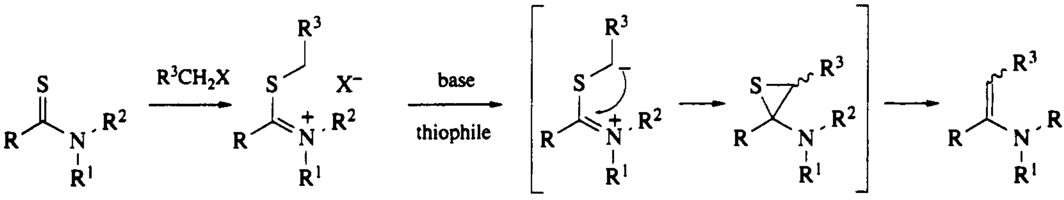

(**7**) (**8**) (**9**) (**10**) (**11**)

**Scheme 2**

### 3.7.2.1 α-Thioiminium Salt Formation

The Eschenmoser coupling reaction is initiated by the selective *S*-alkylation of a thioamide with a suitable electrophile. Thioamides can be prepared conveniently from the corresponding amides by using either phosphorus(V) sulfide[10,11] ($P_4S_{10}$; also known as phosphorus pentasulfide) or Lawesson's reagent[12] (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide). Both reagents are able to convert amides into thioamides, selectively and efficiently, under mild, neutral conditions in the presence of other functional groups, including esters. However, the more reactive Lawesson's reagent will convert ester carbonyls into the thio analogs under more drastic conditions.[13] In some instances, addition of sodium bicarbonate or triethylamine to the phosphorus(V) sulfide improved yields of the thiation.[14,15] Alternative methods to prepare thioamides are available,[16] although these routes have not been employed as extensively. These alternatives include treatment of dithioesters with an amine to produce thioamides[17] and conversion of amides into imidates followed by reaction with hydrogen sulfide.[18]

A variety of thioamides possessing either mono- or di-alkyl substitution on the nitrogen can undergo the Eschenmoser coupling reaction. Primary thioamides are not acceptable substrates because of their ready conversion to nitriles under the condensation conditions. Although alkylation proceeds more readily on secondary rather than tertiary thioamides,[19] use of the latter allows subsequent sulfur extrusion to proceed under milder conditions and with higher yields. The reasons for this difference will be discussed in the following section.

The thioamide can accommodate a number of functional groups since alkylation proceeds under mild conditions, *i.e.* neutral solutions at room temperature. For example, the presence of a sulfide did not interfere with alkylation on the thioamide (equation 4).[20] The range of functional groups compatible with this reaction will become evident in the discussion of its applications in total synthesis (Section 3.7.4).

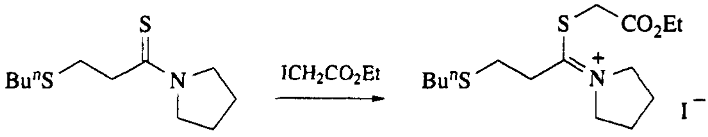

(4)

The electrophile used in thioamide alkylation must possess a sufficiently acidic α-proton for abstraction in the following step to initiate sulfur extrusion. Common electrophiles include α-activated carbonyl compounds such as esters, ketones, malonates and nitriles. However, alkylation with 4-nitrobenzyl bromide (Scheme 3) provided an intermediate iminium species containing a sufficiently acidic benzylic proton to promote subsequent sulfide contraction.[6]

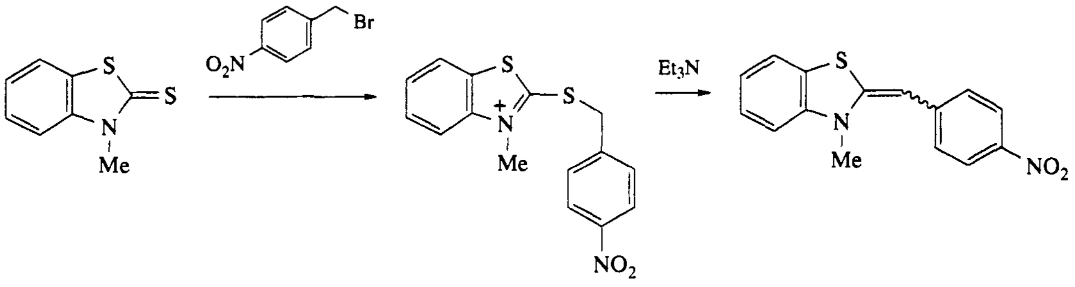

**Scheme 3**

The alkylation of a thioamide is a reversible process when the electrophile bears a nucleophilic leaving group. The reversibility was demonstrated[20] by combining a preformed α-thioiminium salt (**12**) with a second, distinguishable electrophile (**13**; Scheme 4). Upon standing in solution, exchange of the alkyl appendage to form a second α-thioiminium salt (**14**) was observed. As further support, the preformed α-thioiminium salts (**14**) and (**15**) were combined and allowed to equilibrate under the alkylation conditions. The mixture then was subjected to the sulfur-extrusion process, followed by hydrolysis, to produce the β-keto esters (**16a**), (**16b**), (**17a**) and (**17b**). The resulting mixture of products, yielding four rather than two β-keto esters, demonstrated that a scrambling of the side chains through reversible alkylation had occurred.

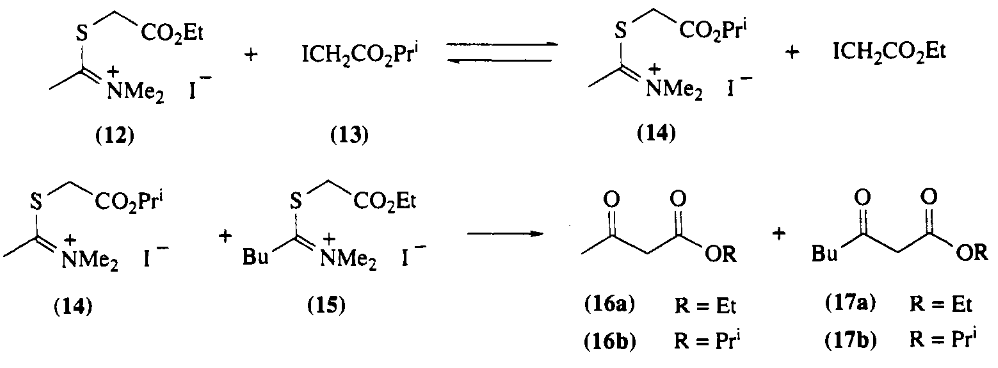

**Scheme 4**

In certain applications, the reversibility has led to problems. For example, alkylation of pivaloylthioamide (**18**) with ethyl 2-bromoisovalerate (**19a**) would not proceed to completion despite the use of forcing conditions (equation 5).[21] This difficulty was attributed to formation of a highly congested α-thioiminium intermediate (**20a**) in which the steric strain could be alleviated by reversion back to starting materials, thereby establishing an unfavorable equilibrium. To eliminate this reversal, alkylation was conducted with an electrophile bearing a non-nucleophilic leaving group. In particular, employing the trifluoromethanesulfonyl reagent (**19b**) enabled complete conversion of thioamide (**18**) to α-thioiminium salt (**20b**). This key finding has expanded significantly the scope of the Eschenmoser reaction to include the preparation of various α-substituted vinylogous products.

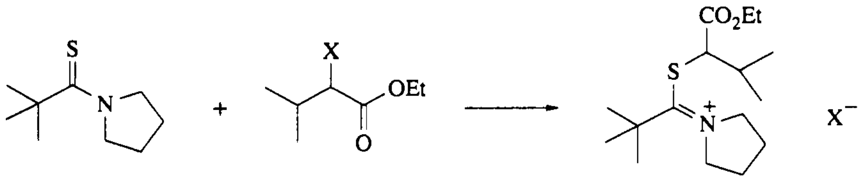

(5)

**(18)**

**(19a)** X = Br

**(19b)** X = $OSO_2CF_3$

**(20a)** X = Br

**(20b)** X = $OSO_2CF_3$

An alternative strategy was devised to overcome similar difficulties encountered while attempting an intramolecular Eschenmoser-based closure of chloro ester (**21**).[20] By immediately routing the intermediate α-thioiminium salt (**22**) as it was being formed through the sulfur-extrusion step, the ring-closed product was obtained in moderate to good yield (Scheme 5). Carefully controlled reaction conditions were developed in which the chloro ester (**21**) was added to a solution containing sodium iodide, base and thiophile at elevated temperature under high dilution.

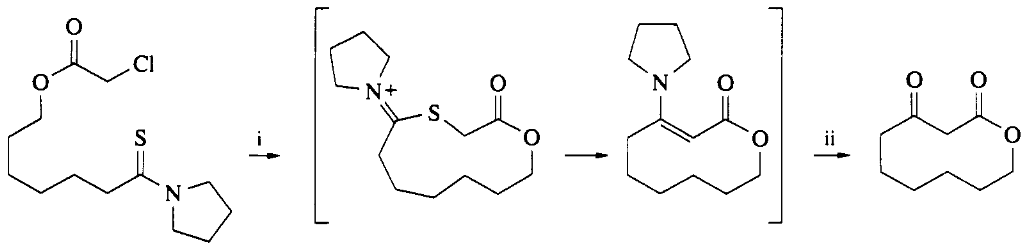

**(21)** **(22)**

i, NaI, $Pr^i_2NEt$, $P(OEt)_3$; ii, $H^+$, $H_2O$

**Scheme 5**

### 3.7.2.2 Sulfide Contraction and Carbon–Carbon Bond Formation

The second step of the Eschenmoser coupling reaction requires the presence of a base to generate an anion in the α-thioiminium intermediate that leads to episulfide formation. Inorganic bases such as bicarbonate, hydroxide, alkoxides and hydrides have been employed successfully, as have various organic bases such as triethylamine, *N*-methylmorpholine and diisopropylethylamine. Since a mild organic base is sufficient for deprotonation in most examples, the reaction is compatible with numerous functional groups and base-sensitive asymmetric centers. For compounds that are highly base sensitive, the base strength can be titrated to levels that permit deprotonation yet preserve stereochemical integrity. Significant improvement in enantiomeric purity can be achieved by conducting the reaction at lower temperatures.[22]

In addition to its basicity, the structural nature of the base can affect the course of the reaction. For example, a sterically imposing base such as diisopropylethylamine was prevented from abstracting proton ($H_a$) residing in a congested environment of the α-thioiminium salt (**23**; Scheme 6).[22] Instead, a less-hindered hydrogen ($H_b$) was abstracted, leading to formation of a proposed S,N-ketene acetal (**24**), which underwent rearrangement to yield the α-alkylated thioamide (**25**) as the major product. A less bulky base, such as triethylamine under the same reaction conditions, abstracted the desired proton ($H_a$) to produce the expected product (**26**) in good yield. The use of a secondary amine gave yet a different result. The addition of morpholine to the same intermediate α-thioiminium salt (**23**) led exclusively to formation of the stable amidinium salt (**27**). These findings emphasize the importance of proper base selection to prevent undesired results in the sulfide contraction.

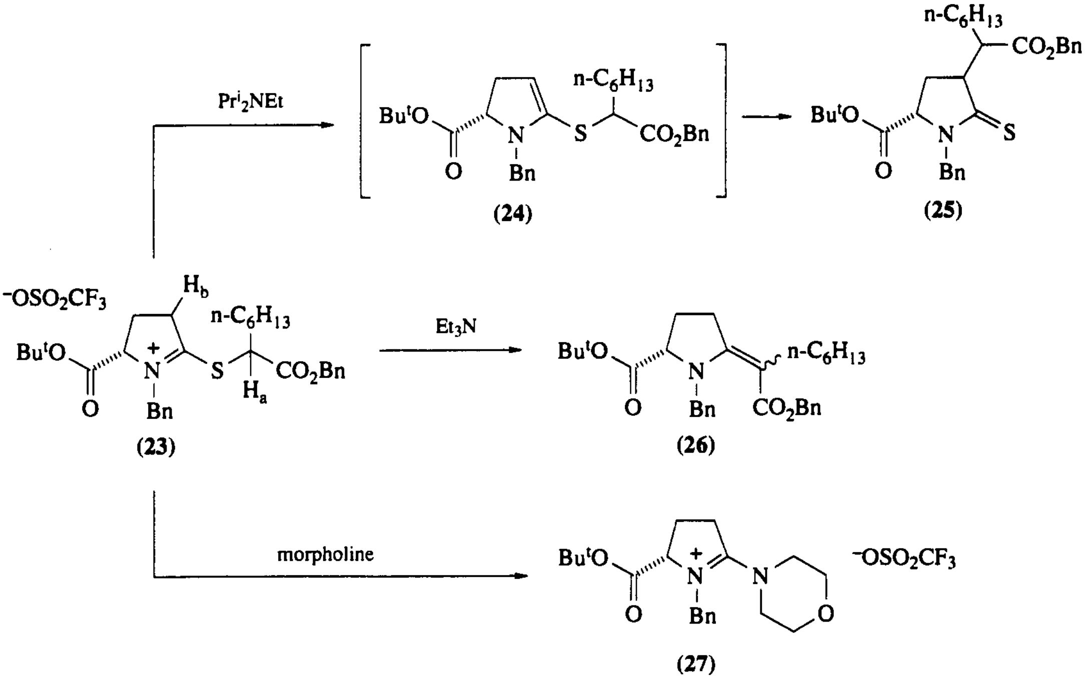

**Scheme 6**

The role of the thiophile is to assist extrusion of the sulfur atom from the episulfide intermediate to produce the unsaturated product. Studies have established that the presence of a thiophile affects the rate as well as the yield of the sulfur-extrusion reaction.[19] This participation was observed by measuring the difference in reaction rates and yields upon inverting the order of addition of the base and thiophile to a given α-thioiminium salt. Better results were obtained when the thiophile was allowed to stand in the presence of the α-thioiminium salt prior to addition of base. Presumably a sulfur–phosphine complex is established that enhances the acidity of the α-proton slated for abstraction and results in shorter reaction times and better yields.

A number of compounds can serve as an acceptable thiophile, including triphenylphosphine, trialkylphosphines and trialkyl phosphites. Eschenmoser developed a dual reagent, bis(*N*,*N*-dimethyl-3-aminopropyl)phenylphosphine (**28**), which contains both base and thiophile.[7] The main advantage of this dual reagent is its efficient removal from the product through aqueous washings, thereby simplifying purification. A derivative of the dual reagent was developed[21] by substituting a less basic morpholine for the trialkylamine to produce a new base–thiophile reagent (**29**) for use with base-sensitive compounds.

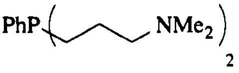

**(28)**

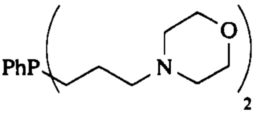

**(29)**

For most examples, addition of both a base and a thiophile is necessary for sulfide contraction to occur. However, the process can proceed in the absence of either reagent when a thioamide is alkylated with an active methylene species such as an α-halo malonate (equation 6)[7] or another 1,3-dicarbonyl compound that exists primarily in the enolized form. In some cases, heat was needed to initiate sulfide contraction; alkylation of monothiouracil (equation 7) with bromoacetophenone yielded an intermediate that extruded sulfur upon heating.[23] Sulfur extrusion also occurred on secondary thioamides alkylated with bromo ketones when heated in the presence of a thiophile.[7]

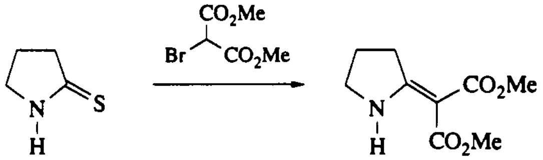

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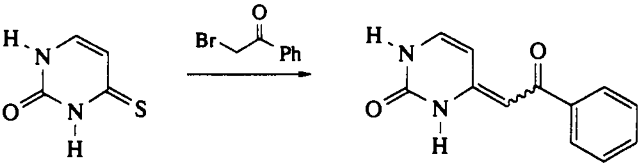

(7)

The degree of alkyl substitution on the thioamide nitrogen has an effect on both the reaction rate and the overall yield of the sulfide-contraction process. Tertiary thioamides produce higher yields of product with shorter reaction times than secondary thioamides under similar reaction conditions. This enhancement in both rate and yield is attributed to generation of a quaternary nitrogen in the α-thioiminium species derived from a tertiary thioamide. In contrast, alkylation of a secondary thioamide yields a tertiary iminium nitrogen that is converted to an imine upon addition of the first equivalent of base. The acidity of the side-chain α-proton in the charged, quaternary iminium species is expected to be greater than in the neutral imine intermediate, thereby facilitating deprotonation and resulting in better yields and shorter reaction times.[20] In addition, charge neutralization upon episulfide formation by the quaternary iminium species helps drive the reaction. An example of a secondary thioamide that would not undergo sulfide contraction until its tertiary derivative was prepared has been reported.[19]

Although the sulfide-contraction reaction is compatible with a wide range of steric and functional groups existing within either the thioamide or the electrophile, some precautions and limitations of the reaction need to be considered. The use of an α-halo ketone as the electrophile can result in an alkylated intermediate in which the thioamide nitrogen can undergo further addition to the keto group of the side chain to form a cyclized species. For example, a solvent-dependent equilibrium was established between the imine (**30**) and thiazolium salt (**31**) (Scheme 7).[7] In ethanol, the cyclized intermediate (**31**) was favored and could be isolated in good yield. Nonpolar solvents such as methylene chloride and chloroform appeared to suppress this side reaction and permitted formation of the desired vinylogous amide (**32**) upon treatment of the intermediate with a base and a thiophile.

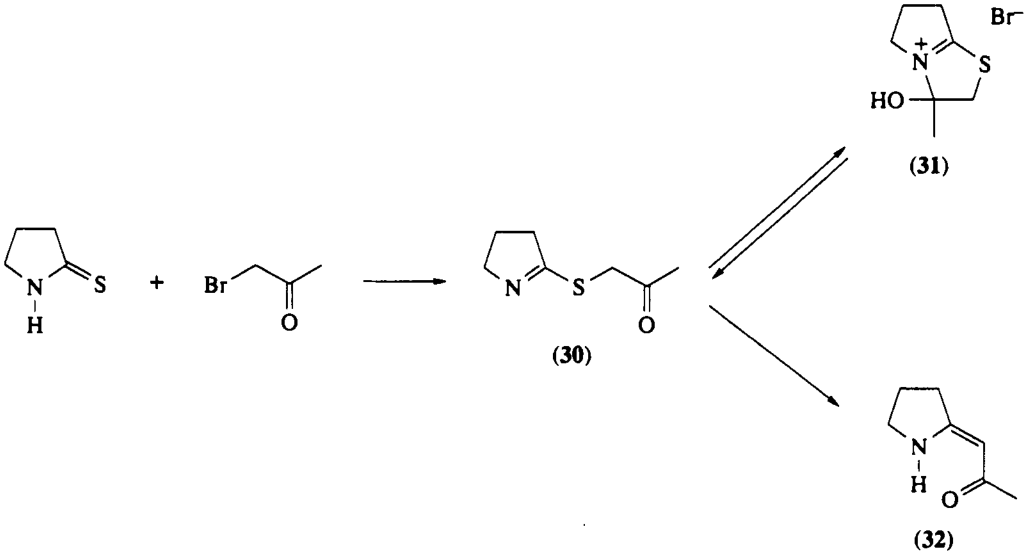

Scheme 7

In another example, α-bromo ketone (**34**) was used to alkylate the thioamide (**33**) in hopes of obtaining directly the vinylogous amide (**35**; Scheme 8).[24] However, abstraction of an undesired proton in the α-thioiminium salt formed the S,N-ketene acetal as in a previously described example. This proposed intermediate then rearranged and dehydrated to produce the thiophene (**36**) as the major product.

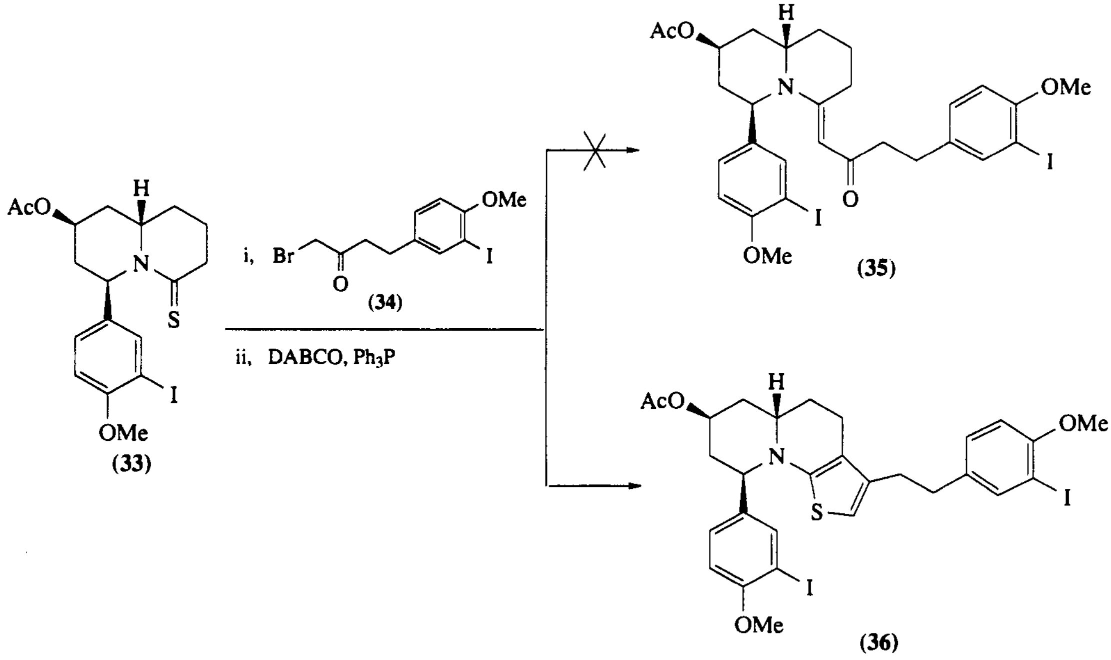

**Scheme 8**

In a similar case, the benzylic proton ($H_b$) in the α-thioiminium species (**37**) was abstracted instead of the α-keto proton ($H_a$) (Scheme 9). The resulting S,N-ketene acetal reacted with the ketonic carbonyl group to produce a similar 2-aminothiophene product (**38**). In contrast, the aliphatic iminium species (**39**) having a less acidic proton ($H_b$) gave the desired sulfide-contraction product.[20]

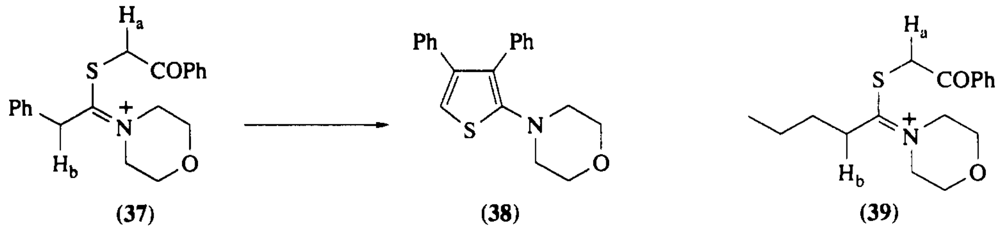

**Scheme 9**

A pair of geometric isomers about the alkene can result from the condensation process. Eschenmoser demonstrated that sulfide contraction on the secondary thiolactam produced exclusively the (*Z*)-isomer (equation 3).[7] Other studies have indicated sole formation of the (*E*)-isomer using tertiary thiolactams and bromoacetates or a mixture of isomers when α-substituted electrophiles were employed (*vide infra*). However, most synthetic applications of the Eschenmoser reaction have not stringently identified the geometry about the resulting alkene since the double bond is later reduced or equilibrated in the final product. A systematic investigation to identify factors that may influence the stereochemical outcome has not been reported.

## 3.7.3 MODIFICATIONS AND EXTENSIONS

### 3.7.3.1 Knoevenagel-based Modification

Several modifications of the sulfide-contraction reaction have appeared since the original report by Eschenmoser, offering complementary methods of conducting the condensation and broadening the scope of its applications. One adaptation, developed by Hart and coworkers,[25] utilized preformed α-thioiminium salts (**40**)–(**42**), generated from alkylation of the corresponding thiolactams with methyl iodide, as substrates for a Knoevenagel-based condensation. The preformed salts (**40**)–(**42**) were condensed with an active methylene compound in the presence of base to produce the corresponding vinylogous products (**43**)–(**45**) (Scheme 10; Table 2). Deacylated side products, *e.g.* (**46a**), (**46b**) and (**48**), were observed when the condensation was conducted with either β-keto esters or 1,3-diketones. However, deacylation could be minimized by proper choice of conditions. Condensation of the α-thioiminium salts (**40**)–(**42**) with the dibasic magnesium salt of ethyl hydrogen malonate followed by decarboxylation was the method of choice to prepare α-unsubstituted vinylogous urethanes (**46a**), (**47**) and (**48**). The advantages of this modification are the excellent handling and storage properties of the iminium salts and the ability to conduct the reaction with mild bases in the absence of a thiophile. This procedure was employed in the preparation of various carboxyl-modified amino acids and peptides.[26]

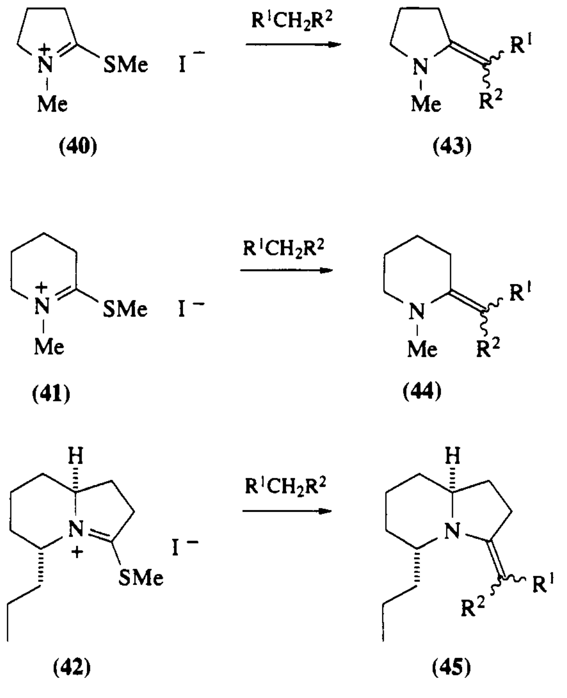

Scheme 10

Table 2 Reactions of α-Thioiminium Salts with Active Methylene Compounds (Scheme 10)[25]

| *Salt* | *R*$^1$ | *R*$^2$ | *Product* | *Yield* (%) |
|---|---|---|---|---|
| (**40**) | H | $NO_2$ | (**43a**) | $53^a$ |
| (**40**) | $CO_2Me$ | $CO_2Me$ | (**43b**) | $85^a$ |
| (**40**) | $CO_2Et$ | CN | (**43c**) | $80^a$ |
| (**40**) | $CO_2Et$ | COMe | (**43d**) | $84^{b,c}$ |
| (**40**) | COMe | COMe | (**43e**) | $53^{a,d}$ |
| (**41**) | $CO_2Me$ | $CO_2Me$ | (**44**) | $71^a$ |
| (**42**) | $CO_2Et$ | COMe | (**45**) | $57^{a,c}$ |

[a] $K_2CO_3$ (2.0 equiv.), DMF, 25 °C. [b] $Et_3N$ (2.0 equiv.), $CH_2Cl_2$, 25 °C. [c] Contains 2% of the deacylated product (**46a**). [d] Contains 23% of the deacylated product (**46b**). [e] Contains 32% of the deacylated product (**48**).

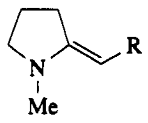

**(46a)** R = $CO_2Et$
**(46b)** R = COMe

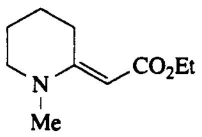

**(47)**

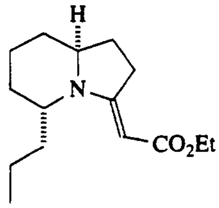

**(48)**

### 3.7.3.2 Thio-Wittig Modification

The thiocarbonyl alkenation procedure developed by Gossauer and coworkers enables the condensation of *N*-acylthioamides with resonance-stabilized phosphorus ylides and can be considered a modification of the Eschenmoser process. The two reactions are formally equivalent and both are believed to proceed through a common episulfide intermediate. This methodology was developed by Gossauer to couple highly functionalized pyrrole-based fragments in the synthesis of bile pigments (equation 8).[27] In contrast to the Eschenmoser method, the thiocarbonyl alkenation procedure is restricted to substrates containing an *N*-acylthioamide. For example, various monothioimides (**49**) were reacted with methyl (triphenylphosphoranylidene)acetate to yield the homologated products (**50**) (equation 9; Table 3). Dithioimides (**51**) were homologated, either singly or doubly, *via* this method (Scheme 11; Table 4).[28] In

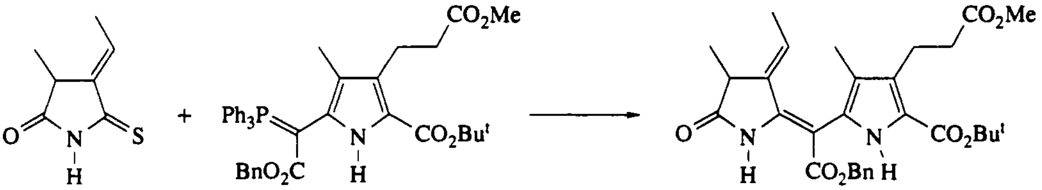

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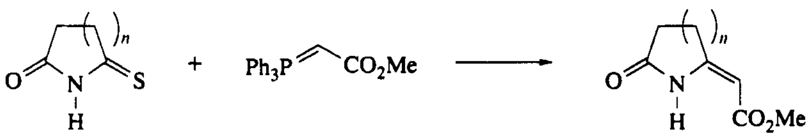

(9)

**(49)** **(50)**

**Table 3** Preparation of Homologated Imides (equation 9)[27]

| *n* | *Yield* (%)[a] |
|---|---|
| 1 | 66 |
| 2 | 45 |
| 3 | 51 |

[a] In boiling toluene for 20 h.

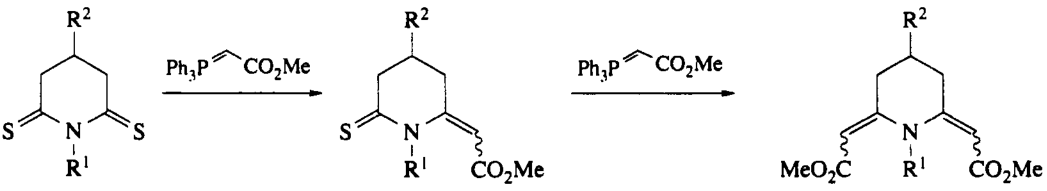

**(51)** **(52)**

**Scheme 11**

**Table 4** Preparation of Homologated Thioimides (**52**; Scheme 11)[28]

| *R*¹ | *R*² | *Yield* (%)[a] |
|---|---|---|
| H | H | 95 |
| Me | H | 94 |
| H | Me | 61 |

[a] Refluxing toluene.

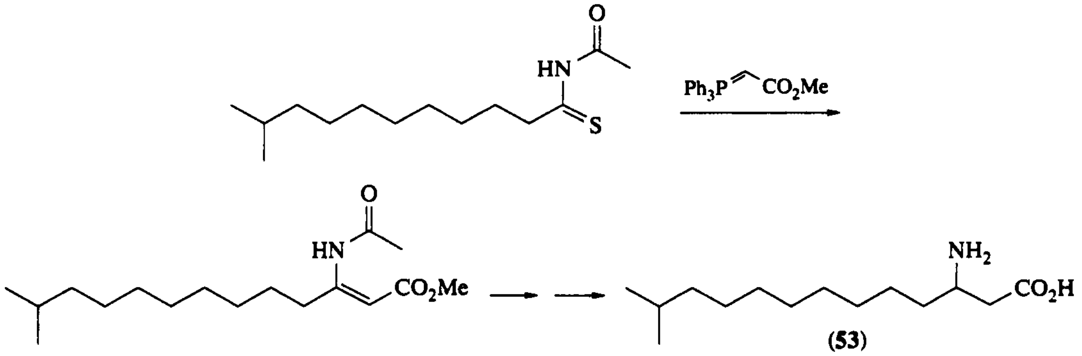

**(53)**

Scheme 12

addition, the thio-Wittig procedure has been conducted on acyclic *N*-acylthioamides and applied in the racemic synthesis of a β-amino acid, iturinic acid (**53**; Scheme 12).[29]

### 3.7.3.3 Preparation of β-Dicarbonyl Compounds

Although most of the synthetic developments and applications of the Eschenmoser reaction have employed thioamides as substrates, the two-step condensation process is applicable to the extension of thiocarboxylic acids (**54**).[30] A parallel mechanism to that described for the thioamide-based process is operating here and affords a direct synthesis of β-dicarbonyl compounds (**55**; Scheme 13). Eschenmoser demonstrated this application in his original report by alkylating various thiocarboxylic acids (**54**) with bromo ketones and esters in the presence of a base such as triethylamine.[7] The *S*-alkylated intermediate then was subjected to the sulfide-contraction process. In contrast to the α-thioiminium species generated from thioamides, the use of a thiophile and an organic base such as triethylamine did not promote sulfur extrusion from the thiol ester intermediate. A stronger base such as potassium neopentyl oxide was required for deprotonation to produce the desired 1,3-dicarbonyl product. For certain examples, an alternative to these strongly basic conditions was developed. The addition of lithium perchlorate or lithium bromide to those intermediates alkylated with α-halo ketones provided sufficient assistance through complexation to allow formation of the β-diketone products using tertiary amines rather than alkoxides. These conditions were not effective in preparing β-keto esters. This application of the Eschenmoser reaction has allowed the preparation of various substituted β-dicarbonyl compounds, in particular those

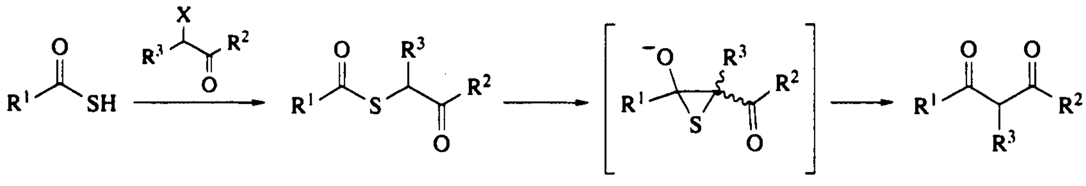

**(54)** **(55)**

Scheme 13

which possess a single α-substitution (Table 5). A complementary route, *via* hydrolysis of the vinylogous product resulting from sulfide-contraction on a thiamide, has provided an efficient method for the synthesis of β-keto esters, ketones and nitriles.[20,21]

**Table 5** Preparation of β-Dicarbonyl Compounds *via* Sulfide-contraction (Scheme 13)[7]

| $R^1$ | $R^2$ | $R^3$ | *Yield* (%) |
|---|---|---|---|
| EtCH$_2$ | Et | H | $85^a$ |
| EtCH$_2$ | Me | Me | $80^a$ |
| EtCH$_2$ | 4-BrC$_6$H$_4$ | H | $80^b$ |
| EtCH$_2$ | OEt | H | $69^c$ |
| EtCH$_2$ | OEt | Me | $79^c$ |

[a] i, Et$_3$N, R$^2$C(O)CHR$^3$Br; ii, bis(*N,N*-dimethyl-3-aminopropyl)phenylphosphine, LiBr, MeCN, 70 °C. [b] i, Et$_3$N, R$^2$C(O)CHR$^3$Br; ii, LiClO$_4$, Et$_3$N, Ph$_3$P, 20 °C. [c] i, Et$_3$N, R$^2$C(O)CHR$^3$Br; ii, potassium neopentyl oxide, Ph$_3$P, 50 °C.

## 3.7.4 APPLICATIONS IN TOTAL SYNTHESIS

The Eschenmoser coupling reaction has found numerous applications in the preparation of a wide-ranging, structurally diverse set of biologically and synthetically intriguing compounds. Since the reaction enables generation of carbon-based extensions from amide carbonyls, it has proven valuable in the synthesis of alkaloids and heterocycles containing various α-substituted amino fragments as structural elements. However, by recognizing the 1,3-dicarbonyl entity masked within the resultant enaminone of the sulfide-contraction process, the application of this reaction has been extended to include the preparation of non-nitrogen containing compounds as well.

### 3.7.4.1 Dendrobatid and Other Neurotoxic Alkaloids

Several synthetic approaches toward the poison-dart frog alkaloids, including pumiliotoxin C (**56**), gephyrotoxin (**57**) and histrionicotoxin (**58**), have utilized the Eschenmoser reaction in a variety of distinct applications. These structurally related alkaloids are isolated from skin extracts of various Central and South American frogs in the *Dendrobates* genus and possess neurotoxic properties. Since their initial isolation and characterization, these toxins have attracted considerable attention for both their synthetic challenge and their interesting biological properties.[32]

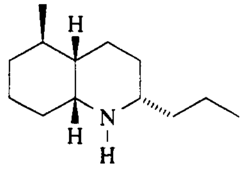

**(56)**

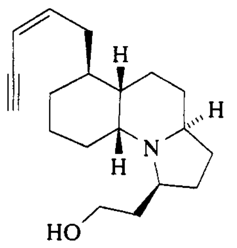

**(57)**

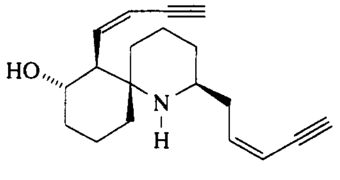

**(58)**

Pumiliotoxin C (**56**) is the prototypic member of a family of related alkaloids isolated from the skin of the poison-dart frog *Dendrobates pumilio* and *D. auratus*.[33] Several synthetic studies of pumiliotoxin C have been reported, including a racemic synthesis[34] in which the Eschenmoser reaction introduced the *n*-propyl side chain onto the decahydroisoquinoline nucleus. An advanced intermediate in the synthesis, the bicyclic lactam (**59**), was converted to the thiolactam with P$_4$S$_{10}$ (Scheme 14). Alkylation with bromoacetone provided the isolable thiazole intermediate (**60**), which was treated with triphenylphosphine and potassium *t*-butoxide to produce the vinylogous amide (**61**) in 71% yield from the starting thioamide. Catalytic reduction of the vinylogous amide (**61**), followed by oxidation, yielded a single amino ketone (**62**) possessing the desired stereochemistry about the piperidine nucleus. Deoxygenation of the amino ketone provided racemic pumiliotoxin C (**56**). Thus, the Eschenmoser reaction was able to introduce the three-carbon segment directly onto the bicyclic lactam and provide an intermediate on which the new stereocenter was established with excellent selectivity.

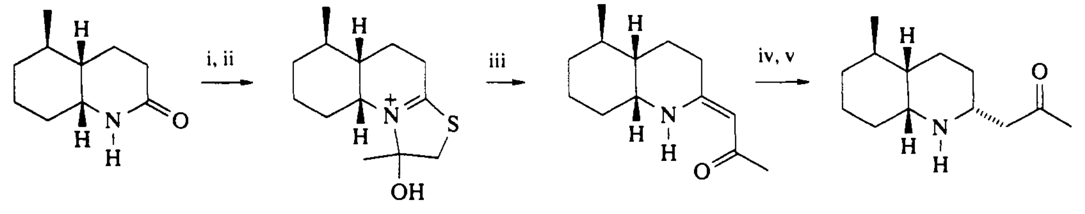

**(59)** **(60)** **(61)** **(62)**

i, $P_4S_{10}$; ii, bromoacetone; iii, $NaHCO_3$, then $PPh_3$, $KOBu^t$; iv, $H_2$, $PtO_2$; v, Jones' reagent

**Scheme 14**

Gephyrotoxin (**57**) is isolated from the frog *Dendrobates histrionicus* and possesses similar neurotoxic properties. Numerous chemical approaches have been developed to synthesize the parent compound and its hydrogenated analogs. Several of these approaches have incorporated the Eschenmoser reaction, each in a different application.

The first synthesis of optically pure gephyrotoxin[35] utilized the Eschenmoser reaction to generate a key disubstituted pyrrolidine intermediate. Thiolactam (**63**), derived from L-pyroglutamic acid to provide an optical center of known configuration at the start of the synthesis, was alkylated with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to yield the α-acyl vinylogous carbamate (**64**; Scheme 15). Deacylation was conducted in the presence of hydroxide and the resulting vinylogous carbamate (**65**) was reduced over Pt–C to yield a 2.3:1 mixture of the *cis* (**66**) and *trans* (**67**) disubstituted pyrrolidines. The optically pure, *cis*-2,5-disubstituted pyrrolidine (**66**) possessing the differentiated side chains served as the starting substrate from which the synthesis of optically pure gephyrotoxin (**57**) was accomplished *via* a previously established route.[36]

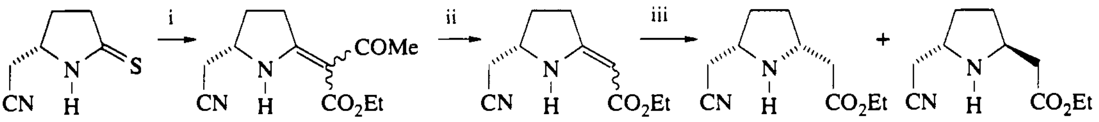

**(63)** **(64)** **(65)** **(66)** **(67)**

i, $MeCOCH(Br)CO_2Et$, $NaHCO_3$; ii, 0.1 N KOH, EtOH; iii, $H_2$, Pt–C, $HClO_4$, MeOH

**Scheme 15**

An alternative synthesis[37] of racemic gephyrotoxin (**57**) and one of its dihydro analogs (**72**) employed the Eschenmoser reaction to introduce a three-carbon segment that would eventually become the pendent hydroxyethyl side chain in the final compound. Alkylation of the tricyclic thiolactam (**68**) with ethyl bromoacetate, followed by treatment of the resulting α-thioiminium salt with triphenylphosphine and triethylamine, afforded the desired vinylogous carbamate (**69**) in good yield (Scheme 16). Reduction of the carbamate (**69**) under a variety of conditions did not proceed with a sufficient degree of selectivity. However, significant improvement in reduction selectivity was accomplished by employing remote functionality to control the stereochemical outcome. To this end, the pendent vinyl group was hydroxylated and protected as the silyl ether (**70**), at which stage reduction of the vinylogous carbamate again was attempted. The bulky silyl group directed preferential approach of the catalyst from the less-hindered side of the vinylogous carbamate to provide a 96:4 ratio in favor of the desired isomer (**71**). The two differentiated side chains extending from the major isomer (**71**) were ultimately elaborated to achieve racemic gephyrotoxin (**57**) and the dihydro derivative (**72**).

A third application of the Eschenmoser reaction in the synthesis of racemic perhydrogephyrotoxin (**76**) is based on an extension of the chemistry developed during the pumiliotoxin C synthesis.[38,39] Beginning with the bicyclic thiolactam (**73**), the sulfide-contraction reaction was used to append to the decahydroisoquinoline a functionalized five-carbon side chain that would later be cyclized and become the α-hydroxyethylpyrrolidine portion of the molecule. Alkylation of the thiolactam (**73**) with methyl 5-bromolevulinate followed by treatment with the Eschenmoser dual base–thiophile reagent (**28**) produced the vinylogous carbamate (**74**) in 81% yield from the starting thiolactam (**73**; Scheme 17). Reduction of the vinylogous amide (**74**), followed by equilibration of the amino ketones in the presence of

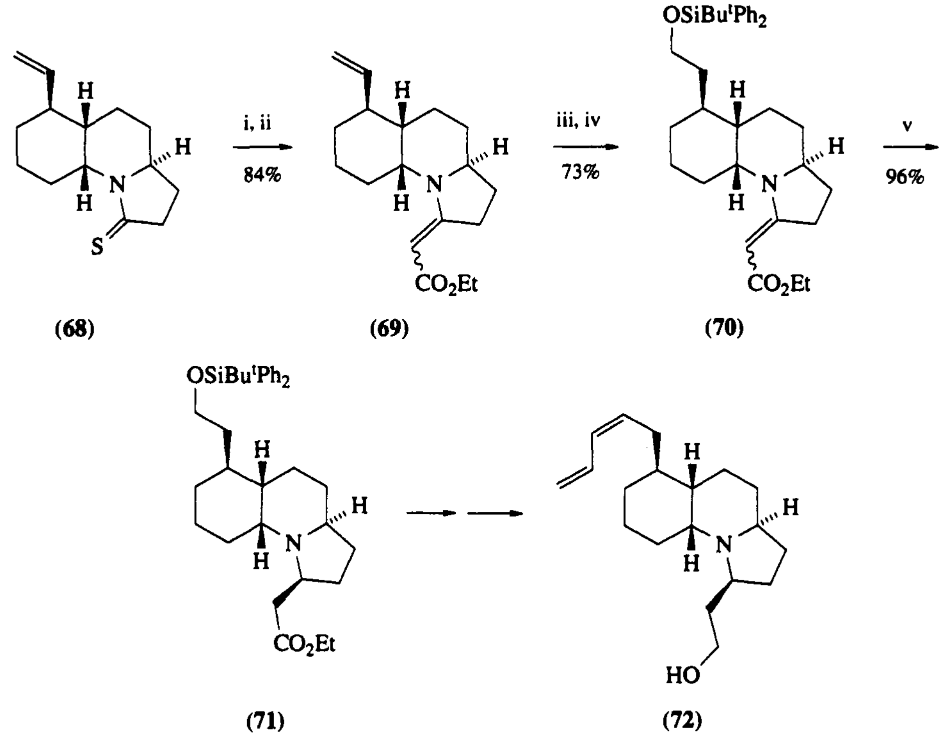

i, $BrCH_2CO_2Et$; ii, $Et_3N$, $Ph_3P$; iii, disiamylborane, 30% $H_2O_2$; iv, $Bu^tPh_2SiCl$, imidazole; v, $H_2$, $Pt/Al_2O_3$

**Scheme 16**

triethylamine, provided a satisfactory ratio favoring the desired isomer (**75**), which was converted to perhydrogephyrotoxin (**76**).

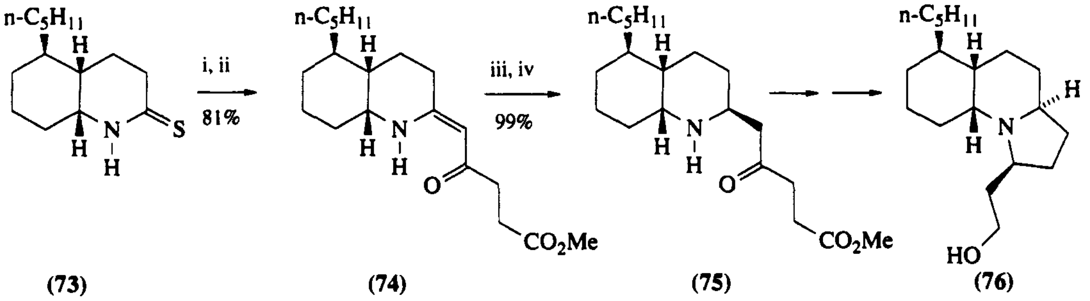

i, $BrCH_2COCH_2CH_2CO_2Me$; ii, $PhP(CH_2CH_2CH_2NMe_2)_2$; iii, $NaCNBH_3$, pH 4.0; iv, $Et_3N$

**Scheme 17**

The first total synthesis[40] of racemic histrionicotoxin (**58**), the parent structure in a family of related spirocyclic alkaloids isolated from the skins of *Dendrobates histrionicus*, utilized the Eschenmoser reaction to generate the anchor of what would become the enyne group extending from the α-position of the piperidine nucleus. The spirothiolactam intermediate (**77**) was condensed with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to produce (**78**) in good yield (Scheme 18). Prior to further reaction on the vinylogous carbamate, the pendent allylic acetate was elaborated to the enyne (**79**). Subsequent deacylation and enyne protection yielded spirobicycle (**80**), which gave a 1:1 mixture of isomers upon reduction. The desired diastereomer (**81**) was isolated and subsequently converted to racemic histrionicotoxin (**58**).

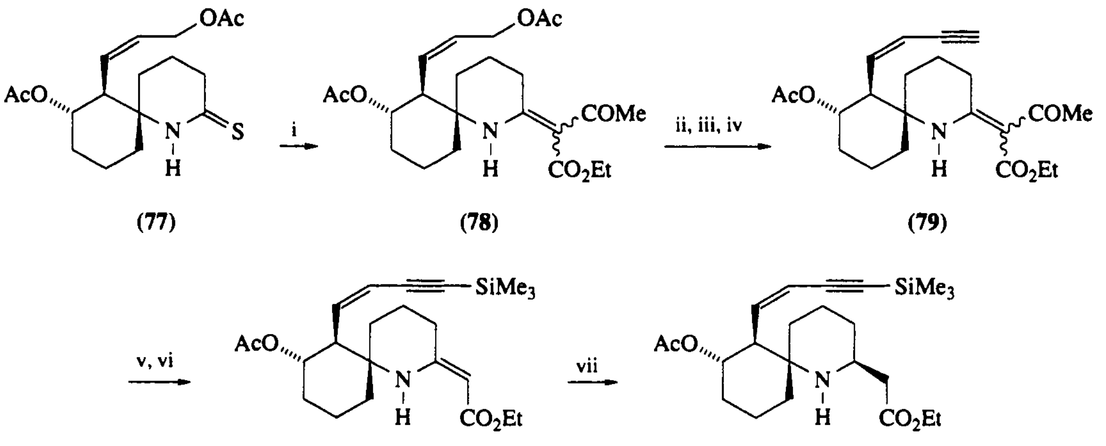

(77) (78) (79) (80) (81)

i, $MeCOCHBrCO_2Et$, $NaHCO_3$; ii, NaOH; iii, PCC; iv, $(Ph)_3\overset{+}{P}CH_2Cl\ Cl^-$, $Bu^nLi$; v, NaOEt; vi, MeLi, TMSCl; vii, $NaCNBH_3$

Scheme 18

The Eschenmoser coupling reaction has been extensively employed to prepare other compounds of biological and chemical interest. Saxitoxin (**85**),[41] one of the most toxic nonproteinaceous neurotoxins known, is isolated from the paralytic shellfish poison associated with episodes of algae-related 'red-tides'. The first total synthesis[42] of racemic saxitoxin employed the Eschenmoser reaction to incorporate a key functional handle from which the piperazine ring was later constructed. The spirothiolactam (**82**) was condensed with methyl 2-bromoacetoacetate in the presence of sodium bicarbonate followed by basic hydrolysis of the α-acetyl group to provide the vinylogous carbamate (**83**; Scheme 19). This key intermediate was condensed with benzyloxyacetaldehyde and silicon tetraisothiocyanate to yield directly the bicyclic thiourea ester (**84**), which was converted into saxitoxin (**85**).

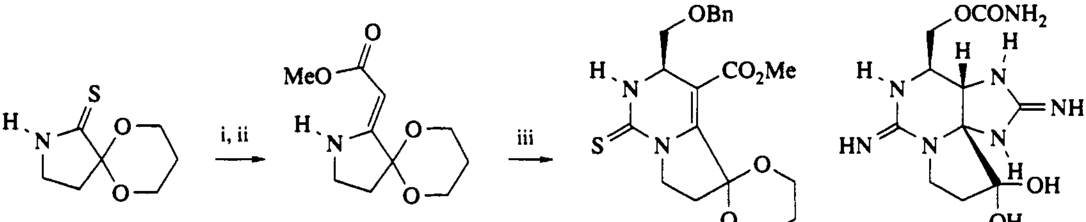

(82) (83) (84) (85)

i, $MeCOCHBrCO_2Me$, $NaHCO_3$; ii, KOH, MeOH; iii, $BnOCH_2CHO$, $(SCN)_4Si$

Scheme 19

The first synthesis[19] of optically pure anatoxin a (**93**), a potent nerve-depolarizing agent isolated from fresh-water blue-green algae, employed the Eschenmoser reaction to construct a functionalized side chain onto the pyroglutamate derivative (**86**) in a stereoselective manner. This side chain would be cyclized later into an iminium species, generated through decarbonylation of the α-amino acid, to form the bicyclic homotropane structure. Two strategies were investigated to build the side chain: a step-wise construction and a direct introduction of the entire side chain at once. Both approaches utilized the sulfide-contraction reaction to accomplish the key condensation onto the pyrrolidine ring. Optically pure thiopyroglutamate (**86**) was alkylated with methyl bromoacetate and the resulting thioiminium salt treated with triphenylphosphine and triethylamine to obtain the desired vinylogous carbamate (**87**; Scheme 20). Catalytic reduction of (**87**) proceeded with excellent transfer of chirality to produce a 98:2 ratio in favor of the *cis* amino diester (**88**). In contrast, reduction of (**87**) with $NaCNBH_3$ (pH 2) afforded a 3:1 mixture of the *cis* and *trans* amino diesters. Studies conducted on the amino diester (**88**) established that the optical purity of the α-center was maintained throughout the course of the sulfide-contraction process. The acetate side chain in the pure *cis* isomer (**88**) was extended to the requisite segment that enabled cyclization to the bicyclic structure of anatoxin a (**93**).

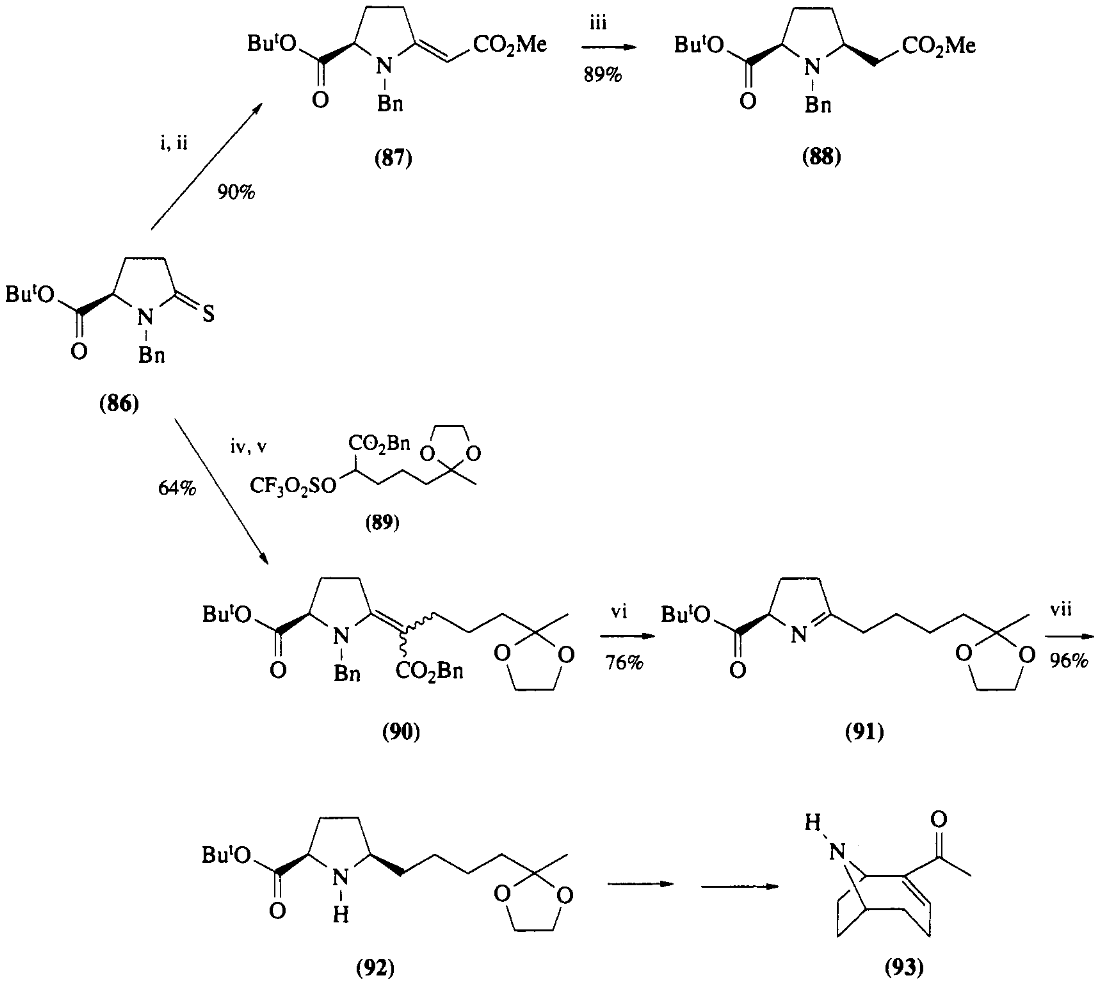

i, $BrCH_2CO_2Me$; ii, $Ph_3P$, $Et_3N$; iii, 5% Pt/C; iv, (**89**); v, $Ph_3P$, $Et_3N$; vi, 5% Pd/C, 1,4-cyclohexadiene; vii, $H_2$, $PtO_2$

**Scheme 20**

To complement the step-wise construction, the Eschenmoser reaction was adapted in a more convergent manner to introduce the entire side chain at once. This required alkylation of the thiopyroglutamate (**86**) with an α-substituted electrophile of the desired chain length and having the correct functionality. As previously noted,[21] this alkylation requires a triflate as the electrophile. Thus the thiopyroglutamate (**86**) was alkylated with (**89**) followed by reaction with triphenylphosphine and triethylamine to yield the anticipated vinylogous carbamate (**90**) as a mixture of geometric isomers. Treatment of the isomeric mixture with palladium using transfer hydrogenolysis conditions removed both benzyl groups; the resulting acid underwent decarboxylation and the enamine isomerized to the disubstituted pyrroline (**91**). Catalytic reduction of the pyrroline proceeded with efficient transfer of chirality to yield a 98:2 ratio favoring the *cis*-disubstituted pyrrolidine (**92**).

### 3.7.4.2 Pyrrolidine Alkaloids

The synthesis of all four possible stereoisomers of 5-butyl-2-heptylpyrrolidine (**94**), components of the trail pheromone of an ant in the genus *Solenopsis*, was conducted in a similar manner through extension of the same pyroglutamate derivative (**86**) *via* the Eschenmoser reaction.[22] Alkylation of the thiolactam (**86**) using an alkyl triflate reagent introduced the entire *n*-heptyl side chain in one step (Scheme 21). The resulting iminium salt intermediate was allowed to undergo sulfide contraction to yield a mixture of the vinylogous carbamates (**95**). The mixture was subjected to the transfer hydrogenolysis conditions and underwent debenzylation, decarboxylation and tautomerization to produce the pyrroline (**96**). Catalytic reduction of the pyrroline (**96**) proceeded with excellent selectivity to produce, in greater than 99:1 ratio, the *cis*-2,5-disubstituted pyrrolidine (**97**).

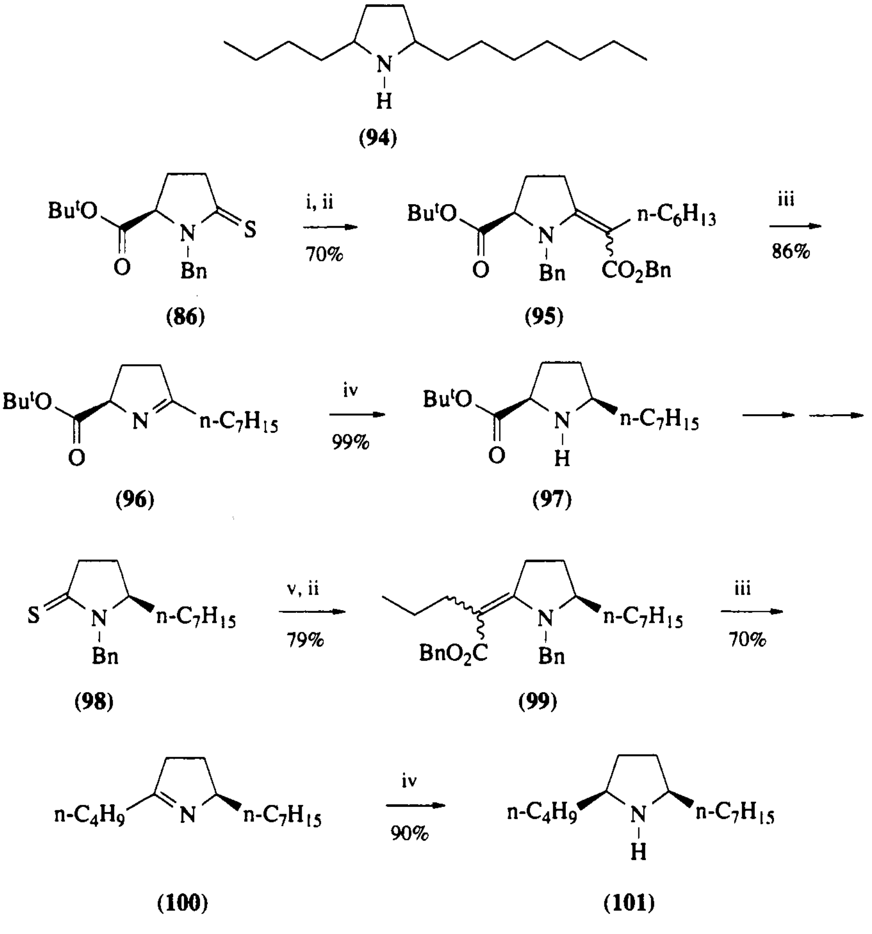

i, $Me(CH_2)_5CH(OSO_2CF_3)CO_2Bn$; ii, $Ph_3P$, *N*-methylmorpholine; iii, 5% Pd/C, 1,4-cyclohexadiene;
iv, $PtO_2$, $H_2$; v, $Me(CH_2)_2CH(OSO_2CF_3)CO_2Bn$

**Scheme 21**

The Eschenmoser reaction was applied a second time as one of the methods to introduce the *n*-butyl appendage. The alkylated α-amino ester (**97**) was oxidized to the monosubstituted thiolactam (**98**), and introduction of the butyl side chain, *via* sulfide contraction as described above, yielded a mixture of vinylogous carbamates (**99**). Treatment of the carbamates (**99**) under transfer hydrogenolysis conditions yielded the optically pure dialkylpyrroline (**100**), another component of the ant trail pheromone. Subsequent reduction of the pyrroline with platinum afforded the optically pure *cis*-2,5-dialkyl-substituted pyrrolidine (**101**). Other pyrrolidine-containing alkaloids have been prepared by similar approaches involving the Eschenmoser reaction.[43]

### 3.7.4.3 Quinolizidine, Pyrrolizidine and Related Alkaloids

The preparation[24,44] of several quinolizidine metacyclophane alkaloids, lythrancepine II (**105**) and III (**106**), employed the sulfide-contraction process to introduce a key segment onto an aryl bicyclic thiolactam (**102**), prepared from the corresponding lactam developed during the synthesis of vertaline alkaloids.[45] As described earlier, attempts to extend directly the thiolactam with the entire side chain containing the substituted phenyl group *via* the sulfide-contraction process did not produce the desired unsaturated ketone (**35**) but yielded the thiophene (**36**) instead. In the light of this finding, a step-wise approach was adopted in which alkylation of thiolactam (**102**) with ethyl iodoacetate, followed by treatment of the intermediate salt with DABCO and triphenylphosphine in refluxing chloroform, produced the desired vinylogous carbamate (**103**) in good yield (Scheme 22). Subsequent reduction of the alkene using sodium cyanoborohydride under acidic conditions yielded the desired amino ester (**104**) and its diastereomer in a ratio of 8.8:1. The acetate was elaborated into the requisite side chain and cyclized to the lythrancepines.

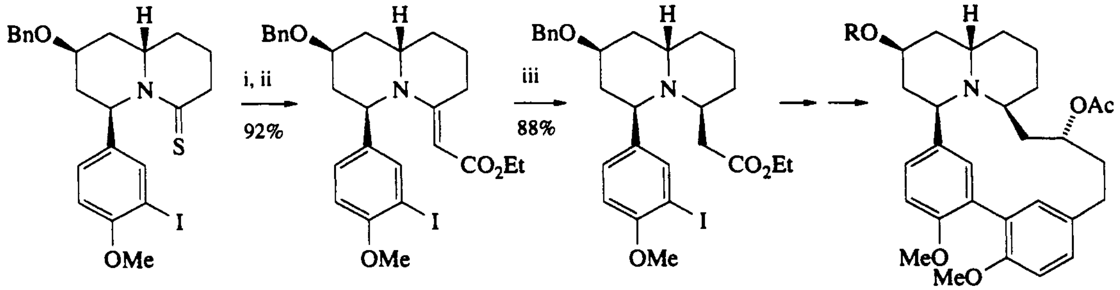

**(102)** **(103)** **(104)** **(105)** R = H; Lythrancepine II

**(106)** R = Ac; Lythrancepine III

i, $ICH_2CO_2Et$; ii, DABCO, $Ph_3P$, $CHCl_3$ (reflux); iii, $NaCNBH_3$

Scheme 22

Warming the above α-thioiminium salt in the presence of the thiophile and base was critical in order to accomplish the sulfide-contraction process. At ambient temperature, work-up of the same reaction mixture produced the oxolactam analog of (**102**) as the major product (74%) along with a small amount (12%) of vinylogous carbamate (**103**). In order to better understand the underlying mechanism that prevailed under ambient *versus* elevated temperatures, NMR studies were conducted on the α-thioiminium salt (**107**). This intermediate, when dissolved in deuterated chloroform at ambient temperature in the presence of DBU, was converted immediately to a proposed S,N-ketene acetal (**108**; Scheme 23). Triphenylphosphine had no effect on the iminium salt. Aqueous work-up yielded the lactam (**109**), which is consistent with formation of the S,N-ketene acetal. However, warming the intermediate (**107**) in the presence of the base and thiophile allowed the reaction to eventually proceed *via* the sulfur-extrusion pathway, due to the reversibility of the S,N-ketene acetal formation.

The Eschenmoser reaction was employed in a general method[46] for preparing other functionalized quinolizidines. The *N*-alkylated thiocaprolactam (**110**) was alkylated with ethyl bromoacetate followed by the standard sulfide-contraction procedure using triphenylphosphine and triethylamine to afford the desired vinylogous carbamate (**111**) in good yield (Scheme 24). The ester in the saturated propionate side chain was selectively reduced to the alcohol, converted to a leaving group and cyclized directly into the vinylogous carbamate (**112**). Step-wise reduction of this intermediate yielded a naturally occurring alkaloid, lupinine (**113**). In addition, a second alkylation on the bicyclic vinylogous carbamate (**112**) produced the α-alkylated derivative (**114**) as the major product along with a minor amount of the γ-substituted isomer. Cyclization of the α-alkylated compound produced the tricyclic structural framework (**115**) that comprises the nucleus of the julolidine alkaloids.

A similar strategy[47] generated two of the simplest members in the pyrrolizidine family of alkaloids, isoretronecanol (**120**) and trachelanthamidine (**121**). The enamino ester (**117**) was prepared *via* the Eschenmoser reaction by the condensation of thiolactam (**116**) and ethyl bromoacetate (Scheme 25). A second alkylation with bromoacetate on the resulting vinylogous carbamate (**117**) yielded the amino diester (**118**). Cyclization of the diester in the presence of potassium hydride generated the bicyclic lactam (**119**), which served as the common intermediate for preparation of both pyrrolizidine alkaloids.

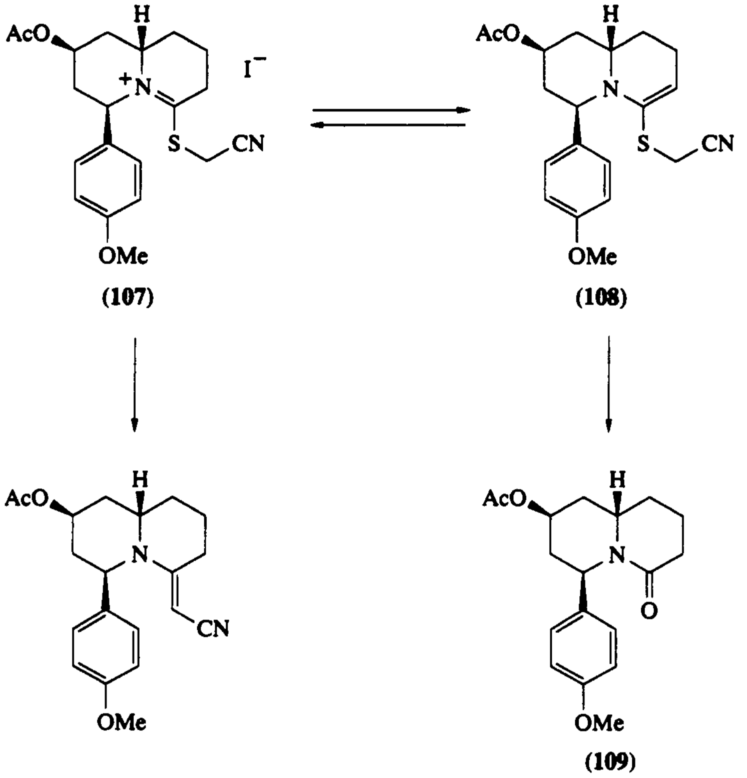

**Scheme 23**

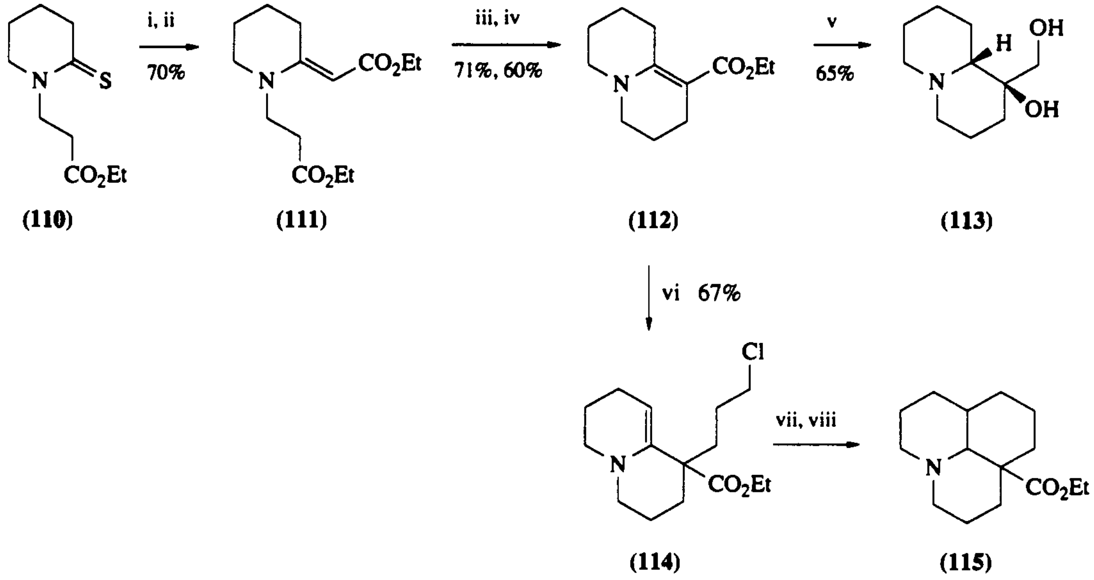
i, ii
70%
iii, iv
71%, 60%
v
65%
vi 67%
vii, viii
(110)
(111)
(112)
(113)
(114)
(115)

i, $BrCH_2CO_2Et$; ii, $Et_3N$, $Ph_3P$; iii, $LiAlH_3OEt$; iv, NaH, TsCl; v, $NaBH_4$ then $LiAlH_4$; vi, $Bu^nLi$, $BrCH_2CH_2CH_2Cl$; vii, NaI; viii, $PtO_2$

**Scheme 24**

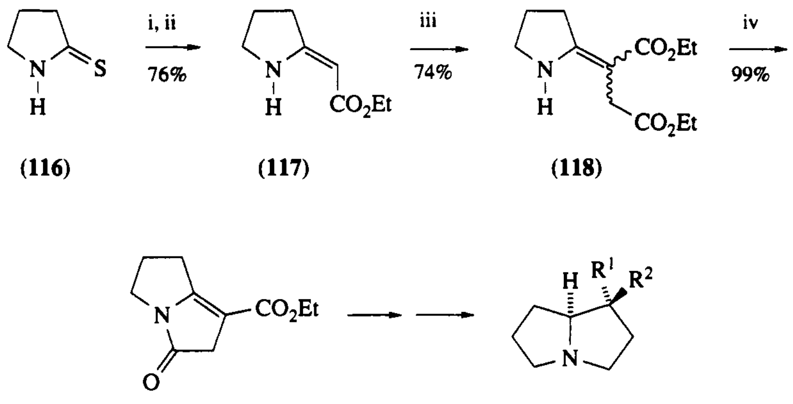
i, ii
76%
iii
74%
iv
99%
(116)
(117)
(118)
(119)

**(120)** $R^1 = H$; $R^2 = CH_2OH$; Isoretronecanol

**(121)** $R^1 = CH_2OH$; $R^2 = H$; Trachelanthamidine

i, $BrCH_2CO_2Et$; ii, $Ph_3P$, $KOBu^t$ iii, LDA, $BrCH_2CO_2Et$; iv, KH

**Scheme 25**

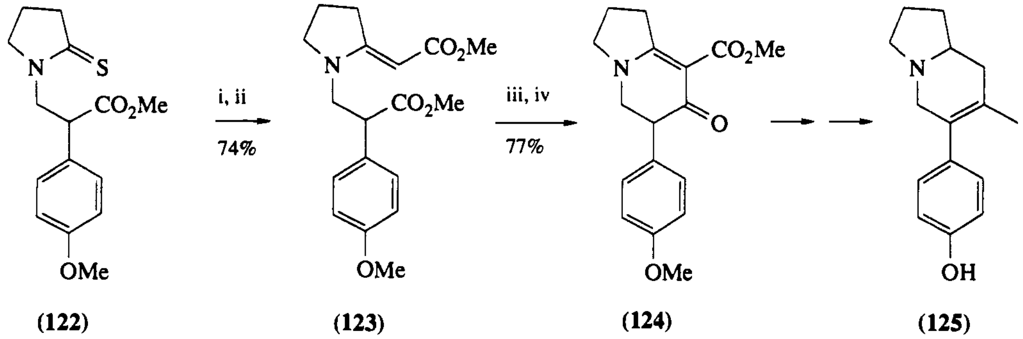
i, ii
74%
iii, iv
77%
(122)
(123)
(124)
(125)

i, $BrCH_2CO_2Me$; ii, $Et_3N$, $Ph_3P$; iii, NaOH, $H_2O$; iv, $Bu_4NI$, $ClCO_2Me$

**Scheme 26**

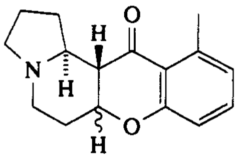

**(126)**

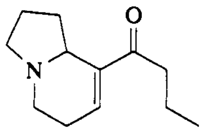

**(127)**

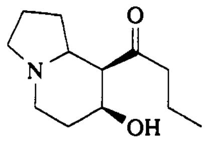

**(128)**

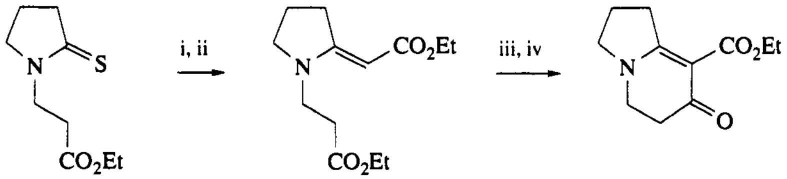

i, $BrCH_2CO_2Et$; ii, $Et_3N$, $Ph_3P$; iii, NaOH, $H_2O$; iv, $Ac_2O$

**Scheme 27**

The synthesis of ipalbidine (**125**),[48] the aglycon of ipalbine, was based on a related approach. The vinylogous carbamate (**123**) was prepared from the *N*-alkylated thiobutyrolactam (**122**) *via* an analogous sulfide-contraction process as described above (Scheme 26). The bicyclic intermediate (**124**) was generated by selective hydrolysis of the saturated ester followed by immediate treatment with methyl chloroformate in the presence of catalytic tetrabutylammonium iodide. The bicyclic compound (**124**) was further elaborated to racemic ipalbidine (**125**). Parallel applications of this strategy were employed to prepare a series of *Elaeocarpus* alkaloids (**126**), (**127**) and (**128**) (Scheme 27)[49] as well a benzomorphan analog (**129**; Scheme 28).[50]

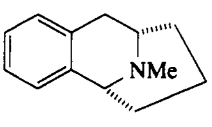

**(129)**

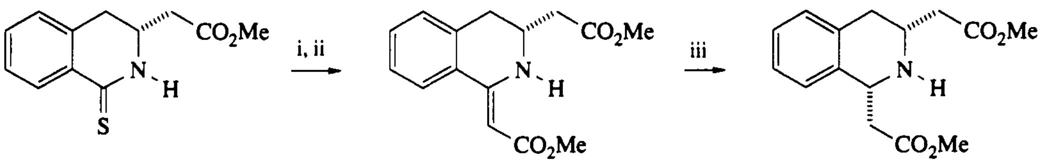

i, $BrCH_2CO_2Me$; ii, $Ph_3P$, $KOBu^t$; iii, $Pt_2O$

**Scheme 28**

A tandem sulfide-contraction and Robinson annelation reaction[51] was used for the synthesis of a mesembrine analog, $\Delta^7$-mesembrenone (**133**). The aryl-substituted thiobutyrolactam (**130**) was treated with chloromethyl vinyl ketone followed by diisopropylethylamine to afford $\Delta^7$-mesembrenone (**133**) in good yield (Scheme 29). The reaction probably proceeds through initial sulfide contraction to the intermediate vinyl enaminone (**131**), which tautomerized to the enamine (**132**) and underwent intramolecular Michael closure to produce (**133**).

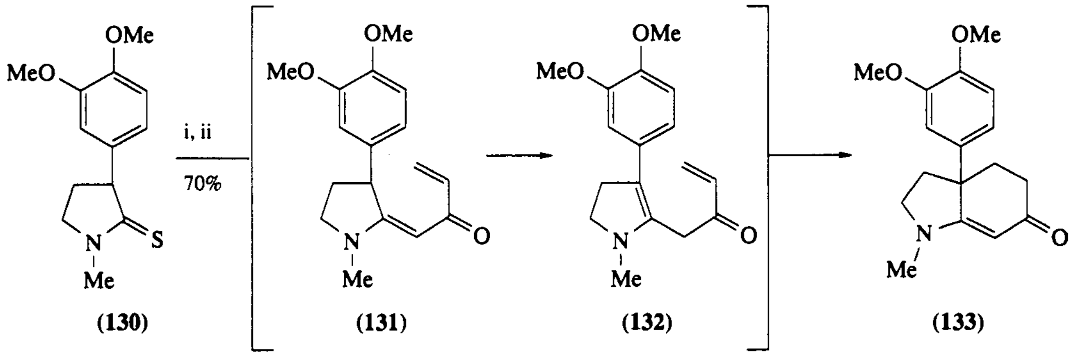

i, chloromethyl vinyl ketone; ii, $Pr^i_2NEt$

**Scheme 29**

### 3.7.4.4 Phosphodiesterase Inhibitor Analogs

The synthesis of several analogs of the phosphodiesterase inhibitors PDE-I (**134**) and PDE-II (**135**)[52] adapted the Eschenmoser reaction to perform a key cyclization that demonstrated its utility in constructing highly functionalized heterocycles. These tricyclic compounds are of additional interest because of their presence in the potent antitumor antibiotic CC-1065 (**136**). Cyclization of the pyrrolylthiopyrrolidinone (**137**) to the tricyclic structure was achieved either by the Eschenmoser reaction or by the Knoevenagel-based modification. To effect ring closure by the former route, the β-diketone was converted to the α-bromo derivative (**138**) through conversion to the diazo intermediate, deacylation and displacement with bromide (Scheme 30). Cyclization afforded the thiepinone (**139**) in quantitative yield after neutralization of the reaction mixture. Treatment of the diazo ketone with boron trifluoride etherate also provided the identical cyclized product. Thiepinone (**139**) underwent an oxidative sulfide contraction with liberation of hydrogen sulfide upon heating to yield the benzodipyrrole, isolated as the acetate (**140**). In the presence of tributylphosphine, equal amounts of the oxidized benzodipyrrole (**140**) and the expected compound (**141**) from the Eschenmoser reaction were isolated as their acetates.

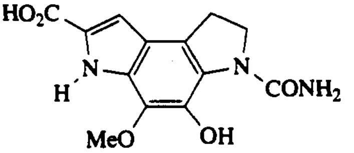

**(134)** PDE I

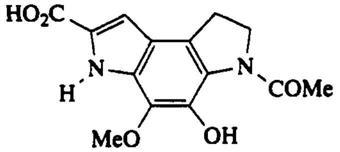

**(135)** PDE II

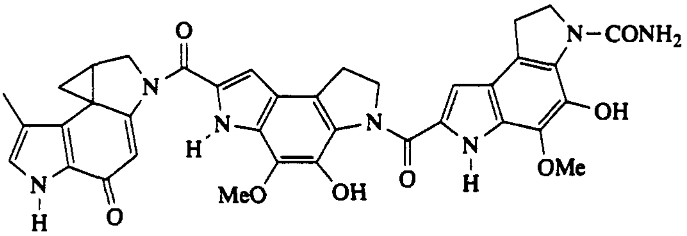

**(136)**

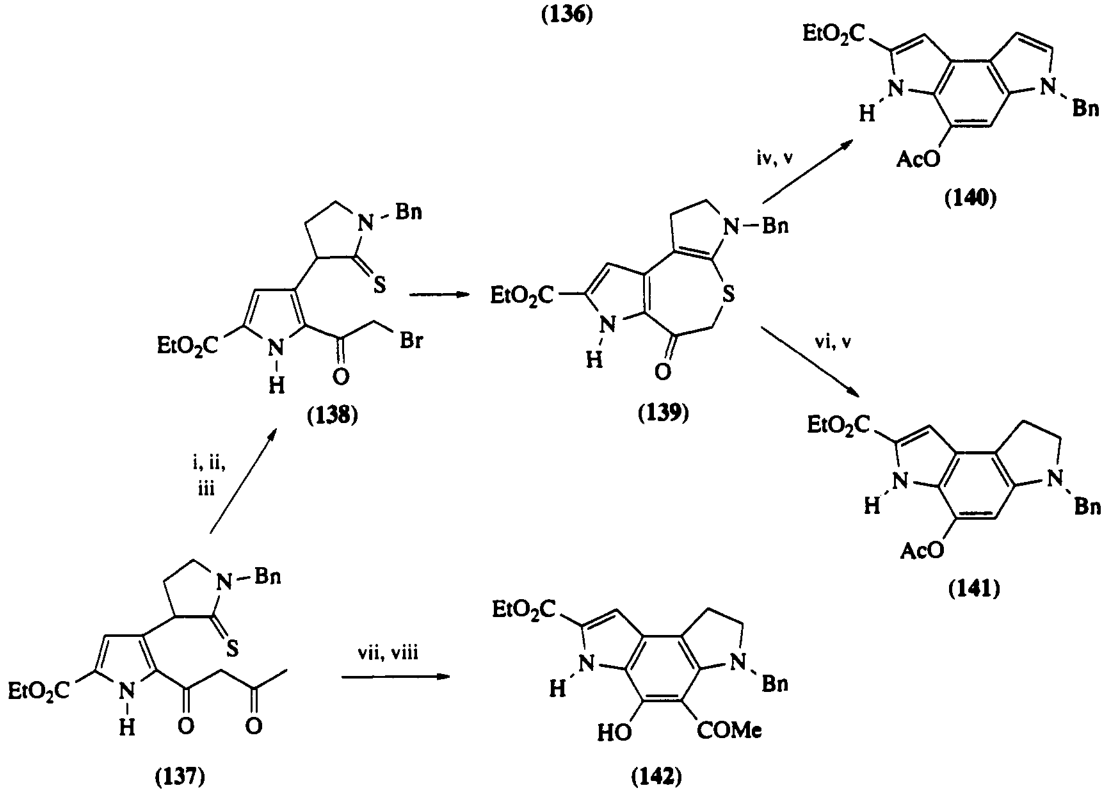

i, $p$-$NO_2C_6H_4SO_2N_3$; ii, pyrrolidine; iii, HBr or $BF_3{\bullet}Et_2O$; iv, MeCN (reflux); v, $Ac_2O$; vi, $Bu_3P$; vii, MeI or $Br_2$; viii, $NaHCO_3$

**Scheme 30**

To implement the Knoevenagel-based modification, the β-diketone derivative (**137**) was treated with methyl iodide to yield a white solid, presumed to be the α-thioiminium salt. Upon treatment of the salt with base, the expected cyclized product (**142**) was isolated in excellent yield. Likewise, the diketone (**137**) was treated with an equivalent of bromine to produce the same product. The bromine-based cyclization is believed to occur by formation of the α-bromo β-diketone and closure *via* the Eschenmoser-based mechanism. A mechanism involving bromination at the sulfur atom also would be consistent with the results.

### 3.7.4.5 Antibiotics

A series of carbapenams have been generated using the sulfide-contraction reaction to construct the constituent β-amino acid segment.[53] The thiopyroglutamate derivative (**143**) was condensed with ethyl 2-bromoacetoacetate in the presence of sodium bicarbonate to afford the α-acyl vinylogous carbamate (**144**; Scheme 31). The use of sodium bicarbonate in the sulfide contraction was critical in this particular

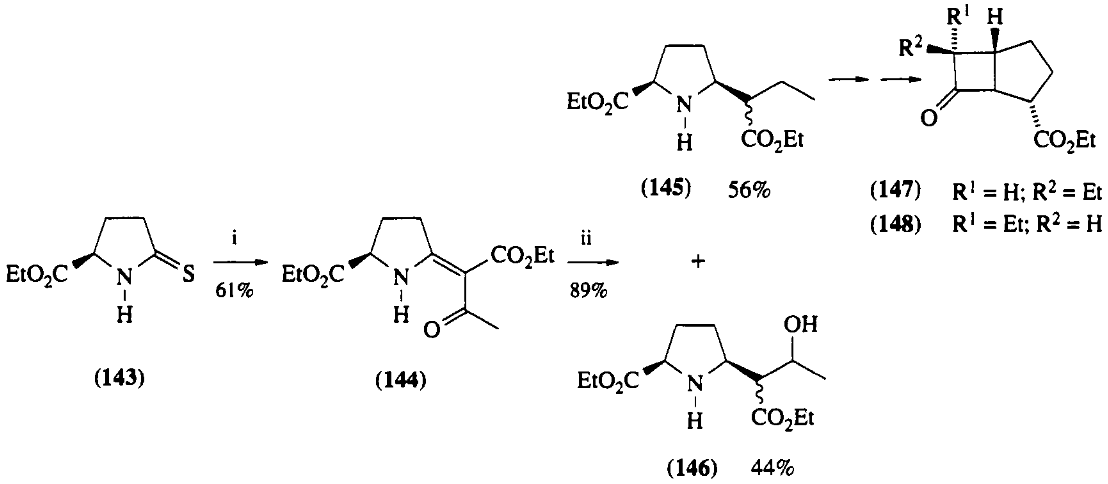

i, MeCOCHBrCO$_2$Et, NaHCO$_3$; ii, PtO$_2$, 20% TFA/MeCO$_2$H

**Scheme 31**

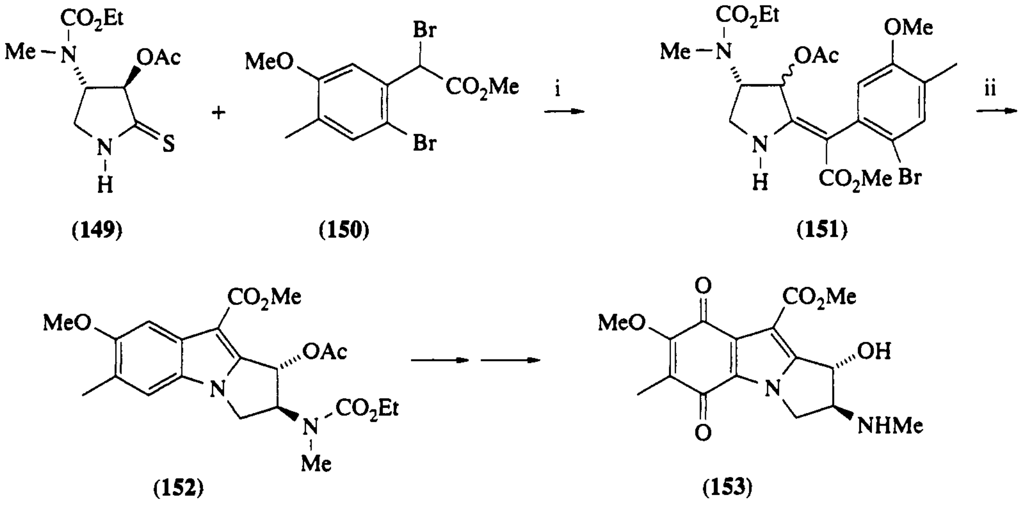

i, DBU; ii, NaH, CuBr

**Scheme 32**

example; stronger bases such as triethylamine, sodium carbonate, sodium hydride and sodium methoxide gave significantly lower yields of the vinylogous carbamate (**144**). The tetrasubstituted, cross-conjugated double bond was quite resistant to standard reducing conditions, although reduction was finally achieved using platinum in 20% TFA/acetic acid. The reduction effectively established the *cis* stereochemistry about the pyrrolidine nucleus but produced a mixture of the desired epimeric saturated ethyl isomers (**145**) along with the hydroxyethyl compounds (**146**). The mixture of fully reduced isomers (**145**) was cyclized to the carbapenams (**147**) and (**148**).

The mitomycins are a class of antitumor antibiotics that has been the target of numerous synthetic efforts. The Eschenmoser reaction was a key coupling step in the synthesis of a mitomycin intermediate, apomitomycin (**153**).[54] Thiopyrrolidinone (**149**) was alkylated with the aryl bromoacetate (**150**), and the intermediate α-thioiminium salt was heated with DBU (Scheme 32). The desired condensation product (**151**) was obtained in excellent yield, although epimerization about the pyrrolidine ring had occurred to produce a 1:1 mixture of the *cis* and *trans* substituted diastereomers. Note that, in contrast to α-alkyl-substituted electrophiles, which require conversion to triflates for complete thioamide alkylation, the more reactive benzylic bromide in (**150**) gave efficient alkylation. The key intermediate (**151**) was cyclized in the presence of sodium hydride and copper(I) bromide to yield a single product (**152**) in nearly quantitative yield. Epimerization to the more stable *trans* isomer occurred under the cyclization conditions. This intermediate was readily converted to the final product (**153**).

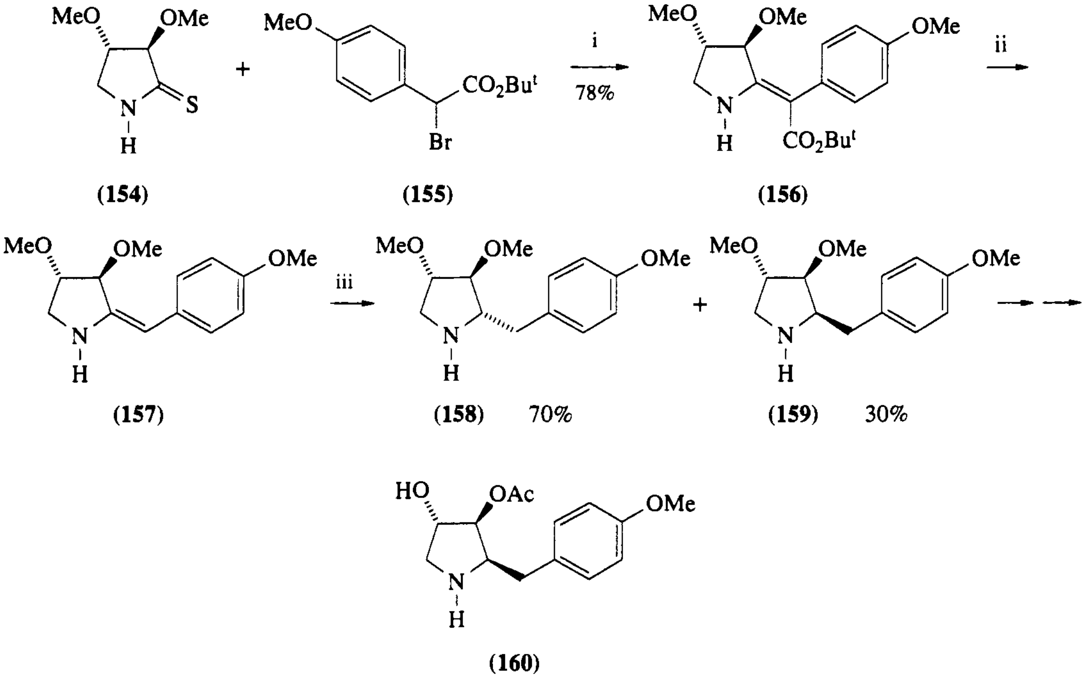

**(154)** **(155)** **(156)**

**(157)** **(158)** 70% **(159)** 30%

**(160)**

i, $(MeO)_3P$, $KOBu^t$; ii, TFA; iii, $H_2$, $PtO_2$

**Scheme 33**

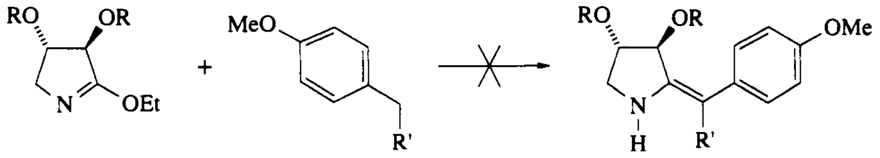

**(161)** **(162)** R' = ester, CN, $NO_2$ **(163)**

**Scheme 34**

The synthesis of the antibiotic anisomycin (**160**)[55] provides another example of the efficient alkylation of a thioamide with an α-bromoarylacetate. Thiolactam (**154**) was alkylated with α-bromo ester (**155**) followed by sulfide contraction to generate the vinylogous carbamate (**156**) in good yield (Scheme 33). In contrast, initial attempts to condense the imidate of the dimethoxylactam (**161**) with various aryl components (**162**) met with failure that was attributed to the steric hindrance created by the alkoxy groups (Scheme 34). The vinylogous carbamate (**156**) was converted to the acid, which decarboxylated to the enamine (**157**). Reduction yielded a 70:30 mixture of pyrrolidines (**158**) and (**159**) and the latter was converted to anisomycin.

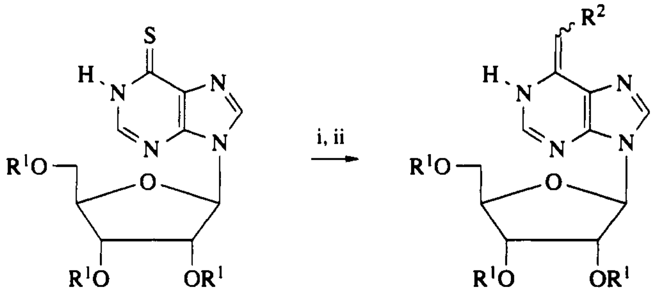

**(164)** **(165)**

(10)

**Table 6** Preparation of Substituted Purines (equation 10)[56]

| *R*$^1$ | *i* | *ii* | *R*$^2$ | *Yield* (%) |
|---|---|---|---|---|
| Ac | $BrCH_2COPh$ | $Bu^tOK, Ph_3P$ | COPh | 77 |
| Ac | $BrCH_2CO_2Bu^t$ | LDA, $Ph_3P$ | $CO_2Bu^t$ | 88 |
| Ac | $BrCH_2C_6H_4$-4-$NO_2$ | LDA, Ph3P | 4-$NO_2C_6H_4$ | 78 |

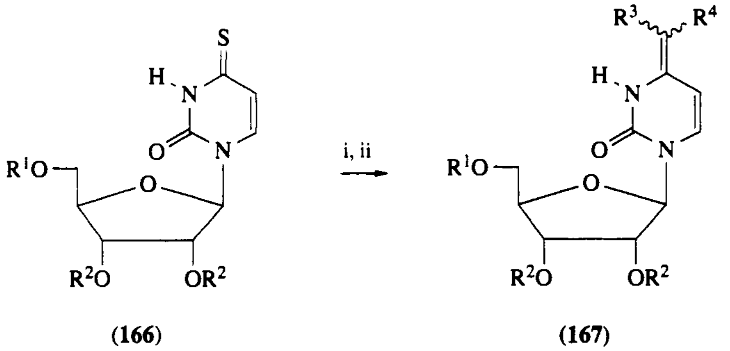

**(166)** **(167)**

(11)

**Table 7** Preparation of Substituted Thiopyrimidines (equation 11)[57]

| *R*$^1$ | *R*$^2$ | *i* | *ii* | *R*$^3$ | *R*$^4$ |
|---|---|---|---|---|---|
| H | H | $BrCH_2COPh$ | $Ph_3P$, $Bu^tOK$ or pyridine (reflux) | COPh | H |
| H | H | $BrCH_2COMe$ | $Ph_3P$, $Bu^tOK$ | COMe | H |
| H | Acetonide | $BrCH(CO_2Et)_2$ | $NaHCO_3$, $CO_2$ | $CO_2Et$ | $CO_2H$ |
| Ac | Acetonide | $BrCH_2CO_2Et$ | NaH, $Ph_3P$ | $CO_2Et$ | H |

### 3.7.4.6 Nucleoside Analogs

The sulfide-contraction process is ideally suited to introduce carbon substituents at various positions of purines and pyrimidines in nucleosides.[56,57,58] Typically, a thio-purine or -pyrimidine was *S*-alkylated with electrophiles such as phenacyl bromide, ethyl bromoacetate or diethyl bromomalonate and then treated with base and a thiophile (not always required) to produce the corresponding carbon-extended nucleoside (equations 10 and 11). Several representative examples of this application are listed in Tables 6 and 7.

### 3.7.4.7 Macrocycles

The Eschenmoser coupling reaction has demonstrated its utility repeatedly in the preparation of various nitrogen-containing compounds of interest. However, its application in synthesizing wholly carbon-based targets has been accomplished as well. A masked β-keto ester resides within the vinylogous carbamate, the product of the sulfide-coupling reaction, which can be unveiled upon mild hydrolysis. This aspect of vinylogous carbamates was applied toward the synthesis of a macrocyclic lactone, diplodialide A, by performing the key macrocyclic ring closure *via* an intramolecular Eschenmoser coupling reaction.[20] A separate study also exploited this feature of vinylogous carbamates and culminated in the development of a general method for preparing substituted β-keto esters and nitriles.[21]

The preparation of substituted five- and six-membered lactones served as a model system to examine the feasibility of this novel ring-forming strategy. A hydroxythioamide (**168**) was allowed to react with chloroacetyl chloride, and the resulting α-chloro ester (**169**) was treated with sodium iodide and the Eschenmoser dual base–thiophile reagent (**28**) to afford the cyclic enamino lactone (**170**) in high yield (Scheme 35). No epimerization of the lactone was observed. Likewise, the five-membered enamino lactone (**172**) resulted from reaction of the hydroxythioamide (**171**) with chloroacetyl chloride followed by sulfide contraction.

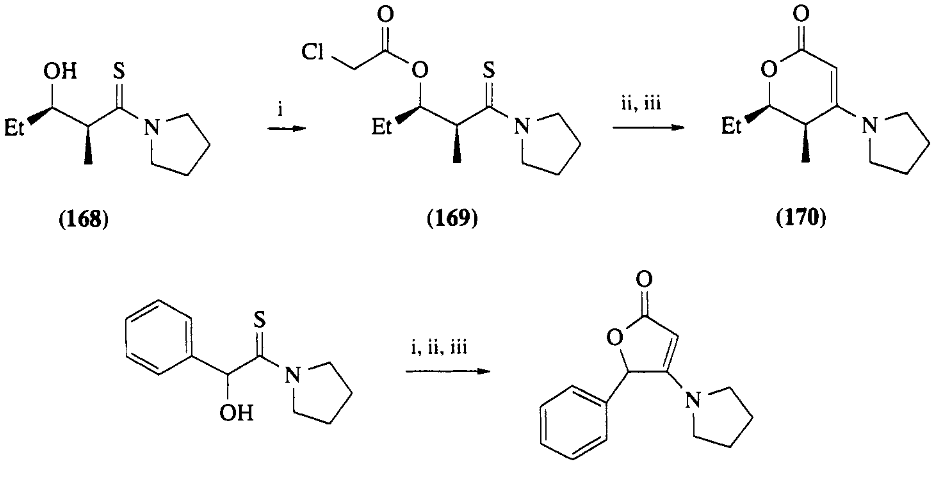

**(168)** **(169)** **(170)**

**(171)** **(172)**

i, $ClCH_2COCl$; ii, NaI; iii, $PhP[(CH_2)_3NMe_2]_2$

**Scheme 35**

Unfortunately, the synthesis of larger ring systems could not be achieved under the above conditions. A modification was therefore developed, previously described in Section 3.7.2.1, that exposed the cyclic α-thioiminium salt as it was being formed to the sulfur-extruding reagents. The preformed α-chloro ester was added to a refluxing solution of sodium iodide, diisopropylethylamine and triethyl phosphite in acetonitrile. Aqueous work-up unveiled the β-keto ester to produce the 10- and 12-membered macrolides in moderate yields (Scheme 36). These conditions were compatible with incorporation of alkynic, alkenic and other functional groups within the macrocycle. A limitation of this method is the inability to construct seven-membered ring systems.

The foregoing conditions were applied successfully in the synthesis of diplodialide A (**175**; Scheme 37). Since earlier studies had demonstrated that the sulfide-contraction conditions were not compatible with α,β-unsaturated thioamides, the β-acetoxy precursor (**173**) was used instead. The intramolecular sulfide-contraction reaction successfully accomplished the cyclization to generate the β-keto lactone (**174**) in modest yields. Elimination of the acetoxy group yielded diplodialide A (**175**).

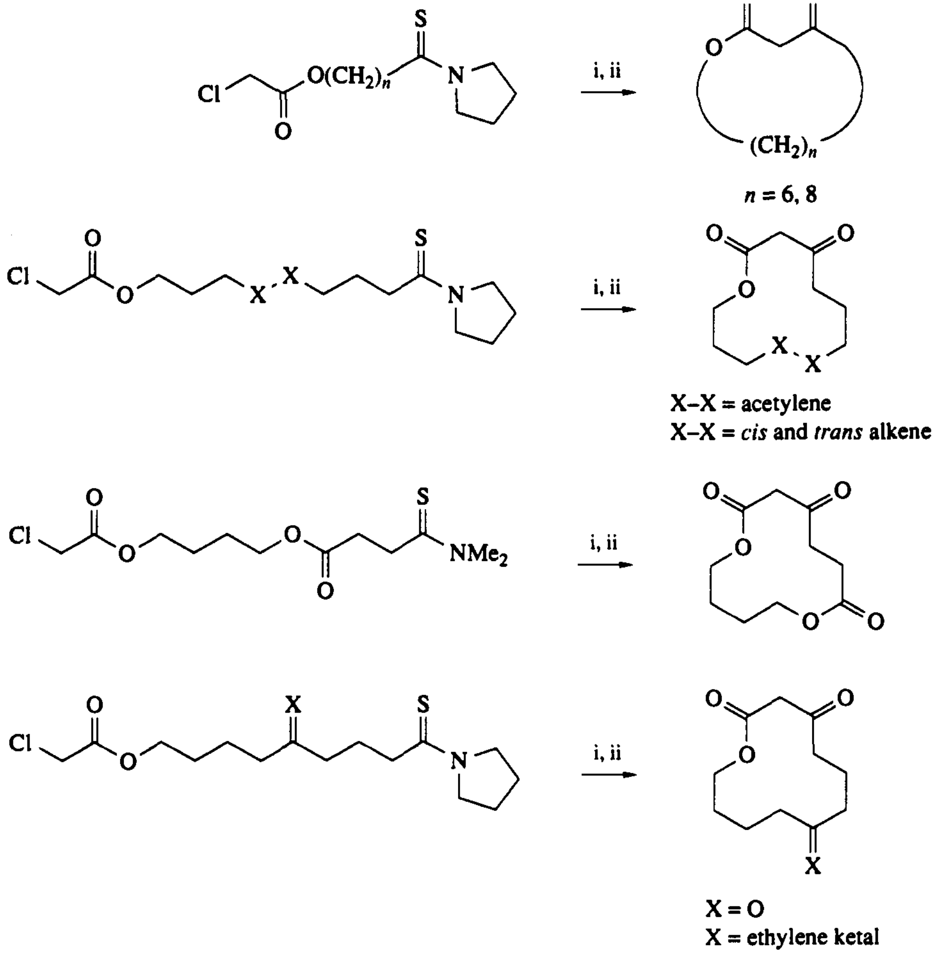
i, ii
(CH2)n
i, ii
i, ii
i, ii

$n = 6, 8$

X–X = acetylene
X–X = *cis* and *trans* alkene

X = O
X = ethylene ketal

i, NaI, $P(OEt)_3$, $Pr^i{}_2NEt$, MeCN (reflux); ii, $H^+$, $H_2O$

Scheme 36

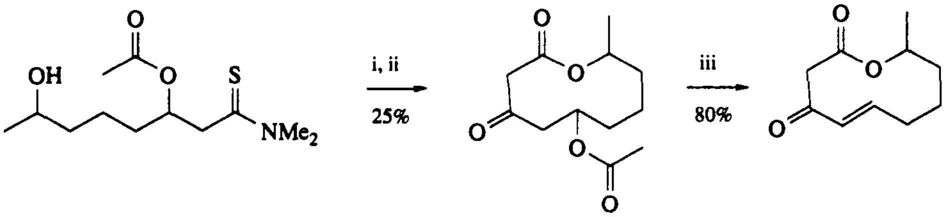
i, ii
25%
iii
80%

(173) (174) (175)

i, $ClCH_2COCl$, pyridine; ii, NaI, $P(OEt)_3$, $Pr^i{}_2NEt$, MeCN (reflux); iii, $Pr^i{}_2NEt$, MeCN (reflux)

Scheme 37

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# 4.1
# The Bimolecular Aliphatic Mannich and Related Reactions

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## 4.1.1 BACKGROUND — THE CLASSICAL MANNICH REACTION

### 4.1.1.1 Introduction

The Mannich reaction is the prototype of carbon–carbon bond forming reactions that involve the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines. In its original and most widely recognized form, the Mannich reaction consists of three components: (i) ammonia, a primary amine, or a secondary amine; (ii) a nonenolizable aldehyde, usually formaldehyde; and (iii) an active methylene compound. These components condense with concomitant release of water to produce a new base, known as a 'Mannich base', in which the active hydrogen is replaced by an aminomethyl group (equation 1). A typical example is the reaction of acetophenone (**1**), paraformaldehyde (**2**) and piperidine (**3**) to produce phenyl β-piperidinoethyl ketone (**4**; equation 2). The formation of both a carbon–carbon and a carbon–nitrogen bond in this aminomethylation process makes the Mannich reaction an extremely useful synthetic transformation. In addition, Mannich bases have important synthetic applications as intermediates for other compounds. They also occur in natural products such as the alkaloids lycopodine (**5**), cocaine (**6**) and elaeocarpine (**7**).

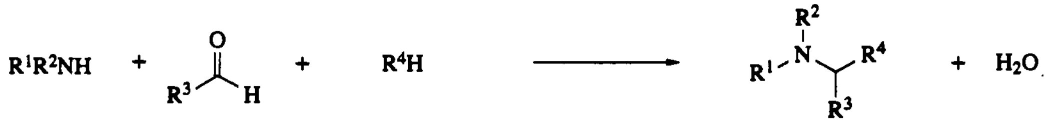

(1)

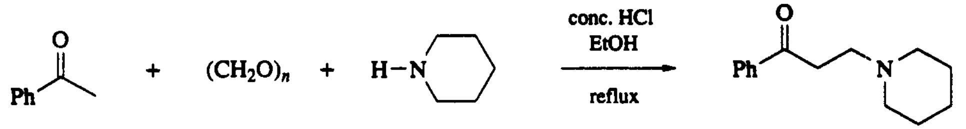

(1) (2) (3) (4)

(2)

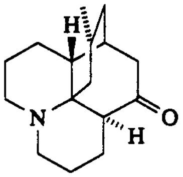

(**5**)

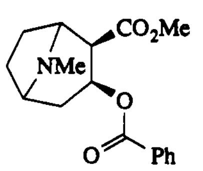

(**6**)

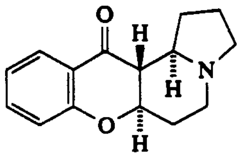

(**7**)

### 4.1.1.2 Earlier Reviews and Scope of this Chapter

The Mannich reaction has been reviewed comprehensively by Blicke (1942),[1] Reichert (1959),[2] Hellmann and Opitz (1960),[3] and Tramontini (1973).[4] These reviews also include synthetic applications of Mannich bases. Mechanistic studies of the Mannich reaction have been reviewed by Thompson (1968).[5] Some variants of the Mannich reaction have been covered as subtopics in other reviews; for example, Layer (1963)[6] and Harada (1970)[7] have reviewed general additions of stabilized carbanions to imines, while Böhme and Haake (1976)[8] have reviewed similar additions to methyleneiminium salts. In more specific reviews, Pai and coworkers (1984)[9] have summarized stabilized carbanion additions to 3,4-dihydroisoquinolines and 3,4-dihydroisoquinolinium salts in connection with the total synthesis of protoberberines and phthalide isoquinolines, and Evans *et al.* (1982)[10] have analyzed the stereochemical aspects of ester enolate and silyl ketene acetal additions to imines.

Since 1973, when the last comprehensive review of the Mannich reaction appeared,[4] there has been an explosive growth in the variant of this reaction that employs preformed iminium salts and imines for the synthesis of Mannich bases. The use of preformed iminium salts and imines, some examples of which date back to the turn of the century, has had a renaissance in recent years primarily because of the advent of modern enolate chemistry, *e.g.* formation of enolates under kinetic control and the use of enol silanes with Lewis acid catalysis. As a result, there have been two major advances in the synthesis of Mannich bases: (i) the development of extremely mild conditions, enabling the use of highly functionalized substrates; and (ii) increasing control of regiochemistry and stereochemistry, two aspects of the Mannich reaction that had been virtually ignored prior to the 1970s. Because of the recent impact which preformed iminium salts and imines have had on the Mannich reaction, this review focuses almost entirely on their applications, which comprise the next two sections. Each of the subsections is arranged according to the type of N-substitution because of the important role N-substituents play in the reactivity of the iminium salt or imine and in the elaboration of the Mannich base. Cyclic preformed iminium salts and imines and *in situ* methods for the formation of imines are also included as subsections. Additional divisions of subsections are used where the literature is more extensive, especially in Sections 4.1.2.2 and 4.1.3.2, and are arranged according to the nature of the active methylene compound. Every attempt has been made to cite review articles covering prior work with the intent of providing the reader with both a direct and an indirect avenue to all of the literature pertaining to the bimolecular Mannich reaction. Due to the number of excellent review articles of the classical tricomponent Mannich reaction and to the lack of significant new methodology (see, however, Section 4.1.1.5), only a brief overview is given. This overview includes a discussion of the scope and limitations of the classical Mannich reaction as a prelude to the more recent methodology. The reader should note that Mannich reactions involving aromatic hydrogen donors are covered in Chapter 4.2.

### 4.1.1.3 Mechanism

A detailed account of the mechanism of the Mannich reaction and factors that affect the selection of conditions has been written by Thompson.[5] Only the salient features of the mechanism are given here. For the conditions under which the Mannich reaction is most commonly performed, *i.e.* protic solvents and acid catalysis (usually by employing the amine component as its hydrochloride salt), the mechanism is thought to involve the intermediacy of a highly reactive, positively charged iminium ion (**10**), which reacts with the active methylene component in its enol form (**11**) to produce the Mannich base (**12**; Scheme 1). This step has an obvious parallel to the aldol condensation. Formation of (**10**) occurs by decomposition of a methylenediamine (**9**) or, to a lesser extent, a hydroxymethylamine (**8**), both of which are generated reversibly by condensation of the aldehyde and amine components. Acid catalysis not only promotes the decomposition of (**8**) and (**9**) to the iminium salt (**10**), but also the enolization of the active methylene component. Protic solvents, by virtue of their high dielectric constant, also support the formation of the charged iminium species. Elevated temperatures are often necessary for generation of sufficient concentrations of iminium ions.

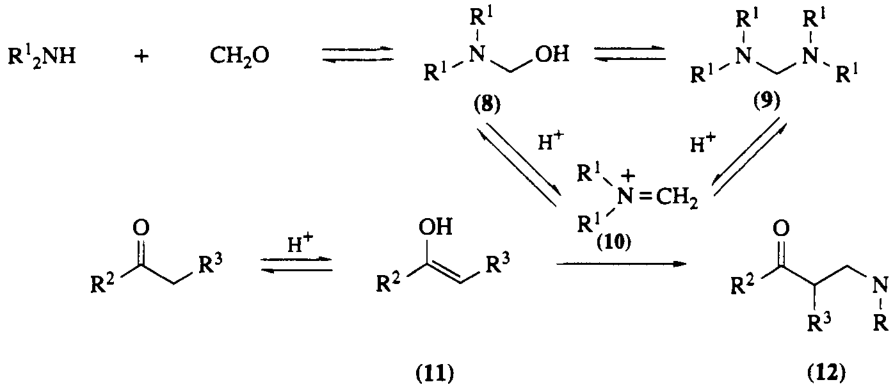

**Scheme 1**

In Mannich reactions performed in basic media, the active aminomethylating species is less well defined. It may be a methylenediamine (**9**), a hydroxymethylamine (**8**), or an alkoxymethylamine ($ROCH_2NR_2'$) (in alcoholic solvents). Aminomethylation in base-catalyzed Mannich reactions, as shown for cyclohexanone, is believed to occur by an $S_N2$ mechanism in which the enolate (**13**) displaces either $NR_2^-$, $OH^-$, or $OR^-$ from one of the intermediates above (Scheme 2).

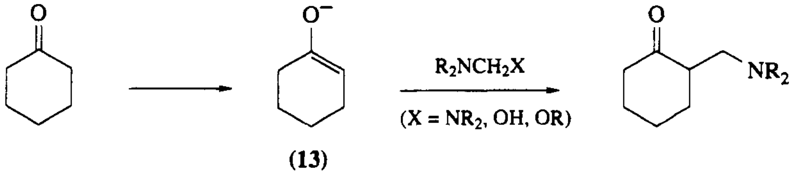

**Scheme 2**

Depending upon the nature of the substrates involved, the Mannich reaction may be reversible. In cases where isomeric products are possible, product ratios may therefore reflect thermodynamic factors.

### 4.1.1.4 Scope and Limitations

Active methylene compounds ranging in acidity from β-keto esters, malonates and nitroalkanes (p$K_a$ = 9–13) to ketones (p$K_a$ = 16–20) can be used in the Mannich reaction. The lack of examples using simple unactivated esters (p$K_a$ = 25) appears to be due to their weaker acidity or to transamination and/or hydrolysis side reactions. Enolizable aldehydes have also been used in certain instances; however, side products arising from subsequent aldol condensation of the resulting β-amino aldehyde often occur. Best results are achieved with α-branched aldehydes, which produce Mannich bases without enolizable protons.

Of the amine components that may be used, secondary amines react the most predictably and in the highest yields, giving tertiary Mannich bases. Here steric factors are important since reactions employing dimethylamine and cyclic amines tend to be more successful than those employing bulkier secondary amines. With primary amines, yields are more unpredictable because the initially formed secondary Mannich base (**14**) can further react to give a tertiary amine (**15**; equation 3). Bulky primary amines[11] and, interestingly, use of amine oxalate salts[12] instead of hydrochloride salts tend to suppress these cross-condensation reactions. The use of ammonia for the synthesis of primary Mannich bases is more complicated because of the greater likelihood of obtaining products derived from multiple substitution. The synthesis of primary Mannich bases can be achieved indirectly, however, by condensing a bulky primary amine containing a cleavable alkyl group. As shown in Scheme 3, benzhydrylamine (**16**) condenses cleanly with acetophenone (**1**) to give a secondary Mannich base (**17**), which upon deprotection affords primary Mannich base (**18**; Scheme 3).[11]

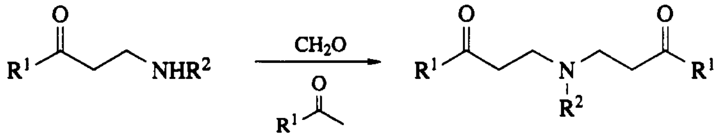

(3)

**(14)** **(15)**

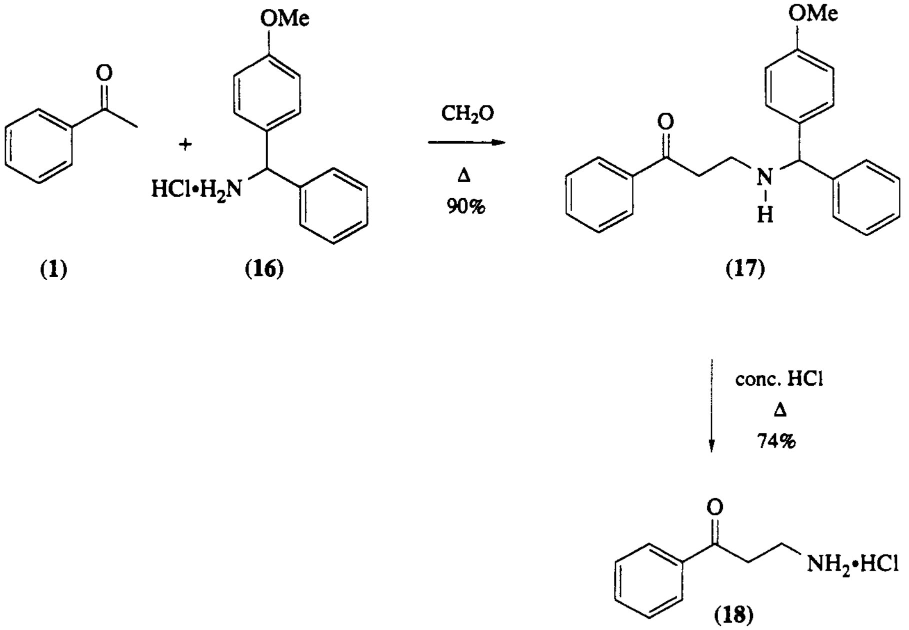

**(1)** **(16)** **(17)** **(18)**

Scheme 3

In cases involving unsymmetrical ketones, mixtures of regioisomeric Mannich bases are usually obtained. As shown in Table 1, aminomethylation occurs predominantly at the site containing the fewest α-hydrogens, reflecting the thermodynamic stability of the corresponding enols.[13]

**Table 1** Mannich Reactions of Unsymmetrical Ketones

| *Ketone* | *Products* | | *Ratio* | *Ref.* |
|---|---|---|---|---|
| 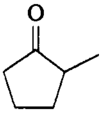 | 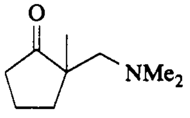 | 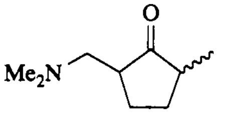 | >4:1 | 13 |
| 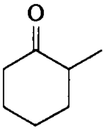 | 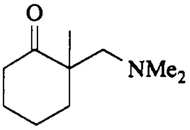 | 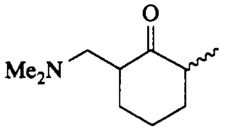 | 7:3 | 13 |
| 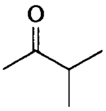 | 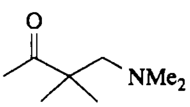 | 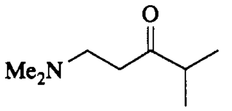 | 3.5:1 | 14 |

In addition to the side reactions mentioned above, deamination of Mannich bases can occur, especially at elevated temperature, to give α,β-unsaturated derivatives. This route of decomposition of Mannich bases has been exploited as a means of *in situ* generation of α,β-unsaturated ketones in the Michael reaction[15] and for the direct synthesis of α,β-unsaturated ketones; several reviews of the Mannich reaction have discussed aspects of these applications.[1–4] Recently, a direct 'one-pot' synthesis of α-methylene ketones has been reported involving condensation of ketones with formaldehyde and *N*-methylaniline trifluoroacetate in aprotic solvents.[16] Also, a less direct method has been described in which Mannich bases prepared from β-keto esters, formaldehyde and dimethylamine are subjected to quaternarization and thermal fragmentation to yield α-methylene ketones.[17] This method is particularly useful for the regiospecific synthesis of α-methylene ketones because the aminomethylation reaction always takes place at the most activated position flanked by the ketone and ester groups.

Bisaminomethylation, occurring when the active methylene compound contains more than one acidic hydrogen, is another possible side reaction. Reported cases of bisaminomethylation are rather infrequent, however, suggesting that the protonated β-ammonium group slows down the rate of enolization of the Mannich base relative to the unreacted active methylene compound. Thermodynamic factors reflected in the steric congestion of the bisaminomethylated product may also be important.

### 4.1.1.5 New Modifications

An interesting $TiCl_4$-mediated modification of the classical tricomponent Mannich reaction using aprotic solvents and low temperatures has recently been reported by Seebach *et al.*[18,19] The reaction is carried out as illustrated in Scheme 4 for the condensation of cyclohexanone, piperidine and benzaldehyde. Piperidine is first deprotonated with *n*-butyllithium and then condensed with benzaldehyde to give a lithium alkoxide (**19**), which is converted to a titanium alkoxide (**20**) by treatment with $TiCl_4$. Condensation of (**20**) at –70 °C with the preformed enolate of cyclohexanone then yields diastereomeric Mannich bases (**21**) and (**22**) (4:1 mixture). The preference for *lk*-addition,[20] favoring diastereomer (**21**), appears to be common to these reactions. The reaction is general for other enolates, including those of acetone, acetophenone and *t*-butyl acetate. Besides benzaldehyde, enolizable aldehydes such as *n*-pentanal can also be used as aldehyde components. Yields are generally good (60–80%) except in cases involving bulky, acyclic amines. Although this reaction is more tedious to perform than the classical Mannich reaction, it has the advantage of requiring milder conditions and permitting the use of enolizable aldehydes and less acidic active methylene compounds such as esters. The mechanism of the reaction needs further clarification, as it is not known whether titanium alkoxides or iminium salts are the reactive aminomethylating species.

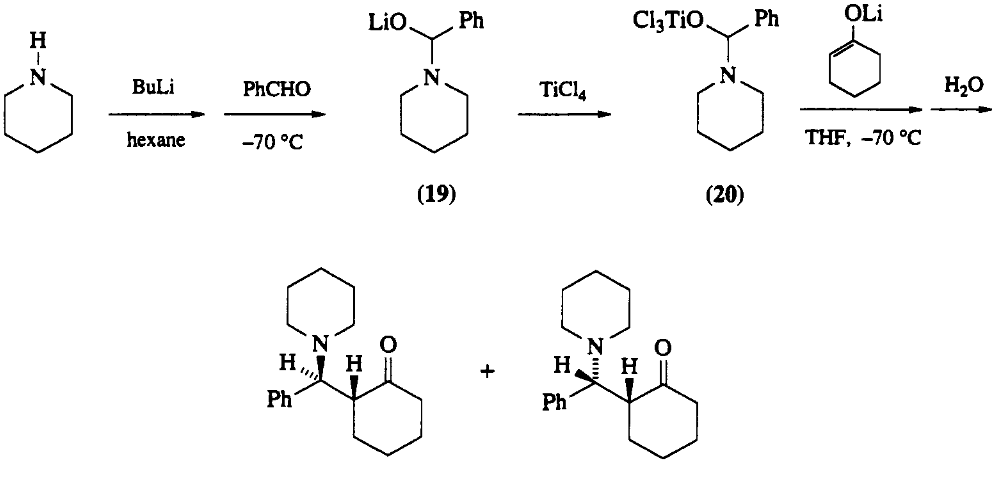

78%; (21):(22) = 4:1

Scheme 4

## 4.1.2 USE OF PREFORMED IMINIUM SALTS

### 4.1.2.1 Introduction

A vast improvement in the scope and efficiency of the Mannich reaction has been achieved using preformed iminium salts. In this variant of the classical Mannich reaction the iminium salt, rather than being generated under equilibrium conditions, is preformed separately and is condensed with the active methylene component in a second step. Higher concentrations of iminium salts than those generated under the reversible conditions of the classical Mannich reaction are achieved; consequently, reactions with preformed iminium salts are faster and can be run under far milder conditions. Another advantage is that reactions employing preformed iminium salts can be carried out in aprotic solvents, permitting regiospecifically generated enolates and enol silanes to be used as active methylene components. From a practical standpoint, preformed iminium salts can be conveniently stored and weighed in stoichiometric amounts, although some tend to be hygroscopic and must be stored in a dry atmosphere to preserve their reactivity.

### 4.1.2.2 Acyclic *N*,*N*-Dialkyliminium Salts

### *4.1.2.2.1 General*

Pioneering investigations by Böhme *et al.* into the synthesis, properties and reactions of preformed iminium salts have provided much of the basis for their recent applications in organic synthesis. These and related investigations are described in his extensive review on 'Methyleneiminium Salts',[8] covering work up to the early 1970s.

Of the numerous methods reported by Böhme *et al.* for the synthesis of preformed iminium salts, the most general and convenient involves cleavage of methylenediamines (**23**) by acyl halides (**24**) or alkyl chlorocarbonates (**25**), providing preformed iminium salts (**26**) in quantitative yield and in near analytical purity (equation 4).[21] The by-product of these reactions, a dialkylamide (**27**) or a dialkylurethane (**28**), is easily removed since it remains in solution during precipitation of the iminium salt. The ionic nature of iminium salts produced by this method is well established, although an equilibrium between the ionic and covalent forms cannot be ruled out (Figure 1). The term 'α-haloamine', which is sometimes used synonymously with iminium salts, can be misleading.

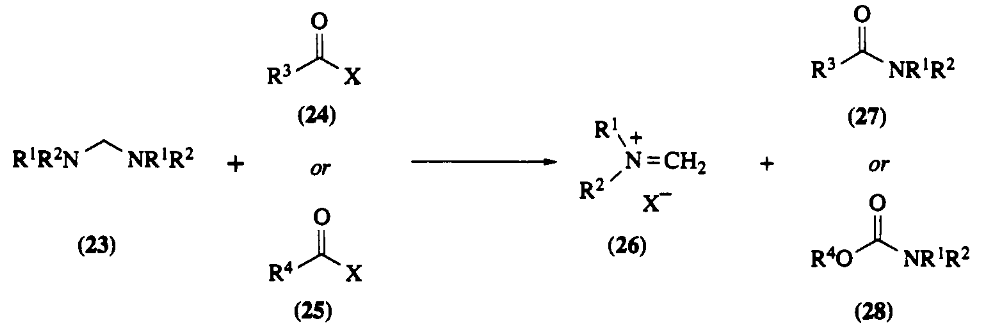

(4)

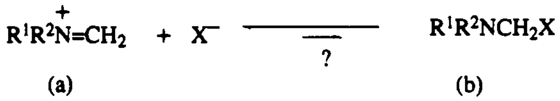

$$R^1R^2\overset{+}{N}{=}CH_2 + X^- \underset{?}{\rightleftharpoons} R^1R^2NCH_2X$$

(a) (b)

**Figure 1** (a) Ionic and (b) covalent forms of iminium salts

Once isolated, the iminium salt can undergo addition reactions with a variety of carbon nucleophiles. Most of the early examples of these reactions were confined to the use of highly acidic active methylene compounds (p$K_a$ = 9–13), and some representative examples are shown in Table 2. It should be noted that less acidic ketone and ester substrates have been used more extensively in reactions with *N*,*N*-dimethyl(methylene)iminium salts; these reactions will be discussed separately in the next section. With malonates, cyano esters, β-diketones, triesters, nitroalkanes and β-disulfones (entries 1–7), the reaction is normally performed using the sodium enolate in MeCN or DMF and at elevated temperature. With the more reactive dithiane anion (entry 8), the reaction occurs at much lower temperature (–30 °C). Some examples have also been reported using iminium salts bearing α-carboxamide and α-carboethoxy groups. These more electrophilic iminium salts react with aryl ketones directly in refluxing $CH_2Cl_2$ without catalysis (entry 9); less acidic alkyl ketones (entry 10) and aldehydes, on the other hand, must be activated as enamine derivatives. It should be noted that the preformed iminium salts used in these examples are limited to those that do not bear α-hydrogens. 'Enolizable' iminium salts (**29**) (*i.e.* those with α-hydrogens) fail in these reactions due to deprotonation to give the enamine (Figure 2).[25]

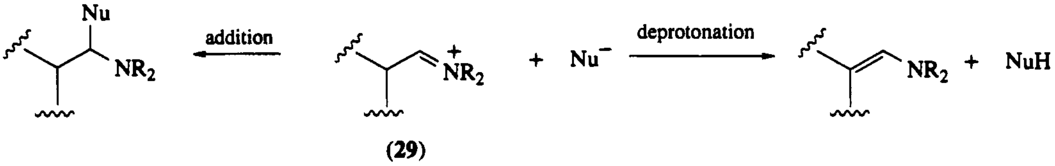

(**29**)

**Figure 2** Competitive deprotonation in the reactions of enolizable iminium salts

#### *4.1.2.2.2* N,N-*Dimethyl(methylene)iminium salts*

##### *(i) Preparation and* in situ *methods*

*N*,*N*-Dimethyl(methylene)iminium salts have been the most widely used class of preformed iminium salts, mainly due to their applications in the synthesis of α,β-unsaturated carbonyl compounds, normally accomplished by subjecting the *N*,*N*-dimethyl Mannich base to quaternarization followed by base-induced elimination. Table 3 outlines various counterion forms of *N*,*N*-dimethyl(methylene)iminium salts that have been used in Mannich reactions as well as their synthetic precursors. The crystalline iodide (**30**), known also as 'Eschenmoser's salt', has seen the most widespread use and is prepared by thermal fragmentation of (iodomethyl)trimethylammonium iodide[27] or, more conveniently, by a variant of the

Böhme procedure involving cleavage of *N,N,N′,N′*-tetramethyl(methylene)diamine (**34**) with TMS-I.[28] Cleavage of (**34**) with acetyl chloride in analogy to the Böhme procedure furnishes the crystalline chloride (**31**),[29] as does cleavage of methyl dimethylaminomethyl ether with methyltrichlorosilane.[30] The trifluoroacetate (**32**), unlike the iodide or chloride, is a liquid and is prepared by Polonovski reaction of

**Table 2** Addition Reactions of Carbon Nucleophiles to Preformed Iminium Salts

| *Entry* | *Nucleophile* | *Iminium salt* | *Product* | *Yield* | *Ref.* |
|---|---|---|---|---|---|
| 1 | $NaC(Me)(CO_2Et)_2$ | $H_2C{=}N^+Et_2\ Cl^-$ | $(EtO_2C)_2C(Me)CH_2NEt_2$ | 70 | 22 |
| 2 | $NaCH(CO_2Et)_2$ | 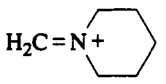 $Cl^-$ | 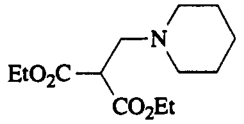 EtO2C N CO2Et | a | 22 |
| 3 | $NaC(Me)(CN)CO_2Et$ | $H_2C{=}N^+Et_2\ Cl^-$ | $EtO_2CC(CN)(Me)CH_2NEt_2$ | a | 22 |
| 4 | 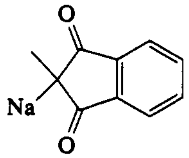 | 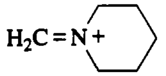 $Cl^-$ | 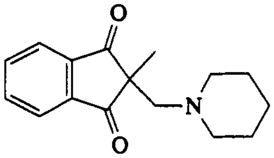 | a | 22 |
| 5 | $NaC(CO_2Et)_3$ | 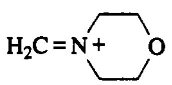 $Cl^-$ | 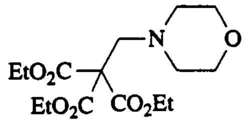 EtO2C N O EtO2C CO2Et | 40 | 23 |
| 6 | $NaCH_2NO_2$ | $H_2C{=}N^+Et_2\ Cl^-$ | $NO_2CH_2CH_2NEt_2$ | 49 | 22 |
| 7 | $NaC(Me)(SO_2Me)_2$ | 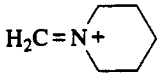 $Cl^-$ | 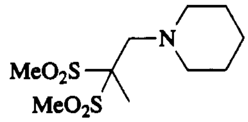 MeO2S N MeO2S | 57 | 24 |
| 8 | 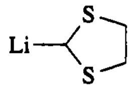 | 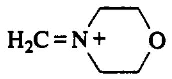 $Cl^-$ | 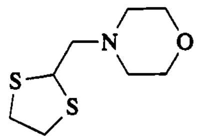 | 54 | 25 |
| 9 | 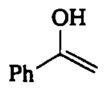 | 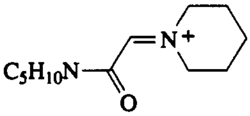 $Cl^-$ | 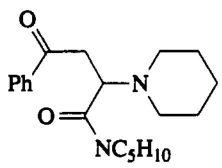 O Ph N O NC5H10 | 93 | 26 |
| 10 | 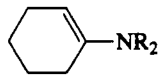 | 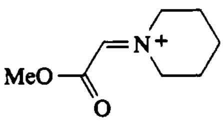 $Cl^-$ | 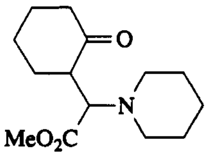 | 65 | 26 |

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[a] No yield given.

trimethylamine oxide with TFAA.[31,32] The triflate (**33**), prepared by treating chloride (**31**) with TMS-OTf, has been recently introduced for use in reactions with 2-silyloxycyclopropanecarboxylates.[33,34]

**Table 3** Preformed Dimethyl(methylene)iminium Salts and Their Preparation

| *Iminium salt* | *Precursor* | *Conditions* | *Ref.* |
|---|---|---|---|
| $[Me_2N{=}CH_2]^+I^-$ (**30**) | $[Me_3NCH_2I]^+I^-$ | Thermolysis (150 °C) | 27 |
| | $Me_2NCH_2NMe_2$ (**34**) | TMS-I, ether, 0 °C | 28 |
| $[Me_2N{=}CH_2]^+Cl^-$ (**31**) | (**34**) | MeCOCl, $CH_2Cl_2$, 0 °C | 29 |
| | $MeOCH_2NMe_2$ | $MeSiCl_3$, MeCN, 25 °C | 30 |
| $[Me_2N{=}CH_2]^+[TFA]^-$ (**32**) | $Me_3NO$ | TFAA, $CH_2Cl_2$, 0 °C | 31, 32 |
| $[Me_2N{=}CH_2]^+[OTf]^-$ (**33**) | (**31**) | TMS-OTf, $CH_2Cl_2$, 0 °C | 33, 34 |

In a comparison study involving Mannich reactions of enol silanes, Holy *et al.* report that iminium salts (**30**)–(**32**) react at similar rates in DMF, where they are soluble, but in less polar solvents reduced solubility slows the rate and adversely affects the yield.[35] For this reason the more soluble trifluoroacetate (**32**) should be used in place of the iodide (**30**) or chloride (**31**) when conducting reactions in less polar solvents such as $CH_2Cl_2$. Iminium salts (**30**)–(**32**) must be stored in the absence of moisture, while the iodide (**30**) should be kept from light. The trifluoroacetate (**32**) is a liquid and must be distilled to remove traces of TFA, which will adversely affect reactions with enol silanes and enolates.

Two *in situ* methods for the generation of *N*,*N*-dimethyl(methylene)iminium salts, which are limited to reactions with enol silanes, are also available and avoid the need to handle these moisture-sensitive reagents. In the first method, iodide (**30**) is prepared *in situ* by treating *N*,*N*,*N*′,*N*′-tetramethyl(methylene)diamine (**34**) with chloroiodomethane (equation 5);[36,37] DMSO must be used as solvent to achieve maximum yields. Cleavage of *n*-butyl dimethylaminomethyl ether (**35**) with TMS-I or TMS-OTf in MeCN comprises the second method (Scheme 5).[38] A silyloxonium ion (**36**) was originally proposed as the reactive aminomethylating species, but a recent $^{13}C$ NMR study of the reactions of aminol ethers with halosilanes in $CD_3CN–SO_2$ did detect the presence of iminium salts.[39] Use of these methods in reactions with enol silanes is discussed in Section 4.1.2.2.2.iii.

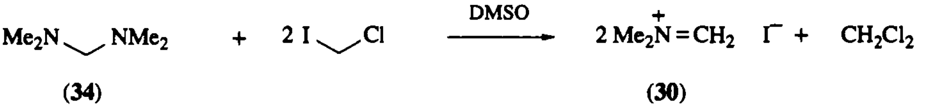

(5)

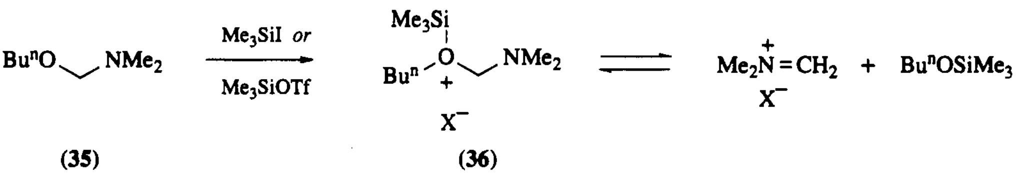

**Scheme 5**

### (ii) Reactions with carbonyl compounds directly

Certain carbonyl compounds will react directly with *N*,*N*-dimethyl(methylene)iminium salts without added catalysts or special activation. It is not known to what extent the highly electrophilic iminium salt may itself act as a catalyst to promote enolization. The mechanism of enolization is an aspect of these reactions that needs further study. Temperatures required to effect aminomethylation range from 0 °C to reflux and depend on the acidity of the carbonyl compound. Early work by Potier[31,32] using steroidal ketone substrates stimulated much of the early interest in these reactions as an alternative to the classical Mannich reaction. An example is shown in equation (6), in which 5α-cholestan-3-one (**37**) reacts with iminium salt (**32**) to give the 3α-*N*,*N*-dimethylaminomethyl derivative (**38**) in high yield. Similar reactions of 3α-5-cyclo-5α-androstan-6-one and 3β,20α-diacetoxy-5α-pregnan-6-one also occur in high yield to give a single equatorially substituted product. The latter case is noteworthy since it is unlikely that the diacetoxy protecting groups would survive under the conditions of the classical Mannich reaction. *N*,*N*-Dimethylaminomethylation of 8α-estrone using iminium salt (**31**) has also been reported by Neef and coworkers.[40]

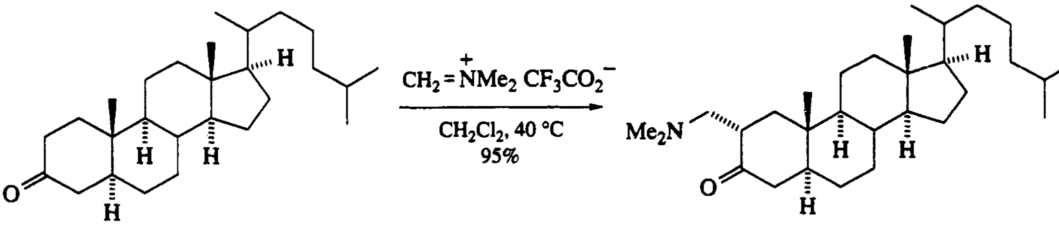

(6)

(**37**) (**38**)

A study by Kinast and Tietze[29] has compared the yields of β-amino ketones obtained using iminium salt (**31**) in refluxing MeCN with those reported using the classical method. The ketone and aldehyde substrates used in this study and yields of the corresponding Mannich bases are shown in Table 4. The superiority of the new method is clearly demonstrated in the case of sterically crowded ketones such as α-methylpropiophenone and the enone 4-phenyl-3-buten-2-one where yields of the corresponding Mannich bases synthesized under the classical conditions are only 6%[41] and 25%,[42] respectively. Higher yields are also observed with two seven-membered ring ketone substrates, cycloheptanone and 1-benzosuberone (yields using the classical method are 37%[43] and 40%,[44] respectively). In one example involving an unsymmetrical ketone substrate, 2-methylcyclopentanone, *N*,*N*-dimethylaminomethylation occurs almost exclusively at the more-substituted position as in the classical Mannich reaction.[13] Other types of ketone substrates reported to react with preformed iminium salts in a superior manner to the classical method include chromanones and thiochromanones[45] and 1*H*-pyrido[3,2,1-*kl*]phenothiazines.[46]

**Table 4** Yields of Mannich Reactions of Ketones and Aldehydes Using *N*,*N*-Dimethyl(methylene)iminium Chloride[29]

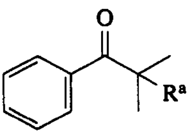

53%; 6%$^b$

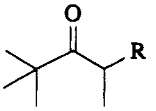

58%

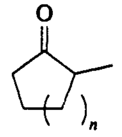

*n* = 1 (82%; 60%$^b$)
*n* = 2 (72%; 37%$^b$)

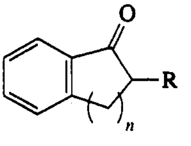

*n* = 1 (96%; 86%$^b$)
*n* = 2 (97%; 65%$^b$)
*n* = 3 (97%; 40%$^b$)

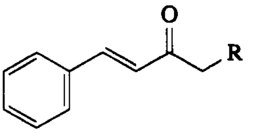

84%; 25%$^b$

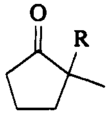

87%

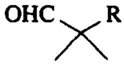

82%

---

[a] R designates the site of aminomethylation. [b] Yield using the classical reaction.

In a regiochemical investigation of the reaction of iminium salt (**32**) with a series of unsymmetrical methyl ketones, Jasor *et al.* have observed that the site of aminomethylation is solvent dependent (equation 7, Table 5).[47] It is found that in MeCN, reaction occurs exclusively at the least-substituted position, while in TFA it occurs mainly at the most-substituted position. Yields are good (70–90%) in TFA but are somewhat reduced in MeCN due to dialkylation, which can be overcome if the more bulky *N*,*N*-diisopropyliminium salt is used. How the solvent influences the two possible rate-determining steps, enolization *versus* aminomethylation, and the extent of reversibility of the reaction need further investigation in order to determine the basis for the observed dichotomy in regiochemistry.

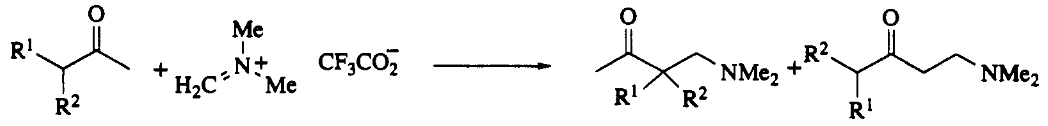

R1
O
R2
+
Me
N+
H2C
Me
CF3CO2−
O
NMe2
R1
R2
+
R2
O
NMe2
R1

(39) (32) (40) (41) (7)

Table 5 Regioselective Mannich Reactions of Methyl Ketones (39) Using *N,N*-Dimethyl(methylene)iminium Trifluoroacetate (32) in Trifluoroacetic Acid *versus* Acetonitrile[47]

| (39) *Methyl ketone* *R*$^1$ | *R*$^2$ | *Solvent* | *Mannich base* (40) | (41) *Ratio* |
|---|---|---|---|---|
| —(CH$_2$)$_4$— | | TFA | 95 | 5 |
| | | MeCN | 0 | 100 |
| —(CH$_2$)$_5$— | | TFA | 69 | 31 |
| | | MeCN | 0 | 100 |
| Me | Me | TFA | 85 | 15 |
| | | MeCN | 0 | 100 |

As reported by Thomas and Fritzen, α-diazo ketones react with preformed iminium salts with loss of $N_2$ to afford vinylogous amides.[48] An example is shown in Scheme 6 involving an α-diazo ketone derivative (**42**) of spectinomycin, which upon treatment with salt (**31**) affords enamide (**44**) *via* the diazonium adduct (**43**). Triethylamine must be present in the reaction to prevent hydrolysis of the enamide. If the iodide salt (**30**) is used instead of the chloride salt (**31**), multiple products are obtained due to the higher reactivity of the counterion. This example elegantly portrays the degree of complex functionality which can be tolerated in Mannich reactions using preformed iminium salts.

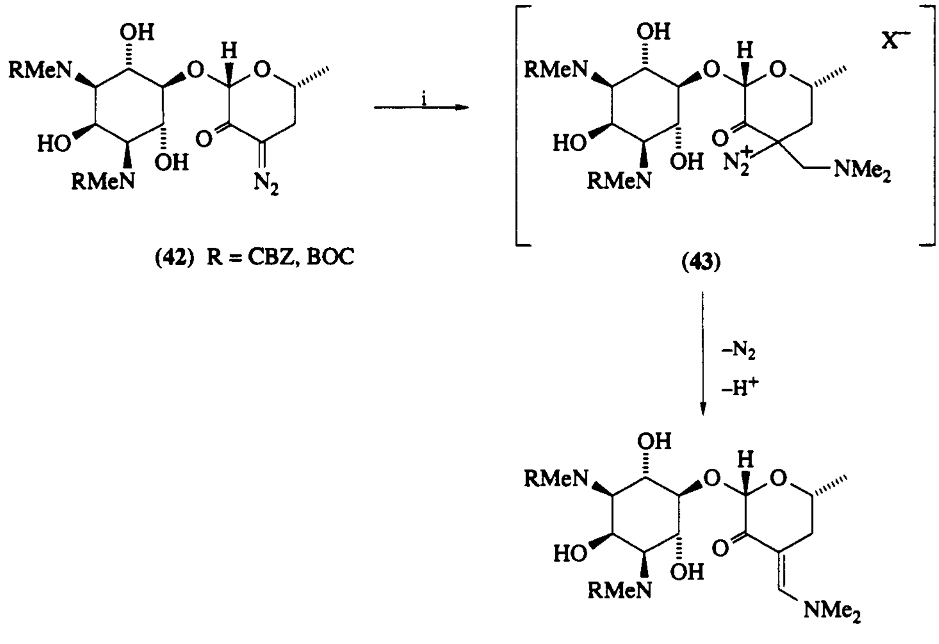

OH
RMeN
H
O
O
HO
O
OH
RMeN
N2
i
OH
RMeN
H
O
O
X−
HO
O
N2+
NMe2
OH
RMeN
-N2
-H+
OH
RMeN
H
O
O
HO
O
OH
RMeN
NMe2

(42) R = CBZ, BOC

(43)

(44)

i, $CH_2{=}\overset{+}{N}Me_2\ Cl^-$, $Et_3N$, MeCN, 25 °C (60% for R = CBZ)

Scheme 6

Esters, which are less acidic than ketones by about 5 p$K_a$ units, do not react directly with preformed iminium salts unless they contain activating groups to boost the acidity of the α-protons. In connection with the total synthesis of shikimate/chorismate biosynthetic metabolites, Mannich bases prepared from α-alkoxymalonates and preformed iminium salts have been employed by Berchtold and coworkers,[49a–d] Chouinard and Bartlett,[50] and Ganem and coworkers[51a–c] as synthons for the sensitive enol pyruvate moiety present in these natural products. For example, α-alkoxymalonate (**45**) is reacted with iminium salt (**30**) to provide Mannich base (**46**), which upon quaternarization and thermal fragmentation yields enol pyruvate (**47**; Scheme 7).[49c] It is noteworthy that during this transformation the epoxycyclohexene ring remains intact, a tribute to the mild conditions of these types of Mannich reactions. In a synthesis of (±)-dimethyl chorismate (**50**) using the more sensitive cyclohexadiene substrate (**48**), Ganem *et al.* have found it necessary to employ the less nucleophilic TFA salt (**32**) instead of the iodide salt (**30**) due to aromatization, probably induced by attack of iodide on the ring (Scheme 8).[51a] The resulting Mannich base is quaternarized to give (**49**), which is converted directly to (±)-dimethyl chorismate (**50**) upon base-induced fragmentation. A similar transformation involving an α-carboxylactone has been used by Landsbury and Mojica in the total synthesis of (±)-arteannuin B to introduce an α-methylenelactone moiety.[52] As demonstrated by Tarzia *et al.*, *N*,*N*-diphenylmethyleneglycinate esters (**51**) are another class of activated esters which add directly to *N*,*N*-dimethyl(methylene)iminium salts (Scheme 9).[53] The resulting Mannich base (**52**) is a convenient synthon for the α-aminoacrylate derivative (**53**), obtained by elimination of the *N*,*N*-dimethylamino group.

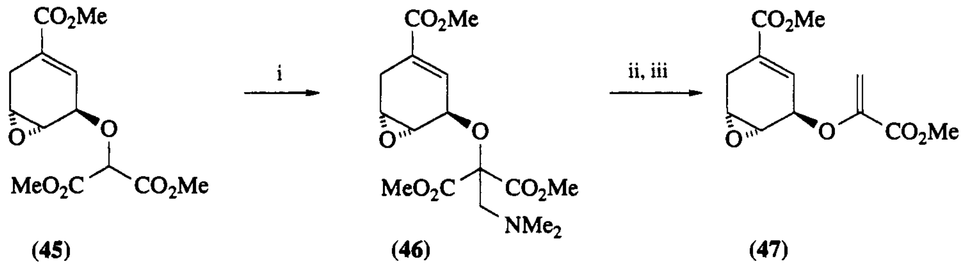
CO2Me
O
MeO2C
CO2Me
(45)
i
CO2Me
O
MeO2C
CO2Me
NMe2
(46)
ii, iii
CO2Me
O
CO2Me
(47)

i, $CH_2{=}\overset{+}{N}Me_2\ I^-$, $Et_3N$, $CH_2Cl_2$, 25 °C; ii, MeI, $CH_2Cl_2$, 25 °C; iii, DMSO, 80 °C (25% overall)

Scheme 7

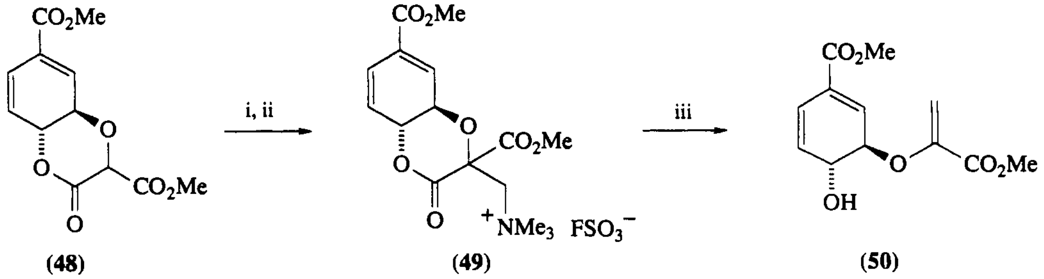
CO2Me
O
O
CO2Me
O
(48)
i, ii
CO2Me
O
CO2Me
O
O
+NMe3 FSO3−
(49)
iii
CO2Me
O
CO2Me
OH
(50)

i, $CH_2{=}\overset{+}{N}Me_2$ TFA$^-$; ii, $MeOSO_2F$ (37%); iii, NaOH, $H_2O$, 0 °C (25%)

Scheme 8

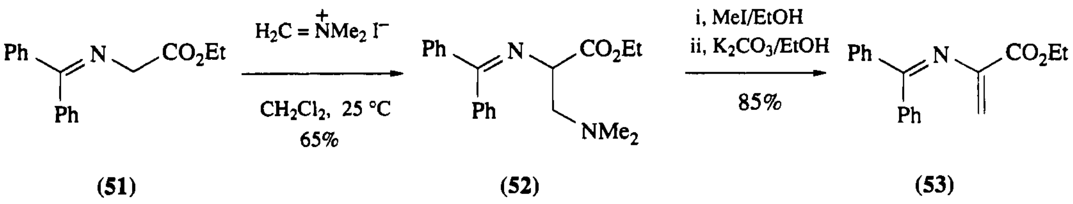
Ph
N
CO2Et
Ph
(51)
H2C = +NMe2 I−
CH2Cl2, 25 °C
65%
Ph
N
CO2Et
Ph
NMe2
(52)
i, MeI/EtOH
ii, K2CO3/EtOH
85%
Ph
N
CO2Et
Ph
(53)

Scheme 9

In addition to activated esters, Möhrle and Schaltenbrand have shown that β-diketones (**54**) add readily to preformed iminium salts (Scheme 10; Table 6).[54] The HCl salt (**55**) of the resulting Mannich base can be isolated under anhydrous conditions but in water it spontaneously eliminates to give an α-methylene β-diketone (**56**).

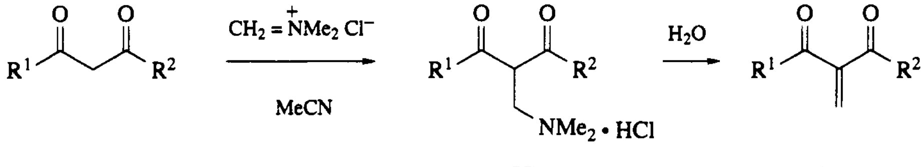

**(54)** **(55)** **(56)**

Scheme 10

Table 6 Reactions of β-Diketones (**54**) with Iminium Salt (**31**)[54]

| | *β-Diketone* | | *Products* | |
|---|---|---|---|---|
| | *(54)* | | *(55)* | *(56)* |
| *Entry* | *R¹* | *R²* | *Yield (%)* | *Yield (%)* |
| 1 | Ph | Ph | | 90 |
| 2 | Me | Me | | 50 |
| 3 | 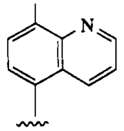 | Ph | | 40 |
| 4 | —CH2C(Me)2CH2— | | 87 | |
| 5 | 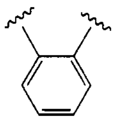 | | 27 | |

### (iii) Reactions with enol silanes

Reactions of enol silanes with *N,N*-dimethyl(methylene)iminium salts occur under milder conditions than those of simple ketones because an initial enolization step is not required. The reaction is normally performed at room temperature, and aprotic solvents must be used to prevent hydrolysis of the enol silane. Danishefsky and coworkers,[55] in their pioneering investigations of this reaction using TMS enol silanes and iminium iodide (**30**), have suggested the intermediacy of a silyloxonium salt (**57**), which loses a proton to give a 2-substituted enol silane (**58**) as its HI salt (Scheme 11). Subsequent hydrolysis of the enol silane during acid–base work-up affords the Mannich base (**59**).

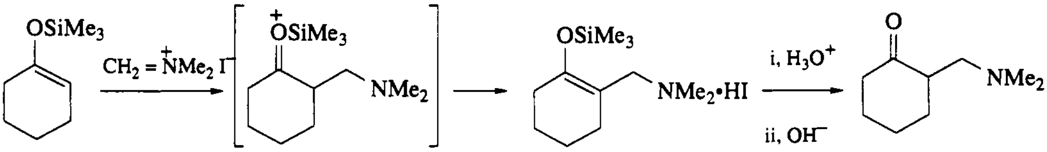

**(57)** **(58)** **(59)**

Scheme 11

In the corresponding reactions of TBDMS enol silanes (**60**), Akiba and coworkers have shown that the more stable TBDMS group is able to survive the work-up, affording Mannich bases as their TBDMS enol silane derivatives (**62**; Scheme 12).[56] Interestingly, acyclic TBDMS enol silanes react with migration of the position of the enol silane double bond (Table 7, entries 1–4). The authors propose that deprotonation of the silyloxy intermediate (**61**) occurs intramolecularly by the neighboring amino group, as illustrated in the transition state depicted in Figure 3. In cyclic cases, such a transition state is disfavored because the amino group must be axial and the more-substituted, thermodynamically favored product is obtained (Table 7, entries 5–6).

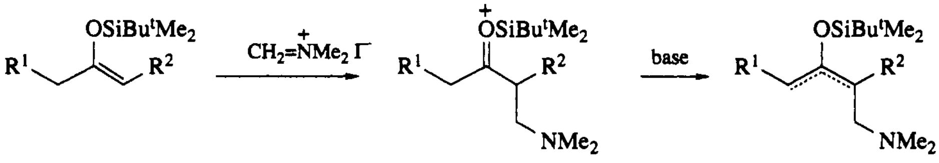

**(60)** **(61)** **(62)**

**Scheme 12**

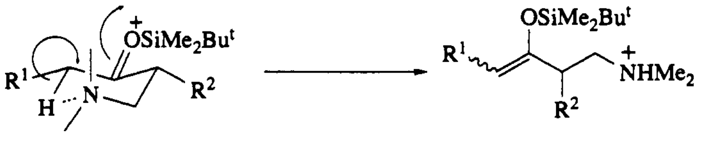

**Figure 3** Proposed intramolecular proton abstraction occurring in Mannich reactions of TBDMS enol silanes

**Table 7** Reactions of *t*-Butyldimethyl Enol Silanes with Iminium Iodide (**30**)[56]

| *Entry* | *Enol silane* | *Conditions* | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 1 | 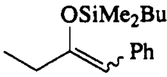 | r.t., 18 h | 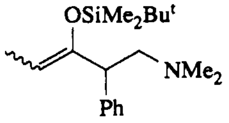 | 89 |
| 2 | 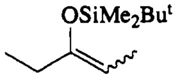 | r.t., 24 h | 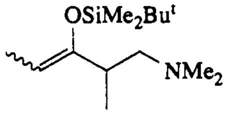 | 76 |
| 3 | 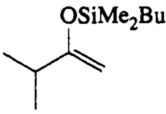 | r.t., 16 h | 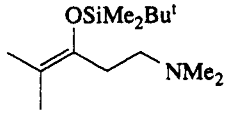 | 58 |
| 4 | 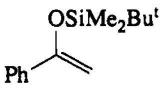 | r.t., 5 h | 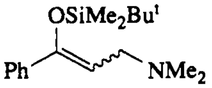 | 92 |
| 5 | 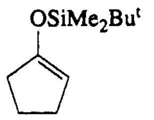 | r.t., 20 h | 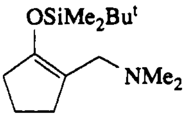 | 71 |
| 6 | 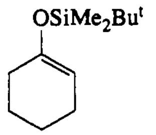 | r.t., 20 h | 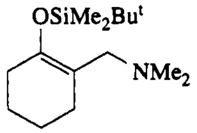 | 76 |

Table 8 highlights some versatile applications of the Mannich reaction of enol silanes, providing Mannich bases that in some cases are very difficult, if not impossible, to obtain using the classical method. Regiocontrol is observed in the preparation of the two Mannich bases of 2-methylcyclohexanone from the corresponding regioisomeric enol silane derivatives (entries 1 and 2).[57] Aminomethylation of the enol

**Table 8** Mannich Reactions of Enol Silanes Using *N,N*-Dimethyl(methylene)iminium Salts

| *Entry* | *Enol silane* | *Product* | *Iminium salt* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 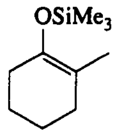 | 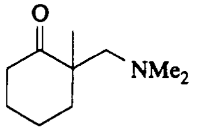 | **(30)** | 65 | 57 |
| 2 | 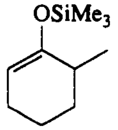 | 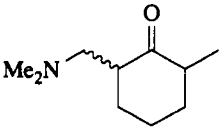 | **(30)** | 79[a] | 57 |
| 3 | 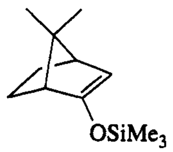 | 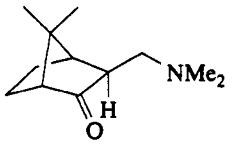 | **(30)** | 86 | 58 |
| 4 | 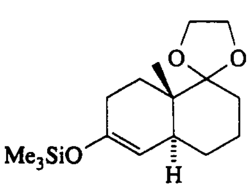 | 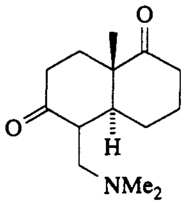 | **(30)** | 95[b] | 55 |
| 5 | 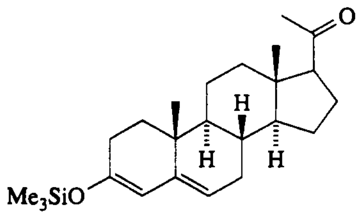 | 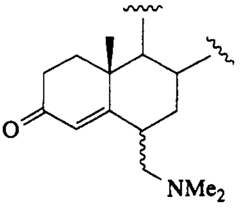 | **(30)** | 58[c] | 57 |
| 6 | 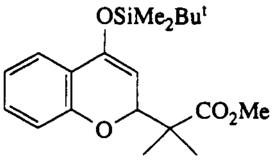 | 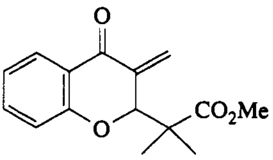 | **(31)** | 66 | 59 |
| 7 | 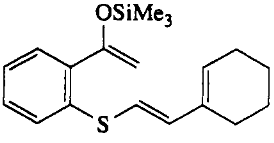 | 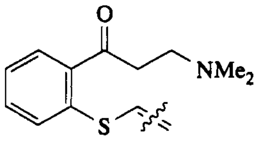 | **(31)** | 92 | 60 |

**Table 8** *(continued)*

| *Entry* | *Enol silane* | *Product* | *Iminium salt* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 8 | 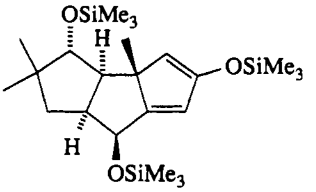 | 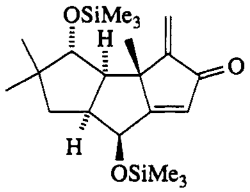 | (30) | 46 | 61 |
| 9 | 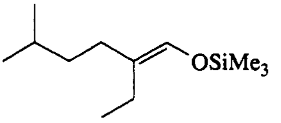 | 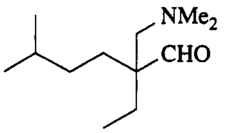 | (32) | 55 | 35 |

---

[a] Contaminated with *ca.* 4% of the 2,2-disubstituted ketone. [b] The ketal is lost during work-up; yield is based on conversion to the methiodide salt. [c] Yield is based on conversion to the dienone.

silane derivative of (+)-camphor (entry 3) occurs under kinetic control to give the *exo* isomer contaminated with less than 3% of the *endo* isomer (the equilibrium mixture is 1:4 *exo:endo*).[58] This example is noteworthy since (+)-camphor fails to react under the classical conditions. Functional groups including ketals (entry 4), ketones (entry 5), esters (entry 6), vinyl sulfides (entry 7), and silyl ethers (entry 8) are

**Table 9** Comparison of the Mannich Reactions of Enol Silanes with *N*,*N*-Dimethyl(methylene)iminium Salts Using *In Situ* and Non *In Situ* Methods

| *Entry* | *Enol silane* | *Product* | *Iminium salt* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 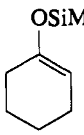 | 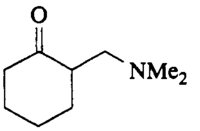 | (30)[a]<br>(30) | 67<br>87 | 36, 37<br>55 |
| 2 | 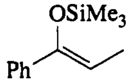 | 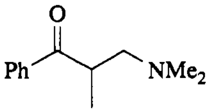 | (30)[a]<br>(31)<br>(32) | 71<br>41<br>60 | 36, 37<br>35<br>35 |
| 3 | $C_5H_{11}CH{=}CHOSiMe_3$ | $C_5H_{11}CH(CHO)CH_2NMe_2$ | (30)[a]<br>(32) | 18<br>70 | 36, 37<br>35 |
| 4 | 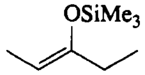 | 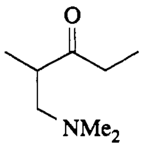 | b<br>(32) | 83<br>60 | 38<br>35 |
| 5 | 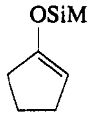 | 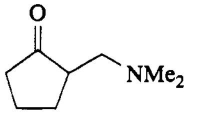 | b | 68 | 38 |

---

[a] Prepared *in situ* from chloroiodomethane and *N*,*N'*,*N*,*N'*-tetramethyldiaminomethane. [b] Prepared *in situ* from n-butyl dimethylaminomethyl ether and a catalytic amount of $Me_3SiI$ or $Me_3SiOTf$; the exact structure of the aminomethylating agent is unknown.

compatible with the reaction. Conjugated (entry 5) and cross-conjugated enol silanes (entry 8) and aldehyde enol silanes (entry 9) also react successfully. For further examples, see the mini-review by Holy.[35]

Some comparisons between the yields of the Mannich reaction of enol silanes using *in situ* methods for preparation of the iminium salt and non *in situ* methods are shown in Table 9. Higher yields (20–30%) of β-amino ketones using *in situ* methods are seen in entries 2 and 4 but not in entry 1. Although a clear advantage of the *in situ* methods is not evident in these limited examples, *in situ* methods may be preferred from the standpoint of convenience. With aldehyde enol silanes (entry 3), the *in situ* method of Miyano *et al.*[36,37] is less practical due to elimination of the amino group, presumably caused by the strongly basic *N,N,N′,N′*-tetramethyl(methylene)diamine present in solution.

### (iv) Reactions with enolates

Enolates, because of their greater nucleophilicity, add to *N,N*-dimethyl(methylene)iminium salts under milder conditions than do enol silanes. Reactions of nonstabilized enolates (*i.e.* those without α-activating groups) are typically performed by adding the iminium salt to the enolate at –78 °C, followed by slow warming to room temperature. With less reactive enolates such as boron enolates and stabilized ester enolates, the reaction is carried out at room temperature. Three methods of enolate generation have been used in these types of Mannich reactions: (1) deprotonation of the active methylene compound with strong base; (2) cleavage of enol silanes and silyl ketene acetals with MeLi; and (3) decomposition of α-diazoketones with trialkylboranes to give boron enolates. These are summarized schematically in Scheme 13. In method 1, which has the advantage of being a one-pot procedure starting with the active methylene compound, LDA has been the most widely used base. The presence of diisopropylamine, however, can lead to reduced yields because of its ability to combine with the iminium salt to form a methylenediamine adduct.[35] In the case of ketone enolates, this complication can be avoided by using Poulter's procedure employing KH as base.[62] Method 2 is useful for the regiospecific synthesis of β-amino ketones if the corresponding regioisomerically pure enol silanes can be prepared. This method is complementary to the enol silane method but is carried out at lower temperatures. Equilibration between regioisomeric enolates generated by this method does not occur during the Mannich reaction.[63,35] One potential limitation, however, is the use of MeLi, which may be incompatible with other functional groups. Method 3 is extremely useful for the regiospecific synthesis of β-amino ketones.[64] It is more advantageous than method 2 because of the ease with which the regioisomeric enolates can be prepared; however, the availability of the starting diazoketones and trialkylboranes may limit its use.

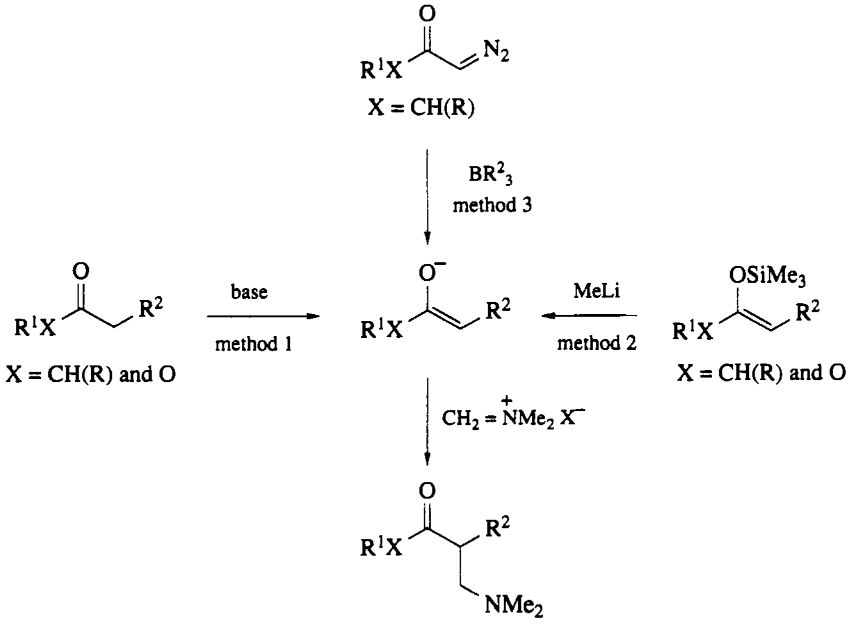

Scheme 13

As illustrated in Table 10, a wide variety of enolates undergo Mannich reactions with *N*,*N*-dimethyl(methylene)iminium salts. They include ester (entries 1), lactone (entries 2–4), α-ethoxycarbonyllactone (entry 5), acyliron (entry 6), aldehyde (entry 7), carboxylic acid (entry 8), and ketone (entries 9–12) enolates. Yields are generally comparable to the direct enol silane method except in the case of aldehydes

**Table 10** Enolate-mediated Mannich Reactions Using Preformed *N*,*N*-Dimethyl(methylene)iminium Salts

| *Entry* | *Starting material (R = H) Mannich base (R = CH$_2$NMe$_2$)* | *Enolate formation* | *Iminium salt* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 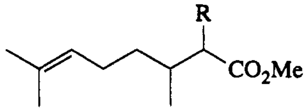 | LDA | (30) | 66 | 65 |
| 2 | 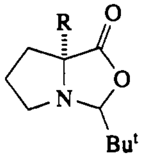 | LDA | (31) | 56 | 66 |
| 3 | 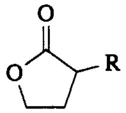 | Enol silane, MeLi | (32) | 60 | 63 |
| 4 | 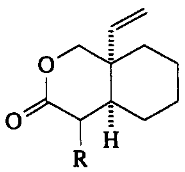 | LDA | (30) | 53[a] | 55 |
| 5 | 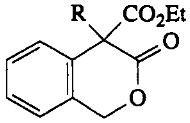 | NaH | (30) | 80[b] | 28 |
| 6 | 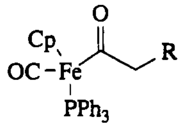 | BuLi | (30) |  | 67 |
| 7 | $C_5H_{11}CH(R)CHO$ | Enol silane, MeLi | (32) | 30 | 63 |
| 8 | $C_{16}H_{23}CH(R)CO_2H$ | Disilyl ketene acetal, MeLi | (32) | 45 | 63 |
| 9 | 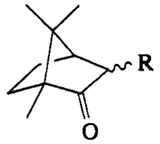 | KH | (32) | 60[c] | 35 |
| 10 | 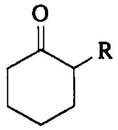 | KH | (30) | 90 | 62 |

**Table 10** *(Continued)*

| *Entry* | *Starting material (R = H)*<br>*Mannich Base (R = $CH_2NMe_2$)* | *Enolate formation* | *Iminium salt* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 11 | 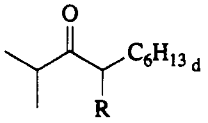 | 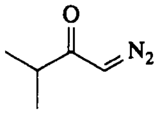 <br>$(C_6H_{13})_3B$ | **(30)** | 84 | 64 |
| 12 | 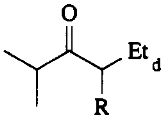 | 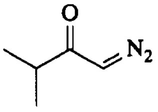 <br>$Et_3B$ | **(30)** | 94 | 64 |

[a] Yield is based on conversion to the α-methylene lactone. [b] Yield is based on conversion to the methiodide. [c] A 1:4 ratio of *exo*:*endo* products was determined independently by Mosher *et al.*[58] but using the iminium salt (**30**) instead of (**32**). [d] The starting materials are shown to the right.

(entry 7), where diminished yields can result due to instability of the enolate or to proton abstraction of the product. For the regiospecific synthesis of simple acyclic β-amino ketones, the method of Hooz (entries 11 and 12) provides regioisomerically pure products in excellent yield. For other, related examples of enolates that have been used in these Mannich reactions, see the references listed in Table 10.

2-Silyloxycyclopropanecarboxylates are masked homoenolate equivalents which can also add to *N*,*N*-dimethyl(methylene)iminium salts. In one of several examples reported by Reissig and Lorey, methyl 2-*t*-butyl-2-(trimethylsilyloxy)cyclopropanecarboxylate and triflate salt (**33**) react to produce α-*N*,*N*-dimethylaminomethyl-γ-oxo ester (**64**; Scheme 14).[33] The reactive intermediate has not been precisely determined but is most likely a ring-opened enolate (**63**) or its silyl ketene acetal derivative. The reaction can also be performed using the chloride iminium salt (**31**) in the presence of $TiCl_4$, but the reproducibility is poor due to reduced solubility. The products of these reactions are convenient precursors to α-methylene-δ-lactones and acrylic acid derivatives.

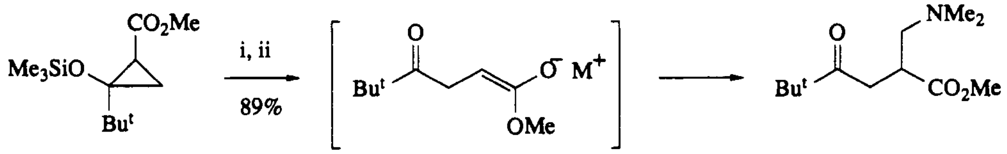

**(63)** **(64)**

i, $CH_2{=}\overset{+}{N}Me_2$ $Cl^-$, $Me_3SiOTf$, $CH_2Cl_2$, 0 °C; ii, add cyclopropyl ester, 0 to 20 °C

**Scheme 14**

Enolate-mediated Mannich reactions using preformed *N*,*N*-dimethyl(methylene)iminium salts have been widely used in the total synthesis of sesquiterpene α-methylene lactones and other natural products for the introduction of α-methylene units by subsequent quaterization and elimination of the tertiary amine. Examples include the sesquiterpene α-methylene lactones vernolepin[55,68] and dehydrocostus lactone,[69] and a carbohydrate analog.[70] In an interesting application used in the synthesis of 3-demethylaflavinine (**68**), Danishefsky *et al.* have prepared β-amino ketone (**66**) regiospecifically by cleavage of enol carbonate (**65**) and subsequent addition to iminium salt (**31**; Scheme 15).[71a] Mannich base (**66**) is used as a synthon for enone (**67**), which serves as a double Michael acceptor for construction of the B- and C-rings of 3-demethylaflavinine (**68**). It should be noted that in an earlier study by these workers, reaction of iminium salt (**31**) with a related 3,3-disubstituted enol silane derivative of (**65**) led, unexpectedly, to the 6-substituted Mannich base.[71b] The reversal of regiocontrol using the enol silane instead of the free enolate is most likely a result of the steric interaction between the adjacent quaternary center at C-3 and the incoming electrophile.

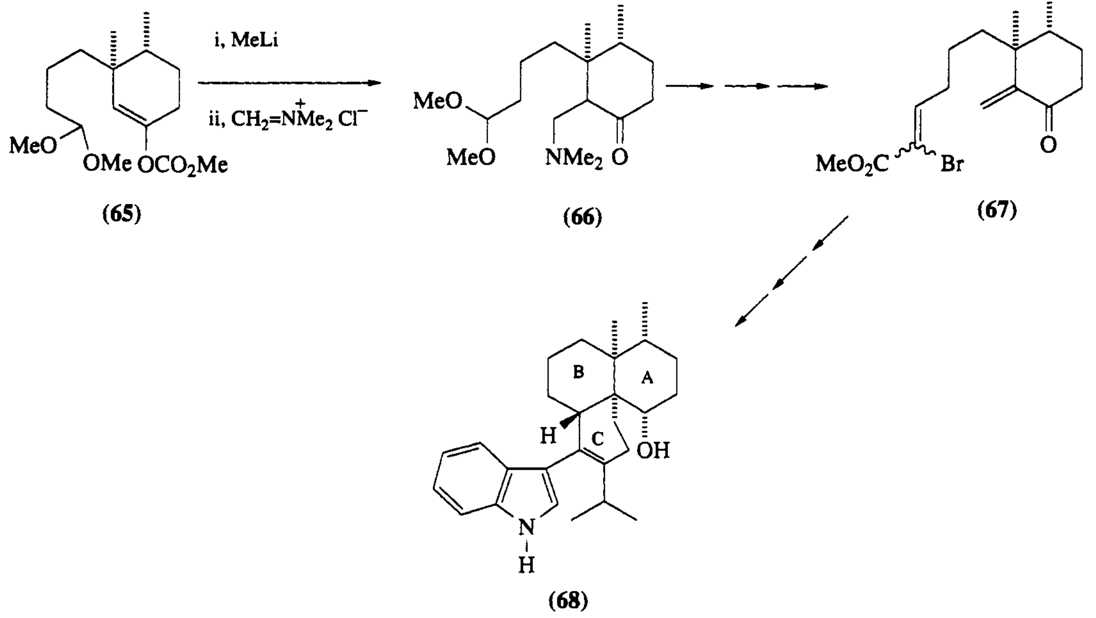

Scheme 15

*(v) Summary*

The use of preformed *N*,*N*-dimethyl(methylene)iminium salts has a number of advantages over the classical method for the synthesis of Mannich bases and corresponding α-methylene compounds. These include (i) mild conditions and toleration of other functional groups; (ii) the ability to regiospecifically synthesize β-amino ketones; and (iii) a broadened scope, including simple, non-α-activated carboxylic acid derivatives as active methylene components. Sterically crowded substrates also react more successfully. Different counterion forms (I$^-$, Cl$^-$, TFA$^-$, OTf$^-$) of the iminium salt may be used for improved solubility and to reduce side reactions. *In situ* methods of iminium salt generation are also available in reactions of enol silanes. The active methylene component can be used directly as in the classical method or preactivated *via* its enol silane or enolate derivative, allowing the reaction to proceed at lower temperatures. For the regiospecific aminomethylation of ketones, regiospecifically generated enol silanes or enolates must be used since regiocontrol is unpredictable when the ketone is employed directly. For the regiospecific synthesis of simple acyclic β-amino ketones, the enol borinate method of Hooz is the method of choice because of the ease with which the enolate can be prepared regiospecifically. The classical method, which is more adaptable to large scale, may be preferred, however, for the synthesis of simple, unfunctionalized Mannich bases.

### 4.1.2.3 Cyclic Iminium Salts

Preformed cyclic *N*,*N*-dialkyliminium salts (*i.e.* where a ring joins the α-carbon and positively charged nitrogen) have been used in enolate condensation reactions. The number of examples, however, is rather limited, probably because of complications arising through abstraction of enolizable protons. $\Delta^4$-Dehydroindolizidinium salt (**69**) represents one of the few examples of an enolizable, cyclic *N*,*N*-dialkyliminium salt known to react with an enolate (equation 8).[72] The use of a soft zinc enolate in this reaction may be crucial. The relative stereochemistry of the resulting β-amino ester (**70**) is undefined. *N*-Alkyl-3,4-dihydroisoquinolinium salts (*e.g.* **71**), a class of nonenolizable, cyclic iminium salts, have had extensive applications in the total synthesis of protoberberine and phthalide isoquinoline alkaloids. A review by Pai and coworkers[9] has covered much of this work. In a more recent application by Yamazaki and coworkers, a dihomoenolate is added to isoquinolinium salt (**71**) to give tetrahydroisoquinoline (**72**), which is converted to (±)-protoemetinol (**73**) in several steps (Scheme 16).[73]

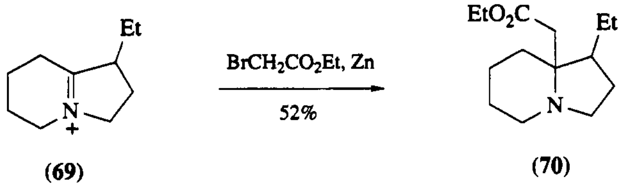

(8)

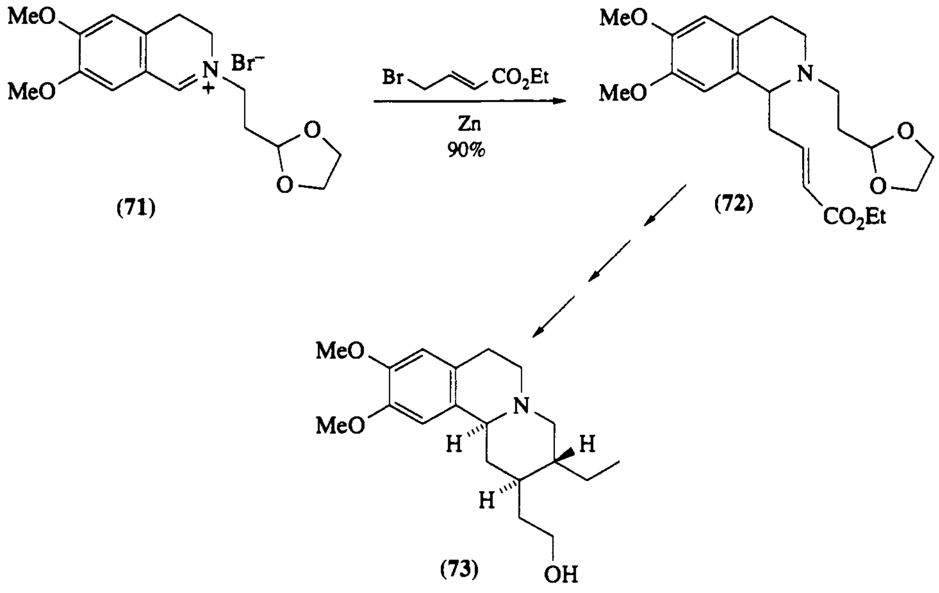

Scheme 16

### 4.1.2.4 *N*-Silyl- and *N,N*-Disilyl-iminium Salts

An inherent limitation in the use of *N,N*-dialkyliminium salts in the Mannich reaction is that the product derived is a tertiary amine, which restricts elaboration of the nitrogen. As a means of overcoming this limitation, MacLean and coworkers[74] have introduced *N*-silyliminium salts, prepared *in situ* from the corresponding imine using TMS-OTf; facile cleavage of the silyl group following the Mannich reaction liberates a free site on the amine. An example is shown in Scheme 17 involving the reaction of *N*-silyliminium salt (**75**) with the lithium salt of 3-cyano-4-methyl-5-vinylpyridine (**76**). The initial adduct cyclizes directly to form a tetracyclic amidine (**77**), an intermediate in the synthesis of (±)-alangimaridine (**78**). It is proposed that the mechanism of amidine formation most likely involves transfer of the silyl group to the exocyclic amidine nitrogen; the silyl group is then lost upon work-up. The *N*-silyl group also has a special role in activating the imine since the parent imine (**74**) fails to react with anion (**76**). *N*-Silyliminium salts of other 3,4-dihydroisoquinolines have been used in the total synthesis of alamaridine[75] and the pentacyclic alkaloids nauclefine, angustidine, angustine and 13b,14-dihydroangustine.[76]

In reactions with silyl ketene acetals (**79**), Sekiya and coworkers have reported two *in situ* methods for the generation of *N*-silyliminium salts. The first method generates *N,N*-disilyliminium salts by TMS-OTf-catalyzed cleavage of *N,N*-bis(trimethylsilyl)methoxymethylamine (**80**); the *N,N*-disilyliminium salt then reacts with silyl ketene acetals (**79**) to afford *N,N*-bis(trimethylsilyl)-β-amino esters (**81**) in high yield (equation 9; Table 11).[77] Desilylation of (**81**) can be easily accomplished by methanolysis to afford the corresponding primary β-amino esters. The overall process introduces a primary aminomethyl group ($NH_2CH_2$), a transformation difficult to perform using the classical method. The compatibility of this method with a-amino substitution in the silyl ketene acetal (entry 6) may render it particularly useful for the synthesis of monobactam antibiotics.[78] An *N,N*-bis(trimethylsilyl)methyleneiminium triflate species [$(TMS)_2N^+{=}CH_2$ OTf$^-$; **83**] is implicated in this reaction, based on the observation that methoxytrimethylsilane (**82**) is released when aminol ether (**80**) and TMS-OTf are reacted in the absence of silyl ketene acetal. The second method involves TfOH-catalyzed cleavage of 1,3,5-trialkylhexahydro-1,3,5-triazines (**84**),[79] prepared by the method of Reynolds and Cossar.[80] The putative iminium species [TMS(R$^3$)N$^+$═CH$_2$ OTf$^-$; **86**] condenses with silyl ketene acetals (**79**) to afford secondary β-amino esters (**85**) after aqueous work-up (equation 10; Table 12). Yields are generally good, even in sterically crowded cases (entries 1 and 8). The method also allows for easy variation of the amino substituent (R$^3$).

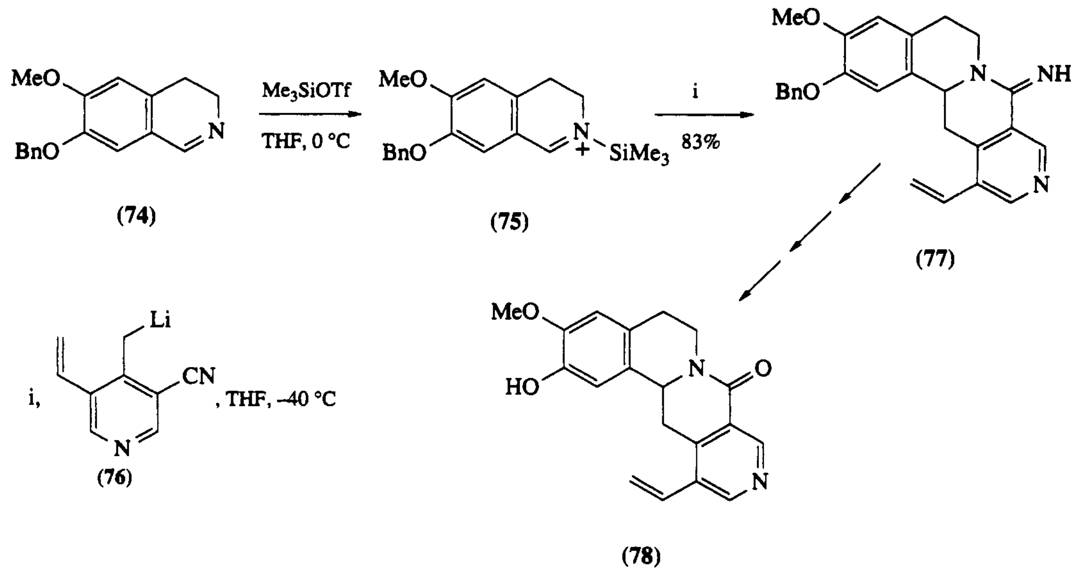
MeO
BnO
N
(74)
Me3SiOTf
THF, 0 °C
MeO
BnO
N+
SiMe3
(75)
i
83%
MeO
BnO
N
NH
N
(77)
i,
Li
CN
N
, THF, –40 °C
(76)
MeO
HO
N
O
N
(78)

Scheme 17

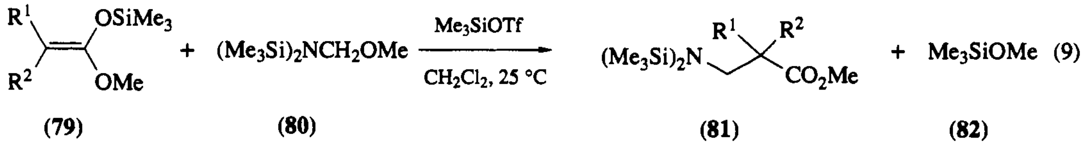
R1
OSiMe3
R2
OMe
(79)
+ (Me3Si)2NCH2OMe
(80)
Me3SiOTf
CH2Cl2, 25 °C
(Me3Si)2N
R1
R2
CO2Me
(81)
+ Me3SiOMe
(82)

(9)

Table 11 Reactions of Silyl Ketene Acetals (**79**) with *N*,*N*-Bis(trimethylsilyl)methoxymethylamine (**80**) Catalyzed by TMS-OTf[77]

| *Entry* | *Silyl ketene acetal (79)* *R*$^1$ | *R*$^2$ | *Product (81) Yield (%)* |
|---|---|---|---|
| 1 | Me | Me | 84 |
| 2 | Me | H | 85 |
| 3 | Ph | H | 95 |
| 4 | —(CH$_2$)$_4$— | | 78 |
| 5 | —(CH$_2$)$_5$— | | 85 |
| 6 | 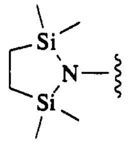 | H | 93 |

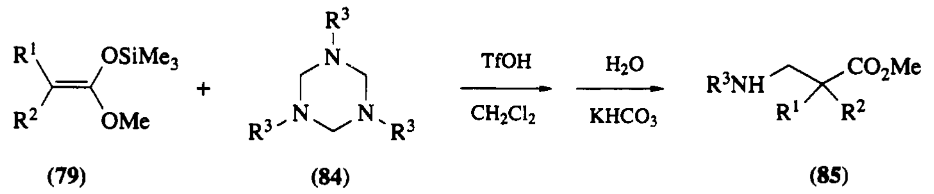
R1
OSiMe3
R2
OMe
(79)
+
R3
N
R3
N
N
R3
(84)
TfOH
CH2Cl2
H2O
KHCO3
R3NH
CO2Me
R1
R2
(85)

(10)

**Table 12** Reactions of Silyl Ketene Acetals (**79**) with 1,3,5-Trialkylhexahydro-1,3,5-triazines (**84**) Catalyzed by TfOH[79]

| *Entry* | *Silyl ketene acetal* (**79**) $R^1$ | $R^2$ | *Triazine* (**84**) $R^3$ | *β-Amino ester* (**85**) *Yield (%)* |
|---|---|---|---|---|
| 1 | Me | Me | $Pr^i$ | 83 |
| 2 | Me | H | $Pr^i$ | 87 |
| 3 | H | H | $Pr^i$ | 41 |
| 4 | Me | Me | Bn | 83 |
| 5 | Me | Me | Et | 58 |
| 6 | Me | Me | Allyl | 76 |
| 7 | Me | Me | Ph | 67 |
| 8 | Me | Me | $Ph(CO_2Me)CH$ | 69 |

### 4.1.3 USE OF IMINES

#### 4.1.3.1 Introduction

Imines are more versatile than preformed iminium salts in reactions with active methylene compounds because the product, a secondary Mannich base, has an additional site on the nitrogen for further elaboration (equation 11). Imine condensation reactions are also superior to the classical method for the synthesis of secondary Mannich bases because cross-condensation reactions do not occur, due to the absence of free aldehyde in solution. The major side reactions occurring in imine condensation reactions are abstraction of enolizable α-protons and self-condensation reactions of enolizable imines at elevated temperature.

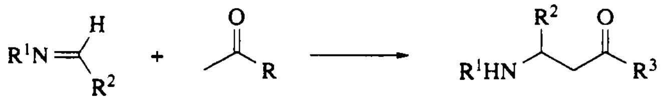

(11)

Imines, being neutral species, are less reactive than iminium salts. Consequently, active methylene compounds with $pK_a$ values greater than ~15–16 must be preactivated as an enolate or enol silane derivative. Lewis acids are sometimes used in reactions with enolates to improve reactivity and stereoselectivity, but in contrast to the reactions of preformed iminium salts, Lewis acids are required in reactions with enol silanes. Additional activation of the active methylene compound or catalysis is not usually required in reactions with more acidic active methylene compounds ($pK_a$ values below ~15–16). In these reactions, higher acidity not only gives higher enol concentrations but also serves to catalyze the reaction through protonation of the imine.

Of the various imines known to condense with active methylene compounds, α-arylimines have been the most widely used, especially in earlier work, because of their stability, ease of preparation and the absence of enolizable protons. Aliphatic imines containing enolizable protons have broader synthetic applications but their use is more restricted because they are prone to deprotonation and self aldol type condensations. As will be discussed, new methods utilizing Lewis acids and the less basic boron enolates have been devised to overcome the problem of deprotonation. Other innovations that have extended the scope of imine condensations include *in situ* methods for the preparation of elusive formaldehyde imines ($CH_2{=}NR_2$) and the utilization of *N*-heterosubstituted imines (N = Si, O and S) for the synthesis of primary Mannich bases and *N*-unsubstituted β-lactams, available *via* hydrolysis or reduction of the N—X bond.

Largely stimulated by the synthesis of β-lactam antibiotics,[78] there have been widespread investigations into the stereochemical aspects of imine condensations, mainly involving reactions of enolates of carboxylic acid derivatives or silyl ketene acetals. In analogy to the aldol condensation, stereoselectivity of imine condensations will be discussed in terms of two types in this chapter: (i) simple diastereoselectivity or *syn–anti* selectivity, when the two reactants are each prochiral (equation 12); and (ii) diastereofacial selectivity, when a new chiral center is formed in the presence of a pre-existing chiral center in one of the reactants (*e.g.* equation 13). The term 'asymmetric induction' may be used synonymously with 'diastereofacial selectivity' when one of the chiral reactants is optically active. For a more explicit explanation of these terms, see Heathcock's review on the aldol condensation.[81]

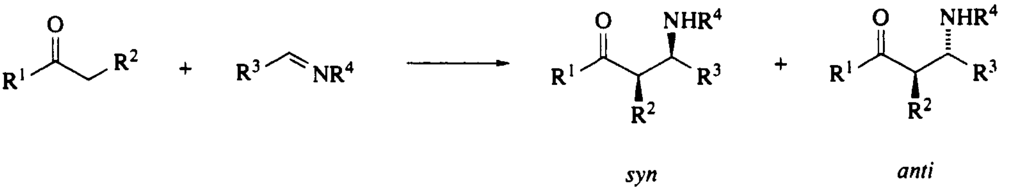

(12)

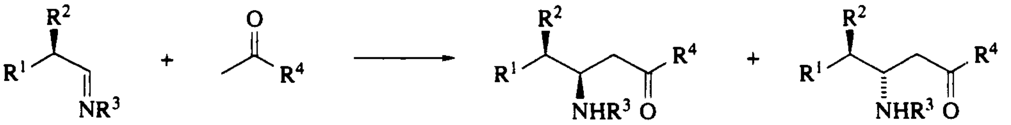

(13)

### 4.1.3.2 Acyclic *N*-Aryl- and *N*-Alkyl-imines

#### *4.1.3.2.1 Reactions with highly acidic active methylene compounds*

Reactions using highly acidic active methylene compounds (p$K_a$ = 9–13) comprise nearly all the early examples of imine condensation reactions, some of which date back to the turn of the century. Reviews by Layer[6] and Harada[7] have summarized many of these reactions and include examples using diethyl malonate, ethyl cyanoacetate, ethyl malonamide, acetoacetic acid, benzoylacetic esters and nitroalkanes. Conditions of these reactions vary; they have been performed both in protic and aprotic solvents, neat, and with and without catalysts. Elevated temperatures are generally required. Reactions with malonates have useful applications for the synthesis of β-amino acids. For example, hydrobenzamide (**87**), a trimeric form of the benzaldehyde–ammonia Schiff base, and malonic acid condense with concomitant decarboxylation to produce β-phenylalanine (**88**) in high yield (equation 14).[82] This is one of the few examples of a Mannich reaction in which a primary Mannich base is produced in a direct manner but is apparently limited to aromatic imines.

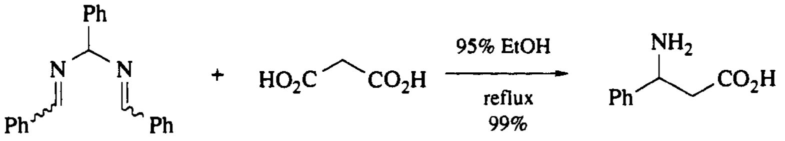

(14)

**(87)** **(88)**

In more recent applications, Takajo and Kambe[83] have reported a new synthesis of perhydropyrimidines (**90**) by a double Mannich reaction (one step is intramolecular) using hydrobenzamide (**87**) and methyl cyanoacetate (**89**; equation 15). The reaction is general for other highly acidic methylene compounds including malononitrile, dimethyl malonate and nitroethane. In some cases, the intramolecular Mannich step is slow and side products arising from decomposition of the initial adduct are formed. This phenomenon is temperature dependent, indicating that intermediates in the reaction are formed reversibly.

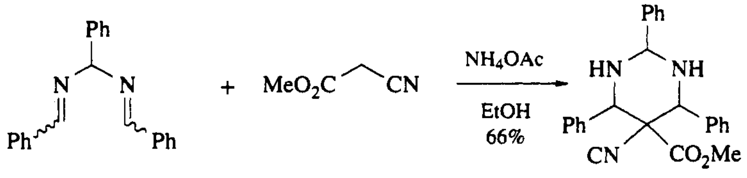

(15)

**(87)** **(89)** **(90)**

In another example of heterocyclic synthesis, Shamma *et al.* have prepared 2-pyridone (**95**) by condensing diethyl glutaconate (**91**) with imine (**92**; Scheme 18).[84] The initial adduct (**93**) cannot be isolated, as it reacts with a second equivalent of (**92**) to give an α-benzylidine derivative (**94**), which can be easily isomerized to (**95**) with base.

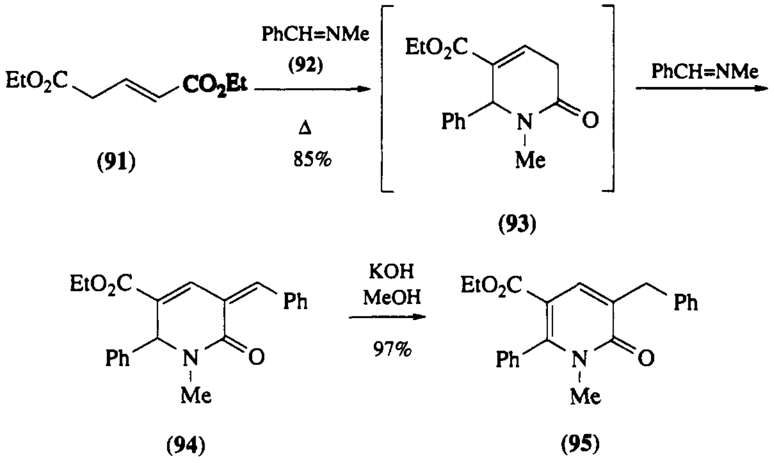

**Scheme 18**

In their synthesis of the pyrimidine segment of the potent antitumor antibiotic bleomycin, Umezawa, Ohno and coworkers have described the reaction of highly functionalized imine (**96**) with malonic acid monoethyl ester to afford β-amino ester (**97**; equation 16).[85] The low yield of (**97**) is largely due to elimination of the amino side chain, giving the corresponding acrylate derivative. A subsequent modification[86] of this reaction using a boron enolate overcomes this problem and will be discussed in Section 4.1.3.2.2.ii.

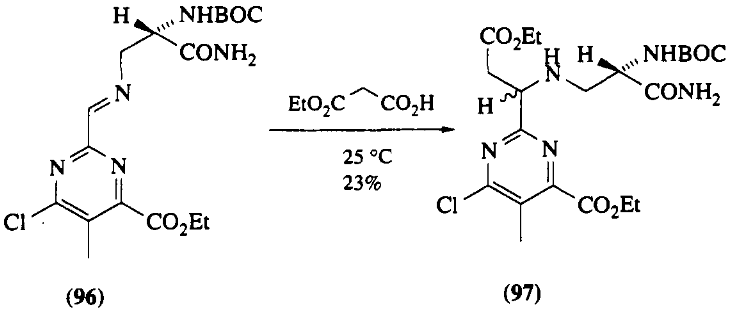

(16)

### 4.1.3.2.2 Reactions with carboxylic acid derivatives

#### (i) Introduction

Condensation reactions of simple carboxylic acids with imines are of intense interest because of their applications to β-lactam synthesis. Activation of the carboxylic acid derivative is accomplished by preforming the enolate *in situ* or by using a silyl ketene acetal derivative with Lewis acid catalysis. The first example of an enolate–imine condensation of this type can be attributed to Gillman and Speeter, who in 1943 reported the synthesis of β-lactams from Reformatsky reagents and Schiff bases.[87] Subsequently, other workers have investigated the mechanism and *syn–anti* selectivity of this reaction. A review of these studies by Evans *et al.* covering work through 1980 has appeared in their review, 'Stereoselective Aldol Condensations'.[10]

The mechanism of β-lactam formation in enolate–imine condensations proceeds by the stepwise pathway depicted in Scheme 19, in which diastereomeric β-lactams (**100**) and (**101**) are formed by cyclization of intermediate, metalated amine adducts (**98**) and (**99**), respectively. The possibility of a less likely [2 + 2] cycloaddition mechanism has been discussed.[88,89] Equilibration between β-lactams (**100**) and (**101**) *via* epimerization at C-3 does not normally occur.[88] The stepwise mechanism is supported by the fact that *trans* β-lactam (**101**; $R^1$ = Pr; $R^2$ = $R^3$ = Ph) is formed from (**99**; M = MgBr) without loss of stereochemistry when it is generated from the corresponding *anti* β-amino ester.[90] Under certain conditions, especially at elevated temperatures, formation of the metalated amine adducts (**98**) and (**99**) can be reversible. Consequently, product ratios of diastereomeric β-lactams (**100**) and (**101**) will reflect this equilibrium, not the kinetic formation of adducts (**98**) and (**99**).[91] Due consideration of this phenomenon should therefore be given when interpreting stereochemical results. It should be noted that cyclization of (**98**) and (**99**) to β-lactams does not always occur and the corresponding β-aminocarboxylic acid derivatives are often isolated upon work-up. The nature of the leaving group X is an important factor in determining whether the metalated amine intermediates cyclize or not. Esters (X = OR), provided they are unhindered, generally give β-lactams, whereas amides (X = NR$_2$), carboxylic acids (X = OH), and thioesters (X = SR) give acyclic products. Bulky substituents at the amine nitrogen (R$^3$) also tend to suppress cyclization to β-lactams.

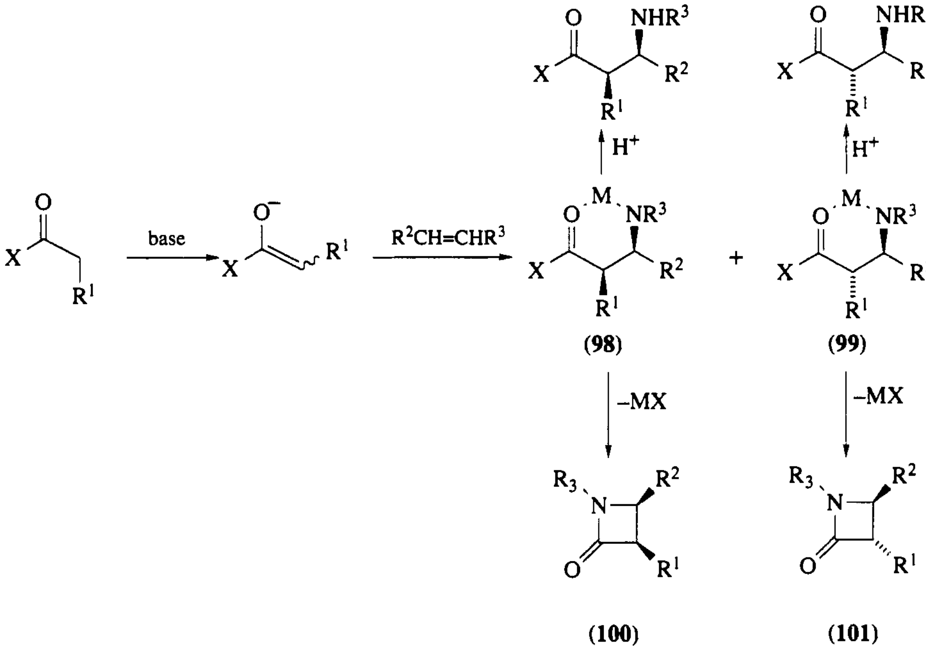

Scheme 19

Evans *et al.*[10] have analyzed *syn–anti* stereoselectivity in enolate–imine condensations using the four postulated pericyclic transition states shown in Figure 4. The indicated three-letter descriptors designate the overall geometry of transition state, chair (*C*) or boat (*B*), and the geometries of the enolate and imine, (*E*) or (*Z*), in that order. In this treatment *syn* products are formed *via* $C(E,E)^‡$ and $B(Z,E)^‡$ transition states and *anti* products are formed *via* $B(E,E)^‡$ and $C(Z,E)^‡$ transition states. These transition states are based on the more stable (*E*)-imine geometry, while for cyclic imines a complementary set of transition states can be derived based on the (*Z*)-imine geometry. In their review, Evans *et al.*[10] have concluded that the dichotomy between the *syn* selectivity of ester enolates and the *anti* selectivity of amide enolates, based on studies from the laboratories of Kagan and Gaudemar (pioneering French workers who first investigated the stereochemical aspects of enolate–imine condensations using Reformatsky reagents, zinc enolates), is a consequence of differing enolate geometries. Thus, ester enolates, which prefer the (*E*)-geometry, react *via* a $C(E,E)^‡$ transition state to give mainly *syn* products, whereas amide enolates, preferring the (*Z*)-geometry, give mostly *anti* products *via* a $C(Z,E)^‡$ transition state. As will be discussed, these trends are upheld in subsequent work using different types of enolates. The reader should note that throughout this chapter, enolate geometry, (*E*) or (*Z*), is assigned based on giving the negatively charged oxygen highest priority.

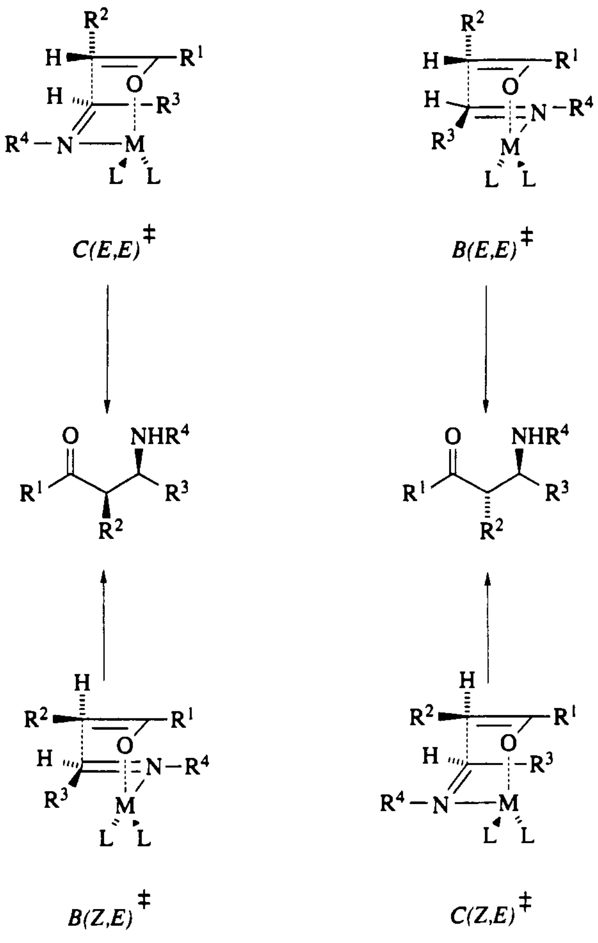

Figure 4 Postulated pericyclic transition states involved in enolate–imine condensations[10]

### (ii) Reactions with enolates

Following the early studies of enolate–imine condensations using Reformatsky reagents, the advent of kinetic deprotonation for the generation of enolates has led to new applications involving other types of enolates. Bergbeiter, Newcomb and coworkers have demonstrated the viability of using lithium enolates of esters (**102**),[89] easily prepared by deprotonation of the ester with LDA. These enolates react with Schiff bases (**103**) under milder conditions (–78 → 25 °C) than do Reformatsky reagents, affording β-lactams (**104**) in 70–90% yield when the α-position of the ester is disubstituted (equation 17). Lower yields (35–45%) are found in cases where $R^1$ and/or $R^2$ is hydrogen, most likely due to the greater susceptibility of the less hindered, monosubstituted enolates to undergo self-condensation reactions in the neighborhood of 0 °C, the temperature at which the imine addition occurs. A further limitation of this method is the restriction to nonenolizable imines, not surprising in view of the strong basicity of lithium enolates. *Trans* β-lactams (**104**) are formed almost exclusively in cases when $R^1$ = Ar, $R^2$ = Me or OLi, and $R^3$ = Et. The basis for the observed *anti* selectivity is not clear. The authors suggest that the carbon–carbon bond-forming step is reversible, and product ratios therefore reflect the thermodynamic stability of the *anti* aldolate. That the disubstituted enolates are probably formed stereorandomly also supports the notion that kinetic factors are not involved. Asymmetric induction can also be achieved using optically active esters. For example, β-lactam (**104**; $R^1$ = Ph; $R^2$ = Me; $Ar^1$ = $Ar^2$ = Ph) is prepared in 60% *ee* from the corresponding (–)-menthyl ester enolate (**102**; $R^3$ = (–)-menthyl). Since asymmetric induction is found with a 3:2 mixture of diastereomeric enolates (demonstrated by trapping experiments), a reversible first step seems likely. Similar applications of the reactions of lithium enolates to the synthesis of monocyclic cephamycin analogs (**104**; $R^1$ = NHCOAr; $R^2$ = OMe) have been reported by Manhas and coworkers.[92]

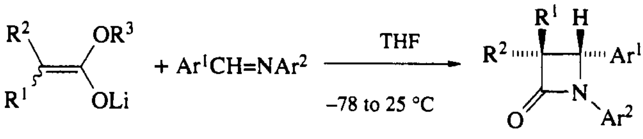

(17)

**(102)** **(103)** **(104)**

Using the boron enolate (or vinyloxyborane) of *t*-butyl thioacetate (**105**), Ohno and coworkers have prepared β-amino thioesters (**107**) *via* reactions with various imines (Scheme 20; Table 13).[86] The products can subsequently be converted to β-lactams[93] if desired, or to other carboxylic acid derivatives. Formation of the boron enolate (**106**) is accomplished using di-*n*-butylboryl triflate and diisopropylethylamine in ether at 0 °C, and the imine addition is performed at 0–25 °C. A hydrogen peroxide work-up is necessary to break up a boron chelation complex of the product. Ether is superior to other solvents in the condensation reaction. Advantages of this method over those using Reformatsky reagents and lithium enolates are (i) compatibility with enolizable imines (Table 13; entries 5–6); and (ii) greater flexibility in terms of elaboration of the product. Also, the combination of mild conditions and weak enolate basicity is compatible with additional ester functionality (entries 3 and 4). Application of this method to the transformation depicted above in equation (16) for the synthesis of bleomycin provides the β-amino thioester derivative of (**97**) in nearly double the yield of the process using malonic half-ester.

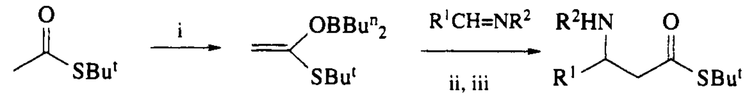

**(105)** **(106)** **(107)**

i, $Bu^n_2BOTf$, $Pr^i_2NEt$, ether, 0 °C; ii, 0 °C to r.t., 1.5 h; iii, 20% $H_2O_2$

**Scheme 20**

**Table 13** Reactions of Boron Enolate (**106**) with Imines[86]

| *Entry* | *Imine* $R^1CH{=}NR^2$ *$R^1$* | *$R^2$* | *β-Amino thioester* *(107)* *Yield (%)* |
|---|---|---|---|
| 1 | Ph | $PhCH_2$ | 80 |
| 2 | $PhCH{=}CH_2$ | $PhCH_2$ | 63 |
| 3 | Ph | $MeO_2CCH_2$ | 52 |
| 4 | Ph | $MeO_2C(CH_2)_2$ | 86 |
| 5 | Et | $PhCH_2$ | 43 |
| 6 | $Pr^i$ | $PhCH_2$ | 45 |

Representative examples of *syn* selective enolate–imine condensations using different types of enolates are shown in Table 14 (entries 1–3). The nonlithium enolates (entries 1–3) are prepared by treating the lithium enolate with different Lewis acids; exchange between the Lewis acid and lithium cation takes place to form a new enolate. All of the lithium enolates are generated using LDA at –78 °C and are treated with the Lewis acid before the addition of the imine. Addition of thioester enolates (entries 2 and 3) employing $CpZrCl_2$[93] and $SnCl_2$[94] additives is conducted at –78 °C to give acyclic products. In the case of the ethyl ester enolate employing $Me_2AlCl$ as additive (entry 1), warming to 25 °C is apparently necessary to induce cyclization to the β-lactam.[95] *Syn* selectivity of these reactions is general for a variety of α-alkyl substituents in the examples of entries 1–3; the reader should consult the individual papers for further examples. It is noteworthy that enolizable imines successfully condense using $Me_2AlCl$ (entry 1), whereas lithium enolates do not. The reaction of the lithium enolate of ethyl glycinate protected as its tetramethyldisilylazacyclopentane (STABASE)[96] adduct has been used in the synthesis of *N*-tetrazol-5-yl substituted β-lactams (entry 4).[97] It is interesting that this reaction is successful despite other claims that lithium enolates do not react with enolizable imines in the absence of a Lewis acid additive.[89] This anomaly may be a result of unusual coordination of the lithium with the glycine nitrogen or with the nitrogens of the tetrazole group of the imine. If (*E*)-enolates are involved in these reactions, *syn* selectivity can be explained by a $C(E,E)^\ddagger$ transition state. In the case of thioester enolates, it is known that the lithium enolate of *t*-butyl thiopropionate[98] and the zirconium enolate of *t*-butyl thiobutyrate[93] are indeed predominately (*E*) (>95:5). It should be noted, however, that the *syn–anti* selectivity of thioester enolates

Table 14 *Syn* Selective Enolate–Imine Condensations[a]

| *Entry* | *Ester* | *Imine* | *Lewis acid* | *Product* | *Yield (%) (syn:anti)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 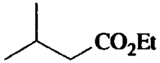 | 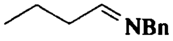 | $Me_2AlCl$ | 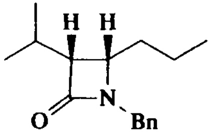 | 58 (9:1) | 95 |
| 2 | 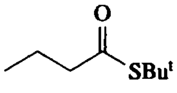 | 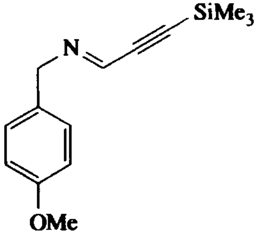 | $Cp_2ZrCl_2$ | 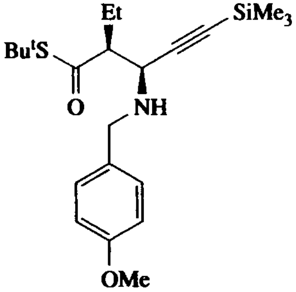 | 57 (5:1) | 93 |
| 3 | 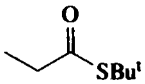 | 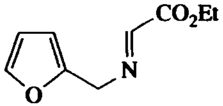 | $SnCl_2$ | 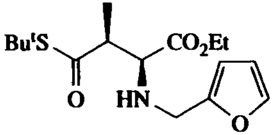 | 82 (95:5) | 94 |
| 4 | 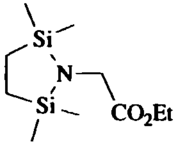 | 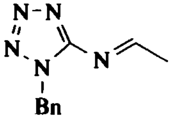 | — | 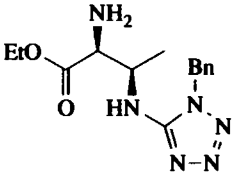 | 44[b] (3:1) | 97 |

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[a] Enolates are generated using LDA. [b] The disilyl protecting group is lost during work-up.

can vary considerably if Lewis acids other than those mentioned above are used.[94] Different enolate geometries could be involved in these cases.

Complementary reactions displaying *anti* selectivity are shown in Table 15. Enolates of STABASE-protected glycinate esters add to enolizable imines in the presence of ZnCl$_2$, giving *trans* β-lactams in high yield (entry 1).[99] This reaction is also general for *N,N*-dialkyl glycinate esters and α-aryl-imines.[99,100] The *anti* selectivity can be explained by a *C(Z,E)*$^‡$ transition state in which the zinc enolate has a (*Z*)-chelated structure (**108**). This model is supported by the tendency of simple α-alkyl zinc enolates (*i.e.* Reformatsky reagents) without an additional coordination site for the zinc cation to give predominantly *cis* β-lactams (see Section 4.1.2.2.i). Apparently, the zinc cation is critical to the formation of a chelate (**108**) since the opposite (*syn*) selectivity is found in the analogous reaction previously described employing the corresponding lithium STABASE-protected glycine enolate (Table 14; entry 4). In entry 2, *anti* selectivity is observed unexpectedly using a similarly protected lithium glycinate enolate, but is most likely due to epimerization induced by the electronegative trifluoromethyl group at the C-4 position of the β-lactam product.[101] As represented in entry 3, tin(II) thioester enolates, formed *in situ* from tin(II) *t*-butylthiolate and ketenes, are *anti* selective in the presence of Sn(OTf)$_2$, affording β-amino thioesters.[102] This example, used in the synthesis of β-lactam antibiotic PS-5 (**109**), demonstrates the compatibility of enolizable imines with these reactions. In other reported examples employing nonenolizable aryl- and styryl-imines, decreased yields are observed with less bulky substituents on the imine nitrogen, perhaps due to oligomerization of the imine.[102] It is interesting to note that the *anti* selectivity of tin(II) thioester enolates generated in this manner and condensed with α-alkyl- and α-aryl-imines in the presence of Sn(OTf)$_2$ contrasts with the *syn* selectivity observed when tin(II) thioester enolates are generated from the corresponding lithium enolates using SnCl$_2$ in reactions with α-carboethoxyimines (Table 12; entry 3).[94] This dichotomy may be a consequence of differing enolate geometries or, perhaps, be attributable to a special role of the α-carboethoxy group in the latter case, involving chelation with the tin(II) cation. *Anti* selectivity is also found in the reactions of aluminum enolates of straight chain thioesters (entry 4).[93] Interestingly, this result stands in contrast to the *syn* selectivity observed in similar reactions of aluminum enolates of ethyl esters (Table 14; entry 1). It is perplexing, moreover, that reversal of *anti* selectivity to *syn* selectivity is reported when the thioester is β-branched (*e.g.* *S*-*t*-butyl isobutylthioate).[93] Clearly, a more detailed study of the geometries of the aluminum enolates is needed before these results can be rationalized.

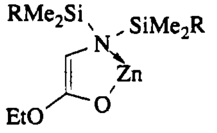

**(108)**

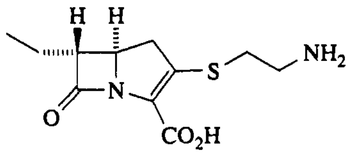

**(109)**

Reactions exhibiting diastereofacial selectivity, which occur when the imine or the enolate contains an endogenous stereocenter or a chiral auxiliary, have important applications for the synthesis of optically active β-lactams and β-amino carboxylic acid derivatives. Early work by Furukawa *et al.* has demonstrated the viability of preparing optically active β-amino acids from chiral imines.[103] For example, the Schiff base derived from (*S*)-α-methylbenzylamine (**110**) reacts with Reformatsky reagent (**111**) to give, after hydrolysis and removal of the chiral auxiliary, 3-amino-2,2-dimethyl-3-phenylpropionic acid (**112**) in 33% *ee* (Scheme 21). Similar Reformatsky reactions have been performed using (–)-menthyl esters but the enantiomeric excess values are lower.[104]

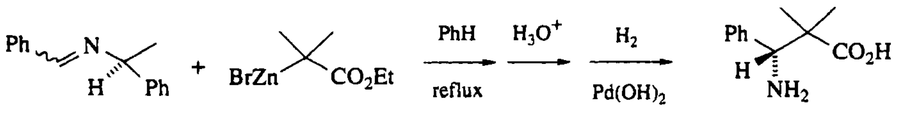

**(110)** **(111)** **(112)**

Scheme 21

Mukaiyama and coworkers have applied their thioester tin enolate methodology, previously described in Table 14 (entry 3), to reactions with chiral imines.[105] As shown in Scheme 22 and Table 16, tin(II) enolates of thioesters (**113**), generated by treating the lithium enolates with SnCl$_2$, add to optically active

**Table 15** *Anti* Selective Enolate–Imine Condensations[a]

| *Entry* | *Ester or equivalent* | *Enolate generation* | *Imine* | *Product* | *Yield (%) (anti:syn)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 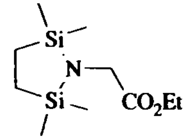 | i, LDA; ii, $ZnCl_2$ | 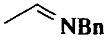 | 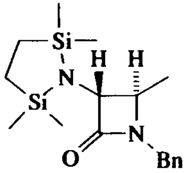 | 98 (100:0) | 99 |
| 2 | 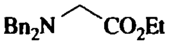 | LDA | 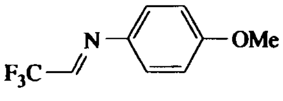 | 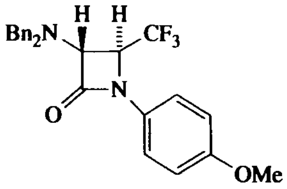 | 63 (100:0) | 101 |
| 3 | 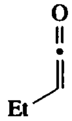 | $Sn(SBu^t)_2$, $Sn(OTf)_2$ | 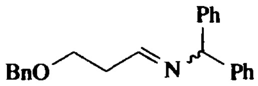 | 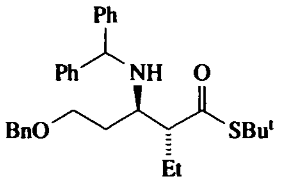 | 60 (88:12) | 102 |
| 4 | 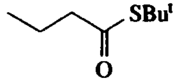 | i, LDA; ii, $Et_2AlCl$ | 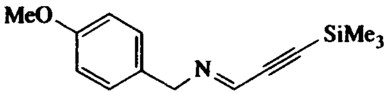 | 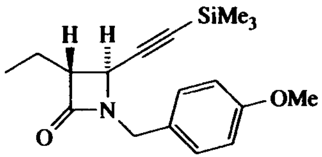 | 80 (3:1) | 93 |

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[a] Enolates are generated using LDA.

imine (**114**), affording predominantly *syn* adducts (**115**) with the indicated absolute stereochemistry in good yield. The authors rationalize the *syn* selective process (*syn*:*anti* > 9:1) by a *C*(*E*,*E*)$^\ddagger$ type of transition state. The diastereofacial selectivity, determined by converting β-amino esters (**115**) to β-lactams (**116**) and measuring their optically purity, is good (≈70% *ee*).

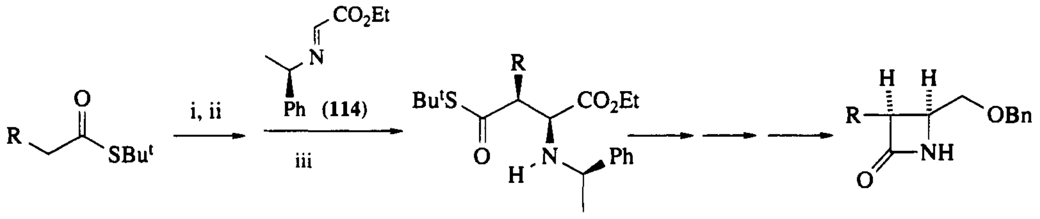

**(113)** **(115)** **(116)**

i, LDA, ether, –70 °C; ii, SnCl$_2$, –78 °C; iii, –70 °C, 3 h

**Scheme 22**

**Table 16** *Syn–Anti* and Diastereofacial Selectivities in the Reactions of Tin(II) Enolates of Thioester (**113**) with Imine (**114**)[105]

| Entry | *Thioester (113)* *R* | *(115)* *Yield (%)* | *Products* *Syn:anti* | *(116)* *ee (%)* |
|---|---|---|---|---|
| 1 | Me | 78 | 91:9 | 70 |
| 2 | Et | 78 | 95:5 | 72 |
| 3 | Pr$^i$ | 79 | 95:5 | 71 |

In another example by Mukaiyama and coworkers related to the synthesis of L-daunosamine (**119**), high diastereofacial selectivity is seen in the addition of the zinc enolate of *N*,*N*-dimethylacetamide to the chiral imine (**117**) derived from 2,3-*O*-cyclohexylidine-4-deoxy-L-threose, providing almost pure β-aminoamide (**118**) in good yield (Scheme 23).[106] This is one of the few examples of a stereoselective enolate–imine addition involving chirality attached to the imine α-carbon chain. A mechanistic rationale has not been proposed for the high level of diastereofacial selectivity, although the zinc cation must play an important role since the corresponding lithium enolate reacts to produce a 1:2 mixture of diastereomers enriched in the opposite C-3 *lyxo* configuration.

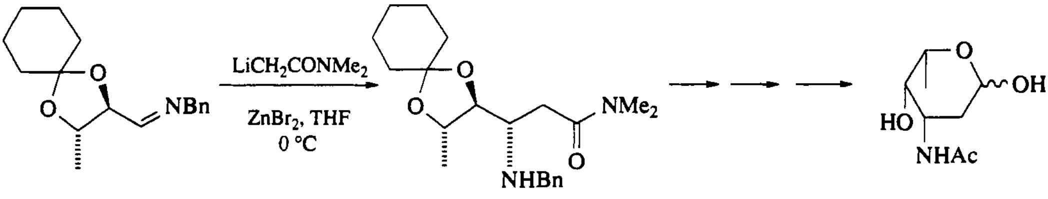

**(117)** **(118)** **(119)**

**Scheme 23**

Hart and coworkers[107] have prepared optically active β-lactams with extremely high *ee* values using lithium enolates of the 10-diisopropylsulfonamide isobornyl esters (**120**) developed by Oppolzer and coworkers for use in chiral Diels–Alder reactions and chiral alkylations.[108a,b] An example is shown in Scheme 24 involving the reaction of butyrate ester (**120**) with cinnamaldimine (**121**) to produce predominantly the *cis* β-lactam (**122**) in 91% *ee* (*cis*:*trans*, 10:1). Similar results are obtained using the corresponding isovalerate ester, with *cis* β-lactams predominating by an even greater ratio (>20:1). The absolute stereochemistry of β-lactam (**122**) is proven by its subsequent conversion to antibiotic (+)-PS-5 (**109**). Similar lithium enolate condensations have also been described by Bergbeiter, Newcomb and coworkers using (–)-menthyl esters; the *ee* values in those cases however are lower (4–60%).[89] Although no mechanistic rationale is proposed to account for the observed asymmetric induction, it is interesting to note that the *syn* selectivity inherent in condensations of enolates of simple alkyl esters is preserved despite the presence of the chiral auxiliary.

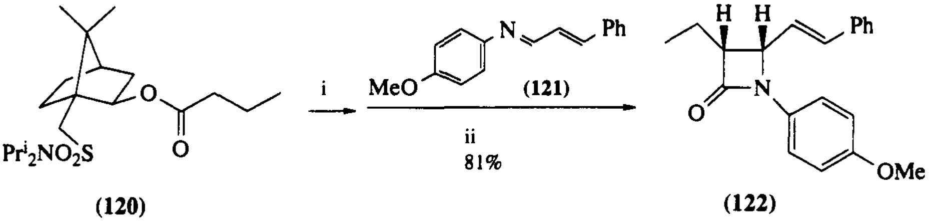

i, LDA, THF, –78 °C; ii, –78 °C to r.t.

Scheme 24

Widespread interest in the synthesis of the potent antibiotic thienamycin (**123**)[78] has led to numerous applications of enolate–imine condensations involving enolates of 3-hydroxybutyrates (**124**). These enolates, which constitute the C(7)–C(6)–C(8)–C(9) backbone of thienamycin according to the widely adopted retrosynthetic analysis in Scheme 25, are attractive intermediates because the corresponding 3-hydroxybutyrate esters are readily available in optically active form. Critical in this approach is good relative diastereofacial control between C-3 and the C-1′ hydroxy group of the β-lactam. The configuration at C-4 is less crucial because it can be easily readjusted later in the synthesis. The lithium dianion of 3-hydroxybutyrate (**125**), which is known to alkylate in a highly diastereoselective (>95:5) *anti* fashion due to the chelated form of the enolate,[109] has been used extensively in reactions with imines and *N*-silylimines since it is expected to produce β-lactam (**126**) with predictable relative stereocontrol between C-3 and C-1′ (Scheme 26). Use of dianion (**125**), however, requires inversion of stereochemistry at the C-1′ hydroxy group of β-lactam (**126**) to establish the correct thienamycin stereochemistry.

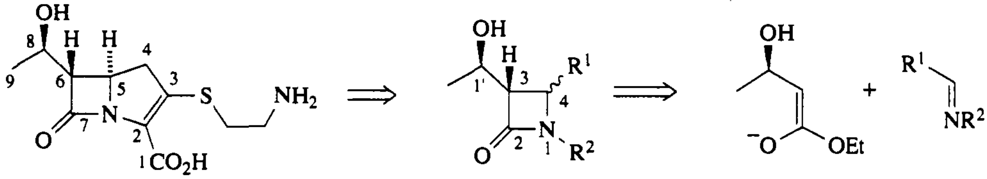

(**123**) (**124**)

Scheme 25

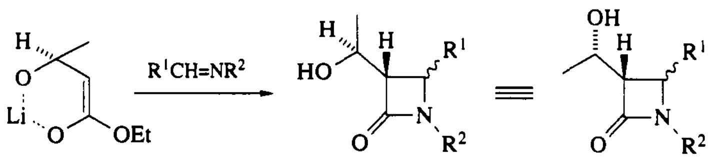

(**125**) (**126**)

Scheme 26

Condensation reactions between the lithium dianion of (*S*)-ethyl 3-hydroxybutyrate (**127**; R$^1$ = OH) and cinnamaldimine (**128**), in connection with the synthesis of thienamycin, have been reported independently by three groups: Georg *et al.*,[110] Cainelli *et al.*[111] and Hart and Ha.[112] Their results are summarized in Scheme 27 and Table 17 (entries 1–3); analogous reactions of dianion (**127**) with *N*-silylimines are discussed in Section 4.1.3.3.1. Of the four possible diastereomeric β-lactams (**129**)–(**132**) that can be produced in this reaction, the two that prevail, (**129**) and (**130**), contain the predicted relative stereochemistry at C-3 and C-1′. Subsequent inversion of the hydroxy groups of (**129**) and (**130**) led to intermediates which constituted formal total syntheses of thienamycin.[111,113] In addition to β-lactams (**129**) and (**130**), *trans* β-lactam (**131**) is sometimes isolated but *cis* β-lactam (**132**) is never observed. The product distributions are not uniform and may reflect the different bases used or the rate at which the reaction mixture is allowed to warm to room temperature. There is only weak *syn–anti* selectivity in these reactions even though the enolate is of known (*Z*)-geometry, which should favor *trans* β-lactam (**130**) *via* a (*Z*,*E*)$^\ddagger$ transition state. Although competing transition states may be involved, it is nevertheless interesting to note that the high level of *syn* selectivity usually observed for the reactions of lithium ester enolates is eroded due to, presumably, the abnormal (*Z*)-geometry of the enolate. When HMPA is used different product distributions are found,[111,114] which has been explained by reversibility in the carbon–carbon bond forming step (see Scheme 19). Possible epimerization of the product has been ruled out in control experiments. In a related reaction using the enolate of (*R*,*S*)-ethyl 3-(dimethylphenylsilyl)butyrate (entry 4) in which the silyl group serves as a synthon for the hydroxy group, there is an even more random product distribution. It is unclear what effect the bulky silyl group has on the enolate geometry or on the transition state.[115]

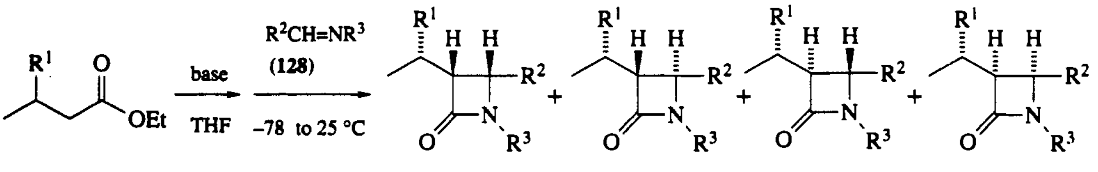

**(127)** **(129)** **(130)** **(131)** **(132)**

Scheme 27

**Table 17** Formation of β-Lactams in the Reactions of the Enolates of 3-Substituted Ethyl Butyrates (**127**) with Imines (**128**)

| | *Reactants* | | | | *Products* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *(127)* | *(128)* | | | *(129)* | *(130)* | *(131)* | *(132)* | |
| *Entry* | *R$^1$(Chirality)* | *R$^2$* | *R$^3$* | *Base* | | *Yield (%)* | | | *Ref.* |
| 1 | OH *(S)* | 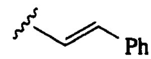 | 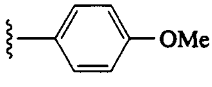 | 2 LICA | 45 | 45 | — | — | 110 |
| 2 | OH *(S)* | 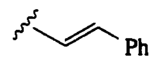 | 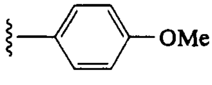 | 2 LHMDS | 35 | 54 | 9 | — | 111 |
| 3 | OH *(S)* | 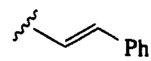 | 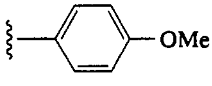 | 2 LDA | 25 | 27 | 6 | — | 112 |
| 4 | SiMe$_2$Ph *(S,R)* | Ph | 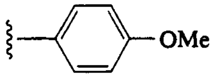 | LDA | 35 | 5 | 15 | 11 | 115 |

The limitation associated with inversion of the C-1′ hydroxy group using the 3-hydroxybutyrate dianion method for the synthesis of thienamycin has been overcome by Shibasaki and Iimori by using the *S*-phenyl thioester derivative of 3-(*R*)-hydroxybutyric acid (**133**; Scheme 28).[116] In this method, thioester (**133**) is converted to its boron enolate (**134**) using 9-BBN-OTf and Hunig's base with simultaneous protection of the 3(*R*)-hydroxy as a 9-BBN ether. Enolate (**134**) is then reacted with enolizable imine (**135**) corresponding to C(3)–C(5) of thienamycin to produce a mixture of β-amino thioesters (**136**). The stereochemical outcome of the condensation is revealed upon conversion of (**136**) to the mixture of O-TBDMS-protected β-lactams (**137**)–(**140**), in which β-lactam (**138**), with the correct stereochemistry for thienamycin, predominates by ~9:1. The possibility that epimerization occurs during the conversion of (**136**) to (**137**)–(**140**) has been ruled out. Based on the presumed (*Z*)-geometry of enolate (**134**),[117] the authors attribute the high level of *anti* selectivity (9:1) to a *C*(*Z*,*E*)$^\ddagger$ type transition state.[118] The *anti* selectivity of enolate (**134**) is also general for reactions with nonenolizable, alkynic and cinnamyl imines.[118,119] The authors discuss in a separate paper possible explanations for the high level of diastereofacial control between C-3 and C-1′.[118]

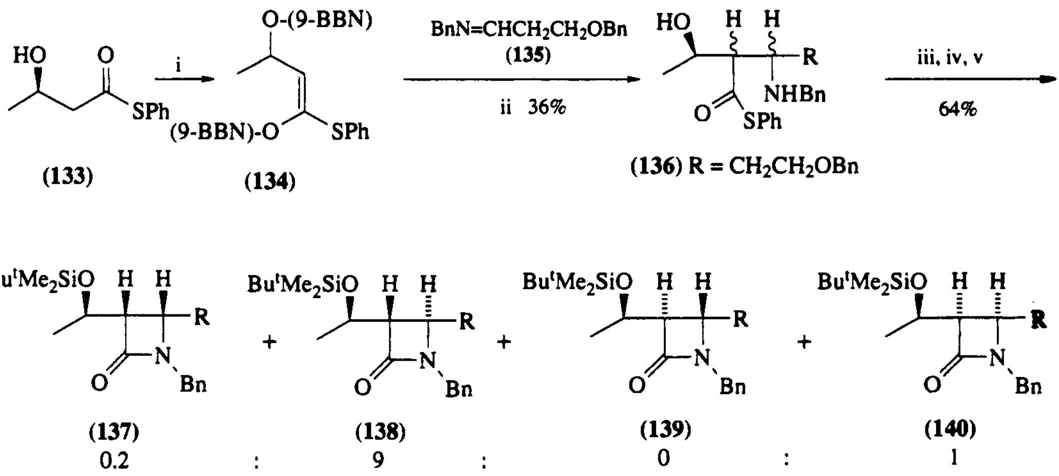
HO
O
SPh
(133)
i
O-(9-BBN)
(9-BBN)-O
SPh
(134)
BnN=CHCH2CH2OBn
(135)
ii 36%
HO H H
R
NHBn
O
SPh
(136) R = CH2CH2OBn
iii, iv, v
64%
Bu'Me2SiO H H
R
N
O
Bn
(137)
0.2
:
+
(138)
9
:
+
(139)
0
:
+
(140)
1

i, (9-BBN)OTf, $Pr^i_2NEt$, –70 to 35 °C; ii, –35 to 25 °C; iii, KOH, $H_2O$, THF; iv, 2,2'-dipyridyl disulfide–$Ph_3P$; v, $Bu^tMe_2SiOTf$, 2,6-lutidine, $CH_2Cl_2$

Scheme 28

Ketenimines, as demonstrated by Battaglia *et al.*,[120] display remarkable diastereofacial selectivity in enolate–imine condensations. In the example illustrated in Scheme 29, enolate (**141**) and ketenimine (**142**) condense to give (*Z*)-4-ethylidene-β-lactam (**144**). The reaction is general for several mono- and di-substituted enolates and is completely stereospecific for the (*Z*)-alkylidene product. The carbon–carbon bond forming step occurs at –78 °C to produce an intermediate metalloenamine (**143**) that cyclizes upon warming to room temperature. When the reaction is quenched at –78 °C, hydrolysis of intermediate (**143**) occurs and the corresponding β-keto ester is isolated. Yields of β-lactams range from 30 to 82% and are highest using α,α-disubstituted enolates; apparently enolization of ketenimine (**142**) is not a serious problem. The stereospecificity of the reaction is attributed to favored attack of the enolate on the diastereotopic face of the ketenimine opposite the α-substituent (Figure 5).[120]

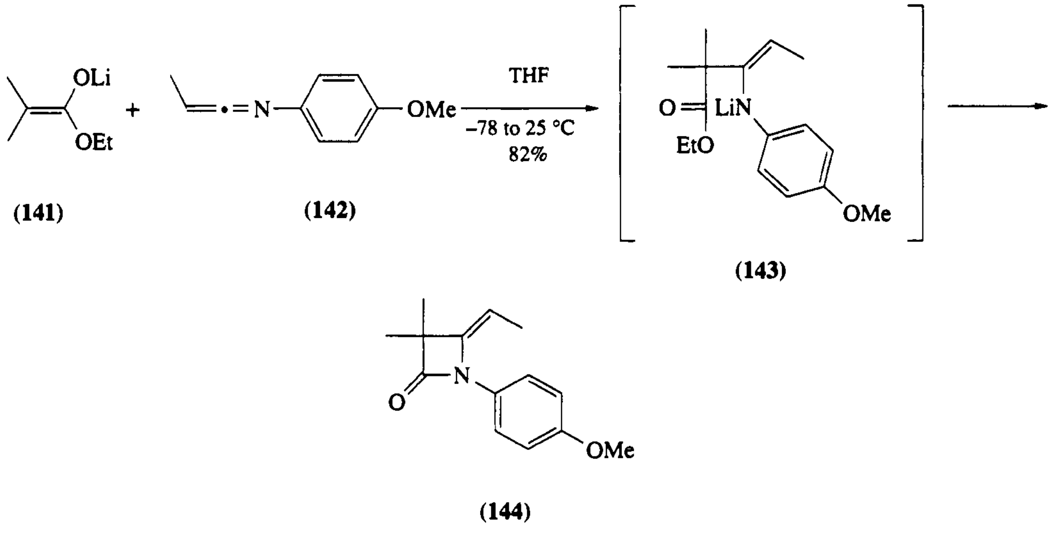
OLi
OEt
(141)
+
=•=N
OMe
(142)
THF
–78 to 25 °C
82%
O
LiN
EtO
OMe
(143)
O
N
OMe
(144)

Scheme 29

Phthalide enolates (**145**), which can be viewed as dihomoenolates, add to Schiff bases to produce intermediate adducts (**146**) that cyclize to mixtures of *cis* and *trans* 3-aryl-4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolones (**147**) and (**148**) (Scheme 30). As originally described by Dodsworth, Sammes and

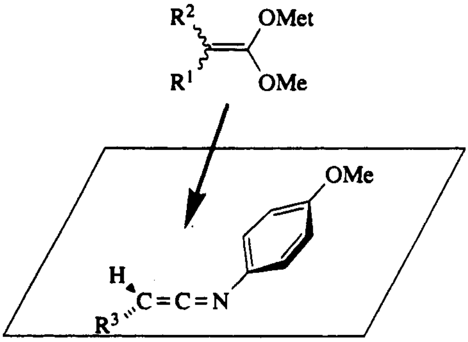

**Figure 5** Addition of enolates to ketenimines occurs on the diastereotopic face opposite the α-substituent ($R^3$)

coworkers,[121,122] *cis* products predominate consistently by ~2:1 over a series of nonenolizable arylimines; yields range from 40 to 70%. The preference for the *cis* isomer has been explained by a cyclic transition state in which the steric interactions of the α-substituent of the imine are minimized by placing it *gauche* to the lactone oxygen instead of to the more bulky aromatic portion of the phthalide (Figure 6). As will be discussed in Section 4.1.3.5, the opposite stereochemical outcome occurs in analogous reactions of cyclic imines (*i.e.* 3,4-dihydroisoquinolines).

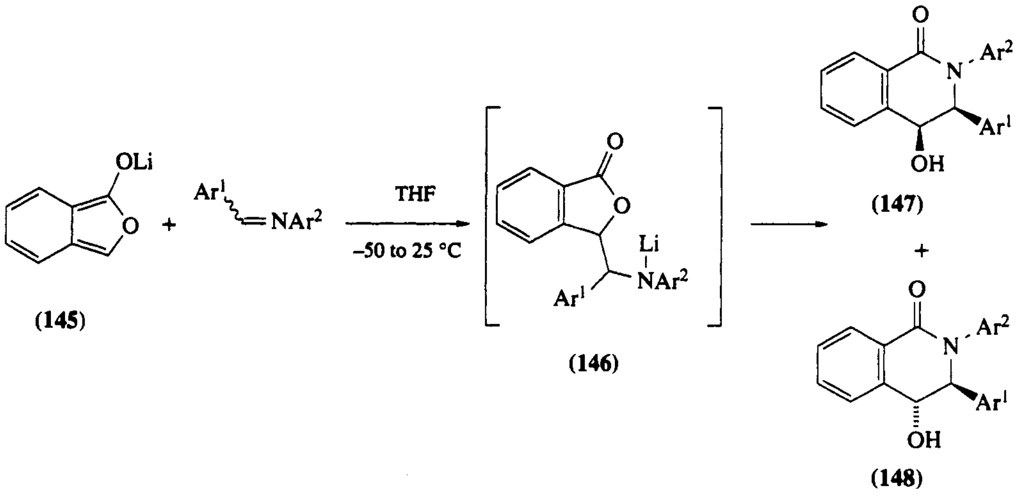

**Scheme 30**

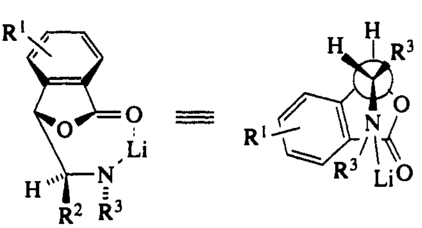

**Figure 6** Proposed transition state involved in the addition of phthalide enolates to imines[122]

Analogous condensations using lithium enolates of *N*,*N*-diethyl-*o*-toluamide (**149**) have been described by Clark and Jahangir for the synthesis of 3,4-dihydro-1(2*H*)-isoquinolones[123,124] (**151**; Scheme 31). It is fortunate that the enolate–imine addition–cyclization process occurs at low temperature, since warming the reaction mixture to room temperature, a common practice in many enolate–imine additions, leads to side reactions due to the instability of the 4-lithiated derivative (**150**) formed by release of lithium diethylamide. The authors have exploited the *in situ* formation of (**150**) for the synthesis of 4-substituted isoquinolones by trapping it with electrophiles. A cycloaddition mechanism *via* an *o*-quinodimethane (a vinyl ketene) formed by possible loss of lithium diethylamide from (**149**) does not seem to be involved. Yields of 3,4-dihydro-1(2*H*)-isoquinolones (**151**) are moderate (30–50%) for the 'one-pot' process. Besides arylimines, certain bulky enolizable imines such as those derived from cyclohexanone and cyclohexanecarbaldehyde also react. Analogous reactions using dilithiated *N*-methyl-*o*-toluamide have also been reported; the adducts, however, do not cyclize *in situ*.

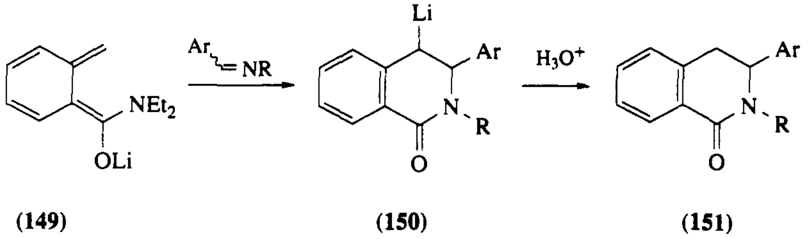

**Scheme 31**

Clark and Jahangir have elegantly applied the above methodology to the total synthesis of (±)-corydalic acid methyl ester (**155**), an alkaloid isolated with protoberberine and benzo[*c*]phenanthridine from *Corydalis incisa* (Scheme 32).[125] The *o*-toluamide enolate (**152**), which in this case is substituted at the methyl group, adds stereospecifically to imine (**153**), affording *trans*-isoquinolone (**154**). The overall yield of (**154**) is based on the isolation of some uncyclized aminoamide (28%), which is cleanly cyclized to (**154**) by treatment with *t*-butyllithium. Because the uncyclized aminoamide contains the same relative stereochemistry as the cyclized material, it is likely that the overall stereospecificity of the reaction is reflected in the carbon–carbon bond forming step and not *via* epimerization at C-4. Conversion of isoquinolone (**154**) to (±)-corydalic acid (**155**) is accomplished by elaboration of the vinyl group and reduction of the lactam.

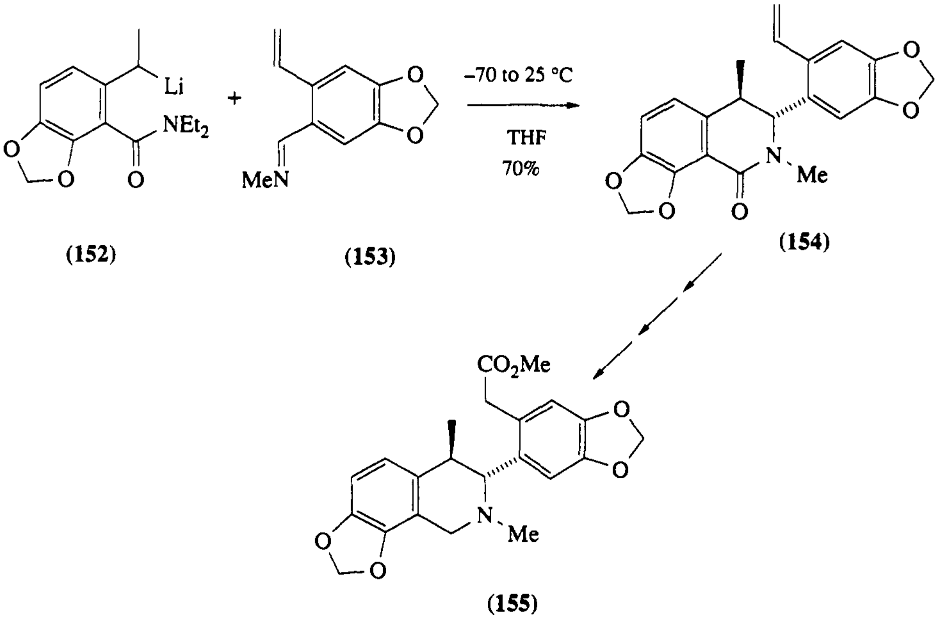

**Scheme 32**

### *(iii) Reactions with silyl ketene acetals*

The condensation of silyl ketene acetals (**156**) with imines in the presence of Lewis acids, usually $TiCl_4$, to afford β-lactams or β-amino esters (equation 18) was first reported by Ojima *et al.*[126] The mechanism of β-lactam formation is similar to the one previously outlined in Scheme 19 for enolate–

imine additions, involving metalated amine intermediates (**98**) and (**99**) (M = TiCl$_3$), which undergo cyclization. Aspects of the initial carbon–carbon bond-forming step, however, are less clear. Ojima *et al.* postulate that titanium enolates generated by cleavage of the silyl ketene acetal by TiCl$_4$ add to imines *via* pericyclic transition states.[126,127] On the other hand, recent stereochemical evidence supports an open transition state. Both mechanisms will be discussed in light of the current investigations.

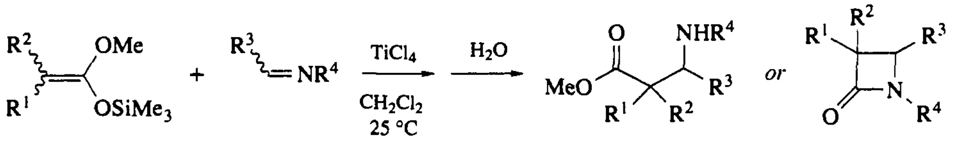

(18)

**(156)** **(157)** **(158)** **(159)**

The review by Evans *et al.*[10] has covered the early investigations of Ojima *et al.*[126–128] and only some brief generalizations are presented here. Yields using nonenolizable imines (**157**; R$^3$ = Ph) are good to excellent (70–95%) based on a twofold excess of imine. Enolizable imines (**157**; R$^3$ = Et, Pr$^i$) also react but in lower yield (40–50%). Formation of β-lactams (**159**) occurs readily with *N*-alkylimines (**157**; R$^4$ = Bn, Me, Ph(Me)CH) but not with *N*-arylimines (**157**; R$^4$ = Ph), in which case β-amino esters (**158**) are isolated. That β-lactam formation occurs with *N*-arylimines in condensation reactions with lithium and zinc enolates indicates that the corresponding titanium amide intermediates (**98**) and (**99**) (R$^3$ = Ph; M = TiCl$_3$; Scheme 19) are less nucleophilic. High levels of diastereofacial selectivity are also observed using chiral imines derived from (*S*)-(1-arylethyl)amines[127] and (*S*)-valine methyl ester.[128] The *ee* values of these β-lactam-forming reactions are 40–70% and 90–98%, respectively. In the latter case, formation of a titanium template between the imine lone pair and the carbomethoxy group is proposed to account for the high level of asymmetric induction.

In an extension of their earlier work, Ojima and coworkers have described analogous reactions using vinyl silyl ketene acetals (**160**; equation 19).[129] The carbon–carbon bond forming step in these reactions occurs exclusively at the terminal carbon of the vinyl silyl ketene acetal (**160**) to give cyclized 5,6-dihydro-2-pyridones (**162**), methyl 5-amino-2-pentenoates (**163**), or mixtures. Steric and electronic factors play an important role in the formation of cyclized products, which are favored by the lack of an α-substituent (R$^1$) and the presence of an *N*-alkyl group on the imine (R$^4$). Formation of (**162**) and (**163**) proceeds by a common metalated intermediate, since in reactions that form cyclized products (**162**), quenching at –50 °C leads to acyclic products. Yields are good to excellent when corrected for recovered imine (**161**), but a 100% excess of vinyl silyl ketene acetal (**160**) must be employed. It is curious to note that these reactions require much lower initial temperatures (–100 °C) than those of silyl ketene acetals.

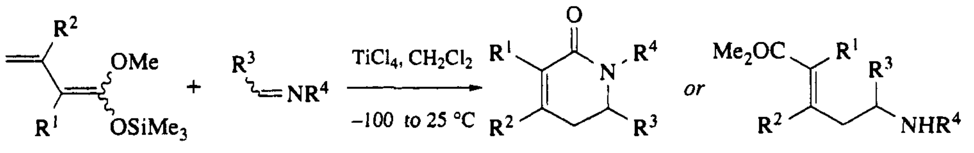

(19)

**(160)** **(161)** **(162)** **(163)**

As noted above, β-lactam formation in reactions of silyl ketene acetals with imines is dependent on the N-substituent of the imine. In a new variation using ketene bis(trimethylsilyl) acetals (**164**), Dubois and Axiotis have reported that β-lactams (**167**) can be obtained exclusively in TiCl$_4$-catalyzed reactions with nonenolizable (R$^3$ = Ph) and hindered enolizable imines (**165**; R$^3$ = Pr$^i$; Scheme 33; Table 18).[130] In contrast to the reactions of silyl ketene acetals which produce acyclic adducts using *N*-arylimines, the exclusive formation of β-lactams in the reactions of ketene bis(trimethylsilyl) acetals (**164**) with *N*-arylimines is attributed to the superior leaving group ability of the trimethylsilyloxy group in the metalated amine intermediate (**166**). Yields of β-lactams (**167**) are good (65–75%) and are based on stoichiometric amounts of reagents. No relative stereochemistry is reported in the cases involving unsymmetrical ketene bis(trimethylsilyl)acetals (entries 4 and 5).

Chiral silyl ketene acetals derived from (1*S*,2*R*)-*N*-methylephedrine (**168**), known to exhibit high levels of *syn–anti* and diastereofacial selectivities in the aldol condensation,[131] have been used by Gennari *et al.* in TiCl$_4$-mediated imine condensations for the asymmetric synthesis of β-lactams (Scheme 34).[132,133] β-Amino esters (**169**) are produced in these reactions, and are characterized by their sub-

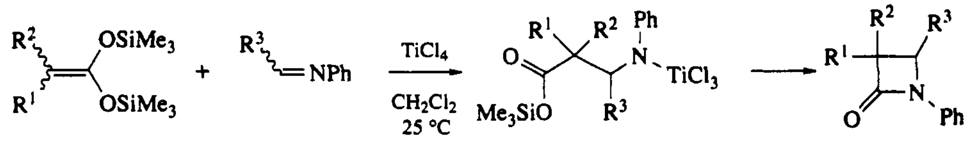

**(164)** **(165)** **(166)** **(167)**

Scheme 33

**Table 18** Formation of β-Lactams (**167**) *via* $TiCl_4$-catalyzed Condensations of Ketene Bis(trimethylsilyl) Acetals (**164**) with Imines (**165**)[130]

| *Entry* | *Ketene bis(trimethylsilyl) acetal* (**164**) *R*$^1$ | *R*$^2$ | *Imine* (**165**) *R*$^3$ | *β-Lactam* (**167**) *Yield (%)* |
|---|---|---|---|---|
| 1 | Me | Me | Ph | 75 |
| 2 | Me | Me | Pr$^i$ | 66 |
| 3 | —$(CH_2)_5$— | | Ph | 60 |
| 4 | Ph | H | Ph | 69 |
| 5 | Ph | H | Pr | 65 |

sequent conversion to the corresponding β-lactam derivatives (**170**). In the examples shown in Table 19, it is interesting to note that *anti* selectivity is observed in the reaction of an (*E*)-silyl ketene acetal with benzylideneaniline (entry 1), since the opposite *syn* selectivity is normally found in the corresponding reactions of (*E*)-enolates, presumably *via* a *C*(*E*,*E*)‡ transition state. This dichotomy between the *syn–anti* selectivity of enolates and silyl ketene acetals possessing like geometry strongly suggests that the mechanisms of the two reactions are different. Thus, addition of silyl ketene acetals to imines may not involve free enolates as originally proposed,[126] but rather direct addition to the activated imine *via* an open transition state to form an oxonium ion intermediate (**171**), followed by cleavage of the silyl group (Scheme 35). Heathcock and coworkers have proposed similar open transition states for related Lewis acid mediated reactions of enol silanes with aldehydes.[134] It is also curious that the opposite *syn* selectivity is observed with α-carboethoxyimines (entries 2 and 3), even when the silyl ketene acetals are 1:1 mixtures of (*E*)- and (*Z*)-isomers. The authors propose that the different stereochemical outcome of reactions of arylimines and α-carboethoxyimines is due to the formation of a five-membered ring titanium chelate complex in the case of the α-carboethoxyimine. Clearly, a more systematic study of the *syn–anti* selectivity of these reactions and its relationship to the geometry of the silyl ketene acetal is needed. The high diastereofacial selectivities of these reactions are also noteworthy, especially in the case involving a single silyl ketene acetal geometry which gives the corresponding β-lactam in >95% *ee* (entry 1). In the analogous $TiCl_4$-mediated aldol condensation of silyl ketene acetals (**168**), which gives similar high levels of asymmetric induction, a six-coordinate intermediate titanium complex with binding to the ephedrine dimethylamine and aldehyde carbonyl groups has been suggested.[131]

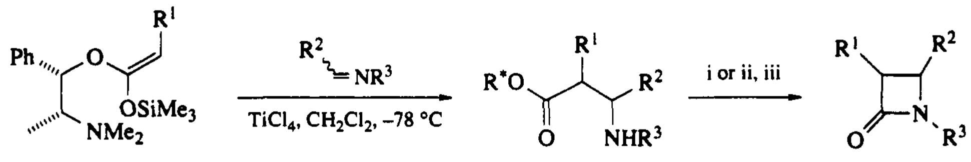

**(168)** **(169)** **(170)**

i, LHMDS, THF, –10 °C; ii, $HCO_2H$, MeOH, Pd–C; iii, 2-chloro-1-methylpyridinium iodide, $Et_3N$, MeCN

Scheme 34

Guanti and coworkers have reported that catalytic amounts (0.1 equiv.) of TMS-OTf can be used in place of stoichiometric amounts of $TiCl_4$ in silyl ketene acetal–imine additions.[135] When conducted at the optimal temperature of –65 °C, β-amino esters enriched in the *anti* diastereomer are obtained in 45–85% yields. Use so far has been limited to nonenolizable imines. Interestingly, the observed *anti* stereoselectivity is independent of the geometry of the silyl ketene acetal, further evidence that a nonpericyclic mechanism is involved in the Lewis acid catalyzed addition of silyl ketene acetals to imines. An applica-

**Table 19** Condensations of Silyl Ketene Acetal (**168**) with Imines Mediated by $TiCl_4$

| *Entry* | *R$^1$* | *Silyl ketene acetal (168) Geometry* | *Imine* | *Conversion to (170)$^a$* | *Major product (170)* | *ee (%)* | *Syn:anti selectivity* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | *(E)* | PhCH=NPh | i | 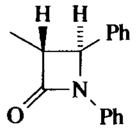<br>59% | >95 | <1:10 | 132 |
| 2 | Et | *(E)*:*(Z)* 1:1 | $EtO_2CCH=NBn$ | ii, iii | 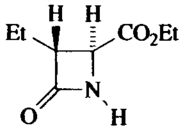<br>46% | 50 | 8:1 | 133 |
| 3 | Et | *(E)*:*(Z)* 1:1 | 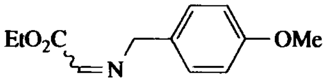 | ii, iii | 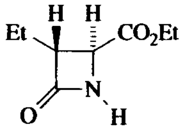<br>46% | 75 | 7:1 | 133 |

[a] See Scheme 34.

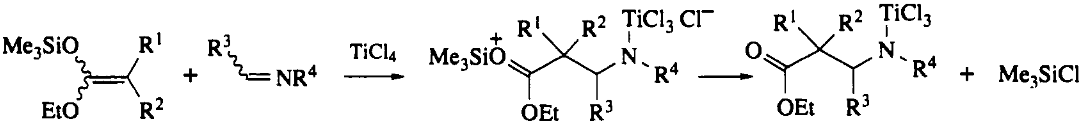

**(171)**

Scheme 35

tion of this method to the synthesis of thienamycin using the hydroxysilylated silyl ketene acetal derived from racemic 3-hydroxybutyrate (**172**) (unspecified enolate geometry) is shown in Scheme 36.[136] The condensation of (**172**) with benzylideneaniline in the presence of TMS-OTf is amazingly stereospecific, giving a single β-amino ester (**173**). The relative stereochemistry of β-amino ester (**173**) was determined upon subsequent conversion to β-lactam (**174**) and was found to be correct for thienamycin at C-3 and C-1′. It is interesting to note that the β-silyloxy group changes the selectivity of these reactions from *anti* to *syn*; the silyl ketene acetal derived from methyl propionate condenses with benzylideneaniline to give exclusively the *anti* β-amino ester.[135]

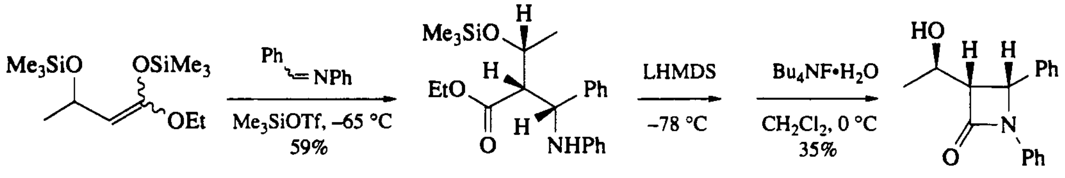

**(172)** **(173)** **(174)**

Scheme 36

### *4.1.3.2.3 Reactions with ketones*

Reactions of free ketones with imines are far more restricted than those with preformed iminium salts. Examples of ketone–imine condensations are included in several reviews[3,4,6,7] and are limited to the use of arylimines, mainly benzylideneaniline. Blatt and Gross have noted that the reproducibility of uncatalyzed additions of ketones to Schiff bases is poor but can be improved by the addition of small amounts of hydrochloric acid.[137] The highest yields of β-amino ketones are obtained using 10 mol % of concentrated hydrochloric acid and 95% ethanol as solvent, and by performing the reaction at room temperature. The reaction, however, is of limited applicability, as it is restricted to methyl ketones and cycloalkanones. Deamination leading to unsaturated ketones is a major side reaction. In addition to hydrochloric acid, boron trifluoride etherate has been used as a catalyst in reactions of aromatic imines with methyl ketones, cyclic ketones[138] and an epoxy ketone.[139]

Examples of ketone–imine additions involving kinetically formed enolates or enol silanes are surprisingly few in comparison to those of carboxylic acid derivatives and silyl ketene acetals. An interesting example, nevertheless, has been reported independently by Broadly and Davies[140] and Liebeskind *et al.*[141] involving the use of the chiral–racemic, acyliron complex [$\eta^5$-CpFe(PPh$_3$)(CO)COMe] (**175**), treated here as a ketone. Enolates of (**175**) condense with nonenolizable imines with impressive levels of 1,4-diastereofacial selectivity to form predominately diastereomer (**177**; Scheme 37). For example, the diethylaluminum enolate (**176**) reacts with benzylidenepropylamine to afford a >20:1 ratio of (**177**):(**178**) ($R^1$ = Ph; $R^2$ = Pr$^n$).[141] Lithium enolates also exhibit high levels of diastereofacial selectivity but are less successful in reactions with *N*-alkylimines. Yields are also good (80–90%) if corrected for recovered ketone (**175**). Liebeskind and coworkers rationalize the diastereofacial selectivity of the reaction by invoking two possible chair-like transition states (**179a**) and (**179b**) (Figure 7). It is argued that the imine prefers to condense in such a way as to minimize the steric interaction between $R^1$ and the bulky PPh$_3$ ligand of the iron enolate; thus attack at the accessible diastereotopic face of the enolate in transition state (**179a**) is favored, leading to diastereomer (**177**). An alternative model suggested by Broadly and Davies proposes that imine addition occurs opposite to the PPh$_3$ group in rotomer (**180**).[140] A detailed discussion of the two mechanisms is presented in a full paper by Liebeskind *et al.*[142] The use of enolates of (**175**) in optically active form should have important applications to the asymmetric synthesis of β-lactams, since β-amino iron acyls can be converted to β-lactams by oxidative insertion.[143]

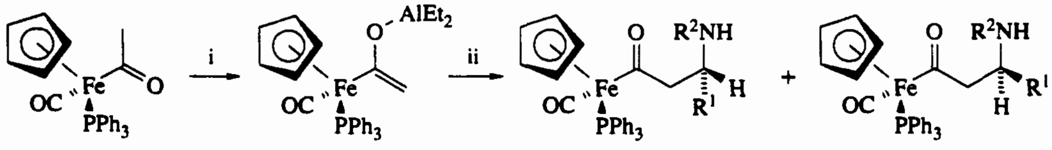

(**175**) (**176**) (**177**) (**178**)

i, LDA, THF, –42 °C, $Et_2AlCl$; ii, $R^1CH=NR^2$, –42 °C

**Scheme 37**

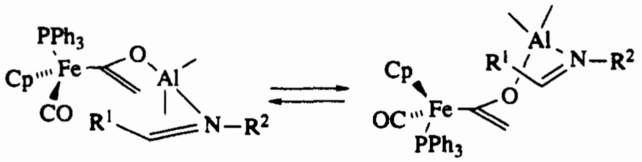

(**179a**) (**179b**)

**Figure 7** Proposed transition states involved in the addition of the enolate of acyliron complex (**175**) to imines[141]

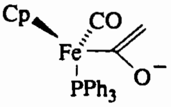

(**180**)

Enol silanes (**181**), as reported by Pilli and Russowsky, add to arylimines (**182**) in the presence of catalytic amounts of TMS-OTf to afford *N*-aryl-β-amino ketones (**183**; equation 20).[144] The reaction is carried out by adding the enol silane to the imine in the presence of 15 mol % of TMS-OTf at 0 °C in $CH_2Cl_2$, followed by aqueous work-up. Yields range from 50% to 98% in a series of benzylideneaniline derivatives using the enol silanes derived from acetophenone and *t*-butyl methyl ketone. The extent to which the reaction may be limited to nonenolizable imines, as in the analogous TMS-OTf-promoted reactions of silyl ketene acetals (see Section 4.1.3.2.2.iii),[135,136] is not reported. The authors describe some spectral characteristics of an insoluble material formed by treating benzylideneaniline with TMS-OTf in $CHCl_3$. The data are consistent with the derived *N*-silyliminium salt of (**182**), the putative reactive intermediate.

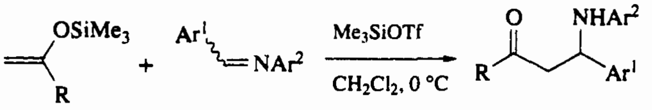

(20)

(**181**) R = Ph, Bu$^t$ (**182**) (**183**)

### 4.1.3.3 N-Heterosubstituted Imines

#### *4.1.3.3.1* N-*Silylimines*

*N*-Silylimines display similar reactivity and stereoselectivity to *N*-arylimines in reactions with enolates and silyl ketene acetals; their advantage is that they provide easy access to *N*-unsubstituted β-lactams by protodesilylation during work-up. Like acyclic imines, they exist in one geometrical form, presumably (*E*). *N*-Silylimines (**187**) are usually prepared *in situ* by condensing lithium hexamethyldisilazide (LHMDS; **185**) with an aldehyde (**184**) to form an initial alkoxide adduct (**186**), which spontaneously loses trimethylsilyl oxide in analogy to the Peterson alkenation (Scheme 38). If desired, *N*-silylimines can be isolated by distillation, providing they are nonenolizable. A more detailed discussion of the preparation of N-TMS and N-TBDMS imines, their mechanism of formation and their structure, is presented in an article by Colvin *et al.* related to condensations of silyl ketene acetals with *N*-silylimines.[145]

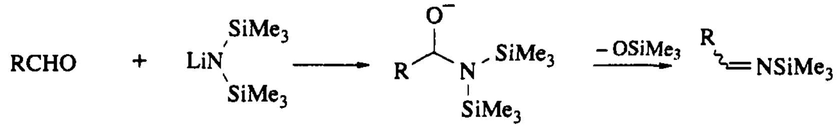

**(184)** **(185)** **(186)** **(187)**

Scheme 38

Pioneering investigations by Hart and coworkers have provided much of the insight into the scope and stereoselectivity of enolate–*N*-silylimine condensations. In the original paper, the viability of these reactions was demonstrated using mainly α,α-disubstituted esters (**188**), which add *via* their lithium enolates to nonenolizable *N*-silylimines (**189**) to afford mixtures of diastereomeric *N*-unsubstituted β-lactams (**190**) and (**191**) following aqueous acidic work-up (Scheme 39; Table 20; entries 1–6).[146] *N*-Silylimines derived from cinnamaldehyde and 3-(trimethylsilyl)propargylaldehyde (entries 4–6) can be used to facilitate further elaboration of C-4 of the β-lactam. The mechanism of β-lactam formation is postulated to be stepwise, based on the analogy to the reactions of *N*-aryl- and *N*-alkyl-imines (see Scheme 19) and the known ability of β-trimethylsilyl(amino) esters to undergo cyclization to β-lactams.[145,147] Further studies by Hart and coworkers have shown that β-lactams can be prepared using lithium enolates of mono-α-substituted esters (entries 8–14).[148] The reported failure of these enolates to produce β-lactams in good yields in reactions with *N*-arylimines[89] implies that the carbon–carbon bond forming step in reactions of *N*-silylimines occurs at lower temperatures than those of *N*-arylimines, and decomposition of the enolate is therefore less likely. However, in the case of the unsubstituted enolate (entry 7), which is more prone to decomposition, the β-lactam is obtained in poor yield. Under the conditions of enolate generation (THF, −78 °C) that produce predominantly (*E*)-enolates, stereocontrol in favor of *cis* β-lactams (**190**) is excellent (entries 8, 10 and 12). These results are consistent with a $C(E,E)^{\ddagger}$ transition state and parallel the earlier investigations of Luche and Kagan where *syn* selectivity is observed in analogous reactions using Reformatsky reagents.[91,149] Not surprisingly, erosion in stereoselectivity occurs using (*Z*)-enolates, prepared according to the Ireland procedure using HMPA,[150] resulting in nearly 50:50 mixtures of *cis* and *trans* β-lactams (entries 9, 11 and 13). Control experiments demonstrate that HMPA affects only the enolate geometry and does not promote epimerization of the β-lactam. It is worth noting that *N*-aryl-β-lactams epimerize in the presence of LDA/HMPA as demonstrated by the conversion of the *cis* *N*-phenyl derivative of β-lactam (**190**) of entry 12 to the *trans* *N*-phenyl derivative of β-lactam (**191**).[148] Thus, in β-lactam-forming reactions that require coordinating solvents, *N*-silylimines should react with more predictable stereocontrol than *N*-arylimines.

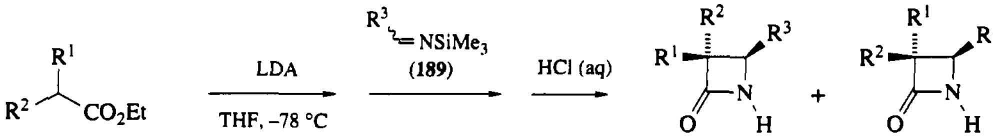

**(188)** **(190)** **(191)**

Scheme 39

Although formation of enolizable *N*-silylimines is usually accompanied by isomerization to the enamine and by deprotonation of the aldehyde precursor,[145] *N*-silylimines derived from enolizable aldehydes have nevertheless been reported by Cainelli, Panunzio and coworkers to condense with enolates (Table 20; entries 15–17).[151] The temperature at which the *N*-silylimine is generated, −30 °C, may be critical since nonenonolizable *N*-silylimines are normally generated at -70 °C. Condensations with enolizable *N*-silylimines, like those with nonenolizable *N*-silylimines, are stereoselective and produce mainly *cis* β-lactams. The yields (30–40%), however, are lower.

**Table 20** β-Lactam-forming Reactions of *N*-Silylimines (**189**) and Lithium

| | *Ester* | | *N-Silylimine* | | *β-Lactams* | |
|---|---|---|---|---|---|---|
| | *(***188***)* | | *(***189***)* | | *(***190***):(***191***)* | |
| *Entry* | $R^1$ | $R^2$ | $R^3$ | *Yield (%)* | *Ratio* | *Ref.* |
| 1 | Me | Me | Ph | 72 | | 146 |
| 2 | Me | SPh | Ph | 58 | 2.4:1 | 146 |
| 3 | H | SPh | Ph | 53 | 9.6:1 | 146 |
| 4 | Me | Me | PhCH=CH | 69 | | 146 |
| 5 | Me | Me | TMSC≡C | 79 | | 146 |
| 6 | Me | SPh | TMSC≡C | 74 | 2.7:1 | 146 |
| 7 | H | H | Ph | 14 | | 148 |
| 8 | Me | H | Ph | 44 | 93:7 | 148 |
| 9 | Me | H | Ph | 44 | 43:57[a] | 148 |
| 10 | Et | H | Ph | 72 | 100:0 | 148 |
| 11 | Et | H | Ph | 66 | 42:58[a] | 148 |
| 12 | Pr$^i$ | H | Ph | 81 | 99:1 | 148 |
| 13 | Pr$^i$ | H | Ph | 86 | 50:50[a] | 148 |
| 14 | Bu$^t$ | H | Ph | 40 | 100:0 | 148 |
| 15 | Me | H | Me | 38 | 86:14 | 151 |
| 16 | Et | H | $C_9H_{19}$ | 44 | 92:8 | 151 |
| 17 | 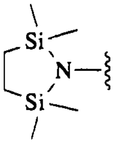 | H | Me | 40 | 90:1[b] | 151 |
| 18 | 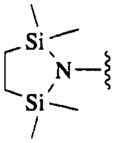 | H | TMSC≡C | 80 | 7:93[c] | 99 |
| 19 | 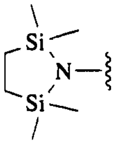 | H | Ph | 90 | 30:70[c] | 99 |
| 20 | $TMS_2N$ | H | Ph | 70 | 11:89[c] | 99 |

[a] HMPA is used as a cosolvent in the generation of the enolate. [b] The product is isolated as its *N*-CBZ derivative. [c] $ZnCl_2$ is added to the lithium enolate in ether prior to addition of the *N*-silylimine.

(*Z*)-Zinc enolates of *N*,*N*-bissilylglycine esters, according to van Koten and coworkers, condense with *N*-silylimines with high *anti* selectivity (Table 20; entries 18–20).[99,100] These results parallel those previously described in Section 4.1.3.2.2.i using *N*-aryl- and *N*-alkyl-imines and are consistent with a *C*(*Z*,*E*)‡ transition state. Reactions of *N*-silylimines are slightly less *anti* selective, however, than those of *N*-aryl- and *N*-alkyl-imines. Retroaldolization prior to cyclization has been cited as a possible cause for the erosion in stereoselectivity based on the slow rates of cyclization found in the reactions of entries 19 and 20.

Condensations of enolates of 3-substituted butyrates (**192**) with *N*-silylimines (Scheme 40), like those with *N*-arylimines (see Section 4.1.3.2.2.ii), have been used widely in the synthesis of thienamycin. Examples are shown in Table 21, where it should be noted that entries 2, 3 and 5 have a direct parallel with entries 3, 2 and 4, respectively, in Table 17, describing related *N*-arylimine condensations. The product distributions of diastereomeric β-lactams (**194**)–(**197**) in *N*-silylimine condensations are similar to those found in *N*-arylimine condensations, which is not surprising in view of their similar *syn–anti* selectivities. *N*-Silylimines exhibit somewhat higher stereoselectivity, however, as evidenced by the minimal formation of β-lactams (**196**) and (**197**). Even the reaction of ethyl 3-(dimethylphenylsilyl)butyrate (entry 5) is considerably more stereoselective than its *N*-aryl counterpart (Table 15; entry 4), providing almost exclusively a single β-lactam (**194**). Nakai and coworkers have noted that in the reactions of the propargyl-*N*-silylimine (entry 4), higher yields are obtained using (*S*,*R*)-methyl 3-hydroxybutyrate instead of the corresponding ethyl ester and LHMDS instead of LDA as base.[152] In an alternative approach to the synthesis of thienamycin, these workers have also prepared the β-lactams of entry 4 in the enantiomeric series using (*R*)-methyl 3-hydroxybutyrate.[153–155]

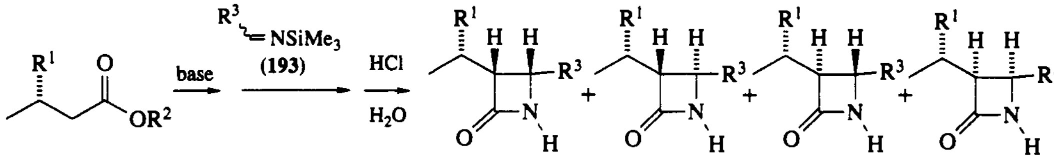

**(192)** **(194)** **(195)** **(196)** **(197)**

**Scheme 40**

**Table 21** β-Lactam-forming Reactions of *N*-Silylimines (**193**) and Enolates of 3-Substituted Ethyl and Methyl Butyrates (**192**)

| *Entry* | *Ester (192)* | | *N-Silylimine (193)* | | *β-Lactams* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *$R^1$ (Chirality)* | *$R^2$* | *$R^3$* | *Base* | *(194)* | *(195)* | *(196)* | *(197)* | *Ref.* |
| | | | | | *Yield (%)* | | | | |
| 1 | OH (*S,R*) | Et | PhSCH=CH | 2LDA | 31 | 8 | 2 | — | 148 |
| 2 | OH (*S*) | Et | PhCH=CH | 2 LDA | $27^{a}$ | $16^{a}$ | — | — | 112 |
| 3 | OH (*S*) | Et | PhCH=CH | 2 LHMDS | 35 | 15 | — | — | 156 |
| 4 | OH (*S,R*) | Me | TMSC≡C | 2 LHMDS | 56 | 19 | — | — | 152 |
| 5 | $Me_2PhSi$ (*S,R*) | Et | Ph | LDA | 63 | — | b | — | 115 |

[a]Products are characterized as *O*-TBDMS derivatives. [b]Trace.

Cainelli, Martelli and coworkers have reported an interesting case of combined *syn–anti* and diastereofacial selectivity using chiral *N*-silylimine (**199**), prepared *in situ* from (*S*)-O-TBDMS-lactic aldehyde (**198**).[157] As shown in Scheme 41, condensation of the lithium enolate of *t*-butyl butyrate with *N*-silylimine (**199**) affords essentially a single β-lactam (**200**), contaminated with only 4% of the corresponding other *trans* diastereomeric β-lactam. The authors propose that the high level of diastereofacial selectivity (14:1) is due to the formation of lithium chelate (**201**), which undergoes attack by the enolate from the least hindered π-face of the imine. The authors do not discuss the unusual *anti* selectivity of this reaction.

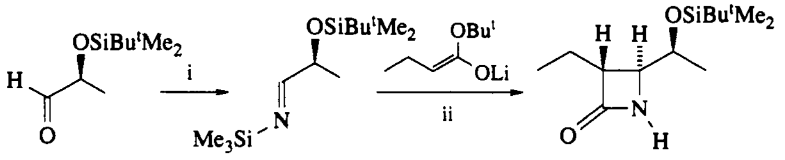

**(198)** **(199)** **(200)**

i, LHMDS, THF, –40 °C; ii, THF, –78 °C to r.t.

**Scheme 41**

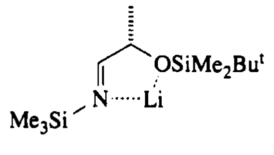

**(201)**

Condensations of *N*-silylimines with silyl ketene acetals have been reported by Colvin and coworkers using $ZnI_2$ as catalyst (Scheme 42; Table 22).[145,158] Interestingly, titanium tetrachloride, the catalyst of choice in the corresponding reactions of silyl ketene acetals with *N*-aryl- and *N*-alkyl-imines, is not effective in these reactions. When an equivalent of Bu$^t$OH is present in the reaction, the products are β-(trimethylsilyl)amino esters (**204**), which can be easily cyclized to β-lactams (**205**) by *in situ* addition of MeMgBr. Without the presence of Bu$^t$OH to protonate the initial adduct, cross-condensation side reactions occur between the adduct and unreacted *N*-silylimine. Yields of β-lactams, 50–80%, are generally comparable to those obtained using enolates. Figure 8 depicts two proposed synclinal transition states, (**206**) and (**207**), leading to *trans* and *cis* adducts, respectively, used by Colvin and coworkers to explain the *anti* selectivity of these reactions.[145] Transition state (**206**) is preferred, based on the more stable *anti* relationship between the silyl ketene acetal and the R group of the *N*-silylimine, whereas in transition state (**207**) they are in a less favored *gauche* relationship. This model is also consistent with the fact that the *syn–anti* selectivity of these reactions is independent of the silyl ketene acetal geometry. These results parallel those found in the reactions of *N*-aryl- and *N*-alkyl-imines and further support a mechanism that does not involve free enolates.

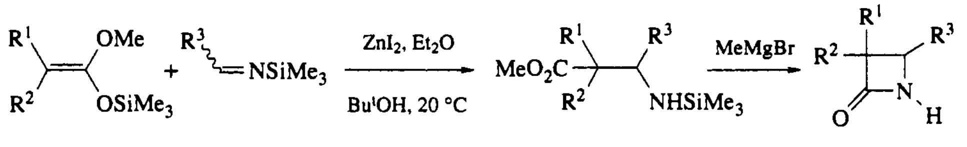

**(202)** **(203)** **(204)** **(205)**

Scheme 42

Table 22 Reactions of Silyl Ketene Acetals (**202**) with *N*-Silylimines (**203**) Catalyzed by $ZnI_2$[145,158]

| *Entry* | *Silyl ketene acetal* (**202**) *R*$^1$ | *R*$^2$ | *N-Silylimine* (**203**) *R*$^3$ | *β-Lactam*[a] (**205**) *Yield (%)* | *Trans:cis ratio* |
|---|---|---|---|---|---|
| 1 | Me | Me | Ph | 75 | |
| 2 | Me | Me | 2-Furyl | 76 | |
| 3 | Me | Me | PhC≡C | 78 | |
| 4 | Me | Me | TMSCH=CH | 75 | |
| 5 | PhO | H | 2-Furyl | 58 | 0.77:1 |
| 6 | Et | H | Ph | 61 | 9:1 |
| 7 | Me | H | PhC≡C | 82 | 3:1 |
| 8 | Me | H | TMSC≡C | 62 | 1.5:1 |
| 9 | Ph | H | TMSC≡C | 53 | 12:1 |

[a] Formed by treating the corresponding β-(trimethylsilyl)amino esters (**204**) with MeMgBr *in situ*.

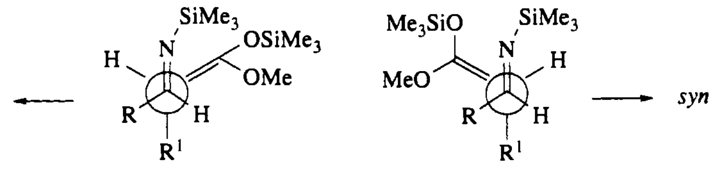

**(206)** **(207)**

Figure 8 Proposed open transition states involved in silyl ketene acetal–*N*-silylimine additions[145]

Similar reactions of silyl ketene acetals with *N*-(*t*-butyldimethylsilyl)imines have also been described by Colvin *et al.*[145] An example is shown in Scheme 43 involving the condensation of the *N*-TBDMS-imine derived from ethyl glycinate (**208**) and the silyl ketene acetal of methyl isobutyrate (**209**). Catalysis by TMS-OTf is preferred over $ZnI_2$ in these reactions, and it is thus unnecessary to use Bu$^t$OH as a proton source because the silyl group of the silyl ketene acetal is transferred to the imine nitrogen, thereby protecting the initial adduct (**210**) from condensation with unreacted *N*-silylimine. Following aqueous work-up, the more stable TBDMS group survives, affording *N*-TBDMS-β-amino ester (**211**), which can be cyclized to *N*-TBDMS-β-lactam (**212**) using MeMgBr. The use of *N*-(*t*-butyldimethylsilyl)imines may be preferred over *N*-trimethylsilylimines if further elaboration of the β-lactam requires protection of the nitrogen.

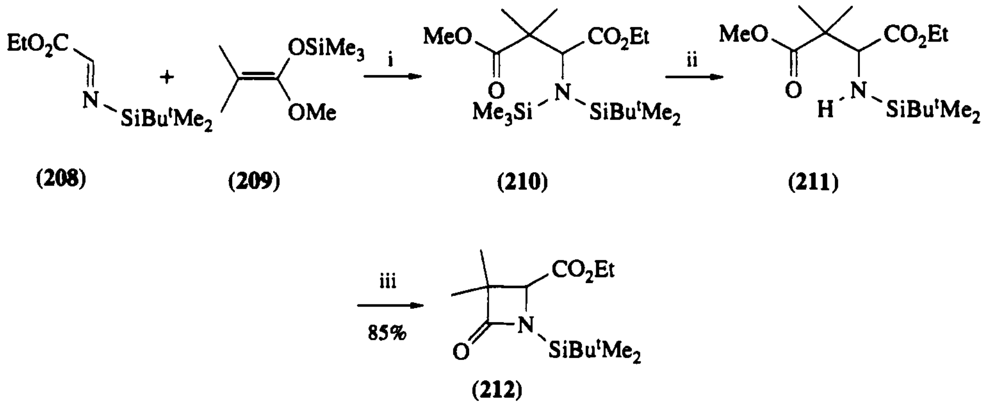

i, $Me_3SiOTf$, 0 to 25 °C; ii, $Na_2HPO_4$, $H_2O$; iii, MeMgBr

Scheme 43

### *4.1.3.3.2 Oxime ethers*

Oxime ethers are alternatives to *N*-silylimines for the synthesis of *N*-unsubstituted β-lactams, uncovered by reductive cleavage of the N—OR bond. They also serve, unlike other classes of imines, as primary aminomethylating reagents $CH_2NH_2$, since the formaldehyde adducts for the introduction of $CH_2NH_2$ ($CH_2$═NOR) are resistant to polymerization. Some examples reported by Sekiya and coworkers of the reactions of *O*-benzyl oxime ethers (**214**) with lithium enolates of methyl esters to produce *N*-benzyloxy-β-lactams (**215**) are shown in Scheme 44 and Table 23.[159] Yields range from 40 to 80% and tend to be higher with the methyleneamino oxime derivatives (entries 1–4) than those containing enolizable protons (entries 5 and 6).

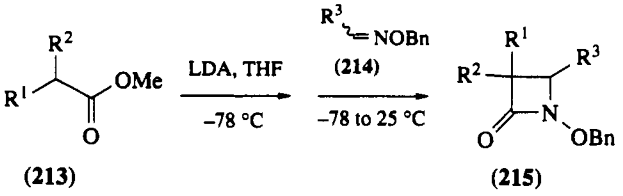

Scheme 44

**Table 23** β-Lactam-forming Reactions of *O*-Benzyl Oxime Ethers (**214**) and Enolates of Ester (**213**)[159]

| Entry | *Ester (213)* *R*$^1$ | *R*$^2$ | *Oxime (214)* *R*$^3$ | *β-Lactam (215) Yield (%)* |
|---|---|---|---|---|
| 1 | Me | Me | H | 67 |
| 2 | Ph | Et | H | 82 |
| 3 | —($CH_2$)$_6$— | | H | 65 |
| 4 | —($CH_2$)$_5$— | | H | 49 |
| 5 | Me | Me | Me | 48 |
| 6 | Me | Me | Et | 40 |

A useful application of an enolate–oxime ether condensation, described by Weeks, Volkmann and coworkers, is found in the synthesis of 6-aminomethylpenicillin derivative (**218**), a potent β-lactamase inhibitor.[160] As shown in Scheme 45, the sensitive penicillin Grignard (**216**) is condensed with ethyl formaldoxime at –80 °C in the presence of $BF_3·OEt_2$ to afford adduct (**217**). The use of $BF_3·OEt_2$ is critical because it allows the reaction to proceed at the low temperature required for the stability of enolate (**216**). Hydrogenolysis of (**217**) simultaneously results in removal of the ethoxy, bromo and benzyl groups, affording (**218**).

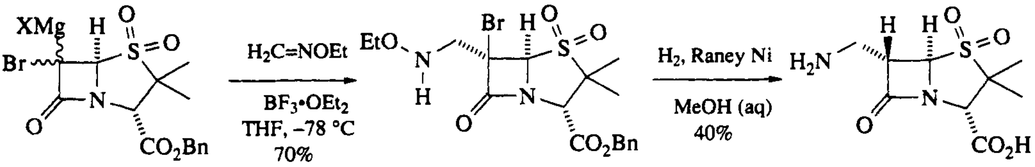

**(216)** **(217)** **(218)**

Scheme 45

Sekiya and coworkers have demonstrated that silyl ketene acetals (**219**) add to *O*-benzyl oxime ethers (**220**) in the presence of catalytic amounts of TMS-OTf to afford β-benzyloxyamino esters (**221**; Scheme 46; Table 24).[161] As in the analogous TMS-OTf-catalyzed reactions of silyl enol ethers with *N*-aryl-[135,136,144] and *N*-silyl-imines,[145] β-lactam formation does not occur because the silyl group is transferred to the amine nitrogen *in situ*, thereby blocking cyclization. Yields are generally good (80–90%) but are reduced when unsubstituted silyl ketene acetal (entry 3) and enolizable oxime ethers (entries 8 and 9) are used. No systematic study of the *syn–anti* selectivity of oxime ether additions to enolates or silyl ketene acetals has been reported. It would be interesting to see if the direction of *syn–anti* selectivity relative to other imine derivatives is changed because of the additional metal coordination site on the oxime ether oxygen.

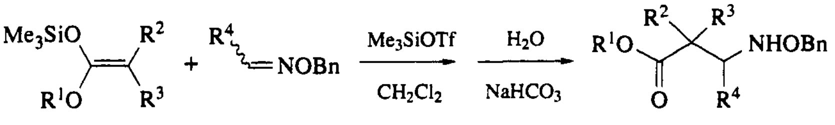

**(219)** **(220)** **(221)**

Scheme 46

**Table 24** Condensation Reactions of Silyl Ketene Acetals (**219**) and *O*-Benzyl Oxime Ethers (**220**) Catalyzed by TMS-OTf[161]

| | Silyl ketene acetal (**219**) | | | Oxime ether (**220**) | β-Benzyloxyamino ester (**221**) |
|---|---|---|---|---|---|
| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) |
| 1 | Me | Me | Me | H | 89 |
| 2 | Me | Me | H | H | 76 |
| 3 | Bn | H | H | H | 42 |
| 4 | Me | —(CH$_2$)$_6$— | | H | 95 |
| 5 | Me | Ph | H | H | 93 |
| 6 | Me | PhO | Me | H | 88 |
| 7 | Me | 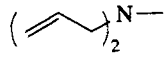 | H | H | 52 |
| 8 | Me | Me | Me | Me | 52 |
| 9 | Bn | H | H | Me | 61 |

#### 4.1.3.3.3 Sulfenimines

Sulfenimines, as demonstrated by Hart and coworkers, behave similarly to *N*-arylimines and *N*-silylimines in enolate condensations with respect to yield and stereoselectivity. Like oxime ethers they are useful for the synthesis of *N*-unsubstituted β-lactams by reductive cleavage.[162] It is important that the alkyl group attached to the sulfur of the sulfenimine is bulky in order to block attack of the enolate on the electropositive sulfur. *S*-Tritylsulfenimines (**223**), prepared according to the method of Branchaud by condensing aldehydes with tritylsulfenamide (**222**) in the presence of MgSO$_4$ and PPTS (equation 21),[163] are well suited for this purpose and condense with lithium ester enolates to afford diastereomeric mixtures of β-lactams (**226**) and (**227**) in good yield (Scheme 47; Table 25). The reaction is also compatible with enolizable sulfenimines (entries 2 and 3). *Syn* selectivity predominates, paralleling the reactions of lithium enolates with other types of imines. Several reagents including tri-*n*-butylphosphine, Raney nickel, TMSI, and lithium–ammonia can be used to convert *N*-tritylsulfenyl β-lactams (**226**) and (**227**) to their corresponding *N*-unsubstituted β-lactams.

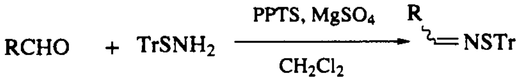

(**222**) (**223**) (21)

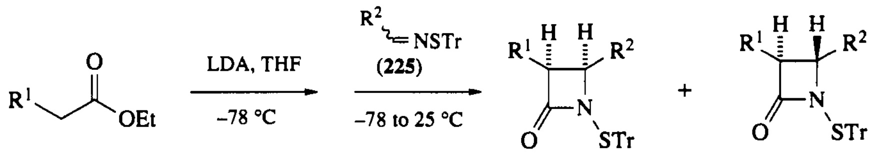

(**224**) (**226**) (**227**)

**Scheme 47**

**Table 25** β-Lactam-forming Reactions of Sulfenimines with Ester Enolates[162]

| *Entry* | *Ester (224) R¹* | *Imine (225) R²* | *Products (226)–(227) Yield (%)* | *Cis:trans ratio* |
|---|---|---|---|---|
| 1 | Pr$^i$ | Ph | 70 | 82:18 |
| 2 | Pr$^i$ | Me | 71 | 97:3 |
| 3 | 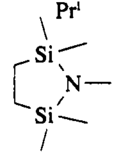 | Me | 78 | 83:17 |

### 4.1.3.4 *In Situ* Methods

An *in situ* method for the preparation of *N*-methyleneamines has been devised by Overman and Osawa for use in condensation reactions with enolates[164] and organometallic reagents.[165] These species, with the exception of very hindered *N*-methyleneamines, cannot be isolated in the condensed phase because they rapidly trimerize to hexahydro-1,3,5-triazines. In this *in situ* method, *N*-methyleneamines (**230**) are generated from *N*-(cyanomethyl)amines (**228**) by deprotonation with an equivalent of enolate to give an intermediate amide (**229**) which loses LiCN (equation 22). When two equivalents of enolate are present, addition to the *N*-methyleneamine occurs and β-lactams (**233**) are obtained in 60–70% yield upon warming the reaction mixture to 25 °C (Scheme 48; Table 26). Uncyclized β-amino esters can be isolated if the reaction is quenched at lower temperature; a possible cycloaddition mechanism is thus ruled out. It is not clear to what extent, if any, the reaction is limited to α,α-disubstituted enolates. *N*-Methyleneamines, like oxime ethers, are useful for the synthesis of 4-unsubstituted β-lactams and should also have important applications in the synthesis of monobactam antibiotics.

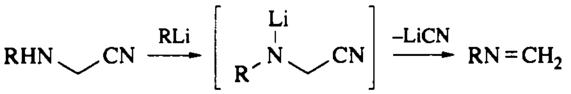

(**228**) (**229**) (**230**) (22)

In an application to asymmetric monobactam synthesis, Overman and Osawa observe a high level of 1,4-diastereofacial selectivity in the reaction of (*S*)-cyanoamine (**235**) with the enolate of STABASE-protected glycine ester (**234**), affording diastereomeric 3-amino-2-azetidinones (**236**) and (**237**) in a 10:1 ratio, respectively, and in 65% yield (Scheme 49).[164] Based on the (*E*)-enolate geometry of glycine ester (**234**), determined in trapping experiments with TMSCl, the authors postulate a chelated, chair-like transition state (**238**) that is consistent with the observed stereoselectivity.

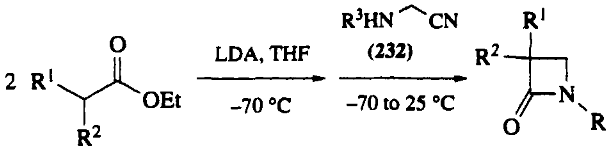

**(231)** **(233)**

**Scheme 48**

**Table 26** β-Lactam-forming Reactions of Enolates of Ester (**231**) and *N*-Methyleneamines Prepared *In Situ* from *N*-(Cyanomethyl)amines (**232**)[164]

| *Entry* | *Ester (231)* *R*$^1$ | *R*$^2$ | *N-(Cyanomethyl)amine (232)* *R*$^3$ | *β-Lactam (233)* *Yield (%)* |
|---|---|---|---|---|
| 1 | Me | Me | Bn | 66 |
| 2 | Me | Me | Ph | 77 |
| 3 | Me | Me | $C_6H_{11}$ | 66 |
| 4 | —$(CH_2)_5$— |  | Bn | 65 |
| 5 | Me | SPh | Bn | 62 |

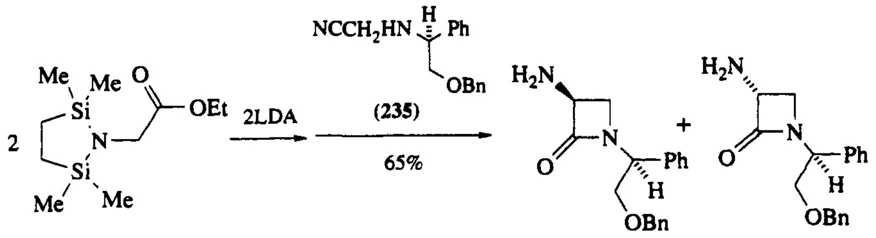

**(234)** **(236)** 10:1 **(237)**

**Scheme 49**

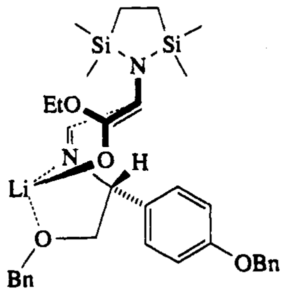

**(238)**

### 4.1.3.5 Cyclic Imines

Condensations of 2-phenyl-2*H*-azirines (**239**) with enolates have been described by Blagoev and Novkova[166] and Laurent *et al.*[167] As shown in Scheme 50, these reactions are often accompanied by fragmentation of the aziridine ring. This occurs by an internal proton transfer in the initial 1,2-adduct (**240**) to generate an enolate (**243**), which suffers a retro-Michael-type reaction leading to *trans*-γ-amino-α,β-unsaturated compounds (**242**) and to products arising from cyclization of the corresponding *cis* isomer (**244**). When enolate (**243**) is not generated, the normal products of 1,2-addition, *i.e.* 2-substituted aziridines (**241**), are isolated upon work-up. Some examples of these reactions are shown in Table 27. Entries 1 and 2 demonstrate an interesting effect of the enolate counterion where the 1,2-addition product is obtained using the magnesium enolate of phenylacetic acid, while fragmentation products are obtained using the corresponding sodium enolate. This dichotomy in reaction pathways can be rationalized by the different basicities of the two amide anions (**240**; Met = Na *vs.* Mg), where internal proton transfer occurs with the more basic sodium anion. The reaction depicted in entry 1 leading to 2-aziridine acetic acids is also general for magnesium dianions of other arylacetic acids (yields = 50–60%). Reactions of sodium ketone enolates (entries 3 and 4), like those of sodium dianions of phenylacetic acid, result in fragmentation of the aziridine ring. Depending upon the degree of substitution of the 2*H*-azirine at position 3, pyrroles (entry 3) or 2*H*-pyrroles (entry 4) are obtained in good yield. The authors conclude that the failure to detect appreciable amounts of *trans*-α,β-unsaturated ketones (**242**; X = Et; $R^1$ = Me; $R^2$ = Me; $R^3$ = Me or H) in these reactions is due to reversible fragmentation of enolate (**243**), where the equilibrium is driven by cyclization of the *cis* fragmentation product.[167]

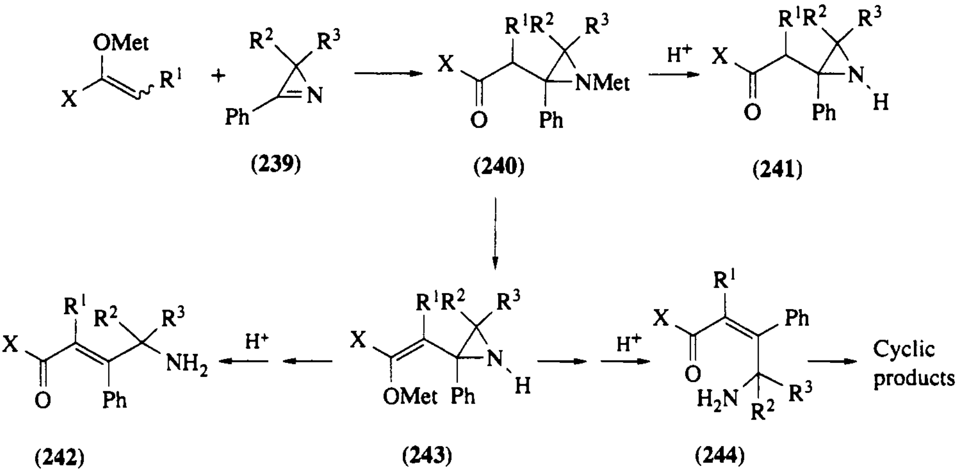

Scheme 50

In the Schopf reaction, five- and six-membered ring imines 3,4-dihydro-2*H*-pyrrole (**245**) and 2,3,4,5-tetrahydropyridine (**246**) condense with β-keto acids to afford β-amino ketones (equation 23). Imine (**246**), for example, condenses with acetoacetic acid to give 2-acetonylpiperidine (**247**) (*n* = 4), an alkaloid known as pelletierine (or isopelletierine).[168] More recent applications of these reactions are shown in Table 28. Imines (**245**) and (**246**) are most conveniently prepared by dehydrohalogenation of *N*-chloropiperidine[169] and *N*-chloropyrrolidine,[170] respectively, but are difficult to isolate due to self-condensation reactions occurring below pH 11.5.[168] To avoid this problem, Rapoport and coworkers have used ether–ethanol solutions of imine (**246**), prepared *in situ* by dehydrohalogenation, in reactions with the sodium salt of oxalylacetate esters (entry 1).[171] The Rapoport modification has also been used by Quick and Oterson in a more efficient synthesis of pelletierine (entry 2).[172] Grisar and coworkers have recently introduced another modification of the Schopf reaction that avoids handling the elusive monomeric forms of imines (**245**) and (**246**).[173] Here, internally chelated magnesium enolates of β-keto acids, prepared from the corresponding methyl ketone derivatives using magnesium methyl carbonate, react with solid α-trimeric forms of imines (**245**) and (**246**) to afford 2-piperidylmethyl and 2-pyrrolidinylmethyl ketones (entries 3–6). 3,4-Dihydroisoquinoline also reacts with these enolates (entry 7). Presumably under the reaction conditions (DMF, 25 °C, $CO_2$ atmosphere), there is slow decomposition of the α-trimers to provide sufficient concentrations of free imines. The use of magnesium salts overcomes also the solubility limitations of other β-keto acid salts. This method, however, is mainly limited to magnesium keto acid enolates derived from aryl and styryl methyl ketones.

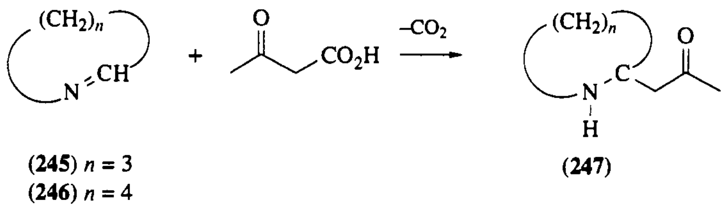

(23)

**Table 27** Condensation Reactions of 2*H*-Azirines with Enolates

| *Entry* | *Carbonyl Compound* | *Azirine* | *Conditions* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | $PhCH_2CO_2H$ | 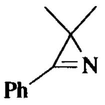 | $\mathrm{Pr^iMgCl}$, DME, reflux | 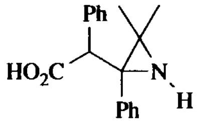 | 65 | 166 |
| 2 | $PhCH_2CO_2H$ | 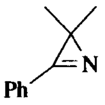 | Na naphthalide, THF, 50°C | 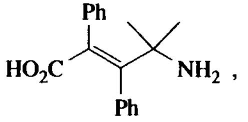 , 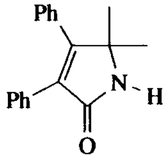 | 25, 41 | 166 |
| 3 | PhCOEt | 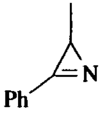 | NaH, DMSO | 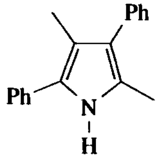 | 90 | 167 |
| 4 | PhCOEt | 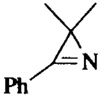 | NaH, DMSO | 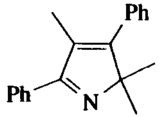 | 72 | 167 |

**Table 28** Condensation Reactions of 3,4-Dihydro-2*H*-pyrrole and 2,3,4,5-Tetrahydropyridine with β-Keto Acid Derivatives

| *Entry* | *Carbonyl compound* | *Imine* | *Product* | *Ref.* |
|---|---|---|---|---|
| 1 | $EtO_2CCOCH(Na)CO_2Bu^t$ | 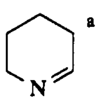 [a] | 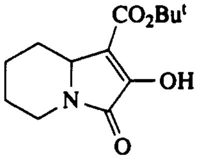<br>60% | 171 |
| 2 | $MeCOCH_2CO_2Na$ | 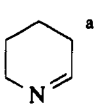 [a] | 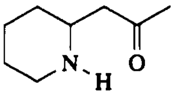<br>42% | 172 |
| 3 | 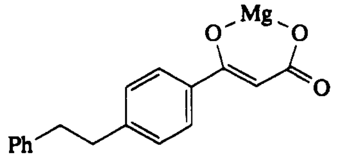 | 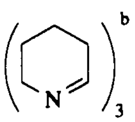 [b] | 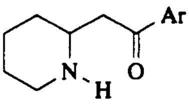<br>63% | 173 |
| 4 | 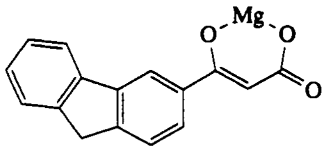 | 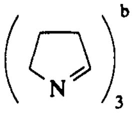 [b] | 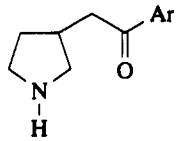<br>65% | 173 |
| 5 | 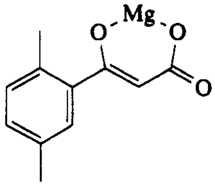 | 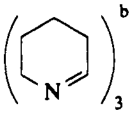 [b] | 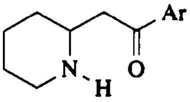<br>75% | 173 |
| 6 | 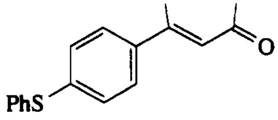 | 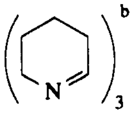 [b] | 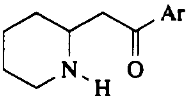<br>50% | 173 |
| 7 | 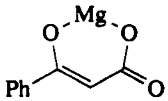 | 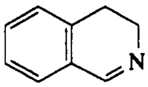 | 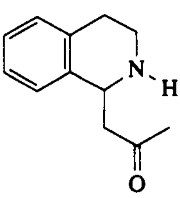<br>60% | 173 |

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[a] Formed *in situ* according to the procedure of Rapoport, see ref. 171. [b] For details of preparation, see ref. 173.

In connection with the synthesis of protoberberine alkaloids, Marsden and MacLean have investigated the addition of phthalide enolates to 3,4-dihydroisoquinolines.[174,175] These reactions are an extension of the previously described work of Dodsworth *et al.*[121,122] involving phthalide additions to acyclic imines (Section 4.1.3.2.2.ii). An example involving the condensation of 3,4-dihydroisoquinoline (**248**) with phthalide (**249**) to yield *trans* tetracyclic lactam (**250**) is shown in Scheme 51. Reduction of (**250**) gives (±)-epiophinocarpine (**251**). In contrast to the modest *cis* stereoselectivity (~2:1) seen in reactions of acyclic imines, reactions of cyclic imines are completely stereospecific and give *trans* adducts exclusively. To explain the difference in stereochemical outcome between reactions of cyclic *vs.* acyclic imines, the authors have revised the model of Dodsworth *et al.* (see Figure 6) by proposing a coordination complex involving the imine lone pair, the two oxygens of the phthalide ring and the lithium cation (Figure 9). The stereochemical outcome of the addition is therefore determined by the geometry of the imine.

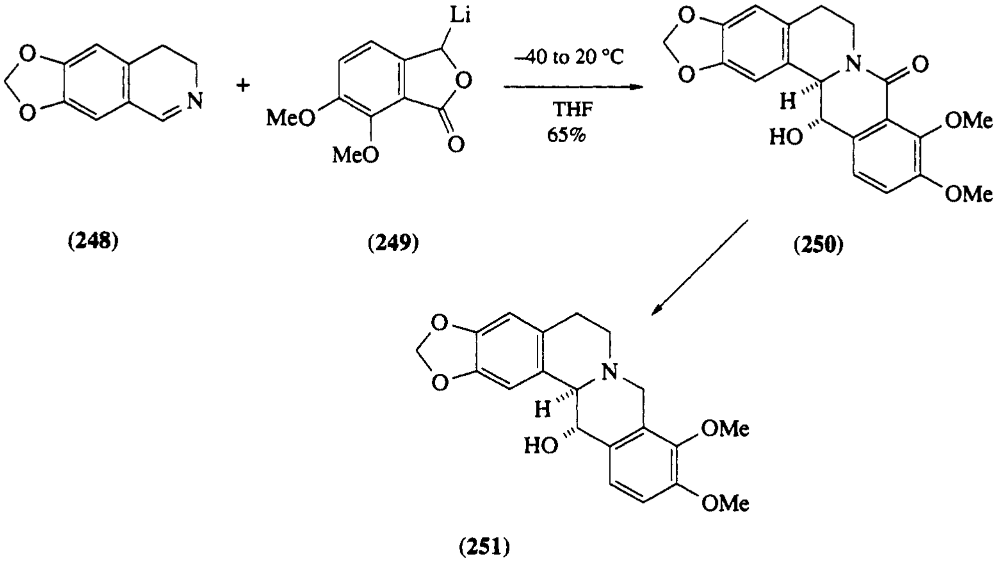

**(248)** **(249)** **(250)** **(251)**

**Scheme 51**

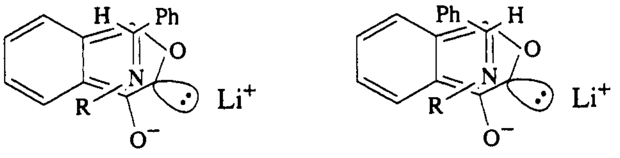

(a) Acyclic, (*E*)-imine (b) Acyclic or cyclic, (*Z*)-imine

**Figure 9** Proposed orientation of reactants in phthalide enolate–imine additions leading to (a) *cis* or (b) *trans* adducts[175]

In studies directed towards the synthesis of (+)-biotin (**252**), Volkmann and coworkers have studied additions of isothiocyanatoacetate enolates (**253**) to 3-thiazolines (**254**), yielding diastereomeric thiazolidines (**255**) and (**256**; equation 24; Table 29).[176,177] Boron trifluoride etherate is a necessary additive to enhance the reactivity of the sterically congested 3-thiazoline ring, which is otherwise inert to nucleophilic attack. The diastereofacial selectivity of these reactions is controlled by attack of the enolate on the face of the imine opposite to the 5-pentyl group and correctly establishes the relative stereochemistry at C-1 and C-2 of biotin. The *syn–anti* selectivity, corresponding to the C-2,C-3 relative configuration of biotin, is not as stereoselective but does favor the desired *anti*-thiazolidine (**255**) (note that (**255**) has the *anti* relative configuration even though the ring is *cis*). Enhancement of *anti* selectivity can be achieved by using more bulky alkyl (entries 1–4) or phenoxy (entries 5–7) esters. It is interesting to note that the BHT ester (entry 7), the most *anti* selective ester known in the aldol condensation,[81] is also the most *anti* selective ester in these reactions. Assuming that (*E*)-enolates are involved, these results can be rationalized by invoking *C*(*E*,*Z*)$^‡$ and *B*(*E*,*Z*)$^‡$ transition states for the formation of diastereomeric 3-thiazolines

(**255**) and (**256**), respectively; thus, bulky esters favor 3-thiazoline (**255**) by destabilization of the *B*(*E*,*Z*)$^‡$ transition state *via* the steric interaction between OR of the enolate and the quaternary carbon of the 3-thiazoline (see Figure 4).

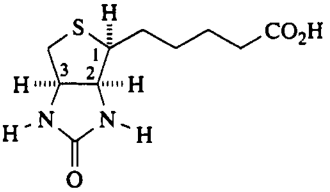
H
S
1
2
3
CO2H
H
H
H
N
N
H
O

**(252)**

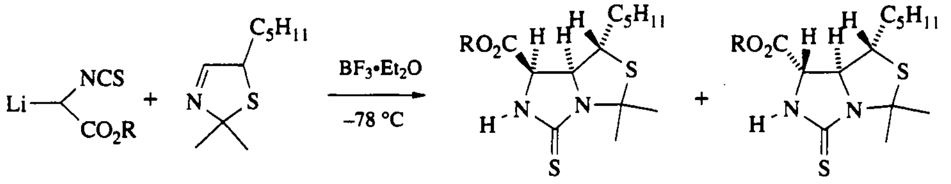
Li
NCS
CO2R
+
C5H11
N
S
BF3•Et2O
−78 °C
RO2C
H
H
H
C5H11
S
N
N
H
S
+
RO2C
H
H
H
C5H11
S
N
N
H
S

(24)

**(253)** **(254)** **(255)** **(256)**

**Table 29** Stereoselective Condensations of Isothiocyanoacetate Enolates With 3-Thiazoline (**254**)[177]

| *Entry* | *Enolate (253) R* | *Products (255):(256) Ratio* | *Entry* | *Enolate (253) R* | *Products (255):(256) Ratio* |
|---|---|---|---|---|---|
| 1 | Me | 1.4 | 5 | 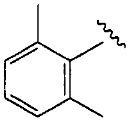 | 1 |
| 2 | MeOCH$_2$ | 2 | 6 | 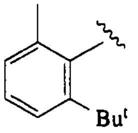 | 3 |
| 3 | Et | 3 | 7 | 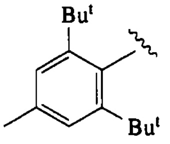 | >5 |
| 4 | Pr$^i$ | 3 | | | |

In addition to ester enolates, ketone enolates and nitronates also add to 3-thiazolines in the presence of $BF_3$·$Et_2O$.[178] Reactions of ketone enolates have been cleverly exploited in the synthesis of 2,3,5-trisubstituted thiophenes (**260**) by hydrolysis of adducts (**259**) and spontaneous cyclization to liberate water and ammonia (Scheme 52; Table 30).[178] The 5-substituent of the thiophene is derived from the 5-substi-

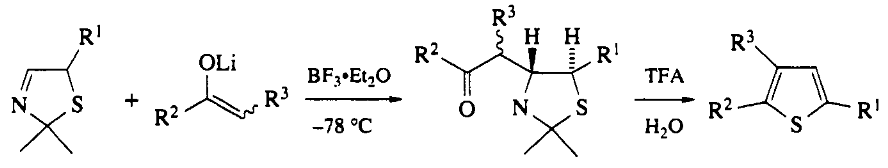
R1
N
S
+
OLi
R2
R3
BF3•Et2O
−78 °C
R3
R2
O
H
H
R1
N
S
TFA
H2O
R3
R2
S
R1

**(257)** **(258)** **(259)** **(260)**

**Scheme 52**

tuent of the 3-thiazoline (**257**), while the 2,3-substituents of the thiophene are derived from the enolate. Overall yields of thiophenes are generally good.

**Table 30** Formation of 2,3,5-Trisubstituted Thiophenes (**260**) from Ketone Enolates and 3-Thiazolines (**257**)[178]

| *Entry* | *3-Thiazoline* (**257**) *R*$^1$ | *Ketone enolate* (**258**) *R*$^2$ | *R*$^3$ | *Thiophene* (**260**) *Yield (%)* |
|---|---|---|---|---|
| 1 | n-$C_5H_{11}$ | Ph | H | 80 |
| 2 | n-$C_5H_{11}$ | Bu$^t$ | Me | 89 |
| 3 | n-$C_5H_{11}$ | —$(CH_2)_4$— | | 87 |
| 4 | n-$C_5H_{11}$ | 1-Adamantyl | H | 70 |
| 5 | $(CH_2)_4CO_2Et$ | —$CH_2CH_2SCH_2$— | | 50 |

## 4.1.4 ADDENDUM

A comprehensive review article on β-lactam formation *via* the ester enolate–imine condensation has been written by Hart and Ha.[179] Achiwa and coworkers have published a full paper detailing their work on the synthesis of *N*-benzyloxy-β-lactams utilizing the reaction of *N*-benzyloxyimines with silylketene acetals in the presence of TMS-OTf, or with lithium ester enolates.[180]

Enolizable *N*-trimethylsilylaldimines can be generated *in situ* by the addition of organolithium reagents to bis(trimethylsilyl)formamide.[181] These undergo addition reactions with enolates to form β-lactams. Phosphonium salts used in catalytic amounts promote the reaction between aryl aldimines and silylketene acetals to form β-amino esters.[182] Mannich bases with *N*-2-hydroxyethyl-*N*-methyl substitution are prepared by the reaction of the iminium salt synthon, 3-methyl-1,3-oxazolidine, with enol silanes in the presence of chloromethylsilanes.[183]

Tramontini has updated his earlier review on the Mannich reaction.[184]

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# 4.2

# The Bimolecular Aromatic Mannich Reaction

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## 4.2.1 INTRODUCTION

The importance of α-aminoalkylation as a method of carbon–carbon bond formation has been recognized for many years, especially among those organic chemists interested in biologically active molecules. The earliest papers were published towards the end of the last century but Mannich was the first to recognize the generality of the reaction and his first paper appeared over 75 years ago. A number of reviews[1] and two books[2] record data up to 1973. The importance of the Mannich reaction relates in part to the fact that the protonated bases are normally water soluble and also to the ease with which the amino function may be converted into a variety of other groups. New examples continue to be published. For example, the nuclear *ortho* methylation of phenols has been reported *via* the reduction of Mannich bases and their quaternary methiodides and *N*-oxides using tributyltin hydride;[3a] sodium cyanoborohydride has also been used.[3b] Chapter 4.1 is concerned with aliphatic bimolecular Mannich reactions, while this chapter deals with intermolecular reactions of Mannich reagents with aromatic substrates. This chapter concentrates on recent advances in synthetic methodology.

The two components that are required in addition to the aromatic substrate are an amine and an aldehyde. Only electron-rich aromatic compounds interact successfully with the relatively weak electrophiles that function as Mannich reagents. In many cases failures may be due to low electrophilicity of the intermediates, resulting from heteroatom stabilization. The reaction is quite general. The least nucleophilic aromatic substrates that have been shown to react are thiophene, *m*-dimethoxybenzene and phenyltrialkylstannanes. Very electron-rich heterocycles, such as indole(s), and carbocyclic compounds, such as phenol(s), react under a wide variety of very mild conditions. It is not possible to formulate a set of general reaction conditions and reagents. The most frequently used classical procedure involves the mixing of all three components simultaneously. There are, however, many examples in which the amine and aldehyde are condensed first, sometimes with the isolation of the initial product. Very few examples are recorded of reactions involving secondary amines other than with formaldehyde (aminomethylation). Some aminoalkylation reactions are successful using 2-naphthol when other aromatic substrates fail. It is clear that 2-naphthol is a good substrate on which to evaluate new reagents or reaction types. In the few cases in which successful reactions with other aldehydes have been reported, yields have usually been extremely poor. For example, pyrrole, acetaldehyde and dimethylamine afford the expected Mannich base in less than 5% yield.[4] The reasons for this are obscure because a range of mechanistic pathways are thought to operate. Many Mannich reactions may proceed by what is essentially an $S_N2$ process and hence are subject to steric hindrance. It is also possible that earlier failures result from the ease of deprotonation of iminium salts to enamines.

Reactions involving primary amines have been successfully carried out *via* Schiff's bases derived from a number of aldehydes. Thus, the reaction of pyrrole with the protonated enamine (**1**), which results in the formation of the pyrrole trimer (**2**; equation 1), constitutes a good example of a Mannich reaction involving an aldehyde other than formaldehyde.[5]

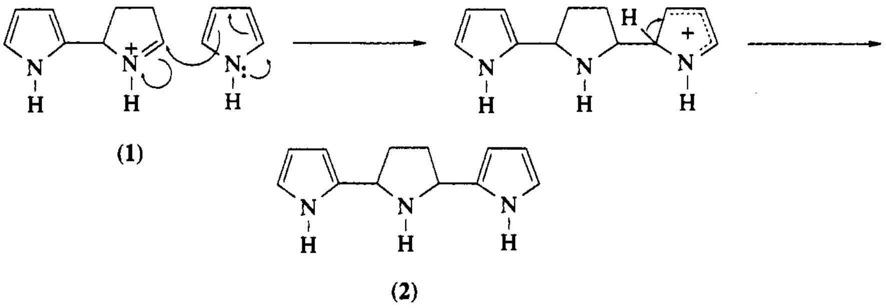

(1)[5]

## 4.2.2 MECHANISMS

An understanding of the mechanism or mechanisms that operate allows one to predict how a synthesis should be planned and so a brief discussion is appropriate. As with Friedel–Crafts alkylation reactions, a number of mechanisms appear to operate. At one end of the spectrum iminium salts are involved in $S_N1$-type reactions and at the other end $S_N2$-like transition states may well be involved. The majority of the work published on mechanistic aspects of the Mannich reaction concerns reactions carried out in aqueous or other protic solvents.[1d,6] There is little evidence for the conversion of hydroxymethyl derivatives into Mannich bases, so the initial steps must involve the interaction of formaldehyde with the amine to give a carbinolamine that is in equilibrium with the reactants. Where the equilibrium lies depends on the pH. At high pH and in the presence of an excess of secondary amine a carbinolamine is converted to a bis(dialkylamino)methane, which itself may be hydrolyzed back to the amine and carbinolamine. A carbinolamine and a bis(dialkylamino)methane can give rise to an iminium salt at low pH. The first suggestion that iminium ions are involved in Mannich reactions appeared in a paper in 1949.[7] Different mechanisms were proposed at an early stage for reactions carried out in acidic or basic media.[8] Although a number of kinetic and a polarographic studies purport to show the involvement of iminium salts at pH values well above 7, it is clear that a carbinolamine would be the predominant species present if an iminium ion were produced in the presence of hydroxide ions. The possibility that the protonated carbinolamine, the required precursor to an iminium ion in acidic media, could function as a Mannich reagent does not appear to have been suggested previously. An $S_N2$ displacement of water from such a cation is at least as likely at intermediate pH values as the displacement of the poorer leaving group (hydroxide) from a carbinolamine in reactions carried out at high pH. These equilibria are summarized in Scheme 1. It has also been argued that reactions carried out in alcoholic solutions may well proceed by way of alkoxydialkylaminomethanes (aminol ethers).

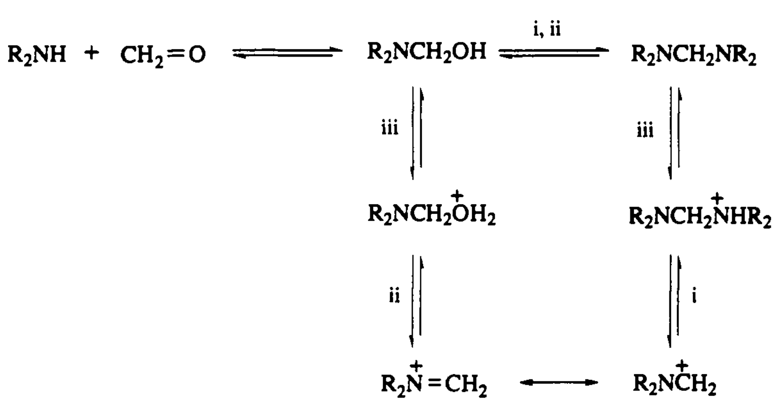
R2NH + CH2=O
R2NCH2OH
i, ii
R2NCH2NR2
iii
iii
R2NCH2OH2+
R2NCH2NHR2+
ii
i
R2N+=CH2
R2NCH2+

i, $R_2NH$; ii, $-H_2O$; iii, $H^+$

Scheme 1

One of the most interesting diaminomethanes that has been investigated is a model for the coenzyme tetrahydrofolate (3), a biological one-carbon transfer agent. The mechanism of its conversion into the imidazolidine derivative *N*$^5$,*N*$^{10}$-methylenetetrahydrofolate (4) has been studied.[9] The pH rate profile apparently results from a change in the rate-determining step with changing acidity. Secondary amines such as morpholine and imidazole catalyze the reaction between tetrahydrofolic acid and formaldehyde *via* a

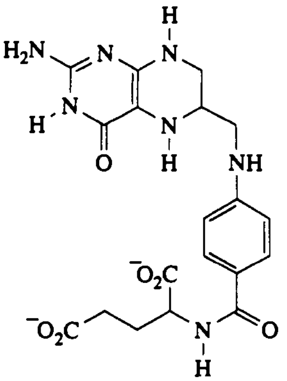

(3)

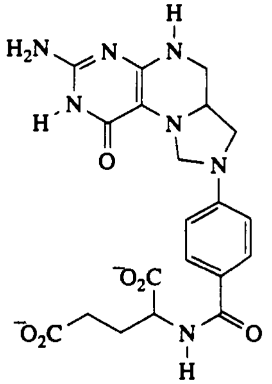

(4)

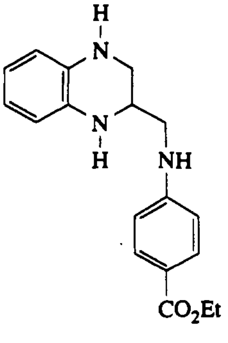

(5)

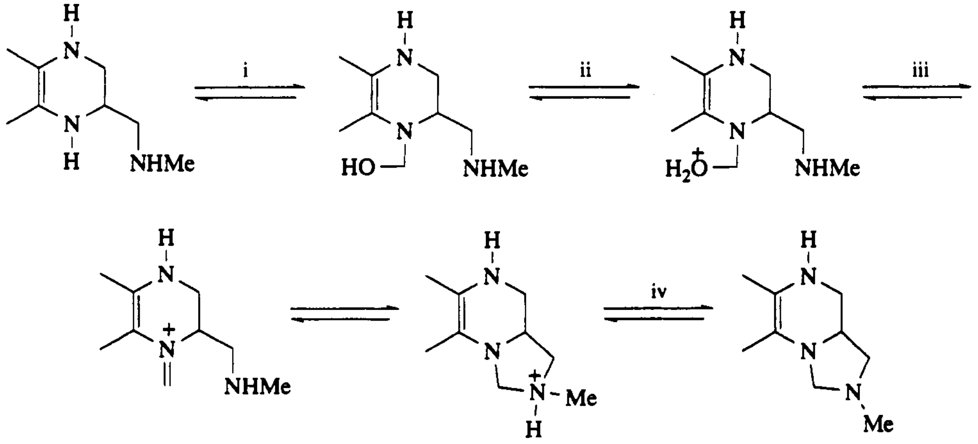
i
ii
iii
iv
NHMe
HO
H2O+
Me

i, $CH_2O$; ii, $H^+$; iii, $-H_2O$; iv, $-H^+$

Scheme 2

pathway involving an iminium ion. The model tetrahydroquinoxaline derivative (**5**) has been studied[10] over a broad pH range and an aminol, an iminium ion and a protonated amine detected in equilibrium, as shown in Scheme 2.

In recent years reactions have been carried out in aprotic solvents with preformed iminium salts. Another recent modification is the use of bis(dialkylamino)methanes (aminals) and alkoxydialkylaminomethanes (aminol ethers) in aprotic solvents in the presence of nonprotic acids. A number of aromatic substrates that do not give Mannich bases under the classical aqueous reaction conditions do react under these aprotic conditions.

## 4.2.3 REACTIONS USING SECONDARY AMINES

### 4.2.3.1 Aminoalkylation Reactions of Phenols

#### *4.2.3.1.1 Reactions using protic solvents*

*(i) Reactions using formaldehyde*

A wide range of phenols take part in Mannich reactions under classical conditions. The precise reaction conditions required depend on the nucleophilicity of the phenol. The two extremes are exemplified by 2-naphthol and 4-nitrophenol. In the case of a reactive phenol such as 2-naphthol, aqueous formaldehyde and the amine, sometimes in ethanolic solution, are either allowed to stand at room temperature for a lengthy period of time or heated for a brief period. When more than one activated position is available it is not usual to obtain one exclusive product. It may even be that polysubstitution is the norm, since the introduction of an aminomethyl group increases the electron density in the ring. This effect is reminiscent of Friedel–Crafts alkylation. Phenol, for example, when heated at *ca.* 60 °C for 2 h with aqueous dimethylamine and formaldehyde affords the 2,4,6-trisubstitution product in 86% yield.[11] In the cases where reactions have been studied over a period of time it is normal for the first substitution to occur at the 2-position. In a recent careful study[12] it was observed that the reaction rate for the interaction of phenol with aqueous formaldehyde and di-*n*-propylamine is increased tenfold when the amount of water is increased from 8.6 to 65.7%. In reactions of 3-pentadecylphenol with formaldehyde and a number of secondary amines three dialkylaminomethyl groups are introduced, with the order being C-6, C-4 and C-2. The observed preference for attack *ortho* to the hydroxy group has resulted in the suggestion that the mechanism of the reaction involves hydrogen bonding of a bis(dialkylamino)methane with the phenolic hydroxy group, as shown in equation (2).[13] The failure of 2,4-dimethyl-6-hydroxymethylphenol to react with morpholine eliminated a possible reaction sequence. We will return to the question of mechanism when we discuss reactions involving preformed intermediates (Section 4.2.3.1.2).

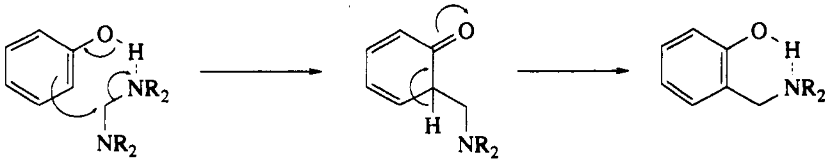

(2)

Yields appear to depend not only on the nucleophilicity of the phenol, but also on the amine. Diethylamine is more sterically demanding than dimethylamine and strongly hindered secondary amines such as diisopropylamine and dicyclohexylamine usually do not take part in Mannich reactions.[14] Dicyclopentylamine is reported to give an exotherm when mixed with formaldehyde, but no bis(dialkylamino)methane has been isolated. In equations (3)–(12) it is seen that reaction almost invariably occurs *ortho* to a hydroxy group; irrespective of the presence of other functional groups. It is worth drawing attention to specific examples. Sarcosine (*N*-methylglycine) gives products (equation 6) that can be transformed, because of the extra functionality, into heterocyclic systems such as benzoxazepinones and dihydroisoquinolones.[18] 4-Hydroxyacetophenone reacts at the enolized ketone function under acidic reaction conditions; reaction at the benzenoid ring (equation 8) only occurs in a mildly basic medium. On the other hand, 3,5-dihydroxyacetophenone affords the ring-substitution product in a reaction using morpholine hydrochloride (equation 9). Reactions of 2,5-dimethylphenol result in substitution at the 4-position, presumably because the normal reagent is too sterically demanding.

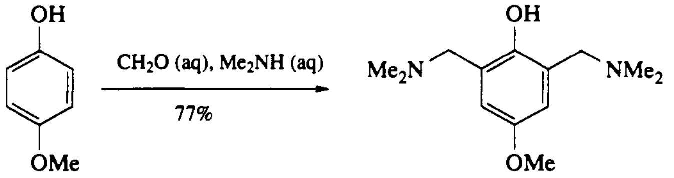
OH
OMe
CH2O (aq), Me2NH (aq)
77%
OH
Me2N
NMe2
OMe

(3)[15]

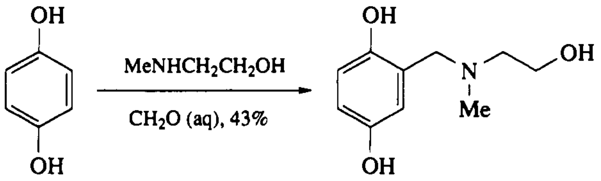
OH
OH
MeNHCH2CH2OH
CH2O (aq), 43%
OH
N
OH
Me
OH

(4)[16]

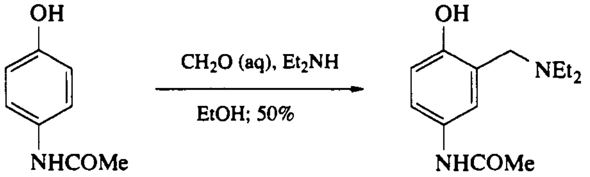
OH
NHCOMe
CH2O (aq), Et2NH
EtOH; 50%
OH
NEt2
NHCOMe

(5)[17]

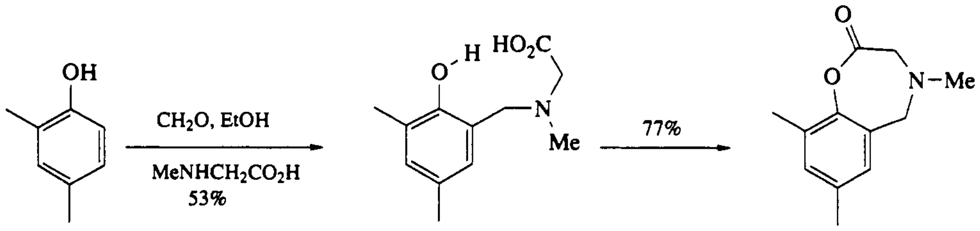
OH
CH2O, EtOH
MeNHCH2CO2H
53%
O
H
HO2C
N
Me
77%
O
O
N−Me

(6)[18]

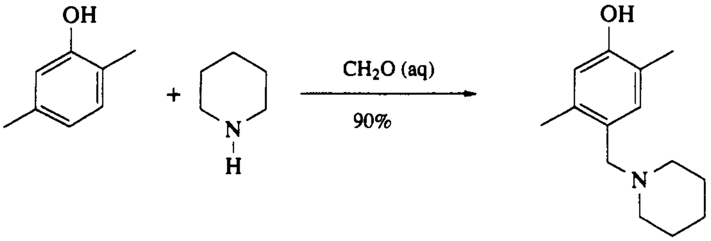
OH
+
N
H
CH2O (aq)
90%
OH
N

(7)[19]

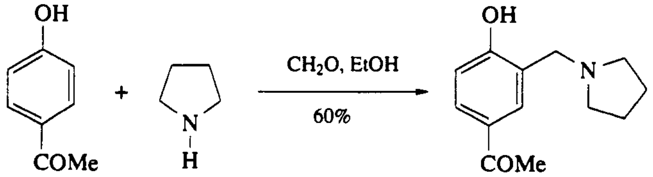
OH
COMe
+
N
H
CH2O, EtOH
60%
OH
N
COMe

(8)[20]

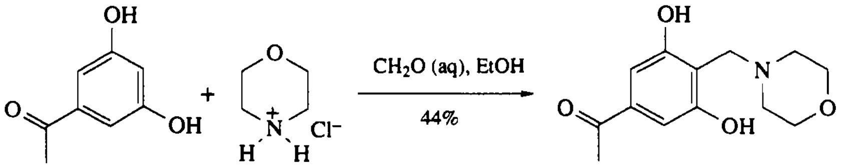
OH
O
OH
+
O
N
Cl⁻
H
H
CH2O (aq), EtOH
44%
OH
N
O
O
OH

(9)[21]

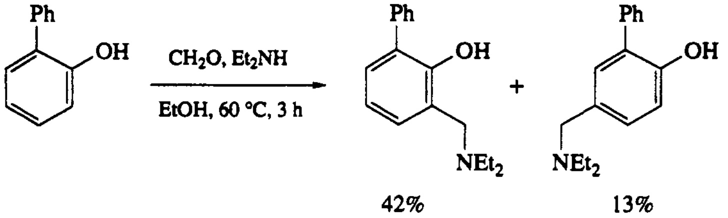

(10)[22]

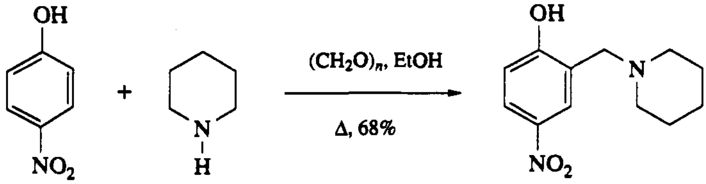

(11)[23]

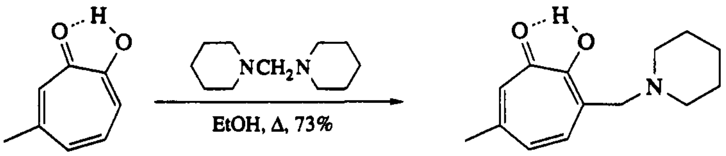

(12)

*(ii) Reactions involving bis(dialkylamino)methanes (aminals) or alkoxydialkylaminomethanes (aminol ethers)*

The rate of the reaction of 2,4-dimethylphenol with formaldehyde and morpholine depends on the concentration of morpholine if it is present at less than twice the formaldehyde concentration, but if the formaldehyde concentration is less than half that of morpholine then the rate depends on the concentration of formaldehyde. These data suggest that di-*N*-morpholinylmethane is an intermediate in the reaction. Di-*N*-morpholinylmethane was shown to give essentially the same kinetics.[13,24] A kinetic study of the reaction of 3-pentadecylphenol with formaldehyde and di-*n*-propylamine led to a similar conclusion.[25] These results suggest that aminals and aminol ethers should take part in Mannich reactions since both can be formed reversibly in the aqueous or alcoholic media used under the more traditional reaction conditions.

1-Naphthol gives the 2-substitution product in 77% yield when heated in ethanolic solution with dipiperidylmethane; 2-naphthol gives the 1-substitution product in 97% yield under similar conditions.[26] The reaction of 4-methyltropolone with dipiperidylmethane affords the 7-substitution product (equation 12).[27] That 5-bromo-1-piperidylmethylisatin reacts with 2-naphthol and results in the exclusive incorporation of the piperidylmethyl residue into the product led to the suggestion that the Mannich reactions with aminals involve the prior hydrogen bonding of the phenolic hydroxy group *via* the more basic nitrogen, as shown in equation (13).[6b] The interesting comment is made[6b] that the *ortho* substitution of the phenol may be comparable to the Claisen rearrangement of allyl ethers, rather than a normal electrophilic

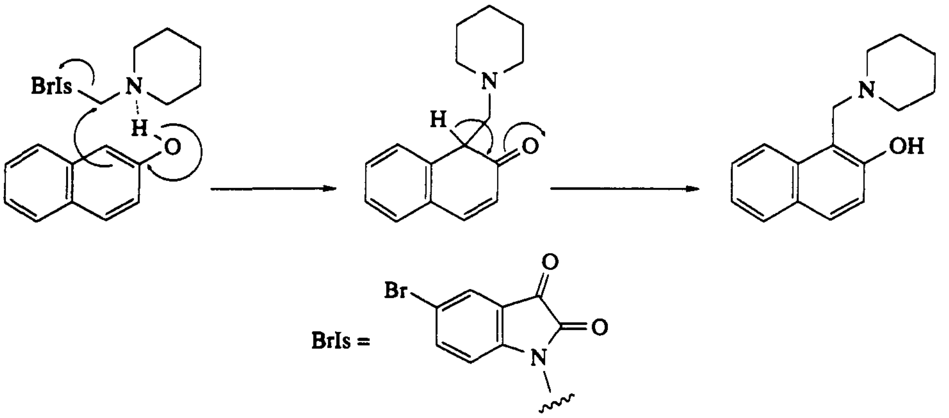

(13)

substitution reaction. It could be that the reactions are more complex than has previously been thought and that *O*-aminoalkylation precedes a concerted intermolecular rearrangement (equation 14). A similar mechanism would account for the rapid formation of products when ketones interact with iminium salts (see Chapter 4.1). Some of the successful reactions shown in the equations have used aminol ethers and it is possible, therefore, that classical reactions using ethanol as a solvent involve the intermediacy of an aminol ether rather than an aminal. It has recently been shown that the yields of the expected products are increased significantly if the reactions of aminals that are carried out in acetonitrile are activated by means of sulfur dioxide. We return to this topic in the next section.

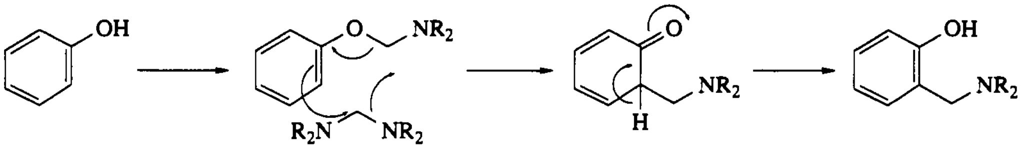

(14)

A number of studies report the use of aminol ethers in reactions with phenols; representative examples are given in equations (15)–(17).

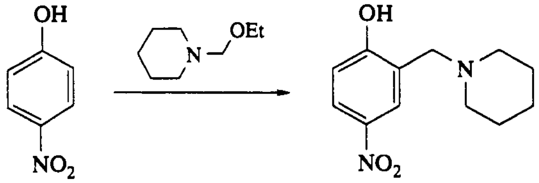

(15)[28]

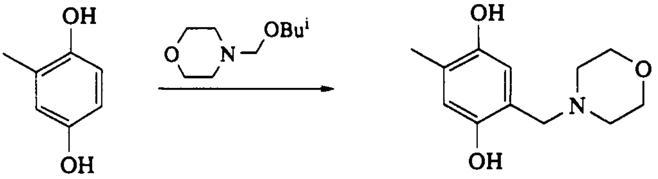

(16)[29]

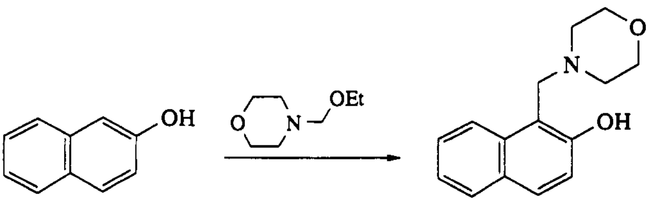

(17)

#### 4.2.3.1.2 Reactions using nonprotic solvents

##### (i) Reactions involving aminals and aminol ethers

Until very recently the only reported example of a reaction being carried out in a nonprotic solvent was that involving the interaction of 2-naphthol with ethoxy-*N*-morpholinylmethane in dioxane (equation 17).[30] A number of other reactions using less-reactive phenols have also been investigated in acetonitrile. The yields of products are normally improved when sulfur dioxide is added to activate the aminal and some improvement also accrues using aminol ethers. We indicated earlier that 2,5-dimethylphenol takes part in the classical Mannich reaction to afford the 4-substitution product (for example equation 7). The reaction of 2,5-dimethylphenol with sulfur dioxide and then with a variety of aminol ethers results in a change in the regioselectivity. The effect is most marked when a low molar ratio of sulfur dioxide to reagent is employed. It has been suggested that a half-sulfite ester interacts with aminol ethers as shown in Scheme 3 and affords the *ortho* substitution product after the elimination of sulfur dioxide.[31] This device may prove to be generally useful in controlling the regiochemistry.

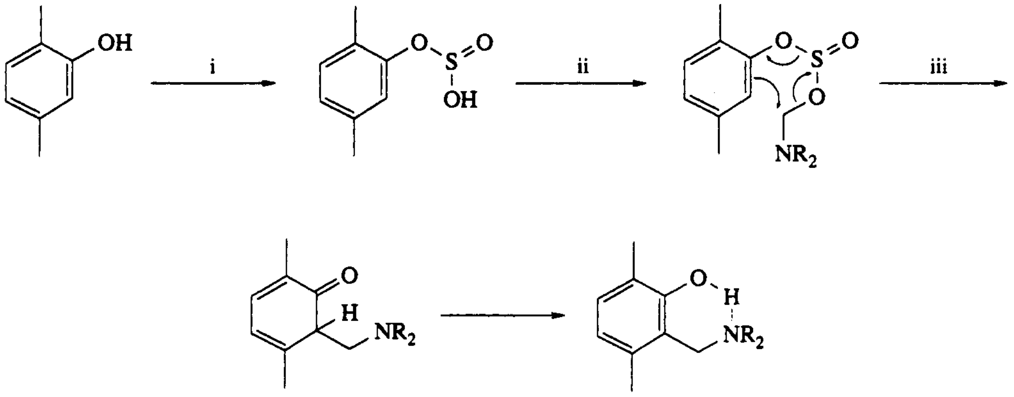

i, $SO_2$; ii, $R_2NCH_2OEt$ or $(R_2N)_2CH_2$; iii, $-SO_2$

Scheme 3

*(ii) Reactions using preformed iminium salts*

Although *N,N*-dialkylmethyleneiminium salts have been widely used in reactions with ketones and a number of heterocyclic systems, phenols have not been investigated in great detail. The regioselective formation of *ortho* substitution products has been reported under what are described as 'solid–liquid phase-transfer conditions'.[32] Excellent yields of *ortho* substitution products were reported under these conditions for electron-rich phenols such as *o*-cresol, 2-*t*-butylphenol and phenol. It was suggested that reactions carried out in the presence of potassium carbonate resulted in gegenion exchange to give the iminium phenoxide ion pair, which collapses to product. However, under the same reaction conditions, 2,5-dimethylphenol gives mixtures of products.[31] A difference has been observed with 2-methyl-1-naphthol between the results of a classical reaction and one involving a preformed iminium salt.[33] Whereas a reaction using *N*-piperidinylmethyleneiminium chloride affords the expected Mannich base hydrochloride, the classical reaction conditions using formaldehyde and piperidine yields the related diarylmethane.

### *4.2.3.1.3 Reactions involving aldehydes other than formaldehyde*

As was indicated in the introduction, few successful studies have been reported with aldehydes other than formaldehyde. For this reason this section is not subdivided. Once again two general points emerge. First, 2-naphthol is the best phenol with which to evaluate new systems, and second, reactions involving diethylamine generally give low yields, presumably for steric reasons.

2-Naphthol reacts with benzaldehyde and secondary amines (equation 18) in ethanolic solution to afford the corresponding Mannich bases in yields ranging from 21% with diethylamine to 72% with piperidine.[34] The aminal derived from benzaldehyde and piperidine is also effective. Aminals and aminol ethers derived from glyoxylic acid and the related iminium salts react efficiently with a number of substrates, including 2-naphthol (equation 19).[35] Although not strictly within the purview of this section, it is worth noting the reactions of 2-hydroxy-1,4-naphthoquinone with acetaldehyde and secondary amines. Once again piperidine gives a significantly higher yield (30%) than diethylamine (5%).[36]

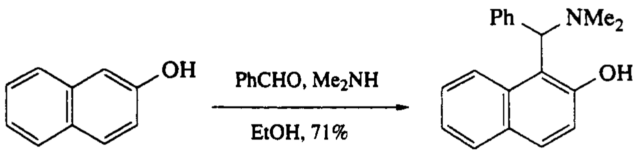

(18)

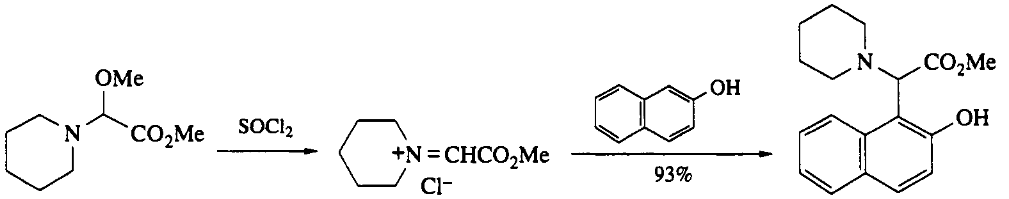
(19)

### 4.2.3.2 Aminoalkylation Reactions of Arylamines

The Mannich reactions of arylamines have not been studied in as much detail as those of phenols. Nevertheless, interesting features have been established and further developments can be envisaged.

*N*,*N*-Dialkylarylamines react under classical conditions at C-4 if that position is unsubstituted. For example, *N*,*N*-dimethylaniline reacts with formaldehyde and dimethylamine to afford 4-*N*′,*N*′-dimethylamino-*N*,*N*-dimethylbenzylamine in 82% yield (equation 20).[37] Under acidic conditions fragmentation of the initial product can occur, leading to the formation of diarylmethanes. In the reaction of *N*,*N*-dimethylaniline with formaldehyde and pyrrolidine the best yield of the Mannich base (44%) is obtained in the presence of 1.5 mol equiv. of acetic acid; with 4.0 mol equiv. the yield is only 7%.[38] The reaction of *N*-methylenemorpholinium chloride with 4-*N*′-morpholinylmethyl-*N*,*N*-dimethylaniline results in the introduction of a second *N*-morpholinylmethyl residue at the 2-position, but with other iminium chlorides quaternary salts are formed by reaction with the nitrogen of the 4-dialkylaminomethyl group.[39] There is also a brief report of the use of the mixed *N*,*N*-dialkylmethyleneiminium salt, *N*-*t*-butyl-*N*-methylmethyleneiminium perchlorate, with *N*,*N*-dimethylaniline.[40]

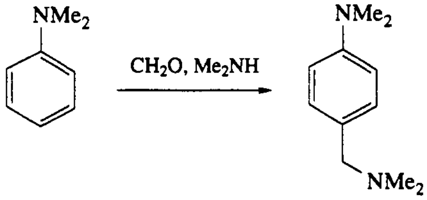
(20)

Secondary arylamines give products of attack at nitrogen as well as ring-substitution products. Thus, *N*-methylaniline reacts with formaldehyde and piperidine in the absence of acids to afford the aminal (**6**). In the presence of 0.5 mol equiv. of acetic acid the ring-substitution product (**7**) is obtained in 40% yield.[41] Another type of aminal has also been obtained in reactions of secondary arylamines; *N*-ethyl-*p*-toluidine gives the important by-product (**8**) in a reaction with piperidine and formaldehyde.[42]

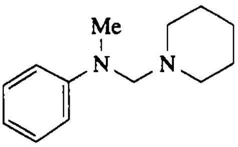
(**6**)

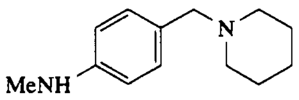
(**7**)

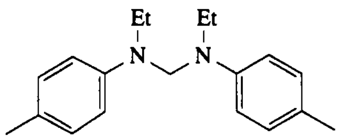
(**8**)

### 4.2.3.3 Aminoalkylation Reactions of other Carbocyclic Compounds

Because the Mannich reaction involves relatively weak electrophiles there are few other substituted benzenes that are sufficiently nucleophilic to react. Thus, anisole is not nucleophilic enough but 1,3-dimethoxybenzene is. Even with the latter compound the classical aqueous reaction conditions cannot be used. The reactions of 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene with preformed methyleneiminium chlorides in aprotic solvents were the first examples that used this procedure, which has subsequently been shown to be one of the most important recent advances in Mannich technology.[43]

1,3-Dimethoxybenzene reacts with *N*-methylenemorpholinium chloride in acetonitrile to afford the Mannich product, characterized as the hydrobromide, in 66% yield. The analogous reaction using the pyrrolidinium salt is shown in equation (21). Ferrocene gives low yields of products, for example with bis(dimethylamino)methane in the presence of protic acids, and as with a number of other electrophiles a substituent is introduced into each of the rings.[44]

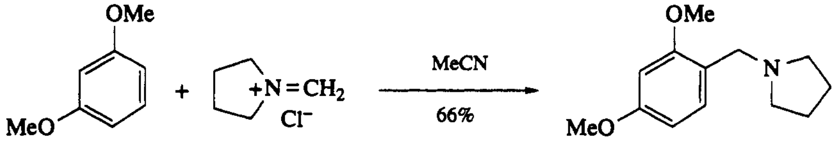

(21)

An alternative strategy for introduction of an aminomethyl residue involves *ipso*-aminoalkylation–destannylation reactions. This type of reaction takes advantage of the relatively high electron density at the carbon *ipso* to tin, and thereby is particularly useful for the formation of products with unusual regiochemistry.[45] We have indicated in Section 4.2.3.1 that Mannich reactions of phenols normally result in the introduction of an *ortho*-aminoalkyl residue. The reaction of 4-tetrahydropyranyloxyphenyltrimethylstannane with *N*,*N*-dimethylmethyleneiminium chloride in acetonitrile results in the formation, after aqueous acidic work-up, of the abnormal regioisomer as shown in equation (22). It is worth noting that aryltrialkylsilanes do not, in general, confer enough nucleophilicity to allow reaction with the weakly electrophilic iminium salts.

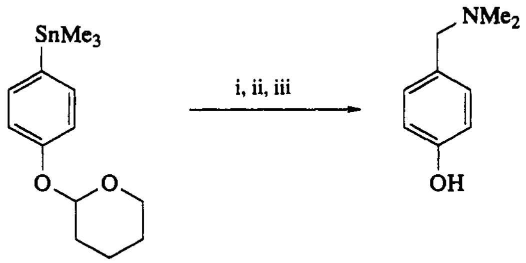

(22)

i, $Me_2\overset{+}{N}{=}CH_2$ $Cl^-$; ii, $H_2O/H_3O^+$; iii, $OH^-$

Because a wide range of aryltrialkylstannanes are available from the corresponding aryl bromides this reaction can be used to introduce one or more dialkylaminomethyl groups into a variety of aromatic substrates. The reaction of *N*,*N*-dimethylmethyleneiminium chloride with 1,4-bis(trimethylstannyl)benzene gives *N*,*N*,*N′*,*N′*-tetramethyl-1,4-diaminobenzene in 58% yield.[45]

### 4.2.3.4 Reactions with Electron-rich Heterocyclic Systems

Because of the wide variation in nucleophilicity of five-membered aromatic heterocycles, this group of compounds has been extensively studied. The different experimental procedures that may be used reflect the π-electron densities in this family of compounds. The most nucleophilic heterocycles, for example pyrrole, react using aqueous solutions of formaldehyde and a secondary amine, whereas relatively unreactive compounds such as thiophene only react successfully with preformed iminium salts. Reactions of certain heterocyclic ring systems have been investigated primarily because of the potential for biological activity of the products. For example, indolizines undergo high-yield *C*-aminoalkylation in the five-membered ring under the classical conditions.[46] Some examples are shown in equations (23) and (24), including the use of (1*S*,2*R*)-ephedrine.[47] The iminium salt derived from methyl 1-morpholino-1-methoxyacetate[35] reacts with 8-acetoxy-3-acetylindolizine in acetonitrile at room temperature to afford the Mannich base hydrochloride (**9**) in quantitative yield.[48] So far, it has not been possible to isolate pure samples of a number of diaminomethanes derived from bulky secondary amines.[14] Nevertheless, successful reactions have been reported, for example that of 1,2-diphenylindolizine with formaldehyde and dicyclohexylamine.[49] The reaction of the 2,3-dihydro-5(1*H*)-indolizinone (**10**) with *N*,*N*-dimethylmethyleneiminium chloride gives compound (**11**); once again, it is noteworthy that the trimethylsilyl group is not involved in the substitution reaction.[50]

Functionalizations of some rather unusual systems have been reported. For example, a Mannich reaction of a 4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine at the free position in the triazole ring occurs on heating with *N*,*N*-dimethylmethyleneiminium chloride in degassed DMF.[51] Although no successful reactions of thiazole have been reported, 2-acetylamino-4-methylthiazole reacts with formaldehyde and

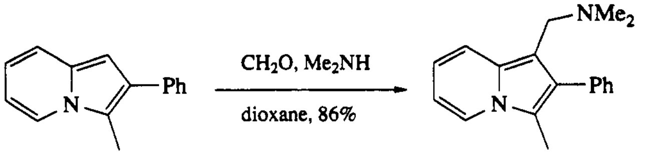
Ph
CH2O, Me2NH
dioxane, 86%
NMe2
Ph
N

(23)

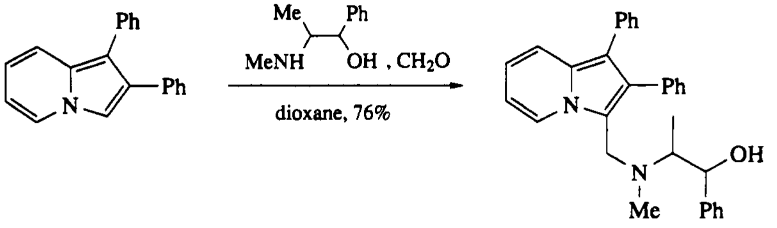
Ph
Ph
N
Me Ph
MeNH OH , CH2O
dioxane, 76%
Ph
Ph
N
OH
N
Me Ph

(24)

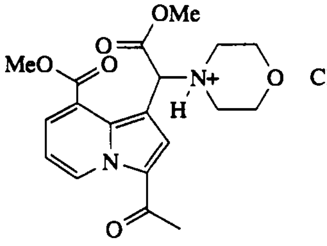
OMe
MeO
O
O
N+
H
O
Cl⁻
N
O

**(9)**

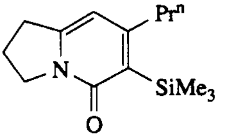
Prⁿ
N
SiMe3
O

**(10)**

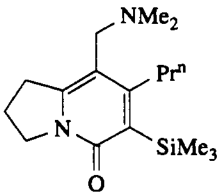
NMe2
Prⁿ
N
SiMe3
O

**(11)**

dimethylamine in acetic acid to afford the 3-*N*,*N*-dimethylaminomethyl derivative in 92% yield.[52] Imidazole reacts at nitrogen at low pH but in basic media *C*-aminoalkylation occurs.[53] We will subdivide the remainder of this section according to the parent ring system.

### *4.2.3.4.1 Reactions of thiophenes*

It has been known for some time that thiophenes that are activated by electron-releasing substituents undergo the Mannich reaction with formaldehyde and secondary amines.[54] Reactions of 2- or 3-methoxythiophene with formaldehyde and dimethylamine, piperidine or morpholine give Mannich bases in 69–89% yield. 3,4-Dimethyoxythiophene is apparently less reactive than the monomethoxy compounds but it also gives the 2-*N*,*N*-dimethylaminomethyl derivative in 66% yield. A modification of the classical procedure, in which gaseous formaldehyde is passed into a hot solution of 2-hydroxymethylthiophene and dimethylamine hydrochloride, gives the expected Mannich base in 25% yield. However, a better yield is obtained (equation 25) by heating the thiophene derivative under reflux with *N*,*N*-dimethylmethyleneiminium chloride in acetonitrile.[55] Thiophene itself gives the Mannich base in 55% yield using the latter reagent and reaction conditions. In all of the examples reported[55] substitution occurs at the 2-position. If a reaction is carried out at room temperature with 3-thienyltrimethylstannane (equation 26) the C-3 isomer is obtained in good yield. In this last experiment no evidence was found for the presence

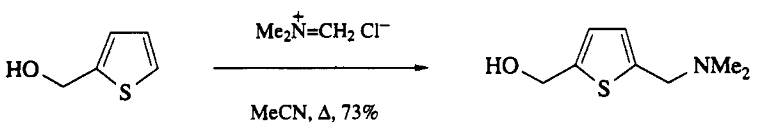
HO
S
Me2N⁺=CH2 Cl⁻
MeCN, Δ, 73%
HO
S
NMe2

(25)

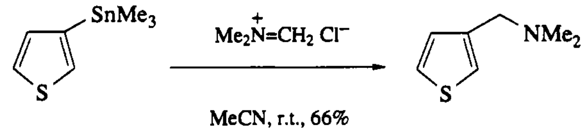
SnMe3
S
Me2N⁺=CH2 Cl⁻
MeCN, r.t., 66%
NMe2
S

(26)

of the 2-substitution product,[45] once again showing the value of using an arylstannane in an *ipso* electrophilic demetallation reaction when control over unusual regiochemistry is desired.

### *4.2.3.4.2 Reactions of furans*

Reactions of 2-methylfuran with aqueous formaldehyde and secondary amines have been reported using a variety of procedures.[56] Thus, 2-methylfuran, formaldehyde and dimethylamine react in aqueous acetic acid at 100 °C to give the expected product (equation 27) in 69–76% yield.[56c] Remarkably, it is reported[56b] that attempted Mannich reactions with furan itself yields no liquid amine. It has been suggested[57] that this type of reaction can only be carried out with alkyl-substituted furans, because of the marked activating effect of methyl substitution on electrophilic substitution reactions.

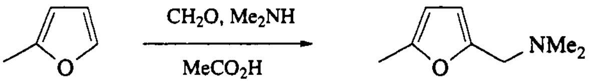

(27)

Competition data for the trifluoroacetylation of a number of heterocycles using trifluoroacetic anhydride at 75 °C give the relative rates: thiophene (1.0), furan (1.4 × $10^2$), 2-methylfuran (1.2 × $10^5$) and pyrrole (5.3 × $10^7$).[58] Similar values, thiophene (1.0), furan (3.0 × $10^3$) and pyrrole (5.0 × $10^5$); are obtained for reactions with $[C_6H_7Fe(CO)_3]^+$.[59] We have already discussed the fact that thiophene does undergo the Mannich reaction using preformed methyleneiminium salts and therefore it is not surprising that furan also affords the aminomethyl derivatives in reactions with iminium salts.

The yields of the Mannich bases obtained when a number of methyleneiminium salts were allowed to interact with furan in acetonitrile at room temperature ranged from 66 to 74%.[60] A representative example is shown in equation (28). The reasons for the earlier failures remain obscure but the amine would not have been lost under the aqueous reaction conditions.

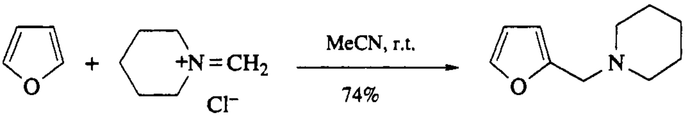

(28)

Preformed methyleneiminium salts react with 2-methylfuran to give the expected products in 65–94% yield.[60] It is even possible to carry out a reaction with *N,N*-diisopropylmethyleneiminium chloride (equation 29), the latter reagent being prepared in excellent yield by the interaction of ethoxy-*N,N*-diisopropylaminomethane with trichloromethylsilane.

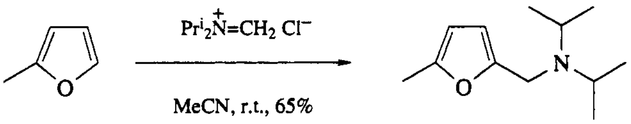

(29)

The possibility of carrying out reactions of furan and 2-methylfuran in nonprotic media without the isolation of reactive intermediates has also been investigated.[61] The results provide some help in understanding the mechanistic complexities involved in Mannich reactions and perhaps explain the failure of furan to afford a product using aqueous reaction conditions. A comparison of the strengths of the silicon–oxygen and silicon–nitrogen bonds also suggested the use of aminol ethers and aminals in *in situ* reactions, activated by derivatives of silicon tetrachloride. The formation of *N,N*-dialkylmethyleneiminium chlorides from ethoxy-*N,N*-dialkylaminomethanes had already been reported[62] using trichloromethylsilane. The $^{13}C$ NMR spectra of aminol ethers showed that iminium salts are also formed on treatment with dichlorodimethylsilane or chlorotrimethylsilane. On the other hand, iminium salts are not detected when aminals interact with chlorotrimethylsilane. Both furan and 2-methylfuran give good yields of Mannich bases when treated with, for example, ethoxypyrrolidinylmethane in the presence of chlorotrimethylsilane. In contrast, no Mannich base is formed when di-*N*-pyrrolidinylmethane is treated with chlorotrimethylsilane in the presence of 2-methylfuran. The conclusion may be drawn that, while both furan and 2-methylfuran are sufficiently nucleophilic to react with iminium salts, the intermediates formed when aminals interact with chlorotrimethylsilane are not electrophilic enough to participate in Mannich reactions with these substrates. We will consider these reagents further in the section concerned with pyrroles (Section 4.2.3.4.3). It is likely, therefore, that the reactions of furan that were attempted in aqueous solution failed because the electrophilic intermediate that is generated in that system was too mild—it was not an iminium salt.

The possibility of carrying out Mannich reactions with cyclic aminol ethers has been alluded to earlier. It has also been shown that the *in situ* method using chlorosilanes can be applied to oxazolidines such as 3-methyl-1,3-oxazolidine.[63] The ring–chain tautomerism of 1,3-oxazolidines in the presence of protic acids has been studied[64] by NMR spectroscopy and the hydroxy Schiff base; oxazolidine tautomerism has been discussed in terms of the apparent violation of Baldwin's rules.[65] The idea that a Mannich reaction could be carried out while at the same time protecting the resulting alcoholic function was explored in a reaction of 2-methylfuran with 3-methyl-1,3-oxazolidine and *t*-butyldimethylchlorosilane. The yield in this reaction is only modest (33%) but catalysis with 1,2,4-triazole results in an improvement to 61% (equation 30). Good yields are obtained in reactions of 2-methylfuran with 3-methyl-1,3-oxazolidine and chlorotrimethylsilane (73%) or trichloromethylsilane (87%). Even the reaction of furan gives a good yield (75%) with trichloromethylsilane.

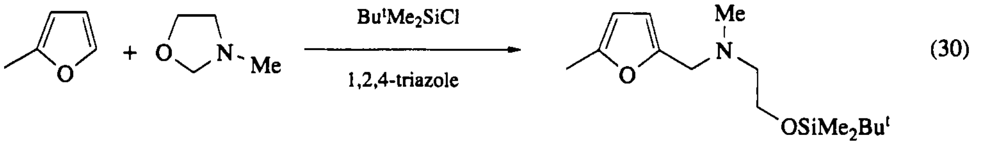

(30)

### 4.2.3.4.3 Reaction of pyrroles

Pyrroles are exceptionally nucleophilic heterocycles and undergo electrophilic substitution reactions with very weak electrophiles. The reactivity of pyrrole may be compared with that of *N*,*N*-dimethylaniline or phenol; all three compounds couple with the benzenediazonium ion. It is no surprise, therefore, that Mannich reactions of pyrrole and substituted pyrroles have been studied in considerable detail. We will concentrate our attention on recent studies.

Pyrrole reacts with aqueous formaldehyde and secondary amines in the presence of acetic acid to afford, in some cases, mixtures of products derived from attack at the 2- and 2,5-positions. The disubstitution products can be obtained in very high yields at about room temperature; for example, a 92% yield of 2,5-bis(piperidylmethyl)pyrrole is obtained using this method.[66] The same procedure apparently does not yield a Mannich base with 1-methylpyrrole, but the use of aqueous formaldehyde and dimethylamine hydrochloride at 60 °C results in the formation of the 2-substitution product in 73% yield.[67] Even highly substituted pyrroles react. Thus, ethyl 4,5-dimethylpyrrole-2-carboxylate and ethyl 2,5-dimethylpyrrole-3-carboxylate both undergo *C*-aminoalkylation at the unsubstituted position in 45 and 68% yields, respectively, with dimethylamine and formaldehyde in ethanolic solution.[68] A number of tri- and tetra-substituted 2-methylpyrroles have been investigated; with the exception of Knorr's pyrrole all gave side-chain substituted products with formaldehyde and a secondary amine in acetic acid.[69]

More modern technology has also produced some interesting results. Quaternization of 1-*N*,*N*-dimethylaminopyrrole and treatment of the product with sodium methoxide in DMSO leads to Stevens-type rearrangement products.[70] No CIDNP was observed in an NMR study of the rearrangement and it was concluded that the ylide fragments to an ion pair, which recombines as shown in Scheme 4.

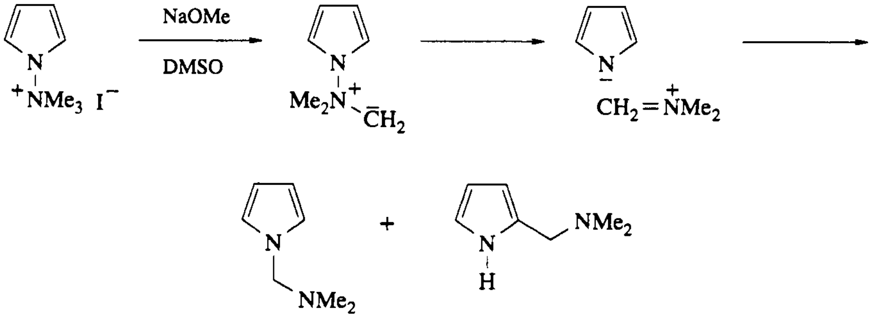

**Scheme 4**

Reactions carried out in nonprotic solvents using *in situ* generation of reactive intermediates have also been studied with *N*-methylpyrrole as the substrate. Attempts to achieve good conversions using acetyl chloride and an aminal were relatively unsuccessful but better yields were obtained using sulfur dioxide in reactions with both aminals and aminol ethers.[71]

Although reactions of di-*N*-morpholinylmethane with acetyl chloride in the presence of *N*-methylpyrrole give good yields of either the 2-substituted (54%) or 2,5-disubstituted (87%) products, reactions with bis-*N*,*N*-(dimethylamino)methane are poor. In the case of a reaction using 1 mol equiv. of aminal and acetyl chloride the yield was only 18% and an attempt to form 1-methyl-2,5-bis-*N*,*N*-(dimethylaminomethyl)pyrrole failed due to the formation of 1,1′-dimethyl-di-2,2′-pyrrylmethane. Reactions using sulfur dioxide as the anhydride-activating agent give high yields of the expected products with a range of aminals and aminol ethers. Iminium salts were not detected in NMR experiments and it was tentatively concluded that dipolar compounds such as (**12**) and (**13**) are the most likely reactive intermediates.

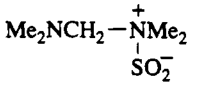

$$\mathrm{Me_2NCH_2{-}\underset{SO_2^-}{\overset{+}{N}}Me_2}$$

(**12**)

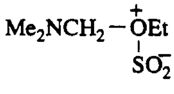

$$\mathrm{Me_2NCH_2{-}\underset{SO_2^-}{\overset{+}{O}}Et}$$

(**13**)

Reactions of *N*-methylpyrrole with aminol ethers and aminals in the presence of derivatives of silicon tetrachloride permit control of the number of aminoalkyl groups that are introduced.[61] The reactions of a number of aminol ethers with chlorotrimethylsilane and trichloromethylsilane give mixtures of 2- and 2,5-disubstitution products. The use of aminals, on the other hand, allows a good measure of control over the degree of substitution. Thus the reaction of di-*N*-pyrrolidinylmethane with *N*-methylpyrrole and trichloromethylsilane affords the monosubstitution product (**14**) in 75% yield, whereas with chlorotrimethylsilane the disubstitution product (**15**) is produced in 70% yield based on the aminal. It was concluded that the reaction leading to the formation of (**14**) is controlled by the formation of a salt of the Mannich base which is less nucleophilic than the starting material. The formation of (**15**) in the reaction involving chlorotrimethylsilane was interpreted as implicating the presence of the free Mannich base (**14**), which would be more nucleophilic than the starting material. This suggests that no accumulation of hydrogen chloride occurs in the reaction and led to the prediction that the reaction should be catalytic in chlorotrimethylsilane. Experiments have confirmed this prediction and in a reaction carried out under reflux with 5 mol % of chlorotrimethylsilane the compounds (**14**) and (**15**) were isolated in 17 and 61% yields respectively.[61] We mentioned in the section on furans (Section 4.2.3.4.2) the failure to detect iminium salts in NMR experiments using aminals and chlorotrimethylsilane. The formation of (**15**) was therefore explained in terms of equations (31)–(33).

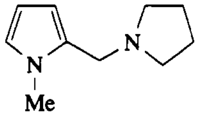

(**14**)

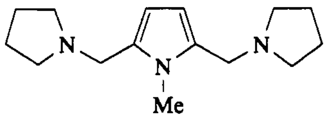

(**15**)

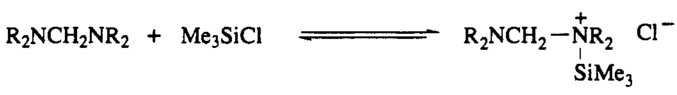

$$\mathrm{R_2NCH_2NR_2 + Me_3SiCl \rightleftharpoons R_2NCH_2{-}\underset{SiMe_3}{\overset{+}{N}}R_2\ Cl^-} \qquad (31)$$

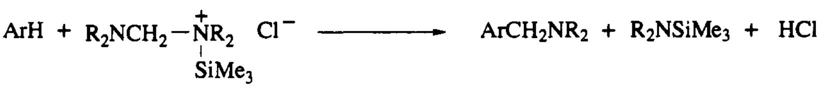

$$\mathrm{ArH + R_2NCH_2{-}\underset{SiMe_3}{\overset{+}{N}}R_2\ Cl^- \longrightarrow ArCH_2NR_2 + R_2NSiMe_3 + HCl} \qquad (32)$$

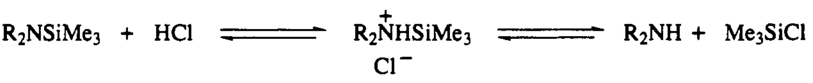

$$\mathrm{R_2NSiMe_3 + HCl \rightleftharpoons \underset{Cl^-}{R_2\overset{+}{N}HSiMe_3} \rightleftharpoons R_2NH + Me_3SiCl} \qquad (33)$$

### *4.2.3.4.4 Reactions of indoles*

Like pyrrole, indole is a highly nucleophilic aromatic heterocycle and takes part in Mannich reactions under a wide variety of reaction conditions, including the very mildest. We will only mention a few important examples from the very large number of reactions carried out under classical conditions.[2]

3-*N*,*N*-Dimethylaminomethylindole (gramine) can be obtained in 90–95% yield and the *N*-methyl analog in 77–80%. 2-Ethoxycarbonyl-5-hydroxyindole undergoes reaction at the 4-position, while the benzyl analog affords the 3-dimethylaminomethyl derivative (equation 34).[72] 1,2,3-Trialkylindoles like *N*-methyltetrahydrocarbazole undergo aminoalkylation on the carbon at the 2-position.[73] This reaction presumably proceeds by a mechanism (Scheme 5) that is similar to those operating when other electrophiles react with highly alkylated indoles. The quaternary salts derived from Mannich bases have been widely used in synthesis. Well-known examples include a tryptophan synthesis and preparations of the plant growth hormones 3-indolylacetonitrile and 3-indolylacetic acid.

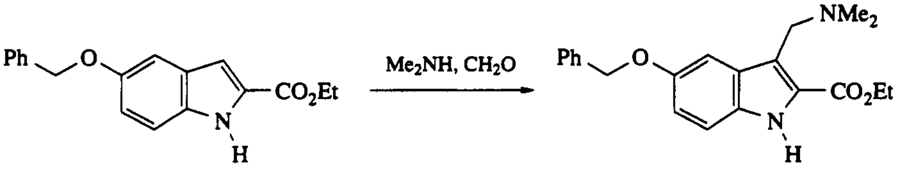

(34)

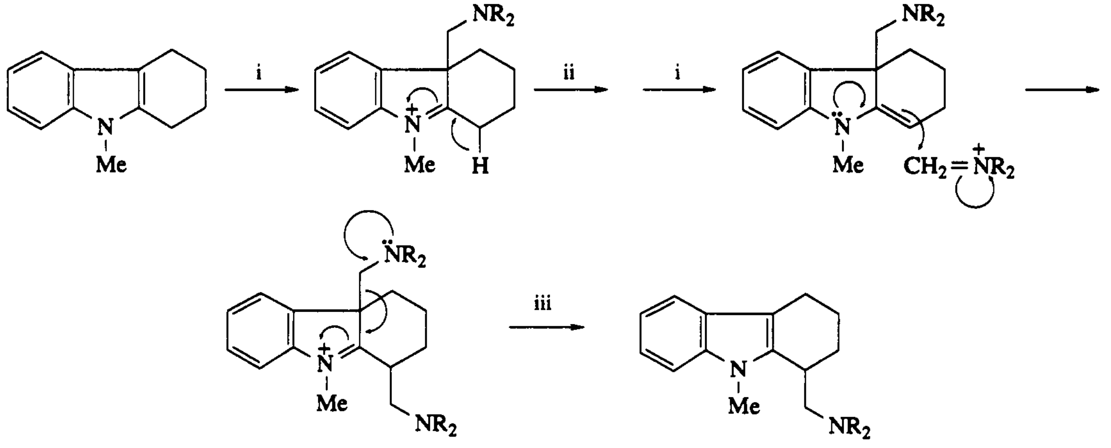

i, $R_2\overset{+}{N}=CH_2$; ii, $-H^+$; iii, $-R_2\overset{+}{N}=CH_2$

Scheme 5

Good yields of the expected Mannich bases are also obtained in reactions using recently described methodology, including *in situ* generation of reactive intermediates.[61,63,71,74] Functionalization of indoles at C-3 and C-4 has been widely studied in connection with syntheses of ergot alkaloids. Reactions with preformed *N*,*N*-dimethylmethyleneiminium chloride are especially useful in this context. A number of 4-substituted indoles give the 3-*N*,*N*-dimethylaminomethyl derivatives in yields ranging from 91 to 100%.[73] This type of reaction is exemplified by equation (35).[75] The synthesis of *cis*- and *trans*-clavicipitic acids from 4-cyanomethylindole also involves functionalization at C-3 by reaction with *N*,*N*-dimethylmethyleneiminium chloride.[76] Classical reaction conditions have also been used in a total synthesis of racemic 6,7-*seco*-agroclavine.[77]

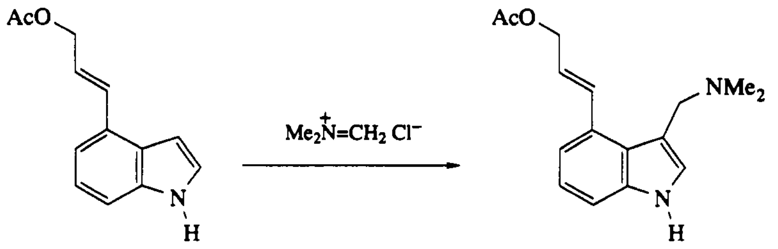

(35)

A reversal of the reaction sequence, that is the introduction of the C-3 substituent first, is accomplished by starting with 1,4-bis(trimethylsilyl)indole. Reaction of this compound with the usual iminium salt gives the product shown in equation (36) in variable yields.[78] Once again, we observe that iminium salts are not electrophilic enough to effect *ipso* substitution of a silyl residue.

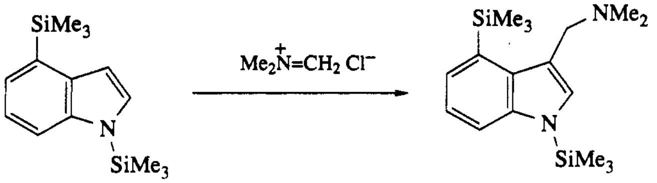

(36)

## 4.2.4 REACTIONS USING PRIMARY AMINES

A number of different types of product can be formed when an aromatic substrate reacts with a primary amine and an aldehyde. The first-formed product will be a secondary amine and can therefore take part in a second Mannich reaction. A third possibility is that another suitable functional group may be correctly positioned to enable a cyclic product to be formed.

### 4.2.4.1 Reactions Leading to Acyclic Products

Mannich reactions of pyrroles with primary amine hydrochlorides give yields that were significantly lower than those obtained with secondary amine hydrochlorides.[67,79] For example, whereas formaldehyde and dimethylamine hydrochloride react with pyrrole to give the expected product in 77% yield, reaction with methylamine hydrochloride only gives a 15% yield of 2-*N*-methylaminomethylpyrrole. A by-product in the reaction is the di(2-pyrrylmethyl)amine derivative (equation 37).[80] Increasing the steric bulk of the group on the nitrogen of the primary amine gives a higher yield of the first-formed product; no di(2-pyrrylmethyl)amine derivative is formed in reactions of pyrrole with formaldehyde and isopropylamine or *t*-butylamine. As expected, increasing the amount of amine hydrochloride used also favors formation of secondary amine. The steric effect of large groups on nitrogen is also observed in products derived from amino acids. The reaction of threonine with formaldehyde and 2,4-dimethylphenol (equation 38) also gives the secondary amine.[81]

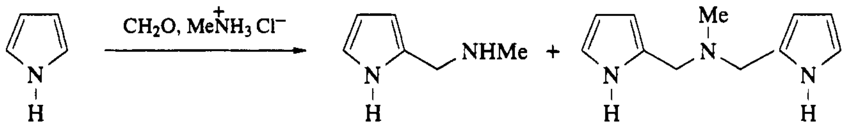

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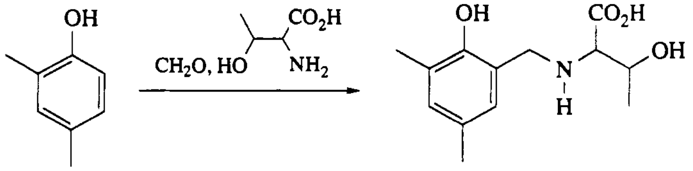

(38)

### 4.2.4.2 Reactions Leading to Cyclic Products and Their Reactions

The reactions of ethyl 2,4-dimethylpyrrole-3-carboxylate with a number of primary amines and an excess of formaldehyde lead to the formation of 2,3-dihydro-1*H*-imidazo[1,5-*a*]pyrroles. The reaction of cyclohexylamine, which, as indicated in the foregoing section, would not be expected to yield a product involving two pyrrole nuclei, does result in the formation of the dihydroimidazopyrrole in 70% yield as shown in Scheme 6.[82]

The main substrates that have been investigated as partners in cyclization reactions are phenols. As with reactions involving secondary amines, phenols react with aldehydes and primary amines principally *ortho* to the hydroxy group. A reaction of the first-formed secondary amine with a second molecule of aldehyde can therefore lead to the formation of a benzoxazine derivative. A wide range of phenols, includ-

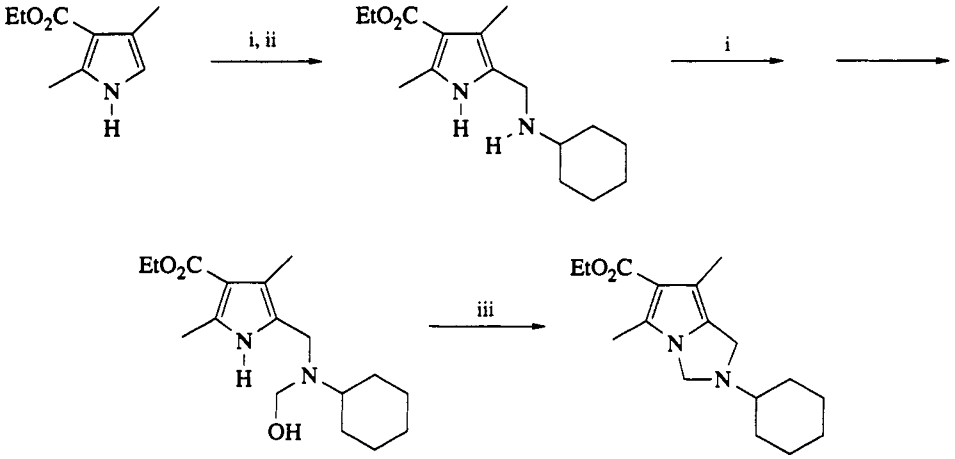

i, $CH_2O$; ii, $C_6H_{11}NH_2$; iii, $-H_2O$

**Scheme 6**

ing for example *p*-cresol (equation 39) and 2,4-dichlorophenol form benzoxazines in good yields using methylamine and formaldehyde.[83] It is interesting to note that of the two possible dioxazine derivatives that can be formed from hydroquinone, the compounds (**16**) (equation 40) are the major products.[84] The possibility of using a diaminol ether as a bisaminoalkylating agent has been investigated briefly in connection with the reaction of 2-methylhydroquinone as shown in equation (41).[29]

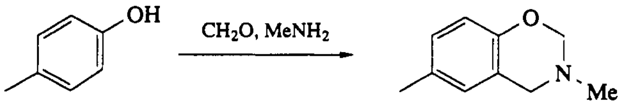

(39)

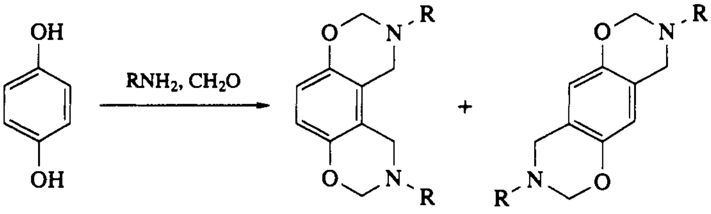

(**16**)

(40)

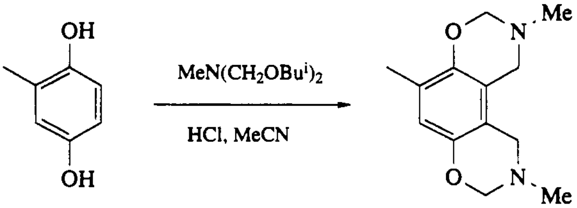

(41)

It was noted at an early stage[83a] that the heterocyclic ring in benzoxazines is easily cleaved, for example by ethanol. The ring–chain tautomerism of 2-aryl-1,3-benzoxazines has been investigated,[85] and it has been shown that the equilibration of benzoxazines in the presence of primary or secondary amines involves Mannich bases and ring-opened coupling products.[86] It is not surprising, therefore, that benzoxazines have been investigated as potential Mannich reagents in reactions with phenols.[83b] What is surprising is that the promised extension to other systems does not appear to have materialized so far. An example of the reaction with a phenol is shown in equation (42).[83b] Electronic effects both in the benzoxazine and also in the phenolic coreactant are, as expected, important. Thus the dichlorobenzoxazine shown in equation (42) is a very reactive species because of the enhanced electrophilicity of the aminoalkylating agent that results from the presence of the chlorine atoms. On the other hand, the most reactive phenolic coreactants are those with high electron density in the aromatic ring. 2-Naphthol is particularly reactive due to the low activation energy involved in reactions with electrophiles at the 1-position.

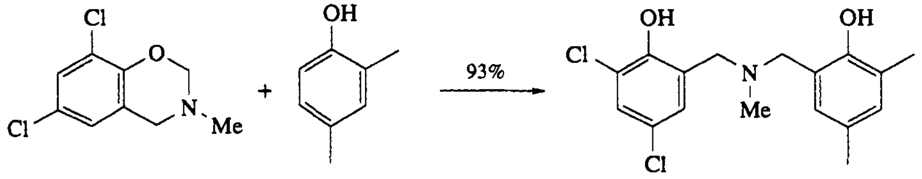

(42)

Amine exchange reactions have been reported in which, for example, a secondary amine replaces the primary amine. This type of reaction is exemplified in equation (43).[29] The use of newer technology, for example involving mild Lewis acids in nonprotic solvents, should allow additional reactions of benzoxazines to be carried out.

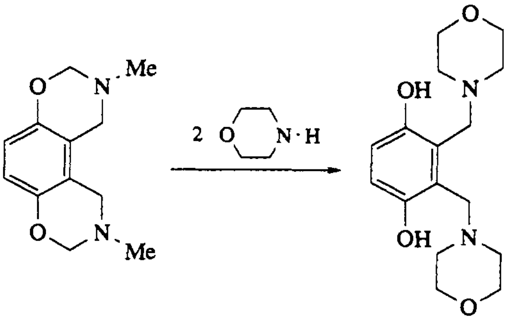

(43)

## 4.2.5 REACTIONS USING IMINES

We indicated in the introduction that the trimerization of pyrrole involves, in the reaction of the third molecule of pyrrole, the interaction with a protonated enamine. Such an intermediate could also be generated by protonation of an imine. Although few examples of intermolecular reactions have been reported, it is clear that this is another method that is capable of further exploitation. Acyclic and cyclic imines have been shown to interact successfully with nucleophilic aromatic substrates such as indole. In the case of the cyclic imines they may be generated *in situ* from relatively stable trimers.

The reactions of indole with the imines derived from acetaldehyde and *t*-butylamine and isopropylamine have been reported using acetic acid as the proton source in benzene.[87] A poor yield (15%) is obtained with ethylidene-*t*-butylamine but a better yield (60%) results with the isopropylamine analog (equation 44). A 'one pot' reaction using indole, acetaldehyde and isopropylamine gives the same product in 40% yield. This type of reaction depends for its success on the stability of the aldimine under the acidic reaction conditions. However, while the more sterically demanding primary amines afford the most stable imines, it appears that this can lead to too great a steric demand in the transition state leading to reaction with, for example, indole, and hence the low yield reported in the *t*-butylamine reaction.

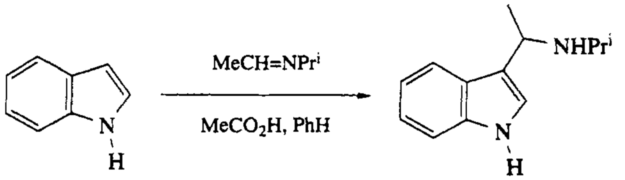

(44)

The trimer of 1-piperidine, best prepared by dehydrochlorination of *N*-chloropiperidine, has been known for some time.[88] 1-Pyrroline also appears to exist largely as the trimer.[89] Both undergo Mannich reactions with electron-rich heterocycles. Indole reacts with 1-piperidine in a citrate buffer to afford 3-(2-piperidyl)indole in 40–55% yield (equation 45).[90] The *N*-methylpiperidyl analog has also been prepared, but only in very low yield. Once again, we note the remarkable variations in yields obtained in Mannich reactions involving primary and secondary amines and aldehydes other than formaldehyde. Although 1-pyrroline is only obtained from its trimer in very low yield,[89] its formation may be inferred by the fact that 2-(2-pyrrolidyl)pyrrole is produced in high yield when the trimer is heated with an excess of pyrrole.[89]

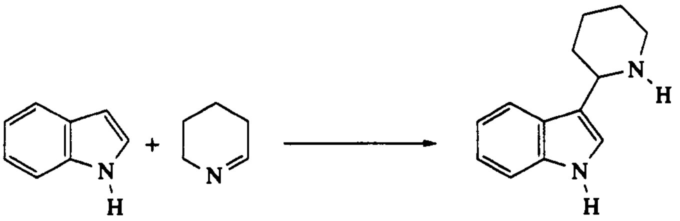

(45)

## 4.2.6 AMIDOALKYLATION REACTIONS

Acyliminium ions are the reactive intermediates in amidoalkylation reactions and are the subject of Chapter 4.5. This section is restricted to a brief coverage to allow comparisons to be made with the earlier sections in this chapter. The topic has been reviewed several times.[91]

The most important feature of the chemistry of amidoalkylating reagents is related to the increased electrophilicity of such reagents compared to those involved in aminoalkylation reactions. It is possible to vary the reactivity of the reagents by adjusting the electron-withdrawing acyl group. A frequently used amidomethylating agent is *N*-hydroxymethylchloroacetamide. This reagent combines the involvement of a reasonably electrophilic reagent with the presence of an easily hydrolyzed acyl residue. Thus, amidoalkylation of, for example, 2,4-dimethylanisole can be achieved.[92] Even more electrophilic is *N*-hydroxymethylphthalimide. Mesitylene gives, with the latter reagent, an 86% yield of product (equation 46).[93]

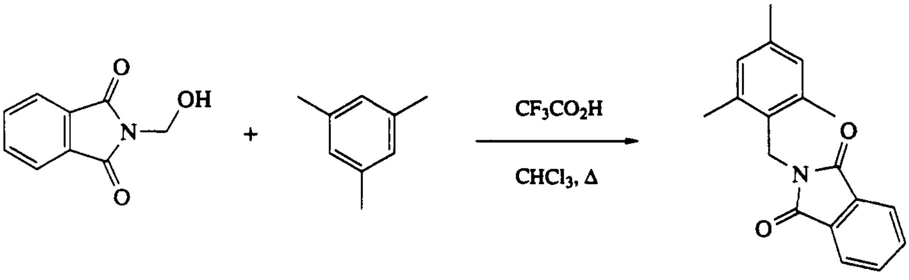

(46)

The reaction of furan with the acetaldehyde derivative (**17**) in the presence of toluene-*p*-sulfonic acid gives (**18**) in 67% yield (equation 47).[94]

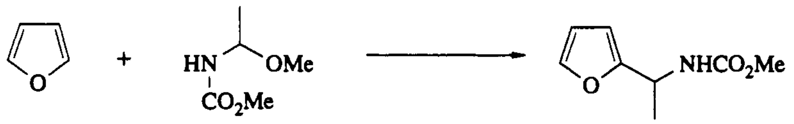

(47)

(**17**) (**18**)

*N*-α-Chloroalkylamides are relatively unstable precursors and form acyliminium ions easily. They are frequently formed *in situ* as indicated in equation (48).[95]

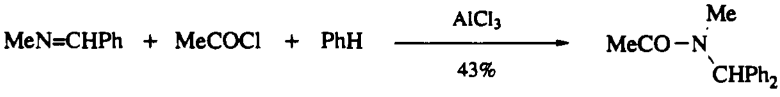

$$\mathrm{MeN{=}CHPh} + \mathrm{MeCOCl} + \mathrm{PhH} \xrightarrow[43\%]{\mathrm{AlCl_3}} \mathrm{MeCO{-}N}\begin{smallmatrix}\mathrm{Me}\\ \mathrm{CHPh_2}\end{smallmatrix}$$

(48)

The chemistry that has been reviewed in this chapter demonstrates that although the bimolecular Mannich reactions of aromatic compounds have now reached the venerable stage, they are still much used by synthetic organic chemists and that they are capable of further development.

## 4.2.7 REFERENCES

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# 4.3

# Reactions of Allyl and Propargyl/Allenic Organometallics with Imines and Iminium Ions

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## 4.3.1 INTRODUCTION

### 4.3.1.1 Reactivity and Structure

Gilman and Eisch were the first to recognize that allyl organometallic reagents possess superior reactivity relative to ordinary, nonresonance-stabilized organometallic reagents in imine addition reactions.[1] In an investigation of the reactions of *N*-diphenylmethyleneaniline (**1**) with organometallic reagents, these workers observed that while imine (**1**) is inert to ordinary Grignard reagents in refluxing ether, it cleanly reacts with allylmagnesium bromide in a 1,2-manner, affording 1-allyl-1,1-diphenylmethylaniline (**2**; Scheme 1). Interestingly, under forcing conditions (refluxing ether–toluene), phenylmagnesium bromide adds in a 1,4-manner to one of the aromatic rings of (**1**) to give amine (**3**). These results, together with the observation that the more ionic, nonresonance-stabilized lithium, potassium, sodium, calcium, barium and strontium organometallics add to imine (**1**) in a 1,2-manner, led to the suggestion that resonance stabilization of the allyl anion in allyl organometallic reagents promotes greater ionization of the carbon–metal bond and, hence, greater reactivity (Figure 1). This conclusion should not be confused with the fact that allyl anions are less nucleophilic than nonresonance-stabilized anions, because it is assumed that the reactivity is not governed by the nucleophilicity of the naked anion but by the ease of heterolysis of the carbon–metal bond.

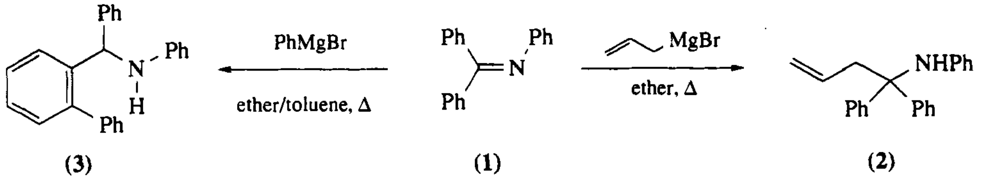

**Scheme 1**

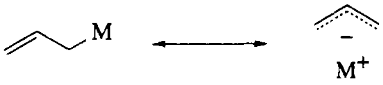

**Figure 1** Resonance stabilization of the allyl anion in allyl organometallic reagents results in greater ionization of the carbon–metal bond[1]

A general survey of the different types of allyl organometallic reagents reported to add in a 1,2-manner to imines, iminium salts and related compounds is shown in Table 1. The organometallic reagents are listed in order of increasing metal electronegativity, reflecting the increased covalent (less ionic) character of the carbon–metal bond. Allyl organometallics containing metals with electronegativities less than or equal to 1.65 add directly to imines while, except for allylboranes, less reactive reagents with electronegativities >1.65 require the use of Lewis acid additives to enhance the electrophilicity of the imine. The reactivity of allylboranes, which is greater than predicted based on the electronegativity of boron, may be attributed to the Lewis acidity of boron which enhances imine reactivity by coordination to the imine lone pair of electrons. Iminium salts, being more electrophilic than imines due to the positively charged nitrogen, are capable of reacting directly with less reactive reagents such as allylsilanes and allylstannanes.

**Table 1** Survey of Allyl Organometallic Reagents Known to React with Imines, Iminium Salts and Related Derivatives

| *Metal* | *Ligand(s)* | *Electronegativity*[a] | *Imines* | *Oximes* | *Sulfenimines* | *Iminium salts* | *gem-Amino ether* |
|---|---|---|---|---|---|---|---|
| Lithium | — | 0.98 | x | x | | x | x |
| Magnesium | Halogen | 1.31 | x | x | x | x | x |
| Titanium | Alkoxy | 1.54 | x | | | | |
| Aluminum | Halogen | 1.61 | x | | | x | x |
| Zinc | Halogen | 1.65 | x | x | x | x | x |
| Tin | Alkyl | 1.72 | x[b] | | | x | |
| Silicon | Alkyl | 1.90 | | | | x | |
| Boron | Alkyl | 2.04 | x | | | | |
| Boron | Alkoxy | | x | x[c] | x | | |
| Lead | d | 2.33 | x[b] | | | | |

[a] Estimated by Pauling's method. [b] Lewis acid additive is necessary. [c] Reaction is performed at high pressure (4–9 kbar). [d] The allyllead reagent is formed *in situ*, the ligand is not known (see ref. 2).

Insight into the structure of several allyl/crotyl organometallic reagents has been obtained spectroscopically. Kramer and Brown have examined the NMR spectra of β-allyl-9-BBN and β-crotyl-9-BBN and conclude that at temperatures above −60 °C, β-allyl-9-BBN exists in a dynamic equilibrium in which the boron exchanges rapidly between the 1- and 3-positions of the allylic system (Figure 2).[3] Since the process is concentration independent, the exchange process must be intramolecular. The Lewis acidity of boron appears to be a critical factor in the exchange process because allylic rearrangement is not observed when a Lewis base such as pyridine is added. In the case of β-crotyl-9-BBN, equilibrating *cis* and *trans* alkene isomers are observed above 0 °C, instead of products of allylic rearrangement. Isomerization is postulated to proceed *via* allylic rearrangement through the transient 1-methallyl isomer (Figure 3). In another study by Gross, *cis* and *trans* forms of crotyl-magnesium, -zinc and -aluminum reagents are indicated in their solution IR spectra in the 1600 cm$^{-1}$ region; it is not clear, however, whether the isomers are in equilibrium.[4]

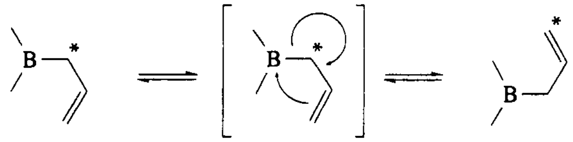

**Figure 2** β-Allyl-9-BBN exists in a state of permanent allylic rearrangement[3]

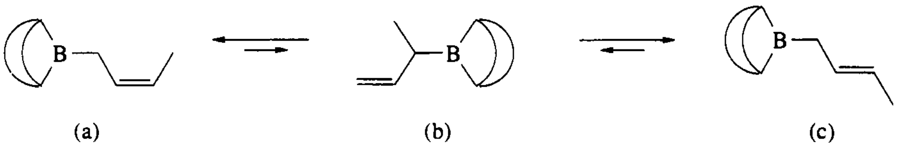

**Figure 3** Equilibrium between *cis* (a) and *trans* (c) β-crotyl-9-BBN involving the intermediacy of the β-methallyl isomer (b)[3]

The isotopic perturbation technique[5] has been used by Schlosser and Stähle to distinguish between the σ- and π-bond structures of allyl- and crotyl-magnesium, -potassium and -lithium reagents.[6] The $^{13}$C NMR spectra of the deuterated crotyl reagents demonstrate that: (i) crotylmagnesium reagents are σ-structures in which the metal is attached to the primary carbon (Figure 4a); and (ii) crotylpotassium and crotyllithium reagents are π-structures in which the metals are bonded to carbons 1 and 3 of the allylic system (Figures 4b and 4c). The data also suggest that the carbon–metal lengths in the crotylpotassium reagents are essentially equal, whereas those of the crotyllithium reagents are unequal. Similar conclusions can be drawn for the corresponding allyl organometallic reagents. As has been noted by Schlosser and Stähle,[6] energy differences between σ- and π-forms of allyl and crotyl organometallic reagents are not large; therefore, caution should be exercised in using structural knowledge for the interpretation of regio- and stereo-selective allyl and crotyl organometallic addition reactions since ground state organometallic structures are not necessarily involved in the rate determining step of the reaction.

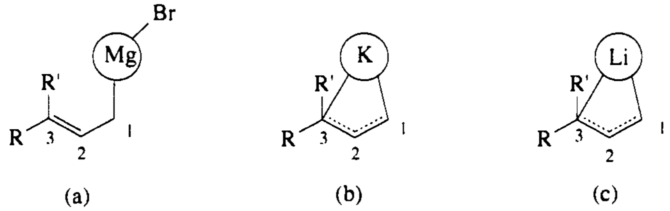

**Figure 4** Structures of allyl- and crotyl-magnesium, -lithium and -potassium reagents as determined by isotopic perturbation studies.[6] The magnesium reagent (a) exists as a σ-structure and the potassium (b) and lithium (c) reagents exist as π-structures

In contrast with the more reactive crotyl reagents discussed above, crotyl-silanes,[7] -stannanes[8] and -boronates[9] can be prepared in isomerically pure *cis* and *trans* forms for use in imine and aldehyde addition reactions. However, isomerization of these reagents under certain reaction conditions, particularly those requiring the presence of Lewis acids, cannot be ruled out. Nonetheless, in connection with a study involving aldehyde additions, Yamamoto *et al.* have shown that *trans*-crotyltri-*n*-butylstannane is stable to $BF_3{\cdot}Et_2O$ at −78 °C.[8]

### 4.3.1.2 Regio- and Stereo-chemistry

Reactions of crotyl organometallics with aldimines can give linear (**4**) and/or branched (**5**) homoallylamines, a result of addition at the α- and γ-crotyl carbon atoms (equation 1). Although branched products usually dominate, the metal (M) and the imine substituents ($R^1$ and $R^2$) can strongly influence the regiochemical outcome of the reaction; similar effects are observed with crotyl in additions to iminium salts and *gem*-amino ethers.

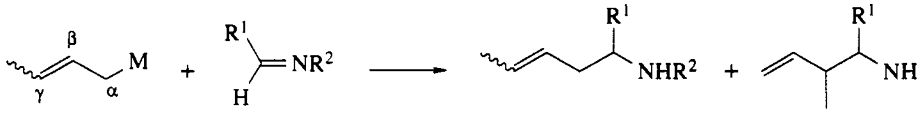

(**4**) (**5**) (1)

Branched homoallylamines obtained in the reaction of crotyl organometallics contain two adjacent stereocenters and therefore can be produced in two diastereomeric forms, *syn* (**6**) and *anti* (**7**).[10] Cyclic and open transition state models have been used by Yamamoto *et al.* to explain *syn–anti* stereoselectivity in reactions of imines and are shown in Figures 5 and 6.[11] The cyclic models involve coordination between the metal and the imine lone pair and comprise two chair (C) and two boat (B) transition states. The substituents are placed axially or equatorially according to the geometry of the crotyl reagent and the preferred (*E*)-geometry of the imine. A complementary set of transition states leading to the opposite diastereoselectivity can be derived from the (*Z*)-imine geometry. The open transition states, drawn as Newman projections, are depicted as antiperiplanar (A) or synclinal (S)[12] and are differentiated by the geometry of the crotyl reagent. The synclinal transition states are divided into two types, $S_g$ and $S_a$, depending upon whether the vinyl group and the imine α-substituent are *gauche* or *anti*, respectively. The open transition states shown are also based on (*E*)-imine geometry; those based on the (*Z*)-imine geometry, unlike the cyclic models, give the same diastereoselectivity. The three letter descriptors designating the overall geometry of the transition state, and the geometries of the crotyl reagent and imine, respectively, are used throughout this chapter.

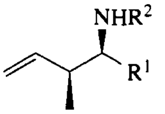

(**6**)

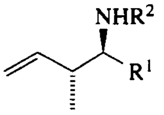

(**7**)

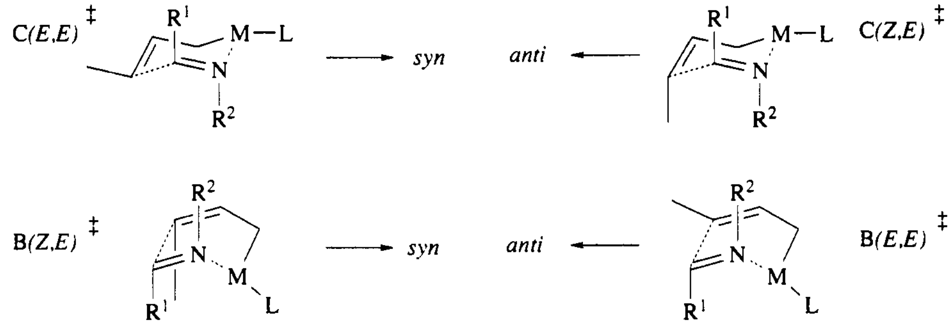

**Figure 5** Postulated cyclic chair and boat transition states involved in the reactions of crotyl organometallics[11]

Diastereofacial selectivity in allyl organometallic additions to aldimines containing one or more stereogenic centers has been studied extensively in recent years. Chiral imines used in these investigations have been derived from: (i) chiral aldehydes and achiral amines, (ii) achiral aldehydes and chiral amines and, in a few cases, (iii) chiral aldehydes and chiral amines. A few examples involving the use of allyl organometallics bearing chiral ligands have also been recorded.

Models used to explain and predict diastereofacial selectivity in related carbonyl addition reactions (Figure 7) can be utilized to predict similar selectivity in allyl organometallic–aldimine condensations. As a consequence of the type of imine substitution, addition reactions can be divided into two types: (i)

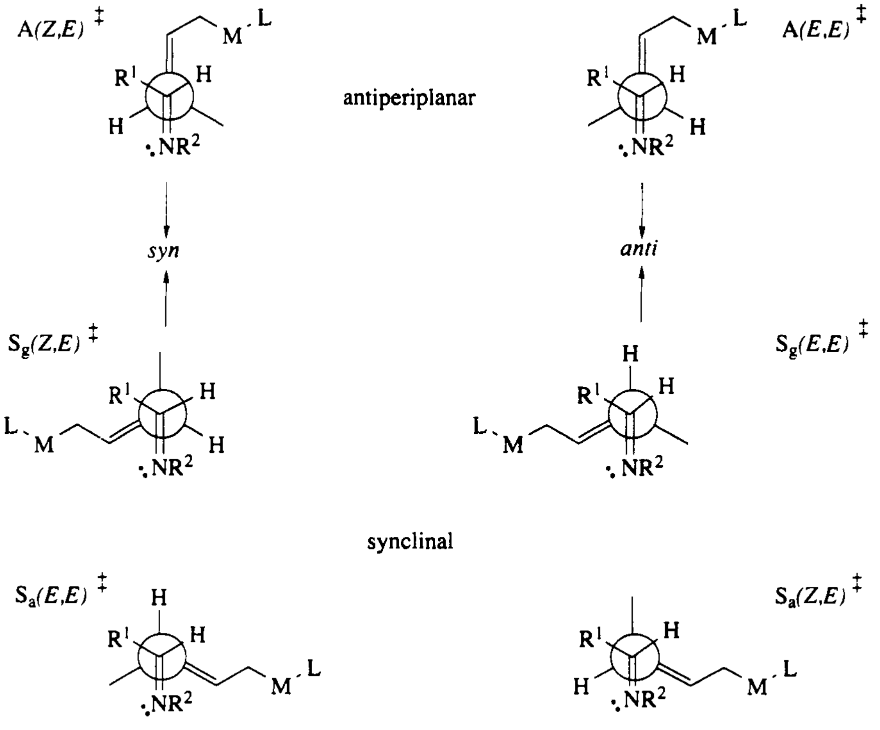
A(Z,E) ‡
antiperiplanar
A(E,E) ‡
syn
anti
$S_g(Z,E)$ ‡
$S_g(E,E)$ ‡
synclinal
$S_a(E,E)$ ‡
$S_a(Z,E)$ ‡
$R^1$
H
M
L
$\cdot NR^2$

**Figure 6** Postulated antiperiplanar and synclinal transition states involved in the reactions of crotyl organometallics with imines[11]

chelation control, in which the formation of metal chelates (A) reduces the degree of freedom of a molecule and renders a diastereotopic face of the imine more accessible for nucleophilic addition; and (ii) nonchelation control (Cram selectivity), in which the addition is governed by steric and/or electronic effects. In nonchelation control, the bias for addition from a diastereotopic face was first predicted by Cram (Cram's rule; B),[13] and is supported by the Felkin–Ahn (C) and Cornforth (D) models.[14] Normally, chelation and nonchelation (Cram) control lead to opposite diastereofacial selectivity. The reader should note that the term 'Cram selectivity' used throughout this chapter does not necessarily reflect a particular transition state but rather selectivity that is consistent with addition as shown in (B). Imines, by virtue of substitution on nitrogen, can contain chiral nitrogen auxiliaries that provide an option not available to aldehydes and ketones for influencing (controlling) diastereofacial selectivity. In these cases diastereofacial selectivity is governed by steric/electronic effects of the chiral nitrogen auxiliary, and a model (E) shown in Figure 7 has been suggested by Yamamoto *et al.*[15,16] Aldimines can also have stereogenic centers on both nitrogen and carbon. Changing the absolute configuration at either center can have a cooperative (matched) or antagonistic (unmatched) effect on reaction diastereofacial selectivity.[17]

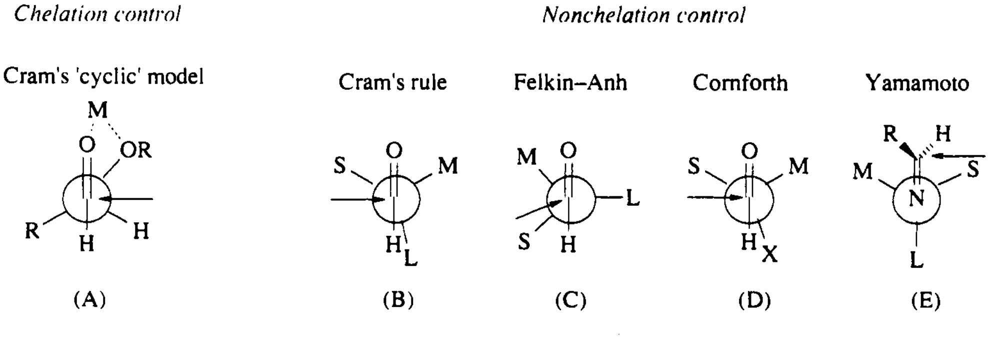
*Chelation control*
*Nonchelation control*
Cram's 'cyclic' model
Cram's rule
Felkin–Anh
Cornforth
Yamamoto
M
O
OR
R
H
S
L
X
N
(A)
(B)
(C)
(D)
(E)

**Figure 7** Models used to explain diastereofacial selectivity in the addition of nucleophiles to C═X

#### 4.3.1.3 Reversibility

Reversibility in the reactions of crotyl-lithium, -magnesium and -zinc reagents with aldimines has been observed at room temperature by measuring changing linear:branched product ratios as a function of time.[18] Aspects of this phenomenon have been covered in a review by Courtois and Miginiac.[19] Branched products are favored kinetically and are converted to the more stable linear products as the reaction proceeds. Reversibility is more common with crotyl-lithium and -zinc reagents than with crotylmagnesium reagents, except when bulky imine substituents are employed. The phenomenon of reversibility in allyl organometallic–aldimine reactions must be fully taken into account when stereochemical results are interpreted by purely kinetic reasoning.

#### 4.3.1.4 Earlier Reviews and Scope of this Chapter

A review by Courtois and Miginiac published in 1974 entitled, 'The Reactivity of Allylic Organometallic Compounds of Lithium, Sodium, Magnesium, Zinc, Cadmium and Aluminum: Recent Advances', covers reactions of the title reagents with a wide range of electrophiles including imines and iminium salt equivalents such as *gem* amino ethers, *gem*-amino nitriles and *gem*-haloamines.[19] Surprisingly, no more recent reviews devoted exclusively to additions of allyl and crotyl reagents to imines, iminium salts and their equivalents have appeared despite the recent surge of interest in allyl organometallic additions. It is the intention of this chapter to fill this void. In addition to imines and iminium salts, reactions of *N*-heterosubstituted imines (oximes, sulfenimines, *etc.*) and *gem*-amino ethers (masked iminium salts) are described. Included also are reactions of propargyl/allenic organometallic reagents. Reactions of allyl, crotyl and propargyl/allenic reagents are discussed separately because each gives rise to different stereochemical issues. The term 'crotyl' is used loosely to describe any γ-substituted allyl reagent, not necessarily methyl. The reader should consult Volume 1, Chapter 1.12 for analogous reactions of nonresonance-stabilized carbanions.

### 4.3.2 REACTIONS WITH IMINES

#### 4.3.2.1 Using Allyl Organometallic Reagents

#### *4.3.2.1.1 Achiral imines*

The reaction of allyl organometallics (**8**) with achiral aldimines (**9**) is the simplest combination of reactants, stereochemically, and affords (except in the case of formaldehyde imines) homoallylamines (**10**) containing one stereocenter (equation 2). These reactions, which typify the general scope of allyl organometallic–imine reactions are surveyed in Table 2. Reactions of allyl-borane, -titanium and -aluminum reagents are not shown in Table 2, only because they have been reported in reactions with chiral imines and are discussed in Sections 4.3.2.1.2 and 4.3.2.2.

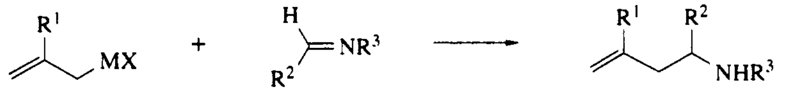

(**8**) (**9**) (**10**) (2)

Examples involving the more reactive allyl-lithium, -magnesium and -zinc reagents are limited to imines that are nonenolizable or contain branched α-alkyl substituents. Presumably, reactions of linear α-alkylaldimines are complicated by α-deprotonation.[20] Higher yields are reported using the less basic magnesium and zinc reagents than the corresponding lithium reagents. Some specific examples deserve further comment. An unstable *N*-cyclohexylmethyleneamine (a formaldehyde imine) which must be prepared *in situ* condenses with allylmagnesium bromide (entry 4, Table 2).[21] The reaction is also general for ordinary, nonresonance-stabilized organometallics. Allyl reagents containing reactive groups (R$^1$) at the β-carbon (entries 5–7, Table 2) can have useful synthetic applications. For example, the Reformatsky reagent (**11**) derived from ethyl α-(bromomethyl)acrylate reacts with α-arylimine (**12**) to afford α-methylene-δ-lactam (**13**) as a result of spontaneous cyclization of the 1,2-adduct (equation 3).[22] In a

**Table 2** Yields of Homoallylamines Formed in the Reactions of Allyl Organometallic Reagents with Achiral Imines (Equation 2)

| Entry | *Organometallic (8)* $R^1$ | *Imine (9)* $R^2$ | $R^3$ | *Yield of products (10) (%) metal* Li | MgBr | ZnBr | $SnBu_3$$^{a}$ | $SnBu_3$$^{b}$ | $B(OMe)_2$ | Pb$^{b,c}$ | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $\mathrm{Pr^i}$ | $\mathrm{Pr^n}$ | 70 | | | | | | | 20 |
| 2 | H | $\mathrm{Pr^i}$ | $\mathrm{Pr^i}$ | 66 | | | | | | | 20 |
| 3 | Me | $\mathrm{Pr^i}$ | $\mathrm{Pr^i}$ | 42 | | | | | | | 20 |
| 4 | H | H | c-$C_6H_{11}$ | | 82 | | | | | | 21 |
| 5 | $CO_2Et$ | Ar$^{d}$ | Me | | | 82$^{e}$ | | | | | 22 |
| 6 | $CH_2OPh$ | $\mathrm{Pr^i}$ | $\mathrm{Bu^n}$ | | | 91 | | | | | 23 |
| 7 | $CH_2OPh$ | Ph | Me | | | 90 | | | | | 23 |
| 8 | H | c-$C_6H_{11}$ | Bn | | | | 81 | 48 | | | 24 |
| 9 | H | $\mathrm{Bu^s}$ | Bn | | | | 75 | 53 | | | 24 |
| 10 | H | Ph | Bn | | | | 53 | 73 | | | 24 |
| 11 | H | Furyl | Bn | | | | 88 | 61 | | | 24 |
| 12 | $CH_2OAc$ | Ph | Ph | | | | | 81 | | | 25 |
| 13 | $CH_2OAc$ | Ph | $\mathrm{Pr^n}$ | | | | | 88 | | | 25 |
| 14 | $CH_2OAc$ | $\mathrm{Pr^i}$ | $\mathrm{Pr^n}$ | | | | | 70 | | | 25 |
| 15 | $CH_2OAc$ | 3-Pyr | Me | | | | | 64 | | | 25 |
| 16 | H | Me | Bn | | | | | | 90 | | 26 |
| 17 | H | $\mathrm{Pr^i}$ | Bn | | | | | | 78 | | 26 |
| 18 | H | n-$C_5H_{11}$ | Bn | | | | | | 70 | | 26 |
| 19 | H | Ph | Bn | | | | | | 65 | | 26 |
| 20 | H | Ph | Bn | | | | | | | 84 | 2 |
| 21 | H | *p*-Cl-Ph | Bn | | | | | | | 94 | 2 |
| 22 | H | *p*-Tol | Bn | | | | | | | 64 | 2 |
| 23 | H | 2-Furyl | Bn | | | | | | | 78 | 2 |
| 24 | H | 3-Heptyl | Bn | | | | | | | 72 | 2 |
| 25 | H | c-$C_6H_{11}$ | Bn | | | | | | | 90 | 2 |
| 26 | H | $Me_2C{=}C$ | Bn | | | | | | | 53 | 2 |

[a] $TiCl_4$ additive is employed. [b] $BF_3{\cdot}Et_2O$ additive is employed. [c] The allyllead reagent is formed *in situ* according to ref. 2, its structure is not known. [d] Ar = 3,4,5-trimethoxyphenyl. [e] The product isolated is the α-methylene-γ-lactam.

useful annellation process reported by Klumpp and coworkers, adducts (**15**) obtained from 2-(phenoxymethyl)allylzinc bromide (**14**) and aldimines can be cyclized to 3-methylenepyrrolidines (**16**) by treatment with palladium(0) (Scheme 2).[23]

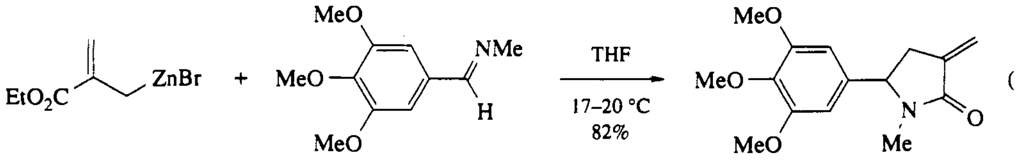

(3)

(**11**) (**12**) (**13**)

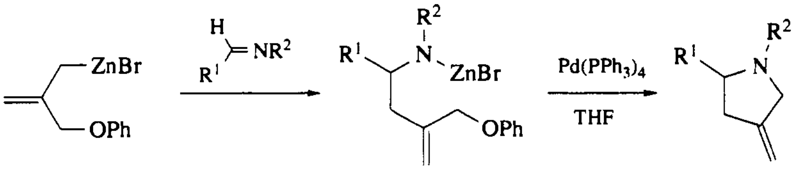

(**14**) (**15**) (**16**)

**Scheme 2**

Allyltri-*n*-butylstannane reacts with aromatic and branched α-alkylimines in the presence of $TiCl_4$ and $BF_3{\cdot}Et_2O$ (entries 8–11, Table 2); yields using $TiCl_4$ tend to be higher. Keck and Enholm have demonstrated that the Lewis acid participates by activating the imine, not by exchanging with the metal of the organometallic reagent.[24] This is confirmed by the fact that no homoallylamines are formed when the

Lewis acid and allylstannane are mixed prior to the addition of the imine. The reaction is normally performed by adding the Lewis acid to the imine at –78 °C, warming the mixture to 23 °C, recooling to –78 °C and then adding the allylstannane. The initial warming period is necessary to insure complete complexation of the imine. As will be discussed in Section 4.3.2.2.2, conditions employed for imine complexation strongly influence the *syn–anti* selectivity of crotyl organometallic additions. Similar reactions using [2-(acetoxymethyl)-3-allyl]-tri-*n*-butylstannane and $BF_3{\cdot}Et_2O$ have also been reported by Trost and Bonk[25] (entries 12–15, Table 2). The survival of the acetate group suggests that the reaction may be compatible with other reactive functional groups. Adducts obtained in these reactions can be cyclized to 3-methylenepyrrolidines using palladium(0), as in the reactions of 2-(phenoxymethyl)allylzinc bromide. As in the reactions of the more reactive allyl reagents, examples of Lewis acid mediated allylstannane additions involve nonenolizable or branched α-alkylaldimines. It is not clear if the scope of this reaction extends to linear α-alkylaldimines.

Hoffmann *et al.*[26] have reported the addition of allyl(dimethoxy)borane to linear and branched α-arylaldimines (entries 16–19, Table 2). The absence of α-deprotonation may be explained by a delicate balance between the basicity and the reactivity of the allylboronate. Allyl(dimethoxy)borane should thus be considered the reagent of choice in reactions with enolizable aldimines. Reactions are conveniently carried out at 25 °C in $CH_2Cl_2$ and work-up is performed using triethanolamine to break up amine–boronate complexes. Allyl(dimethoxy)borane also adds to the cyclic imine, $\Delta^1$-piperideine, in 90% yield. The reported yields for the addition of allyllithium and allylmagnesium chloride to $\Delta^1$-piperideine are low.

An *in situ* method reported by Torii and coworkers for preparing a reactive allyllead reagent is attractive from the standpoint of convenience since it avoids the need to isolate the organometallic reagent.[2] The reagent, which is formed by treatment of allyl bromide with aluminum foil (1.0 equiv.) and a catalytic amount of lead(II) bromide (0.03–0.1 equiv.) in ether, adds to α-aryl- and branched α-alkyl-aldimines in the presence of $BF_3{\cdot}Et_2O$ (entries 20–26, Table 2). Details of the structure of the reactive allyllead species and its mechanism of formation are not clear. The reaction does not extend to enolizable ketimines.

As reported by Mauze, the reaction of *gem*-chloro(methyl)allyllithium (**17**) with aldimines and ketimines (**18**) is an efficient method for the synthesis of 2-vinylaziridines (**20**; Scheme 3).[27] The aziridine ring is formed by intramolecular $S_N2$ chloride displacement *via* the intermediate lithium amide (**19**). The products are formed as diastereomeric mixtures, as indicated by NMR, and ratios of diastereomers vary depending on the imine substitution. Yields tend to be higher with more accessible linear and branched

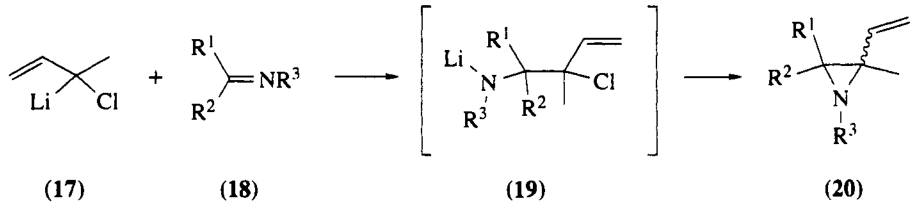

**Scheme 3**

**Table 3** Formation of Vinylaziridines (**20**) in the Reaction of *gem*-Chloro(methyl)allyllithium (**17**) with Imines (**18**; Scheme 3)[27]

| *Entry* | | *Imine (18)* | | *Aziridine (20)* |
|---|---|---|---|---|
| | *$R^1$* | *$R^2$* | *$R^3$* | *Yield (%)* |
| 1 | n-$C_6H_{13}$ | H | Me | 56 |
| 2 | n-$C_6H_{13}$ | H | $Pr^i$ | 60 |
| 3 | $Pr^i$ | H | Me | 28 |
| 4 | $Pr^i$ | H | Et | 38 |
| 5 | $Pr^nMeCH$ | H | Me | 48 |
| 6 | $Et_2CH$ | H | Me | 43 |
| 7 | $Bu^nEtCH$ | H | Me | 65 |
| 8 | $Bu^nEtCH$ | H | Et | 60 |
| 9 | Ph | H | Me | 58 |
| 10 | Ph | H | Et | 68 |
| 11 | Me | Me | $Bu^n$ | 30 |
| 12 | Et | Me | $Bu^n$ | 35 |
| 13 | $Pr^n$ | Me | $Bu^n$ | 38 |
| 14 | —$(CH_2)_5$— | | $Bu^n$ | 57 |

aldimines (entries 1–10, Table 3) than with ketimines (entries 11–14, Table 3). Deprotonation apparently is not a serious problem in these additions, perhaps because of the inductive effect of the α-chlorine, which lowers the basicity of the allyl reagent. Interestingly, reaction at the γ-position of allyllithium is not observed. Very hindered aldimines (**18**; $R^1$ = Bu$^t$, $R^2$ = H, $R^3$ = Me; $R^1$ = Ph, $R^2$ = H, $R^3$ = Bu$^t$; $R^1$ = Pr$^i$, $R^2$ = H, $R^3$ = Pr$^i$) fail to produce aziridines.

The stereochemistry of the addition of allylzinc and allylmagnesium bromide to *N*-methyl-4-*t*-butylcyclohexylimine (**21**) has been studied by Gaudemar and coworkers[28] (equation 4, Table 4). Both reagents favor axial attack in ether or in THF, giving mainly diastereomer (**23**; entries 1 and 2, Table 4). In THF/DMSO, allylzinc bromide gives predominantly diastereomer (**22**) *via* equatorial attack (entry 5, Table 4). The reactions are kinetically controlled as demonstrated by the fact the resubjection of a 34:66 mixture of (**22**):(**23**) under the reaction conditions (THF/DMSO) that normally gives an 85:15 mixture of (**22**):(**23**) does not result in equilibration. Also, product ratios do not change as a function of reaction time. No explanation of the kinetic factors involved in these reactions is given.

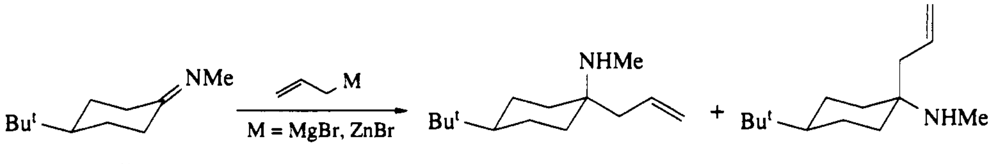

(4)

(**21**) (**22**) (**23**)

Table 4 Reaction of *N*-Methyl-4-*t*-butylcyclohexylimine (**21**) with Allylmagnesium Bromide and Allylzinc Bromide (Equation 4)[28]

| *Entry* | *Metal* | *Solvent* | *Product ratio (22):(23)* | *Yield (%)* |
|---|---|---|---|---|
| 1 | MgBr | Ether | 12:88 | 68 |
| 2 | ZnBr | THF | 34:66 | 57 |
| 3 | ZnBr | THF + LiBr | 37:63 | 67 |
| 4 | ZnBr | THF + HMPA | 40:60 | 66 |
| 5 | ZnBr | THF + DMSO | 85:15 | 67 |

#### *4.3.2.1.2 Imines containing one stereocenter*

##### *(i) 1,2-Asymmetric induction*

Yamamoto *et al.*[15,16] have examined organometallic additions to *N*-propylaldimines (**24**) derived from α-phenylpropionaldehyde to evaluate the influence of a nonchelating α-phenyl substituent on reaction diastereofacial selectivity (equation 5). The allyl organometallic reactions, summarized in Table 5, provide predominantly Cram products (**25**). The addition of allyl-9-BBN to aldimine (**24**; R = Pr$^i$) affords exclusively amine (**25**) in good yield (entry 2, Table 5). The diastereoselectivity is lower in the additions of allylstannanes ($TiCl_4$) and allyl Grignards (entries 3–7, Table 5). The imine nitrogen substituent appears to have a minimal impact on reaction stereoselectivity, although greater structural diversity is needed to better assess the scope of this Cram selectivity.

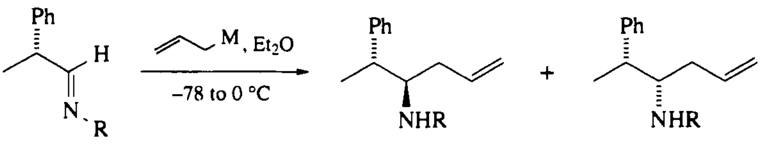

(5)

(**24**) (**25**) Cram (**26**) anti-Cram

M = 9-BBN, MgX; 88–98%
M = $SnBu_3/TiCl_4$; 60–90%

The Cram selectivity is consistent with Felkin–Ahn addition, as shown in Figure 8a, with the large phenyl substituent controlling the organometallic approach. In addition, Yamamoto *et al.*[15,16] have proposed more detailed chair-like transition state models shown in Figures 8b and 8c to account for the un-

**Table 5** Cram Selectivity in Allyl Organometallic Additions to α-Phenylaldimine (**24**; Equation 5)[15,16]

| *Entry* | *Imine (24)*<br>*R* | *Allyl organometallic*<br>*M* | *Product ratio*<br>*(25):(26)* | *α-Phenylpropionaldehyde additions*<br>*Cram:anti-Cram* | *Ref.* |
|---|---|---|---|---|---|
| 1 | $Pr^n$ | 9-BBN | 96:4 | 55:45 | 15,16 |
| 2 | $Pr^i$ | 9-BBN | 100:0 | 55:45 | 15,16 |
| 3 | $Pr^n$ | $SnBu_3/TiCl_4$ | 93:7 | 69:31 | 15 |
| 4 | $Pr^i$ | $SnBu_3/TiCl_4$ | 92:8 | 69:31 | 15 |
| 5 | $Pr^n$ | MgCl | 84:16 | 60:40 | 15,16 |
| 6 | $Pr^i$ | MgCl | 70:30 | 60:40 | 15,16 |
| 7 | $Pr^n$ | MgBr | 68:32 | 60:40 | 15 |

usually high diastereoselectivity. The authors suggest that the additional steric demands created by the axial metal ligands (L; *via* a 1,3-diaxial nonbonded interaction) are responsible for the difference in energy between the Cram (Figure 8b) and anti-Cram (Figure 8c) transition states. This hypothesis is supported, in part, by the poor diastereoselectivity (see Table 5) obtained in analogous organometallic additions to α-phenylpropionaldehyde.[15,16,29] In the aldehyde additions, the Lewis acidic metal can complex the aldehyde oxygen *cis* to the hydrogen; as a result the aldehyde carbon framework will occupy the equatorial position and avoid these severe nonbonded interactions (Figure 8d).

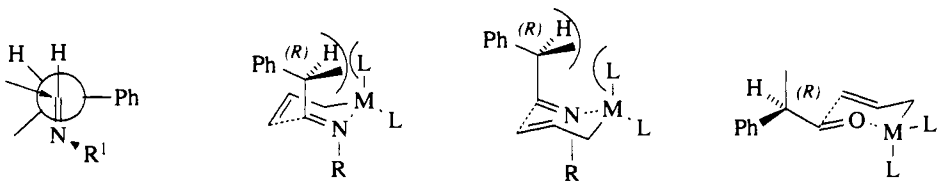

(a) (b) (c) (d)

**Figure 8**

If there is an alkoxy substituent adjacent to the aldimine there is the opportunity for chelation control. Yamamoto *et al.*[30] have examined the addition of allyl organometallic reagents to (*S*)-2-(methoxy)methoxypropanal-derived aldimines (**27**; equation 6, Table 6). Chelation control (Figure 9a) to generate predominantly *syn* homoallylamine (**28**) occurs with reagents capable of α-chelation (allyl-MgCl, $-AlEt_3MgCl$, and -ZnBr). While the level of chelation-controlled 1,2-asymmetric induction is not complete, it is nonetheless synthetically useful and is better than that of the parent α-alkoxyaldehyde itself[29] (see entries 1–3, Table 6). In contrast, the use of allylboronates or $(allyl)Ti(Pr^iO)_3$, which lack the requisite Lewis acidity for chelation, result, as expected, in good Cram selectivity (Figure 9b; entries 4 and 5, Table 6). Once again, allyl-9-BBN (entry 6, Table 6) provides excellent Cram diastereofacial control (>99:1) and is the method of choice for preparing the *anti* homoallylamine (**29**).

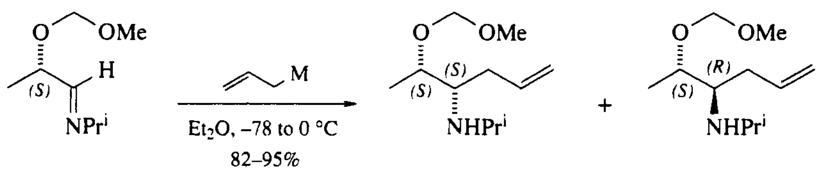

(6)

(**27**) (**28**) chelation (**29**) nonchelation (Cram)

**Table 6** Chelation and Nonchelation Control in Allyl Organometallic Additions to α-Alkoxyaldimines (**27**; Equation 6)[30]

| *Entry* | *Allyl organometallic*<br>*M* | *Product ratio*<br>*(28):(29)* | *(S)-2-(Methoxy)methoxypropanal additions*<br>*chelation:nonchelation control*[29] |
|---|---|---|---|
| 1 | MgCl | 79:21 | 53:47 |
| 2 | $AlEt_3MgCl$ | 93:7 | 58:42 |
| 3 | ZnBr | 78:22 | 41:59 |
| 4 | $Ti(Pr^iO)_3$ | 23:77 | 45:55 |
| 5 | $B(OMe)_2$ | 7:93 | — |
| 6 | 9-BBN | — :>99 | 52:48 |

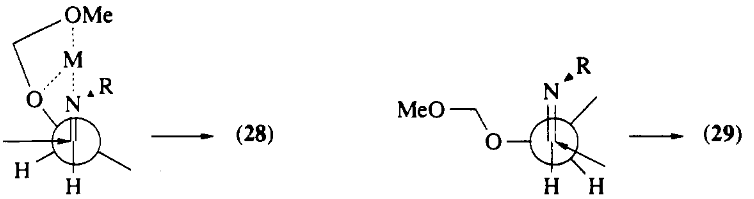

(a) Chelation (b) Felkin–Anh (nonchelation)

**Figure 9**

*(ii) 1,3-Asymmetric induction*

Allyl organometallic additions to chiral β-alkoxyaldimines (**30**) have been investigated for the preparation of amines (**31**) and (**32**; equation 7).[30] The results are summarized in Table 7 and illustrate the limitations of utilizing substituents β to the aldimine for controlling reaction diastereofacial selectivity. Modest chelation control [(**31**):(**32**) = 1.6–9.0:1], which is superior to that of the corresponding β-alkoxyaldehydes,[29] can be obtained using organometallics capable of β-chelation (allyl-MgCl, -AlEt$_3$MgCl, and -ZnBr; entries 1–3, Table 7). On the other hand, little or no diastereoselectivity is observed with reagents incapable of internal chelation such as 9-allyl-BBN or (allyl)Ti(Pr$^i$O)$_3$. These results suggest that the presence of a remote stereocenter does not alone provide synthetically useful Cram diastereofacial control in aldimine additions.

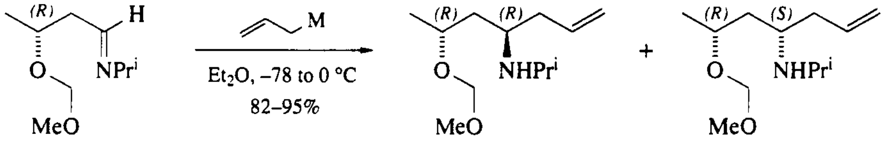

(7)

(**30**) (**31**) chelation (**32**) nonchelation (Cram)

**Table 7** 1,3-Asymmetric Induction in Allyl Organometallic Additions to β-Alkoxyaldimines (**30**; Equation 7)[30]

| *Entry* | *Allyl organometallic M* | *Product ratio (31):(32)* | *(R)-3-(Methoxy)methoxybutanal additions chelation:nonchelation control*[29] |
|---|---|---|---|
| 1 | MgCl | 85:15 | 64:36 |
| 2 | AlEt$_3$MgCl | 90:10 | 42:58 |
| 3 | ZnBr | 62:38 | 68:32 |
| 4 | Ti(Pr$^i$O)$_3$ | 30:70 | 47:53 |
| 5 | 9-BBN | 46:54 | 51:49 |

The addition of organometallic reagents to aldimines derived from chiral amines provides another option (unique to imines) for controlling reaction diastereofacial selectivity. Yamamoto *et al.*[15,16] have examined the addition of allyl organometallics to aldimine (**33**) derived from 1-phenylethylamine (equation 8). Results are shown in Table 8 and indicate that modest selectivity ranging from 1.5:1 to 11:1 (**34**:**35**) can be obtained. Allyl-9-BBN once again provides the best diastereoselectivity (entry 1, Table 8). While the origin of the *re* facial selectivity is unknown, Yamamoto *et al.* have proposed organometallic addition to a low energy conformation of (**33**), shown in Figure 10a, in which the largest (phenyl) substituent is antiperiplanar to the imine, which would render the *re* face of (**33**) more accessible to addition. In the case of allyl organometallics that are capable of internal coordination with the imine, such as

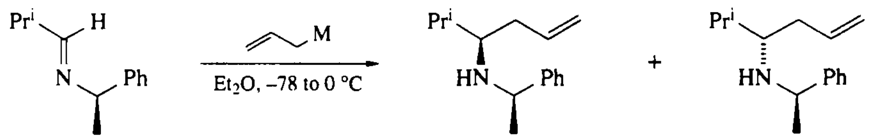

(8)

(**33**) M = 9-BBN, MgX; 88–98% (**34**) (**35**)
M = SnBu$_3$; 60–70%

allyl-9-BBN, cyclic chair versions of this model, shown in Figures 10b and 10c have also been proposed. Cyclic six-membered transition states may not, however, be crucial for 1,3-asymmetric induction since addition of allyltri-*n*-butylstannane in the presence of Lewis acids (entries 3 and 4, Table 8) is stereoselective.

**Table 8** 1,3-Asymmetric Induction in Allyl Organometallic Additions to Aldimine (33) Derived from 1-Phenylethylamine (Equation 8)[15,16]

| *Entry* | *Chirality of imine (33)* | *Allyl organometallic M* | *Product ratio*[a] *(34):(35)* | *Ref.* |
|---|---|---|---|---|
| 1 | (*R,S*) | 9-BBN | 92:8 | 15,16 |
| 2 | (*R,S*) | MgBr | 80:20 | 15 |
| 3 | (*R,S*) | $SnBu_3/TiCl_4$ | 82:18 | 15 |
| 4 | (*R,S*) | $SnBu_3/BF_3$ | 67:33 | 15 |
| 5 | (*R*) | $B(OMe)_2$ | 60:40 | 15 |
| 6 | (*R*) | b | 67:33 | 15 |
| 7 | (*R*) | c | 80:20 | 15 |
| 8 | (*S*) | c | 80:20 | 16 |

[a] Structures (34) and (35) reflect the relative (not the absolute) stereochemistry. [b]

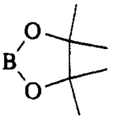

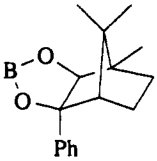

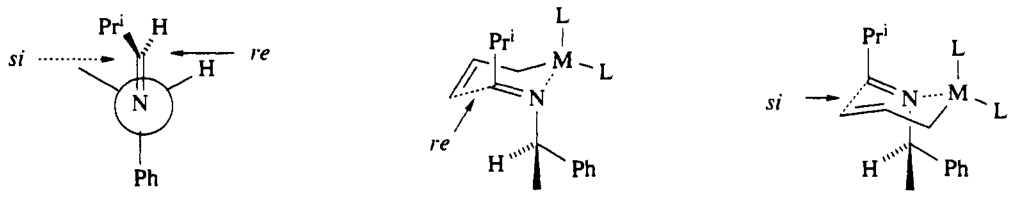

(a) (b) (c)

**Figure 10**

An enantioselective synthesis of amino acids has been examined using chiral nonracemic α-imino esters (**36**) derived from (*S*)-1-phenylethylamine and (–)-1-cyclohexylethylamine (equation 9, Table 9).[15,31] Allyl-magnesium, -copper and -titanium reagents react at both the imine and ester carbon atoms of (**36**), a result of the molecule's ambient electrophilicity. The addition of allyl-, methallyl- and prenyl-9-BBN and -ZnBr to α-imino ester (**36**), however, generates amines (**38**) and (**39**). While the absolute stereochemistry of (**38**) and (**39**; R = Ph) has been determined (entries 1–4, Table 9), that of the cyclohexylethylamine-derived products has not (entries 5–8, Table 9).

In all cases, allyl-9-BBN provides the best diastereoselectivity. The high 1,3-asymmetric induction (96:4) produced in allyl-9-BBN addition to (**36**; R = Ph; entry 1, Table 9) is consistent with a proposed cyclic chair transition state shown in Figure 11a. Diastereofacial selectivity is reversed in methallyl-9-BBN addition to (**36**; R = Ph; entry 3, Table 9). As a result of additional 1,3-diaxial interactions invol-

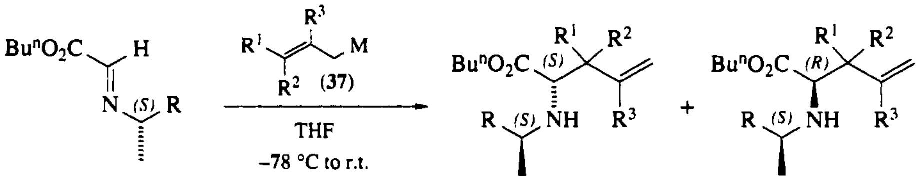

(**36**) (**38**) (**39**) (9)

ving the methallyl methyl group in the chair transition state, shown in Figure 11a, a boat transition state shown in Figure 11b which would provide amine (**39**) has been proposed. Reaction yields and selectivity erodes in the addition of prenyl-9-BBN (**37**; $R^1 = R^2 = Me$; $R^3 = H$) to (**36**; entries 9 and 10, Table 9).

**Table 9** 1,3-Asymmetric Induction in the Addition of Allyl Organometallic Reagents (**37**) to Glyoxylate Aldimines (**36**) Derived from Chiral Amines (Equation 9)[15,31]

| | *Imine (36)* | *Organometallic reagent (37)* | | | | *Product ratio* | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Entry* | *R* | $R^1$ | $R^2$ | $R^3$ | *M* | *(38):(39)* | *de (%)* | *Yield (%)* | *Ref.* |
| 1 | Ph | H | H | H | 9-BBN | 96:4 | 92 | 92 | 15,31 |
| 2 | Ph | H | H | H | ZnBr | — | 10 | 94 | 15,31 |
| 3 | Ph | H | H | Me | 9-BBN | 5:95 | 90 | 80 | 15 |
| 4 | Ph | H | H | Me | ZnBr | — | 16 | 83 | 15 |
| 5 | c-$C_6H_{11}$ | H | H | H | 9-BBN | — | 96 | 94 | 15,31 |
| 6 | c-$C_6H_{11}$ | H | H | H | ZnBr | — | 30 | 53 | 15,31 |
| 7 | c-$C_6H_{11}$ | H | H | Me | 9-BBN | — | 78 | 94 | 15 |
| 8 | c-$C_6H_{11}$ | H | H | Me | ZnBr | — | 14 | 90 | 15 |
| 9 | Ph | Me | Me | H | 9-BBN | — | 54 | 33 | 15,31 |
| 10 | Ph | Me | Me | H | ZnBr | — | 16 | 60 | 15,31 |

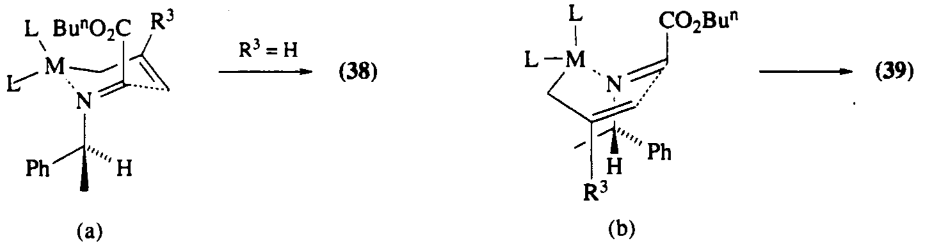

**Figure 11**

### 4.3.2.1.3 *Imines containing two stereocenters*

Yamamoto *et al.*[30] have examined the addition of allyl organometallic reagents to α-alkoxyaldimines (**40**) derived from (*S*)-2-methoxy(methoxy)propionaldehyde and (*R*)- and (*S*)-1-phenylethylamine (equation 10). The results are summarized in Table 10. Chelation control with allyl-$AlEt_3MgCl$, -MgCl and -ZnBr (entries 1–3, Table 10) and nonchelation (Cram) control with allyl-$Ti(Pr^iO)_3$, $-B(OMe)_2$ and -9-BBN (entries 4–6, Table 10) parallels that observed in the allyl metal–α-alkoxyaldimine additions (involving aldimines that lack a chiral nitrogen substituent) shown in Table 6. The chirality of the α-alkoxy

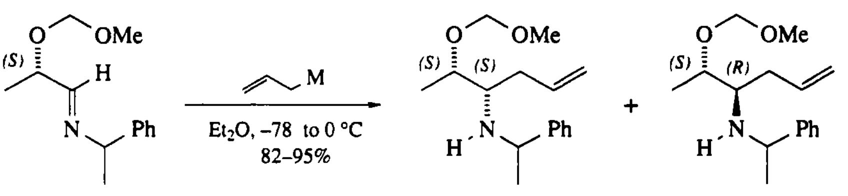

(10)

(**40**) (**41**) chelation (**42**) nonchelation

**Table 10** Chelation and Nonchelation Control in Allyl Organometallic Additions to α-Alkoxyaldimines (**40**) Derived from (*R*)- and (*S*)-1-Phenylethylamine (Equation 10)[30]

| | *Allyl organometallic* | *Product ratios* | |
|---|---|---|---|
| *Entry* | *M* | *(41):(42)*[a] | *(41):(42)*[b] |
| 1 | MgCl | 70:30 | 86:14 |
| 2 | $AlEt_3MgCl$ | 89:11 | 95:5 |
| 3 | ZnBr | 76:24 | 92:8 |
| 4 | $Ti(Pr^iO)_3$ | 6:94 | 20:80 |
| 5 | $B(OMe)_2$ | 10:90 | 10:90 |
| 6 | 9-BBN | 3:97 | —:>99 |

[a] *N*-Imine substituent has (*S*)-chirality. [b] *N*-Imine substituent has (*R*)-chirality.

center (1,2-asymmetric induction) and the type of allyl metal employed are the most important determinants of the stereochemical outcome of the reaction and essentially override the influence of the nitrogen chiral auxiliary (1,3-asymmetric induction).

In the addition of allyl-MgBr and -9-BBN to β-alkoxyaldimines (**43**) derived from (*R*)-3-methoxy(methoxy)butyraldehyde and (*R*)- and (*S*)-phenylethylamine, chelation and nonchelation products (**44**) and (**45**) are generated, respectively (equation 11, Table 11).[30] Of the two remote 1,3-centers of chirality, the chiral nitrogen auxiliary in this small sampling now plays the major role in controlling diastereoselectivity as the (*R*,*S*) combination with ether allyl organometallic reagent provides predominantly (**44**) while the (*R*,*R*) combination provides amine (**45**; entries 1 and 2, Table 11). While the concept of matched *versus* unmatched pairs for diastereofacial selectivity is demonstrated with aldimine (**43**), neither the direction nor the degree of this asymmetric induction is easily rationalized.

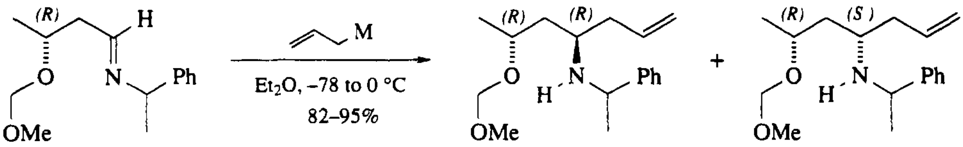

(**43**) (**44**) chelation (**45**) nonchelation (11)

**Table 11** 1,3-Asymmetric Induction in Allyl Organometallic Additions to β-Alkoxyaldimines (**43**) Derived from (*R*)- and (*S*)-Phenylethylamine (Equation 11)[30]

| Entry | Allyl organometallic M | Product ratios (44):(45)[a] | (44):(45)[b] |
|---|---|---|---|
| 1 | MgCl | 92:8 | 38:62 |
| 2 | 9-BBN | 63:37 | 10:90 |

[a] *N*-Imine substituent has (*S*)-chirality. [b] *N*-Imine substituent has (*R*)-chirality.

### 4.3.2.2 Using Crotyl Organometallic Reagents

#### *4.3.2.2.1 Regioselectivity*

The regioselectivity of additions of crotyl-zinc, -magnesium, and -lithium reagents (**46**) to aldimines (**47**) has been studied by Miginiac and coworkers (equation 12).[32,33] Ratios of branched (**48**) and linear (**49**) homoallylamines and yields using ether as solvent are shown in Table 12; similar results are obtained using THF. Neither the *syn–anti* stereochemistry (branched products) nor the alkene geometry (linear products) were determined. Two trends are observed. First, metals favor branched products in the order MgBr > ZnBr > Li for a given imine. Second, linear products (**49**) predominate using α-alkylimines (entries 3–8, Table 12) while branched products (**48**) predominate using formaldehyde imines (entries 1 and 2, Table 12) and α-arylimines (entries 9 and 10, Table 12). Exceptions are found in the α-alkyl-*N*-arylimine series using magnesium and lithium reagents (entries 7 and 8, Table 12) where branched products (**48**) are favored, and in the case of benzylidenemethylamine using the lithium reagent (entry 9, Table 12) where the linear product (**49**) is favored. Also, the zinc cinnamyl reagent (entry 11, Table 12), unlike the aliphatic crotyl reagents, gives almost exclusively the linear product (**49**) in a reaction with an α-arylimine. Miginiac and coworkers note a relationship between the observed trends in regioselectivity and imine basicity, *i.e.* more basic imines with electron-donating α-alkyl groups give linear products while less basic imines lacking α-substituents or containing α-aryl substituents give branched products. If branched products are formed *via* a cyclic six-centered transition state, the reduced nucleophilicity of the imine lone pair is apparently not severe enough to retard coordination with the metal. The fact that the zinc reagent, unlike the magnesium and lithium reagents, gives linear products (**49**) in reactions with branched α-alkyl-*N*-arylimines (entries 7 and 8, Table 12), suggests that its cyclic transition state is more sensitive to the steric environment. Clearly, the influence of the electronic properties of the imine on reaction regioselectivity needs further study. Yields in most cases are good, even when the imine contains bulky substituents.

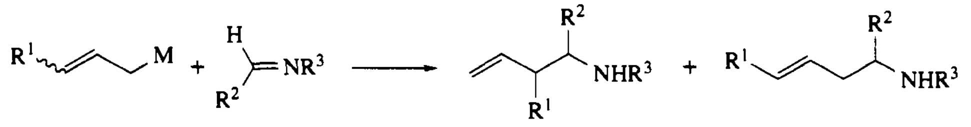

**(46)** **(47)** **(48)** **(49)** (12)

**Table 12** Regioselectivity in the Reaction of Crotyl Organometallic Reagents (**46**) with Aldimines (**47**; Equation 12)

| *Entry* | *Organo-metallic (**46**)* | *Imine (**47**)* | | *Metal* | | | | | | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *ZnBr* | | *MgBr* | | *Li* | | |
| | *$R^1$* | *$R^2$* | *$R^3$* | *Yield (%)* | *(**48**):(**49**)* | *Yield (%)* | *(**48**):(**49**)* | *Yield (%)* | *(**48**):(**49**)* | |
| 1 | Et | H | Ph[a] | 67 | 100:0 | 94 | 100:0 | 92 | 84:16 | 33 |
| 2 | Et | H[b] | $Bu^t$ | 60 | 75:25 | 18 | 99:1 | 55 | 36:64 | 33 |
| 3 | Et | Me | $Pr^n$ | 57 | 1:99 | 56 | 10:90 | 29 | 0:100 | 33 |
| 4 | Et | $Pr^i$ | Me | 84 | 0:100 | 74 | 3:97 | 84 | 1:99 | 33 |
| 5 | Et | $Pr^i$ | $Pr^n$ | 63 | 1:99 | 69 | 1:99 | 31 | 1:99 | 32 |
| 6 | Et | $Bu^t$ | Me | 80 | 0:100 | 89 | 3:97 | 70 | 0:100 | 33 |
| 7 | Et | $Pr^i$ | Ph | 95 | 8:92 | 85 | 92:8 | 88 | 88:12 | 33 |
| 8 | Et | $Bu^t$ | Ph | 91 | 7:93 | 91 | 88:12 | 95 | 65:35 | 33 |
| 9 | Et | Ph | Me | 80 | 72:28 | 82 | 98:2 | 63 | 5:95 | 33 |
| 10 | Et | Ph | Ph | 82 | 84:16 | 88 | 98:2 | 83 | 76:24 | 33 |
| 11 | Ph | Ph | Me | 67 | 1:99 | | | | | 33 |

[a] Generated from $PhSCH_2NHPh$ *in situ*. [b] Imine reacted as the trimer.

### *4.3.2.2.2* Syn–Anti *selectivity*

*Syn–anti* selectivity in the reactions of crotyl organometallic reagents with aldimines (**50**) (equation 13) is surveyed in Table 13. Examples involving crotyl-magnesium, -zinc and -lithium reagents are limited to reactions with α-arylimines because, as noted above, α-alkylimines react to produce primarily linear products. This restriction could apply to crotylaluminum reagents since reported examples using crotylaluminum bromide are also limited to reactions with α-arylimines. In contrast, α-alkylimines react with crotyltri-*n*-butylstannane[24] and crotyl-9-BBN[11] to give branched products, allowing the *syn–anti* selectivity to be examined.

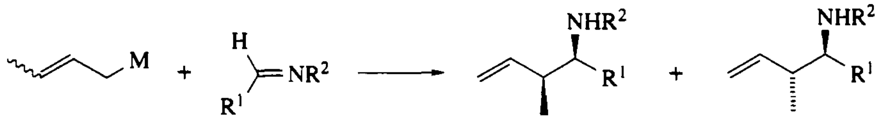

**(50)** **(51)** **(52)** (13)

The levels of *syn–anti* selectivity in the reactions of crotyl-magnesium, -zinc, -lithium and -aluminum reagents are not synthetically useful. Of these reagents, crotyllithium is the most selective, favoring *anti* products (**52**) in additions to *N*-alkyl-α-arylimines (entries 1–3 and 5, Table 13). *Syn*:*anti* ratios are about 1:4. With magnesium and zinc reagents, *syn*:*anti* ratios are very similar to each other and tend to favor *anti* products as the size of the *N*-alkyl substituent ($R^2$) increases. Gaudemar and coworkers have rigorously proven that these reactions are not reversible.[34] To evaluate the effect of the allylic double bond of the crotyl reagent on *syn–anti* selectivity, Moreau and Gaudemar have compared the *syn–anti* selectivity of *s*-butylmagnesium bromide to that of crotylmagnesium bromide in additions to the imines of entries 1–6 (Table 13).[35] Unfortunately, the levels of *syn–anti* selectivity of *s*-butylmagnesium bromide are too low to draw any definitive conclusions.

Reactions of crotyltri-*n*-butylstannane in the presence of $TiCl_4$ (entries 9, 14 and 15, Table 13) favor *syn* products (**51**).[24] Extremely high levels of *syn* selectivity (ratios >20:1) can be obtained if Lewis acid–imine complexation is carried out at –78 °C for 2.5 h prior to the addition of the organometallic reagent, otherwise *syn* selectivity diminishes to 4:1. Keck and Enholm have interpreted the stereoselectivity of this reaction to be a result of two $TiCl_4$–imine complexes, (**53**) and (**54**), formed kinetically and thermodynamically, respectively. Formation of the thermodynamic complex (**54**) at higher temperatures is driven, presumably, by the steric bulk of the $TiCl_4$ moiety. It is suggested that higher *syn* selectivity (>20:1) originates from the kinetic complex (**53**), which is formed slowly at –78 °C, while lower *syn* se-

Table 13 *Syn–Anti* Selectivity in the Reactions of Crotyl Organometallics with Imines (**50**; Equation 13)

| *Entry* | *Imine (**50**)* |  | *Metal* |  |  |  |  |  |  |  |  |  |  |  | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | *MgBr* |  | *ZnBr* |  | *Li* |  | *Al$_{2/3}$Br* |  | *SnBu$_3$*[a] |  | *9-BBN* |  |  |
|  | *R$^1$* | *R$^2$* | *Yield (%)* | *(**51**):(**52**)* | *Yield (%)* | *(**51**):(**52**)* | *Yield (%)* | *(**51**):(**52**)* | *Yield (%)* | *(**51**):(**52**)* | *Yield (%)* | *(**51**):(**52**)* | *Yield (%)* | *(**51**):(**52**)* |  |
| 1 | Ph | Me | 69 | 64:36 | 84 | 63:37 | 95 | 20:80 | 55 | 54:46 |  |  |  |  | 34 |
| 2 | Ph | Et | 66 | 41:59 | 85 | 35:65 | 91 | 21:79 | 65 | 54:46 |  |  |  |  | 34 |
| 3 | Ph | Pr$^i$ | 66 | 38:62 | 60 | 50:50 | 88 | 31:69 | 48 | 50:50 |  |  |  |  | 34 |
| 4 | Ph | Pr$^i$ |  |  |  |  |  |  |  |  |  |  | 79 | 65:35 | 11 |
| 5 | Ph | Bu$^i$ | 65 | 28:72 | 78 | 26:74 | 74 | 15:85 | 38 | 63:37 |  |  |  |  | 34 |
| 6 | Ph | Ph | 48 | 47:53 | 85 | 45:55 | 86 | 46:54 | 30 | 34:66 |  |  |  |  | 34 |
| 7 | Ph | Ph | 95 | 74:26[b] |  |  | 50 | 60:40 |  |  |  |  | 93 | 0:100 | 11 |
| 8 | Ph | Pr$^n$ | 95 | 63:37 |  |  |  |  |  |  |  |  | 95 | 15:85 | 11 |
| 9 | Furyl | Bn |  |  |  |  |  |  |  |  | 84 | 30:1 |  |  | 24 |
| 10 | Pr$^n$ | Pr$^n$ |  |  |  |  |  |  |  |  |  |  | 90 | 75:25 | 11 |
| 11 | Pr$^n$ | Pr$^i$ |  |  |  |  |  |  |  |  |  |  | 97 | 100:0 | 11 |
| 12 | Pr$^i$ | Pr$^n$ |  |  |  |  |  |  |  |  |  |  | 95 | 34:66 | 11 |
| 13 | Pr$^i$ | Pr$^i$ |  |  |  |  |  |  |  |  |  |  | 60 | 30:70 | 11 |
| 14 | Pr$^i$ | Bn |  |  |  |  |  |  |  |  | 60 | 20:1 |  |  | 24 |
| 15 | c-$C_6H_{11}$ | Bn |  |  |  |  |  |  |  |  | 78 | 23:1 |  |  | 24 |

[a] $TiCl_4$ additive is used. [b] The crotyl MgCl reagent is used instead.

lectivity (4:1) results from the thermodynamic complex (**54**). Assuming that TiCl$_4$-promoted additions of allylstannanes to aldimines proceed *via* open transition states (Figure 6), the observed *syn* selectivity can be rationalized by a $S_a(E,E)^\ddagger$ transition state for complex (**53**) and a $S_a(E,Z)^\ddagger$ transition state for complex (**54**; note that the alkene geometry of the crotyl reagent is *E*). These transition states are also consistent with the fact that the direction of *syn:anti* selectivity is preserved despite the change in imine geometry.

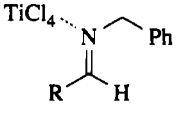

**(53)**

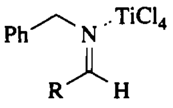

**(54)**

In the case of crotyl-9-BBN, *syn–anti* selectivity is very sensitive to the nature of the imine. For example, the *anti* product (**52**) is formed exclusively with benzylideneaniline (entry 7, Table 13), while the *syn* product (**51**) is formed exclusively with the aliphatic imine, *n*-butylideneisopropylamine (entry 11, Table 13). In these limited examples, α-alkylimines (entries 10 and 11, Table 13) exhibit *syn* selectivity when the α-alkyl group is linear, while α-arylimines (entries 7 and 8, Table 13) exhibit *anti* selectivity when the *N*-substituent is aryl or linear alkyl. In view of the similar carbon–boron, carbon–carbon bond lengths (*ca.* 1.5–1.6 Å), it is reasonable to assume that highly ordered cyclic transition states are involved. Yamamoto *et al.* view the formation of *syn* products as arising *via* a $\mathrm{C}(E,E)^\ddagger$ transition state (Figure 5).[11] The erosion in *syn* selectivity which occurs when the α-substituent is bulky (entries 12 and 13, Table 13) is attributed to destabilizing nonbonded 1,3-diaxial interactions between the aldimine R$^1$ substituent and the 9-BBN ring, and to 1,2-axial–equatorial interactions between R$^1$ and the crotyl methyl group. In these cases, the B(*E*,*E*)‡ transition state (Figure 5) leading to *anti* products may dominate. The anomalous behavior of benzylideneaniline and other α-arylimines, however, has not been satisfactorily explained. In control experiments, the failure to detect (by NMR) isomerization of benzylideneaniline in

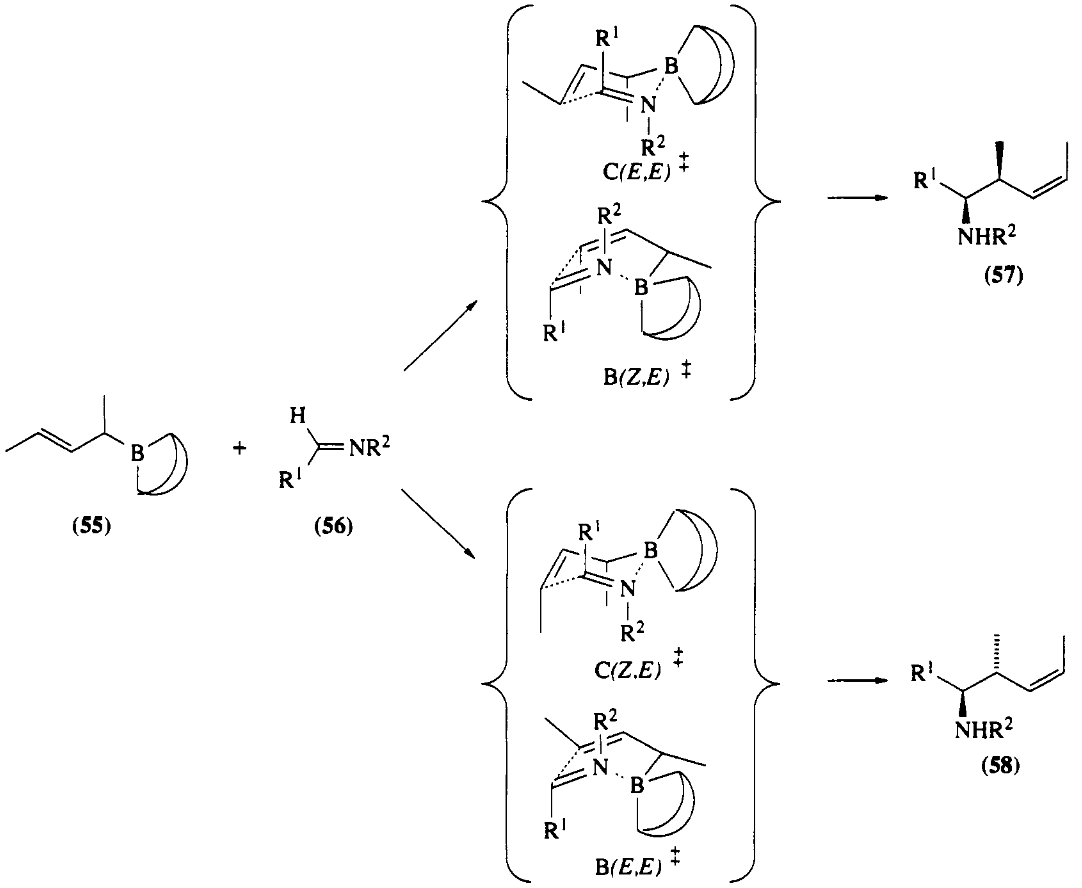

**Scheme 4**

the presence of Bu$^n$-9-BBN or $BF_3{\cdot}Et_2O$ at temperatures ranging from –78 °C to 25 °C suggests that α-arylimines do not react *via* the (*Z*)-isomer.[11]

To further evaluate their transition state hypotheses, Yamamoto *et al.* have examined the *syn–anti* selectivity of pent-3-en-2-yl-9-BBN (**55**), the α-methyl derivative of crotyl-9-BBN (Scheme 4).[11] As shown in Table 14, *syn* selectivity is more dominant in these reactions than with crotyl-9-BBN; even a small amount of *syn* product (**57**) is formed in the reaction of benzylideneaniline (entry 1, Table 14) which gives exclusively the *anti* product (**52**) using crotyl-9-BBN. Both *syn* and *anti* products (**57**) and (**58**) contain the *cis* alkene geometry. The results are consistent with a dominant C(*E*,*E*)$^\ddagger$ transition state (Scheme 4) in which the α-methyl group occupies the axial position, resulting in *cis* alkenic geometry. The increase in *syn* selectivity over the crotyl (des-α-methyl) series is explained by destabilizing interactions of the α-methyl group in the alternative cyclic transition states depicted in Scheme 4. For example, in the C(*Z*,*E*)$^\ddagger$ transition state, the α-methyl group produces an additional 1,3-diaxial interaction, while in both boat transition states there are 1,2-interactions between the α-methyl group and the 9-BBN group. It is interesting that *trans* alkenic products are not produced, since equatorial instead of axial placement of the α-methyl in the C(*E*,*E*)$^\ddagger$ transition state would seem more likely. Perhaps the resulting 1,2-equatorial interaction between the α-methyl and the 9-BBN group is more severe than other 1,3-diaxial interactions in the C(*E*,*E*)$^\ddagger$ transition state.

**Table 14** *Syn–Anti* Selectivity in the Reactions of Pent-3-en-2-yl-9-BBN (**55**) with Imines (**56**; Scheme 4)[11]

| *Entry* | *Imine (56)* $R^1$ | $R^2$ | *Products* *Yield (%)* | *(57):(58)* |
|---|---|---|---|---|
| 1 | Ph | Ph | 90 | 8:92 |
| 2 | Ph | Pr$^n$ | 84 | 100:0 |
| 3 | Pr$^n$ | Pr$^i$ | 75 | 100:0 |
| 4 | Pr$^i$ | Pr$^n$ | 78 | 85:15 |

Some examples of combined *syn–anti* and diastereofacial selectivity employing *N*-*n*-propyl- and *N*-isopropyl-aldimines, derived from α-phenylpropionaldehyde, and crotyl-9-BBN, -magnesium and -zirconium reagents have been reported by Yamamoto *et al.*[15] Cram selectivity, which is observed in the analogous reactions of these chiral imines with allyl organometallics (see Section 4.3.2.1.2i), is preserved as ratios of Cram:anti-Cram products are consistently about 8:1. *Anti* selectivity is also observed but the ratios do not exceed 7:3. The weak *anti* selectivity parallels that observed in reactions of crotyl-9-BBN with branched α-alkylaldimines. Since *syn–anti* selectivity is influenced more by the α-substituent than by the *N*-substituent of the aldimine, more synthetically useful levels of combined *syn–anti* and diastereofacial selectivity might be expected in other series of α-substituted aldimines.

### 4.3.2.3 Using Propargyl/Allenic Organometallics

Additions of propargyl/allenic aluminum, zinc and magnesium reagents (**59**) to aldimines (**60**) have been studied by Moreau and Gaudemar;[36] use of the lithium reagent is mentioned in an earlier study by Huet.[20] Alkynic (**61**) or allenic (**62**) products result from attack of the reagent (**59**) at the methylene or methine carbons, respectively (equation 14). Propargyl/allenic magnesium reagents do not give useful yields of (**61**) and (**62**) due to propargyl–alkynyl anion migration.[36]

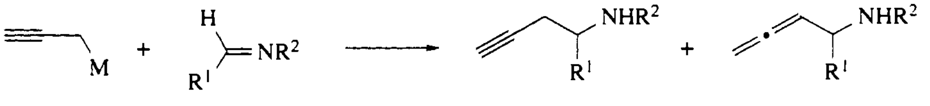

(**59**) (**60**) (**61**) (**62**) (14)

As shown in Table 15, alkynic products (**61**) are obtained exclusively in the reactions of the aluminum reagent, while mixtures enriched mainly in the alkynic product are obtained in the reactions of the zinc and lithium reagents. Yields tend to be lower and more variable than those of allyl organometallics (see Table 2). If cyclic six-centered transition states are involved, the dominance of alkynic products (**61**) could be explained by preference of a transition state in which the metal is coordinated to the more accessible methine instead of methylene carbon.

*Syn-anti* selectivity of the reactions of α-silylallenic organometallic reagents (**63**; M = Ti(Pr$^i$O)$_3$, $AlEt_3$ and Li) with imines (**64**) has been studied by Yamamoto *et al.* (equation 15).[37] The lithium reagent (**63**;

**Table 15** Reaction of Propargyl/Allenyl Organometallic Reagents (**59**) with Imines (**60**; Equation 14)

| *Entry* | *Imine (60)* | | *Metal* | | | | | | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Al$_{2/3}$Br* | | *ZnBr* | | *Li* | | |
| | *R$^1$* | *R$^2$* | *Yield (%)* | *(61):(62)* | *Yield (%)* | *(61):(62)* | *Yield (%)* | *(61):(62)* | |
| 1 | Me | Pr$^i$ | 50 | 99:t$^a$ | 47 | 85:15 | | | 36 |
| 2 | Me | Bu$^n$ | 34 | 99:t | | | | | 36 |
| 3 | Pr$^i$ | Me | 68 | 99:t | | | | | 36 |
| 4 | Pr$^i$ | Bu$^n$ | | | 36 | 60:40 | | | 36 |
| 5 | Pr$^i$ | Pr$^i$ | | | | | 28 | 70:30 | 20 |
| 6 | Pr$^i$ | Ph | 52 | 99:t | 80 | 43:57 | | | 36 |
| 7 | Bu$^t$ | Me | | | 40 | 75:25 | | | 36 |
| 8 | Ph | Me | 57 | 99:t | 34 | 65:35 | | | 36 |
| 9 | Ph | Ph | 25 | 99:t | | | | | 36 |

$^a$t = trace.

M = Li), prepared by deprotonation of 1-trimethylsilyl-1-butyne with Bu$^n$Li, is treated with ClTi(Pr$^i$O)$_3$, and AlEt$_3$, respectively, to generate the corresponding titanium and aluminum (ate) reagents. The reactions are regiospecific, giving only alkynic products (**65**) and (**66**). The α-alkylimine reactions are stereospecific; the *anti* products (**65**) are formed exclusively (entries 1–5, Table 16). Selectivity erodes, however, in additions to α-arylimines (entries 6 and 7, Table 16). It is interesting that the aberrant behavior of α-arylimines witnessed in the reactions of crotyl organometallics[11] is also found in the reactions of these allenic reagents. Yields vary depending on the metal and are highest in reactions with unhindered imines, as hindered imines react sluggishly. A cyclic transition state in which the α-substituent of the imine and the methyl group of the allenic reagent are aligned in a less sterically congested *anti* relationship (Figure 12) has been proposed to rationalize the preference for *anti* selectivity.[37] The erosion in *anti* selectivity which occurs with α-arylimines, however, is not readily explained by this model.

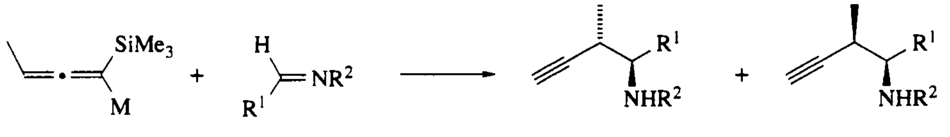

(**63**) (**64**) (**65**) (**66**) (15)

**Table 16** *Syn–Anti* Selectivity in the Reactions of Allenic Organometallic Reagent (**63**) with Aldimines (**64**; Equation 15)[37]

| *Entry* | *Imine (64)* | | *Metal* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Ti(OPr$^i$)$_3$* | | *AlEt$_3$* | | *Li* | |
| | *R$^1$* | *R$^2$* | *Yield (%)* | *(65):(66)* | *Yield (%)* | *(65):(66)* | *Yield (%)* | *(65):(66)* |
| 1 | Et | Bn | 95 | >99:1 | 28 | >99:1 | 65 | >99:1 |
| 2 | Pr$^n$ | Bn | 95 | >99:1 | | | | |
| 3 | Pr$^n$ | Pr$^i$ | 57 | >99:1 | 80 | >99:1 | 46 | >99:1 |
| 4 | Pr$^i$ | Pr$^n$ | 64 | >99:1 | 90 | >99:1 | | |
| 5 | Pr$^i$ | Pr$^i$ | 37 | >99:1 | | | | |
| 6 | Ph | Ph | 97 | 54:46 | 67 | 50:50 | 94 | 65:35 |
| 7 | Ph | Pr$^n$ | 95 | 81:19 | | | | |

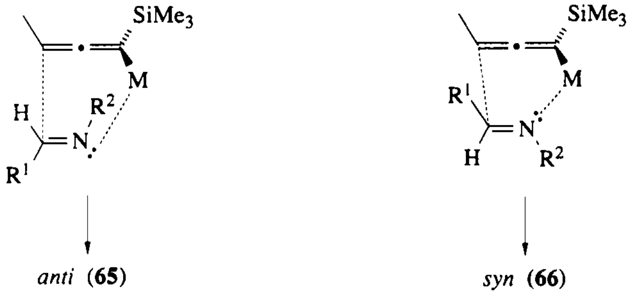

**Figure 12** Proposed transition states for the formation of diastereomeric *syn* and *anti* alkynic amines in reactions of α-silylallenic reagent (**63**) with aldimines[37]

## 4.3.3 REACTIONS WITH *N*-HETEROSUBSTITUTED IMINES

### 4.3.3.1 Introduction

The reaction of *N*-unsubstituted aldimines (**67**; X = H) derived from ammonia with organometallic reagents to generate primary amines (**68**) is not practical because of the inherent instability of these imine substrates. For this reason, masked imines (**67**) with a labile N—X bond such as oximes (X = OH), sulfenimines (X = SAr), trimethylsilylimines (X = $SiMe_3$) and sulfonylimines (X = $SO_2R$) are commonly utilized (Scheme 5). Oximes, including oxime ethers and sulfenimines, have been examined in great detail and react with a variety of allyl (crotyl) organometallic reagents (entries 1 and 2, Table 17). Trimethylsilylimines and sulfonylimines (diarylidinesulfamides) have a more limited role and have been used only for the preparation of α-aryl-substituted homoallylamines (entries 3 and 4, Table 17).

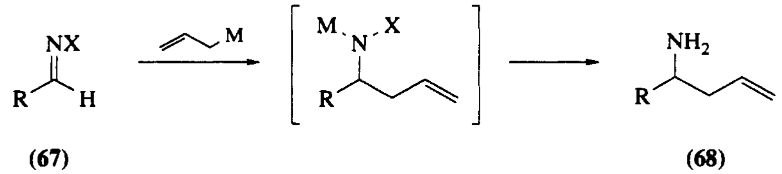

**Scheme 5**

**Table 17** The Use of *N*-Heterosubstituted Aldimines (**67**) for the Preparation of Homoallylamines (**68**; Scheme 5)

| *Entry* | *RCH═NX (67)* | *X* | *RCH═NX preparation* | *Substituent (R) Aryl* | *Alkyl* | *Conditions for NX cleavage* |
|---|---|---|---|---|---|---|
| 1 | Oximes (ethers) | OH(OR) | $NH_2OH(OR)$ + RCHO | x | x | Reduction; iron(II) dihydrolipoate[9] |
| 2 | Sulfenimines | SAr | $(Me_3Si)_2NSAr$ + RCHO[38] | x | x | Aqueous work-up |
| 3 | Trimethylsilylimines | $SiMe_3$ | $LiN(SiMe_3)_2$ + RCHO[39] | x |  | Aqueous work-up |
| 4 | Sulfonylimines | 1/2 $SO_2$ | $NH_2SO_2NH_2$ + RCHO[40] | x |  | $H_2O$/pyridine; NaOH |

### 4.3.3.2 Oximes and Oxime Ethers

Treatment of *syn*/*anti* mixtures of aldoximes (**69**) with allylboronates generates *N*-(homoallyl)hydroxylamines (**70**) in good yield (Scheme 6).[26,41] The *anti* oxime reacts faster than the *syn* isomer. *N*-(Homoallyl)hydroxylamines (**70**) have been converted to homoallylamines (**71**) (with iron(II) dihydrolipoate) and have been treated with aldehydes to generate highly functionalized nitrone intermediates (**72**) for use in 1,3-dipolar addition reactions.

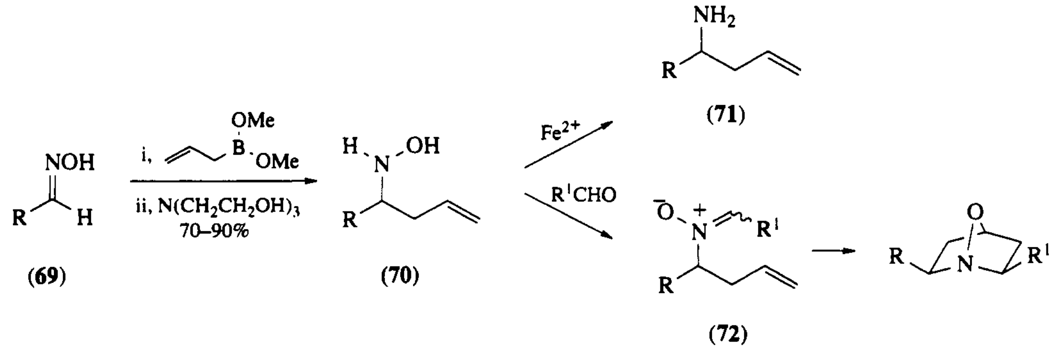

R = Me, Pr$^i$, Pr$^n$ and Ph

**Scheme 6**

Hoffmann *et al.*[26] have also examined the addition of allylboronates (**74**) and (**75**) to 2,3-isopropylidene-D-glyceraldehyde oximes (**73**; *E*:*Z* = 3:7; equation 16 and Table 18). Cram selectivity is obtained. As is the case of the parent 2,3-isopropylidene-D-glyceraldehyde,[42,43] optically pure boronate (**74**; entry 1, Table 18) provides better diastereofacial selectivity than (**75**). The relationship, if any, between oxime geometry and Cram diastereoselectivity has not been established.

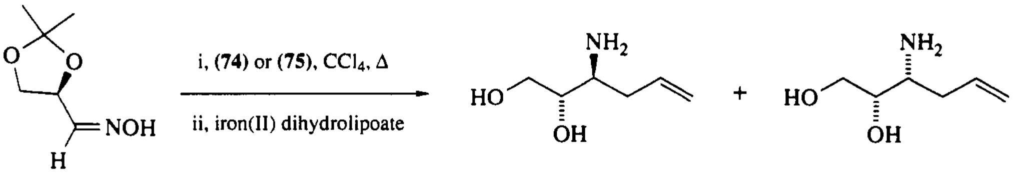

(**73**) (*E*):(*Z*) = 3:7 (**76**) Cram (**77**) anti-Cram (16)

**Table 18** Cram Selectivity in the Addition of Allylboronate Esters to 2,3-*O*-Isopropylidine-D-glyceraldehyde Oximes (**73**; Equation 16)[26]

| *Entry* | *Allyl boronate* | *Product ratio (76):(77)* | *2,3-O-Isopropylidine-D-glyceraldehyde addition (Cram:anti-Cram ratio)*[42,43] |
|---|---|---|---|
| 1 | 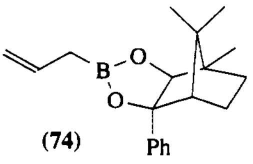 (**74**) | 90:10 | 96:4 |
| 2 | 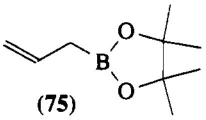 (**75**) | 70:30 | 80:20 |

The addition of allyl organometallic reagents to aldoxime ethers (**78**) has also been explored (equation 17).[44] The course of the reaction is reagent and solvent dependent, as allylzinc bromide affords predominantly *N*-(homoallyl)alkoxyamines (**79**; 60%; 1,2-addition) while allylmagnesium bromide provides amine (**80**; 96%), a Beckmann rearrangement product. Beckmann rearrangement products can also be selectively generated in the addition of organometallic reagents to ketoxime methanesulfonates. For example, treatment of (**81**) in toluene with alkyl Grignard reagents (1.5 equiv.), followed by allyl- or propargyl-magnesium bromide (2 or 4 equiv., respectively) provides the corresponding 2,2-disubstituted-azacycloheptanes (**82**) in *ca.* 70% yield (equation 18).[45]

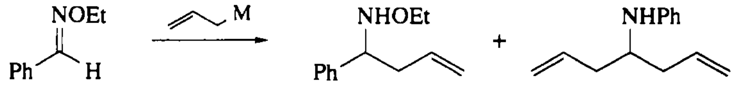

(**78**) (**79**) (**80**) (17)

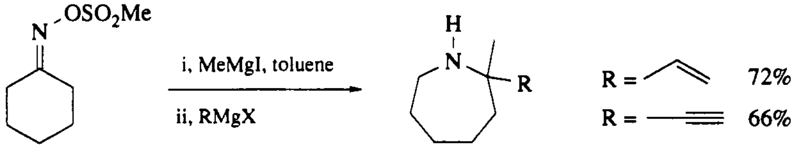

(**81**) (**82**) (18)

The addition of allyl and prenyl organometallics (**84**) to 8-(−)-phenylmenthyl *N*-methoxyiminoacetate (**83**; equation 19) has been examined for the asymmetric synthesis of amino acids.[46] Treatment of (**83**) with allylboronates and allylzinc bromide affords *N*-alkoxyamines (**85**) and (**86**; Table 19). Both allyl-

and prenyl-zinc bromide (entries 1 and 3, Table 19) provide good stereocontrol. Predominant formation of (**85**; $R^1 = R^2 = H$) is consistent with a chelation-controlled allyl addition as shown in Figure 13, with attack occurring from the more accessible *si* face. Parallel results are obtained in the addition of organometallic reagents to *in situ* generated 8-(–)-phenylmenthyl N-acyliminoacetates.[47]

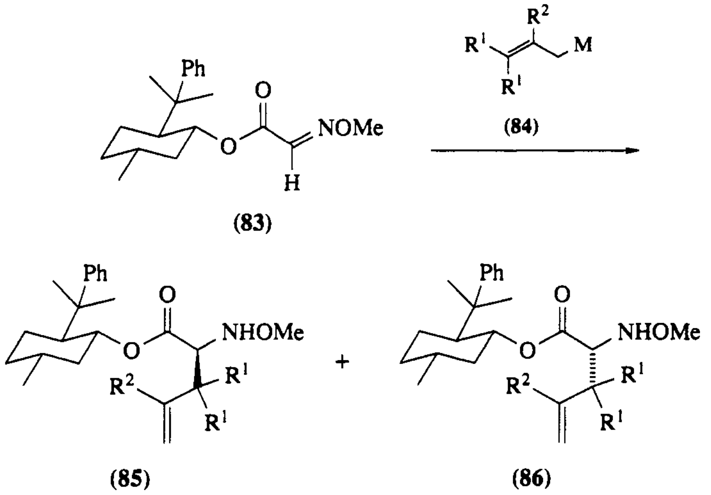

(19)

**Table 19** Diastereoselectivity in the Addition of Allyl Organometallic Reagents (**84**) to 8-(–)-Phenylmenthyl-*N*-methoxyiminoacetate (**83**; Equation 19)[46]

| *Entry* | *Organometallic (84)* $R^1$ | $R^2$ | *M* | *Product ratio (85):(86)* | *de* | *Yield (%)* |
|---|---|---|---|---|---|---|
| 1 | H | H | ZnBr | 87:13 | 74 | 52 |
| 2 | H | H | B(OMe)$_2$ | 53:47 | 6 | 29 |
| 3 | Me | Me | ZnBr | — | >98 | 55 |

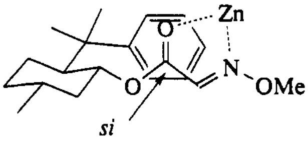

**Figure 13**

The *syn–anti* selectivity of oxime and oxime ether additions has been studied by Hoffmann and Endesfelder using separated (*E*)- and (*Z*)-crotylboronates (**87**) and (**88**; equation 20).[9] The reactions are carried out under high pressure (3.6–9 kbar) because of low oxime reactivity. As shown in Table 20, a good correlation exists between the direction of *syn–anti* selectivity and the geometry of the crotyl boronate, *i.e.* (*E*)-crotyl gives *anti* products (**91**), while (*Z*)-crotyl gives *syn* products (**90**). This trend, unlike the addition of crotyl-9-BBN to imines, is independent of whether the α-substituent on the imine is alkyl or aryl. Cyclic transition states do not satisfactorily explain these results because they are consistent with the boat rather than chair models. The possibility that alternative $C(E,Z)^\ddagger$ and $C(Z,Z)^\ddagger$ cyclic transition states are involved, assuming facile isomerization of the oxime, seems unlikely in view of the fact that no change in the direction of *syn–anti* selectivity is observed in the reactions of geometrically rigid (*E*)- and (*Z*)-benzaldoxime trimethylsilyl ethers (entries 7–10, Table 20). The *syn–anti* selectivity of oxime–crotylboronate additions is more satisfactorily rationalized using open transition state models (Figure 6), which are consistent with the fact that *syn–anti* selectivity is dependent on the geometry of crotyl reagent, and not on the geometry of the imine.

The addition of (*E*)-γ-(trimethylsilyl)allylboronate (**93**)[48] to racemic oxime (**92**) has been utilized by Wuts and Jung in connection with a total synthesis of cannabisativine (Scheme 7).[49] Paralleling the investigations of Hoffmann and Endesfelder using (*E*)-crotylboronate (**87**; see equation 20),[9] the reaction of (**93**) is *anti* selective and affords diastereomeric hydroxylamines (**94**) and (**95**). The diastereofacial se-

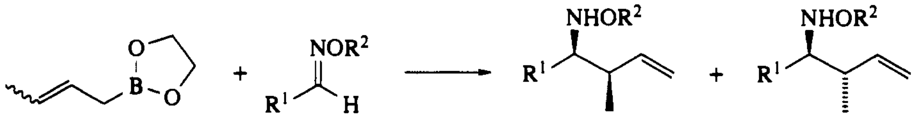

NOR$^2$
R$^1$
H
NHOR$^2$
R$^1$
NHOR$^2$
R$^1$

**(87)** *(E)* **(88)** *(Z)* **(89)** **(90)** **(91)** (20)

**Table 20** *Syn–Anti* Selectivity in the Reactions of Crotyl Boronates (**87**) and (**88**) with Oximes (**89**; Equation 20)[9]

| *Entry* | *Crotylboronate geometry* | *Oxime (89)* $R^1$ | $R^2$ | *Geometry* | *Conditions* | *Yield (%)* | *Product ratio* ***(90)*:*(91)*** |
|---|---|---|---|---|---|---|---|
| 1 | (*E*) | Ph | H | (*E*) | a | 64 | 5:95 |
| 2 | (*Z*) | Ph | H | (*E*) | a | 38 | 88:12 |
| 3 | (*E*) | $Pr^i$ | H | (*E*) | a | 81 | 19:81 |
| 4 | (*Z*) | $Pr^i$ | H | (*E*) | a | 65 | 80:20 |
| 5 | (*E*) | $Bu^t$ | H | (*E*) | a | 84 | 25:75 |
| 6 | (*Z*) | $Bu^t$ | H | (*E*) | a | 60 | 70:30 |
| 7 | (*E*) | Ph | TMS | (*E*) | b | 40 | 5:95 |
| 8 | (*E*) | Ph | TMS | (*Z*) | a | 49 | 5:95 |
| 9 | (*Z*) | Ph | TMS | (*E*) | a | 24 | 87:13 |
| 10 | (*Z*) | Ph | TMS | (*Z*) | a | 25 | 85:15 |

[a] 3.6–9 kbar, 28–88 °C, pet. ether. [b] 9 kbar, 46 °C, $CH_2Cl_2$.

lectivity, however, is modest as the ratio of (**94**):(**95**) is 1.7:1. Diastereomer (**94**) is converted to tetrahydropyridine (**97**), a useful intermediate for the synthesis of cannabisativine, by TMS-OTf-promoted cyclization of the nitrone derivative (**96**).

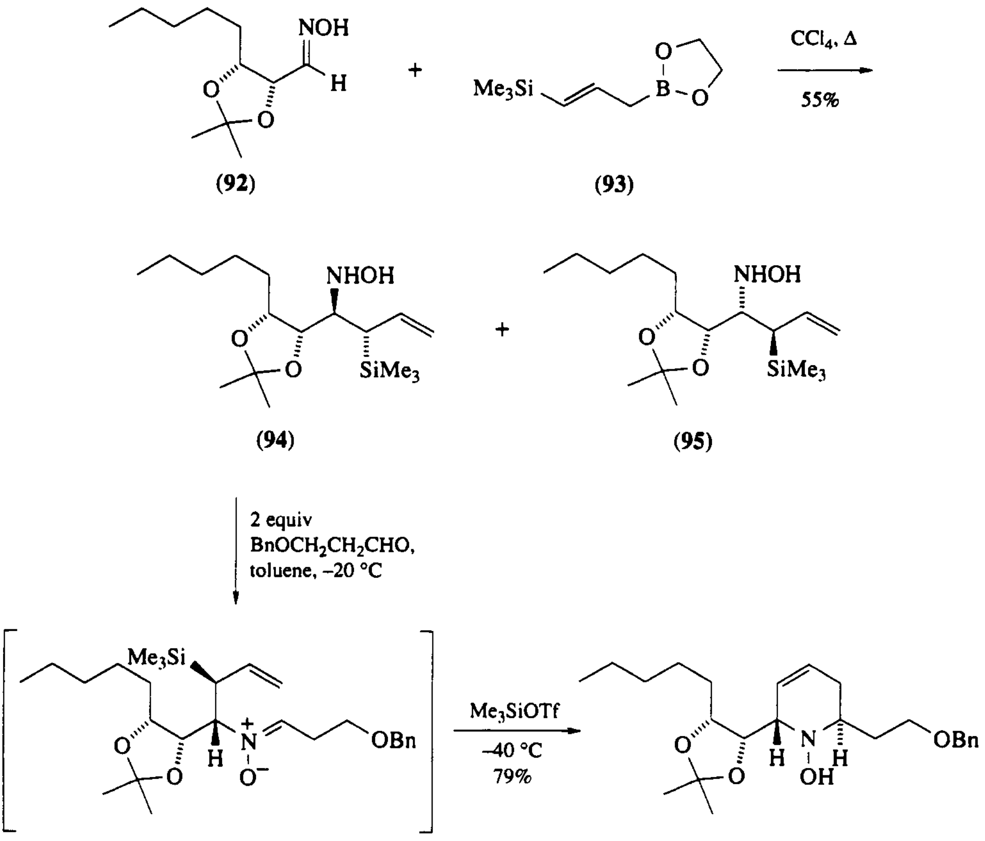

NOH
H
O
O
Me3Si
O
B
O
CCl4, Δ
55%
NHOH
SiMe3
NHOH
SiMe3
2 equiv
BnOCH2CH2CHO,
toluene, –20 °C
Me3Si
H
N
O⁻
OBn
Me3SiOTf
–40 °C
79%
N
H
H
OH
OBn

**(92)** **(93)** **(94)** **(95)** **(96)** **(97)**

**Scheme 7**

### 4.3.3.3 Sulfenimines

The reaction of organometallic reagents with *S*-arylsulfenimines yields sulfenamides whose weak sulfur–nitrogen bond is readily cleaved upon aqueous work-up to generate primary amines. Fuganti *et al.*[50] have examined the addition of diallylzinc and allylmagnesium bromide to sulfenimine (**98**; equation 21) and isomeric sulfenimine (**101**; equation 22) to probe the influence of the α- and β-alkoxy substituents on reaction diastereoselectivity. The results are summarized in Tables 21 and 22. The reaction is performed by treatment of an ethereal solution (–78 °C) of (**98**) and (**101**) with the organometallic reagent (2 equiv.) followed by hydrolysis and benzoylation. Treatment of (**98**) with diallylzinc provides exclusively *N*-homoallylamide (**99**), the product of Cram addition in *ca.* 60% yield (entry 1, Table 21). Similarly, phenylsulfenimine (**101**) provides under identical conditions the Cram product, *N*-homoallylamide (**102**), as the sole product (entry 1, Table 22). The diastereofacial selectivity erodes with the addition of allylmagnesium bromide to (**98**; entry 2, Table 21) and is reversed with Grignard addition to (**101**; entry 2, Table 22).

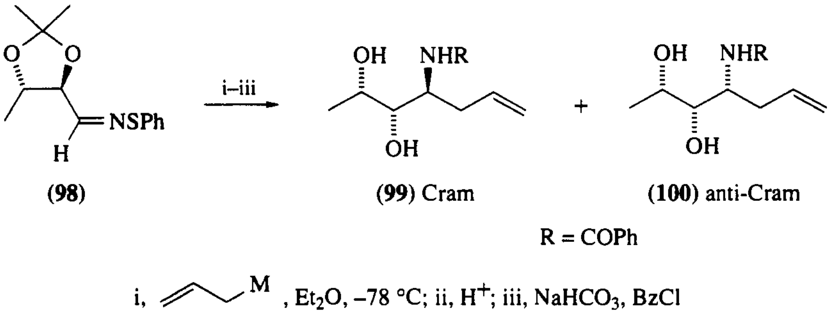

(**98**) (**99**) Cram (**100**) anti-Cram

R = COPh

i, , Et$_2$O, –78 °C; ii, H$^+$; iii, NaHCO$_3$, BzCl

(21)

**Table 21** Cram Selectivity in the Addition of Allyl Organometallic Reagents to Sulfenimine (**98**; Equation 21)[50]

| *Entry* | *Allyl organometallic M* | *Product ratio (99):(100)* | *Aldehyde addition (Cram:anti-Cram ratio)*[51] |
|---|---|---|---|
| 1 | 1/2 Zn | >98:— | 95:5 |
| 2 | MgBr | 55:45 | *ca.* 65:35 |

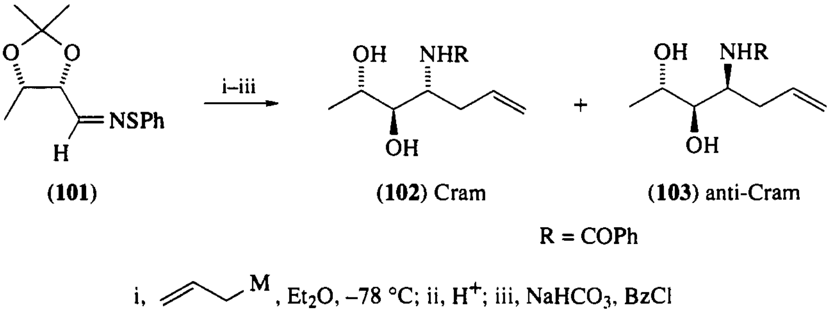

(**101**) (**102**) Cram (**103**) anti-Cram

R = COPh

i, , Et$_2$O, –78 °C; ii, H$^+$; iii, NaHCO$_3$, BzCl

(22)

**Table 22** Cram Selectivity in the Addition of Allyl Organometallic Reagents to Sulfenimine (**101**; Equation 22)[50]

| *Entry* | *Allyl organometallic M* | *Product ratio (102):(103)* | *Aldehyde addition (Cram:anti-Cram ratio)*[51] |
|---|---|---|---|
| 1 | 1/2 Zn | >98:— | 95:5 |
| 2 | MgBr | 30:70 | *ca.* 65:35 |

The diallylzinc-induced Cram diastereofacial selectivity closely parallels that of the corresponding aldehyde precursors[51] (Tables 21 and 22) and is consistent with Felkin–Ahn addition, as is shown in Figure 14. The high selectivity in the addition of diallylzinc to (**101**) is somewhat surprising given the added steric interactions with the incoming nucleophile and the (3*S*)-methyl group of (**101**) with Felkin–Ahn addition (Figure 14b) and that models other than Felkin–Ahn (*i.e.* Cornforth) might be more relevant. β-Chelation transition states involving a six-membered zinc chelate are possible and would have a synergistic effect on diastereofacial selectivity. α-Chelation (five-membered zinc chelate), however, is not likely since it would favor the formation of (**100**) and (**103**). The erosion of diastereoselectivity in the addition of allylmagnesium bromide to sulfenimines (**98**) and (**101**) parallels that observed in the aldehyde additions.[51] The presence of a competing five-membered magnesium chelate involving the α-alkoxy group has been suggested.[50]

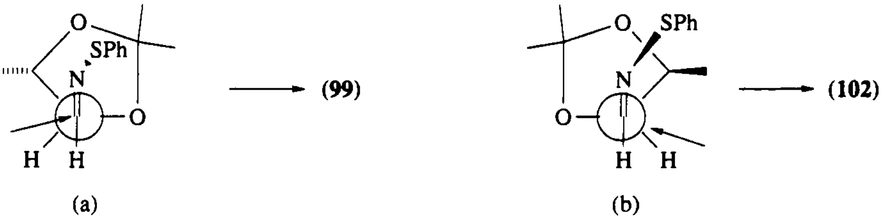

(a) (b)

**Figure 14**

The addition of allylboronates (**105**) and (**106**) to aryl sulfenimines (**104**) to provide sulfenamides (**107**) has also been reported by Wuts and Jung (equation 23).[52] High yields of (**107**) are obtained even though the reaction is slow (4 h to 3 d, refluxing toluene). The reaction rate is a function of the size of the boronate ligand (**106** is slower than **105**). The authors attribute the reaction sluggishness to a cyclic boronate transition state.

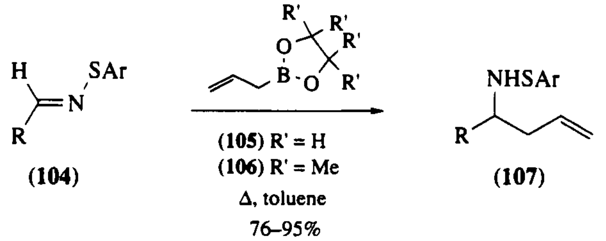

(23)

### 4.3.3.4 *N*-Trimethylsilylimines

*N*-Trimethylsilylimines (**108**) can be conveniently generated *in situ* by treatment of nonenolizable aldehydes with lithium bis(trimethylsilyl)amide.[39] Treatment of a solution of (**108**) with allylmagnesium bromide affords after aqueous work-up homoallylamine (**109**) in good/excellent yield (equation 24).[39] Although the methodology works best with nonenolizable aldimines, it nonetheless provides a convenient method for preparing many primary homoallylamines.

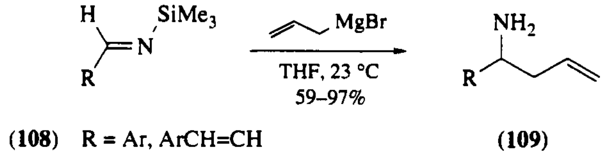

(24)

### 4.3.3.5 Sulfonylimines

Although *N*-sulfonylimines react with a variety of nucleophilic reagents, the products are not particularly useful since the sulfonyl protecting group is not easily removed. To overcome this problem, Davis *et al.*[40] have examined the addition of organometallic reagents including allylmagnesium bromide to diarylidenesulfamides (**110**) derived from nonenolizable aldehydes (equation 25). In this case the reaction products, diaryl sulfamides (**111**) can be hydrolyzed in refluxing aqueous pyridine to afford, after sodium hydroxide treatment, primary homoallylamines (**112**) in good yield.

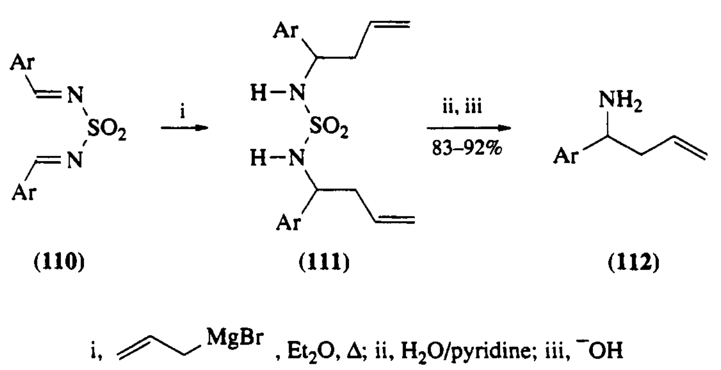

(25)

**(110)** **(111)** **(112)**

i, MgBr, $Et_2O$, Δ; ii, $H_2O$/pyridine; iii, $^-OH$

## 4.3.4 REACTIONS WITH IMINIUM SALTS

### 4.3.4.1 Using Preformed Iminium Salts

Miginiac *et al.* have examined the reactions of crotyl-zinc, -magnesium, -aluminum and -lithium organometallics (**113**) with preformed iminium salts (**114**), for the synthesis of branched and linear tertiary amines (**115**) and (**116**), respectively (equation 26).[53] The iminium salts were prepared by treatment of the corresponding enamines with hydrogen chloride. Neither the (*E*):(*Z*) isomeric ratio of the linear products (**116**) nor the *syn:anti* ratio of branched products (**115**) were determined. α-Deprotonation is not a serious problem since yields are generally good even though the iminium salts are enolizable. The reactions are performed in THF/ether or in ether (with Grignard reagents) and at temperatures between 10 and 25 °C (the more reactive crotyllithium reagents, however, add more effectively at –60 °C). Results are shown in Table 23. The preference for branched homoallylamines (**115**), with the exception of the vinyl crotyl reagents, follows the trend $Al_{2/3}X > ZnX > MgX > Li$, paralleling the covalent character of the carbon–metal bond. Crotylaluminum reagents are noteworthy because they are entirely regiospecific, providing branched products (**115**) when $R^1$ = alkyl or aryl (entries 1–9, Table 23) and linear products (**116**) when the $R^1$ is vinyl (entries 10–12, Table 23). There is little similarity between the regiochemistry of these reactions and that observed in reactions of imines, the latter of which are strongly influenced by imine substitution (see Section 4.3.2.2.1). This is not unexpected because iminium salts do not contain an available lone pair of electrons, which is necessary for the involvement of cyclic transition states. The preference for products of allylic rearrangement in crotyl additions (*i.e.* branched products) could also apply to vinyl crotyl reagents, since linear product formation which dominates in these cases (entries 10–12, Table 23) can be explained by homoallylic transposition, *i.e.* attack at the ε-carbon atom.

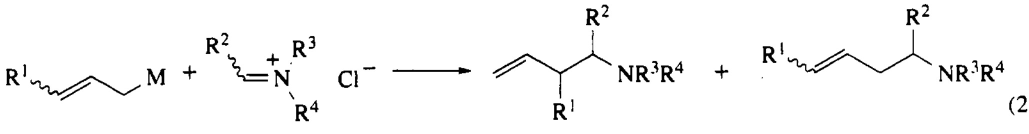

(26)

**(113)** **(114)** **(115)** **(116)**

Additions of propargyl/allenic reagents (**117**) to iminium salts (**118**) have also been studied by Miginiac *et al.* (equation 27).[54] Reaction conditions and yields are similar to those used in the analogous crotyl additions. Results are shown in Table 24. The regioselectivity, paralleling the reactions of imines with propargyl/allenic reagents, is influenced by the presence of a γ-substituent in the propargyl/allenic reagent; thus, the absence of γ-substitution favors alkynic products (**120**; entries 1–4, Table 24), while γ-substitution favors allenic products (**119**; entries 5–11, Table 24). As in crotyl organometallic additions to iminium salts, aluminum reagents are far more selective than zinc, magnesium or lithium reagents. The size of the γ-substituent of the organometallic reagent does not have a large effect on the regiochemical outcome, since replacement of the alkynic methyl group by an *n*-butyl group does not significantly increase the amount of alkynic product (**120**; entries 5 *versus* 9, Table 24). The type of alkylimine substituents (branched, linear or cyclic) also has little impact on regiochemistry.

An interesting example of bis(dimethylamino)methylation has been reported by Reich *et al.* involving the reaction of 1,4-bis(trimethylstannyl)-2-butyne (**121**) with Eschenmoser's salt (**122**) to afford

**Table 23** Reactions of Crotyl Organometallic Reagents (**113**) with Iminium Salts (**114**; Equation 26)[53]

| | | | | | Metal | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Organometallic (113)* | *Iminium salt (114)* | | | *ZnBr* | | *MgX* | | *$Al_{2/3}X$* | | *Li* | |
| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *Yield (%)* | *(115):(116)* | *Yield (%)* | *(115):(116)* | *Yield (%)* | *(115):(116)* | *Yield (%)* | *(115):(116)* |
| 1 | Me | $Pr^i$ | —$(CH_2)_4$— | | 82 | 90:10 | 76 | 86:14 | 75 | 100:0 | 77 | 32:68 |
| 2 | Me | $Pr^n$ | —$(CH_2)_4$— | | | | | | 53 | 100:0 | | |
| 3 | Me | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 74 | 100:0 | | |
| 4 | $Bu^n$ | $Pr^i$ | —$(CH_2)_4$— | | 80 | 90:10 | 68 | 75:25 | 65 | 100:0 | | |
| 5 | $Bu^n$ | $Pr^n$ | —$(CH_2)_4$— | | | | | | 55 | 100:0 | | |
| 6 | $Bu^n$ | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 56 | 100:0 | | |
| 7 | Ph | $Pr^i$ | —$(CH_2)_4$— | | 37 | 56:44 | 51 | 57:43 | 42 | 100:0 | 74 | 16:84 |
| 8 | Ph | $Pr^n$ | —$(CH_2)_4$— | | | | | | 39 | 100:0 | | |
| 9 | Ph | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 56 | 100:0 | | |
| 10 | $CH_2{=}CH$ | $Pr^i$ | —$(CH_2)_4$— | | 31 | 16:84 | 62 | 23:77 | 83 | 0:100 | 73 | 8:92 |
| 11 | $CH_2{=}CH$ | $Pr^n$ | —$(CH_2)_4$— | | | | | | 64 | 0:100 | | |
| 12 | $CH_2{=}CH$ | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 76 | 0:100 | | |

**Table 24** Reactions of Propargyl/Allenic Organometallic Reagents (**117**) with Iminium Salts (**118**; Equation 27)[54]

| | | | | | | Metal | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Organometallic (117)* | | *Iminium salt (118)* | | | *ZnX* | | *MgX* | | *$Al_{2/3}X$* | | *Li* | |
| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *$R^5$* | *Yield (%)* | *(119):(120)* | *Yield (%)* | *(119):(120)* | *Yield (%)* | *(119):(120)* | *Yield (%)* | *(119):(120)* |
| 1 | H | H | $Pr^i$ | —$(CH_2)_4$— | | 32 | 53:47 | 70 | 2:98 | 66 | 2:98 | | |
| 2 | H | Me | $Pr^i$ | —$(CH_2)_4$— | | 40 | 50:50 | 45 | 40:60 | 72 | 10:90 | | |
| 3 | H | H | $Pr^n$ | —$(CH_2)_4$— | | | | | | 65 | 0:100 | | |
| 4 | H | H | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 86 | 0:100 | | |
| 5 | Me | H | $Pr^i$ | —$(CH_2)_4$— | | 73 | 99:1 | 71 | 70:30 | 64 | 91:9 | 65 | 41:59 |
| 6 | Me | H | $Pr^n$ | —$(CH_2)_4$— | | | | | | 49 | 100:0 | | |
| 7 | Me | H | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 87 | 96:4 | | |
| 8 | Et | H | $Pr^i$ | —$(CH_2)_4$— | | 68 | 90:10 | 70 | 61:39 | 69 | 92:8 | | |
| 9 | $Bu^n$ | H | $Pr^i$ | —$(CH_2)_4$— | | 71 | 70:30 | 65 | 57:43 | 70 | 92:8 | | |
| 10 | $Bu^n$ | H | $Pr^n$ | —$(CH_2)_4$— | | | | | | 51 | 95:5 | | |
| 11 | $Bu^n$ | H | $Pr^i$ | $Bu^n$ | $Bu^n$ | | | | | 52 | 90:10 | | |

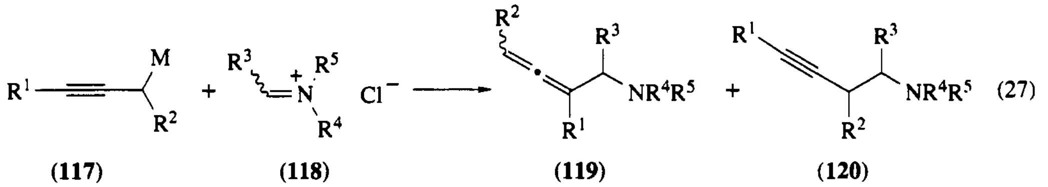

2,3-bis(*N*,*N*-dimethylamino)methyl-1,3-butadiene (**124**) in good yield (Scheme 8).[55] The regiochemical outcome of the reaction suggests the intermediacy of an *N*,*N*-(dimethylamino)-methylated allenic species (**123**).

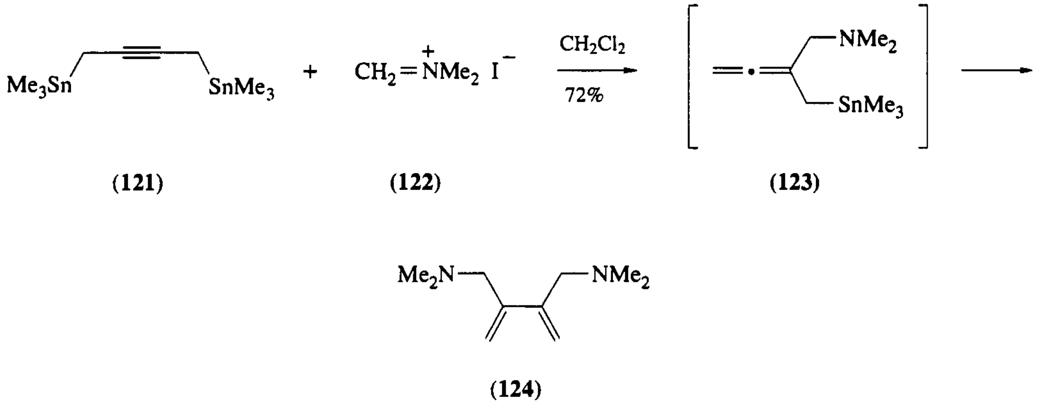

Scheme 8

### 4.3.4.2 Using Iminium Salts Generated *In Situ*

As reported by Grieco and coworkers,[56,57] additions of allyl- and crotyl-silanes and -stannanes to iminium salts can be performed in protic media in which the iminium salt is generated reversibly, as in the Mannich reaction. A typical example is the reaction of allyltrimethylsilane with *N*-benzyl-*N*-methylammonium trifluoroacetate (**125**) and formaldehyde to afford, *via* iminium salt (**126**), tertiary amine (**127**; Scheme 9). Reactions are normally carried out by stirring the allylsilane (1.1 equiv.) in a mixture of 3.0–3.5 M aqueous 37% formaldehyde solution (2.3 equiv.) and the amine trifluoroacetate salt (1.0 equiv.) at room temperature.[56] Slightly higher temperatures are required using secondary amines instead of primary amines. Protodesilylation, surprisingly, is not a serious problem even though the pH of the medium is slightly acidic. As shown in Scheme 10, secondary homoallylamine products (**128**) are difficult to isolate in reactions employing primary amines because *N*-homoallyliminium salts (**129**), formed by further condensation with formaldehyde, cyclize to form 4-hydroxypiperidines (**130**).[56] Overall yields of 4-hydroxypiperidines (**130**) starting with the primary amine salts are in the range of 50–100%. The reaction is also general for β-substituted allyl- and crotyl-silanes.

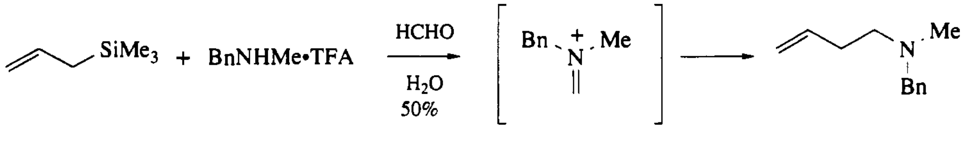

Scheme 9

Analogous reactions of allylstannanes (**131**) with primary amines and aqueous formaldehyde yield bishomoallylamines (**132**; equation 28).[57] Reactions are conducted at ambient temperature in a 1:1 mixture of methanol and chloroform using 37% aqueous formaldehyde (2.1 equiv.), 2.0 equiv. of the allyltri-*n*-butylstannane and 1.1 equiv. of the amine trifluoroacetate. The failure to observe 4-hydroxy-

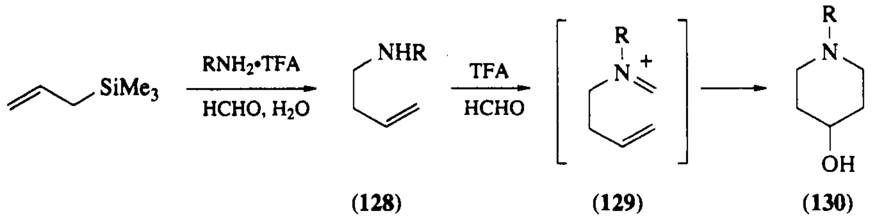

**Scheme 10**

piperidines, as in the reactions of allylsilanes, is attributed to the higher reactivity of allylstannanes (**131**), which add to the derived homoallylamine salt (**129**) faster than the ensuing cyclization process (see Scheme 10). Because allylstannanes react considerably faster than allylsilanes in reactions with iminium salts derived from secondary amines, they are the reagents of choice for preparing tertiary homoallylamines from secondary amines. The reaction has been performed with methallyltributylstannanes (**131**; $R^1$ = Me) and with aromatic amines. Yields are excellent (75–100%).

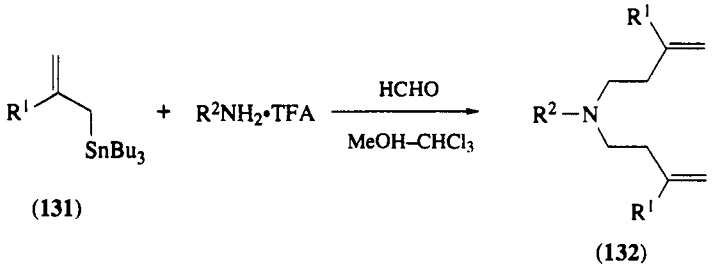

(28)

## 4.3.5 REACTIONS WITH *GEM*-AMINO ETHERS

*gem*-Amino ethers (**133**) behave as masked iminium salts and react with allyl organometallics to afford *N,N*-disubstituted homoallylamines (**136**; Scheme 11). The use of *gem*-amino ethers is preferred over preformed iminium salts for the synthesis of (**136**) because they are more easily handled and can be purified by distillation. The mechanism of addition most likely involves an initial coordination complex (**134**) between the metal and the ether oxygen, which fragments by one of two general pathways: (i) an ionic $S_N1$-like process leading to an iminium salt intermediate (**135**) which captures the allyl anion; or (ii) a cyclic four- or six-centered internal $S_N2$-like process in which the alkoxide is displaced by attack at the α- or γ-carbon of the organometallic reagent, respectively. A third possibility exists in which complex (**134**) undergoes $S_N2$ displacement by another molecule of allyl reagent, regenerating the allyl reagent. Evidence so far has been unable to distinguish between these mechanisms.

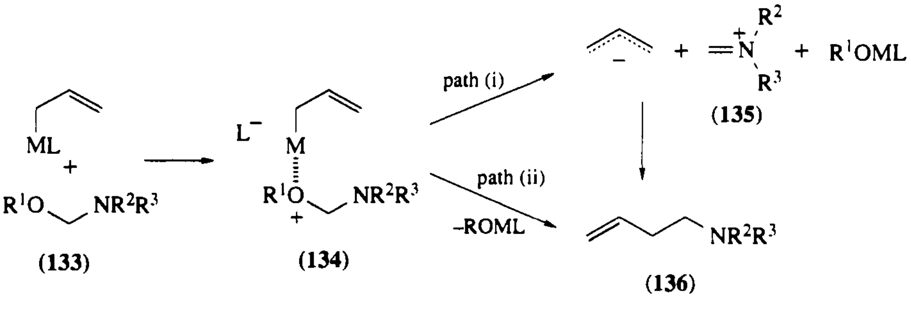

**Scheme 11**

Most of the reported reactions of *gem*-amino ethers have been confined to the use of crotyl or propargyl/allenic reagents. A few examples involving allyl reagents are shown in Table 25 and involve mainly *N*-(trimethylsilyl)- and *N,N*-bis(trimethylsilyl)-*gem*-amino ethers (**133**; $R^2$ = TMS, $R^3$ = alkyl; $R^2 = R^3$ = TMS). These silylated reagents, which also react with nonresonance-stabilized reagents, provide access

**Table 25** Reactions of Allyl Organometallic Reagents with *gem*-Amino Ethers (**133**; Scheme 11)

| *Entry* | *gem-Amino ether (133)*<br>$R^1$ | <br>$R^2$ | <br>$R^3$ | *Yield of products (136) (%)*<br>*MgBr* | <br>$Al_{2/3}Br$ | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Me | TMS | TMS | 70 | | 58 |
| 2 | Me | TMS | TMS | 88 | | 59 |
| 3 | Me | TMS | TMS | | 40 | 60 |
| 4 | Me | TMS | $Bu^t$ | | 45 | 60 |
| 5 | Ph | —$(CH_2)_2O(CH_2)_2$— | | 75 | | 61 |

to *N*-unsubstituted homoallylamines upon protodesilylation during work-up. Although the examples are limited, allylmagnesium reagents appear to be superior to aluminum reagents.

Paralleling their investigations of the additions of crotyl organometallics to preformed iminium salts (see Table 23), Miginiac and coworkers have examined similar additions to *gem*-amino ethers and sulfides (**138**; equation 29 and Table 26).[60,62,63] Branched products (**139**) are favored over linear products (**140**) as in the reactions of preformed iminium salts. The reactions of *gem*-amino ethers (**138**) are somewhat more regioselective than those of preformed iminium salts, although no direct comparison between reactants with identical *N*- and α-substituents has been made. Little difference in regiochemistry is observed between the *gem*-amino ethers and *gem*-amino sulfides (entries 5 *versus* 7, Table 26). The erosion in branched product regioselectivity that occurs with more ionic crotyl reagents (*e.g.* crotyllithium) has been explained by Miginiac and Mauze[62] in terms of greater charge density at the imine carbon induced by the increased polarizability of the π-bond. It is tempting to conclude that iminium salts are involved in these reactions since a similar trend in regiochemistry is observed in the reactions of preformed iminium salts. Further insight into the mechanism could be obtained from the *syn–anti* ratios (in branched products); unfortunately, these were not reported.

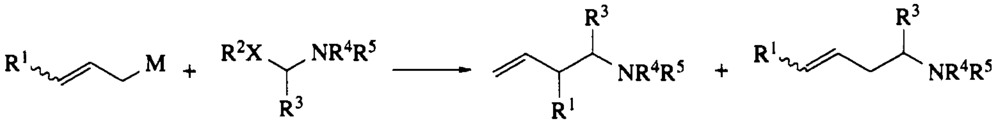

(29)

(**137**) (**138**) X = O, S (**139**) (**140**)

Reactions of propargyl/allenic organometallic reagents (**141**) with *gem*-amino ethers (**142**) (equation 30) have also been studied extensively by Miginiac and coworkers.[60,63] The results are shown in Table 27. Like crotyl reagents, propargyl/allenic reagents (**141**) display similar regiochemistry in their reactions with *gem*-amino ethers as they do with preformed iminium salts (see equation 27 and Table 24). Thus, allenic (branched) products (**143**) are favored with substituted propargyl/allenic reagents ($R^1$ = alkyl) and alkynic (linear) products (**144**) are favored with unsubstituted propargyl/allenic reagents ($R^1$ = H). Also, the more covalent organometallic reagents, aluminum and zinc, are more regioselective than the magnesium reagent. Regioselectivity diminishes, however, as the size of the amino substituents ($R^4$, $R^5$) in (**142**) increases (entries 11, 12 and 15, Table 27). Yields generally range between 40 and 60%.

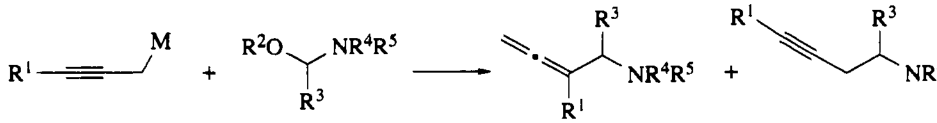

(30)

(**141**) (**142**) (**143**) (**144**)

**Table 26** Reactions of Crotyl Organometallic Reagents (**137**) with *gem*-Amino Ethers (**138**; Equation 29)

| | | | | | | | Metal | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Crotyl reagent (137)* | *gem-Amino ether (138)* | | | | | *ZnX* | | *MgX* | | *Li* | | *$\mathrm{Al}_{2/3}X$* | | |
| *Entry* | *$R^1$* | *$R^2$* | *X* | *$R^3$* | *$R^4$* | *$R^5$* | *Yield (%)* | *(139):(140)* | *Yield (%)* | *(139):(140)* | *Yield (%)* | *(139):(140)* | *Yield (%)* | *(139):(140)* | *Ref.* |
| 1 | Et | $Bu^n$ | O | H | Et | Et | 70 | 100:0 | 77 | 100:0 | 53 | 72:28 | | | 62 |
| 2 | Me | $Bu^n$ | O | H | Et | Et | 65 | 100:0 | 71 | 100:0 | 48 | 80:20 | 70 | 100:0 | 63 |
| 3 | Et | Ph | S | H | Et | Et | 60 | 99:t[a] | 87 | 96:4 | 85 | 76:24 | | | 62 |
| 4 | Ph | $Bu^n$ | O | H | Et | Et | 82 | 100:0 | | | | | | | 62 |
| 5 | Et | $Bu^n$ | O | Ph | Me | Me | 75 | 100:0 | 90 | 87:13 | 14 | 20:80 | | | 62 |
| 6 | Me | $Bu^n$ | O | Ph | Me | Me | 75 | 100:0 | 90 | 90:10 | | | 70 | 100:0 | 63 |
| 7 | Et | $Bu^n$ | S | Ph | Me | Me | 83 | 99:t | 67 | 85:15 | 15 | 11:89 | | | 62 |
| 8 | Me | Me | O | H | $Bu^t$ | TMS | | | | | | | 45 | 95:5 | 60 |
| 9 | Ph | Me | O | H | $Bu^t$ | TMS | | | | | | | 74 | 95:5 | 60 |
| 10 | $Bu^n$ | Me | O | H | $Bu^t$ | TMS | | | | | | | 75 | 95:5 | 60 |
| 11 | Me | Me | O | H | TMS | TMS | | | | | | | 47 | 100:0 | 60 |
| 12 | $Bu^n$ | Me | O | H | TMS | TMS | | | | | | | 74 | 100:0 | 60 |
| 13 | Me | Me | O | H | t-Oct[b] | TMS | | | | | | | 65 | 92:8 | 60 |

[a] t = trace. [b] —$C(Me)_2CH_2Bu^t$.

**Table 27** Reaction of Propargyl/Allenic Organometallics (**141**) with *gem*-Amino Ethers (**142**; Equation 30)

| | *Organometallic (141)* | | *gem-Amino ether (142)* | | | *ZnX* | | *MgX* | | *$\mathrm{Al}_{2/3}X$* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *$R^5$* | *Yield (%)* | *(143):(144)* | *Yield (%)* | *(143):(144)* | *Yield (%)* | *(143):(144)* | *Ref.* |
| 1 | H | Bu | H | Et | Et | 60[b] | 0:100 | 60[a] | 0:100 | 60[b] | 0:100 | 63 |
| 2 | H | Me | H | TMS | TMS | | | 50[c] | 0:100 | | | 58 |
| 3 | H | Bu | Ph | Me | Me | 42[b] | 10:90 | 80[a] | 5:95 | 62[b] | 2:98 | 63 |
| 4 | Me | Bu | H | Et | Et | 38[b] | 90:10 | 80[a] | 65:35 | 65[b] | 93:7 | 63 |
| 5 | Me | Bu | H | Et | Et | | | | | 50[a] | 99:1 | 63 |
| 6 | Et | Bu | H | Et | Et | | | | | 60[a] | 97:3 | 63 |
| 7 | $Bu^n$ | Bu | H | Et | Et | | | | | 60[a] | 98:2 | 63 |
| 8 | Me | Bu | Ph | Me | Me | 49[b] | 88:12 | 88[b] | 70:30 | 52[a] | 90:10 | 63 |
| 9 | Et | Bu | Ph | Me | Me | | | | | 65[a] | 85:15 | 63 |
| 10 | $Bu^n$ | Bu | Ph | Me | Me | | | | | 56[a] | 88:12 | 63 |
| 11 | Me | Me | H | TMS | $Bu^t$ | | | | | 40[a] | 70:30 | 60 |
| 12 | Bu | Me | H | TMS | $Bu^t$ | | | | | 60[a] | 70:30 | 60 |
| 13 | Me | Me | H | TMS | TMS | | | | | 40[a] | 85:15 | 60 |
| 14 | $Bu^n$ | Me | H | TMS | TMS | | | | | 60[a] | 90:10 | 60 |
| 15 | Me | Me | H | TMS | Oct | | | | | 50[a] | 50:50 | 60 |

[a] Solvent is ether: [b] Solvent is THF.

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# 4.4

# The Intramolecular Mannich and Related Reactions

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## 4.4.1 INTRODUCTION

Cyclization reactions of iminium ions, $R^1_2C{=}NR_2^+$, are a recurring theme in the assembly of cyclic nitrogenous compounds by both chemists and Nature.[1] The electron-deficient iminium ion is the nitrogen analog of an α-alkoxycarbenium (oxonium) ion or activated carbonyl group and as such is a fundamental electrophilic component of C—C bond formation. Although it is common practice in synthesis to modify the reactivity of simple iminium ions by introducing electron-withdrawing or electron-donating groups (Figure 1), only cyclization reactions of the parent species will be covered in this chapter. The important cyclization reactions of *N*-acyliminium ions are examined separately (see Volume 2, Chapter 4.5).

As this chapter is concerned with the intramolecular variants of iminium ion initiated condensations, a brief outline of possible cyclization modes is in order (Scheme 1). Examples (a) and (b) depict the generation of monocyclic compounds by way of exocyclic–trigonal and endocyclic–trigonal cyclizations, respectively.[2] Cases (c), (d) and (e) exemplify the construction of bicyclic compounds. Since rotational barriers for simple iminium ions are comparable to those of alkenes,[3] all of these cyclization modes

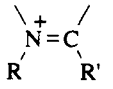

Stabilizing*

R = alkyl
R' = alkyl, alkenyl, aryl, alkynyl, SH, NH$_2$

Destabilizing*

R = acyl, aryl
R' = F, Cl, acyl

* relative to R = R' = H

**Figure 1**

should be subject to Baldwin's suggestions concerning orbital alignment and cyclization aptitude.[2] There is literature precedent for each of the generalized cyclization modes illustrated in Scheme 1.

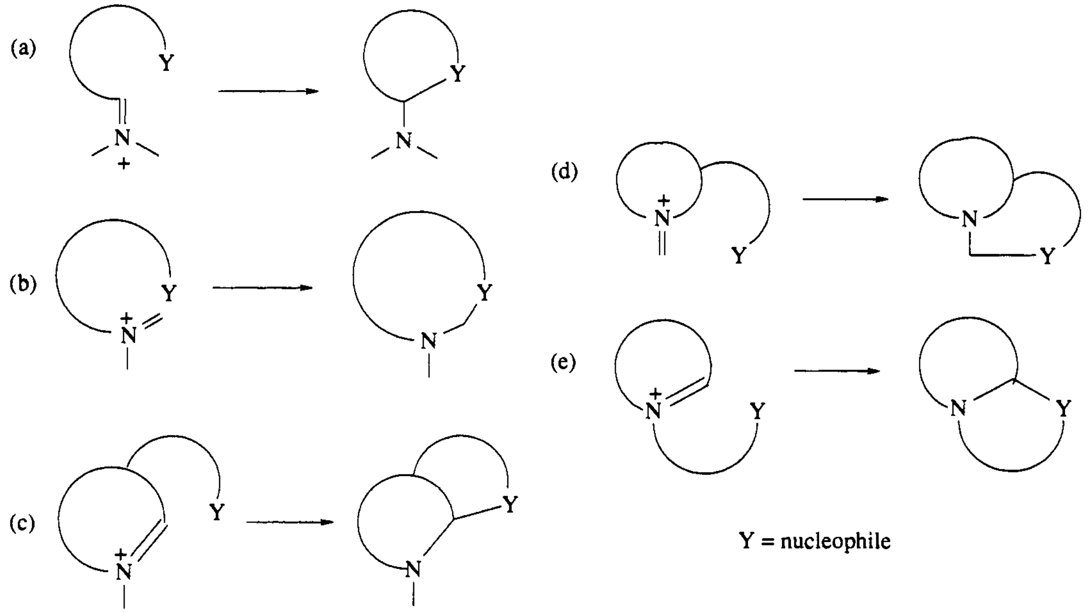

Y = nucleophile

**Scheme 1**

While these various intramolecular cyclization modes make accessible a myriad of azacycles, the practitioner is faced with the delicate art of orchestrating an efficient cyclization. Cyclization conditions must be such that the reactivity of the nucleophile is preserved, while unleashing intramolecularly the electrophilicity of an iminium ion. A listing of the most important routes to iminium ions is found in Scheme 2.[4] It is important to note that many of the methods for iminium ion generation are not conducive to the preservation of certain nucleophiles. The judicious choice of reaction conditions is the key to an effective intramolecular Mannich or Mannich-related reaction.

Since the conjugate base of an iminium ion (*i.e.* an enamine, see transformation c of Scheme 2) is a moderately strong base, iminium ions can be generated in stoichiometric quantities under essentially neutral conditions.[5] In contrast, *N*-acyliminium ions are accessible in stoichiometric quantities only under acidic conditions, since their conjugate bases (enamides) are only weakly basic. Thus, although *N*-acyliminium ions are more reactive cyclization initiators than iminium ions, and consequently react with a broader range of nucleophiles, azacycle synthesis strategies that employ simple iminium ions as the electrophilic components have more flexibility with regard to reaction medium.

Numerous studies over the past 30 years have highlighted the role that stereoelectronic effects can play in determining the success and stereochemical outcome of nucleophilic additions to iminium ions.[6] An antiperiplanar orientation of the forming nonbonded electron pair on nitrogen and the entering nucleophile is typically favored as illustrated in equation (1). Cyclization pathways that allow a nucleophile trajectory of this type and lead, upon rehybridization of the iminium ion carbon and nitrogen atoms, to an energetically nontaxing conformation of the cyclic product are highly favored. Numerous examples to

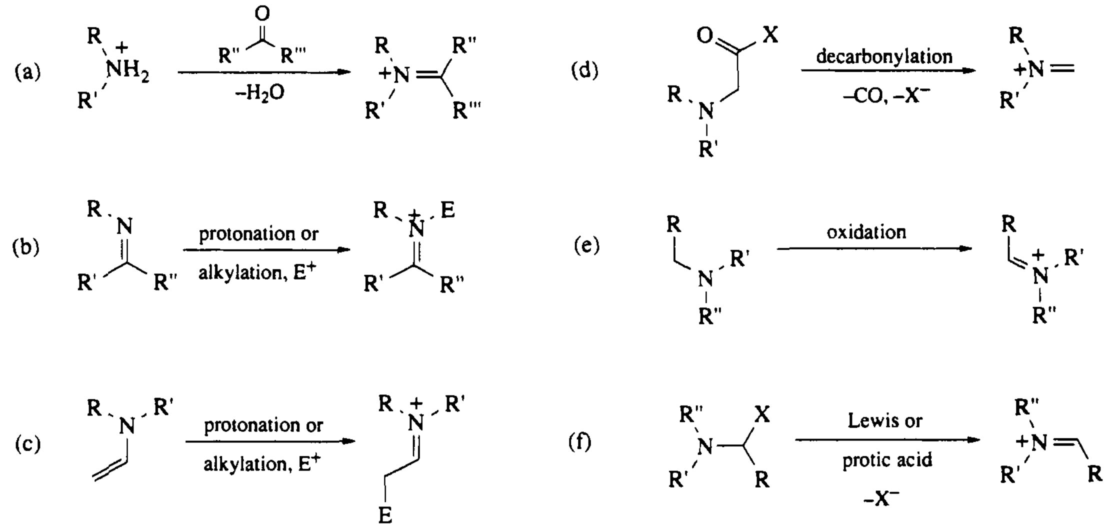
(a)
R
NH2
R'
O
R''
R'''
-H2O
R
R''
+N
R'
R'''
(b)
R
N
R'
R''
protonation or
alkylation, E+
R
E
N
R'
R''
(c)
R
N
R'
protonation or
alkylation, E+
R
+
N
R'
E
(d)
O
X
R
N
R'
decarbonylation
-CO, -X-
R
+N=
R'
(e)
R
N
R'
R''
oxidation
R
+
N
R'
R''
(f)
R''
X
N
R'
R
Lewis or
protic acid
-X-
R''
+N
R'
R

**Scheme 2**

support this conclusion are found in Section 4.4.2 of this chapter. A corollary of the *anti* preference depicted in equation (1) is that iminium ion cyclizations of modes (d) and (e) (Scheme 1) occur preferentially to afford initially only a single conformer of the azacyclic product.[7] This feature is illustrated in Scheme 3 for the specific case of cyclizations that form quinolizidines. Only the *cis*-quinolizidine conformer (**1**) has the favored antiperiplanar orientation of the nonbonded electron pair and the entering nucleophile. Thus, even though the *trans*-quinolizidine (**2**) or alternate *cis*-quinolizidine conformer (**3**) may be more stable, Mannich cyclization is expected preferentially to form (**1**) initially.

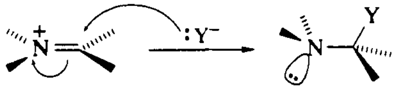

(1)

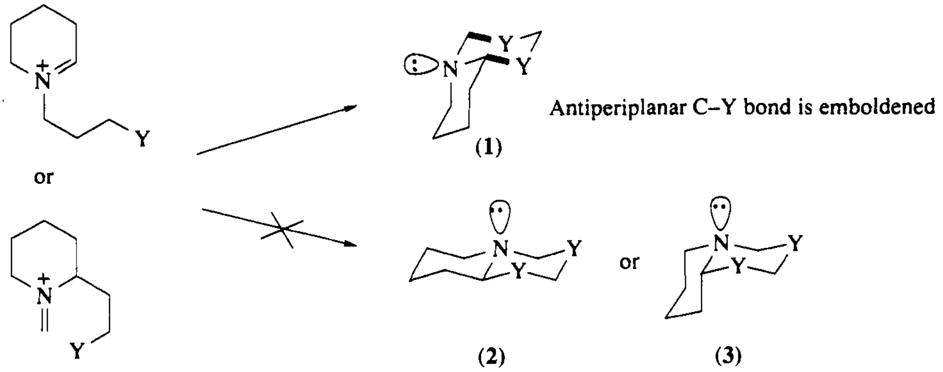
+
N
Y
or
+
N
Y
N
Y
Y
(1)
Antiperiplanar C–Y bond is emboldened
N
Y
Y
or
N
Y
Y
(2)
(3)

**Scheme 3**

## 4.4.2 CYCLIZATION WITH π-NUCLEOPHILES

Carbon–carbon bond formation results from the electronic quenching of electrophilic iminium ions. This chapter will deal with cases where the nucleophilic electrons are supplied intramolecularly by a tethered $sp^2$- or $sp$-hybridized carbon center. The overall result of such a process is to transfer the electron-deficient center from a position α to nitrogen to another center in the molecule. The resulting carbocations funnel into many of the classical manifolds that eventuate molecular electronic neutralization, *e.g.* carbenium ion additions, eliminations and rearrangements.

The following subsections are organized according to the nature of the π-nucleophile. Most classes of π-nucleophiles participate in iminium ion initiated cyclizations. The classes specifically covered in this chapter are: enols, enol ethers, arenes, alkenes, alkynes and organosilanes (vinyl, allyl and benzyl). Attention will be paid to the size of the resulting azacycle and any accompanying diastereoselection. Additional notice will be given to the method of iminium ion generation and its compatibility with each class of π-nucleophile.

### 4.4.2.1 Carbonyl Compounds

The classical Mannich reaction, the condensation of an iminium ion and an enol, remains a powerful method for the chemical synthesis of naturally occurring alkaloids and related nitrogenous materials. Intramolecular condensations are frequently used to construct azapolycyclic ring systems. A recent example of using an intramolecular Mannich cyclization for constructing a linearly fused azacycle is provided in Scheme 4.[8] Imine (4) was secured by a novel [2 + 2] cyclization/retro-Mannich sequence. Subsequent iminium ion generation through alkylation of imine (4) with a Meerwein salt followed by treatment with 4-(dimethylamino)pyridine in refluxing acetonitrile afforded (±)-mesembrine in 84% yield. Note the exclusive formation of the kinetically favored *cis* stereochemistry.

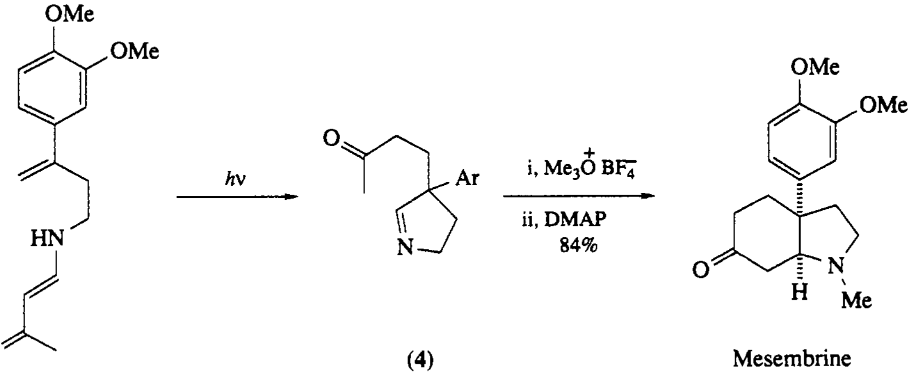

Scheme 4

A variety of quinolizidines and indolizidines may be accessed in good yields by the facile two-step process shown in Scheme 5.[9] Although not noted in this publication, the distribution of diastereomers (where possible) most likely reflects the relative energies of the diastereomeric transition state conformations depicted in Scheme 6. The transition state conformation that orients the larger substituent (R or R′) in the less sterically encumbered equatorial position gives rise to the major diastereomer in all of the per-

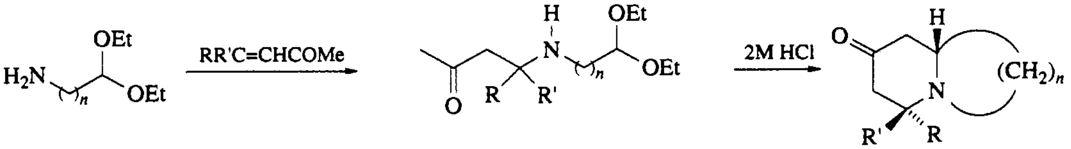

| *n* | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 |
|---|---|---|---|---|---|---|---|---|---|
| *R* | H | Me | H | Me | Pr$^i$ | H | H | Me | H |
| *R′* | H | H | Me | Me | H | Pr$^i$ | H | H | Me |
| *Yield (%)* | 55 | 60 | 15 | 60 | 45 | 20 | 50 | 55 | 20 |

Scheme 5

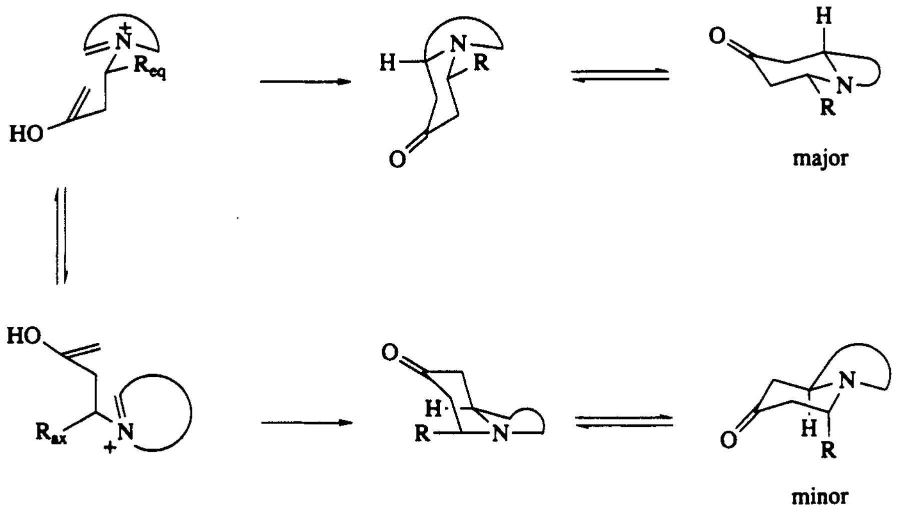
HO
$R_{eq}$
H
R
O
H
N
R
major
HO
$R_{ax}$
N
O
H·
R
N
O
H
R
minor

Scheme 6

tinent trials. Interestingly, although both *trans*-4-phenyl-3-buten-2-one and 2-cyclohexen-1-one formed the initial Michael adducts, these adducts failed to cyclize upon acidolysis. This result was attributed to retro-Michael reactions in these cases.

The reaction of endocyclic enamines with α,β-unsaturated ketones to afford *cis*-fused hydroindolones or hydroquinolones constitutes a complementary and highly useful annulation sequence developed extensively by Stevens and coworkers, see the reaction of (**5**) to give (**6**) in Scheme 7.[10] The importance of stereoelectronic effects is highlighted in the reaction of (**7**) with methyl vinyl ketone, which provided only the alkylated product (**8**) and none of the expected *cis*-hydroindolone (**9**).[11] The failure of intermediate (**8**) to cyclize in this case was attributed to nonbonded interactions between the aryl group and the side chain. This destabilizing allylic ($A^{1,2}$) interaction[12] disfavors formation of conformer (**10**), the intermediate required for antiperiplanar addition of the enol nucleophile (Scheme 8). Cyclization *via* the alternate conformation would require a double boat-like transition state.

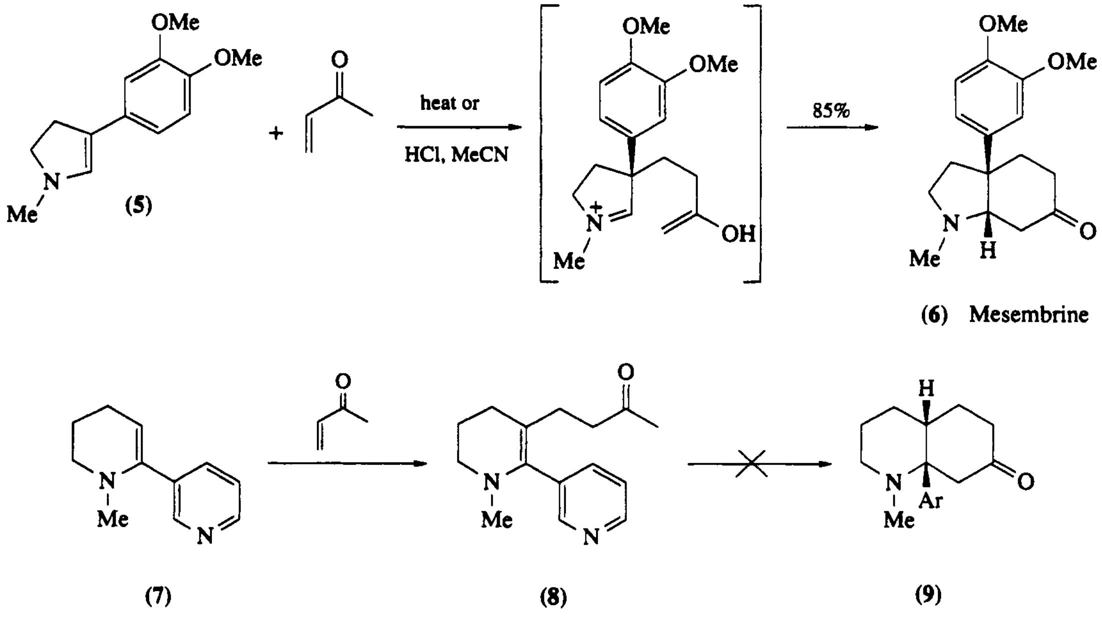
OMe
OMe
N
Me
(5)
+
O
heat or
HCl, MeCN
OMe
OMe
N
Me
OH
85%
OMe
OMe
N
Me
H
O
(6) Mesembrine
N
Me
N
(7)
O
O
N
Me
N
(8)
H
N
Me
Ar
O
(9)

Scheme 7

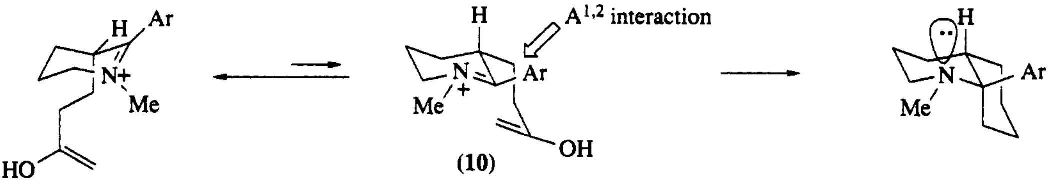

**Scheme 8**

The generation of bridged systems by intramolecular Mannich reactions has served as the cornerstone of several alkaloid constructs.[13–15] An excellent example is Rapoport and coworkers' synthesis of the neuromuscular toxin anatoxin a, a 9-azabicyclo[4.2.1]nonane. Initially, this group developed a high-yielding regiospecific route to iminium salts from α-tertiary amino acids by way of thermal decarbonylation of the corresponding acid chlorides.[16] In this way, iminium salt (**11**) was generated, then cyclized in 47% yield to (**12**) in refluxing acidified methanol (Scheme 9). The moderate yield is thought to result from the potentially reversible Mannich cyclization being followed by a nonreversible polymerization of iminium ion (**11**). A subsequent report details enantioselective syntheses of (+)- and (–)-anatoxin a using D- and L-glutamic acid, respectively, to generate the requisite optically active proline derivatives.[15]

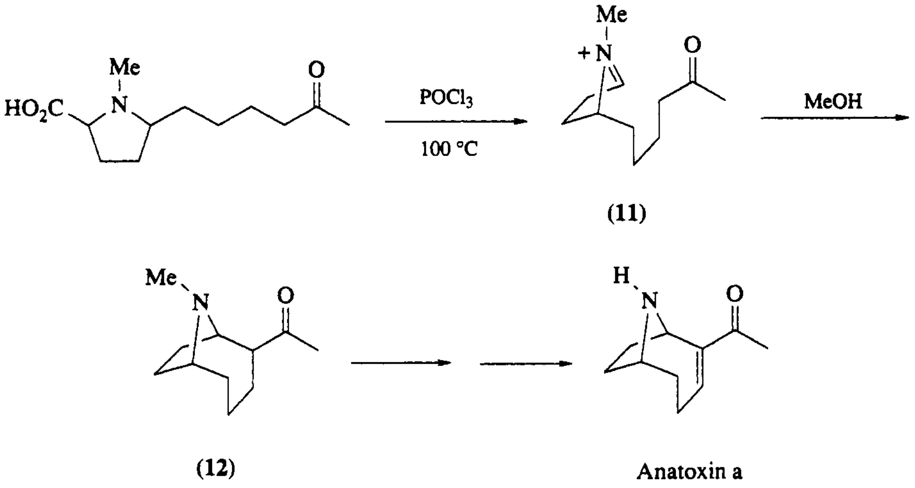

**Scheme 9**

In Heathcock and coworkers' synthesis of the *Lycopodium* alkaloid (±)-lycodoline an interesting solution to the problem of inducing Mannich cyclization in acid-sensitive compounds was found.[17] Treatment of imine (**13**) with 3 M methanolic hydrochloric acid provided complex mixtures, while heating the preformed iminium bromide in refluxing toluene occasioned no cyclization (equation 2). However, when imine (**13**) is dissolved in a 5:1 mixture of toluene and 3-bromo-1-propanol and the resulting solution refluxed for 24 h, the crystalline ammonium salt of (**14**) precipitates from the solution. The authors suggest that formation of (**14**) may involve slow generation of hydrogen bromide by base-catalyzed polymeriza-

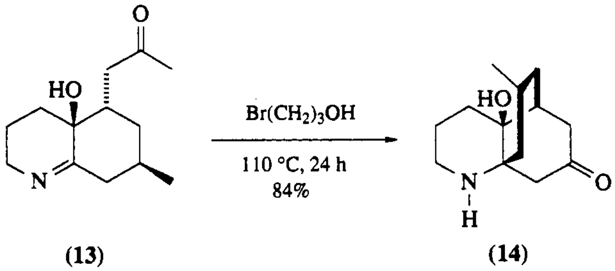

(2)

tion of the bromo alcohol. Under these low acid concentrations, enolization is thought to occur before iminium ion formation, thus obviating formation of the energetically unfavorable dication intermediate which would intervene under more acidic conditions.

Although careful consideration of the stereoelectronics of an iminium ion cyclization (antiperiplanar orientation of the nucleophile and developing nonbonded electron pair) may portend a successful ring closure, a synperiplanar addition is suggested as the key step of Stevens and Pruitt's synthesis of the *Protoberberine* alkaloid (±)-karachine.[18] Treatment of berberine with the silyloxydiene (**15**) gave a 66% yield (based on recovered berberine) of racemic karachine. Stevens proffers the pathway illustrated in Scheme 10 as a potential reaction course. The boat conformation that the tetrahydropyridinium salt is required to adopt in order to allow synperiplanar closure of zwitterion (**16**) is enforced by the geometric constraints of the bicyclooctane framework.

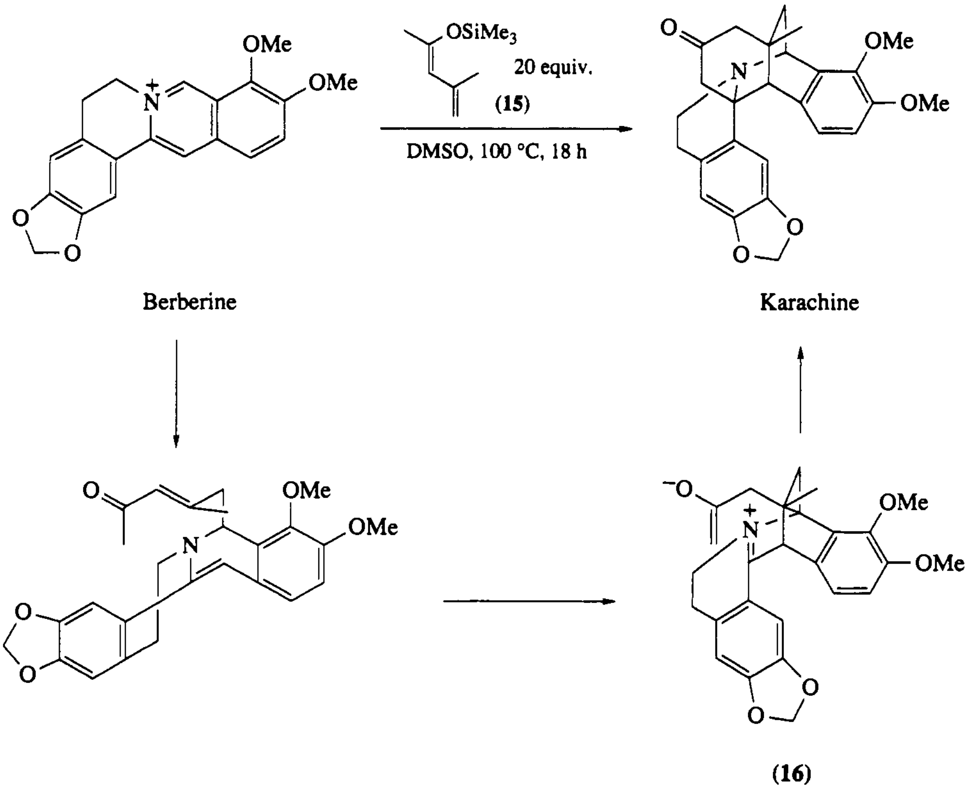

**Scheme 10**

### 4.4.2.2 Acetals and Enol Ethers

Mannich cyclizations are also successful when the carbonyl participant is masked as an acetal or enol ether. Considering the acetal, if the cyclization is conducted in aqueous acid, there is a good possibility that the cyclization terminator is actually the enol of the parent carbonyl (*i.e.* a classic Mannich cyclization). Under anhydrous acid conditions the reactive terminator is most likely the enol ether.

The successful use of acetal-protected carbonyl groups as iminium ion terminators for the construction of alkaloids is typified by Heathcock and coworkers' syntheses of *Lycopodium* alkaloids; to wit, lycopodine and lycodine (Figure 2).[17] A model cyclization that constructs the A-, B- and C-ring nuclei of the *Lycopodium* alkaloids is shown in equation (3). Treatment of diacetal (**17**) (a 1:1 diastereomeric mixture at C-2) with 1.5 equiv. of 3 M hydrochloric acid in methanol at room temperature for 2 d gave a single tricycle (**18**) in 66% yield. The authors advance that only one of the diastereomeric iminium ions will cyclize; however, enolization allows equilibration of these intermediates (Scheme 11). Thus, while diastereomer (**19**) can readily cyclize, (**20**) has no low energy cyclization pathway available, and must epimerize prior to cyclization. Corroborative support for this argument is found in the fact that the separated diastereomers of a related system cyclize to the same extent.[17]

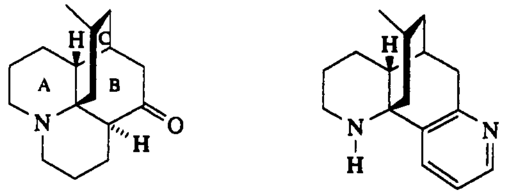
H
A
B
C
N
O
H
H
N
H
N

Lycopodine    Lycodine

**Figure 2**

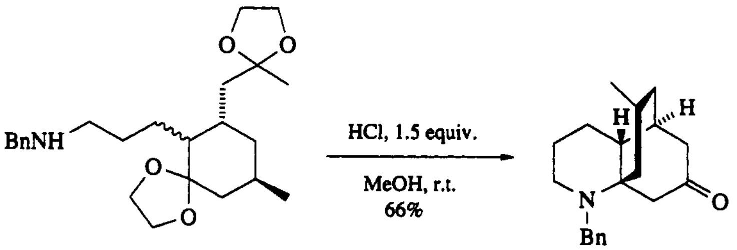
BnNH
O
O
O
O
HCl, 1.5 equiv.
MeOH, r.t.
66%
H
H
N
Bn
O

(17)    (18)

(3)

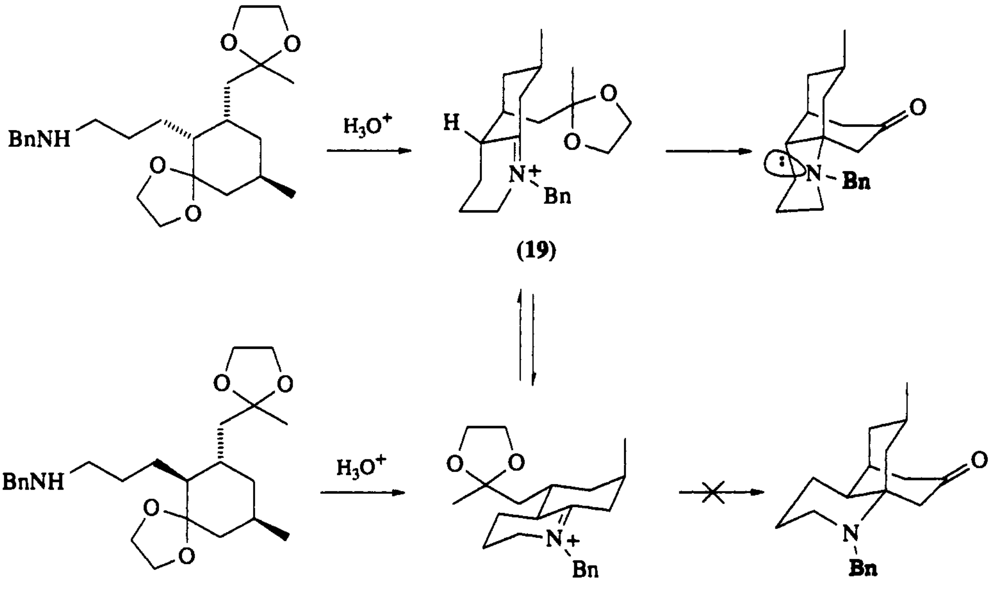
BnNH
O
O
O
O
H$_3$O$^+$
H
N+
Bn
O
O
O
N-Bn
BnNH
O
O
O
O
H$_3$O$^+$
O
O
N+
Bn
O
N
Bn

(19)

(20)

**Scheme 11**

Bridged bicyclic systems can be constructed with equal facility using acetal terminators under hydrolytic conditions. Husson and coworkers' construction of the lady bug alkaloid adaline is exemplary.[19] Aminonitrile (**21**) served as the iminium ion precursor. Refluxing a solution of (**21**) in methanol containing 10% hydrochloric acid for 48 h afforded the bicyclic adaline precursor (**22**) in 90% yield.

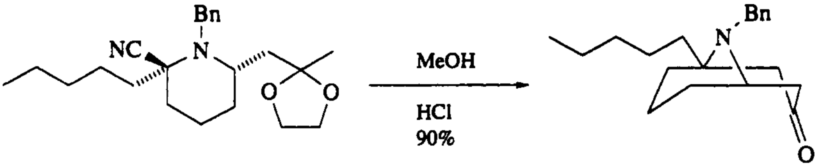
Bn
NC
N
O
O
MeOH
HCl
90%
Bn
N
O

(21)    (22)

As mentioned previously, there are many Mannich-type cyclizations of acetals that undoubtedly occur *via* enol ether intermediates and afford β-amino acetal products. A prototypical example is presented in Scheme 12. In this sequence, due to Wenkert, the iminium ion precursor is formed by semihydrogenation of a nicotinic ester salt.[20]

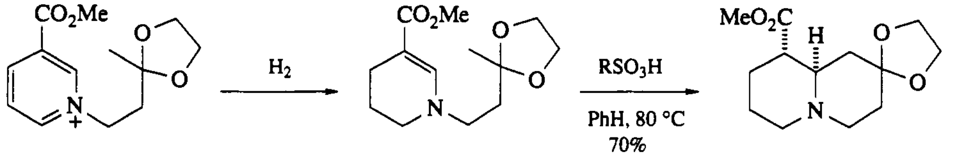

**Scheme 12**

A related example involving a more complex substrate is found in Rapoport and Luly's formal synthesis of the 7-methoxymitosene (**24**).[21] Again, decarbonylation of an α-tertiary amino acid chloride is employed to generate the iminium ion. The indoline acetal (**23**) produced in this way is essentially one diastereomer; however, its stereochemistry was not established (Scheme 13).

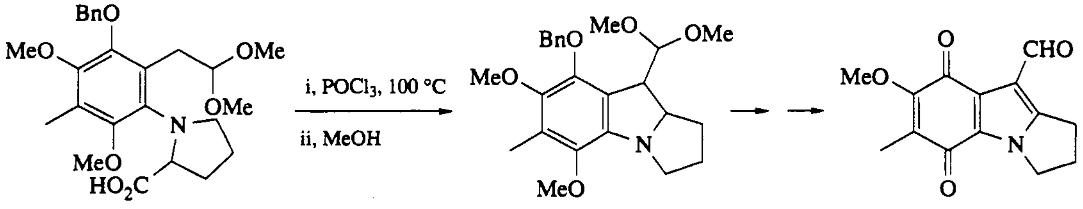

(**23**) (**24**)

**Scheme 13**

Although enol ethers have received moderate notice as nucleophiles to quench intramolecular iminium ions, silyl enol ethers have been given scant attention. The first report of a silyl enol ether participating in an intramolecular Mannich reaction is found in Oppolzer and coworkers' synthesis of (±)-vincamine (Scheme 14).[22] Dihydro-β-carboline (**25**) and silyl enol ether (**26**) were mixed in DMF, then warmed to 70 °C for 64 h in the presence of diisopropylethylamine to provide a 1:1 mixture of *cis* and *trans* tetracyclic aldehydes (**27**) in 74% yield.

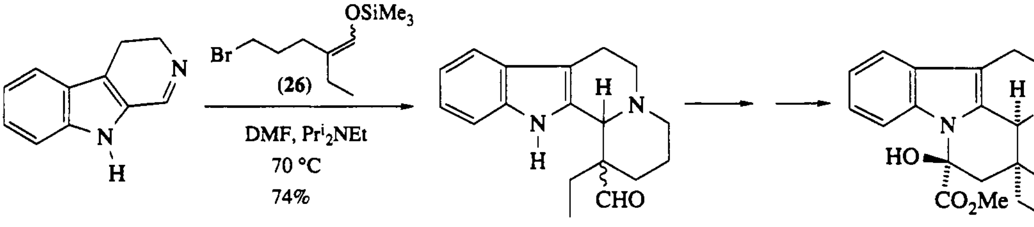

(**25**) (**27**) Vincamine

**Scheme 14**

An example that illustrates the advantages that an enol ether can offer *vis-à-vis* the parent carbonyl compound in iminium ion cyclization is found in Overman and Goldstein's construction of the allopumiliotoxin A alkaloid intermediate (**32**).[23] A variety of Mannich conditions failed to produce (**32**) from amino ketone (**28**), but yielded only cyclopentaoxazolidine (**29**). However, intramolecular Mannich cyclization was accomplished in 52% yield at low temperature by treatment of the bicyclic trimethylsilyl enol ether (**30**) with 1.1 equiv. of trimethylsilyl trifluoromethanesulfonate (Scheme 15). Remarkably, (**32**) produced in this manner was racemic, a result ascribed to facile [3,3] sigmatropic rearrangement of intermediate (**31**).

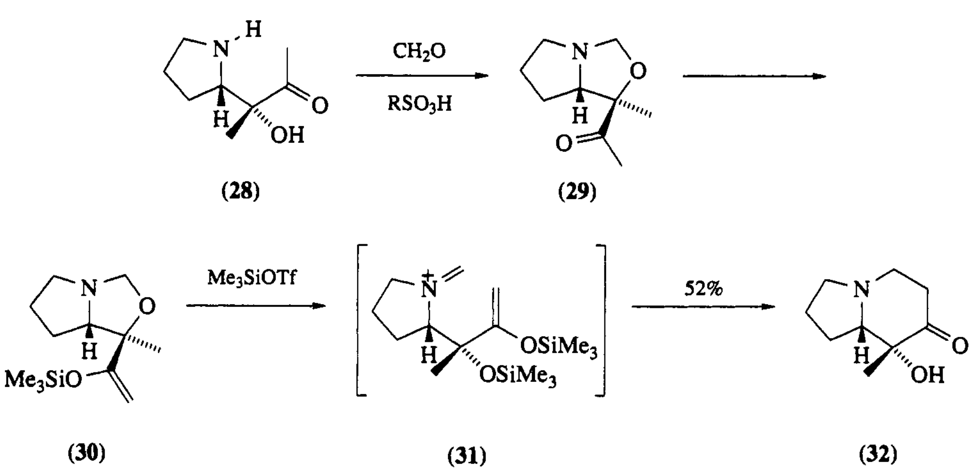
CH$_2$O
RSO$_3$H
Me$_3$SiOTf
52%
(28)
(29)
(30)
(31)
(32)

Scheme 15

### 4.4.2.3 Arenes

Since its discovery the Pictet–Spengler cyclization has formed the basis of numerous syntheses of alkaloids containing aromatic subunits. This high-yielding reaction involves, in its broadest sense, nucleophilic attack on an iminium ion by the π-electrons of a tethered aromatic moiety. In the classical reaction a substituted β-phenethylamine is condensed with an aldehyde under acidic conditions to produce a tetrahydroisoquinoline (Scheme 16).[24,25] A useful variant of the Pictet–Spengler reaction, which provides tetrahydro-β-carbolines and their derivatives,[26] involves the condensation of a tryptamine derivative and an aldehyde (Scheme 16). Whether nucleophilic attack on the resulting iminium ion occurs initially at the α- or β-indole carbon is a topic of current debate and, indeed, there is evidence to suggest that the mechanistic pathway could be substrate dependent.[27]

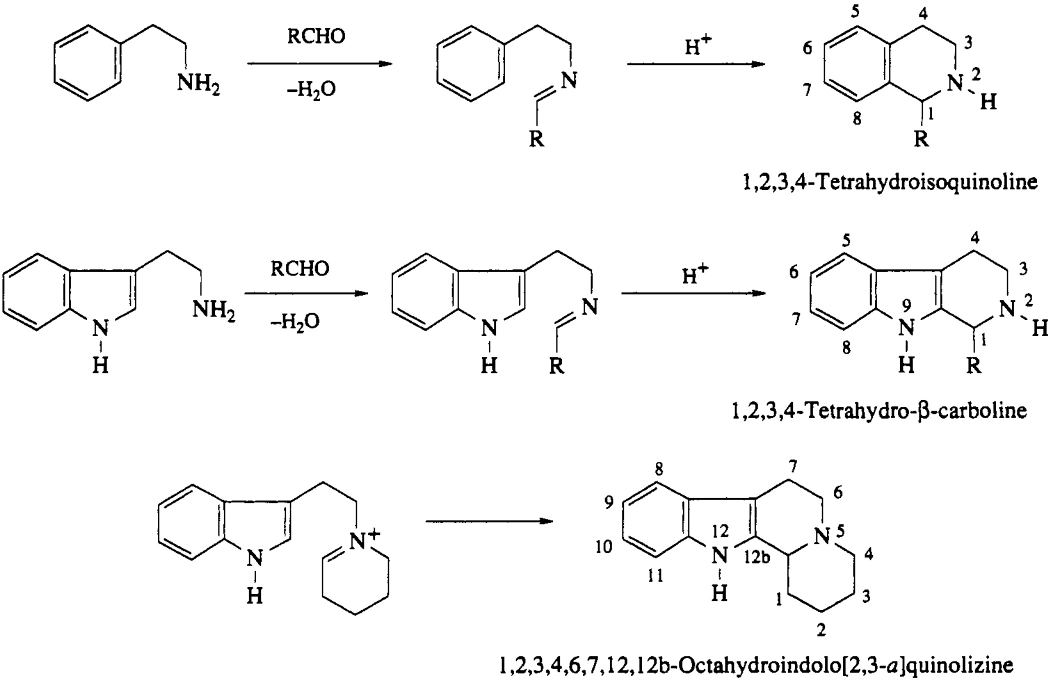
RCHO
-H$_2$O
H$^+$
1,2,3,4-Tetrahydroisoquinoline
RCHO
-H$_2$O
H$^+$
1,2,3,4-Tetrahydro-β-carboline
1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

Scheme 16

Several reviews affirm the invaluable role played by the Pictet–Spengler cyclization in the assembly of almost every class of aromatic alkaloids.[28–30] In this section, we focus on recent examples and pay particular attention to the diastereoselection associated with intramolecular Mannich closures conducted as an integral part of alkaloid syntheses.

### *4.4.2.3.1 1,2,3,4-Tetrahydro-β-carbolines*

A brief look at some of the newer methods for generating these ring systems shall serve as our starting point. Prolonged heating of tryptophan methyl ester and an aldehyde in benzene (with Dean–Stark removal of water) provides excellent yields of 1-alkyl-3-carbomethoxy-1,2,3,4-tetrahydro-β-carbolines (Scheme 17).[31] There is some evidence to suggest that benzoic acid formed by air oxidation of benzaldehyde catalyzes this reaction.[32] These reaction conditions are, however, mild enough to accommodate the cyclization of acid-labile substrates like glyoxal diethyl acetal. In all of the cases reported, these 'aprotic' conditions afforded an increase in yield of the cyclization product when compared to the more classical protic solvent/acid catalyst conditions.

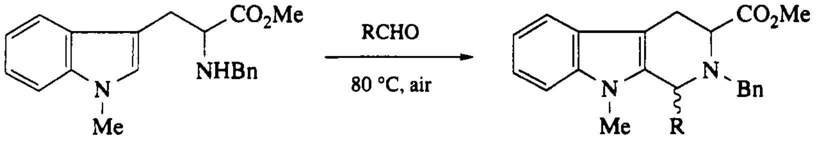

| *R* | *Yield (%) 'aprotic'* | *Yield (%) 'aqueous'* |
|---|---|---|
| $HC(OEt)_2$ | 90 | <20 |
| $CH_2CO_2Et$ | 75 | 59 |
| $CH_2COEt$ | 94 | 25 |

**Scheme 17**

Another newly introduced method generates the iminium ion intermediate by Michael addition of tryptamine to an activated alkyne in an acidic medium.[33] Yields of the resulting 1-alkyltetrahydro-β-carbolines range from good to excellent (Scheme 18).

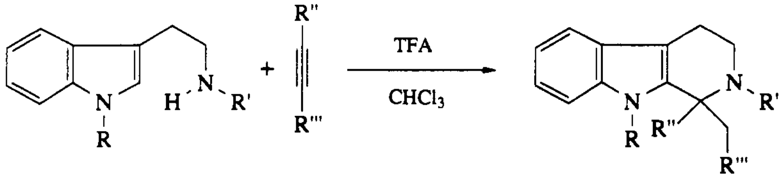

| *R* | *R'* | *R''* | *R'''* | *Yield (%)* |
|---|---|---|---|---|
| H | H | $CO_2Me$ | $CO_2Me$ | 83 |
| Me | Bn | $CO_2Me$ | $CO_2Me$ | 92 |
| H | Bn | H | $CO_2Me$ | 85 |
| H | Bn | H | COMe | 76 |

**Scheme 18**

The factors that control diastereoselection in the construction of 1,3-disubstituted tetrahydro-β-carbolines are not, as yet, well understood. With many aldehydes a slight preference for forming the *trans* diastereomer is observed.[34] This preference is somewhat greater when the indole nitrogen ($N_a$) of the tryptamine is alkylated. Pictet–Spengler cyclizations of $N_b$-benzyltryptophan methyl ester under Cook's 'aprotic' conditions are reported to provide nearly exclusively the *trans*-$N_b$-benzyl-3-methoxycarbonyl-1-substituted-1,2,3,4-tetrahydro-β-carbolines.[35]

In 1983 an approach for forming either enantiomer of a 1-alkyl-1,2,3,4-tetrahydro-β-carboline from L-(–)-tryptophan was published.[36] Specifically, tryptophan was converted into derivatives (**33**) and (**35**) (Scheme 19). When the secondary amine (**33**) was condensed/cyclized with methyl 4-formyl-2,2-

bis(phenylthio)butyrate, ester (**34**) was generated in 75% yield as the only detectable diastereomer ($^{13}C$ NMR). Perhaps more surprising, when the primary amine (**35**) was condensed/cyclized with the same aldehyde, a 70% yield of the *cis* diastereomer (**36**) was obtained (purportedly as the only detectable epimer). The authors also observed that cyclizations of tryptophan methyl esters were significantly less stereoselective than those of tryptophanamides, a trend corroborated by another investigation.[7] There are means which remove the diastereo-directing C-3 acyl functionality, thus providing for selective synthesis of either enantiomer of 1-alkyltetrahydro-β-carbolines.[37–40]

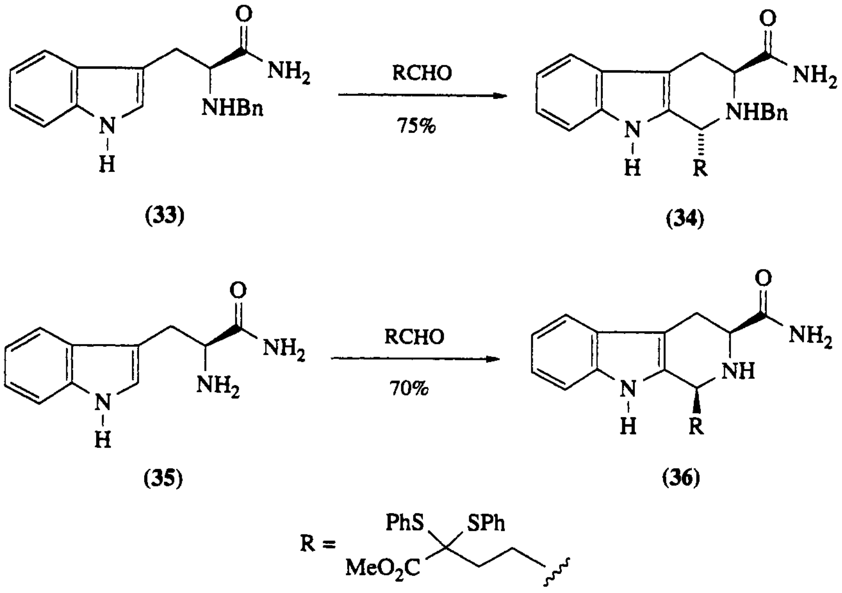

**Scheme 19**

### *4.4.2.3.2 Octahydroindolo[2,3-a]quinolizines*

Numerous classes of biologically active alkaloids contain an indoloquinolizine (sub)nucleus (Scheme 16). The first consideration in the construction of an indoloquinolizine *via* the cyclization of a 1-[2-(3-indolyl)ethyl]-$\Delta^1$-tetrahydropyridinium ion is the issue of iminium ion generation. The oxidation of tertiary amines (Polonovsky–Potier; $Hg(OAc)_2$; Pt, $O_2$) has been widely employed for this purpose; however, mixtures of regioisomeric iminium ions are typically produced.[41] Nevertheless, a number of extant methodologies serve well for regioselective iminium ion generation (Scheme 2).

The construction of indoloquinolizines through Pictet–Spengler cyclization produces a new stereogenic center. Thus, pre-existing stereocenters potentiate diastereomeric cyclization products. For example, cyclization of tryptophan derivative (**37**) affords a 4:1 mixture of stereoisomeric indoloquinolizines in 83% yield.[42] In concurrence with results obtained from tetrahydro-β-carboline studies,[35] the major diastereomer (**38**) possesses a *trans* stereorelationship of substituents on the newly formed ring. Numerous indoloquinolizidine alkaloids contain asymmetric centers in the D-ring and hence a considerable body of information exists concerning diastereoselection in Pictet–Spengler cyclizations of substituted $\Delta^1$-tetrahydropyridinium ions. A few illustrative examples are summarized in Scheme 20.[42–44] The predominant formation of indoloquinolizidines (**40**) and (**41**) is readily rationalized by the stereoelectronic considerations advanced earlier. Thus, for the conversion of (**39**) to (**40**), stereoelectronically favored axial approach of the indole nucleophile to the $\Delta^1$-tetrahydropyridinium ion conformer having the malonic ester side chain in an equatorial orientation would lead to (**40**; equation 4).

When the pre-existing stereocenter is adjacent to the iminium ion carbon atom, Pictet–Spengler cyclization most commonly occurs from the face opposite the substituent, as in the conversion of (**42**) to (**43**) (Scheme 20).[42] A related example is the cyclization of the disubstituted $\Delta^2$-tetrahydropyridine (**44**), which was treated with hydrogen chloride gas in anhydrous methanol to produce three of the four possible diastereomeric products in the indicated abundances (Scheme 21).[45] The relative stereochemistry at C-1 is set by protonation of the enamine, while that at C-12b is determined in the cyclization step. The authors argue that protonation is kinetically controlled and occurs preferentially from the

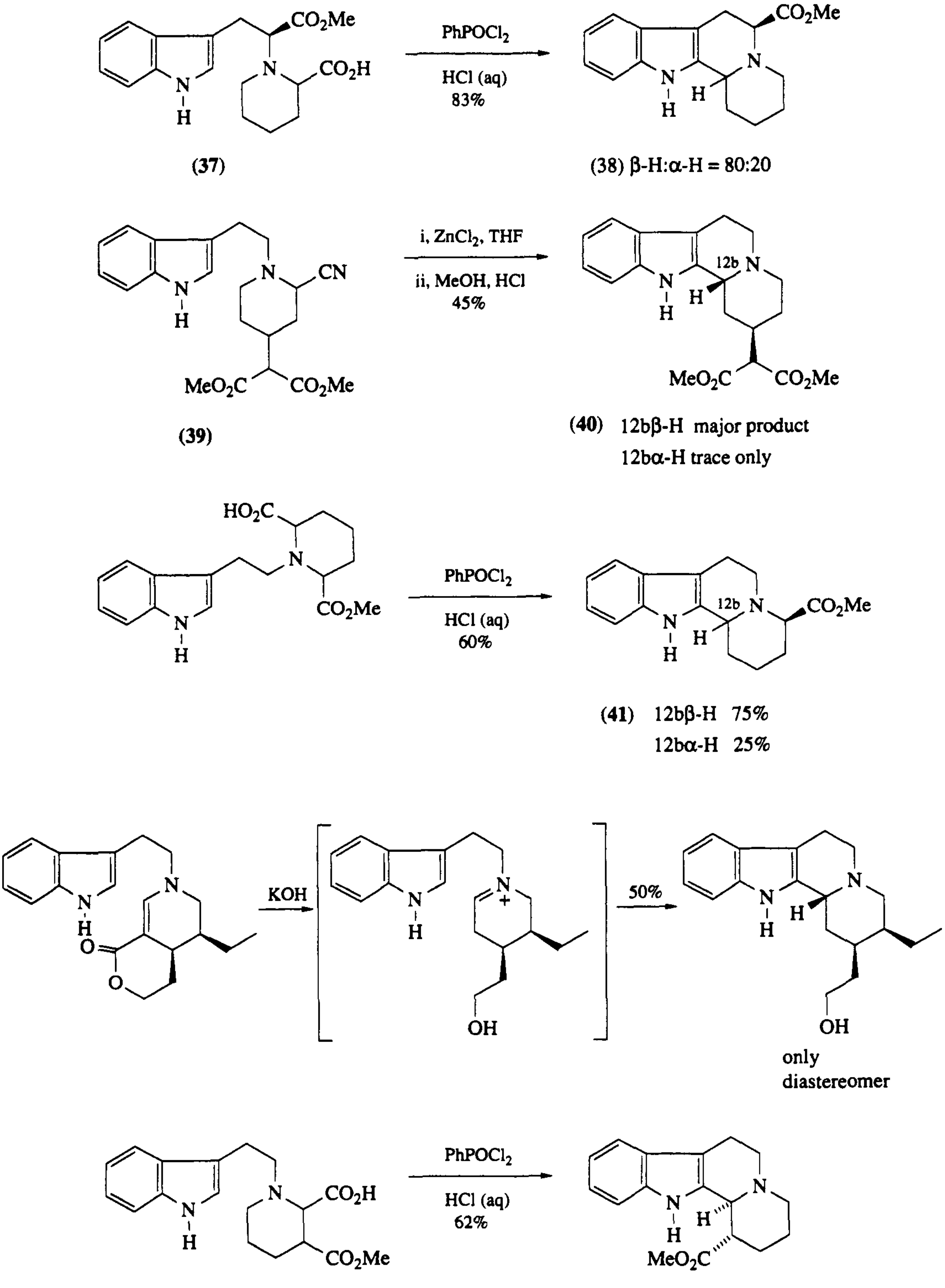

$CO_2Me$
N
$CO_2H$
N
H
PhPOCl$_2$
HCl (aq)
83%
$CO_2Me$
N
N
H
H
$CN$
$MeO_2C$
$CO_2Me$
i, ZnCl$_2$, THF
ii, MeOH, HCl
45%
12b
KOH
50%
OH
O
62%
60%
$HO_2C$
N
+

(37)

(38) β-H:α-H = 80:20

(39)

(40) 12bβ-H major product
12bα-H trace only

(41) 12bβ-H 75%
12bα-H 25%

only
diastereomer

(42)

(43) only diastereomer detected

Scheme 20

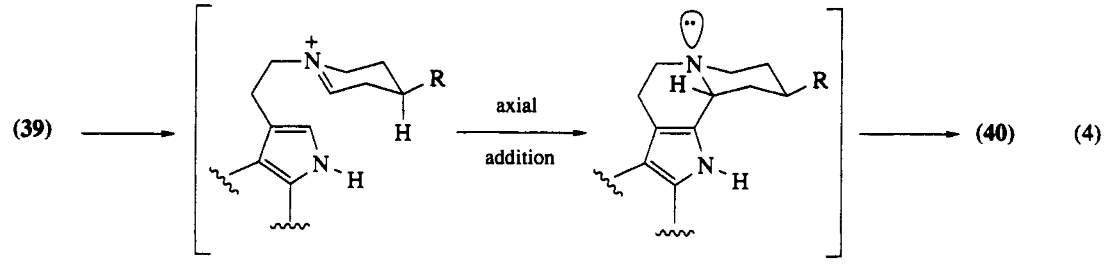

(4)

enamine face opposite to the C-2 malonyl substituent. Once set, the C-1 ethyl group relegates nucleophilic approach of the indole nucleus to a *trans* trajectory. This scenario nicely explains the C-12b/C-1/C-2 relative stereochemistry observed in the major product (**45**).

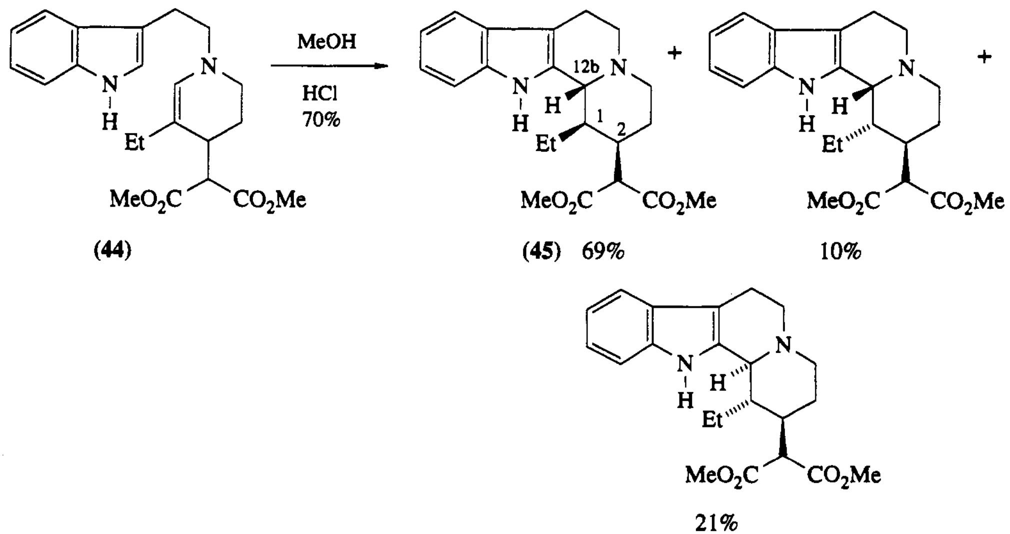

**Scheme 21**

A stereorandom cyclization is reported to result from the reaction of tosyl aldehyde (**46**) with tryptamine.[46] This outcome would be expected if Pictet–Spengler cyclization occurred prior to displacement of the tosylate by the N$_b$ nitrogen.

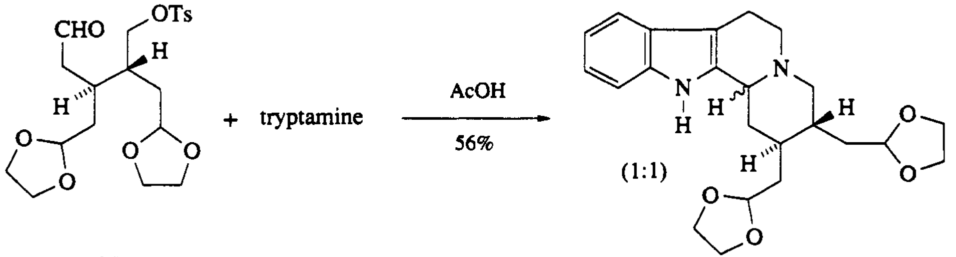

(**46**)

There is an increasing body of evidence which suggests that discrete iminium ions may not intervene in all Pictet–Spengler cyclizations. In particular, the exact nature of the reaction environment can markedly affect the outcome of Pictet–Spengler cyclizations. As an example, treating an anhydrous methanolic solution of dihydropyridine (**47**) with hydrogen chloride gas affords a 97% yield of indoloquinolizine (**48**) as a single diastereomer.[47] Note the exclusive formation of the *cis* C-12b/C-1 stereoisomer; none of the expected *trans* diastereomer was detected (equation 5). The authors explain these results in terms of an exocyclic cyclization, involving tetrahedral intermediate (**50**), in which a methoxy group (from the solvent) is oriented *trans* to the ethyl side chain. A cyclization with $S_N2$ character would then lead to the observed C-12b/C-1 *cis* relative stereochemistry. The low stability of the intermediate iminium ion (**49**), by virtue of its vinylogous carbamate disposition, may contribute to these anomalous results (Scheme 22).

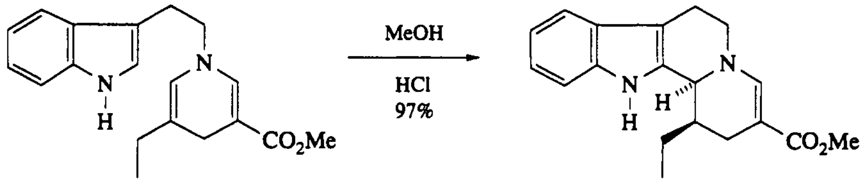

(5)

**(47)** **(48)**

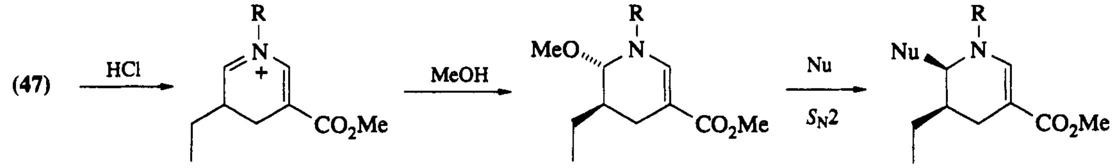

**(49)** **(50)**

**Scheme 22**

In some cases the method of iminium ion generation may have a profound influence on the diastereoselectivity of the resulting cyclization. Cyclization of amine (**51**) by the Polonovsky–Potier method affords the expected C-12b/C-2 *trans*-indoloquinolizine (**52**).[48] In contrast, mercury(II) acetate oxidation of the same amine affords a 60:40 ratio of the *trans* (**52**) and *cis* (**53**) products respectively in 50% yield (Scheme 23). The authors suggest that this discrepancy may be reflective of the relative nucleophilicity of the two counterions. In the Polonovsky–Potier cyclization the relatively non-nucleophilic trifluoroacetate counterion allows the intermediacy of a discrete iminium ion and hence diastereoselection is governed by stereoelectronic determinants. However, mercury(II) acetate oxidation generates a more nucleophilic acetate counterion, which may add to the iminium ion, producing an α-acetoxyamine in equilibrium with the iminium ion. Cyclization of these different intermediate species may explain the formation of the C-12b/C-2 diastereomers. This variance in diastereoselection that is dependent upon the method of amine oxidation has been observed in other systems as well.[49,50]

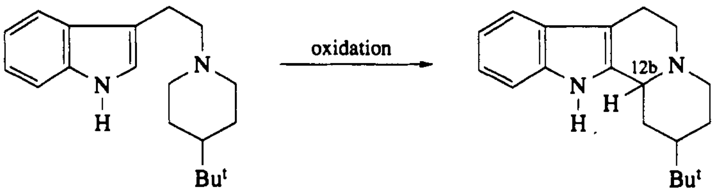

**(51)**

12bβ-H **(52)**

12bα-H **(53)**

| *Oxidant* | *Yield* |
|---|---|
| i, $H_2O_2$; ii, TFAA | 30% (**52**) |
| $Hg(OAc)_2$ | 50% 60:40 (**52**):(**53**) |

**Scheme 23**

### *4.4.2.3.3 Various indole alkaloids*

For years, iminium ion–arene cyclizations have punctuated the construction of members of many classes of indole alkaloids.[51] Cyclizations in these more complex cases often proceed with excellent efficiency and with better levels of stereocontrol than similar conversions in simpler systems, presumably reflecting restricted conformational possibilities in the former cases. To illustrate, lithium aluminum hydride reduction of amide (**54**) provides an intermediate hemiaminal, which upon acid treatment dehydrates to the iminium ion and cyclizes to afford the *Aspidosperma* ring system (equation 6).[52]

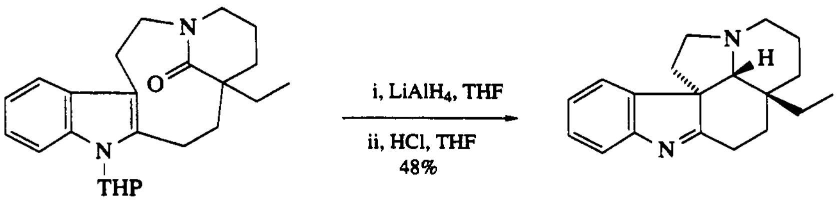
N
O
N
THP
i, LiAlH$_4$, THF
ii, HCl, THF
48%
N
H
N

(**54**)

(6)

As a last example, the concluding stage of Stork and coworkers' recent total synthesis of (±)-reserpine is summarized in Scheme 24.[49] It was expected that the reserpine stereochemistry at C-3 would evolve directly from engagement of the methoxyindole nucleophile from the convex face of the *cis*-hydroisoquinolinium ion intermediate (**56**). Such a tactic would obviate having to invert this stereocenter as was re quired when the order of introducing the hydrogen and indole substituents at C-3 was reversed, as in Woodward's original total synthesis.[53] In accordance with this expectation, treatment of (**55**) with AgBF$_4$ in acetonitrile led stereoselectively to (**57**), a pentacycle readily converted to (±)-reserpine. In striking contrast, these workers report that direct cyclization of (**55**) in refluxing acetonitrile affords the epimeric product (**58**). This latter, unexpected stereochemical outcome is rationalized as resulting from backside attack of the indole moiety on an iminium cation–cyanide anion ion pair intermediate.

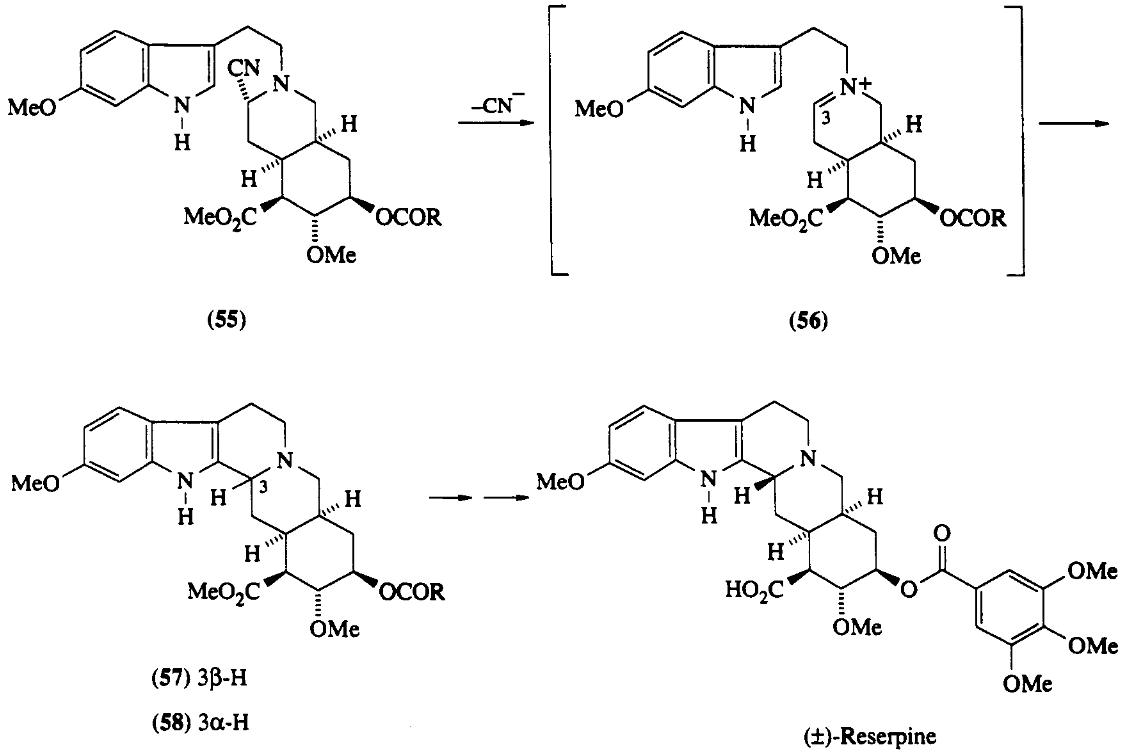
MeO
N
H
CN
N
H
H
MeO$_2$C
OCOR
OMe
(55)
$-CN^-$
MeO
N
H
N+
3
H
H
MeO$_2$C
OCOR
OMe
(56)
MeO
N
H
H
3
N
H
H
MeO$_2$C
OCOR
OMe
(57) 3β-H
(58) 3α-H
MeO
N
H
H
N
H
H
HO$_2$C
O
O
OMe
OMe
OMe
OMe
(±)-Reserpine

Scheme 24

### 4.4.2.4 Alkenes

Most π-nucleophiles employed in iminium ion cyclizations have a predetermined postcyclization destiny. For example, aromatic terminators will rearomatize, organosilanes will eliminate silicon through anticipated pathways and acetals and enol ethers will produce carbonyl compounds. However, the cyclizations of simple alkenes have supplied products that are the formal results of eliminations, additions and Wagner–Meerwein rearrangements. Almost exclusively Mannich-type cyclizations of unsaturated amines have been employed to prepare piperidines.

#### *4.4.2.4.1 Monocyclizations*

Early examples, due to Grewe, dealt with the formation of hydroisoquinolines from the reaction of aldehydes with cyclohexenylethylamine and its derivatives.[54] The *cis* stereochemistry of the 10-hydroxydecahydroisoquinoline (**60**) produced from treatment of (**59**) with formaldehyde and formic acid demonstrates that the alkene participant undergoes *trans* addition.[55,56]

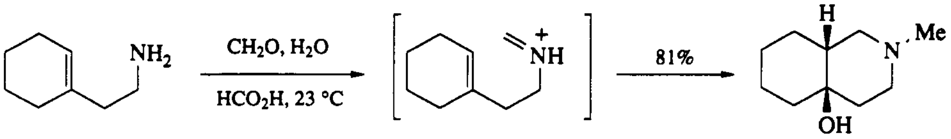
NH$_2$
CH$_2$O, H$_2$O
HCO$_2$H, 23 °C
NH
81%
H
N
Me
OH

(**59**) (**60**)

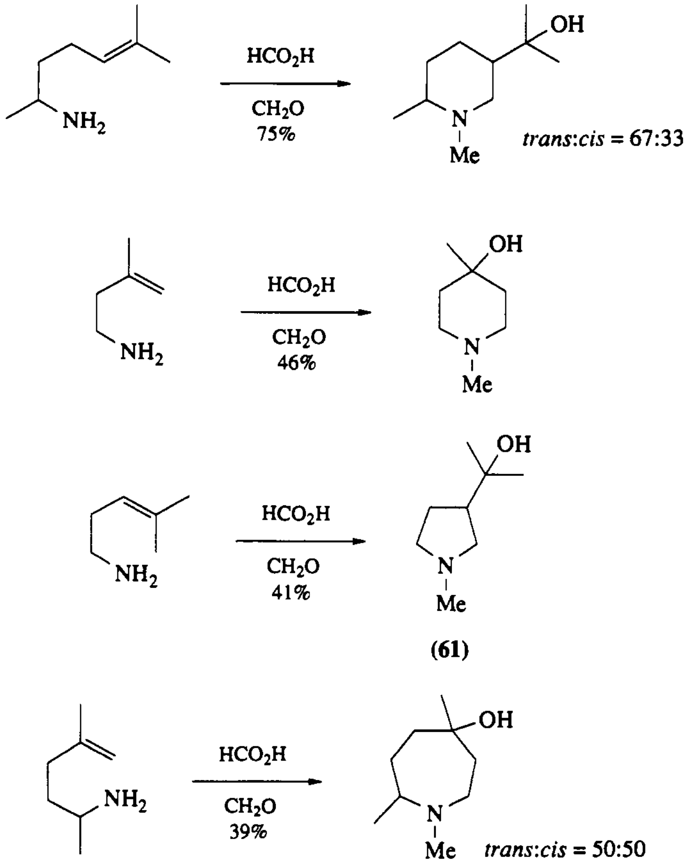
NH$_2$
HCO$_2$H
CH$_2$O
75%
OH
N
Me
*trans*:*cis* = 67:33
NH$_2$
HCO$_2$H
CH$_2$O
46%
OH
N
Me
NH$_2$
HCO$_2$H
CH$_2$O
41%
OH
N
Me
(**61**)
NH$_2$
HCO$_2$H
CH$_2$O
39%
OH
N
Me
*trans*:*cis* = 50:50

**Scheme 25**

Iminium ion–alkene cyclizations accomplished under standard Eschweiler–Clarke methylation conditions have been employed to prepare five-, six- and seven-membered azacycles (Scheme 25).[57,58] It is important to note that under identical conditions amines (**62**) and (**63**) did not cyclize but afforded the corresponding *N*,*N*-dimethylamines. With regard to the alkene participant these results are in full accord with Baldwin's rules for ring formation.[2] However, the formation of pyrrolidine (**61**) demonstrates that 5-*endo*-trig cyclizations[2] can take place with respect to the iminium ion π-participant. The observed regioselectivity and the failure of (**63**) to cyclize are in accord with obligatory formation of an intermediate with tertiary carbocation character.

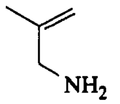

**(62)**

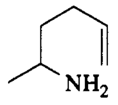

**(63)**

An iminium ion–alkene cyclization has been employed to assemble the phenylmorphan ring system (Scheme 26).[59] The conversion of enamine (**64**) to (**66**) was suggested to arise by 1,5-hydride migration of an initially formed bicyclic cation (**65**). Direct intramolecular ene cyclization of the iminium ion (**67**) produced by protonation of (**64**) provides an alternative rationale for the net *cis* addition to the terminal alkene that occurs in this transformation, and avoids postulating the intervention of a relatively unstable fully formed secondary carbocation.

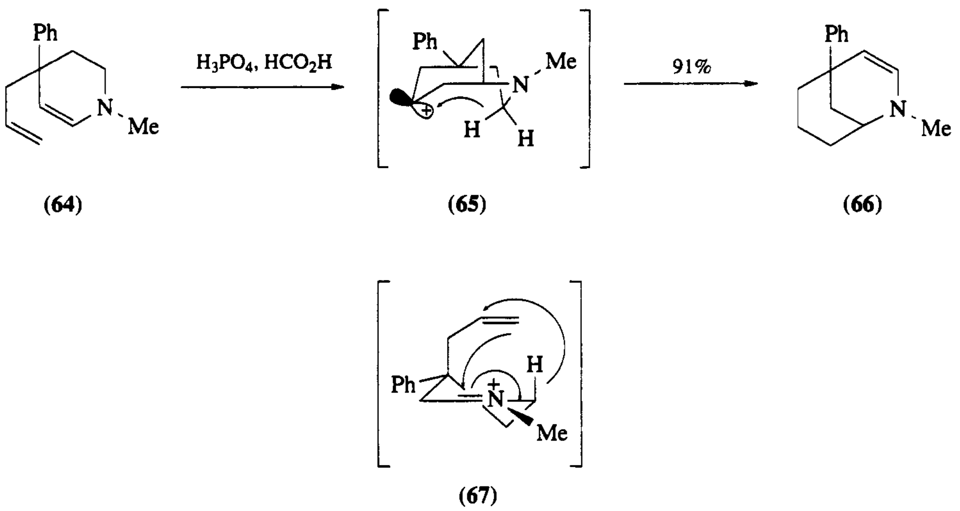

**Scheme 26**

A variety of polycyclic skeletons containing the azabicyclo[3.3.1]nonane ring system have been accessed by employing alkenic π-nucleophiles in iminium ion initiated cyclizations.[60–63] These reactions are conducted in relatively non-nucleophilic solvents and hence afford alkenic products in good yields (Scheme 27). A dramatic example is provided in Heathcock and coworkers' synthesis of (±)-methyl homosecodaphniphyllate (**69**).[63] The key cyclization reaction of dialdehyde (**68**) and ammonia forms four of the five rings of the *Daphniphyllum* alkaloid target in exceptional yield. The high yields and high regioselectivities for forming a single alkene product in cyclizations such as those illustrated in Schemes 27 and 28 have led some authors to suggest a pericyclic 'ene' mechanism for the cyclization step.[61,62] We note that the results of these cyclizations are explained equally well by stepwise cyclizations to form tertiary carbocation intermediates, followed by the tertiary amine thus produced—in the capacity of a general base—removing the most accessible hydrogen β to the carbocationic center.

On the other hand, the SnCl$_4$-promoted cyclization of imine (**70**) to provide the methylenecyclohexane (**71**) is well rationalized as proceeding in a concerted manner as illustrated in Scheme 29.[64] None of the thermodynamically more stable endocyclic double bond isomers were observed in the crude product—a result inconsistent with the formation of a fully developed tertiary carbocation intermediate. The alterna-

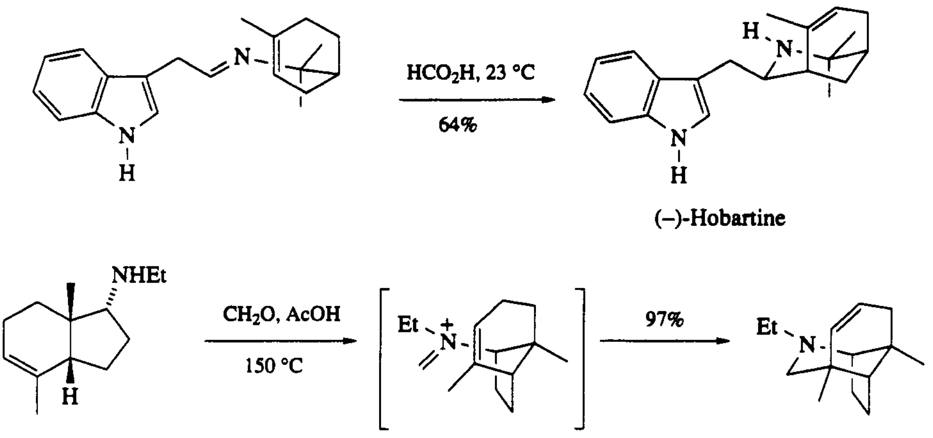
HCO₂H, 23 °C
64%
(–)-Hobartine
NHEt
CH₂O, AcOH
150 °C
97%
Et
N
H

Scheme 27

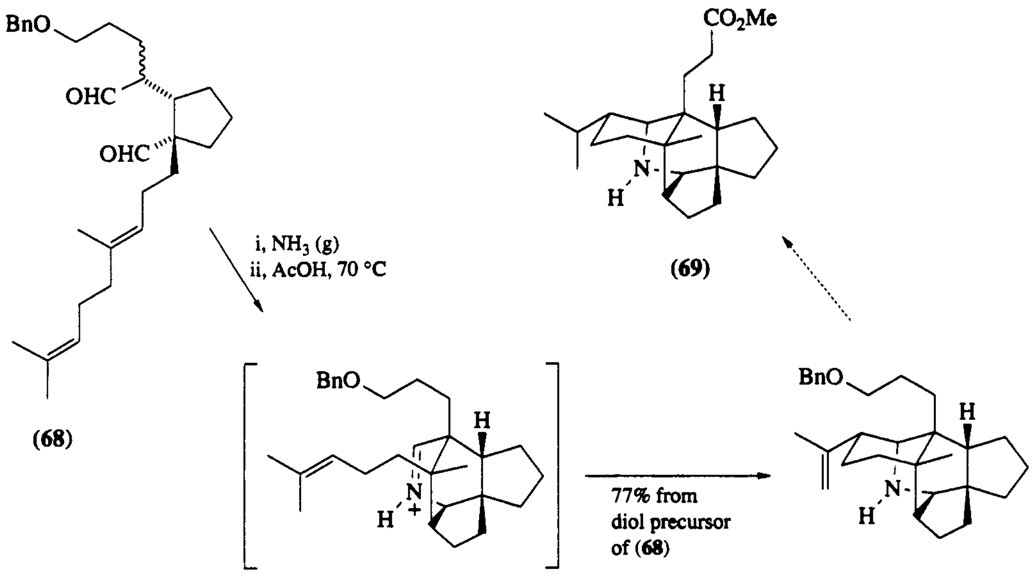
BnO
OHC
OHC
(68)
i, NH₃ (g)
ii, AcOH, 70 °C
CO₂Me
H
N
(69)
77% from
diol precursor
of (68)

Scheme 28

tive stepwise sequence, proceeding *via* a fully formed tertiary cation which then suffers intramolecular general base assisted deprotonation by the amine substituent, is not geometrically feasible in this case. The related cyclization of the chiral imine (72) proceeded with low diastereoselectivity.[65]

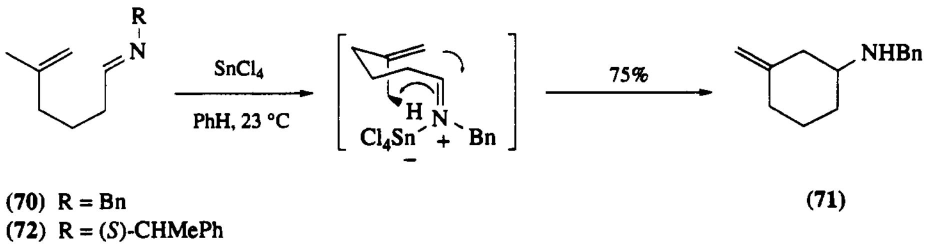
R
N
SnCl₄
PhH, 23 °C
H N Bn
Cl₄Sn
75%
NHBn
(70) R = Bn
(72) R = (S)-CHMePh
(71)

Scheme 29

In contrast, when the stereogenic center is contained within the tether connecting the reacting partners, high levels of stereoinduction can be realized. For example, reaction of optically active amines (**73**) with an acidic methanolic formaldehyde solution proceeded with high stereoselectivity to provide the epimeric pentacyclic alcohols (**74**; Scheme 30).[66] The *cis* D/E-ring junction would be expected, based on earlier work (*vide supra*).[56] It is of interest that cyclization of optically active amine (**75**) under similar conditions afforded racemic (**76**),[66,67] a result perhaps rationalized by enone (**76**) undergoing ready retro-Mannich unraveling.

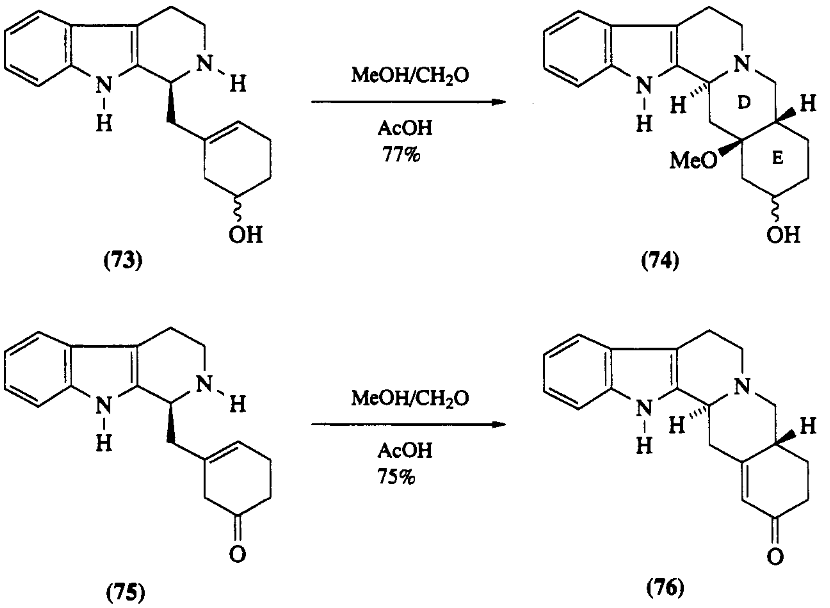

Scheme 30

Related cyclizations of alkenes and electrophilic iminium ion intermediates such as *N*-tosyliminium[68,69] and iminomalonate salts,[70,71] although outside the scope of this chapter, have been employed for assembling a variety of azacyclic materials.

### *4.4.2.4.2 Polycyclizations*

The feasibility of cyclizing polyenes with iminium ion initiators has received only scant attention.[64,72] Cyclization of imine (**77**) under aprotic conditions with $SnCl_4$ affords predominantly *trans*-decalins containing endocyclic unsaturation. This mixture was deduced by $^1H$ NMR analysis to contain diastereomers (**78**) to (**81**) in the indicated abundances as depicted in equation (7). The extent of asymmetric induction in forming the decalin ring system (9*S*,10*S*:9*R*,10*R* = 61:39) is significantly lower than that of related cyclizations of chiral acetal substrates.[73]

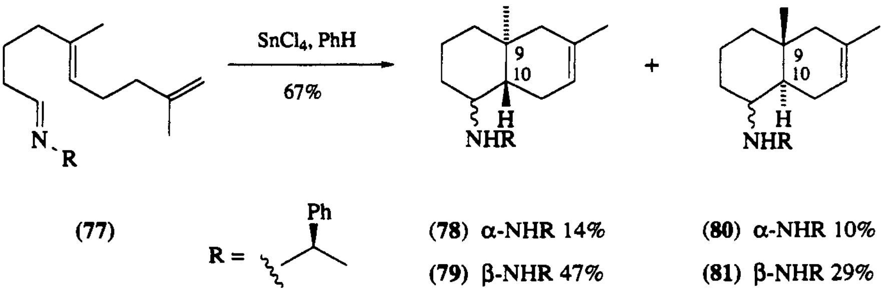

(7)

### *4.4.2.4.3 Importance of reaction medium*

A recent report highlights the critical role that reaction medium (primarily counterion and solvent nucleophilicity) can play in determining the outcome of iminium ion initiated cyclizations.[74] In this study the cyclization of the formaldiminium ion derived from amine (**82**), containing disparate π-nucleophiles, was conducted in a variety of solvents (Scheme 31). In acetonitrile the reaction produced pentylidenepiperidine (**83**), resulting from participation of the vinylsilane terminator, as the sole product. Remarkably, relative terminator reactivity is completely reversed by a change of solvent. Thus, identical treatment of (**82**) in water resulted in cyclization with the butenyl group providing 4-hydroxypiperidine (**84**) as the predominant product. Cyclization of (**82**) in acetic or formic acid shows intermediate behavior, providing substantial amounts of products arising from participation of both nucleophilic terminators. It was thus concluded that the reaction of π-nucleophiles whose participation forms relatively unstable carbocationic intermediates will be favored by increases in solvent polarity and reaction medium nucleophilicity. On the other hand, less polar and less nucleophilic reaction conditions will favor participation of π-nucleophiles that afford more-stabilized carbocationic intermediates or intermediates that can dissipate charge in an intramolecular fashion. These studies and others attest that even weak π-nucleophiles, such as terminal vinyl groups, can effectively participate in iminium ion cyclizations provided that the reaction medium is sufficiently nucleophilic.[75,76]

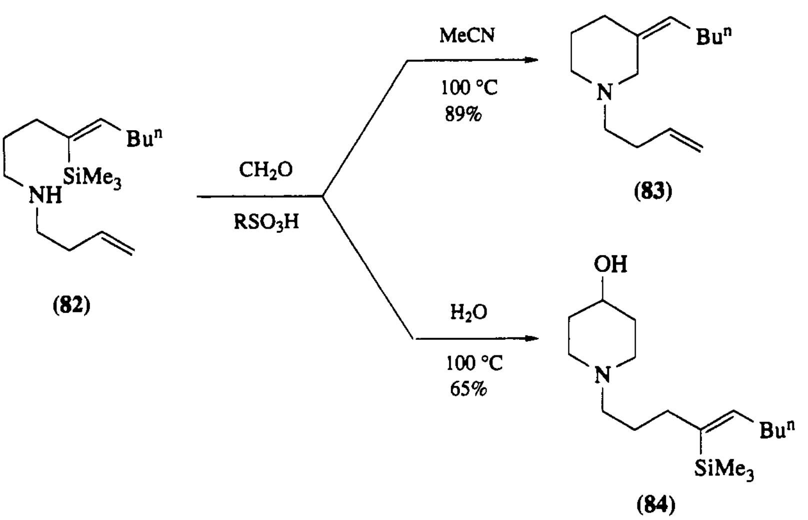

Scheme 31

Halide anions have also been employed to facilitate the cyclization of weakly nucleophilic terminal vinyl π-nucleophiles. For example, the butenylamine (**85**) undergoes Mannich cyclization in the presence of excess NaI to provide the 4-iodopiperidine (**87**) in excellent yield.[74] The success of this cyclization should be contrasted with the failure of related amines to cyclize in formic acid with formaldehyde (Scheme 25). A detailed study[74] of the effect that nucleophile concentration has on the outcome of Mannich cyclizations provides definitive evidence that the cyclization of iminium ions with alkenes is not a concerted process, but rather proceeds *via* a cationic intermediate capable of partitioning between product formation and reversal to the starting iminium ion. A bridged cation or π-complex, *e.g.* (**86**) in equation (8), is a reasonable description of this intermediate.

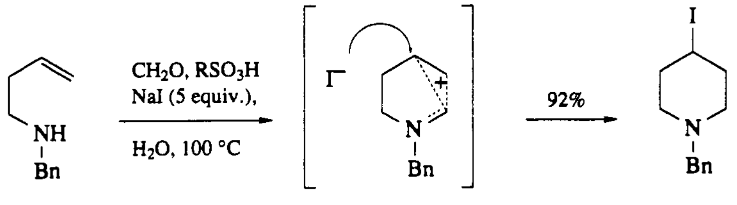

(8)

### 4.4.2.5 Alkynes

Successful cyclization reactions of alkynes with weakly electrophilic iminium ions requires the presence of strong external nucleophiles. The only study to date which addresses the nature of useful cyclization promoters indicates that nonbasic nucleophiles with nucleophilic constants η-MeI > 5.8 are required.[77]

The first example of a successful iminium ion–alkyne cyclization appeared in 1977.[67] The 4-alkynylamine (**88**) was cyclized in acidified aqueous formaldehyde to a mixture of indoloquinolizidine ketones which could be equilibrated in base to provide the more stable epimer (**89**) in 49% yield. Not surprisingly, the six-membered ring was formed exclusively.

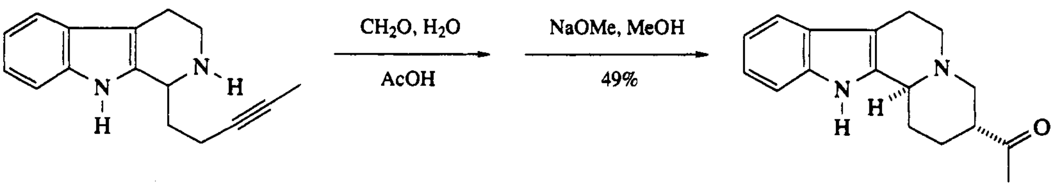

**(88)** **(89)**

The formaldiminium ion formed from the reaction of 4-hexynylamine (**90**; R = R′ = Me) with paraformaldehyde and camphorsulfonic acid is reported not to cyclize when heated for 1 h at 100 °C in the weakly nucleophilic solvent acetonitrile. However, when nucleophilic salts are added the 3-alkylidenepiperidines (**91**) are formed in good yields (Scheme 32).[77] Attempted cyclizations of (**90**) in the presence of weaker nucleophiles such as benzenethiol or methanol were less effective, the former yielding <15% of the expected alkylidenepiperidine product, while the latter provided no products of cyclization. If the strong nucleophile iodide is employed, even a weakly nucleophilic terminal alkyne can be successfully cyclized. In all of these cyclizations of 4-alkynylamines only formation of a six-membered ring product was observed. The (*Z*)-stereochemistry of the alkylidene side chain evolves from antarafacial addition of the internal iminium cation and the external nucleophile to the alkyne.

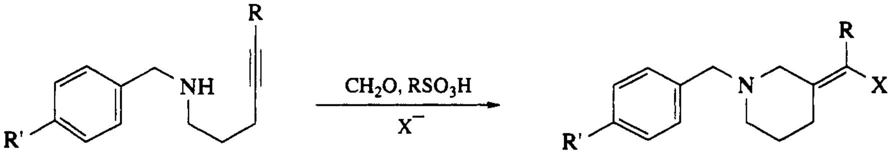

**(90)** **(91)**

| *R′* | *R* | *X* | *Yield* (%) |
|---|---|---|---|
| OMe | Me | Br | 89 |
| OMe | Me | I | 80 |
| H | Me | $N_3$ | 72 |
| H | Me | SCN | 82 |
| OMe | H | I | 56 |
| OMe | Me | SPh | <15 |

**Scheme 32**

A study of 3-alkynylamines (**92**) addressed the question of endocyclic *versus* exocyclic ring closure in nucleophile-assisted alkyne cyclizations (equation 9).[77] Cyclizations of the formaldiminium ion derived from (**92**) occurred only in the endocyclic sense affording tetrahydropyridines (**93**). Terminal as well as substituted alkynes were observed to react with endocyclic regioselectivity in the presence of a variety of nucleophiles.

The utility of stereospecific nucleophile-induced iminium ion–alkyne cyclizations that proceed in the exocyclic mode was recently demonstrated by Overman and coworkers in efficient enantioselective total syntheses of the *Dendrobatid* alkaloids (+)-pumiliotoxin A and (+)-allopumiliotoxin 323B′.[78,79] The piperidine ring and 6-alkylidene side chain of these alkaloids were stereospecifically generated in good

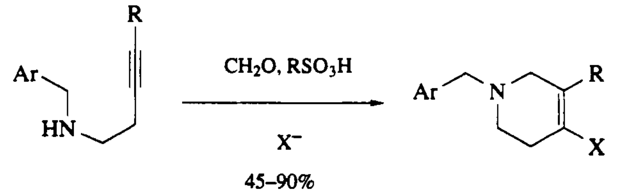

(9)

**(92)**

Ar = 4-methoxyphenyl

**(93)**

| *R* | *X* |
|---|---|
| Me | I, Br, $N_3$ |
| H | I |
| $SiMe_3$ | I, Br |

yield by the iodide-promoted cyclization of iminium ion intermediate (**94**), depicted in Scheme 33. The key cyclization step to form (+)-pumiliotoxin A was accomplished by treating alkynylamine (**95**) with formaldehyde, camphorsulfonic acid and excess NaI in $H_2O$ at 100 °C to provide (**96**) in 60% yield (Scheme 33). Subsequent halogen/metal exchange with BuLi and protonolysis of the resulting lithium reagent afforded (**97**). Debenzylation of (**97**) then provided (+)-pumiliotoxin A in 10% overall yield from L-proline. The two-step conversion of (**95**) to (**97**) is the equivalent of a 'reductive' iminium ion–alkyne cyclization in which the iminium carbon and an external hydride are added in an *anti* fashion to the starting alkyne.

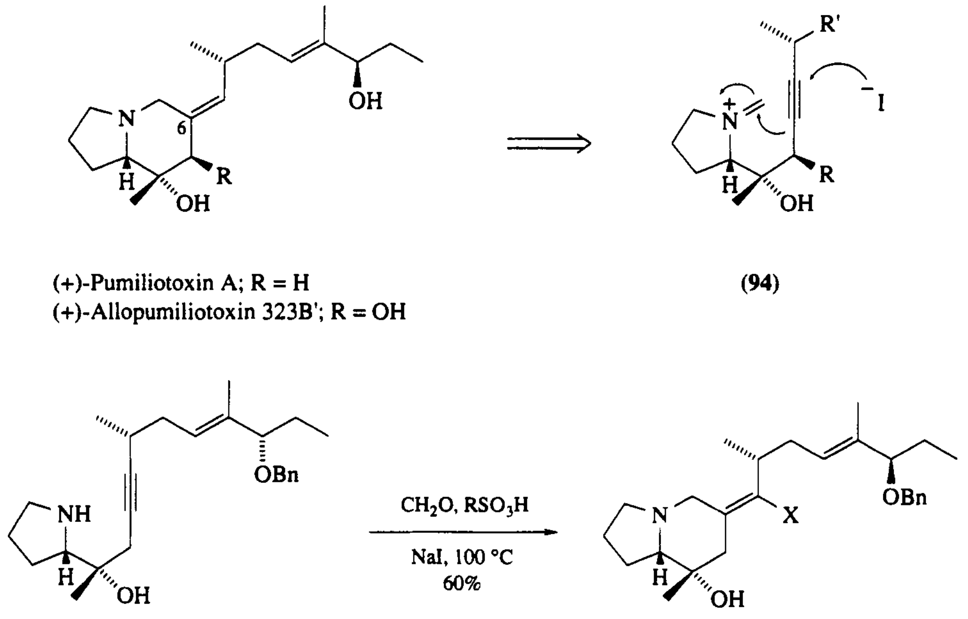

(+)-Pumiliotoxin A; R = H
(+)-Allopumiliotoxin 323B'; R = OH

**(94)**

**(95)**

**(96)** X = I
**(97)** X = H

**Scheme 33**

The pronounced sensitivity of alkynes to cyclization in the presence of external nucleophiles is illustrated in studies of formaldiminium ion (**99**) in which an alkyne and alkene compete as intramolecular π-nucleophiles.[77] While cyclization of (**99**) in water afforded 4-hydroxypiperidine (**98**) in 73% yield, cyclization in the presence of 10 equiv. of NaI gave vinyl iodide (**100**) in 76% yield (Scheme 34). It has been suggested that the mechanism of these nucleophile-promoted iminium ion–alkyne cyclizations probably involves rate-determining attack of the nucleophile on a π-complex or bridged cation produced from reversible interaction of the iminium ion and alkyne groups.[77]

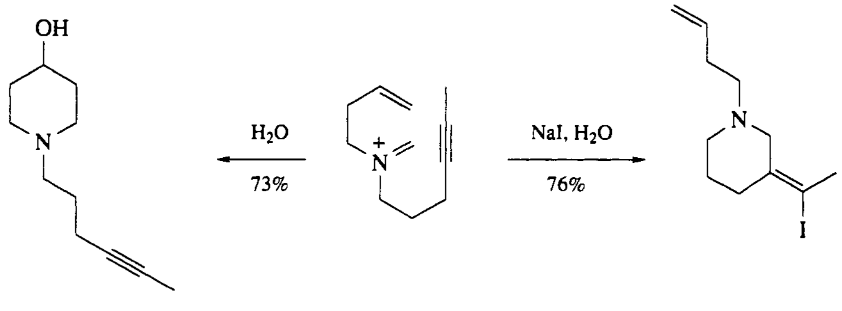

**(98)** **(99)** **(100)**

Scheme 34

### 4.4.2.6 Organosilanes

In less than 10 years, organosilanes have emerged as an unusually versatile class of nucleophiles for terminating Mannich-type cyclizations. Their utility derives from the ability of the silicon substituent to control the regioselectivity of bond formation and dictate the postcyclization destiny of the carbenium ion intermediate produced upon cyclization. The characteristics of silicon that are responsible for this exceptional control have been discussed in several recent reviews.[80–82]

#### *4.4.2.6.1 Vinylsilanes*

Towards electrophiles, the reactivity of vinylsilanes is similar to that of the corresponding alkene. However, incorporating a silicon substituent at the vinylic carbon of a π-nucleophile markedly affects the cyclization outcome. Specifically, iminium ion–vinylsilane cyclizations occur cleanly to substitute, preferentially with retention of double-bond configuration, the iminium ion carbon for the silyl substituent. Both endocyclic and exocyclic modes of intramolecular electrophilic substitution have been demonstrated (Scheme 35).

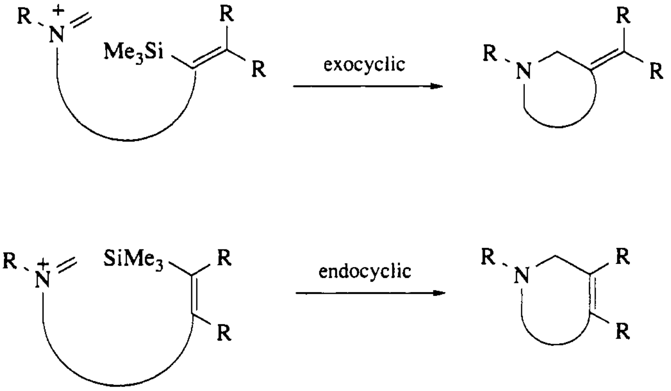

Scheme 35

Mannich-type cyclizations of vinylsilanes have found considerable application in the area of alkaloid total synthesis.[81] Cyclizations that occur in the exocyclic mode with respect to the vinylsilane nucleophile have been widely employed to assemble 3-alkylidenepiperidine substructures with high stereocontrol. Overman and coworkers have made extensive use of the acid-promoted conversion of bicyclic oxazolidines to alkylideneindolizidines in their total syntheses of pumiliotoxin A alkaloids (Scheme 36).[83–85] An illustration of the mild nature of iminium ion–vinylsilane cyclizations is provided in the conversion of (**101**) to (**102**), the penultimate precursor of (+)-pumiliotoxin A. This conversion was accomplished in 71% yield by heating (**101**) at 80 °C in a methanolic pyridine–pyridinium tosylate buffer (pH ≈ 4.5). More strongly acidic conditions had to be avoided since they led to competitive solvolysis of the allylic benzyl ether functionality of the pumiliotoxin A side chain. To the limits of detection by high field NMR and GC, the formation of (**102**) and pumiliotoxin 251D occurred with complete retention of configuration at C-6.

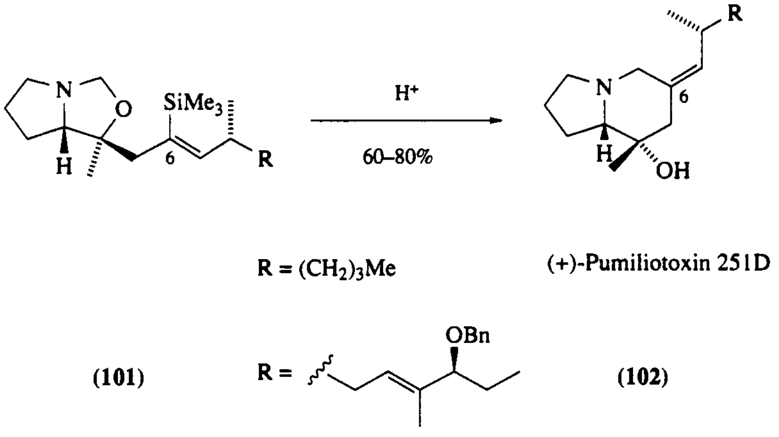

**(101)** **(102)**

**Scheme 36**

The stereocontrolled formation of exocyclic double bonds by stereospecific iminium ion–vinylsilane cyclizations has also been employed by Overman and coworkers as the key step in total syntheses of *Corynanthe* alkaloids.[7,86] The crucial cyclization step in the synthesis of (±)-(19*Z*)-isositsirikine is shown in equation (10). The (*Z*)-vinylsilane (**103**) cyclizes in 1:1 methanol–water to provide, in essentially quantitative yield, the (*Z*)-ethylideneindoloquinolizidine (**104**).

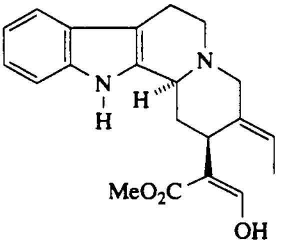

Geissoschizine

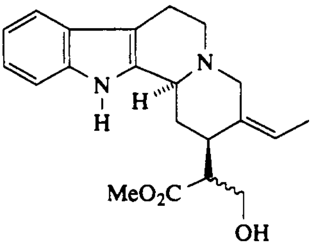

(19*Z*)-Isositsirikine

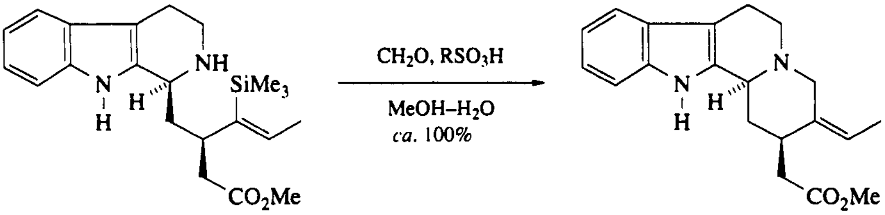

**(103)** **(104)** (10)

In contrast, the stereospecificity of the conversion of (*E*)-vinylsilane (**105**) to (**107**), the key step in the total synthesis of (+)-geissoschizine, was highly solvent dependent (Scheme 37). Stereospecificity was considerably higher when silylphilic solvents (MeOH, $H_2O$) or additives such as NaF were employed. Under optimum conditions the conversion of (**105**) to methyl geissoschizoate (**107**) occurred with 9:1 stereoselectivity and provided enantiomerically pure (**107**) in 80% yield.[7] The lower degree of sterospecificity observed in the cyclization of the (*E*)-stereoisomer was attributed to different lifetimes for the respective β-silyl cation intermediates. The serious steric interaction that would develop between the vinyl methyl group and the acetic acid side chain (an $A^{1,3}$ interaction)[12] if intermediate (**106**) transferred its $SiMe_3$ group to a nucleophile prior to ring inversion is believed to be responsible for the partial erosion of stereochemical integrity in the conversion of (**105**) to (**107**).[7]

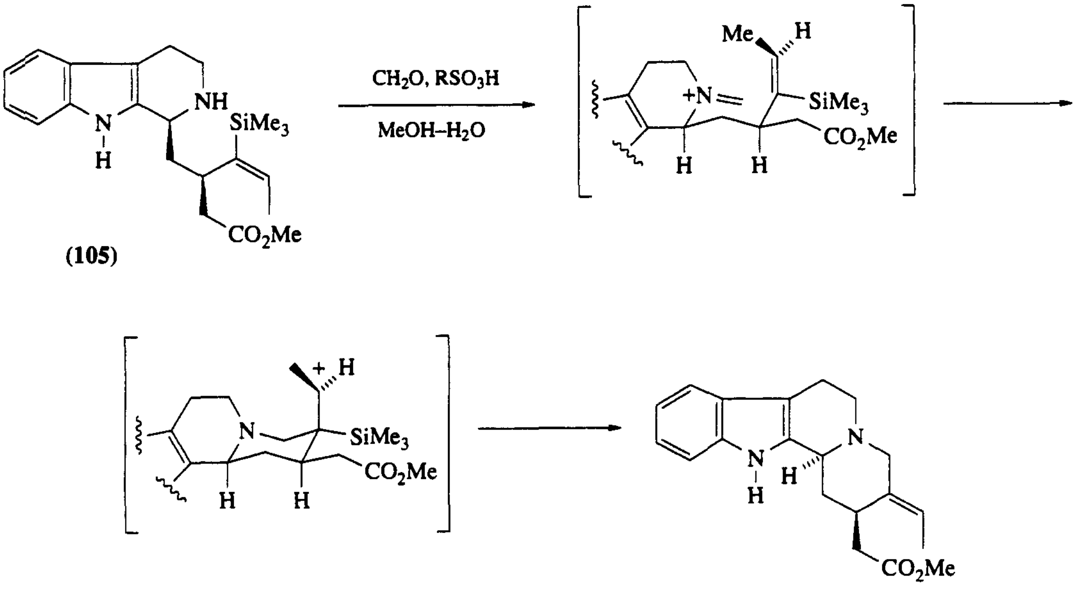
CH₂O, RSO₃H
MeOH–H₂O
NH
SiMe₃
CO₂Me
Me
H
+N
SiMe₃
CO₂Me
H
H
+
H
N
SiMe₃
CO₂Me
N
H
N
H
CO₂Me

(105)

(106)

(107)

Scheme 37

Cyclizations that are endocyclic with respect to the vinylsilane nucleophile have been employed to prepare *Amaryllidaceae* alkaloids.[87] An important stereochemical consideration in the use of a vinylsilane nucleophile in an endocyclic cyclization is illustrated by the disparate behaviors of (**108**) and (**110**). It was found that (*Z*)-vinylsilane (**108**) cyclizes to *cis*-hexahydroindole (**109**), when treated with 1 equiv. of $CF_3CO_2H$, at a rate that is at least 7000 times greater than that of the (*E*)-stereoisomer (**110**). This rate difference is thought to reflect the importance of σ–π hyperconjugative stabilization in the cyclization transition state. Only the (*Z*)-isomer (**108**) can cyclize to initially form a cationic intermediate in which the β-C—Si σ-bond is oriented coplanar with — and thus able to stabilize maximally — the developing vacant *p*-orbital (Scheme 38). The utility of this type of cyclization was demonstrated in Overman and Burk's total synthesis of the *Amaryllidaceae* alkaloid (±)-epielwesine.[87] The exigent step in this construction is the iminium ion–vinylsilane cyclization of (*Z*)-vinylsilane imine (**111**), which proceeded in 90% yield. *cis*-Hexahydroindole (**112**) was hydrated then cyclized under Pictet–Spengler conditions affording the target alkaloid (Scheme 39).

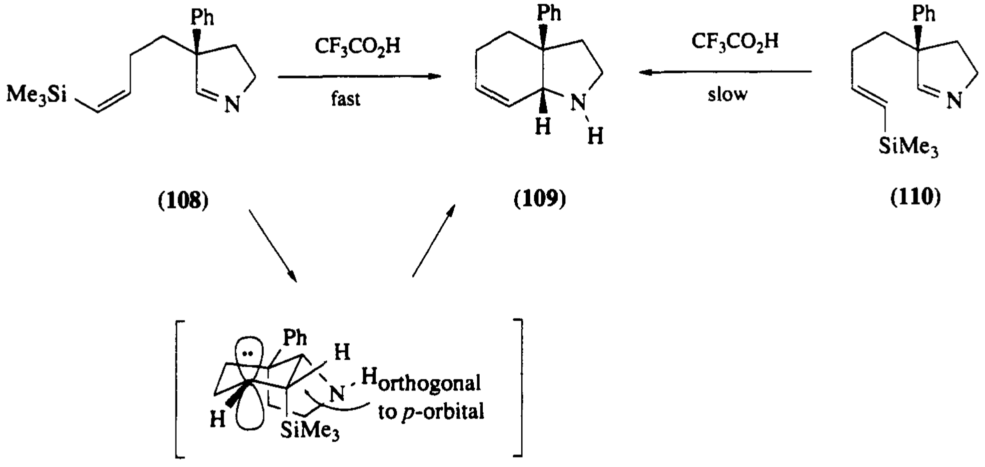
Ph
Me₃Si
N
CF₃CO₂H
fast
Ph
N
H
H
CF₃CO₂H
slow
Ph
N
SiMe₃
Ph
H
N
H orthogonal to *p*-orbital
H
SiMe₃

(108)

(109)

(110)

Scheme 38

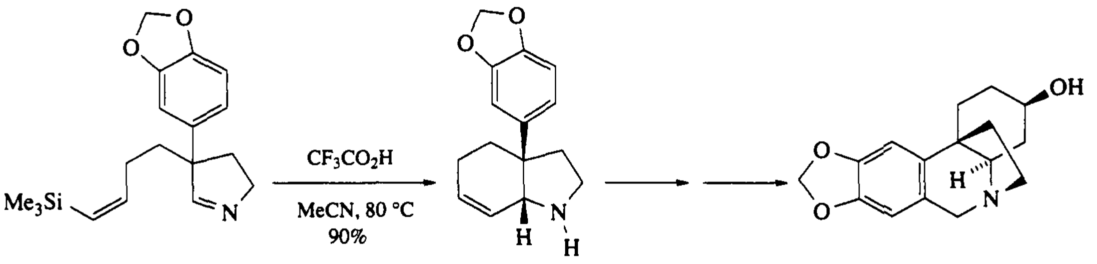
Me₃Si
CF₃CO₂H
MeCN, 80 °C
90%
H
H
OH
H

**(111)** **(112)** (±)-Epielwesine

**Scheme 39**

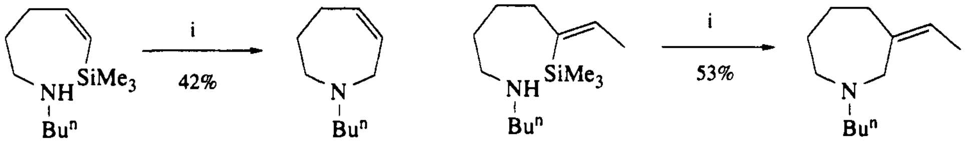
SiMe₃
NH
Buⁿ
i
42%
N
Buⁿ
SiMe₃
NH
Buⁿ
i
53%
N
Buⁿ

i, $CH_2O$ (excess), camphorsulfonic acid (0.95 equiv.), MeCN, 80 °C

**Scheme 40**

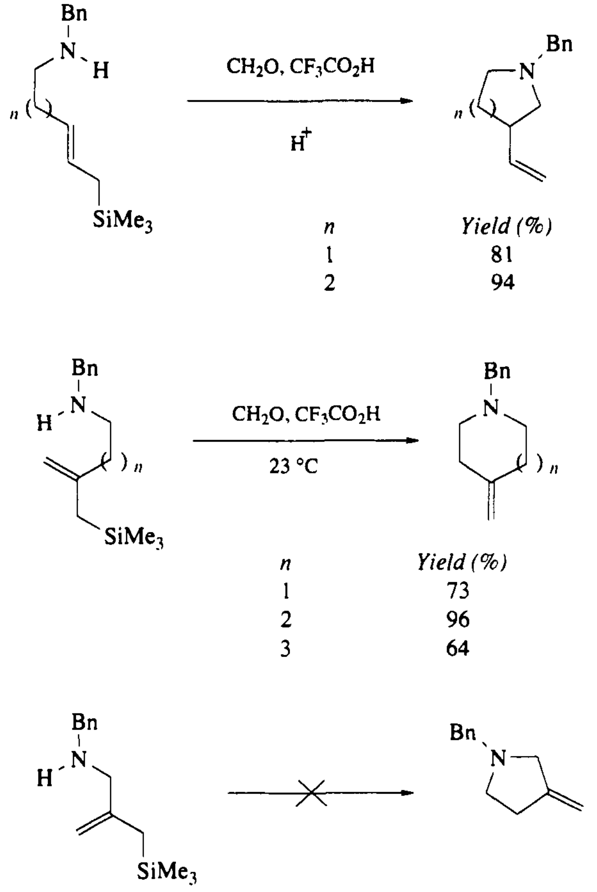
Bn
N
H
n
SiMe₃
CH₂O, CF₃CO₂H
H⁺
Bn
N
n
Bn
N
H
n
SiMe₃
CH₂O, CF₃CO₂H
23 °C
Bn
N
n
Bn
N
H
SiMe₃
Bn
N

| *n* | *Yield (%)* |
|---|---|
| 1 | 81 |
| 2 | 94 |

| *n* | *Yield (%)* |
|---|---|
| 1 | 73 |
| 2 | 96 |
| 3 | 64 |

**(113)**

**Scheme 41**

The use of iminium ion–vinylsilane cyclizations for forming azacyclic rings other than six-membered has received little attention.[82,88] Examples of forming azepines containing either endocyclic or exocyclic unsaturation are shown in Scheme 40.

### *4.4.2.6.2 Allylsilanes*

A number of Mannich-type cyclizations that proceed in an exocyclic mode with respect to the allylsilane terminator have been reported. In this way, five-, six-, seven- and eight-membered azacycles are accessed in good yields.[89] In keeping with Baldwin's suggestion concerning ring closure aptitudes,[2] the iminium ion derived from amine (**113**) could not be cyclized (Scheme 41).

The synthesis of (±)-yohimbone by Grieco and Fobare illustrates the use of an allylsilane to terminate an iminium ion initiated polyene cyclization.[90] The D/E-ring system of the target alkaloid was assembled by treating diene amines (**114**) with formaldehyde and $CF_3CO_2H$ in aqueous THF to give (**115**) in good yield. Only the *trans*-hydroisoquinoline stereoisomer was produced (Scheme 42).

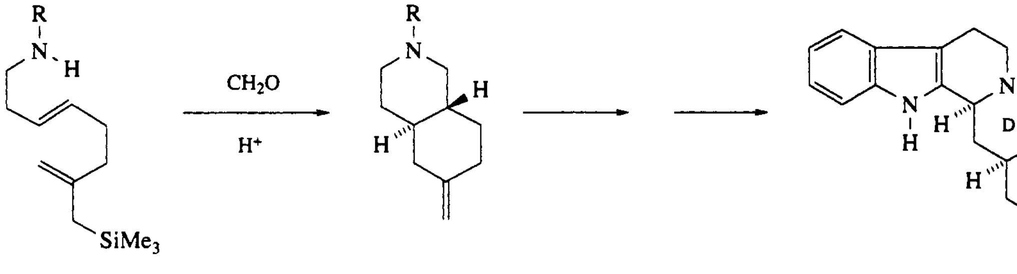

**(114)** **(115)** (±)-Yohimbone

| | |
|---|---|
| R = Bn | 80% |
| R = *N*-tosyltrytophyl | 63% |

**Scheme 42**

A variety of tetrahydropyridines have been prepared with complete regiocontrol by the reaction of 4-(trimethylsilyl)-3-butenylamines with aldehydes and acid (Scheme 43).[88] This reaction, although ostensibly an iminium ion–vinylsilane cyclization, is believed to occur by the pathway illustrated in equation (11), in which ring formation ensues from the allylsilane sigmatropic isomer. Consistent with this mechanism pathway, either the (*E*)- or (*Z*)-vinylsilane amine stereoisomer can be employed.

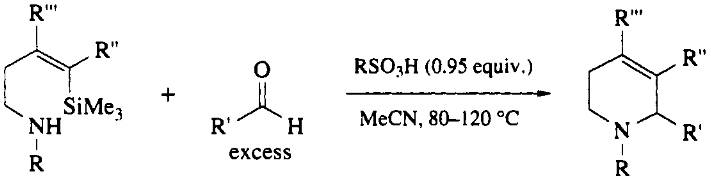

| *R* | *R'* | *R''* | *R'''* | *Yield (%)* |
|---|---|---|---|---|
| 4-Methoxybenzyl | H | H | H | 95 |
| 4-Methoxyphenyl | H | H | H | 85 |
| 4-Methoxybenzyl | n-$C_6H_{13}$ | H | H | 64 |
| Ph | n-$C_6H_{13}$ | H | H | 68 |
| Bu$^i$ | H | H | Me | 66 |
| Bu$^i$ | H | H | Ph | 83 |
| Pr$^n$ | H | SiMe$_3$ | H | 82 |

**Scheme 43**

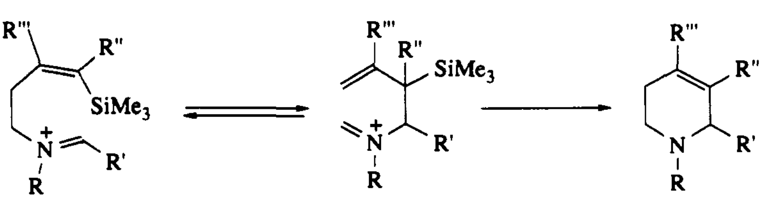

(11)

An alternative sequence in which an α-cyanoalkylamine is employed as an iminium ion precursor has also been described (Scheme 44). This two-step alternative is attractive if the aldehyde component is scarce since only one equivalent of the aldehyde is employed.[88]

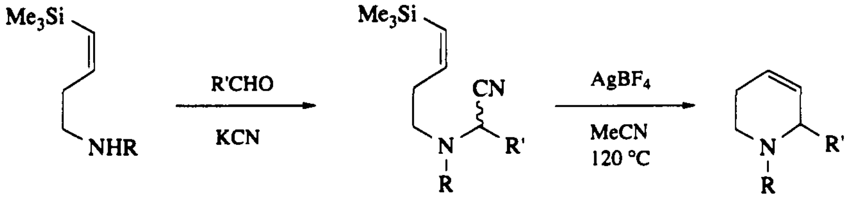

| *R* | *R'* | *Yield (%)* |
|---|---|---|
| $Pr^n$ | $CH_2CH_2Ph$ | 73 |
| 4-Methoxybenzyl | $CH_2CH_2Ph$ | 76 |
| $Pr^n$ | 2-Furyl | 58 |
| 4-Methoxybenzyl | 3-Pyridinyl | 82 |

**Scheme 44**

There is one report of forming 2,6-disubstituted-1,2,5,6-tetrahydropyridines from 4-(trimethylsilyl)-3-butenylamines (equation 12).[91] The *trans* diastereomer is produced with high stereoselectivity only if the nitrogen substituent is an alkyl group. Optically active tetrahydropyridines cannot be prepared in this manner, however, since cyclization of nonracemic (**116**) (from L-alanine) yielded racemic (**117**). Racemization is suggested to derive from both 2-azonia[3,3] sigmatropic rearrangement (equation 11) and iminium ion stereomutation, these being more rapid than the final iminium ion–allylsilane cyclization.[91]

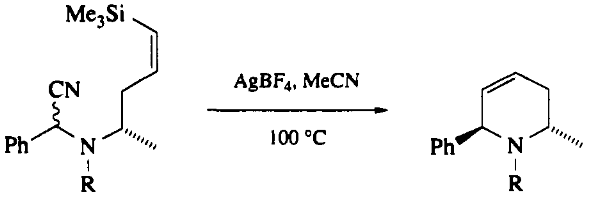

(12)

57% R = Bn
51% R = Me

(**116**) (**117**)

### 4.4.2.6.3 *Benzylsilanes*

Fluoride anion promoted cyclizations of benzylsilane dihydroisoquinolinium salts have been employed to form five- and six-membered azacyclic rings (Scheme 45). For example, CsF in either protic (EtOH–$H_2O$) or aprotic (MeCN) solvents has been used to form the isoquinoline alkaloid (±)-xylopinine (**121**) from (**118**). Yields for this conversion in the range 25–70% have been obtained.[92,93] The *N*-arylisoquinolinium salt (**119**) is reported to cyclize under aprotic conditions only ($Bu^n_4NF$ in refluxing THF) to give (**122**) in 60% yield.[94] A betaine intermediate (**120**) has been proposed for these transformations. The conversion of this intermediate (R = Bn; *n* = 0) to (**122**), formally a 5-*endo*-trig cyclization, can then be formulated as a six-electron electrocyclization. Iminium ion–benzylsilane cyclizations have been accomplished, sometimes with greater efficiency, photochemically (see Section 4.4.3).

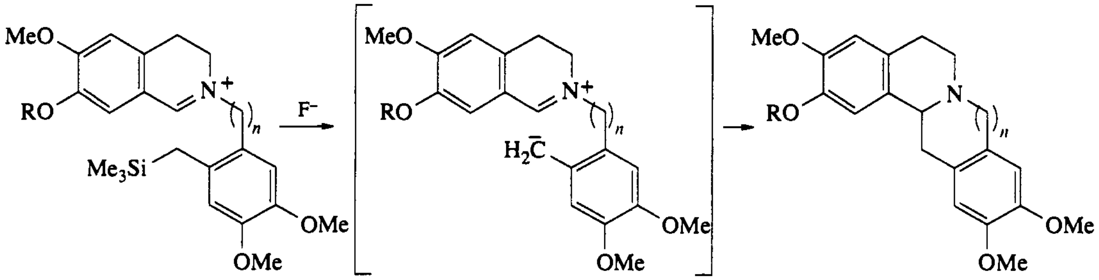

**(118)** R = Me; $n$ = 1
**(119)** R = Bn; $n$ = 0

**(120)**

**(121)** Xylopinine; R = Me; $n$ = 1
**(122)** R= Bn; $n$ = 0

Scheme 45

### 4.4.2.7 Relative Reactivities of Intramolecular π-Nucleophiles

Two of the factors that determine the reactivity of tethered π-nucleophiles in Mannich-type cyclizations have been emphasized: stereoelectronic effects and reaction medium effects. The stereoelectronics of orbital overlaps between the π-nucleophile and the iminium electrophile are best evaluated by considerations such as antiperiplanar addition trajectories and Baldwin's rules for ring formation. The critical importance of the reaction medium has received serious attention only recently. However, it already appears clear that π-nucleophiles that would lead, upon cyclization, to relatively unstable carbocations can have their reactivity markedly increased by carrying out the cyclization in the presence of a nucleophilic solvent or additive which, by nucleophilic participation, can obviate the formation of high energy cyclic carbenium ion intermediates.

The third factor of obvious importance in determining the reactivities of π-nucleophiles is their structure. One recent study examined the relative reactivity of a number of π-nucleophiles in the non-nucleophilic solvent acetonitrile.[95] The approach taken was to order the reactivity of π-nucleophiles from the results of terminator competition experiments such as those shown in equations (13) and (14). The order of terminator reactivity that emerged from this study is summarized in Figure 3. In some cases quantitative comparisons could be made: 3-methyl-3-butenyl (**123**) is twice as reactive as the (Z)-4-(trimethyl-

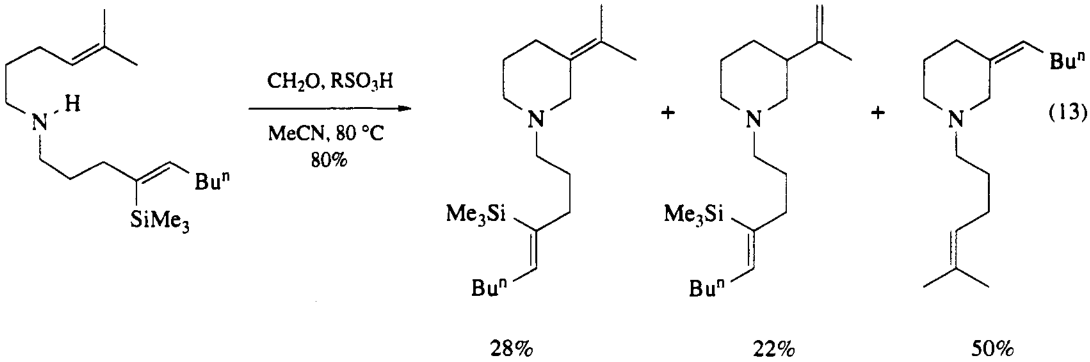

(13)

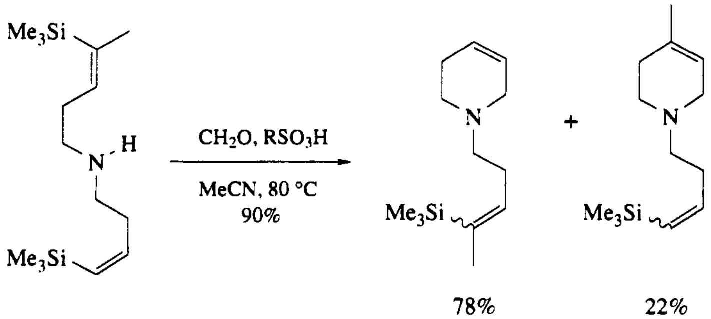

(14)

silyl)-3-butenyl (**124**); and the (*Z*)-vinylsilane (**125**) is twice as reactive as the (*E*)-stereoisomer (**126**). When they were competed against the (*Z*)-vinylsilane terminator (**125**), no products resulting from participation of the six terminators listed at the bottom of Figure 3 were observed. It should be stressed that this reactivity order pertains only to Mannich-type cyclizations conducted in a non-nucleophilic solvent such as acetonitrile.

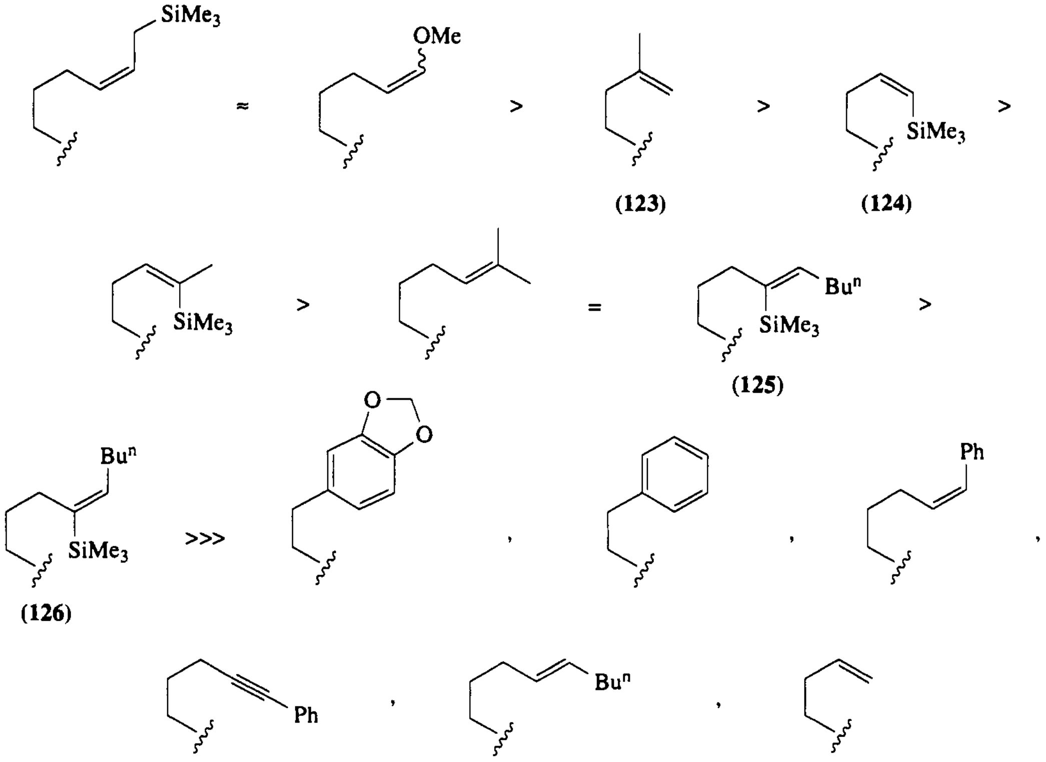

**Figure 3** Relative terminator reactivities in acetonitrile

## 4.4.3 ELECTRON TRANSFER INDUCED PHOTOCYCLIZATIONS

In several instances, Mannich-type cyclizations can be carried out expeditiously under photochemical conditions. The photochemistry of iminium ions is dominated by pathways in which the excited state iminium ion serves as a one-electron acceptor. The photophysical and photochemical ramifications of such single-electron transfer (SET) processes as applied to excited state iminium ions have been expertly reviewed.[96–98] In short, one-electron transfer to excited state iminium ions occurs rapidly from one of several electron donors: electron rich alkenes, aromatic hydrocarbons, alcohols and ethers. Alternatively, an excited state donor, usually aromatic, can transfer an electron to a ground state iminium ion to afford the same reactive intermediates. Scheme 46 adumbrates the two pathways that have found most application in intramolecular cyclizations. Simple alkenes and aromatic hydrocarbons will typically suffer addition processes (pathway A). However, alkenic and aromatic systems with allylic or benzylic groups more electrofugal than hydrogen (*e.g.* silicon, tin) commonly undergo elimination reactions (pathway B) to generate the reactive radical pair.

If the iminium ion and electron donor are tethered, these SET-induced addition reactions can be efficient to the point of synthetic practicality. For example, such photocyclizations have been used to secure reasonable yields of azacycles of monocyclic, bridged and linearly fused topographies (Scheme 47).[99,100] Note that the cyclizations of iminium ions (**127**) and (**128**) occur in an endocyclic mode with respect to both reacting partners. This mode of cyclization has not been observed in related ground state reactions (*vide supra*).

Typically the iminium ion is conjugated, although conjugation is not an absolute prerequisite for a successful cyclization. Perchlorate is selected as the counter anion because it does not offer the possibility of

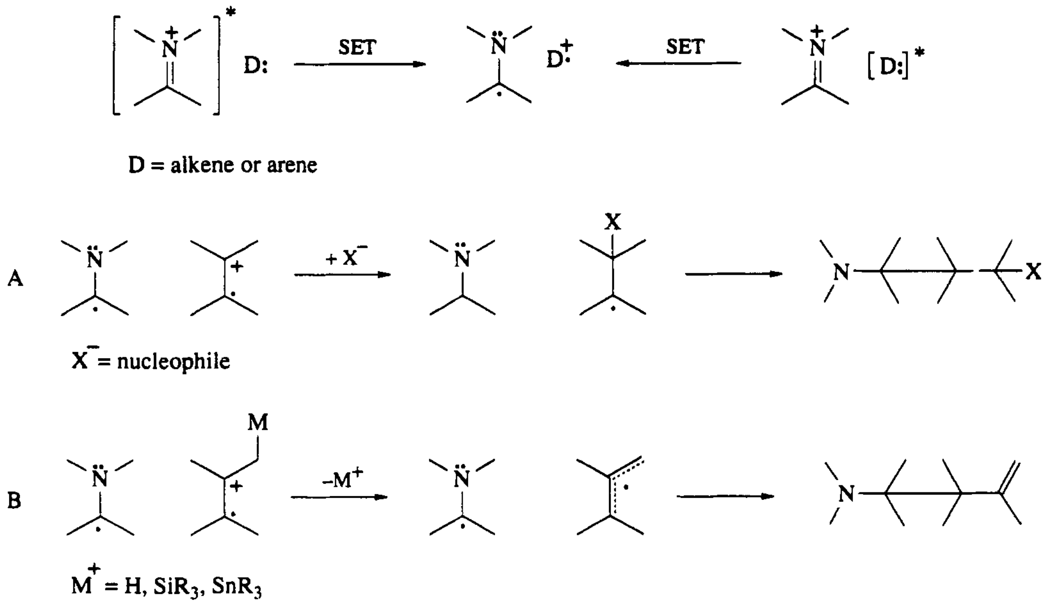

D = alkene or arene

X⁻ = nucleophile

M⁺ = H, SiR$_3$, SnR$_3$

Scheme 46

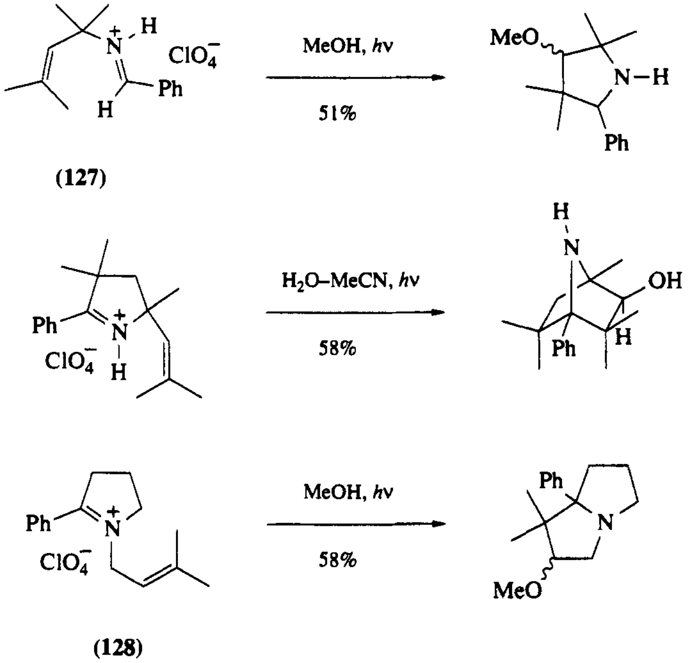

Scheme 47

SET from the counter anion to the excited state iminium salt. In addition, a successful one-electron alkenic donor must be electron rich, in most cases trialkyl substituted.

In studies directed toward the synthesis of members of the *Cephalotaxus* alkaloid family, irradiation of allylsilane iminium ion (**129**) provided a 70% yield (at 45% conversion) of spiroazacycle (**130**).[101] It should again be noted that this 5-*endo*-trig cyclization does not occur without photochemical activation (*cf.* Scheme 25).

A related cyclization was recently used by Mariano and coworkers as the key step in a construction of the skeleton of the *Erythrina* alkaloids. Photocyclization of 3,4-dihydroisoquinolinium perchlorate (**131**) afforded a 60% yield of tricycle (**132**; Scheme 48). This spiro tricycle was converted in eight additional steps to 15,16-dimethoxy-*cis*-erythrinan.[102,103]

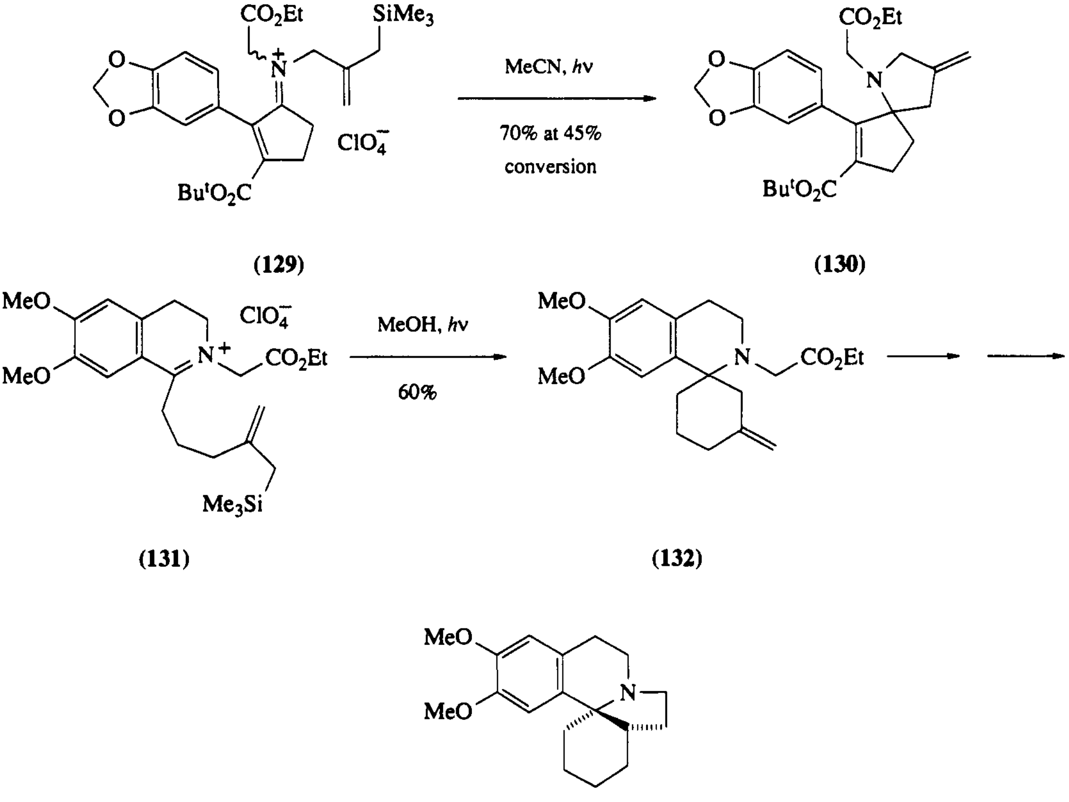
MeCN, *hv*
70% at 45% conversion
(129)
(130)
MeOH, *hv*
60%
(131)
(132)

15,16-Dimethoxy-*cis*-erythrinan

Scheme 48

The electrofugal benzylic trimethylsilyl group will also admirably direct photocyclizations. This directing effect is enunciated in the cyclizations of *N*-xylylpyrrolinium perchlorates (**133**) and (**135**). Upon irradiation in acetonitrile, salt (**133**) is converted to the dimethylbenzopyrrolizidine (**134**) in 90% yield. In comparison, silicon analog (**135**) cleanly photocyclizes at the benzylic site in acetonitrile to yield the benzoindolizidine (**136**; Scheme 49).[104]

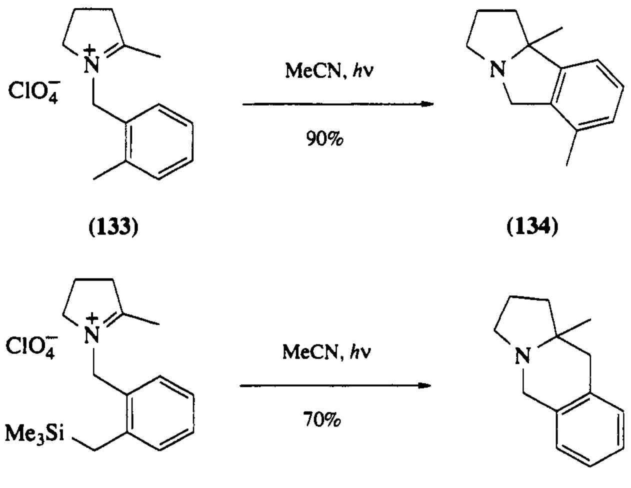
MeCN, *hv*
90%
(133)
(134)
MeCN, *hv*
70%
(135)
(136)

Scheme 49

Photoinduced iminium ion–benzylsilane cyclizations have also been employed to construct the protoberberine and spiro benzylisoquinoline alkaloid skeletons. For example, the spiro benzylisoquinoline (**138**) can be accessed in 50% yield by the photocyclization of isoquinolinium salt (**137**).[105] Photocyclization of the electron rich isoquinolinium salt (**118**) gave a 70% yield of (±)-xylopinine (Scheme 45).[94] This photocyclization is claimed to proceed more cleanly and with higher efficiency than the corresponding fluoride-promoted ground state cyclization.

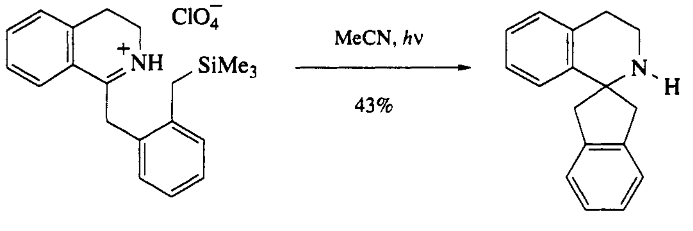

**(137)** **(138)**

Although only recently introduced, it is apparent that photoinduced SET cyclizations of iminium salts are a useful tool in azacycle synthesis. Of particular note is the ability to construct pyrrolidines by endocyclic cyclizations which, as a result of stereoelectronic constraints, cannot be realized with ground state intermediates.

## 4.4.4 MOLECULAR REARRANGEMENTS TERMINATED BY MANNICH CYCLIZATIONS

The intramolecular Mannich reaction has been combined with the facile [3,3] sigmatropic rearrangement of iminium cations to provide a versatile synthesis of 3-acylpyrrolidines and other more complex ring systems containing this subunit.[106] In the simplest case, a homoallylic amine with alkoxy or hydroxy substitution at the allylic site is allowed to react with an aldehyde in the presence of an equivalent or less of acid to yield substituted 3-acylpyrrolidine products (Scheme 50). The mild conditions of this transformation—which occurs at near ambient temperature and neutral pH—are apparent in the success of this sequence with labile aldehydes such as furfural. Ketones can be employed also: in this case a two-step

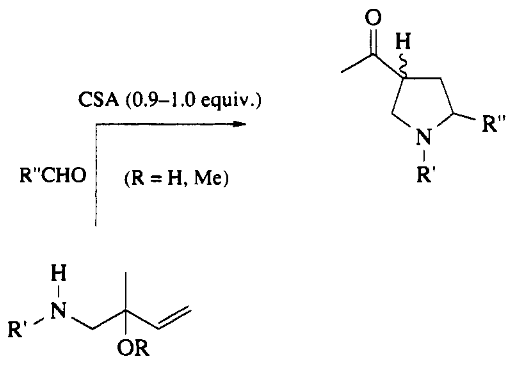

| *R'* | *R''* | *Yield (%)* |
|---|---|---|
| Bn | H | 89 |
| Ph | H | 60 |
| Bn | 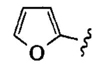 | 95 |
| Me | 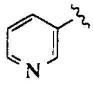 | 84 |

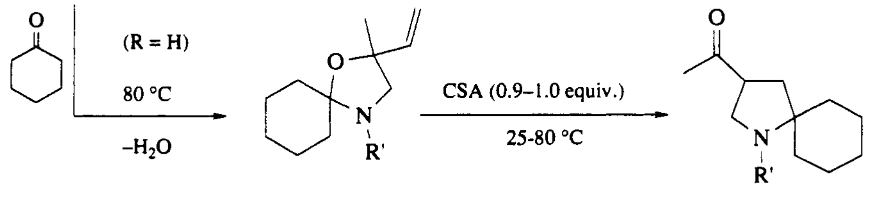

**(139)**

R' = H 69%
R' = Me 54%

Scheme 50

procedure is utilized in which the ketone and a 2-hydroxy-3-butenylamine are condensed to form a 5-vinyloxazolidine (**139**), which is then rearranged in acid to afford the acylpyrrolidine product. A variety of evidence is consistent with these transformations occurring by a sequential cationic aza-Cope (2-azonia[3,3] sigmatropic) rearrangement–Mannich cyclization sequence as depicted in equation(15).[107]

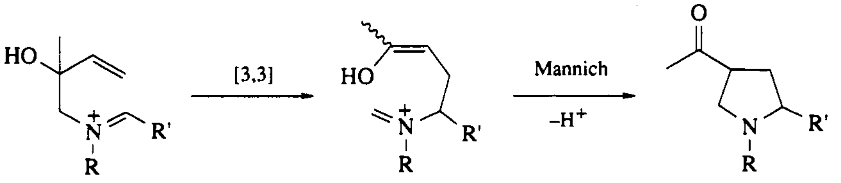

(15)

The above rearrangement has been utilized to assemble pyrrolizidine and indolizidine ring systems from acyclic precursors. The *cis* relationship between the bridgehead hydrogen and the vicinal methyl group in pyrrolizidines (**142**) and (**143**) demonstrates that the rearrangement of (**140**) occurs preferentially in a chair topography, *i.e.* (**141**) in Scheme 51.[108] The indolizidine annulation (**144**) to (**145**) was a key transformation in Overman and Fukaya's synthesis of (±)-perhydrogephyrotoxin (Scheme 52).[109]

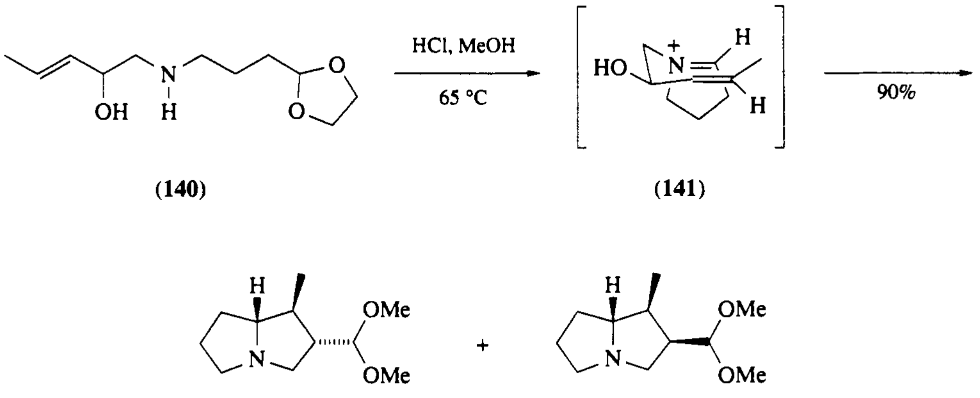

(**140**) (**141**)

(**142**) 93% (**143**) 7%

**Scheme 51**

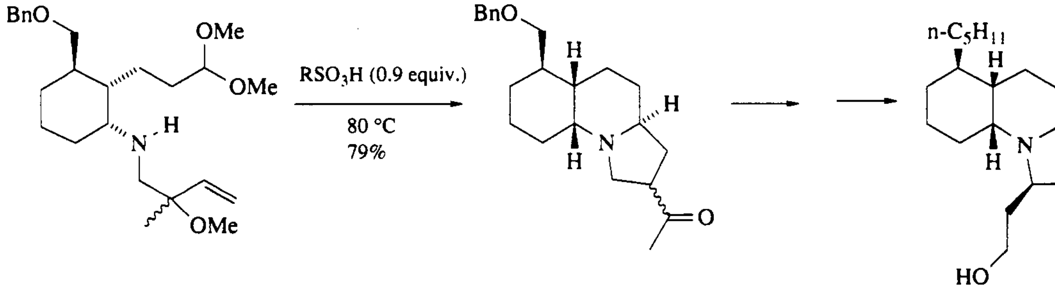

(**144**) (**145**) (±)-Perhydrogephyrotoxin

**Scheme 52**

If the starting amino alcohol is cyclic, the aza-Cope rearrangement–Mannich cyclization reaction provides a pyrrolidine-annulated product in which the initial ring is expanded by one carbon. This transformation has been utilized to prepare a wide variety of *cis*-fused hydroindoles, cyclopenta[*b*]pyrrolidines and cyclohepta[*b*]pyrrolidines (**147**), as shown in Scheme 53.[110–112] The *cis* stereochemistry of the ring fusion as well as the relative orientation of the C-2 substituent are suggested to arise directly from the chair topography of the aza-Cope rearrangement step, as illustrated in equation (16) for the formation of (**149**). The rearrangement can be initiated either by direct reaction of ammonium salt (**148**) with an aldehyde or by cyanide ejection from α-cyanoalkylamine (**146**). This latter precursor is particularly attractive when R = H because (**146**) can be directly assembled from the reaction of a vinyllithium or vinyl Grignard reagent with the corresponding α-cyanomethylcycloalkanone.

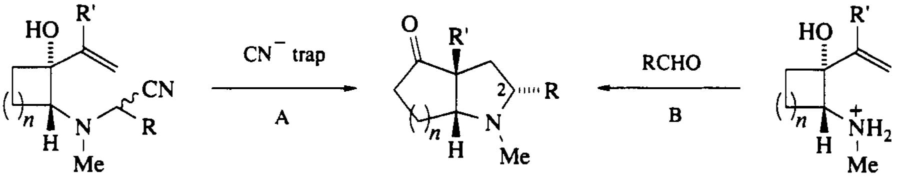

**(146)** **(147)** **(148)**

| *Method* | *n* | *R* | *R'* | *Yield* (%) |
|---|---|---|---|---|
| A ($RSO_3H$) | 3 | H | Ph | 70 |
| A [$Cu(OCOCF_3)_2$] | 3 | H | Ph | 91 |
| A ($AgNO_3$) | 3 | H | Ph | 63 |
| A ($AgNO_3$) | 3 | H | H | 64 |
| A ($AgNO_3$) | 2 | H | Ph | 74 |
| B | 2 | Me | Ph (**149**) | 81 |
| A ($AgNO_3$) | 1 | H | Ph | 78 |
| A ($AgNO_3$) | 1 | Me | Ph | 66 |

**Scheme 53**

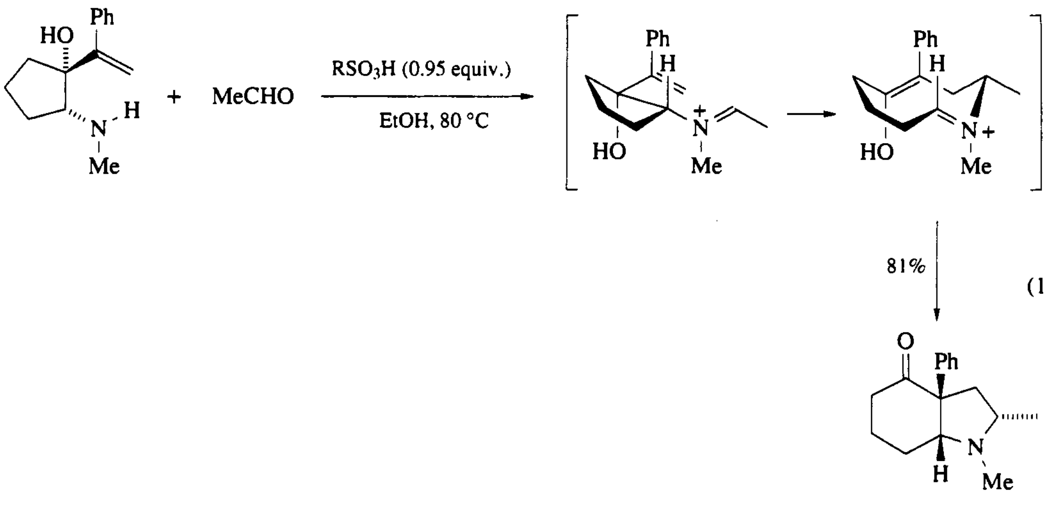

(16)

**(149)**

The ring-enlarging pyrrolidine annulation reaction has been employed by Overman and coworkers as the key step in syntheses of *Amaryllidaceae, Melodinus* and *Aspidosperma* alkaloids. In all cases a *cis*-3a-aryl-4-oxooctahydroindole subunit (**147**; R' = aryl; *n* = 2) is developed during the rearrangement step. Two key steps in the enantioselective synthesis of the *Amaryllidaceae* alkaloid (–)-crinine are summarized in Scheme 54.[113] Addition of lithium reagent (**151**) to the enantiomerically pure ketone (**150**) at –78 °C occurs exclusively from the ketone face opposite the amine substituent to provide (**152**) in 91% yield. Exposure of (**152**) to $AgNO_3$ in EtOH at room temperature proceeded in 80% yield to give the key hydroindolone intermediate (**153**). Debenzylation, Pictet–Spengler cyclization and adjustment of the C-ring functionality then provided (–)-crinine.

The formation of the tricyclic 9a-arylhydrolilolidine ring system is exemplified in the conversion of (**154**) to (**155**).[114] Wolff ring contraction of the ketonic ring of (**155**) and further functional group modifications provided the *Melodinus* alkaloid (±)-meloscine. (Scheme 55).

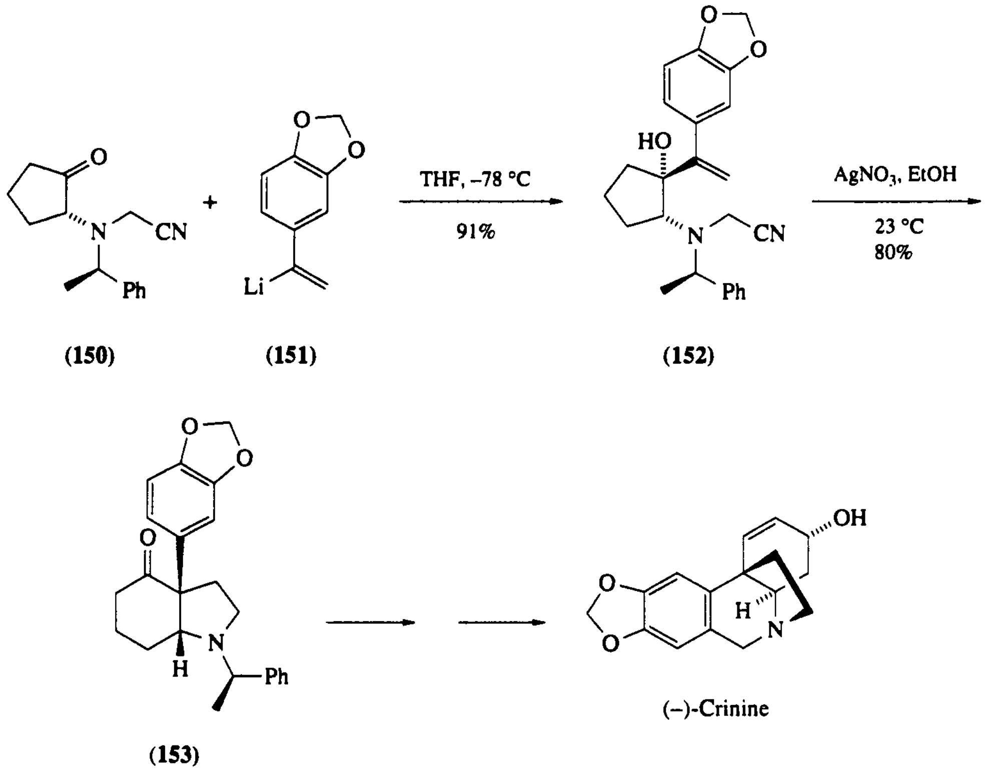
THF, –78 °C
91%
AgNO$_3$, EtOH
23 °C
80%
(150)
(151)
(152)
(153)
(–)-Crinine

Scheme 54

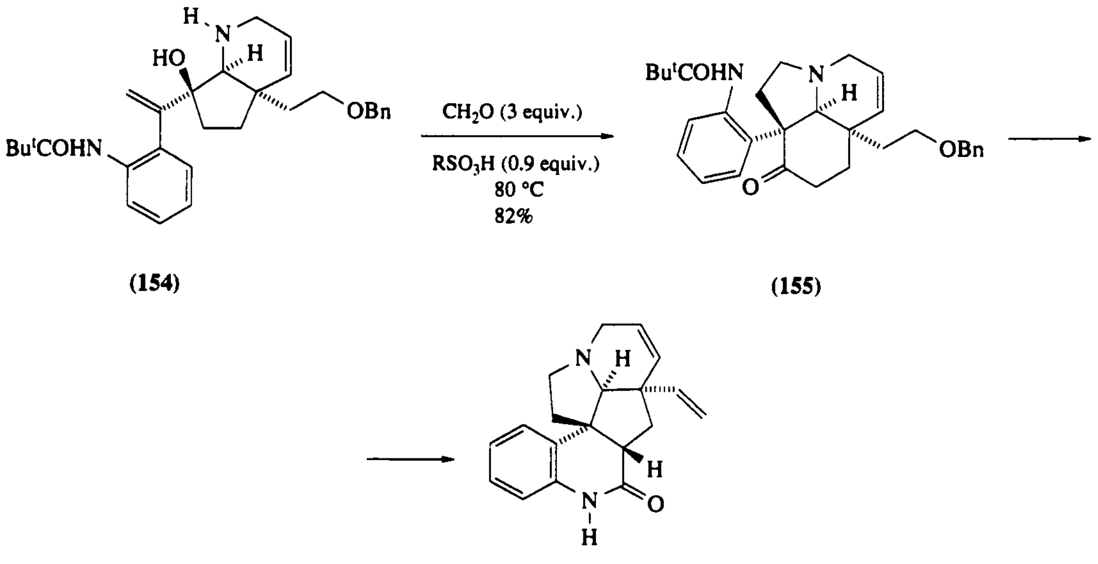
CH$_2$O (3 equiv.)
RSO$_3$H (0.9 equiv.)
80 °C
82%
(154)
(155)
(±)-Meloscine

Scheme 55

Perhaps the best illustration of the utility of tandem aza-Cope rearrangement–Mannich cyclization reactions for assembling complex molecular skeletons is found in the total synthesis of the *Aspidosperma* alkaloid (±)-16-methoxytabersonine (Scheme 56).[115] The crucial step in this synthesis was the high-yielding conversion of aniline (**156**) to 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (**157**), a transformation that stereoselectively develops three of the five rings of the alkaloid target. This reorganization was accomplished by treating (**156**) with paraformaldehyde and anhydrous $Na_2SO_4$ at room temperature to form the corresponding oxazolidine, which was not isolated but directly transformed into (**157**) upon heating in toluene. The authors suggest that the small amount of formic acid present in the paraformaldehyde is sufficient in this case to catalyze the desired molecular rearrangement. Carbon acylation of the lithium derivative of (**157**) then provided (±)-16-methoxytabersonine.

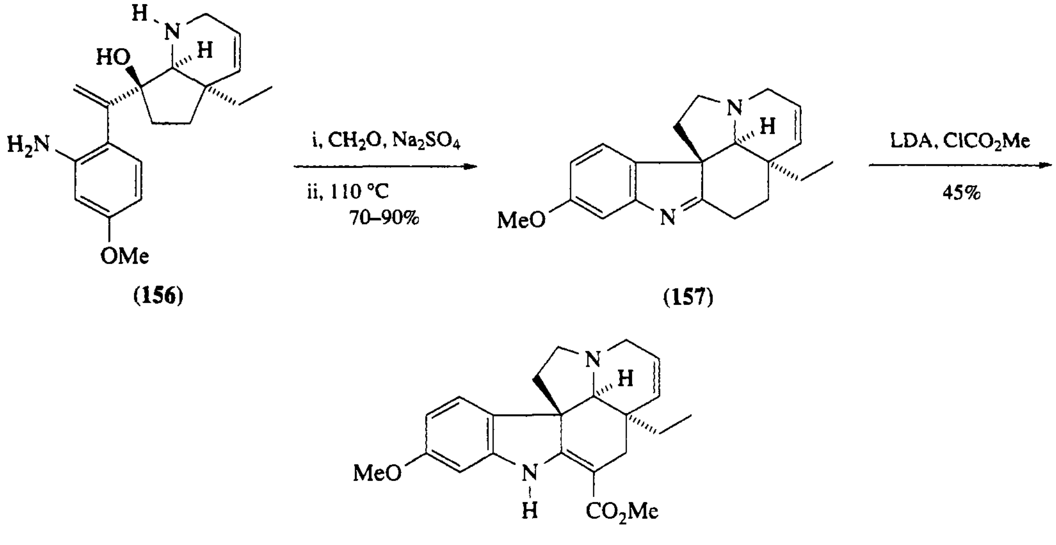

(**156**)

(**157**)

(±)-Methoxytabersonine

**Scheme 56**

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# 4.5

# Additions to *N*-Acyliminium Ions

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## 4.5.1 INTRODUCTION

The addition of strongly polarized carbon–carbon double bonds (enols) to simple iminium ions, known as the Mannich reaction (equation 1), is a fundamentally important route to amines, especially in biosynthetic processes.[1,2] This reaction type is less synthetically useful if weakly polarized or unpolarized carbon–carbon π-bonds are used as nucleophiles (equation 2).[3] Because of the low electrophilic reactivity of the iminium moiety, the reverse reaction, known as the Grob fragmentation (equation 2), is often the more important process.[4] However, if the iminium moiety has a carbonyl substituent on nitrogen, its

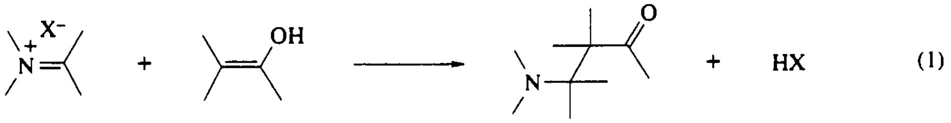

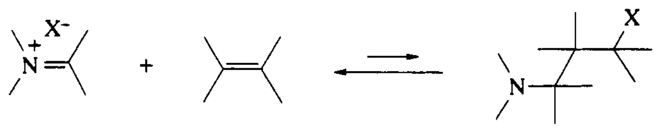

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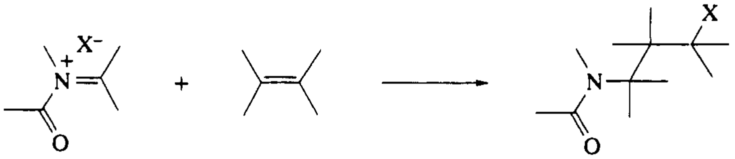

(3)

electrophilicity is strongly enhanced, and reactions with C=C bonds are irreversible and synthetically useful (equation 3).

A number of recent reviews exist about intermolecular[5] and intramolecular reactions[6] of the *N*-acyliminium intermediate. Moreover, detailed accounts of the application in alkaloid synthesis have recently appeared.[7,8] This chapter deals with reactions of species (**1**) with nucleophilic alkenes (and alkynes). Other synthetically useful nucleophiles like aromatic rings, active methylene compounds and organometallics will not be discussed here. In (**1**) R$^1$, R$^2$ and R$^3$ are hydrogen or carbon substituents, and R$^4$ may also be a hetero substituent, such as alkylamino or alkoxy. This chapter differs from previous reviews, as the material is ordered here on the basis of the structural features of the *N*-acyliminium intermediate. Major emphasis is placed on recent developments and stereochemical details.

## 4.5.2 GENERAL ASPECTS

### 4.5.2.1 Methods to Generate *N*-Acyliminium Ions

For synthetic applications the *N*-acyliminium species (**1**) is nearly always generated *in situ* because of its high reactivity. Heterolysis of an acetal-like structure of type (**2**) is a very popular method to effect *N*-acyliminium ion reactions. In most cases X is a hydroxy, alkoxy or acyloxy function and an acidic catalyst is used to generate (**1**). If X is methanesulfonyloxy, no catalyst is required, as thermal conditions suffice to produce the intermediate.[9] If X is methoxy or ethoxy, precursor (**2**) is usually a stable molecule, which allows the execution of diverse reactions under neutral or basic conditions elsewhere in the molecule before the *N*-acyliminium intermediate is employed.

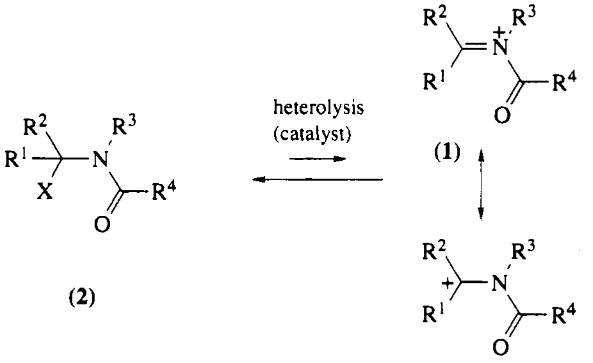

(**2**) (**1**)

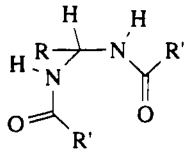

(**3**)

Other X groups in (**2**) that are occasionally used to produce the reactive intermediate (**1**) are chloride, sulfur and nitrogen substituents. Chloride is used for systems that lead to particularly reactive (electrophilic) *N*-acyliminium species, *e.g.* with R$^1$ and R$^2$ hydrogen or with R$^1$ (or R$^2$) a carboxyl function. The latter species can be characterized as glycine cation equivalents and are very useful for the synthesis of α-amino acids.[5] Standard Lewis acids such as $BF_3{\cdot}Et_2O$ and $SnCl_4$ can be used to ionize chloride precursors. The alkyl- or aryl-thio function can be activated as a leaving group in a quite different way to chloride and oxygen leaving groups, which may be beneficial with acid-sensitive substrates like β-lactams. Thus, mercury(II) acetate,[10] chloramine-T[11] and zinc reagents[12] have been used for this purpose, as well as α-diazocarbonyl compounds in the so-called carbenoid displacement reaction.[13] *N*-Acyliminium ion precursors with a nitrogen substituent as leaving group are bisamides, biscarbamates and bisureas (**3**). They are easily prepared from aldehydes and are usually ionized by treatment with a Brønsted acid or $BF_3·Et_2O$.[5]

The ease of formation of (**1**) from (**2**) depends, among other factors, on the nature of the leaving group. The only systematic study pertains to 4-substituted azetidinones, where the order of reactivity Cl > $RCO_2$ > $RSO_2$ > $N_3$ > RO > RS was found for substitution reactions under nonacidic conditions.[14] In an acidic medium this order will very likely be different.

Various methods are available for the preparation of the foregoing precursors to *N*-acyliminium ions. The most straightforward synthesis of *N*-(1-hydroxyalkyl)-amides or -carbamates (**2**; X = OH) involves the addition of primary or secondary amides (carbamates) to aldehydes or ketones. This reaction is an equilibrium process and usually disfavors the adduct except for two special cases. The first involves very reactive aldehydes like formaldehyde, chloral and glyoxylic acid and its esters (equation 4); compounds (**4**)–(**6**) are fairly stable compounds that are frequently used in amidoalkylation reactions.[5,15] The second special case is the intramolecular variant (ring–chain tautomerism), if it leads to five- or six-membered rings (equations 5 and 6). Thus, for *n* = 1 or 2, (**7**) and (**8**) cyclize to (**9**) and (**10**), respectively, although the nature of R has an influence on this process.[5–8,16]

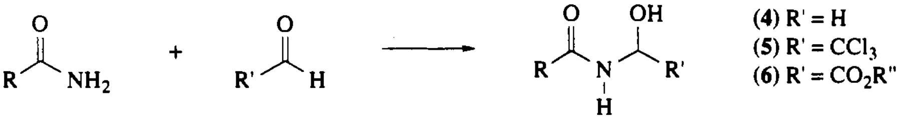

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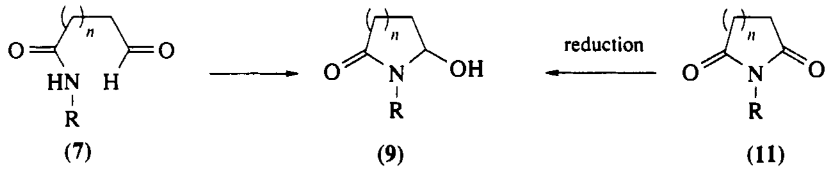

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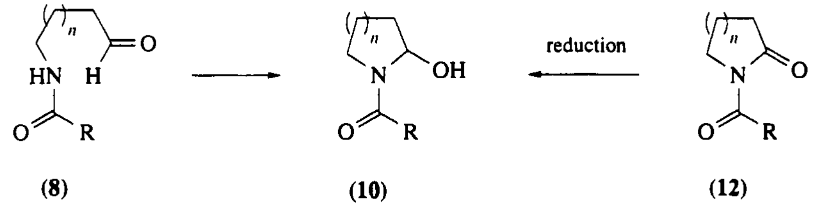

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An alternative method for the preparation of cyclic *N*-(1-hydroxyalkyl)amides (or carbamates) is the partial reduction of cyclic imides (**11**) and (**12**) (equations 5 and 6). The usual reducing agents for this purpose are $NaBH_4$ and DIBAL-H.[17–19] When the $NaBH_4$ reduction is carried out in ethanol solution, addition of acid is usually necessary to obtain good yields.[17] Acid is not required if the reduction is performed in methanol solution with a large excess of $NaBH_4$.[9] Moreover, the reaction temperature for $NaBH_4$ reductions is quite important. Typical temperatures for reductions in ethanol solution are –20 °C for six- and 0 °C for five-membered rings. Higher temperatures give rise to (some) ring-opening, which is irreversible because of further reduction.[17]

Inherent to this reductive method is the problem of regioselectivity. Imide systems in which one carbonyl is part of a carbamate or a urea function (*e.g.* **12**; R = OR′ or $NR'_2$) usually show excellent selectivity for reduction of the other carbonyl group.[7,18] Chemically more symmetrical imides may still provide very high regioselectivity.[20–22] Imides (**13**)–(**18**) are typical examples (the arrows show the carbonyl groups, which are preponderantly or exclusively reduced). Of synthetic relevance is the fact that DIBAL-H and $NaBH_4$ may show opposite regioselectivity.[23] Very recently, the problem of diastereoselective reduction of *meso*-imides has been elegantly solved by using a chiral *N*-substituent. Thus, (**19a**) and (**19b**) are reduced with virtually complete, yet opposite selectivity with $Me_4NHB(OAc)_3$ and L-selectride, respectively.[24]

Addition of Grignard reagents to five- and six-membered systems (**11**) and (**12**) also leads to *N*-acyliminium ion precursors. The products, being tertiary alcohols, are rather susceptible, however, to ring-opening and dehydration, so that their isolation may be problematic. Nevertheless, this methodology has proven highly useful for the synthesis of the amphibian alkaloid histrionicotoxin.[25,26]

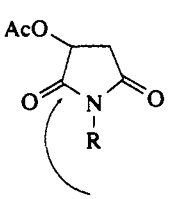

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**(13)**[9,21]

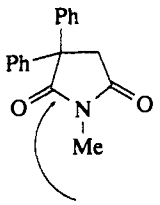

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**(14)**[20]

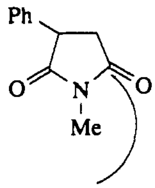

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**(15)**[20]

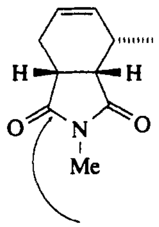

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**(16)**[22]

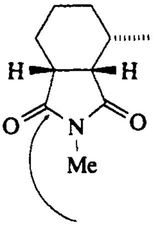

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**(17)**[22]

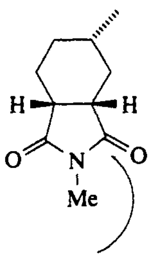

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**(18)**[22]

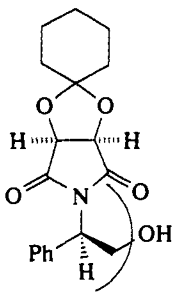

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**(19a)**[23]

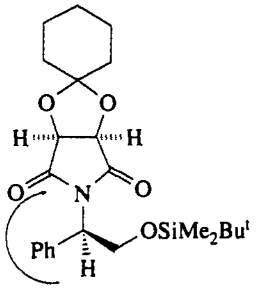

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**(19b)**[23]

*N*-(1-Alkoxyalkyl)-amides or -carbamates (**2**; X = OR), most frequently used as stable precursors for *N*-acyliminium ions, are usually prepared by one of the following routes (equations 7–13). For five- or six-membered cyclic cases a simple acid-catalyzed solvolysis of the hydroxy compound provides the alkoxy derivative (equation 7).[17] A silicon-assisted approach involves the TMSOTf-catalyzed reaction of bis(trimethylsilyl)formamide with aldehydes (equation 8). *N*-(1-Trimethylsilyloxyalkyl)formamides are thus formed in good yields, which on TMSOTf-catalyzed solvolysis lead to the *N*-(1-alkoxyalkyl)formamides.[27] A third method is based on the $NaBH_4$ reduction of imidates (equation 9), and has proved useful for a total synthesis of the insect poison pederine.[28] Addition of reactive acid derivatives to imines constitutes another method (equations 10 and 11). Acylation with acid chlorides followed by treatment with ethanol in the presence of base leads to *N*-(1-alkoxyalkyl)amides.[29–31] A one-step protocol using diethyl dicarbonate provides the corresponding carbamates.[30–32]

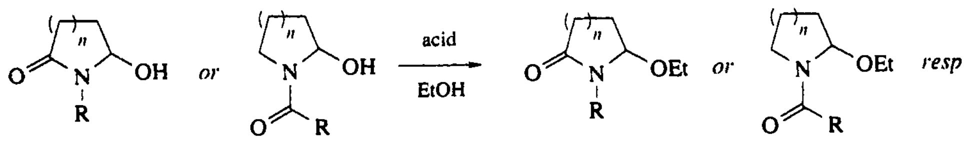

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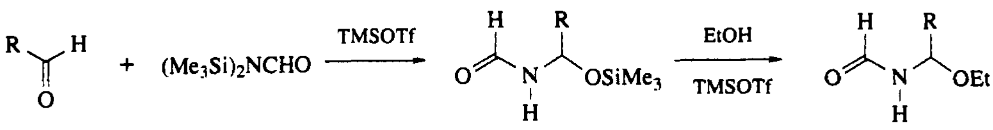

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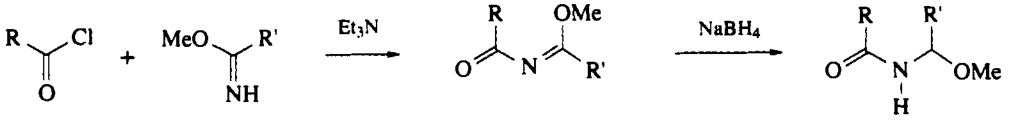

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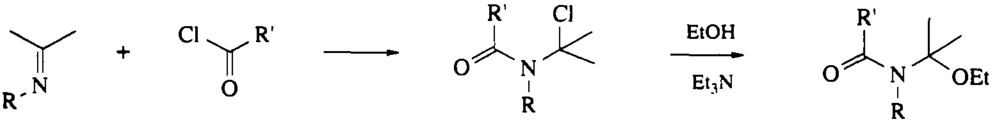

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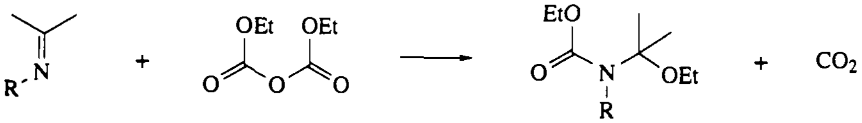
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Two electrochemical methods (equations 12 and 13) deserve special attention.[33,34] The oxidation of amides and carbamates in methanol solution is a very general method (equation 12), applicable to acyclic as well as cyclic systems, varying from four-membered to large rings. Compounds (**20**)–(**26**) are typical products from this process, which is also regioselective in such a way that the least-substituted α-carbon is preferentially oxidized, exemplified with (**25**) and (**26**). *N*-Protected α-amino acid esters are also methoxylated *via* this method.[39] The Kolbe-type decarboxylative electrochemical oxidation of *N*-acylated α-amino acids (equation 13) constitutes a useful synthetic application of (naturally occurring) α-amino acids.[40] This methodology has found several interesting recent applications (equations 14–16).[41–43] Even the sensitive β-lactam ring can be manipulated in high yield to give a useful thienamycin precursor (equation 16).[43]

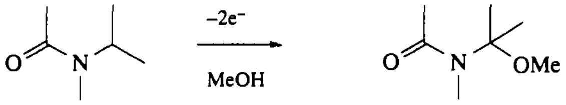

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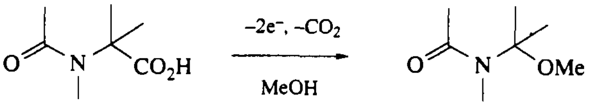

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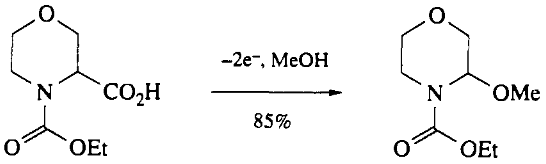

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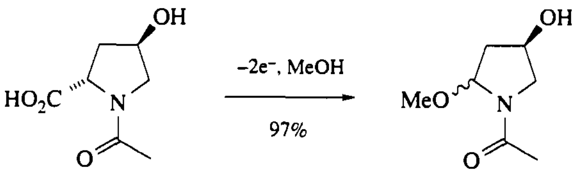

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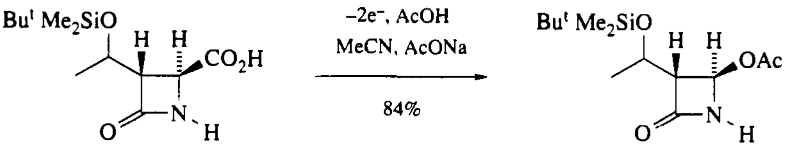

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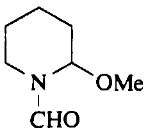
(**20**) 95%[35]

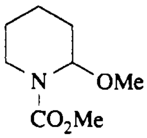
(**21**) 65%[36]

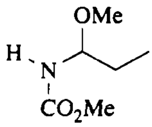
(**22**) 62%[36]

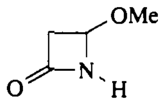
(**23**) 51%[37]

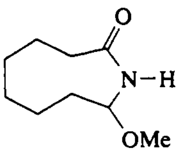

**(24)** 57%[35]

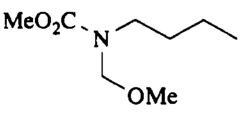

**(25)** 53%[36]

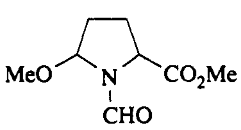
MeO
N
CO$_2$Me
CHO

**(26)** 86%[38]

Various other, more specialized oxidative methods have been developed to synthesize relatively stable *N*-acyliminium ion precursors of type (**2**). To mention a few, free radical mediated oxidation of azetidinones provides 4-benzoyloxy-substituted derivatives (equation 17).[44] A transition metal catalyzed procedure has been described to give a precursor with a *t*-butylperoxy leaving group (equation 18).[45] Important for the synthesis of α-amino acids is the halogenation of glycine equivalents (equations 19–21). The products are precursors to the so-called glycine cation equivalent, which is in fact an *N*-acyliminium intermediate bearing an extra electron-withdrawing carbonyl substituent. These precursors are useful intermediates in the synthesis of both racemic (equation 19)[46] and nonracemic α-amino acids (equations 20 and 21).[47,48]

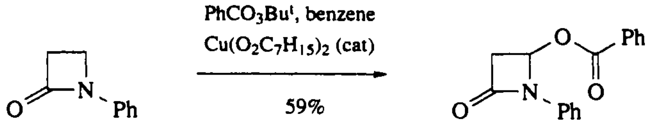
O
N
Ph
PhCO$_3$Bu$^t$, benzene
Cu(O$_2$C$_7$H$_{15}$)$_2$ (cat)
59%
O
Ph
O
O
N
Ph

(17)

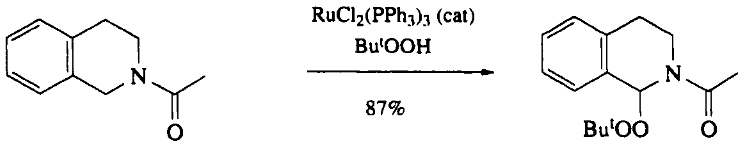
N
O
RuCl$_2$(PPh$_3$)$_3$ (cat)
Bu$^t$OOH
87%
N
Bu$^t$OO
O

(18)

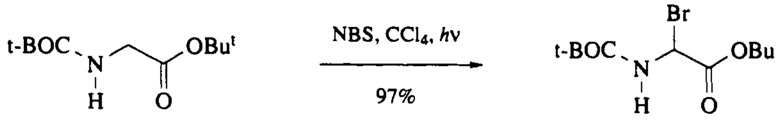
t-BOC
N
H
OBu$^t$
O
NBS, CCl$_4$, *hv*
97%
Br
t-BOC
N
H
OBu$^t$
O

(19)

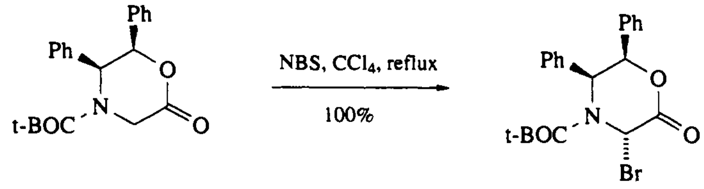
Ph
Ph
O
t-BOC
N
O
NBS, CCl$_4$, reflux
100%
Ph
Ph
O
t-BOC
N
O
Br

(20)

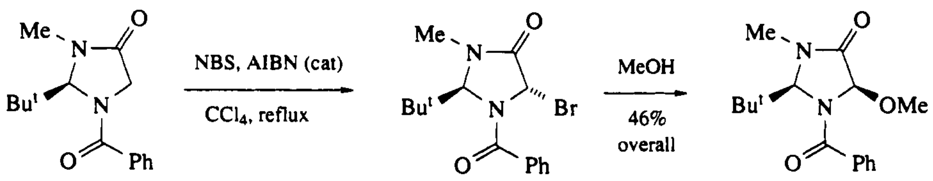
Me
N
O
Bu$^t$
N
O
Ph
NBS, AIBN (cat)
CCl$_4$, reflux
Me
N
O
Bu$^t$
N
Br
O
Ph
MeOH
46%
overall
Me
N
O
Bu$^t$
N
OMe
O
Ph

(21)

In addition to heterolysis of compounds of type (**2**), *N*-acyliminium intermediates (**1**) are also obtained by protonation of *N*-acylimines (**27**) and by protonation of enamides or enecarbamates (**28**). The former method is mainly of theoretical interest,[49] because *N*-acylimines (**27**) are rather unstable compounds. The latter technique is occasionally applied,[50] although compounds (**28**) are usually synthesized through elimination of HX from (**2**).[51] Other preparatively very useful methods for the *in situ* generation of the *N*-acyliminium ion are the acid-mediated coupling of an aldehyde (or ketone) with a primary (or secondary) amide or a nitrile, and the thermal reaction between an acid chloride and an imine.[5]

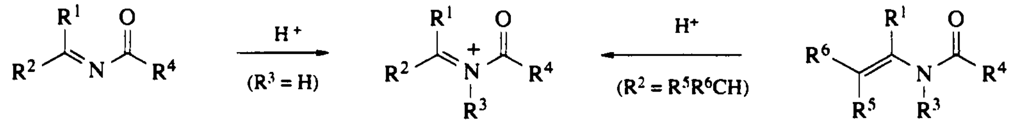

**(27)** **(1)** **(28)**

### 4.5.2.2 Structure *versus* Reactivity

Because of their high reactivity, *N*-acyliminium ions usually occur as transient intermediates in synthetic applications. However, in a few special cases stable *N*-acyliminium salts have been synthesized and characterized.[49,52] Thus, triflate salts (**29**) and (**30**) arise through *N*-protonation of the corresponding acylimines and salt (**31**) is formed as a crystalline colorless solid (m.p. 132–140 °C) through *N*-ethylation of the corresponding acylimine with triethyloxonium hexachloroantimonate. Particularly diagnostic for the structures (**29**) and (**30**) are the $^1$H NMR chemical shifts ($\delta$(NH) = 13.6, $\delta$(CH) = 9.6 p.p.m.) and the coupling constant ($J$ = 16 Hz) of the hydrogens attached to the iminium double bond.[49,52] *Ab initio* calculations on the simple *N*-protonated *N*-methyleneformamide ion indicate, that the *s-cis* form is about 3 kcal mol$^{-1}$ (1 cal = 4.18 J) more stable than the *s-trans* isomer (equation 22).[53] This can be understood by considering the better compensation of the dipole moment vectors of the iminium and the carbonyl bond in the *s-cis* relative to the *s-trans* form. Of course, in highly substituted systems, steric factors may offset this preference for the *s-cis* form.[50]

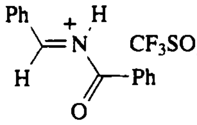

**(29)**

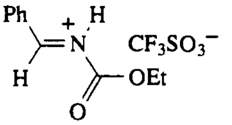

**(30)**

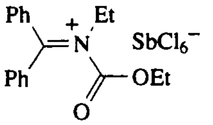

**(31)**

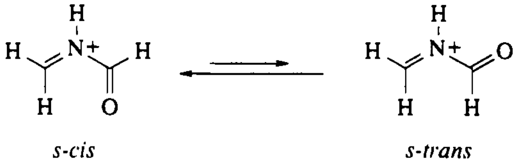

(22)

Elaborate synthetic applications of *N*-acyliminium chemistry usually require mild conditions, so that only a low equilibrium concentration of the reactive intermediate is present. Formation of the *N*-acyliminium ion is probably the rate-determining step in most cases (equation 23).[5,6] This implies that a greater stability of the iminium intermediate leads to a higher reaction rate. This supposition was borne out in one case by competition experiments to determine the relative reactivity of methoxyamides (**32**)–(**35**) towards arylation with 1,3,5-trimethoxybenzene, catalyzed by $AlCl_3$.[54] The order of reactivity (**32**:**33**:**34**:**35** = 30:4.5:1:200) is in good agreement with the expected stability order of the derived *N*-acyliminium ions. Although further data are lacking, one may expect that azetidinone (**36**) is less reactive than (**32**), because of the strain of an iminium double bond in a four-membered ring. Carbamate (**37**), on the other hand, is expected to be more reactive than formamide (**33**) because a carbamate nitrogen lone pair is more available for cation stabilization than an amide nitrogen. Experimental evidence for the latter reactivity difference follows from the cyclization of (**38**), which solely proceeds *via* the carbamate-stabilized cation (equation 24).[55]

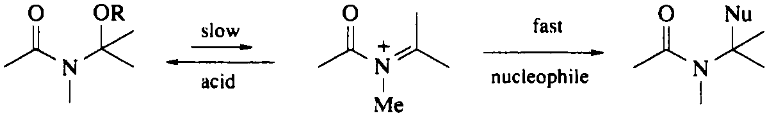

(23)

### 4.5.2.3 Reaction Behavior

For a discussion of the general mechanism of reactions of *N*-Acyliminium intermediates with alkenes (and alkynes) an important distinction has to be made between *N*-acyliminium ions locked in the *s-trans*

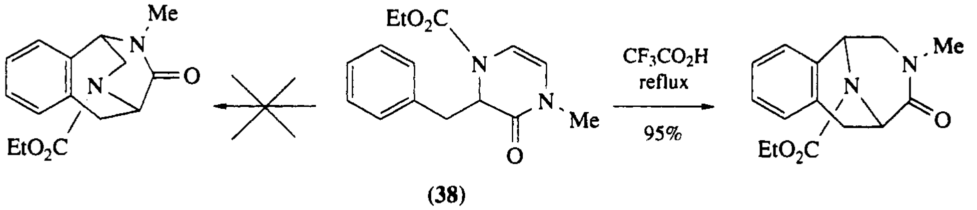

(38)

(24)

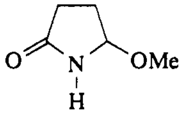

(32)

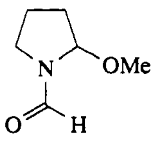

(33)

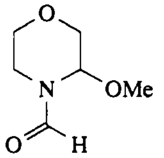

(34)

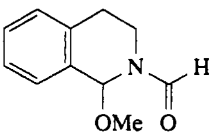

(35)

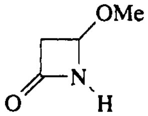

(36)

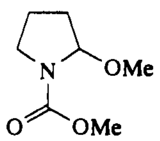

(37)

conformation, and those that (can) adopt the *s-cis* conformation. The former type, represented by cyclic species derived from (**39**)–(**41**), reacts as a (nitrogen-stabilized) carbocation with carbon–carbon multiple bonds. The π-complex theory gives a good description of the mechanistic details of this process.[56] Thus, the *N*-acyliminium ions derived from (**39**)–(**41**) form, in equilibrium processes, π-complexes (**42**)–(**44**), respectively, with chair-like six-membered rings (equations 25–27).[57] In these π-complexes the double bond geometry is retained. Subsequently, formate anion attacks these π-complexes in such a manner that only six-membered rings are formed. Clearly, the strain in the bicyclic π-complexes renders them unsymmetrical. The most positively charged carbon atom of the original alkene is then attacked by formate from behind, leading to high yields of single isomers (**45**) and (**46**). On the contrary, π-complex (**44**) leads to a *ca.* 60:40 mixture of formates (**47**) and (**48**). As the latter isomers do not interconvert under the reaction conditions, a reasonable explanation for the low stereoselectivity of cyclization of (**41**) is the involvement of (classical) tertiary carbocation (**49**).

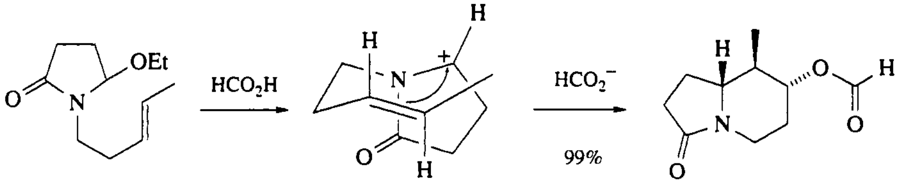

(39) (42) (45)

(25)

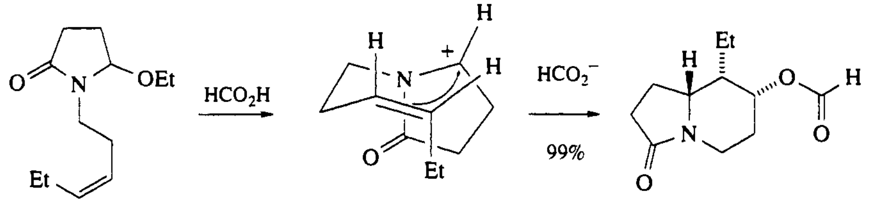

(40) (43) (46)

(26)

For *N*-acyliminium ions that (can) adopt the *s-cis* conformation, the mechanistic picture is quite different. Now the *N*-acyliminium intermediate reacts as a 4π-electron component in a Diels–Alder cycloaddition with inverse electron demand (equation 28).[58–60] This process also shows high regio- and stereo-selectivity in most cases. A nice illustration of high stereospecificity is found in recent work on the intramolecular Diels–Alder reaction of *N*-acyliminium species (equations 29 and 30).[61] The bis-amides (**50**) and (**51**) serve as precursors to the reactive intermediates, which cycloadd to the alkenes with high selectivity to give *trans*-fused bicyclic 5,6-dihydro-1,3-oxazines.

In the case of *N*-acyliminium ions lacking a hydrogen on nitrogen, the Diels–Alder adducts lose their charge in a different way (equations 31 and 32). Thus, carbamate-derived intermediate (**52**) gives 1,3-oxazin-2-one (**53**) as a minor product and the acyclic carbamate (**54**) as the major product.[62] Reaction of the same starting material with the enol silane from acetophenone produces solely the acyclic product (**55**).[63] An interesting mechanistic question pertains to the origin of the acyclic products (**54**) and (**55**). Are these formed *via* a cycloaddition pathway (*via* (**52**) and (**56**), respectively), or do they directly arise from re-

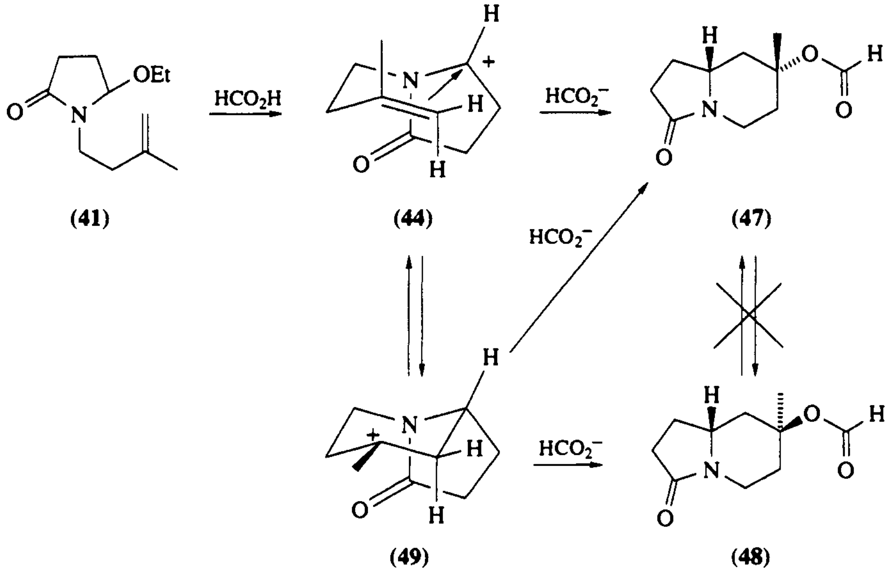
OEt
HCO2H
HCO2⁻
HCO2⁻
HCO2⁻
(41)
(44)
(47)
(49)
(48)

(27)

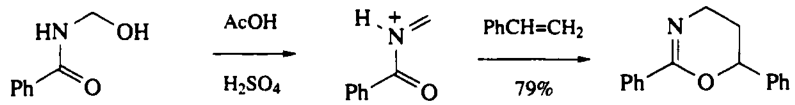
AcOH
H2SO4
PhCH=CH2
79%

(28)

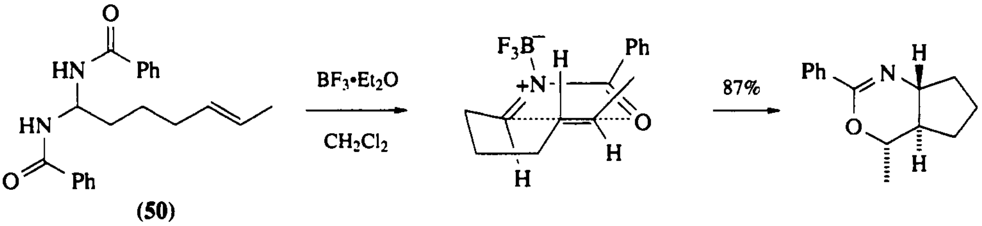
BF3•Et2O
CH2Cl2
87%
(50)

(29)

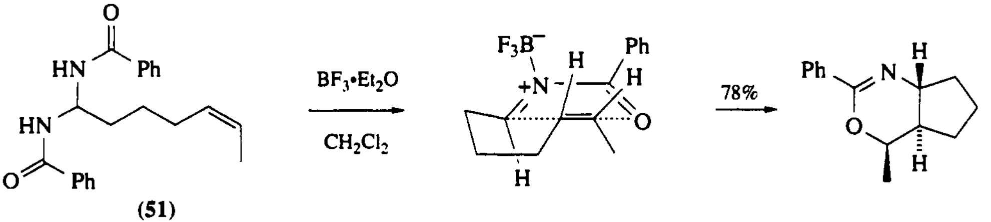
BF3•Et2O
CH2Cl2
78%
(51)

(30)

action of the iminium cation with the carbon–carbon double bond, giving cation (**57**) without mediation of the carbamate carbonyl function? Most probably, the cycloaddition pathway is very general. It should be noted here again that calculations indicate that the *s-cis* form is considerably more stable than the *s-trans* geometry,[53] so that *N*-acyliminium ions usually have the correct geometry for Diels–Alder chemistry.

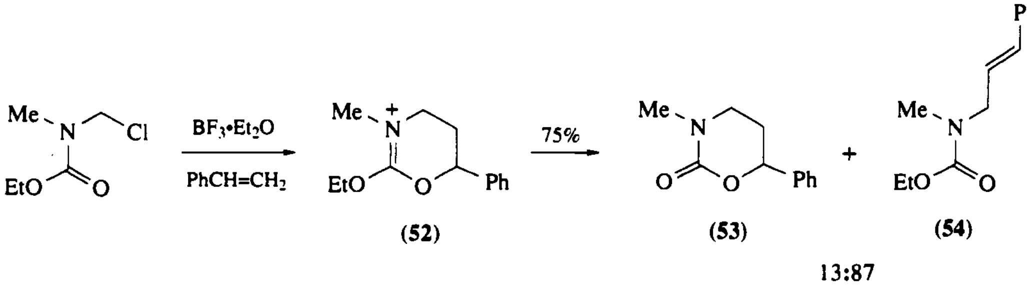
BF3•Et2O
PhCH=CH2
75%
(52)
(53)
(54)
13:87

(31)

*N*-Acyliminium ions may behave as Diels–Alder dienophiles in reactions with conjugated dienes. Thus, biscarbamate (**58**) and cyclohexa-1,3-diene react in the presence of $BF_3{\cdot}Et_2O$ to give cycloadduct

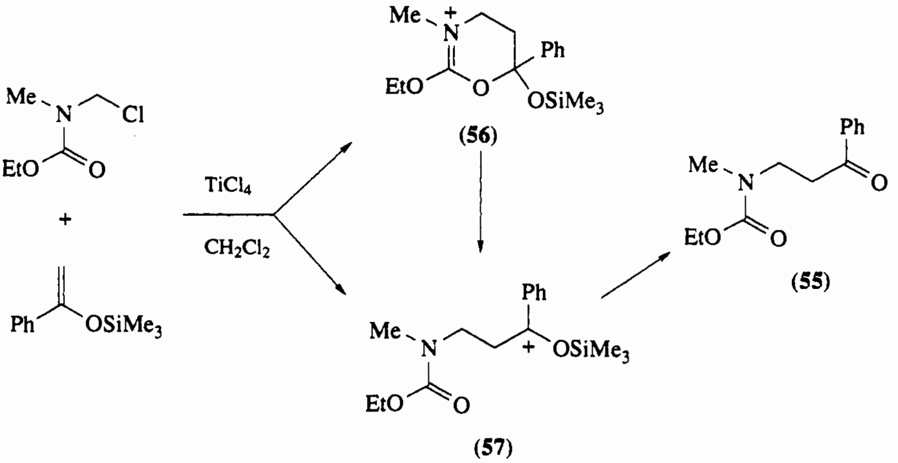

(32)

(**59**) in moderate yield (equation 33).[64] This reaction type has been extensively reviewed and will receive only limited attention here.[65,66]

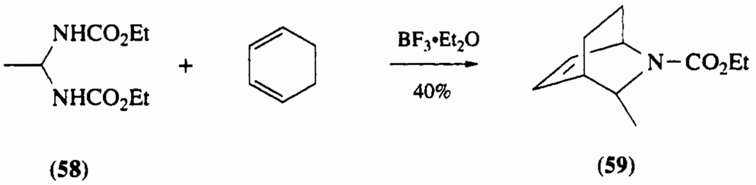

(33)

### 4.5.2.4 Reactivity Compared with Other Electrophilic Species

The greater electrophilicity of the *N*-acyliminium ion as compared with an ordinary iminium ion was nicely illustrated as early as 1957. In experiments directed at the total synthesis of erythrina alkaloids, cyclization of iminium ion (**60**) to the erythrinane skeleton (**61**) fails (equation 34). However, *N*-acyliminium ions (**62**) and (**63**) can both be converted into the desired skeleton in good yields.[67,68] A recent il-

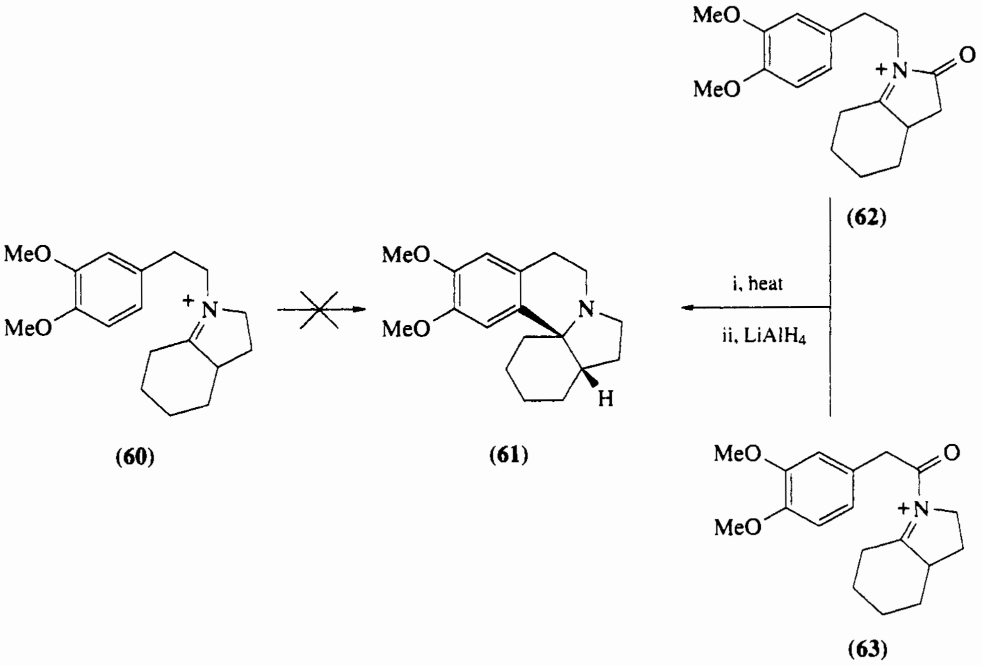

(34)

lustration of this reactivity difference can be found in studies on the use of vinylsilanes as π-nucleophiles (equation 35).[69] Whereas iminium ion (**64**) cannot be cyclized, the *N*-acyliminium species derived from (**65**) undergoes ring closure in refluxing TFA.

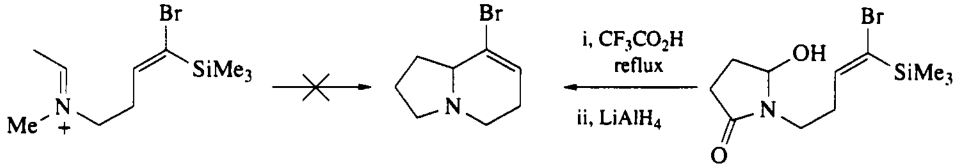

(35)

(**64**) (**65**)

Very recently, the cation-stabilizing ability of a carbamate nitrogen and an oxygen atom were compared.[70] Calculations indicate that *N*-acyliminium ion (**66**) is *ca.* 11 kcal mol$^{-1}$ more stable than oxonium ion (**67**). This difference is confirmed by experiments on oxazoline (**68**). Both Vilsmeier formylation and acid-induced reaction with acetal chloride occur at C-5 (equation 36), indicating a greater charge-donating ability of a carbamate nitrogen compared with an ether oxygen atom.

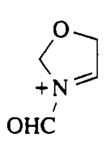

(**66**)

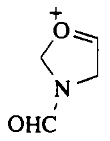

(**67**)

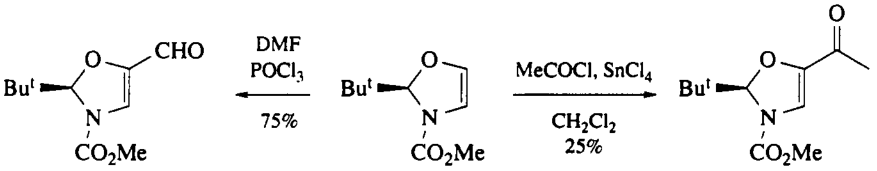

(36)

(**68**)

## 4.5.3 ENDOCYCLIC IMINIUM IONS WITH THE *N*-ACYL GROUP IN THE RING

This section deals with addition reactions to cyclic *N*-acyliminium ions of type (**69**), locked in the *s-trans* conformation. Being unable to participate as a 4π-system in a Diels–Alder type reaction, (**69**) simply reacts as a nitrogen-stabilized carbocation with carbon–carbon multiple bonds. The products can be either the result of addition (**70**) or substitution (**71** and **72**), mainly dependent on the substitution pattern of the nucleophilic multiple bond (equation 37).

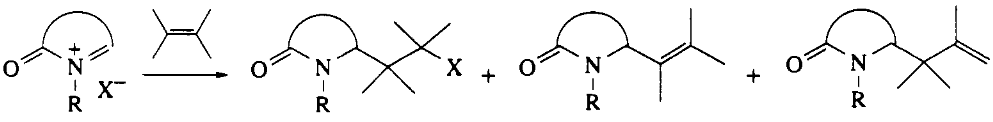

(37)

(**69**) (**70**) (**71**) (**72**)

### 4.5.3.1 Intermolecular Reactions

Intermolecular reactions of species (**69**) with simple alkenes have received little attention. Recently, a study of the reaction of 5-ethoxy-2-pyrrolidinone with several 1,3-dienes in the presence of acid was published.[71] When a mixture of ethoxylactam and 2,3-dimethylbutadiene is stirred in neat formic acid, the formates (**73**) and (**74**) are isolated as the main products in 43% yield. The bicyclic product (**75**) is obtained in only 16% (equation 38). If the reaction is carried out in benzene with *p*-toluenesulfonic acid as catalyst (**75**) is formed in 19% yield. Other dienes show similar behavior, producing bicyclic compounds as byproducts in low to moderate yields except for one or two cases, as illustrated with compounds (**76**)–(**80**) with yields given for reactions in formic acid.[71] The mechanism of these reactions can best be viewed as a stepwise process with the *N*-acyliminium ion as the first intermediate (equation 39). It is rather unclear which factors determine the ratio of mono- and bi-cyclic products.

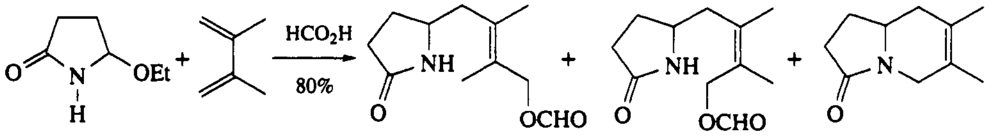
OEt
HCO2H
80%
NH
OCHO
N
O
H

(**73**) (**74**) (**75**)

(38)

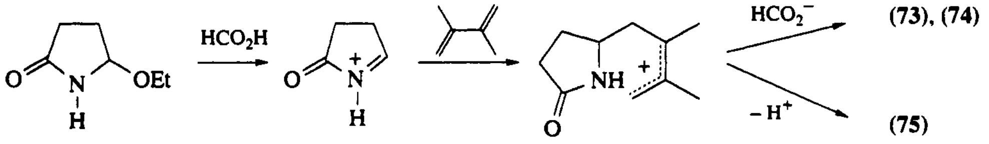
OEt
HCO2H
NH
HCO2−
(73), (74)
−H+
(75)

(39)

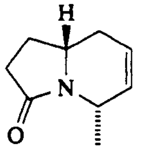
(**76**) 11%

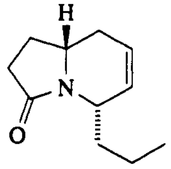
(**77**) 20%

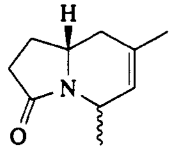
(**78**) 70%

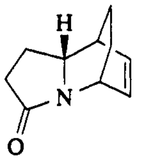
(**79**) 40%

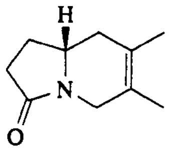
(**80**) 16%

The above reaction type was also applied to the acetoxyazetidinone (**81**).[72] Heating of (**81**) with diene (**82**) and ZnCl$_2$ in acetonitrile at reflux gives *ca.* 60% of (formal) cycloadduct (**83**) as a single *trans* stereoisomer (equation 40). From (**83**) the carbapenam skeleton was readily prepared in three steps. The reaction was repeated for silyloxydiene (**84**) in order to gain access to the more potent 1β-methyl analog of thienamycin.[73] In refluxing acetonitrile the monocycle (**86**) is formed as the major product (equation 41).

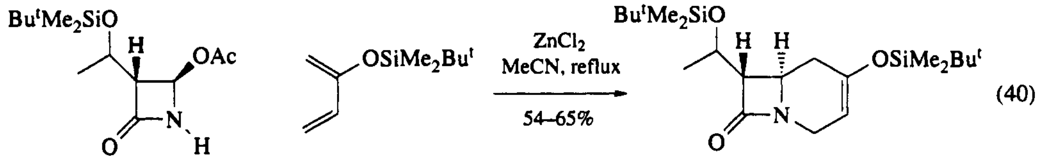
Bu$^t$Me$_2$SiO
H
OAc
N
H
O
OSiMe$_2$Bu$^t$
ZnCl$_2$
MeCN, reflux
54–65%
H H

(**81**) (**82**) (**83**)

(40)

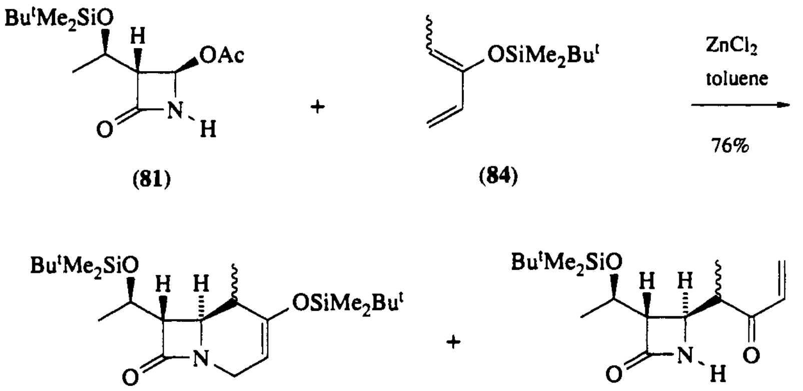
Bu$^t$Me$_2$SiO
H
OAc
N
H
O
+
OSiMe$_2$Bu$^t$
ZnCl$_2$
toluene
76%
H H
(81)
(84)

(**85**) 85:15 (**86**)

(41)

It was finally found that simply changing the solvent to toluene produces bicyclic (**85**) in *ca.* 65% yield as a 70:30 mixture of β- to α-methyl isomers. This isomer ratio well reflects the isomer ratio of the diene, but the diene unfortunately isomerizes under the reaction conditions. The stereospecificity of the formation of (**85**) as well as the success in an apolar solvent points to a more or less concerted cycloaddition pathway.[65]

Lewis acid induced coupling of enolsilanes and ketene acetals with 4-acetoxyazetidinones is an excellent method to introduce a carbon substituent at the 4-position of the β-lactam ring. This reaction tolerates various different substituents on nitrogen (equations 42–44),[74,75] but electron-withdrawing groups lower the yield.[75] Intermediates for the synthesis of 1β-methylcarbapenems can be readily prepared *via* this method[76,77] with remarkably high stereoselectivity in some cases (equation 45[77]). Very high stereoselectivity is also attained by using tin(II) or boron enolates, derived from enantiomerically pure carboximides (equations 46 and 47). Apparently, the conformationally well defined enolates (**87**) and (**88**) highly favor one specific mode of approach of the *N*-acyliminium intermediate.[78-80] Further mechanistic evidence is obtained by starting from simple 4-acetoxyazetidinone[81] or 5-acetoxypyrrolidinone.[82] The prochiral *N*-acyliminium intermediate in (**89**) is functionalized α to nitrogen to give (**90**) with a selectivity of *ca.* 95% (equation 48). The attractive interaction between the imine nitrogen atom and Sn$^{II}$ is important, as follows from the stereochemical result of a similar reaction with 1-methyl- 5-acetoxypyrrolidinone, which gives the opposite ring stereochemistry as compared to (**90**), albeit with somewhat lower selectivity.[83]

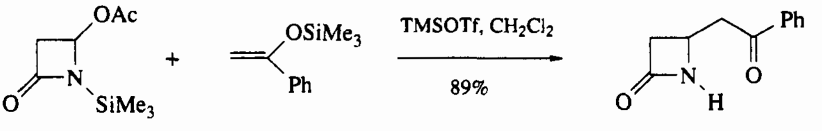
OAc
N
SiMe3
O
+
OSiMe3
Ph
TMSOTf, CH2Cl2
89%
Ph
N
H
O
O

(42)

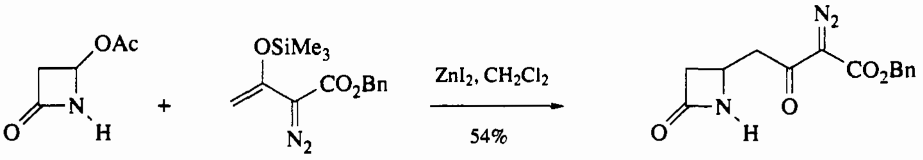
OAc
N
H
O
+
OSiMe3
CO2Bn
N2
ZnI2, CH2Cl2
54%
N2
CO2Bn
N
H
O
O

(43)

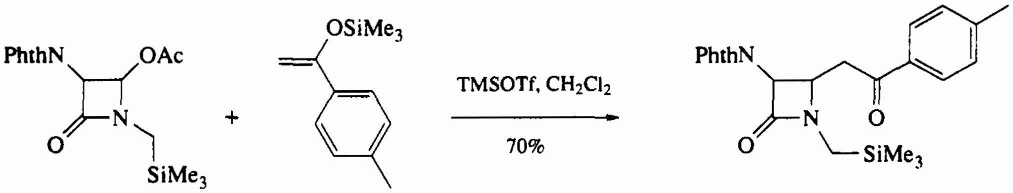
PhthN
OAc
N
O
SiMe3
+
OSiMe3
TMSOTf, CH2Cl2
70%
PhthN
N
O
O
SiMe3

(44)

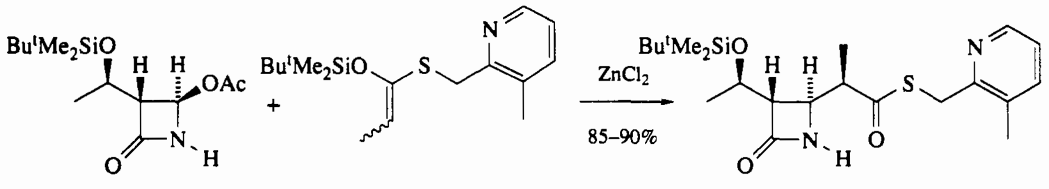
ButMe2SiO
H H
OAc
N
H
O
+
ButMe2SiO
S
N
ZnCl2
85–90%
ButMe2SiO
H H
S
N
N
H
O
O

(45)

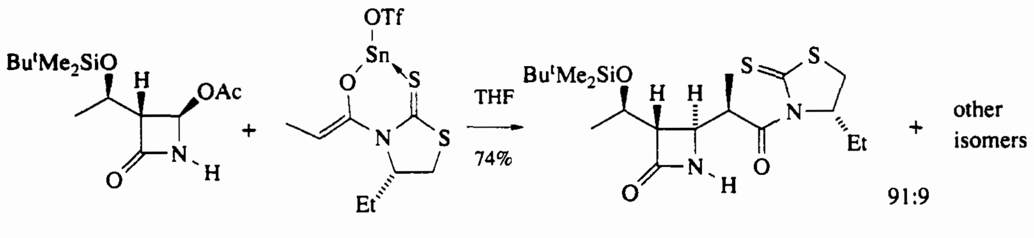
ButMe2SiO
H
OAc
N
H
O
+
OTf
Sn
O
S
N
S
Et
THF
74%
ButMe2SiO
H H
S
S
N
Et
N
H
O
O
+
other
isomers
91:9

(**87**)

(46)

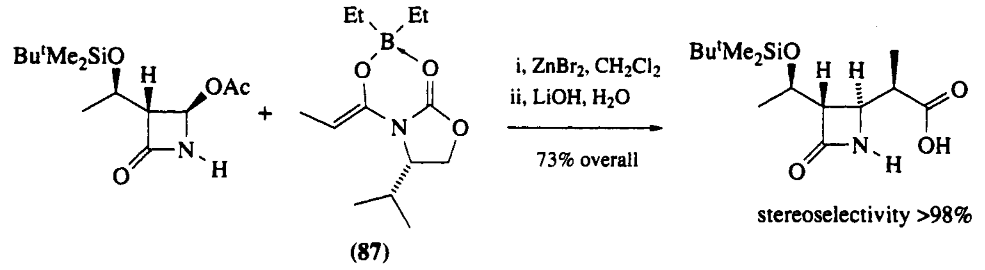
Bu^tMe2SiO
H
OAc
N
H
O
Et
Et
B
O
O
N
O
(87)
i, ZnBr2, CH2Cl2
ii, LiOH, H2O
73% overall
Bu^tMe2SiO
H
H
O
OH
N
H
O
stereoselectivity >98%

(47)

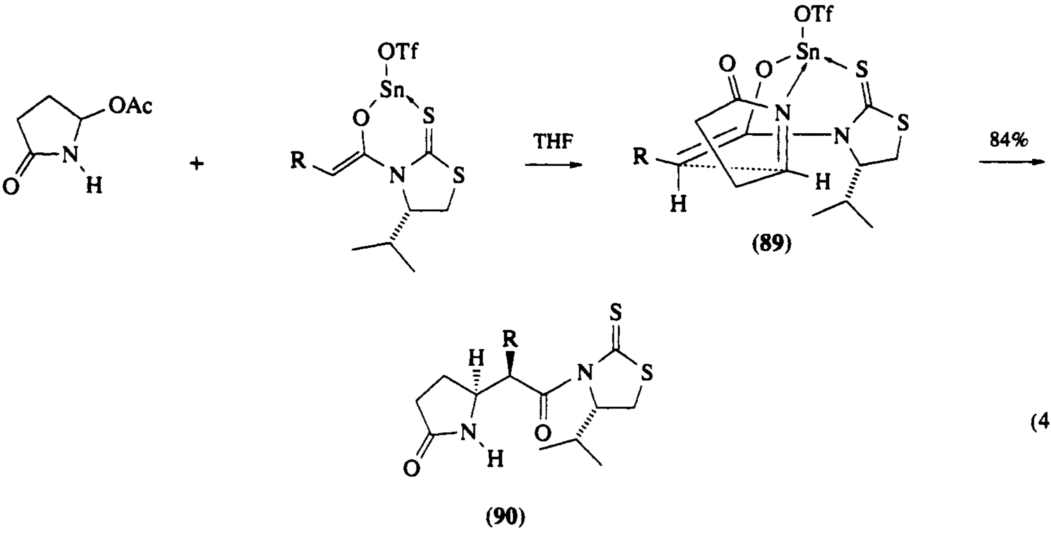
OAc
N
H
O
OTf
Sn
O
S
R
N
S
THF
OTf
Sn
O
O
S
N
N
S
R
H
H
(89)
84%
S
R
H
N
S
N
H
O
O
(90)

(48)

Acid-induced reactions of silicon-containing unsaturated compounds with *N*-acyliminium intermediates have proven particularly useful. Allylsilanes lead to the corresponding allyl-substituted products.[84,85] This reaction proceeds well even for β-lactams (equation 49).[85,86] The penicillin-derived 4-acetoxyazetidinone (**91**) reacts with excess allylsilane in refluxing dichloroethane, catalyzed by TMSOTf, to produce as the sole product *trans* compound (**92**).[86] *N*-Acyliminium ions generated from cyclic ureas[87] and carbamates (**93**)[88] likewise yield allylated products with virtually complete *trans* stereoselectivity (equation 50). Allylstannanes react under somewhat milder conditions than allylsilanes, requiring only a catalytic amount of $BF_3Z{\cdot}Et_2O$ at room temperature for a β-lactam system (equation 51).[89] This allylstannane procedure was applied to cyclic carbamate systems for the stereoselective synthesis of several isomers of statine.[90,91] Thus, ethoxycarbamate (**94**) reacts with methallyltributylstannane in excellent yield and diastereoselectivity (equation 52).[91]

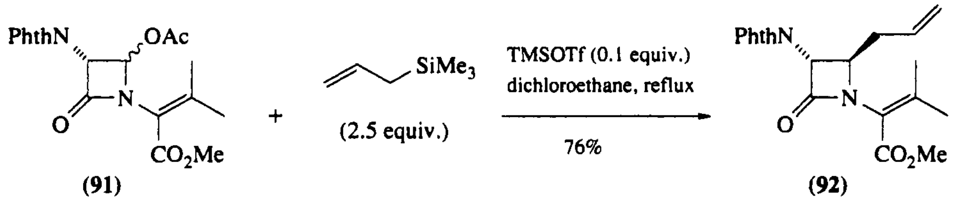
PhthN
OAc
N
O
CO2Me
(91)
SiMe3
(2.5 equiv.)
TMSOTf (0.1 equiv.)
dichloroethane, reflux
76%
PhthN
N
O
CO2Me
(92)

(49)

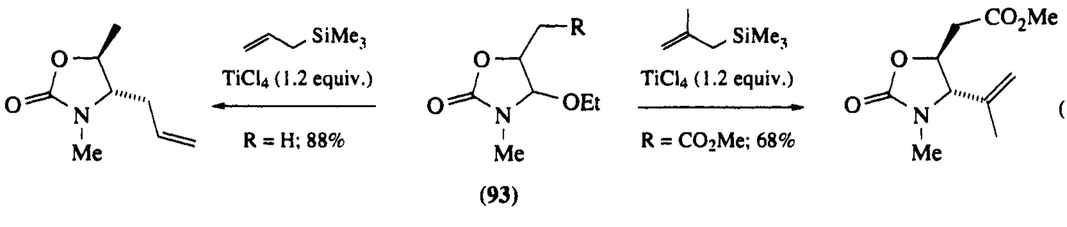
O
O
N
Me
SiMe3
TiCl4 (1.2 equiv.)
R = H; 88%
R
O
O
N
OEt
Me
(93)
SiMe3
TiCl4 (1.2 equiv.)
R = CO2Me; 68%
CO2Me
O
O
N
Me

(50)

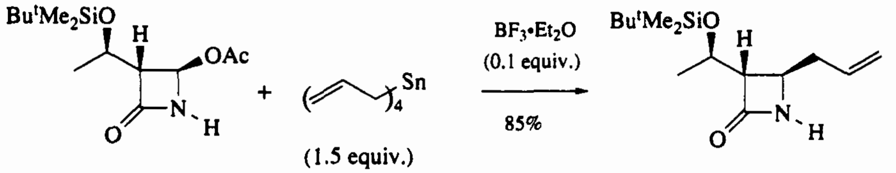
Bu<sup>t</sup>Me2SiO
H
OAc
N
H
O
Sn
4
(1.5 equiv.)
BF3•Et2O
(0.1 equiv.)
85%

(51)

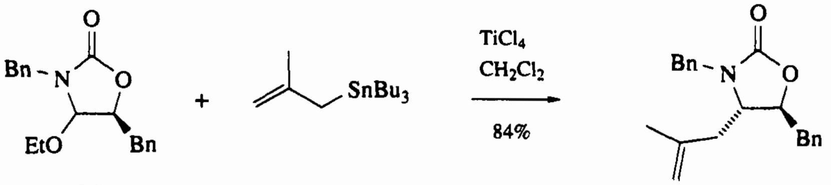
Bn
N
O
O
EtO
Bn
SnBu3
TiCl4
CH2Cl2
84%

(94)

(52)

An intriguing tandem *N*-acyliminium process occurs when allylsilane reacts with *N,N*-bis(alkoxyalkyl)amides under the influence of $TiCl_4$ (equation 53).[92] The initially formed substitution product cyclizes after generation of a second *N*-acyliminium ion in an addition process with chloride acting as nucleophile.

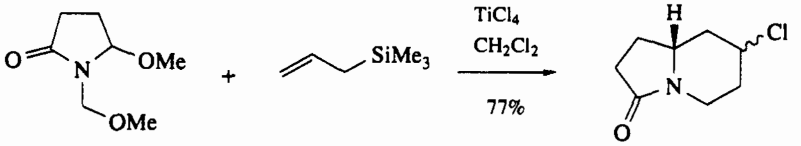
O
N
OMe
OMe
SiMe3
TiCl4
CH2Cl2
77%
H
Cl
N
O

(53)

Propargyltrimethylsilanes give allenyl derivatives on reaction with *N*-acyliminium precursors.[93,94] On the other hand, application of allenyl-silanes or -stannanes provides access to propargyl-substituted lactams.[95,96] All reactions proceed with high regio- and stereo-selectivity (equations 54 and 55). 4-Allenylazetidinones can be cyclized to $\Delta^1$-carbapenem systems, mediated by Ag or Pd salts.[94,96] The reactions of ethoxylactams with allenylsilanes can be modified in such a way that bicyclic systems are obtained in one step (equation 56).[95]

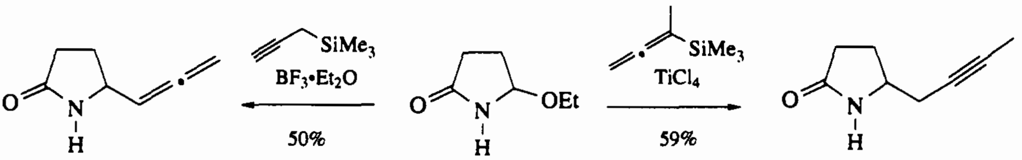
SiMe3
BF3•Et2O
50%
OEt
SiMe3
TiCl4
59%
O
N
H

(54)

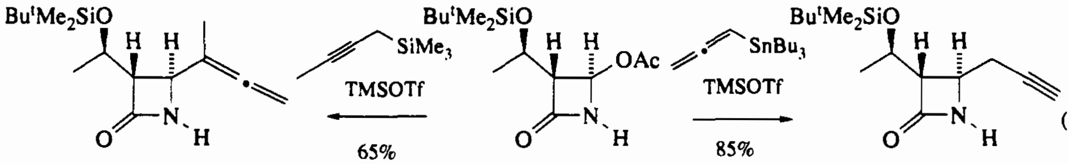
Bu<sup>t</sup>Me2SiO
H H
N
H
O
SiMe3
TMSOTf
65%
OAc
SnBu3
TMSOTf
85%

(55)

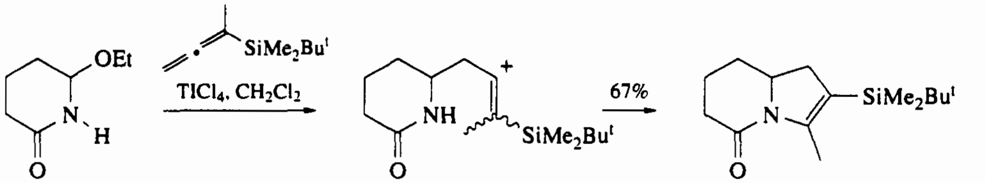
OEt
N
H
O
SiMe2Bu<sup>t</sup>
TiCl4, CH2Cl2
NH
+
SiMe2Bu<sup>t</sup>
67%
N
SiMe2Bu<sup>t</sup>

(56)

### 4.5.3.2 Intramolecular Reactions

#### *4.5.3.2.1 Nucleophiles tethered to nitrogen*

Intramolecular reactions of species (**69**) with simple alkenes have been of great importance in the field of *N*-acyliminium chemistry.[6] In Section 4.4.2.2, the mechanistic principles of *N*-acyliminium cyclizations using these π-nucleophiles have already been treated. If the carbon–carbon double bond tethered to the nitrogen atom does not have an electronic bias, a considerable preference exists for the formation of a six-membered ring by way of a chair-like transition state.[57] Some recent applications of this reaction type are the preparation of bicyclic imidazolidin-2-ones (equation 57)[97] and a cyclization reaction proceeding *via* a tertiary *N*-acyliminium intermediate generated by protonation of an enamide (equation 58).[98] A third example (equation 59) leads to a bicyclic system that apparently prefers proton loss instead of formation of a tertiary formate.[99]

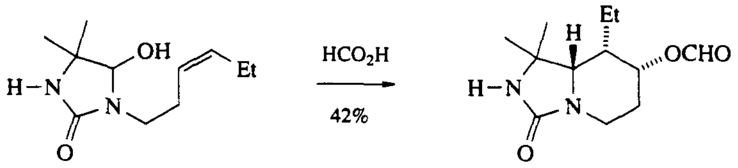

(57)

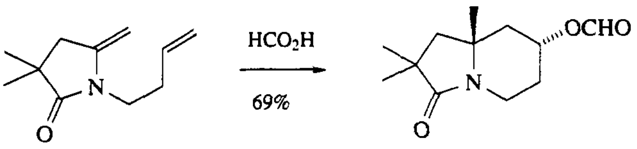

(58)

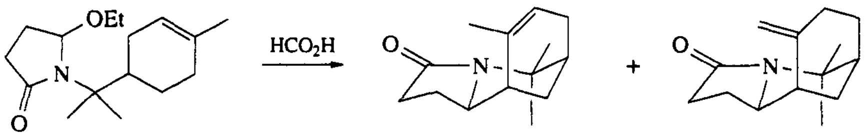

(59)

With alkynes the regiochemical outcome is subject to more subtle factors as is illustrated with the formic acid induced cyclization of two homologous hydroxylactams (equation 60). Starting from a pyrrolidinone, mainly six-membered ring formation occurs, whereas annulation onto a piperidinone ring leads mainly to the five-membered ring.[100] Important factors are the greater stability of linear *versus* bent vinyl cation character, which appears to be important for $n = 2$, and the lesser strain in a [4.3.0] compared to a [3.3.0] bicyclic system, which is dominant for $n = 1$. Terminal alkynes, biased for cyclization in the endo-dig mode, can be used for the preparation of macrocyclic rings (equation 61).[101]

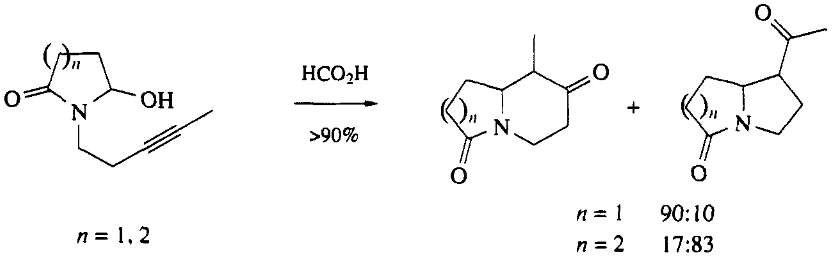

(60)

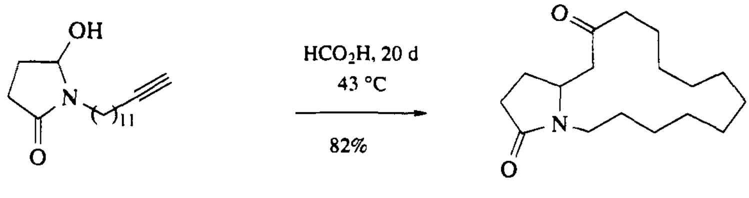

(61)

The effect of stereogenic centers along the chain connecting the π-nucleophile and the iminium moiety has been studied (equation 62 and 63). Hydroxylactam (**95**) cyclizes *via* a π-complex with the methyl group disposed equatorially in a chair geometry.[102] On the other hand, a substituent adjacent to nitrogen as in (**96**) prefers an axial orientation in order to avoid pseudo-allylic strain between the substituent and the lactam carbonyl group.[103] An interesting aspect becomes obvious when other substituents are present in the connecting chain (equation 64). The occurrence of a cationic aza-Cope equilibrium between (**97**) and (**98**) follows from the fact that with appropriate substituents $R^1$ and $R^2$ high yields of pyrrolizidines (**99**) instead of indolizidines (**100**) are obtained.[104,105] Pyrrolizidines are major products if both substituents are methyl groups, and if one is hydrogen and the other is aryl or methoxy. Such substituents clearly stabilize (**98**) relative to (**97**), so the equilibrium shifts to (**98**). Because the alkene is electronically biased with these substituents a five-membered ring (**99**) is preferentially formed. An elaborate application of this chemistry is the highly selective synthesis of (**101**) en route to a pyrrolizidine alkaloid (equation 65).[104] Alkynes also give rise to rearrangement (equation 66), which is obvious from the allenic product.[106] Apparently, the π-cyclization of both *N*-acyliminium ions is slower than hydrolysis of the rearranged species.

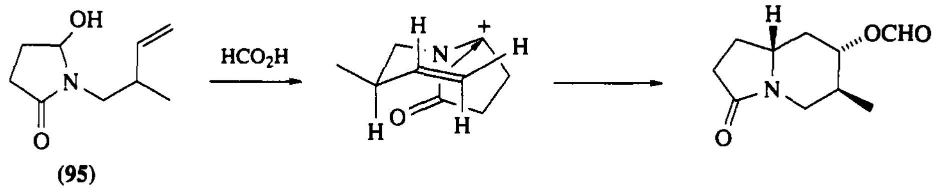
OH
N
O
(95)
HCO2H
H
+
N
H
O
H
H
H
OCHO
N
O

(62)

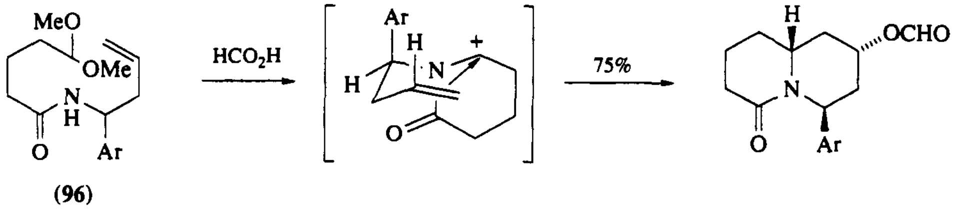
MeO
OMe
N
H
O
Ar
(96)
HCO2H
Ar
H
+
N
H
O
75%
H
OCHO
N
O
Ar

(63)

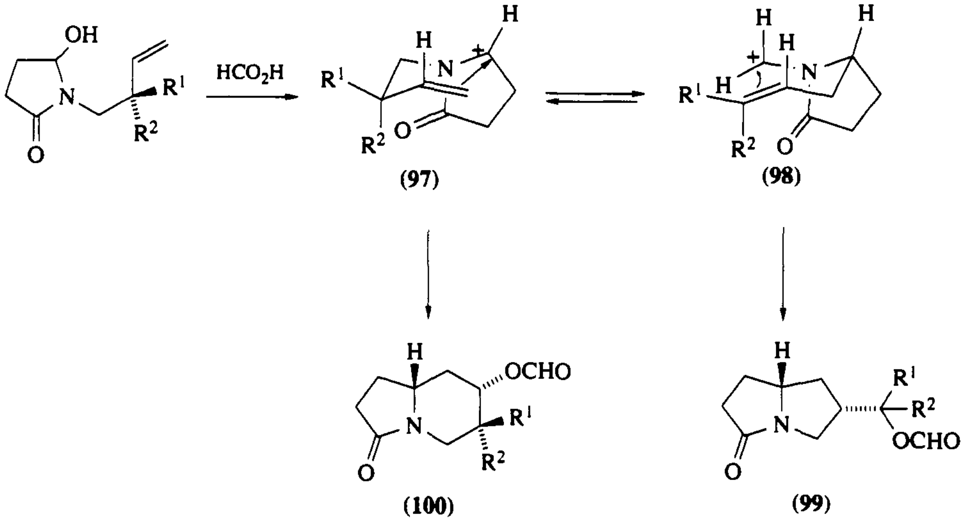
OH
N
O
R1
R2
HCO2H
H
H
+
N
R1
R2
O
(97)
H
H
H
+
N
R1
H
R2
O
(98)
H
OCHO
N
O
R1
R2
(100)
H
N
O
R1
R2
OCHO
(99)

(64)

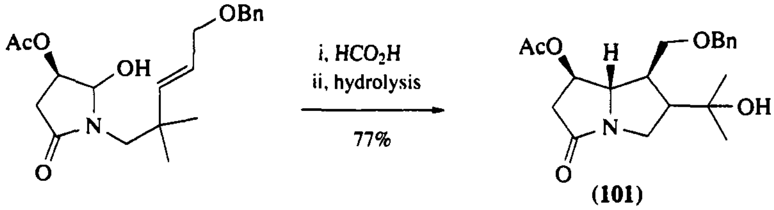
OBn
AcO
OH
N
O
i, HCO2H
ii, hydrolysis
77%
AcO
H
OBn
OH
N
O
(101)

(65)

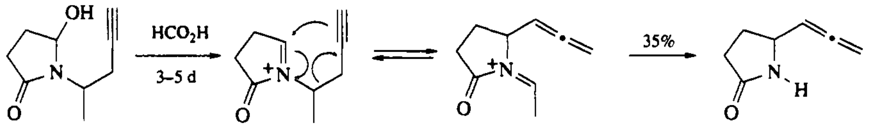

(66)

Special substituents have been introduced onto the alkene in order to direct the cyclization reaction to five-membered formation. Examples of electronically biased alkenes for this purpose are vinyl chlorides,[107] allylsilanes,[108] allylstannanes[109] and ketene thioacetals.[9] The cyclization of allyl-silanes and -stannanes to the pyrrolizidine system is highly stereoselective.[108,109] The chair geometry of π-complex (**102**) explains this selectivity (equation 67).

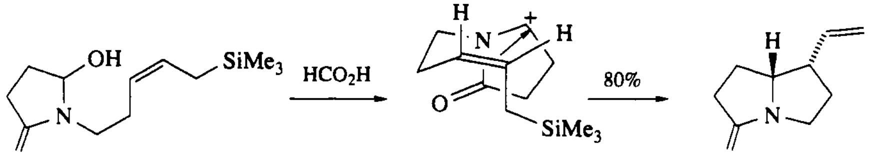

(**102**)

(67)

Vinylsilanes and enol ethers are also useful as π-nucleophiles. A vinylsilane cyclization is an important step in a synthesis of (+)-streptazoline from tartaric acid (equation 68).[110] This reaction also nicely illustrates the high *trans* stereoselectivity of cyclization with respect to the C-4 oxygen substituent.[9] The use of enol ethers is exemplified by two special cases (equations 69 and 70). The keto amide (**103**) is converted into tetracyclic (**104**) in a one-pot procedure involving (**105**) as a key intermediate.[111] A remarkable process is the quantitative cyclization of enone (**106**), despite the low nucleophilicity of an enone double bond (equation 70).[112] The most likely mechanism involves enol ether (**107**). It must be added that the conditions, saturated methanolic HCl, are crucial for the success of this reaction.

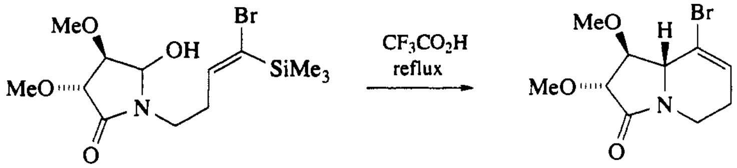

(68)

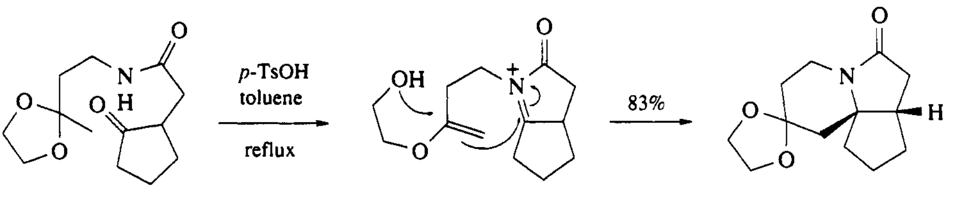

(**103**) (**105**) (**104**)

(69)

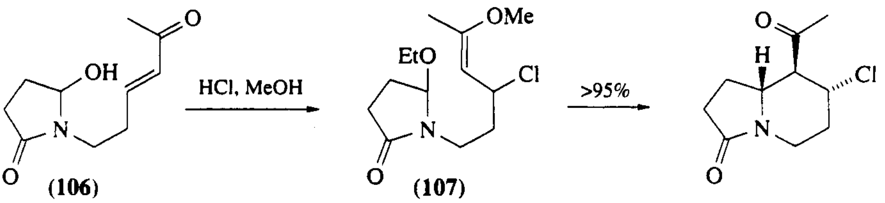

(**106**) (**107**)

(70)

### 4.5.3.2.2 *Nucleophiles tethered otherwise to the* N*-acyliminium moiety*

If the carbon chain containing the nucleophile is not attached to nitrogen, the preference for six-membered ring formation is less pronounced. This is apparent from the spirocyclizations utilized for the synthesis of perhydrohistrionicotoxin (equation 71).[25,26] The tertiary *N*-acyliminium ion derived from (**108**) cyclizes to a mixture of (**109**) and (**110**). Surprisingly, the amount of five-membered ring product (**110**) is much higher for X = O than for X = $CH_2$. Cyclizations of *N*-acyliminium precursors in which the nucleophile is connected to the carbon atom adjacent to the carbonyl function proceed very well, if the more reactive allyl- or propargyl-silanes are employed.[113,114] These reactions lead to bridged systems, containing a vinyl or an allenyl function, respectively (equations 72 and 73). The starting materials are readily synthesized through alkylation of the lithium enolate derived from a simple ethoxylactam. This methodology is used for the synthesis of (–)-peduncularine from (*S*)-malic acid (equation 74).[115] Another type of cyclization precursor, utilized for the total synthesis of mesembrine, bears the nucleophile-containing chain at the carbon adjacent to the iminium carbon atom (equation 75).[116] Ring closure in this case is effected through heterolysis of a mesylate. The final example forms part of a synthetic approach to gelsemine and involves the use of a triisopropylsilyl enol ether as nucleophile (equation 76).[117] A special aspect of this process is its high stereospecificity. The (*E*)-enol ether (**111**) produces aldehyde (**112**) in *ca.* 90% yield, whereas the (*Z*)-isomer yields (**113**) with similar selectivity.

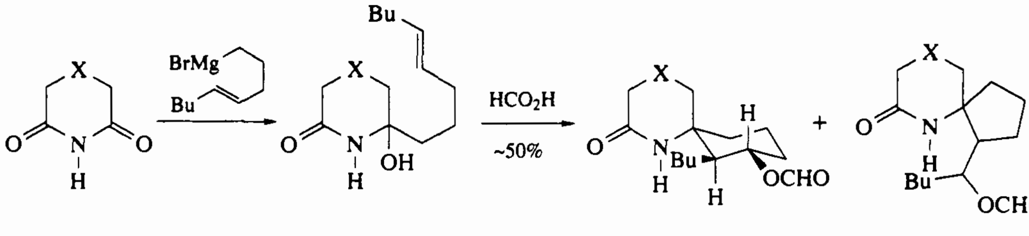
X
O
N
H
O
BrMg
Bu
Bu
X
O
N
H
OH
HCO₂H
~50%
X
O
N
H
Bu
H
H
OCHO
+
X
O
N
H
Bu
OCHO

**(108)** **(109)** **(110)**

(71)

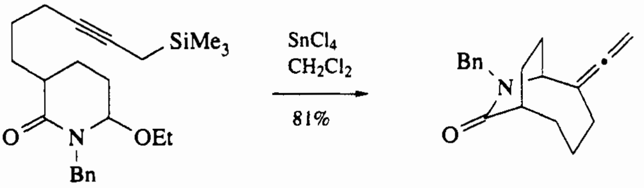
SiMe₃
O
N
Bn
OEt
SnCl₄
CH₂Cl₂
81%
Bn
N
O

(72)

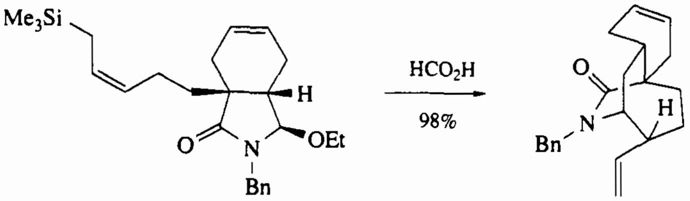
Me₃Si
H
O
N
Bn
OEt
HCO₂H
98%
O
N
Bn
H

(73)

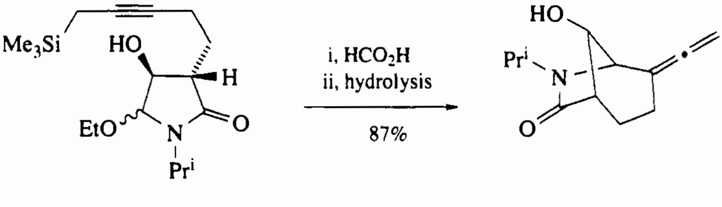
Me₃Si
HO
H
EtO
N
Prⁱ
O
i, HCO₂H
ii, hydrolysis
87%
HO
Prⁱ
N
O

(74)

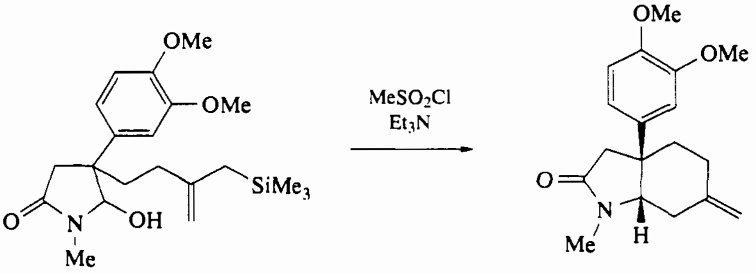
OMe
OMe
O
N
Me
OH
SiMe₃
MeSO₂Cl
Et₃N
OMe
OMe
O
N
Me
H

(75)

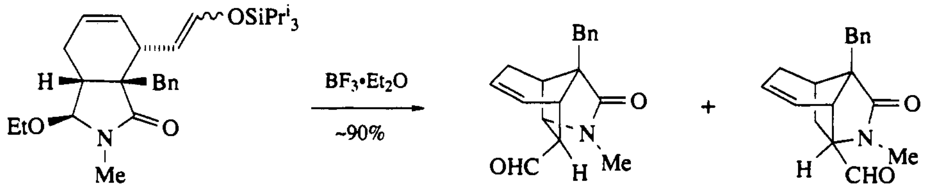
OSiPr$^i_3$
H
Bn
EtO
N
O
Me
BF$_3$•Et$_2$O
~90%
Bn
O
N
OHC
H
Me
+
Bn
O
N
Me
H
CHO

**(111)** **(112)** **(113)**

(76)

### 4.5.4 ENDOCYCLIC IMINIUM IONS WITH THE *N*-ACYL GROUP OUTSIDE THE RING

*N*-Acyliminium ions of this type can adopt the *s-cis* conformation (equation 77), so that Diels–Alder type cycloadducts might be expected on reaction with carbon–carbon multiple bonds. Although they may be intermediates, such cycloadducts have not been isolated thus far, mainly because of the type of π-nucleophile used in these reactions.

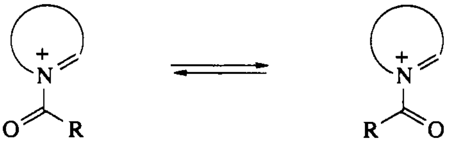

(77)

#### 4.5.4.1 Intermolecular Reactions

Highly nucleophilic alkenes such as enol silanes and enol acetates react very well with this class of iminium ions (equation 78).[118] Slightly more than stoichiometric amounts of $TiCl_4$ or $BF_3{\cdot}Et_2O$ give the best results, and carbamates provide higher yields than amides.[118] The presence of an ester substituent at C-2 of the pyrrolidine system leads to a 70:30 mixture of products with the *cis* isomer in excess (equation 79).[119] Remarkably, a silyloxy substituent at C-4 gives rise to a highly stereoselective reaction with allylsilane, producing the *cis* product in greater than 97% selectivity (equation 80).[120] The origin of this large preference for formation of the *cis* product is unclear. The presence of an acetoxy function adjacent to the iminium carbon atom gives a surprisingly low selectivity in the allylation reaction (equations 81 and 82).[121] Similar reactions in the piperidine system are attended with high selectivity. Thus, an ester substituent at C-2 imparts high preference for *cis* attack in reactions at C-6 (equation 83).[119,122] This is in agreement with the expectation that the C-2 carbomethoxy function is axially disposed and addition at C-6 takes place from an axial direction. Less readily understood is the observation that a C-5 hydroxy func-

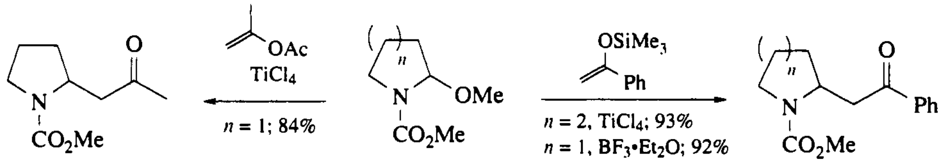
O
N
CO$_2$Me
OAc
TiCl$_4$
n = 1; 84%
n
N
OMe
CO$_2$Me
OSiMe$_3$
Ph
n = 2, TiCl$_4$; 93%
n = 1, BF$_3$•Et$_2$O; 92%
n
N
O
Ph
CO$_2$Me

(78)

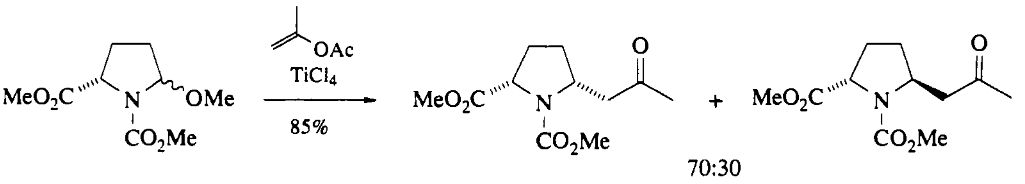
MeO$_2$C
N
OMe
CO$_2$Me
OAc
TiCl$_4$
85%
MeO$_2$C
N
O
CO$_2$Me
+
MeO$_2$C
N
O
CO$_2$Me
70:30

(79)

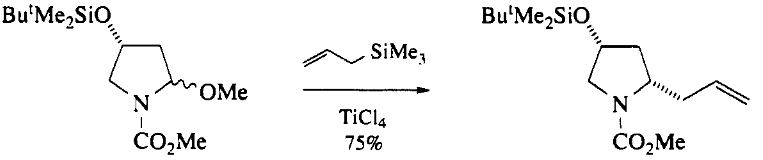
Bu$^t$Me$_2$SiO
N
OMe
CO$_2$Me
SiMe$_3$
TiCl$_4$
75%
Bu$^t$Me$_2$SiO
N
CO$_2$Me

(80)

tion directs allylation at C-2 to occur in a *trans* fashion (equation 84).[123] The oxazolidine (**114**), readily derived from serine, leads mainly to the *cis* product on reaction with allylsilane (equation 85).[124]

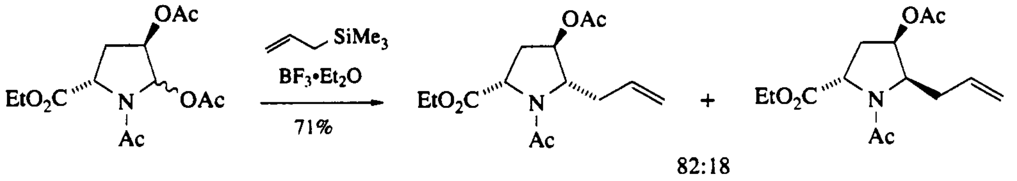
SiMe₃
BF₃•Et₂O
71%
82:18

(81)

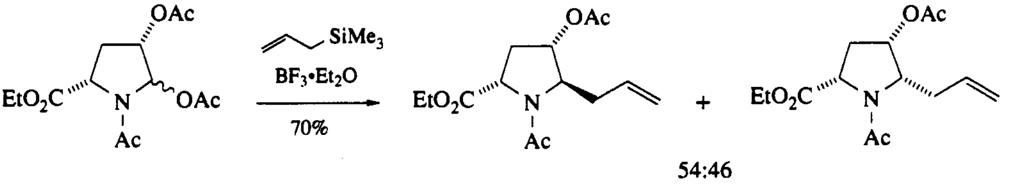
SiMe₃
BF₃•Et₂O
70%
54:46

(82)

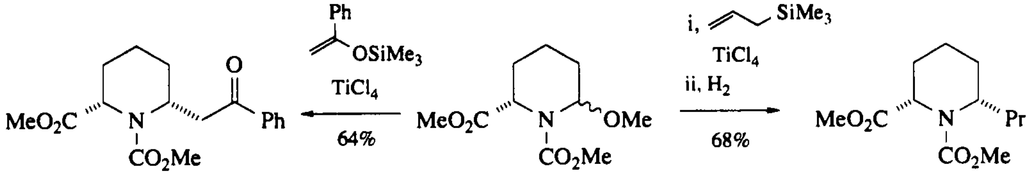
OSiMe₃
TiCl₄
64%
i, SiMe₃
TiCl₄
ii, H₂
68%

(83)

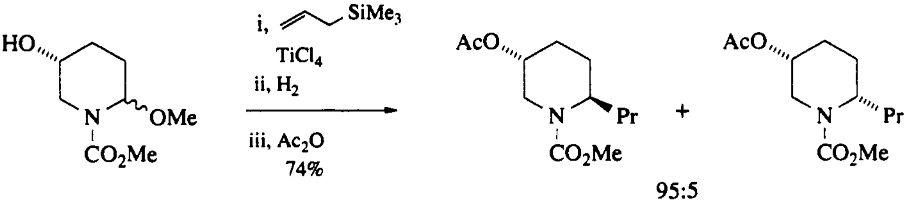
i, SiMe₃
TiCl₄
ii, H₂
iii, Ac₂O
74%
95:5

(84)

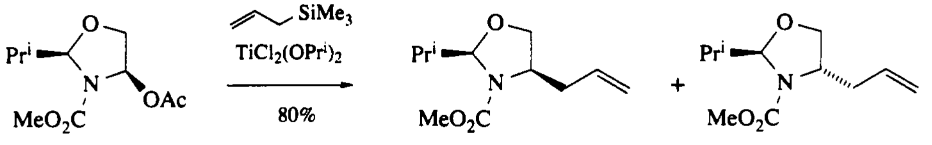
SiMe₃
TiCl₂(OPrⁱ)₂
80%
80:20

(85)

(**114**)

Chirality in the *N*-acyl substituent can also induce stereoselectivity in the iminium addition process (equation 86).[50] The chiral auxiliary in (**115**) appears to be one of the best chiral inductors and reacts with the silyl enol ether from acetophenone in 90% diastereoselectivity. It is argued that the *N*-acyliminium intermediate in this reaction adopts the *s-trans* conformation.[50] Similar methodology is used for the asymmetric synthesis of tetrahydroisoquinolines (equation 87).[125] The reactive intermediate is generated through hydride abstraction from the amide by using the triphenylmethane cation.

*N*-Acyliminium ions, generated from imines by acylation, are trapped in a one-pot reaction with reactive π-nucleophiles like allylstannanes[126] and enol silanes (equation 88).[127] Thus, β-dihydrocarboline

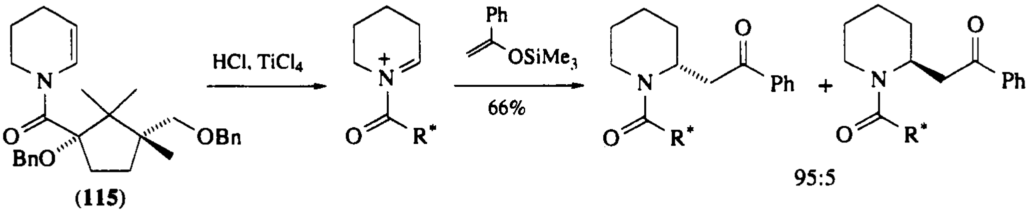
HCl, TiCl₄
OSiMe₃
66%
95:5

(86)

(**115**)

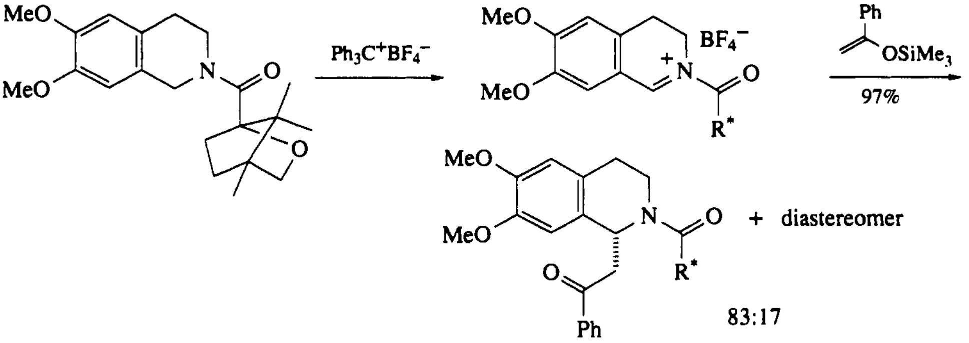
MeO
MeO
N
O
O
$Ph_3C^+BF_4^-$
$BF_4^-$
+
R*
Ph
OSiMe$_3$
97%
+ diastereomer
Ph
83:17

(87)

reacts with crotonyl chloride in the presence of a dienol silane to produce (**116**) in good yield.[127] This methodology is useful for the synthesis of alkaloids.

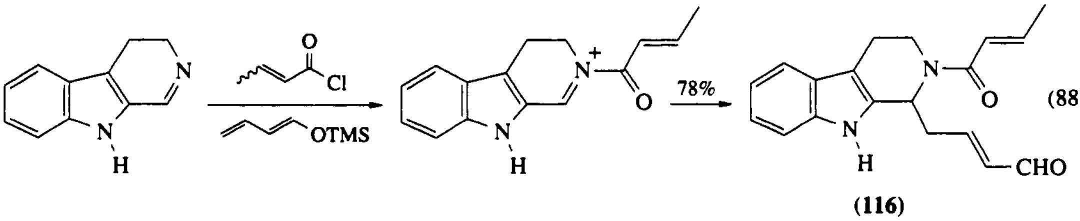
N
N
H
O
Cl
OTMS
+
78%
CHO

(88)

**(116)**

*N*-Acyliminium ions conjugated with an alkene have received particular attention in six-membered rings and are usually prepared from pyridines. Alcohol (**117**) gives on treatment with Lewis acid the delocalized species (**118**), which reacts with allylsilane to produce the 2-substituted product (**119**) as a single regioisomer (equation 89).[128] A different method to generate such reactive intermediates consists of the treatment of dihydropyridines with singlet oxygen, followed by tin(II) chloride (functioning both as reducing agent and Lewis acid) in the presence of a π-nucleophile (equation 90).[129] The reaction with oxygen is very stereoselective and the addition to the iminium species gives mainly the 2,6-*cis* product, exemplified by the reaction with 1-(trimethylsilyl)oxybuta-1,3-diene (equation 90).[130] Another example of this methodology (equation 91) features a simple silyl enol ether as nucleophile and a methyl group at C-5. The nucleophile again enters mainly *cis* with respect to the methyl substituent.[131]

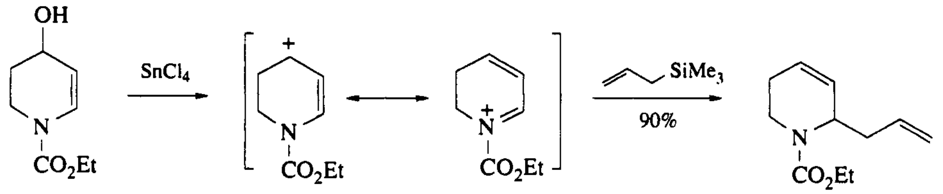
OH
N
CO$_2$Et
SnCl$_4$
+
CO$_2$Et
CO$_2$Et
SiMe$_3$
90%
CO$_2$Et

(89)

**(117)** **(118)** **(119)**

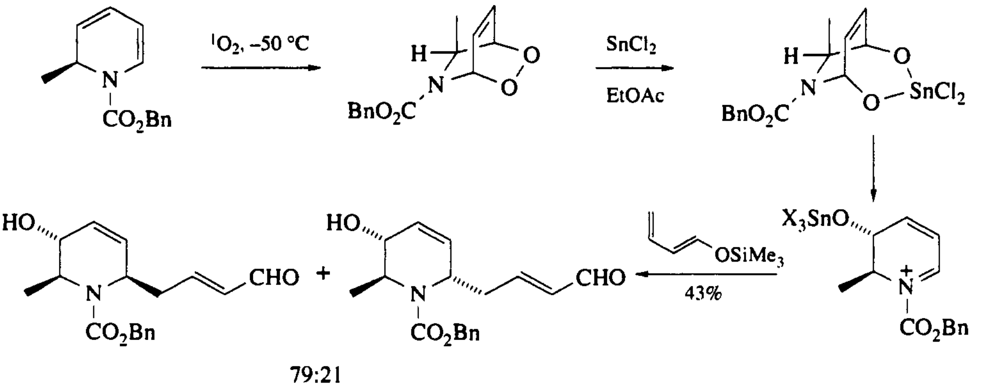
N
CO$_2$Bn
$^1O_2$, −50 °C
H
O
O
N
BnO$_2$C
SnCl$_2$
EtOAc
SnCl$_2$
X$_3$SnO
CO$_2$Bn
OSiMe$_3$
43%
HO
CHO
+
79:21

(90)

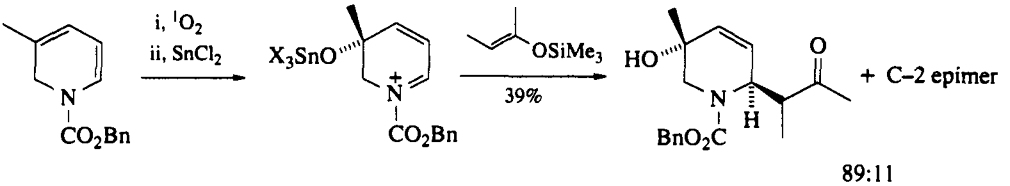
i, $^1O_2$
ii, $SnCl_2$
CO2Bn
X3SnO
CO2Bn
OSiMe3
39%
HO
BnO2C
H
O
+ C-2 epimer
89:11

(91)

If the nitrogen atom in the *N*-acyliminium precursor is flanked by two methoxy groups, two consecutive carbon–carbon bond-forming reactions can occur (equations 92 and 93). Piperidine derivative (**120**) reacts with allylsilane under the influence of $TiCl_4$ to produce azabicycle (**121**) in one step, probably *via* intermediate (**122**).[92] Likewise, pyrrolidine (**123**) directly leads to bicycle (**124**), which is useful for the synthesis of anatoxin-a.[132]

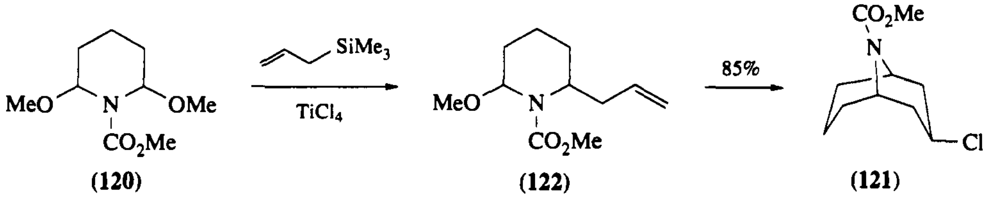
MeO
N
OMe
CO2Me
(120)
SiMe3
TiCl4
MeO
N
CO2Me
(122)
85%
CO2Me
N
Cl
(121)

(92)

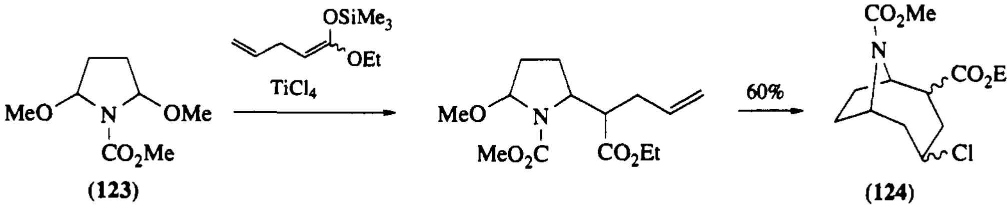
MeO
N
OMe
CO2Me
(123)
OSiMe3
OEt
TiCl4
MeO
N
MeO2C
CO2Et
60%
CO2Me
N
CO2Et
Cl
(124)

(93)

### 4.5.4.2 Intramolecular Reactions

This reaction type is useful for the synthesis of tropane-like azabicycles (equations 94 and 95). Allyl- and propargyl-silanes are excellent nucleophiles in this process.[133] Enone (**125**) is probably first transformed into an enol ether (*cf.* equation 70) before it cyclizes to the homotropane skeleton, which is eventually isolated as a mixture of enone (**126**) and chloride (**127**).[134]

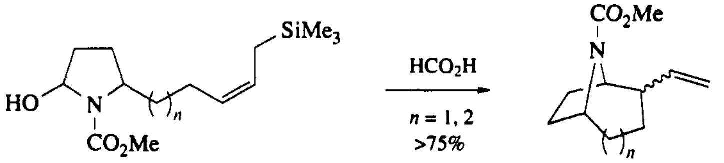
SiMe3
HO
N
n
CO2Me
HCO2H
n = 1, 2
>75%
CO2Me
N
n

(94)

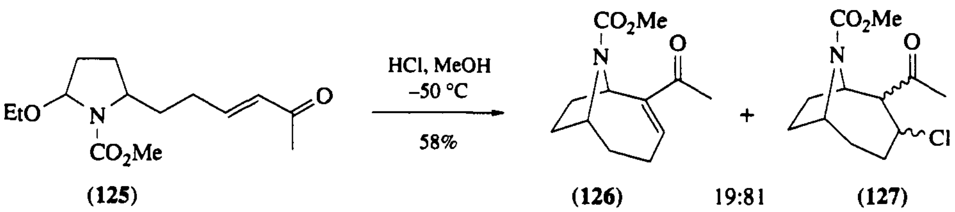
EtO
N
O
CO2Me
(125)
HCl, MeOH
-50 °C
58%
CO2Me
N
O
(126)
+
19:81
CO2Me
N
O
Cl
(127)

(95)

Two more complex examples of this reaction type are used in work on the total synthesis of quinocarcin and gelsemine. A vinyl sulfide is employed as nucleophile in an *N*-acyliminium cyclization to produce the bridged substructure of quinocarcin (equation 96).[135] A genuine equivalent of the Mannich reaction is put to practice in a synthetic approach to gelsemine (equation 97).[136] The iminium intermediate, simply generated by protonation of the enecarbamate, apparently reacts only with the enol shown in (**128**).

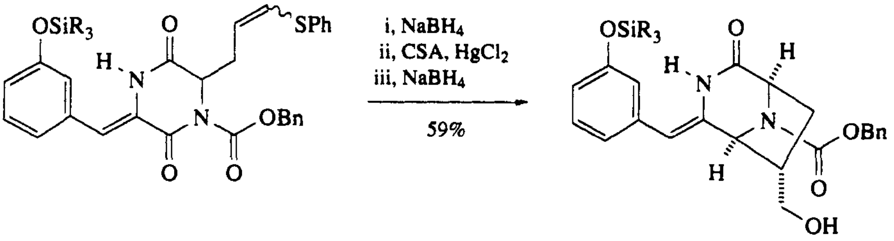
OSiR3
O
SPh
H
N
N
OBn
O
O
i, NaBH4
ii, CSA, HgCl2
iii, NaBH4
59%
OSiR3
O
H
H
N
N
OBn
H
O
OH

(96)

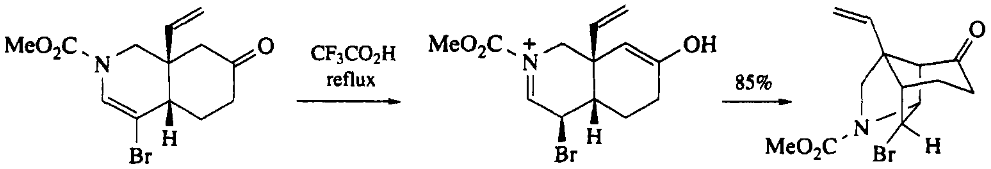
MeO2C
N
O
Br
H
CF3CO2H
reflux
MeO2C
+
N
OH
Br
H
85%
O
MeO2C
N
Br
H

(128)

(97)

## 4.5.5 ACYCLIC *N*-ACYLIMINIUM IONS

### 4.5.5.1 Intermolecular Reactions

The majority of the presently known *N*-acyliminium reactions are of this type and have been reviewed extensively.[5,58,59] Depending on the substitution patterns of iminium species and π-nucleophile, either a cycloadduct is obtained as the product, or an acyclic product is isolated, often *via* the intermediacy of an unstable cycloadduct. When 1,3-dienes are used as nucleophiles they often behave as 4π-electron components in a Diels–Alder type reaction (equation 33).[64–66] Interestingly, cycloocta-1,3-diene, unsuited as a Diels–Alder diene, reacts as an isolated alkene with *N*-acyliminium species (**129**) to give cycloadduct (**130**) in moderate yield (equation 98).[137]

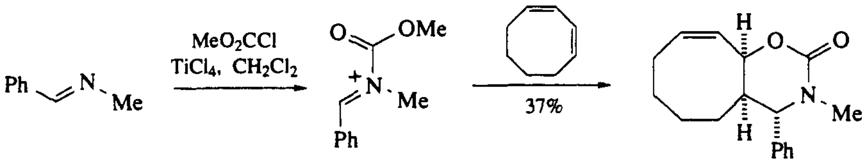
Ph
N
Me
MeO2CCl
TiCl4, CH2Cl2
O
OMe
+
N
Me
Ph
37%
H
O
O
N
Me
H
Ph

(**129**) (**130**)

(98)

The use of enol silanes[118] and allylsilanes[124,138] as π-nucleophiles usually leads to acyclic products. The enantiomerically pure *N*-acyliminium precursors (**131**) and (**132**) are prepared from α-amino acid derivatives.[124] Reaction with allylsilane under the influence of $TiCl_4$ proceeds with 60% stereoselectivity in the case of carbamate (**131**); however, the precursor (**132**) reacts indiscriminately under these circumstances (equations 99 and 100).[124] A more complex allylsilane (**133**) reacts with iminium precursor (**134**) in the presence of $EtAlCl_2$ to produce carbamate (**135**) as a single diastereomer in 48% yield (equation 101).[139]

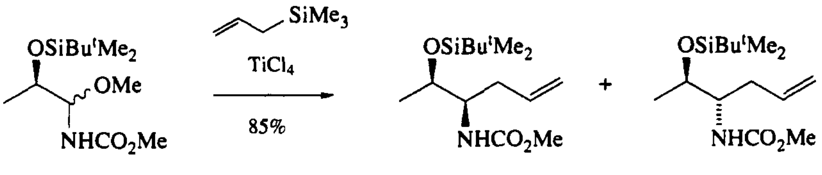
OSiBu$^t$Me2
OMe
NHCO2Me
SiMe3
TiCl4
85%
OSiBu$^t$Me2
NHCO2Me
+
OSiBu$^t$Me2
NHCO2Me

(**131**) 80:20

(99)

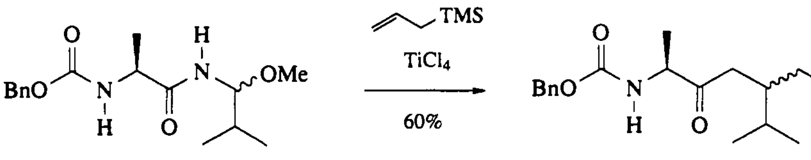

(132)

*ca.* 50:50 mixture

(100)

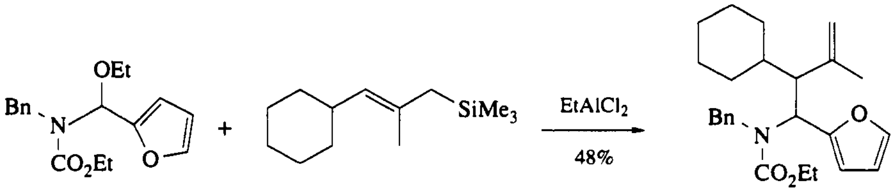

(134) (133) (135)

(101)

The use of propargyltrimethylsilane as π-nucleophile may lead to cyclic products.[138] Thus, reaction of ethoxycarbamate (**136**) in the presence of $SnCl_4$ gives oxazinone (**137**) as the sole product in 56% yield (equation 102). However, when $EtAlCl_2$ is used as Lewis acid, a 75:25 mixture of (**137**) and allene (**138**) is obtained in 63% total yield. Interesting further details are that 1-pentyne does not react with (**136**) under similar conditions and that allyltrimethylsilane produces the allyl analogue of (**138**) in almost quantitative yield. It remains unclear whether (**138**) arises *via* the intermediacy of a cycloadduct or is formed directly from (**136**) without involvement of the carbonyl function.

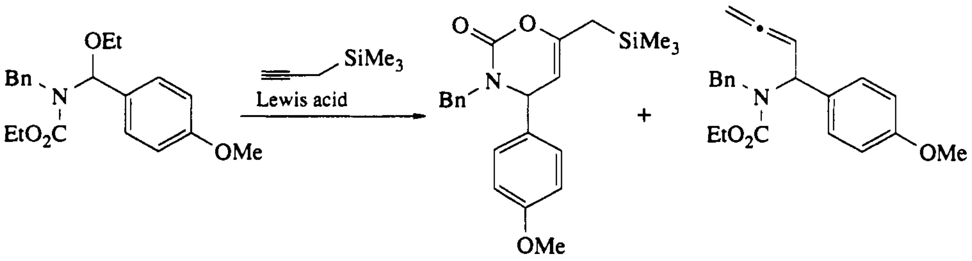

(136) (137) (138)

(102)

An interesting application of allylsilane as π-nucleophile is the tandem *N*-acyliminium coupling with dimethoxycarbamate (**139**). Piperidine derivative (**140**) is obtained as a mixture of diastereoisomers (equation 103).[92]

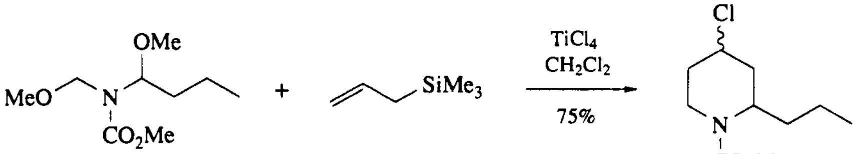

(139)

(103)

### 4.5.5.2 Intramolecular Reactions

If the π-nucleophile is geometrically well positioned with respect to the *N*-acyliminium moiety, an intramolecular cycloaddition takes place with high stereospecificity giving bicyclic 5,6-dihydro-1,3-oxazines (equations 29 and 30).[61] However, geometric or electronic reasons often prevent this cycloaddition, or render the cycloaddition product unstable, so that simple π-cyclization products are usually obtained. Very successful nucleophiles are again propargyl- and allyl-silanes. The former lead to heterocyclic allenes (equation 104)[30] and the latter give rise to formation of vinyl-substituted products (equation 105).[31] Pyrrolidines are obtained as pure *trans* isomers, which is the result of the favorable chair-like conformation (**140**) of the intermediary π-complex with an (*E*)-iminium geometry (equation 105). Piperidines are formed less stereoselectively as a 2:1 mixture, with the *trans* product still as the major isomer.[31] An elegant application of this methodology can be found in a synthetic approach to gelsemine (equation 106).[140]

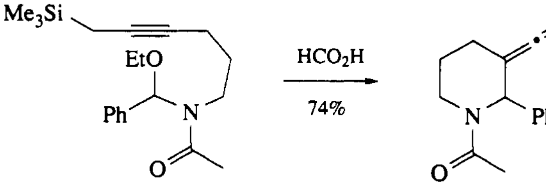

(104)

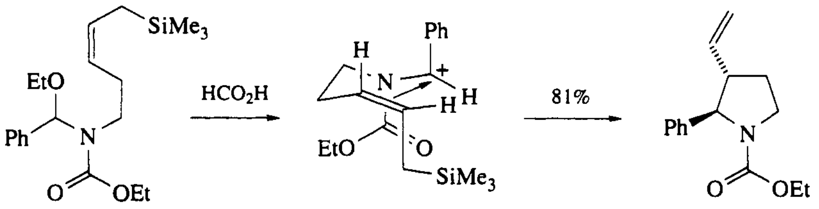

(105)

**(140)**

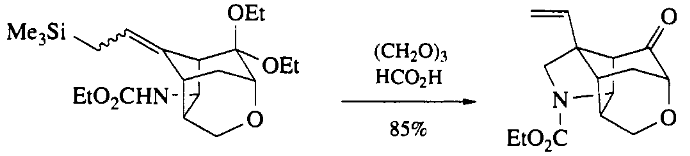

(106)

Recently, cyclizations of the isomeric unsaturated carbamates (**141**) and (**142**) have been investigated (equation 107).[139] These fundamental reactions are not as regio- and stereo-selective as similar cyclizations starting from cyclic *N*-acyliminium ions (equations 25 and 26).[57] The loss of stereoselectivity might have to do with the occurrence of cationic aza-Cope rearrangements in combination with chair–chair interconversions (equation 108). Normal cyclization of (**142**) occurs *via* conformation (**145**) and should lead to (**144**). If sigmatropic rearrangement competes with normal cyclization, (**146**) arises, but this conformation still leads to (**144**). Only after chair–chair interconversion to (**147**) and subsequent cyclization, (**143**) is formed. *Via* the same mechanism (**141**) can produce the abnormal product (**144**).

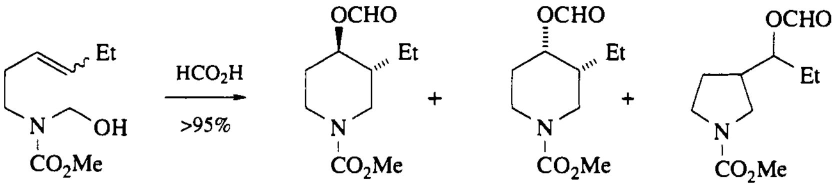

(107)

| | | (143) | | (144) | | |
|---|---|---|---|---|---|---|
| **(141)** | *(E)* | 88 | : | 8 | : | 4 |
| **(142)** | *(Z)* | 18 | : | 73 | : | 9 |

The occurrence of a fast cationic aza-Cope rearrangement has been proven in the case of vinylsilane cyclizations (equation 109).[32] Enantiomerically pure ethoxycarbamate (**148**) cyclizes under the influence of $BF_3\cdot Et_2O$ to a 1:1 mixture of racemic tetrahydropyridines (**149**) and (**150**). Thus, the equilibration of iminium ions (**151**) and (**152**), attended with racemization (equation 110), occurs much faster than π-cyclization. Because allylsilanes are more nucleophilic than vinylsilanes, π-cyclization probably takes place from (**152**). The fast rate of cyclization of allylsilanes is apparent from the cyclization *via* (**140**), where cationic aza-Cope rearrangement cannot compete (equation 105).

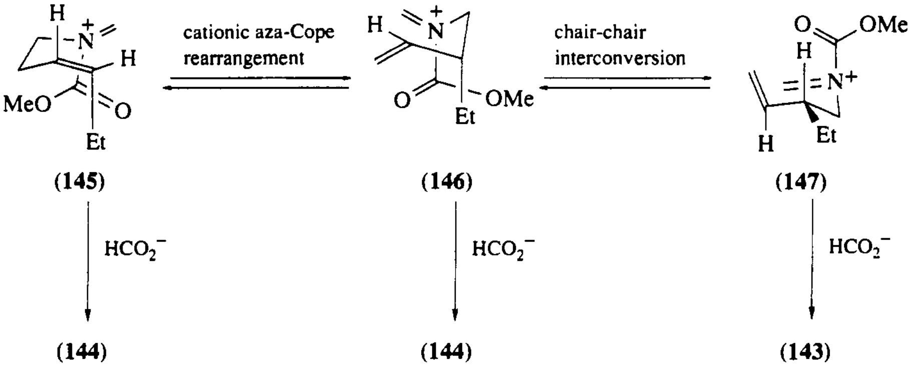
cationic aza-Cope rearrangement
chair-chair interconversion
MeO
Et
OMe
HCO2⁻
(145)
(146)
(147)
(144)
(144)
(143)

(108)

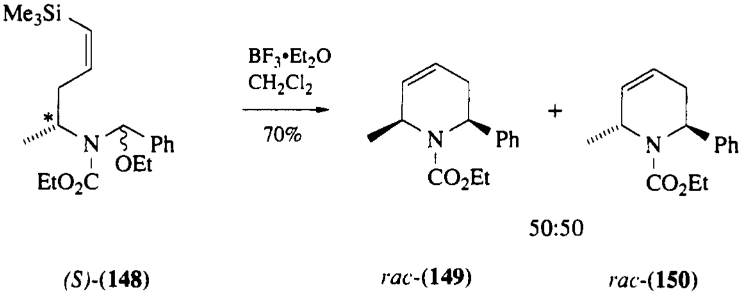
Me3Si
Ph
OEt
EtO2C
BF3•Et2O
CH2Cl2
70%
CO2Et
50:50
(S)-(148)
rac-(149)
rac-(150)

(109)

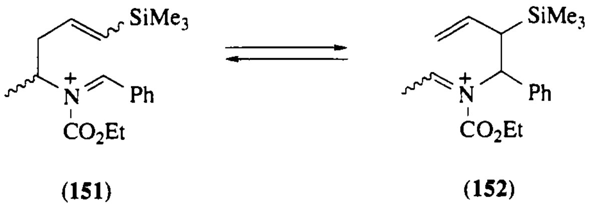
SiMe3
Ph
CO2Et
(151)
(152)

(110)

Two consecutive π-cyclizations take place when carbamates (**153**) and (**154**) are dissolved in formic acid containing paraformaldehyde (equation 111).[141,142] From both starting materials the same single *cis*-fused perhydroisoquinoline (**155**) is obtained. This means that carbocation (**156**) is a common intermediate, which cyclizes further in the conformation as depicted.

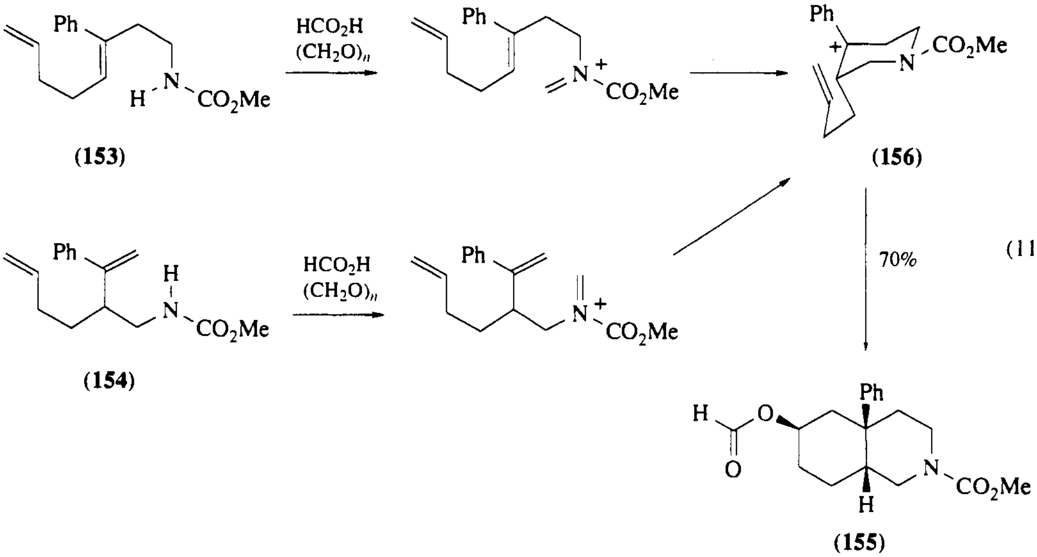
Ph
CO2Me
HCO2H
(CH2O)n
70%
(153)
(154)
(156)
(155)

(111)

## 4.5.6 *C,N*-DIACYLIMINIUM IONS (GLYCINE CATION EQUIVALENTS)

*N*-Acyliminium intermediates (**157**), bearing a carbonyl function at the iminium carbon atom, are of great utility for the synthesis of α-amino acids (equation 112). The presence of the extra electron-withdrawing functionality renders the iminium species (**157**) more electrophilic, compared to the intermediates described heretofore. Therefore, better leaving groups X or stronger acids may be necessary to generate (**157**), which otherwise behaves as a normal *N*-acyliminium intermediate.

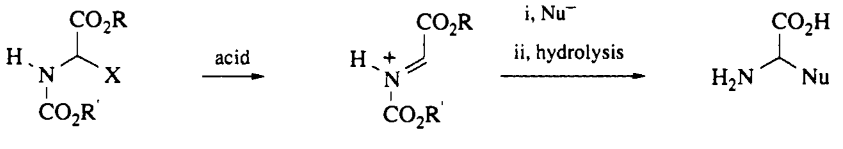

**(157)**

(112)

### 4.5.6.1 Intermolecular Reactions

The first studies of this reaction type were performed with 5-methoxyhydantoin (**158**).[143] Three different products can be formed on reaction with alkenes, dependent on the substitution pattern of the alkene (equation 113). The strongly acidic and non-nucleophilic conditions apparently disfavor formation of addition products. Such conditions lead to similar results in the case of acyclic iminium precursor (**159**),[144,145] although in the case of styrene the double bond ends up in a different position (*cf.* equations 113 and 114).[146] Interestingly, milder conditions ($BF_3 \cdot Et_2O$, 20 °C) lead to cycloadduct (**160**) in good yield. It is probable that protonated (**160**) is an intermediate in the sulfonic acid induced procedure (equation 114). When styrene is allowed to react with the free acid of (**159**) in the presence of sulfuric acid in ice-cold dioxane, the γ-lactone (**161**) is produced as the product, albeit in only 25% yield, presumably by way of rearrangement of intermediate (**162**).[146] A better yield of (**161**) is obtained when the ethylthio function is used as leaving group (equation 115).[147] With 1,3-dienes a similar course of the reaction is observed as the major process, giving, for example, vinyl-substituted γ-lactone (**163**) from 1,3-butadiene (equation 116).[148] A minor portion of the diene reacts as a 4π-electron component with the *N*-acyliminium moiety,[65,66] producing pipecolic acid derivatives, *e.g.* (**164**).

Reaction of glycine cation equivalents with vinylsilanes leads to β,γ-unsaturated α-amino acid derivatives with high regio- and stereo-selectivity.[149] Thus, chloroglycine derivative (**165**) reacts with (*E*)-β-tri-

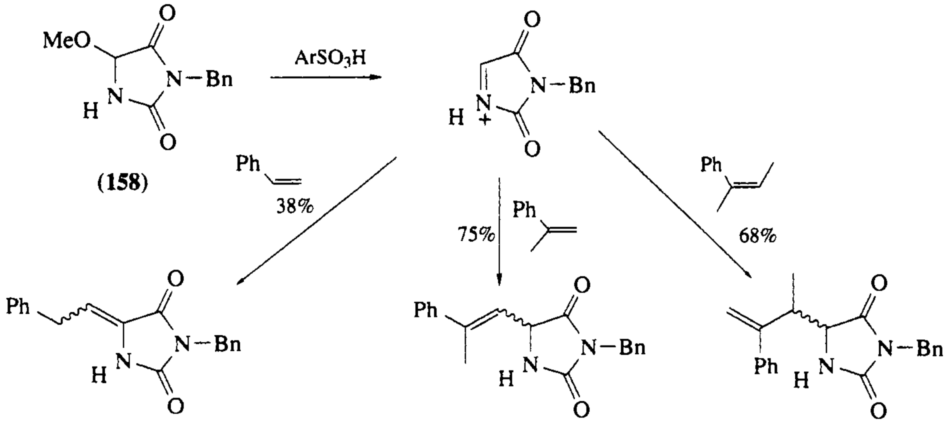

**(158)**

(113)

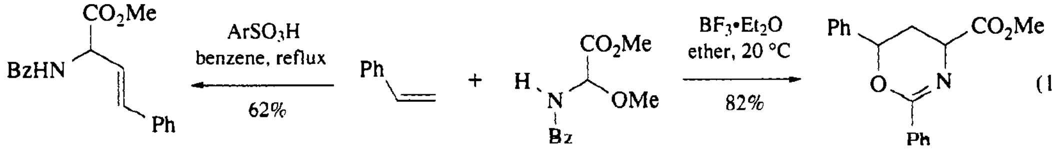

**(159)** **(160)**

*cis*:*trans* = 3:1

(114)

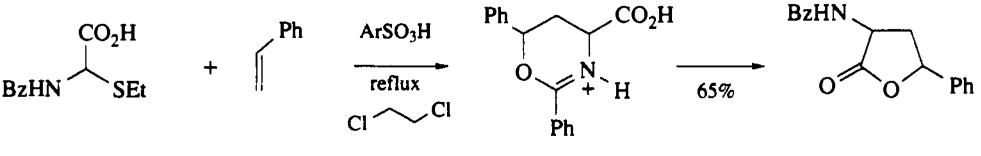

(162) (161)

(115)

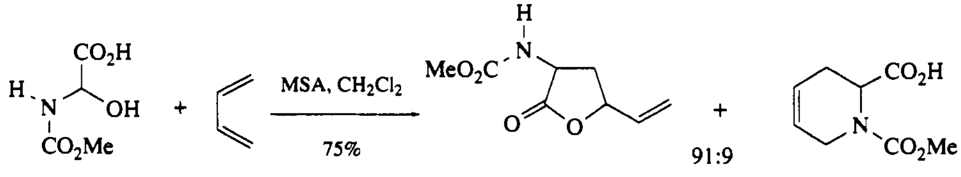

(163) (164)

(116)

methylsilylstyrene to give substitution product (**166**) in >95% stereospecificity. The cycloaddition product (**167**) is isolated in negligible amount. The corresponding (*Z*)-silylstyrene does not react, however, under the same conditions, but requires a stoichiometric quantity of silver cation (equation 118). In this way the (*Z*)-β,γ-unsaturated α-amino acid derivative (**168**) is accessible in good yield.[149]

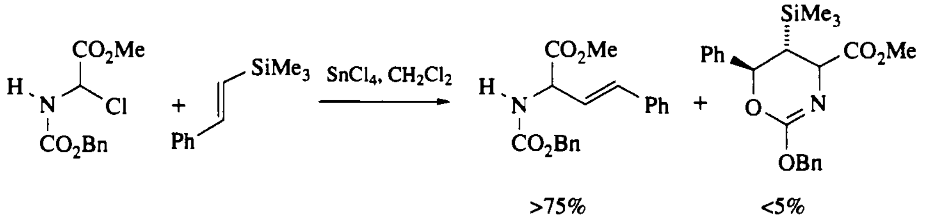

(165) (166) (167)

(117)

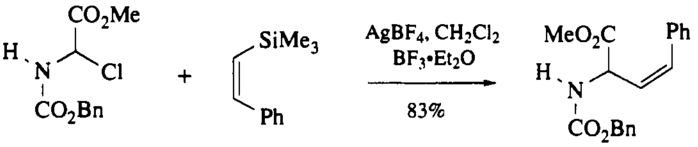

(165) (168)

(118)

The use of allylsilanes as nucleophiles gives γ,δ-unsaturated α-amino acid derivatives.[150,151] These reactions proceed with high regioselectivity, governed by the silicon β-effect, but the stereoselectivity is low (equations 119 and 120).[151] Enol silanes provide a ready access to γ-oxo-α-amino acid derivatives (equation 121).[39,151] Interestingly, propargyltrimethylsilane does not give a linear product, but instead gives rise to formation of stable cycloadduct (**169**) in moderate yield (equation 122).[151] The different outcome of reactions of allyl- and propargyl-silanes bears analogy with earlier results.[138]

The enantiomerically pure cyclic *N*-acyliminium precursor (**170**) has proven useful for the synthesis of α-amino acids in enantiomerically pure form.[48] Both (**170**) and its enantiomer can be obtained from ben-

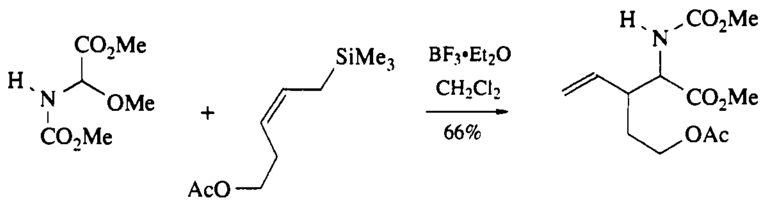

diastereomer ratio 63:37

(119)

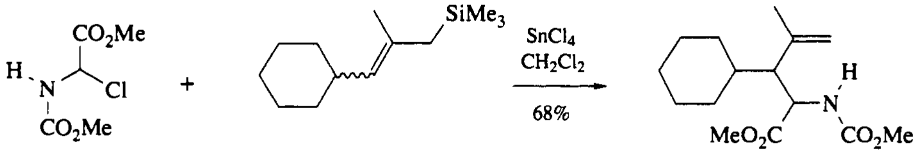

(*E*):(*Z*) = 67:33

diastereomer ratio 50:50

(120)

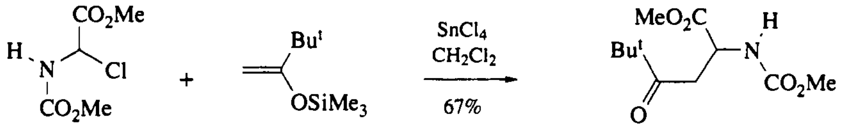

(121)

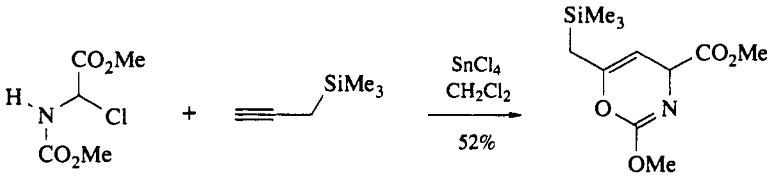

(122)

**(169)**

zoin in a few steps, including the resolution of racemic *erythro*-α,β-diphenyl-β-hydroxyethylamine by recrystallization of its L-glutamic acid salt. Lewis acidic treatment of (**170**) generates *N*-acyliminium species (**171**), which has a preferred conformation as depicted (equation 123). The 5-phenyl function adopts a pseudo-axial orientation, so that nucleophiles preferentially add to (**171**) in a trans fashion with respect to the phenyl substituents. Thus, allylsilanes give solely the trans products as exemplified (equation 124) with the preparation of (**172**), from which both cyclopentenyl- and cyclopentyl-glycine can be synthesized in one step. However, a strongly nucleophilic π-system like a silyl ketene acetal produces the cis product (**173**) almost exclusively (equation 124).[48,152] Apparently, the latter reaction follows a genuine $S_N2$ pathway. That both $S_N1$ and $S_N2$ mechanisms can be operative has been confirmed by using enol silanes as nucleophiles under various conditions, which give mixtures of cis and trans products. The trans/cis ratio increases by using a less nucleophilic enolsilane, a stronger Lewis acid, or a more polar solvent.

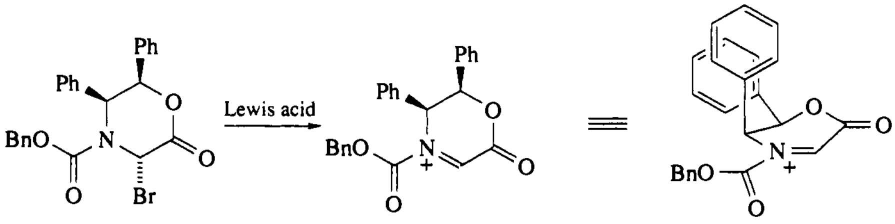

(123)

**(170)** **(171)**

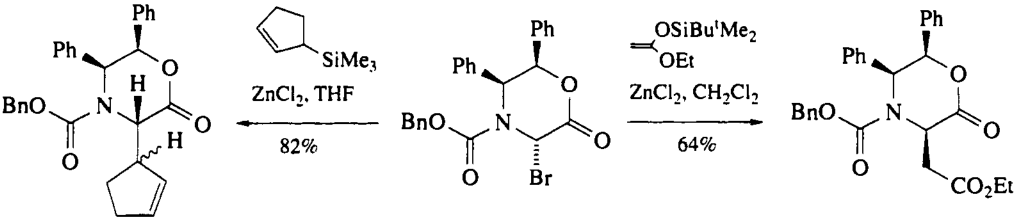

(124)

**(172)** **(170)** **(173)**

Other chiral glycine cation equivalents useful for the synthesis of enantiomerically pure α-amino acids are **(174)**[153,154] and **(175)**.[155] However, acid-catalyzed reactions of these *N*-acyliminium precursors with alkenes or alkynes have not been reported yet. The $BF_3·Et_2O$-mediated electrophilic aromatic substitution of **(175)** onto anisole in 98% diastereoselectivity deserves mention here.[155]

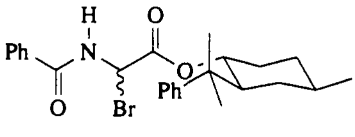

**(174)**

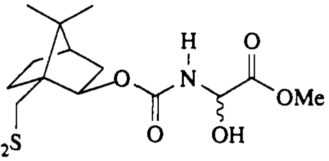

**(175)**

## 4.5.6.2 Intramolecular Reactions

Dissolution of glyoxylic ester adduct **(176)** in formic acid and stirring for 3 d gives rise to formation of two cyclization products **(177)** and **(178)** in good yield (equation 125).[139] If one assumes that cyclization only occurs *via* a chair-like transition state with an (*E*)-iminium geometry, the equilibria between species **(179)** to **(181)** well account for the products obtained (equation 126). In addition, one may expect that the cationic aza-Cope rearrangement between **(179)** and **(180)** lies at the side of the latter, because the electron-withdrawing ester function destabilizes species **(179)**. Evidence for these assumptions has been obtained as follows. First, treatment of carbamate **(182)** with paraformaldehyde in formic acid also leads to a *ca.* 1:1 ratio of **(177)** and **(178)**. Second, reduction of acetate **(183)** with triethylsilane in the presence of $BF_3·Et_2O$ in $CH_2Cl_2$ gives carbamate **(184)** as the only isolable product. The cyclizations (equations 127

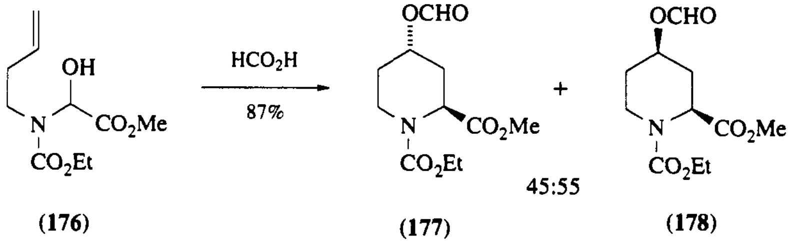
OH
CO2Me
CO2Et
HCO2H
87%
OCHO
CO2Me
CO2Et
+
45:55
(176)
(177)
(178)

(125)

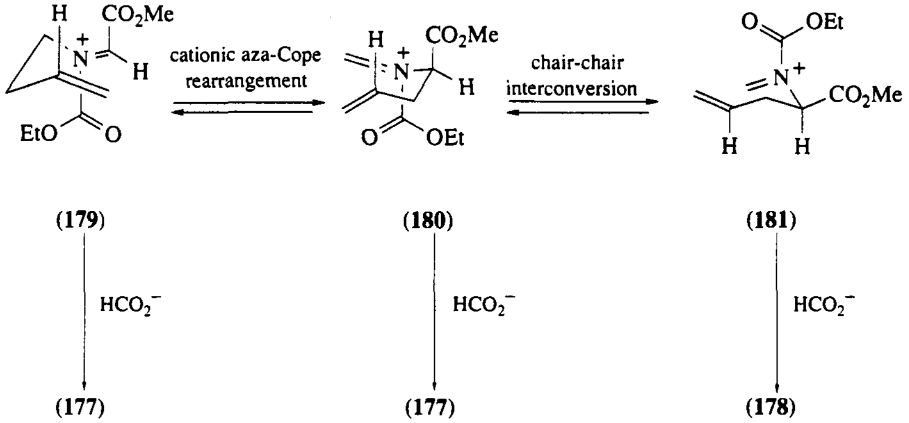
H
CO2Me
+
N
H
EtO
O
cationic aza-Cope rearrangement
CO2Me
chair-chair interconversion
OEt
OEt
CO2Me
(179)
(180)
(181)
HCO2⁻
HCO2⁻
HCO2⁻
(177)
(177)
(178)

(126)

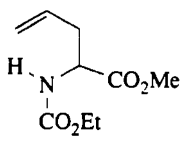

**(182)**

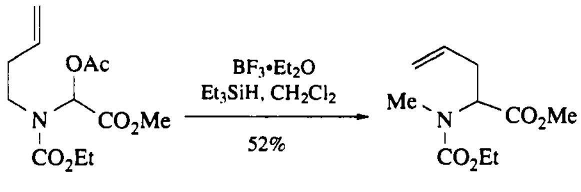
OAc
CO2Me
CO2Et
BF3•Et2O
Et3SiH, CH2Cl2
52%
Me
(183)
(184)

and 128) of the (*E*)- and (*Z*)-ethyl-substituted alkenes (**185**) and (**186**) proceed in a similar way as (**176**).[139] On the other hand, ring closure of allylsilane (**187**) does not show competition with a cationic aza-Cope rearrangement, because only proline derivatives are obtained (equation 129). Apparently, allylsilane cyclization is much faster than rearrangement followed by cyclization of the rearranged system. The major trans product arises from π-complex conformation (**188**). The origin of the minor cis product remains unclear. Thermal cyclization of the mesylate (**189**) gives a better yield and isomer ratio (equation 129). Pipecolic acid derivatives are formed by cyclization of the homolog of (**187**) to give an approximate 1:1 ratio of stereoisomers (equation 130).[15] The use of a propargylsilane moiety as nucleophile leads to an allenic product (equation 131).[15]

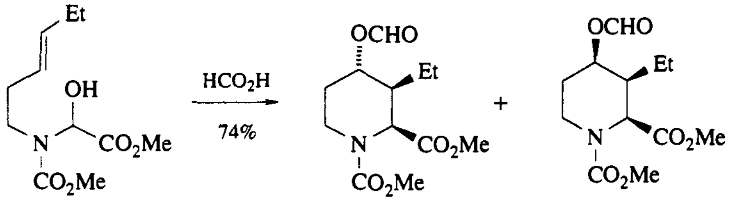
Et
OH
N
CO2Me
CO2Me
HCO2H
74%
OCHO
Et
N
CO2Me
CO2Me
+
OCHO
Et
N
CO2Me
CO2Me

(127)

(**185**) 22:78

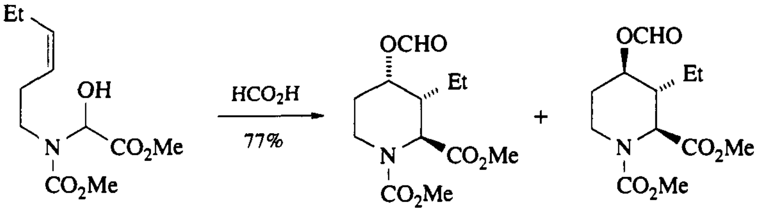
Et
OH
N
CO2Me
CO2Me
HCO2H
77%
OCHO
Et
N
CO2Me
CO2Me
+
OCHO
Et
N
CO2Me
CO2Me

(128)

(**186**) 56:44

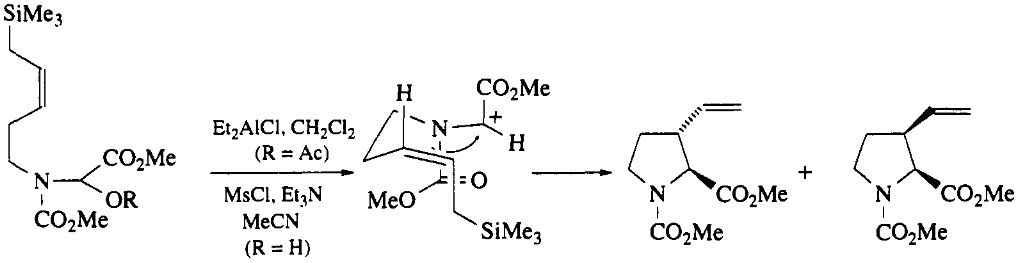
SiMe3
N
CO2Me
OR
CO2Me
Et2AlCl, CH2Cl2
(R = Ac)
MsCl, Et3N
MeCN
(R = H)
H
CO2Me
N
+
H
=O
MeO
SiMe3
N
CO2Me
CO2Me
+
N
CO2Me
CO2Me

(129)

(**187**) R = Ac (**188**) 78% 78:22

(**189**) R = H 88% 89:11

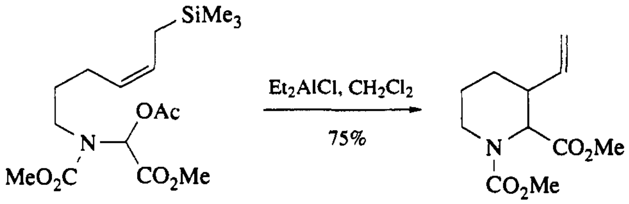
SiMe3
OAc
N
MeO2C
CO2Me
Et2AlCl, CH2Cl2
75%
N
CO2Me
CO2Me

(130)

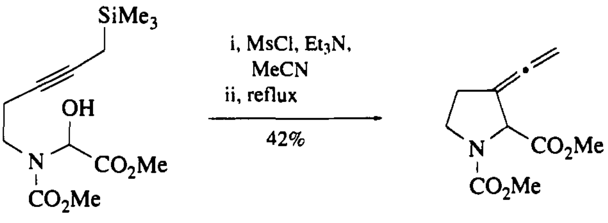
SiMe3
OH
N
CO2Me
CO2Me
i, MsCl, Et3N,
MeCN
ii, reflux
42%
N
CO2Me
CO2Me

(131)

Addition of 5-substituted 2-pyrrolidinones to methyl glyoxylate produces useful precursors (**190**) to exocyclic *N*-acyliminium ions (equations 132).[156] The preferred iminium ion geometry is most probably (*E*) as depicted in (**191**) for steric reasons. This geometry explains the stereochemical relationship between the ring junction hydrogen atom and the ester function in the products (**192**) and (**193**). Best yields are achieved by using the thermal cyclization of intermediate mesylates, and the major products have the ester and vinyl function trans.[156]

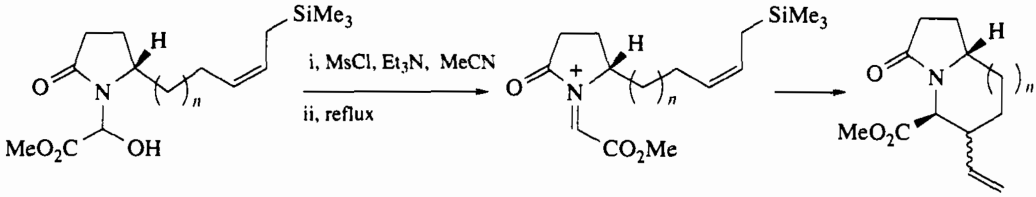
SiMe3
H
O
N
n
MeO2C
OH
i, MsCl, Et3N, MeCN
ii, reflux
SiMe3
H
O
+
N
n
CO2Me
H
O
N
n
MeO2C

(132)

(**190**) (**191**) (**192**) n = 1; 57%
(**193**) n = 2; 97%

A remarkable observation is the cyclization of biscarbamate (**194**) to $\gamma$-lactone (**195**) mediated by methanesulfonic acid (equation 133).[157] No trace of the expected $\delta$-lactone is formed, presumably because of the unfavorable ester geometry in the transition state required for six-membered ring formation. Such problems with $\delta$-lactone formation have been observed also in Diels–Alder chemistry.[158,159] A nice example related to *N*-acyliminium chemistry is the thermal hetero Diels–Alder reaction of acylimine precursor (**196**) to bicyclic $\gamma$-lactone (**197**) in good yield. The corresponding intramolecular cycloaddition of (**198**) fails.[159] Finally, Lewis acid mediated cyclization of allylsilane (**199**) is unsuccessful, although lactonization of (**200**) proceeds very well (equation 135, *cf.* equation 119).[151]

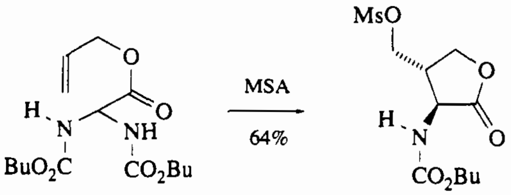
O
O
H
N
NH
BuO2C
CO2Bu
MSA
64%
MsO
O
H
N
O
CO2Bu

(133)

(**194**) (**195**)

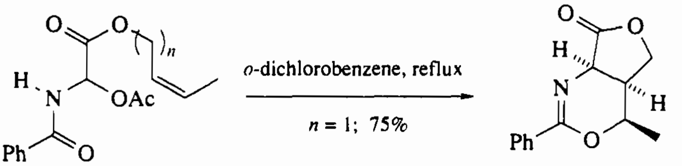
O
O
n
H
N
OAc
Ph
O
o-dichlorobenzene, reflux
n = 1; 75%
O
O
H
N
H
Ph
O

(134)

(**196**) *n* = 1
(**198**) *n* = 2

(**197**)

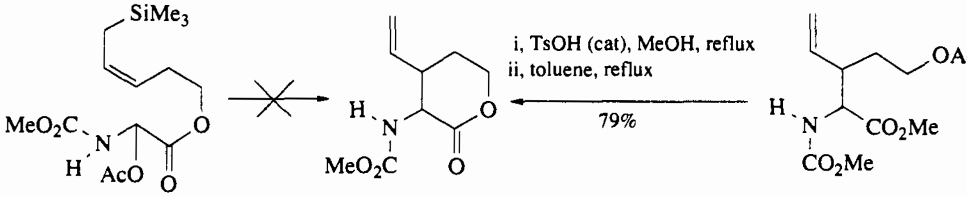
SiMe3
MeO2C
N
H
AcO
O
O
H
N
MeO2C
O
O
i, TsOH (cat), MeOH, reflux
ii, toluene, reflux
79%
OAc
H
N
CO2Me
CO2Me

(135)

(**199**) (**200**)

## 4.5.7 REFERENCES

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# 4.6
# The Passerini and Ugi Reactions

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## 4.6.1 INTRODUCTION AND BRIEF HISTORY OF ISOCYANIDE CHEMISTRY

Among the functional groups of organic chemistry the isocyanide group is not only unique because of its formally divalent carbon atom but also because of its unsurpassed versatility in chemical reactivity. Nevertheless, the chemistry of the isocyanides (2) developed quite sluggishly for a century.

The first isocyanide, allyl isocyanide, was prepared by Lieke in 1859[1,2a] from allyl iodide and silver cyanide; it 'tainted the air in the room for days' and provoked 'continuing complaints in the neighborhood about the vile odor'. At that time it was, however, not noticed that a new distinct class of chemical compounds had been discovered.

The realization that this was a new type of compound, isomeric to the nitriles,[3] and the elaboration of the classical methods for the preparation of isocyanides, the 'alkylation method' and the 'carbylamine method' by Gautier[2b,3] and Hofmann,[2c,4] initiated an active period of isocyanide chemistry that ended by the turn of the century with Nef's investigations on the reactions of the formally divalent carbon atom in the isocyanides.[2d,5] The discovery of the Passerini reaction in 1921[2e,6] led to a brief renaissance of isocyanide chemistry.

The reason why isocyanide chemistry did not attract more researchers in its first century was not the suspected toxicity,[2f] nor the vile smell of the volatile isocyanides, but rather it was the lack of accessibility of pure isocyanides. In general, the aforementioned classical syntheses of isocyanides[2c,g–4] are not suitable for the preparation of any appreciable quantities of pure isocyanides.

The last step of the synthesis of the antibiotic xanthocillin by Hagedorn in 1956[7] is the first published synthesis of an isocyanide (**2**) by dehydration of an *N*-monosubstituted formamide (**1**).

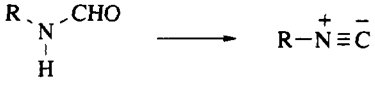

(**1**) (**2**)

Since then most isocyanides have become readily available by the transformation (**1**) → (**2**), the method of choice for the preparation of isocyanides. The best dehydrating agents for (**1**) are phosgene and diphosgene in the presence of triethylamine, and phosphorus oxychloride in the presence of diisopropylamine.[8–10]

As a result of this convenient method of synthesizing isocyanides, their chemistry has flourished vigorously in the past 30 years. Isocyanides are no longer an exotic class of compounds; they are now routinely used as reagents by organic chemists. The preparative methods based on α-metallated isocyanides[11] and the Ugi reaction[12] are amongst the most important contributions of modern isocyanide chemistry to organic synthesis.

## 4.6.2 THE PASSERINI REACTION AND RELATED REACTIONS

The essentially nucleophilic isocyanides react with acid-activated aldehydes and ketones in combination with a nucleophile such as water, hydrazoic acid or carboxylic acids to yield α-hydroxycarboxamides or some of their derivatives. Such reactions are the topic of this section.

### 4.6.2.1 α-Acyloxycarboxamides

In 1921 Passerini[6a] reported the synthesis of the α-acyloxycarboxamides (**6a–e**) according to the scheme below. The formation of α-acyloxycarboxamides by a three-component reaction of carboxylic acids (**3**), carbonyl compounds (**4**) and isocyanides (**5**) is the proper Passerini reaction. The reactions described in Sections 4.6.2.2–4.6.2.4 are closely related to the Passerini reaction; we call them reactions of the Passerini type.[2e,6]

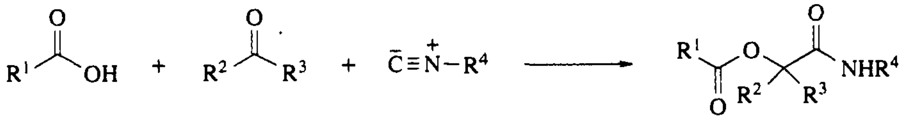

(**3**) (**4**) (**5**) (**6**)

(**6**) a: $R^1$ = Me; $R^2$ = Me; $R^3$ = Me; $R^4$ = Ph
b: $R^1$ = Me; $R^2$ = Me; $R^3$ = Me; $R^4$ = *p*-PhN=NC$_6$H$_4$
c: $R^1$ = Me; $R^2$ = Me; $R^3$ = EtO$_2$CCH$_2$; $R^4$ = Ph
d: $R^1$ = Ph; $R^2$ = H; $R^3$ = Ph; $R^4$ = Ph
e: $R^1$ = Ph; $R^2$ = H; $R^3$ = Ph; $R^4$ = *p*-PhN=NC$_6$H$_4$

Concentrated solutions of the components (**3**)–(**5**) in inert organic solvents react at 0–20 °C to form (**6**); the reaction time varies with the nature of the components and the reaction conditions (1–100 h), as does the yield (18–95%). A wide variety of α-acyloxycarboxamides (**6**) have been prepared by the Passerini reaction,[2i,6] including some depsipeptide derivatives[17] and their phospho analogs.[18a]

The Passerini reaction of α-halogenated carbonyl compounds (**8**; X = Cl, Br) can be used for the protection of the C-terminal carboxyl groups of *N*-protected α-amino acid derivatives (**7**).[19]

The synthesis of 3-acyloxy-2-azetidinones (**13**) from the chloro ketones (**11**)[20] is another example that demonstrates the versatility of the Passerini reaction in syntheses.

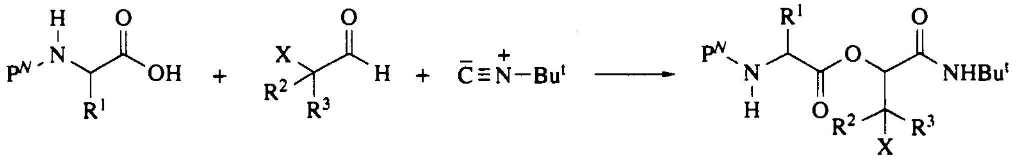
**(7)** **(8)** **(9)** **(10)**

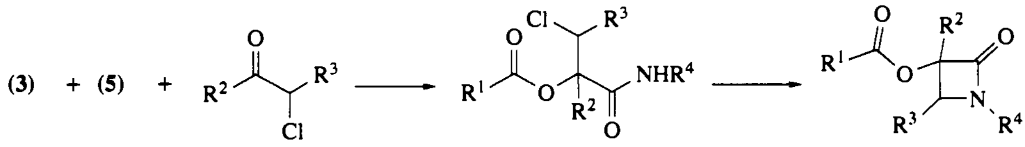

**(11)** **(12)** **(13)**

The synthesis of (±)-hydrastine (**17**) *via* (**16**) is an elegant use of the Passerini reaction in the field of alkaloids.[2l]

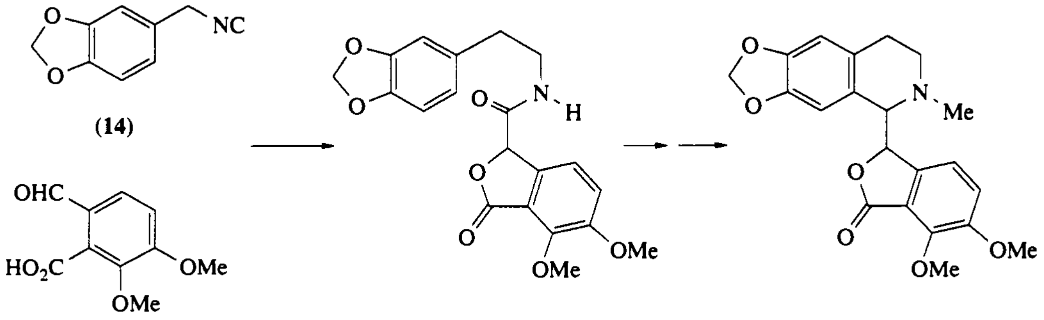
**(14)** **(15)** **(16)** **(17)**

The following experimental evidence is relevant to the mechanistic interpretation of the Passerini reaction:[2j] Baker and Stanonis[22] observed third-order kinetics for the reaction. Polar solvents with strong hydrogen bond affinity interfere with the Passerini reaction.[23] When (**18**) is reacted with acetone (**19**) the α-adduct (**20**) is formed instead of the expected product (**21**).[2k]

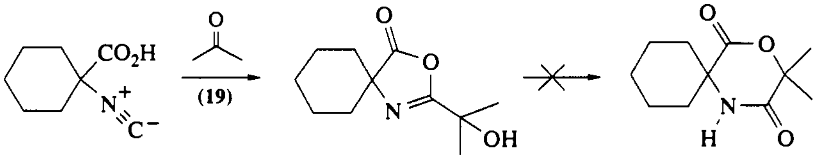
**(18)** **(20)** **(21)**

Based on this evidence, the reaction mechanism (**22**) + (**5**) → (**23**) → (**6**) is the most convincing of the many proposed reaction mechanisms for the Passerini reaction.[2j]

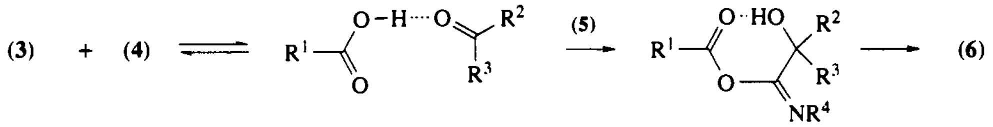

**(22)** **(23)**

### 4.6.2.2 α-Hydroxycarboxamides and α-Alkoxycarboxamides

Aqueous inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid and, preferentially, sulfuric acid, as well as some Lewis acids, *e.g.* boron trifluoride etherate[24] and titanium tetrachloride, catalyze the α-addition of the isocyanides, yielding the α-hydroxycarboxamides (**24**) in 12–88% yield.[2m,6b,d,f,14,25–29] The catalysis of this reaction by acids is due to an enhancement of the electrophilic reactivity of the carbonyl compound (**4**).

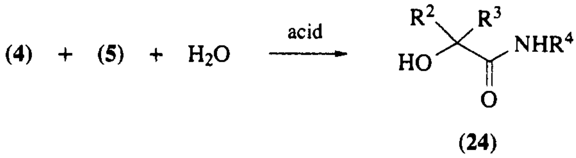

**(24)**

A great variety of carbonyl compounds has been used in this reaction in order to produce the respective α-hydroxycarboxamides, but to the best of our knowledge, formaldehyde had never been reported in the literature as the carbonyl component in the synthesis of (**24**). We wondered whether or not formaldehyde displays any abnormal behavior in the preparation of (**24**), but we noticed that in dilute sulfuric acid paraformaldehyde reacted with isocyanides to form (**24**; $R^2$, $R^3$ = H; $R^4$ = $Bu^t$, $Oct^t$, c-Hex and *o*-$ClC_6H_4$) in yields of 45–60%,[29a] and in the presence of $TiCl_4$[28] even in yields of up to 95%.[29b]

When Lumma[30] synthesized a series of α-hydroxycarboxamides (**6**) as intermediates for analogs of isoproterenol, he observed the formation of (**27**), an unusual reaction of 2-pyridinecarbaldehyde (**25**) with (**26**) in the presence of hydrochloric acid.

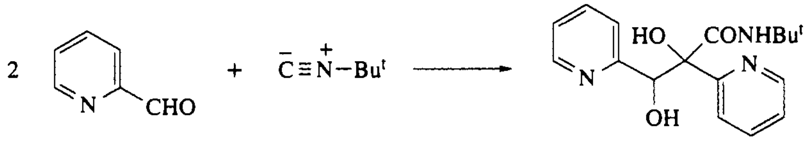

**(25)** **(26)** **(27)**

The $TiCl_4$-mediated synthesis of (**24**) from (**4**) and (**5**) by Seebach *et al.*[28] proceeds particularly well, as has been demonstrated by many examples; yields of up to 98% are encountered. This variant of the α-hydroxycarboxamide synthesis proceeds *via* an α-adduct (**28**) of $TiCl_4$ and presumably a species (**29**) with pentacoordinated Ti.

α-Alkoxynitriles (**32**) and α-alkoxycarboxamides (**33**) are obtained from acetals in the presence of $TiCl_4$.[31]

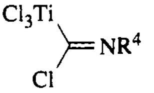

**(28)**

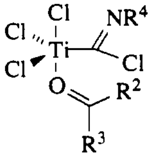

**(29)**

### 4.6.2.3 α-Hydroxyalkyltetrazoles

Besides water and the carboxylic acids (**3**), hydrazoic acid (**34**) is the only acid that can be combined with carbonyl compounds (**4**) and isocyanides (**5**) to form a tetrazole derivative (**37**), a three-component adduct, in 7–95% yield.[2k,32]

With sterically hindered aldehydes and ketones considerably higher yields of (**36**) (68–86% *vs.* 8–32%) are obtained by the use of aluminum azide (**35**) instead of (**34**).

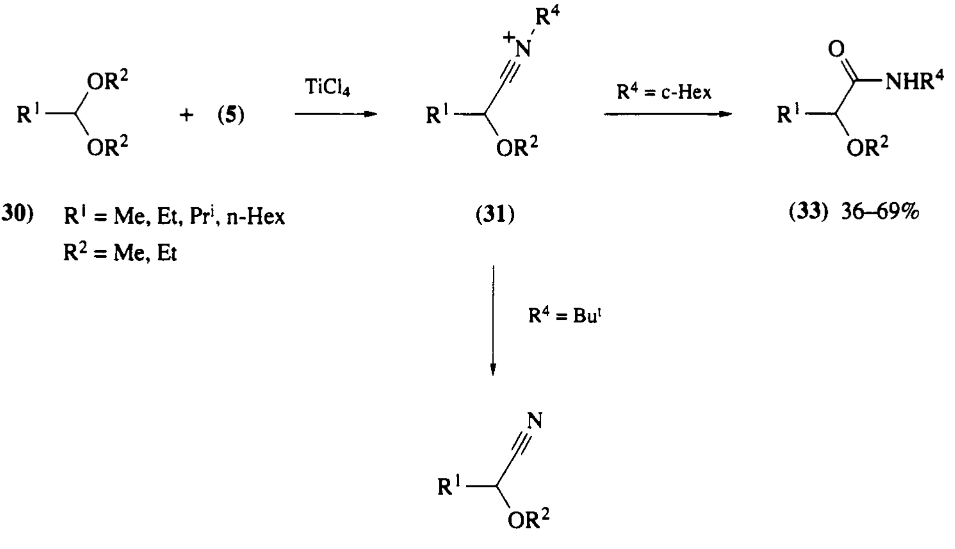

(30) $R^1$ = Me, Et, $Pr^i$, n-Hex
$R^2$ = Me, Et

(31)

(33) 36–69%

(32) 1–14%

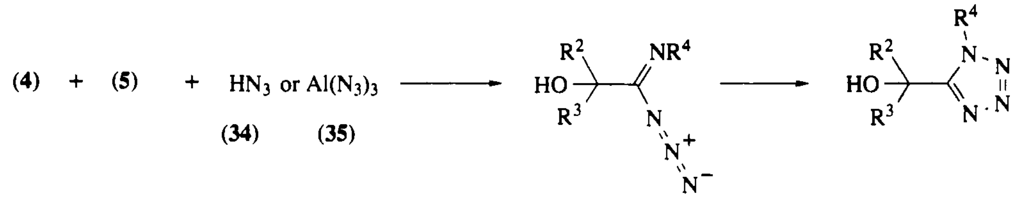

(34) (35) (36) (37)

### 4.6.2.4 α-Acyloxyacrylamides

Carboxylic acids (**3**), diphenylketene (**38**) and isocyanides (**5**) react in analogy to the Passerini reaction to form α-acyloxyacrylamides (**39**).[33-35]

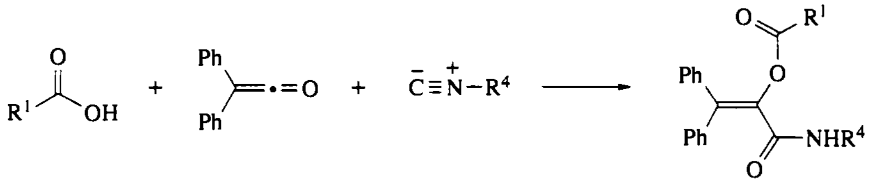

(3) (38) (5) (39)

## 4.6.3 THE UGI REACTION

### 4.6.3.1 General Features, Scope and Limitations

The characteristic feature of the Ugi reaction[12] is the α-addition of an iminium ion (**40**) and the anion $X^-$ of a suitable acid HX to an isocyanide, followed by a spontaneous rearrangement of the α-adduct (**41**) into a stable α-aminocarboxamide derivative (**42**).[2n,16,36,37]

Carbonyl compounds (**4**) and amines (**43**), or their condensation products, such as the imines, enamines and aminals, in combination with the acid HX are generally the source of the iminium ion (**40**) and the anion.

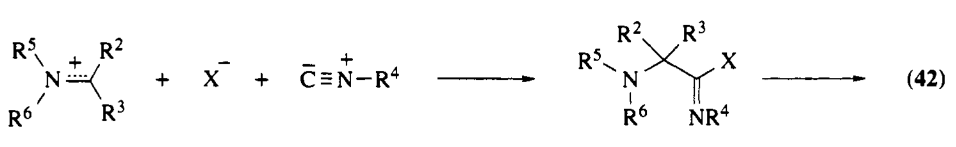
**(40)** **(5)** **(41)**

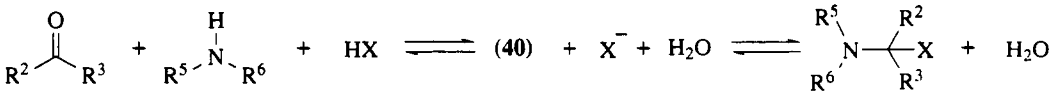
**(4)** **(43)** **(44)**

Thus the product (**42**) results from four distinct reactants, namely (**4**), (**5**), (**43**) and HX, through a condensation reaction. Therefore, such an Ugi reaction was initially called the four-component condensation (4CC).[2n]

Any compound with a sufficiently nucleophilic NH group may serve as the amine component (**43**) of the 4CC, *e.g.* ammonia, primary and secondary amines, hydrazine and its derivatives[38–41] including the diaziridines,[42] as well as hydroxylamine.[43] Diarylamines are not sufficiently nucleophilic to participate as (**43**) in the Ugi reaction.

With the exception of diaryl ketones, all aldehydes and ketones undergo the 4CC as the carbonyl component (**4**). Note that the derivatives of the α-oxocarboxylic acids react very well as the carbonyl components (**4**),[29,44] whereas the derivatives of the β-oxocarboxylic acids may form the resonance-stabilized derivatives of β-aminoacrylic acid, such as ethyl β-aminocrotonate (**45**), which can even be used as the amine component (**43**) of the Ugi reaction.[45]

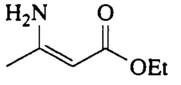
**(45)**

There are no restrictions with regard to the structure of the isocyanide (**5**), as long as it is a *C*-isocyanide.[2n] An acid HX is only suitable as the acid component of the 4CC if it is not irreversibly converted into an α-aminoalkylation product, as happens with the cyanide and the thiolate ions.[46] Furthermore, the acid component HX must yield an α-adduct (**41**) that is capable of rearranging into a stable product (**42**).

The nature of the secondary reaction (**41**) → (**42**) and of its product (**42**) is primarily determined by HX. As the acid component HX, water leads to the α-aminocarboxamides (**42a**),[14,27,42,47,48] thiosulfuric acid to the thioamides (**42b**),[37] hydrogen selenide to the selenoamides (**42c**),[37] hydrazoic acid to the tetrazoles (**42d**)[27,39,44,49–52] and hydroxylamines to the amidines (see also ref. 14) and *N*-hydroxyamidines.[43]

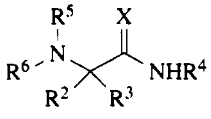
**(42)** **a**: X = O
**b**: X = S
**c**: X = Se

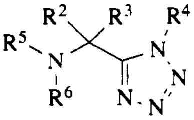
**(42d)**

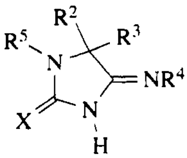
**(42)** **e**: X = O
**f**: X = S

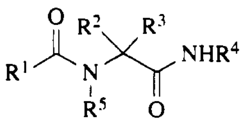
**(42g)**

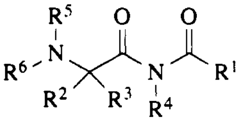
**(42h)**

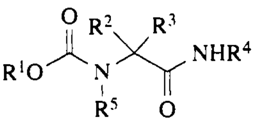
**(42i)**

When primary amines (**43**; $R^6 = H$) are used as the amine component, hydantoinimides (**42e**) and thiohydantoinimides (**42f**) result from hydrogen cyanate and thiocyanate as the acid component HX.[53,54] The most important acid components are the carboxylic acids. With primary amines (**43**; $R^6 = H$) they yield α-acylaminocarboxamides (**42g**),[39,55–57] whereas with secondary amines (**42**; $R^1$, $R^2$ = organyl), the diacylimines (**42h**) are the products, provided that acylatable nucleophiles are absent.[55,58,59] The diacylimides (**42h**) are acylating reagents that transfer an $R^1CO$ group, and so are their precursors, the α-adducts (**41**; $X = R^1CO_2$).[55]

In the presence of bases, carbon dioxide and alcohols such as methanol (**46**; R = Me) form alkyl carbonates.

$$\underset{\textbf{(46)}}{ROH} + CO_2 + B: \rightleftharpoons \underset{\textbf{(47)}}{ROCO_2^-} + {}^+BH$$

When an alkyl carbonate anion participates in an Ugi reaction, a urethane (**42i**) is formed through a reaction between five distinct components.[48,55]

### 4.6.3.2 Reaction Conditions

The Ugi reaction is very easy to execute. Note, however, that it is strongly exothermic. With reactive combinations of amine and carbonyl components (**43**) and (**4**) it suffices to add the isocyanide to a stirring, well-cooled, concentrated methanol solution of the other three components at 0–20 °C. The available temperature range for the reaction is, however, –80 to +80 °C. In some cases the reaction proceeds to completion within a few minutes, but in some cases it takes weeks. It is advisable to exclude oxygen when a slow Ugi reaction is carried out on a small scale (see Section 4.6.3.6). Methanol is generally a suitable solvent, although any other organic solvents lacking interfering functional groups may be used. Often the product crystallizes when the reaction is over. Otherwise the solvent is evaporated and the unreacted components are removed by extraction with acid and base from a solution of the product in a water-immiscible solvent.

When less reactive amine and carbonyl components are used, it is advisable to precondense these components before the reaction with the acid component and the isocyanide. For example, 68% of (**52**) is obtained from (**48**) + (**49**) at 20–25 °C in three weeks, while 94% is produced when (**50**) is reacted for 15 min at 0–10 °C.[50]

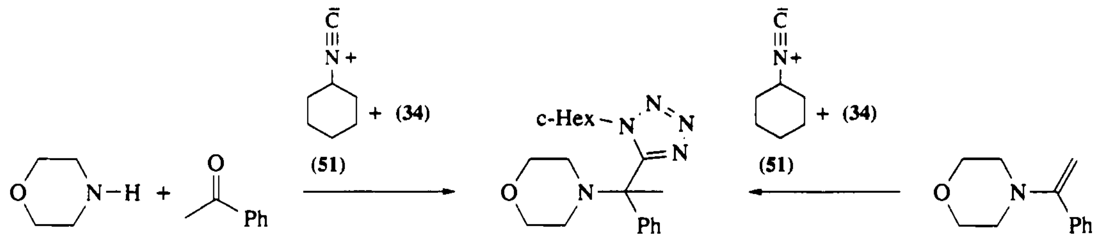

(**48**) (**49**) (**52**) (**50**)

Under suitable conditions the yield is generally very good, in many cases close to quantitative. As a rule, some preliminary experiments are needed in order to determine the optimum reaction conditions for a given combination of components.

### 4.6.3.3 Preparative Advantages

The Ugi reaction is an easily performed one-pot reaction that is applicable to the synthesis of many distinct types (**42a–i**) of organic compounds, mostly in good to excellent yields. Some of the products (**42a–i**) represent important classes of synthetic targets, while others are useful as intermediates for the preparation of a variety of nitrogen compounds.

Thus, the Ugi reaction has a wide range of applications in the preparation of organic compounds. Relative to sequences of other reactions with equivalent results, it has definite advantages, whenever it can be employed, because its use involves fewer steps and higher yields. Whenever the Ugi reaction can be incorporated in a synthesis, as a rule, it shows distinct preparative superiority over any alternative (see Section 4.6.4).

### 4.6.3.4 Grandparents, Parents and Godparents

For organic synthesis and biosynthesis the Mannich reaction[60–62] is the most important multicomponent reaction. The Mannich reaction is an $\alpha$-aminoalkylation[46] (**4**) + (**43**) + HX $\leftrightarrow$ (**40**) + $X^-$ + $H_2O$ $\rightarrow$ (**44**) + $H_2O$, where the anion $X^-$ is a carbanion. Ugi was curious to find out whether or not a carbanion-like isocyanide is capable of undergoing a 'Mannich reaction', and the relevant experiments were conducted by his doctoral student Cornelius Steinbrückner.

Steinbrückner[36] reacted piperidine hydrochloride (**53**), aqueous formaldehyde (**54**) and cyclohexyl isocyanide in concentrated methanol solution without cooling, and he was surprised by the violent exothermic reaction. A more carefully executed repetition of the reaction at 0 °C yielded 78% of (**57**) as the product.

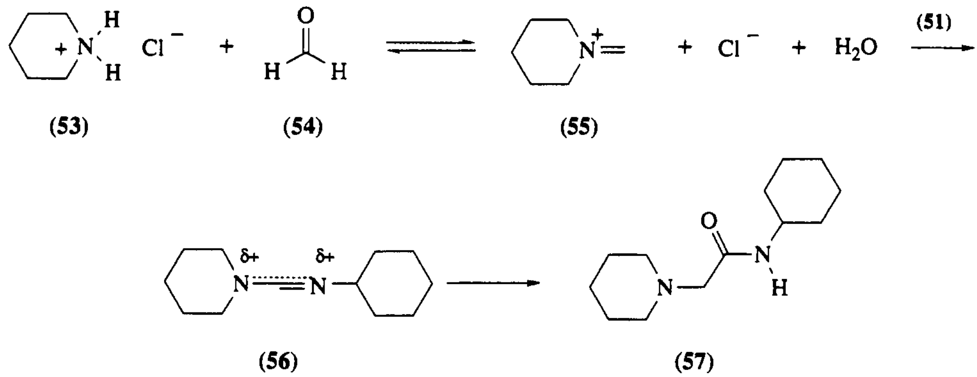

(**51**)

(**53**) (**54**) (**55**)

(**56**) (**57**)

This result was interpreted in terms of the intermediate nitrilium ion (**56**) and its subsequent reaction with water, or a hydroxide ion, as the acid/anion component, to form (**57**). Subsequently a great number of acids/anions were tested in analogous experiments, and the complete set of the suitable acid/anion components 4CC was identified within three weeks.[36]

Accordingly, the Ugi reaction is closely related to the Mannich reaction and may be classified as an $\alpha$-aminoalkylation. However, at the same time, a special type of Ugi reaction, the formation of $\alpha$-acylaminocarboxamides (**42g**) by 4CC of carboxylic acids and primary amines with carbonyl compounds and isocyanides, resembles the Passerini reaction (see Section 4.6.2).

Mannich and Passerini, to whom we owe the two best-known three-component reactions, are the grandparents of the four-component condensation, the Ugi reaction. Its parents are Ugi and Steinbrückner, assisted by coworkers of that period.[36,55] The godparents[12] are Opitz and Merz,[13] McFarland[14] and Sjöberg.[15]

### 4.6.3.5 Stereochemical Course and Reaction Mechanism

When unsymmetrical carbonyl compounds (**4**; $R^2 \neq R^3$) are subjected to the 4CC, a new stereocenter is generated, and two diastereomeric products (**42**) result. Since these are formed *via* pairs of corresponding reactions with diastereomeric transition states,[2o,63–66] the products (**42**) are generally formed at different relative rates, *i.e.* stereoselectively.

Since 1963 stereoselective Ugi reactions have been under investigation.[67–73] It has been demonstrated that such asymmetrically induced[74,75] 4CC proceed only with an appreciable degree of stereoselectivity if a chiral amine component is used whose amino group is directly attached to an asymmetric carbon atom. The chiral $\alpha$-sulfoxido aldehydes would also be promising asymmetrically inducing chiral templates, but they are not available in enantiomerically pure form.[73,76]

The 4CC of benzoic acid (**58**), isobutyraldehyde (**59**) and (*S*)-$\alpha$-phenylethylamine (**60**), or their imine (**61**), with *t*-butyl isocyanide (**26**) has been studied quite extensively as a model reaction for stereoselective 4CC.[64,67–69]

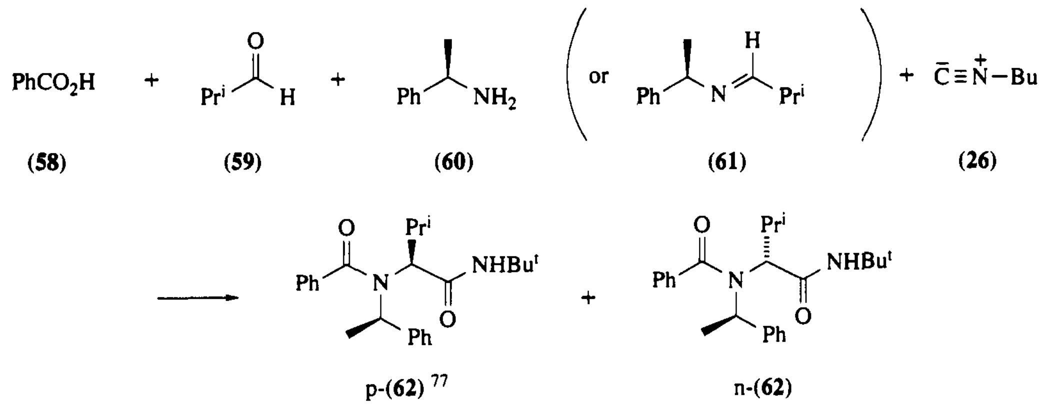

(58) (59) (60) (61) (26)

p-(62)[77] n-(62)

The ratio $Q_{pn}$ of the relative amounts of the products p-(**62**) and n-(**62**) depends strongly on the reaction conditions.[69] $Q_{pn}$ can range from $Q_{pn} \ll 1$ to $Q_{pn} \gg 1$. A mathematical model for the mechanism of the Ugi reaction, a complex system of parallel and consecutive reactions, was established by a computer-assisted analysis of $Q_{pn}$ as a function of the concentration of the reactants in methanol at 0 °C.[2o,64,69] In a solution of (**58**)–(**60**), or (**58**) and (**61**), we have an equilibrium of the species (**63**)–(**66**). The formulas (**63**)–(**66**) describe primarily the stoichiometric composition of the species. The formula (**64**) represents, for instance, the equilibrium system (**64a**)–(**64c**), where (**64a**) is a tight ion pair, (**64b**) is a pair of diastereomers and (**64c**) is a hydrogen-bonded adduct.

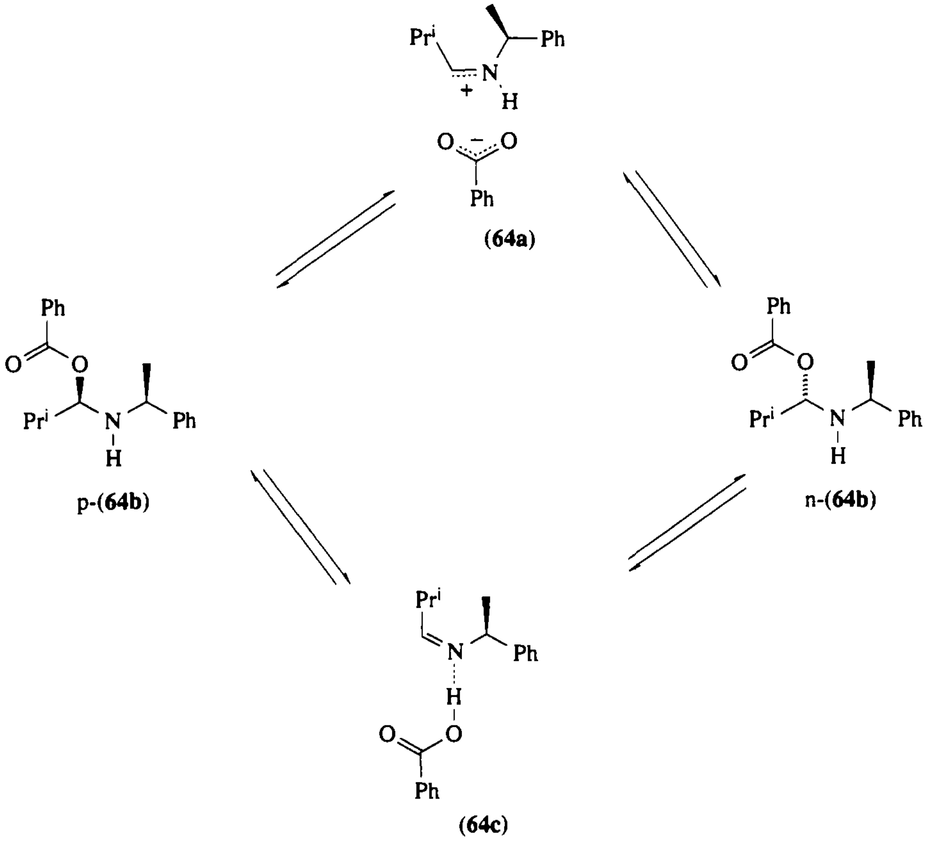

(64a)

p-(64b)

n-(64b)

(64c)

When (**26**) is added sufficiently slowly to this equilibrium system, it is maintained while (**62**) is formed *via* the α-adduct (**67**). Each of the species, or pairs of diastereomers (**63**)–(**66**) belongs to a pair of corresponding reactions whose stereoselectivity is determined by a pair of diastereomeric transition states. Thus (**67**), and thereby also (**62**), is formed by four competing pairs of corresponding reactions. Each one of these has its own intrinsic stereoselectivity $Q_{pn,\nu}$ ($\nu = 63,\ldots,66$). The observed overall stereoselectivity is determined by these $Q_{\mathrm{pn},\nu}$ and the relative contributions of the respective pairs of corresponding reactions.[65]

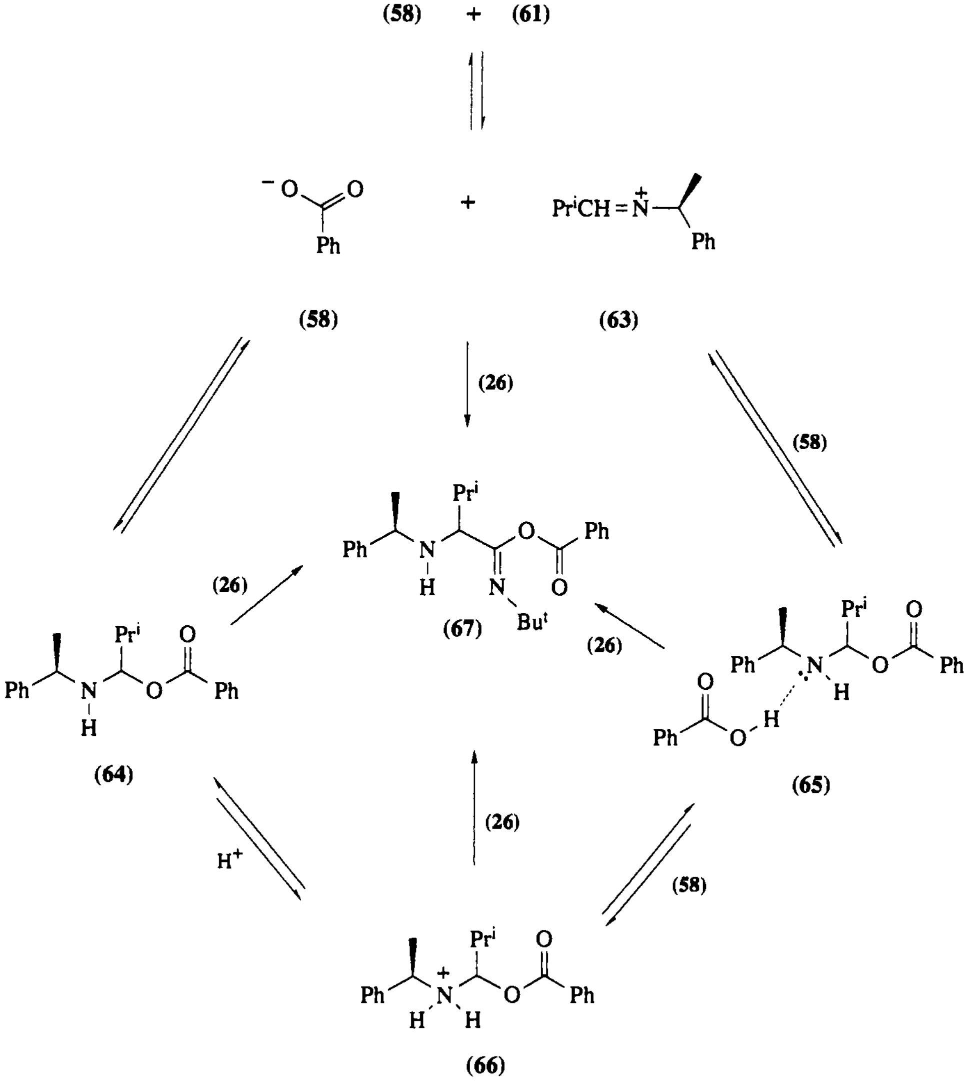

The relative contributions of the individual pairs of corresponding reactions are determined by the equilibrium concentrations of (**63**)–(**66**) and the rates at which these react with (**26**).

The equilibrium concentrations of (**63**)–(**66**) depend on the initial concentrations of (**58**)–(**61**) and of added tetraethylammonium benzoate. Knowing the reaction mechanism, it is possible to influence the contributions of the individual pairs of corresponding reactions, and thereby the overall stereoselectivity, by the choice of the reaction conditions.

### 4.6.3.6 Side Reactions

The four components (**4**), (**5**), (**43**) and HX of the Ugi reaction react with each other in many reversible ways, but, in the ideal case, only the formation of the α-adduct (**41**) and its conversion into the final product are irreversible. Under such conditions a quantitative yield of (**42**) results, as actually happens in some favorable cases.

Generally, the Ugi reaction is, however, in competition with various irreversible side reactions[71] that consume some of the starting materials. Familiarity with the expected side reactions is a prerequisite for avoiding the formation of by-products.

For preparative purposes the Ugi reaction of the carboxylic acids (**3**) is the most important type of 4CC, and their side reactions have been investigated most thoroughly.[71]

The Passerini reaction and the formation of α-hydroxycarboxamides (**24**) may compete with the Ugi reaction.[14] When carboxylic acids (**3**) and carbonyl compounds (**4**) with electron-withdrawing groups are subjected to 4CC in nonpolar solvents such as dichloromethane, the Passerini reaction may compete strongly.[81] Also, with bulky components the Passerini reaction becomes a serious side reaction of the Ugi reaction.[71]

When α-ferrocenylalkylamines are used as (**43**), *N*-dealkylation of the product (**42g**) may occur.[71]

An intriguing and sometimes quite bothersome side reaction is the formation of the malonamide derivatives (**69**)[82,83] that are hard to remove as contaminants of the products (**42g**).

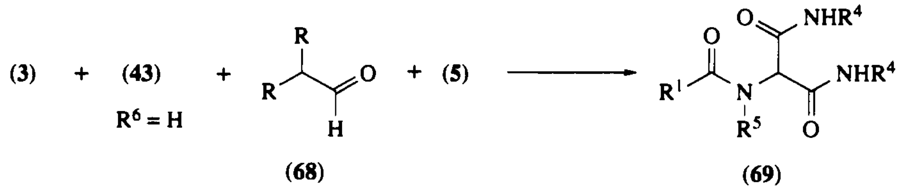

Until recently, none of the attempts to elucidate the nature of this side reaction had been successful. When Ugi was invited to contribute this chapter, we resumed the investigation of the side reaction that produces (**69**), in order to be able to discuss its mechanistic aspect. Since the formation of (**69**) is a minor side reaction of a main reaction that involves at least four distinct participating reactants, its reaction mechanism cannot be elucidated by the customary methods such as kinetic measurements.

For experimental reasons the condensation of (**58**), (**59**), (**70**) and (**71**) was chosen as a model reaction. It was studied by a combination of experimental and computer-assisted methods involving the computer program RAIN (Reaction And Intermediates Networks).[84] The results provide evidence for the intermediacy of (**74**) or a derivative of (**74**).[29b,85]

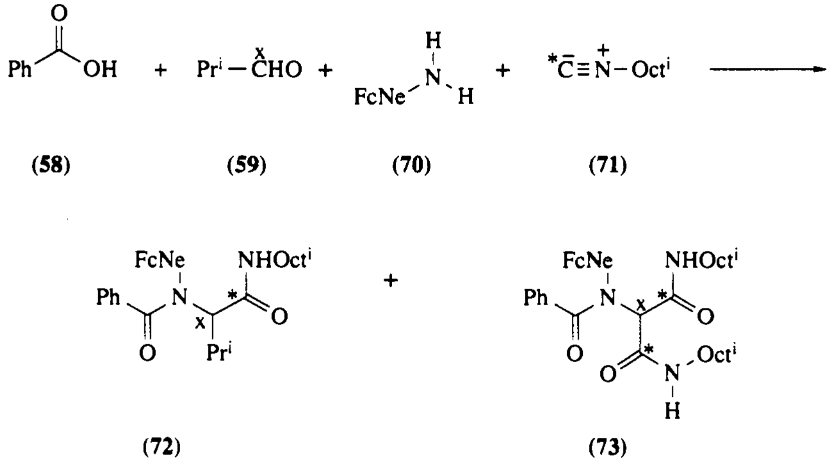

When $^{13}$C-labeled (**71**; $^{13}$C = *C) is employed, the $^{13}$C appears, according to $^{13}$C NMR data, only in the two *N*-isooctylcarboxamide groups of (**73**) with none in the central CH groups, whereas $^{13}$C-labeled (**59**; $^{13}$C = $^{x}$C) leads to (**73**) with the $^{13}$C label at the central CH group. Acetone (**19**) is a coproduct of (**73**). When oxygen is rigorously excluded, no (**73**) is formed. No malonamide derivative is obtained from aldehydes without an α-hydrogen. The 4CC of (**58**), *N*-isooctylglyoxylamide (**74**) with (**70**) and (**71**) proceeds smoothly and gives an almost quantitative yield of (**73**).[29b]

In view of the above experimental evidence, a route *via* (**75**), (**76**), (**77**) and (**78**) is the most plausible among the conceivable reaction pathways from (**58**), (**59**), (**70**), (**71**) and $O_2$ to (**73**) and its coproducts. Accordingly, we have the overall process (**58**) + (**59**) + 2(**70**) + (**71**) + $O_2$ → (**19**) + (**73**), *i.e.* a reaction with six participating molecules.

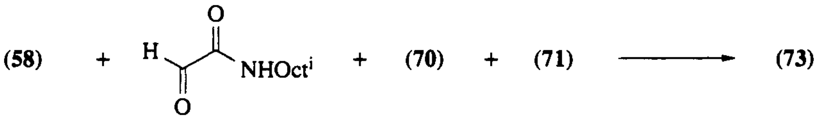

(74)

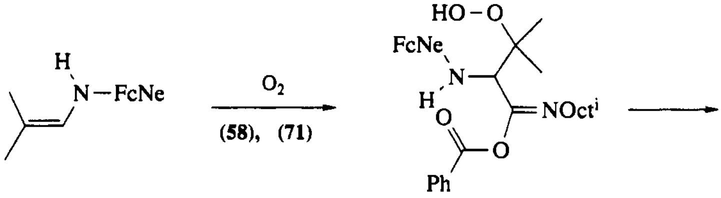

(75) (76)

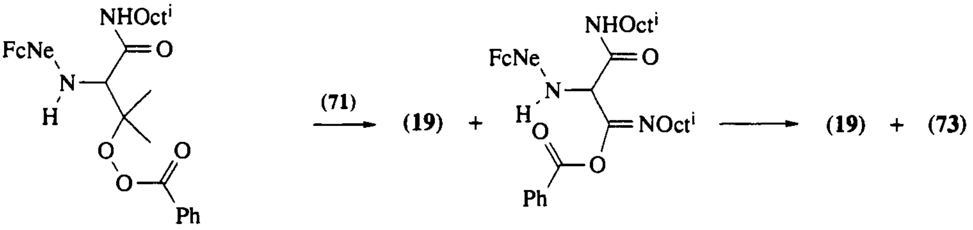

(77) (78)

## 4.6.4 SYNTHESES WITH THE UGI REACTION

### 4.6.4.1 Peptide Coupling

Amino acid or peptide derivatives (**79**) and (**80**) with suitable protective groups at their terminal amino and carboxyl groups can be coupled by the Ugi reaction.

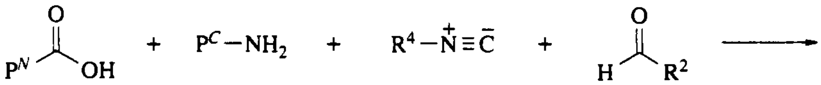

(79) (80) (5) (4) $R^3 = H$

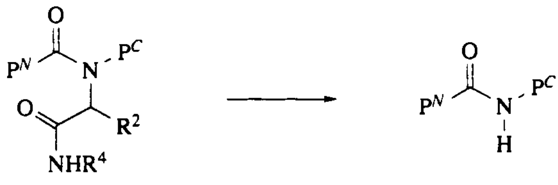

(81) (82)

The aldehyde (**4**; $R^3 = H$) must carry a group $R^2$ that renders the 4CC product (**81**) cleavable in order to obtain the *N*-unsubstituted peptide derivative (**82**).[71,86–90] About 50 aldehydes have been tested as candidates for peptide coupling, but only a few (**4a–d**) undergo the required Ugi reaction (**4**; $R^3 = H$) + (**5**) + (**79**) + (**80**) → (**81**) in sufficient yield of a readily cleaved product (**81**), and with an acceptable degree of racemization.[88] The cleavage of (**81c**, **d**) requires treatment with HBr/AcOH.[91]

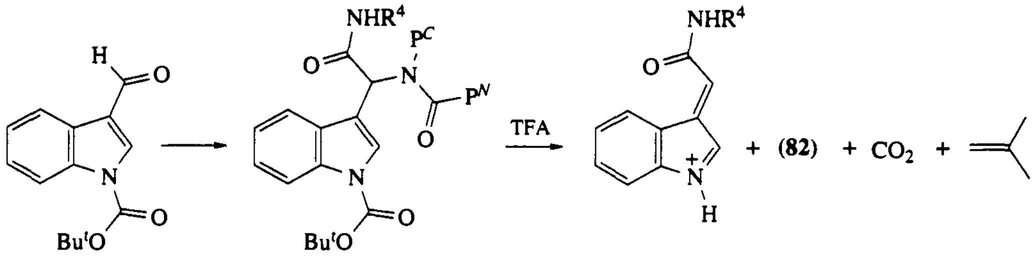

(4a)[89] (81a) (83)

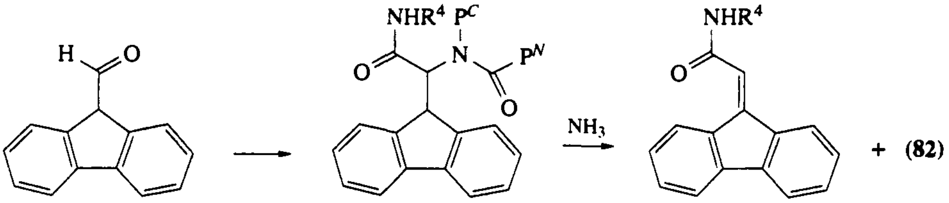

(4b)[90] (81b) (84)

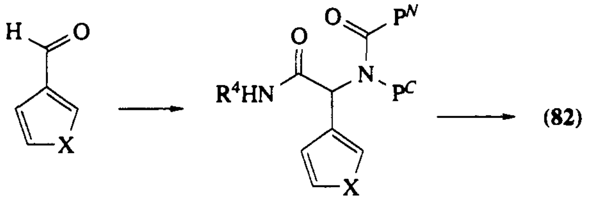

(4)[91] c: X = O
d: X = S
(81)

An elegant application of peptide coupling by 4CC is the synthesis of cyclopeptides by Failli, Immer and Götz.[92]

The main advantage of peptide coupling by the Ugi reaction is that the peptide derivatives (**81**) are generally much more soluble in organic solvents than the *N*-unsubstituted peptides (**82**). Some of the common difficulties in peptide synthesis that are due to insoluble intermediates can be overcome by this type of 4CC.

### 4.6.4.2 α-Amino Acid Derivatives from Achiral Amines

A new amino acid unit can be generated from a carbonyl compound (**4**), during the synthesis of an α-amino acid or peptide derivative (**86**) by the Ugi reaction.

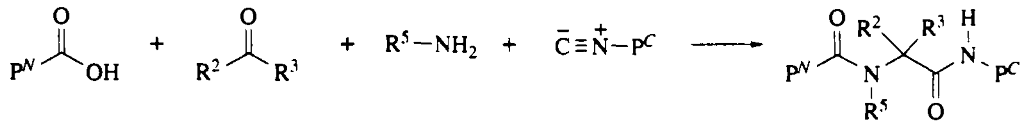

(79) (4) (43) $R^6 = H$ (85) (86)

The required α-isocyano derivatives (**85**) of α-amino acids are prepared from the corresponding α-formylamino acids. If (**85**) is a peptide derivative, no racemization is observed at the α-isocyanoacyl unit.[93] The preparation of chiral α-isocyanocarboxylate esters, however, is possible with phosgene[2q] or diphosgene[28] in the presence of *N*-methylmorpholine. The use of carbonyldiimidazole dimesylate[94] is inadvisable.[95]

By conventional methods the peptides of α-aminoisobutyric acid (Aib) are difficult to synthesize, whereas their preparation by 4CC proceeds very well. The syntheses of the alamethicine segments (**89**) and (**92**)[71] serve as examples.

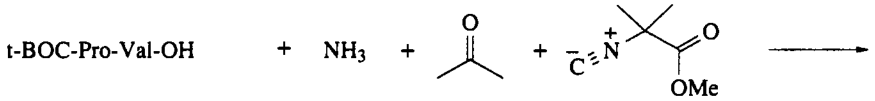
t-BOC-Pro-Val-OH
+ NH3 +
O
+
C
N
O
OMe

(**87**) (**19**) (**88**)

t-BOC-Pro-Val-Aib-Aib-OMe

(**89**) 74%

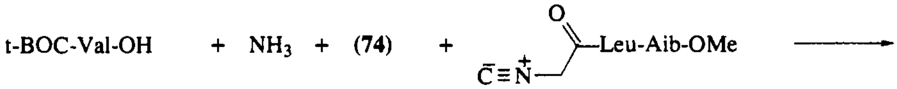
t-BOC-Val-OH
+ NH3 + (74) +
O
Leu-Aib-OMe
C≡N

(**90**) (**91**)

t-BOC-Val-Aib-Gly-Leu-Aib-OMe

(**92**) 93%

A 4CC synthesis of an α,α-di-*n*-propylglycine derivative has been reported by Hardy and Lingham.[96] The synthesis of bicyclomycin (**93**) by Fukuyama *et al.*[97] begins with an Ugi reaction of (**94**)–(**97**).

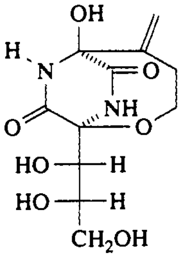
OH
H
N
O
NH
O
O
HO
H
HO
H
CH2OH

(**93**)

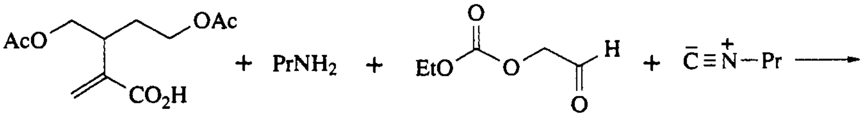
AcO
OAc
CO2H
+ PrNH2 +
EtO
O
O
H
O
+
C≡N−Pr

(**94**) (**95**) (**96**) (**97**)

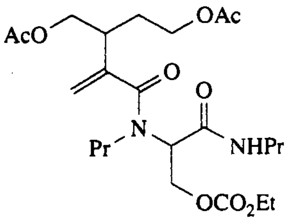
AcO
OAc
O
O
N
Pr
NHPr
OCO2Et

(**98**)

De Laszlo and Williard[98] obtained the marine natural products (+)-dimethyldysidenin (**103**) and (−)-dimethylisodysidenin (**104**) by 4CC.

The syntheses of the nucleoside antibiotics willardiin (**108**) and the analog (**109**)[99] of nikkomycin and sinefugin are based on the Ugi reaction.

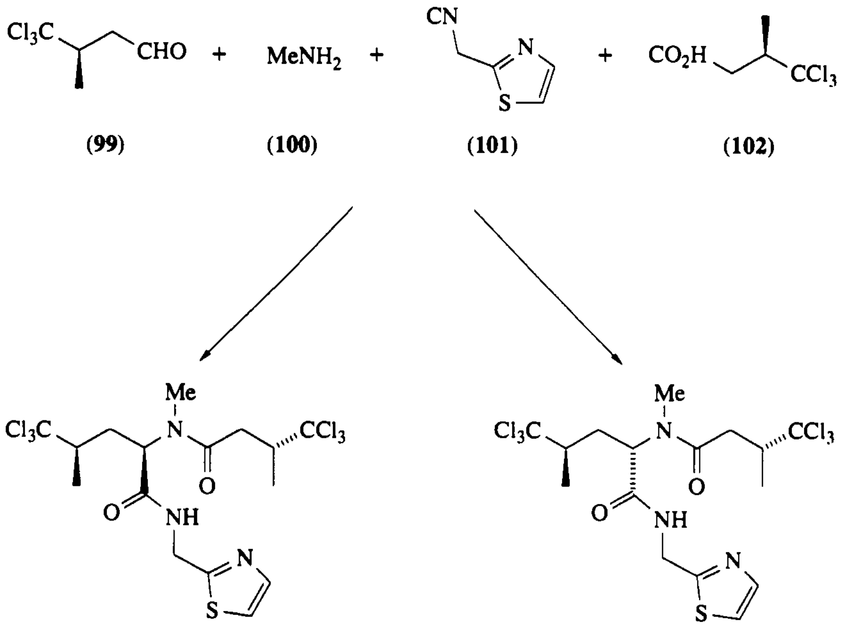

Cl3C
CHO
+
MeNH2
+
CN
N
S
+
CO2H
CCl3
(99)
(100)
(101)
(102)
Me
N
CCl3
O
O
NH
N
S

**(103)** **(104)**

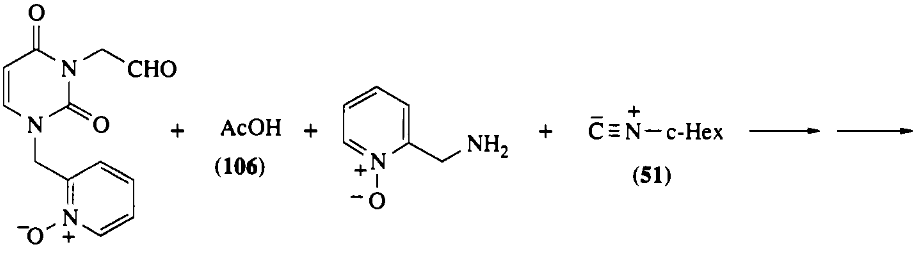

O
N
CHO
N
O
N
O
+
+
AcOH
+
N
O
NH2
+
C≡N—c-Hex

**(105)** **(106)** **(107)** **(51)**

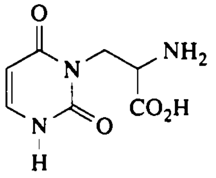

**(108)**

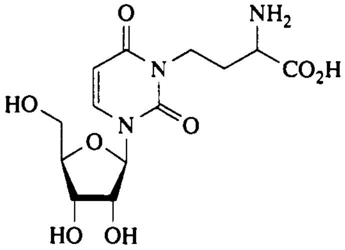

**(109)**

The Ugi reaction also played a key role in the syntheses of the di- and tri-peptide polyoxins (**110**) and (**111**).[100]

Joullié *et al.*[101] have developed a totally novel and very elegant approach to the synthesis of proline peptides that is based on the Ugi reaction of pyrroline derivatives.

Some racemic phospho analogs of tri- and tetra-peptides have been obtained by 4CC of (**112**) in 68–93% yield, *e.g.* (**113**).[18b]

The key step in the syntheses of the antibiotics plumbemycin (**114a**) and (**114b**) by Natchev[102] is the Ugi reaction.

The Ugi reaction has also been used for the synthesis of numerous racemic *N*-amino analogs of eloidisine.[40]

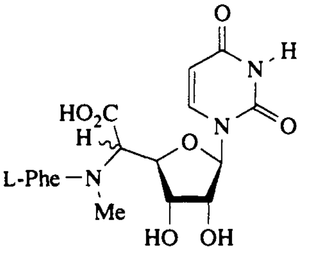

**(110)**

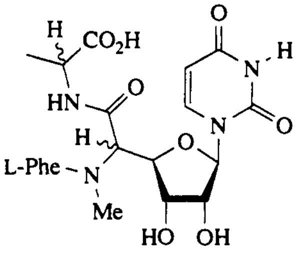

**(111)**

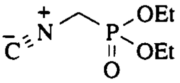

**(112)**

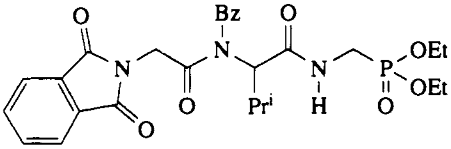

**(113)**

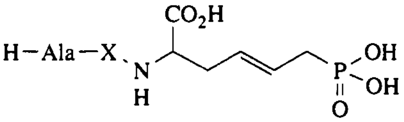

**(114)** a: X = Asn
b: X = Asp

### 4.6.4.3 Asymmetric Syntheses of α-Amino Acid and Peptide Derivatives

The synthesis of α-amino acid and peptide derivatives (**86**) whose newly formed amino acid unit corresponds to a chiral α-amino acid requires an asymmetric 4CC with a high degree of stereoselectivity.

Under suitable conditions the amine component (**43**; $R^6 = H$) for peptide syntheses by a stereoselective Ugi reaction must be a good chiral template, *i.e.* it must have strong asymmetric inducing power, and it must be endowed with a group $R^5$ that is cleavable from the 4CC product (**86**) under mild conditions. The search for a suitable chiral amine component (**43**; $R^6 = H$) has been the most challenging subproblem in the development of peptide syntheses by stereoselective Ugi reactions.[2p,71]

First, the resonance-stabilized vinylamines, *e.g.* ethyl β-aminocrotonate (**45**), were tested as amine components, because their 4CC products are cleavable by mild acidolysis.[45] In amines of the type (**45**) any center of chirality could, at best, be placed three bonds from the newly formed center of chirality. Accordingly, such amines would not be effective as chiral templates.

Next, β-alanine derivatives (**115**) were studied. They are fairly powerful as chiral templates in 4CC. Their 4CC products are, however, only cleavable by strong bases that damage peptide derivatives.

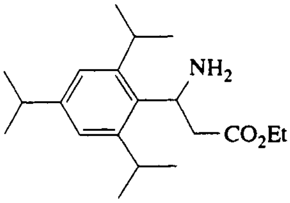

**(115)**

Until recently the most promising chiral amine components (**43**; $R^6 = H$) for peptide syntheses by stereoselective 4CC were the α-ferrocenylalkylamines (**116**).[71,103,104] The α-ferrocenylalkylamines (**116**) have a unique combination of desirable properties: they are easy to synthesize from the aldehydes;[104] any substitution at the α-carbon of alkylferrocenes proceeds with retention;[105] in the presence of (**118**) the acidolytic cleavage of (**117**) yields, besides (**120**), its coproduct (**119**), which is reconvertible into (**116**) with full retention of its configuration;[106] furthermore, the cleavage of (**117**) can be conducted in a destructively stereoselective mode.[107]

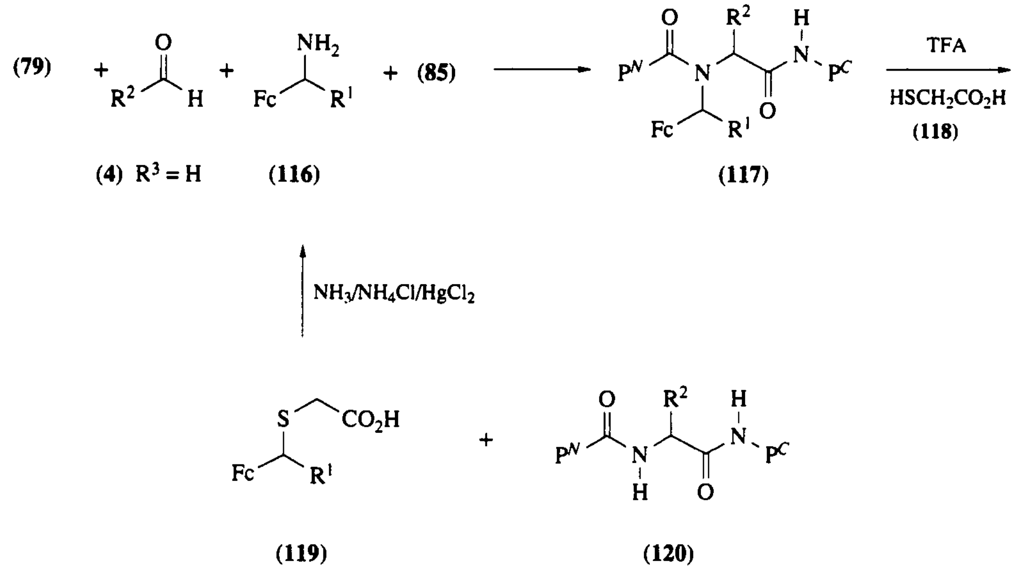

In the early work with the α-ferrocenylalkylamines (**116**), the preferred amine component was (**116**; R = $\mathrm{Pr^i}$).[103] At –40 to –80 °C in methanol this compound undergoes the above 4CC with very good stereoselectivity, but often the results are not reproducible,[108] because sometimes the reactants stay in supersaturated solution, and the reaction proceeds at the low temperature, whereas in other instances some of the reactants precipitate, and the condensation takes place upon warming. Therefore, amine components like (**116**; R = Me) with acceptable selectivity at higher temperatures ($T > 0$ °C) are preferred, due to a low estimated zero selectivity temperature.[66]

In the search for optimum amine components and reaction conditions for the synthesis of peptides by the stereoselective Ugi reaction, model 4CC reactions with TFA as the acid component are very convenient because the products (**121**) are easy to analyze by $^{19}$F NMR.[109,110]

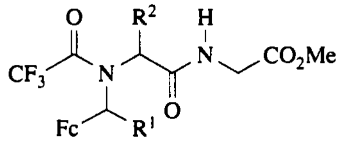

(**121**)

Recently important progress has been made by Kunz *et al.*[111] in the development of the syntheses of chiral amino acid and peptide derivatives by stereoselective 4CC. These authors demonstrated that *O*-acylated 1-aminocarbohydrates, *e.g.* 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**122**), undergo chelate-assisted highly stereoselective 4CC (diastereomer ratio 91:9 to 97:3) in THF in the presence of $ZnCl_2$ at –78 °C.

The acidolytic removal of the chiral auxiliary group from (**124**) is achieved by HCl in methanol. The drastic conditions of acidolysis may limit this method to the synthesis of amino acids.

These results stimulated us to synthesize tetra-*O*-methyl-β-D-glucopyranosylamine (**126**).[112a] The 4CC products of (**126**) undergo acidolytic N—C cleavage under milder conditions than (**124**).[112b] We are now studying the stereoselective model 4CC of (**126**), as well as of (**127**) and (**128**), in the presence of chelating catalysts like $ZnCl_2$ and $\mathrm{Ti(OPr^i)_4}$. The latter enhances the stereoselectivity of 4CC with (**127**) considerably.[109b,113]

By analogy with Carlson's[114] optimization of syntheses by computer-assisted multivariate methods,[115] Fleck[116] is presently conducting a systematic search for an optimum set of conditions (including the chiral amine component and catalysts) for peptide syntheses by stereoselective 4CC.

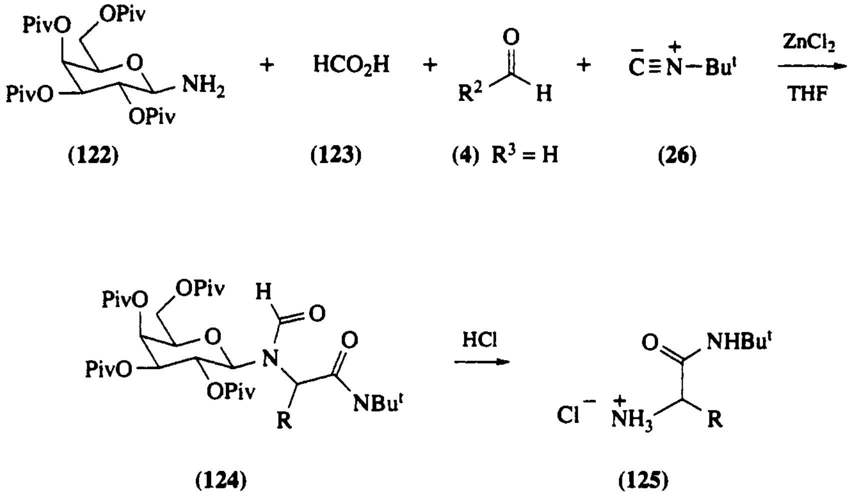
PivO
OPiv
O
NH2
HCO2H
R2
H
C≡N–Bu^t
ZnCl2
THF
HCl
NBu^t
R
NHBu^t
Cl^−
NH3

(122) (123) (4) $R^3 = H$ (26)

(124) (125)

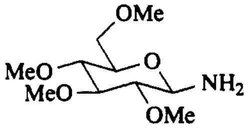
OMe
MeO
MeO
O
NH2
OMe

(126)

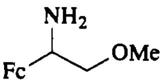

(127)

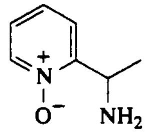

(128)

The potential advantage of amino acid and peptide syntheses by stereoselective 4CC *vs.* the traditional methods is not only the smaller number of steps needed, but also the fact that almost any chiral amino acid can be synthesized in both configurations from carbonyl compounds, also as a moiety of a peptide. *N*-Substituted peptide segments with improved solubility are available using the Ugi reaction.[71] These create new possibilities for the synthesis of large peptides.

Joullié *et al.*[70] have synthesized (+)-furanomycin (**131**) by an asymmetric Ugi reaction. This synthesis led to revision of the assumed structure.

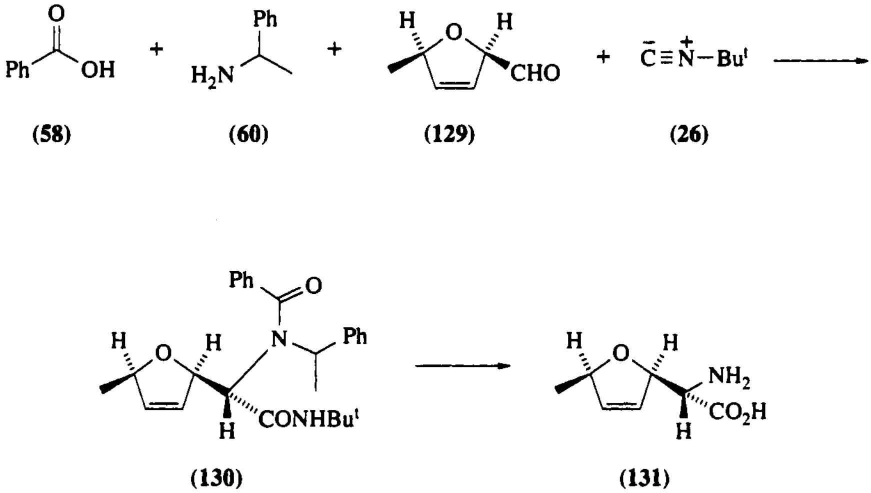
Ph
OH
H2N
CHO
C≡N–Bu^t
CONHBu^t
NH2
CO2H

(58) (60) (129) (26)

(130) (131)

### 4.6.4.4 β-Lactams

As a rule, the synthesis of β-lactams by cyclization of β-amino acids such as (**132**) is impeded by Bayer strain and adverse conformational effects.[117] By contrast, the conversion of β-amino acids into β-lactams by the Ugi reaction occurs with ease and in good yield.[55,118]

In such syntheses of β-lactams a seven-membered cyclic α-adduct (**133**) is formed; from (**133**) the β-lactam system (**134**) results by transannular acyl transfer. As a consequence, the Ugi reaction has been used in numerous syntheses of β-lactam antibiotics and related compounds.[118]

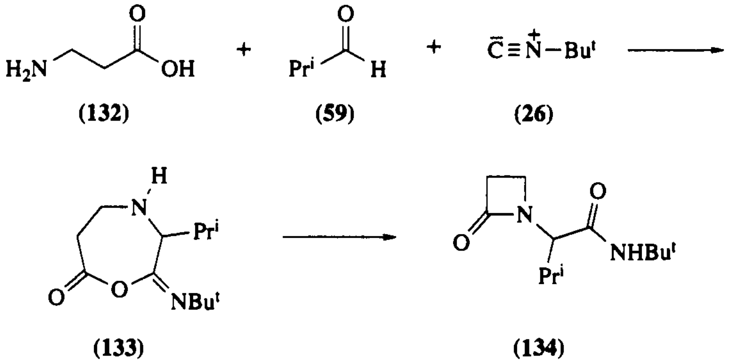

(**132**) (**59**) (**26**)

(**133**) (**134**)

The nocardicins (**135**) are monocyclic β-lactam antibiotics. The essential step in the synthesis of the nocardicins by Isenring and Hofheinz[119] is the formation of (**139**) from (*S*)-isoserine (**136**) by 4CC. Their synthesis of isonocardicin A, a diastereomer of (**135a**) from (*S*)-homoserine follows the same pattern, as well as the preparation of numerous analogs of nocardicin.

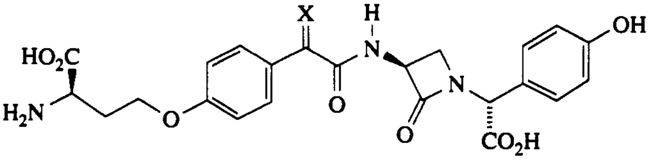

(**135**) **a**: $\mathrm{X} = \mathrm{N}{\diagup}^{\mathrm{OH}}$

**b**: $\mathrm{X} = {}^{\mathrm{HO}}{\diagdown}_{\mathrm{N}}$

**c**: X = O

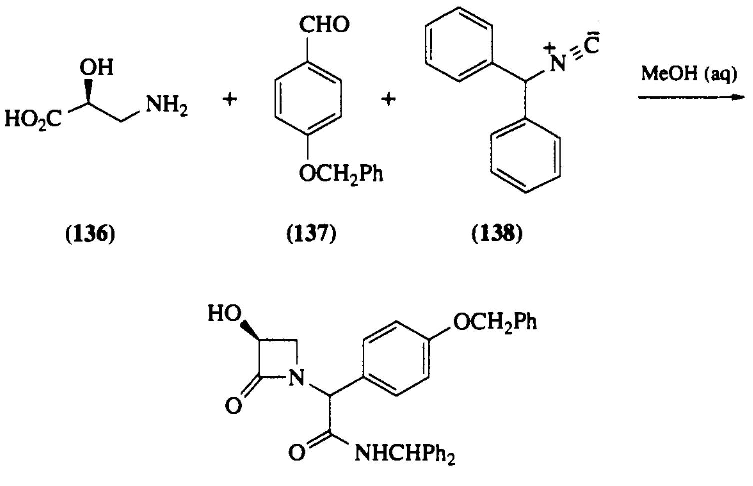

(**136**) (**137**) (**138**)

(**139**)

The synthesis of the β-lactam antibiotics and related compounds (**142**) by the Ugi reaction proceeds *via* the carboxamide derivatives (**141**).

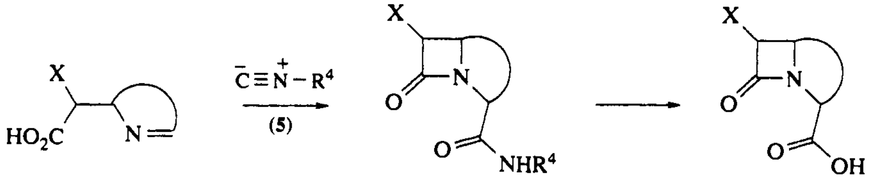

**(140)** **(141)** **(142)**

The latter must be converted into the free carboxylic acids (**142**) in the presence of the relatively labile β-lactam moiety, a conversion that still poses a major problem; for the step (**141**) → (**142**) there is still no generally applicable and satisfactory method available.

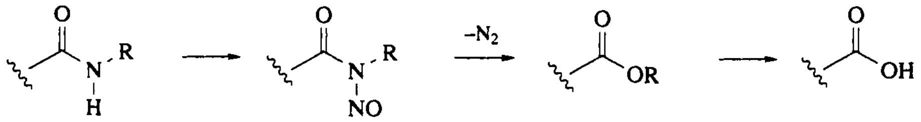

**(143)** **(144)** **(145)** **(146)**

The most promising approach to (**141**) → (**142**) is based on *N*-nitrosation[120] of the carboxamide group, and conversion of (**144**) into an ester (**145**) whose R group can be replaced by H under mild conditions.

In the aforementioned syntheses of the nocardicins and their analogs the benzhydryl group (**145**; R = $CHPh_2$) was removed by hydrogenolysis, and so was the *p*-nitrobenzyl group (**145**; R = Pbn).[121b]

In a previous carbapenem synthesis of Hatanaka *et al.*[121a] *via* the methyl ester (R = Me), the latter was subjected to mild alkaline hydrolysis. As Achatz[122] has found, the *N*-ethoxycarbonylmethylcarboxamides (**143**; R = $CH_2CO_2Et$) undergo the conversion (**143**) → (**145**) particularly well, and the resulting esters are selectively hydrolyzable under mild conditions. The allyl group (R = All) has recently emerged as a most promising protecting group; it is cleavable by nucleophiles in the presence of $Pd(PPh_3)_4$.[123] In the context of (**143**) → (**146**) the allyl group has also performed very well.[73]

The *o*-aminophenyl- and *o*-hydroxyphenyl-carboxamides (**149**) undergo the sequence of reactions (**149**) → (**151**) → (**152**) smoothly.[124] This is the basis of a method for achieving (**141**) → (**142**). The somewhat cumbersome preparative access to the isocyanides (**147**), and the sometimes less than satisfactory yields (58–75%) of penam syntheses by the Ugi reaction (**140**) + (**147**) → (**149**), are the disadvantages of this method.[125,126]

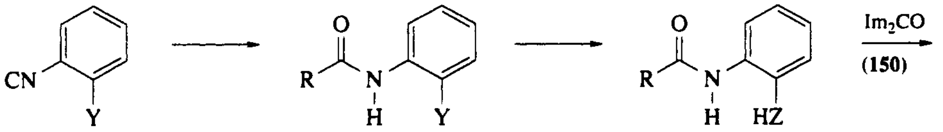

**(147)** Y = $N_3$, OBz,[124] $OSiMe_2Bu^t$ [125] **(148)** **(149)** Z = NH, O

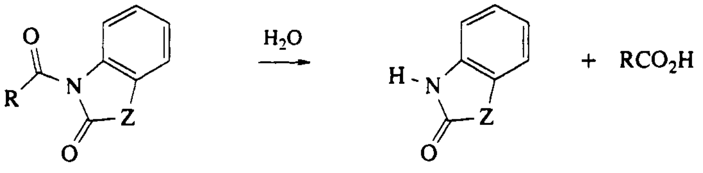

**(151)** **(152)**

The first preliminary studies towards the synthesis of penam derivatives by the Ugi reaction were carried out roughly 30 years ago.[127] 3-Thiazoline derivatives (**153**) were allowed to react with isocyanides in the two-phase system water/petroleum ether to yield up to 95% of the penam derivatives (**154**).

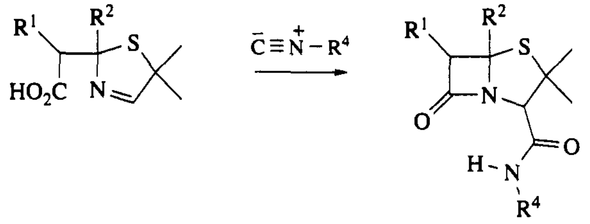

**(153)** $R^1 = R^2 =$ H, Me **(154)** $R^4 =$ Bu$^t$, c-Hex

We were surprised to find that despite the general lability of penam derivatives, the products (**154**) could be purified by sublimation *in vacuo*. Using a similar scheme, Sjöberg[128] synthesized the amide of a stereoisomer of penicillin G, but in very low overall yield, because formation of the required 3-thiazoline derivative by the Asinger condensation did not proceed satisfactorily.

Schutz and Ugi[129] developed the synthesis of penam derivatives (**155**; R = Me) → (**159**; $R^4$ = Bu$^t$). This penam synthesis was improved by the use of R = All and $R^4$ = All or $CH_2CO_2Et$.[122] In these recent β-lactam syntheses the Ugi reaction was executed in trifluoroethanol, a 'magic solvent' for such conversions.[73,125] In a recent carbacephem synthesis ethylene glycol/glycerol gave very good results as the solvent.[118b]

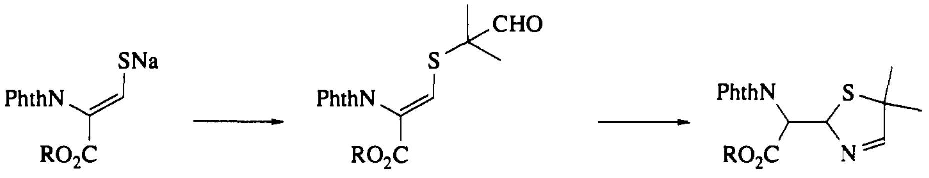

**(155)** **(156)** **(157)**

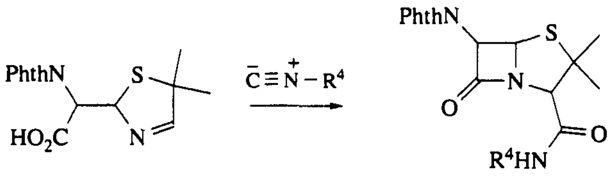

**(158)** **(159)**

Just *et al.*[130] attempted the synthesis of the oxacepham derivatives (**167**) as outlined below. This synthesis was planned as a model for analogous syntheses of cepham derivatives. Its design is ingenious, but it was not a complete success, because (**164**) did not react with $NH_3$ to form (**165**); it gave (**166**). The ring closure with $NH_3$ might have worked better with (**163**). Presumably discouraged by this result of their model study, these authors terminated their efforts in this field.

They demonstrated the effectiveness of the alkylation of enolates (**160**) + (**161**) → (**162**) for preparing precursors of penam and cepham derivatives. The penam synthesis by Schutz and Ugi, as well as the cepham synthesis[131] (**168**) → (**173**) profited from Just *et al.* immensely.[130]

In the field of the carbapenem syntheses Hatanaka *et al.*[121] have set new standards by their elegant syntheses of the carbapenem (**179**) and the synthesis of the carbapenem antibiotic PS-5 (**180**) and its 6-epi analog in remarkably few steps.[121]

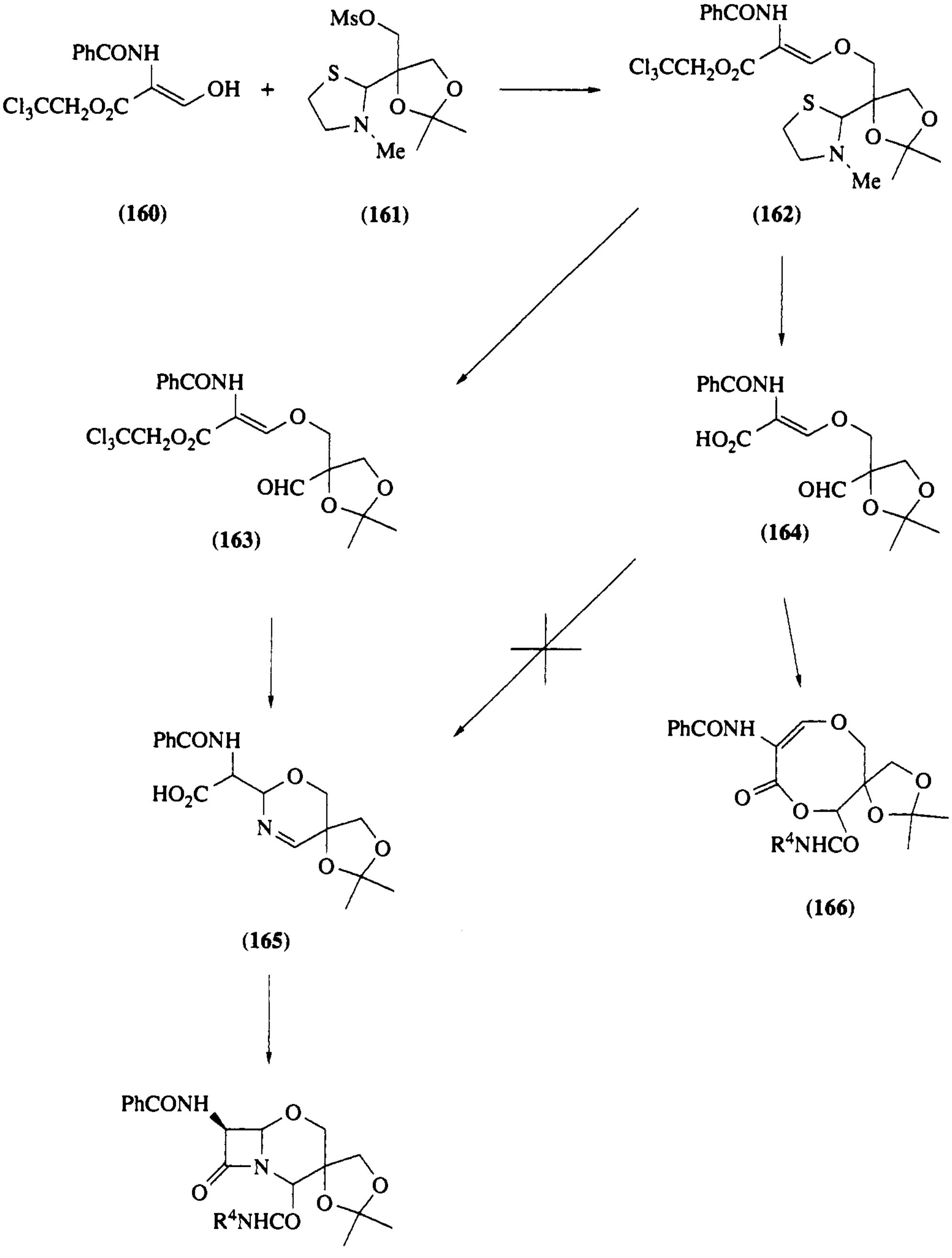

## 4.6.4.5 Macromolecules

The usefulness of the Ugi reaction is not confined to the chemistry of small molecules, but also has applications in macromolecular chemistry.

The Ugi reaction is, for instance, used for the immobilization of enzymes,[132] and it is one of the best methods for attaching peptide and protein molecules to a solid support for sequence analysis by a modified Edman degradation.[133]

Enzymes can be immobilized by inclusion without significant loss of activity through a crosslinking 4CC of alginic acid, bis(*N*-3-aminopropyl)methylamine (**181a**), the corresponding isocyanide (**181b**) and formaldehyde in dilute aqueous solution of the enzyme.[134]

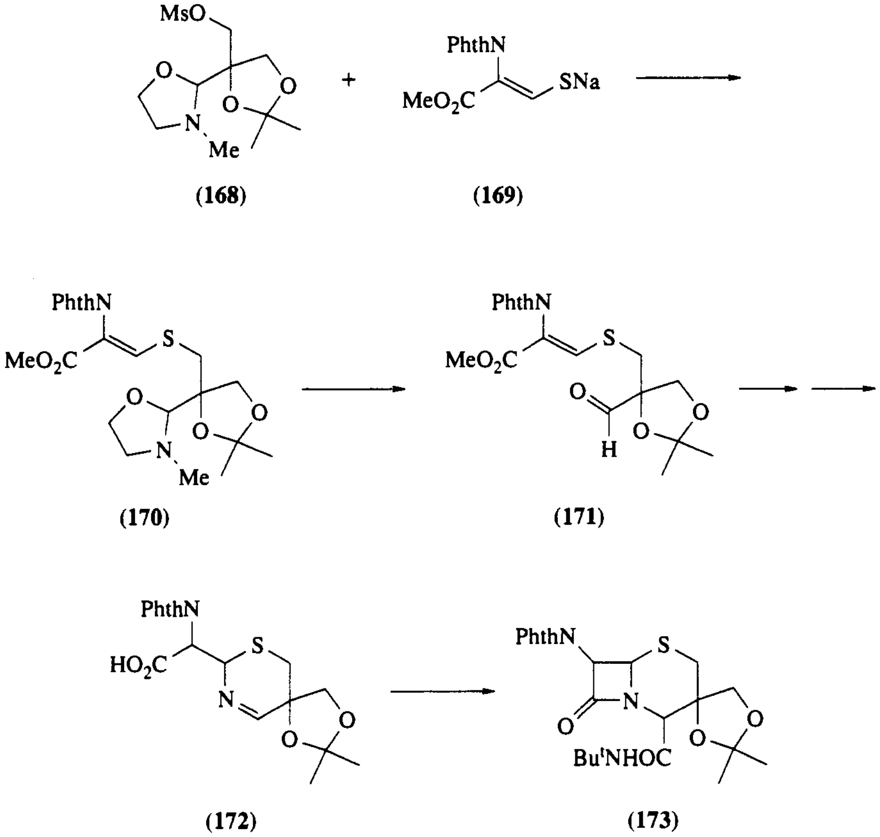
MsO
O
N
Me
O
O
+
PhthN
MeO2C
SNa
(168)
(169)
PhthN
MeO2C
S
(170)
O
H
(171)
HO2C
N
(172)
PhthN
S
N
O
Bu'NHOC
(173)

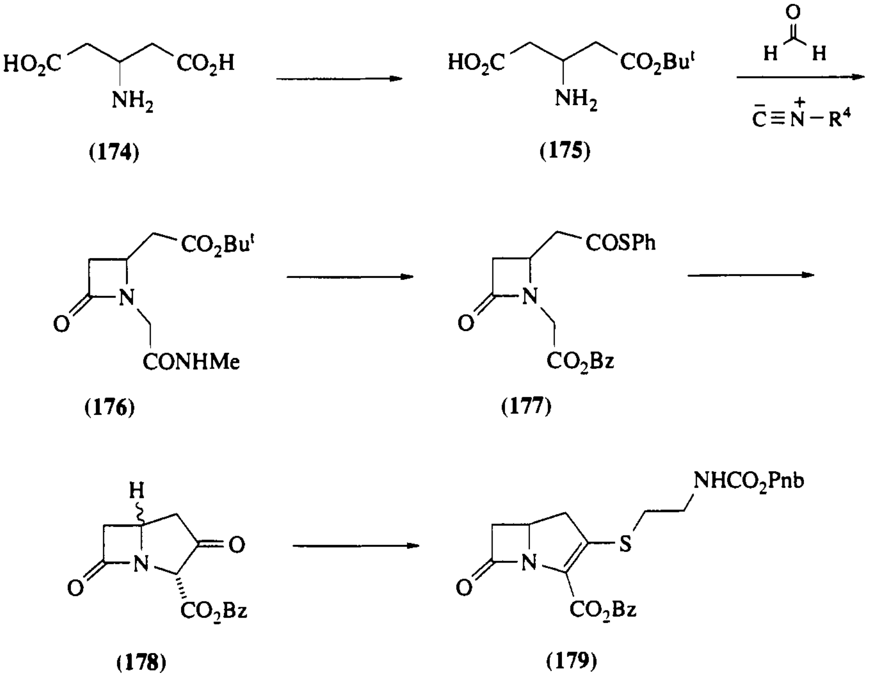
HO2C
CO2H
NH2
(174)
HO2C
CO2Bu'
NH2
(175)
O
H
H
C≡N−R4
CO2Bu'
N
O
CONHMe
(176)
COSPh
CO2Bz
(177)
H
O
CO2Bz
(178)
NHCO2Pnb
S
CO2Bz
(179)

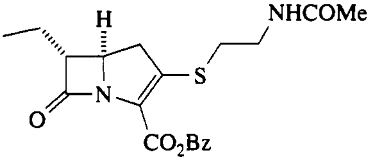

**(180)**

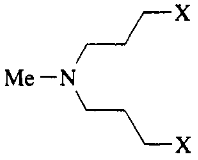

**(181)** a: X = $NH_2$

b: X = NC

## 4.6.5 ABBREVIATIONS

Ac = acetyl; All = allyl; $Bu^t$ = *t*-butyl; Bz = benzyl; Fc = ferrocenyl; FcEt = 1-ferrocenylethyl; FcNe = 1-ferrocenyl-2,2-dimethylpropyl; c-Hex = cyclohexyl; Im = imidazoyl; Me = methyl; $Oct^t$ = 2,4,4-trimethylpentyl; Ph = phenyl; $PhEt(NH_2)$ = (*S*)-1-phenylethyl(amine); Piv = pivaloyl; Pnb = *p*-nitrobenzyl; $Pr^i$ = isopropyl.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N'*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

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The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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## Volume 3

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C $\pi$-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,*** etc.

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N'*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Alkylations of Enols and Enolates

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## 1.1.1 INTRODUCTION

The α-alkylation of carbonyl compounds by their conversion into nucleophilic enolates or enolate equivalents and subsequent reaction with electrophilic alkylating agents provides one of the main avenues for regio- and stereo-selective formation of carbon–carbon σ-bonds.[1–6] Classical approaches to α-alkylation typically involve the deprotonation of compounds containing doubly activated methylene or methine groups and having $pK_a$ values of 13 or below by sodium or potassium alkoxides in protic solvents. Since these conditions lead to monoenolates derived from deprotonation only at the α-site of the substrate, the question of the regioselectivity of *C*-alkylation does not arise (however, there is competition between *C*- and *O*-alkylation in certain cases). In more recent years, dienolates of β-dicarbonyl compounds have been utilized in γ-alkylations with excellent success.

α-Alkylations of active methylene compounds followed by removal of one of the activating groups to produce monofunctional products is quite useful for large scale synthesis of relatively simple carbonyl compounds. Indeed, if one wishes to use conventional methods of enolate formation in alkylations of simple unsymmetrical ketones, extraneous methylene blocking groups or activating groups, which are to be removed eventually, must be applied.[2,4] However, modern synthetic methodology has focused upon α-alkylation of monofunctional carbonyl systems *via* their metal enolates or enolate equivalents produced quantitatively by direct or indirect methods. Since monofunctional carbonyl compounds have $pK_a$ values in the 20–27 range, strong bases in aprotic solvents are required for direct enolate formation by deprotonation. Many of these substrates (aldehydes, carboxylic acid derivatives and certain ketones) contain only one reactive α-site. In these cases, the question of regioselective enolate formation does not arise, although in most cases stereoisomeric (*E*)- or (*Z*)-enolates or mixtures of these species may be produced, depending upon the substrate and reaction conditions.[2] However, the challenging problems encountered in the total synthesis of steroids, terpenoids or other complex molecules have required the development of methods of regioselective alkylation of unsymmetrical ketones, which are capable of enolization in two directions.

Upon treatment with strong bases unsymmetrical ketones such as 2-methylcyclohexanone (**1**) can lose a proton to give the tri- or tetra-substituted enolates (**2**) or (**3**). Under kinetic control, where the ketone is added slowly to a soluble strong base in an aprotic medium, the enolate mixture composition is determined by the relative rates of proton removal from the alternative α-positions. Because the less-substituted α-position is less hindered, the less-substituted enolate, *e.g.* (**2**), is usually favored under kinetic conditions. However, when relatively basic Group I sodium or potassium enolates are employed, enolate equilibration, brought about by proton transfer reactions involving the initially formed alkylated ketones and unalkylated enolates, is normally faster than alkylation. As a result, products derived from alkylation of the more highly substituted enolate (**3**), which is normally the more thermodynamically stable isomer, usually predominate. Rapid proton transfer reactions also account for the formation of di- and even trialkylated products in alkylations involving potassium or sodium enolates.

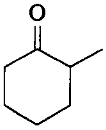

**(1)**

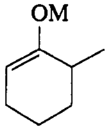

**(2)**

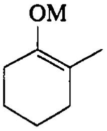

**(3)**

An illustration of this behavior is provided in equation (1). A 67:33 mixture of the less- and more-substituted potassium enolates was produced upon treatment of 2-methylcyclohexanone with tritylpotassium in DME. However, the major product of alkylation of this mixture with methyl iodide was 2,2-dimethylcyclohexanone and significant amounts of tri- and tetra-methylcyclohexanone were also obtained.[7]

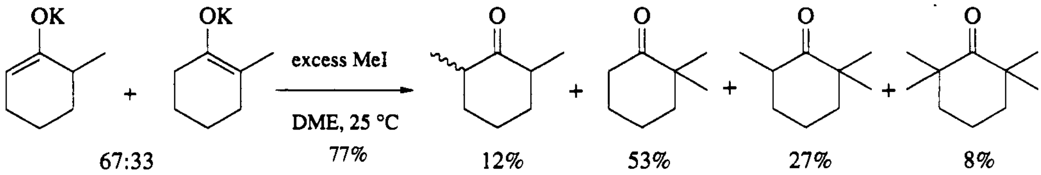

(1)

The modern era of enolate alkylations began in 1961 when Stork *et al.*[8] showed that the less thermodynamically stable lithium 1-enolate (**4**) of *trans*-10-methyl-2-decalone, produced by lithium–ammonia reduction of the corresponding octalone, could be alkylated regiospecifically with reactive alkylating agents in liquid ammonia. Regiospecificity was not maintained if potassium or sodium was employed in the reduction, or if the enolate (**4**) was transferred to DMSO prior to alkylation. These conditions gave 3-alkyl-substituted products *via* the more thermodynamically stable 2-enolate, as did deprotonation of the parent decalone with strong bases.

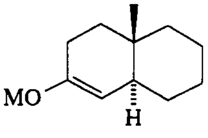

**(4)**

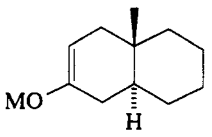

**(5)**

The above results led to an explosion of interest in the use of lithium enolates in α-alkylation reactions. It was quickly demonstrated that specific lithium enolates of a variety of unsymmetrical ketones could be trapped with the more reactive alkylating agents in liquid ammonia or aprotic solvents such as

DME or THF. Clearly, the ratio of the rate of alkylation to the rate of proton transfer is significantly larger for less basic lithium enolates than for their sodium and potassium counterparts.

In order to exploit the unique behavior of lithium enolates, a wide variety of highly hindered, nonnucleophilic bases such as LDA, LICA, LITMP, lithium hexamethyldisilylamide (LHDS) and lithium tetramethyldiphenyldisilylamide (LTDOS), which kinetically convert unsymmetrical ketones to their less-substituted enolates with high regioselectivity, have been developed.[2] Lithium *t*-octyl-*t*-butylamide (LOBA) has recently been shown to be a highly useful base for this purpose.[9] Likewise, a variety of indirect methods for formation of lithium enolates such as lithium–ammonia reduction of enones,[10] conjugate additions of organocuprate reagents to enones[11] and the cleavage of silyl enol ethers with organolithium reagents[12] have been developed or expanded. An excellent survey of methods of formation of lithium and other enolates derived from less electropositive metals is found in Volume 2, Chapter 1.4 of this series.[13]

The majority of α-alkylations currently being reported are accomplished *via* lithium enolates. However, these reactions have several drawbacks, *e.g.* loss of regioselectivity when sterically congested β,β-disubstituted enolates are involved or when less reactive alkylating agents are employed, polyalkylation, elimination rather than substitution of the alkylating agent, and poor π-facial diastereoselectivity in many cases. Fortunately, most of these limitations have been overcome by the methodology to be described below.

This chapter will provide coverage of the scope and limitations of alkylations of metal enolates of saturated and unsaturated ketones, aldehydes and carboxylic acid derivatives, together with a discussion of alkylations of various enols and enolate equivalents. Where applicable, the utility of these reactions for the diastereoselective and enantioselective synthesis of α-substituted carbonyl compounds will be described. Inevitably, the coverage of a vast research area such as this will be incomplete and in part will reflect the author's interests. However, it is hoped that most of the useful methods of carbon–carbon σ-bond formation by alkylations of enolates and enols will be included.

## 1.1.2 ALKYLATIONS OF METAL ENOLATES OF KETONES AND ALDEHYDES

### 1.1.2.1 Regiospecific Alkylations of Unsymmetrical Acyclic and Cyclic Ketones

There are numerous base–solvent combinations that are capable of quantitatively converting even weakly acidic simple ketones into their enolate anions.[1] However, in order to avoid aldol condensation and unwanted equilibration of enolates of unsymmetrical ketones during enolate formation, it is best to choose conditions under which the ketone, the base and the metal enolate are soluble. Likewise, solutions should be produced when indirect methods of enolate formation are employed. While certain metal cations such as $Hg^{2+}$ form α-metallated ketones, most of the metal cations in Groups I, II and III exist as *O*-metallated tautomers.[13] For organotin derivatives both the *O*-metallated and *C*-metallated forms probably exist in equilibrium.[14]

Metal enolate solutions consist of molecular aggregates (**6**) such as dimers, trimers and tetramers in equilibrium with monomeric covalently bonded species (**7**), contact ion pairs (**8**) and solvent-separated ion pairs (**9**), as shown in Scheme 1.[15] The nature of the metal cation, the solvent and, to a degree, the structure of the enolate anion itself may significantly influence the extent of association between the anion and the metal cation.[1] In general, the factors that favor loose association, *e.g.* solvent-separated ion pairs, lead to an increase in the nucleophilicity of the enolate toward alkylating agents and also its ability to function as a base, *i.e.* to participate in proton transfer reactions.

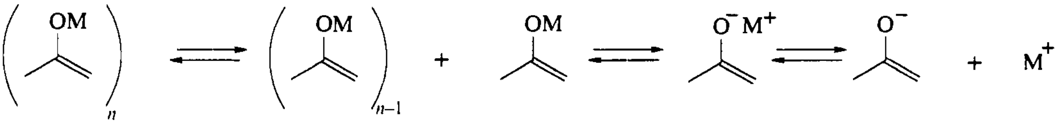

**(6)** **(7)** **(8)** **(9)**

Scheme 1

Both physical measurements[15,16] and kinetic studies[17] show that association between metal cations and enolate anions is stronger, *i.e.* the oxygen–metal bond has more covalent character, when small metal cations and less electropositive metals are involved. The degree of aggregation and extent of association of metal cations and enolate anions is reduced as one goes from monodentate *n*-donor solvents such as diethyl ether and THF to di- and poly-dentate *n*-donor solvents like DME, the higher glymes and crown ethers. These effects are particularly marked in dipolar aprotic solvents such as HMPA, DMSO and DMF, which strongly solvate metal cations by a π-donor mechanism.

The reactivity of metal enolates can be greatly enhanced by adding dipolar aprotic substances to their solutions in ethereal solvents such as THF, where HMPA has become the additive of choice for this purpose.

The geometry of the enolate anion and the degree of substitution on the carbon–carbon double bond may influence the degree of enolate aggregation. Less-substituted metal enolates, which are probably capable of forming larger aggregates, are somewhat less reactive than more-substituted enolates.[18] In the latter species, the increase in nucleophilicity resulting from the presence of an electron-releasing alkyl group is offset by the steric bulk of such groups, which retard alkylation rates. Substituents which are located at positions other than the α-position may influence the extent of enolate aggregation in a particular solvent, or sterically hinder the approach of an alkylating agent. These effects not only influence the rates but the stereochemistry of enolate alkylations (Section 1.1.2.2).

Activated allylic, benzylic and propargylic halides and α-halo esters, as well as methyl and primary halides, are useful reagents for *C*-alkylation of metal enolates. The order of reactivity of the various halogens is as expected for an $S_N2$ process, *i.e.* I > Br > Cl. The order of reactivity of a particular halide is usually benzyl > allyl > primary alkyl and branching at the β-carbon reduces reactivity. Branching at the α-carbon reduces reactivity significantly. Thus, secondary halides react with metal enolates slowly and yields of α-alkylation products are usually poor. Tertiary halides undergo elimination almost exclusively upon reaction with enolates. Elimination is also a serious problem when β-vinyl (homoallylic), β-alkynic and β-phenyl halides as well as β-halo ketones, esters or nitriles are employed in alkylations. Alkyl tosylates and benzenesulfonates are also useful reagents for α-alkylation of metal enolates. Their reactivities are similar to those of the corresponding iodides.

*O*-Alkylation is generally not a problem when lithium and less electropositive metal enolates are involved, unless highly reactive alkylating agents such as dialkyl sulfates, trialkyloxonium salts or α-chloro ethers are employed in solvents of relatively high polarity. As the degree of dissociation between the metal cation and the enolate anion is increased, the anion becomes more capable of exercising its ambident character. The competition between *C*- and *O*-alkylation has been traditionally explained in terms of the Pearson–Klopman principle, which states that hard electrophilic reagents should attack the hard oxygen atom of the enolate anion, while soft reagents should attack the soft α-carbon site.[19,20] However, recent *ab initio* calculations[21] and experimental gas-phase data[22] indicate that free enolate anions react on oxygen irrespective of the hardness or softness of the electrophilic reagent. Coordination of the metal cation with the oxygen must be responsible for reducing its reactivity to the point where *C*-alkylation is usually preferred in solution. Other data on the variations of *C*:*O*-alkylation ratios with the nature of the alkyl halide indicate that it is the ability of the halide to influence the structures of enolate aggregates rather than its 'hardness' or 'softness' which is the controlling factor.[23] This section will be devoted mainly to reactions in which little, if any, *O*-alkylation is observed.

Enolate equilibration and di- and poly-alkylation are the major side reactions, which lead to reduced yields of desired products in ketone alkylations. These processes occur as a result of equilibration of the starting enolate (or enolate mixture) with the neutral monoalkylation product(s) *via* proton transfer reactions. Polyalkylation may also occur when bases, in addition to the starting enolate, which are capable of deprotonating the monoalkylated ketone are present in the medium. With symmetrical ketones, *e.g.* cyclopentanone and cyclohexanone, the problem of regioselectivity does not arise. However, except under special conditions, polyalkylation occurs to a significant extent during enolate alkylations of more kinetically acidic ketones such as cyclobutanone, cyclopentanone and acyclic ketones, particularly methyl ketones.[24] Polyalkylation is also a troublesome side reaction with less acidic ketones such as cyclohexanone.

Scheme 2 shows the results of two studies on the methylation of the lithium enolate of cyclopentanone (**10**), which was prepared by deprotonation of the ketone with tritylllithium in DME[25] or by cleavage of the l-trimethylsiloxycyclopentene with methyllithium in THF.[26] A significant quantity of over-alkylation occurred when the enolate was treated with methyl iodide, particularly when DME was employed as the solvent at room temperature. Also, as indicated in Scheme 2, Noyori and coworkers[26] showed that by adding 3 equiv. of HMPA to the enolate (**10**) and reducing the temperature at which the reaction was conducted, the yield of 2-methylcyclopentanone was greatly improved.

As shown in Scheme 3 conversion of the lithium enolate (**10**) to its complex lithium triethylaluminum enolate prior to alkylation in DME–HMPA at room temperature also significantly reduced the amount of polyalkylation.[25] However, the most dramatic results were obtained by addition of dimethylzinc to the

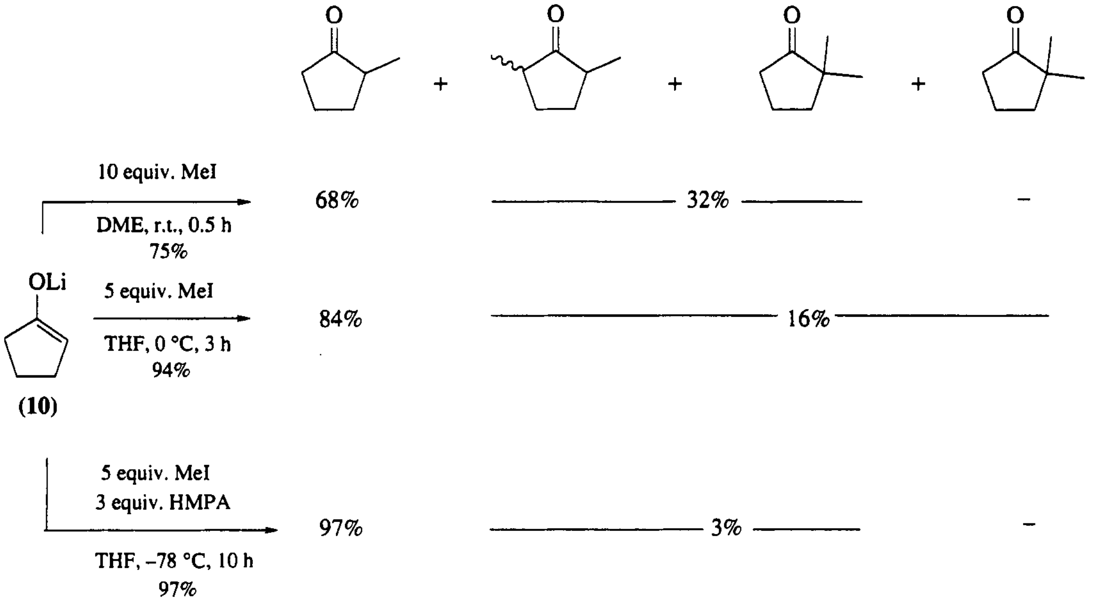

OLi
(10)
10 equiv. MeI
DME, r.t., 0.5 h
75%
68%
32%
–
5 equiv. MeI
THF, 0 °C, 3 h
94%
84%
16%
5 equiv. MeI
3 equiv. HMPA
THF, –78 °C, 10 h
97%
97%
3%
–

**Scheme 2**

solution of (**10**) in THF–HMPA; even when only 0.2 equiv. of the additive was used an insignificant amount of over-alkylation occurred.[26]

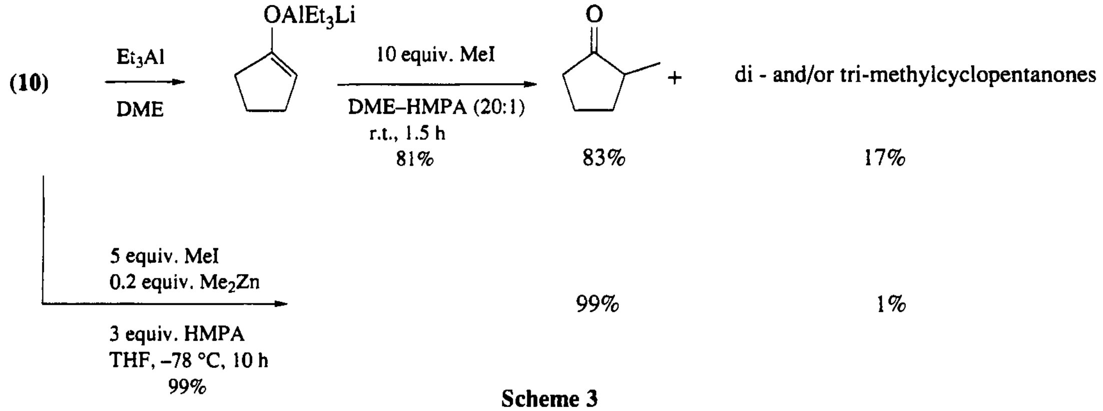

(10)
Et3Al
DME
OAlEt3Li
10 equiv. MeI
DME–HMPA (20:1)
r.t., 1.5 h
81%
di - and/or tri-methylcyclopentanones
83%
17%
5 equiv. MeI
0.2 equiv. Me2Zn
3 equiv. HMPA
THF, –78 °C, 10 h
99%
99%
1%

**Scheme 3**

A comparison of the results of *n*-butylation of the enolate (**10**) in THF–HMPA with and without the addition of 1 equiv. of dimethylzinc is shown in Scheme 4. Although *n*-butyl iodide is 50–100 times less reactive than methyl iodide, monobutylation occurred with high efficiency in the presence of the additive. It is not clear whether dimethylzinc reacts with (**10**) to produce a complex lithium dimethylzinc enolate, or whether it influences the reactivity of the enolate in some other way, possibly by changing its state of aggregation and/or the structures of the aggregates.

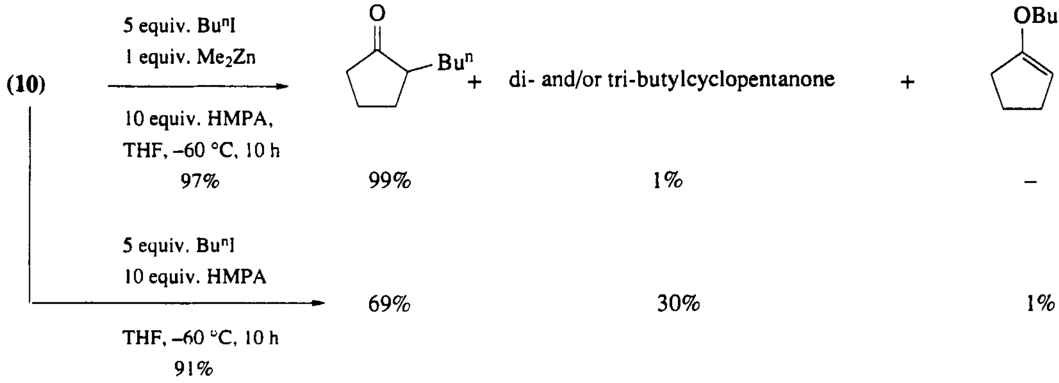

(10)
5 equiv. BunI
1 equiv. Me2Zn
10 equiv. HMPA,
THF, –60 °C, 10 h
97%
Bun
di- and/or tri-butylcyclopentanone
OBun
99%
1%
–
5 equiv. BunI
10 equiv. HMPA
THF, –60 °C, 10 h
91%
69%
30%
1%

**Scheme 4**

The addition of copper(I) salts to THF–HMPA solutions of the lithium enolate (**10**) caused a dramatic reduction in the amount of polyalkylation.[27] The exact role played by the copper(I) cation is not clear. 2-Benzylcyclopentanone, free of the dibenzylation product, was prepared in 67% yield by alkylation of the 'naked' tetraalkylammonium cyclopentanone enolate generated *in situ* by reaction of trimethylsiloxycyclopentene with BTAF in the presence of benzyl bromide in THF;[28] 2-allylcyclopentanone contaminated with ≤3% diallylated ketone was obtained in a similar manner using trimethylsiloxycyclopentene, allyl bromide and TAS difluorotrimethylsiliconate in THF.[29] The less-substituted tri-*n*-butyltin enolate of 2-allylcyclopentanone, prepared by reductive desulfurization of the corresponding β-keto sulfone with lithium in liquid ammonia followed by addition of tri-*n*-butyltin chloride, was alkylated with allyl bromide to give the 2,5-diallyl ketone in good yield (Scheme 5).[30]

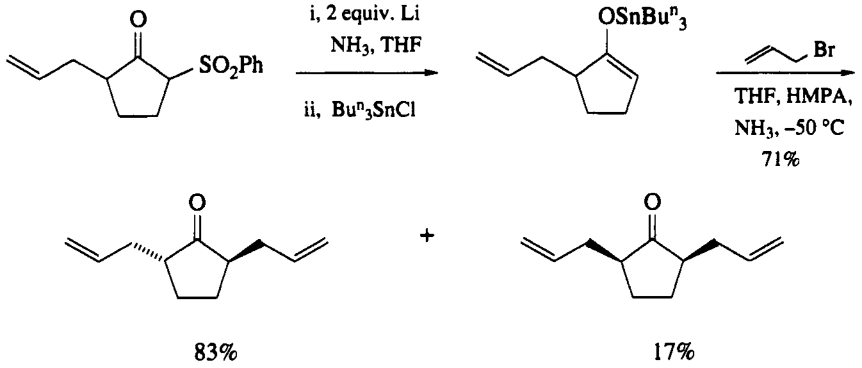
O
SO2Ph
i, 2 equiv. Li
NH3, THF
ii, Bun3SnCl
OSnBun3
Br
THF, HMPA,
NH3, -50 °C
71%
O
+
O
83%
17%

Scheme 5

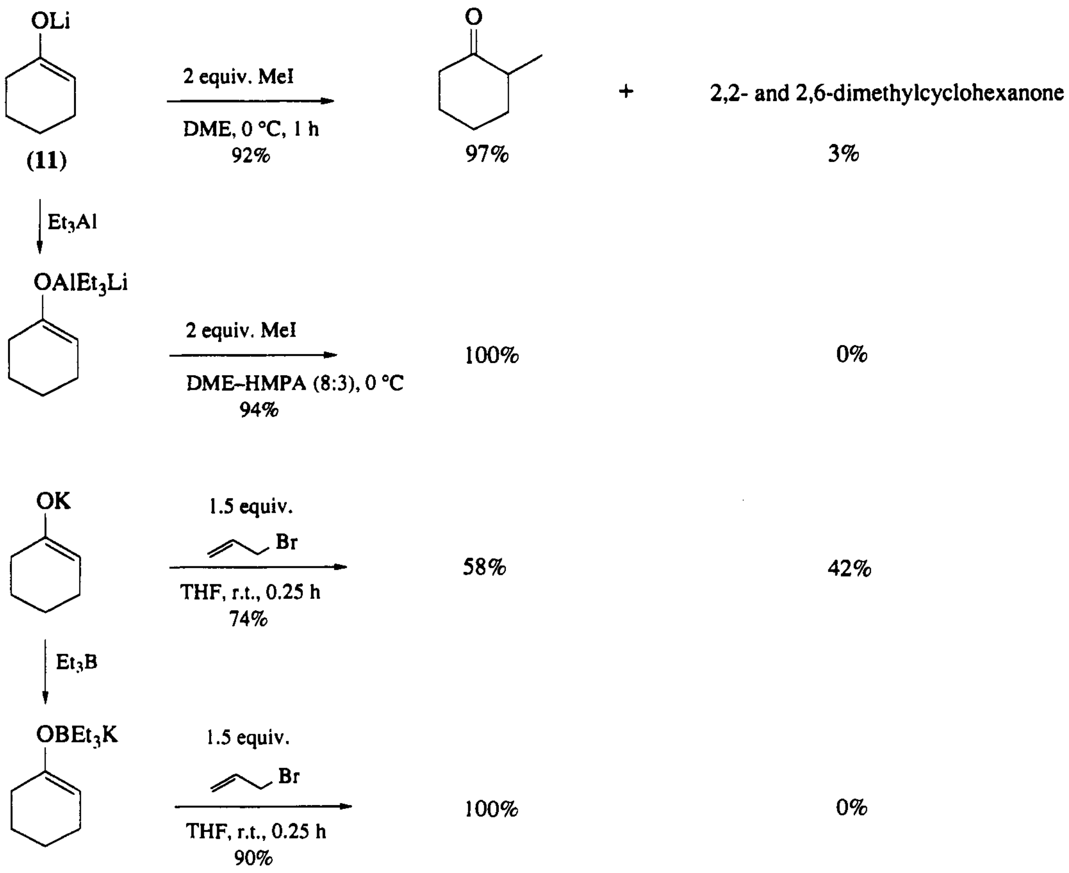
OLi
(11)
2 equiv. MeI
DME, 0 °C, 1 h
92%
O
97%
+
2,2- and 2,6-dimethylcyclohexanone
3%
Et3Al
OAlEt3Li
2 equiv. MeI
DME–HMPA (8:3), 0 °C
94%
100%
0%
OK
1.5 equiv.
Br
THF, r.t., 0.25 h
74%
58%
42%
Et3B
OBEt3K
1.5 equiv.
Br
THF, r.t., 0.25 h
90%
100%
0%

Scheme 6

Lithium,[25] lithium triethylaluminum,[25] sodium triethylboron,[31] sodium triethanolamine borate,[31] potassium triethylboron[32] and tri-*n*-butyltin[25,33] cyclohexanone enolates have been successfully monoalkylated. In Scheme 6 the behavior of the lithium enolate of cyclohexanone (**11**) and the lithium triethylaluminum enolate upon reaction with methyl iodide is compared. The latter enolate gives better results since no dimethylation products were detected, but clearly the cyclohexanone enolate (**11**) is much less prone to dialkylation than the cyclopentanone enolate (**10**). Scheme 6 also provides a comparison of the results of alkylation of the potassium enolate of cyclohexanone, where almost equal amounts of mono- and di-alkylation occurred, with the alkylation of the potassium triethylboron enolate where no polyalkylation occurred. The employment of more covalently bonded enolates offers an advantage in cyclohexanone monoalkylations but not nearly as much as in the cyclopentanone case.

The same conditions which are useful for monoalkylation of enolates of symmetrical ketones also favor regioselective alkylation of specific enolates of unsymmetrical ketones. Since more highly substituted enolates of unsymmetrical ketones are usually the more thermodynamically stable and also undergo alkylation faster than the less-substituted enolates, it is generally possible to successfully alkylate these species.[18] For example, as shown in equation (2), when a (*Z*):(*E*) = 74:26 mixture of the lithium 2-enolates of 2-heptanone (**12**) was benzylated in DME, the 3-benzyl derivative was the only monoalkylation product obtained, although significant amounts of dibenzylated products were produced. However, as shown in equation (3), benzylation of an 84:16 mixture of the lithium 1-(**13**) and a (*Z*)/(*E*)-mixture of the lithium 2-enolates of 2-heptanone (**12**) gave primarily the internally benzylated product. The equilibrium composition of the structurally isomeric lithium enolates of 2-heptanone in DME at 25 °C is 65% (*Z*)-2-enolate, 22% (*E*)-2-enolate and 13% 1-enolate.[34] Thus, substantial enolate equilibrium occurred during the reaction.

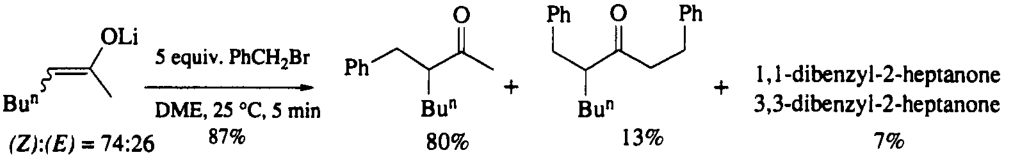
OLi
Bu$^n$
5 equiv. PhCH$_2$Br
DME, 25 °C, 5 min
(Z):(E) = 74:26
87%
O
Ph
Bu$^n$
80%
+
Ph O Ph
Bu$^n$
13%
+
1,1-dibenzyl-2-heptanone
3,3-dibenzyl-2-heptanone
7%
(**12**)

(2)

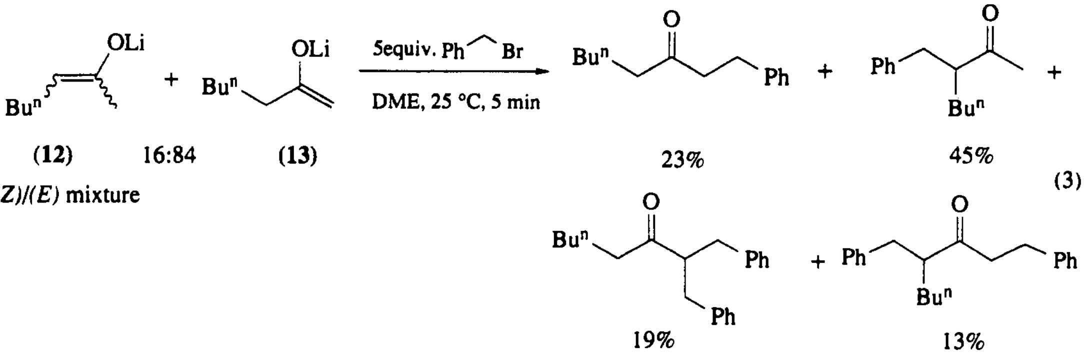
OLi
Bu$^n$
+
Bu$^n$
OLi
(12)
16:84
(13)
(Z)/(E) mixture
5equiv. Ph Br
DME, 25 °C, 5 min
O
Bu$^n$
Ph
23%
+
O
Ph
Bu$^n$
45%
+
O
Bu$^n$
Ph
Ph
19%
+
O
Ph
Ph
Bu$^n$
13%
(3)

Equation (4) shows the results of benzylation of an 87:13 mixture of the enolates (**13**) and (**12**) in the presence of the dipolar aprotic additive HMPA, where a substantial amount of benzylation occurred *via* the terminal enolate.[17] Other additives, such as DMF and benzo-14-crown-4, increased the amount of terminal alkylation in comparison with the use of DME alone. The influence of the additive is possibly to prevent the formation of aggregates of the enolate (**13**) and lithium bromide formed during the reaction. This could cause the terminal enolate to remain as a reactive dimer, which undergoes alkylation more rapidly than equilibration to the internal enolate.[17]

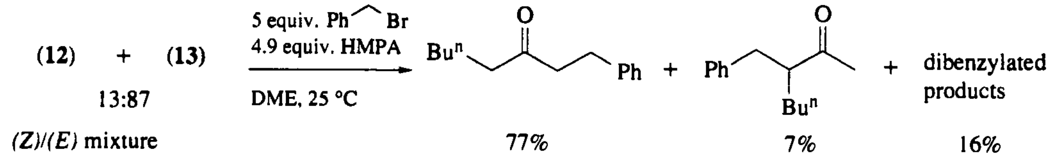
(12) + (13)
13:87
(Z)/(E) mixture
5 equiv. Ph Br
4.9 equiv. HMPA
DME, 25 °C
O
Bu$^n$
Ph
77%
+
O
Ph
Bu$^n$
7%
+
dibenzylated products
16%
(4)

Deprotonations of unsymmetrical ketones with lithium bases under thermodynamic control usually give the more-substituted enolates with good regioselectivity. However, even better results are provided by various indirect methods of enolate formation, such as cleavage of more-substituted TMS enol ethers with organolithium reagents in ethereal solvents[12,18,35] or lithium amide in liquid ammonia[36] or lithium–ammonia reduction of appropriate α,β-unsaturated ketones. The former procedure provides a 'clean' enolate,[37] one free of extraneous bases, which can promote polyalkylation. Several highly regioselective methods of preparing thermodynamic TMS enol ethers of unsymmetrical ketones such as 2-methylcyclohexanone have been reported recently.[38–40] Alkylations with less reactive alkylating agents such as *n*-butyl iodide provide an important test of regiocontrol in enolate alkylations.[1] An excellent yield of 2-*n*-butyl-2-methylcyclohexanone was obtained when the more highly substituted TMS enol ether of 2-methylcyclohexanone was treated with lithium amide in liquid ammonia–THF and the resulting enolate (**3**; M = Li) reacted with *n*-butyl iodide (Scheme 7).[36]

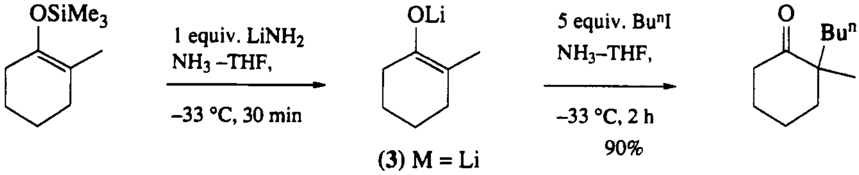

**Scheme 7**

Regioselective alkylations at C-6 of 2-methylcyclohexanone have been accomplished *via* the alkylation of thermodynamically unstable trisubstituted lithium, lithium triethanolamine borate,[31] potassium triethylboron,[32] tri-*n*-butyltin[14] and benzyltrimethylammonium enolates (*cf.* **2**).[28] Alkylation is faster than equilibration for the more reactive alkylating agents. Although enolate equilibration has been shown to compete with butylation using *n*-butyl iodide under certain conditions,[41,42] butylation of the enolate (**2**; M = Li) in liquid ammonia–THF gave a mixture of *cis*- and *trans*-2-methyl-6-butylcyclohexanone along with 2-methylcyclohexanone in an 83:17 ratio in 90% yield; no 2,2-dialkylcyclohexanone was obtained in this reaction (Scheme 8).[36]

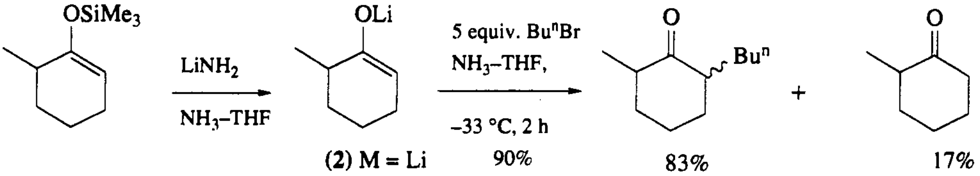

**Scheme 8**

α,β-Dialkylation of enones by conjugate addition–enolate alkylation has been widely used for the synthesis of α,β-dialkyl ketones, particularly cyclohexanones and cyclopentanones. This subject has been recently reviewed by Taylor, who has pointed out the problems associated with tandem, one-pot conjugate addition–enolate alkylation procedures.[11] The most frequently used reagents for conjugate additions are lithium dialkylcuprates, and the enolates produced in such reactions are likely to be largely lithium enolates.[43] However, copper(I) salts, which may influence lithium enolate reactivity even in low concentration, are undoubtedly present in solution.[41] Conjugate additions usually proceed best in ether, but enolate alkylations are unacceptably slow in this solvent. However, if the reactivity of the medium is adjusted by addition of appropriate cation-complexing agents such as TMEDA[41,44] or THF/HMPA,[45] or if the ether is exchanged for a more appropriate solvent for alkylation, *e.g.* DME,[44] regioselective alkylations can be effected with simple, reactive alkylating agents in many cases. Conjugate additions can also be performed in THF.[41] Examples of the use of one-pot conjugate addition–enolate alkylations for the synthesis of 2,3-dialkylcyclohexanones are shown in Scheme 9.[41,44]

A useful technique to accomplish overall vicinal dialkylation of enones is to trap the enolate initially formed in the conjugate addition with TMS-Cl, and then regenerate the enolate under suitable conditions for its alkylation. Lithium 1-enolates of 3,5-dialkylcyclohexanones generated from the reaction of the corresponding TMS enol ethers with lithium amide in liquid ammonia–THF can be alkylated efficiently in liquid ammonia–THF, even with an unreactive alkylating agent such as *n*-butyl iodide (Scheme 10).[36]

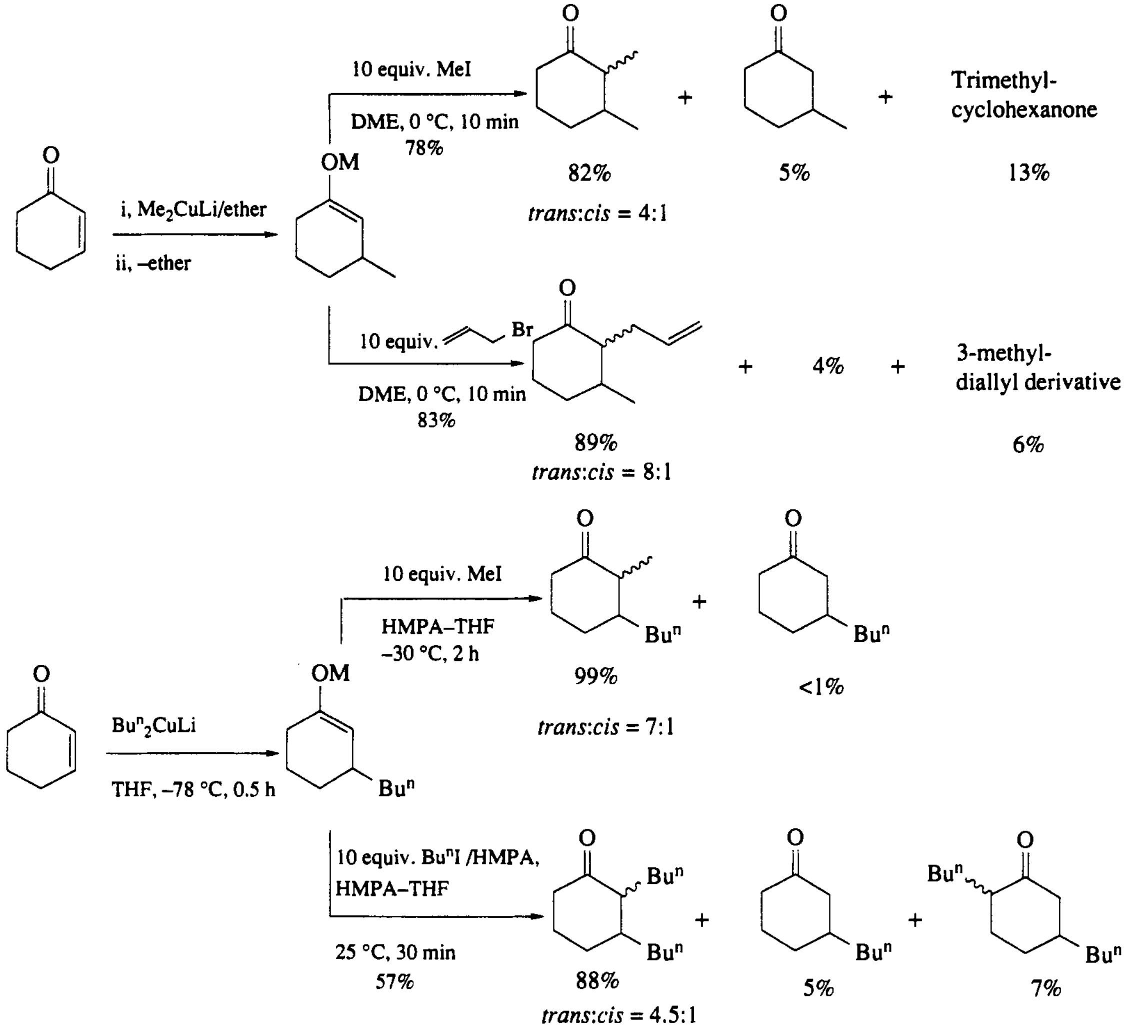

i, Me2CuLi/ether
ii, –ether
OM
10 equiv. MeI
DME, 0 °C, 10 min
78%
82%
trans:cis = 4:1
5%
Trimethyl-cyclohexanone
13%
10 equiv.
Br
DME, 0 °C, 10 min
83%
89%
trans:cis = 8:1
4%
3-methyl-diallyl derivative
6%
Bun2CuLi
THF, –78 °C, 0.5 h
Bun
10 equiv. MeI
HMPA–THF
–30 °C, 2 h
99%
trans:cis = 7:1
<1%
10 equiv. BunI /HMPA,
HMPA–THF
25 °C, 30 min
57%
88%
trans:cis = 4.5:1
5%
7%

**Scheme 9**

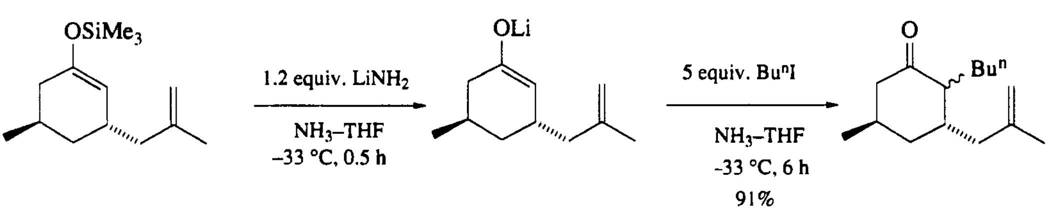

OSiMe3
1.2 equiv. LiNH2
NH3–THF
–33 °C, 0.5 h
OLi
5 equiv. BunI
NH3–THF
–33 °C, 6 h
91%
Bun

**Scheme 10**

2,3-Dialkylcyclopentanones, *e.g.* the prostaglandins, are found widely in nature. An obvious route to the synthesis of these systems is a triply convergent approach involving tandem conjugate addition–enolate alkylation of an appropriate cyclopentenone.[41,46–48] However, the propensity of cyclopentanone enolates toward equilibration has presented difficulties, which until recently have prevented synthesis of the natural products themselves by this approach.[47,48] Using cyclopentenone as the substrate, Posner and co-workers found that tandem conjugate addition–enolate alkylations could be accomplished in reasonable yields with relatively small nucleophiles and electrophiles under carefully controlled conditions (Scheme 11).[41] However, the alkylation failed when bulkier nucleophiles and electrophiles bearing the functionality of prostaglandin side chains were employed.

Patterson and Fried found that the clean lithium enolate (**14**), generated by conjugate addition of the lithium divinylcuprate (**15**) to cyclopentenone with subsequent trapping of the initial enolate with TMS-Cl and cleavage of the TMS enol ether with lithium amide in liquid ammonia–THF, could be alkylated in a reasonable yield with the (*Z*)-allylic iodide (**16**) to give the 11-deoxyprostaglandin derivative (**17**;

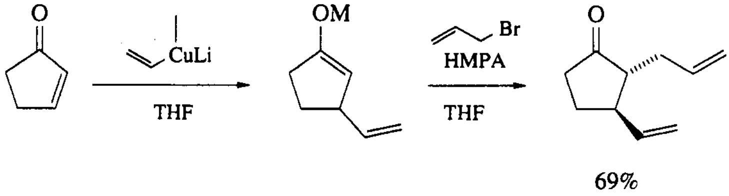
O
CuLi
THF
OM
Br
HMPA
THF
O
69%

Scheme 11

Scheme 12).[46] However, the sequence failed when applied to a protected 4-hydroxycyclopentenone because of equilibration of the initially formed 1-enolate to the 5-enolate followed by β-elimination of the protected hydroxy substituent.

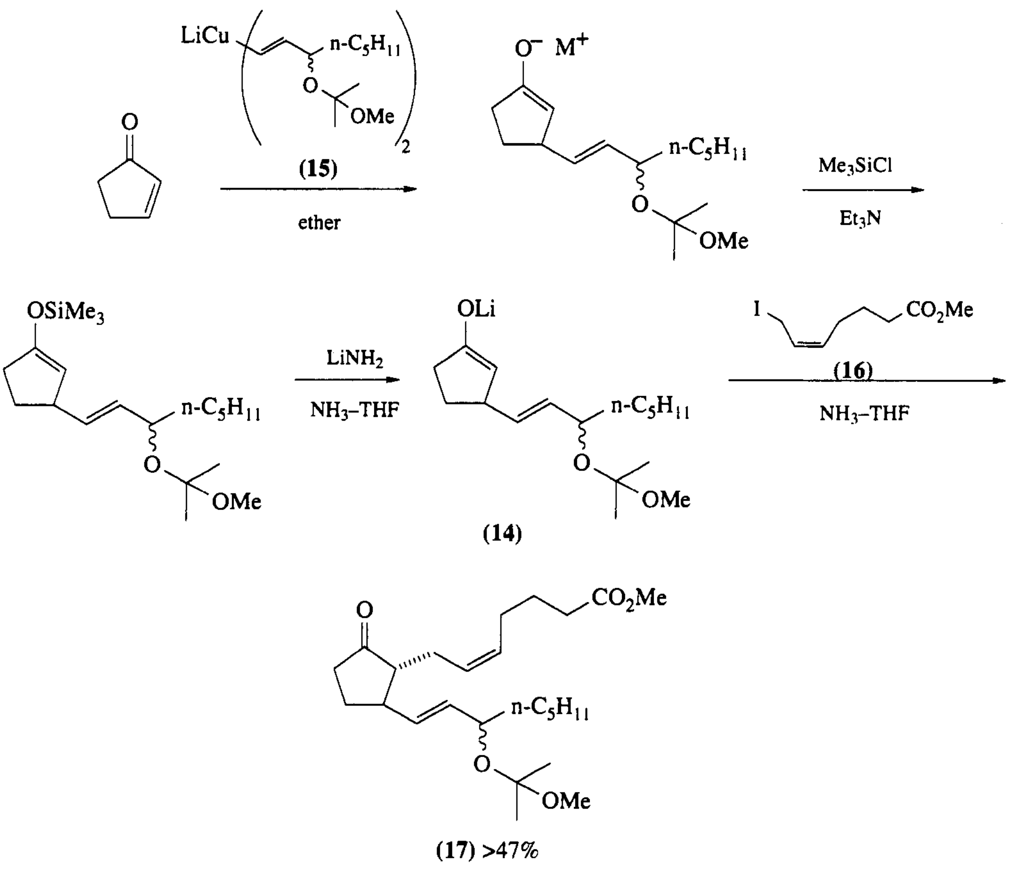
O
LiCu
n-C5H11
O
OMe
2
(15)
ether
O⁻ M⁺
n-C5H11
O
OMe
Me3SiCl
Et3N
OSiMe3
n-C5H11
O
OMe
LiNH2
NH3-THF
OLi
n-C5H11
O
OMe
(14)
I
CO2Me
(16)
NH3-THF
O
CO2Me
n-C5H11
O
OMe
(17) >47%

Scheme 12

Noyori and coworkers[47] have provided an elegant solution to the problem of enolate equilibration by transmetallation of the enolate obtained from addition of the homochiral phosphine-complexed vinylcopper reagent (**19**) to the protected homochiral 4-hydroxycyclopentenone (**18**), with tri-*n*-butyltin chloride, followed by addition of the alkylating agent (**16**). This sequence gave the PGE$_2$-type product (**20**) in 78% yield along with 3% of the C-8 epimer (Scheme 13). Likewise, the propargylic iodide related to (**16**) provided a 5,6-didehydro-PGE$_2$ derivative in 82% yield, but use of methyl 7-iodoheptanoate as the alkylating agent provided only a 20% yield of the corresponding PGE derivative. It was found that halide ions must be present in the medium for alkylation to proceed; thus, penta- or hexa-valent tin species may be involved.

An interesting and simple variation on the three-component coupling protocol for prostaglandin synthesis has been recently reported by Noyori and coworkers.[26] This variation involved conjugate addition of a reagent formed from a 1:1 mixture of dimethylzinc and the (*E*)-vinyllithium reagent (**21**) to the enone (**18**), followed by alkylation of the enolate intermediate with the propargylic iodide (**22**) to give

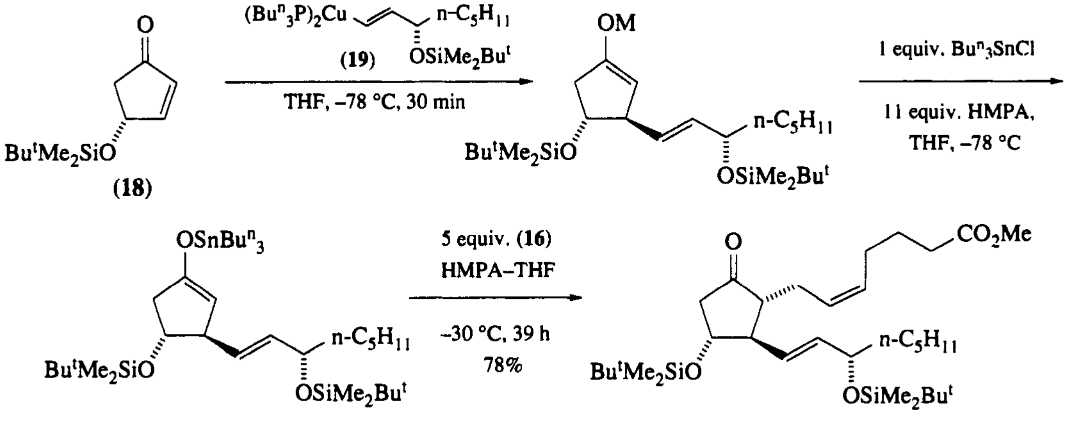

Scheme 13

the prostaglandin derivative (**23**) in 71% overall yield (Scheme 14). The remarkable ability of dimethylzinc to suppress proton transfer reactions of lithium enolates is further illustrated by this experiment.

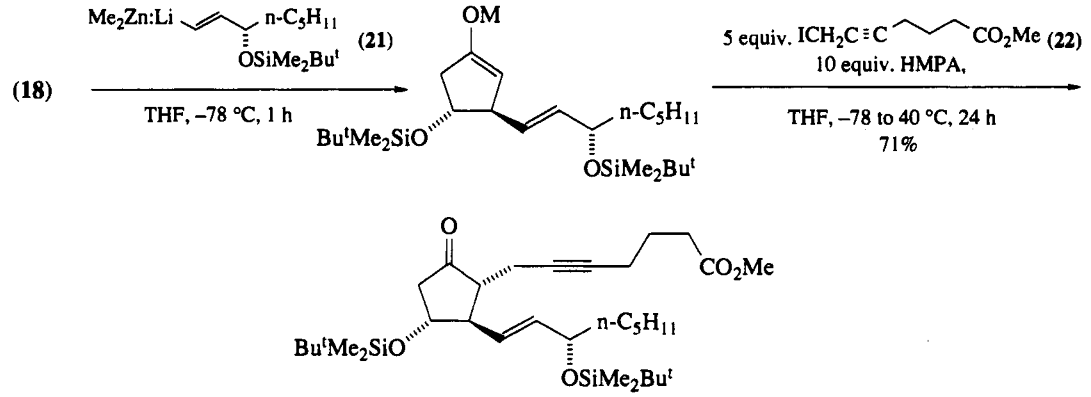

(**23**)

Scheme 14

In related work, Johnson and Penning showed that the vinylcopper reagent (**19**) added to a homochiral protected 4,5-dihydroxycyclopent-2-enone to give an enolate intermediate, which upon trapping with the (*Z*)-allylic iodide (**16**) in the presence of HMPA gave a 2,3-dialkylated precursor of (–)-PGE$_2$ methyl ester in good yield.[48] Apparently, the presence of the oxygen substituent at C-5 of the starting enone reduces the rate of enolate equilibration and allows alkylation to occur at the 2-position.

Regiospecific alkylations have been employed in the synthesis of a large number of alkylated decalones, hydrindanones and tricyclic and steroidal ketones.[1] Regiospecific annulations are often carried out by: (i) regiospecific α-alkylation of a specific enolate with an electrophilic reagent containing latent 2- or 3-ketoalkyl functionality; (ii) transformation of the side chain into a 1,4- or 1,5-diketone; and (iii) formation of a ring by an intramolecular aldol condensation.[49] (*E*)-3-Trimethylsilyl-2-butenyl iodide[50] and *t*-butyl γ-iodotiglate[51] are some of the more useful alkylating agents for this purpose. The requisite lithium enolates are often generated by lithium–ammonia reduction of α,β-unsaturated ketones or cleavage of TMS enol ethers with methyllithium. The use of kinetically generated 1-enolates of *trans*-2-decalones in sequences of this type provide important routes to phenanthrene derivatives, which are useful intermediates in steroid total synthesis (Scheme 15).

Base-promoted alkylations of bicyclic ketones such as 1-decalones and 1-hydrindanones give largely nonangular alkylated products. The application of blocking groups at the 2-position provided an early approach to angular alkylations of such systems.[1,52,53] However, angularly alkylated ketones can be prepared from appropriate lithium enolates generated by indirect methods.[8,18,54] These enolates exhibit a diastereofacial bias toward the formation of *cis*-fused products. A possible explanation for this is presented in Section 1.1.2.2.

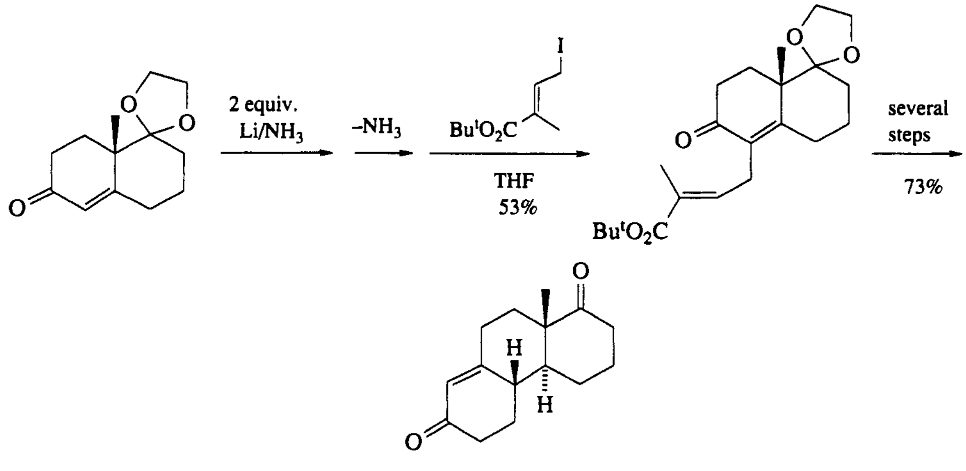

Scheme 15

The focus of this section has been upon uncatalyzed α-alkylations of metal enolates with alkylating agents bearing leaving groups at $sp^3$-hybridized carbon atoms. However, in certain cases where conventional alkylations give poor results, palladium(0)-catalyzed regioselective allylations of complex potassium[55,56] and lithium[57] triethylboron, zinc,[58] trialkyltin[59,60] and other enolates[58] have been accomplished with relatively inert reagents, *e.g.* allylic acetates. These reactions proceed *via* nucleophilic attack of the metal enolate on a π-allylpalladium complex formed by oxidative addition of the allylic reagent to palladium. The reactions of trialkyltin enolates may involve the intermediacy of 'ate' complexes.[60]

α-Arylations and α-vinylations of metal enolates also provide regioselective routes for carbon–carbon bond formation. The literature on this subject prior to 1978 has been reviewed.[61] More recent work in this area has involved palladium-catalyzed reactions of trialkyltin enolates with aryl[62,63] and vinyl bromides.[62]

### 1.1.2.2 Stereochemistry of Enolate Alkylations

Existing evidence indicates that *C*-alkylations of metal enolates with common electrophiles proceeds by an $S_N2$-type mechanism; that is, the highest occupied molecular orbital (HOMO) of the enolate attacks the lowest unoccupied molecular orbital (LUMO) of the alkylating agent. Scheme 16 illustrates the principle of stereoelectronic control,[64,65] which states that the electrophile should approach in a plane perpendicular to the enolate to allow maintenance of maximum orbital overlap in the transition state (**24**) between the developing C—C bond and the π-orbital of the carbonyl group.

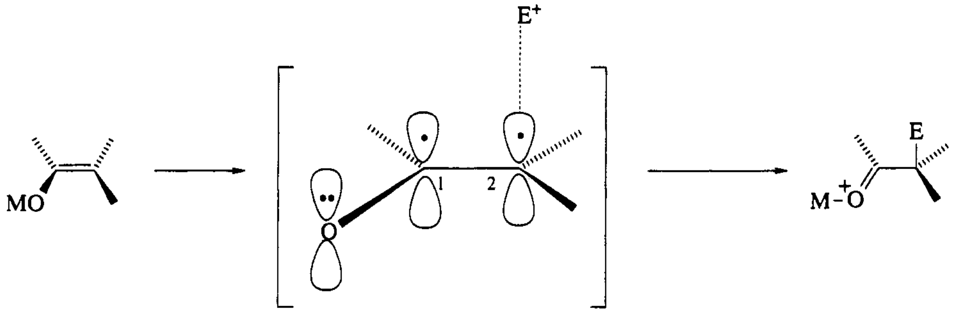

**(24)**

Scheme 16

Recent *ab initio* molecular orbital calculations indicate that the developing electrophile–C(1)–C(2) angle is actually larger than 90°.[21] However, they provide no evidence for the suggestion that the electrophile's trajectory is tilted away from perpendicularity to the enolate plane because of the repulsive interaction between the electrophile LUMO and the oxygen atom of the enolate HOMO.[66]

The suggestion that a cyclic six-membered ring transition state of the type (**25**), in which the metal cation assists the reaction by coordinating with the leaving group seems unlikely.[67] Such a transition state requires very unfavorable bond angles for an $S_N2$ displacement.[68] However, since enolate aggregates are likely to be present, the possibility exists that a transition state (**26**), related to (**24**), in which the cation of a second enolate ion-pair assists the reaction by coordinating with the leaving group, is involved.

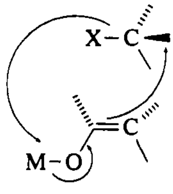

**(25)**

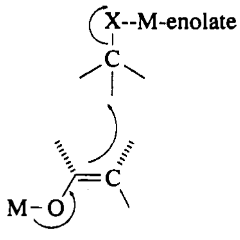

**(26)**

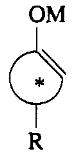

**(27)**

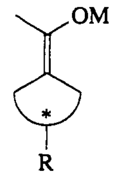

**(28)**

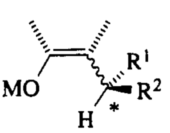

**(29)**

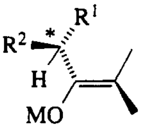

**(30)**

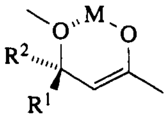

**(31)**

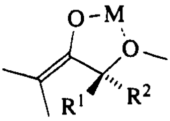

**(32)**

If the metal enolate contains a center of chirality, diastereoselection may be exhibited in the C—C bond formation process. Evans[2] has identified three classes of metal enolates in which chirality transfer may occur: (i) endo- and exo-cyclic enolates such as (**27**) or (**28**), which contain a chiral center (*) in a ring bonded to the enolate at two points; (ii) acyclic enolates such as (**29**) or (**30**), in which the moiety containing the chiral center (*) is bonded to the enolate at only one point; and (iii) chelated enolates such as (**31**) or (**32**), in which the chiral center is a part of the chelate ring. (*Z*)-Endocyclic enolates are also possible for large ring cyclic ketones.

The stereochemical outcome of alkylations can be ascribed to stereoelectronic and steric effects, including the influence of allylic strain[69] on metal enolate conformations. Metal enolate alkylations are strongly exothermic, and the results of many studies indicate that the transition states closely resemble the reactants.[1,2,4] Therefore, steric factors within the enolate play a dominant role in determining π-diastereofacial selectivity. This is illustrated in Scheme 17 for alkylation of the chiral lithium enolate of 4-*t*-butylcyclohexanone (**33a**), which can take place *via* path A, leading to a chair conformation (**34a**) of the product having the alkyl group axial to the ring and *trans* to the *t*-butyl group. Path B attack leads initially to a twist-boat conformation (**35a**), which may undergo conformational inversion to the chair conformation (**36a**) having the new group equatorial to the ring and *cis* to the *t*-butyl group. Paths A and B (Scheme 17) are normally referred to as axial and equatorial alkylation, respectively.

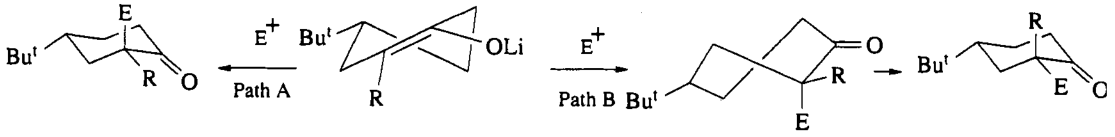

**(34)** **(33)** **(35)** **(36)**

a: R = H
b: R = Me

Scheme 17

In the enolate (**33a**), the top and bottom π-faces of the molecule present about the same degree of steric hindrance to approach of the alkylating agent. However, if the transition state resembled the alkylation product, the thermodynamically more stable chair conformation (**34a**) would be expected to develop much faster than the less stable twist-boat conformation; thus, axial alkylation would be strongly preferred. However, this is not the case. House *et al.*[70] reported that ethylation of (**33a**) with ethyl iodide in DME gave approximately equal amounts of axial and equatorial alkylation products. Similar results were obtained in the alkylation of (**33a**) with methyl iodide.[71] More recent studies on the stereochemistry of alkylation of (**33a**) under carefully controlled conditions and on the alkylation of the corresponding tetraalkylammonium enolate have indicated that there is a small, but apparently real, preference for axial alkylation. For example, axial:equatorial product ratios of 74:26[72] and 70:30[28] have been reported for the reaction of (**33a**) and the corrsponding 'naked' enolate with methyl iodide in THF. If equilibration of the product mixture occurred during alkylation, the axial:equatorial alkylation ratio would be reduced. Perhaps this accounts for the lower ratios obtained in the earlier studies. As expected, alkylations of the lithium enolate (**33a**) were less stereoselective when more reactive alkylating agents than methyl iodide were used.[70,72] Also, when the counterion was varied, the axial:equatorial ratio was shown to follow the order: Li > Na > K.[72] However, the cation effect was quite small.

Lithium enolates having α-methyl substituents, such as (**33b**) and the related species (**37b**), derived from 5-*t*-butylcyclohexanone, show a somewhat greater stereoselectivity of axial alkylation than the corresponding α-unsubstituted compounds.[73] For example, the enolate (**37a**) gave the products (**38a**) and (**39a**) in a 68:32 ratio upon treatment with methyl iodide in THF, while the 2-methyl-substituted derivative (**37b**) gave an 83:17 mixture of (**38b**) and (**39b**) upon reaction with trideuteriomethyl iodide in DME (Scheme 18).[73] Similarly, a greater stereoselectivity for axial alkylation has been observed for other α-substituted enolates compared with their counterparts lacking α-substituents.[71,74–78]

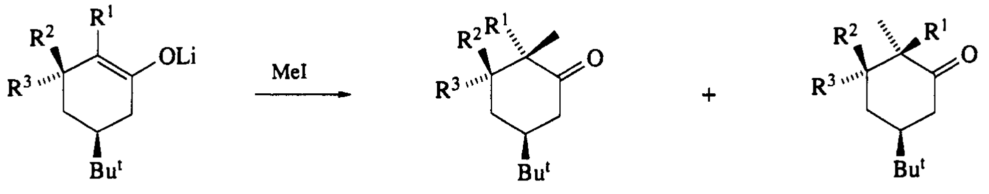

(**37**) (**38**) (**39**)

| | |
|---|---|
| a: $R^1 = R^2 = R^3 = H$ | 68:32 |
| b: $R^1 = Me, R^2 = R^3 = H$ | 83:17 |
| c: $R^2 = Me, R^1 = R^3 = H$ | 25:75 |
| d: $R^3 = Me, R^1 = R^2 = H$ | 96:4 |

**Scheme 18**

As depicted in (**40**), House and Umen have proposed that 2-substituted enolates undergo distortion in order to relieve interactions between the R group and the OM substituent and to avoid eclipsing ($A^{1,2}$-strain)[69] of the OM group by the 6-quasiequatorial group (hydrogen) and of the R group by the 3-quasiequatorial group (hydrogen). Thus, some rehybridization of the *p*-orbital at C-2 toward an $sp^3$-orbital should occur. In such a distorted species, the top π-face of the enolate should be more open to attack by an electrophile than the bottom π-face.[73]

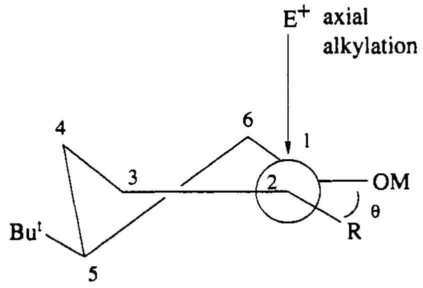

(**40**)

Quasiaxial and quasiequatorial substituents at C-6 in conformationally rigid lithium enolates such as (**33a**) have a very small effect on the stereoselectivity of the reaction.[71,72] In the case of the lithium 1-enolate of *cis*-3-methyl-5-*t*-butylcyclohexanone (**37c**), the steric effect of the quasiequatorial methyl group at C-3 and the stereoelectronic preference of axial alkylation oppose each other, and equatorial alkylation is preferred by 3 to 1. However, in the *trans* isomer (**37d**), where the C-3 methyl group is quasiaxial, these effects reinforce each other and axial alkylation is significantly favored by 24 to 1 (Scheme 18). Relatively rigid 1-enolates of 2-substituted cyclohexanone derivatives having quasiequatorial substituents at C-6[77] or C-3[74–76,78] show an enhanced tendency toward axial alkylation. In such systems, the dihedral angle $\theta$ in structure (**40**) should increase even more with the placement of bulky groups at C-6 and C-3.[73] The stereoselectivity of alkylations of sterically congested enolates such as those derived from 2,6-dimethyl-6-phenyl- and 2-methallyl-6-methyl-6-phenyl-cyclohexanone[77] is probably best accounted for by equatorial alkylation of a conformation of the 1-enolates having the 6-phenyl groups quasiaxial.[2]

The results of several studies (*cf.* Scheme 9) show that alkylations of conformationally mobile 1-enolates of 3-alkyl- and 2,3-dialkyl-cyclohexanones give products having the new groups at C-2 *trans* to the groups at C-3 with stereoselectivities in the 75 to 95% range.[41,44,45,79] Enolates of this type may exist as an equilibrium mixture of conformations (**41**) and (**42**). Conformation (**42**), having the 3-alkyl quasiaxial, is likely to be quite important, particularly when an alkyl group is present at C-2, because $A^{1,2}$-strain would destabilize conformation (**41**), which has a 3-alkyl group quasiequatorial. Steric interactions involving the 3-alkyl group and the approaching electrophilic reagent appear to be minimized in either of the two possible transition states which lead to the introduction of the new group *trans* to the C-3 substitutent. However, it is somewhat surprising that the stereoselectivity in favor of the *trans* product is apparently somewhat greater for the allylation of the C-2-unsubstituted enolate (**41a**) ↔ (**42a**) than for the 2-methyl enolate (**41b**) ↔ (**42b**).[45,79]

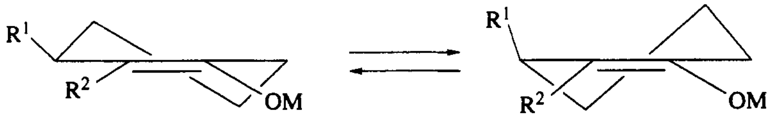

(**41**) (**42**)

a: $R^1$ = Me, $R^2$ = H
b: $R^1$ = $R^2$ = Me

The results of methylations of lithium 1(2)-enolates of (**43a**)[75] and (**43b**)[76] of *trans*-2-decalones are shown in Scheme 19. An enolate such as (**43**) may be regarded as a special case of a conformationally rigid 3-alkylcyclohexanone derivative. As in the case of *t*-butylcyclohexanone derivatives such as (**37**), the presence of a substituent at the α-position of the enolate significantly increases the stereoselectivity in favor of axial alkylation. This may be attributed to a distortion of the enolate, which forces the methyl group at C-1 downward to relieve its interaction with the OLi group and the quasiequatorial 8-methylene group.[73] A tricyclic lithium enolate related to (**43a**) was found to undergo axial alkylation almost exclusively.[80]

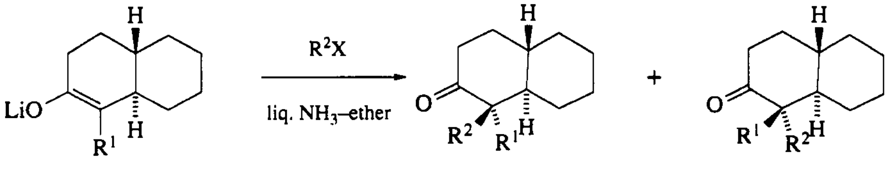

(**43**) a: R = Me
b: R = D

| *Compound* | *$R^2X$* | *Ratio* |
|---|---|---|
| (**43a**) | $CD_3I$ | 83:17 |
| (**43a**) | EtI | >95:<5 |
| (**43b**) | MeI | 40:60 |

**Scheme 19**

A comparison of the data for alkylation of the 10-methyl-2-decalone lithium enolate (**44**)[75] with those for enolate (**43a**) clearly shows that if axial alkylation involves development of a 1,3-interaction with an axial methyl group, equatorial alkylation is the major pathway (Scheme 20). Likewise, alkylations of lithium 2-enolates of *trans*-2-decalones (**45a**) and (**45b**) gave largely axial and equatorial methylation products, respectively (*cf.* Scheme 20).[72]

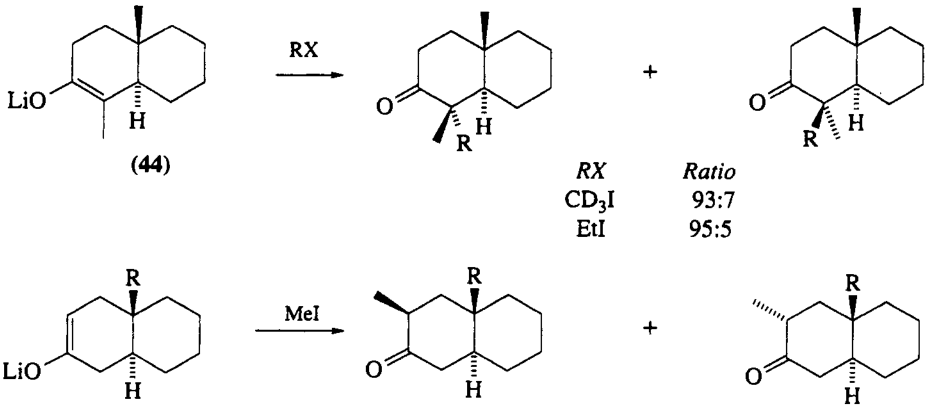

(**44**)

| *RX* | *Ratio* |
|---|---|
| $CD_3I$ | 93:7 |
| EtI | 95:5 |

(**45**) a: R = H
b: R = Me

| *Ratio* |
|---|
| 79:21 |
| 6:94 |

Scheme 20

Methylation of the conformationally rigid exocyclic enolate (**46**) derived from 4-*t*-butylcyclohexyl methyl ketone has been shown to yield an 85:15 mixture of products (**47**) and (**48**) derived from equatorial and axial attack of the electrophile, respectively (Scheme 21).[81] In species such as (**46**) geometric factors associated with a stereoelectronically controlled approach to either π-face of the enolate are very similar. It has been suggested that the interaction of the filled *p*-orbital at C-1 with the vacant symmetrical antibonding orbital of the C(2)—C(3) and C(5)—C(6) bonds causes an increase in electron density on the equatorial π-face of the enolate and favors approach of the electrophile from that side.[82] However, the more generally accepted argument is that in a reactant-like transition state the axial hydrogen atoms at C-3 and C-5 hinder axial attack, while equatorial attack is relatively unencumbered.[81]

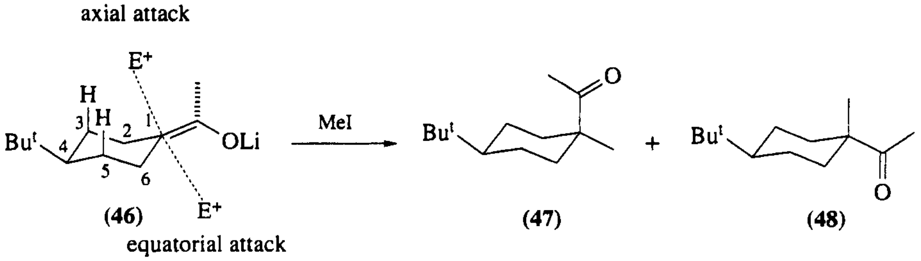

(**46**) (**47**) (**48**)

85:15

Scheme 21

Angular alkylations of the lithium 1(9)-enolate (**49**) of 1-decalone with methyl iodide in liquid ammonia–ether[8] or DME[54] have been shown to yield a mixture of products in which the *cis* isomer (**50**) is favored by 4:1 or 5:1 over the *trans* isomer (**51**; Scheme 22). The 10-methyl derivative of (**49**) also has been reported to give *cis*-9,10-dimethyl-1-decalone exclusively upon methylation.[45] In systems such as (**49**) the enolate double bond is exocyclic to the six-membered nonoxygenated ring. Thus, the same factors that control the stereochemistry of alkylation of simple exocyclic enolates such as (**46**) are likely to be involved. In the axial approach pathway, the electrophile would experience a 1,3-interaction with the axial hydrogen atoms at C-4, C-5 and C-7. Thus, the equatorial approach pathway, which is less sterically hindered, is preferred. The observation that alkylation of (**49**) with the highly reactive alkylation agent trimethyloxonium 2,4,6-trinitrobenzenesulfonate gave 95% of the *cis*-fused ketone (**50**), is in keeping with this explanation.[54] Under these conditions, the transition state should resemble the reactant enolate to an even greater extent than when methyl iodide is employed as the alkylating agent.

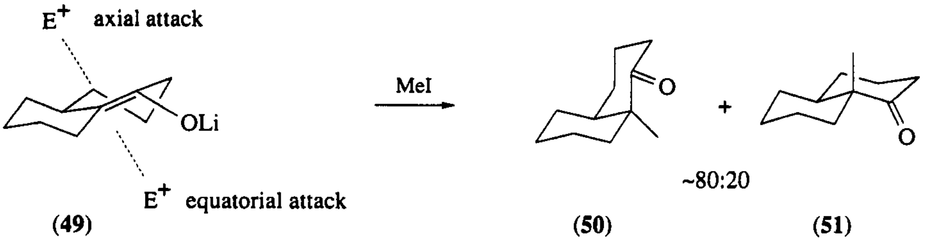

Scheme 22

Angular alkylations of 1-decalone enolates provide important models for angular alkylations of 18-nor-D-homo steroids. The manner in which structural modifications influence *cis:trans* product ratios in alkylations of various enolates of 1-decalones containing blocking groups at C-2 has been thoroughly investigated[52] and reviewed.[1]

Angular alkylations of lithium enolates of hydrindanones with carbonyl groups in the five-[83] or six-membered ring[84] yield *cis*-fused products with almost complete stereoselectivity. The lithium enolate of bicyclo [2.2.1]heptan-2-one undergoes *exo* alkylation with very high stereoselectivity.[72,85] The presence of a *syn* methyl group at C-7 reduces the preference for *exo* alkylation, but it is still preferred over *endo* alkylation by about 3:1 unless a 5,6-double bond is also present;[72] then, *endo* attack is preferred.[86,87] The expected steric effects control the stereochemistry of alkylation of other bridged bicyclic systems.[8,88]

The results presented in Schemes 11 to 14, as well as numerous other studies,[89–91] show that alkylations of 1-enolates of 3-alkyl- and 3-alkenyl-cyclopentanones usually yield *trans*-2,3-disubstituted cyclopentanones with high stereoselectivity. As shown in Scheme 23, the stereoselectivity of alkylation of the 1-enolate of 3-phenylcyclopentanone is dramatically affected by the presence of copper(I) in the medium. Similar results have been obtained for the corresponding 3-methyl-3-phenylcyclopentanone enolates. On the basis of $^{1}H$ and $^{13}C$ NMR evidence and on the results of deprotonation of 3-phenylcyclopentanone with strong bases, Posner and Lentz[27] have proposed that lithium–arene coordination occurs in the enolates that would be present in the reactions shown in Scheme 23 as well as related cyclohexanone enolates. It was proposed that this complexation directs alkylation at C-2 to occur primarily *cis* to the phenyl ring at C-3 in both lithium and 'copper' enolates, but that the presence of copper(I) in the medium retards equilibration of the 2,3-*cis* product to the more stable 2,3-*trans* product. It should be noted that the extent of diallylation was greatly diminished in the presence of copper(I) species compared with the lithium enolate alone. Alkylation was found to occur *trans* to the phenyl group when a methyl substituent was present at C-2.

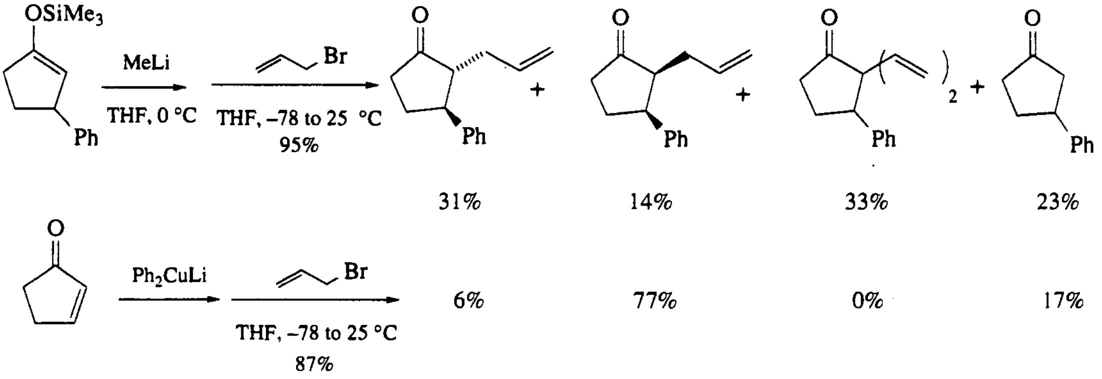

Scheme 23

Extraannular chirality transfer has been observed for alkylations of acyclic ketone enolates having chiral β-carbon atoms (Scheme 24).[92,95] In these reactions, methylation occurs *anti* to the β-dimethylphenylsilyl and β-isopropyl groups with good to excellent diastereoselectivity. Variation in the size of the alkyl group at the β-carbon atom of β-silicon-substituted enolates has indicated that the preference for *anti* attack to silicon is probably electronic in origin. In the transition states for alkylation, *anti* attack of the electrophile may occur on a conformation of the enolate such as (**52**) with the hydrogen atom eclipsing the double bond and the larger groups staggered,[92–94] or a conformation such as (**53**) with the more electron-releasing β-substituent perpendicular to the plane of the enolate.[96] Recent studies by McGarvey and Williams on alkylations of chiral ester enolates indicate that the latter type of transition state is likely to be more favorable.[97] Further discussion of extraannular and chelate-enforced chirality transfer is provided in Sections 1.1.6.3 and 1.1.6.4.

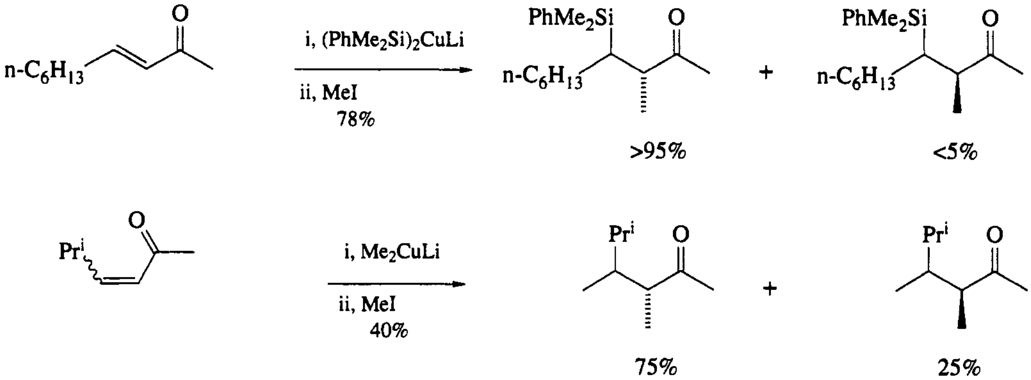

**Scheme 24**

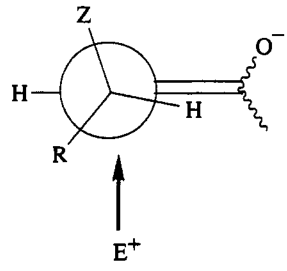

(**52**) a: $Z = SiMe_2Ph$, $R = n\text{-}C_6H_{13}$
b: $Z = Pr^i$, $R = Me$

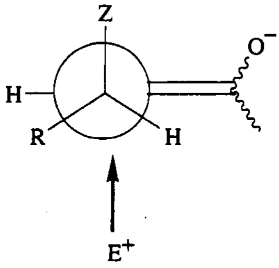

(**53**) a: $Z = SiMe_2Ph$, $R = n\text{-}C_6H_{13}$
b: $Z = Pr^i$, $R = Me$

### 1.1.2.3 Cycloalkylation Reactions of Saturated Ketones

Cycloalkylation reactions have been utilized for the synthesis of a variety of cyclic compounds including monocyclic, fused-ring, spirocyclic and bridged systems. These reactions require the generation of an enolate in the presence of a suitably disposed leaving group (halide, tosylate, epoxide, *etc.*). Possible modes of cycloalkylation are represented in Scheme 25. If the transition state for *C*-alkylation is strained, *O*-alkylation becomes a competitive process. Traditionally, sodium or potassium enolates were employed for these reactions, but, more recently, lithium enolates, generated by treatment of the substrate with bulky, non-nucleophilic bases, have been generally utilized.

Ketone enolate cycloalkylations may be used to form small to medium and even larger rings under appropriate conditions. Space limitations permit only a few examples of these reactions to be covered here. The literature prior to 1978 has been reviewed.[1]

Detailed studies on the modes of cycloalkylation of the terminal lithium enolates of 5-bromo-3,3-dimethyl-2-pentanone (**54**) and 6-bromo-3,3-dimethyl-2-hexanone (**55**)[98,99] have shown that (**54**) undergoes exclusively *O*-cycloalkylation, while (**55**) undergoes only *C*-cycloalkylation (Scheme 26). The transition states for the two modes of alkylation are shown in formulas (**56**) and (**57**). In the *C*-alkylation, the electrophilic ω-carbon atom must approach the enolate α-carbon perpendicularly along a path colinear with the C—Br bond that undergoes cleavage. This pathway is highly strained when $n = 0$ or 1 and *O*-alkylation, which can take place *via* attack of the basic *syn* nonbonding electron pair lying in the plane of the enolate, is favored. When $n = 2$ or larger the *C*-alkylation transition state can be easily attained and this pathway becomes favored.

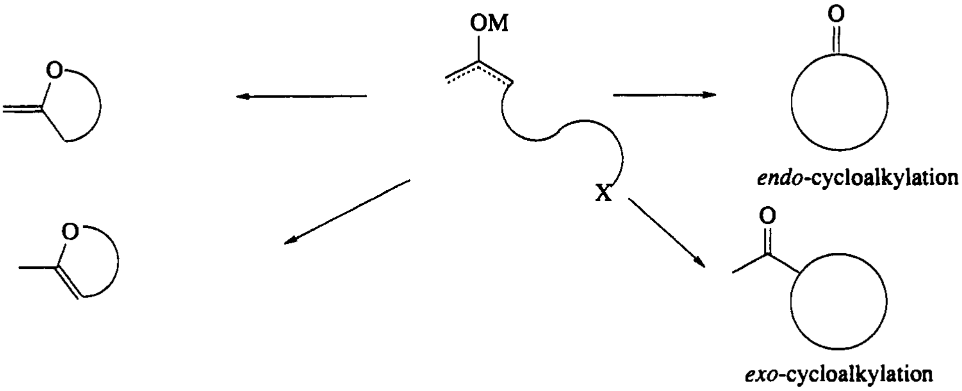
OM
X
O
*endo*-cycloalkylation
*exo*-cycloalkylation

**Scheme 25**

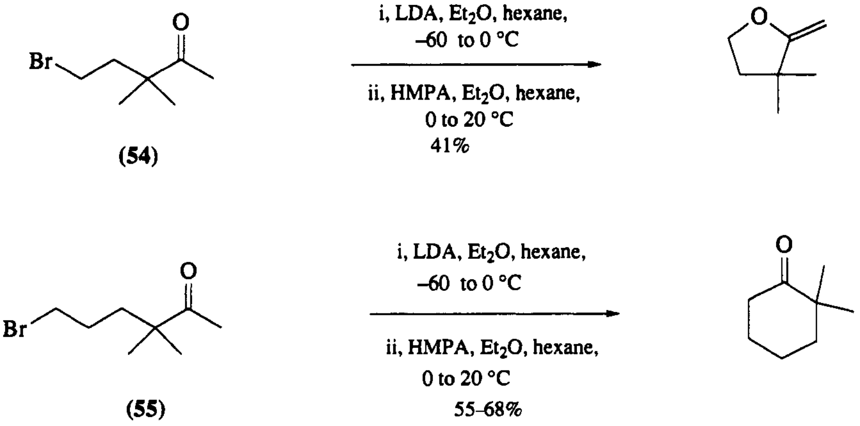
Br
O
(54)
i, LDA, $Et_2O$, hexane, –60 to 0 °C
ii, HMPA, $Et_2O$, hexane, 0 to 20 °C
41%
Br
O
(55)
i, LDA, $Et_2O$, hexane, –60 to 0 °C
ii, HMPA, $Et_2O$, hexane, 0 to 20 °C
55–68%

**Scheme 26**

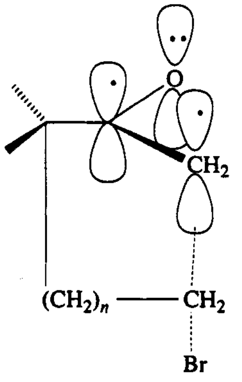
O
$CH_2$
$(CH_2)_n$
$CH_2$
Br

**(56)**

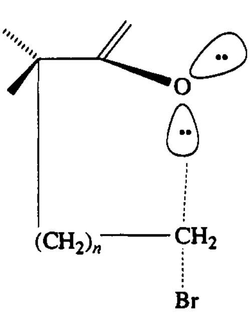
O
$(CH_2)_n$
$CH_2$
Br

**(57)**

Scheme 27 illustrates how different conditions of enolate formation may affect the outcome of cycloalkylation reactions.[100] Deprotonation of the bromo ketone (**58**) under equilibrating conditions with potassium *t*-butoxide in *t*-butyl alcohol resulted in *exo* cycloalkylation *via* the more-substituted metal enolate to give the 5,5-fused bicyclic ketone (**59**) in good yield. On the other hand, when (**58**) was treated with LDA in THF under kinetic conditions, deprotonation occurred at the terminal position and *endo* cycloalkylation was faster than enolate equilibration and gave the 5,7-fused ketone (**60**), also in good yield. The conversions of 3(2-tosyloxyethyl)cyclohexanone to bicyclo[2.2.2]octan-2-one[101] and of 3(2-tosyloxyethyl)-[102] and 3(2-bromoethyl)-cyclopentanones[103] to the corresponding bicyclo[2.2.1]heptan-2-ones provide additional examples of cycloalkylations which lead to bridged ring systems.

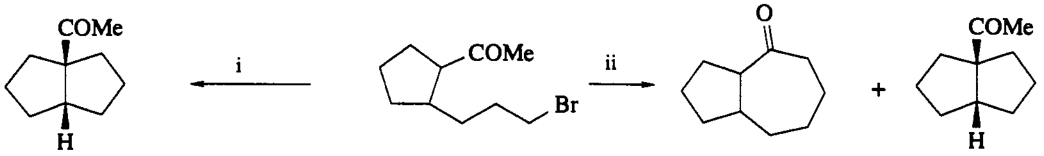

**(59)** 86–94% **(58)** **(60)** 77–84% **(59)** 2%

i, Bu$^t$OK, Bu$^t$OH, pentane, 25 °C, 30 min ; ii, LDA, THF, –72 to 65 °C, 2 h

**Scheme 27**

*Exo* cycloalkylations have been used to synthesize *cis*-1-decalones. For example, treatment of 2-methyl-3(4-tosyloxybutyl)cyclohexanone with sodium *t*-pentylate in benzene gave *cis*-9-methyl-1-decalone (**50**) in 60% yield.[104] Also, as shown in Scheme 28, conjugate addition–cycloalkylation was employed to synthesize a *cis*-fused decalone related to the sesquiterpene, (±)-valerane.[41] Apparently, in these cases, the enolate intermediate adopts a conformation having the 4-bromobutyl side chain quasi-axial, and C—C bond formation occurs *via* equatorial attack to give initially a twist-boat conformation of the product.

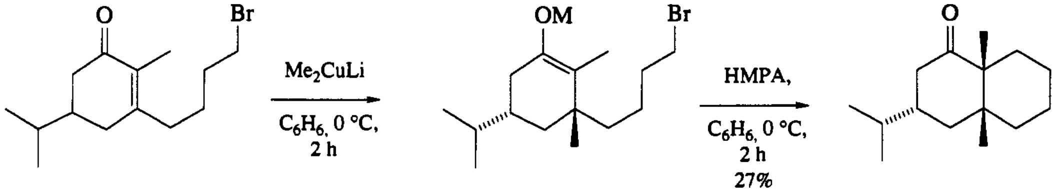

**Scheme 28**

In addition to (±)-valerane, a wide variety of other sesquiterpenes, including (±)-ishwarane,[105] (±)-ishwarone,[106] copaene,[107] ylangene,[107] (±)-seychellene[108,109] (±)-sativene,[110] (±)-longifoline,[111] (±)-copacamphene,[112] (±)-damsin,[113] (±)-$\Delta^{9(12)}$-capnellene,[114] (±)-pentalenene,[115] (–)-β-vetivone[116] and (±)-β-eudesmol[117] have been synthesized by pathways involving cycloalkylation of saturated ketone enolates.

### 1.1.2.4 Alkylations of Metal Enolates of Saturated Aldehydes

Because of their tendency to undergo self (aldol) condensations, Cannizzaro and Tichshenko reactions, the direct alkylation of aldehydes *via* metal enolates has numerous drawbacks.[118] Indeed, poor results have been obtained, even with preformed lithium enolates.[118] However, much better yields have been achieved through the use of enolates derived from less or more electropositive metals than lithium. In early experiments in this area, Odic and Pereyre showed that tri-*n*-butyltin aldehyde enolates, prepared by reaction of aldehyde enol acetates with tri-*n*-butyltin methoxide, were *C*-alkylated in good yields with reactive alkylating agents in THF–HMPA.[119] Although these reactions were slower than those of alkali metal enolates and higher temperatures and longer reaction times were required, *O*-alkylation was not a problem. It was also shown by Jung and Blum that the tri-*n*-butyltin enolate of acetaldehyde could be alkylated by this method.[120] Later, van der Gen and coworkers[121] found that potassium enolates of α,α-disubstituted aldehydes, such as 2-methylpropanal and 2-ethylhexanal, prepared by reaction of the substrate with potassium hydride in THF, were rapidly *C*-alkylated in good yields with reactive alkylating agents at room temperature. When less reactive primary and secondary iodides were used, there was a significant amount of competition between *C*- and *O*-alkylation. When aldehydes containing two α-protons were employed, mixtures of mono- and di-alkylated products were produced because of rapid proton exchange between the alkylated products and the starting enolates. Aldol condensations probably occur in these reactions, but, because potassium is a relatively poor chelating cation, there is likely to be a mobile equilibrium between the potassium aldolate and the enolate so that the alkylation step can proceed to completion.

Aldehydes that contain only one α-hydrogen atom may be alkylated in reasonable yields with reactive alkylating agents such as methyl iodide, allyl chloride or benzyl chloride in an emulsion of benzene and 50% aqueous sodium hydroxide in the presence of a catalytic amount of a tetra-*n*-butylammonium salt.[122] When less reactive alkylation agents were employed or when the aldehyde contained bulky α-substituents, aldol condensations and/or *O*-alkylations became significant problems.

Aldol condensations of more complex aldehydes are often sufficiently slow to allow successful alkylation reactions. There are numerous examples of aldehyde enolate methylations in the field of natural product synthesis.[123,124] As shown in Scheme 29, the methylation of a tricyclic aldehyde, which was employed in the synthesis of (±)-rimuene, provides an illustrative case.[123] As expected for an exocyclic enolate intermediate such as (**61**), the methyl group was introduced equatorial to the six-membered ring with a high degree of stereoselectivity. α-Alkylated aldehydes may be prepared efficiently by alkylations of enamines, Schiff base anions, hydrazone anions and other methods. A discussion of this methodology is provided in Section 1.1.5.

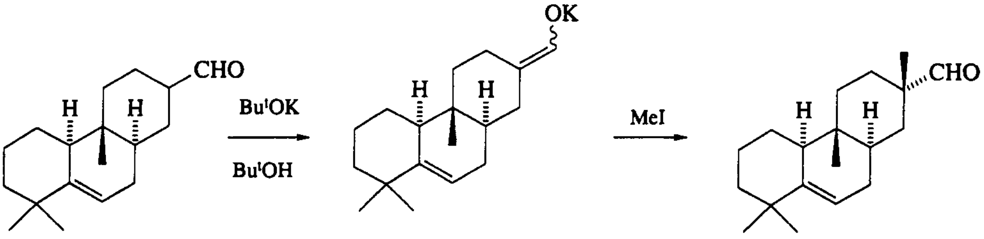

(**61**)

**Scheme 29**

## 1.1.3 ALKYLATIONS OF METAL DIENOLATES OF α,β-UNSATURATED KETONES

α,β-Unsaturated ketones of the general structure (**62**), which contain α′- and γ-protons undergo deprotonation with strong bases under kinetic control to yield cross-conjugated metal dienolates such as (**63**).[1] Under thermodynamic conditions, extended metal dienolates such as (**64**) are produced.[1]

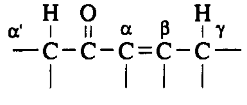

$$\overset{\alpha'}{}\;-\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{O}{\|}}{C}-\overset{\alpha}{\underset{|}{C}}=\overset{\beta}{\underset{|}{C}}-\overset{\overset{H}{|\,\gamma}}{\underset{|}{C}}-$$

(**62**)

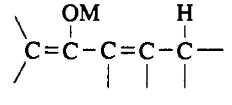

$$\diagdown\!\!\!\!\!\!\underset{/}{}C=\overset{\overset{OM}{|}}{C}-\underset{|}{C}=\underset{|}{C}-\overset{\overset{H}{|}}{\underset{|}{C}}-$$

(**63**)

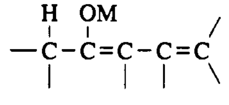

$$-\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{OM}{|}}{C}=\underset{|}{C}-\underset{|}{C}=C\overset{/}{\underset{\diagdown}{}}$$

(**64**)

A variety of lithium dialkylamide bases can be used to produce cross-conjugated lithium dienolates, which may then be alkylated with even less reactive alkylating agents, *e.g.* propyl iodide, in good to excellent yields without equilibration to the corresponding extended dienolates.[125] α′-Alkylations of cyclohex-2-enones, certain cyclopent-2-enones, 1(9)-octalin-2-ones and steroidal 4-en-3-ones have been accomplished by this procedure.[1]

Stork and Danheiser have developed a highly useful procedure for the synthesis of 4-alkylcyclohex-2-enones, which involves α′-alkylations of cross-conjugated lithium dienolates of 3-alkoxycyclohex-2-enones, followed by metal hydride reduction of the carbonyl group and hydrolysis (Scheme 30).[126] Numerous applications of this procedure have been reported.[1,127,128] Two different alkyl groups may be introduced at the 6-position of a cyclohex-2-enone derivative without difficulty.[127] While dialkylation is generally not a problem in alkylations of cross-conjugated dienolates of cyclohex-2-enones, it was observed when relatively acidic 3-chlorocyclohex-2-enones were employed.[129]

A comparison of the data shown in Scheme 31 for methylations of cross-conjugated lithium dienolates of 1(9)-octalin-2-ones (**65a**) and (**65b**) with those shown in Scheme 20 for the corresponding decalone 2-enolates (**45**) reveals that the tendency for axial β-attack is significantly greater in the former systems.[66,130] Similar results have been obtained in alkylations of related steroidal cross-conjugated dienolates.[131] Two explanations for these results have been offered: (i) the cross-conjugated dienolate systems can easily adopt a relatively low energy quasi-*cis* conformation with the β-face exposed to electrophilic attack;[130,131] or (ii) the effect of the 1,9-double bond in species such as (**65**) could alter the trajectory of attack of the electrophile on the HOMO of the dienolate (*cf.* formula **24**).[66] However, Agami *et al.* showed that the cross-conjugated dienolate (**66**), isomeric with (**65b**), gave exclusively the product of equatorial methylation, *i.e.* α-attack at C-1.[130] The electronic factor would be expected to increase the degree of axial alkylation of (**66**) relative to the corresponding simple enolate (**44**). Since this was not

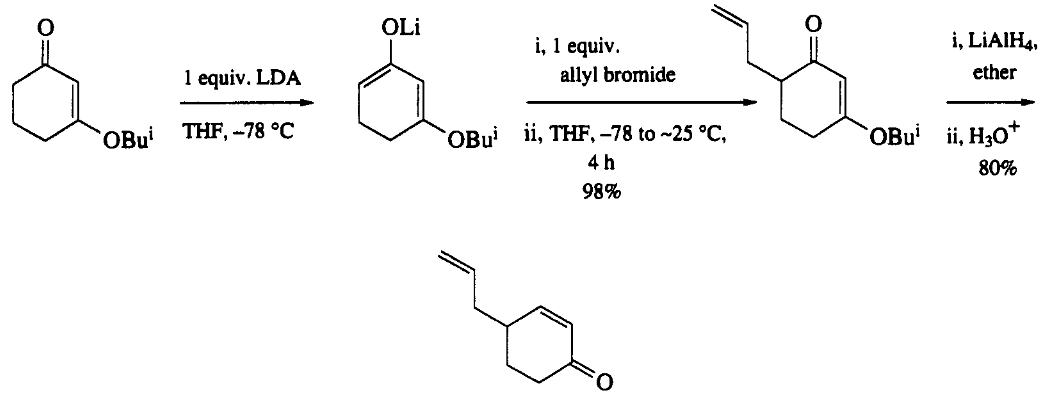
O
OBu$^i$
1 equiv. LDA
THF, -78 °C
OLi
OBu$^i$
i, 1 equiv. allyl bromide
ii, THF, -78 to -25 °C, 4 h
98%
O
OBu$^i$
i, LiAlH$_4$, ether
ii, $H_3O^+$
80%
O

Scheme 30

found to be the case, the conformational factor seems to be the better explanation for the results of the alkylations of (**65a**) and (**65b**).[130]

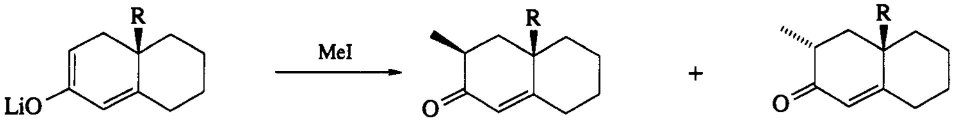
R
LiO
MeI
R
O
+
R
O

(**65**) a: R = H
(**65**) b: R = Me

93:7
50:50

Scheme 31

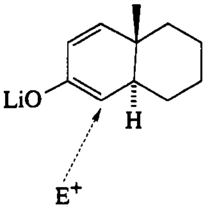

(**66**)

By the use of appropriate dialkylating agents, it is possible to spiroannulate cyclohex-2-enones at the 6-position *via* kinetic lithium dienolates. This method was used by Stork *et al.*[132] to prepare the enone (**67**), a key intermediate for the total synthesis of (±)-β-vetivone (Scheme 32). In the cycloalkylation step the cross-conjugated dienolate presumably adopts a conformation with the 5-methyl group quasiaxial to the ring to avoid $A^{1,2}$-strain and the new C—C bond is formed *trans* to this group.

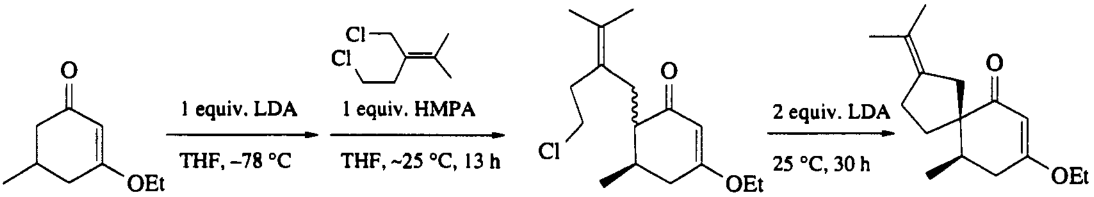
O
OEt
1 equiv. LDA
THF, -78 °C
Cl
Cl
1 equiv. HMPA
THF, -25 °C, 13 h
O
Cl
OEt
2 equiv. LDA
25 °C, 30 h
O
OEt

(**67**)

Scheme 32

Although the reaction failed with cyclopent-2-enone itself, methylations of kinetic lithium dienolates of 3-alkylcyclopent-2-enones have been carried out in acceptable yields.[133] Intramolecular α′-alkylations of 5,6- and 6,6-fused ring bicyclic α,β-unsaturated ketones bearing 2-bromoethyl groups at the angular positions have been reported.[134] A total synthesis of (±)-clovene has been accomplished using an intramolecular α′-enolate cycloalkylation of 4-(3-chloropropyl)-4-methyl-6-(2-ethylallyl)cyclohex-2-enone to give 5-(2-ethylallyl)-1-methylbicyclo[3.3.1]non-2-en-4-one as a key step.[135]

In general, the thermodynamically stable extended dienolates (**64**) have been prepared by deprotonation of enones (**62**) with sodium or potassium alkoxides in protic solvents or with sodium or potassium hydride in aprotic solvents.[1,2,4,49] Kinetically formed cross-conjugated lithium enolates may be converted into the corresponding extended systems in the presence of excess ketone but in certain cases equilibration is quite slow.[136] Presumably, because the π-electron density is higher at the α-carbon than the γ-carbon, extended dienolates normally react with alkylating agents to produce α-alkyl-β,γ-unsaturated ketones.[137]

If the α-position of an extended dienolate is unsubstituted, dialkylation may be an important reaction or, under certain conditions, the major reaction, particularly when reactive alkylating agents, *e.g.* methyl iodide, are employed.[138] Equation (5) provides an example of the synthetic utility of the dimethylation process.[139] Ringold and Malhotra have provided a detailed mechanism to account for the facile dialkylation of these systems.[138] Briefly, deprotonation by bases present in the medium converts the initially formed α-alkylated β,γ-unsaturated ketone to its dienolate, which then undergoes a second alkylation faster than the β,γ-double bond is isomerized to the α,β-position. When the alkylating agent is of low reactivity or its concentration is limited by dropwise addition, the rate at which the double bond moves into conjugation becomes faster than the second alkylation step. As is described in Section 1.1.5.1, extended lithiated dienamines are the nucleophilic reagents of choice for α-methylation of α,β-unsaturated ketones.[140]

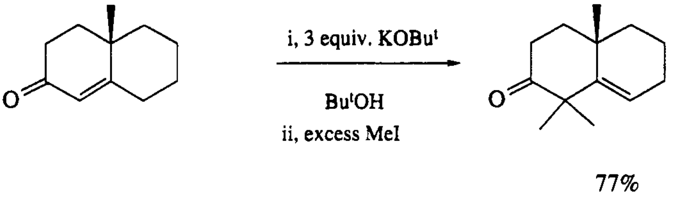

(5)

With less reactive alkylating agents monoalkylation of extended dienolates at the α-position is feasible. In connection with the total synthesis of steroids, dienolates of bicyclic enones such as (**68a**) and (**68b**), or various derivatives of the saturated carbonyl function of these compounds, have been alkylated with a variety of reagents containing latent 3-ketoalkyl functionality.[49] The products of these reactions may be converted into tricyclic enones such as (**69a**) and (**69b**). Even diannulating agents which allow elaboration of both the A and B rings of the steroid skeleton have been utilized.[49]

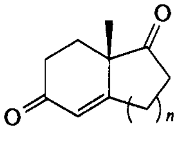

(**68**) a: $n = 1$
b: $n = 2$

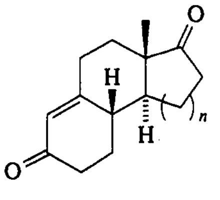

(**69**) a: $n = 1$
b: $n = 2$

Normally *C*-alkylation occurs predominantly in reactions of alkali metal extended dienolates with the usual alkylating agents in solvents of low to medium polarity. However, highly reactive benzyloxymethyl halides yield extensive amounts of *O*-alkylation products;[141] when highly polar solvents are used *O*-alkylation may occur even with unreactive alkylating agents.[142] As expected, the *C*-alkylation:*O*-alkylation ratio is influenced by: (i) the polarity of the solvent; (ii) the nature of the alkylating agent; and (iii) the nature of the metal cation.

The stereochemistry of alkylations of extended dienolates of enones such as (**70**) has been extensively investigated (Scheme 33).[141,143] In general, the results are similar to those found for the related decalone enolates (**43a**) and (**44**), *i.e.* steric factors within the anion play a dominant role. Thus, axial attack is preferred with (**70**; $R^1$ = H), but equatorial attack is strongly favored when an angular methyl group is present (**70**; $R^1$ = Me). There is a modest preference for axial alkylation when an angular ethoxycarbonyl group is present, as in (**70**; R$^1$ = CO$_2$Et). This effect has been attributed to the polar nature of the angular ester group, but since an ethoxycarbonyl group is smaller in size than a methyl group, an explanation based upon steric effects alone possibly can apply.

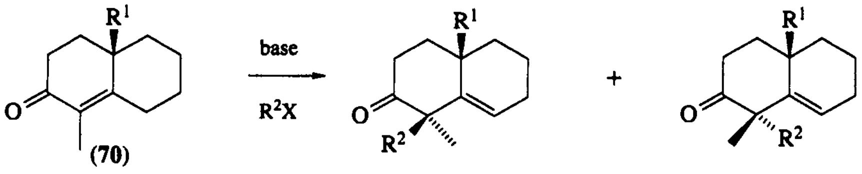

**(70)**

| *R*$^1$ | *Base* (*solvent*) | *R*$^2$X | *Ratio* |
|---|---|---|---|
| H | KOBu$^t$, PhH | CD$_3$I | 70:30 |
| Me | KOBu$^t$, PhH | CD$_3$I | 10:90 |
| Me | NaH, dioxane | PhCH$_2$OCH$_2$Cl | 16:84 |
| CO$_2$Et | NaH, dioxane | PhCH$_2$OCH$_2$Cl | 67:33 |

**Scheme 33**

As shown in Scheme 34, a rather profound solvent effect on dienolate alkylation diastereoselectivity has been noted for the steroidal enone (**71**).[143] Such large solvent effects have not been documented for other systems. Possible explanations based upon the position of the transition state along the reaction coordinate and/or 'specific' solvation of the dienolate have been advanced to account for preferential axial alkylation in benzene and equatorial alkylation in *t*-butyl alcohol.[143] However, in view of the fact that the degree of aggregation of the dienolate as well as the structure of the aggregates may be modified considerably in going from one solvent to the other, rationalization of the results is difficult.

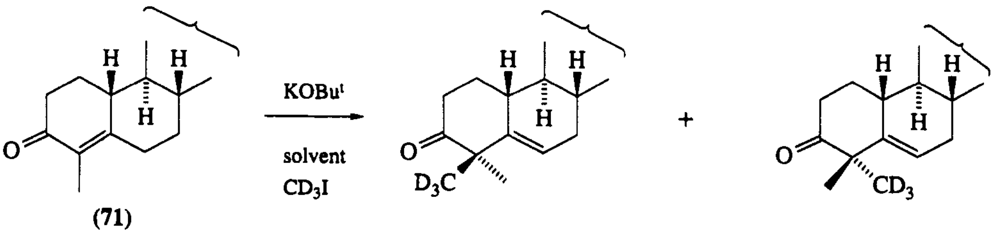

**(71)**

| *Solvent* | *Ratio* |
|---|---|
| PhH | 70:30 |
| Bu$^t$OH | 9:91 |

**Scheme 34**

Stork *et al.* have shown that heteroannular extended dienolates such as (**73**), which contain substituents at both the α- and γ-positions, undergo predominantly equatorial alkylation (Scheme 35).[144] The dienolate (**73**) was produced by lithium–ammonia reduction of the tricyclic dienone (**72**) and the product of its alkylation with 1-bromo-3-chloro-2-butene and hydrolysis of the resulting enol ether, *i.e.* (**74**), was a key intermediate in a short, highly stereoselective synthesis of (±)-adrenosterone. It was pointed out that equatorial alkylation is obtained with dienolates such as (**73**) and related compounds because a *peri* interaction (Me ↔ OMe) of the α- and γ-substituents forces the ring A to adopt a half-boat conformation in which the α-face of the π-system is accessible to attack.

γ-Alkylations of extended dienolates of β-amino-α,β-cyclopentenones,[145] β-amino-α,β-cyclohexenones[136,146] and related acyclic systems[147] have been reported. Koreeda and coworkers[148] have found that deprotonation of β-alkoxy-α,β-cyclopentenones with LHDS in THF gave dienolates, which underwent regioselective γ-alkylations. However, attempted γ-alkylations of β-alkoxy- or β-thioalkoxy-α,β-cyclohexenones were unsuccessful.[146,149]

As shown in Scheme 36, 2,2-disubstituted-5-alkyl-3(2*H*)-furanones also undergo γ-alkylation *via* their extended dienolate intermediates (**75**).[149] Similarly, 4-isopropyl-6-methyl-(2*H*)-pyran-2-one, which may be regarded as a vinylogous 5-alkyl-3(2*H*)-furanone, was deprotonated and alkylated at the methyl group.[150]

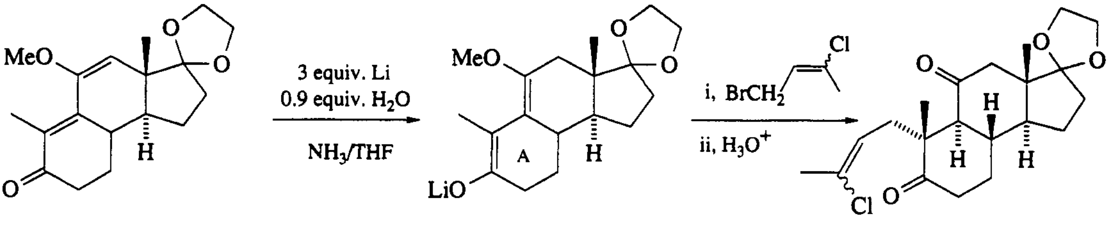

(72) (73) (74)

Scheme 35

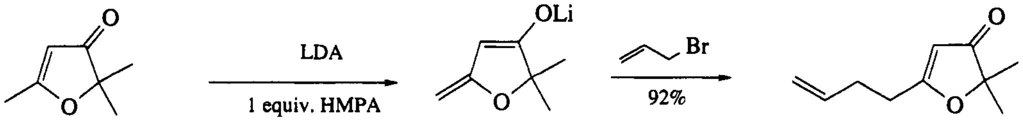

(75)

Scheme 36

The reason γ-alkylations occur in certain systems having heteroatom β-substituents is unclear. The electron density at the γ-carbon of the dienolate may be enhanced through conjugation with the unshared electron pair on the heteroatom. The presence of an exocyclic β,γ-double bond in systems such as (75) seems to be an important structural requirement for γ-alkylation.[149]

The reader is referred to two reviews for numerous examples of intramolecular γ-alkylations of ketone dienolates.[1,2] Lansbury *et al.* have achieved some success in synthesizing γ-alkylated α,β-unsaturated ketones *via* the use of dienolates of γ-benzenesulfonyl enones[151] and trilithiated derivatives of α′-benzenesulfonyl enones[152] as nucleophiles.

Potassium hydride in THF is the base–solvent combination of choice for preparing dienolates of α,β-unsaturated aldehydes. These enolates are more stable than the corresponding saturated aldehyde enolates.[121] Equation (6) shows that excellent yields of α,α-disubstituted β,γ-unsaturated aldehydes can be obtained by trapping α-substituted aldehyde potassium dienolates with allylic halides.

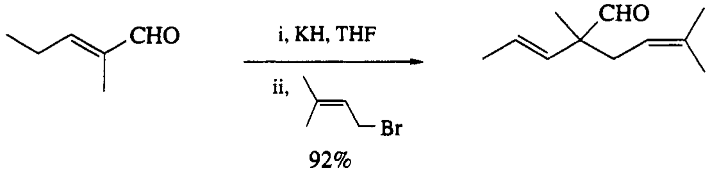

(6)

## 1.1.4 ALKYLATIONS *VIA* SILYL ENOL ETHERS AND OTHER ENOL DERIVATIVES

As discussed in Section 1.1.2, *C*-alkylations of metal enolates are restricted to the use of relatively $S_N2$-reactive alkylating agents. Loss of regioselectivity, failure of the reaction, or at least poor yields are observed with alkylating agents that undergo the $S_N2$ reactions slowly and/or are prone to elimination. A significant advance in *C*-alkylation chemistry was made when it was shown that silyl enol ethers, and also enol esters and alkyl enol ether derivatives of ketones and aldehydes, are effective nucleophiles for combination with $S_N1$-reactive alkylating agents in the presence of Lewis acids.[12,153–157] The most commonly used Lewis acid catalysts are titanium tetrachloride and zinc bromide. Methylene chloride is used as the solvent. Experimentally, best results are obtained by adding the Lewis acid catalyst to a mixture of the enol derivative and the alkylating agent.[156,158] TMS triflate is also an effective catalyst for this type of reaction.[159]

Tertiary halides, acetates and methyl ethers, aryl-activated secondary halides, prenyl halides and acetates, acetals, ketals, thioacetals, α-chloroalkyl ethers, and, particularly, α-chloroalkyl phenyl sulfides have been widely used as alkylating agents. Such reagents may contain a variety of functional groups including alkenes, esters, halides, ketones, nitro groups and silyl ethers.

As illustrated in Scheme 37, using the data of Reetz *et al.*,[160] the more- and less-substituted TMS enol ethers of 2-methylcyclohexanone have been *t*-butylated with high regiospecificity and in good yields by this method. Paterson has also reported that titanium tetrachloride promoted phenylthioalkylations of the more- and less-substituted trimethylsilyl enol ethers of a wide variety of unsymmetrical cyclic and acyclic ketones can be accomplished regiospecifically.[156] Loss of regioselectivity was not observed even for rather hindered systems.

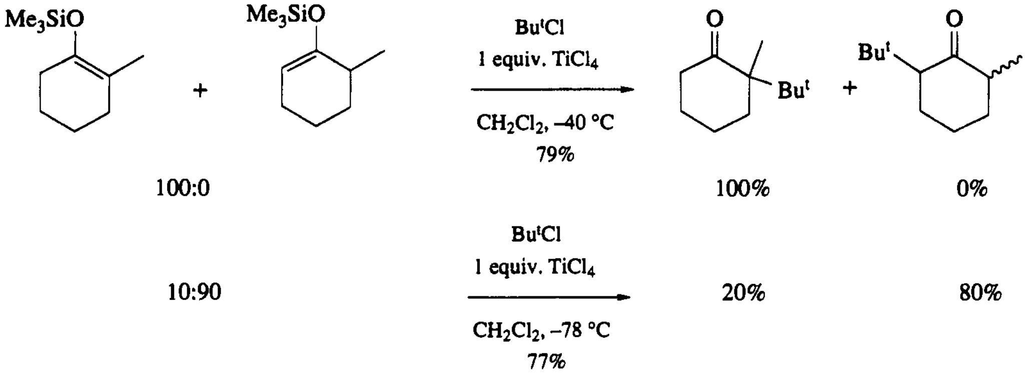

**Scheme 37**

As shown in Scheme 38, several primary alkyl-substituted cyclohexanones have been prepared by Lewis acid catalyzed phenylthioalkylation of the TMS enol ether of cyclohexanone followed by reductive removal of a phenylsulfenyl group.[156] The two-step neopentylation sequence is particularly noteworthy. This methodology has been used to prepare numerous α-alkylated cyclic and acyclic ketones. α-Alkylated aldehydes can be produced in a like manner. α-Alkylidenation can also be accomplished by oxidative removal of sulfur.[156] Lee and coworkers have found that TMS triflate-catalyzed reactions of silyl enol ethers of cyclic ketones and aldehydes with saturated and unsaturated 1,1-dimethoxy-ω-trimethylstannanes, followed by addition of titanium tetrachloride, provide novel routes to fused and spirocyclic ring systems.[161] Phenylthiomethylstannylations of silyl enol ethers have also been reported.[162]

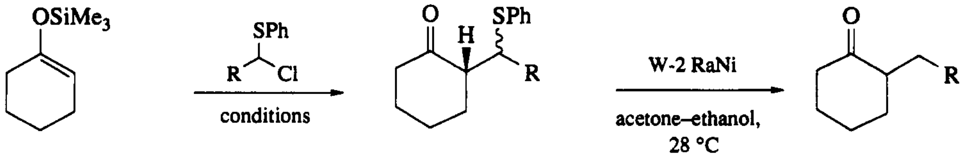

| *R* | *Conditions* | *Yield* (%) | *Yield* (%) |
|---|---|---|---|
| Me | 1.1 equiv. $TiCl_4$,<br>$CH_2Cl_2$, –23 °C | 78 | 95 |
| Pr$^n$ | 1.1 equiv. $TiCl_4$,<br>$CH_2Cl_2$, –23 °C | 83 | 90 |
| Pr$^i$ | 1.1 equiv. $TiCl_4$,<br>$CH_2Cl_2$, –23 °C | 66 | 91 |
| Bu$^t$ | 0.02 equiv. $ZnBr_2$,<br>$CH_2Cl_2$, 20 °C | 78 | 93 |

**Scheme 38**

Studies pertaining to diastereoselectivity in Lewis acid catalyzed alkylations of enol derivatives have been limited. Reetz has reported that *t*-butylation of 1-trimethylsiloxy-4-*t*-butylcyclohex-1-ene gave an 85:15 mixture of *cis*- and *trans*-2,4-di-*t*-butylcyclohexanone, which could result from kinetic equatorial and axial alkylation, respectively. However, equilibration of the products, which would favor formation of the former isomer, was not ruled out. Titanium tetrachloride promoted phenylthiomethylation of the more-substituted TMS enol ether of 1-decalone gave a 4:1 mixture of *cis*- and *trans*-fused 1-decalones.[156] In this case, where equilibration of the product could not occur, the diastereoselectivity was similar to that of methylation of the corresponding lithium enolate (**49**).[8,54]

Lewis acid catalyzed intramolecular alkylations of silyl enol ethers containing $S_N1$-reactive functionality provide useful routes to a variety of carbocyclic systems.[163,164] Smith *et al.*[165] have employed an intramolecular Mukaiyama reaction of the enol derivative (**76**) to produce the tetracyclic system (**77**) (equation 7). This transformation was a key step in their elegant synthesis of jatrophone. The synthesis demonstrated that the molecules involved in the reaction may contain some rather sensitive functionality and that intramolecular formation of large rings is possible. Cycloalkylation of a silyl enol ether has been reported by Magnus and Carter in connection with their research on the antitumor antibiotic esperamicin A (equation 8).[166] They found that upon treatment with titanium chloride the cobalt-complexed propargylic ether (**78**) gave the cyclization product (**79**) as a stable compound. Oxidative decomplexation of (**79**) produced an aromatized tricyclic ketone *via* a diynene intermediate. Lewis acid catalyzed intramolecular cyclizations of enol acetates, containing suitably disposed isopropenyl and isopropylidene groups capable of forming tertiary carbocations, have been employed in a creative manner in the synthesis of several complex natural products.[155]

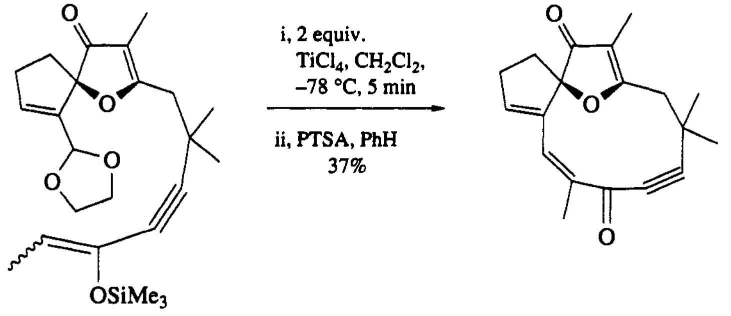

(**76**) (**77**) (7)

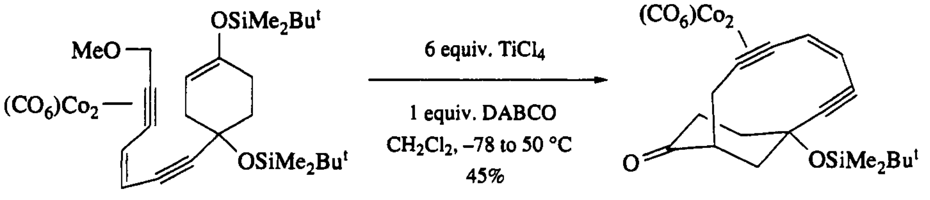

(**78**) (**79**) (8)

Unlike lithium dienolates, where α-alkylation is the rule in simple systems, Lewis acid catalyzed reactions of extended silyl dienol ethers with *S*N1-reactive alkylating agents may give extensively or exclusively γ-alkylation products. Scheme 39 shows some selected data from the work of Fleming and coworkers who have thoroughly studied reactions of silyl enol ethers such as (**80**) derived from crotonophenone.[154] These results clearly show that the γ:α-alkylation ratio is increased by: (i) the use of alkylating agents, which give better-stabilized electrophilic species; and (ii) silyl dienol derivatives which contain electron-withdrawing groups on silicon.[154] The effect of a change in the Lewis acid was not very clear cut because overall product yields often changed dramatically. In other work, it was shown that when methyl groups are present at the γ-position of the dienol ether, the γ:α-ratio is reduced.[167]

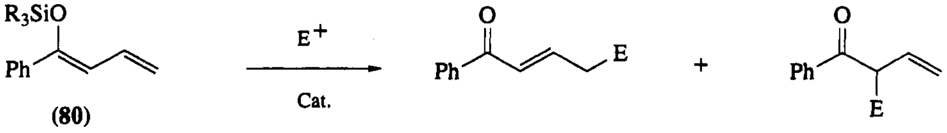

(**80**)

| *R* | *E*$^+$*/Cat.* | γ:α *Ratio* | *Yield* (%) |
|---|---|---|---|
| Me | PhSCH$_2$Cl/ZnBr$_2$ | 45:55 | 65 |
| Ph | PhSCH$_2$Cl/ZnBr$_2$ | 86:14 | 93 |
| Me | (EtO)$_2$CMe$_2$, TiCl$_4$ | 100:0 | 78 |

**Scheme 39**

The position of alkylation of homoannular silyl dienol ethers is apparently dramatically influenced by the nature of the alkylating agent and catalyst. Reetz and coworkers[155] reported that 1-trimethylsiloxy-

1,3-cyclohexadiene is *t*-butylated exclusively at the α-position with *t*-butyl acetate/zinc iodide, while Fleming's research group[154] found that phenylthioalkylation of this compound occurred exclusively at the γ-position with 1-chloro-1-phenylthio-*n*-butane/zinc bromide (Scheme 40). The reasons for these contrasting results are unclear.

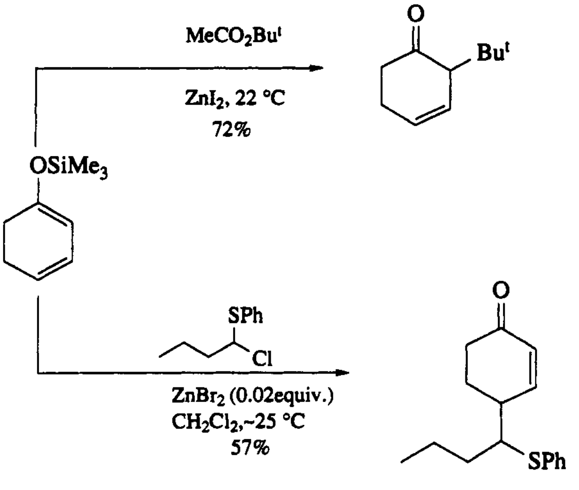

**Scheme 40**

Lewis acid catalyzed alkylations of cross-conjugated silyl dienol ethers provide routes to α′-alkylated ketones. A short synthesis of the sesquiterpene (±)-*ar*-turmerone has been accomplished using the cross-conjugated TMS dienol ether of mesityl oxide (equation 9).[168]

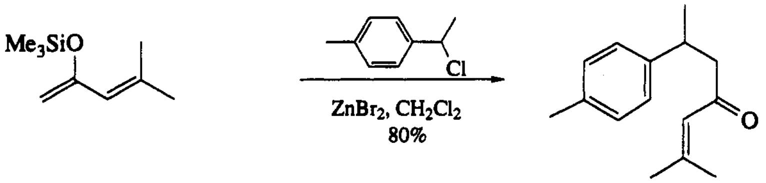

(9)

Palladium(0)-catalyzed α-allylations of TMS enol ethers can be carried out cleanly with allylic carbonates.[169] These reactions are highly regioselective, *e.g.* the more- and less-substituted TMS enol derivative of 2-methylcyclohexanone (*cf.* Scheme 37) gave 2-allyl-2-methylcyclohexanone and 2-methyl-6-allylcyclohexanone, respectively. Allylations of aldehyde silyl enol ethers occur similarly. Allylations of enol acetates occur with allyl carbonates in the presence of catalytic amounts of palladium(0) complexes and tri-*n*-butyltin methoxide.[169]

## 1.1.5 ALKYLATIONS OF CARBONYL COMPOUNDS *VIA* THEIR NITROGEN DERIVATIVES

### 1.1.5.1 Regiochemistry and Stereochemistry of Alkylations of Nitrogen Derivatives of Carbonyl Compounds

Prior to the discoveries that lithium and other less electropositive metal cations were valuable counterions for enolate alkylations, the Stork enamine reaction was introduced to overcome problems such as loss of regioselectivity and polyalkylation that plagued attempts to alkylate sodium or potassium enolates of ketones or aldehydes.[170–172] Methods of synthesis of enamines by reactions of ketones and aldehydes with secondary amines have been thoroughly reviewed.[171,172] Enamine alkylations are usually conducted in methanol, dioxane or acetonitrile. Enamines are ambident nucleophiles and *C*- and *N*-alkylations are usually competitive. Subsequent hydrolysis of the *C*-alkylated product (an iminium salt) yields an α-alkylated ketone, while the *N*-alkylated product (a quaternary ammonium salt) is usually water soluble and relatively inert to hydrolysis.

The monomethylation of the pyrrolidine enamine of β-tetralone shown in Scheme 41 provides a highly successful example of the reaction. Attempted alkylation of the ketone with 1 equiv. of methyl iodide in the presence of a strong base gave almost exclusively the recovered ketone and its dimethylated derivative.

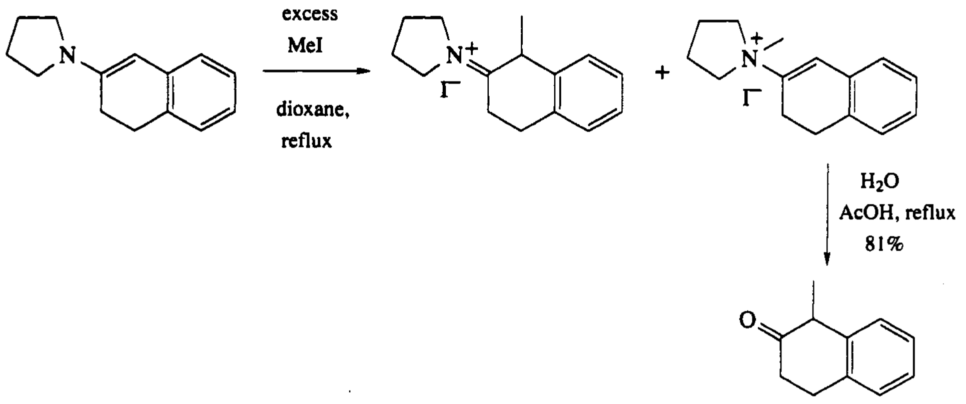

**Scheme 41**

Although dialkylation was not a problem in the above case, it is frequently a significant side reaction. As illustrated in Scheme 42 for the pyrrolidine enamine of cyclohexanone (**81**), the initially formed *C*-alkylated iminium salt (**82**) can transfer a proton to the starting enamine to yield the enamine of the alkylated product, *e.g*. (**83**), which can be further alkylated to give the dialkylated iminium salt (**85**). As a result, the starting ketone (derived from the unalkylated iminium salt **84**), the monoalkylated product and the dialkylated product may be isolated after hydrolysis. Although dialkylation is not such a serious problem when higher molecular weight alkylating agents are used, because mono- and di-alkylated ketones can be separated by distillation, the yields in enamine alkylations are usually rather low.

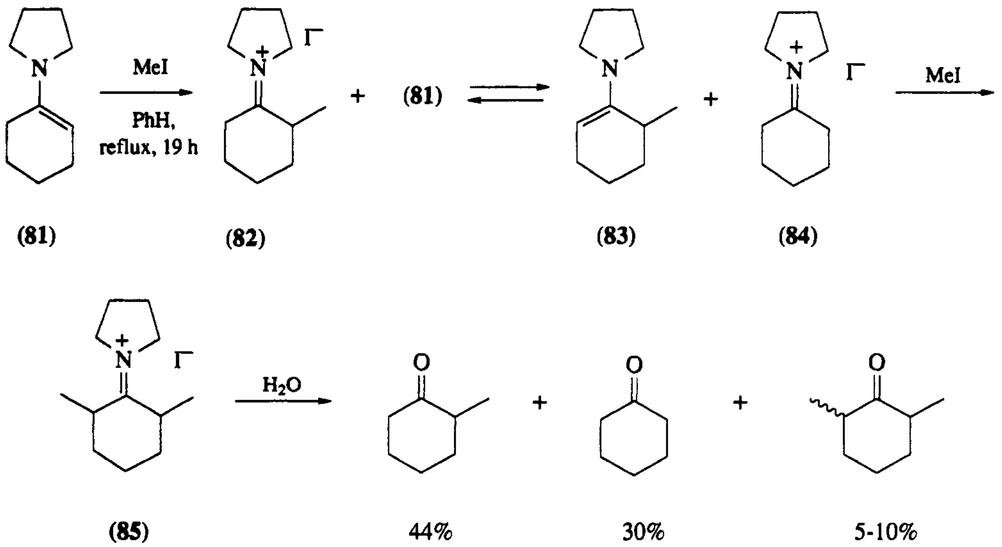

(**81**) (**82**) (**83**) (**84**)

(**85**)

**Scheme 42**

When unreactive alkylating agents are reacted with enamines, both the *C*- and *N*-alkylation processes are essentially irreversible. However, strongly electrophilic reagents such as methyl iodide, allylic halides, benzylic halides, propargylic halides, α-halo ethers and α-halocarbonyl compounds and nitriles can undergo reversible *N*-alkylation. Thus, higher yields of *C*-alkylated products are obtained with these reagents. Allylic and propargylic groups are transferred from nitrogen to carbon by intramolecular 3,3-

sigmatropic rearrangements, but, in other cases, the process is intermolecular. In some cases, it has been found that the *C*- to *N*-alkylation product ratio may be increased by increasing the temperature.[173]

A comparison of the results of the methylation of the pyrrolidine enamine of cyclohexanone (**81**; Scheme 42) with those shown in Scheme 43 for the methylation of the *n*-butylisobutylamine derivative (**86**) shows that yields are improved with the latter compound.[174] Presumably, the more sterically hindered amine reduces the amount of *N*-alkylation and retards the rate of proton transfer between the *C*-alkylated iminium salt and the unreacted enamine.

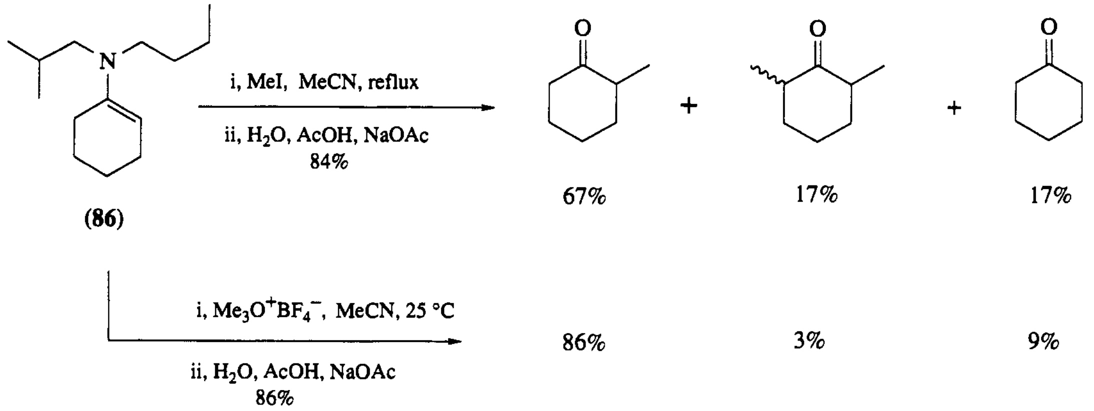

**(86)**

**Scheme 43**

In contrast to the results of base-catalyzed alkylations of sodium or potassium enolates under thermodynamic control, alkylations of enamines of unsymmetrical ketones occur largely or exclusively at the less-substituted α-position. More-substituted ketone enamines are destabilized relative to the less-substituted isomers by $A^{1,2}$-strain involving the substituents on the nitrogen atom and at the β-carbon atom. Although in most systems some of the more-substituted enamine is present in equilibrium with the less-substituted isomer, the former is less reactive toward *C*-alkylation because steric effects prevent effective overlap of the lone pair of electrons on nitrogen with the carbon–carbon π-bond.

Enamines are relatively unreactive nucleophiles and compared with metal enolates the transition states for their alkylations lie much closer to the products. Thus, the stereoelectronic effect is predominant and axial alkylation of cyclohexanone derivatives is observed.[175,176] There is such a high propensity for axial alkylation that it obtains even when a 1,3-interaction of the approaching electrophile and a quasiaxial substituent exists. Thus, methylation of the pyrrolidine enamine (**87**), which is expected to exist largely in the conformation (**87a**) having the C-6 side chain quasiaxial, gave largely the *cis*-2,6-disubstituted ketone (**88**) after hydrolysis under nonequilibrating conditions (Scheme 44).[176] It was considered unlikely that the *cis*-2,6-disubstituted product could have arisen by equatorial alkylation of the conformer (**87b**) of the starting enamine, which has the side chain quasiequatorial.

*C*-Alkylations of hindered aldehyde enamines can be effected with a variety of alkylating agents, but only allylic and benzylic reagents are useful for alkylations of unhindered systems.[177] Acyclic, homoannular and heteroannular dienamines undergo alkylation primarily at the α-positions.[170,178] As discussed above, reactions of enamines with electrophiles containing $sp^3$-hybridized carbon atoms have numerous limitations. On the other hand, enamine reactions with electrophilic alkenes are highly useful and have received wide coverage in the literature.[171]

In order to overcome some of the limitations of enamine alkylations and consequently those associated with metal enolate alkylations, Stork and Dowd introduced metallated imines as metal enolate equivalents in 1963.[179] These reagents, along with the closely related metallated hydrazones introduced by Stork and Benaim[140] and thoroughly investigated by Corey and Enders[180] and oxime dianions[172] provide the synthetic chemist with the potential of achieving an enormous amount of regiochemical and stereochemical control when synthesizing α-alkylated aldehydes and ketones.[171,172,181] Additionally, as described in Section 1.1.5.2, through the use of metallated imines and hydrazones derived from certain chiral, nonracemic imines and hydrazine derivatives, asymmetric syntheses of α-alkyl carbonyl compounds can be achieved with high enantioselectivity.

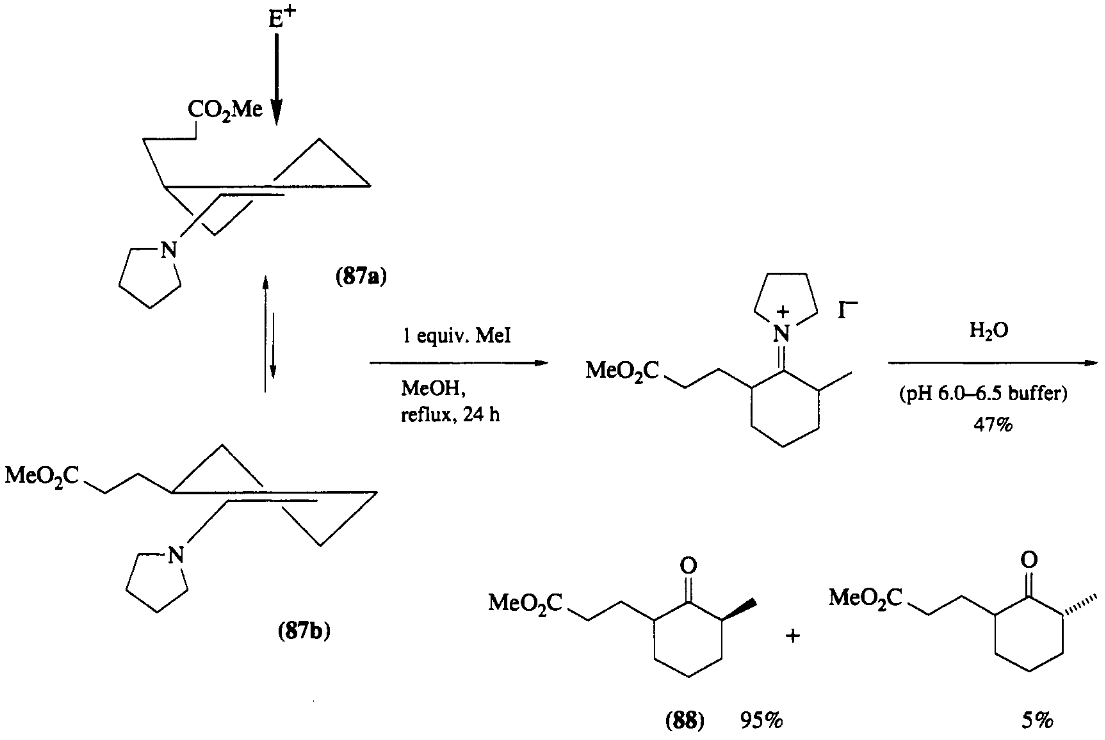

**Scheme 44**

Metallated imines can be formed from imines derived from enolizable carbonyl compounds by deprotonation with Grignard reagents or organolithium reagents, but more recent studies have generally involved the use of lithium dialkylamides, *e.g.* LDA, as the base. Alternative methods of producing metallated imines, *e.g.* addition of *t*-butyllithium to the imine double bond of 2-azadienes,[182] are known.

In their initial work, Stork and Dowd showed that halomagnesium imine alkylations offered the following advantages over enamine alkylations: (i) *C*-alkylations occurred in high yields with unreactive primary and secondary halides, even those prone to elimination; (ii) aldehyde derivatives were directly *C*-alkylated in high yields; (iii) alkylations usually occurred at the less-substituted α-position of unsymmetrical systems; and (iv) formation of the halomagnesium salt could be conducted in the presence of the alkylating agent, which allowed *in situ* generation and trapping of unstable species. Examples of these reactions are presented in Scheme 45. Lithiated imines often exhibit similar behavior to halomagnesium species, but the presence of the more electropositive metal cation, *i.e.* $Li^+$, allows alkylations to be conducted at much lower temperatures. The success of these reactions depends upon the fact that metallated imines undergo proton transfer reactions much more slowly than the corresponding metal enolates. Alkylations of metallated imines are usually conducted in THF or DME. Hydrolysis of the alkylated imine to the alkylated ketone can be effected with aqueous dilute mineral acids, aqueous acetic acid (recommended for aldimine hydrolysis),[118] or, if epimerizations of α-alkyl carbonyl compounds need to be avoided, slightly acidic aqueous buffered solutions.

Whitesell and Whitesell[172] have tabulated some of the many types of electrophilic reagents that *C*-alkylate metallated imines. These are potent nucleophiles and undergo substitution reactions even with weakly electrophilic species such as epoxides and oxetanes. Lithiated ketimines and aldimines have been frequently used in reactions with alkylating agents containing latent 2-keto (or aldehydo) groups[183] or 3-keto (or aldehydo) groups.[184]

Recent research by Bergbreiter, Newcomb, Meyers and their respective coworkers[185] has shown that a variety of factors, such as the base, the temperature of deprotonation, and the size of the substituent on nitrogen, control the structure of the metallated imine and ultimately the regiochemistry of the alkylation reaction. In contrast to metal enolates, where the more-substituted species is usually the more thermodynamically stable, less-substituted *syn*-metallated ketimines, *e.g.* (**89**), are the most thermodynamically stable of the possible isomers of unsymmetrical systems. An explanation for the greater stability of *syn* imine anions compared with *anti* imine anions has been presented by Houk, Fraser and coworkers.[186]

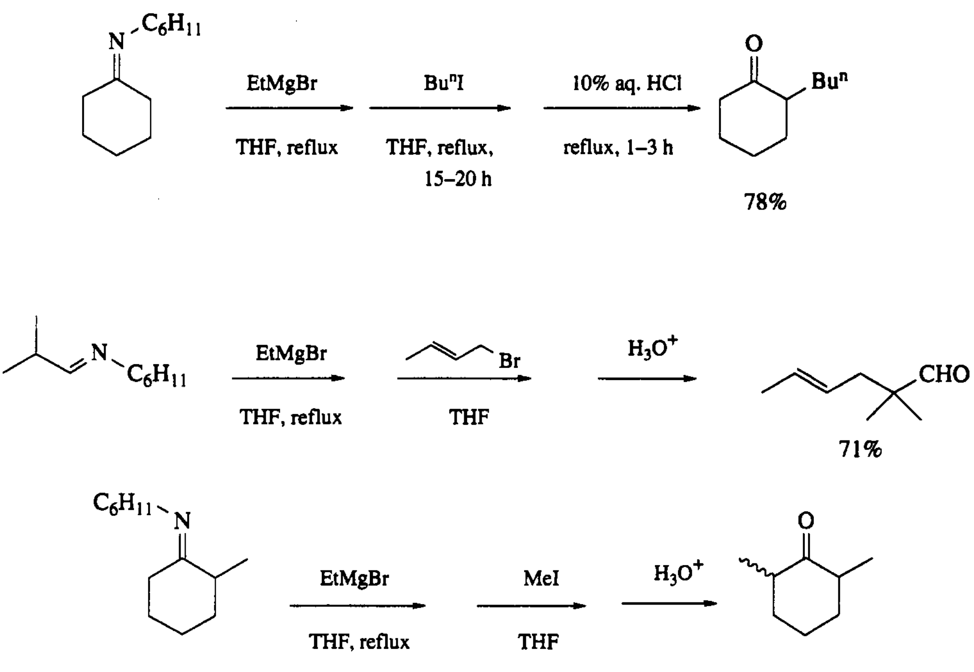

Scheme 45

They suggested that the latter species are destabilized by an electrostatic repulsion between the polar metal–nitrogen bond, which lies in the N—C═C plane and the imine β-carbon atom, which bears a substantial amount of negative charge. Because there is significant carbanion character at the β-carbon, the less-substituted *syn*-metallated ketimine (**89**) would be expected to be more stable than the more-substituted *syn* isomer (**90**).

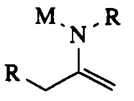

**(89)**

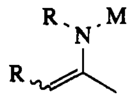

**(90)**

Ironically, species such as (**89**; M = Li) are also the major isomers obtained when unsymmetrical ketimines are deprotonated with LDA at –78 °C.[185] There is a kinetic preference for deprotonation *anti* to the substituent on nitrogen. At very low temperatures, deprotonations with LDA occur at the less-substituted carbon atom *via* the less stable (*Z*)-imine. Rearrangements then occur to the *syn*, less-substituted imine, which is in turn alkylated. On the other hand, deprotonations conducted at –23 to 0 °C with LDA are faster than imine isomerization and the imine anion mixture composition reflects the (*E*):(*Z*) ratio of the starting imine. *Anti–syn* imine anion isomerization occurs to give predominately the more-substituted *syn*-metallated imine (*cf.* **90**), which then undergoes alkylation. These results are summarized in Scheme 46 using the *t*-butylimine of 2-butanone as an example.

The first examples of alkylations at the more-substituted position of an unsymmetrical ketimine were actually reported by Hosomi *et al.*, who carried out deprotonations with alkyllithium reagents at lower temperatures (Scheme 47).[187]

Fraser *et al.* have shown that, unlike the corresponding lithium enolates, conformationally rigid lithiated imines such as (**91**) undergo axial alkylation almost exclusively (Scheme 48).[188] Reaction of (**91**) with methyl iodide at –78 °C gave 90% of the *syn* axial alkylation product (**92**). The small quantities of the *anti* axial (**93**) and *anti* equatorial products (**94**) obtained were considered to arise from isomerization of (**92**). Hydrolysis of the alkylated imine mixture gave largely *trans*-2-methyl-4-*t*-butylcyclohexanone. The preference for axial alkylation is so great that it even occurs when a quasiaxial methyl group is present at C-6 on the cyclohexane ring. Thus, further deprotonation and methylation of the mixture of (**92**)–(**94**) gave 94% of the 2,6-axial–axial dimethylation product and 6% of the 2,6-axial–equatorial isomer, which again probably arose *via* epimerization of the axial–axial product. Apparently, in these systems,

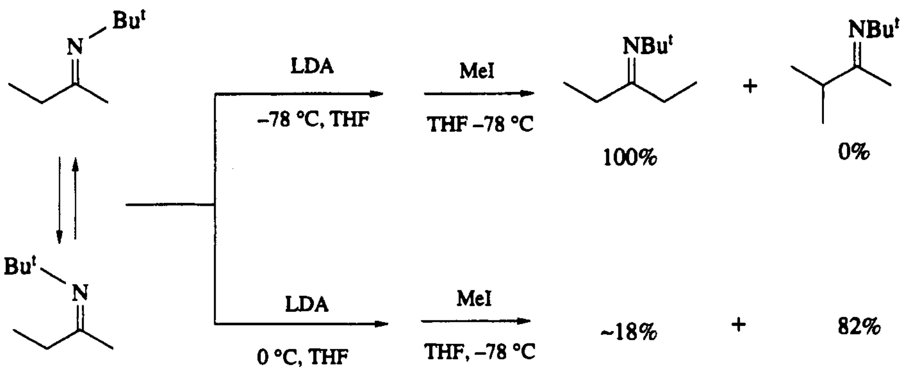
Bu^t
N
Bu^t
N
LDA
−78 °C, THF
MeI
THF −78 °C
NBu^t
NBu^t
+
100%
0%
LDA
0 °C, THF
MeI
THF, −78 °C
~18%
+
82%

Scheme 46

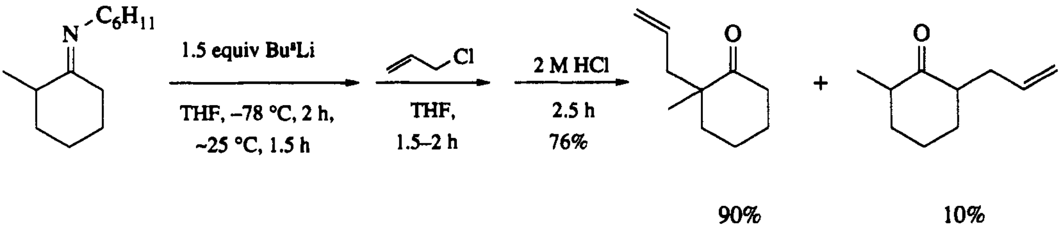
N
C6H11
1.5 equiv Bu^sLi
THF, −78 °C, 2 h,
~25 °C, 1.5 h
Cl
THF,
1.5–2 h
2 M HCl
2.5 h
76%
O
+
O
90%
10%

Scheme 47

the stereoelectronic factor favoring axial alkylation is greatly reinforced by a steric effect of the *syn* substituent on nitrogen, which strongly retards equatorial approach of the electrophile. However, as has been pointed out recently, solvation and aggregation effects may play an important role in determining the stereochemistry of metallated imine alkylations.[189] The remarkably high stereoselectivity observed in alkylations of metallated imines greatly enhances their value as metal enolate equivalents.

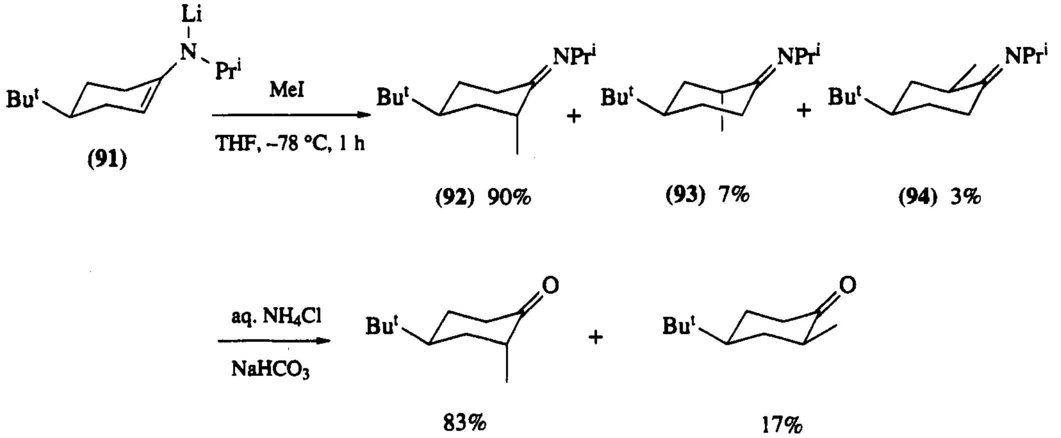
Li
N
Pr^i
Bu^t
(91)
MeI
THF, −78 °C, 1 h
Bu^t
NPr^i
+
Bu^t
NPr^i
+
Bu^t
NPr^i
(92) 90%
(93) 7%
(94) 3%
aq. NH4Cl
NaHCO3
Bu^t
O
+
Bu^t
O
83%
17%

Scheme 48

As shown in Scheme 49, the cyclohexylimine of 10-methyl-1(9)-octalin-2-one has been methylated at C-3 *via* the kinetically formed cross-conjugated dienamine anion (**95**) or monomethylated at C-1 *via* the thermodynamically more stable extended anion (**96**).[140] Steroidal and simpler enones have also been monoalkylated at the α-position *via* their corresponding hetero- or homo-annular extended dienamine anions. Likewise, α-alkylations are the rule for lithiated α,β-unsaturated aldimines.[190] The thermodynamically controlled procedure for the synthesis of α-methyl α,β-unsaturated ketones is a vast improvement over conventional methodology using extended metal dienolates where α,α-dimethylation is a severe complication (Section 1.1.3). It is successful because the unsaturated lithiated dienimine intermediates undergo proton transfer processes too slowly to allow a significant amount of dimethylation to occur.[140]

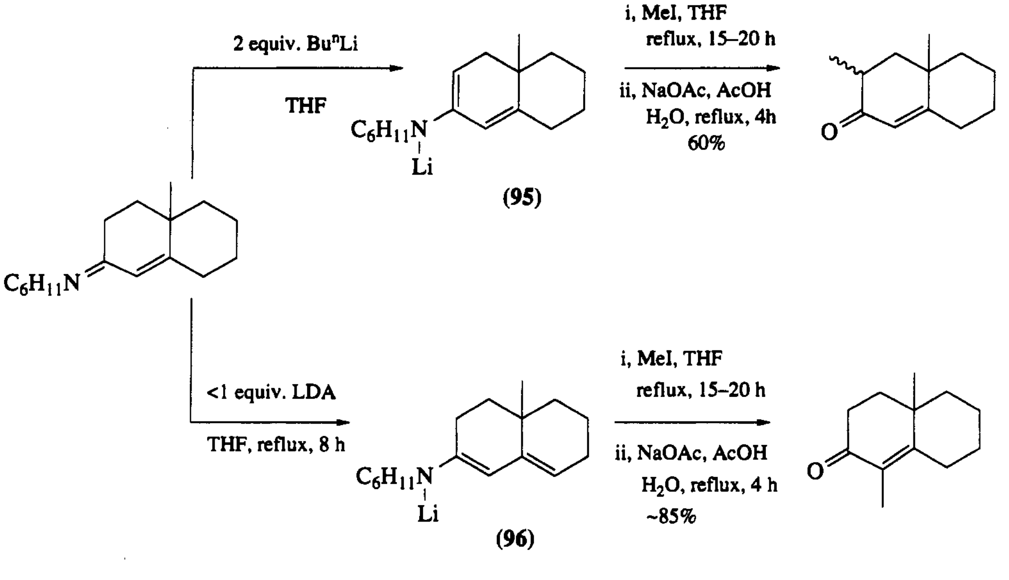
2 equiv. Bu$^n$Li
THF
$C_6H_{11}N$
Li
i, MeI, THF reflux, 15–20 h
ii, NaOAc, AcOH $H_2O$, reflux, 4h
60%
O
$C_6H_{11}N$
<1 equiv. LDA
THF, reflux, 8 h
$C_6H_{11}N$
Li
i, MeI, THF reflux, 15–20 h
ii, NaOAc, AcOH $H_2O$, reflux, 4 h
~85%
O

**(95)**

**(96)**

**Scheme 49**

Metallated *N,N*-dialkylhydrazones exhibit similar regioselectivity and stereoselectivity to metallated imines in alkylation reactions, but the former reagents have higher reactivity, and afford higher yields, among other advantages.[180,191] The diastereoselective and enantioselective synthesis of α-alkylated carbonyl compounds requires mild methods of cleavage of α-alkylated hydrazones. Many of these have been developed by Enders and coworkers[191] and they have been recently reviewed by Bergbreiter and Momongan.[192]

Hydrazone deprotonations are normally carried out with lithium dialkylamides or alkyllithium reagents. *N,N*-Dimethylhydrazones differ from the corresponding imines, which undergo kinetically controlled *anti* deprotonation in that there is little preference for deprotonation *syn* or *anti* to the dimethylamino group on nitrogen in symmetrical systems.[193]

In general, deprotonations of unsymmetrical hydrazones occur with high regioselectivity at the less-substituted α-carbon atom. Since metallated hydrazones are highly resistant to proton transfer reactions with neutral ketone hydrazones, regiospecific, *C*-alkylation then occurs at the less-substituted carbon atom. Scheme 50 provides examples of how complex symmetrical[194] or unsymmetrical[195] α,α′-alkylated acetone derivatives may be prepared in one-pot sequences starting with the *N,N*-dimethylhydrazone of acetone (**97**). The conjugate addition of trimethylsilyllithium to α,β-unsaturated hydrazones, followed by trapping of the lithiated hydrazone intermediates has been reported recently.[196] Both hydrazones[180] and imines[197] may be deprotonated at the more-substituted α-carbon if an electron-withdrawing group is located there.

Conformationally rigid lithiated *N,N*-dimethylhydrazones exhibit axial alkylation preferences exceeding 98%. On the basis of the X-ray crystal structure of lithiated 2-methylcyclohexanone dimethylhydrazone,[198] kinetic studies[199] and other data, Collum, Clardy and coworkers have proposed that the electrophile attacks the anion from the face opposite to an $\eta^4$-coordinated disolvated lithium cation. If the $\eta^4$-complexed lithium cation occupies the 'equatorial' face of the anion, the stereoelectronic factor favoring chair–axial alkylation and the steric factor operate in concert to strongly direct axial alkylation. It was also shown that the lithiated cyclohexanone derivative (**98**) having a methyl group at C-6 yielded mainly *cis*-2,6-dimethylcyclohexanone upon methylation and hydrolysis (Scheme 51).[198] Thus, the stereoselectivity of alkylation of (**98**) was opposite to that originally reported.[180] It appears that, as expected, (**98**) undergoes axial alkylation mainly *via* a conformation with the 6-methyl group quasiaxial to give the *cis*-2,6-disubstituted product.

Cyclic α,β-unsaturated *N,N*-dimethylhydrazones may be monoalkylated cleanly at the α- or α′-position depending upon the conditions of formation of the metallated unsaturated hydrazone.[192] By using: (i) less reactive bases such as sodium hydride; (ii) additives such as HMPA; and/or (iii) allowing the metallated hydrazone to stand for a period of time before the alkylating agent is added, α-alkylations *via* the

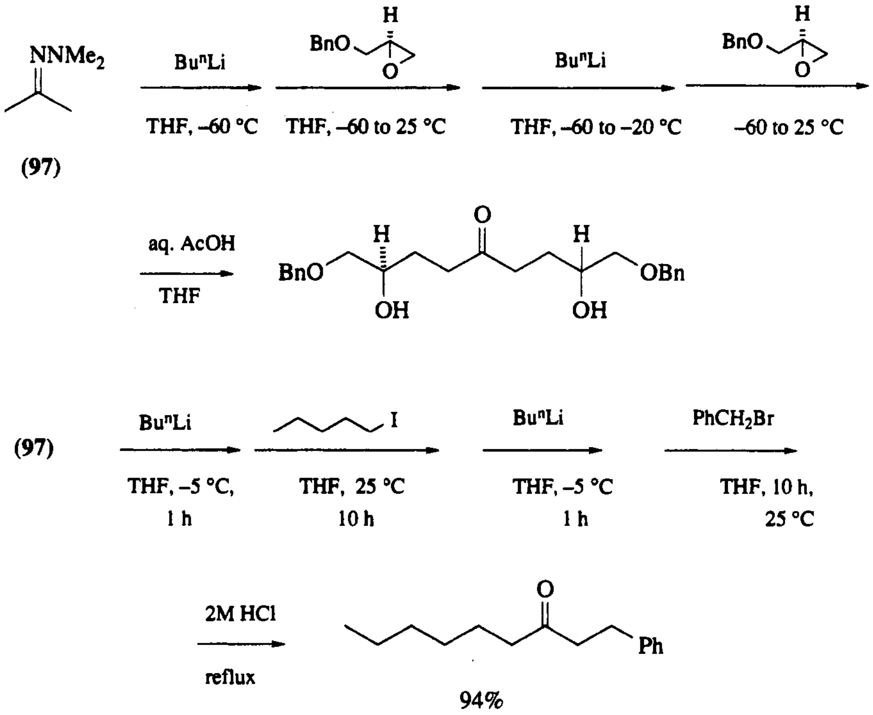
NNMe2
(97)
BuⁿLi
THF, -60 °C
BnO
H
O
THF, -60 to 25 °C
BuⁿLi
THF, -60 to -20 °C
-60 to 25 °C
aq. AcOH
THF
BnO
OH
OBn
(97)
BuⁿLi
THF, -5 °C, 1 h
I
THF, 25 °C 10 h
BuⁿLi
THF, -5 °C 1 h
PhCH2Br
THF, 10 h, 25 °C
2M HCl
reflux
Ph
94%

**Scheme 50**

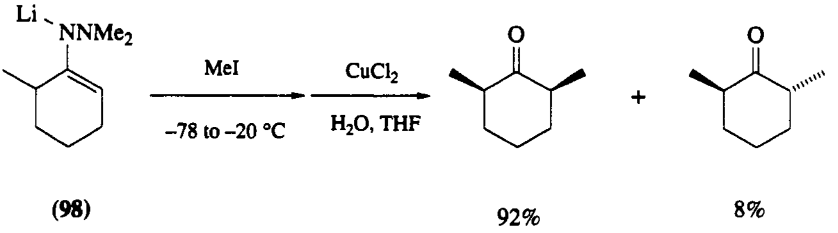
Li
NNMe2
(98)
MeI
-78 to -20 °C
CuCl2
H2O, THF
O
92%
8%

**Scheme 51**

more thermodynamically stable homoannular or heteroannular linearly conjugated anions are favored.[140,200] On the other hand, deprotonations with LDA in THF followed immediately by addition of the alkylating agent have provided high yields of α′-monoalkylated products *via* the kinetically formed cross-conjugated anions.[180,201] α-Alkylations of α,β-unsaturated aldehyde hydrazones containing γ-hydrogen atoms are also known.[202]

Unsymmetrical ketoximes or ketoxime methyl ethers undergo rapid deprotonation to give *syn* dianions or monoanions, which react regioselectively with electrophilic reagents.[203,204] Axial alkylation is observed in conformationally rigid systems. Aldoximes can also be converted to their dianions and alkylated in high yields.[205]

### 1.1.5.2 Enantioselective Syntheses *via* Alkylations

Enamines,[171] metallated imines[171,206,207] and metallated hydrazones[171,191,206,207] derived from chiral, nonracemic amines have proved to be excellent reagents for the enantioselective synthesis of α-alkylated ketones and aldehydes. Although other optically active systems had been studied,[171] the first efficient enantioselective synthesis using a chiral enamine was reported by Whitesell and Felman.[208] They found that the cyclohexanone enamine from (+)-*trans*-2,5-dimethylpyrrolidine (**99**) underwent alkylation and hydrolysis to give 2-substituted cyclohexanones with the (*R*)-configuration in good optical and chemical yields. For the enamine (**99**) the same face of the cyclohexene ring is shielded from attack irrespective of the conformer which undergoes alkylation.

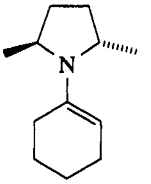

**(99)**

Attempted asymmetric alkylations of metallated chiral imines gave poor results unless, as discovered by Meyers *et al.*[209] and Whitesell and Whitesell,[210] a β-ether group was present in the optically active amine component. This allows formation of a five-membered chelate ring involving the metal cation, which imparts rigidity to the system and restricts the number of conformations available for alkylation. The synthesis of (*S*)-2-ethylcyclohexanone from the imine (**100**) provides an illustration of the method (Scheme 52). Meyers *et al.* have proposed that alkylation occurs on the top-face of the chelated structure (**101**).[209] However, based upon a proposal by Whitesell and Whitesell[210] for a related case and experimental data indicating that the lithiated imine exists largely in a *syn* configuration, a better explanation for the 1,4-asymmetric induction is provided by a structure such as (**102**), which has the chiral center closer to the reaction site and may undergo alkylation from the top-face of the π-system.

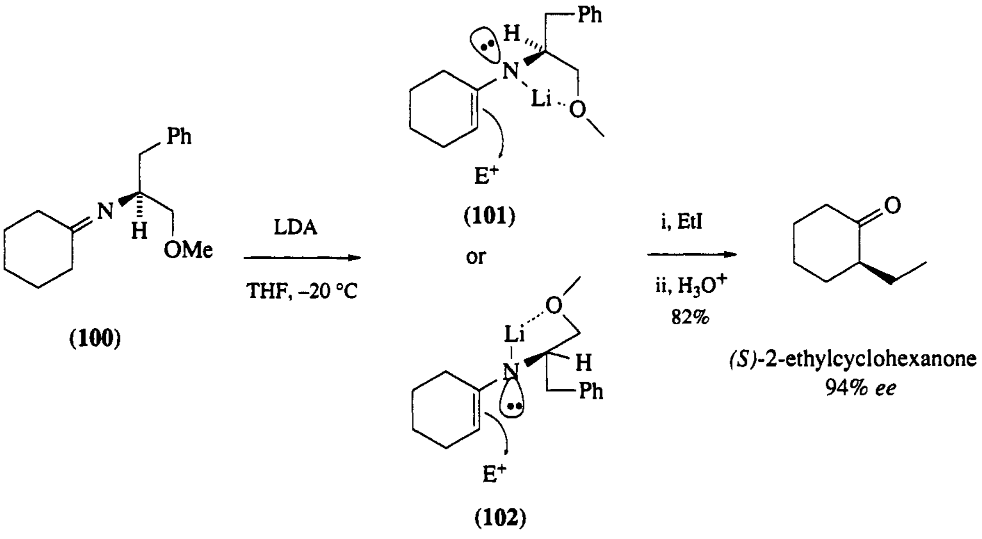

**Scheme 52**

(*S*)-2-Alkyl-2-phenylcycloalkanones have been synthesized in high optical yields using enamines derived from *t*-leucine *t*-butyl ester or valine *t*-butyl ester and 2-phenylcycloalkanones (Scheme 53).[211]

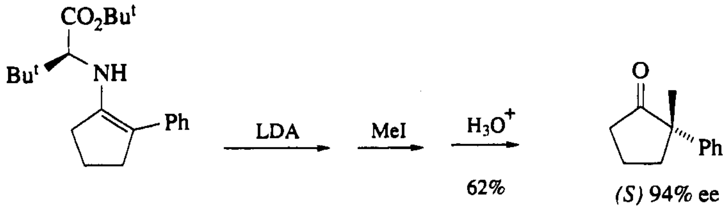

**Scheme 53**

Macrocyclic ketones and acyclic ketones are capable of yielding (*Z*)- or (*E*)-lithiated imines upon deprotonation. For example, Meyers *et al.*[212] found that methylation of the kinetically formed (*E*)-lithiated imine (**103**), derived from cyclododecanone and (*S*)-phenylalaninol methyl ether, gave (*S*)-2-methylcyclododecanone in low enantiomeric excess (*ee*), *i.e.* 59%, upon methylation and hydrolysis (Scheme 54). However, refluxing of (**103**) in THF effected its isomerization into the more thermodynamically stable (*Z*)-isomer (**104**), which upon methylation and hydrolysis gave (*R*)-2-methylcyclododecanone in 81% *ee* (Scheme 54). Likewise, ethylation and hydrolysis of the acyclic (*Z*)-lithiated imine (**105**) gave (*R*)-3-methylhexan-4-one in only 3% *ee*, but isomerizations to the more stable (*E*)-isomer (**106**), followed by ethylation and hydrolysis increased the optical yield of the (*R*)-ketone to 77% (Scheme 54). (Note: the (*Z*)/(*E*) transformation did not lead to a change in configuration of the acyclic ketone product.) Because of problems with (*Z*)/(*E*) isomerism and conformational flexibility, metallated aldimines are rather poor reagents for asymmetric syntheses of α-alkylated aldehydes.

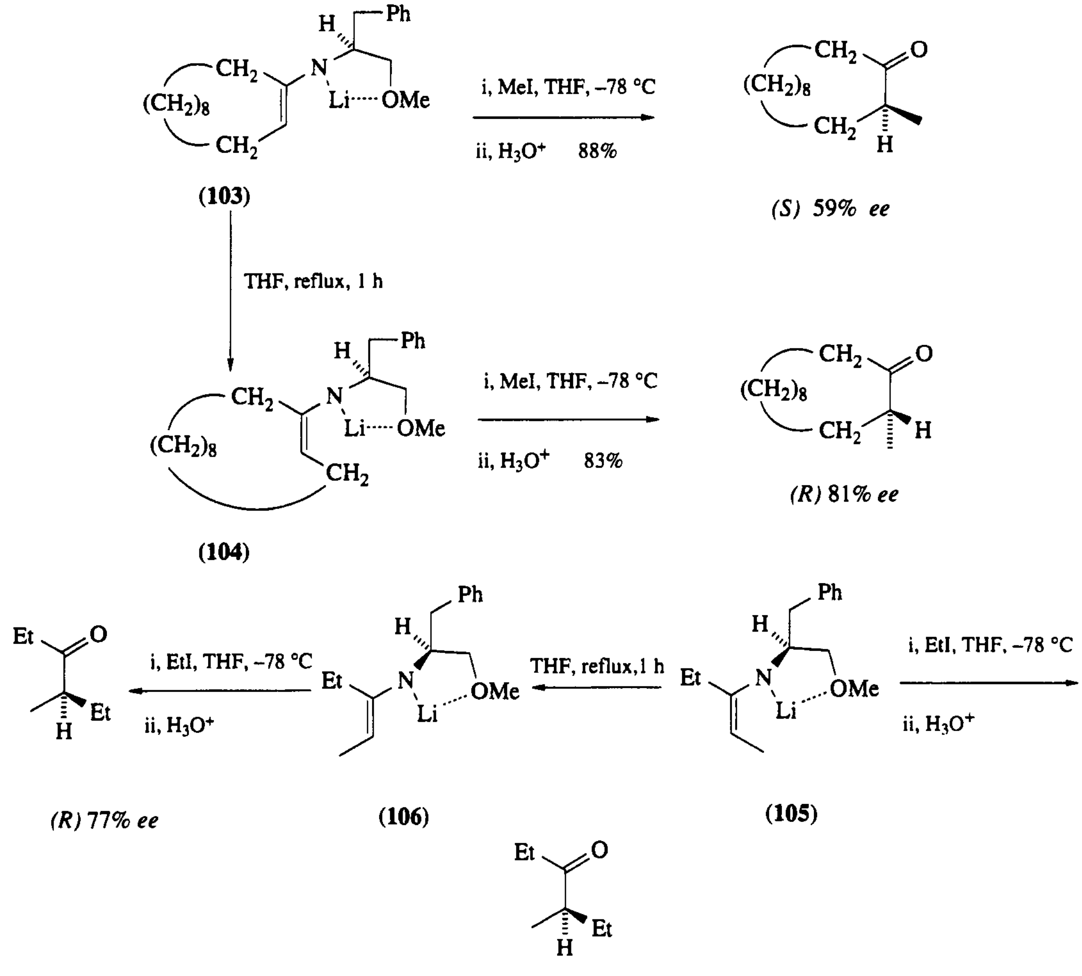

**Scheme 54**

Fortunately, the use of lithiated hydrazones derived from (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP) as nucleophiles for asymmetric alkylations have provided a solution to the problems described above with metallated acyclic ketimines and aldimines.[191] Lithiated SAMP or RAMP hydrazones of cyclic ketones are also alkylated in high yields. A major advantage of these chiral hydrazones is that their derivatives of aldehydes, acyclic and cyclic ketones all yield mainly (*E*)CC-, (*Z*)CN-lithiated species on deprotonation with LDA in ethereal solvents under kinetic control. The (*E*)CC-configuration obtains as a result of the minimization of steric interactions in the usual closed transition

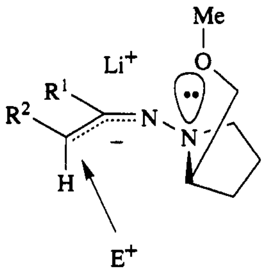
Me
O
Li+
R1
R2
N
N
H
E+

**(107)** $R^1$ = H or alkyl; $R^2$ = alkyl

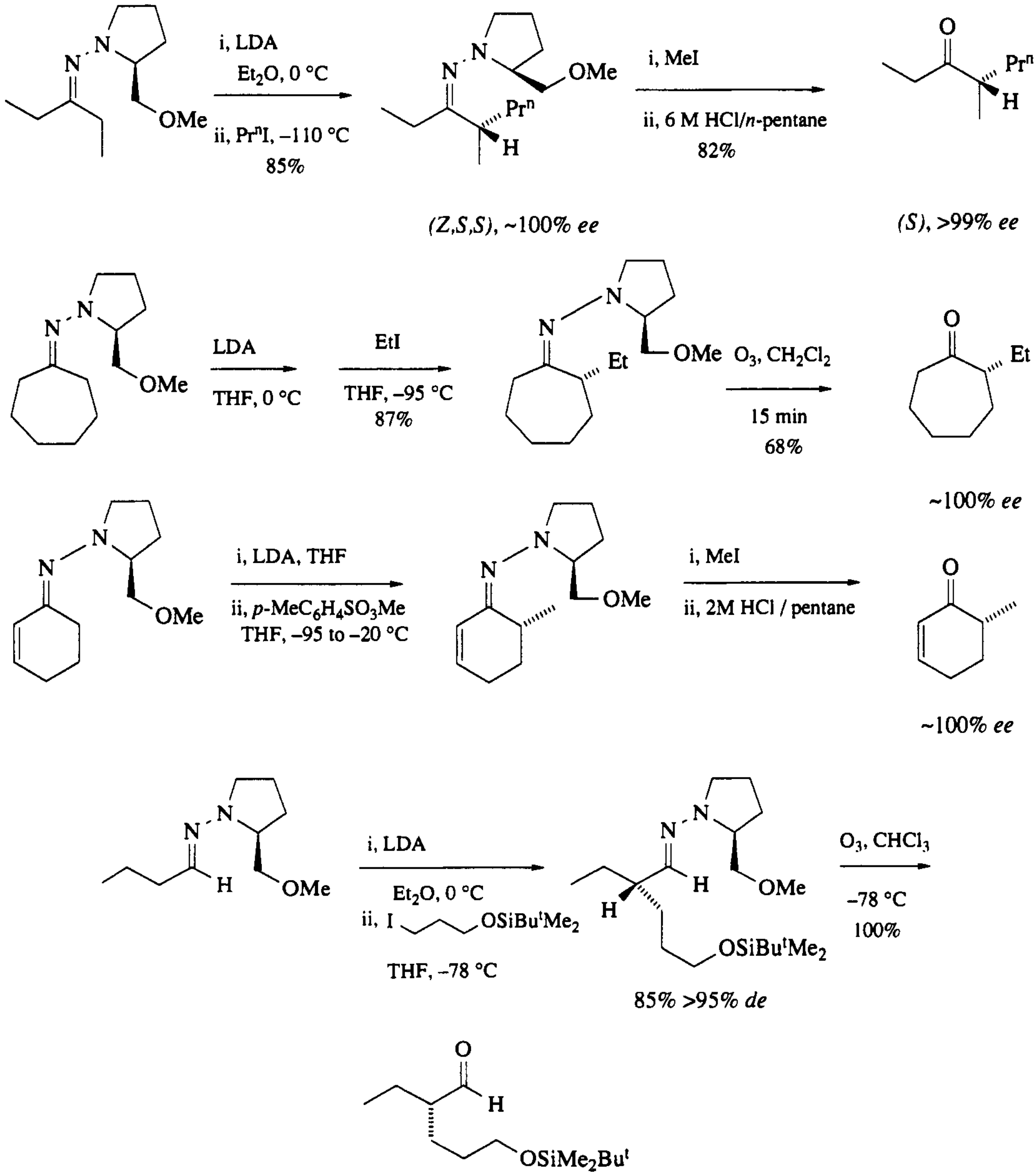
i, LDA
Et2O, 0 °C
ii, PrnI, –110 °C
85%
OMe
(Z,S,S), ~100% ee
i, MeI
ii, 6 M HCl/n-pentane
82%
O
Prn
H
(S), >99% ee
LDA
THF, 0 °C
EtI
THF, –95 °C
87%
Et
O3, CH2Cl2
15 min
68%
~100% ee
i, LDA, THF
ii, p-MeC6H4SO3Me
THF, –95 to –20 °C
i, MeI
ii, 2M HCl / pentane
~100% ee
i, LDA
Et2O, 0 °C
ii, I OSiButMe2
THF, –78 °C
85% >95% de
O3, CHCl3
–78 °C
100%
OSiMe2But

Scheme 55

state for the deprotonation step.[171] These chelated lithiated hydrazones are quite conformationally rigid and they exhibit a high degree of diastereofacial differentiation. The high nucleophlicity of lithiated hydrazones allows alkylations to be performed with a variety of alkylating agents in relatively nonpolar solvents such as diethyl ether at very low temperatures, *e.g.* –110 °C. Such conditions coupled with appropriate hydrazone cleavage methodology[191,192] can yield α-alkylated aldehydes and acyclic ketones in optical yields usually exceeding 90%. In light of the recent model proposed by Collum, Clardy and coworkers[198,199] for the stereoselectivity of lithiated hydrazone alkylations, it appears likely that alkylations of $(E)_{CC}$-,$(Z)_{CN}$-SAMP hydrazones may occur *via* a species such as (**107**), in which the electrophilic reagent attacks from the opposite face of an $\eta^4$-coordinated lithium cation. Considerably lower alkylation enantioselectivities are observed for less rigid $(Z)_{CC}$-,$(E)_{CN}$-SAMP hydrazones, which may be obtained by deprotonation of hydrazones in the presence of HMPA. In this solvent, deprotonation probably proceeds *via* an open transition state.[171]

Asymmetric synthesis *via* chiral, nonracemic hydrazones have gained wide acceptance in the community of synthetic organic chemists. Some examples of asymmetric alkylations of acyclic,[213] saturated[214] and unsaturated cyclic ketones[201,215] and aldehydes,[216] which are applicable in the natural products field, are shown in Scheme 55. Various methods of cleavage of the alkylated hydrazones are also illustrated in Scheme 55.

## 1.1.6 ALKYLATIONS OF METAL ENOLATES OF CARBOXYLIC ACID DERIVATIVES

### 1.1.6.1 Introduction

Although carboxylic acids and their derivatives are somewhat weaker carbon acids than aldehydes and ketones, it is generally possible to quantitatively convert them to the corresponding metal enolates with dialkylamide bases, the most popular of which is LDA.[4,217,218] Thus, monoanions of saturated esters, lactones, nitriles, *N*,*N*-dialkylamides and *N*-alkyllactams and dianions of carboxylic acids and *N*-unsubstituted amides and lactams are easily prepared in aprotic solvents such as THF and *C*-alkylated with a variety of simple and functionalized $S_N2$-reactive alkylating agents at room temperature or below. When more-hindered systems are involved, the basicity of the metal dialkylamide and the reactivity of the metal enolate can be enhanced by the addition of HMPA. Of course, many of the indirect methods used for the generation of aldehyde and ketone enolates are also applicable to the preparation of enolates of carboxylic acid derivatives (Section 1.1.2.1). *O*-Alkylations or dialkylations at carbon generally are of minimal importance with metal enolates of carboxylic acid derivatives.

In recent years, investigations of the diastereoselectivity and enantioselectivity of alkylations of metal enolates of carboxylic acid derivatives have become one of the most active areas of research in synthetic organic chemistry. Intraannular, extraannular and chelate-enforced intraannular chirality transfer may be involved in determining the stereochemistry of these alkylations.

### 1.1.6.2 Diasteroselective Alkylations of Exocyclic and Endocyclic Enolates of Carboxylic Acid Derivatives

Intraannular chirality transfer may control alkylations of both exocyclic and endocyclic enolates. Scheme 56 provides examples of 1,2-, 1,3- and 1,4-asymmetric induction in substituted cyclohexylidine enolates.[219] For compounds such as (**108**) selective *anti* alkylation probably results from axial attack of the alkylating agent on the conformation of the enolate with the methyl substituent quasiaxial. Sterically preferred equatorial attack on a conformation with the ring substituent equatorial seems to provide a reasonable explanation for most of the results of alkylations of compounds (**109**) and (**110**). The proportion of equatorial and axial attack observed in the alkylations of ester (**110a**) is essentially identical to that of the related ketone enolate (**46**). In the case of the acid (**109d**), some sort of chelation phenomenon involving the carboxylate dianion and the methoxy group may cause the ring to prefer a conformation with the methoxy group axial. In such a conformation equatorial alkylation, which would be greatly favored sterically, would give the major product with the carboxylate and methoxy groups *cis* to each other.

Although there are only a few examples of alkylations of carboxylate enolates which are exocyclic to five-membered carbocyclic rings, the usual steric factors seem to control the stereoselectivity of these reactions. Thus, the dienolate (**111**) underwent reaction with 4-bromo-1-butene *anti* to the methoxymethyl substituents with high diastereoselectivity[220] and enolates derived from norbornane-2-carboxylates (**112**)

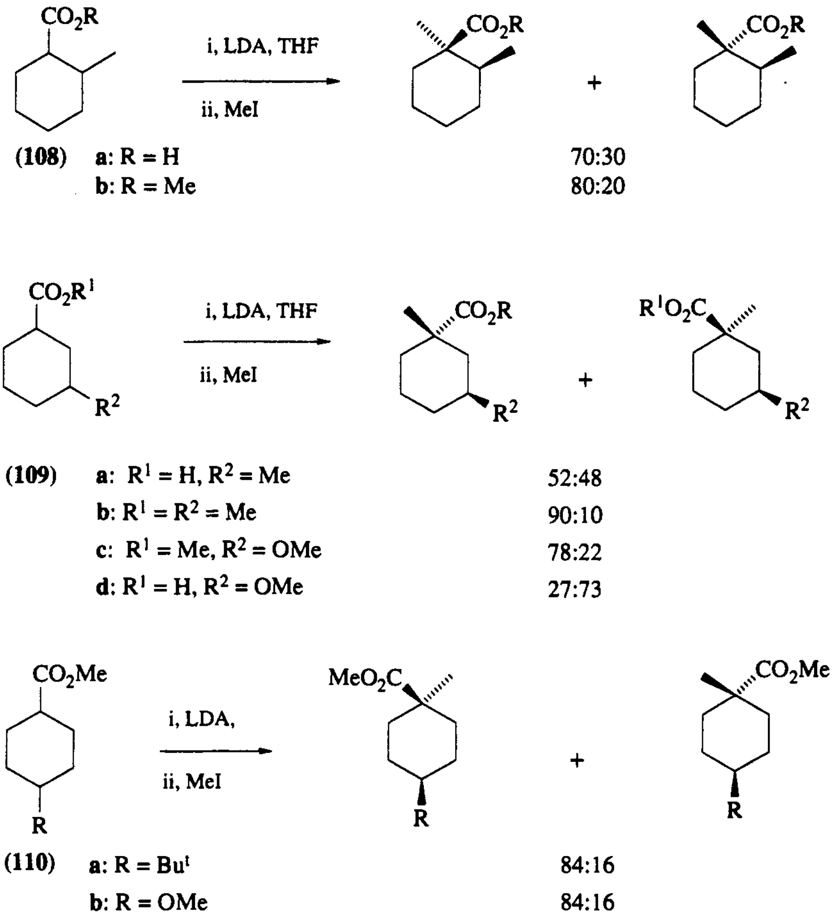
CO2R
i, LDA, THF
ii, MeI
CO2R
+
CO2R
CO2R1
R2
i, LDA, THF
ii, MeI
CO2R
R2
+
R1O2C
R2
CO2Me
R
i, LDA,
ii, MeI
MeO2C
R
+
CO2Me
R

**(108)** a: R = H 70:30
b: R = Me 80:20

**(109)** a: $R^1$ = H, $R^2$ = Me 52:48
b: $R^1$ = $R^2$ = Me 90:10
c: $R^1$ = Me, $R^2$ = OMe 78:22
d: $R^1$ = H, $R^2$ = OMe 27:73

**(110)** a: R = $Bu^t$ 84:16
b: R = OMe 84:16

**Scheme 56**

undergo largely *exo* alkylation.[219] An interesting reversal of the stereoselectivity of alkylations of exocyclic enolates of five-membered ring heterocyclic systems has been observed.[221,222] For example, the dioxalone-derived enolates (**113**)[222,223] and (**114**)[221] are alkylated primarily *syn* to the existing substituents, while for the dihydrooxazole- and oxazolidine-derived enolates (**115**)[221] and (**116**)[221] alkylation occurred *anti* to the substituents. The preference for *syn* attack on enolates of the type (**113**) and (**114**) has been attributed to folding of the hetereocyclic ring to avoid electronic repulsion between the enolate π-system and the nonbonding electron pairs on the heteroatoms.[221,223]

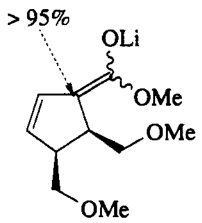
> 95%
OLi
OMe
OMe
OMe

**(111)**

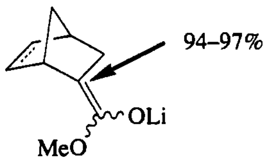
94–97%
OLi
MeO

**(112)**

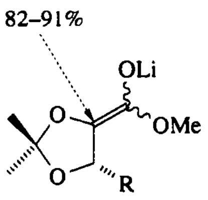
82–91%
OLi
O
OMe
O
R

**(113)** a: R = $CO_2Me$
b: R = Et

The ester precursors of the enolates (**114**) and (**116**) were prepared from reactions of glyceric acid or serine with pivaldehyde. After alkylation, the parent alkylated acids were recovered by hydrolysis. Seebach and coworkers, who have pioneered this type of procedure, have called it 'self-reproduction of chir-

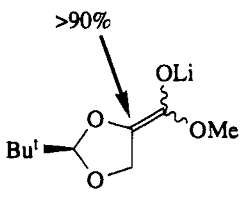

**(114)**

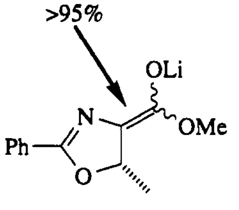

**(115)**

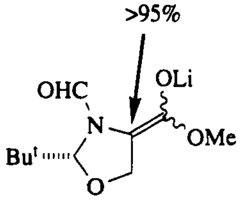

**(116)**

ality.'[223] As will be described below, self-reproduction of chirality can be accomplished through alkylations of endocyclic as well as exocyclic enolates. It generally entails: (i) production of a ring containing a temporary, auxiliary chiral center by derivatization of an optically active α-hydroxy or α-amino ester; (ii) formation of an enolate by deprotonation at the original asymmetric α-carbon atom; (iii) use of intramolecular chirality transfer to control the stereochemistry of alkylation of the enolate; and (iv) generation of the chiral α-alkylated ester by hydrolysis.

The stereochemistry of alkylations of endocyclic enolates derived from lactones has been reviewed recently[2] and will be discussed only briefly. β-Substituted β-lactone enolates undergo alkylation *anti* to the substituent with high stereoselectivity, particularly when the β-substituent is a bulky group. Alkylations of β- and γ-substituted γ-lactones are directed almost exclusively to the π-face of the enolate *anti* to the substituent by 1,2- and 1,3-asymmetric induction.[224] As shown in equation (10), the dilithium dianion (**117**) of (*R*)-β-hydroxy-γ-butyrolactone underwent alkylation *anti* to the alkoxy group, to give the *trans*-α,β-isomer (**118**) exclusively.[225] γ-Lactone enolates which are *cis*-fused at the β- and γ-positions to five- or six-membered rings undergo methylation mainly from the convex π-face of the molecule. If the enolate is *trans*-fused at the β- and γ-positions to a six- or seven-membered ring, alkylation occurs *anti* to the γ-ring residue.

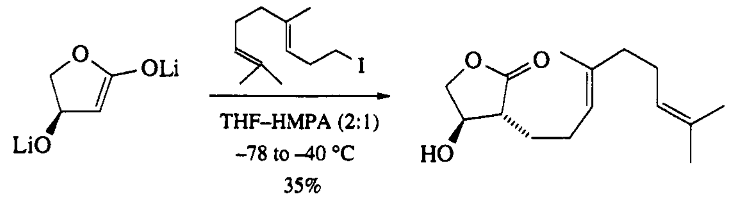

**(117)** **(118)** (10)

Alkylations of β-substituted δ-lactone enolates occur *anti* to the substituent with high diastereoselectivity unless bulky groups are present at the α-position.[224] Then, conformational effects may lead to a reversal of the diastereofacial differentiation. Other δ-lactone enolates are alkylated with poor diastereoselectivity unless they are *cis*-disubstituted at the γ- and δ-positions. Still and Galynker have shown that remote substituents may exert a considerable amount of asymmetric induction in medium-ring lactone enolate alkylations.[226] The remote substituent can determine which of the lower energy conformations of the enolate are available for alkylation.[226]

Within the past several years, Seebach and coworkers have made extensive use of five-membered ring *O,O*-, *S,O*-, *O,N*- and *N,N*-acetals of the general structure (**119**), derived from pivalaldehyde, as protecting groups to preserve both the functionality and the chirality of α-heterosubstituted carboxylic acid derivatives during their conversion to endocyclic enolates and alkylation.[223,227] Frater *et al.* also made an important original contribution in this field.[228] Alkylation of lithium enolates derived from systems such as (**119**) occur *anti* to the *t*-butyl group with high diastereoselectivity. Thus, by the choice of the proper diastereomer it is possible to accomplish enantioselective synthesis of α,α-dialkylated α-amino or α-hydroxy acids with overall inversion (from **119a**) or retention (from **119b**) of configuration. The use of chiral, nonracemic glycine derivatives such as (**119**; $R^3$ = H) obtained by resolution even allowed the enantioselective synthesis of unbranched α-amino acids.[229] More recently the Seebach research group has extended its studies to the alkylations of endocyclic enolates of six-membered ring *O,O*-acetals (**120**) derived from β-hydroxy acids.[230] Highly diastereoselective α-alkylations were accomplished. β-Unsubstituted compounds such as (**120a**) underwent alkylation predominantly *syn* to the *t*-butyl group, but in β-substituted systems such as (**120b**) alkylation occurred predominantly *anti* to the β-substituents. An excellent review provides much more thorough coverage of alkylations of heterocyclic systems such as (**119**) and (**120**) for 'self-reproduction of chirality.'[223]

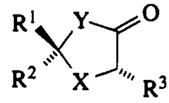

(**119**) a: $R^1 = Bu^t$, $R^2 = H$, $R^3$ = alkyl
b: $R^1 = H$, $R^2 = Bu^t$, $R^3$ = alkyl

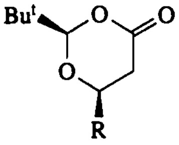

(**120**) a: R = H
b: R = Me

By carrying out sequential alkylations of chiral, nonracemic bicyclic lactams, Meyers and coworkers have developed highly efficient syntheses of chiral compounds containing quarternary carbon atoms with high enantiomeric purity.[231,232] The sequence of steps is illustrated in Scheme 57 using the bicyclic lactam (**121**). The diasteroselectivity of the first alkylation step was low in this case, but the second step yielded the dialkylated lactam (**123**), which resulted from *endo* entry of the second alkyl group, with high diasteroselectivity.[232] In a related system where the angular substituent was a phenyl rather than a methyl group, the *endo*:*exo* ratios were 9:1 and 42:1 for methylation in the first step and benzylation in the second step.[231] Other explanations for the preference for *endo* alkylation of enolates such as that derived from (**122**) have been offered, but most recently Meyers and Wallace proposed that the lone pair electrons on the convex β-face of the molecule perturb the enolate π-system so as to favor *endo* attack by the electrophile.[233]

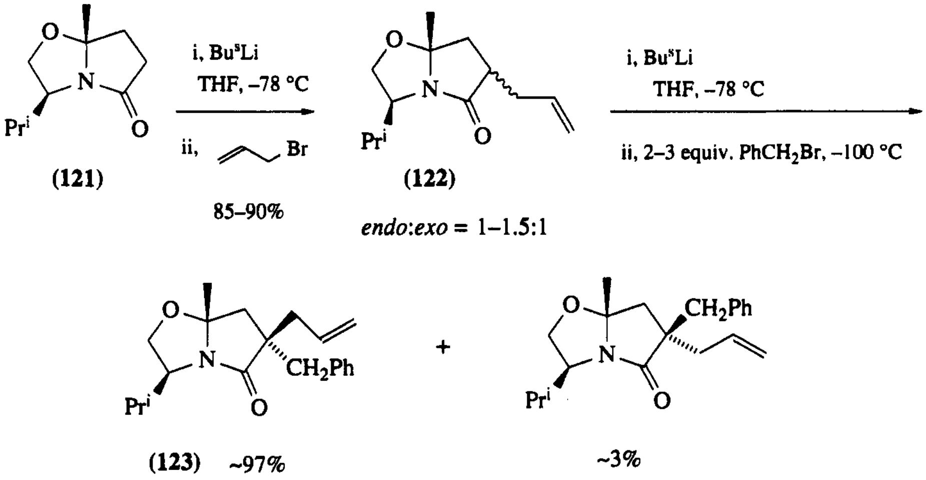

**Scheme 57**

By Red-Al reduction, acid hydrolysis (to a keto aldehyde) and base-catalyzed intramolecular aldol cyclization, compounds such as (**123**) have been converted into 4,4-dialkylcyclopentenones in good chemical yields and 99% enantiomeric purity.[232] The Meyers research group has made extensive use of this exciting methodology for the synthesis of a variety of natural products.[234]

### 1.1.6.3 Diastereoselective Alkylations of Acyclic Enolates of Carboxylic Acid Derivatives

Extraannular and chelate-enforced intraannular chirality transfer in enolate alkylations of carboxylic acid derivatives may occur in cases where: (i) the chiral center, *e.g.* a β-carbon atom, is present and remains in the carboxylic portion of the molecule; or (ii) the substrate contains a chiral auxiliary, *e.g.* the alcohol portion of an ester or the amine portion of an amide, which is removed after the alkylation to generate a chiral carboxylic acid. Alkylations of the former type will be discussed in this section. Alkylations of systems containing chiral auxiliaries are described in Section 1.1.6.4.

Fleming and coworkers[94] and McGarvey and Williams[97] have shown that acyclic ester enolates, *e.g.* (**124**), containing relatively strong electron donor groups such as dimethylphenylsilyl and tri-*n*-butylstannyl at the β-carbon atom, undergo α-alkylation *anti* to such groups with high diastereoselectivity (Scheme 58). These groups presumably do not participate in chelation with the metal cation and enolate oxygen atom. Therefore, a transition state such as (**125**), in which the β-substituent is aligned perpendicular to the plane of the enolate, seems to adequately account for the observed results.[97] The ester enolate alkylations reported by Koga and coworkers[235] and Yamamoto and Maruyana[236] are consistent with this explanation.

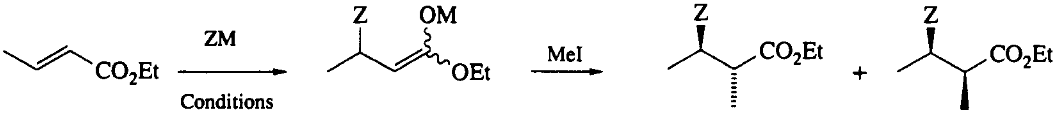

(**124**)

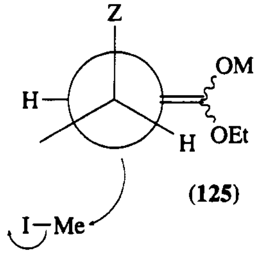

(**125**)

| *ZM/Conditions* | *Ratio* | *Yield (%)* |
|---|---|---|
| $(PhMe_2Si)_2CuLi$, THF, –23 °C | 99:1 | 82 |
| $Bu^n{}_3SnLi$, THF, –78 °C | 98:2 | 86 |

**Scheme 58**

The results of alkylations of ester enolates such as (**126**) with β-methyl and β-$CH_2OR$ substituents (which have similar steric requirements) provide additional evidence that alkylation occurs *anti* to the more strongly electron-releasing β-substituent (Scheme 59).[97] Presumably in (**126**) a lone pair of electrons on oxygen facilitates electron release by the β-carbon–γ-carbon bond. Thus, an alkylation transition state such as (**127**) may obtain in such cases. Alkylations of dilithium dianions of 3-benzoylaminobutanoic acid esters have also been shown to give mainly the *anti* 2,3-disubstituted diastereomers.[237]

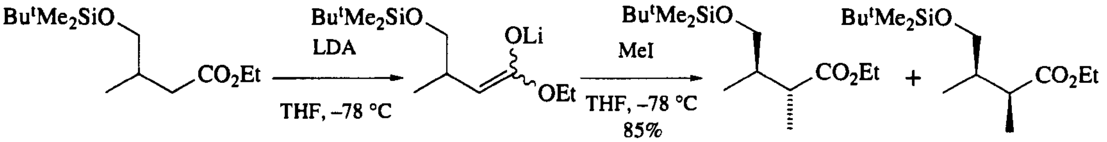

(**126**) 89% 11%

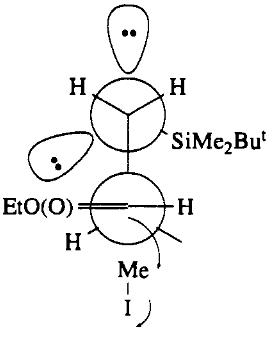

(**127**)

**Scheme 59**

β-Hydroxy esters may be alkylated *via* their dilithium dianions.[238] Deprotonation of the hydroxy group by the base prevents its elimination to form an α,β-unsaturated system. Two recent publications by Frater *et al.*[239] and by Seebach *et al.*[240] provide summaries of the results of the alkylations of nonracemic β-hydroxy esters such as (*S*)-ethyl 3-hydroxybutanoates (**128**) and (*S*)-diethyl malate. A rational explanation for the data shown in Scheme 60 for the alkylation of (**128**) is that a chelated (*Z*)-enolate, *i.e.* (**129**), is formed kinetically and then *C*-alkylation occurs *anti* to the larger group at the β-position. The direct formation of the (*Z*)-enolate contrasts with the situation for simple esters whose kinetic deprotonations with LDA in THF give largely (*E*)-isomers.[2] Presumably, in β-hydroxy systems a chelated β-alkoxy ester is formed initially and its deprotonation at the α-carbon atom leads to the (*Z*)-enolate. The involvement of chelated species similar to (**129**), which undergo alkylation *anti* to the alkoxycarbonyl group, also explains the diastereoselectivity observed in malate ester alkylations.[240] Such diastereoselective alkylations have found extensive use in the synthesis of optically active natural products. Snieckus and coworkers have shown that alkylations of succinamide dienolates yield largely *threo* dialkylation products.[241] It is not clear whether extraannular chirality transfer or chelate-enforced chirality transfer account for these results.[2]

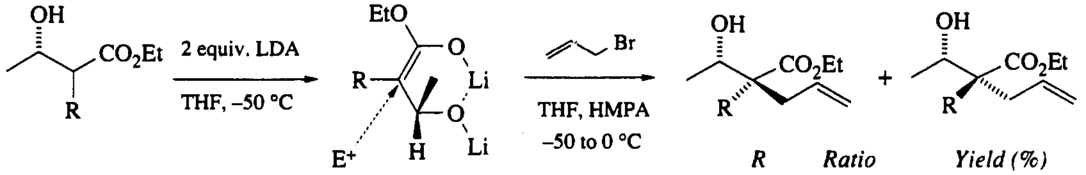

(**128**) (**129**)

| *R* | *Ratio* | *Yield (%)* |
|---|---|---|
| H | 96:4 | 75 |
| Me | 96:4 | 35 |

**Scheme 60**

α-Substituted *N*-(9-phenylfluoren-9-yl)amino ketones, *e.g.* (**130**), have been found to undergo deprotonation and alkylation at the α′-position to give *syn* α,α′-disubstituted products (**132**) with modest diastereoselectivity (Scheme 61). It has been proposed by Lubell and Rapoport that the major alkylation product arises *via* electrophilic attack on the less-hindered face of a chelated (*Z*)-enolate such as (**131**).[242]

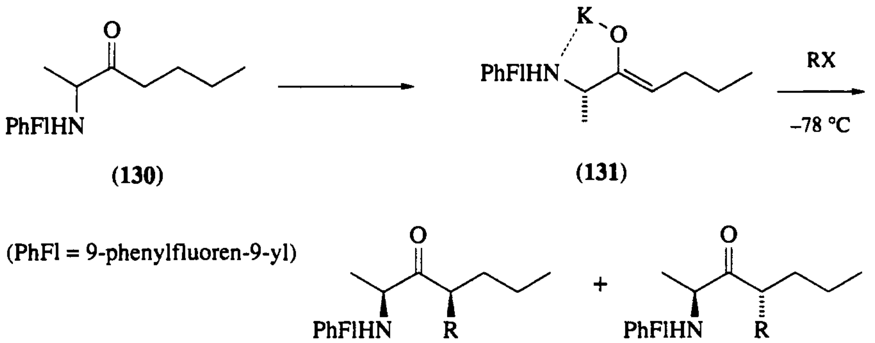

(**130**) (**131**)

(PhFl = 9-phenylfluoren-9-yl)

(**132**)

| *RX* | *Ratio* | *Yield (%)* |
|---|---|---|
| MeI | 69:31 | 94 |
| $PhCH_2Br$ | 83:17 | 80 |
| $CH_2{=}CHCH_2Br$ | 83:17 | 77 |

**Scheme 61**

### 1.1.6.4 Diastereoselective Alkylations of Acyclic Carboxylic Acid Derivatives Containing Chiral Auxiliary Groups

Alkylations of acyclic enolates containing a collection of chiral auxiliary groups have been used successfully for the asymmetric synthesis of carboxylic acids. The chiral, nonracemic substrates that have been used include amides, imides, esters, imine derivatives of glycinates and acyl derivatives of chiral transition metals. In these systems either extraannular or chelate-enforced intraannular chirality transfer may control the sense of the alkylation step.

In 1978, Larcheveque and coworkers reported modest yields and diastereoselectivities in alkylations of enolates of (–)-ephedrine amides.[243] However, two years later, Evans and Takacs[244] and Sonnet and Heath[245] reported simultaneously that amides derived from (*S*)-prolinol were much more suitable substrates for such reactions. Deprotonations of these amides with LDA in the THF gave (*Z*)-enolates (due to allylic strain that would be associated with (*E*)-enolate formation) and the stereochemical outcome of the alkylation step was rationalized by assuming that the reagent approached preferentially from the less-hindered *si*-face of a chelated species such as (**133**; Scheme 62).[246] When the hydroxy group of the starting prolinol amide was protected by conversion into various ether derivatives, alkylations of the corresponding lithium enolates were *re*-face selective. Apparently, in these cases steric factors rather than chelation effects controlled the stereoselectivity of the alkylation.[2,246] It is of interest to note that enolates such as (**133**) are attached primarily from the *si*-face by terminal epoxides.[247]

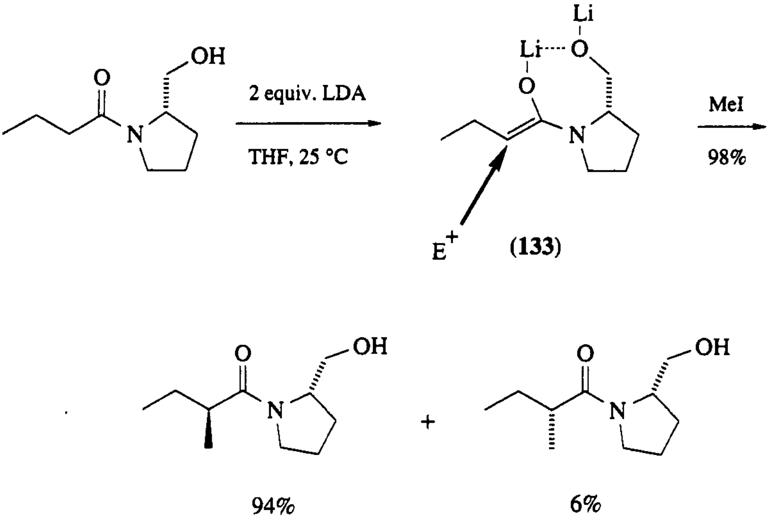

**Scheme 62**

More recently Katsuki and coworkers have reported that (*Z*)-enolates of α-alkyl and α-heterosubstituted amides such as (**134**), derived from pyrrolidine derivatives having a $C_2$ axis of symmetry, undergo very diastereoselective alkylations with secondary alkyl and other alkylating agents in good to excellent chemical yields (Scheme 63).[248] As with prolinol ether amide enolates, it appears that the direction of approach of the alkylating agent to the enolate (**134**) is controlled mainly by steric factors within the chiral auxiliary, *i.e.* chelation effects seem to be of little importance.

In order to overcome the problems associated with acid hydrolysis of amides of prolinol, the Evans research group has investigated the diastereoselectivity of the alkylation of imides derived from chiral 2-oxazolidones.[2,246] Imide enolates are somewhat less nucleophilic than amide enolates, but they have the advantage that their diastereomeric alkylation products are easily separated and the imide linkage is cleaved with a variety of reagents under mild conditions. As shown in Scheme 64, alkylation of the chelated (*Z*)-enolate of the propionimide derived from (*S*)-valinol (**135**) with benzyl bromide occurred in high chemical yield and with high *si*-face diastereoselectivity.[249] In addition to oxazolidones, imidazolidiones have proved to be useful chiral auxiliaries for diastereoselective enolate alkylations.[250]

While deprotonations of *N*,*N*-dialkylamides with lithium dialkylamides in THF yield (*Z*)-enolates both in the presence and absence of HMPA, simple alkanoate esters give predominantly (*Z*)-enolates in the presence of HMPA and predominantly (*E*)-enolates in the absence of the dipolar, aprotic additive.[2] Presumably, deprotonations occur *via* an open transition when HMPA is present to complex with the lithium cation and *via* a closed transition state in THF alone. Helmchen and coworkers have reported that alkylations of esters such as (**136**)–(**138**), containing chiral auxiliaries derived from (+)-camphor, afford the opportunity for an exceptional amount of configurational control.[251] Alkylations of enolates derived from (**136**)–(**138**) occur from the face of the enolate anion opposite the benzenesulfonamide group. Since compound (**136**) is heterochiral with respect to compounds (**137**) and (**138**), as far as the ester and sulfonamide portions of the molecules are concerned, their enolates give alkylation products with opposite configurations under the same reaction conditions. Scheme 65 provides an example of how the configuration of the alkylation product was reversed when the configuration of the enolate was changed by the conditions of deprotonation, *i.e.* the (*E*)-enolate gave largely the (*R*)-alkylation product and the (*Z*)-enol-

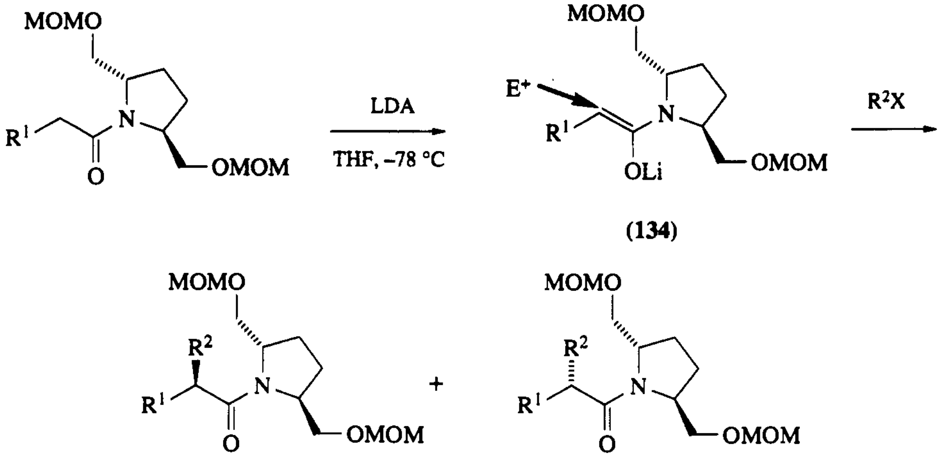
MOMO
R1
N
O
OMOM
LDA
THF, –78 °C
E+
OLi
(134)
R2X
R2
+

| $R^1$ | $R^2X$ | Ratio | Yield (%) |
|---|---|---|---|
| Me | $PhCH_2Br$ | 98:2 | 80 |
| $PhCH_2O$ | $Pr^iOTf$ | 98.5:1.5 | 76 |
| $Me_2C{=}N$ | $HC{\equiv}CCH_2Br$ | 99:1 | 95 |

**Scheme 63**

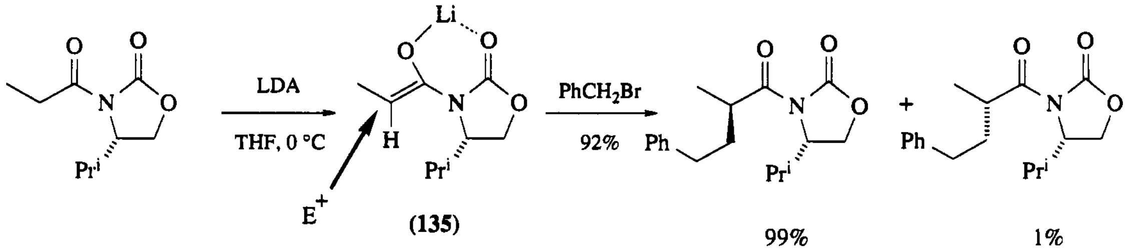
O
N
Pr$^i$
LDA
THF, 0 °C
Li
H
E$^+$
(135)
PhCH$_2$Br
92%
Ph
+
99%
1%

**Scheme 64**

ate gave mainly the (*S*)-alkylated system. Esters of the type **(136)** and **(137)** derived from benzyl-protected glycolates were found to yield (*E*)-enolates both in the absence and presence of HMPA. The (*E*)-enolate of a chiral propionate ester derived from 10-sulfonamidocamphor was diastereoselectivity alkylated from the *si*-face.[252]

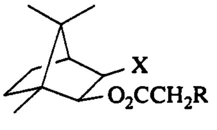

**(136)**

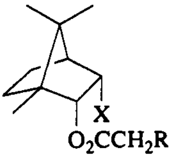

**(137)**

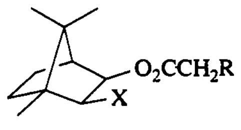

**(138)**

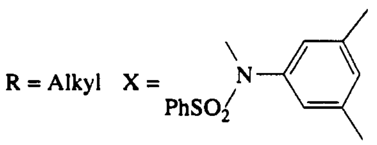
R = Alkyl X =
N
PhSO$_2$

Chiral auxiliaries may be applied to α-amino acid esters by forming imine derivatives. Enolates from 2-hydroxy-3-pinanone glycinate esters have been alkylated to produce mono-[253] and di-substituted[254] α-amino acids in good optical yields after hydrolysis. Recently, McIntosh *et al.*[255] reported the results of alkylations of the enolate **(139)** derived from the (+)-camphor imine of *t*-butyl glycinate with a variety of

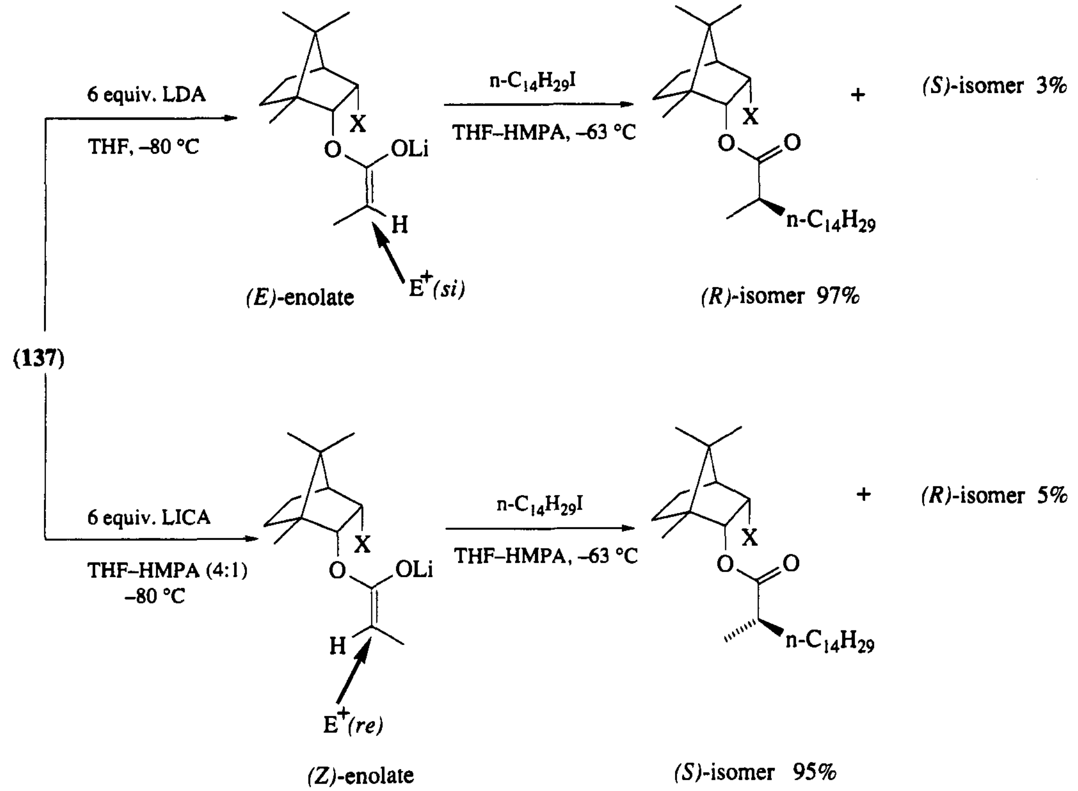
6 equiv. LDA
THF, -80 °C
X
O
OLi
H
E+(si)
(E)-enolate
n-C14H29I
THF-HMPA, -63 °C
X
O
O
n-C14H29
(R)-isomer 97%
+
(S)-isomer 3%
(137)
6 equiv. LICA
THF-HMPA (4:1)
-80 °C
X
O
OLi
H
E+(re)
(Z)-enolate
n-C14H29I
THF-HMPA, -63 °C
X
O
O
n-C14H29
(S)-isomer 95%
+
(R)-isomer 5%

**Scheme 65**

alkylating agents. Selected examples of these reactions are shown in Scheme 66. An electrostatic interaction of the π–π or Li–π type between the lithium enolate and the alkylating agent was suggested as a possible explanation for the high preference for *re*-face selectivity, which was observed when alkylating agents containing electron rich π-systems, *e.g.* benzyl bromide, were employed.[255] Enantioselective alkylations of imines of glycinate esters have been carried out in low optical yields using allyl acetate and palladium(0) catalysts containing chiral phosphine ligands.[256] Diastereoselective alkylations of asymmetrically substituted transition metal acyl enolates is an active area of investigation,[257] but space does not permit coverage of this subject.

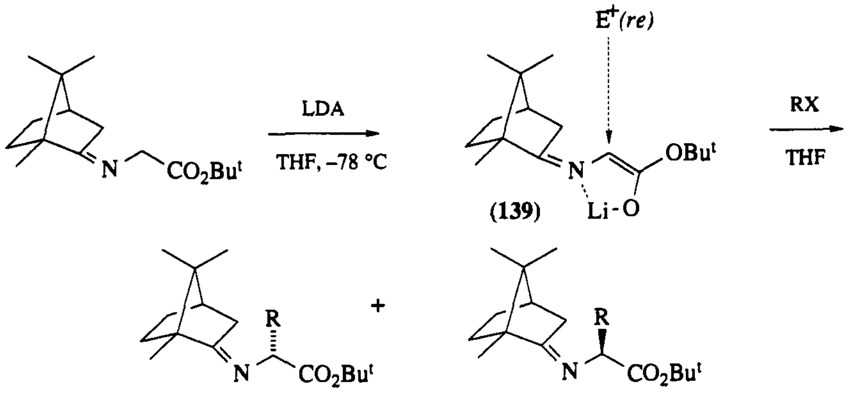
N
CO2Bu^t
LDA
THF, -78 °C
E+(re)
N
OBu^t
Li-O
(139)
RX
THF
R
N
CO2Bu^t
+
R
N
CO2Bu^t

| *RX* | *Ratio* | *Yield (%)* |
|---|---|---|
| EtI | 67:34 | 38 |
| $CH_2$=$CHCH_2Br$ | 82:12 | 85 |
| $PhCH_2Br$ | >99:<1 | 89 |

**Scheme 66**

### 1.1.6.5 Cycloalkylations of Enolates of Carboxylic Acid Derivatives

Like aldehyde and ketone enolates, enolates of carboxylic acid derivatives containing appropriately located leaving groups undergo cycloalkylations to yield monocyclic or more complex ring systems. Intramolecular alkylations of anions of simple nitriles and protected cyanohydrins have been thoroughly reviewed.[218,258] Stork *et al.* have uncovered some interesting aspects of the regiochemistry of intramolecular alkylations of nitriles containing *cis*-epoxides.[259] They showed that these reactions are subject to two important constraints, *i.e.* (i) the usual preference for nucleophilic attack to occur at the less-substituted carbon atom of the epoxide ring; and (ii) the need for a colinear arrangement of the nucleophile and the leaving group in the transition state for cyclization. In cases where both carbons of the epoxide ring were equally substituted, it was observed that the colinearity requirement always favored formation of the smaller ring. The transformation shown in Scheme 67 was a key step in the synthesis of (±)-grandisol, a boll weevil sex attractant.[259] As illustrated in structure (**140**) the preferred transition state for the reaction produces stereoselectively the cyclobutane derivative with the 1,2-alkyl substituents *cis* to each other; the lithium α-nitrile anion appears to have a larger effective size than the α-substituent. Cyclopentane derivatives, which would result from attack at the more remote carbon atom of the epoxide ring were not isolated.

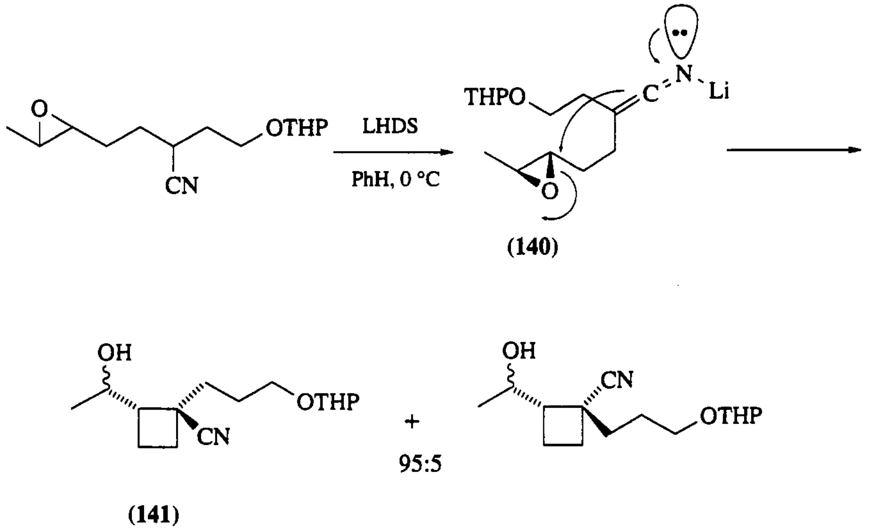

**Scheme 67**

The research group of Stork has also shown that decalin or hydrindane ring systems containing angular cyano groups can be prepared by base-promoted intramolecular cyclizations of cyanocyclohexane derivatives containing ketalized 3-keto-4-halo (or 4-tosyloxy) groups or 2-keto-3-halo groups at C-2.[260] *Cis*-fused hydrindanes were formed irrespective of whether the cation present was potassium or lithium. However, as shown in Scheme 68, the nature of the leaving group, the solvent and, especially, the metal cation profoundly affected the *cis*:*trans* ratio of the decalin products. It was proposed that conditions favoring the *trans* product involved cyclization through a transition state of the anion with the side chain equatorial to the ring. On the other hand, the *cis* product was expected to be obtained in situations where

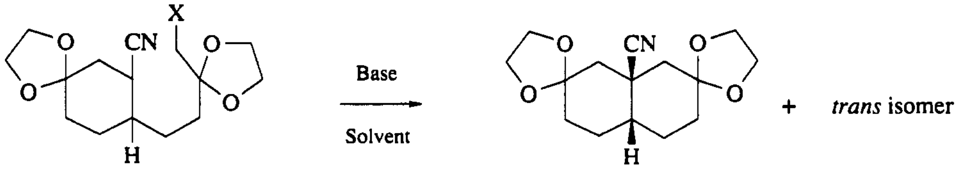

| *X* | *Base* | *Solvent* | *Ratio* |
|---|---|---|---|
| Br | KHDS | PhH | 95:5 |
| Br | LHDS | PhH | 5:95 |
| OTs | LHDS | PhH | 90:10 |
| Cl | LHDS | PhH | 30:70 |
| Cl | LHDS | THF | 80:20 |

**Scheme 68**

the preferred transition state required the side chain to be axial to the ring. Chelation involving the α-nitrile anion, the cation and an oxygen atom of the ketal ring on the side chain may play a role in determining the preferred conformation of the anion for cyclization.

As shown in Scheme 69, Kim and coworkers[261] have reported highly stereoselective routes to *cis*-1,2-dialkylcycloalkanecarboxylates by intramolecular alkylations of tosyloxy esters such as (**142**). The reaction appears to proceed *via* the 'eclipsed' conformations of the enolate (**143**), rather than the 'bisected' one that would result from a 180° rotation about the α,β-sigma bond.

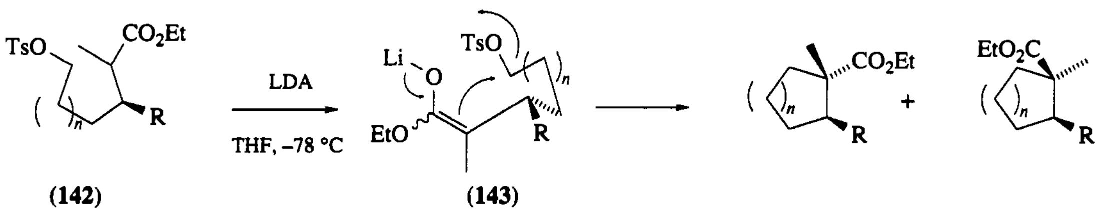

| *n* | *R* | *Ratio* | *Yield* (%) |
|---|---|---|---|
| 0 | isopropenyl | 97:3 | 45 |
| 1 | vinyl | 92:8 | 45 |
| 2 | $\mathrm{Bu^n}$ | 98:2 | - |

**Scheme 69**

Intramolecular alkylations of nitrile-stabilized carbanions have been used to synthesize large rings such as those with 10[262] and 14 members.[263] Tsuji and coworkers carried out a synthesis of the macrocyclic antibiotic zearalenone by this route.[263] As shown in Scheme 70, conversion of either of the protected cyanohydrins (**144**) or (**145**) to the corresponding dianions, resulting from deprotonation at the benzylic positions and α to the nitrile groups, gave the same cyclization product (**146**) in excellent yields. Dianion formation: (i) provided control of the conformation of the side chain; (ii) protected the ester from nucleophilic attack; and (iii) appeared to increase the rate of the intramolecular cyclization.

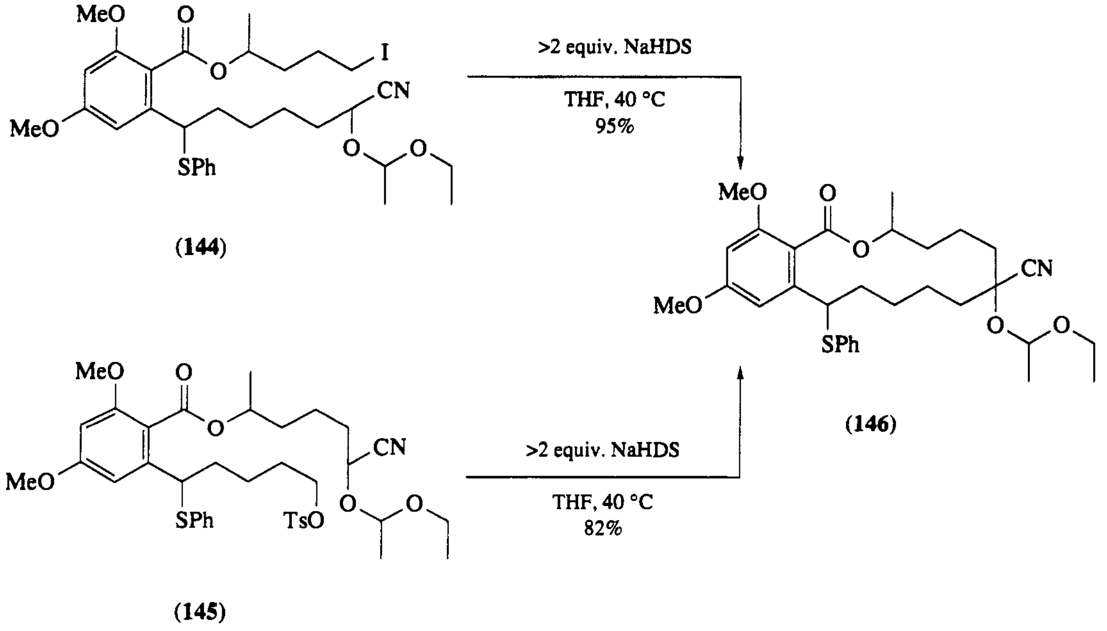

**Scheme 70**

There are many examples of intramolecular cyclizations of carboxylate enolates which lead to fused- and bridged-ring systems. The reaction shown in Scheme 71, which was used by Danishefsky *et al.* as a part of their synthesis of (±)-quadrone, is illustrative.[264]

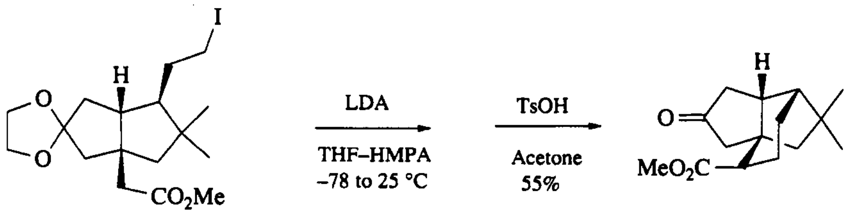

**Scheme 71**

Lewis acid catalyzed reactions of silyl enol derivatives of esters (ketene acetals) with $S_N1$-reactive alkylation agents are well known, but space limitations have prevented coverage of this subject here. The reaction shown in equation (11), which was employed by Pattenden and coworkers[265] in their synthetic studies on forskolin, provides an example of an intramolecular Mukaiyama reaction of a silyl enol ester derivative.

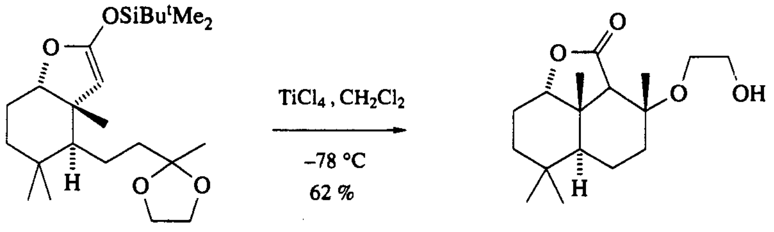

(11)

### 1.1.6.6 Alkylations of Dienolates of α,β-Unsaturated Carboxylic Acid Derivatives

Except in special cases where there is severe steric hindrance,[266] lithium dienolates of all classes of carboxylic acid derivatives undergo almost exclusive α-alkylation with various types of alkylating agents, *e.g.* allyl, benzyl, saturated, *etc.* However, Katzenellenbogen and coworkers,[267] and Snieckus and coworkers,[268] have shown that γ-alkylation may become the predominant mode of reaction when copper(I) dienolates are involved. This was found to be particularly true for dianionic species derived from α,β-unsaturated carboxylic acids and *N*-alkylamides where the negative charge density on the γ-site would be expected to be higher than for the corresponding monoanionic systems, *e.g.* esters or *N*,*N*-dialkylamides.

While γ-alkylations did not occur with saturated and benzylic halides, γ-selectivities in the 62–99% range were observed in reactions of dicopper(I) dianions of a variety of α,β-unsaturated acids with allylic halides.[267] γ-Unsubstituted allylic halides reacted by an $S_N2'$ mechanism, γ-disubstituted compounds underwent direct $S_N2$ displacement and γ-monosubstituted systems reacted by both $S_N2'$ and $S_N2$ pathways. Scheme 72 provides an example of the dramatic reversal in regioselectivity that was observed in the allylation of the dianion (**147**) of tiglic acid when the metal cation was changed from lithium to copper(I).[267] The γ-alkylation product from the latter species was exclusively the (*E*)-isomer.

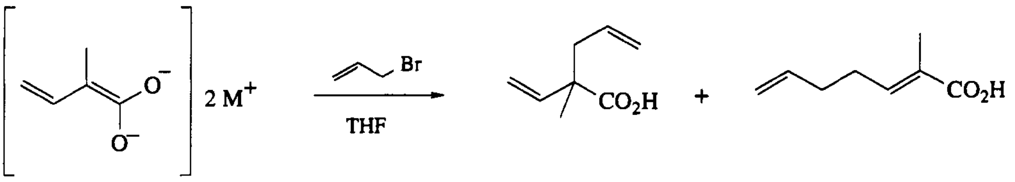

(**147**)

| *M* | *Ratio* | *Yield (%)* |
|---|---|---|
| Li | 100:0 | 80–90 |
| Cu$^I$ | 4:96 | 95 |

**Scheme 72**

Scheme 73 shows the results of alkylations of dilithium and dicopper(I) dianions (**148**) of senecioic acid *N*-isopropylamide with alkylting agents of various classes.[268] A major difference in the behavior of (**148**; M = Cu$^I$) and the corresponding dicopper(I) dianion of senecioic acid itself was that a significant amount of γ-alkylation occurred with methyl iodide and benzyl bromide. Also, the amide dianion was γ-alkylated with higher (*Z*)/(*E*)-stereoselectivity than the acid dianion. The role played by copper(I) in affecting the regiochemistry of alkylations of species such as (**147**) and (**148**) is unclear. Possibly *C*-metallated species are more likely to be involved when copper(I) rather than lithium is employed as the cation.

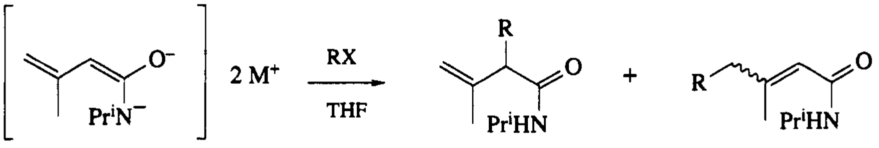

(**148**)

| *M* | *RX* | *Ratio* | *(Z):(E) ratio* | *Yield (%)* |
|---|---|---|---|---|
| Li | MeI | 98:2 | – | 98 |
| $Cu^I$ | MeI | 59:41 | 91:9 | 80 |
| Li | $CH_2{=}CHCH_2Br$ | 98:2 | – | 90 |
| $Cu^I$ | $CH_2{=}CHCH_2Br$ | 30:70 | 60:40 | 90 |
| Li | $PhCH_2Br$ | 98:2 | – | 90 |
| $Cu^I$ | $PhCH_2Br$ | 75:25 | 80:20 | 80 |

**Scheme 73**

Kende and Toder have reported that deconjugative alkylations of (*Z*)-2-alkenoates give the corresponding (*E*)-3-enoate derivatives, while (*E*)-2-alkenoates give (*Z*)-3-enoate isomers unless the 4-substituent is larger than methyl.[269] They suggested that the stereoselectivity of these reactions is probably determined by the conformation of the α,β-unsaturated ester that undergoes deprotonation at C-4.

Birch reductions of arylbenzoic acid derivatives provide a highly useful method of generating enolates of unsaturated carboxylic acid derivatives that can be trapped with a variety of electrophilic reagents. Especially interesting data have been obtained by Schultz *et al.* utilizing arylbenzoic acid derivatives containing chiral auxiliaries derived from L-prolinol.[270] The results of alkylations of the lithium amide enolates (**150**) obtained by reduction of benzoxazepinones (**149**) are shown in Scheme 74. Enolate (**150a**) was found to undergo highly diastereoselective β-face attack at the α-position with a variety of alkylating agents. However, γ-alkylation was the major pathway for reaction of enolate (**150b**). It was proposed that when a methyl group is present at the angular position, the enolate adopts a conformation in which the α-position is shielded from attack on both faces.

Schultz *et al.*[270] have also conducted studies on the methylation of the chiral lithium amide enolate (**152**), which was obtained by lithium–ammonia reduction of the 2-methoxybenzamide (**151**). This compound is an acyclic counterpart of the benzoxazepinone (**149a**). Enolate (**152**) was shown to have the (*Z*)-configuration by $^1H$ NMR analysis. As shown in Scheme 75, methylation of (**152**) in the presence of ammonia gave the amide (**153**), which resulted from attack of methyl iodide at the α-position and from the underside of the enolate almost exclusively. On the other hand, if the ammonia was removed or if the enolate (**152**) was protonated and reformed with *n*-butyllithium prior to alkylation, compound (**154**) resulting from topside attack at the α-position was formed almost exclusively. This dramatic change in diastereoselectivity in the absence of ammonia was attributed to a major change in enolate structure that could result from rotation about the C—N bond and inversion of configuration at nitrogen of the chiral auxiliary. The enolate was considered to exist as a dimer in the presence and absence of ammonia.

Takahashi and coworkers have employed intramolecular reactions of anions of unsaturated protected cyanohydrins to produce unsaturated carbocyclic systems containing 10-, 14- and 16-membered rings which are convertible into natural products.[271] These reactions occur regiospecifically at the α-position and usually do not involve (*E*) → (*Z*) isomerization of β,γ-double bonds. The preparation of 2-cyclopentadecenone (**155**), which is convertible into the macrocyclic perfumes muscone and exaltone, is illustrative of this methodology (Scheme 76).

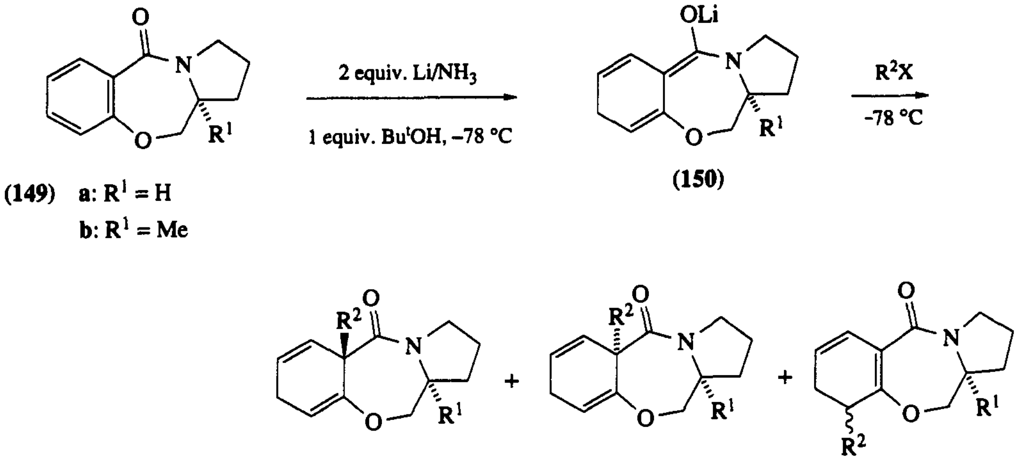
2 equiv. Li/NH$_3$
1 equiv. Bu$^t$OH, –78 °C
R$^2$X
-78 °C
O
N
R$^1$
OLi
R$^2$
+

**(149)** **a**: R$^1$ = H
**b**: R$^1$ = Me

**(150)**

| *R$^1$* | *R$^2$X* | | | *Yield (%)* | |
|---|---|---|---|---|---|
| H | MeI | 57 | | 10 | 3 |
| H | EtI | 81 | | 1 | 0 |
| H | 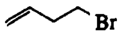 Br | ~87 | | ~2 | 0 |
| Me | MeI | — | 18 | — | 80<br>(80:20 mixture) |

Scheme 74

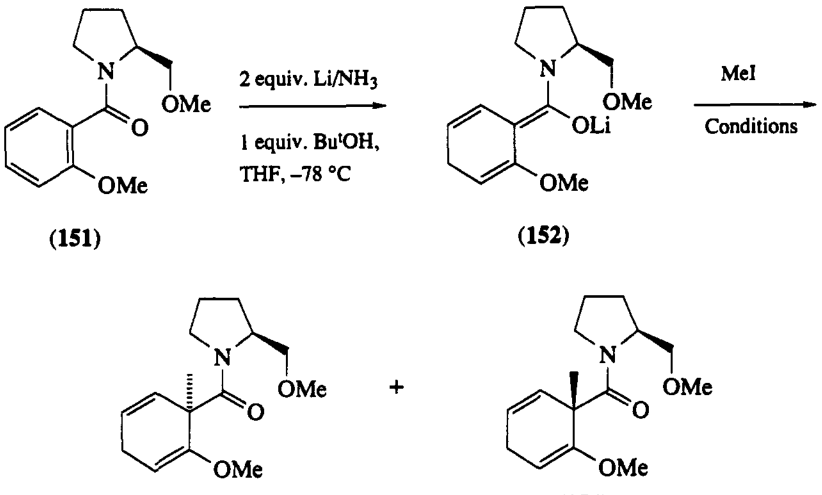
2 equiv. Li/NH$_3$
1 equiv. Bu$^t$OH, THF, –78 °C
MeI
Conditions
N
OMe
O
OLi
+

**(151)**

**(152)**

**(153)**

**(154)**

| *Conditions* | *Ratio* | *Yield (%)* |
|---|---|---|
| NH$_3$–THF, –78 °C | 99.6:0.4 | 85 |
| i, warm to 25 °C with loss of NH$_3$<br>ii, THF, –78 °C | 1:99 | 80 |

Scheme 75

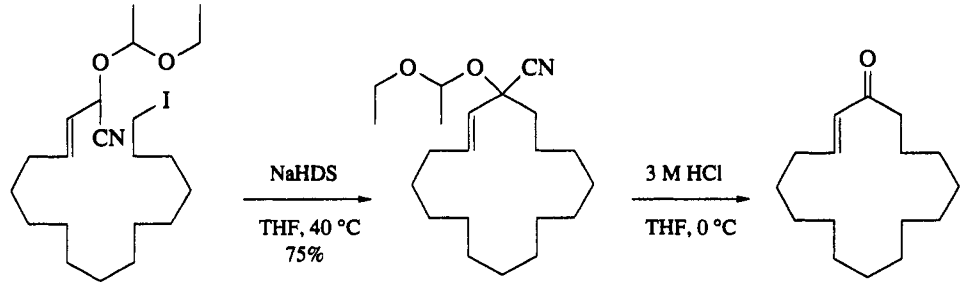

**(155)**

Scheme 76

### 1.1.6.7 Asymmetric Synthesis *via* Alkylations of Anions of Masked Carboxylic Acid Derivatives

Over the past 20 years, Meyers and coworkers have developed an elegant methodology for the synthesis of complex carbonyl compounds, which involves alkylations of anions of masked carboxylic acid derivatives. Their earlier work, which involved the use of heterocyclic analogs of imino esters such as 2-alkyldihydro-1,3-oxazines, 2-alkylthiazolines and 2-alkyloxazolines has been thoroughly reviewed.[5,6,272] Anions of 2-alkyloxazolines turned out to be the most useful reagents for the synthesis of alkylated carboxylic acids and esters, and, by using chiral, nonracemic oxazolines such as (**156**), derived from commercially available amino alcohols, the research group of Meyers extended this methodology to the asymmetric synthesis of $\alpha,\alpha$-dialkylcarboxylic acids.[273] It was found that both enantiomers of a carboxylic acid derivative could be produced by starting with selectively substituted oxazolines or reversing the order in which the alkyl groups were introduced.

As shown in Scheme 77, deprotonation of compound (**156**) with LDA in THF at –78 °C gave a 95:5 (*E*)/(*Z*)-mixture of lithiated anions (**157**) and (**158**). Upon addition of an alkylating agent at –78 °C or below, the major anion (**157**) was attacked from the underside with high diastereoselectivity. The highly effective intramolecular chirality transfer was ascribed to the fact that (**157**) exists as a rigid chelated structure with the lithium cation located on the underside of the molecule and the phenyl group sterically shielding the topside of the molecule. The presence of both the methoxy group and the phenyl were essential for high diastereoselectivity to be observed. Alkylations of (**157**) with ethyl, propyl or *n*-butyl iodide followed by unmasking of the carboxylic acid by hydrolysis gave the corresponding (*S*)-2,2-dialkylacetic acids in 72–78% enantiomeric excess (*ee*) and good chemical yields. The optical purity of the product was reduced because the minor azaenolate (**158**) gave the corresponding (*R*)-acids.

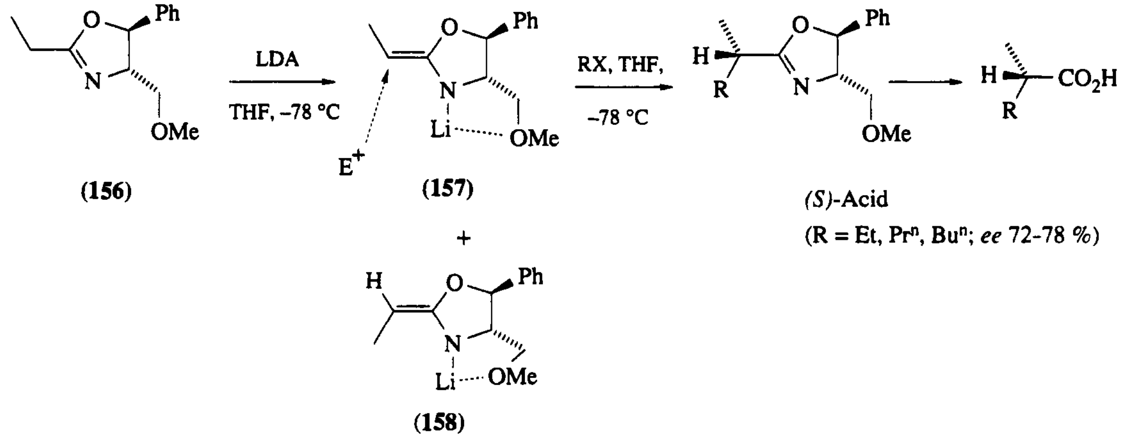

**(156)** **(157)** **(158)**

(*S*)-Acid

(R = Et, Pr$^n$, Bu$^n$; *ee* 72-78 %)

Scheme 77

Schöllkopf and coworkers have pioneered the development of anions of another type of masked carboxylic acid derivative, *i.e.* bislactim ethers such as (**159**), derived from (*S*)-valine and glycine or alanine, for the asymmetric synthesis of amino acids.[274] As shown in Scheme 78, compounds such as

(**159**) are deprotonated exclusively at C-5 with *n*-butyllithium or LDA in THF to give endocyclic chiral enolate equivalents such as (**160**). Alkylations of (**160**) with saturated primary, allylic and benzylic halides occur *anti* to the 2-isopropyl substituent with high diastereoselectivity. It has been proposed that both coordination of the lithium cation and attack of the alkylating agent occurs on the π-face of the delocalized anion opposite the bulky substituent. When the C-2 substituent was smaller than isopropyl or when systems with C-2 disubstituted were employed, alkylation diastereoselectivities were reduced somewhat. A disadvantage of this method is that after acidic methanolysis of the new bislactim ethers, two amino acid esters which must be separated are produced.

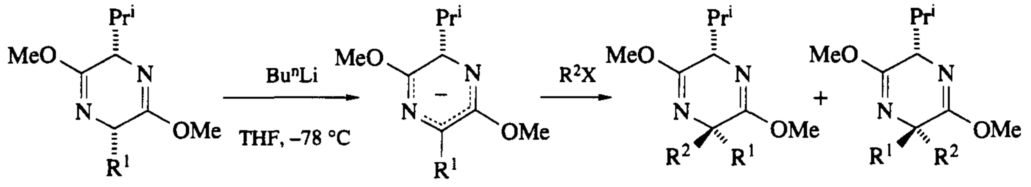

(**159**) (**160**)

| *R$^1$* | *R$^2$X* | *Ratio* | *Yield (%)* |
|---|---|---|---|
| H | $PhCH_2Br$ | >95:5 | 81 |
| Me | $PhCH_2Br$ | >98:2 | 68 |
| H | $PhCH{=}CHCH_2Br$ | >95:5 | 90 |
| Me | $PhCH{=}CHCH_2Br$ | >98:2 | 89 |
| H | $Me(CH_2)_5CH_2Br$ | >87:13 | 62 |
| Me | $Me(CH_2)_5CH_2Br$ | >98:2 | 43 |

**Scheme 78**

## 1.1.7 ALKYLATIONS OF STABILIZED METAL ENOLATES

### 1.1.7.1 Alkylations of Monoanions of β-Dicarbonyl and Related Compounds

Conventional methods of alkylation of stabilized metal enolates such as those derived from β-diesters, β-cyano esters, β-keto esters, β-keto aldehydes, β-diketones, β-keto sulfoxides and β-keto sulfones have been thoroughly discussed elsewhere.[4,5,6,15] *O*-Alkylation often competes strongly with *C*-alkylation in these systems. Factors which tend to favor *O*-alkylation generally include the use of: (i) substrates that are highly enolic, *e.g.* β-keto aldehydes and cyclic β-diketones; (ii) electropositive metals, *e.g.* potassium, as counterions; (iii) highly dipolar aprotic solvents, *e.g.* HMPA; and (iv) highly reactive alkylating agents, *e.g.* chloromethyl alkyl ethers or secondary alkyl halides. Factors that favor *C*-alkylation include the use of: (i) hetereogeneous conditions; (ii) less electropositive metal cations, *e.g.* lithium; (iii) nonpolar or protic solvents; and (iv) polarizable alkylating agents such as alkyl iodides and allylic, propargylic and benzylic halides. In addition to *O*-alkylation, side reactions such as dialkylation, Claisen condensation, β-keto cleavage and oxidative coupling may compete with *C*-alkylation.

Two methods which reduce or avoid *O*-alkylation and employ heterogeneous reaction conditions include: (i) the heating of crystalline thallium(I) enolates of β-keto esters or β-diketones with primary or secondary alkyl iodides;[275] and (ii) the heating of stabilized sodium enolates with methyl- or ethyl-sulfonium salts.[276] However, the reproducibility and generality of the former method has been questioned.[277]

Excellent yields of *C*-alkylation products have been obtained by the reaction of β-dicarbonyl compounds with alkyl halides in the presence of tetraalkylammonium fluorides[278] or salts such as (**161**).[279] The latter method appears to have broad generality. Scheme 79 provides a comparison of the alkylation of acetylacetone with *n*-hexyl iodide in the presence of reagent (**161**) and *via* conventional methodology. Reagent (**161**) was assumed to generate quaternary ammonium enolate intermediates from β-dicarbonyl compounds. However, it seems possible that the alkylating agent actually attacks an enol intermediate which is hydrogen-bonded to the pyrrolidone anion. This type of pathway was proposed in cases where quaternary ammonium fluorides were utilized.

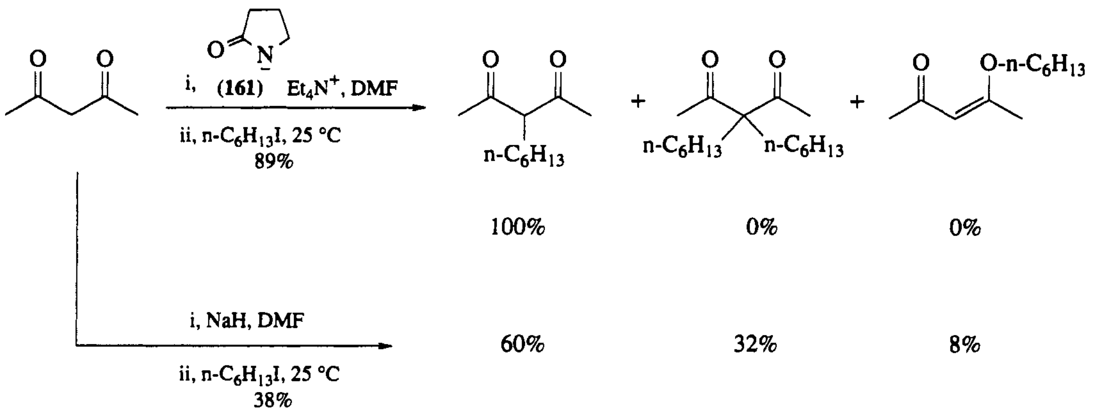

Scheme 79

Enolates of cyclic 1,3-diketones, such as 2-methyl-1,3-cyclopentanedione and 2-methyl-1,3-cyclohexanedione, are especially prone to *O*-alkylation because of their 'W' geometry and steric hindrance at carbon. However, *C*-alkylations of these species can be conducted reasonably successfully in protic solvents, *e.g.* water.[280] Trost and Curran[281] have reported high yields for the *C*-alkylation of cyclic 1,3-diketones with allylic acetates in the presence of palladium(0) catalysts and DBU (Scheme 80).

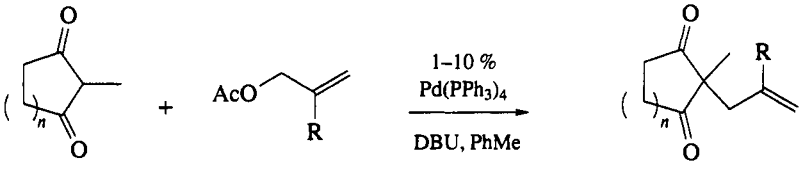

| *n* | *R* | *Yield (%)* |
|---|---|---|
| 1 | OEt | 76 |
| 1 | H | 94 |
| 2 | OEt | 81 |

Scheme 80

The stereochemical results of methylations of stabilized metal enolates such as (**162**), derived from 4-*t*-butylcyclohexanone, and (**163**) and (**164**), derived from *trans*-10-methyl-2-decalone, are shown in Scheme 81. Kuehne and Nelson[282] found that the unhindered α-cyano and α-methoxycarbonyl enolates (**162a**) and (**162b**) both underwent stereoelectronically controlled axial alkylation preferentially, although not with high diastereoselectivity. Also, the related pair of 3-substituted 2-decalone enolates (**163a**) and (**163b**) both underwent mainly equatorial alkylation, presumably because the 10-methyl group provides significant hindrance to axial attack of the electrophile.[282] These stereochemical results are entirely consistent with those obtained for the alkylations of related unstabilized enolates discussed in Section 1.1.2.2. However, the 1-substituted 2-decalone enolates (**164a**) and (**164b**) were found to undergo alkylation in the opposite sense, *i.e.* the α-cyano species underwent primarily equatorial methylation,[282] while the related α-methoxycarbonyl species underwent largely axial methylation[283] (similar results were obtained for alkylations of related pairs of enolates derived from tri- or tetra-cyclic β-keto esters[2]). Kuehne and Nelson have suggested several factors which may account for the difference in the behavior of (**164a**) and (**164b**).[282] A major reason may be that in (**164b**) a *peri* interaction between the methoxy group of the chelated enolate ring and the B-ring methylene group (C-8), which is not present in (**164a**), distorts the A-ring so as to open up the top π-face of the enolate to attack.

The formation of cyclic compounds by intramolecular alkylations of stabilized enolates has been widely used in organic synthesis. A recent study of the kinetics of the reaction of diethyl (ω-bromoalkyl)malonates in DMSO using tetramethylammonium hydroxide as the base has shown that relative rates of closure of rings of varying size follow the order: 3 > 5 > 6 > 4 > 7 > 12–21 > 8 > 9 > 11 > 10.[284] These results are consistent with earlier studies in which other base–solvent combinations were employed.[4] The high rates of closure of three-membered rings allow the formation of a variety of cyclopropane deriva-

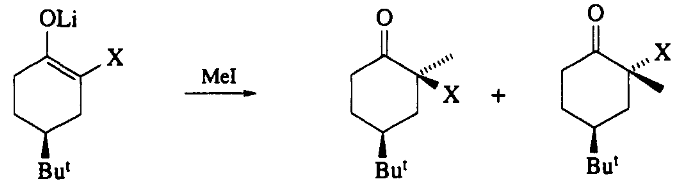

**(162)** a: $X = CN$
b: $X = CO_2Me$

| *Compound* | *Ratio* | *Yield (%)* |
|---|---|---|
| **(162a)** | 77:23 | 84 |
| **(162b)** | 83:17 | 97 |

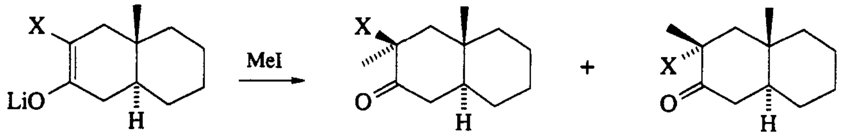

**(163)** a: $X = CN$
b: $X = CO_2Me$

| *Compound* | *Ratio* | *Yield (%)* |
|---|---|---|
| **(163a)** | >90:<10 | 46 |
| **(163b)** | 83:17 | 94 |

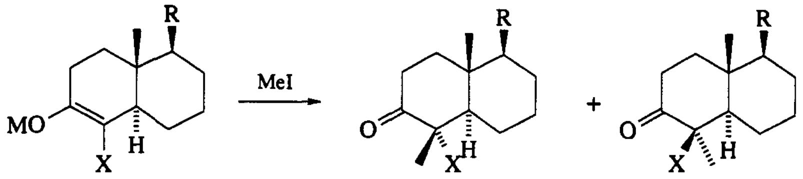

**(164)** a: $M = Li, X = CN, R = H$
b: $M = Na, X = CO_2Me, R = OTHP$

| *Compound* | *Ratio* | *Yield (%)* |
|---|---|---|
| **(164a)** | <10:>90 | 58 |
| **(164b)** | 93:7 | 67 |

**Scheme 81**

tives from active methylene compounds under mild conditions. Quinkert *et al.*[285] have shown that base-promoted reactions of chiral malonic esters, prepared from chiral, nonracemic alcohols such as (–)-8-phenylmenthol, with 1,4-dihalo-2-butenes lead to intermolecular alkylation followed by $S_N2'$ closure of a three-membered ring to give chiral 2-alkenyl-1,1-cyclopropanedicarboxylates. These products have been shown to be useful building blocks for the synthesis of a variety of natural products.

Ten-membered rings are formed slowly in cycloalkylations because the entropy factor is unfavorable and transannular interactions are severe in the transition state for ring closure. Deslongchamps *et al.*[286] have shown that the introduction of double and triple bonds into the carbon chain reduces the importance of these factors by restricting the degrees of freedom of the molecule and partially eliminating transannular interactions. As shown in equation (12), the cyclization of the malonic ester derivative (**165**) was carried out in good yield without the use of high dilution techniques.

The research group of Trost has shown that stabilized enolates derived from β-diesters and α-phenylsulfonyl esters are excellent nucleophiles for palladium(0)-catalyzed reactions with allylic acetates.[287] Since these reactions involve π-allylpalladium intermediates, they proceed with net retention of configuration and, therefore, differ from traditional displacement reactions where inversion is the rule. Moreover, the transition metal imposes a template effect on intramolecular versions of these reactions and

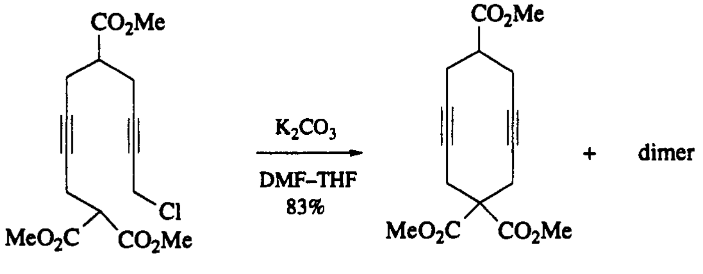
CO2Me
Cl
MeO2C
CO2Me
K2CO3
DMF–THF
83%
CO2Me
MeO2C
CO2Me
+
dimer

(12)

**(165)** 84% 16%

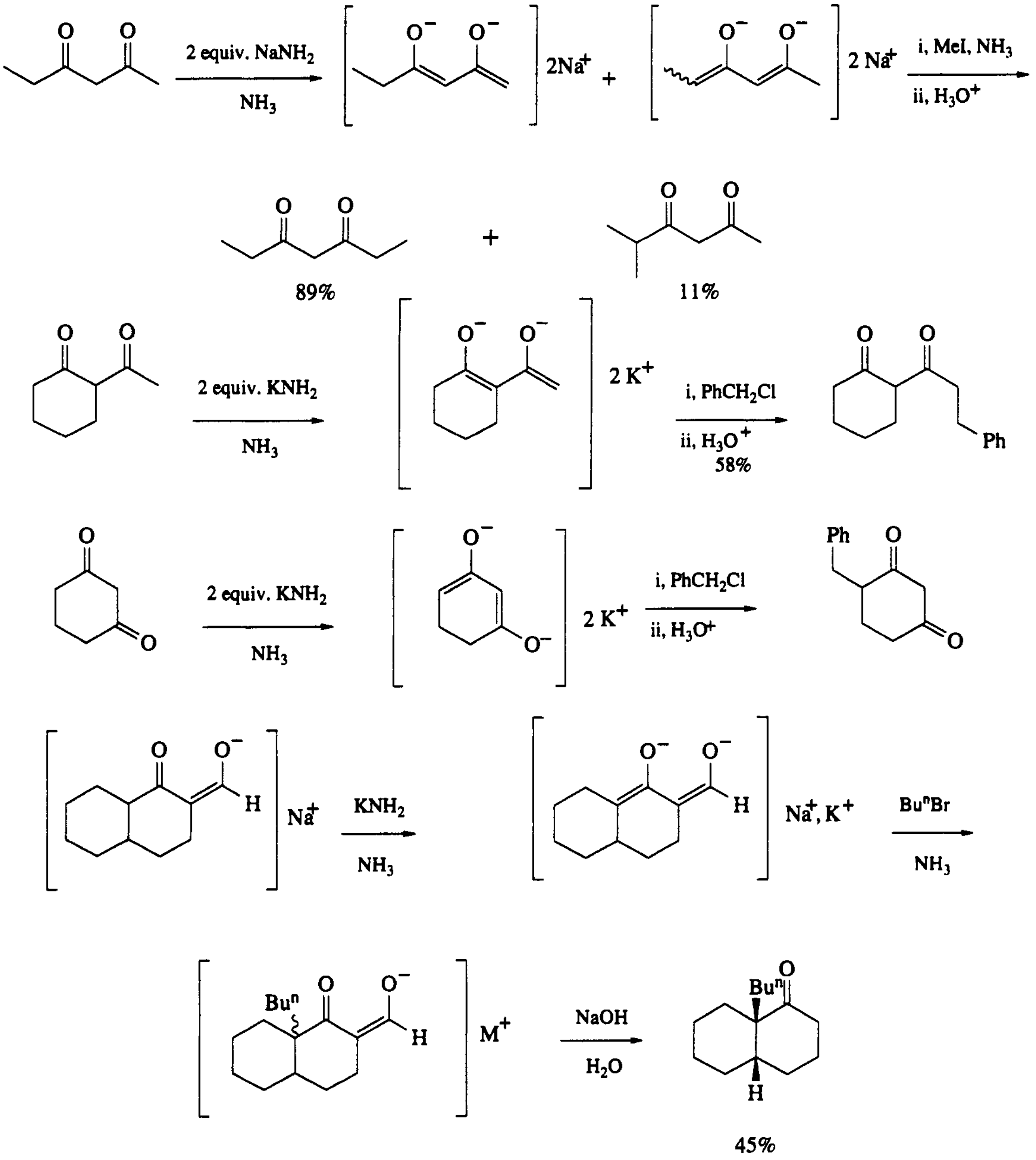
O
O
2 equiv. NaNH2
NH3
O−
O−
2Na+
+
2 Na+
i, MeI, NH3
ii, H3O+
+
89%
11%
2 equiv. KNH2
NH3
2 K+
i, PhCH2Cl
ii, H3O+
58%
Ph
2 equiv. KNH2
NH3
2 K+
i, PhCH2Cl
ii, H3O+
Ph
H
Na+
KNH2
NH3
Na+, K+
BunBr
NH3
Bun
M+
NaOH
H2O
Bun
H
45%

**Scheme 82**

medium and large rings which are difficult to obtain by traditional methods can be formed easily. The reader is referred to recent reviews for thorough coverage of this important methodology.[287]

### 1.1.7.2 γ-Alkylations of Dianions of β-Dicarbonyl Compounds

The synthetic flexibility of β-dicarbonyl compounds was greatly expanded when it was discovered by Hauser and Harris that many of these systems can be converted to their dianions by treatment with 2 equiv. of potassium or sodium amide in liquid ammonia.[288] These dianions could then be monoalkylated at the γ-position with high regioselectivity. Early research in this area was devoted to studies on β-diketones and β-keto aldehydes, and this is covered in an excellent review by Harris and Harris.[289] It was found that unless activating groups were present, the second proton was removed regioselectively from the less-substituted γ-position of unsymmetrical β-diketones. Of course, β-keto aldehydes are capable of yielding only a single dianion. Scheme 82 provides examples of these reactions. The last reaction in Scheme 82 is particularly interesting since it involves preparation of an angularly alkylated 1-decalone derivative.

Attempted γ-alkylations of β-keto esters by forming their dipotassium dianions with potassium amide and alkylating them in liquid ammonia gave poor results. However, Huckin and Weiler[290] found that treatment of methyl acetoacetate with 1 equiv. of sodium hydride, followed by 1 equiv. of *n*-butyllithium, or 2 equiv. of LDA in THF gave dimetal dienolates (**166**) which alkylated in good yields with several different alkylating agents including isopropyl iodide at 0–25 °C (Scheme 83).

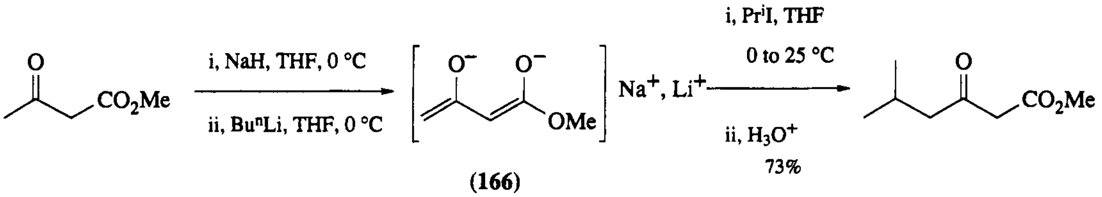

**(166)**

**Scheme 83**

The method of Huckin and Weiler has enjoyed widespread use in synthesis. For example, recently reported syntheses of *trans*-bicyclo[4.3.1]decan-10-one[291] and a bicyclo[4.4.1]undecan-7-one derivative[292] have employed γ-alkylations of β-keto ester dianions as key steps. This methodology has also been extended to the formation and γ-alkylation of dianions of γ,δ-unsaturated β-keto esters.[293]

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# 1.2

# Alkylations of Nitrogen-stabilized Carbanions

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## 1.2.1 INTRODUCTION

The deprotonation of an $sp^3$-hydrogen α to nitrogen has been developed into a highly useful synthetic tool in recent years.[1,2] Although some authors have suggested that this type of reactivity is a reversal of the 'normal' reactivity adjacent to nitrogen,[2,3] we submit that this notion is inappropriate and should be discontinued. The α-deprotonation of dimethyldodecylamine[4] and triethylamine[5] was reported over 20 years ago. In 1984, Ahlbrecht reported that *s*-butylpotassium readily deprotonates *N*-methylpiperidine, *N*-methylpyrrolidine and triethylamine, and that the derived organometallics add readily to aldehydes, ketones and alkyl halides.[6] An example is shown in Scheme 1.

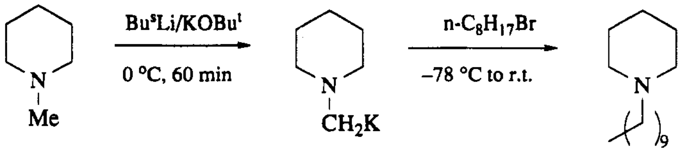

Scheme 1

The above examples notwithstanding, for an efficient and mild deprotonation the nitrogen is best derivatized. Two closely related amine derivatives activate the α-protons: nitrosamines[1,2,7,8] and amides.[2] The chemistry of nitrosamine and amide anions and related systems was thoroughly reviewed in 1984,[2] and so this chapter concentrates on recent developments. Most of these developments are in the area of dipole-stabilized species: amides, amidines and similar compounds. Synthetic applications of these systems have been investigated in two broad categories of substrates: achiral (or racemic) and chiral (nonracemic). In the latter case, the dipole-stabilized organometallic is chiral and nonracemic, affording interesting opportunities for asymmetric synthesis. Indeed, highly stereoselective methods for the preparation of enantiomerically pure compounds have been developed that employ the stereoelectronic requirements of the organometallic to advantage. Thus, this chapter is divided along the following lines: synthetic applications of achiral and racemic systems, followed by synthetic applications of homochiral systems. Within each class, the examples are further categorized as either acyclic or heterocyclic according to the location of the carbanion/metal.

The geometries of amide and nitrosamine anions differ in a fundamental way, and this difference has important implications for synthesis. Although cyclic nitrosamines lose the axial proton *syn* to the nitrosamine oxygen[9] and alkylate by axial approach of the electrophile,[10] cyclic amides lose the equatorial proton and alkylate equatorially[11] to give the thermodynamically less stable product,[12] as illustrated in Scheme 2.

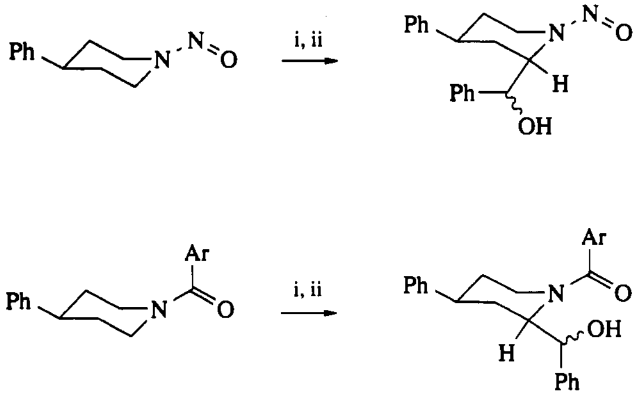

i, BuLi; ii, PhCHO

**Scheme 2**

Thus the nitrosamine anion is a resonance-stabilized species in which the carbanionic lone pair overlaps the π-system of the nitrosamine. By contrast, the amide anion is a dipole-stabilized species in which the lone pair remains in or near the nodal plane of the amide π-system. Given the similarity of the two systems, this difference in behavior is striking. Although the geometry observed in nitrosamine anion alkylations is similar to that of their isoelectronic counterparts, oxime dianions,[13,14] it is puzzling that amide anions differ, since they are also isoelectronic, as shown in Figure 1.

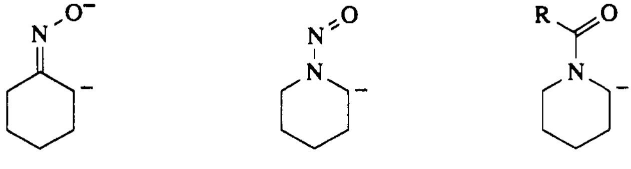

Alkylation: *syn*-axial *syn*-axial *syn*-equatorial

**Figure 1** Isoelectronic anions

One explanation of the unique stereoelectronic requirements of amide anions ensues from *ab initio* studies conducted by Houk *et al.*,[12] Bach *et al.*,[15] and Bartolotti and Gawley.[16] To explain the equatorial alkylation, Bach argued, on the basis of calculations on a model system, that the rotation of the carbanion lone pair of $HCONHCH_2^-$ out of the amide nodal plane and into conjugation with the p-system results in a large increase in energy (16–18 kcal $mol^{-1}$; 1 cal = 4.18 J). The source of the increase is a destabilizing interaction between the HOMO of the amide and the carbanion lone pair. When mixed, $\Psi_3$ of the amide is raised 44.6 kcal $mol^{-1}$, while $\Psi_2$ is lowered only 27.4 kcal $mol^{-1}$, resulting in a net increase of 17 kcal $mol^{-1}$ for the two frontier orbitals.[15] Even so, it is the *less* stable anion geometry (**1**; Figure 2) that is *syn* to the carbonyl.[15,16] It is not until the effect of the lithium cation is considered that the *syn* geometry is seen to be the more stable (Li-**2**; Figure 2), by 28 kcal mol$^{-1}$.[16] It therefore seems most appropriate to call the reactive species 'dipole-stabilized organometallics'.

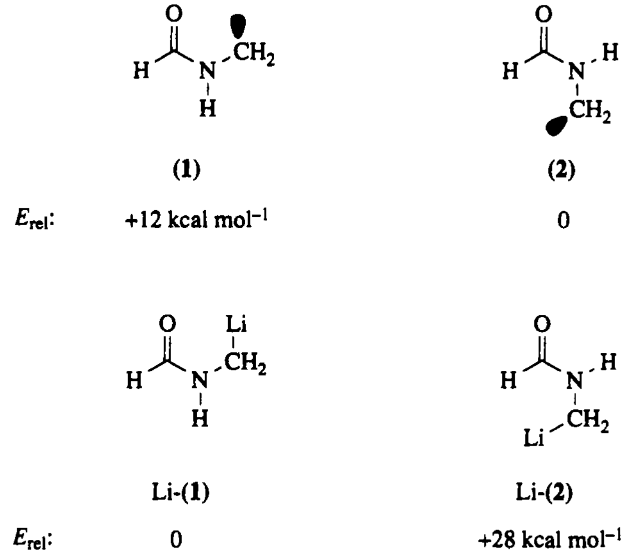
(1)
(2)
$E_{rel}$:
+12 kcal mol$^{-1}$
0
Li-(1)
Li-(2)
$E_{rel}$:
0
+28 kcal mol$^{-1}$

**Figure 2** *Ab initio* structures and relative energies of N-methylformamide anion

The amide deprotonation step involves a prior coordination complex between the amide (or amidine) and the butyllithium base.[17,18,19] As shown in Scheme 3, formation of a coordination complex between an amide or amidine substrate and butyllithium is observed by IR shortly after mixing, but before the deprotonation. A recent mechanistic study has shown that this coordination complex is between the amide and the *s*-butyllithium aggregate, and that the effect of the coordination is to increase the reactivity of the complex.[20] In fact, the aggregate may be activated by adding TMEDA prior to the amide, with a similar increase in reactivity. However, because these studies were conducted in cyclohexane, extrapolation of these observations to ethereal solvents is somewhat problematic.[20]

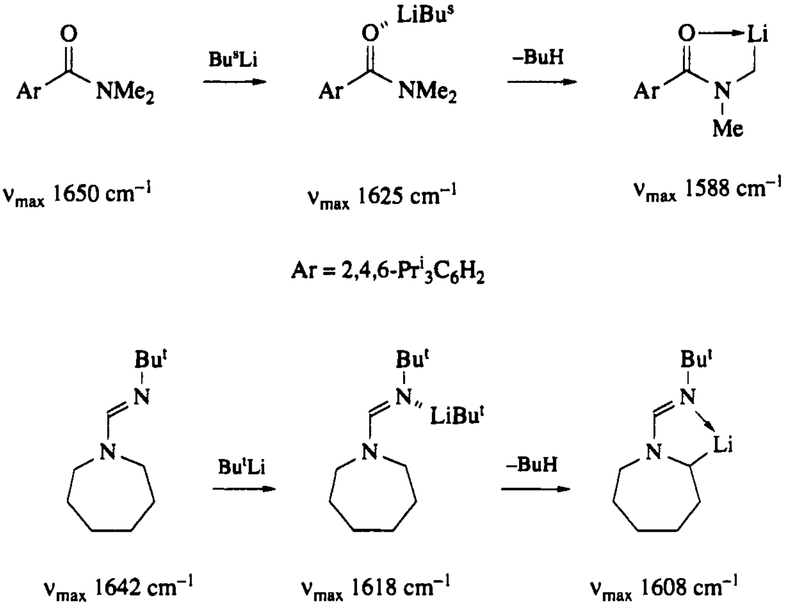
Bu$^s$Li
-BuH
$\nu_{max}$ 1650 cm$^{-1}$
$\nu_{max}$ 1625 cm$^{-1}$
$\nu_{max}$ 1588 cm$^{-1}$
Ar = 2,4,6-Pr$^i_3$C$_6$H$_2$
Bu$^t$Li
-BuH
$\nu_{max}$ 1642 cm$^{-1}$
$\nu_{max}$ 1618 cm$^{-1}$
$\nu_{max}$ 1608 cm$^{-1}$

**Scheme 3**

When the α-protons are allylic or benzylic, the selectivity of the deprotonation is attenuated by the competing stereoelectronic requirements of allylic activation and dipole stabilization. Stabilization of a developing negative charge by resonance delocalization into a double bond and stabilization by an amide dipole which avoids resonance delocalization must be accommodated in the transition state and a balance of both effects must be achieved.[21] Moreover, the organolithium species must accommodate the amide dipole as well as the allyl system, since reaction with electrophiles at the γ′-position is common. These aspects of reactivity are discussed further in Section 1.2.3.1, in the context of deprotonation and alkylation of homochiral substrates.

## 1.2.2 ACHIRAL AND RACEMIC PRECURSORS

### 1.2.2.1 Acyclic Systems

The alkylation of carbons α to nitrogen in acyclic systems has not developed much since the 1984 review.[2] Although amides may serve as excellent precursors of dipole-stabilized organolithiums, they are quite difficult to remove. For example, the two amide systems shown in Scheme 4 were designed to hinder approach of a nucleophile to the carbonyl carbon in order to preclude addition of the butyllithium base. Metalation on the carbon *syn* to the carbonyl oxygen is then the favored process, and alkylation occurs smoothly. The triisopropylbenzamides, however, could not be cleaved under a variety of acidic, basic, or reductive conditions. The diethylbutanamides behaved similarly in the alkylation step, and could be cleaved in good yield by acid hydrolysis.[22]

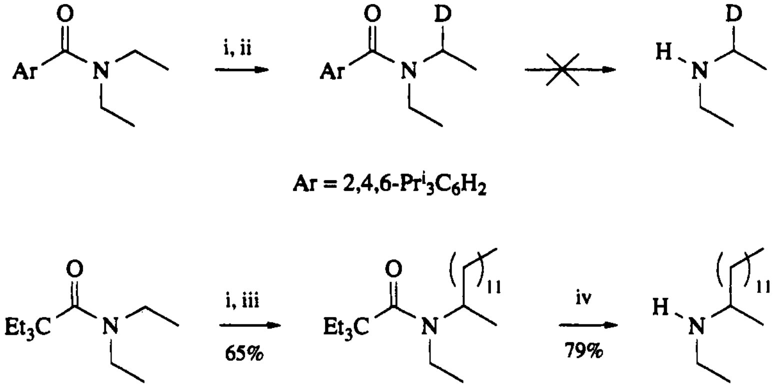

Ar = 2,4,6-$Pr^i_3C_6H_2$

i, $Bu^sLi$, TMEDA, $Et_2O$, –78 °C; ii, MeOD; iii, $Me(CH_2)_{11}I$; iv, HCl, $H_2O$, reflux 72 h

Scheme 4

Even though the diethylbutanamides are cleavable, the conditions required are quite harsh: aqueous hydrochloric acid at reflux for 3 d. A much better activating group was introduced in 1980 by Meyers: the formamidines shown in Scheme 5.[23] The decreased reactivity of the C═NR bond relative to the C═O bond toward nucleophilic attack obviates the need for a bulky group to shield the carbonyl carbon. In the initial report, both *N*-cyclohexyl-, *N*-*n*-butyl- and *N*-*t*-butyl-formamidines were employed, but subsequent reports have focussed on the latter.

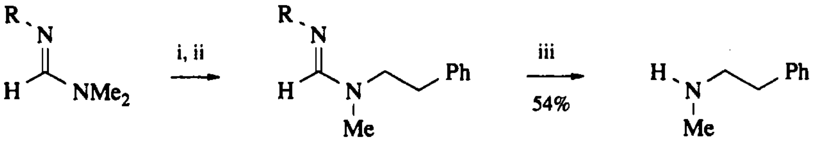

R = cyclohexyl, $Bu^n$, $Bu^t$

i, BuLi, THF, –78 °C; ii, BnBr, iii, HCl, $H_2O$, MeOH

Scheme 5

One aspect of the reactivity of unsymmetrical formamidines such as those shown in Scheme 6 is the selective deprotonation at a benzylic position. This selectivity was used in the illustrated synthesis of nicotine, which also demonstrates the mild conditions for removal of the formamidine activating group by hydrazinolysis.[24]

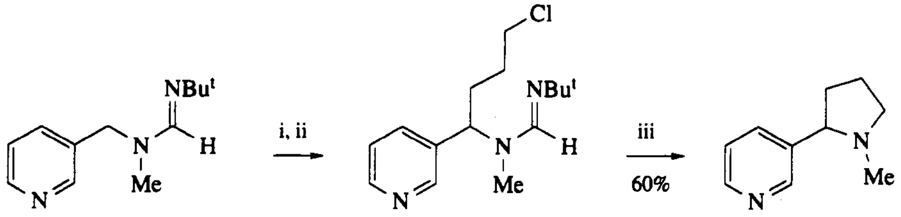

i, BuLi, THF, –78 °C; ii, $I(CH_2)_3Cl$; iii, $N_2H_4$, AcOH, EtOH, r.t.

Scheme 6

### 1.2.2.2 Heterocyclic Systems

Because of the difficulty of removing other activating groups, most of the work since the 1984 review[2] has been done with the formamidine auxiliary. In discussing this chemistry, an important point is that the acidity of the α-protons is considerably enhanced when they are also allylic or benzylic, and their chemistry is also somewhat different. The most important difference is the occurrence of single-electron transfer (SET) processes in the reaction of the lithiated amidines of five-, six- and seven-membered ring saturated heterocycles. For example, reaction of benzophenone with the lithiated piperidine (3), shown in Scheme 7, affords only benzophenone ketyl with no addition.[25] Reaction of (3) with alkyl halides results in low yields of alkylation products such as (5), with an oxidation product (6) being produced as well. That radical processes are involved is suggested by the reaction of (3) with hexenyl bromide,[26] affording a coupling product (5; $R^2$ = cyclopentylmethyl).[25] Conformationally locked systems such as (3; R = Bu<sup>t</sup>) seem less likely to oxidize, and it was suggested that a conformationally mobile system might undergo ring inversion, thus placing the C—Li bond in an electronically unfavorable axial orientation, thereby encouraging SET.[25] Once oxidized, the radical (4) probably produces (6) by disproportionation.

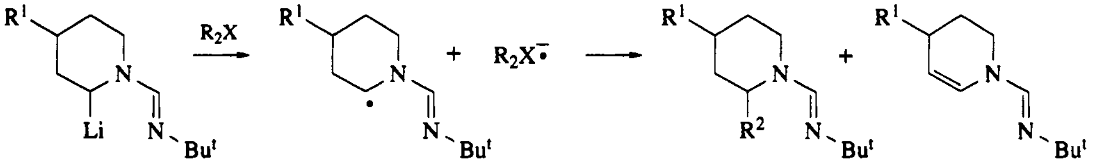

(3) (4) (5) (6)

Scheme 7

Two protocols circumvent, or at least minimize, the SET processes discussed above. One is addition of HMPA to the lithiated formamidines prior to addition of the alkyl halides, while the second is transmetalation to a cuprate.[25] Heterocycles having the C—Li bond in an allylic or benzylic position do not undergo SET at all.

The following discussion is organized by the type of heterocycle being alkylated, beginning with pyrrolidines. Pyrrolidine formamidines, as their pentynyl cuprate derivatives, may be alkylated in good yield;[25] a process for the synthesis of 1-azabicyclic ring systems utilizing this methodology is illustrated in Scheme 8.[27] An analogous process was also reported for piperidine formamidines.

Metalated piperidine amides[22] and formamidines[25] may be converted to α-alkylated piperidines, as illustrated in Scheme 9. Again, the two examples illustrate the superiority of the formamidine moiety in both yield and ease of removal.

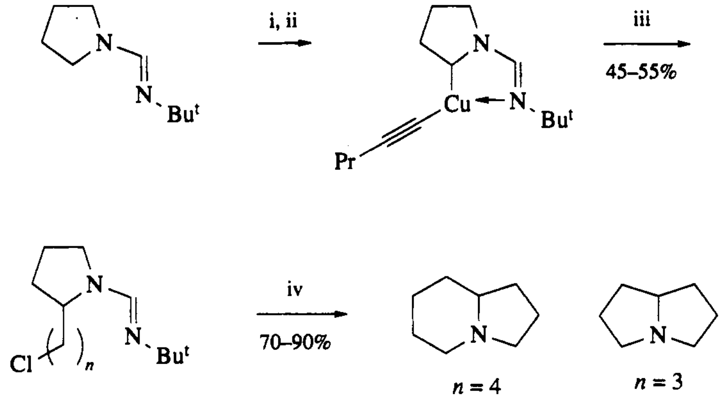

i, Bu$^t$Li, Et$_2$O–THF, –78 to –20 °C, 1 h; ii, PrC≡CCu; iii, I(CH$_2$)$_n$Cl; iv, KOH, MeOH, H$_2$O, 55 °C, 8–12 h

**Scheme 8**

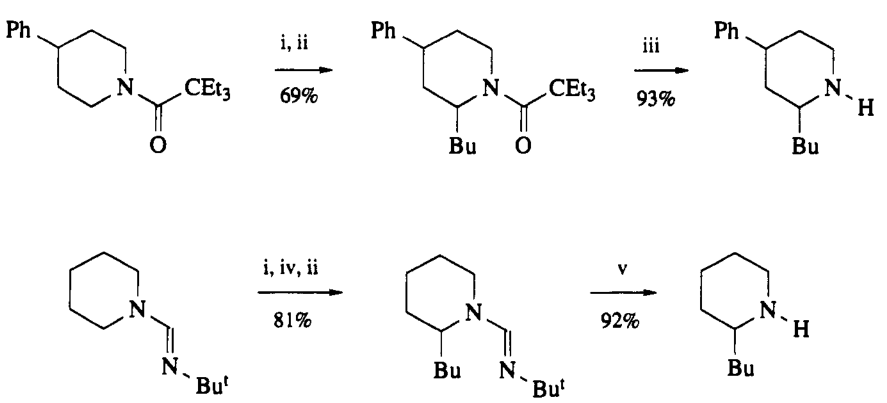

i, Bu$^s$Li, –78 to –25 °C; ii, BuI; iii, HCl, H$_2$O, reflux, 3 d; iv, PrC≡CCu; v, KOH, MeOH, H$_2$O, 8–12 h

**Scheme 9**

An α-substituted piperidine formamidine may be metalated at the α′-position selectively, but the alkylation is not stereoselective, providing a 1:1 mixture of *cis* and *trans* stereoisomers, as illustrated in Scheme 10.[25]

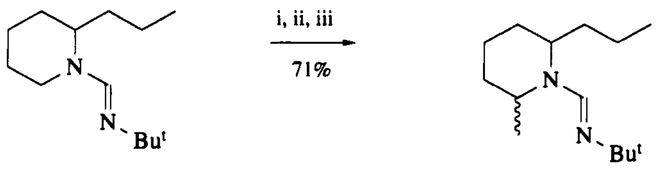

1:1 mixture of isomers

i, Bu$^s$Li, –78 to –25 °C; ii, PrC≡CCu; iii, MeI

**Scheme 10**

When the α-position is allylic, metalation is easier, and the resulting organolithium is not prone to oxidation; γ-substitution then predominates over α-substitution, as shown by the example in Scheme 11.[25]

The stereoelectronic preference of dipole-stabilized organolithiums for the nodal plane of the amide or amidine π-system makes possible the directed metalation of bridgehead positions. Two examples are il-

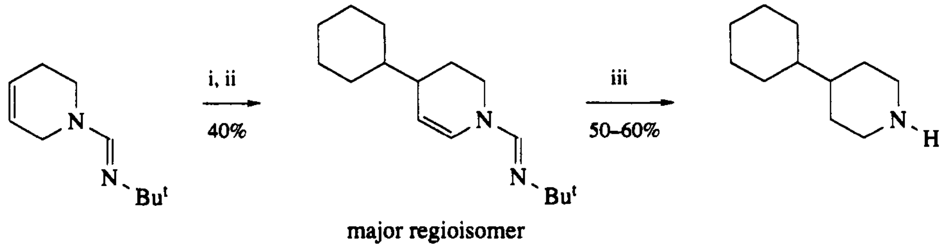

i, Bu$^n$Li, THF, –78 °C; ii, $C_6H_{11}I$; iii, $NaBH_4$, pH 6

**Scheme 11**

lustrated in Scheme 12. In the first, compound (7) is metalated selectively at the bridgehead methine, in preference to the methyl.[28] In the second, the bridgehead methine that is bisbenzylic is preferentially deprotonated.[29] The second example is the key step in the synthesis of the anticonvulsant agent MK-801; similar reactions afford access to a number of structural analogs.

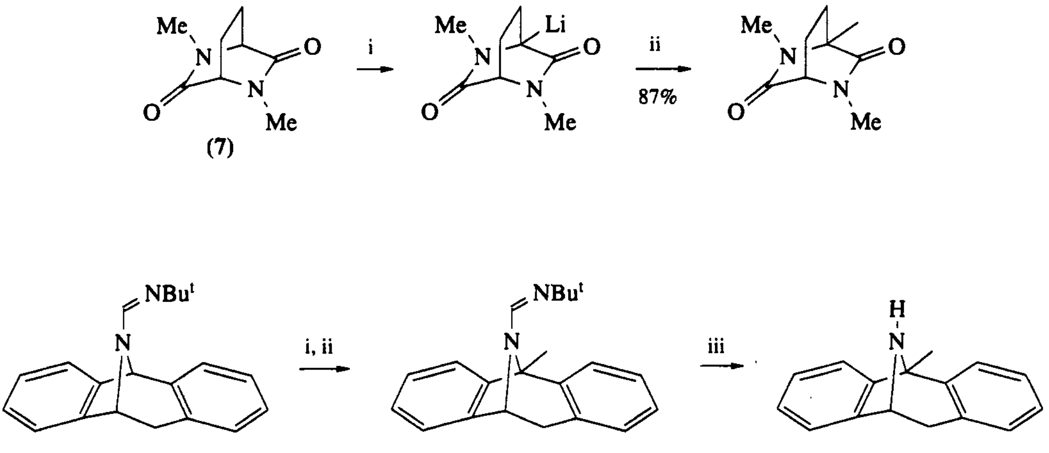

(7)

MK-801

i, BuLi, THF, –78 °C; ii, MeI; iii, KOH, $HO(CH_2)_2OH$ or $H_2SO_4$, EtOH

**Scheme 12**

In 1981, several papers appeared detailing the alkylation of the 1-position of tetrahydroisoquinolines through the intermediacy of lithiated amides[30,31] phosphoramides,[32,33] and formamidines.[34] These systems are discussed thoroughly in Beak's 1984 review,[2] and so we will only provide one illustration of each in Scheme 13.

More recently, an ingenious 'one-pot' procedure for the activation, alkylation and deactivation sequence was reported by Katritzky.[35] Reaction of tetrahydroisoquinoline with *n*-butyllithium followed by carbon dioxide affords the lithium carbamate (**8**), which can be further metalated with *t*-butyllithium and alkylated, as shown in Scheme 14.

Both tetrahydroisoquinoline amides[31] and formamidines[34] may be successively alkylated at the 1-position. The second deprotonation is somewhat less facile, however, since it entails removal of a methine proton. In applying this methodology to the synthesis of naturally occurring tetrahydroisoquinoline alkaloids, a problem is encountered. The presence of oxygen substituents on the aromatic ring destabilizes the benzylic carbanion, and since this effect is felt in the transition state, the acidity of the benzylic protons is lowered. Thus, successive alkylation of *t*-butylformamidines of oxygenated tetrahydroisoquinolines is not possible. To circumvent the decreased acidity, a study of the relative acidity of various *N*-substituted formamidines was done[36] that resulted in a solution to the problem.[37] As shown in Scheme 15, successive alkylation of the methoxymethylphenylformamidine (**9**) is readily achieved.

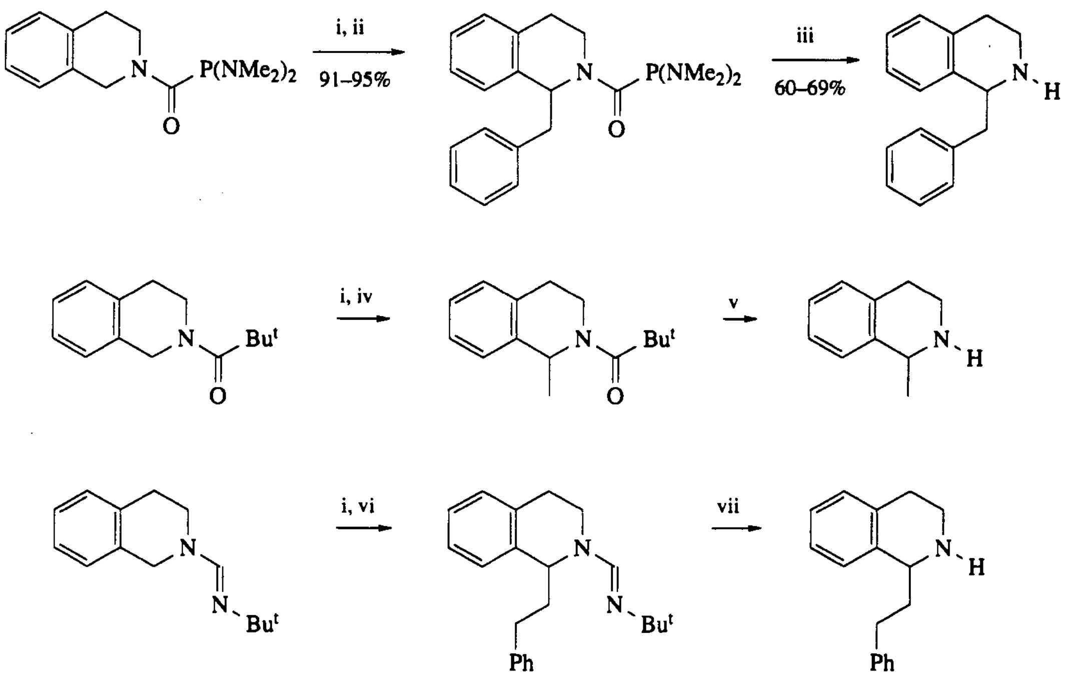

i, BuLi, THF, –78 °C; ii, BnCl; iii, HCl, MeOH, $H_2O$, reflux; iv, MeI; v, Red-Al, $C_6H_6$; vi, $Ph(CH_2)_2Br$; vii, KOH, MeOH, $H_2O$, reflux

**Scheme 13**

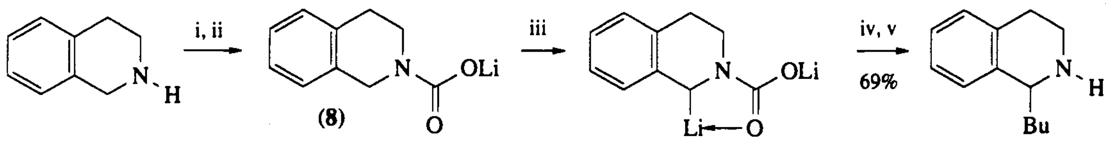

i, $Bu^nLi$, THF; ii, $CO_2$; iii, $Bu^tLi$, –20 °C; iv, BuI; v, 2 M HCl

**Scheme 14**

In 1982, Meyers extended the formamidine methodology to the elaboration of β-carbolines.[38] The indole nitrogen of the β-carboline is protected as either its MOM derivative[38] or its potassium salt.[39] The latter method was used in the short synthesis of (±)-yohimbone illustrated in Scheme 16.[40]

Finally, formamidines may be used to mediate the alkylation of perhydroazepines, as illustrated in Scheme 17.[25] As was the case with alkylation of the saturated heterocycles above, transmetalation to a cuprate or addition of HMPA was necessary to preclude SET reactions.

## 1.2.3 HOMOCHIRAL PRECURSORS

### 1.2.3.1 Mechanistic Aspects

The vast majority of stereoselective reactions in organic chemistry, especially in asymmetric synthesis, involve diastereofacial differentiation of a trigonal, $sp^2$-atom. The stereoelectronic considerations outlined in the introduction to this chapter afford a rare opportunity in stereoselective synthesis: the preparation of a chiral organometallic in which the carbon bearing the metal is stereogenic. As a result of the

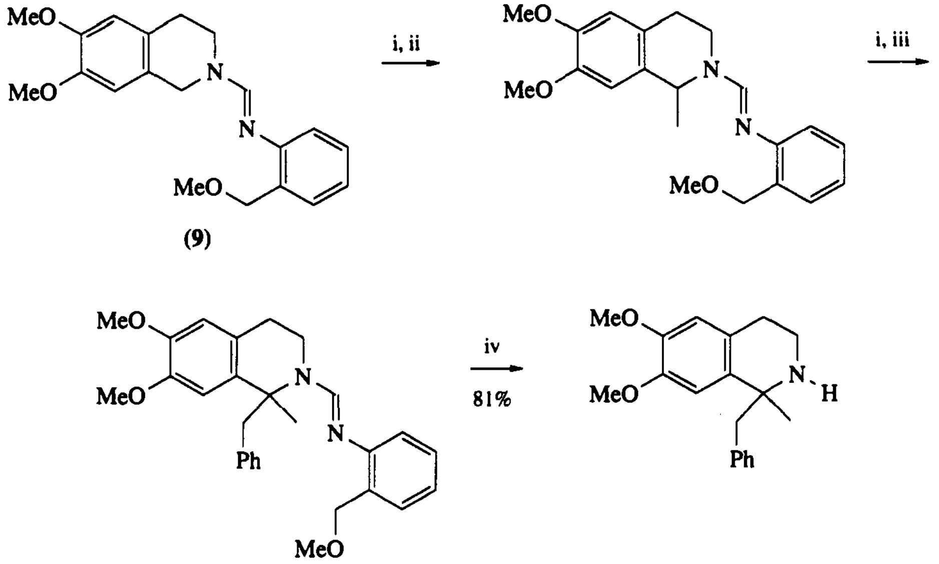

(9)

i, $Bu^nLi$, THF, −78 °C; ii, MeI, −100 °C; iii, BnX; iv, $N_2H_4$, EtOH, $H_2O$, AcOH, reflux

**Scheme 15**

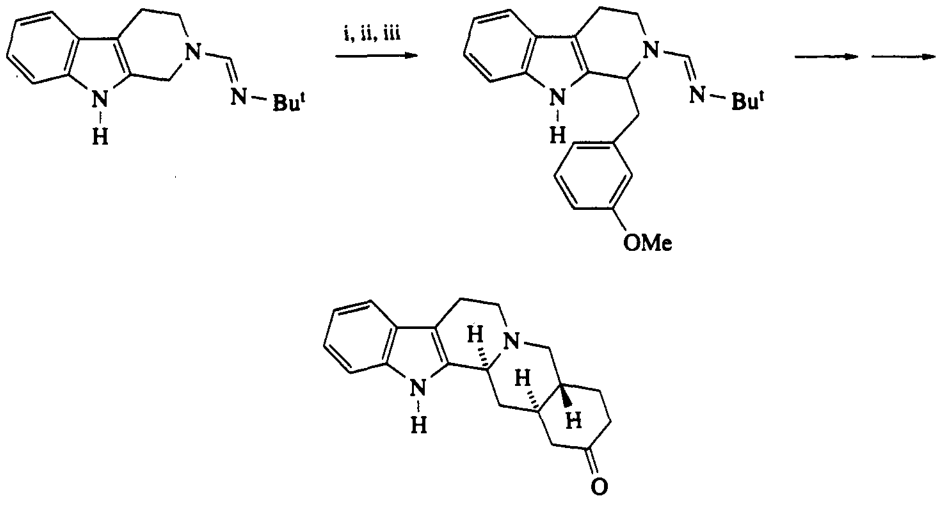

Yohimbone; 38% overall

i, KH, THF; ii, $Bu^tLi$, −78 °C; iii, $ArCH_2Cl$

**Scheme 16**

tendency of the carbon–metal bond of a dipole-stabilized organometallic to orient in the nodal plane of the amide (or amidine) π-system, the carbanion retains $sp^3$-geometry, as illustrated above in Figure 2.

When the precursor is achiral, two enantiomeric dipole-stabilized organolithiums may be formed. On the other hand, if the precursor is chiral, the two organolithiums are diastereomeric (Figure 3), and of unequal energy. The chirality center of the substrate may in principle be anywhere in the molecule, but the examples reported to date all have the stereocenter immediately adjacent to one end or the other of the amide group. Thus, the stereogenic carbon bearing the lithium may be influenced by an existing stereocenter either three or five atoms distant.

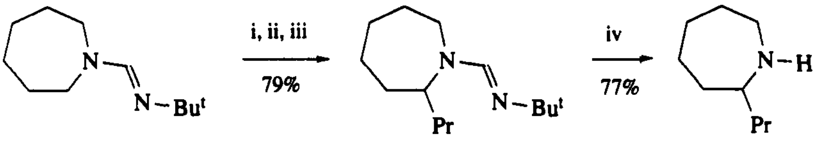

i, Bu$^t$Li, THF, −78 to −20 °C; ii, PrC≡CCu; iii, PrI; iv, KOH, MeOH, $H_2O$

Scheme 17

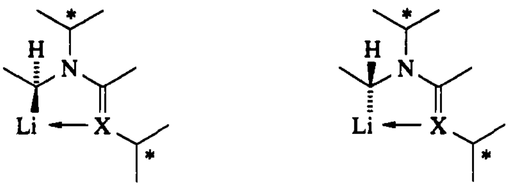

X = O, N; * = stereocenter

**Figure 3** Diastereomeric dipole-stabilized organolithium compounds

There are two steps in the overall alkylation process: (i) deprotonation of diastereotopic protons; and (ii) electrophilic attack on the intermediate dipole-stabilized organolithium(s). Either of these processes might, in principle, be the source of the diastereoselectivity observed in the overall process. *Ab initio* studies suggest that the barrier to inversion for a free dipole-stabilized anion is 16–18 kcal mol$^{-1}$,[15] and that the *syn* lithiated species is 28 kcal mol$^{-1}$ more stable than the *anti* (Figure 2).[16] Thus, in the absence of other functionality, the two diastereomers shown in Figure 3 do not invert. Because the stereoelectronic effects of dipole stabilization are felt in the transition state for deprotonation of conformationally locked piperidines, the equatorial proton is removed selectively in both amides[11,12] and amidines,[25] as shown in Scheme 3 above. Note also that prior coordination of the alkyllithium base promotes selective removal of the equatorial proton *syn* to the amide oxygen or amidine nitrogen by a complex-induced proximity effect.[41] In a conformationally mobile piperidine having an oxazoline chiral auxiliary, the selective removal of the equatorial proton from one of two chair conformers has been postulated to explain the formation of a single diastereomer of alkylation product, as shown in Scheme 18.[42]

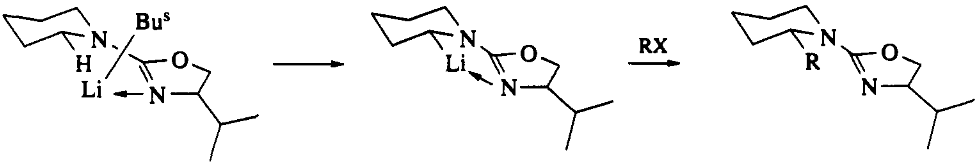

Scheme 18

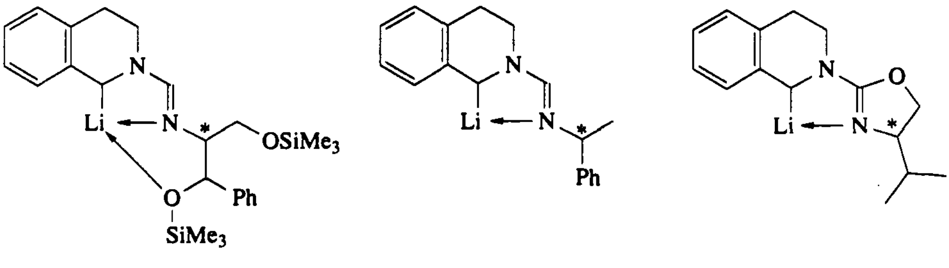

| | (a) | (b) | (c) |
|---|---|---|---|
| Selectivity at −78 °C | 9:1 | 1.2:1 | 9:1 |

**Figure 4** Chiral auxiliaries for isoquinoline alkylation

Virtually all of the synthetic applications of chiral dipole-stabilized organolithiums reported to date have the C—Li bond in an allylic or benzylic system. The most important consequence of this fact is that the two stereoisomers shown in Figure 3 *can interconvert* by pyramidal inversion. Therefore, the stereoselectivity of the deprotonation is irrelevant to the stereoselectivity as manifested in the product diastereomer ratio.[43] The source of the selectivity in the organolithium alkylation step has not been determined. The available data do not permit a distinction between at least three possibilities: thermodynamic control as determined by the equilibrating organolithium diastereomers,[43,44] kinetic control according to Curtin–Hammett kinetics,[45] or increased carbon–lithium covalency at low temperature.[46]

The seminal paper on the stereoselective alkylation of chiral dipole-stabilized organolithiums appeared in 1983. In the preliminary communication[47] and the full paper which followed,[48] Meyers made the important observation that formamidines lacking an oxygen atom in the auxiliary afford poor selectivity. The mechanistic rationale originally provided[47] for this observation was later revised.[49,50] The current picture can be explained by comparison of the structures illustrated in Figure 4. In (a), the dipole-stabilized organolithium is internally chelated by both the nitrogen and the oxygen of the formamidine, an effect which prevents rotation around the bond from the chelating formamidine nitrogen to the stereocenter (*).[47] In (b), this bidentate chelation is absent and free rotation diminishes the efficient transfer of stereochemical information and poor stereoselection ensues. In (c), free rotation is again precluded, this time by incorporation of the stereocenter into an oxazoline ring.[42,43,51]

There is another important feature of these systems to keep in mind: the effect of alkylation temperature on the diastereomer ratio. The selectivity observed in the alkylation of the tetrahydroisoquinoline formamidine illustrated in Figure 4(a) (with methyl iodide) increases from 9:1 to 99:1 when the temperature is lowered from –78 to –100 °C.[47,48] Similarly, the selectivity with the oxazoline illustrated in Figure 4(c) (with methyl iodide) increases from 9:1 at –78 °C to 19:1 at –100 °C.[43,51]

One last effect is seen in alkylations of chiral isoquinoline derivatives: the effect of oxygen substitution on the aromatic nucleus.[43] When electron-donating oxygen substituents are present in the 6- and/or 7-positions of the tetrahydroisoquinoline, the stereoselectivity of the alkylations is increased. This may be interpreted as a decreased tendency of the benzylic carbanion to be delocalized into the ring, and a consequential increase in the importance of dipole stabilization, with its strict stereoelectronic requirements.

### 1.2.3.2 Acyclic Systems

Whereas acyclic stereoselection in enolate alkylations is now a relatively mature field,[52] the stereoselective alkylation of acyclic dipole-stabilized systems is virtually undeveloped. The only report to date

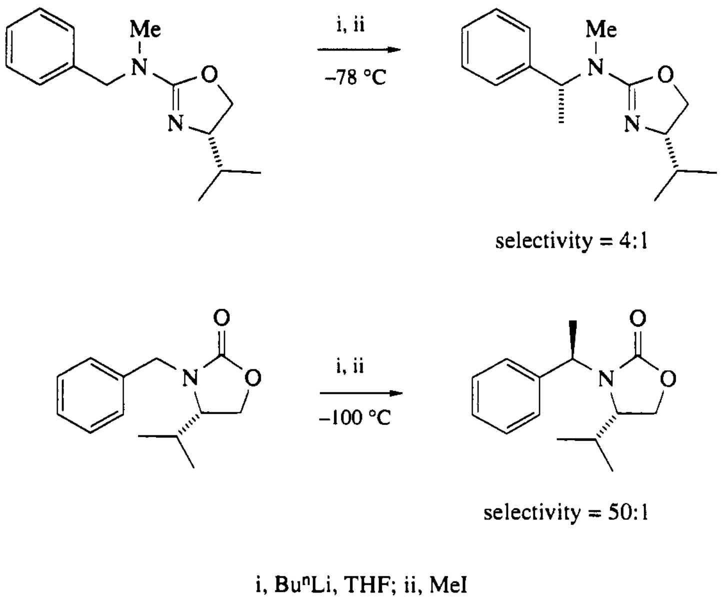

Scheme 19

originates from our own laboratories.[53] We made a comparison between two systems having the existing stereocenter on either end of the amide/amidine function (*cf.* Figure 3). The pertinent results are shown in Scheme 19. In the first instance, the stereocenter is in a chiral auxiliary appended to *N*-methylbenzylamine, and is a case of 1,5-asymmetric induction. Not surprisingly, the selectivity is poor (4:1), although the absolute configuration of the new stereocenter is the same as the well-studied[43] tetrahydroisoquinolyloxazolines (*vide infra*). The second example moves the stereocenter to the other end of the amide system (1,3-asymmetric induction, *cf.* Figure 3), and the selectivity is improved dramatically to 50:1.[53]

The second example has been used in a stereoselective synthesis of α-alkylbenzylamines, as shown by the example illustrated in Scheme 20.[53] Note that this sequence destroys the existing stereocenter. Because the original stereocenter is deliberately destroyed after the creation of a new one, the overall process constitutes a 'self-immolative chirality transfer'.[54]

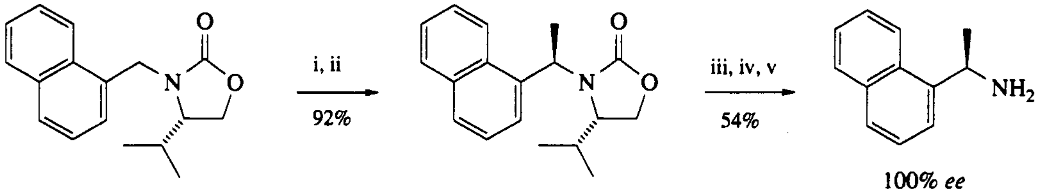

i, $Bu^nLi$, −78 °C; ii, MeI, −100 °C; iii, KOH, ether; iv, $Pb(OAc)_4$, $CH_2Cl_2$, MeOH; v, HCl, EtOH

Scheme 20

### 1.2.3.3 Heterocyclic Systems

The following discussion is organized according to the type of heterocycle being alkylated, as follows: dehydropyrrolines and isoindolines, followed by dehydropiperidines, tetrahydroisoquinolines and β-carbolines. As mentioned previously, the alkylation of saturated heterocycles (the acidic protons being neither allylic nor benzylic) is problematic. Either they fail to metalate when the nitrogen contains a

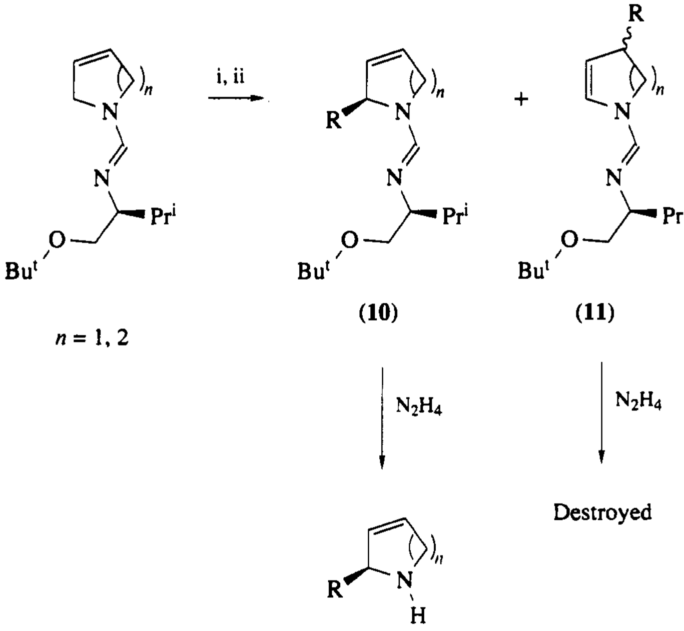

i, $Bu^nLi$, −78 °C; ii, RX, −100 °C

Scheme 21

chiral formamidine auxiliary,[55] or they fail to undergo cross-coupling after metalation when the nitrogen contains a chiral oxazoline auxiliary.[42] In the latter instance, SET processes predominate.

These shortcomings have been circumvented by using a heterocycle containing a double bond, as illustrated by the examples in Scheme 21. As was the case with the achiral systems (*cf.* Scheme 11), a mixture of regioisomers is obtained, but now the α-substitution product (**10**) predominates. The amount of γ-substitution product (**11**) produced depends on the ring size, and may be as high as 30% of the product mixture for the dehydropiperidines.[55] Nevertheless, the unwanted γ-isomer (**11**) is destroyed chemoselectively when the mixture is treated with hydrazine to remove the chiral auxiliary. Double bond reduction would then give the α-alkylated saturated heterocycle.

The asymmetric alkylation of $\Delta^2$-pyrroline has been used in the synthesis of anisomycin in 90% *ee* using a formamidine chiral auxiliary, as shown in Scheme 22.[56]

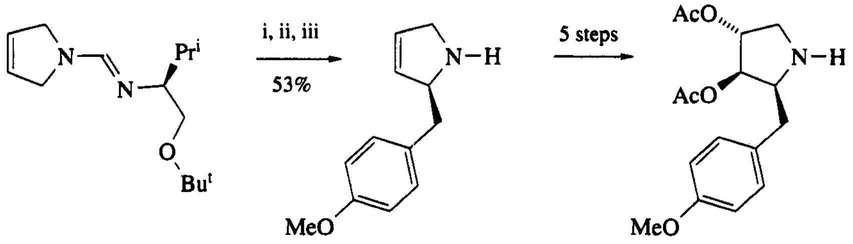

i, $\mathrm{Bu^tLi}$, THF, −78 °C; ii, $\mathrm{ArCH_2Cl}$, −100 °C; iii, $\mathrm{N_2H_4}$, AcOH, EtOH

**Scheme 22**

An oxazoline auxiliary has been used to alkylate stereoselectively and regioselectively isoindoline at the α- and α′-positions to produce the $C_2$-symmetric amine (**12**), as shown in Scheme 23.[57]

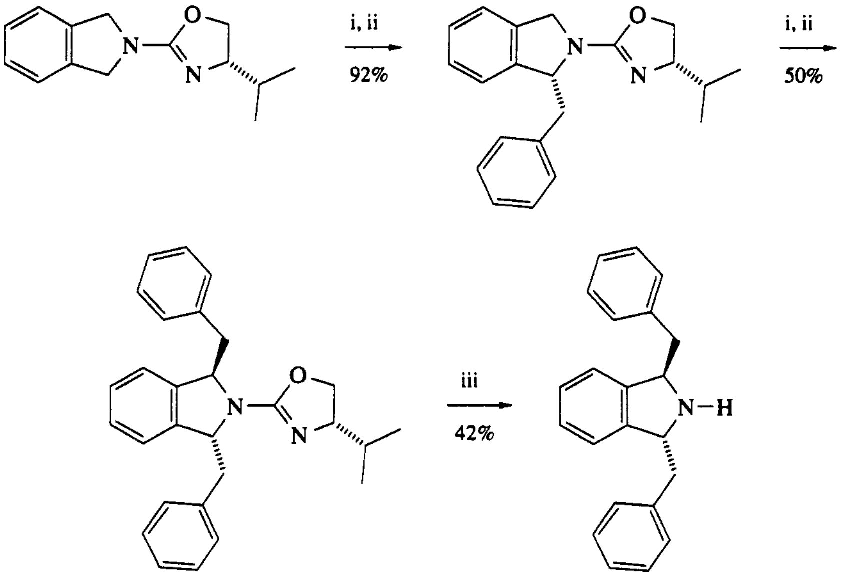

(**12**) 100% *ee*

i, $\mathrm{Bu^nLi}$, −78 °C, THF; ii, BnCl; iii, $\mathrm{N_2H_4}$, *p*-TsOH, EtOH, reflux

**Scheme 23**

Scheme 24 illustrates the use of a formamidine auxiliary for asymmetric alkylation of dehydropiperidine derivatives in the synthesis of metazocine[55] and dextrorphan[58] in 98% and 99% *ee*, respectively.

The enormous number of naturally occurring isoquinoline alkaloids, and their importance biologically,[59] has stimulated a great deal of effort in their synthesis. The asymmetric alkylation of the 1-position of the tetrahydroisoquinoline nucleus affords an extremely valuable method for the construction of

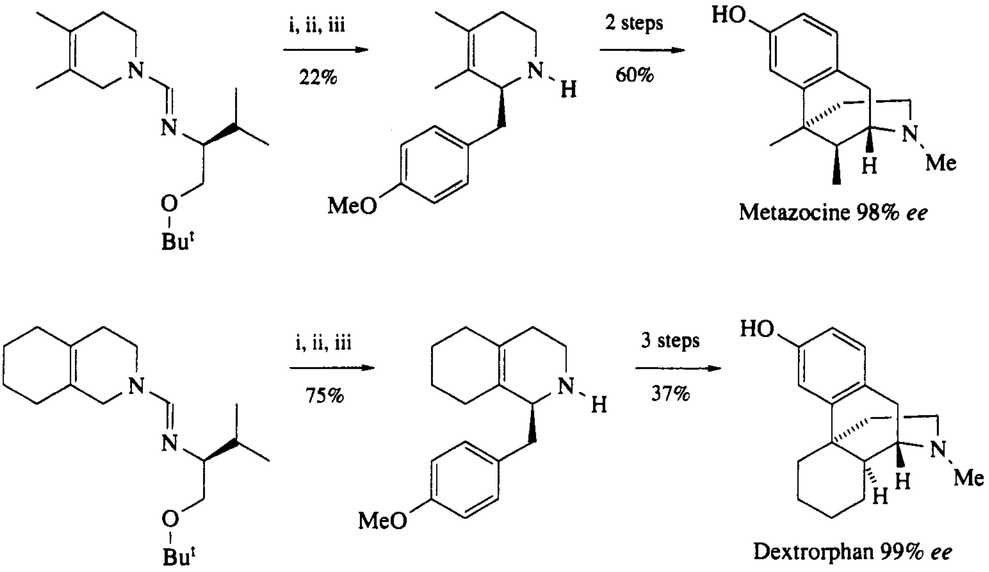

i, Bu$^n$Li, –78 °C; ii, ArCH$_2$Cl, –100 °C; iii, N$_2$H$_4$, AcOH

**Scheme 24**

both simple and complex isoquinoline alkaloids by the simple retrosynthesis illustrated in Figure 5. The following discussion presents selected examples of the synthesis of simple isoquinoline alkaloids, followed by a few examples of the use of this method for the synthesis of key intermediates in the preparation of more complex systems.

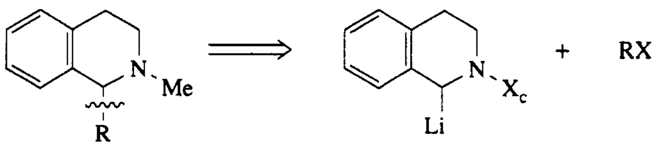

**Figure 5** Retrosynthesis of simple isoquinoline alkaloids

Perhaps the simplest of the isoquinoline alkaloids is salsolidine. It has been synthesized by asymmetric alkylation of 6,7-dimethoxytetrahydroisoquinoline using either a formamidine[60,61] or oxazoline[51] chiral auxiliary. Scheme 25 illustrates the recently published *Organic Syntheses* preparation of salsolidine on a 5 g scale.[62] It is of interest to note that, in this and all subsequent examples of asymmetric alkylation of tetrahydroisoquinolines, formamidines derived from L-valine afford (1*S*)-tetrahydroisoquinolines, while oxazolines derived from L-valine afford the (1*R*)-enantiomer. The reason is simply the opposite orienta-

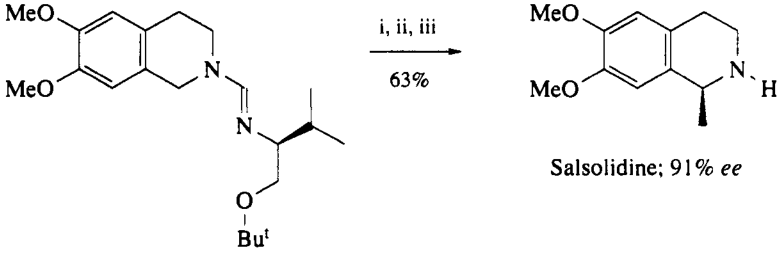

i, Bu$^t$Li, THF, –78 °C; ii, MeI, –100 °C; iii, N$_2$H$_4$, AcOH, EtOH

**Scheme 25**

tion of the isopropyl group in the two auxiliaries. In the lithiated formamidine, bidentate chelation by both heteroatoms places the isopropyl on the β-face, whereas it is on the α-face in the oxazolines.

The stereoselective alkylation of tetrahydroisoquinoline pivalamides containing a stereocenter at the 3-position was reported in 1987 by Seebach.[63] The self-immolative chirality transfer process illustrated in Scheme 26 affords only one diastereomer. Oxidative decarboxylation and reduction afford the alkylation products in ≥95% *ee*.

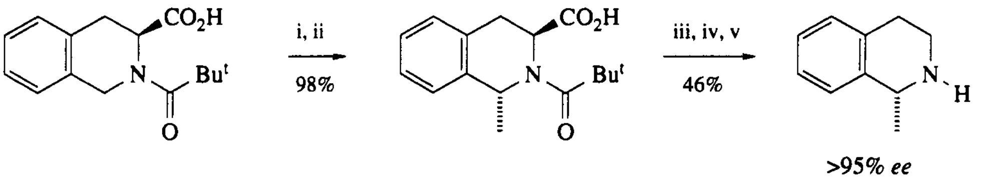
CO2H
N
But
O
i, ii
98%
CO2H
N
But
O
iii, iv, v
46%
N
H
>95% ee

i, 2 Bu$^t$Li, THF, –75 °C; ii, MeI; iii, anode, MeOH; iv, NaCNBH$_3$; v, NaAlH$_4$

**Scheme 26**

The alkylation of the tetrahydroisoquinoline nucleus, mediated by a formamidine auxiliary, with a dimethoxyphenethyl iodide has afforded (*S*)-homolaudanosine in 95–96% *ee*, as shown in Scheme 27.[60,61]

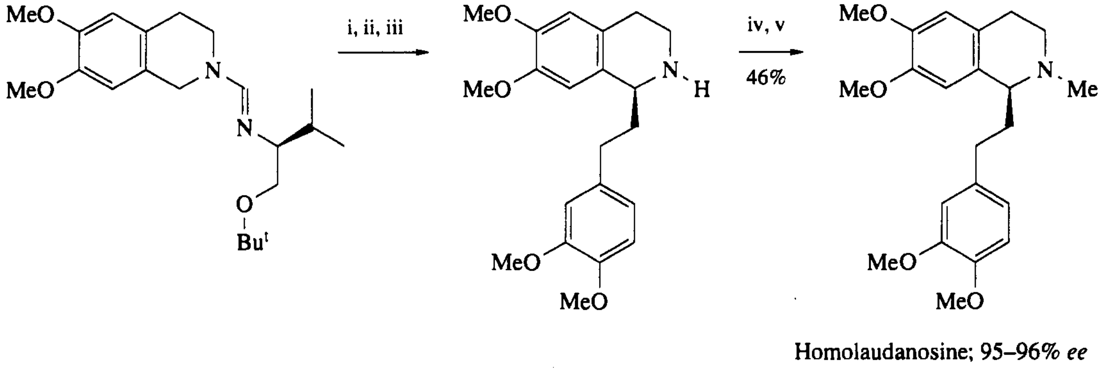
MeO
MeO
N
N
O
But
i, ii, iii
MeO
MeO
N
H
MeO
MeO
iv, v
46%
MeO
MeO
N
Me
MeO
MeO
Homolaudanosine; 95–96% ee

i, Bu$^t$Li, THF, –78 °C; ii, Ar(CH$_2$)$_2$I, –100 °C; iii, N$_2$H$_4$, AcOH; iv, HCO$_2$Et; v, LiAlH$_4$

**Scheme 27**

Reticuline, the biosynthetic precursor of all the morphine alkaloids, was synthesized by a similar approach (97% *ee*), as shown in Scheme 28.[64]

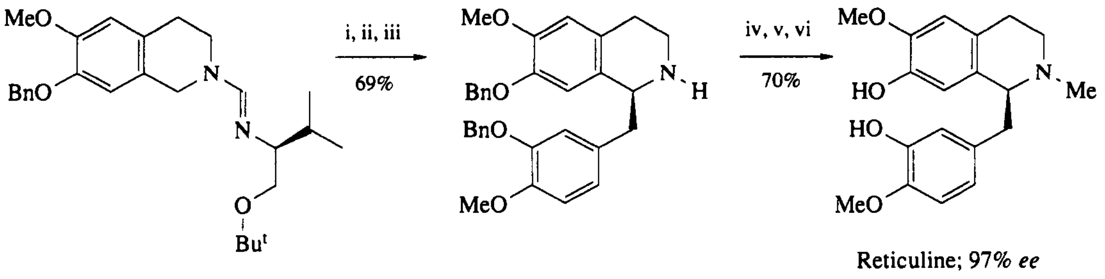
MeO
BnO
N
N
O
But
i, ii, iii
69%
MeO
BnO
N
H
BnO
MeO
iv, v, vi
70%
MeO
HO
N
Me
HO
MeO
Reticuline; 97% ee

i, Bu$^t$Li, THF, –78 °C; ii, ArCH$_2$Br, –100 °C; iii, N$_2$H$_4$, AcOH, EtOH; iv, ClCO$_2$Et; v, LiAlH$_4$; vi, H$_2$, Pd/C

**Scheme 28**

Another benzylisoquinoline alkaloid, laudanosine, is the synthetic precursor of morphinans. It has been synthesized in 95–96% *ee* by asymmetric alkylation of an isoquinolyloxazoline, as shown in Scheme 29.[43,65] An interesting point here is the discovery of a shortcut for removing the auxiliary and

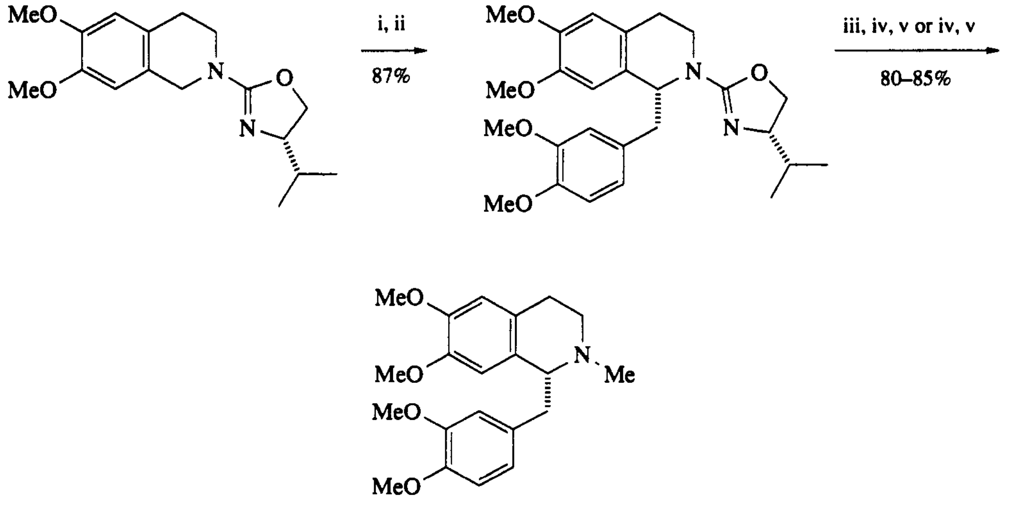

Laudanosine; 94–96% *ee*

i, Bu$^t$Li, THF, –78 °C; ii, ArCH$_2$Cl, –100 °C; iii, $N_2H_4$•$H_2O$, *p*-TsOH, EtOH; iv, $HCO_2COMe$; v, $LiAlH_4$

**Scheme 29**

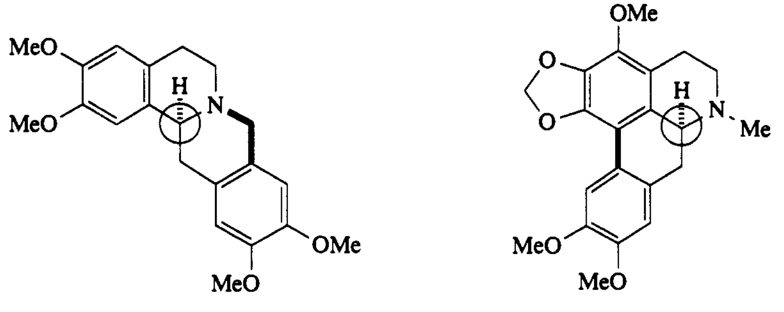

Norcoralydine; 99% *ee*

Octoeine; 93% *ee*

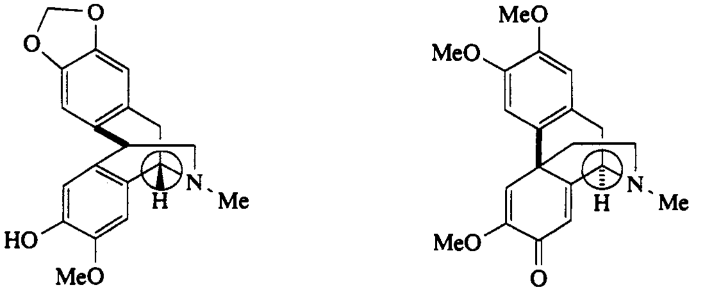

Reframoline; 98–99% *ee*

*O*-Methylflavinantine; 94–96% *ee*

**Figure 6** Complex isoquinoline alkaloids synthesized by elaboration of simple benzylsoquinolines. The bond(s) formed after the asymmetric alkylation are bold; the stereocenter created in the asymmetric alkylation is circled

methylating the nitrogen. Treatment of the alkylated isoquinolyloxazoline with acetic formic anhydride removed the oxazoline and formylated the nitrogen in a single operation.[65]

Because benzylisoquinolines have been available synthetically (in racemic form) for decades, there is quite a bit of chemistry known regarding their use as key intermediates in the synthesis of a number of more complex isoquinoline alkaloids. The asymmetric synthesis of benzylisoquinolines has been used to complete total synthesis of representative members of several of these alkaloid classes. As shown in Figure 6, the protoberberine alkaloid norcoralydine,[60,61] the aporphine alkaloid ocoteine,[61,66] the isopavine alkaloid reframoline[61] and the morphinan *O*-methylflavinantine[65] have been made available in optically active form for the first time (except by isolation or resolution) using this approach.

The asymmetric alkylation of the β-carboline ring system affords access to indole alkaloids. The simplest is tetrahydroharman, whose synthesis is mediated by asymmetric alkylation of a formamidine, as shown in Scheme 30.[67] In the racemic series (*cf.* Scheme 16), the indole nitrogen may be protected simply by deprotonation with potassium hydride. However, in the chiral series the presence of a potassium ion lowers the selectivity. Thus, the methoxymethyl protecting group was used.

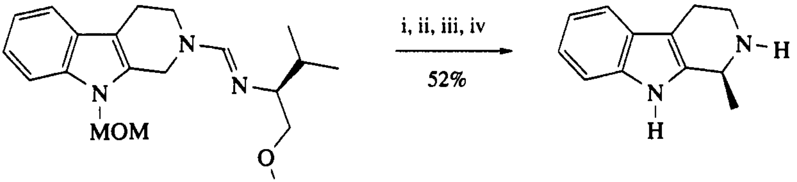

Tetrahydroharman; 98% *ee*

i, Bu$^n$Li, THF, –78 °C; ii, MeI, –100 °C, iii, $N_2H_4$, AcOH; iv, $H^+$

Scheme 30

The asymmetric alkylation of the β-carboline formamidine was also used in the asymmetric synthesis of deplancheine in 96% *ee* (Scheme 31), a synthesis which served to correct the previously assigned absolute configuration of the natural product.[68]

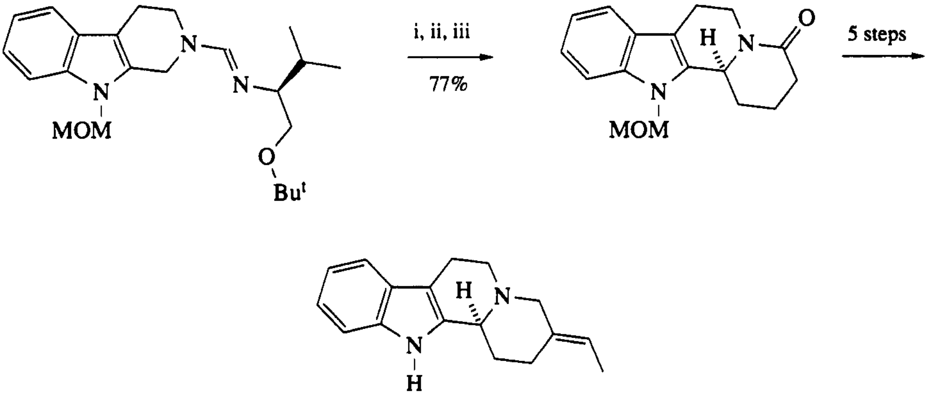

Deplancheine; 96% *ee*

i, Bu$^n$Li, THF, –78 °C; ii, $Br(CH_2)_3OBO$; iii, $N_2H_4$, $H^+$

Scheme 31

A similar approach was used for the asymmetric synthesis of yohimbone,[40] a process that uses the stereocenter created by asymmetric alkylation as the control element for the stereoselective formation of two more stereocenters, as shown in Scheme 32.

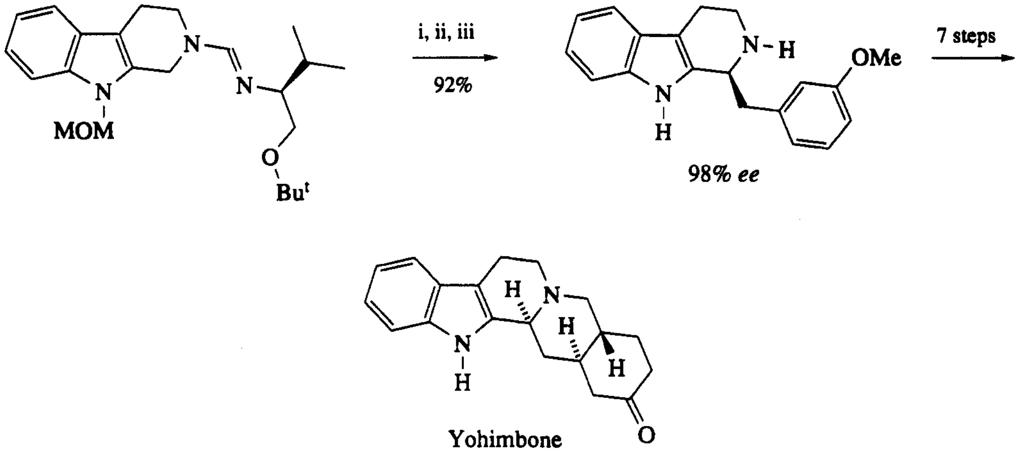

i, Bu$^n$Li, THF, –80 °C; ii, ArCH$_2$Cl, –80 °C; iii, N$_2$H$_4$, H$^+$

Scheme 32

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## 1.3

# Alkylations of Sulfur- and Selenium-containing Carbanions

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## 1.3.1 INTRODUCTION

α-Thio organometallics[1–44] and their seleno analogs[1,3-6,10,11,17,18,23,25,45-56] have proved to be extremely useful reagents and they have been used extensively in synthesis over the past 20 years. Upon reaction with compounds bearing an electrophilic carbon atom, they allow the efficient formation of a new carbon–carbon bond to which the heteroatomic moiety is directly linked. The large variety of reactions possible through use of organosulfur and organoselenium reagents with subsequent selective removal of the heteroatomic moiety permits the synthesis of a large variety of compounds.

This chapter is devoted exclusively to the alkylation of the above mentioned organometallic reagents with alkyl halides, epoxides and oxetanes. It includes a large variety of organosulfur- and organoselenium-stabilized carbanions derived from saturated and unsaturated sulfides, selenides, sulfoxides, selenoxides and sulfones as well as those carbanions bearing another heteroatomic moiety. The chapter excludes, however, those organometallics which can be viewed as α-thio and α-seleno enolates.

Although α-thio and α-seleno organometallics can be prepared by a large array of reactions[4,23,57] which are listed in Scheme 1 and involve: (i) hydrogen–metal exchange, (ii) halogen–metal exchange, (iii) addition of organometallics on α-heterosubstituted carbon–carbon double bonds, and (iv) heteroatom (Sn,Se)–metal exchange, the first reaction has proved to be by far the most convenient due to the availability of the starting material and of a large array of bases.

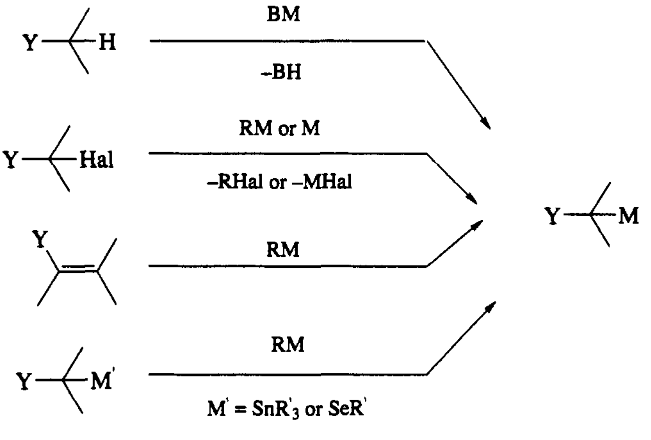

**Scheme 1**

Butyllithiums in THF (often without an additive, and in some cases with the help of a complexing agent such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA),[58] diazabicyclooctane (DABCO),[59] hexamethylphosphoramide (HMPA),[60] and crown ethers) have been used successfully for the metallation of sulfides such as dimethyl sulfide,[58] methyl phenyl[59] and primary alkyl phenyl sulfides,[60,61] cyclopropyl phenyl sulfide,[17,25,61] as well as allyl,[14,16,24] benzyl[14,16] and vinyl sulfides,[20] thioacetals,[20,26,27,30] sulfoxides,[14,16,32,33] sulfones[36,37] and sulfoximides (sulfoximines).[62] However these bases are not able to metallate *s*-alkyl sulfides, due to their low acidity,[60] or sulfonium salts[41] (except Bu$^t$Li in some cases) or almost all selenium derivatives[23,25,52,54] due to their high propensity to react at the sulfur and selenium atoms respectively of these compounds. The last reaction which leads finally in the case of selenides to a butyl selenide and to a novel organometallic, the one possessing the most stabilized carbanionic center, (Scheme 2) is the method of choice[23,25,46,52,54] for the synthesis of a large variety of α-selenoorganolithium compounds.

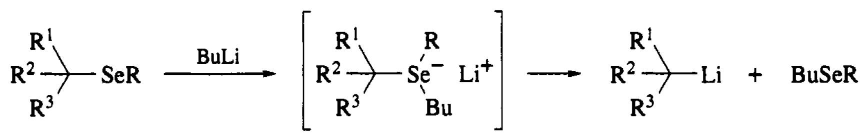

**Scheme 2**

Thus, α-selenoalkyllithiums[23,25,45,47,54,63–75] (see Volume 1, Chapter 2.6), α,α-di(seleno)alkyllithiums[64,65,76–78] as well as related α-selenobenzyl-,[72,79,80] α-selenoallyl-[81] and α-selenovinyl-lithiums[82,83] belonging to the phenyl- and the methyl-seleno series have been successfully synthesized from the corresponding selenoacetals,[64,74,84–87] selenoorthoesters[64,65,76] and keteneselenoacetals[88–90] respectively using *n*-butyllithium in THF or *s*-butyllithium in ether. The Se/Li exchange method has also proved to be particularly efficient for the synthesis of α-thioalkyllithiums including those which possess dialkyl-substituted carbanionic centers from mixed S,Se acetals.[68,69,73,91–93]

α-Selenoallyl-,[81,94–101] α-selenopropargyl-,[102,103] α-selenoallenyl-[103] and α-selenobenzylmetals,[74,80,104–106] 1,1-di(seleno)alkylmetals,[64,74,76,107,108] 1,1-di(seleno)benzylmetals,[80] and α-selenovinylmetals[107–111] have been produced by metallation of the corresponding carbon acid with metalloamides. Although lithium diethylamide, lithium diisobutyramide, lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LITMP) in THF or THF–HMPA have been used for that purpose, KDA[80,108] (a 1:1 mixture of LDA and potassium *t*-butoxide) has proved to be by far the most suitable base for this purpose. However the metallation reaction is strictly limited (except rare cases) to the arylseleno series and does not apply to their methylseleno analogs; hence the method employing the Se/Li exchange is preferred. The metallation reaction is the only reasonable route to α-metalloalkyl selenoxides,[112–115] α-metallovinyl selenoxides,[107] α-metalloalkyl sulfonium salts,[41] α-metalloalkyl selenonium salts[116,117] and α-metalloalkyl selenones.[117–119]

Successful alkylation or hydroxyalkylation of the above mentioned species requires that these organometallics, which are potential carbenoids: (i) do not decompose to carbene or to an isomeric organometallic under the conditions required for their reactions with electrophiles; and (ii) that they act as nucleophiles rather than as bases. This has effectively proved to be the case for most of them.

As will be discussed later in this chapter, although the alkylation reaction is in almost all cases reasonably successful with methyl iodide and primary alkyl halides, ethylene oxide and terminal epoxides, it is

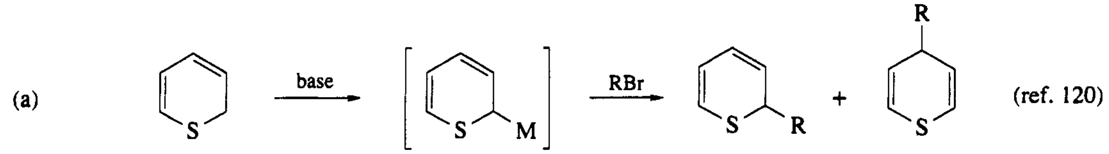

| *Base* | *R* | *Yield (%)* | *Product ratio* |
|---|---|---|---|
| $KNH_2/NH_3$ | c-$C_6H_{11}$ | 82 | 85:15 |
| $KNH_2/NH_3$ | $Bu^t$ | 54 | 100:0 |
| LDA, THF–HMPA | $Bu^t$ | 31 | 100:0 |

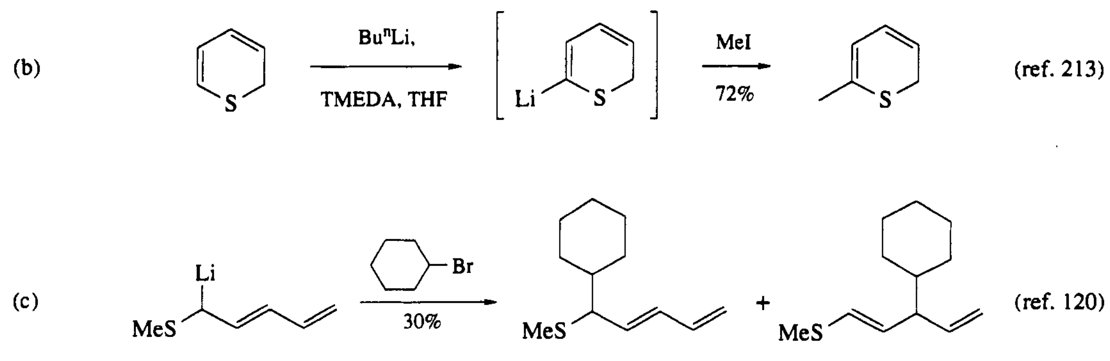

product ratio not given

**Scheme 3**

less general with *s*-alkyl halides and α,β-disubstituted epoxides and is exceptional with tertiary alkyl halides[120] (Scheme 3, entries a and c) and almost unprecedented with tetraalkyl-substituted oxiranes.

The alkylation reaction has proved to be more efficient with the softer organometallics of the series and proceeds *via* an ionic pathway, and *via* radical species with the most substituted alkyl halides.[120,121] Although alkyl iodides are usually more reactive than the corresponding bromides and chlorides, the use of the former compounds does not seem to be crucial.

Allylation and benzylation reactions usually take place more efficiently than alkylation reactions due to the higher reactivity of the former derivatives. Allylation and benzylation is however difficult with the hardest organometallics of the series such as seleno- or thio-alkyllithiums. Finally, alkyl halides are usually less reactive towards α-thio- and α-seleno-alkyllithiums than aldehydes or ketones (see Scheme 11)[25,122] which seem to possess a reactivity closer to that of allyl halides (see Scheme 12).[123]

## 1.3.2 REACTIONS OF α-THIO- AND α-SELENO-ALKYLLITHIUMS BEARING HYDROGEN AND/OR HYDROCARBON SIDE CHAINS ON THEIR CARBANIONIC CENTER

### 1.3.2.1 Alkylation

#### *1.3.2.1.1 Alkylation of α-thio- and α-seleno-alkyllithiums*

α-Thioalkyllithiums (even those derived from polymer-bound derivatives)[124] bearing hydrogen or alkyl groups on their carbanionic center have been alkylated efficiently in the presence of TMEDA,[58] DABCO[59,124–126] or HMPA[60] (usually required in the metallation step) by primary,[58,59,125] secondary[59] and allylic halides (Scheme 4, entries a–d; see Scheme 53, entry a). The alkylations are much less successful in the absence of HMPA[125,127] but addition of copper(I) iodide (CuI)[125] or CuI·SMe$_2$ complex (Scheme 4, entry e), which probably leads to the formation of a cuprate intermediate, restores the reactivity. Under these conditions phenylthiomethyl carbanion reacts[125] in a regioselective manner with geranyl bromide and produces homogeranyl phenyl sulfide with preservation of the (*E*)-stereochemistry of the carbon–carbon double bond (see Scheme 53, entry b).[125]

The latter conditions also proved to be much more successful than those involving lithium derivatives[128] for the methylation[129] and the allylation[127] of phenylthiocyclopropane (Scheme 5), but none of the above mentioned α-thio organometallics can be benzylated in reasonable yield since stilbene, rather than the expected benzylated sulfides, was produced quantitatively, probably *via* benzylidene formation (Scheme 4, entry e).[60]

Use of α-thioalkylmetals whose carbanionic centers are dipole-stabilized, such as α′-lithioalkyl carbamates,[130,131] α′-lithioalkyl thioesters,[130,131] α-lithioalkyl thiothiazolines[132,133] and related species[134] offer interesting advantages over the classical α-alkylthio- and α-phenylthio-alkyllithiums (Scheme 6, entries a–d) since not only is there a large variety of such species, including those bearing two alkyl substituents on the carbanionic center, available by metallation of the corresponding carbon acid (this is not for example feasible for 2-phenylthio-2-propyllithium[60]) but also because they can be alkylated,[130–135] allylated[130–133] and even benzylated[131–134] in reasonably good yields (Scheme 6, entries a–d).

In fact all these organometallics can be viewed as chelated species which are softer than unchelated ones. In that respect the behavior of the methylthioamidines described in Scheme 6 (entries e and f) is interesting in that the anion derived from the seven-membered ring compound where negative charge can be stabilized by internal chelation is cleanly metallated and alkylated at the SMe group, whereas its lower homolog whose analogous carbanion is expected to be less prone to chelation leads instead to an alkylated enamine.[135]

Haloalkyl phenyl sulfides produce cycloalkyl phenyl sulfides on treatment with base. The synthesis of cyclopropyl phenyl sulfides has attracted particular interest since these compounds can be metallated[17,25,61] by Bu$^n$Li in THF and the resulting 1-phenylthiocyclopropyllithium has been used for spiroannelation of various cycloalkanones.[17,25] Thus, 3-chloro-1-phenylthiopropane leads[136,137] to phenylthiocyclopropane on reaction with potassium amide in liquid ammonia (Scheme 7, entry a), but attempts to prepare 2-methylcyclopropyl phenyl sulfide from 3-chloro-1-phenylthiobutane by an analogous route failed in the cyclization step.[61] Neither 3-mesyloxy- and 3-tosyloxy-1-phenylthiododecanes[138] nor 3-tosyloxy-1-phenylthiobutane produce cyclopropane derivatives either on reaction with LDA in THF[139] (Scheme 7, entry b). Failure in these ring closure reactions has been attributed to inadequate car-

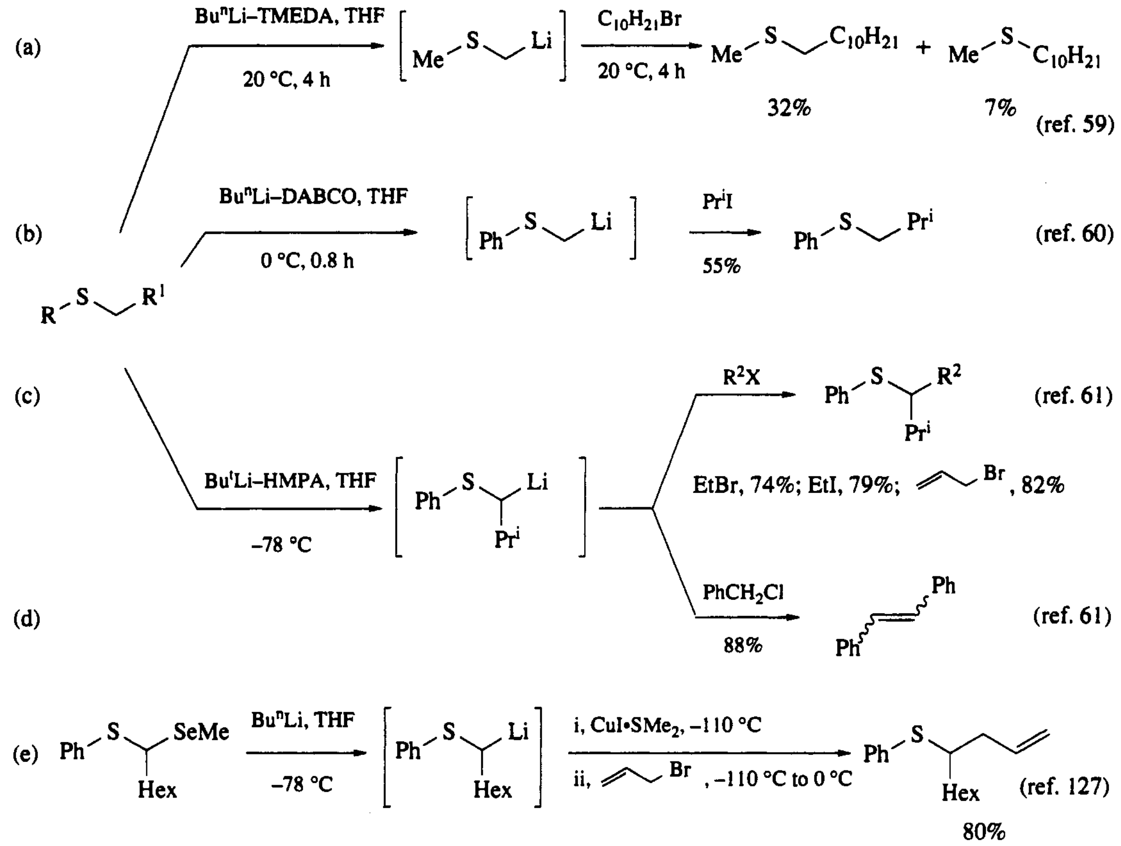
(a)
Bu$^n$Li-TMEDA, THF
20 °C, 4 h
C$_{10}$H$_{21}$Br
20 °C, 4 h
32%
7%
(ref. 59)
(b)
Bu$^n$Li-DABCO, THF
0 °C, 0.8 h
Pr$^i$I
55%
(ref. 60)
(c)
R$^2$X
(ref. 61)
EtBr, 74%; EtI, 79%; Br, 82%
Bu$^t$Li-HMPA, THF
-78 °C
(d)
PhCH$_2$Cl
88%
(ref. 61)
(e)
Bu$^n$Li, THF
-78 °C
i, CuI•SMe$_2$, -110 °C
ii, Br, -110 °C to 0 °C
(ref. 127)
80%

**Scheme 4**

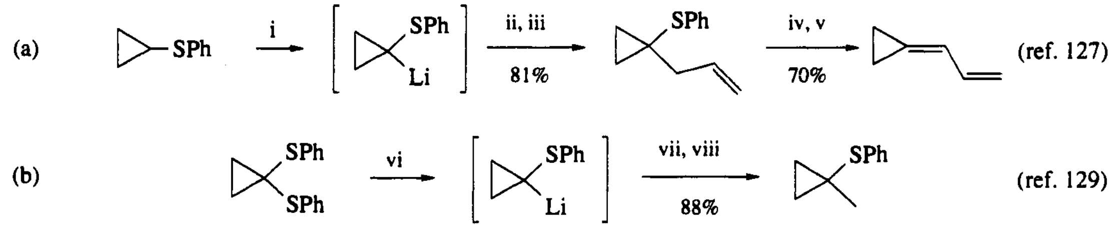
(a)
i
ii, iii
81%
iv, v
70%
(ref. 127)
(b)
vi
vii, viii
88%
(ref. 129)

i, Bu$^n$Li; ii, CuI•SMe$_2$; iii, CH$_2$=CHCH$_2$Br, -78 to 0 °C; iv, MeSO$_3$F; v, KOH, DMSO;
vi, LDMAN, THF, -45 °C; vii, CuI, -78 °C; viii, MeI

**Scheme 5**

banion stabilization by the phenylthio group since closure of the corresponding sulfones (see Section 1.3.6.1.2, Scheme 109) proceeds easily under the same conditions.[138,139] Addition of methyl iodide to the sulfide shown in Scheme 7 (entry b) gives the 4-ethylbenzenesulfonate, suggesting that a successful ring closure might be achieved if the benzenesulfonate was used instead of the tosylate. Indeed, with the corresponding benzenesulfonate (Scheme 7, entry c) a mixture of isomers (*Z*:*E* = 63:37) of 2-methylcyclopropyl phenyl sulfide is obtained in high yield. Interestingly, the isomer distribution obtained complements that resulting from an alternative route involving 3-chloro-2-methyl-1-phenylthiopropane and potassium amide (*Z*:*E* = 17:83; Scheme 7, entry d).[61]

The alkylations of α-selenoalkylmetals share some similarities with those of their thio analogs. Thus α-methylseleno- and α-phenylseleno-alkyllithiums, available by cleavage of the corresponding selenoacetals by *n*-butyllithium in THF or *s*-butyllithium in ether, usually react with methyl iodide and primary alkyl halides to produce the corresponding alkylated selenides.[23,25,52,68,70,71,110,122,127,140–145]

The alkylations of α-selenoalkyllithiums, bearing one or two alkyl substituents on the carbanionic center, with primary alkyl halides take place at low temperatures (–78 °C) in THF[68,143] but at much higher

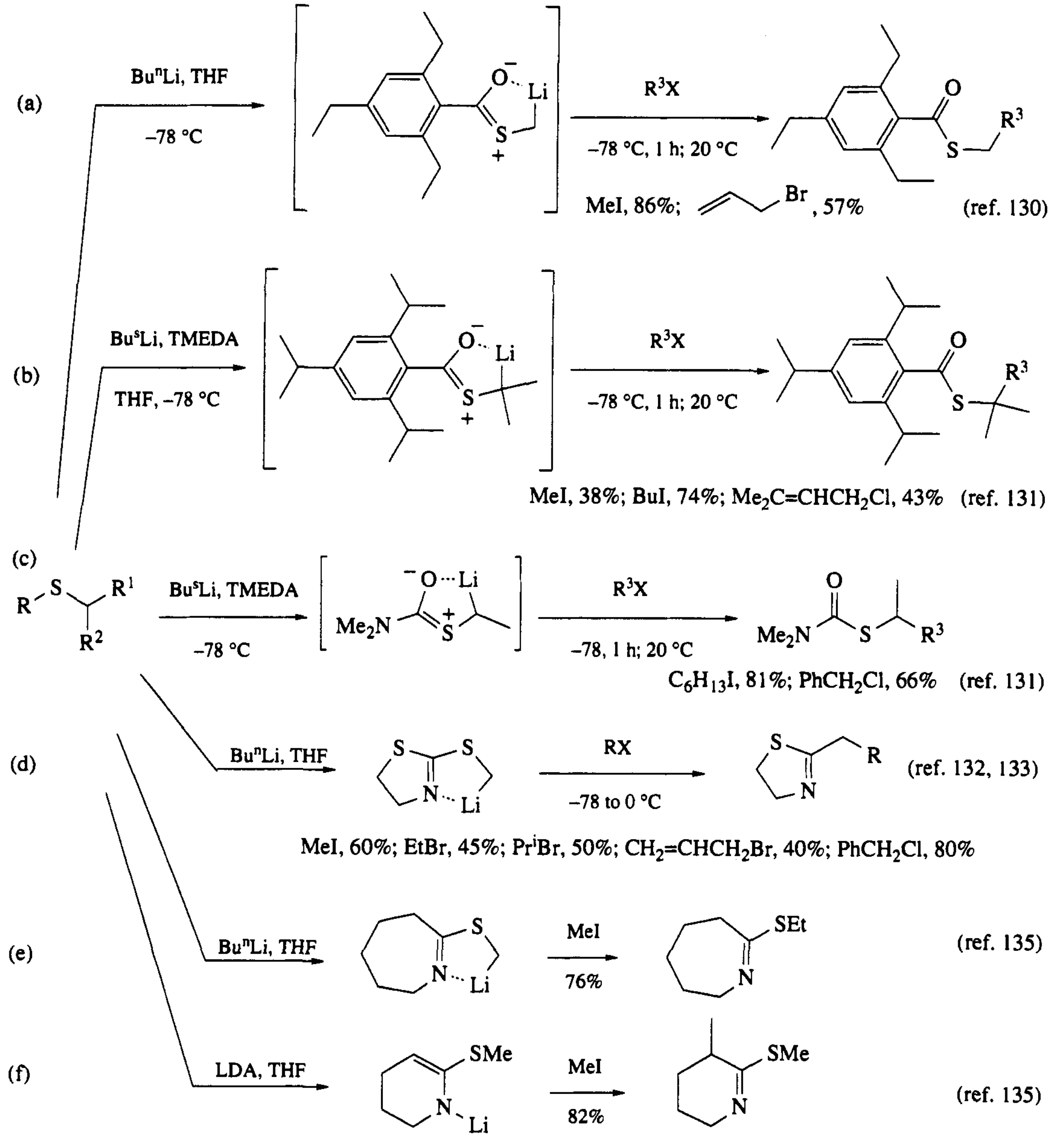
(a)
Bu$^n$Li, THF
-78 °C
R$^3$X
-78 °C, 1 h; 20 °C
MeI, 86%; Br, 57%
(ref. 130)
(b)
Bu$^s$Li, TMEDA
THF, -78 °C
R$^3$X
-78 °C, 1 h; 20 °C
MeI, 38%; BuI, 74%; Me$_2$C=CHCH$_2$Cl, 43%
(ref. 131)
(c)
Bu$^s$Li, TMEDA
-78 °C
R$^3$X
-78, 1 h; 20 °C
C$_6$H$_{13}$I, 81%; PhCH$_2$Cl, 66%
(ref. 131)
(d)
Bu$^n$Li, THF
RX
-78 to 0 °C
(ref. 132, 133)
MeI, 60%; EtBr, 45%; Pr$^i$Br, 50%; CH$_2$=CHCH$_2$Br, 40%; PhCH$_2$Cl, 80%
(e)
Bu$^n$Li, THF
MeI
76%
(ref. 135)
(f)
LDA, THF
MeI
82%
(ref. 135)

**Scheme 6**

temperatures (20 °C for 1 h) when performed in ether. Best results are obtained by use of methylseleno derivatives and when the reaction is performed in THF at the lowest possible temperature (Scheme 8).

The parent compounds, methylselenomethyllithium and phenylselenomethyllithium, are less reactive towards alkylating agents than their higher homologs. They require higher temperatures (–20 °C instead of –78 °C) for a reasonable reaction rate irrespective of whether ether or THF is used.[141] Unfortunately they produce, along with the expected alkylated selenides, appreciable amounts of the selenide resulting from substitution of the alkyl halide by the selenolate ion (Scheme 8, entry a). Apparently, under these conditions, the selenoalkyllithiums are in equilibrium with methylene and lithium selenolates. This side reaction can be avoided if the reactions are performed in THF–HMPA,[140] under which conditions alkylation proceeds at temperatures as low as –78 °C (Scheme 8, compare entry b to a). In several cases HMPA aids the alkylation of α-selenoalkyllithiums. For example HMPA has been used[145] for the alkylation of 1-phenylseleno-1-hexyllithium, and also for 1-selenocyclopropyl-[25,70] and 1-selenocyclobutyllithiums[25,71] (Scheme 8, entries c and e).

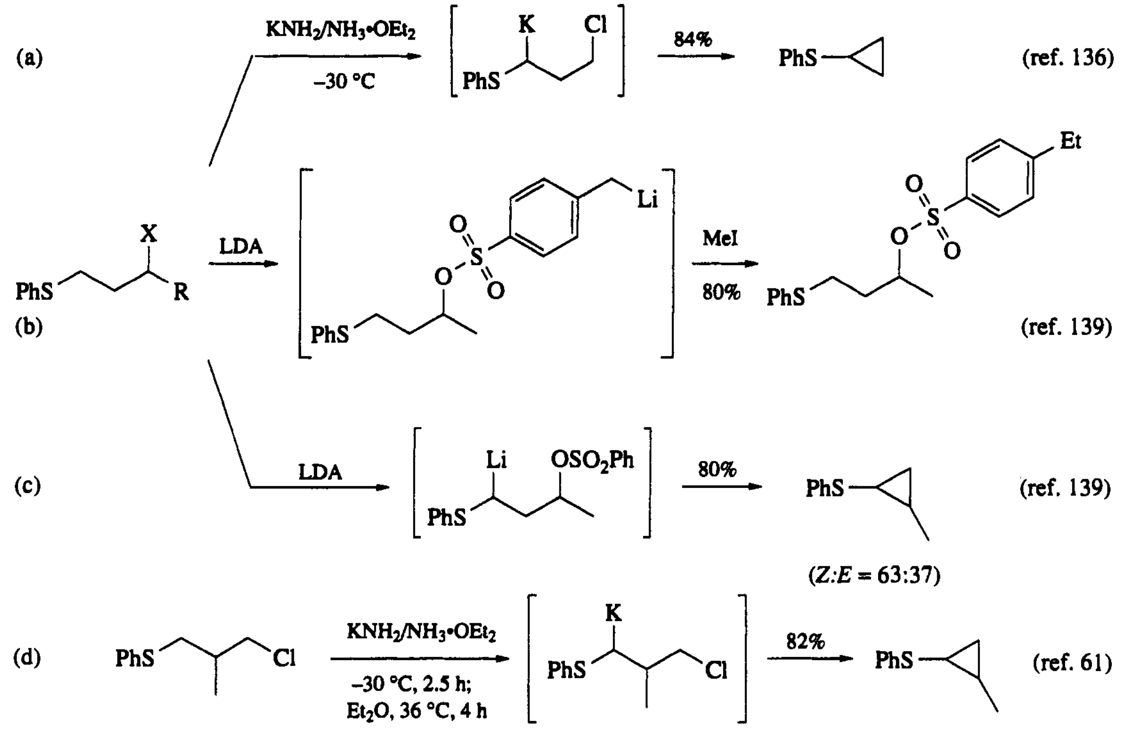

**Scheme 7**

α-Selenoalkyllithiums cannot be alkylated with secondary alkyl halides[141] (Scheme 9); instead either an alkene resulting from an elimination reaction or a selenide, derived from substitution of the halide by the selenolate ions formed as mentioned earlier, is produced, depending upon the conditions employed (THF or THF–HMPA; Scheme 9).[141]

Allylation of α-selenoalkylmetals takes place[140] rather sluggishly and leads to homoallyl selenides in modest yields (Scheme 10, entry a). However the yields are greatly improved by using instead[123,127] the corresponding cuprate[146] (formed from the organolithium compound and copper iodide–dimethyl sulfide complex at –110 °C; Scheme 10, entries b and c). The reaction must be performed at low temperatures since the novel species decomposes around –30 °C, and instead produces an alkene resulting from coupling of the hydrocarbon framework of two units. When applied to neryl and geranyl halides the reaction occurs regioselectively at their primary carbon and does not affect the original stereochemistry of the carbon–carbon double bond.[147] Unfortunately benzylation of α-selenoalkyllithiums could not be achieved even by use of the corresponding cuprates.[147]

As far as chemoselectivity is concerned, α-selenoalkyllithiums react exclusively with the carbonyl carbon of aldehydes or ketones rather than with alkyl halides (Scheme 11).[25,122]

Allyl bromide and benzaldehyde appear to be equally reactive towards α-selenoalkyllithiums (Scheme 12, entries a and c), whereas α-selenoalkylcuprates exhibit a different behavior with allylation occurring almost exclusively, even when the reaction is performed in the presence of benzaldehyde (Scheme 12, entries b and d).[123]

The alkylation of a highly functionalized α-selenoalkyllithium has been reported once. In this study the di(methylseleno)acetal resulting from the conjugate addition of 1,1-di(methylseleno)-1-ethyllithium to cyclohexenone, followed by trapping the resulting enolate with trimethylsilyl chloride, led to the corresponding methylated selenide on cleavage of one of the C—Se bonds followed by reaction with methyl iodide (Scheme 8, entry f).[148]

α-Selenoalkyllithiums also react with terminal epoxides[71,141,149,150] and oxetanes[141,149] to provide γ- and δ-hydroxy selenides in good yields (Scheme 13). The reactions are usually carried out in THF, except in the case of selenomethyllithiums which require the use of HMPA as the cosolvent in order to prevent formation of a by-product resulting from opening of the heterocyclic ring by selenolate ions. Similar observations have already been made for the reaction of alkyl halides (see above).[23,52,141]

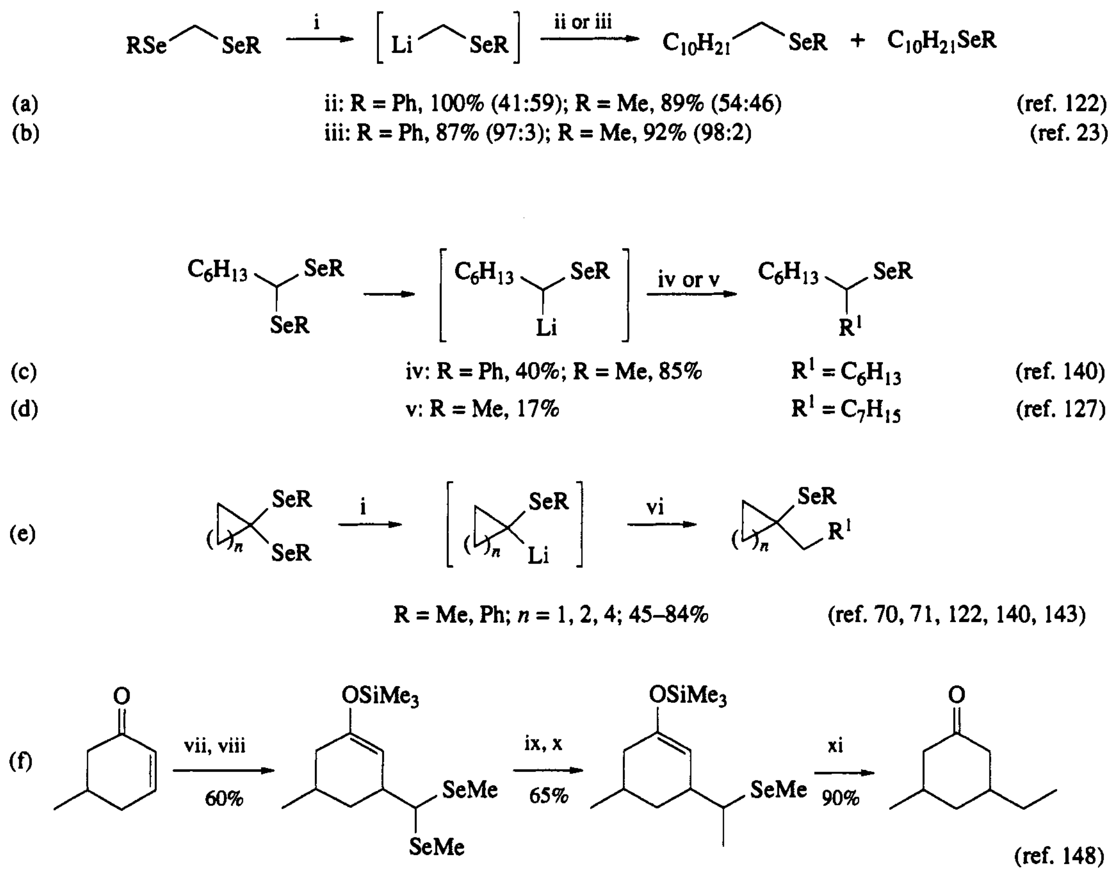
RSe⌒SeR
i
[Li⌒SeR]
ii or iii
$C_{10}H_{21}$⌒SeR + $C_{10}H_{21}$SeR
(a) ii: R = Ph, 100% (41:59); R = Me, 89% (54:46) (ref. 122)
(b) iii: R = Ph, 87% (97:3); R = Me, 92% (98:2) (ref. 23)
$C_6H_{13}$
SeR
Li
iv or v
$R^1$
(c) iv: R = Ph, 40%; R = Me, 85% $R^1 = C_6H_{13}$ (ref. 140)
(d) v: R = Me, 17% $R^1 = C_7H_{15}$ (ref. 127)
(e)
vi
$(\ )_n$
R = Me, Ph; *n* = 1, 2, 4; 45–84% (ref. 70, 71, 122, 140, 143)
(f)
O
vii, viii
60%
OSiMe₃
SeMe
ix, x
65%
xi
90%
(ref. 148)

i, Bu$^n$Li, THF, –78 °C; ii, $C_{10}H_{21}Br$, THF, –78 °C; iii, $C_{10}H_{21}Br$, THF–HMPA, –78 to 0 °C; iv, $C_6H_{13}Br$, THF, –78 °C, 1 h, then MeOH, –78 °C; v, CuI, –78 °C, then $C_7H_{15}I$, –78 to 20 °C; vi, $R^1CH_2X$, THF or THF–HMPA; vii, $LiCH(SeMe)_2$, THF–HMPA; viii, $Me_3SiCl$, $Et_3N$; ix, 1 equiv. Bu$^n$Li; x, excess MeI; xi, $Bu_3SnH$, *p*-TsOH

Scheme 8

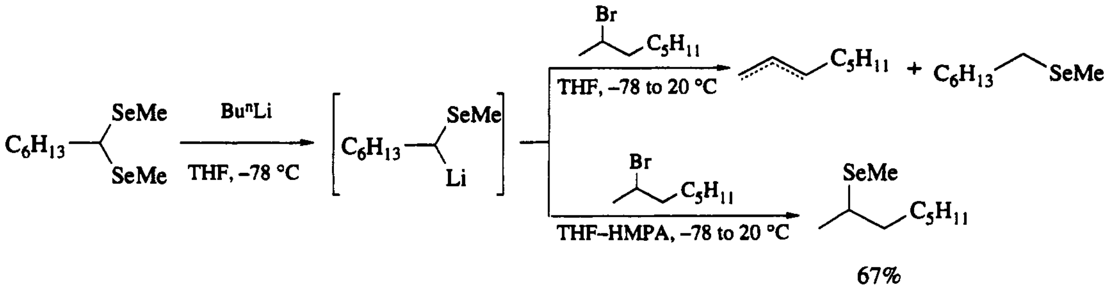
SeMe
$C_6H_{13}$
Bu$^n$Li
THF, –78 °C
Li
Br
$C_5H_{11}$
THF, –78 to 20 °C
+ $C_6H_{13}$⌒SeMe
THF–HMPA, –78 to 20 °C
67%

Scheme 9

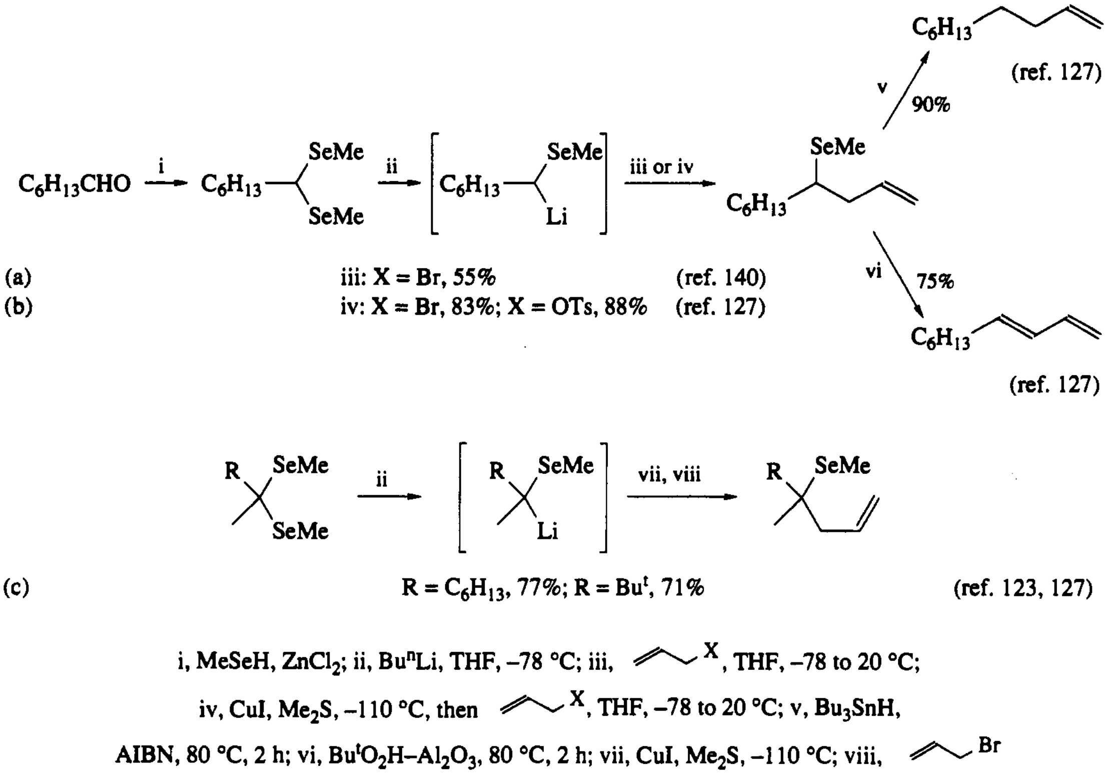

$C_6H_{13}CHO$
i
ii
iii or iv
v
90%
vi
75%
(ref. 127)
(ref. 127)
ii
vii, viii

(a) iii: X = Br, 55% (ref. 140)

(b) iv: X = Br, 83%; X = OTs, 88% (ref. 127)

(c) R = $C_6H_{13}$, 77%; R = Bu$^t$, 71% (ref. 123, 127)

i, MeSeH, $ZnCl_2$; ii, Bu$^n$Li, THF, –78 °C; iii, X, THF, –78 to 20 °C; iv, CuI, $Me_2S$, –110 °C, then X, THF, –78 to 20 °C; v, $Bu_3SnH$, AIBN, 80 °C, 2 h; vi, Bu$^t$$O_2$H–$Al_2O_3$, 80 °C, 2 h; vii, CuI, $Me_2S$, –110 °C; viii, Br

**Scheme 10**

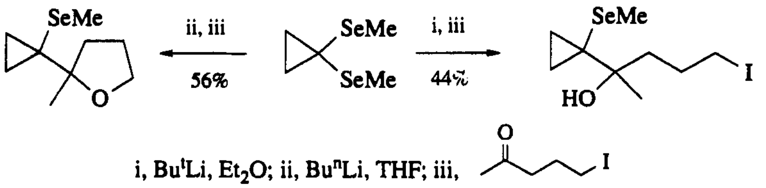

ii, iii
56%
i, iii
44%

(ref. 25, 122)

i, Bu$^t$Li, $Et_2O$; ii, Bu$^n$Li, THF; iii, I

**Scheme 11**

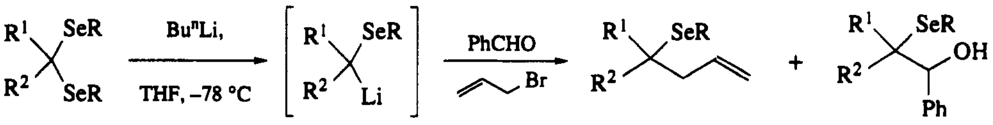

Bu$^n$Li,
THF, –78 °C
PhCHO
Br
+

| | $R^1$ | $R^2$ | Conditions | Yield (%) | Yield (%) |
|---|---|---|---|---|---|
| (a) | H | $C_6H_{13}$ | i | 38 | 40 |
| (b) | H | $C_6H_{13}$ | ii | 83 | 0 |
| (c) | Me | Bu$^t$ | i | 21 | 15 |
| (d) | Me | Bu$^t$ | ii | 52 | trace |

i, addition of electrophile to organolithium at –100 °C, then –100 to 20 °C; ii, addition of CuI•$SMe_2$ to organolithium at –78 °C, addition of electrophile, then –78 to –30 °C

**Scheme 12**

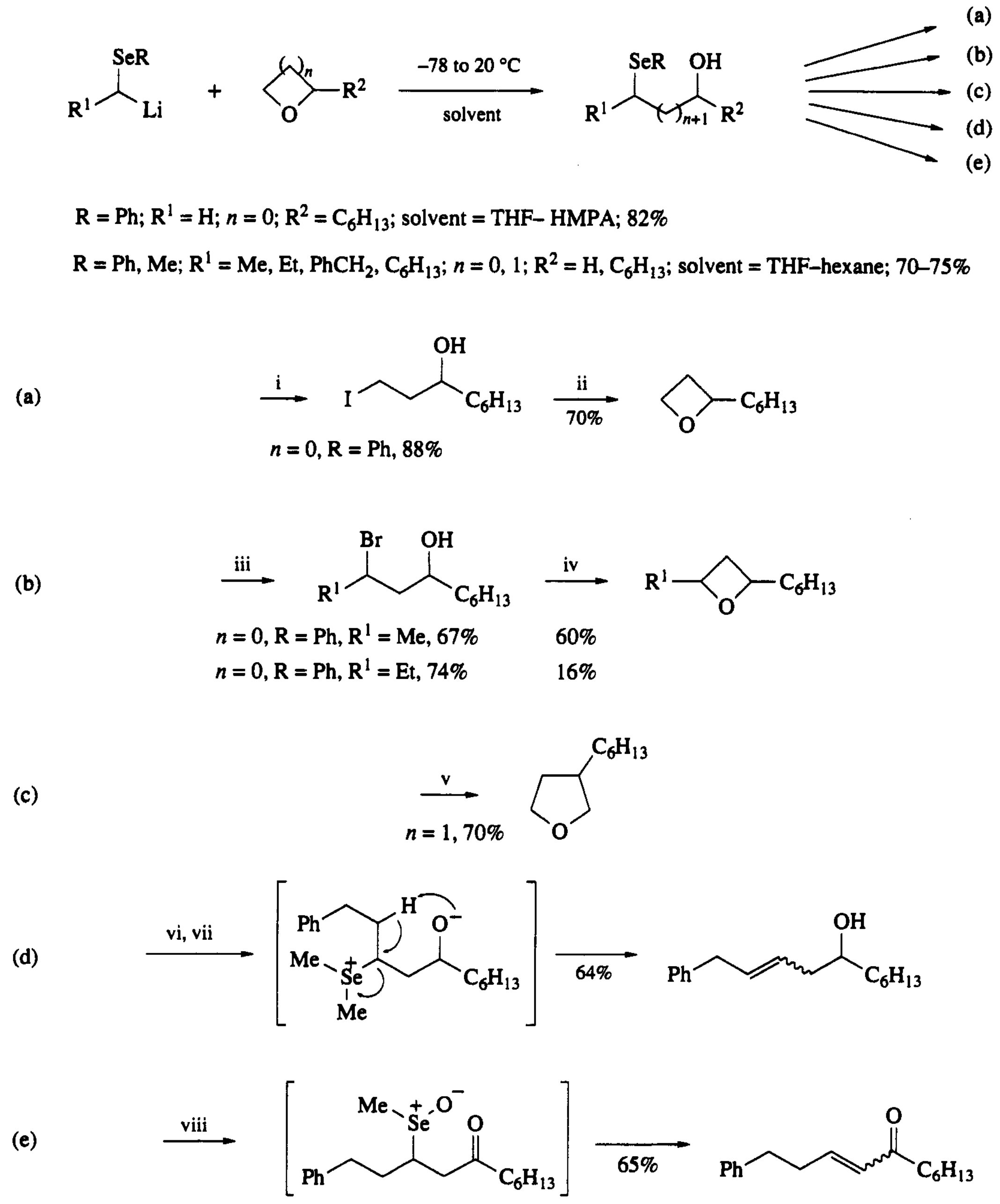
SeR
R1 Li
+
R2
O
n
−78 to 20 °C
solvent
SeR OH
R1 R2
n+1
(a)
(b)
(c)
(d)
(e)
R = Ph; R1 = H; n = 0; R2 = C6H13; solvent = THF– HMPA; 82%
R = Ph, Me; R1 = Me, Et, PhCH2, C6H13; n = 0, 1; R2 = H, C6H13; solvent = THF–hexane; 70–75%
(a)
i
I
OH
C6H13
n = 0, R = Ph, 88%
ii
70%
O
C6H13
(b)
iii
Br OH
R1 C6H13
n = 0, R = Ph, R1 = Me, 67%
n = 0, R = Ph, R1 = Et, 74%
iv
60%
16%
R1
O
C6H13
(c)
v
n = 1, 70%
C6H13
O
(d)
vi, vii
Ph
H
O−
Me
+
Se
Me
C6H13
64%
Ph
OH
C6H13
(e)
viii
Me + O−
Se
O
Ph C6H13
65%
Ph
O
C6H13

i, MeI, NaI, DMF, $CaCO_3$, 80 °C, 1 h; ii, Bu$^t$OK, DMSO, 20 °C; iii, $Br_2$, EtOH–$H_2O$, 20 °C;
iv, MeMgBr, HMPT, 80 °C; v, $Br_2$, EtOH–$H_2O$, 20 °C, 3 h; vi, MeI; vii, Bu$^t$OK, DMSO, 20 °C;
viii, $CrO_3$, $H_2SO_4$, acetone, 0 °C, 3 h, then 25 °C, 29 h

Scheme 13

### *1.3.2.1.2 Alkylation of α-thio- and α-seleno-benzyl metals*

α-Thio-[14] and α-seleno-benzylmetals[17,18,23,25,45,52–56] are more accessible than their alkyl counterparts, probably due to the extra stabilization afforded by the aromatic ring. Also they are usually more nucleophilic towards organo halide derivatives presumably due to their relative softness. α-Thiobenzyllithiums are however prone to rearrange to benzylthiolates *via* a Wittig type rearrangement.[14,23]

A series of benzyllithiums bearing a phenylthio (Scheme 14, entries a and d, Scheme 15; see Scheme 43),[14,126,151–155] a thiothiazolino (Scheme 14, entry b)[132a,133] or a dithiocarbamato[156,157] group (Scheme 14, entry c; see Scheme 49 and Scheme 50) have been successfully alkylated with primary[151–156] and secondary alkyl halides,[126] benzylated[157] or allylated (see Scheme 43)[151,153,156,157] without special requirements. Intramolecular alkylation has allowed the synthesis of cyclic compounds, including aromatic lactones of medium and large ring size (14- and 15- but not 12-membered rings)[153] and cyclopropane derivatives.[137] Furthermore, benzyl 1-(3-chloropropyl) sulfide cyclizes[137] on reaction with $KNH_2$ to 2-phenyltetrahydrothiophene rather than to benzylthiocyclopropane (Scheme 14, entry e).

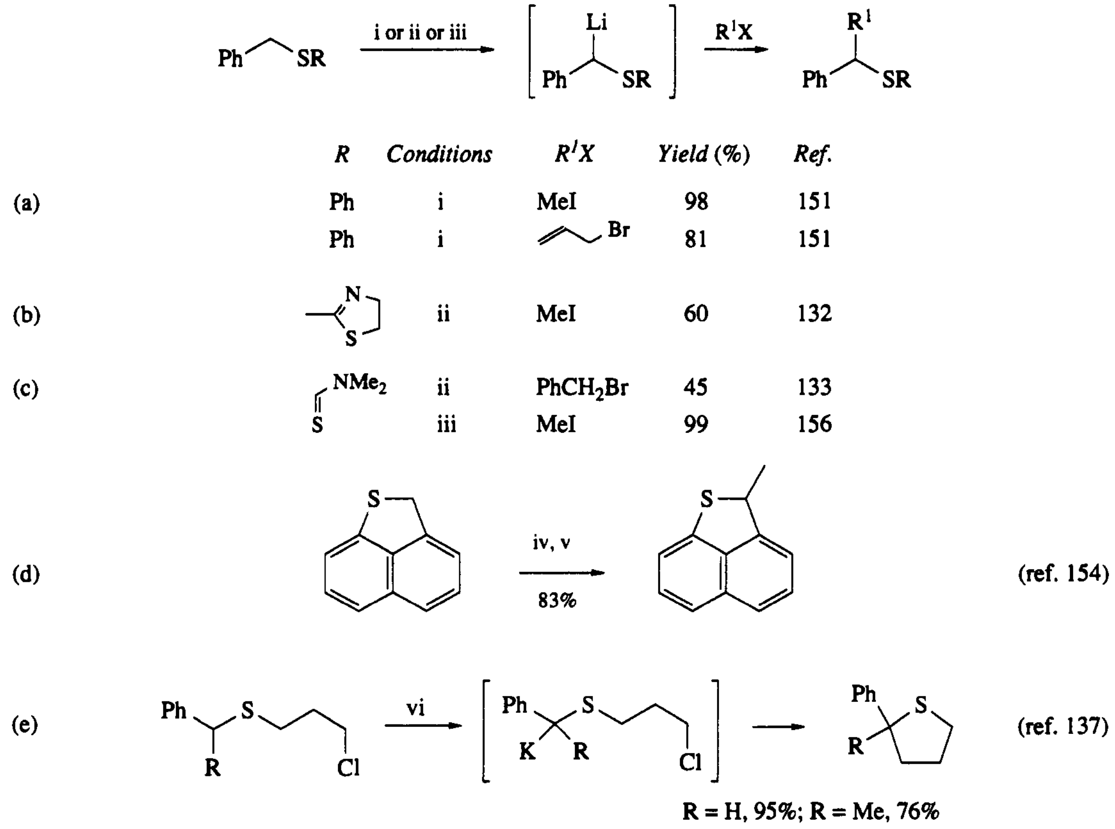

i, $Bu^nLi$–DABCO, THF, 0 °C, 0.5 h; ii, $Bu^nLi$, THF, –30 °C, 0.5 h; iii, LDA, THF, –78 °C, 0.1 h;
iv, $Bu^nLi$, THF, –60 °C, 0.1 h; v, MeI; vi, $KNH_2$, $NH_3$–$Et_2O$

Scheme 14

The case of thiobenzaldehyde dianions, which are available from benzylthiol and two equivalents of *n*-butyllithium–TMEDA complex, merits further comment since alkylation or allylation of these species occurs selectively at the carbanionic site and then a second alkylation can be carried out on the thiolate group (Scheme 16, entry a).[158,178]

α-Selenobenzyllithiums, even those bearing a bulky alkyl group at their carbanionic center, react efficiently not only with primary and secondary alkyl halides[72,74,79,80,104–106] but also with allyl halides,[159] benzyl halides (Scheme 17)[105,159] and epoxides (Scheme 18)[106,160] without requiring an additive or the formation of a cuprate intermediate (see above).

### *1.3.2.1.3 Alkylation of α-thio- and α-seleno-allylmetals*

α-Thio-[14,16,24] and α-seleno-allylmetals[17,18,23,46,52,54] display a reactivity profile similar to their benzylic analogs, but they also exhibit a tendency to act as ambident nucleophiles.[14] They can react at either the carbon directly linked to (α-carbon) or that which is two carbons away (γ-carbon) from the

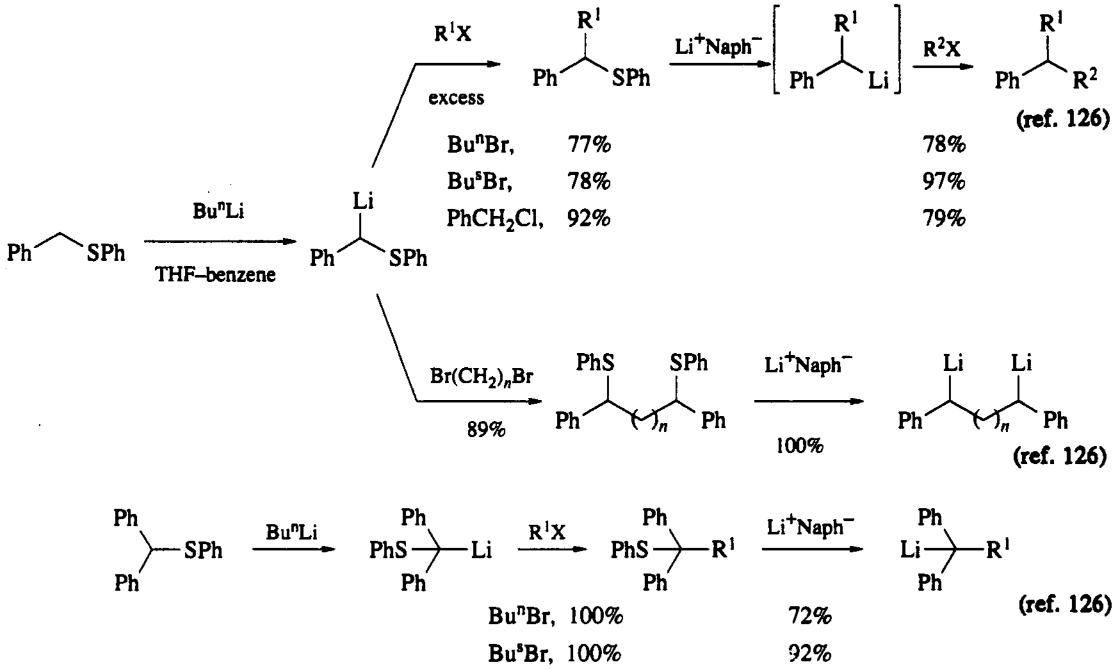
Ph SPh
Bu$^n$Li
THF–benzene
Ph Li SPh
R$^1$X excess
Ph R$^1$ SPh
Bu$^n$Br, 77%
Bu$^s$Br, 78%
PhCH$_2$Cl, 92%
Li$^+$Naph$^-$
Ph R$^1$ Li
R$^2$X
78%
97%
79%
Ph R$^1$ R$^2$
(ref. 126)
Br(CH$_2$)$_n$Br
89%
PhS SPh Ph Ph
Li$^+$Naph$^-$
100%
Li Li Ph Ph
(ref. 126)
Ph Ph SPh
Bu$^n$Li
PhS Li Ph Ph
R$^1$X
PhS R$^1$ Ph Ph
Bu$^n$Br, 100%
Bu$^s$Br, 100%
Li$^+$Naph$^-$
72%
92%
Li R$^1$ Ph Ph
(ref. 126)

Scheme 15

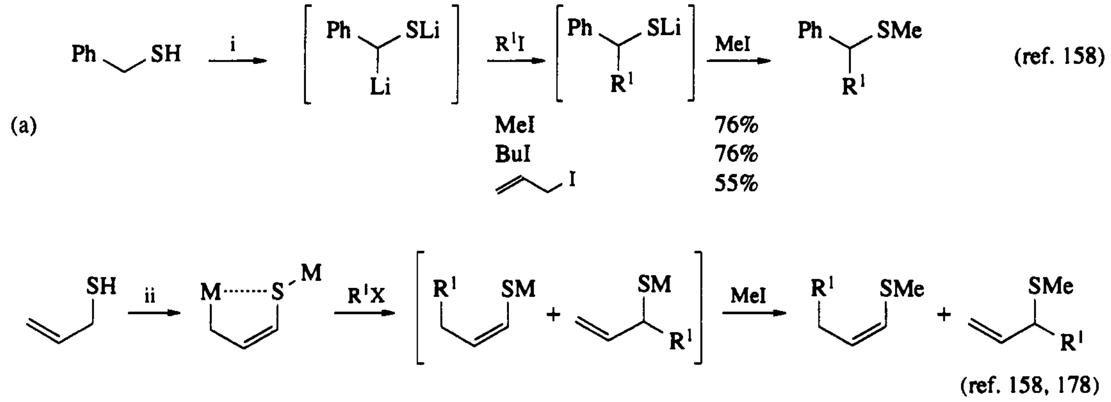
Ph SH
i
Ph SLi Li
R$^1$I
Ph SLi R$^1$
MeI
Ph SMe R$^1$
(ref. 158)
(a)
MeI 76%
BuI 76%
I 55%
SH
ii
M S M
R$^1$X
R$^1$ SM + SM R$^1$
MeI
R$^1$ SMe + SMe R$^1$
(ref. 158, 178)

| | *R$^1$X* | *Additive* | *Yield (%)* | *Product ratio* |
|---|---|---|---|---|
| (b) | n-$C_8H_{17}Cl$ | none | 81 | 73:27 |
| | Pr$^i$Cl | none | 85 | 59:41 |
| (c) | Pr$^i$Cl | 30% HMPA | 82 | 22:78 |
| (d) | $C_8H_{17}Cl$ | Bu$^t$OK, 12% HMPA | 80 | 88:12 |
| | Pr$^i$Cl | Bu$^t$OK, 12% HMPA | 50 | 35:65 |

i, 2 Bu$^n$Li, THF–TMEDA, –80 °C; ii, 2 Bu$^n$Li, THF, 2 TMEDA

Scheme 16

heteroatom itself. The regioselectivity is in general highly dependent upon the location of the metal on the system.

Alkyl,[151,161,162] aryl (Scheme 19; Scheme 20)[16,151,161,164,165] and vinyl thioallyllithiums (Scheme 21)[166,167] react selectively with organic halides at their α-site (α:γ ratio = 95:5 to 80:20) when the reaction is carried out in THF without any additive such as TMEDA, DABCO or HMPA. In contrast to the above mentioned cases, thioallyllithiums in which there is the possibility of lithium chelation at the α-site [such as 2-pyridylthio (Scheme 19; see Scheme 45),[15,16,168,169] thioimidazoyl (Scheme 19; see

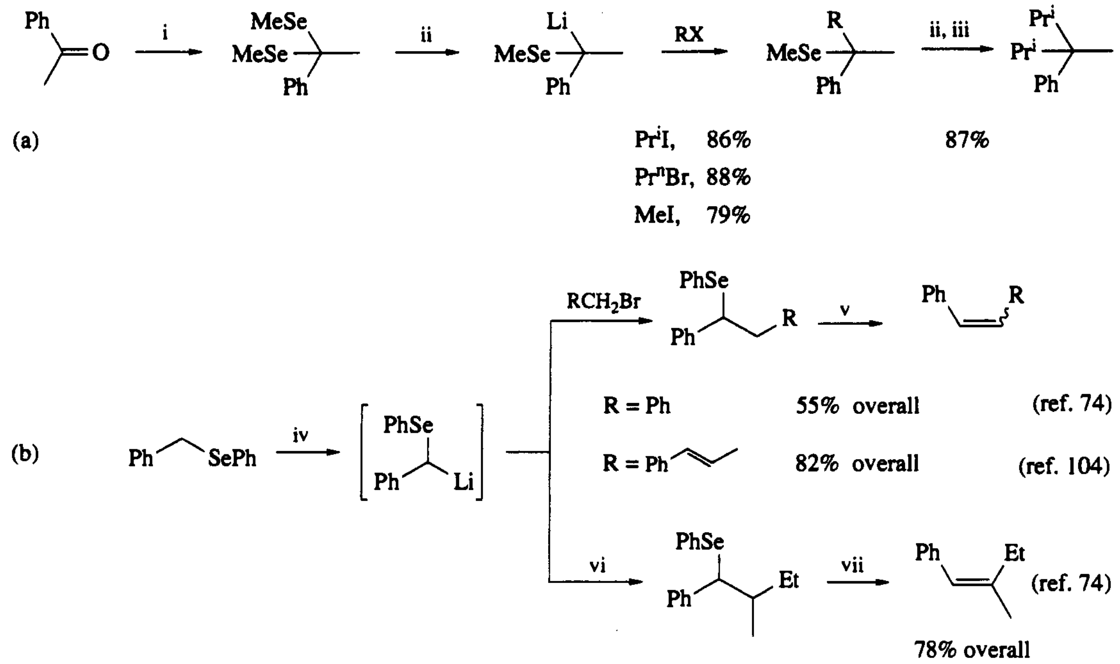

i, MeSeH, $TiCl_4$; ii, Bu^nLi, THF, −78 °C; iii, Pr^iI, THF, −78 to 0 °C; iv, LDA, THF, −78 °C; v, $H_2O_2$, THF, 20 °C; vi, Bu^sBr; vii, $O_3$

Scheme 17

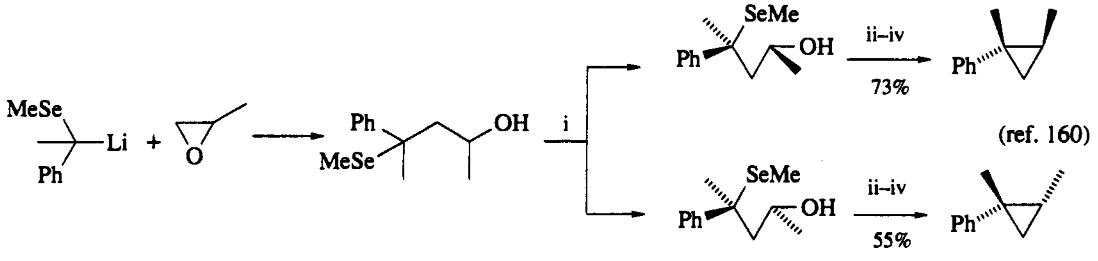

The stereochemistries of the products have not yet been established

i, separation of stereoisomers on silica; ii, Bu^nLi; iii, TosCl; iv, Bu^nLi, −78 °C

Scheme 18

Scheme 51)[16,170,171] and dithiocarbamato (see Scheme 50 and Scheme 51)[16,156,172–177] moieties] exhibit a dramatic selectivity for α-alkylation (Scheme 19).

The *N*-methylthioimidazoyl moiety, among the various aromatic and heteroaromatic moieties used in the sulfur series, proved to be the one with the highest propensity to direct the alkylation of the corresponding organometallics (even those bearing an alkyl group in the α-position) to the α-carbon atom (Scheme 19, entry e).[16,170]

On the other hand, doubly metallated 2-propanethiol (thioacrolein dianion) reacts preferentially (γ:α ratio ≈ 70:30, Scheme 16, entries b and d) at its γ-position[158,178] with alkyl and benzyl chlorides and bromides and with epoxides. The *cis* stereochemistry found in the γ-adduct suggests that the organometallic is internally chelated as shown in Scheme 16. The nature of the metal (Li or K) does not affect the percentages of the alkylated vinyl sulfides,[158] whereas addition of HMPA to the dilithio derivative inverts the regioisomeric ratio obtained (Scheme 16, entry c, compare to entries b and d).[158]

There is some evidence that factors other than chelating capability operate in altering the regioselectivity of alkylation. For example a higher α:γ ratio is observed[16] when phenylthio is replaced by a 4-pyridylthio moiety, neither of which can participate in intramolecular chelation. Consequently an explanation

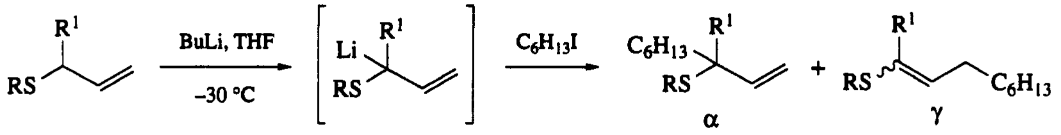

(ref. 16)

| | *R* | *R¹* | *Yield (%)* | *THF (α:γ)* | *THF–HMPA (α:γ)* |
|---|---|---|---|---|---|
| (a) | 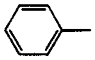 | H | 93 | 75:25 | 68:32 |
| | | Me | 84 | 75:25 | 70:30 |
| (b) | 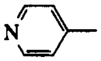 | H | 78 | – | 88:12 |
| (c) | 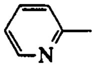 | H | 90 | 99:1 | >99:1 |
| | | Me | 79 | 90:10 | 79:21 |
| (d) | 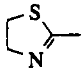 | H | 95 | – | 99:1 |
| | | Me | 94 | – | 80:20 |
| (e) | 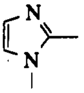 | H | 92 | 99:1 | >99:1 |
| | | Me | 86 | 92:8 | 84:16 |

**Scheme 19**

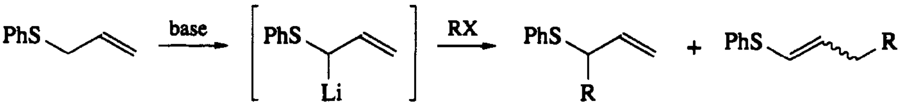

(ref. 151)

| | *Base* | *RX* | *Yield (%)* | *Product ratio* |
|---|---|---|---|---|
| (a) | $Bu^sLi$, THF | MeI | – | 71:29 |
| (b) | $Bu^nLi$, DABCO | MeI | 100 | 95:5 |
| | $Bu^nLi$, DABCO | 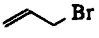 | – | 62:38 |

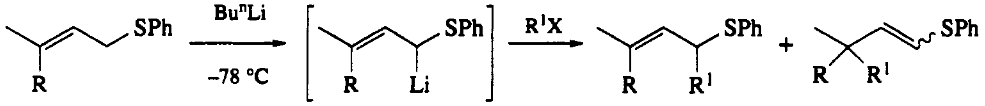

| | *R* | *Additive* | *R¹X* | *Yield (%)* | *Product ratio* | |
|---|---|---|---|---|---|---|
| (c) | H | DABCO | MeI | 92 | 98:2 | (ref. 161) |
| (d) | Me | None | MeI | 100 | 95:5 | (ref. 164) |
| (e) | Me | DABCO | MeI | 100 | 99:1 | (ref. 164) |
| (f) | Me | HMPA | MeI | 100 | 98:2 | (ref. 164) |
| (g) | Me | [2.2.2] crown ether | MeI | 80 | 60:40 | (ref. 164) |
| (h) | Me | DABCO | 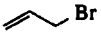 | 100 | 87:12 | (ref. 164) |
| (i) | Me | [2.2.2] crown ether | 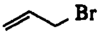 | 60 | 50:50 | (ref. 164) |

**Scheme 20**

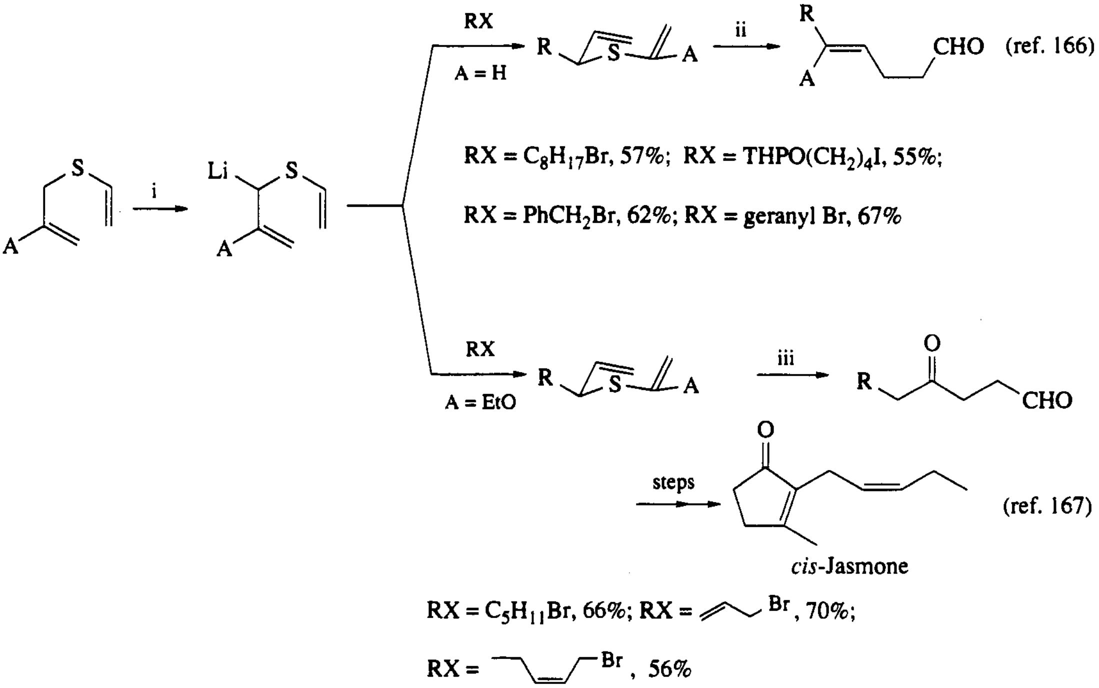
RX
A = H
ii
CHO (ref. 166)
RX = C8H17Br, 57%; RX = THPO(CH2)4I, 55%;
RX = PhCH2Br, 62%; RX = geranyl Br, 67%
i
RX
A = EtO
iii
CHO
steps
(ref. 167)
*cis*-Jasmone
RX = C5H11Br, 66%; RX = Br, 70%;
RX = Br, 56%

i, $Bu^sLi$, THF, −78 °C; ii, $DME/H_2O$ (3:1), $CaCO_3$, reflux 12 h; iii, $DME/H_2O$ (3:1), reflux 12 h

**Scheme 21**

that attributes high alkylation regioselectivity exclusively to intramolecular chelation must be considered tenuous.[16] Furthermore benzyl allyl sulfide is predominantly metallated[179] at the allylic site with *n*-butyllithium–TMEDA complex and provides almost exclusively the α-methylated homolog (Scheme 22, entry a). Surprisingly however the α:γ ratio of alkylation of the related dilithio salt derived from allyl carboxymethyl sulfide, shown in Scheme 22 (entry b) depends upon the nature of the ester.[180]

There are several examples where the α:γ ratio of alkylation depends to some extent on the nature of the halide and of the organic residue.[164,181] In that respect, the softer the electrophile, the higher the percentage of γ-attack observed. Typical examples are displayed in Scheme 23.

In several cases the conditions used are crucial for control of the regiochemistry. The highest percentage of α-attack has been achieved in THF, with *s*-butyllithium being used as the base (Scheme 19; Scheme 20, entry a).[16,166,181] The presence of an additive such as DABCO,[151] TMEDA, crown ethers or HMPA, required in some cases for successful metallation of the allyl sulfide has a detrimental effect on the regiochemical control (Scheme 16; Scheme 19; Scheme 20).[16,151,158,164,166,178] This result tends to support the theory that 'internal chelation' may play a role in defining regiochemistry. Such cation-coordinating cosolvents appear to partially negate the directive effect: (i) of the heterocyclic ligand (Scheme 24),[16] or (ii) of the internal chelation in dilithiothioacrolein (Scheme 16)[158,178] or (iii) to disrupt, in the case of phenylthioallyllithiums[151,164,166] the intimate and/or solvated ion pairs which are expected to react at the α-position to finally produce solvent-separated ion pairs or free ions more inclined to react unselectively at the α- and γ-sites (Scheme 19; Scheme 20).

Phenylthioallylpotassium and phenylthioprenylpotassium in petroleum ether exhibit a higher tendency for methylation at the γ-site compared to their lithium analogs, and addition of THF to the medium tends to increase the γ-selectivity (Scheme 24).[182]

Reactions between α-thioallyllithiums and allyl halides, which usually proceed predominantly *via* α–α′ (head-to-head) coupling, have proved to be valuable in synthesis.[132a,133,165,183–192] They have been used successfully for example in the synthesis of 1,5-dienes such as squalene,[132a,133,165] (*R*)-(+)-10,11-epoxyfarnesol,[184] (*R*)-(+)- and (*S*)-(−)-2,3-oxidosqualene[184] and mokupalide,[188] dendrolasin,[187] cembranolides,[189] methyl ceriferate[190] and *Cecropia* juvenile hormone (Scheme 25 and Scheme 26).[191,192]

However, allylation of alkylthioallylcopper compounds, generated in ether from alkylthioallyllithium and CuI at −78 °C (the synthesis of phenylthio analogs fails[162]), affords exclusively[98,162,163] γ–γ′ (tail-to-tail) coupled products (Scheme 27), whereas alkylthio allylic aluminum and boron 'ate' complexes, readily available from reaction of alkylthioallyllithium compounds with trialkylaluminum[98] and

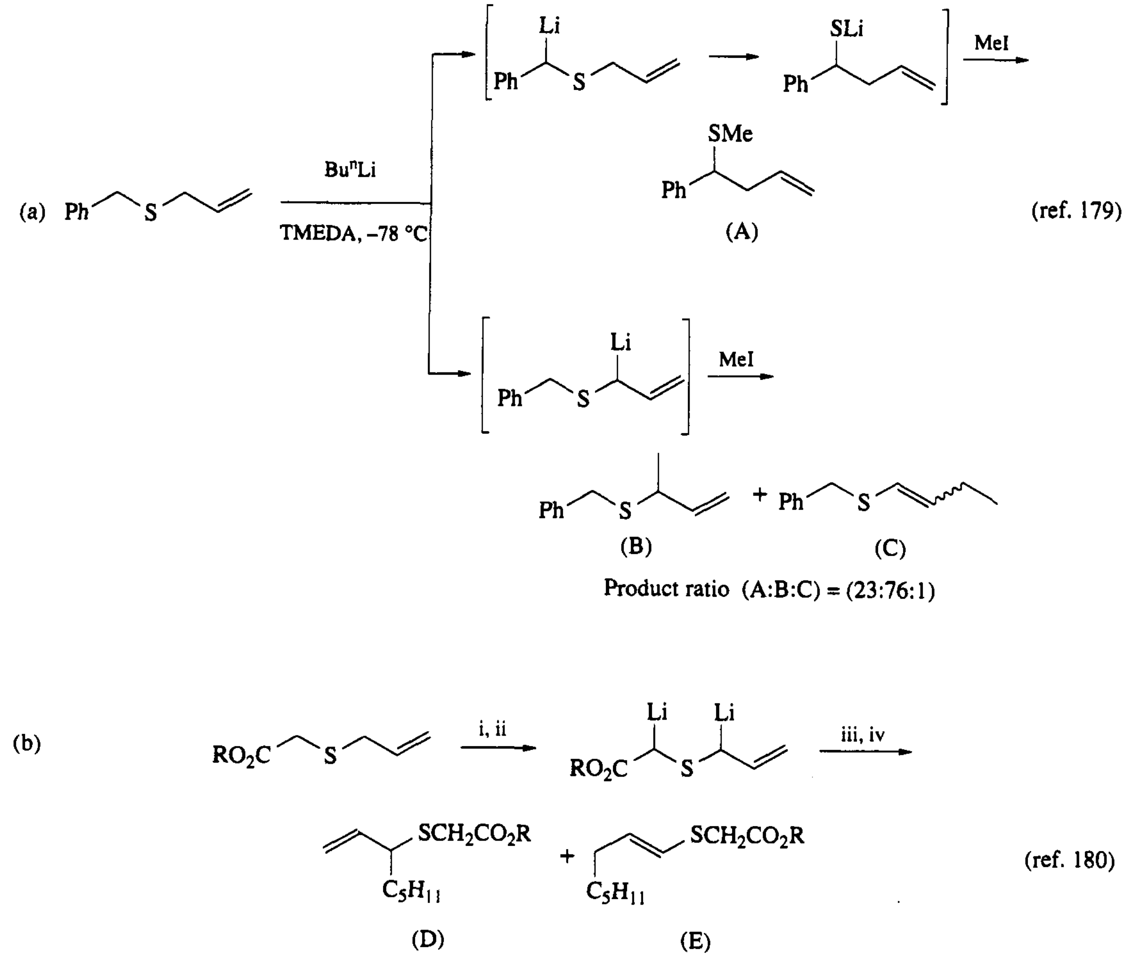
(a)
Ph
S
Bu$^n$Li
TMEDA, -78 °C
Li
SLi
MeI
SMe
(A)
(ref. 179)
MeI
(B)
(C)
Product ratio (A:B:C) = (23:76:1)
(b)
$RO_2C$
i, ii
iii, iv
$SCH_2CO_2R$
$C_5H_{11}$
(D)
(E)
(ref. 180)

| *R* | *Yield* (%) | *Product ratio (D:E)* |
|---|---|---|
| Me | 68 | 90:10 |
| Et | 69 | 80:20 |
| Pr$^i$ | 48 | 72:28 |
| Bu$^t$ | 0 | – |

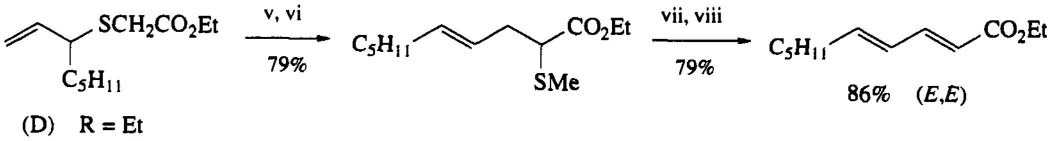
$SCH_2CO_2Et$
$C_5H_{11}$
(D) R = Et
v, vi
79%
$CO_2Et$
SMe
vii, viii
79%
86% (*E,E*)

i, LDA; ii, Bu$^s$Li; iii, $C_5H_{11}Br$; iv, $H_3O^+$; v, LDA, -78 to 0 °C; vi, MeI, 0 °C; vii, MCPBA; viii, $CaCO_3$, benzene, Δ, 24 h

**Scheme 22**

trialkylboranes respectively, undergo regiocontrolled α–γ′ (head-to-tail) coupling with allylic halides[183] (Scheme 28). In general, both the regioselectivity and the yields are higher with Bu$^n$-9-BBN-ate complexes than with triethylaluminum[98] or tri-*n*-butylboronates;[98,183] and allylic bromides give better results[98,183] than the corresponding chlorides.

Reactions between α-thioallyllithiums and epoxides have been used in a large number of important syntheses.[14,193–202] In one example involving an epoxy alcohol,[202] the concomitant use of magnesium

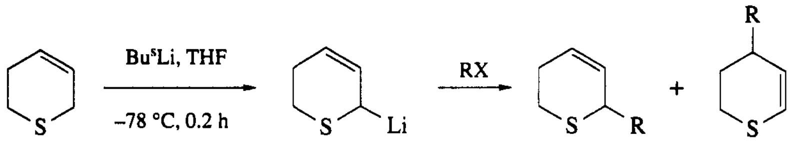
Bu$^s$Li, THF
−78 °C, 0.2 h
RX
S
Li
R
+

(ref. 181)

| *RX* | *Yield* (%) | *Product ratio* |
|---|---|---|
| $\mathrm{Bu^nCl}$ | 70 | 97:3 |
| $\mathrm{Bu^nBr}$ | 79 | 91:9 |
| $\mathrm{Bu^nI}$ | 100 | 70:30 |
| $\mathrm{PhCH_2Cl}$ | 96 | 73:27 |

**Scheme 23**

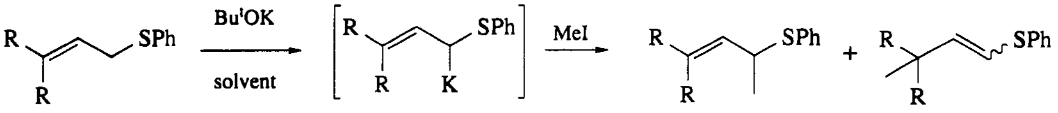
R
SPh
Bu$^t$OK
solvent
K
MeI
+

(ref. 182)

| *Solvent* | *R* | *Product ratio* |
|---|---|---|
| Pet. ether 25 °C, 2 h | H | 45:55 |
| Pet. ether 25 °C, 2 h | Me | 77:23 |
| Pet. ether–THF | H | 94:6 |
| Pet. ether–THF | Me | 98:2 |

**Scheme 24**

(a)

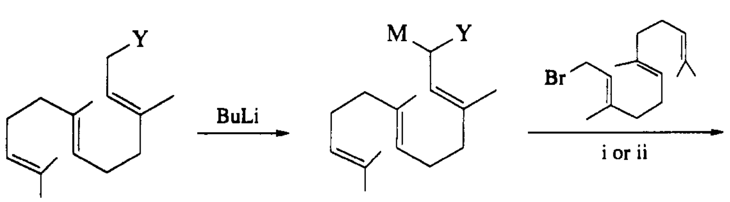
Y
BuLi
M
Br
i or ii

| | | |
|---|---|---|
| Y = SPh | i, | 82% |
| Y = 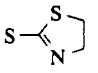 | i, | 44% |
| Y = $p$-$\mathrm{MePhSO_2}$ | ii, | 86% |

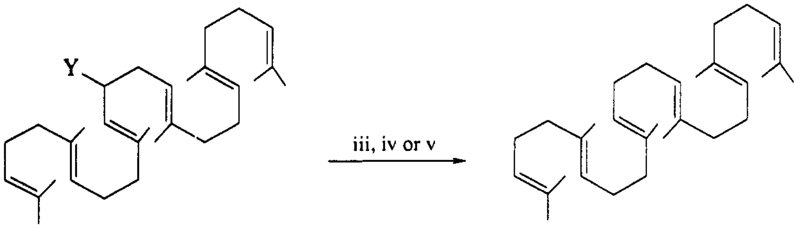

| | | |
|---|---|---|
| iii, | 70% | (ref. 165) |
| iv, | 80% | (ref. 132a, 133) |
| v, | 80% | (ref. 506) |

i, $\mathrm{Bu^nLi}$, THF, −78 °C; ii, $\mathrm{Bu^nLi}$, THF, −20 °C, RBr, −78 to 0 °C; iii, Li, $\mathrm{H_2NEt}$, −30 °C; iv, Raney Ni, EtOH–THF; v, Li, $\mathrm{H_2NEt}$

**Scheme 25**

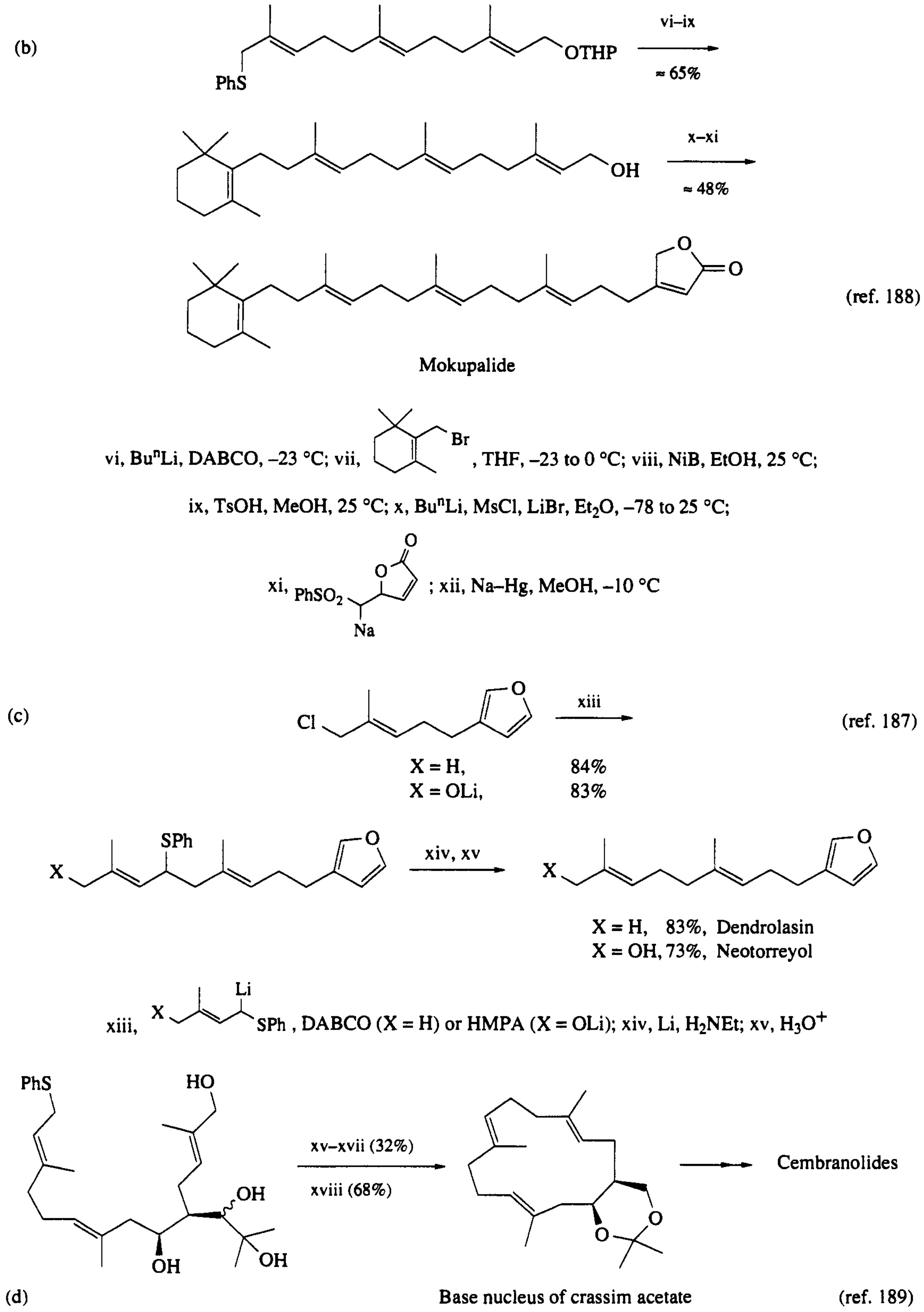
(b)
PhS
OTHP
vi–ix
≈ 65%
OH
x–xi
≈ 48%
O
O
(ref. 188)
Mokupalide
Br
O
O
$PhSO_2$
Na
(c)
Cl
O
xiii
(ref. 187)
X = H, 84%
X = OLi, 83%
X
SPh
O
xiv, xv
X
O
X = H, 83%, Dendrolasin
X = OH, 73%, Neotorreyol
X
Li
SPh
PhS
HO
OH
OH
OH
xv–xvii (32%)
xviii (68%)
O
O
Cembranolides
(d)
Base nucleus of crassim acetate
(ref. 189)

vi, $Bu^nLi$, DABCO, –23 °C; vii, [structure], THF, –23 to 0 °C; viii, NiB, EtOH, 25 °C; ix, TsOH, MeOH, 25 °C; x, $Bu^nLi$, MsCl, LiBr, $Et_2O$, –78 to 25 °C; xi, [structure]; xii, Na–Hg, MeOH, –10 °C

xiii, [structure], DABCO (X = H) or HMPA (X = OLi); xiv, Li, $H_2NEt$; xv, $H_3O^+$

xv, TosCl, DMAP, 0 °C, 3 h; xvi, LDA, THF–hexane, –78 °C; xvii, MeOH, –78 °C; xviii, Li, $Et_2NH$

**Scheme 25** *(continued)*

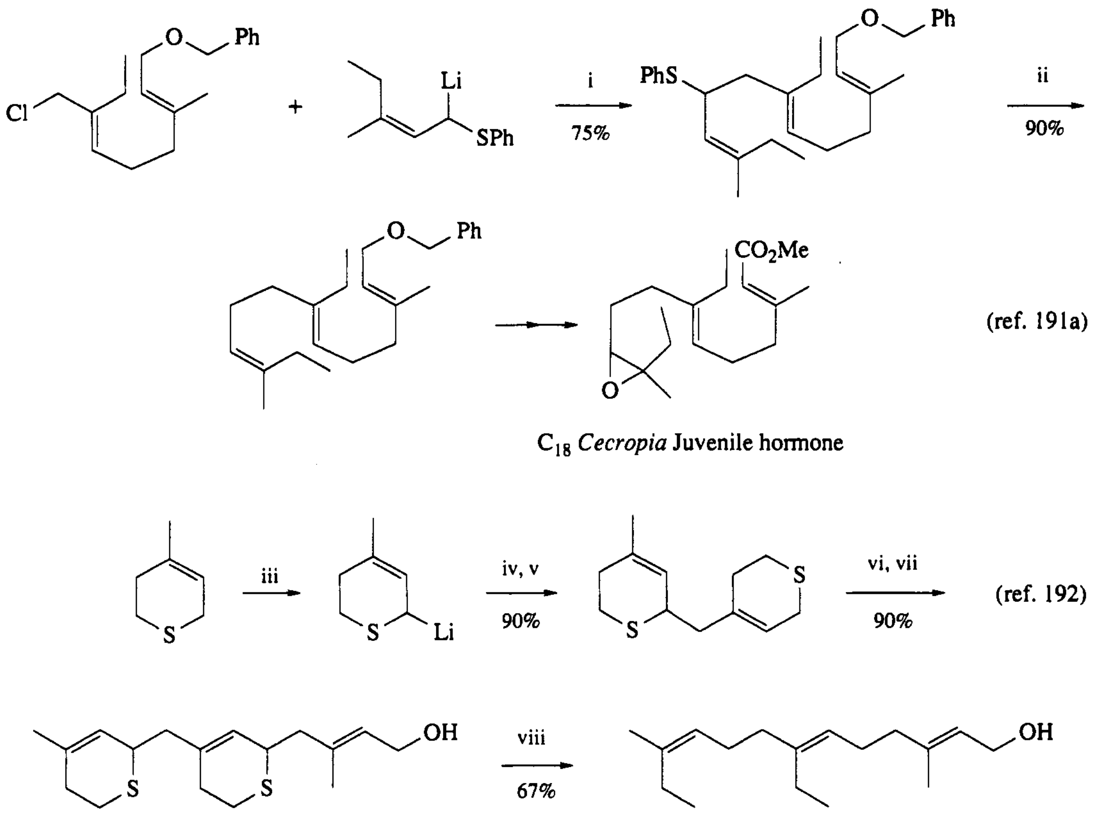

$C_{18}$ *Cecropia* Juvenile hormone

(ref. 191a)

(ref. 192)

i, THF, –78 °C, 1 h; ii, Li, EtNH$_2$, –78 °C, 0.3 h; iii, Bu$^s$Li, TMEDA, THF, –50 °C;

iv, 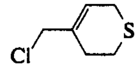 ; v, POCl$_3$; vi, Bu$^s$Li, TMEDA; vii, 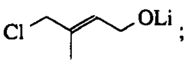 ; viii, Li, EtNH$_2$ (excess), –78 °C

**Scheme 26**

alkoxide in HMPA increased both the rate of the reaction and its yield. Most of these reactions involve intramolecular reactions and allow the synthesis of macrocyclic terpenoids from trisubstituted epoxides.[193–195,198,200,201] Racemic 6,7-epoxygeranyl *t*-butyl sulfide on reaction with Bu$^n$Li–TMEDA produces two cyclobutyl carbinols possessing the fragranol and grandisol carbon skeletons and a single cyclopentanol of undefined stereochemistry.[198] The latter compound arises from the reaction of the α-lithio allyl sulfide at its γ-site, although it is fully substituted (Scheme 29). Higher homologs react from the less hindered site and provide 10-membered,[194,195,200] 12-membered[201] and 14-membered[193] ring terpenoids (Scheme 30).

Several functionalized α-metalloallyl sulfides have been successfully alkylated or hydroxyalkylated on reaction with organic halides or epoxides. Among them, 1-metallo-1,3-di(thio)propenes[203–205] which play the role of β-metallo-α,β-unsaturated aldehydes (—CH=C—CHO; Scheme 31) have proved[203,206,207] particularly useful for the synthesis of δ-alkoxy-α,β-unsaturated aldehydes; they have been used in[203,206] the neat synthesis of prostaglandin $F_{2\alpha}$ from a functionalized oxidocyclopentene derivative (Scheme 31, entry e).

Similar transformations can be achieved from γ-methylthioallyl thiocarbamates[176] or from allyl thiocarbamates[176] (Scheme 32, entries c and d). Both reaction sequences take advantage of the easy sigmatropic rearrangement of allyl thiocarbamates. Furthermore, β-methoxyallyl thiocarbamates have played the role of an acetone enolate (Scheme 32, entry a).[175]

As already mentioned, α-metalloallyl vinyl sulfides[166] and their 2-ethoxy analogs[167] have been selectively alkylated, benzylated and allylated at their α-site, then the resulting compounds have been thermally rearranged to γ,δ-unsaturated aldehydes or γ-oxo aldehydes on heating in aqueous DME (Scheme 21).

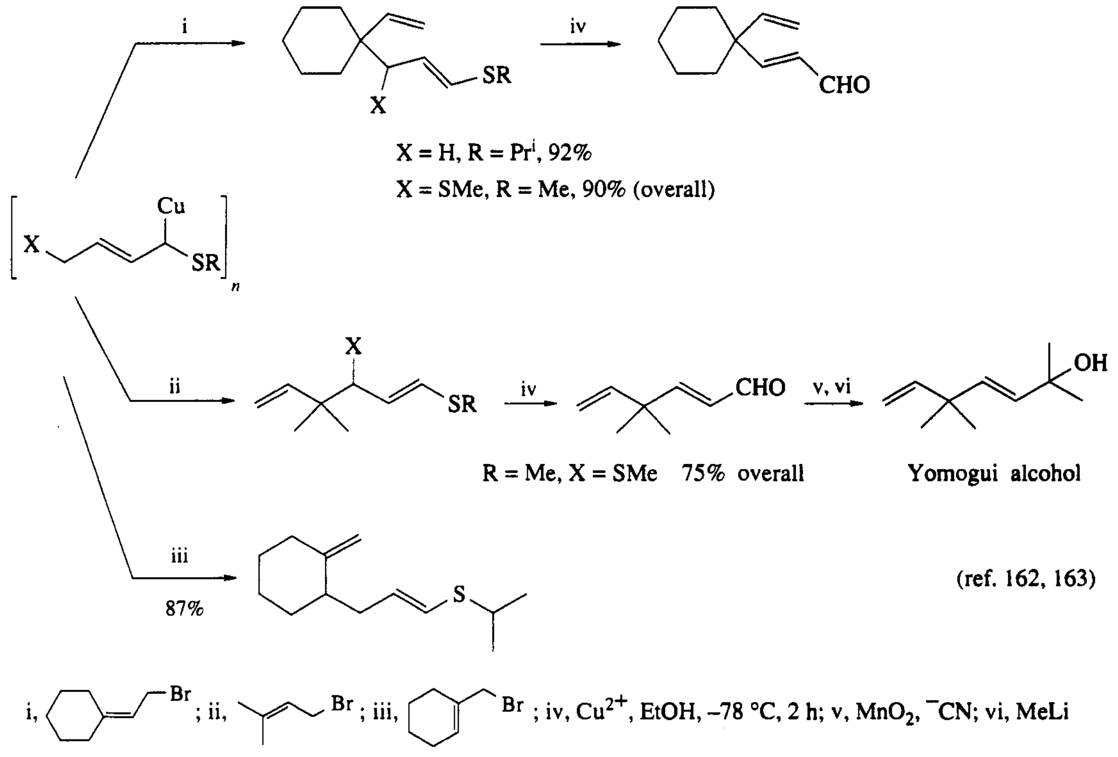
i
X
SR
iv
CHO
X = H, R = Pr$^i$, 92%
X = SMe, R = Me, 90% (overall)
Cu
X
SR
n
ii
X
SR
iv
CHO
v, vi
OH
R = Me, X = SMe 75% overall
Yomogui alcohol
iii
87%
S
(ref. 162, 163)
i, Br ; ii, Br ; iii, Br ; iv, Cu$^{2+}$, EtOH, –78 °C, 2 h; v, MnO$_2$, $^-$CN; vi, MeLi

**Scheme 27**

Relatively few α-selenoallylmetals have been prepared[81,95,96,99,101,208,209] compared to their thio analogs (Scheme 33). These species have proved to be powerful nucleophiles which react efficiently with primary,[81,95,100,101,208,209] secondary[95,100] and benzylic bromides[95,208] and with *N*-(bromomethyl)phthalimide–ZnCl$_2$,[96] as well as with terminal and α,β-dialkyl-substituted epoxides[95,100] (Scheme 33). The reactions take place almost instantaneously (<0.2 h) at low temperature (–78 °C) with primary alkyl halides[95] but require higher temperatures and/or longer reaction times with secondary halides. As for the sulfur analogs α-alkylation prevails (α:γ ratio from 80:20 to 90:10) with allyl phenyl selenides but, in contrast to the 2-thiopyridyl derivative,[16,168,169] 2-pyridylselenoallyllithium[95] did not display efficient enhancement of alkylation from the α-site. This has been associated with the presence of diisopropylamine resulting from the metallation of the selenide with LDA (Bu$^n$Li cannot be used since it leads to allyllithium by Se/Li instead of H/Li exchange)[101] which might prevent[95] lithium chelation with the pyridine nitrogen. Alkylation takes place selectively at the α-position of ω-alkoxy-,[99] γ-chloro-,[95] γ-seleno-[100] and γ-seleno,γ-silyl-substituted α-selenoallyllithiums (Scheme 33).[100]

### *1.3.2.1.4 Alkylation of α-thio-*[21,31] *and α-seleno-propargylic metal derivatives*

Propargylic sulfides[210,211] and selenides have been metallated[102,103] with *n*-butyllithium and lithium amide respectively, and allylated[211] or alkylated selectively at the propargylic position (Scheme 34) with primary and secondary alkyl halides.[102,103,210]

Phenyl propargyl sulfide[211] and selenide[102,103] are rapidly deprotonated by 2 equiv. of base. The resulting dilithio derivatives react at their allylic rather than at their alkynic carbon centers (Scheme 34, entries c and d). Reduction of the sulfides allows the synthesis of 1,5-enynes (Scheme 34, entry b), whereas oxidation of the selenides leads to α-phenylseleno-α,β-unsaturated carbonyl compounds (Scheme 34, entry d).[102,103]

### *1.3.2.1.5 Alkylation of α-metallovinyl sulfides and selenides*

Vinyl sulfides[20] and selenides can be alkylated efficiently at the α-position in a two step–one pot reaction which involves their α-metallation and further reaction of the resulting anion with alkyl halides.

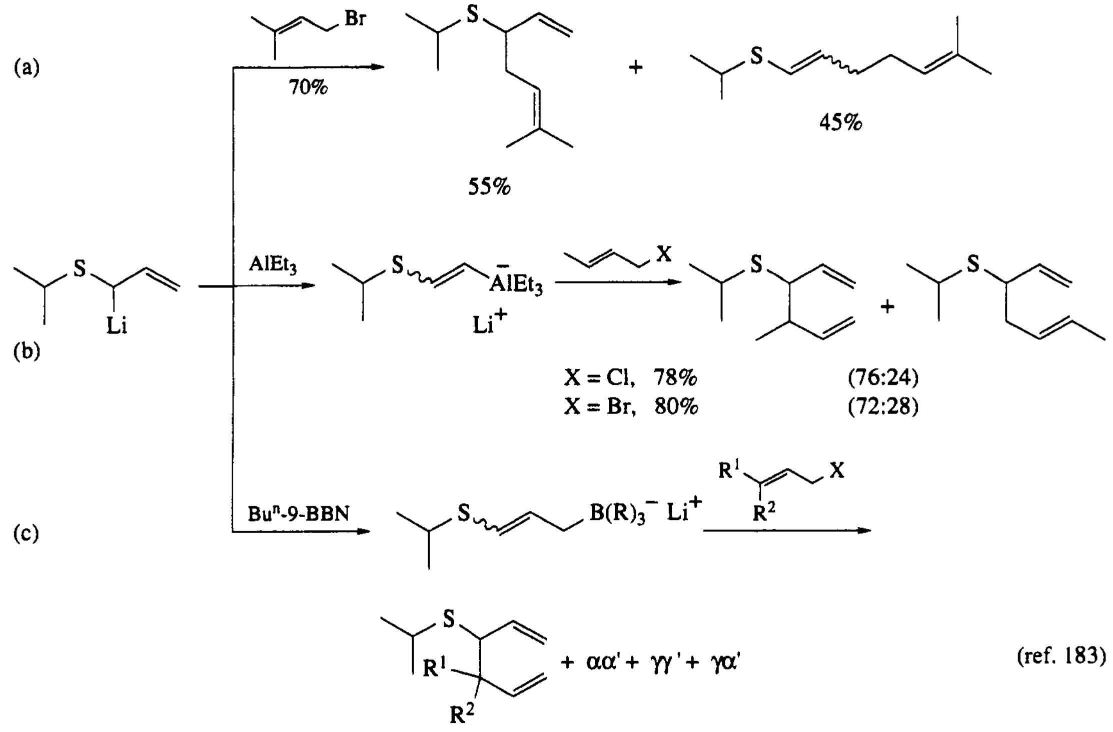

| *R¹* | *R²* | *X* | *Yield (%)* | αγ′ | αα′ | γγ′ | γα′ |
|---|---|---|---|---|---|---|---|
| Me | Me | Cl | 68 | 97 | 3 | – | – |
| Me | H | Br | 77 | 99 | 1 | – | – |
| H | H | Br | 52 | 90 | – | 5 | 5 |

**Scheme 28**

Side reactions which involve Michael type addition of the metallating agent at the terminus of the alkenic double bond[27,110,145,212–214] or cleavage of the C—Se bond[110,145] can be avoided by employing low temperatures and using nonnucleophilic metallating agents in the case of sulfides, and avoiding the use of alkyllithiums for vinyl selenides.

Thus, aryl[107,131,166,215] and alkyl[216] vinyl sulfides have been transformed to the corresponding 1-metallovinyl sulfides with LDA in THF alone,[107,215] or in THF–HMPA,[107] and also with Bu$^s$Li in THF[131] or in THF–HMPA[131,166,216] (Scheme 35, entries a–c), and have been subsequentely alkylated with primary alkyl halides and α,ω-dihalides (Scheme 35). However it has not proved possible to extend the reaction to 1-(2-methylpropenyl) phenyl sulfide.

The corresponding 1-(lithiovinyl) sulfides and related derivatives can be produced in THF alone by reaction of ketene thioacetals with lithium naphthalenide (Scheme 36, entry b).[129,217] This reductive lithiation is however less preferable to deprotonation when alkylation of the anion is planned, since the thiophenoxide anion which is necessarily present, destroys one equivalent of the alkylating agent.[217] Alternatively 1-metallovinyl sulfides, which have been prepared by Sn/Li exchange[82] from 1-(stannyl)vinyl phenyl sulfide or by thiophilic addition[218] of phenyllithium on thioketones, have been methylated with methyl iodide (Scheme 35, entry d).[82,218]

The alkylations of 2-ethoxy-[219] and 2-(*Z*)-alkylthio-1-(alkyl or phenylthio)ethylenes[220] with primary alkyl halides and ethylene oxide have been reported (Scheme 37). The metallations are usually easy, but the alkylation of the former organometallic can be achieved only with primary alkyl halides and on condition that HMPA is used as a cosolvent. Unfortunately the reaction does not take place with benzyl bromide or isopropyl iodide.[219]

1,3-Dienyl sulfides,[213,221] which have been otherwise efficiently alkylated[120] at the allylic position using $KNH_2$ or LDA as the base (Scheme 3, entries a and c) or have added *n*-butyllithium at their δ-site (Scheme 38, entry a),[213] have been selectively alkylated at their α-vinylic site by use of a strong metallating base such as Bu$^n$Li–TMEDA (Scheme 3, entry b) or Bu$^n$Li–Bu$^t$OK (Scheme 38, entry b).[213]

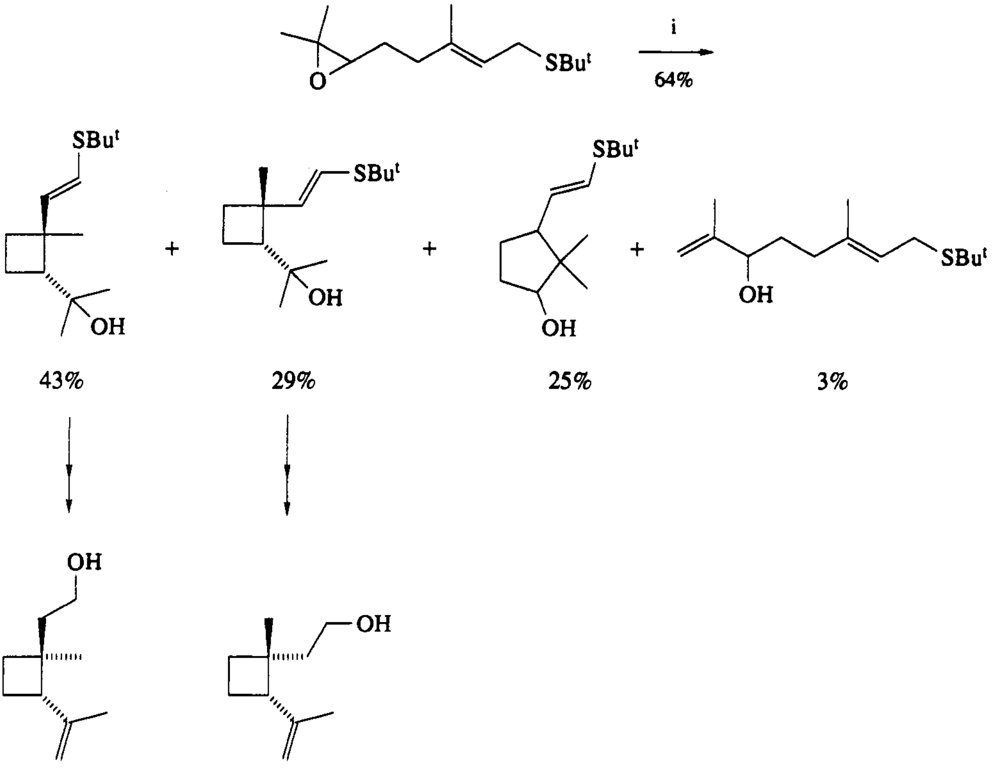

i, Bu$^n$Li–TMEDA, THF–hexane, –75 °C, 3 h; 5 °C, 2 h

Scheme 29

Metallation of various 1-alkynyl sulfides,[222-224] followed by alkylation of the resulting anion leads exclusively to α-alkylated allenyl sulfides (Scheme 39).

The alkylation of aryl vinyl selenides has been carried out by the usual metallation/alkylation sequence.[107,108,110,111] Although the metallation of phenyl and *m*-$CF_3C_6H_4$ vinyl selenide can be achieved with LDA–HMPT,[110] or LDA alone,[107] best results have been obtained with KDA in THF in the case of phenyl vinyl selenide,[108] and with LDA for pyridyl vinyl selenide (Scheme 40).[111] The latter combinations proved valuable for the synthesis of higher homologs bearing one alkyl group in the β-position,[108,111] especially because metallation and alkylation both occur stereoselectively with retention of configuration. Unfortunately, however, alkylation of those aryl vinyl selenides bearing two alkyl groups in the β-positions has not yet been achieved.[107,108]

Alternatively, 1-lithio-1-alkenyl phenyl and methyl selenides have been obtained on reduction of the C—Se bond of 1,1-di(seleno)alkenes with alkyllithiums; this reaction is the only one which allows the synthesis of the methylseleno derivatives (Scheme 41).[83]

Furthermore, allenyl phenyl selenides have been prepared by alkylation of 1-lithioallenyl phenyl selenide, itself produced[103] on metallation of phenyl 1-propynyl selenide or of allenyl phenyl selenide[103] (Scheme 42). 1-Lithioallenyl phenyl selenide has poorer nucleophilic properties[103] than that of α-selenoallyllithiums, since the reaction of the former with 2-phenyl-1-bromoethane gives predominantly styrene, whereas the latter leads to products of substitution in good yield.[103]

## 1.3.2.2 Synthetically Useful Transformations of Alkylated Sulfides and Selenides

### *1.3.2.2.1 Synthetic transformations involving the reduction of sulfides and selenides*

Alkyl, benzyl, allyl and propargyl sulfides and selenides arising from the alkylation of the corresponding heterosubstituted organometallics have been used in several interesting transformations. These transformations take advantage of the easy reduction of the C—S and of the C—Se bond which can be carried

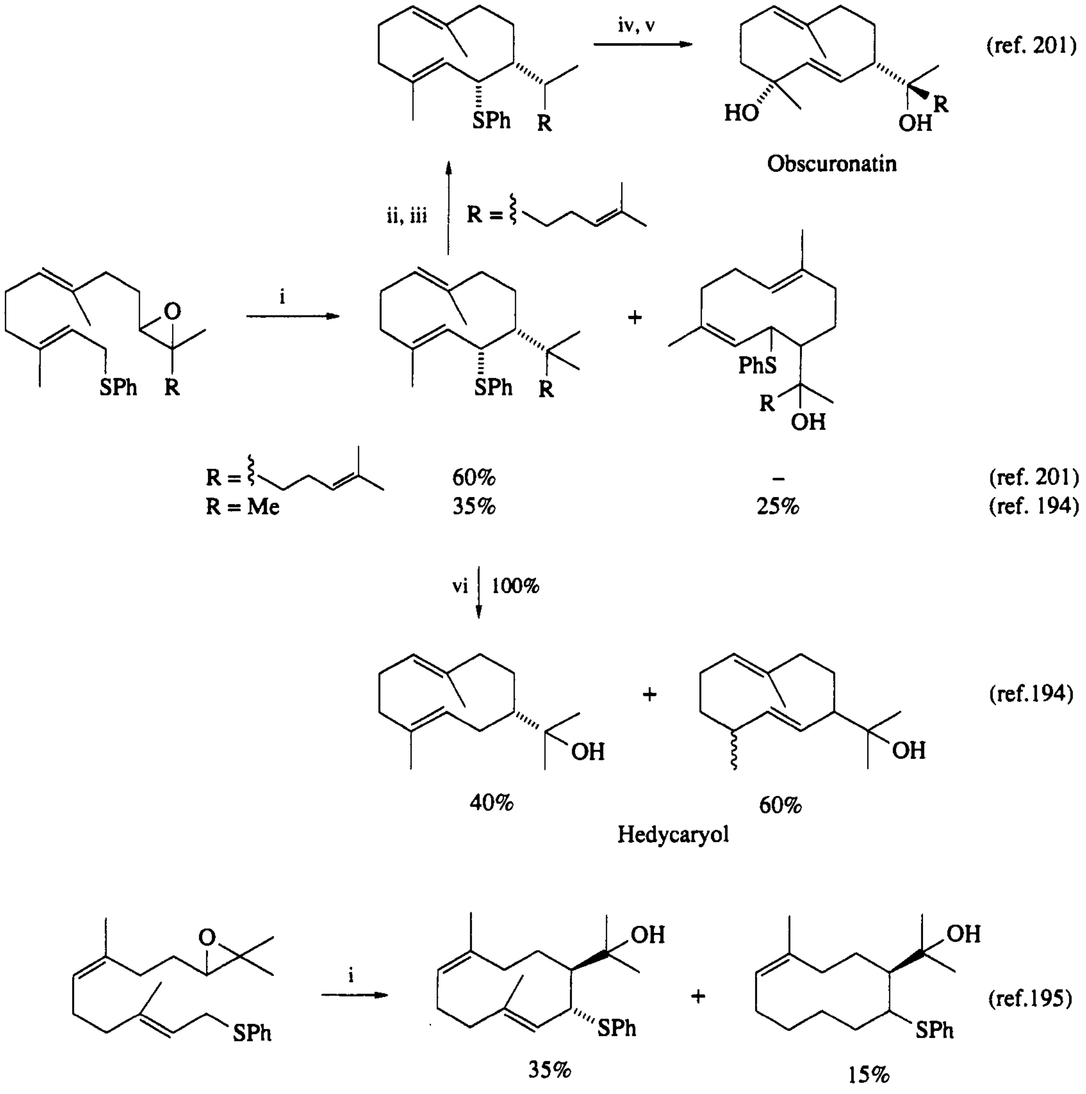

i, $Bu^nLi$, THF, –78 to 20 °C; ii, $POCl_3$, pyridine; iii, $H_2$, $Rh(PPh_3)_3Cl$; iv, $NaIO_4$; v, $Et_2NH$; vi, Li, $Et_2NH$, –78 °C

**Scheme 30**

out in both cases with Raney nickel (Scheme 25; Scheme 43; Scheme 44, entry a),[132a,133,140,153] lithium in ethylamine (Scheme 25, entries a, c and d; Scheme 26; Scheme 34, entry b; Scheme 43),[140,165,186,187,189,191,192,211] nickel boride (Scheme 25),[188] or lithium naphthalenide (Scheme 15).[126] Tributyl- or triphenyl-tin hydrides[144] for their part proved particularly efficient for the reduction of selenides (Scheme 44, entry b).[225,226] Care must be taken in performing such reactions however in the presence of C—C double bonds, to prevent the formation of a five- or a six-membered ring by cyclization of the radical intermediate formed.[227–229]

Selective reduction of allyl sulfides implies that no scrambling of the carbon–carbon double bond occurs during the process. Effectively this has proved to be the case especially when lithium in ethylamine is used, and the method has allowed the regio- and stereo-selective synthesis of a large variety of 1,5-dienes including squalene[165] (Scheme 25, entry a),[165] mukapolide (Scheme 25, entry b),[188] dendrolasin (Scheme 25, entry c), the basic nucleus of crassin acetate (Scheme 25, entry d)[189] from γ,γ-dialkylallyl sulfides and allyl halides, and also of 1,5-enynes[211] from propargyl sulfides and allyl halides (Scheme 34, entry b).

Two original syntheses of $C_{18}$ *Cecropia* juvenile hormones are depicted in Scheme 26,[191,192] both of which use the strategy presented above. The second synthesis is particularly ingenious since the dihydro-

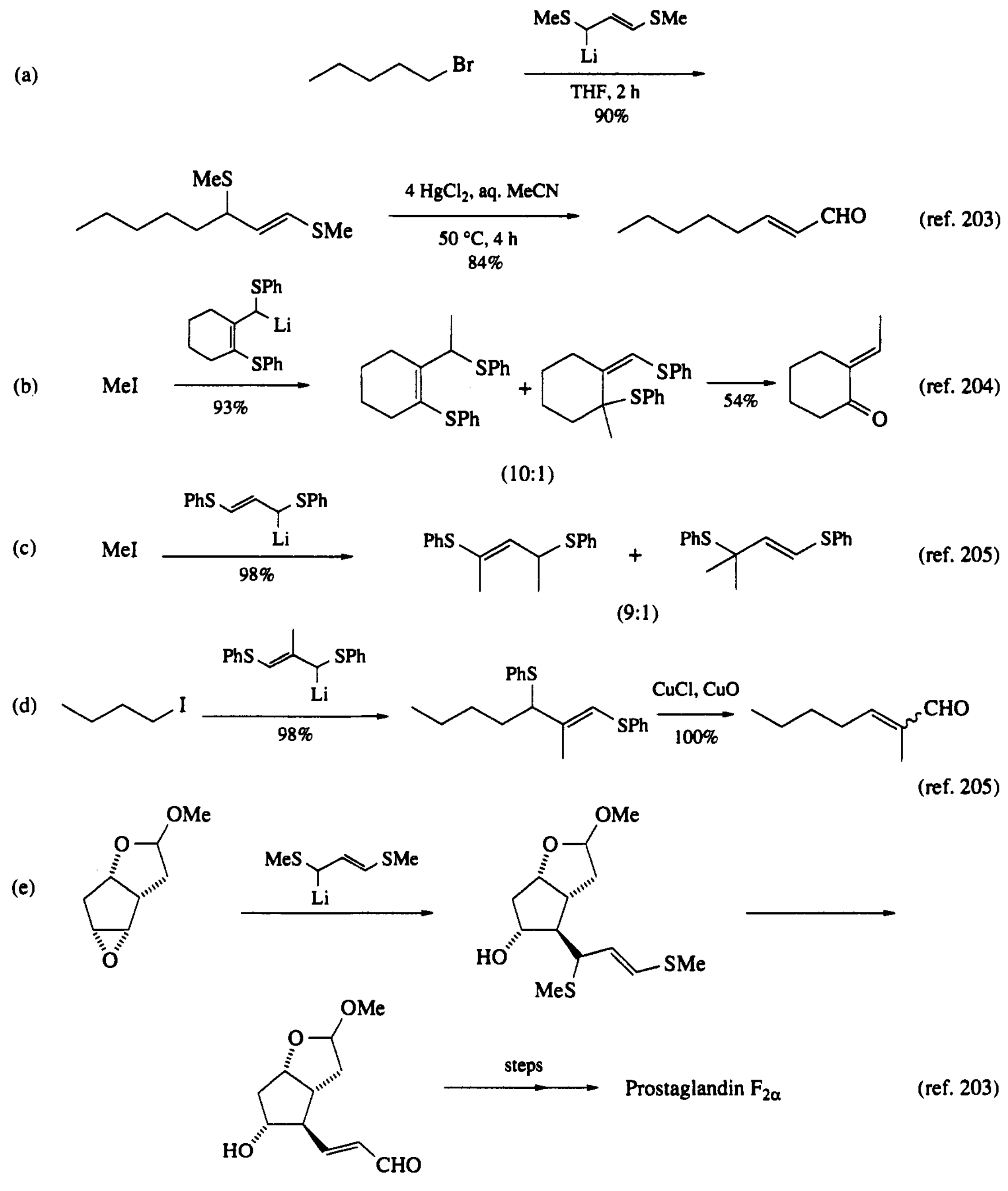
(a)
Br
MeS
SMe
Li
THF, 2 h
90%
4 HgCl2, aq. MeCN
50 °C, 4 h
84%
CHO
(ref. 203)
(b)
MeI
SPh
Li
93%
(10:1)
54%
O
(ref. 204)
(c)
PhS
98%
(9:1)
(ref. 205)
(d)
I
CuCl, CuO
100%
(ref. 205)
(e)
OMe
HO
steps
Prostaglandin F2α
(ref. 203)

**Scheme 31**

thiopyran building block allows both the regioselective construction of the polyenic system and the control of the stereochemistry of the (*Z*)-trisubstituted carbon–carbon double bonds. Reduction of benzyl and allyl sulfides, including allyl 2-pyridyl sulfides has also been performed[168,169] with $CuCl_2$–$LiAlH_4$, in some cases in the presence of lithium methoxide.[169] Sequential alkylation of allyl 2-pyridyl sulfide and reduction with $CuCl_2$–$LiAlH_4$ proceeds regioselectively and leads[15,168] to terminal as well as trisubstituted alkenes (Scheme 45).[169] Under similar conditions γ,γ-dimethylallyl 2-pyridyl sulfide is alkylated or benzylated selectively in the α-position, but finally leads to a mixture of alkenes resulting from the partial scrambling of the carbon–carbon double bond. This set of reactions has been applied to the synthesis of *cis*-bergamotene (Scheme 45, entry b).[169]

Otherwise, reduction of allylic dithiocarbamates proved regio- and stereo-selective when carried out with lithium in ethylamine (Scheme 32),[177] but leads to a mixture of alkenic compounds when carried out with Raney nickel.[174]

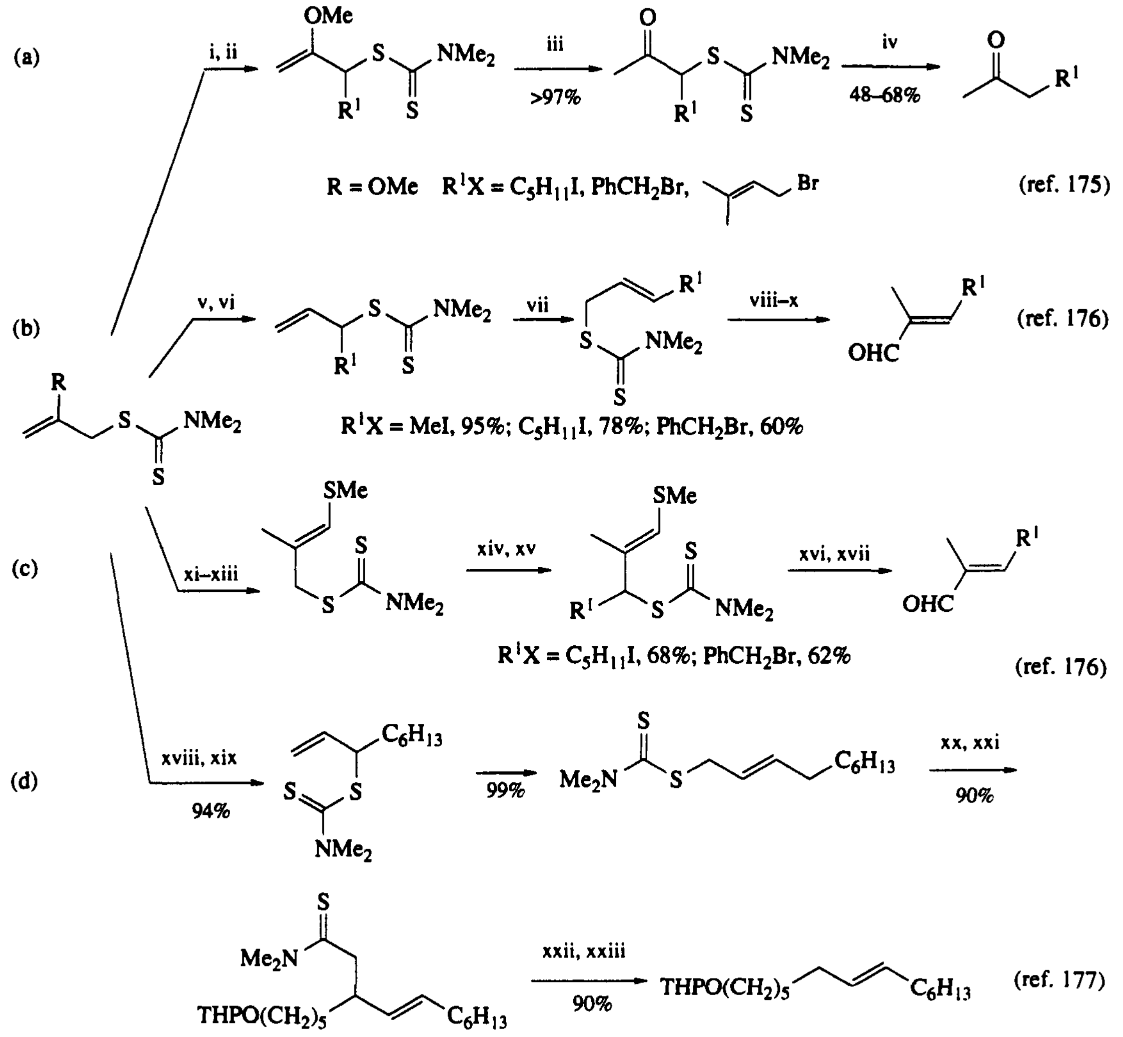
(a)
i, ii
OMe
NMe2
iii
>97%
iv
48–68%
R = OMe R'X = C5H11I, PhCH2Br, Br
(ref. 175)
(b)
v, vi
vii
viii–x
OHC
(ref. 176)
R'X = MeI, 95%; C5H11I, 78%; PhCH2Br, 60%
(c)
xi–xiii
SMe
xiv, xv
xvi, xvii
R'X = C5H11I, 68%; PhCH2Br, 62%
(ref. 176)
(d)
xviii, xix
94%
C6H13
99%
Me2N
xx, xxi
90%
xxii, xxiii
90%
THPO(CH2)5
(ref. 177)

i, LDA; ii, $R^1X$; iii, $H_3O^+$, MeOH; iv, Raney Ni, acetone, reflux, 3 h; v, LDA; vi, $R^1X$; vii, Δ, 3 h; viii, LDA; ix, MeSSMe; x, $Hg^+$, aq. MeCN; xi, LDA; xii, MeSSMe; xiii, Δ; xiv, LDA; xv, $R^1X$; xvi, Δ; xvii, $Hg^+$, aq. MeCN; xviii, LDA; xix, $C_6H_{13}I$; xx, $Pr^i(C_6H_{13})NLi$; xxi, $THPO(CH_2)_5I$; xxii, Li, $H_2NEt$; xxiii, 3-hexyne

**Scheme 32**

Benzyl phenyl sulfides can be sequentially metallated and alkylated. The cleavage of the carbon–sulfur bond in the resulting product leads to a benzyllithium and lithium phenylthiolate.[126] Alkylation of the former organometallic then produces an alkylbenzene (Scheme 15), but competing alkylation on the thiolate is however observed.[126]

An efficient geminal 'reductive alkylation' of the carbonyl group of aliphatic aldehydes and ketones, including that of cyclic ketones, takes advantage of: (i) the great availability of α-selenoalkyllithiums (themselves readily prepared from the corresponding carbonyl compounds *via* the selenoacetals);[84] (ii) their alkylation with primary alkyl halides; and (iii) the reduction of the corresponding selenides.[140] A specific example of this process, presented in Scheme 44 (entry a), describes an efficient synthesis of vitamin D.[144] A related reaction involving the reductive allylation of heptanal is recorded in Scheme 10.[123,127,147,226] The case of aromatic aldehydes and ketones is even more interesting since (i) the related α-selenobenzyllithiums can be alkylated even with *s*-alkyl halides[74,79,80,105,106] as well as with benzyl bromide,[105] and (ii) because the resulting benzyl selenides on reaction with *n*-butyllithium can be cleaved to produce benzyllithiums. The benzyllithiums in turn can be alkylated even with secondary alkyl

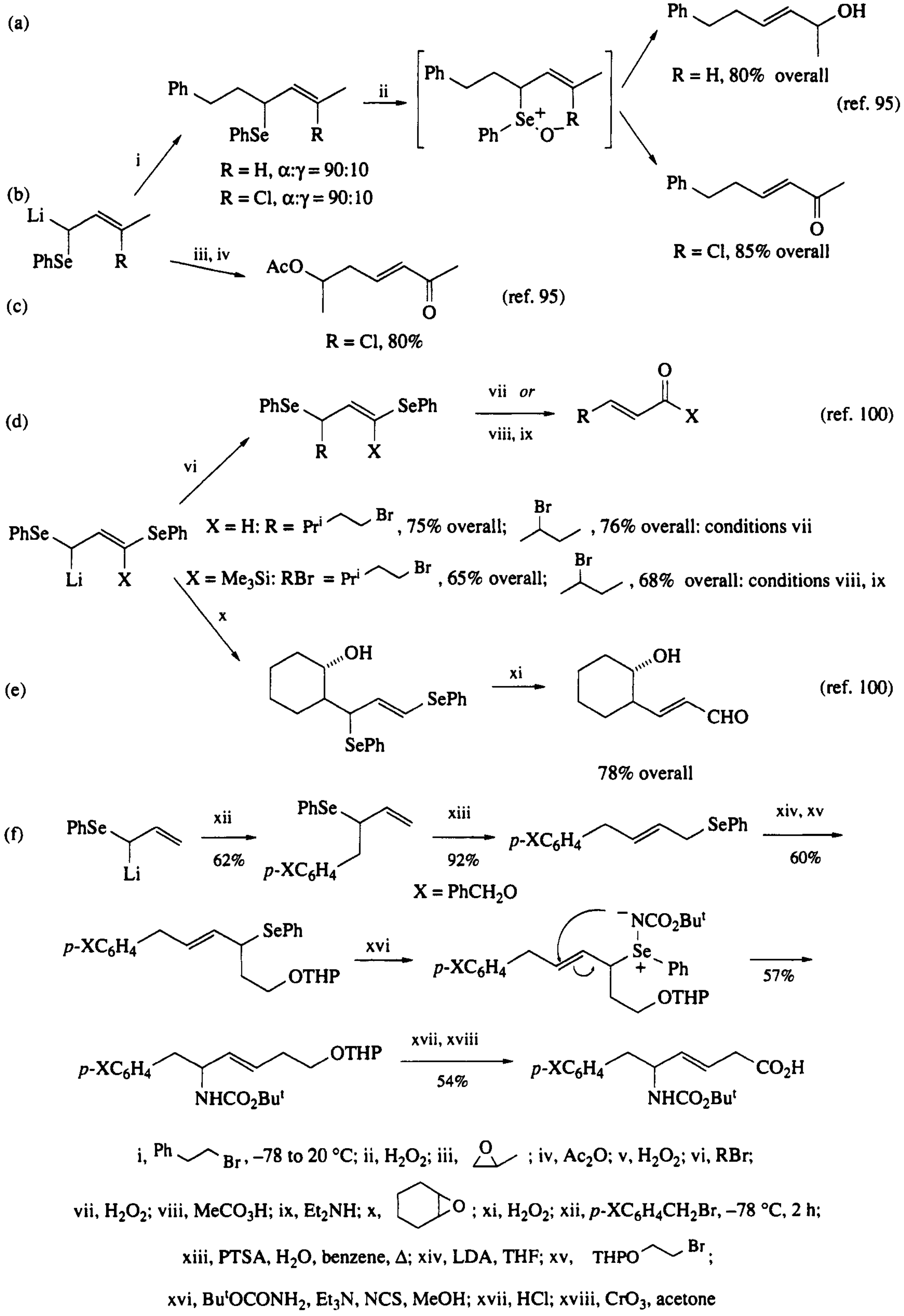
(a)
(b)
(c)
(d)
(e)
(f)
i
ii
iii, iv
PhSe
Ph
R
Li
R = H, α:γ = 90:10
R = Cl, α:γ = 90:10
Se+
O−
R = H, 80% overall
R = Cl, 85% overall
(ref. 95)
AcO
O
R = Cl, 80%
(ref. 95)
vi
vii or
viii, ix
SePh
X
(ref. 100)
X = H: R = Pri Br, 75% overall; Br, 76% overall: conditions vii
X = Me3Si: RBr = Pri Br, 65% overall; Br, 68% overall: conditions viii, ix
x
xi
OH
CHO
78% overall
(ref. 100)
xii
62%
xiii
92%
p-XC6H4
X = PhCH2O
xiv, xv
60%
OTHP
xvi
−NCO2But
Se
+
Ph
57%
NHCO2But
xvii, xviii
54%
CO2H

i, Ph Br, −78 to 20 °C; ii, $H_2O_2$; iii, ; iv, $Ac_2O$; v, $H_2O_2$; vi, RBr;

vii, $H_2O_2$; viii, $MeCO_3H$; ix, $Et_2NH$; x, ; xi, $H_2O_2$; xii, p-$XC_6H_4CH_2Br$, −78 °C, 2 h;

xiii, PTSA, $H_2O$, benzene, Δ; xiv, LDA, THF; xv, THPO Br;

xvi, $Bu^tOCONH_2$, $Et_3N$, NCS, MeOH; xvii, HCl; xviii, $CrO_3$, acetone

Scheme 33

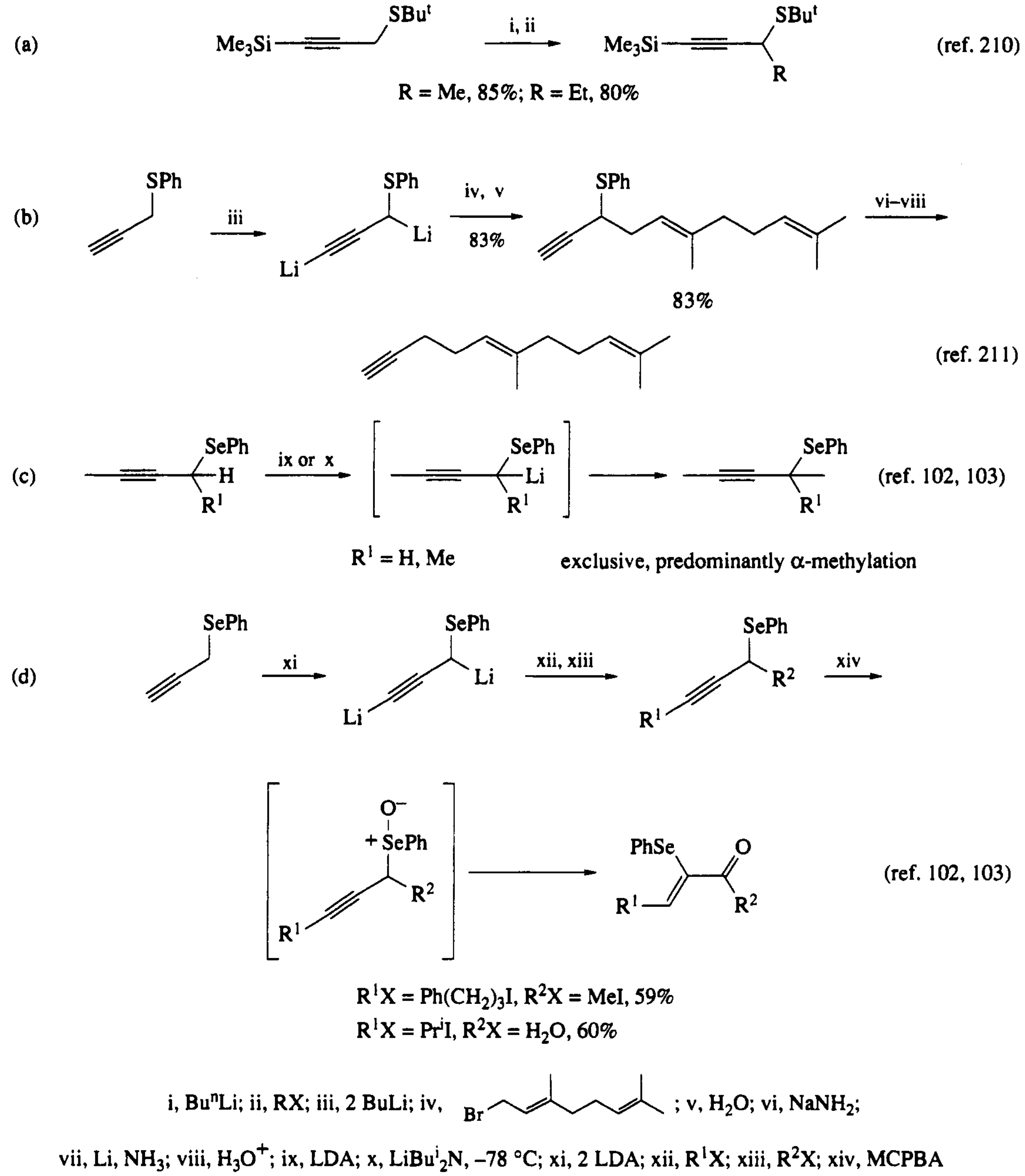
(a)
Me3Si
SBut
i, ii
R
R = Me, 85%; R = Et, 80%
(ref. 210)
(b)
SPh
iii
Li
iv, v
83%
vi–viii
83%
(ref. 211)
(c)
SePh
H
R1
ix or x
Li
R1 = H, Me
exclusive, predominantly α-methylation
(ref. 102, 103)
(d)
SePh
xi
Li
xii, xiii
R1
R2
xiv
O−
+SePh
PhSe
O
(ref. 102, 103)
R1X = Ph(CH2)3I, R2X = MeI, 59%
R1X = PriI, R2X = H2O, 60%
i, BunLi; ii, RX; iii, 2 BuLi; iv,
Br
; v, H2O; vi, NaNH2;
vii, Li, NH3; viii, H3O+; ix, LDA; x, LiBui2N, −78 °C; xi, 2 LDA; xii, R1X; xiii, R2X; xiv, MCPBA

**Scheme 34**

halides. This process therefore allows the geminal dialkylation of the carbonyl group of aromatic aldehydes and ketones, and permits the synthesis of particularly hindered alkylbenzenes (Scheme 17, entry a).[79,80,230] Selenoacetals derived from aromatic carbonyl compounds as well as benzyl selenides bearing carbon–carbon double bonds in a suitable position possess a high tendency to cyclize leading to aryl cycloalkanes on reaction with tin hydrides or on reaction with *n*-butyllithium, followed by hydrolysis of the resulting alkyllithium (Scheme 46).[228,231,232] The reaction of tin hydrides with the benzyl selenide shown in Scheme 46 (entry c) leads to a mixture of cyclopentane and cyclohexane derivatives (Scheme 46, entry d).[228] The reaction is much more selective when carried out with BunLi since not only does it provide the five-membered cycle exclusively, but it also produces stereoselectively each of the two stereoisomers depending upon the solvent used.[228]

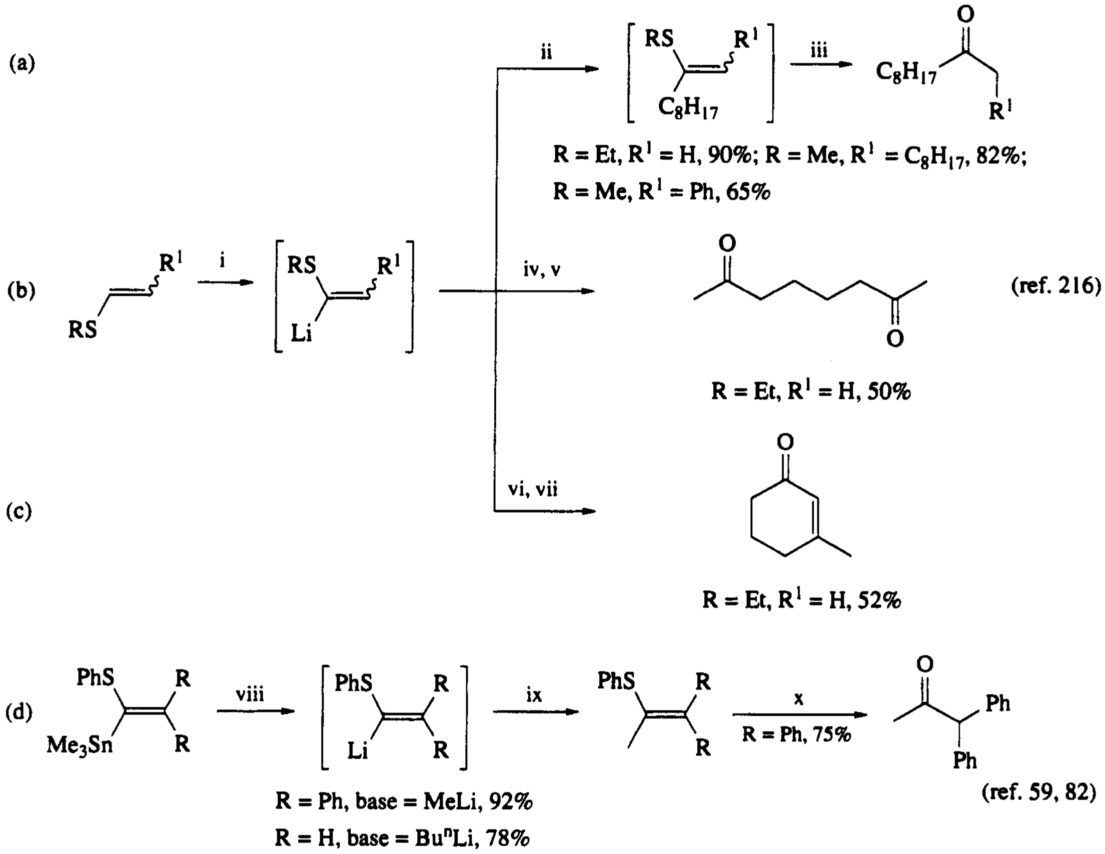
(a)
(b)
(c)
(d)
RS
R¹
Li
C₈H₁₇
O
i
ii
iii
iv, v
vi, vii
R = Et, R¹ = H, 90%; R = Me, R¹ = C₈H₁₇, 82%;
R = Me, R¹ = Ph, 65%
R = Et, R¹ = H, 50%
R = Et, R¹ = H, 52%
(ref. 216)
PhS
Me₃Sn
R
Ph
viii
ix
x
R = Ph, 75%
R = Ph, base = MeLi, 92%
R = H, base = BuⁿLi, 78%
(ref. 59, 82)

i, $Bu^sLi$, THF–HMPA, –78 °C; ii, $C_8H_{17}Br$; iii, $HgCl_2$, aq. MeCN; iv, $Br(CH_2)_4Br$; v, $HgCl_2$, aq. MeCN; vi, $Br(CH_2)_3Br$; vii, $HgCl_2$, aq. MeCN; viii, base; ix, MeI; x, $TiCl_4$, aq. $MeCO_2H$

Scheme 35

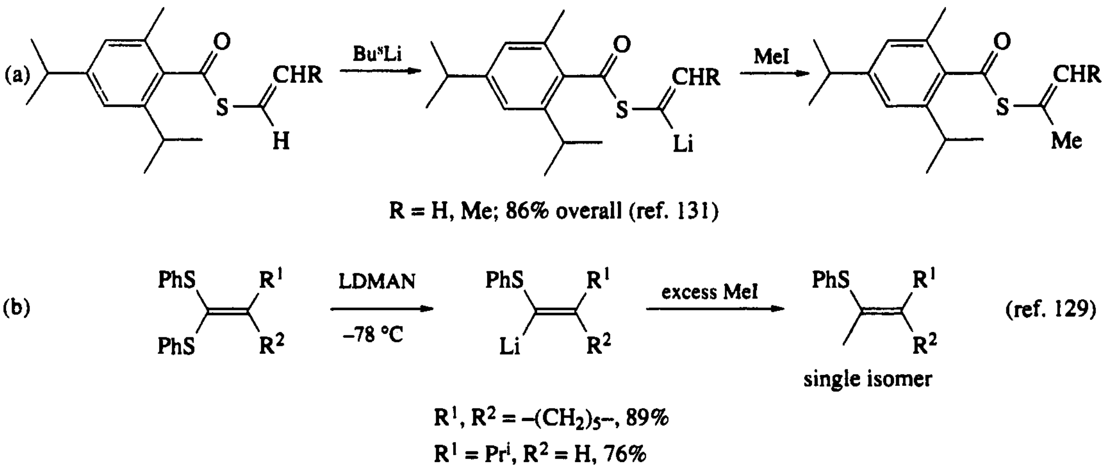
(a)
O
S
CHR
H
BuˢLi
Li
MeI
Me
R = H, Me; 86% overall (ref. 131)
(b)
PhS
R¹
R²
LDMAN
–78 °C
Li
excess MeI
single isomer
(ref. 129)
R¹, R² = –(CH₂)₅–, 89%
R¹ = Prⁱ, R² = H, 76%

Scheme 36

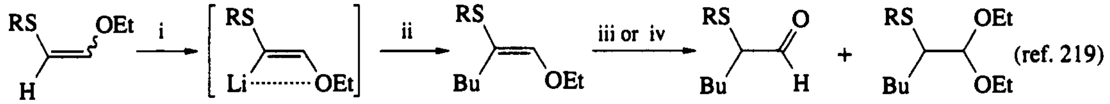
RS
OEt
H
i
RS
Li
OEt
ii
RS
Bu
OEt
iii or iv
RS
O
Bu
H
+
RS
OEt
Bu
OEt
(ref. 219)

(a) $R = C_5H_{11}$, X = Br, 42% iii, exclusively –

$R = C_5H_{11}$, X = I, 60% iv, – exclusively

(b) R = Ph, X = I, 55%

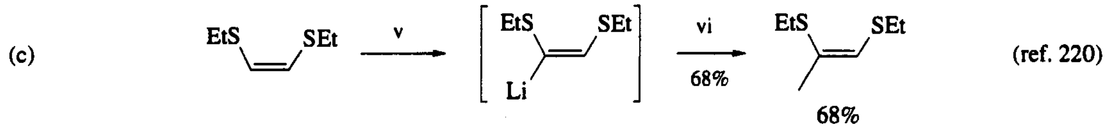
(c)
EtS
SEt
v
EtS
SEt
Li
vi
68%
EtS
SEt
68%
(ref. 220)

i, Bu$^t$Li, THF, –70 °C, 1 h; ii, BuX, THF–HMPA; iii, AcOH, 50%; iv, *p*-TsOH, EtOH, 50 °C; v, LDA, THF, –78 °C, 1 h; vi, MeI

**Scheme 37**

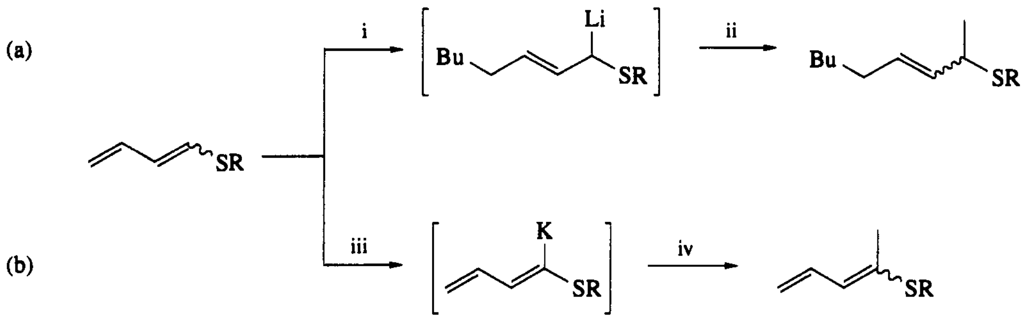
(a)
i
Li
Bu
SR
ii
Bu
SR
SR
(b)
iii
K
SR
iv
SR

Starting material *(E)*: R = Me, 90% *(E)*; R = Bu$^t$, 85% *(E)*

Starting material *(Z)*: R = Me, 85% *(Z)*; R = Bu$^t$, 83% *(Z)*

i, Bu$^n$Li; ii, MeI; iii, Bu$^n$Li–Bu$^t$OK, THF, –65 °C; iv, MeI

**Scheme 38**

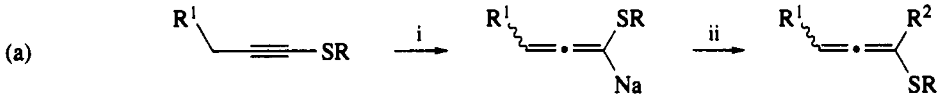
(a)
R1
SR
i
R1
SR
Na
ii
R1
R2
SR

R = Et; $R^1$ = H, Me; $R^2$ = Et, Pr$^i$; 70–75% (ref. 222)

R = Me; $R^1$ = OMe; $R^2$ = Et, 93%; $R^2$ = Pr$^i$, 56%; $R^2$ = Pr$^i$, 86% (using 1 equiv. HMPA) (ref. 224)

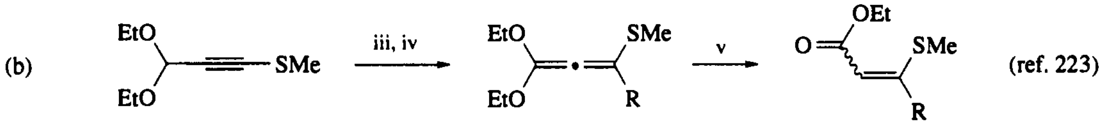
(b)
EtO
EtO
SMe
iii, iv
EtO
EtO
SMe
R
v
OEt
O
SMe
R
(ref. 223)

R = Me, 90%; R = Et, 89%; R = Bu$^i$, 80%

i, $NaNH_2$, liq. $NH_3$; ii, $R^2Br$, THF; iii, $LiNEt_2$; iv, RX; v, $HgCl_2$, MeOH

**Scheme 39**

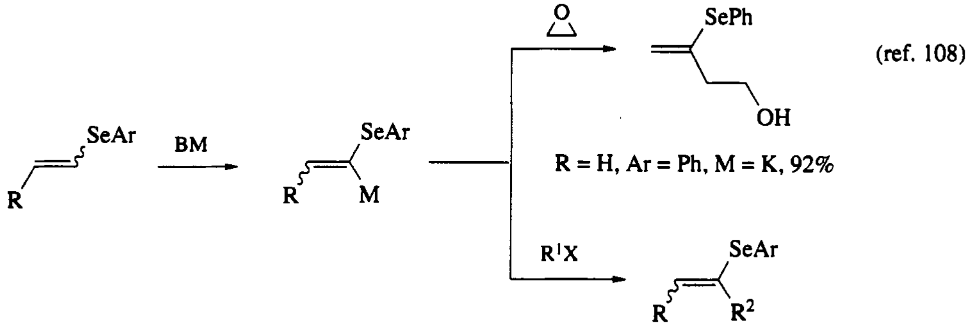
SeAr
R
BM
SeAr
R
M
O
SePh
OH
R = H, Ar = Ph, M = K, 92%
(ref. 108)
R¹X
SeAr
R
R²

| | *Reactants* | *Temperature* (°C) | *R* | *Ar* | *$R^1X$* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | LDA, THF–HMPA | –78 | H | Ph | $C_{10}H_{21}Br$ | 70 | 110 |
| (b) | LDA, THF–HMPA | –78 | H | *m*-$CF_3C_6H_4$ | BuI | 85 | 107 |
| (c) | KDA, THF | –78 | H | Ph | MeI | 98 | 108 |
| | KDA, THF | –78 | H | Ph | $C_{10}H_{21}Br$ | 94 | 108 |
| (d) | KDA, THF | –78 | Bu | Ph | MeI | 85[a] | 108 |
| (e) | LDA, THF | –78 | $C_6H_{13}$ | Pyr | MeI | 94[a] | 111 |

[a] *(E/Z)* stereochemistry retained

**Scheme 40**

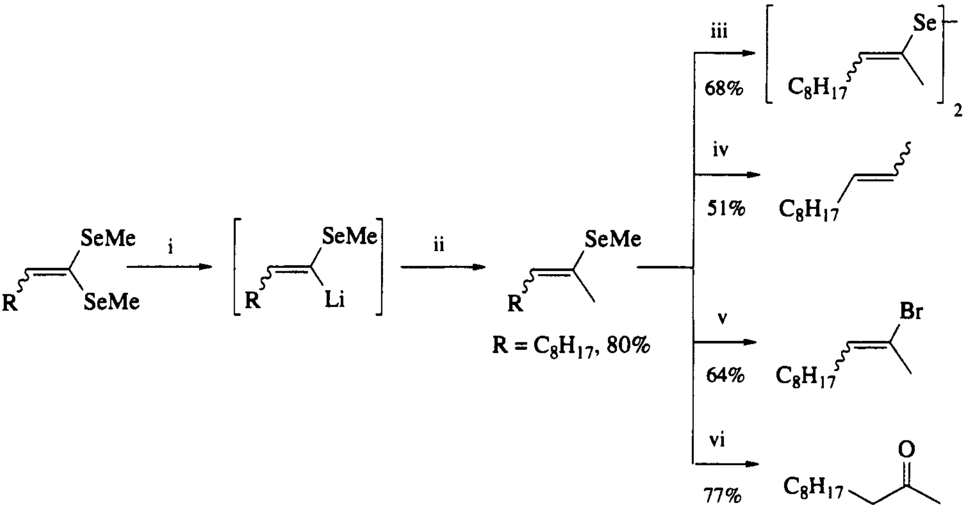
SeMe
R
SeMe
i
SeMe
R
Li
ii
SeMe
R
R = C₈H₁₇, 80%
iii
68%
Se
C₈H₁₇
2
iv
51%
C₈H₁₇
v
64%
Br
C₈H₁₇
vi
77%
O
C₈H₁₇

i, $Bu^nLi$, THF, –78 °C; ii, MeI; iii, Li, $EtNH_2$, –15 °C, 1 h; iv, $Bu_3SnH$, AIBN, 90 °C, 3 h; v, $Br_2$, benzene; vi, $Br_2$, EtOH, 90 °C, 6 h

**Scheme 41**

### *1.3.2.2.2 Transformations of sulfides and selenides to alkenes*

Alkyl sulfides and selenides have proved to be valuable precursors of alkenes (Scheme 17, entry b; Scheme 47; Scheme 48; Scheme 49; Scheme 50).[74,104,157] These transformations can be achieved *via* the corresponding sulfoxides (Scheme 47)[153,233] and selenoxides (Scheme 17, entry b)[23,45,47,52,53,63,74,104,234] which collapse to alkenes and sulfenic or seleninic acid respectively on thermolysis. The elimination reaction takes place under particularly mild and neutral conditions with selenides ($Bu^tO_2H$, $Al_2O_3$, THF,

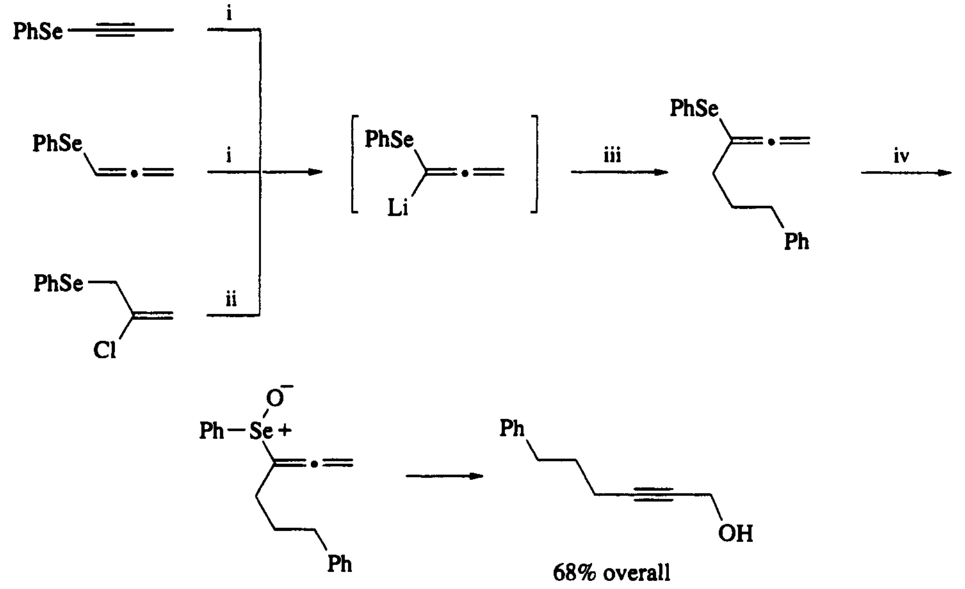
PhSe
i
ii
iii
iv
PhSe
Li
Ph
Ph—Se+
O⁻
Cl
OH
68% overall

i, LDA, THF, −78 °C; ii, 2LDA, THF, −78 °C; iii, $Ph(CH_2)_3I$, 1 h; iv, 30% aq. $H_2O_2$, $CH_2Cl_2$, pyridine

**Scheme 42**

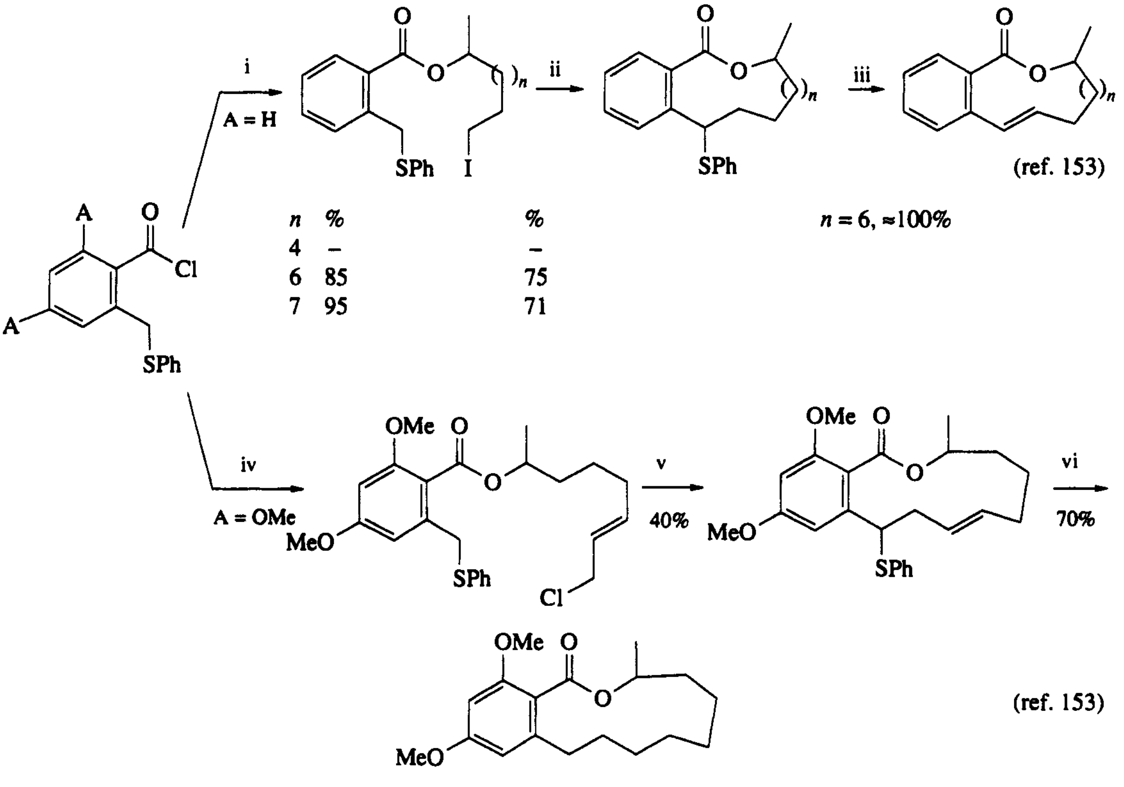
A = H
A = OMe
i
ii
iii
iv
v
vi
40%
70%
SPh
I
Cl
OMe
MeO
n %
4 –
6 85
7 95
%
–
75
71
n = 6, ≈100%
(ref. 153)
(ref. 153)

*O*-Methyllasiodiplodin

i, 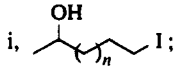 ; ii, $KN(SiMe_3)_2$, 40 °C, 2 h; iii, $NaIO_4$, toluene, 110 °C; iv, 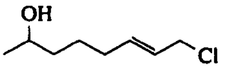 ;
v, $KN(SiMe_3)_2$, 40 °C; vi, Raney Ni, EtOH, 80 °C

**Scheme 43**

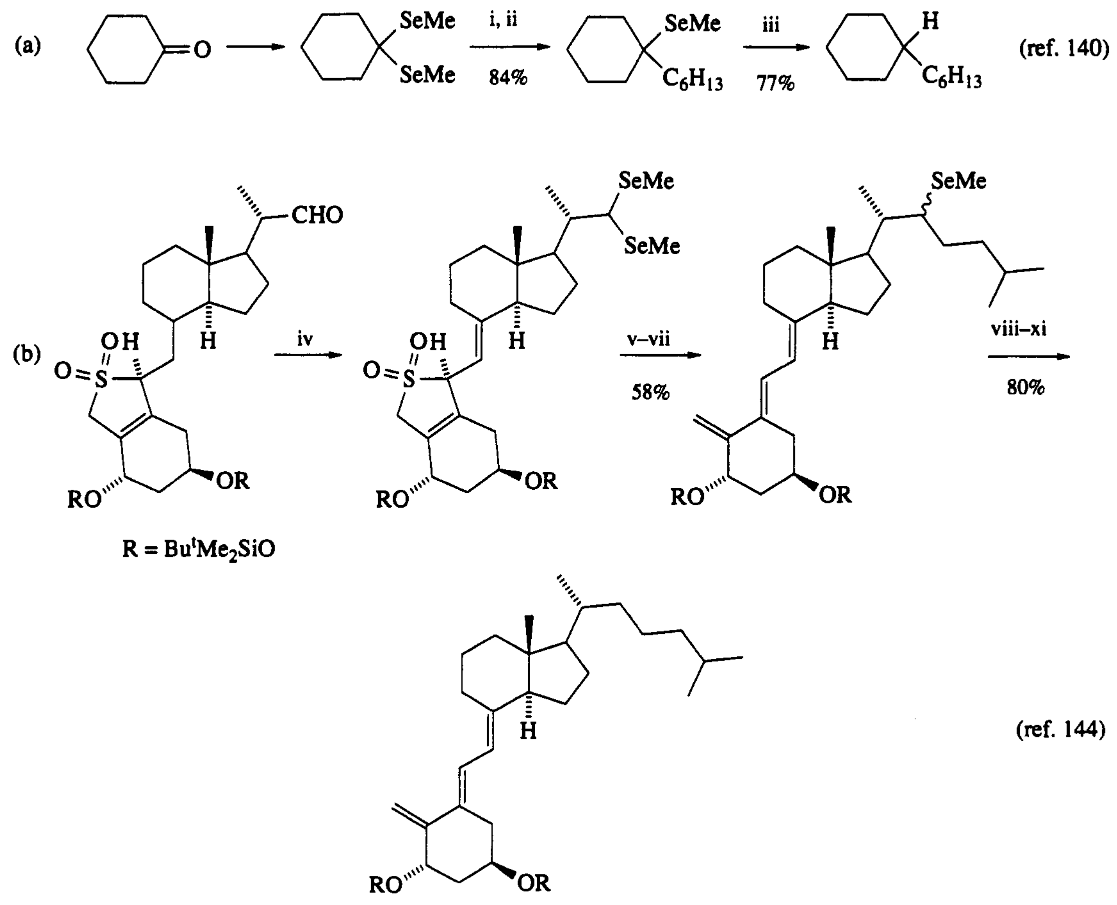

i, Bu$^n$Li, ii, $C_6H_{13}I$; iii, Li/$H_2NEt$; iv, $B(SeMe)_3$, $CF_3CO_2H$, $CH_2Cl_2$, 5 °C; v, $NaHCO_3$, EtOH, 80 °C;

vi, 1 Bu$^n$Li, 0.2 h; vii, 1.5 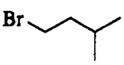 ; viii, $Bu_3SnH$, AIBN, toluene, 100 °C; ix, $SO_2$;

x, 2.2 $Bu_3SnH$, *hv*, toluene, 20 °C; xi, $NaHCO_3$, EtOH, 80 °C

**Scheme 44**

60 °C, 3 h or $H_2O_2$, THF, 20 °C),[142] but usually leads to a regioisomeric mixture of alkenes. It is however, particularly useful for the synthesis of 1-alkenes and 1-arylalkenes from the corresponding selenides, themselves available from alkyl halides and selenomethyllithiums or selenobenzyllithiums[74,104,105] respectively, since, in these examples, there is only one possible regiochemical outcome, and also for the synthesis of 1,3-dienes from allyl halides[74,127] and α-selenoalkyllithiums (Scheme 10; Scheme 17, entry b) because the presence of an allylic hydrogen in the β-position to the selenoxide directs the elimination towards the original double bond. The overall strategy is particularly useful for the synthesis of terminal alkenes, alkylidene-cyclopropanes and -cyclobutenes from primary alkyl halides and selenomethyllithium,[52,70] 1-selenocyclopropyllithiums[70] and 1-selenocyclobutyllithiums[71] respectively (Scheme 48), and for the synthesis of allylidene cyclopropanes from allyl halides and 1-seleno-[70] or 1-thio-cyclopropyllithiums (Scheme 5, entry a).[127]

The other set of reactions which allow the transformation of sulfides and selenides to alkenes require the intermediary formation of a sulfonium or selenonium salt, and their treatment with a base such as KOH or Bu$^t$OK.[52,70,71,127] Furthermore, conjugated dienes, trienes and polyenes have been produced[157,172,173] from allyl halides and benzyl and allyl dithiocarbamates respectively, using the set of reactions illustrated in Schemes 48, 49 and 50, and the transformation has been applied *inter alia* to the synthesis of β-parinaric acid (Scheme 50).[172]

The oxidation of allylic sulfides with equivalent amounts of, for example, peroxyacids or sodium periodide leads to allylic sulfoxides.[16] These sulfoxides do not usually eliminate sulfenic acid to provide

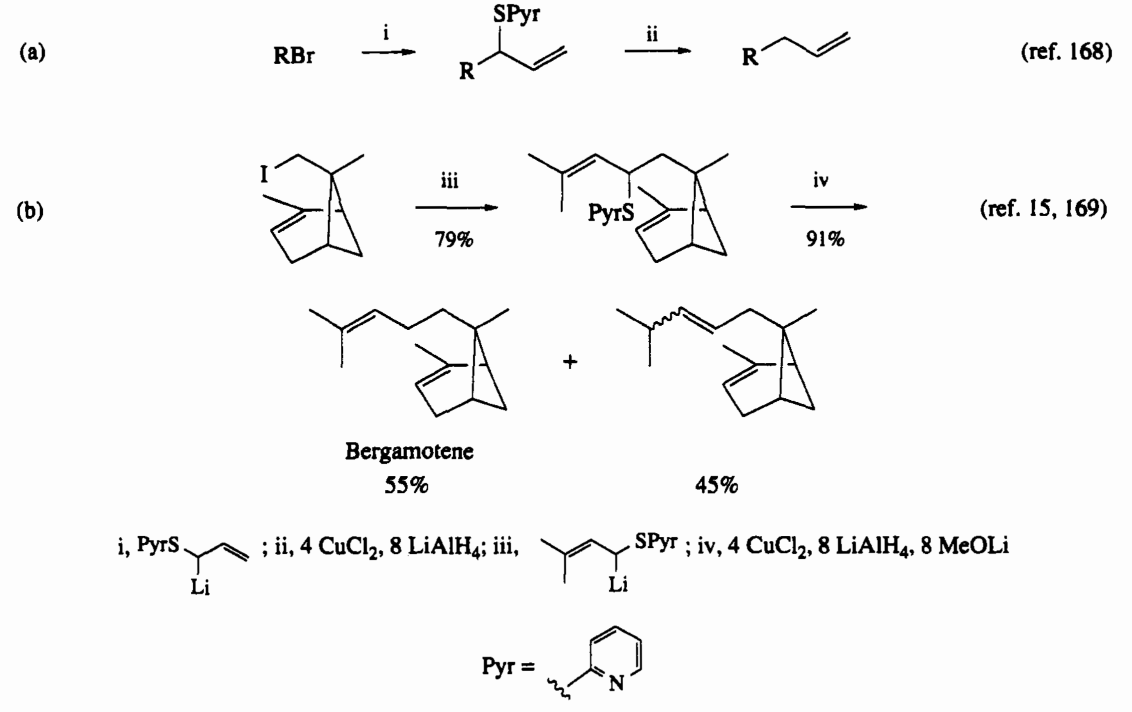

**Scheme 45**

dienes, but instead produce[16,170] allyl alcohols *via* a [2,3] sigmatropic rearrangement when treated with a thiophilic agent such as a secondary amine or a phosphite (Scheme 51).[235,236]

The rearrangement of allyl selenoxides is even easier; it takes place directly at room temperature when allyl selenides are oxidized with hydrogen peroxide (30% aq. solution in THF)[45,46,52-54,56,63] or peroxyacids. Allyl selenides produce allyl alcohols, whereas γ-chloro-,[95] γ-seleno-[100] and γ-seleno-γ-trimethylsilyl analogs[100] lead to α,β-unsaturated aldehydes, ketones and trimethylsilyl ketones respectively (Scheme 33, entries a–e). Therefore the corresponding α-lithium salts play the role of a masked β-lithioallyl alcohol (Li—C═C—COH) or a masked β-lithio-α,β-unsaturated carbonyl compound (Li—C═C—C(═O)X) respectively.

Oxidative rearrangements of allylic selenides in the presence of various amine nucleophiles provide synthetic access to a variety of allylic amine derivatives.[208,209] The stereochemical outcome of these reactions is consistent with a [2,3] sigmatropic rearrangement. The reaction has been applied to the synthesis of β,γ-unsaturated-α-amino acids[209] or to their *trans*-alkene isosteres (see for example Scheme 33, entry f). The [2,3] rearrangement of allylic selenoxides has been successfully extended to the propargylic[102,103] and allenyl[103] analogs, and provides α-seleno-α,β-unsaturated carbonyl compounds and propargylic alcohols respectively (Scheme 34, entry d; Scheme 42). This process does not occur with sulfur analogs as a consequence of the greater stability of the sulfoxide compared to the rearranged sulfenate.[102]

Finally, α-alkylated allylic dithiocarbamates bearing a terminal C—C bond rearrange smoothly to the allylic dithiocarbamates in which the heteroatomic moiety is terminal (Scheme 52, entry b).[174]

As shown earlier, alkenes and allylic alcohols can be prepared from alkyl and allyl sulfides or selenides by a series of reactions which involve alkylation of the corresponding organometallic, followed by oxidation of the resulting sulfides or selenides and further reaction of these species. One can think of the reverse order of reactions involving first the oxidation of the sulfide or selenide followed by alkylation of the resulting oxide. This procedure has in fact been performed in some cases as will be shown in the next section (Section 1.3.5). Of course the second approach offers the advantage of an easier metallation reaction. However, it possesses several disadvantages which have been observed from time to time. For example, alkyl selenoxides are prone to eliminate and are hygroscopic and therefore their metallation, although efficiently achieved, requires tedious manipulation in order to avoid these side reactions.[46,47,54] As mentioned above, allyl selenoxides are too unstable and have only been postulated in the oxidation of allyl selenides. Their metallation and alkylation have not yet been attempted. Furthermore it has been reported in many instances that selective alkylation at the α-site of allyl sulfides can be

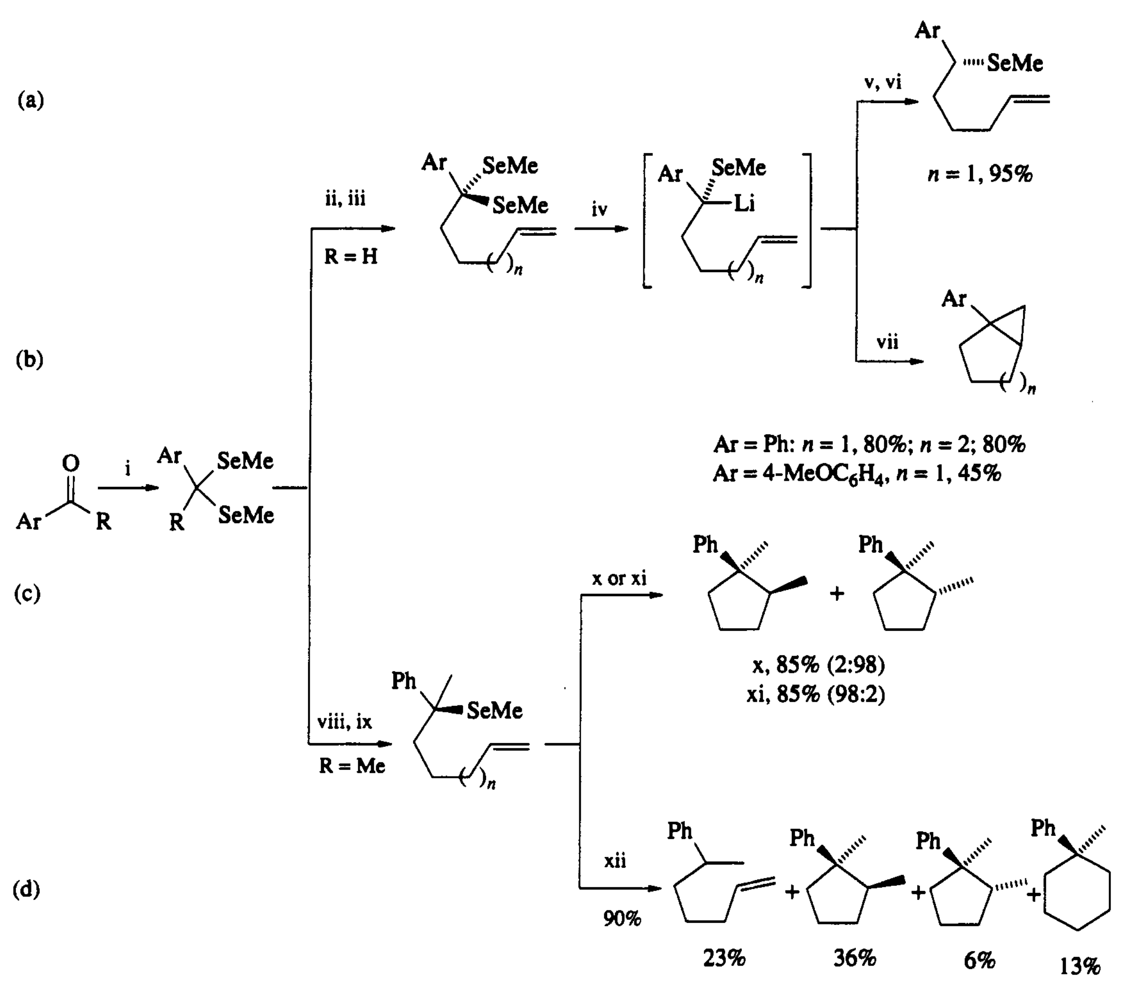

i, 2 MeSeH, $ZnCl_2$ or $TiCl_4$; ii, KDA, THF, −78 °C; iii, 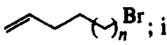; iv, $Bu^nLi$, THF, −78 °C;
v, −78 °C, 0.5 h; vi, MeOH; vii, 0 °C, 1 h; viii, $Bu^nLi$, THF; ix, 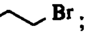;
x, $Bu^nLi$, THF, −78 °C, 0.1 h; xi, $Bu^nLi$, $Et_2O$, −30 °C, 0.1 h; xii, $Bu_3SnH$, AIBN, 80 °C

Scheme 46

achieved on condition that a substituent is chosen which is suitable for metal chelation. This is not possible with the corresponding sulfoxide.[16] Therefore, at least in these cases, the approaches reported in this section offer definite advantages over related ones.

### *1.3.2.2.3 Transformations of sulfides and selenides to organic halides: the haloalkylation and halopropenylation of alkyl and allyl halides*

Alkyl and allyl sulfides and selenides can be transformed readily into the corresponding alkyl and alkenyl halides respectively. This reaction takes advantage of the easy formation of the corresponding sulfonium and selenonium salts on reaction with alkyl halides,[125,143] alkyl bromoacetates[141] or bromine[143,237] (Scheme 53). A related process involves the intermediary formation of a selenoxide and its further reaction with hydrochloric or hydrobromic acids.[238]

These reactions, coupled with the alkylations of sulfides and selenides, allow the homologation of primary alkyl halides[124,125,141,143,237,238] and the transformation of allyl halides to homoallyl halides.[125] A related process, employing 2-methylthio- and 2-allylthio-thiazoline, allows the iodomethylation ($ICH_2$—) and the iodopropenylation ($ICH_2CH{=}CH$—) of alkyl halides (Scheme 54).[131a,132,171]

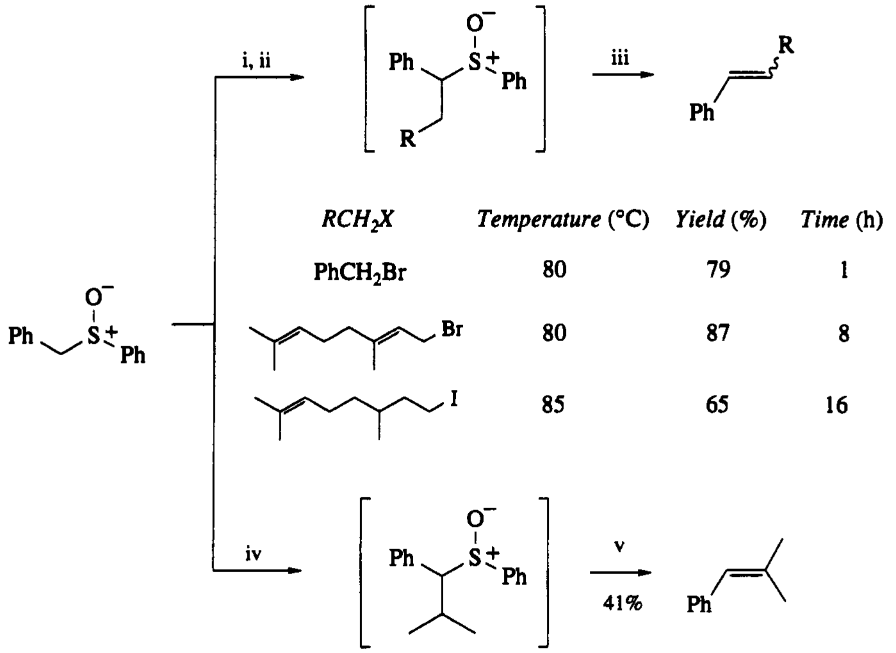
i, ii
iii
iv
v
41%
Ph
R
O⁻
S+

| *RCH₂X* | *Temperature* (°C) | *Yield* (%) | *Time* (h) |
|---|---|---|---|
| PhCH$_2$Br | 80 | 79 | 1 |
| Br | 80 | 87 | 8 |
| I | 85 | 65 | 16 |

i, LICA, DME; ii, RCH$_2$X, 20 °C, 1 h; iii, DMF; iv, LICA, DME, Pr$^i$I, 20 °C, 0.3 h; v, heat, 180 °C, 0.2 h

Scheme 47

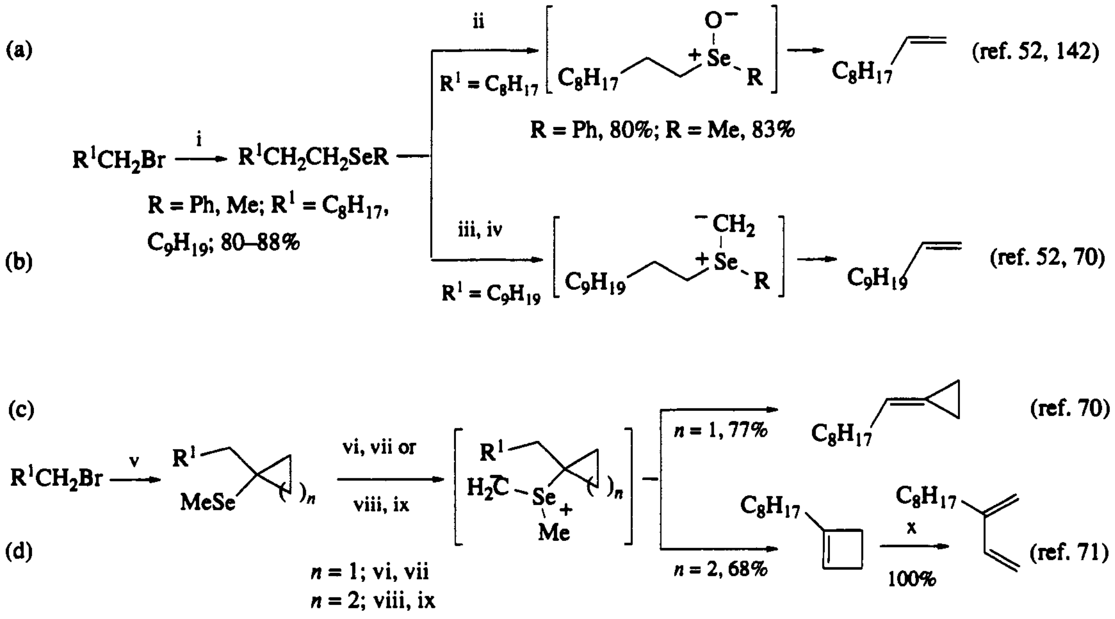
(a)
(b)
(c)
(d)
ii
R¹ = C₈H₁₇
R = Ph, 80%; R = Me, 83%
(ref. 52, 142)
R¹CH₂Br → R¹CH₂CH₂SeR
i
R = Ph, Me; R¹ = C₈H₁₇, C₉H₁₉; 80–88%
iii, iv
R¹ = C₉H₁₉
(ref. 52, 70)
R¹CH₂Br
v
vi, vii or viii, ix
n = 1; vi, vii
n = 2; viii, ix
n = 1, 77%
n = 2, 68%
x
100%
(ref. 70)
(ref. 71)

i, RSeCH$_2$Li, THF, HMPA, –78 °C to 20 °C; ii, Bu$^t$O$_2$H, THF, –60 °C, 3 h; iii, MeI, AgBF$_4$; iv, Bu$^t$OK, DMSO, 20 °C; v, 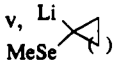 ; vi, MeSO$_3$F; vii, Bu$^t$OK, DMSO, 20 °C, viii, MeI, AgBF$_4$; ix, Bu$^t$OK, DMSO, 20 °C; x, 180 °C

Scheme 48

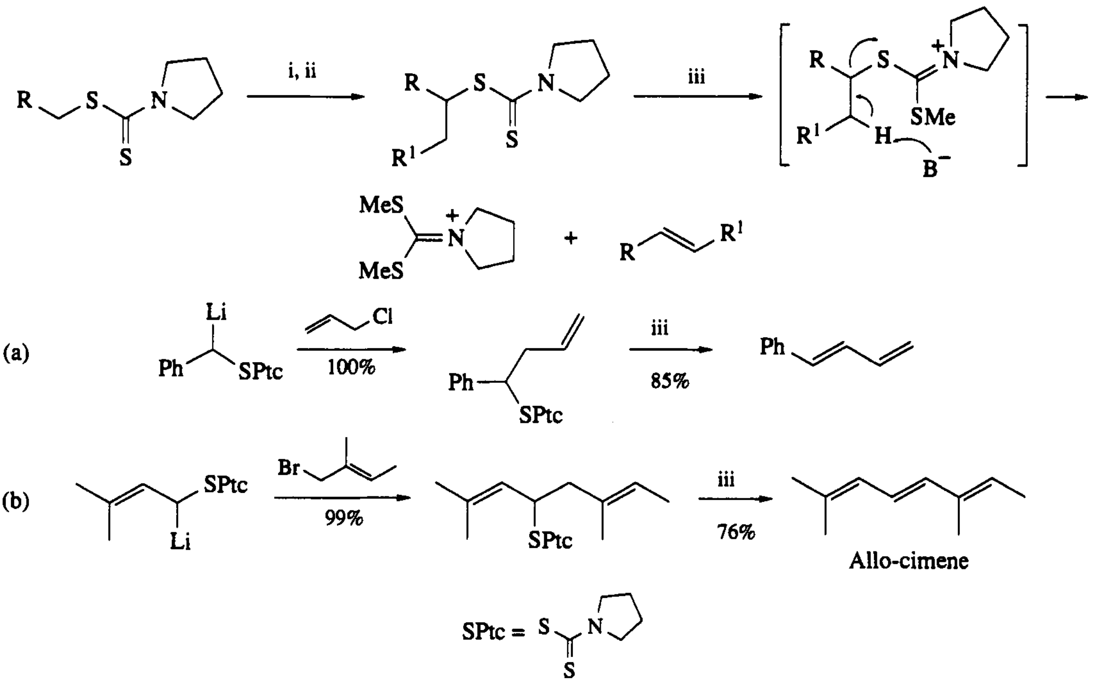

i, LDA; ii, $R^1CH_2X$; iii, MeI, HMPA, $Li_2CO_3$, LiF

Scheme 49

γ- and δ-hydroxy selenides which result from the reactions of α-selenoalkyllithiums with epoxides have been transformed to various selenium-free compounds. Thus γ-hydroxyalkyl iodides and bromides have been produced in good yields from γ-hydroxyalkyl selenides and methyl iodide or bromine respectively (MeI, NaI, $CaCO_3$, DMF, 80 °C, 1 h; $Br_2$, EtOH–$H_2O$ or $Et_3N$, $CH_2Cl_2$, 20 °C, 3 h). Under similar conditions δ-hydroxyalkyl selenides instead produce tetrahydrofurans directly.[149] The high propensity of the hydroxyalkyl selenonium salt intermediates to cyclize to a five-membered rather than to a four-membered heterocycle is responsible for these differences. Oxetanes however are available on treatment of the above mentioned γ-hydroxyalkyl halides with base (Bu$^t$OK, DMSO, 20 °C or MeMgBr–HMPA, 20 to 80 °C; Scheme 13, entries a and b). The reaction works well with those compounds in which the bromine is attached to a methine group, but increasing the substitution at this carbon dramatically lowers the yield of the heterocycle (Scheme 13, entry b) due to the concomitant formation of homoallyl alcohols.[149] The synthesis of the latter compounds is best achieved by first preparing the γ-hydroxyalkyl selenonium salts (MeI, neat, 20 °C for methylseleno derivatives) then treating them with a base (Bu$^t$OK, DMSO, 20 °C or 50% aq. KOH, $CH_2Cl_2$, phase-transfer catalyst).[150] The high regioselectivity observed for this process has been explained by the cyclic transition state depicted in Scheme 13 (entry d). Oxidation of γ-hydroxyalkyl selenides under Sharpless conditions ($H_2O_2$, THF, 20 °C) produces a mixture of allyl and homoallyl alcohols which suggests that the corresponding selenoxides lead to an indiscriminate elimination reaction.[150] Selective elimination leading to the α,β-unsaturated ketones can however be achieved using Jones' reagent ($CrO_3$–$H_2SO_4$, acetone; Scheme 13, entry e).[150]

γ-Hydroxyalkyl selenides derived from α-selenobenzyllithiums and epoxides have proved to be valuable precursors of arylcyclopropanes.[160] The reaction proceeds through the corresponding γ-tosyloxybenzyllithiums. Although the synthesis of the γ-hydroxyalkyl selenides is not stereoselective, the subsequent steps occur with high stereoselectivity, and have led to the conclusion that the benzyllithiums possess the opposite stereochemistry to that of the selenides and that this stereochemistry is retained in the next step (Scheme 18).[160]

### *1.3.2.2.4 Transformation of alkylated vinyl sulfides and selenides to carbonyl compounds*

Vinyl sulfides[20,82,162,163,166,240] and selenides[82,83,90,239,241-244] available on alkylation of α-metallovinyl sulfides and selenides[107,108,110,239] (Scheme 35), themselves available from the corresponding vinyl

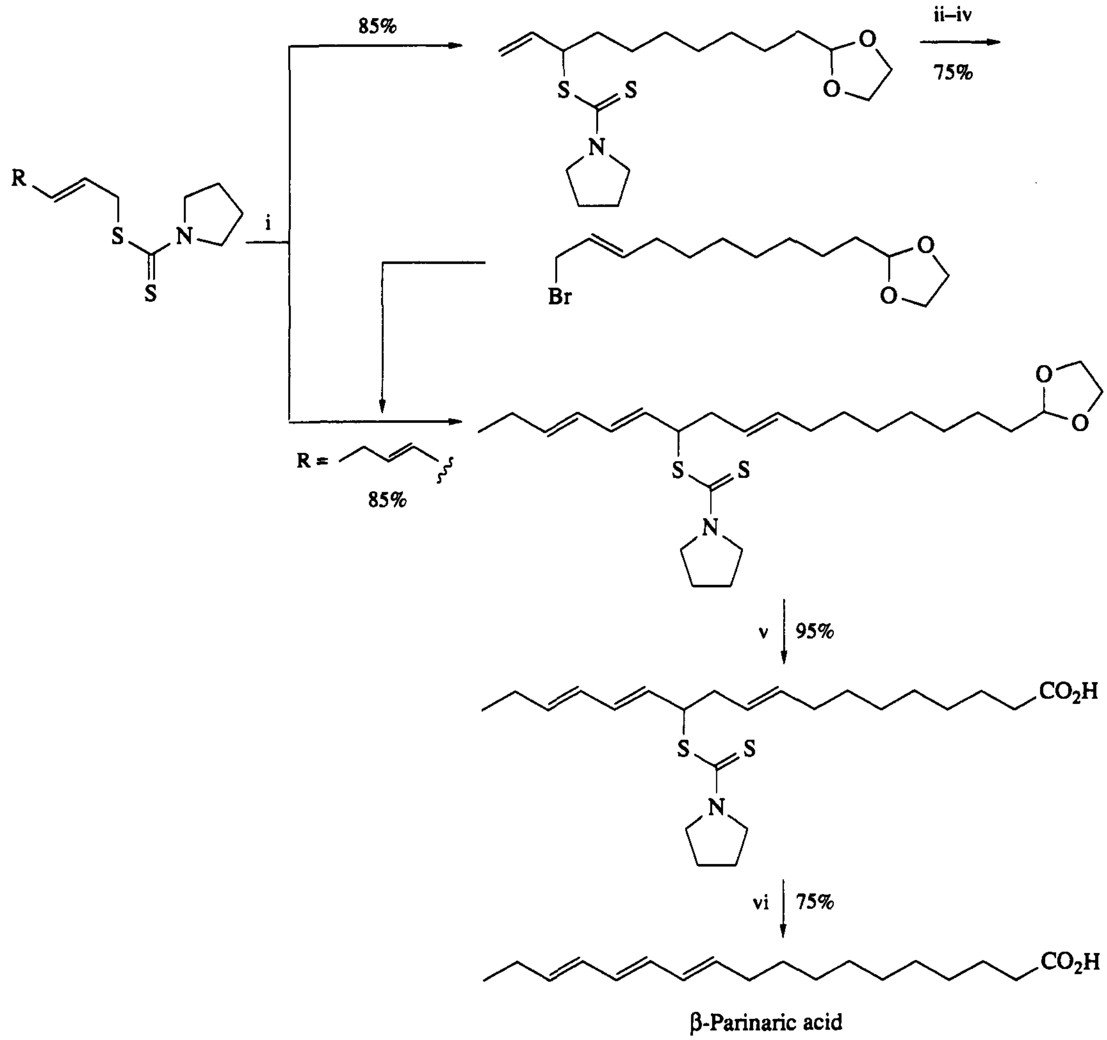

i, LDA, $R^1X$, −78 °C, 0.5 h; ii, Δ, $CHCl_3$, 4.5 h; iii, MeI; iv, NaBr, DMF, 50 °C, 24 h;
v, HCl, acetone, $O_2$, 5 °C, 1 week; vi, MeI, LiF, $LiCO_3$, DMF, 20 °C, 24 h

Scheme 50

sulfides and selenides or from 1,1-diselenoalkenes, (Scheme 41),[83] or on γ-alkylation of α-metalloallyl sulfides,[158,162,163] Scheme 27 and Scheme 52a) have been hydrolyzed to the corresponding carbonyl compounds *inter alia* with acids, mercury(II) or copper(II) salts. Therefore α-metallovinyl sulfides and selenides play the role of acyl anion equivalents in these transformations.

## 1.3.3 REACTIONS OF α-THIO- AND α-SELENO-ALKYLMETALS BEARING FURTHER HETEROATOMIC MOIETIES ON THEIR CARBANIONIC CENTER. APPLICATION TO THE FORMATION OF ACYL ANION EQUIVALENTS

### 1.3.3.1 Alkylations of 1-Metallo-1,1-dithioalkanes Bearing Hydrogen and/or Alkyl Groups on Their Carbanionic Center and Their Synthetic Applications

Organometallics bearing two heteroatomic moieties on their carbanionic center have found an important place in organic synthesis since the first report of Arens.[245] In particular, they have played a crucial role as formyl or acyl anion equivalents.[7,8,18–22,26–30]

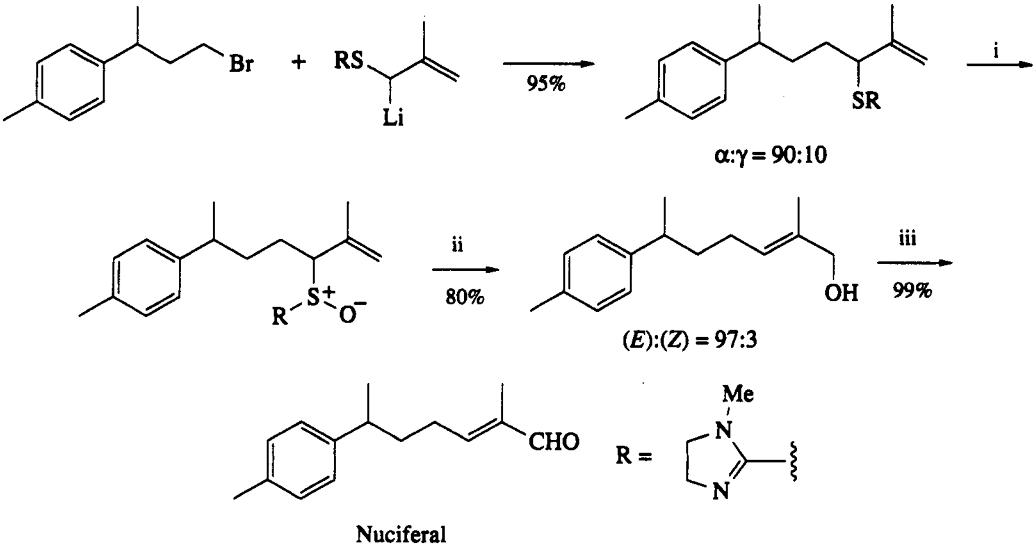
Br
RS
Li
95%
SR
α:γ = 90:10
i
R
S+
O−
ii
80%
OH
(E):(Z) = 97:3
iii
99%
CHO
Nuciferal
R =
Me
N
N

i, MCPBA, $CH_2Cl_2$, 20 °C; ii, $Et_2NH$, MeOH, 20 °C; iii, $MnO_2$

**Scheme 51**

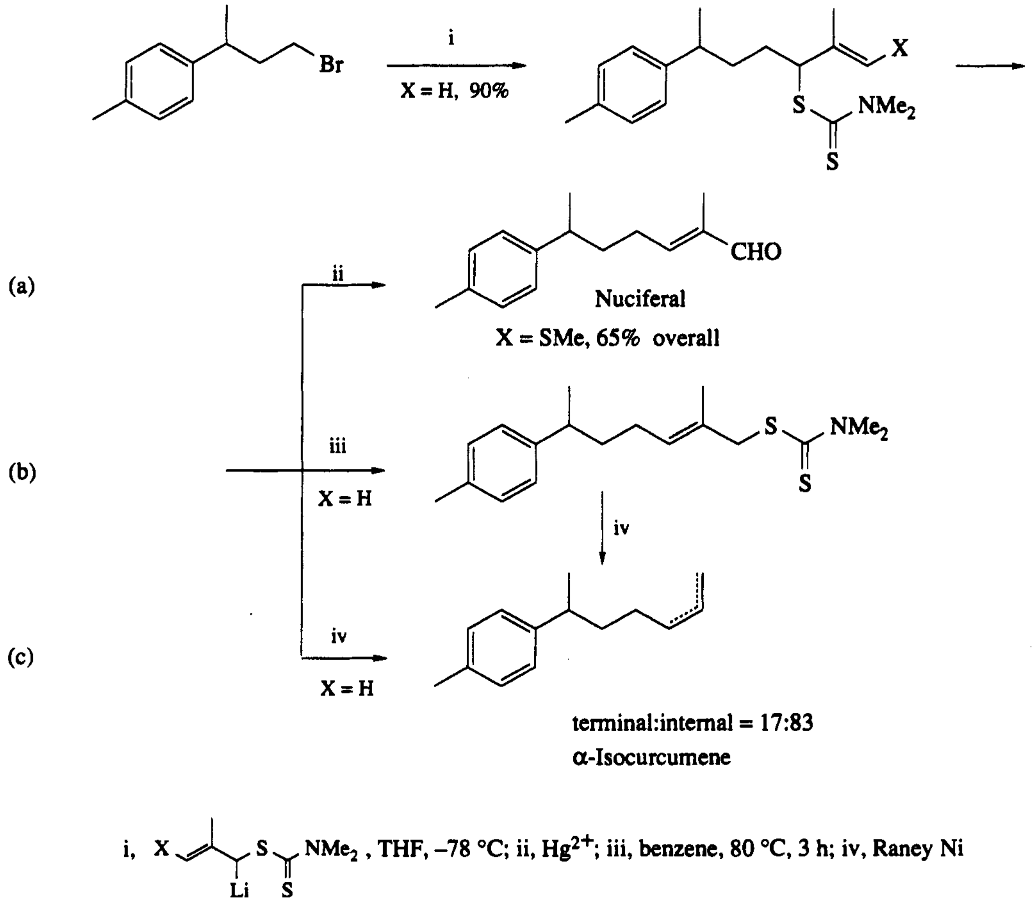
Br
i
X = H, 90%
X
S
NMe2
S
(a)
ii
CHO
Nuciferal
X = SMe, 65% overall
(b)
iii
X = H
S
NMe2
S
iv
(c)
iv
X = H
terminal:internal = 17:83
α-Isocurcumene
i, X
S
NMe2
Li
S

i, X–C(Me)=CH–CH(Li)–S–C(=S)NMe$_2$, THF, –78 °C; ii, $Hg^{2+}$; iii, benzene, 80 °C, 3 h; iv, Raney Ni

**Scheme 52**

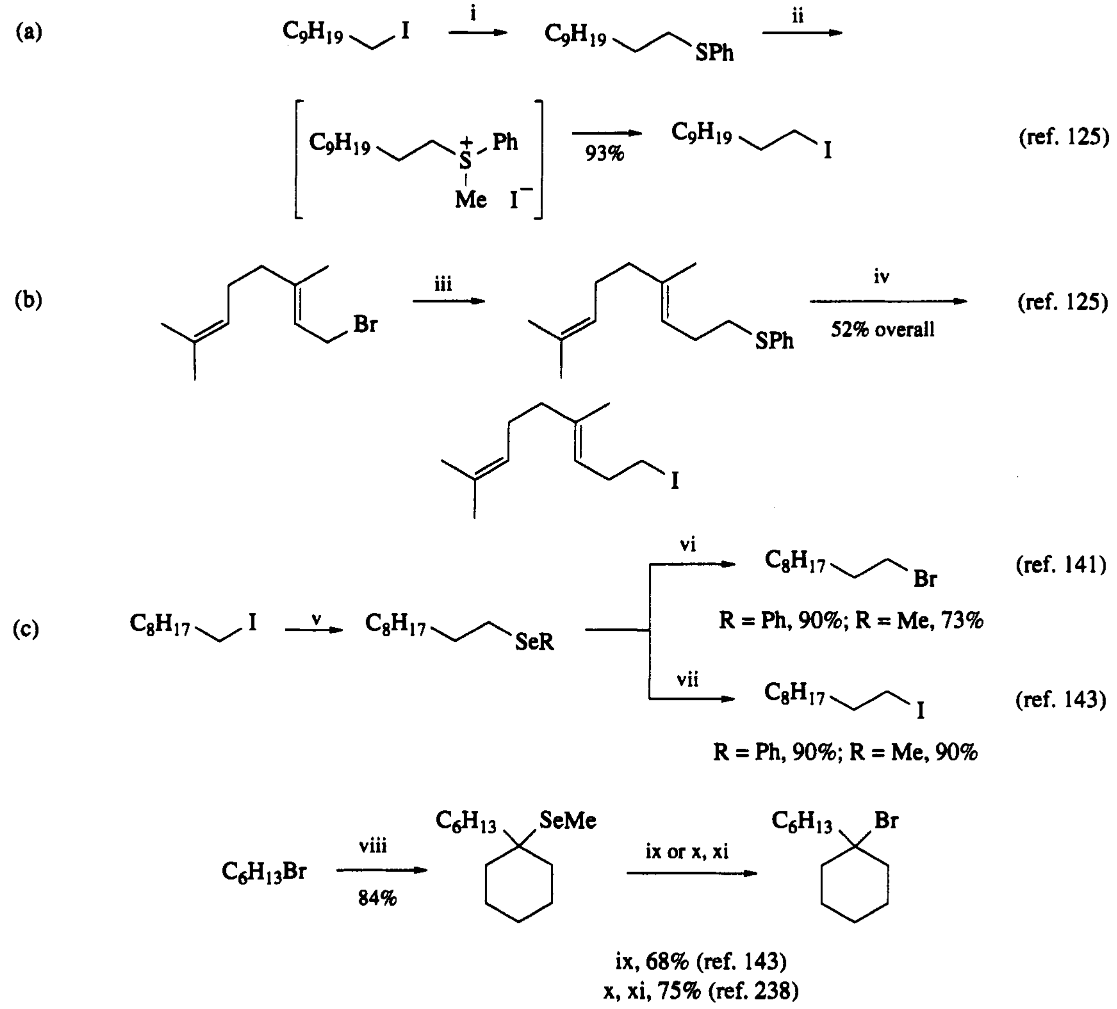
(a)
$C_9H_{19}$ I
i
$C_9H_{19}$ SPh
ii
$C_9H_{19}$ S Ph Me $I^-$
93%
$C_9H_{19}$ I
(ref. 125)
(b)
Br
iii
SPh
iv
52% overall
(ref. 125)
I
(c)
$C_8H_{17}$ I
v
$C_8H_{17}$ SeR
vi
$C_8H_{17}$ Br
(ref. 141)
R = Ph, 90%; R = Me, 73%
vii
$C_8H_{17}$ I
(ref. 143)
R = Ph, 90%; R = Me, 90%
$C_6H_{13}Br$
viii
84%
$C_6H_{13}$ SeMe
ix or x, xi
$C_6H_{13}$ Br
ix, 68% (ref. 143)
x, xi, 75% (ref. 238)

i, $PhSCH_2Li$, THF, –70 °C, 3 h, then 20 °C; ii, MeI, NaI, DMF, 75 °C, 18 h; iii, $PhSCH_2Li$, CuI, –50 °C, 2 h, then 20 °C; iv, MeI, NaI, DMF, 75 °C, 18 h; v, $RSeCH_2Li$, THF, HMPA; vi, $BrCH_2CO_2Et$, NaBr, DMF, 80 °C; vii, MeI, NaI, $CaCO_3$, DMF, 80 °C, 5 h; viii, 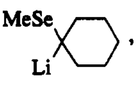, THF, –78 to 20 °C; ix, $Br_2$, $Et_3N$, $CH_2Cl_2$, 20 °C, 3 h; x, $O_3$; xi, HBr, $Et_3N$, $CH_2Cl_2$, 20 °C

Scheme 53

### 1.3.3.1.1 Synthetic uses of 1-metallo-1,1-di(alkylthio)alkanes and -di(phenylthio)alkanes

1,1-Di(ethylthio)alkanes have been alkylated by sequential reaction with metalloamides in liquid ammonia[245,246] or in HMPA[247] followed by addition of alkyl halides. The reaction, which is usually conducted with 2 equiv. of the base is more efficient when carried out with sodium rather than lithium amides[246] and, although it works well with all primary alkyl halides, only the parent compound and the one bearing an aryl substituent on the carbanionic center are alkylated with *s*-alkyl halides (Scheme 55, entry a).

Di(phenylthio)methyllithium[59,126] and di(phenylthio)benzyllithium,[248,249] which are synthesized from the corresponding carbon acids and *n*-butyllithium in THF, have been monoalkylated with primary but not with secondary alkyl halides. Higher homologs have not found widespread use because of the difficulties encountered in their alkylation.[59,126,250–252] The successful alkylation of such compounds has been achieved[252] by carrying out the reactions in TMEDA (1 equiv.) in hydrocarbons (Scheme 55, entry c). Even the presence of THF with TMEDA almost completely suppresses the alkylation. However, double

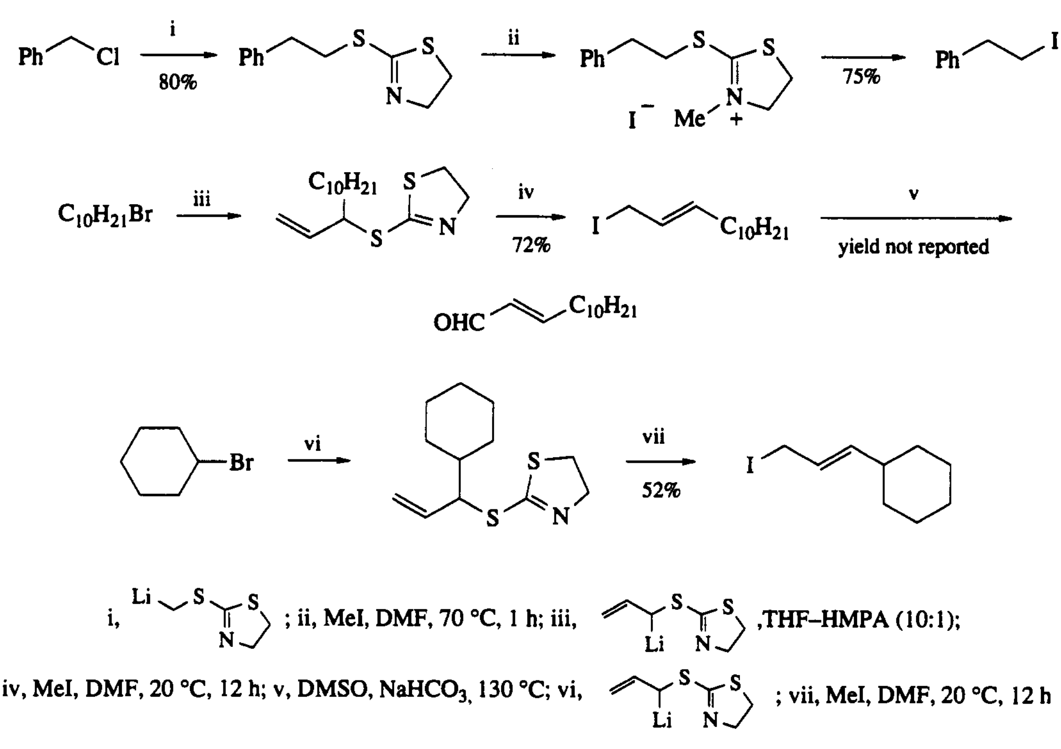

Scheme 54

alkylation of di(phenylthio)methane is possible[250] in the presence of 2 equiv. of alkyl halides and an excess (4 equiv.) of sodium amide in THF. Interestingly the dianion derived from the conjugate addition of lithio tri(phenylthio)orthoformate on cyclohexenone followed by S/Li exchange involving *s*-butyllithium, has been methylated selectively at the carbanionic site (Scheme 56, entry a).[253]

A further interesting example is the use of 1,1-di(phenylthio)methyllithium to open an epoxide[254] followed by a Grob fragmentation process as shown in Scheme 56 (entry b). The reaction of 1,1-di(thio)methyllithium with epoxides has also been used[255,256] in the one-pot synthesis of 1,1-di(thio)cyclopropanes involving an intramolecular cyclization of the γ-tosyloxydi(phenylthio)alkyllithium. This intramolecular alkylation reaction proceeds even more efficiently than its intermolecular version, and allows the synthesis of a large variety of 1,1-di(thio)cyclopropanes from 3-chloro-[257] and 3-phenylthio-1,1-di(thio)alkanes[258] and *n*-butyllithium in THF (Scheme 57 and Scheme 58).

1,1-Di(methylthio)cyclopropanes have been converted[255,256] into ketones resulting from the fission of the C(2)—C(3) bond and elimination of dimethyl disulfide on reaction with aqueous trifluoroacetic acid (Scheme 58). Since the epoxides are usually synthesized by oxidation of an alkene, the sequence alkene → cyclopropanone → thioacetal → ketone allows the insertion of a carbonyl group in between the $sp^2$ carbons of the alkene (Scheme 58).[255] Furthermore, reaction of di(phenylthio)cyclopropanes sequentially with lithium dimethylaminonaphthalene, carbonyl compounds and acid allows the synthesis of cyclobutanones by ring expansion of the intermediary 1-(1-hydroxyalkyl)-1-phenylthiocyclopropanes.[17,25,61,128]

Related reactions involve the alkylation, allylation or benzylation of: (i) α,α-di(thio)alkylmagnesium halides, resulting from the thiophilic addition of Grignard reagents on dithioesters (Scheme 55, entry b);[259,260] (ii) 2-lithio-1,3-benzodithioles (Scheme 55, entry d);[261] (iii) 2-aryl-2-lithio-1,3-dithiolanes[262] and 2-lithio-1,3-dithianes derived from the 1,2-dimethyl-4,5-di(mercapto)methylbenzene (Scheme 55, entry e).[263,264]

### *1.3.3.1.2 Synthetic uses of 2-metallo-1,3-dithianes and related derivatives*

2-Lithio-1,3-dithianes, (the Corey–Seebach reagent) have proved by far the most widely used organometallic reagents of this series (Scheme 59).[27–29,265] This is due to: (i) the easy preparation of 1,3-dithianes from aldehydes and 1,3-propanedithiol; (ii) their metallation reaction which proceeds efficiently with $\mathrm{Bu^nLi}$ in THF, irrespective of whether the parent formyl derivative, higher homologs or 1-aryl-substituted derivatives are involved;[267–271] (iii) the high nucleophilicity of all these species towards various electrophiles,[27,28] including alkyl,[265,266,270,272–284] allyl,[266,268,269,285–289] and benzyl halides,[266] and arenesulfonates derived from primary alcohols[290] as well as with terminal,[255,266,279,289,291-300] α,β-disubstituted,[255,299,301] and α,β-unsaturated epoxides[255] and with oxiranes;[266] and (iv) selective removal of the dithianyl moiety which produces[27-29] a carbonyl group on reaction with metal ion, alkylative or oxidative hydrolysis[302,303] such as $HgCl_2$ alone[291] or with $CaCO_3$,[280,292] HgO,[268,272,275,283-285,304] HgO–$BF_3OEt_2$,[279,286,300,305,306] HgO–aq. $HBF_4$,[307] $CdCO_3$,[281,301] NClS,[275] NBS[275] alone or with $AgNO_3$;[275] with $CuCl_2$ and CuO,[308] an aroyl peroxide,[304] thallium(I) trinitrate[309] or bis(trifluoroacetoxy)iodobenzene.[302]

This reaction has been used for the synthesis of a large variety of aldehydes and ketones[20,27,28,278] including: (i) deuterio aldehydes;[313] (ii) optically active aldehydes and ketones;[283,284] (iii) alicyclic (Scheme 60, entry d)[282] and cyclic diketones (Scheme 60, entry c),[274,278,281] including those derived from metacyclophanes,[267,271] 1,9-dienes and macrocyclic acetylacetone ligands for metal cations;[281] (iv) silyl and germyl ketones;[314] and (v) the synthesis of many natural products or their model compounds, notably

(a)

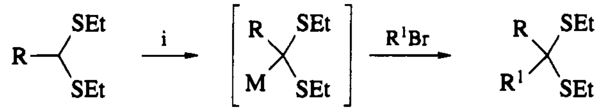

(ref. 246)

| *R* | *R¹* | *M* | *%* | *R* | *R¹* | *M* | *%* |
|---|---|---|---|---|---|---|---|
| H | Et | Li | 44 | Me | Et | Na | 44 |
| H | Et | Na | 87 | Me | $C_7H_{15}$ | Na | 30 |
| H | $C_7H_{15}$ | Na | 82 | Me | $Bu^s$ | Na | 0 |
| H | $Bu^s$ | Li | 18 | Ph | Et | Na | 87 |
| H | $Bu^s$ | Na | 55 | Ph | $Bu^n$ | Na | 85 |
|  |  |  |  | Ph | $Bu^s$ | Na | 84 |

(b)

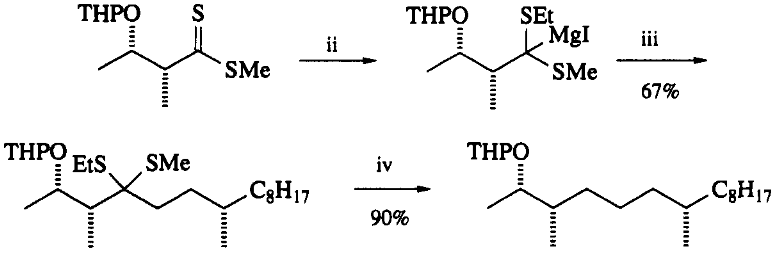

(ref. 259)

(c)

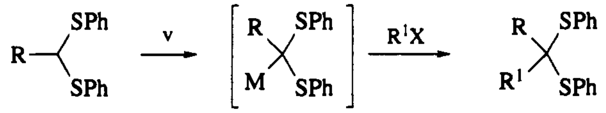

| *R* | *Conditions* (v) | *R¹X* | *%* | *Ref.* |
|---|---|---|---|---|
| H | $Bu^nLi$, THF, 1 h | $Bu^nBr$ | 96 | 59, 126 |
|  |  | $Bu^sBr$ | 0 |  |
| H | 4 $NaNH_2$, THF–HMPA | $Bu^nBr$ (2 equiv.)<br>($R = R^1 = Bu^n$) | 70 | 250 |
| $C_5H_{11}$ | $Bu^nLi$, TMEDA, 0 °C | EtI | 91 | 248 |
|  |  | PrI | 89 |  |
|  |  | $PhCh_2Br$ | 56 |  |
| Ph | $Bu^nLi$, TMEDA | EtI | 87 | 248 |
|  |  | PrI | 91 |  |
|  |  | $PhCH_2Br$ | 44 |  |

i, 2 $MNH_2$, liq. $NH_3$; 2 EtMgI; 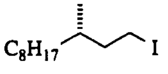, THF–HMPA; iv, Raney Ni

**Scheme 55**

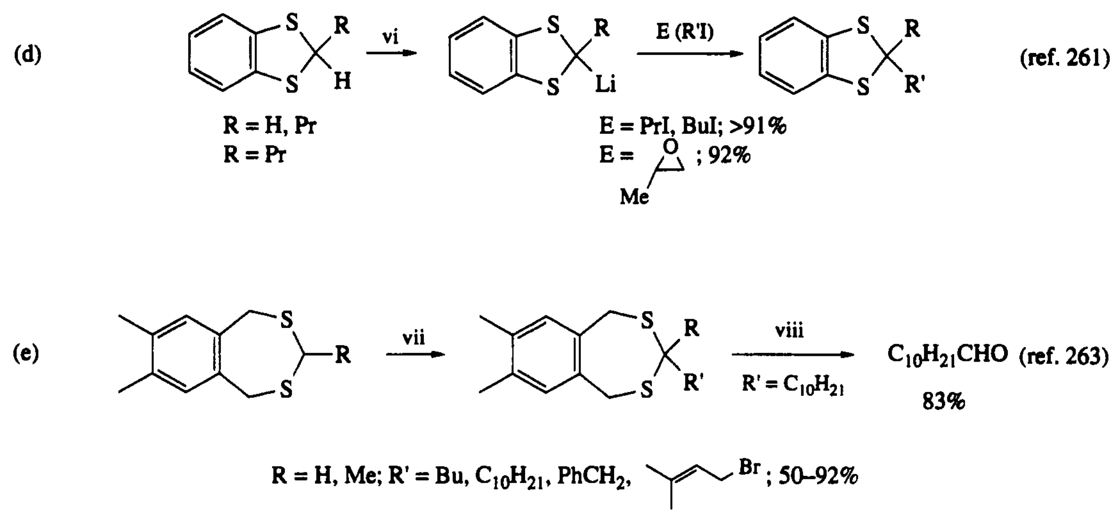
(d)
vi
E (R'I)
R = H, Pr
R = Pr
E = PrI, BuI; >91%
E = ; 92%
Me
(ref. 261)
(e)
vii
viii
R' = C10H21
C10H21CHO (ref. 263)
83%
R = H, Me; R' = Bu, C10H21, PhCH2, Br; 50–92%

vi, Bu$^n$Li, THF, −30 °C; vii, Bu$^n$Li, R'Br; viii, $CuCl_2$, CuO

Scheme 55 *(continued)*

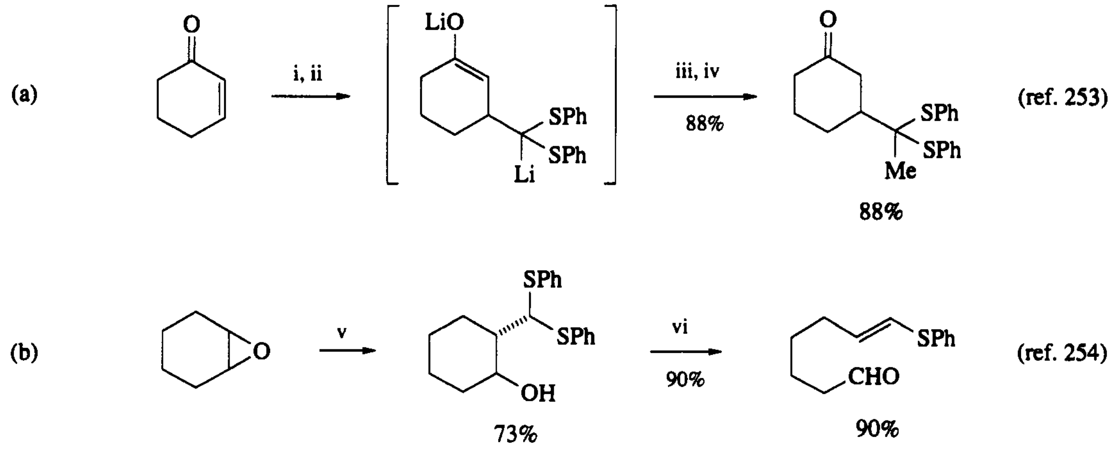
(a)
i, ii
LiO
SPh
SPh
Li
iii, iv
88%
Me
88%
(ref. 253)
(b)
v
OH
73%
vi
90%
CHO
90%
(ref. 254)

i, $(PhS)_3CLi$; ii, Bu$^s$Li; iii, MeI; iv, $H_2O$; v, $(PhS)_2CHLi$; vi, Bu$^n$Li, 4 $CF_3CO_2Cu$, 20 °C, 3 h

Scheme 56

calcimycin,[280] norpyrenophorin, pyrenophorin and vermiculin antibiotics,[279] carbohydrates,[315–317] 2-methyllysergic acid,[311] terpenes and terpenoid derivatives[268,285,318] (including α-turmeron[268] (Scheme 61, entry a), *cis*-verbenol[318] and linaloyl oxide,[298]), alnusone,[20,319] rethrolones,[20,272] prostaglandins[276] and analogs,[301] debromoaplysiatoxin and aplysiatoxin (which are extracted from marine blue green algae),[294] (3*R*)- and (3*S*)-2,3-epoxysqualene,[20,304] 11α-hydroxyprogesterone,[320] modified steroids,[20,296] corticosteroids,[295] laurencin (a representative of naturally occurring halo compounds possessing a medium-sized cyclic ether skeleton as well as an enyne moiety),[306] and the northern part of maytansin.[291,292]

Reduction of the dithianyl moiety to a methylene group has been achieved[20] with Raney nickel,[267,293,305,310] or Na in $NH_3$ or in ether,[285,305,311] or with $LiAlH_4$ in the presence of $CuCl_2$ and $ZnCl_2$.[312]

The whole process, which involves the synthesis of the 1,3-dithiane and the reduction of the product resulting from its alkylation, has been used *inter alia* for the synthesis of metacyclophanes (Scheme 60,

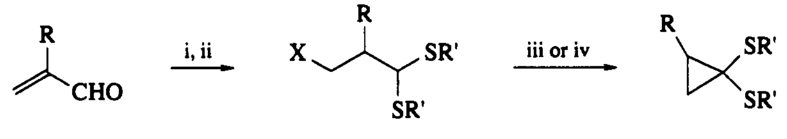

R
CHO
i, ii
X
SR'
SR'
iii or iv
SR'
SR'

| *X* | *R* | % | *Conditions* | % | *Ref.* |
|---|---|---|---|---|---|
| Cl | H | 90 | iii | 71 | 257 |
| Cl | Me | 68 | iii | 68 | 257 |
| PhS | H | 98 | iv | 99 | 258 |
| PhS | Me | – | iv | 100 | 258 |

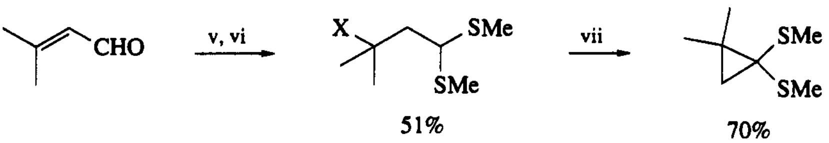

CHO
v, vi
X
SMe
SMe
51%
vii
SMe
SMe
70%

(ref. 257)

i, HX; ii, EtSH; iii, Bu$^n$Li, THF; iv, MeLi, THF–TMEDA; v, HCl; vi, PhSH; vii, Bu$^n$Li, THF

**Scheme 57**

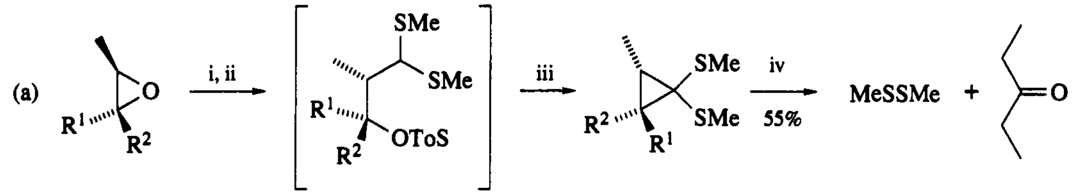

(a)
O
R1
R2
i, ii
SMe
SMe
R1
OToS
R2
iii
SMe
SMe
R2
R1
iv
55%
MeSSMe +
O

$R^1$ = Me, $R^2$ = H, 66%; $R^1$ = H, $R^2$ = Me, 67%

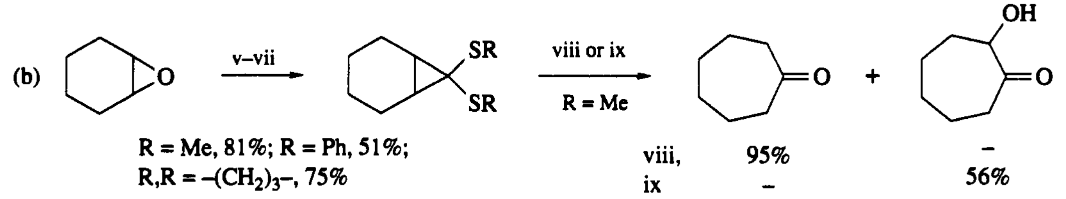

(b)
O
v–vii
SR
SR
R = Me, 81%; R = Ph, 51%;
R,R = –(CH2)3–, 75%
viii or ix
R = Me
O
+
OH
O
viii,
ix
95%
–
–
56%

i, $(MeS)_2CHLi$, –78 °C, then 0 °C, 15 h ; ii, TosCl; iii, Bu$^n$Li, THF, –50 °C then 0 °C, 15 h; iv, $CF_3CO_2H$, $H_2O$, reflux, 30 h; v, $(RS)_2CHLi$, THF, –78 °C, then 0 °C, 15 h; vi, TosCl; vii, Bu$^n$Li, –50 to 0 °C; viii, $CF_3CO_2H$, $H_2O$, reflux, 7 h; ix, $HCO_2H$, $H_2O$, 100 °C, 20 h

**Scheme 58**

entries a and b),[267,270,271] the cannabinoid side chain[305] and terpenes such as α- and β-curcumin (Scheme 61, entry b)[268] and (20*S*)-hydroxycholesterol (Scheme 62).[293]

The key step in all these transformations is without doubt the reaction of 1-lithio-1,3-dithianes with organic halides and epoxides.[27–29] The alkylation usually proceeds extremely rapidly with primary alkyl iodides[265] (–78 °C, 0.2 h) and with allylic[265,286] and benzylic halides[265,267,271] (Scheme 59, entry a) but is much slower with secondary alkyl iodides and bromides. The reaction is best carried out at low temperature in order to obtain good yields by lowering the competitive elimination reaction; it has been found to proceed with inversion of the configuration at the asymmetric carbon when optically active alkyl halides are used.[283]

Tertiary and cyclic alkyl halides (cyclohexyl iodide), secondary alkyl chlorides and primary and secondary tosylates cannot be used in these intermolecular alkylations.[266] This is also the case with dibromoethane[28,274] and 2-bromo-2-nitropropane,[321] which both lead instead to α,β-dithianylalkanes resulting from the oxidative coupling of the carbanion.

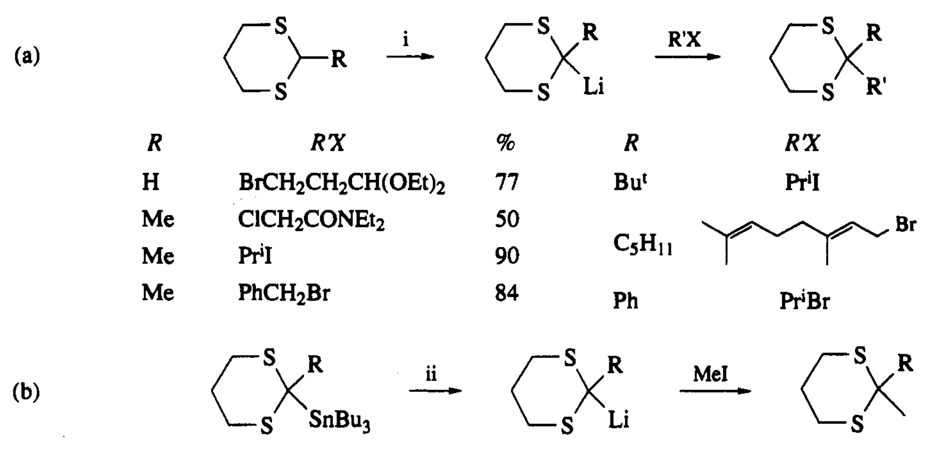

(ref. 265)

(ref. 322)

| *R* | *R'X* | % | *R* | *R'X* | % |
|---|---|---|---|---|---|
| H | $BrCH_2CH_2CH(OEt)_2$ | 77 | $Bu^t$ | $Pr^iI$ | 45 |
| Me | $ClCH_2CONEt_2$ | 50 | $C_5H_{11}$ | Br | 90 |
| Me | $Pr^iI$ | 90 | | | |
| Me | $PhCH_2Br$ | 84 | Ph | $Pr^iBr$ | 77 |

i, $Bu^nLi$, THF, –78 °C; ii, $Bu^nLi$, THF, –78 °C, 0.2 h

**Scheme 59**

Dialkylation of bis-dithianes has proved to be an efficient route to diketones.[266,270,271,282] This might be carried out by successive monoalkylations, each requiring the metallation of the intermediate bisdithiane) followed by treatment with the alkylating agent (Scheme 63, entry a) or in an operationally simpler alternative by adding 2 equiv. of the base ($Bu^nLi$) followed by 2 equiv. of the alkylating agent (Scheme 63, entry b). The success of the latter approach depends either on the possibility of generating the dianion directly or more likely on the ability of the excess alkylating agent to survive attack by the second equivalent of base while the first alkylation step on the monoanion is in progress.

Stepwise alkylations have been carried out successfully with primary alkyl halides,[282] isopropyl iodide,[282] 1-chloro-3-iodopropane[278] and benzyl bromide[282] (Scheme 63, entry b). Other secondary halides and *t*-butyl halides fail to react.[282]

The proof given in support of dianion formation does not however seem to be sufficient.[282] Nevertheless the single step process is reasonably efficient when primary alkyl halides are used but none of the dialkylated compound is produced with isopropyl iodide and benzyl bromide. 2-(ω-Haloalkyl)-1,3-dithianes have proved to be valuable precursors of 1,3-dithianes derived from cyclic ketones.[278] Halogenated 1,3-dithianes have been in turn prepared from 2-lithio-1,3-dithiane and stoichiometric amounts of ω-chloro- or bromo-alkyl iodides or with an excess of the corresponding dichloride[278] (Scheme 64, entry c). Use of ω-bromoalkyldithianes is often impractical because of the ease with which these compounds are transformed into cyclic sulfonium salts.[278]

Another, but longer, synthesis of such ω-haloalkyldithianes has been achieved by reaction of 1-lithio-1,3-dithianes with epoxides (see below)[255,256,278,322] followed by tosylation of the corresponding alkoxides and displacement of the tosylate with chloride ion (LiCl, DMF, 30 °C, 6 d; Scheme 64, entries a and b; Scheme 58, entry b).[278]

Furthermore specifically 2-deuterated-4,6-dimethyl-1,3-dithiane[273,287,323] and 2-phenyl-4,6-dimethyl-1,3-dithiane[287,288] produce, on sequential reaction with *n*-butyllithium in THF or in THF—HMPA and with methyl iodide, the corresponding 2-*cis*-4,6-trimethyldithianes in which the 2-methyl group lies in the equatorial position (Scheme 65).

The results displayed in Scheme 65 (entry a) show that, although equatorial abstraction of hydrogen is favored kinetically,[287] the ratio of equatorial to axial proton abstraction is considerably less than the ratio of equatorial to axial methylation. Most probably the lithium derivative rapidly reorients itself in such a way as to have the lithium held in the equatorial position by the cooperative effect of the two sulfur atoms.[287,288,323]

Epoxide[255,266,278,300] and oxirane[266] ring opening by 2-lithio-1,3-dithianes requires the use of low temperatures (–20 to 0 °C), since these organometallics are not sufficiently stable in THF at higher temperatures. Under these conditions the reaction is often slow (1 or 2 h) and requires in some cases 1 or even 2 days to go to completion (Scheme 58, entry b; Scheme 62; Scheme 66; Scheme 67).[293,296,297]

The reaction usually occurs at the less substituted carbon of the oxirane ring (Scheme 62 and Scheme 67).[293,297] However regioisomeric dithianyl alcohols are obtained[301] from 2-lithio-1,3-dithianes and the protected β,γ-epoxy alcohols shown in Scheme 66 (entry b). The observed regioselectivity is very different when methoxymethyl or benzyl protecting groups are used. This has been explained by the different

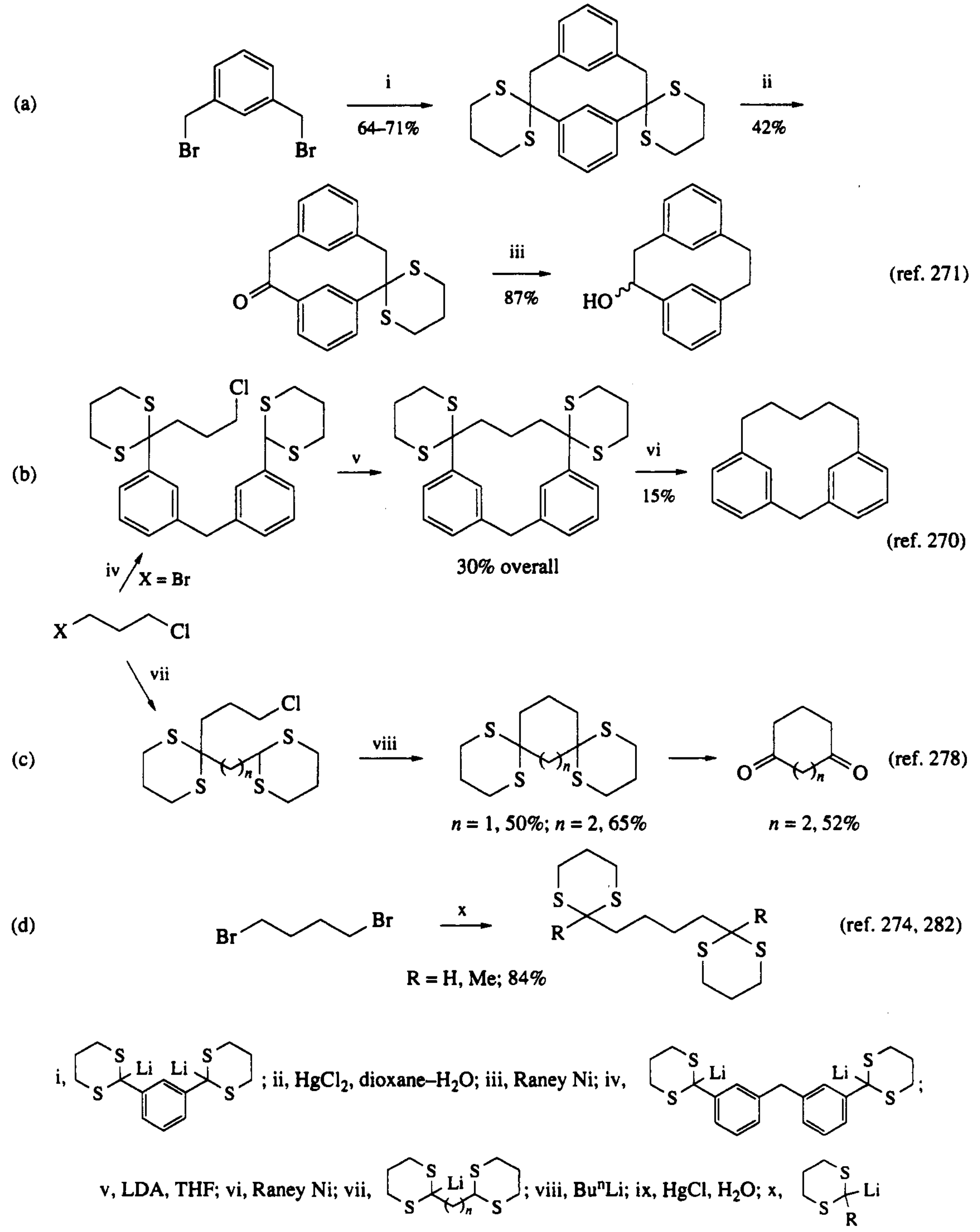
(a)
Br
Br
i
64–71%
S
S
S
S
ii
42%
O
S
S
iii
87%
HO
(ref. 271)
(b)
Cl
S
S
S
S
v
S
S
S
S
vi
15%
iv
X = Br
30% overall
(ref. 270)
X
Cl
vii
(c)
Cl
S
S
S
S
n
viii
S
S
S
S
n
O
O
n
(ref. 278)
n = 1, 50%; n = 2, 65%
n = 2, 52%
(d)
Br
Br
x
S
S
R
R
S
S
R = H, Me; 84%
(ref. 274, 282)
i,
S
S
Li
Li
S
S
; ii, HgCl2, dioxane–H2O; iii, Raney Ni; iv,
S
S
Li
Li
S
S
;
v, LDA, THF; vi, Raney Ni; vii,
S
S
Li
S
S
n
; viii, BunLi; ix, HgCl, H2O; x,
S
S
Li
R

**Scheme 60**

capacities of these two protecting moieties to form initial coordination complexes with the lithiodithiane reagent.[301]

The reaction of 2-lithio-1,3-dithianes with epoxides has been used in a large number of valuable synthetic transformations including the synthesis of: (i) the corresponding thioacetals of cyclopropanones and of carbonyl compounds resulting from their acid-catalyzed ring opening (Scheme 58, entry b);[255] (ii) γ-hydroxy[297,301] or acetoxy[300] aldehydes resulting from the selective hydrolysis of the related thioacetals (Scheme 66); and (iii) α,β-unsaturated aldehydes, including functionalized ones as shown in Scheme 66.[300]

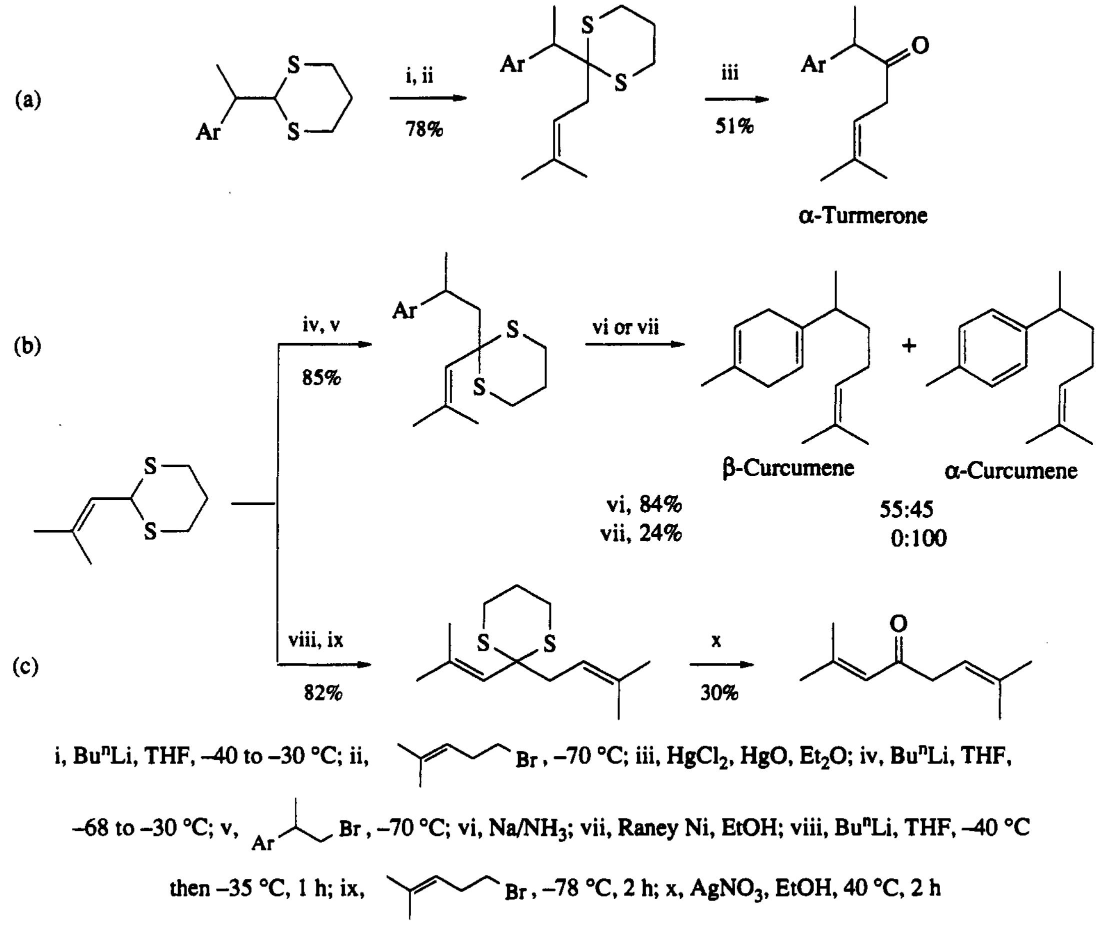
(a)
Ar
S
S
i, ii
78%
Ar
S
S
iii
51%
Ar
O
α-Turmerone
(b)
iv, v
85%
Ar
S
S
vi or vii
+
β-Curcumene
α-Curcumene
vi, 84%
vii, 24%
55:45
0:100
(c)
viii, ix
82%
S
S
x
30%
O

i, Bu$^n$Li, THF, –40 to –30 °C; ii, Br, –70 °C; iii, $HgCl_2$, HgO, $Et_2O$; iv, Bu$^n$Li, THF, –68 to –30 °C; v, Ar Br, –70 °C; vi, Na/$NH_3$; vii, Raney Ni, EtOH; viii, Bu$^n$Li, THF, –40 °C then –35 °C, 1 h; ix, Br, –78 °C, 2 h; x, $AgNO_3$, EtOH, 40 °C, 2 h

Scheme 61

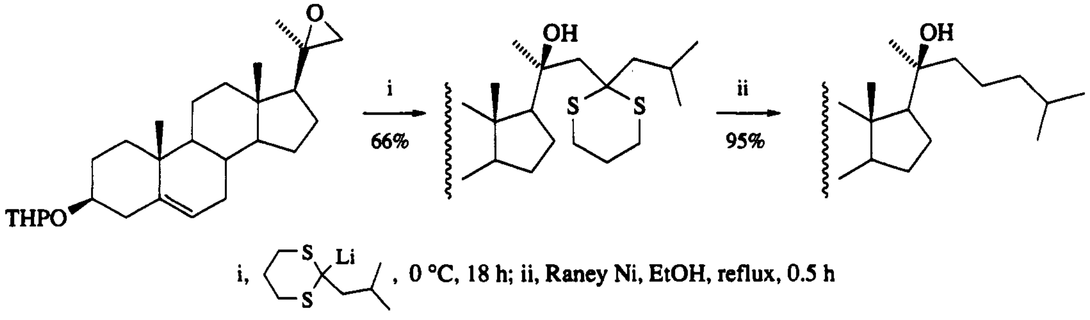
O
THPO
i
66%
OH
S
S
ii
95%
OH
S
Li
S

i, , 0 °C, 18 h; ii, Raney Ni, EtOH, reflux, 0.5 h

Scheme 62

It has also been shown[322] that the Sn/Li exchange at the 2-position of 2-stannyldithiane takes place within minutes at –78 °C, whereas H/Li metallation does not occur at all at this temperature (Scheme 59, entry b). This reaction, when applied to 2-(ω-oxidoalkyl)-2-stannyl-1,3-dithiane, takes place within a few minutes and the intramolecular nucleophlic reaction, which immediately follows, is usually complete within 0.1 h at –78 °C. The total yield of cyclization products by the tin route has proved to be twice as high as that by direct metallation (Scheme 68).[322]

Finally, although 2-lithio-1,3-dithianes do not usually react with tetrahydrofurans, an intramolecular ring opening of such heterocycles has been once reported and has been applied to the synthesis of a dithiane derived from a functionalized cyclohexanone (Scheme 67).[297,298]

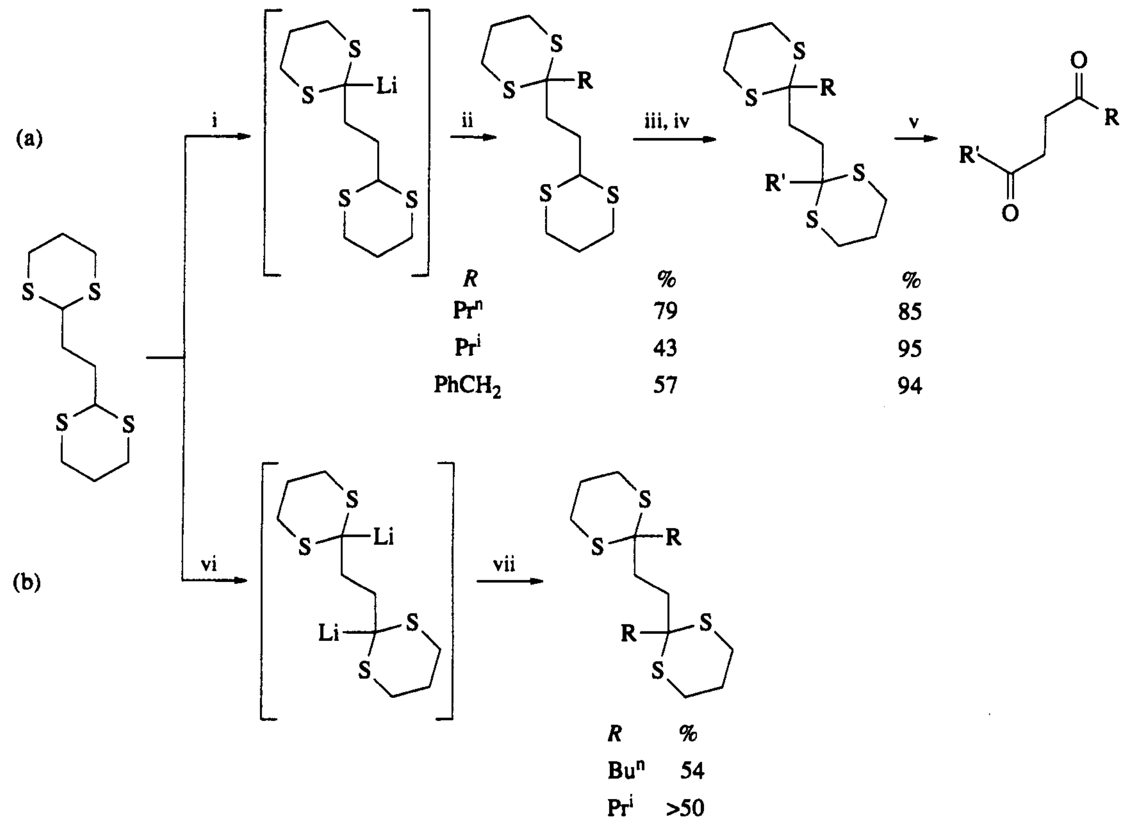

| *R* | % | % |
|---|---|---|
| $Pr^n$ | 79 | 85 |
| $Pr^i$ | 43 | 95 |
| $PhCH_2$ | 57 | 94 |

| *R* | % |
|---|---|
| $Bu^n$ | 54 |
| $Pr^i$ | >50 |

i, $Bu^nLi$, THF, –30 °C; ii, RX (X not cited); iii, $Bu^nLi$; iv, R'X; v, $HgCl_2$, HgO; vi, $2Bu^nLi$, THF, –78 °C; vii, 2 RX

Scheme 63

### 1.3.3.2 Alkylations of 1,1-(Dithio)allyl- and 1,1-(Dithio)propargyl-metals and their Synthetic Uses

1,1-(Dithio)allyllithiums, which are available on metallation of ketene thioacetals (Scheme 69, entry a; Scheme 70, entry c)[324–327] or 1,1-(dithio)alk-2-ene (Scheme 61, entries b and c)[268,328–330] and from the addition of alkyllithiums to unsaturated ketene thioacetals) a (Scheme 71, entry a),[331] possess a high propensity to be alkylated[324,326,331] or benzylated[324,326] at their α-site (Scheme 70, entries a–c; Scheme 71, entry a). The 1,3-dithianyl derivative bearing a phenyl group at the γ-position (the softer site) however exhibits a greater aptitude for reaction at this site (Scheme 70, entries d and e).[328,329] The α:γ ratio in this case increases by increasing the hardness of the electrophile at both the acid ($PhCH_2^+$ < $Me^+$ < $Et^+$) or the leaving group ($I^-$, $Br^-$ < $Cl^-$ < $^-OTs$ < $^-SO_4Me$).[332] The latter effect was found to be greatest in the case of methylation (Scheme 70, entry d).[328,329]

Allylation of all these species is apparently less selective (Scheme 69, entry a),[325] and among the various thioacetals tested 1,3-dithianes proved to be the ones which lead to the highest α:γ ratio.[325,326,327,330] The use of HMPA as a cosolvent was shown to have no effect on the regioselectivity of the allylation.[325] However, both exclusive γ-allylation and γ-methylation have been achieved by performing the reaction in the presence of copper(I) iodide–trimethyl phosphite complex (Scheme 69, entries a–e). The reaction is best achieved with allylic chlorides, bromides and phosphate esters and does not occur with acetates, although these compounds usually react with cuprates. In all cases where isomers could be formed with respect to the electrophile, the ratio of $S_N2'$:$S_N2$ products was found to be greater than 0.67 (Scheme 69, entries b–e).[325] Related reactions have already been described with allylic sulfides (Scheme 27, see Section 1.3.2.2.4).[162,163]

On the one hand, thioacetals of α,β-unsaturated ketones resulting from the α-alkylation reaction reported above have been transformed efficiently into the corresponding unsaturated ketones on reaction with mercury(II) chloride and oxide in methanol (Scheme 71, entry a)[329,331] or on reaction[326,333] with methyl iodide or methyl fluorosulfonate followed by hydrolysis, with sulfonyl hydroxylamine.[324] On the

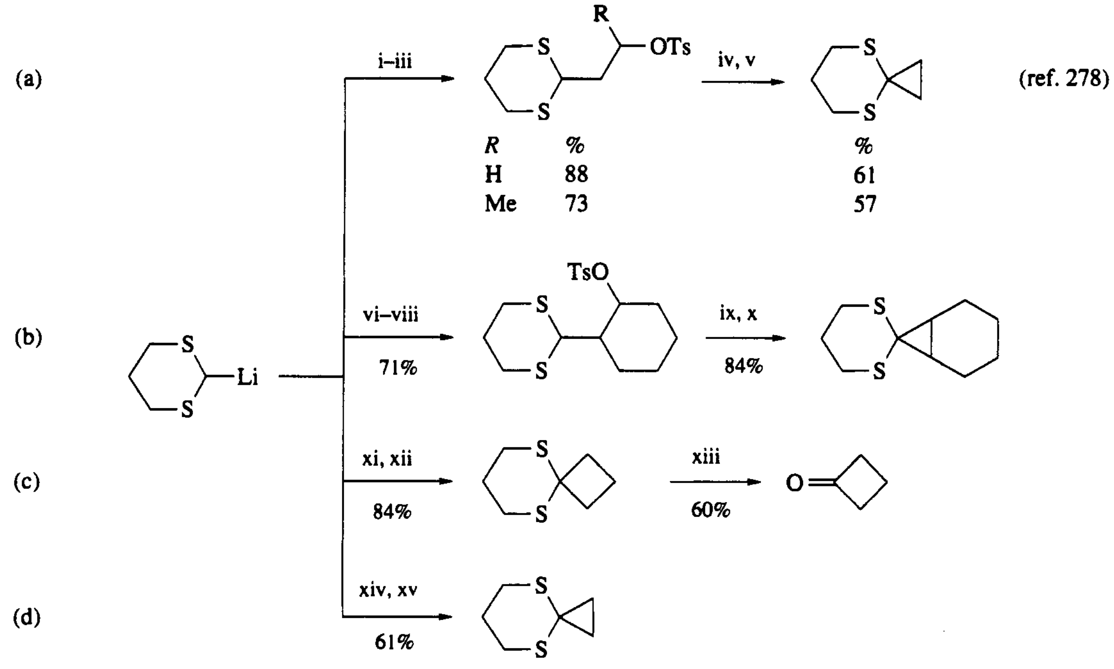
(a)
i–iii
R
OTs
iv, v
(ref. 278)
R %
H 88
Me 73
%
61
57
(b)
TsO
vi–viii
71%
ix, x
84%
(c)
xi, xii
84%
xiii
60%
O
(d)
xiv, xv
61%
Li
S

i, 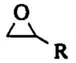 ; ii, $H_3O^+$; iii, TsCl, pyridine; iv, LiCl, DMF; v, $Bu^nLi$, THF; vi, 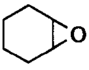 ; vii, $H_3O^+$;
viii, TsCl, pyridine; ix, LiCl, DMF; x, $Bu^nLi$; xi, 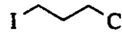 ; xii, $Bu^nLi$, THF; xiii, $HgCl_2$, HgO, 80 °C, 3 h;
xiv, 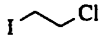 , THF; xv, $Bu^nLi$, THF

Scheme 64

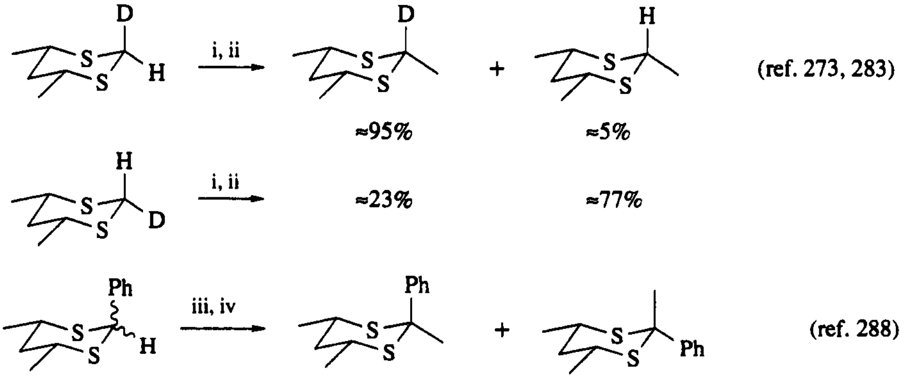
D
H
i, ii
D
+
H
(ref. 273, 283)
≈95%
≈5%
H
D
i, ii
≈23%
≈77%
Ph
iii, iv
Ph
+
Ph
(ref. 288)

| Solvent | % | % |
|---|---|---|
| THF | >99.9 | <0.1 |
| THF–HMPA | 99.9 | 0.1 |

i, $Bu^nLi$, THF, −78 °C; ii, MeI; iii, $Bu^nLi$, solvent, −78 °C; iv, MeI

Scheme 65

other hand, ketene thioacetals resulting from a γ-alkylation reaction lead to carboxylic acids on reaction with mercuric chloride and oxide.[329] Thus the 2-metallo-2-vinyl-1,3-dithianes in the above mentioned transformations have played the role of α,β-unsaturated acyl anion or homoenolate equivalents respectively.

2-Ethynyl-1,3-dithiane when treated with 1.1 equiv. of *n*-butyllithium then with methyl iodide affords[334] only the γ-products as a 1:1 mixture of alkyne and allene, resulting from the direct methylation of the lithioalkyne and of the γ-methylation of 2-ethynyl-2-lithio-1,3-dithiane respectively (Scheme 72,

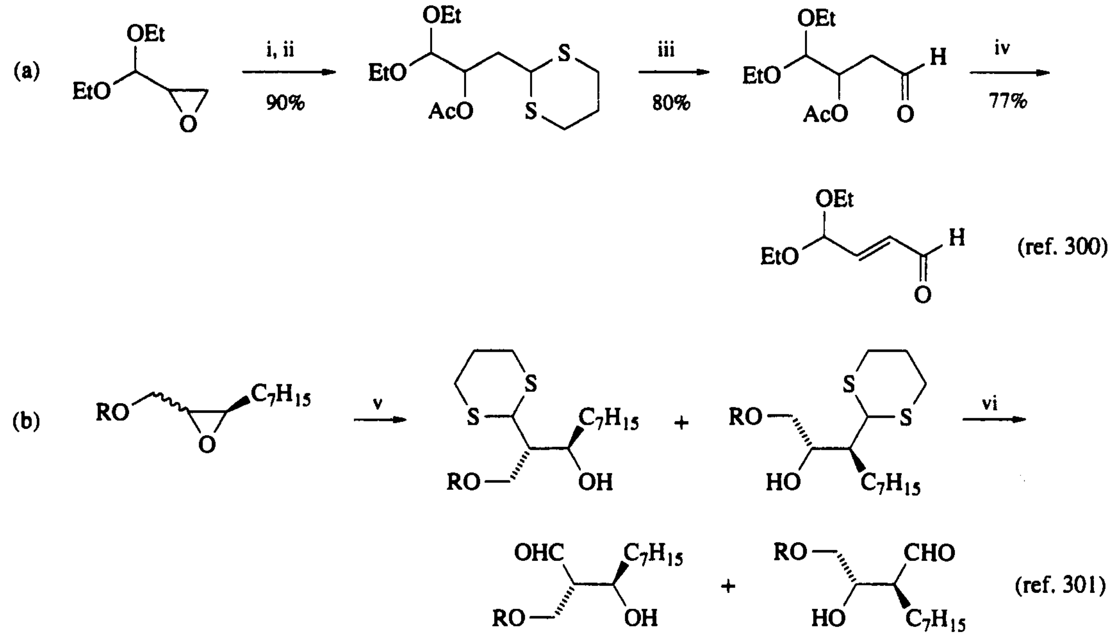
(a)
OEt
EtO
O
i, ii
90%
OEt
EtO
AcO
S
S
iii
80%
OEt
EtO
AcO
O
H
iv
77%
OEt
EtO
H
O
(ref. 300)
(b)
RO
O
$C_7H_{15}$
v
S
S
$C_7H_{15}$
RO
OH
+
RO
S
S
HO
$C_7H_{15}$
vi
OHC
$C_7H_{15}$
RO
OH
+
RO
CHO
HO
$C_7H_{15}$
(ref. 301)

i, Li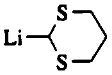, THF, –30 °C, 3 h; ii, $Ac_2O$, HgO–$BF_3$, THF, 0.3 h; iv, DBU, >30 °C, 0.3 h; v, Li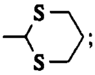; vi, $HgCl_2$, $CdCO_3$, reflux, 5 h

**Scheme 66**

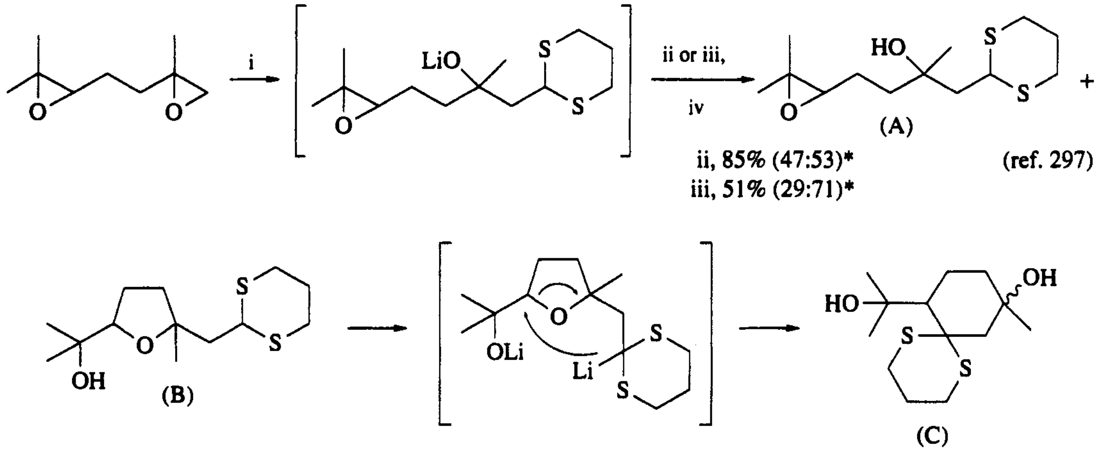
O
O
i
LiO
S
S
O
ii or iii,
iv
HO
S
S
O
(A)
+
ii, 85% (47:53)*
iii, 51% (29:71)*
(ref. 297)
S
S
O
OH
(B)
O
OLi
Li
S
S
HO
OH
S
S
(C)

i, Li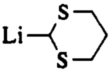; ii, 1.6 $Bu^nLi$ + 1.25 BuLi–TMEDA, –20 °C, 3 d; iii, 2 $Bu^nLi$ + 1.25 BuLi, 20 °C, 3 d; iv, $H_3O^+$

* Refers to A:(B + C) ratio

**Scheme 67**

entry a). Interestingly, the dilithio species produced on reaction with 2.5 equiv. of *n*-butyllithium (0.5 h at –70 °C) leads[334] exclusively to the ethynyl product by selective alkylation at the propargylic site, to the virtual exclusion of the allene (Scheme 72, entry b). 2-Lithio-2-(2′-silylethynyl)-1,3-dithiane has proved to be a valuable reagent which can be methylated[334] or allylated[335] exclusively at its 2-position (Scheme 72, entries c and d). The resulting products have been transformed into the corresponding functionalized ketones on successive treatment with thallium(III) nitrate trihydrate and hydrochloric acid (Scheme 72, entries c and d).[335]

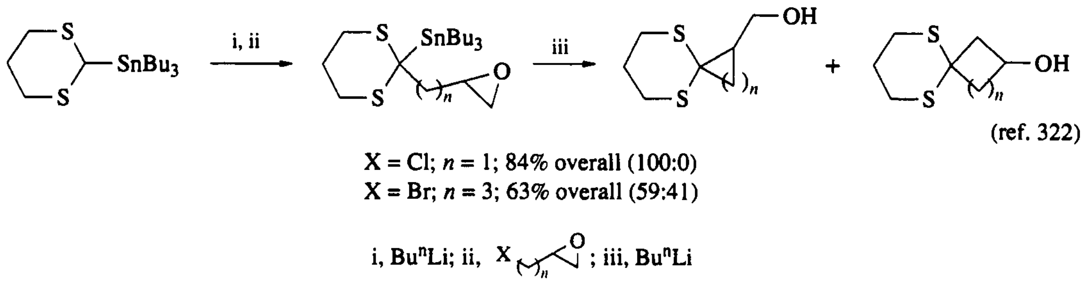

(ref. 322)

X = Cl; $n$ = 1; 84% overall (100:0)
X = Br; $n$ = 3; 63% overall (59:41)

i, Bu$^n$Li; ii, X ; iii, Bu$^n$Li

Scheme 68

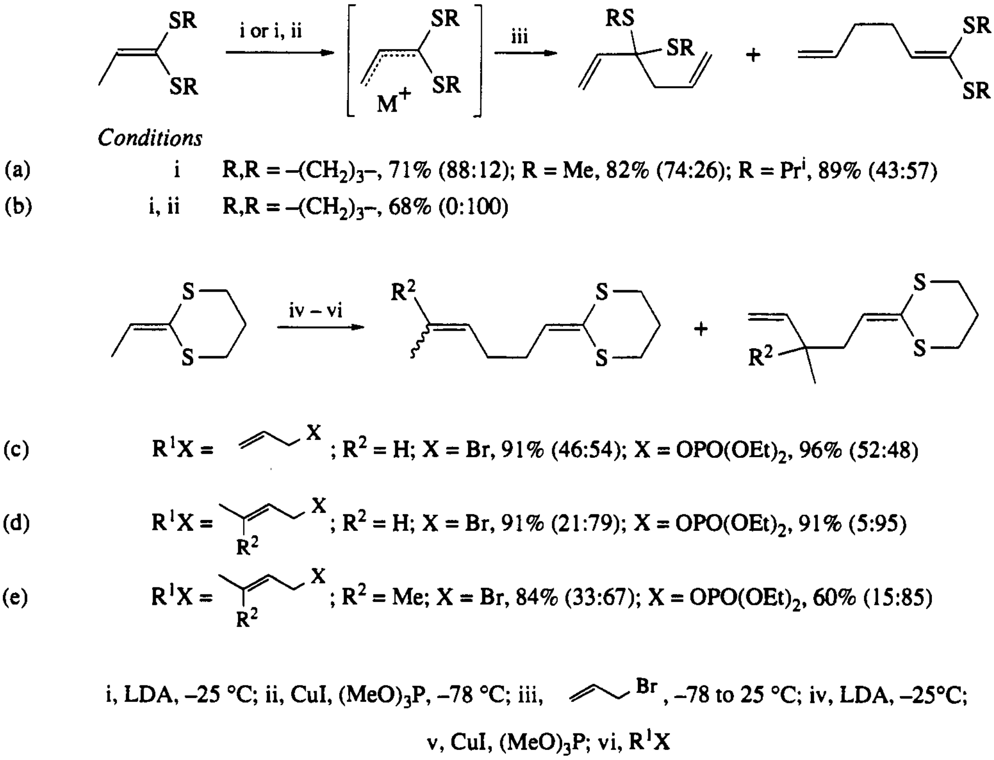

*Conditions*
(a) i R,R = –(CH$_2$)$_3$–, 71% (88:12); R = Me, 82% (74:26); R = Pr$^i$, 89% (43:57)
(b) i, ii R,R = –(CH$_2$)$_3$–, 68% (0:100)

(c) R$^1$X = ; R$^2$ = H; X = Br, 91% (46:54); X = OPO(OEt)$_2$, 96% (52:48)
(d) R$^1$X = ; R$^2$ = H; X = Br, 91% (21:79); X = OPO(OEt)$_2$, 91% (5:95)
(e) R$^1$X = ; R$^2$ = Me; X = Br, 84% (33:67); X = OPO(OEt)$_2$, 60% (15:85)

i, LDA, –25 °C; ii, CuI, (MeO)$_3$P, –78 °C; iii, Br, –78 to 25 °C; iv, LDA, –25°C;
v, CuI, (MeO)$_3$P; vi, R$^1$X

Scheme 69

## 1.3.3.3 Alkylations of Acyl Anion Equivalents Containing at Least One Sulfur or Selenium on their Carbanionic Center

### *1.3.3.3.1 Alkylations of sulfur-containing acyl anion equivalents*

Although 2-lithio-1,3-dithianes are easily synthesized and have proved to be valuable nucleophiles towards, *inter alia*, alkyl halides, their use has been limited by the not infrequent difficulty of generating the carbonyl function.[302] Thus several functionalized α-thioalkylmetals have been proposed as their alternative.

The methylations of 1,3-dilithio-5,7-dimethyl-2,4,6,8-adamantane[336] and of 1,3,5,7-tetrathiacyclooctane tetraanion[337] are of theoretical value only. 1,3,5-Trithiane and both mono- and 2,4,6-trialkyl-substituted derivatives have been metallated[28,338,339] with *n*-butyllithium and alkylated[338,339] with reactive alkylating agents such as primary alkyl iodides or bromides and benzyl bromide (Scheme 73, entries a and b). The metallation of monoalkylated trithianes occurs at one of the two unsubstituted sites and leads eventually to the product having both substituents in the equatorial position.[273,323] Thus the high equatorial preference for lithium in 2-lithio-1,3-dithiane is also present in 2-lithio-2-methyl-1,3,5-trithiane. Mer-

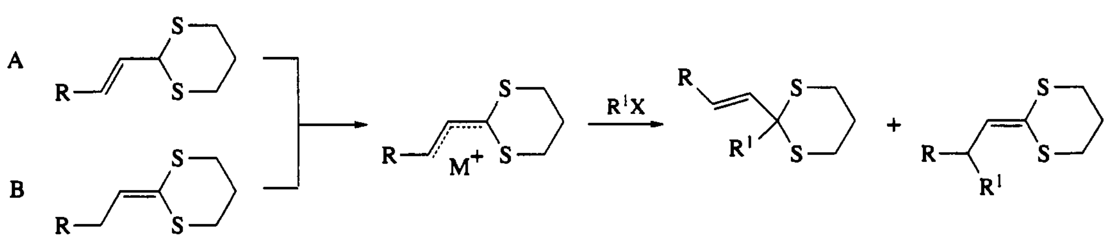

| *Entry* | *A or B* | *R* | *Conditions* | *$R^1X$* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (a) | B | Pr | LDA, THF–HMPA | MeI | 88 | 100:0 | 326 |
| (b) | B | Pr | $Bu^nLi$, THF–HMPA | MeI | 90 | 100:0 | 324 |
| (c) | A | H | $Bu^nLi$, THF | MeI | 50 | 100:0 | 324 |
| (d) | A | Ph | $Bu^nLi$, THF | MeI | 60 | 56:44 | 328, 329 |
| | | | | MeOTs | 80 | 82:18 | |
| | | | | $Me_2SO_4$ | 55 | 100:0 | |
| (e) | A | Ph | $Bu^nLi$, THF | $PhCH_2Cl$ | 66 | 22:78 | 328, 329 |
| | | | | $PhCH_2Br$ | 75 | 14:86 | |
| | | | | $PhCH_2I$ | 60 | 10:90 | |

**Scheme 70**

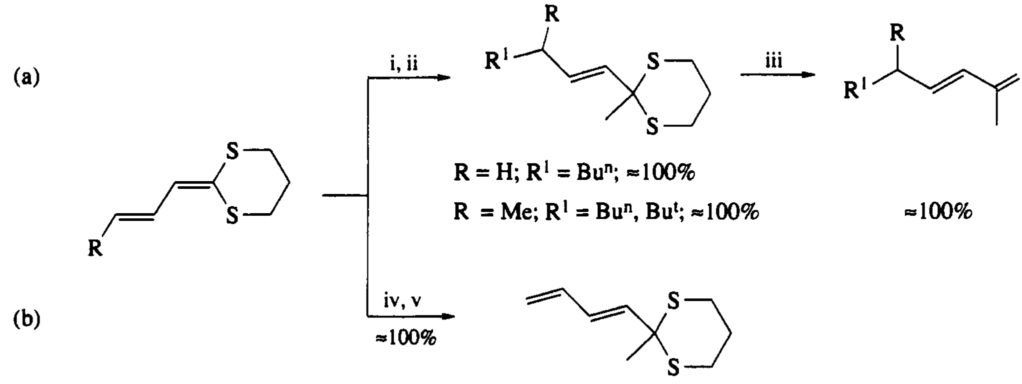

i, $R^1Li$, −80 to 20 °C; ii, MeI; iii, $HgCl_2$, HgO; iv, LDA; v, MeI

**Scheme 71**

cury(II)-assisted solvolysis of the alkyl trithianes then liberates the most highly substituted carbonyl compounds (Scheme 73, entry b).[338,339] Thus 1,3,5-trithiane after monoalkylation leads finally to aldehydes, whereas alkylation of lithio-2,4,6-trialkyl-substituted analogs would lead to the corresponding alkyl ketones (Scheme 73, entry b).

Several other acyl anions or potential acyl anion equivalents bearing at least one nonoxidized sulfur atom have since been proposed, and some of them have been alkylated successfully. This is effectively the case for the following metallated compounds: (i) *N*-methylthioformaldine (Scheme 73, entry c);[340] (ii) 1,3-oxathianes,[341,342] and α-trimethylsilylmethyl analogs;[343] (iii) α-methoxythioanisole (Scheme 74, entry a; Scheme 75, entry c);[344–347] the parent compound also allows[345] the synthesis of acetals (on acid-catalyzed methanolysis), of vinyl ethers (on oxidation to the sulfoxide and heating at 120 °C) and carboxylic acids ($CrO_3$, $H_2SO_4$, Jones reagent; Scheme 75, entry b) and its α-vinyl-substituted derivatives (Scheme 76);[347,348] (iv) α-trimethylsilylmethylthioanisole (Scheme 77, entries a–c; Scheme 78, entries e and f),[252,349–354] and its α-aryl derivative (Scheme 77, entry c);[355] (v) methylthiomethyl methyl sulfoxide (Scheme 74, entry b; Scheme 79; Scheme 80, entries b and c),[356–364] its α-alkyl homologs (Scheme 79; Scheme 80, entries b and c)[356,359–362] and related diethyl (Scheme 74, entries c and d; Scheme 80, entry a)[358,365,366] or di-*t*-butyl[365] derivatives as well as 1,3-dithiane-1-oxide[367,368] and its 2-alkyl- and 2-phenyl-

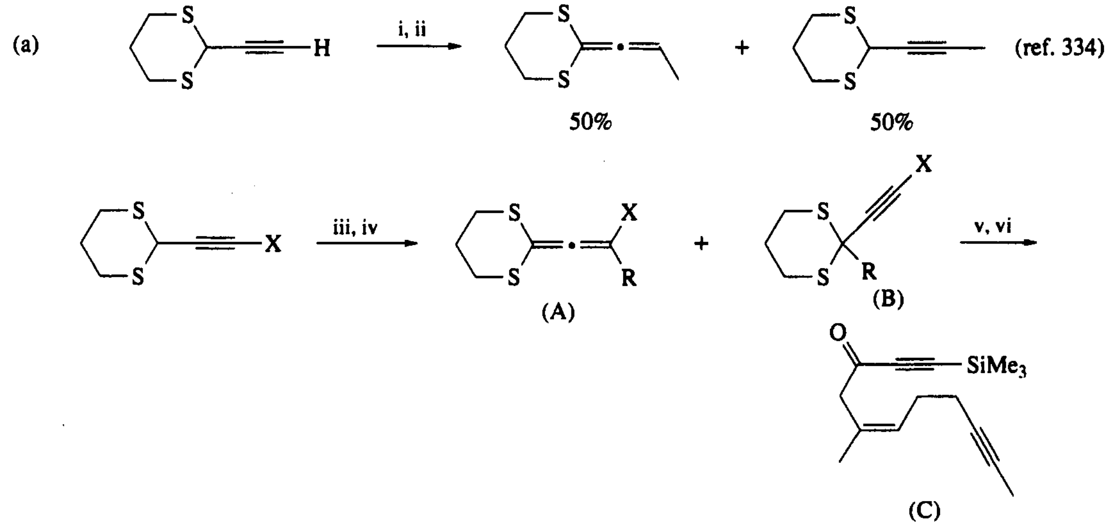

| | X | Base | RX | Yield of A + B (%) | A:B ratio | Yield of C (%) | Ref. |
|---|---|---|---|---|---|---|---|
| (b) | H | 2.5 $\mathrm{Bu^nLi}$ | excess MeI | – | 0:100 | | 334 |
| (c) | $\mathrm{SiMe_3}$ | 1 $\mathrm{Bu^nLi}$ or LDA | MeI | >90 | 0:100 | | 334 |
| (d) | $\mathrm{SiMe_3}$ | 1 $\mathrm{Bu^nLi}$, −20 °C<br>4 h | 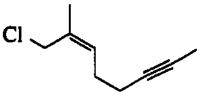 | 84 | 0:100 | 86 | 335 |

i, 1.1 $\mathrm{Bu^nLi}$; ii, MeI; iii, base; iv, RX; v, $\mathrm{Tl(NO_3)_3}$, MeOH; vi, 5% HCl

**Scheme 72**

substituted homologs;[368] (vi) methylthiomethyl *N,N*-dimethyl dithiocarbamate (Scheme 74, entry e);[369] (vii) methylthiomethyl *p*-tolyl sulfone and homologs (Scheme 74, entries f–h; Scheme 80, entry d);[370,371] (viii) bis(*N,N*-dimethyldithiocarbamato)methane;[372] and (ix) 4,4-dimethyloxathiolane 3,3-dioxide.[373]

### *1.3.3.3.2 Alkylations of selenium-containing acyl anion equivalents*

Related reactions involve 1-metallo-1,1-di(arylseleno)-[64,65,76,78,106,108,122] and 1-lithio-1,1-di(methylseleno)-alkanes (Scheme 81; Scheme 82),[76,78,122] 1-lithio-1-phenylseleno-1-phenyltelluromethane (Scheme 78, entry h)[374] as well as 1-trimethylsilyl-1-arylselenomethyllithiums (Scheme 78, entries a–f)[74,106,353,375] and their 1-aryl homolog[74,106] and 1-trimethylsilyl-1-methylselenoalkyllithiums (Scheme 78, entry g).[77] Intramolecular cyclizations of 3-halo-1,1-di(seleno)alkanes[78,122] and of 3-tosyloxy-1,1,1-tri(seleno)alkane[78] with LDA and *n*-butyllithium respectively lead to the corresponding 1,1-di(seleno)cyclopropanes (Scheme 82, entries b–g). These in turn have proved to be valuable precursors of 1-seleno-1-cyclopropyllithiums (Scheme 8, entry e; Section 1.3.2.1.1).

Interestingly, the synthesis of 1,1-di(phenylseleno)cyclopropane has been performed[78,122] from 3-chloro-1,1-di(phenylseleno)propane and $\mathrm{Bu^tOK}$ (Scheme 82, entry c) or, in a longer sequence, on reaction of 1-(3-chloropropyl)-1-phenylseleno-1-phenyl selenoxide[113] with LDA and further reduction of the resulting 1-phenylseleno-1-phenylselenoxycyclopropane (Scheme 82, entry a). Surprisingly the reaction of $\mathrm{Bu^tOK}$ with 3-chloro-1,1-di(methylseleno)propane takes another course and leads to 1,1-di(methylseleno)-1-propene rather than to 1,1-di(methylseleno)cyclopropane.[78]

Most of the organometallics reported above, with the exclusion of 1,1-di(methylseleno)- (Scheme 81, entry e)[76,78] and α-silyl-α-methylselenoalkyllithiums (Scheme 78, entry e)[77] have been prepared by metallation of the corresponding carbon acid. The Se/Li exchange method however proved to be the method of choice for the synthesis of almost all the α-selenoalkylmetals described in this section.[64,65,76,78,106,108,122]

As far as the further reaction of the above mentioned organometallics with electrophiles is concerned, most of these reagents work well with primary[341–344,347–352,356–360,362,363,365,366,368–373,375] and secondary[341–343,349,350,352,358,360,361] alkyl halides, benzyl bromides[341–344,348,350,352,357,369–373] and allylic bro-

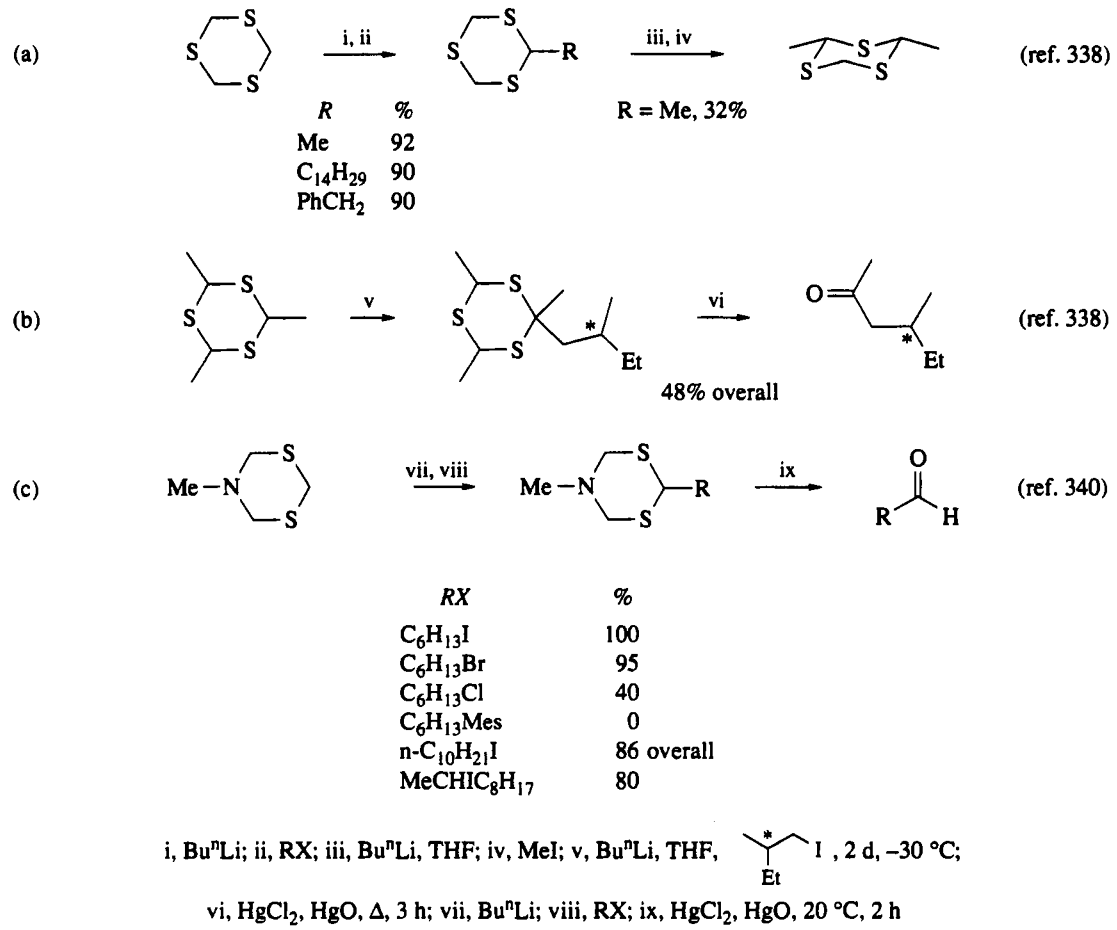

| *R* | % |
|---|---|
| Me | 92 |
| $C_{14}H_{29}$ | 90 |
| $PhCH_2$ | 90 |

| *RX* | % |
|---|---|
| $C_6H_{13}I$ | 100 |
| $C_6H_{13}Br$ | 95 |
| $C_6H_{13}Cl$ | 40 |
| $C_6H_{13}Mes$ | 0 |
| n-$C_{10}H_{21}I$ | 86 overall |
| $MeCHIC_8H_{17}$ | 80 |

i, $Bu^nLi$; ii, RX; iii, $Bu^nLi$, THF; iv, MeI; v, $Bu^nLi$, THF, I , 2 d, −30 °C;
vi, $HgCl_2$, HgO, Δ, 3 h; vii, $Bu^nLi$; viii, RX; ix, $HgCl_2$, HgO, 20 °C, 2 h

**Scheme 73**

mides[344,347,350,358,370,373] or chlorides.[347,360,361] Only a few have been reacted with epoxides[298,344,349,376] and even fewer with trialkyl-substituted halides (Scheme 77, entries f and g).[349]

Some of the reactions reported above merit further comment. This is especially the case of methylthioformaldine (Scheme 73, entry c)[340] and trimethylsilylmethylthioanisole (Scheme 77)[349,355] which can be alkylated once, but not twice, because of the lack of basic reagents sufficiently reactive to metallate the monoalkylated compound. Alternative routes to trimethylsilyl(*s*-alkyl)thioanisoles however exist.[254,352] It must be pointed out that the synthesis of fully alkylated seleno analogs also cannot be achieved by metallation reaction,[77] but takes place by Se/Li exchange from 1-silyl-1,1-di(methylseleno)alkanes and butyllithium and further alkylation of the resulting organometallics (Scheme 78, entry e). Trimethylsilyl(phenylthio)methyllithium is a particularly nucleophilic reagent toward primary and secondary alkyl halides[349,352,353,355] and epoxides (Scheme 77; Scheme 78; entries c and d).[349] Its successful alkylation with trisubstituted epoxides[349] and cyclohexyl iodide[349] is exceptional (Scheme 77, entries d and e). Alkylation of α-heterosubstituted organometallics with cyclohexyl halides[350,352] is usually unsuccessful and poor yields result from reaction with *s*-alkyl halides.[353] Allyl halides,[350] but surprisingly not propargyl halides,[351] also react efficiently with this organometallic. Most of these reactions have been carried out in THF, even though it has been suggested that better results are obtained in TMEDA–hexane.[350]

2-Lithio-1,3-oxathiane[341,342] has proved to be much less reactive than phenylthiomethyllithium (Scheme 74, entry a).[344] Although the latter reacts well with alkyl or benzyl bromides and with alkyl iodides without distinction, 2-lithio-1,3-oxathiane works well only with alkyl iodides.[341]

Monoalkylation of the carbanion generated from methyl thiomethyl sulfoxide[357] and 1,3-dithiane 1-oxide[368,377] has been reported (Scheme 74, entry b) but reexamination of both reactions[358,359] proved unsatisfactory under conditions similar to those previously described or slightly modified. Neither the stepwise[359] nor the one-pot dialkylation[357] was successful at 20 °C, but the latter reaction was apparently achieved by Schill[359] by performing it at 50 °C with a slight excess (2.2 equiv.) of *n*-alkyl bromides in

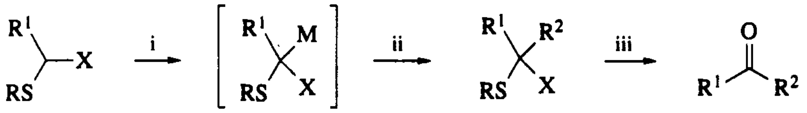
R¹
RS
X
i
R¹
M
RS
X
ii
R¹
R²
RS
X
iii
O
R¹
R²

| | R | R¹ | X | i | ii | % | iii | % | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| (a) | Ph | H | OMe | Bu$^t$Li, THF, −78 °C | MeI | 94 | – | – | 344 |
| | | | | | $C_6H_{13}I$ | 84 | | | |
| | | | | | $PhCH_2Br$ | 88 | | | |
| | | | | | $H_2C{=}CHCH_2Br$ | 76 | | | |
| (b) | Me | H | S(O)Me | NaH, THF, 20 °C | MeI, 20 to 40 °C | 92 | HCl, $H_2O$ | 84 | 357 |
| | | | | | BuI | 72 | | 91 | |
| | | | | | $PhCH_2Br$ | 92 | | 88 | |
| (c) | Et | H, Et | S(O)Et | Bu$^n$Li or LDA, THF, 2 °C | EtI, 25 °C, 2 h | >95 | $HgCl_2$, HCl, THF, 0 °C, 1 h | >80 | 357 |
| | | | | | Pr$^i$Br | | | >80 | |
| | | | | | $H_2C{=}CHCH_2Br$ | | | >80 | |
| (d) | Me | H | $SC(S)NMe_2$ | Bu$^n$Li, THF, −50 °C | $C_8H_{17}I$, −60 °C, 1 h, 20 °C | | aq. HCl, 20 °C | 66 overall | 369 |
| | | | | | $PhCH_2Br$ | | | 68 overall | |
| (e) | Me | H | $SO_2Tol$ | 50% aq. NaOH, toluene | $C_{12}H_{25}Br$, 20 °C, 4 h | 84 | Dioxane, $H_2O$, NaOH, *hν* | 72 | 370 |
| | | | | | $PhCH_2Br$, 50 °C, 3 h | 88 | | – | 371a |
| (f) | Me | H | $SO_2Tol$ | 2.5 equiv. NaH, DMF | 2 $C_{12}H_{25}Br$, 20 °C, 48 h | | $H_2SO_4$, MeOH, Δ, 3 h | 90 overall | 371a |
| | | | | | 2 $PhCH_2Br$, Δ, 3 h | | | 74 overall | 371a |

**Scheme 74**

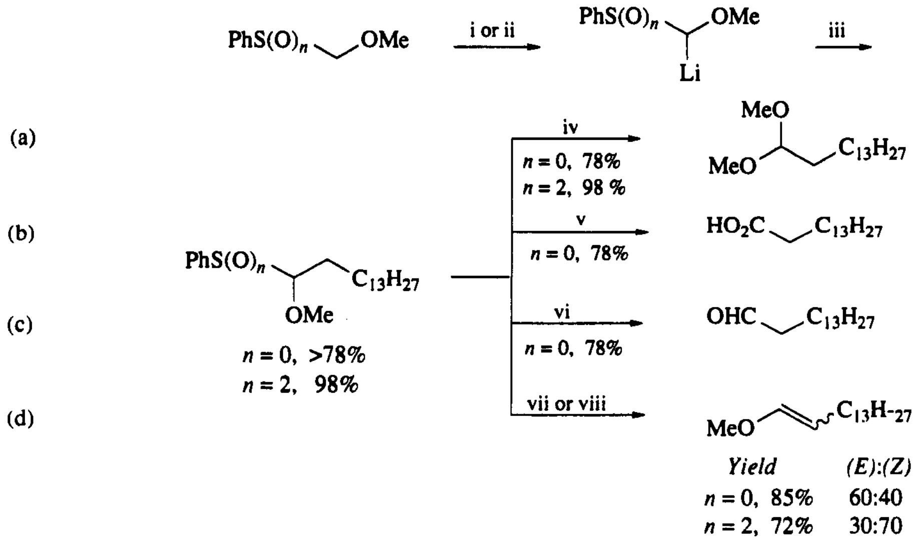
PhS(O)ₙ
OMe
i or ii
PhS(O)ₙ
OMe
Li
iii
(a)
(b)
(c)
(d)
PhS(O)ₙ
C₁₃H₂₇
OMe
n = 0, >78%
n = 2, 98%
iv
n = 0, 78%
n = 2, 98 %
v
n = 0, 78%
vi
n = 0, 78%
vii or viii
MeO
MeO
C₁₃H₂₇
HO₂C
C₁₃H₂₇
OHC
C₁₃H₂₇
MeO
C₁₃H₂₇
Yield
(E):(Z)
n = 0, 85%
60:40
n = 2, 72%
30:70

i, Bu$^n$Li, THF, −78 °C (*n* = 0); ii, LDA, THF, −78 °C (*n* = 2); iii, RX; iv, cat. TosOH, MeOH, Δ, 2 h; v, $CrO_3$, $H_2SO_4$, 0 °C, 1 h, acetone; vi, MCPBA, −5 to 0 °C, toluene, then 40 °C; vii, MCPBA, toluene, 0 °C, then 120 °C (*n* = 0); viii, Bu$^t$OK, THF (*n* = 2)

**Scheme 75**

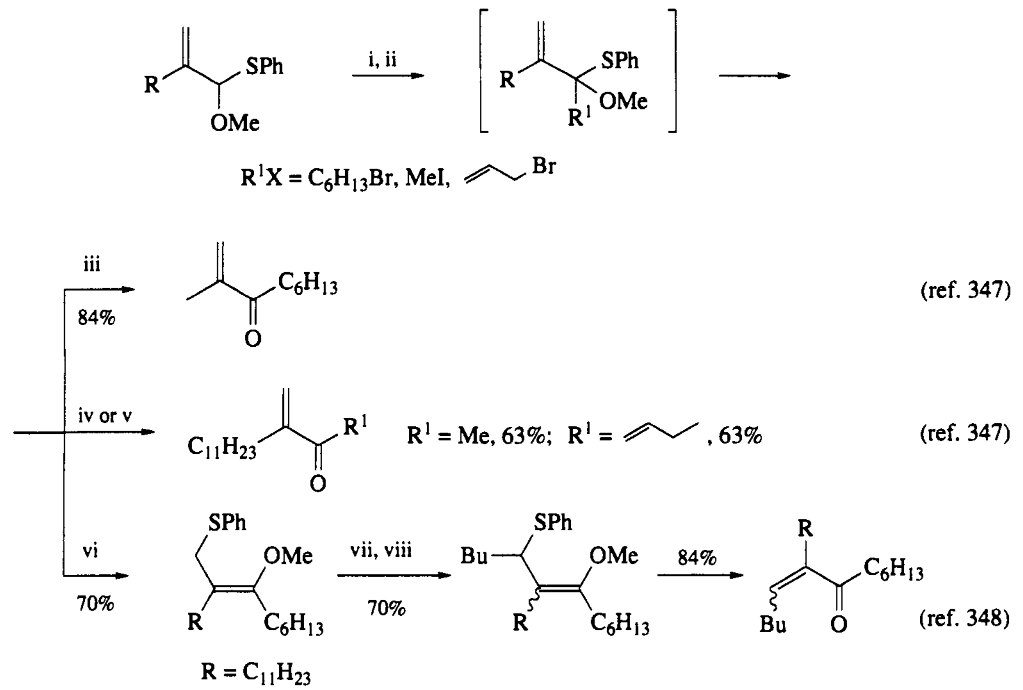

i, $Bu^nLi$, HMPA; ii, $R^1X$; iii, $SiO_2$–$H_2O_2$, 20 °C, 3 h; iv, $NaIO_4$, dioxane, 20 °C, 3 h;
v, MCPBA, $CH_2Cl_2$, −30 °C, 1 h; vi, $SiO_2$, hexane; vii, $Bu^nLi$–TMEDA, THF, 0 °C, 0.5 h; viii, BuI

Scheme 76

the presence of an excess of sodium hydride in THF. More recently, this reaction has been successfully used by Evans in a synthesis of the ionophore antibiotic A-23187 (Scheme 79, entry b).[363]

Slight variations of the structure of this acyl anion equivalent have led in fact to the discovery of particularly valuable alternative reagents. Among them, ethyl ethylthio sulfoxide can be both monoalkylated[358,365,366] or sequentially dialkylated[359] (Scheme 74, entries c and d). *t*-Butyl methylthio sulfoxide[359,365] and phenyl methylthio[378] analogs have also been monoalkylated but not dialkylated (Scheme 79, entry c; Scheme 80, entry a).

Reaction of methyl methylthio sulfoxide with 1,*n*-dihalo or 1,*n*-(tosyloxy)alkanes in the presence of 2 to 2.8 equiv. of $Bu^nLi$ or KH as a base gave three- to six-membered not seven-membered 1-methylsulfinyl-1-methylthiocycloalkanes (Scheme 80, entries b and c). These cycloalkanes have been subsequently transformed to the corresponding ketones under mild conditions.[356,360–362,364] The tosyloxy route, which is often inefficient[340] with related organometallics has proved to be particularly attractive[360,364] for the construction of the cyclopropane ring which cannot be produced from 1,2-dibromoethane (Scheme 80, compare entries b and c). This cyclization reaction may involve[360,361] the formation of an intermediary sulfonium salt (see Scheme 80, entry b), which is metallated and then rearranges to the desired product, *via* a Stevens-type rearrangement. This process allows the high yielding synthesis of diversely substituted (even in the 2-position) cyclobutanones,[360] 3-cyclopentenone from (*Z*)-1,4-dichlorobut-2-ene (Scheme 83, entry a)[360] and of (*R*)- and (*S*)-4-hydroxycyclopentenones,[362] which are valuable precursors of prostaglandins (Scheme 83, entry c). Particularly impressive is the efficiency of the last mentioned synthesis, which uses tartaric acids and methyl methylthio sulfoxide as the two building blocks. An unusually facile cyclization employing a mesyloxycyclopentane, and leading finally to a bicyclo[3.3.0]octanone (Scheme 79 entry a), a valuable precursor of isocarbacyclin, has also been reported.[364]

As expected (*E*)-1,4-dichlorobut-2-ene reacts[360] differently from its (2*Z*)-isomer with methyl methylthiomethyl sulfoxide, and produces a vinylcyclopropane instead of the cyclopentene derivative (Scheme 83, entry b, compare to entry a).

Methyl methylthiomethyl sulfone and methylthiomethyl *p*-tosyl sulfone have been monoalkylated, benzylated or alkylsilylated with 1.5 equiv. of the electrophile in the presence of aqueous sodium hydroxide and trioctylmethylammonium chloride (TOMAC).[370,371] Without doubt the organometallic is less reactive than the one derived from the corresponding sulfoxide since the reaction is rather slow with

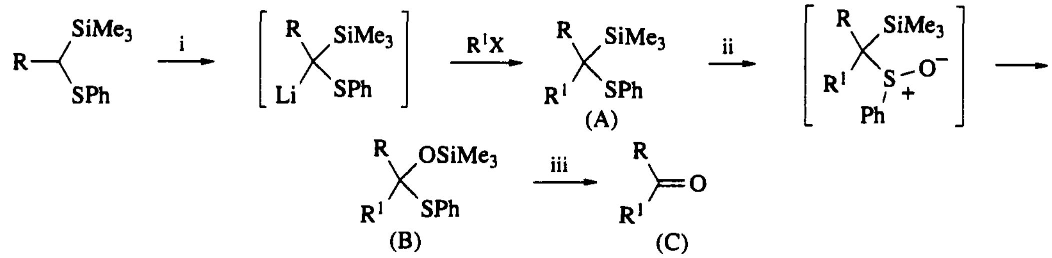

| *Entry* | *R* | *R$^1$X* | *A (%)* | *B (%)* | *C (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| (a) | H | MeI | 99 | 80 | - | 352 |
| | H | Bu$^n$Br | 84 | 70 | 72 | |
| | H | Bu$^s$Br | 45 | 76 | 74 | |
| (b) | H | PhCH$_2$Br | 83 | 87 | 77 | 352 |
| | | c-C$_6$H$_{11}$Br | 0 | - | - | |
| (c) | H | 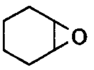 | 90 | | 62 | 349 |

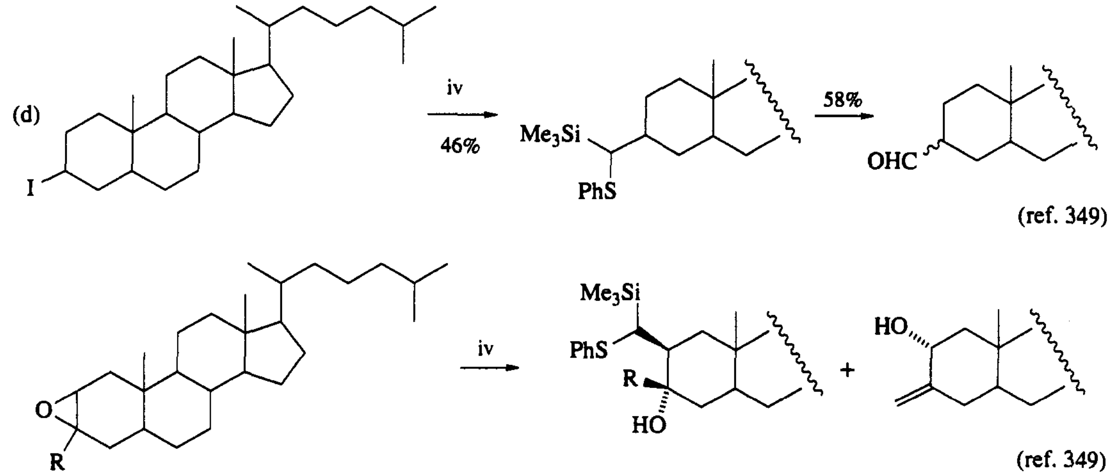

(e) R = Me 65% (40:60)
(f) R = H 91% (100:0)

i, Bu$^n$Li, TMEDA, 0 °C; ii, MCPBA, −15 °C; iii, H$_2$O; iv, LiCH(SiMe$_3$)SPh

Scheme 77

allyl and benzyl halides (20 °C, 48 h) and requires heating to 60 °C to go to completion with primary alkyl bromides. The second alkylation, alkynylation and benzylation have been carried out[370] with NaH in DMF (1.3 equiv.) at 20 °C for long periods of time (19 to 48 h) or more rapidly with heating (3 h at 60 °C). Cyclo-butane, -pentane and -hexane[371] as well as cyclopentene derivatives[380] have been obtained from the corresponding dibromides. The synthesis of the cyclobutane derivative requires the use of an excess of NaH in DMF[371a] or Bu$^n$Li in THF.[371b] For the other cases, however, phase-transfer conditions can be used (Scheme 80, entry d). Unfortunately, as with methyl methylthio sulfoxide (Scheme 80, entry c), seven-membered rings cannot be synthesized[371b] (Scheme 80, entry d) by this method.

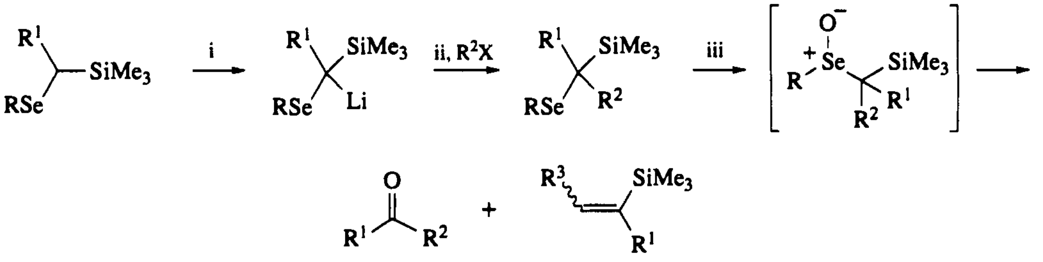

(a) $R^1 = H$; R = Ph; i, LDA, -30 °C, 0.5 h; ii, $C_{10}H_{21}Br$, 75%; iii, $H_2O_2$, THF (ref. 77, 375)

(b) $R^1 = H$; $R = 4\text{-}CF_3C_6H_4$; i, LDA, –78 °C, 0.5 h; ii, $PhCH_2Br$, 83%; iii, MCPBA, THF, $Pr^i_3N$, 71% (66:34) (ref. 74, 106)

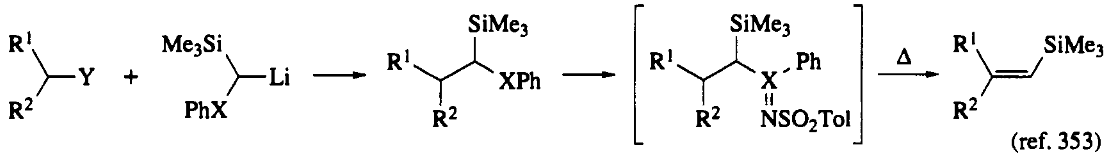

(ref. 353)

| | | |
|---|---|---|
| (c) $R^1CHR^2 = n\text{-}C_9H_{19}$ | X = S, 92% | X = S, 69%, 100 °C |
| | X = Se, 82% | X = Se, 70%, 20 °C |
| | X = Te, 64% | X = Te, 72%, 40 °C |
| (d) $R^1CHR^2 = C_6H_{13}CHMe$ | X = S, 30% | X = S, 42%, 100 °C |
| | X = Se, 34% | X = Se, 48%, 20 °C |

(e)

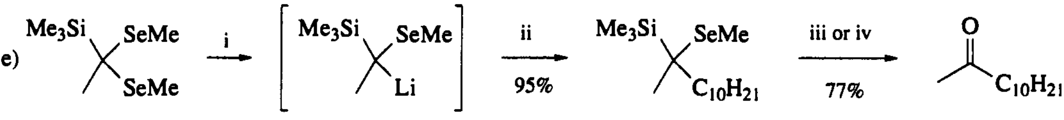

(ref. 77)

(f)

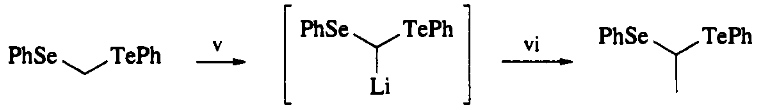

(ref. 374)

i, $Bu^nLi$, THF, –78 °C; ii, $C_{10}H_{21}Br$; iii, $H_2O_2$, THF; iv, $NaIO_4$, EtOH; v, LDA, THF, –78 °C, 0.5 h; vi, MeI

**Scheme 78**

### *1.3.3.3.3 Synthesis of aldehydes and ketones from α-heterosubstituted sulfides and selenides and related compounds*

Most α-heterosubstituted alkyl sulfides discussed in this section have proved to be much easier to transform to aldehydes or ketones than the corresponding 1,3-dithianes. In particular this is the case of (i) formaldines[340] ($HgCl_2$, HgO, 20 °C, 2 h; Scheme 73, entry c), (ii) α-methoxyalkenyl phenyl sulfide[348] ($NaIO_4$, $H_2O$, dioxane, 20 °C; Scheme 77) and (iii) the α-silylalkyl phenyl sulfides[349–351,355] (MCPBA, –15 °C then $H_2O$; Scheme 77) and α-silylalkyl selenides[74,77,106,375] ($H_2O_2$, THF, $NaIO_4$, MCPBA, 20 °C; Scheme 78, entries a–e). The last mentioned reactions involve the transformation of the α-silyl sulfoxide or selenoxide first produced to the corresponding trimethylsilyl hemithio or hemiseleno acetal *via* a Sila–Pummerer rearrangement. This requires overnight reaction at 20 °C or 0.5 h at 60 °C in the case of sulfur, but proceeds almost instantaneously with the seleno analog. Interestingly, this rearrangement can be sup-

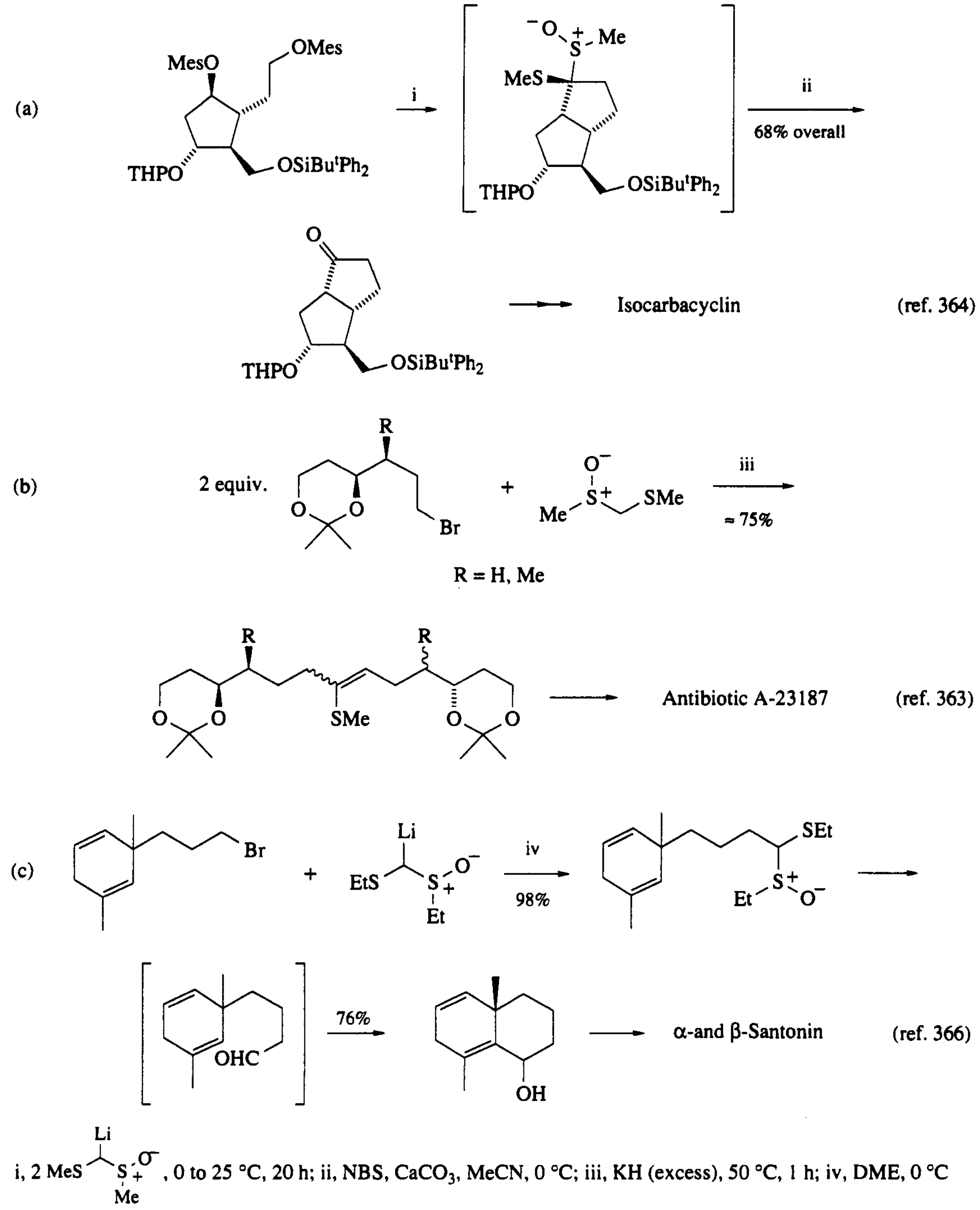
(a)
MesO
OMes
THPO
OSiBu$^t$Ph$_2$
i
$^-$O
+
S
Me
MeS
ii
68% overall
O
Isocarbacyclin
(ref. 364)
(b)
2 equiv.
R
O
Br
+
O$^-$
S+
SMe
Me
iii
≈ 75%
R = H, Me
SMe
Antibiotic A-23187
(ref. 363)
(c)
Br
Li
EtS
S+
O$^-$
Et
iv
98%
SEt
76%
OHC
OH
α-and β-Santonin
(ref. 366)

i, 2 MeS(Li)CHS$^+$(O$^-$)Me, 0 to 25 °C, 20 h; ii, NBS, $CaCO_3$, MeCN, 0 °C; iii, KH (excess), 50 °C, 1 h; iv, DME, 0 °C

Scheme 79

pressed and the elimination reaction which leads to vinylsilane favored if the α-silyl sulfide, selenide or telluride is instead treated with chloramine T (Scheme 78, entries c and d).[353]

1,1-Di(seleno)alkanes have been easily transformed to carbonyl compounds on reaction with a large array of reagents including $HgCl_2$–$CaCO_3$, $CuCl_2 \cdot 2H_2O$–CuO,[86,243] hydrogen peroxide,[86] benzeneseleninic anhydride[86] or clay-supported metal nitrates[379] in ways similar to those used with thio analogs. In some cases, an elimination reaction produces vinyl selenides instead of the carbonyl compound. In such an event, the latter derivative can be obtained by further hydrolysis[243,244] of the vinyl selenide, for example with $HgCl_2$ in the absence of an added base (Scheme 81).

The transformations of thioacetal monosulfoxides to carbonyl compounds[357-361,365,366] have been

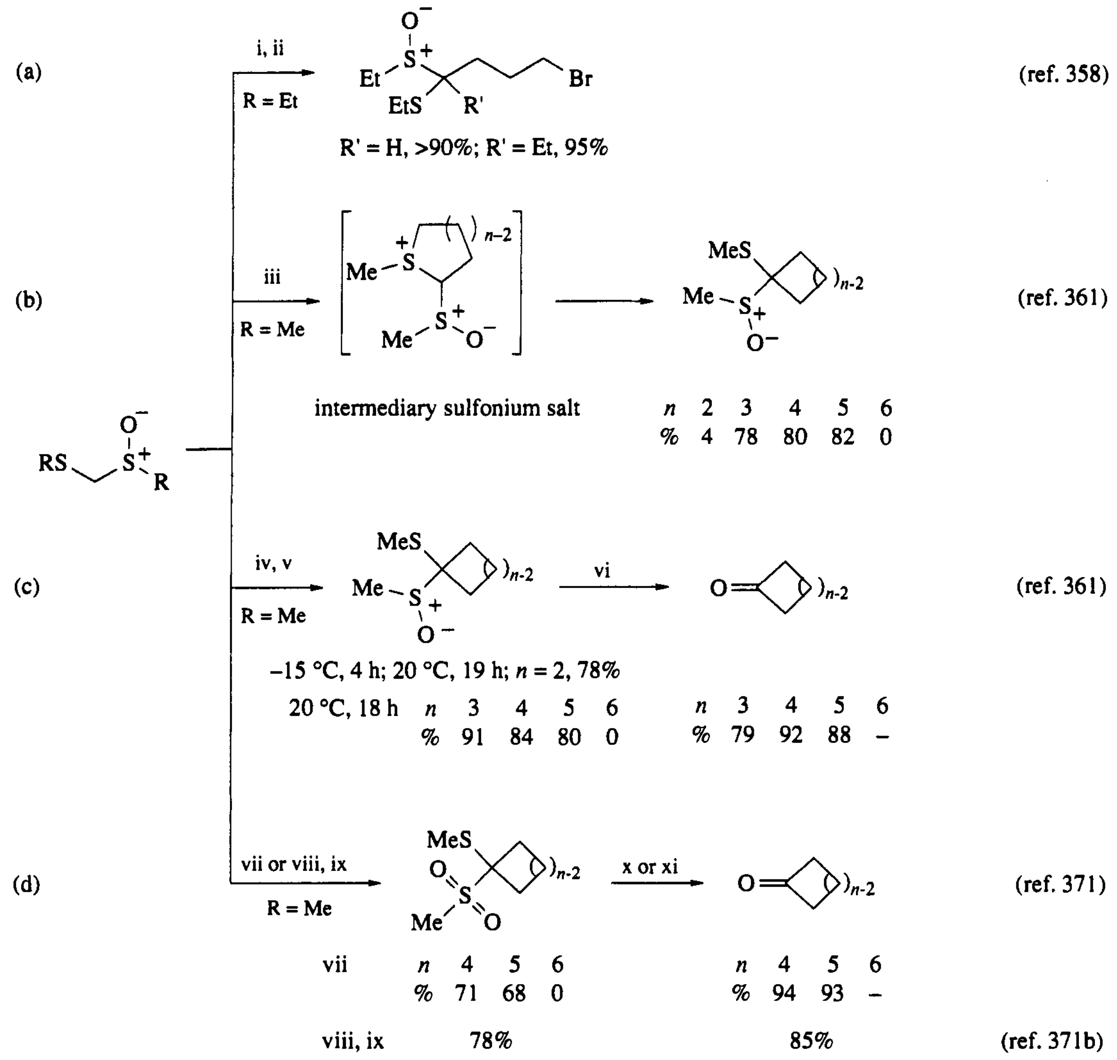
(a)
i, ii
R = Et
R' = H, >90%; R' = Et, 95%
(ref. 358)
(b)
iii
R = Me
intermediary sulfonium salt
n 2 3 4 5 6
% 4 78 80 82 0
(ref. 361)
(c)
iv, v
R = Me
vi
−15 °C, 4 h; 20 °C, 19 h; n = 2, 78%
20 °C, 18 h n 3 4 5 6
% 91 84 80 0
n 3 4 5 6
% 79 92 88 –
(ref. 361)
(d)
vii or viii, ix
R = Me
x or xi
vii n 4 5 6
% 71 68 0
n 4 5 6
% 94 93 –
viii, ix 78% 85%
(ref. 371)
(ref. 371b)

i, 1 LDA; ii, $Br(CH_2)_3Br$, 25 °C, 2–10 h; iii, $Br(CH_2)_nBr$, 2.8 KH, THF, 20 °C, 19–48 h; iv, $Bu^sLi$; v, 0.5 $Tos(CH_2)_nTos$; vi, 4.5 M $H_2SO_4$, 20 °C, 4–15 h (or 20 h, 45 °C if $n = 3$); vii, 50% aq. NaOH, toluene, TOMAC, 60 °C, 64–144 h, $Br(CH_2)_nBr$; viii, BuLi; ix, 0.5 $Br(CH_2)_3Br$, 20 °C, 22 h; x, conc. HCl, MeOH; xi, conc. HCl, dioxane, Δ, 3.5 h

Scheme 80

carried out with hydrochloric, perchloric, or sulfuric acid in water, ether or THF (Scheme 80, entries c and d; Scheme 83, entries a and c) and often in the presence of mercury(II) salts in order to remove the disulfide concomitantly produced,[358] or with NBS in the presence of $CaCO_3$ (Scheme 74, entries b–d; Scheme 79, entries a and c).[364] These conditions are sufficiently mild to allow, for example, the almost exclusive formation[360] of 3-cyclopentenone from (*Z*)-1,4-dichlorobut-2-ene without substantial isomerization to the thermodynamically more stable 2-cyclopentenone (Scheme 83, entry a). The synthesis of the more strained cyclobutanone requires slightly more drastic conditions however to go to completion (4.5 M $H_2SO_4$, 20 °C, 18 h and 45 °C, 5 h).[371b]

Finally, ketone dimethylthioacetal *S*,*S*-dioxides[371] are more difficult to transform to ketones than their *S*,*S*-monoxides[357] (Scheme 74, entries f–h). Effective transformation usually requires heating at reflux in the presence of concentrated acid. Moreover, dimethyl thioacetal *S*,*S*-dioxides[371a] derived from aldehydes resist the above mentioned hydrolysis conditions and require, in order to be transformed to the aldehyde, preliminary photochemical cleavage of the C—$SO_2$ bond[371a] (*hν* then aq. NaOH; Scheme 74,

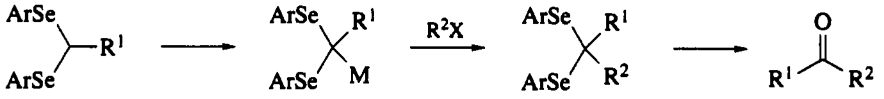

| Entry | Ar | Conditions | $R^1$ | $R^2$ | % | Conditions | % | Ref. |
|---|---|---|---|---|---|---|---|---|
| (a) | Ph | i | H | $C_6H_{13}$ | 80 | | | 64, 65 |
| (b) | | ii | Me | $C_6H_{13}$ | 74 | | | 76 |
| | | | $C_6H_{13}$ | $C_6H_{13}$ | 44 | | | |
| (c) | | iii | Me | $C_6H_{13}$ | 82 | | | |
| | | | $C_6H_{13}$ | $C_6H_{13}$ | 86 | | | |
| (d) | | iv | Me | $C_{10}H_{21}$ | 95 | v | 64 | 86, 108 |
| | | | Me | $Pr^i$ | 70 | | | |
| | | | $Pr^i$ | $PhCH_2$ | 71 | | | |
| (e) | $4\text{-}CF_3C_6H_4$ | vi | H | $C_6H_{13}$ | 85 | | | 106 |

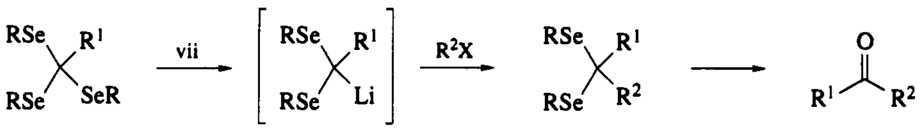

(f) R = Ph $R^1 = R^2 = Me$; 72% (ref. 64, 65, 76)

(g) R = Me $R^1 = R^2 = C_6H_{13}$; 75%

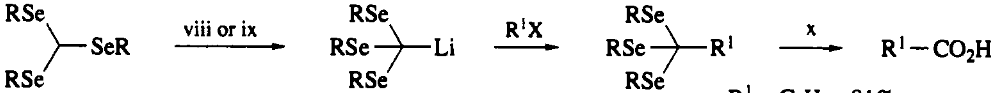

$R^1 = C_6H_{13}$, 81%

(h) R = Ph viii $R^1X$ = MeI, 93% (ref. 64, 65)

| (i) | R = Me | ix | $R^1X$ | MeI | $C_{10}H_{21}Br$ | $C_6H_{13}Br$ | (ref. 76, 77) |
|---|---|---|---|---|---|---|---|
| | | | % | 80 | 66 | 80 | |

i, $Bu^i_2NLi$, THF, –78 °C, then –30 °C, 0.2 h; ii, LDA, THF–HMPA; iii, LiTMP, THF–HMPA, –30 °C, then 20 °C, 0.2 h; iv, KDA, THF, –78 °C, 0.2 h; v, $HgCl_2$, $CaCO_3$, 20 °C, 2 h; vi, LDA, THF, –78 °C, 0.1 h; vii, $Bu^nLi$, THF–hexane, –78 °C; viii, LIDBA, THF, –78 °C; ix, LDA, THF, –78 °C; x, $H_2O_2$, THF

**Scheme 81**

entry f). Similar conditions can be used for ketones but they are less efficient than acid-catalyzed hydrolysis.[371a]

In conclusion, the 1,3-dithiane unit still remains among the most valuable acyl anion equivalents, although that involving methyl methylthio sulfoxide or its diethyl analog offers the definite advantages of proceeding with metal hydride or even under phase-transfer catalysis conditions and of producing the carbonyl compound under reasonably mild conditions.

Otherwise α-methoxy allyl sulfides have played the role of an α-methylenated acyl anion[347] (Scheme 76, entry a) or a homoenolate dianion[348] (Scheme 76, entry b) equivalent.

## 1.3.4 α-METALLOORTHOTHIO- AND α-METALLOORTHOSELENO-FORMATES AS PRECURSORS OF ESTERS

Metallated orthothioformates and their seleno analogs (available by metallation of orthothio-[28,381–383] and orthoseleno-formate[64,65,76–78] with lithium amides or on S/Li or Se/Li exchange between orthothio-[381,382] and orthoseleno-carbonates[65] react efficiently with methyl iodide[64,65,381,382,384] as well as with reactive electrophiles such as benzyl chloride and *n*-butyl iodide (Scheme 84, entry a).[383]

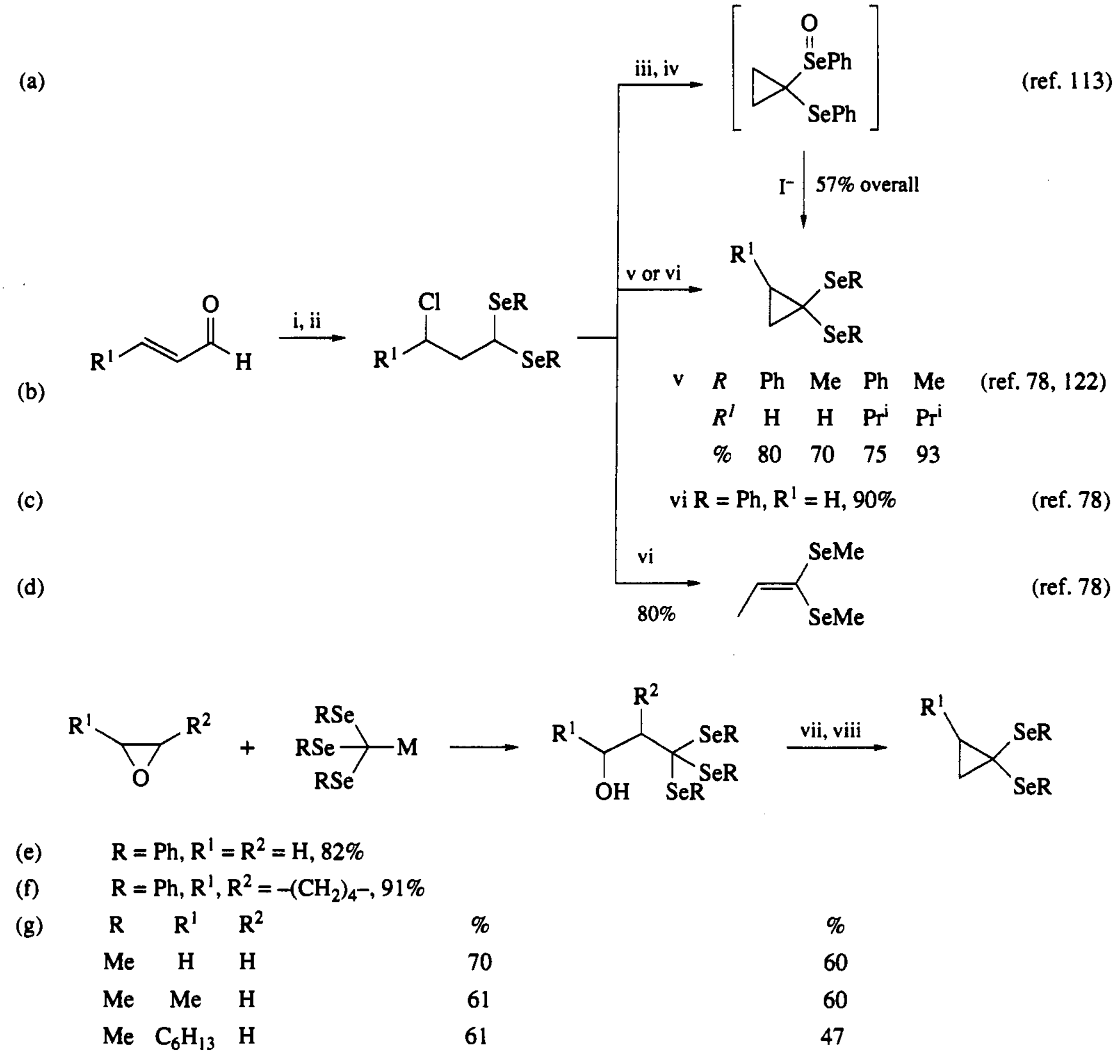
(a)
(b)
(c)
(d)
i, ii
iii, iv
(ref. 113)
I⁻
57% overall
v or vi
v R Ph Me Ph Me
R¹ H H Pr^i Pr^i
% 80 70 75 93
(ref. 78, 122)
vi R = Ph, R¹ = H, 90%
(ref. 78)
vi
80%
(ref. 78)
vii, viii
(e) R = Ph, R¹ = R² = H, 82%
(f) R = Ph, R¹, R² = –(CH₂)₄–, 91%
(g) R R¹ R² % %
Me H H 70 60
Me Me H 61 60
Me C₆H₁₃ H 61 47

i, HCl, benzene; ii, RSeH, $ZnCl_2$; iii, MCPBA; iv, LDA; v, LDA, THF, 0 °C; vi, $Bu^tOK$, DMSO, 20 °C; vii, TosCl, pyridine, 20 °C; viii, $Bu^nLi$, THF, –78 to 20 °C

**Scheme 82**

Tri(phenylthio)methyllithium does not react properly with less reactive electrophiles such as *n*-butyl chloride,[382] 2-iodopropane (Scheme 84),[381,382] propylene oxide (Scheme 85)[381,382] and especially cyclohexene oxide (Scheme 85, entry b)[382] owing to its high propensity to decompose into $(PhS)_2C$ and PhSLi (see below).[381,382,384,385]

1-Lithio-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane, which is far more stable due to its favorable stereochemistry gives the highest alkylation yields.[381] Tri(phenylseleno)methyllithium[25,64,65,78] and especially its methylseleno[25,76–78] analog, although they share similar behavior, have proved to be more stable however than their thio analogs and have provided reasonable yields of alkylated (Scheme 81, entries f and g)[64,65,76,77] or hydroxyalkylated (Scheme 82, entries e–g)[25,78] compounds on reaction with alkyl halides and epoxides respectively.

The resulting orthothio- and orthoseleno-esters are valuable precursors of carboxylic esters and acids.[383,386] The former conversion requires quite drastic conditions ($HgCl_2$, HgO, MeOH–$H_2O$, 100 °C, 6 h; Scheme 84, entry b),[383] whereas the same transformation takes place under very mild conditions with the seleno derivatives (aq. $H_2O_2$, THF, 20 °C, 0.1 h; Scheme 81, entry g).[76]

Tri(thio)- and tri(seleno)-alkyllithiums possess a high propensity to act as carbenoids, and they have been found to add to various nucleophilic alkenes, leading to 1,1-di(thio)-[382] and 1,1-di(seleno)-cyclopropanes (Scheme 85, entry c).[64,65]

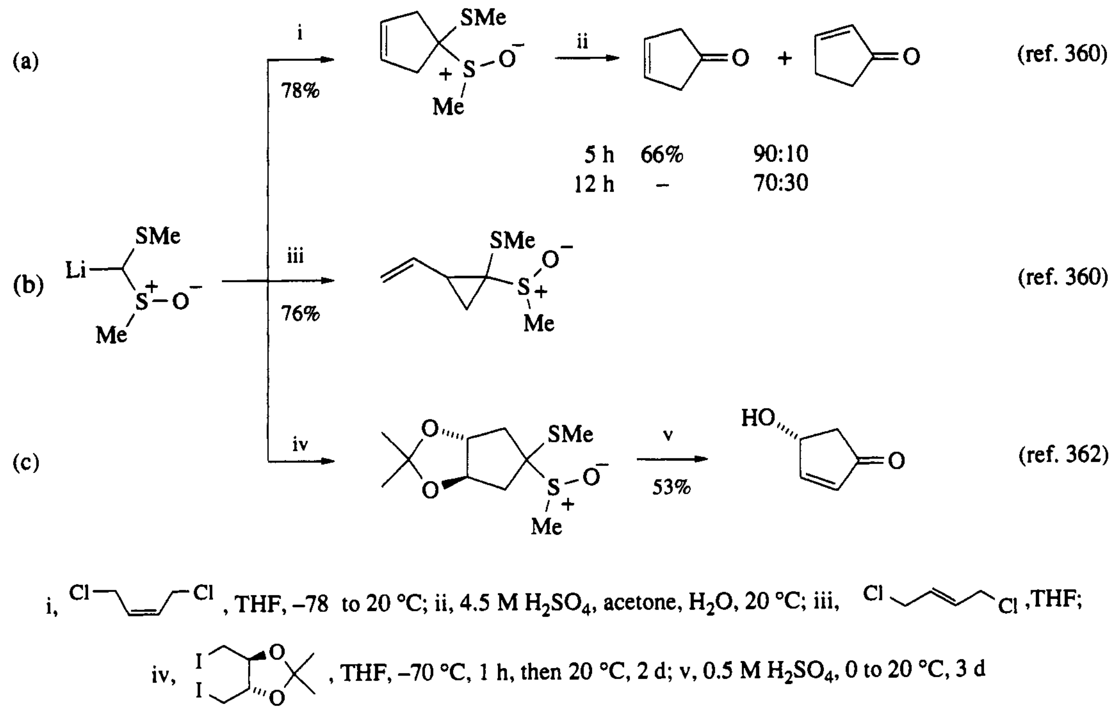
(a)
(b)
(c)
i
78%
iii
76%
iv
ii
5 h 66% 90:10
12 h – 70:30
v
53%
(ref. 360)
(ref. 360)
(ref. 362)
SMe
Me
Li
HO
i, THF, –78 to 20 °C; ii, 4.5 M $H_2SO_4$, acetone, $H_2O$, 20 °C; iii, THF;
iv, THF, –70 °C, 1 h, then 20 °C, 2 d; v, 0.5 M $H_2SO_4$, 0 to 20 °C, 3 d

**Scheme 83**

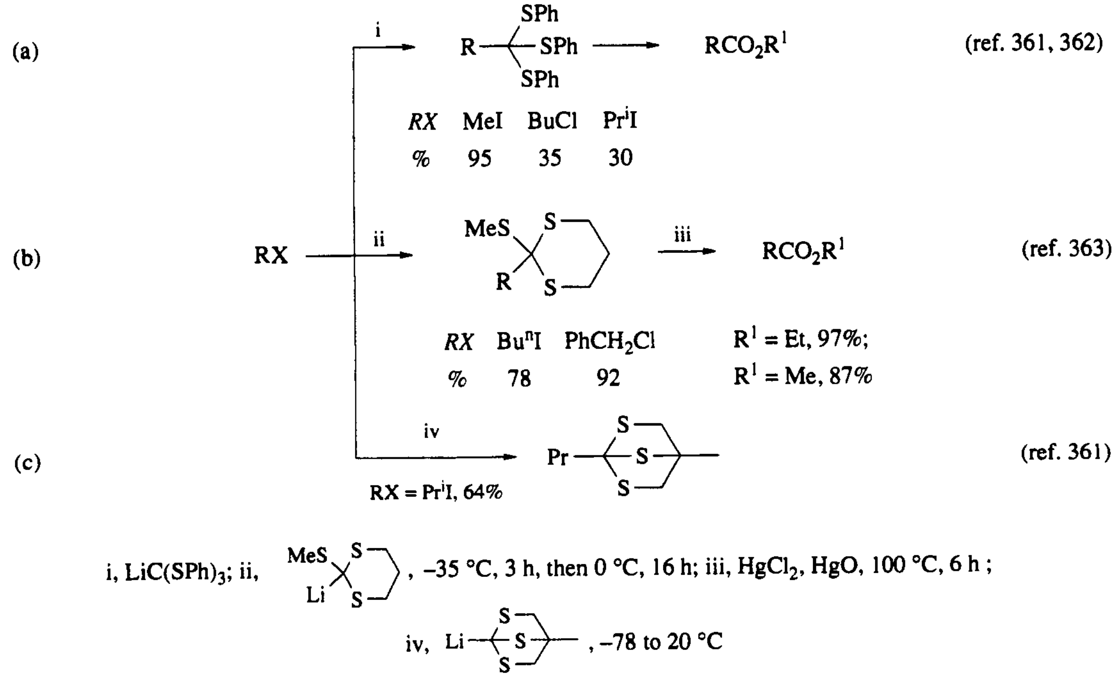
(a)
(b)
(c)
RX
i
ii
iii
iv
$RCO_2R^1$
$RCO_2R^1$
RX MeI BuCl $Pr^iI$
% 95 35 30
RX $Bu^nI$ $PhCH_2Cl$
% 78 92
$R^1$ = Et, 97%;
$R^1$ = Me, 87%
RX = $Pr^iI$, 64%
(ref. 361, 362)
(ref. 363)
(ref. 361)
i, $LiC(SPh)_3$; ii, –35 °C, 3 h, then 0 °C, 16 h; iii, $HgCl_2$, HgO, 100 °C, 6 h ;
iv, –78 to 20 °C

**Scheme 84**

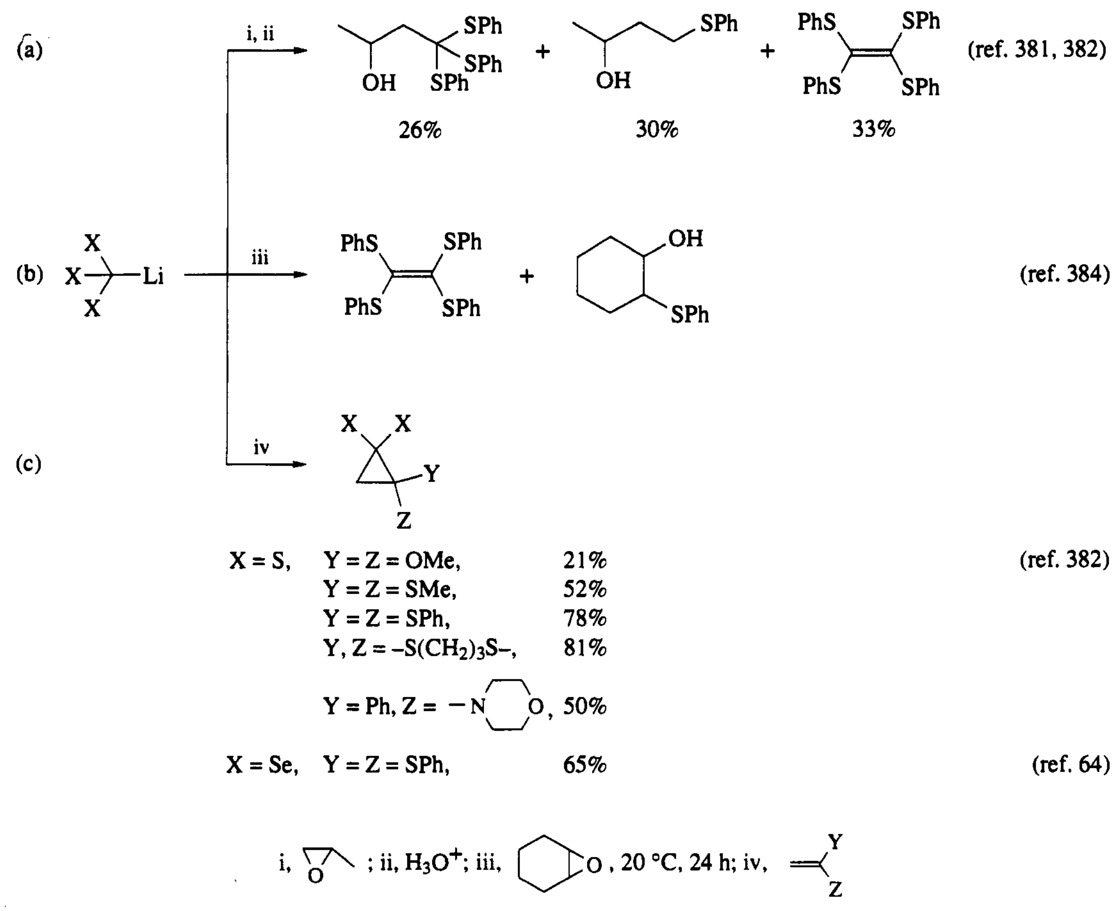
(a)
i, ii
SPh
SPh
OH SPh
26%
+
SPh
OH
30%
+
PhS SPh
PhS SPh
33%
(ref. 381, 382)
(b)
X
X—Li
X
iii
PhS SPh
PhS SPh
+
OH
SPh
(ref. 384)
(c)
iv
X X
Y
Z
X = S, Y = Z = OMe, 21%
Y = Z = SMe, 52%
Y = Z = SPh, 78%
Y, Z = –S(CH2)3S–, 81%
Y = Ph, Z = —N O, 50%
(ref. 382)
X = Se, Y = Z = SPh, 65%
(ref. 64)
i, O ; ii, H3O+; iii, O, 20 °C, 24 h; iv, Y Z

**Scheme 85**

## 1.3.5 REACTIONS INVOLVING α-METALLOALKYL SULFOXIDES AND SELENOXIDES

### 1.3.5.1 Reactions Involving Sulfoxides

#### *1.3.5.1.1 Reactions involving alkyl sulfoxides*

*(i) Alkylations of α-metalloalkyl sulfoxides and selenoxides*

The reactions between α-metalloalkyl sulfoxides and electrophiles[8,31–34,387] have been extensively studied. Although alkylations of the sodium or potassium salts of dialkyl sulfoxides are not always very efficient since α,α′-dialkylated sulfoxides[388,389] are often produced (or stilbene in the case of methylsulfinyl carbanion and benzyl bromide[391]), those employing the lithioalkyl aryl sulfoxides work more efficiently with alkyl or allyl halides[32,34,390,392,393] and with epoxides.[394–396] Typical examples of these alkylations, allylations and hydroxyalkylations (from epoxides) are illustrated in Scheme 86.

The chirality present at the sulfur atom of, for example, *p*-tolylsulfinyl carbanion leads to the formation of a diastereoisomeric mixture of γ-hydroxy sulfoxides on reaction with prochiral epoxides[394] (Scheme 87). This reaction, coupled with the efficient desulfurization of the resulting sulfoxide by Raney nickel, has been used ingeniously[394] for the enantioselective synthesis of *trans*-2-methylcyclohexanol from epoxycyclohexane and (+)-*p*-tolylsulfinylmethyllithium (Scheme 87).

Both the metallation of sulfoxides and the reaction of α-lithio sulfoxides in THF are known to be highly stereoselective.[32,34,390,397–399] It has been found that, on reaction with base, the diastereotopic methylene protons of benzyl methyl sulfoxide exchange at different rates, the relative ratio being

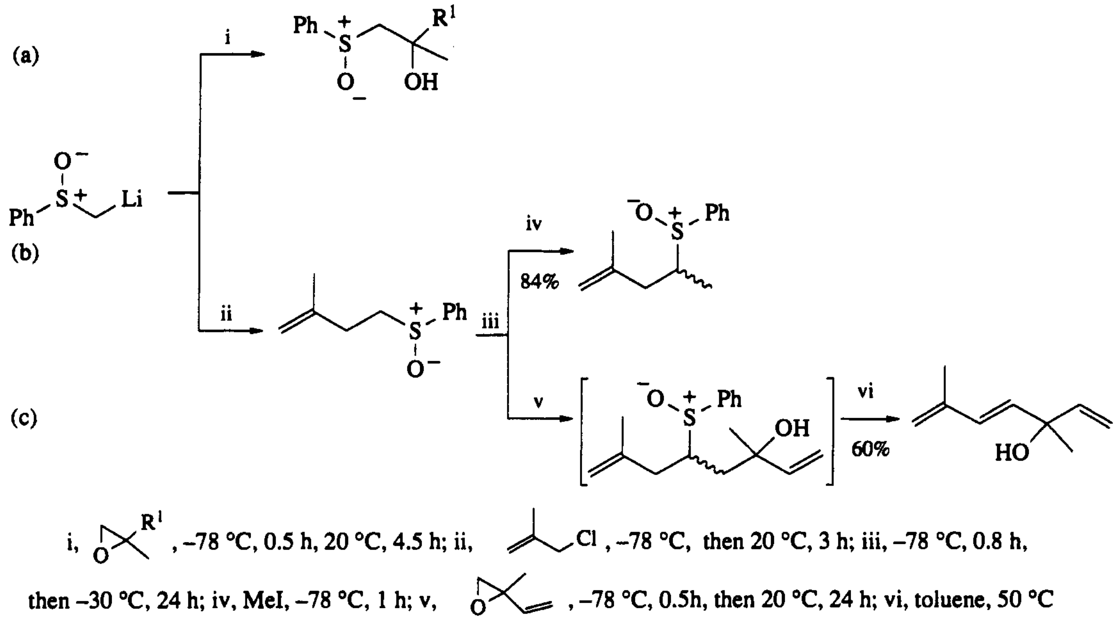
(a)
(b)
(c)
i
ii
iii
iv
v
vi
84%
60%
Ph
Li
OH
HO
$R^1$

i, , –78 °C, 0.5 h, 20 °C, 4.5 h; ii, , –78 °C, then 20 °C, 3 h; iii, –78 °C, 0.8 h, then –30 °C, 24 h; iv, MeI, –78 °C, 1 h; v, , –78 °C, 0.5h, then 20 °C, 24 h; vi, toluene, 50 °C

Scheme 86

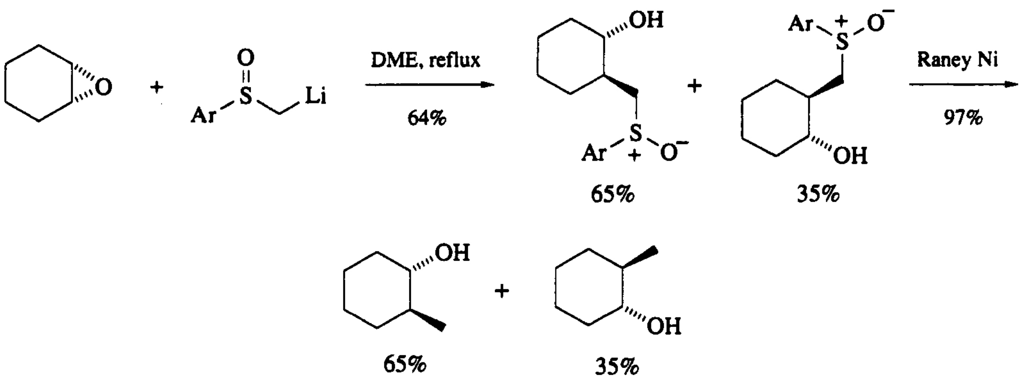
DME, reflux
64%
Raney Ni
97%
65%
35%
65%
35%
Ar
Li
OH

Scheme 87

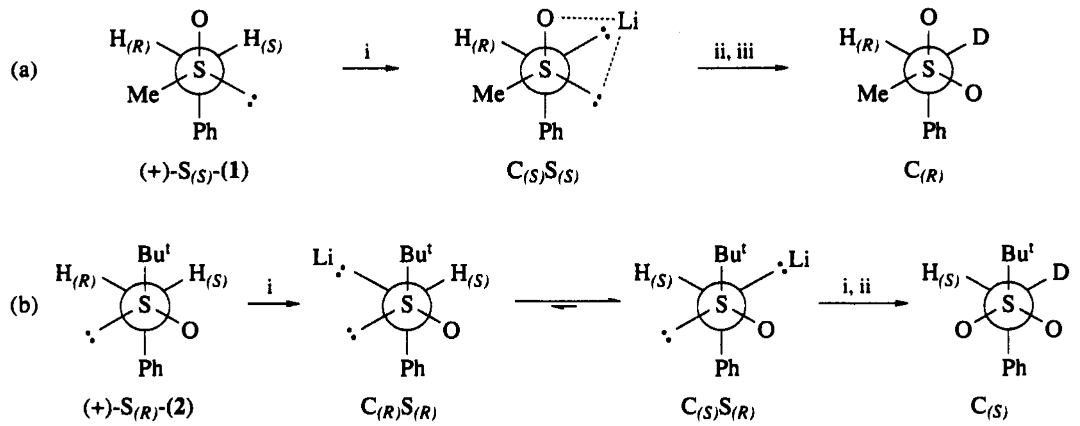
(a)
i
ii, iii
$(+)$-$S_{(S)}$-(1)
$C_{(S)}S_{(S)}$
$C_{(R)}$
(b)
i
i, ii
$(+)$-$S_{(R)}$-(2)
$C_{(R)}S_{(R)}$
$C_{(S)}S_{(R)}$
$C_{(S)}$

i, BuLi, THF, –78 °C; ii, $D_2O$; iii, oxidation

Scheme 88

15:1.[34,390,397,398] Since this discovery the stereochemistry of the H:D exchange, as well as the stereochemical course of deuteration (Scheme 88) and of alkylation (Scheme 88; Scheme 89; Scheme 90; Scheme 91; Scheme 92), a number of acyclic (Scheme 89)[392,397,400–406] and cyclic sulfoxides (Scheme 90; Scheme 91; Scheme 92)[390,398,407–413] have been intensively studied and have been the subject of intense controversy.[387]

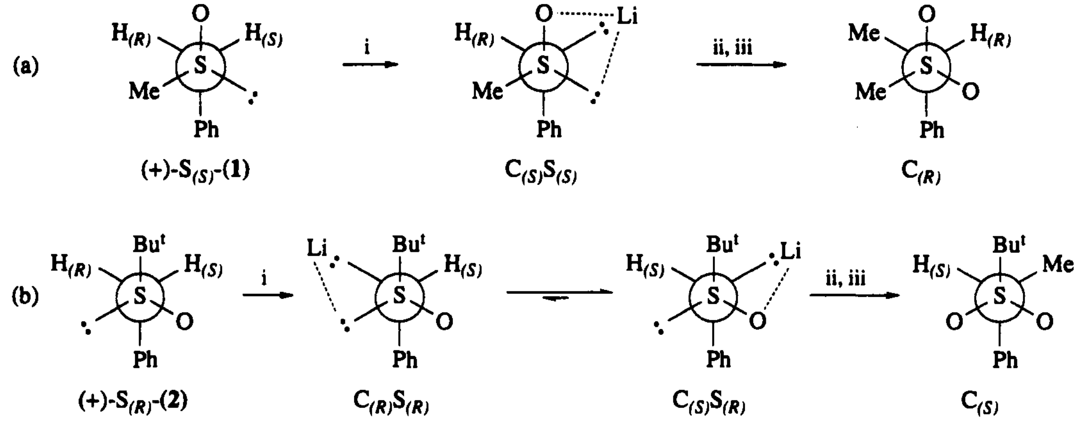
(a)
(+)-S(S)-(1)
C(S)S(S)
C(R)
(b)
(+)-S(R)-(2)
C(R)S(R)
C(S)S(R)
C(S)
i
ii, iii

i, MeLi, THF, –78 °C; ii, MeI; iii, oxidation

**Scheme 89**

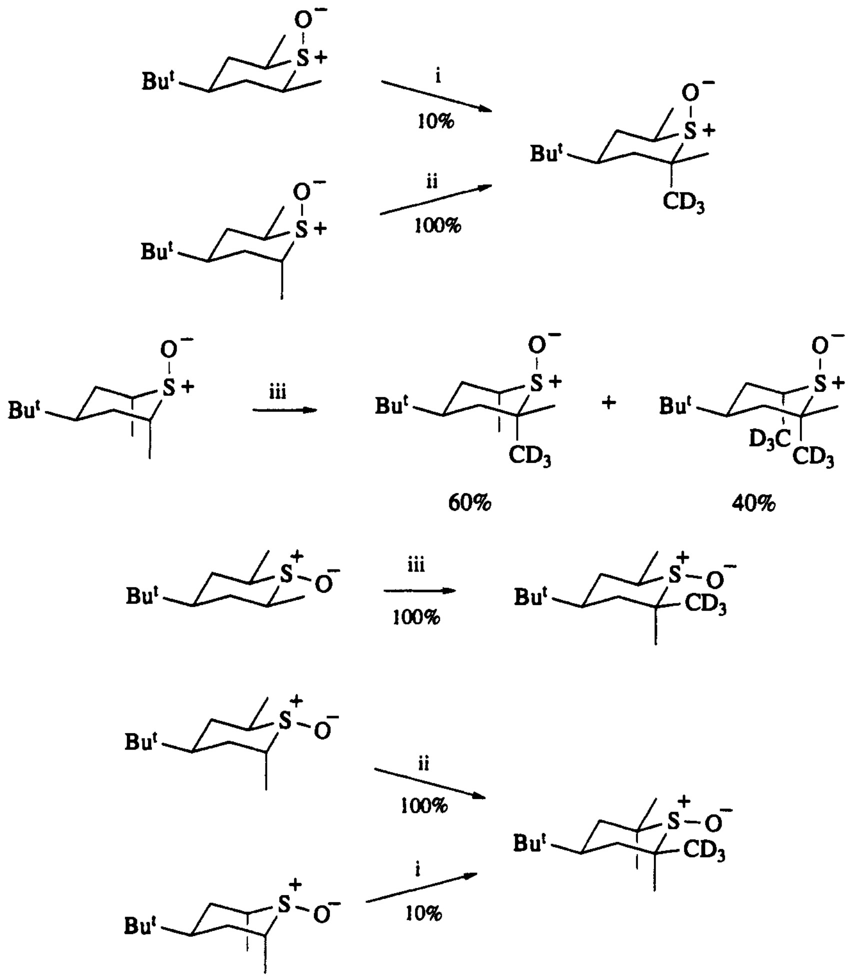
i
10%
ii
100%
iii
60%
40%
iii
100%
ii
100%
i
10%

i, 4 BuLi, CD$_3$I; ii, 1.5 BuLi, CD$_3$I; iii, 3 BuLi, CD$_3$I

**Scheme 90**

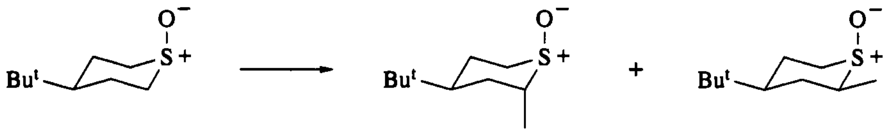

| | | | | |
|---|---|---|---|---|
| (a) | i, ii 75% | 100% | 0% | (ref. 407, 411) |
| (b) | i, iii | 30% | 70% | (ref. 407) |
| (c) | i, iv | 92% | 8% | (ref. 407) |

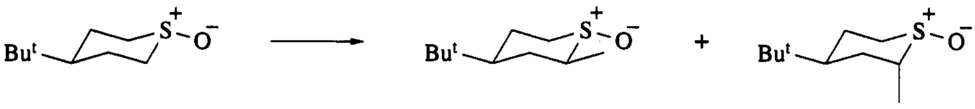

| | | | | |
|---|---|---|---|---|
| (d) | i, ii | 90% | 10% | (ref. 411) |
| (e) | i, v | 80% | 20% | (ref. 407) |
| (f) | i, iii | 7% | 93% | (ref. 407) |
| (g) | i, vi | 60% | 40% | (ref. 407) |

(h)

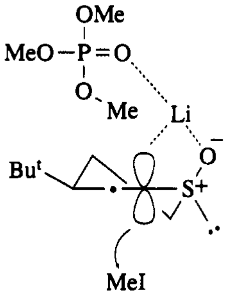

(3)

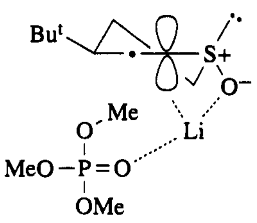

(4)

i, Bu$^n$Li, THF, −78 °C, 0.3 h; ii, MeI, −30 °C; iii, $(MeO)_3PO$, 20 °C; iv, $(MeO)_3PO$, 10 $LiClO_4$; v, MeI, 20 °C; vi, $(MeO)_3PO$, 10 $LiClO_4$, 20 °C

**Scheme 91**

It was found[34,397,402,403] (see ref. 34, and ref. 387 for a correction) that for α-deuterated benzyl methyl and benzyl *t*-butyl sulfoxides of known configurations, methyllithium in THF at −78 °C abstracts the *pro*-(*S*) hydrogen of (*S*)-benzyl methyl sulfoxide (**1**) with a selectivity of 15:1 (Scheme 88 and Scheme 89, entries a), whereas the same reaction performed on the (R)-benzyl *t*-butyl sulfoxide (**2**; Scheme 88 and Scheme 89, entries b) possessing the same chirality as (**1**) (it should be noted that the (*R*,*S*) notation appears different in methyl and *t*-butyl sulfoxides because of the definition) leads almost exclusively to the removal of the *pro*-(*R*) hydrogen (selectivity 117:1; note that an incorrect absolute configuration of the (+)-(**2**) sulfoxide was quoted in the original paper, ref. 397).[34,387] Finally the *pro*-(*S*) hydrogen atom of (*S*)-benzyl *t*-butyl sulfoxide is abstracted preferentially by a kinetic factor of 1.7:1. As far as alkylation is concerned, the reactions proceed with high stereoselectively, in all cases by inversion of configuration of the originally produced benzyllithiums (Scheme 89); deuteration (or protonation) on the other hand usually occurs with retention with benzyl phenyl sulfoxides and with inversion with benzyl *t*-butyl sulfoxides (Scheme 88).[34,410]

The stereochemistry of the reaction products is dependent on the nature of the α-sulfinyl carbanion. Thus: (i) its kinetic acidity, controls the stereochemistry of the organometallics initially formed; (ii) its thermodynamic acidity defines the stereochemistry or the conformation of the intermediate organometallic; and (iii) reactivity of the organometallic towards the electrophile controls the stereochemistry of the product. The alkylation reaction has proved to be far more selective than is the metallation. Therefore the contribution of kinetic acidity can be neglected because the carbanion in THF has sufficient time to reorganize into its most stable conformation before it reacts with an electrophile.[387] The α-sulfinyl benzyllithiums produced from $S_{(S)}$-(**1**) and $S_{(R)}$-(**2**) should adopt the more stable conformations shown in

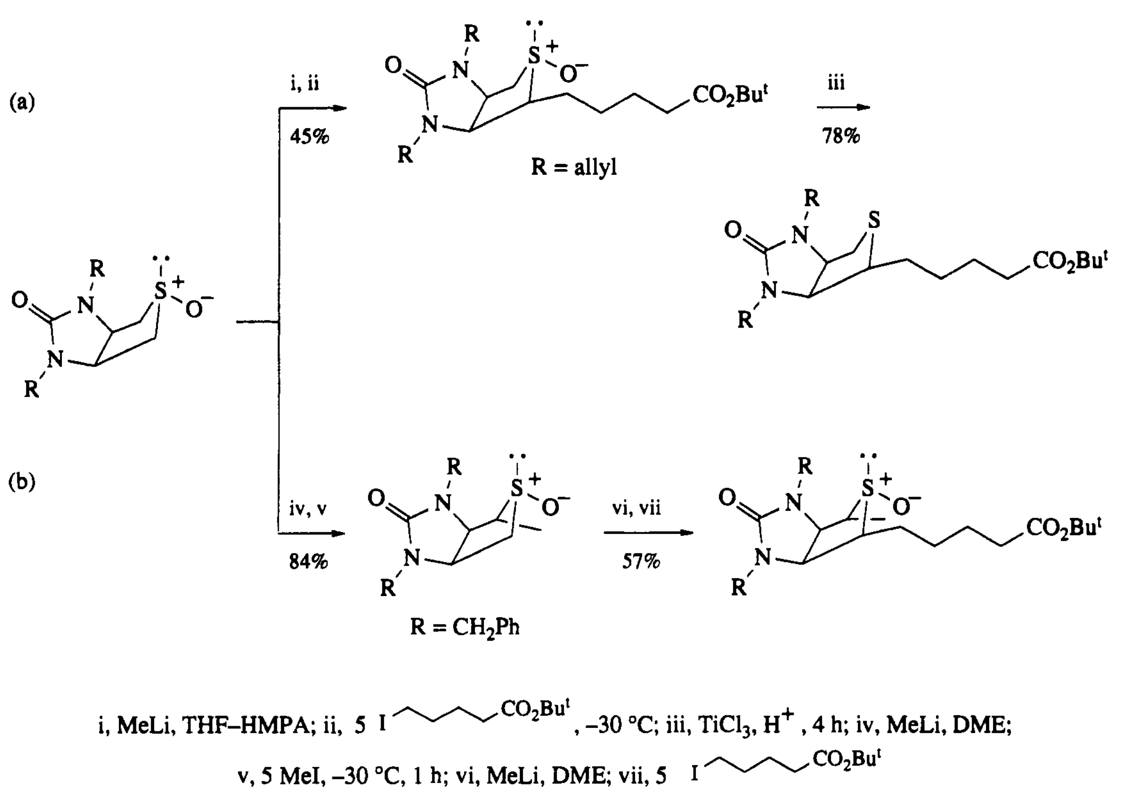

i, MeLi, THF–HMPA; ii, 5 I $CO_2Bu^t$, –30 °C; iii, $TiCl_3$, $H^+$, 4 h; iv, MeLi, DME; v, 5 MeI, –30 °C, 1 h; vi, MeLi, DME; vii, 5 I $CO_2Bu^t$

**Scheme 92**

Schemes 88 and 89, in which the lithium cation is coordinated to the sulfinyl oxygen and, in the former, with the sulfur lone pair also. Methyl iodide, which is a nonpolar substrate, prefers to react at the more nucleophilic side which is *anti* to the sulfur lone pair. It has been suggested,[387] in other words, that the *si* and the *re* faces of the benzyllithium derived from $S_{(S)}$-(**1**) are hard and soft reaction centers respectively, whereas the same *si* face has both hard and soft reaction centers; therefore the soft methyl iodide is expected[387] to react at the *re* face in the first case and at the *si* face in the second one, which in fact explains the observed products. This type of rationalization also explains[387] the stereochemistry of the protonation (deuteration) of these organometallics (for a controversal discussion see ref. 34).

The metallations of rigid molecules such as 4-*t*-butylthiacyclohexane take place more efficiently with hydrogens *syn* to the S—O bond[390] (Scheme 90), and the alkylation with alkyl halides gives products of *anti* attack with respect to the S—O bond[390,397,407–411] (Scheme 90; Scheme 91). The last reaction has been purposely used by Marquet[408–410] in an original synthesis of ±-biotin and its analogs (Scheme 92).[409,410]

The overall process takes advantage also[409,410] of: (i) the selective oxidation of the sulfur in the corresponding sulfide, leading to the predominant formation of the isomer with the S—O bond *cis* to the junction hydrogens, which is the isomer required for the stereoselective alkylation; and (ii) of the easy reduction of the alkylated sulfoxide to the desired sulfide which has been *inter alia* achieved with $Ti^{3+}$ (Scheme 92). The alkylation yield does not exceed 30% if the reaction is carried out with *n*-butyllithium in THF since both starting material and products resulting from β-elimination of the sulfoxide are isolated.[408–410] This elimination reaction can be suppressed if methyllithium is used instead[409,410] but the yield remains quite low, even when a large excess of the alkylating agent is added (Scheme 92, entry a).

Alkylation takes place predominantly on the less substituted site of dialkylsulfoxides,[388,407,409,410] and this feature has been used advantageously for the synthesis of biotin analogs bearing a methyl group in the α′-position on the thiophane ring (Scheme 92, entry b).[410]

Although reactions with epoxides[413] proceed with a similar stereochemical outcome to that of the alkylation reaction, the deuteration ($D_2O$),[397,402,403,406] and carbonation[405] reactions occur predominantly with opposite stereochemistry.

The finding that the stereochemistry of such reactions can be drastically affected as shown in Scheme 93, by: (i) a solvent change,[392,404] (ii) addition of macrocyclic polyethers[404] (especially if the reaction is carried out in TMEDA), or (iii) addition of lithium salts[392,406,407] has supported the idea that the stereochemistry may be largely governed by cation–carbanion interactions,[390,413] and more particularly by the ability of $Li^+$ to form a chelate structure involving the carbanionic carbon and the sulfoxide oxygen (Scheme 89; Scheme 91, entry h, structures 3 and 4).[404,407]

This chelate would undergo electrophilic displacement of $Li^+$ with predominantly retention of configuration when the electrophile-donating species can itself act as a chelating agent but with inversion in the absence of this chelating ability.[406,407] Strong support for these hypotheses has been provided by the experiments with chelating methylating agents such as trimethyl phosphate[406,407] as compared to nonchelating methyl iodide (Scheme 91, compare entries b to a and entry f to d and e; Scheme 93; similar differences between chelating $D_2O$ and nonchelating proton donors $Et_3ND^+$ and $D^+$-sponge have been reported[406]).

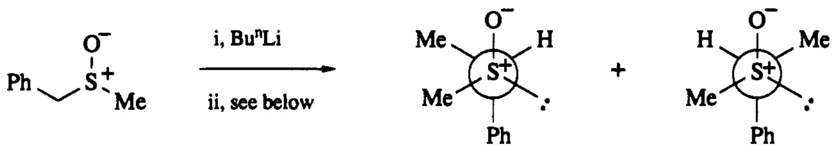

| | | | | |
|---|---|---|---|---|
| (a) | MeI, THF, 0.1 or 0.5 h; 100% | 95% | 5% | (ref. 404) |
| (b) | MeI, THF, excess HMPA; 100% | 90% | 10% | (ref. 404) |
| (c) | MeI, [2.2.2]macrobicyclic polyether, 2 h | 83% | 17% | (ref. 404) |
| (d) | MeI, TMEDA, [2.2.2], 1 h | 80% | 20% | (ref. 404) |
| (e) | $(MeO)_3PO$, 0 °C | 40% | 60% | (ref. 406) |
| (f) | $(MeO)_2SO_4$, 0 °C | 95% | 5% | (ref. 406) |

Scheme 93

This interpretation satisfactorily explains all the results reported so far with the exception of those involving the methylations of α-lithiotiepane 1-oxide and thiocane 1-oxide (the seven- and eight-membered homologs of thiacyclohexane)[413] which provide mainly the compounds having *cis* stereochemistry between the methyl group and the S—O bond (*cis*:*trans* ratio of 93:7 and 83:17 respectively). The

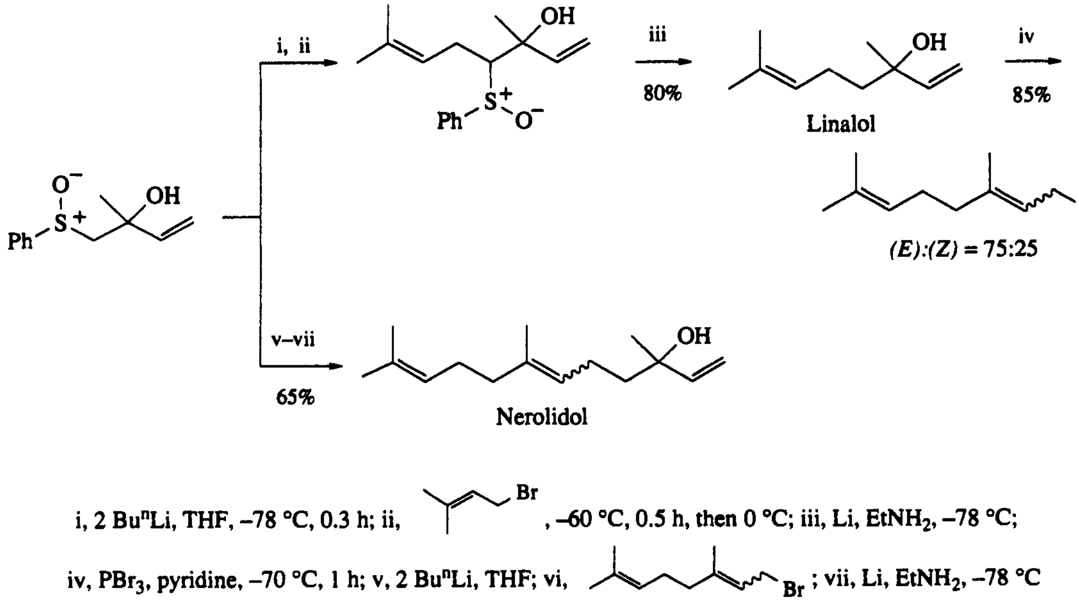

i, 2 Bu$^n$Li, THF, −78 °C, 0.3 h; ii, , −60 °C, 0.5 h, then 0 °C; iii, Li, $EtNH_2$, −78 °C; iv, $PBr_3$, pyridine, −70 °C, 1 h; v, 2 Bu$^n$Li, THF; vi, ; vii, Li, $EtNH_2$, −78 °C

Scheme 94

reactions of oxiranes with these species are slower, but the stereochemical results are substantially the same as in alkylation with methyl iodide.[396,413]

Alkylations[414–416] of the dianions derived from β-hydroxyalkyl sulfoxides, shown in Scheme 94 and in Scheme 95, occur stereoselectively.[415,416]

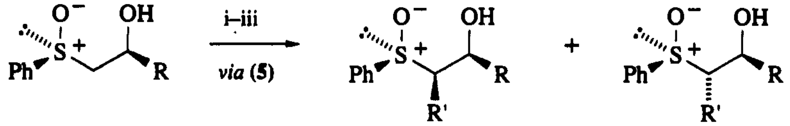

| *Entry* | *R* | *R'* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|
| (a) | Me | Me | 86 | 89:11 | 415 |
| | $C_9H_{19}$ | Me | 70 | 95:5 | |
| | $PhCH_2$ | Me | 84 | 97:3 | |
| (b) | $C_9H_{19}$ | $C_6H_{13}$ | 59 | 99:1 | 415 |
| (c) | i-$C_7H_{15}$ | $C_{10}H_{21}$ | 58 | 80:20 | 416 |

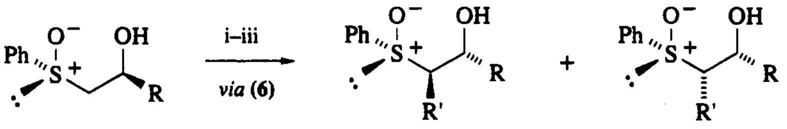

| *Entry* | *R* | *R'* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|
| (d) | Me | Me | 86 | 72:22 | 415 |
| | $C_9H_{19}$ | Me | 72 | 81:19 | |
| | $PhCH_2$ | Me | 58 | 95:5 | |
| (e) | $C_9H_{19}$ | $C_6H_{13}$ | 42 | 98:2 | 415 |
| (f) | i-$C_7H_{15}$ | $C_{10}H_{21}$ | 75 | 95:5 | 416 |

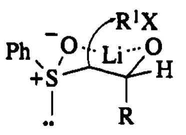

**(5)**

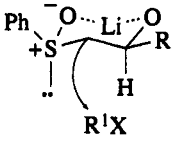

**(6)**

i, 2.2 $Bu^nLi$, THF, –78 °C; ii, $R^1I$, –78 °C; iii, $H_3O^+$

**Scheme 95**

The steroselectivity increases by increasing the bulkiness of the R and $R^1$ groups, and is not affected when the reactions are carried out in the presence of TMEDA or HMPA (2 equiv.).[415] The alkylation is therefore controlled by the stereochemistry of the carbon bearing the hydroxy group rather by that of the sulfinyl group.[416] The preference for *threo* stereochemistry has been explained by the six-membered chair transition states (**5** and **6**; Scheme 95) produced by the chelation of both oxygens of the hydroxy and sulfinyl groups to the lithium cation. The axial attack of the alkylating agent from the upper side, due to the steric interaction with the axial R group, leads to the selectivity shown in Scheme 95 (entries a–c), whereas equatorial attack on (**6**) leads to the thermodynamically more stable *threo* derivatives shown in Scheme 95 (entries d–f). In contrast to the reported reversal of the stereochemistry in the reaction of α-lithiobenzyl methyl sulfoxide with methyl iodide and trimethyl phosphate respectively,[406,407] the reaction of the dianion derived from β-hydroxyalkyl sulfoxide with trimethyl phosphate leads to the same *threo* stereoisomer produced with methyl iodide[416] supporting therefore the chelated structures shown in Scheme 95. This reaction when performed on optically active β-hydroxyalkyl selenides, shown in Scheme 95 (entries c and f), afforded *threo* β-hydroxyalkyl sulfoxides which are useful precursors of optically active *cis*-epoxides.[416] The utility of the above mentioned reactions has been demonstrated in the asymmetric synthesis of (+)- and (−)-*cis*-7,8-epoxy-2-methyloctadecanes, the female-produced pheromone of the gypsy moth (Scheme 95, entry f).[416]

Sulfoxides are known to produce alkenes on heating, by elimination of sulfenic acids.[8,31,32,233,417–420] This reaction has been applied successfully to a large variety of alkyl sulfoxides and functionalized alkyl sulfoxides. Many of these sulfoxides have been synthesized from simpler sulfoxides by alkylation of the corresponding lithium salts. Thus, methylbenzyl[378] (Scheme 47), 3,4-dioxomethylenebenzyl,[378] phenylsulfinylmethyl,[378] phenylsulfonylmethyl,[380,421] fluoromethyl,[422] chloromethyl,[423] iodomethyl[424] and dichloromethyl[425] phenyl sulfoxides have been metallated with lithium amides[378,421–423,425,426] or butyllithium[378] in THF or in DME[378] then alkylated,[378,422–425] benzylated[378,421,422,424,425] and allylated (Scheme 96).[378,380]

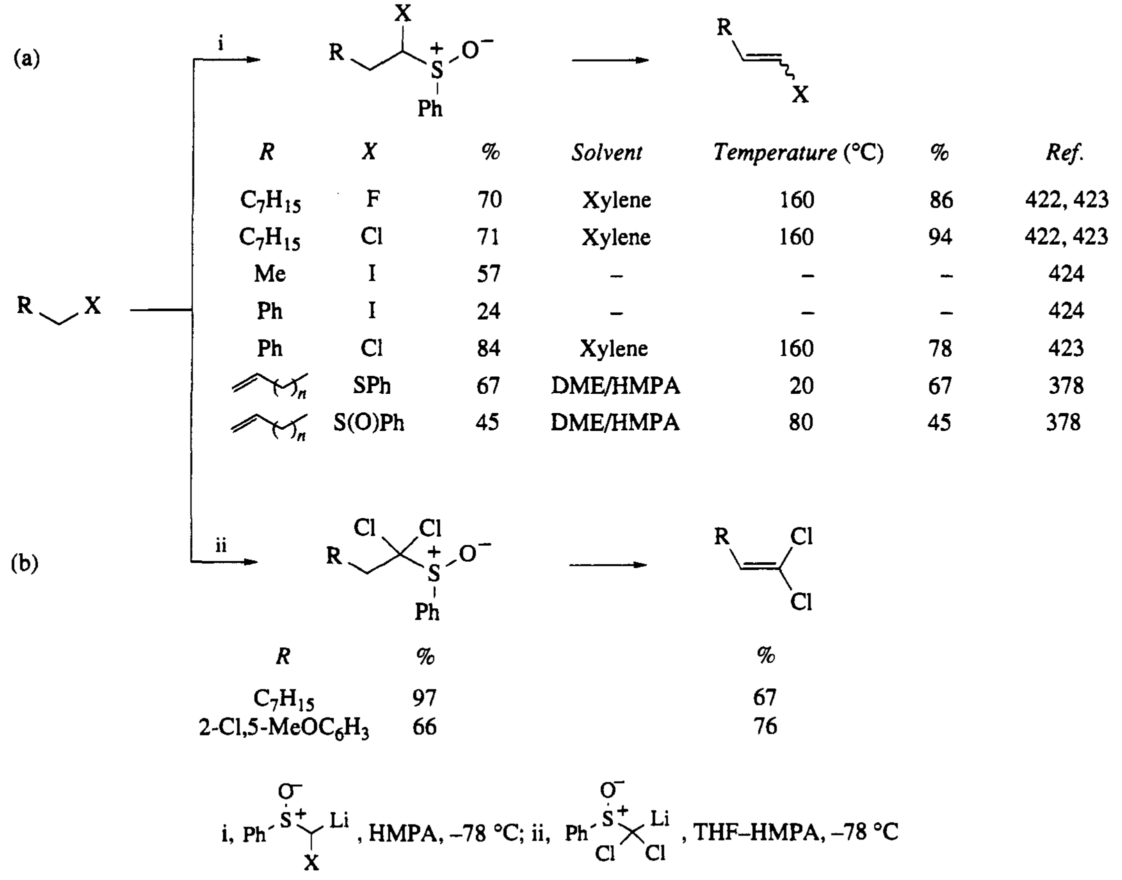
(a)
(b)
i
ii
R X
X
R
S
O
Ph
Cl
i, Ph S Li X, HMPA, −78 °C; ii, Ph S Li Cl Cl, THF–HMPA, −78 °C

(a)

| *R* | *X* | *%* | *Solvent* | *Temperature* (°C) | *%* | *Ref.* |
|---|---|---|---|---|---|---|
| $C_7H_{15}$ | F | 70 | Xylene | 160 | 86 | 422, 423 |
| $C_7H_{15}$ | Cl | 71 | Xylene | 160 | 94 | 422, 423 |
| Me | I | 57 | – | – | – | 424 |
| Ph | I | 24 | – | – | – | 424 |
| Ph | Cl | 84 | Xylene | 160 | 78 | 423 |
| $n$ | SPh | 67 | DME/HMPA | 20 | 67 | 378 |
| $n$ | S(O)Ph | 45 | DME/HMPA | 80 | 45 | 378 |

(b)

| *R* | *%* | *%* |
|---|---|---|
| $C_7H_{15}$ | 97 | 67 |
| 2-Cl,5-$MeOC_6H_3$ | 66 | 76 |

**Scheme 96**

The reactions are usually carried out at 20 °C except with α-halomethyl sulfoxides whose lithium salts are particularly unstable and which have instead been reacted in THF at −78 °C in the presence of HMPA (Scheme 96).[422–425] α-Lithiobenzyl phenyl sulfoxide has proved to be the most nucleophilic species among the different functionalized sulfoxides used (Scheme 47).[378] Thus, it has been smoothly alkylated, allylated or benzylated in THF and is the only one which has been reported to undergo alkylation with secondary alkyl halides.[378] The sluggish alkylation of the organolithium compound derived from di(sulfinyl) methane with an unactivated alkylating agent dictated the use of HMPA and elevated temperatures, although no complications were encountered.[378]

### *(ii) Synthetic uses of alkylated sulfoxides*

(*a*) *Synthesis of alkenes and dienes* via *sulfoxide elimination reactions.* The pyrolysis of various sulfoxides takes place between 80 and 150 °C.[378,421,422,425,426] In some instances the elimination reaction has been carried out in the same pot and the same solvent in which the alkylation reaction has been achieved.[378] In other cases trimethyl phosphite, a scavenger of sulfenic acid, has been employed to avoid decomposition and to facilitate isolation of the product.[378] Aryl and phenylthio substituents α to the sulfinyl moiety facilitate the elimination of sulfenic acid whereas a phenyl sulfinyl moiety decelerates elimination.[378] The ease of hydrogen abstraction decreases in the order allylic > benzylic > secondary > tertiary. Thus in the absence of conformational restraints there exists the possibility of regioselection. Finally, in several cases (*E*)-alkenic double bonds are produced selectively.[378]

The method employing the sequential alkylation and elimination of sulfoxides, reported above, has been successfully applied to the synthesis of dienes (Scheme 86, entry c),[395] aryl alkenes and dienes (Scheme 47),[378] vinyl sulfides,[378] α,β-unsaturated sulfoxides,[378] vinyl fluorides[422] and vinyl chlorides (Scheme 96, entry a),[423] and 1,1-dichloro-1-alkenes (Scheme 96, entry b).[425]

(*b*) *Reactions employing the reduction of alkyl sulfoxides.* Reduction of sulfoxides to sulfides have been successfully carried out with a large variety of reducing agents including $TiCl_3$,[408–410] $Me_3SiI$, $NaHSO_3$[396] and $PI_3$,[427] and they have been used advantageously, as already mentioned, for the synthesis of biotin (Scheme 92, entry a).[408–410] The PhSO/H exchange can be performed with Raney nickel[418] or with lithium in ethylamine;[414] the latter procedure has allowed the synthesis of linalol and nerolidol (along with 25% of its *Z*-isomer; Scheme 94).[414] A number of other interesting transformation of sulfoxides can be cited, including: (i) a synthesis of trisubstituted alkenes which takes advantage of the regio- and stereo-selective γ-substitution of allylic sulfoxides with lithium dimethylcuprate;[428] and (ii) the transformation of primary alkyl halides into alkanethiols which have a carbon chain longer by one methylene unit than the original halides (Scheme 97).[429] The key step in this reaction involves the alkylation of cyclohexanone dimethyl acetal *S*-oxide, followed by acid hydrolysis and reduction of the resulting compound with lithium aluminum hydride (Scheme 97).

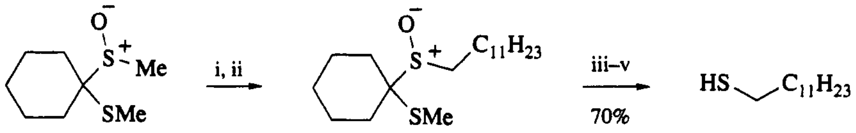

i, $Et_2NLi$, THF, –15 °C; ii, $C_{11}H_{23}I$, –78 °C, then 20 °C, 2 h; iii, $H_3O^+$; iv, $LiAlH_4$; v, $H_3O^+$

Scheme 97

### *1.3.5.1.2 Reactions involving allylic sulfoxides*

A range of diverse substituted allyl phenyl sulfoxides, which are available by addition of dimethyl cuprate to allenyl sulfoxides[430] or more generally by alkylation of simpler analogs,[16,235,236,414,431] have been converted into allylic alcohols possessing predominantly (*E*)-stereochemistry (*E*:*Z* ≥ 90:10) following simple admixture with trimethyl phosphite[235,236] or thiophenolate (MeOH, 60 °C, 7 h; Scheme 98; Scheme 99; for a lower selectivity see Scheme 98, entry a).[431]

Metallations of allyl sulfoxides have been achieved at –78 °C with *n*-butyllithium in THF[431] or more efficiently with LDA under similar conditions.[16,235,236] Alkylations with primary alkyl iodides[16,235,236,431] and allylations with allyl[235,430] or phenyl[236] bromides proceed in good yield, usually below –20 °C and in less than 6 h. The reaction takes place predominantly at the α-site but there is often competition from γ-alkylation leading to α-alkenyl sulfoxides (Scheme 98; Scheme 99). Changing the solvent, or introducing metal ion complexing agents, such as TMEDA were unsuccessful in changing the α:γ ratios observed in THF.

α-Alkylation occurs almost exclusively when the γ-carbon is dialkylated (Scheme 99, entry e) or with 1-phenylsulfinyl-2-cycloalkenes (Scheme 98, entries e and f). Apart from these cases the α:γ ratio ranges between 80:20 and 55:45. In general, allyl halides react less selectively than alkyl halides,[235,236] which in fact lead to the highest α:γ ratio. This competing reaction lowers the overall yield of allyl alcohols resulting from the reaction of allylic sulfoxides with thiophilic reagents. Therefore the route employing: (i) the alkylation of allyl sulfides, (ii) their transformation to the corresponding sulfoxide, and (iii) the rearrangement of the latter to allyl alcohols, which has been reported in Section 1.3.2.2.2, is preferred to that just described due to higher regiocontrol. The first reported set of reactions has been ingeniously applied to the synthesis of a series of cyclopentene-3,5-diols, which are potential precursors of the prostaglandins (Scheme 100).[166]

Alkylations of 1-alkenyl aryl sulfoxides have attracted little attention compared to other cases.[432,433] However it has been found that α-metallation occurs on reaction with LDA and that alkylation, allylation and benzylation occur there as a result (Scheme 101). Interestingly, γ-alkylation resulting from a competitive γ-metallation reaction has not been observed. The last mentioned reaction, coupled with treatment

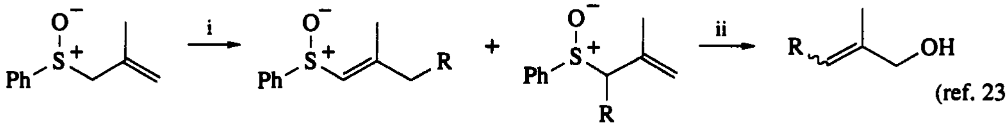

(ref. 236)

| Entry | RX | Product ratio | Yield (%) | (E):(Z) |
|---|---|---|---|---|
| (a) | MeI | 27:73 | 59 | |
| | EtI | 26:74 | 48 | 73:27 |
| | $Me_2C=CHCH_2Br$ | 45:55 | 35 | 93:7 |
| (b) | $Me_2C=CH(CH_2)_2I$ | 30:70 | 55 | 90:10 |

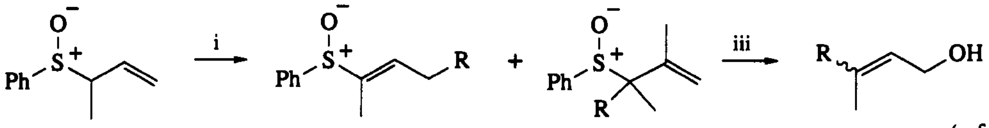

(ref. 236)

| Entry | RX | Product ratio | Yield (%) | (E):(Z) |
|---|---|---|---|---|
| (c) | MeI | 9:91 | 75 | >96:4 |
| | $C_6H_{13}I$ | 28:72 | 42 | >96:4 |
| | $Me_2C=CHCH_2Br$ | 33:67 | 46 | >96:4 |
| (d) | 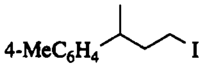 4-MeC$_6$H$_4$ I | 33:67 | 43 | 95:5 |

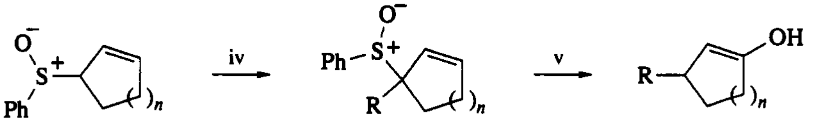

(ref. 235)

| | | | | |
|---|---|---|---|---|
| (e) | $n = 1$ | MeI | >96% | 99% |
| (f) | $n = 2$ | MeI | >96% | 100% |
| | | EtI | >96% | 45% |
| | | $Me_2C=CHCH_2Br$ | >96% | 32% |

i, LDA, THF, –78 °C, RX, –60 or –8 °C, 1 or 0.2 h; ii, $(MeO)_3P$, MeOH, 20 °C, 12 h; iii, $(MeO)_3P$, MeOH, 20 °C, 1 h; iv, LDA, THF, –78 °C, –50 or –40 °C, 0.5 or 2 h; v, $(MeO)_3P$, MeOH, 1 h

**Scheme 98**

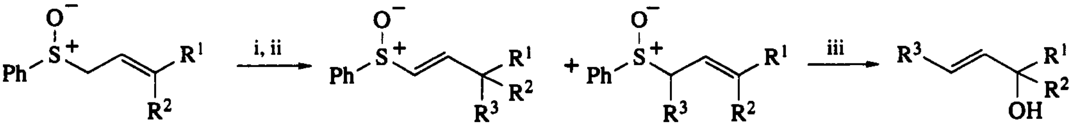

| Entry | R¹ | R² | R³X | Product ratio | Overall yield (%) |
|---|---|---|---|---|---|
| (a) | H | H | MeI | 15:85 | 74 |
| | H | H | EtI | 25:75 | 60 |
| | H | H | 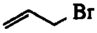 Br | 45:55 | 45 |
| (b) | Me | H | MeI | 9:91 | 85 |
| | | | EtI | 12:88 | 50 |
| (c) | Me | Me | $C_6H_{13}I$ | 9:91 | 70 |

i, LDA, THF, –60 °C; ii, $R^3X$, –50 or –30 °C, 0.5 to 4 h; iii, $(MeO)_3P$, MeOH, 12 h, 20 °C

**Scheme 99**

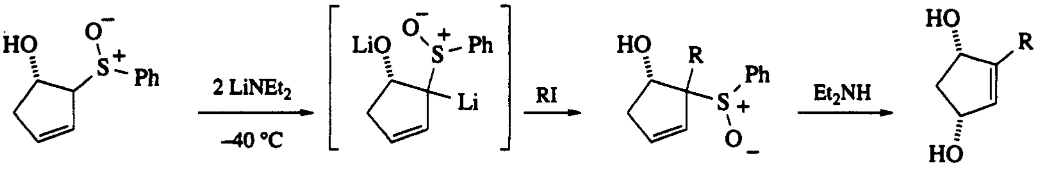

| R | $C_6H_{13}$ | $PhCH_2$ | $(CH)_6CO_2Bu^t$ |
|---|---|---|---|
| % | 65 | 40 | 45 |

Scheme 100

of the α-methylated vinyl sulfoxides with lithium tetramethylpiperidide, provides an original synthesis of allenes (Scheme 101).[433]

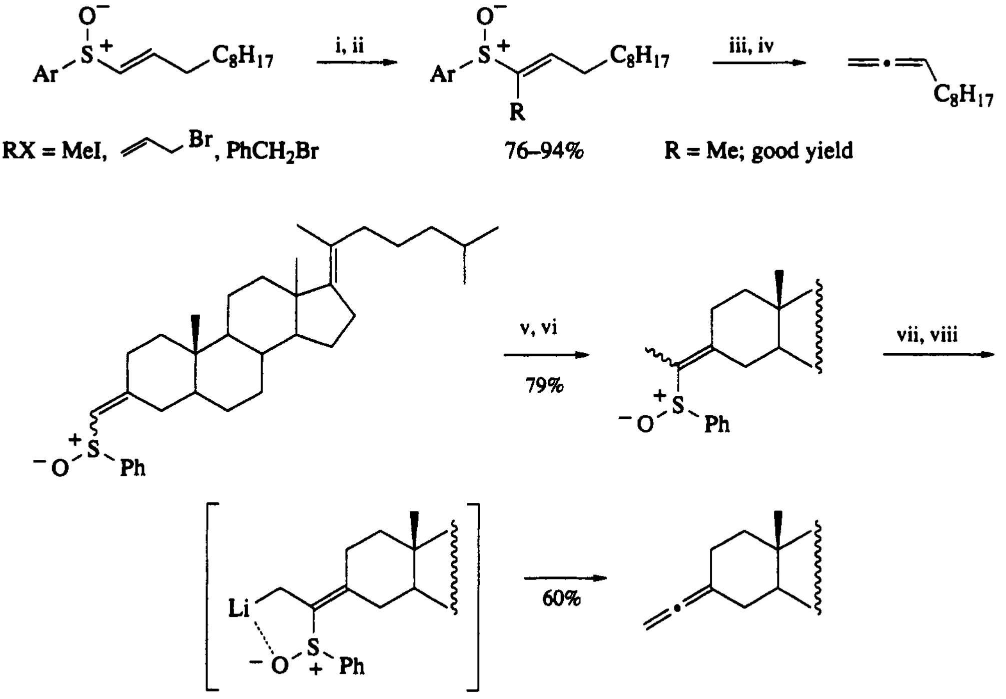

i, LDA, –78 °C, 0.3 h; ii, RX; iii, LITMP, THF, –100 °C, 0.8 h; iv, $NH_4Cl$; v, LDA, –78 °C; vi, MeI; vii, LITMP, THF, –100 °C, 0.8 h; viii, $NH_4Cl$

Scheme 101

### 1.3.5.2 Alkylations of α-Metallo-alkyl and -vinyl Selenoxides

α-Lithioalkyl selenoxides, which are available from *in situ* oxidation–metallation of the corresponding alkyl aryl selenides, have been alkylated at –78 °C with methyl iodide and allyl bromides (Scheme 102).[98,112,113] Unfortunately the utility of this process is limited,[113] as in the case of the corresponding sulfoxides, by the lack of regioselectivity of the subsequent *syn* elimination (Scheme 102, compare entries a and b to entry c) since two alkenes are formed, unless structural features dictate the formation of only a single isomer (Scheme 102). The α-deprotonation of vinyl phenyl selenoxide with LDA has been studied[107] at –78 °C for different time spans. A maximum of 50% of the expected methylation product, α-phenylseleno-2-propene, was isolated after reduction of the intermediate selenoxide with NaI in acetic acid. Deprotonation, even in the presence of methyl iodide, gave poor results.[107]

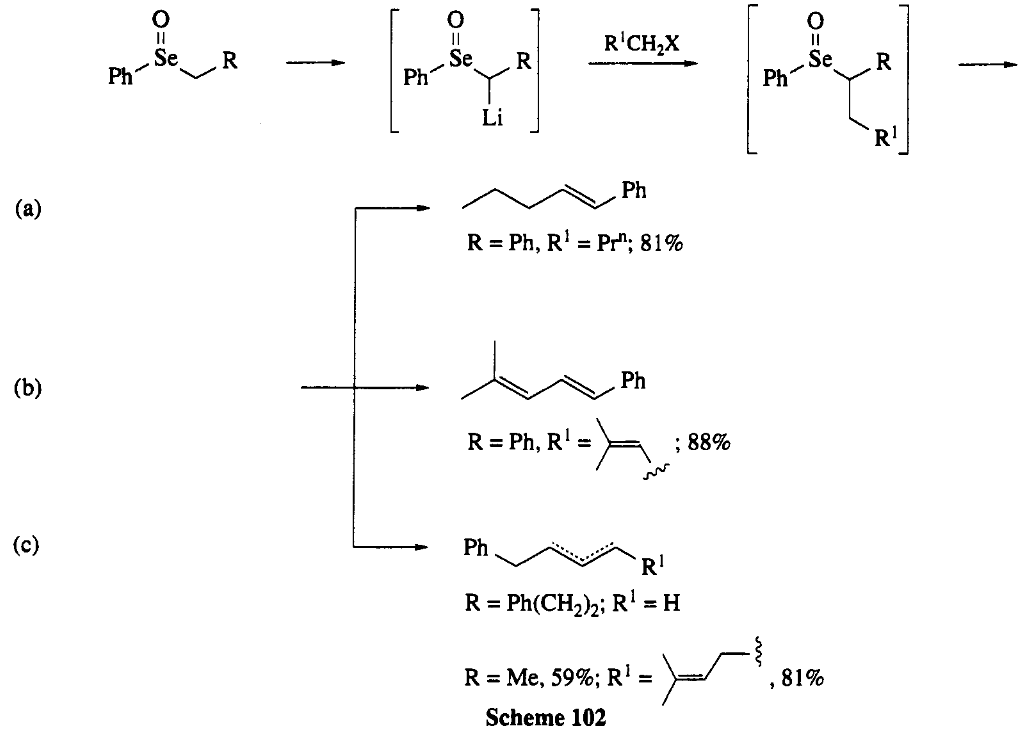
R$^1$CH$_2$X
(a)
R = Ph, R$^1$ = Pr$^n$; 81%
(b)
R = Ph, R$^1$ = ; 88%
(c)
R = Ph(CH$_2$)$_2$; R$^1$ = H
R = Me, 59%; R$^1$ = , 81%

**Scheme 102**

## 1.3.6 REACTIONS INVOLVING SULFONES

### 1.3.6.1 Reactions Involving α-Metalloalkyl Sulfones

#### *1.3.6.1.1 Alkylations of α-metalloalkyl sulfones*

Although the sulfone functional group has been an integral part of organic chemistry for more than a century, it has been only within the last few decades that a more diverse range of chemistry involving this group has been discovered and used, particularly in the total synthesis of various natural products. Various aspects of sulfone chemistry have been reviewed earlier by Magnus[36] and by Durst[37,38] Typically, sulfones exhibit a high degree of chemical and thermal stability. They are stable to oxidizing agents and to acids, but can be reduced to sulfides.[36–38] The sulfonyl group can be replaced[36,37] by hydrogen using Raney nickel, lithium in ethylamine or under less severe experimental conditions (6% Na/Hg). On reaction with a base they are usually readily metallated, and when the hydrogen attached to the carbon β to the one bearing the sulfonyl group is sufficiently acidic (*e.g.* α to a carbonyl group or to a C=C double bond) elimination of sulfinic acid occurs leading to a new C=C double bond. Furthermore, the sulfone oxygen atoms show only relatively weak bonding with electrophiles as compared to sulfoxides and selenoxides. These possibilities and this chemistry, as well as the aptitude of some specific sulfones to take part in the Ramberg–Bäcklund reaction[434] and extrude $SO_2$ thermally or photochemically, have led to an increasing use of sulfones in synthesis.[434,435]

The alkylation of sulfones has played an important role in this development. Most of this work has been performed with aryl sulfones, and in only rare cases have triflones ($RSO_2CF_3$)[436] or dialkyl sulfones been employed.[437–440]

Sulfones, including dimethyl sulfones, have been routinely converted into their monoanions by a variety of basic reagents which *inter alia* include: (i) Grignard reagents,[439–441] (ii) organolithiums,[36–38,440,442] (iii) potassium *t*-butoxide,[442] (iv) sodium hydride,[391,436] (v) metallo amides,[438,443,444] and (vi) in rare cases, with phenylsodium or phenylpotassium.[442]

The presence of another group such as an aryl,[436,445–447] an allyl,[448] or an isocyanide,[449] capable of further stabilization of the carbanionic center allows the use of less strong bases such as 50% sodium hydroxide solution under phase-transfer catalysis,[445,446,448] sodium hydroxide in DMF (Scheme 103, entries a and b)[447] or even potassium carbonate in acetonitrile (Scheme 103, entry d).

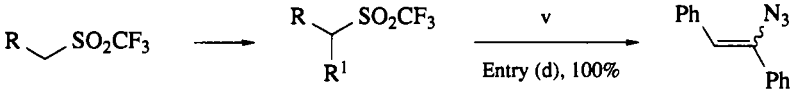

| *Entry* | *R* | *R¹X* | *Conditions* | *Yield* (%) | (ref. 436) |
|---|---|---|---|---|---|
| (a) | H | $Ph(CH_2)_2Br$ | i | 73 | |
| | | $PhCH_2Br$ | i | 18 (48% dialkylation) | |
| (b) | H | $Pr^iI$ | ii | 60 | |
| (c) | Me | MeI | iii | 60 | |
| (d) | Ph | $PhCH_2Br$ | iv | 70 | |

i, $R^1X$, NaH, DMF, 25 °C, 10–18 h; ii, $R^1X$, NaH, glyme, HMPA, reflux, 8 h; iii, $R^1X$, NaH, glyme, 25 °C, 2.5 h; iv, $K_2CO_3$, MeCN, 84 °C, 36 h; v, 2 NaH, *p*-$TolSO_2N_3$, 0 °C, 0.5 h

**Scheme 103**

α-Sulfonyl Grignard reagents are not usually alkylated efficiently; for example phenylsulfonylmethylmagnesium bromide does not undergo alkylation[441] with *n*-hexyl iodide or *t*-butyl chloride. However it reacts with benzyl chloride, but leads to the corresponding product in only very modest yield (34%).[441] Similarly α-(*p*-tolylsulfonyl)isopropylmagnesium bromide is alkylated only to the extent of 38% when treated with 3-chloropropyl *p*-toluenesulfonate, but steric hindrance may intervene in this instance (for an intramolecular version of this reaction see Scheme 109).[441]

The alkylations of related organolithium derivatives bearing hydrogen or alkyl groups on their carbanionic centers proceed with much better yields, but often involve primary alkyl (Scheme 103; Scheme 104, entries a, b, and d; Scheme 105, entries a and b; Scheme 106, entries a–d; Scheme 107; Scheme 108, entries a and b; Scheme 109),[13,24,138,436,443,450,451–461] benzyl[138,436,437,451,454,456,459] or allyl[138,445,452,454,455,459,460,462] halides or sulfonates as well as 2,3-dihalogeno- and 1,3-dihalogeno-1-propenes[463] and related dihalides (Scheme 110).[463]

In one case considerable difficulty was encountered in the alkylation of the anion of methyl phenyl sulfone with *o*-chlorobenzyl bromide since, under a variety of conditions, mixtures containing starting sulfone, mono- and di-alkylated products were obtained.[37] Allylation of α-lithio sulfones with allylvinyl dihalides[463] has been reported to produce a large amount of the monoallylated compound in addition to some diallylated derivative. The formation of the latter compound can be avoided however if the reaction is carried out in the presence of copper(I) iodide (Scheme 110, entry a).[463]

Although alkylations of α-metallo sulfones with sodium iodoacetate proceed efficiently (Scheme 105, entry b),[455] 1:1 mixtures of products are formed on reaction with ethyl iodoacetate in THF (Scheme 110, entry b).[461] The mixtures arise from the expected alkylation reaction and from competitive addition to the carbonyl group of the ester. The product resulting from the alkylation reaction is almost exclusively produced however if the above mentioned reaction is performed in the presence of HMPA (10%) and a trace amount of potassium iodide (Scheme 110, entry c). The resulting β-sulfonyl ester has been further transformed to an α,β-unsaturated ester, taking advantage of the facile elimination of sodium phenyl sulfinate (Scheme 110, entry c).

Alkylations of sulfones with secondary alkyl halides have been described only rarely.[456,458] They usually proceed with modest yields and require both long reaction times and the presence of HMPA (Scheme 106, entry b). The presence of an aryl group on the carbanionic center softens this site however, and usually favors the alkylation reaction.[445,461,463]

Mono- or di-alkylation of dimetalloalkyl sulfones has been reported from time to time. Apparently the geminally dilithiated alkyl aryl sulfones are more reactive towards alkyl halides than the monolithiated species. Therefore they can be monoalkylated (Scheme 111, entries a and b)[443,464] or dialkylated (Scheme 111, entries c and d),[438,464,466,467] depending upon the conditions employed (*i.e.* excess of alkylating agent and more severe conditions for dialkylation) but success also depends upon the structures of the sulfones and the nature of the alkylating agents. Thus, ferrocenylmethyl phenyl sulfone is efficiently dimethylated or transformed to the corresponding cyclopropane derivative on sequential treatment with 2

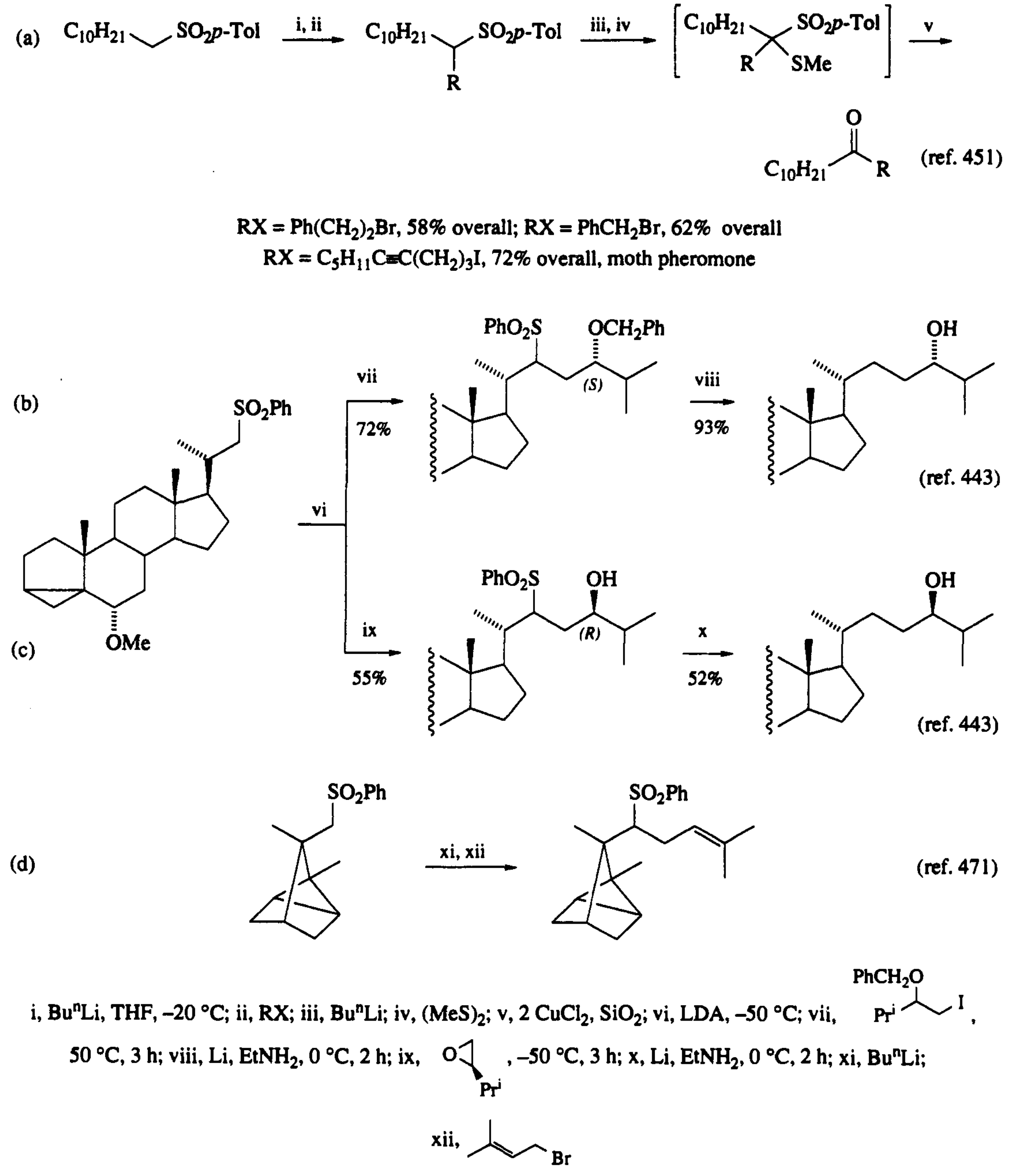
(a)
$C_{10}H_{21}$ $SO_2p$-Tol
i, ii
R
iii, iv
SMe
v
O
(ref. 451)
(b)
$SO_2Ph$
vi
vii
72%
$PhO_2S$
$OCH_2Ph$
(S)
viii
93%
OH
(ref. 443)
(c)
OMe
ix
55%
OH
(R)
x
52%
(ref. 443)
(d)
xi, xii
(ref. 471)
$PhCH_2O$
$Pr^i$
I
O
Br

RX = $Ph(CH_2)_2Br$, 58% overall; RX = $PhCH_2Br$, 62% overall
RX = $C_5H_{11}C{\equiv}C(CH_2)_3I$, 72% overall, moth pheromone

i, Bu$^n$Li, THF, –20 °C; ii, RX; iii, Bu$^n$Li; iv, $(MeS)_2$; v, 2 $CuCl_2$, $SiO_2$; vi, LDA, –50 °C; vii, , 50 °C, 3 h; viii, Li, $EtNH_2$, 0 °C, 2 h; ix, , –50 °C, 3 h; x, Li, $EtNH_2$, 0 °C, 2 h; xi, Bu$^n$Li;
xii,

Scheme 104

equiv. of *n*-butyllithium and 2 equiv. of methyl iodide or 1 equiv. of 1,2-dichloroethane respectively, but it is monoalkylated with *n*-butyl or benzyl bromide under similar conditions (Scheme 111, entry b).[465]

Reactions of dimethyl,[438] and dibenzyl[437] sulfones (Scheme 112) and of tetrahydrothiophene 1,1-dioxide (Scheme 107, entry a)[453] with 2 equiv. of base, followed by 2 equiv. or more of alkyl halides, take another course since α,α′-dialkylated rather than α,α-dialkylated derivatives are produced.

### *1.3.6.1.2 Synthetic applications of alkyl sulfones*

Alkylation or allylation reactions of α-metalloalkyl sulfones followed by oxidation of the carbon center bearing the sulfonyl group (Bu$^n$Li and dimethyl disulfide,[451] or a three-fold excess of molybdenum peroxide[468] or a slight excess of bis(trimethylsilyl) peroxide, BTSP[469]) have led to novel routes to

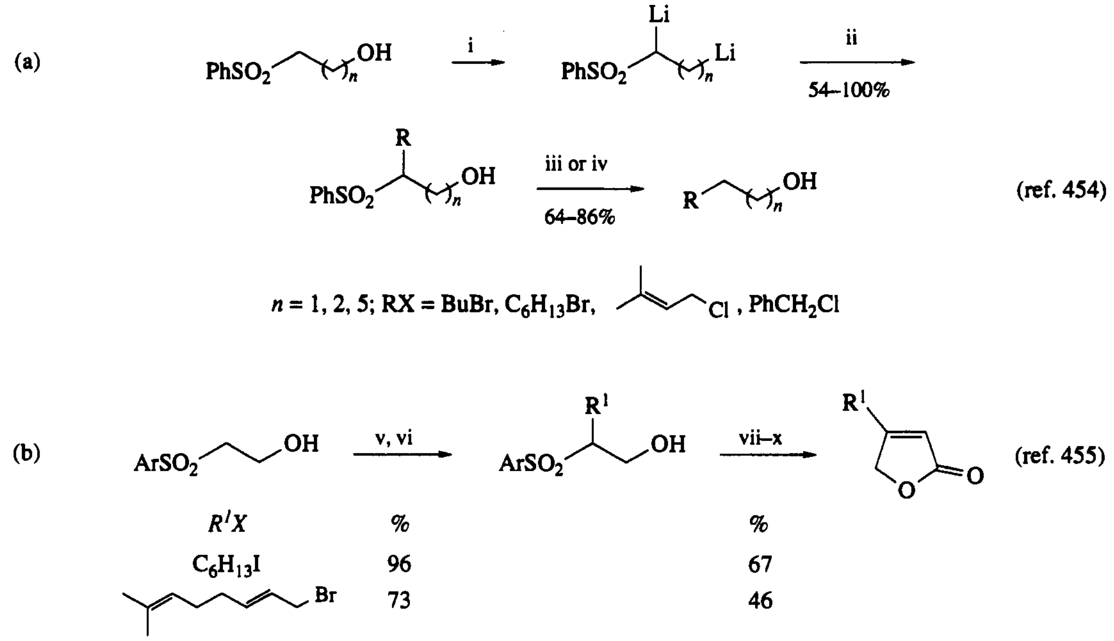

i, 2 Bu$^n$Li, –78 °C; ii, RX, –78 °C, 0.5 h, then 25 °C, 2–3 h; iii, Raney Ni; iv, Hg/Na; v, 2.2 Bu$^n$Li, THF–TMEDA; vi, R$^1$X; vii, 2.2 Bu$^n$Li, THF–TMEDA; viii, 1.2 ICH$_2$CO$_2$Na; ix, $p$-TsOH, benzene, Δ; x, 2.5 equiv. Et$_3$N, benzene, 20 °C

**Scheme 105**

ketones.[451] The first reagent has been used,[451] *inter alia*, in a synthesis of the sex pheromone of Douglas fir tussock moth (Scheme 104, entry a). Furthermore by taking advantage of the fact that one oxygen of BTSP becomes the carbonyl oxygen of the product, it is possible to label specifically this oxygen by using the readily available (TMS$^{18}$O)$_2$.[469] Reduction of the sulfonyl group, subsequent to alkylation, has been used for the synthesis of 24-hydroxycholesterols (Li/H$_2$NEt; Scheme 104, entry c),[443] (+)-dihydrocompactin (NaHg; Scheme 111, entry a)[464], sesquifenchene (Li/EtNH$_2$)[462], α-santalene (Na/Hg, HMPA),[470] cyclopropane (Scheme 108, entry a)[444] or phenylcyclopropane (Scheme 109),[138] benzocyclobutane (Na/Hg; Scheme 107, entries c and d)[460] as well as for the coupling of: (i) an alkyl side chain with a functionalized alkyl or alkenyl halide (see for example Scheme 108, entry a);[463] and (ii) a functionalized side chain with an alkyl, alkenyl or benzylic halide (Scheme 105, entry a; Scheme 106, entry a; Scheme 107, entries c and d).[454,456,458,460] In the above mentioned transformations the sulfone has therefore played the role of an alkyl- or functionalized alkyl-metal.

Thus β-, γ- and ω-hydroxy,[454] β-dioxy- and ω-carboxy-alkyl sulfones have proved to be valuable precursors of alcohols (Scheme 105, entry a),[454] acetals, aldehydes or ketones (Scheme 106, entries a–d)[456,458] and carboxylic acids,[471] respectively, whereas 1-(ω-alkenyl) halides have been synthesized[463] from 1,3-dichloropropene and α-metalloalkenyl sulfones (Scheme 110, entry a). 1-(ω-Alkenyl)-1-sulfonylbenzocyclobutanes are good precursors of quinodimethanes, which are themselves particularly useful reactive intermediates.[460] Although an internal Diels–Alder reaction leading to the tricyclic compound shown in Scheme 107 (entry c), takes place efficiently on thermolysis of the compound missing the sulfonyl group, the reaction takes another course with the highly electron-deficient diene bearing the sulfonyl moiety which instead leads to the aryl vinyl sulfone shown in Scheme 107 (entry d).

Furthermore, several syntheses of α,β-unsaturated carbonyl compounds have involved the alkylation of suitably functionalized sulfones, followed by the base-promoted elimination of the sulfenate moiety on related alkyl sulfones bearing an oxygen atom at the γ-position (Scheme 106, entries b–d; Scheme 110, entry c; Scheme 105, entry b).[455,456,458,461] Particularly interesting is the synthesis of nuciferal (Scheme 106, entry d)[458] which involves sequential alkylation of γ,γ-dioxy sulfones, deblocking of the acetal moiety and sulfenate elimination. In this and related reactions γ,γ-dioxy-α-metalloalkyl sulfone has played the role of a masked β-metallo-α,β-unsaturated carbonyl compound (MC═C—C—C═O), which is not a directly available synthon.

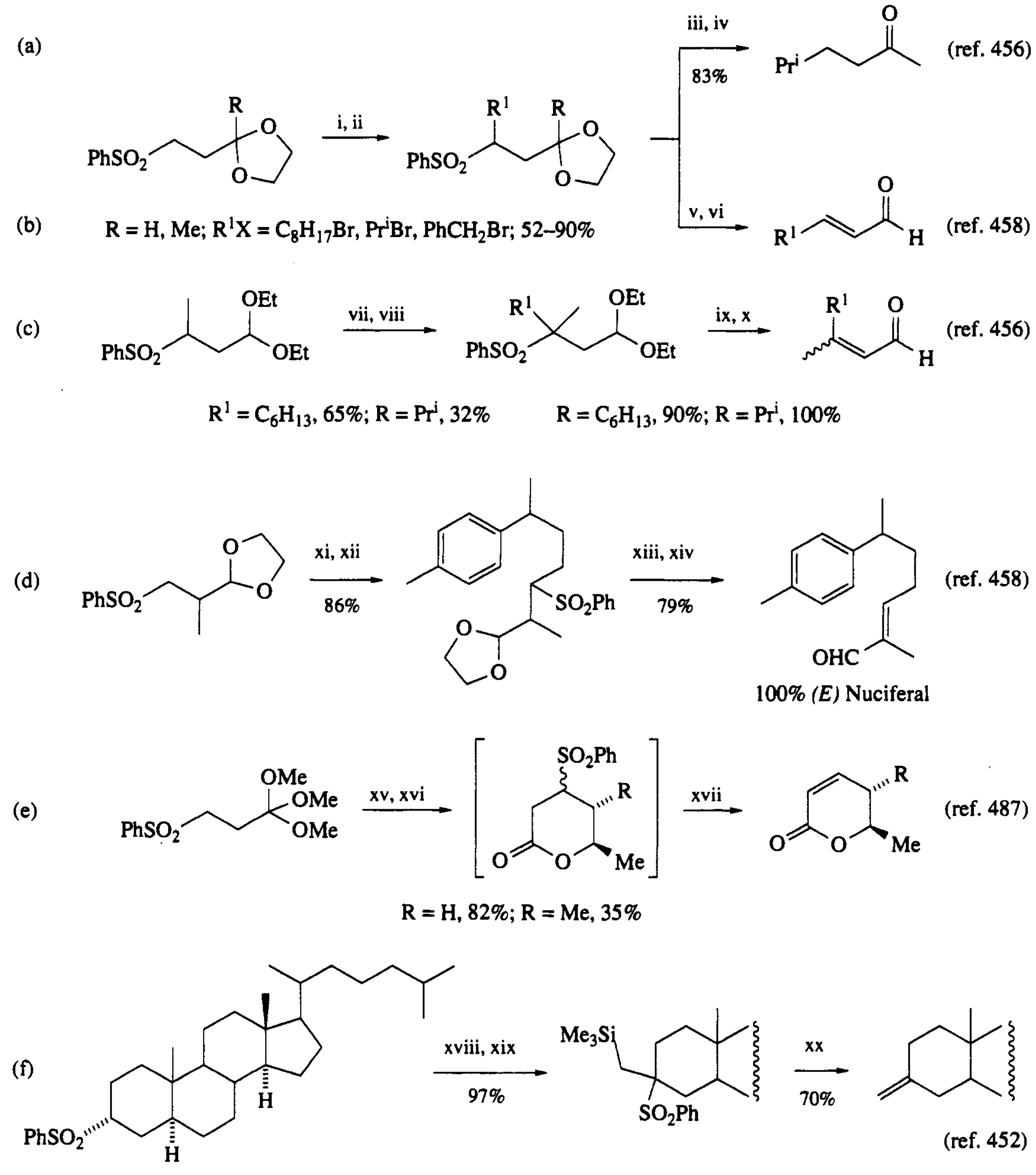
(a)
PhSO2
R
O
O
i, ii
R1
R
iii, iv
83%
Pri
O
(ref. 456)
v, vi
R1
O
H
(ref. 458)
(b)
R = H, Me; R1X = C8H17Br, PriBr, PhCH2Br; 52–90%
(c)
OEt
OEt
vii, viii
ix, x
(ref. 456)
R1 = C6H13, 65%; R = Pri, 32%
R = C6H13, 90%; R = Pri, 100%
(d)
xi, xii
86%
SO2Ph
xiii, xiv
79%
OHC
(ref. 458)
100% (E) Nuciferal
(e)
OMe
OMe
OMe
xv, xvi
SO2Ph
R
Me
xvii
(ref. 487)
R = H, 82%; R = Me, 35%
(f)
H
H
xviii, xix
97%
Me3Si
SO2Ph
xx
70%
(ref. 452)

i, Bu$^n$Li, THF, –30 °C; ii, R$^1$X, 20 °C, 6–8 h; iii, Na/Hg, MeOH, 0 to 20 °C; iv, $H_3O^+$; v, $H_3O^+$;

vi, $Et_3N$, THF, $H_2O$; vii, Bu$^n$Li, THF; viii, R$^1$Br; ix, $H^+$; x, base; xi, Bu$^n$Li, THF; xii, 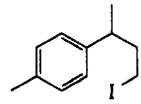 ;

xiii, $H^+$; xiv, base; xv, Bu$^n$Li, THF; xvi, 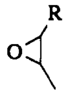 ; xvii, $Et_3N$ or DBU; xviii, Bu$^n$Li, THF, 0 °C; xix, $Me_3SiCH_2I$;

xx, Bu$^n_4$NF, THF, reflux

**Scheme 106**

Nonfunctionalized alkenes such as terminal alkenes are not available on similar treatment of, for example, 2-sulfonylalkanes with bases. However, these have been obtained on alkylation of α-metallo sulfones with trimethylsilylmethyl iodide[452] and subsequent reaction of the resulting β-silyl sulfone with

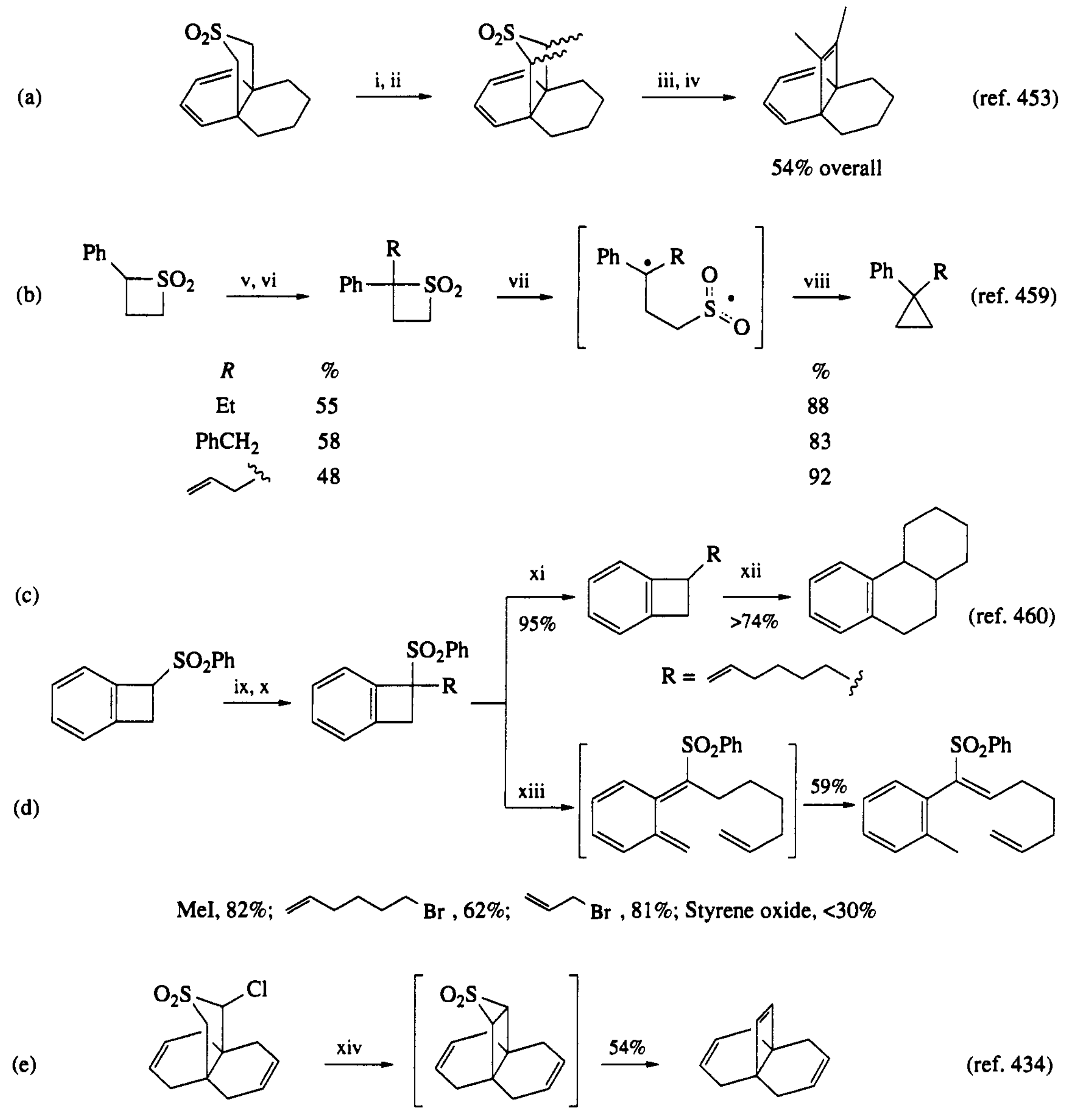
(a)
$O_2S$
i, ii
$O_2S$
iii, iv
54% overall
(ref. 453)
(b)
Ph
$SO_2$
v, vi
R
Ph
$SO_2$
vii
Ph
R
O
S
O
viii
Ph
R
(ref. 459)
R % %
Et 55 88
$PhCH_2$ 58 83
48 92
(c)
(d)
$SO_2Ph$
ix, x
$SO_2Ph$
R
xi
95%
R
xii
>74%
(ref. 460)
R =
xiii
$SO_2Ph$
59%
$SO_2Ph$
MeI, 82%; Br, 62%; Br, 81%; Styrene oxide, <30%
(e)
$O_2S$
Cl
xiv
$O_2S$
54%
(ref. 434)

i, 2 Bu$^n$Li, THF, –80 °C; ii, excess MeI; iii, Bu$^n$Li; iv, $LiAlH_4$, dioxane, Δ; v, Bu$^n$Li, $Et_2O$, –78 °C, 1 h; vi, RBr, –78 °C, then 20 °C, 2 h; vii, *h*ν (254 nm), $CH_2Cl_2$; viii, $-SO_2$; ix, MeLi, THF, –78 °C; x, RX, –78 to 20 °C, <1 h; xi, Na/Hg, MeOH, $NaHPO_4$; xii, 250 °C, 24 h; xiii, 250 °C, c-$C_6H_{12}$, 20 h; xiv, Bu$^t$OK, THF, 0 °C, 5 h

**Scheme 107**

fluoride ion (Scheme 106, entry f). A related procedure involving the alkylation,[452] the allylation,[452] and the reaction of α-metallo-β-(trimethylsilyl)alkyl phenyl sulfones with epoxides[471] allows the synthesis of 1-alkenes,[452] 1,4-dienes[452] and cyclopropyl sulfones[471] respectively.

Extrusion of sulfur dioxide from the products resulting from the alkylation of tetrahydrothiophene 1,1-dioxides[453,472] and the 2-phenylthietane 1,1-dioxides,[459] using *n*-butyllithium and lithium aluminum hydride[453] or photochemically[459] leads to the synthesis of the corresponding cyclobutenes[453] and cyclopropanes,[459] respectively (Scheme 107, entries a and b).

Internal alkylation takes place on reaction of α-haloalkyl alkyl sulfones with bases and produces episulfones as intermediaries. These intermediates are usually unstable and provide alkenes by thermal extrusion of sulfur dioxide. This reaction, known as the Ramberg–Bäcklund rearrangement, has been widely used in synthesis and has been thoroughly reviewed (Scheme 107, entry e).[36,38,434,473]

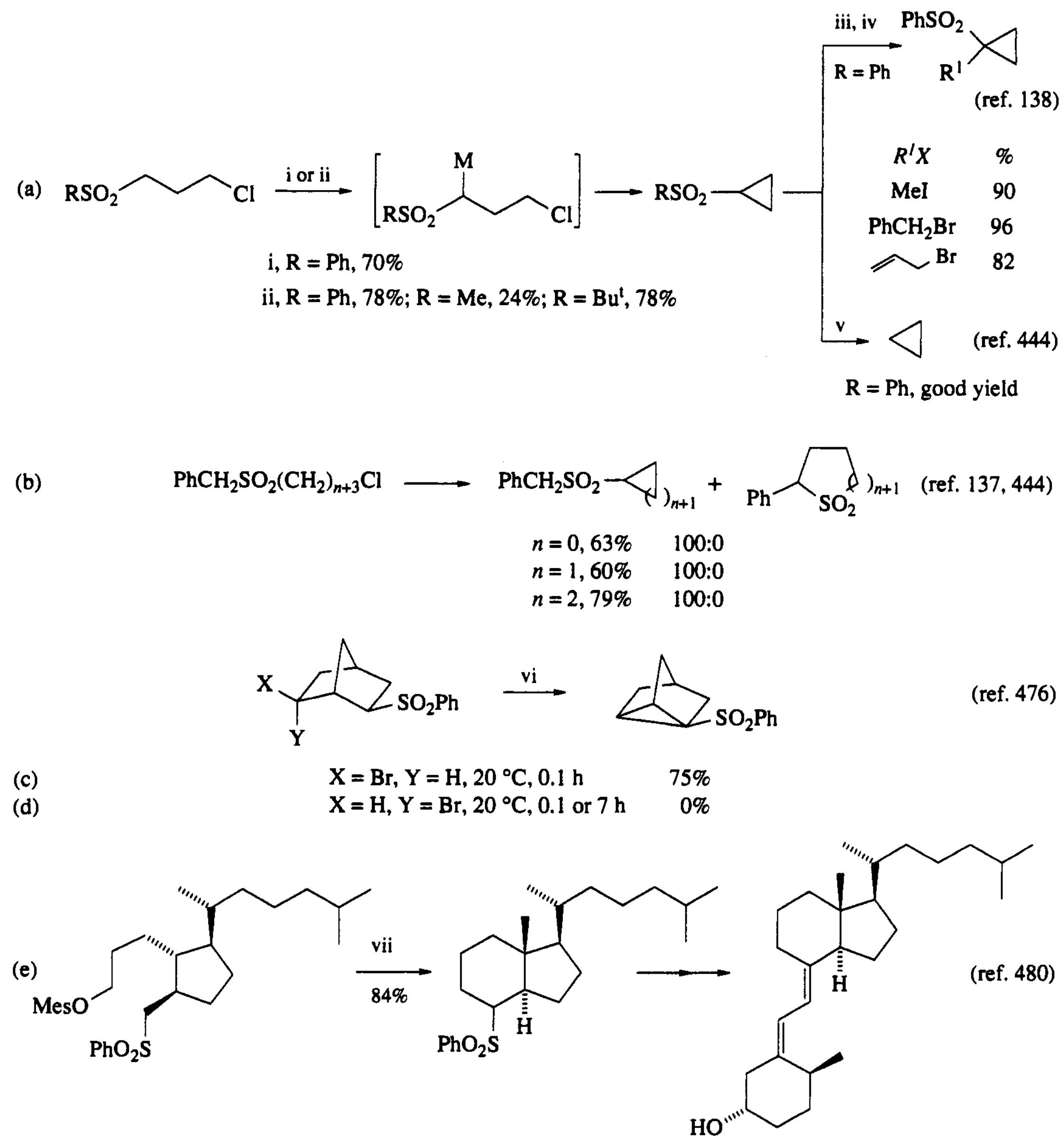
(a)
RSO2
Cl
i or ii
M
RSO2
Cl
RSO2
iii, iv
R = Ph
PhSO2
R1
(ref. 138)
R1X %
MeI 90
PhCH2Br 96
Br 82
v
(ref. 444)
R = Ph, good yield
i, R = Ph, 70%
ii, R = Ph, 78%; R = Me, 24%; R = But, 78%
(b)
PhCH2SO2(CH2)n+3Cl
PhCH2SO2
)n+1
+
Ph
SO2
)n+1
(ref. 137, 444)
n = 0, 63% 100:0
n = 1, 60% 100:0
n = 2, 79% 100:0
X
Y
SO2Ph
vi
SO2Ph
(ref. 476)
(c) X = Br, Y = H, 20 °C, 0.1 h 75%
(d) X = H, Y = Br, 20 °C, 0.1 or 7 h 0%
(e)
MesO
PhO2S
vii
84%
H
PhO2S
H
HO
(ref. 480)

i, $\mathrm{Bu^tOK}$, $\mathrm{Bu^tOH}$, Δ, 6 h; ii, $\mathrm{NaNH_2}$, DME, 60 °C, 2 h; iii, $\mathrm{Bu^nLi}$, THF; iv, $\mathrm{R^1X}$, 0 °C;
v, Raney Ni, EtOH; vi, $\mathrm{Bu^tOK}$, DMSO; vii, LDA, THF, –78 to 20 °C

**Scheme 108**

Treatment of γ-halo[444,474,475] or γ-tosyloxy sulfones[138] with base results in their conversion to cyclopropyl sulfones in good yields (Scheme 108; Scheme 109).[35,37,138,450,475] The base/solvent systems that have been used in this reaction include $\mathrm{Bu^tOK/Bu^tOH}$,[442,475] $\mathrm{NaNH_2}$/glyme (but not $\mathrm{NaNH_2}$ in ether),[444] LDA/THF[138] and $\mathrm{Bu^nLi}$/THF (Scheme 108, entry a; Scheme 109, entry a).[474] Treatment of the *exo* bromide shown in Scheme 108 (entry c) with base results in the rapid formation of the sulfonyl quadricyclane,[476] while the *endo* bromide, whose carbanion cannot assume the suitable semi-ω conformation in the transition state,[477] does not cyclize under similar or even forcing conditions (Scheme 108, compare entry d to c). Alkylation, benzylation or allylation of the resulting cyclopropyl sulfone has in turn been performed successfully[138] (Scheme 108, entry a). Its reduction to cyclopropane was achieved[138] with Raney nickel (Scheme 108, entry a). Cyclopropyl and cyclopentyl phenyl sulfones have been obtained directly[478] from (phenylsulfonyl)methylenedilithium and 1,2-dichloroethane and 1,4-diiodopentane, and from related ferrocenyl species and dichloroethane (Scheme 111, entry b).[465] *trans*-2-Substituted-cyclopropyl sulfones have been produced in up to 80% yield by addition of allylic, propargylic, aryl and

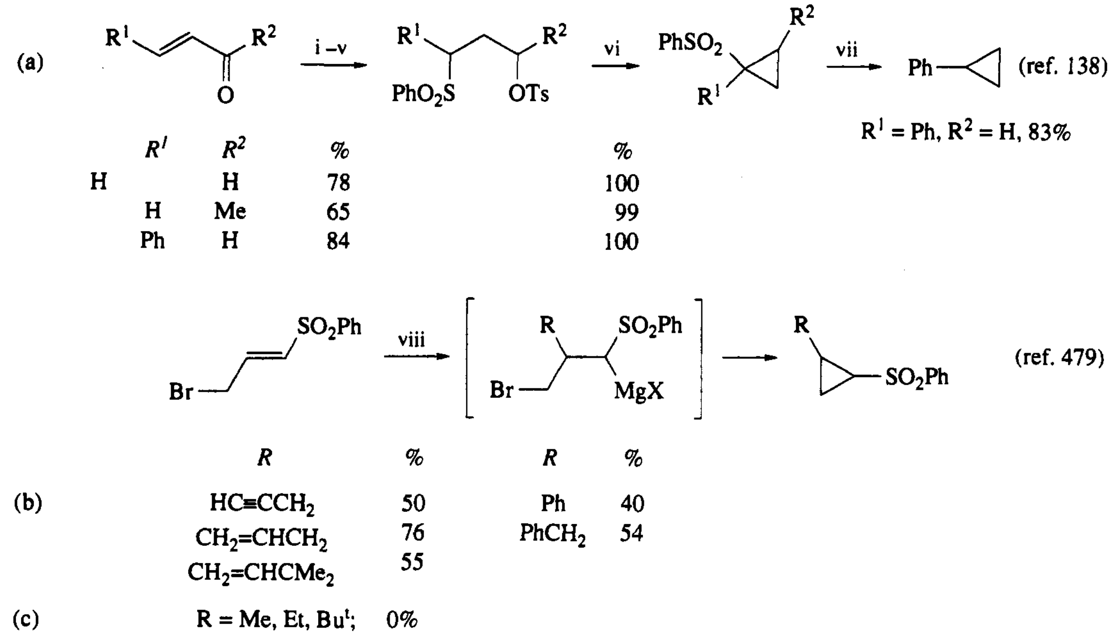
(a)
R1
R2
O
i -v
R1
R2
PhO2S
OTs
vi
PhSO2
R2
R1
vii
Ph
(ref. 138)
R1 = Ph, R2 = H, 83%
R1 R2 % %
H H 78 100
H Me 65 99
Ph H 84 100
SO2Ph
Br
viii
R
SO2Ph
Br
MgX
R
SO2Ph
(ref. 479)
R % R %
(b) HC≡CCH2 50 Ph 40
CH2=CHCH2 76 PhCH2 54
CH2=CHCMe2 55
(c) R = Me, Et, Bu^t; 0%

i, PhSNa; ii, $NaBH_4$; iii, $H_2O_2$, HOAc; iv, $K_2CO_3$, MeOH; v, TosCl, pyridine; vi, LDA, THF; vii, Na/Hg; viii, RMgX

Scheme 109

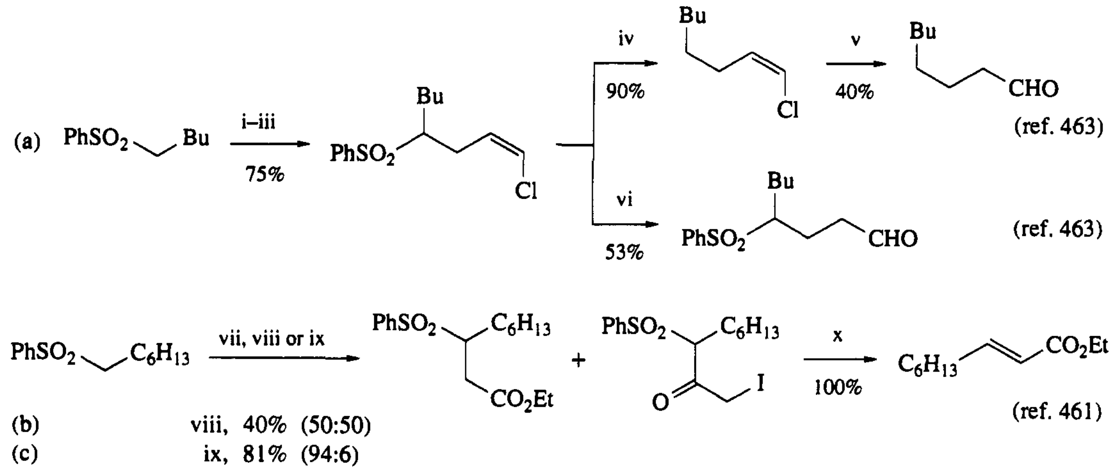
(a) PhSO2
Bu
i–iii
75%
Bu
PhSO2
Cl
iv
90%
Bu
Cl
v
40%
Bu
CHO
(ref. 463)
vi
53%
Bu
PhSO2
CHO
(ref. 463)
PhSO2
C6H13
vii, viii or ix
PhSO2
C6H13
CO2Et
+
PhSO2
C6H13
O
I
x
100%
C6H13
CO2Et
(ref. 461)
(b) viii, 40% (50:50)
(c) ix, 81% (94:6)

i,Bu$^n$Li, THF, –78 °C; ii, CuI, –25 °C, 1 h; iii, 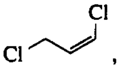, THF, 24 h; iv, Na/Hg, MeOH, 0 °C; v, HgOAc, 65 °C, 60 h; vi, HgOAc, 60 °C, 60 h; vii, Bu$^n$ Li, THF; viii, $ICH_2CO_2Et$, THF; ix, $ICH_2CO_2Et$, THF–HMPA (10%), KI; x, $Na_2CO_3$, EtOH, reflux, 5 h

Scheme 110

benzyl Grignard reagents to 3-bromo-1-(phenylsulfonyl)-1-propene (Scheme 109, entry b).[479] Unfortunately however, alkyl Grignard reagents do not lead to the corresponding cyclopropyl sulfones (Scheme 109, entry c).[479]

Cyclobutyl,[137] cyclopentyl[137] and cyclohexyl[137,480] aryl sulfones can also be prepared by the analogous cyclization involving the corresponding halo[137] or sulfonyloxyalkyl sulfones (Scheme 108, entries b and e).[480] This reaction has been used as a key step in the stereoselective synthesis of de-A,B-cholestanes

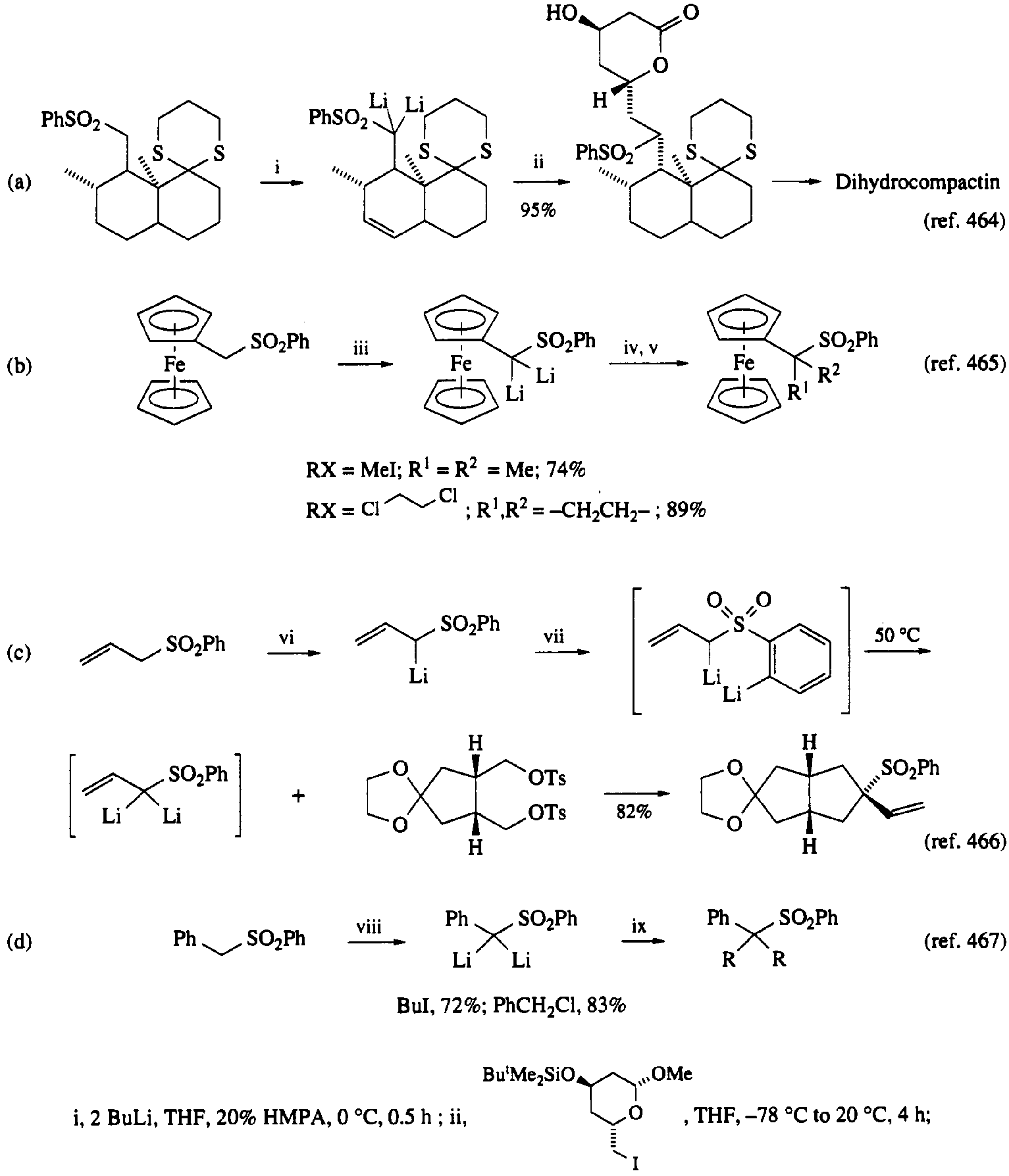
(a)
PhSO2
S
S
i
Li
ii
95%
HO
O
H
Dihydrocompactin
(ref. 464)
(b)
SO2Ph
Fe
iii
Li
iv, v
$R^1$
$R^2$
(ref. 465)
RX = MeI; $R^1 = R^2$ = Me; 74%
RX = Cl⁀Cl ; $R^1,R^2$ = $-CH_2CH_2-$ ; 89%
(c)
vi
vii
50 °C
+
OTs
82%
(ref. 466)
(d)
Ph
viii
ix
R
(ref. 467)
BuI, 72%; $PhCH_2Cl$, 83%
$Bu^tMe_2SiO$
OMe
I

i, 2 BuLi, THF, 20% HMPA, 0 °C, 0.5 h ; ii, [structure], THF, −78 °C to 20 °C, 4 h;

iii, 2 BuLi, THF, 20 °C, 0.5 h; iv, 2 RX, reflux, 0.5 h; v, $H_3O^+$; vi, $Bu^nLi$, THF; vii, $Bu^nLi$, low temp.; viii, 2 $Bu^nLi$, THF, 1 h; ix, 2 RX, THF, reflux, 24 h

**Scheme 111**

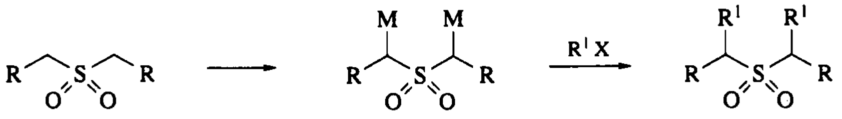

(a) R = H; $NaNH_2$, $NH_3$ or $Bu^nLi$, THF — 2 BuBr; 44% (ref. 438)

(b) R = Ph; $KNH_2$, $NH_3$ — 2 $PhCH_2Cl$; good yield (ref. 437)

**Scheme 112**

(Scheme 108, entry e). When the possibility of forming rings of different size exists, the product of cyclization is controlled by ring size and not by the acidity of the potential carbanion sites as in sulfides (compare scheme 108, entry b to Scheme 14, entry e).[137,444]

α-Metallo-alkyl or -benzyl sulfones[294,443,460,470,478,481–484] and also triflones[483] have been reacted with a large variety of terminal epoxides (Scheme 104, entry c)[294,443,458,460,478,483,484] and with α,β-di[470,483] and tri-substituted epoxides[483] (Scheme 106, entry e) including allylic epoxides[481] and those which are part of the alkyl side chain of the sulfone (Scheme 113).[482,485,486] The reactions often require heating (45 to 65 °C) for a prolonged period[483] but take place under milder conditions when dilithio derivatives are

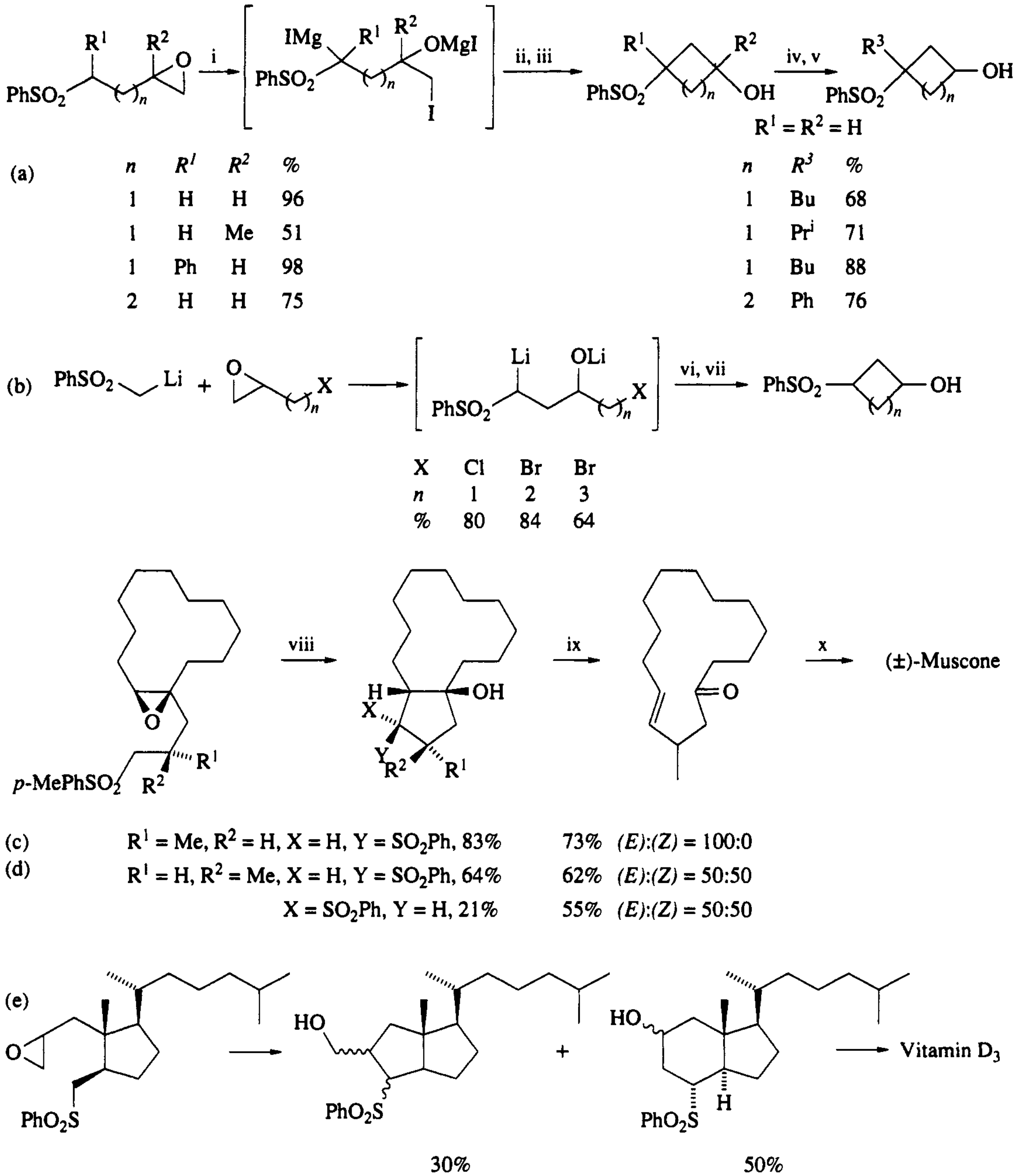
(a)
PhSO2
R1 R2 O
i
IMg R1 R2 OMgI
PhSO2
I
ii, iii
R1 R2
PhSO2 OH
iv, v
R3
PhSO2 OH
R1 = R2 = H
n R1 R2 %
1 H H 96
1 H Me 51
1 Ph H 98
2 H H 75
n R3 %
1 Bu 68
1 Pri 71
1 Bu 88
2 Ph 76
(b)
PhSO2 Li + O X
Li OLi
PhSO2 X
vi, vii
PhSO2 OH
X Cl Br Br
n 1 2 3
% 80 84 64
viii
ix
x
(±)-Muscone
O
p-MePhSO2 R1 R2
H OH
X Y R2 R1
O
(c) R1 = Me, R2 = H, X = H, Y = SO2Ph, 83% 73% (E):(Z) = 100:0
(d) R1 = H, R2 = Me, X = H, Y = SO2Ph, 64% 62% (E):(Z) = 50:50
X = SO2Ph, Y = H, 21% 55% (E):(Z) = 50:50
(e)
O
PhO2S
HO
PhO2S
+
HO
PhO2S H
Vitamin D3
30%
50%

i, MeMgI, THF, –70 °C, then 20 °C; ii, cyclization; iii, $H_3O^+$; iv, 2 MeLi, THF; v, $R^3Br$; vi, cyclization; vii, $H_3O^+$; viii, $NaNH_2$, toluene, reflux, 5–10 h; ix, Bu$^t$OK, HMPA, toluene, 12 °C, 6 h; x, $H_2$ (catalyzed)

**Scheme 113**

used instead.[294,380] The sequence has been used[481] in conjunction with reduction of the sulfonyl group on the resulting γ-hydroxysulfone *inter alia* for the synthesis of diastereoisomers of (±)-labda-7,14-dien-13-ol[484] isolated from *Aster spathulifolins* Maxim, debromoplysiatoxin[294] and aplysiatoxin[294] from α-sulfonyl dianions and of 24-hydroxycholestane derivatives (Scheme 104, entry c).[443]

Using 3-(phenylsulfonyl)orthopropionate and epoxides, Ghosez *et al.*[487] have described a practical synthesis of 6-alkyl, 6,6-dialkyl and 5,6-dialkyl α,β-unsaturated-δ-lactones, and this reaction has been used in a synthesis of argentilactone (Scheme 106, entry e).[487]

3,4-Epoxybutyl and 4,5-epoxypentyl sulfones react with about 2 equiv. of methylmagnesium iodide in THF to give 3-phenylsulfonyl-cyclobutanols and -cyclopentanols in good to excellent yields (Scheme 113, entry a).[486]

The cyclization reaction does not apparently take place on the epoxide ring, but instead occurs on the β-oxido alkoxide resulting from the epoxide ring opening.[486] The synthesis of both γ-sulfonyl-cyclobutanols and -cyclopentanols could also be achieved in 'one pot' sequentially from α-lithioalkyl phenyl sulfones, ω-bromo-1-oxidoalkenes and butyllithium,[486] or even more expediently and in higher yield from the 1,1-dilithioalkyl sulfones and the same electrophile.[478] The last reaction, which was found to take place chemoselectively on the epoxide ring has been successfully extended to the synthesis of 3-phenylsulfonylcyclohexanol (Scheme 113, entry b).

Application of the above mentioned epoxy sulfone cyclization reaction has been ingeniously used in a synthesis of muscone (Scheme 113, entries c and d)[485] and also of vitamin $D_3$ (Scheme 113, entry e).[482] In the latter case surprisingly the terminal epoxide, when subjected to the intramolecular cyclization gave a mixture of sulfonylcyclopentane and sulfonylcyclohexane derivatives arising respectively from the epoxide ring opening at the most (30%) and the least (50%) substituted carbons.[482]

### 1.3.6.2 Reactions Involving α-Metalloallyl Sulfones

α-Metalloallyl sulfones, which are readily available on metallation of allyl[202,448,481,488–504,506–508] or in a few cases, of 1-alkenyl[505] sulfones (Scheme 114), have proved to be the most valuable organometallics of this series. In almost all cases the alkylation,[488,489,499,505,506] the benzylation[488,495,505] and the allylation[490,491,493,494,497–502,504,505,507,508] as well as the reaction with epoxides[202,481] take place selectively at the α-position (Scheme 114; Scheme 115; Scheme 116) even if this site is already substituted by an alkyl group (Scheme 114; Scheme 115, entry c; Scheme 116; for one exception see ref. 496).[489,503,505]

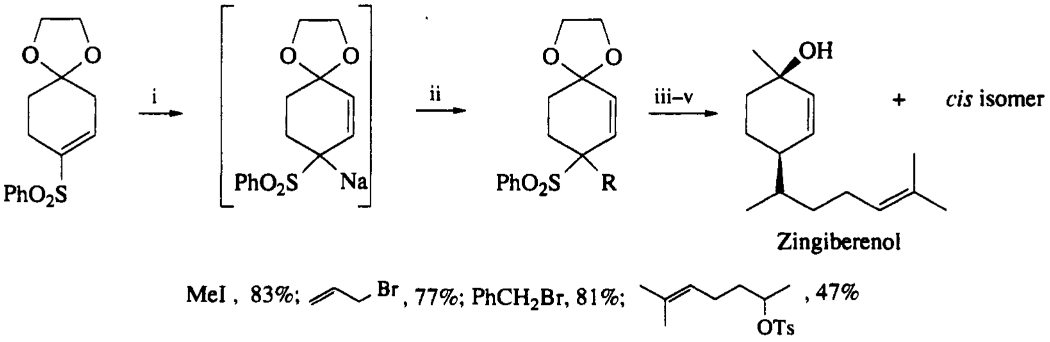

i, NaH, DMF; ii, RX; iii, desulfonation; iv, PPTS, acetone, NaOMe, MeOH; v, MeLi

Scheme 114

These results are particularly significant since mixtures of regioisomers are usually observed when related sulfoxides or sulfides are used instead (Sections 1.3.2.1.3 and 1.3.5.1.2). In the latter case, as already mentioned in Section 1.3.2.1.3, the presence of a heteroaryl group capable of chelation with the lithium salt is required in order to observe any α-selectivity comparable to that obtained with allyl sulfones.[16]

The methylation of the cyclohexenyl sulfone shown in Scheme 116 (entry a) proved most interesting in that equatorial attack predominates.[489] Such a result is quite surprising since a twist boat conformation leading to (**7**; Scheme 116, entry a) would be required as an initial product in order to maintain orbital overlap.[489] The stereochemistry resulting from the methylation of the bicyclic sulfones (**9**) and (**10**) is also most unusual (Scheme 116, entries b and c). Not only is the stereochemistry of the alkylation inde-

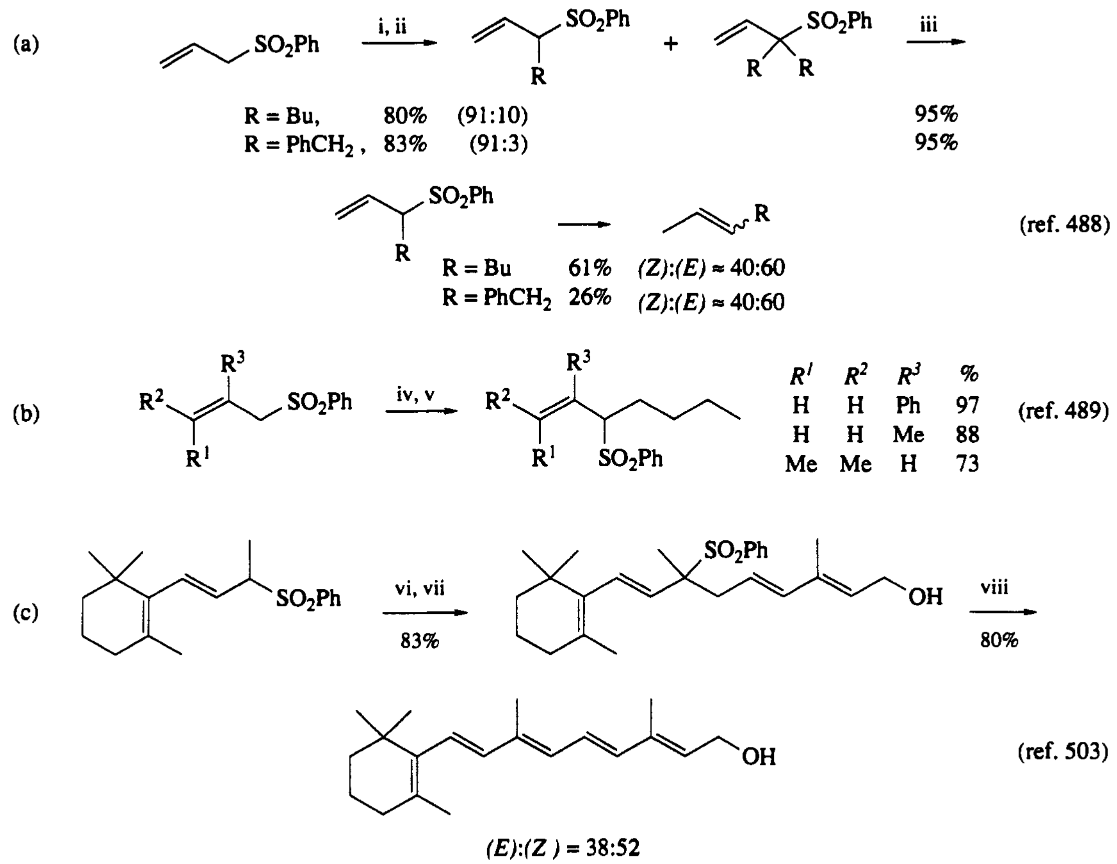

i, $Bu^nLi$, THF, TMEDA, −60 °C; ii, RX, −60 °C, 3 h; then 0 °C; iii, $Bu^tOK$, THF, 20 °C, 3 h; iv, $Bu^nLi$, THF;

v, $Bu^nI$; vi, $Bu^tOK$, DMF, THF; vii, 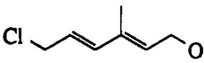, −78 to −40 °C; viii, KOH, MeOH, reflux

**Scheme 115**

pendent of the stereochemistry of the sulfone (**9**), but while the norbornenyl sulfone is mainly alkylated, as expected, from the least hindered *exo* face, the norbornyl system gives[489] predominantly *endo* attack in a contrasteric approach (Scheme 116, entry b).

Allyl sulfones have been used in a large number of valuable syntheses, but notably in the synthesis of alkenes, dienes and polyenes. Thus α-alkylallyl tolyl sulfones afford terminal alkenes regioselectively when treated sequentially with 2 equiv. of tin hydride and concentrated hydrochloric acid (Scheme 117, entry b).[509] Allyltin derivatives, which are intermediates in this transformation, can be isolated if the acidic treatment is omitted (Scheme 117, entry a).

Allyl sulfones produce 1,3-dienes directly on sequential reaction with *n*-butyllithium and tri(*n*-butyl)stannylmethyl iodide.[492] Interestingly, the reaction is completely stereoselective as the (*E*)- or (*Z*)-1,3-dienes are obtained selectively from (*E*)- or (*Z*)-sulfones.[492] The procedure has been applied[492] to the synthesis of the major sex pheromone of the red bollworm moth. Ferruginol, which is a precursor of taxodione, a tumor inhibitory diterpene, has been prepared[495] by coupling of $C_{10}$ units between 2-(phenylsulfonylmethyl)-1,3,3-trimethylcyclohexane and 3-isopropyl-4-methoxybenzyl bromide followed by desulfonation and acid-catalyzed cyclization. The same α-metallo sulfone also proved to be a valuable precursor of other alicyclic terpenoids, such as deoxytrisporone[499] and the methyl ester of vitamin A acid.[500] Allylation of related metalloalkyl sulfones followed by base-assisted desulfonation of the resulting sulfones has been used in several different syntheses of vitamin A[491,493,503,507] (selected syntheses of vitamin A using allylic sulfones are gathered in Scheme 118 and Scheme 115, entry c) as well as in syntheses of retinoic acid methyl ester,[508] of the 11-*cis*-locked cyclopentatrienylidene retinals,[490] and of carotenoids[498,502] including β-carotene.[502]

The allylation of α-metalloallyl sulfones followed by reduction of the carbon–sulfur bond, usually with lithium in ethylamine,[36,494,501,504,510] or with Na/Hg[501,506] (the first cited method being the most se-

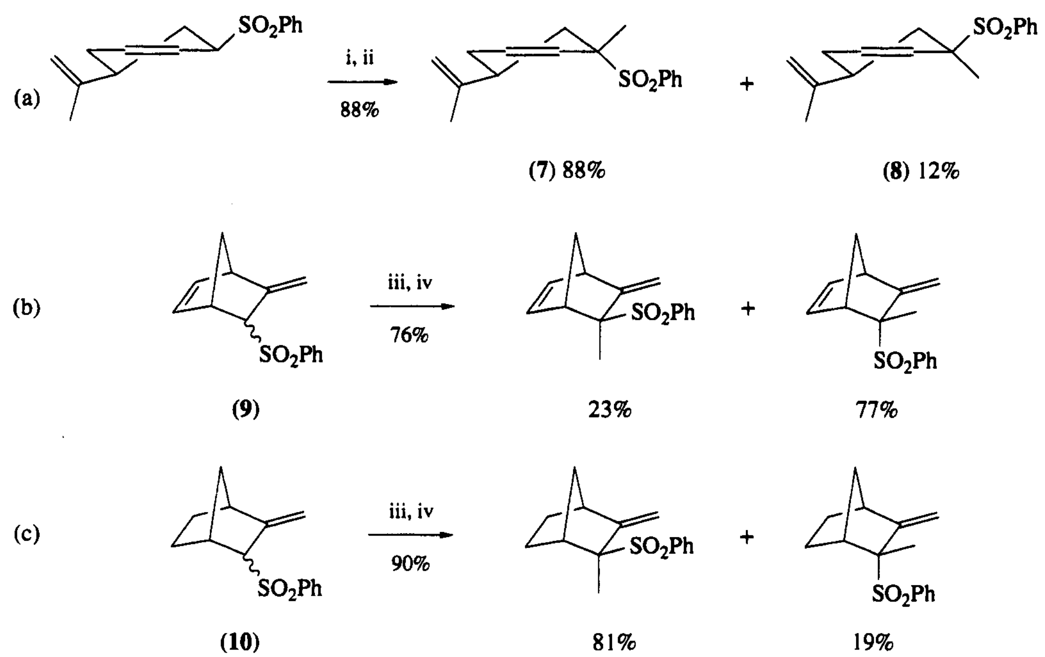

i, LDA, THF; ii, MeI; iii, $Bu^nLi$, –78 °C, 0.7 h; iv, MeI, –78 to 20 °C

**Scheme 116**

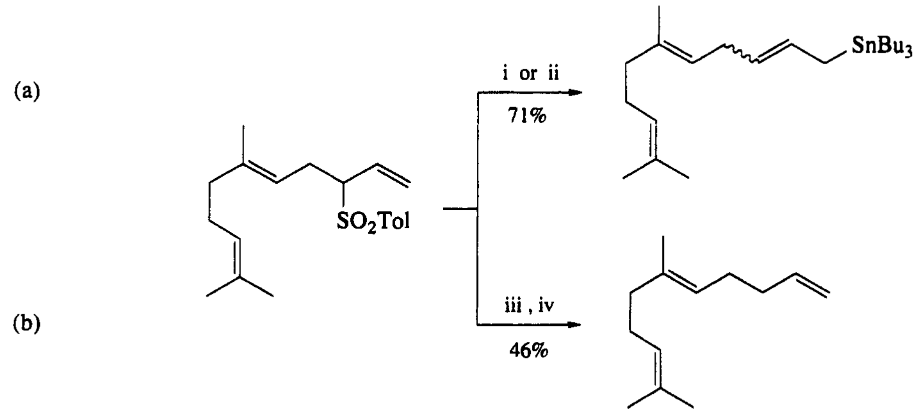

i, $Bu_3SnH$, AIBN, benzene, Δ, 2 h; ii, hv, 20 °C, 10 h; iii, $Bu_3SnH$, AIBN, Δ, 2 h; iv, conc. HCl, 20 °C, several hours

**Scheme 117**

lective one), has been used in stereoselective syntheses of squalene (Scheme 25, entry a),[506] bisgeranyl[506] and several polyprenols, including (*Z,Z*)-farnesol (*Z,Z,Z*)-nerylnerol,[504] solanesol[497,501] and a series of betulaprenols.[494] Related reactions involving allyl sulfones and α,β-unsaturated epoxides have also allowed the syntheses of linalol, (*Z*)-nerolidol and vitamin A (Scheme 119, entry a).[481]

The α-lithioallylic sulfone (**11a**; Scheme 119, entry b) obtained upon deprotonation with *n*-butyllithium in THF–HMPA of the corresponding carbon acid undergoes smooth coupling with the epoxymagnesio alkoxide (**12a**) at –78 °C to give the β,γ-dihydroxy sulfone diol (**13**) in high yield. A facile coupling is also observed when the same epoxide (**12a**) is reacted with the related lithiated sulfide (**11b**). In contrast, the epoxy lithium alkoxide (**12b**) is only slowly attacked by the lithiated sulfide (**11b**), but not at all by the lithiated sulfone (**11a**).[202]

Stereoselective syntheses of (*E,Z*)- and (*E,E*)-conjugated dienes have also been performed, with alkylation of 3-sufolenes as the key step (Scheme 120; Scheme 121).

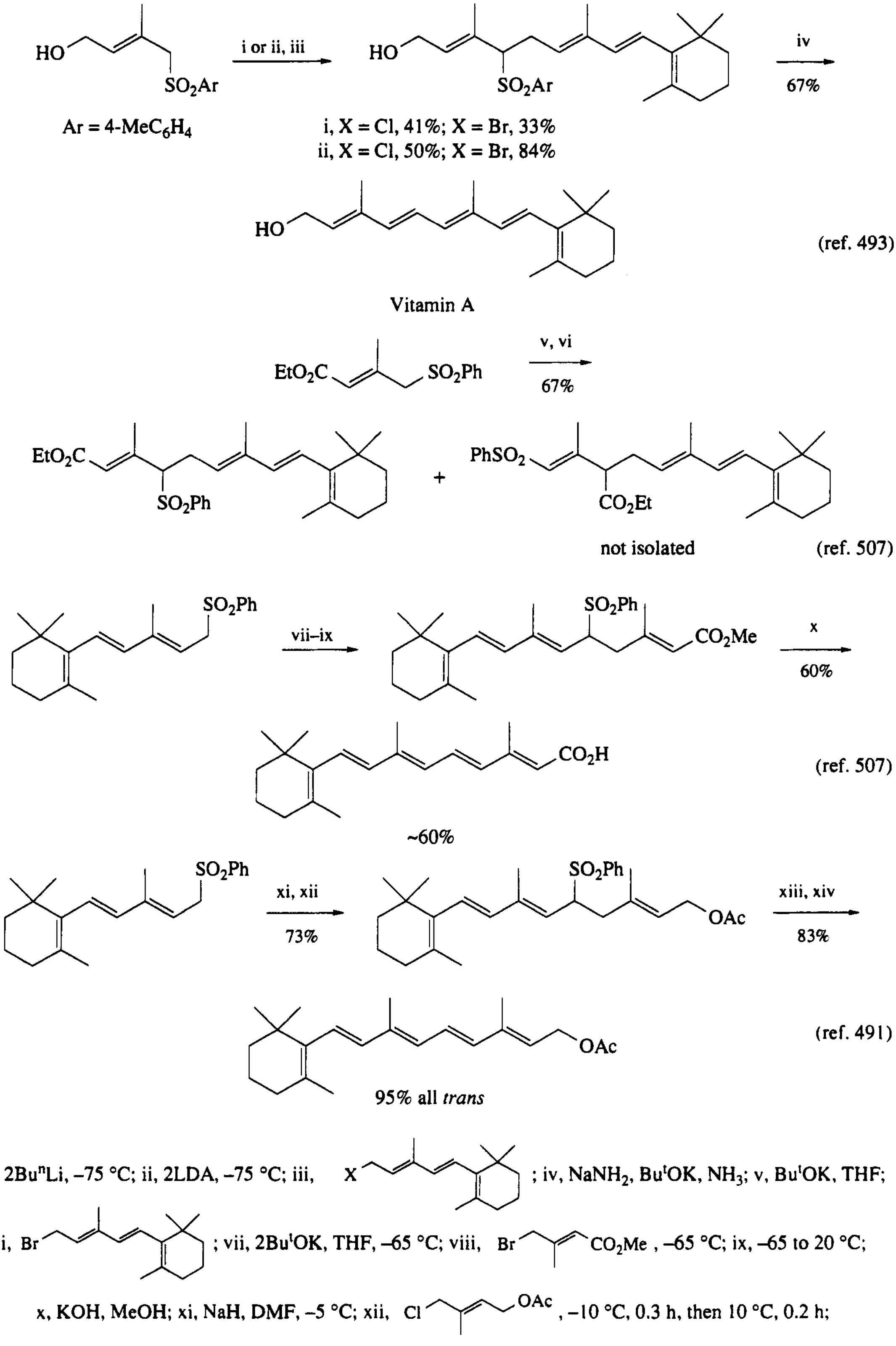
HO
SO2Ar
Ar = 4-MeC6H4
i or ii, iii
HO
SO2Ar
i, X = Cl, 41%; X = Br, 33%
ii, X = Cl, 50%; X = Br, 84%
iv
67%
HO
Vitamin A
(ref. 493)
EtO2C
SO2Ph
v, vi
67%
EtO2C
SO2Ph
+
PhSO2
CO2Et
not isolated
(ref. 507)
SO2Ph
vii–ix
SO2Ph
CO2Me
x
60%
CO2H
(ref. 507)
~60%
SO2Ph
xi, xii
73%
SO2Ph
OAc
xiii, xiv
83%
OAc
(ref. 491)
95% all *trans*
X
Br
Br
CO2Me
Cl
OAc

i, 2Bu$^n$Li, –75 °C; ii, 2LDA, –75 °C; iii, ; iv, $NaNH_2$, Bu$^t$OK, $NH_3$; v, Bu$^t$OK, THF;

vi, ; vii, 2Bu$^t$OK, THF, –65 °C; viii, , –65 °C; ix, –65 to 20 °C;

x, KOH, MeOH; xi, NaH, DMF, –5 °C; xii, , –10 °C, 0.3 h, then 10 °C, 0.2 h;

xiii, EtONa, EtOH; xiv, $Ac_2O$, $Et_3N$

**Scheme 118**

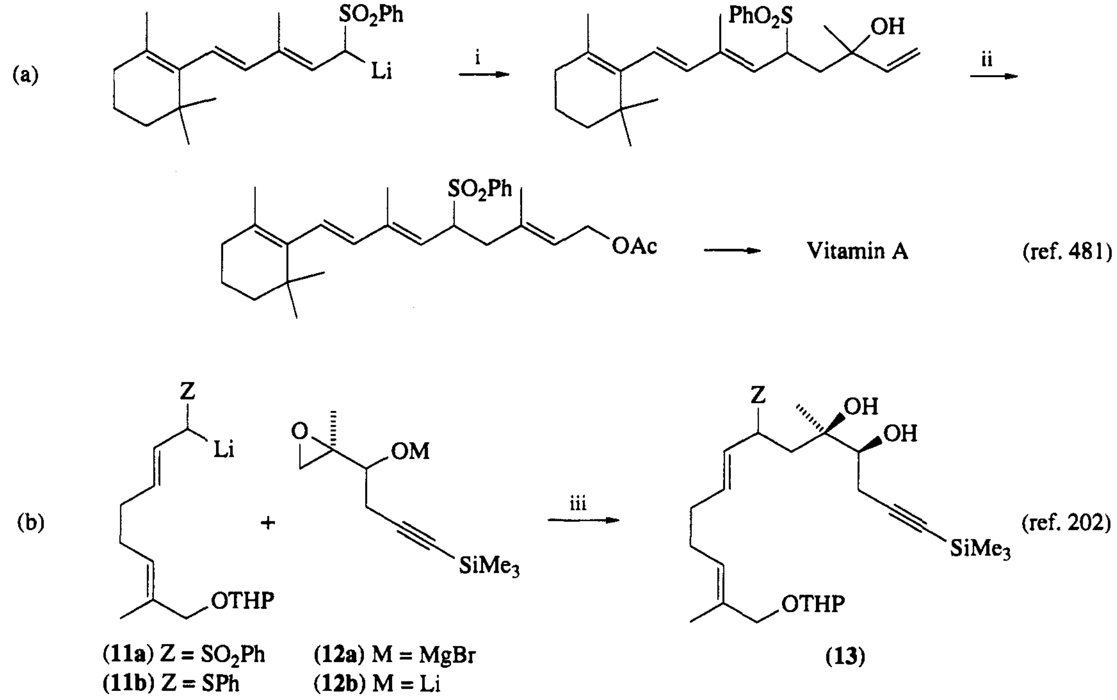

**(11a)** Z = $SO_2Ph$
**(11b)** Z = SPh

**(12a)** M = MgBr
**(12b)** M = Li

**(13)**

| | | | | |
|---|---|---|---|---|
| **(11a)** | + **(12a)**, | 6 h, | 70% |
| **(11b)** | + **(12a)**, | 0.5 h, | 77% |
| **(11a)** | + **(12b)**, | 6 h, | 9% |
| **(11b)** | + **(12b)**, | 0.5 h, | – |

i, 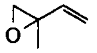 , THF, –78 to 20 °C, 4 h; ii, AcOH, $Ac_2O$, TosOH, 0 °C, 3 h; iii, THF–HMPA, –78 °C

**Scheme 119**

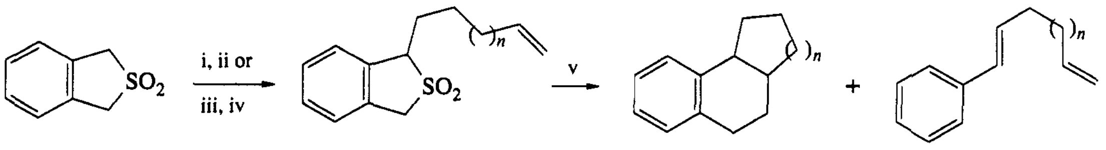

i, ii: *n* = 1, 76%; *n* = 2, 61%
iii, iv: *n* = 3, 52%

*n* = 1, 95% (90:10); *n* = 2, 87% (92:8)

i, LITMP, –78 °C, HMPA; ii, 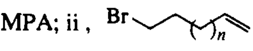 , –78 to 0 °C; iii, BuLi, –78 °C;
iv, 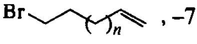 , –78 to –10 °C; v, Δ

**Scheme 120**

Although the 3-sulfolene α-carbanion is labile it is possible to synthesize the mono- and the di-alkylated derivatives by performing the metallation in the presence of an alkylating agent.[511–513] The most successful conditions have used lithium hexamethyldisilazide in THF as the base in the presence of HMPA as the cosolvent.[511] The reactions proceed in reasonable yield with primary alkyl iodides, including functionalized ones, and also with benzyl iodides and lead to α-monoalkylated derivatives (Scheme 121, entry a). It is much less efficient with the corresponding bromides and does not occur with *s*-alkyl halides.[511,512] A remarkable directing effect of the substituent on the double bond of 3-sulfolene has been found in reactions with alkyl iodides[510,514] or allylic bromides.[513] Electron-donating groups effect selective substitution at the 2-position while electron-withdrawing groups effect exclusive substitution at the 5-position (Scheme 121, entries c and d).[510,514] Vitamin D–sulfur dioxide adducts can be alkylated regioselectively at either the 6-position when the adduct is treated with sodium hydride in the presence of an alkyl iodide,[515] or at the 19-position when the adduct is treated under similar conditions but with a stronger and more bulky base such as lithium tetramethylpiperidide.[515,516]

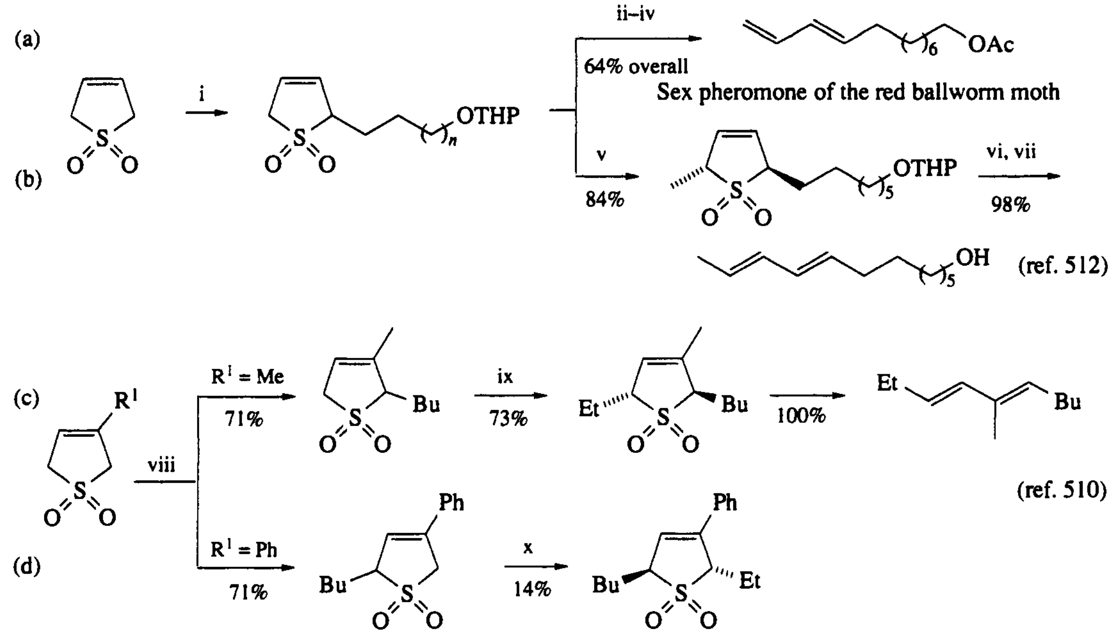

i, I $\sim(\sim)_n\sim$ OTHP, $(Me_3Si)_2NLi$, HMPA; ii, PPTS, MeOH, $CH_2Cl_2$; iii, $Ac_2O$, pyridine; iv, $NaHCO_3$, aq. EtOH, 125 °C; v, MeI, $(Me_3Si)_2NLi$, HMPA; vi, PPTS, MeOH; vii, $K_2CO_3$, aq. EtOH, 125 °C; viii, 0.5BuI, $0.5(Me_3Si)_2NLi$, HMPA; ix, EtI, THF, HMPA; x, EtI, THF, HMPA, 7 °C

Scheme 121

The alkylation of 2-alkyl-substituted sulfolenes takes place with complete regio- and high stereo-selectivity to yield approximately 60% of *trans*-2,5-disubstituted 3-sulfolenes. When 1,4-diiodobutane[517] and 1,3-diiodopropane[517] are used instead, one-pot dialkylation occurs at the 2-position in the first case and leads to a spiro sulfolene, whereas 2,3-dialkylation proceeds in the second case leading to a fused bicyclic product. Interestingly 2,5-dialkylation has been achieved, from 3-bromo(bromomethylpropene), thus allowing the synthesis of bicyclo[3.2.1]sulfones.[517]

Sulfolenes are valuable precursors of 1,3-dienes. Thermolytic desulfonylations of 2,5-disubstituted derivatives lead exclusively to (*E,Z*)-dienes in agreement with the symmetry rules.[435] The stereoselectivity of the reaction is dramatically changed however by carrying out the reaction in a protic solvent and in the presence of a base (which probably isomerizes the *trans* sulfolene to the *cis* isomer), since (*E,E*)-dienes are now obtained exclusively and contrary to the symmetry rules.[435] α-Metallo sulfolenes may be viewed therefore as masked 1,3-dienyl anion equivalents ($^-$C═C—C═C—R). The above mentioned set of reactions has been used for the regioselective syntheses of 6- and 16-alkyl-substituted vitamin $D_3$ analogs,[515,516] as well as *trans*-β-ocimene[513] and α-farnesene.[513]

Related reactions have been reported by Oppolzer[457] from the benzosulfolene derivative shown in Scheme 120 which has proved to be a valuable precursor of *o*-quinodimethane, and by Bloch[518] from the corresponding cyclopentadiene–sulfolene adduct.

### 1.3.6.3 Reactions Involving α-Metallovinyl Sulfones

The alkylation of α-lithiovinyl sulfones, which are available by metallation[519,520] of vinyl sulfones or by bromine–lithium exchange[519] on α-bromovinyl sulfones, takes place efficiently when the β-carbon carries an aryl, a methyl or a methoxy group (Scheme 122, entries a, b and d). Surprisingly however the alkylation does not proceed with the β-alkoxymethyl-substituted derivatives (Scheme 122, entry c).[479]

The chemistry of sulfoximides (sulfoximines)[62] is somewhat related to that of sulfones.[8,35–38] Although several methods are available for the preparation of free sulfoximines from di- and tri-valent sulfur compounds, the methods are of limited applicability when the desired sulfoximines contain labile functional groups. An alternative approach involving alkylating the readily available anion derived from *N*-substituted methylsulfoximides has been described[521] but preparation of the free sulfoximides has proved

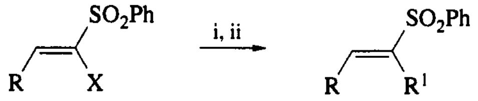

(a) X = H; R = Ph, Me; $R^1$ = Me, Bu; 75–90%

(b) X = Br; R = Ph, Me; $R^1$ = Me; 75–90%

(c) X = H; R = $CH_2OLi$; $R^1$ = alkyl; 0%

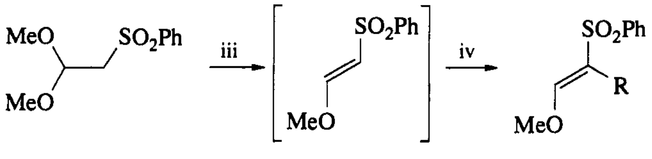

RX = MeI, 88%; RX = $PhCH_2Br$, 77%

i, MeLi, THF, –95 °C; ii, $R^1I$; iii, $Bu^nLi$; iv, $Bu^nLi$, RX

Scheme 122

difficult.$^{522}$ These compounds have in fact been synthesized on reaction of *S*-lithiomethyl-*N*-trimethylsilyl-*S*-phenylsulfoximide with alkyl halides or epoxides, followed by ready desilylation with bis(trimethylsilyl)acetamide (BSA) or (trimethylsilyl)diethylamine (Scheme 123).$^{522}$

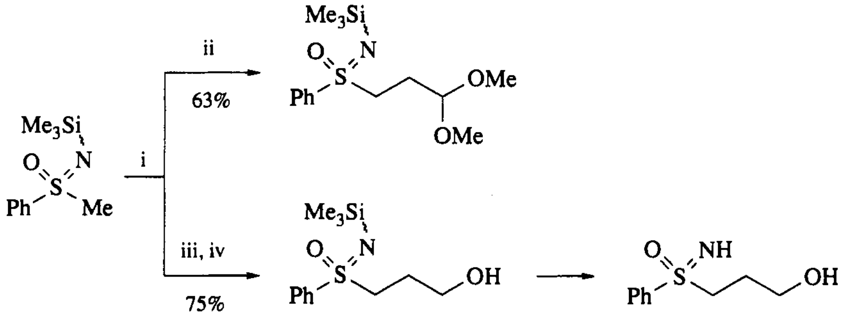

i, BuLi, THF, –78 °C; ii, $BrCH_2CH(OMe)_2$, HMPA, –78 to 20 °C, 16 h; iii, , –78 to 0 °C, 1 h; iv, $H_3O^+$

Scheme 123

### 1.3.6.4 Reactions Involving α-Metallo-α-heterosubstituted Alkyl Sulfones

Alkylation reactions of α-metallo sulfones bearing another heteroatomic moiety at their α-site have been widely used in synthesis. These reactions include the alkylations of α-isocyanoalkyl sulfones$^{449,523,524}$ α-alkoxyalkyl sulfones$^{36,345,525-527}$ (including 2-benzenesulfonyltetrahydropyrans$^{527}$) α-haloalkyl$^{528}$ or α-haloallyl$^{529}$ sulfones, α-silylalkyl sulfones,$^{530}$ α-sulfonylalkyl$^{380,531-535}$ and α-sulfonylalkenyl$^{536,537}$ or α-triflylalkyl$^{538,539}$ sulfones. Among these compounds alkoxyalkyl phenyl sulfones (Scheme 75, entries a and d)$^{36,345,526}$ and tosylmethyl isocyanide (TosMIC)$^{449,523,524}$ have been used as precursors of acyl anion equivalents, the latter being the most popular due to the ease with which it can be metallated.

#### *1.3.6.4.1 Reactions involving 2-lithio-2-benzenesulfonyltetrahydropyrans*

2-Lithio-2-benzenesulfonyltetrahydropyrans which are readily available on metallation ($Bu^nLi$, THF, 78 °C) of 2-benzenesulfonyltetrahydropyrans, have been alkylated$^{527a,b}$ with a large variety of organic halides including allyl (Scheme 124, entry a), alkyl and benzyl halides (Scheme 124, entry b) as well as with 3- or 4-(3-tetrahydro-2*H*-pyran-2-yl)oxy- or (*t*-butyldimethylsilyl)oxy-1-haloalkanes (Scheme 124, entry c). Benzenesulfinic acid is usually eliminated spontaneously from the intermediate alkylated products as the reaction warms to room temperature, presumably due to the slightly basic medium and the inherent leaving ability of the benzenesulfonyl group. The *endo* hydrogen is usually removed (Scheme

124, entry a), except with the allylated product, (Scheme 124, entry b) in which case the *exo* hydrogen is taken off selectively. Many of the resulting enol ethers undergo acid-catalyzed cyclization to spiroketals, which are found in many natural products (Scheme 124, entry c). This sequence of reactions has been used for the synthesis of several insect pheromones such as those derived from the olive fly *Dacus oleae* (Scheme 124, entry c)[527a,b] and the common wasp *Paravespula vulgaris*.[527a]

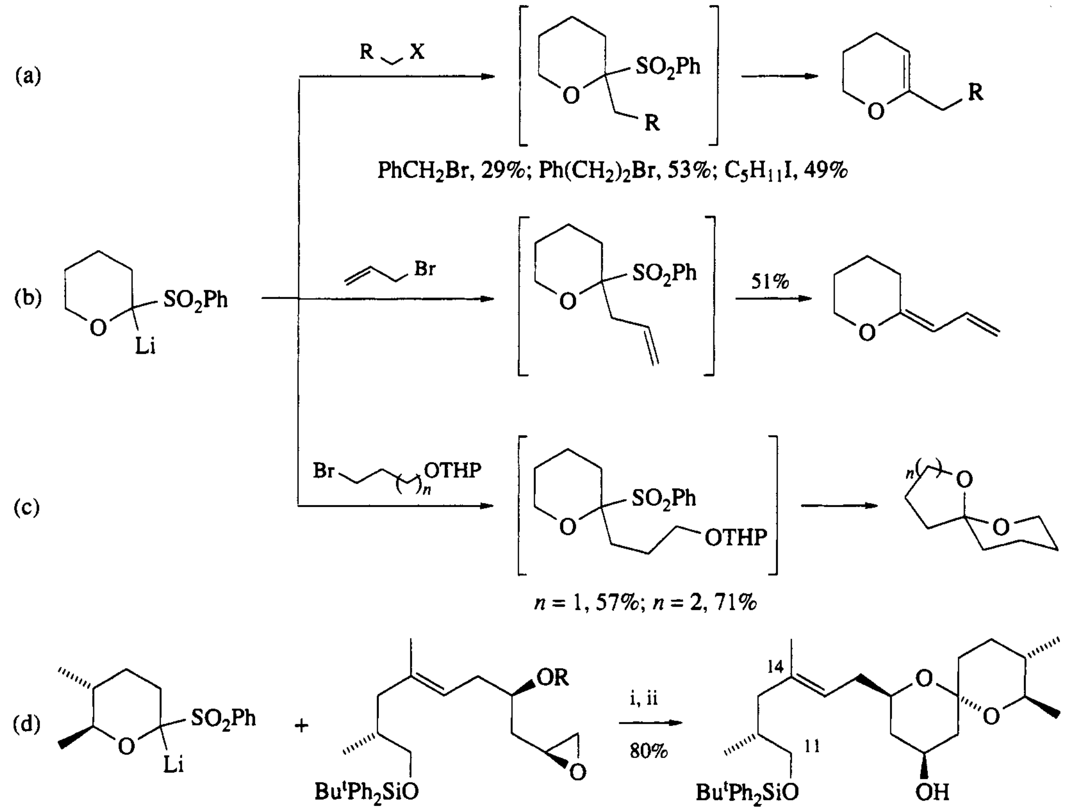

PhCH$_2$Br, 29%; Ph(CH$_2$)$_2$Br, 53%; C$_5$H$_{11}$I, 49%

$n$ = 1, 57%; $n$ = 2, 71%

i, Ti(OPr$^i$)$_4$; ii, 5% H$_2$SO$_4$

**Scheme 124**

2-Lithio-2-benzenesulfonyltetrahydropyrans also add[527c] to epoxides which contain additional oxygen functionality to permit, after acid hydrolysis, spiroketal formation. The whole process, which is an extremely rapid and efficient entry to hydroxy substituted spiroketals, has allowed the synthesis of a minor component of the insect pheromone derived from the olive fly *Dacus oleae*[527c] as well as of the C-11 to C-25 fragment of the milbemycins which are potent antiparasitic agents (Scheme 124, entry d). In the latter case the epoxide ring opening was carried out in the presence of titanium isopropoxide. In all of these reactions the lithio sulfones behave as the equivalents of 2-lithiodihydropyrans, but with the added advantage that the initial sulfones are stable, crystalline and easily handled materials.

### *1.3.6.4.2 Reactions involving α-isocyanoalkyl sulfones*

TosMIC can be efficiently alkylated with primary alkyl halides, isopropyl iodide and benzyl bromide both to the corresponding mono-[523] or di-alkyl[449] derivatives using NaH in DMSO or 40% aq. NaOH in CH$_2$Cl$_2$[449,523] and in the presence of Bu$^n$$_4$NI (Scheme 125). The resulting compounds have then been transformed to aldehydes and ketones, including cycloalkanones,[449] and the method has been successfully applied to the synthesis of optically active 2-methylcyclobutanone from the chiral sulfonylmethyl isocyanide and 1,3-dibromobutane.[524]

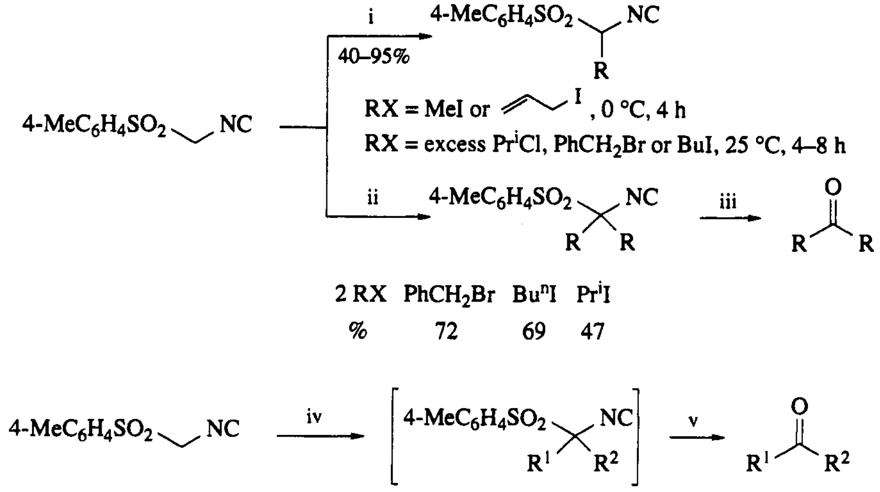

| 2RX | $PhCH_2Br$ | $Bu^nI$ | $Pr^iI$ |
|---|---|---|---|
| % | 72 | 69 | 47 |

$R^1 = PhCH_2$: $R^2$ = Me, 58%; $R^2 = Bu^i$, 41%

i, aq. NaOH, $CH_2Cl_2$, $Bu^n{}_4NI$, RX; ii, aq. NaOH, $CH_2Cl_2$, $Bu^n{}_4NI$, 2RX; iii, 38% HCl; iv, aq. NaOH, $CH_2Cl_2$, $Bu^n{}_4NI$, $R^1I$, 0.5 h, then $R^2I$; v, 38% HCl

Scheme 125

### *1.3.6.4.3 Reactions involving α-sulfinyl sulfones*

1,1-Disulfones have been increasingly used in synthesis over the last decade. Their alkylation takes place smoothly and has allowed a large variety of synthetically useful reactions (Scheme 127; Scheme 128; Scheme 129).[380,531,532,535–537] Although most of the alkylations have been carried out *via* metallation of the corresponding carbon acid (see below), some of the alkylations have been performed[540] on the sodium, potassium or copper salts derived from the ring opening of 1,1-di(benzenesulfonyl)cyclopropane, performed with a variety of nucleophilic reagents (Scheme 126).

These nucleophilic reagents include thiolates, alkoxides, metallo amides, Grignard reagents in the presence of copper salts, and enolates.[540] The reductive cleavage of the sulfonyl moiety in protic media, which can be readily achieved by lithium phenanthrenide, offers the opportunity to pursue further carbanionic chemistry. Therefore this new conjunctive reagent[540] can serve as the equivalent of species such as $^+CH_2CH_2CH_2^-$ and $^+CH_2CH_2CH^{2-}$ as well as $^+CH_2CH_2C^{3-}$. Furthermore, homoallyl and allyl disulfones have proved valuable precursors of 1,3-dienes[537] and (*E*)-alkenes,[536] respectively (Scheme 127, entries a and b). The former derivatives have been produced stereoselectively by allylation of 1,1-di(sulfonyl)methane with (*Z*)- or (*E*)-allyl halides and they can be transformed to the corresponding (*Z,E*)- or (*Z,Z*)-1,3-dienes respectively by a sequence of reactions which involves the reduction of one of the two sulfonyl groups, followed by the elimination of the remaining one (Scheme 127, entry a).[537]

This route to 1,3-dienes is more efficient than the more direct one employing homoallyl sulfones.[537] 1,1-(2-Alkenyl) disulfones display[536] only (*E*)-geometry, whereas corresponding monosulfones are difficult to isolate at the same level of stereochemical purity (*i.e. ca.* 20% of the (*Z*)-isomer at equilibrium). Alkylation, which can be readily achieved in the presence of NaH in DMF, takes place predominantly at the α-position, but less selectively than with the corresponding monosulfone (α:γ ratio 90:10 instead of 100:0) probably due to the steric hindrance of the two bulky sulfonyl groups (Scheme 127, entry b). The product resulting from the α-alkylation leads quantitatively to the (*E*)-allylic sulfone on reduction with aluminum amalgam (Scheme 127, entry b)[536] or to (*E*)-alkene upon total reduction by lithium in ethylamine.[536]

1,1-Disulfonyl-cycloalkanes[534,535] and -cycloalkenes[380,531] have been synthesized by treatment of ω-halo-alkyl- or -alkenyl 1,1-disulfones with sodium ethoxide in ethanol or from 1,1-di(sulfonyl)methylmetals and 1,4-dihalo-(2*Z*)-alkenes, respectively (Scheme 127, entry c; Scheme 128, entry a).

The rate of cyclization of the 1,1-di(phenylsulfonyl) carbanion bearing distal leaving groups has been determined[534,535] and proved to be very sensitive to the ring size. For iodides in ethanol the ratios for ring size 3:4:5:6:7 are $1:1.1 \times 10^{-5}:1.0 \times 10^{-2}:1.6 \times 10^{-6}:1.6 \times 10^{-6}:7.3 \times 10^{-10}$. The contribution of strain in the product to the enthalpy of activation is slight, whereas the entropy of activation for cyclopropane formation is so favorable as to make this by far the most rapid process observed.[534,535] 1,1-Di(sulfonyl)cy-

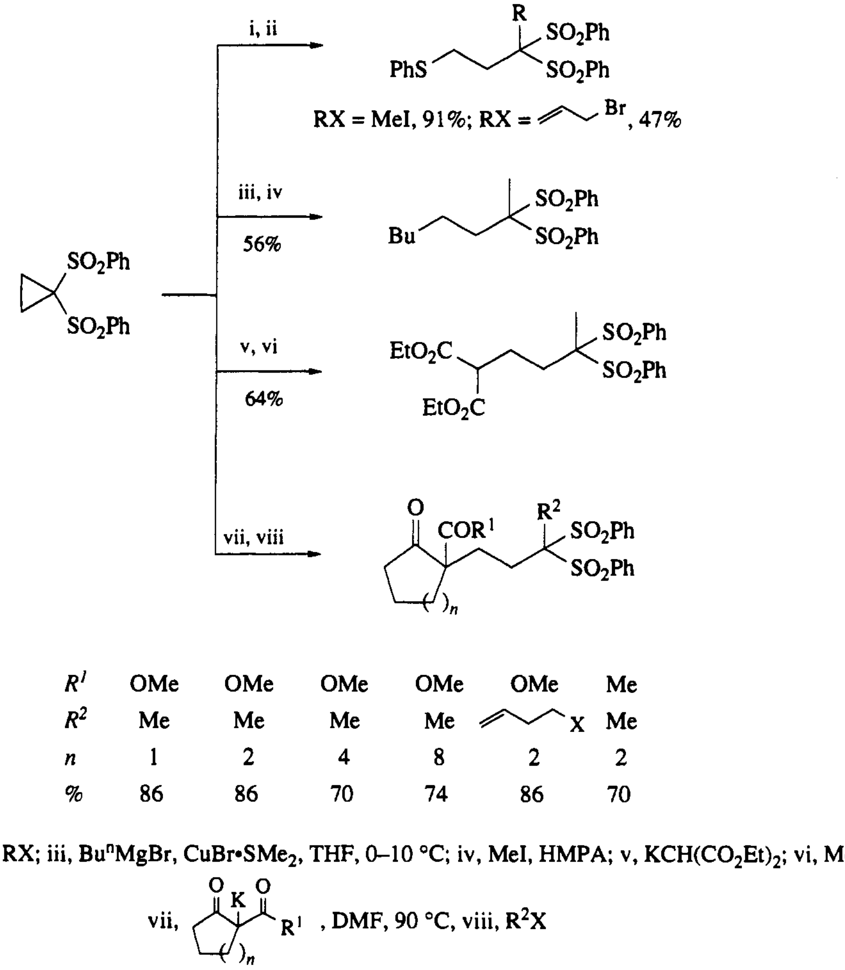

| $R^1$ | OMe | OMe | OMe | OMe | OMe | Me |
|---|---|---|---|---|---|---|
| $R^2$ | Me | Me | Me | Me | $CH_2{=}CHCH_2X$ | Me |
| $n$ | 1 | 2 | 4 | 8 | 2 | 2 |
| % | 86 | 86 | 70 | 74 | 86 | 70 |

i, PhSNa, DMF; ii, RX; iii, Bu$^n$MgBr, CuBr•SMe$_2$, THF, 0–10 °C; iv, MeI, HMPA; v, KCH(CO$_2$Et)$_2$; vi, MeI; vii, , DMF, 90 °C, viii, R$^2$X

Scheme 126

clopent-3-ene, produced from the allylation of di(sulfonyl)methane with 1,4-dihalo-2-alkenes, has been transformed selectively to cyclopentene and to 3-cyclopentenone derivatives by di-reduction (Na/Hg) or by sequential mono-reduction and oxidation α to the sulfonyl moiety (Scheme 128, entry a). Therefore 1,1-di(sulfonyl)methane plays the role of masked dimetallomethane and formyl dianion equivalents.[531]

1,1-Di(sulfonyl)alkanes have been reacted with allylic epoxides in the presence of polymerically bound transition metal catalysts.[532] This reaction has allowed the synthesis of macrolides in a sequence of reactions in which neither the nucleophilic nor the electrophilic centres are unmasked until the substrate encounters an active site on the polymer (Scheme 127, entry d). The sequence is completely regioselective since it occurs at only one (the terminal alkene) of the three potential active sites, and provides, in around 70% yield, a single 17- or 27-membered ring macrolide from the corresponding substrates.[39,532]

The alkoxydi(sulfonyl)methane shown in Scheme 128 (entry b) has been used as a useful carbonyl 1,1-dipole synthon (±C=O). Its alkylation with alkyl halides is best achieved using $Cs_2CO_3$ in DMF at 50 °C, and its palladium-catalyzed allylation requires the use of phase-transfer conditions (Scheme 128, entry b).[533] The unmasking of the carbonyl group was then achieved by reacting the resulting disulfone with boron trichloride (–78 °C, $CH_2Cl_2$) followed by the addition of alcohols or amines to provide esters or amides respectively (Scheme 128, entry b).[533]

Finally, α-triflyldimethyl sulfone ($CF_3SO_2CH_2SO_2Me$) is a reagent which allows successive polyalkylations of the $CH_2$ and $CH_3$ carbon centers with regiocontrol (Scheme 129). The polyalkylated triflylsulfones then undergo Ramberg–Bäcklund reactions with loss of triflinate anion and extrusion of sulfur dioxide to form alkenes (Scheme 129, entry e).[538,539]

In synthetic terms the net structural change is equivalent to regiospecific alkylation of tetrametalloethylene ($M_2C{=}CM_2$). The monoalkylated derivative is available on alkylation of the α,α-dilithio-

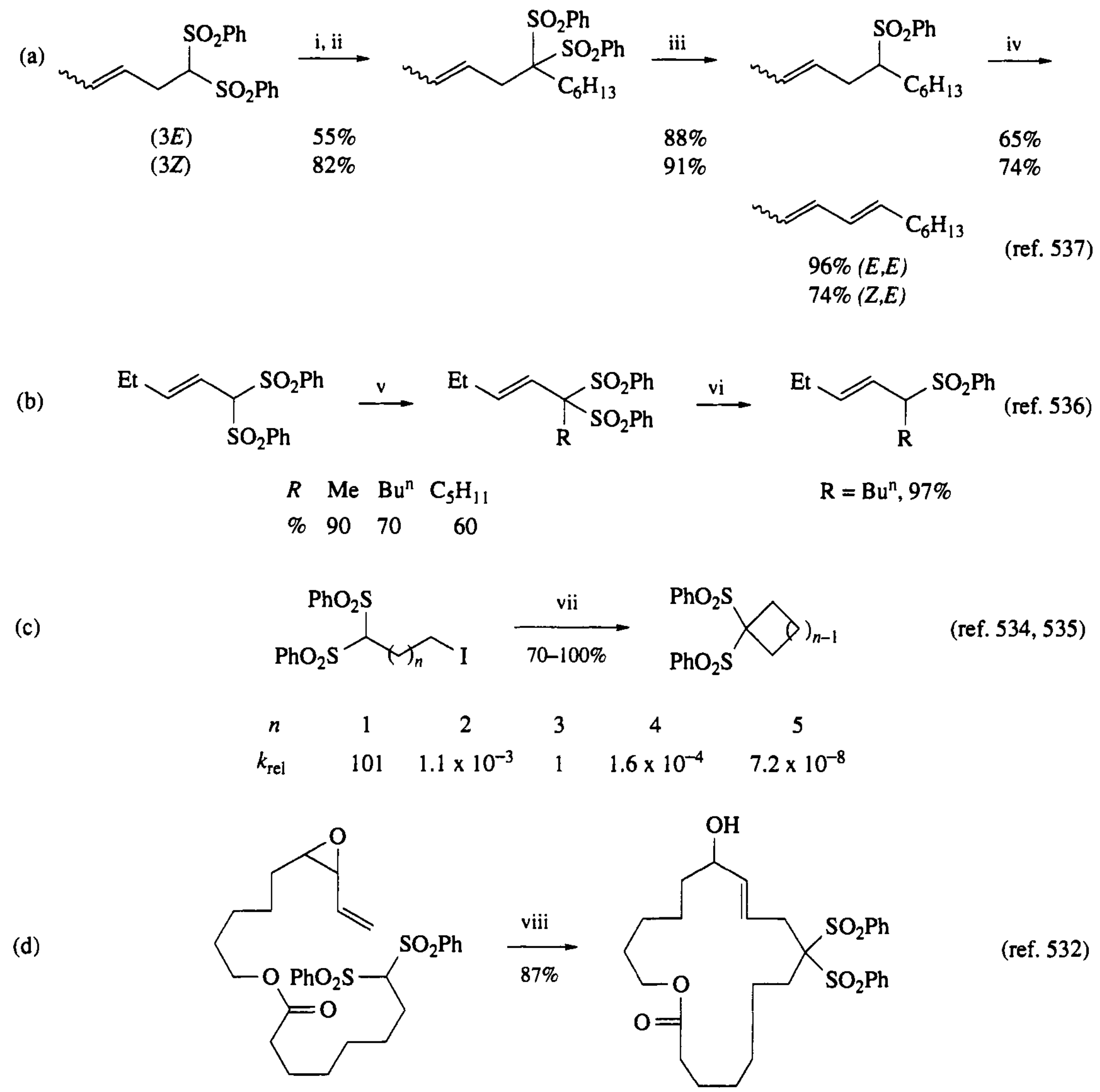
(a)
i, ii
iii
iv
(3E) 55% 88% 65%
(3Z) 82% 91% 74%
96% (E,E)
74% (Z,E)
(ref. 537)
(b)
v
vi
R Me Bu$^n$ $C_5H_{11}$
% 90 70 60
R = Bu$^n$, 97%
(ref. 536)
(c)
vii
70–100%
n 1 2 3 4 5
$k_{rel}$ 101 $1.1 \times 10^{-3}$ 1 $1.6 \times 10^{-4}$ $7.2 \times 10^{-8}$
(ref. 534, 535)
(d)
viii
87%
(ref. 532)

i, NaH, DMF, 80 °C, 5 to 15 h; ii, $C_6H_{13}I$; iii, Al/Hg, THF, $H_2O$, 20 °C, 1 h; iv, Bu$^t$OK, THF; v, NaH, DMF, 70 °C, RI; vi, Al/Hg, THF, 0 °C, 3 d; vii, 0.5 M EtONa, EtOH; viii, polymerically bound Pd, THF, 20 °C, 0.3 h

**Scheme 127**

methane derivative (Scheme 129, entry a), whereas the α,α′-dialkylated compounds can be selectively synthesized from the corresponding α,α,α′-trilithio compound (Scheme 129, entry b). Further alkylations of the above mentioned derivatives, as well as one example of alkene formation, are displayed in Scheme 129 (entries c, d and e).

## 1.3.7 ALKYLATION OF SULFUR YLIDES

Several examples of the alkylation of sulfur ylides are known.[41,541–544] This reaction is particularly useful for the synthesis of *s*-alkyl diphenylsulfonium salts which cannot otherwise be prepared from diphenyl sulfide, *s*-alkyl iodides and silver tetrafluoroborate, since the latter reaction usually leads to a mixture of regioisomeric sulfonium salts.[41] Diphenylsulfonium methanide on reaction with [$^{14}$C]methyl iodide allows the synthesis of [$^{14}$C]isopropyl diphenyl sulfonium salt which has been used for the synthesis of [$^{14}$C]-2,3-epoxysqualene[545] (Scheme 130, entry a). This reaction unfortunately is not general

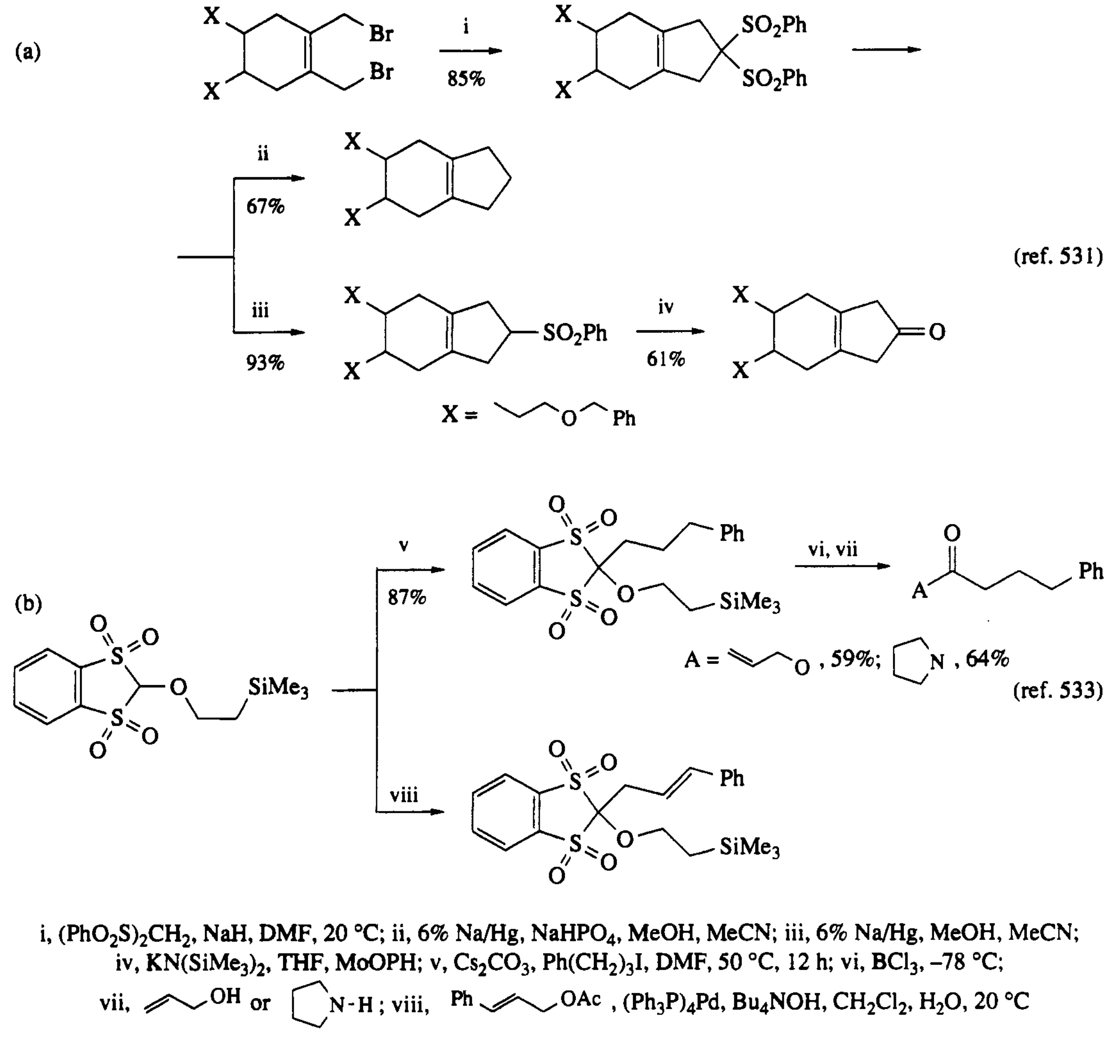

i, $(PhO_2S)_2CH_2$, NaH, DMF, 20 °C; ii, 6% Na/Hg, $NaHPO_4$, MeOH, MeCN; iii, 6% Na/Hg, MeOH, MeCN; iv, $KN(SiMe_3)_2$, THF, MoOPH; v, $Cs_2CO_3$, $Ph(CH_2)_3I$, DMF, 50 °C, 12 h; vi, $BCl_3$, −78 °C; vii, OH or N-H ; viii, Ph OAc , $(Ph_3P)_4Pd$, $Bu_4NOH$, $CH_2Cl_2$, $H_2O$, 20 °C

Scheme 128

and, for example, attempted methylation of diphenyl sulfonium allylide, a more stable ylide, has led only to recovered starting material.[546]

Intramolecular alkylations of ylides appear facile.[41,543] For example, the cyclizations of diphenyl-3-halo-1-propylsulfonium fluoroborate and 3-halo-1-butylsulfonium fluoroborate proceed[543] on reaction with suitable bases at 25 °C *via* the intermediate ylides (Scheme 130, entry b). The chloro derivatives have proved more efficient than the corresponding iodides.[543] Low temperature methylations of five- and six-membered sulfur ylides have been performed,[542,547] and all three methylations shown in Scheme 130 (entry c) occur with a high degree of stereoselectivity on the thianium salts since a *trans* arrangement of the entering methyl and the *S*-phenyl groups is always obtained. The behavior closely matches that observed with the corresponding thiane-1-oxides (see Section 1.3.5.1.1.i). Thiolanium ylides however appear to react without any significant stereoselectivity (Scheme 130, entry d).[547] Dimethylsulfoxonium methanide reacts with diazomethane, iodoethane and dimethyl sulfate to form complex mixtures of products.[43] This is not the case of aryl(dimethylamino)oxosulfonium ethanide, whose sequential metallation and methylation produces aryl(dimethylamino)oxosulfonium isopropanide.[548] The intramolecular version of this reaction has been used for the synthesis of the corresponding cyclopropyl derivative (Scheme 130, entry e).[136]

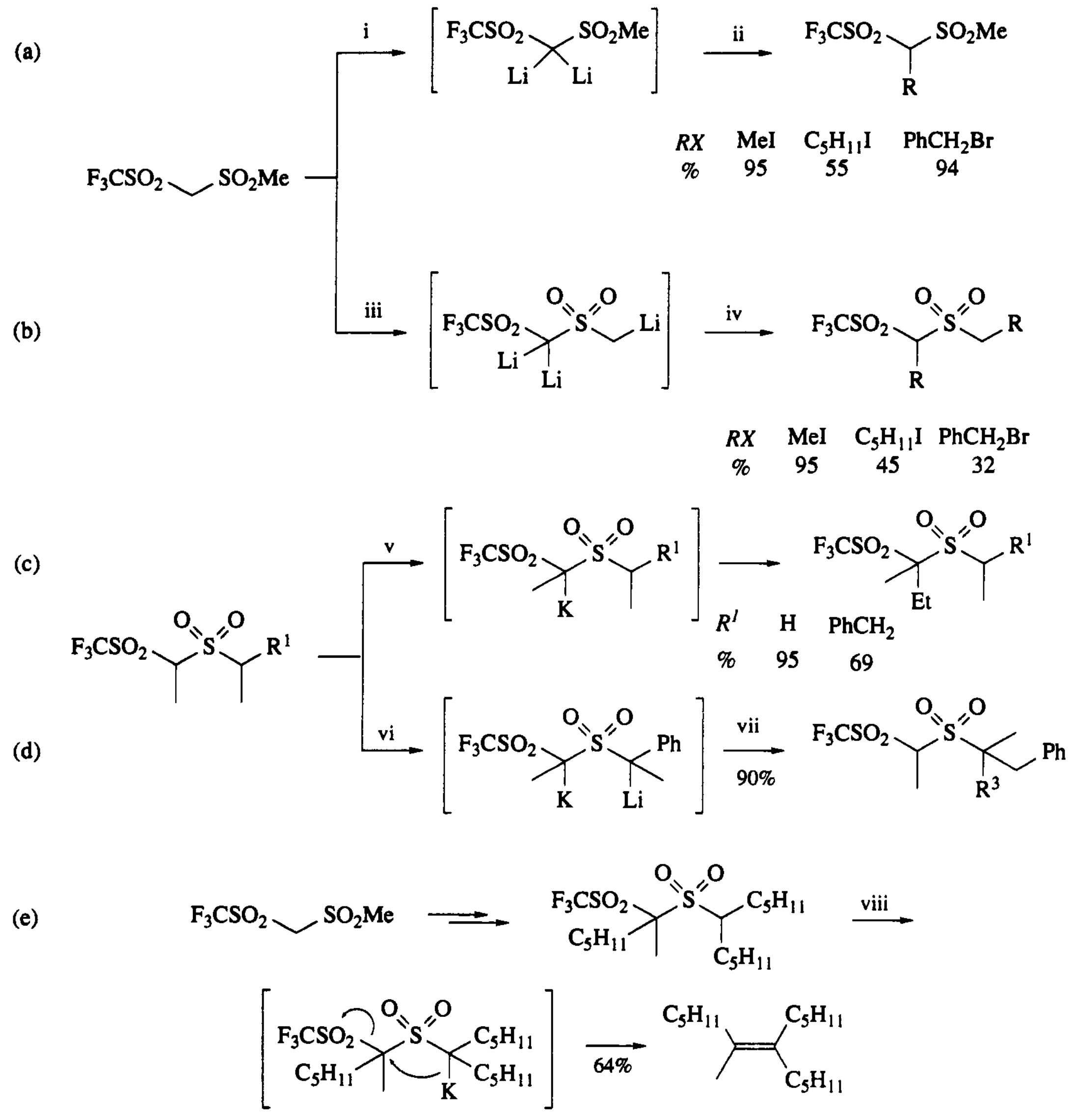

i, 2 $Bu^nLi$, THF, −78 to −55 °C, 0.5 h; ii, RX, −78 to 20 °C; iii, 3.2 $Bu^nLi$, THF, −78 to −50 °C, 1.5 h; iv, 2.4 RX, −78 to 20 °C; v, $K_2CO_3$, DMF, EtOTf, 70 °C, 24 h; vi, 2 $Bu^nLi$, THF, −78 °C; vii, $R^3X$, −78 to 20 °C; viii, 1.2 $Bu^tOK$, THF, 0 °C, 1 h

**Scheme 129**

### 1.3.8 ALKYLATION OF ALKYL SULFONATES, SULTONES AND SULFONAMIDES

Metallation of alkyl α-toluenesulfonates and alkyl alkanesulfonates and subsequent alkylations of the corresponding anions allow the facile synthesis of a range of substituted sulfonates (Scheme 131, entries a and b).[549] This method offers a useful route to esters of tertiary sulfonic acids which are otherwise difficult to obtain. Similar reactions, performed at low temperature (−78 °C) in order to avoid competing ring opening, permit the alkylations of 1,3-propanesultone with highly reactive alkylating agents such as methyl iodide and benzyl bromide (Scheme 131, entry b).[550] Less reactive electrophiles such as ethyl bromide or isopropyl iodide react[550] sluggishly however. The intramolecular version of this reaction permits the synthesis of *t*-butyl cyclopropanesulfonate (Scheme 131, entry d).[474]

Mono-*N*-substituted alkanesulfonamides react with 2 equiv. of *n*-butyllithium or LDA generating the corresponding dilithium salts which can then be alkylated chemoselectively on the carbon atom.[551]

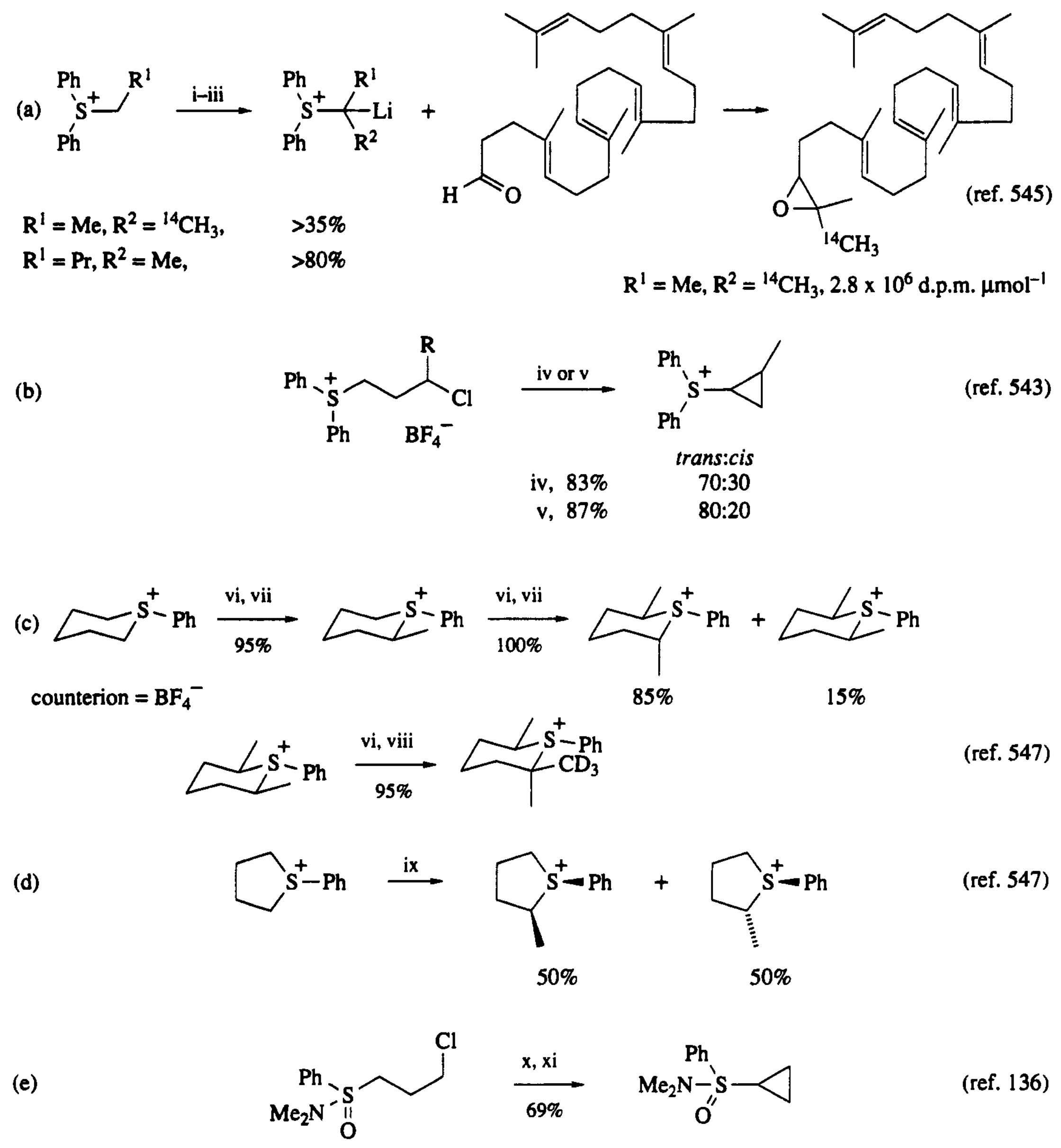
(a)
i–iii
$R^1 = Me, R^2 = {}^{14}CH_3$, >35%
$R^1 = Pr, R^2 = Me$, >80%
(ref. 545)
$R^1 = Me, R^2 = {}^{14}CH_3$, 2.8 x $10^6$ d.p.m. µmol$^{-1}$
(b)
iv or v
$BF_4^-$
*trans:cis*
iv, 83% 70:30
v, 87% 80:20
(ref. 543)
(c)
vi, vii
95%
vi, vii
100%
85%
15%
counterion = $BF_4^-$
vi, viii
95%
(ref. 547)
(d)
ix
50%
50%
(ref. 547)
(e)
x, xi
69%
(ref. 136)

i, LDA, DME, −78 °C; ii, RI; iii, $LiCHCl_2$; iv, NaH, THF, 25 °C, 12 h; v, $Bu^tOK$, DMSO–THF, 20 °C, 0.1 h; vi, $LiCHCl_2$, DME, 1 h; vii, MeI; viii, $CD_3I$; ix, LDA, DME, −78 °C, 0.1 h,; x, NaH, DMSO, 25 °C, 1 h; xi, $HBF_4$

**Scheme 130**

Treatment of *N*-methanesulfonyl-1,4-dihydropyridine with *n*-butyllithium, followed by benzyl bromide, leads to the corresponding *N*-1-(2-phenylethyl)sulfonyl-1,4-dihydropyridine in low yield.[552] The sulfonamide shown in Scheme 131 (entry c) has proved a valuable *cis*-isoprenoid synthon which allows the two-step $C_5$-homologation of allyl halides.[553] This synthon was used for the remarkable two-step stereoselective synthesis of nerol from 3-methyl-2-butenyl chloride (Scheme 131, entry c).[553] Finally, the α-chloro dicarbanion of 4-(α-chloromethanesulfonyl)morpholine is readily available[554] on reaction with 2 equiv. of *n*-butyllithium in THF, and it leads to the corresponding dimethyl derivative with no detectable monoalkylated product or starting sulfonamide on methylation.[554] Intramolecular versions of these reactions allow the low yield synthesis of neopentyl cyclopropanesulfonate (scheme 131, entry d)[474] and the efficient preparation of cyclopropanesulfomorpholine (scheme 131, entry e).[474]

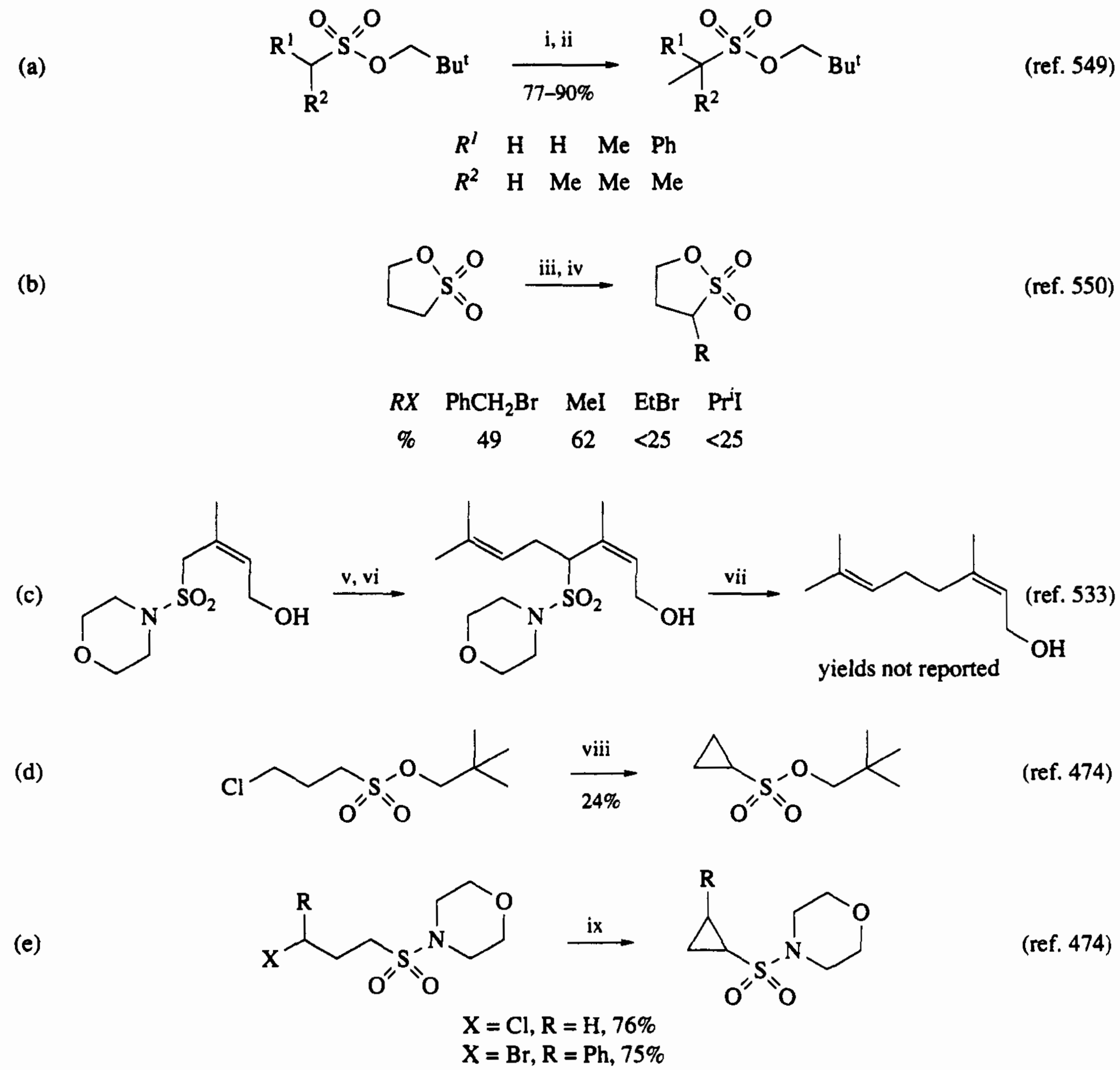
(a)
i, ii
77–90%
(ref. 549)
(b)
iii, iv
(ref. 550)
(c)
v, vi
vii
yields not reported
(ref. 533)
(d)
viii
24%
(ref. 474)
(e)
ix
(ref. 474)

| *R¹* | H | H | Me | Ph |
|---|---|---|---|---|
| *R²* | H | Me | Me | Me |

| *RX* | $PhCH_2Br$ | MeI | EtBr | $Pr^iI$ |
|---|---|---|---|---|
| % | 49 | 62 | <25 | <25 |

X = Cl, R = H, 76%
X = Br, R = Ph, 75%

i, 1.1$Bu^nLi$, THF, –78 °C, 0.3 h; ii, MeI, –78 °C, 2–12 h, then $H_2O$; iii, $Bu^nLi$, THF, –78 °C, 0.1 h; iv, RX, –78 °C, 0.1 h, then –20 °C, 2 h; v, 2$Bu^nLi$, THF, –70 °C; vi, 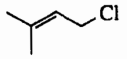 , –70 to 20 °C; vii, 2 equiv. metal/amine or $2e^-$; viii, KH, THF, 20 °C, 5 d; ix, $Bu^nLi$, THF, 50 °C, then 20 °C, 3 h

**Scheme 131**

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# 1.4
# Alkylations of Other Heteroatom-stabilized Carbanions

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## 1.4.1 INTRODUCTION

The use of heteroatom-substituted carbanions has allowed the chemist to access a broad range of relatively stable and selective reagents capable of a wide range of synthetic transformations.[1-3]

This chapter deals with the formation of new C—C bonds by alkylation of $sp^3$-hybridized carbanions stabilized by a range of heteroatoms, including oxygen, boron, silicon, phosphorus and the halogens. The properties of the same carbanions with additional stabilization provided by an adjacent C=C double bond are also discussed.

## 1.4.2 CARBANIONS STABILIZED BY OXYGEN

Considering the prevalence of oxygen-containing groups in naturally occurring substances, synthetic methods based upon the reaction of α-alkoxy carbanions would be of considerable value. Such methods have been realized only recently despite theoretical evidence that these carbanions should be relatively stable. The stabilizing effect of the more electronegative first row elements is inductive in nature, whilst the second row elements stabilize negative charges much more effectively, in part due to their greater polarizability. The first row elements may coordinate to the base, causing an increase in kinetic acidity.[2] Recently Schleyer *et al.*[4] have determined theoretically that a major factor contributing to the stabilization of first row heterosubstituted organolithiums is the possibility of bridging between lithium and the heteroatom.

### 1.4.2.1 Preparation by Hydrogen–Metal Exchange

Early attempts by Ziegler and Gellert[5] to deprotonate dimethyl ether with *n*-butyllithium gave products apparently derived from the decomposition of methoxymethyllithium. A number of attempts to deprotonate tetrahydrofuran also failed, as the desired metallated species underwent a facile cleavage reaction to give ethylene and the lithium enolate of acetaldehyde.[6] The successful preparation of the potassium salts of tetrahydrofuran, *t*-butyl methyl ether and dimethyl ether using lithium salt free *t*-butylpotassium was reported by Lehmann and Schlosser.[7] Corey and Eckrich[8] have described a method for the preparation of *t*-butoxymethyllithium (**1**), a synthetic equivalent of the hydroxymethyl anion (Scheme 1). Treatment of the *t*-butyl ethers with anhydrous iron(III) chloride in acetic anhydride affords the acetates.

$$\mathrm{Bu^tOCH_3} \xrightarrow{\text{i, ii}} \left[\mathrm{Bu^tOCH_2Li}\right] \xrightarrow[83\%]{\text{iii}} \mathrm{Bu^tOCH_2CH_2Ph}$$

**(1)**

i, $\mathrm{Bu^sLi}$, $\mathrm{Bu^tOK}$, –78 °C; ii, LiBr, 2 equiv., THF; iii, $\mathrm{PhCH_2Br}$

**Scheme 1**

The research groups of Seebach[9] and Beak[10] independently developed the use of hindered aryl esters for the preparation of heteroatom-stabilized carbanions. The success achieved in creating anions adjacent to nitrogen *via* the *N,N*-dialkylarylamides, and to sulfur *via* the analogous aryl thioesters led to the preparation of alkyl 2,4,6-triisopropylbenzoates, which have been successfully metallated with a strong base. For example, the lithium reagent (**2**), prepared as shown in equation (1), can be reacted with a wide range of electrophiles. It is suggested that the stabilization of these anionic carbanions is due to the dipole of the ester.[11] The bulky aromatic substituents force the plane of the aromatic ring to be orthogonal to that of the carbonyl, protecting it from the organolithium reagent.

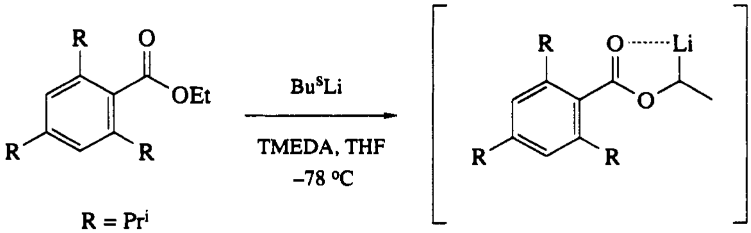

(1)

**(2)**

A recent report describes the use of magnesium (2-ethoxy)ethoxide as an additive in reactions to prepare organolithium reagents.[12] The additive moderates the basicity of the prepared anion and prevents unwanted side reactions, for example with the solvent.

### 1.4.2.2 Preparation by Halogen–Metal Exchange

Schollkopf *et al.*[13] successfully prepared methoxymethyllithium by the reaction of lithium metal with chloromethyl methyl ether. The Grignard reagents of a variety of α-chlorodialkyl ethers have been prepared.[14] Although thermally unstable, they react with carbonyl compounds. A more recent example is the preparation of 1-ethoxy-1-lithiocyclopropane (**3**) from 1-bromo-1-ethoxycyclopropane using *t*-butyllithium as the metallating agent (Scheme 2).[15] The adducts between (**3**) and aldehydes or ketones can be rearranged to form cyclobutanes in good yields.

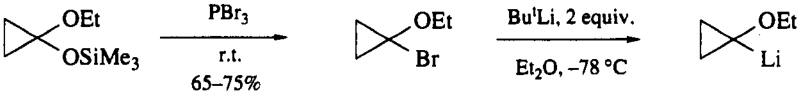

(3)

Scheme 2

### 1.4.2.3 Preparation by Tin–Lithium Exchange

The use of organostannanes has considerably expanded the chemistry of α-alkoxy organolithiums.[16] As seen in Section 1.4.2.1, the conditions necessary for the generation of these species by hydrogen–lithium exchange are harsh and can result in their destruction. Halogen–metal exchange allows generation of α-alkoxylithiums, but the anions can be contaminated with reactive alkyl halides. These problems can be avoided by the use of tin–lithium transmetallation, producing as the side product the relatively inert tetraorganostannanes. The process is an equilibrium, the position of which is determined by the relative stability (basicity) of the organolithium species. Schollkopf[17] first described the preparation of a number of α-lithio ethers by reaction of *n*-butyllithium with the tetraalkoxystannanes as shown in equation (2).

$$(ROCH_2)_4Sn \quad + \quad 4Bu^nLi \xrightarrow[-60\ °C]{Et_2O \text{ or } THF} 4LiCH_2OR \quad + \quad Bu^n{}_4Sn \qquad (2)$$

$R = Me$ (60%), Et (70%), $Pr^i$ (70%), $PhCH_2$ (65%)

Meyer and Seebach[18] have described the preparation of the 'ate' complex (4) as a nucleophilic hydroxymethylating reagent (Scheme 3). Still[19] improved the potential of the method, approaching the preparation of the required organostannanes by reacting tributylstannyllithium with the appropriate carbonyl compound. The labile nature of the addition products necessitated their protection as the stable ethoxyethyl ethers. The α-lithio ethers were then smoothly generated by treatment of the organostannanes with *n*-butyllithium in THF at –78 °C. Still has demonstrated the use of the overall procedure by synthesizing dendrolasin from furan-3-carbaldehyde and geranyl chloride (Scheme 4).

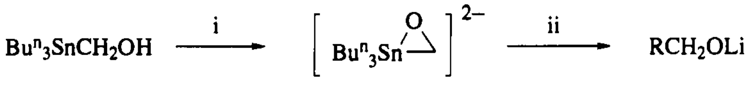

(4)

i, $Bu^nLi$, 2 equiv., petroleum ether, –20 °C; ii, RX = $n\text{-}C_8H_{17}Br$ (45%), $PhCH_2Br$ (45%)

Scheme 3

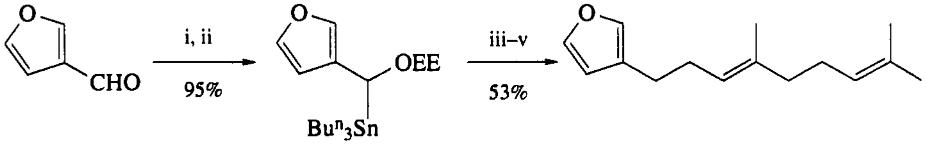

EEO = ethoxyethyl ether

i, $Bu^n{}_3SnH$, LDA, THF, –78 °C; ii, α-chloroethyl ethyl ether, $PhNMe_2$, $CH_2Cl_2$, 0 °C;
iii, $Bu^nLi$, THF:glyme, –78 °C; iv, geranyl chloride, –78 °C; v, Li, $NH_3$, THF, –33 °C

Scheme 4

An exciting new dimension to the chemistry of α-alkoxy organolithium reagents was reported by Still and Sreekumar in 1980.[20] Thus, the aldehyde 2-methyl-3-phenylpropanal was treated with tributylstannyllithium and the diastereomeric carbinols were then protected as their methoxymethyl ethers. Each diastereomeric adduct was next treated separately with *n*-butyllithium. The products resulting from trapping with acetone and TMS-Cl were isomerically pure, showing that the anions were configurationally stable under the reaction conditions. Retention of configuration was implied by the recovery of starting material when the anions were quenched with tributylstannyl chloride. Thus α-alkoxy organolithiums represented 'a new class of configurationally stable carbanions'. Still reported the preparation of optically active (*R*)-2-butanol (>95% *ee*) by chromatographic separation of the diastereomeric Moshers ester derivatives of the addition product between propanal and tributylstannyllithium. Transmetallation of the protected homochiral α-alkoxystannane with *n*-butyllithium (THF, –78 °C) gave the configurationally stable carbanion, which was alkylated with dimethyl sulfate.

A recent report by Chan and Chong[21] describes the enantioselective reduction of acylstannanes to the α-alkoxy organostannanes by the chiral 2,2′-dihydroxy-1,1′-binaphthyl modified lithium aluminum hydrides. Matteson has also described a possible route to such chiral organostannanes utilizing the chiral α-chloroboronic esters.[22]

Gadwood *et al.*[15] have prepared the 1-bromo-1-tributylstannylcyclopropane. The transmetallation proceeds easily in THF at –78 °C. The lower basicity of cyclopropyl carbanions compared with their acyclic analogs explains this ease of metallation. The group of Macdonald and McGarvey[23] has made a thorough investigation of α-alkoxy organolithiums, and estimate that each alkyl substituent destabilized the anion by 3–4 kcal $mol^{-1}$ (1 cal = 4.18 J). A number of examples demonstrated the utility of tertiary α-alkoxy carbanions for the synthesis of highly substituted carbon centers.

Duchene and Quintard[24] have described the preparation of a number of *O*-ethyl organostannanes, for example by the reaction of ethoxy-α-chloromethyltributylstannane with Grignard reagents. (Diethoxymethyl)tributylstannane has been transmetallated to provide the formyl anion synthetic equivalent $(EtO)_2CHLi$.[25] Another report concerning tin–lithium transmetallation describes the preparation of the configurationally stable α- and β-glycosyllithiums from the α- and β-D-tributylstannylglucopyranosides.[26] In addition, α-alkoxy organocopper reagents derived from α-alkoxy organostannanes have been studied.[27]

### 1.4.2.4 Preparation from α-Sulfides

Cohen and coworkers[28] have described the preparation of α-lithio ethers from α-sulfides by a mechanistically novel route in the presence of lithium (dimethylamino)naphthalenide. The reaction is postulated to proceed through the radical anion produced by single electron transfer (SET) and subsequent homolytic cleavage (loss of thiophenoxide anion) to give a radical. Further reduction of the radical then leads to the α-alkoxy carbanion.

## 1.4.3 α-OXYGEN CARBANIONS WITH ADDITIONAL STABILIZATION

The introduction of an additional stabilizing influence on the α-alkoxy anion may serve two purposes. Firstly the anions are easier to prepare, generally by hydrogen–lithium exchange. Secondly the effective oxidation state of the α-carbon atom is increased.

### 1.4.3.1 Allylic and Benzylic α-Alkoxy Carbanions

A number of reviews exist describing the preparation and reactions of allylic heteroatom-stabilized organometallic species.[29] Reactions of the ambident anions can occur at either the α- or γ-carbon atoms (with respect to the heteroatom). There is no general rule for predicting the regioselectivity of the reaction, but experimental evidence indicates that alkylation generally occurs at the γ-carbon atom with alkyl or trialkylsilyl allylic ethers.[30] Attempts have been made to influence the regioselectivity of the reaction. Thus, Yamamoto *et al.*[31] have described the use of allylic 'ate' complexes to direct the reaction toward the α-position. The 'ate' complex is formed by reaction of triethylaluminum or trialkylboranes at the least-substituted γ-position, effectively blocking it to further attack by electrophiles.

An example of an oxaallylic carbanion has been described by Oppolzer *et al.*[32] In the alkylation of 3-triethylsilyloxypentadienyllithium (**5**; X = H) the γ-alkylated product predominated. With the anion (**5**; X = SMe) alkylation occurs exclusively at the γ-carbon atom. The synthetic potential of the anions (**5**) was demonstrated by the synthesis of bicyclic compounds *via* intramolecular Diels–Alder reactions of the alkylation products (Scheme 5).

Hoppe[29] has investigated the regioselectivity of the reaction of oxaallylic anions generated from the *N*,*N*-diisopropyl carbamates of a variety of allylic alcohols. With carbonyl compounds reaction was found to take place predominantly at the γ-carbon. The directing influence of the carbamoyloxy group was unfortunately diminished in alkylation reactions.

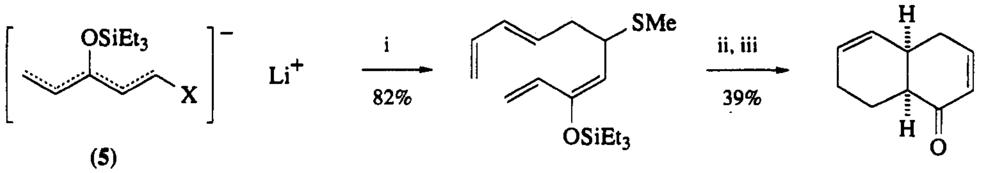

**(5)**

i, 1-bromo-2,4-pentadiene, THF; ii, KF, MeOH, –10 °C; iii, $NaIO_4$, aqueous MeOH, then refluxing $CCl_4$

**Scheme 5**

The rearrangement of 1-(trimethylsilyl)allylic alcohols to 3-(trimethylsilyloxy)allyllithiums in the presence of base is a convenient source of lithium homoenolates.[33] These can be alkylated to yield the corresponding silyl enol ethers.

α-Alkoxy carbanions generated from benzyl ethers are unstable and undergo the Wittig rearrangement in preference to reaction with electrophiles.[34] Yeh has reported, however, that deprotonation of benzyl methyl ether by *n*-butyllithium in the presence of TMEDA leads to the stable benzylic anion, which could then be alkylated.[35] Katriztky *et al.*[36] have described the successful lithiation of lithium benzyl carbonate generated by the reaction of the lithium benzylalkoxide with carbon dioxide. The chromium tricarbonyl complex of benzylic ethers also allows metallation to occur without rearrangement. A variety of bases can be employed for benzylic deprotonation. Davies *et al.*[37] have described the preparation of chromium tricarbonyl complexes of benzyl ethers and their subsequent alkylation chemistry (Scheme 6).

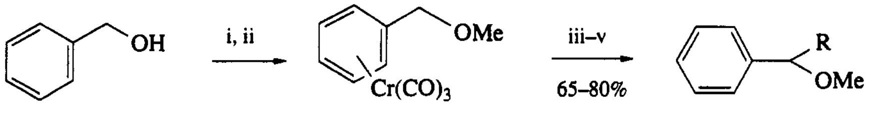

i, $Cr(CO)_6$, heat; ii, MeOH, $HBF_4$; iii, $Bu^nLi$, THF, –40 °C; iv, RX = MeI, EtBr, $Pr^iBr$, $PhCH_2Br$;
v, sunlight or air, $Et_2O$

**Scheme 6**

### 1.4.3.2 α-Alkoxy Carbanions from Protected Cyanohydrins

Protected cyanohydrins, when deprotonated by a suitable base, are synthetic equivalents of the acyl anion.[38] They display 'umpolung' reactivity as the normally electrophilic carbonyl carbon is transformed into a nucleophile. Stork and Maldonado[39] first described the use of such anions for the synthesis of ketones. They found that the cyanohydrins, protected as their ethoxyethyl ethers can be deprotonated with LDA (Scheme 7). After reaction with the alkylating reagent the carbonyl function is restored by treatment with dilute acid and then base. A number of alkylating reagents were investigated, and no problems from competing elimination reactions were noted. The same authors also found similar reactivity in the more stable anions derived from aromatic aldehydes. Deprotonation of the cyanohydrin derivatives of α,β-unsaturated aldehydes gives rise to the ambident allyl anion. Interestingly, Stork found that alkylation occurred at the α-position allowing the synthesis of α,β-unsaturated ketones.

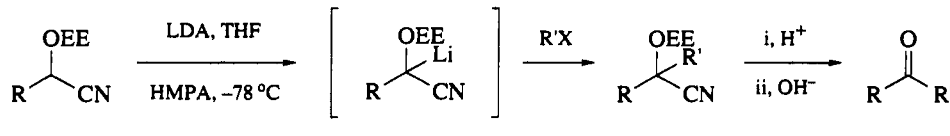

EEO = ethoxyethyl ether

**Scheme 7**

The alkylation chemistry of a considerable number of *O*-trimethylsilyl cyanohydrins derived from aryl and heteroaryl aldehydes has been reported by Hunig and coworkers.[40] The protected cyanohydrins are easily prepared by heating the aldehydes with trimethylsilyl cyanide in the presence of a Lewis acid. The use of dialkyl sulfates and tosylates as alkylating agents was also reported. Hata *et al.*[41] failed to alkylate the anion of the adduct of trimethylsilyl cyanide and acetaldehyde, suggesting that the trimethylsilyl group is incompatible with the more basic anions derived from aliphatic aldehydes. Ficini *et al.*[42]

demonstrated the utility of cyanohydrins in their synthesis of (±)-juvabione; a more recent example is the synthesis of (±)-trichostatin A.[43] Stork and his coworkers have applied the alkylation procedure to the synthesis of small rings,[44] for example in prostaglandins $PGE_1$[45] and $PGF_{2\alpha}$[46] as shown in equation (3). The cyanohydrin served as an effective equivalent of the sensitive carbonyl function.

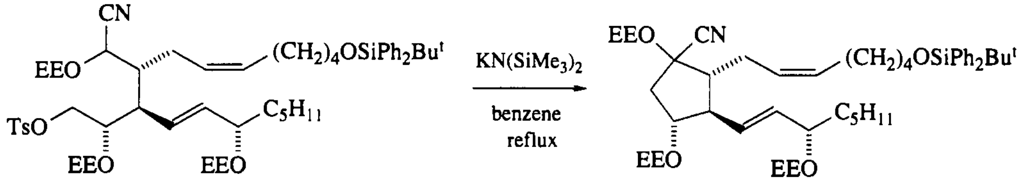

(3)

Takahashi, Tsuji and coworkers have demonstrated that the intramolecular alkylation of carbanions derived from protected cyanohydrins can be applied to the synthesis of both large and medium-sized rings. Their first report described the synthesis of cyclohexadecanone.[47] Slow addition of a THF solution of the protected cyanohydrin of 16-iodohexadecanal to a THF solution of sodium hexamethyldisilazane gave the cyclized product. Treatment with acid and then base gave cyclohexadecanone in 60% overall yield. An advantage of the procedure is that high dilution conditions are not necessary. The method was later extended to the synthesis of several naturally occurring macrocyclic lactones.[38] Another development was to employ the cyclization reaction for the synthesis of (*E*,*E*)-2,6-cyclodecadienones and hence the synthesis of various sesquiterpenes.[48] The synthesis of germacrone, which contains the thermally labile (*E*,*E*)-1,5-cyclodecadiene system, serves to illustrate the strategy (Scheme 8). Deprotonation of (**6**) and cyclization yielded, after restoration of the carbonyl group, germacrone (**7**) in 66% yield.

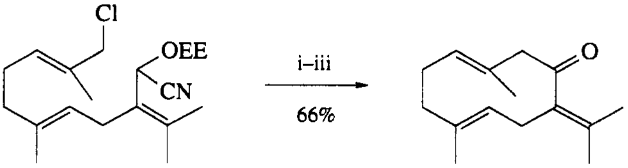

(**6**) (**7**)

i, $NaN(SiMe_3)_2$, THF; ii, PTSA, MeOH, 0 °C; iii, aqueous 2% NaOH, $Et_2O$

**Scheme 8**

Garcia *et al.*[49] have described the synthesis of α-hydroxy-γ-lactones by the alkylation of protected cyanohydrin anions with epoxides.

### 1.4.3.3 α-Alkoxy Carbanions Stabilized by Silicon

Eisch and Galle[50] have described the alkylation with methyl iodide of the configurationally stable anions derived by deprotonation of α,β-epoxyalkylsilanes. The alkylation chemistry is presently restricted to methylation, which is unfortunate as the α,β-epoxyalkylsilanes are easy to prepare and undergo a range of synthetically useful reactions.[51] Unsubstituted α-lithio epoxides derived by tin–lithium transmetallation decompose at –85 °C.

Recently Yoshida *et al.*[52] have employed silyl-stabilized α-alkoxy organolithium reagents for the synthesis of a variety of carbonyl compounds. Methoxy(trimethylsilyl)methane and methoxybis(trimethylsilyl)methane, when deprotonated with $Bu^sLi$ and $Bu^nLi$ respectively, give anions which can be alkylated with a variety of electrophiles. Electrolysis of a solution of the alkylated product in methanol yields, by virtue of the reduced oxidation potential of ethers α-substituted with silicon, either the dimethyl acetal or in the latter case the orthoester. The mildness of the electrolytic process recommends the method for the preparation of a variety of carbonyl compounds.

### 1.4.3.4 α-Alkoxy Carbanions Stabilized by Phosphorus

Hata and coworkers[41] have reported the preparation of unsymmetrical ketones employing the adducts of aldehydes with diethyl trimethylsilylphosphite (**8**). The adducts are easily deprotonated and then alkylated; treatment of the alkylated products with base provides the ketone (Scheme 9).

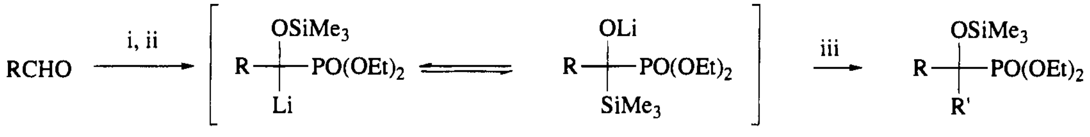

R = H, Me, Et, Pr$^i$, n-$C_7H_{15}$, *etc.*; R'X = MeI, EtI, $PhCH_2Br$/I, *etc.*

i, $Me_3SiOP(OEt)_2$, (**8**), benzene; ii, LDA, THF, −78 °C ; iii, R'X

**Scheme 9**

The anions generated from the adducts of α,β-unsaturated aldehydes and (**8**) are alkylated exclusively at the γ-position. Evans *et al.*[53] have also reported the alkylation of similar oxaallylic anions and the alkylation chemistry of diethyl (2-trimethylsilyl)ethoxymethylphosphonate has been reported.[54]

Sturtz *et al.*[55] have described the deprotonation of the allyl bis(dimethylamido)phosphonate (**9**). Treatment of (**9**) with two equivalents of base, followed by reaction with an epoxide and hydrolysis, yields the γ-lactone (Scheme 10). Alkylation with alkyl and alkenyl halides occurs at the γ-carbon and hydrolysis yields the saturated and unsaturated carboxylic acids respectively.

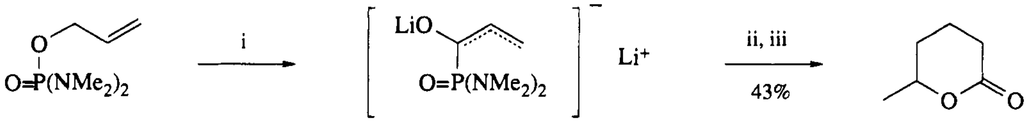

(**9**)

i, Bu$^n$Li, 2 equiv., THF, −50 °C; ii, propylene oxide; iii, $H^+$, $H_2O$

**Scheme 10**

## 1.4.4 CARBANIONS STABILIZED BY BORON

The stabilization of a negative charge adjacent to boron has been known for some time.[56] Zweifel and Arzoumanian[57] demonstrated the facile base-induced cleavage of a geminal diboroalkane to give the boron-stabilized anion, which was then alkylated. A later approach employed 3,6-dimethylborepane (**10**) as the hydroborating agent.[58] After dihydroboration, addition of one equivalent of methyllithium forms the boron-stabilized anion, which upon alkylation and oxidation gives the secondary alcohol (Scheme 11). Matteson[59] has described the alkylation of the anion derived from the base cleavage of tris(dimethoxyboryl)methane.

Rathke and Kow[60] first reported the preparation of a boron-stabilized carbanion by direct deprotonation of the carbon acid. They made the important observation that the deprotonation needed a sterically demanding base to prevent its complexation with boron. Thus the anion of *B*-methyl-9-borabicyclo[3.3.1]nonane, prepared by deprotonation with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in benzene, can be alkylated successfully.

Matteson and coworkers have described the deprotonation and alkylation of bis(1,3,2-dioxaborin-2-yl)methane (**11**).[61] Deprotonation with LiTMP yields the stabilized anion, which can be alkylated with a variety of primary alkyl halides. Oxidation under basic conditions then unmasks the carbonyl group. Matteson has also described the deprotonation of some substituted boronic esters (**12**; X = SPh, $SiMe_3$).[62,63] The alkylated products derived from (**12**; X = SPh) can be treated with *N*-chlorosuccinimide under mild basic conditions to yield either the monothioacetals or the acetals.[64] Boron-stabilized carbanions can also be generated by transmetallation of the organostannanes.[65]

Pelter and Wilson[66] have described the deprotonation of the air stable dimesitylboranes. The use of two mesityl groups represents a compromise between steric shielding of the boron against the possible complex formation with the base, and easy oxidation of the product. Alkylation of the anion generated

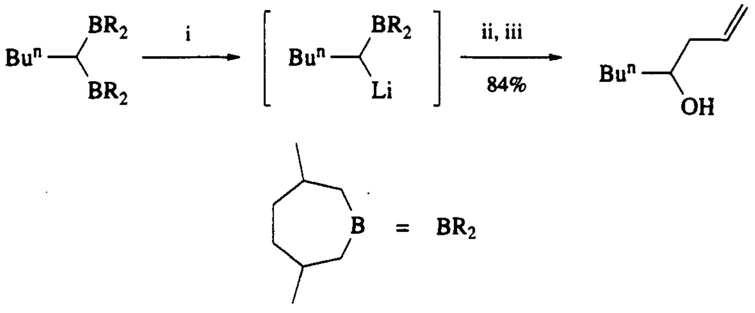

(10)

i, MeLi, 1 equiv., 0 °C; ii, allyl bromide; iii, 3 N aqueous NaOH, 30% $H_2O_2$

Scheme 11

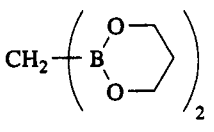

(11)

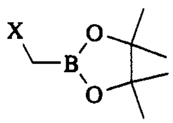

(12)

by deprotonation of dimesitylmethylborane can be effected with a range of primary alkyl halides. The secondary anions derived from ethyl- and propyl-dimesitylborane can also be alkylated, but oxidation is more difficult. Allyldimesitylborane was also deprotonated using mesityllithium. Alkylation with primary halides occurs at the $\gamma$-position and the resulting *trans*-vinylboranes can be oxidized to give aldehydes.

## 1.4.5 CARBANIONS STABILIZED BY SILICON

The preparation and use of silicon-stabilized carbanions is well documented;[67] the vast majority of reports are concerned with the reaction of these reagents with carbonyl compounds to form alkenes.

Tamao *et al.*[68] have described the use of (diisopropoxymethyl)silylmethylmagnesium chloride as a reagent for effecting hydroxymethylation of reactive alkyl halides. The alkylation of tris(trimethylsilyl)methyllithium has also been reported.[69]

There are a number of examples where additional stabilization for the $\alpha$-silicon anion is derived from the presence of one or more halogen atoms. For example, Larson and Rosario[70] have described the alkylation of a number of trialkylsilyldichloromethyllithiums; dehydrochlorination yields the *trans*-1-chloroalkenylsilanes.

Chan and coworkers[71] have investigated the regioselectivity in the alkylation of $\alpha$-silicon allyllithiums. The alkylation of $\alpha$-trimethylsilylallyllithium usually occurs at both the $\alpha$- and $\gamma$-carbons, but if the reagent is prepared using Schlosser's base ($Bu^tOK/Bu^nLi$ in hexane), $\gamma$-alkylation predominates, affording the *trans*-alkenylsilanes. Chan[72] has also recently described the successful use of metal-chelating substituents on the silyl group to direct the reaction toward the $\alpha$-position.

## 1.4.6 CARBANIONS STABILIZED BY PHOSPHORUS

The Wittig reaction of phosphorus ylides derived from phosphonium salts with carbonyl compounds to form alkenes is widely used in synthetic chemistry. The alkylation of phosphorus ylides offers a route to a variety of phosphonium salts which can be further manipulated. Bestman and coworkers[73] have been responsible for a large number of reports based upon this and other aspects of phosphorus chemistry. Their work includes many examples of the intramolecular alkylation of ylides derived from phosphonium salts to form cyclic compounds. The salts can be prepared from dihalides either with triphenylphosphine or triphenylphosphine methylide. The cyclic phosphonium salt formed can then be eliminated to form an alkene, or reduced or deprotonated to give a new ylide.

Axelrod *et al.*[74] have described the synthesis of 1,5-dienes by alkylation of an allylic phosphonium ylide with an allylic bromide. The method was used to synthesize pure all-(*E*)-squalene from (*E*,*E*)-farnesyl bromide and its tributylphosphonium salt. No isomerization occurred during the reaction and reduction of the resulting phosphonium salt with lithium in ethylamine gave squalene in 65% yield.

Alkylation chemistry has also been reported for alkylphosphine oxides and dialkyl phosphonates. The phosphonate carbanions are often preferred as they offer many advantages over the phosphonium ylides.[75] In particular, the phosphonate group is highly acidifying and the resulting organolithium can be smoothly alkylated.

Warren and coworkers[76] have described the alkylation of (diphenylphosphinoyl)alkyllithiums with epoxides as an effective means of synthesizing β-(diphenylphosphinoyl) ketones, homoenolate anion equivalents. The treatment of the adducts of lithiated phosphine oxides and epoxides with base to form cyclopropanes was reported by Toscano *et al.*[77]

Pietrusiewicz and coworkers[78] have developed methods for the synthesis of homochiral phosphine oxides. They play an important role in asymmetric synthesis as chiral ligands for catalysts. The readily prepared ($S_p$)-ethyl[(menthoxycarbonyl)methyl]phenylphosphine oxide (**13**) can be deprotonated, alkylated and then decarboxylated to afford the homochiral ($R_p$)-alkylethylphenylphosphine oxides (Scheme 12). Pietrusiewicz and Zablocka have also described the synthesis of chirally pure α,β-unsaturated phosphine oxides.[79]

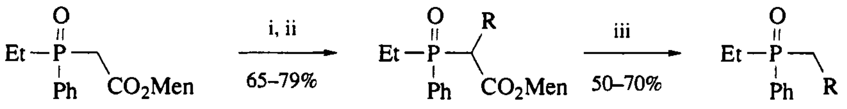

(**13**)

Men = L-menthyl

i, NaH, THF, 0 °C; ii, RX = $CD_3I$, EtI, $H_2C{=}CHCH_2Br$, $PhCH_2Br$; iii, LiCl, wet DMSO, 180 °C

**Scheme 12**

Recently there has been interest in the synthesis of analogs of the naturally occurring mono- and diphosphate group. Corey and Volante[80] have reported the alkylation of (dimethylphosphoryl)methyllithium with, for example, geranyl, farnesyl and 3-methyl-2-butenyl bromides. The products were assessed for their ability to inhibit the biosynthesis of squalene. McClard and coworkers[81] described the alkylation of the phosphonylphosphinyl anion (**14**) to yield the 'P—C—P—C' compounds, proven enzyme inhibitors (Scheme 13). The free acid derivatives were obtained by treatment of the alkylated products with bromotrimethylsilane.

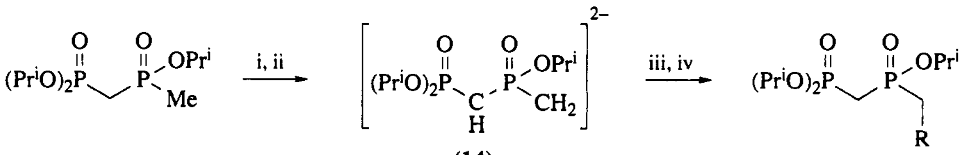

(**14**)

RX = EtI, $Pr^iI$, $Me_2C{=}CHCH_2Br$, geranyl bromide, $PhCH_2Br$, *etc.*

i, NaH, THF, 20 °C; ii, $Bu^nLi$, −78 °C; iii, RX, −78 °C; iv, $H^+$, $H_2O$

**Scheme 13**

Alkylation of (diethoxyphosphoryl)methylcopper(I)[82] and (dialkoxyphosphoryl)trimethylsilylalkyllithiums[83] with a variety of alkyl iodides and bromides has been reported by Savignac and coworkers. Tsuge *et al.*[84] have demonstrated the regioselective dipolar addition of (diethoxyphosphoryl)acetonitrile oxide with monosubstituted alkenes to yield the 3-[(diethoxyphosphoryl)methyl]-2-isoxazolines. The phosphonates can be deprotonated and alkylated in good yields.

The incorporation of fluorine into biologically active compounds can greatly enhance their potency; fluoroalkyl phosphonates are isosteres of the natural phosphonate monoesters. The alkylation chemistry of α-fluoro- and α,α-difluoro-alkyl phosphonates has been reported.[85] Burton and Sprague[86] have described the alkylation of (diethoxyphosphoryl)difluoromethylzinc bromide with allylic halides; the reaction is catalyzed by copper(I) bromide. The alkylation of (diethoxyphosphoryl)dichloromethyllithium was reported by Normant and coworkers.[87] The products can be transmetallated and further alkylated.

A method for the preparation of alkenes has been described by Tunemoto and coworkers,[88] whereby regioselective α-alkylation of γ-substituted allyl phosphonates, followed by reduction with LAH, gives the (*E*)-alkenes (Scheme 14).

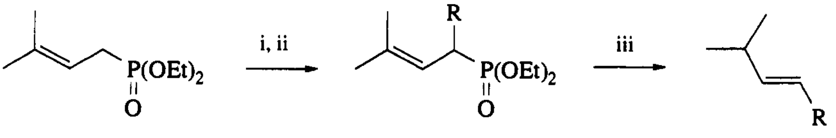

i, Bu$^n$Li, THF, –60 °C; ii, X = Cl, Br, 25 °C; iii, LiAlH$_4$, Et$_2$O, 0 °C

**Scheme 14**

A range of heteroaryl methyl phosphonates have been alkylated with alkyl halides; the anions were generated with sodium amide in liquid ammonia.[89]

## 1.4.7 CARBANIONS STABILIZED BY THE HALOGENS

Organolithiums bearing a halogen on the α-carbon are termed carbenoids.[90] Bromine and chlorine are sufficiently acidifying to allow preparation of the halocarbenoids, but fluorine requires additional stabilization, for example by phosphorus (*vide supra*). Lithium halocarbenoids are thermally unstable species whose chemistry must be performed at low temperatures and this feature has hindered their use in preparative synthetic organic chemistry.

Villieras and coworkers[91] have contributed a considerable number of synthetic methods employing lithium halocarbenoids. An early example was the alkylation of dibromomethyllithium and higher homologs (Scheme 15). The anion (**15**) is easily generated from 1,1-dibromoalkanes by deprotonation with LDA in THF at low temperature. Alkenes can then be generated simply by treating the products with Bu$^n$Li in Et$_2$O. Alkylation of dichloromethyllithium with primary alkyl halides followed by reaction of the dichloroalkanes with Bu$^n$Li represents a method for the preparation of 1-alkynes.[92]

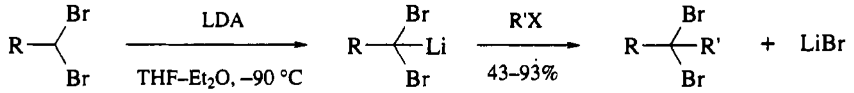

(**15**)

R = H, Bu$^n$, Me$_3$Si; R'X = H$_2$C=CHCH$_2$Br, Bu$^n$I, n-C$_5$H$_{11}$I, *etc.*

**Scheme 15**

Geminal substituted dibromoalkenes can be prepared by the alkylation of dibromomethyllithium with α-chloroalkyl methyl ethers.[93] Deprotonation of the alkylation products results in the elimination of methanol and the formation of the corresponding 1,1-dibromoalkenes. Despite the lower acidity of 1-bromo-1-chloroalkyllithiums relative to the dibromo analogs they exhibit similar nucleophilic properties.[94] Alkyl dichloroacetates can also be deprotonated with lithium diethylamide and alkylated with a range of alkyl halides.[95]

Cyclopropylidenelithium halocarbenoids are easily prepared by halogen–lithium exchange of the dibromocyclopropanes, and they undergo a variety of synthetically useful reactions including alkylation.[96] A recent report by Hiyama *et al.*[97] for example, describes the synthesis of alkyl-substituted 2-cycloheptenones (Scheme 16).

Seyferth and coworkers have prepared 1,1-dichloroallyllithium[98] and 1,1-difluoroallyllithium.[99] The former can be alkylated, the reaction occurring at the 'CCl$_2$' terminus, *i.e.* with α-regioselectivity. The latter reagent, however, is rather unstable and its alkylation chemistry has not yet been explored.

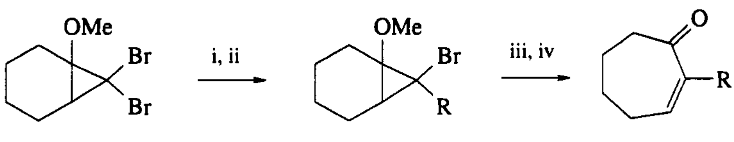

RX = $Me_2C{=}CHCH_2Br$ (46%) or n-$C_5H_{11}I$ (40%)

i, $Bu^nLi$, THF, HMPA, −95 °C; ii, RX; iii, MeOH, $K_2CO_3$; iv, $H^+$, $H_2O$

**Scheme 16**

## 1.4.8 CARBANIONS STABILIZED BY ARSENIC, GERMANIUM, TIN, ANTIMONY, LEAD AND BISMUTH

The chemistry of carbanions stabilized by the heavy main group elements has been extensively investigated by Kauffmann, and a thorough description of his work can be found in a recent review.[100] There are many similarities between the elements. The anions stabilized by the heavy main group elements listed above can generally be alkylated, and in some cases their reaction with carbonyl compounds is a useful alternative to the Wittig reaction. All the stabilized metallomethyl lithium anions (except bismuth) exhibit marked thermal stability.

Among the heavy main group elements arsenic has received the most attention. Arsonium ylides react with carbonyl compounds to yield either the alkenes or epoxides, depending upon the structure of the ylide and the reaction conditions.[101] Despite their toxicity, arsenic compounds can be handled safely.

Diphenylarsinomethyllithium (**16**) can be prepared by transmetallation of bis(diphenylarsino)methane (Scheme 17), or by halogen–lithium exchange of diphenylarsinomethyl iodide. The anion derived by the former method can be alkylated.

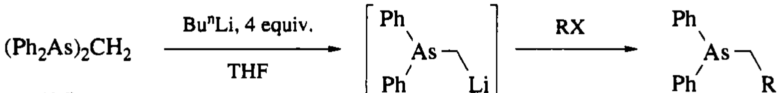

(**16**)

RX = $Pr^nI$ (93%), $Bu^nBr$ (85%), n-$C_8H_{17}Br$ (57%)

**Scheme 17**

Alkylarsino compounds undergo halogenolysis of the metal–carbon bond as do the bismuth and antimony analogs (Scheme 18). Diphenylarsinomethyllithium can also be alkylated with epoxides.

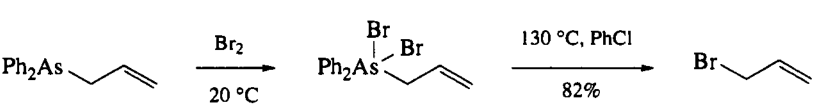

**Scheme 18**

The major drawback to the use of diphenylarsinomethyllithium is the necessity to use a fourfold excess of *n*-butyllithium in order to prepare it. The arsane oxides offer a good alternative, as the diphenylarsinoyl group is strongly acidifying. Diphenylarsinoylmethane is easily deprotonated with LDA in THF and can be alkylated with alkyl halides and epoxides.

Addition of organolithium reagents to diphenylarsenoethene provides another route to α-arseno anions. This reaction is general to the second and third row elements (Si, P, S, Ge, As and Se) but does not occur with elements from the fourth and fifth rows (Sn, Sb, Te, Pb and Bi). Unlike their phosphorus analogs, triphenylarsonium salts cannot be prepared by reaction of triphenylarsine with an alkyl halide. Their preparation can be achieved by reaction of triphenylarsine with the more electrophilic alkyl triflates. It is also possible to alkylate arsonium ylides.[101,102]

The organometallic species $Ph_nMCH_2Li$ (**17**; M = Sn, Pb, $n = 3$; M = Sb, Bi, $n = 2$) can be prepared by transmetallation of $(Ph_nM)_2CH_2$ with phenyllithium. In the case of germanium, the anion (**17**; M = Ge, $n = 3$) is prepared from the lead-, selenium- or tin-substituted triphenylgermanylmethane. The synthesis of (**17**) is sometimes possible *via* halogen–metal exchange of the appropriate iodide. Alkylation of the anions, except (**17**; M = Bi, $n = 2$), is possible with alkyl halides and with epoxides in preparatively useful yields. With (**17**; M = Sb) transmetallation with copper is necessary for efficient alkylation.

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# 1.5

# Alkylations of Nonstabilized Carbanions

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## 1.5.1 INTRODUCTION

The formation of carbon–carbon bonds is truly one of the cornerstones of organic synthesis. While the early organic chemists had the ability to modify the molecules of nature and to degrade them into simpler components, the possibility that complex molecules could be constructed from simpler precursors appeared inconceivable. The development of methodology for the construction of C—C bonds revolutionized that way of thinking, and the field of organic synthesis was born.

Conceptually, perhaps the simplest method of forming a σ-bond between two carbon fragments is the reaction of a carbanion with an electrophilic carbon center. Nature relies heavily upon reactions of carbanions stabilized by adjacent electron-withdrawing substituents, which can be generated under equilibrium conditions at physiological pH. Similarly stabilized carbanions form the basis of much commonly used synthetic methodology as well, as discussed in Chapters 1.1–1.4 of this volume and also in a number of chapters in Volumes 1, 2 and 4 of the series. However, by a variety of techniques, the chemist is also able to introduce a metal atom at a carbon center that lacks heteroatom stabilization.

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The properties and reactivity of the organometallic compounds so produced vary greatly, depending upon the metal counterion.[1] The bonds of carbon to the most electropositive metals, such as sodium and potassium, are predominantly ionic in character. Carbanions of this type are strongly basic, highly reactive and poorly able to discriminate between electrophiles. Also highly reactive are the alkyl and aryl compounds of lithium, magnesium and aluminum, in which the M—C (M = metal) bond is strongly polarized, albeit essentially covalent in nature. By contrast, less electropositive metals form covalent, only slightly polar bonds with carbon, producing organometallic reagents that are less prone to undergo undesired side reactions with functional groups present in the substrate, but that are also correspondingly less reactive. An additional metal catalyst is often necessary in order to achieve suitable reactivity with these reagents.

In this chapter, the substitution reactions of organometallic reagents with organic halides and related electrophiles are reviewed.[2,3] The major portion of the chapter is devoted to a discussion of organocopper compounds, which first transformed the alkylation of nonstabilized carbanions into a reaction of general synthetic utility. More recently, transition metals other than copper have also found widespread application in such coupling reactions, and developments in this area are outlined in Section 1.5.3.

## 1.5.2 ORGANOCOPPER REAGENTS

Although organoalkali metal reagents derived from stabilized carbanions can usually be alkylated smoothly in high yields, those derived from weak hydrocarbon acids are prone to undergo numerous competing side reactions (*e.g.* metal–halogen exchange, α-metalation, α- and β-elimination, and homocoupling to form symmetrical dimers). Neither type of reagent is effective in direct substitution reactions of vinyl or aryl halides. Other organometallics, such as organo-aluminum, -zinc, -cadmium and -magnesium reagents, although often useful for specific reactions, are also susceptible to undesirable side reactions or are unreactive toward important classes of noncarbonyl electrophiles.

That the chemical behavior of traditional organolithium and Grignard reagents can be significantly altered in the presence of copper salts has been known for many years, prominent examples being the $Cu^I$-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated compounds[4] and the transition metal catalyzed coupling of aryl Grignard reagents with vinyl halides,[5] both reported by Kharasch in the 1940s. Stoichiometric organocopper compounds also are not new, the oldest members of the class, copper acetylides,[6] having been reported as early as 1859. Phenylcopper[7] was prepared by Reich in 1923, and Gilman and coworkers reported preparations of methylcopper[8] and lithium dimethylcuprate[9] in 1936 and 1952, respectively. However, it was not until the mid-1960s that the widespread synthetic utility of organocopper reagents was finally appreciated. Their use in coupling reactions with organic electrophiles has been reviewed previously.[10]

The past 20 years have witnessed a virtual explosion in research involving organocopper reagents, as reactions employing them have become established in the organic chemist's growing arsenal of consistently reliable methodology. However, the term 'organocopper reagent' itself encompasses a vast array of reagents, possessed of widely divergent chemical behavior. The formulae by which these compounds are represented are indicative of stoichiometry only and are not true reflections of structure, about which information has traditionally been scarce. In addition, factors such as solvent, method of reagent preparation and the nature and purity of the copper source have proven to be critically important in determining the stability and reactivity of the reagents. Not surprisingly, many chemists have tended to view organocopper chemistry as an art as much as a science. Fortunately, during the past decade a rapidly increasing volume of structural and mechanistic data have become available,[11] promising eventually to dispel the mystery surrounding reactions of both stoichiometric and catalytic organocopper reagents.

### 1.5.2.1 Preparation of the Reagents

Commonly employed organocopper reagents can be divided into five general classes:

(1) catalytic organocopper compounds [RM + CuX(cat)]
(2) monoorganocopper compounds (RCu)

(3) homocuprates ($R_2CuM$, $RR'CuM$)
(4) heterocuprates [$RCu(Z)M$]
(5) higher-order cuprates [$R_2Cu(Z)Li_2$, $R_{m+n}Cu_mLi_n$ ($m + n > 2$)].

In each case, an additional ligand (usually an amine, phosphine, phosphite or sulfide) or other additive (usually a Lewis acid, especially $BF_3$) may be present, altering the physical and chemical properties of the reagent.

Typically, organocopper reagents are prepared according to one of the general methods outlined in equations (1)–(3) (with or without additional ligands). The choice of the copper salt employed in these reactions is often critical to the outcome. For example, in early investigations, Cu(SCN) and CuI were often used interchangeably, it being assumed that each gave rise to the same organocuprate, according to equation (1). It has since been established, however, that both Cu(SCN) and CuCN, when combined with 2 equiv. of an organolithium reagent RLi, produce, not the expected homocuprate $R_2CuLi$, but rather the higher-order mixed organocuprates $R_2Cu(Z)Li_2$ (Z = CN, SCN; equation 3). Even among the copper(I) halides differences are often observed, and debate continues as to whether the use of CuI or CuBr is to be preferred.[12] While copper(I) iodide continues to be most commonly employed for the preparation of dialkylcuprates, copper(I) bromide must be used for the preparation of diarylcuprates.

$$n\mathrm{RM} + \mathrm{CuX} \longrightarrow \mathrm{R}_n\mathrm{CuM}_{n-1} + \mathrm{MX} \qquad (1)$$

$$n\mathrm{RM} + m\mathrm{RCu} \longrightarrow \mathrm{R}_{(m+n)}\mathrm{Cu}_m\mathrm{M}_n \qquad (2)$$

$$n\mathrm{RM} + \mathrm{CuZ} \longrightarrow \mathrm{R}_n\mathrm{Cu(Z)M}_n \qquad (3)$$

Since the presence of trace impurities (*e.g.* $Cu^{II}$ salts) may have a profound effect on the course of reactions employing organocopper reagents, the purity of the copper source is of critical importance. Copper(I) iodide is usually purified by soxhlet extraction or recrystallization,[13] followed by *in vacuo* drying, while copper(I) bromide is recrystallized as its dimethyl sulfide complex.[14] If $CuBr{\cdot}SMe_2$ is to be used, it is important that the reagent not be dried *in vacuo*, since such handling may significantly alter its composition.[15] Tedious and repetitive recrystallizations of $CuBr{\cdot}SMe_2$ can be avoided by simply treating the reaction solution containing $CuBr{\cdot}SMe_2$ with copper wire, which serves to reduce any $Cu^{II}$ that might be present.[16] Copper(I) cyanide offers the advantages that it is neither hygroscopic nor light sensitive, it is less easily oxidized than copper(I) halides, and it is less expensive than CuI.

A number of metals (M) have been employed in reactions (1)–(3), including lead, zinc, mercury, boron, aluminum, thallium, zirconium, lithium and magnesium, the latter two being the most commonly used. Catalytic organocopper compounds are best prepared from Grignard reagents, while organolithiums usually provide the most effective stoichiometric organocopper compounds. This requirement for organo-lithium or -magnesium precursors represents a significant synthetic limitation, prohibiting the formation of many reagents that bear functional groups with which the organocopper compound itself, once formed, would be compatible. In an effort to circumvent this difficulty, Behling[17] has prepared higher-order vinyl cuprate reagents by *in situ* transmetalation between $Me_2CuCNLi_2$ and the corresponding vinylstannane. Similarly, Knochel has reported[18] the successful preparation of functionalized benzylic cuprates by transmetalation of the organozinc bromides.

Particularly exciting within this context is recent research in the Reike group,[19] which has demonstrated that organocopper compounds can be prepared directly from organic halides upon treatment with the highly reactive zerovalent copper obtained by lithium naphthalenide reduction of copper(I) halides. Oxidative addition of the reactive copper to alkyl bromides occurs at temperatures as low as –78 °C, while aryl halides react at room temperature or below. Importantly, ester, nitrile, chloride, nitro, epoxide and ketone functionalities are all compatible with this procedure to varying degrees. The method works best in the presence of phosphine ligands, which render the reduced copper more reactive toward oxidative addition, and which also serve to produce a more nucleophilic organocopper species. Moderate to good yields have been obtained in cross-coupling reactions with acid chlorides and alkyl halides.

Several other methods of limited generality have been used to prepare specific types of organocopper compounds. Copper(I) acetylides are routinely prepared from the corresponding alkyne and a copper(I) halide in ammoniacal solution or in HMPA.[20] Metalation of compounds with acidic hydrogens has also been accomplished with $Cu(OBu^t)$. Alkenylcopper reagents have been prepared by stereospecific *syn* addition of organocopper reagents to alkynes.[21] Finally, it should be noted that the Ullmann biaryl synthesis,[22] thought to proceed *via in situ* generated arylcopper intermediates, may be considered to be an early predecessor to the Rieke method for the preparation of organocopper reagents.

## 1.5.2.2 Nature of the Reagents

### *1.5.2.2.1 Catalytic copper compounds [RM + CuX(cat)]*

Copper(I)-catalyzed reactions of organolithiums and Grignard reagents have been reviewed.[10] The term catalytic here refers to the use of copper salts in amounts not exceeding 20 mol %; commonly employed quantities range from 1 to 20%, with 5 and 10% being most typical. While CuCl was an often-used catalyst in the years following Kharasch and Tawney's orginal report,[4] its virtual insolubility in ether has led to the more frequent use of CuI, CuBr or Kochi's catalyst, $Li_2CuCl_4$.[23] Although copper-catalyzed reactions of organometallics are generally believed to proceed by way of *in situ* generated organocopper compounds, little is known about the exact nature of the reactive species involved.

### *1.5.2.2.2 Monoorganocopper compounds (RCu)*

Alkylcopper reagents decompose readily at temperatures above –15 °C, with β-hydrogens and branching at the α-position contributing to decreased stability. By contrast, phenylcopper is stable in an inert atmosphere up to 100 °C, while copper(I) acetylides are even resistant toward hydrolysis. In general, the stability of RCu increases in the order alkyl < aryl ≈ alkenyl < alkynyl. Steric hindrance near the copper–carbon bond has a stabilizing influence on aryl- and alkenyl-copper compounds.[11] Organocopper reagents are more stable in THF than in ether, and thermal stability is further enhanced in the presence of donor ligands such as sulfides, phosphines and amines. The use of dimethyl sulfide as the solvent in reactions of alkylcopper compounds has recently been recommended.[24] Since solvent molecules occupy all available coordination sites on copper, hydride transfer cannot occur and decomposition by β-elimination is effectively minimized. In addition, organocopper reagents form more readily at lower temperatures in dimethyl sulfide than in ethereal solvents, solubility may be increased, and enhanced reactivity has also been observed.

Polynuclear structures have been suggested for most organocopper compounds, which tend to be insoluble in conventional organic solvents. In dimethyl sulfide solution, phenylcopper apparently exists as an equilibrium mixture of trimeric and tetrameric aggregates, while methylcopper is a yellow precipitate, presumably of polymeric composition.[24] A recurrent feature of known organocopper crystal structures[11a] is a central metal atom core, in which copper typically adopts a digonal or trigonal coordination geometry. The formation of 1:1 ArCu·CuBr adducts is not uncommon,[25] and the exact synthetic protocol often plays a critical role in determining the nature of the cuprate species isolated.

Particularly interesting bonding patterns have been observed for arylcopper derivatives with nitrogen-containing *ortho* substituents (**1–3**).[26] Tetrameric in the solid state, with the four copper atoms positioned in a butterfly arrangement, these compounds adopt one of the configurations schematically depicted in Scheme 1. As indicated by X-ray crystallography, diastereomer (**6**) is the ground-state structure for compound (**1**), while for (**2**) it may represent an intermediate in the interconversion of enantiomeric configurations (**4**) and (**5**), a process that is rapid on the NMR time-scale. The situation is more complex for

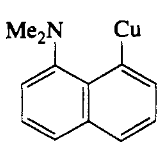

(**1**)

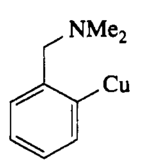

(**2**)

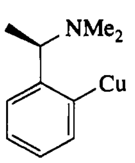

(**3**)

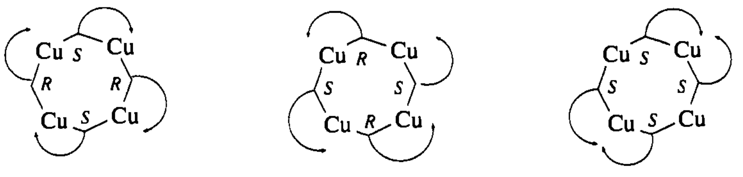

(**4**) (**5**) (**6**)

**Scheme 1**

compound (3), which possesses a chiral *ortho* substituent. The ways in which this ligand chirality influences the structures of the derived arylcopper and arylcuprate compounds may have relevance to the design of chiral cuprate reagents for asymmetric synthesis.

### *1.5.2.2.3 Heterocuprates [RCu(Z)Li]*

The enhanced thermal stability of organocopper reagents imparted by the presence of donor molecules, as well as the high value of some R groups, prompted the development of heterocuprates, in which the donor ligand is incorporated into the reagent itself. Prepared according to the general equation (3), the same reagent is obtained regardless of the order of addition. Thus, the lithium anion of the donor ligand can be added to a solution of the alkylcopper compound, or an alkyllithium reagent can be added to a preformed heterocopper compound. Dicyclohexylamido-, dicyclohexylphosphido- and diphenylphosphido-cuprates have been particularly recommended, based on the enhanced thermal stability and reactivity of these reagents relative to other heterocuprates.[27] More recently, it has been reported[28] that di-*t*-butylphosphidocuprates exhibit significantly improved stability, while maintaining reactivity comparable to that of other phosphidocuprates. In contrast to diphenylphosphidocuprates, for which dimeric structures have been suggested, X-ray analysis indicates that $RCuP(Bu^t)_2Li$ is a monomer, presumably a result of the steric hindrance of the *t*-butyl substituents. In the crystal structure, both phosphorus and lithium exhibit tetrahedral geometries, with solvent molecules occupying three of the coordination sites on lithium (Figure 1).

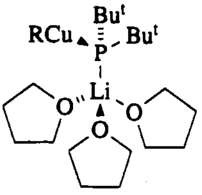

Figure 1

### *1.5.2.2.4 Homocuprates ($R_2CuLi$)*

Diorganohomocuprates continue to be the most widely used organocopper reagents. These compounds are both more stable and more nucleophilic than their monoorganic counterparts.[29] They are, however, considerably less basic and less nucleophilic than the corresponding alkyllithiums. Like other organocopper compounds, diorganocuprates are very sensitive to heat and oxidants; oxidative decomposition to give the symmetrical organic dimer R—R occurs readily in the presence of oxygen, even at –78 °C. Of the dialkylcuprates, $Me_2CuLi$ is the most stable, showing little decomposition at 0 °C, while secondary and tertiary organocuprates are best prepared at low temperature (–78 °C) in the presence of a stabilizing ligand. Very recently, the immobilization of cuprate reagents on solid supports has been described.[30] The dry polymer-bound cuprates are stable for up to two to three weeks at room temperature when stored under an argon atmosphere.

The dimeric structure (7) has long been suggested for $Me_2CuLi$, based on $^1H$ NMR, solution X-ray and vapor pressure depression data.[31] The proposed $Cu_2Li_2$ metal core with bridging organic substituents is, in fact, evidenced in the crystal structure of $Cu_2Li_2(o\text{-}C_6H_4CH_2NMe_2)_4$ (Figure 2a),[32] the only neutral cuprate for which X-ray crystallographic data are available. On the basis of spectroscopic information, a similar structure (Figure 2b) has also been proposed for $Cu_2Li_2(p\text{-tolyl})_4{\cdot}2Et_2O$, in which two solvent molecules are required to fill the lithium coordination sites occupied by the *o*-amino substituents in Figure 2(a). Evidence suggests that, in all of these compounds, the organic moiety is bonded more strongly to copper than to lithium, creating 'nucleophilic' and 'electrophilic' sites within the metal cluster.[33]

In the most pivotal structural investigation of organocuprates in recent years, Lipshutz reported[34a] the startling discovery that the classical Gilman reagent, $Me_2CuLi$, exists in halide-free THF solution, not as a discrete species, but rather as an equilibrium mixture containing significant amounts of free methyllithium. Attesting to the often crucial role played by lithium salts, the addition of a stoichiometric amount of LiI suppresses the equilibrium, and no methyllithium is detected. Interestingly, no equilibrium is observed when $Me_2CuLi$ is prepared in ether, even if THF is then added to the mixture. However, the

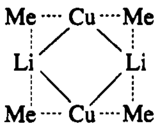

**(7)**

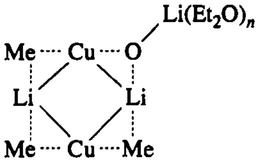

**(8)**

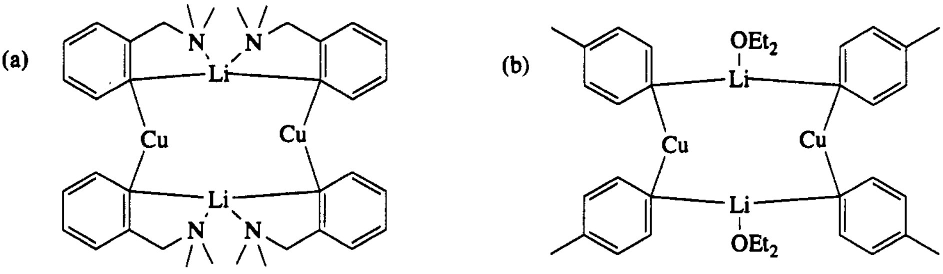

**Figure 2**

reagent is spectroscopically different from that prepared in THF or THF–ether.[35] Clearly, much remains to be learned about organocuprate reagents, but these findings do carry important synthetic implications.

The addition of $BF_3\cdot OEt_2$ to a solution of an organocopper compound often results in a reagent of enhanced reactivity and/or selectivity.[36] That organocopper compounds are compatible with $BF_3\cdot OEt_2$ at low temperature (*i.e.* transmetalation does not occur) has long been established, and the observed experimental results have been attributed primarily to substrate activation by complexation with the Lewis acid. However, recent spectroscopic and chemical evidence[34b,c] suggests that, when used in combination with an organocuprate, $BF_3\cdot OEt_2$ serves not only to activate the substrate, but also to modify the cuprate reagent itself. In particular, one equivalent of alkyllithium is irreversibly sequestered from the $R_4Cu_2Li_2$ reagent in the form of $RLi\cdot BF_3$, leaving $R_3Cu_2Li$ as the species predominantly responsible for chemical reactivity. Excess $BF_3\cdot OEt_2$ must then function in its second, substrate-activating capacity, since $R_3Cu_2Li$ is comparatively unreactive in its absence.

Corey has reported[37] the preparation of yet another type of modified cuprate reagent by mixing lithio dimethylcuprate and water in a 3:1 ratio. Of proposed structure (**8**), this new reagent exhibits enhanced reactivity and stereoselectivity in reactions with enones, effects that are proposed to be due to an increased ability of lithium to coordinate to the substrate. The Corey group has also prepared a rationally designed chiral heterocuprate reagent,[38] which undergoes highly enantioselective conjugate addition reactions with cycloalkenones.

### *1.5.2.2.5 Mixed homocuprates (RR′CuLi)CuLiCuLi*

An obvious disadvantage of homocuprates is the fact that one potentially valuable organic ligand is necessarily wasted. Therefore, over the years considerable effort has been devoted to the search for suitable nontransferable (or 'dummy') ligands. A number of heteroatom substituents have been used for this purpose (see Section 1.5.2.2.3), and it should be noted that RCu(SPh)Li allows the successful transfer of secondary and tertiary alkyl groups, a feat not readily accomplished by homocuprates.[39] However, heterocuprates, including cyanocuprates, are generally less reactive than homocuprates. Alkynyl ligands have often been successfully employed as 'dummy' ligands; $MeOC(Me)_2C{\equiv}CH$ offers the advantage that the corresponding monoorganocopper compound is soluble in organic solvents. Most recently, the use of DMSO as a nontransferable ligand has been proposed.[40] Since product isolation is often complicated by the presence of added ligands, the fact that DMSO can be simply washed away represents a significant advantage.

### *1.5.2.2.6 Higher-order cuprates [$R_2Cu(Z)Li_2$, $R_{m+n}Cu_mLi_n$ ($m + n > 2$)]*

In contrast to earlier reports,[41] recent spectroscopic evidence[34a] indicates that cuprate reagents in which the stoichiometric ratio of RLi:RCu is >1:1 are not discrete species in ether or THF solution, but rather mixtures of the Gilman reagent, $R_2CuLi$, and free alkyllithium. The excess alkyllithium present in these mixtures may serve a beneficial role in some cases (*e.g.* converting the by-product RCu back into reactive $R_2CuLi$), accounting for the improved experimental results that have reportedly been obtained with '$R_3CuLi_2$'.[42] By contrast, the higher-order cuprate $Ph_3CuLi_2$ is apparently observable in dimethyl sulfide solution.[43] Cuprate reagents in which the RLi:RCu ratio is <1:1 have also been described. $R_3Cu_2Li$ is a discrete species in THF, while $R_5Cu_3Li_2$ is the first soluble cuprate formed upon addition of RLi to RCu in ether.[42b] The $R_5Cu_3Li_2$ reagent has proven to be particularly useful for effecting 1,4-conjugate addition to enals,[44] and it also exhibits better regio- and stereo-selectivity than does the Gilman reagent in $S_N2'$ reactions with allylic carbamates.[45]

Better established are the higher-order cyanocuprates ($R_2CuCNLi_2$) extensively investigated by Lipshutz and coworkers.[46] These reagents represent a compromise between lower-order cyanocuprates and homocuprates, offering the increased stability of the former, while maintaining reactivity nearly comparable to that of the latter. The mixed gegenion compounds $R_2CuCNLiNa$ and $R_2CuCNMgX$ have also been examined; both are less reactive than the corresponding dilithio cyanocuprates.

Ashby[41] has reported that, like $Me_2CuLi$, $Me_3Cu_2Li$ is dimeric in THF solution, but that $Me_5Cu_3Li_2$, which is formed only in ether, is monomeric. Lipshutz[46c] has presented spectroscopic evidence suggesting that higher-order cyanocuprates ($R_2CuCNLi_2$) are also dimeric in THF. However, for these reagents, the poorer Lewis basicity of ether apparently promotes higher states of aggregation in that solvent. The spectroscopic investigations conducted by the Lipshutz group have also provided fascinating insight into the dynamic behavior of organocuprates in solution, which stands in sharp contrast to the common perception of the essentially static nature of the reagents.

Like their lower-order homocuprate analogs, higher-order cyanocuprates suffer the disadvantage that only one organic ligand is transferred. Ligand transfer ability decreases in the order Bu > Ph > Me > vinyl, rendering selective vinyl transfer especially difficult. The 2-thienyl (2-Th) group has proven to be a particularly useful 'dummy' ligand for these reagents, allowing even vinyl substituents to be transferred with high selectivity.[47] The preparation of the mixed cyanocuprate $R(2\text{-Th})CuCNLi_2$ is most conveniently accomplished by simply adding an alkyllithium reagent to preformed 2-thienylcyanocuprate [(2-Th)CuCNLi], which is stable in THF solution for three weeks or more at room temperature and two months or more at −20 °C.[48]

## 1.5.2.3 Mechanism of the Reaction

Although much is now known about the coupling of organocopper reagents with organic electrophiles, many details of the reaction mechanism remain incompletely understood. In fact, recent findings indicate that more than one mechanism may be operative, depending upon the nature of the substrate involved (*vide infra*). Several general features of the reaction are clear: (i) the rate law is usually first order in both substrate and organocuprate; (ii) substrate reactivity follows the pattern typical for $S_N2$ reactions: primary > secondary >> tertiary; (iii) reactions of secondary bromides and tosylates proceed predominantly with inversion of configuration; (iv) alkenyl halides and alkenylcuprates both couple predominantly with retention of configuration; and (v) the reactivity of the transferred group decreases in the order primary > secondary > tertiary. These facts all argue against a process involving free radical intermediates, in agreement with the finding that free radical traps generally have little effect on the course of the reaction.

On the basis of this information, the reaction is now believed to proceed by way of an oxidative addition–reductive elimination pathway, in which the rate-determining oxidative addition step occurs with inversion of substrate configuration by a bimolecular nucleophilic substitution mechanism (Scheme 2). The retention of $sp^2$-configuration is also consistent with an oxidative addition process,[3b,49] and a stereoelectronic rationale for this stereochemical outcome has been proposed.[50] The intermediate (**9**) has been the focus of much debate, however, since a $Cu^{III}$ species of this type is expected to be very unstable.[51,52] In a modification of this mechanism, it has been suggested[31] that the dimeric structure of the organocuprate reagent plays a critical role in the reaction, allowing the formal $2e^-$ oxidation to take place by way of cooperative single-electron oxidations of both copper atoms in the metal cluster, thereby eliminating the need to generate a high energy $Cu^{III}$ transient intermediate (equation 4).

Inconsistent with both of the above mechanistic proposals is the recent finding that secondary iodides, unlike bromides and sulfonates, undergo nearly complete racemization in coupling reactions with organocuprates.[54] In addition, bicyclic compounds are produced in reactions of 6-iodocyclooctene with

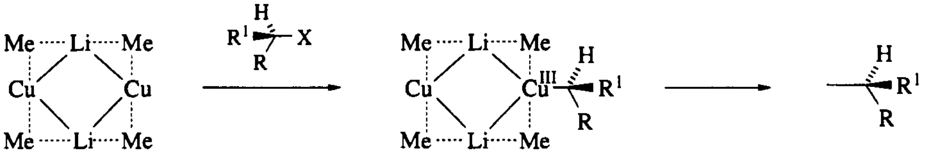

(7) (9)

**Scheme 2**

$$[\mathrm{Cu^{I}_2Li_2Me_4}] + \mathrm{RI} \longrightarrow [\mathrm{Cu^{II}_2Li_2Me_4R}]\mathrm{I} \longrightarrow \mathrm{MeR} \qquad (4)$$

lithium cuprate reagents (equation 5),[55] strongly supportive evidence for the intermediacy of free radicals in these reactions. In fact, bicyclic products are also found in reaction mixtures of the alkenic bromide substrate. By contrast, elimination is the only competing pathway observed in reactions of the corresponding *p*-toluenesulfonate.

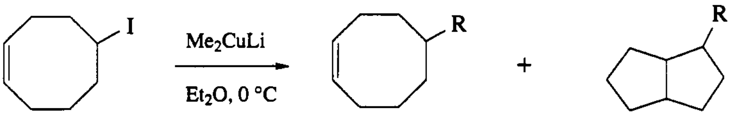

(5)

R = H; 17%
R = Me; 13%

R = H; 23%
R = Me; 4%

An explanation for these results may be found in a comparison of the electrochemical reduction potentials for the various substrates.[56] Secondary alkyl iodides give two waves at potentials considerably more positive than the single wave exhibited by alkyl bromides, while reductive cleavage of alkyl sulfonates occurs at the S—O bond rather than the C—O bond. Two competitive pathways therefore appear to be operative for reactions of organocuprates: (i) the $S_N2$-like mechanism depicted in Scheme 2; and (ii) an alternative mechanism involving single-electron transfer (SET). The observed difference in reactivity order between primary substrates (OTs ≥ I > Br > Cl) and secondary substrates (I >> OTs > Br > Cl) is a reflection of this mechanistic duality. Thus, while an energetically favorable electron transfer pathway is available for secondary alkyl iodides, secondary tosylates are constrained to react by the much slower $S_N2$-like mechanism. For primary alkyl substrates, on the other hand, the $S_N2$-like process is considerably more competitive, reactivity follows the standard order of leaving group ability, and the occurrence of free radical side reactions (*e.g.* cyclization, alkylative cyclization, reduction) is diminished. Even primary iodides give significant amounts of the dehalogenated by-product in reactions with $R_2CuCNLi_2$, however.[57]

More extensive investigations[55] have revealed additional complexities in the SET mechanism. Thus, evidence supportive of both free radical and radical anion ($S_{RN}1$) chain processes has been observed in reactions of alkyl iodides, both pathways presumably being initiated by electron transfer between cuprate and substrate. Although incapable of sustaining free radical chain processes, alkyl bromides do apparently react, at least in part, by an $S_{RN}1$ mechanism. While the intervention of free radical processes in reactions of alkyl bromides would appear to be inconsistent with the predominant stereochemical inversion exhibited by these substrates, Ashby has demonstrated[58] that electron transfer processes can occur with inversion of configuration.

In summary, while alkyl sulfonates react exclusively by the $S_N2$-like mechanism of Scheme 2 (or equation 4), evidence for alternative SET processes in reactions of both alkyl iodides and alkyl bromides has recently accumulated. The relative contributions of $S_N2$ and SET mechanisms in reactions of alkyl halides is difficult to quantify, however, since the 'normal' substitution product can arguably arise *via* either pathway.

### 1.5.2.4 Reactions With Organic Substrates

#### *1.5.2.4.1 Alkyl halides and sulfonates*

Primary alkyl halides and sulfonates react readily with organocopper reagents, the order of reactivity being that typical of nucleophilic substitution reactions (OTs > I > Br >> Cl). Since alkene, ester, amide, ketone and nitrile functionalities are all tolerated, the method is of widespread generality, and innumerable synthetic applications have been reported in the literature. The spectacular success enjoyed by organocopper reagents in reactions with unactivated alkyl halides is to be contrasted with the general failure of other transition metal catalyzed cross-coupling reactions of these substrates (see Section 1.5.3), in which β-elimination is usually a predominating side reaction.

Monoorganocopper compounds are generally less reactive than organocuprates and are therefore less often used in reactions with unactivated alkyl halides. Interestingly, however, in one recently reported[59] reaction, an alkylcopper species derived from the Grignard reagent and one equivalent of CuI coupled satisfactorily at a neopentyl center, while all other reagents failed. Vinylcopper compounds, although not especially reactive, can be alkylated smoothly in the presence of HMPA and a trialkyl phosphite.[21a] In an application of this procedure, tetrasubstituted alkenes have been prepared in a stereodefined fashion from (2-stannylalkenyl)boranes by sequential transmetalation and alkylation of the borane and stannane moieties.[60] A similar strategy was utilized in recently reported syntheses of (*E*)- and (*Z*)-γ-bisabolene (**10**).[61] Alkynyl copper reagents are not effective coupling partners with alkyl halide substrates.

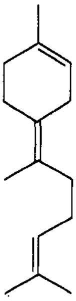

**(10)**

The coupling of organocopper reagents with primary alkyl substrates is often accomplished as effectively under catalytic conditions as it is with stoichiometric organocopper reagents. Whereas a large excess of the stoichiometric reagent is often necessary, the use of copper in catalytic amounts appears to ameliorate this requirement. Alkyl sulfonates are reported to be particularly successful substrates in copper-catalyzed coupling reactions.[62] Grignard reagents are by far the most frequently employed organometallics in these reactions, but copper-catalyzed alkylations of alkyllithium reagents are not uncommon.[10c,63] The copper-catalyzed alkylation of a vinyl aluminate has also been reported.[64] Copper catalysis is known to alter the regioselectivity of reactions of allylic Grignard reagents. Thus, although allylic Grignard reagents ordinarily exhibit a strong preference for reaction at the γ-position, even when that position is the more sterically hindered, under copper catalysis, prenylmagnesium chloride is alkylated at the primary α-position with >99% regioselectivity.[65]

As a rule, stoichiometric cuprate reagents have provided the most consistently successful results in reactions with primary alkyl electrophiles. Diethyl ether is the solvent of choice for reactions of alkyl sulfonates, while reactions of alkyl halides appear to be facilitated by THF. The enhanced basicity of the cuprate reagent in THF may be problematic, however, when racemization of an adjacent chiral center or elimination is a competing side reaction. For example, reactions of serine-derived β-halo esters must be performed in ether, since elimination by-products are the only products isolated when THF is employed as the solvent;[66] elimination is more problematic with sulfonate than with halide leaving groups.

A number of mixed homocuprates and heterocuprates have been successfully employed in coupling reactions with alkyl halides (see Sections 1.5.2.2.5 and 1.5.2.2.3). The phosphido heterocuprates $RCuP(Bu^t)_2Li$[28] and $RCuPCy_2Li$[27b] react readily with primary bromides and iodides, providing coupled products in yields comparable to those obtained with homocuprates. Heterocuprates, of course, offer the advantage that only one equivalent of the organic ligand is required. In a recently reported[67] synthesis of

12-HETE, a new higher-order heterocuprate of the type $RCu(CN)_2NBu_4Li$ was the only reagent to provide satisfactory yields in the coupling of a 1,4-dienylcuprate with an alkyl iodide.

Higher-order cyanocuprates $(R_2CuCNLi_2)$[46] have proven to be the most reactive of all organocopper reagents in reactions with alkyl halides.[68,69] In fact, the reagents are too reactive with primary iodides for the reaction to be of general synthetic utility, since reduction is usually a serious side reaction even at low temperature. Coupling with primary bromides, on the other hand, is facile at –50 °C, and less than 2 equiv. of the cuprate reagent are required. Even primary chlorides, typically very poor substrates, react well with $R_2CuCNLi_2$, although chemospecific displacement of bromide in the presence of chloride is easily accomplished.

Higher-order cyanocuprates are particularly useful for reactions of secondary alkyl substrates. Although substitution of secondary halides can be successfully effected with lower-order cuprate reagents, results are variable due to competing elimination and reduction side reactions. By contrast, the $R_2CuCNLi_2$ reagents generally provide reproducibly high yields of coupled products in reactions with secondary iodides and bromides. Exceptions are transfers of phenyl and *s*-alkyl, for which the corresponding Gilman reagents are more effective. Secondary chlorides are not reactive with any of the reagents. Interestingly, higher-order cyanocuprates do not react with secondary mesylates and react only sluggishly with secondary tosylates. By contrast, sulfonates are more reactive than halides in reactions with lower-order homocuprates.

Double substitution of geminal dibromides is best accomplished by treatment with an organocuprate, followed by the addition of an alkyl iodide to the crude reaction mixture.[70] The reaction has found especial application for the synthesis of dimethylcyclopropanes, ubiquitous in natural product chemistry. Excellent yields are often obtained with $Me_2CuLi$,[71] but with less reactive substrates higher order cyano- and thiocyano-cuprates sometimes provide better results.[72] Spiro dialkylation of geminal dibromides has also been accomplished.[73] Vicinal dibromides, on the other hand, afford alkenes upon treatment with dialkyl cuprates.[74]

The issue of stereochemistry in reactions of organocopper reagents with secondary electrophiles was addressed briefly in Section 1.5.2.3. In general, bromides and sulfonates react predominantly with inversion of configuration, while iodides undergo extensive racemization by a free radical pathway. Iodide (**11**), with a strong bias for substitution from the *exo* face, was reported[75] to react with complete retention of configuration (equation 6). The corresponding tosylate, for which an electron transfer pathway is not available, was unreactive. Net retention of configuration has also been observed in reactions of secondary sulfonates, although not in this case by an SET mechanism. In one example, intramolecular carbamate participation was invoked to explain the observed stereochemical results.[76] Poor stereospecificity in reactions of alkyl sulfonates may also result from a competing double inversion process when $I^-$ is present in the reaction mixture.[77]

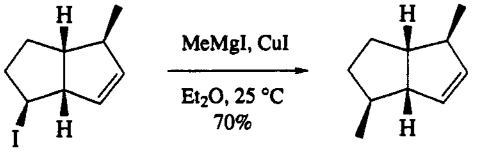

(6)

**(11)**

*C*-Glycosides have been prepared by the reaction of α-glycosyl halides with dialkylhomocuprates (equation 7).[78] The reaction proceeded with complete inversion of configuration, despite the fact that α-halo ethers are expected to be especially susceptible to electron transfer processes. Reductive elimination was a serious side reaction, however. With these substrates, higher-order cyanocuprate reagents were surprisingly unreactive, while Grignard reagents gave mixtures containing both α- and β-glycosides, as well as elimination and reduction by-products.

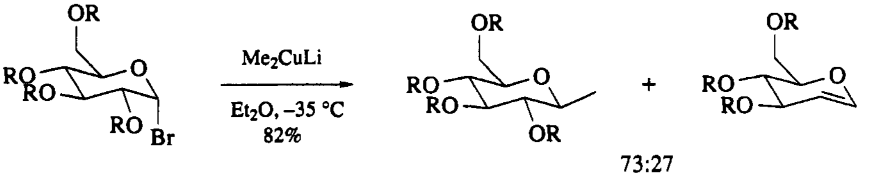

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### *1.5.2.4.2 Alkenyl halides and related electrophiles*

Cross-coupling of alkylcopper compounds with alkenyl halides is not generally successful, because the reagents are unstable at the temperatures usually required to effect reaction. Vinyl halides do undergo facile substitution by lithium dialkylcuprate reagents, however. As mentioned in Section 1.5.2.3, alkenic geometry is predominantly retained, but stereochemical scrambling may be observed when an alternative conjugate addition–elimination pathway is available.[2] In combination with hydrometalation and halometalation methodology, the procedure allows the regio- and stereo-specific preparation of trisubstituted alkenes from alkynic precursors. Methyl substitution is an especially common synthetic operation, due to its application to the synthesis of terpenoid natural products. Substitution reactions of vinyliodonium salts, themselves derived from vinylsilanes, have also been reported.[79]

Cuprate reactions of allenyl halides have been the focus of considerable investigation. The ratio of product resulting by a direct substitution pathway (Scheme 3, path a) to that produced by an $S_N2'$ mechanism (path b) is dependent upon both the nature and structure of the reagent and the substitution pattern of the substrate.[80] In general, the Gilman reagents, $R_2CuLi$, afford allenic products exclusively, while RCuCNLi and (RCuBr)MgX·LiBr exhibit highly selective $S_N2'$ reactivity, except when this pathway would be strongly disfavored due to steric hindrance (R = secondary or tertiary alkyl). Unpredictably, phenylcyanocuprate affords the product of direct substitution with high regioselectivity, while (PhCuBr)MgBr·LiBr provides the alkynic $S_N2'$ product with equally high selectivity.

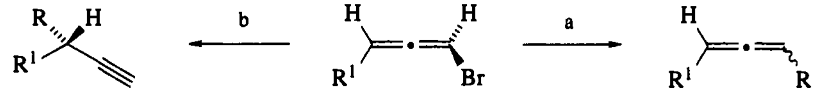

Scheme 3

The stereochemistry of the direct substitution reaction has been the subject of some debate.[81] Most recently, it has been reported[80b] that reactions of alkylheterocuprates proceed with high *syn* selectivity, while inversion of allenyl configuration, or *anti* selectivity, is observed in reactions of phenylcopper reagents. The degree of selectivity is variable and may be a reflection of product isomerization under the reaction conditions.[82] Predominant *anti* stereoselectivity (*anti*:*syn* ratios range from 91:9 to >99:1) is observed also in $S_N2'$ reactions of allenyl halides (see Scheme 3),[80b,83] a finding that is consistent with the known preference for *anti* substitution of allylic substrates (see Section 1.5.2.4.5). This method for alkyne preparation has found application in the leukotriene area,[84] and also for the synthesis of alkoxy alkynes.[85]

Vinylcopper reagents, in contrast to their alkyl analogs, have proven to be extremely unreactive toward vinyl halide substrates. However, the desired cross-coupling reaction can be effected in the presence of a palladium catalyst, providing access to stereodefined 1,3-dienes, valuable synthetic intermediates. The procedure has been extensively investigated by Normant and Alexakis,[21] who have additionally discovered that zinc halide cocatalysts allow the transfer of both vinyl ligands of cuprates derived from Grignard reagents. Likewise, although lithium cuprates transfer only one organic ligand in these zinc–palladium catalyzed reactions, both groups can be successfully transferred if a magnesium halide is also added to the reaction mixture. These reactions are all highly stereospecific, proceeding with virtually exclusive retention of configuration in both components.

In a recent application of similar methodology, α-vinyl acrylates were prepared by palladium-catalyzed cross-coupling of lithium (α-carbalkoxyvinyl)cuprates with vinyl halides.[86] Use of the dicyclohexylamido group as the nontransferable ligand in this reaction was necessary, since alkyne ligands transferred preferentially over the α-carbalkoxy moiety. It should be noted that (α-carbalkoxyvinyl) cuprates are, in general, extremely unreactive reagents, reacting in the absence of catalysts only with activated halides (allylic, propargylic, acyl, α-halo ethers).[87] α-Cupriopyrone, a special member of the class, is, in fact, the least nucleophilic organocopper reagent known.[88]

Palladium catalysis is also involved in an exceptionally mild procedure for the stereospecific preparation of enynes.[89] A catalytic version of the Stephens–Castro coupling,[90] the reaction presumably involves *in situ* generated copper(I) acetylide intermediates and proceeds with retention of alkenyl configuration. Several experimental modifications have been reported.[91] Notable synthetic applications include ynenol lactone inhibitors of human leukocyte elastase,[92] an irreversible inhibitor of soybean lipoxygenase,[93] and a number of eicosanoid metabolites of arachidonic acid.[94] Most recently, the reaction has been utilized extensively in synthetic approaches[95] to the bicyclic enediyne core common to the esperamicin, *e.g.* (**12**), and calichemicin antitumor agents, compounds that are of considerable biological interest. The reaction sequence depicted in Scheme 4[95a] is representative of the general approach and is illustrative of the efficiency of the coupling procedure. The coupling of alkynes with allenyl bromides has also been reported.[96] Palladium-catalyzed coupling reactions of organometallics other than organocopper reagents are discussed in Section 1.5.3.2.

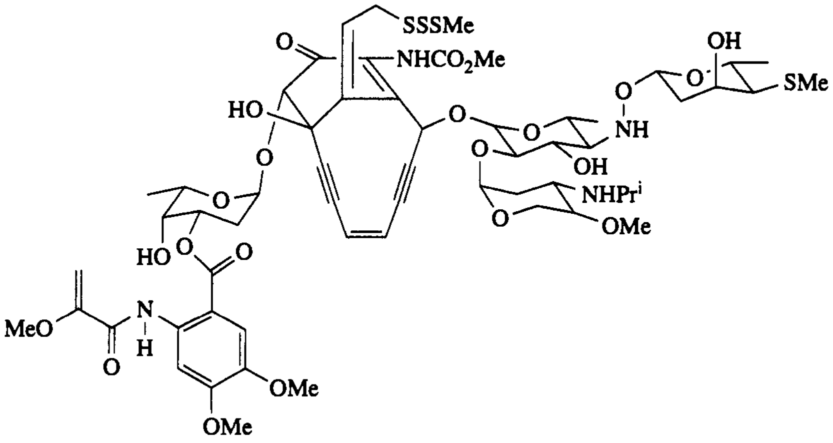

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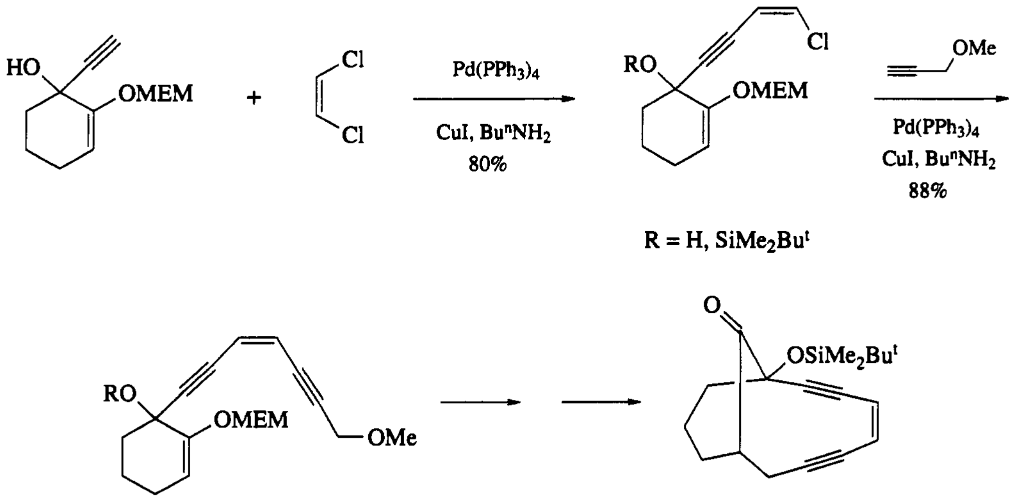

**Scheme 4**

The coupling of organocopper reagents with nonhalide vinyl electrophiles has also been accomplished. Displacement of enol phosphates can be effected in good yields with very reactive dialkylcuprates.[97] However, less reactive cuprates (*e.g.* $Me_2CuLi$) give low yields of the coupled product, and hindered enol phosphates are unreactive. Diphenyl phosphates derived from chlorodifluoromethyl aryl ketones do not undergo direct substitution of the enol phosphate moiety, but are rather metalated to give a fluorinated vinylcopper intermediate, which can then be alkylated with allylic halides.[98] Like enol phosphates, vinyl triflates can be regioselectively prepared from the corresponding ketones, and they have proven to be more reactive than enol phosphates in reactions with cuprates.[99] Again, retention of alkenyl configuration is the rule, but some isomerization may occur.

Dihydrofuran and dihydropyran substrates react with organocopper reagents to provide homoallylic and bishomoallylic alcohols of (*E*)-configuration (equation 8).[100b] This reaction works best with ratios of RLi:CuX well exceeding 2:1; in fact, only 2 mol % of CuCN is required.[100] The stereochemical outcome of the reaction is attributed to the formation of a mixed dihydrofuranylalkylcuprate, followed by migratory insertion with inversion of configuration, a process that is well precedented in organoboron chemistry.

Organometallic substitution of iron-complexed dioxolenes has been reported.[101] The reaction proceeds with net inversion of configuration, the result of a two-step addition–elimination pathway. Dialkylcuprates, higher order cyanocuprates and Grignard reagents have all been employed, and sequential dis-

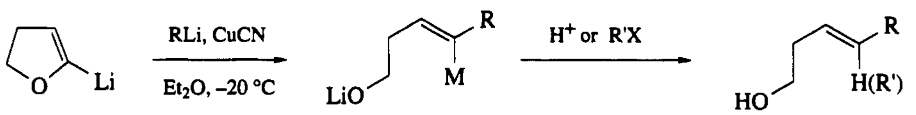

(8)

placements of both vinyl ether substituents can be accomplished. A single diastereomeric product is produced in reactions of enantiomerically pure dioxolene substrates.[102]

### *1.5.2.4.3 Alkynyl halides*

Like the Stephens–Castro reaction, Cadiot–Chodkiewicz coupling of terminal alkynes with alkynyl halides is presumed to proceed by way of copper(I) acetylide intermediates. The use of preformed copper acetylide reagents is also successful and, in fact, circumvents the problem of homocoupling sometimes encountered in the classical procedure. The reaction is convenient and high yielding, and is compatible with numerous functionalities, including free hydroxy and carboxy groups.[103] Arylcopper compounds react analogously with alkynyl halides,[104] providing a route to arylalkynes that is complementary to the Stephens–Castro coupling (see Section 1.5.2.4.4).

Metal–halogen exchange is a competing side reaction in the coupling of vinylcopper reagents with alkynyl halides. With monovinylcopper compounds, this problem can be overcome by performing the reaction in a mixture of THF–TMEDA, but lithium divinylcuprates undergo nearly exclusive metal–halogen exchange regardless of the reaction conditions.[21a] They can, however, be converted to the corresponding vinylcopper compounds by treatment with another equivalent of copper(I) halide prior to the addition of the alkynyl halide substrate, an advantageous procedure in light of the ready availability of divinylcuprates by carbocupration of alkynes.[21b] High yields of stereoisomerically pure 1,3-enynes can be obtained in this fashion. More recently, Stang and Kitamura have reported the stereospecific preparation of conjugated enynes by direct coupling of vinylcopper compounds with alkynylphenyliodonium tosylates.[105]

### *1.5.2.4.4 Aryl halides*

Because aryl ligands are better able than alkyl ligands to adopt the bridging, two-electron three-center bonding pattern characteristic of organocopper reagents (see Section 1.5.2.2),[11a] metal–halogen exchange predominates in reactions of aryl halides with alkylcopper reagents, especially dialkylcuprates. Therefore, alkyl–aryl coupling is often better accomplished by the alternative reaction of an arylcopper reagent with an alkyl halide. If aryl halide substitution must be effected, RCu·Lig reagents are more successful than $R_2CuLi$. Alkyl substitution of halopyridines has been accomplished with magnesium dialkylcuprates;[106] copper-free Grignard reagents, lithium dialkylcuprates, and nickel- or palladium-catalyzed coupling procedures were all ineffective for this transformation.

Aryl triflates undergo successful cross-coupling with higher-order cyanocuprates.[99] Heterocyclic triflates are also reactive, but the yield may be strongly dependent upon the structure of the reagent.[107] Lower-order Gilman reagents, although effective in coupling reactions with vinyl triflates, cause only S—O bond cleavage in reactions with aryl triflates.

The majority of reported reactions of aryl and heteroaryl substrates with organocopper reagents are examples of Stephens–Castro coupling[90] or the more recent catalytic version of that reaction.[89] The reaction has found recent application in syntheses of C-(6)-substituted pterins and pteridines,[108] substituted pyridines,[109] and the antitumor antibiotic fredericamycin A,[110] to name a few. Aryl iodide can be chemospecifically displaced in the presence of bromide,[110] and 2,5-dibromopyridine is regioselectively substituted at the 2-position.[109] Substitution of halobenzenes by propargyl alcohol, followed by oxidative cleavage, provides a convenient route to terminal arylalkynes.[111] Fused heterocycles are formed in reactions of aryl halides bearing nucleophilic *ortho* substituents.[90,112]

The classical Ullmann reaction has also attracted renewed interest in recent years. Miyano has prepared optically enriched binaphthyl derivatives by intramolecular biaryl coupling, as shown in equation (9).[113] Diastereoselectivities of up to 70% have been obtained with a binaphthol chiral auxiliary in the linking chain. Intermolecular cross-coupling is best accomplished with preformed arylcopper compounds.[114]

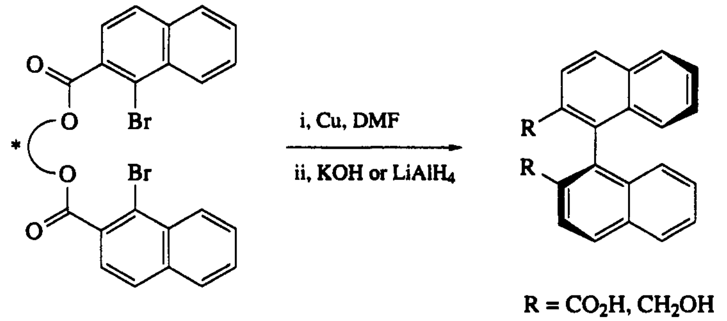

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### 1.5.2.4.5 Allylic, benzylic and propargylic electrophiles

Allylic, benzylic and propargylic electrophiles are more reactive than the corresponding saturated compounds toward nucleophilic attack, and organocopper reagents of virtually every description, both catalytic and stoichiometric, have been employed successfully in reactions with these activated substrates. In addition to the typical halide and sulfonate leaving groups, ordinarily unreactive ether, ester, sulfone,[115] phosphonate,[116] carbonate[117] and carbamate[118] moieties can all be displaced from an allylic or propargylic position. Apart from their obvious synthetic potential, reactions of allylic and propargylic electrophiles are also of considerable mechanistic interest, because of the intriguing regio- and stereochemical questions posed by these substrates. It is primarily these issues that will be addressed in the following section.

Primary allylic halides exhibit a preference for direct substitution (α-attack) in reactions with a variety of organocopper reagents, including lithium cuprates, copper(I) acetylides and catalytic organocopper compounds. Regioselectivity is often quite high, especially with γ,γ-disubstituted substrates, and alkenic stereochemistry is usually retained. For example, in a recently reported synthesis of (15*S*)-HETE (**13**) sequential substitution at both primary positions of (*Z*)-1,4-dichlorobutene was accomplished without loss of the (*Z*)-alkenic geometry.[119] Palladium-catalyzed Stephens–Castro coupling (see Section 1.5.2.4.2) was another key step in the synthesis.

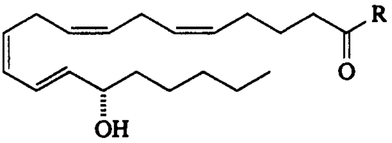

**(13)**

Secondary allylic halides, on the other hand, exhibit regioselective $S_N2'$ reactivity (γ-attack), particularly when the γ-position is unsubstituted. Thus, although sometimes highly regioselective, reactions with these reagents are not regiospecific.[120] Regioselectivity is also dependent upon the substitution pattern of the substrate in reactions of allylic esters with lithium cuprates and catalytic organocopper compounds. Again, a preference for nucleophilic attack at the less hindered position is evidenced, and regioisomeric substrates give rise to the same product mixtures.[121] Reactions of acyclic substrates that proceed with allylic rearrangement (γ-attack) often display moderate to good (*E*)-selectivity in formation of the new double bond.

Regioselectivity is less predictable when both termini of the allylic system are comparably substituted. Results can be dependent on the leaving group; oxygen leaving groups appear to favor α-attack more than halides, and chloride is more $S_N2$ selective than bromide.[122] Very high $S_N2'$ selectivity has been reported for reactions of some cyclic allylic esters with lithium cuprate reagents,[123] but exclusive α-substitution has been observed when γ-attack was disfavored by steric crowding at the δ-position.[124] Regioselective (*ca.* 9:1) α-attack has also been reported for reactions of (*Z*)-4-hexenolide with both lithium and magnesium cuprates.[125] As part of research efforts directed toward the total synthesis of ginkgolide B, Corey and Gavai[126] discovered that highly selective (≥98:2) $S_N2'$ displacement of cyclopentenyl pivalate (**14**) could be effected with a Grignard reagent and 3 mol % of CuCN (equation 10). By contrast, the stoichiometric higher-order lithium cyanocuprate was much less regioselective and favored direct substitution.

A number of organocopper reagents reportedly exhibit $S_N2'$ selectivity even when steric factors would appear to favor α-attack. Magnesium cuprates, in general, show greater propensity to undergo reaction

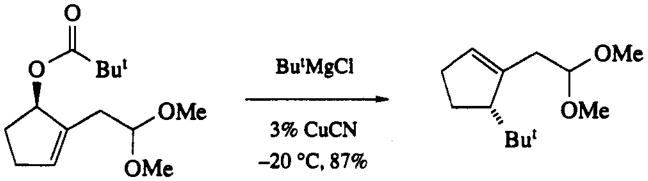

**(14)**

$S_N2':S_N2$ = >98:2

(10)

with allylic rearrangement than do their lithium counterparts.[127] The complex organocopper species RCu·MgBrX·LiBr displayed high (≥98:2) $S_N2'$ selectivity in reactions with 1,4-diacetoxy-2-butene,[128] but only with R = alkyl; reactions of the phenyl reagent were low yielding and $S_N2$ selective. Curran has reported[129] almost exclusive $S_N2'$ stereospecificity, regardless of substitution pattern, in reactions of the bicyclic lactones (**15**) with MeMgBr–CuBr·Me$_2$S (1:1) (equation 11). One full equivalent of CuBr·SMe$_2$ was required for high regiospecificity, and CuBr·SMe$_2$ produced a more selective reagent than did CuI or CuCN. Reactions of the same substrates with lithium cuprates, on the other hand, were controlled by the substrate substitution pattern, but were highly regioselective in favorable cases. This procedure has found recent application in syntheses of the triquinane sesquiterpenes, (±)-hypnophilin (**16**) and (±)-coriolin (**17**).[130]

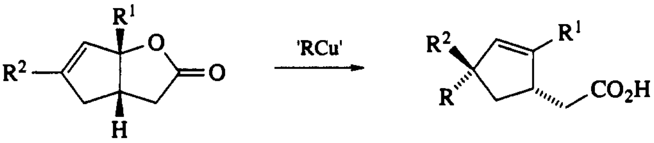

**(15)**

(11)

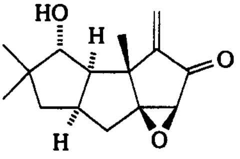

**(16)**

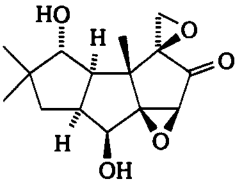

**(17)**

Copper-catalyzed reactions of organozinc reagents exhibit high $S_N2'$ regiospecificity in reactions with allylic halides, even when steric and/or electronic factors would appear to favor $S_N2$ attack.[131] The regiospecificity of these copper-catalyzed reactions stands in contrast to nickel- or palladium-catalyzed reactions of organozinc reagents, in which attack occurs regioselectivity at the least hindered position. Very recently, Nakamura[132] has reported virtually complete diastereofacial selectivity in $S_N2'$ reactions of organocopper reagents with 4-alkoxyallylic chlorides (equation 12). Whereas lithium dialkylcuprates reacted with (**18**) predominantly by an $S_N2$ pathway, Bu$_2$CuZnCl,[133] Bu$_2$CuTi(OPr$^i$)$_3$, BuCu·BF$_3$, and Bu$_2$Zn/cat. CuBr·SMe$_2$ all provided the γ-substituted products with regioselectivities of ≥98:2 and *anti*-diastereoselectivities of ≥99:1. Reactions of other substrates and reagents were also highly *anti*-$S_N2'$ selective. This procedure promises to find widespread application for the stereoselective construction of acyclic quaternary centers.

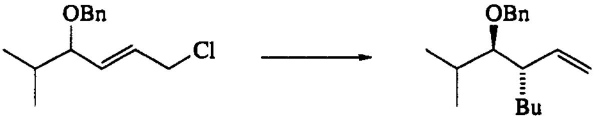

**(18)**

(12)

Suzuki reported[134] that copper borates (R$_3$MeB$^-$Cu$^+$) exhibit predominant $S_N2'$ reactivity toward allylic halides. A similar 'ate' complex (RF$_3$B$^-$Cu$^+$) is also proposed to be the reactive intermediate in the RCu·BF$_3$ system developed about the same time by Yamamoto and coworkers.[36] This latter reagent exhibits remarkable $S_N2'$ regiospecificity in reactions with a variety of allylic substrates, including halides, esters and alcohols. Lithium cuprates[135] and higher-order cyanocuprates[136] have also been used in conjunction with $BF_3{\cdot}OEt_2$, again with $S_N2'$ regiospecificity. The $R_2CuCNLi_2{\cdot}BF_3$ reagent has proven especially useful for $S_N2'$ reactions of γ-oxygenated α,β-unsaturated esters, substrates which are highly susceptible to reduction side reactions. It should be noted, however, that a seemingly similar reagent, $RCu-(AlCl)_n$, effects highly selective $S_N2$ substitution (α:γ = 97:3) of γ-acetoxy-α,β-unsaturated esters.[137]

A mechanistic proposal that accommodates these diverse experimental results is presented in Scheme 5. The result of extensive research efforts in Goering's laboratory,[121c,138] it postulates that coordination of the organocopper reagent to the alkenic π-system is followed by formation of a σ-complex with attachment of copper at the γ-position. Immediate reductive elimination then directly affords the $S_N2'$ product, whereas prior isomerization to a π-complex results in the loss of regiochemical information and leads to the possible formation of both α- and γ-substituted products. Investigations with isotopically labeled, symmetrical substrates confirm that, as required by the proposed mechanism, *all* organocopper reagents exhibit some degree of $S_N2'$ regiospecificity in completely unbiased systems. In agreement with the experimental observations discussed earlier, this $S_N2'$ specificity is barely detectable in reactions of lithium dialkylcuprates, a result attributable to rapid σ–π isomerization. By contrast, isomerization is minimized in reactions of lower-order cyanocuprates RCuCNLi or $RCu{\cdot}BF_3$, and virtually exclusive $S_N2'$ substitution obtains. Bäckvall[139] has invoked a similar mechanistic rationale to explain his finding that regioselectivity in copper-catalyzed reactions of allylic acetates with alkyl Grignard reagents is strongly dependent upon the rate of addition of the organometallic reagent to the reaction mixture.

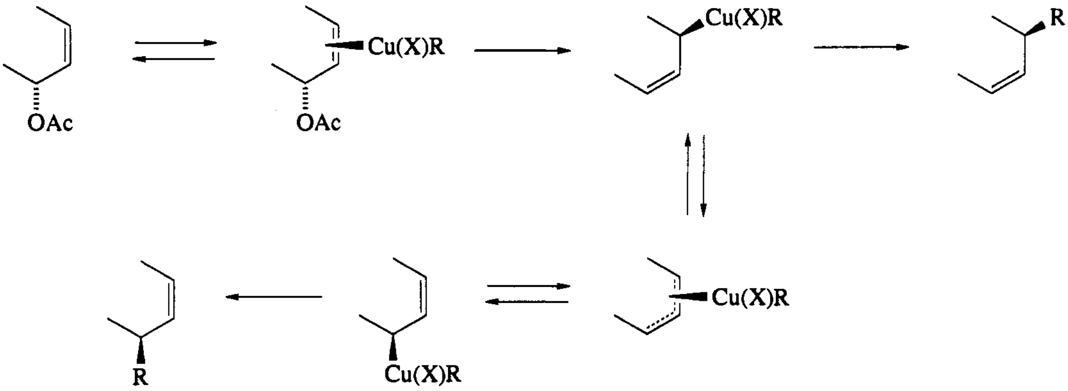

**Scheme 5**

The stereochemical outcome of the substitution of allylic substrates by organocopper reagents can also be explained by the mechanism depicted in Scheme 5.[138b] Initial coordination of the organocopper reagent is expected to occur on the less hindered face of the allylic system. In most substrates, this will be the face opposite the leaving group, thus accounting for the predominant *anti* substitution observed in all of the reactions (both $S_N2$ and $S_N2'$) discussed thus far. It should be noted, however, that *syn* substitution may prevail when *anti* attack is strongly disfavored by steric factors.[138b,140]

By contrast, reactions of allylic *N*-phenylcarbamates with lithium cuprates proceed with very high *syn*-$S_N2'$ selectivity, regardless of steric considerations.[118,141] Goering proposes that the reversal in stereoselectivity and the enhanced regiospecificity observed in reactions of carbamate substrates are both consequences of a modified reaction mechanism, in which initial complexation of the copper reagent to nitrogen is followed by intramolecular, *syn*-facial delivery of copper to the γ-position of the allylic system.[142] A similar mechanism is presumably operative in the substitution of allylic alcohols by $RCu{\cdot}BF_3$, a reaction that also proceeds with *syn*-$S_N2'$ specificity. On the other hand, selective *anti*-$S_N2'$ substitution of allylic alcohols can be effected by means of the procedure developed by Murahashi,[143,144] which apparently involves addition of an *in situ* generated heterocuprate to a phosphonium ion intermediate.

Calo has reported[145] very high $S_N2'$ regiospecificity in reactions of benzothiazolyl ethers with RMgX–CuBr. Again, the enhanced regiospecificity is attributed to coordination of the reagent to the ether moiety, and the isolation of coordination complexes lends credence to the proposal. Regioselectivity is completely reversed if the substrate is pretreated with copper(I) bromide prior to addition of the Grignard reagent, however. In that case, the Grignard reagent apparently attacks regioselectively at the least hindered position of a presumed copper(I) halide–substrate complex. The stereospecificity of the reaction has not been investigated. Ammonium salts are apparently also capable of intramolecular participation, as indicated by the *syn*-$S_N2'$ reaction of **(19)** with lithium cuprates (equation 13).[16] However, reaction of the regioisomeric substrate occurs in an *anti*-$S_N2$ fashion, since in that case the *syn*-$S_N2'$ pathway is disfavored by steric hindrance of the adjacent silyloxy moiety.

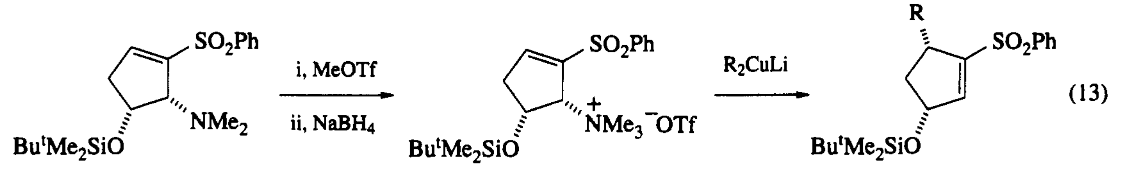

(13)

**(19)**

Much of the foregoing discussion regarding allylic substrates applies also to propargylic electrophiles, which exhibit an even greater propensity to undergo reaction with organocopper reagents by an $S_N2'$ mechanism. The preparation of allenes from propargylic substrates by this method has been reviewed elsewhere,[146] and will be discussed only briefly here. Among numerous synthetic applications, the reaction plays a central role in Okamura's synthetic approach to vitamin D[147] and vitamin A[148] analogs, and it has also been utilized for the synthesis of oxabetweenallenes.[149] Propargyl esters and sulfonates are the most commonly employed substrates, but halogen, amide, carbonate, phosphonate, ether and epoxide leaving groups have also been used. Direct conversion of propargyl alcohols to the corresponding allenes can be accomplished by means of the Murahashi procedure.[150] α-Allenyl phosphates and imides also undergo $S_N2'$ substitution by organocopper reagents, in this case providing dienyl products.[183]

Regioselectivity is subject to steric control[152] when dialkylcuprates are employed as the nucleophilic reagents, but the complex organocopper species RCu·MgBrX·LiBr affords the allenic product exclusively, regardless of substrate structure.[153] In addition, monoorganocopper compounds are less susceptible than cuprate reagents to reduction side reactions. Higher-order cyanocuprates appear to be more effective than Gilman reagents for transfer of phenyl or of secondary or tertiary alkyl groups, although the reverse is true for *n*-alkyl reagents. *Anti* stereospecificity is observed in all of these reactions,[154] allowing the preparation of enantiomerically enriched allenes from optically active propargylic substrates. In the presence of donor ligands, racemization of the product allene by the cuprate reagent is minimized, and the stereospecificity of the reaction is increased.

In contrast to reactions of all other organocopper reagents, reactions of copper(I) acetylides with propargylic substrates result in regiospecific α-substitution. This procedure for the preparation of 1,4-diynes has proven useful in pheromone synthesis.[155]

### *1.5.2.4.6 Epoxides*

Long valued by organic chemists as versatile synthetic intermediates, epoxides have experienced a resurgence in popularity over the past decade as a result of newly developed and highly efficient procedures for their preparation in homochiral form.[156] Owing to the polarity and strain of the three-membered ring, epoxides undergo reaction with a wide variety of reagents, the reactions proceeding in a stereospecific and often highly regioselective fashion.[157] Ring opening by carbon nucleophiles is arguably among the most synthetically useful of epoxide transformations, and organocopper reagents have proven to be especially well suited for this purpose. Not only are they more reactive toward epoxides than are organolithium or organomagnesium compounds, but the side reactions (*e.g.* rearrangement, elimination) that are promoted by the basicity or Lewis acidity of these other organometallics are not usually observed in reactions of organocopper reagents.

The reaction between epoxides and Gilman reagents was first reported in 1970,[158] and in the 20 years since, both lithium and magnesium homocuprates have been widely employed to effect ring opening of reactive mono- and di-substituted epoxide substrates. In reactions of monosubstituted epoxides, comparable results are also obtained with the heterocuprates, RCuCNLi,[159] but yields drop dramatically with less reactive di- and tri-substituted epoxides. In light of their enhanced reactivity toward alkyl halides (see Section 1.5.2.4.1), it is perhaps not surprising that the higher-order cyanocuprates, $R_2CuCNLi_2$, are also significantly more reactive than lower-order cuprates toward epoxide substrates.[46,160] Less than 1.5 equiv. of the cuprate reagent are usually sufficient, in contrast to the 2–5 equiv. commonly required in reactions of lithium homocuprates, and even poorly reactive cyclic and trisubstituted epoxides are successfully substituted under mild conditions. Tetrasubstituted epoxides afford only elimination by-products, however.

Epoxide opening has also been effectively accomplished with catalytic organocopper compounds.[161,162] Owing to the easy accessibility of many Grignard reagents, this is often the most convenient procedure by which to effect the desired transformation. In some cases, results are superior to those obtained with stoichiometric reagents.[163] However, epoxide opening by the halide ion of the Grignard reagent or of the copper halide catalyst is a common side reaction, and at times the halohydrin may become the sole product of the reaction.[163a,164] In fact, treatment with $Li_2CuCl_4$ constitutes a preparatively useful procedure for the synthesis of chlorohydrins from the corresponding epoxides.[165] It should be noted that the lithium halide salts present in most preparations of monoorganocopper compounds and homocuprate reagents may also participate in the epoxide opening reaction to produce halohydrin by-products.[166] This side reaction is virtually eliminated with higher-order cyanocuprate reagents, which are both more reactive and can easily be prepared in halide-free form.

Unreactive epoxides[166,167] and/or reagents[168] undergo successful reaction in the presence of $BF_3{\cdot}OEt_2$, which has proven to be uniquely effective among the Lewis acids examined in activating epoxides toward nucleophilic attack by organocuprate reagents. Lithium and magnesium homocuprates and higher-order cyanocuprates have all been used in combination with $BF_3{\cdot}OEt_2$ to good effect. The closely related reaction of aziridines with organocopper reagents is also facilitated by $BF_3{\cdot}OEt_2$.[169]

In general, the rate of epoxide opening by organocuprate reagents is more rapid in diethyl ether than in the more highly coordinating solvent, THF, which interferes with the coordination of the epoxide to Lewis acidic components in the reaction mixture. Also, elimination to form an allylic alcohol is a more problematic side reaction in THF than in ether.[170] On the other hand, organocopper compounds are often only poorly soluble in ether, and mixed solvent systems have proven advantageous in some cases.[171]

Chemoselectivity in reactions of functionalized epoxides is an issue of growing importance in light of the increasingly widespread use of epoxy alcohols and related derivatives as synthetic building blocks. Epoxy halides undergo reaction with organocopper reagents primarily by way of epoxide opening when both groups are comparably substituted.[172] In contrast, 'hard' nucleophiles, such as organolithium compounds, react with these substrates exclusively at the halo-substituted position.[172b,173] Steric factors have an overriding influence on chemoselectivity, however, and reactions of unsymmetrically substituted epoxy halides with organocopper reagents occur predominantly at the least hindered position. Thus, a primary iodide can be displaced in the presence of an internal, disubstituted epoxide. Although no substitution at the epoxide center is detected, reaction conditions must be carefully controlled in order to prevent reductive cleavage of the iodide, with concomitant epoxide opening and formation of an allylic alcohol.[174] The regio- and chemo-selective displacement of a primary allylic chloride in the presence of a trisubstituted epoxide has also been reported.[175]

Chemoselective reaction of epoxy sulfonates represents a more significant challenge, since the two electrophilic moieties are reported to be of nearly equivalent reactivity toward organocuprate reagents.[176] As expected on the basis of the epoxy halide results just discussed, the displacement of a primary tosylate can be smoothly accomplished in the presence of an adjacent disubstituted epoxide,[174c,177] and this reaction has been utilized in syntheses of disparlure and of other insect pheromones.[177] On the other hand, a recently reported[178] reaction of a cyclic glucopyranose-derived epoxide with either $Me_2CuLi$ or MeMgCl–CuBr afforded in high yield the desired ring-opened product, leaving intact an exocyclic primary mesylate.

Symmetrically substituted vicinal epoxy mesylates undergo chemoselective epoxide opening by $R_2CuCNLi_2$–$BF_3{\cdot}OEt_2$ to provide the corresponding hydroxy sulfonates in good yield.[179] In the absence of $BF_3{\cdot}OEt_2$, ring closure occurs *in situ*, and doubly substituted compounds are produced. Similarly, the reaction of homochiral glycidyl tosylate with $Ph_2CuCNLi_2$ proceeds *via* a hydroxy sulfonate intermediate to afford the substituted epoxide, along with varying amounts of the product of double addition (Scheme 6).[180] In reactions of the same substrate with RMgBr–CuI, ring closure does not occur, and the hydroxy tosylates can be isolated in moderate to good yield. The very high chemoselectivity exhibited by this sterically unbiased epoxy tosylate substrate may be attributable in part to a deactivating effect of the adjacent epoxide moiety on the reactivity of the sulfonate toward $S_N2$ attack.

Like chemoselectivity, regioselectivity is also governed largely by steric factors, with attack occurring preferentially at the least hindered epoxide center. This generalization holds true even for reactions performed in the presence of $BF_3{\cdot}OEt_2$. However, stereoelectronic factors predominate in reactions of cyclic epoxides, which generally proceed predictably in a *trans*-diaxial fashion.

Epoxide substitutents that are capable of stabilizing a positive charge may direct nucleophilic attack to the α-position. For example, styrene oxide exhibits a greater proclivity than other terminal epoxides for substitution at the internal position;[166,181] regioselectivity is dependent upon the nature of the organocopper reagent. Ring opening of epoxysilanes occurs regiospecifically at the α-position, and this reaction forms the basis for the Hudrlik version of the Peterson alkene synthesis.[182] The use of vinylcuprate

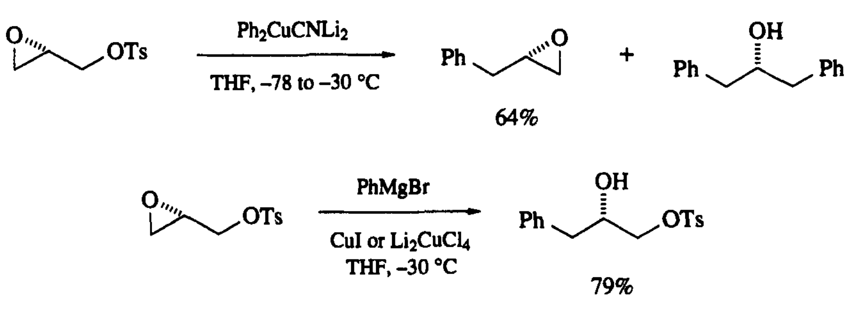

**Scheme 6**

reagents allows the stereospecific synthesis of conjugated dienes (Scheme 7),[167b] and homochiral allylic alcohols have been prepared by combining kinetic resolution of a silyl-substituted secondary allylic alcohol with Hudrlik–Peterson reaction of the resulting epoxysilane.[183] It should be noted, however, that epoxysilanes in which silicon bears at least one isopropoxy substituent undergo deoxygenation rather than substitution upon treatment with $Pr^iMgBr$–CuCN.[184]

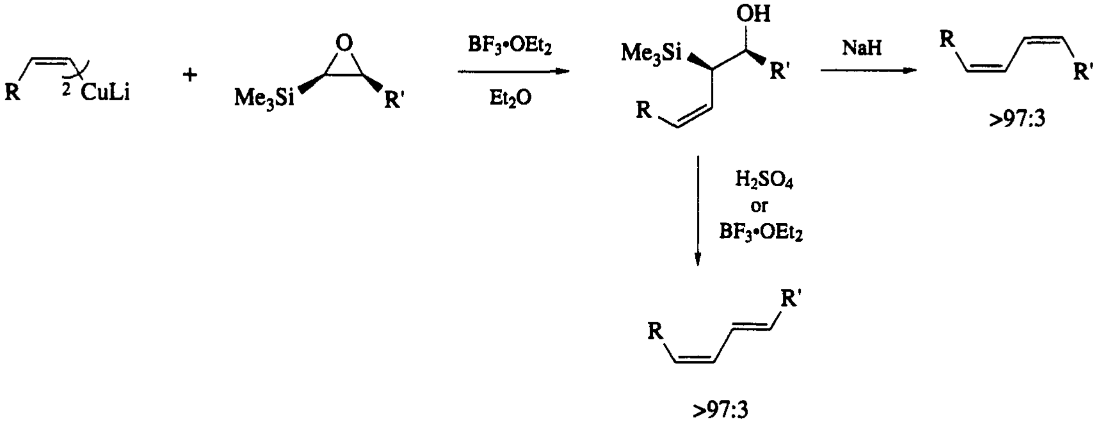

**Scheme 7**

2,3-Epoxy alcohols that are branched at C-4 (γ-position) undergo exclusive substitution at C-2,[185] but in the absence of steric constraints reactions are usually nonregioselective. Significant regioselectivity has been observed in reactions of some sterically unbiased γ-oxygenated epoxy alcohols, however. In one case, it was reported that RMgBr–CuI provided a higher ratio of the C(2)-substituted product than did $R_2CuLi$.[171] Recently, Chong has reported[186] that C-2 selectivity is improved when reactions of unbranched epoxy alcohols are conducted in coordinating solvents, while the addition of $BF_3 \cdot OEt_2$ results in enhanced C-3 selectivity. Epoxy ethers exhibit a slight preference for reaction at C-3,[187] but, again, regioselectivity is subject to numerous contributing factors and is not easily predictable. Substitution at C-1 of a 2,3-epoxy alcohol can be accomplished under Payne rearrangement conditions (equation 14).[188] Lithium dialkylcuprates exhibit poor regioselectivity, but less reactive reagents (*e.g.* RCu, RCuCNLi) attack at C-1 with very high selectivity.

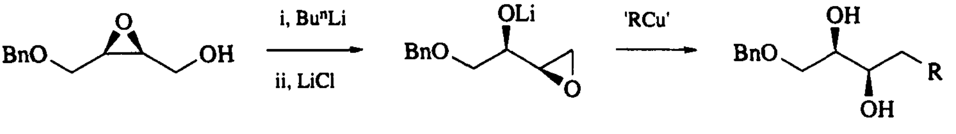

(14)

Although unsubstituted glycidic esters undergo reaction with organocuprate reagents exclusively at the terminal (C-3) position,[189] predominant C-2 attack is observed in reactions of substituted glycidic esters.[164,190] Moderate to high C-2 selectivity is also observed in reactions of (*E*)-glycidic acids, but sterically unbiased (*Z*)-glycidic acids react with unexpectedly high C-3 selectivity.[191]

Vinyl epoxides, like allylic halides and carboxylates, have available both $S_N2$ and $S_N2'$ reaction pathways. For the most part, regio- and stereo-selectivity follow patterns similar to those discussed in Section

1.5.2.4.5. Although first reported in 1970,[192] the $S_N2'$ addition of organocopper reagents to vinyl epoxides was not further investigated until nearly a decade later. In the past 10 years, research efforts have concentrated primarily on rigid cyclic systems, which exhibit a pronounced preference for *anti*-$S_N2'$ reactivity. The stereospecificity of the reaction has been exploited to introduce steroidal side chains with the proper exocyclic stereochemistry.[193]

Reactions of cycloalkadiene monoepoxides have received considerable attention. In general, cyanocuprates have provided better $S_N2'$ selectivity than lithium homocuprates, and the alternative $S_N2$ reaction is more competitive with vinyl- or phenyl-cuprates than with alkylcuprate reagents.[194] Reactions of cyclopentadiene monoepoxides with cyanocuprates have found application in prostaglandin synthesis.[194a] Effective electrophilic α′-alkylation of cyclic enones can be accomplished by $S_N2'$ cuprate addition to the corresponding epoxy enolate,[195] enol phosphate[196] or silyl enol ether.[194]

Macrocyclic α-methylenecycloalkylidene epoxides undergo exclusive $S_N2'$ reaction with RMgBr–CuI.[197] By contrast, the corresponding allylic halides and phosphonates provide mixtures of $S_N2$ and $S_N2'$ products. With ring sizes of 10–14, these substrates exhibit a strong preference for *syn*-$S_N2'$ reaction from an *exo–trans* conformation. Smaller ring substrates are, of course, constrained to a *cis* conformation. α-Alkenylcyclohexylidene epoxides exhibit a preference for *anti*-$S_N2'$ reaction with lithium homocuprates, but regio- and stereo-selectivity are both subject to steric control.[198]

Recently, reactions of acyclic vinyl epoxides have attracted increased attention. In many cases, regioselectivity is strongly dependent upon substrate structure, with (*E*)- and (*Z*)-isomers providing different results.[199] Similarly, stereoselectivity is the result of a complex interplay of steric and conformational effects, but *anti* addition to an *s-trans* conformation appears to be preferred. The regio- and stereo-selective α-alkylation of γ,δ-epoxy-α,β-enoates has been reported recently.[200] Again, $S_N2'$ selectivity was greater with cyanocuprates than with the 'harder' homocuprates, but in no case was conjugate addition detected.

### 1.5.2.4.7 Acyl halides

The reactivity of organic electrophiles toward organocopper reagents follows the general order RCOCl ≈ RCHO > tosylate, epoxide > RI > ketone > ester > nitrile. Therefore, the addition of organocuprates to acyl halides occurs cleanly and rapidly at temperatures low enough that the product ketone is essentially inert. Because most other functional groups are also stable to the reaction conditions, halo-, cyano- and carbonyl-substituted ketones can all be prepared from the corresponding acyl chlorides.[201] Acyl bromides and fluorides are also suitable substrates. Phenylthiocuprates have proven to be more effective than homocuprates in these reactions; fewer equivalents of the reagent are required, and secondary and tertiary alkyl groups can be successfully transferred.[39a,d] More recently, Rieke has achieved the preparation of functionalized ketones by the coupling of acyl halides with functionalized organocopper reagents.[202]

The preparation of α,β-unsaturated ketones by direct acylation of vinylcopper reagents has proven more problematic, since lithium cuprates do add to the product enones.[203] Better results are obtained with the less reactive monovinyl copper compounds in the presence of a palladium catalyst. Alkynic ketones have been prepared by a variation of the Stephens–Castro coupling.[204]

### 1.5.2.4.8 Acetals

Widely employed as protecting groups for carbonyl functionalities, acetals do not ordinarily react with organometallic reagents such as organo-lithium, -magnesium or -copper compounds, or lithium cuprates. However, in the presence of a Lewis acid, the carbon–oxygen bond is activated toward nucleophilic attack, and the cleavage of one C—O bond can be achieved. For example, Grignard reagents react with acetals in the presence of $TiCl_4$ to provide the monosubstituted ethers in high yields.[205] The reaction of allylic acetals with alkyl Grignards occurs regiospecifically at the α-position, and diastereomeric ratios of up to 96:4 have been observed in reactions of chiral acetals.[206] Cuprate reagents are not stable to $TiCl_4$, however, and provide only poor yields of the substitution products.

As mentioned in earlier sections (1.5.2.4.5 and 1.5.2.4.6), $BF_3·OEt_2$ has proven to be uniquely well-suited for use in combination with organocopper reagents.[36] In fact, in the presence of $BF_3·OEt_2$, acetals react smoothly in ether solution with either RCu or $R_2CuLi$, the latter being more reactive.[207] No reaction occurs in THF, which competes with the substrate for Lewis acid complexation. Mixtures of cyclic and ring-opened substitution products are obtained upon treatment of tetrahydropyranyl ethers with RCu–

$BF_3{\cdot}OEt_2$, but $R_2CuLi–BF_3{\cdot}OEt_2$ affords only the ring-opened products. Similarly, exclusive ring cleavage is also observed in reactions of THP ethers or glycopyranosides with $Me_2BBr$ and $R_2CuLi$.[208]

Research efforts have focused primarily on reactions of chiral, nonracemic acetals,[205] compounds that have found increasingly widespread application in asymmetric synthesis. Acetals derived from $C_2$-symmetrical diols provide the best stereocontrol, and the major product is in every case that produced by *anti* nucleophilic displacement of the oxygen adjacent to the axial ring substituent (equation 15). This result has been rationalized on the basis of both steric and electronic considerations, arguments that are supported by the finding that the *meso* (diequatorial) compounds are much less reactive. Diastereomeric ratios are generally highest for six-membered cyclic acetals, which are possessed of greater conformational rigidity than the corresponding five- or seven-membered rings. Reactions of propargylic acetals proceed in a net *anti*-$S_N2'$ fashion, again with cleavage of the C—O bond adjacent to the axial ring substituent. Allylic acetals also undergo regiospecific $S_N2'$ substitution by aryl- and vinyl-copper compounds, but alkylcopper reagents afford mixtures of $S_N2$ and $S_N2'$ products.

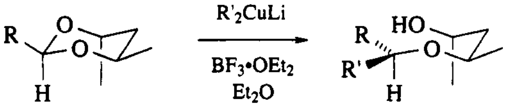

(15)

Recently, it was reported that acetals derived from homochiral β-hydroxybutyric acid react with $R_3Cu_2Li$ in the absence of $BF_3{\cdot}OEt_2$.[209] These reactions proceed with highly diastereoselective *anti* displacement of the carboxylate, and treatment of the product with base liberates a secondary alcohol of high enantiomeric purity.

### *1.5.2.4.9 β-Lactones*

While most organolithium and Grignard reagents attack the carbonyl group of lactone substrates, regiospecific carboxylate displacement can be effected with both stoichiometric and catalytic organocopper reagents.[210] The reaction provides a convenient method for three-carbon homologation that has proven useful in natural product synthesis.[211] The regiospecific $S_N2'$ reaction of β-ethynyl-β-propiolactone has also been accomplished.[212] In general, these reactions are best performed in THF, and magnesium cuprates often provide better results than their lithium counterparts. Phenyl, vinyl and allyl transfers are more difficult to achieve than alkyl transfer, and stoichiometric magnesium cuprates have been most successful for these transformations.

Very recently, Vederas has reported[213] the extension of this methodology to serine β-lactone substrates (equation 16), providing an important addition to the growing number of procedures for amino acid synthesis. These substrates raise the specter of potentially worrying elimination and racemization side reactions in addition to the possibility of competitive 1,2-addition. In fact, substantial racemization was observed when diprotected amino-β-lactones were employed, but the use of monoprotected substrates (which exist in deprotonated form under the reaction conditions) minimized abstraction of the α-hydrogen. By the same token, racemization following substitution is disfavored by the adjacent carboxylate anion (*cf.* reactions of β-haloserine esters, Section 1.5.2.4.1). Although lithium homocuprates and higher order cyanocuprates provided reasonable yields of the desired products, catalytic magnesium cuprate reagents proved most successful.

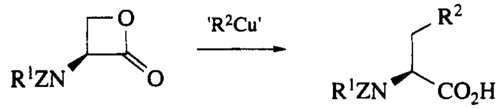

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## 1.5.3 NICKEL AND PALLADIUM CATALYSTS

The modification of organo-lithium and -magnesium reagents by the addition of catalytic amounts of copper salts was discussed in Section 1.5.2. Other transition metals also have been found to promote the cross-coupling reactions of organometallic reagents with carbon electrophiles, and dramatic advances in this technology over the past decade have served to extend significantly the synthetic utility of cross-coupling reactions for the selective construction of carbon skeletons. Of the transition metals examined, nickel and palladium have produced the most successful results and have been the most widely used; the following section is limited to a discussion of reactions catalyzed by these two metals.

Given that the catalytic cycles proposed to be operative for reactions employing nickel and palladium catalysts are essentially identical, it is not surprising that the two may be used interchangeably for many reactions. Significant differences in reactivity and selectivity do exist, however, and an effort will be made to point out those differences in the discussion that follows. While meant to cover the important contributions in this area, this account is not intended to be exhaustive. The reader is referred to several excellent reviews[214] and to other chapters in this volume for additional information on the subject.

### 1.5.3.1 Organonickel Catalysis

More than 15 years ago, Corriu[215] and Kumada[216] independently discovered that organonickel complexes greatly facilitated the reactions of Grignard reagents with alkenyl and aryl halides. Since that time, the reaction has been intensively investigated[217] and has proven to be quite general for the coupling of C($sp^2$) halides with virtually any Grignard reagent. The proposed mechanism[53] of the reaction involves initial reaction of a $Ni^{II}$ complex with the Grignard reagent, oxidative addition of the substrate to the resulting $Ni^0$ species, and transmetalation of the Grignard reagent. Reductive elimination then liberates the coupled product and regenerates the active catalyst. Reactions of alkenyl halides exhibit predominant retention of alkene geometry, while reactions of alkenyl Grignard reagents are complicated by competing (*Z*) to (*E*) isomerization.

In general, nickel complexes bearing phosphine ligands have been the most successful catalysts for these reactions, with bidentate phosphine ligands providing the greatest catalytic activity. The preferred catalyst for a particular reaction is dependent upon the nature of the Grignard reagent and of the halide substrate, with $NiCl_2$(dppp) (dppp = 1,3-bis(diphenylphosphino)propane) being most effective for simple alkyl and aryl Grignard reagents, $NiCl_2$(dmpe) (dmpe = 1,2-bis(diphenylphosphino)ethane) for vinylic and allylic Grignard reagents, and $NiCl_2(PPh_3)_2$ for sterically hindered aryl Grignard reagents and halides. In many cases, the corresponding palladium complexes are also suitable catalysts.

The choice of catalyst is particularly important for reactions of secondary alkyl Grignard reagents. Although primary Grignard reagents couple without rearrangement of the alkyl group, in reactions of secondary Grignard reagents that bear β-hydrogens, β-elimination competes with reductive elimination, resulting in the formation of both reduced and isomerized by-products.[218] β-Elimination is especially troublesome in reactions with hindered alkenyl halides, since the rate of product-forming reductive elimination is retarded. The catalysts $NiCl_2$(dppf)[219] and $PdCl_2$(dppf)[220] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) minimize these side reactions by accelerating the rate of desired reductive elimination relative to undesired β-elimination. By contrast, alkyl halides that possess β-hydrogens are not usually suitable substrates, regardless of catalyst, because the transmetalation step is slow in comparison to β-elimination.

Stereochemistry is an additional factor involved in reactions of secondary Grignard reagents in which the metal is attached to a chiral carbon atom, and this has proven to be a particularly fertile area of research for Hayashi, Kumada and their coworkers.[221] The first examples of asymmetric induction in reactions of secondary Grignard reagents employing a homochiral nickel catalyst were reported[222] shortly after the discovery of the original reaction. These early results were obtained using $NiCl_2$(DIOP) (*cf.* **20**) as the chiral catalyst, and the observed enantioselectivities were quite low (≤17%). In the years following these initial reports, numerous ligands have been examined, with ferrocenylphosphines (*e.g.* **21, 22**) and β-(dimethylamino)alkylphosphines derived from amino acids (**23**) being the most extensively investigated.

Of the ferrocenylphosphine ligands, (*R*,*S*)-PPFA (**21**) proved to be the most successful, with $NiCl_2$(PPFA) and $PdCl_2$(PPFA) producing comparable results. Organozinc reagents were somewhat more selective than the corresponding Grignard reagents in reactions employing $PdCl_2$(PPFA), but they

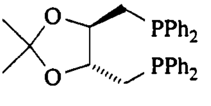

**(20)** (–)-DIOP

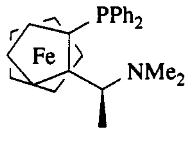

**(21)** *(R,S)*-PPFA

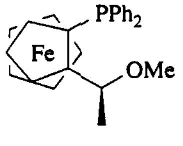

**(22)** *(S,R)*-PPFOMe

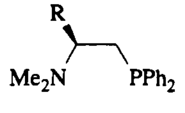

**(23)**

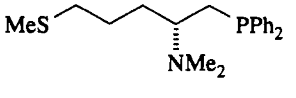

**(24)** Homomethphos

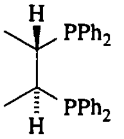

**(25)** *(S,S)*-Chiraphos

did not react with nickel catalysts. Higher enantioselectivities (up to 94%) were achieved when some of the amino acid derived ligands were used, although with these ligands palladium was less efficient than nickel. Ligands derived from (*S*)-amino acids generally give rise to the (*S*)-product, but it has been reported[223] that this trend is reversed in the presence of $ZnX_2$ (X = Br, I).

The use of alternative classes of ligands for these reactions has been explored, but with only moderate success.[224] In the most promising example of this work,[224a,b] a sulfide-containing side chain was appended to the familiar dimethylaminophosphine ligand. The sulfide moiety offers a third site for coordination to the metal, and it was hoped that such intramolecular participation would accelerate the rate of reductive elimination, minimizing the loss of enantiomeric purity resulting from competitive β-elimination. In fact, the enantioselectivity of the homomethphos ligand (**24**) is comparable to that of *t*-leuphos (**23**; R = Bu$^t$).

The asymmetric Grignard cross-coupling reaction has been utilized in syntheses of (*R*)-(–)-curcumene[225] and of optically active antiinflammatory agents.[226] A particularly successful application of the methodology has been for the preparation of optically active allylsilanes,[227] in which enantioselectivities of up to 95% have been achieved. Interestingly, $PdCl_2$(PPFA) was the most effective catalyst for silyl-substituted Grignard reagents, with nickel catalysts providing lower yields and selectivities. Most recently, substituted binaphthyls[228] and ternaphthyls[229] have been prepared in high enantiomeric purity by asymmetric biaryl cross-coupling with $NiCl_2$(PPFOMe) as the catalyst (*e.g.* equation 17). As in the original work with secondary alkyl Grignards, nickel catalysts were more successful than palladium catalysts, but, in this case, complexes containing bidentate ligands (*e.g.* diphosphines and aminophosphines) were unreactive due to steric hindrance.

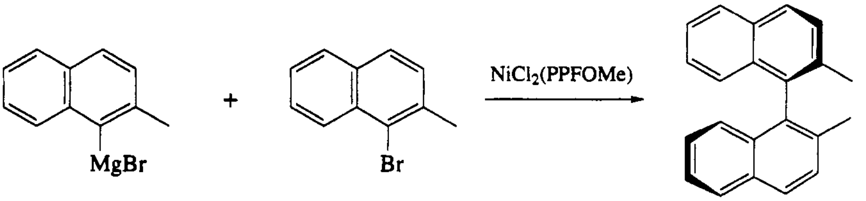

(17)

Asymmetric induction is also observed in nickel-catalyzed reactions of Grignard reagents with allylic alcohols and ethers.[230] Examples of high enantioselectivity have been reported;[230a] however, the enantioselectivity of the reaction is strongly and unpredictably dependent upon the allylic substrate, the Grignard reagent and the catalyst. In most cases, the best results have been obtained with $NiCl_2$(chiraphos) (*cf.* **25**) as the homochiral catalyst. Palladium complexes are not suitable catalysts for this reaction. In contrast to transition metal catalyzed reactions of allylic ethers and esters with 'soft', stabilized carbanions, in which the stereochemistry of the starting material is retained in the product, reactions with Grignard reagents proceed with net inversion of configuration.[231] There is a slight tendency favoring reaction at the more highly substituted allylic position of unsymmetrical electrophiles, but mixtures of regioisomers are usually obtained.

Vinyl and aryl ethers also react with Grignard reagents under nickel catalysis. Substitution reactions of aryl tetrazolyl ethers are reported[232] to be particularly facile, an effect that may be attributable to the ability of the tetrazolyl moiety to coordinate to magnesium. Reactions of dihydrofuran and dihydropyran substrates with Grignard reagents afford homoallylic and bishomoallylic alcohols, respectively (equation 18).[233] Retention of alkene geometry is predominantly observed, and by carefully controlling the workup conditions, stereoselectivities of ≥98:2 can be achieved.[234] By contrast, reactions of the same substrates with cuprate reagents proceed with inversion of configuration (see Section 1.5.2.4.2, equation 8). As mentioned earlier, β-elimination with resulting substrate reduction is a competing process when Grignard reagents with β-hydrogens are employed. In reactions with dihydrofuran substrates, $NiCl_2$(dppe) provided the highest ratios of coupled products.

The nickel-catalyzed substitution of vinyl sulfides by Grignard reagents forms the basis of a procedure for the stereoselective synthesis of alkenes by sequential cross-coupling reactions developed by Naso and

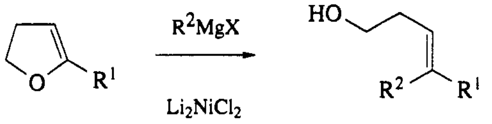

(18)

coworkers (equation 19).[235] The first step of the sequence is chemospecific, with only the bromide being displaced. Better stereoselectivity is obtained in the initial reaction of (Z)-1-bromo-2-phenylthioethylene when $PdCl_2(PPh_3)_2$ is employed as the catalyst. Nickel catalysts must be used for the second step, and the particular choice of catalyst can be critical to the stereochemical outcome. In a variation of the method,[236] a dienyl sulfide is stereospecifically prepared by addition of a vinyl cuprate reagent to phenylthioacetylene. Nickel-catalyzed Grignard cross-coupling then affords the desired dienyl product.

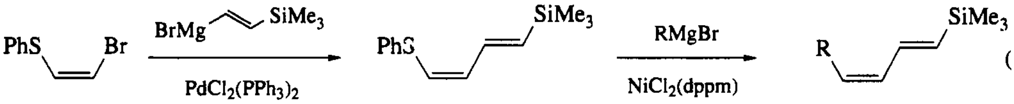

(19)

Optically active alkenylsulfoximines undergo nickel-catalyzed cross-coupling with organozinc reagents in the presence of an additional magnesium, lithium or zinc salt (equation 20).[237] No reaction occurs in the absence of the cocatalyst, and palladium catalysts are unreactive. The reaction proceeds with 99% retention of alkene geometry, and sulfoximine of ≥98% enantiomeric purity is liberated. Interestingly, reaction of (**26**) with Grignard reagents at –20 °C failed to afford the coupled product, but instead resulted in α-metalation.[238] At 0 °C, coupling with a second equivalent of Grignard reagent occurred to provide an α-functionalized alkenyl metal, but as a 1:1 mixture of (E)- and (Z)-isomers.

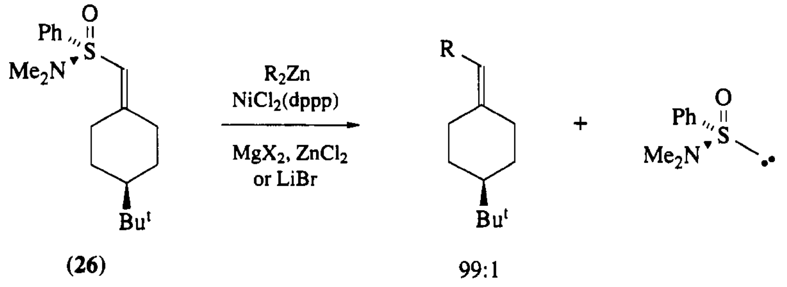

(**26**)

(20)

## 1.5.3.2 Organopalladium Catalysis

### *1.5.3.2.1 Aluminum, zinc and zirconium reagents*

While ease of preparation and commercial availability contribute to the popularity of simple Grignard reagents for use in cross-coupling reactions, the scope of the reaction is seriously limited by the poor chemoselectivity of these reagents. In addition, alkenyl Grignard reagents are often isomerized under the reaction conditions, rendering them unsuitable for stereospecific diene synthesis. It is particularly this latter consideration that provided the impetus for an intensive investigation into the use of other organometallics in transition metal catalyzed cross-coupling reactions conducted by Negishi and coworkers.[239] Aluminum and zirconium reagents have received particular attention, since the corresponding alkenyl metals can be prepared in a regio- and stereo-defined fashion utilizing hydrometalation and carbometalation procedures.

(E)-Alkenylalanes and (E)-alkenylzirconium derivatives readily undergo nickel-catalyzed cross-coupling with aryl halides to provide the arylalkenes in high yield and with ≥98% retention of alkene geometry. Ester, nitrile, ether and halide functional groups are compatible with the reaction. Alkenyl–alkenyl cross-coupling also proceeds in moderate to good yield, but homocoupling is a competing side reaction and the stereoisomeric purity of the product is only 95% for (E,E)-dienes and 90% for (Z,E)-dienes. Better results are obtained with palladium catalysts ($Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$), which provide both products in ≥98% stereoisomeric purity with only trace amounts of homocoupled byproducts.

In contrast to β-monosubstituted alkenyl metals, more highly substituted alkenyl metals containing aluminum or zirconium are only poorly reactive. This limitation is overcome by the addition of a catalytic amount of a zinc halide. In general, zinc reagents are far more reactive than the corresponding aluminum or zirconium reagents,[240] and their use is particularly advantageous in coupling reactions of aryl, alkynyl and heteroaryl metals. It is additionally noteworthy that, despite the potential problem of β-elimination, cross-coupling of homoallylic and homopropargylic organozinc compounds with alkenyl halides may be successfully accomplished, enabling the selective synthesis of 1,5-dienes and 1,5-enynes.[241] Palladium-catalyzed coupling reactions of β-, γ-, δ-, ε- and ζ-zinc ketones have also been reported.[242] Recently, Negishi has reported[243] the application of palladium-catalyzed cross-coupling reactions of organozinc compounds to the regio- and stereo-specific α-alkenylation and α-arylation of ketones.

### 1.5.3.2.2 Boron reagents

Like hydroalumination and hydrozirconation, hydroboration of alkynes also provides a convenient and stereospecific route to alkenyl metal reagents. However, initial attempts to achieve palladium-catalyzed cross-coupling of alkenylboranes with alkenyl halides were unsuccessful, due to the poor carbanionic character of these reagents. Later, Suzuki[244] discovered that the desired transformation could be effected in the presence of an alkoxide or hydroxide base; weaker bases, such as sodium acetate or triethylamine, were not generally effective. The reaction is suitable for the preparation of (*E*,*E*)-, (*E*,*Z*)- and (*Z*,*Z*)-dienes. Since reactions of alkenylboronates are higher yielding than those of alkenylboranes, the recent availability of (*Z*)-1-alkenylboronates[245] substantially improves the Suzuki method for the preparation of (*Z*)-alkenes.[246] An extension of the methodology to the synthesis of trisubstituted alkenes has also been reported.[247]

In an approach similar to the Naso alkene synthesis described earlier, Suzuki has reported[248] the stereospecific synthesis of alkenes from (*E*)-(2-bromo-1-alkenyl)dibromoborane by sequential cross-coupling reactions (equation 21). The reaction sequence can be carried out in one pot, without isolation of the intermediate. Transmetalation from boron to palladium occurs only after base has been added.

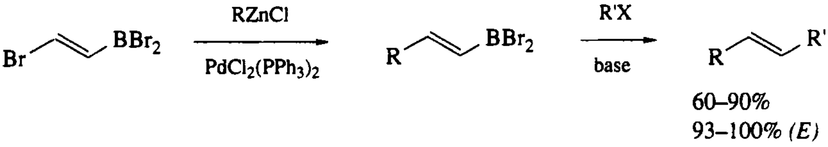

(21)

In addition to alkenyl halides, alkynyl, aryl, allylic and benzylic halides and β-haloenones[249] all couple efficiently with alkenylboron reagents in the presence of a palladium catalyst and 2 equiv. of base. The cross-coupling of aryl halides with arylboronic acids, regioselectively prepared by directed *ortho* lithiation methodology, has been investigated by Snieckus and coworkers. Applications to the synthesis of phenanthrols[250] and phenanthridines[251] have been reported most recently. Very recently, Suzuki reported[252] the extension of this methodology to include the coupling of alkylboron reagents with vinyl and aryl halides.

It was originally believed that addition of a base to reactions of organoboranes would facilitate the transmetalation step by increasing the carbanionic character of the boron reagent *via* formation of an 'ate' complex. However, the failure of alkenylborates to undergo efficient cross-coupling indicates that the base is not functioning in this manner, and suggests instead the involvement of an alkoxypalladium(II) intermediate, the formation of which is apparently rate limiting. It should be noted, however, that lithium tetraalkylborates do couple successfully.[252] Recently, Kishi and coworkers[253] reported that the use of thallium hydroxide had a dramatic rate-enhancing effect on these coupling reactions, allowing application of the methodology to palytoxin synthesis. The high molecular weight substrates involved in that study proved unreactive under the standard reaction conditions.

### 1.5.3.2.3 Tin reagents

Organotin reagents have proven to be particularly versatile partners in palladium-catalyzed coupling reactions. As impressively demonstrated by Stille and coworkers over the past decade,[254] organostannanes of many structural types undergo efficient cross-coupling with an assortment of organic electrophiles, including halides, triflates, acid chlorides and epoxides. Reaction conditions are mild, and a wide variety of functional groups may be present in either component, allowing application of the methodology to the synthesis of sensitive and complex target molecules. Unlike most other organometallics, organotin reagents are easily prepared by a number of different routes, and they are not especially oxygen or moisture sensitive.

Of the electrophiles examined, vinyl triflates have received particular attention.[255] These compounds are conveniently prepared from the corresponding ketones, utilizing well-established methodology for regioselective enolate formation.[256] Coupling with organostannanes proceeds smoothly in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(Pd_3P)_4$] and a stoichiometric amount of LiCl. No reaction occurs in the absence of LiCl, which apparently allows formation of the catalytically active alkenylchlorobis(triphenylphosphine)palladium(II) complex. Aryl triflates, easily prepared from the corresponding alcohols, are also suitable electrophiles under similar reaction conditions.[257] Although successful in THF and other ethereal solvents, the reaction is faster in solvents such as DMF, which can both solubilize LiCl and act as good ligands.[258]

In reactions of unsymmetrically substituted organotins, unsaturated substituents transfer preferentially over saturated alkyl groups. For synthetic convenience, methyl and butyl groups are usually employed as the nontransferable ligands. In some cases,[259] the trimethyltin derivative provides better results due to a decrease in steric crowding, and trimethylorganostannanes offer the additional advantage that the by-products are water soluble. On the other hand, lower toxicity and greater stability are factors favoring the use of tributyltin derivatives.

Few limitations are imposed on the choice of the transferring group. Alkyl, vinyl, allyl and alkynyl compounds all couple effectively with aryl and vinyl triflates. Phenyl and benzyl reagents are unreactive toward vinyl triflates,[260] but biaryl coupling is successful. Because reductive elimination occurs more rapidly than β-elimination, organostannanes with β-hydrogens are acceptable coupling partners. However, β-hydrogens attached to an $sp^3$-carbon are not usually tolerated in the electrophile, since β-elimination is faster than the rate-determining transmetalation step.[261] Recent applications of the methodology include syntheses of vitamin D,[262] amphimedine[263] and cephalosporin analogs.[264]

Like the other coupling reactions discussed thus far, palladium-catalyzed coupling reactions of organotin reagents proceed stereospecifically, with the alkene geometries of both vinyltin reagents and vinyl electrophiles being retained in the product. However, the utility of cross-coupling between vinyltins and vinyl triflates for 1,3-diene synthesis is seriously limited by the fact that no method currently exists for the preparation of acyclic vinyl triflates in a stereodefined manner. As mentioned in previous sections, stereospecific 1,3-diene synthesis has been accomplished by palladium-catalyzed coupling of organometallics with stereoisomerically pure vinyl halides, for which synthetic methodology is available. However, initial attempts to achieve the coupling of vinylstannanes with vinyl halides in the presence of $Pd(PPh_3)_4$ resulted in only modest yields of the desired products.[239a]

Recently, improved experimental procedures for the cross-coupling of organotin reagents with vinyl iodides have been reported,[265] which allow the preparation of (*E,E*)-, (*E,Z*)- and (*Z,Z*)-dienes in high yields and isomeric purities.[266] Bis(triphenylphosphine)dichloropalladium [$PdCl_2(PPh_3)_2$] and di(acetonitrile)dichloropalladium [$PdCl_2(MeCN)_2$] proved to be much more reactive than $Pd(PPh_3)_4$ in these reactions, with $PdCl_2(MeCN)_2$ in DMF providing the most reactive catalyst. The lower temperatures and shorter reaction times allowed by this system minimized alkene isomerization, which was a problem when less reactive catalysts were used. The coupling of alkynylstannanes with vinyl iodides under the same conditions provided stereoisomerically pure enynes, from which (*E,Z*)- and (*Z,Z*)-dienes could be prepared by stereospecific alkyne reduction.[259b] One limitation of this methodology is the fact that substantial amounts of homocoupled by-products are produced in reactions of silyl-substituted vinyltin reagents, limiting yields of the synthetically useful silyldienes.

While not useful for reactions of vinyl halides, $Pd(PPh_3)_4$ is a suitable catalyst for coupling reactions of organotins with aromatic bromides and iodides; a number of applications to the synthesis of coupled heterocycles have been reported recently.[267] Reactions of substituted bromobenzenes with vinyltributylstannane afford the corresponding styrene derivatives in high yield.[268] Exclusive displacement of halogen in the presence of a triflate substituent is simply accomplished by performing the reaction in the absence of LiCl, as evidenced in a recently reported synthesis of indole derivatives.[269] In the presence of LiCl, the order of electrophilic reactivity is I > Br > OTf when $Pd(PPh_3)_4$ is employed as the catalyst, but $PdCl_2(PPh_3)_2$ causes a reversal in this selectivity to I > OTf > Br.[257] In general, aromatic chlorides are insufficiently reactive to be suitable substrates for this reaction; however, chloroarylchromiumtricarbonyl complexes do undergo successful palladium-catalyzed cross-coupling with organotin reagents.[270]

Allylic halides couple effectively with vinyltin reagents to provide the corresponding 1,4-dienes in high yields.[271] Like nickel- and palladium-catalyzed Grignard reactions with allylic ethers, this reaction also proceeds with net inversion of configuration at the allylic center. Similarly, vinyl epoxides react stereoselectively with aryl- and vinyl-stannanes to give the *anti*-substituted allylic alcohols.[272] In both cases, reaction occurs regioselectively at the least hindered allylic position of unsymmetrically substituted substrates. In the absence of steric bias, predominant 1,4-addition is observed in reactions of vinyl epoxides, while allylic chlorides apparently afford the products of α- and γ-attack in a 1:1 ratio. Interestingly, regioselectivity is improved when reactions of vinyl epoxides are performed in the presence of 10 equiv. of water (equation 22).

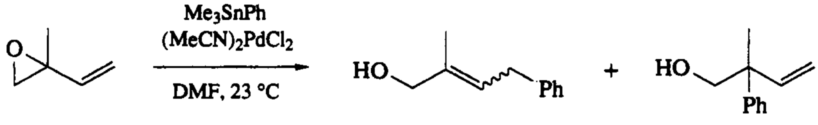

(22)

no additive: 70%; 96:4; *(E)*:*(Z)* = 52:48
10 equiv. $H_2O$: 85%; 98.5:1.5; *(E)*:*(Z)* = 69:31

### 1.5.3.2.4 Silicon reagents

Although low reagent nucleophilicity has proven advantageous in cross-coupling reactions of organostannanes, the extremely low polarity of the carbon–silicon bond has prohibited use of the analogous organosilanes in these reactions. Recently, however, it has been discovered that tris(diethylamino) sulfonium difluorotrimethylsilicate (TASF) renders the compounds more anionic, facilitating the transmetalation step and allowing successful palladium-catalyzed coupling with organic halides.[273] Allylpalladium chloride dimer is the catalyst of choice for these reactions, and the presence of triethyl phosphite as a cocatalyst markedly accelerates the rate of reaction with alkenyl iodides. More recently, it has been reported[274] that dimethylfluorosilanes are considerably more reactive than the corresponding trimethylsilanes; advantage may be taken of this fact in order to prepare 1-silyl-1,3-dienes. Although tetrabutylammonium fluoride (TBAF) was not effectual in reactions of trialkylsilanes, it was used successfully with the more reactive dimethylfluorosilane substrates.

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# 1.6

# Alkylations of Vinyl Carbanions

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## 1.6.1 INTRODUCTION

The scope of this chapter is limited to carbon–carbon bond forming reactions between $sp^2$-centered carbanions and alkyl halides, alkanesulfonates, epoxides and related carbon centered electrophiles. It does not include reactions between vinylic carbanions and electrophiles such as silyl chlorides, disulfides or other heteroaromatic electrophiles. Some members of this last group of electrophiles are often used to determine the extent to which a particular vinyl carbanion intermediate is formed; having shown that formation has occurred to a large or complete extent, many authors do not then proceed to examine the alkylation reactivity of a particular carbanionic species beyond using methyl iodide. Methyl iodide is such a special electrophile, however, that successful alkylations with it cannot usually be used as an indication that alkylations with higher homologs or with more reactive alkylating agents such as allylic or benzylic halides, will necessarily be so rewarding. Therefore, many potentially useful $sp^2$-carbanionic species are not mentioned in this review, specifically because their behavior with such alkylating reagents has not been reported. In general, the nucleophilicity of vinyl carbanions lies in between similar $sp$- and $sp^3$-centered species, and as such they usually react very well with aldehydes and ketones, and with the simple heteroaromatic electrophiles of the type mentioned above, whereas alkylation reactions give variable yields, depending upon the particular species involved. The high yields normally obtained with reactive electrophiles such as $Me_3SiCl$ and MeI are often not extended to couplings with allylic or benzylic halides, despite the fact that satisfactory results may be obtained using saturated alkyl halides as electrophiles. Presumably in many cases, the carbanion acts as a base rather than a nucleophile and simply abstracts a proton from these more reactive electrophiles.

This review is organized primarily on the basis of the electrophiles used, with a view to allowing easy access to the information. However, within each section, a variety of routes to the same target type are included, as for example in alkylations using simple alkyl halides where both lithium- or magnesium-based carbanions can be used equally well. Both subsections should therefore be consulted.

## 1.6.2 ALKYLATIONS USING ALKYL HALIDES AND SULFONATES

### 1.6.2.1 Alkylations of Vinyl and Aryl Grignard Reagents

The most direct method for effecting alkylation of a vinylmagnesium halide is simply to heat the organometallic species with a primary alkyl bromide at 90–100 °C (Scheme 1).[1] The Grignard reagent (a slight excess) is usually generated in tetrahydrofuran (THF) solution, the bromoalkane added and the THF removed by distillation until the required temperature is reached. However, the more reactive allyl halides can be used to alkylate Grignard reagents under milder conditions. Indeed the ease with which allylic halides undergo such couplings can lead to low yields during the attempted preparations of allylic or benzylic magnesium halides. In a nonpolar solvent such as toluene, temperatures of around 100 °C are still required to give good yields of alkylated products such as the phenylpropene (**1**) (from PhMgBr and 1,3-dichloropropene).[2] However, similar alkylations of arylmagnesium halides using allylic chlorides or bromides occur at much lower temperatures (15–30 °C) in ether[3] or THF,[4] and also lead to good to excellent yields of allylbenzene derivatives. Despite their generally greater popularity as carbanionic intermediates in alkylation reactions, many $sp^2$-centered carbanions having lithium as the countercation do not react efficiently with allylic halides (*vide infra*); in such cases, transmetallation to the corresponding magnesio species can sometimes obviate this limitation. One such example is the *ortho*-lithiated benzamide (**2**), which reacts cleanly with allyl bromide after treatment with magnesium bromide to give the *o*-allyl homolog (**3**) in good yield.[5]

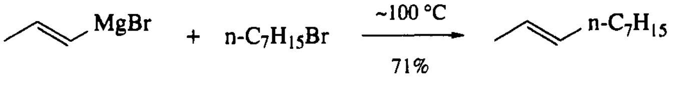

**Scheme 1**

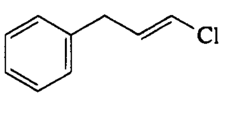

**(1)**

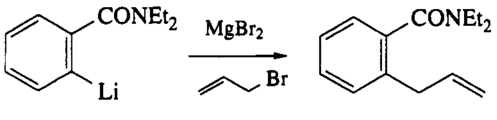

**(2)** **(3)**

Another series of highly active electrophiles which react smoothly with vinyl and aryl Grignard reagents to give, overall, the products of direct alkylation, are the α-halo ketones; however, this type of reaction is a two-step process which proceeds *via* an intermediate halohydrin arising from initial attack on the ketone group (Scheme 2).[6] Similarly, vinylmagnesium halides can be transformed in a single flask reaction to α-ethenyl ketones, *e.g.* (**4**),[7] whereas vinyllithium species lead to isolable halohydrins, *e.g.* (**5**), which only rearrange to the α-ethenyl ketone upon reionization using a simple Grignard reagent as base.[8] The relative dearth of good vinyl cation equivalents lends particular significance to the latter methodology. α-Halo ethers and related species also couple in moderate to good yields with Grignard reagents,[9] an example being the reactions between 2-chloro-1,3-dithiane and RMgX (Scheme 3) in which the typical umpolung reactivity of the dithiane functionality is returned to normality.[10] The special reactivity of α-halo ethers means that good yields can be obtained by this method, despite the fact that secondary halides generally react poorly as alkylating electrophiles with organomagnesium and organolithium intermediates.

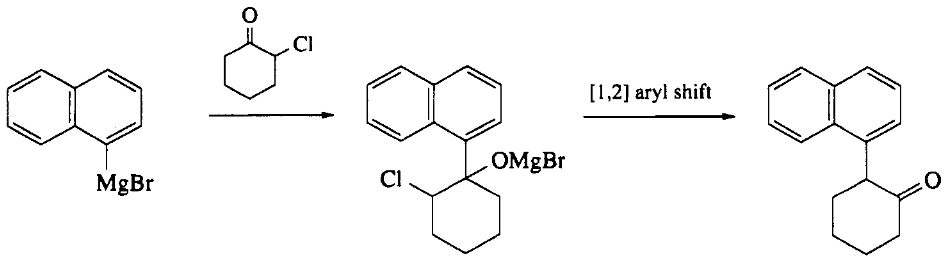

**Scheme 2**

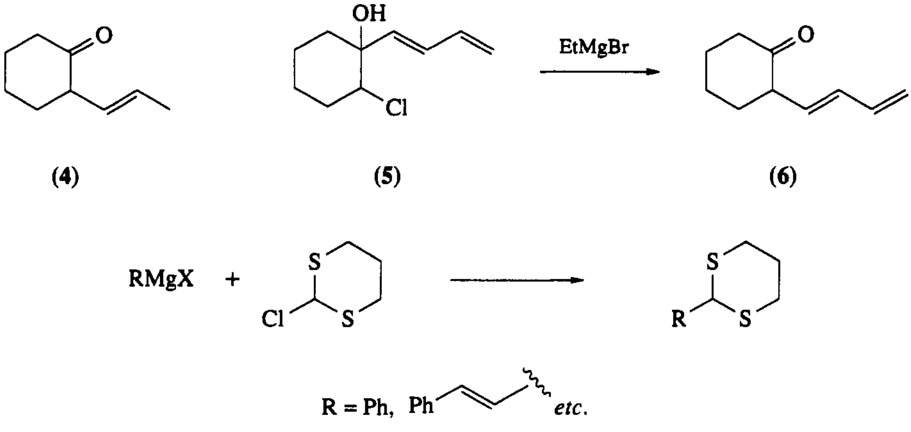

**(4)** **(5)** **(6)**

Scheme 3

An indirect way to effect alkylation at an $sp^2$-carbanionic center is by reaction with a trialkylborane (Scheme 4).[11] Decomposition of the intermediate borate results in overall alkylation of the original Grignard species by B → C alkyl migration; one drawback is that two of the alkyl groups are wasted and hence applications would probably be somewhat limited.

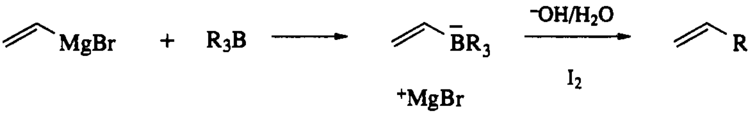

Scheme 4

In general, however, alkylations of both organomagnesium and organolithium intermediates (*vide infra*) more often rely on the presence of a copper salt, either in catalytic or stoichiometric quantities, or another transition metal species.[12] A general method is the alkylation of vinylmagnesium bromides by primary iodides or tosylates (Scheme 5)[13] in the presence of copper(I) iodide, which proceeds under much milder conditions than those required for the direct alkylation of vinyl Grignards by unactivated alkyl halides.[1] Less reactive alkyl bromides give much poorer yields (*ca.* 20%) and it is crucial that the copper catalyst is of a high quality. An alternative copper catalyst, $Li_2CuCl_4$ (*vide infra*) can also be used, but excess Grignard reagent is required if good yields are to be realized. The addition of copper salts to Grignard reagents gives rise to some useful modulations in the reactivity of the latter. For example, direct coupling between RMgX and 2-bromoethyl acetate is possible, leading to homologs (**7**),[14] and even bromoethanol (**8**) can be used to give phenethyl alcohols (**9**)[14] in this modification of an original Grignard method.[15] A useful source of vinyl magnesiocuprates is by the addition of alkylmagnesium halides to terminal alkynes, in the presence of stoichiometric amounts of a copper(I) salt; the usefulness of these reagents is indicated in Scheme 6 in which is shown an early stage in a synthesis of the insect pheromone trogodermal.[16] However, other authors[17] have indicated that closely related species derived from a monosubstituted alkyne can only be alkylated efficiently by allylic halides or epoxides (see Section 1.6.6). Much the same pattern of reactivity has been found with related lithium divinylcuprates similarly derived from alkynes (*vide infra*). An alternative catalyst system, CuX–TMEDA, has been shown to be useful for the alkylation of arylmagnesium halides, ArMgX, by primary iodides or benzylic chlorides.[18] Yields are usually around 80% but, as with most of these alkylations, the method fails with a secondary iodide.

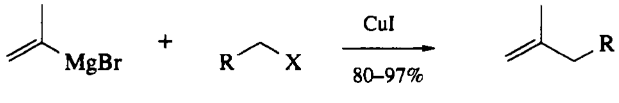

R = Et, n-$C_7H_{15}$; X = I or OTs

Scheme 5

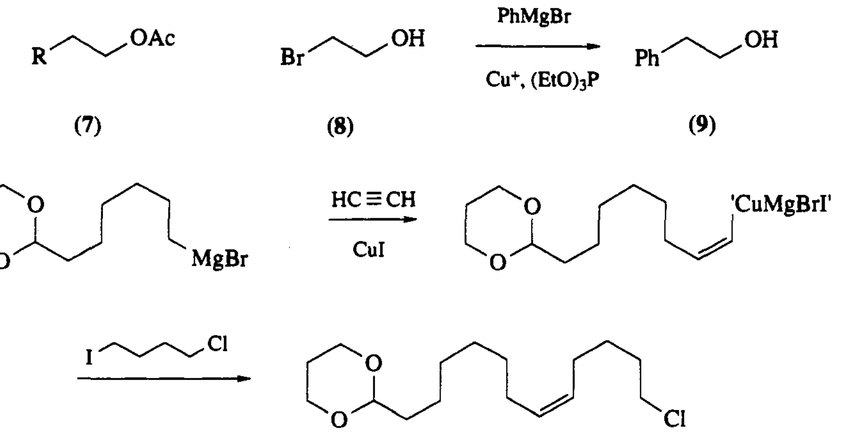

(7) (8) (9)

Scheme 6

Dilithium tetrachlorocuprate, $Li_2CuCl_4$, sometimes referred to as the Tamura–Kochi complex, has also found many applications in the alkylation of Grignard reagents in general.[19] Although originally reported to work best with primary alkyl iodides,[19] subsequent research indicated that primary tosylates are the best electrophiles.[20] The use of $Li_2CuCl_4$ allows alkylations of Grignard reagents by α,ω-dibromides leading to monobromides, *e.g.* (**10**) from PhMgBr, to be effected in moderate to good yields.[21] Similar couplings of aryllithiums require the presence of TMEDA (*cf.* ref. 18). $Li_2CuCl_4$ has also been found to be the catalyst of choice for conversions of the dienylmagnesium chloride (**11**) into the butadiene homologs (**12**).[22]

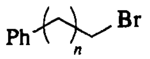

(**10**) $n$ = 2–5, 9

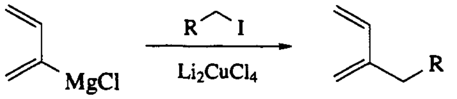

(**11**) (**12**)

Palladium and nickel catalysts also occupy an important position in this type of chemistry. The readily prepared palladium complex $[(Ph)Pd^I(PPh_3)_2]$ effectively catalyzes the cross-coupling of arylmagnesium halides and alkyl halides, even when the former is sterically hindered, and is reported to be superior to many related nickel-based catalysts.[23] A ferrocene–palladium complex can also be used.[24] A combination of a nickel catalyst $[Ni(dppp)Cl_2]$ and *t*-butyl 2-bromopropionate (rather than the methyl ester)[23] allows direct coupling of the latter with ArMgX to provide respectable yields of 2-arylpropionates (**13**).[25] α-Silylvinylmagnesium bromides (**14**), prepared in general by Ni-catalyzed addition of an alkyl Grignard to a silylalkyne, undergo *in situ*, presumably nickel-catalyzed, alkylations by methyl iodide (50%) and allyl bromide, the latter leading to the potentially useful 'skipped' dienes (**15**).[26] The simpler α-silyl species (**16**) couples efficiently with primary alkyl iodides (but not primary bromides or tosylates) in the presence of a copper(I) salt to give good yields of homologs (**17**); both α- (**16**) and β-silylvinyl Grignards can also be alkylated using a palladium catalyst.[27] As expected,[3,4] alkylations using allylic halides do not require the addition of a catalyst. Alkoxide residues are tolerated in such reactions; thus hydromagnesiation of the silylpropargyl alcohol (**18**), followed by treatment with iodobutane–CuI leads to the allylic alcohol (**19**) with 95% retention of stereochemistry.[28] Such vinyl Grignard reagents can also be obtained by intramolecular cyclizations; again, homologation using an allylic halide proceeds without recourse to a catalyst (Scheme 7).[29]

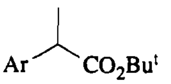

(**13**)

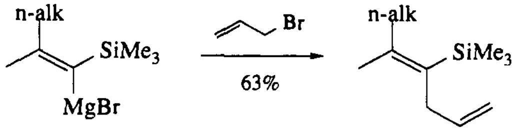

(**14**) (**15**)

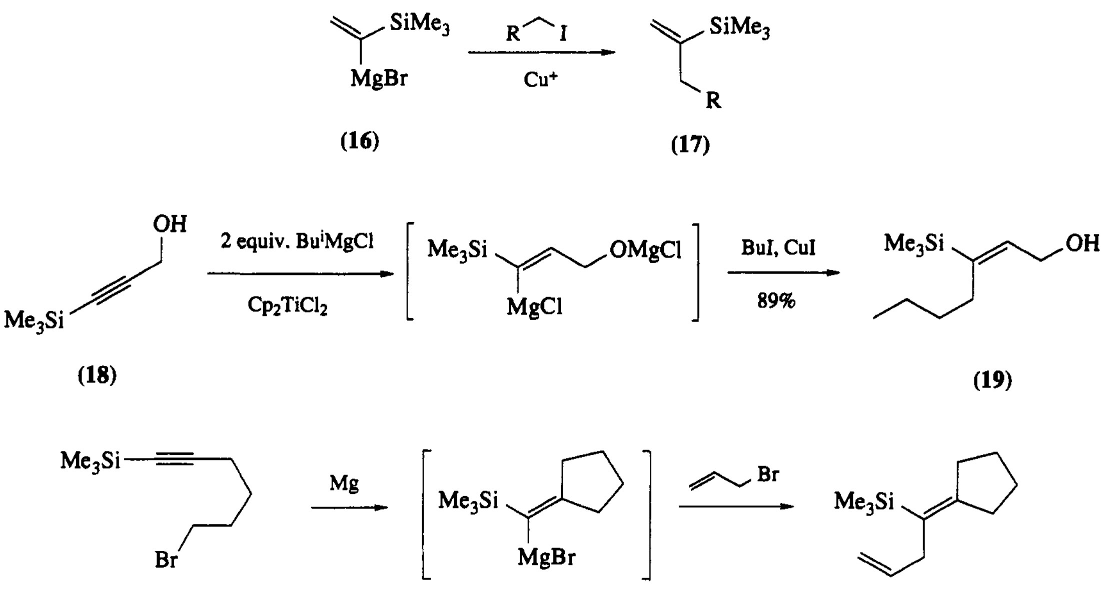
SiMe3
MgBr
R⌒I
Cu+
SiMe3
R
(16)
(17)
OH
Me3Si
2 equiv. BuiMgCl
Cp2TiCl2
Me3Si
OMgCl
MgCl
BuI, CuI
89%
Me3Si
OH
(18)
(19)
Me3Si
Br
Mg
Me3Si
MgBr
Br
Me3Si

**Scheme 7**

Copper-modified Grignard reagents can also be alkylated using β-lactones, resulting in a useful three-carbon homologation procedure in which attack occurs regioselectively with displacement of carboxylate (Scheme 8).[30] In general, reagents prepared using a stoichiometric quantity of copper give higher yields, based on the lactone. The propensity for undergoing conjugate or $S_N2'$ additions imparted upon Grignard reagents by the presence of copper allows this methodology to be extended to ω-ethenyl lactones; thus, reactions between a variety of such species and β-lactone (**20**) afford good to excellent yields of the dienoic acids (**21**; R = $CH_2CH$, 49%; R = Ph, 84%).[31] This approach can also be extended to include 5-ethenylbutyrolactone and the corresponding valerolactone (**22**). Once again, good to excellent yields of dienoates (**23**) can be obtained, especially with the former substrate (*i.e.* $n = 1$).[32]

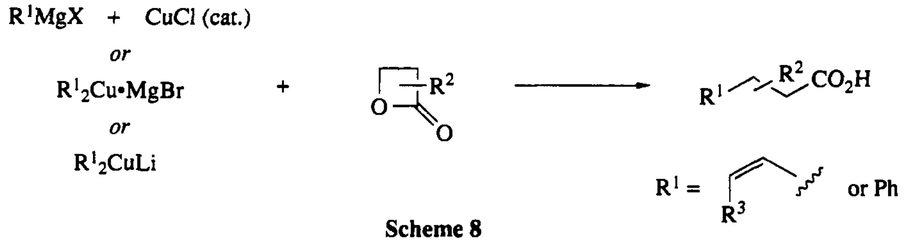
R1MgX + CuCl (cat.)
or
R12Cu•MgBr
or
R12CuLi
+
O
R2
O
R1
R2
CO2H
R1 =
R3
or Ph

**Scheme 8**

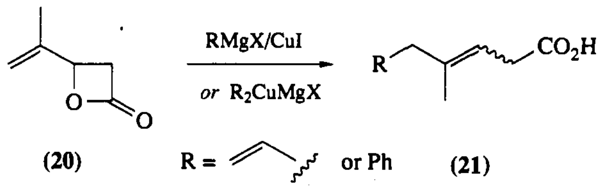
O
O
RMgX/CuI
or R2CuMgX
R
CO2H
(20)
R =
or Ph
(21)

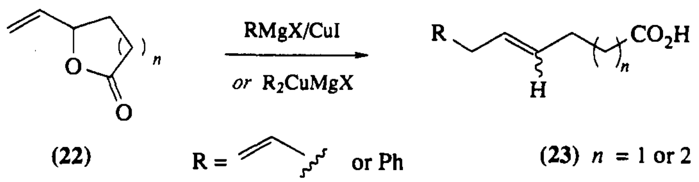
O
n
O
RMgX/CuI
or R2CuMgX
R
CO2H
n
H
(22)
R =
or Ph
(23) n = 1 or 2

These unsaturated lactones are special cases of a much more general theme whereby Grignard reagents can be alkylated by a wide variety of allylic systems, usually in the presence of a nickel- or copper-based catalyst. Arylmagnesium bromides react in an $S_N2'$ fashion with allylic acetates and a nickel catalyst; when the latter is chiral, allylaryls of up to 89% enantiomeric enrichment can be obtained (**24** → **25**).[33] Copper catalysts, such as $Li_2CuCl_4$, can also be employed in such displacements, but usually *via* a direct $S_N2$ mechanism.[34] Similarly, primary allylic phosphates react with Grignard reagents under copper(I) catalysis exclusively *via* $S_N2$ displacement; usually no products from allylic rearrangement are observed.[35] Chiral allylaryl compounds (**25**) can also be prepared by alkylations of ArMgX using an allyl phenyl ether and a chiral Ni–phosphine catalyst. Optical yields are fair to good but a more serious problem is poor regioselectivity.[36] Much more regioselective are the related reactions with allyl silyl ethers (**26**); with a ferrocenepalladium(II) catalyst, either isomer of the ether gives very largely the internal alkenes (**27**) when treated with ArMgX, whereas nickel(II) catalysts lead mainly to the isomeric terminal alkenes (**28**; Scheme 9).[37]

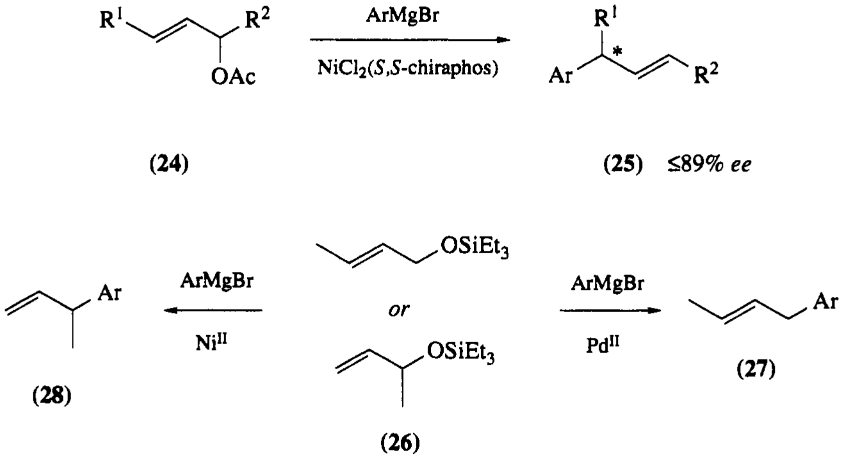

**Scheme 9**

In contrast, a whole range of allylic systems, including allylic alcohols, undergo nickel-catalyzed coupling reactions with arylmagnesium bromide to give, usually exclusively, primary allylaryl compounds uncontaminated by the corresponding conjugated isomers (Scheme 10).[38] The reactions proceed *via* an ω-allylnickel complex and require an excess, typically 4 equiv., of the Grignard reagent in examples of electrophiles with a labile proton (*e.g.* allyl alcohol). Allylic alcohols can be activated for this type of coupling by conversion to the iminium salts (**29**); subsequent coupling with Grignard reagents then occurs directly *via* $S_N2$ displacement (Scheme 11).[39] If, however, the Grignard reagent is treated with copper(I) iodide and HMPA prior to the coupling step, the alternative, $S_N2'$, products are usually formed. In a related sequence, exclusively $S_N2'$ products (**31**) are formed when 2-allyloxybenzothiazoles (**30**) are reacted with Grignard reagents in the presence of copper(I) bromide.[40] Finally, the modified aryl Grignard species, $PhCu{\cdot}MgBr_2{\cdot}LiBr$, react in an $S_N2'$ fashion with allenic bromides (*e.g.* **32**) to give very largely alkynes (*e.g.* **33**) contaminated with very little of the corresponding allene.[41] Some less conventional electrophiles have also been used in efficient alkylations of Grignard reagents. For example, benzylamines (*e.g.* **34**) are available from alkylations of PhMgBr using either alkoxymethyl- or phenylthiomethyl-amines [$RXCH_2NR_2$];[42] similar products are obtainable from reactions between Grignard reagents or organolithium species and Eschenmoser's salt.[43] Finally, Grignard reagents can be efficiently allylated using allyltrialkylammonium salts in the presence of $Li_2CuCl_4$.[44]

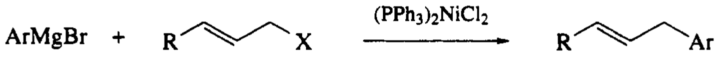

X = OH, OMe, OEt, SH or SMe

**Scheme 10**

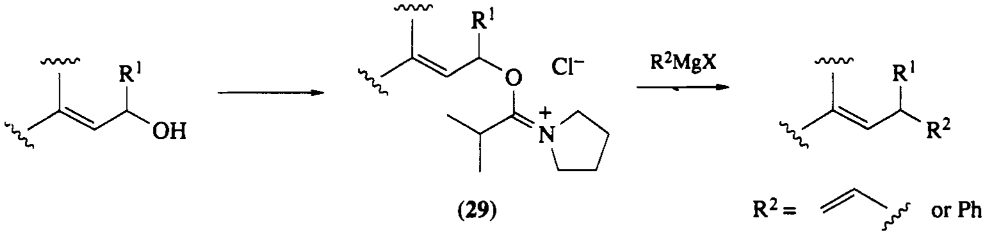

**(29)**

**Scheme 11**

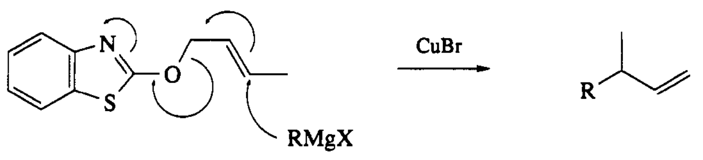

**(30)** **(31)**

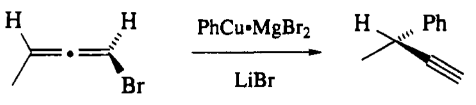

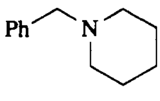

**(32)** **(33)** **(34)**

### 1.6.2.2 Alkylations of Vinyl- and Aryl-lithium Species

The simplest possible reaction in this section, that between a vinyllithium and a primary alkyl halide in general works extremely well (Scheme 12).[45] The corresponding alkyl iodide can equally well be used, but the reaction fails with secondary halides or primary tosylates and is much less satisfactory with alkyl chlorides or when performed in other ethereal solvents. ω-Bromoalkenes can even be obtained from 1,ω-dibromoalkanes in good yields;[18,21,46] virtually no alkene isomerization is observed and therefore both *trans*- and *cis*-alkenes are available using this method. 1-Alkylcycloalkenes (*e.g.* **35**) as well as acyclic trisubstituted alkenes can also be prepared in this way;[46] an alternative strategy is to treat the vinyl bromide with an alkyllithium at −70 °C thus generating the vinyllithium and alkyl bromide by halogen–metal exchange. Upon warming to room temperature, alkylation proceeds smoothly.[46] However, this latter method is limited by the availability of alkyllithiums. A way around this is to treat the vinyl halide with 2 equiv. of $Bu^tLi$, the extra equivalent of base serving to trap the *t*-butyl halide produced.[47] An excellent alternative is to employ tin–lithium exchange reactions between a vinyltrialkylstannane and an alkyllithium, usually MeLi or $Bu^nLi$, which results in the formation of an essentially inert tetraalkyltin by-product. This method has been used, for example, to generate the useful cyclopentenyllithium (**36**) which, although it couples efficiently with reactive electrophiles such as allyl bromide and benzyl chloromethyl ether, is reported to react poorly (*ca.* 30% yields) with primary alkyl iodides.[48] An extremely useful reagent in this respect is *trans*-1,2-bis(tri-*n*-butylstannyl) ethylene, which, upon treatment with $Bu^nLi$ (THF, −78 °C), affords the vinyllithium (**37**), alkylation of which with a range of alkyl halides is reported to be very efficient.[49] The initial products, being vinylstannanes, can clearly be further homologated by the same methodology. An example of this type of strategy is to be found in the approach to 5,6-dehydroarachidonic acid outlined in Scheme 13.[50] Additional features of note in this scheme are the efficient alkylations of the intermediate vinyllithiums by allylic acetates and the $S_N2'$-like reaction[41] with an allenic bromide.

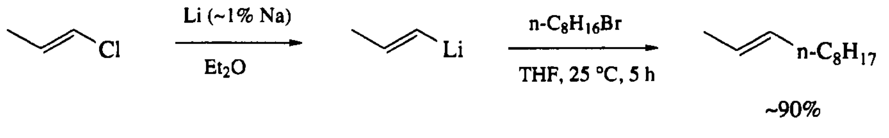

**Scheme 12**

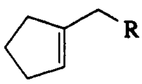

**(35)**

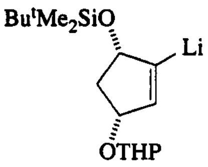
Bu$^t$Me$_2$SiO
Li
OTHP

**(36)**

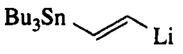

**(37)**

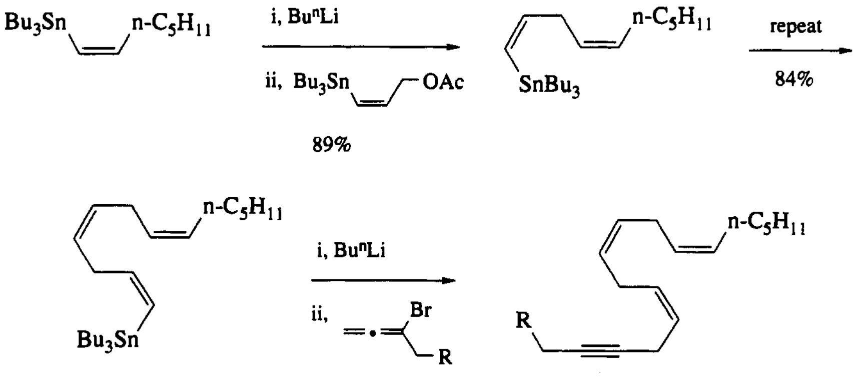
Bu$_3$Sn
n-C$_5$H$_{11}$
i, Bu$^n$Li
ii, Bu$_3$Sn OAc
89%
n-C$_5$H$_{11}$
SnBu$_3$
repeat
84%
n-C$_5$H$_{11}$
Bu$_3$Sn
i, Bu$^n$Li
ii, Br R
n-C$_5$H$_{11}$
R

**Scheme 13**

Further examples of useful vinyllithium intermediates which have been generated using tin–lithium exchange include the substituted butadiene precursors (**38**),[51] (**39**)[52] and (**40**),[52] and the cyclohexadiene (**41**);[53] all four intermediates react efficiently (60–86% yields) and directly with a range of primary alkyl bromides or iodides. Such alkylations can also be performed intramolecularly, as for example in a preparation of the hydrindane (**43**) from the vinylstannane (**42**).[54]

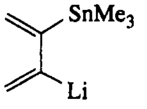

**(38)**

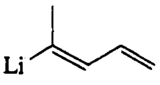

**(39)**

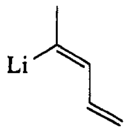

**(40)**

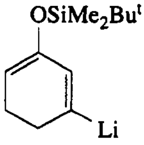
OSiMe$_2$Bu$^t$
Li

**(41)**

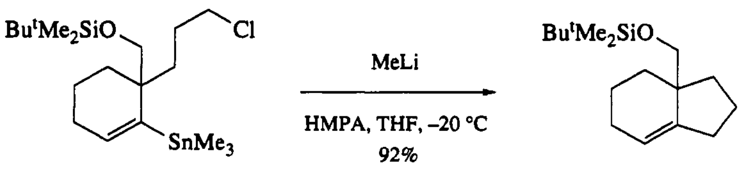
Bu$^t$Me$_2$SiO
Cl
SnMe$_3$
MeLi
HMPA, THF, -20 °C
92%
Bu$^t$Me$_2$SiO

**(42)** **(43)**

A very popular and often complementary alternative to the foregoing vinyllithium chemistry is the use of lithium divinyl- or diaryl-cuprate species, $R_2CuLi$, which also can be alkylated using primary alkyl bromides or iodides but often only in the presence of various additives, typically a stabilizing phosphine ligand and the correct solvent. For example, lithium divinylcuprate is alkylated by *n*-octyl iodide, after treatment with tri-*n*-butyl phosphine, to give 1-decene in 91% yield.[55] In contrast to the simple aryllithium species, $Ph_2CuLi$ reacts smoothly with a secondary alkyl bromide to give an alkylbenzene with 84–92% inversion of stereochemistry, as expected of an $S_N2$ process.[55] Alkylations of this type generally result in almost complete retention of the original alkene geometry.[56]

Two key differences in reactivity between vinyl- or aryl-lithiums and the corresponding $R_2CuLi$ species are firstly that the cuprates couple efficiently (and more rapidly than with alkyl halides) with both primary and secondary tosylates,[55,57] which the lithiums do not,[45] and secondly the general lack of reactivity between the cuprates and carbonyl functions such as those present in ketones, esters and acetates.[14,57] Thus, for example, cuprate species react with bromoethyl tosylate (**44**) to give excellent yields of the bromides (**45**),[14] and the cuprate (**46**) reacts smoothly with an acetoxy iodide leading to the acetoxydiene (**47**).[58]

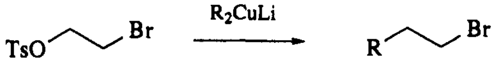

(**44**) (**45**)

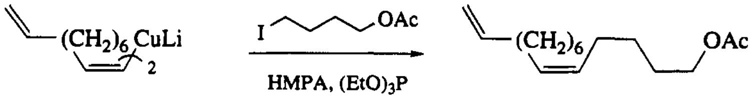

(**46**) (**47**)

A major drawback in the use of homocuprates, $R_2CuLi$, is that one of the alkenyl or aryl groups can often be wasted; clearly, however, this is not a serious problem if the cuprate is derived from a simple organolithium. With reactive electrophiles such as allylic halides or α-halo ethers, both organic ligands are alkylated in the presence of 1 equiv. of HMPA, but with less reactive alkyl halides, at least 3 equiv. of $(EtO)_3P$ are required to stabilize the intermediate cuprate species during the much slower transfer of the second alkenyl ligand.[59]

Further extensions of this general methodology include a useful (*E*,*Z*)-diene synthesis (Scheme 14)[60] and an approach to (*Z*)-alkenols (Scheme 15).[61] Unfortunately such sequences are ineffective when applied to monosubstituted alkynes, a limitation which also applies to the corresponding alkenylmagnesiocuprates.[17] These intermediates also react smoothly with allylic halides to provide 1,4-dienes, especially when dimethyl sulfide is present as an extra ligand,[62] which is fortunate as some of the most convenient sources of copper(I) salts having the high purity requirements for this type of chemistry are the sulfide complexes $CuX{\cdot}SMe_2$ (X = Br or I).[63] One such allylation reaction forms a key step in an approach to α-*trans*- and β-*trans*-bergamotene (Scheme 16);[64] an additional noteworthy feature is that the cuprate species does not suffer from β-elimination of the amino function prior to alkylation.

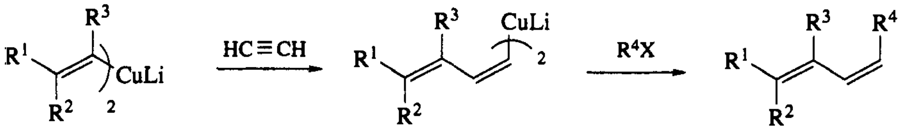

R = Me, $Bu^n$ or $CH_2NEt_2$ (50–80%)

Scheme 14

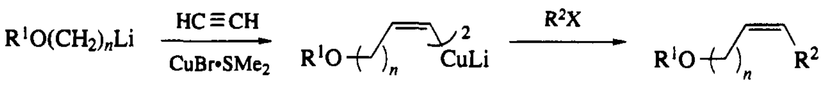

Scheme 15

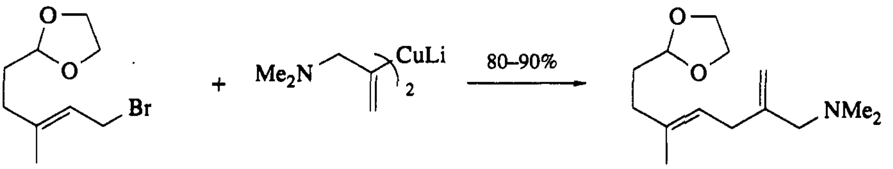

Scheme 16

Alternative methods for obtaining these types of cuprates, $R_2CuX$ (where R = alkenyl or aryl), include treatment of RBr with lithium metal and copper(I) iodide under ultrasonication,[65] reaction between a dialkylvinylborane and $CuBr{\cdot}Me_2S$[66] or between a chlorodivinylborane and methylcopper.[67] The latter two intermediates react efficiently with allyl bromide to provide 1,4-dienes, but alkylations by simple alkyl halides require the addition of an extra ligand such as a phosphine or phosphonite, usually in considerable excess. A significant side reaction can be dimerization of the intermediate cuprates. Trialkylborons can also be used to alkylate vinyllithiums and related species.[68]

A neat combination of some of the foregoing chemistry is use of the cyclic stannane (**48**) as an equivalent of the 1,4-pentadienyl dianion (**49**).[69] Thus, treatment of the stannane (**48**) with Bu$^n$Li, copper(I) iodide–dimethyl sulfide complex and the iodoallene (**50**) smoothly leads to the dienyne (**51**) and thence, by a repetition of this sequence but using electrophile (**52**), to 3-dehydroarachidonic acid methyl ester (**53**).

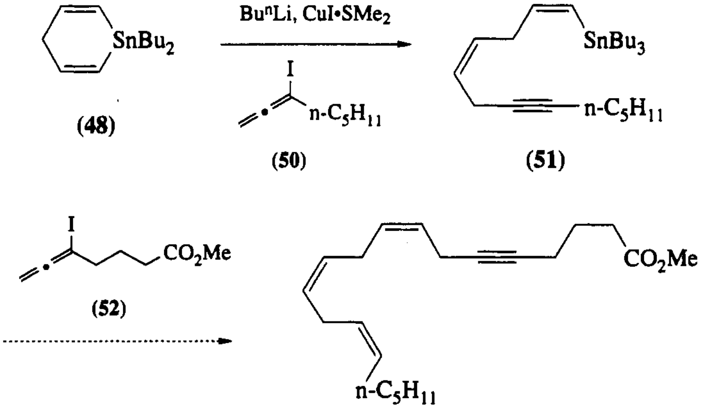

**(48)** **(50)** **(51)** **(52)** **(53)**

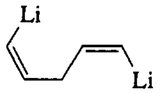

**(49)**

A valuable method whereby the wastage of one organic ligand in R$_2$CuLi species can be avoided is to employ mixed cuprates R$^1$R$^2$CuLi, where R$^2$ is a nontransferable ligand, such as an acetylide, cyanide or benzenethiolate. For example, conversion of the vinylstannane (**54**) into the corresponding vinyllithium followed by the addition of 1-pentynylcopper gives a mixed cuprate intermediate (**55**), which is then alkylated by transfer of only the vinyl ligand (Scheme 17).[70] Similarly, the mixed cuprate (**56**; *cf.* ref. 49) can be alkylated using 3-bromomethylfuran to provide the stannane (**57**), ready for further homologation.[71] A further important development in this area has been the introduction of 'higher order' cuprates in which various stoichiometries of the vinyl- or aryl-lithium are mixed with copper salts.[12,72] Particularly of note is the ability of the higher order cuprate (**58**) to couple efficiently with an *s*-alkyl iodide (Scheme 18);[73] in contrast, the corresponding lithium divinylcuprate gives only a 23% yield. The analo-

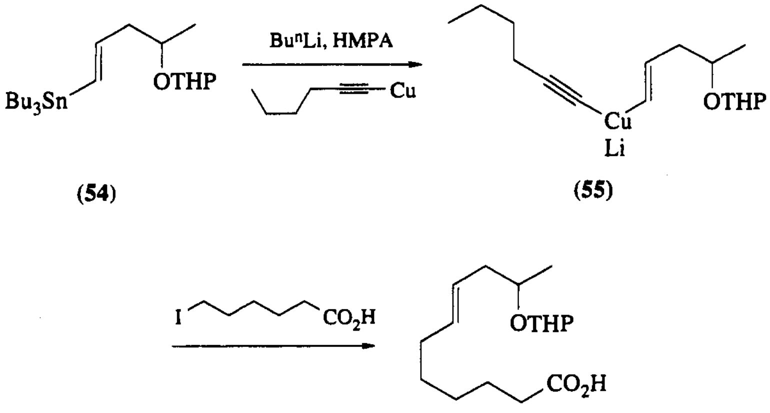

**(54)** **(55)**

**Scheme 17**

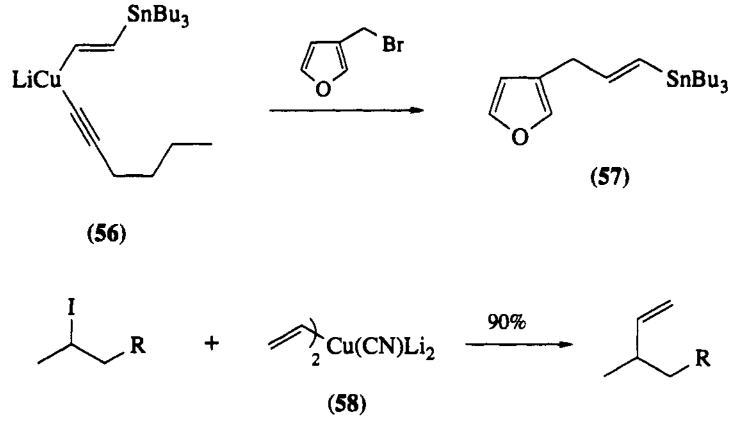

**Scheme 18**

gous aryl species, $Ph_2Cu(CN)Li_2$, is not alkylated efficiently by secondary iodides but does react extremely efficiently with primary chlorides and especially bromides or tosylates[74] (the simpler species, $Ph_2CuLi$, also couples efficiently with both primary and secondary bromides and tosylates).[55-57] An excellent illustration of the power of vinyl- and aryl-cuprates in synthesis is the finding that such intermediates couple smoothly with the halides (**59**; X = Br or I) to provide a racemization-free approach to chiral non-natural α-amino acids (Scheme 19).[75] As well as the regioselectivity of attack, it is especially noteworthy that no elimination to give dehydroalanine occurs with the lower homologs (**59**; *n* = 1). An excellent and convenient reagent for the preparation of mixed higher-order cuprates ($R^1R^2Cu(CN)Li_2$) is the shelf-stable, commercially available complex (2-thienyl)Cu(CN)Li; the cuprates formed from this species and R′Li react smoothly with primary alkyl iodides with transfer of only R′, the 2-thienyl ligand being essentially inert.[76]

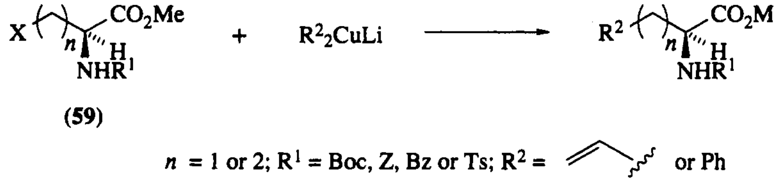

**Scheme 19**

Alkylations of vinyl carbanions can also be carried out intramolecularly to provide three-, four-, five- and six-membered rings (see also refs. 99 and 100). For example, treatment of the dibromides (**60**) with $Bu^tLi$ at low temperature results in selective bromine–lithium exchange at the $sp^2$-center; on warming 'Parham-type' cyclization occurs, thus providing a useful route to substituted benzocyclobutanes (**61**).[77] Similarly, the vinyl iodide (**62**), upon treatment with $Bu^nLi$ (–78 °C → +20 °C) smoothly cyclizes to give an 86% yield of the ylidenecyclopentane (**63**), with no scrambling of the alkene stereochemistry.[78] Similar approaches to related cyclohexane systems also work well.[78] Another useful method for generating vinyllithium species is the Shapiro reaction (such intermediates can be alkylated reasonably efficiently by primary alkyl bromides);[79] this methodology can also be applied intramolecularly (Scheme 20).[80] Presumably, in some cases, the intermolecular version could be improved by the addition of various ligands such as HMPA or $(EtO)_3P$ (*vide supra*).

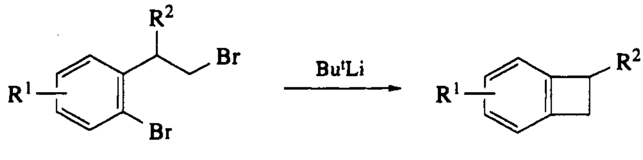

**(60)** **(61)**

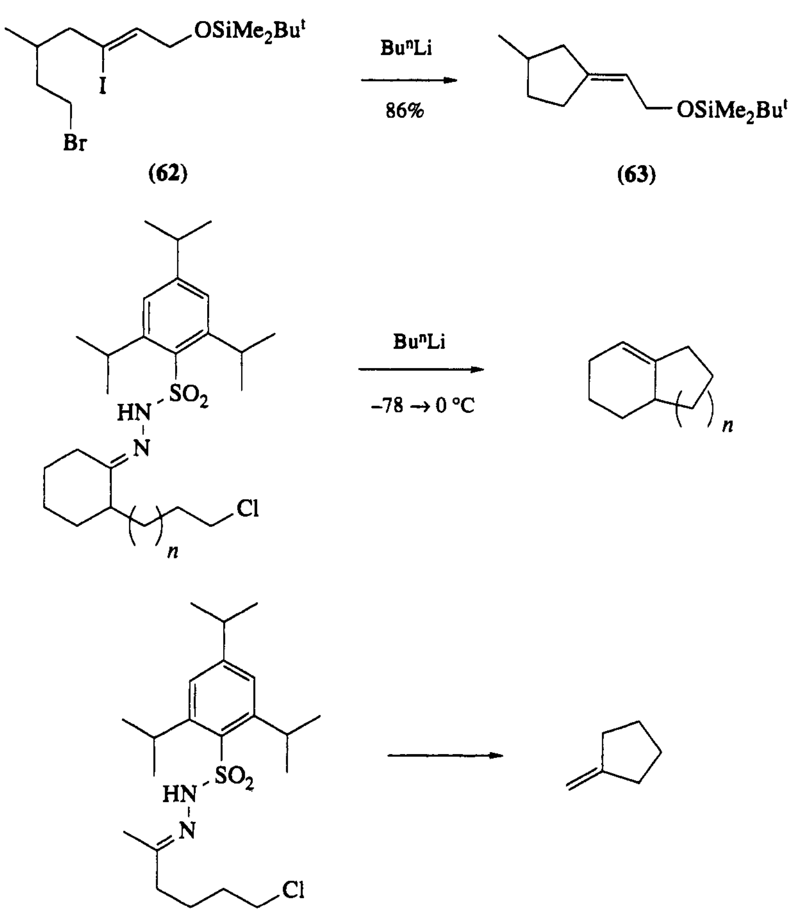

**(62)** **(63)**

**Scheme 20**

### 1.6.2.3 Alkylations of Heteroatom-substituted Vinyl Carbanions

The presence of a heteroatom either α or β to an *sp*$^2$-carbanion opens up many additional synthetic possibilities. Furthermore, their presence can often modify the reactivity of the intermediate and allow its generation by direct hydrogen–lithium exchange rather than halogen–lithium exchange, thus contributing an extra degree of simplicity to the reaction sequences. An excellent illustration of these features is the generation of vinyllithium (**64**) by treatment of methyl vinyl ether with Bu$^t$Li.[81] Formally an acyl anion equivalent, this intermediate can be alkylated efficiently by primary alkyl iodides or primary allylic bromides, although not by benzylic bromides, which instead react *via* halogen–lithium exchange. The corresponding cuprate, however, does couple smoothly with benzylic bromides as well as with secondary allylic bromides.[81,82] The vinyllithium (**64**) can also be generated using Sn–Li exchange and Bu$^n$Li,[83] while the higher homolog (**65**) can be generated directly only in the presence of the MOM function using Bu$^n$Li–TMEDA.[84] Cyclic analogs of the vinyllithium (**64**) have also proven useful in a variety of synthetic schemes, and can often be alkylated in high yield; for example metallation of 2,3-dihydropyran affords the vinyllithium species (**66**), which, upon alkylation using a protected ω-iodo alcohol (**67**), followed by acidification affords good yields of the spiro-acetals (**68**).[85]

As expected, related sulfur species can also be generated and used to good effect, an example being the vinyl sulfide (**69**), which can be alkylated with good efficiency (*e.g.* Bu$^n$I, 68% yield).[86] Similarly the β-lithio species (**70**) reacts satisfactorily with, at least, methyl iodide (99%) and allyl bromide (68%). It

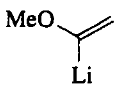

**(64)**

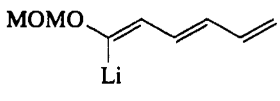

**(65)**

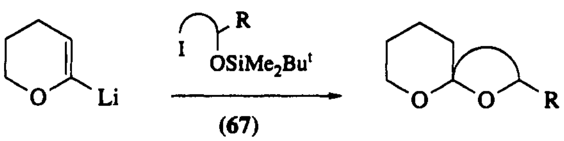

**(66)** **(67)** **(68)**

should be noted in this context that methyl iodide is a very special electrophile, often more suited to assaying the extent of anion generation rather than to synthetic utility. A much better indicator, and by no means a trivial change, is to examine the reactions of a new carbanion with ethyl or *n*-butyl iodides; good yields from these electrophiles bode well for the general utility of the intermediate. For instance, the α-thio enamine (**71**) is reported to give quantitative yields with both methyl and ethyl iodide;[87] the latter result is of much more significance. The related sulfones also show some promise as intermediates. Generated from either the acetal (**72**) by sequential $E_2$ elimination and deprotonation[88] or by direct deprotonation of either the (*E*)- or (*Z*)-vinyl sulfone,[89] the intermediates (**73**) can be alkylated using Bu$^n$I (76%), or benzyl bromide (60–77%), thus indicating at least a reasonably wide utility. The homologous acetal (**74**) has also been reported, although it has only been alkylated with MeI (96%) and with allyl bromide (81%).[90] Similarly, the vinyl selenide (**75**) can be obtained and reacts with *n*-octyl bromide to give the expected homolog in 69% yield,[91] indicating a good range of reactivity. These examples are relatively typical in that full ranges of electrophiles are often not examined (or at least not reported), and it is therefore sometimes difficult to judge the likely overall importance of a particular intermediate.

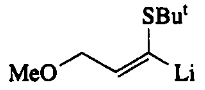

**(69)**

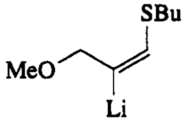

**(70)**

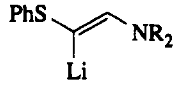

**(71)**

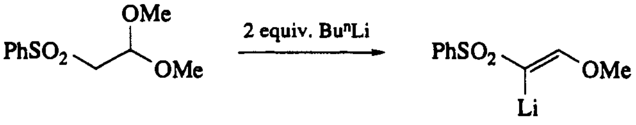

**(72)** **(73)**

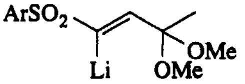

**(74)**

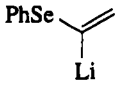

**(75)**

Despite the presence of a potential β-leaving group, the α-lithio acrolein derivative (**76**)[92] can be obtained at low temperatures but only condenses efficiently with primary allylic halides after conversion to the corresponding mixed cuprate using PhSCu; direct, rather than $S_N2'$, attack occurs at least with (*E*)-1-bromo-2-butene to give the functionalized 'skipped' diene (**77**). With many other intermediates, the problem of $S_N2$ *vs.* $S_N2'$ attack is often only resolved by experimentation using the desired electrophile. The vinyl ortho ester (**78**) can be lithiated by halogen–lithium exchange and subsequently alkylated to provide the homologs (**79**) *via* a synthetic equivalent of β-lithio acrylate.[93] This example is reasonably typical of many such alkylations of lithiovinyl carbanions which work well with methyl iodide (and other reactive and simple electrophiles such as R$_3$SiCl, PhSSPh or CO$_2$), but are not so useful with homologous primary iodides. Vinyl carbanions can be generated α to an unprotected ester group in certain cases by Sn–Li exchange. For example, treatment of α,β-unsaturated esters (**80**) sequentially with Bu$^n$Li and RX leads to the homologs (**81**); once again, a typical pattern emerges in that methyl iodide and primary allylic halides afford high yields, whereas 3-chloro-1-iodopropane gives only a 42% yield of the homolog (**81**; R$^1$ = (CH$_2$)$_3$Cl).[94] Similarly, the β-stannyl analog (**82**) can be obtained; this intermediate exhibits essentially the same characteristics.[95] Subsequent conversion of the initial products arising from alkylations of the ester (**82**) into the allylic alcohol (**83**) (effectively the β-lithio analog) followed by alkylation results in a stereospecific approach to tetrasubstituted alkenes. The latter alkylations are somewhat more efficient, as primary alkyl iodides afford 65–72% isolated yields.

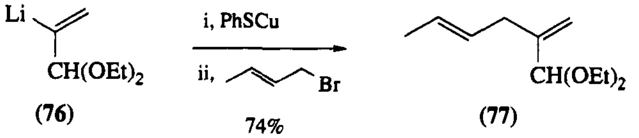
Li
CH(OEt)$_2$
(76)
i, PhSCu
ii,
Br
74%
CH(OEt)$_2$
(77)

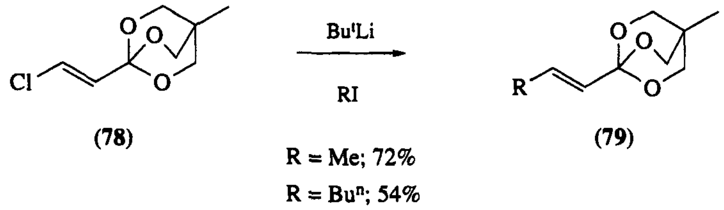
O
O
Cl
O
(78)
Bu$^t$Li
RI
R = Me; 72%
R = Bu$^n$; 54%
O
O
R
O
(79)

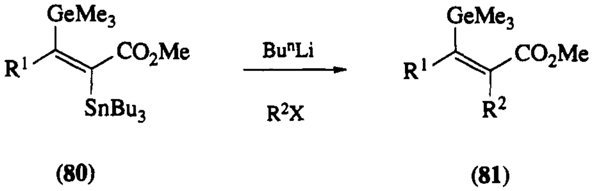
GeMe$_3$
R$^1$
CO$_2$Me
SnBu$_3$
(80)
Bu$^n$Li
R$^2$X
GeMe$_3$
R$^1$
CO$_2$Me
R$^2$
(81)

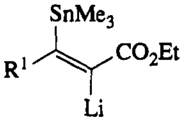
SnMe$_3$
R$^1$
CO$_2$Et
Li

**(82)**

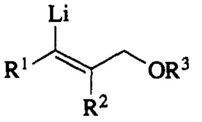

**(83)**

Vinyl carbanions positioned α to a silicon substituent have also proven to be valuable synthetic intermediates, which in general undergo highly efficient alkylations by primary alkyl iodides or tosylates as well as by allylic halides, especially when a vinylcuprate species is used. Such intermediates (**85**) can be generated either by the addition of a copper-modified Grignard reagent to silyl alkyne (**84**)[96] or by a stereochemically complementary boron–lithium exchange procedure involving vinylboranes (**86**) derived from the corresponding silylalkyne.[97] The related vinyllithium species, obtained by halogen–lithium exchange, are also reported to react efficiently with, at least, primary alkyl iodides.[98] Such alkylations can also be carried out intramolecularly,[77–80] a rather spectacular example being the elaboration of silylcyclopropenes (**88**) upon treatment of allylic chloride (**87**) with Bu$^n$Li;[99] the methodology has been extended to the corresponding unsaturated four-, five- and six-membered rings.[100] The isomeric β-lithio silane (**89**), generated by Sn–Li exchange, shows little tendency to undergo elimination and can be alkylated using Bu$^n$Br (81%), indicating a reasonably wide utility for this species.[101]

In general, *ortho*-substituted aryllithiums give variable results in alkylation reactions, and in some cases only after conversion to a cuprate species. For example, the cuprate (**90**) can be allylated efficiently and then electrolyzed to provide the protected benzoquinone (**91**) in excellent overall yield.[102] Coupling

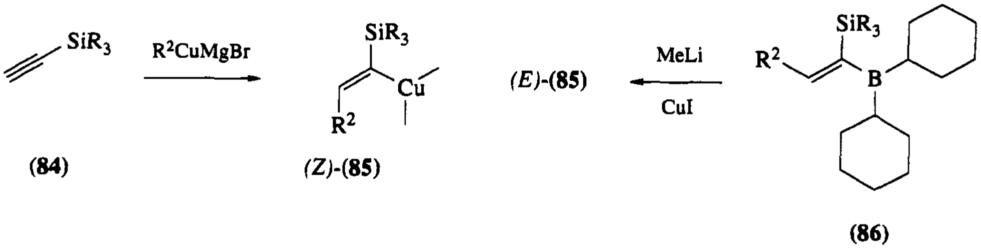
SiR$_3$
(84)
R$^2$CuMgBr
SiR$_3$
Cu
R$^2$
(Z)-(85)
(E)-(85)
MeLi
CuI
SiR$_3$
R$^2$
B
(86)

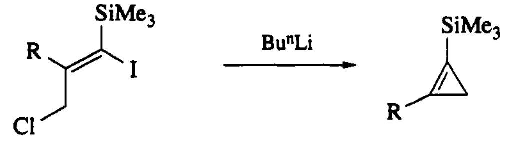

**(87)** **(88)**

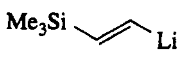

**(89)**

reactions with benzyl bromide are also viable when it appears that, unusually, more than 1 equiv. of the organic ligand in the cuprate (**90**) is alkylated, and direct allylations of the related naphthoquinone-derived species (**92**) are also successful, but again only after conversion to the corresponding cuprate.

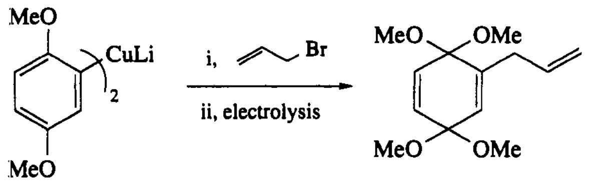

**(90)** **(91)**

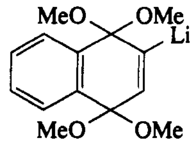

**(92)**

The oxazoline function is one of the most powerful directing groups in metallation chemistry, and allows the direct generation of the *ortho* lithio species (**93**).[103] These have been used with varying success in alkylation reactions; a particularly useful aspect is as precursors to *o*-allylbenzaldehydes (**94**) following allylation and reduction–hydrolysis of the oxazoline function.[104] Alkylations with iodomethyltrimethylsilane also work well, leading to quinodimethane precursors (*e.g.* **95**).[105] However, in common with many nucleophiles, alkylations using homoallylic or propargylic halides fail due to competing deprotonation and overall elimination of HX from the electrophile. A solution to this limitation, which can often be applied in the aromatic and heteroaromatic areas, is first to alkylate the $sp^2$-center with methyl iodide (usually a very efficient step), then remetallate to generate a (usually) more reactive $sp^3$-carbanion and finally alkylate with an allylic or propargylic halide. This technique is illustrated in Scheme 21, which forms the early stages of the preparation of enediynes suitable for Vollhardt-type cobalt-catalyzed cyclizations.[106] The closely related imidazolidine (**96**), however, requires an excess of alkylating agent, and even then only reacts well with methyl iodide (95%); with *n*-butyl bromide only a 45% yield is realized, while alkylation with benzyl bromide gives a 30% yield of the dialkylated product (**97**), a not uncommon feature with this type of reactive halide.[107] In contrast, the dianionic species (**98**) derived (Bu$^n$Li–TMEDA) from benzyl alcohol reacts best with *n*-butyl chloride (55%) and gives only traces of product with primary alkyl iodides; presumably in these cases deprotonation of the iodides by the highly basic dianion takes precedence.[108] A related dianionic species (**99**) derived from benzaldehyde by sequential hemi-aminal formation using *N*-lithio-*N'*-methylpiperazine and deprotonation (Bu$^n$Li) does react reasonably well with Bu$^n$Br (47%), but only after the addition of copper(I) iodide.[109] The dianion (**100**), derived from the tosylhydrazone of benzophenone, provides yet another contrast as it does undergo efficient (>80%) alkylation by primary alkyl halides with no detectable reaction at the potentially competing nitrogen center.[110] Related *ortho*-lithiated aryl isocyanides can be similarly useful.[111]

Finally, the useful cyclohexadienyllithium (**102**; Scheme 22), obtained from the dioxolane (**101**) by sequential deprotonation, β-elimination and halogen–metal exchange, can be alkylated using ethyl iodide,

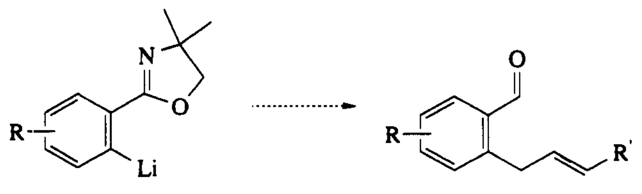

**(93)** **(94)**

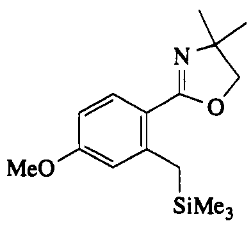

**(95)**

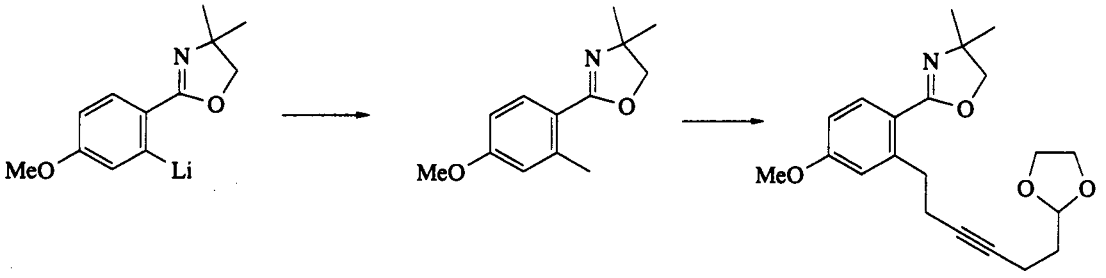

Scheme 21

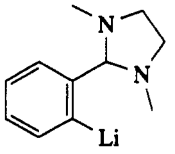

(96)

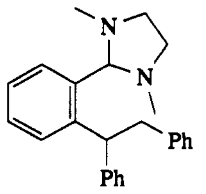

(97)

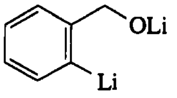

(98)

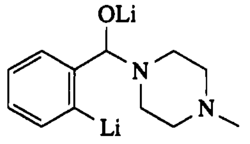

(99)

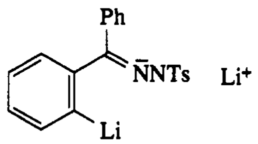

(100)

and hence probably by higher, primary homologous iodides, to provide a useful route to 3-substituted cyclohexenones.[112]

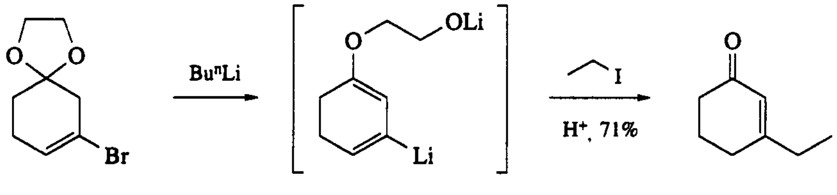

(101) (102)

Scheme 22

It is hoped that the foregoing examples provide an indication of the variety of outcomes, both good and bad, which can result from alkylations of this type of $sp^2$-carbanion, together with some useful methods for obtaining good yields. Many anionic species are not included in the discussion simply because their alkylation chemistry has not been reported, except sometimes with methyl iodide which, as discussed above, is not always a typical or representative electrophile in this type of chemistry.

### 1.6.2.4 Alkylations of Allene Carbanions

Allenes can be directly deprotonated using alkyllithiums, and the intermediate lithio allenes can then be alkylated efficiently by primary alkyl bromides or iodides.[113] For example, good yields of homologated allenes can be realized under the conditions specified in Scheme 23 (the brief reaction time appears to be crucial) when very little of the alkynic isomer is formed. Similarly, the corresponding lithium diallenylcuprates, obtained either by hydrogen– or halogen–lithium exchange can also be alkylated.[114] In common with methyl vinyl ether,[81,82] methoxyallene can be directly deprotonated, although the resulting intermediate (**103**) gives only moderate to good yields of alkylated products upon treatment with a variety of primary alkyl or allylic halides.[115] Once the intermediate (**103**) has been alkylated, the products can be again deprotonated to provide the new lithio allene (**104**), and thence the dialkylated products (**105**), following treatment with a primary alkyl iodide (the addition of a copper(I) species is not necessary); these final educts are useful as precursors to α,β-unsaturated ketones, to which they are converted simply by acidic hydrolysis.[116] Much the same double alkylation sequence can be carried out using the phosphoramide (**106**), although the range of suitable alkylating reagents appears to be more limited.[117] The related silyloxy species (**108**), generated by rearrangement of the propargylsilane (**107**), can also be alkylated using a range of primary alkyl halides (71–87%) to give the expected homologs, again useful precursors to α,β-unsaturated ketones.[118]

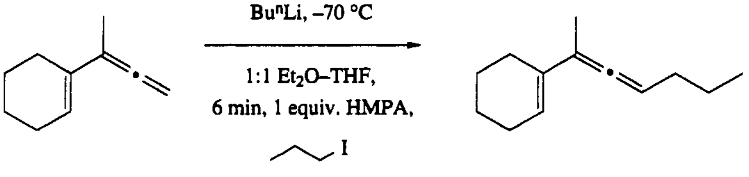

**Scheme 23**

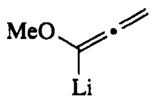

**(103)**

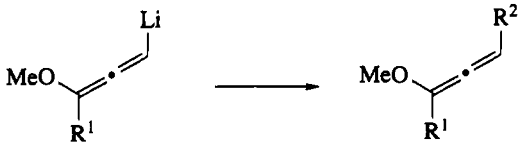

**(104)** **(105)**

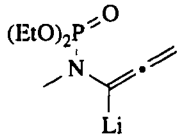

**(106)**

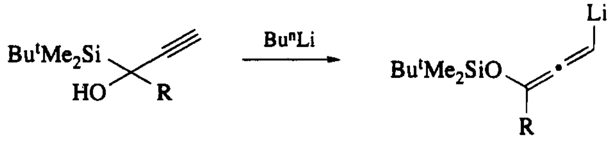

**(107)** **(108)**

### 1.6.2.5 Alkylations by an $S_N2'$ Process

Many of the foregoing alkylations with allylic halides have only been carried out with symmetrical examples of the latter, and therefore it is not clear whether alkylation occurs *via* an $S_N2$ or $S_N2'$ process. However, in common with Michael addition chemistry, vinyl and aryl carbanions generally add in a conjugate $S_N2'$ fashion in the presence of a copper(I) salt, and in the absence of excessive steric demands.[33,39–41] Thus, in a typical example, lithium diphenylcuprate adds to the allylic acetate (**109**), derived from the corresponding α-lithio vinylsilane,[98] to provide a 61% yield of only the (*E*)-vinylsilane (**110**);[119] with other examples, the regioselectivity can be poorer.[120] Often such cuprates react with α-bromo ketones to give only poor yields of α-aryl ketones, a common side or even major pathway being halogen–metal exchange. This problem can be overcome by employing the corresponding enamine (*e.g.* **111**), which reacts smoothly with $Ph_2CuLi$, presumably *via* an $S_N2'$ displacement, to give, in 87% yield, 2-phenylcyclohexanone after hydrolysis[121] (see also refs. 6–8). However, in cases of extreme steric and/or electronic demands, vinyllithium species will react in an $S_N2'$ fashion as illustrated in Scheme 24.[122] The cyclohexene derivative (**112**) reacts similarly; these are perhaps not typical examples, despite the overall $S_N2'$ process, since the first step is a Michael-type addition.

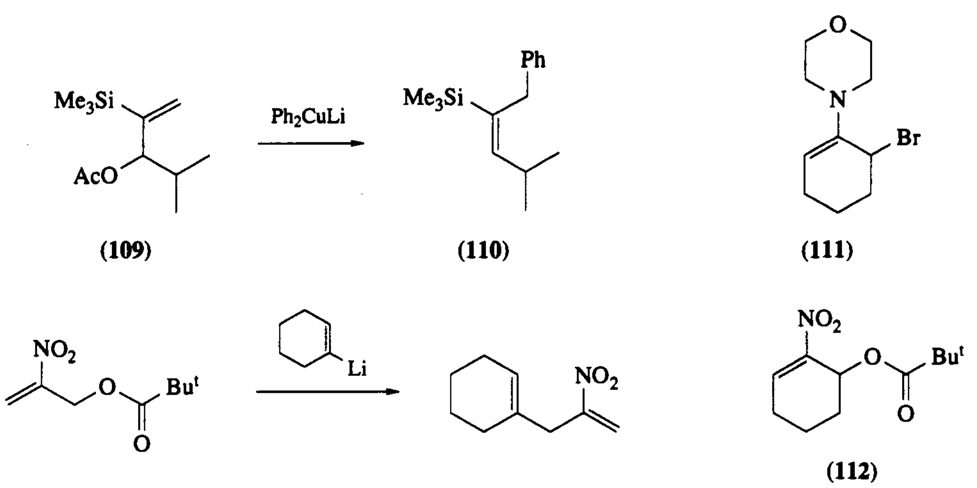

Scheme 24

## 1.6.3 ALKYLATIONS WITH LESS CONVENTIONAL ELECTROPHILES

Some examples of less conventional electrophiles which react well with $sp^2$-carbanionic centers are grouped together here mainly for reasons of emphasis and because a variety of organometallic species are involved. Aminomethylations of Grignard reagents, for example, can be effected either using an aminomethyl ether[42,123] or an amino sulfide (Scheme 25).[124] The latter electrophiles also react well with (*Z*)-divinylcuprates (**113**), derived from alkylcuprate additions to acetylene, to provide a useful route to (*Z*)-allylamines (**114**).[125] Methyleneammonium salts (*e.g.* Eschenmoser's salt)[43] can also be applied in this way; for example, the dilithiated aromatic intermediate (**115**) reacts to form the diamino derivative (**116**).[126] Two useful extensions of this are that treatment of the precursor of the dianion (**115**) with 1 equiv. of base results in regioselective metallation of the furan and hence leads to the aminomethylfuran derivative; not unreasonably therefore, treatment of the dianion (**115**) with 1 equiv. of the electrophile gives the aminomethylphenyl isomer. Although aminoethylation can be achieved by condensations between (usually *N*-tosyl) aziridines and cuprates (**113**), much better yields are often obtained using mixed higher-order cuprates, $R_2Cu(CN)Li_2$.[127] With less reactive cuprates, the addition of $BF_3$ can be beneficial.

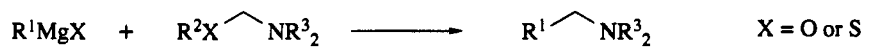

Scheme 25

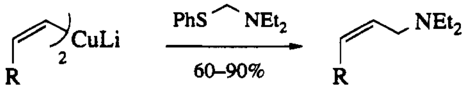

**(113)** **(114)**

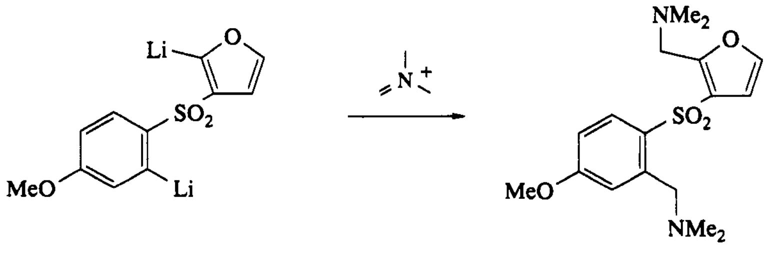

**(115)** **(116)**

A variety of Grignard reagents also react with ortho esters and acetals leading to acetals and ethers respectively.[128] A particularly useful extension of this methodology is in its application to alkylations of divinylcuprates (**113**).[129] Thus, the ether (**117**) can be obtained from heptanal dimethylacetal, the appropriate cuprate and $BF_3$ in 93% yield; similarly acetaldehyde diethylacetal reacts with $PhCu{\cdot}BF_3$ to give an equally good yield of the ether (**118**). With unsaturated acetals, mainly and sometimes exclusively $S_N2'$ addition takes place; thus acrolein diethylacetal and cuprate (**113**; $R = Bu^n$) modified using $BF_3$ react to give vinyl ether (**119**) in 66% yield. At the higher oxidation level, reactions with ortho esters provide a useful method for homologation to the (protected) aldehyde level as, for example, in the coupling of $PhCu{\cdot}BF_3$ and triethyl orthoformate to give benzaldehyde diethylacetal (92%).

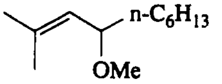

**(117)**

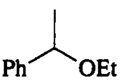

**(118)**

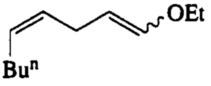

**(119)**

A somewhat unusual reaction is the coupling of phenyllithium–copper(I) iodide mixtures directly with allylic alcohols, in the presence of the salt $Ph_3PNMePh^+I^-$, allowing a usually stereoselective preparation of hydrocarbons (**120**).[130] Similar phenyllithium species can be directly alkylated using diazoacetates to give phenylacetates in moderate (*ca.* 50%) yields,[131] the latter usually being inferior to those produced by related boron-based methodology.[6] Divinylcuprates (**113**) also add efficiently to vinylphosphonium salts (*e.g.* Schweizer's reagent) to give ylides (**121**) and thence 'skipped' dienes (**122**).[132]

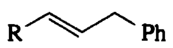

**(120)**

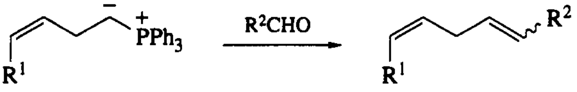

**(121)** **(122)**

## 1.6.4 ALKYLATIONS OF VINYL AND ARYL CARBANIONS, RM, WHERE M ≠ Li, Mg or Cu

Some of the most important members in this group are the alkenylalanes (**123**), which are readily prepared by the addition of DIBAL-H to a terminal alkyne; however, in general, these can only be alkylated in respectable yields following formation of the corresponding 'ate' complexes, often using *n*-butyllithium.[133] Unfortunately, even these more reactive intermediates tend to give really good yields only with allylic bromides, although the very reactive chloromethyl methyl ether alkylates the alanes (**123**) directly, without the need to form an 'ate' complex, to give the expected ethers in 72–80% yield.[134] 'Ate' complex formation is also necessary in alkylations of the related alanes derived by the zirconium-catalyzed addition of trimethylaluminum to 1-alkynes.[133] Much the same is true of more highly substituted derivatives such as the α-silylalane (**125**)[135] or the β-stannyl homolog (**126**),[136] both of which react well (68–84%) with allylic halides after conversion to an 'ate' complex, whereas reactions with iodo-ethane or -butane are much less efficient. In contrast, the alkenylaluminum (**127**), the first example of such a species to contain a free carbonyl group, does alkylate directly with a variety of primary and secondary alkenyl bromides,[137] although $S_N2$ *vs.* $S_N2'$ attack is a problem with appropriate electrophiles such as crotyl bromide. In a rather different reaction type, the allylic acetate (**129**) couples smoothly with the alane (**128**) under the influence of a $Pd^0$ catalyst to provide only the product (**130**) of overall $S_N2$ attack.[138]

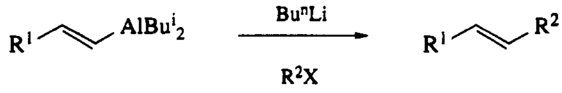

**(123)** **(124)**

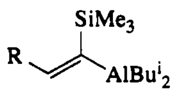

**(125)**

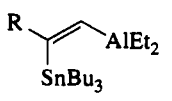

**(126)**

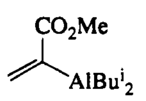

**(127)**

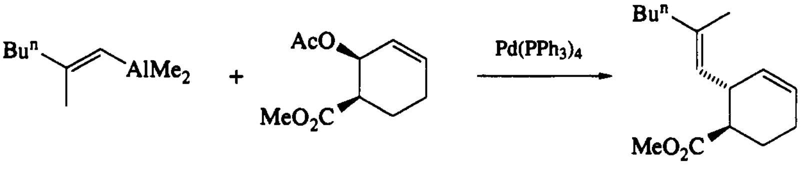

**(128)** **(129)** **(130)**

A related set of conditions (Scheme 26) provides an alternative to 'ate' complex formation, at least in alkylations using benzylic or allylic chlorides.[139,140] The reverse sense of coupling between benzylzinc species and alkenyl halides is also a viable option. In a similar fashion, arylzincs can be coupled readily with allylic halides (Scheme 27).[140] Both alkenylalanes and zinc species can be similarly coupled with allylic acetates, aluminum alkoxides, phosphates or silyl ethers. Again, problems can arise when the electrophiles can readily undergo both $S_N2$ and $S_N2'$ displacements. In such examples, the ratio of products obtained is more dependent on the nature of the aryl metal and the solvent than on the position or nature of the allylic leaving group. Arylzinc intermediates can also be alkylated by bromoacetates to give phenylacetates, provided a nickel catalyst and phosphine ligand are present;[141] the corresponding aryl (and heteroaryl) acetonitriles can be similarly obtained using bromoacetonitrile as electrophile.[142] Phenylboranes can also be alkylated using haloacetonitriles.[143]

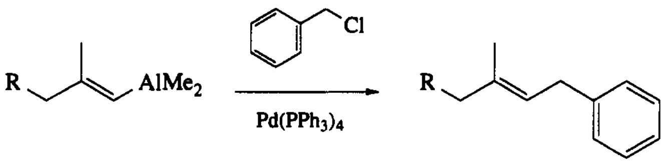

Scheme 26

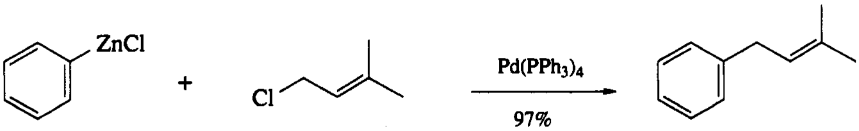

Scheme 27

The rather unreactive arylcadmium reagents, ArCdCl, do react satisfactorily with both primary and secondary α-bromo esters and with secondary allylic bromides, but curiously they react much more poorly with allyl and benzyl bromide, and α-chloro ethers (*ca.* 40% yields); no coupling occurs using primary alkyl bromides.[144] Finally, the old Wurtz–Fittig methodology, whereby an aryl bromide and an alkyl iodide are coupled in the presence of elemental sodium, can sometimes lead to acceptable yields (40–60%); no rearrangement products are formed, and it is likely that free radicals are not involved.[145]

## 1.6.5 ALKYLATIONS OF HETEROAROMATIC CARBANIONS

Despite the plethora of metallated heteroaromatic intermediates which are available, there is often a dearth of information regarding their alkylation chemistry. Many such intermediates are claimed to be generally useful when the evidence provided only mentions very reactive electrophiles such as $CO_2$, MeSSMe, $Me_3SiCl$ or MeI. As mentioned above, MeI however is not a typical alkylating agent and is often more suitable as an assay reagent to determine the extent of metallation. In general, alkylations of heteroaromatics give a wide variety of yields in coupling reactions with primary alkyl bromides or iodides (secondary halides usually give only poor yields); if an electrophile such as ethyl iodide affords a good yield, it is likely that other higher homologs will be similarly effective. Results from more reactive allylic and benzylic halides and α-halo ethers tend to be even more variable, and certainly not always an improvement upon alkylations using saturated analogs as is often the case with enolates. Two serious side reactions can account for this; firstly deprotonation of the allylic or benzylic species by the reactive intermediate, and secondly double alkylation. Typically, but by no means exclusively, such alkylations are best performed in THF rather than ether, sometimes using HMPA as a cosolvent. Excellent yields are usually obtained with methyl iodide (and also especially aldehydes and ketones), moderate to good yields with higher primary homologs and variable, often poor yields with allylic halides and relatives.[146]

Both 2-lithiofuran and 2-lithiothiophene often afford respectable yields with a variety of alkylating reagents. The former furan species can be alkylated by *n*-butyl bromide (77%),[147] by the less reactive diethyl acetal of bromoacetaldehyde (70%)[148] and by allylic bromides generally but not always[148] in high yield.[146,149] The latter thiophene intermediate tends to give somewhat lower yields (*e.g.* $Bu^nBr$, 47%; $BrCH_2CH(OEt)_2$, 40%; $PhCH_2Br$, 62%),[150] while 2-lithiopyrroles can be even less satisfactory intermediates.[151] Much the same is true of the benzo analogs of these simple heterocyclic systems.[146]

Conversion of these species to various mixed or higher-order cuprate species (*vide supra*) does not usually improve this situation as the heteroaromatic ligands usually transfer sluggishly from copper; indeed the mixed cuprates $R(2\text{-thienyl})Cu(CN)Li_2$ alluded to above[76] are valuable precisely because the thiophene ligand is *not* transferred to an attacking electrophile. However, some other transition metal reagents have proven useful in this area, such as 2-lithiofuran alkylation using allylic or benzylic halides in the presence of $Pd(PPh_3)_4$,[152] and the alkylation of heteroarylzinc chlorides by bromoacetonitrile using a combination of $Ni(acac)_2$ and a phosphine ligand (Scheme 28).[142]

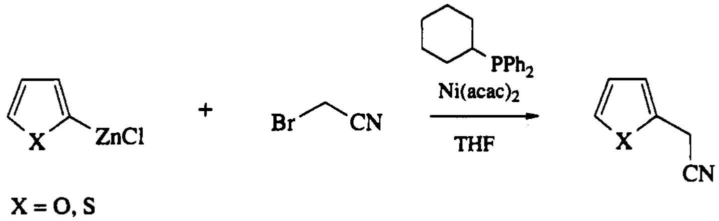

**Scheme 28**

The concept that doubly ionized species could be 'more reactive' and hence lead to enhanced yields is often not true, an example being the dianion (**131**), which follows a typical pattern, reacting exceptionally well with aldehydes and ketones (>90%), poorly with primary alkyl halides (30–40%) except methyl iodide (>95%), and not at all, in the sense of giving alkylated products, with allylic or benzylic halides.[153] By contrast however the dianion (**132**) does react well with allyl bromide to give the corresponding dialkylated product in 72% yield.[154]

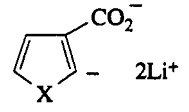

(**131**) X = O, S

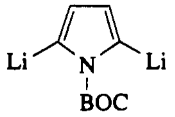

(**132**)

In general, six-membered nitrogen heteroaromatics are not easily converted into carbanionic species,[146] and even if this is achieved, alkylation reactions are often poor.[146,155] An exception to this is the oxazoline derivative (**133**), which is metallated smoothly at the 3-position using methyllithium ($Bu^nLi$ or LDA are not suitable); the resulting 3-lithio derivative can then be alkylated in reasonably good yields (*ca.* 55%) by primary alkyl iodides and allylic bromides.[103,156] The corresponding 3-oxazolinyl isomer reacts much less effectively. The yields in these types of reactions can often be increased by conducting the reactions intra- rather than inter-molecularly; this is the case in a synthesis of 7-methoxymitosene (**135**) in which the ring system is established by cyclization of an intermediate *N*-chloropropylindolecarboxylate (**134**) following treatment with LDA ($Bu^nLi$ can be used in related examples).[157]

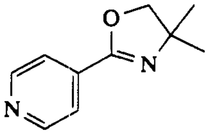

(**133**)

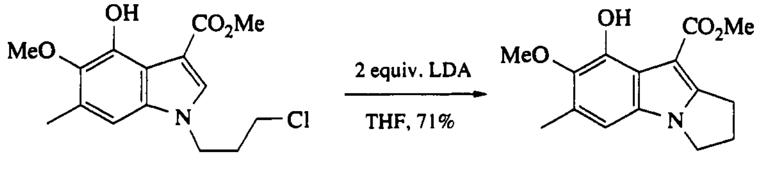

(**134**) (**135**)

An alternative to this type of chemistry is to react the intermediate lithiated heteroaromatics with trialkylboranes and then induce B → C alkyl migration using iodine or *N*-chlorosuccinimide in the intermediate lithium boronates.[158] With simple trialkylboranes, two of the alkyl groups are wasted, although this can be avoided by using 9-BBN derivatives. A particularly notable feature of this methodology is that it is often more successful with secondary or tertiary alkyl groups, thus circumventing a currently universal limitation on direct *sp*$^2$-alkylation, that of the use of tertiary halides.

## 1.6.6 ALKYLATIONS AT *sp*$^2$-CENTERS USING EPOXIDES

Often, though not always, successful alkylations of vinyl carbanions using epoxides rely on the presence of copper, either in catalytic (*e.g.* CuI) or stoichiometric (*e.g.* $R_2CuLi$) amounts.[12] In the older literature, a common method was to form, say, an aryl Grignard species in ether then replace the solvent with higher boiling benzene or toluene prior to addition of the epoxide.[159] A later, systematic study revealed however that THF was also an eminently suitable solvent for this type of reaction,[160] although conversely for similar reactions of $R_2CuLi$, ether is a superior solvent (*vide infra*). Problems inherent with this method are usually associated with the inevitable presence of $MgX_2$ which, being a Lewis acid, can induce either epoxide opening and subsequent rearrangements or halohydrin formation, thus giving rise to sometimes poor yields of the expected products (*i.e.* those formed by attack at the less substituted carbon of the epoxide) possibly contaminated with difficult to separate regioisomers. The more sterically hindered the epoxide, often the more essential is the presence of copper. For example, the conversion (**136**) to (**137**) proceeds in only 3% yield in the absence of a copper salt; vinylmagnesium halides behave similarly.[161] The related process using $Ph_2CuLi$ is significantly more wasteful as 1 equiv. of the organic ligand is lost,[162] hence the attraction of some of the mixed cuprates described below. This procedure is commonly employed in a wide range of Grignard additions to epoxides, two specific examples being extension of the vinylsilane (**138**) to give the butyrolactone precursors (**139**)[163] and elaboration of the allylsilanes (**140**) from the homologous Grignard reagent.[164] Copper(I) cyanide can be equally as effective as a copper(I) halide.[165] Similarly, while some aryllithiums are alkylated efficiently by simple epoxides,[166] the addition of a catalytic copper salt is usually necessary if good yields are to be realized.[167]

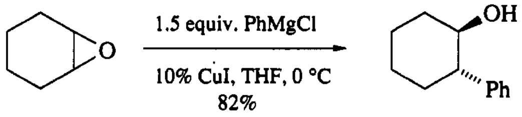

(**136**) (**137**)

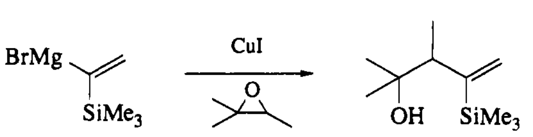

(**138**) (**139**)

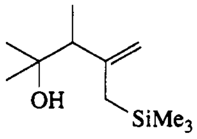

(**140**)

A more recent method for the activation of epoxides, especially in reactions with alkylcoppers and related species, is to add boron trifluoride etherate to the system.[168] Such additions will also facilitate alkyllithium additions to epoxides,[169] two specific examples being homologation of the pyridylindole (**141**) into the hydroxyethyl derivative (**142**)[170] and alkylation of the sulfone (**73**) using propylene oxide, which requires the presence of $BF_3$ if a good yield, in this example 80%, of the desired product (**143**) is to be obtained.[89]

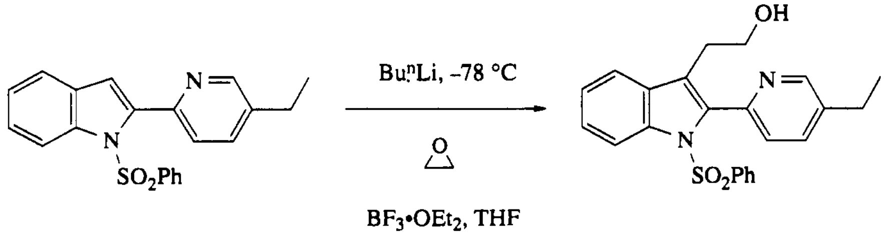

(**141**) (**142**)

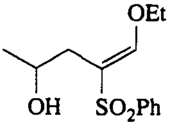

**(143)**

The bulk of methodology in this area has however been centered on the use of stoichiometric amounts of a copper reagent. A recently developed procedure for the preparation of 'active' elemental copper, by lithium naphthalide reduction of the CuI–PBu$_3$ complex, is capable of directly producing alkylcuprate species and could be of particular interest in the formation of the cuprate (**144**) and related intermediates which cannot be obtained *via* the corresponding organolithium or Grignard species[171] (in general, cuprates do not react with esters).[14,57] Both intermediates (**144**) and cuprates derived from aryl iodides and this active copper react well with epoxides without the need for further catalysis. Similarly, magnesiocuprates (**145**), obtained by copper-mediated additions of Grignard reagents to 1-alkynes, react well with ethylene oxide or monosubstituted epoxides but in general yields of the homologs (**146**) are improved by prior formation of an 'ate' complex using a lithium acetylide.[17,172] 1,2-Disubstituted epoxides, however tend to react poorly.

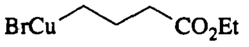

**(144)**

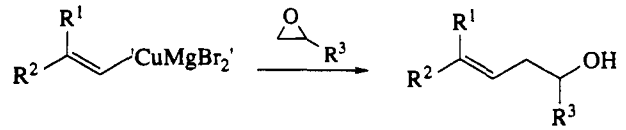

**(145)** **(146)**

The related (*Z*)-lithium dialkenylcuprates (**147**) derived from acetylene itself also react well with epoxides to provide a useful route to (*Z*)-homoallylic alcohols; the lack of reactivity with esters allows an easy access to lactones (**148**) by condensations between epoxy esters and this type of cuprate (Scheme 29).[173] Likewise, the lower homologs (**149**) and (**151**), both of which are relatively easy to prepare in optically active forms, can be readily converted into homoallylic and bishomoallylic alcohols (**150**)[174] and (**152**)[175] respectively. An ester unit can also be incorporated into the cuprate functions; thus, addition of a mixed lithium cuprate, 'RCuYLi', to ethyl propiolate gives the cuprates (**153**), which add to epoxides to give unexpectedly the (*Z*)-crotonates (**154**).[176] Such isomerization is not uncommon with vinyl carbanions in general, and is obviously a limitation when isomeric mixtures are produced.

The origins of much of this methodology lie in the classical studies of Gilman, which were followed by an extensive investigation into the reaction between lithium diphenylcuprate and epoxides.[177] Whereas cyclohexane epoxide (**136**) is essentially inert to phenyllithium, Ph$_2$CuLi reacts well allowing the transformation (**136**) to (**137**) to be effected in high yield but using ether rather than THF[160–162] as the solvent and using 2 equiv. of the cuprate. Ph$_2$CuLi also does not usually attack esters. From the yields re-

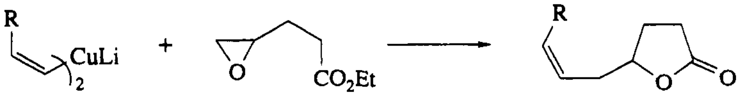

**(147)** **(148)**

**Scheme 29**

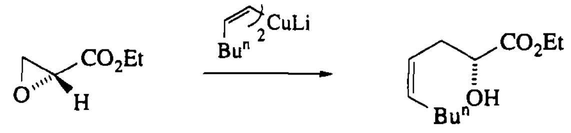

**(149)** **(150)**

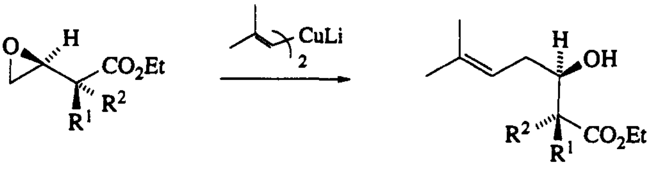

**(151)** **(152)**

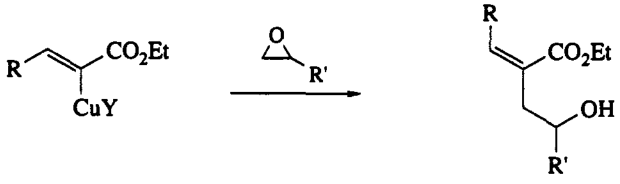

**(153)** **(154)**

ported, there is often little to choose between $Ph_2CuLi$ and a combination of PhMgBr and CuI (see also ref. 186). A wide variety of substituted vinyllithium species also react well with epoxides, after conversion to the corresponding lithium divinylcuprate. For example the dihydropyran derivative (**155**) couples efficiently with the the epoxy ether (**156**) to give a good yield of the spiro-acetal precursor (**157**).[178] Allenyllithiums provide something of a contrast to this general pattern in that they condense efficiently and directly with monosubstituted epoxides,[179] especially in the presence of HMPA,[180] to provide a good route to alcohols (**158**). In all of these reactions, regioselectivity problems can clearly arise with 1,2-disubstituted epoxides; however, some useful regioselectivities have been discovered[181] including 1,2-diol formation from β,γ-epoxy alcohols (**159**)[182] and β-hydroxy ketone formation from α,β-epoxy ketones (**160**).[183]

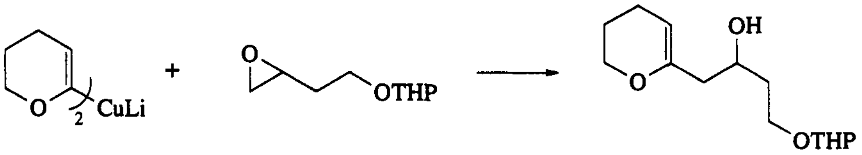

**(155)** **(156)** **(157)**

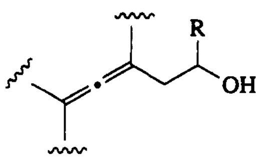

**(158)**

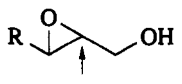

**(159)**

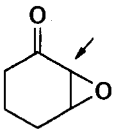

**(160)**

In common with lithioallenes, many lithiated heteroaromatic species react well with unhindered epoxides directly to give respectable yields of the expected homologous alcohols. For example, 2-furyllithium in THF reacts almost quantitatively with propylene oxide[146,148] but yields are rather lower in ether.[184] Returns are also generally poorer in examples of lithiated heteroaromatics which contain two heteroatoms.[146] In the cases of indoles and pyrroles, the corresponding Grignard reagents formed from the *N*-unsubstituted heterocycles can also be used, although yields are usually only good in the former group, when 3-hydroxyethylindoles are obtained.[159] Limited use has been made of the corresponding lithium diarylcuprates because in general the heteroaryl ligands, when 2-substituted, are very unreactive[76] (*vide infra*). However, such derivatives of 3-lithiofuran do add efficiently to monosubstituted epoxides, the best stoichiometry found being that indicated in formula (**161**).[185] Indeed, one of the best reagents for the transfer of a vinyl ligand to an epoxide is the mixed cuprate (**162**) in which the 2-thienyl ligand is essentially inert;[76,186] the simpler species $R_2Cu(CN)Li_2$ are also particularly useful in this respect, giving exceptionally high yields even with disubstituted epoxides.[72]

When vinyl epoxides are substrates for this type of reaction, Grignard reagents usually give mixtures of 1,2 (both possibilities) and 1,4 addition products; synthetically useful yields can nevertheless be ob-

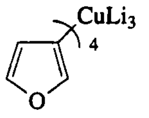

**(161)**

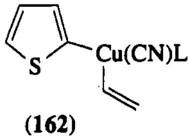

**(162)**

tained in some cases. For example, phenylmagnesium bromide in ether reacts with vinyloxirane to give largely (84%) the perhaps least expected product (**163**), whereas the corresponding 2-naphthyl reagent gives the alcohol (**164**) as the only isolated product in 58% yield, and 2-thienylmagnesium bromide the 1,4 addition product (**165**) but only in 26% isolated yield.[187] In contast, and in line with their excellence as Michael nucleophiles, lithium diorganocuprates usually react almost exclusively by the 1,4-pathway, a typical example being $Ph_2CuLi$ in ether–benzene, which with vinyloxirane gives an 85% yield of the conjugate addition product (**166**), accompanied by only 15% of the alternative product (**163**).[72,187] In just the same way, (*Z*)-lithium divinylcuprates (**167**) can be used in a stereospecific synthesis of the 'skipped' dienes (**168**).[188] Similarly, cyclic allylic epoxides can participate in this useful type of reaction which is generally favored in ether rather than THF.[189] Thus, the epoxy enolate (**169**) undergoes a highly regio- and stereo-selective conversion into the cyclohexenol (**170**), formally by an umpolung process in which a nucleophile is added α to a ketone function.[190] Likewise, the simpler epoxycyclopentene (**171**) undergoes predominantly 1,4-attack to give mainly cyclopentenol (**172**).[191]

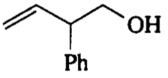

**(163)**

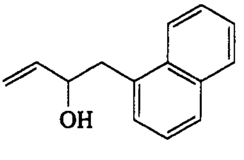

**(164)**

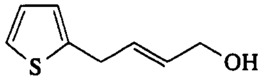

**(165)**

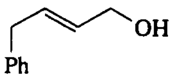

**(166)**

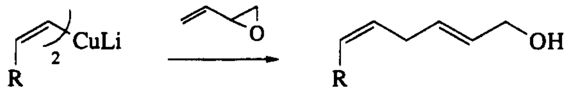

**(167)** **(168)**

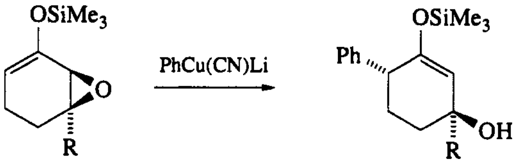

**(169)** **(170)**

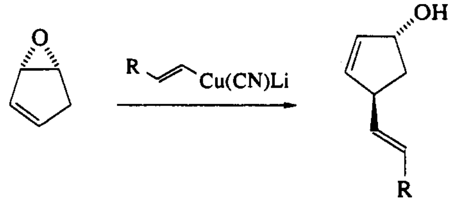

**(171)** **(172)**

Intramolecular alkylations of epoxides at $sp^2$-centers are also possible; thus treatment of the epoxyamide (**173**) with *s*-butyllithium affords moderate to good yields of the dihydrobenzofurans (**174**).[192] However, the homologous system (**175**) is converted into the tetralin framework (**176**) rather than to an indan derivative, with the magnesium bromide presumably serving to activate the epoxide.[193] Under similar conditions, the styrene oxide (**177**) is converted into the benzocyclobutanol (**178**) presumably by

Lewis acid-induced rearrangement of the epoxide function to the corresponding aldehyde *via* a benzylic carbonium ion.[194]

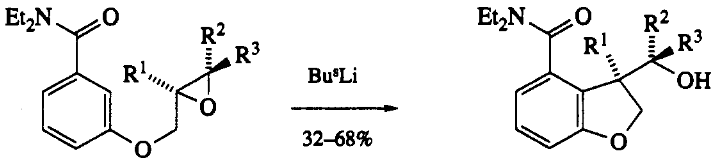

**(173)** **(174)**

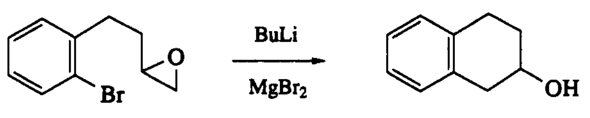

**(175)** **(176)**

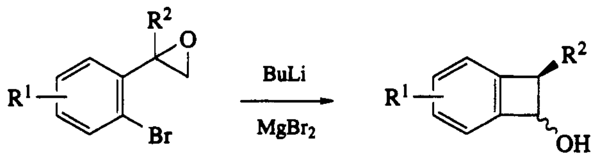

**(177)** **(178)**

A final group of $sp^2$-carbanions which have been found to react well with at least monosubstituted epoxides are the vinylalanes formed either by direct hydroalumination[195] or by zirconium-catalyzed carboalumination[196] of a terminal alkyne. Both species are insufficiently reactive to couple with epoxides and must first be converted into their corresponding 'ate' complexes, usually by treatment with *n*-butyllithium (Scheme 30).

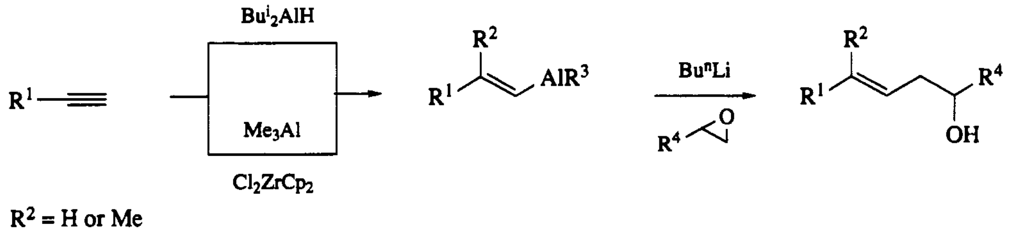

**Scheme 30**

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# 1.7
# Alkylations of Alkynyl Carbanions

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## 1.7.1 INTRODUCTION

The alkylation of *sp*-carbon can, in principle, involve the alkyne (acetylene) either as the nucleophile or the electrophile. In practice by far the most important process involves the alkyne as nucleophile since the acidity of the alkyne proton ($pK_a \approx 25$) allows the ready formation of alkynide ions. These are excellent nucleophiles and they readily undergo acylation and alkylation with appropriate electrophiles. The recent introduction of palladium-catalyzed reactions, usually involving copper(I) salts but also other cations, has greatly increased the use made of arylation and vinylation reactions.[1] In this chapter only the alkylation of the alkynide ion will be discussed; acylation, vinylation and arylation reactions are discussed elsewhere. The alkylation of alkynide anions is a reaction of considerable synthetic use and has been extensively reviewed.[2]

## 1.7.2 METALLATIONS OF ALKYNES

Monometallation of acetylene itself is possible under special conditions, and solutions of $LiC{\equiv}CH$ and $NaC{\equiv}CH$ in liquid ammonia, for example, can be prepared by simply adding pieces of metal to boiling ammonia while introducing acetylene. When acetylene is introduced into a solution of BuLi in ether (or THF) at 0 °C a fine suspension of $LiC{\equiv}CLi$ is formed immediately. Ammonia (or other amines) stabilizes the monolithium species. Thus acetylene with BuLi–TMEDA at low temperatures gives a clear solution of $LiC{\equiv}CH$. The preparation of $BrMgC{\equiv}CH$ is not easy, but can be achieved by adding a solution of EtMgBr to a solution of acetylene in THF kept below 30 °C. Solutions of $BrMgC{\equiv}CMgBr$ and $LiC{\equiv}CLi$ are produced by simply introducing acetylene into a solution of EtMgBr in THF (>40 °C) and BuLi in $Et_2O$ (>0 °C) respectively.

The low acidity of 1-alkynes means that strong bases must be used to form the alkynide ions and that water is not a suitable solvent; aqueous solutions have a very low concentration of alkynide ions.[2] Some transition metal alkynides can be prepared by precipitation from aqueous solution because their solubilities are very low.[2] Suitable solvents for the preparation of alkynide ions must be less acidic than the alkyne, and preferably allow the alkyne and the alkynide ion to remain in solution. Liquid ammonia, tetrahydrofuran, ether and hydrocarbons have all been used, particularly the first, the alkynide anion being readily formed by metal amides. Alkynides of many types have been prepared from various metals. Besides Groups I and III, copper(I), silver, gold(I), zinc, mercury and, more recently, aluminum alkynides have been synthesized. The alkynides of Groups I and II have been principally used as nucleophiles in alkylation reactions, but there are now many examples of other metal alkynides in this role. Palladium-catalyzed reactions, as remarked above, have become increasingly important for the reactions of alkynides of metals other than Groups I and II, but these have not usually involved alkylation.

## 1.7.3 ALKYLATIONS OF ALKYNIDE IONS

### 1.7.3.1 Alkylations with Alkyl Halides and Sulfates

The alkynide ion can undergo alkylation with a variety of alkylating reagents, such as haloalkanes and alkyl sulfates, with the formation of a carbon–carbon bond. The alkynide ion is also strongly basic so that elimination reactions may accompany or subvert the substitution reaction. Group I metal alkynides in liquid ammonia give mainly substitution products with primary haloalkanes but secondary and tertiary haloalkanes give mainly elimination products, as do 2-substituted primary haloalkanes (equation 1).

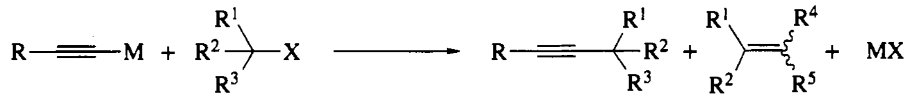

(1)

Lithium alkynides in tetrahydrofuran or dioxane often give substitution products with secondary haloalkanes, while alkynide Grignard reagents do not usually react with haloalkanes except in the presence of other metals such as cobalt and copper. Substitution of iodine or bromine for chlorine in the haloalkane often leads to an increased yield of the alkylation product and alkanesulfonates may give greater yields than haloalkanes. Scheme 1 illustrates examples of alkylation of haloalkanes and alkyl sulfates with alkynides of Group I metals.

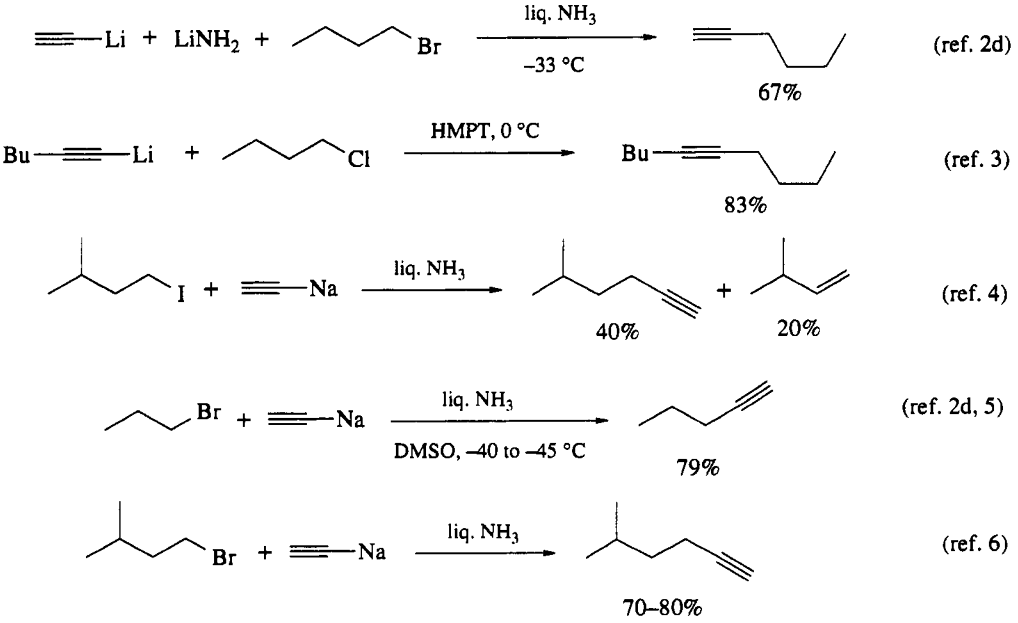

**Scheme 1**

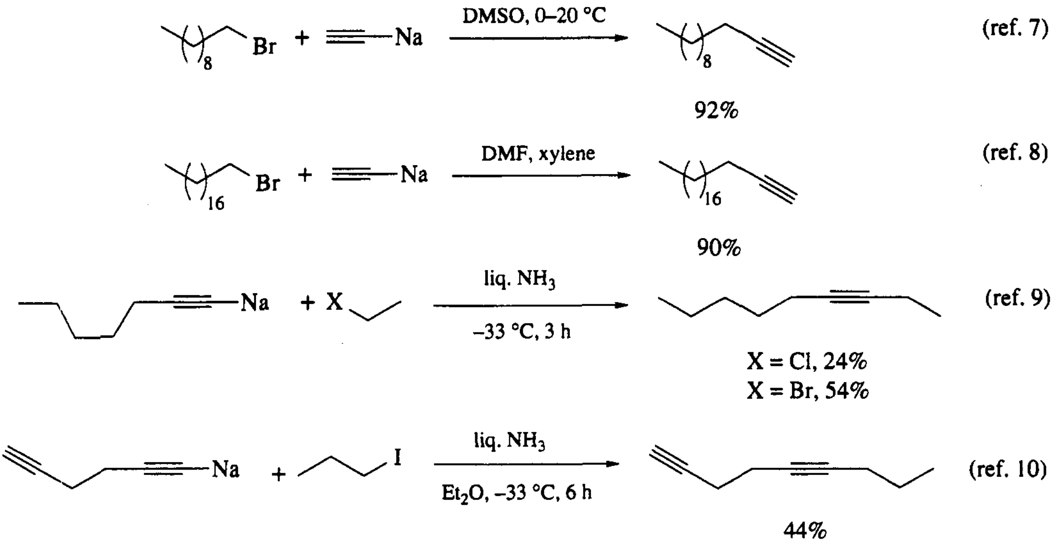
Br
Na
DMSO, 0–20 °C
8
92%
(ref. 7)
Br
Na
DMF, xylene
16
90%
(ref. 8)
Na
X
liq. NH3
–33 °C, 3 h
X = Cl, 24%
X = Br, 54%
(ref. 9)
Na
I
liq. NH3
Et2O, –33 °C, 6 h
44%
(ref. 10)

**Scheme 1** ***(continued)***

Alkylations of Grignard reagents usually require the presence of copper or other transition metal salts. Scheme 2 illustrates typical reactions involving Group II metals. Reaction between 1-bromo-2-octyne and the Grignard prepared from propargyl alcohol leads to undeca-2,5-diyn-1-ol in good yield (Scheme 3).[15] Similarly, treatment of 1-iodo-2-octyne with 3-butyn-1-ol in the presence of copper(I) iodide and DBU gave dodeca-3,5-diyn-1-ol in 70% yield (Scheme 3).[16]

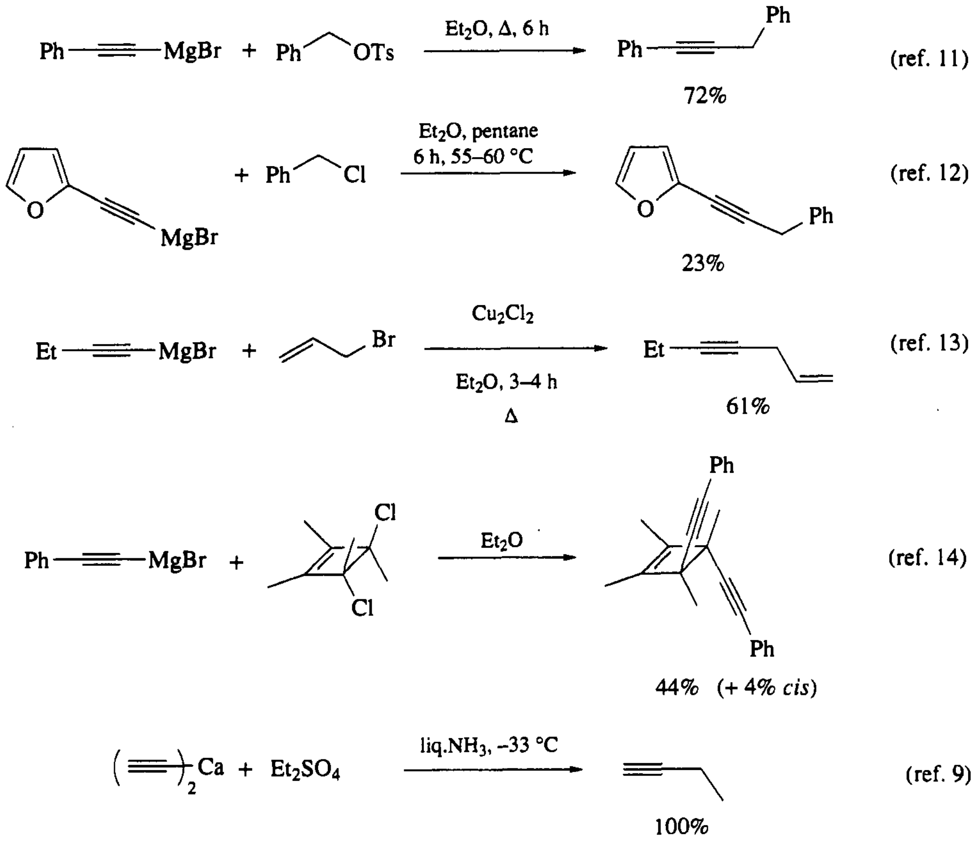
Ph
MgBr
Ph
OTs
Et2O, Δ, 6 h
Ph
Ph
72%
(ref. 11)
O
MgBr
Ph
Cl
Et2O, pentane
6 h, 55–60 °C
O
Ph
23%
(ref. 12)
Et
MgBr
Br
Cu2Cl2
Et2O, 3–4 h
Δ
Et
61%
(ref. 13)
Ph
MgBr
Cl
Cl
Et2O
Ph
Ph
44% (+ 4% cis)
(ref. 14)
Ca
2
Et2SO4
liq.NH3, –33 °C
100%
(ref. 9)

**Scheme 2**

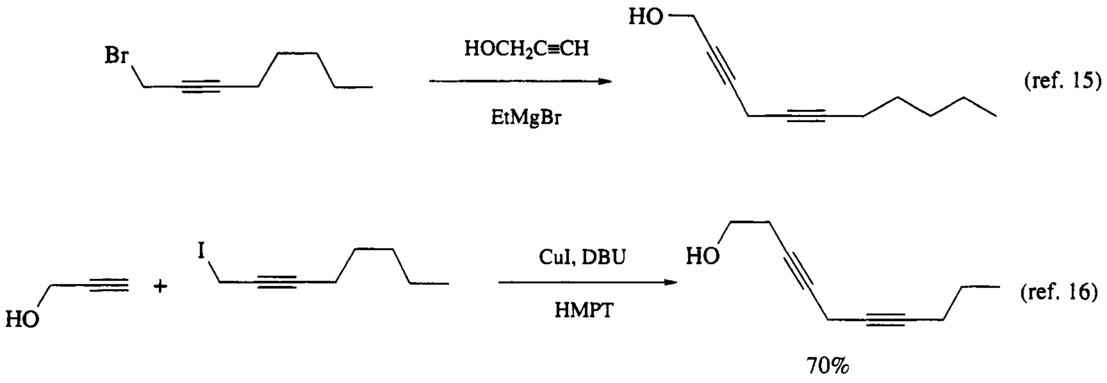

**Scheme 3**

Lithium alkynylcuprates react with haloallenes to give similar 'skipped' diacetylenes (see below). The related 'skipped' enynes can be prepared by treatment of (pentadienyl)iron(tricarbonyl) halide complexes with dilithium trialkynylcuprates, the compounds being isolated as the iron(tricarbonyl)(diene) complexes (Scheme 4).[17] Further examples of alkylation reactions of copper alkynides are illustrated in Scheme 5. Reaction between a lithium cyanoalkynecuprate and an iodoallene leads to a 'skipped' diacetylene. This useful reaction has been used by Corey in his synthesis of hybridalactone (Scheme 6).[20]

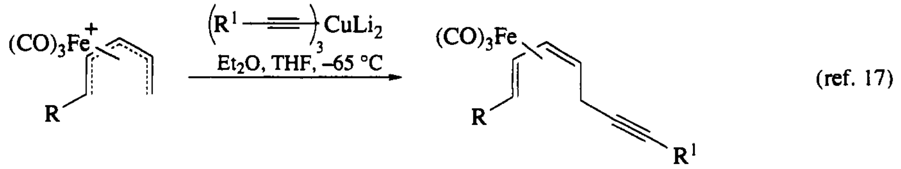

**Scheme 4**

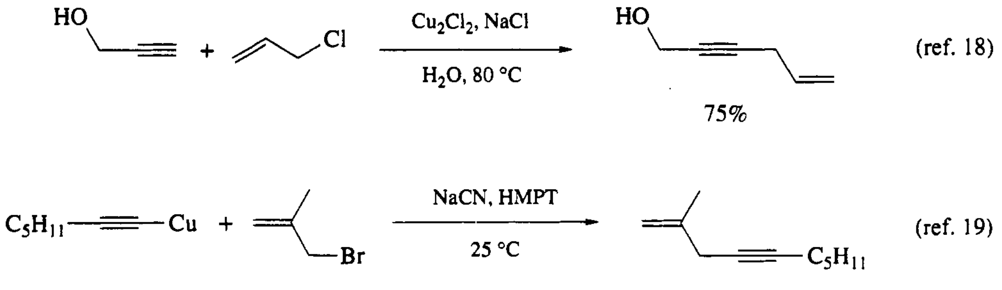

**Scheme 5**

Both boron and aluminum alkynides undergo alkylation. Thus, treatment of trialkylboron with lithium acetylide leads to a lithium trialkylethynylboride which, on treatment with iodine[21] or methanesulfonyl chloride,[22] gives the alkyl-substituted acetylene (Scheme 7). The lithium tris(alkylethynyl)boride intermediate can be trapped with an alkylating agent leading to the disubstituted acetylene or the adduct can be oxidized with basic hydrogen peroxide to give the corresponding ketone (Scheme 8).[23]

Treatment of lithium alkynides with aluminum trichloride leads to tri(ethynyl)aluminum intermediates, which on treatment with haloalkanes give the corresponding disubstituted acetylenes.[24] The reaction is successful with tertiary haloalkanes and a variety of alkynes have been prepared (Scheme 9). An interesting variation of this method has been reported by Trost and Ghadri who reacted a diethylethynylaluminum with an allyl sulfone in the the presence of the Lewis acid aluminum trichloride.[25] When the allyl sulfone was part of a six-membered ring, then the alkyne was introduced exclusively in a pseudo axial orientation (Scheme 10).

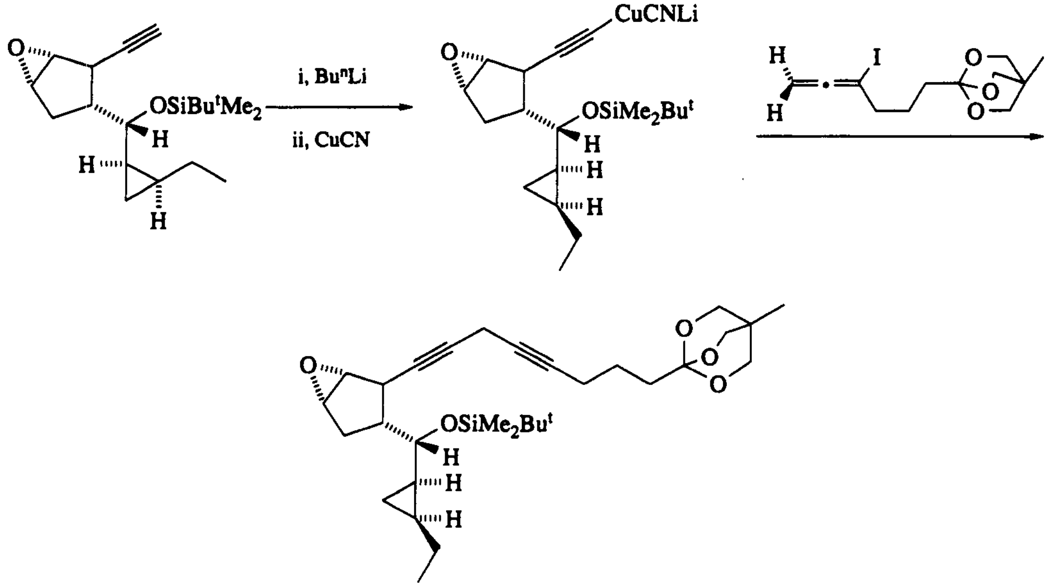
OSiBu$^t$Me$_2$
i, Bu$^n$Li
ii, CuCN
CuCNLi
OSiMe$_2$Bu$^t$

**Scheme 6**

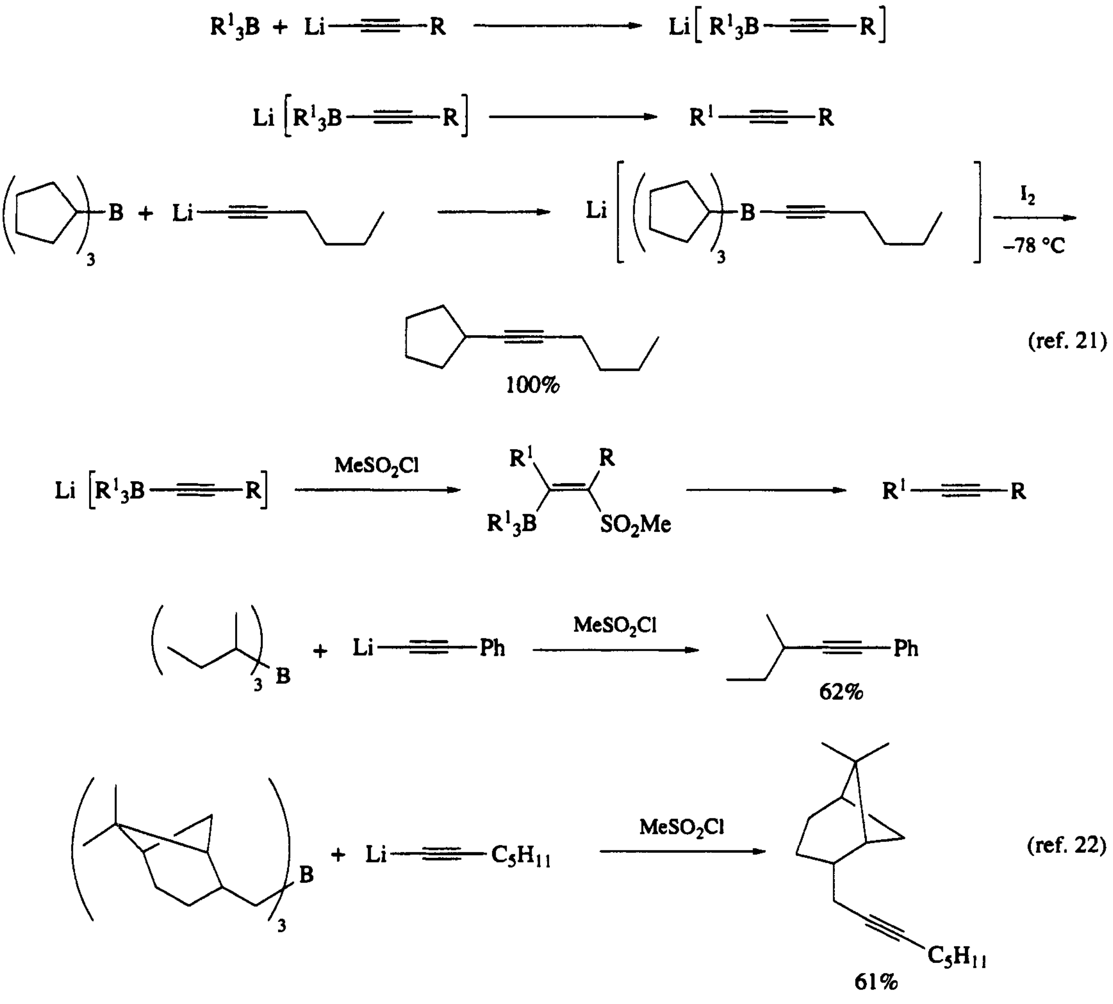
$R^1_3B$ + Li—≡—R → Li[$R^1_3B$—≡—R]
Li[$R^1_3B$—≡—R] → $R^1$—≡—R
$I_2$
–78 °C
100%
(ref. 21)
MeSO$_2$Cl
$R^1_3B$
SO$_2$Me
Li—≡—Ph
62%
Li—≡—C$_5$H$_{11}$
61%
(ref. 22)

**Scheme 7**

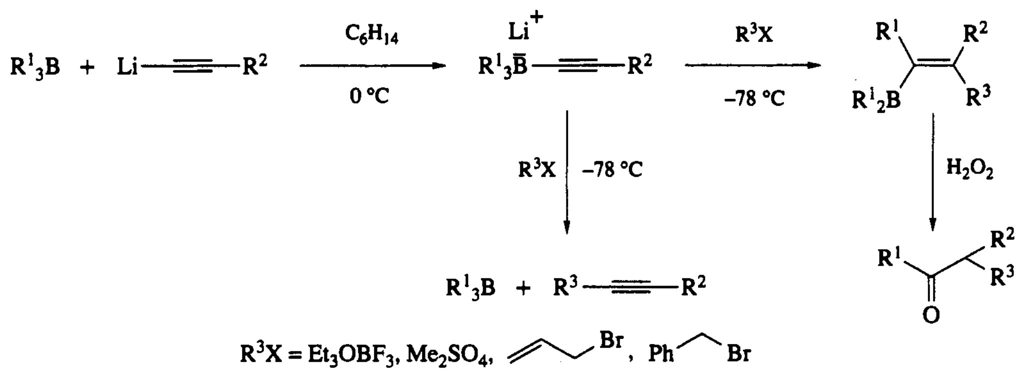
$R^1_3B$ + Li—≡—$R^2$
$C_6H_{14}$
0 °C
$Li^+$
$R^1_3\bar{B}$—≡—$R^2$
$R^3X$
−78 °C
$R^1$
$R^2$
$R^1_2B$
$R^3$
$R^3X$
−78 °C
$H_2O_2$
$R^1_3B$ + $R^3$—≡—$R^2$
$R^1$
$R^2$
$R^3$
O
$R^3X$ = $Et_3OBF_3$, $Me_2SO_4$,
Br
, Ph
Br

**Scheme 8**

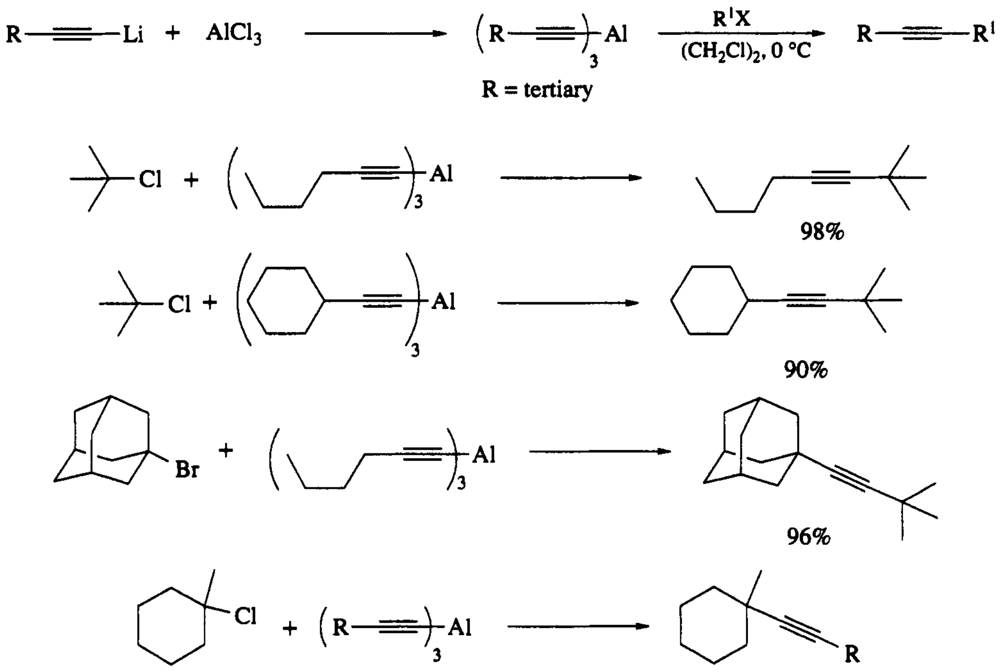
R—≡—Li + $AlCl_3$
(R—≡—)$_3$Al
R = tertiary
$R^1X$
$(CH_2Cl)_2$, 0 °C
R—≡—$R^1$
Cl
Al
3
98%
Cl
Al
3
90%
Br
Al
3
96%
Cl
(R—≡—)$_3$Al
R

**Scheme 9**

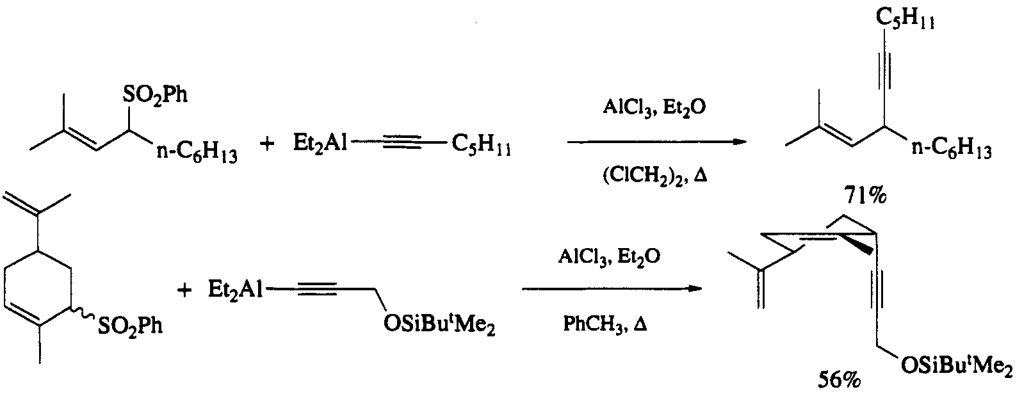
$SO_2Ph$
n-$C_6H_{13}$
+ $Et_2Al$—≡—$C_5H_{11}$
$AlCl_3$, $Et_2O$
$(ClCH_2)_2$, Δ
$C_5H_{11}$
n-$C_6H_{13}$
71%
$SO_2Ph$
+ $Et_2Al$—≡—
$OSiBu^tMe_2$
$AlCl_3$, $Et_2O$
$PhCH_3$, Δ
$OSiBu^tMe_2$
56%

**Scheme 10**

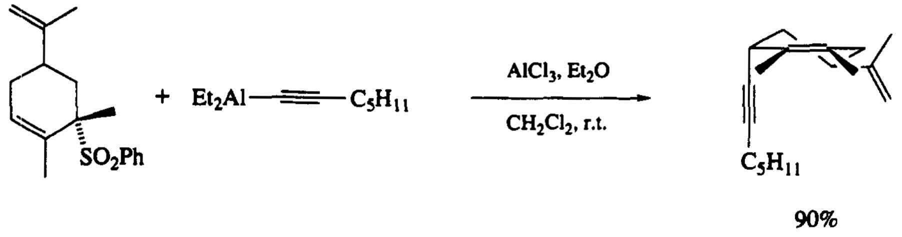

$Et_2Al$—≡—$C_5H_{11}$
SO₂Ph
AlCl₃, Et₂O
CH₂Cl₂, r.t.
C₅H₁₁
90%

**Scheme 10** ***(continued)***

Examples of nucleophilic substitution with tin alkynides are also known. Thus, treatment of a masked α-bromo amino acid with tin alkynides in the presence of zinc chloride has been shown to lead to the corresponding ethynyl derivative (Scheme 11).[26]

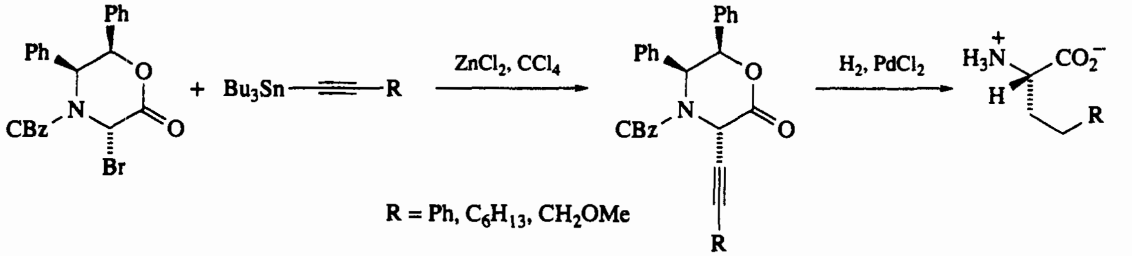

Ph
Ph
O
CBz
N
O
Br
Bu₃Sn—≡—R
ZnCl₂, CCl₄
R = Ph, C₆H₁₃, CH₂OMe
R
H₂, PdCl₂
H₃N⁺
CO₂⁻
H
R

**Scheme 11**

### 1.7.3.2 Alkylations with Epoxides

The reactions between alkynide ions and oxiranes (epoxides) are of considerable synthetic value, and generally provide two functional groups with known relative stereochemistry. Alkynide anions associated with many of the metal cations discussed above have been used, but the lithium alkynides have been by far the most popular, mainly because of their ease of synthesis from alkyllithiums. Examples are shown in Scheme 12; the last example in the scheme may involve rearrangement of the oxirane ring. This is certainly the case in the reactions of a number of hydroxymethyloxirane derivatives with lithium alkynides described by Yamaguchi and Hirao.[33] The reaction gives mixtures of rearranged and unrearranged products with the rearranged material predominating in a number of cases (Scheme 13).

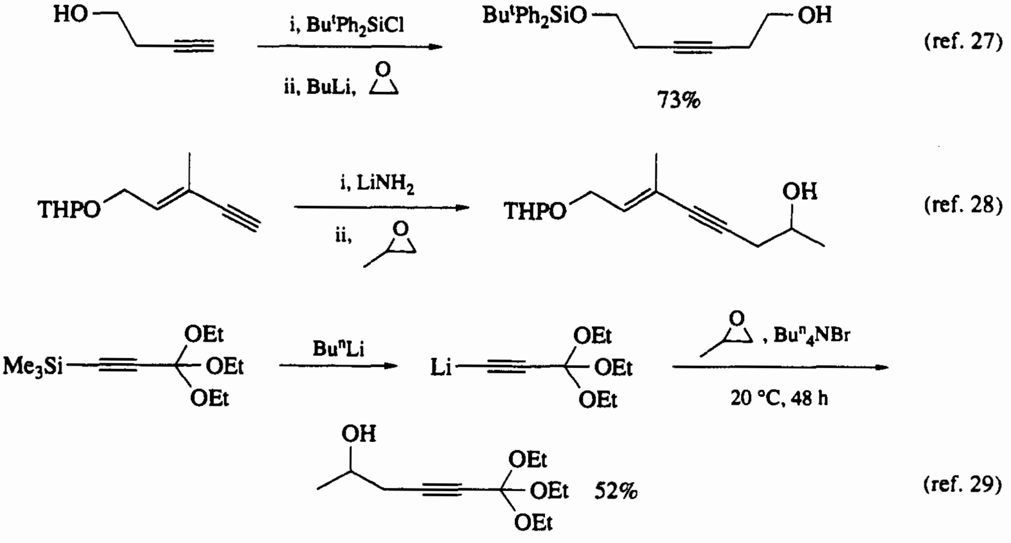

HO
i, Bu^tPh₂SiCl
ii, BuLi,
O
Bu^tPh₂SiO
OH
73%
(ref. 27)
THPO
i, LiNH₂
ii,
O
THPO
OH
(ref. 28)
Me₃Si
OEt
OEt
OEt
Bu^nLi
Li
OEt
OEt
OEt
O
, Bu^n₄NBr
20 °C, 48 h
OH
OEt
OEt
OEt
52%
(ref. 29)

**Scheme 12**

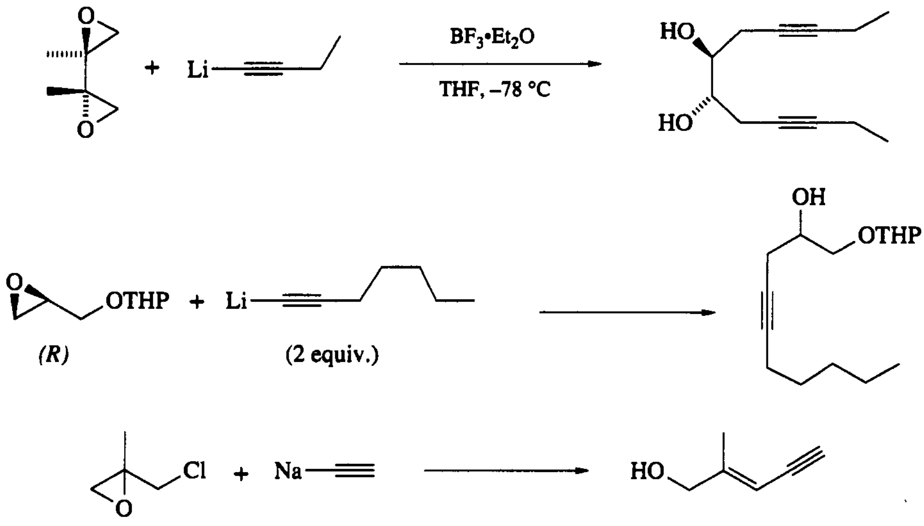
BF3•Et2O
THF, -78 °C
(R)
(2 equiv.)

(ref. 30)

(ref. 31)

(ref. 32)

**Scheme 12 *(continued)***

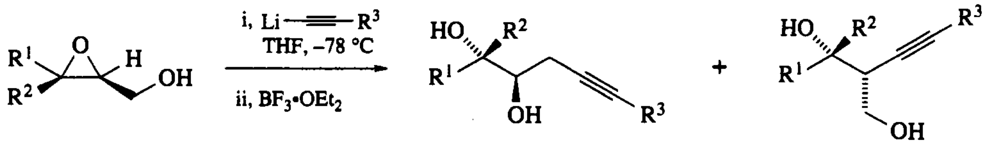
i, Li—≡—R3
THF, -78 °C
ii, BF3•OEt2

(1) (2) (3)

| $R^1$ | $R^2$ | $R^3$ | *Ratio (2):(3)* | *Yield (%)* |
|---|---|---|---|---|
| $(CH_2)_2CH=CMe_2$ | Me | Ph | 55:45 | 94 |
| $(CH_2)_2CH=CMe_2$ | Me | n-$C_5H_{11}$ | 80:20 | 87 |
| $Pr^n$ | H | Ph | 72:28 | 77 |
| $Pr^n$ | H | n-$C_5H_{11}$ | 81:19 | 81 |
| Me | $(CH_2)_2CH=CMe_2$ | n-$C_5H_{11}$ | 50:50 | 100 |
| H | $Pr^n$ | Ph | 42:58 | 81 |

**Scheme 13**

Carlson and Olger have reacted the dilithium salt of propargylic acid with oxiranes and shown that the resulting δ-hydroxycarboxylic acids could be cyclized with solvation to 5,6-dihydro-2-pyrones (Scheme 14).[34] The method was subsequently used in a neat synthesis of pestalotin (R = $Bu^nCHMe$).

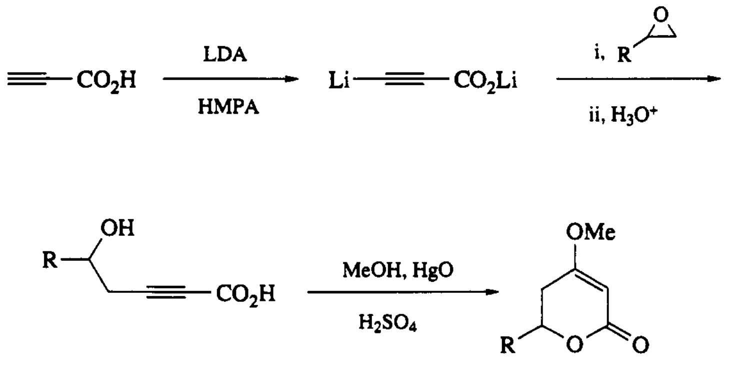
LDA
HMPA
ii, H3O+
MeOH, HgO
H2SO4

**Scheme 14**

Yamaguchi and Hirao found that alkyneboron difluorides, which are prepared from the alkynide ion and boron trifluoride etherate, react with oxiranes to give the 2-alkynols (Scheme 15).[35] The same research group also found that ring opening of oxetane could be accomplished,[36] but in this case boron trifluoride had to be added as a Lewis acid (Scheme 15).

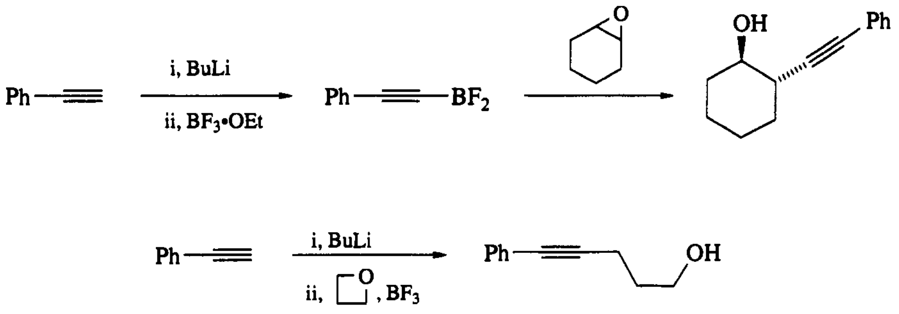

Scheme 15

In some instances only a low yield of product has been obtained during nucelophilic ring opening of oxiranes with lithium alkynides and it has been shown that in a number of these cases the yields can be greatly improved by the addition of a catalytic amount of trimethylgallium.[37] This is illustrated in Scheme 16, where the yields shown in brackets are those without the addition of the trimethylgallium. The improvement in yields by the addition of trimethylgallium may not be surprising in view of the fact that aluminum alkynides have been particularly successful as nucelophiles in additions to oxiranes. Fried and Sih, for example, in the course of a prostaglandin synthesis, prepared a methoxymethylaluminum alkynide which opened an oxirane in a regiospecific manner (Scheme 17).[38] The replacement of methyl for methoxy greatly reduced the regiospecificity.

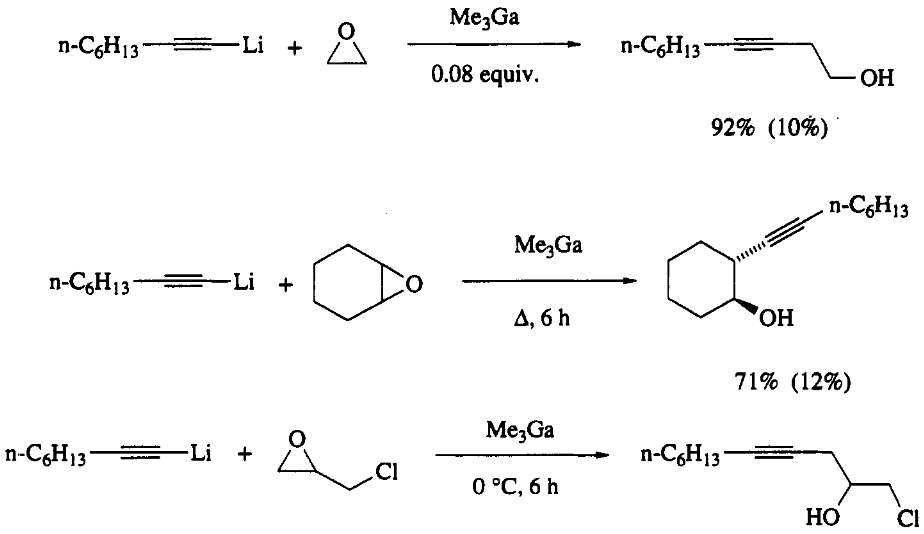

Scheme 16

3,4-Epoxycyclopentene (4) undergoes nucelophilic addition with the ethylaluminium alkynide (5) in a mixture of THF, toluene and hexane to give predominantly the isomer (6) in which the alkyne has been introduced at carbon 3, adjacent to the double bond (Scheme 18).[39] When the reaction was run in toluene at low temperature, the unexpected 4-hydroxy-4-(1-hexynyl)cyclopentene (7) was obtained, which the authors suggest may arise from an 'aluminum'-catalyzed rearrangement of the epoxide to cyclopent-3-enone, which then undergoes nucleophilic addition.

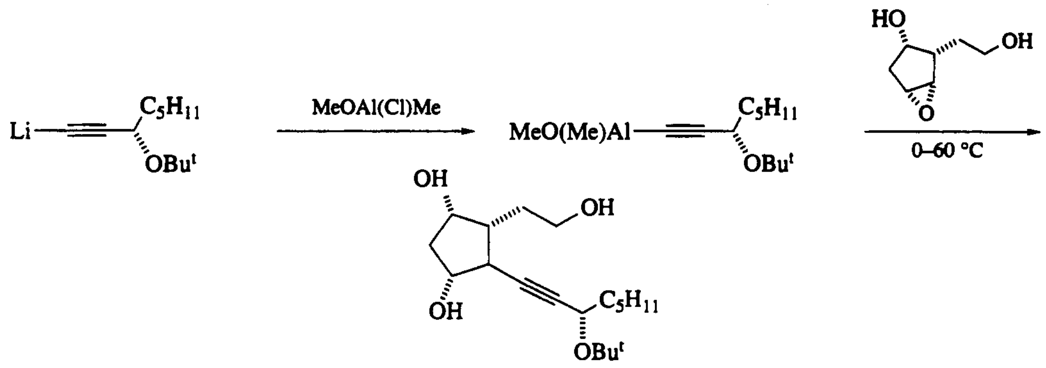
Li
C5H11
OBut
MeOAl(Cl)Me
MeO(Me)Al
C5H11
OBut
HO
OH
O
0–60 °C
OH
OH
OH
C5H11
OBut

**Scheme 17**

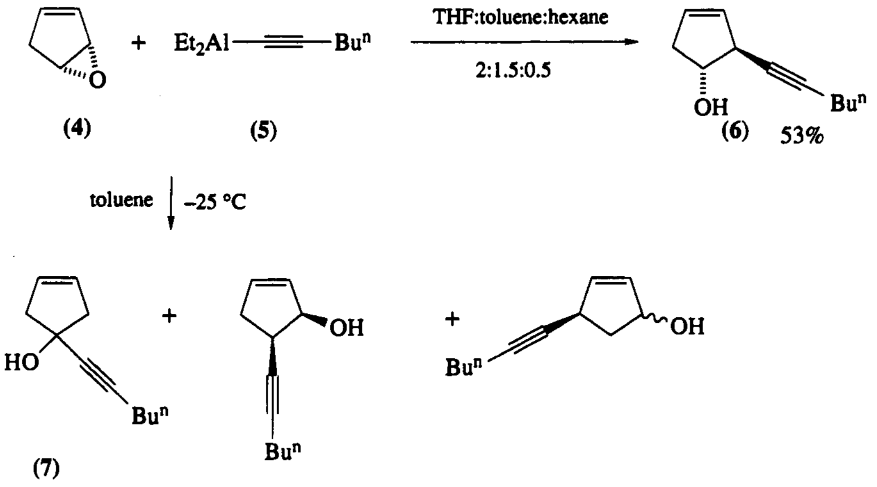
O
+
Et2Al
Bun
THF:toluene:hexane
2:1.5:0.5
OH
Bun
(4)
(5)
(6) 53%
toluene
-25 °C
HO
Bun
+
OH
Bun
+
Bun
OH
(7)

**Scheme 18**

Heathcock and coworkers[40] in the course of their synthesis of vernolepin reacted the oxirane (**8**) with the diethylaluminum alkynide (**9**), when regiospecific ring opening of the oxirane occurred, leading to (**10**; Scheme 19). Interestingly, the stereoisomer (**11**) did not react under the same conditions.

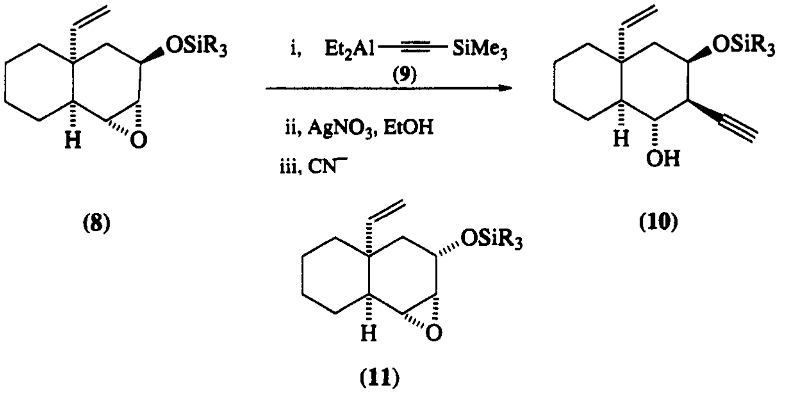
OSiR3
H
O
i, Et2Al—≡—SiMe3
(9)
ii, AgNO3, EtOH
iii, CN−
OSiR3
H
OH
(8)
(10)
OSiR3
H
O
(11)

**Scheme 19**

### 1.7.3.3 Other Alkylation Reactions

Bhanu and Scheinmann[41] have shown that the dilithium salt of propyne alkylates firstly on the methyl group and then on the alkyne. The process occurs sequentially and two different electrophiles can be used. The reaction gave superior yields when the second electrophile underwent nucleophilic addition rather than substitution (Scheme 20).

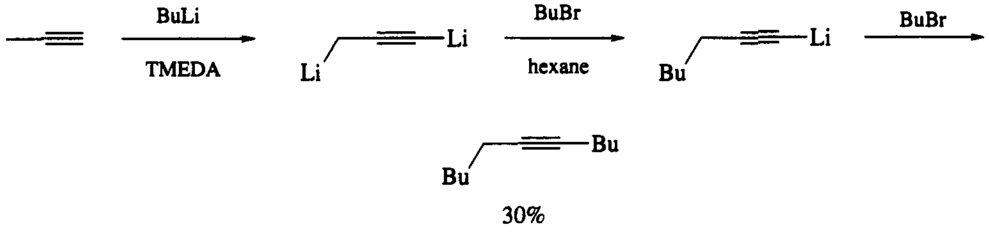
BuLi
TMEDA
Li
Li
BuBr
hexane
Bu
Li
BuBr
Bu
Bu
30%

Scheme 20

Reactions between ω-hydroxyalkynes and ω-bromo- or ω-iodo-carboxylic acids in the presence of two equivalents of butyllithium give rise to ω-hydroxyynoic acids (Scheme 21).[42] Likewise, dilithiated propargyl alcohol has been found to react with α,ω-dibromoalkanes in liquid ammonia, leading to the corresponding diynediols (Scheme 22).[43]

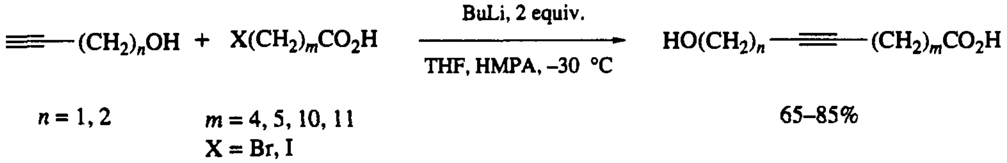
(CH2)nOH + X(CH2)mCO2H
BuLi, 2 equiv.
THF, HMPA, -30 °C
HO(CH2)n
(CH2)mCO2H
n = 1, 2
m = 4, 5, 10, 11
X = Br, I
65–85%

Scheme 21

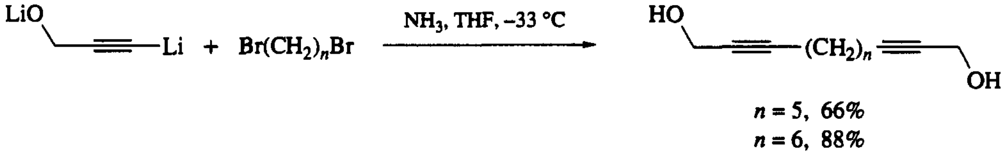
LiO
Li + Br(CH2)nBr
NH3, THF, -33 °C
HO
(CH2)n
OH
n = 5, 66%
n = 6, 88%

Scheme 22

A variety of other leaving groups have been used in alkylation reactions of alkynides. Thus, Chiu and Peterson[44] have treated lithium alkynides with the methyl triflate (**12**) to give the trimethylsilylmethylalkynes (Scheme 23). The reaction also worked with the corresponding chloride. Johnson and coworkers[45] had previously used the fluorosulfonate (**13**) in a similar reaction. In addition, Carling and Holmes[46] have used triflate as a leaving group in an alkylation step in their synthesis of gloeosporone, a germination self-inhibitor (Scheme 24).

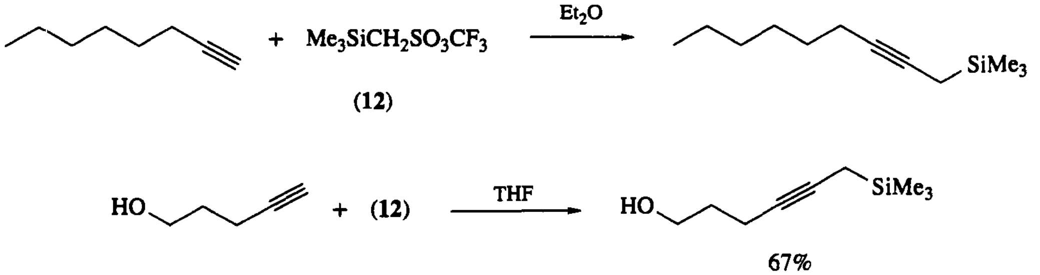
+ Me3SiCH2SO3CF3
(12)
Et2O
SiMe3
HO
+ (12)
THF
HO
SiMe3
67%

Scheme 23

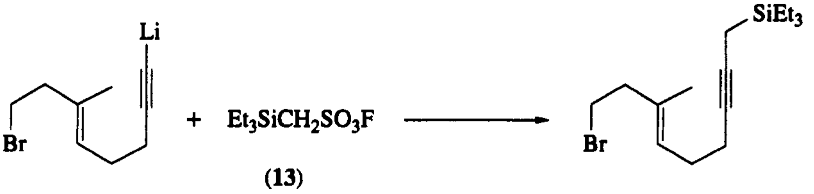
Li
Br
+ Et3SiCH2SO3F
(13)
SiEt3
Br

(2)

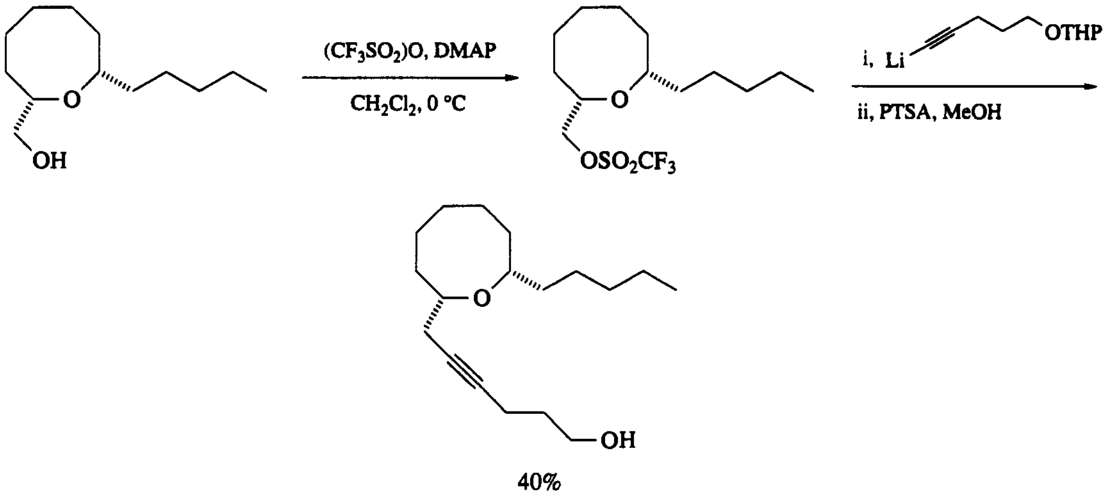
O
OH
(CF3SO2)O, DMAP
CH2Cl2, 0 °C
O
OSO2CF3
i, Li
OTHP
ii, PTSA, MeOH
O
OH
40%

**Scheme 24**

Nitrogen derivatives have been used as leaving groups in reactions with alkynides. Thus, Katritzky and coworkers,[47] for example, have reacted *N*-substituted benzotriazolines (**14**) with lithium alkynides, which, after a basic work up, give the alkylated alkyne. This reaction was used to prepare α-amino-alkynes (Scheme 25). Reactions of α-arylamino ethers with lithium alkynides also gave α-amino-alkynes.[48] Mechanistically, this reaction may be considered to be an acylation since it probably proceeds through the corresponding methaldimine (Scheme 26).

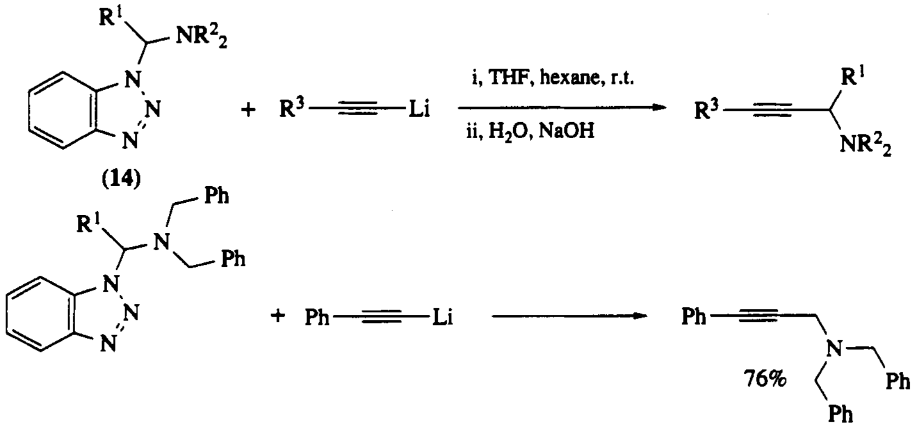
R1
NR22
N
N
N
(14)
+ R3—Li
i, THF, hexane, r.t.
ii, H2O, NaOH
R3
R1
NR22
R1
N
Ph
Ph
N
N
N
+ Ph—Li
Ph
N
Ph
Ph
76%

**Scheme 25**

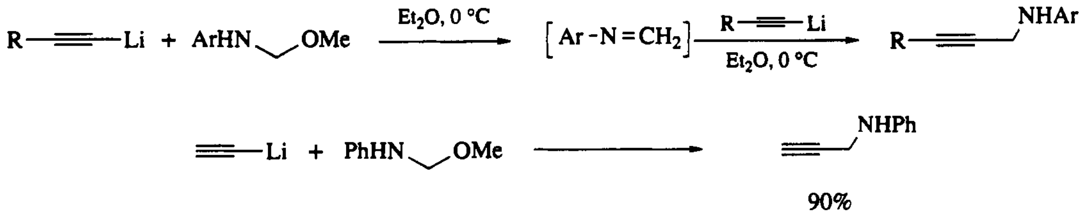
R—Li + ArHN OMe
Et2O, 0 °C
[Ar-N=CH2]
R—Li
Et2O, 0 °C
R
NHAr
—Li + PhHN OMe
NHPh
90%

**Scheme 26**

2-Hydroxybenzothiazole has also been used as a leaving group in allylic displacement reactions with copper alkynides.[49] Furthermore, the copper alkynides can be used in wet solvents, THF normally being used (Scheme 27).

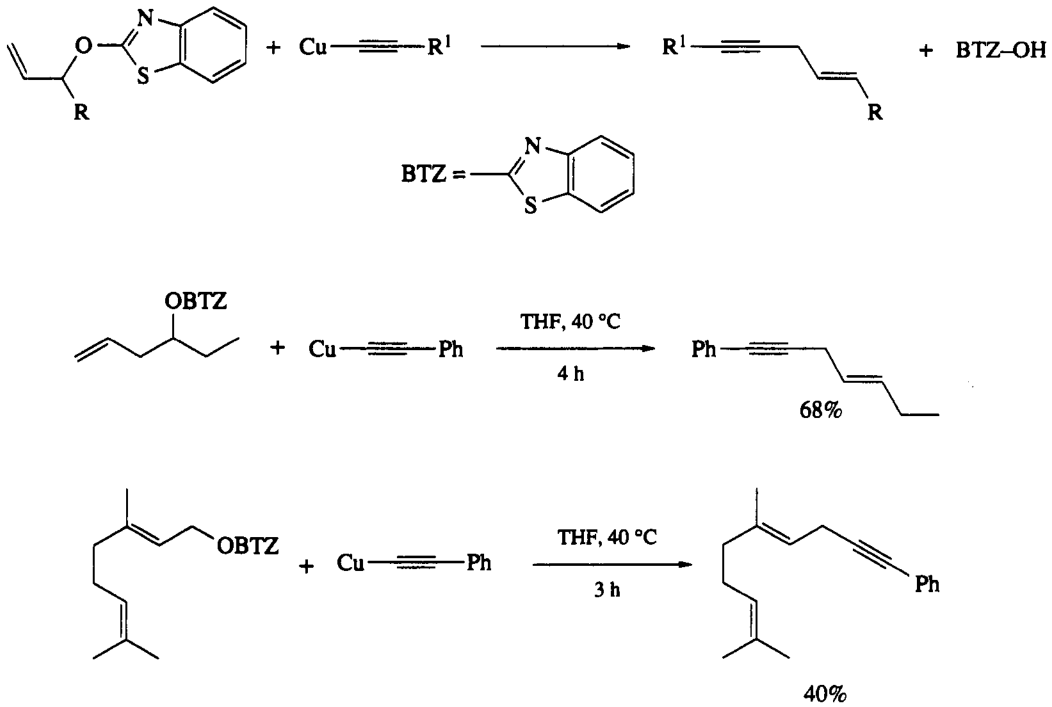
+ Cu—≡—R¹
R¹
+ BTZ–OH
R
BTZ =
N
S
OBTZ
+ Cu—≡—Ph
THF, 40 °C
4 h
Ph
68%
OBTZ
THF, 40 °C
3 h
Ph
40%

**Scheme 27**

Trost and Martin[50] have used the dimethylsulfoxonium ion to provide a leaving group. Thus, a *cis* addition of DMTSF to alkenes first led to adducts of the type (**15**), which then reacted with lithium alkynides in the presence of diethylaluminum chloride to give the *trans* adduct (Scheme 28). The reaction is presumed to involve the episulfonium ion, which then ensures the observed stereospecificity. The reaction is also regiospecific, the anti-Markovnikov addition being illustrated by the second example in Scheme 28. The adducts can be converted to alkanes with Raney nickel and to alkenes by sulfoxide formation and elimination.

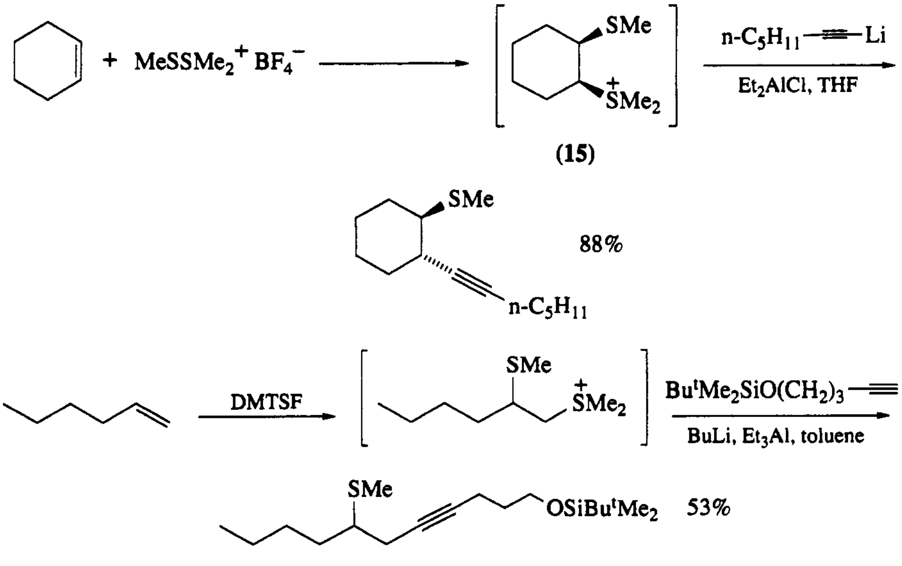
+ MeSSMe₂⁺ BF₄⁻
SMe
+SMe₂
(15)
n-C₅H₁₁—≡—Li
Et₂AlCl, THF
SMe
n-C₅H₁₁
88%
DMTSF
SMe
+SMe₂
BuᵗMe₂SiO(CH₂)₃—≡
BuLi, Et₃Al, toluene
SMe
OSiBuᵗMe₂
53%

**Scheme 28**

As was previously remarked, water and its associated base are, respectively, too acidic and insufficiently basic to act as solvent and base for the preparation of alkynide ions. Lissel has shown,[51] however, that with the addition of the crown ether 18-crown-6, alkylation of phenylacetylenes can occur with KOH and an iodoalkane (Scheme 29).

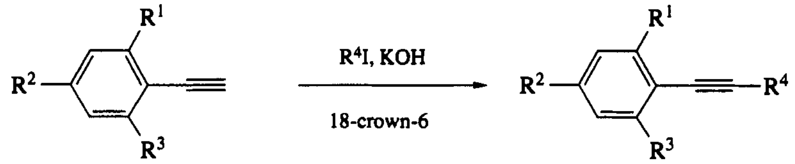

| | |
|---|---|
| $R^1 = R^2 = R^3 = H, R^4 = Me$ | 74% |
| $R^1 = R^2 = R^3 = R^4 = Me$ | 69% |
| $R^1 = R^2 = R^3 = H, R^4 = Et$ | 70% |
| $R^1 = R^2 = R^3 = H, R^4 = n\text{-}C_8H_{17}$ | 63% |

Scheme 29

1,3-Butadiyne has also been alkylated through the lithium alkynide. Thus, Holmes and Jones[52] treated bis(trimethylsilyl)buta-1,3-diyne with MeLi in the presence of lithium bromide and obtained the monolithium alkynide, which was then alkylated in HMPA (Scheme 30). If the lithium alkynide was complexed with ethylenediamine then DMSO could be used as solvent. In addition, Himbert and Feustel[53] prepared the lithium derivative of 1-*N*,*N*-dialkylbuta-1,3-diyne by treatment of 4-*N*-dialkyl-1,1,2-trichlorobut-1-en-3-yne with butyllithium. The lithium salt was not isolated but was alkylated to the 1-alkyl-4-*N*-dialkylbuta-1,3-diyne (Scheme 31).

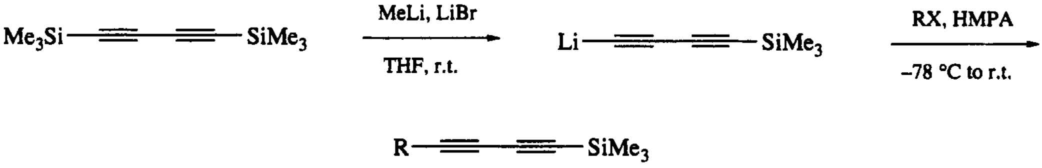

RX = EtI, 65%; BuI, 64%; EtBr, 50%; $C_6H_{11}CH_2Br$, 57%

Scheme 30

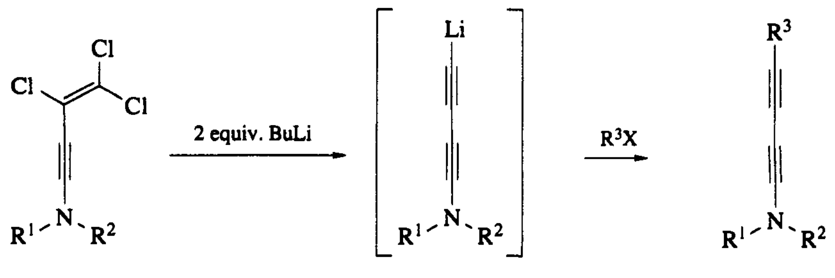

Scheme 31

## 1.7.4 ELECTROPHILIC SUBSTITUTION OF HALOALKYNES

This process is much less common than nucleophilic substitution by alkynide anions and the actual mechanisms of the reactions in which electrophilic substitution of an *sp*-carbon appears to occur probably do not involve simple substitution. Kende and coworkers,[54] for example, have reacted tertiary enolate anions with chloroalkynes and obtained the corresponding alkylated products (Scheme 32). These reactions appear to be addition–elimination reactions, and they only occur with chloroalkynes in which the other alkyne substituent is halo, aryl or a similar substituent capable of stabilizing a negative charge. Primary and secondary enolates gave rise to unidentifiable products except for the anion of dimethyl malonate, which adds twice to dichloroacetylene.

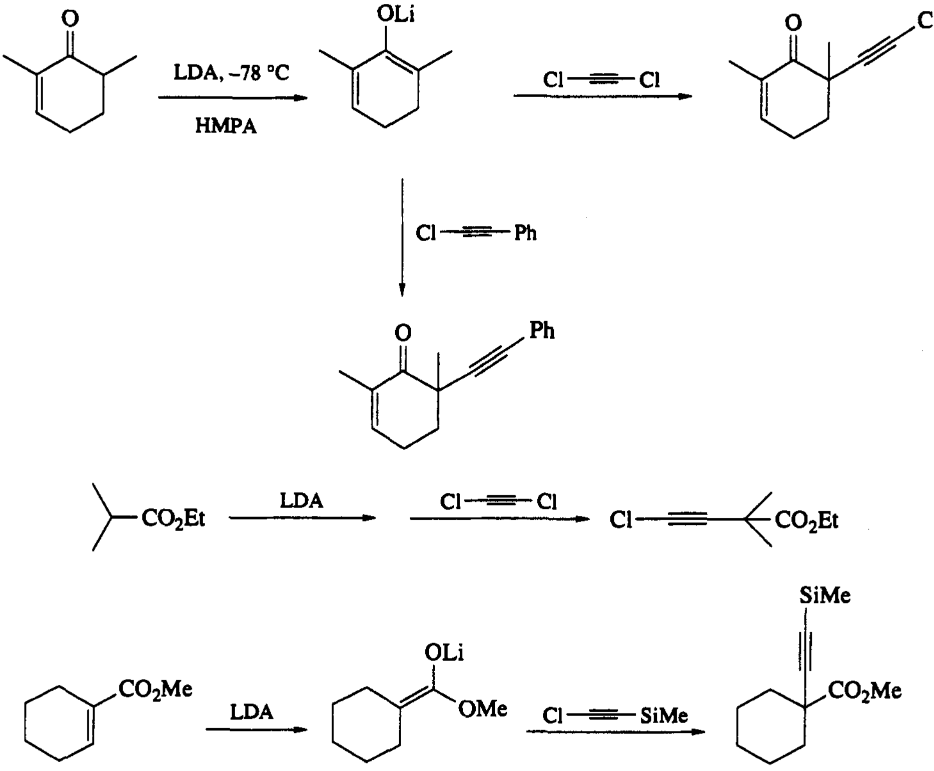
O
LDA, -78 °C
HMPA
OLi
Cl—≡—Cl
O
Cl
Cl—≡—Ph
O
Ph
CO2Et
LDA
Cl—≡—Cl
Cl
CO2Et
SiMe
CO2Me
LDA
OLi
OMe
Cl—≡—SiMe
CO2Me

**Scheme 32**

Giacomelli and Lardicci[55] have treated bromoalkynes with trialkylaluminum in the presence of bis(*N*-methylsalicylaldimine)nickel and obtained an alkyl-substituted alkyne (Scheme 33). This reaction probably involves: (i) insertion of the nickel into the alkyne–bromine bond; (ii) exchange of alkyl for bromine; and (iii) formation of the alkyne–alkyl bond. Thus, although the process appears to be an electrophilic substitution, it is actually nucleophilic in character.

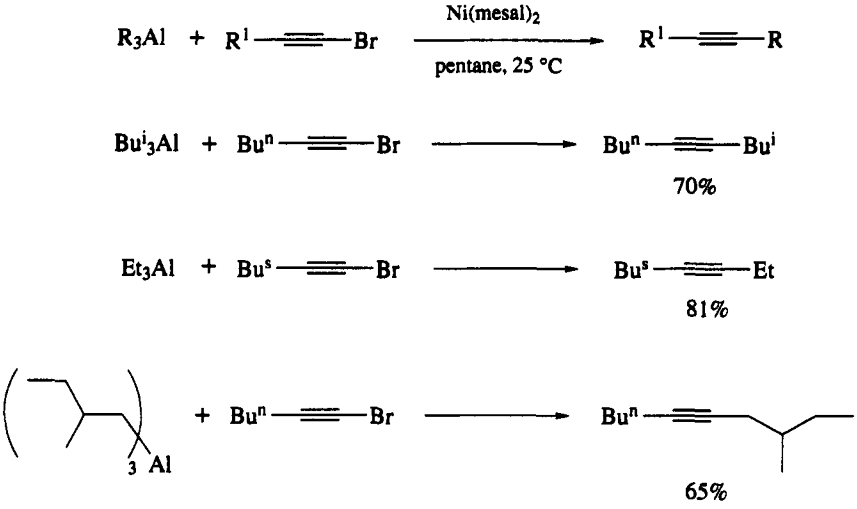
R3Al + R1—≡—Br
Ni(mesal)2
pentane, 25 °C
R1—≡—R
Bui3Al + Bun—≡—Br
Bun—≡—Bui
70%
Et3Al + Bus—≡—Br
Bus—≡—Et
81%
3 Al
+ Bun—≡—Br
Bun
65%

**Scheme 33**

Treatment of enolate anions derived from β-dicarbonyl compounds with either ethynyl(phenyl)iodonium tetrafluoroborate (**16**)[56a] or with ethynyl–lead tetraacetate[56b] provides a neat and direct synthesis of α-ethynyl-1,3-dicarbonyl compounds. The former reaction probably proceeds *via* 1,2-hydrogen migration of an alkylidenecarbene intermediate (see Scheme 34).

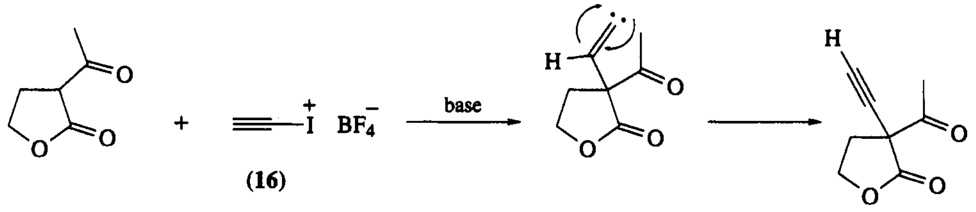

**Scheme 34**

## 1.7.5 SYNTHETIC APPLICATIONS

The ethynyl group is an extremely versatile two-carbon synthon and can be transformed to a variety of functions. The process is illustrated by a simple synthesis of the sex attractant disparlure (**17**) shown in Scheme 35.[57] Here the ethynyl group is first converted to the (*Z*)-alkene, which is then oxidized with *m*-chloroperbenzoic acid to give the oxirane.

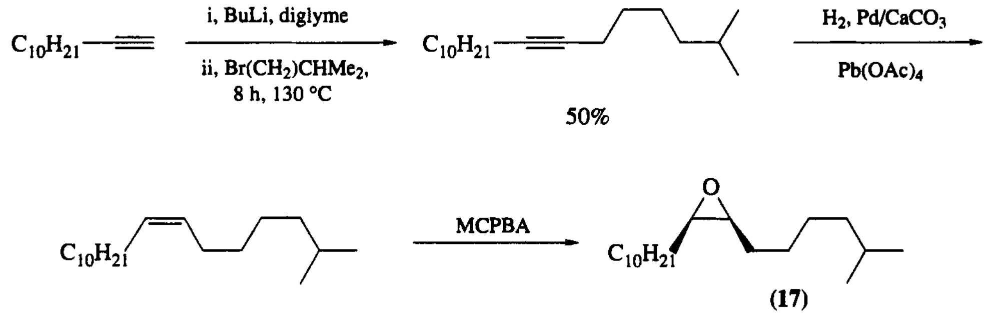

**Scheme 35**

A large variety of natural products and biological materials have been prepared with reaction sequences involving alkylation of *sp*-carbon at some stage. Representative examples of the use of this synthetic manipulation in different classes of compounds are given below, but the examples are in no sense exhaustive.

### 1.7.5.1 Macrolides

Both the Mukaiyama[58] and Bestmann[59] syntheses of the macrocyclic lactone recifeiolide (**18**), isolated from *Cephalosporium recifei*, involve *sp*-carbon alkylation steps (Scheme 36), and Shenvi and Gerlach[60] have synthesized diplodialides A (**19**) *via* a route that involved the *sp*-carbon alkylation step shown in Scheme 37.

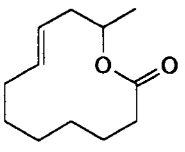

**(18)**

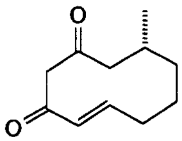

**(19)**

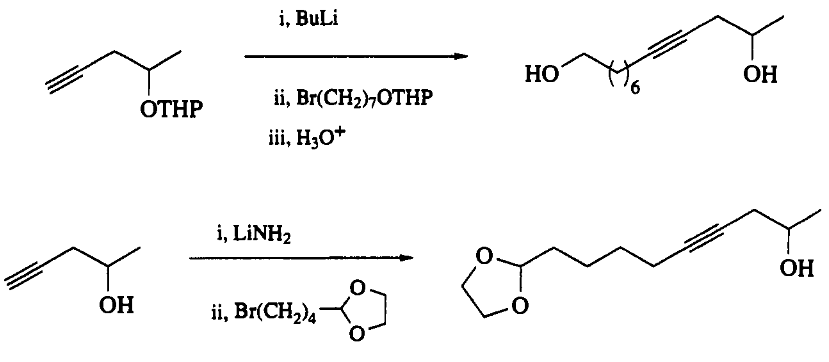
OTHP
i, BuLi
ii, Br(CH2)7OTHP
iii, H3O+
HO
6
OH
OH
i, LiNH2
ii, Br(CH2)4
O
O
O
O
OH

Scheme 36

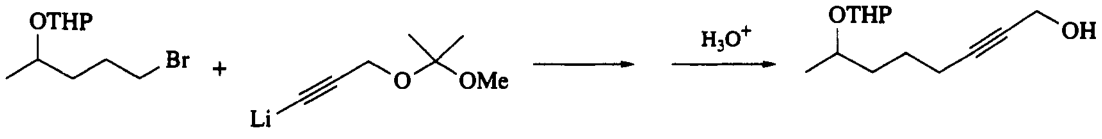
OTHP
Br
+
Li
O
OMe
H3O+
OTHP
OH

Scheme 37

Brefeldin (**20**) is a 13-membered lactone isolated from a number of sources and has a wide spectrum of biological activity. Many of the syntheses of this lactone use alkynes as intermediates. Thus, Livinghouse and Stevens[61] used an elegant ring opening of a bicyclo[3.1.0]hexane to give the desired *trans* stereochemistry (Scheme 38), whereas in the synthesis of Kitahara and coworkers,[62] a more conventional alkynide alkylation was involved (Scheme 39).

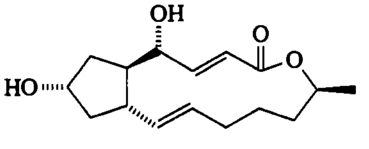

**(20)**

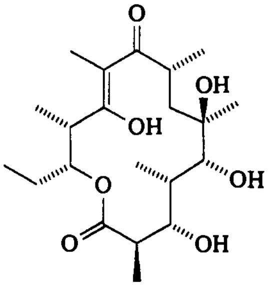
O
OH
OH
O
OH
O
OH

**(21)**

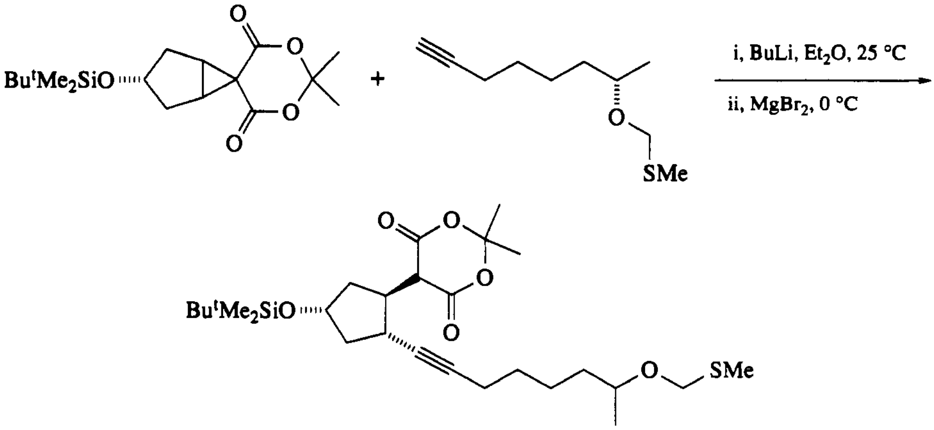
O
O
O
O
Bu$^t$Me2SiO
+
O
SMe
i, BuLi, Et2O, 25 °C
ii, MgBr2, 0 °C
O
O
O
O
Bu$^t$Me2SiO
O
SMe

Scheme 38

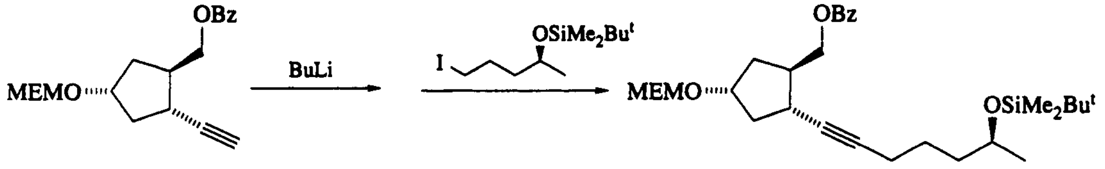
OBz
MEMO
BuLi
OSiMe$_2$Bu$^t$
I
OBz
MEMO
OSiMe$_2$Bu$^t$

**Scheme 39**

In their synthesis of erythronolide B (**21**), Corey and coworkers[63] used two alkylations of an alkynide ion in the preparation of one half of the molecule. One alkylation involved regiospecific ring opening of a resolved oxirane to provide the desired compound with the correct absolute stereochemistry, while the second used a simple methylation (Scheme 40).

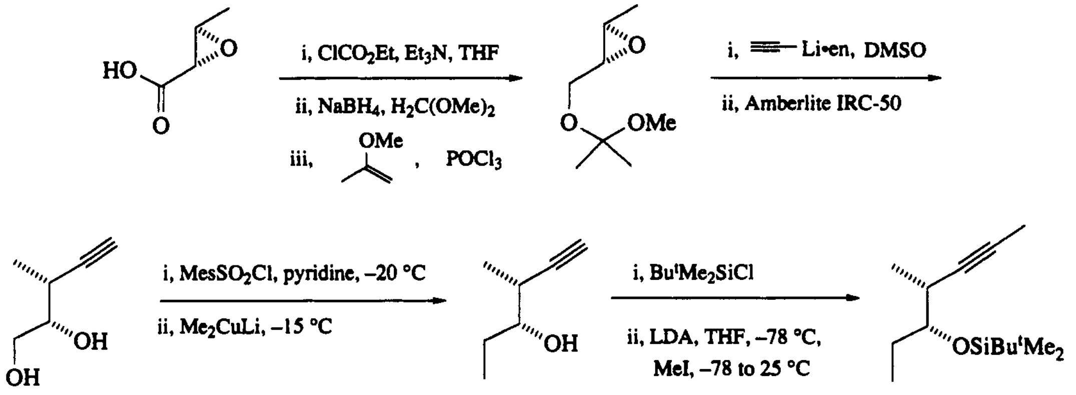
HO
O
O
i, ClCO$_2$Et, Et$_3$N, THF
ii, NaBH$_4$, H$_2$C(OMe)$_2$
iii, OMe, POCl$_3$
O
O
OMe
i, ≡—Li•en, DMSO
ii, Amberlite IRC-50
OH
OH
i, MesSO$_2$Cl, pyridine, –20 °C
ii, Me$_2$CuLi, –15 °C
OH
i, Bu$^t$Me$_2$SiCl
ii, LDA, THF, –78 °C, MeI, –78 to 25 °C
OSiBu$^t$Me$_2$

**Scheme 40**

## 1.7.5.2 Sesquiterpenes

Corey *et al.*[64] treated an allylic bromide with the THP-protected lithium propynol in their synthesis of (±)-sirenin, a sperm attractant of the water mold *Allomyces*, and the same reaction was also used in a synthesis of (±)-sesquicarene (Scheme 41). In addition, Meyers and Bienz[65] used an alkyne alkylation (**22**) → (**23**) to prepare the final intermediate for radical cyclization in their synthesis of the unnatural (+) isomer of the sesquiterpene, $\Delta^{9(12)}$-capnellene (**24**; Scheme 42).

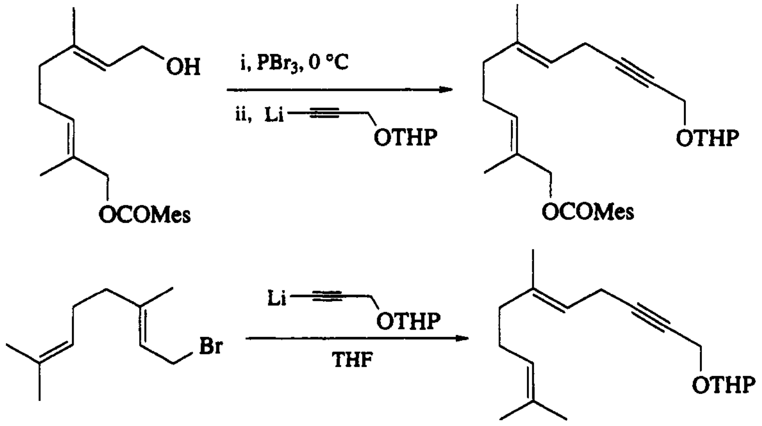
OH
OCOMes
i, PBr$_3$, 0 °C
ii, Li—≡—OTHP
OTHP
OCOMes
Br
Li—≡—OTHP
THF
OTHP

**Scheme 41**

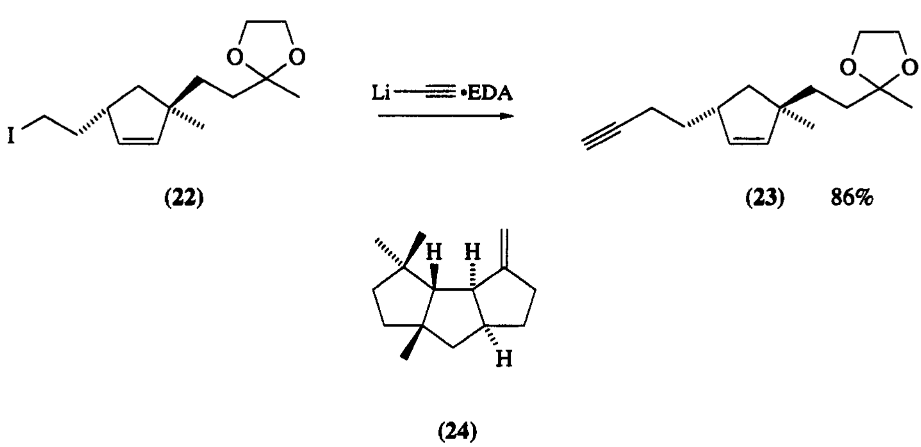

Scheme 42

### 1.7.5.3 Leukotrienes and Prostaglandins

Some of the first syntheses of the leukotrienes involved alkynes as intermediates, since these are excellent synthons for the stereospecific formation of alkenes. The alkylation with the allyl bromide occurred quite late in the Merck–Frosst synthesis of 5-HETE (Scheme 43).[66]

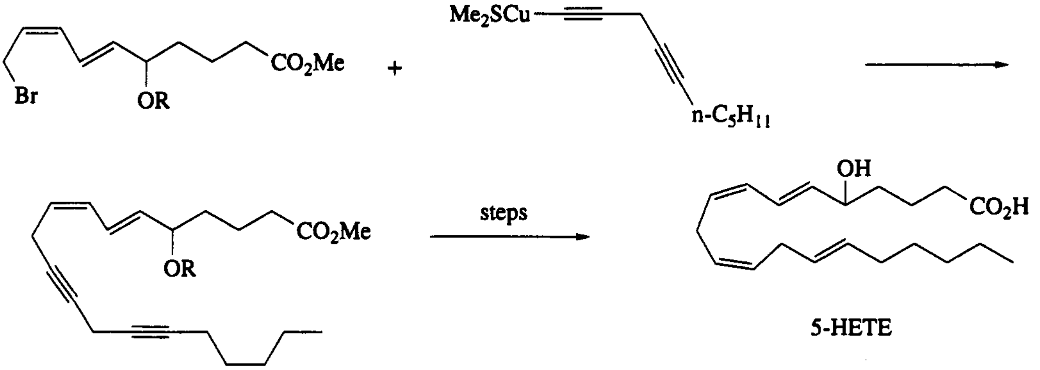

Scheme 43

The bromolithium cuprate analogue of the copper dimethyl sulfide shown in Scheme 42 was also alkylated by the *O*-protected allyl bromide to give a 65% yield of the same product. The Merck-Frosst group[67] also used a simple alkyne alkylation step in the synthesis of 14,15-dehydro-LTB$_4$ (Scheme 44).

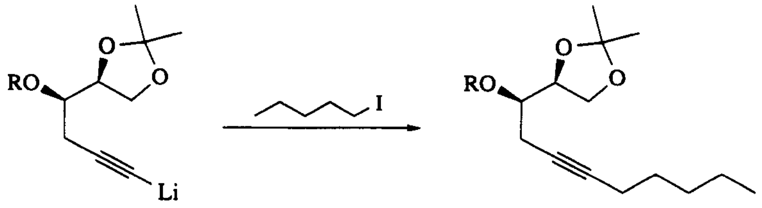

Scheme 44

In the course of their synthesis of LTB$_4$, Nicolaou and coworkers ring opened the THP-protected hydroxymethyloxirane (Scheme 12, ref. 31) in a regiospecific manner and they used a similar reaction in a later synthesis of (12*R*)-HETE.[68] A group at Hoffmann-La Roche[69] alkylated with a substituted propargyl bromide in a synthesis of (±)-LTA$_4$ (Scheme 45).

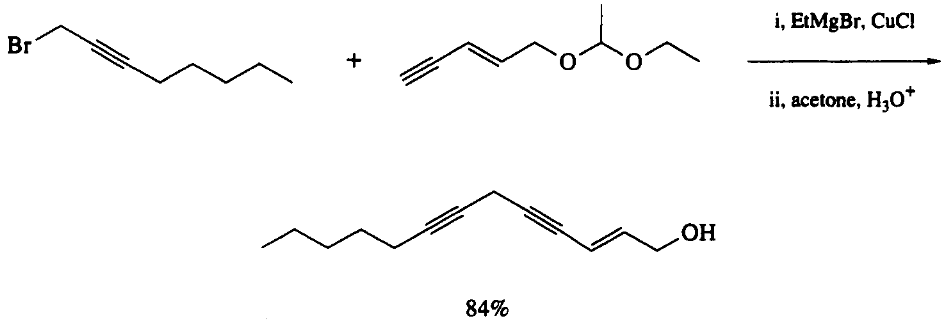
Br
+
O
O
i, EtMgBr, CuCl
ii, acetone, $H_3O^+$
OH
84%

**Scheme 45**

A Glaxo research group has used an oxirane ring opening with a dimethylaluminum alkynide, *i.e.* **(25)** → **(26)**, in one of their syntheses of prostaglandin $F_{2\alpha}$ (Scheme 46).[70] (The alkylation step in the Corey synthesis of hybridalactone was illustrated in Scheme 6.)

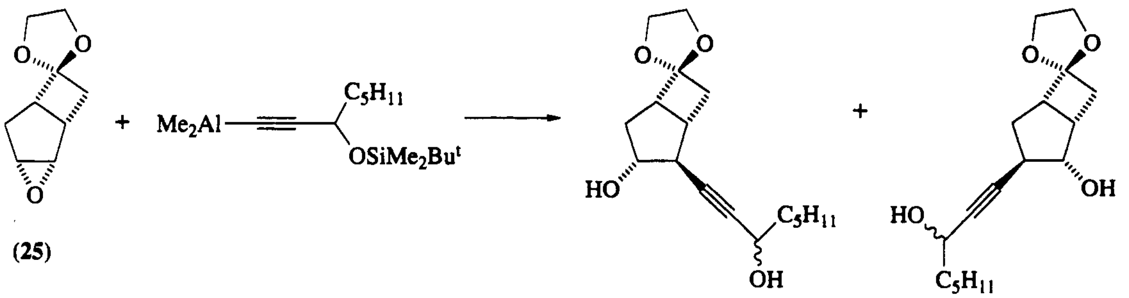
O
O
O
+
$Me_2Al$
$C_5H_{11}$
$OSiMe_2Bu^t$
O
O
HO
$C_5H_{11}$
OH
+
O
O
OH
HO
$C_5H_{11}$

**(25)**

**(26)**

**Scheme 46**

## 1.7.5.4 Non-natural Products

As an example of the use of alkynes in the synthesis of non-natural products, Hubert and Hubert[71] have synthesized the novel bicyclic macrocycle **(29)** by high dilution treatment of the tris alkynide **(27)** with the tribromide **(28)**.

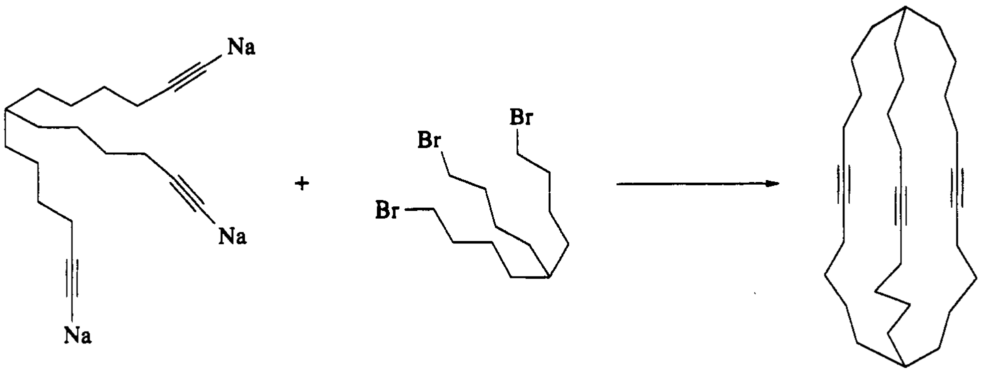
Na
Na
Na
+
Br
Br
Br

**(27)** **(28)** **(29)**

**Scheme 47**

## 1.7.6 REFERENCES

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# 1.8

# Friedel–Crafts Alkylations

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## 1.8.1 INTRODUCTION

In May 1877, Charles Friedel and James Mason Crafts made two communications to the Chemical Society of France of what were to become known as Friedel–Crafts reactions. Realizing the practical importance of their discovery, they lost no time in patenting their findings in France and Great Britain. Friedel and Crafts extended their studies of the catalytic effect of $AlCl_3$ in processes such asG: (i) reactions of organic halides and unsaturated compounds with aromatic and aliphatic hydrocarbons; (ii) reactions of anhydrides of organic acids with aromatic hydrocarbons; (iii) reactions of oxygen, sulfur, sulfur dioxide, carbon dioxide and phosgene with aromatic hydrocarbons; (iv) cracking of aliphatic and aromatic hydrocarbons; and (v) polymerization of unsaturated hydrocarbons.

Aluminum chloride and related catalysts bring about reactions between aromatic and aliphatic compounds, and inorganic and organic compounds; they also serve in the degradation of aromatic and aliphatic compounds, in substitution and addition reactions and various other reactions, such as polymerizations. Generally, any organic reaction effected by the catalytic action of $AlCl_3$, or related catalysts, is regarded as a Friedel–Crafts reaction. Many important industrial processes such as the manufacture of high-octane gasoline, ethylbenzene, synthetic rubber, plastics and detergent alkylates are based on Friedel–Crafts chemistry. The scope of Friedel–Crafts reactions is extremely wide, and forms a large part of the more general field of electrophilic reactions. A very large volume of literature has been published and the reader is referred to monographs,[1,2] comprehensive reviews[3,4] and an excellent treatise on Friedel–Crafts alkylation chemistry[5] for more detailed information.

For some time the main emphasis of Friedel–Crafts reactions was chiefly on aromatic compounds. The development of aliphatic Friedel–Crafts chemistry was of minor importance until World War 2, when isomerization of alkanes and cycloalkanes, preparation of high-octane aviation gasoline and synthetic rubber, and polymerization of alkenes achieved considerable importance; these contributed to the growth of aliphatic Friedel–Crafts chemistry.

Despite their seemingly wide variety, Friedel–Crafts reactions can be divided into two general categories: alkylations and acylations. Within these two broad areas, there is considerable diversity. Friedel–Crafts alkylations allow C—C bond formation in both aromatic and aliphatic systems, and are of substantial synthetic and industrial significance.

## 1.8.2 NATURE OF ALKYLATING AGENTS AND CATALYSTS

### 1.8.2.1 Alkylating Agents

Some of the earliest-known examples of Friedel–Crafts reactions were alkylations of arenes using alkyl halides. Since then, however, a wide variety of alkylating agents has been used (Table 1); they include alkenes, alkynes, alcohols and various other reagents.

**Table 1** Most Frequently Used Alkylating Agents in Aromatic Alkylations

| | |
|---|---|
| Alkyl halides | Ethers |
| Alkenes | Aldehydes and ketones |
| Alkynes | Alkanes and cycloalkanes |
| Alcohols | Mercaptans |
| Esters (of carboxylic and inorganic acids) | Thiocyanates |

Alkyl fluorides are the most reactive alkyl halides in aromatic alkylation reactions. The high reactivity of the C—F bond over C—Cl, C—Br and C—I bonds enables the preferential reaction of alkyl fluorides to occur in a system containing mixed halides. However, due to their availability and low cost, alkyl chlorides and bromides are most frequently used as alkylating agents. The reactions that employ alkyl iodides as the alkylating agents are generally accompanied by side reactions and decomposition. The relative ease of alkylation with alkyl halides follows the order: tertiary, benzyl > secondary > primary. In the series of primary alkyl halides, methyl halides are the least reactive. A similar sequence of activity is also observed in alkylations with alcohols, ethers and esters. In alkylation reactions with alkyl halides and alkenes the catalyst is required only in very small quantities. However, with alcohols and related alkylating agents (esters, ethers, *etc.*) considerably larger quantities of catalyst are necessary because of the complexity of the reaction and interaction of the catalyst with the alkylating agents.

A number of important commercial applications of the Friedel–Crafts reaction are based on the alkylation of aromatic compounds with alkenes, as in the synthesis of styrene from benzene and ethylene, and cumene from benzene and propene. When di- and poly-functional alkylating agents are employed, a wide variety of products such as diarylalkanes, polycyclic arenes, indans, tetralins and alicyclic arenes are formed. In the case of an unsaturated alkyl halide, the reaction with an arene may occur either involving the halide and/or the double bond, depending on the type of catalyst and the reaction conditions. Protic acid catalysts generally favor reaction at the double bond, and metal halides favor reaction of the halide. Rearrangements of alkylating agents catalyzed by metal halides and strong acids have been extensively studied in order to understand the results of alkylations utilizing these reagents.[5] Particularly, much effort has been expended in determining whether or not these rearrangements occur simultaneous with or consecutive to the alkylation reactions. Reactions involving primary alcohols, ethers and esters give different results depending on whether the Friedel–Crafts catalyst is a strong or a weak acid.

### 1.8.2.2 Catalysts

Friedel and Crafts themselves observed that aluminum chloride is by no means the only specific catalyst in the Friedel–Crafts reaction. A number of other acidic metal halides could also be employed; however, these were less reactive. The 'strength' or 'coordinating power' of different Lewis acids can vary widely against different Lewis bases. Hence it is extremely difficult to establish a scale of strength of Lewis acids in a manner analogous to that used for Brønsted acids. Despite the difficulties, a number of qualitative orders of reactivity have been proposed.[6] A comparative study of the activity of various Friedel–Crafts catalysts was performed by Olah and coworkers.[7] Thus the activity index[8] (the lowest temperature at which reaction occurs) of a large number of Lewis acid halides was measured using the benzylation reaction as the probe.

#### *1.8.2.2.1 Acidic halides (Lewis acids)*

Acidic metal halides, of which $AlCl_3$ and $AlBr_3$ are the most frequently used, comprise a large number of Lewis acid catalysts for Friedel–Crafts reactions. Other, frequently used active metal halide catalysts include: $BeCl_2$, $CdCl_2$, $ZnCl_2$, $BF_3$, $BCl_3$, $BBr_3$, $GaCl_3$, $GaBr_3$, $TiCl_4$, $TiBr_4$, $ZrCl_4$, $SnCl_4$, $SnBr_4$, $SbCl_5$, $SbCl_3$, $BiCl_3$, $FeCl_3$ and $UCl_4$. Such Lewis acids possess an electron-deficient central atom, capable of accepting electrons from basic substances. $AlCl_3$ and $BF_3$ (*vide infra*) are very important Friedel–Crafts catalysts and their applications cover a wide area of Friedel–Crafts-type reactions, including alkylations (both aromatic and aliphatic), different types of cyclizations, isomerizations, polymerizations and many other reactions.[2] One of the chief advantages in the use of $BF_3$ as a Friedel–Crafts catalyst is the fact that, being a low-boiling gas (b.p. –101 °C), it is easy to handle and to remove (or recover) from the reaction mixtures. Another advantage is that tarry and undesirable by-products are usually not obtained. Aluminum chloride has been particularly attractive in the industrial area due to its low cost and availability. Olah *et al.*[9] have prepared a new class of Friedel–Crafts catalysts which are triflate derivatives of boron, aluminum and gallium [$M(SO_3CF_3)_3$; M = B, Al, Ga]. These catalysts have been studied in detail for their effectiveness in catalyzing reactions such as alkylation with alkyl halides and isomerization processes. Due to the extreme moisture sensitivity of Lewis acids such as $AlCl_3$, it is rather difficult to carry out a Friedel–Crafts reaction under strictly anhydrous conditions. Trace amounts of acids (generated by hydrolysis of the metal halides), oxygen and organic halides invariably tend to be present in the reaction medium. However, such impurities, the so-called cocatalysts, have been found to accelerate rather than retard the reaction.[10]

Two main groups of cocatalysts can be identified in Friedel–Crafts systems: (i) proton-releasing substances, which consists of all hydroxy compounds (water, alcohol) and proton acids (HCl, $H_2SO_4$, $H_3PO_4$ and other organic and inorganic acids); and (ii) cation-forming substances (cations other than protons), which includes alkyl and acyl halides and a variety of other donor substances (O, S, N, halogen, *etc.* donors). Alkyl and acyl halides form carbocations as the activators. Other positively charged species, such as oxonium, sulfonium and halonium complexes, can also act as cocatalysts in different Friedel–Crafts reactions.

Anhydrous Lewis acids themselves are suitable catalysts for Friedel–Crafts reactions of compounds containing *n*-donor groups. However, they are generally insufficient as acceptors in reactions of alkenes or alkynes or isomerization of hydrocarbons. These reactions generally require a cocatalyst, such as a hydrogen halide or other cationic species.

Generally, Friedel–Crafts catalysts cannot be reused after aqueous work-up of the reaction mixture, although in some cases they can be recovered by special treatment. Fujiwara and coworkers,[11] however, found that lanthanide trihalide compounds ($ScCl_3$, $YCl_3$, $LaCl_3$, $CeCl_3$, $PrCl_3$, $NdCl_3$, $SmCl_3$, $EuCl_3$, $GdCl_3$, $TbCl_3$, $LuCl_3$, $DyCl_3$, $HoCl_3$, $ErCl_3$, $TmCl_3$ and $YbCl_3$) catalyzed the alkylation of aromatics, and the catalyst could be reused with no apparent loss of catalytic activity.

A Lewis acid catalyst can interact with the reagent containing a functional group having a donor atom with nonbonded pairs of electrons. This gives rise to a positively polarized complex or a carbocationic species, which then reacts with the $\pi$-donor substrate (aromatic, alkenic or alkynic hydrocarbons). Though this process can occur under strictly anhydrous conditions, this generally is not the case as impurity, moisture, or other cocatalysts are usually present. In the case of reactions of alkenes and alkynes it is essential to have a cocatalyst to form a strong conjugate acid or carbocation, which then initiates the reaction. Neat Lewis acids by themselves generally do not initiate Friedel–Crafts alkylation with alkenes. Impurities, physical state and the method of preparation of the catalyst affect both yield and the course of a reaction. For example, although traces of moisture in $AlCl_3$ may accelerate the effect, other impurities, such as $FeCl_3$, can decrease the yield.

### *1.8.2.2.2 Metal alkyls and alkoxides*

Alkyl derivatives of metals such as aluminum, boron and zinc are fairly active Friedel–Crafts catalysts. However, hyperconjugative effects result in a lowering of the electron deficiency. In the case of metal alkoxides this effect is even stronger, and, as a result, they are fairly weak Lewis acids. Metal alkyls, such as alkylaluminums, alkylaluminum halides and sesquihalides are also vital components of Ziegler–Natta catalyst systems which sometimes are utilized for Friedel–Crafts-type reactions. For example, alkylations of aromatics with alkenes in the presence of a Ziegler–Natta catalyst such as $AlR_3 + TiCl_4$ results in lower-chain alkylates. Even alkylaluminum halides and sesquihalides serve as Friedel–Crafts catalysts.

Among metal alkoxides, aluminum phenoxide is one of the most important Friedel–Crafts catalysts in the alkylation of phenol.[12]

### *1.8.2.2.3 Acidic oxides and sulfides (acidic chalcogenides), modified zeolites*

A large variety of solid oxides and sulfides, both natural and synthetic, such as alumina, silica and mixtures of alumina and silica (either natural or synthetic), in which other oxides such as chromia, magnesia, molybdena, thoria, tungstic oxide and zirconia may also be present, as well as certain sulfides of molybdenum, come under this category of catalyst. Many synthetic chalcogenides other than silica–alumina systems are known; these include BeO, $Cr_2O_3$, $P_2O_5$, $TiO_2$, $Al_2(SO_4)_3$, $Al_2O_3{\cdot}xCr_2O_3$, $Al_2O_3$, $Fe_2O_3$, $Al_2O_3{\cdot}MnO$, $Al_2O_3{\cdot}CoO$, $Al_2O_3{\cdot}Mo_2O_3$, $Al_2O_3{\cdot}V_2O_3$, $Cr_2O_3{\cdot}Fe_2O_3$, $MoS_2$ and $MoS_3$. In the case of silica–alumina systems, which are the most extensively studied, the acidity could reside either at Lewis acid or Brønsted acid sites. It has been estimated that silica–alumina is quantitatively at least as acidic as 90% sulfuric acid.[13] Both natural and synthetic zeolites are very important catalysts for many commercial processes. They have good thermal and hydrothermal stabilities, and have the ability to absorb and concentrate hydrocarbons. The well-defined crystal structure enables these zeolites to have pores with one or more discrete diameters approaching molecular dimensions (<1 nm). This property is responsible for their molecular-sieving action and their ability to effect selective transformations. Shape-selective zeolite catalysis is a very powerful means of effecting selective processes. Factors that determine shape selectivity include pore shape (circular, elliptical), intersections of the channels within the zeolite, sizes and shapes of cavities, side pockets and crystal symmetry. Three types of shape selectivities are possible: (i) *reactant selectivity* — one part of the reacting molecules can pass through the catalyst pores; (ii) *product selectivity* — only products with proper dimensions can diffuse out from the pores; and (iii) *restricted transition state selectivity* — only those reactions occur where the transition state 'fits' the internal cavity.

One of the most active areas of zeolite chemistry involves efforts to improve the selectivity of zeolite catalysts. It includes selective deactivation of external acid sites with substances such as amines; replacement of the cationic sites by ion exchange with transition metal ions; and modification of the silica/alumina ratio to achieve optimum hydrophilicity (which increases with decreasing aluminum concentration), acid strength and good thermal, hydrothermal and acid stability. The literature, particularly the patent literature, abounds with numerous examples of these areas and others.[14] Various types of clays are being studied for their ability to catalyze shape-selective reactions. For example, pillared clays can provide discrete pore sizes between 6 and 40 Å. However, they suffer from the disadvantages of catalyst deactivation and thermal instability. Stabilized pillared clay catalysts have been prepared by pillaring the layers with suitable moieties. For example, boron trihalides react with the hydroxy groups on clay and form stable pillars. The resulting catalysts are especially useful for transalkylation reactions.[15]

### *1.8.2.2.4 Acidic cation-exchange resins*

Solid acids are widely used to catalyze electrophilic reactions. Sulfonated styrene–divinylbenzene cross-linked polymers are efficient solid acids. These resins, such as Dowex 50, Amberlite IR-112 and

Permutit Q are effective catalysts for the alkylation of phenols with alkenes such as propene, isobutene and 2,5-dimethyl-2-hexene, and alkyl halides and alcohols.[16]

Modifications of these resins are also known. For example, aluminum phenoxide bonded to an acidic Dowex resin has been used as a heterogeneous catalyst for alkylation and transalkylation of phenols and polysubstituted phenols, respectively.[17]

### *1.8.2.2.5* ***Proton acids (Brønsted acids)***

Reactions that are catalyzed by metal halide catalysts are also catalyzed by proton acids. The most commonly used Brønsted acids are $H_2SO_4$, $H_3PO_4$ and HF.

### *1.8.2.2.6* ***Superacids***

Acids which are stronger than 100% sulfuric acid are called superacids.[18] Fluorosulfuric acid ($HSO_3F$) is one of the strongest Brønsted acids known, with $H_0$ (Hammett's acidity function) = −15.1. Its acidity is comparable to that of highly concentrated oleum, $H_2SO_4{\cdot}SO_3$; however, because of its stability, ease of purification, wide liquid range (m.p. = −89 °C, b.p. = 162 °C) and relatively low viscosity (1.56 cP at 28 °C), and lesser oxidizing ability, it is more convenient to use.

Perfluoroalkanesulfonic acids also show high acidity. The parent trifluoromethanesulfonic acid (triflic acid), $CF_3SO_3H$, is prepared commercially by electrochemical fluorination of methanesulfonic acid.[19] It has an $H_0$ value of −14.1. Because it is not a sulfonating agent, its use as an acid catalyst is advantageous. The higher homologs show somewhat decreasing acidities. Perchloric acid and chlorosulfuric acid are also examples of Brønsted superacids.

### *1.8.2.2.7* ***Lewis superacids***

Any Lewis acid that is stronger than anhydrous $AlCl_3$ has been arbitrarily defined as a Lewis superacid.[20] Examples of such Lewis superacids include $SbF_5$, $NbF_5$, $BF_3$, $AsF_5$, $TaF_5$ and $BiF_3$.

### *1.8.2.2.8* ***Brønsted–Lewis superacids***

When a suitable Lewis acid halide and proton acid are combined, conjugate Friedel–Crafts acids are formed, which are, indeed, superacids with a wide range of acidity. Anhydrous HF–$BF_3$ and HCl–$AlCl_3$ (stable as conjugate pair only under pressure) are widely used examples of such acids. They effectively catalyze hydrocarbon transformations.[20] In the early 1960s, much stronger acid systems were prepared[21] comprising a pentafluoride of a Group V element, particularly $SbF_5$, and a strong Brønsted acid such as HF, $FSO_3H$, $CF_3SO_3H$, *etc.* Magic acid ($HSO_3F$–$SbF_5$) and fluoroantimonic acid (HF–$SbF_5$) are two of the best-known examples. The acidity of HF or $HSO_3F$ is increased sharply by adding $SbF_5$.[22,23] For example, a composition of 4 mol % $SbF_5$ in HF has an $H_0$ value of −19, and with higher $SbF_5$ concentrations acidities can increase to −22. These very highly acidic systems are utilized for petrochemical transformations such as isomerization of straight chain alkanes, alkane–alkene alkylations, and the like.[24] Ternary systems, such as $HSO_3F$–HF–$SbF_5$ are also highly efficient superacid catalysts.[21] Vol'pin and coworkers[25] have reported novel, highly active systems derived from aluminum trihalide complexes of acyl and aryl halides, *viz.* $RCOX{\cdot}2AlX_3$ (R = alkyl, aryl; X = Br, Cl). These effective electrophilic systems are termed aprotic organic superacids. They were found to catalyze efficiently the transformations of alkanes and cycloalkanes under mild conditions.

### *1.8.2.2.9* ***Solid superacids***

Solid or supported catalysts are preferred in petrochemical and chemical industrial processes. Hence, solid superacid catalysts are of substantial interest. Acidic oxides, discussed earlier, are used extensively; however, their relatively low acidity necessitates higher operating temperatures. Even at higher temperatures, they are inefficient in promoting such reactions as the transethylation of benzene with di- and polyethylbenzenes. Consequently, new solid acid systems have been developed with considerably higher acidities than those of acidic oxides. These include acidic zeolites, such as ZSM-5, which combine shape selectivity with high acidity. Graphite-intercalated $AlCl_3$ is an effective solid Friedel–Crafts catalyst but loses catalytic activity because of ready hydrolysis and leaching of the Lewis acid halide from the graphite.[20] Aluminum chloride can also be complexed to sulfonated polystyrene resins, but again the stability of the catalyst is limited. Anhydrous $GaCl_3$ coated on polystyrene–divinylbenzene copolymer beads forms a stable complex which shows good catalytic activity in a number of organic synthetic reactions. Most notably, the catalyst can be reused several times without losing its activity and it is easily separated from the reaction mixtures.[26] Similarly, $TiCl_4$ supported on polystyrene–divinylbenzene copolymer has been used as a reusable catalyst for many organic reactions including Friedel–Crafts alkylation.[27]

More stable catalysts are obtained by using fluorinated graphite or fluorinated alumina as backbones and Lewis acid halides, such as $SbF_5$, $TaF_5$ and $NbF_5$, which have a relatively low vapor pressure. These Lewis acids are attached to the fluorinated solid supports through fluorine bridging. They show high reactivity in Friedel–Crafts reactions including the isomerization of straight chain alkanes such as *n*-hexane.

Another type of solid superacid is based on perfluorinated resin sulfonic acids, such as the acid form of DuPont's Nafion resin, a copolymer of a perfluorinated epoxide and vinylsulfonic acid, or higher perfluoroalkanesulfonic acids such as perfluorodecanesulfonic acid, $CF_3(CF_2)_9SO_3H$. Such solid catalysts were found to be very efficient in alkylation of aromatic hydrocarbons and other Friedel–Crafts reactions. A comprehensive review is available on the application of Nafion-H in organic catalysis.[28]

### *1.8.2.2.10 Metathetic cation-forming agents*[2]

A number of metathetic agents are capable of forming carbocations from halide precursors. These materials react stoichiometrically with the carbocation precursor, and therefore cannot be considered strictly as catalysts, but initiate Friedel–Crafts-type reactions. Anhydrous silver salts, such as $AgClO_4$, $AgBF_4$, $AgSbF_6$, $AgPF_6$, $AgAsF_6$, $Ag_3PO_4$, *etc.* are representatives of this class of compounds.

## 1.8.3 ALKYLATION OF ARENES

In the alkylation of aromatic hydrocarbons generally, a hydrogen atom of the aromatic nucleus is replaced by an alkyl group through the interaction of an alkylating agent in the presence of a Friedel–Crafts catalyst. As pointed out earlier, a variety of alkylating agents can be used for this reaction. The reactions in equations (1) to (3) are characteristic of the most commonly employed alkylations of aromatic hydrocarbons.

$$\mathrm{PhH} + \mathrm{RX} \xrightarrow{\mathrm{AlCl_3}} \mathrm{PhR} + \mathrm{HX} \qquad (1)$$

$$\mathrm{PhH} + \mathrm{ROH} \xrightarrow{\mathrm{AlCl_3}} \mathrm{PhR} + \mathrm{H_2O} \qquad (2)$$

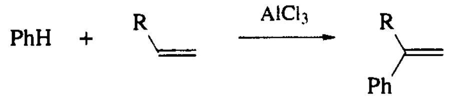

(3)

The mechanism of alkylation of arenes can be best understood as a carbocationic electrophilic aromatic substitution — a review on this aspect is available.[29] The alkylating agent and the catalyst first form an alkyl cation or related polarized complex, which then reacts with the aromatic ring *via* a Wheland intermediate (arenium ion; Scheme 1).

Because of the exhaustive literature on the alkylation of aromatics with a variety of alkylating agents, it is most convenient to discuss the reaction according to various alkylating agents.

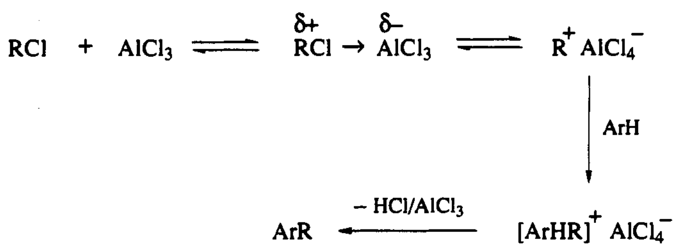

Scheme 1

### 1.8.3.1 Alkylation with Alkyl Halides

Methyl and benzyl halides were the earliest alkylating agents for the Friedel–Crafts alkylation of arenes. In fact Friedel and Crafts themselves reported the alkylation of benzene with methyl and benzyl chloride catalyzed by $AlCl_3$.[30] An earlier review by Price[31] covers the field until 1946, but more extensive treatment of this subject was presented by Olah in 1964 and 1973.[32] Further developments up to 1984 have been dealt with by Roberts and Khalaf in their book.[5] No repetition of the detailed and exhaustive discussion of the topic is, therefore, necessary. Instead, we point out briefly some of the significant work carried out to highlight the most important aspects of the reaction.

Central to the understanding of the Friedel–Crafts alkylation is the nature of the intermediate complexes formed between the catalysts and reactants. Earlier studies[33] on the exchange reactions of alkyl halides with Lewis acids such as $AlCl_3$ and $GaCl_3$ led to the postulation of dialkylchloronium ions as the intermediates formed when excess alkyl halide interacts with the Lewis acid. Olah *et al.* in their extensive studies indeed succeeded in preparing and studying dialkylhalonium ions, and the topic was covered in a monograph.[34a] Olah *et al.*[34b] also studied alkyl fluoride–antimony fluoride mixtures in solvents such as $SO_2$ and $SO_2ClF$, and suggested that they were tight donor–acceptor complexes (*e.g.* $MeF{\rightarrow}SbF_5$ and $EtF{\rightarrow}SbF_5$), which underwent rapid intramolecular fluorine exchange. They also observed that the $MeF{\rightarrow}SbF_5$–$SO_2$ solution was an extremely powerful methylating agent, capable of reacting with *n*-, π- and σ-donor bases as shown in equations (4) to (8). Even the solvents $SO_2$ and $SO_2ClF$ are *O*-methylated by this system. These reactions showed that $MeF{\rightarrow}SbF_5$ and $EtF{\rightarrow}SbF_5$ can behave like methyl and ethyl hexafluoroantimonates, respectively.

$$\mathrm{MeF{\rightarrow}SbF_5 + CO \longrightarrow Me\overset{+}{C}O\,SbF_6^- \longrightarrow MeCO\overset{+}{O}H_2\,SbF_6^- \xrightarrow{-\overset{+}{H}\,SbF_6^-} MeCO_2H} \qquad (4)$$

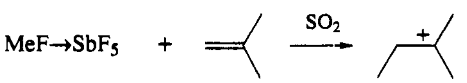

(5)

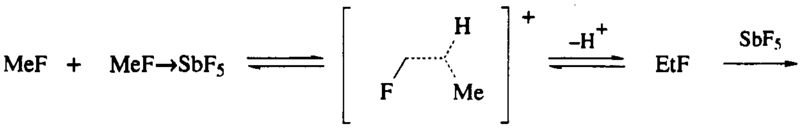

$$\mathrm{EtF{\rightarrow}SbF_5 \xrightarrow{EtF} Me_3C^+},\ \textit{etc.} \qquad (6)$$

$$\mathrm{SO_2 \xrightarrow{MeF\rightarrow SbF_5} Me\overset{+}{O}{=}S{=}O\ \bar{S}bF_5\ (or\ Sb_2F_{11}^-)} \qquad (7)$$

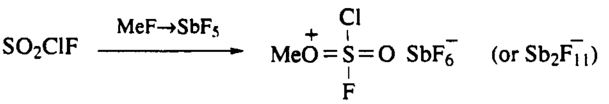

(8)

$$\mathrm{SO_2ClF \xrightarrow{MeF\rightarrow SbF_5} Me\overset{+}{O}{=}\underset{F}{\overset{Cl}{S}}{=}O\ SbF_6^-\ \ (or\ Sb_2F_{11}^-)} \qquad (8)$$

The first kinetic study of the Friedel–Crafts alkylation reaction was reported by Brown and Grayson in 1953.[35] This involved the reactions of some substituted benzyl halides with aromatic compounds in the presence of $AlCl_3$–$PhNO_2$ catalyst. The transition state for the rate-determining step (attack of the aromatic component on a polar alkyl halide–$AlCl_3$ addition compound) was depicted as a σ-complex.

Further studies by Brown and coworkers[36] lent additional support to this mechanism and the absence of a free alkyl cation. Olah and coworkers[37] have applied the concept of competitive alkylation to the case of naphthalene in order to study both positional and substrate selectivities, and to clarify the nature of kinetically *versus* thermodynamically controlled product composition. They explained the observed results by suggesting that a π-complex, such as (**1**), was the intermediate involved when highly electrophilic catalysts or strongly basic aromatics were employed, and a σ-complex (as proposed earlier by Brown) was involved in reactions with weakly electrophilic catalysts or less basic aromatics.

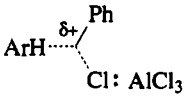

(**1**)

Similar explanations were put forth later by Nakane and coworkers[38] to explain their observed results. Olah's group[39] investigated the Friedel–Crafts alkylation of anisole and the analogous reaction with toluene.[31] A significantly lower degree of *meta* substitution was observed with anisole. The experimental data suggested that in the alkylation of anisole, in contrast to that of toluene, electrophilic attack by the alkylating agent at the *ortho* and *para* positions is less readily or not at all followed by thermodynamically controlled alkyl and hydrogen shifts, which could lead to increased *meta* substitution. Speranza and coworkers[40] have recently investigated the gas-phase benzylation of 2,6-dimethylanisole. Besides Friedel–Crafts catalysts, many other catalysts have also been utilized for studies on the benzylation reaction. Notable examples are arene tricarbonylmolybdenum, *i.e.* $[ArMo(CO)_3]$,[41] metal oxides[42] and calcined sulfate salts of Fe, Zn, Co, Mn and Cu.[31,43] Recently, Laszlo and Mathy[44] have studied the utility of K10 montmorillonite as a Friedel–Crafts catalyst by exchange of the interstitial cations with various transition metal ions such as $Zn^{II}$, $Cu^{II}$ and $Zr^{IV}$. For example, in the benzylation of benzene using benzyl chloride, excellent conversion of benzyl chloride and good isolated yields (up to 66%) of the monobenzylated product were obtained. The effect of the nature of the metal ion on the reactivity and selectivity of alkylation reactions has also been dealt with.[5]

Alkylations of arenes by ethyl halides under Friedel–Crafts conditions have been carried out by numerous workers. Excellent accounts of the developments made in this area are available from a review,[31] as well as a recent book.[5] Equations (9) to (11) illustrate some ethylation reactions.[37–39]

In 1979, Olah and Meidar[45] found that alkylation of toluene offered solely a mixture of isopropyltoluenes. No *n*-propyltoluenes were detected. This was explained as proceeding by the initial formation of the Cl-protonated *n*-propyl chloride (**2**; Scheme 2), which rapidly rearranges to the isopropyl cation, followed by reaction with the aromatic ring.

Masuda and coworkers[46] have found that both of the alkylating agents (–)-2-chloro-1-phenylpropane [(–)-**3**] and (+)-1-chloro-2-phenylpropane [(+)-**4**] react with benzene in the presence of $AlCl_3$ to give the same product, (–)-1,2-diphenylpropane [(–)-**5**] in 45–100% *ee*, which was not racemized under the

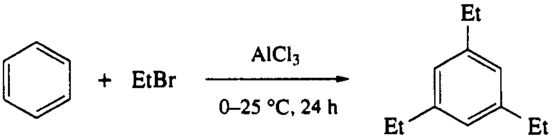

(ref. 37) (9)

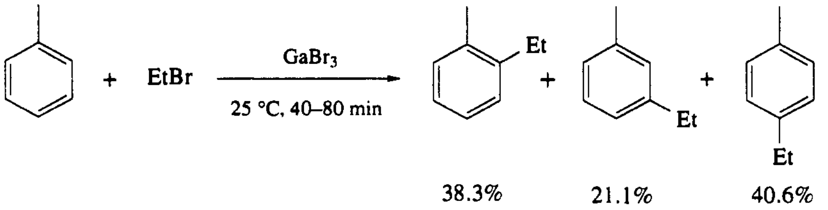

(ref. 38) (10)

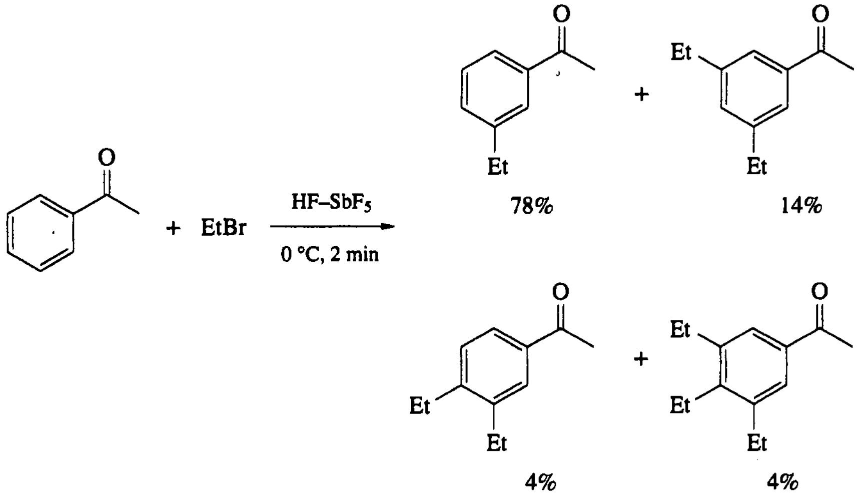

(ref. 39) (11)

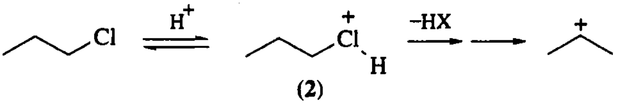

**Scheme 2**

reaction conditions (Scheme 3). A phenyl π-assisted cation (**6**) with an unsymmetrical bridging group has been proposed to account for the observed asymmetric induction.

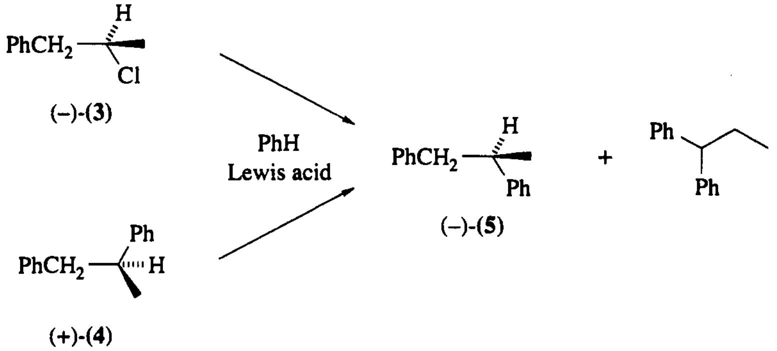

**Scheme 3**

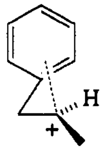

(**6**)

Kebarle and coworkers[47] have addressed the question of stability of the *t*-butylbenzenium ion obtained by gas-phase reaction of benzene with *t*-butyl cation.

Besides its application in mechanistic studies, the Friedel–Crafts alkylation has also been used to prepare synthetically useful compounds. Roth and Aig[48] attempted the Friedel–Crafts ethylation of *p*-ethylacetophenone (equation 12) under carefully optimized conditions to obtain the 3,4,5-triethyl derivatives (**7**) in reasonable yield. They also noted that when less ethyl bromide was employed, the product, surprisingly, was hexaethylbenzene. Compound (**7**) is a key intermediate in the synthesis of 2,4-diamino-5-(3,4,5-triethylbenzyl)pyrimidine (**8**), an antibacterial agent.

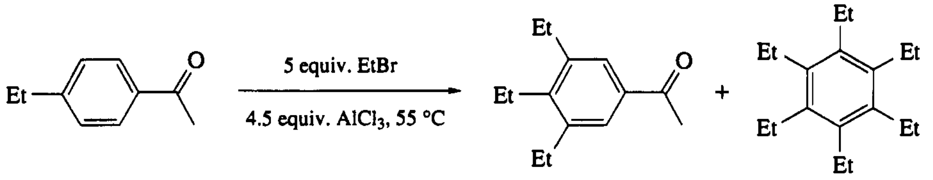

(7)

(12)

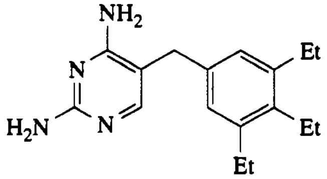

(8)

Highly selective (87%) isopropylation of an aniline at the *para* position has been achieved[49] by employing a particular mole ratio of the catalyst (aluminum halide) and the aniline (equation 13). Conversion of the substrate in the reaction was 87%.

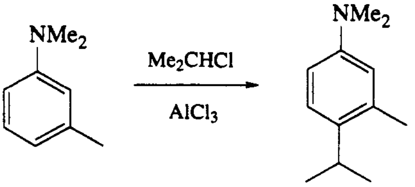

(13)

Zhukov and coworkers[50] alkylated naphthalene with 1-bromoadamantane in the presence of $ZnCl_2$–$H_2O$ to afford 2-(1-adamantyl)naphthalene in 90% yield (equation 14).

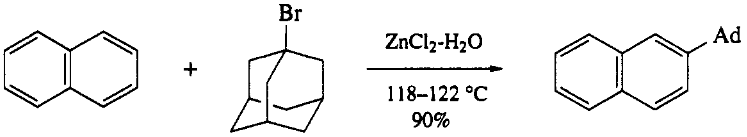

Ad = adamantyl

(14)

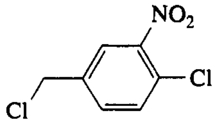

(9)

The Friedel–Crafts benzylation reaction has been employed to prepare polymer-bonded 2-mercaptopyridine and 2-mercaptonitrobenzene derivatives as new reagents for peptide synthesis.[51] Crosslinked polystyrene was subjected to benzylation using the benzyl chloride (**9**) as the alkylating agent, followed by further manipulation of the polyalkylated polymers. These polymeric reagents were used for the thiolytic cleavage of the 2-$(O_2N)C_6H_4S$ group in peptide synthesis.

Fujiwara and coworkers[11] have discovered that anhydrous lanthanoid trichloride salts[52] are reusable Friedel–Crafts catalysts for the benzylation of benzene. All of the lanthanoid trichlorides offer fairly good yields of benzylated product (equation 15). The yields do not drop if the recovered catalyst is used for a second time, or in some cases even a third time, for the benzylation of benzene.

Asymmetric Friedel–Crafts alkylations, besides affording interesting mechanistic problems, also offer valuable synthetic utility. For example, reaction of benzene with optically active 2-chloro-1-phenylpropane or 1-chloro-2-phenylpropane in the presence of $AlCl_3$ affords good yield (60%) of alkylated product with up to quantitative optical yields (see Scheme 3).[46]

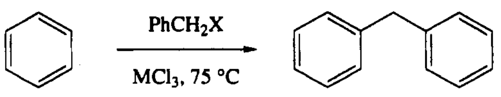
PhCH2X
MCl3, 75 °C

(15)

M = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

Optically active 2-arylglycine esters, such as (**10**), have been prepared[53] by Friedel–Crafts alkylation of alkoxybenzenes and naphthalenes with the chiral cation of the bislactim ether of cyclo-(L-Val-Gly). For example, when the chloride (**12**), prepared from the bislactim ether (**11**), was allowed to react with 1,4-diethoxybenzene in the presence of tin tetrachloride as the Lewis acid (equation 16), the adduct (**13**) was obtained in 65% yield. Acid hydrolysis of (**13**) furnished the previously unknown (*R*)-α-arylglycine methyl ester (**10**). The active species in the alkylation step has been proposed to be the ion pair (**14**). Unactivated arenes were found not to react under these conditions. 2-Arylglycines such as (**10**) are of pharmacological interest due to their potential biological activity and as components of drugs such as semisynthetic penicillins, ampicillins and amoxycillins.

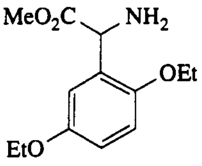
MeO2C
NH2
OEt
EtO

**(10)**

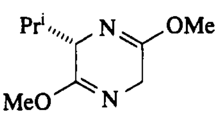
Pri
N
OMe
MeO
N

**(11)**

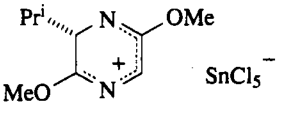
Pri
N
OMe
+
MeO
N
SnCl5−

**(14)**

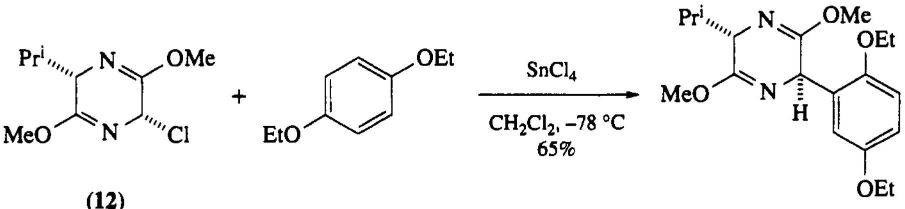
Pri
N
OMe
MeO
N
Cl
+
OEt
EtO
SnCl4
CH2Cl2, −78 °C
65%
Pri
N
OMe
OEt
MeO
N
H
OEt

**(12)**

**(13)**

(16)

A practical application[54] of the benzylation reaction is the $AlCl_3$-catalyzed Friedel–Crafts alkylation of a styrene–ethylene–butene–styrene block copolymer with benzyl chloride to afford modified thermoplastic alkene elastomers. Another application[55] of Friedel–Crafts-type regiospecific alkylation of arenes with cycloalkyl fluorides derived from sugars (equation 17) constitutes a facile methodology to prepare *C*-arylglycosides, some of which are potent antitumor agents. The glycosyl fluorides are activated by the novel Lewis acid system, $Cp_2ZrCl_2$–$AgClO_4$.[56]

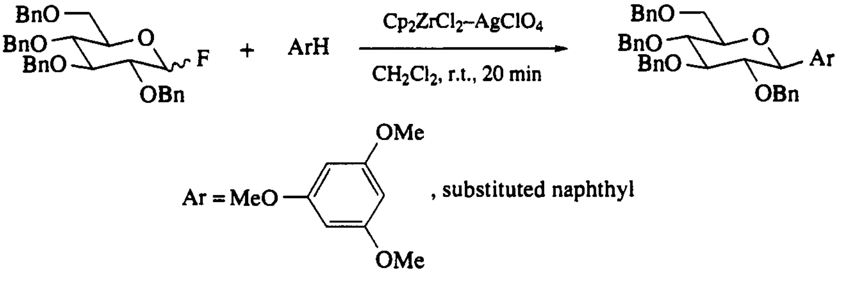
BnO
BnO
BnO
O
F
OBn
+
ArH
Cp2ZrCl2–AgClO4
CH2Cl2, r.t., 20 min
BnO
BnO
BnO
O
Ar
OBn
Ar = MeO
OMe
OMe
, substituted naphthyl

(17)

Alkylation of benzene by ω-chloroalkanoic acids $Cl(CH_2)_nCO_2H$ and their methyl esters and nitriles has also been studied.[57] It was found that introduction of electron-acceptor substituents such as $—CO_2H$, $—CO_2Me$ and —CN into *n*-alkyl chlorides decreased the extent of isomerization of the alkyl chain below that of the corresponding 1-chloroalkanes, as seen from the examples in equations (18) and (19).

Besides these more recent examples, many instances of the use of benzylation reactions to prepare a variety of substituted aromatic compounds are known.[5] Some examples are shown in equations (20)[58] and (21).[58b]

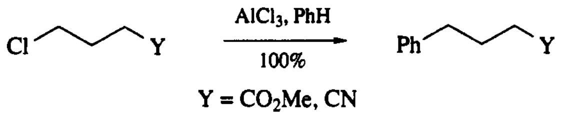

(18)

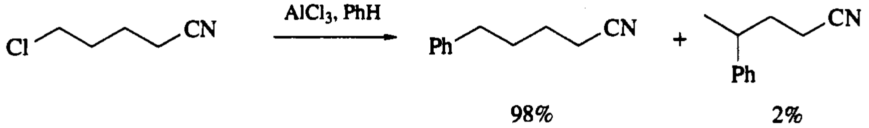

(19)

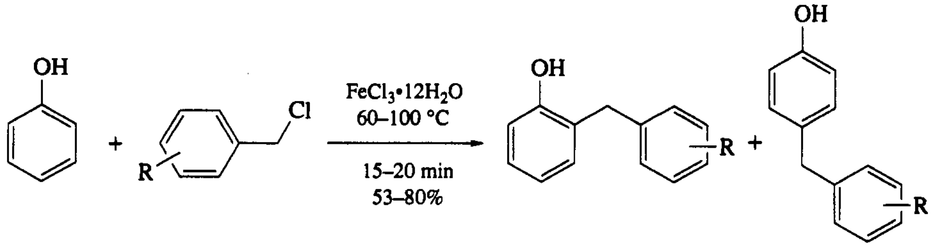

(20)

| | | |
|---|---|---|
| R = *o*-Me | 54% | 46% |
| R = *m*-Me | 60% | 40% |
| R = *p*-Me | 58% | 42% |

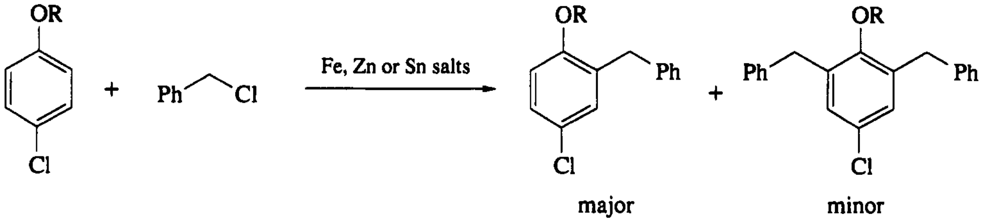

(21)

### 1.8.3.2 Alkylation with Alkenes

The alkylation of arenes with alkenes such as ethylene and propene are of great commercial interest. Ethylbenzene and isopropylbenzene (cumene), products of the Friedel–Crafts alkylation of benzene with ethylene and propene, respectively, are two of the most important petrochemical raw materials.[59] Roberts and Khalaf[5] have followed the developments made in this vast field up to the early part of this decade. This is evident from the large number of references quoted, most of which describe efforts to evaluate conditions for optimal production in the presence of various catalyst systems.

Reports of kinetic studies of positional and substrate selectivities for Friedel–Crafts ethylation and propylation reactions are available in the literature. Thus ethylene was used to alkylate aromatics such as toluene,[60] naphthalene[61] and biphenyl[62] using a variety of catalysts. Ethylation and propylation of aromatics such as naphthalene and biphenyl can give rise to varying mixtures of isomeric alkylated products depending on the nature of the catalyst and the severity of the reaction conditions. For example, in the isopropylation of naphthalene nonisomerizing catalysts such as $BF_3$–$H_3PO_4$, HF, $BF_3{\cdot}Et_2O$ or $P_2O_5$ gave higher 1-isomer:2-isomer ratios than the isomerizing catalysts.[63] Mechanistic studies on the alkylation of arenes with alkenes, particularly with propene, have been carried out using many techniques, such as standard kinetic methods and $^{14}C$- and $^{2}H$-labeling methods. These aspects are well documented.[5] More recent kinetic and mechanistic studies include: kinetic modeling of the liquid-phase alkylation of toluene with *n*-butenes;[64] thermodynamic analysis of the alkylation of phenols with branched alkenes;[65] kinetics of benzene alkylation with 1-decene in the presence of soluble quantities of $AlCl_3$ catalyst complex;[66] isomer distribution studies on the Friedel–Crafts alkylation of toluene with cycloalkenes;[67] a mathematical model for the homogeneous alkylation of benzene by ethylene in the presence of an aluminum chloride catalyst;[68] and kinetics of cycloalkylation of phenol and cresols by cyclohexene and cyclopentene using $H_2SO_4$ as catalyst.[69]

Friedel–Crafts alkylation of aromatics with a wide variety of alkenes has led to many useful applications in organic synthesis. Particularly, much effort has been devoted to choosing appropriate catalysts and reaction conditions to produce predominantly or selectively one product isomer. This is especially true of alkylations with both linear and branched $C_4$, $C_5$ and higher alkenes as the alkylating agents. Other factors such as steric and electronic interactions could also lead to regioselective formation of products as seen in equations (22) to (26).[70–74]

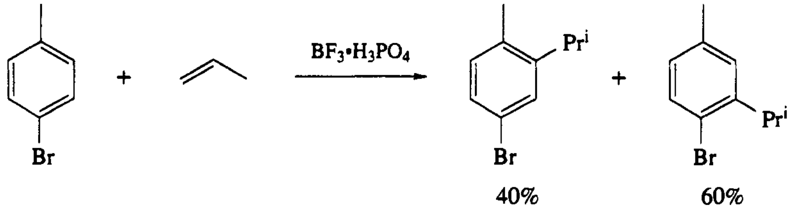
BF3•H3PO4
Br
Pri
40%
60%

(ref. 70) (22)

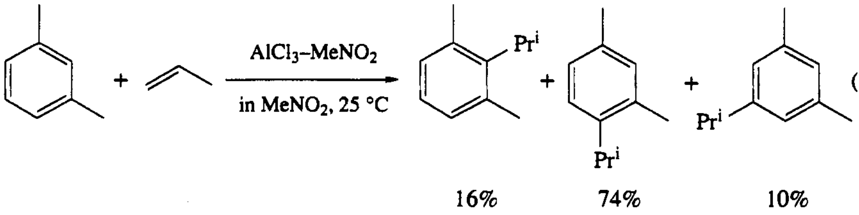
AlCl3–MeNO2
in MeNO2, 25 °C
Pri
16%
74%
10%

(ref. 71) (23)

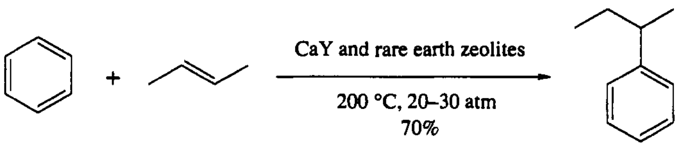
CaY and rare earth zeolites
200 °C, 20–30 atm
70%

(ref. 72) (24)

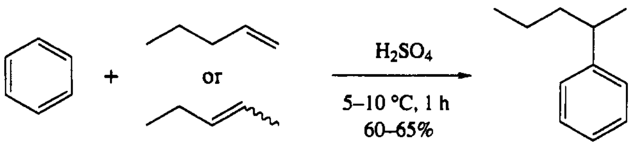
or
H2SO4
5–10 °C, 1 h
60–65%

(ref. 73) (25)

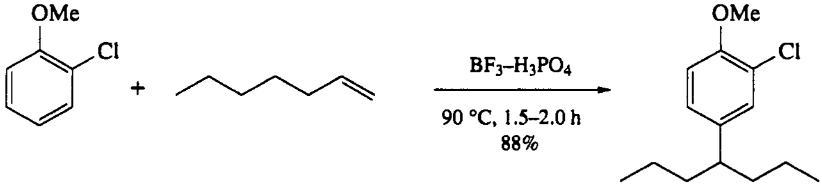
OMe
Cl
BF3–H3PO4
90 °C, 1.5–2.0 h
88%

(ref. 74) (26)

The effect of the acidity of polyfunctional zeolite catalysts on their activity in benzene alkylation by propene has been examined.[75a] Crystalline zeolites exist with a variety of characteristic pore and channel sizes. In the case of ZSM-5 zeolite, the interconnected channels formed by 10-membered rings of oxygen atoms allows certain benzene derivatives to fit rather closely, diffuse into the pores, and, after undergoing a reaction, diffuse out. This is the origin of the high *para* selectivity in reactions such as alkylation of toluene by methanol catalyzed by zeolites like ZSM-5 and related modifications.[75b,c]

Olah[76] has found perfluoroalkanesulfonic acids, such as perfluorodecanesulfonic acid (PDSA, $C_{10}F_{21}SO_3H$), to be very effective catalysts for regioselective isopropylation of naphthalene (equation 27).

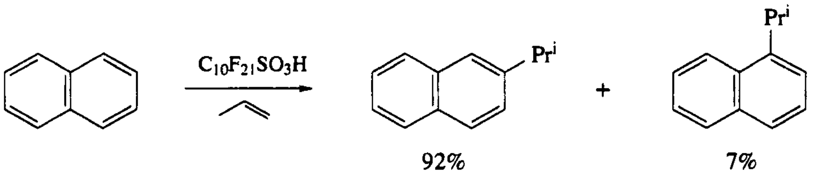
C10F21SO3H
Pri
92%
7%

(27)

Controlled *ortho* alkylation of phenol by 1-hexene to produce the mono- or di-alkylated product has been achieved by using aluminum phenolate as the catalyst under carefully optimized reaction conditions.[77] Sterically hindered phenols such as (**15**) are of particular interest as antioxidants (Scheme 4).

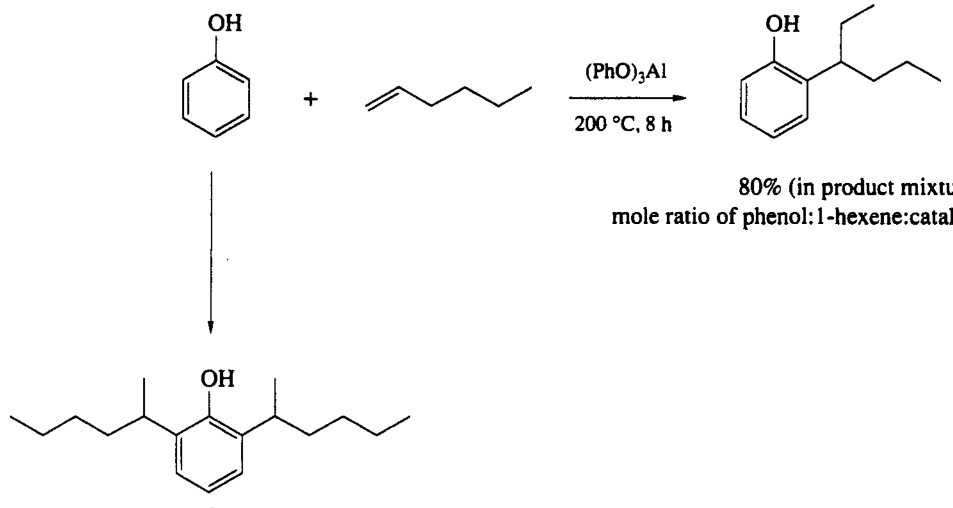

80% (in product mixture)
mole ratio of phenol:1-hexene:catalyst = 3:1:0.3

**(15)**

72% (in product mixture)
mole ratio of phenol:1-hexene:catalyst = 1:2.7:0.3

**Scheme 4**

Shudo and coworkers[78] have reported that *O,O*-diprotonated nitroalkenes (**16**) behave as novel electrophilic species which can efficiently alkylate aromatics such as benzene, anisole, chlorobenzene, naphthalene, *etc.* under extremely mild conditions (equation 28). The reaction enables the synthesis of α-arylated ketones (**17**) which are difficult to synthesize by conventional Friedel–Crafts reactions.

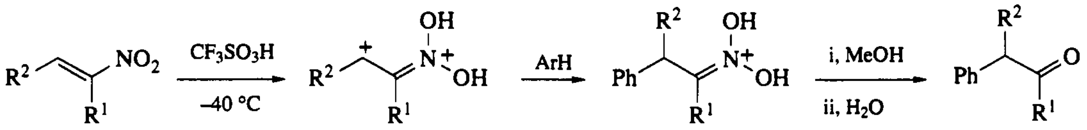

(**16**) (**17**) (28)

Crotonic acid has been used as a carboxyalkylating agent in its reaction with benzimidazolin-2-ones (equation 29).[79] It must be emphasized, however, that when long chain linear alkenes are used as alkylating agents, one frequently encounters a mixture of products containing rearranged forms of the alkyl group. With isobutene as the alkylating agent, the products are found to be exclusively *t*-butylated derivatives. A number of isomerically pure *t*-butylated aromatics have been thus prepared. The regioselectivity is also appreciably enhanced because of the greater steric factors operative. Alkylations with branched $C_5$ and higher alkenes, in general, are accompanied by side reactions,[80] such as reorientation, disproportionation, fragmentation, polymerization, hydride transfer and skeletal rearrangement of the alkylating group. However, use of moderated reaction conditions, including a milder catalyst, can afford one product selectively. Examples illustrating the synthetic utility of alkylations with isobutene and higher branched alkenes are shown in equations (30) to (34).[81–85]

Alkylation of phenols with isobutene has also been accomplished[86] using a heterogeneous catalyst system comprising an aluminum phenoxide bonded to a solid polymeric resin having acidic functional

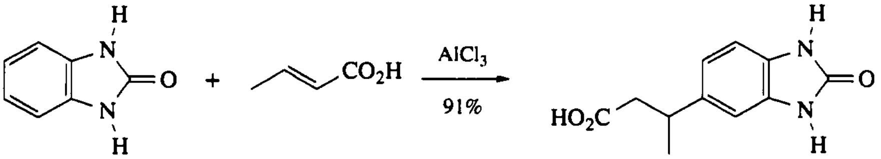

(29)

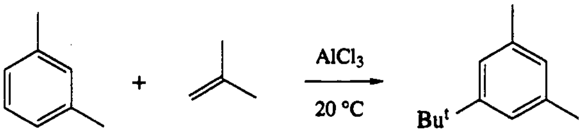
AlCl3
20 °C
Bu^t

(ref. 81) (30)

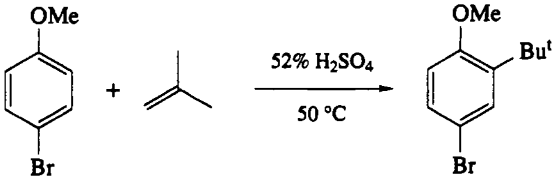
OMe
Br
52% H2SO4
50 °C
OMe
Bu^t
Br

(ref. 82) (31)

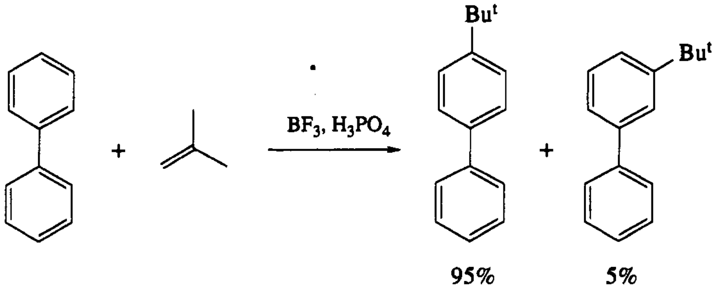
BF3, H3PO4
Bu^t
Bu^t
95%
5%

(ref. 83) (32)

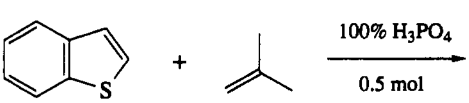
S
100% H3PO4
0.5 mol
Bu^t
S

(ref. 84) (33)

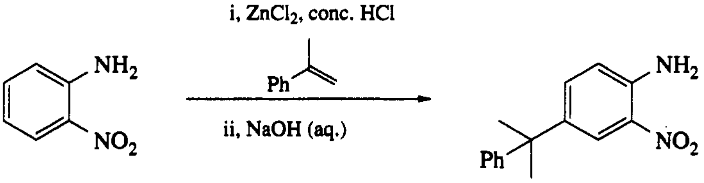
NH2
NO2
i, ZnCl2, conc. HCl
Ph
ii, NaOH (aq.)
NH2
NO2
Ph

(ref. 85) (34)

groups. A strongly acidic ion-exchanger has been employed[87] as the catalyst for the Friedel–Crafts alkylation of phenols with diisobutene to afford *p*-*t*-octylphenol. Such alkylations in heterogeneous media are of great importance due to the ease of separation of the product from the catalyst.

The *t*-butyl group has been extensively utilized as a positional protective group in both separation and synthesis problems. This is due to the ease with which *t*-butyl groups can be introduced (by alkylation) and removed (by dealkylation). Tashiro's review[88] covers this topic very well. Examples to illustrate the utility of the *t*-butyl group for the selective preparations of phenolic compounds (equations 35 and 36),

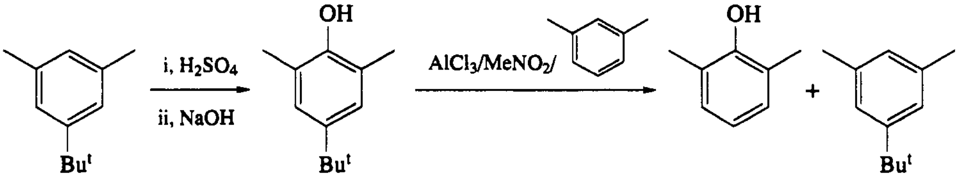
Bu^t
i, H2SO4
ii, NaOH
OH
Bu^t
AlCl3/MeNO2/
OH
Bu^t

(35)

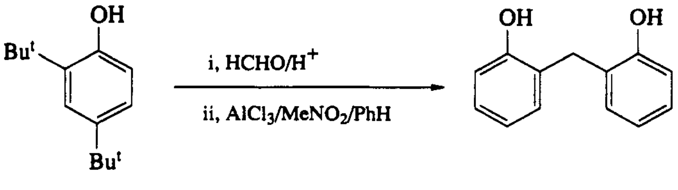
OH
Bu^t
Bu^t
i, HCHO/H+
ii, AlCl3/MeNO2/PhH
OH
OH

(36)

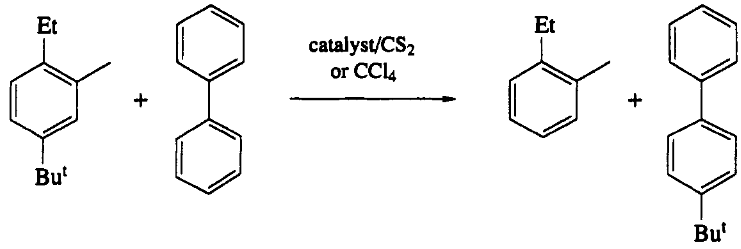
Et
Bu^t
catalyst/CS2
or CCl4
Et
Bu^t

(37)

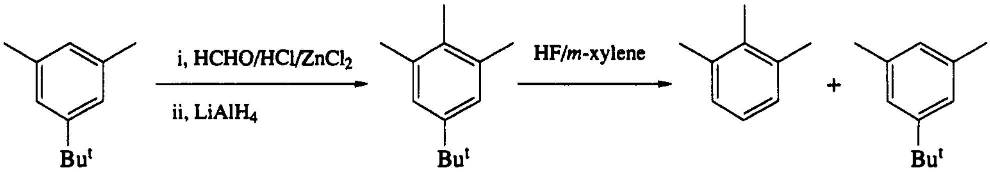
Bu^t
i, HCHO/HCl/ZnCl2
ii, LiAlH4
Bu^t
HF/m-xylene
Bu^t

(38)

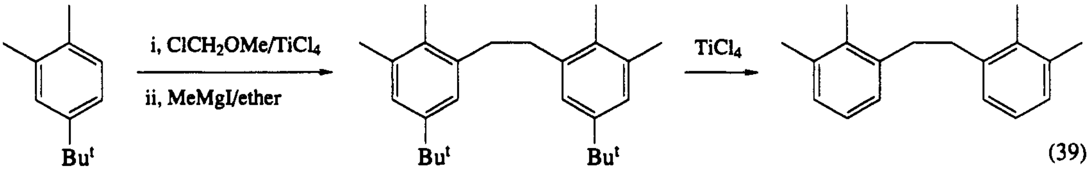
Bu^t
i, ClCH2OMe/TiCl4
ii, MeMgI/ether
Bu^t
Bu^t
TiCl4

(39)

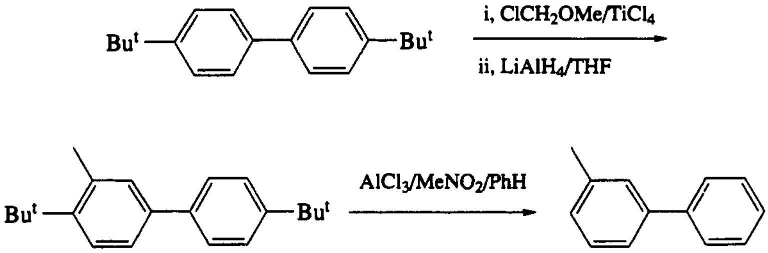
Bu^t
Bu^t
i, ClCH2OMe/TiCl4
ii, LiAlH4/THF
Bu^t
Bu^t
AlCl3/MeNO2/PhH

(40)

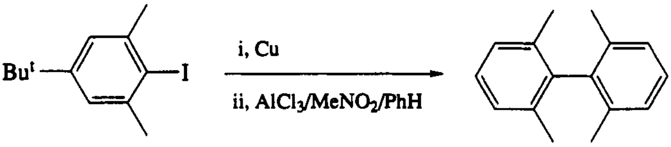
Bu^t
I
i, Cu
ii, AlCl3/MeNO2/PhH

(41)

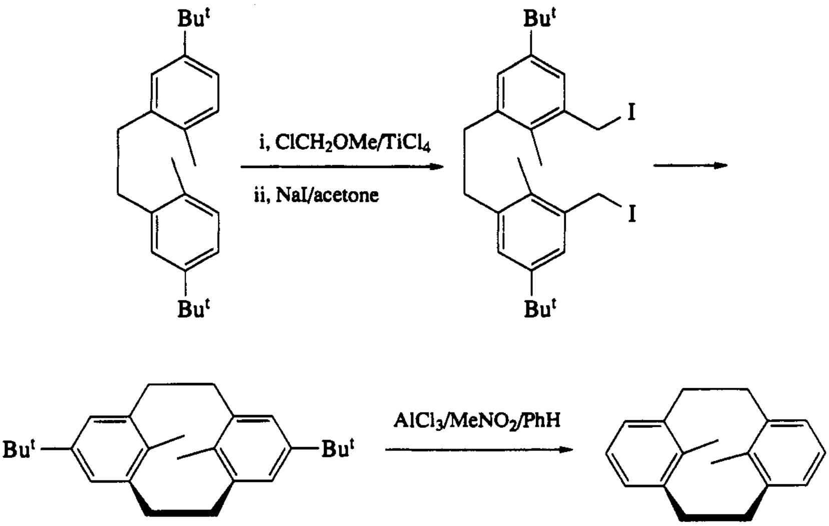
Bu^t
Bu^t
i, ClCH2OMe/TiCl4
ii, NaI/acetone
Bu^t
I
I
Bu^t
Bu^t
Bu^t
AlCl3/MeNO2/PhH

(42)

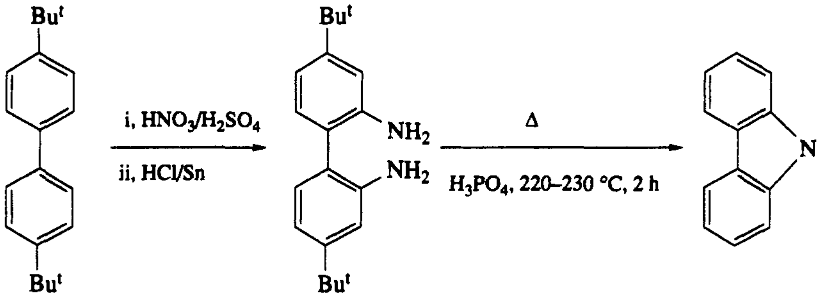

(43)

1,2-di- and 1,2,3-tri-substituted benzenes (equations 37 and 38), diarylalkanes (equation 39), 2-mono- and 2,2′-di-substituted biphenyls (equations 40 and 41), [2,2]metacyclophanes (equation 42) and carbazoles (equation 43) are shown.

Alkylation of arenes with cycloalkenes (cycloalkylation) is also well documented in the literature. A variety of Lewis and Brønsted acids have been used as catalysts for these reactions. These reactions share many similarities with the alkylation reactions of arenes with other alkylating agents such as alkenes. The selectivity of the cycloalkylation reaction depends upon the conditions and catalyst. A few examples of cycloalkylation reactions are presented in equations (44) to (46).[89–91]

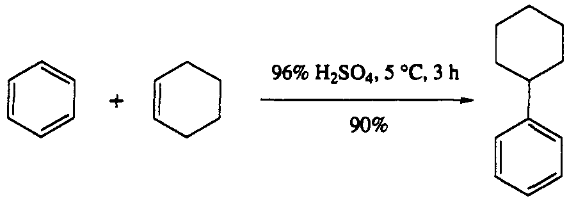

(ref. 89) (44)

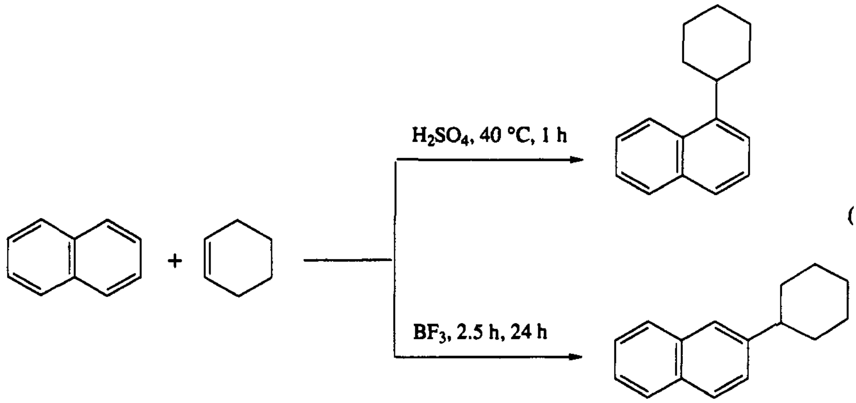

(ref. 90) (45)

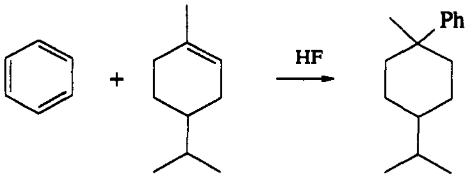

(ref. 91) (46)

### 1.8.3.3 Alkylation with Alcohols, Ethers, Esters, Epoxides and Lactones

The alkylations of arenes by alcohols, ethers and esters, as well as with epoxides and lactones, are of considerable interest, and constitute a significant part of the field of Friedel–Crafts alkylations. Some of the earliest examples are the alkylations of arenes with primary alcohols,[92a] esters[92b] and ethers.[92c] Subsequent work over the years has revealed that these alkylations are often accompanied by various side

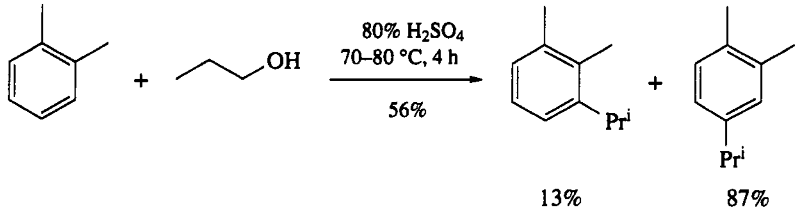
+
OH
80% $H_2SO_4$
70–80 °C, 4 h
56%
$Pr^i$
+
$Pr^i$
13%
87%

(ref. 93) (47)

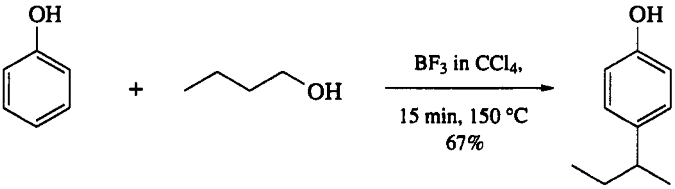
OH
+
OH
$BF_3$ in $CCl_4$,
15 min, 150 °C
67%
OH

(ref. 94) (48)

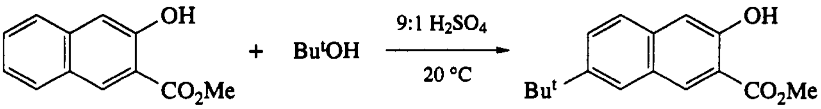
OH
$CO_2Me$
+ $Bu^tOH$
9:1 $H_2SO_4$
20 °C
$Bu^t$
OH
$CO_2Me$

**(18)**

(ref. 95) (49)

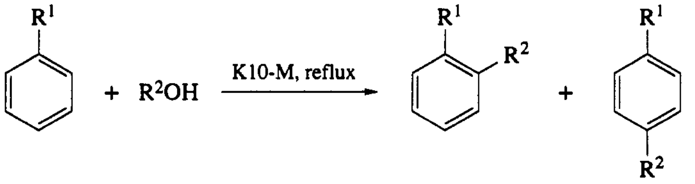
$R^1$
+ $R^2OH$
K10-M, reflux
$R^1$
$R^2$
+
$R^1$
$R^2$

(ref. 44) (50)

$R^1$ = H, Me; $R^2$ = $PhCH_2$, c-$C_6H_{11}$, 2-pentyl, 3-pentyl

M = $Al^{III}$, $Ti^V$, $Fe^{III}$, $Co^{II}$, $Cu^{II}$, $Zn^{II}$, $Zr^{IV}$, $Nb^V$, $Ta^V$

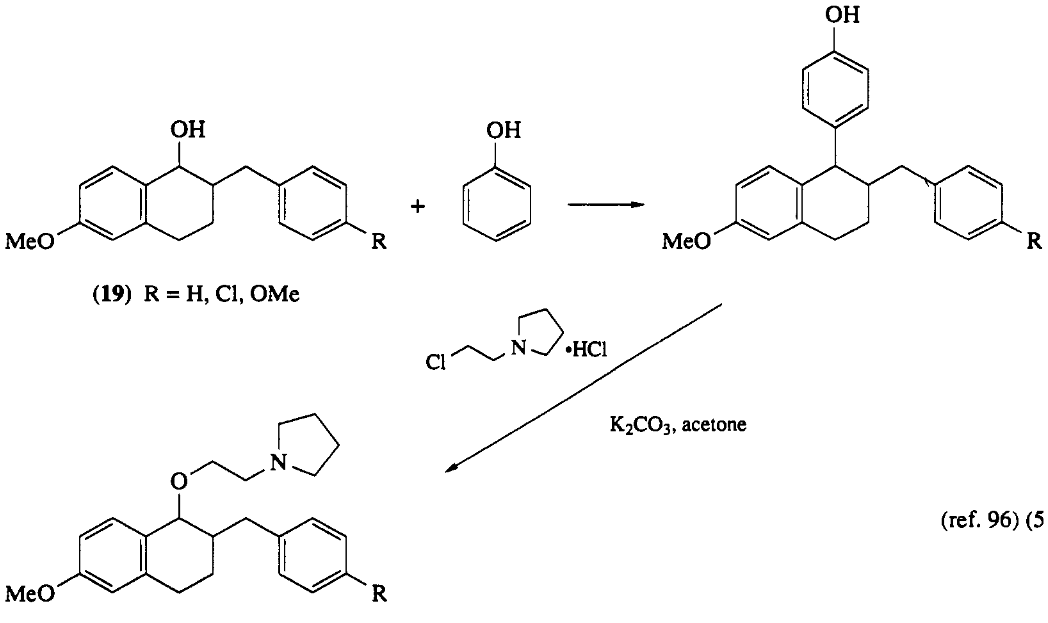
OH
MeO
R
+
OH
OH
MeO
R
Cl
N
•HCl
$K_2CO_3$, acetone
O
N
MeO
R

**(19)** R = H, Cl, OMe

**(20)** R = H, Cl, OMe

(ref. 96) (51)

reactions, such as isomerization, fragmentation and dealkylation, together with side-chain and positional rearrangements.

Early studies have shown that, compared to alkylations with alkyl halides or secondary alcohols, alkylations with primary alcohols require larger amounts of the Lewis acid catalyst (*ca.* 2 mol for 1 mol of alcohol) and longer heating at higher temperatures. The relative ease of alkylation with alcohols follows the order: benzyl, allyl, tertiary > secondary > primary > methyl. Besides using catalysts such as $BF_3$ and $AlCl_3$, many milder catalysts have been used for the alkylation of aromatics with alcohols, ethers and esters. These include weakly acidic metal halides, such as $AlCl_3$–$MeNO_2$, $FeCl_3$, $TiCl_4$, $SnCl_4$ and $ZnCl_2$; protic acids such as $H_3PO_4$, HF, $H_2SO_4$ and polyphosphoric acid; solid superacids such as Nafion-H; and inorganic acidic oxides such as $P_2O_5$, alumina, natural and synthetic aluminosilicates and zeolites. These milder catalysts afford solely or mostly the rearranged secondary alkylates.

A careful choice of catalyst and reaction conditions is necessary to obtain selective Friedel–Crafts alkylation. The following examples illustrate reactions with alcohols as the alkylating agent (equations 47 to 51).[44,93–96]

The *t*-butylated naphthalene derivative (**18**; equation 49) is of interest as an intermediate[95] for the synthesis of fungicides. Tetrahydronaphthalene derivatives, such as (**20**), have been evaluated[96] as antifertility agents. Sugita *et al.*[97] have studied the $AlCl_3$-catalyzed Friedel–Crafts alkylation of benzene with 1-phenyl-2-propanol and 2-phenyl-1-propanol in the presence of additives, such as $CuCl_2$, $Cu_2Cl_2$ and decalin. Highly regioselective formation of 1,1-diphenylpropane was observed with $Cu^I$ or $Cu^{II}$ chloride as the additive. Some pertinent results of synthetic value are shown in Scheme 5. The addition of decalin diminished the alkylation reaction to give the reduction product 1-phenylpropane.

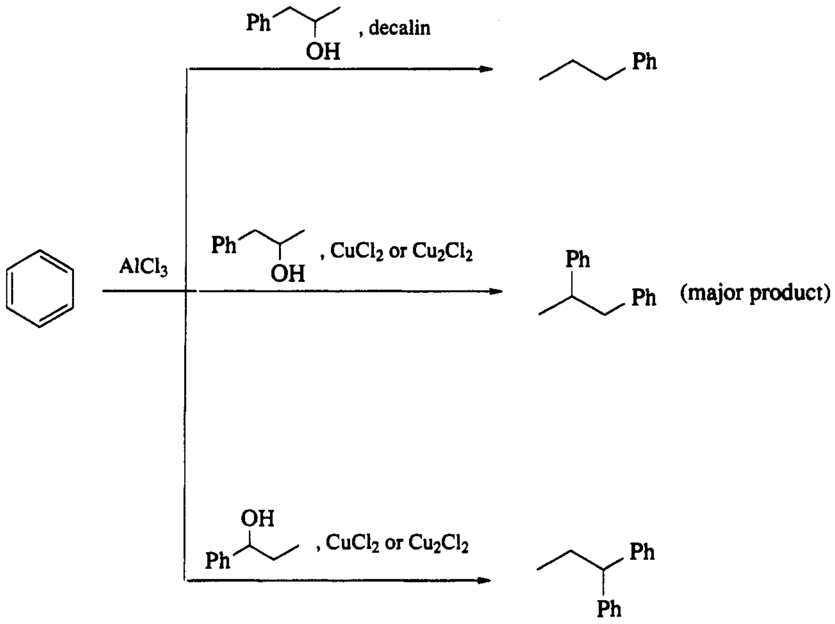

Scheme 5

Nutaitis and Gribble[98] have found that arenes react with $NaBH_4$ in $CF_3CO_2H$ to afford 1,1,1-trifluoro-2,2-diarylethanes, which were otherwise difficult to prepare. They proposed a Friedel–Crafts-type (Baeyer) condensation to give an intermediate carbinol (**21**; equation 52), which further alkylates benzene to give the observed products. The reaction with sterically congested arenes such as mesitylene and durene stops at the carbinol stage (equation 53).

Isopropylation of toluene by isopropyl halo- and alkyl-sulfonates (equation 54) has been performed by Olah *et al.*[99] A variety of catalysts, such as $AlCl_3$, $AlCl_3$–$MeNO_2$ and Nafion-H were employed, and the isomer distribution (*o, m, p*) in the product was determined. Sartori *et al.*[100] have recently reported an unusual Friedel–Crafts alkylation of lithium phenolates with ethyl pyruvate in the presence of $AlCl_3$ to afford α-(2-hydroxyphenyl)ethyl lactates (**22**), which are the precursors of 3-methyl-2,3-dihydrobenzofuran-3-ols (**23**; Scheme 6).

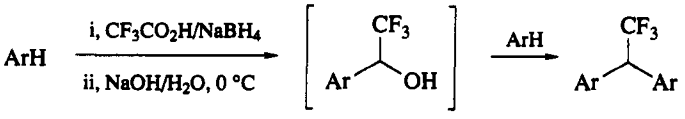
ArH
i, $CF_3CO_2H/NaBH_4$
ii, $NaOH/H_2O$, 0 °C
$CF_3$
Ar
OH
ArH
$CF_3$
Ar
Ar

**(21)**

(52)

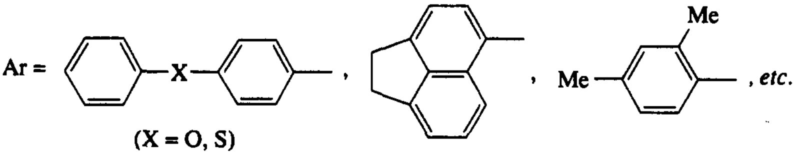
Ar =
X
(X = O, S)
Me
Me
, etc.

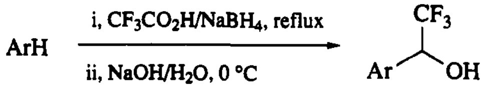
ArH
i, $CF_3CO_2H/NaBH_4$, reflux
ii, $NaOH/H_2O$, 0 °C
$CF_3$
Ar
OH

(53)

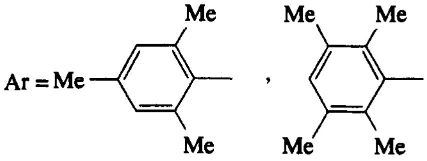
Ar = Me
Me
Me
Me
Me
Me
Me

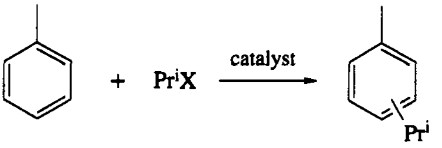
+ $Pr^iX$
catalyst
$Pr^i$

(54)

X = $OSO_2Cl$, $OSO_2F$, $SO_2Ph$, $SO_2Cl$, $OSO_2$-*p*-Tol, OCOCl

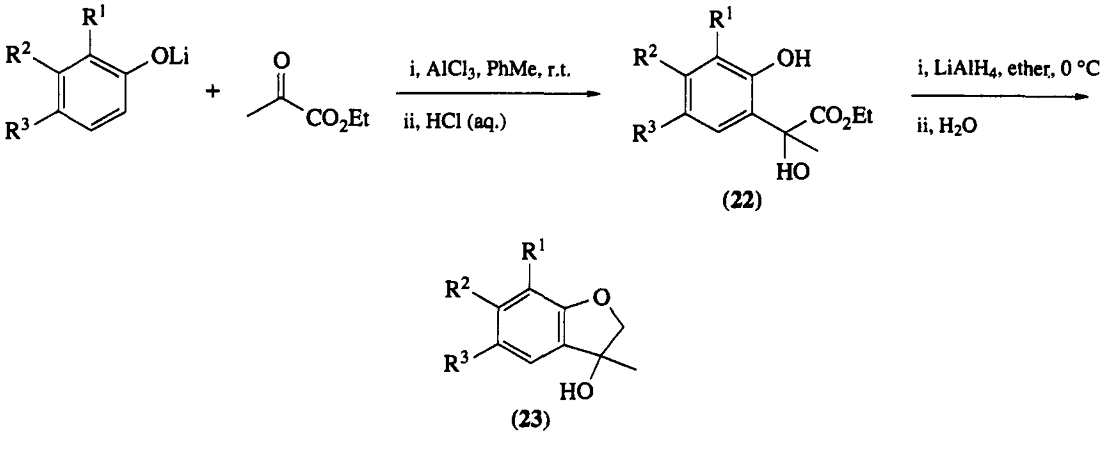
$R^1$
$R^2$
OLi
$R^3$
+
O
$CO_2Et$
i, $AlCl_3$, PhMe, r.t.
ii, HCl (aq.)
$R^1$
$R^2$
OH
$R^3$
$CO_2Et$
HO
i, $LiAlH_4$, ether, 0 °C
ii, $H_2O$
$R^1$
$R^2$
O
$R^3$
HO

**(22)**

**(23)**

**Scheme 6**

Optically active 2-arylalkanoic acid esters (**24**) have been prepared (equation 55)[101] by the Friedel–Crafts alkylation of arenes with optically active esters in the presence of $AlCl_3$. Piccolo and coworkers[102] have also found that alkylation of benzene with optically pure (*S*)-methyl 2-(chlorosulfonyloxy)- or 2-(mesyloxy)-propionate, in the presence of $AlCl_3$, gave (*S*)-methyl 2-phenylpropionate in good chemical (50–80%) and excellent optical yield (>97% *ee*, as determined by rotation), with inversion of configuration at the attacking carbon atom. In view of the ready availability of optically pure lactic acid derivatives, this reaction offers an attractive general method of preparing optically active compounds by further elaboration of the phenyl and ester groups in the alkylated product (**25**; $R^1C^*H(Ar)Y$, $R^1$ = Me; Y = $CO_2Me$, $CO_2Et$).

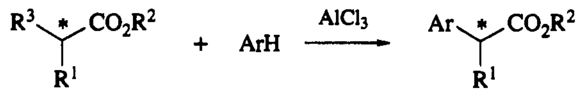

$R^1, R^2$ = alkyl;
$R^3$ = Cl, Br, $ClSO_3$

$R^1, R^2$ = alkyl
**(24)**

(55)

Steroidal alkenol esters have been employed as alkylating agents to introduce aryl groups (equation 56).[103]

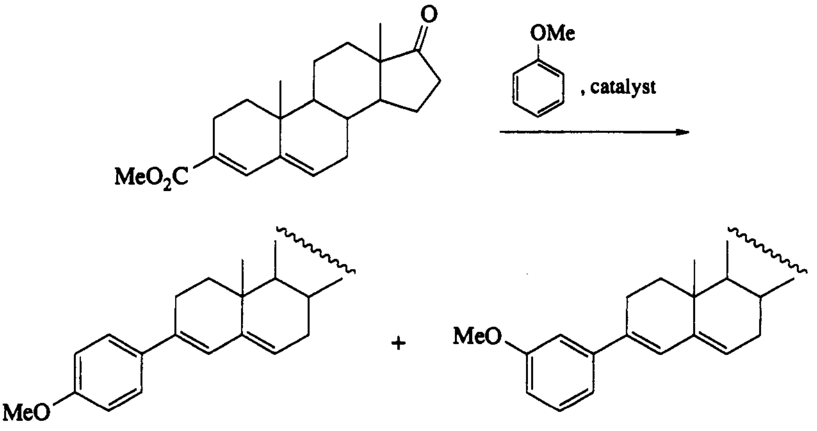

(56)

Examples of Friedel–Crafts alkylations of arenes with acyclic ethers are rare in the literature. With cyclic ethers (epoxides, oxetanes, *etc.*), however, a number of interesting alkylation reactions are known. With epoxides alkylation proceeds with ring opening to give β-hydroxyarylalkanes, which, depending on catalyst type and reaction temperatures, can react further with aromatics to produce 1,2-diarylalkanes. Milstein[104] found that benzene, for example, was alkylated by 1,2-epoxypropane in the presence of $AlCl_3$ to give a 64% yield of 2-phenyl-1-propanol (equation 57); the isomeric 1-phenyl-2-propanol was observed only in trace amounts. This was rationalized by suggesting that the $AlCl_3$–coordinated epoxide complex initially undergoes ring opening to give the most stable ion pair (**26**) before attacking the benzene (equation 58).

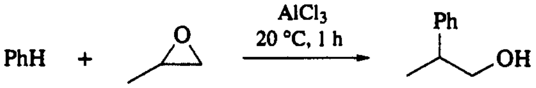

(57)

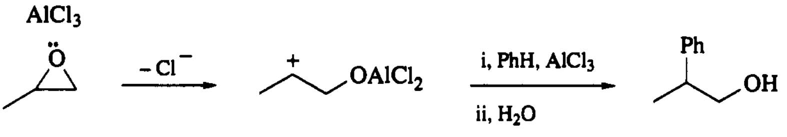

**(26)**

(58)

Suga *et al.*[105] studied the $SnCl_4$- or $AlCl_3$-catalyzed Friedel–Crafts alkylation of benzene with (*R*)-(+)-1,2-epoxybutane (**27**) to investigate the stereochemistry of the ring-opening process. The primary products were (*R*)-(–)-(**28**), with almost 100% optical purity, and (*S*)-(–)-(**29**), with 55–56% optical purity (Scheme 7).

Under the influence of mild acid catalysts, such as $MgBr_2$, $ZnCl_2$ and $BF_3{\cdot}Et_2O$, epoxides are initially isomerized to an aldehyde which then alkylates the arene to afford 1,1-diarylated products (Scheme 8). With strong Lewis acids, however, an $S_N2$-type ring opening of the activated epoxide by the reactive aromatic component occurs to give the normal Friedel–Crafts alkylation product. Thus, in those cases where ring opening of the epoxide gives a more stable secondary or tertiary carbocation, good yields of diarylated products are obtained. Some examples using anisole as the arene are shown in equations (59) and (60).[106]

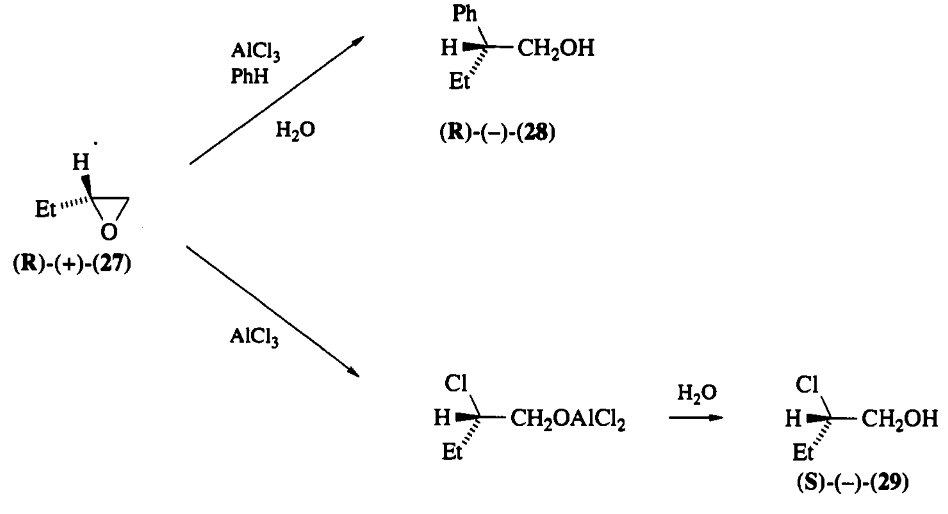
AlCl3
PhH
H2O
AlCl3
(R)-(+)-(27)
(R)-(–)-(28)
H2O
(S)-(–)-(29)

**Scheme 7**

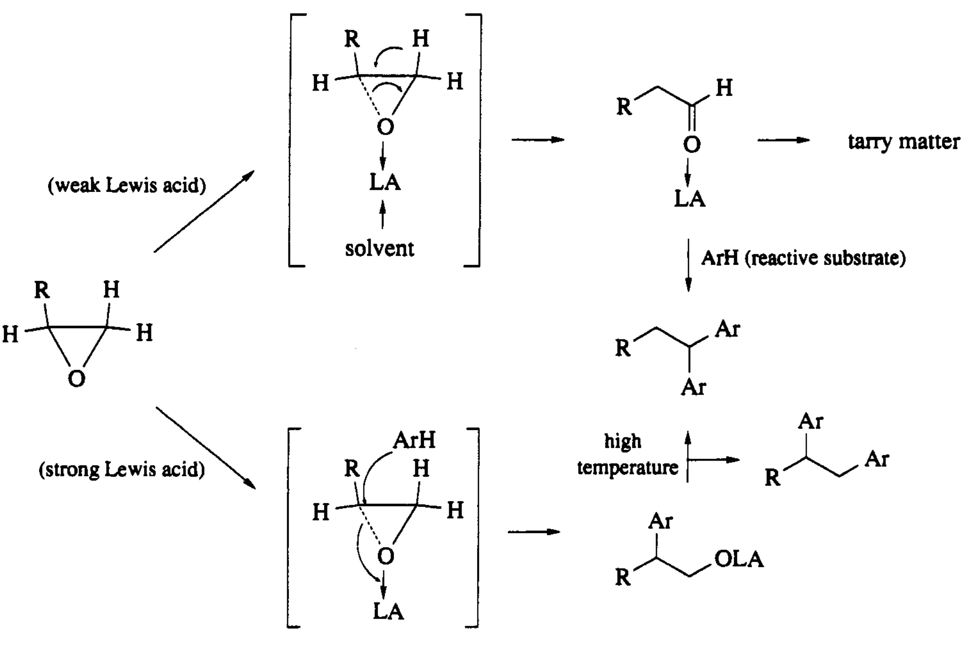
(weak Lewis acid)
(strong Lewis acid)
solvent
tarry matter
ArH (reactive substrate)
high temperature

**Scheme 8**

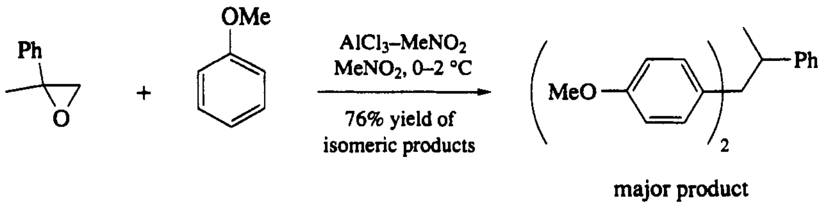
AlCl3–MeNO2
MeNO2, 0–2 °C
76% yield of isomeric products
major product

(59)

The alkylation of arenes by an oxetane affords the carbinol *via* a ring-opening reaction as seen in equation (61).[107] Suga and coworkers[108] have examined the stereochemistry of the ring-opening process by carrying out the alkylations of benzene with (+)-2-methyloxetane in the presence of $AlCl_3$, $SnCl_4$ or $TiCl_4$.

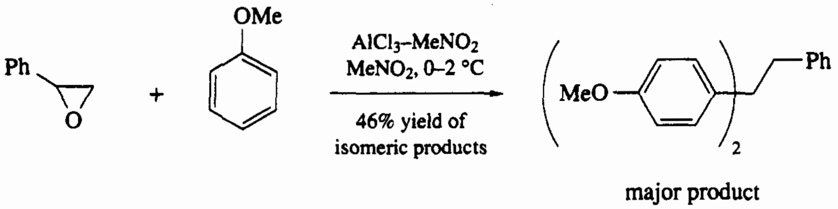
Ph
O
OMe
+
AlCl3–MeNO2
MeNO2, 0–2 °C
46% yield of
isomeric products
MeO
Ph
2
major product

(60)

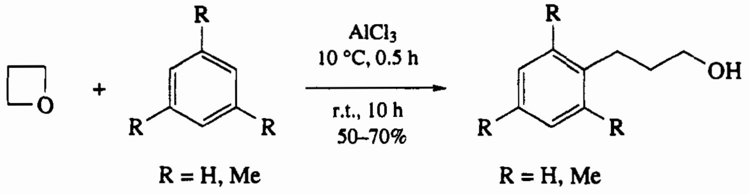
O
+
R
R
R
R = H, Me
AlCl3
10 °C, 0.5 h
r.t., 10 h
50–70%
R
R
R
OH
R = H, Me

(61)

Friedel–Crafts alkylations of arenes with higher cyclic ethers such as tetrahydrofurans and pyrans are often accompanied by many side reactions such as intramolecular alkylation, condensation and further transformations of the initial alkylated product. However, it is possible to obtain one product selectively by choosing the proper reaction conditions. An example is shown in equation (62).[109]

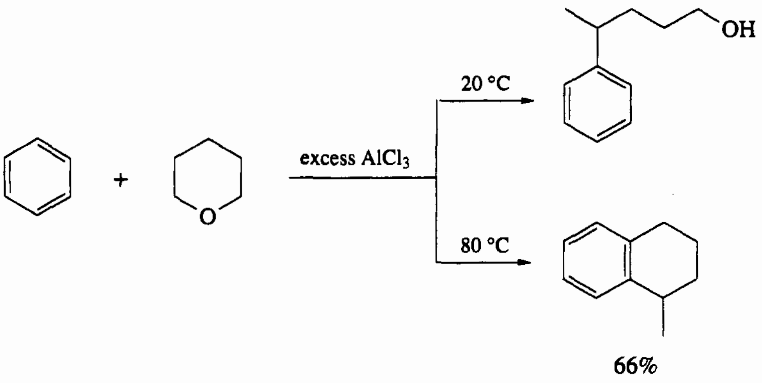
+
O
excess AlCl3
20 °C
OH
80 °C
66%

(62)

The ease with which cyclic ethers alkylate arenes is in the order[110]

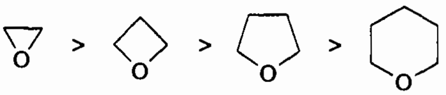

It also decreases with the degree of branching,[111] as in

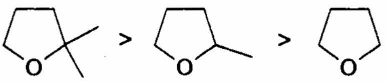

Brauman *et al.*[112] have alkylated benzene with (*S*)-(+)-2-methyltetrahydrofuran to give (*R*)-(–)-4-phenyl-1-pentanol. The reaction occurred with at least 35% inversion of configuration (equation 63). This result has been explained by an $S_N2$-type attack of benzene on a cyclic ion pair such as in (**30**). Studies on stereospecific Friedel–Crafts reactions by Sugita and coworkers[113] have also lent support to the suggestion that stereospecifity might be general for Friedel–Crafts reactions of cyclic compounds.

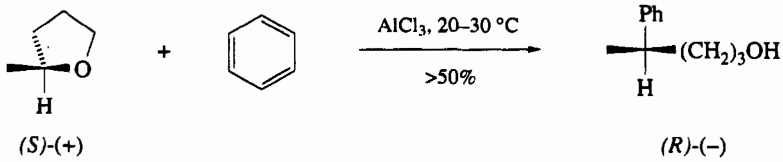
O
H
(S)-(+)
+
AlCl3, 20–30 °C
>50%
Ph
(CH2)3OH
H
(R)-(–)

(63)

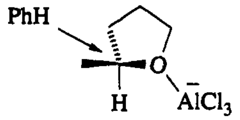
PhH
O
H
AlCl3

**(30)**

Aziridines also are capable of alkylating arenes to form β-arylethylamines. Milstein's work[114] on the alkylation of arenes with 2-methylaziridine revealed the formation of two isomeric products (equation 64). This was explained by the occurrence of two competing pathways, (a) and (b), as shown in Scheme 9.

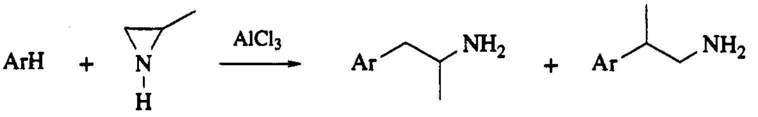
ArH
+
N
H
AlCl3
Ar
NH2
+
Ar
NH2

(64)

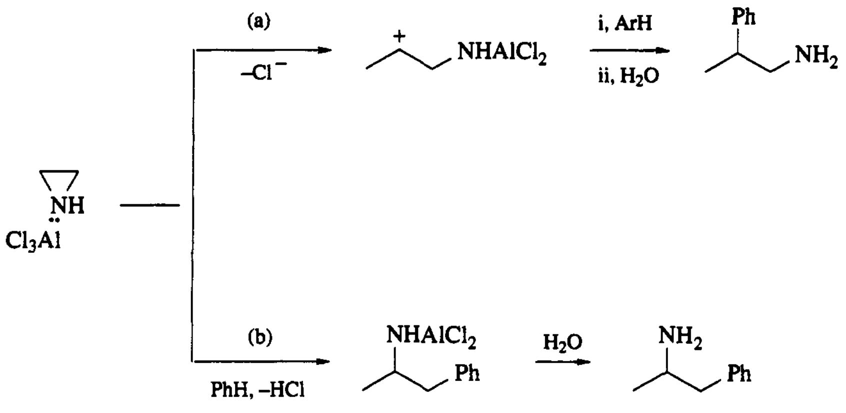
(a)
-Cl⁻
+
NHAlCl2
i, ArH
ii, H2O
Ph
NH2
NH
Cl3Al
(b)
PhH, -HCl
NHAlCl2
Ph
H2O
NH2
Ph

**Scheme 9**

The Friedel–Crafts alkylation of arenes with lactones provides a convenient method for the synthesis of arylalkanoic acids. However, depending on the nature of the arene, catalyst, temperature and reaction time, the resulting arylalkanoic acids can undergo partial or complete cyclization to the corresponding cyclic ketones (Scheme 10). Equations (65) to (68) show examples of Friedel–Crafts alkylations using lactones as the alkylating agents.[115–118]

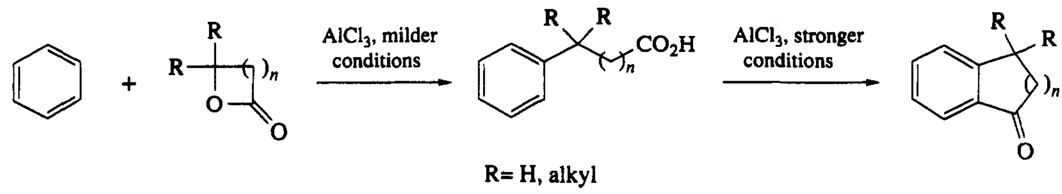
+
R
R
)n
O
O
AlCl3, milder conditions
R
R
CO2H
n
R= H, alkyl
AlCl3, stronger conditions
R
R
)n
O

**Scheme 10**

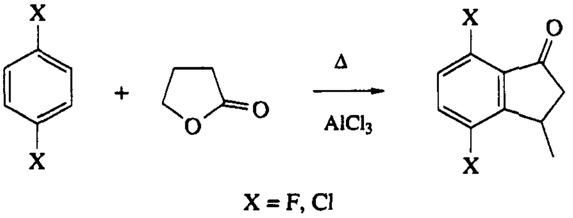
X
X
+
O
O
Δ
AlCl3
X
O
X
X = F, Cl

(ref. 115) (65)

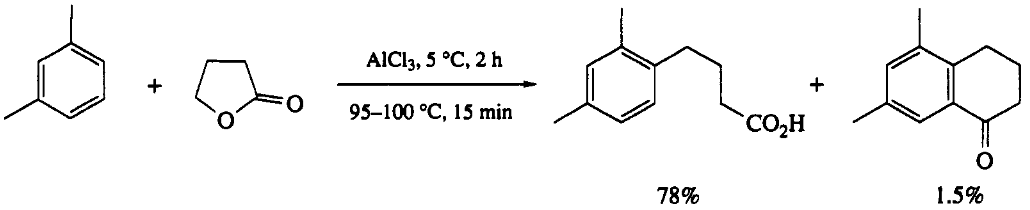
AlCl3, 5 °C, 2 h
95–100 °C, 15 min
CO2H
O
78%
1.5%

(ref. 116) (66)

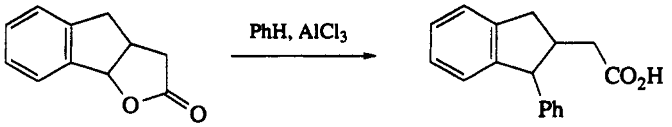
PhH, AlCl3
O
CO2H
Ph

(ref. 117) (67)

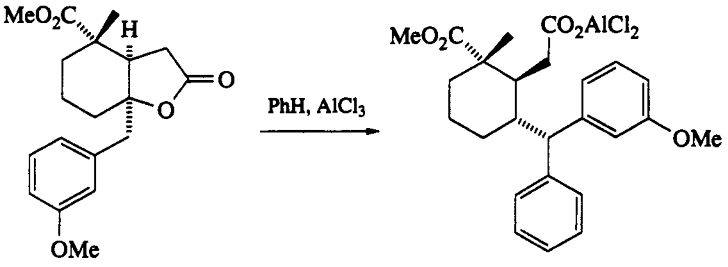
MeO2C
H
O
PhH, AlCl3
OMe
CO2AlCl2
OMe

(ref. 118) (68)

Brauman *et al.*[119] have examined the mechanism of the alkylation of lactones by reacting optically active γ-valerolactone with benzene in the presence of $AlCl_3$. They found the reaction to proceed with nearly 50% net inversion of configuration (equation 69). The mechanism put forth to account for this result is similar to that proposed for the observed stereochemistry of the Friedel–Crafts alkylation of (*S*)-(+)-2-methyltetrahydrofuran[112] (*vide supra*).

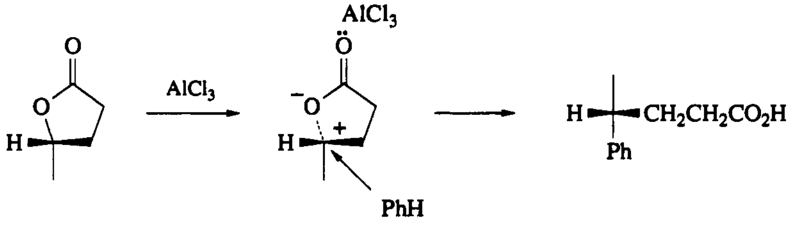
O
O
H
AlCl3
AlCl3
O
O
+
H
PhH
H
CH2CH2CO2H
Ph

(69)

Sultones have been shown to alkylate arenes in the presence of $AlCl_3$ (equation 70)[120] to give arylalkenesulfonates.

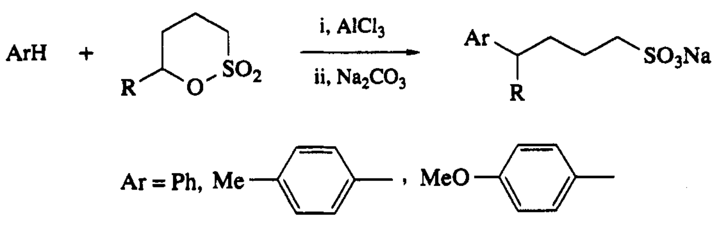
ArH +
R
O
SO2
i, AlCl3
ii, Na2CO3
Ar
SO3Na
R
Ar = Ph, Me
MeO

(70)

## 1.8.3.4 Alkylation with Di- and Poly-functional Alkylating Agents

In 1884, Friedel and Crafts reported that the alkylation of benzene or toluene with dichloromethane in the presence of $AlCl_3$ afforded the corresponding diarylmethanes, besides other products derived from further alkylation and other transformations.[121] The products from the reaction with benzene are shown in equation (71). Subsequent work on the alkylation reactions with toluene, other substituted arenes and naphthalene describes the efforts to understand the formation of a number of alkylated products derived from competing processes, such as isomerization and dealkylation.

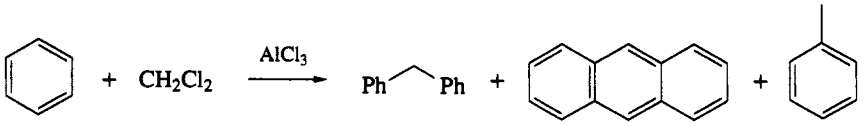

(71)

1,2-Dihaloethanes alkylate arenes under Friedel–Crafts catalysis by Lewis acids to afford 1,2-diarylated ethanes. Dolgov and Larin[122] suggested that the reaction proceeds *via* the intermediate monoarylated haloethane (Scheme 11) which affords the final product *via* a phenonium-type intermediate.

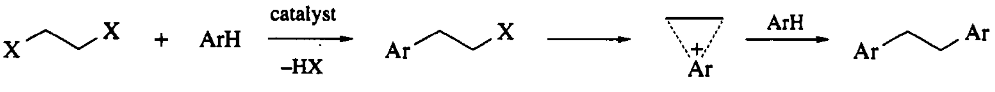

**Scheme 11**

The reaction of 1,2-dihalo-2-phenylethane with arenes in the presence of $TiCl_4$ afforded a number of 1,1-diaryl-2-haloethanes in 40–73% yield (equation 72).[123]

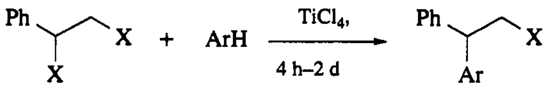

(72)

$X = Cl, Br; Ar = Ph, p\text{-}MeC_6H_4, p\text{-}PhOC_6H_4,$ *etc.*

Friedel–Crafts alkylations with higher dihaloalkanes generally give a mixture of products derived from processes such as isomerization, multiple addition and dehydrogenation (caused by $AlCl_3$), as seen from the examples shown in equations (73)[124] and (74).[125]

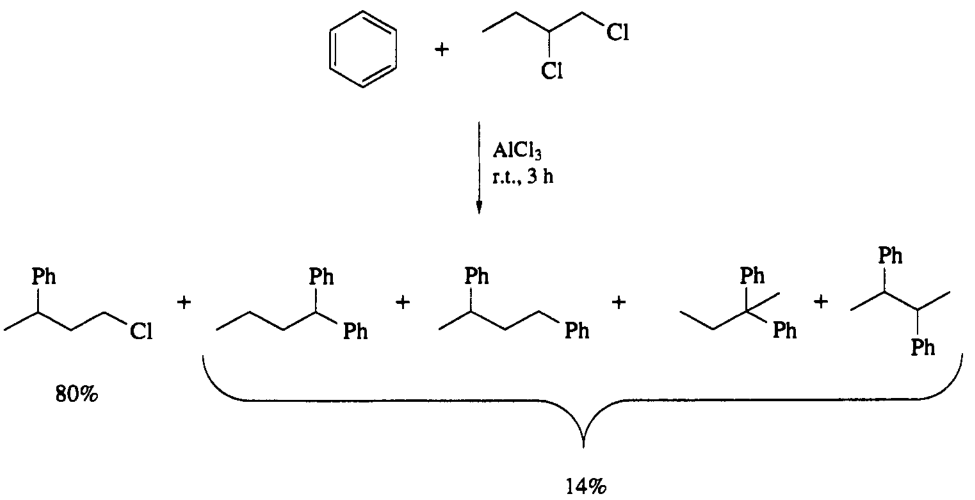

(73)

Ransley[126] has examined in detail the $AlCl_3$-catalyzed alkylation of benzene with a series of α,ω-dichloroalkanes, and suggested possible mechanisms for the formation of the various phenylated products. With 2,4-dihalohexanes as the alkylating agents for benzene, Gelin *et al.*[127] found that about 90% of the products consisted of 1,4-dimethyltetralin and compounds derived from it. The alkylation of 1,3-dimethylbenzene by 2,5-dichloro-2,5-dimethylhexane in the presence of $AlCl_3$ has been reported[128] to give a moderate yield of the tetrahydronaphthalene derivatives, as in equation (75).

Stereospecific (ranging from 15 to 60%) alkylation of benzene with optically active 1,2-, 1,3-, 1,4- and 1,5-dihaloalkanes in the presence of $AlCl_3$ has also been reported.[129] In the case of 1,3- and 1,5-dihaloal-

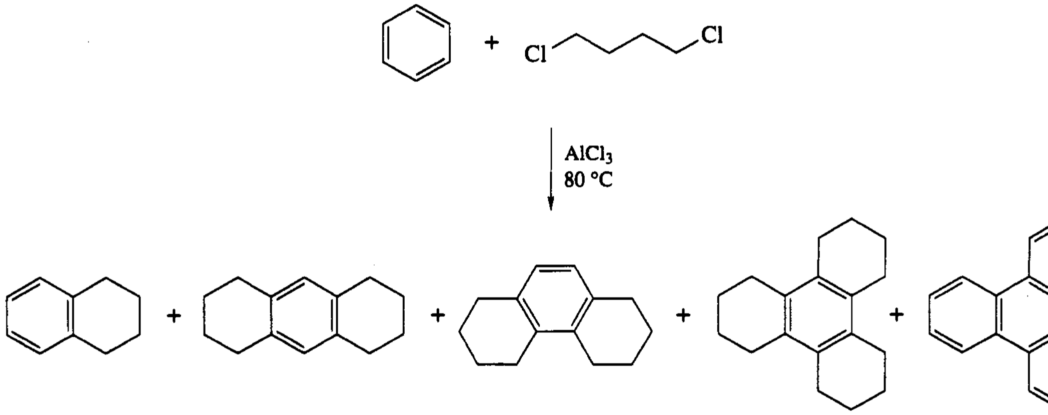

(74)

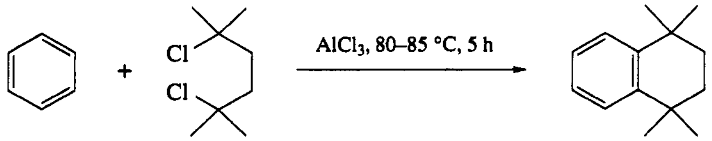

(75)

kanes, alkylation with inversion of configuration at the secondary halogen positions occurred predominantly.

Branched dihaloalkanes in general give a mixture of products resulting from processes such as isomerization and cycloalkylation. These processes in turn depend on the structure of the dihaloalkanes, the strength of the catalyst and the severity of the reaction conditions.

Other polyhaloalkanes, such as dichloromethane, chloroform and carbon tetrachloride, have also been used as alkylating agents. The examples in equations (76) to (79) serve to illustrate this aspect.[130–132]

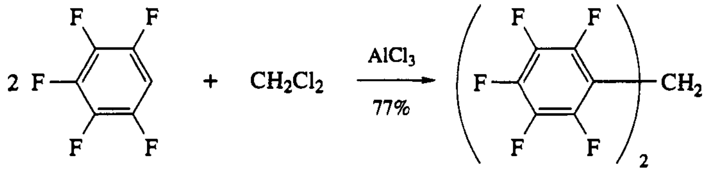

(ref. 130) (76)

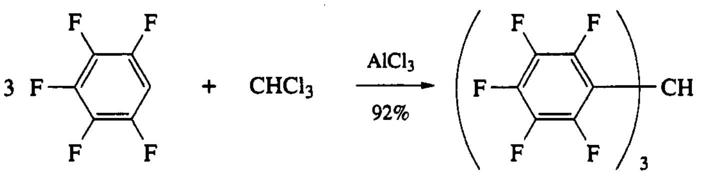

(ref. 130) (77)

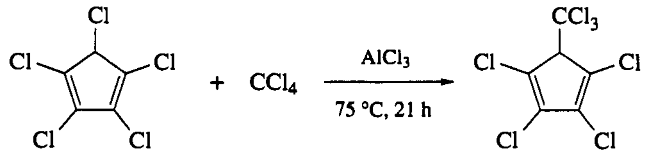

(ref. 131) (78)

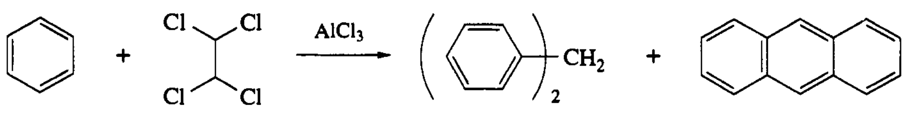

(ref. 132) (79)

### 1.8.3.5 Haloalkylation

Haloalkylation of arenes by unsymmetrical or mixed halides occurs when one of the halogen atoms has a greater reactivity towards the Lewis acid catalyst. It is then possible to isolate the comparatively less reactive haloalkylated products. An example is the reaction of chloroform with benzene in the presence of $AlCl_3$. The major product (90%) is dichlorodiphenylmethane (equation 80).[133]

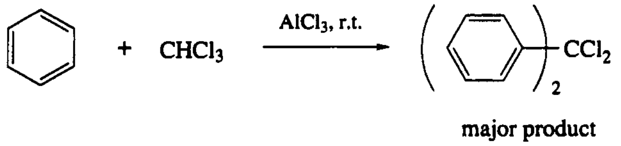

(80)

Haloalkylations have also been carried out with branched, unsymmetrical simple di- and poly-halides, straight-chain, unsymmetrical simple di- and poly-halides, and mixed di- and poly-halides. Schmerling *et al.*[133] have studied the Friedel–Crafts reactions of benzene with 1,3-dichloro-3-methylbutane in the presence of $AlCl_3$ and obtained a 28–29% yield of 1-chloro-3-methyl-3-phenylbutane (equation 81).

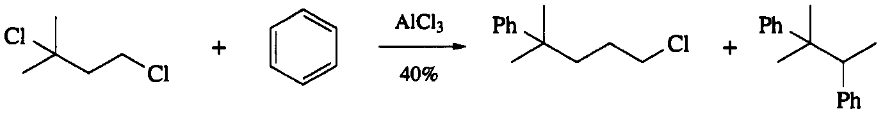

(81)

In the case of dihalides containing two different halogens, alkylation with an arene is influenced by factors such as reactivity and steric accessibility of the halogens with respect to the Lewis acid catalyst. Bugrova and Tsukervanik[134] have demonstrated this by carrying out the four reactions in equations (82) to (85). Higher reactivity of Br over Cl is seen in equations (82) and (83), and steric effects are demonstrated in equations (84) and (85).

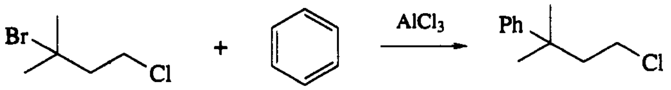

(82)

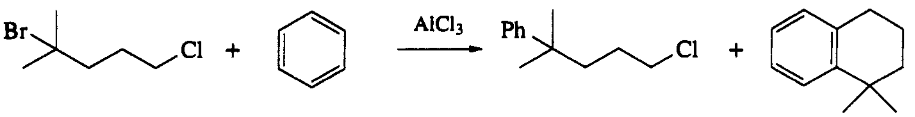

(83)

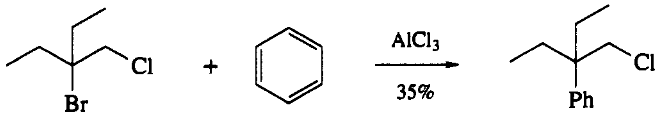

(84)

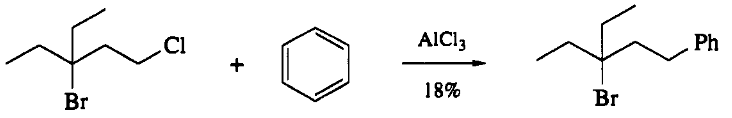

(85)

Olah and Kuhn[135] found that fluorochloro-, fluorobromo- and fluoroiodo-alkanes are effective chloro-, bromo- and iodo-alkylating agents, respectively, in Friedel–Crafts alkylations of arenes in the presence of boron halide catalysts (equation 86). Boron trihalides catalyze reactions of only the C—F bonds, but not of the C—Cl, C—Br or C—I bonds. The order of reactivity of the catalysts was found to be $BI_3 > BBr_3 > BCl_3 > BF_3$, and that of the carbon–halogen bonds C—F > C—Cl > C—Br > C—I.

$$\mathrm{ArH} + \mathrm{F(CH_2)}_n\mathrm{X} \xrightarrow{\mathrm{BX_3}} \mathrm{Ar(CH_2)}_n\mathrm{X} \qquad (86)$$

$n > 1$; X = Cl, Br, I

Allyl halides have been used to effect selective haloalkylations catalyzed by proton acids. For example, 3-chloropropylene reacts with benzene and toluene in the presence of $H_2SO_4$ to give haloalkylated products almost exclusively (equation 87).[136] The same result is obtained when $ZnCl_2$ is used as the catalyst.[137]

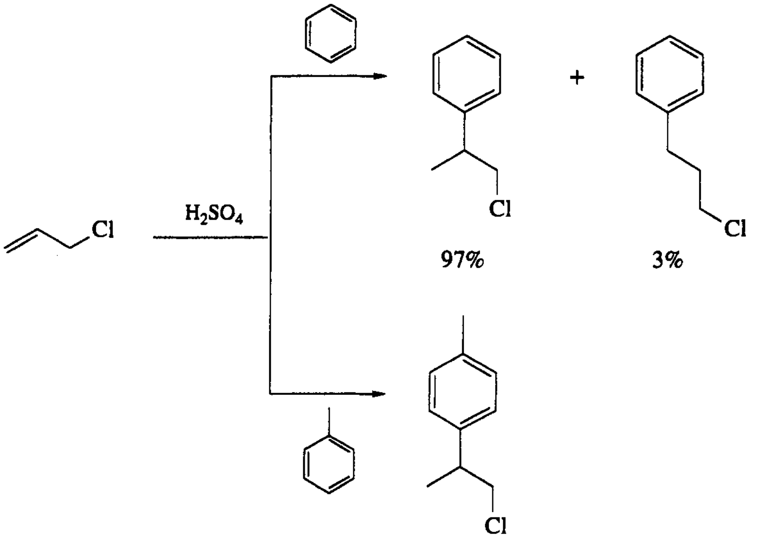

(87)

Selective haloalkylation of aromatic compounds has also been achieved by employing alkyl haloalkyl ethers as the haloalkylating agents, as seen from equations (88)[138] and (89).[139] However, the use of chloromethyl ethers in chloromethylation (equation 89) is discouraged due to the carcinogenic nature of the ether substrate. As an alternative, chloromethylation reactions can also be carried out using paraformaldehyde–HCl in the presence of $ZnCl_2$ or $SnCl_4$ as catalyst.[2]

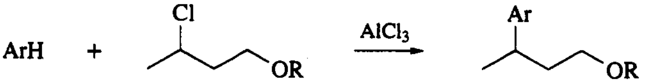

(88)

Ar = phenyl or alkylated phenyl; R = alkyl

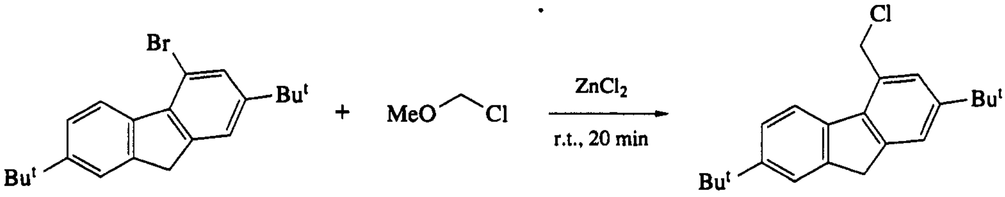

(89)

Unsaturated alkyl halides, alcohols and ethers can also act as alkylating agents to give products derived by alkylation at one or more reactive sites. Tsukervanik and Yuldashev[140] examined the reaction of vinyl chloride with toluene and anisole in the presence of $AlCl_3$ by varying the ratio of reactants. For example, with anisole (equation 90) two products were formed. The diarylated product resulted from reaction of anisole with both reactive centers in vinyl chloride.

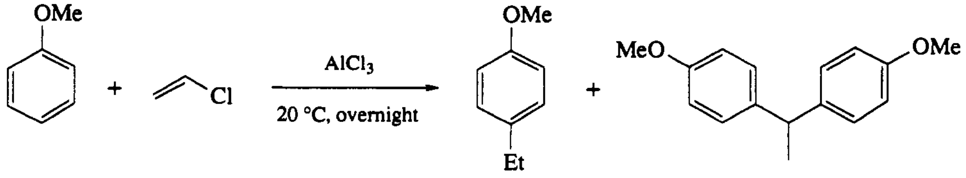

(90)

The nature of the catalyst also influences the course of the reaction. α-Substituted vinyl halides react more selectively with arenes to give diarylated products.

Allyl alcohols and ethers also react with arenes in the presence of Lewis and Brønsted acid catalysts to give alkylated products. The nature of the product depends upon the nature of the Lewis acid. However, in most cases the products are mixtures of regioisomeric allylated arenes.

Dienes also can alkylate arenes to give products which are generally cyclic. For example, isoprene reacts with 1,2,4-trimethylbenzene in the presence of $H_2SO_4$ to give an indane derivative (equation 91).[141] A large number of phenols have been used for alkylations with dienes. The products are either allylated phenols, or products derived by further ring closure of the phenolic oxygen with the side chain derived from the diene.

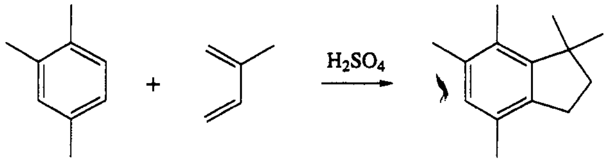

(91)

### 1.8.3.6 Alkylation with Alkanes

Friedel–Crafts alkylation of arenes with alkanes was studied extensively by Olah and coworkers[142a] as part of the general investigation of electrophilic reactions at single bonds. Benzene was alkylated with $C_1$–$C_5$ alkanes, alkane–alkene, and alkane–alkylbenzene mixtures in the presence of anhydrous HF–$SbF_5$ ($HSbF_6$). Products arising from alkylation by the alkanes as well as side reactions, such as isomerization and disproportionation, were observed. In the presence of added alkene, greater amounts of both alkane and alkene alkylation products resulted. When a *t*-alkylbenzene was present, products deriving from both transalkylation and alkylation by the alkanes were obtained. Kröger and coworkers[142b] studied the alkylation of benzene with cyclohexane in the presence of catalysts such as HBr–$AlBr_3$, HCl–$AlCl_3$ and HF–$SbF_5$, with isobutane as the promoter, under varying temperatures and reaction times. Four representative groups of hydrocarbons were found including cycloalkylbenzenes, substituted indanes or tetralins, $C_1$–$C_6$ alkylbenzenes and isomeric dicycloalkyls. Their formation was explained by a competition between alkylation (with or without isomerization), ring fission with cycloalkylation or fragmentation, and self-alkylation. Phenylcycloalkyl cations and phenylalkyl cations were proposed as intermediates. Mechanisms for the formation of complex product mixtures were also discussed.

Miethchen *et al.*[143] have carried out ultrasound-induced alkylation of benzene with 2,2,4-trimethylpentane in the presence of various highly acidic catalysts such as $CF_3SO_3H$–$SbF_5$, $H[B(SO_3CF_3)_4]$, $AlBr_3$, HF–$TaF_5$, HF–$NbF_5$ and HF–$TiF_4$ (equation 92). The effect of temperature and duration of the reaction on the yield and composition of *t*-butylbenzene and di-*t*-butylbenzenes was also determined.

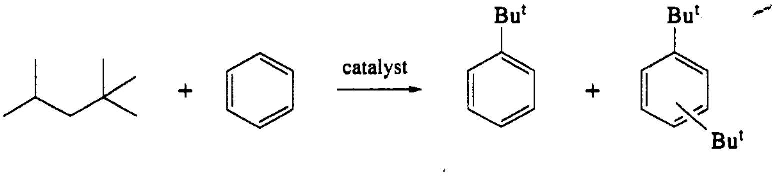

(92)

Laszlo and coworkers[144] achieved the direct arylation of adamantane by employing $FeCl_3$-doped K10 montmorillonite (equation 93). Depending upon the amounts of adamantane, $FeCl_3$, the catalyst and the reaction time, varying proportions of mono- and di-arylated adamantanes were obtained. The results were taken to support the intermediacy of a 1-adamantyl cation.

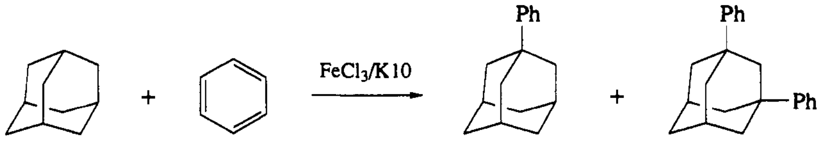

(93)

### 1.8.3.7 Cycloalkylation

A Friedel–Crafts cycloalkylation reaction occurs intramolecularly when an aryl-substituted monofunctional compound cyclizes to attach a new ring to the aromatic nucleus. In many instances, this process occurs during the course of the reaction between a difunctional alkylating agent and an aromatic compound — the intermediate arylated monofunctional compound subsequently undergoes cycloalkylation. However, only those cycloalkylation reactions involving intramolecular ring closures will be discussed at length here.

Arylalkyl halides undergo cycloalkylation reactions in the presence of a variety of Lewis acids. Depending upon the nature of the Lewis acid, varying amounts of cycloalkylated and other products can be obtained. Equations (94) to (96) show some cycloalkylation reactions of arylhaloalkanes.[145]

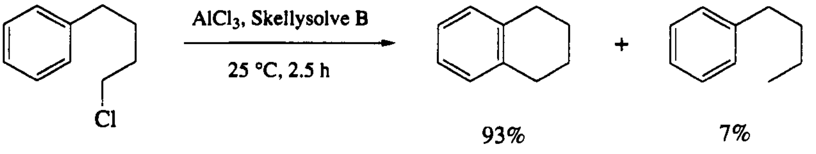
AlCl3, Skellysolve B
25 °C, 2.5 h
Cl
+
93%
7%

(94)

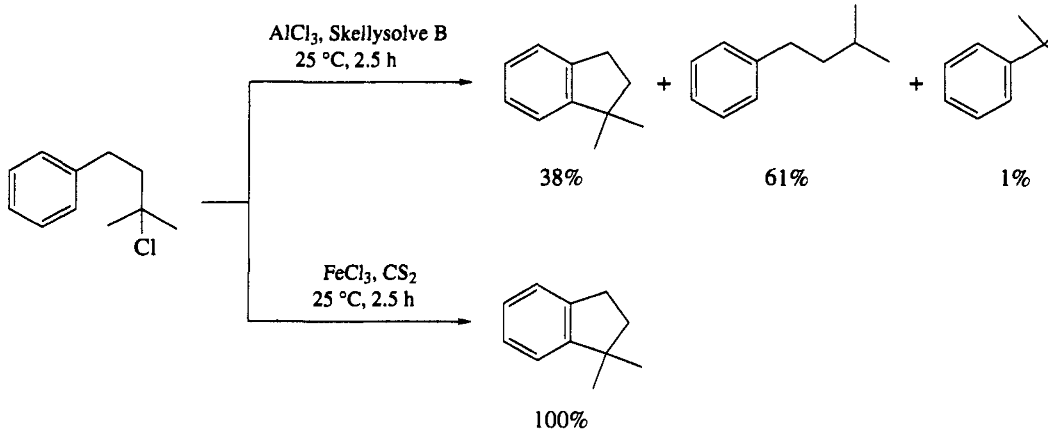
AlCl3, Skellysolve B
25 °C, 2.5 h
Cl
+
+
38%
61%
1%
FeCl3, CS2
25 °C, 2.5 h
100%

(95)

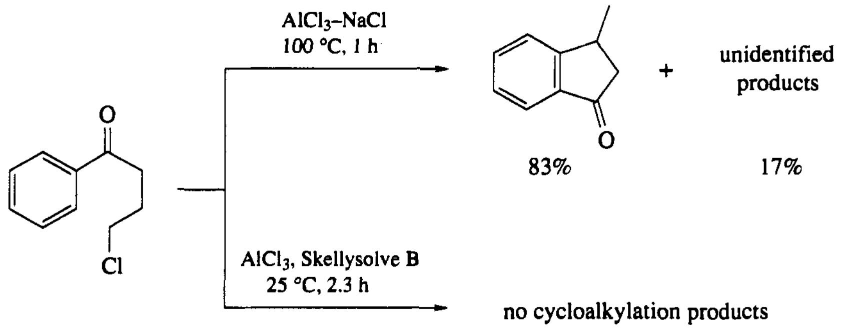
AlCl3–NaCl
100 °C, 1 h
O
Cl
+
unidentified
products
O
83%
17%
AlCl3, Skellysolve B
25 °C, 2.3 h
no cycloalkylation products

(96)

Yang and Young[146] have observed a novel Friedel–Crafts metallocyclization of halomethyl(arylphosphine)platinum(II) complexes (**30**) in the presence of AgBF$_4$ and a triarylphosphine to afford cationic metallacyclic species (**32**; equation 97).

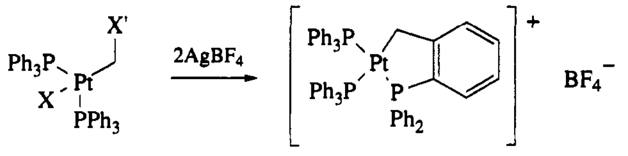
X'
Ph3P
Pt
X
PPh3
2AgBF4
Ph3P
Pt
Ph3P
P
Ph2
+
BF4 −

(97)

X = X' = I
X = I or Br; X' = Cl

**(32)**

Cycloalkylations with primary and secondary phenylalkyl chlorides are often accompanied by rearrangements. The ease of formation of a six-membered ring (tetralin derivative) is much greater than that of a five-membered ring (indane derivative), based on entropy and strain factors. Khalaf and Roberts[147] have performed stereochemical studies on cycloalkylation reactions to determine the effect of stereochemistry and steric factors in the formation of six-membered rings.

Aryl esters such as those of α-halopropionic and α-halobutyric acids undergo cycloalkylation reactions, probably *via* preliminary Fries rearrangement to β-halohydroxy ketones, giving the corresponding substituted indanones (equation 98).[148]

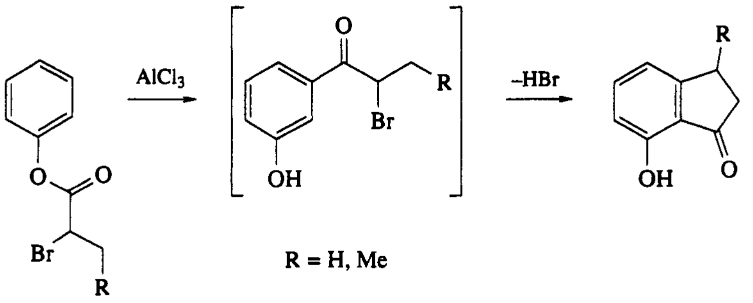

(98)

Similarly, arylalkylamides, haloalkylarylamines, haloalkylaryl ketones and haloalkyl ethers undergo Friedel–Crafts cycloalkylation to give six- or five-membered ring closure products. Representative examples of these reactions are shown in equations (99) to (103).[150–154] An excellent review by Bradsher[149] on the cycloalkylation of arylcarbonyl compounds is available.

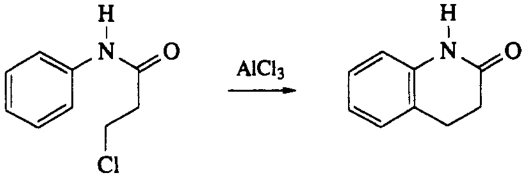

(ref. 150) (99)

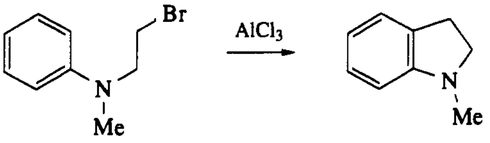

(ref. 151) (100)

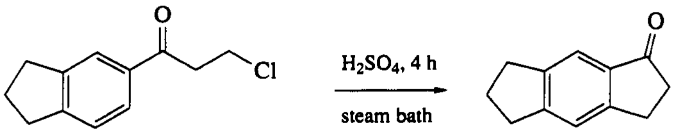

(ref. 152) (101)

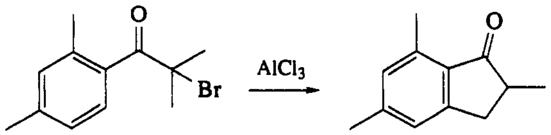

(ref. 153) (102)

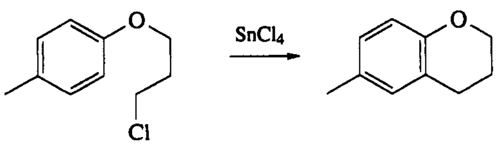

(ref. 154) (103)

Charpentier-Morize and coworkers[155] have developed conditions for the cycloalkylation of γ-aryl-α-trifluoromethyl ketones selectively to either the cycloalkene (33) or the cycloalkyl chloride (34; Scheme 12) by varying the catalyst.

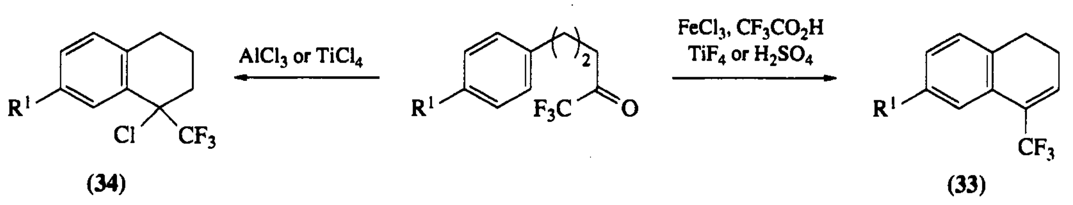

**Scheme 12**

Cycloalkylations of arylalkanols and related systems are very well known in the literature. Many of the earlier examples were fraught with ambiguities in terms of product identification. However, Khalaf and Roberts[156] have carefully investigated an extensive series of variously substituted arylalkanols to help clear the ambiguities and provide more insight into the mechanism. Some examples from their study are shown in equations (104) to (106).

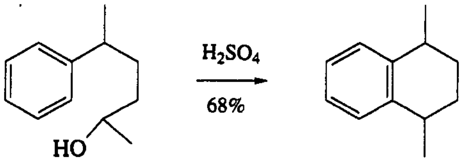

(104)

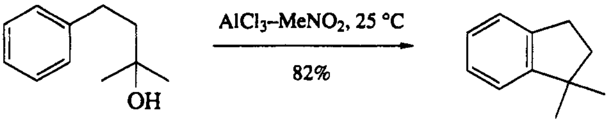

(105)

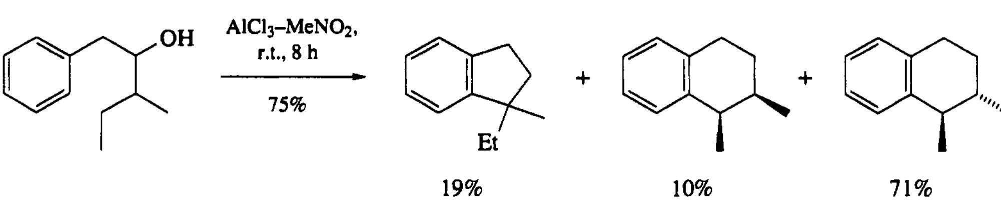

(106)

The cycloalkylation reactions of suitable arylalkyl carbinols leading to tricyclic diterpenoids have been examined for their synthetic and mechanistic significance,[157] and the syntheses of some octahydrophenanthrenes, such as in equation (107), have been reported.

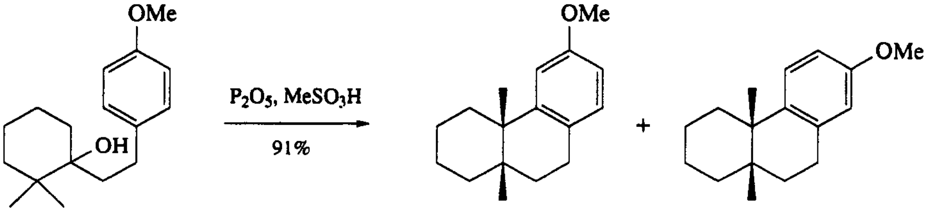

(107)

Khalaf and coworkers[158] have described a facile synthesis of substituted acenaphthenes (equation 108), and Sharma *et al.*[159] have reported a synthesis of the precursor for 8-methylbenzo[*j*]fluoranthene using the cycloalkylation of an arylalkylcarbinol precursor (equation 109).

Khalaf and coworkers[160] recently reported an interesting case of carbonyl retardation of cycloalkylation of the enone (**35**) in the presence of AlCl$_3$. The isomeric enone (**36**), however, reacted to give the perinaphthenones (**37**) and (**38**) (Scheme 13). Numerous other examples of cycloalkylation reactions of aryl-substituted enones exist in the literature.

The cycloalkylations of arylalkyl epoxides were studied in detail by Taylor and coworkers,[161] in view of their applications[162] in natural product synthesis. Equation (110)[161a] shows an example of this reaction.

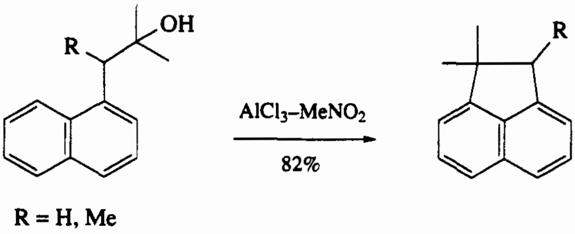
OH
R
AlCl3–MeNO2
82%
R
R = H, Me

(108)

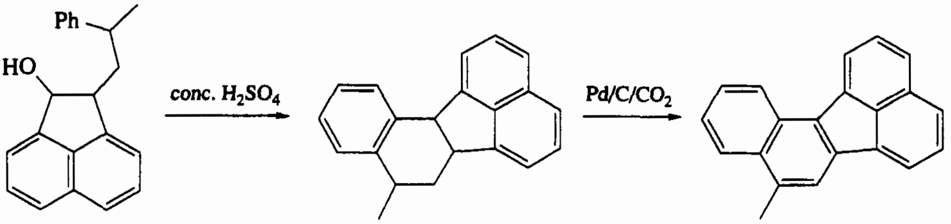
Ph
HO
conc. H2SO4
Pd/C/CO2

(109)

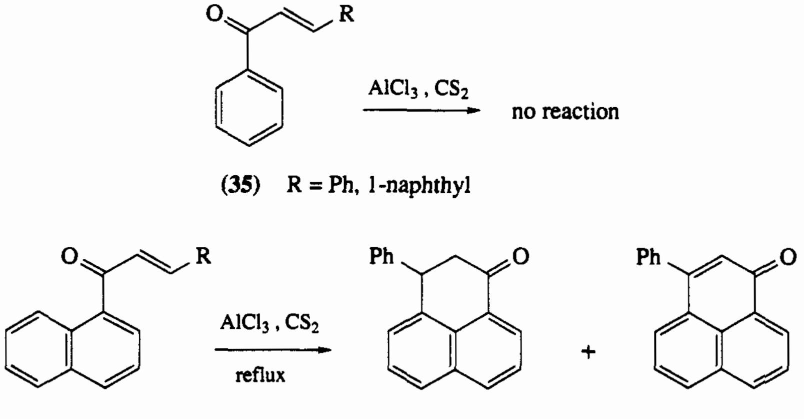
O
R
AlCl3, CS2
no reaction
O
R
AlCl3, CS2
reflux
Ph
O
+
Ph
O

**(35)** R = Ph, 1-naphthyl

**(36)** R = Ph **(37)** **(38)**

**Scheme 13**

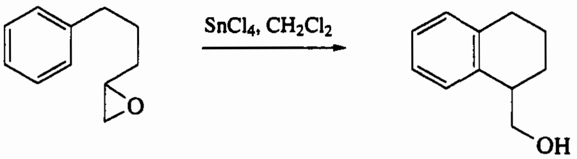
O
SnCl4, CH2Cl2
OH

(110)

Superacids such as HF–SbF$_5$ have been used to cyclize alkyl phenyl ketones to the corresponding tetralone derivatives in good yield, as shown by the example in equation (111).[163]

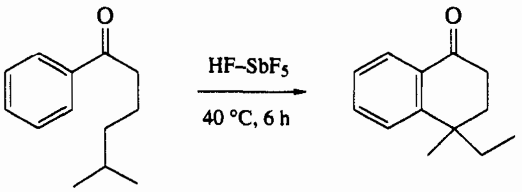
O
HF–SbF5
40 °C, 6 h
O

(111)

Multiple intramolecular ring closures of aryl-substituted unsaturated long chain alcohols, acids, acid chlorides and ethers in the presence of Friedel–Crafts catalysts have been extensively employed to synthesize polynuclear hydroaromatic hydrocarbons and polycyclic ketones. This is illustrated by two examples shown in equations (112)[164] and (113).[165] The application of stereospecific cycloalkylations in approaching the synthesis of complex organic molecules has been reviewed by Barclay.[166]

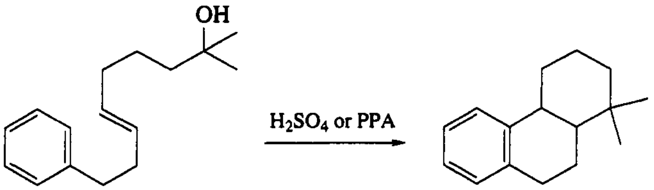

(112)

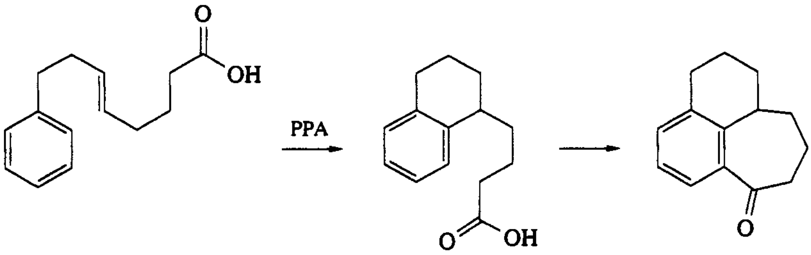

(113)

As pointed out earlier, cycloalkylation reactions can also result from the reaction of arenes with bifunctional alkylating agents or in cases where bifunctional intermediates are involved. An example of the former is shown in equation (114),[167] where a chiral, lactone-substituted alkene cyclizes with the arene to produce a chiral tetrahydronaphthalene derivative.

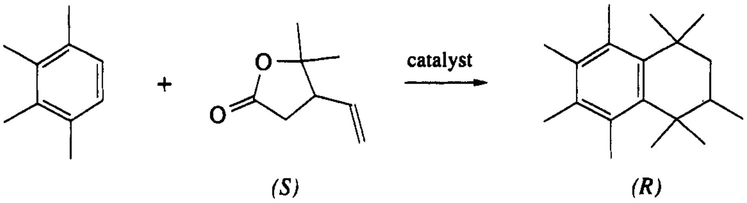

(114)

### 1.8.3.8 Transalkylation, Isomerization, Disproportionation and Dealkylation

The general process of transfer of alkyl groups between aromatic rings is called transalkylation. When an alkylbenzene is converted into a mixture of benzene and dialkylbenzene which may further afford a trialkylbenzene, the process is termed disproportionation. Dealkylation of an alkylbenzene is a process where an alkyl group is removed to form the corresponding alkane. The isomerization of di- or polyalkylbenzenes refers to the process where the alkyl groups on the ring change their relative orientations. Such a process can occur either in an inter- or an intra-molecular fashion depending on the nature of the alkyl groups on the ring.

Transalkylation of alkylbenzenes, polyalkylbenzenes and other arenes can be brought about by a variety of catalysts including Lewis acids, Brønsted acids and various zeolites and silicates with or without being doped with various transition metals or their oxides. There has been a particularly explosive growth in the volume of literature pertaining to the use of various natural and modified zeolites. Recent developments include the study and applications of shape-selective catalysis by zeolites. Much of the work is patented, and largely applies to industrial processes.

Friedel–Crafts alkylation reactions are, in general, accompanied by isomerization processes. Olah *et al.*[168] reported the results of the water-promoted, $AlCl_3$-catalyzed isomerization of *o*-, *m*- and *p*-di-*t*-butylbenzene. No *ortho* isomer was present in the equilibrium mixture. The isomerization of *o*-di-*t*-butylbenzene was very rapid largely due to relief of steric strain. In these and other related sterically hindered arenes, intramolecular isomerization and not dealkylation was observed. Isomerization of di- and mono-methylnaphthalenes, catalyzed by $HF–BF_3$, was also reported.[169] Isomerization of *n*-alkyltoluenes and -xylenes, catalyzed by $AlCl_3$ at room temperature, afforded chiefly *m*-*n*-alkyltoluenes and *m*-*n*-alkylxylenes, respectively.[170] The process leading to the *meta* isomer has a lower energy than the other processes.

Due to the greater industrial importance of benzene and xylenes than toluene, a large number of studies have concentrated on the transalkylation and disproportionation of these two arenes.

Camacho *et al.*[171] have found that during the alkylation of benzene with ethylene in the presence of $AlCl_3$ as the catalyst, both alkylation and transalkylation (of the produced ethylbenzene) occur simultaneously. They also found that the ethylene absorption rate was almost constant when the concentrations of polyalkylates higher than diethylbenzene (formed as in equation 115) were negligible.

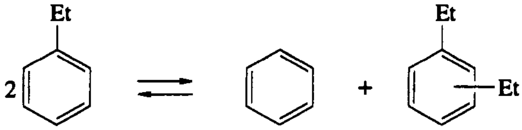

(115)

Among alkylarenes, methylarenes are unique in that they may undergo intramolecular isomerizations without any observable transalkylations. The other alkylarenes such as ethyl-, *n*-propyl- and *n*-butyl-benzenes, however, undergo isomerization and disproportionation reactions without rearrangements in the alkyl side chains. The mobilities of the alkyl groups in alkylbenzenes were measured using $^{14}$C-labeling techniques,[172] and showed the ethyl group to have higher mobility than other *n*-alkyl groups. However, recent studies[173] on the transalkylations of *p*-ethylalkylbenzenes with $^{14}$C-labeled benzene, using $AlBr_3$ as catalyst, revealed no marked difference in the mobilities of the ethyl and the other alkyl groups. Reactivity–selectivity relationships in the transalkylation of monoalkylbenzenes revealed an inverse sense for electrophilic reagents.[174] The mechanism and product distribution during the transalkylations of toluene[175] and alkyl and dialkylarenes[176] catalyzed by ZSM-5 zeolites have been discussed. The significance of shape-selective catalysis occurring in these processes was also pointed out. Again, it must be emphasized that ZSM-5 exhibits high *para* selectivity, and this property has been utilized for the production of aromatics such as *p*-xylene and *p*-ethyltoluene.

Buchanan *et al.*[177] conducted model studies on the hydrocracking of coal by studying in detail the action of $SbCl_3$ melts with (and in some cases without) $AlCl_3$ on α,ω-diphenylalkanes. They observed selective $sp^2$–$sp^3$ bond cleavage for the four classes of diphenylalkanes studied, as shown in equations (116) to (118). Notably, 1,3-diphenylpropane and 1,4-diphenylbutane gave only the indan and tetralin derivatives, respectively.

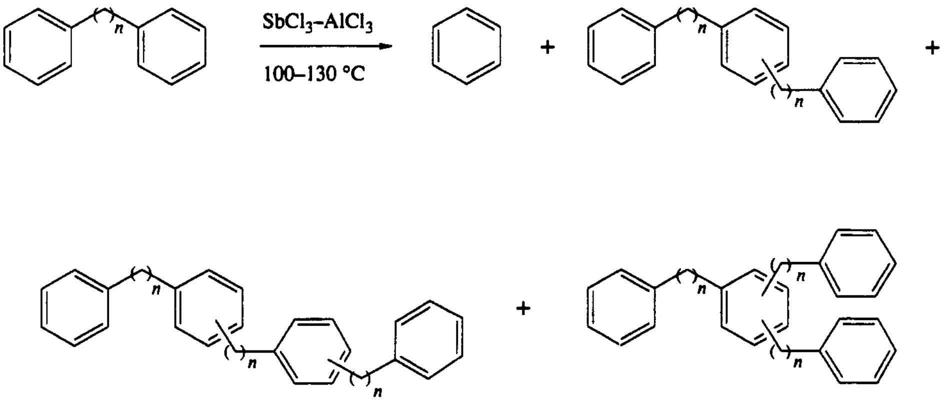

(116)

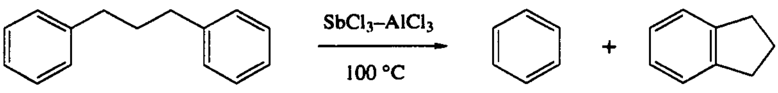

(117)

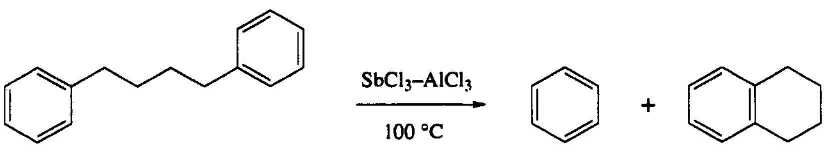

(118)

Besides the transarylalkylation reactions described above (equation 116), debenzhydrylation and transbenzhydrylation reactions are also well known, and these have been extensively reviewed.[178] Applications of the benzhydryl group as a protective group have also been discussed.

Transalkylation reactions of simple aromatics such as benzene and toluene with various coals, have proved to be a valuable means of investigating the composition and structural features of coal.[179]

Wu and Leu,[180] and Bursian *et al.*[181] have carried out disproportionation and transalkylation of toluene with pseudocumene, using various modifications of mordenite zeolite catalysts. The disproportionation of *o*- and *p*-cresol, and the transmethylation between isomeric xylenols and phenol have been examined using a chromia–alumina catalyst.[182] It was found that *p*-cresol underwent disproportionation more readily than *o*-cresol, whereas *m*-cresol did not undergo this reaction. Also 2,6-, 2,4- and 3,4-xylenols underwent transalkylation reactions with phenol, whereas 3,5-xylenol did not. Mechanistic interpretations for these observations were also given. Transalkylation of phenol with ethyl- and isopropyl-benzene and ethyltoluene has also been reported.[183]

Trans-*t*-butylation and de-*t*-butylation reactions are facile processes, and form the basis of many applications of the *t*-butyl group as a positional protective group. This aspect was well reviewed by Tashiro,[88] and is also discussed in Section 1.8.3.2. Tashiro and coworkers[184] have more recently applied the trans-*t*-butylation and de-*t*-butylation reactions to prepare metacyclophanes (**39**) and related compounds.

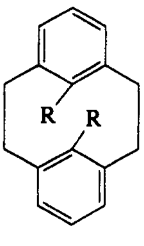

(**39**) R = Me, OH, F

Olah *et al.*[185] showed Nafion-H to be a very efficient de-*t*-butylation agent for aromatic compounds, and Rosevear and Wilshire[186] have applied the trans-*t*-butylation reaction to the synthesis of a variety of ultraviolet absorbers of the general structure (**40**), as shown in Scheme 14.

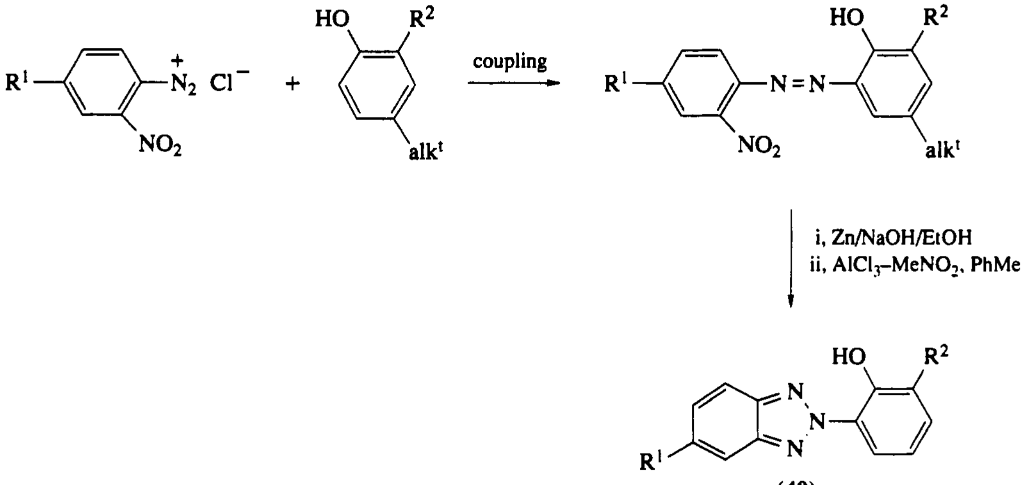

(**40**)

**Scheme 14**

Transbenzylation reactions are also used on occasion for deprotection as seen from the reaction shown in equation (119).[187]

In 1937, Ipatieff and Pines[188] found that the ease of dealkylation of alkylbenzenes in the presence of $AlCl_3$ at 65–80 °C to give the corresponding alkane decreased in the order of the side chains: *t*-butyl > *s*-butyl > isopropyl. Ethyl and methyl groups were not cleaved.

From their studies on dealkylation of alkylbenzenes with $AlCl_3$ at 100 °C, Roberts *et al.*[189] found that, in general, the catalyst and experimental conditions required to produce dealkylation are forceful enough to effect several other reactions, such as disproportionation, isomerization, rearrangement of the side chain and fragmentation. The latter refers to a process in which the alkylbenzene affords alkanes and alkylbenzenes with fewer carbons than those in the original alkyl side chain. Formation of alkanes in the dealkylation process can take place even in the absence of an added hydride donor agent. In this case, a second molecule of the alkylbenzene acts as the hydride donor.

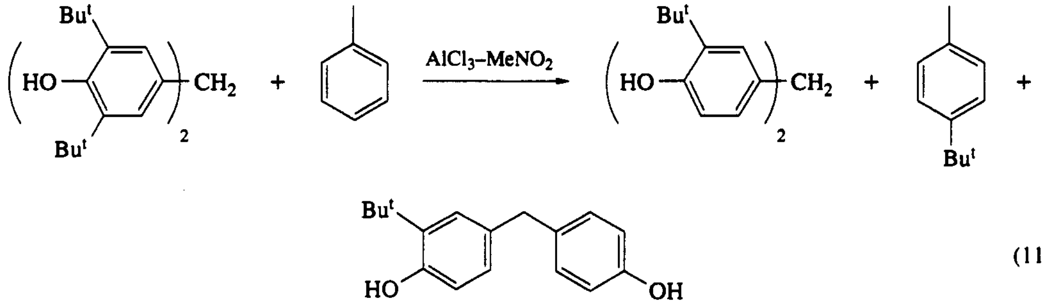

(119)

Due to the ease of dealkylation of *t*-alkylbenzenes, such as *t*-butylbenzene, some interesting applications of this process in both the synthetic and mechanistic areas have resulted. The intermediacy of the *t*-butyl cation was hinted to account for the observed products. Thus, Knight *et al.*[190] obtained excellent yields of pivalic acid by dealkylating *t*-butylbenzene and 1,3-dimethyl-5-*t*-butylbenzene in the presence of carbon monoxide and $BF_3{\cdot}H_2O$ as the catalyst (equation 120). They also found that $H_3PO_4$, $H_2SO_4$ and $MeSO_3H$ were ineffective for the dealkylation–carbonylation of *t*-butylbenzene.

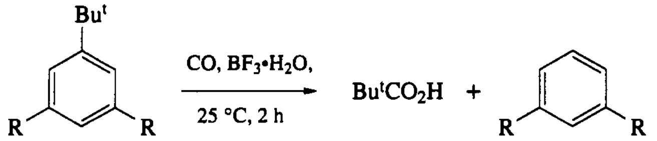

(120)

Brouwer[191] and Olah *et al.*[192] obtained direct evidence for the *t*-butyl cation intermediate by $^1$H NMR studies of *t*-butylbenzene in superacid solutions at low temperature. Fărcasiu and Schlosberg[193] demonstrated that, in the presence of carbon monoxide, the *t*-alkyl cation generated *in situ* from the dealkylation of a tertiary alkyl arene resulted in acylation of the dealkylated arene, as shown in Scheme 15.

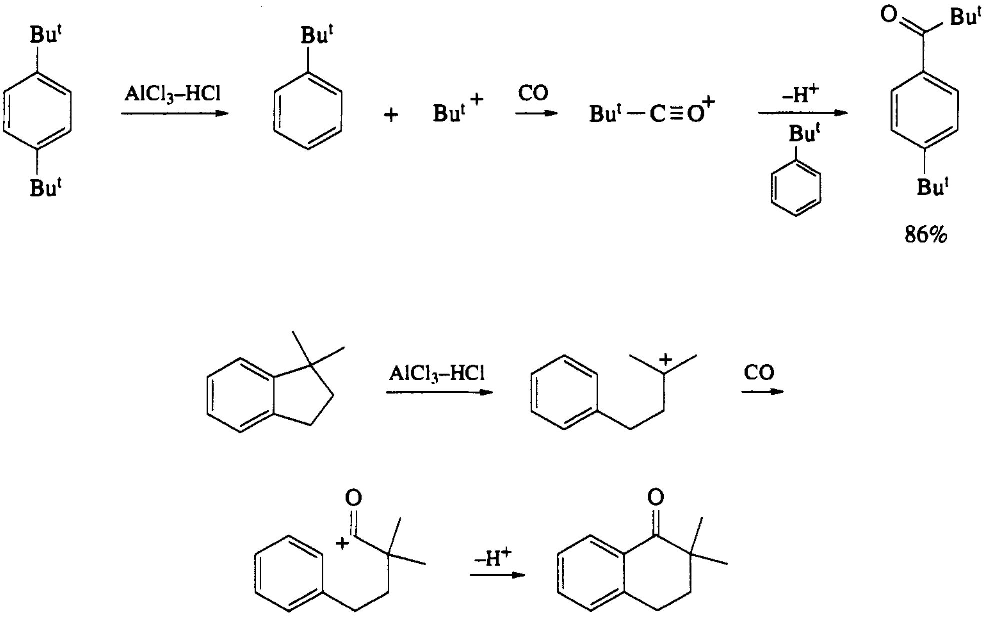

Scheme 15

Olson and Haag[194] observed a high selectivity for xylene isomerization *versus* disproportionation in the presence of ZSM-5 zeolite, and ascribed it to a transition state selective process rather than shape-selective diffusion. They were also able to produce *p*-xylene in high selectivity (up to 80%) from toluene disproportionation by using suitable modifications of the ZSM-5 catalyst. This selectivity was said to arise from shape-selective diffusion due to the unique pore size of the catalyst. Ratnasamy *et al.*[195] reported that shape-selective zeolites isomerized *m*-xylene to *p*- and *o*-xylene with higher selectivities.

Balaban *et al.*[196] have reported the catalytic automerization of [1-$^{13}$C]- or [3-$^{13}$C]-phenanthrene in the presence of a 1:1 mixture of $AlCl_3$–NaCl. They found that [1-$^{13}$C]phenanthrene transferred part of the label to C-3, but [3-$^{13}$C]phenanthrene transferred the label to two positions, *i.e.* mainly C-1 and to a lesser extent C-4, as shown in Scheme 16. Possible reaction mechanisms to account for these observations were also proposed.

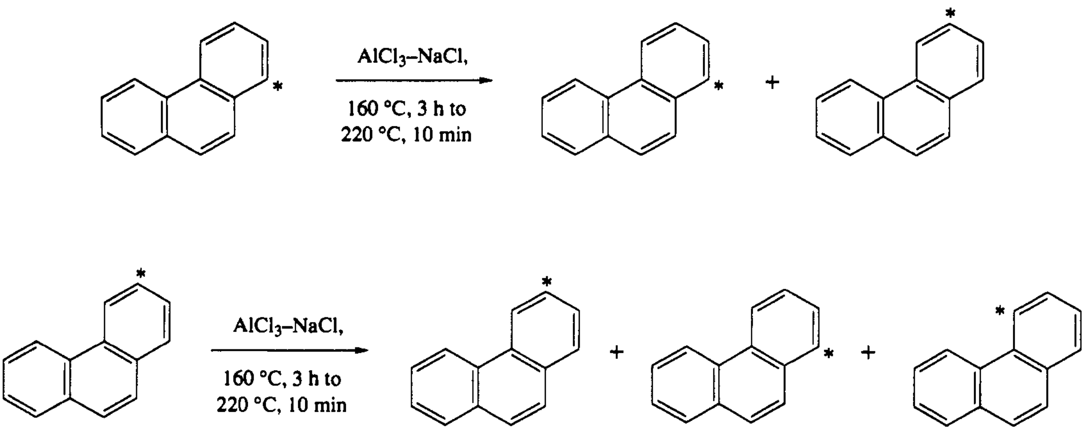

**Scheme 16**

### 1.8.4 ALKYLATION OF ALKENES

Ipatieff and coworkers[197] carried out the first alkylation with alkenes and branched and normal chain alkanes (except methane and ethane) in the presence of $AlCl_3$ as the catalyst. The sulfuric acid catalyzed alkylation reaction of arenes and isoalkanes, developed in 1938, is a still widely used industrial process[198] to produce alkylates with high octane numbers. For synthetic applications, however, Friedel–Crafts-type alkylations of alkenes and alkanes have limited value since they tend to give mixtures of products, including oligomers of alkenes.[199]

Oligomerization of aliphatic alkenes such as ethylene and propene, and aromatic alkenes, such as styrene, indene and their derivatives, catalyzed by a variety of Lewis acids, such as $AlCl_3$, $BF_3$, $AlBr_3$, and Brønsted acids, such as $H_3PO_4$, is a well-studied subject.[199] These reactions are important, particularly in the industrial arena.

Olah and coworkers,[200a] and Mayr and Striepe[200b] discussed the scope and limitations of aliphatic Friedel–Crafts alkylations. In particular, they considered factors that would favor reactions of the type shown in equation (121), where an alkene is alkylated by an alkyl halide.[201] They reasoned that formation of the 1:1 addition products (**42**) can be expected, if (**41**) reacts faster with the alkene than (**42**), otherwise higher addition products will be formed. Mayr[202] suggested that the relative dissociation rates of (**41**) and (**42**) induced by the Lewis acid should reflect their relative rates of addition to a common alkene. Furthermore, it was assumed that the solvolysis rates in 80% ethanol were proportional to the Lewis acid induced dissociation constants. A few examples where good yields of alkylated (addition) products were obtained are shown in equations (122) and (123).

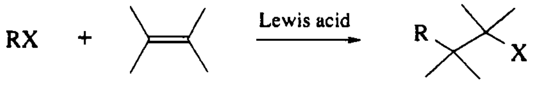

(121)

**(41)** **(42)**

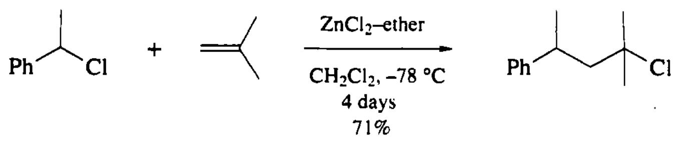

(122)

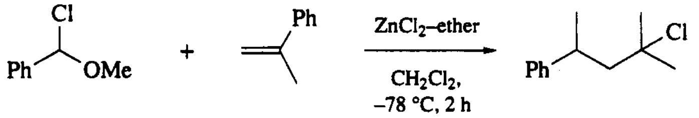

(123)

## 1.8.5 ALKYLATION OF ALKYNES

The benzylation reaction of 3-hexyne with benzyl chloride was reported to give a mixture of *cis* and *trans* addition compounds and 2,3-diethylindenone (equation 124).[203] It was found that in high polarity solvents the yield of the *trans* addition compound and of the indenone increased. An ionic mechanism was suggested to account for the *trans* addition compound, and a more covalent complex or ion pair to account for the *cis* isomer.

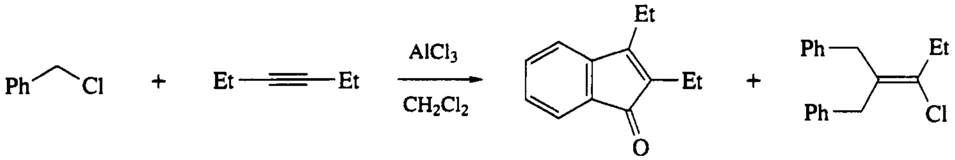

(124)

## 1.8.6 ALKYLATION OF ALKANES

The electrophilic alkylation of alkanes using superacidic catalysts, allowing elimination or minimization of any equilibrium with related alkenes, has been successfully studied.[204,205] These alkylations demonstrate the difference between conventional acid-catalyzed alkylations, where alkenes always play a key role in the reactions, and superacidic chemistry which allows carbocationic reactions with the alkanes themselves.

The nonexistence of alkane–alkene equilibrium in superacid medium has been elegantly demonstrated by the behavior of isobutane in deuterated superacid medium ($DSO_3F–SbF_5$ or $DF–SbF_5$).[206] Isobutane at low temperature undergoes hydrogen–deuterium exchange only at the methine position through the involvement of a three-center bound pentacoordinate carbonium ion (Scheme 17).

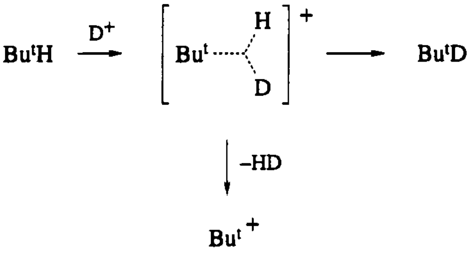

**Scheme 17**

On the other hand, Otvos *et al.*[207] showed that acid treatment ($D_2SO_4$) of isobutane effects hydrogen–deuterium exchange at the methyl groups, involving isobutene as an intermediate. They suggested that under the reaction conditions a small amount of *t*-butyl cation is formed in an oxidative step which deprotonates to isobutene. The reversible protonation (deuteration) of isobutene is responsible for the H–D exchange on the methyl hydrogens, whereas tertiary hydrogen is involved in intermolecular hydride transfer from unlabeled isobutane (at the CH position, see Scheme 18).

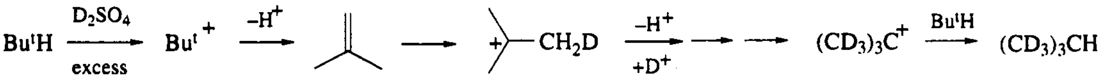

**Scheme 18**

Olah and coworkers[34,208] have observed that alkyl fluoride–$SbF_5$ complexes, such as $MeF{\cdot}SbF_5$ and $EtF{\cdot}SbF_5$, or stable prepared alkylcarbenium hexafluoroantimonate salts directly alkylate alkanes (equations 125 and 126).

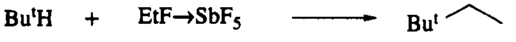

(125)

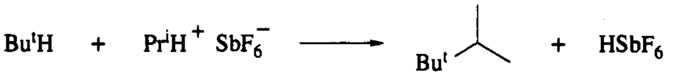

(126)

The pathway of these alkylations was clearly demonstrated by Olah *et al.*[209] from their extensive work on the alkylation of the lower alkanes by stable carbocations under superacidic, stable ion conditions. They found that the order of reactivity of C—C and C—H bonds reflected their σ-donor abilities and was in the order: tertiary C—H > C—C > secondary C—H >> primary C—H, although various specific factors, such as steric hindrance, can influence the relative rates.

Olah and his group[210] also investigated the direct ethylation of methane with ethylene using $^{13}C$-labeled methane over solid superacid catalysts, such as $TaF_5$–$AlF_3$, $TaF_5$ and $SbF_5$–graphite. A high selectivity (up to 96% of label content of $C_3$ fraction) for monolabeled propane ($^{13}CC_2H_8$) was observed. This clearly indicated a direct electrophilic attack of the ethyl cation on methane *via* a pentacoordinated carbonium ion, as in Scheme 19.

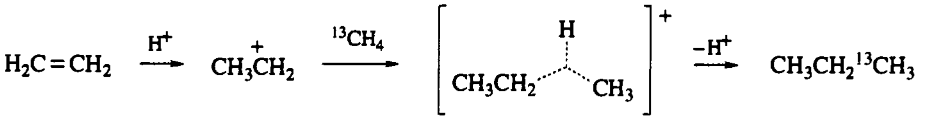

**Scheme 19**

Similarly, Siskin[211a] found that when ethylene was allowed to react with ethane in a flow system, only *n*-butane was obtained. This was explained by the direct alkylation of ethane by ethyl cation through a pentacoordinated carbonium ion (equation 127). The absence of a reaction between ethyl cation and ethylene was explained by the fact that no rearranged alkylated product (isobutane) was observed.

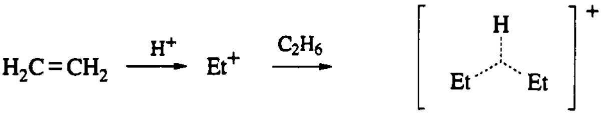

(127)

Alkylations of alkanes, such as propane, isobutane and *n*-butane, by *t*-butyl or *s*-butyl carbenium ions are always accompanied by competing hydride transfer and rearrangement processes. In general, once an incipient carbocation is produced, further alkylations and carbocation rearrangements can continue until the cation is quenched. This process constitutes a potentially powerful method of converting lower alkanes into higher alkylates in the gasoline range.[211b] Typically, these reactions are performed by first preparing the alkylcarbenium hexafluoroantimonates from the corresponding alkyl halides and $SbF_5$ in sulfuryl chloride fluoride as the solvent, and treating them in the same solvent with alkanes. For example, propylation of propane by the isopropyl cation gave a significant amount (26% of the $C_6$ fraction) of the primary alkylation product (equation 128). The $C_6$ isomer distribution, 2-methylpentane (28%), 3-methylpentane (14%) and *n*-hexane (32%), was very far from the thermodynamic equilibrium. This suggests that not only the isopropyl, but also the *n*-propyl cation was involved as intermediate (as shown by $^{13}C(2)$–$^{13}C(1)$ scrambling in the stable ion[212]) as illustrated in Scheme 20.

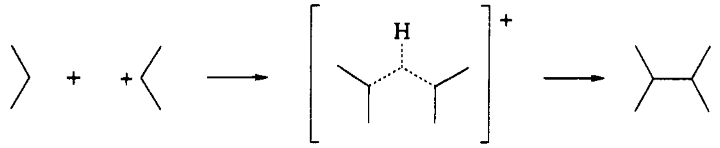

(128)

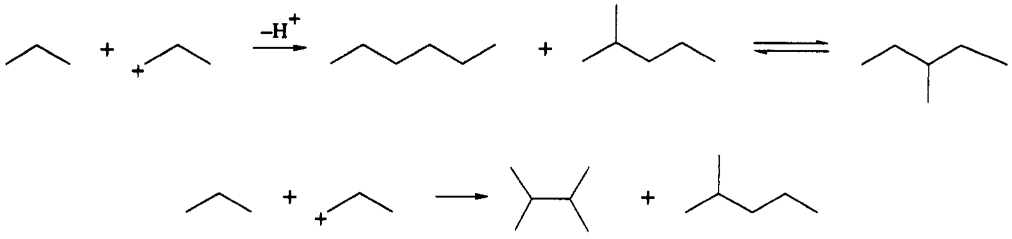

Scheme 20

Lower alkanes such as methane and ethane have been polycondensed in superacid solutions at 50 °C to yield higher alkanes.[213] Subsequently Roberts and Calihan[214] were able to prepare oligomeric and polymeric alkanes with molecular weights of up to 700 by direct condensation of $C_1$ to $C_4$ alkanes over the superacid $FSO_3H–SbF_5$ at room temperature. Alkylation of adamantane with lower alkenes (ethylene, propene and butenes) catalyzed by $CF_3SO_3H$ or $CF_3SO_3H–B(O_3SCF_3)_3$ was studied recently by Olah *et al.*[215] A number of potential processes[216] were developed to use natural gas instead of pure methane in the alkylation of methane by alkenes. When natural gas is dehydrogenated, the $C_2$–$C_4$ alkanes it contains are converted into alkenes. The resulting methane–alkene mixture can then, without separation, be passed through a superacid catalyst resulting in exothermic alkylation condensation.

Isomerizations of alkanes catalyzed by superacidic media are very important reactions, particularly in the industrial arena. Conversion of linear $C_5$–$C_8$ alkanes to their branched counterparts substantially improves their combustion properties. The isomerization of *n*-butane to isobutane is of great importance because isobutane reacts under mildly acidic conditions with alkenes to give highly branched hydrocarbons in the gasoline range.[217] Various difficulties are encountered in handling liquid superacids and in separating the product from the catalyst. Solid superacids, such as $SbF_5$–intercalated graphite, $SbF_5–SiO_2–TiO_2$ and $TiO_2–ZrO_2–SbF_5$ have proved to be very efficient catalysts for the isomerization of alkanes and resulted in easy product separation.

The isomerization of a large number of isomeric tricyclic $C_{10}$ hydrocarbons under Lewis acid catalysis gives the unusually stable isomer adamantane.[218] This unusual reaction was originally developed by Schleyer.[219] The method since has been adopted in the synthesis of diamantane and triamantane from the appropriate $C_{14}$ and $C_{18}$ precursors.[220] Olah *et al.*[221] extended this reaction by isomerizing a series of $C_{4n+6}H_{4n+12}$ ($n$ = 1–3) polycyclic precursors to diamondoid hydrocarbons using superacidic catalysts[221a] as well as the $NaBH_4–CF_3SO_3H$ reagent, which is used as a reagent for mild reductive isomerizations.[221b] Paquette's synthesis[222] of 1,16-dimethyldodecahedrane (**44**) from the alkene (**43**) involved a superacid-catalyzed isomerization (equation 129).

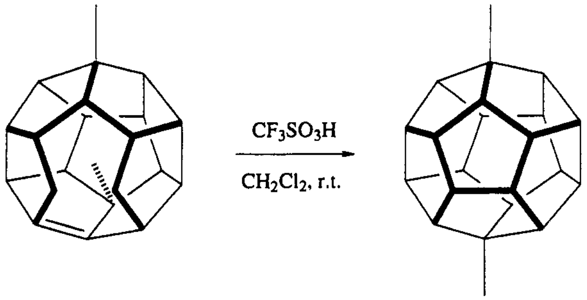

(129)

(**43**) (**44**)

Vol'pin *et al.*[25] found that complexes of the type $RCOX·2AlX_3$ (termed aprotic organic superacids)[25] are extremely reactive towards alkanes, and catalyze a variety of hydrocarbon transformations. These complexes were prepared simply by mixing 1 mol of distilled acyl halide (MeCOX, $Pr^nCOX$, PhCOX, *etc.*; X = Br, Cl) with 2 mol of sublimed $AlX_3$ (X = Br, Cl) at room temperature. The liquid $RCOX·2AlBr_3$ and solid $RCOX·2AlCl_3$ complexes were stable at room temperature under anhydrous conditions. The superacidic systems appear attractive in terms of their availability, nontoxicity and ease of use. Facile coupling of $C_5$–$C_6$ cycloalkanes was observed in the presence of these catalysts. For example, high yields of isomeric mixtures of dimethyldecalins were formed when cyclohexane or methylcyclopentane were employed in excess (12:1) relative to $RCOX·2AlBr_3$ (Scheme 21). With a lower cycloalkane:complex ratio, acylation of the cycloalkane was observed. Mechanisms for such alkylation reactions, as well as applications of these complexes to catalyze efficiently other processes such as cracking, isomerization and ionic bromination of linear and cyclic alkanes, have been discussed.

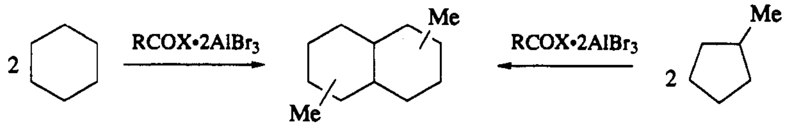

Scheme 21

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# 1.9
# Polyene Cyclizations

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## 1.9.1 INTRODUCTION

Much of the early work on polyalkene cyclizations derives from the classical structural investigations on terpenes[1] and this, together with speculation concerning their biosynthesis and stereochemistry, culminated in the Stork–Eschenmoser hypothesis of 1955.[2] This postulated that polyalkenes could react in defined conformations which, in combination with antiperiplanar addition to the double bonds, allowed prediction of the relative stereochemistry of the cyclization products (Scheme 1). The attractiveness of these ideas as the basis of a general synthetic method is clear, not least because it suggests methods for forming C—C bonds between highly substituted atoms where organometallic methods are often subject to severe steric hindrance. To establish the method required the development of (a) suitable initiators for cyclization, (b) methods for the stereoselective synthesis of alkenes (Volume 1, Chapters 3.1 and 3.2) and (c) termination of cyclization by a single mechanism. Johnson's group has made major contributions to the development of polyalkene cyclization as a viable synthetic method; their earlier work has been reviewed[3] as has that of other groups.[4] There is also an excellent general review by Bartlett.[5]

In this chapter emphasis will be placed on preparatively useful procedures, the general 'rules' which pertain in polyene cyclization, and the circumstances under which the Stork–Eschenmoser hypothesis is valid. The success, or otherwise, of polyalkene cyclization depends on a complex interplay between the

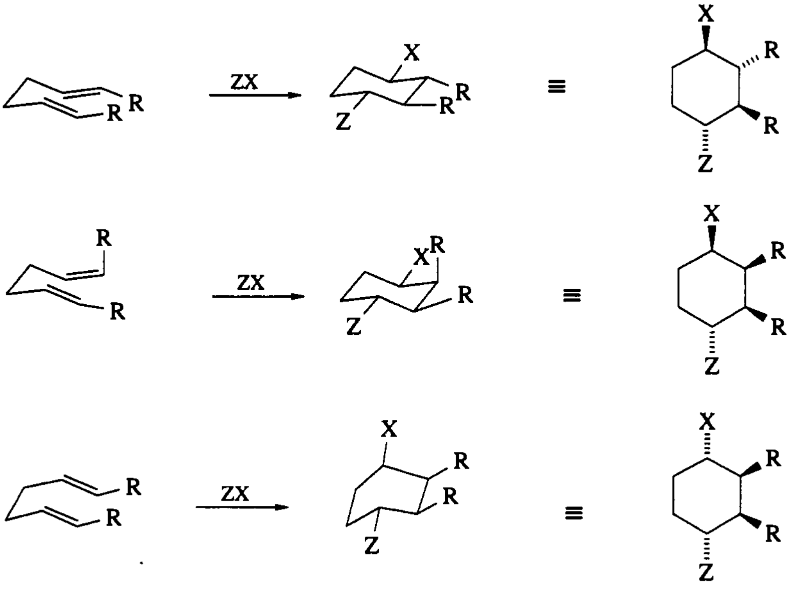

**Scheme 1**

method of initiation, the nucleophilicity of the double bonds involved, and the mechanism of termination. Because of this, it is rather artificial to consider these separately but still useful in a pedagogic sense. Since the mechanism of polyalkene cyclization is by no means firmly established (indeed, there is unlikely to be a unique mechanism) the process will be represented as involving 'simple' carbocations; this does not exclude concerted and part-concerted mechanisms or those involving bridged cations or π-complexes. Formulae representing racemates are drawn showing only one enantiomer. Where a single enantiomer is represented, it is described as chiral.

## 1.9.2 INITIATION OF CYCLIZATION

Cyclization is initiated by formation of a putative cation either by electrophilic addition to a double bond or by ionization, usually from an $sp^3$-hybridized carbon. Protonic and Lewis acids have been the most frequently used electrophiles but successful monocyclizations have been reported using HOBr,[6] $MeCOBF_4$,[7] $MeOCH_2BF_4$,[8] $Br_2$–$AgBF_4$,[9] $PhSBF_4$,[10] $PhSeBF_4$,[11] $Tl(ClO_4)_3$,[12] $Hg(OAc)_2$,[13] $Hg(OCOCF_3)_2$[14] and $HgTf_2$ (with and without $PhNMe_2$). The $Hg(OCOCF_3)_2$ reagents have been used successfully for the bicyclization of farnesol derivatives to drimnanes (Section 1.9.6.2). The Semenovskii group has shown[14] that, of the electrophiles tested, $Hg(OCOCF_3)_2$ is the only reagent which effects antiperiplanar addition to the initiating double bond; whether this is due to the bridged mercuricinium ion maintaining stereochemical integrity or a concerted cyclization is not known. Cyclization with $H_2SO_4$ gave a 1:1 mixture of equatorial and axial $CD_3$, establishing that it is a nonconcerted reaction (Scheme 2). This contrasts with the cyclization of 2,6-octadiene[15] (where a less-stable secondary cation would be the equivalent intermediate) having the characteristics of concerted protonation–ring formation (Scheme 3). $PhSOMe$–$BF_3$ and *N*-phenylselenylsuccinimide–$BF_3$ have also been established as initiators of bicyclizations (Section 1.9.6.2). Understandably, the electrophile-induced cyclizations are most efficient when the initial reaction occurs at the most nucleophilic double bond. However, these initiators have not been tested with a sufficient range of substrates to allow generalizations about their individual effectiveness.

Ionization methods for production of the initiating cation have been more generally tested and shown to be ineffective at inducing cyclization at primary and secondary centers where the ion does not have additional stabilization. Acid-catalyzed cyclization of tertiary derivatives has been more successful. From a preparative viewpoint, biomimetic epoxide cleavage as a means of cyclization has been disappointing, though much useful mechanistic and structural information has been gleaned from this work, in particular that of the van Tamelen group.[4a] Certain methylcyclohexene epoxides give acceptable yields in monocyclizations[4d] but are not useful for bi- and tri-cyclizations. The most efficient general initiators of cyclization are cations which are stabilized by a heteroatom, a double bond or both. The allylic cations (**1**), (**2**), (**3**) and (**4**) introduced by the Johnson group and the acyclimonium ion (**5**) used by Speckamp

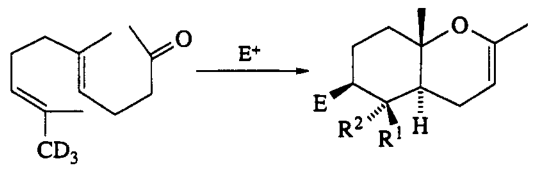

E = HgOCOCF$_3$   R$^1$ = Me, R$^2$ = CD$_3$

E = H   1:1 mixture

**Scheme 2**

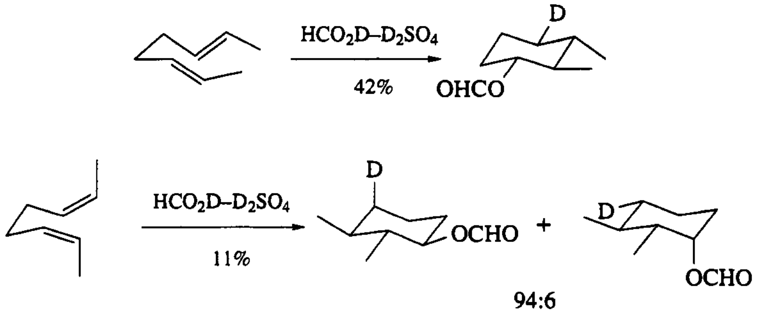

**Scheme 3**

(Volume 2, Chapter 4.5) have been tested with a wide variety of substrates and shown to be efficient at inducing mono- and poly-cyclizations. The Johnson group has also used oxonium ions (derived from acetal cleavage) as initiators, in particular for preparing chiral cyclized products. Imonium[16] and acycloxallyl cations (**6**) are also useful initiators;[17] with the latter, carbon bond formation does not occur at the O-terminus. It is worth noting that the cyclopentenyl and cyclohexenyl cations with two hydrogens at the terminus are not particularly good initiators and that the trialkylated ions are preferentially attacked at the least-alkylated terminus when the choice is open. To summarize, monocyclizations can be achieved using a variety of electrophilic reagents or ionization methods, carbabi- or carbatri-cyclizations are achievable in good yield when preparing drimnane terpene derivatives; otherwise initiation of cyclization by stabilized cations is the preferred strategy.

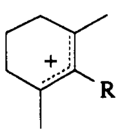

**(1)**

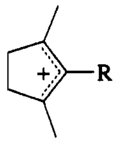

**(2)**

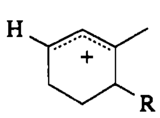

**(3)**

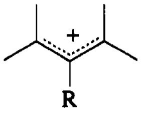

**(4)**

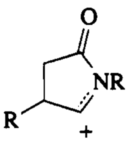

**(5)**

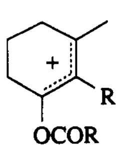

**(6)**

### 1.9.3 PROPAGATION OF CYCLIZATION

There are a host of examples of carbamonocyclizations, many bicyclizations, a substantial number of tricyclizations and a few tetracyclizations. Where cyclohexane rings are being formed, the overwhelming number of cases can be interpreted as forming *via* a chair-like transition state. Where ring junctions are formed in bi- and tri-cyclizations (Scheme 4) most examples are of (*E*)-alkenes cyclizing to form *trans*-fused rings giving the thermodynamically stable product. The corollary of the Stork–Eschenmoser hypothesis that a *cis* ring junction would form from the (*Z*)-alkene has been tested infrequently (Section 1.9.6.2). Where the comparison has been carried out, it is clear that the extent to which the hypothesis is upheld is dependent on the initiator and the nucleophilicity of the double bonds participating. Where a double bond is 5,6 to the initiating center and electronically unbiased or substituted at C-5, then 6-*endo* cyclization is almost invariably favored over the 5-*exo* mode (Scheme 5); the cyclization of (**7**) is a rare exception to this rule.[18] When there is additional substitution at C-6 polarizing the double bond, then 5-

*exo* cyclization is preferred; the products of cyclization can be complicated by the cyclopentylmethyl cation undergoing rearrangement following cyclization. A double bond 6,7 to the initiating center leads to 6-*exo* cyclization unless this contravenes the Markovnikov rule, in which case 7-*endo* cyclization ensues (Scheme 5). With 4,5 double bonds, 5-*endo* cyclization is seldom observed, in accord with Baldwin's rules.

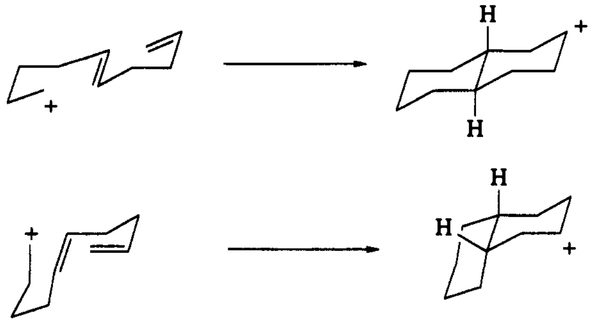

Scheme 4

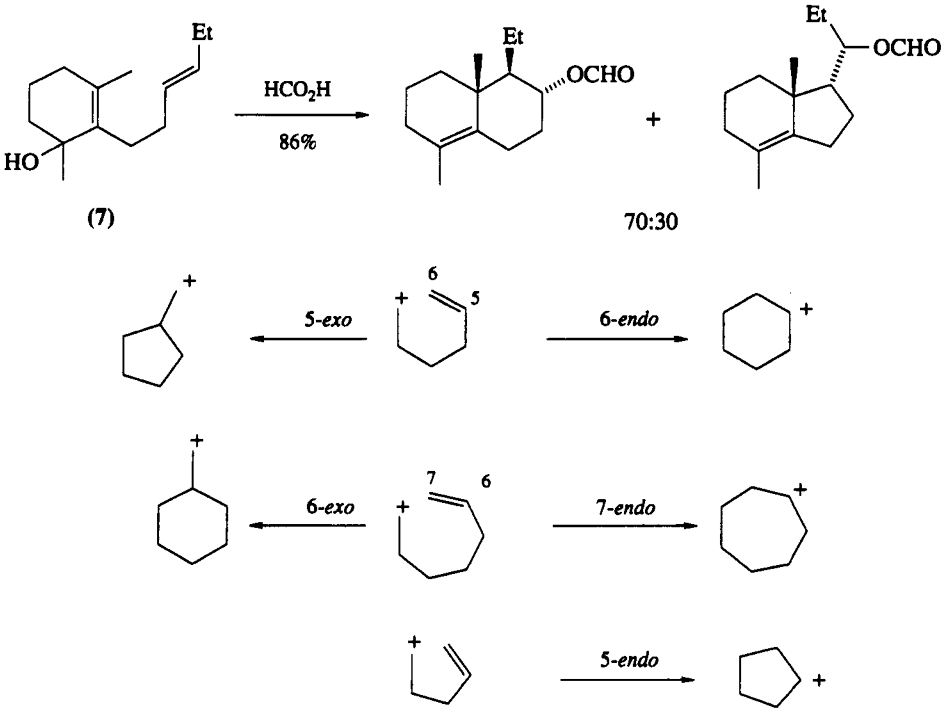

Scheme 5

Allenyl and alkynyl functions can also participate in cyclization, usually in the formation of the terminal ring. Alkynyl groups 5,6 to the cationic center cyclize 6-*endo* when the terminal group is hydrogen or silyl (Scheme 6) but dialkylalkynes have a kinetic preference for 5-*exo* cyclization though under certain conditions the 5-*exo* cations can rearrange to the thermodynamically more stable 6-*endo* ion. The homologous 6,7-alkynes behave in a parallel manner, *i.e.* terminal alkynes give seven-membered rings while dialkylalkynes cyclize 6-*exo* to cyclohexenes. An allenyl group 4,5,6 relative to the initiating center with at least one terminal alkyl group induces five-membered ring formation, whereas with a $CH_2$ terminus both five- and six-membered ring formation has been noted (Scheme 6). The reluctance of 4,5-alkynes to cyclize in either 4-*exo* or 5-*endo* modes is illustrated by the cyclizations to the bridged bicyclics (Scheme 7).[19]

When substituents are bonded to the $sp^3$-hybridized carbons between reacting double bonds then, for six-membered ring formation, the model with the substituent adopting an equatorial disposition in a

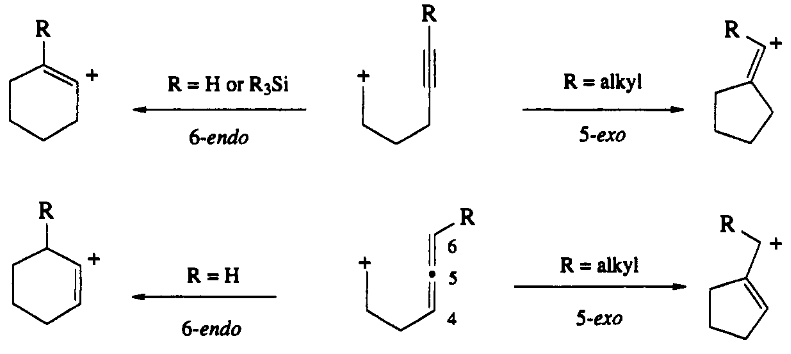

Scheme 6

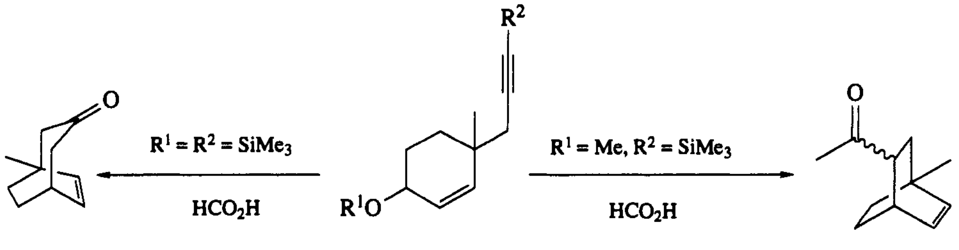

Scheme 7

chair-like transition state has strong predictive value; however, there are occasions when an axial disposition is adopted for understandable reasons.

## 1.9.4 TERMINATION OF CYCLIZATION

The ideal for a synthetically useful polyalkene cyclization would be termination by one mechanism giving a single product. Termination can be achieved by elimination and/or attack by an internal or external nucleophile. Proton elimination can be regioselective or random. The cyclization of geraniol and its derivatives has been extensively investigated, in particular by the groups of Schinz[20] and Semenovskii.[21] Both (*Z*)- and (*E*)-isomers cyclize initially to the α-isomers when an electron-withdrawing group is conjugated to the second double bond (Scheme 8). It is suggested that the reduced nucleophilicity of the double bond leads to a concerted cyclization–elimination being favored over the two-step process. Where the nucleophilicity of the double bond is not reduced then (*E*)-isomers give the α-series and (*Z*)-isomers the β-compounds, consistent with elimination of an axial proton to give the most stable alkene attainable. This rule does not apply when there is oxygen functionality in the vicinity of the second double bond. Geraniol and its derivatives (**8**) cyclize initially to α-isomers. Utilization of the oxygen function as an internal base for proton removal has been invoked; this would require conformational inversion placing $CH_2OR$ axial. The contrary behavior of lavandulol (**9**) illustrates that some subtle features are involved. Together with the allogeraniol (**10**) cyclization, the one common feature appears to be that elimination remote from the *gem*-dimethyl group is preferred. Another rule which seems to have some predictive value is that bicyclo[4.4.0]decenes (both *cis* and *trans*) formed from the C-2 cation favor the $\Delta^{2,3}$- rather than $\Delta^{1,2}$-double bond. However, in many cases, eliminations are not regioselective and the device of $R_3Si$ elimination introduced by Fleming[22] is becoming increasingly popular as a method for preparing compounds of defined regiochemistry. Other terminating groups which remove any ambiguity concerning the structure of the product are alkynes, allenes, enols and enol derivatives. Aryl and heteroaryl rings, particularly if they are electron rich, are good terminators, but when appropriately substituted can give mixtures of positional isomers.

Proton elimination is the most common termination mode for tertiary cations and also for secondary cations when the cyclizing reagent is a Lewis acid. With protonic acids, nucleophilic attack is often observed and is usually stereoselective; in many cases, due to the electron deficiency of the double bonds involved, nucleophilic attack may be concerted with ring formation. Cyclization of the acids (**11**) is in

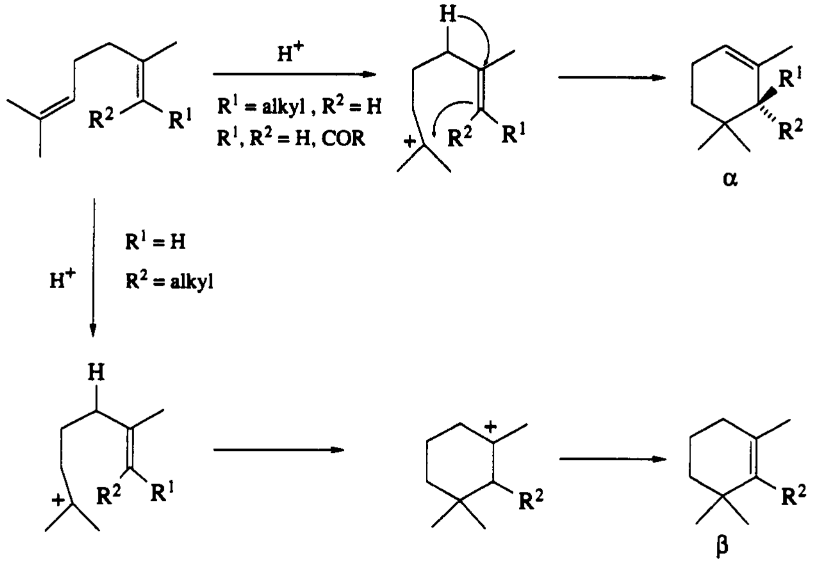
H+
R1 = alkyl, R2 = H
R1, R2 = H, COR
α
H+
R1 = H
R2 = alkyl
β

**Scheme 8**

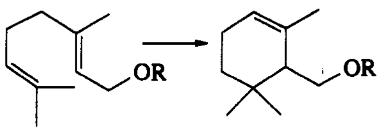

**(8)** R = H, Me, OAc

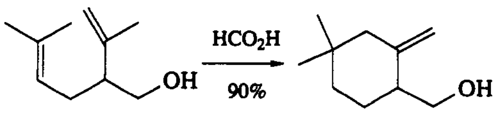

**(9)**

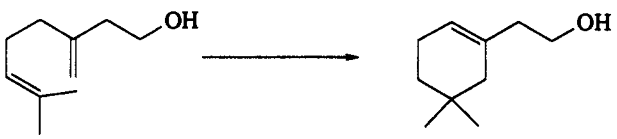

**(10)**

accord with this view.[23] In the few cases where a tertiary center undergoes intermolecular nucleophilic attack, epimeric mixtures have been obtained. However, intramolecular nucleophilic attack by heteroatoms can be stereospecific and efficient, as in the cyclization of geranylacetone (**12**).[24] The lack of predictability when alkenes terminate cyclizations has led to the development of terminators where the products can be more precisely anticipated.

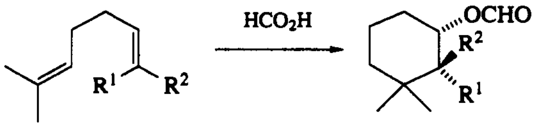

**(11)**

$R^1 = CO_2H$, $R^2 = H$
$R^1 = H$, $R^2 = CO_2H$

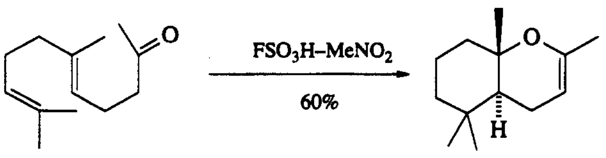
FSO3H-MeNO2
60%

**(12)**

## 1.9.5 MONOCYCLIZATIONS

### 1.9.5.1 Five-membered Ring Formation

Examples of acyclic compounds being cyclized to cyclopentanes are sparse, but there are significantly more where an annulation is involved. 5-*Exo* cyclization of alkenes electronically biased to achieve this mode was used successfully, in particular by the Landsbury group.[25] Use of the chlorovinyl functionality gave acetylcyclopentanes with a preference for the *cis* ring junction with conformationally mobile substrates (**13**). When a conformationally rigid precursor (**14**) was used then predominant formation of a *trans* ring junction resulted; similar results were reported for the propargyl terminating group. Stereochemically constrained dienes,[26] *e.g.* (**15**), can be cyclized under mild conditions with high efficiency. Limitation of the degrees of rotational freedom of a diene is likely to increase the rate of cyclization provided that the double bonds are suitably aligned.

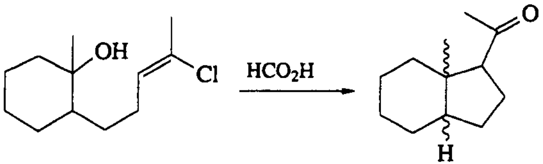

(**13**)

*cis*:*trans* = 3:1

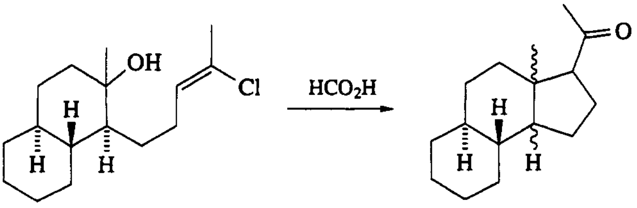

(**14**)

*cis*:*trans* = 1:2

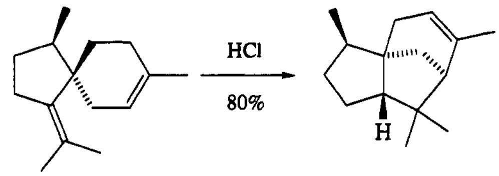

(**15**)

Anti-Markovnikov 5-*exo* cyclizations of geraniol derivatives (**16**) have been reported with $Tl(ClO_4)_3$;[12] however, a more normal 6-*endo* cyclization followed by ring contraction could account for the products. The most reliable prescription for cyclopentane annulations is to use allylic ion initiators with appropriate terminators. In Scheme 9 the *cis* stereochemistry of the ring junctions arises in two ways; for the 4-substituted cyclohexenone derivatives, the axial attack of the nucleophilic side chain on the allylic ion requires this stereochemistry. In the 2-substituted cyclohexenones the immediate product of cyclization is an enol ester which is hydrolyzed, giving the thermodynamically more stable *cis* ring junction. Other points to note are that stereochemical control in example 3 (Scheme 9) is consistent with the $Pr^i$ group being equatorial and the isopropylidene being oriented '*endo*'. The subsidiary rearrangement seen in example 4 (Scheme 9) does not occur with the unmethylated compound. In example 6 (Scheme 9) there is a substantial difference in yield between the methyl and nor series. There are few examples of 5-*endo*

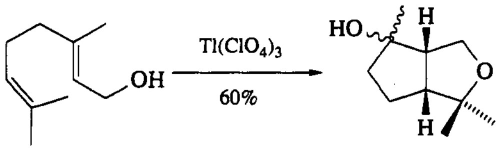

(**16**)

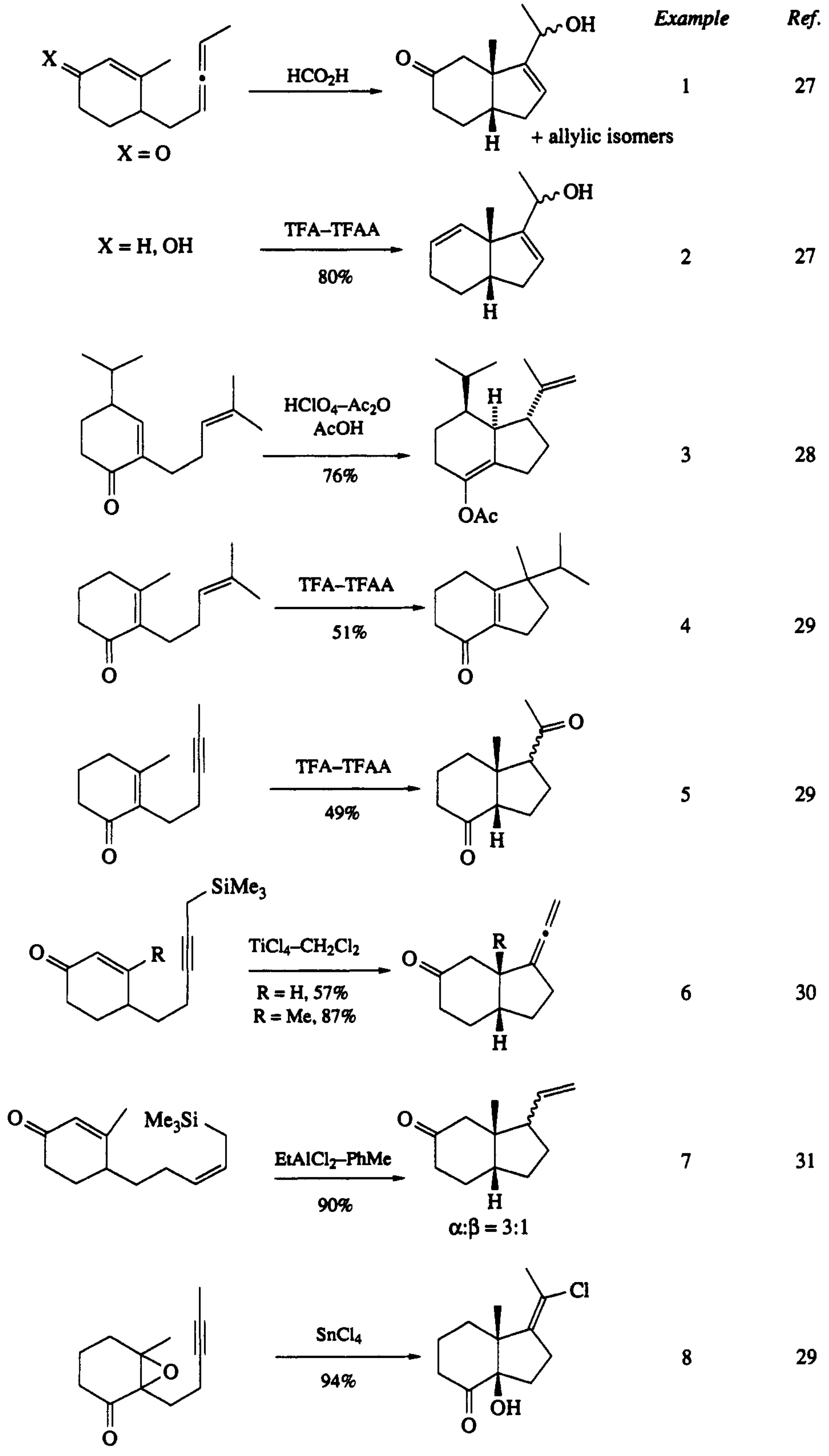
Example
Ref.
X
X = O
HCO$_2$H
O
OH
H
+ allylic isomers
1
27
X = H, OH
TFA–TFAA
80%
OH
H
2
27
O
HClO$_4$–Ac$_2$O
AcOH
76%
H
OAc
3
28
O
TFA–TFAA
51%
O
4
29
O
TFA–TFAA
49%
O
O
H
5
29
SiMe$_3$
O
R
TiCl$_4$–CH$_2$Cl$_2$
R = H, 57%
R = Me, 87%
O
R
H
6
30
O
Me$_3$Si
EtAlCl$_2$–PhMe
90%
O
H
α:β = 3:1
7
31
O
O
SnCl$_4$
94%
Cl
O
OH
8
29

Scheme 9

cyclizations; the conversion of the menthadiene (17)[32] to the camphor derivative is both 5-*endo* and 5-*exo*. The silylenol ether (18) cyclizes to cyclopentanone only when the allyl terminus is dimethylated;[33] with monomethyl derivatives the major mode of cyclization is 7-*endo* (Section 1.9.5.3). The Cookson group has shown (Scheme 10) that 4-en-l-als can be cyclized to cyclopentanones;[34] labeling and other evidence support the mechanism shown.

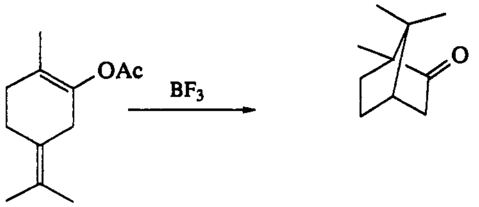

(17)

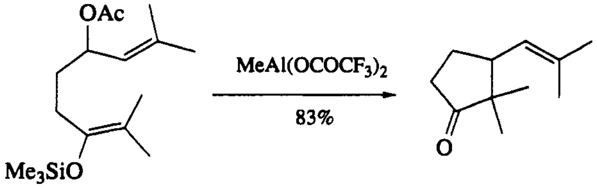

(18)

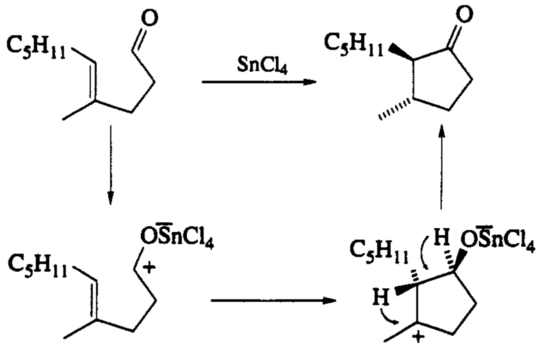

Scheme 10

### 1.9.5.2 Six-membered Ring Formation

This is by far the most common mode of monocyclization. Some aspects of the cyclization of monoterpenes have been described (Sections 1.9.6.3 and 1.9.6.4). Proton-induced cyclizations are successful when an initial tertiary cation is formed, then participation of electron-deficient and other double bonds occurs provided the Markovnikov rule is not violated. The rare examples of cyclization induced by protonation to form a notional secondary cation probably do not involve such a species, but rather ring formation is concerted with cyclization. Such cyclizations do not occur when the ring-forming double bond is electron deficient. When the initiating double bond is tetraalkylated then intriguing differences from the trialkyl system appear (Scheme 11). It is known that in the proton-induced cyclization of geranylacetone the stereochemical distinction between the two methyls of the isopropylidene group is lost. However, the homolog (19) cyclizes stereoselectively,[35] implying either a concerted protonation cyclization or, less likely, that the axial orientation of the methyl group is favored in a two-step cyclization. Lewis acid induced cyclization of ψ-irone (20) takes a different stereochemical course, giving (21), while the (*Z*)-trisubstituted double bond isomer gives the product with the pendant groups *trans*.[36] The proton-induced cyclization of (20) follows a different path,[40] giving (22); applying similar conditions of cyclization to ψ-ionone gives α-ionone. The divergent stereochemical behavior of (19) and (20) requires both reactions to be concerted and the Lewis acid–carbon bond of the cyclization product leading to (**21**) to be protonated with inversion of configuration. Alternatively, the cyclization of (**20**) can be stepwise, due to the electron-deficiency of the ring-forming double bond, and the transition state with methyl equatorial and $BF_3$ axial favored. With $TiCl_4$ ψ-ionone cyclizes in yet another fashion to give (**23**).[37]

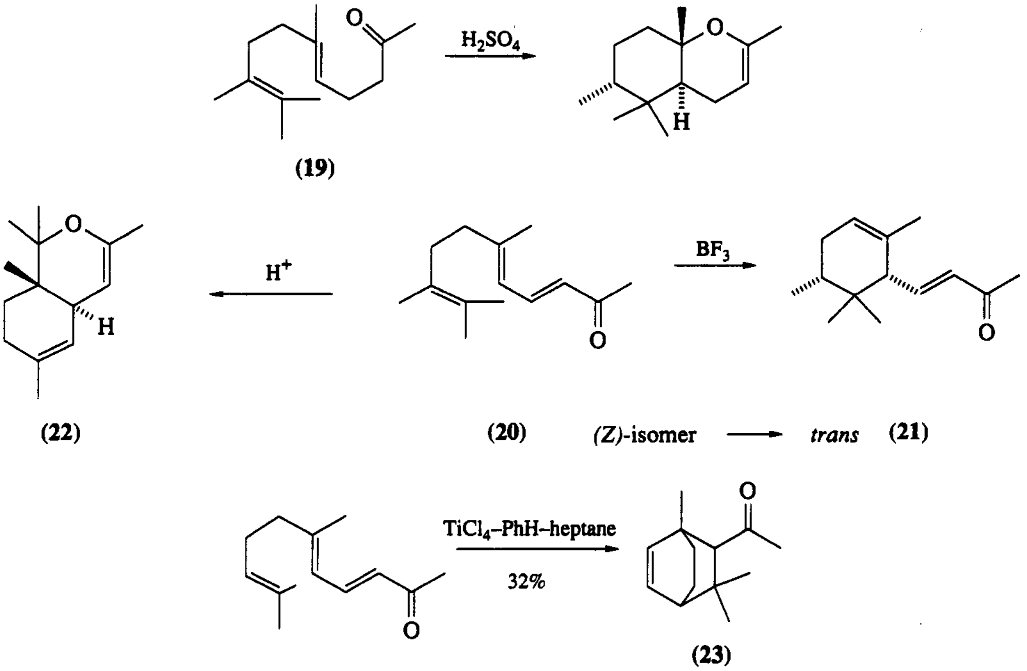

**Scheme 11**

In Scheme 12 some annulations leading to decalins are shown. The formation of *cis* isomers (examples 1 and 2, Scheme 12) accords with a fully-concerted mechanism, while the cyclization of both the α- and β-isomers of the acids (example 3, Scheme 12) to the *trans* compound supports stepwise formation of the cyclohexyl cation followed by concerted cyclization–elimination due to the electron-deficient double bond. The cyclization of the acetonyl β-isomer (example 4, Scheme 12) to the *trans* isomer implies a stepwise mechanism, which is perhaps surprising in the light of the first two results, since the ring-forming double bond is not electron deficient. There appears to be an unfavorable steric interaction between the angular methyl and two axial hydrogens in ring B (**24**). This may make the concerted reaction energetically unfavorable compared to the stepwise process. Cyclization of the isomer (example 5, Scheme 12) takes a different course and must involve some type of concerted process to give the unexpected stereochemistry found. A chair–chair transition state is disfavored due to the similarity with (**24**). A twist-boat ring B conformation suffers from similar interactions with the angular methyl. Diequatorial addition to the double bond in a chair–chair conformation has little precedent. However, a more plausible model

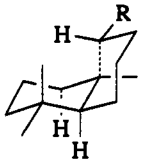

(**24**)

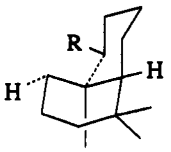

(**25**)

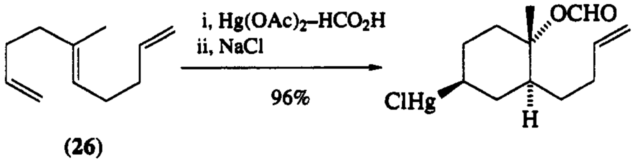

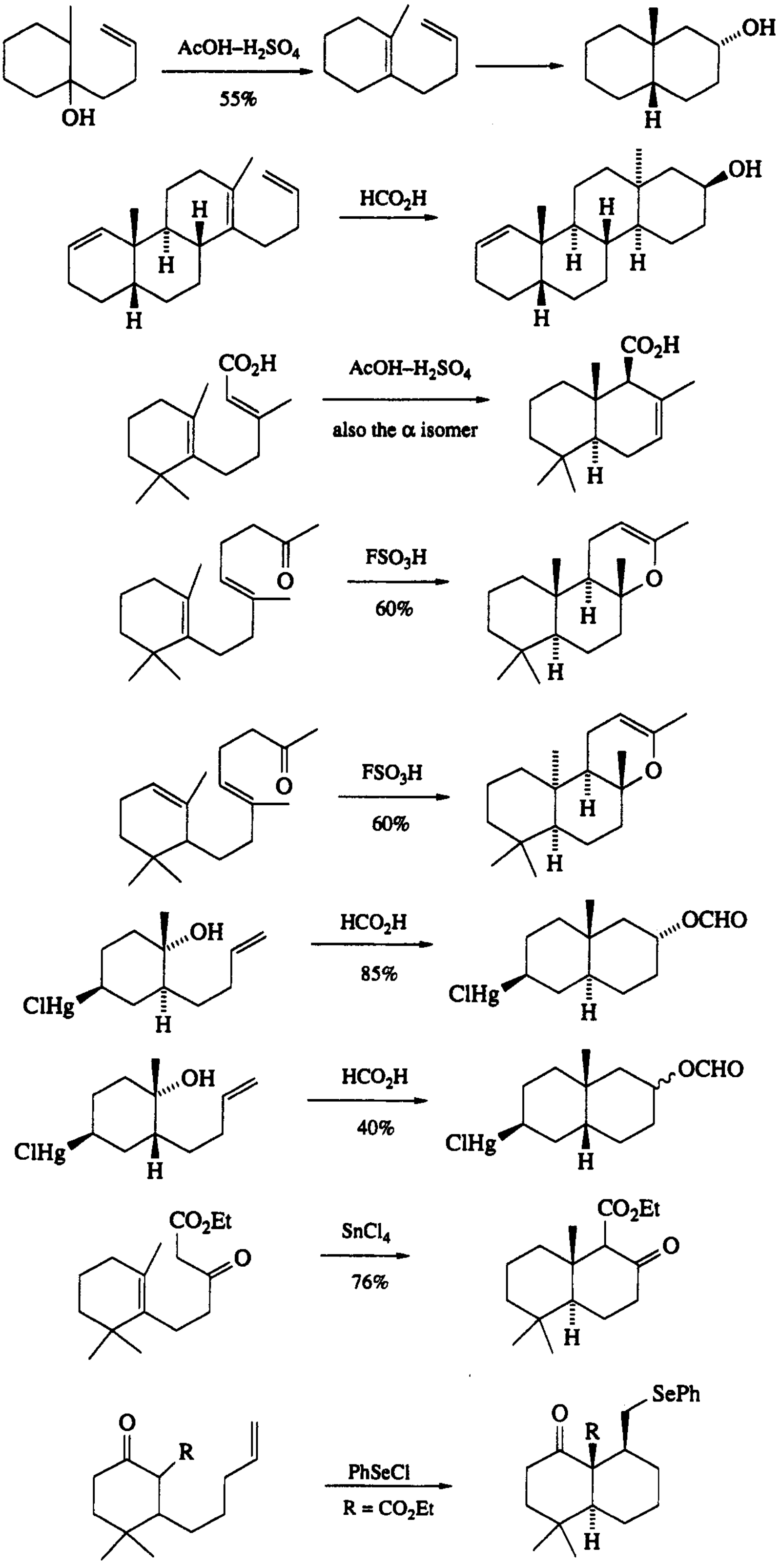
AcOH–H₂SO₄
55%
OH
OH
H
H
H
H
HCO₂H
OH
H
H
H
H
CO₂H
AcOH–H₂SO₄
also the α isomer
CO₂H
H
O
FSO₃H
60%
O
H
H
O
FSO₃H
60%
O
H
H
OH
ClHg
H
HCO₂H
85%
OCHO
ClHg
H
OH
ClHg
H
HCO₂H
40%
OCHO
ClHg
H
CO₂Et
O
SnCl₄
76%
CO₂Et
O
H
O
R
PhSeCl
R = CO₂Et
SePh
O
R
H

| *Example* | *Ref.* |
|---|---|
| 1 | 38 |
| 2 | 40 |
| 3 | 39 |
| 4 | 41 |
| 5 | 41 |
| 6 | 42 |
| 7 | 42 |
| 8 | 43a |
| 9 | 44 |

**Scheme 12**

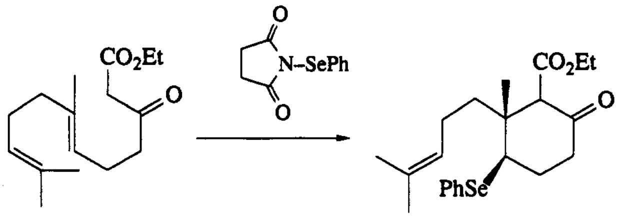

**(27)**

which effectively leads to diequatorial attack has ring A as a twist-boat (**25**) which minimizes interactions with the angular methyl and improves orbital overlap at the reacting centers. If this model is correct, it would imply that concerted cyclization of a 1,6-diene is energetically more favorable than the 1,5-diene concerted reaction. It should be noted that the *cis*-decalin conformations involved in the annulations are inverted compared to those obtaining in bicyclizations. The Julia group has observed remarkable stereochemical control on annulation stereochemistry by the chloromercuri substituent (examples 6 and 7, Scheme 12); similar control is found in the cyclization to hydrindanes. The dienes (from dehydration) do not exhibit this effect. The β-keto ester terminator has been successfully used in annulations (example 8, Scheme 12) as has the alkynyl group to form the cyclohexanone ring (example 1, Scheme 17).

Other electrophiles have been applied mainly to geraniol derivatives (Section 1.9.2). Product stereochemistry is as anticipated except for initial addition to the double bond where, of the reagents examined, mercury salts appear to be unique in maintaining the stereochemical integrity of the double bond. $Hg(OAc)_2$ has the useful property of initiating cyclization at a vinyl group in the presence of a trisubstituted double bond (**26**);[42] this accords with the relative rates of reaction established for differently substituted alkenes.[43b] The reversible formation of the mercuricinium ion may also play its part. Phenylselenation provides a rare example[44] of initial attack at an 'internal' double bond to give (**27**).

The initiation of cyclization by ionization is best achieved using stabilized ions. The prototypical cyclization of allyl derivatives is the conversion of linalool to terpineol (Scheme 13), which the Arigoni group[45] has shown, in an elegant investigation, cyclizes with inversion of configuration. The Johnson group has examined a number of allylic alcohols which can be used as initiators (Scheme 14). Where ring junction stereochemistry is discernible in annulations (examples 1 and 5, Scheme 14) then *cis* stereochemistry, consistent with axial attack of the double bond, is observed. Terminal allenyl and alkynyl groups undergo *endo* cyclization, ultimately forming a cyclohexanone ring (example 4, Scheme 14).

**Table 1** Isomer Ratios Formed from Regioisomeric Allylic Alcohols

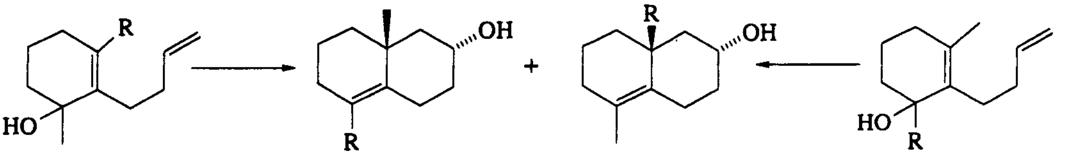

| *R* | | | *R* |
|---|---|---|---|
| Et | 48 | 52 | — |
| — | 60 | 40 | Et |
| $Pr^n$ | 70 | 30 | — |
| — | 85 | 15 | $Pr^n$ |
| $Bu^n$ | 70 | 30 | — |
| — | 88 | 12 | $Bu^n$ |

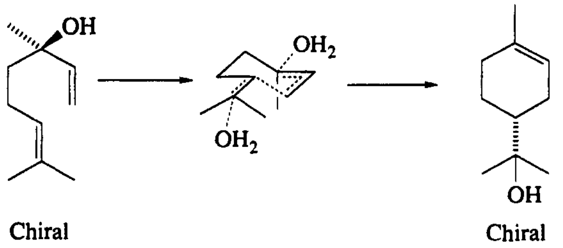

**Scheme 13**

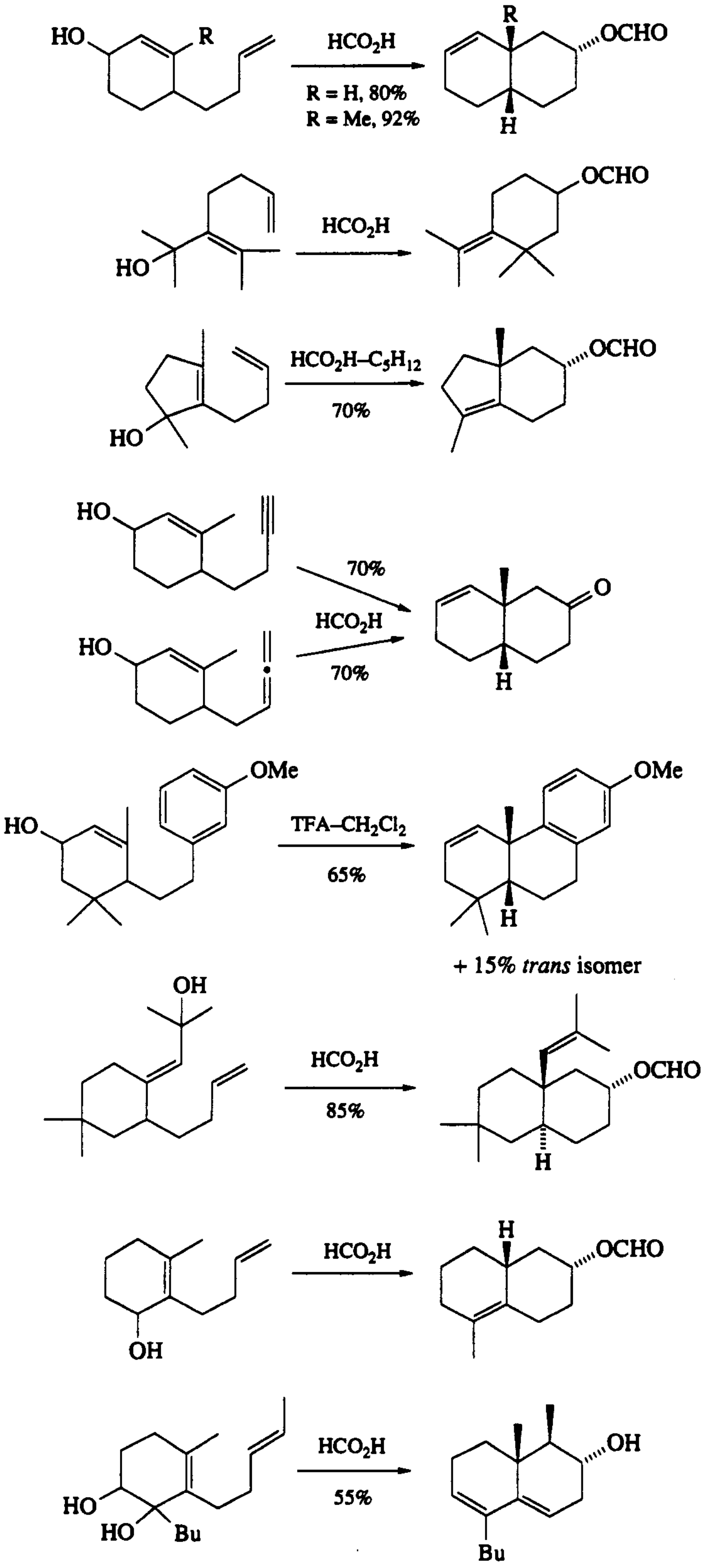
HO
R
HCO₂H
R = H, 80%
R = Me, 92%
R
OCHO
H
HCO₂H
HO
OCHO
HCO₂H–C₅H₁₂
70%
HO
OCHO
HO
70%
HCO₂H
HO
70%
O
H
HO
OMe
TFA–CH₂Cl₂
65%
OMe
H
+ 15% *trans* isomer
OH
HCO₂H
85%
OCHO
H
HCO₂H
OH
H
OCHO
HO
HO
Bu
HCO₂H
55%
OH
Bu

| *Example* | *Ref.* |
|---|---|
| 1 | 46 |
| 2 | 3 |
| 3 | 47 |
| 4 | 48 |
| 5 | 49 |
| 6 | 50 |
| 7 | 51 |
| 8 | 52 |

**Scheme 14**

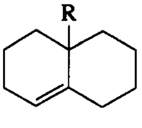

**(28)**

The anisyl ring is an efficient terminator (example 5, Scheme 14) and reacts mainly *para* to the methoxy, but *ca.* 15% of *ortho* reaction is also found. The exocyclic allylic alcohol cyclizes predominantly to a *trans*-decalin (example 6, Scheme 14); this parallels the stereochemical behavior of cyclohexyl cations. Where the putative allylic cation is unsymmetrical and cyclization to a six-membered ring can occur at either terminus, then reaction at the least-alkylated position is preferred (example 7, Scheme 14). Table 1 clearly establishes that a common allylic cation is not formed from the structurally isomeric alcohols, and reveals a tendency for bond formation at the least-hindered center.[50] Additionally there is a preference for bonding remote from the leaving group; however, unlike the linalool cyclization, chirality at the tertiary alcohol center does not lead to the formation of chiral products.[51] Little is known of the stereochemical fate of substituents on the cyclohexenyl ring; the diol (example 8, Scheme 14) cyclizes but under the reaction conditions dehydrates to a diene product. Prediction is complicated by the inability of octalins (**28**) to adopt a half-chair–chair conformation other than with the bridgehead substituent axial; with the substituent equatorial one of the rings must adopt a twist-boat conformation. Thus, to achieve efficient overlap at the reacting centers, it is likely that the cyclohexene ring is in a twist-boat conformation.

In spirocyclizations using the allylic initiators, the stereochemical question arises as to whether the initiator double bond shows a preference for the equatorial or axial position relative to the ring being formed. The Harding group has shown that the equatorial disposition is favored, especially when a 1,2-disubstituted alkene is cyclized, *e.g.* (**29**).[4c] As expected, when there is a choice between seven-membered ring formation or spirocyclization to a six-membered ring, the latter is observed (**30**).[60]

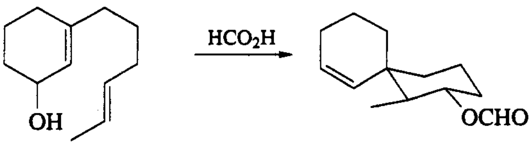

**(29)**

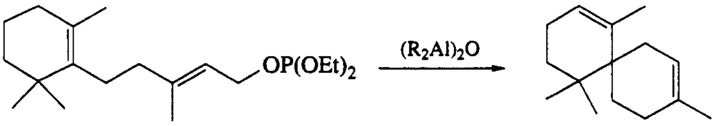

**(30)**

Enones are precursors of oxyallyl cations, either by enol ester formation and protonation as developed by the Harding group, or by coordination with Lewis acids. In Scheme 15 some typical cyclizations are illustrated. Under certain circumstances (example 4, Scheme 15) secondary rearrangement can occur by hydride migration. The vinyl compound (example 2, Scheme 15) does not give a rearrangement product, suggesting that the hydride migrations are not concerted. It is notable that cyclization of this enone in the absence of acetic anhydride leads to termination predominantly by elimination. In example 5 (Scheme 15) stereochemical control is exerted at four centers; in the cyclization a chair transition state with the pendant methyl group equatorial and the double bond oriented *exo* accounts for the relative stereochemistry at three centers. The fourth center is established by stereoselective alkylation of the immediate cyclization product, presumably a titanium enolate. Scheme 16 shows how oxonium ions derived from aldehydes or their acetals can induce cyclization. In certain cases (examples 1 and 4, Scheme 16) the stereochemistry found is consistent with a catalyzed 'ene' reaction. The oxidative cyclizations reported by the Corey group (example 5, Scheme 16) may involve oxonium ion intermediates. The successful cyclization[61] of the epoxide (**31**) suggests that benzylic ions could be useful initiators. Another ion which has not been widely examined is that derived from the ketene dithioacetal group (**32**).[62]

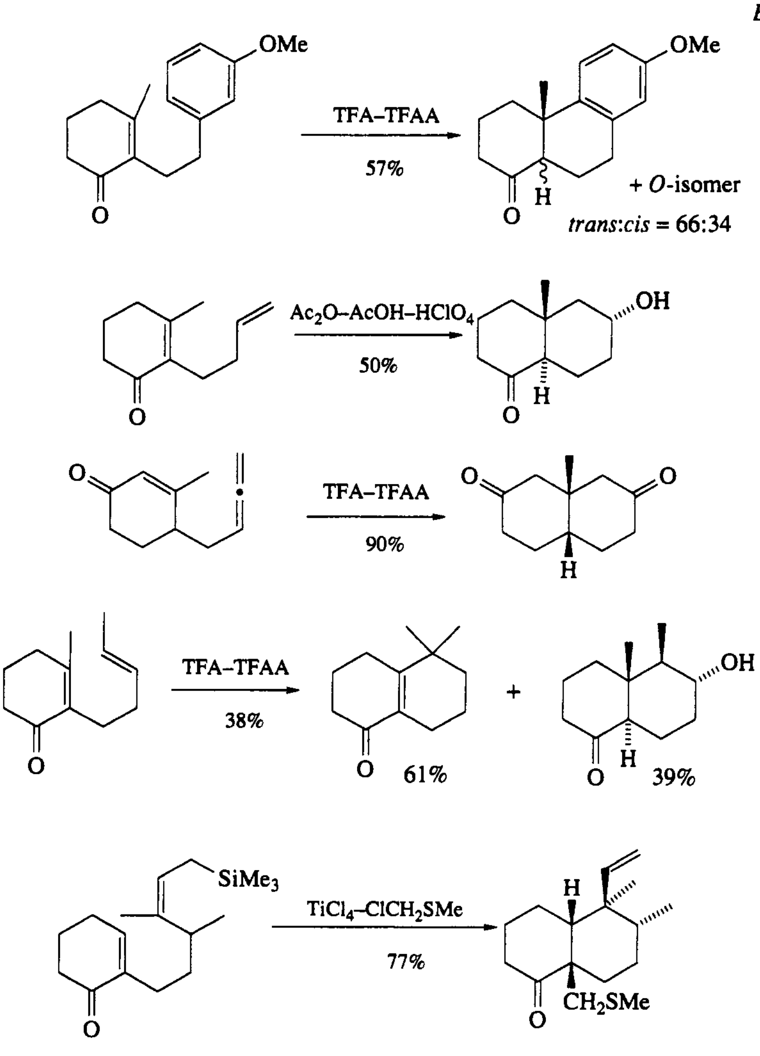
OMe
TFA–TFAA
57%
OMe
H
O
O
+ *O*-isomer
*trans*:*cis* = 66:34
$Ac_2O$–AcOH–$HClO_4$
50%
OH
H
O
O
TFA–TFAA
90%
O
O
O
H
TFA–TFAA
38%
O
O 61%
+
OH
H
O 39%
$SiMe_3$
$TiCl_4$–$ClCH_2SMe$
77%
H
$CH_2SMe$
O
O

| Example | Ref. |
|---|---|
| 1 | 53 |
| 2 | 17 |
| 3 | 48 |
| 4 | 53 |
| 5 | 54 |

**Scheme 15**

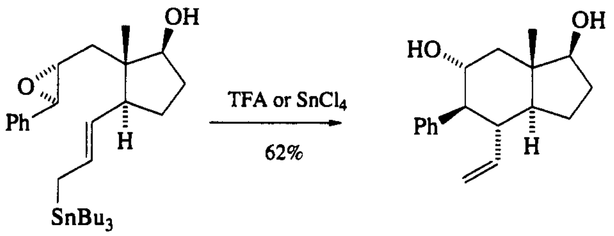
OH
O
Ph
H
$SnBu_3$
TFA or $SnCl_4$
62%
HO
OH
Ph
H

**(31)**

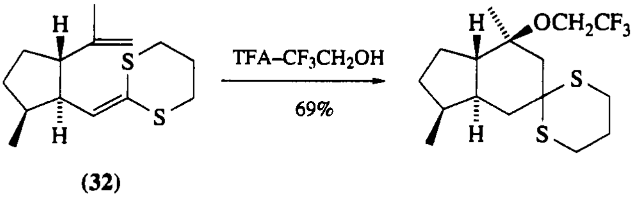
H
S
S
H
TFA–$CF_3CH_2OH$
69%
H
$OCH_2CF_3$
S
S
H

**(32)**

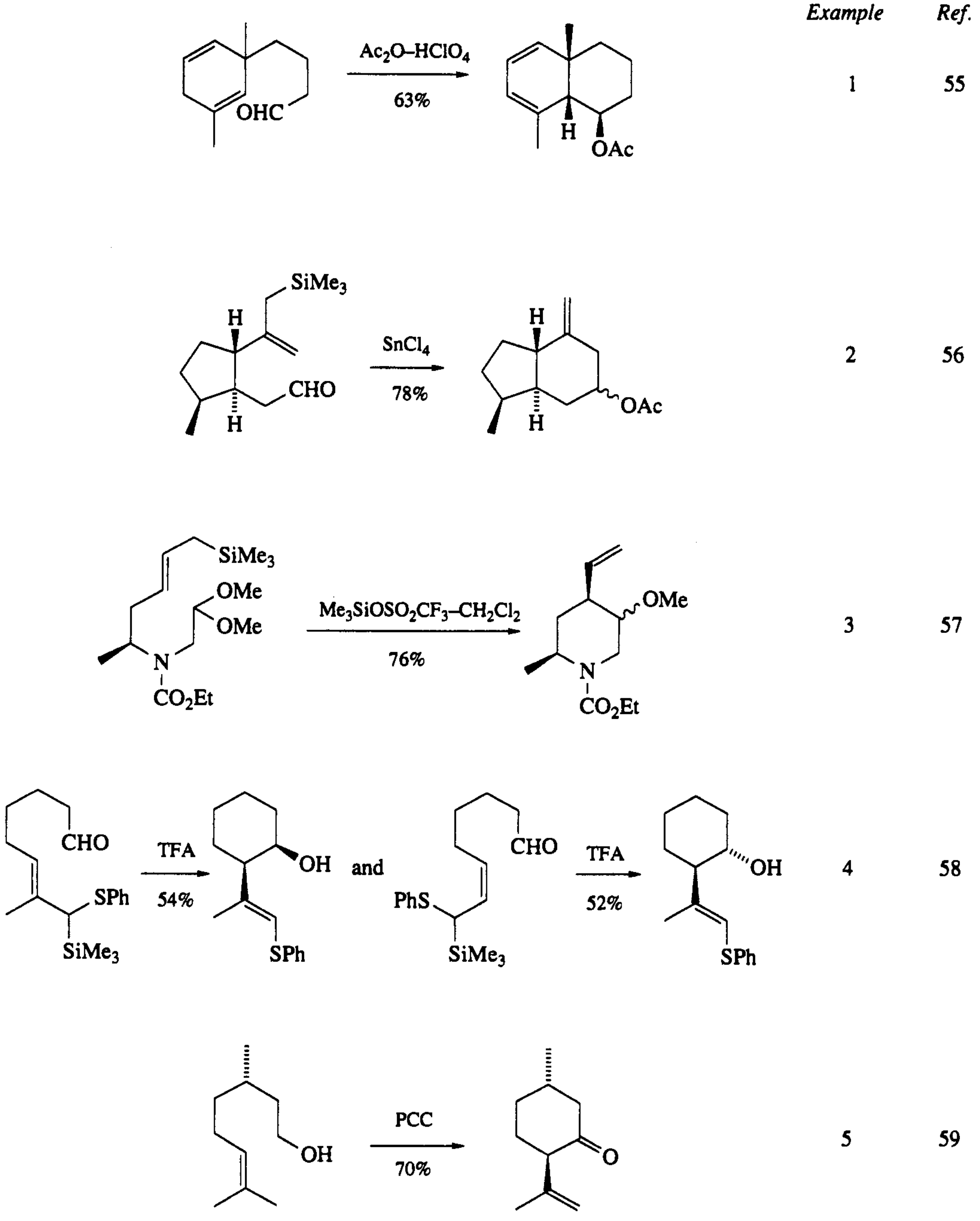

Example
Ref.
OHC
Ac2O–HClO4
63%
H
OAc
1
55
SiMe3
H
CHO
H
SnCl4
78%
H
OAc
H
2
56
SiMe3
OMe
OMe
N
CO2Et
Me3SiOSO2CF3–CH2Cl2
76%
OMe
N
CO2Et
3
57
CHO
SPh
SiMe3
TFA
54%
OH
SPh
and
CHO
PhS
SiMe3
TFA
52%
OH
SPh
4
58
OH
PCC
70%
O
5
59

**Scheme 16**

Ionization methods leading to unstabilized cations can give preparatively useful yields when the center is tertiary. In Scheme 17 a variety of examples is shown. Cyclohexene epoxides (example 2, Scheme 17) are generally useful initiators for monocyclizations. The cyclopropyl ketone is effective with aryl termination (example 4, Scheme 17), but in example 5 (Scheme 17) the ion obtained on cyclization is quenched by intramolecular attack of the enol.

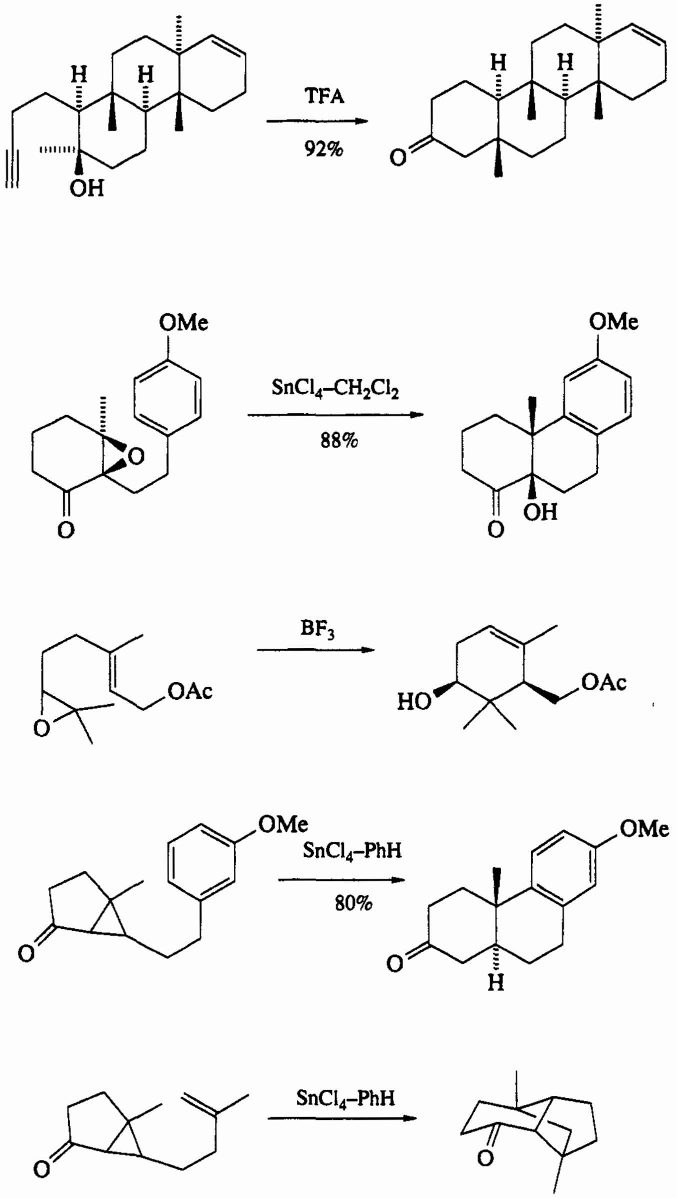

| Example | Ref. |
|---|---|
| 1 | 63 |
| 2 | 53 |
| 3 | 4a |
| 4 | 64 |
| 5 | 64 |

Scheme 17

### 1.9.5.3 Seven-membered Ring Formation

The 7-*endo* cyclization has been little investigated and can be complicated by secondary reactions. Some examples are shown in Scheme 18. The more stringent conditions required and the lower yield obtained in example 1 (Scheme 18) compared with the lower homolog (**11**) illustrate the difficulties associated with seven-membered ring formation. A common complicating factor (examples 2 and 3, Scheme 18) is further 5-*endo* cyclization of the ion (**33**) from monocyclization. This does not occur with the alkynyl compound (example 4, Scheme 18) nor when the double bond is endocyclic to the newly formed ring (examples 6 and 7, Scheme 18). Cyclization in the 7-*exo* mode (example 5, Scheme 18) is also accompanied by bicyclization and the Johnson group has made use of this in an elegant synthesis of longifolene. The use of recently developed terminators might prevent the second cyclizations occurring.

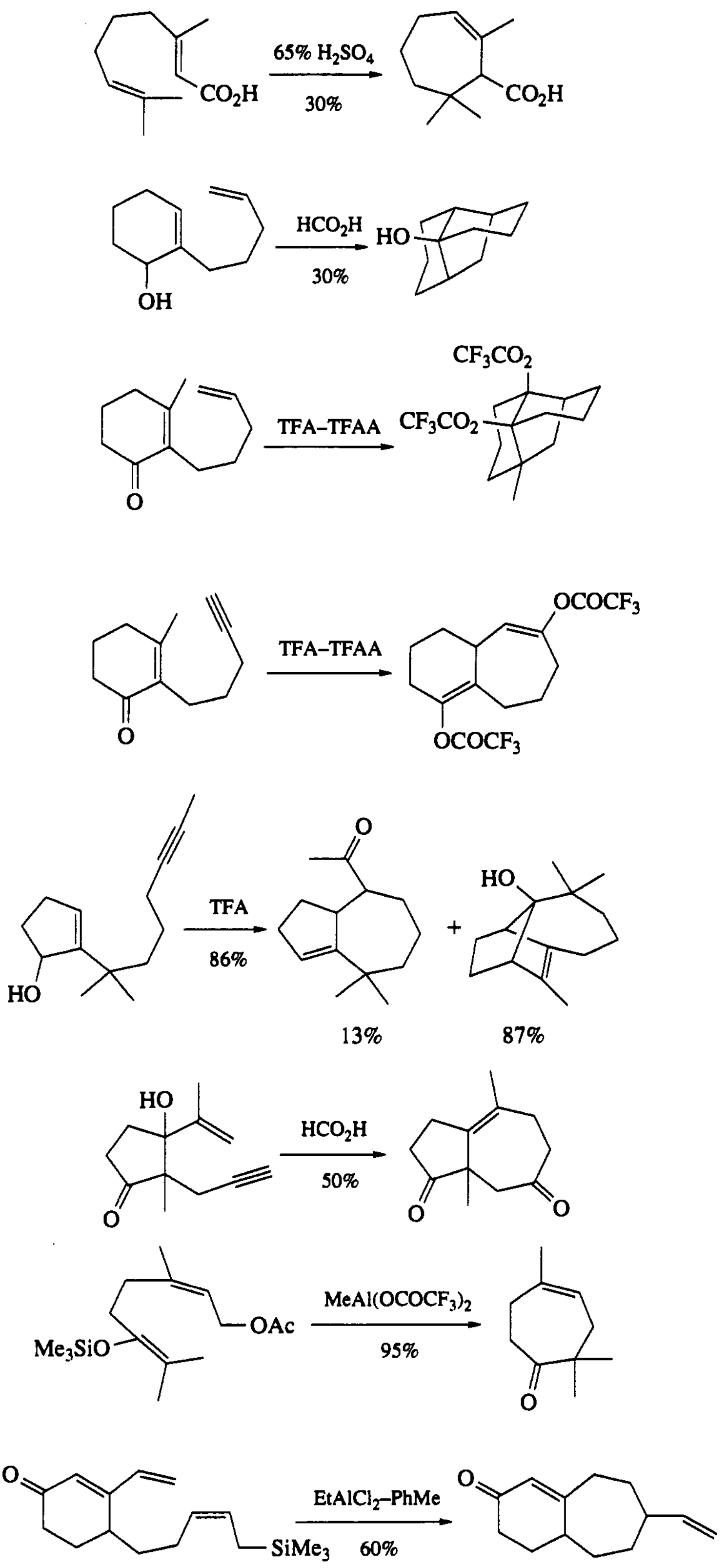
65% $H_2SO_4$
30%
$CO_2H$
$CO_2H$
$HCO_2H$
30%
OH
HO
TFA–TFAA
$CF_3CO_2$
$CF_3CO_2$
O
TFA–TFAA
$OCOCF_3$
$OCOCF_3$
O
TFA
86%
HO
O
HO
13%
87%
$HCO_2H$
50%
HO
O
O
O
$MeAl(OCOCF_3)_2$
95%
$Me_3SiO$
OAc
O
$EtAlCl_2$–PhMe
60%
O
$SiMe_3$
O

| *Example* | *Ref.* |
|---|---|
| 1 | 65 |
| 2 | 66 |
| 3 | 68 |
| 4 | 68 |
| 5 | 67 |
| 6 | 69 |
| 7 | 33 |
| 8 | 31 |

**Scheme 18**

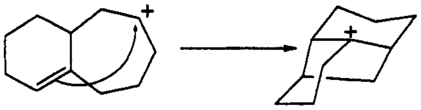

(33)

## 1.9.6 BICYCLIZATIONS

### 1.9.6.1 Bicyclo[4.3.0] Ring Formation

The Johnson group has used the tetramethylallyl cation as initiator for the synthesis of *trans*-hydrindanes (Scheme 19) using a variety of different terminating groups. The chiral acetal (34) has been

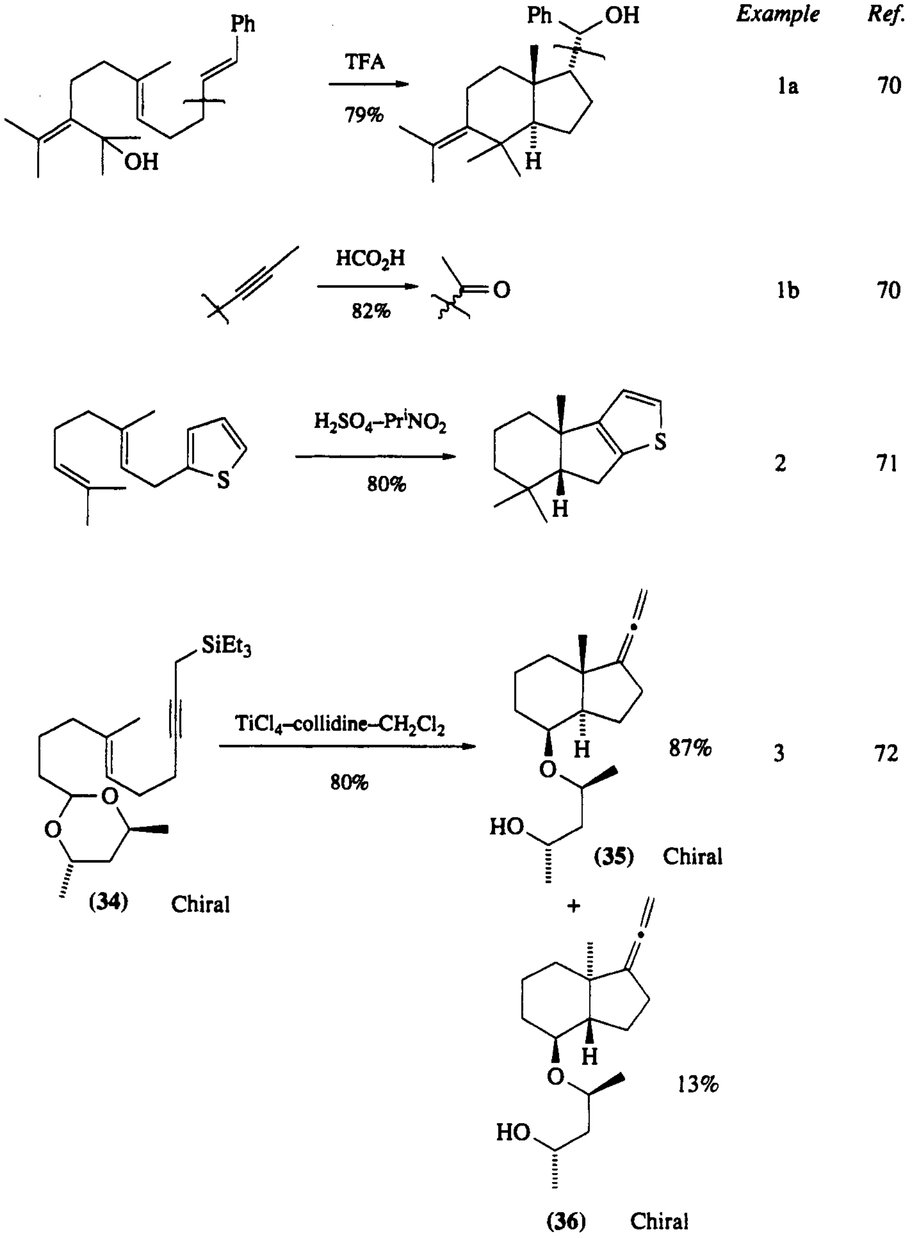
Example
Ref.
Ph
OH
TFA
79%
Ph
OH
H
1a
70
HCO₂H
82%
O
1b
70
S
H₂SO₄–PrⁱNO₂
80%
S
H
2
71
SiEt₃
TiCl₄–collidine–CH₂Cl₂
80%
O
O
(34) Chiral
H
O
HO
87%
(35) Chiral
3
72
+
H
O
HO
13%
(36) Chiral

Scheme 19

cyclized[72] in an enantioselective manner to the *trans*-hydrindanes (**35**) and (**36**). This accords with the stereochemical model in which the C—O bond next to the axial methyl in the acetal ring breaks and the double bond attacks from the opposite face; the driving force for this selection is postulated to be relief of the axial methyl–hydrogen interaction in the acetal ring. There are two chair–chair conformations (**37** → **35**) and (**38** → **36**) which have this feature, and it is not immediately obvious why (**37**) is favored over (**38**).

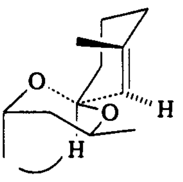

(**37**)

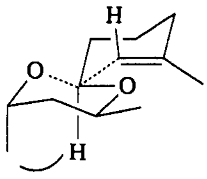

(**38**)

### 1.9.6.2 Bicyclo[4.4.0] Ring Formation

The majority of bicyclizations described lead to *trans*-decalin derivatives and the most extensive results relate to the cyclization of farnesol derivatives and the synthesis of estrone-related compounds (see Section 1.9.8.1). Early work was concerned with testing the validity of the Stork–Eschenmoser hypothesis in accounting for ring junction stereochemistry, and showed that both (*Z*)- and (*E*)-isomers gave *trans*-decalins when the terminating double bond was electron deficient due to conjugation with carboxylic acid or ester functions, *e.g.* (**39** → **40**).[2] The cyclization was shown to be a stepwise process *via* a common intermediate formed from (*Z*)- or (*E*)-alkenes. Subsequently, the Semenovskii group has shown that alkenes with internal (*Z*)-double bonds can be cyclized to *cis*-decalins in acceptable yields (Scheme 20). Other cases where good yields have been reported for *cis*-decalins are from the acetal (example 3, Scheme 20), the acylimonium ion initiated cyclization (example 5, Scheme 20) and with the estrone precursor (example 4, Scheme 20). However, there are a significant number of cases where varying proportions of *trans*-decalins are formed. As a route to *cis*-decalins this approach must be treated with some caution, and careful planning in terms of initiator, nucleophilicity of participating double bonds and termination is required to ensure success. The annulation approach (see Scheme 14) to *cis*-decalins is more predictable. There is no such reservation in applying the bicyclization route to the synthesis of *trans*-decalins. Scheme 21 shows a variety of farnesyl derivatives which have been cyclized to give useful synthetic intermediates. Where the stereochemical integrity of the initiating double bonds needs to be reflected in the product then, as for monocyclization, $Hg(OCOCF_3)_2$ is the reagent of choice (example 2, Scheme 21). Phenyl-selenyl and -sulfenyl cations offer promise in inducing bicyclizations (examples 4 and 5, Scheme 21), whereas epoxide ring opening and bromonium ion formations have given disappointing results in terms of yield. Undoubtedly the substituted allylic cations and oxonium ions are the most generally effective initiators of bicyclizations. In Scheme 22 some results obtained in these cyclizations are listed. In example 2 (Scheme 22) and example 5 (Scheme 22) bicyclization around a tetraalkylalkene is shown to be possible. The sulfur-stabilized cation, derived from the ketene dithioacetal (example 6, Scheme 22) shows promise as an initiator, as does the acylium ion (example 4, Scheme 22). In the latter case, the vinylsilane terminator is used and the chair–chair transition state geometry is adopted where the bulkier group is equatorial. Use of a chiral acetal allows enantioselective cyclization (example 3, Scheme 21). The preference for one series is in accord with the explanation developed for enantioselection in (**34**).

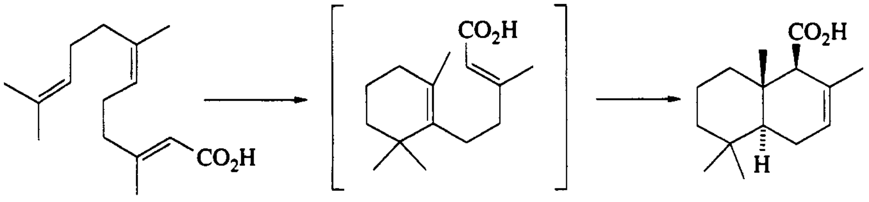

(**39**) (**40**)

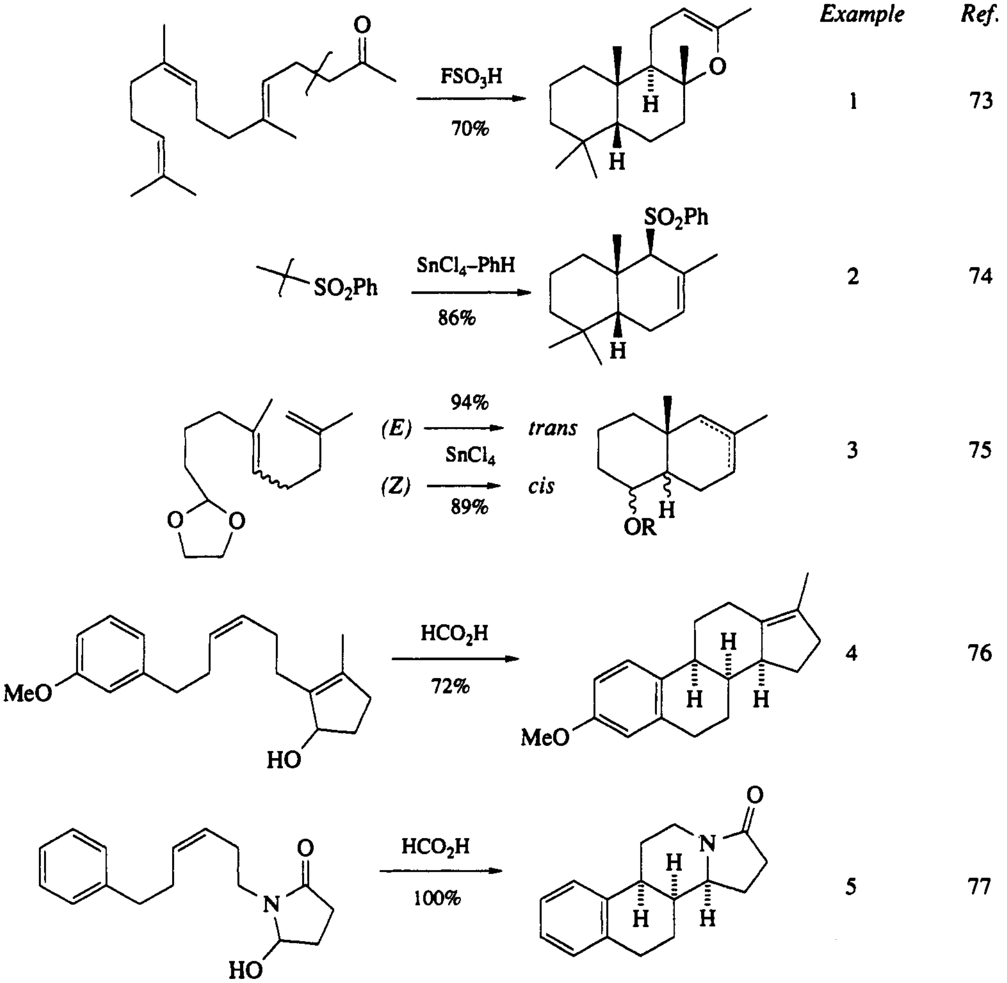
Example
Ref.
O
FSO$_3$H
70%
H
O
H
1
73
SO$_2$Ph
SnCl$_4$–PhH
86%
SO$_2$Ph
H
2
74
94%
(E)
trans
SnCl$_4$
(Z)
cis
89%
O
O
OR
H
3
75
HCO$_2$H
72%
MeO
HO
H
H
H
MeO
4
76
O
HCO$_2$H
100%
N
HO
O
N
H
H
H
5
77

**Scheme 20**

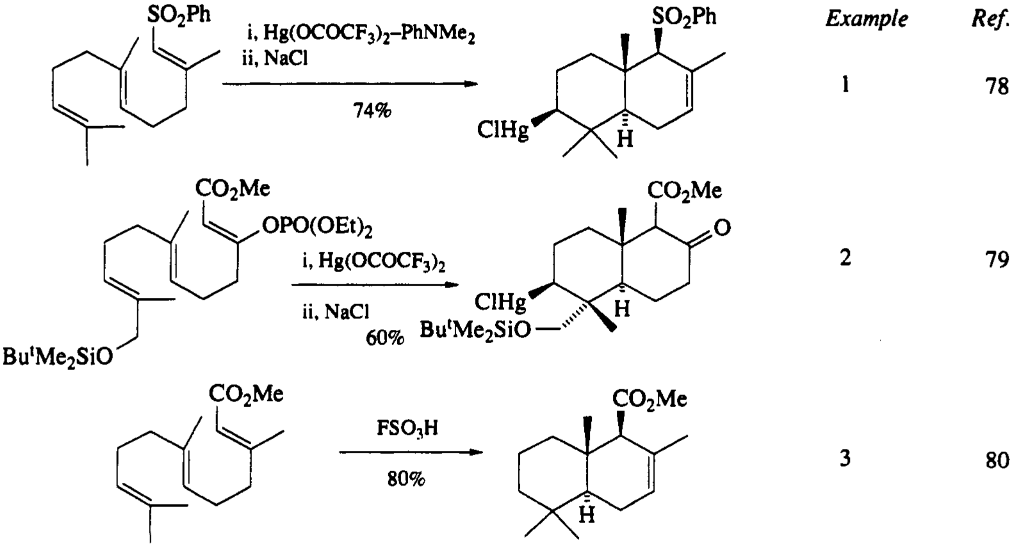
SO$_2$Ph
i, Hg(OCOCF$_3$)$_2$–PhNMe$_2$
ii, NaCl
74%
SO$_2$Ph
ClHg
H
Example
Ref.
1
78
CO$_2$Me
OPO(OEt)$_2$
i, Hg(OCOCF$_3$)$_2$
ii, NaCl
60%
Bu$^t$Me$_2$SiO
CO$_2$Me
O
ClHg
H
Bu$^t$Me$_2$SiO
2
79
CO$_2$Me
FSO$_3$H
80%
CO$_2$Me
H
3
80

**Scheme 21**

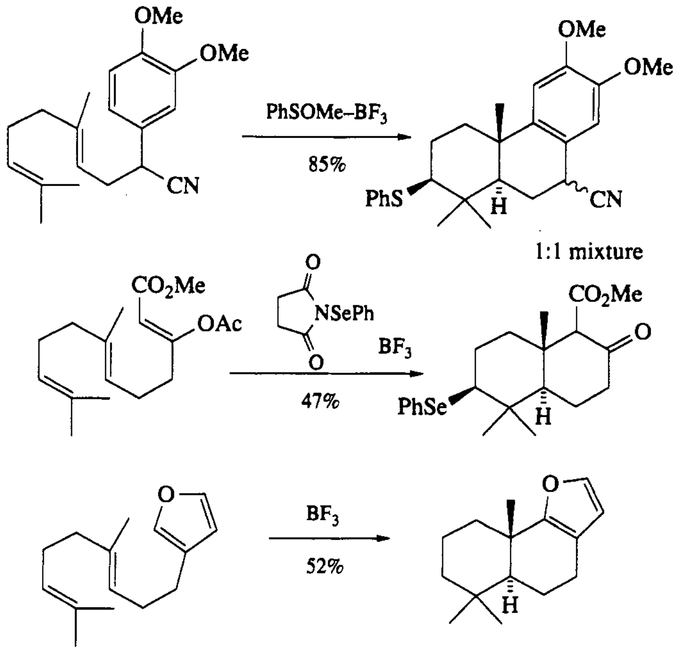
OMe
OMe
CN
PhSOMe–BF$_3$
85%
OMe
OMe
PhS
H
CN
1:1 mixture
CO$_2$Me
OAc
O
NSePh
O
BF$_3$
47%
CO$_2$Me
O
PhSe
H
O
BF$_3$
52%
O
H

| *Example* | *Ref.* |
|---|---|
| 4 | 81 |
| 5 | 81 |
| 6 | 82 |

**Scheme 21** ***(continued)***

## 1.9.7 TRI- AND TETRA-CYCLIZATIONS

Most cyclizations in this category were designed to form steroids and related compounds and are discussed in Section 1.9.8. Early attempts to cyclize geranylgeraniol derivatives were not promising and it was not until the late 1960s that the Johnson group demonstrated that substantial yields of tri- and tetracyclic compounds could be prepared by Lewis acid induced cyclization of acetals, *e.g.* **(41)** → **(42)**[89] and **(43)** → **(44)**;[90] mixtures of isomers were obtained due to initiation and termination not being specific, but the carbon skeletons were shown to be *trans–anti–trans–(anti)*. Later the same group showed that the

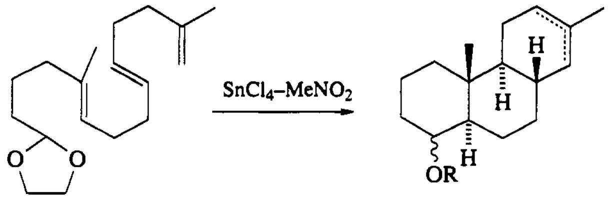
O
O
SnCl$_4$–MeNO$_2$
H
H
H
OR

**(41)** **(42)**

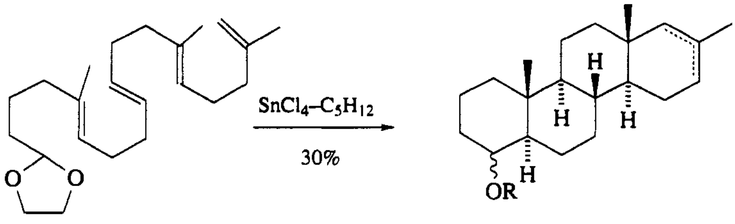
O
O
SnCl$_4$–C$_5$H$_{12}$
30%
H
H
H
H
OR

**(43)** **(44)**

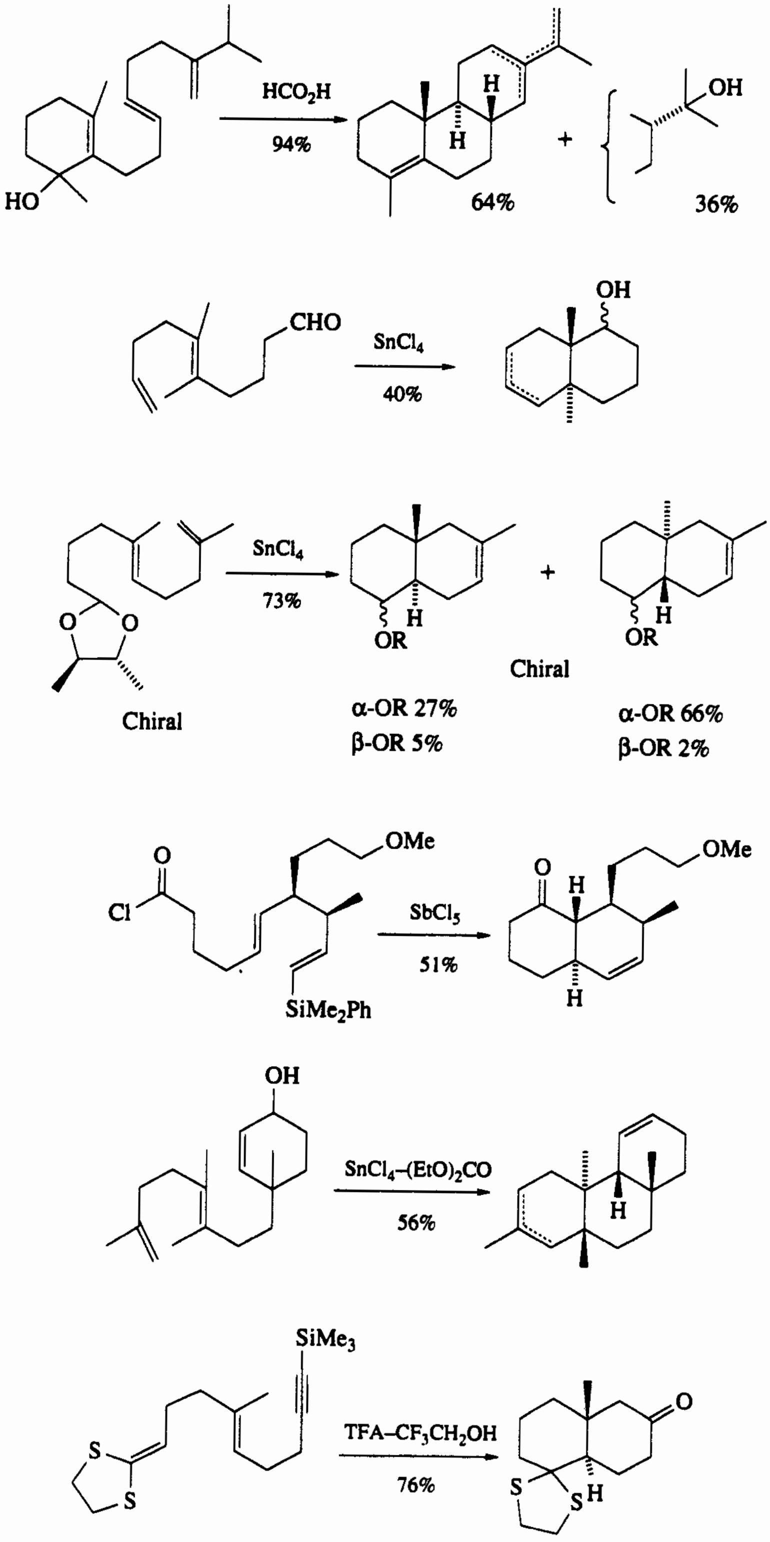
HCO$_2$H
94%
64%
36%
HO
H
H
OH
CHO
SnCl$_4$
40%
OH
SnCl$_4$
73%
O
O
Chiral
H
OR
H
OR
Chiral
α-OR 27%
β-OR 5%
α-OR 66%
β-OR 2%
O
Cl
OMe
SiMe$_2$Ph
SbCl$_5$
51%
O
H
H
OMe
OH
SnCl$_4$–(EtO)$_2$CO
56%
H
SiMe$_3$
S
S
TFA–CF$_3$CH$_2$OH
76%
O
S
S
H

| *Example* | *Ref.* |
|---|---|
| 1 | 83 |
| 2 | 84 |
| 3 | 85 |
| 4 | 86 |
| 5 | 87 |
| 6 | 88 |

**Scheme 22**

tetramethylallyl initiating group was also effective (Scheme 23) in forming 6,6,6 and 6,6,7 ring systems. It is not surprising that two diastereoisomers are formed in example 2 (Scheme 23) since the initiating group is remote from the chiral terminating function and unable to induce enantioselections in the formation of the first two rings. The alkyne (example 3, Scheme 23) cyclized as anticipated with five-membered ring formation being favored. However, the acylimonium ion induced cyclization[77] of (**45**) generates the azasteroid skeleton (**46**), perhaps due to rearrangement of an intermediate cyclopentylidene cation. Polyalkene cyclizations to form triterpenes have also been examined (Scheme 24). The van Tamelen group has investigated epoxyalkene cyclizations (examples 1 and 2, Scheme 24) extensively, with yields varying from moderate to poor; however, true assessment of the method is difficult since the cyclization precursors were, in a number of cases, mixtures of diastereoisomers. The Ireland group assessed a number of initiating groups (examples 3, 4 and 5, Scheme 24) again with yields varying from moderate to poor. In all of the Scheme 24 examples substantial amounts of bicyclization products were

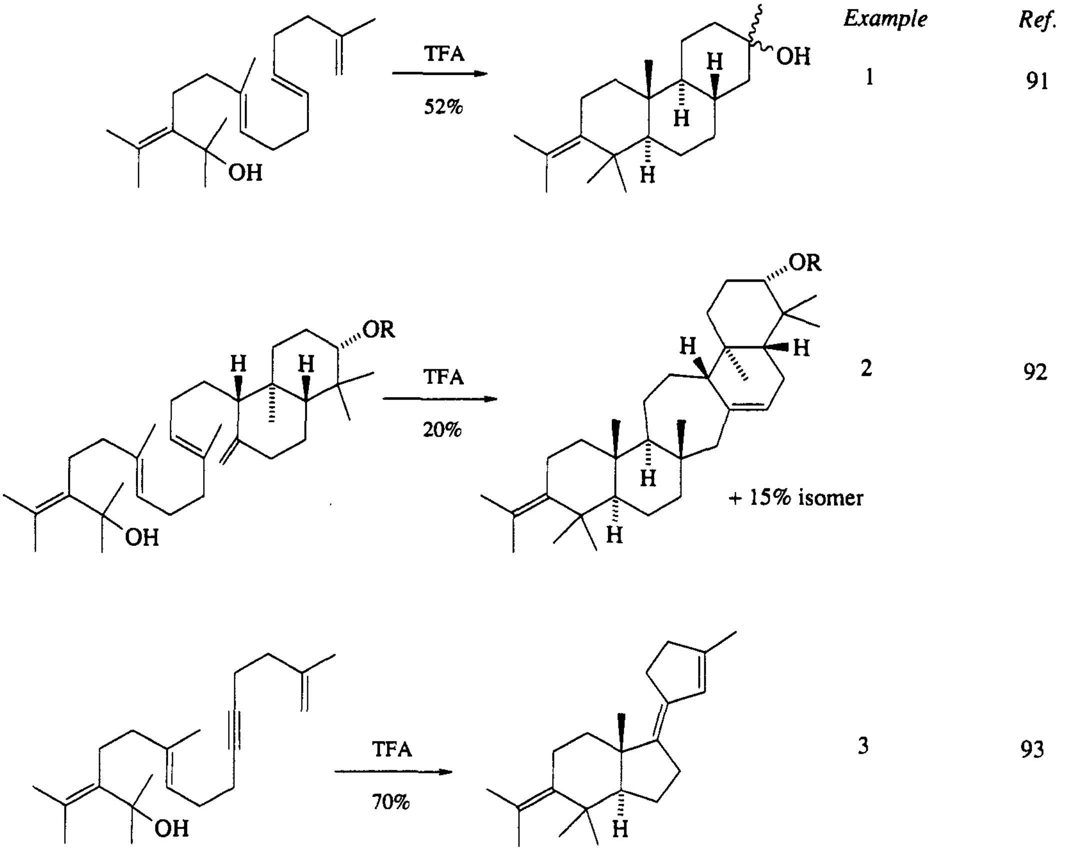

**Scheme 23**

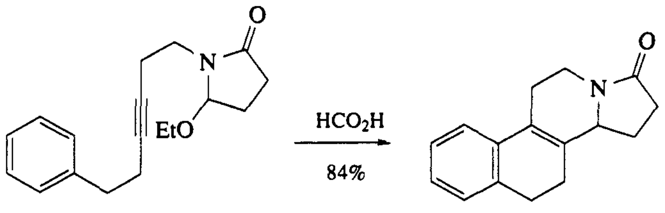

(**45**)

(**46**)

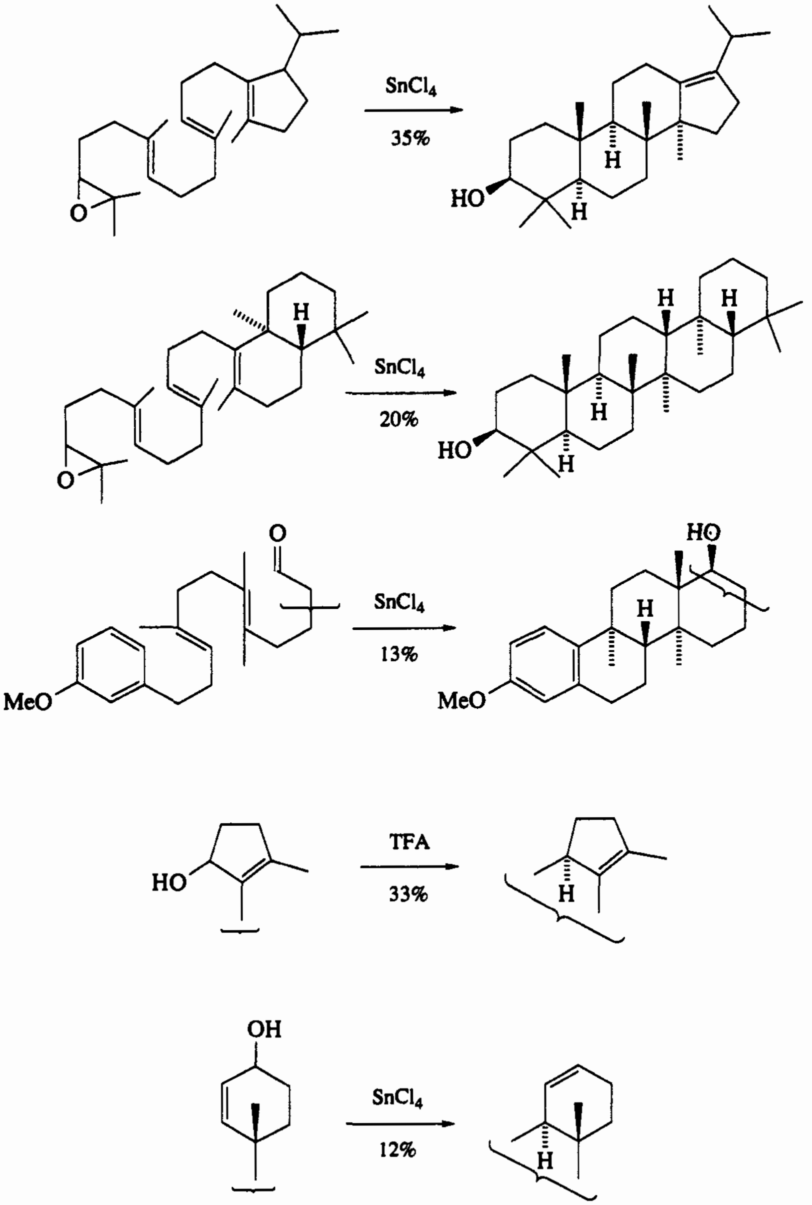

| *Example* | *Ref.* |
|---|---|
| 1 | 94 |
| 2 | 95 |
| 3 | 63 |
| 4 | 63 |
| 5 | 87 |

**Scheme 24**

obtained. This was also observed by the Corey group[96] in the cyclization of the ester (**47**). The cyclization of the furan (**48**)[97] shows diastereoselection in favor of the isomer with the sulfonyl group axial. This can be rationalized using Bartlett's suggestion[5] that only bicyclizations are concerted (Section 1.9.10). The diastereoselection is then not determined by a chair-like conformation for the incipient ring C; instead it is dependent on the relative rates at which conformers form the enantiomeric bicyclic ring systems (**49**). In particular, the rates of cyclization of the rotamers about the bond indicated will influence diastereoselection. A similar explanation accounts for the formation of two diastereoisomers from cyclization of the alcohol (example 2, Scheme 23); the chiral unit is too distant to have any significant influence in determining the absolute configuration adopted by rings A and B. The tricyclization of the furan (**50**) must involve independent monocyclization and bicyclization and suggests that this might be a strategy worth exploring further.[98]

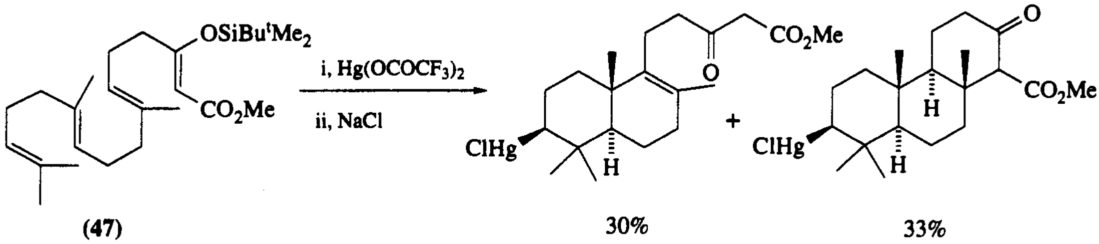
OSiBu$^t$Me$_2$
CO$_2$Me
i, Hg(OCOCF$_3$)$_2$
ii, NaCl
CO$_2$Me
O
ClHg
H
+
O
CO$_2$Me
ClHg
H
H
30%
33%

**(47)**

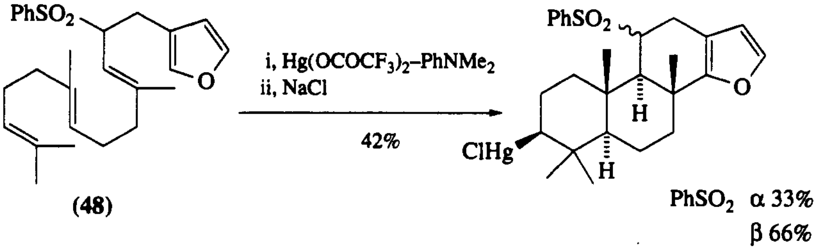
PhSO$_2$
O
i, Hg(OCOCF$_3$)$_2$–PhNMe$_2$
ii, NaCl
42%
PhSO$_2$
O
H
ClHg
H
PhSO$_2$ α 33%
β 66%

**(48)**

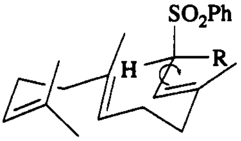

**(49)**

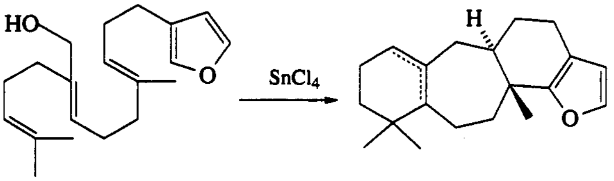
HO
O
SnCl$_4$
H
O

**(50)**

## 1.9.8 SYNTHESIS OF STEROIDS AND RELATED COMPOUNDS

### 1.9.8.1 Aromatic Steroids

The Johnson group's approach to estrone (Scheme 25)[99] has been much developed since variants of the basic cyclization have been used to elicit further stereochemical and mechanistic information. Groen

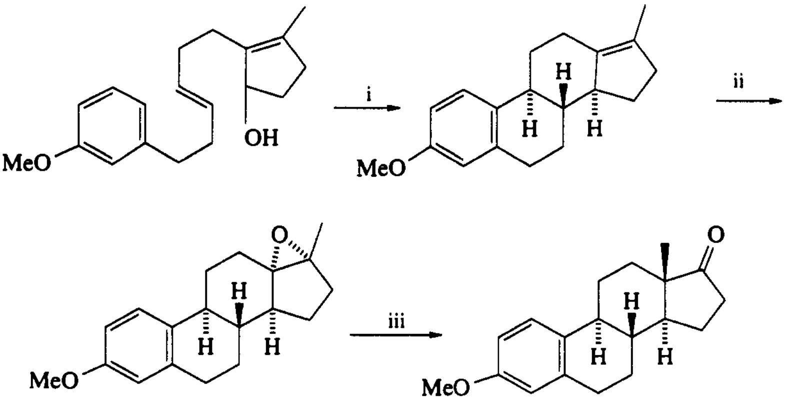
MeO
OH
i
MeO
H
H
H
ii
O
MeO
H
H
H
iii
O
MeO
H
H
H

i, $HCO_2H$; ii, HOBr, KOH; iii, $BF_3$

**Scheme 25**

and Zeelen[100] examined the diastereoselection obtained when a methyl group was introduced at varying positions on the methylenes of the carbon chain (Table 2). The results agree with a product-like chair–chair transition state where methyls at C-7 or C-12 favor the equatorial orientation. The methyl at C-6 is found only in the axial orientation, presumably to relieve an unfavorable equatorial methyl interaction with the vinylic methyl group. Axial disposition of the methyl at C-11 is also preferred, presumably to avoid the steric repulsion which would ensue with C-1 if the methyl were equatorial. Cyclization of the thiophene analogs (examples 1 and 2, Scheme 26) gives analogous results. With the dimethyl compound

**Table 2** Stereochemistry of Cyclization of Monomethyl Derivatives

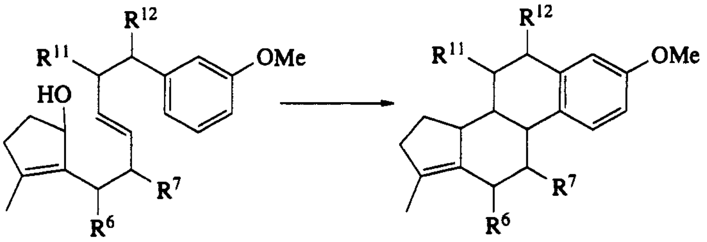
R12
R11
HO
OMe
R7
R6
R12
R11
OMe
R7
R6

| *Me position* | *Yield (%)* | *Axial:equatorial* |
|---|---|---|
| $R^{12}$ | 64 | 10:90 |
| $R^{11}$ | 42 | 86:14 |
| $R^{7}$ | 60 | 12:88 |
| $R^{6}$ | 65 | 100:0 |

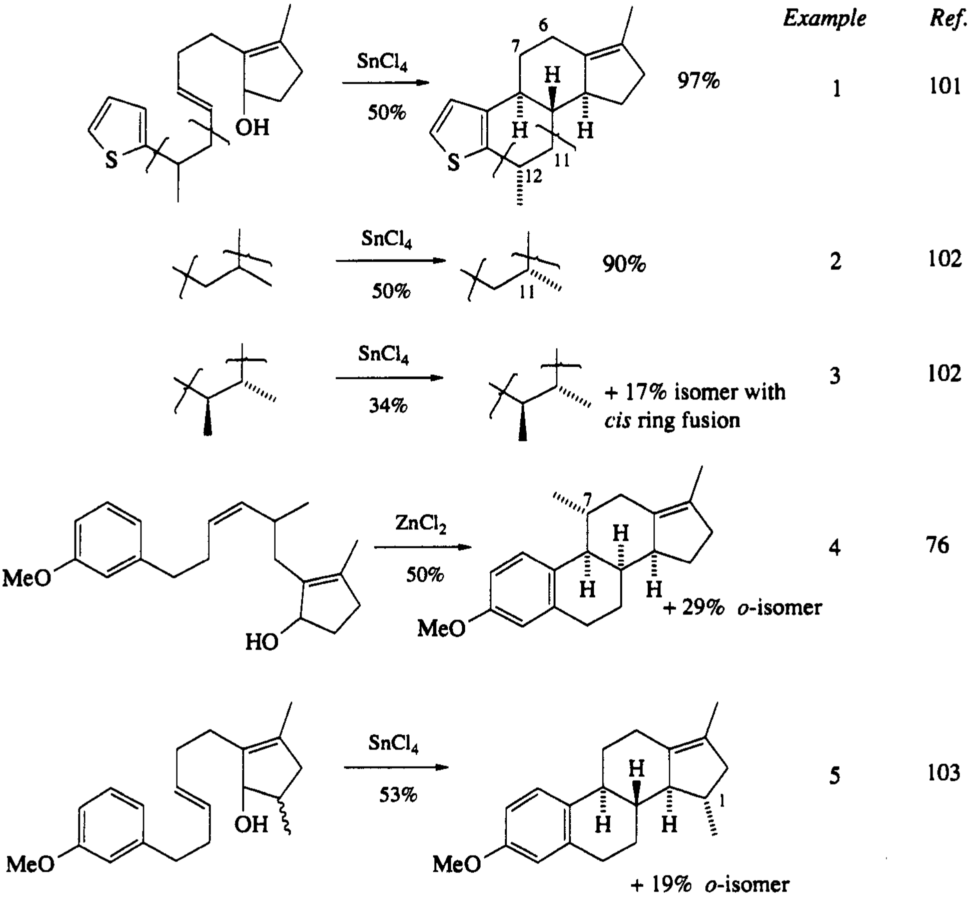
Example
Ref.
OH
S
SnCl4
50%
6
7
H
H
H
11
12
S
97%
1
101
SnCl4
50%
11
90%
2
102
SnCl4
34%
+ 17% isomer with cis ring fusion
3
102
MeO
HO
ZnCl2
50%
7
H
H
H
MeO
+ 29% o-isomer
4
76
MeO
OH
SnCl4
53%
H
H
H
1
MeO
+ 19% o-isomer
5
103

**Scheme 26**

(example 3, Scheme 26), the diaxial dimethyl compound is the major product but appreciable amounts of the product with *cis* ring fusion are formed by a stepwise mechanism. A *cis* product is also formed from the (Z)-alkene (example 4, Scheme 26) with the methyl adopting an equatorial orientation. Diastereoselection is also found when a methyl is introduced at C-1 (example 5, Scheme 26), leading to preferred attack on the least-hindered face of the allyl cation. An azasteroid has been prepared by the Speckamp group[104] in excellent yield by cyclization of the amide (**51**), while the Ziegler group[105] has described the novel cyclization of the aldehyde (**52**). A comparison of different initiators by the Sutherland group (Scheme 27) showed that the epoxide (example 1, Scheme 27) was unsatisfactory, giving mainly monocyclization, but that both the enone (example 2, Scheme 27) and the derived methylcyclohexenol (example 3, Scheme 27) could be cyclized in acceptable yields.

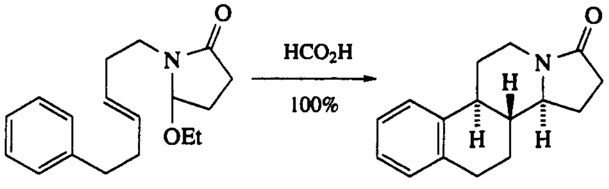

**(51)**

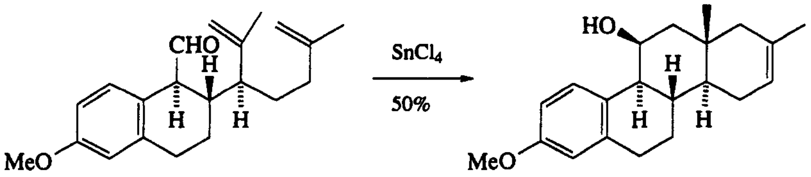

**(52)**

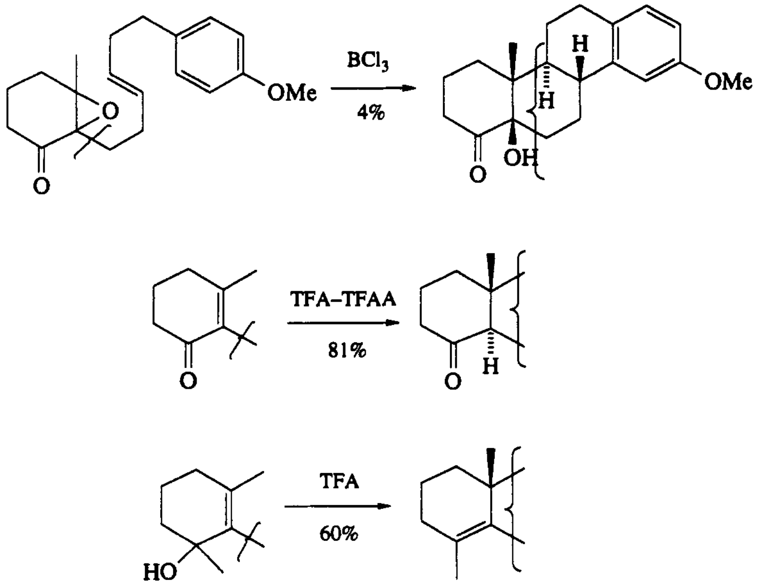

| *Example* | *Ref.* |
|---|---|
| 1 | 106 |
| 2 | 106 |
| 3 | 106 |

**Scheme 27**

### 1.9.8.2 Nonaromatic Steroids and Related Compounds

In the first successful production of tetracycles by polyalkene cyclization the Johnson group used oxonium ion initiation to convert an acetal to a D-homosteroid (**43**). The yield was moderate but *trans–anti–trans–anti* stereochemistry was demonstrated. Subsequently the steroid skeleton was prepared using the allylsilane terminator (example 1, Scheme 28) and, more recently, the yield has been almost doubled by stabilization of the ion notionally produced by bicyclization (example 2, Scheme 28); perhaps two consecutive concerted bicyclizations are involved. The methylcyclohexenyl cation was also an effective trigger for cyclization to D-homosteroids (Scheme 29) when the terminating group was methylene (example 1, Scheme 29) or trimethylsilylalkynyl (example 3, Scheme 29). With the isopropylidene terminator (example 2, Scheme 29) the steroid skeleton was formed, but the cation then underwent hydride and methyl migration. These migrations could be suppressed by stabilization of the terminal cation with aryl groups (example 4, Scheme 29) of which α-naphthyl was the most effective. The *p*-methoxystyryl group was ineffective, probably due to the independent formation of the highly stabilized *p*-methoxybenzyl cation by protonation of the *p*-methoxystyryl group. Clearly if the terminating cation is formed more readily or competitively with the initiating cation, successful cyclizations are unlikely. Cyclization of the alkyne (example 5, Scheme 29) forms the steroid skeleton without rearrangement. Trapping of the vinylic cation with ethylene carbonate prevents ring expansion to the D-homosteroid. When the terminal group was vinyl[40] then control over the C–D ring junction stereochemistry was lost; *cis* isomer was formed by a proton elimination–monocyclization sequence. The intervention of this mechanism can be detected by use of *O*-deuterated acids, since it leads to deuterium incorporation (Scheme 30).

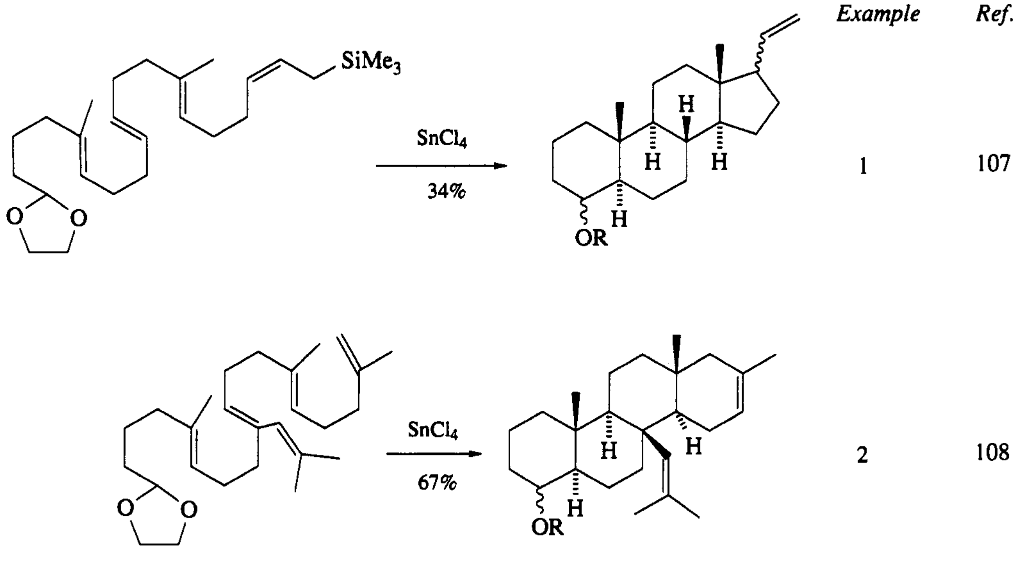

Scheme 28

The dimethylcyclohexenyl cation has been used to prepare D-homosteroid (example 1, Scheme 31) and steroid skeletons (example 2, Scheme 31). One solution to the problem of preparing steroids without an alkyl substituent at C-4 is the use of a phenyldimethylsilyl substituent at one terminus of the allyl cation. Carbon bond formation occurs remote from the silyl substituent, which is then eliminated by protodesilylation *in situ* (Scheme 32). Reduction of the number of alkyl substituents on the allylic cation has a dramatic effect on yield (example 4, Scheme 31), suggesting that useful yields are obtained only when the allylic cations have three or four carbon substituents.

The initiator which has been studied most extensively (Scheme 33)[117–125] is the dimethylcyclopentenyl cation, which is generated from the corresponding alcohol by reaction with protonic or Lewis acids. An

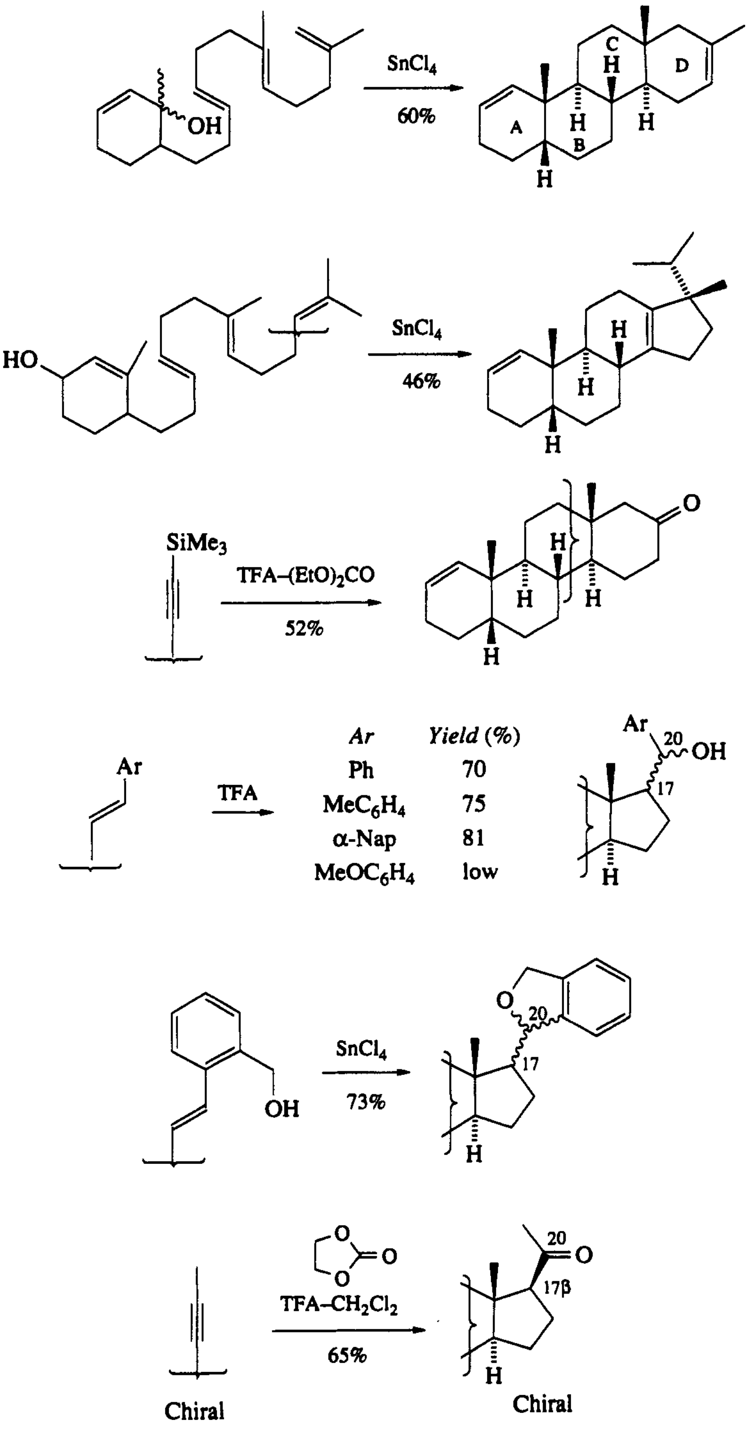
SnCl$_4$
60%
OH
A
B
C
D
H
SnCl$_4$
46%
HO
SiMe$_3$
TFA–(EtO)$_2$CO
52%
O
Ar
TFA
20
OH
17
SnCl$_4$
73%
O
TFA–CH$_2$Cl$_2$
65%
17β
Chiral
Chiral

| Ar | Yield (%) |
|---|---|
| Ph | 70 |
| $MeC_6H_4$ | 75 |
| α-Nap | 81 |
| $MeOC_6H_4$ | low |

| *Example* | *Ref.* |
|---|---|
| 1 | 109 |
| 2 | 111 |
| 3 | 110 |
| 4 | 112 |
| 5 | 113 |

**Scheme 29**

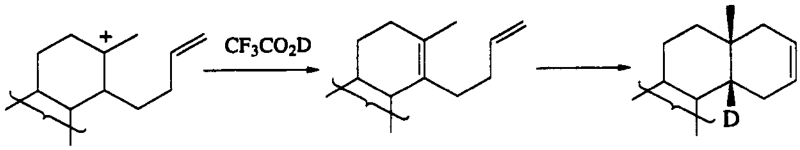

**Scheme 30**

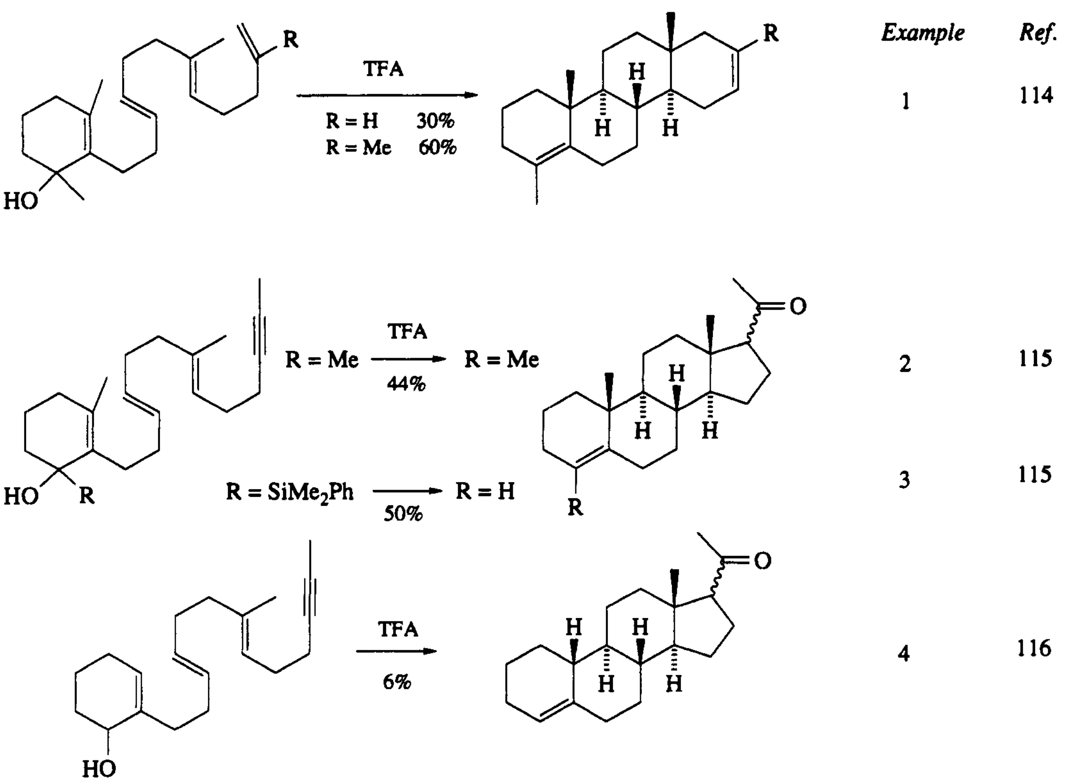

Scheme 31

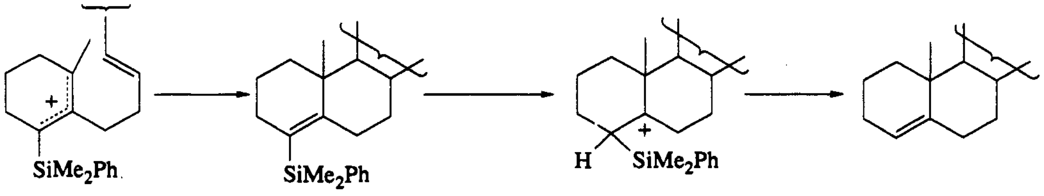

Scheme 32

early testosterone synthesis was based on the cyclization (example 1, Scheme 33); ozonolysis and aldol cyclization of the product formed the steroid skeleton. 19-Norsteroids could also be prepared by this route (example 2, Scheme 33). Much time and ingenuity have been spent in deriving direct methods for forming the *trans*-C,D ring fusion of steroids. Besides the stereochemistry of the ring junction, the question of the orientation of pendant group on the cyclopentane also arises. The alkynyl group in various forms is an efficient terminator but up to 20% of the *cis*-C,D isomer (13α) is formed. The styryl (example 6, Scheme 33), fluorovinyl (example 7, Scheme 33), and allylsilyl (examples 8 and 9, Scheme 33) lead to significantly lesser amounts of 13α-isomer but roughly equivalent quantities of 17α- and 17β-isomers. This is not a major drawback as 20-ketones can be isomerized to mixtures rich in the 17β natural isomers at later stages. This lack of selectivity is to be contrasted with mono- and bi-cyclizations using these terminating groups where there is a distinct preference for the α-isomers.

As in the estrone cyclization (Scheme 25) substituents introduced on to the methylene chains can induce diastereoselection. The Johnson group cyclized a precursor with a methyl group at pro-C-11 to give only the 11α-isomer (example 1, Scheme 34). The origin of the diastereoselection is likely to lie with the unfavorable interaction between the vinylic methyl and the axially oriented 11β-methyl (**53**) excluding cyclization in this conformation; cyclization of the compound lacking the vinylic methyl exhibits no diastereoselection. When the methyl group was replaced by hydroxyl (example 2, Scheme 34), the yield and rate of reaction were both reduced, presumably due to the inductive effect of the hydroxyl reducing the double bond nucleophilicity; however, complete diastereoselection was observed and using chiral alcohol an enantiospecific synthesis of 11-hydroxyprogesterone was achieved. This must be regarded as the

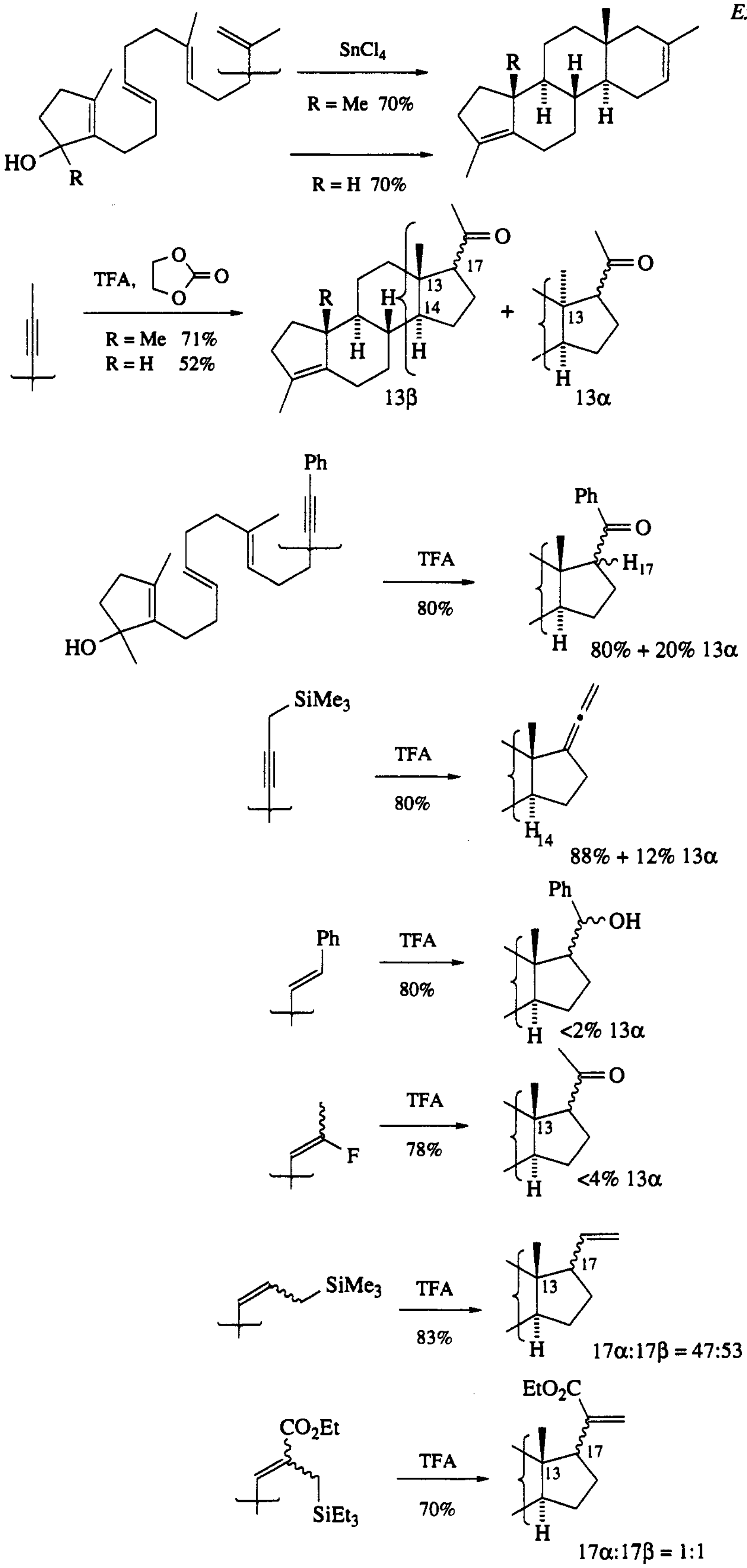
SnCl$_4$
R = Me 70%
R = H 70%
HO
R
R
H
H
H
TFA,
O
O
O
R = Me 71%
R = H 52%
13β
13α
17
13
14
+
Ph
TFA
80%
H$_{17}$
80% + 20% 13α
SiMe$_3$
TFA
80%
H$_{14}$
88% + 12% 13α
Ph
TFA
80%
OH
<2% 13α
F
TFA
78%
<4% 13α
SiMe$_3$
TFA
83%
17α:17β = 47:53
CO$_2$Et
SiEt$_3$
TFA
70%
EtO$_2$C
17α:17β = 1:1

| *Example* | *Ref.* |
|---|---|
| 1 | 117 |
| 2 | 117 |
| 3 | 118<br>119 |
| 4 | 122 |
| 5 | 122 |
| 6 | 120 |
| 7 | 121 |
| 8 | 124 |
| 9 | 125 |

**Scheme 33**

major achievement of polyalkene cyclization up to the present. With a benzyloxy at pro-C-7 diastereoselection in favor of the axial 7α-ether was found (example 3, Scheme 34). This diastereoselection was improved in the cyclization of the normethyl secondary alcohol in contrast to the pro-C-11-substituted series. These results also contrast with the diastereoselections found in the closely related estrone cyclizations (Scheme 26) where the pro-C-11 methyl favors axial orientation; the absence of the 1,3 methyl–methyl interaction in the estrone precursor may offer a rationalization. The differing selectivities for the pro-C-7 compounds are more difficult to understand. Recently the Johnson group has used the device of two possible consecutive bicyclizations (example 4, Scheme 34) and achieved impressive yields and diastereoselectivity; the effectiveness of this approach is apparent when compared with the relatively poor yields obtained when the ion from bicyclization is not stabilized (example 5, Scheme 34). The Brunke steroid synthesis[130] has as its basis the cyclization of the tetraene (**54**) to the tetracycle (**55**). Presumably the first cyclization forms the allylic cation (**56**), which undergoes equatorial attack to form the tetracyclic ion. Equatorial attack is preferred over the more usual axial addition to allylic ions since the latter would require ring C to adopt a twist-boat conformation. This form of 'remote' stereochemical control might be capable of further exploitation. Van Tamelen and Hwu[131] have described a progesterone synthesis based on cyclization of a cyclohexene epoxide (**57**).

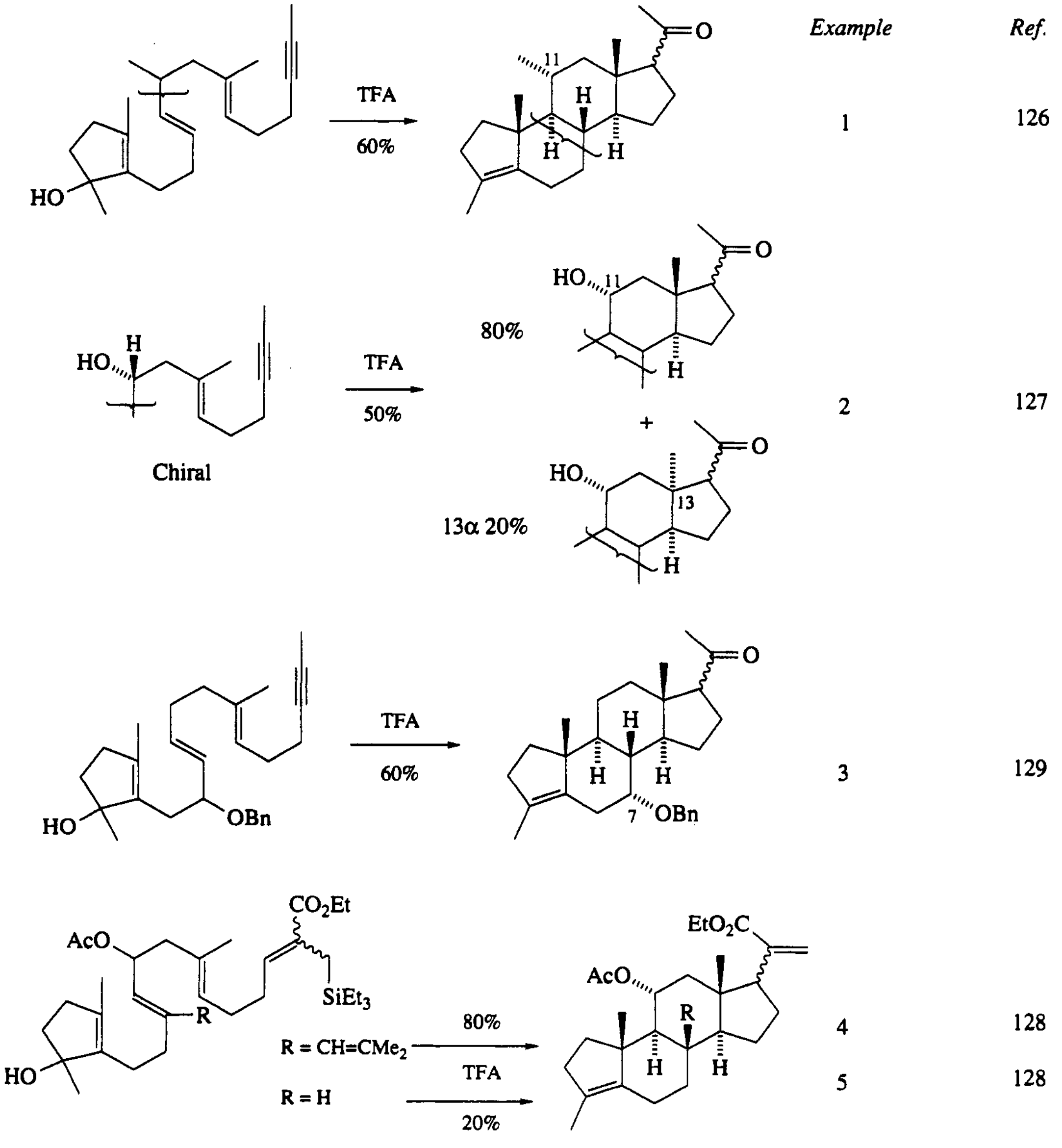

**Scheme 34**

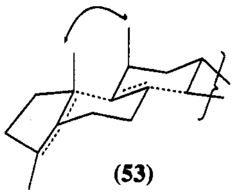

**(53)**

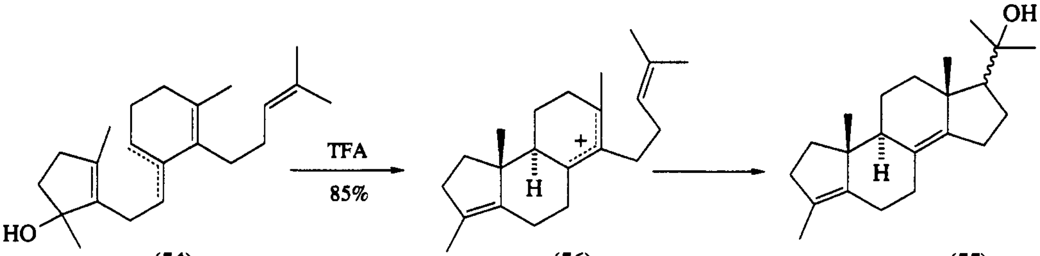

**(54)** **(56)** **(55)**

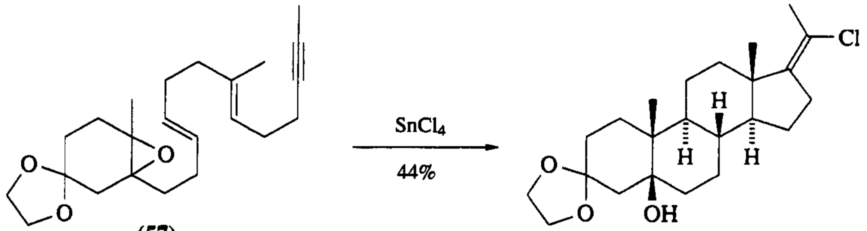

**(57)**

## 1.9.9 MECHANISM

In 1983 Bartlett wrote an excellent and well-balanced account discussing possible mechanisms for polyalkene cyclizations. In it is summarized the powerful evidence that structural and electronic features in the incipient second ring can influence both the rate and the stereochemical outcome of a reaction. In one case Borčić *et al.*[132] found that the diene (**58**) solvolyzed nine times faster than the alkene (**59**), and that there were dramatic differences in the enthalpies ($\Delta H^{\ddagger}$) and entropies ($-\Delta S^{\ddagger}$) of activation. In his article[5] Bartlett asks 'is there concertedness beyond the second ring?', and argues persuasively that the likely answer is 'no', due to the entropic debt which would result in 'freezing' additional bonds. To account for the various effects in bicyclizations there are three distinct options — a concerted reaction, a concerted cyclization to a π-complex, or a stepwise process in which the cyclizations are reversible (Scheme 35). The geometric restrictions on the first two options are similar and distinction between them is difficult; thermodynamic arguments militate against the retrocyclization mechanism. Another mechanistic question arises from the strong tendency of cyclohexyl cations to undergo equatorial attack, particularly when produced by the cyclization route. This raises the possibility of two types of cyclohexyl cation separated by a small energy barrier, one arising from C—C hyperconjugation, the other from C—H hyperconjugation, with the empty *p*-orbital; the former would lead to equatorial attack. Recent work suggests that there could be two methylcyclohexyl cations.[133]

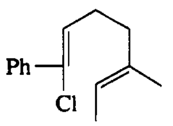

**(58)**

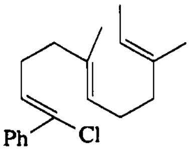

**(59)**

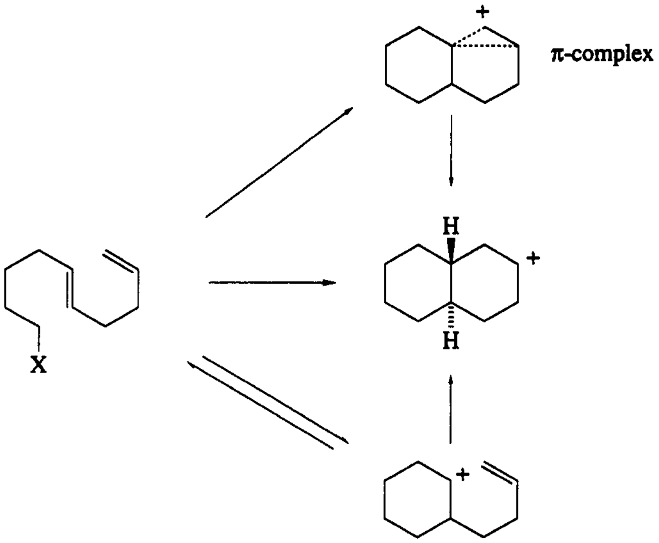

Scheme 35

## 1.9.10 SUMMARY

Polyalkene cyclization is a powerful synthetic method for the preparation of alicyclic compounds containing certain combinations of five-, six- and seven-membered rings. The Stork–Eschenmoser hypothesis can be adopted as a guiding principle in synthetic planning but it is not universally applicable. However, using stabilized cations as initiators and participating double bonds of appropriate nucleophilicity then the notion of concerted bicyclization *via* chair–chair transition states has good predictive value. It is the synthesis of *cis*-fused rings from (*Z*)-alkenes that requires the most careful planning. For tri- and tetra-cyclizations the formations of the third and fourth rings are governed by the rules for the cyclization of cycloalkyl cations. In future synthetic planning it may be advantageous to plan a tricyclization as a bicyclization followed by a monocyclization, and a tetracyclization as two consecutive bicyclizations, *i.e.* the initial bicyclization produces a cation which is itself a good initiator of cyclization. This will require a delicate 'tuning' of reactivity since initiation at the second center would be unproductive; indeed the approach of generating the second cyclization initiator from the terminator of the first cyclization in a separate chemical step may be more productive.

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# 1.10

# Transannular Electrophilic Cyclizations

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## 1.10.1 INTRODUCTION

It is now almost 40 years since Cope and Prelog first described the phenomenon of 'transannulation' reactions during their independent studies of electrophilic additions to medium ring cycloalkenes.[1,2] Since that time transannular reactions have been encountered in an enormous variety of carbo- and hetero-cyclic medium ring compounds having a wide array of differing functionalities. Indeed, the chemistry of these fascinating processes has now become part of the day-to-day armoury of the modern synthetic chemist.[3]

Transannular reactions are defined as those reactions which lead to the formation of a covalent bond between atoms on opposite sides of a ring compound. They occur frequently in medium, *i.e.* 8-, 9-, 10- and 11-membered, rings where favored conformations allow opposite sides of the rings to come close to each other for bond formation. Probably the most commonly encountered transannulation processes are those involving H-transfer reactions,[4] from, for example, ring epoxides, *i.e.* (**1**) → (**2**; equation 1),[5] and those involving ring closure reactions, *i.e.* (**3**) → (**4**; equation 2)[6] from cyclic polyenes in the presence of electrophilic reagents, *i.e.* conditions which favor carbonium ion formation. Transannular ring closure reactions *via* intermediate carbanions,[7] carbenes[8] and radicals,[9] and *via* pericyclic processes,[10] are also known. So too are several reactions involving nitrogen,[11] sulfur,[12] and oxygen[13] heterocyclic ring formation.

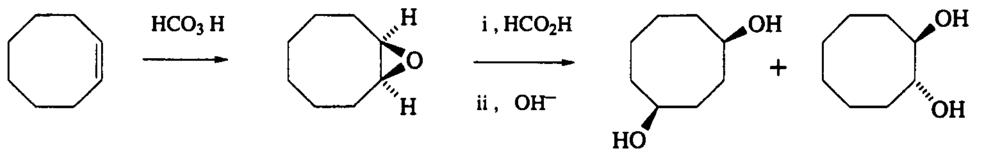

(**1**) (**2**) (1)

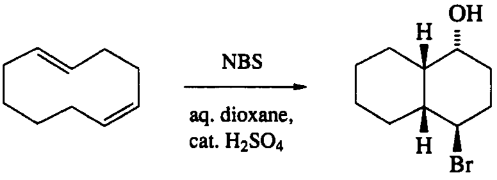

(**3**) (**4**) (2)

The chemistry of transannular cyclizations involving 1,5-diene units in medium ring carbocycles has been studied with particular vigor in recent years because of the relevance of this chemistry to the biogenetic origins of cyclic terpenes.[14] Indeed, these fundamental studies have now led to a number of novel 'biogenetically inspired' syntheses of a large range of complex ring-fused natural products of both biosynthetic significance and biological importance.[15]

This chapter summarizes those transannular reactions in medium ring carbocycles which result in carbon–carbon bond formation *via* alkylation of carbon, in the presence of electrophilic reagents. It is therefore a logical extension of two other chapters in this volume, covering Friedel-Crafts Alkylations (Chapter 1.8), and Polyene Cyclizations (Chapter 1.9). The discussion of these processes is organized according to the size of the cycloalkene from which transannular cyclization is effected.

## 1.10.2 CYCLOOCTENES

### 1.10.2.1 Bicyclo[3.3.0]octane and Bicyclo[3.2.1]octane Ring Formation

Following on from earlier work on transannular H-transfer reactions in cyclooctenes (*i.e.* equation 1), Cope and collaborators[1,5] carried out extensive studies of the solvolyses of a wide range of substituted cyclooctenes in a search for further unusual transannular processes. Thus, both the tosylate (**5a**) and the brosylate (**5b**) of cyclooct-4-en-1-ol were shown to produce the bicyclo[3.3.0]octanes (**6**) and the bicyclo[3.3.0]octene (**7**) on solvolysis and acetolysis respectively (equation 3).[16] The bicyclic molecules (**6**) and (**7**) are formed from (**5**) by transannular interaction in the cyclooctenyl carbonium ion (**8**), followed by quenching of the resulting carbonium ion (**9**) with a nucleophilic counterion (to form **6**), or deprotonation (to form **7**). In the case of acetolysis of (**5a**), a small amount of the bicyclo[3.2.1]octane (**10**) was produced concurrently *via* the rearranged carbonium ion (**11**; Scheme 1). Interestingly, the corresponding isomeric cyclooct-3-en-1-ol brosylate (**12**; equation 4) and the homologous brosylate (**14**; equation 5)

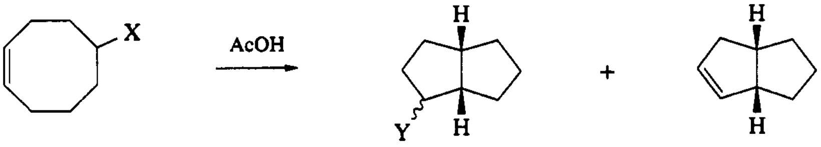

(3)

(**5a**) X = OTs
(**5b**) X = OBs

(**6**)
Y = OH and OAc

(**7**)

under the same conditions undergo transannulation to the bicyclic products (**13**) and (**15**), respectively.[16a,17–19]

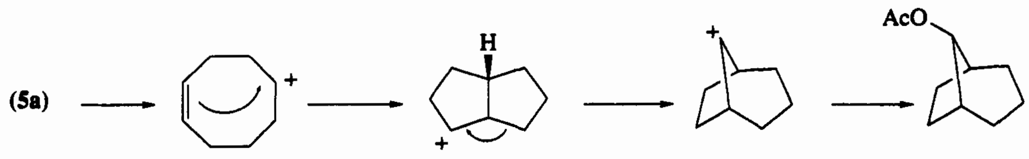

(**8**) (**9**) (**11**) (**10**)

**Scheme 1**

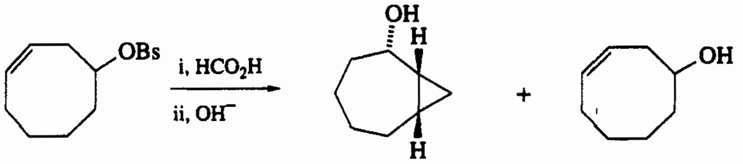

(**12**) (**13**) 52%; α:β = 3:1 25% (4)

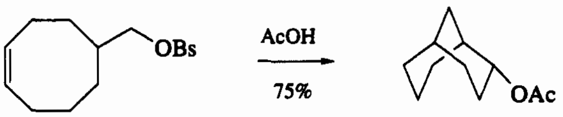

(**14**) (**15**) (5)

Transannular cyclization in cycloocta-1,5-diene (**16**; equations 6 and 7) can be brought about by a wide variety of electrophilic reagents.[18–32] These reactions lead to a range of functionalized bicyclo[3.3.0]octanes (Tables 1 and 2), many of which have found widespread use in general synthesis.[33] Although the use of mineral acids favors the formation of bicyclo[3.3.0]octanes, other electrophilic agents

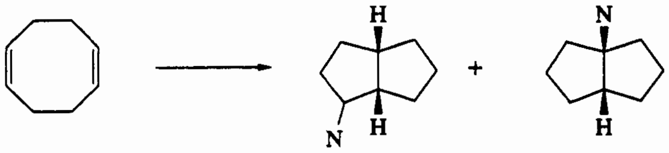

(**16**) (**17**) (**18**) (6)

**Table 1** Transannular Cyclization of (**16**; Equation 6)

| *Reagents* | *N* | *Yield (%)* *(17)* | *(18)* | *Ref.* |
|---|---|---|---|---|
| HF/H$_2$O/CO | CO$_2$H | 17 | — | 20 |
| CuCO$_3$/CO | CO$_2$H | — | 15 | 21 |
| HCO$_2$H/H$_2$SO$_4$ | CO$_2$H | — | 33 | 22 |

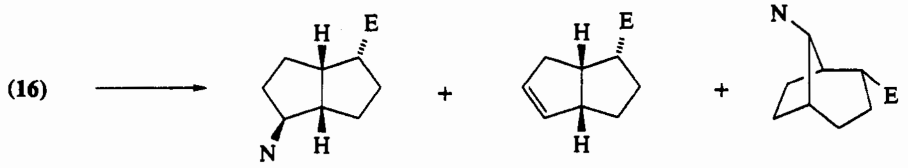

(**19**) (**20**) (**21**) (7)

instead lead to bicyclo[3.2.1]octanes, *i.e.* (**21**), or to products resulting from hydride shifts, *i.e.* (**18**), and/or Wagner–Meerwein rearrangements, *i.e.* (**21**; see Scheme 2).

**Table 2** Transannular Cyclization of (**16**; Equation 7)

| *Reagents* | *E* | *N* | *Yield (%)* | | | *Ref.* |
|---|---|---|---|---|---|---|
| | | | *(19)* | *(20)* | *(21)* | |
| $H_3PO_4$/silica | H | — | — | 72 | — | 23 |
| $MeOCH_2OAc/BF_3$ | $CH_2OMe$ | OAc | 24 | 26 | 11 | 24 |
| $Hg(OAc)_2/HClO_4$ | OAc | OAc | 13 | 38 | — | 25 |
| $I_2/CCl_4$ | I | I | 77 | — | — | 26 |
| $(PhSe)_2/I_2$/MeCN | SePh | NHAc | 63 | — | — | 27 |
| NBS/HF/pyridine | Br | F | 66 | — | — | 28 |
| $SbCl_5/CCl_4$ | Cl | Cl | — | — | 70 | 29 |
| $Tl(OCOCF_3)_2$ | $OCOCF_3$ | H | — | 31 | — | 30 |
| $Ni^{II}/EtAlCl_2$ | H | — | — | 96 | — | 31 |

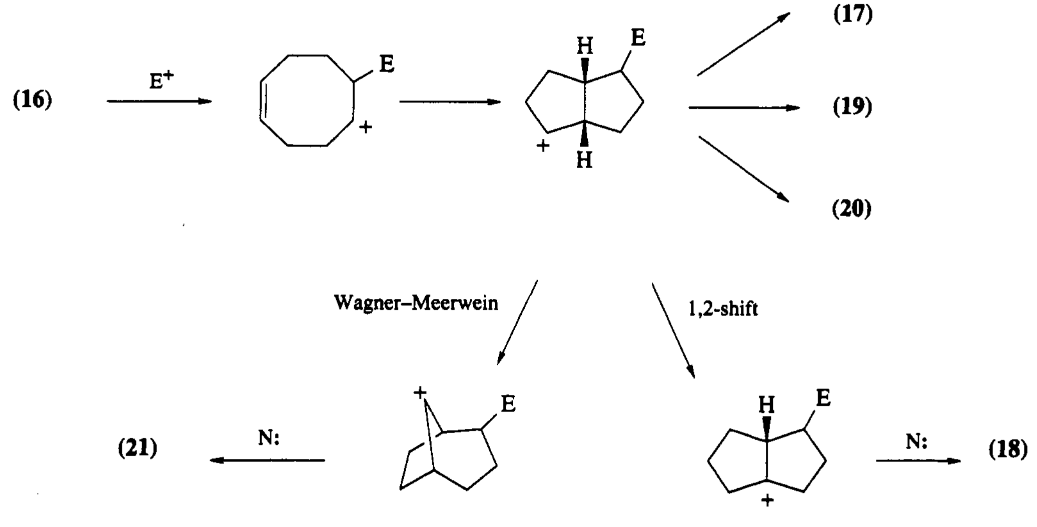

**Scheme 2**

The high degree of selectivity observed in the aforementioned transannulation process can be rationalized in terms of Baldwin's rules,[34] and the possible low energy conformation available to the ring.[35,36] This situation becomes complicated however in the case of 1,5-dimethylcycloocta-1,5-diene (**22**), since transannulation first leads to the more stable bicyclo[4.2.0]octane carbonium ion (**23**), which then undergoes a series of Wagner–Meerwein rearrangements (Scheme 3) before producing either the bicyclo[3.3.0]octane (**24**) or the bicyclo[3.2.1]octane (**25**), as shown in Table 3.[37–39] Surprisingly the monoepoxide derived from 1,5-cyclooctadiene affords only a small yield of bicyclo[3.3.0]octane-2,6-diol on transannular cyclization.[3b,40]

**Table 3** Transannular Cyclization and Rearrangement of (**22**; Scheme 3)

| *Reagents* | *N* | *Yield (%)* | | *Ref.* |
|---|---|---|---|---|
| | | *(24)* | *(25)* | |
| $BF_3{\cdot}OEt_2$ | H | 60 | — | 37 |
| TsOH | OTs | — | 70 | 37 |
| $HCO_2H/HClO_4$ | OCHO | 16 | 62 | 38 |
| $AcOH/HClO_4$ | OAc | 32 | 38 | 38 |

### 1.10.2.2 Caged Compounds

Numerous examples of transannulation reactions amongst caged compounds, which can be considered as conformationally restricted medium rings, have been studied, and some representative examples are

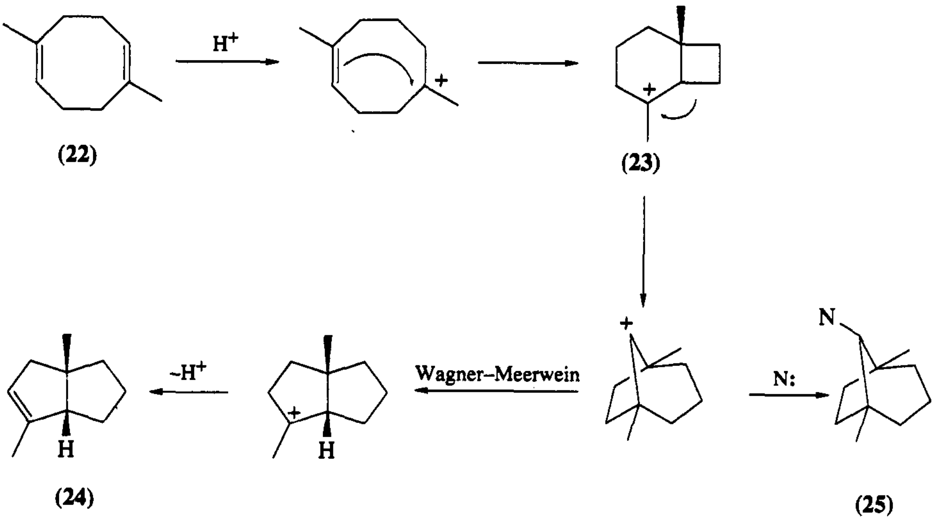

Scheme 3

collected in Scheme 4.[41–44] Generally, such reactions lead to the products of ‘crossed’ rather than ‘parallel’ cyclization, *i.e.* fused 5,5-ring products predominate over fused 6,4-rings.[45]

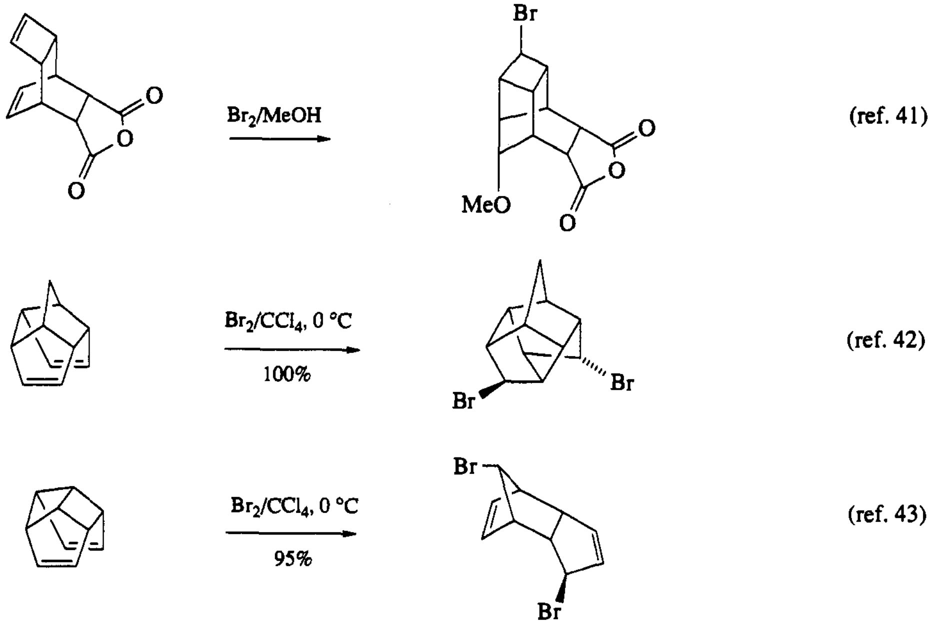

Scheme 4

### 1.10.2.3 Endocyclic 1,3- and 1,4-Cyclooctadienes

Transannulation reactions involving cyclooctenes are not restricted to endocyclic alkenes or to those systems which require a 1,5-relationship of the reacting centers. Thus, the exocyclic polyenes (**26**; equation 8) and (**27**; equation 9) take part in some novel transannulation processes when treated with bromonium ion,[46,47] and both cycloocta-1,3-diene and cycloocta-1,4-diene undergo transannulation reactions under favorable conditions producing the bicycles (**28**; equation 10) and (**29**; equation 11), respectively, in very acceptable yields.[48,49] Perhaps even more novel is the transannular cyclization of 5-methylenecyclooctanecarbaldehyde (**30**) in water, leading to the unstable bicyclo[3.3.0]octanecarbaldehyde (**32**); this reaction is best formulated as proceeding *via* the corresponding enol (**31**) under acid catalysis (equation 12).[50]

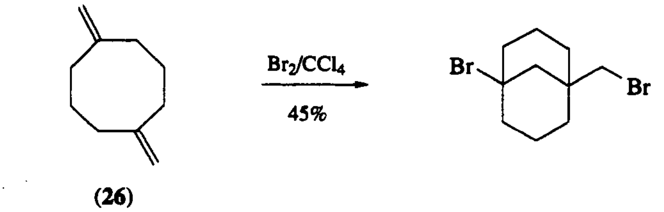
Br$_2$/CCl$_4$
45%
Br
Br
(26)

(ref. 46) (8)

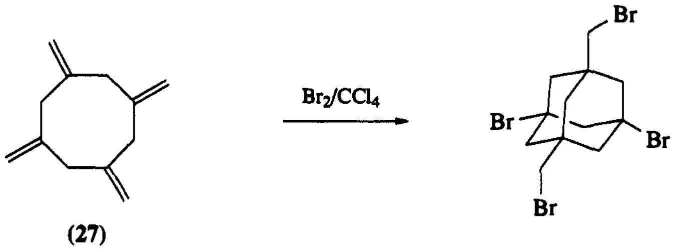
Br$_2$/CCl$_4$
Br
Br
Br
Br
(27)

(ref. 47) (9)

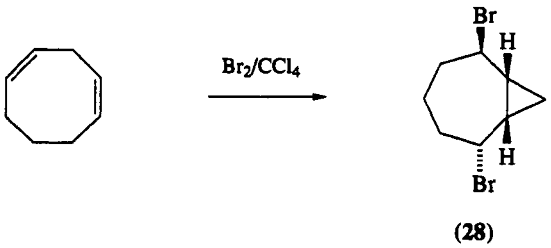
Br$_2$/CCl$_4$
Br
H
H
Br
(28)

(ref. 48) (10)

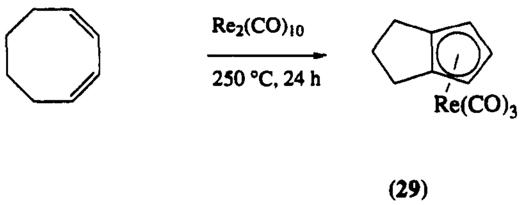
Re$_2$(CO)$_{10}$
250 °C, 24 h
Re(CO)$_3$
(29)

(ref. 49) (11)

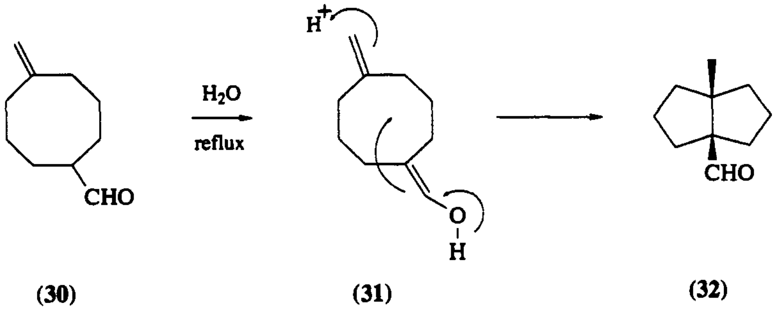
CHO
H$_2$O
reflux
H+
O
H
CHO
(30)
(31)
(32)

(12)

### 1.10.2.4 Synthesis of Natural Products

Transannulation of the mesylate (**33**), derived from 4,8-dimethylcycloocta-4-en-1-ol, using sodium carbonate in aqueous dioxane has provided the bicyclo[3.3.0]octanol (**34**), a central precursor to the monoterpene iridomyrmecin (**35**; equation 13).[51] In studies of the biomimetic synthesis of the natural triquinanes capnellene (**37**; equation 14) and pentalenene (**40**; equation 15) Pattenden *et al.* have shown that both molecules can be produced from appropriate cycloocta-1,5-diene precursors, *i.e.* (**36**) and (**39**) [or indeed their corresponding positional isomers (**38**) and (**41**), respectively] by treatment with boron trifluoride.[52,53] Mehta *et al.* have described an alternative transannulation approach to the triquinane unit found in pentalenene,[54] *i.e.* (**42**) → (**43**; equation 16), and also to the ring system (**44**; equation 17) found in the diterpene laurenene (**45**).[55] The key feature of Chatterjee's approach to the sesquiterpene isocomene (**47**) is the transannular cyclization of the alkene epoxide (**46**) in the presence of TFA in $CH_2Cl_2$ at –78 °C (equation 18); however, doubt has been cast on these results.[56]

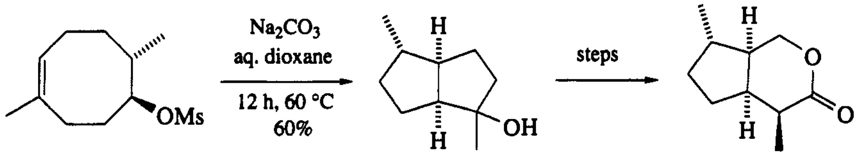
OMs
$Na_2CO_3$
aq. dioxane
12 h, 60 °C
60%
H
H
OH
steps
H
O
H
O

**(33)** **(34)** **(35)**

(13)

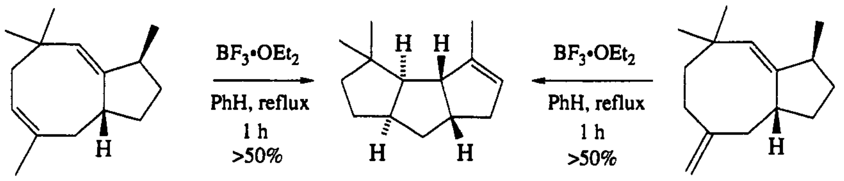
H
$BF_3{\bullet}OEt_2$
PhH, reflux
1 h
>50%
H H
H H
$BF_3{\bullet}OEt_2$
PhH, reflux
1 h
>50%
H

**(36)** **(37)** **(38)**

(14)

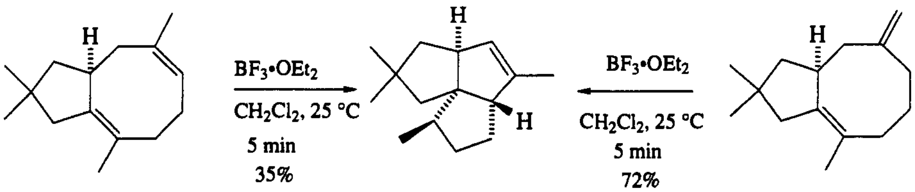
H
$BF_3{\bullet}OEt_2$
$CH_2Cl_2$, 25 °C
5 min
35%
H
H
$BF_3{\bullet}OEt_2$
$CH_2Cl_2$, 25 °C
5 min
72%
H

**(39)** **(40)** **(41)**

(15)

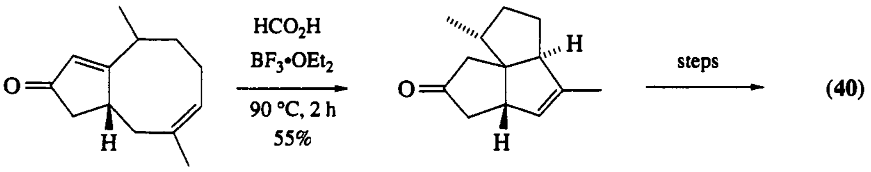
O
H
$HCO_2H$
$BF_3{\bullet}OEt_2$
90 °C, 2 h
55%
H
O
H
steps
(40)

**(42)** **(43)**

(16)

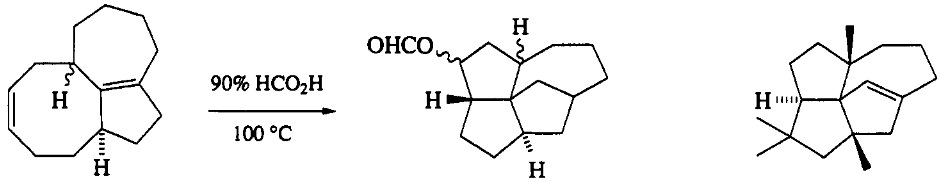
H
H
90% $HCO_2H$
100 °C
OHCO
H
H
H
H

**(44)** **(45)**

(17)

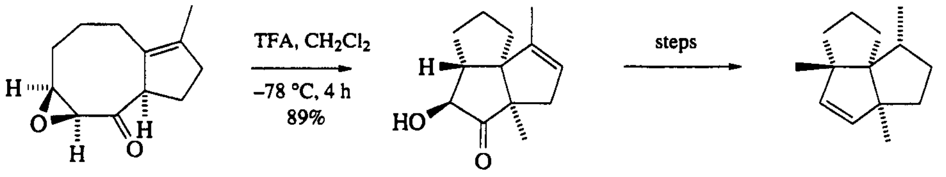
H
O
H
H
O
TFA, $CH_2Cl_2$
–78 °C, 4 h
89%
H
HO
O
steps

**(46)** **(47)**

(18)

## 1.10.3 CONFORMATIONAL ARRANGEMENTS OF 1,5-DIENES IN MEDIUM RINGS

Three distinct conformational arrangements for a 1,5-diene set within a medium ring have been identified, and these are shown in formulae (**48**)–(**50**).[3c] Conformation (**48**) is referred to as 'crossed', abbreviated to C, whereas the conformation (**49**) is 'parallel', abbreviated to T. Formula (**50**) indicates an extended conformation. Models show that the C-conformation (**48**) can be adopted by (*E,E*)- and (*Z,E*)-1,5-dienes in medium rings, whereas the T-conformation (**49**) is possible for (*E,E*)-, (*Z,E*)- and (*Z,Z*)-isomers. The extended conformation (**50**) is available only to (*Z,Z*)-1,5-dienes. The conformations adopted by an isomeric 1,5-diene in a medium ring are crucial in determining the stereochemical outcome of any transannular cyclization product. These principles have been amply demonstrated during studies of the stereospecificities in the cyclizations of 9-, 10- and 11-membered cyclic 1,5-dienes, summarized below.[57]

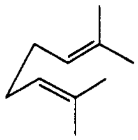

**(48)**

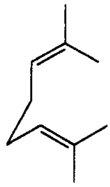

**(49)**

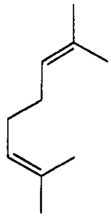

**(50)**

## 1.10.4 CYCLONONA-1,5-DIENES

Transannular cyclization of the (*Z,Z*)-isomer (**51**) of cyclonona-1,5-diene in the presence of a variety of electrophilic reagents provides a useful synthesis of a range of substituted *cis*-hydrindane derivatives (**53**; Table 4).[58–61] In each of these cases the 1,5-diene unit in (**51**) is reacting in the T-conformation shown in (**52**).

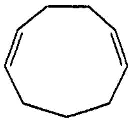

**(51)**

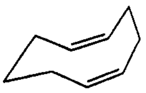

**(52)**

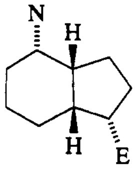

**(53)**

**Table 4** Synthesis of *cis*-Hydrindane Derivatives (**53**) from 1,5-Diene (**51**)

| *Reagents* | *E* | *N* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| $Br_2$/AcOH | Br | OAc | 71 | 58, 59 |
| $Hg(OAc)_2$/$NaBH_4$ | H | OH | 68 | 58, 60 |
| $Br_2$/$CCl_4$ | Br | Br | | 58 |
| PhSeCl/AcOH | SePh | OAc | 68 | 60 |
| NBS/$H_2O$ | Br | OH | 44 | 59 |
| NBS/MeOH | Br | OMe | 90 | 59 |

Several (*Z,E*)-cyclonona-1,5-dienes of the type (**55**; equation 19) have been prepared *via* rearrangement of dibromobicyclo[6.1.0]nonenes (**54**) in the presence of silver salts.[62] On treatment with aqueous NBS these molecules undergo transannular cyclization, following initial attack on the (*Z*)-disubstituted double bonds, producing the corresponding *trans*-hydrindanes (**56**).[63] In related studies, Sutherland and his coworkers have also shown that similar treatment of (**57**; equation 20) leads to the bromo ketone (**58**),[64] and that when the epoxide (**59**; equation 21) is simply crystallized, it undergoes a unique transannular cyclization, producing a mixture of (**60**) and (**61**).[3c,65]

Some of the most remarkable transannular cyclizations have been uncovered during the treatment of natural caryophyllene (**63**) with mineral acids.[66–68] Thus, treatment of (**63**) with concentrated sulfuric acid has been shown to lead to a mixture of clovene (**62**), caryolan-1-ol (**64**) and neoclovene (**65**;

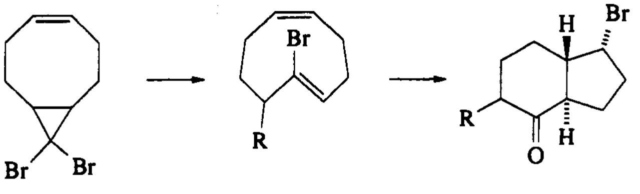

Br
Br
Br
R
H
Br
R
O
H

(54)

(55a) R = OAc
(55b) R = Br
(55c) R = OH

(56)

(19)

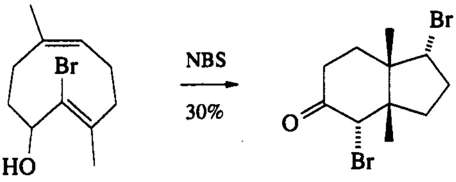

Br
HO
NBS
30%
Br
O
Br

(57) (58)

(20)

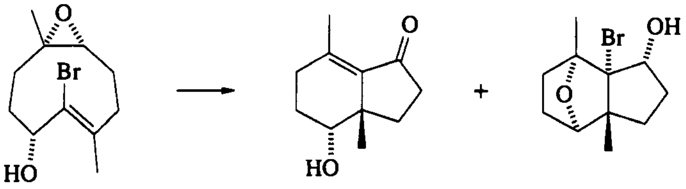

O
Br
HO
O
HO
+
Br
OH
O

(59) (60) (61)

(21)

Scheme 5). Similarly, isocaryophyllene (**66**) undergoes transannular cyclization in mineral acid to (**65**) and to the tricyclic alkene (**67**; Scheme 6) in high yield.

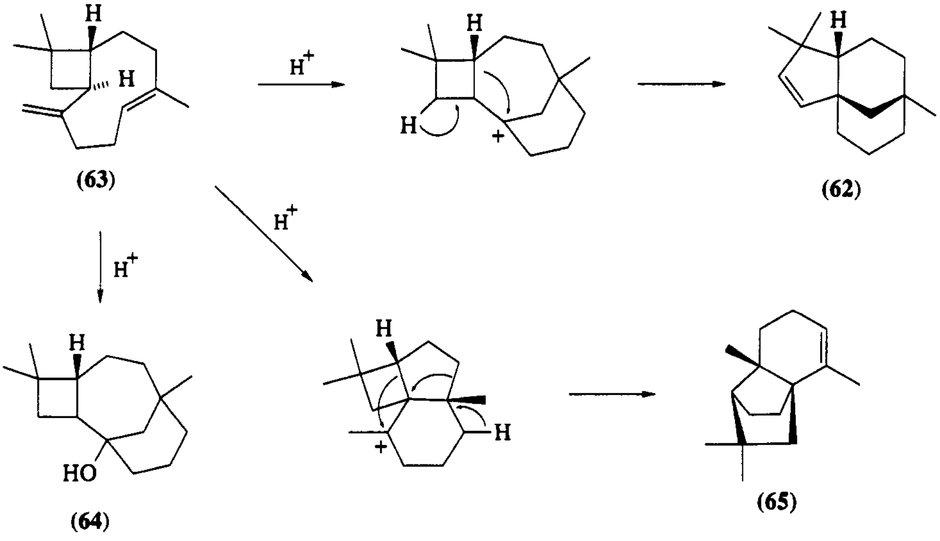

H
H
(63)
$H^+$
H
H
+
H
(62)
$H^+$
$H^+$
H
HO
(64)
H
+
H
(65)

**Scheme 5**

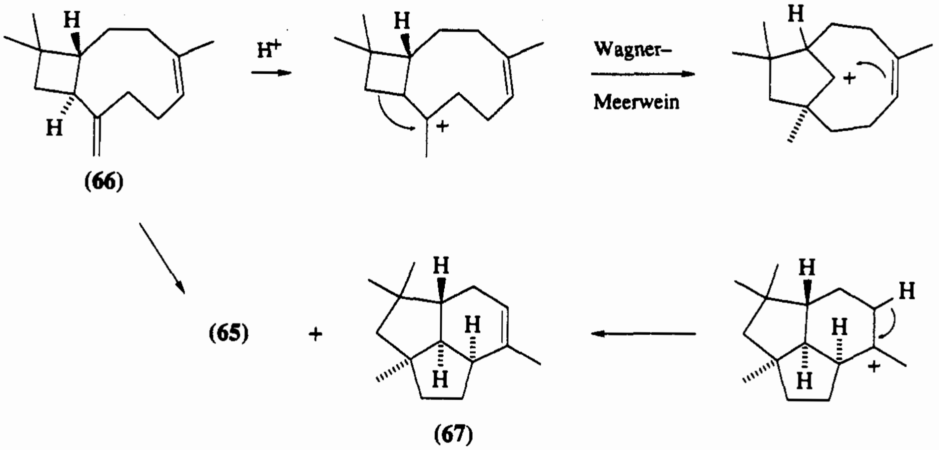

Scheme 6

## 1.10.5 CYCLODECENES

### 1.10.5.1 Relevance to the Biosynthesis of Polycyclic Sesquiterpenes

Transannular cyclizations involving carbonium ions generated from cyclodeca- and cycloundeca-polyenes have been the subject of extensive research, largely as a consequence of their relevance to our understanding of the biosynthesis of a wide range of polycyclic sesquiterpenes.[14] Thus, macrocyclization of farnesyl pyrophosphate (**68**) first produces both the 10-ring (**69**) and the 11-ring (**70**) carbonium ion intermediate precursors to germacrene (**71**) and humulene (**72**), respectively (Scheme 7). According to biogenetic speculation, transannulation involving the cyclodeca-1,5-diene system in germacrene (**71**) then produces the eudesmane (**73**) and guaiane (**74**) groups of natural sesquiterpenes.[14] It is generally accepted that the eremophilane (**75**) and the pseudoguianane (**76**) carbon skeletons are derived in nature by rearrangement of eudesmane and guaiane derivatives, respectively (see Scheme 8). In like manner, and using a series of regio- and stereo-selective transannulation reactions, sometimes in tandem with carbo-

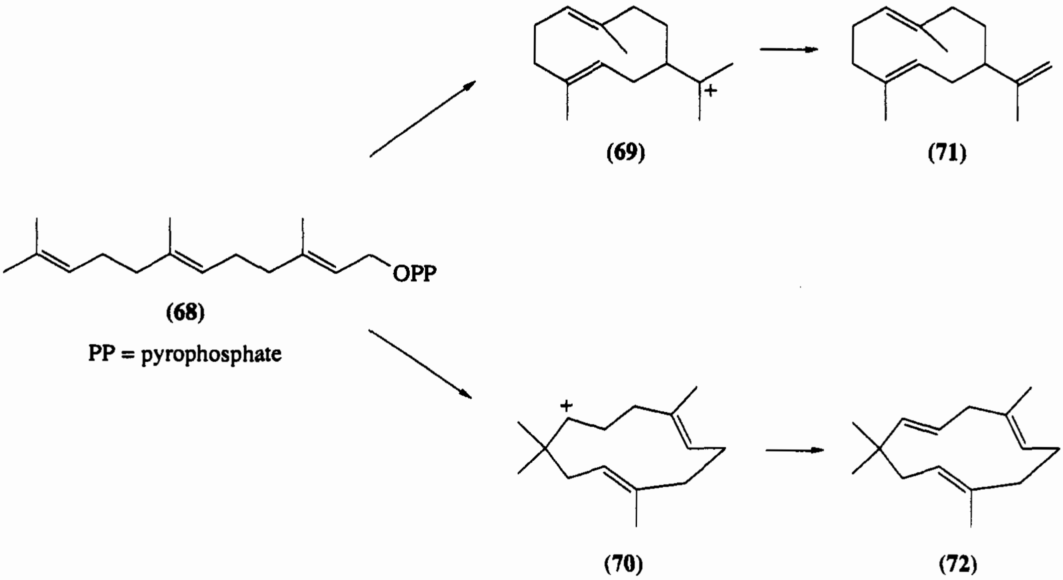

Scheme 7

nium ion rearrangements, the 11-ring humulene (**72**) gives rise to the caryophyllane (**77**), protoilludane (**78**), hirsutane (**79**), capnellane (**80**), pentalenane (**81**) and other families of sesquiterpenes (Scheme 9).[14]

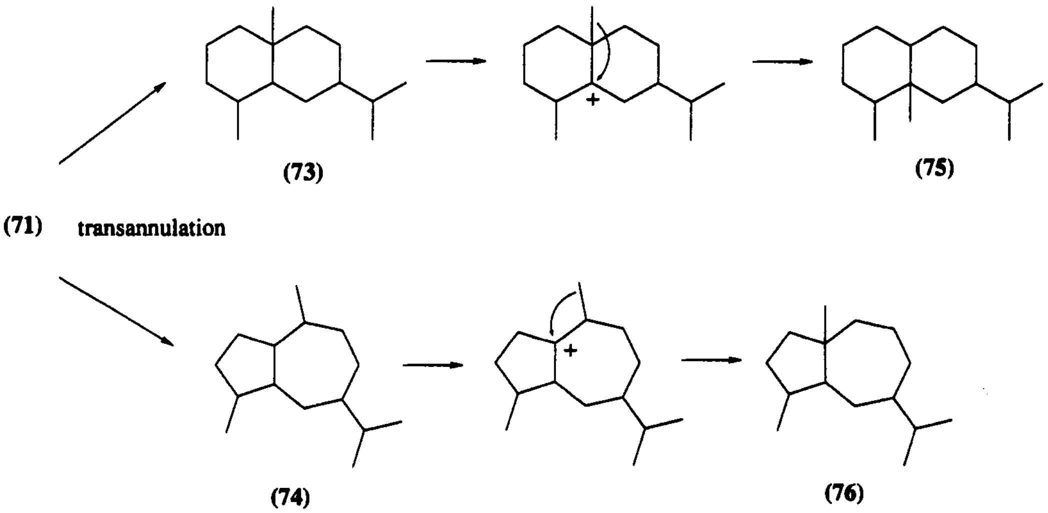

Scheme 8

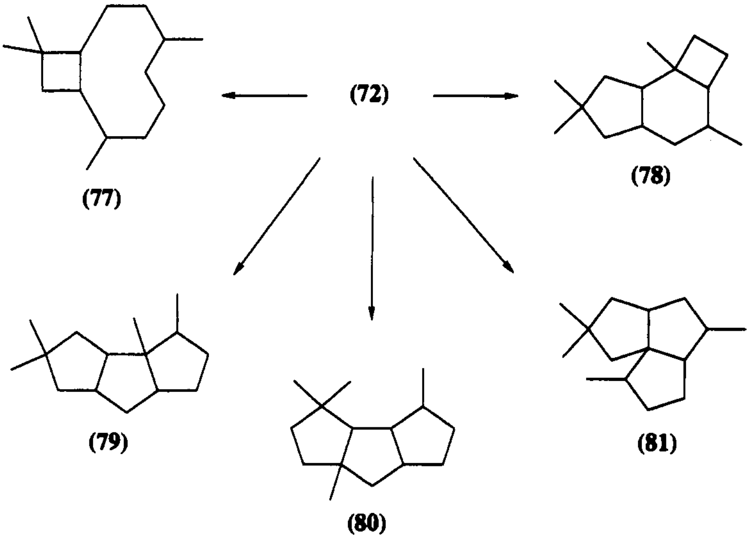

Scheme 9

## 1.10.5.2 Cyclodecadienes

### *1.10.5.2.1 Cyclodeca-1,5-dienes*

Although some detailed and fundamental studies of transannulation reactions involving cyclodeca-1,5-diene itself have been made, the main body of published work in this area has been associated with transannular reactions of germacrenes (**71**). These reactions generally proceed in both regio- and stereo-selective fashion leading to bicyclo[4.4.0]decanes of defined stereochemistry. This stereochemistry is determined largely by the geometrical configurations of the double bonds in the cyclodecadienes. Thus, the (*E*,*E*)-isomer (**82**; equation 22) of a cyclodeca-1,5-diene undergoes electrophilic cyclization producing the *trans*-decalin (**83**), whereas the corresponding (*E,Z*)-isomer (**84**; equation 23) leads to the *cis*-decalin (**85**).

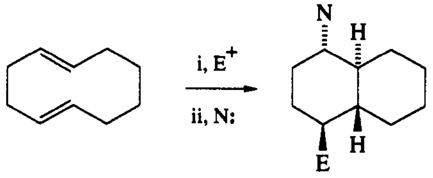

(**82**) (**83**) (22)

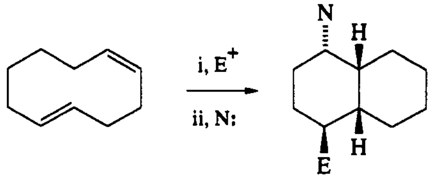

(**84**) (**85**) (23)

In a detailed study of transannular cyclizations of all the possible isomers of naturally occurring hedycaryol (**86**) in the presence of formic or tosic acid, Itô *et al.* have been able to rationalize the reaction pathways on the basis of the preferred conformations, *i.e.* crossed conformation (CC, CT) or parallel conformations (TT, TC), of the reacting dienes (Scheme 10).[69,70]

A selection of examples (equations 24–31) demonstrate the considerable scope for transannular reactions of cyclodeca-1,5-dienes in the synthesis, including biomimetic synthesis, of a wide range of isomerically pure, substituted bicyclo[4.4.0]decanes.[71–86]

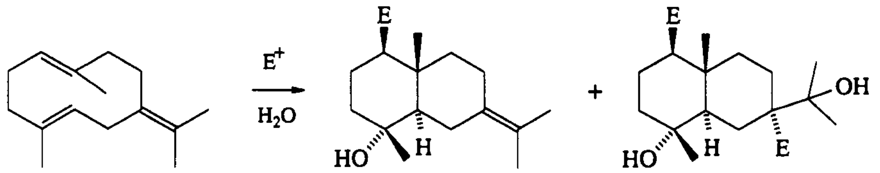

(24)

| *Reagents* | *E* | | | *Ref.* |
|---|---|---|---|---|
| NBS, aq. acetone | Br | 31% | – | 71, 72 |
| $Hg(OAc)_2/NaBH_4$ | H | 24% | 10% | 72 |
| $H_2SO_4$, aq. acetone | H | – | 95% | 72 |

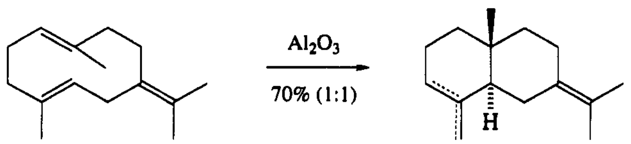

(ref. 72) (25)

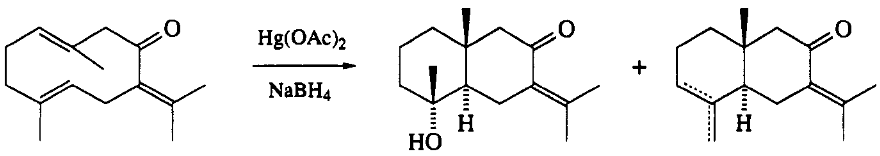

70% 15% (60:40)

(ref. 73) (26)

### 1.10.5.2.2 Other cyclodecadiene systems

Treatment of the bicyclogermacrene (**89**; equation 32), containing a cyclopropane ring, with dilute sulfuric acid leads to the aromadendrene (**90**; *cf.* guaiane **74**), together with the bicyclo[4.4.0]decadiene

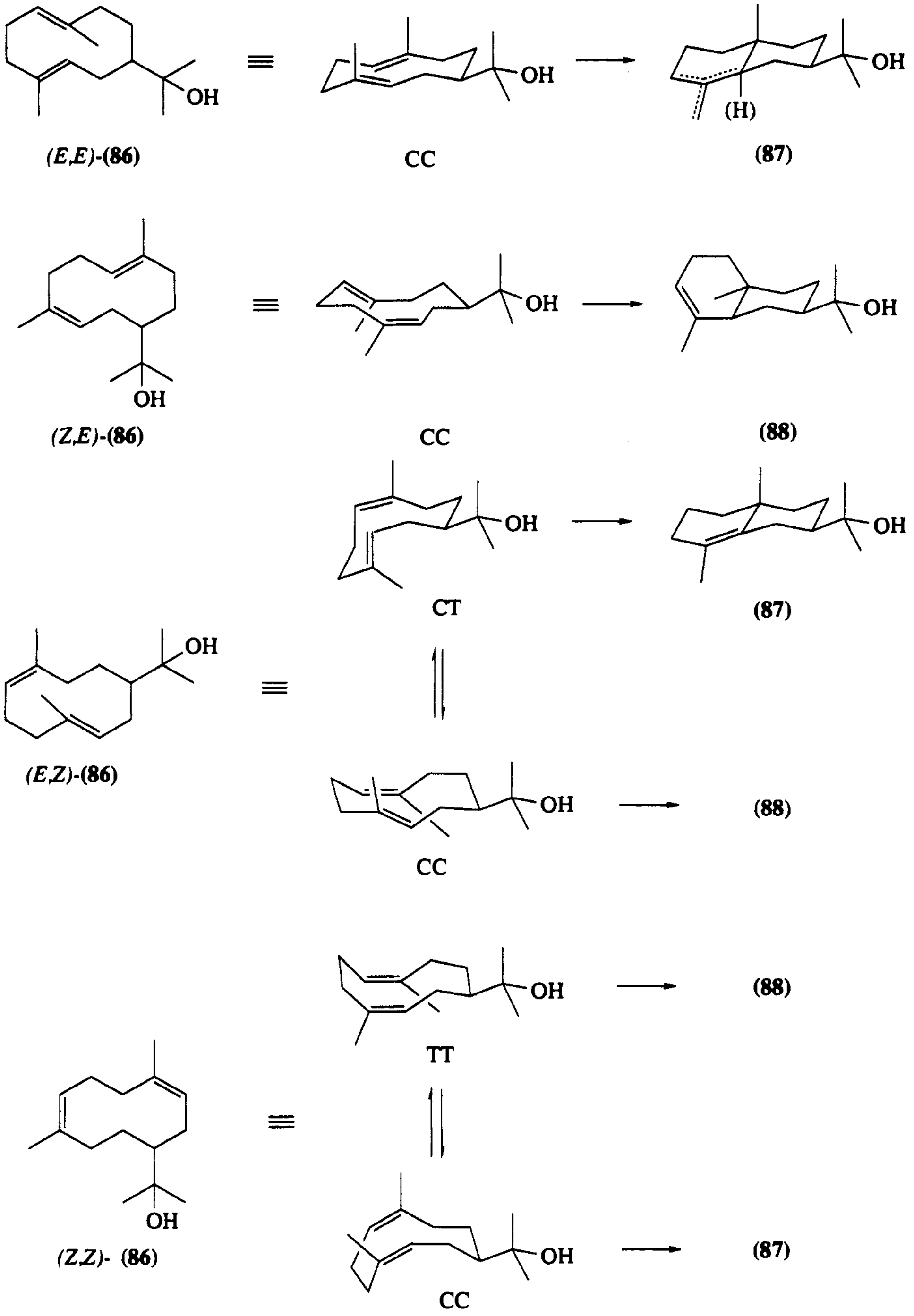

**Scheme 10**

(**91**).[87] Interestingly, when the 1,5-vinylcyclopropane (**92**; equation 33) is treated with acetic acid under reflux for six days it produces largely the tricyclic acetate (**93**; 58%).[88]

Geometrical isomers of cyclodeca-1,6-dienes show a similar reactivity profile to the corresponding 1,5-dienes in their transannular cyclizations to bicyclo[4.4.0]decanes, *i.e.* (*Z,Z*)-isomers lead to *cis*-decalins, whereas (*E,E*)-isomers produce *trans*-decalin products.[89–91] Some pertinent examples are shown in equations (34–37).

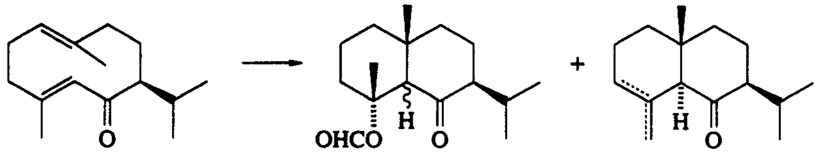

(ref. 74) (27)

|  |  |  |
|---|---|---|
| 80% $HCO_2H$ | 34% (1:1) | – |
| $AlCl_3$, $Et_2O$ | – | 78% (55:23) |

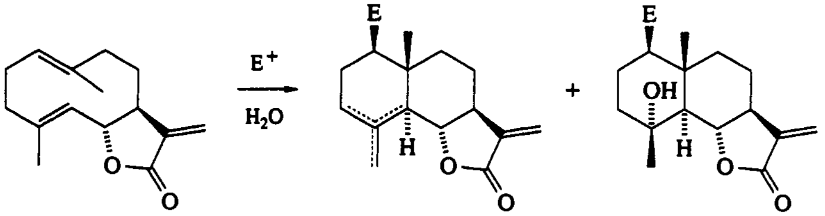

(28)

| *Reagents* | *E* |  |  | *Ref.* |
|---|---|---|---|---|
| $BF_3{\bullet}OEt_2$ | H | 65% | 1.5% | 75 |
| Amberlite IR-120 | H | 67% | – | 76 |
| $SOCl_2$ | H | 96% | – | 77 |
| aq. NBS | Br | 41% | 50% | 78 |

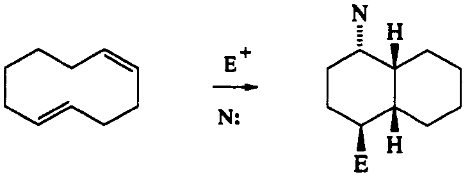

(29)

| *Reagents* | *E* | *N* |  | *Ref.* |
|---|---|---|---|---|
| HCl, aq. dioxane | H | OH | 40% | 80 |
| $Hg(OAc)_2/NaBH_4$ | H | OH | 80% | 81 |
| $Pb(OAc)_4$, AcOH | OAc | OAc | 60% | 81 |
| $I_2$, $CCl_4$ | I | I | 90% | 82 |

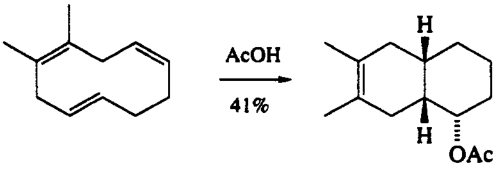

(ref. 84) (30)

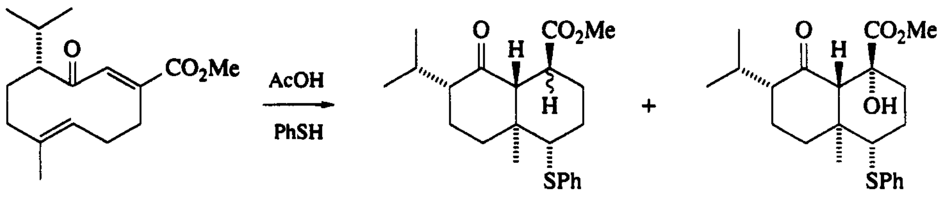

(ref. 85) (31)

36% (4:1) 11%

The cyclodecatetraene (**94**), incorporating an allene unit, undergoes transannulation accompanied by rearrangement in the presence of $HgSO_4$, producing a mixture of the bicyclo[4.4.0]decenol (**95**) and the vinylcyclopropane (**96**; Scheme 11).[92]

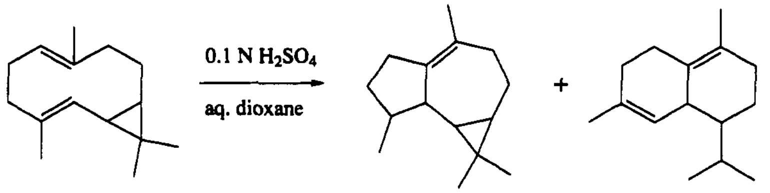
0.1 N $H_2SO_4$
aq. dioxane
+

**(89)** **(90)** **(91)**

(32)

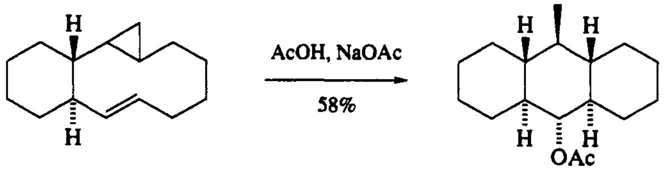
H
H
AcOH, NaOAc
58%
H
H
H
H
OAc

**(92)** **(93)**

(33)

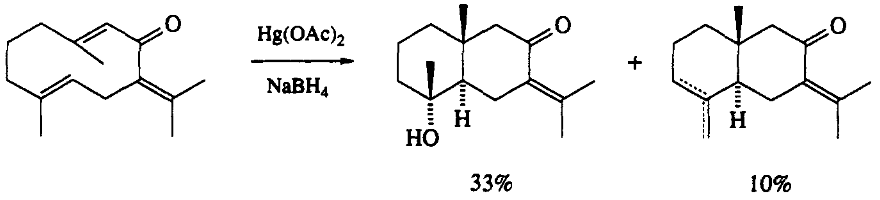
O
$Hg(OAc)_2$
$NaBH_4$
O
HO
H
33%
+
O
H
10%

(ref. 37) (34)

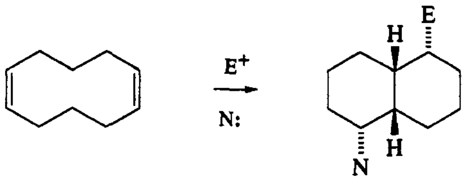

(ref. 61) (35)

AcOH: E = H, N = OAc; $Br_2$: E = Br, N = Br (ref. 3d)

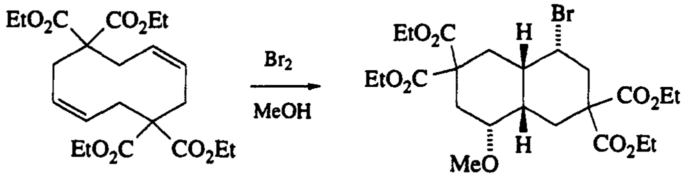
$EtO_2C$
$CO_2Et$
$EtO_2C$
$CO_2Et$
$Br_2$
MeOH
$EtO_2C$
$EtO_2C$
H
Br
$CO_2Et$
$CO_2Et$
MeO
H

(ref. 89) (36)

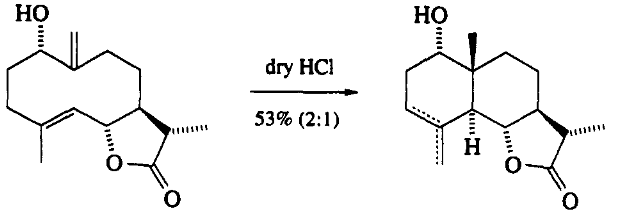
HO
O
O
dry HCl
53% (2:1)
HO
H
O
O

(ref. 90) (37)

### 1.10.5.3 Cyclodecenols

Very early on in the development of the principles of transannulation, Cope and coworkers showed that the tosylates (**97**; equation 38) and (**100**; equation 39), derived from (*Z*)- and (*E*)-cyclodec-5-enol, underwent smooth transannulation in the presence of acetic acid, leading to mixtures of the isomeric bicyclo[4.4.0]decenes (**98**), (**99**) and (**101**) together with the cyclodecenol (**102**).[93] Later work by Goering *et al.* demonstrated that the rate of solvolysis of the *p*-nitrobenzoate derivative of (*E*)-cyclodec-5-enol was such that chiral starting materials led to chiral products, (*e.g.* **103** → **104**; equation 40).[94] Similar to

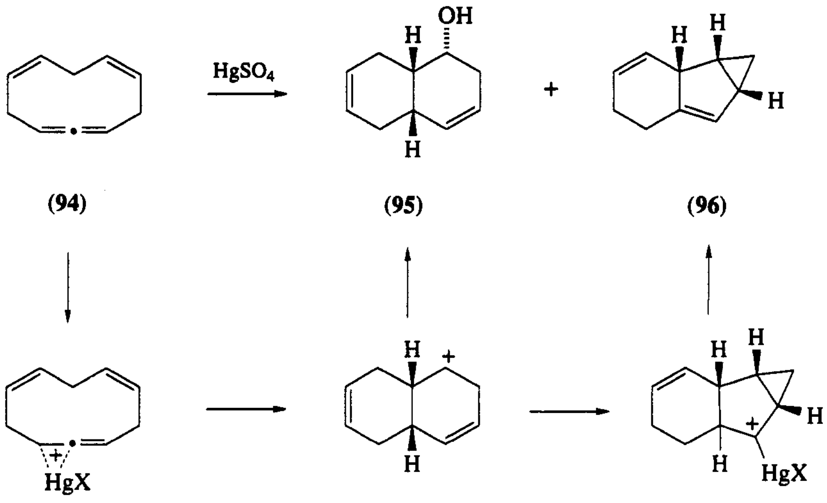
HgSO$_4$
OH
H
H
(94)
(95)
(96)
HgX
HgX
+

**Scheme 11**

the observation made with geometrically defined cyclodeca-1,5-dienes, described earlier, the (*Z*)-cyclodecene (**105**; equation 41), corresponding to (**97**), produced the *cis*-decanol (**106**) on solvolysis in acetone at 100 °C.[95]

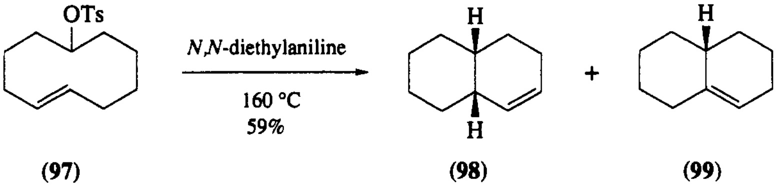
OTs
*N*,*N*-diethylaniline
160 °C
59%
H
H
(97)
(98)
(99)

(38)

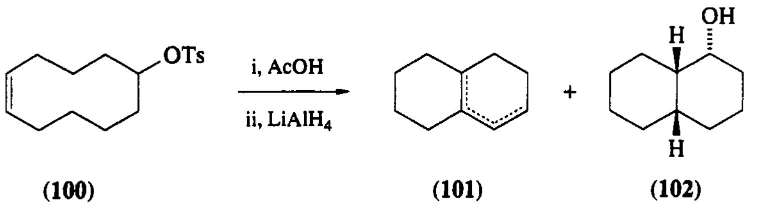
OTs
i, AcOH
ii, LiAlH$_4$
OH
H
H
(100)
(101)
(102)

(39)

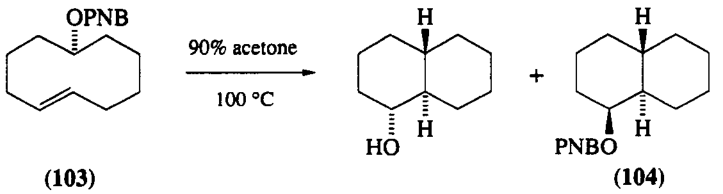
OPNB
90% acetone
100 °C
H
HO
H
PNBO
(103)
(104)

(40)

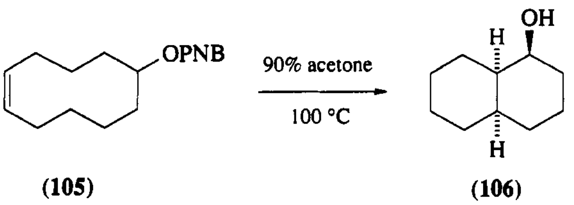
OPNB
90% acetone
100 °C
OH
H
H
(105)
(106)

(41)

Marshall and Huffman have employed a neat combination of the aforementioned principles to access the hydroazulene system (**109**) by solvolysis of (**107**) in the presence of aqueous dioxane; the reaction (**107**) → (**109**; equation 42) proceeds *via* the incipient allylic carbonium ion intermediate (**108**).[96] Indeed, subsequent to this work, a wide range of cyclodecenols (many naturally occurring) have been used to synthesize both hydroazulene (guaiane) and bicyclo[4.4.0]decane ring systems, and a selection is given in equations (43–48).[97–102]

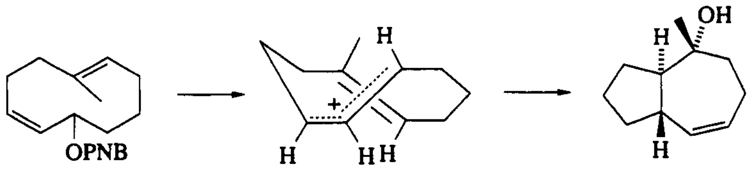
OPNB
H
+
H
HH
H
OH
H
H

**(107)** **(108)** **(109)**

(42)

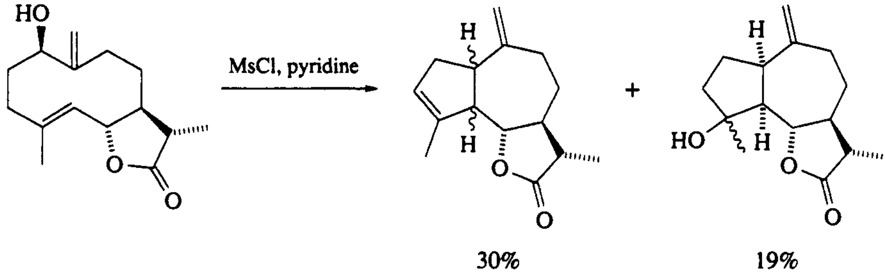
HO
O
O
MsCl, pyridine
H
H
O
O
+
H
HO
H
O
O
30%
19%

(ref. 97) (43)

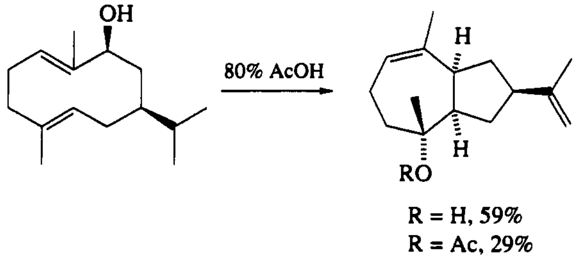
OH
80% AcOH
H
H
RO
R = H, 59%
R = Ac, 29%

(ref. 98) (44)

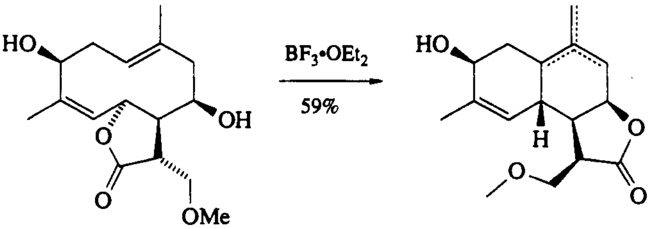
HO
OH
O
O
OMe
BF₃•OEt₂
59%
HO
H
O
O
O

(ref. 99) (45)

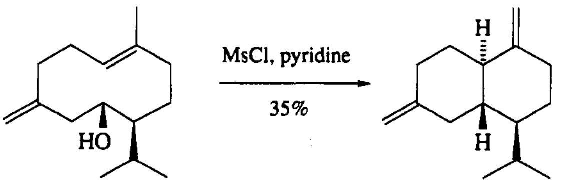
HO
MsCl, pyridine
35%
H
H

(ref. 100) (46)

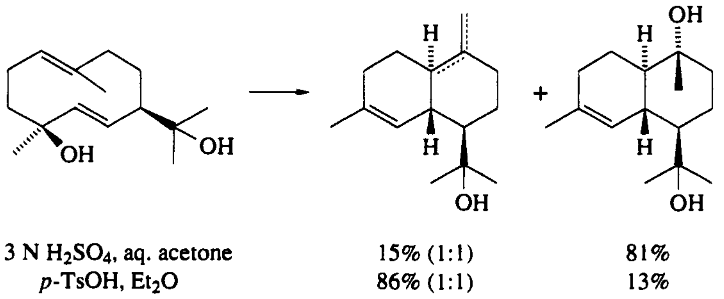
OH
OH
H
H
OH
+
OH
H
H
OH
3 N H₂SO₄, aq. acetone
p-TsOH, Et₂O
15% (1:1)
86% (1:1)
81%
13%

(ref. 101) (47)

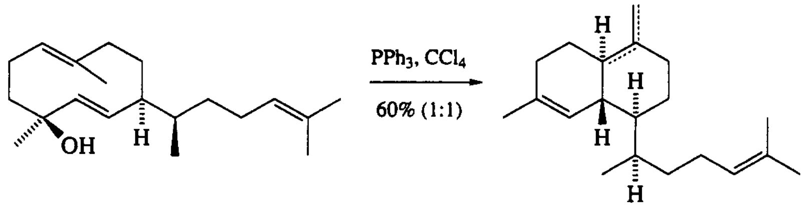
PPh$_3$, CCl$_4$
60% (1:1)
OH
H
H
H
H
H

(ref. 102) (48)

Transannulations involving cyclodec-5-ynols have also been described, and they lead largely to bicyclo[4.4.0]decanones (equations 49–53).[103,104]

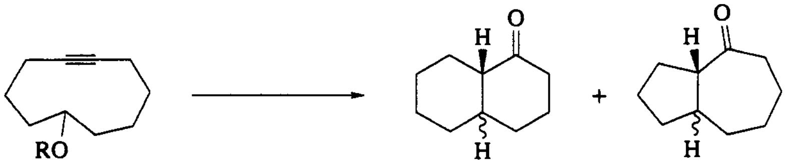

(49)

| | | | | | |
|---|---|---|---|---|---|
| R = H | HCl, MeOH | | 75% | | (ref. 103) |
| R = Ts | 80% EtOH, 2,6-lutidine, 110 °C | 93% | | 7% | (ref. 104) |
| R = PNB | 50% EtOH, 2,6-lutidine, 110 °C | 92% | | 8% | (ref. 104) |

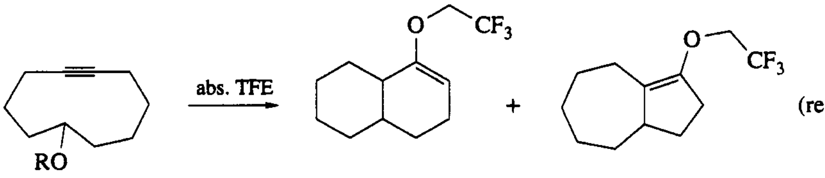
RO
abs. TFE
O
CF$_3$
+
O
CF$_3$

96% 4%

(ref. 104) (50)

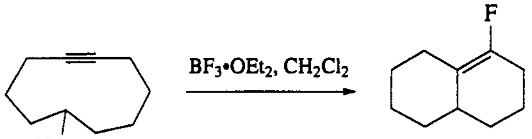
HO
BF$_3$•OEt$_2$, CH$_2$Cl$_2$
F

65%

(ref. 103) (51)

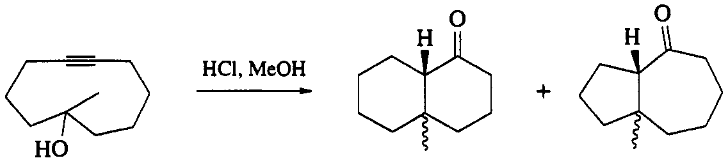
HO
HCl, MeOH
H
O
+
H
O

(ref. 103) (52)

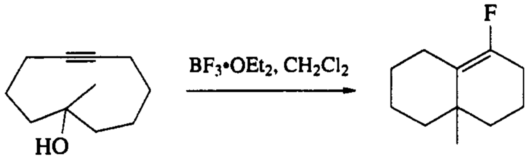
HO
BF$_3$•OEt$_2$, CH$_2$Cl$_2$
F

87%

(ref. 103) (53)

### 1.10.5.4 Cyclodecadiene Monoepoxides

Transannular cyclizations of cyclodecadiene monoepoxides have been studied in exhaustive detail, particularly amongst natural germacranolides, because of their relevance to biogenetic models for the synthesis of eudesmane- and guaiane-type sesquiterpenes.[105–115] A full discussion of this topic is beyond the scope of this chapter, but the examples collected in equations (54–64) provide the reader with an indication of the scope for this transannulation strategy in synthesis. The specificity of cyclization to either the [3,5]- or [4,4]-bicyclodecane systems can be predicted largely on the basis of the stability of the carbonium ion resulting from initial epoxide ring opening. In some instances rearrangement of the product resulting from transannulation of certain cyclodecene epoxides has been found to be a significant problem, *e.g.* (**110**) → (**111**; Scheme 12).[116]

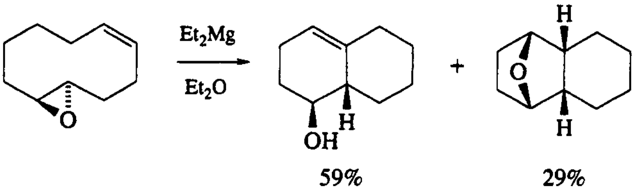
$Et_2Mg$
$Et_2O$
O
OH
H
+
H
O
H
59%
29%

(ref. 105) (54)

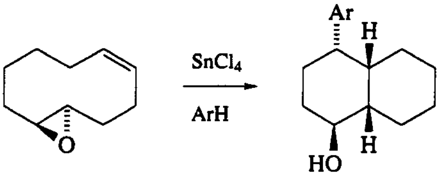
$SnCl_4$
ArH
O
Ar
H
HO
H

(ref. 106) (55)

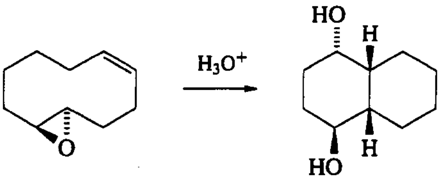
$H_3O^+$
O
HO
H
HO
H

(ref. 107) (56)

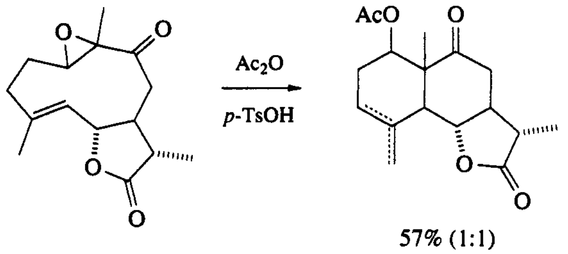
O
O
O
O
$Ac_2O$
$p$-TsOH
AcO
O
O
O
57% (1:1)

(ref. 108) (57)

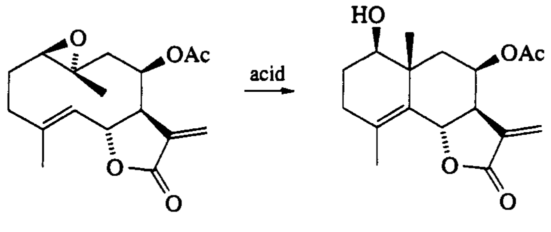
O
OAc
O
O
acid
HO
OAc
O
O

(ref. 109) (58)

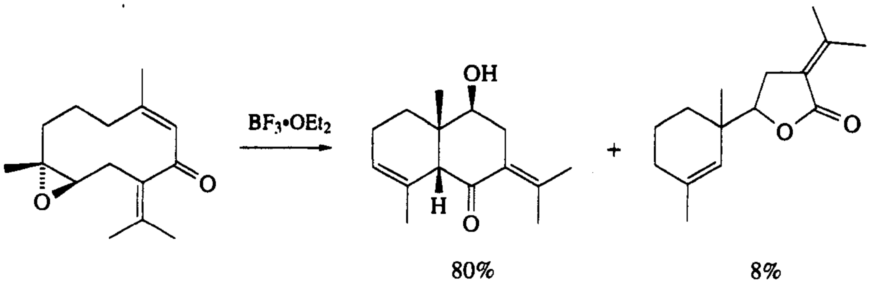
O
O
$BF_3{\bullet}OEt_2$
OH
H
O
+
O
O
80%
8%

(ref. 110) (59)

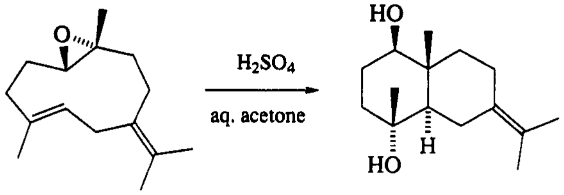

$H_2SO_4$
aq. acetone
HO
HO
H

(ref. 111) (60)

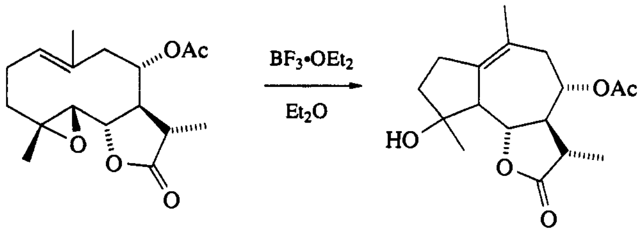

OAc
O
O
O
$BF_3•OEt_2$
$Et_2O$
OAc
HO
O
O

(ref. 112) (61)

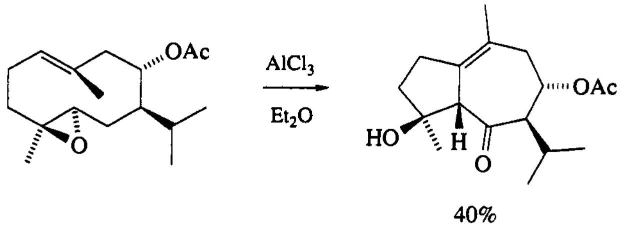

OAc
O
$AlCl_3$
$Et_2O$
OAc
HO
H
O
40%

(ref. 113) (62)

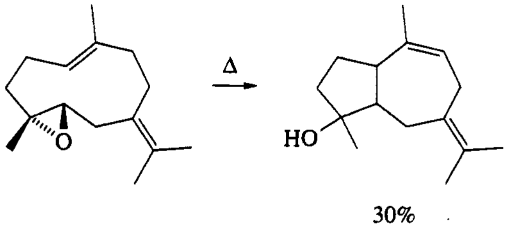

(refs. 111, 114) (63)

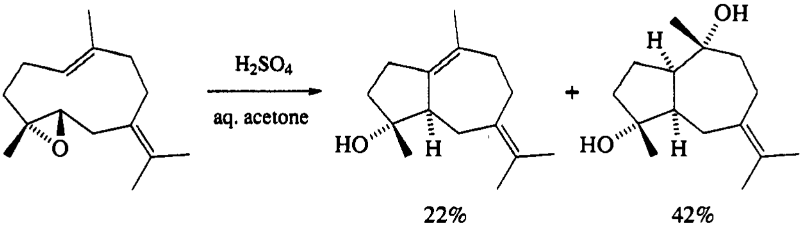

O
$H_2SO_4$
aq. acetone
HO
H
+
OH
H
HO
H
22%
42%

(ref. 111) (64)

## 1.10.6 CYCLOUNDECENES

As summarized in the above discussion (Section 1.10.5.1) and in Scheme 9, the 11-ring triene humulene (**72**) is a central intermediate in the biosynthesis of a very wide range of polycyclic sesquiterpenes. Consequently, studies of the chemistry, the stereochemistry and the conformation of humulene, together with its use in biomimetic synthesis have been the subjects of considerable research. Indeed, studies of transannulation reactions amongst cyclononadecenes have been dominated by humulene, and this is reflected in this discussion. The humulene ring system is numbered here according to the IUPAC recommendations, and this numbering is shown on formula (**112**). It should be noted that some authors, *e.g.* Shirahama *et al.*, use an alternative numbering scheme in their publications.

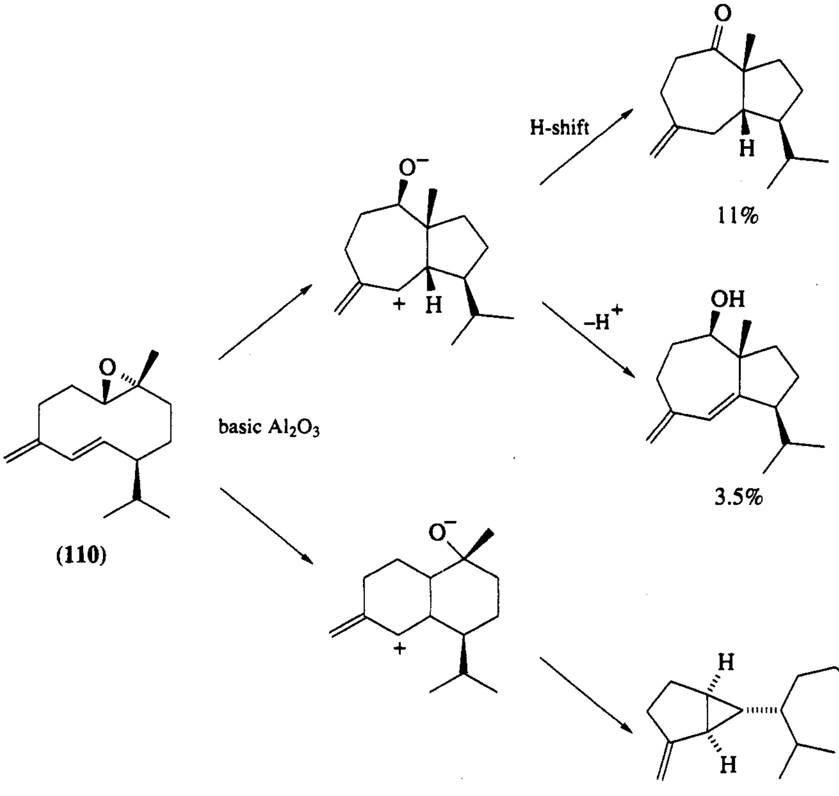

**(110)**

**(111)** 10%

**Scheme 12**

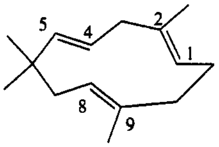

**(112)**

### 1.10.6.1 Humulene

More than 20 years ago Sutherland *et al.*[117] first showed that when humulene (**72**) was treated with *N*-bromosuccinimide in aqueous acetone it underwent a remarkable transannulation, leading to the tricyclic bromohydrin (**113**) in 25% yield. Hydrolysis of (**113a**) then led to tricyclohumuladiol (**113b**), which was later found as a constituent of hop oil, and two synthetic steps converted (**113b**) into the cyclononadiene caryophyllene (**63**; equation 65).

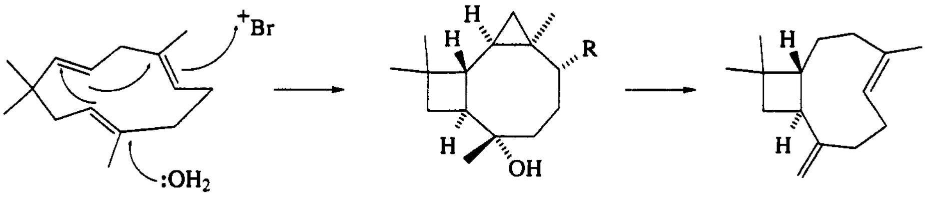

**(72)** **(113a)** R = Br **(113b)** R = OH **(63)** (65)

Later work by Parker *et al.*[118] demonstrated that extended treatment of humulene with aqueous sulfuric acid in acetone led largely to the bicyclo[5.3.0]deca-2,10-diene (**115**), *via* initial formation of humulol

(**114**). Other products which were isolated from this study were the related fused 5,7-ring molecules (**117**)–(**119**), together with α-caryophyllene alcohol (**116**; Scheme 13).

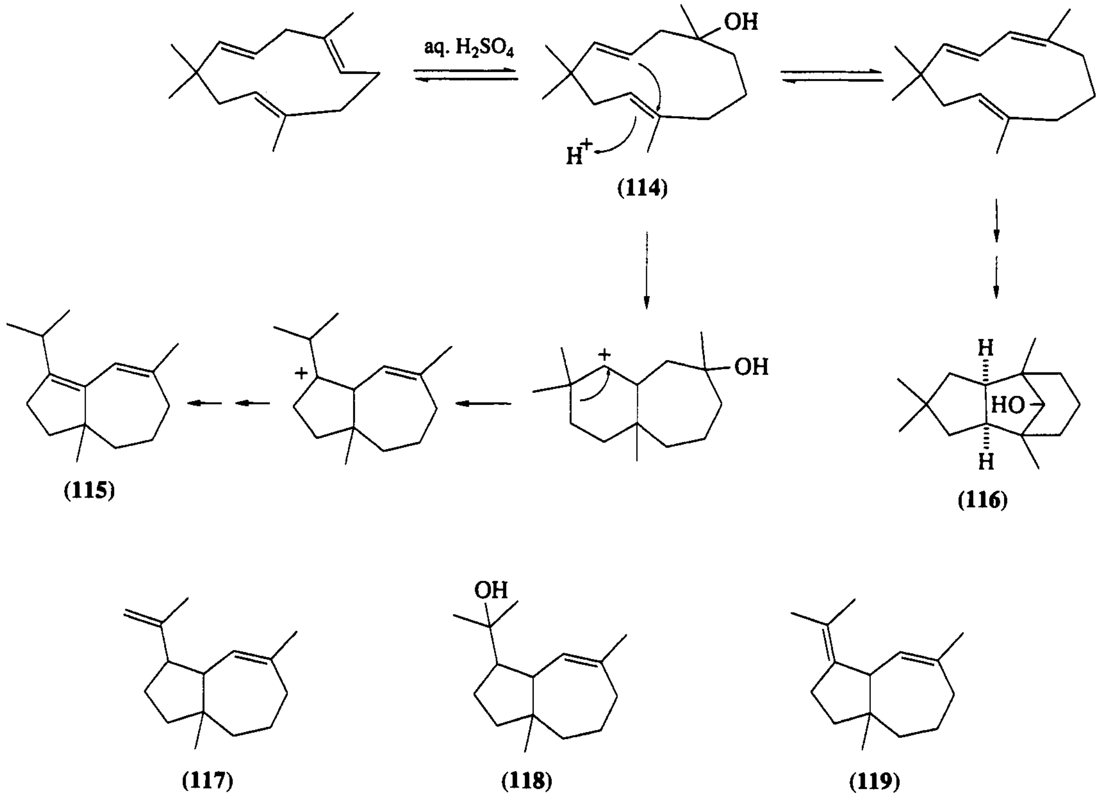

**Scheme 13**

In extensive studies of oxymercuration reactions of humulene, Matsumoto and Shirahama have shown that, whereas oxymercuration with $Hg(OAc)_2$ in $THF–H_2O$ followed by demercuration leads largely to the tricyclic ether (**120**; equation 66),[119] use of $Hg(NO_3)_2$ in $AcOH–H_2O$ instead produces mainly the isomeric ether (**121**).[120] Interestingly, when humulene was treated with $Hg(NO_3)_2$ followed by aqueous HBr, chromatography led to the two bromomercury compounds (**122**) and (**123**) in a combined yield of 52%.[121] The mercury compounds were then elaborated, in several steps, to the novel cyclooctenol (**124**) which was beautifully set-up for a further transannulation reaction leading to the hydroxypentalenene (**125**); several synthetic steps then led to pentalenic acid (**126**; equation 67).[122] In further extensive studies Matsumoto and Shirahama and their collaborators have also shown how the 10α-alcohol (**127**), derived from (**123**), can be used to elaborate pentalenolactones G and H, (**128**) and (**129**) respectively (Scheme 14),[123] and how the ether (**121**) can be converted into pentalenene, pentalenolactone E (**130**) and pentalenolactone F (**131**; Scheme 15.[124] These studies are therefore based on the biogentic speculation alluded to earlier whereby the 11-ring humulene is converted into the angular fused pentalenane 5,5,5-ring system in sequence, *via* the intermediate fused 5,8-ring system (**132**; Scheme 16). In related work Pattenden and Teague[53] have also described a total synthesis of pentalenene (**40**), based on the transannulation reaction shown earlier, *i.e.* (**39**) or (**41**) → (**40**; Scheme 15). Other extensive studies of the transannulation chemistry of the tricyclic ether (**134**) by the same Japanese group, led by Matsumoto

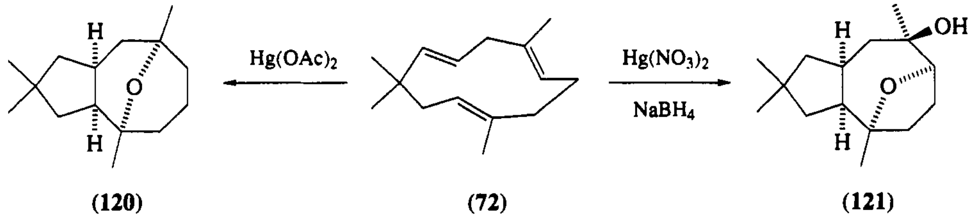

(66)

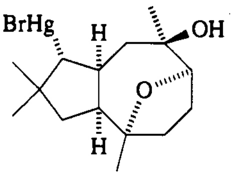

**(122)**

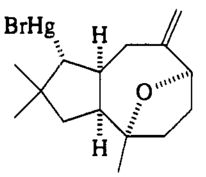

**(123)**

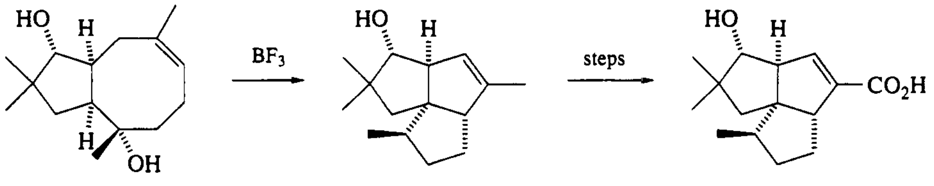
HO
H
H
OH
BF$_3$
HO
H
steps
HO
H
CO$_2$H

**(124)** **(125)** **(126)**

(67)

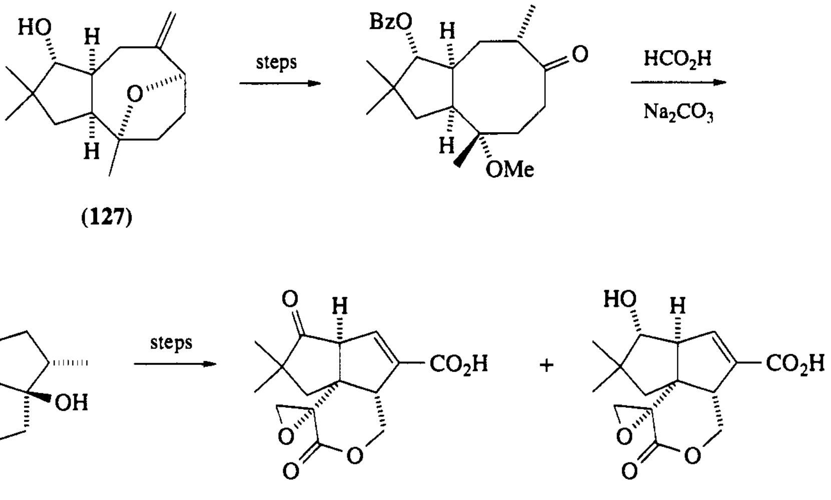
HO
H
O
H
steps
BzO
H
O
H
OMe
HCO$_2$H
Na$_2$CO$_3$
HO
H
OH
steps
O
H
CO$_2$H
O
O
O
+
HO
H
CO$_2$H
O
O
O

**(127)** **(128)** **(129)**

**Scheme 14**

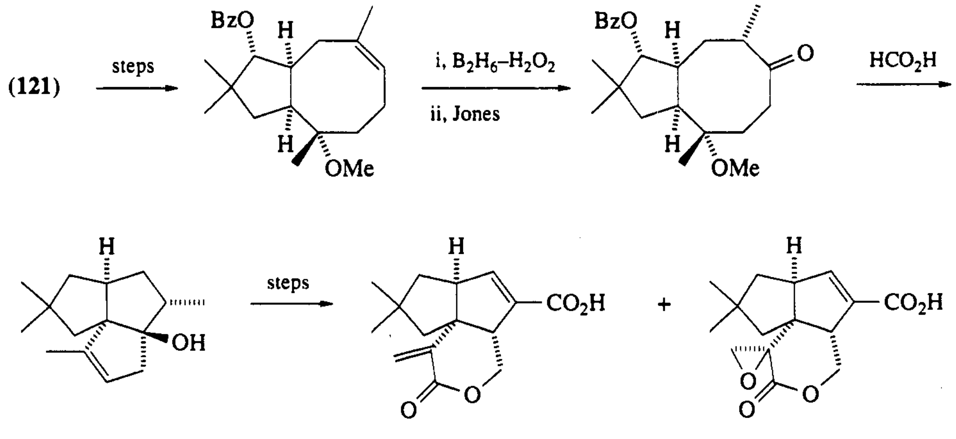
(121)
steps
BzO
H
H
OMe
i, B$_2$H$_6$–H$_2$O$_2$
ii, Jones
BzO
H
O
H
OMe
HCO$_2$H
H
OH
steps
H
CO$_2$H
O
O
+
H
CO$_2$H
O
O
O

**(130)** **(131)**

**Scheme 15**

and Shirahama, have led to the synthesis of natural sterpurene (**133**)[125] and of hirsutene (**135**; equation 68).[126]

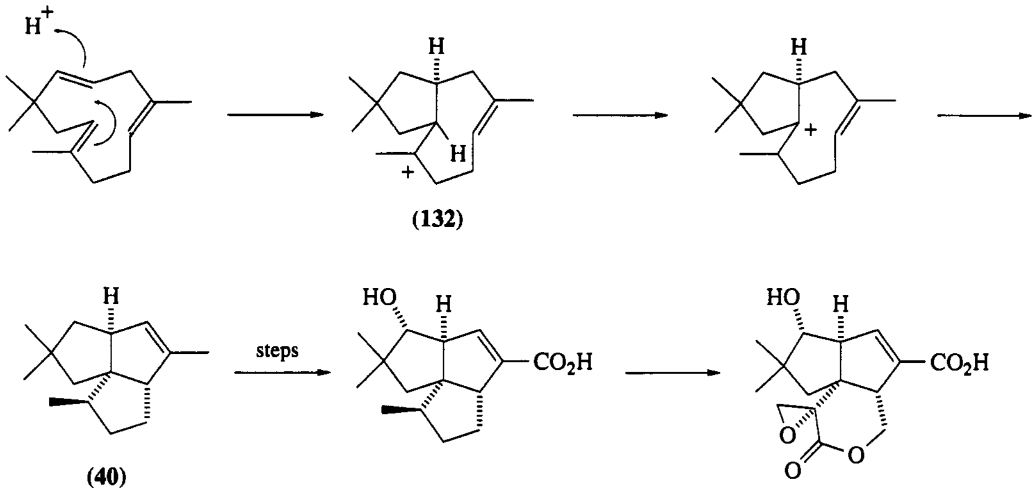

**Scheme 16**

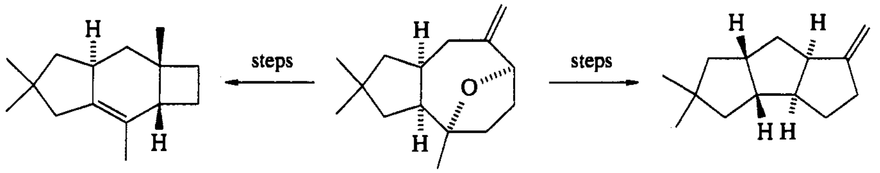

(**133**) (**134**) (**135**) (68)

## 1.10.6.2 Humulene Epoxides

The three monoepoxides of humulene, *i.e.* (**136**), (**150**) and (**162**), occur in nature,[127] and there is every reason to assume that each epoxide is involved separately in transannulation processes leading to various fused-ring systems found amongst the sesquiterpenes. All three humulene monoepoxides have been synthesized and their individual chemistry with Lewis acids has been examined in an effort to effect their biogenetic conversions to natural terpenes.

### *1.10.6.2.1 Humulene-1,2-epoxide*

The $\Delta^{1,2}$-double bond in humulene (**72**) has been found to be the most reactive towards electrophiles, and hence the chemistry of the corresponding 1,2-epoxide (**136**) was the first to be studied. Thus, early work of McKervey and Wright[128] demonstrated that when (**136**) was treated with 20% $H_2SO_4$ in acetone, it produced the tricyclohumuladiol (**113b**), described earlier by Sutherland *et al.*[117] Subsequently Takahashi and his coworkers[129] showed that the diol (**113b**) could be produced in 95% yield from humulene-1,2-epoxide when the latter is treated with aqueous $H_2SO_4$ in acetone at 0 °C instead of at room temperature. Continuation of this reaction at room temperature for 7 h, however, gave rise to the new [6.3.0.0$^{2,4}$]undec-9-enol (**138**) in *ca.* 25% yield. Even later work by Shirahama *et al.*[130] showed that when (**136**) was treated with trimethylsilyl triflate (TMSOTf) at –75 °C the alkene (**139**) corresponding to (**138**) could be produced cleanly, in one step in 80% yield (Scheme 17).

Contemporaneous studies of the conformational behavior of humulene (**72**) by Shirahama *et al.*[131] using empirical force calculations have suggested that, although the molecule can assume any of the four stable conformations (**140**), (**141**), (**142**) and (**143**), abbreviated to CT, CC, TT and TC respectively, (see Section 1.10.3), only the CT- and the CC-conformers (**140**) and (**141**) are involved in biosynthetic transannulation reactions. Thus, Shirahama *et al.* have suggested that the transannulation reaction leading from (**136**) to (**139**) in the presence of TMSOTf proceeds *via* the CT-conformer (**137**) of humulene-1,2-epoxide. Interestingly, when (**139**) was converted into the epoxide (**144**), treatment with TMSOTf trig-

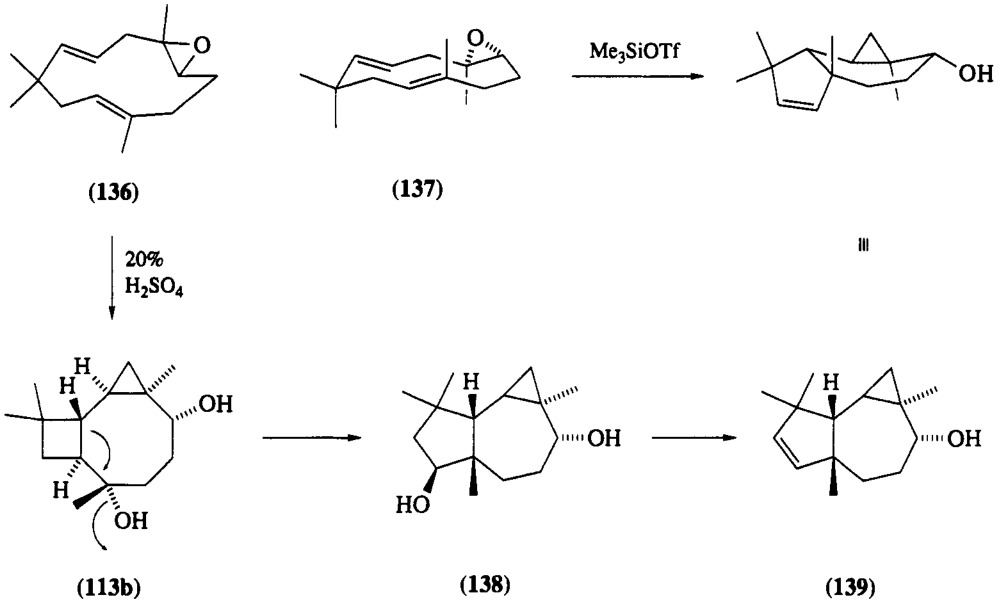
(136)
(137)
$Me_3SiOTf$
OH
20% $H_2SO_4$
(113b)
(138)
(139)
H
OH
HO

Scheme 17

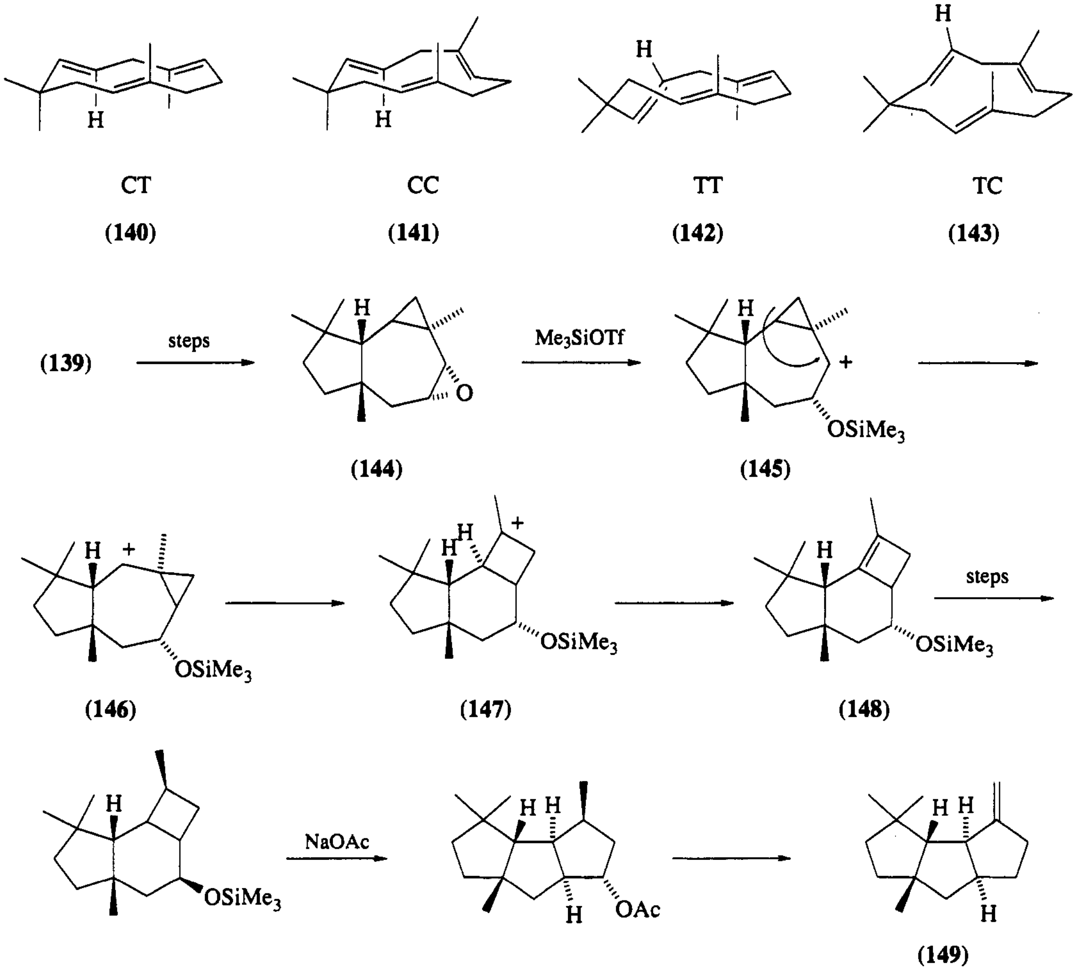
CT
(140)
CC
(141)
TT
(142)
TC
(143)
(139)
steps
(144)
$Me_3SiOTf$
(145)
$OSiMe_3$
(146)
(147)
(148)
steps
NaOAc
OAc
(149)
H

Scheme 18

gered a series of carbonium ion rearrangements, *i.e.* (**145**) → (**146**) → (**147**) leading to the intermediate (**148**), which could be transformed into naturally occurring capnellene (**149**; Scheme 18).[132]

### *1.10.6.2.2 Humulene-4,5-epoxide*

The biosynthesis of the hirsutane, protoilludane, marasmane, illudane and africane families of sesquiterpenes are all thought to occur *via* initial protonation of the $\Delta^{4,5}$-double bond in humulene (*cf.* Scheme 9). Attempts to mimic these reactions in the laboratory were frustrated for many years due to the inaccessibility of the 4,5-epoxide (**150**) of humulene. An indirect synthesis of humulene-4,5-epoxide permitted Roberts and coworkers[133] to study the cyclization of (**150**) in the presence of $BF_3 \cdot OEt_2$ (equation 69). This study led to the formation of the two alcohols (**152a**) and (**153**), which had the same tricyclic carbon framework to that found in naturally occurring africanol (**154**) and the related ester (**152b**).[134]

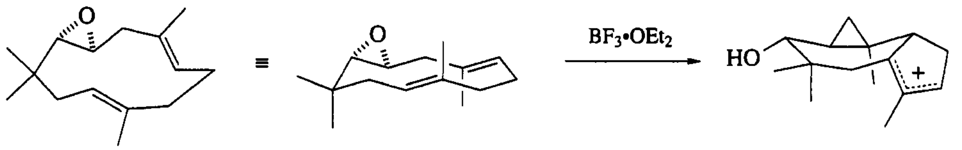

(69)

**(150)** **(151)**
CT-conformation

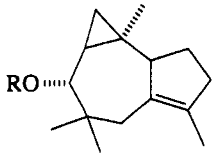

**(152a)** R = H
**(152b)** R = angelate

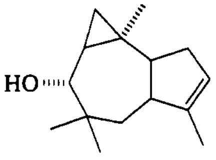

**(153)**

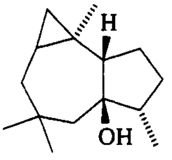

**(154)**

Sometime later, Matsumoto and Shirahama[135] demonstrated that when humulene-4,5-epoxide (**150**) was treated with $BF_3 \cdot OEt_2$ in HOAc at –50 °C, the only product isolated was the bicyclohumulenediol (**156**), in 70% yield. The formation of (**156**) was rationalized as occurring *via* the CC-conformation (**155**; equation 70) of the epoxide, whereas the production of the africanol system (**152**) occurs *via* the corresponding CT-conformation (**151**) of (**150**).

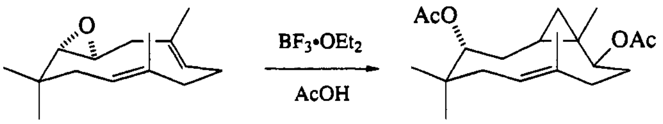

(70)

**(155)**
CC-conformer

**(156)**

Appropriate manipulations of the tricycle (**152a**) resulting from transannulation of humulene-4,5-epoxide permitted Roberts and Shirahama and their respective collaborators to access africanol (**154**) and 8-oxysenoxyn-4-en-3-one (**157**).[136] Shirahama *et al.*[137] have also described the *in vitro* conversion of africanol (**154**) to dactylol (**158**), found in the sea hare *Aplsysia dactyloma*, *via* the novel and unusual cyclopropane-sliding reaction, summarized in Scheme 19.

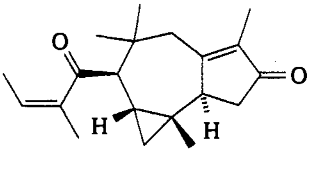

**(157)**

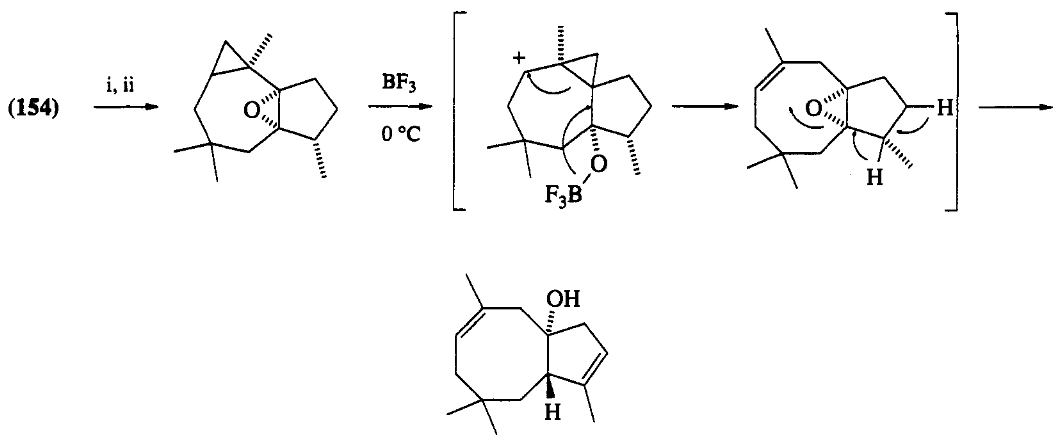

**(158)**

i, $POCl_3$/pyridine; ii, MCPBA + chromatography

**Scheme 19**

Finally, transannular cyclization involving the $\Delta^{8,9}$- rather than the $\Delta^{1,2}$-double bond in humulene-4,5-epoxide (**150**) can be achieved by first converting (**150**) to the corresponding aldehyde (**159**). Treatment of (**159**) with TMSOTf is then shown to lead to the fused 5,7-ring system (**160**) in good yield (equation 71).[138]

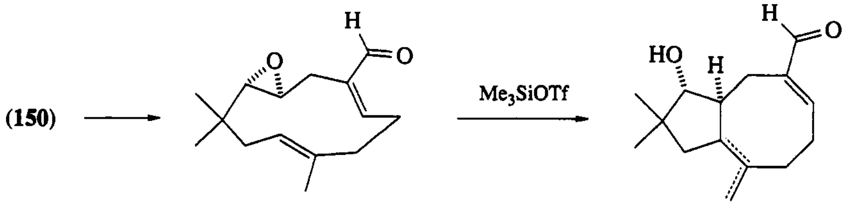

**(159)** **(160)** (71)

### *1.10.6.2.3 Humulene-8,9-epoxide*

In contrast to the fascinating transannulation reactions associated with humulene-1,2- and humulene-4,5-epoxides, humulene-8,9-epoxide (**161**) undergoes transannulation and rearrangement in the presence of $SnCl_4$ leading only to the bicyclic alcohol (**162**), related to the rearrangement product (**115**) of humulene itself (Scheme 20).[139]

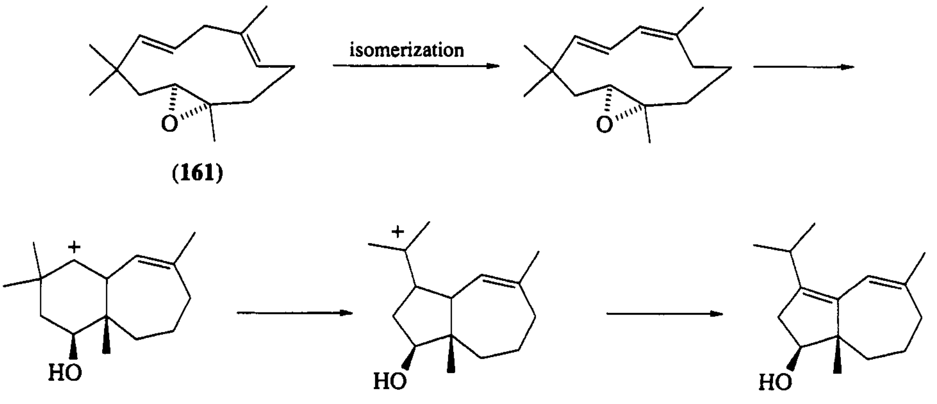

**(162)**

**Scheme 20**

Formic acid catalyzed transannulation of the 8,9-epoxide (**163**), derived from natural zerumbone, has been shown to lead to a mixture of the bicyclo[6.3.0]undecane (**164**) and the hydroazulene (**165**; equation 72).[140]

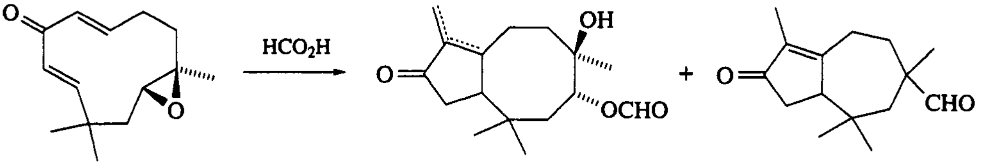
$HCO_2H$
OH
OCHO
CHO
+

(72)

**(163)** **(164)** **(165)**

## 1.10.7 OTHER CYCLOALKENES

The transannular cyclizations described in Sections 1.10.1–1.10.6 are unique to medium-sized ring systems. Although transannular electrophilic processes are known with smaller rings, *i.e.* 3- to 7-rings, many of these processes can best be reviewed in terms of nonclassical carbonium ion phenomena. Some selected examples are collected in equations (73–77).[141-145]

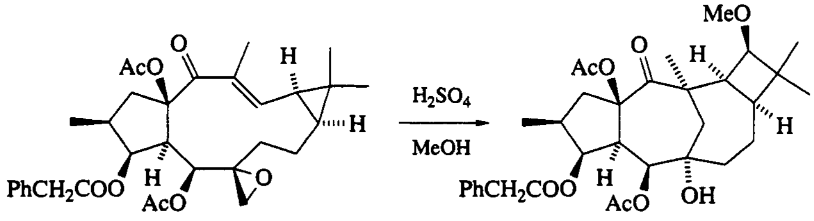
$H_2SO_4$
MeOH
AcO
PhCH$_2$COO
MeO
OH

(ref. 141) (73)

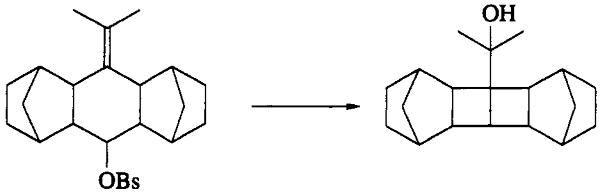

(ref. 142) (74)

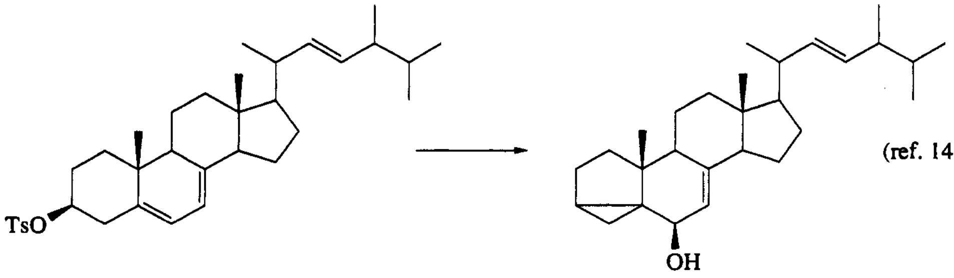

(ref. 143) (75)

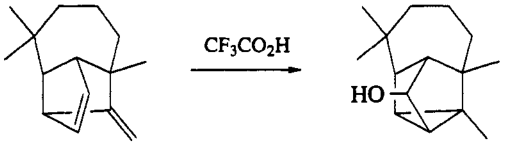

(ref. 144) (76)

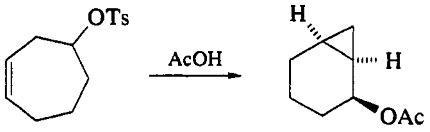
OTs
AcOH
H
OAc

(ref. 145) (77)

Although transannular electrophilic cyclizations involving large rings have not been studied in any great detail, the available information suggests that these reactions occur only with difficulty. Thus, the cembranoid diterpene sarcophine (**166**) produces only the oxepine derivative (**167**; equation 78) on transannulation in acid,[146] and all attempts to synthesize the taxane ring system (**169**) *via* transannular cyclization of the 12-ring precursor (**168**; equation 79) have so far failed.[147] Interestingly however, when the 14-membered diterpene ovatodiolide (**170**) is treated with hot methanolic hydrochloric acid[148] or with *p*-toluenesulfonic acid (PTSA)[149] it produces the product (**171**; equation 80). In addition, the tobacco constituent (**172**) is reported to produce the tetracyclic ether (**173**; equation 81) upon heating with PTSA in benzene.[150]

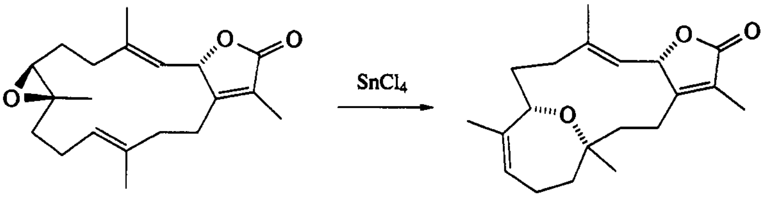

(78)

**(166)** **(167)**

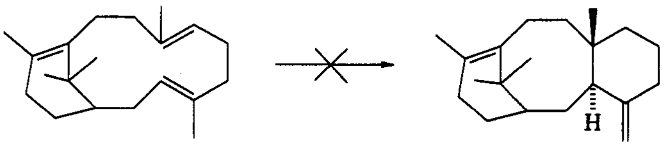

(79)

**(168)** **(169)**

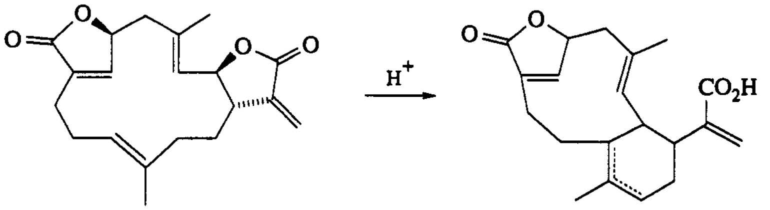

(80)

**(170)** **(171)**

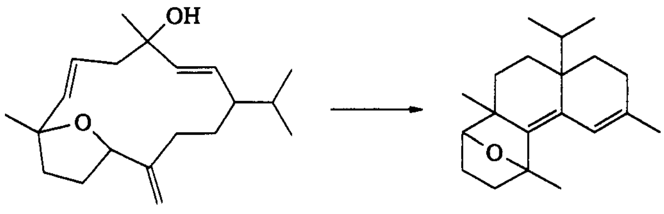

(81)

**(172)** **(173)**

## 1.10.8 REFERENCES

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2. V. Prelog and K. Schenker, *Helv. Chim. Acta*, 1952, **35**, 2044.
3. (a) V. Prelog and J. G. Traynham in 'Molecular Rearrangement', ed. P. de Mayo, Wiley, New York, 1963, p. 593; (b) A. C. Cope, M. M. Martin and M. A. McKervey, *Q. Rev., Chem. Soc.*, 1966, **20**, 119; (c) J. K. Sutherland, *Tetrahedron*, 1974, **30**, 1651; (d) G. Haufe and M. Mühlstädt, *Z. Chem.*, 1979, **19**, 170; (e) G. Haufe and G. Mann, 'Chemistry of Alicyclic Compounds: Structure and Chemical Transformations', Elsevier, Amsterdam, 1989.
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# 2.1

# Coupling Reactions Between *sp*³ Carbon Centers

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## 2.1.1 INTRODUCTION AND SCOPE

The classical method of coupling two *sp*³-carbon centers is the Wurtz reaction (equation 1; M = Na). This chapter covers the generalized transformation shown in equation (1), where R and $R^1$ may be the same (dimerization) or different (cross-coupling) and where R and $R^1$ may represent a single molecule (intramolecular cyclization). In synthetic terms the most valuable type of coupling is the cross-coupling reaction. This reaction also presents the most problems, as the possibility of halogen–metal exchange and disproportionation of the reagents may lead to homo-coupled products ($R{-}R$ and $R^1{-}R^1$ in equation 1), in addition to the desired cross-coupled product. As dimerization reactions are in general of less synthetic value, this treatment of the Wurtz-type coupling concentrates on cross-coupling reactions for each reagent considered, with less emphasis on dimerization reactions. The uses of coupling reactions for the synthesis of cyclic systems are treated separately in Section 2.1.2.5.

$$\mathrm{R{-}X} \;+\; \mathrm{R^1{-}X} \xrightarrow{\mathrm{M}} \mathrm{R{-}R} \;+\; \mathrm{R^1{-}R^1} \;+\; \mathrm{R{-}R^1} \qquad (1)$$

R = $sp^3$ center, X = halogen, M = metal

Severe limitations on the usefulness of the classical Wurtz reaction in the production of cross-coupled products have led to the development of many more generally useful variants. In particular, the use of copper catalysis and of stoichiometric organocuprate species have proved very valuable. The reactions of π-allylnickel halides with $sp^3$ halides is also represented by equation (1), and the uses of these reagents are treated separately. In order to provide a balanced view of the value of π-allylnickel halides, some additional reactions with centers other than $sp^3$ are described.

## 2.1.2 THE WURTZ REACTION AND VARIANTS

### 2.1.2.1 The Classical Wurtz Reaction

The Wurtz reaction involves the coupling of alkyl halides using sodium metal according to equation (1). The reaction is severely limited in scope as demonstrated by the following observations. (i) In the synthesis of noncyclic systems (dimerization or cross-coupling) reasonable yields require the use of primary alkyl halides, with iodides giving the best results. Secondary halides give very poor results. (ii) Cross-coupling reactions give approximately statistical ratios of cross-coupled:dimeric products, due to the high reactivity of the organosodium intermediates involved. Thus, in the synthesis of 3-methyluntriacontane (**4**; equation 2)[1] coupling of the iodide (**1**) with l-iodooctadecane (**2**) under standard Wurtz conditions gave a mixture of (**3**) from dimerization of (**1**), (**4**) from the desired cross-coupling, and (**5**) from dimerization of (**2**), in the ratio 21:50:29. The classical reaction is however of value in the preparation of cyclic systems, notably [2.2]phanes and bicyclobutanes and in the preparation of symmetric dimers.

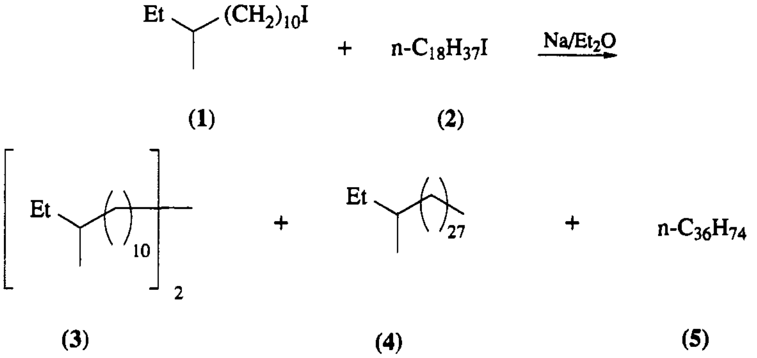

(2)

ratio of products (3):(4):(5) = 21:50:29

The synthesis of [2.2]phanes has been reviewed.[2,3] The Wurtz reaction provides one of the most successful approaches to this class of compounds, by ring-closure reactions. The reaction may proceed either intra- or inter-molecularly (as shown in equation 3), with intramolecular couplings giving better yields. The most efficient procedure[4] involves the reaction of the halo compounds with sodium metal in THF at –78 °C in the presence of catalytic quantities of tetraphenylethylene (TPE). Under these conditions the sodium metal dissolves as the disodium species, allowing a homogeneous reaction to take place, leading to better yields of coupled products. The modest yields of these products are due to competing oligomerization/cyclization reactions. This is demonstrated by the product distribution obtained on treatment of the dibromide (**6**) with sodium/TPE in THF at –80 °C (equation 4).[2] A homologous series of products is obtained under these conditions, the approximate yields of the metacyclophanes being 61%, 15%, 3.5%, 9%, 7%, 1%, 1%, 1%, 0.5%, for $n$ = 2, 3, 4, 5, 6, 7, 8, 9, 10, respectively. Organolithium species also give acceptable yields of [2.2]phanes, from the treatment of suitable dibromides with phenyllithium.

The classical Wurtz reaction is also of value in the preparation of small cyclic systems such as bicyclo[1.1.0]butane and other cyclopropane derivatives. Treatment of the 1,3-dihalide (**7**) with sodium metal in refluxing dioxane,[5] for example, gives a high yield (78–90%) of bicyclobutane (**8**; equation 5). Although sodium may be used for the synthesis of other small rings, *e.g.* cyclobutane from dibromobutane, in general other metals (particularly zinc and potassium) give higher yields (equation 6).

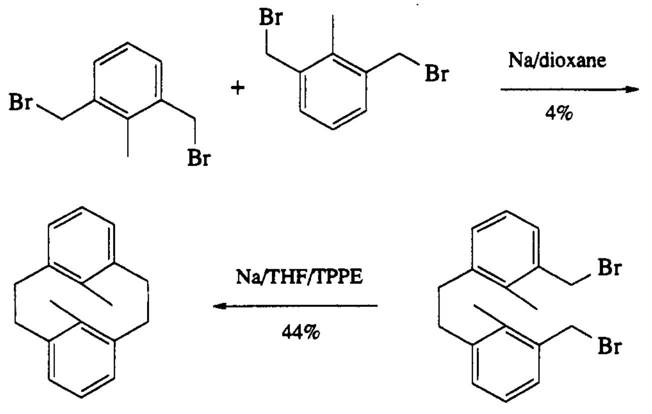

(3)

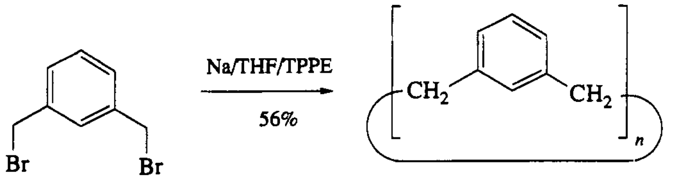

(6)

(4)

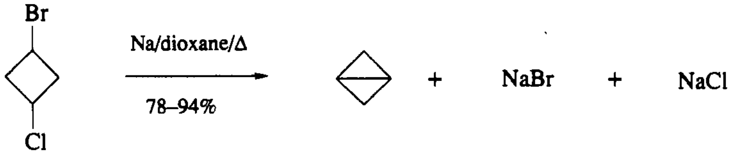

(7) (8)

(5)

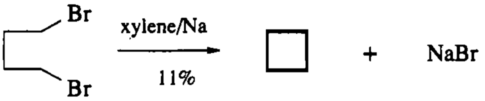

(6)

### 2.1.2.2 Organomagnesium-derived Reagents

Direct coupling of alkyl halides *via* conversion of one reactant to the Grignard reagent has limited synthetic utility. Simple Grignard reagents couple in rather low yields with tertiary alkyl halides,[6] improved yields being obtained by running the coupling reaction in a nonpolar solvent such as hexane or heptane. This method gives reasonable results for the preparation of highly branched hydrocarbons such as neopentane and hexamethylethane.[7] Examples of the use of this reaction are given in Scheme 1.[8] Grignard reagents derived from activated halides such as benzyl or related halides couple readily to give alkylbenzenes. *n*-Pentylbenzene and *n*-propylbenzene for example, may both be prepared in high yield by this procedure.[9] Intramolecular uncatalyzed Grignard coupling reactions are of value in the preparation of small ring cyclic systems (see Section 2.1.2.5).

In general, the cross-coupling of Grignard reagents with alkyl halides becomes much more synthetically useful in the presence of catalytic quantities of other metals, particularly copper species. Treatment of Grignard reagents with simple copper salts such as CuBr or CuI, or more complex species such as $Li_2CuCl_4$, leads to coupling with alkyl halides *via* transient organocopper species (equation 7). A very generalized order of reactivity of electrophiles toward organocopper species is as follows: acid chlorides > aldehydes > tosylates/epoxides > iodides > bromides > chlorides > ketones > esters > nitriles >> alkenes. In terms of coupling of $sp^3$ carbon centers, the approximate order of reactivity of alkyl halides is: allylic/benzylic > primary > secondary >> tertiary. In general, primary alkyl halides have been most widely used as sources of the Grignard reagent. Following the pioneering studies of Tamura and Kochi,[10]

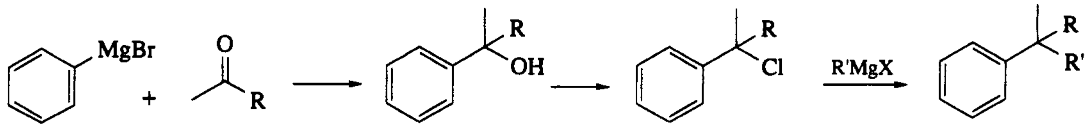

**(9a)–(9c)** **(10a)–(10c)**

a: R = $C_5H_{11}$, R' = $C_{10}H_{21}$; 30%
b: R = $C_6H_{11}$, R' = $C_8H_{17}$; 32%
c: R = $C_5H_{11}$, R' = Bu; 17%

**Scheme 1**

widespread use has been made of the THF-soluble dilithium tetrachlorocuprate as a catalyst for the coupling of alkyl halides *via* their Grignard reagents.

$$R^1{-}X \xrightarrow{Mg} R^1{-}MgX \quad + \quad R^2{-}X \xrightarrow{Cu^I} R^1{-}R^2 \tag{7}$$

X = halogen; $Cu^I$ = *e.g.* CuI or $Li_2CuCl_4$; $R^1$ and $R^2$ = alkyl $sp^3$ carbon

Under suitable conditions, the yields of homodimeric products ($R^1$—$R^1$ and $R^2$—$R^2$) are negligibly small and high yields of cross-coupled products are obtained (equation 7). These reactions are normally performed in THF, at low temperatures (–20 to 0 °C) and require only catalytic quantities of the readily prepared copper species. The reaction characteristics may be summarized by the following general observations.[11–22] (i) Coupling proceeds very readily with primary halides; iodides and bromides giving good yields and chlorides giving lower yields. (ii) Secondary iodides also give good yields; secondary bromides and chlorides do not react. (iii) Activated halides, such as allylic or benzylic bromides or chlorides, give good yields for both primary and secondary substrates. (iv) Tertiary halides generally give very poor results, with disproportionation of the reagents predominating. (v) The degree of substitution of the Grignard reagent is not very important in determining reactivity. From the examples in equations (8)–(18) it can be seen that high yields of the desired cross-coupled products are normally obtained

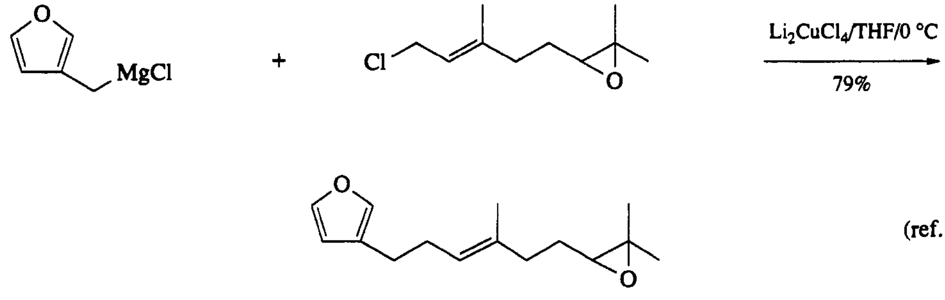

(ref. 11) (8)

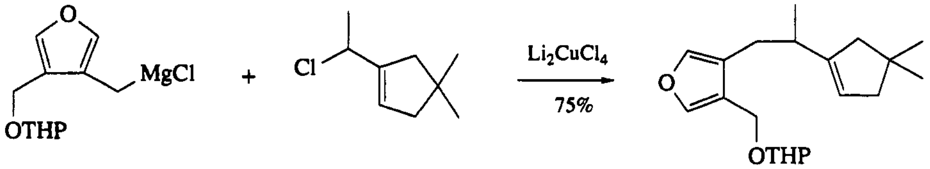

(ref. 12) (9)

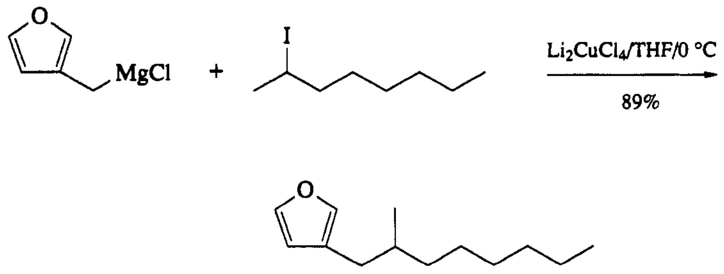

(ref. 11) (10)

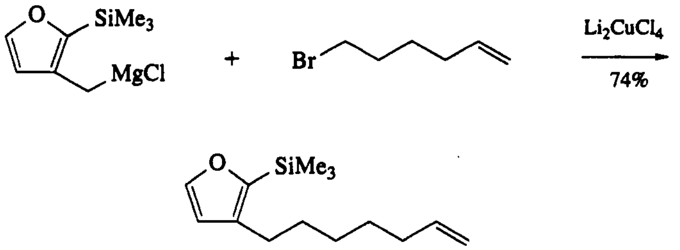
SiMe3
MgCl
Br
Li2CuCl4
74%
SiMe3

(ref. 13) (11)

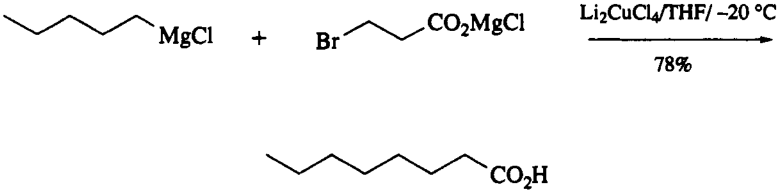
MgCl
Br
CO2MgCl
Li2CuCl4/THF/ -20 °C
78%
CO2H

(ref. 14) (12)

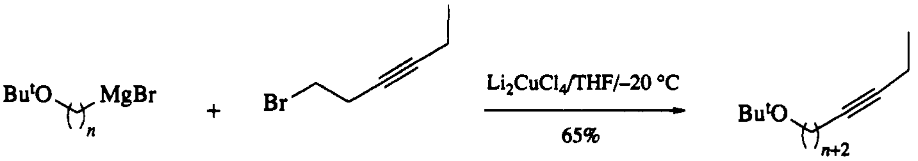
BuᵗO
MgBr
n
Br
Li2CuCl4/THF/–20 °C
65%
BuᵗO
n+2

(ref. 15) (13)

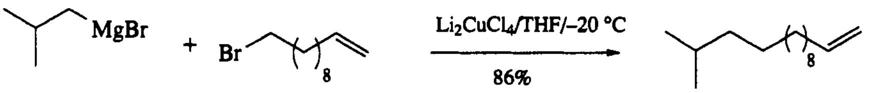
MgBr
Br
8
Li2CuCl4/THF/–20 °C
86%
8

(ref. 16) (14)

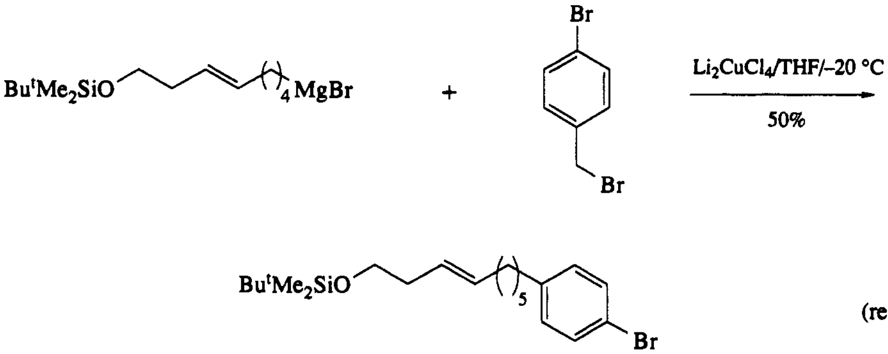
BuᵗMe2SiO
4
MgBr
Br
Br
Li2CuCl4/THF/–20 °C
50%
BuᵗMe2SiO
5
Br

(ref. 17) (15)

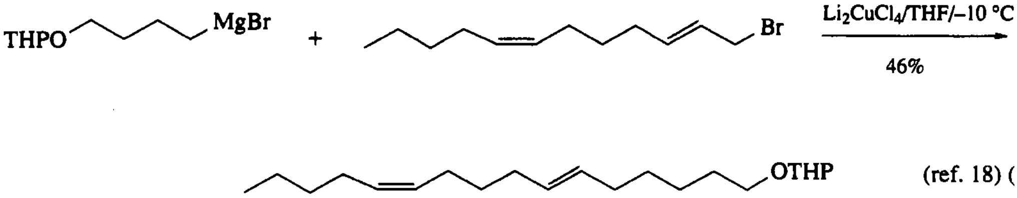
THPO
MgBr
Br
Li2CuCl4/THF/–10 °C
46%
OTHP

(ref. 18) (16)

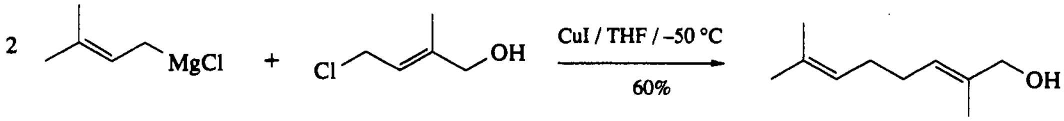
2
MgCl
Cl
OH
CuI / THF / -50 °C
60%
OH

(ref. 20) (17)

and that a number of functional groups are inert in the reaction. Functionality that is tolerated includes alkynes, ethers, alcohols protected as THP or TBDMS ethers, epoxides, furans and unprotected alcohols and carboxylic acids, as their chloromagnesium salts. These observations have allowed the use of this catalyzed Grignard coupling in the preparation of a range of natural products, intermediates towards some of which are shown in equations (8)–(18). Other copper species used for the catalysis of Grignard couplings include copper(I) chloride, bromide and iodide[23] and some recent examples are given in equations (17) and (18).

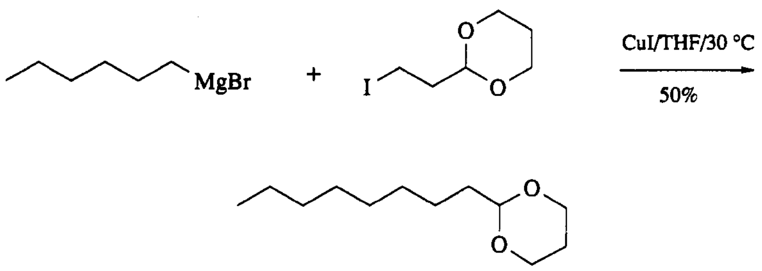

(ref. 23) (18)

The dimerization of $sp^3$ centers *via* conversion of the alkyl halide to a Grignard reagent, followed by homo-coupling is promoted by a number of metals. Treatment of a Grignard reagent with a copper(I) species such as tetrakis[iodo(tri-*n*-butylphosphine)copper(I)],[24] followed by oxidation of the resulting ate complex with either oxygen or copper(II) salts, lead to dimerization (equation 19). 'Soluble silver' in THF may be prepared from silver nitrate and ethylmagnesium bromide in THF. The silver reagent is stable at greater than molar concentrations in THF for prolonged periods at 0 °C. Grignard reagents undergo efficient homo-coupling at room temperature in the presence of this silver catalyst.[10] Cross-couplings give approximately equimolar quantities of the two possible homo-coupled products together with the desired cross-coupled product (*cf.* equation 1). Disproportionation of the reagent becomes a major pathway for secondary and tertiary halides.[10,25,26] The special case of intramolecular homo-coupling *via* this method is treated in Section 2.1.2.5.

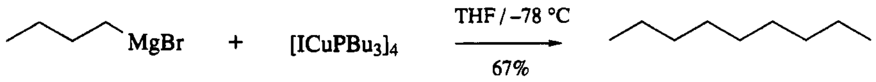

(ref. 24) (19)

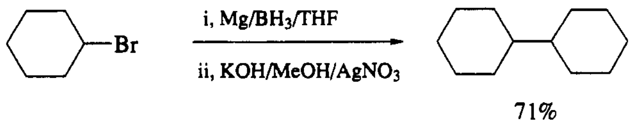

(ref. 27) (20)

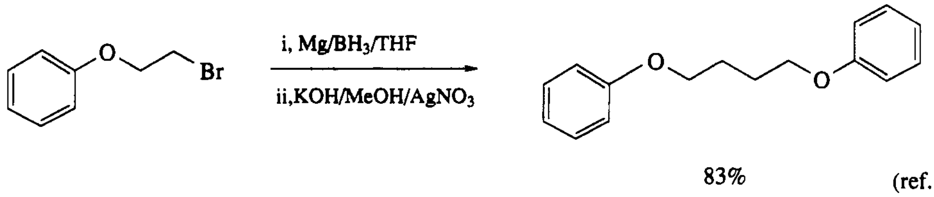

(ref. 27) (21)

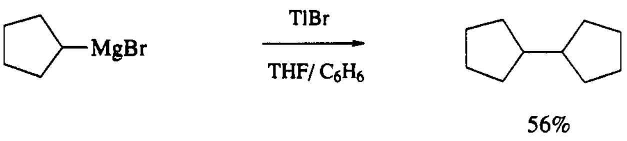

(ref. 28) (22)

The *in situ* synthesis of organoboranes *via* reaction of alkyl halides with magnesium in the presence of diborane can also be used to prepare coupled products (equations 20 and 21).[27] Oxidation of the reaction mixture with alkaline silver nitrate leads to good yields of dimeric products. The reaction is successful for primary and secondary halides. A related reaction is the coupling of secondary alkyl halides in the presence of catalytic quantities of thallium salts.[28] This procedure fails for primary alkyl halides and gives modest yields for secondary alkyl halides (equation 22).

### 2.1.2.3 Organolithium-derived Reagents

The noncatalyzed coupling between organolithium reagents and organic halides leads to mixtures of hydrocarbons similar to the classical Wurtz reaction. The strongly basic and weakly nucleophilic nature of simple organolithium species leads to products derived from halogen–metal exchange, α-metalation and β-elimination, in addition to the desired coupling reactions. These factors mean that, in general, simple organolithium reagents are not useful intermediates for Wurtz-type couplings. Exceptions to this generalization include: the reaction of dihalides with *t*-butyllithium, to give cyclic systems (see Section 2.1.2.5);[29,30] the coupling of *t*-butyllithium with benzylic halides, giving highly branched systems (equation 23);[31] and the coupling of charge-delocalized alkyllithiums (*e.g.* benzyl- or allyl-lithiums) with organic halides (equation 24).[32,33] Several reviews concerning halogen–metal exchange reactions and the coupling behavior of organolithiums are available.[34–36]

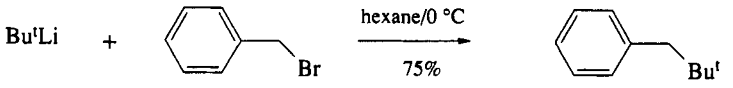

(ref. 31) (23)

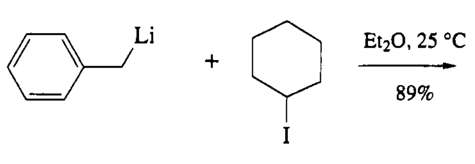

(refs. 32, 33) (24)

Reaction of an organolithium species with a copper(I) species at low temperature generates an organocopper reagent, which may have one of several different constitutions depending on the stoichiometry, exact reaction conditions, additives present, *etc.* Many types of organocopper reagent have proven very valuable in organic synthesis, and the use of these reagents is described in detail elsewhere in this work. In terms of the coupling of $sp^3$ carbon centers, the following general observations may be made about lithium organocopper species. (i) For catalytic reactions involving copper(I) intermediates, in general, Grignard reagents are preferred over organolithium species due to ease of preparation, and higher yields obtained in coupling reactions (see Section 2.1.2.2). (ii) For stoichiometric copper reagents, $R_2CuLi$ reagents are more reactive, and give better results in coupling reactions than simple RCu species. (iii) A generalized order of reactivity towards lithium diorganocopper reagents is acid chlorides > aldehydes > tosylates/epoxides > iodides > bromides > chlorides > ketones > esters > nitriles >> alkenes. (iv) The relative reactivity of alkyl halides towards lithium diorganocopper reagents is allylic/benzylic > primary > secondary >> tertiary. (v) The kinetics of coupling are roughly first order in both cuprate reagent and alkyl halide. (vi) The cuprate reagent may be derived from a primary, secondary or tertiary halide.

Many reviews dealing with the chemistry of organocopper species have appeared,[37–42] and a comprehensive listing of organocopper substitution reactions reported prior to 1975 together with a detailed discussion of the factors influencing the reactions is available.[38] Many natural product syntheses have used cuprate couplings to prepare key intermediates and some representative examples of both stoichiometric and catalytic reactions are given in equations (25)–(29).[43–47] For a general introduction to the field of organocopper chemistry the reader is recommended to consult the excellent book by Posner.[42] Most organocopper reagents are extremely sensitive to heat and to oxidants, decomposing to the dimeric products of homo-coupling. Many organocopper species have been dimerized by heating or simple oxidation with oxygen.[38] Little use has been made synthetically of this method of coupling $sp^3$ carbon centers.

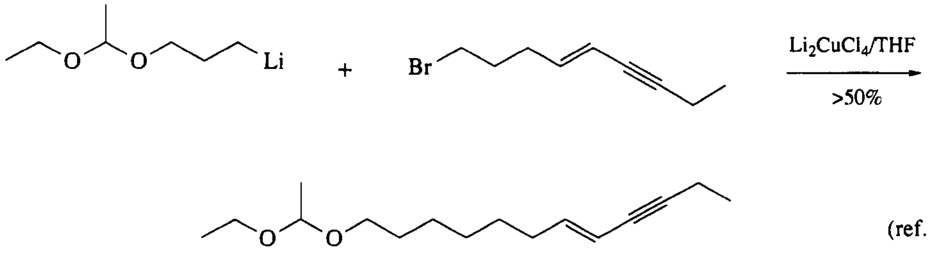

(ref. 43) (25)

$$\mathrm{Bu_2CuLi} + \mathrm{I(CH_2)_{10}CO_2H} \xrightarrow[76\%]{-40\ ^\circ\mathrm{C}\,/\,\mathrm{Et_2O}} \mathrm{n\text{-}C_{14}H_{29}CO_2H}$$ (ref. 44) (26)

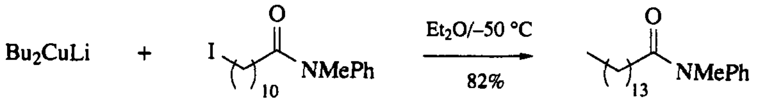

(ref. 44) (27)

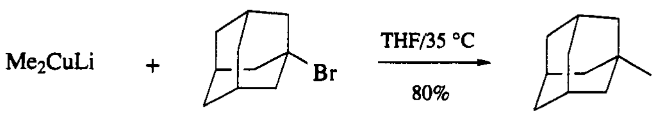

(ref. 45) (28)

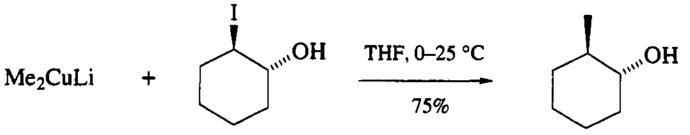

(ref. 46) (29)

### 2.1.2.4 Other Organometallic Reagents

Many other metals, in addition to magnesium, lithium and copper, promote Wurtz-type couplings. In most cases cross-couplings are not possible and the methods are only of value in producing homocoupled dimers. Reagents which do permit cross-coupling reactions are normally very limited in either the type of halide used for preparation of the metal derivative, or the halide to be cross-coupled, or both.

Organozinc species show some valuable facets for cross-coupling reactions. Primary iodo esters may be converted into organozinc species by direct treatment with a zinc–copper couple.[48] In the presence of catalytic copper cyanide these organozinc reagents couple efficiently with allylic halides and tosylates, unfortunately with low regioselectivity (equation 30).[49] Perfluoroalkyl-magnesium and -lithium halide species decompose readily into perfluoroalkenes and metal halides and are of little value for the introduction of perfluoroalkene substituents. In contrast, perfluoroalkylzinc species are much more stable and in the presence of ultrasound and a palladium catalyst, couple with allylic halides showing high δ-regioselectivity (equation 31).[50]

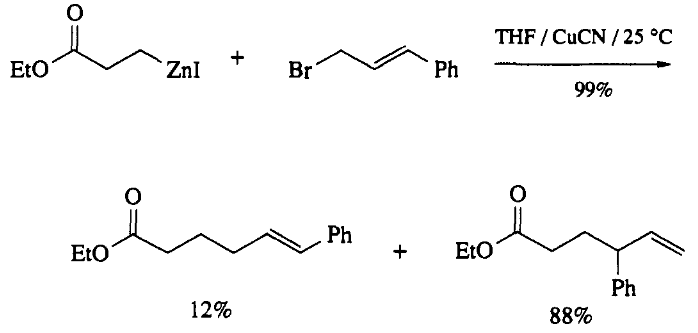

(ref. 49) (30)

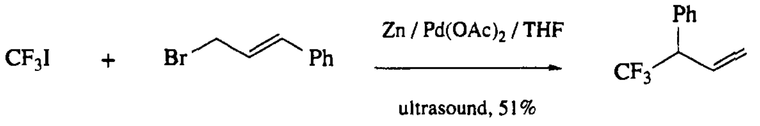

(ref. 50) (31)

Organozinc reagents prepared from allylic bromides couple regioselectively in a δ-selective manner with *N*-chloromethyl-*N*-methylformamide, to give unsaturated tertiary formamides (equation 32).[51] Treatment of these formamides with butyllithium followed by hydrolysis removes the formyl group, giving secondary amines. In a total synthesis of retronecic acid, coupling of the allylic bromo ester (**11**) with the secondary chloride (**12**) was the only convenient way of obtaining the desired cross-coupled product

(**13**), albeit in low yield (equation 33).[52] Cross-coupling of allylic with benzylic halides may be achieved by oxidation of a mixture of the halides and triethylborane in THF with oxygen.[53]

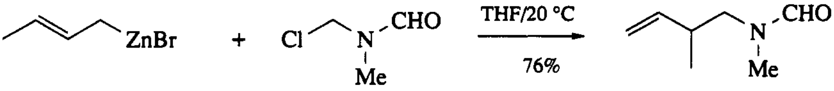

(ref. 51) (32)

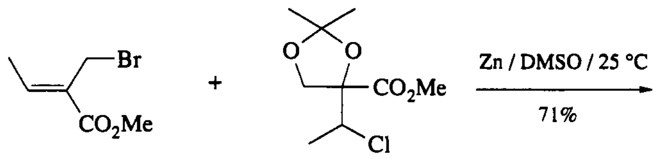

**(11)** **(12)**

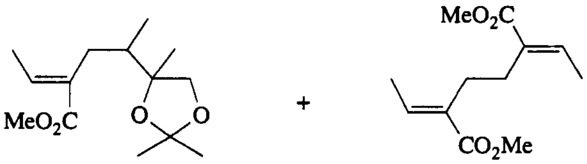

(ref. 52) (33)

**(13)** 75% 25%

Iodofluoroacetate copper reagents can be prepared directly from the halide using copper powder in DMSO and the reagents couple with a range of electrophilic centers, including primary iodides and allylic bromides (equation 34).[54] Benzylic halides couple with bromoacetonitrile in the presence of metallic nickel in refluxing glyme (85 °C).[55] Organometallic species derived from methyllithium and manganese, cobalt or iron are all less suitable for cross-coupling reactions than the analogous species ($R_2CuLi$) derived from methyllithium and copper salts.[56]

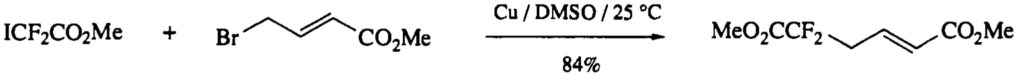

(ref. 54) (34)

Methyltitanium(IV) chlorides have been used for the methylation of tertiary alkyl halides, with good results. The reagents are prepared by treatment of dimethylzinc species (available from methyl iodide and zinc metal) with $TiCl_4$ and similar results are obtained by using dimethylzinc in the presence of catalytic quantities of $TiCl_4$.[57,58] The methylations are chemoselective, with esters and alkenes remaining unaffected and coupling only occurs at tertiary centers, primary and secondary alkyl halides being inert (equations 35 and 36). The method also works well in systems prone to skeletal rearrangements.

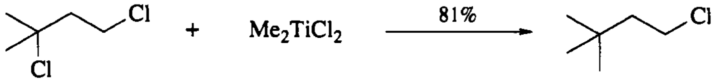

(ref. 57) (35)

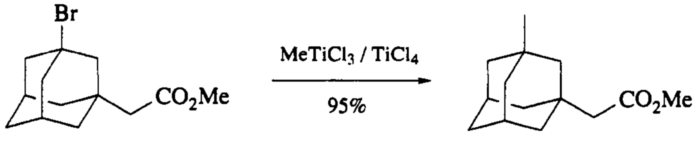

(ref. 57) (36)

Benzylic and allylic halides dimerize (homo-couple) readily in the presence of a number of metal species. Synthetically useful yields of homo-coupled products have been obtained using chlorotris(triphenylphosphine)cobalt(I),[59] nickel(0) complexes generated *in situ*,[60] $Te^{2-}$ species,[61] $VCl_3$/LAH,[62] $CrCl_3$/LAH[63] and $TiCl_3$ or $TiCl_4$/LAH.[64] Representative examples are given in equations (37) and (38). Treatment of δ-bromocrotonates with zinc(0) in DMSO leads to dimerization.[65]

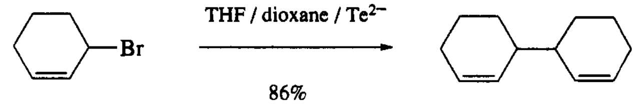

(ref. 61) (37)

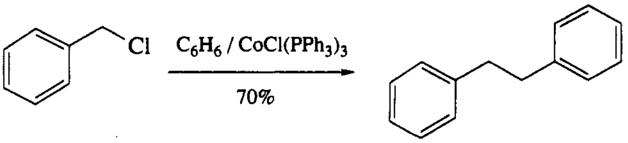

(ref. 59) (38)

### 2.1.2.5 Formation of Cyclic Systems

The classical Wurtz-type coupling leads to cyclic systems when applied to suitable dihalides. This intramolecular version of the Wurtz reaction is more efficient when metals other than sodium, and in particular zinc or Li/Hg amalgam, are used. A comprehensive review of the older literature on this intramolecular reaction is available.[66] The Wurtz coupling has proved particularly valuable for the synthesis of strained small ring systems. Bicyclobutane (**8**), for example, can be obtained in 80–90% yield by treatment of 1-bromo-3-chlorocyclobutane (**7**) with sodium at high temperatures (equation 5).[5] Other examples of the synthesis of strained cyclopropane-containing systems are given in equations (39) and (40).[67,68] The synthesis of cyclopropanes by reductive coupling reactions has also been reviewed.[69]

Cyclobutanes may also be prepared by this type of Wurtz reaction, but the approach is not successful for carbocyclic ring sizes greater than four. Studies of the reagents able to generate cyclobutane from 1,4-dihalo substrates have indicated that the use of Li/Hg amalgam in dioxane at high temperature gives the best yield.[70]

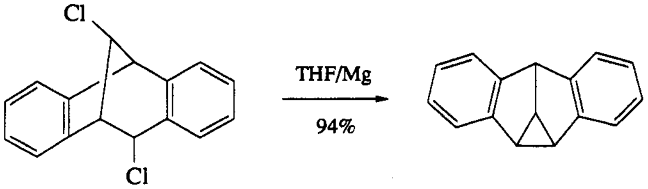

(ref. 67) (39)

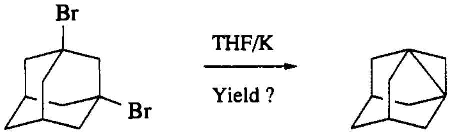

(ref. 68) (40)

Treatment of primary α,ω-haloalkanes with *t*-butyllithium at low temperature leads to efficient production of cycloalkanes, provided at least one of the halides is an iodide.[29,30] This method provides very good yields of three-, four- and five-membered rings, but produces only minor amounts of cyclic products for 1,6-dihalides. Examples of this approach are given in equations (41) and (42).

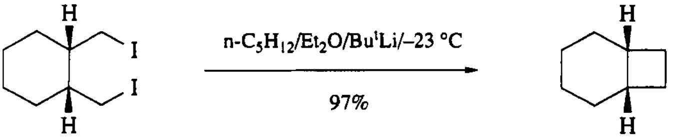

(ref. 29) (41)

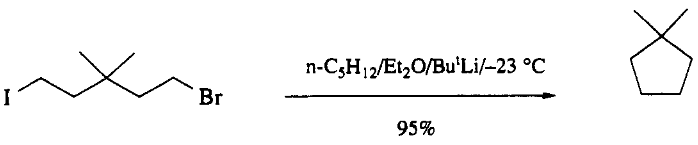

(ref. 30) (42)

A valuable modification to the coupling of alkylmagnesium halides involves the treatment of di-Grignard reagents with soluble silver salts, leading to cyclization. This method gives high yields of four-, five- and six-membered rings, but fails for larger ring sizes.[71] Examples of this synthesis are given in equations (43) and (44). An interesting application of organocopper-type Wurtz coupling uses the novel 'cyclocuprate' (**14**),[72] which reacts with *gem*-dihalides to give spiro-annulation products (equation 45).

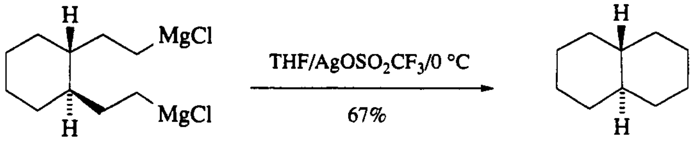

(ref. 71) (43)

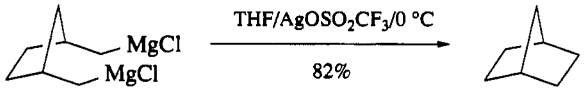

(ref. 71) (44)

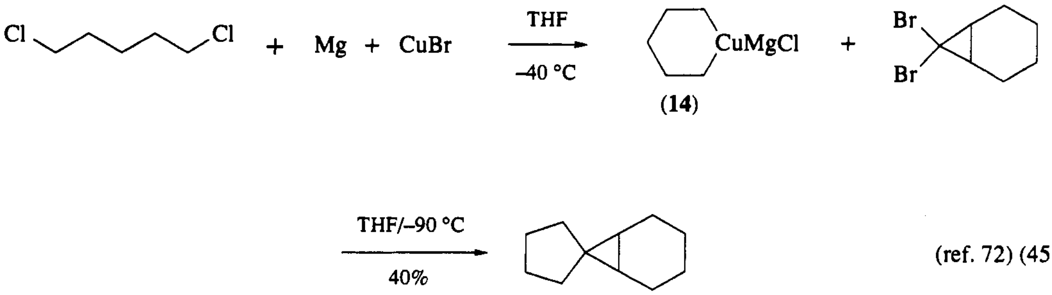

(ref. 72) (45)

## 2.1.3 π-ALLYLNICKEL HALIDES

In recent years transition metal π-allyl complexes have emerged as efficient reagents for the introduction of allyl units into organic substrates.[73–78] The main advantage of the transition metal π-allyl complexes over normal allyl-magnesium, -lithium, -zinc, *etc.* systems is their much higher chemoselectivity. Two classes of reagents have proved particularly valuable, the π-allyl complexes of palladium[75,78] and π-allylnickel halides.[73,74,76,77] These complexes are complementary, since π-allylpalladium complexes react with electron-rich centers (*e.g.* stabilized anions) and π-allylnickel halides react with electron-poor centers, (*e.g.* alkyl halides and carbonyl groups). The high reactivity of π-allylnickel halides towards alkyl halides, coupled with their chemoselectivity and the use of heteroatom-substituted complexes make these reagents valuable alternatives to the normal Wurtz-type reagents.

### 2.1.3.1 Preparation, Structure and Experimental Techniques

The dimeric π-allylnickel halide complexes are most conveniently prepared from allylic halides and nickel(0) species, such as $Ni(COD)_2$ and $Ni(CO)_4$.[73] Although other allylic systems have been used,[79] the most common procedure involves treatment of an allylic bromide with $Ni(CO)_4$ at 50–70 °C.[80] This gives rise to the moderately air-sensitive dimeric π-allyl species (equation 46). In polar coordinating solvents, (DMF, HMPA, *N*-methylpyrrolidone, *etc.*) these dimeric species are converted into highly reactive monomeric species (equation 47).[81]

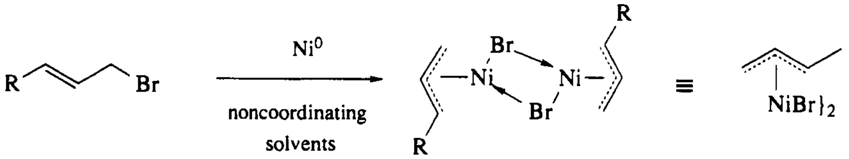

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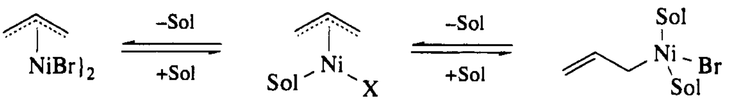

(47)

The following general protocol describes the preparation and use of the complexes. Treatment of an allylic halide with $Ni(CO)_4$ in benzene at 50 °C, or $Ni(COD)_2$ at *ca.* 0 °C generates the dimeric complex. Solvent removal, followed by addition of a polar coordinating solvent and the substrate leads to cross-coupling of the reactive monomeric allylnickel species with the substrate. Excellent practical details are available for these reactions and their synthetic uses have been reviewed,[73] together with the structure and bonding of the complexes.

## 2.1.3.2 Reactivity Patterns

### *2.1.3.2.1 Chemoselectivity*

The π-allylnickel halides show quite different reactivity profiles to the more normal organo-lithium, -sodium or -copper species used in Wurtz-type couplings. In particular, many functional groups which react rapidly with the conventional organometallic reagents are inert to π-allylnickel halides. Functional groups which are either inert to the complexes or react very slowly under forcing conditions include acid chlorides, esters, ethers, nitriles, alkynic protons, alkenes, alcohols, aryl, vinyl and alkyl chlorides, allylic ethers and acetals. Functional groups which react under forcing conditions (*i.e.* above 55 °C leading to extensive thermal decomposition of the complexes) include simple ketones and α,β-unsaturated ketones, with only 1,2-addition being observed (even in the presence of CuI). The complexes react slowly, with temperatures of 40–50 °C required for synthetic utility, with aldehydes, cyclic (and some acyclic) ketones, allylic chlorides and, in one report, epoxides. Examples of these reactions are given in equations (48)–(51).

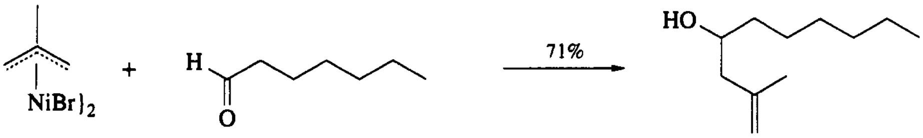

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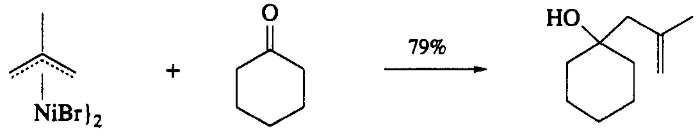

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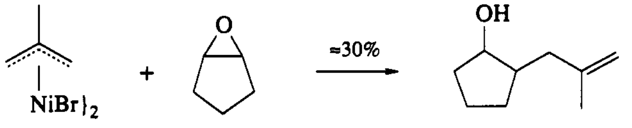

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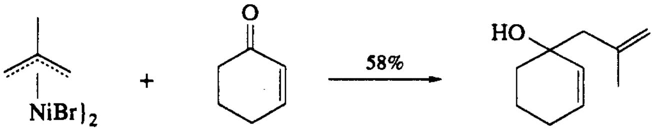

(51)

In contrast to this low reactivity towards many electron-poor centers, the complexes react at or below room temperature with primary and secondary alkyl iodides, bromides and allyl, vinyl and aryl bromides and iodides, giving cross-coupled products. Phenyl ketones react to give homoallylic alcohols, whereas quinones give allyl-substituted quinones or hydroquinones. 1,2-Diketones give α-ketohomoallylic alcohols (even in the presence of excess complex, reaction occurs at only one carbonyl group) and 2-pyridyl carboxylates give β,γ-unsaturated ketones as the major products. Examples illustrating this reactivity profile are given in equations (52)–(59).[73] This chemoselectivity allows the reaction of the complexes with substrates containing more than one functional group, *e.g.* secondary iodide and secondary alcohol or iodide and chloride in the same molecule (equations 59–61). It is also possible to prepare a range of complexes containing functional groups; thus the coupling reaction both forms a C—C bond and intro-

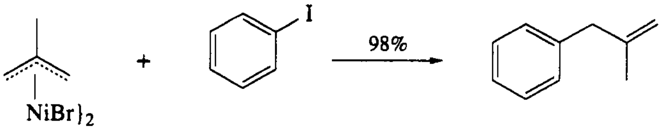

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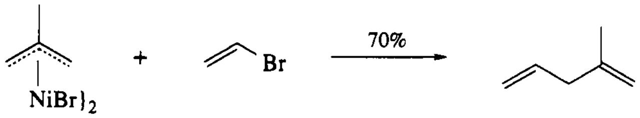

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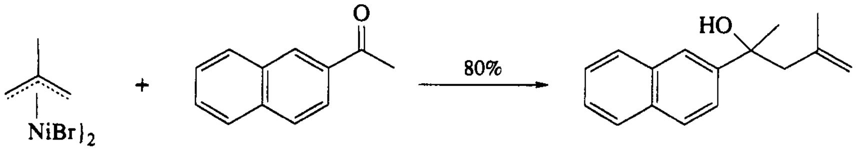
NiBr}2
+
O
80%
HO

(54)

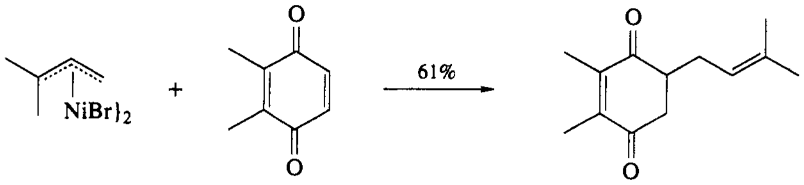
NiBr}2
+
O
O
61%
O
O

(55)

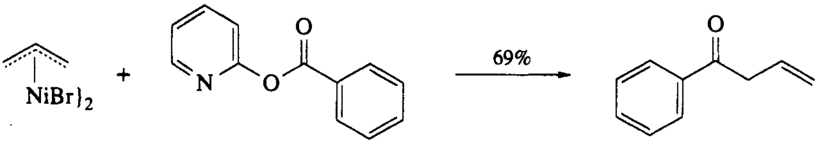
NiBr}2
+
N
O
O
69%
O

(56)

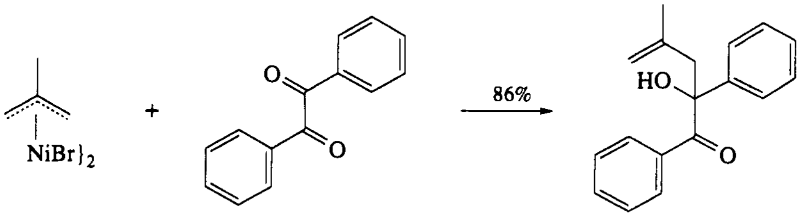
NiBr}2
+
O
O
86%
HO
O

(57)

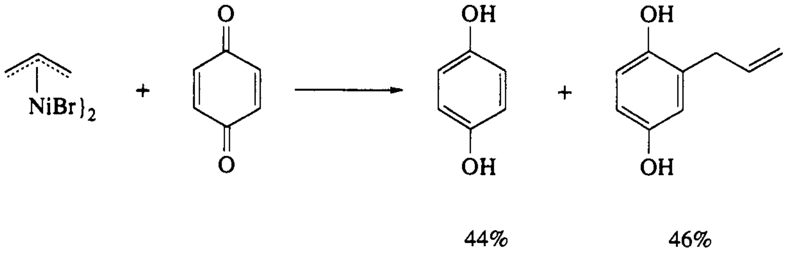
NiBr}2
+
O
O
OH
OH
+
OH
OH
44%
46%

(58)

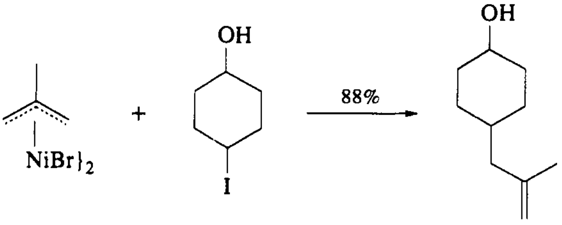
NiBr}2
+
OH
I
88%
OH

(59)

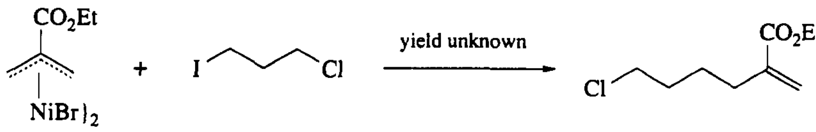

(60)

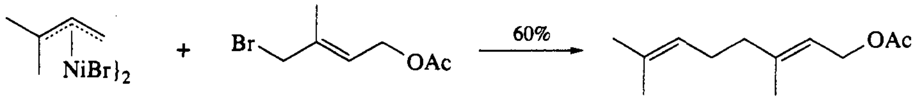

(61)

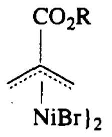

**(15)**

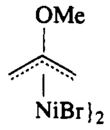

**(16)**

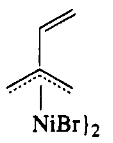

**(17)**

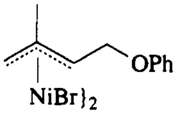

**(18)**

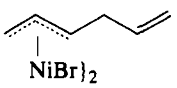

**(19)**

duces a functional group, possibly in a masked form, into the product. Examples of substituted complexes which have been prepared successfully and used in synthesis include structures (**15**)–(**19**).[73]

### *2.1.3.2.2 Regioselectivity*

Substituted π-allylnickel complexes which could give products derived from reaction either at a primary or a secondary/tertiary terminus almost invariably react only at the primary center (equations 62 and 63).[82]

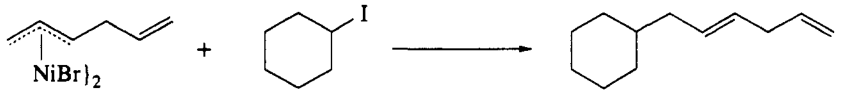

(62)

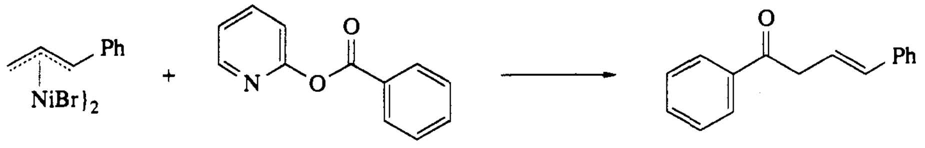

(63)

### *2.1.3.2.3 Stereoselectivity*

Coupling of a π-allylnickel halide with an alkyl halide regenerates the double bond originally present in the allyl halide, in addition to forming a new carbon–carbon bond. For trisubstituted double bonds, the products are normally mixtures of (*E*)- and (*Z*)-alkenes, either in a close to 1:1 ratio or with the (*E*)-isomer in excess. In certain favorable cases[83,84] (*E*):(*Z*) ratios of up to 98:2 have been achieved, albeit at the expense of rather low yields of coupled products (see Scheme 2). In general, highly coordinating solvents (HMPA, DMF) give high yields but rather low stereoselection, whereas solvents of lower coordinating power give better stereoselection, coupled with lower overall yields.[83,84] Optically active halides couple with the reagents to give racemic products.[74]

## 2.1.3.3 Coupling with $sp^3$ Carbon Centers

### *2.1.3.3.1 Alkyl halides*

In natural product synthesis, the 1,1-dimethylallyl complex (**20**) has been used to introduce a 5-carbon unit into a number of complex carbon skeletons. Examples of the use of this complex include the prep-

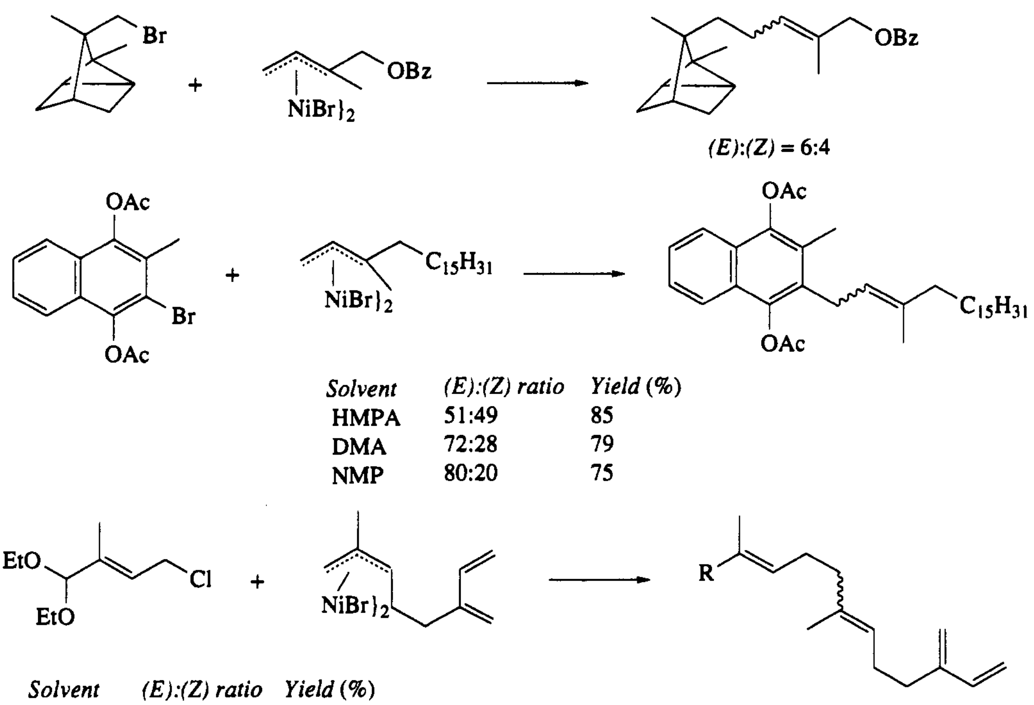
Br
NiBr}2
OBz
(E):(Z) = 6:4
OAc
Br
C15H31
EtO
Cl
R

| *Solvent* | *(E):(Z) ratio* | *Yield (%)* |
|---|---|---|
| HMPA | 51:49 | 85 |
| DMA | 72:28 | 79 |
| NMP | 80:20 | 75 |

| *Solvent* | *(E):(Z) ratio* | *Yield (%)* |
|---|---|---|
| DMF | 93:7 | 50 |
| THF | 98:2 | 23 |

**Scheme 2**

aration of α-santalene (**21**) and epi-β-santalene (**22**),[85] campherenone (**23**) and epi-campherenone (**24**),[86] and desmosterol (**25**)[87] (equations 64–68). It is interesting that more traditional approaches to α-santalene *via* coupling with Grignard reagents give only very low yields, compared to the excellent yield obtained with the nickel complex.[88]

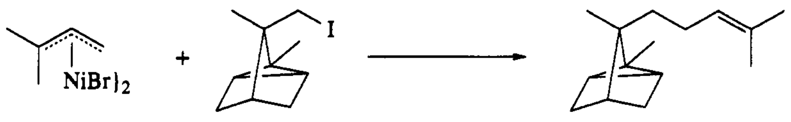

**(20)** **(21)** (64)

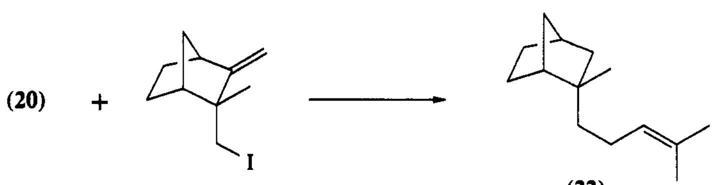

**(22)** (65)

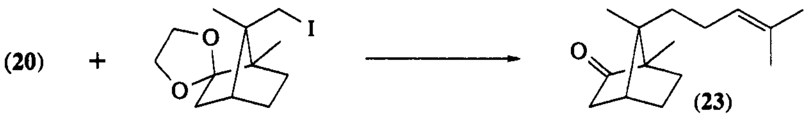

**(23)** (66)

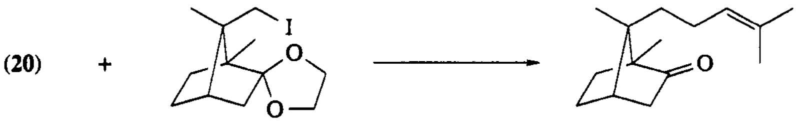

**(24)** (67)

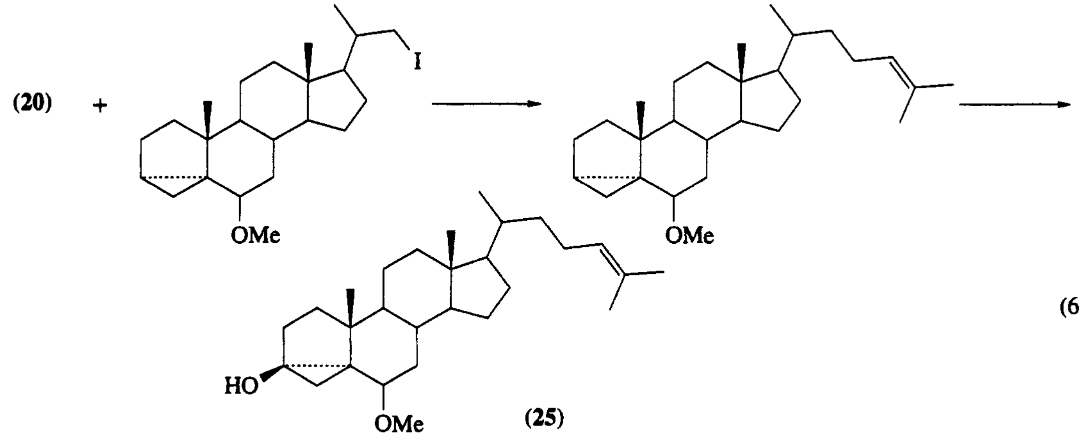

(68)

### 2.1.3.3.2 Allyl halides

Allylic halides may be coupled in the presence of Ni(CO)$_4$ to give 1,5-dienes (Scheme 3).[89] This approach is very attractive for the synthesis of terpenes by sequential addition of isoprene units. Reaction of 1,1-dimethylallylnickel bromide (**20**), for example, with the allylic halide shown in Scheme 3a gives the geranyl carbon skeleton.[90] Unfortunately this approach is complicated by the fact that the $\pi$-allylnickel halide complex can undergo ligand exchange with the substrate allyl halide,[91] giving a new complex (Scheme 3b); thus homo-coupling products derived from both of the allyl units result (Scheme 3b). The relative proportions of the homo- and cross-coupled products depend on the relative rates of ligand exchange and the rates of reaction of each complex with the allylic halides present. These reactions normally generate all possible 1,5-diene products in the expected statistical distribution; for example in Scheme 3b the ratio of the three 1,5-diene products is $C_6$:$C_7$:$C_8$ = 25:52:25. For simple complexes, the ratio of these products is not altered significantly by changes in solvent, addition of competing ligands or changes in the leaving group in the allylic substrate.[73] This approach has found application for certain complexes which undergo ligand exchange reactions only slowly. The 1,1-dimethylallyl complex (**20**) for example, reacts with a range of allylic bromo ethers and esters giving the geranyl derivatives (**26**), (**27**) and (**28**), cross-coupled products, in reasonable yields.[90] Only small quantities of homo-coupled products were observed in these reactions (equation 69). In contrast, the reaction of the bromo ester (**29**) with the complex (**20**) gave 70% of (**30**), the product of homo-coupling (*i.e.* dimerization of the substrate) as shown in equation (70).

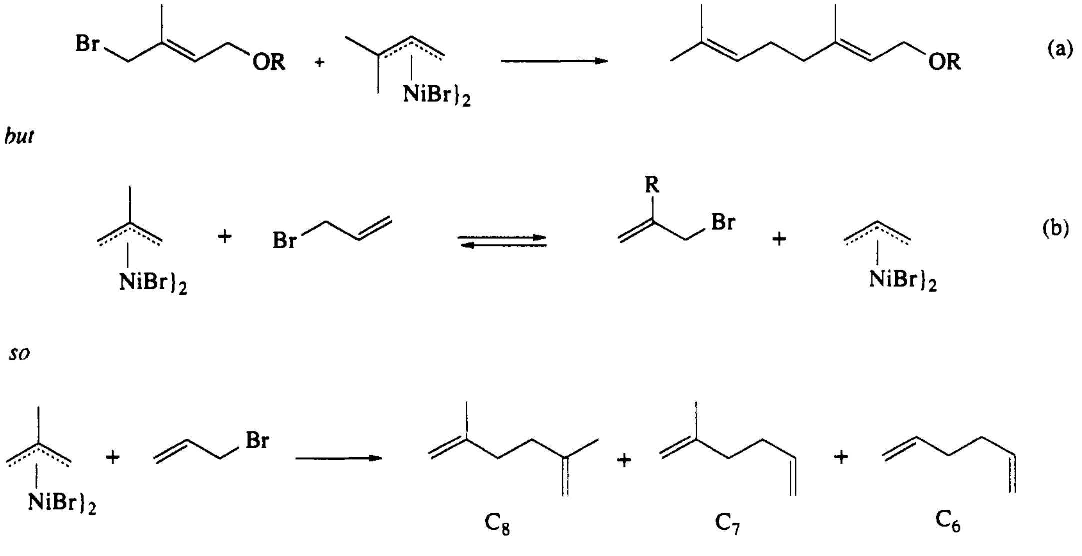

Scheme 3

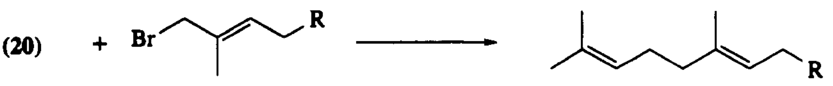

**(26)** R = $CO_2Et$, 40% yield
**(27)** R = OEt, 45% yield
**(28)** R = OAc, 60% yield

(69)

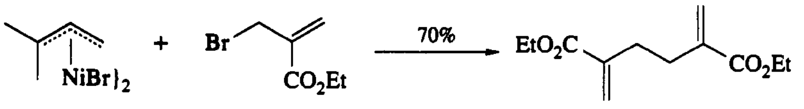

**(20)** **(29)** **(30)**

(70)

The substituted π-allylnickel bromide complexes **(31)** and **(32)** have been reacted with prenyl bromide to give geranyl ethers and with geranyl bromide to give farnesyl ethers (equation 71)[91]; (*E*):(*Z*) ratios of up to 93:7 were observed in these cross-couplings. The substituted complex **(33)** has been used to introduce the isoprene unit into a range of terpenoid skeletons;[82] thus reaction with prenyl bromide leads to myrcene and with geranyl bromide β-farnesene is formed, both reactions giving (*E*):(*Z*) mixtures. β-Sinensal has been prepared from the allylic chloride **(34)**, by coupling with the π-allylnickel bromide complex (**35**; equation 72). The desired cross-coupled material (50% yield) was accompanied by lesser quantities (20% and 26%) of the homo-coupled products. The (*E*):(*Z*) ratio of the desired product was 93:7 in DMF and this ratio could be improved to 98:2 in THF, although the chemical yield fell to 23% under these conditions.

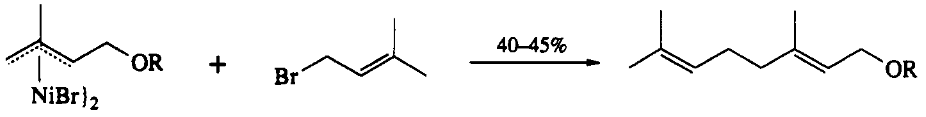

**(31)** R = Ph
**(32)** R = $CH_2Ph$

(71)

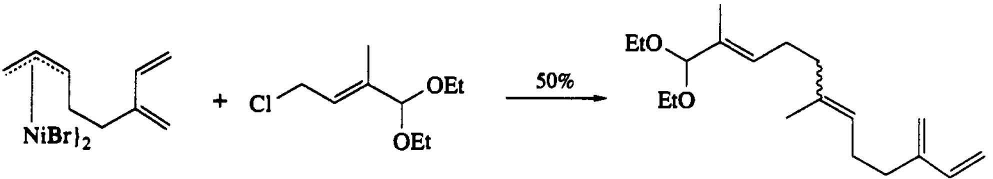

**(35)** **(34)**

(72)

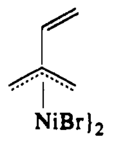

**(33)**

### 2.1.3.3.3 *Formation of cyclic systems*

Two allylic halides in the same molecule may, under high dilution conditions, be coupled using $Ni(CO)_4$ to give a cyclic 1,5-diene. As each allyl group can react to one of two positions, three possible cyclic products may result. In Table 1 this corresponds to ring sizes of *n* + 2, *n* + 4 and *n* + 6. In the generalized example shown, this corresponds to secondary–secondary, primary–secondary, and primary–primary coupling respectively. The relative proportion of each product for a given value of *n* is determined by the normal rules governing ring closure effects, together with the preference for primary–primary coupling shown by the π-allylnickel halide intermediates. The accepted normal rates of ring closure reactions are 3 < 4 < 5 > 6 > 7 > 8 < 9 <10 < 11 < 12, *etc.* up to 18, with the relative rate differences becoming smaller as the ring size increases. From the results in Table 1[92] it can be seen that for $n = 6$, 8 and 12, the ring size obtained is governed by the primary–primary bias of the coupling reaction as the largest available ring size predominates, rather than formation of a mixture of ring sizes due to roughly similar rates of closure, as would be predicted. For $n = 2$ and $n = 4$, however, the normal preference for formation of six-membered rings overcomes this bias and six-membered rings are formed by primary–secondary and secondary–secondary closures, respectively. The observed high yields for ring sizes > 12, coupled with the fact that regardless of starting geometry of the allyl halides the products are >95% (*E*),(*E*)-isomers, has led to the use of this method for the synthesis of macrocyclic natural products. Somewhat different results are obtained for exocyclic alkenes[93] and these are summarized in Table 2. It can be seen that this method is of no value for 12-membered rings. A cyclization with one endocyclic and one exocyclic alkenic bond gives intermediate results (equation 73). Related to these results is the interesting trimerization of (**36**) giving (**37**; Scheme 4). Corey *et al.* showed that (**36**), (**38**) and (**39**) added to (**36**) all give (**37**) on treatment with $Ni(CO)_4$.[94] This behavior is very interesting, as it requires (**39**) to undergo intermolecular reaction with (**36**), followed by ring closure to the nine-membered ring (**37**),

**Table 1** Ring Closures with $Ni(CO)_4$ in DMF

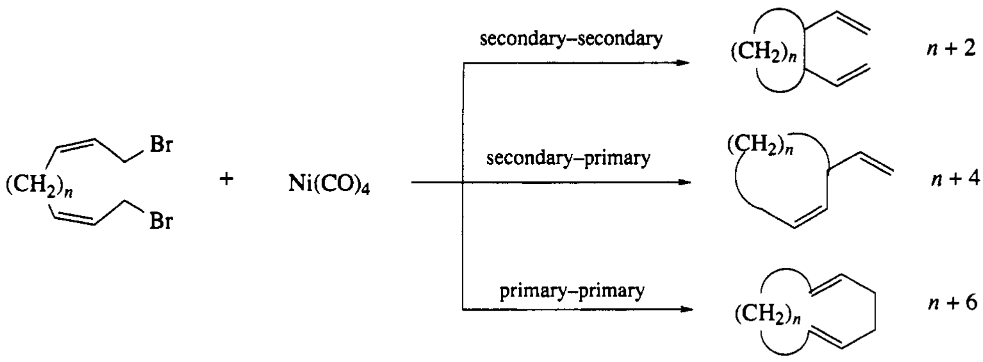

| *Value of n* | *Possible ring size of product* | *Observed ring size of product* | *Yield (%)* |
|---|---|---|---|
| 2 | 4/6/8 | 6 | 42 |
| 4 | 6/8/10 | 6 | a |
| 6 | 8/10/12 | 12 | 59 |
| 8 | 10/12/14 | 14 | 74 |
| 12 | 14/16/18 | 18 | 84 |

[a]Yield unknown.

**Table 2**

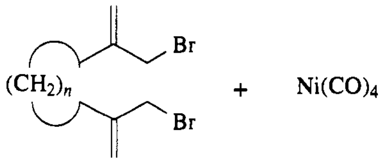

| *Value of n* | *Possible ring size* | *Observed ring size* | *Yield (%)* |
|---|---|---|---|
| 6 | 8/10/12 | | — |
| 8 | 10/12/14 | 14 | 37 |
| 10 | 12/14/16 | 16 | 81 |
| 14 | 16/18/20 | 20 | 40 |

rather than intramolecular coupling to give a six-membered ring system. Indeed, treatment of (**39**) with excess $Ni(CO)_4$ gives only 10% of the six-membered ring derived from intramolecular coupling. Two 14-membered macrocyclic natural products have been prepared using this methodology, *i.e.* cembrene (**40**; equation 74)[95,96] and casbene (**41**; equation 75)[97,98] and the 11-membered macrocycle humulene (**43**; equation 76) has been prepared *via* its geometric isomer (**42**) obtained from a bisallylic bromide precursor.[99,100] In none of these cases were the reactions as clean or as high yielding as the simple model cyclizations would predict. The preference for formation of six-membered rings in this intramolecular coupling has been exploited in a synthesis of elemol (**44**; Scheme 5).[101] The stability of esters to the $\pi$-allylnickel reagents has allowed the extension of this method to the synthesis of macrocyclic lactones.[102]

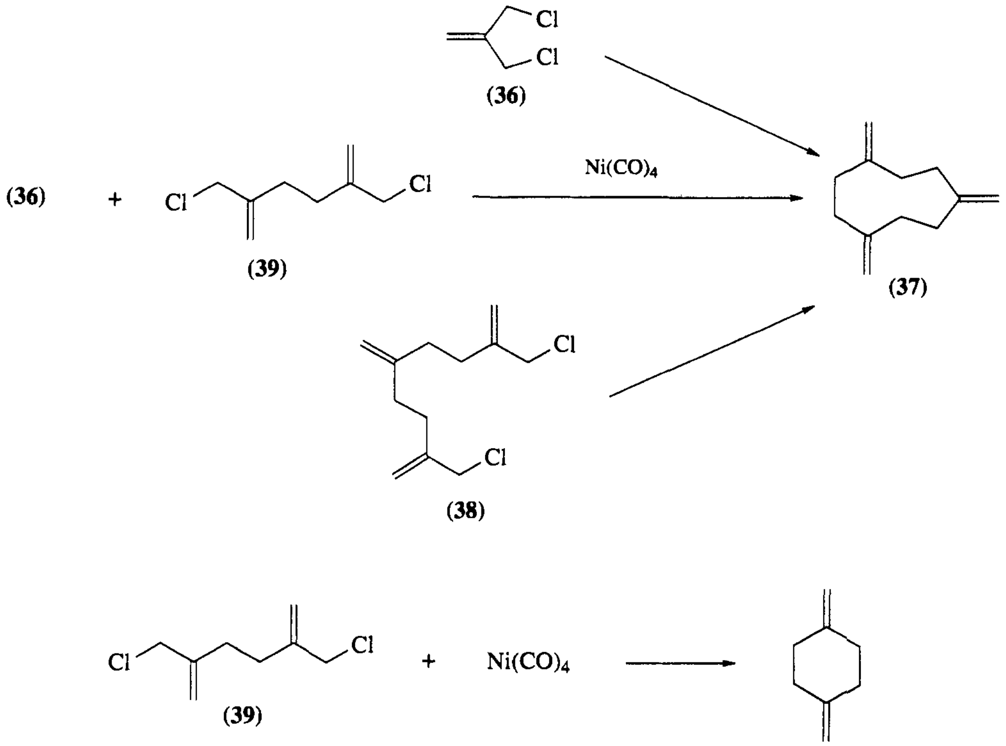

**Scheme 4**

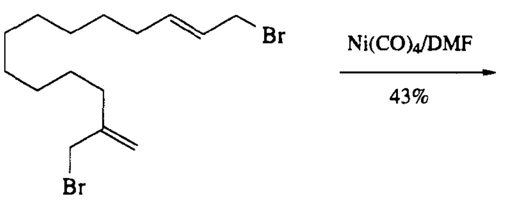

(73)

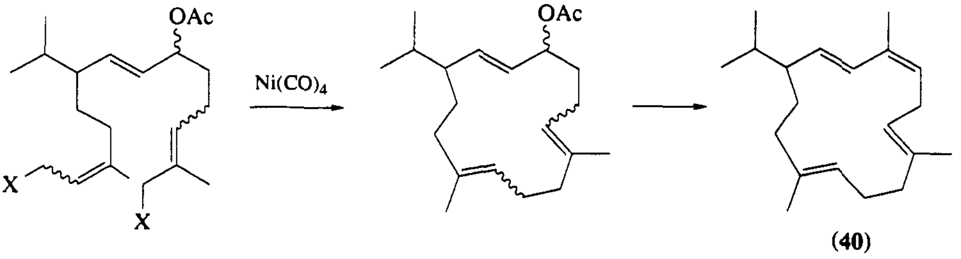

(74)

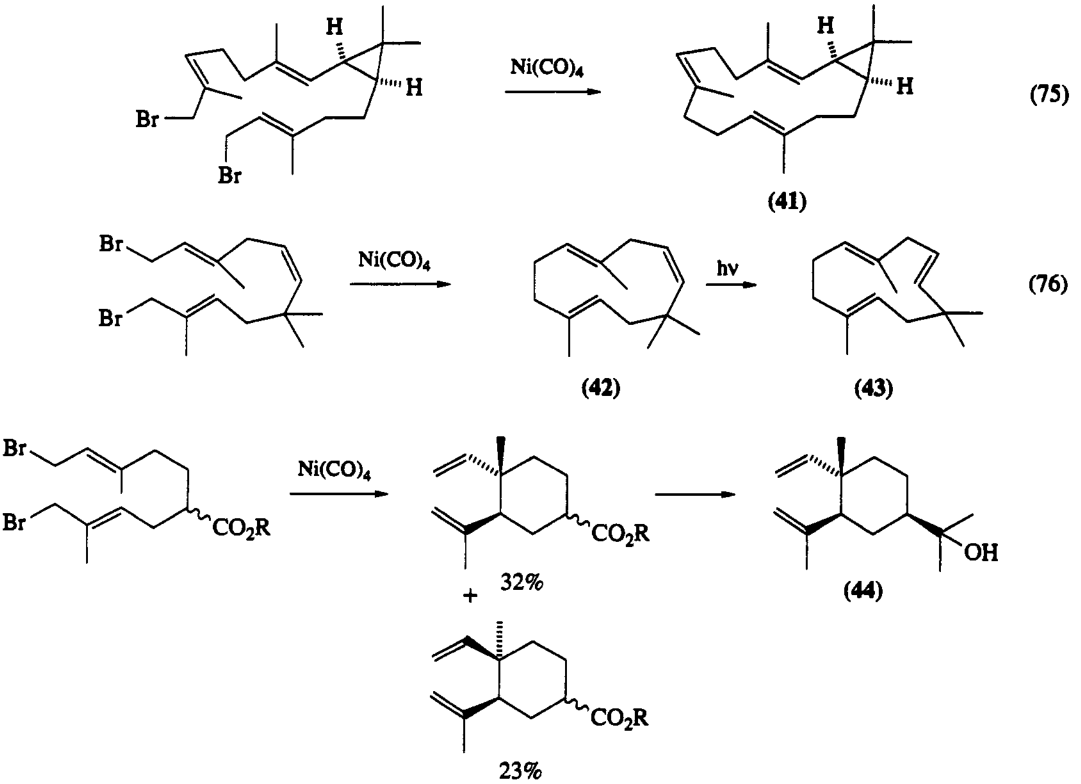

Scheme 5

## 2.1.4 REFERENCES

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# 2.2

# Coupling Reactions Between $sp^3$ and $sp^2$ Carbon Centers

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## 2.2.1 INTRODUCTION

Selective cross-coupling reactions between $C(sp^3)$ and $C(sp^2)$ centers had been one of the most difficult tasks in carbon–carbon bond synthesis until the early 1970s, when it was first reported that iron,[1,2] nickel,[3,4] palladium[5] and copper[2,6] catalysts are extremely effective for cross-coupling of Grignard reagents with organic halides. Now, nearly 20 years later, transition metal catalyzed cross-coupling has become the reaction of first choice for this purpose.

This section describes the cross-coupling reactions between organometallic reagents and organic halides and related reactions catalyzed by transition metal complexes or salts (<10 mol %). The following two types of reaction (equations 1 and 2) are treated, where R = primary, secondary or tertiary alkyl, alicyclic, allyl or functionalized alkyl groups; R′ = alkenyl, aryl or heteroaryl groups; M = Li, Mg, Cu, Zn, B, Al, Si, Sn, Cd, Hg, Ti or Zr; X = F, Cl, Br, I, OH, OR, OCOR, OTs, OTf, $OP(O)(OR)_2$, SH, SR, $SO_2R$, $SR_2^+$, SeR or $NR_3^+$; and catalyst = Mn, Fe, Ru, Co, Ni, Pd or Cu complex or salt. Among the catalysts listed above, Fe, Ni and Pd catalysts seem to be most effective for the coupling $R(sp^3)—M + R'(sp^2)—X$, while the coupling $R(sp^3)—X + R'(sp^2)—M$ is catalyzed best by Cu complexes and the allylic $R(sp^3)—X + R'(sp^2)—M$ by Cu, Ni or Pd complexes. Whilst coupling reactions are achieved efficiently with primary alkyl organometallics in the reaction shown by equation (1) and with primary alkyl halides in the reaction shown by equation (2), irrespective of the presence or absence of β-hydrogens, there are some limitations on the secondary and tertiary alkyl organometallics and halides. Thus, coupling reactions of β-H-bearing secondary and tertiary alkyl metallic reagents with $C(sp^2)$ halides are frequently accompanied by reduction of halides or by alkyl group isomerization owing to β-H elimination in alkyl–transition metal intermediates, especially in Ni- or Pd-catalyzed reactions; these problems, however, may be suppressed by the appropriate choice of ligand or metallic reagent. The reaction occurring in equation (2) may also be complicated with β-H-bearing secondary alkyl halides owing to the competing β-H elimination. Not yet achieved are the coupling reactions between tertiary alkyl organometallics and aromatic halides and between tertiary alkyl halides and $C(sp^2)$-organometallics.

$$R(sp^3)—M \quad + \quad R'(sp^2)—X \xrightarrow{\text{catalyst}} R(sp^3)—R'(sp^2) \quad + \quad M—X \qquad (1)$$

$$R(sp^3)—X \quad + \quad R'(sp^2)—M \xrightarrow{\text{catalyst}} R(sp^3)—R'(sp^2) \quad + \quad M—X \qquad (2)$$

The literature has been surveyed up to 1988. Some recent reviews relevant to this section are as follows: Ni-,[7–12] Pd-,[7,11–17] and Cu-catalyzed[7,18] coupling reactions. Catalytic asymmetric cross-coupling reactions are not treated in this section, since the subject has recently been well reviewed.[19]

## 2.2.2 COUPLING BETWEEN $C(sp^3)$-ORGANOMETALLICS AND ALKENYL HALIDES

### 2.2.2.1 Primary Alkyllithium and Alkylmagnesium Reagents

### *2.2.2.1.1 Fundamental aspects of alkene stereochemistry*

The coupling reactions between $C(sp^3)$-organometallics and alkenyl halides provide synthetically useful methods for the stereoselective synthesis of di-, tri- and tetra-substituted alkenes, since the reactions proceed with retention of alkene geometry of the stereodefined alkenyl halides in most cases. The most fundamental stereochemical aspects are summarized first. Thus, (*E*)- and (*Z*)-bromopropenes or bromostyrenes couple with the methyl Grignard reagent to form the methylated products in higher than 90% yields and with almost complete retention of configuration in the presence of $Fe(DBM)_3$ (DBM = dibenzoylmethanato),[20] $NiCl_2(DPPP)$[21] or $Pd(PPh_3)_4$[5] (equations 3 and 4). Similar stereospecific coupling

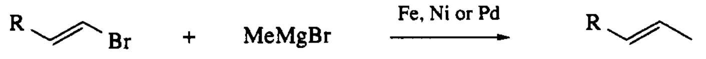

(3)

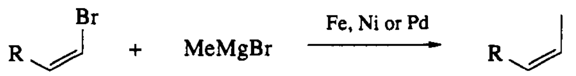

(4)

occurs with methyllithium in the presence of $Pd(PPh_3)_4$[22,23] or $RuCl(PPh_3)_3$[22] in refluxing benzene. Silver-catalyzed coupling of (*Z*)-bromopropene with MeMgBr proceeds with loss of stereochemistry.[24] The most useful catalysts seem to be Ni, Pd, or Fe complexes.

### 2.2.2.1.2 Alkenyl chlorides

Couplings between alkenyl chlorides and alkyl Grignard reagents are catalyzed best by nickel complexes,[25,26] as exemplified by the synthesis of terminal alkenes,[25] disubstituted alkenes,[27] cyclic alkenes[25] and a silylmethyldiene (equations 5–8),[28] while $Pd(PPh_3)_4$ has also been claimed to be useful for a few cases.[26]

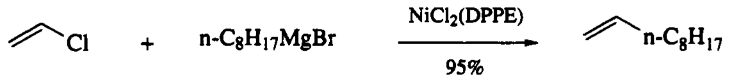
Cl
+
n-C8H17MgBr
NiCl2(DPPE)
95%
n-C8H17

(5)

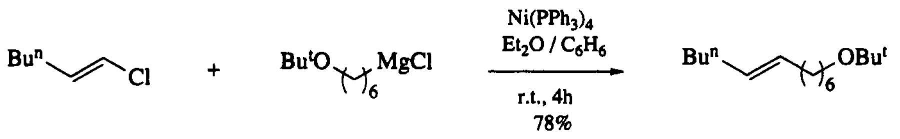
Bun
Cl
+
ButO
MgCl
6
Ni(PPh3)4
Et2O / C6H6
r.t., 4h
78%
Bun
OBut
6

(6)

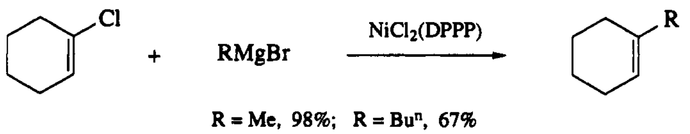
Cl
+
RMgBr
NiCl2(DPPP)
R
R = Me, 98%; R = Bun, 67%

(7)

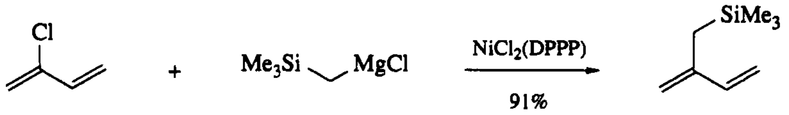
Cl
+
Me3Si
MgCl
NiCl2(DPPP)
91%
SiMe3

(8)

### 2.2.2.1.3 Alkenyl bromides

In addition to Ni catalysts, Fe and Pd complexes are also effective for couplings involving alkenyl bromides. Although organolithium reagents are not generally useful for transition metal catalyzed coupling reactions, moderate yields are achieved in the coupling of *n*-butyllithium with (*E*)- and (*Z*)-bromostyrene in the presence of $Pd(PPh_3)_4$ in benzene, the solvent being chosen to minimize side reactions such as metalation (equation 9).[22]

Coupling reactions of alkyl Grignard reagents lacking β-H substitution are exemplified by the stereoselective synthesis of a trideuteriomethylated alkene (equation 10)[29] and of allylsilanes (equations 11 and 12).[30,31] Cyclic bromoalkenes also undergo coupling smoothly (equation 13).[31]

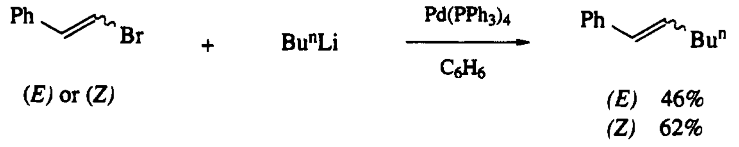
Ph
Br
(E) or (Z)
+
BunLi
Pd(PPh3)4
C6H6
Ph
Bun
(E) 46%
(Z) 62%

(9)

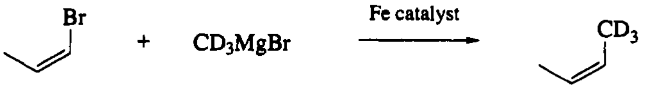
Br
+
CD3MgBr
Fe catalyst
CD3

(10)

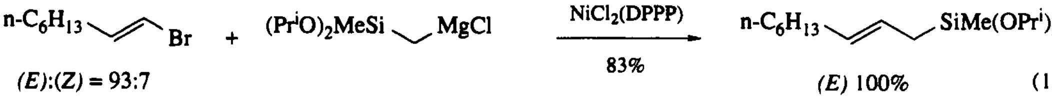
n-C6H13
Br
(E):(Z) = 93:7
+
(PriO)2MeSi
MgCl
NiCl2(DPPP)
83%
n-C6H13
SiMe(OPri)2
(E) 100%

(11)

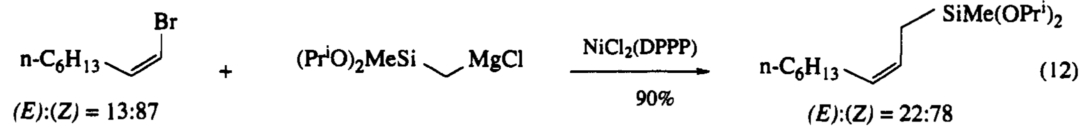
Br
n-C6H13
(E):(Z) = 13:87
+
(PriO)2MeSi
MgCl
NiCl2(DPPP)
90%
SiMe(OPri)2
n-C6H13
(E):(Z) = 22:78

(12)

Coupling reactions of β-H-bearing alkyl Grignard reagents with parent vinyl bromide, (*Z*)- and (*E*)-alkenyl bromides are catalyzed by Fe,[2,20] Ni[32] and Pd[33] respectively (equations 14–16). Similar Pd-catalyzed alkylations can be applied to 1- and 2-bromoethenylsilanes (equations 17 and 18).[34] β-Branched primary alkyl Grignard reagents also undergo Fe-[35] or Pd- catalyzed[36] coupling smoothly (equations 19 and 20).

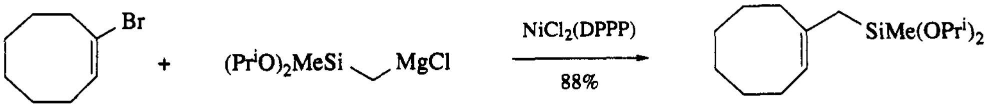
Br
+
$(Pr^iO)_2MeSi$ MgCl
$NiCl_2(DPPP)$
88%
$SiMe(OPr^i)_2$

(13)

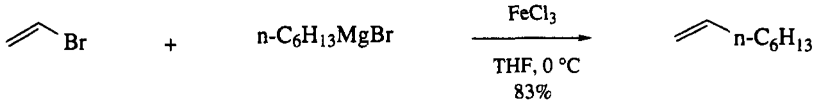
Br
+
$n-C_6H_{13}MgBr$
$FeCl_3$
THF, 0 °C
83%
$n-C_6H_{13}$

(14)

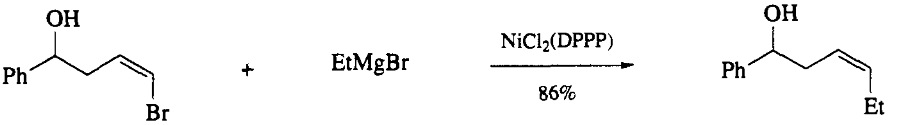
OH
Ph
Br
+
EtMgBr
$NiCl_2(DPPP)$
86%
OH
Ph
Et

(15)

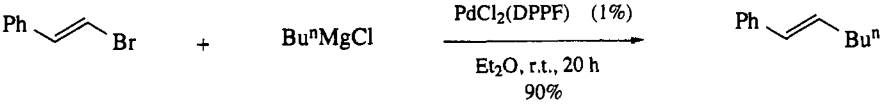
Ph
Br
+
$Bu^nMgCl$
$PdCl_2(DPPF)$ (1%)
$Et_2O$, r.t., 20 h
90%
Ph
$Bu^n$

(16)

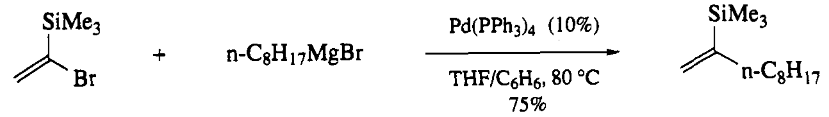
$SiMe_3$
Br
+
$n-C_8H_{17}MgBr$
$Pd(PPh_3)_4$ (10%)
$THF/C_6H_6$, 80 °C
75%
$SiMe_3$
$n-C_8H_{17}$

(17)

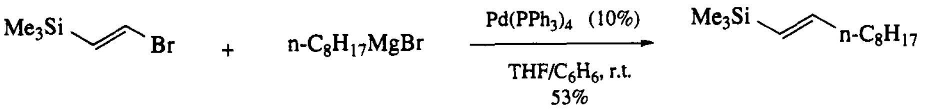
$Me_3Si$
Br
+
$n-C_8H_{17}MgBr$
$Pd(PPh_3)_4$ (10%)
$THF/C_6H_6$, r.t.
53%
$Me_3Si$
$n-C_8H_{17}$

(18)

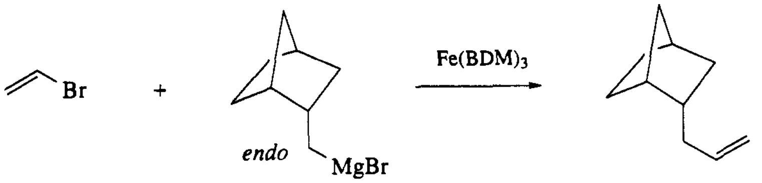
Br
+
endo
MgBr
$Fe(BDM)_3$

(19)

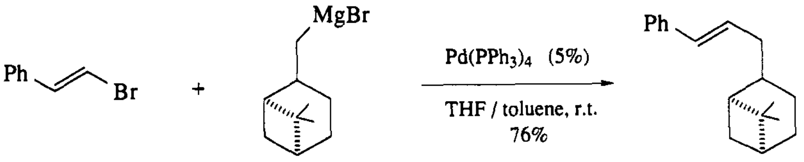
Ph
Br
+
MgBr
$Pd(PPh_3)_4$ (5%)
THF / toluene, r.t.
76%
Ph

(20)

Interestingly, there seems to be a striking difference in reactivity between (*E*)- and (*Z*)-isomers of 1-bromoalkenes. (*E*)-Isomers are more reactive than the (*Z*)-isomers in the Pd-catalyzed reaction.[37] The reverse order is found in the Fe-catalyzed coupling reaction with β-H-bearing primary alkyl Grignard reagents,[20] but with the methyl and *s*-and *t*-alkyl Grignard reagents (*E*)-isomers seem to be more reactive. Therefore, coupling reactions of a geometrically isomeric mixture with molarly deficient alkyl Grignard reagent can afford isomerically pure disubstituted alkenes, *i.e.* (*E*)-alkenes with Pd catalyst and (*Z*)-alkenes with Fe catalyst (equations 21 and 22).

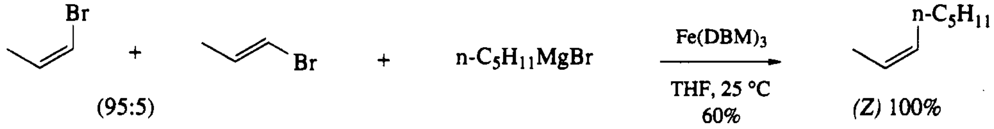
Br
+
Br
+
n-C$_5$H$_{11}$MgBr
(95:5)
Fe(DBM)$_3$
THF, 25 °C
60%
n-C$_5$H$_{11}$
(Z) 100%

(21)

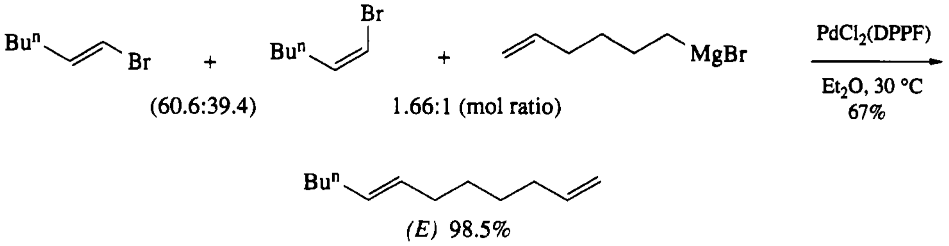
Bu$^n$
Br
+
Bu$^n$
Br
+
MgBr
(60.6:39.4)
1.66:1 (mol ratio)
PdCl$_2$(DPPF)
Et$_2$O, 30 °C
67%
Bu$^n$
(E) 98.5%

(22)

Axially chiral, optically active alkenyl bromides couple with methyllithium[38] or with alkyl Grignard reagents[39] with retention of configuration (96% retention) in the presence of NiCl$_2$(DPPE) or Fe(DBM)$_3$; the reaction may be useful for the synthesis of optically active liquid crystals (equation 23). Allenyl bromides also undergo coupling with alkyl Grignard reagents under the catalysis by Ni(mesal)$_2$ (mesal = *N*-methylsalicylaldiminato); coupling of optically active allenyl bromides proceeds with retention, but with substantial loss of stereochemistry (equation 24).[40,41]

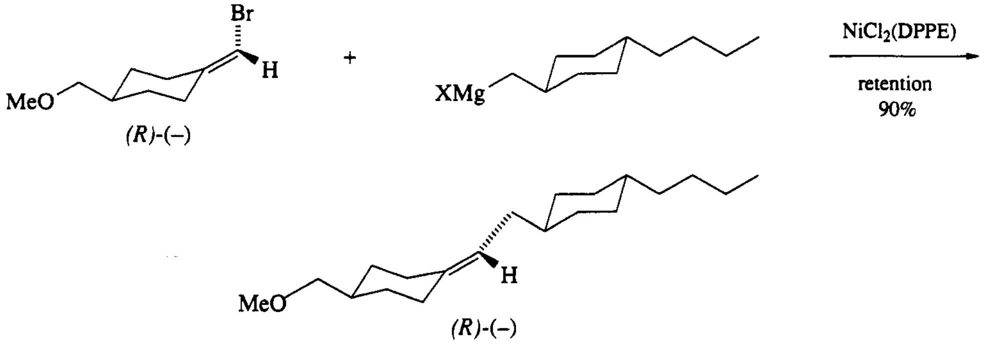
Br
H
MeO
(R)-(–)
+
XMg
NiCl$_2$(DPPE)
retention
90%
H
MeO
(R)-(–)

(23)

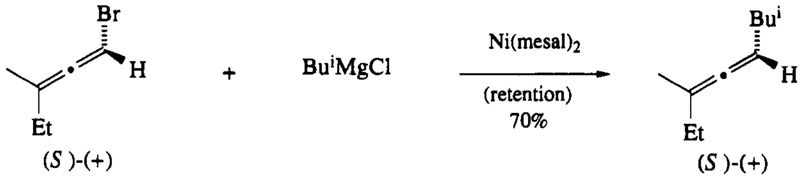
Br
H
Et
(S)-(+)
+
Bu$^i$MgCl
Ni(mesal)$_2$
(retention)
70%
Bu$^i$
H
Et
(S)-(+)

(24)

### 2.2.2.1.4 *Alkenyl iodides*

In addition to Ni and Pd catalysts, Li$_2$CuCl$_4$ is also an effective catalyst for the coupling of alkenyl iodides with Grignard reagents.[42] Since the stereochemistry of alkenyl iodides is also retained, the coupling reactions are useful for the stereoselective synthesis of disubstituted alkenes,[36,43] trisubstituted alkenes,[42] allylsilanes,[44] allyl alcohols[45] and tetrasubstituted alkenes (equations 25–29).[46]

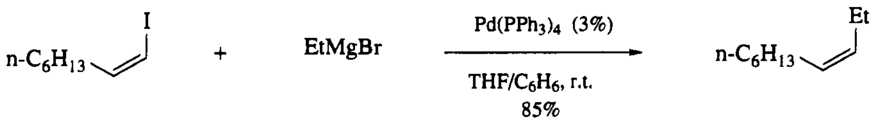
I
n-C$_6$H$_{13}$
+
EtMgBr
Pd(PPh$_3$)$_4$ (3%)
THF/C$_6$H$_6$, r.t.
85%
Et
n-C$_6$H$_{13}$

(25)

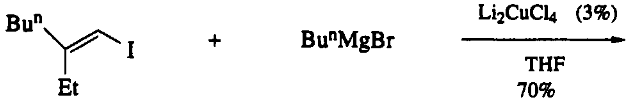

(26)

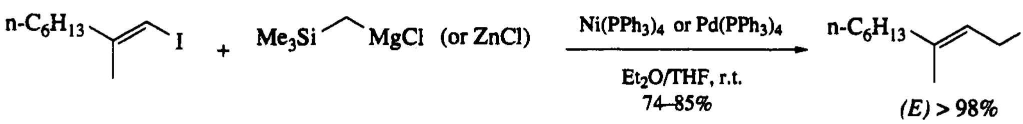

(27)

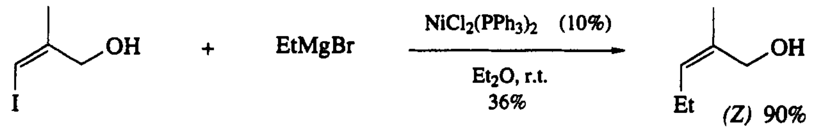

(28)

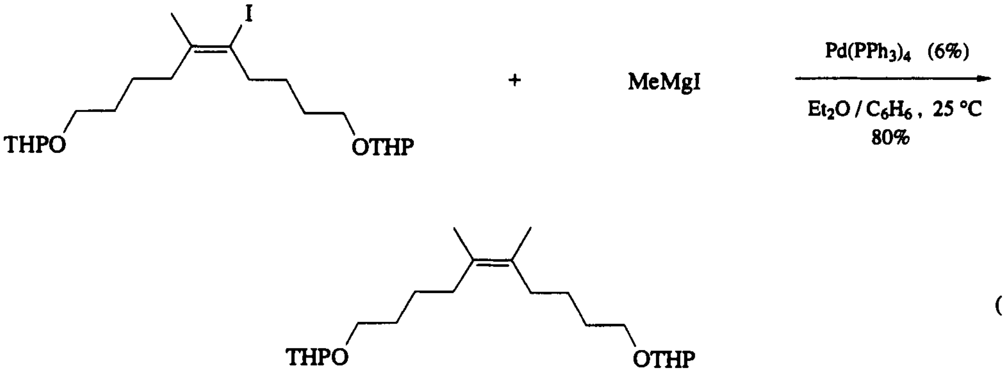

(29)

### 2.2.2.2 Secondary Alkyl Grignard Reagents

The cyclohexyl Grignard reagent couples smoothly with vinyl chloride in the presence of $NiCl_2(DPPP)$ (equation 30).[25] Alkyl group isomerization from secondary to primary is frequently observed in the coupling of secondary alkyl Grignard reagents with alkenyl halides catalyzed by Ni or Pd complexes; the extent of the isomerization is strongly dependent upon the nature of ligand and metal in the catalyst as well as the organic halides (see also Section 2.2.5.2). Thus, in the coupling of (*E*)-bromostyrene with the *s*-butyl Grignard reagent (equation 31), while $NiCl_2(DPPP)$ or $PdCl_2(DPPP)$ as catalysts induce the isomerization to some extent, no isomerization is observed with $PdCl_2(DPPF)$ at all, only the *s*-butylated product being formed in almost quantitative yields and with retention of the alkene stereochemistry.[47] The catalyst $PdCl_2(DPPF)$ is also effective for similar coupling of less reactive alkenyl bromides, such as 2-bromopropene, without alkyl isomerization (equation 32).[47]

Cross-coupling reactions between the isopropyl Grignard reagent and alkenyl bromides or iodides are also catalyzed by Fe[20] or Cu[42] complexes, no alkyl group isomerization being observed (equations 33

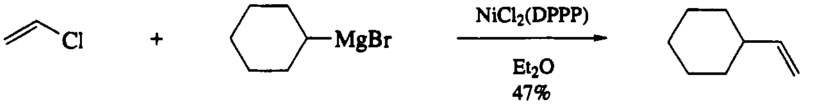

(30)

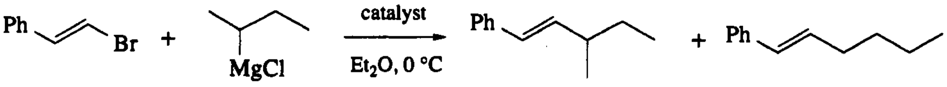

(31)

| | | |
|---|---|---|
| $PdCl_2(DPPF)$ | 97% | 100:0 |
| $NiCl_2(DPPP)$ | 89% | 99:1 |
| $PdCl_2(DPPP)$ | 81% | 86:14 |
| $Pd(PPh_3)_4$ | 69% | 48:52 |

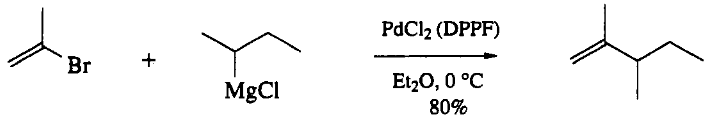
Br
+
MgCl
PdCl$_2$ (DPPF)
Et$_2$O, 0 °C
80%

(32)

and 34). Here again, (*Z*)-1-bromoalkenes seem to be more reactive than the (*E*)-isomers in the Fe-catalyzed reactions.[20] In the cross-coupling reaction of (*E*)- and (*Z*)-1-bromo-2-phenylthioethylenes with secondary alkyl Grignard reagents, however, the extent of isomerization is less with $NiCl_2(DPPE)$ than with $PdCl_2(DPPF)$, no isomerization being observed with $Fe(DPM)_3$ (DPM = dipivaloylmethanato); stereoselectivities are higher than 97% in all cases (equation 35; see also Section 2.2.4).[48,49]

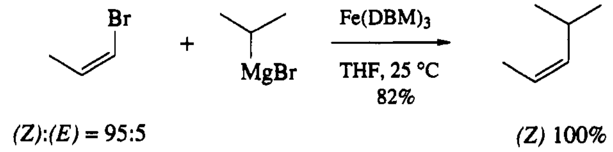
Br
+
MgBr
Fe(DBM)$_3$
THF, 25 °C
82%
(Z):(E) = 95:5
(Z) 100%

(33)

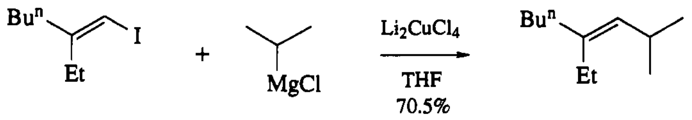
Bu$^n$
I
Et
+
MgCl
Li$_2$CuCl$_4$
THF
70.5%
Bu$^n$
Et

(34)

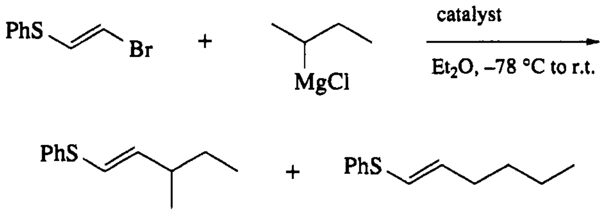
PhS
Br
+
MgCl
catalyst
Et$_2$O, –78 °C to r.t.
PhS
+
PhS

(35)

| | | |
|---|---|---|
| $Fe(DPM)_3$ | 80% | 100:0 |
| $NiCl_2(DPPE)$ | 86% | 100:0 |
| $PdCl_2(DPPF)$ | 74% | 94:6 |

### 2.2.2.3 Tertiary Alkyl Grignard Reagents

There have been only three reports on cross-coupling of *t*-butylmagnesium chloride with alkenyl halides. An Fe-catalyzed reaction with (*Z*)-1-bromopropene affords a mixture of (*Z*)- and (*E*)-isomers of *t*-butylated product with some loss of stereochemistry (equation 36).[20] In the presence of $NiCl_2(DPPF)$, (*E*)-bromostyrene couples with Bu$^t$MgCl without alkyl group isomerization and stereochemical scrambling, while alkyl group isomerization is induced by $NiCl_2(DPPP)$ as catalyst (equation 37); the $NiCl_2(DPPF)$-catalyzed *t*-butylation, however, seems to be restricted only to a reactive alkenyl halide such as (*E*)-bromostyrene.[50] Trisubstituted alkenyl iodides undergo coupling with Bu$^t$MgCl in the presence of $Li_2CuCl_4$ with retention of configuration (equation 38).[42]

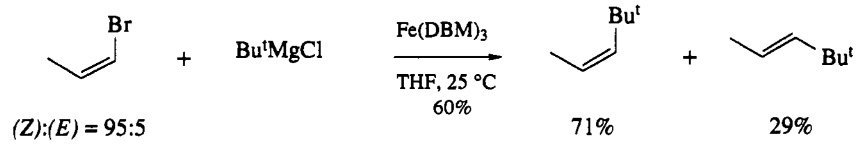
Br
+
Bu$^t$MgCl
Fe(DBM)$_3$
THF, 25 °C
60%
(Z):(E) = 95:5
Bu$^t$
71%
+
Bu$^t$
29%

(36)

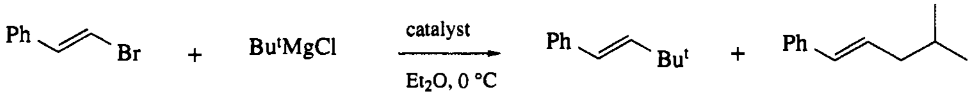
Ph
Br
+
Bu$^t$MgCl
catalyst
Et$_2$O, 0 °C
Ph
Bu$^t$
+
Ph

(37)

| | | |
|---|---|---|
| $NiCl_2(DPPF)$ | 67% | 100:0 |
| $NiCl_2(DPPP)$ | 59% | 78:22 |

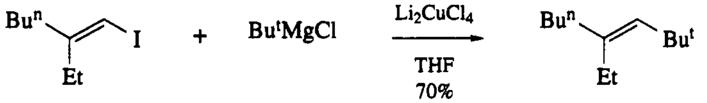
Bu$^n$
I
Et
+
Bu$^t$MgCl
Li$_2$CuCl$_4$
THF
70%
Bu$^n$
Bu$^t$
Et

(38)

### 2.2.2.4 Organozinc and Organotin Reagents

Coupling reactions of alkylzinc and alkyltin reagents with alkenyl halides are catalyzed efficiently by Pd and, in some cases, by Ni complexes.

### *2.2.2.4.1 Primary and secondary alkylzinc reagents*

The advantages of zinc reagents over Grignard reagents are that yields of coupled products are generally higher and a wider degree of functionality can be tolerated. It should be noted that coupling of β-H-bearing alkylzinc reagents, as well as β-H-lacking alkylzinc reagents, with alkenyl bromides or iodides are catalyzed even by unidentate phosphine-ligated Pd complexes such as Pd(PPh$_3$)$_4$, as illustrated in equation (39).[51] *n*-Butyl–,[51] benzyl–,[52] 2-phenylethyl–,[53] homoallyl–[51,54] and homopropargyl–zinc[51,55] reagents all have been shown to couple with trisubstituted alkenyl iodides and β-bromo-α,β-unsaturated carboxylates with retention of the alkene stereochemistry, as exemplified by the stereoselective synthesis of terpenoid skeletons (equations 40 and 41).

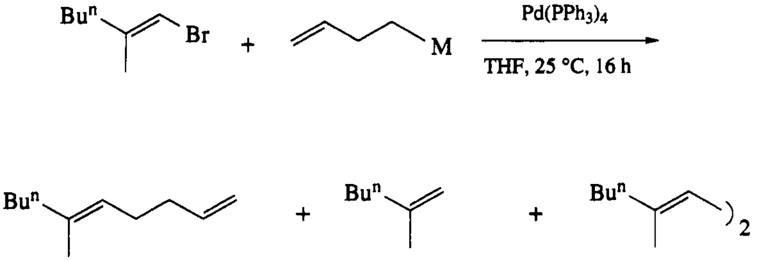
Bu$^n$
Br
+
M
Pd(PPh$_3$)$_4$
THF, 25 °C, 16 h
Bu$^n$
+
Bu$^n$
+
Bu$^n$
2

(39)

M = ZnCl 89% 91:trace: 9
M = MgBr 69% 30:54:16

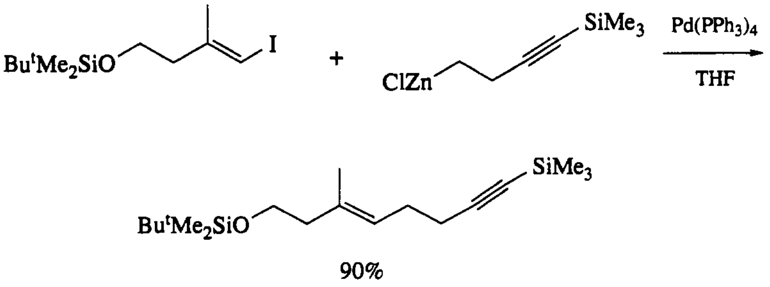
Bu$^t$Me$_2$SiO
I
+
ClZn
SiMe$_3$
Pd(PPh$_3$)$_4$
THF
Bu$^t$Me$_2$SiO
SiMe$_3$
90%

(40)

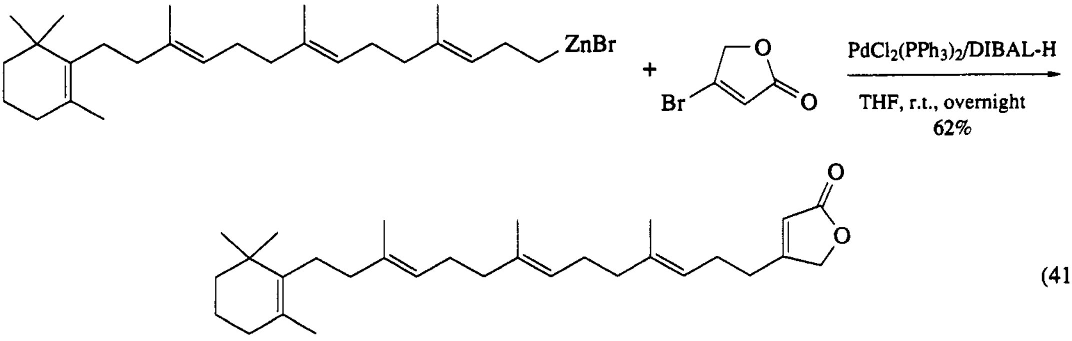
ZnBr
+
O
Br
O
PdCl$_2$(PPh$_3$)$_2$/DIBAL-H
THF, r.t., overnight
62%
O
O

(41)

Mokupalide 62%

Secondary alkylzinc reagents also couple with a trisubstituted alkenyl iodide under similar conditions, but the coupling is accompanied by alkyl group isomerization from secondary to primary (sec:prim = 60:40);[51] no alkyl group isomerization has been observed in the Pd-catalyzed coupling of a *s*-butylzinc reagent with an (*E*)-bromovinylboron derivative (equation 42).[56] A cyclopropylzinc reagent undergoes a facile coupling with (*E*)-iodoalkenes catalyzed by $Pd(PPh_3)_4$ (equation 43).[57]

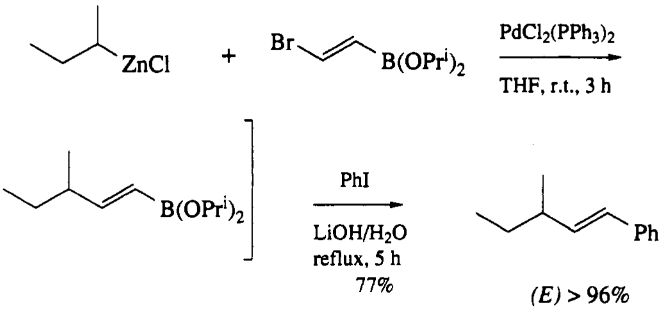
ZnCl
+
Br
B(OPr$^i$)$_2$
PdCl$_2$(PPh$_3$)$_2$
THF, r.t., 3 h
B(OPr$^i$)$_2$
PhI
LiOH/H$_2$O
reflux, 5 h
77%
Ph
(E) > 96%

(42)

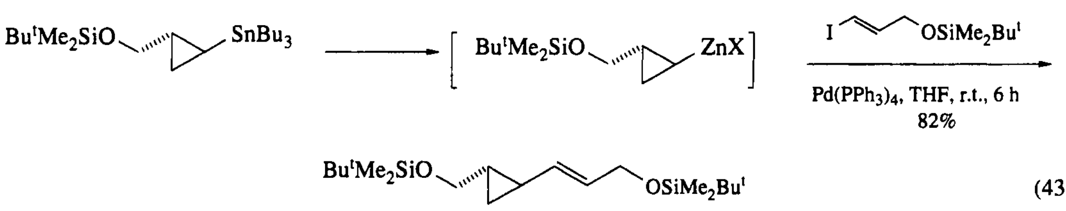
Bu$^t$Me$_2$SiO
SnBu$_3$
Bu$^t$Me$_2$SiO
ZnX
I
OSiMe$_2$Bu$^t$
Pd(PPh$_3$)$_4$, THF, r.t., 6 h
82%
Bu$^t$Me$_2$SiO
OSiMe$_2$Bu$^t$

(43)

### 2.2.2.4.2 *Reformatsky and related reagents*

Cross-coupling reactions of the Reformatsky reagent with vinyl, 2-propenyl and styryl bromides are catalyzed by $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$ (10 mol %) in HMPA as an essential solvent to form β,γ-unsaturated esters in moderate yields.[58] While the (*E*)-stereochemistry of alkenyl bromides is almost retained, stereochemical scrambling is often observed with (*Z*)-isomers (equations 44 and 45). It may be mentioned here that similar, but stoichiometric, Ni-promoted couplings of lithium ester enolates with alkenyl bromides are also known.[59,60] Zinc reagents derivable *in situ* from ω-iodoalkyl ketones with Zn/Cu also undergo Pd-catalyzed coupling with iodoalkenes (equation 46).[61]

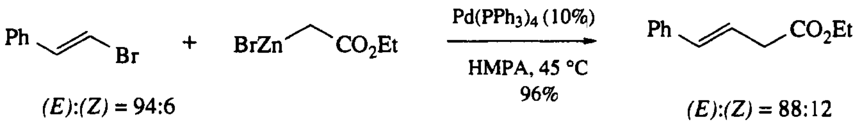
Ph
Br
+
BrZn
CO$_2$Et
Pd(PPh$_3$)$_4$ (10%)
HMPA, 45 °C
96%
Ph
CO$_2$Et
(E):(Z) = 94:6
(E):(Z) = 88:12

(44)

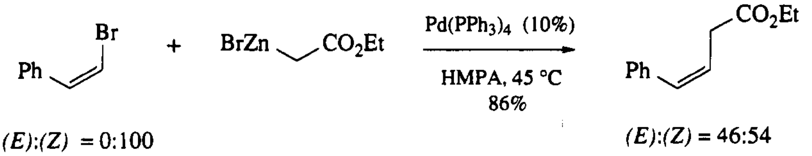
Br
Ph
+
BrZn
CO$_2$Et
Pd(PPh$_3$)$_4$ (10%)
HMPA, 45 °C
86%
CO$_2$Et
Ph
(E):(Z) = 0:100
(E):(Z) = 46:54

(45)

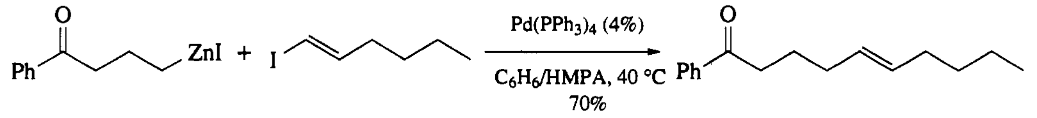
O
Ph
ZnI
+
I
Pd(PPh$_3$)$_4$ (4%)
C$_6$H$_6$/HMPA, 40 °C
70%
O
Ph

(46)

γ-Stannyl-α,β-unsaturated esters have been shown to couple with an alkenyl bromide at the γ-position selectively, but in low yield (equation 47).[62] α-Sulfonylalkylstannanes also undergo the Pd-catalyzed coupling with alkenyl iodides (equation 48).[63]

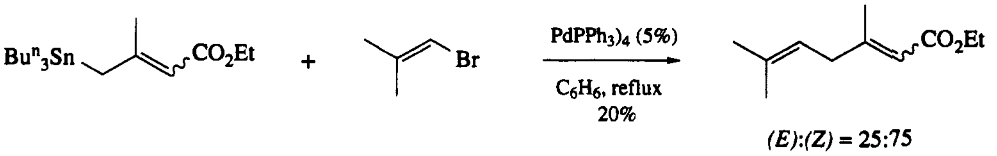
Bu$^n_3$Sn
CO$_2$Et
+
Br
PdPPh$_3$)$_4$ (5%)
C$_6$H$_6$, reflux
20%
CO$_2$Et
(E):(Z) = 25:75

(47)

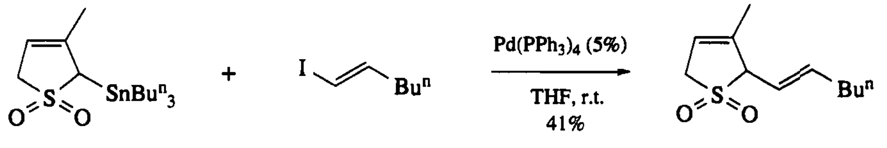
SnBu$^n_3$
S
O
O
+
I
Bu$^n$
Pd(PPh$_3$)$_4$ (5%)
THF, r.t.
41%
S
O
O
Bu$^n$

(48)

#### 2.2.2.4.3 *Perfluoroalkylzinc reagents*

Perfluoroalkylzinc iodides, generated *in situ* from the iodides and zinc powder under ultrasound irradiation, couple smoothly with alkenyl bromides in the presence of Pd(PPh$_3$)$_4$ as catalyst, linear and branched perfluoroalkyl groups being coupled with retention of the (*E*)-alkene stereochemistry (equation 49).[64]

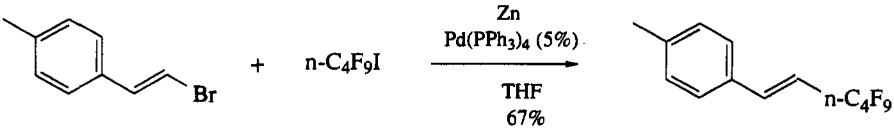
Br
+
n-C$_4$F$_9$I
Zn
Pd(PPh$_3$)$_4$ (5%)
THF
67%
n-C$_4$F$_9$

(49)

### 2.2.3 COUPLING OF C($sp^3$)-ORGANOMETALLICS WITH ALKENYL O, S, Se AND Te COMPOUNDS

Only primary alkyl–metal reagents have been used in these cases, except in the instance of the Fe-catalyzed coupling of alkenyl sulfones.

#### 2.2.3.1 Enol Ethers, Enol Carboxylates, Enol Phosphates and Enol Sulfonates

Enol ethers (equation 50),[65] dihydrofurans (equation 51),[66,67] dihydropyrans (equation 52)[65,68] and benzofuran (equation 53)[65] react with alkyl Grignard reagents in the presence of Ni catalysts to form the cross-coupling products through cleavage of C($sp^2$)–oxygen bonds. Benzene is used as a suitable solvent for the coupling of enol ethers. NiCl$_2$(PPh$_3$)$_2$ is used mostly for alkyl Grignard reagents lacking β-H substitution, while NiCl$_2$(DPPP) is suitable for β-H-bearing alkyl Grignard reagents. Only primary alkyl Grignard reagents can be used in all cases. The stereochemistry present in the cyclic ethers is highly retained, especially in those cases where the oxygen-bearing carbon contains an exocyclic substituent (equations 51 and 52), thus providing stereoselective synthesis of trisubstituted alkenes with a hydroxy group on the side chain.

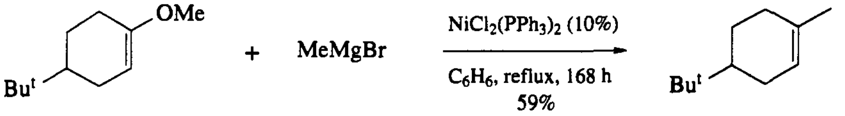
OMe
Bu$^t$
+
MeMgBr
NiCl$_2$(PPh$_3$)$_2$ (10%)
C$_6$H$_6$, reflux, 168 h
59%
Bu$^t$

(50)

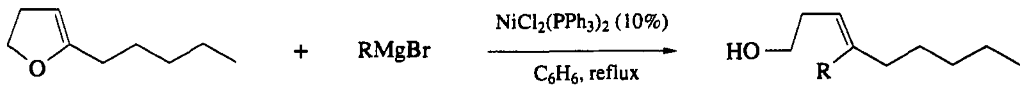
O
+
RMgBr
NiCl$_2$(PPh$_3$)$_2$ (10%)
C$_6$H$_6$, reflux
HO
R

(51)

| | |
|---|---|
| R = Me | 87% |
| R = PhCH$_2$ | 79% |
| R = Me$_3$SiCH$_2$ | 77% |
| R = Bu$^n$ | 82% |

(*E*) > 95%

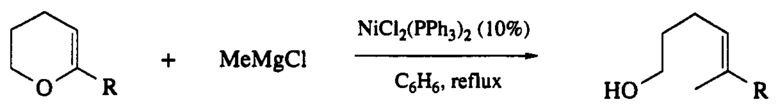

+
MeMgCl
NiCl$_2$(PPh$_3$)$_2$ (10%)
C$_6$H$_6$, reflux
O
R
HO
R

(52)

R = H 74% (Z):(E) = 76:24

R = Bu$^n$ 85% (E) > 97%

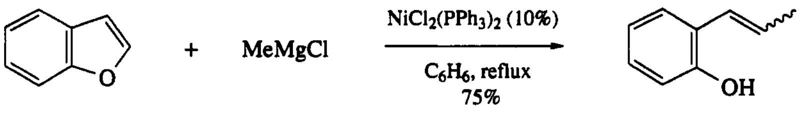

O
+
MeMgCl
NiCl$_2$(PPh$_3$)$_2$ (10%)
C$_6$H$_6$, reflux
75%
OH

(53)

(Z):(E) = 80:20

Cross-coupling of enol silyl ethers with primary alkyl Grignard reagents is also catalyzed by Ni complexes, as exemplified by the conversion of an enol silyl ether into an allylsilane (equation 54)[69] and by stereoselective alkylation (equation 55).[70]

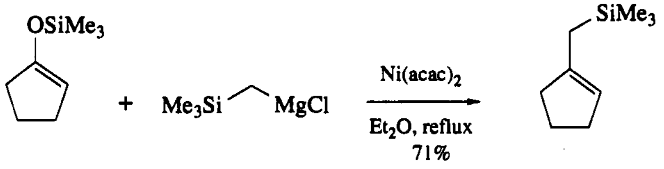

OSiMe$_3$
+
Me$_3$Si MgCl
Ni(acac)$_2$
Et$_2$O, reflux
71%
SiMe$_3$

(54)

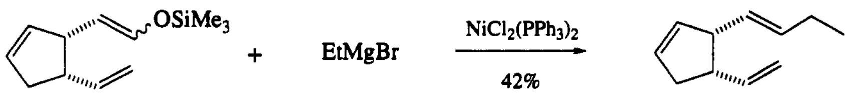

OSiMe$_3$
+
EtMgBr
NiCl$_2$(PPh$_3$)$_2$
42%

(55)

Enol phosphates couple with primary alkyl Grignard reagents in the presence of Ni complexes. While NiBr$_2$ is a suitable catalyst for trimethylsilylmethylation (equation 56),[71] NiCl$_2$(DPPP) should be used for β-H-bearing alkyl Grignard reagents (equation 57)[71,72] Enol phosphates also undergo Pd(PPh$_3$)$_4$-catalyzed coupling reactions with trimethyl- or triethyl-aluminum with retention of the enol stereochemistry (equation 58)[73] and with trialkylmanganates, R$_3$MnLi.[74]

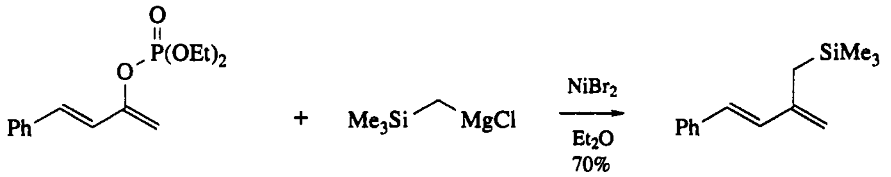

O
P(OEt)$_2$
O
Ph
+
Me$_3$Si MgCl
NiBr$_2$
Et$_2$O
70%
SiMe$_3$
Ph

(56)

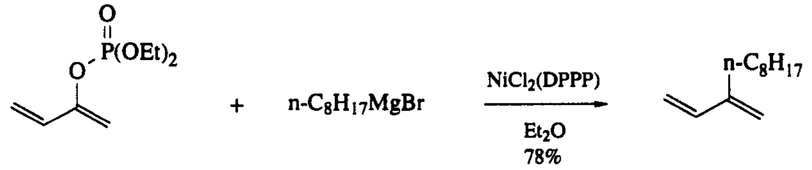

O
P(OEt)$_2$
O
+
n-C$_8$H$_{17}$MgBr
NiCl$_2$(DPPP)
Et$_2$O
78%
n-C$_8$H$_{17}$

(57)

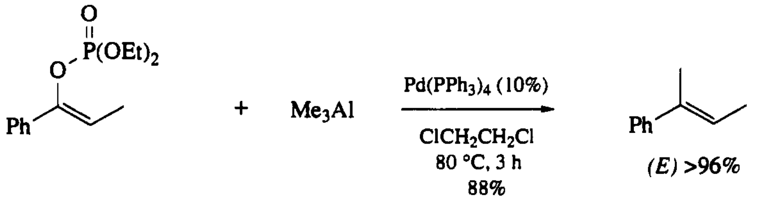

O
P(OEt)$_2$
O
Ph
+
Me$_3$Al
Pd(PPh$_3$)$_4$ (10%)
ClCH$_2$CH$_2$Cl
80 °C, 3 h
88%
Ph
(E) >96%

(58)

Enol triflates couple with the allyl or benzyl Grignard reagent in the presence of Li$_2$MnCl$_4$ as a catalyst to give coupling products in high yields (equation 59).[74] Enol triflates can be alkylated with alkylzinc[61] and alkyltin reagents[75] under catalysis by $Pd(PPh_3)_4$ with β-H-bearing alkyl groups being introduced; in the latter case LiCl is required as an essential additive (equations 60 and 61).

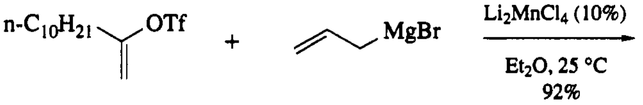
n-$C_{10}H_{21}$
OTf
+
MgBr
$Li_2MnCl_4$ (10%)
$Et_2O$, 25 °C
92%
n-$C_{10}H_{21}$

(59)

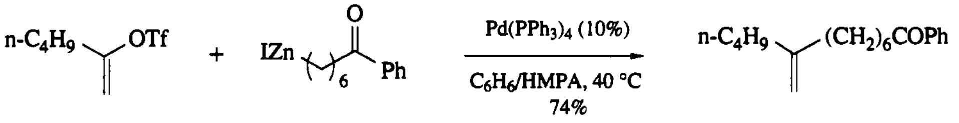
n-$C_4H_9$
OTf
+
IZn
O
6
Ph
$Pd(PPh_3)_4$ (10%)
$C_6H_6$/HMPA, 40 °C
74%
n-$C_4H_9$
$(CH_2)_6COPh$

(60)

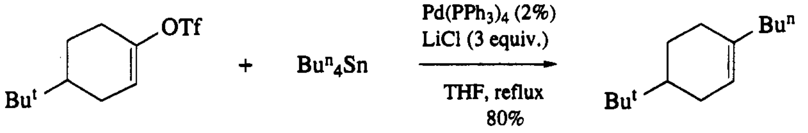
OTf
$Bu^t$
+
$Bu^n{}_4Sn$
$Pd(PPh_3)_4$ (2%)
LiCl (3 equiv.)
THF, reflux
80%
$Bu^n$
$Bu^t$

(61)

Diketene, a cyclic enol carboxylate, reacts with Grignard reagents in the presence of Ni[76,77] or Co[78] salts or complexes to form 3-methylenealkanoic acids; in addition to methyl, trimethylsilylmethyl (equation 62)[76] or benzyl groups and β-H-bearing primary alkyl groups can be introduced if $NiCl_2(DPPP)$[77] or $CoI_2$ (equation 63)[78] are used as a catalyst at low temperatures.

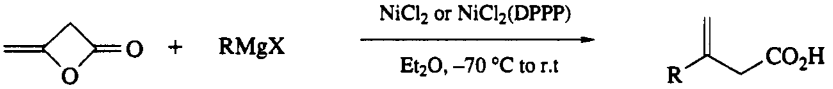
O
O
+
RMgX
$NiCl_2$ or $NiCl_2(DPPP)$
$Et_2O$, –70 °C to r.t
R
$CO_2H$

(62)

R = $Me_3SiCH_2$ 95%
R = $Bu^n$ 51%

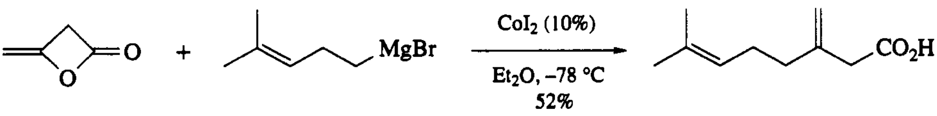
O
O
+
MgBr
$CoI_2$ (10%)
$Et_2O$, –78 °C
52%
$CO_2H$

(63)

### 2.2.3.2 Alkenyl Sulfides, Sulfones, Selenides and Tellurides

Nickel complexes, mostly $NiCl_2(PPh_3)_2$ and $NiCl_2(DPPP)$, are effective catalysts for cross-coupling reactions between alkyl Grignard reagents and alkenyl–S and alkenyl–Se compounds. Although the sulfide leaving groups may be alkylthio or arylthio groups, aryl–S bonds (see Section 2.2.6) are also cleaved competitively in coupling of alkenyl phenyl sulfides, thus requiring excess amounts of Grignard reagents. The coupling reaction proceeds with retention (>94%) of alkene geometry (equations 64 and 65).[79,80] The coupling reaction of alkenyl sulfides has been applied to the stereoselective synthesis of di-[81] and tri-substituted alkenes (equation 66),[82,83] cyclic alkenes (equation 67),[84] 1,3-dienes (equations 68–70)[85–88] and 1,3,5-trienes (equation 71);[89] in the case of (*Z*)-silyldienyl sulfides, $NiCl_2(DPPM)_2$ (DPPM = $Ph_2PCH_2PPh_2$) seems to be the most suitable catalyst.[87]

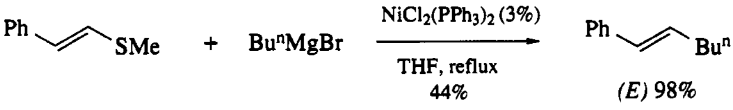
Ph
SMe
+
$Bu^nMgBr$
$NiCl_2(PPh_3)_2$ (3%)
THF, reflux
44%
Ph
$Bu^n$
(*E*) 98%

(64)

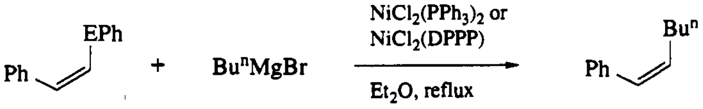
EPh
Ph
+
$Bu^nMgBr$
$NiCl_2(PPh_3)_2$ or
$NiCl_2(DPPP)$
$Et_2O$, reflux
$Bu^n$
Ph

(65)

E = S 45% (*Z*) 94%
E = Se 76%

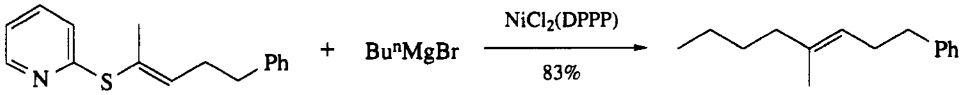
N
S
Ph
+ Bu^nMgBr
NiCl2(DPPP)
83%
Ph

(66)

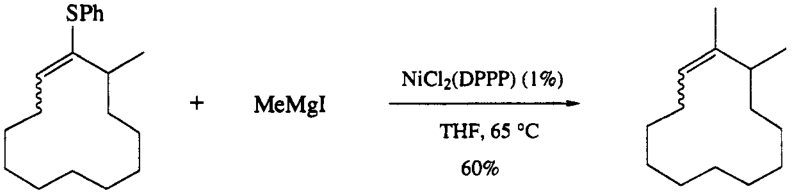
SPh
+ MeMgI
NiCl2(DPPP) (1%)
THF, 65 °C
60%

(67)

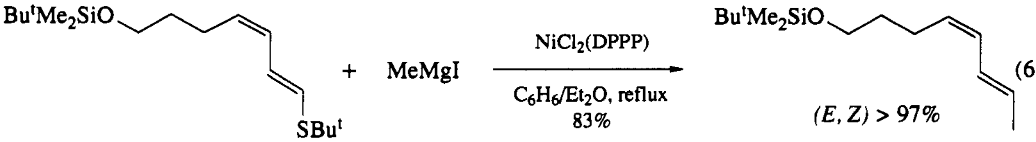
Bu^tMe2SiO
SBu^t
+ MeMgI
NiCl2(DPPP)
C6H6/Et2O, reflux
83%
Bu^tMe2SiO
(E, Z) > 97%

(68)

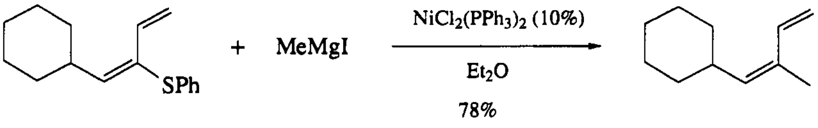
SPh
+ MeMgI
NiCl2(PPh3)2 (10%)
Et2O
78%

(69)

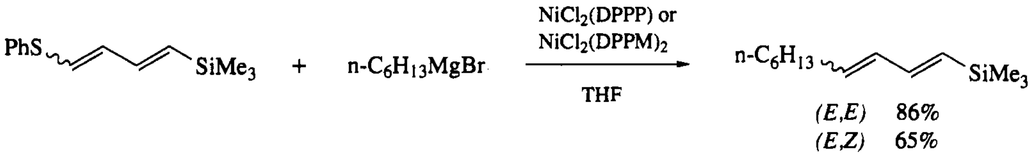
PhS
SiMe3
+ n-C6H13MgBr
NiCl2(DPPP) or
NiCl2(DPPM)2
THF
n-C6H13
SiMe3
(E,E) 86%
(E,Z) 65%

(70)

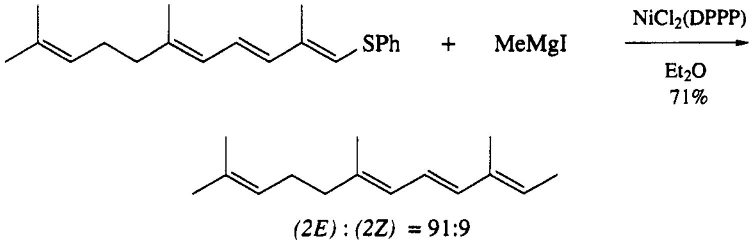
SPh
+ MeMgI
NiCl2(DPPP)
Et2O
71%
(2E) : (2Z) = 91:9

(71)

2,3-Dihydrothiopyran undergoes a ring-opening coupling with primary alkyl Grignard reagents catalyzed by $NiCl_2(DPPP)$ in benzene to form, after *S*-methylation, a methylthio-containing (*Z*)-alkene stereoselectively (equation 72).[90] Thiophene, selenophene and tellurophene also undergo similar coupling reactions to form symmetrical (*Z*,*Z*)-1,3-diene derivatives (equation 73),[91,92] furan being almost inert under similar conditions. 1-Benzothiophene reacts with 1 equiv. of the methyl Grignard reagent in the presence of $NiCl_2(DPPP)$ as a catalyst (50 mol %) to form an *o*-[(*Z*)-1-propenyl]phenyl sulfide derivative stereoselectively. The sequence occurs *via* preferential cleavage of the S–alkenyl bond rather than the S–aryl bond, the latter also being cleaved with excess amounts of the Grignard reagent to form a double methylation product (equation 74, see also Section 2.2.6).[90]

Alkenyl sulfones are methylated with MeMgX in the presence of $Ni(acac)_2$, the stereoselectivity being dependent upon the magnesium salt in the order MgCl > MgBr > MgI (equation 75).[93] Coupling of (*E*)- and (*Z*)-alkenyl sulfones with primary alkyl (except methyl) Grignard reagent occurs stereospecifically

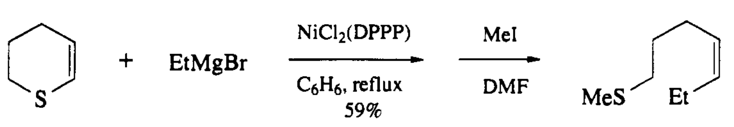
S
+ EtMgBr
NiCl2(DPPP)
C6H6, reflux
59%
MeI
DMF
MeS
Et

(72)

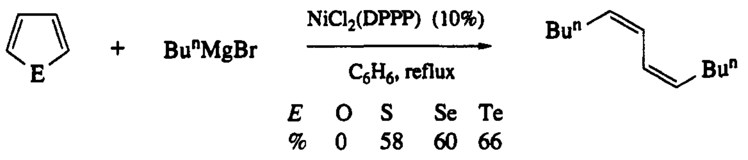
E
+
Bu^nMgBr
NiCl2(DPPP) (10%)
C6H6, reflux
Bu^n
Bu^n
E O S Se Te
% 0 58 60 66

(73)

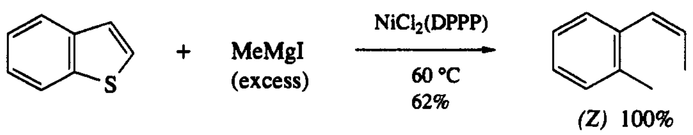
S
+
MeMgI
(excess)
NiCl2(DPPP)
60 °C
62%
(Z) 100%

(74)

in the presence of Fe(acac)3 as a catalyst to afford trisubstituted alkenes (equation 76).[94] Fe catalysts, rather than Ni, afford better results in the coupling of secondary alkyl Grignard reagents with alkenyl sulfones; the coupling is, however, accompanied by reduction and alkyl group isomerization (equation 77).[95]

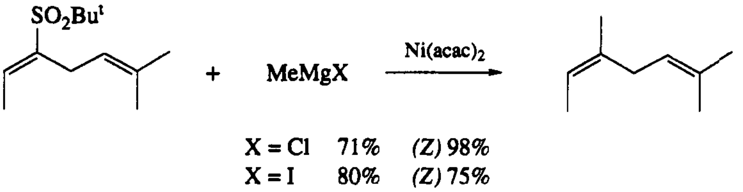
SO2Bu^t
+
MeMgX
Ni(acac)2
X = Cl 71% (Z) 98%
X = I 80% (Z) 75%

(75)

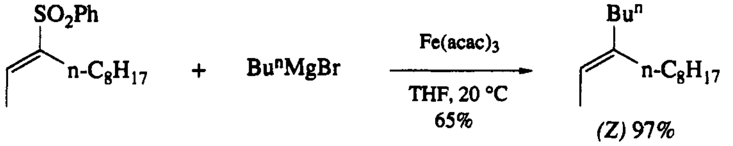
SO2Ph
n-C8H17
+
Bu^nMgBr
Fe(acac)3
THF, 20 °C
65%
Bu^n
n-C8H17
(Z) 97%

(76)

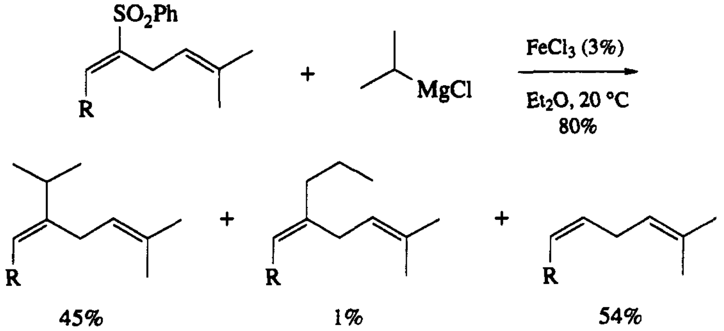
SO2Ph
R
+
MgCl
FeCl3 (3%)
Et2O, 20 °C
80%
R
+
R
+
R
45%
1%
54%

(77)

## 2.2.4 COUPLING BETWEEN C($sp^3$)-ORGANOMETALLICS AND DIFUNCTIONAL ALKENES

1,1-Dichloroethylene undergoes a Ni-catalyzed double coupling reaction with the benzyl Grignard reagent (equation 78), but a complex mixture of products may result with β-H-bearing alkyl Grignard reagents.[25] Stereoselective, stepwise coupling of 1,1-dichloroalkenes can be achieved with a β-H-bearing primary alkylzinc reagent in the presence of $PdCl_2$(DPPB), followed by reaction with an alkyl Grignard reagent catalyzed by $NiCl_2$(DPPP) (equation 79); the higher reactivity of the chlorine atom *trans* to the 2-substituent may be noted (*cf.* Section 2.2.2.1.1).[96] 1,1-Disulfide analogs (ketene dithioacetals) also undergo stereoselective, stepwise coupling with primary alkyl Grignard reagents in the presence of Ni complex (equation 80).[97] These two reactions may be useful for the stereoselective synthesis of trisubstituted alkenes.

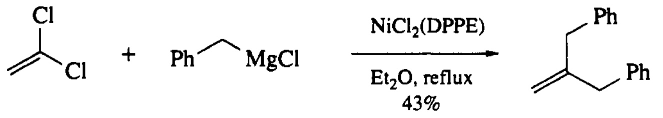
Cl
Cl
Ph
MgCl
NiCl2(DPPE)
Et2O, reflux
43%
Ph
Ph

(78)

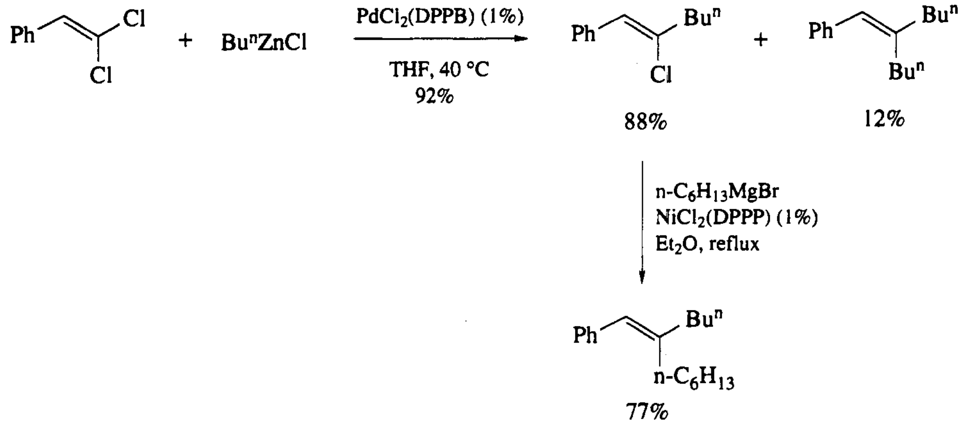
Ph
Cl
Cl
BunZnCl
PdCl2(DPPB) (1%)
THF, 40 °C
92%
Ph
Bun
Cl
88%
Ph
Bun
Bun
12%
n-C6H13MgBr
NiCl2(DPPP) (1%)
Et2O, reflux
Ph
Bun
n-C6H13
77%

(79)

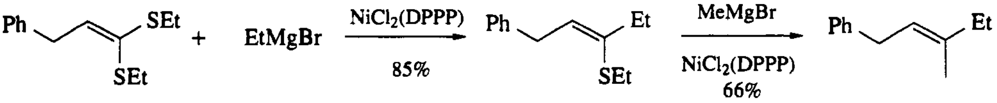
Ph
SEt
SEt
EtMgBr
NiCl2(DPPP)
85%
Ph
Et
SEt
MeMgBr
NiCl2(DPPP)
66%
Ph
Et

(80)

The predictabilities of Ni-catalyzed Grignard reactions involving 1,2-dichloroethylenes are not simple. Thus, whilst with the benzyl Grignard reagent bibenzyl is formed predominantly, double coupling products are obtained in moderate yields with β-H-bearing primary alkyl or cyclohexyl Grignard reagents, together with homocoupling of the Grignard reagent; only (*E*)-dicyclohexylethylene is formed both from (*E*)- and (*Z*)-dichloroethylenes (equation 81).[25] On the other hand, in the presence of excess amounts of (*E*)- or (*Z*)-dichloroethylene, selective monoalkylation by alkyl Grignard reagents may be realized in the presence of Ni(PPh$_3$)$_4$ as a catalyst to afford (*E*)- or (*Z*)-1-chloro-1-alkenes stereoselectively (equation 82).[98]

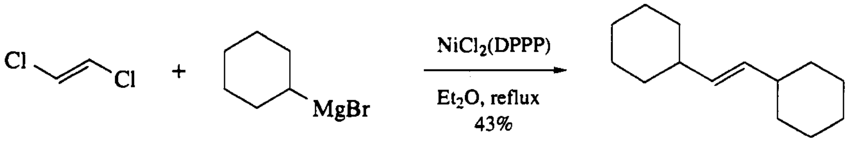
Cl
Cl
MgBr
NiCl2(DPPP)
Et2O, reflux
43%

(81)

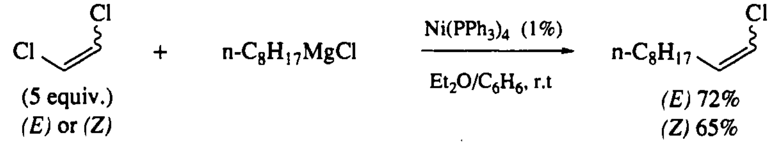
Cl
Cl
(5 equiv.)
(E) or (Z)
n-C8H17MgCl
Ni(PPh3)4 (1%)
Et2O/C6H6, r.t
Cl
n-C8H17
(E) 72%
(Z) 65%

(82)

A chemoselective monoalkylation of two unlike leaving groups on alkenes can more easily be attained based on the general reactivity order Br > Cl > SR > OR in Ni-catalyzed reactions. Grignard coupling reactions of α-bromoenol ethers catalyzed by NiCl$_2$(DPPP) generally stop cleanly at the monoalkylation stage to provide new routes to various enol ethers, primary alkyl, including β-H-bearing alkyl, Grignard reagents being employed (equations 83 and 84).[99,100] (*E*)- and (*Z*)-1-Bromo-2-phenylthioethylenes can be transformed into disubstituted alkenes stereoselectively [(*E*) > 99%, (*Z*) > 98%] by stepwise alkyl Grignard coupling in a one-pot manner; whilst the first step with the (*Z*)-isomer may be catalyzed best by PdCl$_2$(PPh$_3$)$_2$, the first step with the (*E*)-isomer and the second step with both isomers are catalyzed most efficiently by NiCl$_2$(DPPE) (equation 85).[101] In the first step, secondary alkyl Grignard reagents may be used without alkyl group isomerization (*cf.* Section 2.2.2.2; equation 86).[48] In Pd-catalyzed reactions of trimethylaluminum, the reactivity is in the order alkenyl–OP(O)(OPh)$_2$ > –SPh (equation 87).[73]

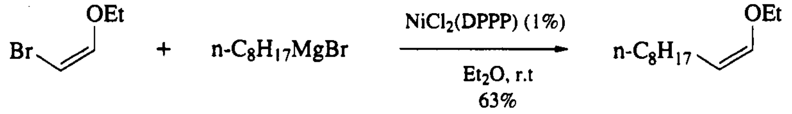
OEt
Br
n-C8H17MgBr
NiCl2(DPPP) (1%)
Et2O, r.t
63%
n-C8H17
OEt

(83)

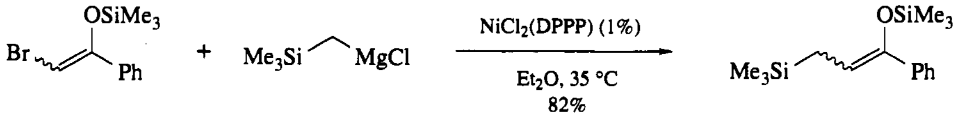
OSiMe3
Br
Ph
Me3Si
MgCl
NiCl2(DPPP) (1%)
Et2O, 35 °C
82%
Me3Si
OSiMe3
Ph

(84)

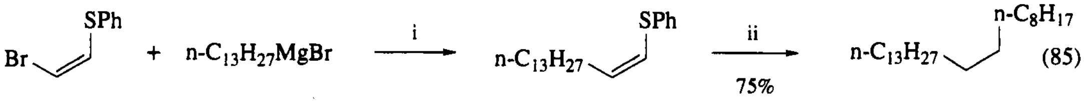
SPh
Br
n-C13H27MgBr
i
n-C13H27
SPh
ii
75%
n-C8H17
n-C13H27

(85)

i, $PdCl_2(PPh_3)_2$ (3%), $Et_2O$, r.t., ii, n-$C_8H_{17}MgBr$, $NiCl_2(DPPE)$ (6%), $Et_2O$, r.t.

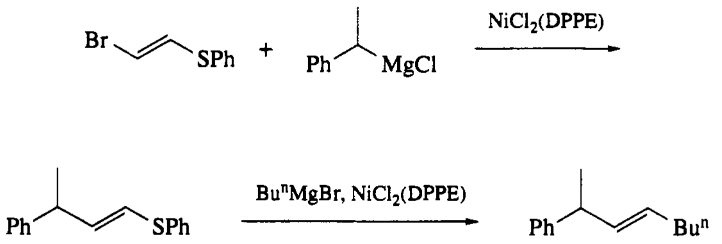
Br
SPh
Ph
MgCl
NiCl2(DPPE)
Ph
SPh
BunMgBr, NiCl2(DPPE)
Ph
Bun

(86)

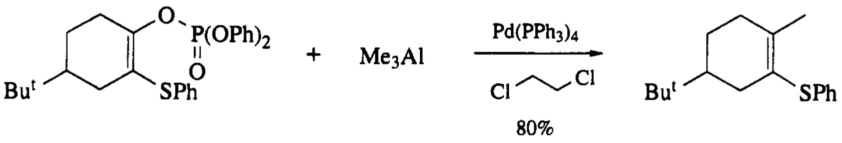
O
P(OPh)2
O
But
SPh
Me3Al
Pd(PPh3)4
Cl
Cl
80%
But
SPh

(87)

## 2.2.5 COUPLING BETWEEN C($sp^3$)-ORGANOMETALLICS AND AROMATIC HALIDES

Cross-coupling reactions of alkyl–metal reagents with aromatic halides are catalyzed efficiently by Ni or Pd complexes.

### 2.2.5.1 Coupling of Primary Alkyl Grignard Reagents with Aromatic Halides

Primary alkyl Grignard reagents, regardless of the presence or the absence of β-hydrogens, couple with aromatic halides most efficiently in the presence of $NiCl_2L_2$ as catalyst, $NiCl_2(DPPP)$ being most active and of general use.[25,26] The catalytic activity of the Ni complexes, however, depends strongly upon not only the nature of the ligands (L), but also on the combination of Grignard reagent and organic halide, as will be mentioned at appropriate positions. While Pd catalysts are usually used for coupling of β-H-lacking alkyl (Me or $PhCH_2$) Grignard reagents with aromatic bromides and iodides,[102,103] $PdCl_2(DPPF)$ is also effective for coupling of β-H-bearing alkyl Grignard reagents with aryl bromides.[33]

The reactivity order of halides is generally ArI > ArBr > ArCl >> ArF for Ni-catalyzed reactions and ArI > ArBr >> ArCl, ArF for Pd-catalyzed reactions. In the Ni-catalyzed reactions, chlorides usually give the most satisfactory results, since they exhibit a reasonable reactivity and give little side product; notably even fluorobenzene undergoes coupling (equation 88).[25] For couplings with bromobenzene, $PdCl_2(DPPF)$ seems to be more effective (equation 89).[33] Generally, an electron-withdrawing substituent on the aromatic ring accelerates the coupling and an alkyl substituent deactivates the halide; methoxy group, however, seems to be an activating substituent (equation 90).[25] Dichlorobenzenes[25] and trichlorobenzenes[104] undergo dialkylation smoothly in the presence of $NiCl_2(DPPP)$; even *o*-dialkylation is possible (equation 91, see Section 2.2.7 for monocoupling of polyfunctional compounds).[25,26] Coupling reactions of alkyl Grignard reagents, lacking β-H substitution, with sterically hindered aromatic halides are also catalyzed by Ni complexes,[25,105] but $NiCl_2(PEt_3)_2$ is better than $NiCl_2(DPPP)$ in some cases (equations 92 and 93).[25] It should be noted that a reaction of sterically hindered mesityl bromide with

$Bu^nMgBr$ catalyzed by $NiCl_2(DPPP)$ results in the formation of reduction product instead of coupling.[25] Coupling of the allyl Grignard reagent with bromobenzene is catalyzed by the complexes $NiCl_2(DMPE)$ (DMPE = $Me_2PCH_2CH_2PMe_2$) or $NiCl_2(PEt_3)_2$ that contains more electron-donating ligands than $NiCl_2(DPPP)$.[25]

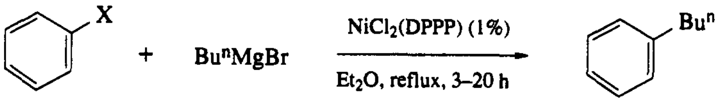
X
+ Bu^nMgBr
NiCl2(DPPP) (1%)
Et2O, reflux, 3–20 h
Bu^n

(88)

| X | F | Cl | Br | I |
|---|---|---|---|---|
| % | 31 | 95 | 54 | 80 |

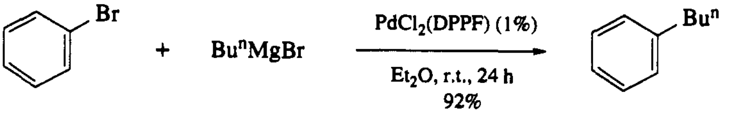
Br
+ Bu^nMgBr
PdCl2(DPPF) (1%)
Et2O, r.t., 24 h
92%
Bu^n

(89)

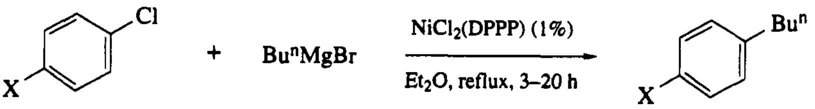
Cl
X
+ Bu^nMgBr
NiCl2(DPPP) (1%)
Et2O, reflux, 3–20 h
Bu^n
X

(90)

| X | Me | OMe | $CF_3$ |
|---|---|---|---|
| % | 58 | 90 | 56 |

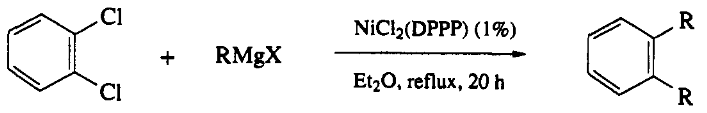
Cl
Cl
+ RMgX
NiCl2(DPPP) (1%)
Et2O, reflux, 20 h
R
R

(91)

$R = Bu^n$ 83%

$R = Me_3SiCH_2$ 75%

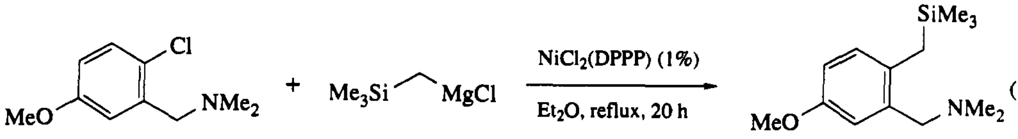
Cl
MeO
NMe2
+ Me3Si MgCl
NiCl2(DPPP) (1%)
Et2O, reflux, 20 h
SiMe3
MeO
NMe2

(92)

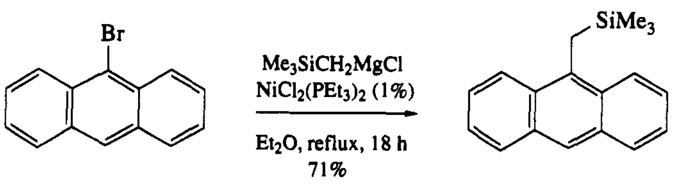
Br
Me3SiCH2MgCl
NiCl2(PEt3)2 (1%)
Et2O, reflux, 18 h
71%
SiMe3

(93)

A β-branched, optically active primary alkyl Grignard reagent has been shown to undergo coupling with chlorobenzene without loss of optical activity in the presence of $NiCl_2(DPPP)$, while about 10% racemization is induced when $NiCl_2(PPh_3)_2$ or $NiCl_2(DMPE)$ are used as catalysts, possibly due to β-H elimination–addition sequences (equation 94).[106]

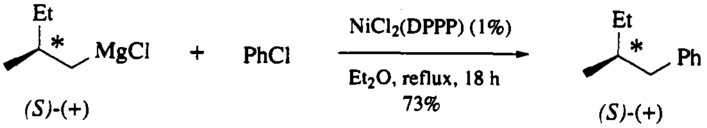
Et
*
MgCl
(S)-(+)
+ PhCl
NiCl2(DPPP) (1%)
Et2O, reflux, 18 h
73%
Et
*
Ph
(S)-(+)

(94)

Di-Grignard reagents couple with *m*-dichlorobenzene to form *m*-cyclophanes in one step but in up to 20% yields depending on the chain lengths; oxamethylene bridges can also be introduced (equations 95 and 96).[107]

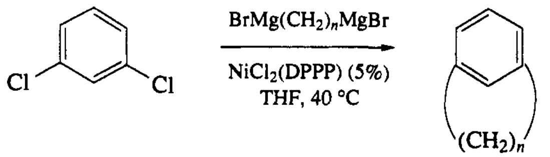

(95)

| n | 9 | 10 | 12 |
|---|---|---|---|
| % | 9 | 19 | 22 |

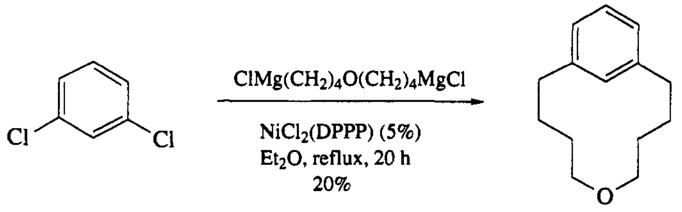

(96)

### 2.2.5.2 Coupling of Secondary and Tertiary Alkyl Grignard Reagents with Aromatic Halides

The cyclopropyl Grignard reagent undergoes coupling with bromobenzene in the presence of $NiCl_2(DMPE)$ rather than $NiCl_2(DPPP)$, but in only moderate yields (equation 97).[25] Coupling reactions of the cyclohexyl Grignard reagent are catalyzed by $NiCl_2(DPPP)$ (equation 98)[25] or less effectively by a Pd complex.[108]

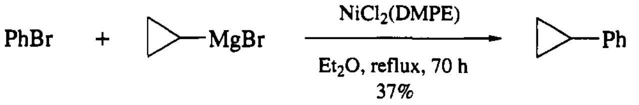

(97)

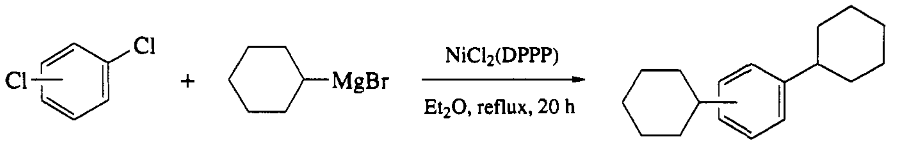

(98)

*ortho* 31%; *meta* 73%; *para* 63%

Alkyl group isomerization from secondary to primary occurs frequently in the Ni- or Pd-catalyzed coupling reactions of secondary alkyl Grignard reagents with aromatic halides, as described in the coupling reactions with alkenyl halides (Section 2.2.2.2). The isomerization is strongly dependent upon the nature of the phosphine ligands[33,106,109,110] and of the substituents on the aromatic ring;[111] while $NiCl_2(DMPE)$ induces the isomerization most readily,[106] with $PdCl_2(DPPF)$ the isomerization is completely suppressed (equation 99).[33] The 1-phenylethyl Grignard reagent undergoes $NiCl_2(DPPP)$-catalyzed coupling with chlorobenzene without isomerization.[109]

The reaction of the *t*-butyl Grignard reagent with chlorobenzene in the presence of $NiCl_2(DMPE)$ results in the formation of isobutylbenzene in low yields through tertiary to primary group isomerization; no reaction whatsoever is observed with $NiCl_2(DPPP)$ (equation 100).

### 2.2.5.3 Organozinc and Organotin Reagents

Couplings of alkylzinc and alkyltin reagents with aromatic halides, mostly bromides, are catalyzed by Pd or Ni complexes; toleration of functional groups such as CN, COR, $CO_2R$, $NO_2$, Cl and F is the most outstanding feature.

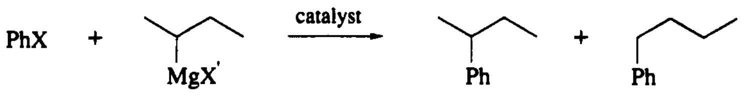
(99)

| | | | |
|---|---|---|---|
| X = Cl | $NiCl_2(DPPP)$ | 90% | 93:7 |
| X = Cl | $NiCl_2(DMPE)$ | 67% | 5:95 |
| X = Br | $NiCl_2(DPPF)$ | 95% | 100:0 |
| X = Br | $NiCl_2(DPPB)$ | 76% | 67:33 |
| X = Br | $NiCl_2(DPPP)$ | 62% | 69:31 |

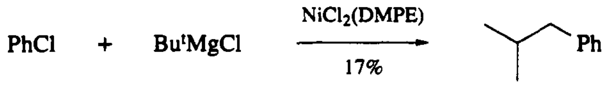
(100)

### *2.2.5.3.1 Primary alkylzinc and alkyltin reagents*

Benzyl-, phenylethyl-, homoallyl-, homopropargyl- and silylmethyl-zinc reagents undergo coupling with aryl halides in the presence of Ni or Pd complexes (equations 101–103).[31,53,103] Methyl-,[112] hydroxymethyl-,[113] methoxymethyl-[113] and allyltin[114,115] compounds also couple with aryl bromides under the catalysis of Pd—$PPh_3$ complexes: the first two reagents require HMPA as solvent and in the last allylation the unusual reactivity order ArI < ArBr > ArCl has been noted (equations 104–106). With an α-ethoxyallyltin compound, the coupling occurs selectively at the γ-position, together with a low stereoselectivity at the resulting vinyl ether group (equation 107).[115]

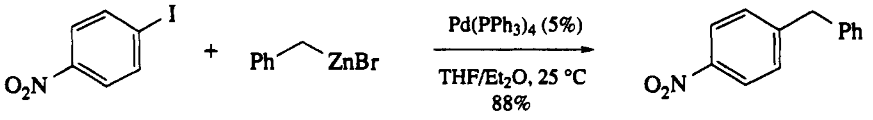
(101)

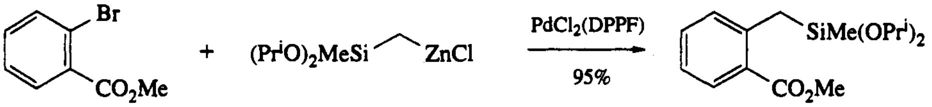
(102)

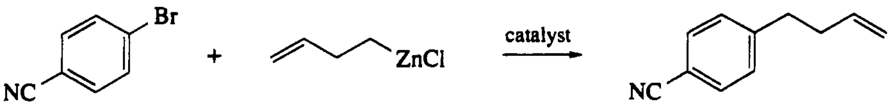
(103)

$Ni(PPh_3)_4$ (5%) 82%
$Pd(PPh_3)_4$ (5%) 78%

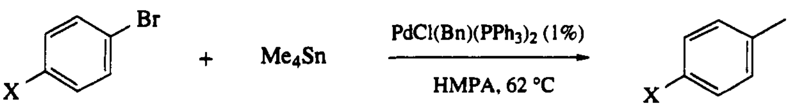
(104)

X = F, Me, OMe, COMe
84–95%

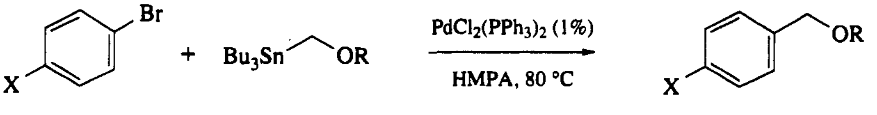
(105)

| | | |
|---|---|---|
| R = H; | X = H | 60% |
| R = Me; | X = OMe, CN, $NO_2$ | 57–80% |

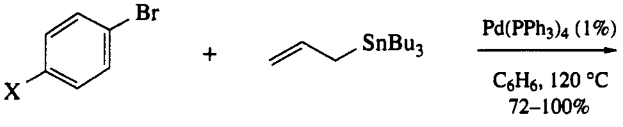
Br
X
+
SnBu3
Pd(PPh3)4 (1%)
C6H6, 120 °C
72–100%
X

(106)

X = Cl, OMe, COMe, $NO_2$

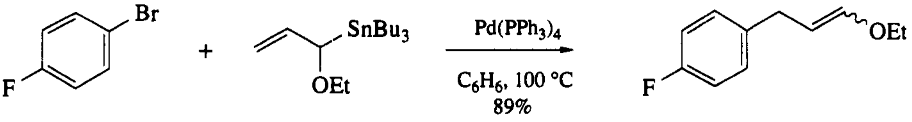
Br
F
+
SnBu3
OEt
Pd(PPh3)4
C6H6, 100 °C
89%
F
OEt

(107)

*(E)*:*(Z)* = 40:60

Chloroarene chromium tricarbonyl complexes undergo Pd-catalyzed coupling with tetrabutyltin, the butylated arenes being freed from chromium by oxidation with iodine; activation of the otherwise inert C—Cl bond by the electron-withdrawing $Cr(CO)_3$ group may be noted (equation 108).[116]

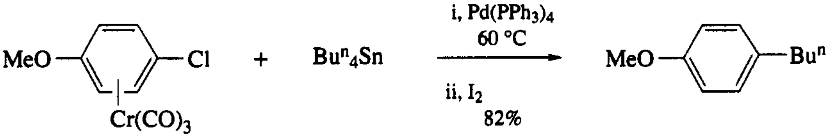
MeO
Cl
Cr(CO)3
+
Bun4Sn
i, Pd(PPh3)4
60 °C
ii, I2
82%
MeO
Bun

(108)

### 2.2.5.3.2 *Reformatsky and related reagents*

Couplings between Reformatsky reagents and aromatic halides are catalyzed by $Ni(PPh_3)_4$[117] or $Pd(PPh_3)_4$,[117,118] with DMF, NMP or HMPA being used as the essential cosolvents. While the Ni-catalyzed reaction can be applied to aromatic chlorides, bromides and iodides, the Pd-catalyzed reaction is useful only for iodides. Compatibility of the free carboxylic acid may especially be noted (equation 109).

Enol silyl ethers undergo Pd-catalyzed coupling with aromatic bromides in the presence of tributyltin fluoride, which converts the enol silyl ethers into the stannyl ethers or α-stannyl ketones regarded as real active species; chemoselective α-arylation of terminal ketones is possible (equation 110).[119]

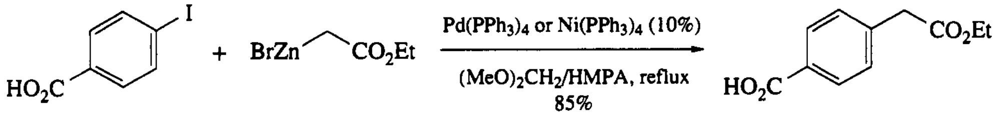
I
HO2C
+
BrZn
CO2Et
Pd(PPh3)4 or Ni(PPh3)4 (10%)
(MeO)2CH2/HMPA, reflux
85%
HO2C
CO2Et

(109)

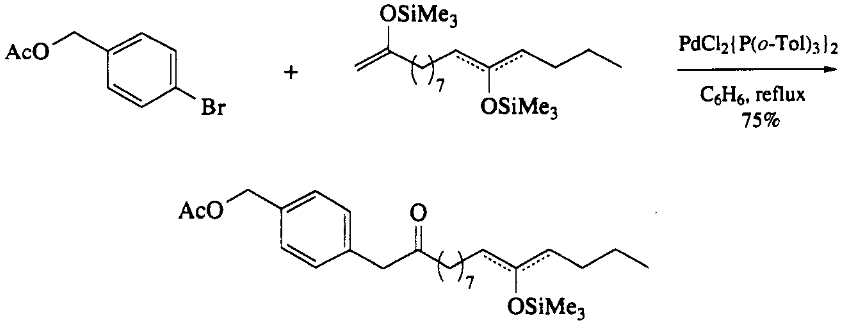
AcO
Br
+
OSiMe3
7
OSiMe3
PdCl2{P(o-Tol)3}2
C6H6, reflux
75%
AcO
O
7
OSiMe3

(110)

Cyanomethyltributyltin is a reagent for Pd-catalyzed cyanomethylation of aryl bromides with the Me, MeO or Cl substituent, but not with the MeCO, CN or $NO_2$ substituent (equation 111).[120] Dicyanomethylation of aryl iodides can be achieved with a sodium salt of malononitrile in the presence of Pd complexes (equation 112).[121]

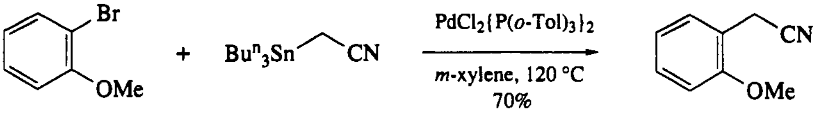
Br
OMe
+
Bu$^n{}_3$Sn
CN
PdCl$_2${P(*o*-Tol)$_3$}$_2$
*m*-xylene, 120 °C
70%
CN
OMe

(111)

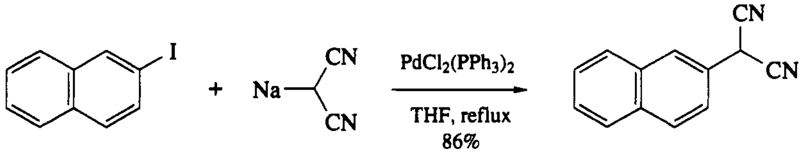
I
+
Na
CN
CN
PdCl$_2$(PPh$_3$)$_2$
THF, reflux
86%
CN
CN

(112)

## 2.2.6 COUPLING OF C($sp^3$)-ORGANOMETALLICS WITH ARYL O, S AND Se COMPOUNDS

Aryl phosphates undergo Ni-catalyzed coupling with primary alkyl Grignard reagents and triethylaluminum (equations 113–115).[122] Arene triflates[123,124] or homologous perfluoroalkanesulfonates[124] couple with primary alkyltin,[123] benzylzinc[124] and ester-containing alkylzinc (ester homoenolate) reagents[124] in the presence of Pd complexes as catalysts and LiCl as an essential additive (equations 116 and 117); compatibility of the free OH group in the coupling of alkyltin compounds is worthy of note. Allylation with allyltin compounds is accompanied substantially by 1-propenylation *via* alkene isomerization.[123] Siloxycyclopropanes serve as aldehyde, ketone and ester homoenolate equivalents in Pd-catalyzed coupling reactions with aryl triflates to form β-aryl carbonyl compounds (equations 118–120).[125]

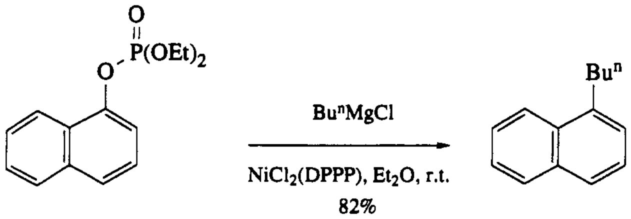
O
P(OEt)$_2$
O
Bu$^n$MgCl
NiCl$_2$(DPPP), Et$_2$O, r.t.
82%
Bu$^n$

(113)

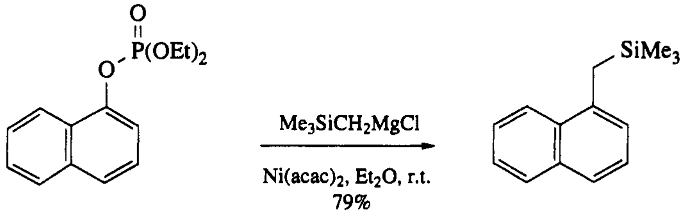
O
P(OEt)$_2$
O
Me$_3$SiCH$_2$MgCl
Ni(acac)$_2$, Et$_2$O, r.t.
79%
SiMe$_3$

(114)

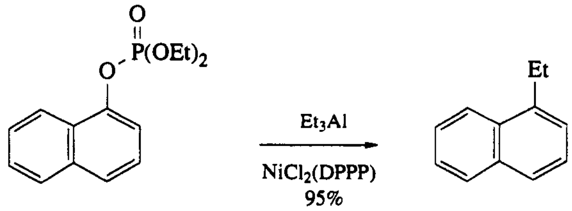
O
P(OEt)$_2$
O
Et$_3$Al
NiCl$_2$(DPPP)
95%
Et

(115)

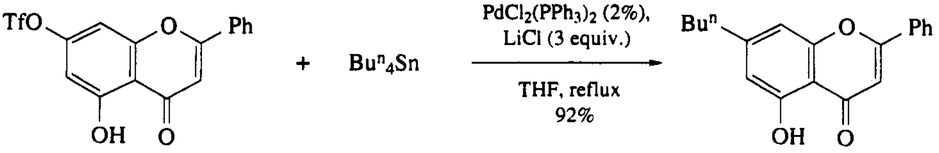
TfO
O
Ph
OH
O
+
Bu$^n{}_4$Sn
PdCl$_2$(PPh$_3$)$_2$ (2%), LiCl (3 equiv.)
THF, reflux
92%
Bu$^n$
O
Ph
OH
O

(116)

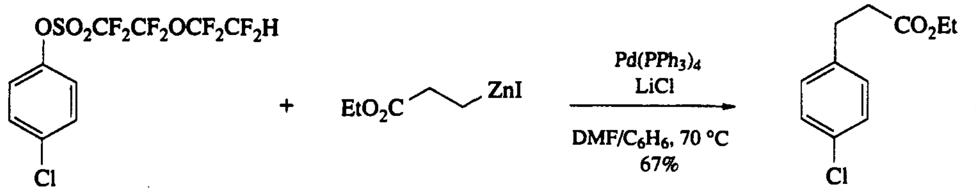

OSO2CF2CF2OCF2CF2H
Cl
EtO2C
ZnI
Pd(PPh3)4
LiCl
DMF/C6H6, 70 °C
67%
CO2Et
Cl

(117)

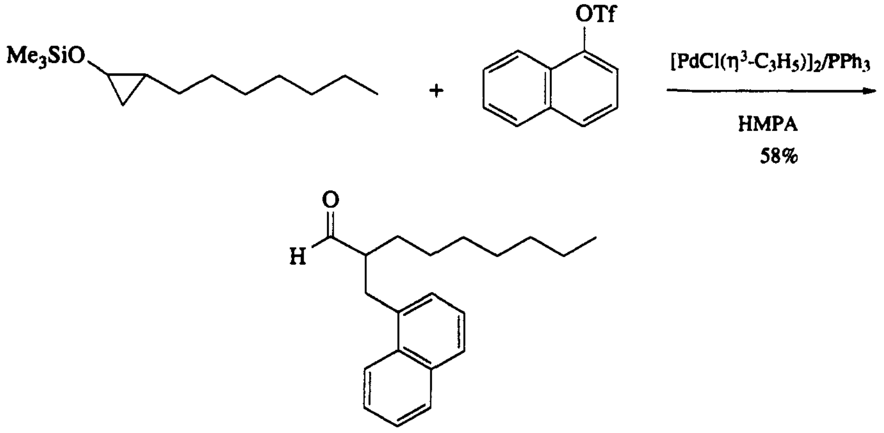

Me3SiO
OTf
[PdCl(η3-C3H5)]2/PPh3
HMPA
58%
O
H

(118)

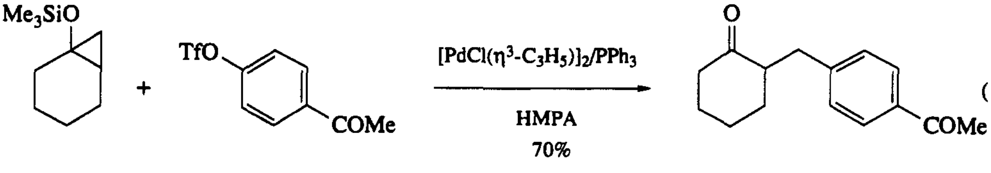

Me3SiO
TfO
COMe
[PdCl(η3-C3H5)]2/PPh3
HMPA
70%
O
COMe

(119)

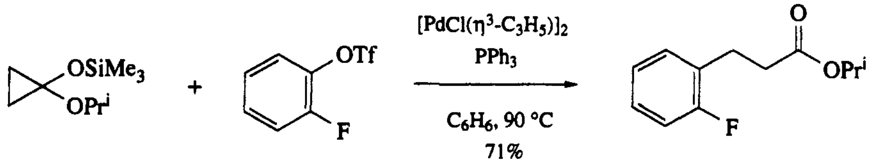

OSiMe3
OPri
OTf
F
[PdCl(η3-C3H5)]2
PPh3
C6H6, 90 °C
71%
O
OPri
F

(120)

Nickel-catalyzed Grignard coupling reactions can be applied to arenethiols,[126] sulfides,[79,90,126] sulfoxides,[126] sulfones[126] and selenides.[80] Whilst the methyl Grignard reagent couples efficiently with all of them, β-H-bearing alkyl Grignard reagents give rather low yields of coupling products even in the presence of active $NiCl_2(DPPP)$; the reactivity order is PhSeMe >> PhCl > PhSMe (equations 121 and 122).[80] Similarly, while benzothiophene may be converted into *o*-(*Z*)-1-propenyltoluene (see Section 2.2.3.2) and thioanthrene into *o*-xylene by the Ni-catalyzed methylation, dibenzothiophene gives a monomethylation product mainly, even in the presence of 2 equiv. of MeMgI (equation 123).[90]

$$\mathrm{PhX} + \mathrm{MeMgBr} \xrightarrow{\mathrm{NiCl_2(PPh_3)_2}} \mathrm{PhMe} \qquad (121)$$

$X$ = SH, 64%; SMe, 97%; SOPh, 77%; $SO_2Me$, 97%

$$\mathrm{PhSeMe} + \mathrm{Bu^nMgBr} \xrightarrow[\mathrm{Et_2O,\ reflux} \atop 95\%]{\mathrm{NiCl_2(DPPP)}} \mathrm{PhBu^n} \qquad (122)$$

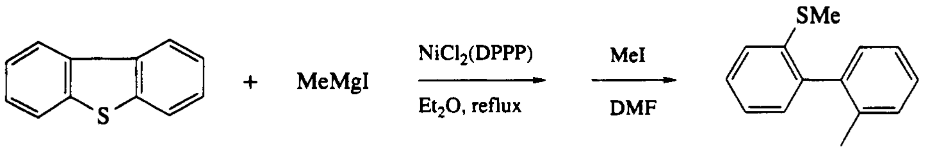
S
+ MeMgI
NiCl$_2$(DPPP)
Et$_2$O, reflux
MeI
DMF
SMe

(123)

## 2.2.7 COUPLING OF C($sp^3$)-ORGANOMETALLICS WITH POLYFUNCTIONAL AROMATICS

Chemoselective couplings of polyfunctional aromatic compounds may be achieved by Ni- or Pd-catalyzed coupling with alkyl Grignard reagents. Whereas Grignard coupling reactions of aromatic polyhalides catalyzed by active $NiCl_2(DPPP)$ or $NiCl_2(DPPE)$ tend to result in the complete alkylation of all the halogen atoms present (see Section 2.2.5.1), a highly selective monoalkylation of dichlorobenzenes and trichlorobenzenes can be achieved with 1 equiv. of primary alkyl Grignard reagents in the presence of $[Ni(triphos)Cl]PF_6$[127] (triphos = $PhP(CH_2CH_2PPh_2)_2$) or $Ni(acac)_2$[128] as catalyst (equations 124 and 125). Dibromobenzenes and 1,3,5-tribromobenzene can also be monoalkylated with primary alkyl Grignard reagents or with benzylzinc halides in the presence of $PdCl_2(DPPF)$ or $PdCl_2(DPPB)$ as catalyst (equation 126).[129,130]

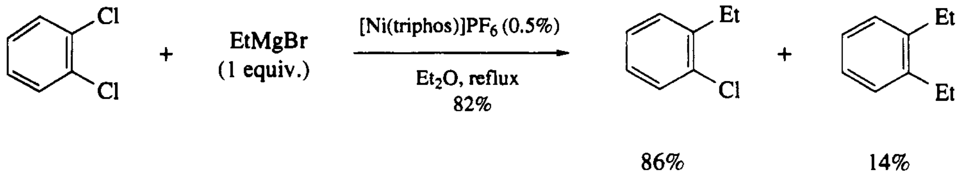
Cl
Cl
+
EtMgBr
(1 equiv.)
[Ni(triphos)]PF$_6$ (0.5%)
Et$_2$O, reflux
82%
Et
Cl
+
Et
Et
86%
14%

(124)

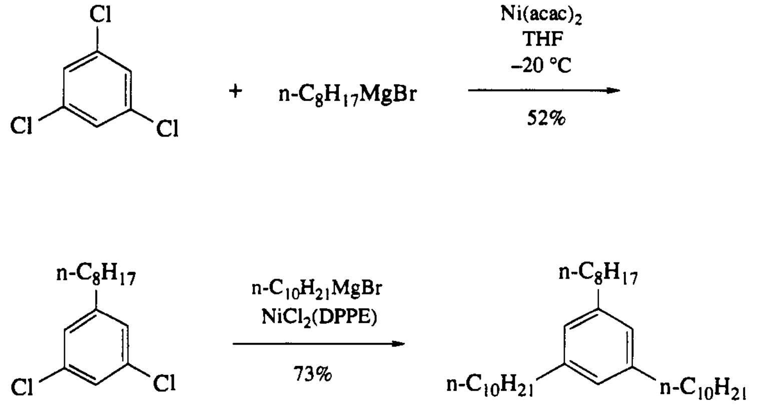
Cl
Cl
Cl
+ n-C$_8$H$_{17}$MgBr
Ni(acac)$_2$
THF
-20 °C
52%
n-C$_8$H$_{17}$
Cl
Cl
n-C$_{10}$H$_{21}$MgBr
NiCl$_2$(DPPE)
73%
n-C$_8$H$_{17}$
n-C$_{10}$H$_{21}$
n-C$_{10}$H$_{21}$

(125)

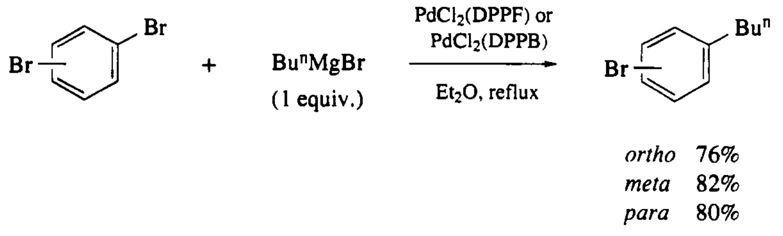
Br
Br
+
Bu$^n$MgBr
(1 equiv.)
PdCl$_2$(DPPF) or
PdCl$_2$(DPPB)
Et$_2$O, reflux
Bu$^n$
Br
ortho 76%
meta 82%
para 80%

(126)

Certain substituents can activate one halogen atom specifically in polyhalogen compounds, as exemplified by monoalkylation directed by methyl,[127] methoxy,[127,131] and oxazolinyl groups (equations 127–130).[132] A stepwise Grignard coupling of two unlike leaving groups is also possible based on the reactivity order Cl > SR (equation 131).[133]

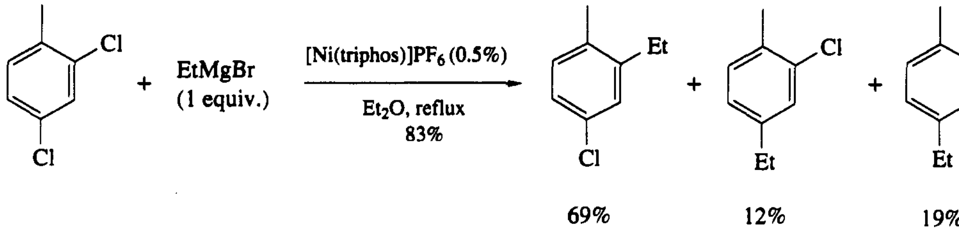
Cl
Cl
+
EtMgBr
(1 equiv.)
[Ni(triphos)]PF6 (0.5%)
Et2O, reflux
83%
Et
Cl
+
Cl
Et
+
Et
Et
69%
12%
19%

(127)

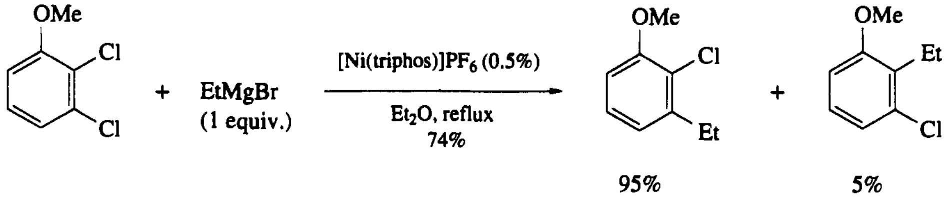
OMe
Cl
Cl
+
EtMgBr
(1 equiv.)
[Ni(triphos)]PF6 (0.5%)
Et2O, reflux
74%
OMe
Cl
Et
+
OMe
Et
Cl
95%
5%

(128)

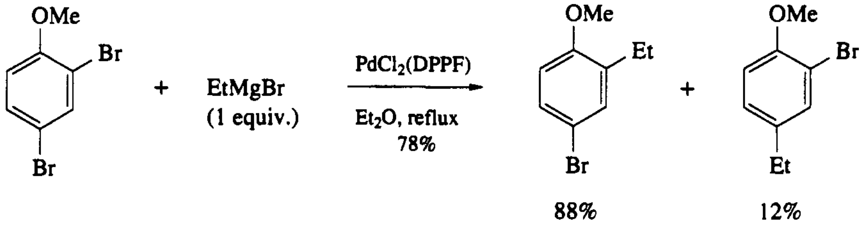
OMe
Br
Br
+
EtMgBr
(1 equiv.)
PdCl2(DPPF)
Et2O, reflux
78%
OMe
Et
Br
+
OMe
Br
Et
88%
12%

(129)

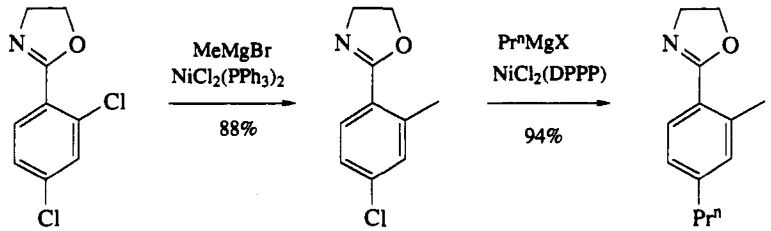
N
O
Cl
Cl
MeMgBr
NiCl2(PPh3)2
88%
N
O
Cl
PrnMgX
NiCl2(DPPP)
94%
N
O
Prn

(130)

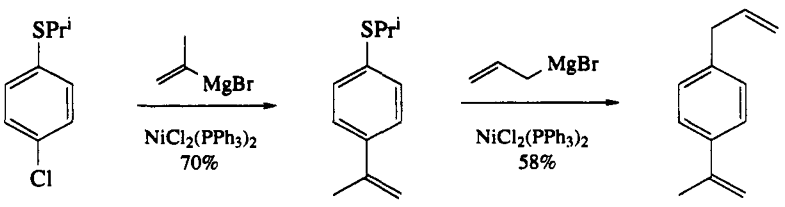
SPri
Cl
MgBr
NiCl2(PPh3)2
70%
SPri
MgBr
NiCl2(PPh3)2
58%

(131)

Monoalkylation of 2,3-dichloro-1,4-naphthoquinone is achieved by Pd-catalyzed reaction with tetra-alkyltins or, less efficiently, with alkylzirconium complexes (equation 132).[134]

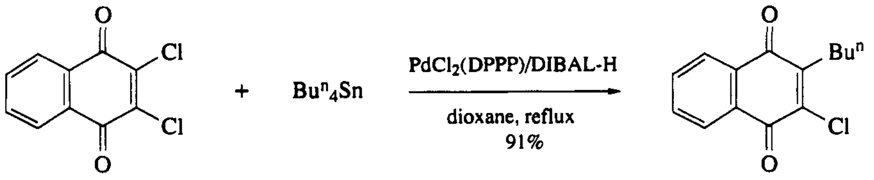
O
Cl
Cl
O
+
Bun4Sn
PdCl2(DPPP)/DIBAL-H
dioxane, reflux
91%
O
Bun
Cl
O

(132)

## 2.2.8 COUPLING OF C($sp^3$)-ORGANOMETALLICS WITH HETEROAROMATIC HALIDES AND SULFIDES

Nickel- or palladium-catalyzed coupling reactions of alkyl Grignard or zinc reagents can be applied to heteroaromatic halides and sulfides. The characteristic features are, therefore, based on those described in the preceding sections and hence details are not repeated in this section. Aspects are summarized by the types of heteroaromatic compounds; $NiCl_2$(DPPP) is used as catalyst, unless stated otherwise hereafter.

### 2.2.8.1 Furans and Thiophenes

A chlorobenzofuran[135] and a 2-furyl sulfide[136] have been shown to couple with primary alkyl Grignard reagents (equations 133 and 134). 2-Bromothiophene undergoes a halogen–metal exchange reaction mainly with a basic primary alkyl Grignard reagent such as $Bu^nMgBr$ to give only trace amounts of coupling products, but it couples smoothly with less basic Grignards such as $(TMS)CH_2MgCl$ (equation 135).[137] 3-Bromothiophene shows no such problem and undergoes the Ni-catalyzed coupling with primary and secondary alkyl (Me, $Bu^n$, $PhCH_2$, $(TMS)CH_2$, cyclopentyl) Grignard reagents (equation 136);[137,138] the Pd-catalyzed coupling with a silylmethylzinc reagent is also possible (equation 137).[31] One-step double coupling[137] and stepwise coupling[139] reactions of 3,4-dibromothiophene are possible under the catalysis by $NiCl_2$(DPPP) and $PdCl_2$(DPPF), respectively (equations 138 and 139).

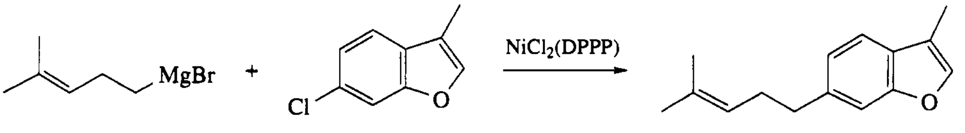
MgBr
+
Cl
O
NiCl2(DPPP)
O

Furoventalene

(133)

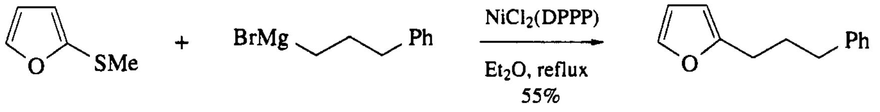
O
SMe
+
BrMg
Ph
NiCl2(DPPP)
Et2O, reflux
55%
O
Ph

(134)

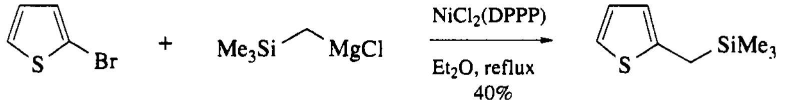
S
Br
+
Me3Si
MgCl
NiCl2(DPPP)
Et2O, reflux
40%
S
SiMe3

(135)

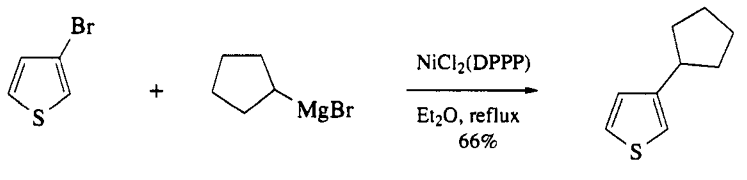
Br
S
+
MgBr
NiCl2(DPPP)
Et2O, reflux
66%
S

(136)

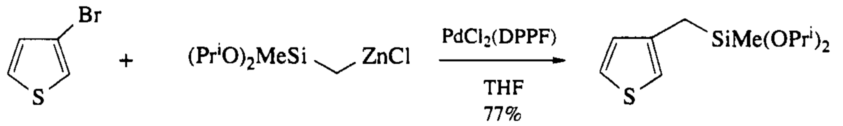
Br
S
+
(PriO)2MeSi
ZnCl
PdCl2(DPPF)
THF
77%
S
SiMe(OPri)2

(137)

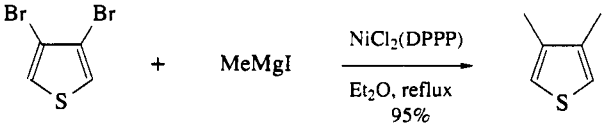
Br
Br
S
+
MeMgI
NiCl2(DPPP)
Et2O, reflux
95%
S

(138)

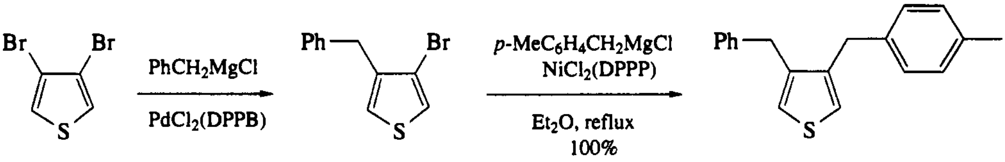
Br
Br
S
PhCH2MgCl
PdCl2(DPPB)
Ph
Br
S
p-MeC6H4CH2MgCl
NiCl2(DPPP)
Et2O, reflux
100%
Ph
S

(139)

### 2.2.8.2 Pyridines and Quinolines

2-Chloro- and 2-bromo-pyridines undergo Ni-catalyzed coupling reactions with primary alkyl Grignard reagents (equation 140);[137,140,141] 3-halopyridines are less reactive and an '*ortho*' methyl substituent retards the coupling substantially.[140] Couplings of bromo- and iodo-pyridines with alkylzinc reagents seem to be catalyzed by Pd-complexes (equations 141 and 142).[142,143] 2-Pyridyl sulfides[136] and triflate[125] also undergo Ni-catalyzed Grignard coupling and Pd-catalyzed coupling with siloxycyclopropanes, respectively (equations 143 and 144).

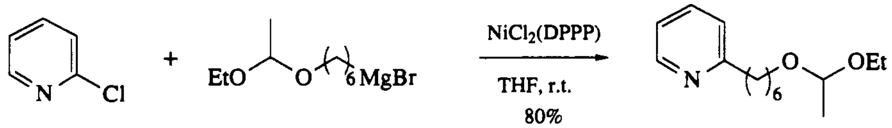
N
Cl
+
EtO
O
6
MgBr
NiCl2(DPPP)
THF, r.t.
80%
N
6
O
OEt

(140)

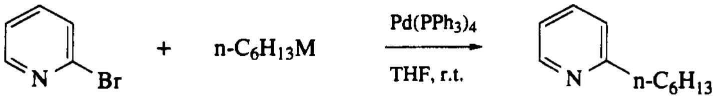
N
Br
+
n-C6H13M
Pd(PPh3)4
THF, r.t.
N
n-C6H13

(141)

M = ZnCl 100%
M = MgBr <2%

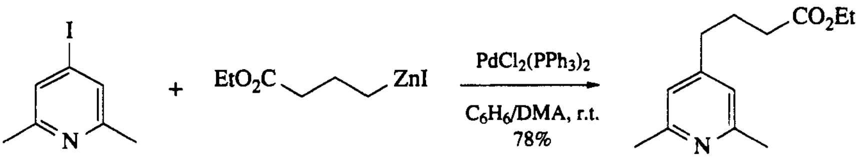
I
N
+
EtO2C
ZnI
PdCl2(PPh3)2
C6H6/DMA, r.t.
78%
CO2Et
N

(142)

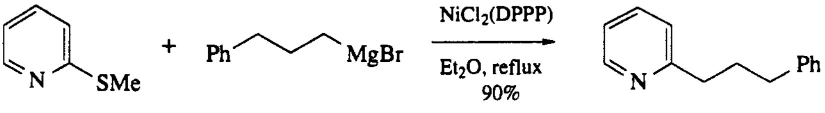
N
SMe
+
Ph
MgBr
NiCl2(DPPP)
Et2O, reflux
90%
N
Ph

(143)

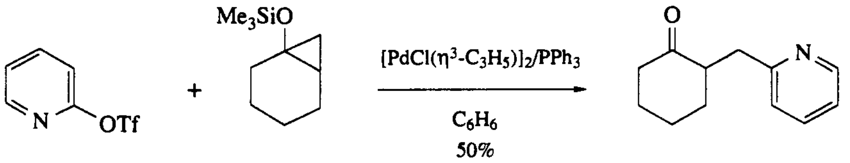
N
OTf
+
Me3SiO
[PdCl(η3-C3H5)]2/PPh3
C6H6
50%
O
N

(144)

2,6-Dichloropyridine undergoes Ni-catalyzed double coupling reactions readily with primary alkyl Grignard reagents[137] and with di-Grignard reagents[107] as exemplified by the one-step synthesis of muscopyridine (equation 145). Pd-catalyzed monocoupling reactions occur selectively at the 2-position in 2,3-, 2,5- and 2,6-dichloropyridines and hence unsymmetrical dialkylpyridines are readily available (equation 146).[130]

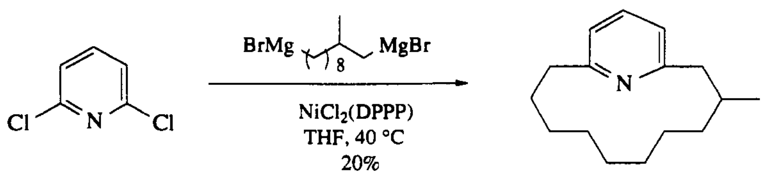
Cl
N
Cl
BrMg
8
MgBr
NiCl2(DPPP)
THF, 40 °C
20%
N

(145)

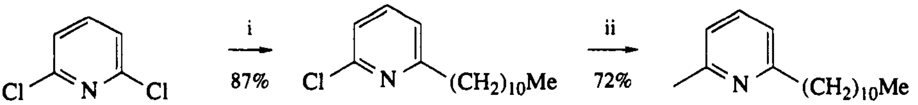
Cl
N
Cl
i
87%
Cl
N
(CH2)10Me
ii
72%
N
(CH2)10Me

(146)

i, $Me(CH_2)_{10}MgBr$, $PdCl_2(DPPB)$, $Et_2O$, reflux; ii, MeMgI, $NiCl_2(DPPP)$, $Et_2O$, reflux

2-Chloro- and 3-bromo-quinolines and 2- and 4-chloroisoquinolines undergo Ni-catalyzed coupling with primary alkyl, allyl and cyclohexyl Grignard reagents; selective monoalkylation in 4,5-dichloroisoquinoline may be noted (equations 147–150).[137,144]

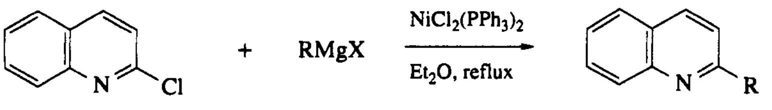
N
Cl
+
RMgX
NiCl2(PPh3)2
Et2O, reflux
N
R

(147)

$R = CH_2{=}CHCH_2$ 54%
$R = c\text{-}C_6H_{11}$ 90%

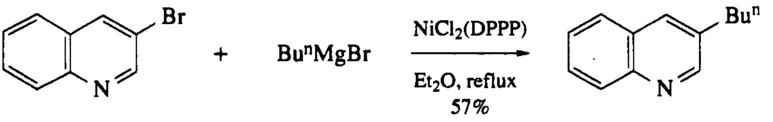
Br
N
+
BunMgBr
NiCl2(DPPP)
Et2O, reflux
57%
Bun
N

(148)

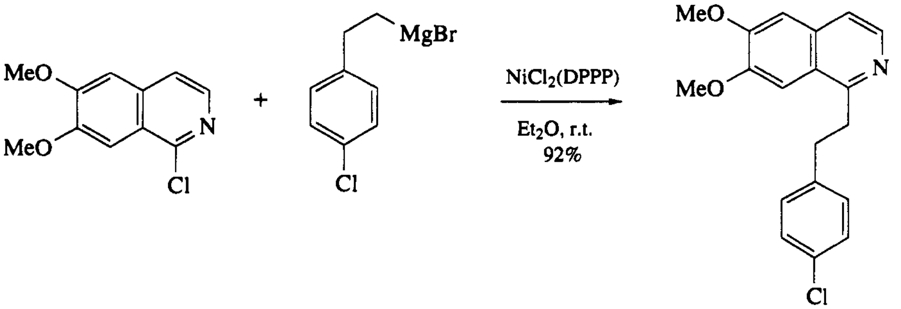
MeO
MeO
N
Cl
+
MgBr
Cl
NiCl2(DPPP)
Et2O, r.t.
92%
MeO
MeO
N
Cl

(149)

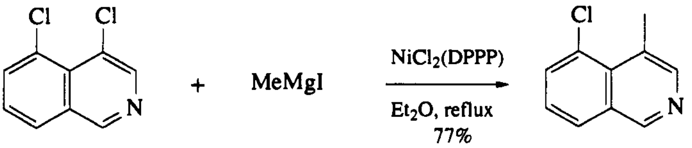
Cl
Cl
N
+
MeMgI
NiCl2(DPPP)
Et2O, reflux
77%
Cl
N

(150)

### 2.2.8.3 Heteroaromatic Compounds containing more than Two Heteroatoms

2-Chloro-[145] and 2-methylthio-benzothiazoles[136] undergo Ni-catalyzed coupling with alkyl Grignard reagents and the isopropyl group may also be introduced with ease (equations 151 and 152). 2-Methylthiobenzoimidazole is inert under similar conditions.[136] 2-Chloropyridazines,[146] 2-chloro-, 4-chloro-, 2,4-dichloro-, 4,6-dichloro- and 2,4,6-trichloro-pyrimidines[147] and 2-methylthiopyrimidines[136] are readily alkylated by primary alkyl Grignard reagents (equations 153–155). The Reformatsky reagent and homologs couple with 2- and 4-halopyrimidines in the presence of Pd complexes (equation 156).[143,148] Lower reactivities of halogens β to nitrogen are noted in all of these cases.

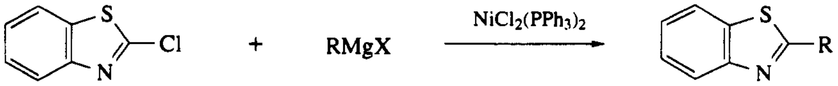
S
N
Cl
+
RMgX
NiCl2(PPh3)2
S
N
R

(151)

R = Me, Et, $Pr^i$, $Bu^n$; 50–95%

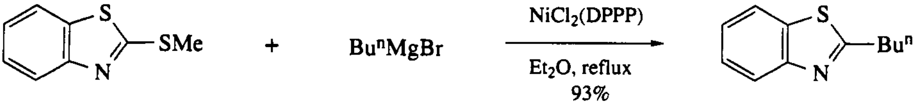
SMe
+
Bu^nMgBr
NiCl2(DPPP)
Et2O, reflux
93%
Bu^n

(152)

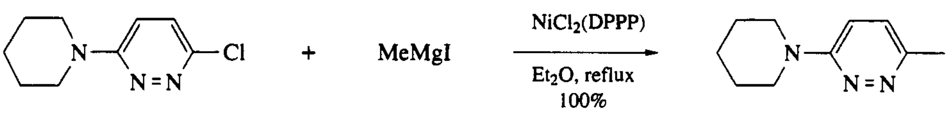
N
N=N
Cl
+
MeMgI
NiCl2(DPPP)
Et2O, reflux
100%
N
N=N

(153)

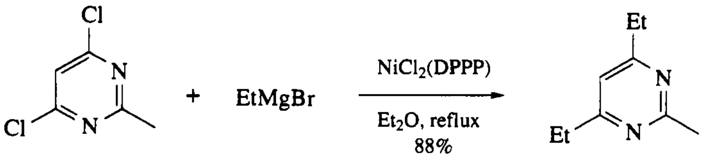
Cl
N
Cl
N
+
EtMgBr
NiCl2(DPPP)
Et2O, reflux
88%
Et
N
Et
N

(154)

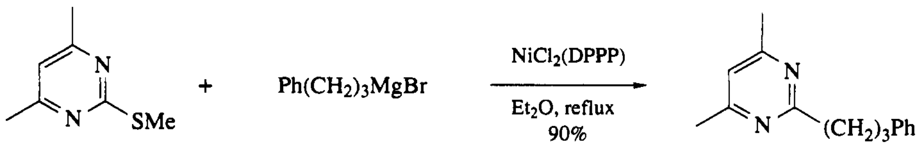
N
N
SMe
+
Ph(CH2)3MgBr
NiCl2(DPPP)
Et2O, reflux
90%
N
N
(CH2)3Ph

(155)

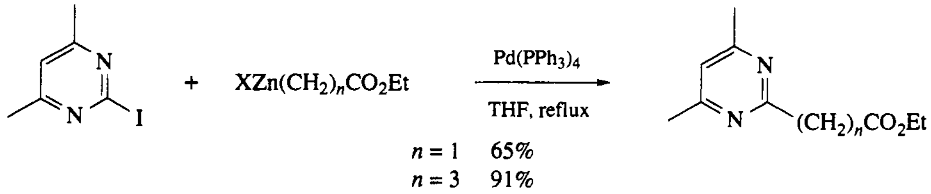
N
N
I
+
XZn(CH2)nCO2Et
Pd(PPh3)4
THF, reflux
n = 1 65%
n = 3 91%
N
N
(CH2)nCO2Et

(156)

6-Chloro-[149] and 6-methylthio-purine[150] derivatives undergo Ni-catalyzed coupling reactions with primary alkyl Grignard reagents; the reactions have been applied to the synthesis of 6-alkylpurine nucleosides (equation 157). Similarly, 8-alkyl- and 8-allyl-adenosine derivatives are obtained by Pd-catalyzed Grignard coupling reactions of 8-bromoadenosines (equation 158).[151,152]

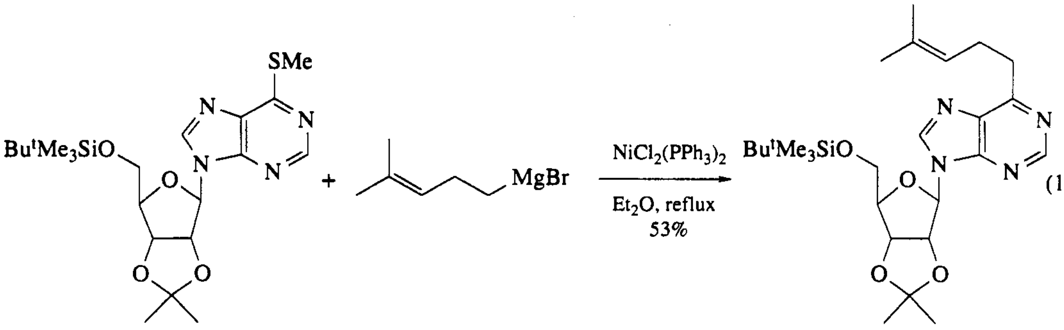
SMe
Bu^tMe3SiO
N
N
N
N
O
O
O
+
MgBr
NiCl2(PPh3)2
Et2O, reflux
53%
Bu^tMe3SiO
N
N
N
N
O
O
O

(157)

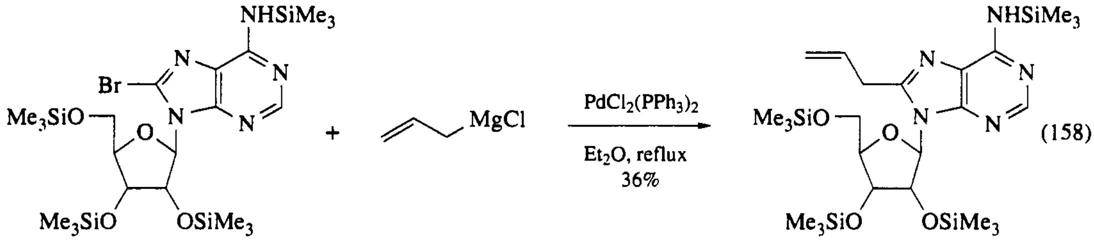
NHSiMe3
Br
N
N
N
N
Me3SiO
O
Me3SiO
OSiMe3
+
MgCl
PdCl2(PPh3)2
Et2O, reflux
36%
NHSiMe3
N
N
N
N
Me3SiO
O
Me3SiO
OSiMe3

(158)

## 2.2.9 COUPLING OF C(*sp*$^3$)-ORGANOMETALLICS WITH ACYL CHLORIDES AND RELATED COMPOUNDS

This section describes ketone synthesis by transition metal catalyzed cross-coupling of alkyl metal reagents with acyl chlorides and related compounds. Carboxylic acids react with excess amounts of alkyl Grignard reagents in the presence of a Ni catalyst to form unsymmetrical ketones (equation 159).[153] Acyl chlorides readily couple with primary alkyl Grignard reagents in the presence of Fe(acac)$_3$ as catalyst even in the presence of functional groups, such as ester and cyano groups, susceptible to Grignard reagents (equation 160).[154,155] Acyl chlorides also undergo Pd-catalyzed coupling with primary and secondary alkylzinc reagents (equations 161 and 162),[156,157] with the Reformatsky reagents (equation 163)[158] and homologs (equation 164),[157,159] with alkyltins (equation 165)[160–162] and with dialkylmercurials;[163] coupling of allyl- and benzyl-tins with acyl chloride is also catalyzed by a Rh complex (equation 166).[164] Acyl chlorides and acid anhydrides also couple with tetraalkylaluminates in the presence of CuCl (equation 167).[165] While chloroformates undergo Pd-catalyzed coupling with alkylzinc reagents to form esters,[156] a chlorothioformate (carbonochloridothioate) is transformed into unsymmetrical ketones by a stepwise Grignard coupling; the first step is catalyzed by Ni and the second step by Fe complexes, secondary alkyl Grignard reagents being applicable in the second step (equation 168).[166] Finally, an imidoyl chloride couples with primary alkyl Grignard reagents in the presence of PdCl$_2$(DPPF) (equation 169).[167]

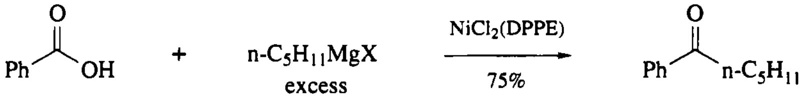
O
Ph
OH
+
n-C5H11MgX
excess
NiCl2(DPPE)
75%
O
Ph
n-C5H11

(159)

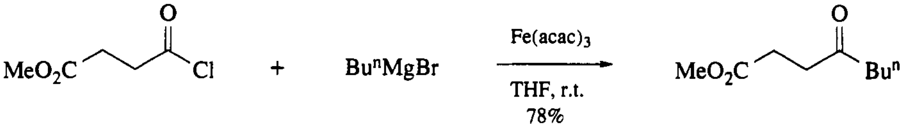
O
MeO2C
Cl
+
BunMgBr
Fe(acac)3
THF, r.t.
78%
O
MeO2C
Bun

(160)

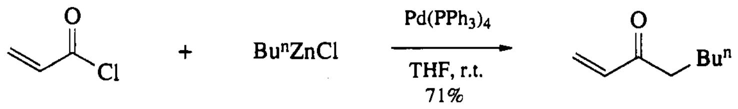
O
Cl
+
BunZnCl
Pd(PPh3)4
THF, r.t.
71%
O
Bun

(161)

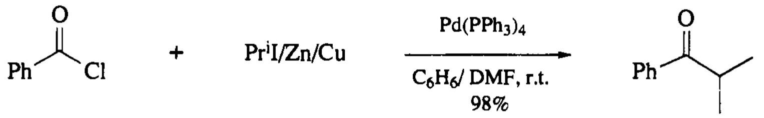
O
Ph
Cl
+
PriI/Zn/Cu
Pd(PPh3)4
C6H6/ DMF, r.t.
98%
O
Ph

(162)

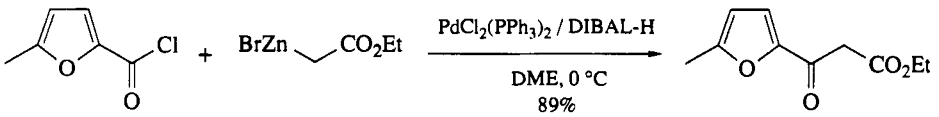
O
Cl
O
+
BrZn
CO2Et
PdCl2(PPh3)2 / DIBAL-H
DME, 0 °C
89%
O
O
CO2Et

(163)

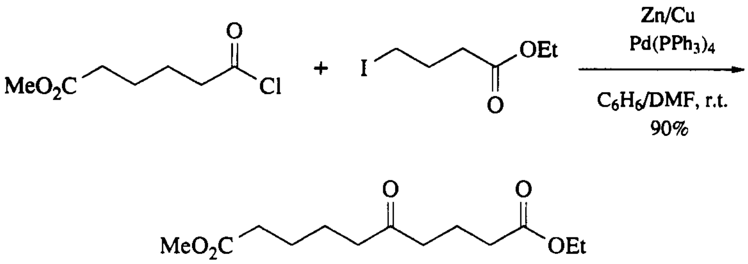
O
MeO2C
Cl
+
I
OEt
O
Zn/Cu
Pd(PPh3)4
C6H6/DMF, r.t.
90%
O
O
MeO2C
OEt

(164)

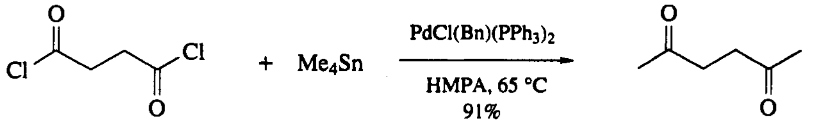

(165)

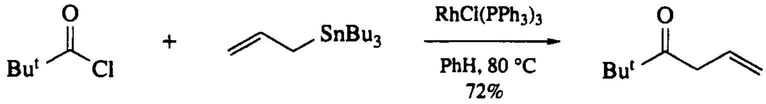

(166)

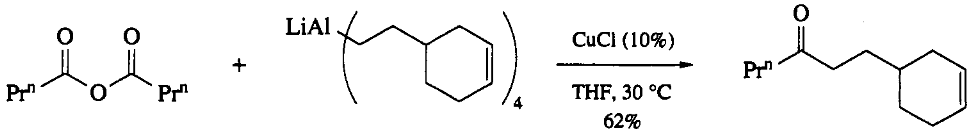

(167)

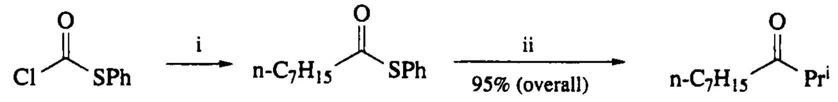

(168)

i, n-$C_7H_{15}$MgBr, NiCl$_2$(DPPE), THF, r.t.; ii, Pr$^i$MgCl, Fe(acac)$_3$, THF, 0 °C

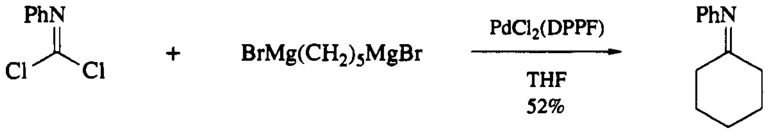

(169)

## 2.2.10 COUPLING OF C($sp^2$)-ORGANOMETALLICS WITH C($sp^3$) HALIDES AND RELATED COMPOUNDS

Coupling reactions between C($sp^2$)-organometallics, mostly Grignard reagents, and C($sp^3$) halides and related compounds are usually achieved with Cu catalysts. Primary alkyl halides react smoothly, secondary alkyls are applicable in only a few cases, and no successful coupling has been reported for tertiary alkyl halides. Allylic halides and related compounds are treated separately, since there are important regiochemical problems.

### 2.2.10.1 Coupling between C($sp^2$)-Organometallics and Primary Alkyl Halides

Primary alkyl bromides and iodides and benzyl chlorides smoothly couple with aryl Grignard reagents in the presence of $Li_2CuCl_4$[168] or CuCl together with TMEDA (equation 170).[169] Cross-coupling of aryl Grignard reagents with primary alkyl iodides are also reported to be catalyzed by PdCl$_2$(DPPF).[170] In the presence of NiCl$_2$(DPPP), 3-butenyl bromide couples with the phenyl Grignard reagent to form mainly 3-phenyl-1-butene *via* primary to secondary isomerization (equation 171).[171] Bromohydrin undergoes Cu-catalyzed coupling with aryl Grignard reagents to give arylethanols (equation 172).[172] $\alpha,\omega$-Dibromoalkanes afford monoarylation products selectively with aryl Grignard reagents in the presence of $Li_2CuCl_4$ (equation 173),[173] while double coupling is also possible.[174,175]

Vinyl, 1-alkenyl and 2-alkenyl Grignard reagents couple with alkyl bromides or iodides in the presence of CuI[34,176,177] or AgNO$_3$;[24] the configuration of the alkenyl Grignard reagent is essentially

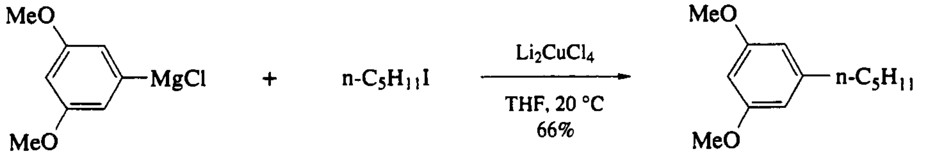

(170)

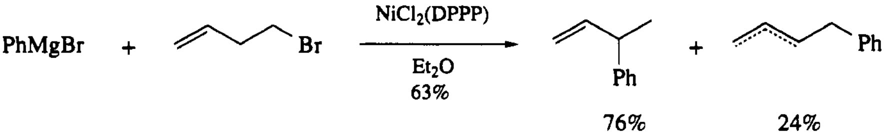
PhMgBr
+
Br
NiCl$_2$(DPPP)
Et$_2$O
63%
Ph
76%
+
Ph
24%

(171)

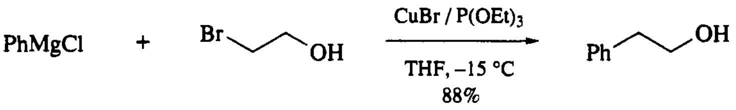
PhMgCl
+
Br
OH
CuBr / P(OEt)$_3$
THF, −15 °C
88%
Ph
OH

(172)

$$\mathrm{PhMgBr} + \mathrm{Br(CH_2)_5Br} \xrightarrow[\text{THF, 10 °C; 77\%}]{\mathrm{Li_2CuCl_4}} \mathrm{Ph(CH_2)_5Br} \qquad (173)$$

retained (equations 174–177). Alkenylboranes couple with benzyl bromides in the presence of Pd(PPh$_3$)$_4$ and NaOH also with retention of configuration (equation 178).[178] The 2-butadienyl Grignard reagent undergoes Cu-catalyzed couplings with alkyl bromides and iodides even in the presence of functional groups such as ester and cyano groups (equation 179); it may be noted that aromatic iodides are inert under these conditions (equation 180).[179]

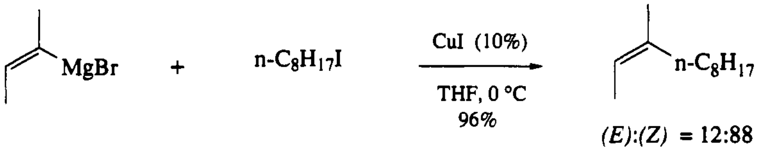
MgBr
+
n-C$_8$H$_{17}$I
CuI (10%)
THF, 0 °C
96%
n-C$_8$H$_{17}$
(E):(Z) = 12:88

(174)

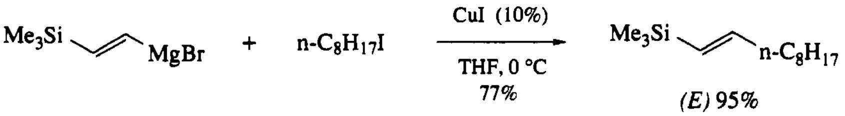
Me$_3$Si
MgBr
+
n-C$_8$H$_{17}$I
CuI (10%)
THF, 0 °C
77%
Me$_3$Si
n-C$_8$H$_{17}$
(E) 95%

(175)

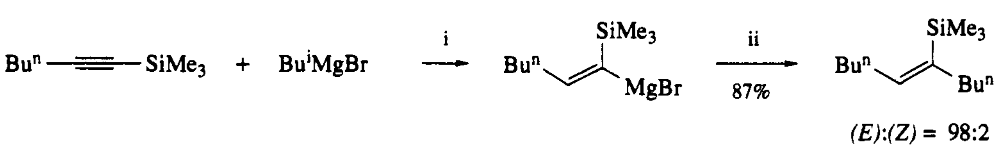
Bu$^n$
SiMe$_3$
+
Bu$^i$MgBr
i
Bu$^n$
SiMe$_3$
MgBr
ii
87%
Bu$^n$
SiMe$_3$
Bu$^n$
(E):(Z) = 98:2

(176)

i, Cp$_2$TiCl$_2$; ii, Bu$^n$I, CuI (10%), THF, 0 °C

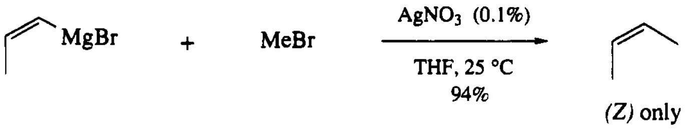
MgBr
+
MeBr
AgNO$_3$ (0.1%)
THF, 25 °C
94%
(Z) only

(177)

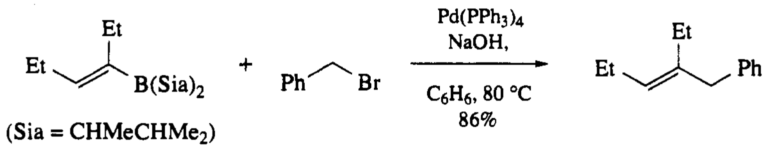
Et
Et
B(Sia)$_2$
(Sia = CHMeCHMe$_2$)
+
Ph
Br
Pd(PPh$_3$)$_4$
NaOH,
C$_6$H$_6$, 80 °C
86%
Et
Et
Ph

(178)

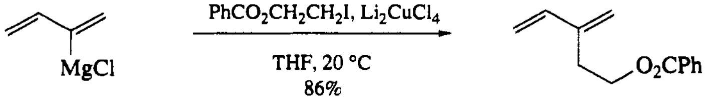
MgCl
PhCO$_2$CH$_2$CH$_2$I, Li$_2$CuCl$_4$
THF, 20 °C
86%
O$_2$CPh

(179)

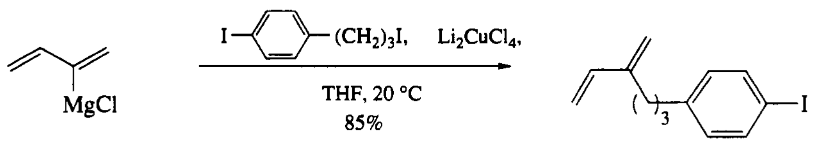
MgCl
I
(CH2)3I, Li2CuCl4,
THF, 20 °C
85%
3
I

(180)

Arylzinc reagents couple with ethyl bromoacetate[180] and with bromoacetonitrile[181] in the presence of Ni complexes (equation 181).

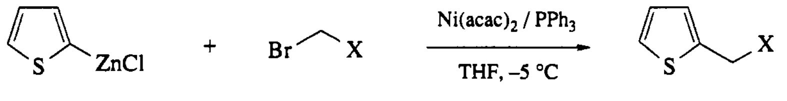
S
ZnCl
+
Br
X
Ni(acac)2 / PPh3
THF, -5 °C
S
X

(181)

X = $CO_2Et$ 60%
X = CN 46%

### 2.2.10.2 Coupling between C($sp^2$)-Organometallics and Secondary Alkyl Halides

Coupling reactions between vinyl Grignard reagents and 2-oxy secondary alkyl bromides are reported to be catalyzed by Cu[182] or Fe salt (equations 182 and 183).[183]

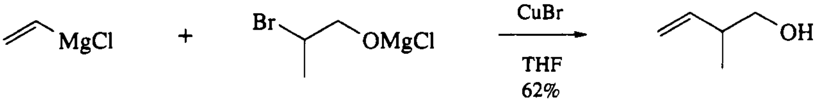
MgCl
+
Br
OMgCl
CuBr
THF
62%
OH

(182)

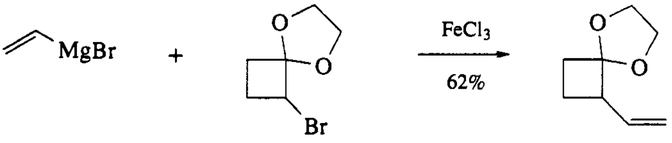
MgBr
+
O
O
Br
FeCl3
62%
O
O

(183)

### 2.2.10.3 Coupling between C($sp^2$)-Organometallics and C($sp^3$)-Oxygen Compounds

Primary alkyl tosylates are more reactive than halides in the Cu-catalyzed coupling with Grignard reagents.[184] Aryl,[184] alkenyl,[176] silylalkenyl[34] and 2-butadienyl[185] Grignard reagents have been used successfully for the coupling in the presence of CuI or $Li_2CuCl_4$; the coupling of optically active tosylates[186] and ditosylates[187] having chiral center(s) at the 2-position may also be noted (equations 184–186).

Ring opening of epoxides with Grignard reagents is greatly promoted by Cu catalysts;[188] terminal epoxides and epoxycyclohexane are readily cleaved by aryl,[188,189] and alkenyl[188,190,191] Grignard reagents (equations 187–189) Oxetane also undergoes similar Cu-catalyzed coupling with phenyllithium[192] and phenyl Grignard reagent (equation 190).[188] β-Propiolactone reacts with the phenyl Grignard reagent in the presence of CuBr to form β-phenylpropionic acid *via* cleavage of the C($sp^3$)—O bond (equation 191).[193]

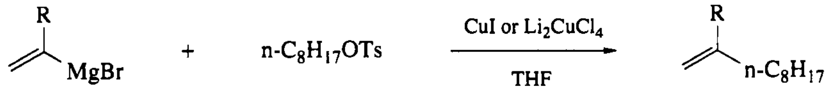
R
MgBr
+
n-C8H17OTs
CuI or Li2CuCl4
THF
R
n-C8H17

(184)

R = Me 80%
R = $SiMe_3$ 83%
R = $CH_2$=CH 55%

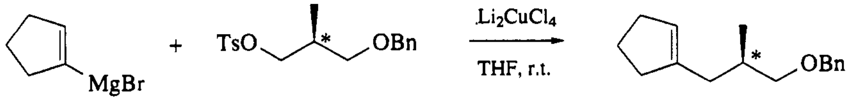
MgBr
+
TsO
*
OBn
Li2CuCl4
THF, r.t.
*
OBn

(185)

90–95%

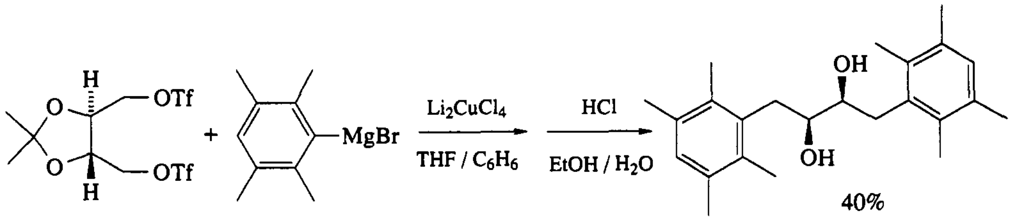
H
O
OTf
O
OTf
H
+
MgBr
Li$_2$CuCl$_4$
THF / C$_6$H$_6$
HCl
EtOH / H$_2$O
OH
OH
40%

(186)

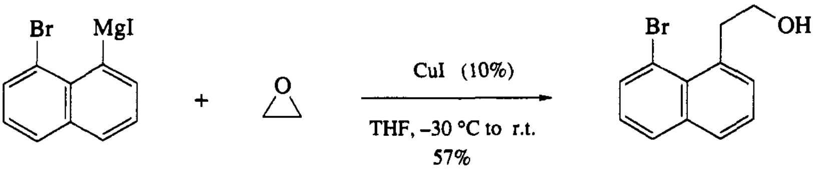
Br
MgI
+
O
CuI (10%)
THF, -30 °C to r.t.
57%
Br
OH

(187)

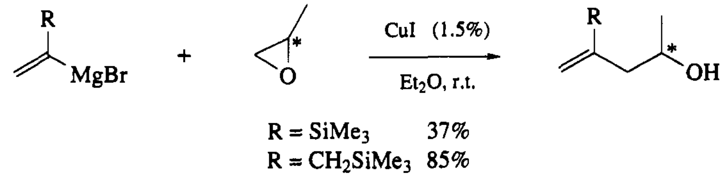
R
MgBr
+
O
*
CuI (1.5%)
Et$_2$O, r.t.
R
*
OH
R = SiMe$_3$ 37%
R = CH$_2$SiMe$_3$ 85%

(188)

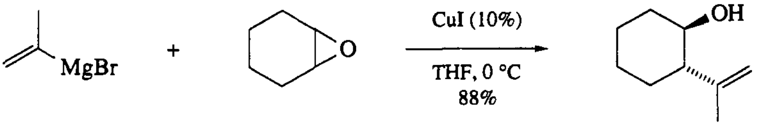
MgBr
+
O
CuI (10%)
THF, 0 °C
88%
OH

(189)

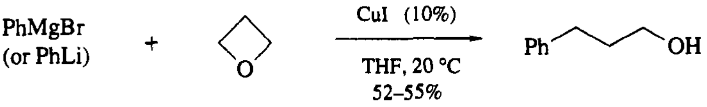
PhMgBr
(or PhLi)
+
O
CuI (10%)
THF, 20 °C
52-55%
Ph
OH

(190)

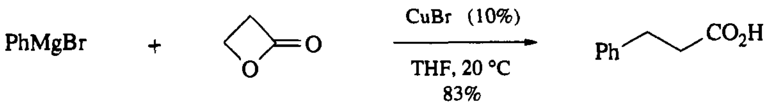
PhMgBr
+
O
O
CuBr (10%)
THF, 20 °C
83%
Ph
CO$_2$H

(191)

### 2.2.10.4 Coupling of C($sp^2$)-Organometallics with Allylic Halides and Related Compounds

The most fundamental and important problem in coupling of allylic compounds with organometallic reagents is the regio- and stereo-control, as shown by the following general scheme (equation 192).[194]

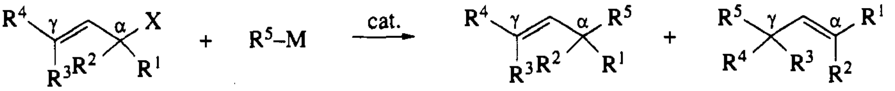
R$^4$
γ
α
X
R$^3$
R$^2$
R$^1$
+
R$^5$–M
cat.
R$^4$
γ
α
R$^5$
R$^3$
R$^2$
R$^1$
+
R$^5$
γ
α
R$^1$
R$^4$
R$^3$
R$^2$

(192)

Allylic halides, alcohols, ethers, acetates, lactones, phosphates, epoxides, sulfides, sulfonium salts, selenides and ammonium salts undergo transition metal catalyzed coupling reactions with C($sp^2$)—Li, —Mg, —B, —Al, —Sn, —Zr, —Cd and —Hg reagents. Table 1 summarizes the allylic leaving groups, alkenyl and aryl metallic reagents, catalytically active metals and references and Table 2 the regio- and stereo-chemical aspects.

**Table 1** Coupling of C($sp^2$)-Organometallics with Allylic Halides and Related Compounds

| *Allylic leaving group* | *C($sp^2$)-metallics*[a] | *Catalyst metal* | *Ref.* |
|---|---|---|---|
| Cl, Br | 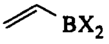 | Pd<br>Cu | 178, 195, 205<br>196, 197 |
| Cl, Br | 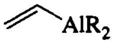 | Pd | 198–200 |
| Cl, Br | 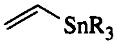 | Pd | 201 |
| Cl, Br | 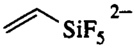 | Pd | 203 |
| Cl, Br | 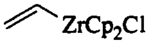 | Pd | 202 |
| Cl, Br | 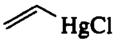 | Pd | 204 |
| Cl, Br | ArMgX | Ni, Pd | 219 |
| Cl, Br | $ArSnR_3$ | Pd | 201, 208 |
| Cl, Br | ArHgCl | Pd | 218, 220 |
| Cl, Br | $RCOSnR_3$ | Pd | 216 |
| OH | ArMgX | Ni | 80, 221 |
| OR | 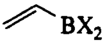 | Pd | 206 |
| OR | ArMgX | Ni | 80, 221 |
| $OSiR_3$ | ArMgX | Ni, Pd | 219 |
| OCOR | 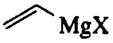 | Cu | 212, 213 |
| OCOR | 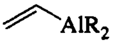 | Pd | 199, 210 |
| OCOR | 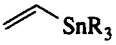 | Pd | 211, 215 |
| OCOR | ArMgX | Cu | 209, 212, 213 |
| OCOR | ArZnX | Pd | 199, 210 |
| OCOR | ArCdX | Pd | 199 |
| OCOR | $ArAlR_2$ | Pd | 199 |
| OCOR | $ArSnR_3$ | Pd | 215 |
| $OCO_2Me$ | 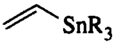 | Pd | 199 |
| $OP(O)(OR)_2$ | 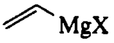 | Cu | 223 |
| $OP(O)(OR)_2$ | 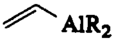 | Pd | 215 |
| $OP(O)(OR)_2$ | ArMgX | Cu | 223 |
| $OP(O)(OR)_2$ | $ArSnR_3$ | Pd | 215 |
| Epoxide | 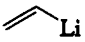 | Cu | 214 |
| Epoxide | 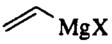 | Cu | 214 |
| Epoxide | 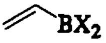 | Pd | 207 |
| Epoxide | $ArSnR_3$ | Pd | 211 |
| SH | ArMgX | Ni | 80 |
| SR | ArMgX | Ni | 224 |
| $SR_2^+ X^-$ | 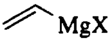 | Cu | 225 |
| $SR_2^+ X^-$ | ArMgX | Cu | 225 |
| SeR | ArMgX | Ni | 79 |
| $NR_3^+ X^-$ | 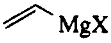 | Cu | 226 |
| $NR_3^+ X^-$ | ArMgX | Cu | 226 |

**Table 2** Regioselectivity in Coupling of C($sp^2$)-metallics with Allylic Halides and Related Compounds

| *Allyl–X* | *C($sp^2$)–M* | *Catalyst* | *Ref.* |
|---|---|---|---|
| *Alkenylmetallics* | | | |
| 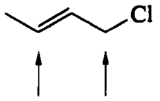 | | | |
| 25 75 | Sn | $Pd(DBA)_2/PPh_3$ | 216 |
| 90 10 | Zr | $[PdCl(C_3H_5)]_2/PPh_3$ | 202 |
| 8 92 | Zr | $[PdCl(C_3H_5)]_2/MA^a$ | 202 |
| 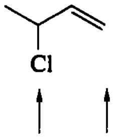 | | | |
| 0 100 | Si | $Pd(OAc)_2$ | 203 |
| 25 75 | Sn | $Pd(DBA)_2/PPh_3$ | 216 |
| 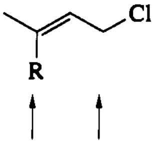 | | | |
| 0 100 | Al | $Pd(PPh_3)_4$ | 198–200 |
| 0 100 | Sn | $PdCl_2(MeCN)_2/PPh_3$ | 201 |
| 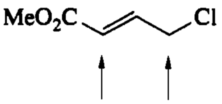 | | | |
| 0 100 | Sn | $PdCl_2(MeCN)_2/PPh_3$ | 201 |
| 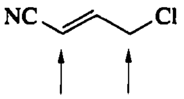 | | | |
| 0 100 | Sn | $PdCl_2(MeCN)_2/PPh_3$ | 201 |
| 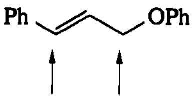 | | | |
| 0 100 | [B] | $Pd(PPh_3)_4$ | 206 |
| 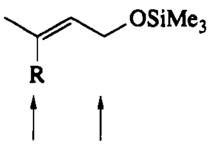 | | | |
| 0 100 | [Al] | $Pd(PPh_3)_4$ | 199 |
| 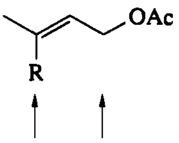 | | | |
| 0 100 | [Al] | $Pd(PPh_3)_4$ | 199 |

**Table 2** *(continued)*

| *Allyl–X* | *C(sp$^2$)–M* | *Catalyst* | *Ref.* |
|---|---|---|---|
| 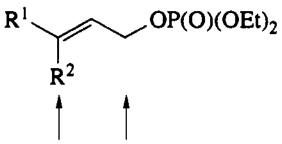 | | | |
| 0 100 | [Mg] | CuBr | 223 |
| 0 100 | [Al] | Pd(PPh$_3$)$_4$ | 199 |
| 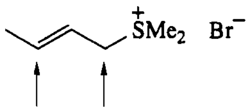 | | | |
| 35 65 | [Mg] | CuBr | 225 |
| 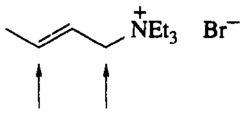 | | | |
| 0 100 | [Mg] | CuBr | 226 |
| 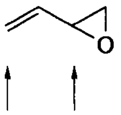 | | | |
| 26 74 | B | Pd(DBA)$_2$ | 207 |
| 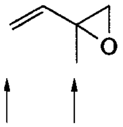 | | | |
| 100 0 | Li | CuBr | 214 |
| 100 0 | Mg | CuBr | 214 |
| 100 0 | Sn | PdCl$_2$(MeCN)$_2$ | 211 |
| 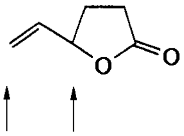 | | | |
| 100 0 | Mg | CuI | 213 |
| *Arylmetallics* | | | |
| 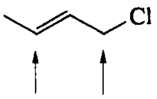 | | | |
| 75 25 | Mg | NiCl$_2$(DPPF) | 219 |
| 18 82 | Mg | PdCl$_2$(DPPF) | 219 |

**Table 2** *(continued)*

| *Allyl–X* | *C(sp$^2$)–M* | *Catalyst* | *Ref.* |
|---|---|---|---|
| 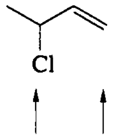 | | | |
| 0 100 | Sn | Pd(DBA)$_2$/PPh$_3$ | 201 |
| 0 100 | Hg | LiPdCl$_3$ | 220 |
| 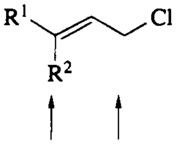 | | | |
| 0 100 | Sn | Pd(DBA)$_2$/PPh$_3$ | 201, 208 |
| 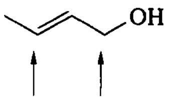 | | | |
| 34 66<br>(*E*) > 99% | Mg | NiCl$_2$(PPh$_3$)$_2$ | 221 |
| 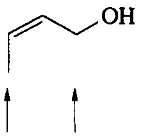 | | | |
| 41 59<br>(*E*) = 84% | Mg | NiCl$_2$(PPh$_3$)$_2$ | 221 |
| 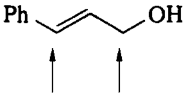 | | | |
| 0 100 | Mg | NiCl$_2$(PPh$_3$)$_2$ | 80 |
| 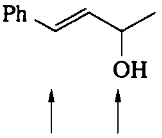 | | | |
| 0 100 | Mg | NiCl$_2$(PPh$_3$)$_2$ | 221 |
| 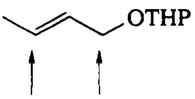 | | | |
| 81 19 | Mg | NiCl$_2$(DPPF) | 219 |
| 11 89 | Mg | PdCl$_2$(DPPF) | 219 |
| 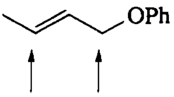 | | | |
| 86 14 | Mg | NiCl$_2$(DPPF) | 219 |
| 10 90 | Mg | PdCl$_2$(DPPF) | 219 |

**Table 2** *(continued)*

| *Allyl–X* | *C(sp$^2$)–M* | *Catalyst* | *Ref.* |
|---|---|---|---|
| 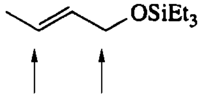 | | | |
| 88 12 | Mg | $NiCl_2(DPPF)$ | 219 |
| 33 67 | Mg | $NiCl_2(PPh_3)_2$ | 219 |
| 4 96 | Mg | $PdCl_2(DPPF)$ | 219 |
| 10 90 | Mg | $Pd(PPh_3)_4$ | 219 |
| 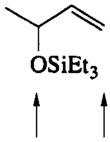 | | | |
| 81 19 | Mg | $NiCl_2(DPPF)$ | 219 |
| 9 91 | Mg | $PdCl_2(DPPF)$ | 219 |
| 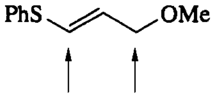 | | | |
| 0 100 | Mg | $NiCl_2(PPh_3)_2$ | 222 |
| 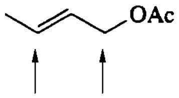 | | | |
| 52 48 | [Mg] | $Pd(PPh_3)_4$ | 199 |
| 23 77 | [Zn] | $Pd(PPh_3)_4$ | 199 |
| 23 77 | [Cd] | $Pd(PPh_3)_4$ | 199 |
| 38 62 | [Al] | $Pd(PPh_3)_4$ | 199 |
| 54 46 | [Zr] | $Pd(PPh_3)_4$ | 199 |
| 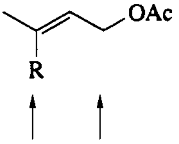 | | | |
| 0 100 | [Mg] | $Li_2CuCl_4$ | 209 |
| 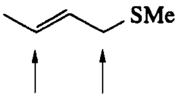 | | | |
| 32 68 | [Mg] | $NiCl_2(PPh_3)_2$ | 224 |
| 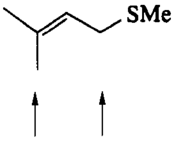 | | | |
| 36 64 | [Mg] | $NiCl_2(PPh_3)_2$ | 224 |

**Table 2** *(continued)*

| *Allyl–X* | *C(sp$^2$)–M* | *Catalyst* | *Ref.* |
|---|---|---|---|
| 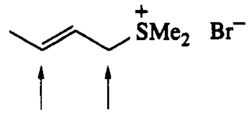<br>5 95 | [Mg] | CuBr | 225 |
| 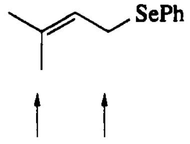<br>39 61 | [Mg] | $NiCl_2(PPh_3)_2$ | 79 |
| 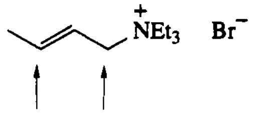<br>11 89 | [Mg] | CuBr | 226 |
| 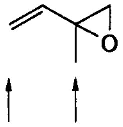<br>98 2 | [Sn] | $PdCl_2(MeCN)_2$ | 211 |
| 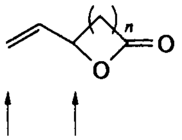<br>100 0 | (n = 1, 2 or 3)<br>[Mg] | CuI | 214, 215 |
| 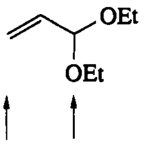<br>100 0<br>(*E*/*Z* = 42/58) | [Mg] | CuBr | 217 |

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[a] MA = maleic anhydride.

Some other characteristic features, in focus on the stereochemical aspects, are described hereafter. Allylic chlorides and bromides couple with alkenyl–$BR_2$,[178,195–197] –$AlR_2$,[198–200] –$SnR_3$,[201] –$ZrCp_2Cl$,[202] –$SiF_5^{2-}$,[203] and –$HgCl$[204] compounds in the presence of Pd or Cu catalysts to form 1,4-dienes with retention of stereochemistry of alkenylmetals (equations 193–200); in the Si and Hg cases, only allylic chlorides having a terminal alkene react with the complete allylic transposition. An intramolecular coupling of alkenylborane has been applied to the synthesis of humulene (equation 201).[205] In the Pd-catalyzed coupling of alkenyl–Al reagents the reactivity of allylic substrates depends on the leaving group in the order Cl, OAc > $OAlMe_2$ > $OP(O)(OEt)_2$ >> $OSiR_3$.[199] In contrast, the reverse order OPh >> OAc, Cl is found in the Pd-catalyzed coupling of alkenyl–B reagents, the alkene geometry being retained (equation 202); the reaction condition may be compared with that in the reaction occurring in equation (193), where the hydroxide ion is needed as the essential additive.[206] The stereochemistry of alkenyl–B reagents is retained also in the Pd-catalyzed coupling with epoxides.[207]

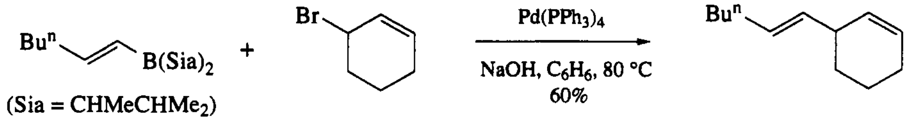
Bu^n
B(Sia)2
(Sia = CHMeCHMe2)
+
Br
Pd(PPh3)4
NaOH, C6H6, 80 °C
60%
Bu^n

(193)

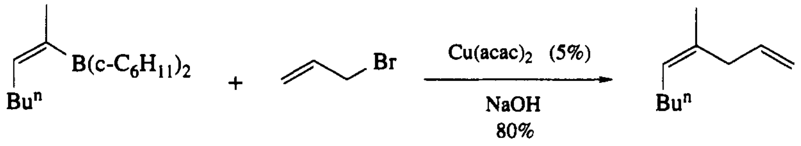
B(c-C6H11)2
Bu^n
+
Br
Cu(acac)2 (5%)
NaOH
80%
Bu^n

(194)

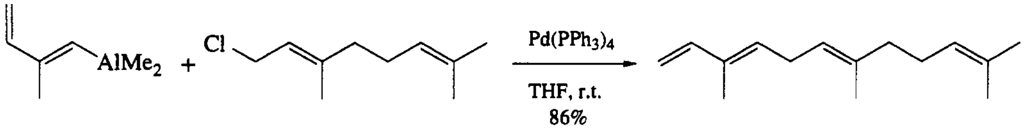
AlMe2
+
Cl
Pd(PPh3)4
THF, r.t.
86%

(195)

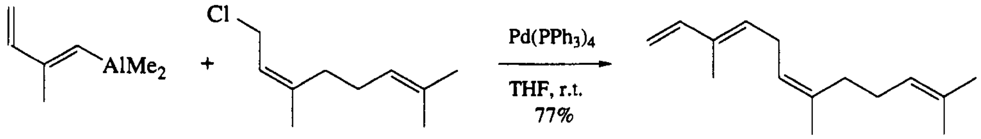
AlMe2
+
Cl
Pd(PPh3)4
THF, r.t.
77%

(196)

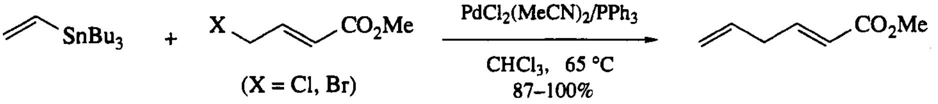
SnBu3
+
X
CO2Me
(X = Cl, Br)
PdCl2(MeCN)2/PPh3
CHCl3, 65 °C
87–100%
CO2Me

(197)

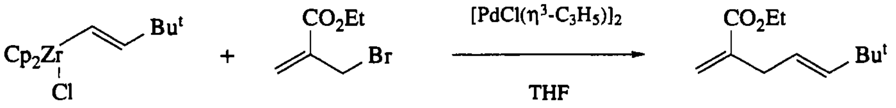
Bu^t
Cp2Zr
Cl
+
CO2Et
Br
[PdCl(η3-C3H5)]2
THF
CO2Et
Bu^t

(198)

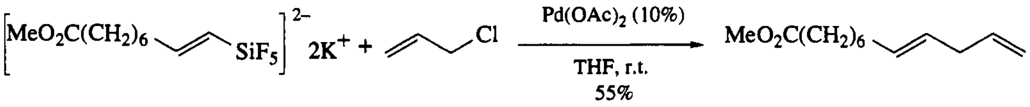
MeO2C(CH2)6
SiF5
2−
2K+ +
Cl
Pd(OAc)2 (10%)
THF, r.t.
55%
MeO2C(CH2)6

(199)

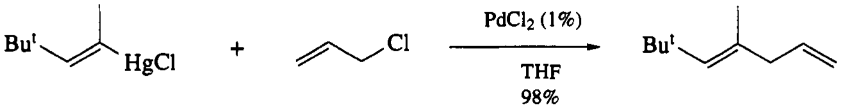
Bu^t
HgCl
+
Cl
PdCl2 (1%)
THF
98%
Bu^t

(200)

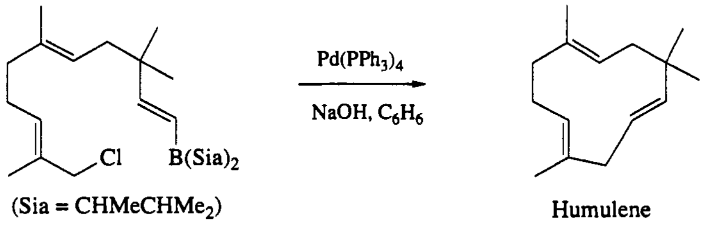
Cl
B(Sia)2
(Sia = CHMeCHMe2)
Pd(PPh3)4
NaOH, C6H6
Humulene

(201)

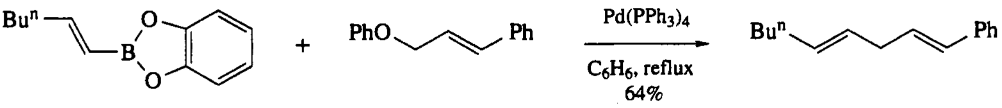
Bu^n
O
B
O
+
PhO
Ph
Pd(PPh3)4
C6H6, reflux
64%
Bu^n
Ph

(202)

Remarkably, alkene stereochemistry in allylic chlorides is completely retained in the Pd-catalyzed coupling with alkenyl–Al (equations 195 and 196)[200] and aryl–Sn reagents (equation 203),[201] whereas stereochemical scrambling is also encountered in some cases (equation 204).[208] Retention of alkene stereochemistry is also observed in the Cu-catalyzed Grignard coupling of allylic acetates (equation 205).[209]

The Pd-catalyzed coupling reactions of cyclic allyl chlorides,[201] carboxylates[210] and epoxides[211] with alkenyl–Al, alkenyl–Sn and aryl–Sn reagents proceed with inversion of configuration of the allylic *sp*$^3$ carbon centers (equations 206–208).

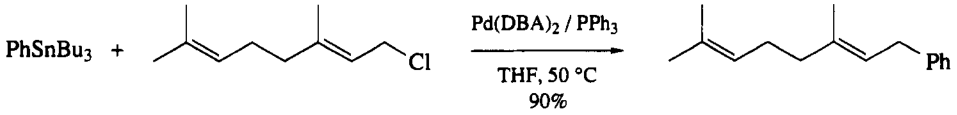
PhSnBu3 +
Cl
Pd(DBA)2 / PPh3
THF, 50 °C
90%
Ph

(203)

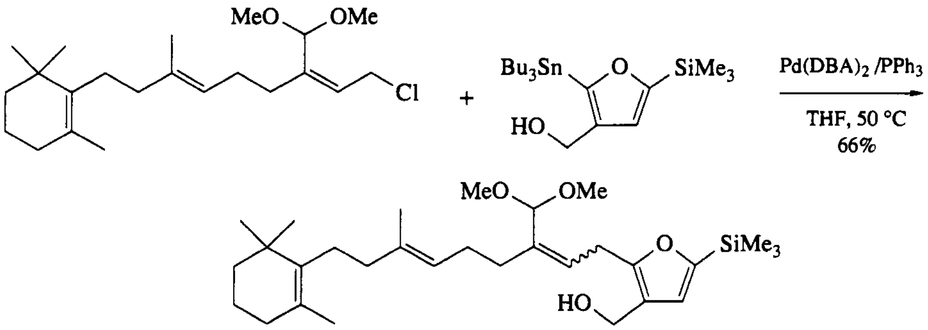
MeO
OMe
Cl
+
Bu3Sn
O
SiMe3
HO
Pd(DBA)2 /PPh3
THF, 50 °C
66%
MeO
OMe
O
SiMe3
HO

(204)

*(E)*:*(Z)* = 1:1

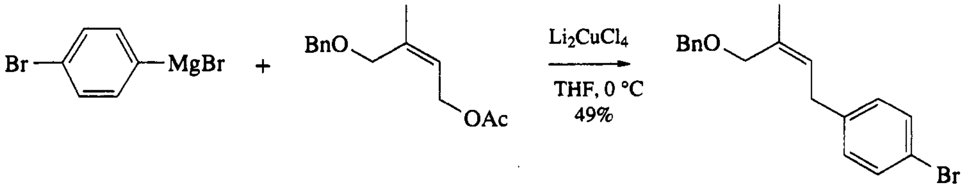
Br
MgBr
+
BnO
OAc
Li2CuCl4
THF, 0 °C
49%
BnO
Br

(205)

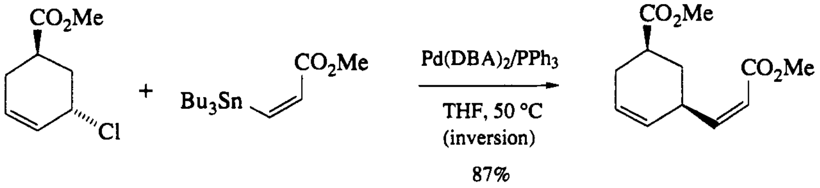
CO2Me
Cl
+
Bu3Sn
CO2Me
Pd(DBA)2/PPh3
THF, 50 °C
(inversion)
87%
CO2Me
CO2Me

(206)

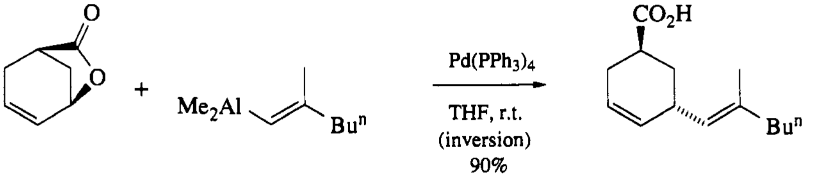
O
O
+
Me2Al
Bun
Pd(PPh3)4
THF, r.t.
(inversion)
90%
CO2H
Bun

(207)

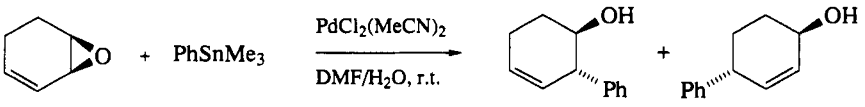
O
+ PhSnMe3
PdCl2(MeCN)2
DMF/H2O, r.t.
OH
Ph
+
OH
Ph

(208)

Some other synthetically interesting reactions are listed below. Thus, vinyl lactones undergo ring-opening and coupling with Grignard reagents in the presence of CuI to form β,γ-, γ,δ- or δ,ε-unsaturated carboxylic acids (equation 209),[212,213] and isoprene monoepoxide couples with alkenyl–Grignard reagents[214] or alkenyl–Sn reagents[211] to form terpenoid allylic alcohols (equation 210). Pd-catalyzed coupling of 1-ethoxyvinyl–[215] and acyl–Sn[216] reagents with allylic acetates, carbonates, phosphates or chlorides forms unsaturated vinyl ethers and ketones, respectively (equations 211 and 212). The formation of alkenyl ethers is also attained by Cu-catalyzed Grignard coupling with an allylic acetal (equation 213).[217] Finally, allyluridines can be obtained by Pd-catalyzed allylation of the corresponding mercury intermediates (equation 214).[218]

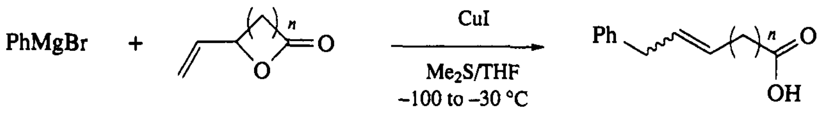
PhMgBr
+
n
O
O
CuI
Me2S/THF
–100 to –30 °C
Ph
n
O
OH

(209)

$n = 1$ 91% $(E):(Z) = 83:17$
$n = 2$ 75% $(E):(Z) = 62:38$
$n = 3$ 56% $(E):(Z) = 67:33$

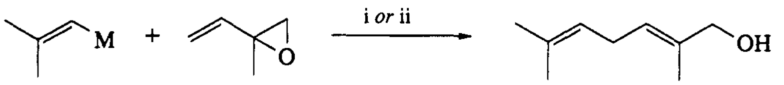

(210)

i, M = Li 94% $(E):(Z) = 88:12$
i, M = MgBr 77% $(E):(Z) = 96:4$
ii, M = $SnMe_3$ 72%

i, CuBr, $Et_2O$, –15 °C; ii, $PdCl_2(MeCN)_2$, DMF, $H_2O$, r.t.

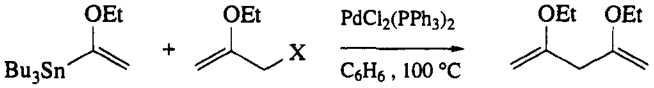
OEt
Bu3Sn
+
OEt
X
PdCl2(PPh3)2
C6H6, 100 °C
OEt
OEt

(211)

X = OAc 72%
X = $OP(O)(OEt)_2$ 99%
X = $OCO_2Me$ 63%

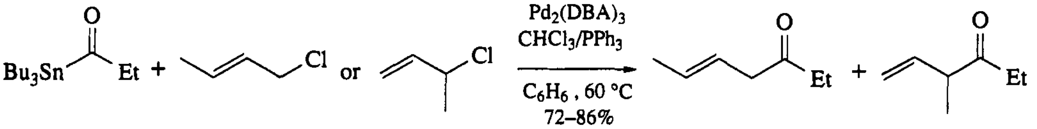
O
Bu3Sn
Et
+
Cl
or
Cl
Pd2(DBA)3
CHCl3/PPh3
C6H6, 60 °C
72–86%
O
Et
+
O
Et

(212)

75% 25%

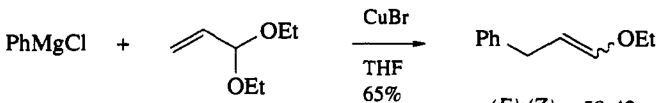
PhMgCl
+
OEt
OEt
CuBr
THF
65%
Ph
OEt

(213)

$(E):(Z) = 58:42$

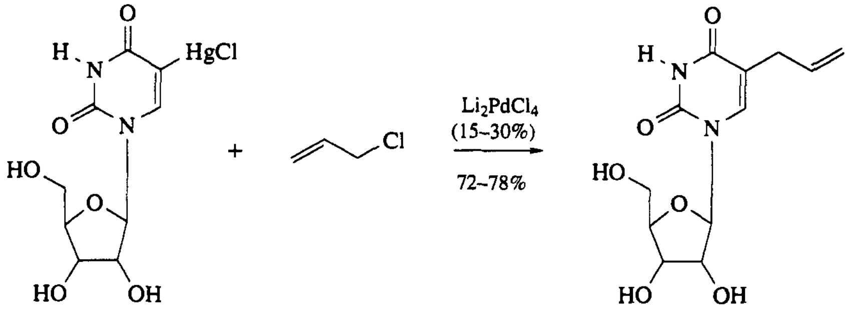
O
H
N
HgCl
O
N
HO
O
HO
OH
+
Cl
Li2PdCl4
(15–30%)
72–78%
O
H
N
O
N
HO
O
HO
OH

(214)

## 2.2.11 REFERENCES

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# 2.3

# Coupling Reactions Between *sp*$^2$ Carbon Centers

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## 2.3.1 INTRODUCTION

The scope of this chapter is largely confined to the direct coupling reactions of *sp*$^2$-carbons as outlined in equation (1), where both X and Y are groups or atoms other than hydrogen. In retrosynthetic terms, such processes are usually best regarded as 'illogical' and indeed prior to the early 1970s, with the exception of the classical Ullmann biphenyl synthesis, few examples of such reactions were in general use. During the past 15 years, however, enormous progress has been made in this area, particularly since the introduction of zerovalent palladium and nickel catalysts for carrying out the coupling reactions.

Two important groups of reactions of the type outlined in equation (1) are not included in this chapter, as they are reviewed elsewhere in Comprehensive Organic Synthesis. Firstly, Heck-type processes (Y = H; equation 1) are discussed in Volume 4, Chapter 4.3. A second way to effect the overall process indi-

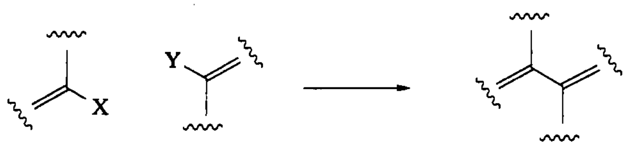

(1)

X, Y ≠ H

cated in equation (1) is by a tandem Michael addition–elimination sequence, such as the addition of a vinylcuprate species to methyl β-bromoacrylate; such methods are also covered in Volume 4.

The chapter has been organized so as to give rapid access to information regarding a particular structural type. This inevitably requires the inclusion of extensive cross-referencing as, not surprisingly, many of the coupling methods can and have been applied to targets belonging to more than one of these groups.

## 2.3.2 COUPLING REACTIONS INVOLVING ALKENES

### 2.3.2.1 Alkene–Alkene Dimerization

In common with the well-established Ullmann biphenyl synthesis, many methods for alkene dimerization feature the use of a copper species, either formed *in situ* using a copper salt (and often of an undefined nature) or by using a preformed vinylcuprate and a coupling reagent. For example, iodofumarates (**1**) can be converted into tetraesters (**2**) simply by using activated copper powder,[1] although later work has revealed that copper(I) triflate and saturated aqueous ammonia in acetone is a more effective reagent mixture.[2] The couplings are highly stereoselective and work almost equally well with iodomaleates. A general method for coupling vinyl halides consists of conversion to the corresponding lithium divinylcuprate followed by treatment with molecular oxygen (Scheme 1).[3] The method is general and usually high yielding and is also effective in coupling mixed vinylmagnesiocuprate species. The latter type of intermediate (*e.g.* **3**) also undergoes efficient dimerization when treated with dilithium tetrachlorocuprate ($Li_2CuCl_4$ from $CuCl_2$ + 2LiCl) resulting, in this particular example, in an expedient and stereospecific approach to bis(allylsilanes) (**4**).[4] The conversion (**3**) → (**4**) represents a general type of oxidative coupling which is also applicable to a wide range of vinyllithium and vinyl Grignard species, and which can be effected using CuCl or $CuCl_2$ in addition to $Li_2CuCl_4$, as well as by a variety of cobalt, manganese and chromium salts.[5] Symmetrical 1,3-butadienes can also be obtained from vinylcopper species and the corresponding vinylsilver(I) salts by a simple thermal decomposition process; in general both the yields and stereochemical retentions are high, even in the preparations of (*Z*,*Z*)-1,3-butadienes.[6] Silver salts can also be used to carry out dimerizations of vinyl Grignard reagents, in conjunction with a nitrogen-containing oxidizing agent such as $LiNO_3$, $MeNO_3$ or $NO_2$.[7] A wide range of simple transition metal halides have also been examined for their suitability as mediators of such coupling reactions. One of the best turned out to be palladium(II) chloride, which at the time it was described was certainly a signal for many of the later spectacular advances in $sp^2$–$sp^2$-coupling reactions. Two

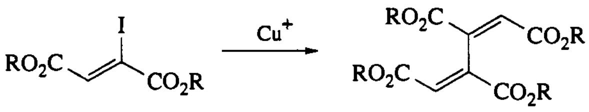

(**1**) (**2**)

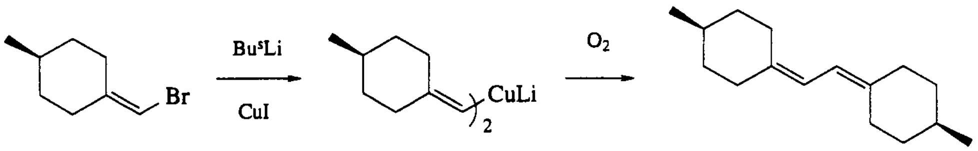

**Scheme 1**

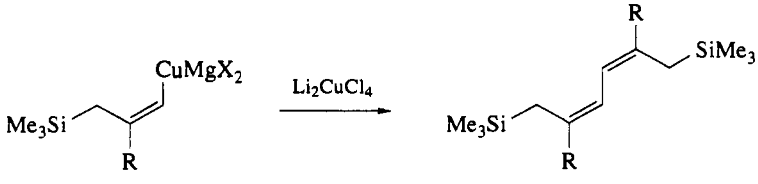

(**3**) (**4**)

other reagents that have been used in this type of Grignard dimerization are $K_4[Ni_2(CN)_6]$[8] and, rather unexpectedly, thionyl chloride.[9]

Alkenylboranes have also been found to be valuable precursors of 1,3-butadienes and, once again, copper reagents play a crucial role in these procedures. For example, hydroboration of an alkyne using monochloroborane (Scheme 2) leads to a divinylborane, and thence to an (*E*,*E*)-1,3-butadiene (**5**) following treatment with 3 equiv. of methylcopper.[10] Monoalkenyldibromoborane species can be coupled in a similar fashion and both sequences are stereospecific; two limitations, however, are the potential lack of regioselectivity in the first step with unsymmetrical alkynes and the possibility of side reactions between the hydroborating reagent and other functional groups contained in the substituents $R^1$ and $R^2$. Both (*E*)- and (*Z*)-vinylboranes (**6**) can be coupled by sequential treatment with sodium methoxide and copper(I) bromide–dimethyl sulfide complex, thus providing a useful alternative approach to (*E*,*E*)-dienes (**5**; $R^2$ = H) as well as to (*Z*,*Z*)-butadienes (**7**).[11] Both procedures are reported to be stereospecific. A rather older procedure can be used to prepare (*E*,*Z*)-butadienes (**8**); thus, hydroboration of a terminal alkyne using thexylborane first affords an (*E*)-alkenyldithexylborane, which upon treatment with iodine and sodium hydroxide is then converted selectively into the (*E*,*Z*)-isomer (**8**).[12] Similarly, the (*E*,*Z*)-isomers of tetra-substituted butadienes (**5**; $R^1$ = $R^2$) can be prepared from symmetrical internal alkynes.

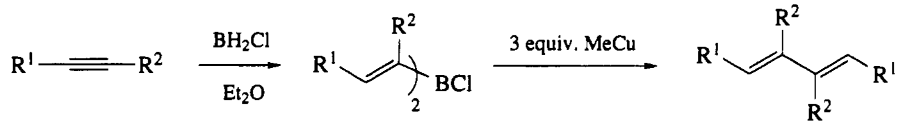

**(5)**

**Scheme 2**

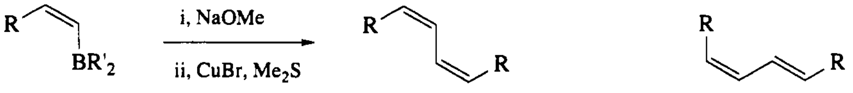

**(6)** R = *n*-alkyl **(7)** **(8)**

A closely related sequence which has been used for the specific preparation of (*E*,*E*)-butadienes (**10**) from terminal alkynes involves hydroalumination, usually using DIBAL-H, followed by coupling of the intermediate vinylalane (**9**) using copper(I) chloride (*vide supra*).[13] In much the same manner, hydrozirconation of a terminal alkyne and transmetallation using copper(I) iodide also leads smoothly to butadienes (**10**).[14] A rather different source of copper, hydrated copper(II) nitrate, is very effective for the rapid and efficient coupling of vinylstannanes (**11**), leading to butadienes (**10**).[15] (*Z*,*Z*)-Butadienes (**7**) can also be produced from (*Z*)-vinylstannanes by this method, which will also tolerate a substituent α to the tin functionality. A final example of the use of both copper(I) and silver(I) salts is as reagents for the coupling of (*E*)-alkenyl pentafluorosilicates to give symmetrical (*E*,*E*)-butadienes (**5**) in moderate to good yields; in contrast, reactions with copper(II) salts give only monomeric products by protonolysis of the C—Si bond.[16]

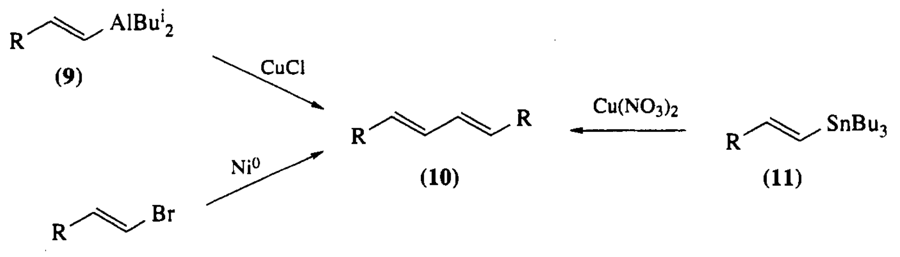

**(9)** **(10)** **(11)** **(12)**

The direct dimerization of an alkenyl halide offers a potentially attractive alternative to many of the above two-step procedures. Such a transformation, (**12** → **10**), can be achieved using bis(1,5-cyclooctadiene)nickel(0) in the presence of triphenylphosphine.[17] This mild method tolerates the presence of sensitive functional groups such as acrylic esters[1,2] and has been improved since the original report by the introduction of more convenient catalyst systems such as triphenyl-[18] and trialkyl-phosphine–nickel(0)[19] species and an $Ni^0$ reagent prepared by reduction of nickel(II) chloride using zinc in the presence of potassium iodide and/or thiourea.[20] An even simpler method for effecting such dimerizations is to employ 5 mol % $Pd(OAc)_2$ as catalyst in the presence of triphenylphosphine and potassium carbonate.[21] This methodology looks particularly attractive for various intramolecular dimerizations, such as in the conversion of the bis(vinyl bromide) (**13**) into the cyclopentane (**14**) in 95% yield. Simple vinylic chlorides have also been coupled using a catalyst system composed of platinum chloride and cesium fluoride in the presence of $Et_4NSnCl_3$ in aqueous DMF.[22]

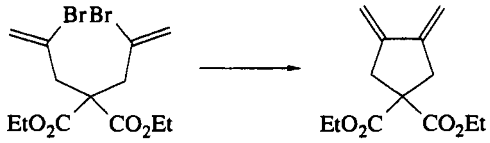

**(13)** **(14)**

Vinylmercury species (**15**) are very efficiently dimerized to dienes (**16**) upon treatment with palladium chloride and lithium chloride [$Li_2PdCl_4$].[23] In addition to the high yields, a further attraction is the wide range of functionality which can be tolerated (this type of coupling does not appear to be too seriously affected by steric hindrance); this includes both α- and β-alkenyl and -alkynyl groups as well as aryl and β-acetoxy functions. An important disadvantage, however, along with the requirement for HMPA, is the need to use stoichiometric quantities of expensive $PdCl_2$; this can be overcome in many examples by using a rhodium species, [$Rh_2(CO)_4Cl_2$]·LiCl, which is only required in catalytic quantities.[24] A most unusual turnaround occurs with these couplings when they are carried out in nonpolar benzene using 0.5 equiv. of $PdCl_2$, in that the 'head to tail' product is obtained instead (*e.g.* **17** → **18**), thereby adding a useful facet to such vinylmercury chemistry.[25]

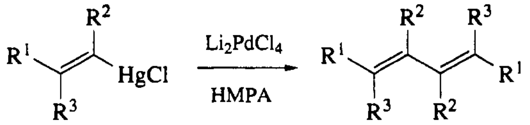

**(15)** **(16)**

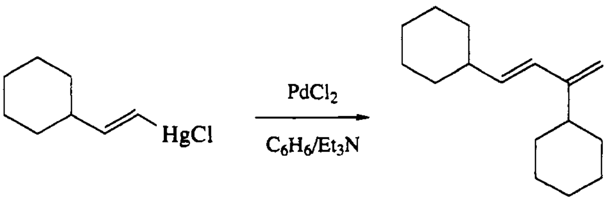

**(17)** **(18)**

### 2.3.2.2 Crossed Alkene–Alkene Coupling

This type of coupling reaction has only become a really viable option in synthesis during the past 15 years or so, with the advent of a number of nickel and palladium complexes, especially zerovalent species. The direct coupling of alkenyl and aryl Grignard reagents with alkenyl and aryl halides, catalyzed by various nickel complexes, has been extensively studied by Kumada and his coworkers in particular, with the result that some of the most suitable catalysts discovered, such as [$NiCl_2(PPh_3)_2$] and [$NiCl_2(DPPP)$], are sometimes referred to as Kumada- or Tamao–Kumada-type catalysts, as is the zerovalent species [$Ni(PPh_3)_4$]. These catalysts are particularly effective in conjugated diene synthesis of the type indicated in equation (2).[26] In general, the reactions proceed efficiently and under mild conditions, although with a lack of stereospecificity in some cases, even though vinyl Grignard reagents tend to be relatively less reactive in such reactions than the corresponding aryl species. Given protection against the Grignard reagent, a wide range of functional groups can be tolerated and in sterically hindered examples it is usually best to utilize the more hindered Grignard reagent, rather than to couple a relatively unhindered vinyl Grignard with a crowded alkenyl halide. In those examples with similar steric demands, the ordering can still be important. For example, coupling between the allylsilane (**19**) and Grignard reagent (**20**) produces a 75% yield of the useful butadiene (**21**); coupling in the opposite sense leads to a lower (56%) yield.[27] Vinyl Grignard reagents obtained by Ni(acac)-catalyzed additions of RMgX to silylalkynes can also be coupled directly to vinyl bromides to provide silylbutadienes (*e.g.* **22**, from vinyl bromide) in moderate yields; the second step is presumably also nickel catalyzed.[28] Isomeric silanes, as well as a variety of other butadienes, can be obtained by nickel-catalyzed displacements of thiol groups using vinyl Grignards (*e.g.* **23** → **24**).[29] Such reactions are quite general and have been successfully applied, for example, in styrene syntheses (Section 2.3.2.4).

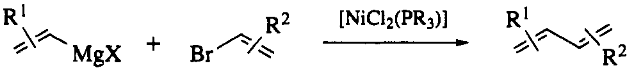

(2)

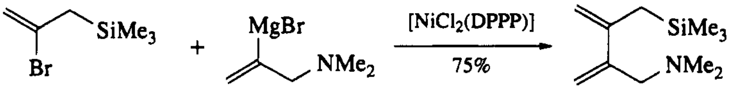

**(19)** **(20)** **(21)**

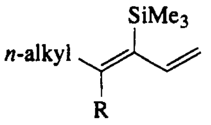

**(22)**

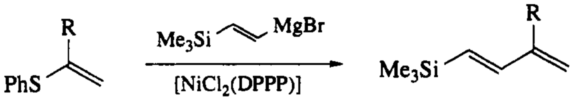

**(23)** **(24)**

A major advance in this area came with the discovery that vinyl Grignard species could be smoothly coupled with vinyl halides using tetrakis(triphenylphosphine)palladium(0) as catalyst (Scheme 3).[30] Typical yields for such coupling reactions are 75–87% and stereochemical retention is normally excellent in both components, facts which often render this method more useful than a number of alternatives, such as couplings between various vinylcuprates and vinyl iodides (*vide infra*). As will be seen from the subsequent discussion, $Pd^0$ catalysts, especially $[Pd(PPh_3)_4]$, are undoubtedly the most important in this whole area of $sp^2$–$sp^2$-coupling reactions. As an example, the reaction shown in Scheme 3 can also be carried out using $Cu^I$ catalysts, but yields are generally around 50% and the method cannot be applied to vinylmagnesium bromide itself, due to polymer formation.[31] However, preformed vinylmagnesiocuprates can be coupled to vinyl halides using 5 mol % of $[Pd(PPh_3)_4]$ or $[Pd(PO_3)_4]$[4] as catalyst in good yields (50–70%) and with high stereochemical retention.[32] A specific example is the formation of the (*Z,Z*)-diene (**27**) from the magnesiocuprate (**25**) and the iodide (**26**); two notable features of this particular transformation are the highly selective production of the (*Z,Z*)-isomer and the high degree of substitution present in both components.[33] A further important discovery[33,34] is that these and related reactions also benefit from the addition of a zinc salt, typically zinc chloride, an observation first reported by Negishi and coworkers (*vide infra*) during their studies on vinylaluminum coupling reactions. Not surprisingly perhaps, lithium divinylcuprates (*e.g.* **28**) can also be coupled with vinyl iodides (**29**) using $[Pd(PPh_3)_4]$ and $ZnCl_2$ as catalysts.[34] This route to (*E,Z*)-butadienes (**30**) also displays a further useful feature, *i.e.* couplings with the diiodide (**31**) proceed as expected in the usual ethereal solvents to give, for example, the dienyl iodide (**32**), whereas when HMPA is added alkylation of the vinyl carbanion occurs to give the alternative product, the homologated vinyl iodide (**33**). While this methodology can also be used to prepare (*Z,Z*)-butadienes, one major disadvantage is that one of the vinyl groups in the cuprate (**28**) is wasted, clearly a serious problem in cases when this function is valuable. This problem can be overcome by treating a divinyl species (**34**) with $ZnCl_2$; transmetallation then ensues to give two intermediates, (**35**) and (**36**), which both couple with a vinyl halide under the influence of a $Pd^0$ catalyst.[35] Such palladium(0) catalysts, especially $[Pd(PPh_3)_4]$, are also very useful for effecting couplings between organolithiums and vinyl halides, although this type of reaction has been used mostly with examples of aryl- and heteroaryl-lithium species, as well as alkyllithiums, and is discussed more fully in the relevant sections which follow.[36] In general, such couplings involving alkenyllithiums cannot be carried out directly using $Pd^0$ or related nickel catalysts. However, the discovery of the value of zinc chloride in $Pd^0$-catalyzed $sp^2$–$sp^2$-couplings has subsequently led to the development of what is perhaps the method of choice for coupling alkenyllithiums with alkenyl halides, which proceeds *via* transmetallation with zinc chloride followed by $[Pd(PPh_3)_4]$-[37] or $[Pd(DBA)_2]\cdot 2PPh_3$-catalyzed[38] coupling with an (*E*)- or (*Z*)-alkenyl halide. Yields and preservation of stereochemical integrity are generally very good and the method

(Scheme 4) is also applicable to aryl halides and to allenyllithium reagents (*vide infra*). One drawback is that an excess of the vinylzinc species is usually required if good yields are to be obtained. The method is not limited to hetero substituted alkenyllithiums and, for example, has subsequently been used to prepare homologs, (**38**) and (**39**), from the alkenylzinc bromide (**37**) and the corresponding vinyl iodides, in 50–70% yields.[39] One of the first generally useful methods in this area of crossed couplings was between alkenylaluminum reagents and vinyl halides, catalyzed by either nickel or palladium salts and $ZnCl_2$. The couplings are essentially stereospecific, except in examples of nickel-catalyzed reactions of (*Z*)-vinyl iodides, where this usually falls to *ca.* 90% and they sometimes fail when the aluminum species carries bulky substituents.[40] A specific example (Scheme 5) has been described in detail[41] and, overall, the procedure complements many of the approaches developed by Normant and his coworkers[31–35] involving (*Z*)-alkenyl organometallics generated by stereospecific additions to terminal alkynes. In this present Negishi procedure, (*E*)-alkenylaluminum reagents are obtained by stereospecific hydroalumination of 1-alkynes, usually using DIBAL-H. As a stoichiometric amount of $ZnCl_2$ is employed, this method is clearly closely related to the foregoing examples (Scheme 4).[37–39] Zirconium species, which are prepared by hydrozirconation of terminal alkynes using Schwartz's reagent [$Cp_2Zr(H)Cl$], react in a similar fashion to that shown in Scheme 5 and are sometimes preferable to the corresponding alkenylaluminum species.[42] A number of functional groups can be tolerated in the vinyl halide partner, including acetals (OTHP), ethers, ketones and esters.[43] As would be expected from the foregoing results, mixed aluminum–zirconium species (**41**), obtained from 1-alkynes (**40**), also undergo smooth $Pd^0$- or $Ni^0$-catalyzed cross-coupling reactions with alkenyl bromides, but only following the addition of $ZnCl_2$ (or $CdCl_2$).[44] In examples where the alkenylaluminum intermediate is highly hindered, it can sometimes be advantageous to convert it to the corresponding vinyl iodide (using $I_2$) and then couple this with a (less-hindered) organometallic.

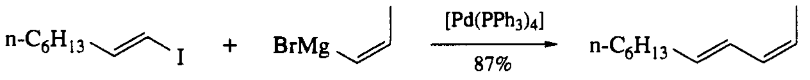

**Scheme 3**

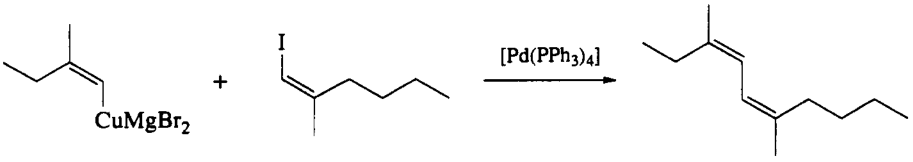

(**25**) (**26**) (**27**)

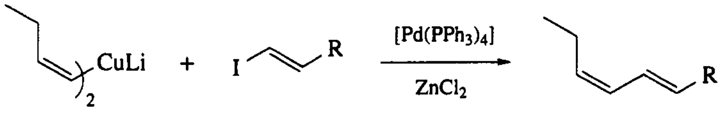

(**28**) (**29**) (**30**)

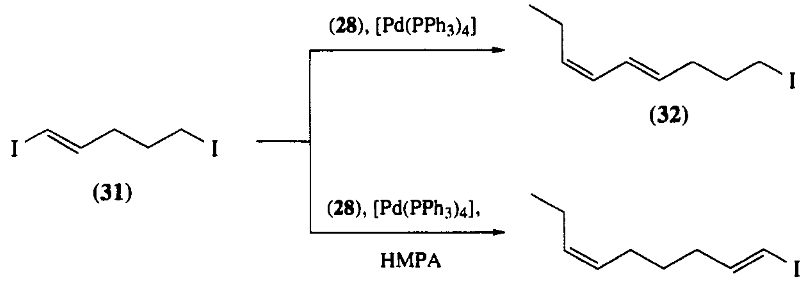

(**31**) (**32**) (**33**)

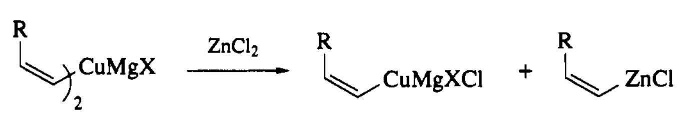
R
CuMgX
2
ZnCl2
R
CuMgXCl
+
R
ZnCl

**(34)** **(35)** **(36)**

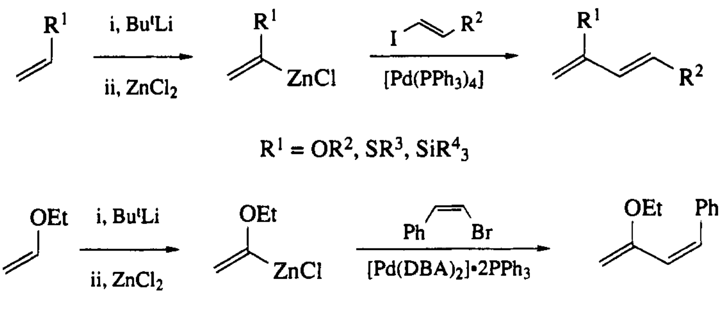
R1
i, ButLi
ii, ZnCl2
R1
ZnCl
I R2
[Pd(PPh3)4]
R1
R2
R1 = OR2, SR3, SiR43
OEt
i, ButLi
ii, ZnCl2
OEt
ZnCl
Ph Br
[Pd(DBA)2]•2PPh3
OEt Ph

**Scheme 4**

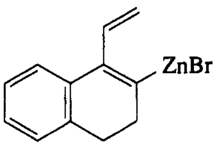

**(37)**

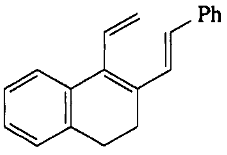

**(38)**

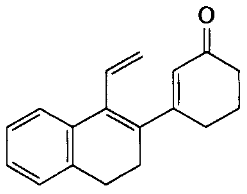

**(39)**

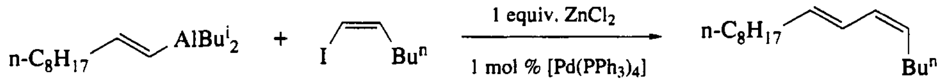
n-C8H17
AlBui2
+
I
Bun
1 equiv. ZnCl2
1 mol % [Pd(PPh3)4]
n-C8H17
Bun

**Scheme 5**

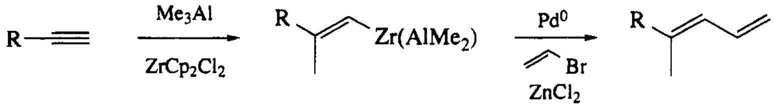
R
Me3Al
ZrCp2Cl2
R
Zr(AlMe2)
Pd0
Br
ZnCl2
R

**(40)** **(41)**

A useful series of coupling reactions with polychloroethylenes has been developed, based upon the foregoing type of chemistry. For example, 1 equiv. only of the vinyl Grignard reagents (**42**) can be added to (*Z*)-1,2-dichloroethylene to provide the (*E*,*Z*)-chlorobutadienes (**43**) in good yield.[45] The method also works for (*E*)-1,2-dichloroethylene, which can be coupled similarly to (*E*)-alkenylaluminums,[46] both routes leading to (*E*,*E*)-1-chlorobutadienes (**44**). The latter aluminum species can also be coupled with 1,1-dichlorethylene (**45**), using a $Pd^0$ catalyst at ambient temperature, leading to the useful 2-chlorobutadienes (**46**) in good yields.[47]

A further significant advance in the general area of $sp^2$–$sp^2$-coupling has been the finding that enol triflates can be coupled directly with lithium divinylcuprates (in addition to many related species) to provide butadienes in high yields and with good stereoselectivity (*ca.* 90% in the example shown in Scheme 6).[48] Enol triflates are readily prepared from the corresponding ketones, and are usually stable and easy to handle, and so the subsequent discovery that such intermediates could be smoothly coupled with vinylstannanes, under the catalytic influence of the ubiquitous $[Pd(PPh_3)_4]$, has enhanced their utility even further.[49] This latter protocol is of considerable merit, being highly efficient (80–100% yields) and stereoselective, as well as applicable to a wide range of substrates, both of which can be heavily substituted. The specific example shown in Scheme 7 represents a simple and efficient synthesis of the furanosesquiterpene pleraplysillin 1. Many further examples have been described in full,[50] including a simple approach to 1-silylbutadienes (Scheme 8), and the elaboration of an advanced model precursor of anthramycin (Scheme 9).[51] In this latter example, the isolated yield was 78%, in contrast to a direct

Heck-type coupling using ethyl acrylate, which afforded a lower 40% return. Such couplings can also be carried out intramolecularly, thus providing a novel disconnection in the retrosynthetic analysis of a wide range of targets, which is especially attractive because the required precursors are often highly accessible. Some generalized examples are the conversions shown in Scheme 10[52,53] for the formation of five- and six-membered rings; an application in the natural products area is in a neat synthesis of a dolastane diterpene in which the key cyclization (*cf.* Scheme 10) was effected in 81% yield by *in situ* formation of the vinyl triflate from the corresponding ketone (LDA, THF, HMPA, $PhN(SO_2CF_3)_2$) followed by the addition of $[Pd(PPh_3)_4]$ (catalytic) and work-up after only 5 min at 30 °C.[53] In general, such cyclizations are faster when carried out in acetonitrile rather than in THF. In a similar fashion, vinylstannanes can be coupled with vinyl iodides, both inter- and intra-molecularly. For example, a recently reported approach to the natural fatty acid 13-HODE (the hydroxy acid corresponding to ester **49**) had as a key step a palladium-catalyzed reaction between the vinyl iodide (**47**) and the stannane (**48**).[54] A notable feature with this and many related processes is the tolerance of function groups such as carboxylic esters, the presence of which would be precluded in much of the more well-established carbanion chemistry. The

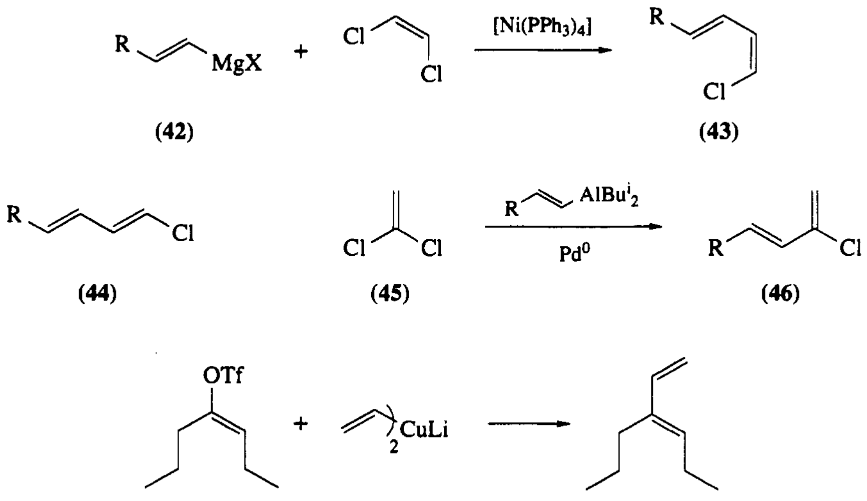
R
MgX
+
Cl
Cl
[Ni(PPh3)4]
R
Cl
R
Cl
Cl
Cl
R
AlBui2
Pd0
R
Cl
OTf
+
CuLi
2

**(42)** **(43)**

**(44)** **(45)** **(46)**

**Scheme 6**

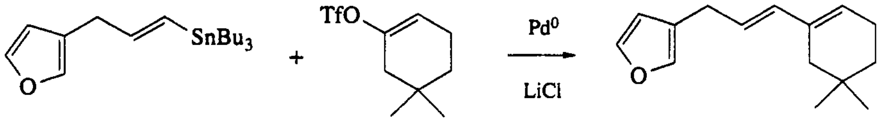
SnBu3
O
+
TfO
Pd0
LiCl
O

**Scheme 7**

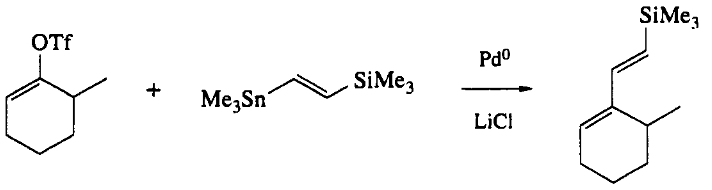
OTf
+
Me3Sn
SiMe3
Pd0
LiCl
SiMe3

**Scheme 8**

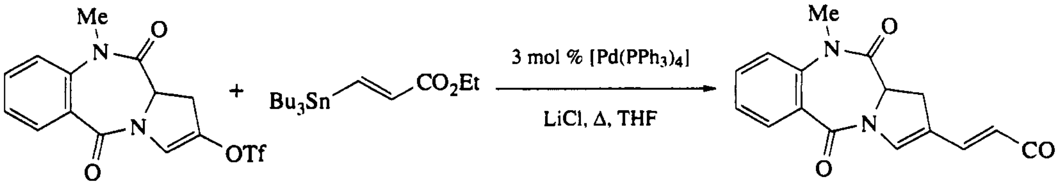
Me
N
O
N
O
OTf
+
Bu3Sn
CO2Et
3 mol % [Pd(PPh3)4]
LiCl, Δ, THF
Me
N
O
N
O
CO2Et

**Scheme 9**

intramolecular version of this reaction type, *e.g.* (**50**) → (**51**), is also catalyzed by a palladium(II) species, and is notable in this example for producing a 55% yield of a rather strained bicyclo[3.3.0]octadiene (**51**).[55]

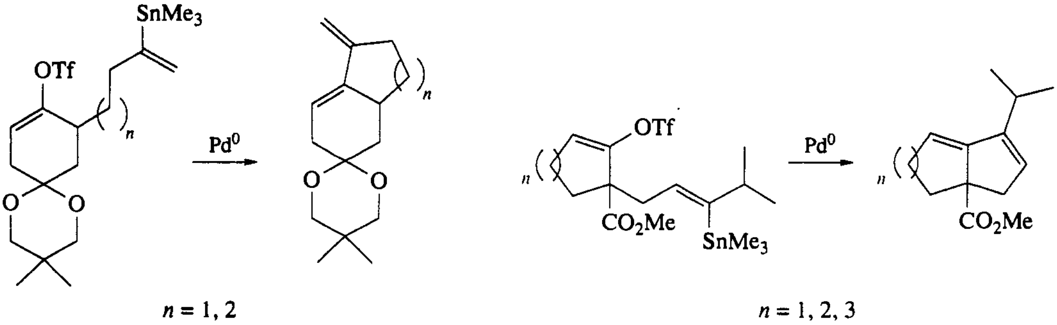

**Scheme 10**

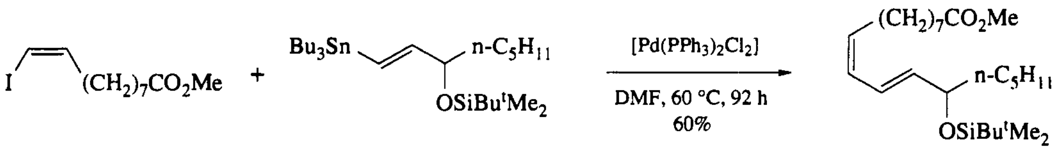

**(47)** **(48)** **(49)**

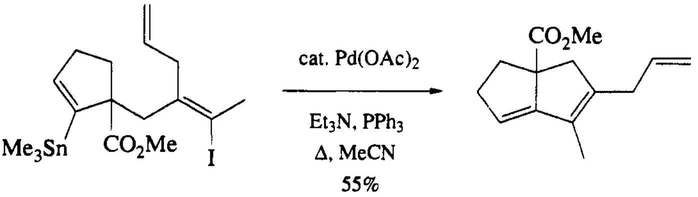

**(50)** **(51)**

In a similar manner to vinyl triflates (Scheme 6),[48] vinylmercury chlorides also undergo direct coupling with vinylcuprates leading to butadienes in *ca.* 60–66% yield, but only when a higher order cuprate, $R_3CuLi_2$, is used.[56]

A final class of intermediates which are valuable in the synthesis of conjugated dienes are alkenylboranes and alkenylboronates; indeed such species were employed in some of the first reasonably satisfactory diene syntheses.[57] As with many of the foregoing reaction types, the advent of $[Pd(PPh_3)_4]$ as a coupling catalyst has considerably transformed this area of chemistry. Much of the progress has been due to contributions made by Suzuki and coworkers, to the extent that such reactions involving alkenylboron species are often referred to as Suzuki couplings. In essence, the reactions consist of bond formation between an alkenylborane and an alkenyl halide in the presence of both $[Pd(PPh_3)_4]$ and a base such as a sodium alkoxide (Scheme 11).[58] (*E,E*)-Butadienes can generally be obtained stereochemically pure by this method, but similar couplings involving (*Z*)-alkenyl halides often lead to isomeric mixtures, although in some cases even (*Z,Z*)-butadienes (**53**) have been obtained from (*Z*)-alkenylboranes (**52**), but in relatively low yields.[59,63,64] With more weakly basic conditions, head to tail coupling tends to occur. Under similar conditions, (*E*)-alkenylboronic acids couple smoothly and stereospecifically with alkenyl iodides (Scheme 12).[60] As the alkenylboronic acids are readily obtained by hydroboration of terminal alkynes, this method is especially suitable for the synthesis of (*E,E*)- or (*E,Z*)-dienes. A third class of intermediates are the alkenylboronates. All three species have been compared for their suitability in the synthesis of the diene-containing insect pheromone bombykol and its three geometric isomers.[61] The choice of method can often be important; for example, coupling the boronic acid (**54**) and the bromide (**55**) provides an 82% yield of the target (**56**), whereas an alternative using the vinyl iodide (**57**) and the borane (**58**) produces only a 50% yield. However, the latter type of coupling has been used successfully in a scaled-up preparation of leukotriene $B_4$ (Scheme 13).[62] Despite these successful applications,[63] most of the methods are still not satisfactory for the elaboration of (*Z,Z*)-conjugated dienes as, in general, yields are rather poor in such preparations. Perhaps the best way to gain access to this class of compound is by coupling alkenylboronates with alkenyl bromides, using the usual Suzuki-type conditions (Scheme 14).[64] This methodology is now viable as the required (*Z*)-alkenylboronates can be readily obtained from 1-alkynes *via* the corresponding 1-bromo-1-alkenylboronate. The method can also be used to prepare (*E*,*Z*)-dienes from (*E*)-alkenyl bromides and has also been extended to the stereospecific elaboration of more highly substituted dienes, *e.g.* (**59**) and (**60**), by using 1,2-disubstituted alkenylboronates.[65] Related (*Z*,*Z*)-1-bromo-1,3-butadienes can be obtained using a haloboration–hydroboration sequence involving two alkynes; further elaboration of these initial products by, for example, halogen–lithium exchange and homologation provides yet another route to (*Z*,*Z*)-butadienes.[66]

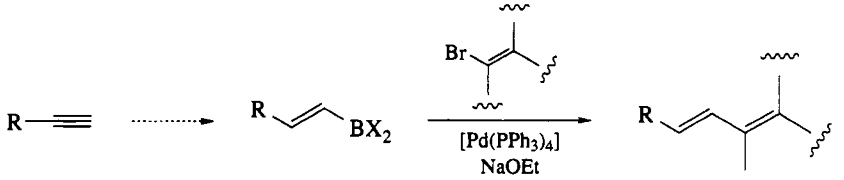

R
R
BX2
Br
[Pd(PPh3)4]
NaOEt
R

**Scheme 11**

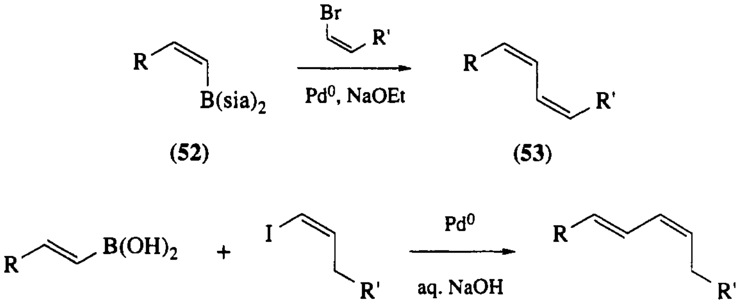

R
B(sia)2
Br
R'
Pd0, NaOEt
R
R'
R
B(OH)2
+
I
R'
Pd0
aq. NaOH
R
R'

(**52**) (**53**)

**Scheme 12**

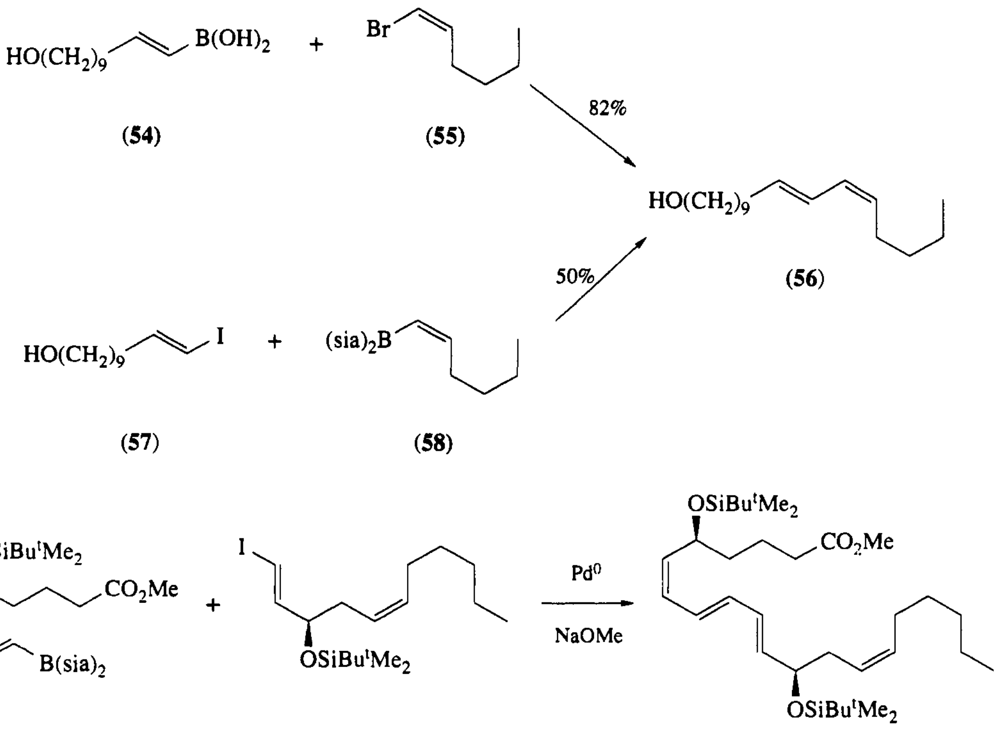

HO(CH2)9
B(OH)2
+
Br
82%
HO(CH2)9
50%
HO(CH2)9
I
+
(sia)2B
OSiBu'Me2
CO2Me
B(sia)2
+
I
OSiBu'Me2
Pd0
NaOMe
OSiBu'Me2
CO2Me
OSiBu'Me2

(**54**) (**55**) (**56**) (**57**) (**58**)

**Scheme 13**

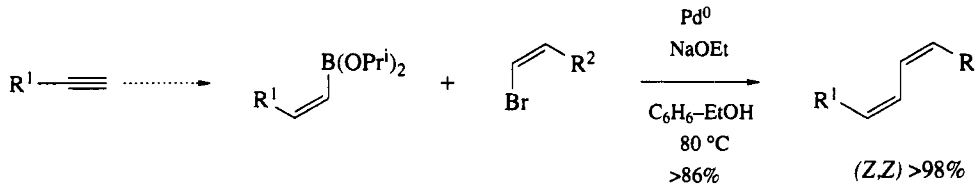

Scheme 14

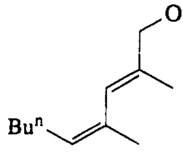

**(59)**

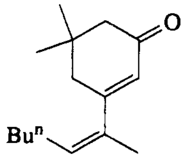

**(60)**

### 2.3.2.3 Allene Synthesis by $sp^2$–$sp^2$ Coupling

Not surprisingly, many of the methods which can be used in the synthesis of conjugated dienes can also be applied to dimerization of allenes. Thus, the bromoallenes (**61**) can be smoothly dimerized, for example, by treatment with 2 equiv. of copper(I) chloride in DMF at ambient temperature to give good yields of the diallenes (**62**).[1,2,67]

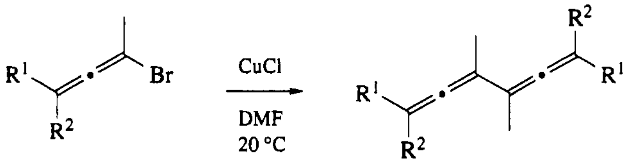

**(61)** **(62)**

The aforementioned method for coupling alkenylzinc halides with vinyl halides[37–39] is also applicable to the bromoallenes (**61**) (the corresponding bromoalkyne can also be used), which react smoothly with both 1-alkenylzinc chlorides and phenylzinc chloride in the presence of [Pd(PPh$_3$)$_4$] to give the homologs (**63**) in good yields.[68] By studying such reactions with chiral haloallenes, a duality of mechanism has been found.[69] Iodoallenes react with ArZnCl–Pd$^0$ with retention of configuration suggesting that oxidative insertion by palladium into the C—I bond is the key step, whereas the corresponding chloro- and bromo-allenes react with moderate levels of inversion implying the participation of an *anti*-$S_N2$ like reaction followed by a [1,3] Pd shift with inversion. A direct $S_N2$-type inversion is observed when chiral bromoallenes, *e.g.* (**64**), are treated with the Lipshutz higher order cyanocuprates resulting in the generation of essentially enantiomerically pure homologs, *e.g.* (**65**), in 70–80% yields.[70] Other reagents such as 'PhCuMgBr$_2$' give poorer optical yields and large amounts of the corresponding alkynic product.

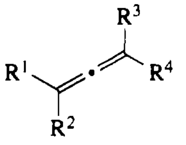

**(63)** R$^4$ =

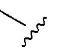

or Ph (Ar)

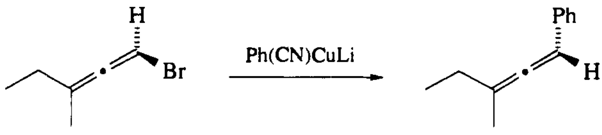

**(64)** **(65)**

Aryl Grignard reagents also coupled satisfactorily with bromoallenes, using [Pd(PPh$_3$)$_4$] as catalyst,[30] to give good yields of arylallenes (**63**; R$^4$ = Ar),[71] whereas couplings in the opposite sense between allenyllithiums derived from allenyl ethers or allenylsilanes and aryl iodides can also be achieved,[72] again using Pd$^0$ catalysts. This is in contrast to similar reactions with vinyllithiums,[36–39] which usually require prior transmetallation to the corresponding alkenylzinc species before successful couplings can be achieved (for an example using an allenylzinc intermediate, see ref. 38).

### 2.3.2.4 Alkene–Aryl Coupling

Many of the methods outlined in Section 2.3.2.2 (alkene–alkene coupling) are equally suited to alkene–aryl coupling reactions simply by either substituting an aryl halide for the alkenyl halide or conversely using an aryl organometallic in place of the corresponding alkenyl species. For example, arylmagnesium halides can be coupled to alkenyl halides using a variety of nickel(II) species as catalysts (Scheme 15).[26] In general, due to the relatively lower reactivity of vinylmagnesium halides, it is preferable to carry out these coupling reactions as shown, rather than the converse of reacting a vinylmagnesium species with an aryl halide. An exception to this could be with examples where the alkenyl function is highly substituted as, in general, it is better to use the Grignard reagent derived from the more sterically crowded partner in this type of coupling. A recent specific example of the utility of this general method is the elaboration of 2-arylallylamines (**68**) from arylmagnesium bromides (**66**; Ar = *m*- and *p*-$MeOC_6H_4$, -$FC_6H_4$ and -$ClC_6H_4$) and the vinyl chloride (**67**).[73] An additional key feature in the success of this method is the use of the Magnus stabase function ($Me_2Si(CH_2)_2SiMe_2$) to protect the amino group. Using these conditions, aryl Grignard reagents also couple in a regiospecific manner with β-halovinyl ethers (*e.g.* Scheme 16; silyl enol ethers[76] can also be used).[74] It should be noted that a variety of vinylic ether and sulfide groups can also be directly displaced by aryl Grignard and other organometallic species using nickel catalysts. For example, enol ethers (*e.g.* **69**) and phenylmagnesium bromide (**70**) react together in the presence of the usual type of nickel catalyst to give substituted styrenes (*e.g.* **71**) in >70% yields.[75] However, such coupling reactions are limited to relatively simple substrates as the reactions are rather sensitive to steric effects; enolates and enamines fail to react in a similar fashion. However, silyloxy groups in simple *O*-silyl enolates, *e.g.* (**72**), can be displaced by phenyl groups in the same way (PhMgBr, $[NiCl_2(PPh_3)_2]$) to give styrenes, *e.g.* (**73**), with a high degree (92%) of stereochemical retention,[76] while a method related to this and previously applied to butadiene synthesis (*vide supra*) consists of coupling lithium diarylcuprates with enol triflates (**74** → **75**).[48] In much the same way, enol phosphate groups can also be displaced (*e.g.* **76** → **77**) using an aryl Grignard reagent and $[NiCl_2(DPPE)]$ as catalyst.[77] This type of coupling can also be carried out in the reverse sense by reacting aryl phosphates (**78**), which are readily available from the corresponding phenol, with alkenylaluminums and using $[Ni(acac)_2]$ as catalyst.[78,94]

The sulfur function in vinyl sulfides can be displaced in the same manner, using Ni or Pd catalysts, and the methodology has been extended to tandem couplings using 1-bromo-2-phenylthioethene (Scheme 17).[79] The regioselectivity of the first step is exactly as that observed with the corresponding β-bromovinyl ether (Scheme 16).[74] In just the same way the 1,1-disubstituted alkene (**79**) can be converted into

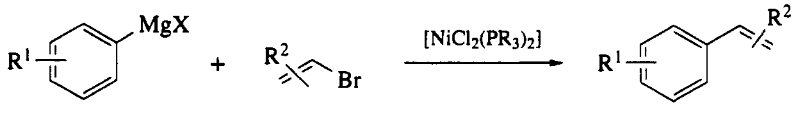

**Scheme 15**

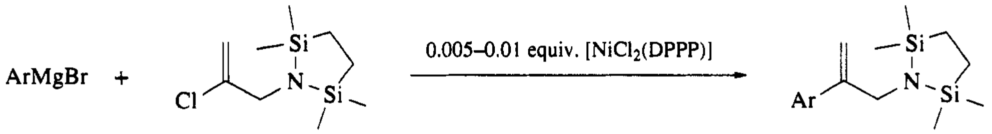

(**66**) (**67**) (**68**)

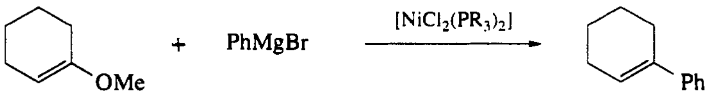

(**69**) (**70**) (**71**)

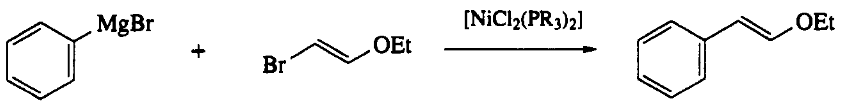

**Scheme 16**

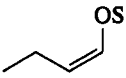

**(72)**

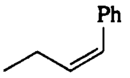

**(73)**

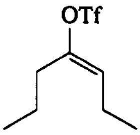

**(74)**

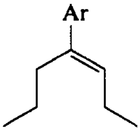

**(75)**

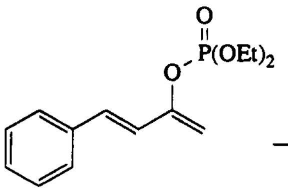

**(76)**

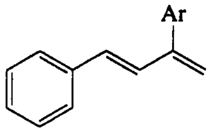

**(77)**

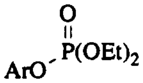

**(78)**

the derivatives (**80**);[29] although the whole sequence can be carried out in one pot, overall yields are higher if the intermediate vinyl sulfide is isolated. A recent application of this methodology has been in the homologation of the pyrrolizidine sulfide (**81**) to the phenyl-substituted alkaloid (**82**) using PhMgBr–[$NiCl_2(PPh_3)_2$], usually the catalyst of choice for this type of displacement.[80] Vinyl sulfones[81] and vinyl selenides[82] also undergo such displacement reactions with aryl Grignard reagents; with the former substrates, the reactions proceed with complete retention of stereochemistry using either nickel or iron catalysts, while the latter reactions require the use of excess (*e.g.* 2.5 equiv.) aryl Grignard reagent and use $Ni^{II}$–phosphine complexes as catalysts. Both sequences afford good to excellent yields, at least for the relatively simple examples studied (Scheme 18).

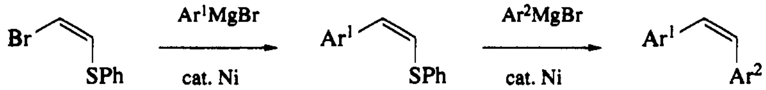

$Ar^1$, $Ar^2$ = Ph, naphthyl

**Scheme 17**

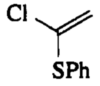

**(79)**

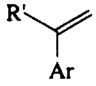

**(80)**

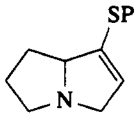

**(81)**

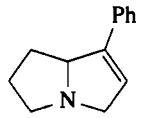

**(82)**

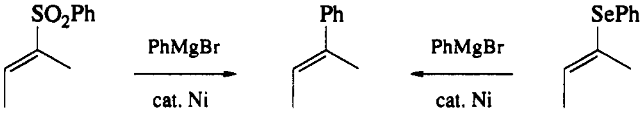

**Scheme 18**

The sulfide displacement method has also been carried out successfully in the opposite sense (*cf.* Scheme 17), wherein aryl sulfides are reacted with vinylmagnesium halides, as well as with a variety of other Grignard reagents, using a nickel catalyst.[83] In examples with bis-sulfides, a high degree of regioselectivity is observed if the sulfur groups are differentially substituted, the less-hindered reacting much faster (Scheme 19).

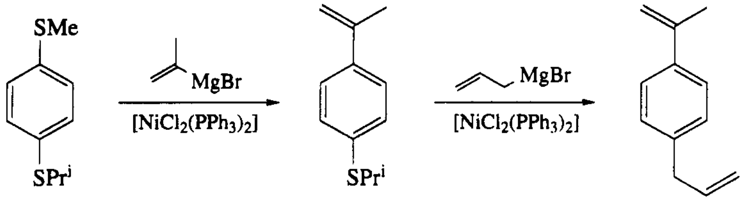

Scheme 19

Despite the great preponderance of nickel(II) catalysts used in the foregoing methods, aryl Grignard reagents and alkenyl halides have been successfully coupled using other catalysts, most notably examples of iron(III) complexes, including $FeCl_3$,[84] $Fe(acac)_3$[84] and $Fe(DBM)_3$ [tris(dibenzoylmethido) iron(III)].[85] Yields are often not as good as with the nickel catalysts, but the relative cheapness of these reagents could be an advantage.

An entirely different method for effecting, overall, an $sp^2$–$sp^2$-coupling of aryl Grignard reagents is by reaction of the latter with pyridazine *N*-oxide (Scheme 20).[86] In the simple cases studied, yields of enynes were 52–77%. The possibility of applying this approach to more highly substituted substrates does not appear to have been examined.

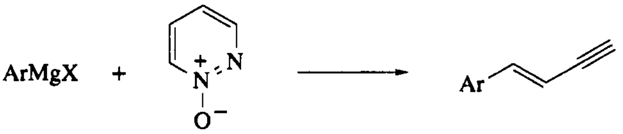

Scheme 20

Aryllithium species can also be efficiently coupled with alkenyl halides (Scheme 21) but using a palladium(0) catalyst (usually [$Pd(PPh_3)_4$]) or a related rhodium species; in general, nickel catalysts are not suitable for couplings involving organolithiums.[36] The reactions have a broad scope, within the limitation of providing protection for groups sensitive to organolithium species, and are generally very efficient and essentially stereospecific (*cf.* Scheme 15).[26] A way in which the requirement for an expensive catalyst can be avoided is to couple an alkenyl halide with a lithium diarylcuprate directly (Scheme 21).[87] The addition of various ligands, such as LiBr or $Bu^n_3P$, and the correct choice of solvent are all necessary considerations if high yields are to be obtained using this method. In view of its greater simplicity, the ArLi–$Pd^0$ combination is probably the method of choice. However, the latter method has been put to good use in the homologation of arylchromium complexes (**83**) to substituted styrene complexes (**84**), which are useful as benzofuran precursors.[88]

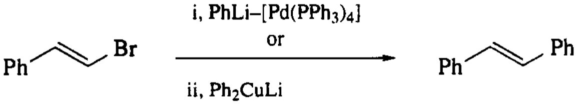

Scheme 21

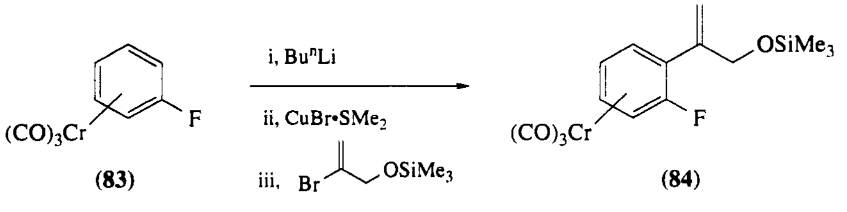

A combination of the foregoing methods has been used to obtain (*Z*)-styrenes (**86**) by the alternative approach of employing an alkenyl organometallic, initially a divinylcuprate (**85**) derived by addition of $R_2CuLi$ to acetylene.[89] In contrast to the foregoing methods involving aryl organometallics, the aryl ring in the product (**86**) can be substituted by a wider variety of functional groups, including Br, OMe, $NO_2$ and $CO_2Me$. This procedure is also useful for the synthesis of conjugated dienes[34,35] and is notable for its stereospecificity and efficiency, in that both alkenyl groups in the precursor (**85**) are utilized. However, there can sometimes be problems in forming this latter species cleanly and avoiding further addition of acetylene to give a bis(dienyl)cuprate species. Not surprisingly in view of the foregoing, alkenylzinc species,[37–39] directly generated by H/Li exchange and transmetallation ($ZnCl_2$), undergo smooth coupling with aryl iodides using [$Pd(PPh_3)_4$] as catalyst. Conversely, arylzinc chlorides can also be linked to alkenyl bromides (Scheme 22), again using a $Pd^0$ catalyst.[49,90] A notable feature of this example is the highly substituted nature of the alkenyl bromide. Usually, it is better to convert the more crowded partner into the initial organometallic species,[26] although in this case the success of the scheme probably reflects the higher reactivity of arylzinc species.[40]

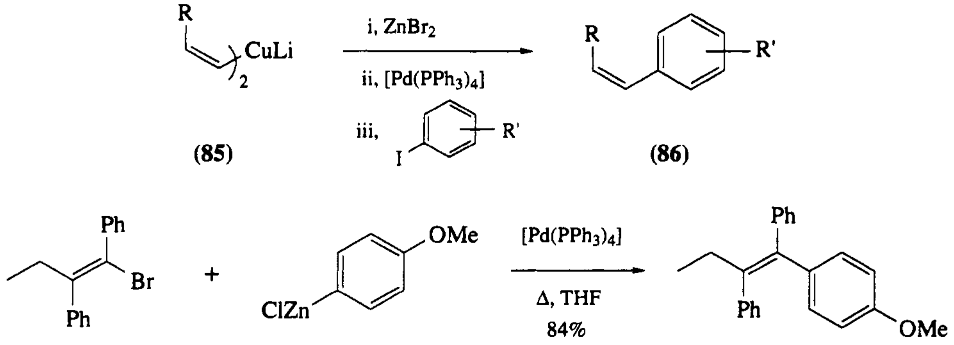

(**85**) (**86**)

Scheme 22

Both $Ni^0$ and $Pd^0$ catalysts induce the coupling of alkenylaluminum reagents to aryl halides (Scheme 23),[40,91] an approach which has been employed in an alternative synthesis, in a converse manner, of tetrasubstituted alkenes of the type shown in Scheme 22.[92] One limitation with this approach is the lack of flexibility in the available stereochemistries of the alkenylaluminum species; usually only the (*E*)-isomer is readily available. In just the same way, alkenylzirconium species, obtained either by hydrozirconation or the addition of $R_3Al–Cl_2ZrCp_2$ to a terminal or symmetrical internal alkyne, can also be coupled with aryl iodides using either $Ni^0$ or $Pd^0$ catalysts,[43,44] to give styrene derivatives in generally excellent yields. With hindered examples, the addition of zinc chloride is essential if good yields are to be obtained and in extreme cases, it has been recommended[44] that the best tactic may be to convert a hindered alkenylaluminum species into the corresponding alkenyl iodide ($I_2$) and then couple this with an organometallic species.

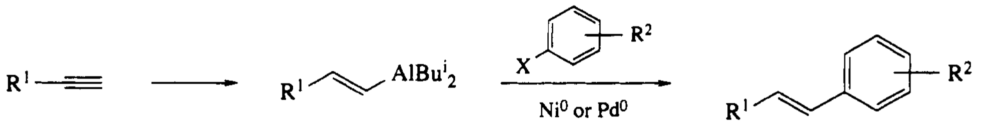

Scheme 23

Palladium(0)-catalyzed coupling of alkenyl halides with vinylstannanes[54,55] also constitutes a useful approach to styrenes (Scheme 24);[93a] a particularly attractive feature of this method is the toleration of a wide variety of substituents on the aromatic ring which include methoxy, nitro and bromide as well as unprotected carbonyls, acetate and 1,3-dione functions. One small limitation is that the reaction fails when free amino groups are present. β-Silylvinylstannanes can also be used, leading to β-silylstyrenes.[93b] A valuable extension to this method is the finding that aryl triflates, *e.g.* (**87**), can also be coupled to vinylstannanes to give generally excellent yields of arylalkenes (*e.g.* **88**).[94] Closely related to similar couplings of vinyl triflates[48–53] and of arylphosphates,[78] such reactions are mild (dioxane or DMF, <100 °C) and widely applicable, although the stereochemical integrity of the vinylstannane is not always preserved. An alternative approach to less readily available (*Z*)-arylalkenes is by palladium-catalyzed coupling reactions between aryl bromides and (*E*)-vinylsilanes,[95] which proceed with overall inversion (Scheme 25).[96]

In the same manner that various alkenylboron species can be coupled with alkenyl halides,[57–65] so too can aryl halides be homologated to styrenes (Scheme 26).[60,97] In general, such reactions require a $Pd^0$ catalyst and the presence of a base, such as sodium ethoxide, in order to achieve this type of head to head coupling.[59] In sharp contrast, mainly head to tail products are formed when a weak base, such as triethyl-

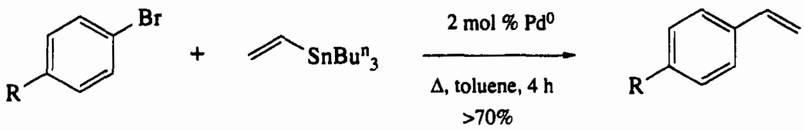
Br
R
+
SnBu$^n_3$
2 mol % Pd$^0$
Δ, toluene, 4 h
>70%
R

Scheme 24

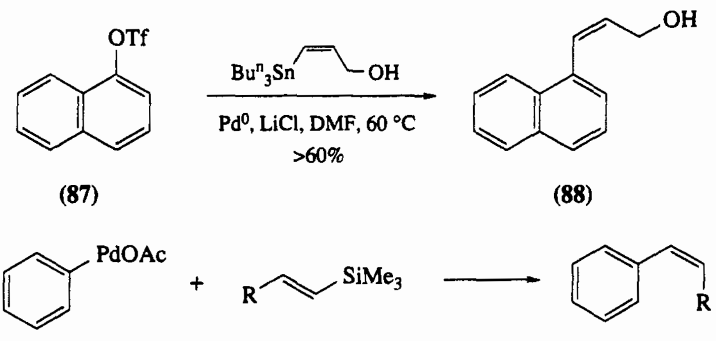
OTf
Bu$^n_3$Sn
OH
Pd$^0$, LiCl, DMF, 60 °C
>60%
OH
PdOAc
+
R
SiMe$_3$
R

(87) (88)

Scheme 25

amine, is used in place of ethoxide in such reactions with alkenylboronates (Scheme 27).[98] A particularly attractive route to (*Z*)-styrenes, as well as to arylbutadienes, is by reaction between an aryl halide and a (*Z*)-alkenylboronate (*cf.* Scheme 14);[64,65] similar reactions using (*Z*)-alkenylboranes are generally much less satisfactory. Using standard Suzuki-type conditions ([Pd(PPh$_3$)$_4$], NaOH), the β-ethoxyboronates (**90**) derived from the corresponding ethoxyalkyne (**89**) and catecholborane, also couple smoothly with aryl iodides to give excellent yields of substituted styrenes (**91**).[99]

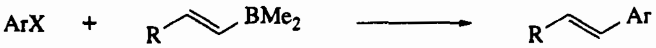
ArX
+
R
BMe$_2$
R
Ar

Scheme 26

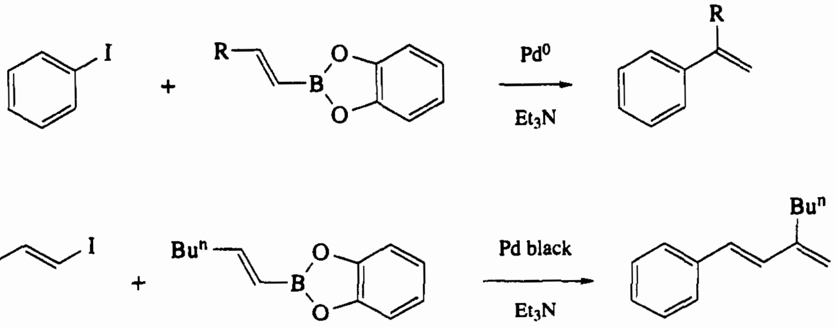
I
+
R
O
B
O
Pd$^0$
Et$_3$N
R
I
+
Bu$^n$
O
B
O
Pd black
Et$_3$N
Bu$^n$

Scheme 27

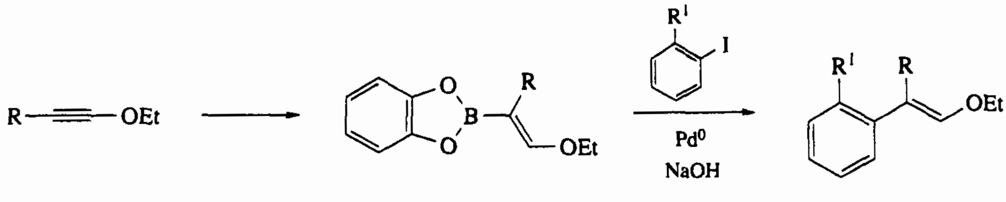
R
OEt
O
B
O
R
OEt
R$^1$
I
Pd$^0$
NaOH
R$^1$
R
OEt

(89) (90) (91)

R = *n*-alkyl; R$^1$ = OR$^2$, NR$^2_2$, X

As in some examples of the synthesis of conjugated dienes,[56] arylmercuric chlorides (**92**) react directly with vinylcuprates (**93**) (other stoichiometries are less satisfactory) to give substituted styrenes (**94**).[23] A number of relatively sensitive functions, such as $CO_2Me$, can be present on the aryl ring. An alternative method for the direct coupling of alkenyl iodides to mercurals (**92**) is to heat the two together in HMPA containing lithium chloride and Wilkinson's catalyst $[RhCl(PPh_3)_3]$; unfortunately, (*Z*)-1-alkenyl iodides give largely (*e.g.* 3:1) the (*E*)-substituted styrene.[23,100]

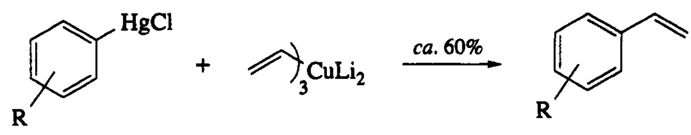

(**92**) (**93**) (**94**)

Another useful approach to styrenes *via* $sp^2$–$sp^2$-coupling reactions, which is beyond the scope of this section, is Meerwein-type arylations in which aryldiazonium salts undergo usually copper(I)- or palladium-catalyzed couplings with electron deficient alkenes, indicating a radical-based mechanism.[101] The method is also useful for the synthesis of stilbenes from unsubstituted styrenes[102] or β-silylstyrenes.[103]

### 2.3.2.5 Alkene–Heteroaryl Coupling

Not surprisingly, much of the methodology suitable for alkene–aryl coupling is also applicable to the elaboration of conjugated alkenyl heteroaromatic systems. In many cases, both types of reaction, either between an alkenyl organometallic and an aryl halide or *vice versa*, are possible, with the optimum pathway often dependent on the relative substrate availability. Although many of the examples involve only the simplest of heteroaromatic compounds, such as 2-furyl- or 2-thienyl-lithium or the corresponding bromides, the mildness of the procedures and their generality in other areas strongly suggests that they should be applicable to the synthesis of many, more complex, targets.

2-Furyl- and 2-thienyl-lithium reagents undergo smooth $Pd^0$-catalyzed coupling with alkenyl bromides (Scheme 28); yields are generally excellent, as is the degree of stereochemical retention.[36] The method would certainly not be applicable to the corresponding 3-lithio species which undergo ring opening at well below the reaction temperature. 2-Thienyllithium can also be coupled to the vinyl chloride (**67**) using a nickel catalyst, $[NiCl_2(DPPP)]$, to give the vinylthiophene (**95**) (*cf.* **67** → **68**).[73] In related work, access to the 2- and 3-vinylthiophenes, (**96**) and (**97**), has been shown to be possible by coupling a Grignard species with the appropriate bromide or, in the latter 3-substituted case, specifically by reaction between 3-bromothiophene and the alkenylmagnesium bromide in the presence of the palladium catalyst $[PdCl_2(DPPB)]$.[104]

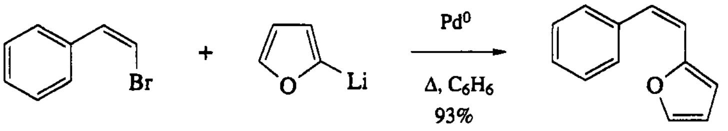

Scheme 28

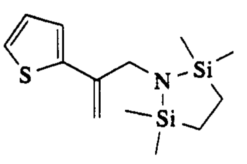

(**95**)

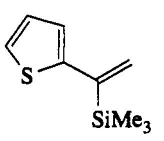

(**96**)

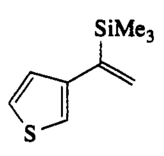

(**97**)

As mentioned in the foregoing sections, some of the most suitable intermediates for $sp^2$–$sp^2$-coupling reactions are alkenyl- or aryl-zinc species. In general, these species tend to be relatively the most reactive in such Pd- or Ni-catalyzed reactions and often lead to the highest yields.[40] For example, 2-furylzinc chloride reacts smoothly and efficiently with a range of alkenyl iodides (Scheme 29)[105] and this method has been used to prepare the Lophotoxin intermediate (**98**) in 70% yield.[106] Such coupling reactions can also be catalyzed by $[Pd(PPh_3)_4]$ and can be carried out in either sense; thus the thienyldihydronaphthalene (**99**) has been obtained both from 2-thienylzinc bromide or from the corresponding alkenylzinc bromide and 2-iodothiophene.[39] Similarly, a variety of fluorinated vinylzinc chlorides can be reacted with a range of iodinated heteroaromatics to give the expected vinyl derivatives (*e.g.* **100**, from 2-iodopyridine and $CF_2CHZnCl$).[107] Vinylpyridines, *e.g.* (**101**), can also be obtained from alkenylalanes (prepared from terminal alkynes using $Me_3Al–Cl_2ZrCp_2$)[40] and bromopyridines using a $Pd^0$ catalyst.[40]

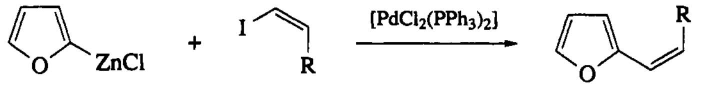

**Scheme 29**

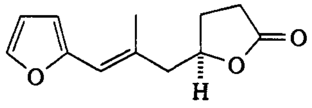

**(98)**

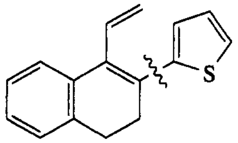

**(99)**

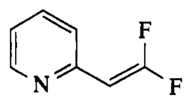

**(100)**

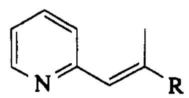

**(101)**

A variety of methods have been examined for the preparation of the vinyl ether homolog (**102**) of the corresponding 4-bromo-3-iodoindole.[108] Clearly, relatively unreactive species were required which would not displace the 4-bromo atom. The best approach was found to be a Negishi-type $Ni^0$-catalyzed coupling with an alkenylzirconium species obtained by hydrozirconation of ethoxyacetylene using Schwartz's reagent.[42] Other procedures such as Pd-catalyzed coupling reactions with alkenylboranes[99] or Heck-type reactions were less successful. However, related organoboronates have been found to be very suited as intermediates for the elaboration of trisubstituted alkenes *via* $sp^2$–$sp^2$-coupling reactions.[65] For example, formation of an 'ate' complex using 2-thienyllithium and the boronate (**103**), derived from 1-bromo-1-hexyne, followed by base-induced migration leads to the vinylboronate (**104**), and, thence to the alkene (**105**) following $Pd^0$-catalyzed coupling[59,64,98,99] with iodobenzene (Scheme 30). The overall yield in this particular case was 94% of material with >97% isomeric purity. Related isomers can be obtained by using an iodothiophene in the last step. Coupling reactions in the reverse sense, between pyridylboranes and vinyl bromides, also catalyzed by zerovalent palladium species, have been used to obtain a series of vinylpyridines.[109] Heteroaromatic mercurals can also be coupled directly to alkenyl halides, but using Wilkinson's catalyst.[100]

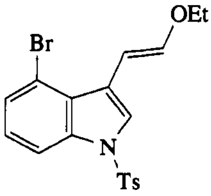

**(102)**

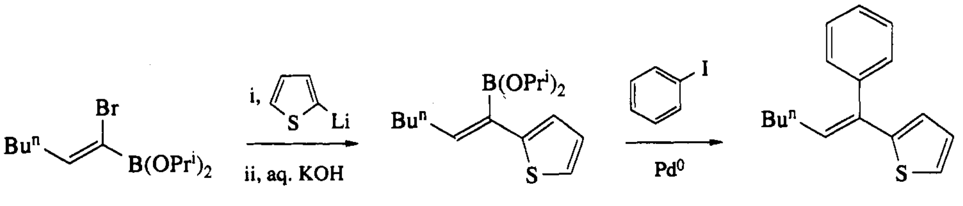

**Scheme 30**

## 2.3.3 ARYL–ARYL COUPLING REACTIONS

### 2.3.3.1 Aryl–Aryl Dimerization

Within the confines of equation (1), the most extensively studied and exploited methodology for the elaboration of symmetrical biaryls is the classical Ullmann reaction,[110] which is usually defined as the copper-mediated coupling of aryl halides (equation 3). The types of copper used in the older literature are copper powder itself, copper bronze[111] or copper(I) oxide, although this latter reagent is often more suited[112] to the Ullmann biaryl ether synthesis from phenols and aryl halides. The most common solvents employed are pyridine, quinoline, DMF and tetramethylurea (for reactions requiring higher temperatures than DMF[113]); temperatures of up to 260 °C have been used with success in examples involving robust substrates and such couplings can also be effected without the use of a solvent in sealed tubes. Rather more recent methods for obtaining activated copper reagents include pretreatment of the copper powder by EDTA[114] and generation of copper powder by zinc reduction of copper(II) sulfate[115] or by reduction of copper(I) iodide using potassium naphthalenide.[116] These methods, especially the latter, produce highly activated material which can allow Ullmann couplings to be conducted at lower temperatures. One of the mildest reagents discovered is copper(I) triflate in association with 5% aqueous ammonia in acetone or acetone–acetonitrile mixtures.[2,117,118] For example, 2-iodonitrobenzene (**106**) is converted into biphenyl (**107**) at 20 °C in just 5 mins. Unfortunately, other substrates often take an alternative pathway consisting of replacement of the halide by $NH_2$ or OH; thus methyl 2-iodobenzoate is transformed largely into methyl salicylate.

$$\mathrm{Ar{-}X} \xrightarrow{\text{'Cu'}} \mathrm{Ar{-}Ar} \qquad (3)$$

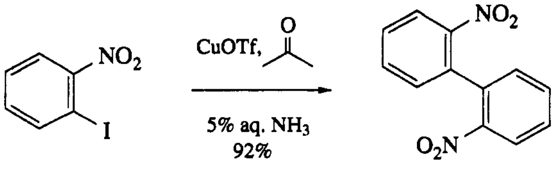

**(106)** **(107)**

The mechanism of Ullmann couplings most likely proceeds *via* discrete arylcopper species[1,110] and it is therefore not surprising that preformed arylcopper species can be used in such reactions, for which DMF rather than pyridine or quinoline is often the preferred solvent.[119] Arylcopper reagents can be generated by direct lithiation followed by Li/Cu exchange as exemplified by the facile synthesis of a tetramethoxybiphenyl (Scheme 31).[120,140] This type of approach is especially useful for sterically crowded cases, where the classical Ullmann approach (equation 3) fails,[121] and also for the elaboration of fluorinated biphenyls using pentafluorophenylcopper.[122] Such couplings are not limited to Li–Cu systems; oxidative couplings of both aryllithiums and arylmagnesium halides can be achieved using a variety of copper, cobalt, chromium, iron and manganese salts.[5,7,128] Silver salts, in the presence of a nitrogen-containing oxidizer, such as $LiNO_3$ or $MeNO_3$, are particularly effective in dimerizations of aryl Grignards,[7] which can also be carried out using thallium(I) bromide.[123] This latter method is relatively mild and high yielding although some drawbacks, beyond the need to protect Grignard-sensitive groups, include failure in attempted couplings of *ortho*-substituted Grignards and reagent toxicity, as excess of the thallium salt is usually required. Direct dimerizations of electron rich arenes, such as examples containing alkoxy groups, can be smoothly carried out using thallium tris(trifluoroacetate) (TTFA) in carbon tetrachloride or acetonitrile containing boron trifluoride etherate.[124] In general, classical Ullmann-type dimerizations are less satisfactory with electron rich substrates; a further bonus of the TTFA method is that halogen atoms are preserved (*e.g.* Scheme 32), allowing further manipulation of the initial biphenyl. Palladium(II) acetate can also be used as a catalyst in this type of coupling,[125] which is also especially suitable for the synthesis of binaphthyls and in intramolecular coupling reactions (Section 2.3.3.3).[140]

Many substituents are tolerated during classical Ullmann couplings. Nitro (*e.g.* **106** → **107**) and alkoxycarbonyl functions strongly activate the reactions when these groups are positioned *ortho* to the reaction site, but not when they are *meta* or *para*. Alkyl and alkoxy groups can activate from all positions, although with polysubstituted examples, excessive electron donation can be deleterious.[124] Ullmann couplings are not especially sensitive to steric effects, but are usually inhibited by the presence in either reactant of free OH, $CO_2H$ or $NH_2$ groups. Fortunately, these can all be readily masked (and sub-

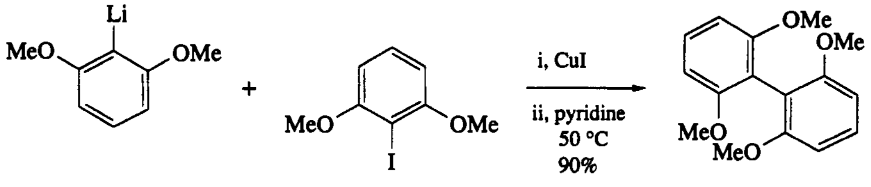

**Scheme 31**

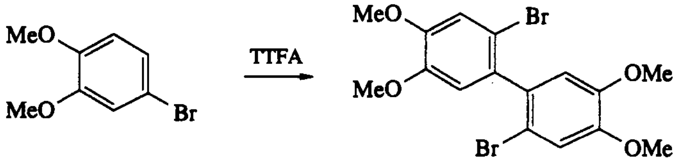

**Scheme 32**

sequently easily deprotected) by trimethylsilylation[126] or, in the case of phenolic functions, by mesylation.[127]

A major advance on the traditional Ullmann method (equation 3) was made in the early 1970s, when Semmelhack and his coworkers discovered that $Ni^0$ species could be used in place of elemental copper.[128] The original complex used was bis(1,5-cyclooctadiene)nickel(0) which, as an indication of the much greater mildness of this and related procedures, affords an 82% yield of biphenyl from bromobenzene at 50 °C in DMF (Scheme 33). The limitations associated with nickel-based approaches are similar to the Ullmann reaction in that free hydroxy groups (OH, $CO_2H$) prevent coupling, although the former method does sometimes suffer more from the steric effects of *ortho* substituents, two of which usually prevent reaction entirely. The toleration of methoxy, methoxymethyl, ester and especially formyl groups renders this general approach more attractive than ones based on aryllithium or Grignard intermediates (*vide supra*). Subsequent developments have essentially been aimed at discovering alternative nickel catalysts to $[Ni(COD)_2]$ which do not require dry box techniques, *etc*. Successful examples include triphenylphosphine–$Ni^0$ complexes generated by zinc reduction of the corresponding nickel(II) chloride,[18] a process which can be catalytic in nickel[129] and which is promoted by the addition of various salts (*e.g*. KI,[129] NaI[130]) and of 2,2′-bipyridine[130] to such an extent that aryl chlorides can be coupled without excessive heating (65–80 °C), and aryl iodides coupled at room temperature.[129] Similar species derived by reduction of bis(trialkylphosphine)nickel(II) dichlorides[19] or from the related system ($NiBr_2$–Zn–HMPT–KI)[131] also lead to high yields of symmetrical biaryls under mild conditions. A full report from Semmelhack's research group indicates that $[Ni(PPh_3)_4]$ is a good reagent both for this type of coupling and especially for intramolecular versions.[132] Aryl triflates can also be dimerized using a nickel(0) catalyst similar to some of the foregoing examples generated *in situ* from nickel(II) chloride and zinc powder, in the presence of triphenylphosphine and sodium iodide.[133] A relatively large excess of the latter reagents is required and rates are considerably enhanced by sonication. Yields are generally above 80% with *ca*. 10% of the deoxygenated arene being formed as a by-product.

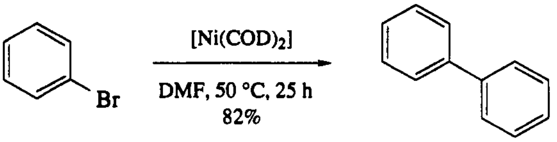

**Scheme 33**

In just the same way that vinylstannanes can be dimerized, (**11**) → (**10**), aryltri-*n*-butylstannanes react rapidly (10–30 min) with hydrated copper(II) nitrate in THF at 20 °C to afford high yields of biaryls,[15] although once again, *ortho* and especially bis-*ortho* substituents inhibit the coupling.

Biaryls can also be derived (70–90%) from mercury salts, ArHgX, using methodology very similar to a normal Ullmann coupling (copper powder, pyridine, reflux), except that a catalytic amount of $PdCl_2$ is also required.[23,134] Less basic solvents do not lead to such good yields, but otherwise the reaction characteristics are very similar to the Ullmann method except that free amino groups can be present. Related procedures can also be used to extrude elemental mercury from diarylmercurals, $Ar_2Hg$, to give biaryls.[23,110] Excellent yields of biaryls can also be obtained from dimerizations of arylmercuric salts using a rhodium catalyst, $[Rh(CO)_2Cl]_2LiCl$, or stoichiometric amounts of $Li_2PdCl_4$.[24]

Palladium, in the form of palladium(II) acetate, has also been used to catalyze biaryl formation directly from aryl iodides ($R_3N$; 100 °C), especially *p*-$NO_2$ and *p*-Cl derivatives. As usual, *ortho* substituents severely hinder this type of coupling.[135] Related reductive couplings of aryl halides have been achieved using hydrazine and a Pd–Hg catalyst,[136] electrochemically generated $Pd^0$ catalysts,[137] or a palladium on carbon catalyst in the presence of aqueous sodium formate, sodium hydroxide and, crucially, a catalytic amount of a surfactant.[138] The first two procedures look to be particularly selective and efficient, while the latter, rather different, method is not so efficient but does look amenable to large scale work.

Symmetrical biaryls can of course also be prepared using methods designed for the elaboration of unsymmetrical biaryls, by a judicious choice of substrate.

### 2.3.3.2 Crossed Aryl–Aryl Coupling

The standard Ullmann methodology can be applied to examples where sufficient differences exist between the two reactants that the desired crossed product is formed most rapidly. Usually, electronic factors are the most useful in this respect as in the example shown (Scheme 34), wherein one component is extremely electron deficient at the site of coupling.[110] Two such coupling reactions can also be viable as shown by a preparation of the tetraphenyl (**109**) from the biphenyl (**108**); despite a lowish yield (43%), this is still a rapid and efficient route to such compounds.[110] Quite complex biphenyls can be made in this way, given a sufficient electronic and reactivity (I > Br > Cl) difference. Thus, a good combination is the iodide of the more electron rich component, which will presumably form an arylcopper species more rapidly, and the bromide of the more electron deficient partner (Scheme 35).[127] This and the following example further exemplify the relative insensitivity of such couplings to steric crowding. An additional tactic for such reactions is to use a large excess of unactivated copper powder and a reaction temperature which is lower than that required for self-coupling of the less reactive component. The excess copper results in much shorter reaction times (Scheme 36),[139] even with such crowded substrates. Despite these successes, an obvious drawback with such reactions is the often very high temperature required. This can be circumvented by using the method of Ziegler and coworkers in which a preformed arylcopper, having the copper atom ligated both by triethyl phosphite and the lone pair of a substitutent atom, couples at below ambient temperature with an *o*-iodobenzaldehyde imine; an example (Scheme 37) is an approach to steganone.[140] In addition to the low temperature, once again steric hindrance is not a problem, which is certainly not the case with many of the related transition metal catalyzed processes using $Ni^0$ or $Pd^0$ catalysts, for example. The method is also very useful for the dimerization of *o*-bromobenzaldehydes, and in general appears to be the method of choice for obtaining this type of highly substituted biphenyl, given that a suitable ligand is present in the *ortho* position.

A less general but related method for obtaining 2,6-dinitrobiphenyls consists of metallation of 2,6-dinitrobenzene using copper(I) *t*-butoxide in a mixture of pyridine and DME followed by coupling with an

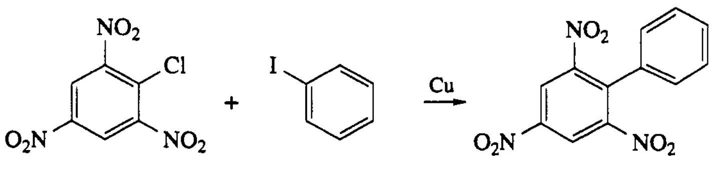

Scheme 34

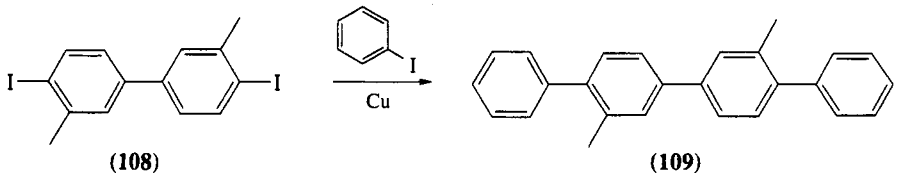

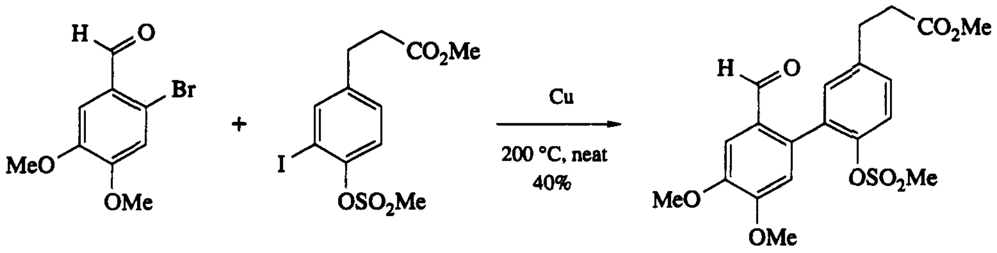
H
O
Br
MeO
OMe
+
CO2Me
I
OSO2Me
Cu
200 °C, neat
40%
H
O
CO2Me
OSO2Me
MeO
OMe

Scheme 35

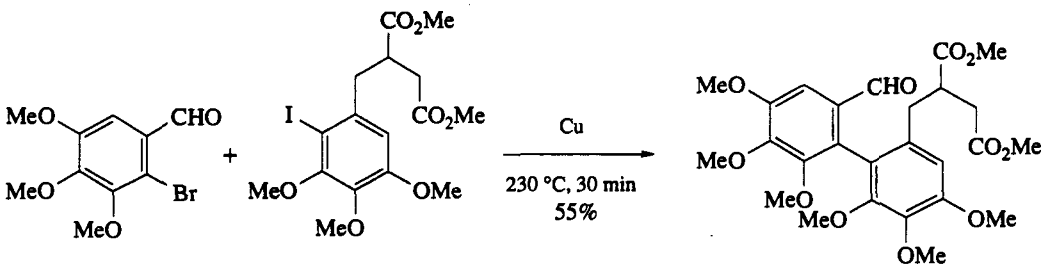
MeO
CHO
MeO
Br
MeO
+
CO2Me
I
CO2Me
MeO
OMe
MeO
Cu
230 °C, 30 min
55%
CO2Me
MeO
CHO
CO2Me
MeO
MeO
MeO
OMe
OMe

Scheme 36

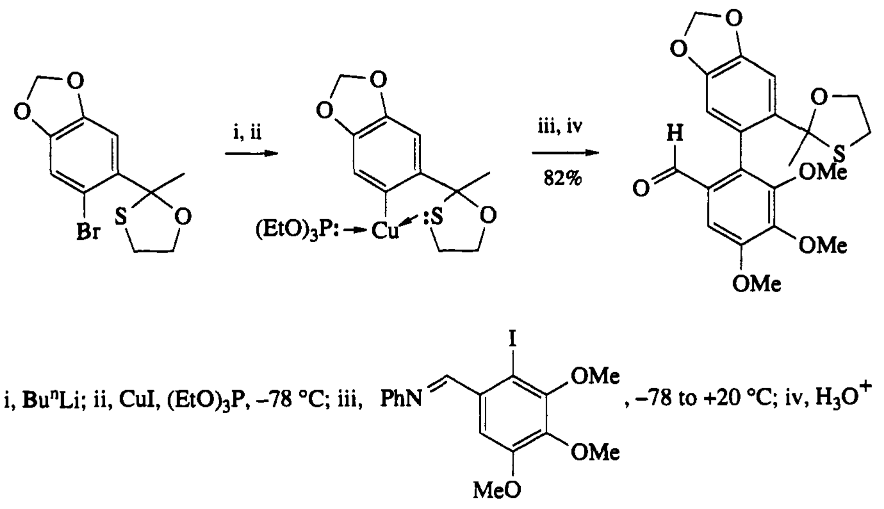
O
O
Br
S
O
i, ii
O
O
(EtO)3P:
Cu
:S
O
iii, iv
82%
O
O
H
O
O
S
OMe
OMe
OMe
I
PhN
OMe
OMe
MeO

i, Bu$^n$Li; ii, CuI, (EtO)$_3$P, −78 °C; iii, PhN=CH–C$_6$H(I)(OMe)$_3$, −78 to +20 °C; iv, H$_3$O$^+$

Scheme 37

iodoarene (Scheme 38).[141] Yields are generally in the range 50–95%. As would be expected from the foregoing discussion[140] (*cf.* Scheme 21), lithium diarylcuprates in general couple with iodoarenes to give good yields, at least in sterically unencumbered examples of unsymmetrical biaryls, given an appropriate additive (*e.g.* LiBr or Bu$^n{}_3$P) and solvent.[87]

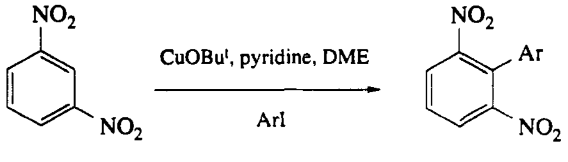
NO2
NO2
CuOBu$^t$, pyridine, DME
ArI
NO2
Ar
NO2

Scheme 38

The by now well-established nickel-catalyzed procedure for coupling Grignard reagents with alkenyl and aryl halides (equation 2 and Scheme 15) is also highly suitable for biaryl synthesis, except in examples where both of the substrates have *ortho* substituents. In cases where one component does carry *ortho* substituents, it is preferable to generate the Grignard from this component, rather than the converse (Scheme 39).[26] In addition to the Tamao–Kumada catalysts, $[NiCl_2(PR_3)_2]$, a wide range of other nickel catalysts can also be used[142,143] and sequential replacement of two halogens in a dihaloarene is also possible.[143] Unsymmetrical 1,1′-binaphthyls can be prepared similarly in a procedure which is greatly facilitated by the application of ultrasound.[144] Full details of a related coupling (not $sp^2$–$sp^2$) using the Tamao–Kumada method have been given which will be of use to those wishing to use these procedures.[145] The same type of catalyst can also be used to induce the displacement of aryl methoxy groups (*cf.* **69** → **71**) by Grignard reagents.[75] As expected, this type of coupling (Scheme 40) can suffer from steric effects. Sulfide groups can be displaced similarly[29,79] by arylmagnesium bromides; a particularly attractive feature of this chemistry is its application to terphenyl synthesis by sequential introduction of two different aryl groups to a chlorophenyl alkyl sulfide (Scheme 41).[146] Presumably a wide variety of combinations of both alkenyl[29,79] and aryl groups could be introduced by this methodology, which is also applicable to both *o*- and *m*-chlorophenyl sulfides.

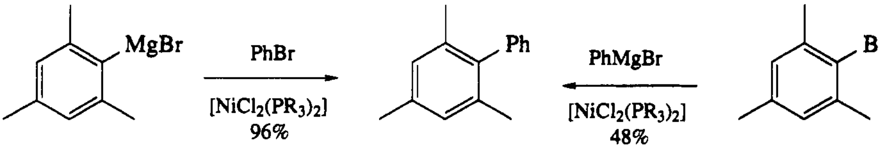

**Scheme 39**

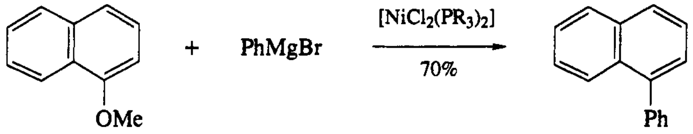

**Scheme 40**

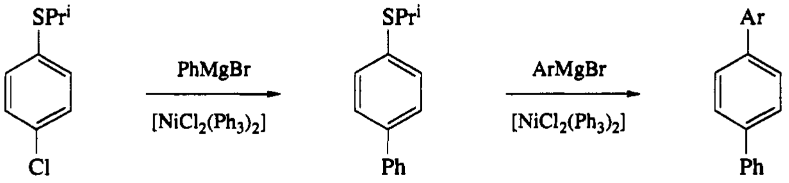

**Scheme 41**

Often, reactions catalyzed by nickel species can also be effected using closely related palladium compounds; this is certainly the case with cross-coupling reactions between aryl Grignard reagents and aryl halides, which can be effected using a variety of palladium catalysts.[147] These reactions often show greater selectivity than the related nickel catalysts in, for example, couplings between ArMgX and 4-bromo-1-chlorobenzene, where the more reactive bromo substituent is displaced. A more recent study has shown that this approach is particularly suitable for the elaboration of polyoxygenated biphenyls.[148] An important feature of the chemistry of aryl Grignard reagents, which should be noted when contemplating the use of this type of coupling, is that such species are capable of directly displacing methoxy groups adjacent to electron-withdrawing functions; indeed such reactions constitute a rapid and simple entry into a variety of substituted biphenyls and binaphthyls (Scheme 42).[149] In general, poorer yields are obtained using the corresponding aryllithium species.

The Negishi method for coupling alkenyl- or aryl-zinc halides to $sp^2$-centers[37–40,90] can equally well be used to obtain biphenyls (Scheme 43).[150] This excellent method, in which the arylzinc species is usually generated by transmetallation of the corresponding aryllithium, has been described in graphic detail.[151] Related coupling reactions can also be achieved by using an arylstannane in place of an arylzinc species.[152] A special case of this type of reaction is useful for the elaboration of phenylaryls by transfer

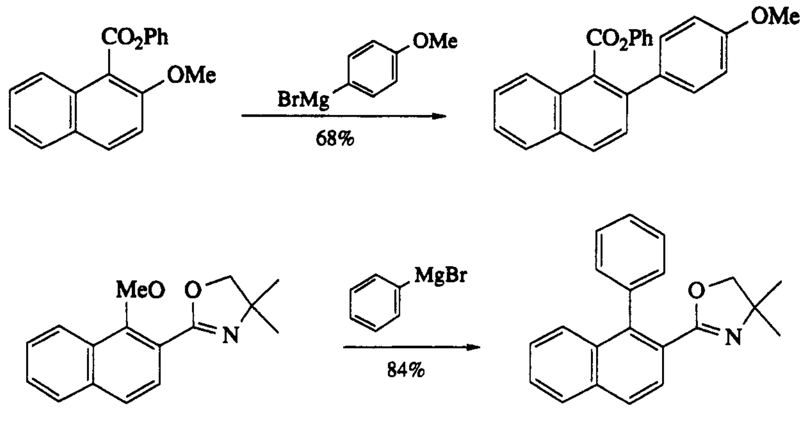

Scheme 42

of one (only) phenyl ligand from tetraphenyltin to an aryl halide using a palladium(II) catalyst.[153] Of potentially more general use is the finding that, under the influence of a $Pd^0$ catalyst, an aryl group can be transferred selectively from an aryltrialkylstannane to an aryl triflate; yields of biaryls are generally high, at least in the relatively simple cases so far studied.[94]

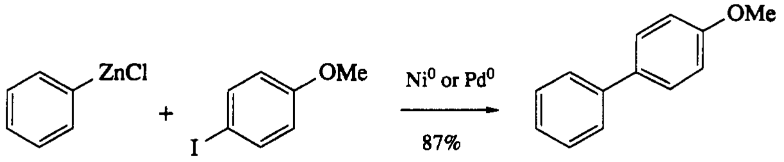

Scheme 43

The Suzuki method, using alkenylboronic acids as intermediates,[60–63,97] can also be applied with great effect to the synthesis of biaryls (Scheme 44).[154] Yields are generally excellent and either aryl bromides or iodides (but not chlorides) can be used. Methoxy, methoxycarbonyl and nitro functions at least do not interfere and the method seems to be relatively insensitive to steric factors; furthermore catalyst levels as low as 3 mol % are adequate. A useful combination for the elaboration of substituted biaryls and higher homologs is the *o*-lithiation methodology, due mainly to Snieckus and coworkers, followed by Suzuki-type coupling (Scheme 45).[155] A good method for formation of the intermediate boronic acid species proceeds *via* sequential *o*-silylation (TMS-Cl) and *ipso*-boro-desilylation using boron tribromide. A simple hydrolytic work-up using 5% aqueous HCl then delivers the boronic acid.

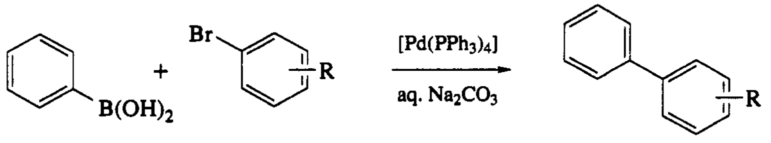

Scheme 44

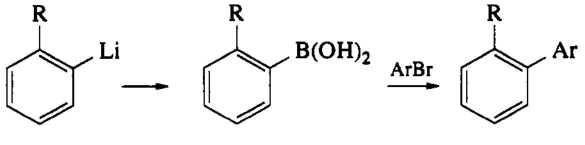

R = $OCONEt_2$; $CONPr^i_2$; OMOM; $NHCO_2Bu^t$

Scheme 45

Although not strictly belonging to the class of reactions indicated in equation (1), a number of other approaches to biaryls are worth noting as these can be very useful in some circumstances. For example, reactions proceeding *via* $S_{RN}1$ mechanisms can be especially useful for the introduction of aryl groups at positions adjacent to either amino[156] or hydroxy[157] functions (Scheme 46). The latter type of transformation can also be effected using triphenylbismuth carbonate[158] or other pentavalent bismuth species.[159] Aryllead triacetates [$ArPb(OAc)_3$] are also useful for aromatic arylation reactions, especially with electron rich substrates.[160] A classical method for biaryl synthesis, again somewhat outside the scope of this chapter, consists of basification of an aryldiazonium salt in the presence of a second aryl component, often benzene itself. Variously referred to as the Gomberg, Gomberg–Bachmann or Gomberg–Bachmann–Hey process,[161] this and related free radical type methods[162] give only moderate yields of biaryls, but at least they are generally simple reactions to carry out. Also closely related is the Meerwein arylation procedure,[101] wherein aryldiazonium species are coupled with aryls usually using copper(II) salts as catalysts. In general, the reactions work well only with electron poor substrates. A more recent development with the Gomberg reaction is the possibility of using phase transfer conditions resulting in considerable increases in yields relative to the classical methods.[163] The method is, however, still largely limited to the elaboration of relatively simple 2- and 4-monosubstituted biaryls. Related alternatives include the photolysis of aryl iodides in an aromatic solvent[164] or similarly of arylthallium trifluoroacetates; this latter method often delivers yields in excess of 80%, although it is rather limited to relatively simple products.[165] Many of the above methods are perhaps more suited to intramolecular biaryl formation.

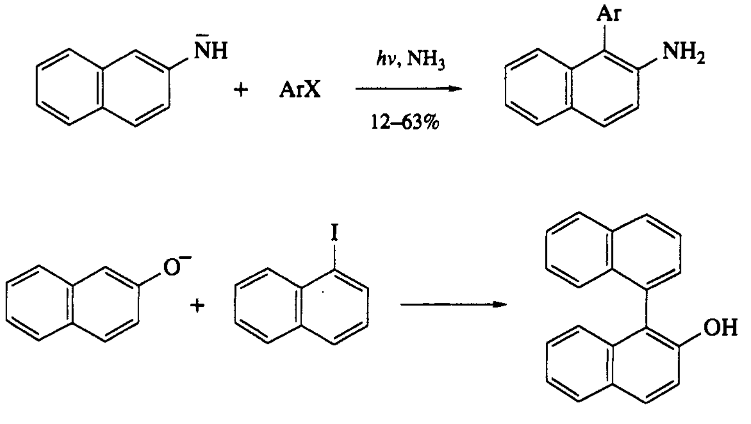

Scheme 46

### 2.3.3.3 Intramolecular Aryl–Aryl Coupling

The classical Ullmann procedure[110] has often been applied to ring closure reactions by formation of an aryl–aryl bond. In general, yields are much higher when electron-withdrawing groups are positioned *ortho* to the halogen atoms, which should be iodine rather than bromine (Scheme 47). Similar conditions (Cu bronze, reflux in DMF) can also be used to close a four-membered ring in respectable yield (Scheme 48). As with the intermolecular version, it is often preferable to use one of the usual copper reagents rather than copper(I) oxide.[166] At the other end of the scale, both 12- and 24-membered rings have been formed from substituted 1,1′-binaphthyls using this methodology, although in rather poor yields (*ca.* 10%).[167] Identical types of substrates can be cyclized under somewhat milder conditions by using conditions developed by Semmelhack and his coworkers, in which [$Ni(PPh_3)_4$] is used in place of copper powder.[132] This methodology has been elegantly illustrated in the natural product area by syntheses of the alnusone precursor (**110**) and the erythrina alkaloid skeleton (**111**; Scheme 49), although it is not suitable for syntheses in the steganone area (*vide infra*), possibly indicating a sensitivity to excessive steric crowding. Copper-mediated intramolecular coupling reactions of Grignard reagents[5] have also found occasional use in this area, as illustrated by a preparation of the 14π-aromatic system (**112**; Scheme 50).[168] The much lower temperatures required in this case are a particularly attractive feature. Similarly, aryllithium species can be coupled intramolecularly using copper salts; the particular example shown (Scheme 51) affords a 53% yield of the dimeric product, accompanied by only 3% of the monomeric dibenzocyclobutane.[5] More recently, palladium(II) catalysis has been found to be particularly effective for the ring closure of a monobromo precursor (Scheme 52).[169] The product (**113**), an advanced precursor of the unusual isoquinoline alkaloid ancistrocladine, is formed with reasonable stereoselectivity being accompanied by *ca*. 25% of the alternative diastereoisomer.

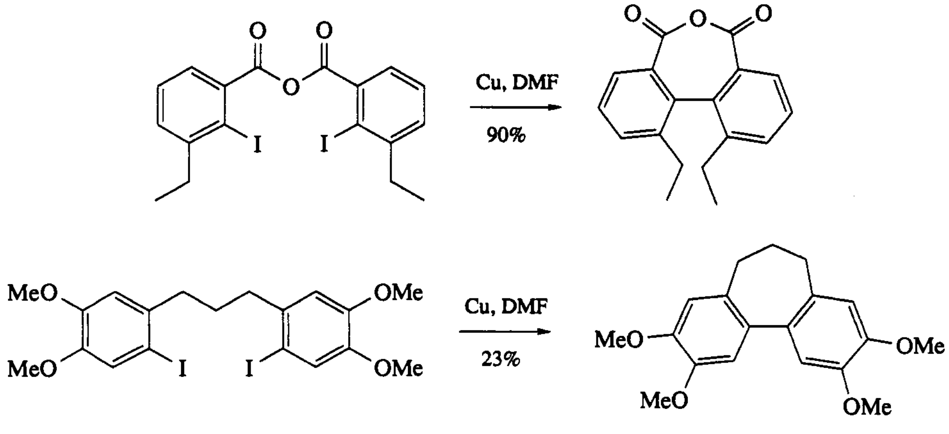

Cu, DMF
90%
Cu, DMF
23%
MeO
OMe
I

Scheme 47

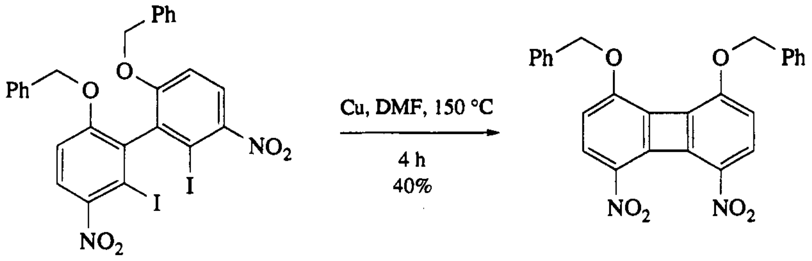

Ph
O
I
NO2
Cu, DMF, 150 °C
4 h
40%

Scheme 48

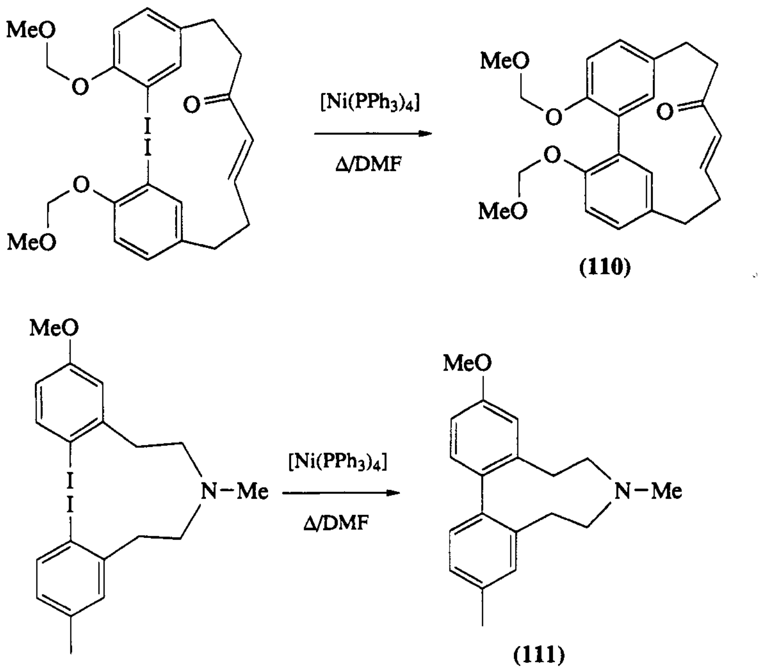

MeO
O
I
[Ni(PPh3)4]
Δ/DMF
N−Me

(110)

(111)

Scheme 49

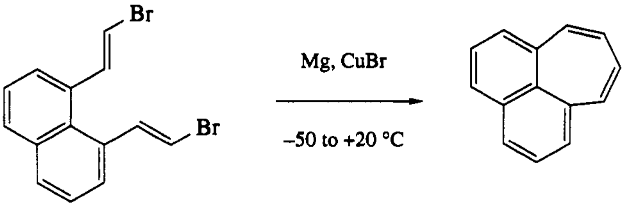

**(112)**

**Scheme 50**

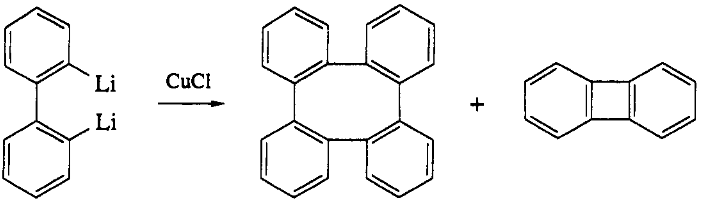

**Scheme 51**

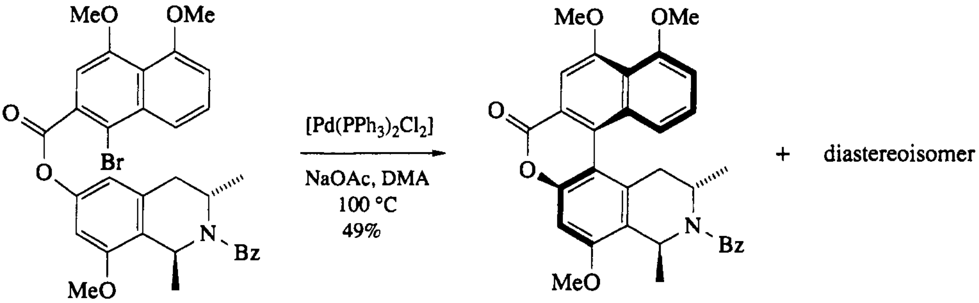

**(113)**

**Scheme 52**

In spite of the foregoing methods however, many of the most useful ring closure reactions of this type tend to involve either radical or aryl cationic intermediates. Although beyond the formal scope of this review, a brief survey is included here for the sake of completeness. A classical method is the Pschorr ring closure (Scheme 53), essentially an intramolecular version of the Gomberg–Bachmann–Hey process,[161,162] which can be triggered using the usual Gomberg conditions (*i.e.* basification) or by Meerwein-type arylation procedures by treatment with Cu$^I$ salts.[170] The poor yields which usually result from Pschorr closures have meant that the method does not enjoy a particularly prominent position in synthesis. However, one area where the reaction is particularly useful is in phenanthrene synthesis, especially when carried out under modified conditions. For example, when sodium iodide rather than a copper reagent is used, respectable yields can be realized (Scheme 54),[171] while a further improvement is to position a phenylsulfonyloxy function *para* to the site of attack (Scheme 54; R = $OSO_2Ph$).[172] A related photochemical cyclization of aryl iodides, the intramolecular version of methodology discussed above,[164] is also effective both for phenanthrene synthesis (Scheme 55)[173] and also for the elaboration of some alkaloid ring systems (Scheme 56).[174] Closely related to this is the overall oxidative ring closure between two unsubstituted positions by photolysis in the presence of iodine; the particular example shown (Scheme 57)[175] constitutes a key step in a synthesis of the natural alkaloid cryptopleurine. Indeed, some of the most useful methods in this area, especially for the elaboration of polymethoxylated natural products having at least one oxygen function *para* to the site of coupling (*cf.* Scheme 57), involve direct cyclization of substrates having no substituents at the two carbon sites to be coupled. In this respect, a combination of thallium(III) trifluoroacetate (TTFA) and boron trifluoride etherate is especially useful and has been used, for example, to prepare the biphenyl (**114**) from the unsubstituted precursor, in 81% yield, and aporphine (**115**), in 46% yield.[124] Similar nonphenolic oxidative couplings using vanadium(V)

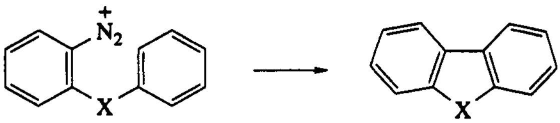

$\overset{+}{N}_2$
X
X

**Scheme 53**

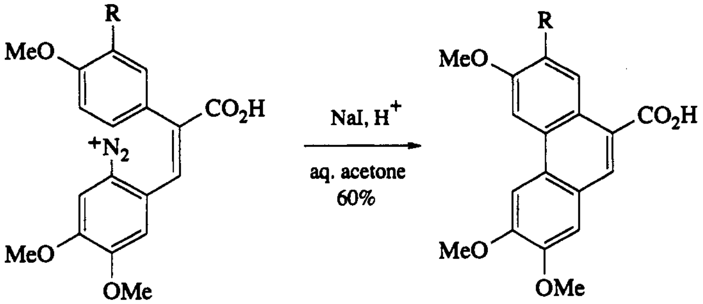

R
MeO
$CO_2H$
$^+N_2$
MeO
OMe
NaI, $H^+$
aq. acetone
60%
R
MeO
$CO_2H$
MeO
OMe

R = H

**Scheme 54**

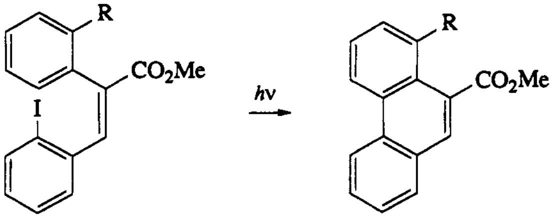

R
$CO_2Me$
I
$h\nu$
R
$CO_2Me$

**Scheme 55**

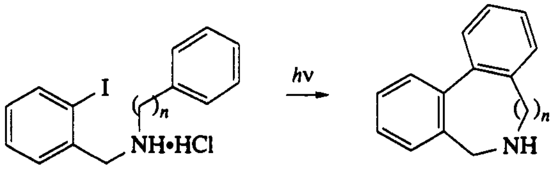

I
$( )_n$
NH•HCl
$h\nu$
$( )_n$
NH

$n = 1$, 57%; $n = 2$, 25%

**Scheme 56**

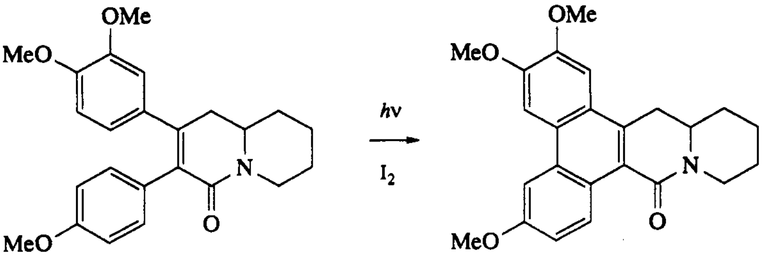

OMe
MeO
N
O
MeO
$h\nu$
$I_2$
OMe
MeO
N
O
MeO

**Scheme 57**

oxyfluoride generally produce lower yields than TTFA.[176] Subsequently, ruthenium(IV) tetrakis(trifluoroacetate) (RUTFA) has been found to be especially useful for carrying out such couplings in the steganane area.[177] The reagent is prepared from ruthenium dioxide, TFA–TFAA and boron trifluoride etherate and is said to be generally superior to TTFA; a particularly impressive example is a preparation of the highly crowded steganane (**116**) in 90–95% isolated yield using RUTFA at ambient temperature. The reagent is also useful for aporphine synthesis (*cf.* **115**).

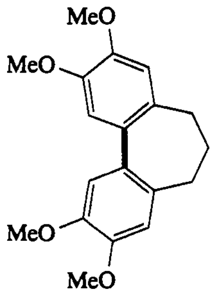

**(114)**

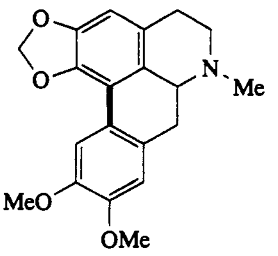

**(115)**

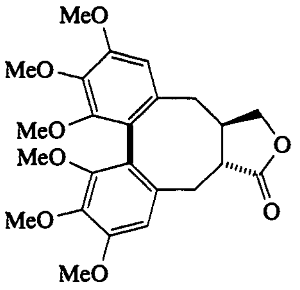

**(116)**

## 2.3.4 COUPLING REACTIONS INVOLVING HETEROARYLS

### 2.3.4.1 Heteroaryl–Heteroaryl Coupling

Not surprisingly, many of the methods described above are equally well-suited to the coupling of heteroaromatic intermediates. The Ullmann method[110] can be applied successfully to the dimerization of haloheteroaromatics (*e.g.* **117** → **118**) and to some cross-coupling reactions, where the reactivity differences[139] are sufficiently large (*e.g.* **119** → **120**). In general, this method is, however, less satisfactory when applied to five-membered heteroaromatics, although the intramolecular version has been used to prepare derivatives of this group (*e.g.* Scheme 58). Intermolecular dimerizations of furans and thiophenes are more efficiently carried out *via* the corresponding chloromercury derivatives, when the addition of catalytic amounts of palladium(II) chloride to a typical Ullmann system is particularly beneficial (Scheme 59).[23,134] The corresponding heteroaryllithium species can also be dimerized by treatment with a variety of transition metal salts.[5] The intermediacy of carbanions and the rather harsh Ullmann conditions can be avoided by direct coupling of heteroaryl halides using a variety of nickel(0) species. Although the earlier Semmelhack reagent, [Ni(COD)$_2$], does not appear to be particularly suitable,[128] bis(trialkylphosphine)nickel(0) species can give rise to excellent yields (*e.g.* Scheme 60).[19] In this particular case, an anionic intermediate would normally be precluded due to facile ring opening. This approach is also successful with similar coupling reactions of halothiophenes but fails with halopyridines. However, both of the latter substrate types can be dimerized using catalytic nickel salts in the presence of triphenylphosphine and a reducing metal such as zinc or magnesium.[130] An arylnickel(I) complex may well be involved. Such a system has been found to be superior to Ullmann-type methods in a synthesis of the mushroom toxin orellanine (Scheme 61).[178] An excellent alternative is the system NaH–Bu$^t$ONa–Ni(OAc)$_2$–PPh$_3$ which gives high yields of homocoupled products from chloro- or bromo-pyridines and -quinolines under mild conditions (DME, 30–60 °C, 1.5–3.5 h).[179] It has been established for some time that the parent of this class, 2,2′-bipyridyl, can be prepared directly from pyridine by oxidative coupling using Raney nickel;[180] much better yields are obtained by heating 2-bromopyridine or simple alkyl derivatives with stoichiometric quantities of Raney nickel in toluene.[181,196] Electrochemically generated palladium(0) species can also be used for the very efficient homocouplings of bromopyridines.[137]

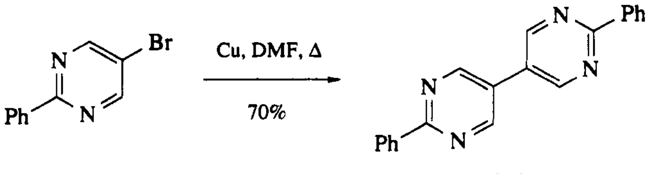

**(117)** **(118)**

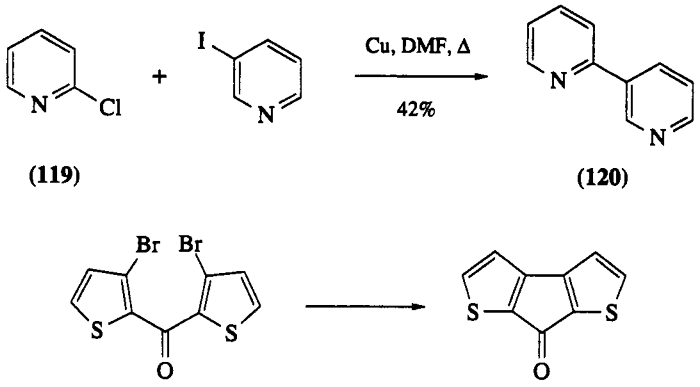

**(119)** **(120)**

Scheme 58

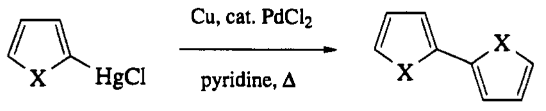

X = O, 86%; X = S, 95%

Scheme 59

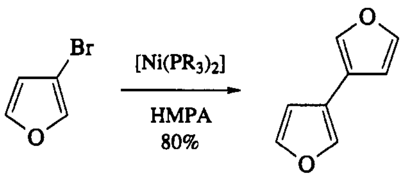

Scheme 60

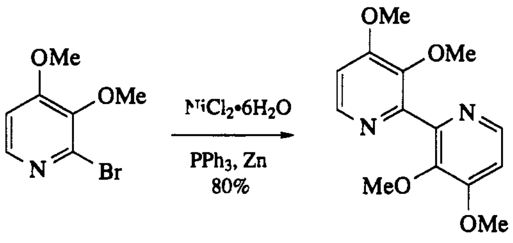

Scheme 61

Unsymmetrical bipyridyls can be readily obtained, although in variable yields (14–75%), by direct coupling reactions between pyridyl Grignard reagents and pyridyl sulfoxides.[182] A more versatile type of reaction of heterocyclic Grignard reagents is their palladium(0)-catalyzed coupling reaction with heteroaryl halides.[183,206] As well as being useful for the elaboration of a wide variety of unsymmetrical dimers, a whole range of oligomers can also be prepared using this methodology by, for example, sequential coupling with a heterocyclic dihalide, in which the two halogens have different reactivities (Scheme 62). A particularly good alternative to this procedure is the closely related Negishi method, wherein arylzinc species (derived from the corresponding aryllithium or aryl Grignard) undergo $Pd^0$-catalyzed coupling reactions with aryl halides (Scheme 63).[184] The method is applicable to both 2- and 3-pyridylzinc chlorides. Even more general, given the availability of the starting materials, is the corresponding coupling reactions between pyridylstannanes and bromopyridines (Scheme 64).[185] Also applicable to quinolines and presumably many related systems, the method has one significant drawback, that of the requirement for lengthy heating (*ca.* 12 h) in xylene. Chloropyridines are inert, which should allow some useful regioselective couplings to be carried out; furthermore two groups can be added at once, as in the conversion of the distannylpyridine (**121**) into the tripyridylnicotelline (**122**). It is probable that this type of coupling between a bromoaryl and an aryltin derivative will be very widely applicable and perhaps the method of choice in very many cases. For example, the 2-stannyloxazole (**123**) has been coupled with a wide variety of heteroaromatic bromides (2- and 3-thienyl, -furyl, -pyridyl and -quinonyl, 2-bromothiazole) to give excellent yields of the expected derivatives (**124**),[186] while a whole range of symmetrical and unsymmetrical thiazoles have been similarly prepared (Scheme 65).[187] However, another excellent route to unsymmetrical heterobiaryls, which also relies on a palladium(0) catalyst, is the Suzuki method,[58–66,97–99,154,155] wherein a heteroarylboronic acid is coupled with a heteroaryl halide.[188,212] Sequential additions of two aryl ligands to trialkoxyboranes can be used to obtain boronate species, which then collapse to give biaryls upon treatment with bromine or NBS; the methodology affords a variety of yields and is generally most suited to heteroaryl–heteroaryl coupling.[189]

Although beyond the scope of this section, some related approaches to these compounds are worth mentioning. 2-Substituted pyridines and quinolines can be obtained in two steps from the parent compounds following nucleophilic attack by an aryllithium (*e.g.* 2-thienyllithium) and then oxidation.[190] Intramolecular oxidative coupling reactions between the 2-positions of two indole nuclei can be achieved using DDQ, in the presence of a trace of tosic acid.[191] A very efficient route to a variety of unsymmetri-

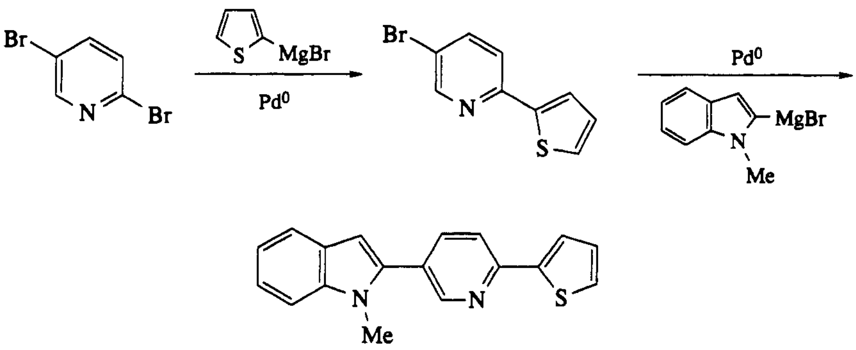

Scheme 62

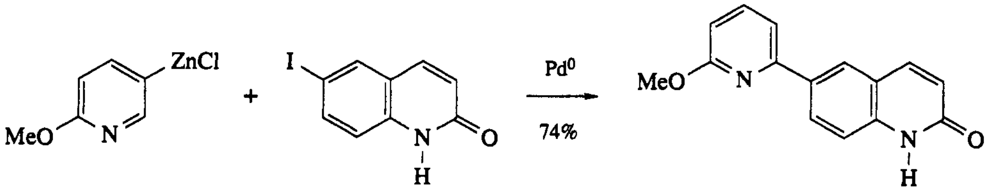

Scheme 63

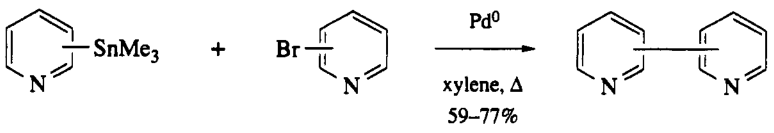

Scheme 64

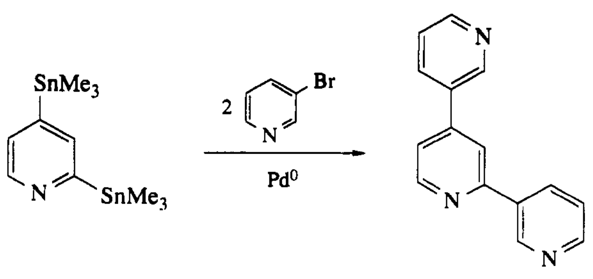

(**121**) (**122**)

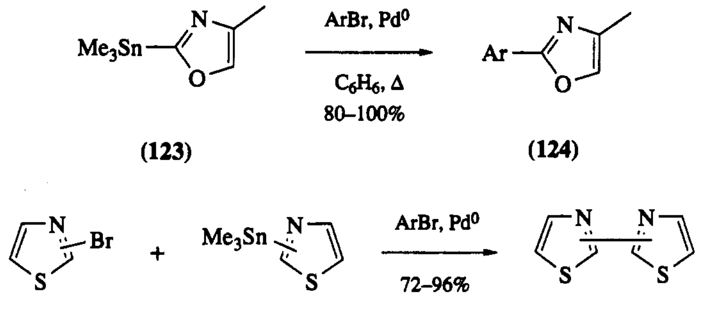

Scheme 65

cally substituted bithiophenes is by photolysis[164] of an iodothiophene in the presence of an excess of an α-unsubstituted thiophene.[192,213] Finally, a wide variety of Gomberg–Bachmann–Hey processes have been used to prepare biheterocyclic systems.[162]

### 2.3.4.2 Aryl–Heteroaryl Coupling

Almost all of the foregoing methods which can be used to prepare unsymmetrical biaryls or biheteroaryls have been, or probably could be, applied to the elaboration of targets belonging to this section. Given sufficient reactivity differences[139] between the two components, Ullmann-type coupling[110] can be one of the simplest and most efficient methods in this area. 2-Substituted thiophenes are particularly suitable adducts (Scheme 66),[193] whereas 2-furylcoppers are not such good substrates,[194] although the convenience could sometimes outweigh the relative inefficiency (Scheme 67).[126] Good yields (50–80%) of 2-arylpyridines (**125**) can also be obtained by the Ullmann approach from 2-pyridylcopper species and aryl halides, but using rather different conditions consisting of heating the reactants together with triphenylphosphine in toluene, rather than the more usual basic solvent.[195] In general, 2-arylpyridines (**125**) are among the most accessible of this group as they can be obtained by direct nucleophilic attack by aryllithiums or Grignard reagents at the 2-position of a pyridine nucleus, followed by a facile oxidation back to the aromatic level. For example, reaction between phenyllithium and 2,2′-bipyridyl in ether affords a 54% yield of the 2-phenyl derivative (**126**) after oxidation.[196] Similarly, reaction with 2-lithiopyridine leads to the expected terpyridine.[197] More highly substituted pyridines can be obtained from similar reactions with stannylated pyridinium salts (Scheme 68).[198] The bulk of the tin substituent directs the incoming nucleophile and hence the tricyclohexylstannyl derivative is preferred. The intermediate stannyldihydropyridine can be easily acylated using an acyl chloride and a palladium catalyst and finally oxidation, using *o*-chloranil, regenerates the pyridine nucleus. Similarly, pyridine *N*-oxides can be converted to 2-arylpyridines (**125**) by reaction with arylmagnesium bromides followed by acetylation ($Ac_2O$) and spontaneous elimination of acetic acid.[199] Alkoxysulfonyl groups in the 2-position of a pyridine nucleus can be displaced by aryllithiums, leading directly to 2-arylpyridines (**125**) in good to excellent yields;[200] halopyridines can undergo similar couplings.[201] A related approach to 4-arylpyridines relies on activation of the 4-position by an adjacent oxazoline function;[149] attack by phenylmagnesium bromide, or better phenyllithium, leads to a dihydropyridine and thence to the corresponding pyridine (**127**), following oxidation.[202] Presumably, other aryl- and heteroaryl-lithiums could also be used. Activation of the usually nucleophilic 3-position of an indole to nucleophilic substitution can be achieved by formation of the iodonium species (**128**) which upon reaction with phenyllithium, in the presence of boron trifluoride etherate, leads to 3-phenylindole (**129**) in 62% yield.[203]

In common with much of the foregoing chemistry, some of the most flexible and versatile methods in this area are based on nickel- or palladium-catalyzed coupling reactions between organometallic species

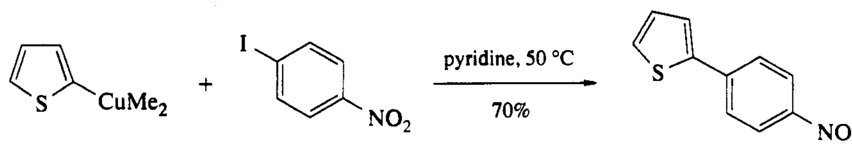

Scheme 66

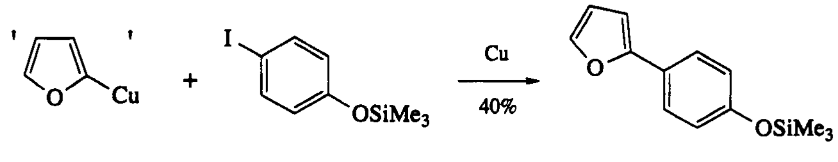

Scheme 67

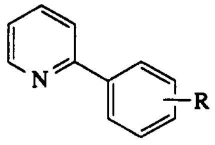

**(125)**

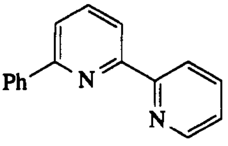

**(126)**

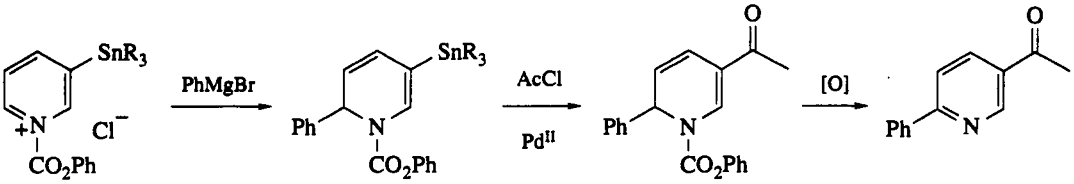

Scheme 68

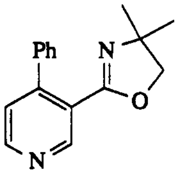

**(127)**

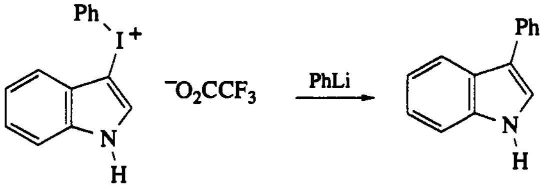

**(128)** **(129)**

and aryl halides. Particularly useful in this respect are nickel(II)-catalyzed couplings involving arylmagnesium halides;[26] for example, Grignard reagent (**130**) can be coupled to 3-bromothiophene to give the arylthiophene (**131**) in 67% yield.[204] Double couplings can similarly be carried out, as in the case of a preparation of the diarylthiophene (**132**) from the corresponding 2,5-dibromothiophene and 2 equiv. of an arylmagnesium bromide, which requires only 1 mol % of the catalyst [Ni(DPPP)$Cl_2$].[205] It is even possible to prepare unsymmetrical derivatives of thiophenes (**132**) by sequential coupling reactions with different Grignard reagents, but using a palladium catalyst in the first step. In addition to bromothiophenes, the methodology can also be extended to chloropyridines and various homologs, such as chloroquinolines,[206] and to the elaboration of nucleoside analogs (**133** and **134**).[207] The nickel-catalyzed displacement of alkylthio groups from $sp^2$-centers using Grignard reagents[29,79,83,146] has also been used to prepare purine analogs under closely similar conditions, (**135** → **136**);[208] the method can also be applied to highly efficient preparations of 4-phenylpyridines (**137**) and 2-phenylindole (**138**) from the respective 4- and 2-methylthio derivatives.

Equally useful palladium-catalyzed coupling reactions between aryl halides and aryl organometallics have been developed, in which the latter component is usually either a trialkylstannane derivative or the corresponding arylzinc chloride species. In contrast to the foregoing nickel-mediated couplings with

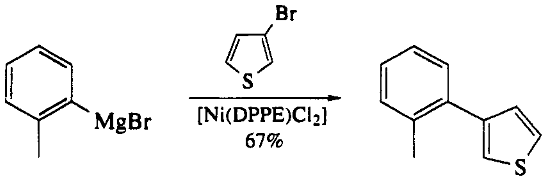

**(130)** **(131)**

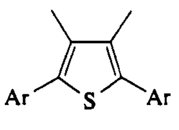

**(132)**

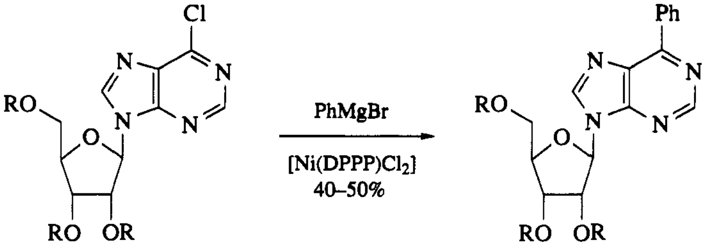

**(133)** **(134)**

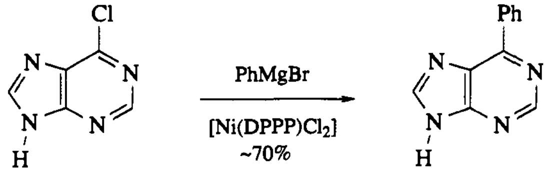

**(135)** **(136)**

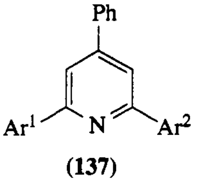

**(137)**

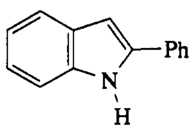

**(138)**

arylmagnesium halides, the palladium-catalyzed processes often work best when the organometallic component is derived from the heteroaromatic substrate which is then reacted with an aryl halide, usually the bromide or iodide. A study in which compounds (**139**)–(**144**) were prepared in generally excellent yields from the corresponding heteroaryltrimethylstannane and iodobenzene serves to exemplify the potential of this methodology.[209] In all these examples, [$PdCl_2(PPh_3)_2$] was used as the catalyst; in a related study, coupling between a rather unstable 2-trimethylstannylbenzofuran and a protected iodoresorcinol has been achieved using [$Pd(PPh_3)_4$], leading to the arylbenzofuran (**145**).[210] In this example, coupling reactions with the tin derivative of the benzofuran were found to be more suitable than either use of the corresponding zinc bromide (*vide infra*) or coupling in the reverse sense, between the 2-bromobenzofuran and an arylzinc bromide. Particularly notable in this type of coupling is the tolerance of a wide range of functional groups, especially esters, acetates, nitriles and chlorines. Further examples of this approach are provided by coupling reactions between the 2-stannyloxazole (**123**) and a range of substituted bromobenzenes, including the 4-F, 4-Me, 4-SPh and 2-CN derivatives.[186] Also, using [$Pd(PPh_3)_4$] as catalyst, the process is relatively mild (reflux, $C_6H_6$, 12–24 h) and usually very efficient (80–100% yields), even when a 2-substituent is present. The related procedure wherein arylstananes are coupled with aryl triflates[94] has been applied to an arylheteroaryl example, the alkaloid dubamine (**146**), which was obtained in 79% yield from the corresponding 2-quinolyltriflate and 5-(trimethylstannyl)-1,3-benzodioxole ([$Pd(PPh_3)_4$], LiCl, dioxane, 98 °C, 68 h); it seems highly probable that this approach will find wide application in the elaboration of substituted heteroaromatics.

Despite some of the foregoing observations,[210] Negishi-type coupling reactions between furylzinc chlorides and bromobenzenes catalyzed by [$Pd(PPh_3)_4$] have been found to be valuable for the preparation of arylfurans (Scheme 69).[211] Also applicable to the corresponding thiophenes, a particularly interesting aspect of this chemistry is the coupling of the bis(zinc chloride) (**147**) with 1,4-dibromobenzene,

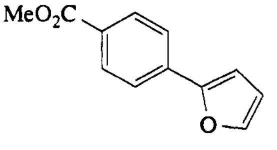

**(139)**

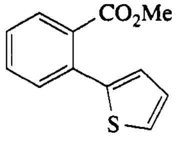

**(140)**

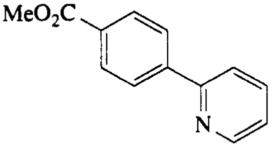

**(141)**

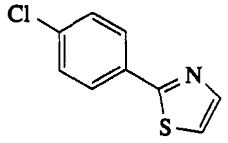

**(142)**

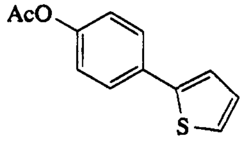

**(143)**

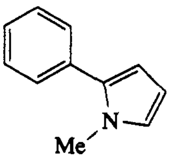

**(144)**

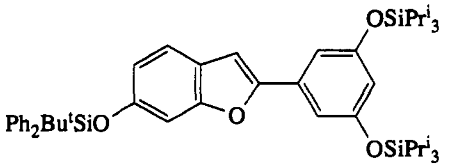
OSiPr$^i_3$
Ph$_2$Bu$^t$SiO
O
OSiPr$^i_3$

**(145)**

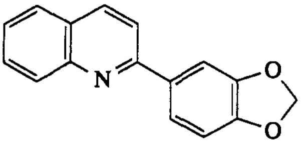

**(146)**

which gives rise to a series of potentially useful polymers. One or both of the zinc groups in the dianion (**147**) can be replaced by monobromobenzene simply by using 1 or 2 equiv. of the latter.

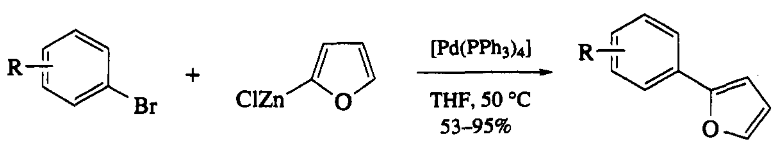
R
Br
+
ClZn
O
[Pd(PPh3)4]
THF, 50 °C
53–95%
R
O

**Scheme 69**

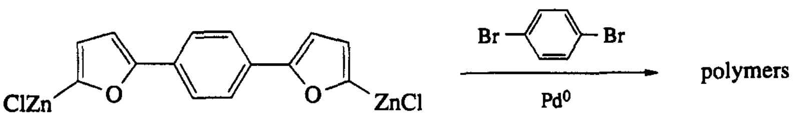
ClZn
O
O
ZnCl
Br
Br
Pd0
polymers

**(147)**

The Suzuki boronic acid method[58–66,97–99,154,155,188] is also likely to enjoy many applications in this area; one example is a brief and efficient synthesis of 5-arylnicotinates (Scheme 70).[212] One limitation of this approach, however, is its sensitivity to substituents *ortho* to the site of coupling.

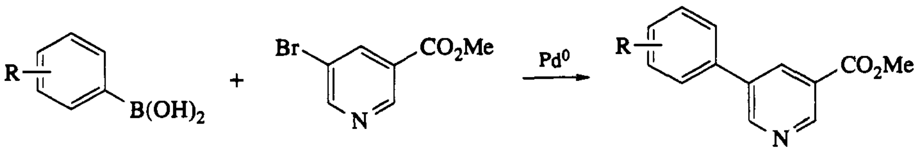
R
B(OH)2
+
Br
CO2Me
N
Pd0
R
CO2Me
N

**Scheme 70**

A simple route to the phenylthienyl ketones and aldehydes (**148**) and (**149**) consists of photolysis of the corresponding bromothienylcarbonyl compounds in benzene,[213] in a similar fashion to the preparation of phenylbenzenes from iodobenzenes[164] and of bithiophenes from iodothiophenes.[192]

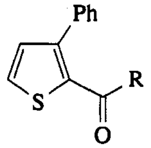

**(148)**

R = H or alkyl

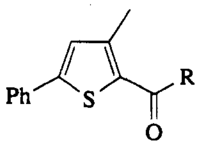

**(149)**

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# 2.4

# Coupling Reactions Between *sp*$^2$ and *sp* Carbon Centers

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## 2.4.1 INTRODUCTION

A $\sigma$-bond between *sp*$^2$- and *sp*-carbon centers can be formed either by vinylation of a 1-alkyne or an organometallic alkynyl, or by alkynylation of a vinyl organometallic reagent.[1–3] Several copper(I) alkynides undergo successful coupling reactions with halogen compounds in which the halogen is linked to an *sp*$^2$-carbon center (vinylic, allenic, aromatic and heteroaromatic carbon). In all cases, however, a stoichiometric amount of a copper(I) salt appears to be necessary, which makes the synthesis less attractive for performance on a large scale.[4–6]

During the past 15 years, enormous advances have been made in the area of transition metal mediated reactions in organic synthesis. Two important transition metal mediated reactions are available for the coupling of alkynes with the halogen-bearing *sp*$^2$-carbon compounds mentioned above. These are: (i) reaction of the free alkyne with the halide in the presence of a catalytic amount of Pd$^0$ or Pd$^{II}$ complexes, copper(I) iodide and an excess of an amine; here the amine is not only used as the solvent but also as a scavenger for the hydrogen halides generated during the reaction (equation 1);[7] and (ii) reaction of metallated alkynes, preferably alkynylzinc halides, with the halogen compound in the presence of catalytic amounts of Pd$^{II}$ or Pd$^0$ compounds (equation 2).[8,9] As usual, the reactivity order with respect to the halogen bound to the $sp^2$-carbon is I > Br > $Cl^2$ and with respect to the $sp^2$-center is vinylic > allenic > heteroaromatic > aromatic.

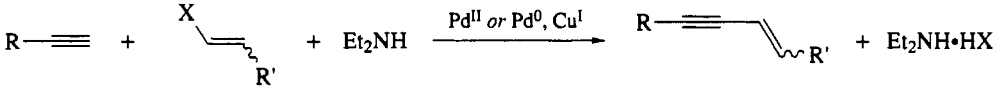

(1)

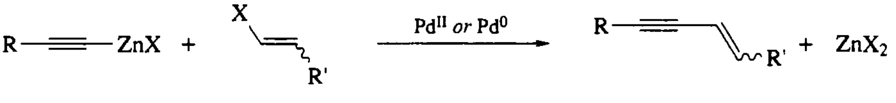

(2)

## 2.4.2 CROSS-COUPLING REACTIONS BETWEEN ORGANOMETALLIC REAGENTS AND VINYL, ARYL AND ALKYNYL HALIDES AND RELATED COMPOUNDS

### 2.4.2.1 Organocopper Reagents

Organocopper and organolithium alkylcuprate reagents are finding ever-increasing usage in organic synthesis. Normally, these reagents are produced from the reaction between an organolithium or Grignard reagent and an appropriate copper(I) salt. Accordingly, the types of functional groups that can be tolerated are rather limited.[4–6] Rieke and his coworkers[10] have reported the preparation of a highly reactive zerovalent copper slurry, which readily undergoes oxidative addition to aryl, vinyl, alkynyl and alkyl halides under mild conditions. The corresponding organocopper reagents are stable and they undergo the usual types of homo- and cross-coupling reactions. Moreover, these reagents can be prepared in the presence of a variety of functional groups such as nitro, nitrile, ester and ketone.

The reaction of aryl halides with copper(I) alkynides is known as the Castro reaction (equation 3).[4] The reaction has proved to be particularly important in the synthesis of a wide range of tolan and heteroaromatic alkynes. Vinyl and allenic halides[11–13] can also be used and several reviews of the reaction have been published.[5,6,14–16]

$$\mathrm{Ar{-}{\equiv}{-}Cu} + \mathrm{XAr'} \xrightarrow{\text{pyridine } or \text{ TMEDA}} \mathrm{Ar{-}{\equiv}{-}Ar'} \qquad (3)$$

Aryl and alkenyl copper compounds also couple reasonably well with haloalkynes, leading to conjugated enynes (equations 4 and 5).[17,18] Normant *et al.* have reported that TMEDA is essential to promote the clean coupling of alkenylcopper reagents with 1-halo-1-alkynes (equation 5).[18,19] Alkenylcopper(I) derivatives undergo substitution with retention of configuration about the C—C double bond, leading to conjugated and functionalized enynes. However, Brown and his coworkers have pointed out that the TMEDA is not necessary and is, in fact, detrimental to the desired process.[20] Thus, alkenylcopper intermediates, which are readily generated from alkenylboron derivatives of 9-BBN, undergo coupling with 1-haloalkynes to provide stereodefined conjugated enynes of high isomeric purity and in 90–98% yields (Scheme 1). The same coupling reaction can be catalyzed using bis (acetylacetonate)copper.[21]

More recently, the stereoselective formation of 1,3-enynes has been reported, *via* a new carbon–carbon bond-forming reaction, involving the direct coupling of alkenyliodinium tosylates (**1**) with alkenylcopper(I) reagents.[22] A wide variety of alkynylcopper reagents (**2**) are easily made by addition of alkylcop-

$$\mathrm{PhCu} + \mathrm{I{-}{\equiv}{-}SiMe_3} \longrightarrow \underset{64\%}{\mathrm{Ph{-}{\equiv}{-}SiMe_3}} \qquad (4)$$

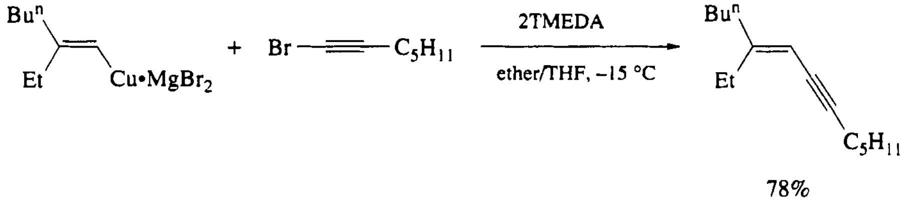

(5)

78%

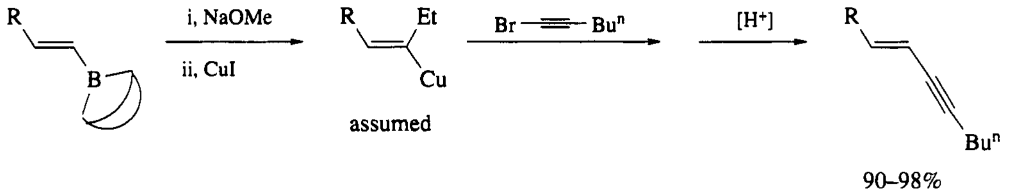

**Scheme 1**

per reagents to terminal alkynes. The reaction is highly selective and occurs with complete retention of the alkenyl geometry. Furthermore, this stereospecific high-yielding route to conjugated enynes has been utilized in the synthesis of insect pheromones and other interesting natural products. What makes the method particularly attractive, as demonstrated by Scheme 2, is that by simple choice of the order of addition of the alkenylcopper reagent to the alkyne, either geometric isomer around the C—C double bond in the 1,3-enyne product may be obtained in pure form. This simple process, complementing the Pd–Cu-catalyzed *sp*$^2$–*sp* carbon couplings, will be of considerable synthetic utility (see Section 2.4.3.5).

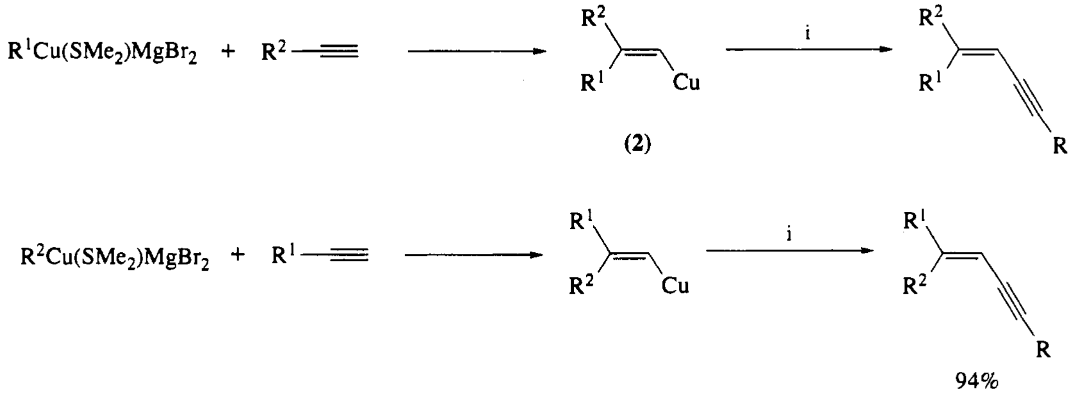
$R^1Cu(SMe_2)MgBr_2$ + $R^2$—≡
(2)
i
$R^2Cu(SMe_2)MgBr_2$ + $R^1$—≡
i
94%

i, R—≡—$\overset{+}{I}$Ph TsO$^-$, Et$_2$O, −78 to 25 °C, 12 h
(1)

**Scheme 2**

### 2.4.2.2 Alkynylboranes

The reactions of alkenyl- and alkynyl-boranes can provide efficient and selective methods for the coupling between two unlike boron-bound groups. General, highly stereoselective (>99%) syntheses of conjugated *trans*-enynes can be obtained by treatment of alkenylalkynylboranes (4), derived from the alkenylborane (3) and alkynyllithiums, with iodine (Scheme 3).[23] In addition, the alkynyl-9-BBN·THF complexes (5) undergo a facile reaction with enol alkyl ethers of β-keto aldehydes in hexane at room temperature to provide conjugated enynones (6) in excellent yields (Scheme 4).[24]

The (*Z*)-alkynylhaloalkenes (7) can be synthesized in relatively good yields from 1-alkynes in a regio- and stereo-selective manner, following haloboration with Br-9-BBN and subsequent treatment with lithium alkynides and iodine (Scheme 5).[25,26]

## 2.4.3 PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING REACTIONS

Transmetallations from main group metals to organometallic species produced by oxidative addition processes are becoming increasingly important in *sp*$^2$–*sp* carbon-coupling reactions (Scheme 6). In contrast to *sp*$^2$–*sp*$^2$ or *sp*$^3$–*sp*$^2$ coupling reactions, the product yields in Ni-catalyzed *sp*$^2$–*sp* coupling processes such as aryl–alkynyl and alkenyl–akynyl have been substantially lower than those realized with Pd catalysts, presumably because the alkynyl starting compound and/or product tends to react with the Ni catalyst to afford polymers and cyclic oligomers.

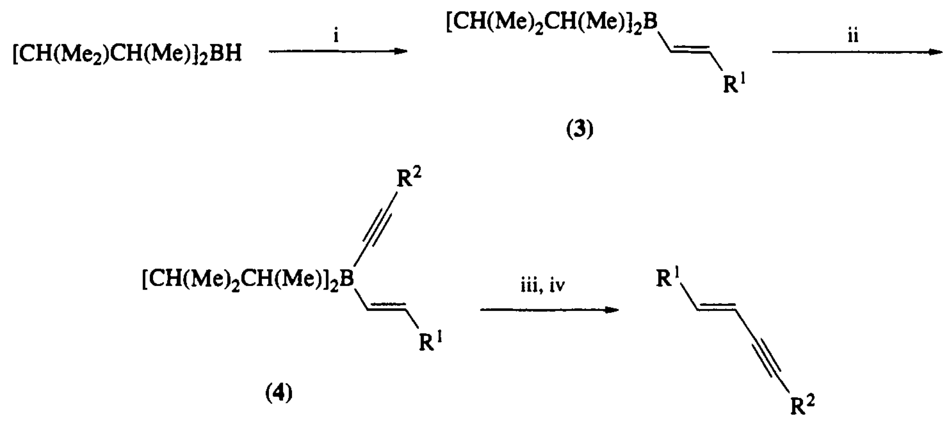

i, H—≡—R$^1$, THF, 0 °C, 1 h; ii, Li—≡—R$^2$, THF/hexane, –50 °C, 1 h;

iii, $I_2$, THF, –78 to 25 °C; iv, 3 N NaOH, 25 °C

**Scheme 3**

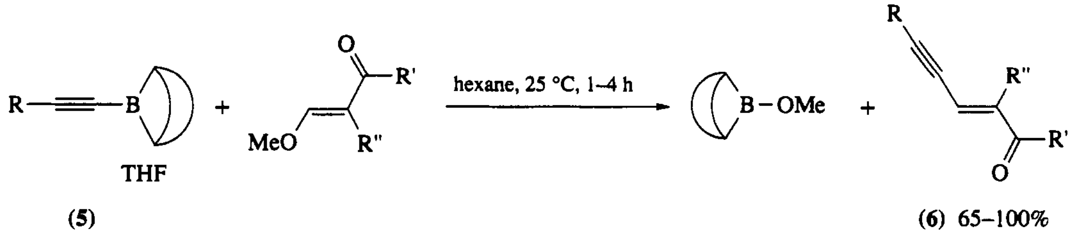

**Scheme 4**

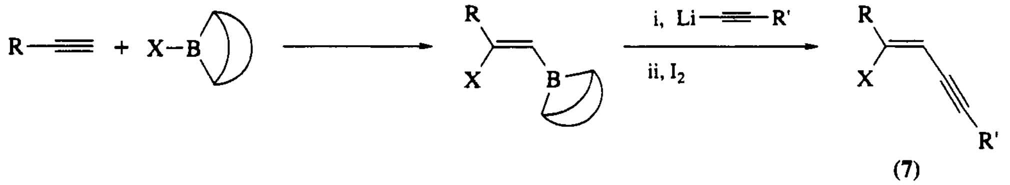

R = R' = alkyl, cycloalkyl; X = Br, I

**Scheme 5**

A species such as (**8**), formed *via* transmetallation, often undergoes reductive elimination to complete a very useful coupling reaction. Thus, magnesium,[27] boron, zinc and tin are effective. The major asset of this method is the complete retention of the configuration in the alkene, resulting in products of exceptional isomeric purity. The halides involved include aromatic, alkenyl and allenyl. Several reviews of this method have been published.[8,9,28–34]

### 2.4.3.1 Alkynylzinc Chlorides

The Pd-catalyzed reactions of alkynylzinc chlorides, which are readily obtainable from zinc chloride, with alkenyl iodides or bromides provide the corresponding terminal or internal enynes in high yield and with high (>97%) stereospecificity (Scheme 7).[35] Aryl bromides or iodides can also be used to produce arylalkynes (equation 6).[36,37]

The interesting stereospecific Pd-catalyzed cross-coupling reactions of 1-alkynylzinc chlorides (**9**) with a diastereoisomeric mixture of alkenyl halides (**10**) have been described. The (*E*)-bromoalkene reacts preferentially in these reactions to afford good yields of (*E*)-enynes (**11**), (**12**) and (**13**) having very

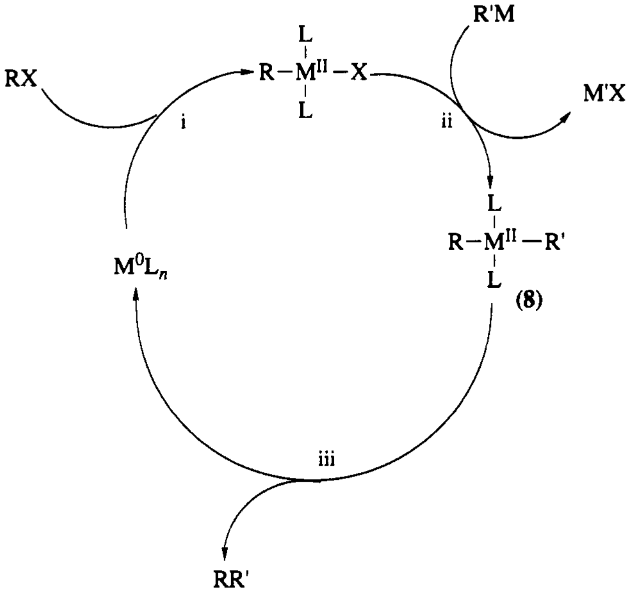

i, oxidative addition; ii, transmetallation; iii, reductive elimination

**Scheme 6**

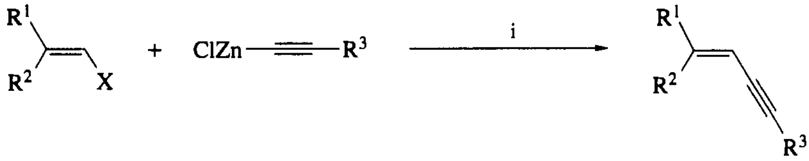

70–87%

$R^1$ = H, $Bu^n$, $CO_2Me$; $R^2$ = H, Me, Et, $Bu^n$; $R^3$ = H, $Bu^n$, n-$C_5H_{11}$; X = Br, I

i, Catalyst $PdL_n$ (L = $PPh_3$), 0–25 °C, THF

**Scheme 7**

$$R{-}{\equiv}{-}ZnCl + ArX \xrightarrow{PdL_n,\ 25\ °C,\ THF} R{-}{\equiv}{-}Ar \qquad (6)$$

66–94%

R = H, alkyl, aryl; X = I or Br

high stereoisomeric purities (equations 7, 8 and 9).[38–40] The enynes can easily be selectively transformed into the corresponding dienes, which may be used to prepare stereodefined polyunsaturated natural products.

Several fluorinated enynes (**14**) have been prepared by the reaction of alkynylzinc chlorides with fluoroalkenyl iodides (equation 10),[41] and the Pd-catalyzed cross-coupling reactions of aryl fluoroalkanesulfonates with organozinc reagents have been reported (equation 11).[42]

A general and convenient route to conjugated diynes, especially terminal diynes from the corresponding chloroenynes, has been developed.[43] Thus, readily available (*E*)-iodochloroethylene is first reacted with alkynylzinc derivatives in the presence of a Pd–phosphine complex catalyst to produce (*E*)-chloroenynes (**15**) in high yield. The chloroenynes (**15**) can then be readily converted into the corresponding

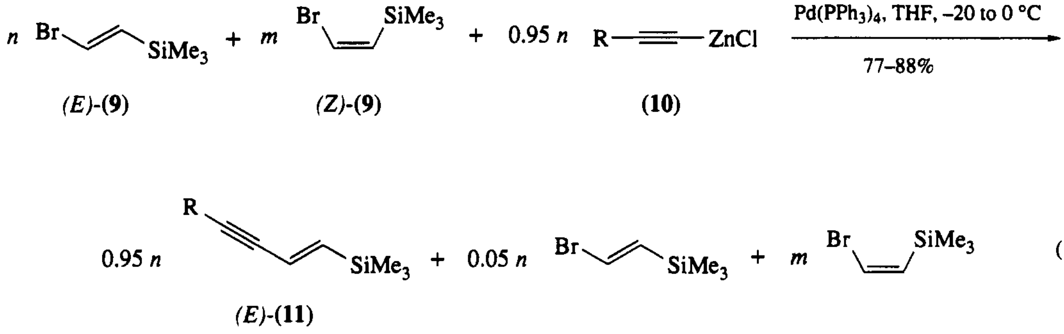
n
(E)-(9)
m
(Z)-(9)
0.95 n
(10)
Pd(PPh3)4, THF, -20 to 0 °C
77–88%
0.95 n
(E)-(11)
0.05 n
m

(7)

stereoisomeric purity ≈ 99.5%; R = n-$C_5H_{11}$, Ph, $Me_3Si$

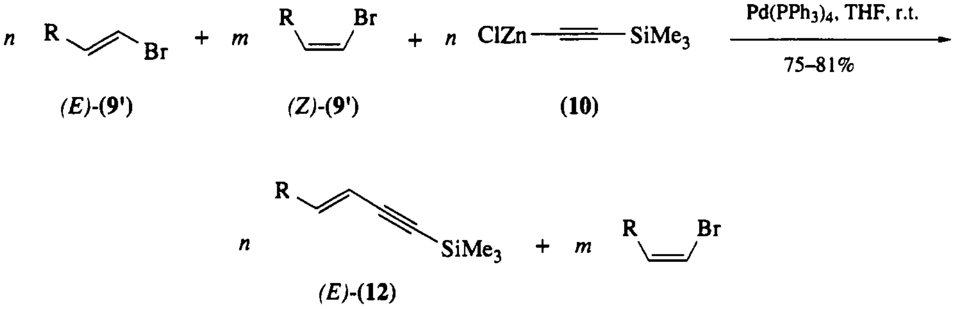
n
(E)-(9')
m
(Z)-(9')
n
(10)
Pd(PPh3)4, THF, r.t.
75–81%
n
(E)-(12)
m

(8)

stereoisomeric purity ≈ 95.5–98.4%; R = $Pr^n$, $Bu^n$, n-$C_5H_{11}$

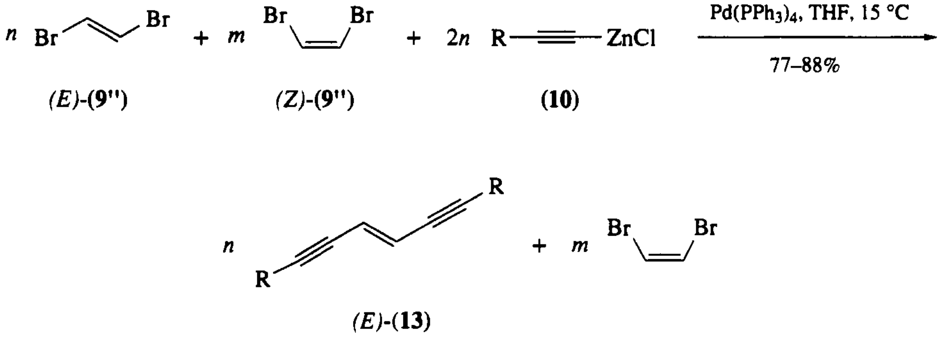
n
(E)-(9'')
m
(Z)-(9'')
2n
(10)
Pd(PPh3)4, THF, 15 °C
77–88%
n
(E)-(13)
m

(9)

stereoisomeric purity ≈ 99.5%; R = $Bu^n$, n-$C_5H_{11}$, Ph, $Me_3Si$

$$R_fI + R{-}{\equiv}{-}ZnCl \xrightarrow[\phantom{x}]{Pd(PPh_3)_4,\ THF,\ 20\ °C,\ 1\text{–}24\ h} \underset{\substack{62\text{–}90\% \\ \mathbf{(14)}}}{R_f{-}{\equiv}{-}R} \qquad (10)$$

$R_f$ = $CF_2{=}CF$, $CF_2{=}CH$, $Bu^sCF{=}CF$ *(Z)*, $C_7H_{15}CF{=}CF$ *(E)*; R = $Bu^n$, n-$C_6H_{13}$

sodiodiynes (**16**), which can be transformed into terminal diynes (**17**), silylated diynes (**18**) and internal diynes (**19**; Scheme 8).

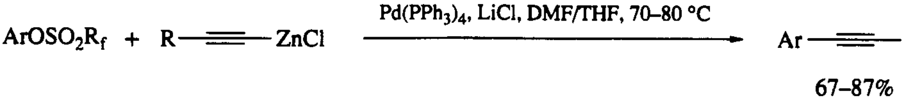
ArOSO$_2$R$_f$ + R—≡—ZnCl
Pd(PPh$_3$)$_4$, LiCl, DMF/THF, 70–80 °C
Ar—≡—R
67–87%

(11)

R = Bu$^n$, MeOCH$_2$, Ph; Ar = Ph, $p$-ClC$_6$H$_4$, $o$-ClC$_6$H$_4$, $m$-MeOC$_6$H$_4$, $p$-NO$_2$C$_6$H$_4$
R$_f$ = CF$_3$, H(CF$_2$CF$_2$)$_n$OCF$_2$CF$_2$ ($n$ = 1, 2)

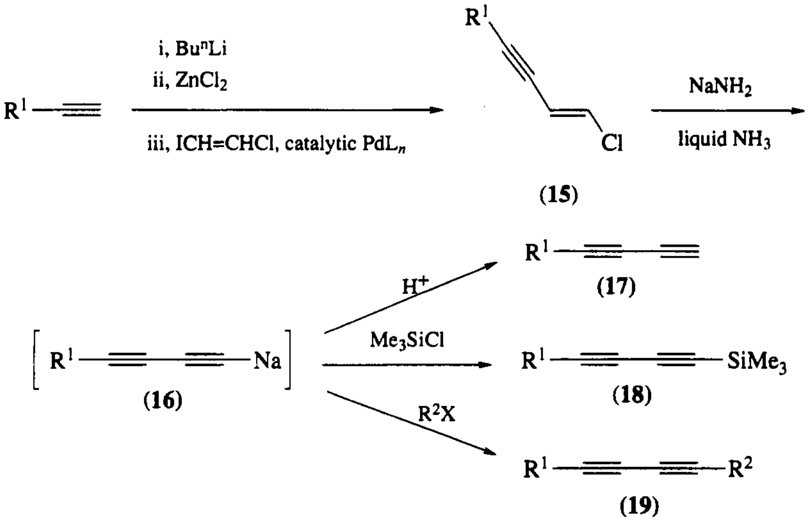
R$^1$—≡
i, Bu$^n$Li
ii, ZnCl$_2$
iii, ICH=CHCl, catalytic PdL$_n$
R$^1$
Cl
(15)
NaNH$_2$
liquid NH$_3$
R$^1$—≡—≡—Na
(16)
H$^+$
R$^1$—≡—≡
(17)
Me$_3$SiCl
R$^1$—≡—≡—SiMe$_3$
(18)
R$^2$X
R$^1$—≡—≡—R$^2$
(19)

**Scheme 8**

### 2.4.3.2 Alkynylmagnesium Halides

The palladium-catalyzed cross-coupling reactions of vinyl iodides with alkynylmagnesium halides have been found to occur with retention of configuration (>97%; equation 12).[44] Using this procedure, the dithienylenyne (**20**), which is a natural antifungal and nematicidal agent, can be prepared by a combination of Pd-catalyzed cross-couplings (Scheme 9).[45]

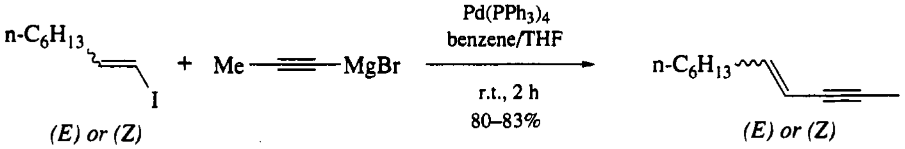
n-C$_6$H$_{13}$
I
(E) or (Z)
+ Me—≡—MgBr
Pd(PPh$_3$)$_4$
benzene/THF
r.t., 2 h
80–83%
n-C$_6$H$_{13}$
(E) or (Z)

(12)

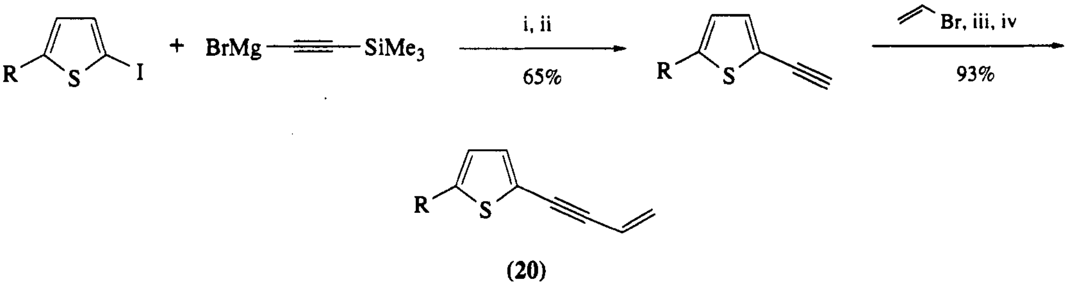
R
S
I
+ BrMg—≡—SiMe$_3$
i, ii
65%
R
S
Br, iii, iv
93%
R
S
(20)

R = 2-thienyl, phenyl

i, Pd(PPh$_3$)$_4$, THF, benzene; ii, KOH, MeOH; iii, EtMgBr, THF; iv, CH$_2$=CHBr, Pd(PPh$_3$)$_4$, benzene

**Scheme 9**

The Ni-catalyzed cross-coupling reaction of alkynyl Grignard reagents (**21**) with *trans*-dichloroethylene (**22**) has been applied to a simple procedure for the preparation of the protected form (**23**) of an extremely unstable synthon, hexadiynene (**24**). Separation of the diastereomers (**23a** from **23b**) is facile since the former is an oil and the latter is a solid (Scheme 10).[46]

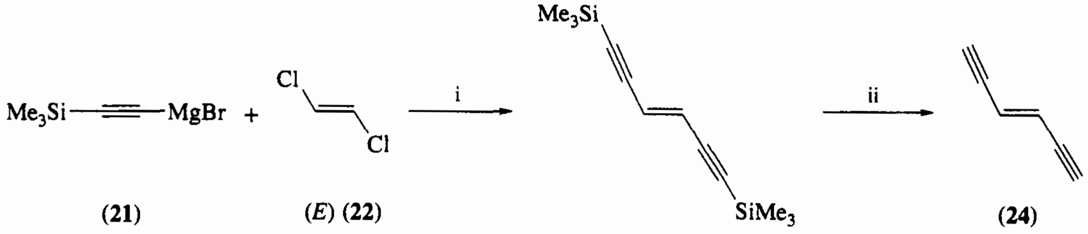
Me3SiC≡CMgBr +
Cl
Cl
i
Me3Si
SiMe3
ii
(21)
(E) (22)
(24)

(**23a**) (*E*)-isomer
(**23b**) (*Z*)-isomer

i, Ni(dppp)Cl$_2$, dppp = Ph$_2$P(CH$_2$)$_3$PPh$_2$; ii, NaH–catalyst, MeOH/dry THF

**Scheme 10**

Recently, a mechanism for the cross-coupling reaction between phenyl iodide and methylmagnesium iodide, catalyzed by *cis*- and *trans*-[(PEt$_2$Ph)$_2$Pd(Ph)(I)], was proposed (Scheme 11).[47] The toluene produced from *cis*-(**25**) is thought to result *via* an intramolecular reductive elimination process without predissociation of the phosphine ligand.

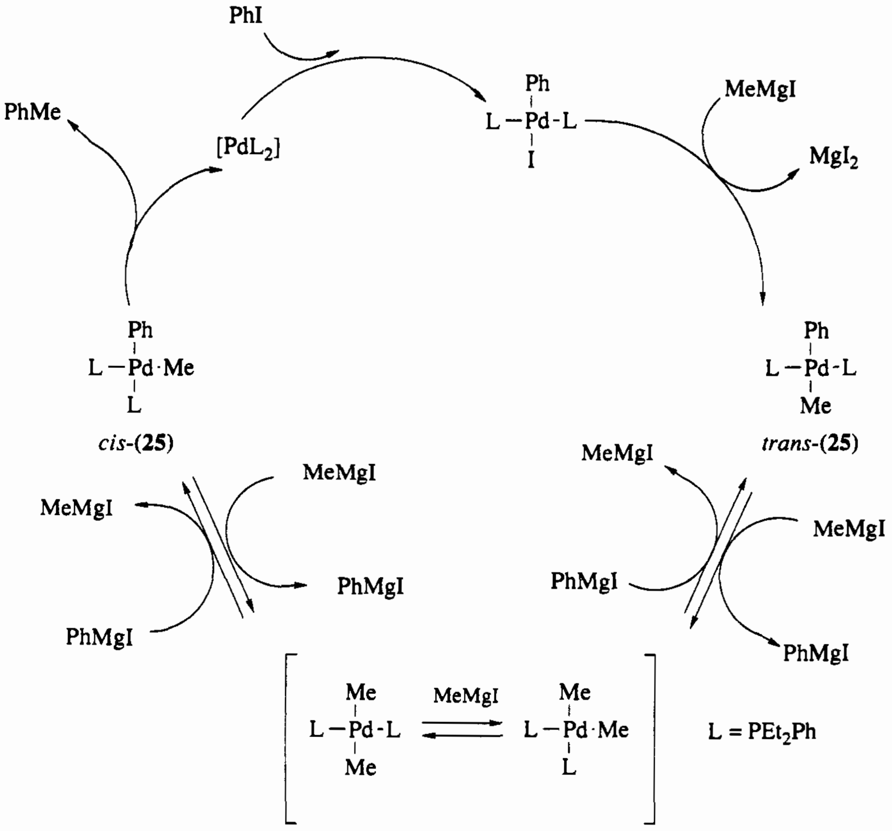
PhI
PhMe
[PdL2]
Ph
L−Pd-L
I
MeMgI
MgI2
Ph
L−Pd·Me
L
cis-(25)
Ph
L−Pd-L
Me
trans-(25)
MeMgI
MeMgI
PhMgI
PhMgI
MeMgI
MeMgI
PhMgI
PhMgI
Me
L−Pd-L
Me
MeMgI
Me
L−Pd·Me
L
L = PEt2Ph

**Scheme 11**

### 2.4.3.3 Alkynyltin Reagents

The reactivity of tin–carbon bonds allows the creation of new *sp–sp*$^2$ carbon to carbon bonds through substitution reactions. General reviews of the organotin route for carbon–carbon bond formation are available.[28-31] With Pd catalysis, alkynyl groups are more readily transferred than alkyl groups to the aryl or vinyl iodides to afford *sp–sp*$^2$ carbon bonds (equations 13 and 14).[48,49]

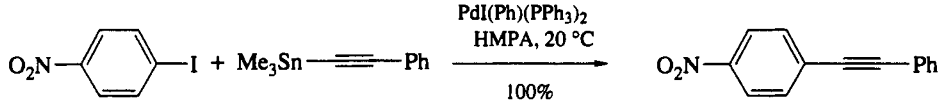
O$_2$N
I
Me$_3$Sn
Ph
PdI(Ph)(PPh$_3$)$_2$
HMPA, 20 °C
100%
O$_2$N
Ph

(13)

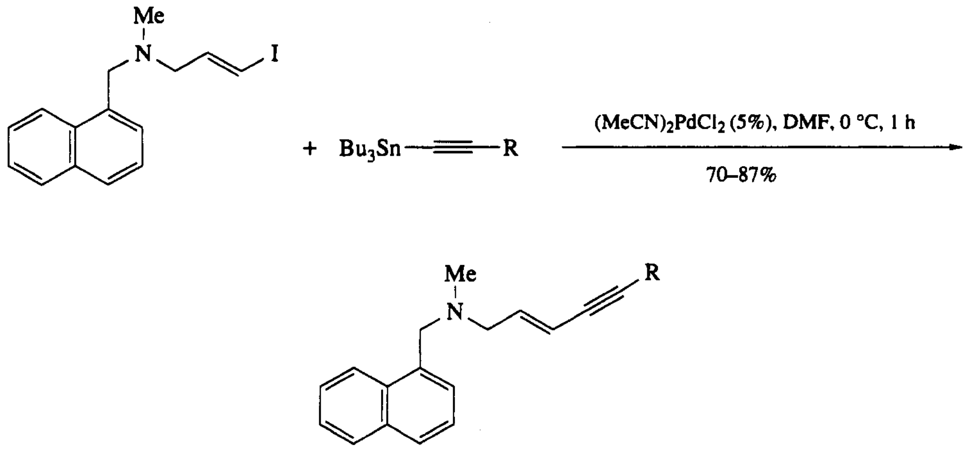
Me
N
I
Bu$_3$Sn
R
(MeCN)$_2$PdCl$_2$ (5%), DMF, 0 °C, 1 h
70–87%
Me
N
R

(14)

R = Bu$^t$, Bu$^n$, SiMe$_3$

Extensions to *sp*$^2$–*sp* cross-coupling reactions with vinyl triflates can be successfully achieved, as exemplified by the synthesis of the enyne (**26**). It is noteworthy that this reaction is compatible with the presence of alkynylsilanes, emphasizing the different behavior of organosilicon and organotin derivatives (equation 15).[50]

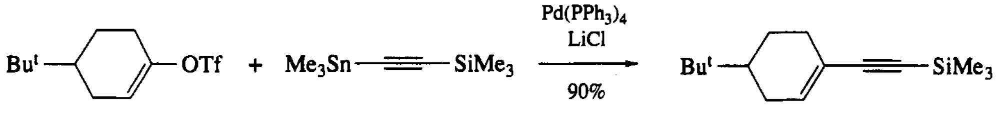
Bu$^t$
OTf
Me$_3$Sn
SiMe$_3$
Pd(PPh$_3$)$_4$
LiCl
90%
Bu$^t$
SiMe$_3$

(15)

(**26**)

Finally, imidoyl chloride can be transformed into the corresponding ketimines *via* palladium complex catalyzed cross-coupling reactions with alkynyltins (equation 16).[51,52]

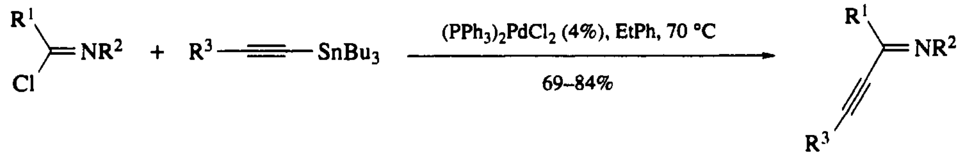
R$^1$
NR$^2$
Cl
R$^3$
SnBu$_3$
(PPh$_3$)$_2$PdCl$_2$ (4%), EtPh, 70 °C
69–84%
R$^1$
NR$^2$
R$^3$

(16)

R$^1$ = Ph, 2-thienyl, Et, Cl; R$^2$ = *p*-tolyl, Bu$^n$, *p*-C$_6$H$_4$CO$_2$Et; R$^3$ = Bu$^n$, SiMe$_3$, EtC≡C

### 2.4.3.4 Reactions of 1-Alkenyl Metals with 1-Alkynyl Halides

Using (*E*)-methylalkenylalanes, obtained by highly stereo- and regio-selective Zr-catalyzed carboalumination of alkynes, the stereochemically defined enynes (**27**) can be synthesized by Pd-catalyzed cross-coupling reactions with 1-haloalkynes (Scheme 12).[53] Although the mechanism of the Zr-catalyzed carboalumination is not very clear, certain aspects have been clarified,[54] and general reviews have been published.[9,55,56]

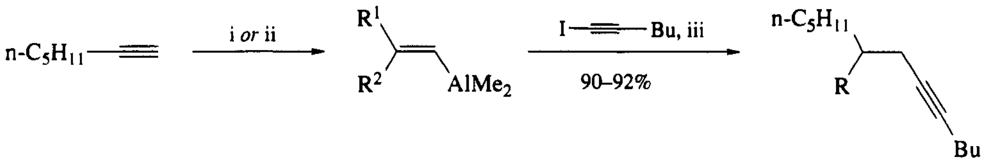

**(27a)** R = H
**(27b)** R = Me

i, $Me_3Al–Cl_2ZrCp_2$, 50 °C, 6 h; ii, $H_2O$ for the case of R = Me; $Bu^i{}_2AlH$ for the case of R = H;
iii, $ZnCl_2$, $Pd(PPh_3)_4$ (5 mol %), 20–25 °C

**Scheme 12**

Cross-coupling reactions between 1-alkynyl halides and 1-alkenylboranes, which are readily available *via* hydroboration of alkynes, can also be catalyzed by the Pd–phosphine complex (Scheme 13).[57,58]

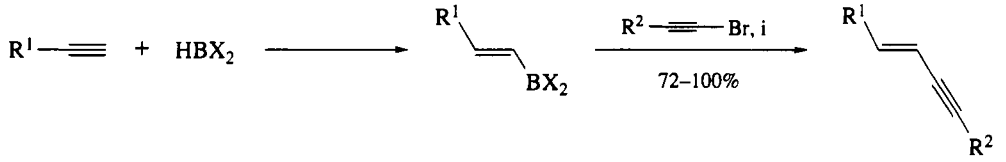

isomeric purity > 96%

$X_2$ = $Sia_2$; $R^1$ = Bu, Ph, Me; $R^2$ = $C_6H_{13}$, Ph

i, $Pd(PPh_3)_4$, benzene, NaOMe/MeOH, 80 °C, 2 h

**Scheme 13**

## 2.4.3.5 Reactions of Terminal Alkynes with *sp*²-Carbon Halides

### *2.4.3.5.1 General aspects*

Terminal alkynes can be coupled directly to aryl and to vinyl halides in the presence of a palladium catalyst and a base. The mechanism of this reaction appears to involve oxidative addition of the $sp^2$ halide to palladium(0), followed by alkynylation of the intermediate organopalladium halide and reductive elimination of the disubstituted alkyne (equations 17 and 18).[7,59,60]

Different conditions have been employed for this reaction, depending on the reactivity of the halide, the alkynes and the base used. Copper(I) iodide is a particularly effective cocatalyst, allowing the reactions to occur at room temperature.[7] Additional examples of this type of coupling reaction are given in Table 1.[61–83]

$$2\ \mathrm{ArX}\ +\ \equiv\ \xrightarrow[\text{60–85\%}]{\mathrm{(PPh_3)_2PdCl_2–CuI,\ Et_2NH,\ r.t.,\ 3–6\ h}}\ \mathrm{Ar}—\!\equiv\!—\mathrm{R} \qquad (17)$$

Ar = Ph, 2-pyridyl

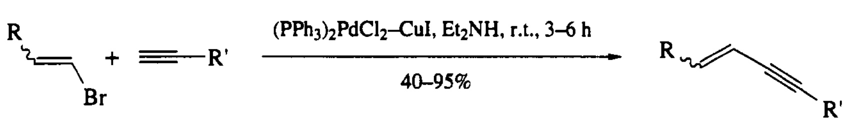

(18)

R = H, Ph; R' = Ph, $CH_2OH$

Aryl triflates, like aryl halides, can undergo Pd-catalyzed coupling reactions with terminal alkynes (Scheme 14),[67] and bromoallenes react with terminal alkynes[84,85] or acetylene[86] under similar conditions to form allenynes (Schemes 15 and 16).

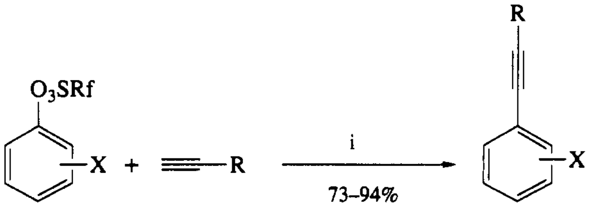

R = Ph, $Me_3Si$; $R_f$ = $CF_3$, $H(CF_2)_2O(CF_2)_2$

i, $(PPh_3)_2PdCl_2$, $Et_3N$/DMF, 90 °C, 3–17 h

**Scheme 14**

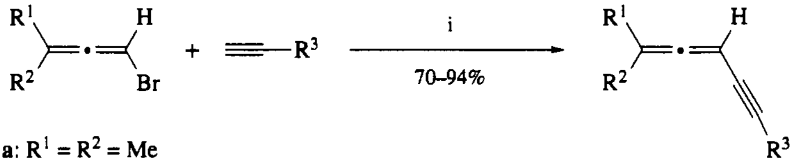

a: $R^1 = R^2 = Me$
b: $R^1 = Pr^n$; $R^2 = H$

$R^3$ = Ph, n-$C_6H_{13}$, $CH_2OH$, $CH(OH)Pr^n$, $Pr^iNEt_2$, $SiMe_3$, $(CH_2)_8OAc$

i, $Pd(PPh_3)_4$–CuI, $Et_2NH$, r.t., 2–3 h

**Scheme 15**

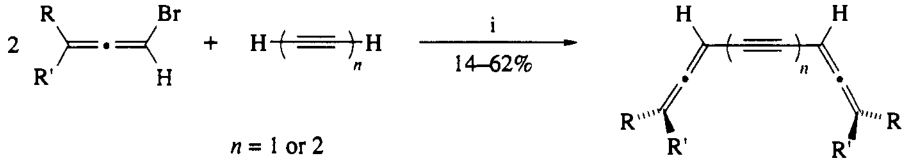

$n$ = 1 or 2

i, $Pd(PPh_3)_4$–CuI cat., $Et_2NH$, 20 °C, 1 h

a: R = R' = Me
b: R = R' = Et
c: R = Me; R' = Et

**Scheme 16**

### *2.4.3.5.2 Synthesis of terminal alkynes*

The *sp*$^2$–*sp* coupling reaction can be extended to the synthesis of terminal alkynes by use of protected alkynes such as trimethylsilylacetylene (**28**; TMSA) or 2-methyl-3-butyn-2-ol (**29**), followed by subsequent removal of the protecting group (Schemes 17, 18 and 20).[61,87,88] Thus, commercially available TMSA (**28**) reacts with aryl bromides or iodides in the presence of a palladium complex and copper(I) iodide, followed by treatment with dilute aqueous potassium hydroxide in methanol or a $F^-$ source, such

**Table 1** Formation of Disubstituted Alkynes by the Reaction of *sp*$^2$ Halides or Their Related Compounds with Terminal Alkynes

| *Alkyne RC≡CH* | *Halide* | *Catalyst*$^b$ | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| R = H | 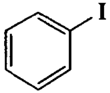 | A | r.t., 6 h | Ph—≡—Ph | 85 | 7 |
| | 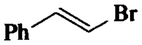 | A | r.t., 6 h | 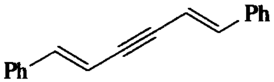 | 95 | 7 |
| | 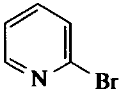 | A | r.t., 6 h | 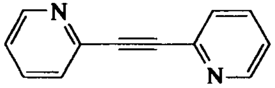 | 60 | 7 |
| R = SiMe$_3$ | 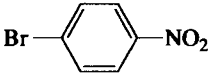 | A' | r.t., 4 h | 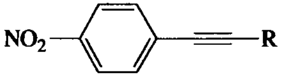 | 92 | 61 |
| | 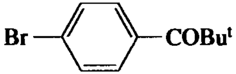 | A | r.t. | 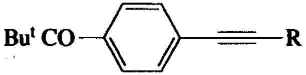 | — | 62 |
| | 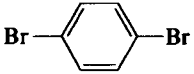 | A' | 50 °C | 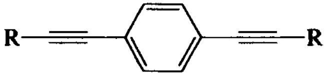 | 77 | 61 |
| | 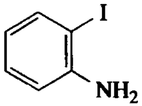 | A | 30 °C | 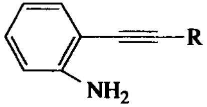 | 68 | 63 |
| | 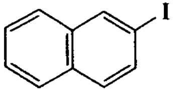 | A' | r.t. | 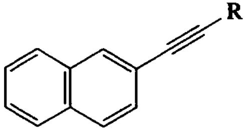 | 85 | 61 |

**Table 1** *(continued)*

| *Alkyne RC≡CH* | *Halide* | *Catalyst*[b] | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| R = $SiMe_3$ | 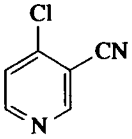 | A' | 100 °C,[a] 20 h | 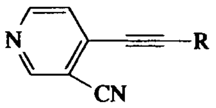 | 76 | 64 |
| | 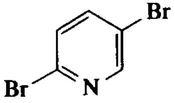 | A' | 5 °C, 1 h, r.t., 1 h | 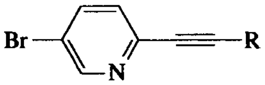 | 74 | 65 |
| | 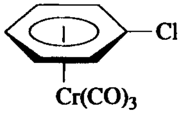 | A' | 20 °C, 18 h | 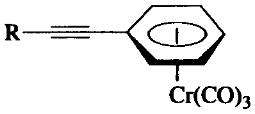 | 85 | 66 |
| | 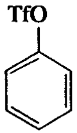 | A'/DMF | | Ph—≡—R | 87 | 67 |
| | 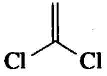 | D | r.t., 5 h | 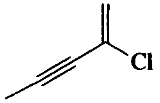 | 82 | 68 |
| | 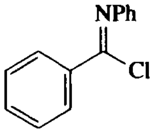 | B | 80 °C, 2 h | 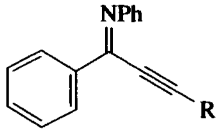 | 78 | 69 |

**Table 1** *(continued)*

| *Alkyne RC≡CH* | *Halide* | *Catalyst*[b] | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| R = SiMe$_3$ | 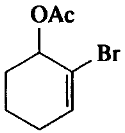 | | 80 °C,[a] 3 h | 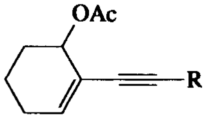 | 47 | 70, 71 |
| | 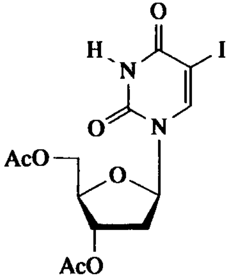 | A | 50 °C, 2 h | 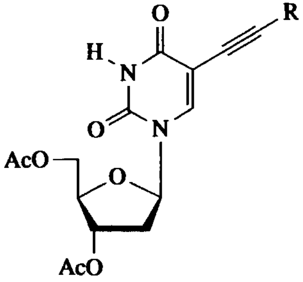 | 80 | 72 |
| PhC≡CCu | $p$-MeOC$_6$H$_4$Br | G | >20 | $p$-MeOC$_6$H$_4$C≡CR | 98 | 73 |
| Ph—≡ | 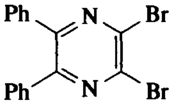 | A'/DMSO | r.t., 6 h | 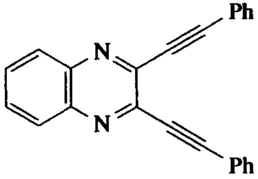 | 74 | 74 |
| Ph—≡ | 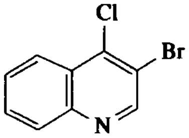 | A | r.t., 4 h | 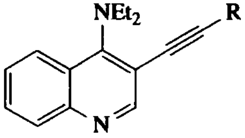 | 37 | 75 |
| R = CH$_2$CH$_2$OCOCH$_2$Pr$^i$ | 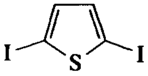 | F | 80 °C, 6 h | 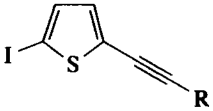 | 50 | 76 |

**Table 1** *(continued)*

| *Alkyne RC≡CH* | *Halide* | *Catalyst*[b] | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| R = $Me(CH_2)_4$ | 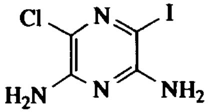 | A | r.t., 24 h | 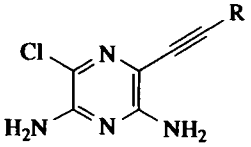 | 63 | 77 |
|  | 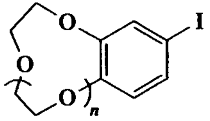<br>$n = 3, 4$ | A | Reflux, 24 h | 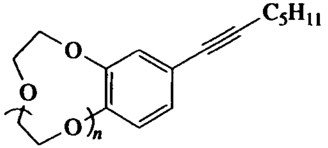 | 84 | 78 |
| R = $CF_3CONHCH_2$ | 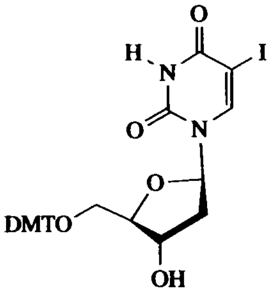 | A/EtOAc | r.t., 40 h | 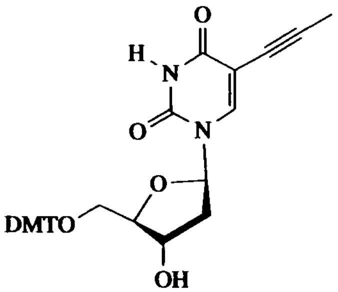 | 53 | 79 |
| 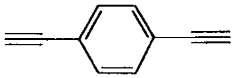 | 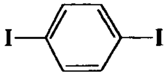 | A' | 89 °C, 0.05 h | 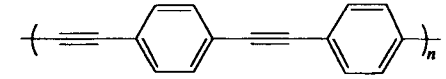 | 100 | 80 |

Table 1 *(continued)*

| *Alkyne RC≡CH* | *Halide* | *Catalyst*$^b$ | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| R = 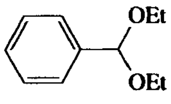 | 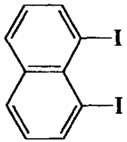 | A | 80 °C, 10 h | 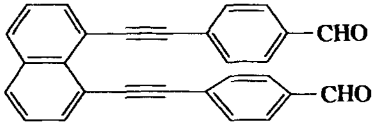 | 35 | 81, 82 |
|  | 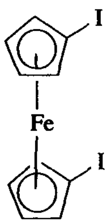 | A |  | 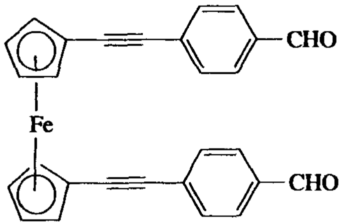 | 27 | 83 |

$^a$ In sealed tube. $^b$A = $(PPh_3)_2PdCl_2$, CuI/$Et_2NH$; A' = $(PPh_3)_2PdCl_2$, CuI/$Et_3N$; B = $Pd(OAc)_2$, $PPh_3$, CuI/$Et_3N$; C = $(PPh_3)PdCl_2$, CuI/$Me_2NH$; D = $Pd(PPh_3)_4$, CuI/$Bu^nNH_2$; E = $Pd(PPh_3)_4/Et_3N$; F = $Pd(PPh_3)_4$, CuI/$Et_3N$; G = $PhPd(PPh_3)_2I$, $Bu_4N^+I^-$/HMPA; Tf = $CF_3SO_2$; TMT = dimethoxytrityl.

as KF–crown ether in DME or tris(dimethylamino)sulfonium trimethyldifluorosilicate (TASF), to give arylalkynes.[61,69,89,90]

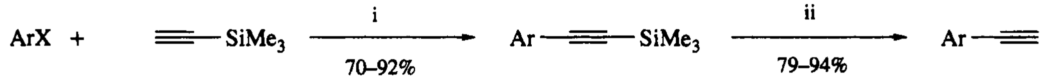

**(28)**

i, $(PPh_3)_2PdCl_2$–CuI cat., $Et_3N$ or pyridine, r.t. to 60 °C; ii, 1N aq. KOH/MeOH, r.t., 1 h

Scheme 17

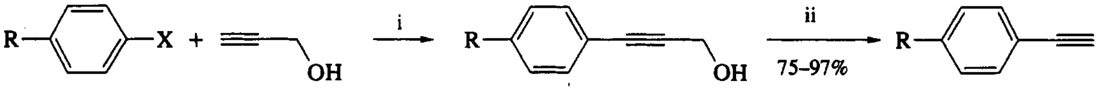

R = $NO_2$, CN, COMe, $CO_2Me$, $OPr^n$; X = Cl, Br, I

i, $PhPdI(PPh_3)_2$, $CuI/NEt_3/C_6H_6$, r.t. to 80 °C, 10 min to 2 h; ii, 10 equiv. $MnO_2$/5 equiv. $KOH/C_6H_6$, r.t., 10 min

Scheme 18

Terminal arylalkynes can be prepared by oxidation–decarbonylation of 3-arylpropargyl alcohols using manganese dioxide in the presence of alkali. The corresponding arylpropargyl alcohols are available by palladium-catalysed cross-coupling of aryl halides with commercial propargyl alcohol. The yield of the second step can be improved by the addition of a phase-transfer catalyst (18-crown-6; Scheme 18).[88]

The coupling reaction between an aromatic halide and TMSA (**28**) in the presence of a Pd$^0$ catalyst generated *in situ*, followed by treatment with potassium carbonate in methanol, provides a simple approach to various ethynylated aromatic derivatives (Scheme 19).[69] By this method even hindered, electron-rich arylalkynes, such as (**30**), can be prepared from the corresponding aryl iodide by refluxing for 2 d in triethylamine.[89]

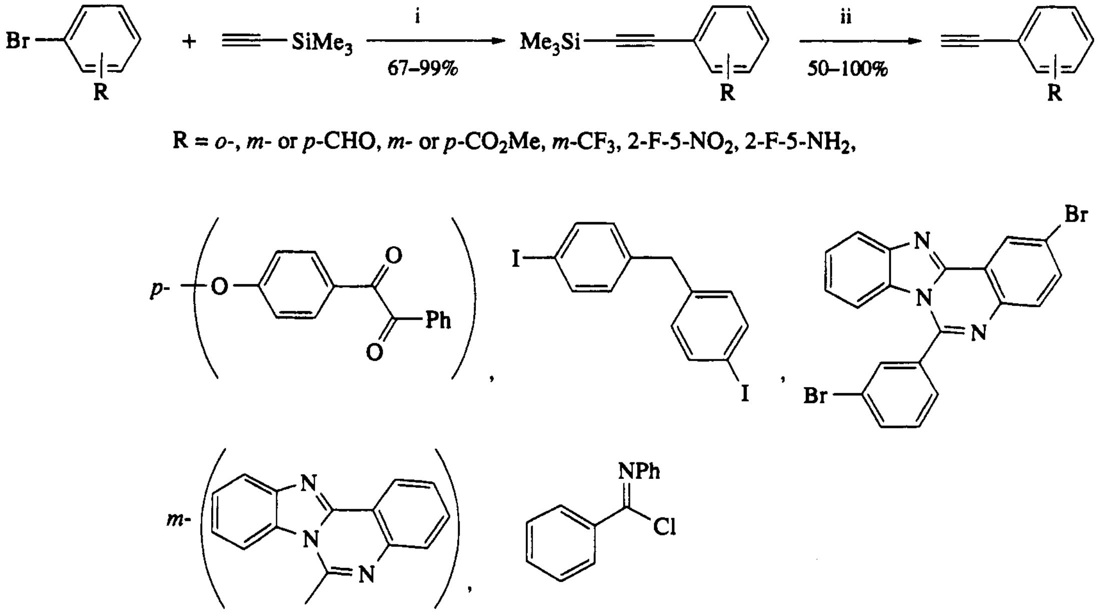

R = *o*-, *m*- or *p*-CHO, *m*- or *p*-$CO_2Me$, *m*-$CF_3$, 2-F-5-$NO_2$, 2-F-5-$NH_2$,

i, $(PPh_3)_2Pd(OAc)_2$, $Et_3N$, reflux for 2–20 h; ii, $K_2CO_3$, MeOH, 25 °C

Scheme 19

Using the above procedure, a wide variety of aromatic and heteroaromatic polyethynyl derivatives have been prepared, *e.g.* (**31**),[92] (**32**)[90] and (**33**).[91,93]

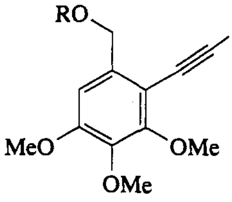

**(30)**

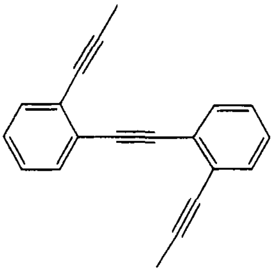

**(31)**

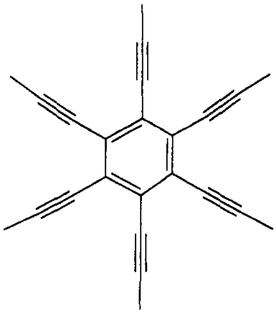

**(32)**

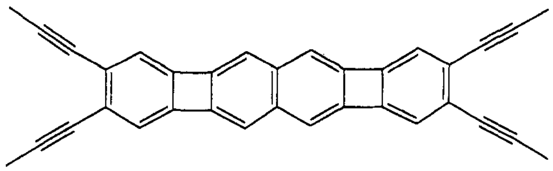

**(33)**

The more easily available starting material (**29**), as a protected alkyne, can condense with aryl halides, followed by treatment with sodium hydroxide and toluene also to provide terminal alkynes (Scheme 20).[87,94]

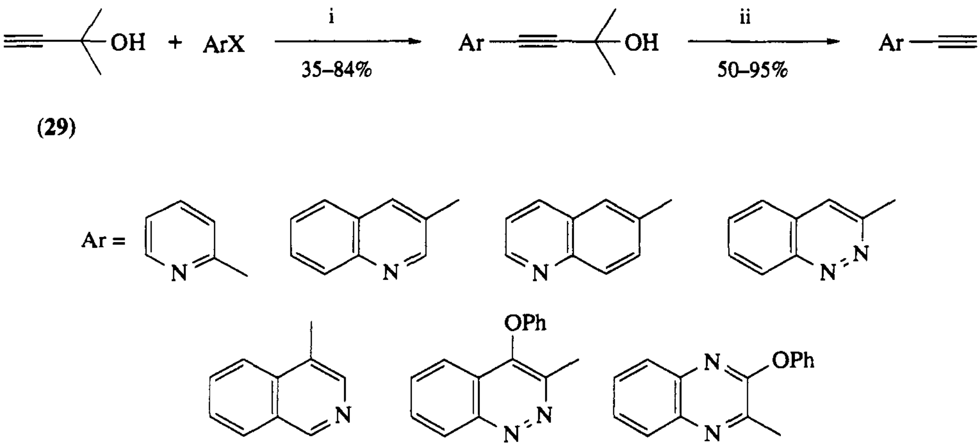

i, $(PPh_3)_2PdCl_2$–CuI, $Et_2NH$; ii, NaOH/toluene, reflux 2 h

**Scheme 20**

In the presence of TASF as a reagent for cleavage of the Si—C bond and allylpalladium dimer as a coupling catalyst, alkynylsilanes react with aryl and vinyl halides to give the corresponding coupled products in high yield and in a stereospecific manner (Scheme 21).[95] In a special case, piperidine and formic acid can also cleave the Si—C bond (Scheme 22).[96] This technique has been extended to a one-pot synthesis of conjugated dienynes or arylalkynes by a palladium-mediated three-component cross-coupling reaction, as shown in Scheme 23.[97] Thus, the Pd-catalyzed reaction of the silylstannylacetylene, first with an alkenyl iodide (**34**) and secondly with another *sp*$^2$ iodide in the presence of newly added TASF, affords the conjugated dienyne (**35**) or arylenyne (**36**) with high stereospecificity.

### *2.4.3.5.3 Stereospecific synthesis*

The coupling reaction between *sp*$^2$- and *sp*-carbon centers is stereospecific with (*Z*)- and (*E*)-vinylic bromides. For example, (*Z*)-methyl-3-bromoacrylate reacts with 1-hexyne in the presence of a Pd catalyst to form the (*Z*)-enzyne as the only product (Scheme 24).[98] This technique has also been applied in the stereoselective synthesis of 1-chloroenynes from (*Z*)-dichloroethylene (Scheme 25).[99]

Trimethylsilylacetylene affords the 2:1 coupled endiyne product (**37**) in a stereospecific manner on coupling with geometrical isomers of 1,2-dichloroethylene (Scheme 26). In the absence of copper(I) iodide, no reaction occurs.[100]

### *2.4.3.5.4 Phase-transfer catalysis*

The technique of phase-transfer catalysis is useful for a variety of interesting metal-catalyzed reactions.[101,102] For the synthesis of 1,3-enynes, the procedure based on the Pd-catalyzed reaction of alkenyl halides with 1-alkynes under phase-transfer conditions offers distinct advantages, in terms of single procedure and cost, over methods involving the use of organometallic compounds or of amines as solvents. Moreover, this procedure can tolerate the presence of functional groups such as hydroxy groups. Better yields are obtained when the coupling reactions are carried out under phase-transfer conditions, at room temperature, employing benzyltriethylammonium chloride (1 mol %) as the phase-transfer agent, a large excess of 2.5 N aqueous sodium hydroxide as the base, and a mixture of tetrakis (triphenylphosphine)palladium (1 mol %) and copper(I) iodide (0.5–2 mol %) as catalyst. Using these conditions, a variety of alkenyl halides (**38**) react with aliphatic 1-alkynes (**39**; Scheme 27).[103,104]

The Pd-catalyzed coupling reactions of alkenyl bromides with heterocyclic alkynes (**40**) under the above phase-transfer conditions have been employed to prepare a large number of heterocyclic alkyne derivatives, including some naturally occurring compounds (Scheme 28).[45] The experimental conditions

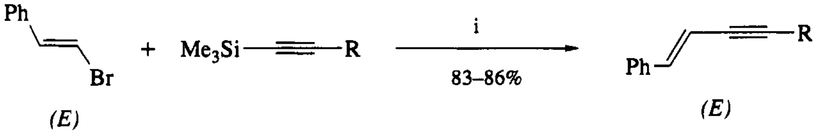

R = Ph, n-$C_5H_{11}$, $CH_2OH$

i, TASF, 2.5 mol % of [($\eta^3$-$C_3H_5$)PdCl]$_2$, THF, r.t.

**Scheme 21**

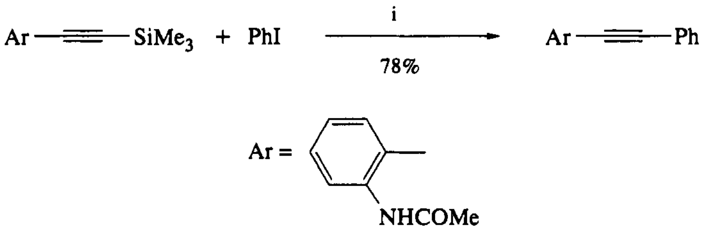

i, Pd(OAc)$_2$(PPh$_3$)$_2$, piperidine, $HCO_2H$/DMF, 60 °C, 8 h

**Scheme 22**

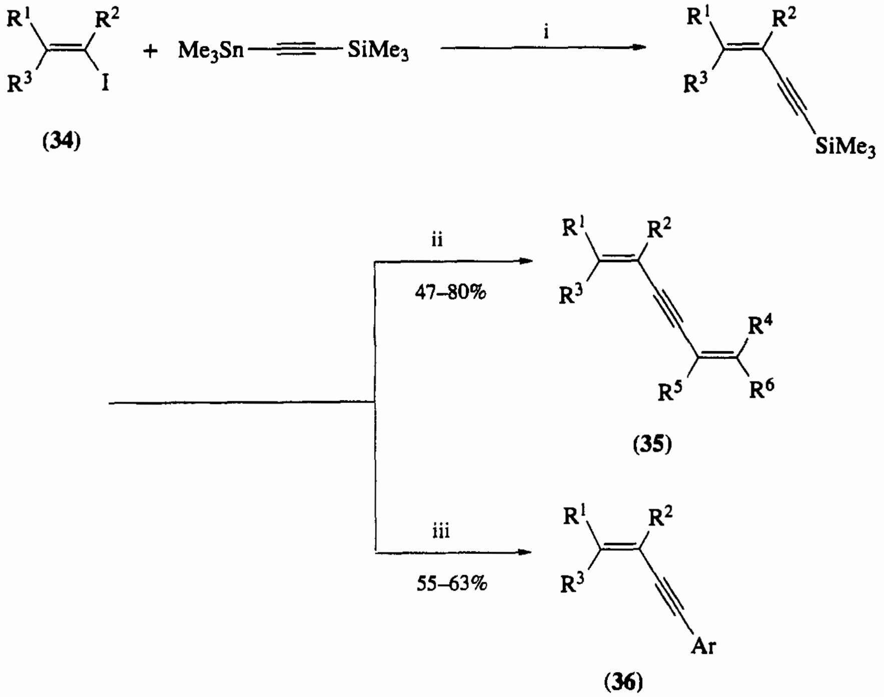

$R^1$
$R^2$
$R^3$
I
+ $Me_3Sn$—≡—$SiMe_3$
i
$SiMe_3$
ii
47–80%
$R^4$
$R^5$
$R^6$
iii
55–63%
Ar

(34)

(35)

(36)

$R^1$ = H, $(CH_2)_4$ (cyclo), $AcOCH_2$, Ph, $Pr^n$, n-$C_6H_{13}$; $R^2$ = H, $Bu^n$, $(CH_2)_4$ (cyclo); $R^3$ = H, n-$C_6H_{13}$, n-$C_8H_{17}$; $R^4$ = H, n-$C_6H_{13}$, n-$C_8H_{17}$; $R^5$ = H, $Bu^n$; $R^6$ = H, $Pr^n$, n-$C_6H_{13}$; Ar = 1-naphthyl, 2-thienyl

i, 1 mol % of $Pd(PPh_3)_4$, 2.4 mol of TASF, THF, 50 °C; ii, $I(R^5)C{=}CR^4R^6$, TASF; iii, ArI, TASF

**Scheme 23**

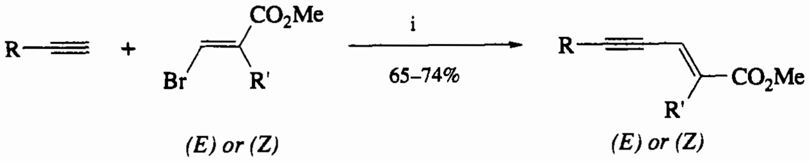

R—≡
+
$CO_2Me$
Br
R'
i
65–74%
R—≡
$CO_2Me$
R'
(E) or (Z)
(E) or (Z)

R = cyclohexyl, Ph, $Bu^n$; R' = H, Me

i, $Pd(OAc)_2$ + $2PPh_3$, $NEt_3$, r.t., 40 h

**Scheme 24**

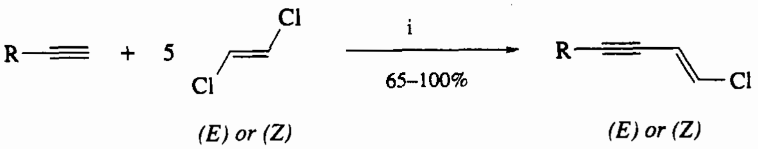

R—≡
+ 5
Cl
Cl
i
65–100%
R—≡
Cl
(E) or (Z)
(E) or (Z)

>99% isomeric purity

R = n-$C_5H_{11}$, $CH_2OTHP$, $CH_2OAc$, $CH_2SMe$

i, $Pd(PPh_3)_4$–CuI cat., *n*-butylamine, r.t., 5 h

**Scheme 25**

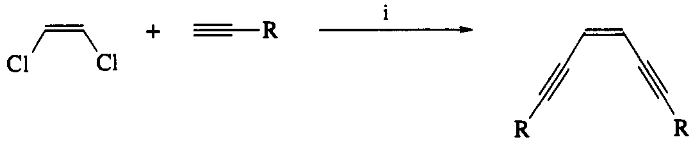

R = Ph, $Me_3Si$ (**37**)

i, $Pd(PPh_3)_4$–CuI cat., n-butylamine, benzene, r.t., 1 h

**Scheme 26**

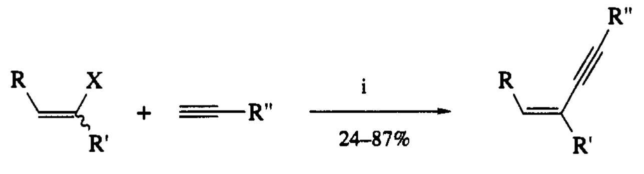

(**38**) (**39**)

R = H, Bu$^n$, n-$C_8H_{17}$; R' = H, Me; R'' = n-$C_5H_{11}$, $CH_2OH$, n-$C_6H_{13}$, $(CH_2)_2OH$, $(CH_2)_8OH$

i, $Pd(PPh_3)_4$–CuI cat., 10% aq. NaOH, benzene, $BzEt_3\overset{+}{N}\ Cl^-$

**Scheme 27**

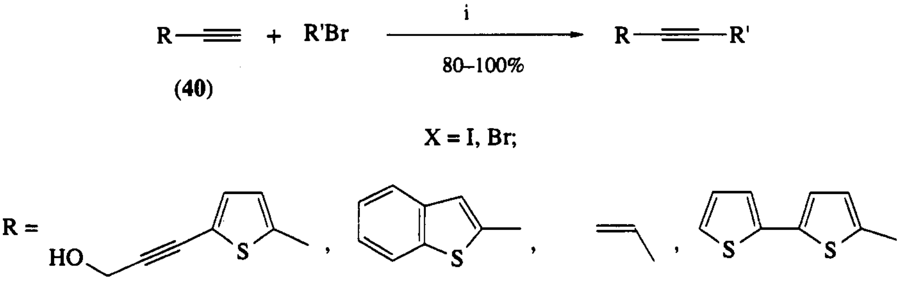

(**40**)

X = I, Br;

2-furyl, 2-pyridyl;

R' = 2-thienyl, $HO(CH_2)_2$, $HOCH_2$, 2-furyl, 2-pyridyl, Ph, $(EtO)_2CH$

i, $Pd(PPh_3)_4$, CuI, $C_6H_6$, $BzEt_3\overset{+}{N}\ Cl^-$, aq. 2.5 N NaOH

**Scheme 28**

of the procedure allow the direct preparation of alkynic derivatives starting from 1-alkynyltrimethylsilanes (**41**) and heteroaryl halides (Scheme 29).[45] An efficient one-pot synthesis of arylalkynes can be achieved by application of the phase-transfer reaction using commercially available 2-methyl-3-butyn-2-ol (**42**) as the protected alkyne starting material (Scheme 30).[105] Using a similar method, oligo(thienylalkyne)s (**43**) have been synthesized in a stepwise manner.[105,106]

### *2.4.3.5.5 Syntheses of aromatic and heterorings* via sp$^2$–sp *coupling reactions*

Alkynic intermediates derived from *sp*$^2$–*sp* coupling reactions can be applied to the syntheses of a variety of aromatic and heterocyclic molecules.[107–116] For example, a one-step synthesis of the aminoindolizines (**44a–e**) and the 5-aza analog (**44f**) from α-haloaza aromatics has been reported as outlined in Scheme 31.[107] The mechanism of this reaction appears to involve the initial formation of pyridylacetylene (**45**), followed by ring closure *via* the intermediate (**46**; Scheme 32).[107]

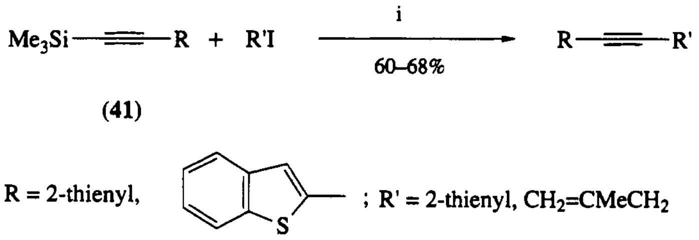

$Me_3Si$—≡—R + R'I
i
60–68%
R—≡—R'
S

**(41)**

R = 2-thienyl, ; R' = 2-thienyl, $CH_2{=}CMeCH_2$

i, $Pd(PPh_3)_4$–CuI cat., $C_6H_6$, 40 °C, $BzEt_3\overset{+}{N}Cl^-$, aq. 2.5 N NaOH

Scheme 29

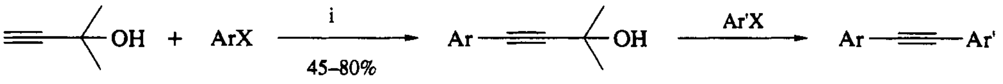

OH
+ ArX
i
45–80%
Ar
OH
Ar'X
Ar—≡—Ar'

**(42)**

R = 2-thienyl, 2-pyridyl, nitrophenyl; R' = phenyl, 2-thienyl, 5-(2,3-benzothienyl)

i, $(PPh_3)_4Pd$–CuI cat., $BzEt_3\overset{+}{N}Cl^-$, 5.5 N NaOH/benzene, r.t.

Scheme 30

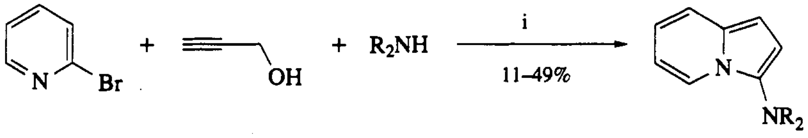

N
Br
+
OH
+ $R_2NH$
i
11–49%
N
$NR_2$

**(44)** **a**: $NR_2 = N(CH_2)_5$
**b**: $NR_2$ = N, O
**c**: $NR_2 = NEt_2$

i, $(PPh_3)_2PdCl_2$–CuI cat., 70–80 °C, 3–16 h

Scheme 31

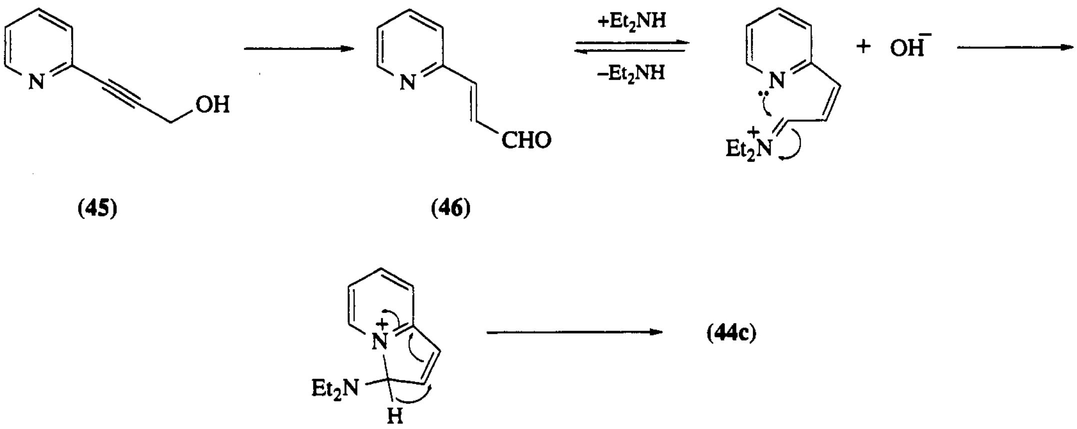

N
OH
N
CHO
$+Et_2NH$
$-Et_2NH$
N
$Et_2\overset{+}{N}$
+ $OH^-$
(45)
(46)
$\overset{+}{N}$
$Et_2N$
H
(44c)

Scheme 32

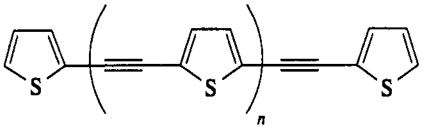

**(43)** $n = 0, 1, 2, 3$

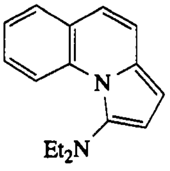

**(44d)**

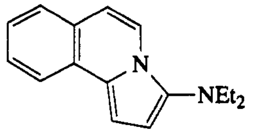

**(44e)**

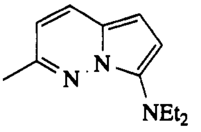

**(44f)**

Although the stoichiometric ethynylation of (**47**) with copper(I) phenylacetylide gives the product (**48**) of a normal double ethynylation, the Pd-catalyzed coupling reaction affords the fluorene derivative (**49**) instead. The reaction leading to (**49**) can be rationalized as proceeding *via* the σ-fluorenyl–Pd complex (**50**; Scheme 33).[116]

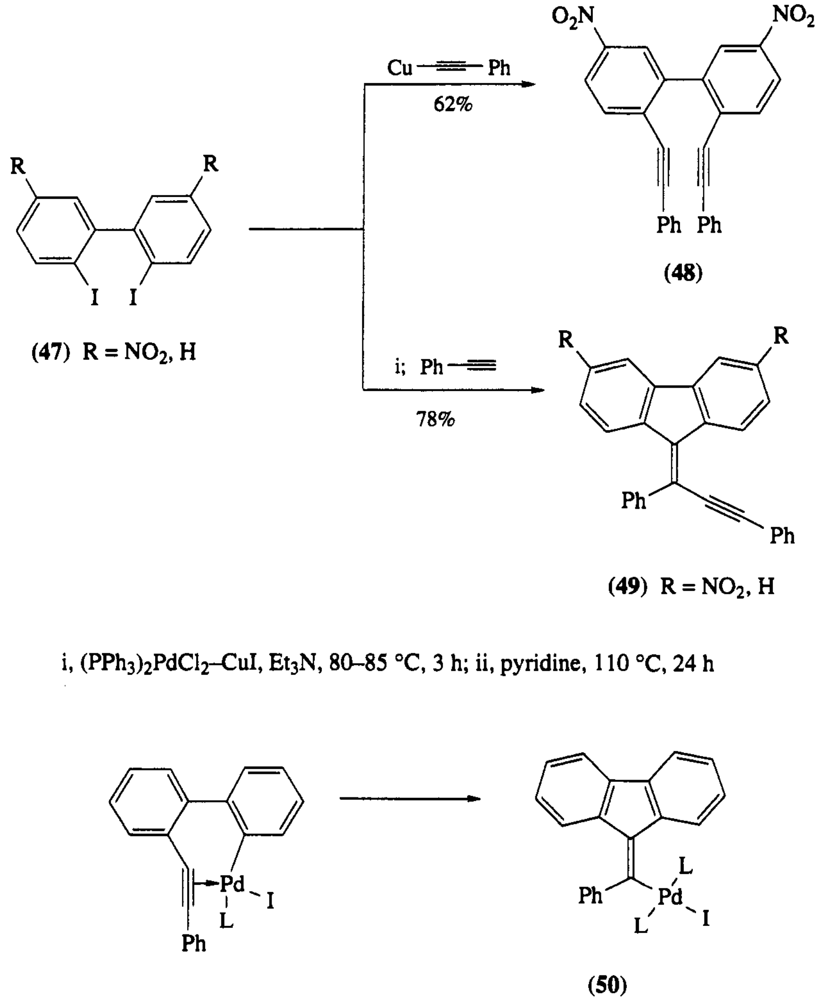

i, $(PPh_3)_2PdCl_2$–CuI, $Et_3N$, 80–85 °C, 3 h; ii, pyridine, 110 °C, 24 h

**Scheme 33**

Pyridopyrimidines and pyrimidines fused with five- or six-membered heterocycles can be prepared *via* the ring closure of intermediate ethynylpyrimidines, which are themselves obtained by the Pd-catalyzed cross-coupling of halopyrimidines with alkynic compounds (Scheme 34).[108–110]

*o*-Alkynylanilines such as (**51**), which are made by Pd-catalyzed coupling reactions of alkynes with *o*-haloaniline precursors, are easily cyclized to the indoles in the presence of base (Scheme 35).[111,112] Similar methods can be employed in the synthesis of isocoumarins,[113] thienopyridines,[117] furopyridines[117] and the marine alkaloid asptamine.[118]

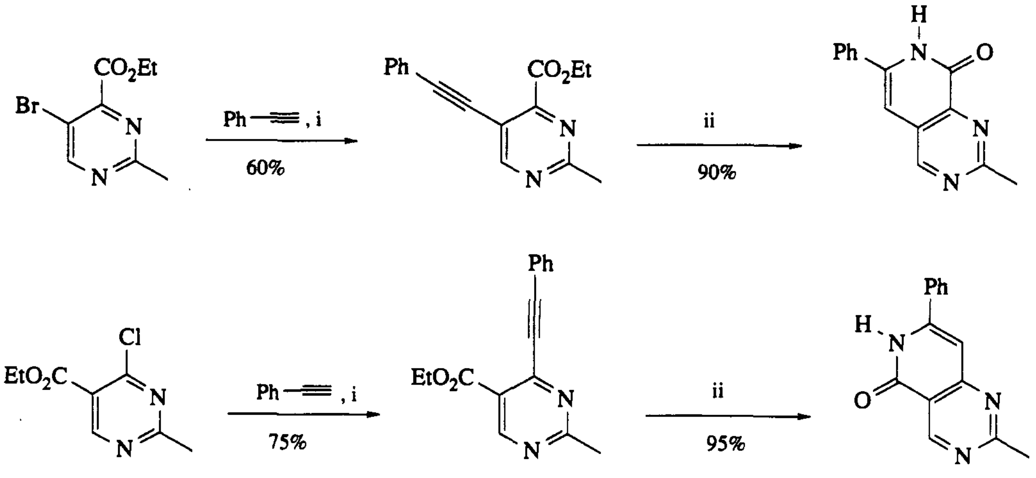

i, $(PPh_3)_2PdCl_2$–CuI cat., $Et_3N$, reflux 24 h; ii, $Et_3N$, EtOH, 120 °C, in a sealed tube, 12 h

Scheme 34

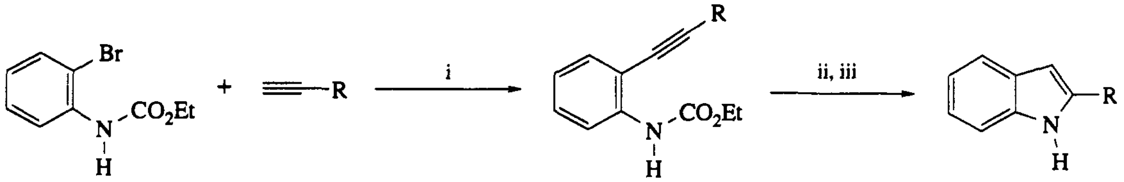

(51)

R = H, Bu, Ph; 65–93%

i, $(PPh_3)_2PdCl_2$ cat., $Et_3N$, 100 °C; ii, NaOEt; iii, $H_2O$

Scheme 35

### 2.4.3.6 Palladium-catalyzed Vinylation of Alkynic Iodides

Heck-type vinylations of alkynic halides proceed only under solid–liquid phase-transfer conditions. These mild conditions allow the reaction to be performed with thermally unstable substrates. Thus, methyl (*E*)-enynoates can be obtained from the reaction of 1-iodoalkynes with methyl 2-propenoate in DMF at room temperature in the presence of potassium carbonate, tetrabutylammonium chloride and a catalytic amount of palladium acetate (Scheme 36).[119]

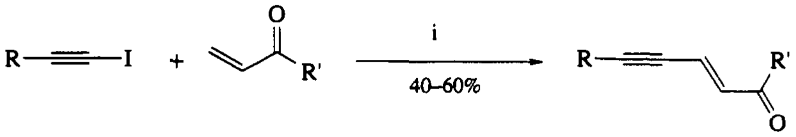

R = n-$C_6H_{13}$, $Bu^n$, $SiMe_3$, Ph, n-$C_5H_{11}$; R'= OMe, Me

i, $Pd(OAc)_2$ cat., $K_2CO_3$ or $Na_2CO_3$, $Bu^n{}_4NCl$/DMF, r.t.

Scheme 36

### 2.4.4 APPLICATIONS TO THE SYNTHESIS OF NATURAL PRODUCTS

As described already, Pd-catalyzed *sp*$^2$–*sp* coupling reactions are extremely useful in the synthesis of natural products. For example, the novel antitumor esperamycins have strong DNA binding/damaging properties which are related to the strained enediyne bridge present in their structures. A plausible biosynthetic pathway to the bicyclic core of the esperamycins could involve intramolecular [4 + 2] cycloaddition of a conjugated polyenyne (**54**).[120] This polyenyne precursor (**54**) has been assembled by palladium-catalyzed stepwise coupling reactions of two different alkyne units to *cis*-dichloroethylene (**52**),[99] leading to (**54**), which was then further elaborated to (**55**), which showed a striking similarity to the esperamycin bicyclic core (Scheme 37).

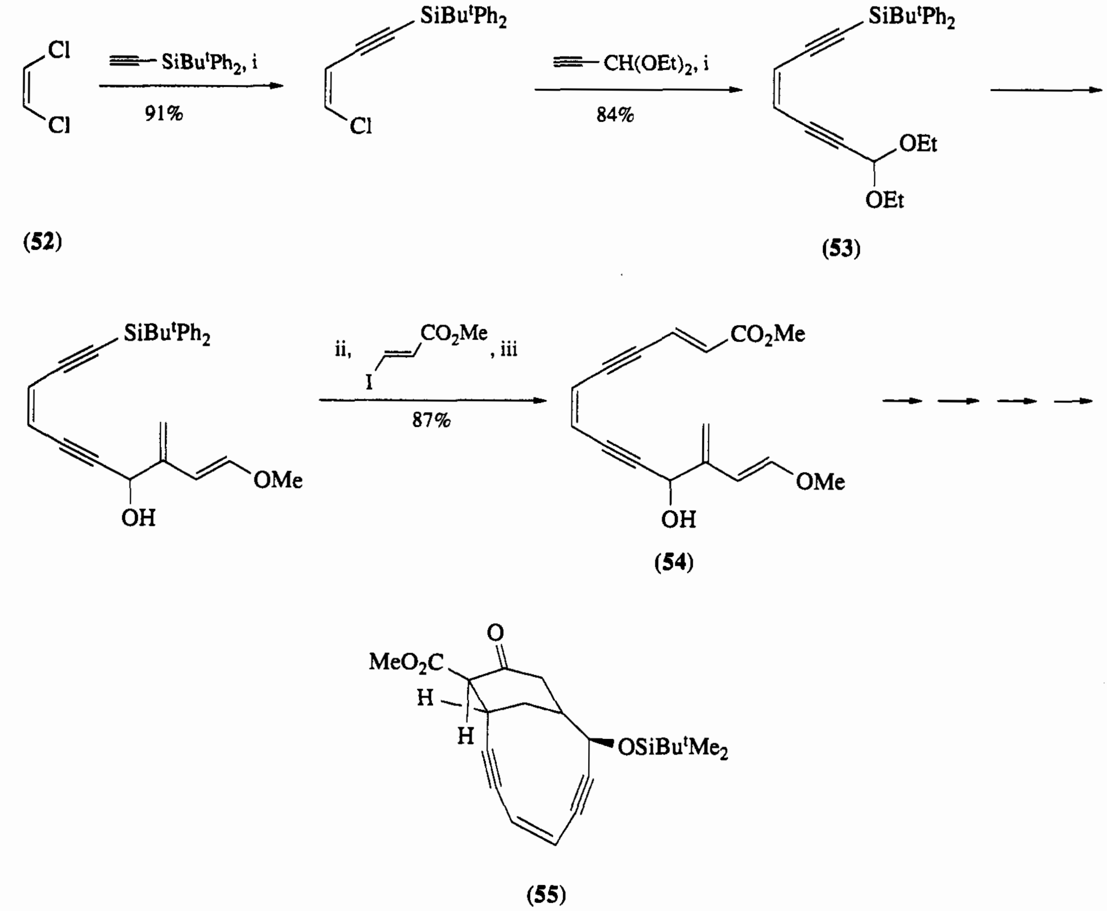

i, Pd(PPh$_3$)$_4$ (5 mol %), CuI (20 mol %), propylamine; ii, Bu$^n_4$NF (98%); iii, Pd(PPh$_3$)$_4$ (5 mol %), CuI (20 mol %), methylamine

**Scheme 37**

Enynes of the structural type (**57**) have been used as key intermediates in the total synthesis of vitamin D. The enyne (**57**) can be obtained by a simple synthesis based on Pd-catalyzed coupling of the keto–enol triflate (**56**) and an alkynic compound containing the vitamin D A-ring fragment (Scheme 38).[121]

The insecticidally active natural isobutylamides, such as dehydropipercide (**60**), and their synthons have been synthesized by Pd-catalyzed coupling reactions. For example, the aryl iodide (**58**) can couple in the dark with the alkynic amide (**59**) in the presence of a Pd–CuI catalyst in triethylamine to give dehydropipercide (**60**).

Enynes of the type (**62**), which are similar to those occurring in *Achillea tomentosa*, are made by a similar coupling reaction between vinyl bromide (**61**) and the alkyne (**59**). The stereoisomers of (**62**) can be separated by HPLC to give pure (*E*)- and (*Z*)-isomers in 24% and 19% yields, respectively (Scheme 39).[122]

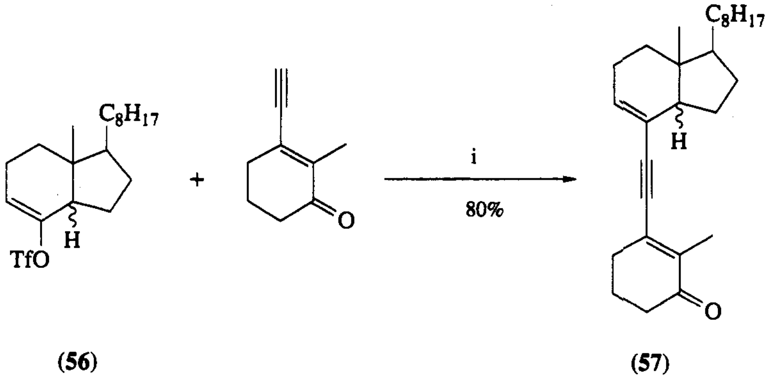
$C_8H_{17}$
TfO
H
+
O
i
80%
$C_8H_{17}$
H
O

(56) (57)

i, $(PPh_3)_2PdCl_2$ (2 mol %), $Et_3N$ (3.4 equiv.) in DMF, 75 °C, 4 h

**Scheme 38**

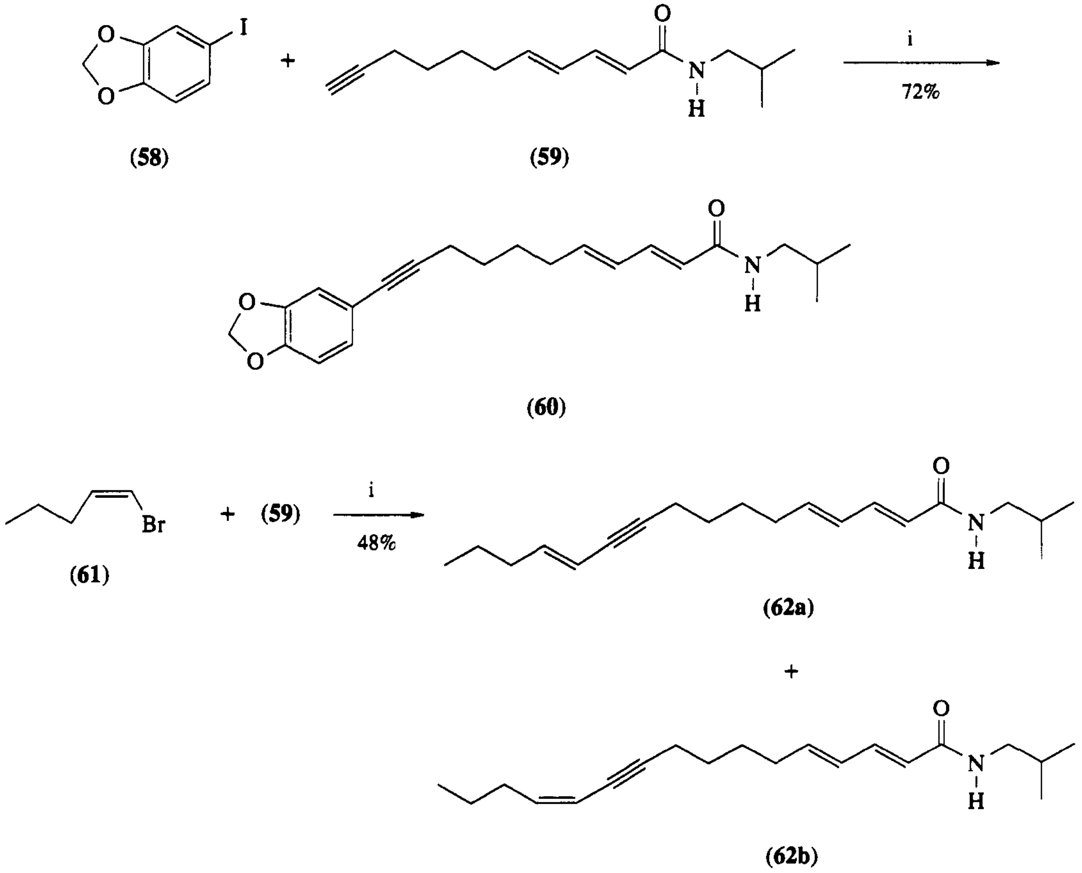
O
O
I
+
O
N
H
i
72%
O
O
O
N
H
Br
+ (59)
i
48%
O
N
H
+
O
N
H

(58) (59) (60) (61) (62a) (62b)

i, $(PPh_3)_2PdCl_2$–CuI cat., $Et_3N$

**Scheme 39**

Palladium-catalyzed coupling reactions have been utilized in the total synthesis of ginkgolide B, which has been extracted from the ginkgo tree and is a most active anti-PAF (platelet-activating factor) agent. The important intermediate (**65**) is obtained from the reaction between the enol triflate (**63**) and the alkynic OBO ester (**64**; Scheme 40).[123]

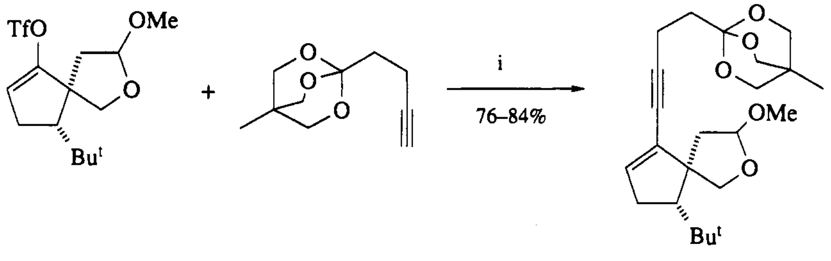
TfO
OMe
O
Bu^t
+
O
O
O
i
76–84%
O
O
O
OMe
O
Bu^t

**(63)** **(64)** **(65)**

i, $Pd(PPh_3)_4$ (5.7 mol %), CuI (0.5 equiv.), n-propylamine (2.3 equiv.), in benzene, 16 °C, 4 h

**Scheme 40**

Despite the multitude of functional groups present and the insolubility of the nucleosides in inert solvents, palladium-catalyzed coupling reactions have been used in their synthesis. Thus, the coupling of terminal alkynes with iodinated uracyl nucleosides proceeds in high yield in the presence of a $Pd^0$–$Cu^I$ catalyst in warm triethylamine, and several of the products obtained by this route have shown useful antiviral activity (Scheme 41).[124]

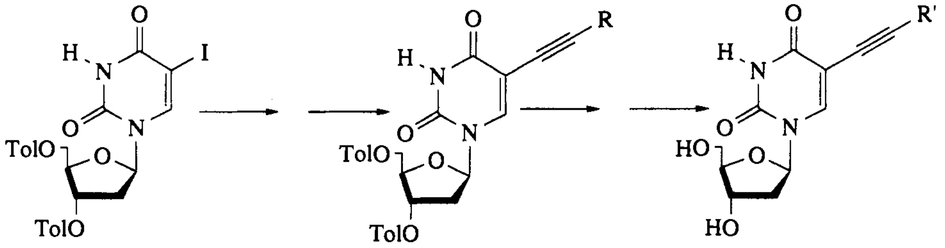
O
H
N
I
O
N
TolO
O
TolO
O
R
H
N
O
N
TolO
O
TolO
O
R'
H
N
O
N
HO
O
HO

**(66)** **(67)** **(68)**

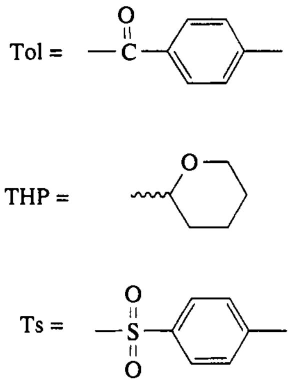
Tol =
O
C
THP =
O
Ts =
O
S
O

| | *R* | | *R'* |
|---|---|---|---|
| **a** | Et | **a** | Et |
| **b** | $Pr^n$ | **b** | $Pr^n$ |
| **c** | $Bu^n$ | **c** | $Bu^n$ |
| **d** | $n\text{-}C_5H_{11}$ | **d** | $n\text{-}C_5H_{11}$ |
| **e** | $Bu^t$ | **e** | $Bu^t$ |
| **f** | Ph | **f** | Ph |
| **g** | $SiMe_3$ | | |
| **h** | H | **h** | H |
| **i** | $CH_2OTHP$ | | |
| **j** | $CH_2OH$ | **j** | $CH_2OH$ |
| **k** | $CH_2CH_2OTHP$ | | |
| **l** | $CH_2CH_2OTol$ | | |
| **m** | $CH_2CH_2OH$ | **m** | $CH_2CH_2OH$ |
| **n** | $CH_2CH_2OTs$ | **n** | $CH_2CH_2OTs$ |
| | | **o** | $CH{=}CH_2$ |
| **p** | $CH_2CH_2CH_2OTol$ | | |
| | | **q** | $CH_2CH_2CH_2OH$ |

**Scheme 41**

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# 2.5

# Coupling Reactions Between *sp* Carbon Centers

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## 2.5.1 INTRODUCTION

Some of the most useful synthetic transformations of terminal alkynes involve intermolecular and intramolecular homo- and cross-coupling reactions between their *sp*-carbon centers, leading to butadiyne or polyyne derivatives. The two most widely used and practical systems are: (i) oxidative homocoupling reactions, *i.e.* Glaser and Eglington reactions; and (ii) heterocoupling reactions, *i.e.* Chodkiewicz–Cadiot coupling of a terminal alkyne with a haloalkyne.

Other methods for the synthesis of butadiynes and polyalkynes using organometallic alkynide derivatives are less widely used. Reviews describing the above two coupling methods have been published.[1–6] Oxidative couplings of terminal alkynes by a copper(I) catalyst or a copper(II) reagent (Glaser or Eglington reaction) are the best methods of preparing symmetrically substituted butadiyne or polyyne derivatives (equation 1). Unsymmetrically substituted butadiyne derivatives can be prepared by Chodkiewicz–Cadiot type couplings (equations 2 and 3).

These methods have been applied to the syntheses of a wide variety of alkynic compounds.[3] Recently there have been a number of reports describing the syntheses of natural products by oxidative coupling

$$2\ R{-}{\equiv} \xrightarrow{Cu^{+}\text{ or }Cu^{2+},\ O_2} R{-}{\equiv}{-}{\equiv}{-}R \qquad (1)$$

$$R-\!\equiv \quad + \quad Br-\!\equiv\!-R' \xrightarrow{Cu^+,\ NH_2OH\cdot HCl} R-\!\equiv\!-\!\equiv\!-R' \qquad (2)$$

$$R-\!\equiv\!-M \quad + \quad Br-\!\equiv\!-R' \longrightarrow R-\!\equiv\!-\!\equiv\!-R' \qquad (3)$$

reactions of terminal alkynes, followed by stereo- or regio-selective addition of hydrogen or organometallic reagents (see Section 2.5.6.4 and Chapter 2.4).

## 2.5.2 OXIDATIVE HOMOCOUPLING REACTIONS OF TERMINAL ALKYNES

The oxidative coupling of terminal alkynes by copper salts, discovered in 1869 by Glaser, has evolved to the modified method reported in 1962 by Hay.[7] In the Hay procedure, oxygen is passed through a solution of the alkyne and a catalytic amount of a copper(I) salt in a complex-forming solvent, such as pyridine and TMEDA. Although the oxidative coupling by $Cu^I$ salt catalysts in suitable amines has wide scope,[2–6] it is less successful for less acidic terminal alkynes, such as alkyl- or silyl-alkynes.

An essential step in the above process is the reversible formation of the alkynic anion, $R—C\equiv C^-$, which is less acidic and less reactive than that of active alkynes such as phenylacetylene or conjugated polyynes. It has been found that the coupling rate can be accelerated[6] when a small amount of DBU is added to the solution in pyridine (equation 4). The addition of the stronger base facilitates the proton removal from the alkyne. If the product or reactants are oxygen sensitive, it may be necessary to shorten the reaction time.[6] Coupling in a nitrogen atmosphere by using a large excess of the Hay reagent has also been recommended.[8]

$$2\ Et-\!\equiv \quad + \quad O_2 \xrightarrow[\substack{30\text{–}35\ ^\circ C \\ \sim 90\%}]{CuCl,\ DBU,\ pyridine} Et-\!\equiv\!-\!\equiv\!-Et \quad + \quad H_2O \qquad (4)$$

Another modification of the coupling conditions for alkylalkynes has been reported by Knol *et al.*[9] Thus, the oxidative polymerization of 1,8-nonadiyne was carried out using a catalyst complex prepared by reacting a solution of TMEDA and CuCl in *o*-dichlorobenzene with oxygen gas at 1 atm. It proved to be necessary to dry the reagents as well as the monomer before use, and to add some molecular sieve to the reaction mixture in order to remove the water generated during the reaction.

A study of the kinetics of coupling has established that the reaction rate decreases with increasing water content and that it is enhanced by increasing the concentration and the basicity of the ligand.[10] The formation of water may occur in reversible reaction steps from alkynic end groups and a dimeric copper(II) complex (**1**), followed by intramolecular oxidative coupling of two complexed alkynic groups (Scheme 1). Reviews summarizing the mechanism of the oxidative couplings have been published.[3,5]

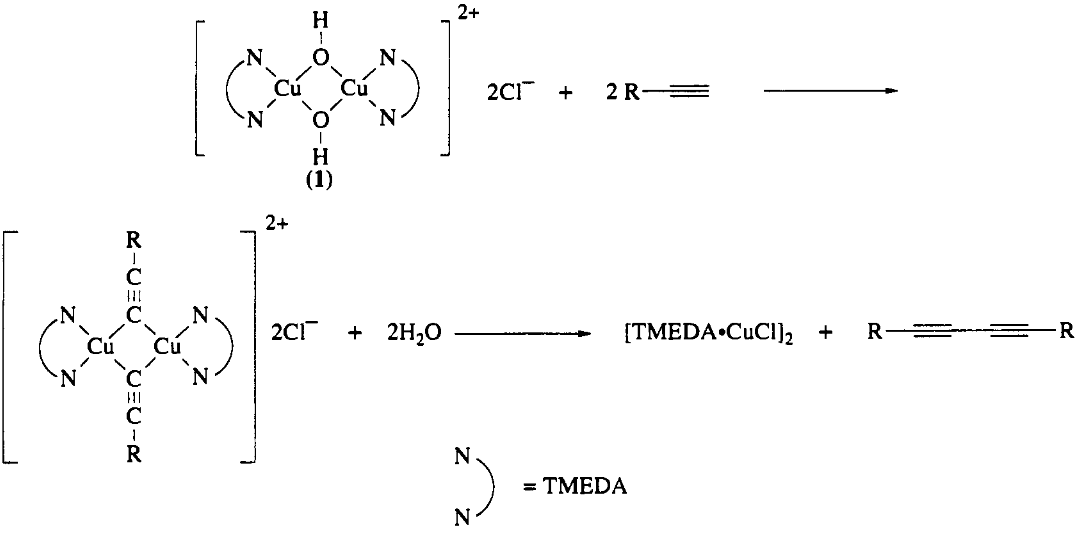

**Scheme 1**

Coupling by copper(II) acetate in pyridine is also a useful procedure for active alkynes such as phenylacetylene and conjugated polyynes. This method is also a useful procedure for making cyclic alkynes.

### 2.5.3 CHODKIEWICZ–CADIOT REACTION

The heterocoupling of a terminal alkyne with a 1-bromoalkyne in the presence of an aliphatic amine and a catalytic amount of a copper(I) salt affords unsymmetrically substituted diynes (**2**; equation 5). This useful reaction, discovered by Chodkiewicz and Cadiot,[11] can be employed advantageously for the synthesis of several polyunsaturated systems.

$$\mathrm{R{-}{\equiv}} + \mathrm{R'{-}{\equiv}{-}Br} + \mathrm{EtNH_2} \xrightarrow[\mathrm{NH_2OH{\cdot}HCl,\ 30\text{–}40\ ^{\circ}C}]{\mathrm{MeOH,\ H_2O,\ CuCl}} \underset{\textbf{(2)}}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R'}} + \mathrm{EtNH_2{\cdot}HCl} \quad (5)$$

$$\mathrm{R{-}{\equiv}} \xrightarrow{\mathrm{Cu^+}} \mathrm{R{-}{\equiv}{-}Cu} + \mathrm{H^+} \quad (6)$$

$$\mathrm{R{-}{\equiv}{-}Cu} + \mathrm{Br{-}{\equiv}{-}R'} \longrightarrow \mathrm{R{-}{\equiv}{-}{\equiv}{-}R'} + \mathrm{Cu^+} + \mathrm{Br^-} \quad (7)$$

$$2\ \underset{\textbf{(3)}}{\mathrm{R'{-}{\equiv}{-}Br}} + \mathrm{Cu^+} \longrightarrow \underset{\textbf{(4)}}{\mathrm{R'{-}{\equiv}{-}{\equiv}{-}R'}} + \mathrm{CuBr_2} \quad (8)$$

Generally the bromoalkyne $RC{\equiv}CBr$ is introduced dropwise to a mixture of the alkyne $RC{\equiv}CH$, ethylamine, methanol or ethanol, in the presence of a catalytic amount of copper(I) chloride, and a small amount of $NH_2OH{\cdot}HCl$. The reaction is usually exothermic and efficient cooling is required during the introduction of the bromoalkyne. The copper(I) alkynyl (equation 6) is assumed to be the reactive intermediate, and the copper(I) ion generated in equation (7) can be employed in equation (6).

The formation of the symmetrical diyne (**4**), generated as in equation (8), can be suppressed by maintaining the concentration of the bromoalkyne (**3**). This side reaction is particularly serious in the case of less acidic alkynes such as alkylalkynes. The reducing agent, $NH_2OH{\cdot}HCl$, is used to reduce the copper(II) ion.

### 2.5.4 COUPLING OF ORGANOMETALLIC ALKYNIDES WITH 1-HALOALKYNES

The coupling reaction between alkyne Grignard derivatives and 1-haloalkynes has been investigated in some detail. Copper(I) and cobalt(I) salts are used as catalysts (equation 9; M = MgBr)[12,13] and the most effective alkynides appear to be organocopper reagents. Such reagents can be used in the presence of a range of functional groups (*e.g.* OH, equation 10;[14] $CO_2H$, equation 11[15]).

$$\mathrm{R{-}{\equiv}{-}M} + \mathrm{X{-}{\equiv}{-}R'} \longrightarrow \mathrm{R{-}{\equiv}{-}{\equiv}{-}R'} + \mathrm{MX} \quad (9)$$

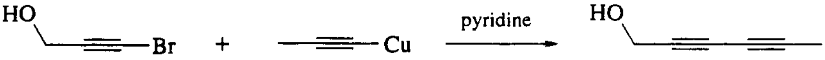

(10)

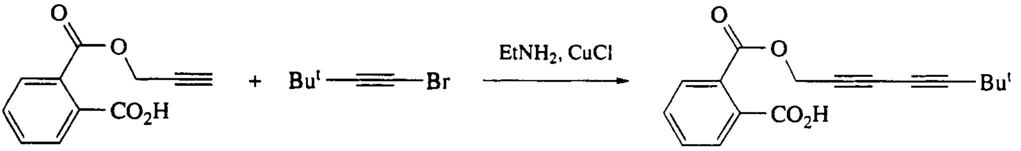

(11)

A useful and convenient synthesis of 1-trimethylsilyl-1,3-diynes (**7**) by the reaction of copper(I) alkynides (**5**) with bromoalkynes (**6**) has been reported by Zweifel and coworkers (Scheme 2).[16]

A highly reactive copper slurry, prepared by the reduction of $CuI{\cdot}PEt_3$ with 1 equiv. of lithium naphthalide, undergoes rapid oxidative addition to alkynyl halides under mild conditions, and induces their homocoupling when oxygen is bubbled through the mixture.[17]

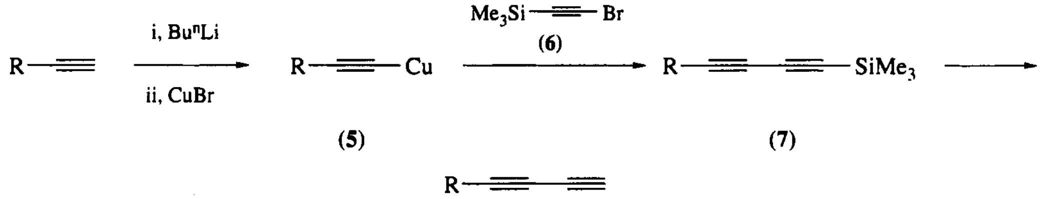

(5) (7)

R = *n*-hexyl, cyclohexyl, 1-cyclohexenyl, *t*-butyl, THP-O($CH_2$)$_9$

Scheme 2

## 2.5.5 OXIDATIVE COUPLING REACTIONS OF ORGANOMETALLIC ALKYNIDES

Conjugated diynes may be prepared by the reaction of organometallic alkynides with iodine or other oxidants (equation 12).[18,19]

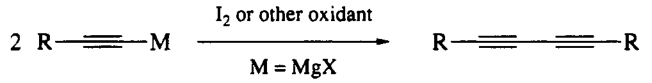

$$2\ \mathrm{R{-}{\equiv}{-}M} \xrightarrow[\mathrm{M\,=\,MgX}]{\mathrm{I_2\ or\ other\ oxidant}} \mathrm{R{-}{\equiv}{-}{\equiv}{-}R} \qquad (12)$$

Alkynyllithium reagents add readily to metal carbonyls, leading to thermally unstable anionic alkynic metal carbonylates (**8**), which give mainly the 1,3-diyne, by treatment with iodine–methanol in THF (Scheme 3).[20,21]

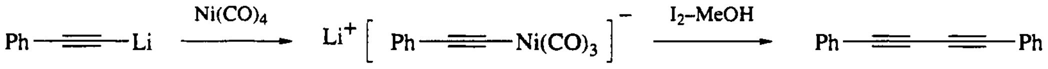

(**8**)

Scheme 3

The reactions of alkynylborates can provide an efficient and selective method of coupling two unlike boron-bound groups. Both symmetrical and unsymmetrical conjugated diynes can be synthesized *via* iodination of the borates prepared by utilizing two cyclohexyl or siamyl groups as blocking groups (equation 13).[22–24] These intramolecular coupling reactions of organoborons provide viable alternatives to the more conventional cross-coupling procedures.

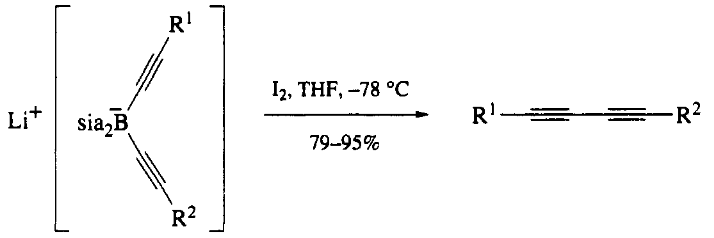

(13)

$R^1$ = *n*-hexyl; $R^2$ = Et, Bu$^t$, Ph

Conjugated diynes can also be prepared by decarbonylation of the corresponding diethynyl ketones using $(PPh_3)_3RhCl$ in boiling xylene (equation 14).[25] High temperatures may be needed to produce the intermediate dialkynyl–rhodium complex.

Alkynylpalladium reagents can be useful intermediates in the synthesis of diynes by catalytic coupling reactions since the dialkynyl–palladium complex $(PPh_3)_2Pd(C{\equiv}CR)_2$ (**9**) has been shown to easily produce the corresponding diyne on reductive elimination.[26]

Reactions of benzene solutions of arylalkynes with 1 equiv. of chloroacetone and 2 equiv. of $Et_3N$, using a mixture of $(PPh_3)_4Pd$ and CuI as a catalyst, afford 1,4-diarylbutadiynes in very good yields. Under similar reaction conditions aliphatic 1-alkynes yield a mixture of symmetrically disubstituted 1,4-dialkynyl-1,3-butadiynes and 3-alkyl-4(1-alkynyl)-hexa-1,5-diyn-3-enes (**10**; equations 15 and 16).[27] This method may represent a good alternative, in nonpolar organic solution, to the Glaser reaction.

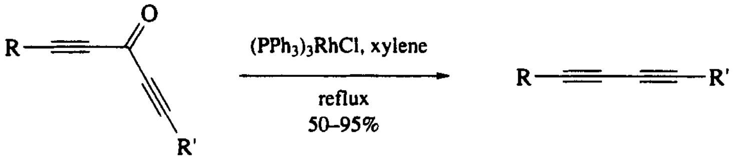

(14)

R = Ph, $p$-MeC$_6$H$_4$, $p$-MeOC$_6$H$_4$, 2,4,6-Me$_3$C$_6$H$_2$

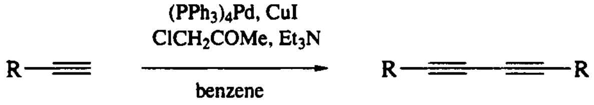

(15)

R = Ph, 2-thienyl

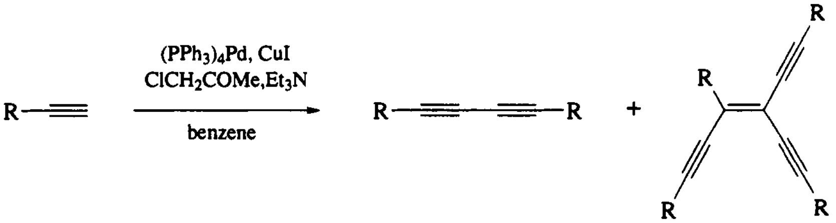

**(10)**

(16)

R = Bu$^n$, $n$-hexyl, Pr$^n$

Ito and his coworkers have reported that palladium-catalyzed oxidative coupling reactions of Grignard reagents in the presence of $N$-substituted isocyanide dichloride afford diynes (equation 17). Isocyanide dichloride may serve as a reoxidant of the palladium catalyst in this sequence *via* a catalytic cycle.[28] In addition Kiji and his coworkers have described the oxidative coupling of phenylacetylene by a Pd–Cu catalyst in the presence of 4-iodo-(3$H$)-phenothiazin-3-one.[29]

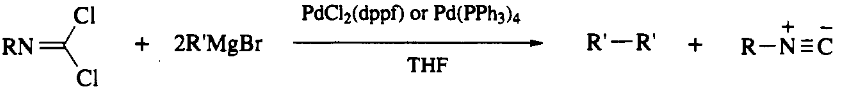

(17)

R = Ph, cyclohexyl; R$^1$ = PhC≡C, Me$_2$(MeO)CC≡C; dppf = 1,1-bis(diphenylphosphino)ferrocene

## 2.5.6 APPLICATIONS

### 2.5.6.1 Linear Polyalkynes

Many stabilized higher polyynes terminated with bulky groups such as $t$-butyl or trialkylsilyl can be derived from alkyne coupling reactions. Thus polyyne chain extensions using Et$_3$Si(C≡C)$_m$H ($m$ = 1, 2, 3, 6) in mixed oxidative couplings using the modified Hay method,[30] have been reported by Walton and coworkers (Scheme 4).[31] Another polyyne chain extension has been used in the synthesis of the unsymmetrically substituted octatetraynediamines (**13**) *via* the reaction of the lithium alkynide (**11**) with perchlorobutenyne (**12**) (Scheme 5).[32]

$$\mathrm{Et_3Si(C{\equiv}C)_2H} \;+\; \mathrm{Et_3SiC{\equiv}CH} \longrightarrow \mathrm{Et_3Si(C{\equiv}C)_3SiEt_3} \longrightarrow \mathrm{Et_3Si(C{\equiv}C)_3H} \longrightarrow$$

$$\mathrm{Et_3Si(C{\equiv}C)_6H} \longrightarrow \mathrm{Et_3Si(C{\equiv}C)_{12}SiEt_3} \longrightarrow \mathrm{H(C{\equiv}C)_{12}H}$$

**Scheme 4**

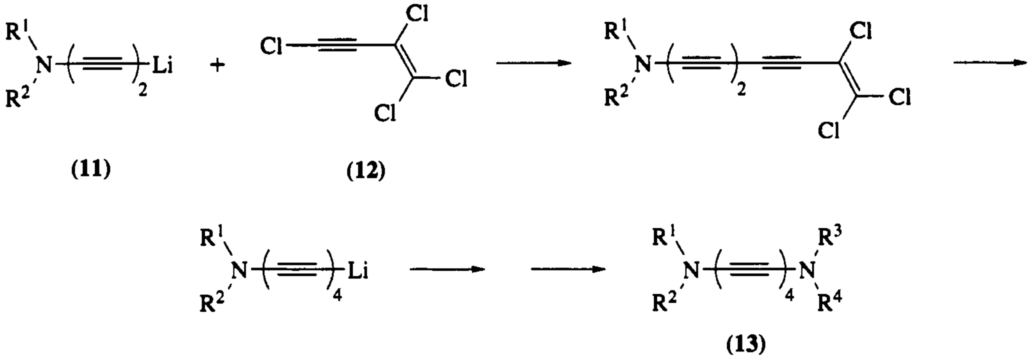

**(11)** **(12)** **(13)**

Scheme 5

### 2.5.6.2 Cyclic Alkynes

The oxidative coupling of α,ω-diethynyl derivatives by the Eglington method, which can be performed under homogeneous high dilution conditions, is suitable to obtain cyclic diynes. A general review of cyclic alkynes is available.[33–35] A wide variety of dehydroannulenes have been synthesized by oxidative coupling reactions, *e.g.* the oxidative coupling reaction of the α,ω-diethynyl compound (**14**) to give the cyclic polyyne (**15**) (which could be separated into *meso* and racemic diastereomers), followed by base-induced prototropic rearrangement to provide the novel cyclic polyenepolyyne (**16**; Scheme 6).[36]

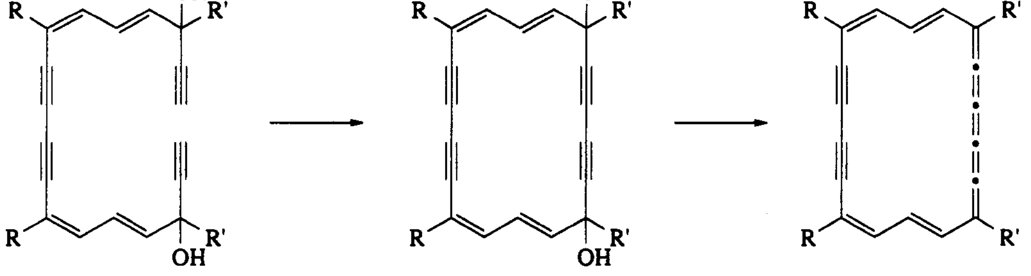

**(14)** **(15)** **(16)**

Scheme 6

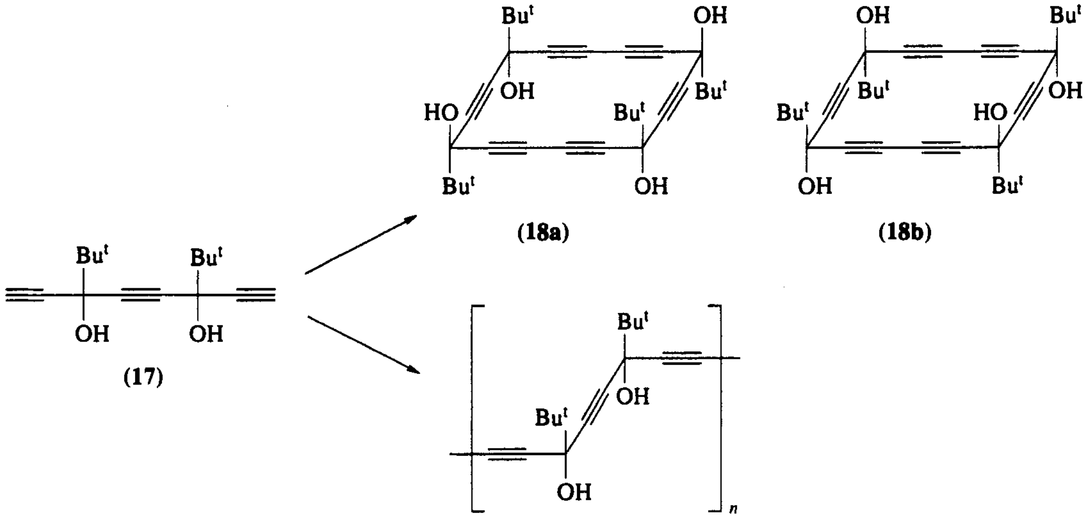

**(18a)** **(18b)**

**(17)**

**(19)**

Scheme 7

Toda and coworkers have found drastic differences in the reaction behavior of racemic and optically active 3,6-di-*t*-butylocta-1,4,7-triyne-3,6-diol (**17**) upon oxidative coupling by the Eglington method.[37,38] Thus, the noncentrosymmetric cyclic dimers, (**18a**) and (**18b**), can be obtained from the racemic monomer, but the corresponding optically active monomer does not lead to any of the cyclic dimer. In the latter case the optically active polymer (**19**) is obtained as the sole isolable product (Scheme 7).

Recently oxidative coupling reactions of α,ω-diethynyl compounds have been applied in the synthesis of cyclophanes, which are interesting functional host molecules.[39–42] Whitlock and coworkers,[43] for example, have reported the synthesis of the water-soluble cyclophane (**21**), designed as an esterase mimic by the Eglington reaction of (**20**; Scheme 8).

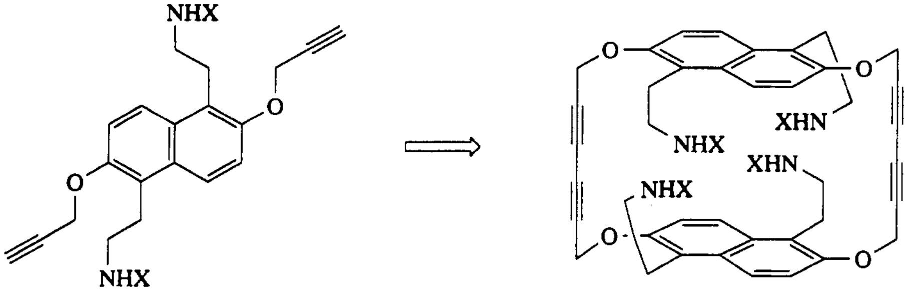

**(20)** **(21)**

Scheme 8

### 2.5.6.3 Polymer Synthesis

Since the yield in the oxidative coupling is practically quantitative, the oxidative polymerization of α,ω-diethynyl monomers would be expected to yield high molecular weight, linear polymers, as shown in equation (18). Hay has reported that almost any diethynyl monomer, even organometallic monomers, can be polymerized to high molecular weight polymers in the presence of a soluble amine complex catalyst of a copper(I) salt (Hay modification).[44,45]

$$n\ \equiv\!-\mathrm{Y}-\!\equiv\ +\ 1/2\,\mathrm{O_2}\ \longrightarrow\ \left[\mathrm{Y}-\!\equiv\!-\!\equiv\right]_n\ +\ n\mathrm{H_2O} \qquad (18)$$

#### 2.5.6.3.1 *Synthesis of organic polymers*

*m*-Diethynylbenzene gives a pale yellow polymer in quantitative yields when treated by the Hay procedure. The polymer is soluble in solvents such as chlorobenzene and nitrobenzene above 100 °C.[45,46] Recent commercial developments of organic solids from alkynic precursors date from the discovery of the above soluble butadiynylenephenylene polymer. The molecular weight and solubility of the polymer can be controlled by using a mixture of *m*-diethynylbenzene and phenylacetylene in the polymerization. The oligomers produced can then be further processed at high temperatures to form carbon films and fibers.[46]

In order to obtain high molecular weight polymers by the oxidative coupling of α,ω-diethynylalkanes as described in Section 2.5.2, higher temperatures (to increase the polymer solubility), optimized concentrations of the reagents, and addition of molecular sieves (to remove the water generated during the polymerization) have all been shown to lead to best results.[9]

#### 2.5.6.3.2 *Synthesis of organometallic polymers*

The Hay modification can be applied to organometallic diethynyl compounds such as Group IV alkynes.[45] Parnell and coworkers,[47] for example, have successfully used the procedure to carry out the oxidative coupling of 1,3-bis(dimethylethynyl)disiloxane (**22**). However, diethynyldimethylsilane (**23**) did not give the polymer, as cleavage of the silicon–ethynyl bond occurred instead.

An interesting class of polymers, *e.g.* (**25**) and (**27**), containing conjugated alkynic groups and σ-bonded transition metal atoms in the main chain has been reported.[48,49] Oxidative coupling reactions of

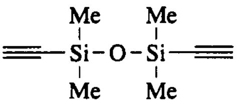

$$HC\equiv C-Si(Me)_2-O-Si(Me)_2-C\equiv CH$$

**(22)**

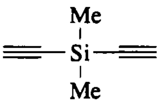

$$HC\equiv C-Si(Me)_2-C\equiv CH$$

**(23)**

dialkynyl complexes are used as one of three methods for preparing the polymers. Polymerization using the Hay modification affords a high molecular weight product, *e.g.* $M = 1.5 \times 10^5$ (**25b**). However, there is a severe restriction on this method since it cannot be applied to monomer complexes such as alkynylnickel complexes which are unstable to the oxidant.

A platinum–polyyne polymer, containing diethynylsilane groups in the main chain, can be synthesized by the Hay reaction conditions after appropriate modification to protect the cleavage of Si—C bonds. The characteristics of the synthesis are as follows: (a) since the Si—C≡C bond may be cleaved by uncomplexed copper(II) chloride, a large excess of TMEDA, which is added to catch free copper(II) ion, may retard the formation of the oxygen complex; (b) a homogeneous catalyst solution is prepared by oxygen-bubbling for many hours to complete the formation of the oxygen complex in methylene chloride in the presence of molecular sieves; (c) polymerization is carried out in methylene chloride over the molecular sieves using 3.5 equiv. of the above reagent; (d) to optimize the molecular weight of the polymer the coupling is monitored by GPC, and it requires 7 h. Under the above conditions a white polymer film (**28**; $M$ = 77 000) can be obtained.[50]

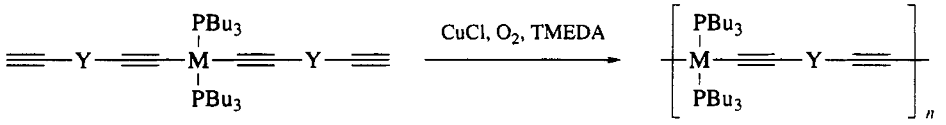

(19)

**(24)** a: M = Pt; Y = —
b: M = Pt; Y = 1,4-$C_6H_4$

**(25)** a: M = Pt; Y = —
b: M = Pt; Y = 1,4-$C_6H_4$

**(26)** a: M = Pd; Y = —
b: M = Pd; Y = 1,4-$C_6H_4$

**(27)** a: M = Pd; Y = —
b: M = Pd; Y = 1,4-$C_6H_4$

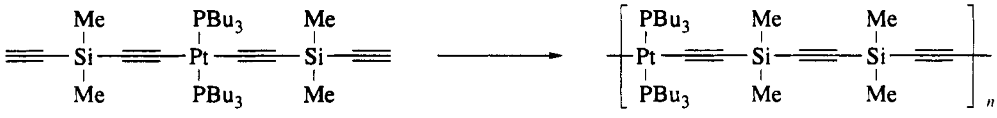

(20)

**(28)**

## 2.5.6.4 Natural Product Synthesis

There is a very wide variety of natural products which, with their biological precursors, have structures based on straight-chain fatty acids, containing conjugated alkenic and/or alkynic linkages. Many of these natural polyalkynes have been prepared from alkynic precursors using oxidative couplings. For example, Nicolaou and his coworkers have reported the stepwise, stereocontrolled total synthesis of endiandric acids, utilizing the alkadiynic diol (**30**) as a key intermediate, which was readily available from *trans*-pent-2-en-4-yn-1-ol (**29**) by Glaser coupling.[51] Similarly the biomimetic precursor (**33**) of endiandric acids A–G was prepared by coupling (**31**) (1 equiv.) with the more plentiful (**32**) (5 equiv.) in pyridine–methanol (1:1), containing Cu(OAc)2 (2 equiv.; Eglington method).[52] A further example is the coupling of the ω-alkynic synthon (**35**) with the bromoalkyne (**34**), by the Chodkiewicz–Cadiot method, to give anacyclin (**36**), an insecticide found in *Anacyclus pyrethrum*.[53]

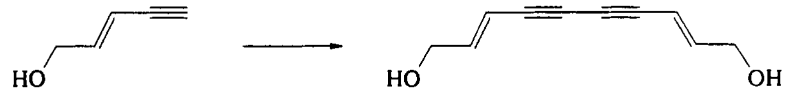

**(29)** **(30)**

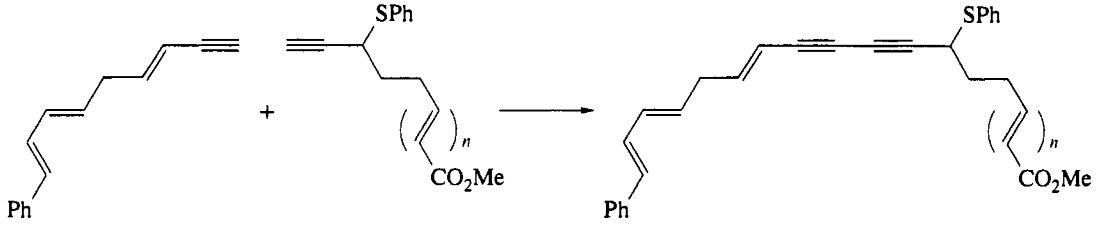

**(31)** **(32)** **(33)**

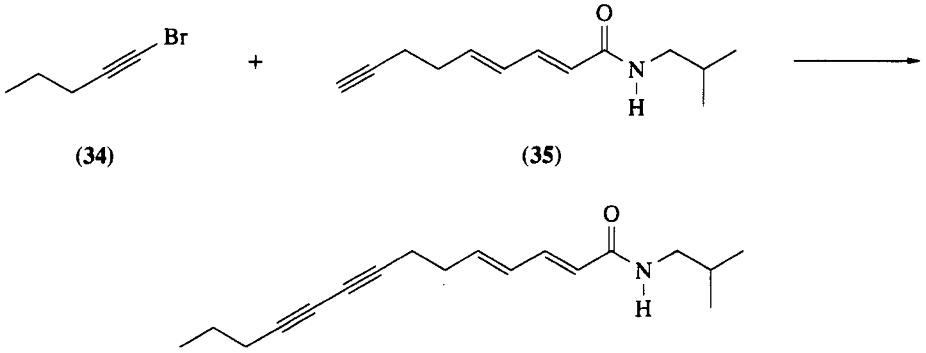

**(34)** **(35)**

**(36)**

## 2.5.6.5 Phase-transfer Catalysts

Phase-transfer catalysis is a useful procedure for a variety of interesting metal-catalyzed reactions.[54,55] However, only one example of this approach has been reported for the synthesis of diynes by the *sp–sp* carbon coupling reaction. Thus vinylic dibromides derived from aromatic aldehydes have been shown to react with carbon monoxide, in the presence of zerovalent palladium compounds as the metal catalyst, and under phase-transfer conditions in a two-phase system (benzene, 5 M NaOH), to give the corresponding diynes in reasonable yields (equations 21 and 22).[56]

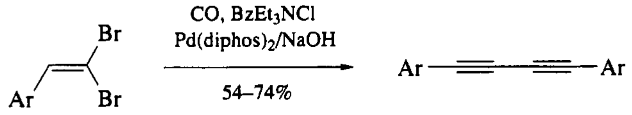

(21)

Ar = Ph, $p$-MeC$_6$H$_4$, $p$-ClC$_6$H$_4$, $p$-MeOC$_6$H$_4$

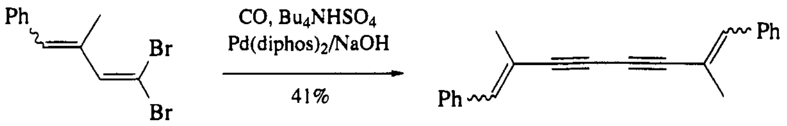

(22)

## 2.5.6.6 Copper–Polymer Complexes as Catalysts for Oxidative Coupling Reactions

The oxidative coupling reaction of terminal alkynes is critically dependent on the water concentration in the reaction mixture (see Section 2.5.2). Since water is produced during the reaction, careful elimination of it may be required. Challa and Meinders[57] have demonstrated that the polymer catalyst derived from copper(II) chloride and either *N*,*N*-dimethylbenzylamine or *N*,*N*-dimethylaminomethylated atactic polystyrene (**37**) provides an extra protection of the catalytic copper complexes against water in the coupling reaction of phenylacetylene (equation 23), resulting in a higher reaction rate than the low molecular weight catalyst.

$$\text{Ph}{-}{\equiv} \quad + \quad 1/2\ \text{O}_2 \longrightarrow \text{Ph}{-}{\equiv}{-}{\equiv}{-}\text{Ph} \qquad (23)$$

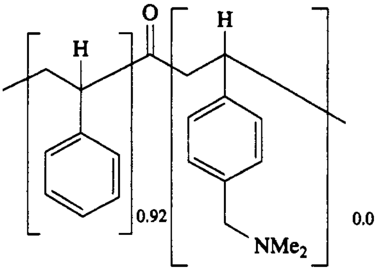

(37)

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# 2.6
# Pinacol Coupling Reactions

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## 2.6.1 INTRODUCTION

The reductive coupling of carbonyl compounds, especially ketones, to give pinacols is an important method for the formation of vicinally functionalized C—C bonds.[1] In addition, the related coupling of carbonyls to give alkenes, the McMurry reaction, provides a complementary route for C=C bond elaboration.[117]

The intermolecular pinacolic coupling of carbonyl compounds was first described in 1859[2] and, although the classical reagents lacked selectivity, it has since been refined into a mild and selective method for the synthesis of 1,2-diols. Coupling can be initiated photochemically, electrochemically, or with a range of metal reducing agents. A number of mechanisms have been proposed[3] and these can be generalized into two basic types, as shown in Scheme 1. Coupling is propagated by single-electron reduction of the carbonyl group to form a ketyl radical anion (**1**), which either undergoes radical–radical coupling (route a), or is further reduced to the corresponding dianion (**2**) and then nucleophilically attacks a second carbonyl group (route b), so leading to pinacol formation.

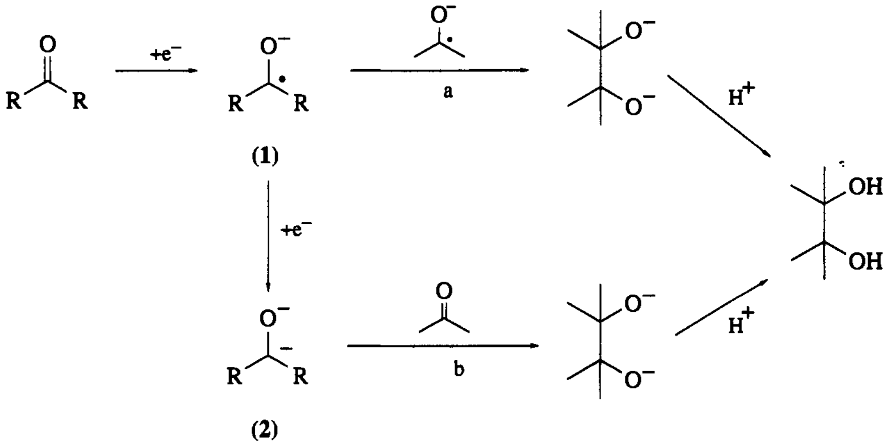

Scheme 1

By far the majority of pinacolic couplings occur *via* radical–radical coupling and generally afford a mixture of (±) (*like*) and *meso (unlike)* diols.[4] An alternative and often competing reaction to pinacolization is reduction to the corresponding alcohol.[5] Indeed, selective pinacol formation is critically dependent on many factors, including the reductant used, the solvent[6] and the reaction pH.[30,31,79] The traditionally used reducing agents such as alkali metals[7] or metal amalgams[8] suffered from lack of selectivity and/or sluggish reaction with only low to modest yields. Moreover electrochemical[9,10] and photochemical[11] methods were largely limited to aryl (activated) systems, as was the extensively used Gomberg–Bachman procedure, using $Mg/MgI_2$.[12] The first major improvement in reaction methodology was the use of aluminum amalgam in dichloromethane or THF (equation 1).[13] The use of these solvents greatly facilitates product isolation, thus improving yields to 40–60%.

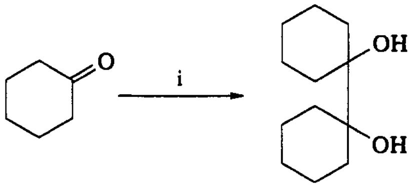

(1)

i, Al(Hg), $CH_2Cl_2$ (or THF), reflux, 40–60%

More recently the introduction of low-valent transition metal and lanthanoid based reducing systems, especially those based on titanium, has provided dramatic advances in efficiency and selectivity. It is now possible to select appropriate conditions for efficient coupling of all types of carbonyl compounds, often with high chemo-, regio- and stereo-selectivity. Moreover, imino- and thio-carbonyl derivatives are also coupled *via* pinacolic methodology. The coupling of imines to 1,2-diamines is particularly effective, with excellent control of vicinal stereochemistry.

## 2.6.2 INTERMOLECULAR COUPLINGS

### 2.6.2.1 Aromatic Carbonyl Compounds

The relative ease of pinacolization is primarily determined by the reduction potential of the carbonyl group involved. Many reductants are therefore selective for aromatic and other electronically activated systems. Moreover, as a result of this ready reduction, pinacolization of such carbonyls can be effected by either anionic or radical routes. For example, treatment of aromatic aldehydes or ketones with Mg/TMSCl in HMPA promotes pinacolization *via* formation of an α-silyloxy carbanion[14,15] and nucleophilic attack on a second carbonyl group (equation 2). Furthermore, with benzaldehyde the reaction is stereodirecting with a preference for *lk*-coupling.[4] Whilst an alternate coupling method using the milder conditions of Zn/TMSCl in THF proceeds *via* radical–radical coupling,[16] interestingly ultrasonication of this reaction increases yields by up to 50%. In a similar manner reaction of aromatic aldehydes with hexamethyldisilane and a fluoride catalyst also gives 1,2-diarylethanediols in moderate to good yields, after hydrolytic work-up (equation 3).[17]

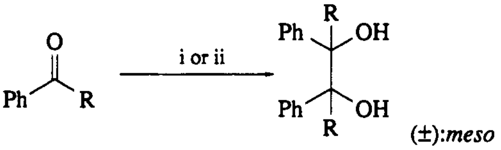

R = H, 90% 3:1
R = Me, 88% 1:1

(2)

i, Mg, $Me_3SiCl$, HMPA, 95 °C; ii, Zn, $Me_3SiCl$, THF, 0–81% (stirring), 56–85% (ultrasonication)

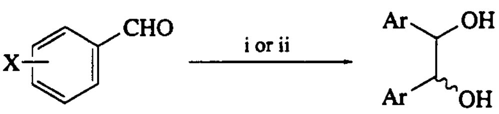

(3)

i, $(Me_3Si)_2$, $Bu_4NF$, HMPA, 61-95%; ii, $(Me_3Si)_2$, CsF, HMPA, 26-100%

One-electron reductants promoting radical-mediated pinacolic coupling are more common however. Early examples were the use of organometallic species derived from vanadium(II)[18] or chromium(II) salts (equation 4)[18,19] which convert aromatic aldehydes to mixtures of pinacols and the corresponding monoalkyl ethers. Vanadium salts also effect the coupling of capto-datively activated carbonyls such as (**3**) to provide a convenient route to tartaric acid derivatives in good yields (70–80%; equation 5).[20] In contrast, chromium and europium salts give only reduction to the corresponding alcohols.

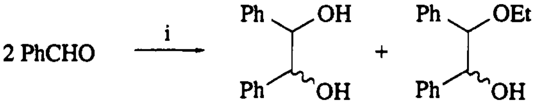

69% 11%

(4)

i, $Cr(ClO_4)_2$, HCl, EtOH, r.t.

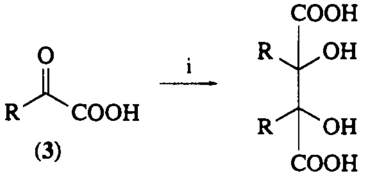

(**3**)

R = Me, 80%
R = Ph, 70%
R = Bn, 80%

(5)

i, $V(ClO_4)_2$, 1 M $HClO_4$, r.t., 10 h

Treatment of aromatic aldehydes with $Fe(CO)_5$ or $Fe_3(CO)_{12}$ in pyridine (equation 6) gives the corresponding pinacols in good yield, together with some reduction.[21] Alternative iron-based reducing systems such as BuLi/$FeCl_3$ or BuLi/$Fe_4S_4(SPh)_4$ also reductively couple aromatic aldehydes and ketones to 1,2-diols (equation 7).[22] The former reagent, however, also produces significant amounts of the corresponding alcohol.

Of more general application are the titanium-based reagents first introduced by Mukaiyama[23] and by Trylik (equation 8).[24] Mukaiyama demonstrated that $TiCl_4$/Zn selectively coupled both aromatic or aliphatic aldehydes and ketones to either pinacols or alkenes by judicious choice of the appropriate reaction

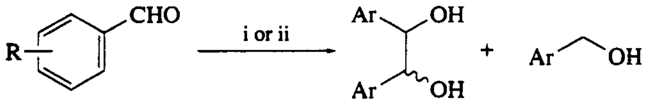

(6)

| | | |
|---|---|---|
| i, Fe(CO)$_5$, pyridine, 80 °C, | 74–95% | 6–16% |
| ii, Fe$_3$(CO)$_{12}$, pyridine, 80 °C, | 72–96% | 6–19% |

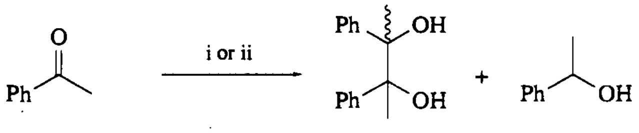

(7)

| | | |
|---|---|---|
| i, BuLi, [Fe$_4$S$_4$(SPh)$_4$][Bu$_4$N]$_2$, Et$_2$O, hexane, −93 °C | 57% | 3% |
| ii, BuLi/FeCl$_3$, Et$_2$O, hexane, −93 °C | 43% | 30% |

conditions.[25] In contrast, the Trylik reagent, TiCl$_3$/Mg, gave alkenes with aromatic systems, but coupled aliphatic carbonyls to pinacols in moderate yields. Stable soluble Ti$^{II}$ species can be prepared from TiCl$_4$ and Bu$^i_2$Te in an inert solvent.[26] In DME this reagent promotes selective *lk*-coupling of benzaldehyde to the corresponding (±)-pinacol (equation 9). More recently Seebach reported that the TiCl$_4$/BuLi system also promotes selective *lk*-coupling of aromatic aldehydes (equation 10).[27] The stereoselectivity is, however, dependent on the nature of the aryl substituent. Thus when R = H, 4-Me, 4-Cl or 2-Me the *l*-pinacol is formed selectively, but when R = 2-Me both *l*- and *u*-isomers are formed.[4] Reduction of Cp$_2$TiCl$_2$ with Bu$^s$MgCl also produces a titanium species exhibiting high *l-(threo)*-selectivity (equation 11).[28] In addition, this reagent is also capable of coupling both aromatic and α,β-unsaturated aldehydes.[28,29] Although most titanium-mediated pinacolic couplings employ Ti$^0$ or Ti$^{II}$ as the reductant, Ti$^{III}$ has also been used. The reducing power of Ti$^{III}$ redox systems is strongly pH dependent. Thus whilst highly activated carbonyl compounds such as 2- or 4-acetylpyridines are coupled to their respective pinacols by treatment with aqueous acidic TiCl$_3$ (equation 12),[30] less reactive species like 3-acetylpyridine or benzaldehyde require the more strongly reducing basic TiCl$_3$ (equation 13).[31] A similar effect is observed in the electro-[32] and photo-pinacolization[33] of pyridinyl ketones, where the 3-isomers react more slowly.

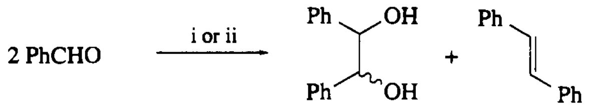

(8)

| | | |
|---|---|---|
| i, TiCl$_4$ / Zn, THF, 0 °C | 98% | 1% |
| ii, TiCl$_4$ / Zn, dioxane, reflux | – | 98% |

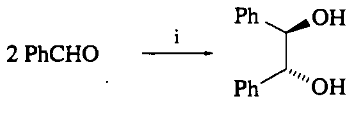

(9)

i, TiCl$_4$, Bu$^i_2$Te, DME, r.t., 99%

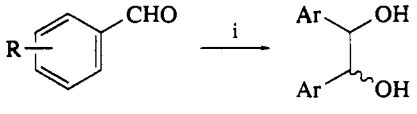

(10)

i, BuLi, TiCl$_4$, Et$_2$O, 50–92%

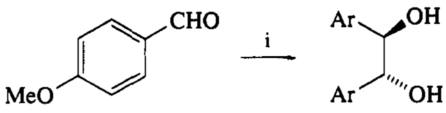

(11)

*ds* = 100:1

i, $Cp_2TiCl_2$, $Bu^sMgCl$, THF, -78 °C to r.t., 96%

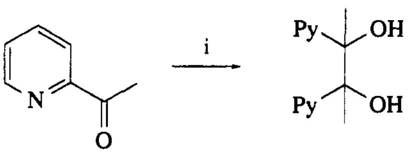

(12)

(±):*meso* = 1:7

i, AcOH, aq. $TiCl_3$, r.t., 72%

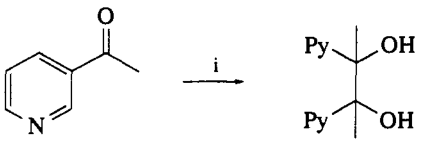

(13)

i, 30% NaOH, aq. $TiCl_3$, MeOH, pH 10–12, r.t., 73%

Chemoselective pinacolization has recently been established with the advent of lanthanoid metal based coupling reagents. Imamoto *et al.* employed low-valent cerium as a mild selective reagent (equation 14) suitable for both aromatic and aliphatic compounds.[34] Under these conditions carboxyl, cyano and vinyl halide groups are unaffected. This is in sharp contrast to the relatively low chemoselectivity shown by most titanium-based reagents. Similarly Kagan and coworkers have used samarium diiodide as an alternative chemoselective reductant for the coupling of either aromatic or aliphatic carbonyls (equation 15). With aromatic aldehydes this reagent exhibits complete selectivity for the carbonyl group in the presence of either carboxyl, cyano or nitro moieties.[35] Recently Fujiwara demonstrated that aromatic aldehydes and ketones can be coupled to pinacols using 0.5 equiv. of ytterbium metal (equation 16).[36] The reaction proceeds *via* the formation of an intermediate ytterbium species (**4**) which acts as a nucleophile toward a second carbonyl group.[190]

Photo-[11] and especially electro-chemical[9] pinacolizations of aromatic systems are well established routes to 1,2-diols. Furthermore, stereoselective pinacol formation is possible *via* both routes through control of the reaction media. For example, photopinacolization requires the use of an external hydrogen donor, usually a secondary alcohol or an amine,[37] and stereoselection can be influenced through changes in these hydrogen donors. Thus under neutral conditions approximately 1:1 (±):*meso* mixtures are

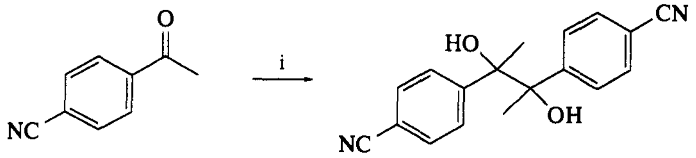

(14)

i, $CeI_2$, THF, 0 °C to r.t., 91%

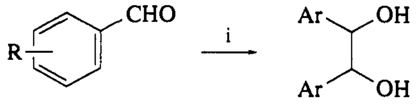

(15)

i, 2 $SmI_2$, THF, 66–95%

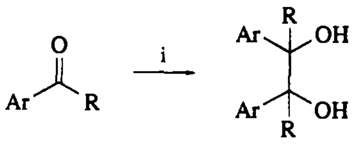
(16)

i, Yb (0.5 equiv.), THF, HMPA, 58–99%

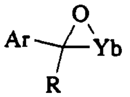
(4)

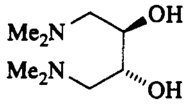
(5)

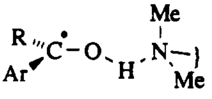
(6)

formed (equation 17), but under basic conditions *lk*-coupling, to give the (±)-pinacol, is favored due to increased charge interactions.[38] Amines are more efficient hydrogen donors than alcohols and therefore favor *meso* pinacol formation *via ul*-coupling of neutral ketyl radicals.[39] Recently homochiral amines have been studied as a method for chiral induction.[40] Optical yields of up to 23% have been obtained using the amine (**5**) *via* formation of complexes of the type (**6**).

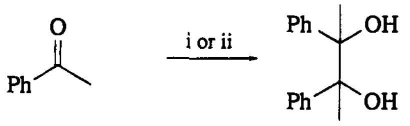
(17)

| | (±):*meso* |
|---|---|
| i, $h\nu$, $\mathrm{Pr^iOH}$ | 1.08:1 |
| ii, $h\nu$, $\mathrm{Pr^iOH}$, 0.01 M $\mathrm{NaOPr^i}$ | 2.98:1 |

Electropinacolization can be a highly stereoselective and in some cases a stereospecific reaction. The degree of selectivity has been ascribed to both solution and cathode surface effects. For example, the electropinacolization of hydroxybenzaldehyde in an aqueous basic medium gives the *meso* hydrobenzoin (**7**) stereospecifically (equation 18).[41] The related coupling of benzoin (**8**; X = OH) is also stereospecific, giving only one of six possible diastereomeric products, the *threo* isomer (**9**) in 50% yield *via* an *lk*-coupling.[42] However when X = Me, that is in the absence of an additional hydrogen-bonding site, two diastereomers are formed. In agreement with photopinacolic couplings, Stocker and Jenevein demonstrated[43] that at basic pH *lk*-coupling to give (±)-products is again favored (equation 20). A major drawback of electropinacolizations carried out in aqueous media is competing reduction to the corresponding alcohol. Selectivity for pinacol formation is much improved in aprotic media. Under these conditions coupling occurs between neutral radicals, and by the use of conditions that minimize protonation and hydrogen-bonding, (±):*meso* ratios of up to 19:1 can be obtained (equation 21).[44,45] Tetraalkylammonium salts have proven particularly useful in promoting high yielding selective pinacolizations under aprotic conditions, giving almost quantitative yields of pinacols (equation 22).[46] These salts not only lower the reaction potential, a feature that permits the electropinacolic coupling of aliphatic ketones,[57] but also facilitate very high (±):*meso* ratios of up to 50:1.[47] Increased yields have also been obtained using added bivalent transition metal cations, such as $Cr^{2+}$, $Mn^{2+}$, $Fe^{2+}$, $Co^{2+}$ or $Zn^{2+}$. Product distribution is dependent on the Lewis acidity and complexing power of the cation used.[48] The logical extension of using homochiral coelectrolytes to promote asymmetric couplings has also been investigated but with

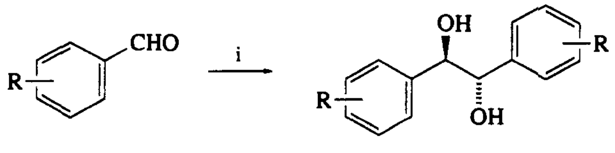
(18)

(7)

i, Hg, 2 M NaOH, or Hg, 4 M NaOH, EtOH, −1.6 to −2.0 V only limited sucess. Thus Seebach[49] has obtained optical yields of *ca.* 6% using the amine (**5**; equation 23), whilst van Tilborg[50] has obtained optical yields of up to 21% with the β-hydroxyamine salt (**10**).

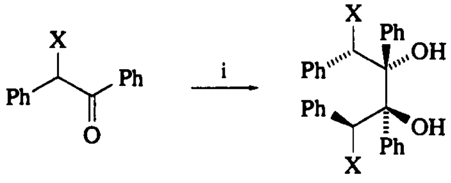

X
Ph
O
Ph
i
X
Ph
OH
Ph
Ph
OH
Ph
X

(19)

(**8**) X = OH, $NH_2$ (**9**)

i, Hg/Cu, basic aq. EtOH, 50%

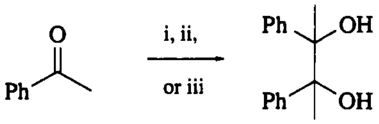

O
Ph
i, ii,
or iii
Ph
OH
Ph
OH

(20)

| | | | (±):*meso* |
|---|---|---|---|
| i, | acidic | Hg, aq. AcOH, LiCl, 60% | 1.2:1 |
| ii, | neutral | Hg, aq. $NH_4OH$, aq. $NH_4OAc$, 46% | 1.1:1 |
| iii, | basic | Hg, 2M KOAc, 61% | 2.8:1 |

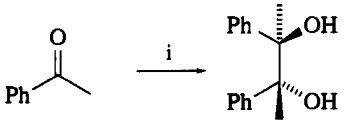

O
Ph
i
Ph
OH
Ph
OH

(21)

(±):*meso*
19:1

i, Hg, DMF, $Bu_4NClO_4$, aq. $LiClO_4$

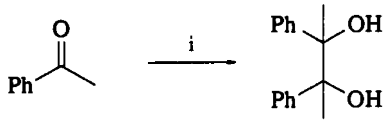

O
Ph
i
Ph
OH
Ph
OH

(22)

i, Hg, MeCN, −1.8 V, 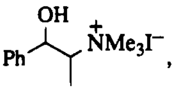 , 98%

OH
Ph
$\overset{+}{N}Me_3I^-$

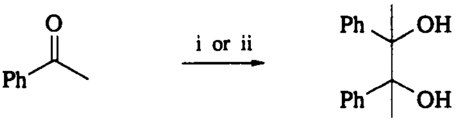

O
Ph
i or ii
Ph
OH
Ph
OH

(23)

| | optical yield % |
|---|---|
| i, Hg, DDB (**5**), MeOH, LiBr, 95% | 6.4 |
| ii, Hg, MeCN, 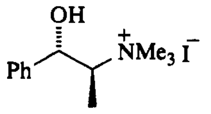 (**10**) | 20.6 |

OH
Ph
$\overset{+}{N}Me_3I^-$

### 2.6.2.2 Aliphatic Carbonyl Compounds

The synthesis of pinacols from aliphatic carbonyl compounds requires the use of more efficient redox systems than does the corresponding reductive coupling of aromatic systems. Until the early 1970s there were few general efficient methods available. The classical alkali or alkaline metal amalgam reagents are not very selective and are of little use with complex substrates. The first general method for the intermolecular coupling of aliphatic aldehydes was reported in 1975[51] and employs TMSCl/Li as the reductant (equation 24). The use of TMSCl is essential for the *in situ* trapping of the intermediate alkoxides. Titanium(II)-based pinacolic coupling reagents are of more general use, but unfortunately both Mukaiyama's reagent, $TiCl_4/Zn$,[23] and Trylik's reagent, $TiCl_3/Mg$,[24] offer only limited scope. A systematic analysis of titanium-based reagents by Corey and his coworkers[52–54] led to the development of three generally applicable reagents. Thus $TiCl_4/Mg(Hg)$ efficiently promotes intermolecular couplings, whilst $CpTiCl_3/LiAlH_4$ or the hexamethylbenzene complex of $(Cl_2AlCl_2)Ti$ are more suitable for intramolecular examples.[53] The nature and yield of product are highly dependent on the type of titanium(II) species used. The relative efficacy of a selection of these reagents for the coupling of cyclohexanone is shown in Table 1.

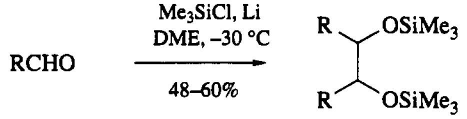

(24)

**Table 1** Relative Efficacy of $Ti^{II}$ Reagents at the Pinacolic Coupling of Cyclohexanone

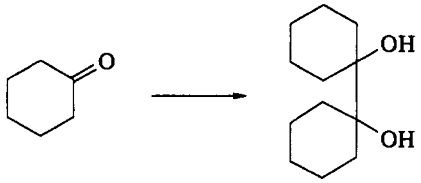

| *$Ti^{II}$ system* | *Yield (%)* |
|---|---|
| $Mg(Hg)/TiCl_4$ | 93 |
| $Mg/TiCl_3$ | 45 |
| $Zn/TiCl_4$ | 24 |
| $LiAlH_4/TiCl_3$ | (Alkene) |

Both aldehydes and ketones are efficiently coupled (80–95%) by $TiCl_4/Mg(Hg)$, which is also suitable for unsymmetrical couplings (equation 25). For low molecular weight aldehydes $CpTiCl_3/LiAlH_4$ is the reagent of choice. Recently Wiedmann has introduced graphite-suspended magnesium, $C_8Mg$, and titanium, $C_8Ti$, as simple to use, universally applicable reagents.[55] These reagents couple both aromatic and aliphatic aldehydes or ketones efficiently in good yields (48–93%) with a high tolerance for other reducible substituents. Unlike many other reducing agents these reagents are also effective at both inter- and intra-molecular coupling. In addition $C_8Ti$ also promotes McMurry-type coupling of carbonyls to alkenes[129] and the related cyclization of keto esters. Other highly chemoselective reagents based on low-valent lanthanoid metals[1h] have also been applied to aromatic and aliphatic couplings.[34,35] Thus, low-valent cerium ($CeI_2$) couples cycloalkanones in good yields (64–95%), although competing reduction can be a problem.[34] Organocerium reagents (RCeI) have also been used;[56] however these reagents also give Grignard-type products and reduction in addition to pinacols. Samarium diiodide, an efficient reagent for stereoselective intramolecular couplings, also promotes intermolecular couplings in high yields (80–95%).[35] Recently Kariv-Miller and Mahachi reported a potentially useful method for the electropinacolization of aliphatic carboyl compounds through the use of dimethylpyrrolidinium tetrafluoroborate ($DMPBF_4$) as an electrode potential reducing catalyst (equation 26).[57] In the absence of $DMPBF_4$ only reduction is observed, but using $DMPBF_4$ selective pinacolization occurs.

Although a range of chemoselective pinacolic coupling methods is becoming available the problem of stereoselective coupling of aliphatic carbonyls is less well defined. This is in contrast to couplings of aromatic systems, where both pinacolic coupling to 1,2-diols and reductive (McMurry-type) pinacolic couplings to alkenes can be highly selective. Controlling the stereochemistry of the diol formed from aliphatic carbonyls remains a problem. For example, Mundy *et al.* have shown that the coupling of homochiral

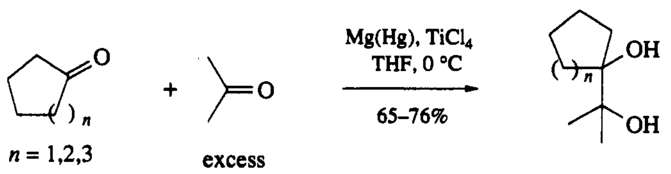

(25)

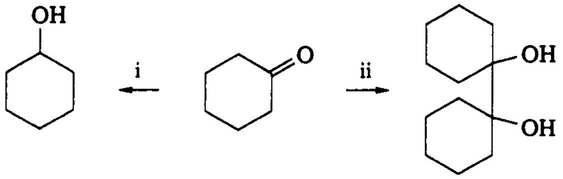

(26)

i, Hg, DMF, aq. diglyme, –2.9 V, 76%; ii, Hg, DMF, aq. diglyme, –2.7 V, DMPBF$_4$, 95%

methyl cyclohexanones gives a mixture of stereoisomeric products whose distribution differs when using Al(Hg) or the strongly coordinating TiCl$_4$/Mg(Hg) reagent (Scheme 2).[58] Stereoselective *lk*-coupling of aliphatic aldehydes to (±)-pinacols with up to 100% selectivity (typically 70–96%) has however been achieved *via* photoinduced formation of 2-stanna-1,3-dioxolanes.[59] Formation of the cyclic organometallic intermediate (**11**) controls the stereochemical outcome of the reaction (equation 27). Unfortunately this method is not suitable for ketones since the transition state becomes too sterically hindered. A convenient method for stereoselective coupling of ketones is to link them *via* a chain containing a removeable heteroatom. Such intramolecular cyclizations are then equivalent to stereoselective intermolecular couplings (*e.g.* equation 40).[74,75] Highly *lk*-selective hydrodimerization of α,β-unsaturated aldehydes is possible using the Cp$_2$TiCl$_2$/Bu$^s$MgCl reagent (equation 28).[28] Again metal templating accounts for the observed stereoselection, with the complex (**12**) postulated as the stereocontrolling intermediate.

In some instances the carbonyls in pinacolic coupling reactions exhibit chirality (enantiomer) recognition, that is the ability of an enantiomer to recognize a molecule of like chirality and react exclusively

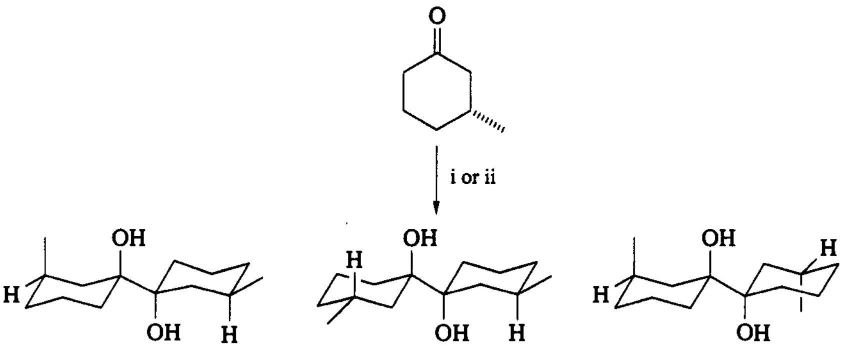

(1*R*,1′*R**) (1*R*,1′*S**) (1*S*,1′*R**)

| *Reaction conditions* | *% Yield* | | |
|---|---|---|---|
| | (1*R*,1′*R**) | (1*R*,1′*S**) | (1*S*,1′*R**) |
| i, Al(Hg), C$_6$H$_6$, reflux | 53 | 16 | 31 |
| ii, TiCl$_4$, Mg(Hg), THF, –10 °C | 17 | 83 | – |

**Scheme 2**

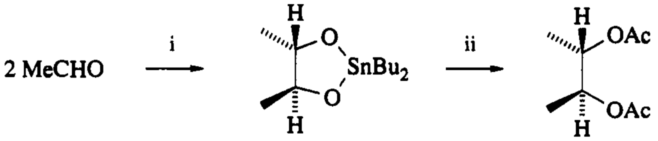

(**11**) (±) only

(27)

i, Bu$_8$Sn$_3$, *h*ν, C$_6$H$_6$; ii, AcCl, 70%

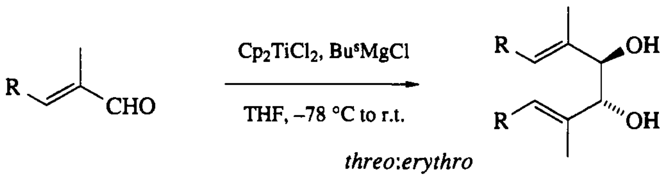

(28)

| | *threo*:*erythro* |
|---|---|
| R = H, 98% | 100:1 |
| R = Me, 87% | 60:1 |

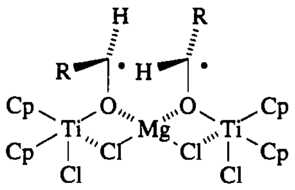

**(12)**

with it or its mirror image. For pinacolic couplings a reaction between two like ketones, (*R*) + (*R*) or (*S*) + (*S*), giving a homodiol is energetically preferred over reaction between opposite enantiomers to give heterodiols. Thus Tuoboul and Dana have shown that electropinacolization of racemic (**13**) yields exclusively the *trans-threo-trans* diol (**14**) in an enantioselective manner *via* an *lk*-type coupling (equation 29).[60,61] As part of a program directed towards the synthesis of dodecahedrane, Paquette and coworkers investigated the hydrodimerization of both homochiral and racemic ketone (**15**) promoted by mercury amalgam (equation 30).[62] In each case pinacolic coupling occurred only between molecules of the same absolute configuration to give homodiols. Chirality recognition has also been observed with (–)-carvone using the $TiCl_4$/Mg reagent[63] and with homochiral and racemic camphor using lithium in THF or liquid ammonia.[64]

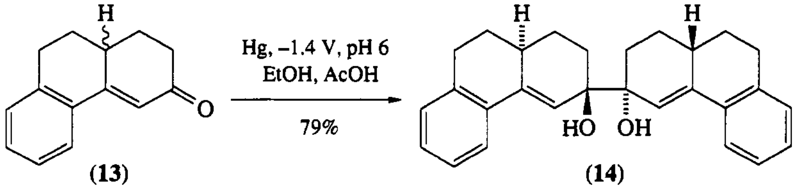

**(13)** **(14)** (29)

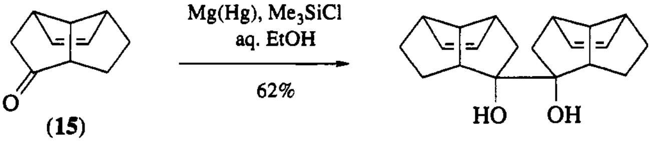

**(15)** (30)

## 2.6.3 INTRAMOLECULAR COUPLINGS

Intramolecular pinacolic coupling reactions are a powerful and selective method for ring construction, enabling the synthesis of a variety of structures ranging from small-ring 1,2-diols to macrocyclic systems.[65] The success of these reactions over such a large range of ring sizes is largely due to the templating effect offered by coordination with the low-valent metal reductants employed, especially titanium. Such templating overcomes the angle strain invoked in synthesis of small rings and the entropic factors associated with macrocycle formation. The reaction can even be applied to the synthesis of cyclopropanediols (equation 31),[66] despite their high sensitivity towards acid or base. The classical methods for pinacolic coupling are generally not very effective in the intramolecular domain;[53] *e.g.* compare the efficacy of the Mg/$MgI_2$ reagent[67] with that of Corey's $TiCl_4$/Mg(Hg) reagent[53] in the formation of cyclobutane-1,2-diols (equation 32).[68]

Corey and coworkers have developed a number of reagents (equations 33 and 34) for intramolecular pinacolic couplings during their studies on the synthesis of gibberellic acid (**17**)[52,69] *via* cyclization of the keto aldehyde (**16**). These reagents include Mg(Hg)/$Me_2SiCl_2$,[52] $TiCl_4$/Mg(Hg), and

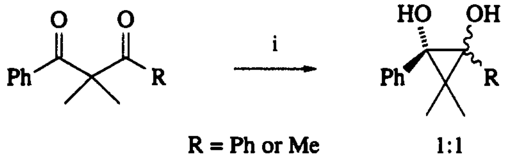
O
O
Ph
R
i
HO
OH
Ph
R
R = Ph or Me
1:1

(31)

i, Hg, aq. MeOH, pH 3.7, –1.25 V (*vs.* SCE), 80%

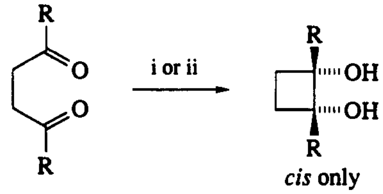
R
O
O
R
i or ii
R
OH
OH
R
*cis* only

(32)

i, R = Ph  Mg, $MgI_2$, 30%
ii, R = Me  $TiCl_4$, Mg(Hg), THF, 90%

$CpTiCl_3/LiAlH_4$.[53,69] Titanium-based reagents have also been employed in a new approach to propellane systems, including the quadrone ring skeleton (equation 35).[70] More recently Takeshita *et al.* demonstrated the chemoselectivity of such reagents in a formal synthesis of cuparene (**18**; equation 36).[71] Similar chemoselectivity is observed in pinacolic cyclizations promoted by TMSCl/Zn (equation 37).[72]

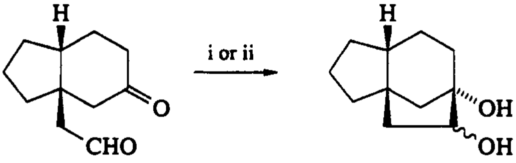
H
O
CHO
i or ii
H
OH
OH

(33)

i, Mg(Hg), $Me_2SiCl_2$, THF, 75%; ii, $TiCl_4$, Mg(Hg), THF, 90%

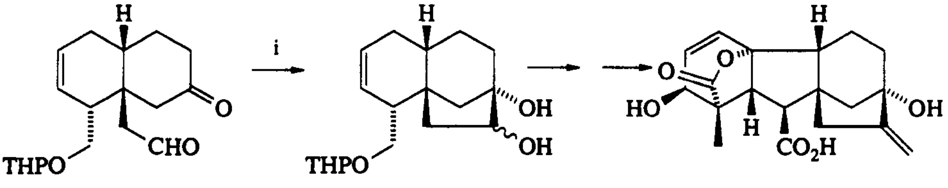
H
O
THPO
CHO
i
H
OH
THPO
OH
O
O
HO
H
H
CO$_2$H
OH

(34)

**(16)** **(17)**

i, $TiCl_3$, K, THF, 55% or $TiCl_3$, $LiAlH_4$, THF, 40–45%

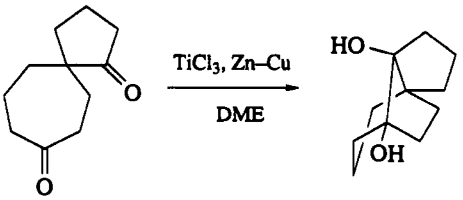
O
O
TiCl$_3$, Zn–Cu
DME
HO
OH

(35)

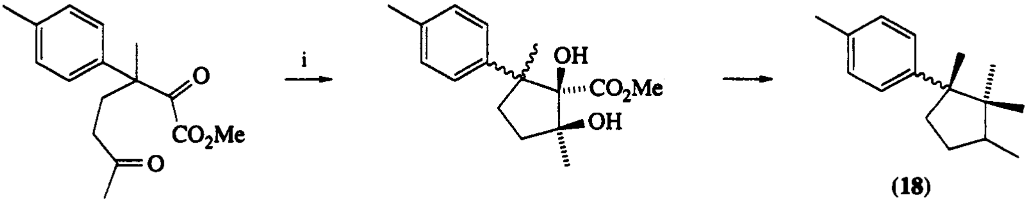
O
CO$_2$Me
O
i
OH
CO$_2$Me
OH

(36)

**(18)**

i, $TiCl_3$, Zn, pyridine, THF, reflux, 69%

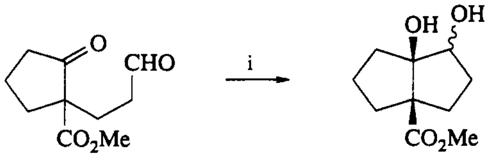

(37)

α:β = 1:3

i, Me$_3$SiCl, Zn, 2,6-lutidine, THF, reflux, 75%

A more versatile reducing agent is samarium diiodide, which promotes chemoselective cyclizations of functionalized keto aldehydes in a stereodefined manner to form 2,3-dihydrocyclopentane carboxylate derivatives in good yields and with diastereoselectivities of up to 200:1 (equation 38).[73] The reaction proceeds *via* selective one-electron reduction of the aldehyde component and subsequent nucleophilic attack on the ketone moiety. Stereochemical control is established by chelation of the developing diol (**19**) with Sm$^{3+}$ which thereby selectively furnishes *cis* diols (equation 39). The stereoselective *ul*-cyclization of 1,5-diketones to *cis* cyclopentane-1,2-diols using TiCl$_4$/Zn has been used to prepare stereodefined sterically hindered acyclic 1,2-diols when a removable heteroatom, such as sulfur[74] or selenium,[75] is included in the linking chain (equation 40).

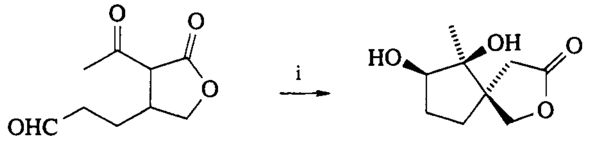

(38)

*ds* = 200:1

i, 2 SmI$_2$, MeOH, THF, −78 °C, 44%

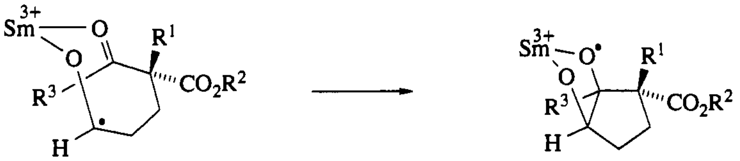

(39)

(**19**)

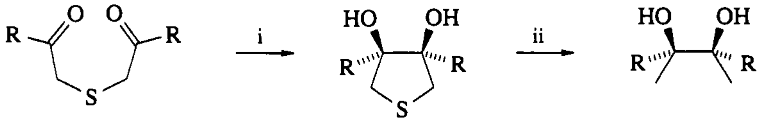

(40)

i, TiCl$_4$, Zn, THF, 0 °C; ii, Raney nickel, EtOH, reflux, 51–81%

Cyclopentane-1,2-diols have also been prepared by cyclization of aromatic diketones *via* electrochemical pinacolization (equation 41).[76] In contrast to chemically induced reactions, electropinacolizations involve an anionic addition process and not a ketyl radical coupling.[77] Substituents on the aromatic ring can have a profound effect on the stereoselectivity of the reaction (equation 42),[78] as can the pH of the reaction medium.[79] In strongly acidic media *cis* 1,2-diols are formed preferentially *via* coupling of neutral radicals. In basic media a radical anion or anionic attack mechanism is operative and *trans* diols are favored due to charge interactions. In the medium pH range the two mechanisms are in competition and mixtures of *cis* and *trans* diols are formed. As would be expected, increasing steric hindrance decreases the efficacy of electropinacolization.[80]

Larger ring size carbocyclic 1,2-diols can be synthesized *via* extension of the methods used for cyclopentane formation (equations 43–45). Thus, cyclizations of 1,6-dicarbonyls give the corresponding *cis*

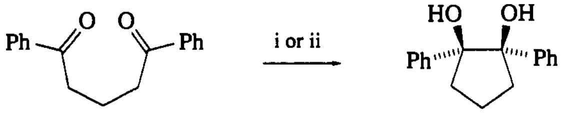

(41)

i, Mg cathode, NaI, pyridine, 20%; ii, Al(Hg), EtOH, 50%

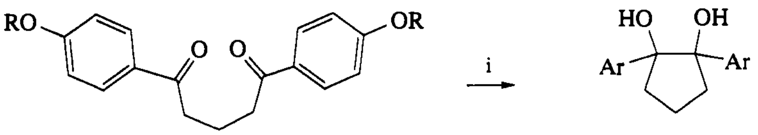

(42)

i, Hg, –2.0 V, 2M aq. (or ethanolic) KOH, r.t.

| | *Yield (%)* | | |
|---|---|---|---|
| *R* | *cis* | *trans* | *ratio* |
| H | 42 | 47 | 0.9 |
| Me | 79 | 3 | 26.3 |

cyclohexane-1,2-diols *via* *ul*-selective pinacolizations.[53,73] Intramolecular pinacolic coupling is a particularly efficient method for the construction of cyclooctanes *via* cyclization of 1,8-dialdehydes. Takeshita and coworkers for example have used this route in their syntheses of the fusicoccin (**20**; equation 46)[81] and the ophiobolins (**21**) and (**22**; equation 47).[82] Pinacolic cyclizations are not restricted to the formation of small- and medium-sized rings. Through the use of high dilution techniques macrocycle synthesis, *via* C—C bond formation, is highly effective. Thus, nickel-promoted coupling of the diketone (**23**) gives the *meso* diol (**24**; equation 48) stereoselectively,[83] whilst the (+)-antipode (**26**) of the macrocyclic antibiotic (*S*,*S*)-(–)-grahamimycin A was recently synthesized using the chemoselective pinacolization of the homochiral dialdehyde (**25**; equation 49).[84]

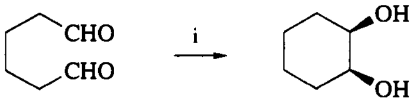

(43)

i, $TiCl_4$, Mg(Hg), THF, 32%

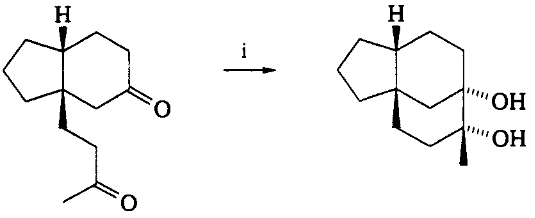

(44)

i, $TiCl_4$, Mg(Hg), THF, 43%

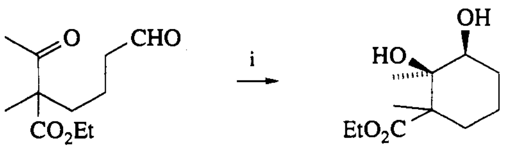

(45)

i, 2 $SmI_2$, THF, 47%

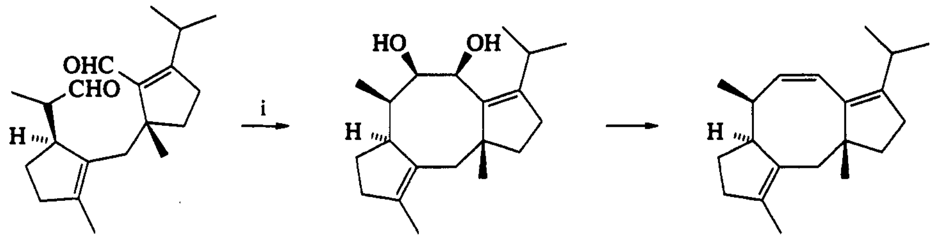

β:α = 8:1

**(20)**

(46)

i, $TiCl_4$, Zn, pyridine, THF, 0 °C, 84%

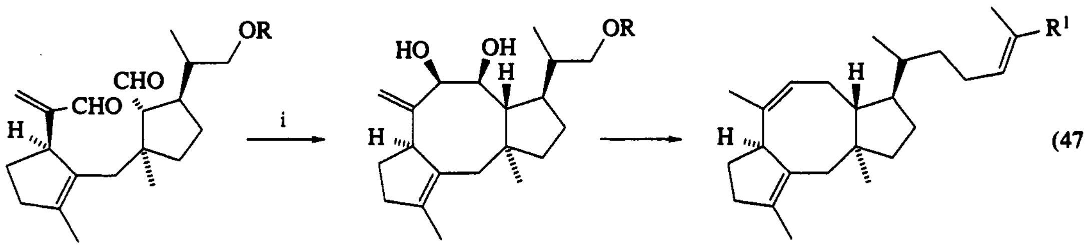

(47)

**(21)** $R^1 = CO_2H$

**(22)** $R^1 = CH_2OH$

i, $TiCl_4$, Zn, THF, reflux, 96%

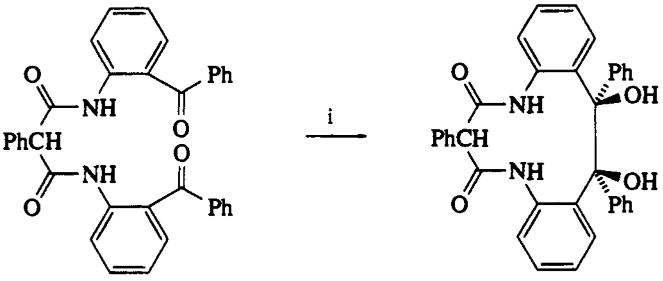

(48)

**(23)**

**(24)**

i, $Ni(OAc)_2$, pyridine, DMF, $H_2O$, 1,2-diaminobenzene, 120 °C, 43%

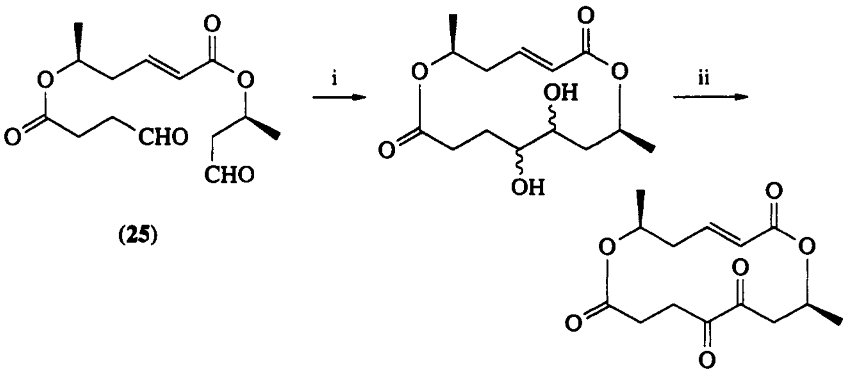

**(25)**

(49)

**(26)**

i, $TiCl_4$, Zn/Cu, THF, reflux, 35%; ii, PDC, DMF, 4 °C, 20%

## 2.6.4 α,β-UNSATURATED CARBONYL COMPOUNDS

The reductive coupling of α,β-unsaturated carbonyl compounds can lead to three types of dimerization products; pinacols (1,2-coupling), 1,6-diones (1,4-coupling), and γ-hydroxycarbonyl compounds (mixed coupling). These couplings are further complicated by the ability of the initially formed dimerization products to undergo further reactions and complex product mixtures can sometimes result.[85,86]

In electrochemically initiated reactions coupling at the β-carbon to give 1,6-diones is preferred; even 2,2,6,6-tetramethyl-4-hepten-3-one couples selectively *via* this mode.[87] Pinacol formation is favored when β-coupling is sterically hindered. Thus polyenones, such as retinal, are hydrodimerized to the corresponding pinacol in the presence of efficient hydrogen donors (equation 50).[88] In the absence of added hydrogen donors the yield of retinal pinacol is much reduced, even though α- and β-ionone are efficiently coupled under these conditions (equation 51).[89]

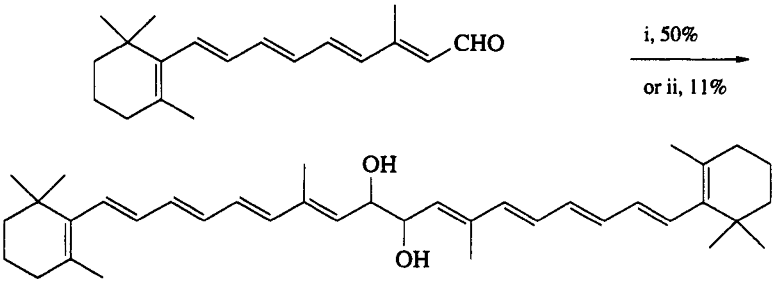

(50)

i, Hg, MeCN, $Bu_4NClO_4$, $CH_2(CO_2Et)_2$; ii, Hg, MeCN, $Bu_4NOAc$, 1 M AcOH

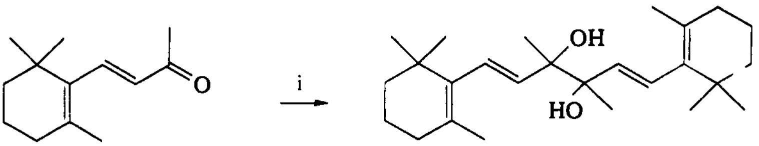

(51)

i, Hg, MeCN, $Bu_4NOAc$, 1M AcOH, 46%

Product distribution in couplings promoted by low-valent metals is dependent on the Lewis acidity/complexing power of the metal employed, and either 1,2- or 1,4-coupling is possible. Thus, cyclohexenone is selectively coupled at the β-position using a TMSCl, $TiCl_4$, Mg, HMPA reagent system (equation 52),[90] whilst methyl vinyl ketone couples *via* the 1,2-mode to give the corresponding pinacol with the less coordinating $TiCl_4$, Mg, Bu$^t$OH reagent system (equation 53).[91] Unsaturated carbonyls are

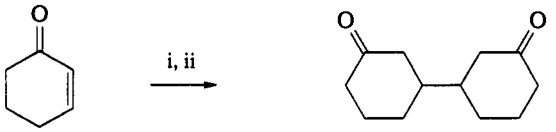

(52)

i, $Me_3SiCl$, Mg, $TiCl_4$, HMPA, 80 °C; ii, HCl, aq. EtOH, 65%

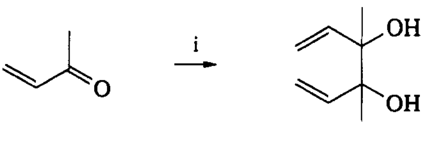

(53)

*meso*:(±) = 3:7

i, Mg, $TiCl_4$, Bu$^t$OH, 25%

also coupled to pinacols under acidic conditions using low-valent zinc as the radical initiator (equation 54).[16,92] Indeed efficient cross-coupling is possible with this reagent. Organomanganese reagents are normally associated with oxidative radical coupling processes. Organomanganese(II) compounds however can effect β-dimerization of enones (equation 55), although generally a mixture of conjugate addition and hydrodimerization results.[93]

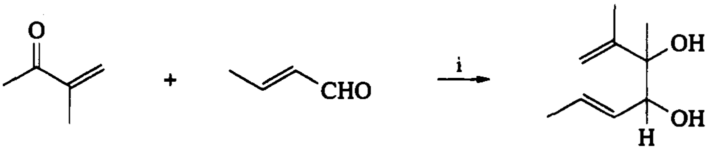

(54)

i, Zn, AcOH, $Et_2O$, –10 °C, 80%

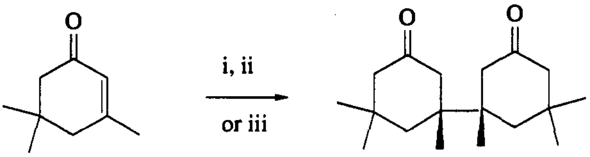

(55)

i, $Pr^iMn$, THF, –30 °C to r.t., 89%; ii, $Pr^iMnMgCl$, THF, –30 °C to r.t., 80%;
iii, BuMgCl, 5% $MnCl_2$, THF, r.t., 77%

Generally the 1,2-coupling of α,β-unsaturated carbonyls is not highly stereoselective and generates a mixture of stereoisomeric products. A recently developed low-valent titanium species derived from $Cp_2TiCl_2/Bu^sMgI$ overcomes this problem and is very effective at promoting such pinacolizations with high *lk-threo*-selectivity (equation 56).[28] Intramolecular coupling of enones is also possible and by using

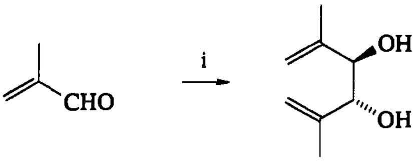

(56)

*lk*:*ul* = 100:1

i, $Cp_2TiCl_2$, $Bu^sMgCl$, THF, 98%

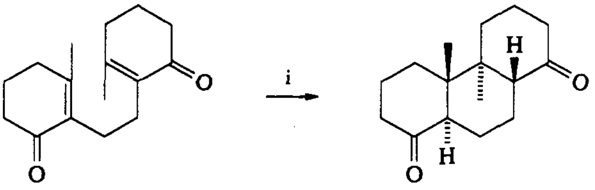

(57)

i, Hg, $Et_4NCl$, aq. MeCN, –1.80 V, 81%

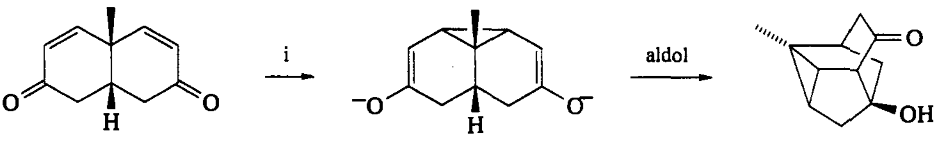

(58)

**(27)** **(28)** **(29)**

i, Hg/Pt, $Bu_4NBF_4$, DMF, –2.35 V

linked cyclohexenones provides a stereoselective method for perhydrophenanthraene synthesis, suitable for application to steroidal systems (equation 57).[94] In a related manner, selective 1,6-coupling of the *cis* decalin dione (**27**) gives the tricycle (**28**), which then undergoes aldol cyclization to give the tetracycle (**29**; equation 58).[95]

## 2.6.5 IMINE COUPLINGS

### 2.6.5.1 Intermolecular Couplings

The reductive couplings of imines show some significant differences from those of their carbonyl counterparts.[96] Thus in the coupling of *N*-acylimines promoted by low-valent metals the product 1,2-diamines are frequently formed with higher (±)-selectivity than are similar 1,2-diols (equation 59).[97] Smith and coworkers have shown that this phenomenon results from equilibration of dimeric dianions (**31**) and the precursor monomeric radical anions (**30**), to give the thermodynamically preferred (±)-isomer, rather than from selective *lk*-coupling (equation 60).[98] Coupling of *N*-benzylimines also shows some selectivity for the (±)-amine.[99]

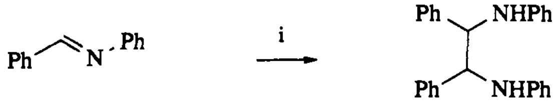

(±):*meso* = 15:1

(59)

i, Na, THF, 45–50 °C, 99%

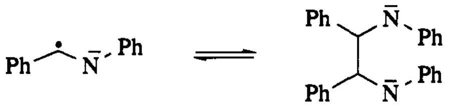

(**30**) (**31**)

(60)

In general, *N*-alkylimines show little reactivity with McMurry-type titanium reagents.[125] Mangeney however has demonstrated that symmetrical vicinal (±)-diamines can be prepared using low-valent titanium species generated from $TiCl_4$/Mg(Hg) (equation 61).[100] Furthermore with this reagent coupling is not restricted to aryl (activated) imines. *N*-Alkylimines derived from aldehydes or ketones are efficiently coupled using a Pb/Al bimetal redox system (equation 62);[101] while unsubstituted 1,2-diamines can be prepared from either *N*-(trimethylsilyl)imines or nitriles using the niobium reagent $NbCl_4(THF)_2$ (equation 63).[102] Coupling proceeds with excellent *lk*-diastereoselectivity with (±):*meso* ratios typically 16:1

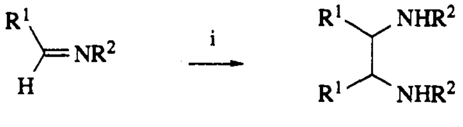

(±):*meso* = 9:1 to 7:3

(61)

i, $HgCl_2$, Mg, THF, 0 °C to r.t., 40–75%

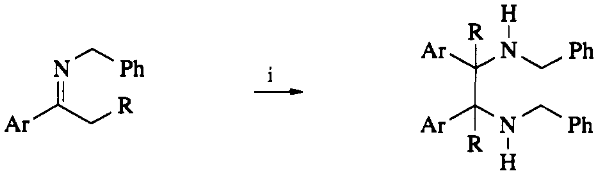

(62)

i, $PbBr_2$, Al, TFA, THF, r.t., 62–84% (aldimines)
i, $PbBr_2$, Al, $AlBr_3$, THF, r.t., 63–90% (ketimines)

to 24:1. Aldimines can also be coupled *via* an aminative reduction of aldehydes using either $VCl_3$[103] or McMurry-type conditions[104] to give 1,2-diarylethylenediamines (Scheme 3). Electroreductive dimerizations of *N*-benzylimines generally give (±):*meso* ratios of *ca.* 1:1.[105] Modest chiral induction has been observed using chiral coelectrolytes (equation 64).[106] In contrast to metal-promoted dimerizations, photopinacolic reactions of *N*-arylimines show a high preference for the *meso* product *via ul*-coupling of neutral ketyl-type radicals (equation 65).[107] For *N*-alkylimines, however, the ratio is dependent on the nature of the alkyl substituent (equation 66).[108]

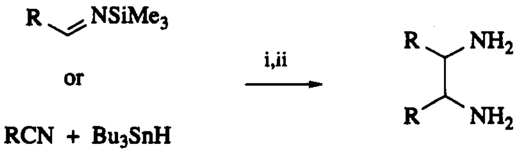
R NSiMe3
or
RCN + Bu3SnH
i,ii
R NH2
R NH2

(63)

i, $NbCl_4(THF)_2$; ii, KOH or KF, 40–73%

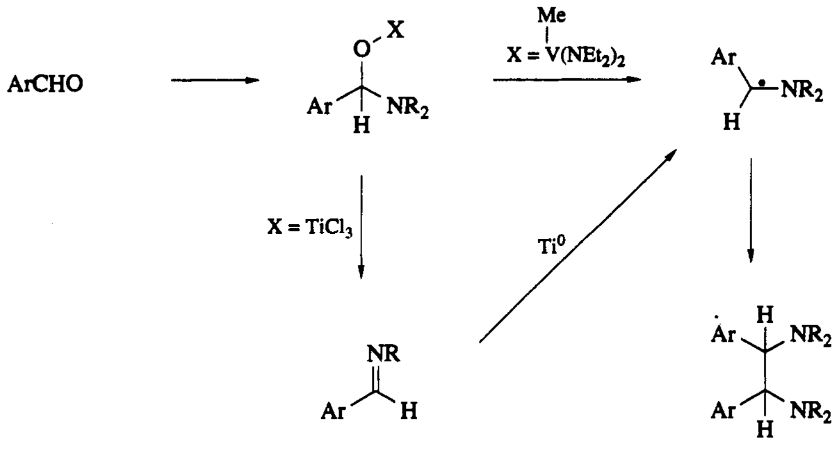
ArCHO
X
O
Ar NR2
H
Me
X = V(NEt2)2
Ar
NR2
H
X = TiCl3
Ti0
NR
Ar H
H
Ar NR2
Ar NR2
H

(±):*meso* = 1:1

$VCl_3$, $LiNR_2$, 14–54%
$TiCl_4$, $LiNR_2$, 23–81%

**Scheme 3**

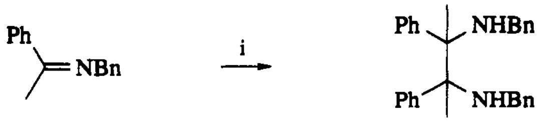
Ph
NBn
i
Ph NHBn
Ph NHBn

(64)

*de* 5.3% (+)-(*S*)

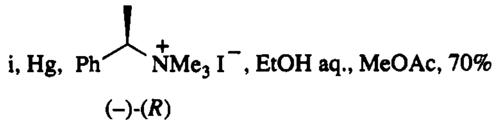

i, Hg, $Ph\overset{+}{N}Me_3\ I^-$, EtOH aq., MeOAc, 70%

(–)-(*R*)

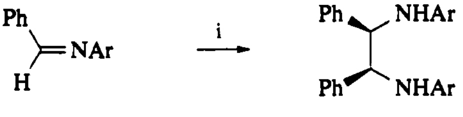
Ph
NAr
H
i
Ph NHAr
Ph NHAr

(65)

i, *hν*, EtOH, 65–95%

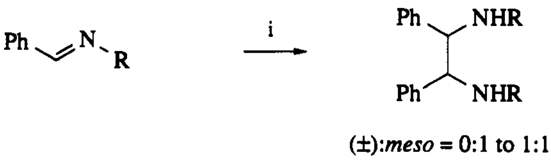
Ph
N
R
i
Ph
NHR
Ph
NHR
(±):*meso* = 0:1 to 1:1

(66)

i, *h*ν, EtOH, 50–70%

### 2.6.5.2 Intramolecular Couplings

Diastereoselective reaction of diimines with sodium in ether leads to the formation of macrocyclic ethers of the type (**32**; equation 67) and (**33**; equation 68) in modest yields.[109] However, there are no reports of examples using the templating effect of low-valent transition metals, as used to good effect for intramolecular carbonyl couplings. Electrochemical reduction of imines has been used to produce a variety of bicyclic structures *via* cyclization–aromatization (equation 69) or transannular cyclization (equation 70).[110]

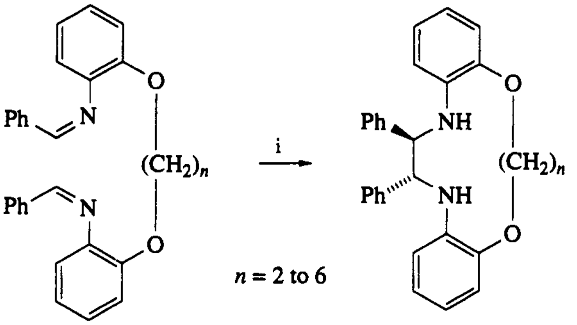
Ph
N
Ph
N
O
(CH₂)ₙ
O
i
*n* = 2 to 6
Ph
NH
Ph
NH
O
(CH₂)ₙ
O

(67)

(**32**)

i, Na, $Et_2O$, reflux, 6–16%

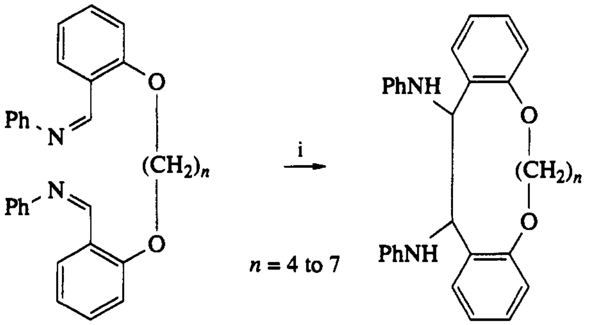
Ph
N
Ph
N
O
(CH₂)ₙ
O
i
*n* = 4 to 7
PhNH
PhNH
O
(CH₂)ₙ
O

(68)

(**33**)

i, Na, toluene, reflux, 6–15%

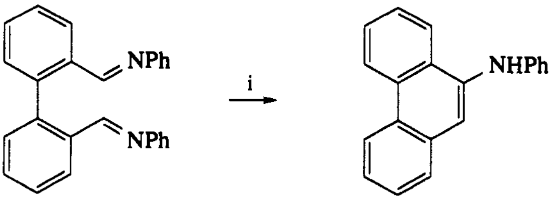
NPh
NPh
i
NHPh

(69)

i, Hg, –2.70 V, $Bu_4NNO_3$, DMF, 60%

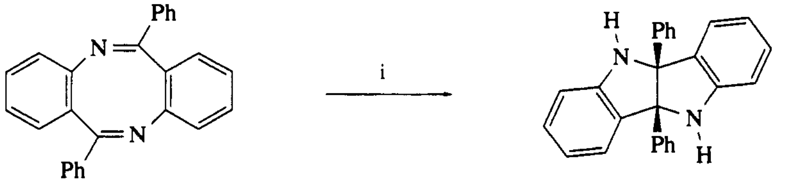

(70)

i, Hg, –2.6 to –2.7 V, $Bu_4NClO_4$, glyme, 94%

## 2.6.6 THIOCARBONYL COUPLINGS

The reductive coupling of thiocarbonyl compounds to give alkenes can be performed under a range of conditions.[111] This process, the Gatterman reaction,[112] in general requires the presence of conjugated electron-withdrawing groups to facilitate reaction. The traditionally used metal initiators such as copper or iron powder or zinc dust were initially replaced by more efficient initiators such as antimony, bismuth, dehydrogenated Raney nickel or silver.[111,113] Thus, for example, thioacetophenone can be coupled to give the *trans*-stilbene (**34**) by Raney nickel (18% yield)[113] or bismuth (35% yield),[114] but not by copper (equation 71). These initiators have in turn been superseded by even more efficient reductants, including copper powder in DMSO,[115] $FeCl_3/NaBHEt_3$,[116] $TiCl_3/K$,[125] and $MgC_8$ (Scheme 4).[55]

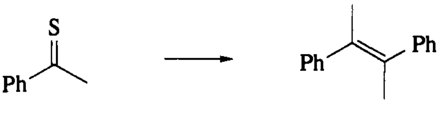

(**34**)

(71)

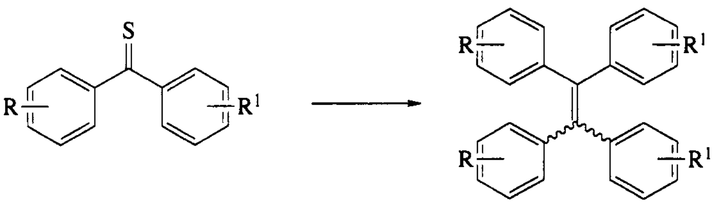

*(E)*:*(Z)* = 1:1

| *Reagent* | *Yield* (%) |
|---|---|
| Cu, DMSO | 98 |
| $FeCl_3$, $NaHBEt_3$ | 34 |
| $TiCl_3$, K | 90 |
| $C_8Mg$ | 86 |

**Scheme 4**

Interestingly, there are no examples of the synthesis of thiopinacols by the coupling of thioketyl radicals. Moreover the longer C—S bond allows for the possibility of alternate reaction pathways and both episulfides and 1,2-dithietanes have been postulated as reaction intermediates.[111] Finally, certain thiocarbonyls can also undergo thermally induced alkene formation (equation 72).[117]

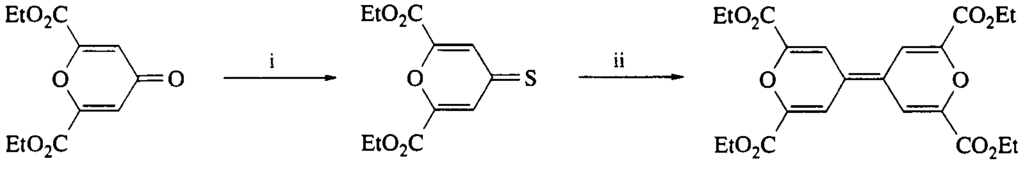

(72)

i, $P_2S_5$, $C_6H_6$, reflux; ii, 100 °C, 2 h, 50–70%

## 2.6.7 McMURRY-TYPE COUPLINGS

Although the reduction of carbonyls to alcohols or hydrocarbons is well documented, no general method was available for the reductive coupling of carbonyl compounds directly to alkenes prior to the use of low-valent transition metals. The reductive coupling of carbonyl compounds by low-valent transition metals is now an important method for C=C bond formation, and has been widely reviewed.[118]

### 2.6.7.1 Intermolecular Couplings

The reductive pinacolic coupling reaction was introduced by Sharpless, who demonstrated that alkenes could be synthesized from aldehydes or ketones by treatment with tungsten-based reagents derived from $WCl_6$/BuLi (Scheme 5).[119] Aryl aldehydes are more efficiently coupled using the $WCl_6/LiAlH_4$ system developed by Fujiwara (equation 73).[120] Electrochemically generated tungsten species have also been used (equation 74).[121] Active metal slurries prepared from $MoCl_5/LiAlH_4$, $ZrCl_4/LiAlH_4$, and $VCl_3/LiAlH_4$ also promote coupling but with only modest to poor yields (8–33%).[122] Low-valent niobium generated from $NbCl_5/NaAlH_4$ or $NbCl_5/LiAlH_4$ is more effective and reductively couples both aromatic aldehydes and ketones stereoselectively (equation 75).[123] Interestingly the reaction selectively gives (*E*)-alkenes from aldehydes but (*Z*)-alkenes from ketones.

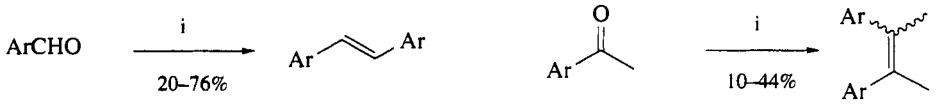

i, $WCl_6$, BuLi, THF, r.t.

**Scheme 5**

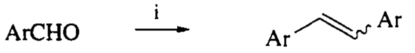

(73)

(*E*):(*Z*) =13:1 to 31:1

i, $WCl_6$, $LiAlH_4$, THF, r.t., 60–80%

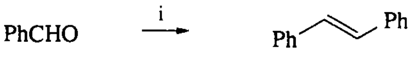

(74)

(*E*):(*Z*)=10:1

i, $WCl_6$, Pt, –1.9 V, THF, 96%

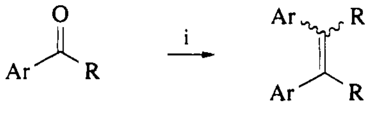

(75)

i, $NbCl_5$, $NaAlH_4$, $C_6H_6$, THF, reflux

R = H 56–95% (*E*)-selective
R = Me 73–75% (*Z*)-selective

The most widely used systems are those employing low-valent titanium species. The reductive coupling of carbonyl compounds by titanium reagents was independently discovered in 1973 by Trylik[24] and Mukaiyama,[23] and has since been extensively developed by McMurry and his coworkers.[118d,124–126] The McMurry reaction, as it has become known, has proved to be a valuable synthetic tool for the construction of C=C bonds.

There are in fact 10 titanium-based reagents commonly used for the reductive coupling of carbonyls to alkenes; these are $TiCl_3$/Mg,[24] $TiCl_4$/Zn,[23] $TiCl_3/LiAlH_4$,[124] $TiCl_3$/K or /Li,[125,127] $TiCl_2$/Zn,[128] $TiCl_3$/Zn/Cu,[125] $TiCl_4/Al/AlCl_3$,[53] $TiCl_4$/Mg(Hg),[53] $CpTiCl_3/LiAlH_4$[53] and $TiCl_3/C_8K$.[55,129] By far the most widely used reagent is the McMurry reagent, $TiCl_3/LiAlH_4$. However more reliable and consistent results are obtained using potassium or lithium metal for generation of the titanium(0) species,[125,127] whilst $TiCl_3/Zn/Cu$ is the reagent of choice for intramolecular variants.[125] The nature of the titanium species formed is dependent on the method employed. Thus the $TiCl_3/LiAlH_4$ system can produce $Ti^0$ or $Ti^I$ depending on the molar ratio of $TiCl_3$ to $LiAlH_4$, whilst the reactive species generated from either the $TiCl_3$/alkali metal or Zn/Cu systems is $Ti^0$.[125] The mechanism outlined in Scheme 6 has been proposed,[130] and proceeds through an intermediate titanium pinacolate. Indeed pinacols can be isolated from these reductive couplings after short reaction times. It has also been shown that 1,2-diols are deoxygenated to alkenes by $Ti^0$ reagents.[125] The stereochemistry of the alkene formed from aliphatic carbonyls is controlled by the rate-determining deoxygenation step. When the energy difference between the (*E*)- and (*Z*)-alkene exceeds 4–5 kcal $mol^{-1}$ (1 kcal = 4.18 kJ) the (*E*)-isomer is formed selectively (Scheme 7).[131] Alkyl aryl ketones however can couple reductively to give predominately the (*Z*)-isomer (equation 76).[132] This phenomenon has been rationalized as arising from π-complex formation (**35**) between the phenyl rings and $Ti^0$.[132] Increased steric hindrance favors the (*E*)-isomer whilst *para* electron-withdrawing groups promote pinacol formation.

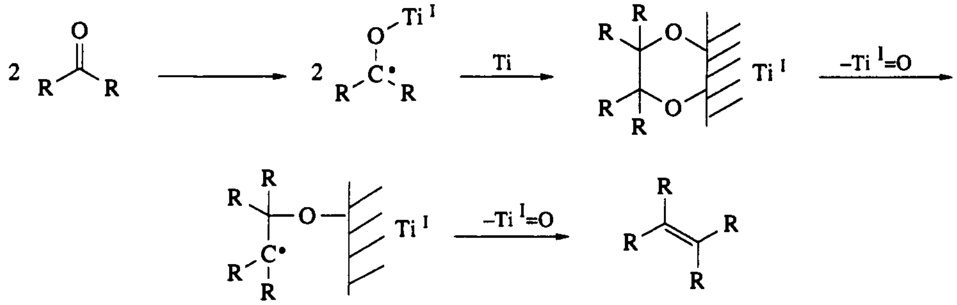

**Scheme 6**

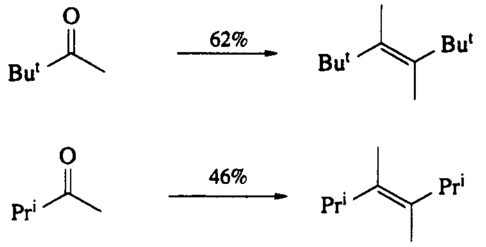

$\Delta E$ = 7.1, (*E*) only

$\Delta E$ = 0.0, (*E*):(*Z*) = 1.5:1

**Scheme 7**

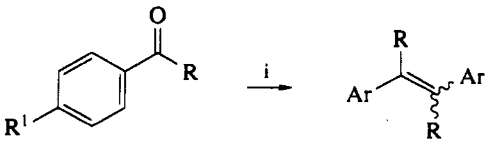

(76)

(*E*):(*Z*) = 1:3 to 1:9

i, $TiCl_4$, Zn, pyridine, THF, reflux, 44–81%

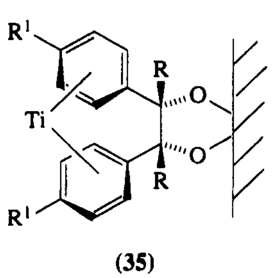

(**35**)

In general the McMurry reaction has been limited to substrates lacking other reducible functional groups.[125] More recently, and contrary to earlier results, various ester[133] and haloaryl groups[134] have proven to be compatible with the reaction conditions. Indeed such selectivity was observed in a new synthesis of the antitumor agent tamoxifen (**36**) using modified McMurry conditions (equation 77).[135]

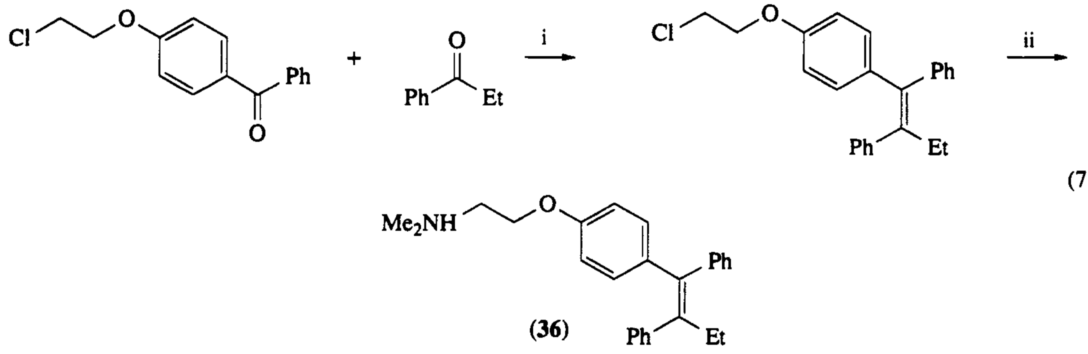

**(36)**

(77)

i, $TiCl_4$, Zn, THF, reflux, 54%; ii, $Me_2NH$, EtOH, 75 °C, 83%

The intermolecular McMurry reaction has proven a particularly valuable route to alkenic hydrocarbons. This is especially true for polyenes and sterically hindered alkenes. For example, β-carotene (**37**; equation 78) can be prepared in 85% yield by reductive dimerization of retinal.[124,136] Isorenieratene (**38**; equation 78) is similarly synthesized in 96% yield,[137] and the aldehyde (**39**; equation 79) has been ela-

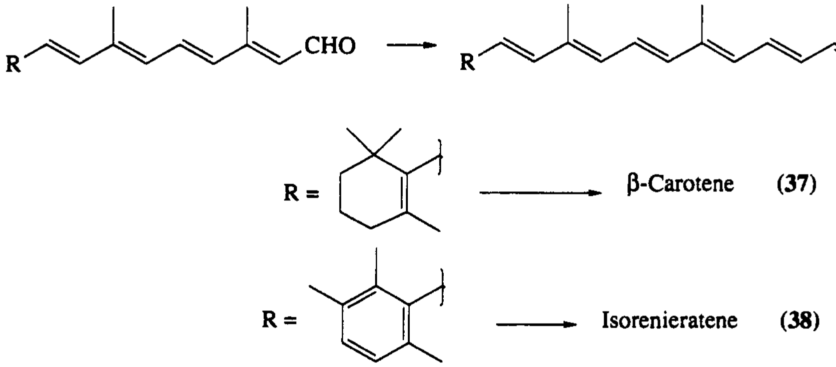

(78)

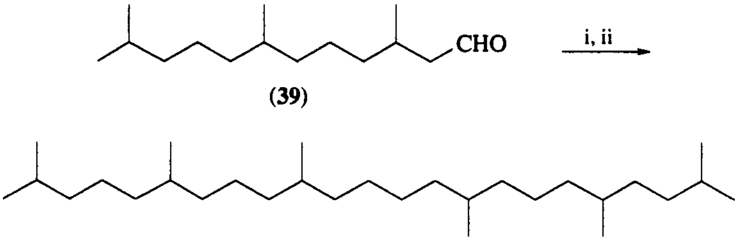

**(39)**

(79)

i, Mg(Hg), $TiCl_4$, THF, r.t.; ii, Pd/C, $H_2$, EtOH, 63%

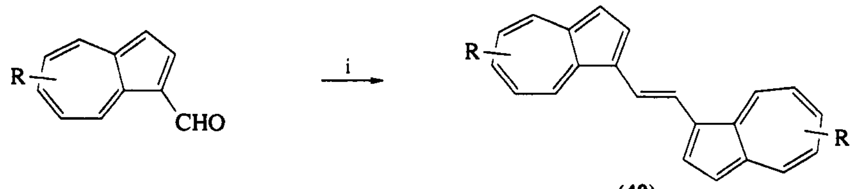

**(40)**

(80)

i, $TiCl_3$, Li, DME, reflux, 40–70%

borated into perhydrosqualene *via* coupling followed by hydrogenation.[138] Highly conjugated alicyclic systems such as ω,ω′-diazulenylpolyenes (**40**; equation 80)[139] and di-2-thienylpolyenes (**41**; equation 81)[140] have also been prepared.

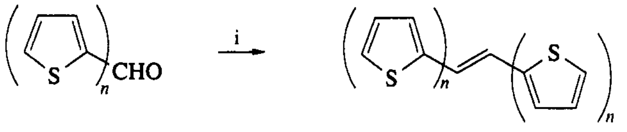

(81)

$n = 1, 2, \text{or } 3$ **(41)**

i, $TiCl_3$, Zn, THF, reflux, 63–71%

Strained and sterically hindered alkenes are of special interest in physical organic chemistry. By their very nature these structures are difficult to synthesize and the McMurry reaction represents the only viable route to many such compounds (see Table 2). Torsionally distorted alkenes, capable of exhibiting optical activity without a chiral center, have also been prepared.[151] If the reaction is carried out in a chiral solvent the (±) isomer is formed selectively (equation 82).

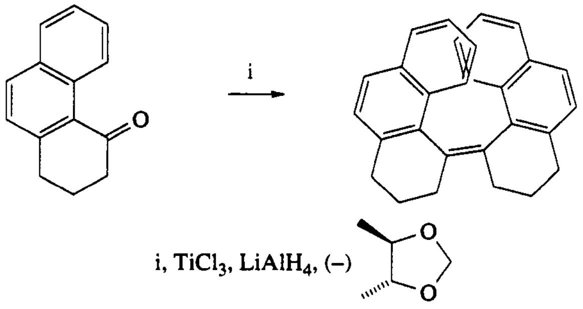

(82)

i, $TiCl_3$, $LiAlH_4$, (–)

Unsymmetrical alkenes can be prepared by mixed intermolecular reactions if one of the components, commonly acetone, is used in excess (equation 83).[152] As the isopropyl group is a common subunit of many terpenes this method provides a valuable route for its introduction. Pattenden and Robertson used such a reaction followed by a Grob-type fragmentation in their preparation of the daucenone (**42**) from the readily enolized ketone (**43**).[153] The bicycle (**42**) was used as an intermediate for the synthesis of the diterpene (±)-isoamijiol (**44**; equation 84). Mixed couplings are not restricted to acetone, and almost any carbonyl may be used. For example, Paquette *et al.* employed the aldehyde (**45**)[154] in a synthesis of (±)-α-vetispirene (**46**; equation 85).[155] More complex mixed couplings are also possible. For example, the aldehydes (**47**) and (**48**) are coupled efficiently to the stilbene (**49**), which in turn is converted to phenanthrene alkaloids such as atherosperminine and thalictuberine (equation 86).[156]

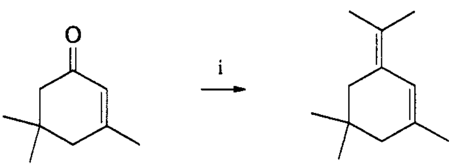

(83)

i, $TiCl_3$, $LiAlH_4$, acetone (4 equiv.), reflux, 63%

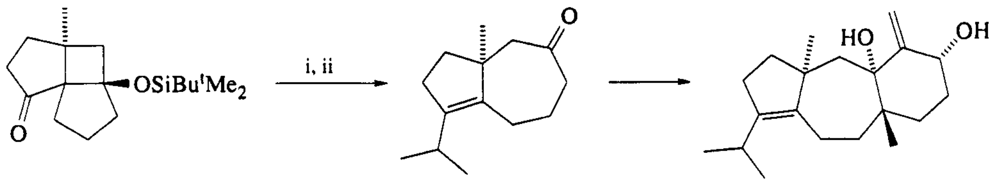

(84)

**(43)** **(42)** **(44)**

i, $TiCl_3$, Li, acetone, DME, reflux, 76%; ii, HF, THF, reflux, 62%

**Table 2** Preparation of Sterically Hindered Alkenes by the McMurry Coupling Reaction

| *Substrate* | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|
| 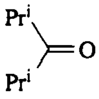 | 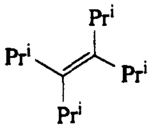 | 6–12 | 141, 142 |
| 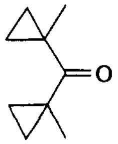 | 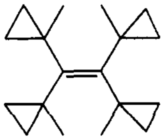 | 13 | 143 |
| 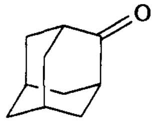 | 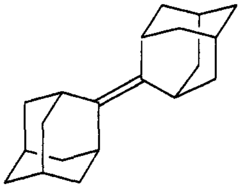 | 85–87 | 124, 144, 145 |
| 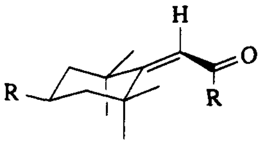 | 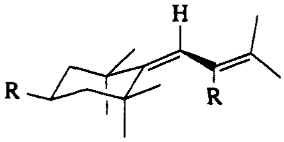 | 28–85 | 146 |
| 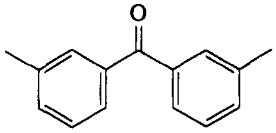 | 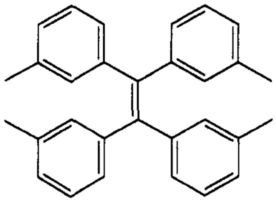 | 55–77 | 147, 148 |
| 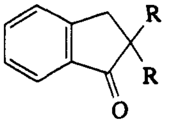 | 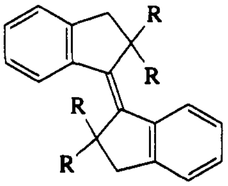 | 53–95 | 149, 150 |

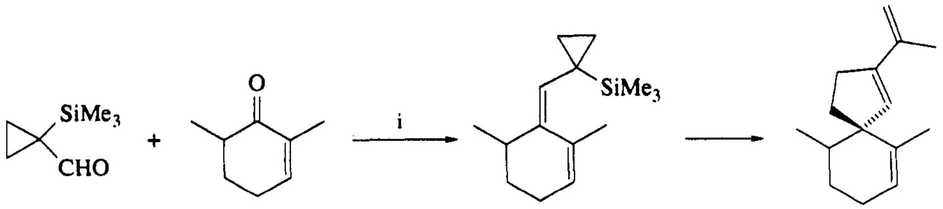

**(45)** **(46)** (85)

i, TiCl$_3$, Li, DME, reflux, 50–60%

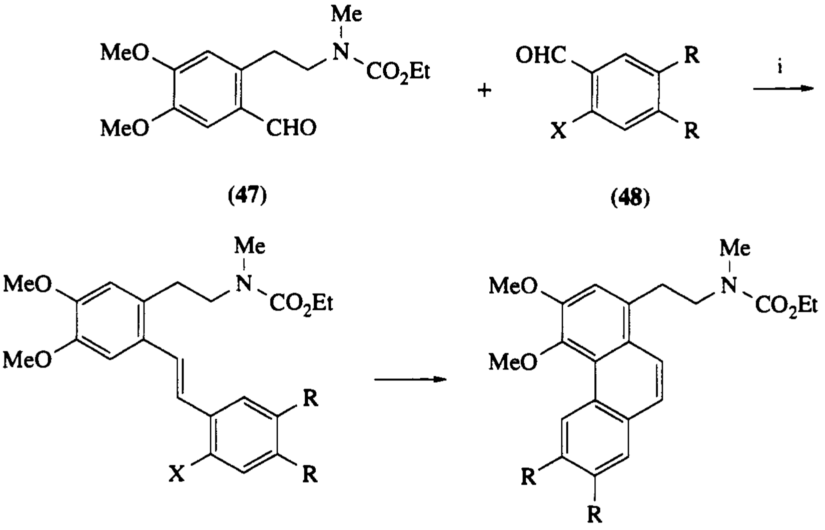

**(47)** **(48)** **(49)**

(86)

i, $TiCl_3$, Li, DME, reflux, 55–67%

When one of the reactants in a mixed coupling is a diaryl ketone an excess of the second component is not always necessary (Scheme 8),[125,152] since diaryl ketones are readily reduced to dianions, which then react selectively with unreduced aliphatic carbonyls.

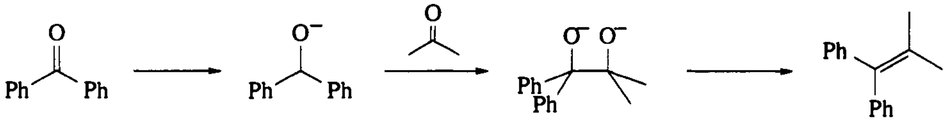

**Scheme 8**

## 2.6.7.2 Intramolecular Couplings

The intramolecular McMurry reaction has been used to prepare cycloalkenes of ring size 3 through 16 and up to 22, in good yields (46–95%).[157,159] The method is quite general and is applicable to the intramolecular coupling of dialdehydes, keto aldehydes or diketones. Through utilization of the templating effect conferred by deoxygenation on a titanium surface the reaction is highly efficient and is not affected by ring size effects in contrast to the related acyloin and Thorpe–Zeigler cyclizations. The versatility of the intramolecular McMurry reaction is demonstrated by the variety of ring types that have been synthesized. These range from highly strained cyclopropenes (equation 87)[157] and cyclobutenes[158] through medium-sized rings,[157,159] and on up to macrocycles such as (**50**; equation 88).[159] Although a number of titanium reagents have been employed for intramolecular couplings, the $TiCl_3$/Zn/Cu system[125] generally gives the best yields and represents the reagent of choice for the synthesis of medium ring and macrocyclic alkenes.

A variety of natural products have been synthesized *via* application of reductive pinacolic couplings. An early example is the cyclization of the keto aldehyde (**51**) to the alkene (**52**; equation 89); a precursor to the terpene, cuparene (**18**).[127a] A modified McMurry procedure provides a novel route to steroids such as estrone methyl ether, *via* chemoselective cyclization of the keto aldehyde (**53**; equation 90).[160] The

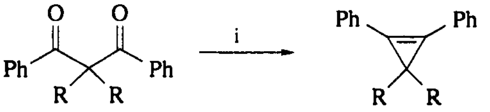

(87)

i, $TiCl_3$, $LiAlH_4$, THF, reflux R = Me, 46%; R = Et, 40%

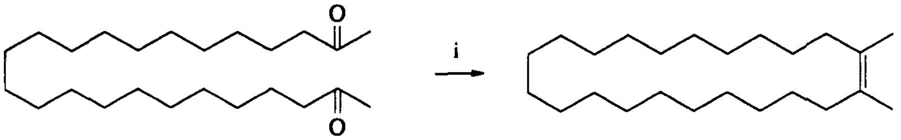

(50)

(88)

i, $TiCl_3$, Zn/Cu, DME, reflux, 83%

critical importance of the type of titanium reagent used is emphasized in Clive's recent synthesis of (+)-compactin and (+)-mevinolin (equations 91 and 92). Model studies[161] demonstrated that coupling of the keto aldehyde (**54**) was efficiently promoted by McMurry's $TiCl_3$/Zn/Cu reagent (equation 91). For the total syntheses however cyclization of the key keto aldehyde (**55**; equation 92) required the use of the Weidmann reagent $TiCl_3$/$C_8K$ in a specific molar ratio with respect to (**55**).[162] The use of any other low-

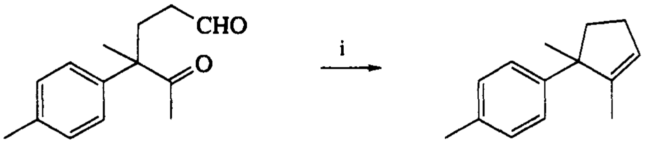

(**51**) (**52**)

(89)

i, $TiCl_3$, K, THF, reflux, 55%

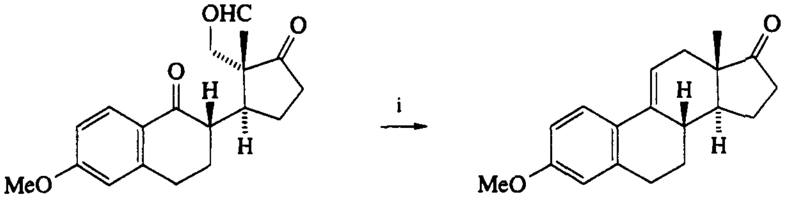

(**53**)

(90)

i, $TiCl_3$, Zn/Ag, DME, reflux, 56%

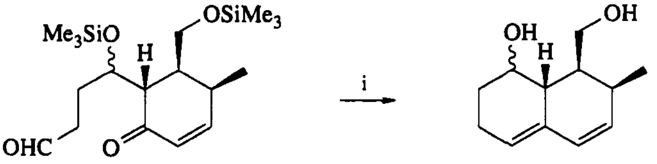

(**54**)

(91)

i, $TiCl_3$, Zn/Cu, DME, reflux, 72%

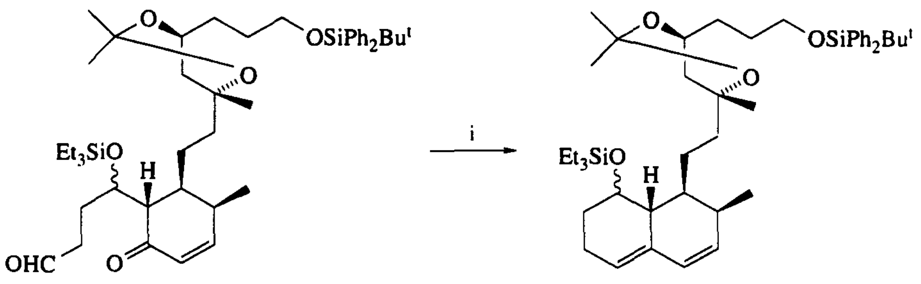

(**55**)

(92)

i, $TiCl_3$, $C_8K$, DME, r.t. to reflux, 85%

valent titanium reagent or departure from the ratio keto aldehyde:$TiCl_3$:$C_8K$ of 1:17:34 gave much reduced yields. Transannular coupling of the diketone (**56**) is a key step in a short photochemical route to (±)-hirsutene (equation 93),[163] whilst regioselective coupling of the triketone (**57**) provides a new route to zizaene sesquiterpenes such as (±)-isokhusimone (**58**; equation 94).[164]

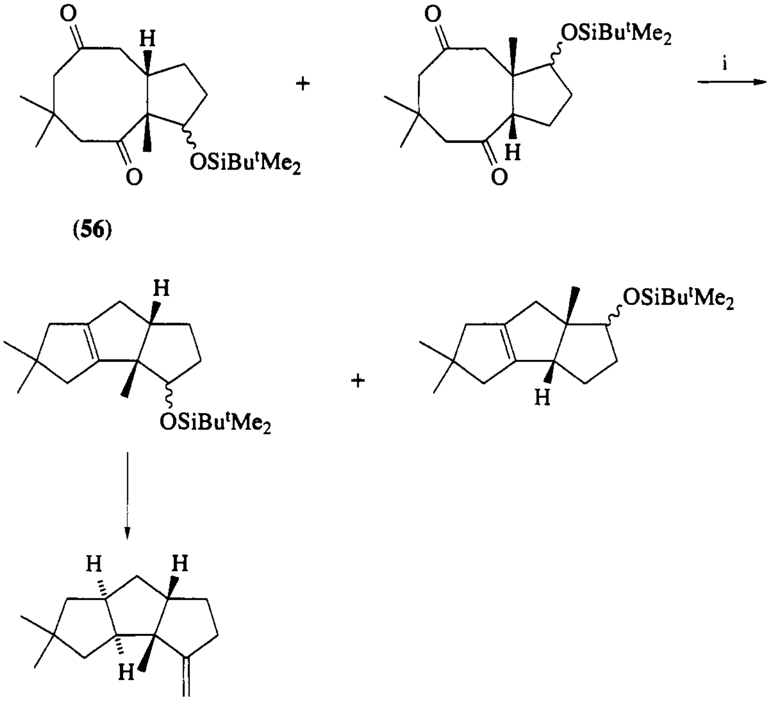

(**56**)

(93)

i, $TiCl_3$, K, THF, reflux, 55%

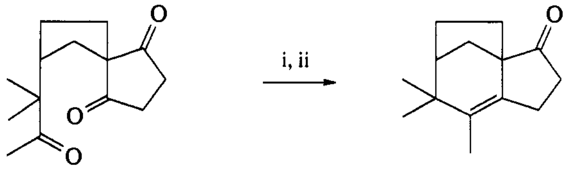

(**57**) (**58**)

(94)

i, $TiCl_3$, Zn/Cu, DME, reflux; ii, PCC, 78%

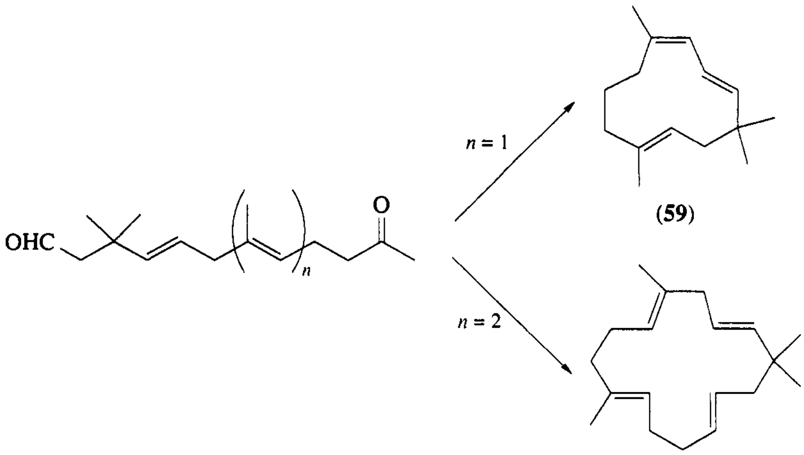

(**59**)

(**60**)

(95)

McMurry and coworkers have synthesized a range of medium and macrocyclic terpenes using the TiCl$_3$/Zn/Cu system.[165–168] Of particular note are the syntheses of (±)-humulene (**59**) and (±)-flexibilene (**60**) which provide a show-case for transition metal based methodology (equation 95).[165] In a related fashion Jackson and Pattenden synthesized verticillene (**62**), a putative biogenetic precursor to the taxane alkaloids, by selective 1,2-coupling of the 1,12-dialdehyde (**61**; equation 96)[169] Several macrocyclic crown ethers of the type (**63**; equation 97) which act as enzyme catalytic models, have been prepared using titanium(0) or titanium(I) reagents.[170] Reductive coupling of the related dialdehyde (**64**) provides cyclophanes of the type (**65**; equation 98), which can be further elaborated to phenanthrenes, of which cannithrene II (**66**) is representative.[171]

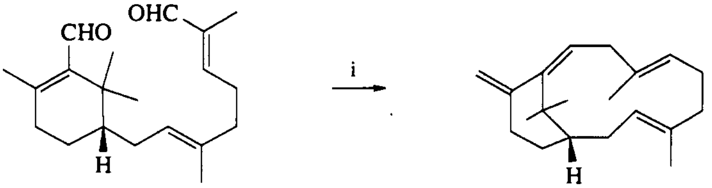

(96)

**(61)** **(62)**

i, TiCl$_3$, Zn/Cu, DME, reflux, 25%

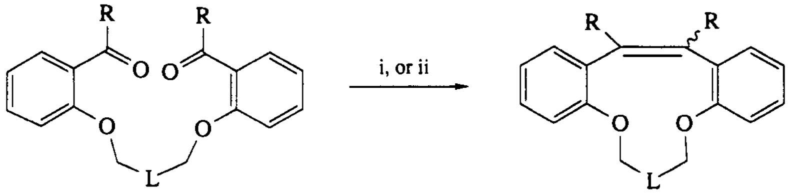

(97)

**(63)**

i, TiCl$_4$, Zn, dioxane, reflux, 83%
ii, TiCl$_3$, Zn, dioxane, reflux, 91%

R = H; L = CH$_2$OCH$_2$
R = Me; L = (CH$_2$)$_3$

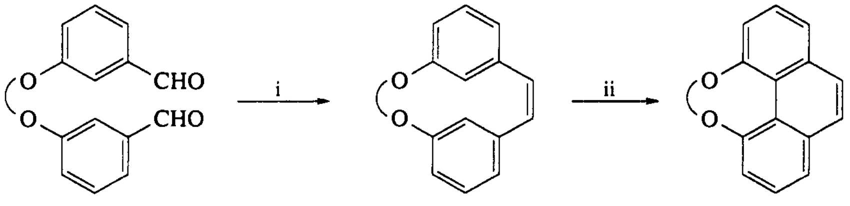

(98)

**(64)** **(65)**

i, TiCl$_3$, Zn/Cu, THF, reflux, 57–78%; ii, Cu$^{II}$ decanoate, I$_2$, Et$_2$O, *h*v, 450 W, 51–78%

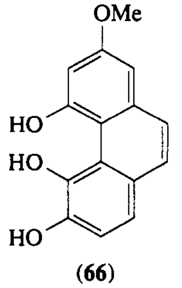

**(66)**

A wide range of alkenic compounds exhibiting interesting properties associated with their π-systems have been elaborated *via* the reductive coupling carbonyls. For example, Marshall and coworkers have studied the intramolecular McMurry reaction as a route to betweenanenes, a class of conformationally flexible bicyclic alkenes (equation 99).[172] Nakazaki *et al.* have used a similar approach to optically active doubly bridged allenes of the type (**67**; equation 100).[173] A class of compounds with interesting intracyclic electronic properties are compounds such as (**68**) and (**69**) (equation 101). McMurry and coworkers have prepared these alkenes *via* cyclization of the appropriate diketones (**70**)[174] and (**71**)[175] respectively. It is worth noting that these cyclizations overcome considerable strain associated with distortion of the cyclohexane rings to boat topographies during coupling.[175] The alkene (**68**) exhibits an intracyclic $\pi$-sys-

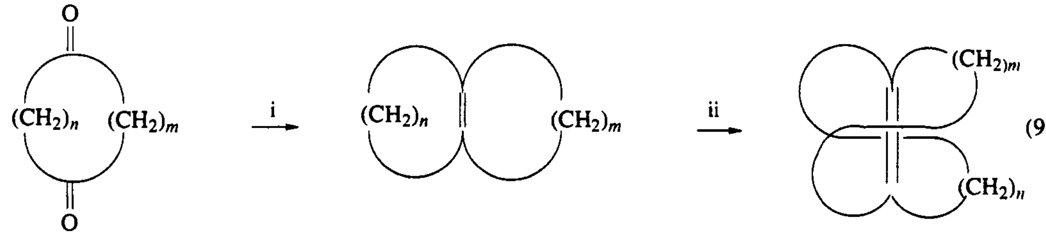
O
$(CH_2)_n$
$(CH_2)_m$
O
i
$(CH_2)_n$
$(CH_2)_m$
ii
$(CH_2)_m$
$(CH_2)_n$

(99)

i, $TiCl_3$, Li, DME, reflux, 34–73%; ii, hν, 450 W, xylene

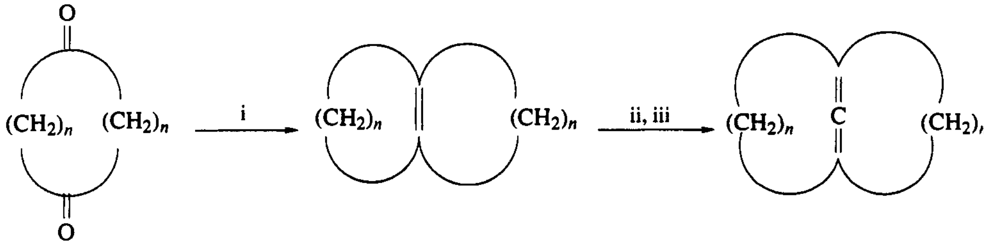
O
$(CH_2)_n$
$(CH_2)_n$
O
i
$(CH_2)_n$
$(CH_2)_n$
ii, iii
$(CH_2)_n$
C
$(CH_2)_n$

(100)

**(67)**

i, $TiCl_3$, Zn/Cu, DME, reflux, $n = 5$, 91%; $n = 6$, 72%;
ii, $KOBu^t$, $CHBr_3$, pentane, 55–81%; iii, MeLi, $Et_2O$, pentane, –78 °C, 71–89%

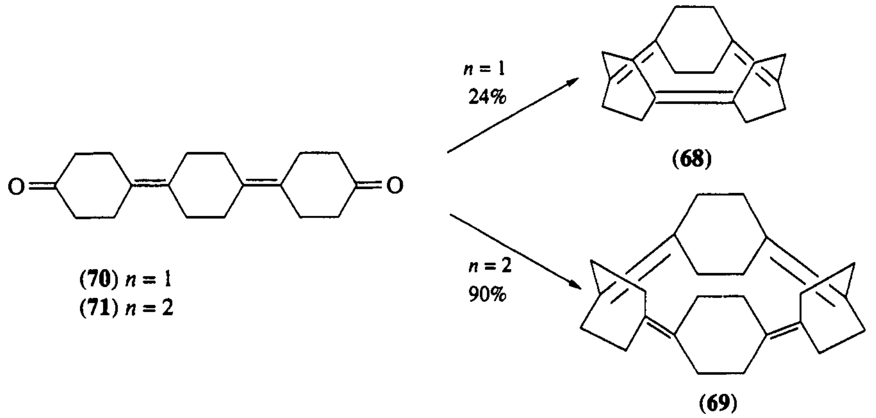
O
O
$n = 1$
24%
$n = 2$
90%

**(68)**

(101)

(**70**) $n = 1$
(**71**) $n = 2$

**(69)**

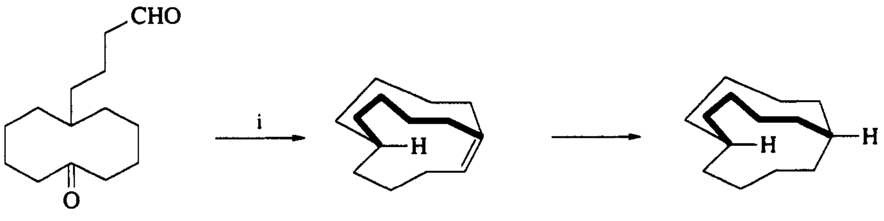

(102)

**(73)** **(72)**

i, $TiCl_3$, Zn/Cu, DME, reflux, 30%

**Table 3** Preparation of Cyclic Polyenes by the McMurry Coupling Reaction

| *Substrate* | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|
| 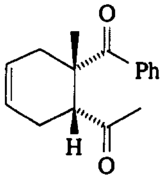 | 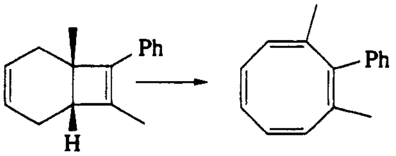 | 97 | 177 |
| 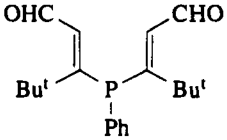 | 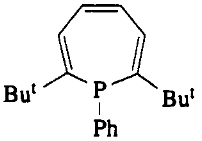 | 8–10 | 178 |
| 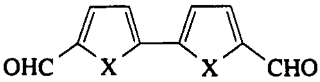 | 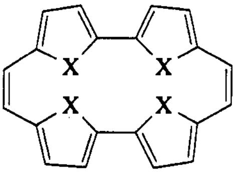 | X = NH, O<br>2–3 | 179 |
| 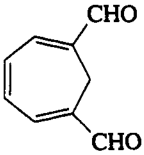 | 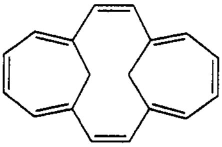 | 2–5 | 180 |
| 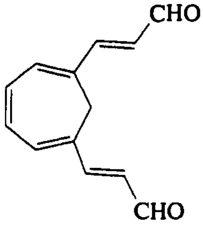 | 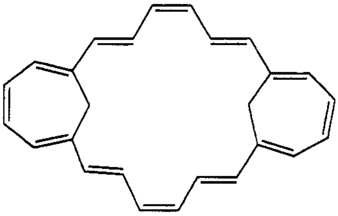 | 5 | 181 |
| 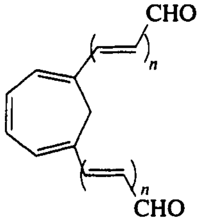 | 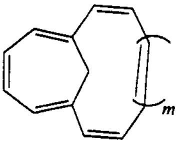 | 4–12 | 182 |
| 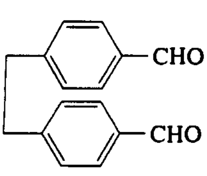 | 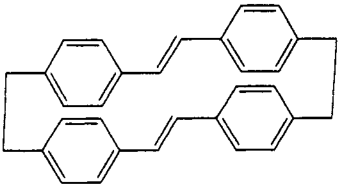 | 23 | 183 |

**Table 3** *(continued)*

| *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 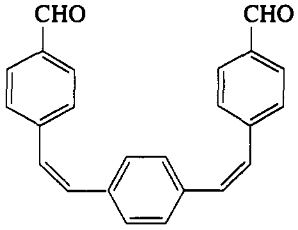 | 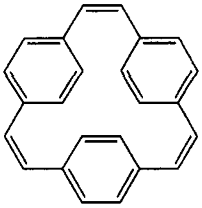 | 50 | 184 |
| 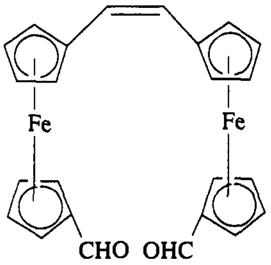 | 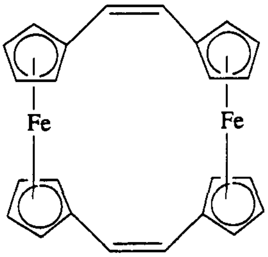 | 43 | 185 |

tem capable of forming a stable square planar $d^{10}$-complex with silver.[174] The in–out bicycloalkane (**72**) was recently synthesized by McMurry and Hodge *via* the coupling of the keto aldehyde (**73**) followed by hydrogenation. Protonation of (**72**) gives a stable μ-hydrido-bridged carbocation (equation 102).[176]

A wide range of cyclic polyenes, such as annulenes, porphycenes, cyclophanes and ferrocenophanes, have been prepared using McMurry methodology, and these are summarized in Table 3.

Cyclization of 1,5-diketones linked by a methylthiomethyl chain gives dihydrothiophenes (**74**), which upon oxidation and elimination provide stereodefined 1,3-dienes (equation 103).[186] Thus, *meso* diketones give *cis,cis* 1,4-disubstituted dienes whilst (±)-diketones give the *trans,cis* isomers.

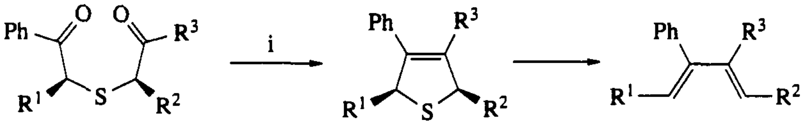

(103)

(**74**)

i, $TiCl_4$, Zn, THF, 66–86%

Finally an interesting system for the synthesis of alkenes from carbonyls based on TMSCl/Zn has been developed by Motherwell *et al.*,[187] and is compatible with esters and halogen groups (equation 104). The reaction does not however proceed *via* a ketyl radical coupling but rather *via* an organozinc carbeniod (**75**) which is trapped by a second carbonyl molecule to give an intermediate epoxide (**76**). The intermediate epoxide is then deoxygenated to the product alkene (Scheme 9).

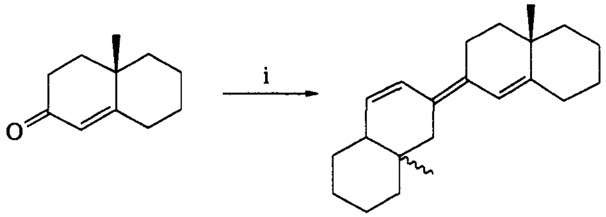

(104)

i, $Me_3SiCl$, Zn, THF, –50 °C, 85%

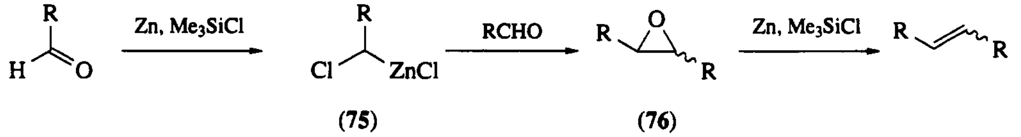

**Scheme 9**

## 2.6.8 MIXED COUPLINGS

This section will deal with pinacolic couplings of fundamentally different C=X (X = O or NHR) groups, that is those with different reduction potentials. Examples involving similar C=X groups, such as aldehyde–ketone couplings have already been discussed under the relevant sections and will only be mentioned briefly.[188] A number of efficient methods have been devised for the cross-coupling of carbonyl compounds to mixed pinacols. This type of reaction is especially facile for the cross-coupling of aromatic and aliphatic ketones. Aromatic carbonyls especially diaryl ketones are much more readily reduced than their aliphatic counterparts. Indeed chemoselective reduction of aromatic systems in the presence of aliphatic carbonyls allows for efficient cross-coupling *via* nucleophilic attack of the aryl anion/radical.[125,190] Clerici and coworkers have extensively studied such reactions of aryl ketones (**77**) with saturated and α,β-unsaturated carbonyl compounds, promoted by aqueous TiCl$_3$ (Scheme 10).[189] Under these conditions chemoselective formation of capto-datively stabilized radicals such as (**78**) is followed by subsequent trapping by the aliphatic carbonyl group. The use of an excess of the aliphatic carbonyl compound increases the ratio of mixed pinacol to dimer up to a maximum of 6:1. These reactions provide the first examples of radical addition to saturated carbonyls such as acetone and proceed *via* activation of the saturated carbonyl by coordination with titanium to give the electrophilic intermediate (**79**) followed by combination with the ketyl radical (**78**; equation 105). Fujiwara has published a potentially important method for the coupling of diaryl ketones with electrophiles, including ketones, nitriles, epoxides and CO$_2$, mediated by ytterbium metal (equation 106).[190]

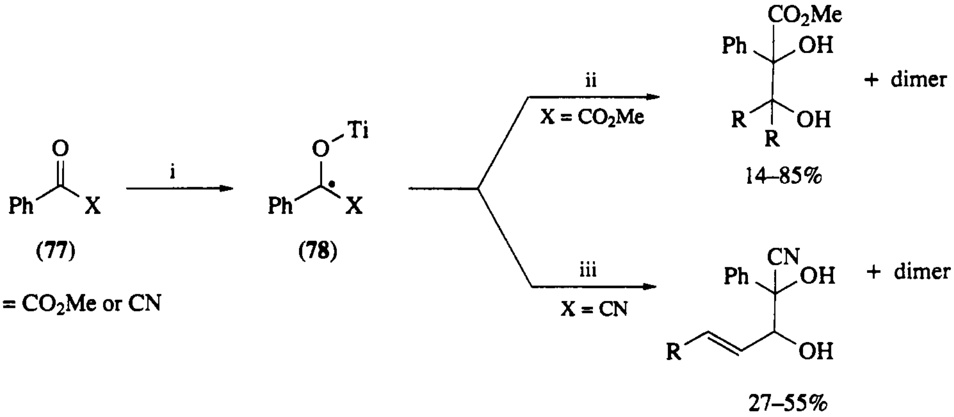

i, AcOH, 15% aq. TiCl$_3$, r.t.; ii, excess RCOR; iii, excess RCH=CHCHO

**Scheme 10**

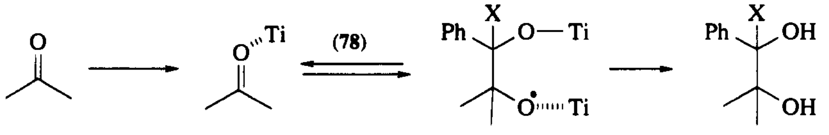
(79) (105)

Mixed coupling of ketones and α,β-unsaturated ketones can be profoundly affected by the pH of the solution. Thus the Wieland–Miesher ketone (**80**) undergoes intramolecular coupling to give the cyclopropanol (**81**) under basic conditions;[191] whilst in neutral media 1,2-hydrodimerization occurs leading to the pinacol (**82**; equation 107).[192]

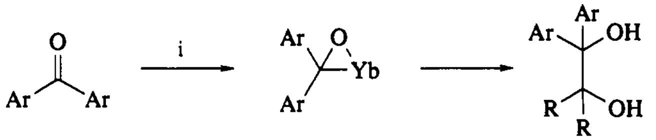

(106)

i, Yb, HMPA, THF, RCOR, r.t., 63–90%

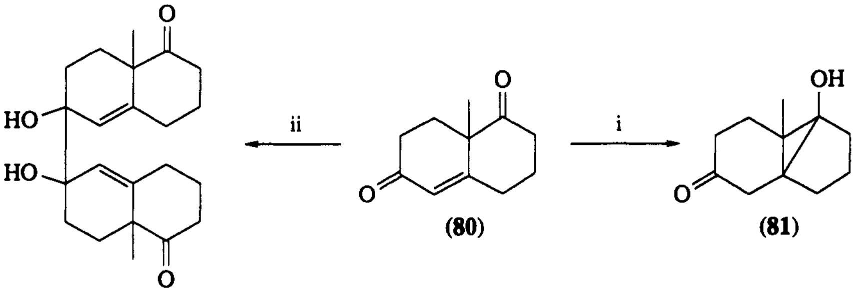

(107)

**(80)** **(81)**

**(82)**

i, Li, $NH_3$, THF, −78 °C, 87%; ii, Hg, MeOH, 0.1M KCl (1:1), −1.7 V, 71%

The mixed coupling of aliphatic compounds is also well established. Through the use of an excess (usually 10-fold) of one of the reactants cross-coupling of aliphatic carbonyls is highly effective.[193] This protocol was first developed by Corey[53] and then applied to reductive pinacolic couplings by McMurry.[125] Li *et al.* applied this method to the synthesis of the alkaloid isoharringtonine (**83**; equation 108).[194]

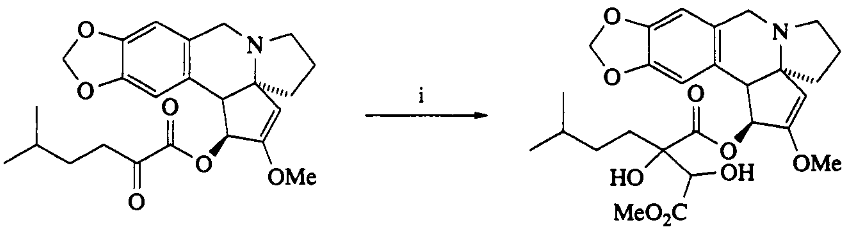

(108)

**(83)**

i, $CpTiCl_3$, $LiAlH_4$, THF, $MeO_2CCHO$

Early work on the electropinacolic coupling of aldehydes with imines was not promising since, as the reaction is reversible, complex product mixtures are formed.[195] However, recent developments in mixed coupling reactions have established some highly efficient and selective methods for the coupling of aldehydes or ketones with oximes or imines.[72,196] Thus stereoselective nonreversible coupling of ketones with oximes using TMSCl/Zn proceeds in excellent yield to give compounds of the type (**84**; equation 109),[72] and a highly versatile and selective method for the intermolecular coupling of imines with aldehydes or ketones uses a niobium(III) reagent providing a diastereoselective route to α-aminoalcohols

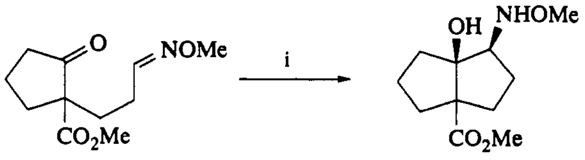

(109)

**(84)**

i, $Me_3SiCl$, Zn, 2,6-lutidine, THF, reflux, 84%

(equation 110).[196] Chemoselective formation of the metallaaziridine (**85**) in the latter reaction is followed by a highly efficient reaction with the carbonyl compound, even with only a 1.5 molar excess of the imine; no doubt this excellent method will be well exploited in the near future.

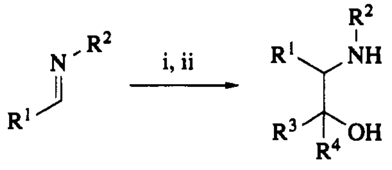

(110)

*ds* = 3:1 to 83:1

i, $NbCl_3$ (DME), THF; ii, $R^3COR^4$, THF, 33–97%

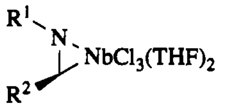

(**85**)

## 2.6.9 MISCELLANEOUS COUPLINGS

There are a number of alternative methods for the synthesis of 1,2-diols and their derivatives that do not proceed *via* the coupling of two carbonyl groups. Ketyl radicals can be generated by the alkylative deoxygenation of carboxylic acids, and in the presence of $TiCl_3$ coupled to give 1,2-diols (equation 111).[197] However, yields are limited (22–33%) and complex product mixtures are often formed.

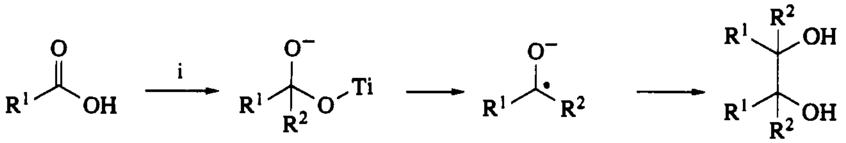

(111)

i, $TiCl_3$, $R^2Li$, DME, –78 °C to r.t., 22–33%

The formation of pinacols *via* the dimerization of alcohols is not feasible because of disproportionation or oxidation of the intermediate radical. Alcohols do however couple with ketyl radicals in photochemically initiated cross-pinacolization reactions (equation 112).[198] Product distribution is highly dependent on the light intensity. Photochemical cross-pinacolization has been used for a one-step conversion of osulose compounds to the corresponding hydroxymethyl branched derivatives (equation 113).[199] Alcohols protected as silyl ethers are efficiently coupled under free-radical conditions using di-*t*-butyl peroxide, to give, after hydrolysis, the corresponding pinacols in moderate to good yields (26–89%; equation 114).[200] Electroreductive cross-coupling of diaryl ketones with aldehyde-derived enol acetates yields unsymmetrical pinacols (equation 115) *via* nucleophilic attack onto the enol double bond.[201]

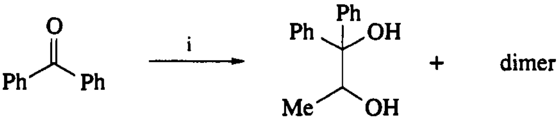

(112)

7 : 3

i, *h*ν, MeOH

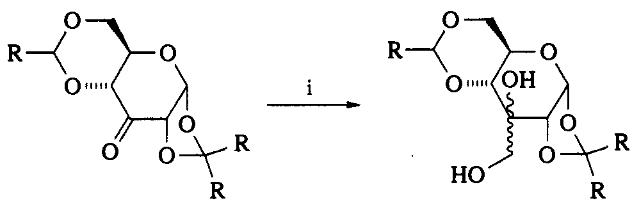

(113)

i, MeOH, $h\nu$, 450 W

| | *Yield* (%) | |
|---|---|---|
| | α-OH | β-OH |
| $R^1 = R^2 = R^3 = Me$ | 20 | 22 |
| $R^1 = H, R^2 = Et, R^3 = Ph$ | 30 | 25 |

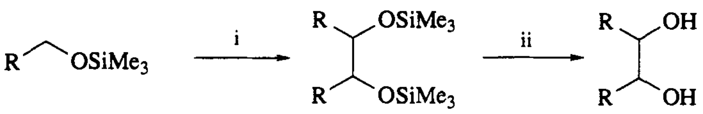

(114)

(±):*meso* = 1:1

i, $(Bu^tO)_2$, 145 °C, $N_2$ pressure; ii, ROH, 26–89%

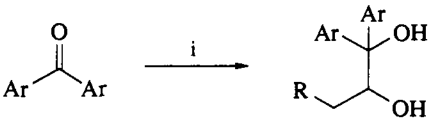

(115)

i, C-electrode, RCH=CHOAc, $Et_4NTs$, DMF, $H_2O$, 200 mA, 45–76%

The reduction of dialkyl acetals of aromatic aldehydes or ketones with a titanium(II) reagent gives pinacol ethers or the corresponding alkene in high yield (46–100%; equation 116).[202] Acetals derived from aliphatic aldehydes or ketones are reduced to the corresponding ethers.

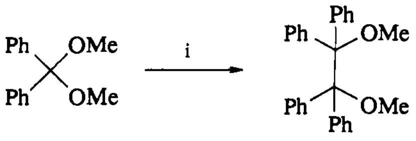

(116)

i, $TiCl_4$, $LiAlH_4$, THF, r.t., 100%

## 2.6.10 CARBONYL–ALKENE CYCLIZATIONS

In addition to coupling with heteroalkenes (C=O, C=N and C=S) carbonyls also undergo intramolecular reaction with nonconjugated C=C bonds. Together with the related reactions with alkynes and allenes these cyclizations provide regio- and often stereo-selective routes to five- and six-membered rings *via* C—C bond formation with net retention of functionality.[9c,203] Although there are no intermolecular examples, the intramolecular variant is a powerful method for the synthesis of polycyclic systems. Thus, electroreductive cyclization of ω-unsaturated alkenic ketones gives cyclic tertiary alcohols of the type

(**86**) regio- and stereo-selectively (equation 117).[204,205,222] Cyclization occurs through formation of the ketyl radical anion and *exo* radical addition to the alkene to form the intermediate (**87**). The developing charge interactions formed between the alkyl radical and the oxyanion in (**87**), within the electrode double layer, control the stereochemical integrity of the reaction. The reaction is completely regio- and stereo-specific in contrast to similar chemically induced cyclizations with either $TiCl_4$/Mg,[204] or Na/$Bu^tOH$/*N*-ethylpyrrolidine,[206] both of which are stereorandom. A related cyclization of the ketoalkene (**88**) with TMSCl/Zn shows a 5:1 preference for the *trans* isomer (**89**; equation 118).[72]

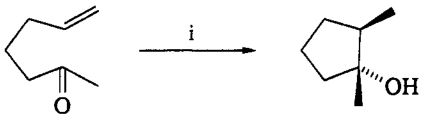

(117)

i, C-electrode, MeOH, dioxane, $Et_4NTs$, –2.70 V (*vs.* SCE), 32–98% or Hg, $DMPBF_4$, DMF, –3.10 V (*vs.* SCE), 98%

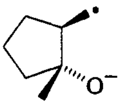

(**87**)

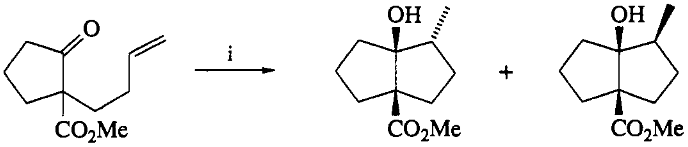

(**88**) (**89**) 5:1

(118)

i, $Me_3SiCl$, Zn, 2,6-lutidine, THF, reflux, 75%

The cyclizations of ketyl radicals onto double bonds occurs in an antiperiplanar fashion as demonstrated by the respective cyclizations of the epimers (**90**) and (**91**).[207] In ketone (**90**) the ether moiety is suitably disposed to act as a leaving group allowing *endo* cyclization to the alkene (**92**), whilst the epimeric ether (**91**) gives the cyclopentane (**93**) *via* the *exo* mode (equations 119 and 120). Stereochemical control can also be imparted by use of a chelating auxiliary as in the samarium-mediated cyclization of the ketone (**94**) to the spirolactone (**95**; equation 121).[73,208] The lactone moiety of (**94**) functions as a Lewis base enabling chelation of the $Sm^{3+}$ ion and thus stereoselective cyclization (equation 122). Photochemical radical generation can also be stereoselective, thus the ketones (**96**) and (**97**) give their respective bicyclic tertiary alcohols in good yields (equation 123).[209] A short synthesis of the monoterpenoid (±)-actinidine (**98**) has been accomplished using a photoreductive cyclization of the ketone (**99**; equation 124).[210]

The radical cyclization of aldehydes onto alkenes was first demonstrated by Hutchinson and coworkers using a TMSCl/Mg reducing agent (equation 125).[211] The cyclization of the aldehyde (**100**) to loganin tetraacetate (**101**) serves as a model reaction for studying the mechanism of the biological conversion of loganin to secologanin. In a related fashion cyclization of the (stannyloxy)alkyl radical gener-

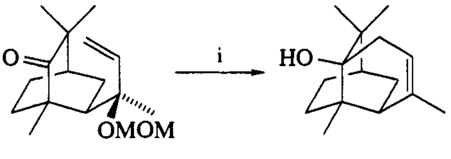

(**90**) (**92**)

(119)

i, Na, THF, 64%

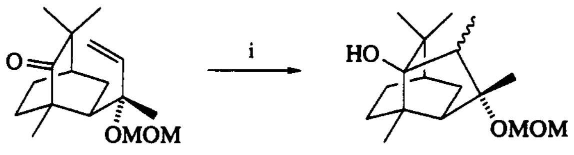

**(91)** **(93)**

(120)

i, Na, THF, 70%

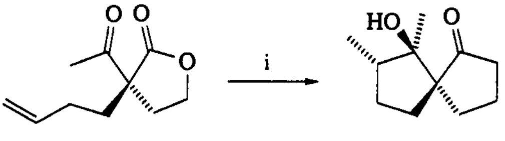

**(94)** **(95)**

(121)

i, 2 $SmI_2$, Bu$^t$OH, THF, −78 °C to r.t., 87%

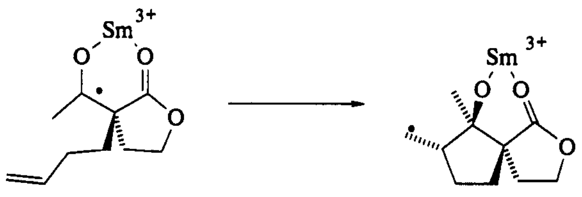

(122)

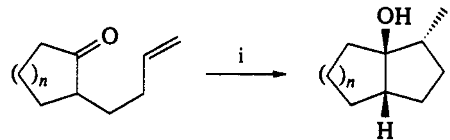

**(96)** $n$ = 1; **(97)** $n$ = 2

(123)

i, $h\nu$, HMPA, $n$ = 1, 81%; $n$ = 2, 76%

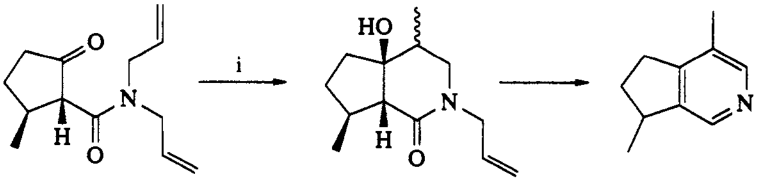

**(99)** **(98)**

(124)

i, $h\nu$, $Et_3N$, MeCN, 50%

ated from aldehyde (**102**) gives the alcohol (**103**; equation 126).[212] Further exploitation of the cyclization of aldehyde-derived radicals should provide a general route to polycyclic secondary alcohols.

Transannular cyclization of ketoalkenes was first reported in 1965. Treatment of the conformationally restricted ketone (**104**) with sodium in moist ether gave the alcohol (**105**; equation 127).[213] Similarly the ketoalkene (**106**) transannulated in 73% yield by exposure to sodium in refluxing propanol (equation 128).[214] Conformational restriction is not a prerequisite for transannular reaction; thus the caryophyllene (**107**) undergoes cyclization to the alcohol (**108**) with lithium in liquid ammonia (equation 129).[215] Transannulation across a nine-membered ring has also been observed upon treatment of ketone (**109**; equation 130) with samarium diiodide, *via* cyclization of the ketoalkene (**110**).[216] Of more practical importance, the electrochemical transannulation of the cyclooct-4-en-1-one gives the bicyclo[3.3.0]octanol (**111**; equation 131).[217]

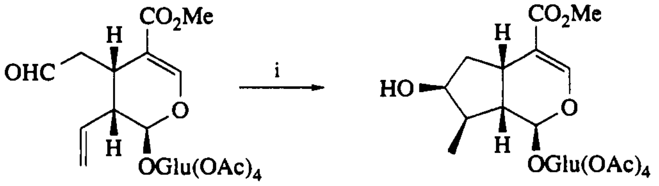
CO2Me
H
OHC
O
H
OGlu(OAc)4
i
HO
CO2Me
H
O
H
OGlu(OAc)4

(125)

**(100)** **(101)**

i, Mg, $Me_3SiCl$, THF, r.t., 55%

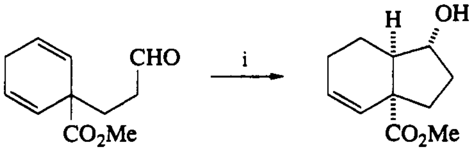
CHO
CO2Me
i
H
OH
CO2Me

(126)

**(102)** **(103)**

i, $Bu_3SnH$, AIBN, $C_6H_6$, reflux, 90%

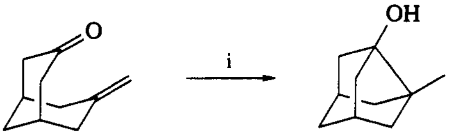

(127)

**(104)** **(105)**

i, Na, moist ether

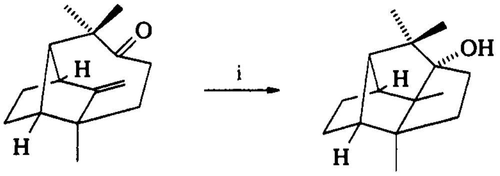

(128)

**(106)**

i, Na, $Pr^nOH$, reflux, 73%

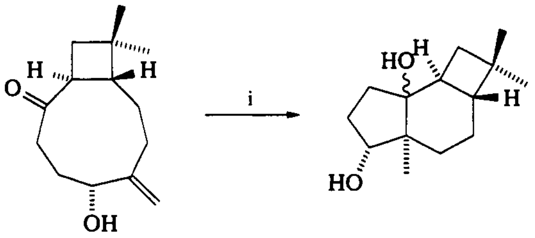
H
H
O
OH
i
HO
H
H
HO

(129)

**(107)** **(108)**

i, Li, $NH_3$, 30%

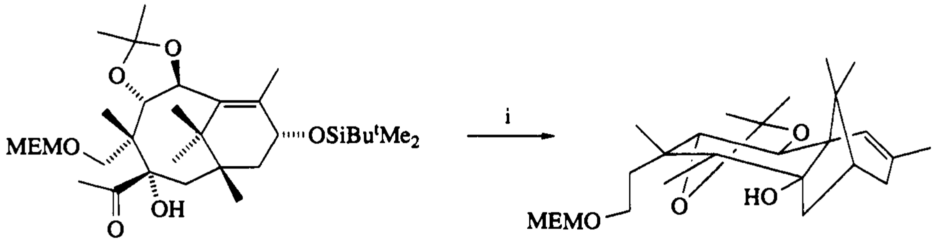

(130)

**(109)** i, 2 $\mathrm{SmI_2}$,THF, 25 °C, 92%

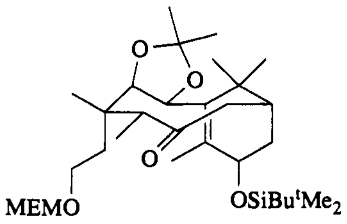

**(110)**

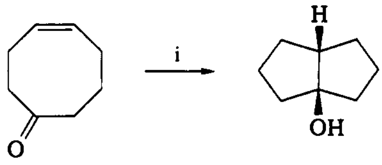

(131)

**(111)**

i, C-electrode, MeOH, dioxane, $\mathrm{Et_4NTs}$, –2.70 V (*vs.* SCE), 69%

## 2.6.11 CARBONYL–ALKYNE CYCLIZATIONS

Cyclizations of ketoalkynes constitute an important method for the synthesis of ring junction allylic alcohols such as those in the polycyclic systems of gibberellins, capnellenols, and amijiols. Thus reductive cyclization of ketones (**112**; equation 132) and (**113**; equation 133) form the C/D rings of the gibberellic acid[218–220] and provide a one-step alternative to the corresponding pinacolic coupling/alkenation of the keto aldehyde (**16**).[69] Ketoalkynes have also been cyclized *via* electroreduction,[221,222] photoreduction,[223] and using the sodium naphthalene radical anion[224,225] or TMSCl/Zn (equations 134–139).[72] It should be noted that the enone (**114**) is cyclized by sodium naphthalene radical anion, but is 1,4-reduced under protic conditions using $\mathrm{Na/NH_3}$ (equation 138).[224,225] Treatment of the homochiral ketone (**115**) with $\mathrm{Na/NH_3}$ furnishes the hydrindane (**116**), a potential synthon for optically active steroids and terpenes (equation 140).[226]

The capnellene and hirsutene marine sesquiterpenes are ideal candidates for radical cyclizations and both have been elaborated *via* carbonyl–alkyne cyclizations (equations 141–143). Thus treatment of the ketone (**117**) with the sodium naphthalene radical anion gives the triquinane (**118**). Subsequent allylic

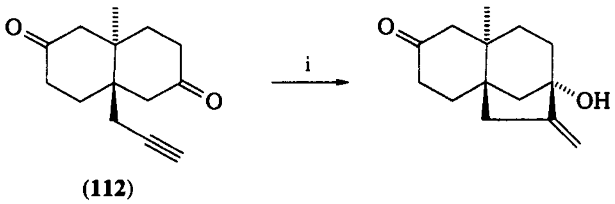

(132)

**(112)**

i, Li, $\mathrm{NH_3}$, $\mathrm{Et_2O}$, $\mathrm{NH_4SO_4}$, ~50%

oxidation and inversion gives (±)-$\Delta^{9(12)}$-capnellene-8$\beta$,10$\alpha$-diol (**119**).[227] Similar photoreduction of the ketone (**120**) gives the tertiary alcohol (**121**) from the $\alpha$-epimer, whilst the $\beta$-isomer of (**120**) is reduced to the alcohol (**122**).[228] Conversion of the tertiary alcohol in (**121**) to a methyl group completes the synthesis of hirsutene. A particularly elegent tandem radical cyclization of the aldehyde (**123**) with $SmI_2$ provides the alcohol (**124**), a key intermediate in the synthesis of corriolin and hypnophilin stereoselectively (equation 143).[229] A synthesis of the dolastane diterpene, (±)-isoamijiol (**44**; equation 144), utilizing only seven C—C bond-forming reactions, of which four involve radical intermediates, is completed by stereospecific reductive cyclization of the ketoalkyne (**125**) to the alcohol (**126**) followed by allylic

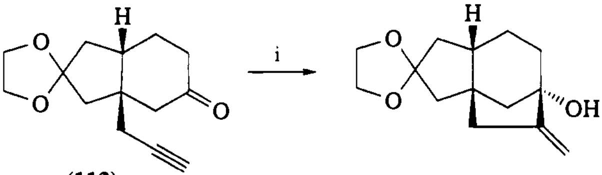

**(113)**

(133)

i, Li, $NH_3$, $NH_4SO_4$, 50% or K, $NH_3$, THF, $NH_4SO_4$, 60–70%

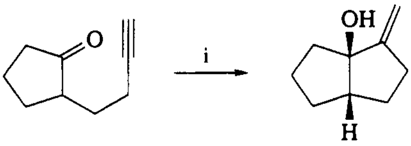

(134)

i, C-electrode, $Et_4NTs$, DMF, 75%

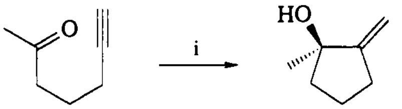

(135)

i, Hg, $DMPBF_4$, DMF, −2.70 V (*vs.* SCE), 85%

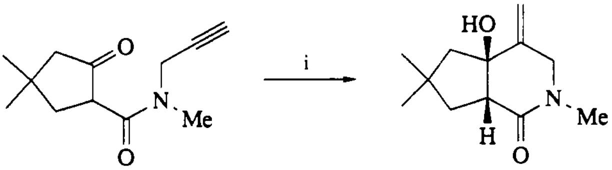

(136)

i, *h*v, $Et_3N$, MeCN, 58%

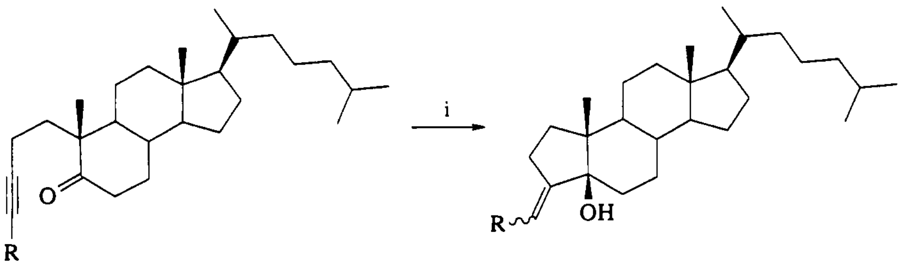

(137)

i, Na, $C_{10}H_8$, THF, 69–72%

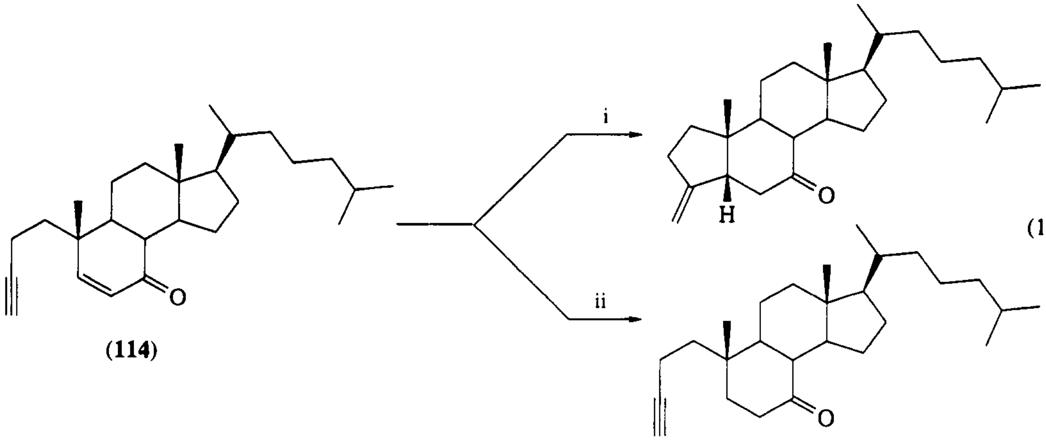

**(114)**

(138)

i, Na, $C_{10}H_8$, THF, 20–25%; ii, Na, $NH_3$, THF, 94%

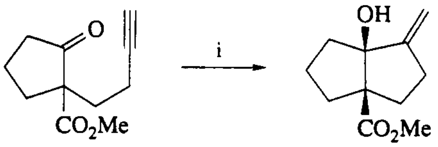
O
$CO_2Me$
i
OH
$CO_2Me$

(139)

i, $Me_3SiCl$, Zn, 2,6-lutidine, THF, reflux, 77%

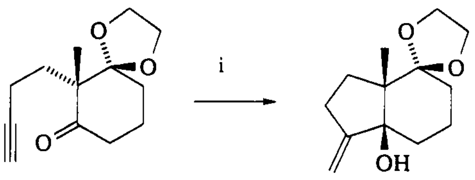

**(115)** **(116)**

(140)

i, Na, $NH_3$, $(NH_4)_2SO_4$, ~90%

oxidation.[153] The stereochemical integrity of the unusual *trans* ring junction is controlled by steric interactions of the alkynic side chain and the azulenone nucleus. This cyclization has also been effected using homochiral (**125**) to furnish (+)-isoamijiol.[230]

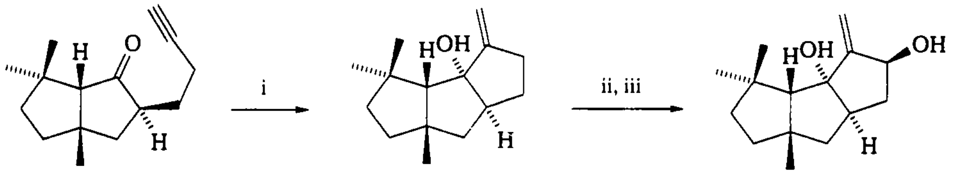
H
O
H
i
HOH
H
ii, iii
HOH
OH
H

**(117)** **(118)** **(119)**

(141)

i, Na, $C_{10}H_8$, THF, 30%; ii, $SeO_2$, $Bu^tO_2H$, $CH_2Cl_2$, 40%; iii, MsCl, $Et_3N$, $CH_2Cl_2$; $KO_2$, DMSO, DMF, –5 °C to r.t., 40%

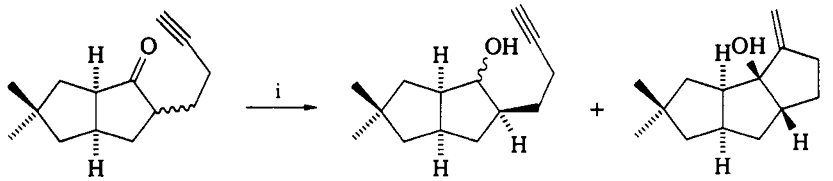

**(120)** **(121)** 58% **(122)** 20% (142)

i, $h\nu$, 254 nm, $Et_3N$, MeCN

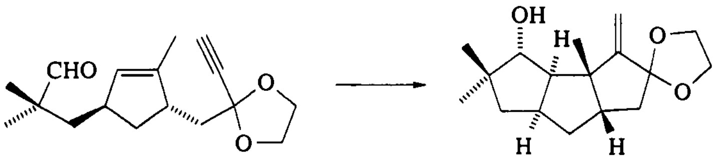

**(123)** **(124)** (143)

i, 2 $SmI_2$, THF, HMPA

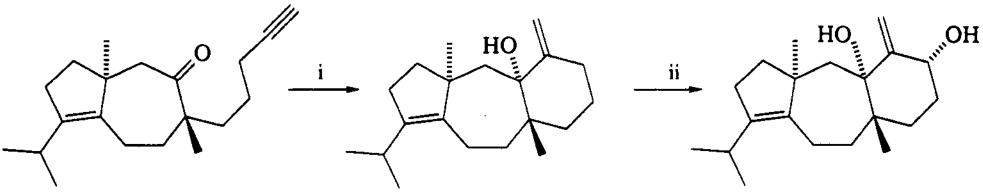

**(125)** **(126)** **(44)** (144)

i, Na, $C_{10}H_8$, THF, 41%; ii, $SeO_2$, $Bu^tO_2H$

## 2.6.12 CARBONYL–ALLENE CYCLIZATIONS

Reductive cyclization of ketoallenes (**127**) and (**128**) either electrochemically, or by brief exposure to the sodium naphthalene radical anion, gives the tertiary alcohols (**129**) and (**130**) respectively, *via* regio- and stereo-specific reactions in an *exo* mode (equations 145 and 146)[231] The stereochemistry at the ring junction in (**130**) is *cis* with a *trans* relationship between the pendant vinyl group and the tertiary alcohol, in a similar fashion to ketoalkene cyclizations. Best yields are obtained electrochemically under nonenolizing conditions. In contrast, prolonged exposure to excess sodium naphthalene radical anion is not regioselective; thus ketone (**131**) gives a mixture of *exo* and *endo* double bond isomers (equation 147).[232]

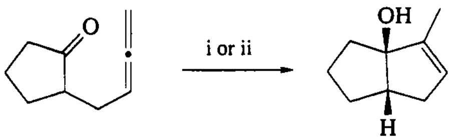

**(127)** **(129)** (145)

i, Hg, –2.43 V (*vs.* $Ag/AgI_2$), $Et_4NTs$, DMF, 41%; ii, Na, $C_{10}H_8$, THF, 28%

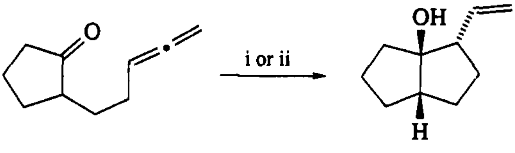

**(128)** **(130)**

(146)

i, Hg, –2.43 V (*vs.* $Ag/AgI_2$), $ET_4NTs$, DMF, 37%; ii, Na, $C_{10}H_8$, THF, 28%

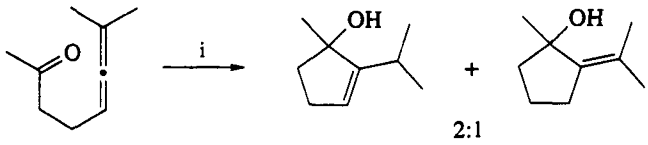

**(131)**

(147)

i, Na, $C_{10}H_8$, THF, r.t., 5 h, 46%

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# 2.7

# Acyloin Coupling Reactions

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## 2.7.1 THE REDUCTION OF CARBOXYLIC ESTERS BY ALKALI METALS

Under certain circumstances the reduction of a carboxylic ester by an alkali metal leads to an enediolate. Protonation then gives an acyloin, an α-hydroxy ketone, in which two atoms which were originally the carbon atoms of the ester carbonyl groups are joined by a new single carbon–carbon bond. This coupling reaction, in both its intermolecular mode (Scheme 1) and, particularly, in its intramolecular mode (Scheme 2), is a useful synthetic operation.[1] It is, however, only one of a number of processes which can occur as a result of the reduction of a carboxylic ester by an alkali metal. For example, whereas the use of molten sodium dispersed in refluxing toluene converts a simple ester into the acyloin, the use of an excess of sodium in ethanol converts a simple methyl or ethyl ester into the corresponding primary alcohol (*i.e.* the Bouveault–Blanc reduction). A different reduction occurs when, for example, hindered esters are reduced by lithium in ethylamine[2] or sodium in HMPA in the presence of 2-methylpropan-2-ol.[3] Acyloin formation does not occur, and instead the alkoxy portion of the ester is deoxygenated (equation 1).

If the ester group is conjugated with a π-electron system, alternative reduction processes can occur. Benzoate esters are reduced to the 1,4-dihydrobenzoates by sodium in the system $NH_3$/THF/$H_2O$.[4] For

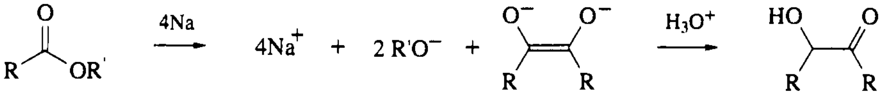

**Scheme 1**

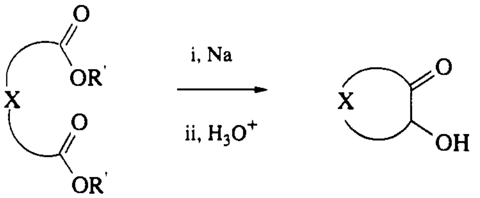

**Scheme 2**

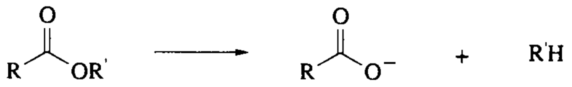 (1)

$\alpha,\beta$-alkenic esters both simple reduction at the carbon–carbon double bond and hydrodimerization at the $\beta$-position have been observed,[1] as a result of the action of alkali metals under particular conditions.

A further reductive process is often observed in the case of hindered vicinal diesters, where fragmentation occurs;[5] the cleaved products, still diesters, have sometimes then, in a separate step, been submitted to the acyloin coupling reaction. A typical sequence from the diester (**1**) is shown in Scheme 3.[6]

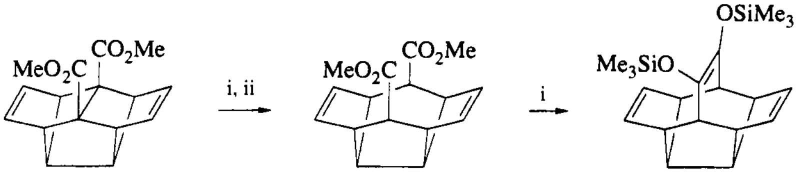

(**1**)

i, Na, toluene, $Me_3SiCl$, reflux; ii, MeOH

**Scheme 3**

In addition, many nonreductive side reactions occur. The choice of suitable reagents and conditions for an acyloin coupling reaction is still based on analogy and empiricism.

## 2.7.2 NECESSARY REACTION CONDITIONS FOR THE ACYLOIN COUPLING REACTIONS OF ESTERS

Two sets of conditions have commonly been employed in order to effect the acyloin coupling of esters. In each case it is important that both the condensation and the work-up should be performed in the absence of moisture and of oxygen.

### 2.7.2.1 Heterogeneous Conditions

The solvent is usually refluxing toluene or xylene, though occasionally benzene or ether has been used. The substitution of DME, THF or dioxane offers no advantages. At the higher temperatures obtaining in refluxing toluene (b.p. 111 °C) or xylene, the alkali metal is molten. The reaction is a surface reaction and it is essential that the metal is finely dispersed, for example by efficient stirring. A slight excess of the metal is normally used.

### 2.7.2.2 Homogeneous Conditions

The solvent is liquid ammonia, at its boiling point −33 °C. The exact amount of the metal is used. In particular cases one or other set of conditions may give the better yield. In investigating a new acyloin coupling reaction the first choice would be heterogeneous conditions.

### 2.7.2.3 Reaction Variables

The initial interaction between an alkali metal and an ester leads, by single electron transfer, to the alkali metal derivative of a radical anion. Radical anions from nonphenolic esters normally fragment, to give the carbonylate anion and a radical derived from the alkyl group. It has been pointed out[2] that this makes the acyloin coupling a curiosity and difficult to rationalize. The alkali metal is usually sodium. The choice has an effect on the course of the reaction, partly due to the potential at which the initial single electron transfer step occurs, and partly due to differences in the nature and stability of the alkali metal derivative of the radical anion under the prevailing conditions. No systematic study of this aspect of the reaction has ever been undertaken. At the higher temperatures of the heterogeneous conditions, the reaction of the radical anion must be a surface reaction. At the lower temperatures used in the homogeneous conditions the free radical anion is formed, but only undergoes the competing fragmentation slowly, so that the acyloin coupling is favored. The use of a sodium–potassium alloy (with its lower melting point relative to the pure metals) allows the heterogeneous conditions to be used at lower temperatures. This type of procedure has been found to be particularly successful for thiophene-containing systems (Scheme 4).[7]

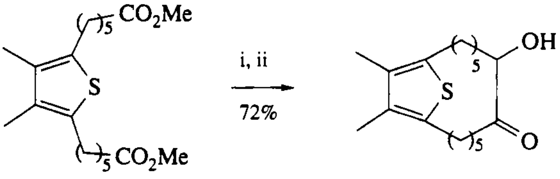

i, Na/K, xylene, 55–60 °C; ii, $H_3O^+$

Scheme 4

The products of an acyloin coupling reaction are an enediolate dianion and alkoxide ions. In the presence of the alkoxide the enediolate may be oxidized to the corresponding diketone by molecular oxygen.[8] It is therefore important that, even when the coupling is complete, all reaction mixtures should be worked up in an oxygen-free atmosphere so long as the mixture remains alkaline. For reactions performed in liquid ammonia, all the ammonia should be allowed to evaporate before the reaction is worked up.

## 2.7.3 COMPETING BASE-CATALYZED REACTIONS AND THEIR SUPPRESSION. TRAPPING WITH TRIMETHYLSILYL CHLORIDE

### 2.7.3.1 Side Reactions

Low yields in acyloin coupling reactions in the past were often the consequence of competing base-catalyzed processes, although the exact nature of the by-products, especially those of high molecular mass, has often not been established. The conditions which lead to Claisen or Dieckmann condensations are quite similar to those used in the acyloin coupling reaction and sometimes such processes predominate. For example, an attempt to prepare the cyclic acyloin from either the (±)- or *meso*-form of diethyl 3,4-diphenylhexanedioate, using sodium in benzene, gave only the Dieckmann product, 2-ethoxycarbonyl-3,4-diphenylcyclopentan-1-one,[9] and other similar cases have been collected.[10] Other base-catalyzed reactions have intervened. An attempt to prepare 2-hydroxycyclopentan-1-one, from dimethyl pentane-1,5-dioate, gave, instead, a $C_{10}$ product derived by an aldol condensation,[1] and an attempt to effect the acyloin coupling reaction with the diester (**2**) led only to the products of base-catalyzed elimination (equation 2).[1] Problems like these can now be overcome by carrying out the coupling reaction in the presence of the trapping agent TMS-Cl or by adding it before the work-up.[11]

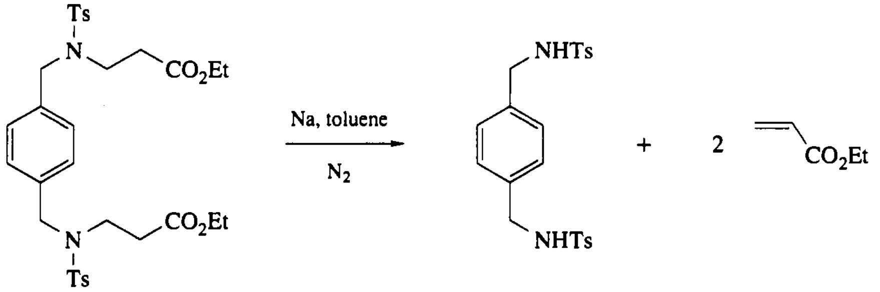
Ts
N
CO2Et
CO2Et
N
Ts
Na, toluene
N2
NHTs
NHTs
+
2
CO2Et

(2)

(2)

## 2.7.3.2 Trapping with Trimethylsilyl Chloride

In the presence of TMS-Cl the enediolate dianion and, importantly, the alkoxide ions, are trapped as their neutral silyl ethers (Scheme 5). This leads to much improved yields of the coupled product; the acyloin is isolated in the form of its silyl enediol ether (**3**). Work-up is much easier. It is only necessary to filter the solution, evaporate the solvent, and isolate the product by distillation or chromatography. The TMS-Cl should be purified by distillation from calcium hydride, under a nitrogen or argon atmosphere, before use. A convenient procedure when using an organic solvent is to add the ester and the TMS-Cl together, dropwise, to the alkali metal finely dispersed in the solvent, at a rate sufficient to maintain the reaction. An explosion has been reported where this procedure was not followed.[1] For a reaction conducted in liquid ammonia[1] the TMS-Cl is added at the end of the reaction and after all the ammonia has been allowed to evaporate. Particularly in cases where sodium–potassium alloy has been used, a pyrophoric residue may have formed, so that the filtration must be carried out under an inert atmosphere.

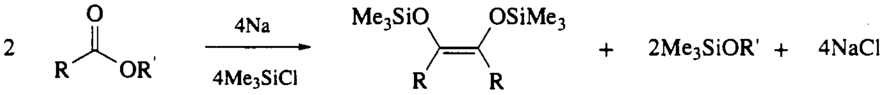
2
O
R
OR'
4Na
4Me3SiCl
Me3SiO
OSiMe3
R
R
+ 2Me3SiOR' + 4NaCl

(3)

Scheme 5

The kinetic product of an acyloin coupling is the enediolate, which may be formed in (*Z*)- and (*E*)-forms, and is accompanied by some of the thermodynamic product, the corresponding $\alpha$-hydroxy enolate. Each of these dianions is trapped by the TMS-Cl. The products, and the proportions in which they are formed, for the reactions of ethyl ethanoate[12] and diethyl hexane-1,6-dioate[13] are shown in Scheme 6. Use of dichlorodimethylsilane in conjunction with the reduction of ethyl ethanoate[12] gave the *acyclic*

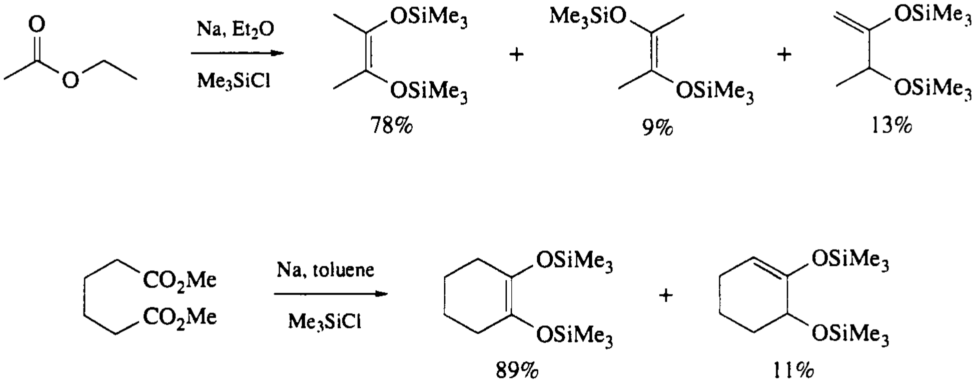
O
O
Na, Et2O
Me3SiCl
OSiMe3
OSiMe3
78%
+
Me3SiO
OSiMe3
9%
+
OSiMe3
OSiMe3
13%
CO2Me
CO2Me
Na, toluene
Me3SiCl
OSiMe3
OSiMe3
89%
+
OSiMe3
OSiMe3
11%

Scheme 6

products shown in Scheme 7. All the silylated products can be converted into the corresponding acyloin by hydrolysis with dilute aqueous acid, but better yields are obtained by treatment with methanol which has been completely deoxygenated by the passage of a stream of nitrogen.[5a,14] It is normally advantageous to prepare the acyloin as it is required, since most acyloins give dimers, through hemiacetal formation, on standing. Moreover several reactions, for example the oxidation to the α-diketone, can be performed on the silyl enediol ether without prior isolation of the acyloin.

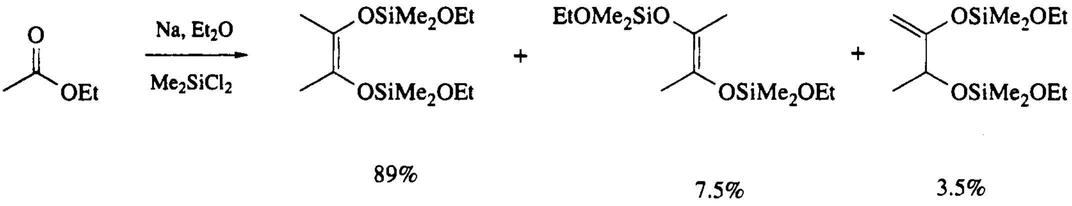

**Scheme 7**

Although ethyl 3-methylbutanoate on reduction with sodium in the presence of TMS-Cl in benzene or ether gives the expected silyl enediol ether (**4**), in DME or THF the product is the noncoupled product (**5**).[15]

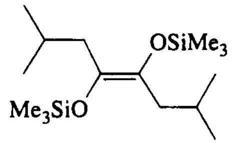

(**4**)

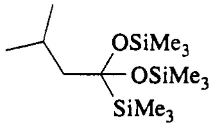

(**5**)

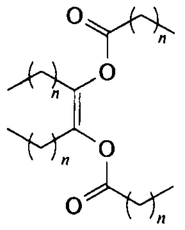

(**6**) *n* = 10, 12, 14 and 16

### 2.7.3.3 Preferred Reaction Conditions for an Attempted Acyloin Coupling Reaction

The preferred procedure at the present time would thus be to react an ester (or diester) in a heterogeneous system consisting of a highly dispersed alkali metal, probably sodium, in an organic solvent such as toluene, in the presence of trimethylsilyl chloride and under an inert atmosphere, and to decompose the isolated silylated products to the required acyloin by treatment with oxygen-free methanol.

## 2.7.4 ACYLOIN COUPLING REACTIONS WITH ACYL CHLORIDES AND ACID ANHYDRIDES

In principle the acyloin coupling of acyl chlorides, in which the enediolate dianion is trapped by unreacted acyl chloride, might be an effective alternative to trapping with TMS-Cl, but the method has rarely been used. Good yields of the enediol diesters (**6**) were obtained with several fatty acid chlorides using sodium in ether, and the enediol diesters could easily be hydrolyzed to give the acyloins.[16]

The coupling of aroyl chlorides to give 1,2-diaroyloxy-1,2-diarylethylenes has been known since 1865. The best reagent, from many which have been tried, is activated copper powder (Scheme 8).[17] It does not couple aliphatic acyl chlorides. The acyloin coupling of terephthaloyl chloride under either heterogeneous or homogeneous conditions, using sodium, has been shown to give a *para*-linked copolymer containing benzoin and benzil residues.[18]

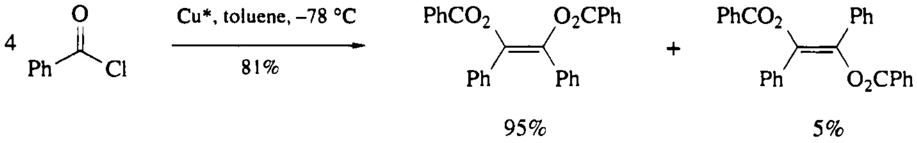

**Scheme 8**

For the modern TMS-Cl trapping technique it has been shown that esters give considerably better yields than the corresponding acyl chlorides or acid anhydrides.[11,19]

## 2.7.5 REDUCTIVE COUPLING OF THIOESTERS

Nicolaou has recently shown that reductive coupling of thioesters can be accomplished using sodium naphthalenide; the resulting dianion can then be trapped, for example with an alkyl halide (Scheme 9). One of the six examples cited by Nicolaou[20] is shown in Scheme 10, where the tricyclic bisthiolactone (**7**) is reduced to the tetracyclic compound (**8**). A related coupling can be achieved photochemically. Ultraviolet irradiation of (**7**) for a short period, gives the stable 1,2-dithietane, dithiatropazine (**9**), together with a little of the tetracyclic alkene (**10**). Longer irradiation of (**7**) or the thermal decomposition of (**9**) also leads to (**10**).[21]

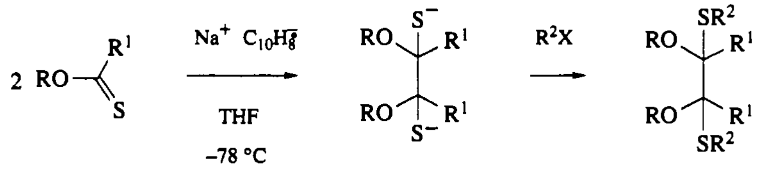

Scheme 9

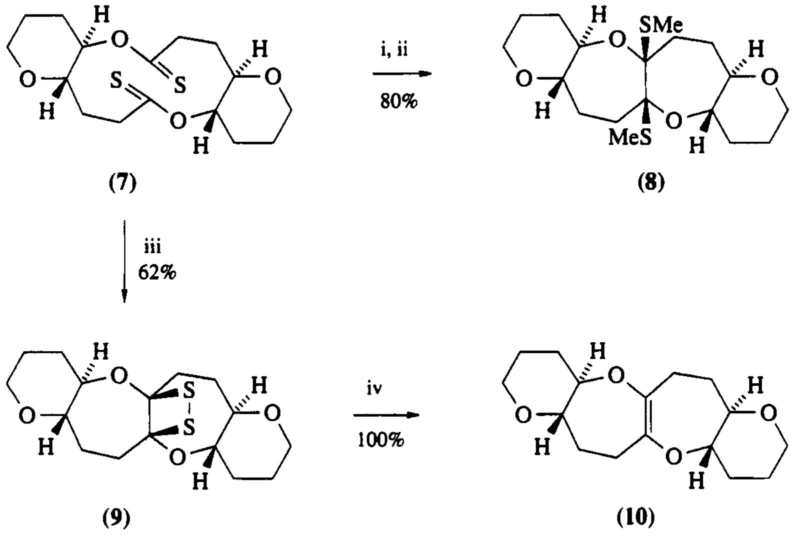

i, Na+, $C_{10}H_8^{\bullet -}$, THF, −78 °C; ii, excess MeI, −78 to 0 °C;
iii, UV light, toluene, room temperature, 15 min; iv, heat alone, or in xylene

Scheme 10

## 2.7.6 APPLICATIONS TO SPECIFIC SYSTEMS

### 2.7.6.1 Acyclic Systems

### *2.7.6.1.1 Symmetrical condensations*

Early applications of the acyloin coupling reaction to the esters of aliphatic monocarbocyclic acids, before the introduction of the TMS-Cl trapping technique, gave variable yields and the separation of the pure acyloins from by-products was often troublesome. Nevertheless a satisfactory preparation of 5-hydroxyoctan-4-one in 65–70% yield, by the use of sodium dispersed in xylene, is described in *Organic Syntheses*.[22] Yields in the 50–75% range were recorded[22] for other acyloins prepared in the same way, including 4-hydroxy-2,2,5,5-tetramethylhexan-3-one (pivaloin). Even higher yields were recorded for the esters of fatty acids.[1] It was shown that a nonconjugated double bond and a nonconjugated, nonterminal triple bond in an aliphatic ester were unaffected by these simple coupling conditions.[1] Other successful acyloin coupling reactions[1] using the earlier procedures were those on methyl phenylacetate and ethyl 3-thienylpropionate, containing aromatic residues, and alicyclic esters such as methyl cyclohexanecarboxylate and ethyl adamantane-l-carboxylate.

The introduction of the trimethylsilyl chloride trapping technique[11] led to improved yields in the case of simple aliphatic esters. The initial silylated products are easily isolated and can be converted into the acyloins simply and in high yield. For simple aliphatic esters the yields are in the range 56–92%. Use of trimethylsilyl esters, rather than simple alkyl esters, leads to faster reactions, but lower yields.[11,15] Substituted esters which have been successfully used in the newer procedure include ethyl 2-ethylhexanoate (83%),[23] ethyl trimethylsilylacetate (90%),[11] ethyl 3-trimethylsilylpropionate (65%),[11] ethyl phenylacetate (48%),[11] ethyl 3-phenylpropionate (79%)[11] and 2-(2-methoxycarbonylethyl)-2-methyl-1,3-dioxolane derived from levulinic acid (65%).[11] In the case of ethyl adamantane-1-carboxylate the yield using the newer procedure is reported to be inferior to that using the earlier procedure.

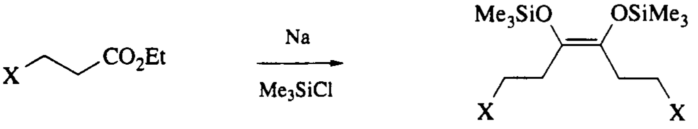

X = OEt (47%); SEt (69%); NEt$_2$ (62%)

**Scheme 11**

Because TMS-Cl scavenges basic products, the coupling reaction in its presence can be successfully conducted on esters containing a potential leaving group in the β-position, without any elimination occurring (Scheme 11).[11] However the reaction fails for β-halogen-substituted esters, due to reactions consequent on an initial reductive dehalogenation.[11] Reduction of either ethyl or trimethylsilyl benzoate with sodium only gives <15% of benzoin;[1] the trimethylsilyl enediol ether is formed in ~40% yield if trapping with TMS-Cl is employed.[11] However, an 86% yield is reported for the corresponding trimethylsilyl enediol ether when trimethylsilyl, but not ethyl, 4-methylbenzoate is used.[11] Reduction of ethyl benzoate with sodium in liquid ammonia gives a 50% yield of benzoin;[1] if water is added before the sodium, reduction of the benzene ring occurs (see Section 2.7.1).[4] Reduction of ethyl benzoate with sodium naphthalenide in THF gives benzoin in 86% yield,[24] but much lower yields of the acyloins are produced by the reduction of the esters (**11**) and (**12**) with lithium naphthalenide in THF.[25]

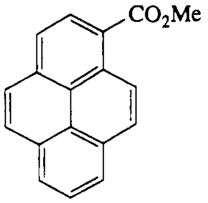

(**11**)

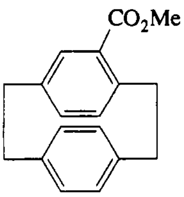

(**12**)

Reaction of methyl or ethyl benzoate with the potassium–graphite intercalation compound C$_8$K, in DME or THF under argon at 25 °C, followed by quenching with water and air oxidation, gives a 30% yield of phenanthraquinone (equation 3).[26] The conversion of benzoin into phenanthraquinone by C$_8$K at the layer edge of the intercalate, with loss of molecular hydrogen, had been described earlier.[27] The overall process (equation 3) has been described by its discoverers as the hyperacyloin condensation. The conversion of methyl 4-alkylbenzoates into 3,6-dialkylphenanthraquinone has also been reported.[26]

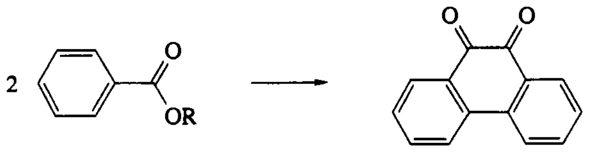
(3)

#### 2.7.6.1.2 *Mixed condensations*

Very few intermolecular mixed acyloin coupling reactions using two different monocarboxylic esters have been attempted.[1] Inevitably, mixtures result, and the yields are low, especially when one component is a benzoate. No attempts to use the TMS-Cl trapping technique seem to have been made.

### 2.7.6.2 Cyclic Acyloins

#### 2.7.6.2.1 *Carbocyclic systems*

*(i) Small rings*

A single example of the formation of a cyclopropane on reduction of a malonate has been reported (equation 4);[1] most of the products of the reduction were acyclic, and the cyclopropane (**13**) is not a derivative of an acyloin.

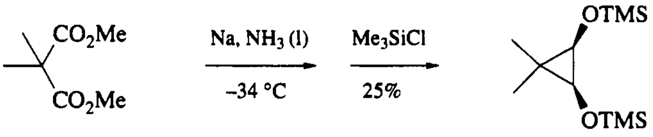

(4)

**(13)**

The intramolecular acyloin coupling reaction, on the other hand, is a useful method for constructing cyclobutane rings, although by no means all vicinal esters can be used successfully in this way. Diethyl succinate is not converted into 2-hydroxycyclobutanone (succinoin) by sodium and refluxing toluene alone, but using trapping with trimethylsilyl chloride a 78% yield of the corresponding trimethylsilyl enediol ether can be obtained.[1,11] The procedure is described in detail in *Organic Syntheses*.[14] Although dimethyl tetramethylsuccinate is not reduced by sodium in refluxing toluene or sodium in liquid ammonia, treatment with sodium–potassium alloy in xylene gives the acyloin in 35% yield. It is better, however, to carry out the reduction with sodium in toluene in the presence of TMS-Cl, and then hydrolyze the trapped product with aqueous acid, when the overall yield rises to 60%. Other simple substituted succinates have been reduced by this preferred procedure.[1] Dimethyl (+)-(*R*)-2-methylsuccinate and dimethyl (–)-(*S*)-2-methylsuccinate both give the corresponding chiral trimethylsilyl cyclobutenediol ethers,[28] and the (±)- and *meso*-forms of dimethyl dideuteriosuccinate give deuterium-labeled products of known stereochemistry (Scheme 12).[29] Diethyl (±)-2,3-di-*t*-butylsuccinate is reduced by sodium in toluene, in

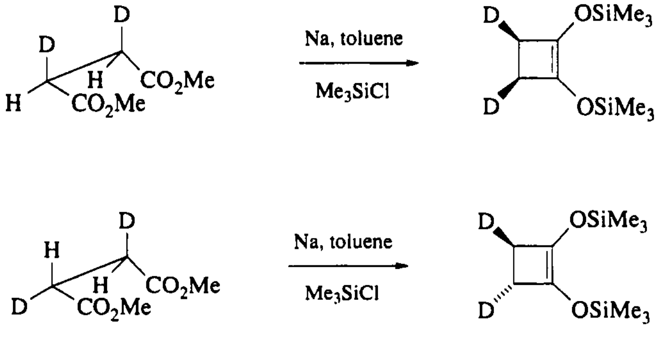

Scheme 12

the absence of TMS-Cl, to give the *trans*-di-*t*-butylsuccinoin in 90% yield,[1] but the corresponding *meso* form does not react,[1] presumably because of the severe steric interaction between the two adjacent *t*-butyl groups which would be involved during the coupling step. The successful acyloin coupling of simple succinates using sodium in THF in the presence of TMS-Cl has also been reported.[15]

Other vicinal diesters which have been used successfully in the acyloin coupling reaction, using TMS-Cl trapping, are shown in Figure 1.[1,30,31]

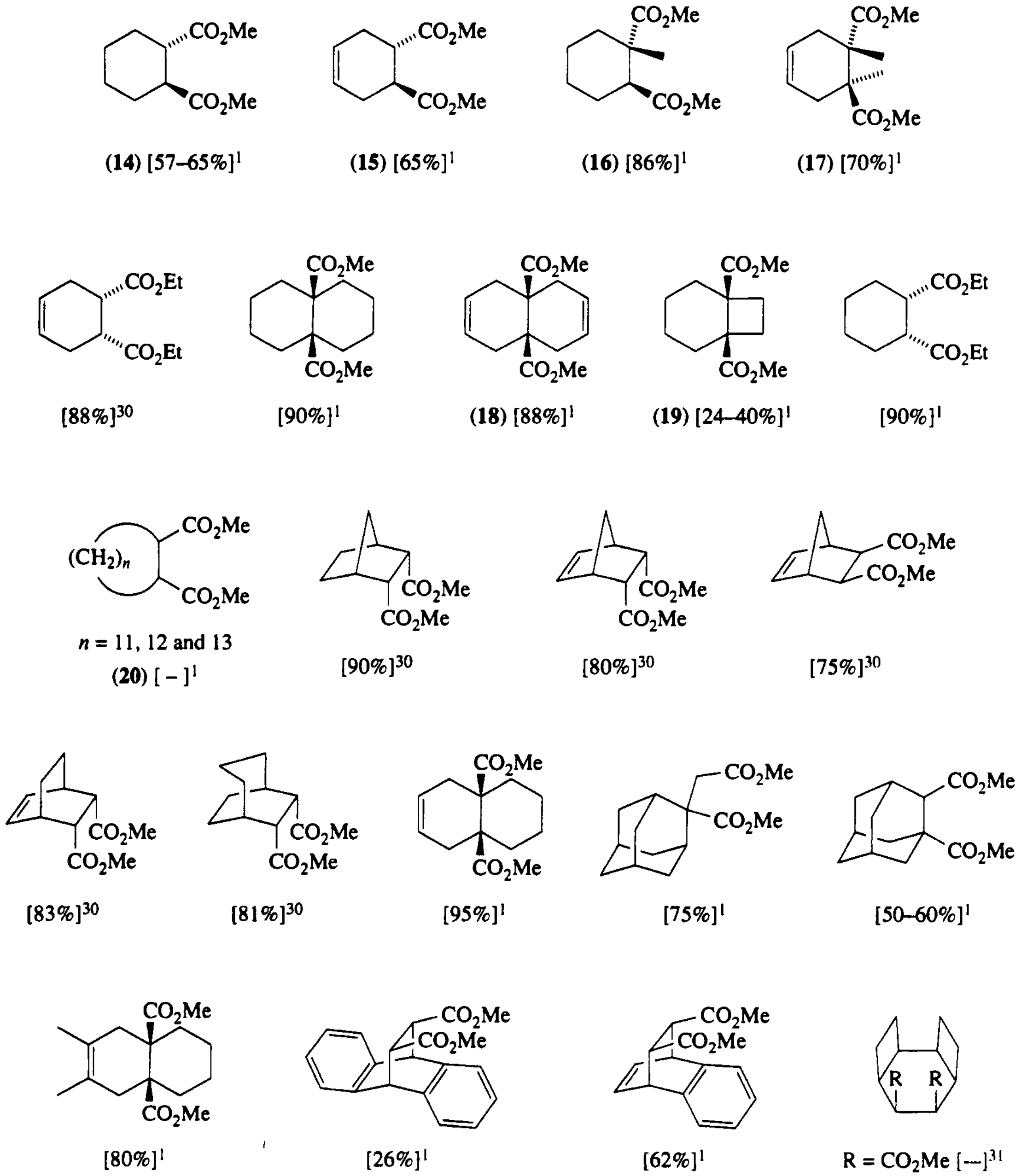
(14) [57–65%]1
(15) [65%]1
(16) [86%]1
(17) [70%]1
[88%]30
[90%]1
(18) [88%]1
(19) [24–40%]1
[90%]1
(CH2)n
n = 11, 12 and 13
(20) [ - ]1
[90%]30
[80%]30
[75%]30
[83%]30
[81%]30
[95%]1
[75%]1
[50–60%]1
[80%]1
[26%]1
[62%]1
R = CO2Me [—]31
CO2Me
CO2Et

**Figure 1** Vicinal diesters (in addition to those discussed in the text) which undergo the acyloin coupling reaction. Yields (in brackets), where quoted, and literature citations are given

The derivatives of dimethyl *trans*-cyclohexane-1,2-dicarboxylate (**14**–**17**) give trimethylsilyl enediol ethers which are thermally labile and undergo an electrocyclic ring opening to give a derivative of *cis*-*cis*-octa-1,3-diene.[1] The acyloin coupling can be accomplished using sodium–potassium alloy at room temperature; in refluxing toluene the monocyclic product is formed (Scheme 13).[1] The corresponding products from dimethyl *cis*-cyclohexanedicarboxylate are thermally stable at the boiling point of toluene.[1] With the medium-sized ring systems (**20**; *n* = 11, 12 or 13) a mixture of the *cis*- and *trans*-diesters was used. Owing to the larger ring size both the *cis*- and *trans*-trimethylsilyl cyclobutadienol ethers underwent thermal ring opening, at 140 °C, and hydrolysis then gave the medium ring α-diketones (Scheme 14).[1]

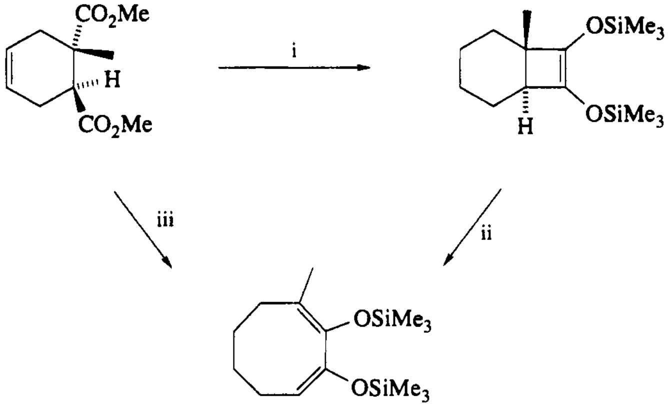

$CO_2Me$
H
$CO_2Me$
i
$OSiMe_3$
H
$OSiMe_3$
iii
ii
$OSiMe_3$
$OSiMe_3$

i, Na/K, $Me_3SiCl$, inert solvent, 20 °C; ii, Δ; iii, Na, $Me_3SiCl$, toluene, reflux

Scheme 13

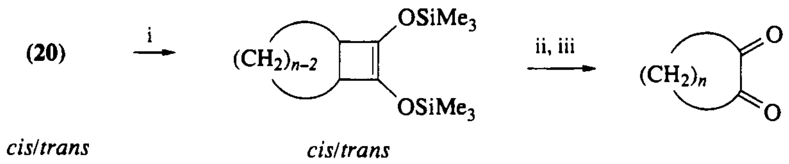

(20)
i
$(CH_2)_{n-2}$
$OSiMe_3$
$OSiMe_3$
ii, iii
$(CH_2)_n$
O
O
cis/trans
cis/trans

i, Na, xylene, $Me_3SiCl$; ii, 140 °C; iii, $H_3O^+$

Scheme 14

The diester (**18**) gives the trimethylsilyl enediol ether, a propellane, in 88% yield, using the preferred TMS-Cl trapping procedure,[1] although sodium–potassium alloy in benzene gives a 76% yield of the acyloin directly.[1]

The diester (**19**) with sodium and TMS-Cl in an inert solvent gives the trimethylsilyl enediol ether, another propellane, in only 24–40%, together with 58–40% of the silylated compound (**21**), formed by reductive cleavage of the central bond (**19**; Scheme 15).[1]

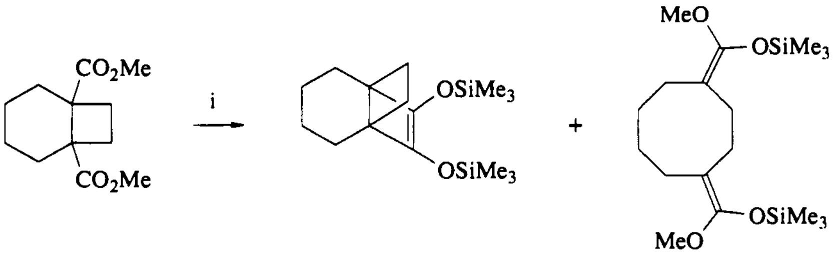

$CO_2Me$
$CO_2Me$
i
$OSiMe_3$
$OSiMe_3$
+
MeO
$OSiMe_3$
$OSiMe_3$
MeO

(**19**) (**21**)

i, Na, $Me_3SiCl$, inert solvent

Scheme 15

A combination of the alternative pathways illustrated in Schemes 13 and 15 explains why the derivative of dimethyl *trans*-cyclohexane-1,2-dicarboxylate (**22**) fails to give any of the silylated coupled enediol; even at 25 °C, using sodium–potassium alloy in benzene, thermal rearrangement to an octa-1,3-diene occurs, whereas use of sodium in liquid ammonia, at –78 °C, cleaves the bond joining the two functionalized carbon atoms, leading to dimethyl 2,7-dimethyloctane-1,8-dioate.$^{1}$

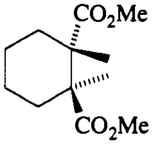

**(22)**

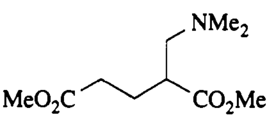

**(23)**

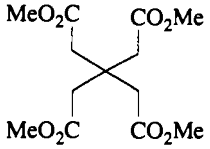

**(24)**

The vicinal diester (**1**) is one of a number of complex vicinal diesters investigated by Paquette and his coworkers,$^{6,32}$ which does not undergo the acyloin coupling reaction but rather undergoes bond cleavage as shown in Scheme 3. Other vicinal diesters which have been reported *not* to undergo the acyloin coupling reaction are shown in Figure 2.$^{1,33-35}$

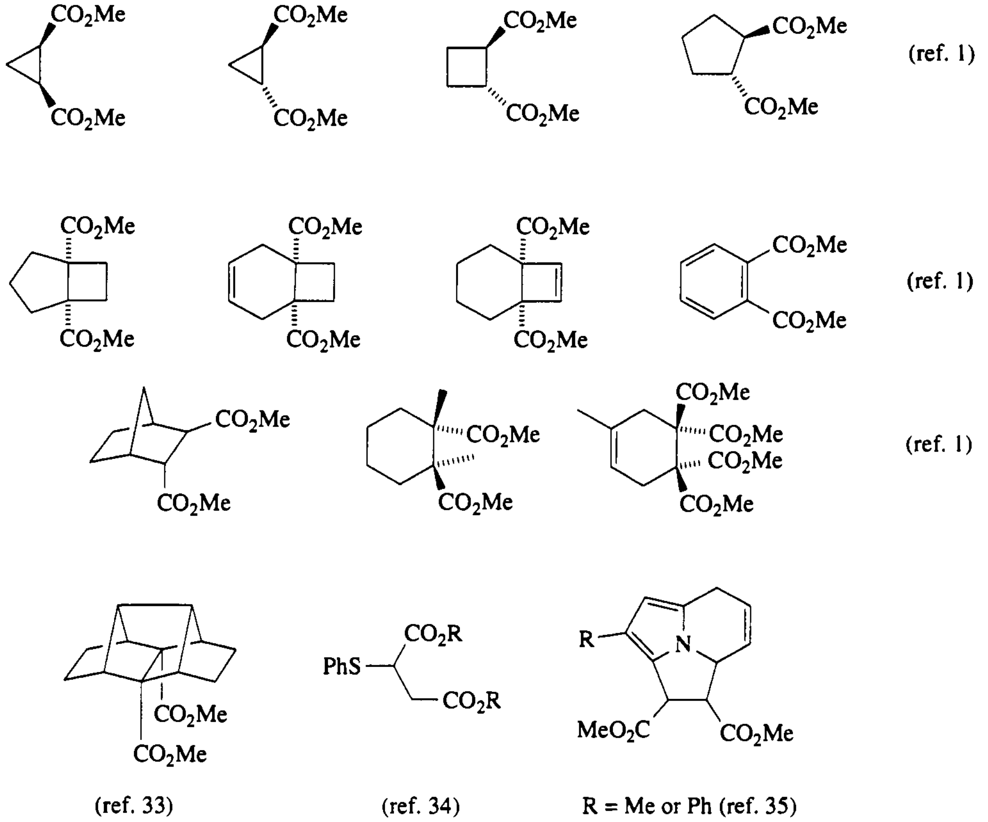

**Figure 2** Vicinal diesters (in addition to those discussed in the text) which fail to undergo the acyloin coupling reaction. References are given in brackets

The acyloin condensation has also been used to construct five-membered rings. Very high yields are obtained using trapping with TMS-Cl after carbon–carbon bond formation following reduction with sodium in toluene. The reaction is also reported to succeed using THF as the solvent.$^{15}$ Diethyl glutarate, labeled with $^{13}C$ at the 2- and 4-positions, gives the cyclic trimethylsilyl enediol ether in 94% yield.$^{36}$ Similarly 2-substituted glutarates, *e.g.* (**23**),$^{37}$ and 3,3-disubstituted glutarates$^{1,38}$ give excellent yields of the corresponding cyclic enediol silyl ethers, including spiro ring systems formed from 1,1-bis(methoxycarbonylmethyl)cycloalkenes$^{1,11}$ and the tetraester (**24**).$^{1,11}$ A further spiroannelation$^{39}$ is illustrated in equation (5). Acyloin coupling has also been applied to the elaboration of fused systems incorporating a

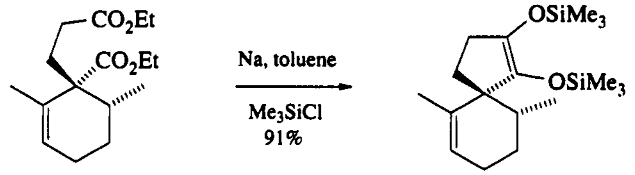
CO2Et
CO2Et
Na, toluene
Me3SiCl
91%
OSiMe3
OSiMe3

(5)

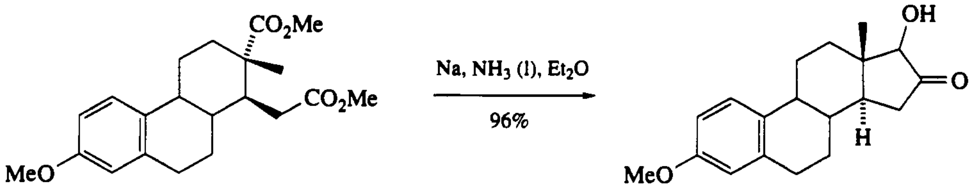
CO2Me
CO2Me
MeO
Na, NH3 (l), Et2O
96%
OH
O
H
MeO

(6)

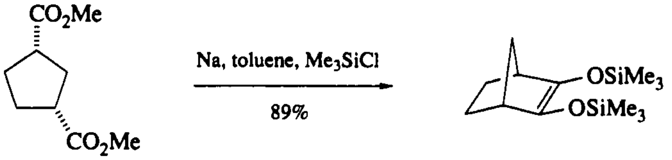
CO2Me
CO2Me
Na, toluene, Me3SiCl
89%
OSiMe3
OSiMe3

(7)

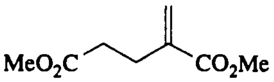
MeO2C
CO2Me

**(25)**

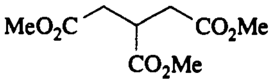
MeO2C
CO2Me
CO2Me

**(26)**

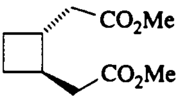
CO2Me
CO2Me

**(27)** [22%][1]

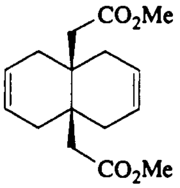
CO2Me
CO2Me

**(28)** [89–92%][1]

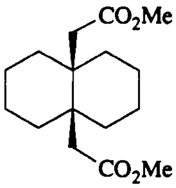
CO2Me
CO2Me

**(29)** [88–90%][1]

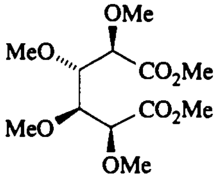
OMe
MeO
CO2Me
CO2Me
MeO
OMe

[51%][1]

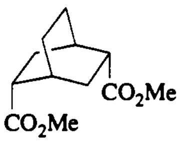
CO2Me
CO2Me

[ – ][1]

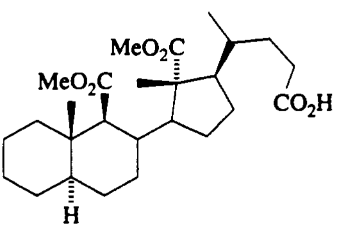
MeO2C
MeO2C
CO2H
H

[75–80%][1]

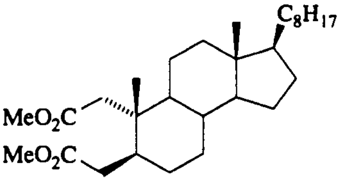
C8H17
MeO2C
MeO2C

[82%][1]

**Figure 3** Diesters (in addition to those discussed in the text) which give six-membered carbocyclic acyloins on reduction. Yields (in brackets), where quoted, and literature citations are given

five-membered ring. Earlier work, not using TMS-Cl trapping, has been summarized[1] and includes several examples using seco-steroidal diesters. A high-yielding example is shown in equation (6). A few examples using the more modern procedures have also been reported,[1,11] including the one shown in equation (7).

Two 1,3-diesters which are reported *not* to undergo acyloin coupling are the unsaturated ester (**25**)[37] and the triester (**26**).[1]

Six-membered rings can be made by the acyloin coupling reaction. Dimethyl 2,2,5,5-tetramethylhexane-1,6-dioate gives the corresponding acyloin in 91% yield on reduction with sodium and xylene,[1] but for dimethyl hexane-1,6-dioate itself a comparable yield is only achieved using a TMS-Cl trapping technique.[1] Some other diesters which give six-membered acyloins are shown in Figure 3. In the case of the diesters (**27**), (**28**) and (**29**), TMS-Cl trapping was used and the yields refer to the trimethylsilyl enediol ethers. A key step in the synthesis of corannulene was the acyloin coupling reaction shown in equation (8).[1] It was necessary to avoid any excess of sodium and to operate at the temperature of an acetone/solid carbon dioxide bath, to prevent reduction of the ester function in the product. Some work has been reported on the reduction by alkali metals of ester lactones in the diterpene field. Complex mixtures of products result. In the example illustrated in Scheme 16 products which are the cyclic hemiacetals of six-membered ring acyloins were isolated.[1] Two six-membered ring trimethylsilyl enediol ethers are produced in the acyloin coupling reaction of dimethyl 5-methylenenonane-1,9-dioate (**30**), as shown in equation (9). Their genesis must involve transannular bond formation after the initial coupling to give a nine-membered ring intermediate.[40]

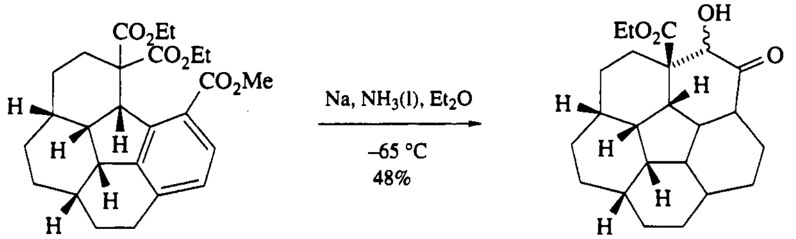

(8)

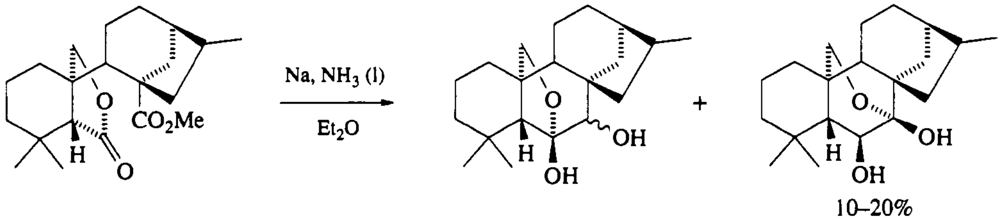

**Scheme 16**

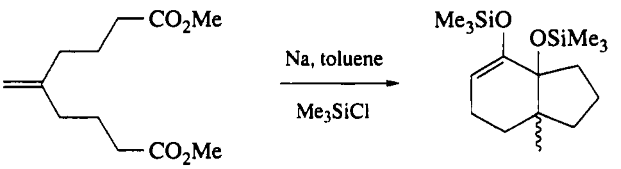

(9)

**(30)**

*cis*:*trans* 1:2.3

Attempts to bring about the acyloin coupling reaction with the diester (**31**) were unsuccessful.[41] The failure can be attributed to the severe nonbonded interactions between the two ester groups in the cisoid conformation required for coupling to occur.

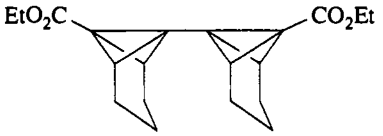

**(31)**

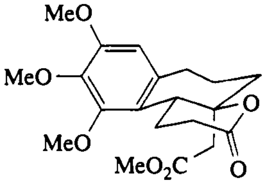

**(32)**

Examples of the formation of seven-membered rings by the acyloin coupling reaction are collected in Figure 4. The reduction of the ester lactone (32) to give an acyloin hemiacetal (*cf.* Scheme 16) in very low yield was reported as part of a synthetic route to colchicine.[1] In both these reductions of ester lactones, TMS-Cl trapping was not employed, and base-catalyzed β-elimination of the lactone oxygen would have been a competing process.

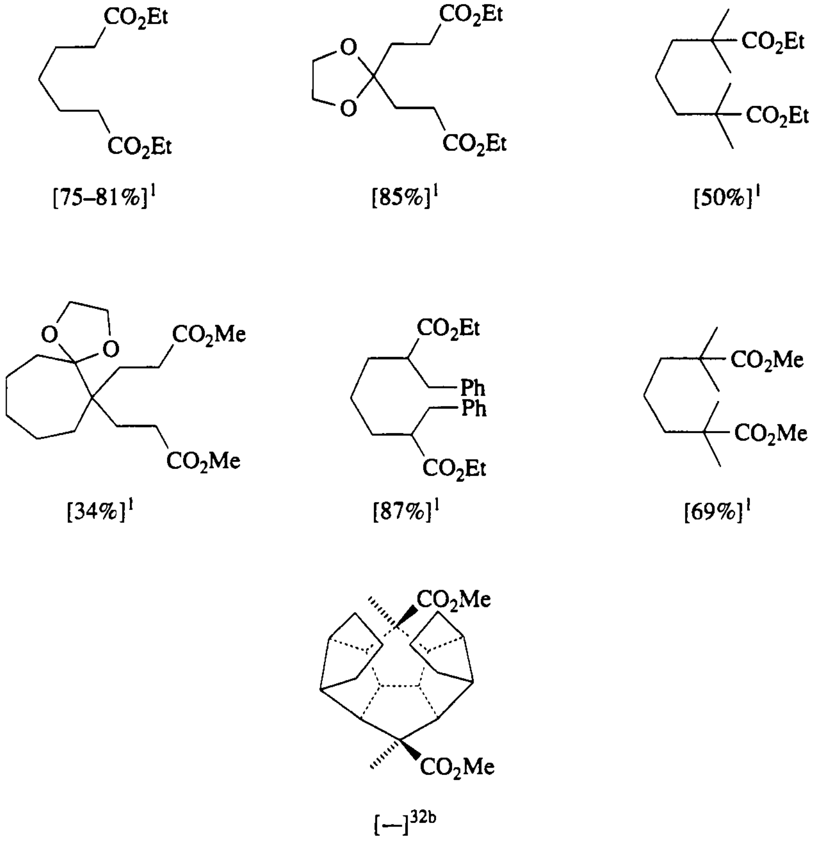
[75–81%][1]
[85%][1]
[50%][1]
[34%][1]
[87%][1]
[69%][1]
[—][32b]

**Figure 4** Diesters which give seven-membered carbocyclic acyloins on reduction. Yields (in brackets), where quoted, and literature citations are given

*(ii) Medium rings*

The yields in the Dieckmann and Thorpe–Ziegler cyclizations drop to almost zero for the production of nine- to twelve-membered rings. Fortunately the yields in the acyloin coupling reactions leading to the same ring sizes are quite good, making this procedure uniquely effective for the synthesis of medium-sized carbocyclic rings.

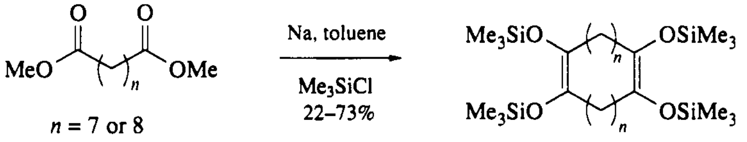

**Scheme 17**

The yields obtained in the preparation of medium-sized ring trimethylsilyl enediol ethers using TMS-Cl trapping and a high dilution strategy are shown in Table 1.[42] With rapid addition of the diester considerable dimer formation occurs (Scheme 17). The acyloin coupling reaction was earlier used without TMS-Cl trapping to prepare many eight-, nine-, ten- and eleven-membered cyclic acyloins directly, with yields in the range 24–97%.[1] For example (+)-dimethyl 2-methylnonanoate was converted into the (–)-form of the corresponding acyloin in 33% yield. Dimethyl decane-1,10-dioate behaves like a simple monocarboxylic ester in not undergoing the acyloin coupling reaction with sodium and TMS-Cl when the solvent is THF.[15] Medium-sized ring acyloins in which the ring is fused to a smaller ring have been prepared by applying the acyloin coupling reaction to the diesters (**33**) and (**34**). The product from (**33**) was obtained in 75% yield using sodium in xylene,[1] but the product from (**34**) was only obtained in a reasonable yield, of 36%, by using sodium in dioxane.[1] No coupling product could be obtained from the diastereomeric ester (**35**) under a variety of conditions.[1] In more complex systems a coupling reaction leading to an eight-membered ring[6] is shown in Scheme 3, and the reduction of the diester (**36**) provides a further example.[6] On the other hand the diester (**37**) failed to take part in the acyloin coupling reaction;[43] the failure was attributed to the severe nonbonded interactions which would arise as the two carbon atoms, which would have to be linked together, align themselves for the reaction. A polycyclic system incorporating eight- and nine-membered trimethylsilyl enediol ether rings is formed by the reaction shown in equation (10).[1] As part of a program leading to the synthesis of betweenanenes and triannulenes, Marshall has used the acyloin coupling reaction to prepare trimethylsilyl enediol ethers possessing two fused medium-sized rings with a *trans* double bond common to both rings (Scheme 18).[44]

**Table 1** Yields of Trimethylsilyl Enediol Ethers in the Acyloin Coupling Reactions of α,ω-Diesters Using High Dilution

| *Substance* | *Yield (%)* | *Substance* | *Yield (%)* |
|---|---|---|---|
| $MeO_2C(CH_2)_6CO_2Me$ | 72–85 | $MeO_2C(CH_2)_9CO_2Me$ | 48 |
| $MeO_2C(CH_2)_7CO_2Me$ | 68 | $MeO_2C(CH_2)_{10}CO_2Me$ | 68 |
| $MeO_2C(CH_2)_8CO_2Me$ | 58–69 | | |

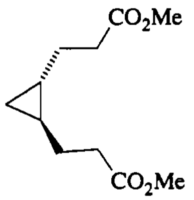

(**33**)

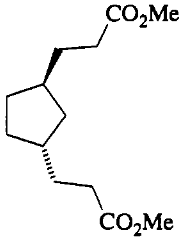

(**34**)

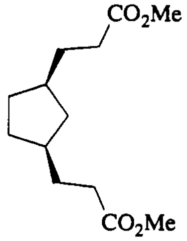

(**35**)

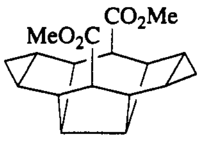

(**36**)

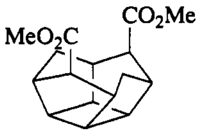

(**37**)

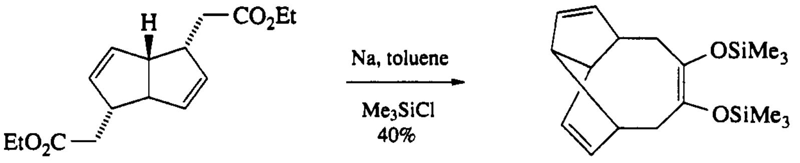

(10)

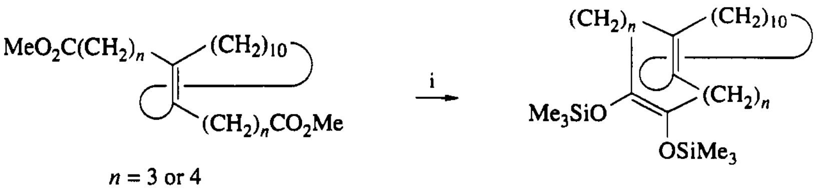

i, Na/K, xylene, $Me_3SiCl$, reflux

**Scheme 18**

### *(iii) Large Rings*

Even without the use of TMS-Cl trapping the acyloin coupling reaction was reported to give cyclic acyloins from dimethyl or diethyl esters of unsubstituted α,ω-diacids containing from 12 to 20 carbon atoms in yields of 64–96%.[1] Using TMS-Cl trapping, the cyclic trimethylsilyl enediol ethers are formed in similar yields;[1] for example, the cyclic trimethylsilyl enediol ethers containing 22 and 42 atoms in the ring are formed in *ca.* 90% yield, using sodium and toluene in the presence of TMS-Cl under argon.[45] An early route to paracyclophanes[1] completed the large ring by an acyloin coupling reaction using diesters containing two separated cyclohexane rings (equation 11); several of the yields were low, but moderate yields were obtained in other cases.[1] The presence of a (*Z*)-alkenic or an alkyne linkage near the center of a long chain α,ω-diester allows cyclic acyloins containing double or triple bonds to be constructed in good yield.[1] Similarly, a centrally placed ketone function, protected as a cyclic ethylene ketal, allows the synthesis of a large ring ketoacyloin.[1] The acyloin coupling reaction has also been performed with long chain α,ω-diesters with one or more alkyl branches.[1] An example of the synthesis of a 14-membered acyloin ring fused to a thiophene ring is illustrated in Scheme 4.

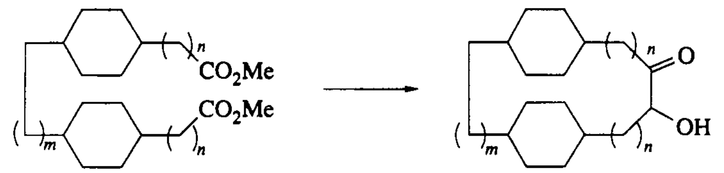

(11)

The acyloin coupling reaction, at high dilution, of the *cis* and *trans* forms of 1,9-bis(3-methoxycarbonylpropyl)cyclooctadecane was the key step in the synthesis of homeomorphic isomers of bicyclo[8.8.8]hexacosane.[1] The reaction of the *cis* isomer to give an acyloin, which was converted into the *in*, *in*-isomer of the hydrocarbon, is shown in equation (12).

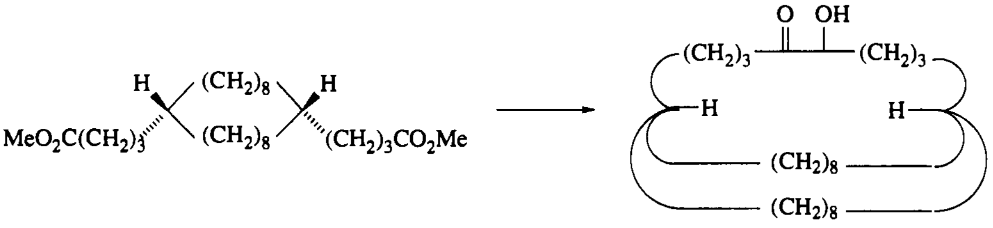

(12)

The first claim to have prepared a catenane was based on the use of the acyloin coupling reaction to prepare both the interlocking rings.[46] A pentadeuteriotetratriacontane was first prepared by chemical modification of the large ring acyloin obtained from diethyl tetratriacontane-1,34-dioate. A second acyloin coupling reaction in the presence of the deuterated hydrocarbon using diethyl tetratriacontane-1,34-dioate for the second time was then undertaken in the hope that some of the newly formed ring would interlock with the first ring.[46]

Other large ring acyloins have been prepared in connection with the preparation of rotaxanes, the acyloins forming the 'wheel' on the 'axle'. Using a slow addition technique dimethyl octacosane-1,28-dioate gave the acyloin in 78% yield.[47] Lower yields were earlier reported for the cyclization of diethyl pentacosane-1,25-dioate and diethyl hexacosane-1,26-dioate in the presence of molecules which might have led to rotaxanes, although no rotaxanes were detected.[1] The preparations of 30- and 32-membered cyclic acyloins, and of a mixture containing *every* cyclic acyloin with 14–42 carbon atoms in the ring, have also been reported.[1]

### *(iv) Paracyclophanes*

Early work on the use of the acyloin coupling reaction in the synthesis of paracyclophanes has been summarized by Smith.[48] The intramolecular coupling of diesters of the type (**38**),[1] (**39**)[1] and (**40**),[49] using sodium and xylene under conditions of high dilution, is generally successful, but some failures, *e.g.* with (**38**) and (**39**); *n* and/or *m* = 1, have been reported, largely attributable, in the absence of TMS-Cl trapping, to base-catalyzed side reactions. The only example of the use of TMS-Cl trapping seems to be the one shown in Scheme 19.[50]

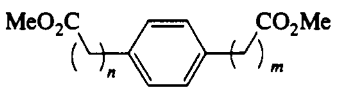

**(38)**

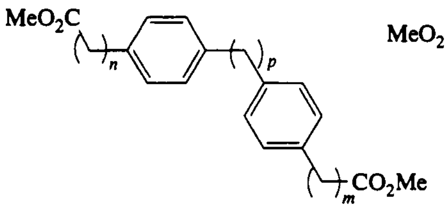

**(39)**

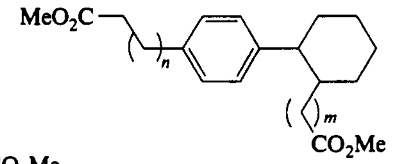

**(40)**

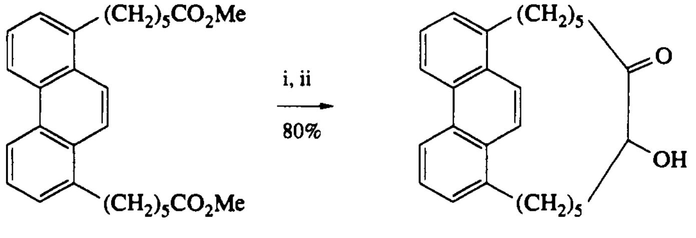

i, Na, toluene, $Me_3SiCl$; ii, $H_3O^+$

Scheme 19

### 2.7.6.2.2 *Heterocyclic systems*

The acyloin coupling reaction has been used to prepare cyclic acyloins with ring sizes from six to 23, in which one of the ring atoms is a nitrogen atom bearing an alkyl, cycloalkyl, or aryl substituent, as shown in equation (13). The use of TMS-Cl trapping may be advisable for the synthesis of azacyloheptane derivatives,[1,51] but in most cases good yields have been reported without the use of TMS-Cl, particularly with diesters possessing no hydrogen atoms $\alpha$ to the ester groups. The yield of the acyloin from the diester (**41**; R = Et) was only 10%, but its tetramethyl derivative (**42**) gave the acyloin in 83% yield. However, using TMS-Cl, trapping the diester (**41**; R = Me) gave the trimethylsilyl enediol ether in 74% yield. Similarly the lactone ester (**43**) gave yields of the acyloin (**44**) of 35–62%, but with TMS-Cl trapping, followed by hydrolysis, the yield was improved to 68%.[52] The diester (**45**) underwent the acyloin coupling reaction in the presence of highly dispersed sodium in xylene in 56% yield, and the product was converted into a 3-aza[10]paracyclophane.[53] The related diesters (**46**) and (**47**; *n* = 1 or 2) all failed to give an acyloin, even in the presence of TMS-Cl.[54]

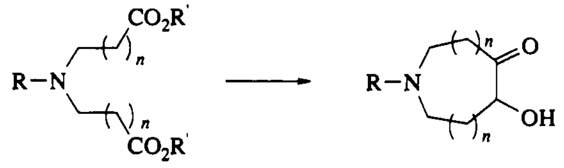

(13)

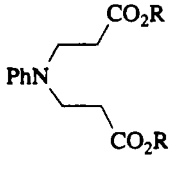

**(41)**

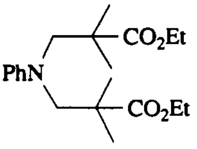

**(42)**

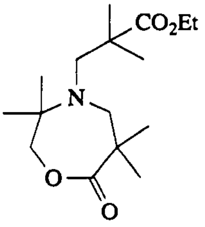

**(43)**

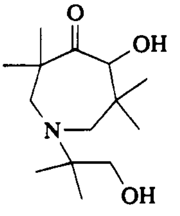

**(44)**

The acyloin coupling reaction has also been used to prepare cyclic acyloins in which one of the ring atoms is an oxygen, sulfur or silicon atom.[1] For seven- or eight-membered rings the use of TMS-Cl trapping may give improved yields.[1] An example is shown in Scheme 20.[1]

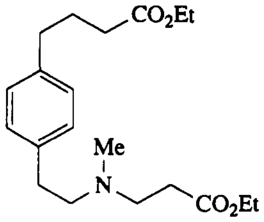

**(45)**

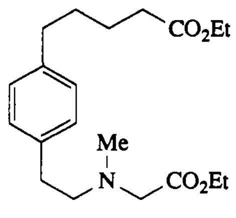

**(46)**

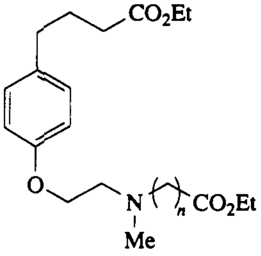

**(47)**

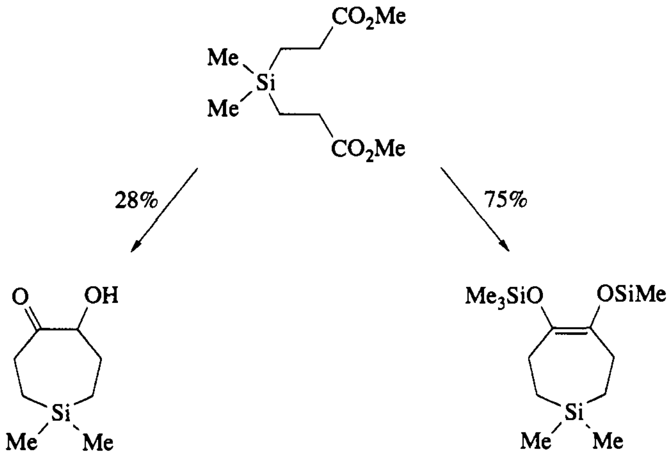

**Scheme 20**

Various acyloins which are 2,5-bridged thiophenophane derivatives have been prepared by the intramolecular coupling of the appropriate diesters; a typical example is given in Scheme 4. Attempts to effect the intramolecular acyloin coupling reaction with the benzoate-type diester (**48**) were unsuccessful under several standard conditions.[55]

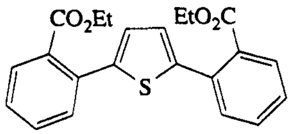

**(48)**

## 2.7.7 COUPLING REACTIONS BETWEEN ESTERS AND KETONES

Under conditions which have been used for the acyloin coupling reaction without TMS-Cl trapping, certain δ-keto esters, instead of undergoing intramolecular ester coupling to give diketoacyloins, give products derived by intramolecular coupling of the two carbonyl carbon atoms, and a five-membered carbocyclic ring is formed. In the few cases studied a mixture containing a range of functional groups was formed on reduction with sodium in ether–liquid ammonia or sodium naphthalenide in THF, and the method was not an attractive one.[1]

More recently a much superior and more generally applicable method for the intramolecular coupling of keto esters has been reported by McMurry.[56] The procedure leads to an enol ether, which can be isolated, but is normally hydrolyzed to a ketone (Scheme 21). McMurray used a heterogeneous coupling reagent formed by the action of lithium aluminum hydride on titanium(III) chloride in the presence of triethylamine in DME under argon. Recently titanium on graphite, produced by the action of the potassium–graphite intercalate on titanium(III) chloride, has been shown to give a higher yield in at least one case; no tertiary amine is necessary with this reagent, which was used in THF under argon employing a high dilution technique.[57] Table 2 lists the known examples of these coupling procedures; ring sizes of from four to 14 atoms have been prepared in this way. In the case of the keto ester (**51**), containing an

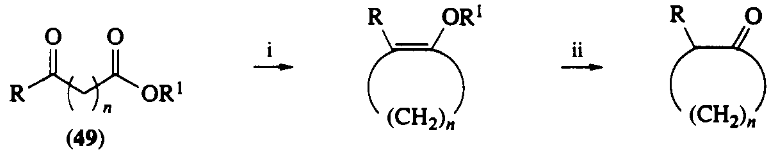

**(49)**

i, $TiCl_3$, $LiAlH_4$, $Et_3N$; ii, $H_3O^+$

**Scheme 21**

(*E*)-double bond, the product is the cyclic ketone **(52)** containing a (*Z*)-double bond.[58] The isomerization of the double bond is thought to be connected uniquely with the highly strained fused system which is being constructed, and the phenomenon is unlikely to be a general one.

**Table 2** Yields of Ketones from the Intramolecular Coupling of Keto Esters by the McMurry Method

| *Compound* | *R* | *R*$^1$ | *n* | *Ring size formed* | *Isolated yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| **(50)** | Bu$^t$ | Et | 1 | 4 | 57 | 56 |
| **(50)** | H | Et | 2 | 5 | 75 | 56 |
| **(50)** | H | Me | 3 | 6 | 91 | 57 |
| **(50)** | H | Et | 3 | 6 | 80 | 56 |
| **(49)** | Me | Et | 4 | 6 | 77 | 57 |
| **(50)** | H | Et | 4 | 7 | 82 | 56 |
| **(50)** | H | Et | 5 | 8 | 52 | 56 |
| **(50)** | H | Et | 6 | 9 | 50 | 56 |
| **(51)** | | | | 9 | 38 | 58 |
| **(49)** | Me | Me | 8 | 10 | 56 | 56 |
| **(49)** | Et | Me | 9 | 11 | 45 | 56 |
| **(49)** | Et | Me | 10 | 12 | 63 | 56 |
| **(49)** | Me | Me | 11 | 13 | 60 | 56 |
| **(50)** | H | Et | 11 | 14 | 54 | 56 |

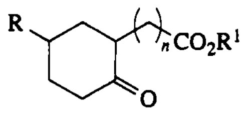

**(50)**

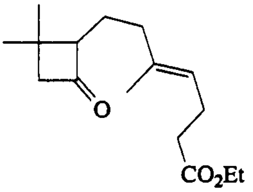

**(51)**

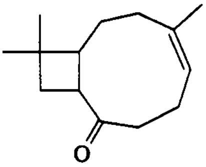

**(52)**

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# 2.8

# Kolbe Reactions

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## 2.8.1 INTRODUCTION AND HISTORICAL BACKGROUND

By anodic decarboxylation carboxylic acids can be converted simply and in large variety into radicals. The combination of these radicals to form symmetrical dimers or unsymmetrical coupling products is termed Kolbe electrolysis (Scheme 1, path a). The radicals can also be added to double bonds to afford additive monomers or dimers, and in an intramolecular version can lead to five-membered heterocycles and carbocycles (Scheme 1, path b). The intermediate radical can be further oxidized to a carbenium ion (Scheme 1, path c). This oxidation is favored by electron-donating substituents at the α-carbon of the carboxylic acid, a basic electrolyte, graphite as anode material and salt additives, *e.g.* sodium perchlorate. The carbocations lead to products that are formed by solvolysis, elimination, fragmentation or rearrangement. This pathway of anodic decarboxylation is frequently called nonKolbe electrolysis.

Faraday probably experienced in 1834 the first example of a radical dimerization by anodic decarboxylation, when he noticed an inflammable gas whilst studying the conductivity of acetate.[1] However, it took another 15 years until Kolbe in 1849 recognized the nature and dimensions of this conversion.[2] This way the name of the reaction was coined. In 1855 Wurtz obtained unsymmetrical coupling products, when he coelectrolyzed two different carboxylates.[3] Crum-Brown and Walker later opened a simple entry to α,ω-dicarboxylic esters, useful products for the synthesis of 1,*n*-difunctionalized alkanes or medium- and large-sized rings, when they electrolyzed half esters of 1,*n*-diacids.[4] In the 1950s and 1960s Weedon *et al.* extensively applied the Kolbe electrolysis to the synthesis of rare fatty acids and to acyclic natural products.[5]

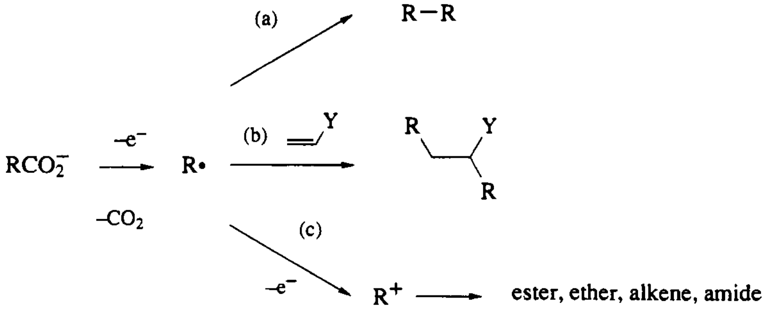

**Scheme 1**

Major contributions to the mechanism of the Kolbe electrolysis have been made by Conway *et al.*,[6] who mainly used electroanalytical techniques, and by Eberson[7] and Utley,[8] who drew their conclusions from the dependence of product structures on reaction conditions.

A large number of reactions have been published in the last 140 years on the Kolbe and nonKolbe electrolysis. Many of them have been compiled in reviews[5,6,9–15] and books.[8,16–23]

## 2.8.2 REACTION CONDITIONS FOR THE KOLBE ELECTROLYSIS

The pathway leading to radical products (Kolbe electrolysis) and/or cationic intermediates (nonKolbe electrolysis) is determined mainly by the substituents in the α-position of the carboxylic acid and some experimental factors.

The electrolysis products of different carboxylates have been compared with the ionization potentials of the intermediate radicals.[7c] From this it appeared that alkyl radicals with gas-phase ionization potentials smaller than 8 eV mainly lead to carbenium ions. Accordingly, α-substituents such as carboxy, cyano or hydrogen support the radical pathway, whilst alkyl, cycloalkyl, chloro, bromo, amino, alkoxy, hydroxy, acyloxy or aryl more or less favor the route to carbenium ions. Besides electronic effects, the oxidation seems also to be influenced by steric factors.[24] Bulky substituents diminish the extent of coupling. The main experimental factors that affect the yield in the Kolbe electrolysis are the current density, the pH of the electrolyte, ionic additives, the solvent and the anode material.

High current densities, together with high carboxylate concentrations favor the formation of dimers. This results from a high radical concentration at the electrode surface that supports the dimerization. Furthermore, at higher current densities a critical potential of 2.4 V (*versus* the normal hydrogen electrode) is reached,[25a] which seems to be a prerequisite for the Kolbe electrolyis, because at and above this potential the oxygen evolution and solvent oxidation is effectively suppressed.[6,26,27]

A weakly acidic medium favors the Kolbe electrolysis. Therefore the carboxylic acid is in most cases neutralized to an extent of only 2 to 5%. In an undivided cell the concentration of the carboxylate remains constant until near the end of the electrolysis, because when the carboxylate is converted at the anode it is continously regenerated from the carboxylic acid by the base formed at the cathode. The endpoint of the electrolysis is recognizable by a steep rise of the pH in the electrolyte. This procedure is called the salt-deficit method. The degree of neutralization can be as low as 0.5%. Low cell voltages, in spite of low conductivity, are obtained in these cases by using cells with a very small electrode distance (0.1 to 2 mm),[25b–28] as shown in the flow-through cell in Figure 1. Sometimes the carboxylic acid must be converted totally into the carboxylate to increase its solubility in aqueous solution or to achieve a uniform discharge in mixed Kolbe electrolysis, when the acidities of the two acids are too different. A mercury cathode is then applied, and the electrolyte stays neutral, because the alkali metal cations are discharged as amalgams.[29] In such cases a divided cell with a permselective ion-exchange membrane may also be suitable.

Temperature has only a minor effect on the Kolbe electrolysis. In the Kolbe coupling, temperatures higher than 50 °C should be avoided because they favor unwanted side reactions such as disproportionation or the esterification of the carboxylic acid.[30]

Ionic additives to the electrolyte can influence the Kolbe electrolysis in a negative way. Anions other than the carboxylate should be excluded, because they hinder the formation of a carboxylate layer at the anode, that seems to be a prerequisite for the decarboxylation. In the electrolysis of phenyl acetate the coupling to dibenzyl is totally suppressed when sodium perchlorate is present in concentrations of $5 \times 10^{-3}$ mol $l^{-1}$; benzyl methyl ether, the nonKolbe product, is formed instead.[24] This shift from the radical

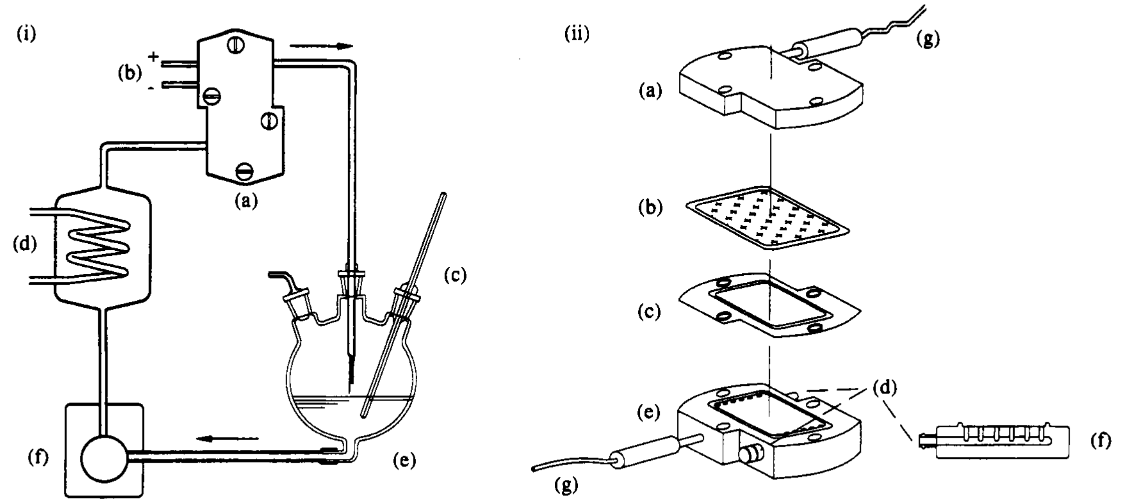

**Figure 1** (i) Flow-through cell and accessories: (a) cell; (b) electrical connection to regulated d.c. power supply; (c) thermometer; (d) heat exchanger; (e) vessel for gas outlet, sample withdrawal and temperature control; (f) circulation pump. (ii) Exploded view of the flow-through cell: (a) brass lid (10 mm); (b) platinum anode (0.01 × 30 × 60 mm); (c) silicon seal (0.5 mm); (d) electrolyte in/out; (e) V4A-steel base (cathode); (f) V4-A steel base (side view); (g,h) electrical connections

to the carbenium ion pathway can be rationalized by a partial obstruction of the anode surface by co-adsorption of perchlorate. That way the radical concentration at the electrode is lowered, which disfavors the bimolecular dimerization and supports an electron transfer from the radical to the electrode to form a carbenium ion.

Whilst cations such as $Fe^{2+}$, $Co^{2+}$, $Mn^{2+}$ and $Pb^{2+}$ lower the yield in the Kolbe electrolysis,[11] alkali and alkylammonium ions have no effect[31] and are therefore preferably used as counterions for the carboxylate.

Methanol is the solvent of choice for the Kolbe electrolysis.[5,32] The following electrolytes with methanol as solvent have been used: methanol/sodium carboxylate, methanol/sodium methoxide/carboxylic acid,[33,34] methanol/water/sodium hydroxide/carboxylic acid,[35] methanol/triethylamine/pyridine/carboxylic acid.[36] An increasing amount of water often decreases the yield of dimer.

Dimethylformamide is also a useful solvent;[37] its relatively low oxidation potential,[38] however, prevents its frequent application. The ternary system water/methanol/dimethylformamide has been systematically studied, when the electrolyses of ω-acetoxy- or ω-acetamido-carboxylic acids were optimized.[25b] Wet acetonitrile has also been used as solvent.[39] The influence of various solvents on the ratio of Kolbe to nonKolbe products is shown in Table 1.[40]

**Table 1** Anodic Decarboxylation[a] of Cyclohexanecarboxylic Acid in Different Solvents

| *Solvent* | *Bicyclohexyl:carbenium ion product*[b] |
|---|---|
| $H_2O$/MeOH (30% v/v)[c] | 0.97:1 |
| MeOH[c] | 1.76:1 |
| MeCN[d] | 2.26:1 |
| $HCONMe_2$[d] | 4.32:1 |

[a] Acid (0.78 M), neutralized to 25%; platinum anode, 0.25 A $cm^{-2}$. [b] Alcohol, ester, ether and acetamide according to solvent. [c] Sodium salt. [d] Tetrabutylammonium salt.

Other electrolytes that have been applied, are dimethyl sulfoxide/sodium hydride,[41] glycol methyl ether/water/potassium carbonate[42] or acetic acid/potassium carboxylate.[11]

As anode material, smooth platinum, as foil or net, is most widely used.[25b,26] In nonaqueous solvents, additionally, platinized titanium, gold, hard graphite[43] and ruthenium dioxide on titanium[44] have been employed. To keep the amount of the costly platinum low, the foils have been glued to a graphite support.[27] With vitreous or baked carbon in protic solvents (methanol, ethanol, water) dimer yields nearly comparable to those at platinum have been obtained.[36]

The nature of the cathode material is uncritical in the Kolbe electrolysis. The discharge of protons from the carboxylic acid is in most cases the only cathode reaction, which allows the convenient electrolysis in an undivided cell. For the electrolysis of unsaturated carboxylic acids, however, platinum as cathode material should be avoided, since cathodic hydrogenation can occur; in this case a steel cathode should be used instead.

In summary, good yields and selectivities in the Kolbe electrolysis are favored by the following experimental conditions: an undivided beaker-type cell is sufficient for most cases, it should be equipped with a smooth platinum anode of small size (area of 1 to 10 cm$^2$) to assure a high current density (0.25 A cm$^{-2}$ and higher) and a platinum, steel or nickel cathode in close distance; the current is provided by a regulated d.c. power supply (Figure 2); methanol is preferred as solvent, and the concentration of the carboxylic acid should be as high as possible. It is neutralized to an extent of 2 to 10% with sodium methoxide. A double-walled cell should be used to maintain temperatures between 10 to 45 °C by external cooling.

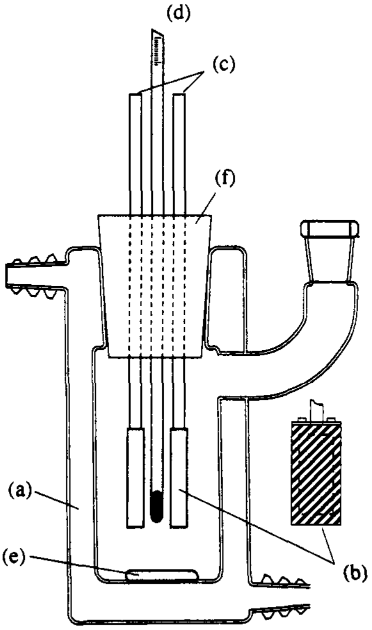

**Figure 2** Beaker-type cell: (a) double-walled cell; (b) platinum sheet or grid on teflon support; (c) electrode leads (steel rods) to d.c. power supply; (d) thermometer; (e) magnetic stirring bar; (f) teflon stopper

## 2.8.3 MECHANISM OF THE KOLBE ELECTROLYSIS

In the past, widely differing mechanisms have been proposed for the Kolbe electrolysis. The free-radical theory, which assumed acyloxy radicals as intermediates, was suggested by Crum-Brown and Walker.[45] According to Glasstone and Hickling[46] in aqueous solution hydroxyl radicals and hydrogen peroxide were formed, which converted the carboxylic acids into dimers and alcohols or esters, the so-called Hofer–Moest products.[47] Schall[48] and Fichter[16] proposed that the carboxylates are oxidatively coupled to diacyl peroxides, that subsequently decomposed. These mechanistic proposals have been reviewed.[49,50] The presently accepted mechanistic schemes have been reviewed,[6–8,51–54] and the general scheme summarized in Scheme 2 is assumed.

Current potential curves exhibit a critical potential at 2.1 to 2.4 V *versus* the normal hydrogen electrode. At this critical potential the coverage of the electrode with carboxylate increases sharply.[55] From electroanalytical data[55,56] it is deduced that at the critical potential, and higher, a rigid layer of adsorbed acyloxy or alkyl radicals is formed on top of the metal[7c,56,57] or metal oxide,[50] which inhibits oxygen evo-lution or solvent oxidation and promotes the Kolbe electrolysis.[6,7a,b,58] The oxide formation and the adsorption of intermediates during the Kolbe electrolysis have also been followed by modulated specular reflectance spectroscopy.[59] Examination of the electrode surface by polaromicrotribometry has indicated that at the critical potential a hydrophobic film is formed that seems to inhibit the oxygen discharge.[60] The rate-determining step for the Kolbe reaction is most probably an irreversible single electron transfer

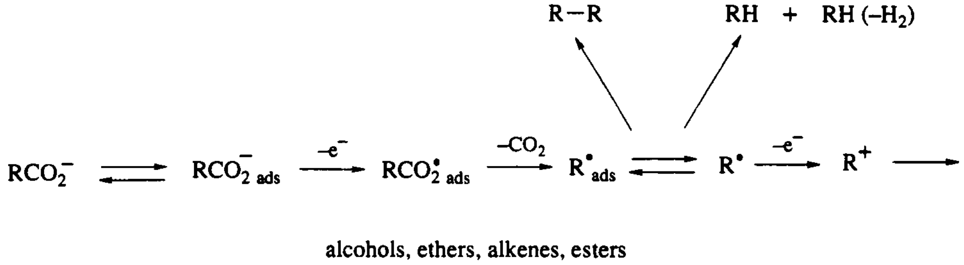

Scheme 2

from the carboxylate with simultaneous bond-breaking, leading to the alkyl radical and carbon dioxide.[7] The electroanalytical data have been interpreted in favor of a mechanism where adsorbed radicals couple.[6,61] On the other hand, the stereochemistry of the products and the regioselectivity of the coupling reaction indicates that adsorption of alkyl radicals plays a minor role. This is indicated by the dimers of cyanoalkyl radicals (**1**),[7] which can combine at carbon and/or nitrogen. Here the same ratios of carbon to carbon and carbon to nitrogen coupling products are obtained, irrespective of whether (**1**) is generated by photolytic or thermal decomposition of the corresponding azonitrile, by persulfate oxidation or electrolysis of α-cyanoacetic acid in different solvents. However, when azonitrile is adsorbed on silica the decomposition yields only the carbon to carbon coupling product. The radical (**4**; Scheme 3) can add to butadiene to yield 1,1-, 1,3- and 3,3-additive dimers. The reaction gives a further indication that adsorption is not involved. The same product ratio is found, independent of the formation of (**4**) either by anodic or persulfate oxidation of methyl malonate (**2**) or reductive cleavage of the hydroperoxide (**3**).[62]

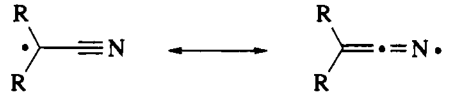

(**1**)

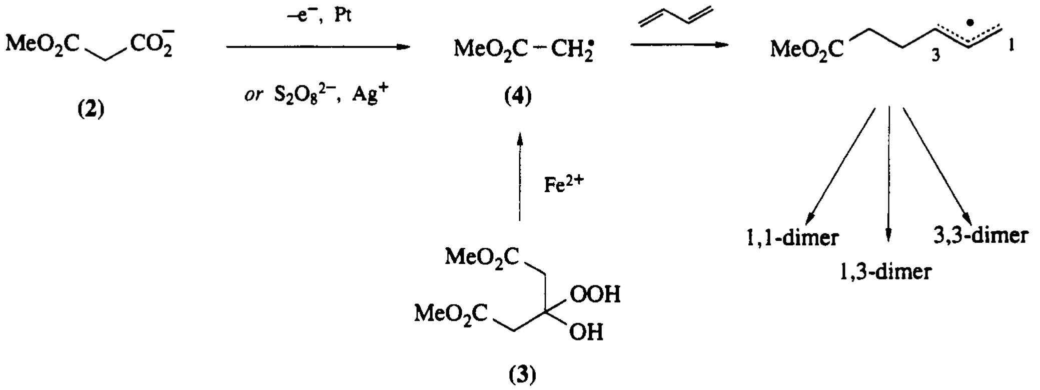

Scheme 3

Carboxylic acids, that bear an asymmetric center at C-2, lose all their optical activity in the Kolbe electrolysis.[63,64] This racemization can be interpreted as the result of a free radical or a fast equilibrium during desorption and adsorption at the electrode. A more detailed picture has been obtained by looking at the diastereoselectivity of the coupling of the cyclohexane- and cyclohexene-carboxylic acids (**5**)–(**9**).[65,66] The saturated acids (**5**) and (**6**) couple randomly, which indicated that the intermediate radicals in these cases are not significantly adsorbed. With the unsaturated acids (**7**)–(**9**) the ratio of dimers was not totally statistical, reflecting somewhat the different stabilities of the products. This result can be interpreted to be due to a more product-like transition state that indicates some adsorption of the unsaturated radical.

The intermediate radical can be further oxidized to form a carbenium ion, that undergoes solvolysis, rearrangement and elimination. This conversion is strongly influenced by the structure of the carboxylic acid, the electrolyte, the presence of foreign anions and the anode material (see Section 2.8.2). Besides

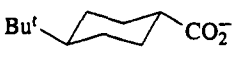

**(5)**

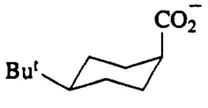

**(6)**

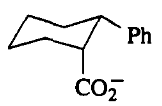

**(7)**

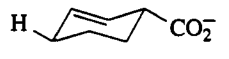

**(8)**

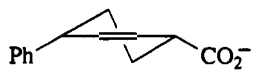

**(9)**

the dimerization or addition to double bonds (Sections 2.8.4–2.8.6) disproportionation products of the radicals are also found. The ratio of disproportionation to coupling seems to be higher in the electrolysis than in the homogeneous reaction.[67]

## 2.8.4 SYMMETRICAL COUPLING REACTIONS OF CARBOXYLIC ACIDS

The alkyl groups of two identical carboxylic acids can be coupled to symmetrical dimers in the presence of a fair number of functional groups (equation 1). Since free radicals are the reactive intermediates, polar substituents need not be protected. This saves the steps for protection and deprotection that are necessary in such cases when electrophilic or nucleophilic C—C bond-forming reactions are involved. Furthermore, carboxylic acids are available in a wide variety from natural or petrochemical sources, or can be readily prepared from a large variety of precursors. Compared to chemical methods for the construction of symmetrical compounds, such as nucleophilic substitution or addition, decomposition of azo compounds or of diacyl peroxides, these advantages make the Kolbe electrolysis the method of choice for the synthesis of symmetrical target molecules. No other chemical method is available that allows the decarboxylative dimerization of carboxylic acids.

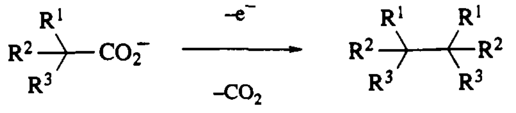

$$R^1R^2R^3C{-}CO_2^- \xrightarrow[-CO_2]{-e^-} R^1R^2R^3C{-}CR^1R^2R^3 \qquad (1)$$

$R^1, R^2, R^3$ = H, alkyl, arylalkyl

$R^1, R^2$ = H; $R^3$ = $CO_2Me$, $(CH_2)_nX$ (X = COR, $CO_2R$, $n \geq 1$; X = OAc, NHAc, Hal, $n \geq 4$)

A large number of different Kolbe dimerizations has been compiled.[8,10,19,20] Without attempting a complete coverage of the published reactions, the scope and limitations of the Kolbe electrolysis to afford symmetrical compounds are indicated in Table 2. In general, only the substituents at C-2 are critical for the yield of dimer. Electron-attracting groups (cyano, alkoxycarbonyl, carbonyl substituents) or hydrogen favor the radical coupling. Electron-donating substituents (two or three alkyl groups at C-2, phenyl, vinyl, halo, hydroxy or amino groups) on the other hand, more or less shift the reaction towards nonKolbe products. The experimental conditions that favor the radical coupling, namely high current density, slightly acidic electrolyte, platinum as anode material and no anions other than the carboxylate, have been treated in Section 2.8.2. The dimerization of two identical carboxylic acids has been used for the efficient synthesis of symmetrical natural products. Thus, the Kolbe electrolysis of **(10)** is the key step in a (+)-α-onocerin synthesis,[89] and by dimerization of **(11)** a pentacyclosqualene has been prepared.[90] An alkane with two quaternary carbon atoms has been obtained from **(12)**,[91] and 2,6,10,15,19,23-hexamethyltetracontane was accessible from **(13)**.[92]

For the preparation of long chain alkanes from fatty acids it is useful to extract the electrolyte continously with a high-boiling nonpolar solvent,[93] *e.g.* 2-methylheptane. Cyclopropanecarboxylic acids in some cases have been dimerized, *e.g.* **(14)**[94] or **(15)**;[34] in other cases the radical is further oxidized to a carbocation which then undergoes ring opening and solvolysis to allylic compounds. Specifically substituted 1,2-diphenylethanes have been prepared from phenylacetic acids (Table 2, entries 22 and 23). A variety of 2,3-disubstituted succinic acids and their derivatives have become accessible from malonic

**Table 2** Symmetrical Coupling Reactions of Selected Carboxylic Acids

| *Entry* | *Substituents in $R^1R^2R^3CCO_2^-$* | | | *Yield*[a] *of coupling product (%)* | *Ref.* |
|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | | |
| 1 | H | H | H | 93 | 5, 8 |
| 2 | Alkyl ($C_1$–$C_{17}$) | H | H | 30–90 | 5, 8 |
| 3 | Alkyl | Alkyl | H | 0–26 | 8 |
| 4 | $RO_2C(CH_2)_n$ | H | H | 40–95 | 5 |
| | $n$ = 3–15, R = Me, Et | | | | |
| 5 | Alkyl | $EtO_2C$ | H | 20–85 | 68, 69 |
| 6 | Alkyl | Alkyl | $EtO_2C$ | 15–35 | 68, 70 |
| 7 | Alkyl | CN | H, Alkyl | 30–60 | 71 |
| 8 | Alkyl | $CONH_2$ | H, Alkyl | 5–55 | 72 |
| 9 | AlkylCO | Alkyl, H | Alkyl, H | 32–40 | 73 |
| 10 | $MeCO(CH_2)_n$ | H | H | | |
| | $n = 1$ | | | 70 | 74 |
| | $n = 5$ | | | 63 | 75 |
| 11 | F, Br, Cl, I, OH, $NH_2$ | H | H | 0 | 5, 8, 76 |
| 12a | F | F | F | 93 | 56b, 77 |
| 12b | F | F | Cl | 43 | 78 |
| 13 | $X(CH_2)_n$ | H | H | | |
| | X = F, $n > 3$ | | | 45–70 | 79 |
| | X = Cl, $n$ = 1, 3, 4, 5, 7, 8, 9, 11 | | | 40–80 | 79, 80, 81 |
| | X = Br, $n$ = 4–11, 14 | | | 54–71 | 30a, 79 |
| 14 | $RO_2C(CF_2)_n$ | F | F | High yield | 82 |
| | $n$ = 0–3, R = Me, Et | | | | |
| 15 | $H(CF_2)_n$ | F | F | 40–86 | 83 |
| | $n$ = 3, 5 | | | | |
| 16 | $CF_3(C_2F_5)_2C$ | H | H | 75 | 84 |
| 17 | $MeCO_2(CH_2)_n$ | H | H | 70–83 | 25b |
| | $n$ = 2–5 | | | | |
| 18 | $MeCONH(CH_2)_4$ | H | H | 24–39 | 25b, 85 |
| 19 | Phthaloyl-$NCH(CO_2H)CH_2$ | H | H | 32 | 86 |
| 20 | 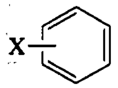 | H | H | | |
| | X = $p$-OMe to X = $F_5$ | | | <1–74 | 24 |
| 21 | Ph | Ph | H | 25 | 87 |
| 22 | 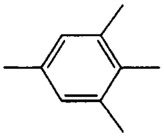 | H | H | 45 | 87 |
| 23 | 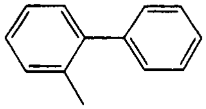 | H | H | 39 | 88 |

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[a] Electrolyses are normally performed at a platinum anode in water, methanol, ethanol or ethanol/water.

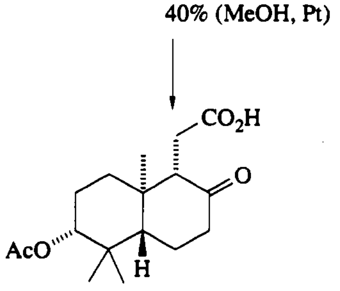
40% (MeOH, Pt)

**(10)**

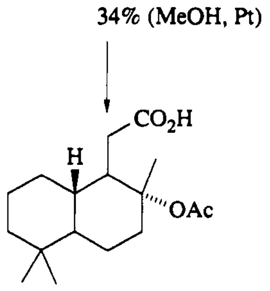
34% (MeOH, Pt)

**(11)**

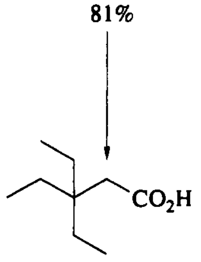
81%

**(12)**

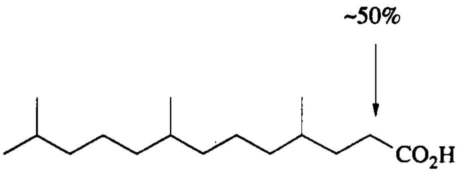

**(13)**

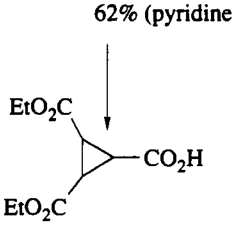

**(14)**

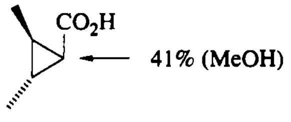

**(15)**

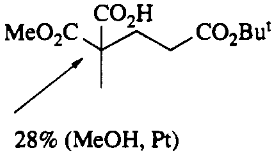

**(16)**

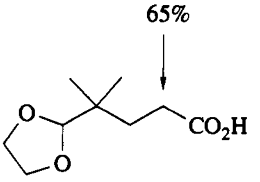

**(17)**

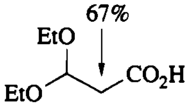

**(18)**

half esters, nitriles or amides (Table 2, entries 5–8). The anodic coupling of **(16)** has been used as part of a semibullvalene synthesis.[95]

The dimerization of half esters to 1,*n*-diesters is also called Brown–Walker electrolysis. Thereby valuable intermediates for the synthesis of medium-sized rings or 1,*n*-difunctionalized compounds can be prepared (Table 2, entry 4). This reaction is also of industrial interest since in this way sebacic acid can be prepared from adipic acid half ester.[96] This process has been scaled-up in Germany,[97] the USSR[98] and Japan,[99] and yields as high as 93% have been reported.[100] Reaction conditions and yields for the coupling of other half esters have also been studied in detail.[98] 1,*n*-Polyethylene- or polydifluoromethylene-dicarboxylic acids are reported to be formed by electrolysis of azelaic acid[101] or perfluoroglutaric acid.[102] Ketocarboxylic acids can be coupled to 1,4-, 1,6- or 1,14-diketones (Table 2, entries 9 and 10). Aldehydes must be dimerized in the form of their acetals to obtain good yields, as has been shown for **(17)**[103] and **(18)**.[104] The arrow on **(10)**–**(18)** indicates the location of dimerization, along with the yield and reaction conditions.

Carboxylic acids that carry a halide, hydroxy or amino group at C-2 generally cannot be dimerized (Table 2, entry 11). In the case of trifluoroacetic acid, however, high yields of hexafluoroethane are reported (Table 2, entry 12). When the halide substituent is more distant from the carboxyl group the dimer yields are in general good (Table 2, entry 13). The coupling of fluorocarboxylic acids has been investigated intensively (Table 2, entries 14–16) because of the interesting properties of the fluorohydrocarbons produced.

Hydroxy- and amino acids can be dimerized in good to moderate yields, provided the substituents are not at C-2 or C-3 and are additionally protected against oxidation by acylation (Table 2, entries 17–19). 2-Alkenoic acids cannot be dimerized, but lead to a severe passivation of the anode due to the formation of polymer films.[105] 3- and 4-alkenoic acids can be dimerized in moderate yields, when they are neutralized with tributyl- or triethyl-amine.[105] 3-Alkenoic acids, obtained from Stobbe condensations, can be dimerized in 14–30% yield; major side products arise from further oxidation of the allyl radical to its cation and subsequent solvolysis.[106] The 3-alkenoic acids dimerize to three isomeric 1,5-dienes (Scheme 4), that arise by 1,1′-, 1,3′- and 3,3′-coupling of the intermediate allyl radical.[107] By steric shielding of the 3-position the proportion of 3-coupling decreases. Depending on the bulkiness of the 3-substituent, the relative yield of the 1,1′-dimer can vary from 52 to 73% (Table 3). The configuration of the double bond is retained to a high degree.[107a]

In the case of 6-alkenoic acids the intermediate 5-hexenyl radical cyclizes to a cyclopentylmethyl radical in a 5-*exo-trig* cyclization (Scheme 5; see also Section 2.8.6)[107a,108,109] In some cases double bond migration has been observed. This can be avoided, however, when the electrolyte is prevented from becoming basic by using a mercury cathode. (*Z*)-4-Enoic acids isomerize partially to the corresponding (*E*)-isomers. The products from methyl- and deuterium-labeled carboxylic acids indicate that this isomerization occurs *via* a reversible ring closure to cyclopropylcarbinyl radicals. (*Z*)-Enoic acids where the double bond is more distant from the carboxylic acid group retain totally their configuration.[109] A key step in a perhydrophenanthrene synthesis involves the dimerization of **(19)** by Kolbe electrolysis.[110]

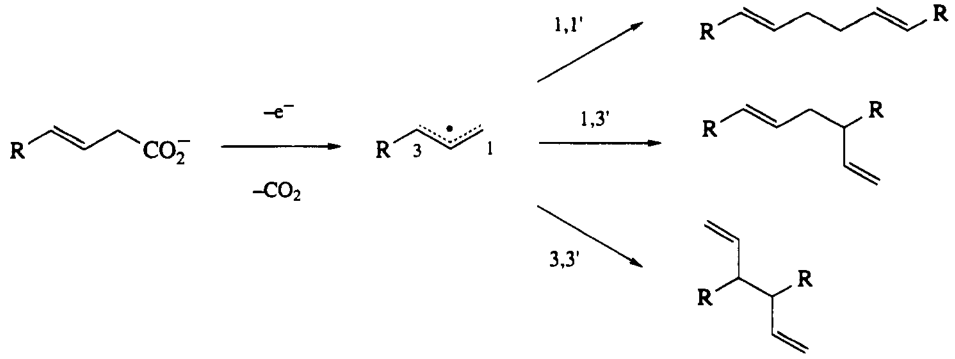
–e⁻
–CO2
R
CO2⁻
3
1
1,1'
1,3'
3,3'

**Scheme 4**

**Table 3** Yields in the Kolbe Dimerization of 3-Alkenoic Acids[107b]

| *Carboxylic acid*[a] | *Product distribution (%)* *1,1′* | *1,3′* | *3,3′* | *Yield (%)* |
|---|---|---|---|---|
| $Me(CH_2)_7CH{=}CHCH_2CO_2^-$ | 52 | 39 | 9 | 67 |
| $Me_2CHCH{=}CHCH_2CO_2^-$ | 59 | 41 | — | 79 |
| $Me_3CCH{=}CHCH_2CO_2^-$ | 60 | 40 | — | 15 |
| 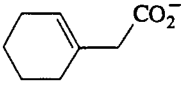 | 60 | 40 | — | 45 |
| $Me_2CH{=}CHCH_2CO_2^-$ | 65 | — | 36 | 42 |
| 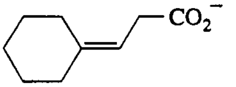 | 76 | 24 | — | 29 |

[a] 10–150 mmol were dissolved in 25–100 mL methanol, neutralized to 8–50% with triethylamine and electrolyzed in an undivided cell at platinum electrodes at 400–800 mA cm$^{-2}$ with change of polarity of the electrodes until pH = 8 was reached.

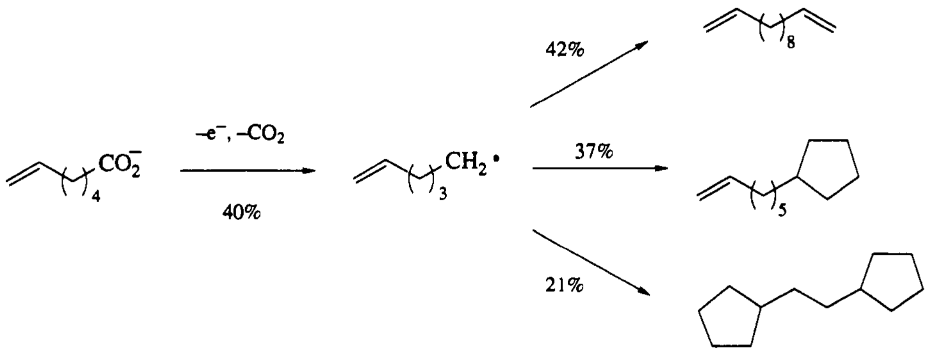
–e⁻, –CO2
40%
42%
37%
21%
CO2⁻
CH2•
4
3
8
5

**Scheme 5**

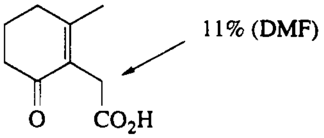
11% (DMF)
O
CO2H

**(19)**

In unsaturated carboxylic acids, where the oxidation of the double bond is facilitated by alkyl substitution, the double bond rather than the carboxylic group is oxidized, and a lactone is formed (Scheme 6).[111]

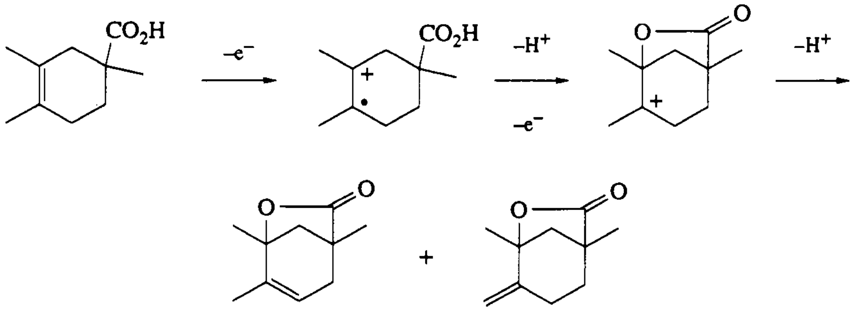

**Scheme 6**

Other alkenoic acids that have been coupled without change of the double bond configuration are oleic acid (24% yield of dimer), elaidic acid (44%)[112] and erucic acid.[113]

### 2.8.4.1 Experimental Procedure for Symmetrical Kolbe Electrolysis — Preparation of Dimethyl Hexadecanedioate

A solution of 55 g (0.27 mol) of methyl azelate in 350 mL methanol, neutralized to the extent of 6% with KOH in methanol, is electrolyzed in a flow-through cell (Figure 1) at 35–40 °C at a cell voltage of 40 V between a platinum anode (area = 17 $cm^2$) and a steel cathode at a current density of 200 mA $cm^{-2}$ until 1.2 F $m^{-1}$ were consumed. The methanol is then evaporated, and the residue is dissolved in 500 mL ether and extracted with a saturated aqueous $NaHCO_3$ solution (3 × 100 mL) and subsequently washed with water. After drying ($MgSO_4$) and removal of the ether, fractionated distillation affords at b.p. 107–113 °C/0.02 Torr, 34.14 g (80%) dimethyl hexadecanedioate.[113] For the preparation of dimethyl decanedioate from methyl adipate see ref. 114.

## 2.8.5 CROSS-COUPLING REACTIONS OF DIFFERENT CARBOXYLIC ACIDS

Cross-coupling reactions of two carboxylates with different alkyl groups by anodic decarboxylation (mixed Kolbe electrolysis) is an electrochemical method that allows the synthesis of unsymmetrical compounds (Scheme 7).

$$4R^1CO_2H + 4R^2CO_2H \xrightarrow[-CO_2]{-e^-} 4R^1\bullet + 4R^2\bullet \longrightarrow R^1{-}R^1 + 2\,R^1{-}R^2 + R^2{-}R^2$$

**Scheme 7**

A disadvantage of this reaction is the statistical coupling of the intermediate radicals. This results in the additional formation of two symmetrical dimers as major side products. However, by taking the less costly acid in excess the number of products is lowered to two, the unsymmetrical product and one symmetrical dimer. When the chain length of the two acids is properly chosen, the two products can usually be separated by distillation. Furthermore, the more costly acid is incorporated to a major extent into the mixed dimer. The calculated yields for mixed couplings are listed in Table 4, and the experimental results for the coupling of methyl azelate with pentanoate are shown in Table 5.[113]

When one of the two acids is used in excess and the acidity of the two acids differs strongly, the salt-deficit method should be used with caution, as one of the acids might be preferentially converted into the carboxylate. In such a case it is useful to neutralize both acids completely.

For the selective preparation of unsymmetrical coupling products on a small scale, the photolysis of peroxides is a favorable alternative to the mixed Kolbe electrolysis. By photolysis of unsymmetrical diacyl peroxides at –60 to –70 °C in the solid state two different alkyl groups can be joined selectively.[115]

**Table 4** Calculated Theoretical Yields for Mixed Coupling Reactions Products $R^1$—$R^2$

| Ratio $R^1CO_2H$ | $R^2CO_2H$ | Yield of $R^1$—$R^2$ (%)[a] |
|---|---|---|
| 1 | 1 | 50 |
| 1 | 2 | 66 |
| 1 | 4 | 80 |
| 1 | 6 | 86 |
| 1 | 8 | 89 |

[a] Calculated according to Yield (%) = $100n/(1+n)$ with $1{:}n$ as ratio of $R^1CO_2H{:}R^2CO_2H$.

**Table 5** Yield of Methyl Dodecanoate in the Cross-coupling Reactions of Methyl Azelate and Valerate[113]

| Ratio $HO_2C(CH_2)_7CO_2Me$ | $Me(CH_2)_3CO_2H$ | Yield of $MeO_2C(CH_2)_{10}Me$ in MeOH (%) |
|---|---|---|
| 1 | 2 | 56 |
| 1 | 4 | 72 |
| 1 | 8 | 83 |

Problems with passivation, that is, the coverage of the anode with insulating films which increase the cell voltage, or with the competitive oxidation to carbenium ions, are often less pronounced in crossed coupling.[113,116]

The mixed Kolbe electrolysis has turned out to be a widely used synthetic method, despite its disadvantage that at least one symmetrical dimer is formed as major side product, which has to be separated and which consumes a greater part of the coacid. Crossed Kolbe electrolyses have been used for the efficient synthesis of rare fatty acids and related compounds, of pheromones and of chiral building blocks. Weedon *et al.* during the 1950s and 1960s did much of the pioneering work in these type of syntheses.[5] Selected examples from the numerous reactions that have been published are compiled in Tables 6 and 7 and in the formulae (**20**)–(**39**). In some of the formulae the end-product of several transformations is shown; the bond formed in the mixed Kolbe electrolysis is marked by an arrow and the yield is indicated. Further examples of crossed couplings can be found in refs. 8 and 12.

**Table 6** Cross-coupling Reactions by Kolbe Electrolysis of Unsubstituted (A) with Substituted Carboxylic Acids (B)

| Carboxylic acids A—$CO_2H$ | B—$CO_2H$ | Yield of cross-coupling product (A—B) (%) | Ref. |
|---|---|---|---|
| $Me(CH_2)_6CO_2H$ | $MeO_2C(CH_2)_4C{\equiv}C(CH_2)_4CO_2H$ | 23 | 117 |
| $Me(CH_2)_{14}CO_2H$ | $Me_2CHCO_2H$ | 40 | 118 |
| $Me(CH_2)_5CO_2H$ | ($E$)-$Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ | 37 | 118 |
| $CD_3CO_2H$ | $CF_3CO_2H$ | 68 | 119 |
| $CD_3CO_2H$ | $CF_3CF_2CO_2H$ | 75 | 119 |
| $MeCO_2H$ | $HC{\equiv}C(CH_2)_8CO_2H$ | 36 | 120 |
| $MeCH_2CO_2H$ | $Ph(CH_2)_2CO_2H$ | 44 | 121 |
| $Me(CH_2)_3CO_2H$ | $MeO_2C(CH_2)_7CO_2H$ | 69 | 113 |
| $Me(CH_2)_5CO_2H$ | $MeO_2C(CH_2)_7CO_2H$ | 61 | 113 |
| $Me(CH_2)_2CO_2H$ | $MeO_2CCH(OCOMe)CO_2H$ | 29 | 122 |
| $Me(CH_2)_2CO_2H$ | $MeCO(CH_2)_4CO_2H$ | 62 | 123 |
| Methylhexadecanoic acid | $MeO_2C(CH_2)_4CO_2H$ | 42 | 124 |
| $Me(CH_2)_8CO_2H$ | $MeO_2C(CH_2)_4CO_2H$ | 38 | 125 |
| $Me(CH_2)_2CO_2H$ | $MeO_2CCH_2CHMeCH_2CO_2H$ | 30 | 126 |
| 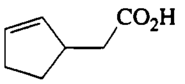 | $MeO_2C(CH_2)_{11}CO_2H$ | 30 | 127 |
| $Bu^t(CH_2)_2CHMeCH_2CO_2H$ | $MeO_2CCH_2CHEtCH_2CO_2H$ | 15 | 128 |
| $Me(CH_2)_{10}CO_2H$ | $MeO_2CCH(OMe)CH_2CO_2H$ | 21 | 129 |
| $Me(CH_2)_7CHMeCH_2CO_2H$ | $MeO_2C(CH_2)_7CO_2H$ | 30 | 130 |
| $Me(CH_2)_mCO_2H$<br>$m = 8$–16, 18 | $MeO_2C(CH_2)_nCO_2H$<br>$n = 4, 7, 8, 12$–20 | — | 131 |
| $Me_2CHCH_2CO_2H$ | $Et_2C(CO_2Et)CO_2H$ | 38 | 132 |

**Table 7** Cross-coupling Reactions by Kolbe Electrolysis of Substituted Carboxylic Acids (A) with Substituted Carboxylic Acids (B)

| *Carboxylic acids* | | *Yield of cross-coupling product (A—B) (%)* | *Ref.* |
|---|---|---|---|
| *A—$CO_2H$* | *B—$CO_2H$* | | |
| $CH_2{=}CH(CH_2)_2CO_2H$ | $MeO_2C(CH_2)_{10}CO_2H$ | 68 | 133 |
| $Me_2CHCH{=}CHCH_2CO_2H$ | $MeO_2C(CH_2)_nCO_2H$<br>$n = 1, 2, 4$ | Good | 134a |
| (*Z*)-$MeO_2C(CH_2)_2CH{=}CH(CH_2)_2CO_2H$ | $Me(CH_2)_2CO_2H$ | 30 | 134b |
| $CH_2{=}CH(CH_2)_8CO_2H$ | $MeO_2C(CH_2)_2CO_2H$ | 52 | 134c |
| $RC{\equiv}C(CH_2)_3CO_2H$<br>R = Et, Pr, Bu | $MeO_2C(CH_2)_nCO_2H$<br>$n = 2, 3, 4, 6$ | 45–59 | 135 |
| (*Z*)-$Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ | $MeO_2C(CH_2)_2CO_2H$ | 15–20 | 136 |
| $CF_3CF_2OCF_2CO_2H$ | $MeO_2C(CF_2)_nCO_2H$<br>$n = 1–3$ | 24–34 | 137 |
| $CF_3OCF_2CF_2CO_2H$ | $MeO_2C(CF_2)_nCO_2H$<br>$n = 1–3$ | 24–34 | 137 |
| $CF_3CO_2H$ | $MeO_2CCH_2CO_2H$ | 46 | 138 |
| $Br(CH_2)_{10}CO_2H$ | $MeO_2C(CH_2)_7CO_2H$ | 50 | 113 |
| $Br(CH_2)_{10}CO_2H$ | $EtO_2C(CH_2)_8CO_2H$ | 54 | 139 |
| $Br(CH_2)_{10}CO_2H$ | $MeO_2C(CH_2)_4CO_2H$ | 37 | 30b |
| $AcO(CH_2)_4CO_2H$ | $EtO_2C(CH_2)_{10}CO_2H$ | 27–32 | 140, 141 |
| $Me_3SiCH_2CO_2H$ | $MeO_2C(CH_2)_nCO_2H$<br>$n = 4, 7$ | 71–76 | 142 |
| $MeO_2C(CH_2)_{11}CO_2H$ | $MeO_2C(CH_2)_4CO_2H$ | — | 143 |
| $MeO_2C(CH_2)_{10}CO_2H$ | $MeO_2C(CH_2)_4CO_2H$ | — | 144 |
| $MeO_2C(CF_2)_nCO_2H$<br>$n = m = 1–4$ | $MeO_2C(CF_2)_mCO_2H$ | 25–38 | 82 |
| $MeCO(CH_2)_2CO_2H$ | $MeCO(CH_2)_4CO_2H$ | 31 | 145 |
| $MeCO(CH_2)_8CO_2H$ | $MeO_2C(CH_2)_4CO_2H$ | 32 | 146 |

Tables 6 and 7 contain the syntheses of esters of trialkylacetic acids, specifically deuterated carboxylic acids, of branched acids, of enoic and ynoic acids, of ω-halo-, acetoxy- or trimethylsilyl-carboxylic acids, of perfluorinated 1,*n*-diacids, of keto esters and of diketones.

Crossed coupling has also been applied to the extension of the carbon chain in fatty acids. Extension by two carbon atoms is achieved with succinate half esters,[120,147–149] whereby separation problems can be simplified by using the benzyl half ester.[148a] Expansion by the propane unit has been accomplished with methyl glutarate,[150] by the isoprene unit with ethyl 3-methyladipate,[151] by four carbons with methyl adipate,[112] by the pentane unit with methyl pimelate,[152] and by six carbon atoms with methyl suberate.[153]

A variety of pheromones have been prepared in few steps using the crossed coupling reaction. Muscalure (**20**), the pheromone of the housefly, becomes available from the natural pool of unsaturated fatty acids, namely oleic or erucic acid.[154–156] The synergist of muscalure, (*Z*)-11-heneicosene (**21**), was similarly prepared.[155] Methyl (*Z*)-4-octenedioate, which is accessible from (*Z*,*Z*)-1,5-cyclooctadiene by partial ozonolysis, is a valuable starting acid to prepare (**22**),[134b] a precursor of the cabbage looper pheromone, or disparlure (**23**),[157] the sex attractant of the gypsy moth. The optically active *Trogoderma* pheromones (*E*)- and (*Z*)-(**24**) have been synthesized using 4-pentynoic acid and (*S*)-citronellic acid as precursor from the chiral pool.[158] Alkatrienes (**25**), which are sex attractants of certain *Lepidoptera*, become accessible in a one step synthesis using linolenic acid from the pool of polyunsaturated fatty acids.[159] Compound (**26**), the pheromone of the German cockroach *Blattela germanica*, was obtained from 3-methyl heneicosanoic acid.[160] The bromide (**29**), which is an important intermediate for the synthesis of natural α-tocopherol has been synthesized starting from (*R*)-(+)-citronellic acid.[161] The coelectrolysis of (*Z*)-4-nonenoic acid with methyl glutarate provided an alternative approach to looplure (**31**),[162] the pheromone of the Cabbage looper. Similarly the pheromone of the fruit pest insect *Dacus cucurbitae* (**32**)[163] and of the false codling moth (**33**)[164] became accessible by crossed coupling. Brevicomin (**34**), the sex attractant of the western pine beetle, became available in a short route by mixed Kolbe electrolysis of (*E*)-3-hexenoic acid with levulinic acid.[165] Besides (**23**), a number of other compounds have been prepared by successive cross couplings. (±)-Tuberculostearic acid (**27**) has been obtained in two consecutive Kolbe electrolyses from 2-methylsuccinate.[166] 10,16-Dimethylicosanoic acid (**28**) was synthesized in three subsequent Kolbe electrolyses.[147] The alkane (**30**) with three quaternary carbon atoms was prepared in two successive crossed couplings.[91] Pure (*E*)- or (*Z*)-configurated unsaturated pheromones are accessible by mixed coupling with 5-alkynoic acids and subsequent selective hydrogenation (Table 7).[135] The mixed Kolbe electrolysis of protected L- or D-glutamic acids provides access to dicarba analogs of cystine peptides (**35**).[167] Enantiomerically pure β-hydroxybutyric acid derivatives have been converted into the useful chiral building blocks **(36)**–**(38)**.[168] Chiral γ-lactones **(39)** could be obtained from (*R*)-3-cyclohexene-1-carboxylic acid.[169]

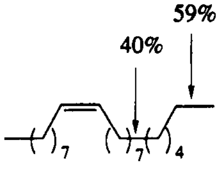

**(20)**

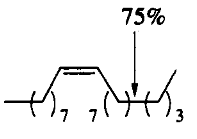

**(21)**

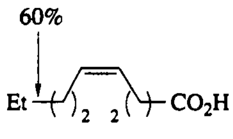
60%
Et
2
2
CO2H

**(22)**

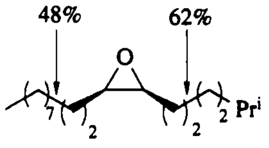
48%
62%
O
7
2
2
2
Pri

**(23)**

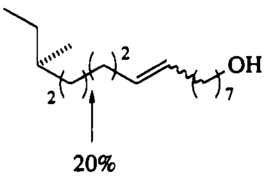

**(24)**

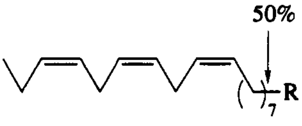

**(25)** R = Et, Prⁿ, Buⁿ

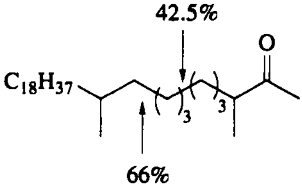
42.5%
O
C18H37
3
3
66%

**(26)**

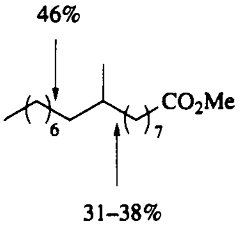
46%
CO2Me
6
7
31–38%

**(27)**

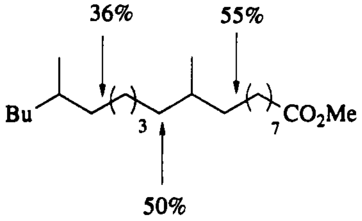
36%
55%
Bu
3
7
CO2Me
50%

**(28)**

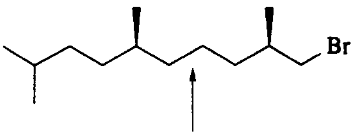

**(29)**

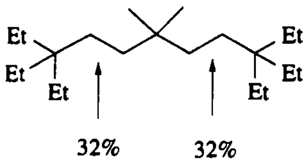
Et
Et
Et
Et
Et
Et
32%
32%

**(30)**

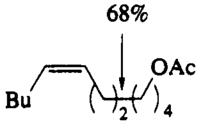

**(31)**

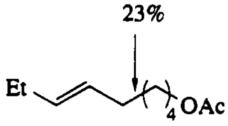

**(32)**

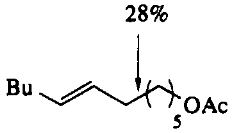

**(33)**

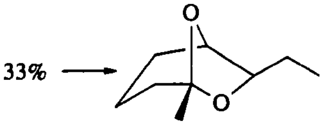

**(34)**

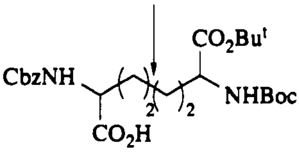
CO2But
CbzNH
NHBoc
2
2
CO2H

**(35)**

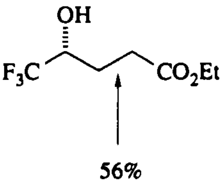
OH
F3C
CO2Et
56%

**(36)**

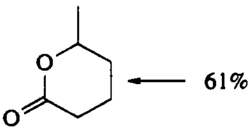

**(37)**

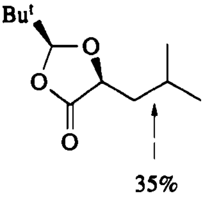

**(38)**

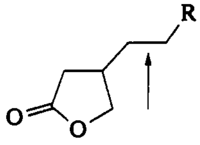

**(39)** R = Me, high yield; R = $C_8H_{17}$, 21%

### 2.8.5.1 Experimental Procedure for Mixed Kolbe Electrolysis — Preparation of 11-Hexadecynoic Acid

In a beaker-type cell (Figure 2) equipped with two platinum electrodes (area 10 $cm^2$, thickness 0.05 mm, supported on a teflon frame), a solution of 14.3 mmol 5-decynoic acid and 86 mmol methyl suberate in 40 mL methanol, neutralized to 5% with KOH, was electrolyzed at 22 °C and a current density of 100 mA $cm^{-2}$, provided from a regulated d.c. power supply, until a pH of 8–9 was reached. After evaporation of the methanol the crude product was refluxed with equimolar amounts of KOH in 100–200 mL methanol for 24 h; thereafter the mixture was evaporated to dryness and extracted with petroleum ether. The remaining salt was dissolved in water, acidified with 15% HCl, and continuously extracted with petroleum ether. The precipitated tetradecanoic dicarboxylic acid (72%, m.p. 126 °C) was filtered off, and after evaporation of the petroleum ether 8.43 mmol (59%) 11-hexadecynoic acid was isolated by bulb to bulb distillation; m.p. (from pentane) 40–41 °C.[135]

## 2.8.6 ADDITION OF KOLBE RADICALS TO DOUBLE BONDS

The radicals generated by anodic decarboxylation of carboxylic acids can be intercepted by alkenes that are present in the electrolyte. The adduct radical can couple with the radical generated from the carboxylate to form an additive monomer I (Scheme 8 path a), it can dimerize to form an additive dimer II (path b), it can be further oxidized to a cation, which reacts with a nucleophile to form III (path c), or it can disproportionate (path d).

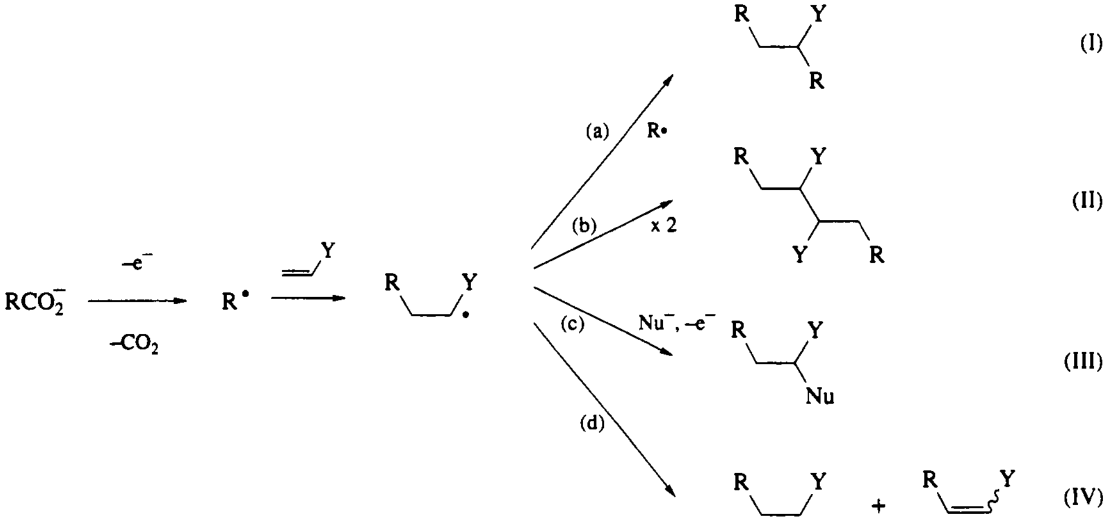

Scheme 8

As the reactive intermediates in electrolyses are confined to narrow reaction layers in front of the electrode, the radical concentration is much higher there than in homogeneous radical reactions. Therefore the propagation step of a polymerization is suppressed and the termination step leading to products I and II predominates. The products I and II appear to be exclusive products of electrolysis.

The high radical concentration at the anode, on the other hand, favors the dimerization of the radical generated from the carboxylate, which leads in the case of less reactive alkenes, like cyclohexene or 2-methylpropene (Table 8, entry 11), to low yields of adducts and the predominant formation of Kolbe dimers. With reactive alkenes (butadiene, isoprene, styrene) the yields of adducts are in general good (Table 8, entries 1–10). However, in the case of unreactive ethylene high adduct yields have also been claimed (Table 8, entry 12). Higher yields are found in the reaction of nucleophilic radicals with electrophilic alkenes (Table 8, entries 17–22) or *vice versa* (Table 8, entries 23–27). The ratio of additive monomer I Scheme 8 to additive dimer II can be controlled to some extent by the current density. High current densities aid the formation of I, low ones that of II (Table 8, entries 4 and 5). These results can be interpreted according to Scheme 8. When high current densities prevail, which correspond to high radical concentrations in the reaction layer, the alkene can trap only some of the radicals generated from the carboxylate (Kolbe radicals). This leads to their preferred combination with the primary adduct leading to I and their dimerization to the Kolbe dimer. At low current densities, on the other hand, the major proportion of the Kolbe radicals are trapped by the alkene, which leads to a preferential formation of II.

In the addition of Kolbe radicals to 1,3-dienes allyl radicals are intermediates, that can then couple to form 1,1′-, 1,3′- and 3,3′-dimers (Scheme 9). In general, the reactivity of the allyl radical is two to three times higher at C-1 than at C-3, so that the 1,1′-dimer predominates.[170] Besides the examples given in Table 8, further additions of Kolbe radicals to dienes can be found in refs. 33, 179 and 191.

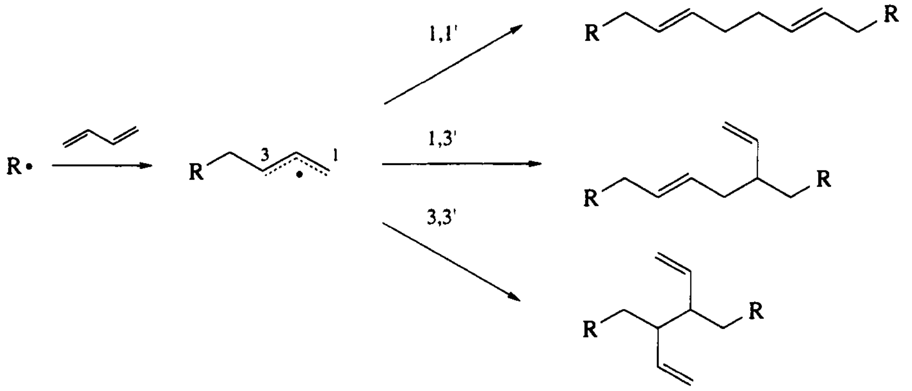

Scheme 9

The addition of the 5-pentanoate radical from methyl adipate to butadiene has been intensively investigated, because in this way long chain 1,*n*-diacids are easily accessible; a total yield of 96% has been claimed for this reaction (Table 8, entry 7). Different Kolbe radicals from acetic acid, monochloroacetic acid, trichloroacetic acid, oxalic acid, methyl adipate and methyl glutarate have been added to ethylene, propylene, fluoroalkenes and dimethyl maleate.[177] In this detailed study the influence of current density, alkene type and alkene concentration on the product yields and product ratios have been discussed.

In some cases reactive alkenes can be polymerized with Kolbe radicals as initiators, *e.g.* styrene,[176] acrylonitrile,[176] vinyl acetate,[192] methyl acrylate,[192] acrylic acid,[193] acrylamide[194] or vinyl chloride.[193] The addition of Kolbe radicals to pyridine,[195] benzotrifluoride or benzonitrile[196] affords only low yields.

The addition of alkyl radicals to less reactive alkenes becomes more efficient if the addition is conducted intramolecularly. The Kolbe electrolysis of $\Delta^{6,7}$- and $\Delta^{7,8}$-unsaturated carboxylates produces five- and six-membered rings in a 5- or 6-*exo-trig*-cyclization.[108] Such a cyclization was first observed by Weedon[107] and later studied in more detail.[109] By intramolecular addition of appropriate precursors, 3-substituted tetrahydrofurans (Scheme 10; **40**, 41%),[197] pyrrolidines (**41**, 53%),[198] and cyclopentanes (**42**, 74%), and (**43**, 75%)[199] are obtained. In the reactions leading to cyclopentanes the extent of cyclization

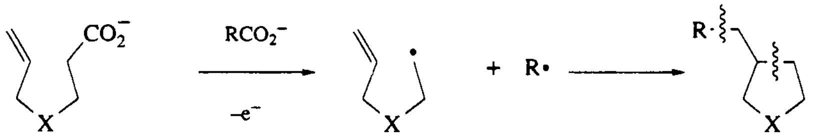

X = O, NCOR, $CMe_2$

Scheme 10

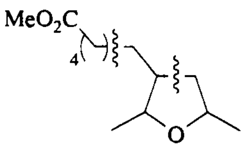

**(40)**

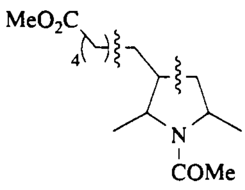

**(41)**

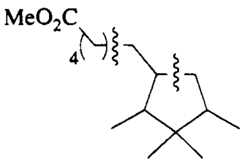

**(42)**

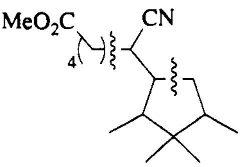

**(43)**

**Table 8** Addition of Kolbe Radicals to Alkenes

| *Entry* | *Carboxylic acid* | *Alkene* | *Yield of additive monomer (%)* | *Yield of additive dimer (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | $MeO_2CCH_2CO_2H$ | Styrene | 4 | 38$^a$ | 170 |
| 2 | $MeO_2CCH_2CO_2H$ | Butadiene | 17 | 18 | 170 |
| 3 | $MeO_2CCH_2CO_2H$ | Isoprene | 1 | 43 | 170 |
| 4 | $EtO_2CCO_2H$ | Butadiene ($i = 0.025$ A cm$^{-2}$) | 4 | 66 | 170, 171 |
| 5 | $EtO_2CCO_2H$ | Butadiene ($i = 0.66$ A cm$^{-2}$) | 15 | 8 | 170 |
| 6 | $EtO_2CCO_2H$ | Isoprene | 8 | 59 | 170 |
| 7 | $MeO_2C(CH_2)_4CO_2H$ | Butadiene | 48 | 48 | 172, 173 |
| 8a | $HO_2CCO_2H$ | Butadiene | — | 20 | 174 |
| 8b | $HO_2CCO_2H$ | 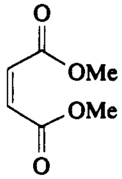 | 62 | 34 | 175 |
| 9 | $MeO_2CCH_2CO_2H$ | α-Methylstyrene | — | 46$^b$ | 107b |
| 10 | $MeCO_2H$ | Styrene |  | 15 | 176 |
| 11 | $EtO_2CCO_2H$ | Isobutene | 9 |  | 170 |
| 12 | $MeCO_2H$ | $CH_2=CH_2$ | ≈70 |  | 177 |
| 13 | $Cl_3CCO_2H$ | $CH_2=CH_2$ | — | — | 178 |
| 14 | $HO_2CCO_2H$ | $CH_2=CH_2$ | 25 | 46 | 177 |
| 15 | $MeO_2C(CH_2)_4CO_2H$ | $CH_2=CH_2$ | 15 |  | 177 |
| 16 | $MeCO_2H$ | $Bu^tCH=CH_2$ | 46 | — | 179 |
| 17 | $MeCO_2H$ | $CH_2=CMeCHO$ | — | 80 | 180 |
| 18 | $MeCO_2H$ | $CH_2=CHCO_2Et$ | — | 70 | 180 |
| 19 | $MeCO_2H$ | 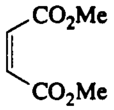 | 21–high | — | 181, 182 |
| 20 | $PhCH_2CO_2H$ | 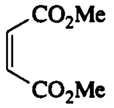 | 24 | — | 183 |
| 21 | $MeCO_2H$ | 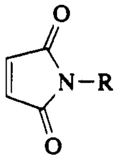<br>R = Et, Ph | 80–88 | — | 182, 183 |
| 22 | $RCO_2H$, R = Me, Et, Bu$^i$ | $PhSO_2CH=CH_2$ | 37–69 |  | 184 |
| 23 | $CF_3CO_2H$ | $MeC(OAc)=CHCO_2C_8H_{17}$ | 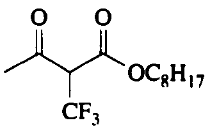<br>64 | 185 |  |
| 24 | $MeO_2CCH_2CO_2H$ | $CH_2=CHOEt$ | — | 35 | 186 |
| 25 | $CF_3CO_2H$ | 1-Pentene | — | 40 | 187 |
| 26 | $CF_3CO_2H$ | $CH_2=C(Me)OAc$ | 18$^a$ |  | 188 |
| 27 | $CF_3CO_2H$ | 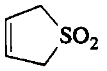 | 31 | — | 189 |
| 28 | $CF_3CO_2H$ | $CH_2=CHCO_2Me$ | 5 | 50 | 187 |
| 29 | $CF_3CO_2H$ | $CH_2=CHCO_2H$ | 17 | 28 | 138 |
| 30 | $CF_3CO_2H$ | $CH_2=CHCF_3$ |  | 40 | 177 |
| 31 | $CF_3CO_2H$ | $CHF=CF_2$ |  | 30 | 177 |

**Table 8** Addition of Kolbe Radicals to Alkenes (*continued*)

| *Entry* | *Carboxylic acid* | *Alkene* | *Yield of additive monomer (%)* | *Yield of additive dimer (%)* | *Ref.* |
|---|---|---|---|---|---|
| 32 | $CF_3CO_2H$ | 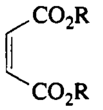<br>R = Me, Et | 30<br>41 | 10<br>27 | 177<br>189 |
| 33 | $CF_3CO_2H$ | 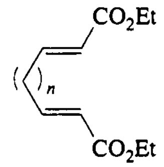<br>*n* = 0–3 | 4–42 | | 190 |

[a]Additional 16% disproportionation product. [b]6% Product type IV, Scheme 8.

can be considerably increased by lowering the current density (300 mA cm$^{-2}$, ratio of cyclized:uncyclized product = 32:35; 10 mA cm$^{-2}$ ratio = 74:8). The intramolecular cyclization has also been applied to the stereoselective synthesis of a prostaglandine precursor (equation 2).[200] The bonds formed in the Kolbe radical reactions are shown in (**40**)–(**43**).

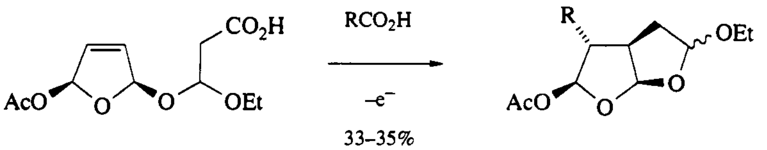

(2)

R = Me, $(CH_2)_2CO_2Me$

Compared to chemical radical cyclizations,[201] the ring closures *via* Kolbe radicals have the advantage that here two carbon–carbon bonds can be joined in one step, whilst in the majority of chemical alternatives only one carbon–carbon bond is formed. Furthermore electrolysis avoids the toxic tributyltin hydride, that is usually needed as initiator or reagent in chemical radical cyclizations.

## 2.8.7 THE NONKOLBE ELECTROLYSIS

Besides the aforementioned Kolbe dimers, alcohols, esters or ethers can become the major products in the electrolysis of carboxylic acids. These results have suggested that in anodic decarboxylation the intermediate radicals were further oxidized to carbocations that yielded solvolysis and elimination products.[202] This part of the anodic decarboxylation, which leads to carbenium ions, is frequently called nonKolbe electrolysis. Applications of the nonKolbe electrolysis to synthesis and to mechanistic investigation of carbocations are summarized in refs. 8, 19, 20 and 23 .

The oxidation of carboxylates to radicals (Scheme 2) has to be extended by the additional steps, shown in Scheme 11. The radical is further oxidized to a carbocation, which can solvolyze to ethers, alcohols or esters, can lose a proton to form an alkene or can undergo rearrangement or solvolysis prior to those reactions.

The formation of alcohols or ethers is favored by low current densities,[8,24] porous graphite as anode material,[203–205,206b] a solvent such as water/pyridine[206] instead of methanol, a pH of the electrolyte above 7 and anions, such as bicarbonate, sulfate or perchlorate, as additives.[24] Electron-donating substituents at C-2 of the carboxylic acid favor the oxidation of the intermediate radical. Thus α-alkyl, α-cycloalkyl[207,208] α-chloro,[209] α-bromo, α-amino, α-alkoxy, α-hydroxy, α-acyloxy and α,α-diphenyl substituents more or less promote the formation of nonKolbe products.

The nonKolbe electrolysis can lead to complex product mixtures, especially when there are equilibrating carbenium ions of about equal energy involved. On the other hand, the conversion of carboxylic acids to ethers, acetals, esters or alkenes can become very selective when the intermediate carbocation is

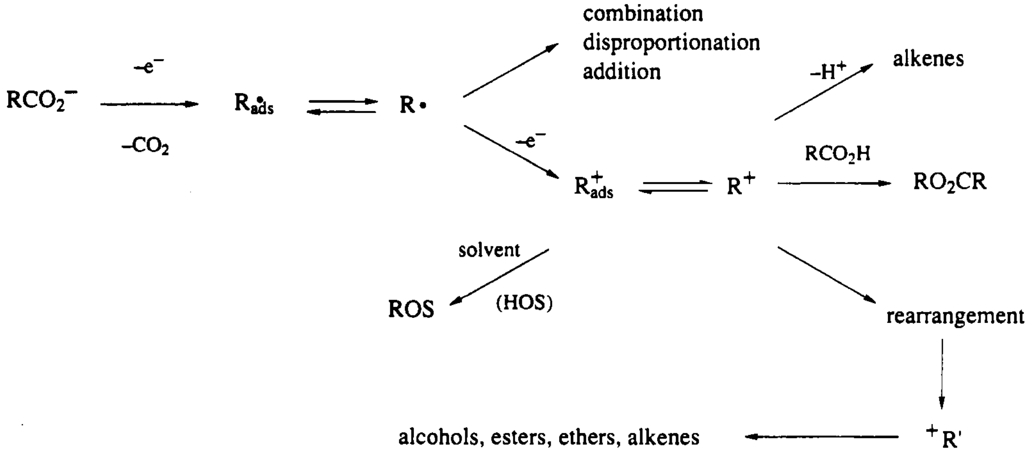

$RCO_2^-$
$-e^-$
$-CO_2$
$R^{\bullet}_{ads}$
R•
combination
disproportionation
addition
$-e^-$
$R^+_{ads}$
$R^+$
$-H^+$
alkenes
$RCO_2H$
$RO_2CR$
solvent
(HOS)
ROS
rearrangement
$^+R'$
alcohols, esters, ethers, alkenes

**Scheme 11**

**Table 9** Preparation of Ethers, Esters and Alcohols by NonKolbe Electrolysis of Carboxylates

| *Entry* | *Carboxylate* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 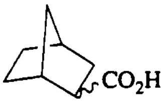<br>*exo* or *endo* | MeOH, Pt | 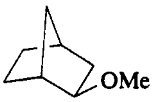 | 35–40 | 202c |
| 2 | 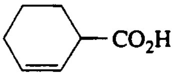 | MeOH | 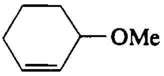 | 100 | 66 |
| 3 | 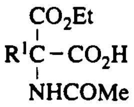<br>$R^1C(CO_2Et)(NHCOMe)-CO_2H$<br>$R^1$ = H, Me, Et, $Pr^i$, $PhCH_2$ | $R^2OH$ | 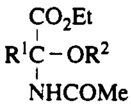<br>$R^1C(CO_2Et)(NHCOMe)-OR^2$<br>$R^2$ = Me, Et, $Pr^i$, MeCO | 79–96 | 210c |
| 4 | 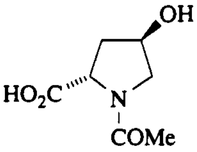 | MeOH, Pt | 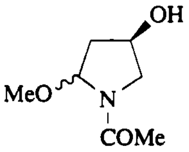 | 97 | 210b |
| 5 | $Me(CH_2)_nCH(SPh)CO_2H$<br>*n* = 2, 7 | MeOH, $LiClO_4$, Pt | $Me(CH_2)_nCH(OMe)_2$ | 72–98 | 211 |
| 6 | 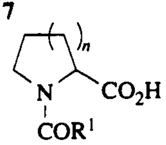<br>*n* = 1, 2; $R^1$ = H, Me, Ph, OEt<br>$R^2$ = Me, Et, H, $Pr^i$ | $R^2OH$ | 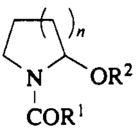 | 75–98 | 212 |
| 7 | 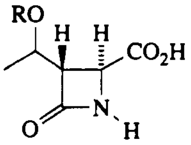 | AcOH, NaOAc, MeCN | 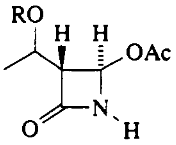 | 84 | 213 |

stabilized, and either solvolysis or elimination can be favored. This is substantiated below with some selected examples. Suitably substituted carboxylates can be converted into ethers or acetals (Table 9).

Both *exo*- and *endo*-norbornane-2-carboxylic acids are converted to the *exo*-2-methyl ethers, indicating that a bridged norbornyl cation is the intermediate (Table 9, entry 1). 2-Cyclohexene-1-carboxylic acid yields quantitatively 2-cyclohexen-1-yl methyl ether (Table 9, entry 2). Substituted *N*-acetylaminomalonic half esters are transformed in high yields into the corresponding aminoacetals (Table 9, entry 3). 4-Hydroxy-L-proline is converted into the corresponding 2-methoxypyrrolidine (Table 9, entry 4), which can be used to prepare optically active 2-substituted pyrrolidines.[210c] α-Phenylthio carboxylates are converted with loss of one carbon to dimethyl acetals (Table 9, entry 5). Cyclic acetals of β-ketocarboxylic acids react to form 2-methoxy-1,4-dioxacycloalkanes, that subsequently can be converted to 1,4-dioxenes. 4-Acetoxyazetidinone can be prepared by nonKolbe electrolysis of the corresponding carboxylic acid (Table 9, entry 7); it can serve as a valuable intermediate for the synthesis of β-lactams.

**Table 10** Conversion of Carboxylic Acids into Alkenes

| *Entry* | *Carboxylic acid* | *Reaction condition* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 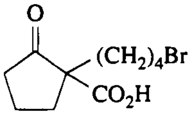 | $H_2O$, KOH | 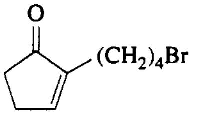 | 50 | 73b, 214 |
| 2 | 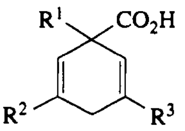 <br>$R^1 = Pr^i$; $R^2$ = Me, MeO; $R^3$ = H<br>$R^1 = Me(CH_2)_4$; $R^2 = R^3$ = OMe | MeOH, NaOMe | 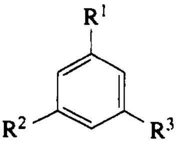 | 60–70 | 215 |
| 3 | 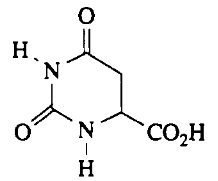 | C anode, NaOMe, MeOH | 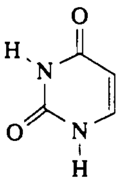 | 91 | 216 |
| 4 | 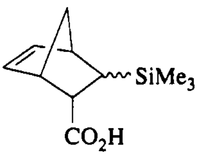 | MeCN, EtOH, C anode | 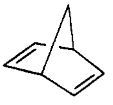 | 76 | 217 |
| 5 | 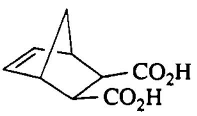 | 90% pyridine/$H_2O$ | 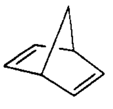 | 15 | 218 |
| 6 | 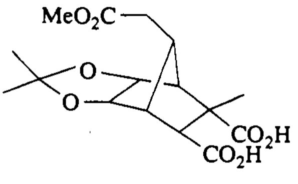 | MeOH, NaOMe, Pt anode | 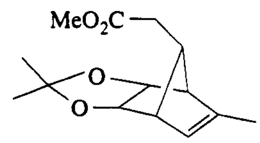 | 50 | 219 |

Carboxylic acids can be transformed into alkenes when they contain a leaving group like H (Scheme 12), $SiMe_3$, SPh or $CO_2H$ in the β-position. The alkene is formed by an *E*1-elimination from the intermediate carbocation. Some examples are summarized in Table 10. The decarboxylative elimination of 1,4-cyclohexadiene-6-carboxylic acids (Table 10, entry 2) is part of a useful method for the alkylation of aromatic compounds. This involves first a reductive alkylation using a Birch reduction, which is then fol-

**Table 11** Rearrangements by NonKolbe Electrolysis

| *Entry* | *Carboxylic acid* | *Reaction conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 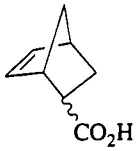<br>*exo* or *endo* | MeOH, $Et_3N$ | 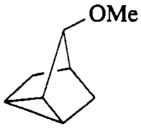 | 56 | 202c |
| 2 | 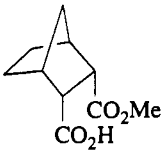 | AcOH, $Bu^tOH$, $Et_3N$ | 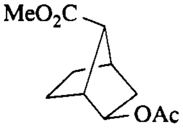 | 56 | 220 |
| 3 | 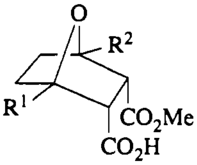<br>$R^1 = R^2$ = Me, H | MeOH, NaOMe | 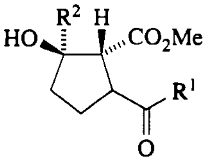 | 87 | 221 |
| 4 | 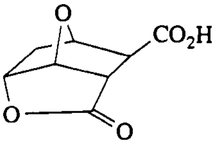 | MeOH, NaOMe | 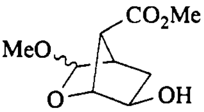 | 49–58 | 222 |
| 5 | 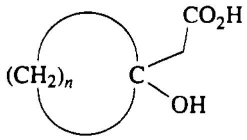 | Pt anode, MeCN | 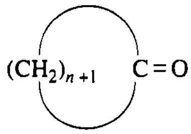 | | |
| | | | *n* = 4 | 54–63 | 202c |
| | | | *n* = 5 | 54–63 | 202c |
| | | C anode, pyridine/$H_2O$ | *n* = 9 | 82 | 223 |
| | | | *n* = 11 | 82 | 223 |
| 6 | 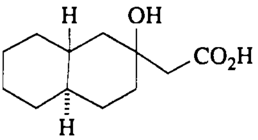 | C anode, DMF | 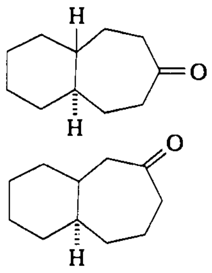 | 56 | 224 |

lowed by a nonKolbe electrolysis. 1,4-Cyclohexadienes are obtained from β-trimethylsilylcarboxylic acids (Table 10, entry 4); the latter are prepared by a Diels–Alder reaction of dienes with β-trimethylsilylacrylic acid or its derivatives. Vicinal dicarboxylates can be converted into alkenes by bisdecarboxylation (Table 10, entries 5 and 6). The reaction can be combined with a [4 + 2] or [2 + 2] cycloaddition, *e.g.* with maleic anhydride, whereby polycyclic hydrocarbons can be prepared in few steps.

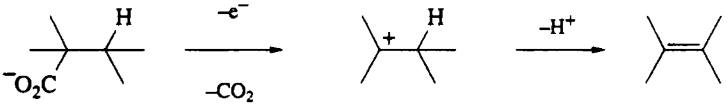

Scheme 12

The carbocations generated by nonKolbe electrolysis can rearrange by alkyl, phenyl or oxygen migration. Some examples are given in Table 11. The carbocations generated from *exo-* or *endo*-5-norbornene-2-carboxylic acid react by double bond participation and subsequent rearrangement to 3-methoxynortricyclene (Table 11, entry 1); the same compounds were also obtained by solvolysis.[225] The product in Table 11 (entry 2) has been used in a methyl (±)-jasmonate synthesis. Stereospecifically substituted cyclopentanes can be prepared by decarboxylation of oxabicycloheptanecarboxylic acids (Table 11, entries 3 and 4). A one-carbon ring extension of cyclic ketones is possible by first converting the ketones to β-hydroxycarboxylic acids by way of a Reformatzky reaction, and then subjecting these to a nonKolbe electrolysis (Table 11, entries 5 and 6).

The nonKolbe electrolysis of carboxylic acids can be used for a selective fragmentation, when the carbocation formed initially is stabilized in the γ-position by a hydroxy or trimethylsilyl group. This way the reaction can be used for a four-carbon ring extension (Table 12, entries 1 and 2). Furthermore it can be applied for the stereospecific construction of *cis-* or *trans*-disubstituted cyclopentenes from 6-hydroxynorbornane-2-carboxylic acids (Table 12, entries 3 and 4).

**Table 12** Fragmentation of Carboxylic Acids by NonKolbe Electrolysis

| *Entry* | *Carboxylic acid* | *Reaction conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 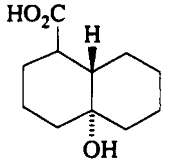 | MeOH | 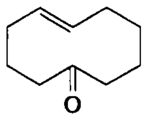 | 44<br>35 | 226<br>223 |
| 2 | 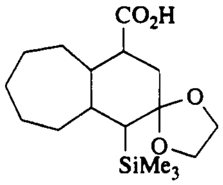 | C anode, MeCN, EtOH | 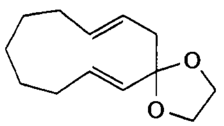 | 85 | 15 |
| 3 | 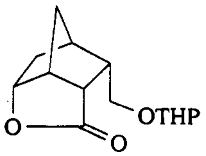 | C anode, MeCN, EtOH | 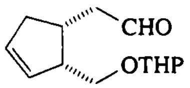 | 38 | 227 |
| 4 | 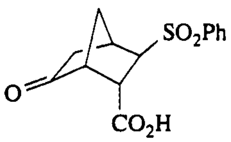 | MeOH, C anode | 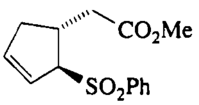 | 63 | 227 |

### 2.8.7.1 Experimental Procedure for NonKolbe Electrolysis — Preparation of Methyl 2-(*t*-2-Phenylsulfonyl-3-cyclopenten-*r*-1-yl)acetate

A solution of 0.5 g (1.69 mmol) 6-oxo-*c*-3-phenylsulfonylbicyclo[2.2.1]heptane-*t*-2-carboxylic acid in methanol (50 mL), neutralized to 100% with 1 M NaOH in methanol, was electrolyzed at graphite electrodes (anode area 15 cm$^2$) in an undivided cell (Figure 2) with a current density of 100 mA cm$^{-2}$ at 0 °C until consumption of 4 F mol$^{-1}$. The solution was then evaporated to dryness, treated with a saturated NaCl solution and extracted five times with $CH_2Cl_2$. After drying ($MgSO_4$) and removal of the $CH_2Cl_2$, 0.3 g (1.07 mmol, 63%) methyl 2-(*t*-2-phenylsulfonyl-3-cyclopenten-*r*-1-yl)acetate was obtained as a colorless oil by column filtration (silica gel, petroleum ether:ether = 2:1). Acidification of the aqueous phase with concentrated HCl to pH 1 and threefold extraction with $CH_2Cl_2$ afforded 0.04 g (9%) starting acid.[227]

## 2.8.8 CONCLUSIONS

Carboxylic acids can be converted by anodic decarboxylation into radicals and/or carbocations. The reaction conditions are simple; an undivided beaker-type cell as reaction vessel, controlled current supplied from an inexpensive d.c. power supply and methanol as solvent are in most cases sufficient. A scale-up is fairly easy and the yields are in general good. By the radical pathway 1,*n*-diesters, -diketones, -dienes and -dihalides, chiral intermediates for synthesis, pheromones and unusual fatty acids are accessible in just a few steps. The addition of the intermediate radicals to double bonds affords additive dimers, whereby four building units, two alkyl radicals from the carboxylates and two alkenes, can be coupled in one step. Five-membered hetero- or carbo-cyclic compounds can be prepared by intramolecular addition starting from unsaturated carboxylic acids.

The cationic pathway allows the conversion of carboxylic acids into ethers and acetals. The decarboxylative elimination of vicinal diacids or β-silylcarboxylic acids in combination with cycloaddition reactions leads efficiently to cyclobutenes or cyclohexadienes. Cationic rearrangements or fragmentations initiated by anodic decarboxylation allow the synthesis of specifically substituted cyclopentanes and ring extensions by one or four carbon atoms.

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# 2.9

# Oxidative Coupling of Phenols and Phenol Ethers

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## 2.9.1 INTRODUCTION

### 2.9.1.1 General

The ready oxidation of phenols to dimeric products has been well known for more than a century. The invaluable survey of the area by Musso[1] lists over 20 papers published before 1900 on, for example: the formation of the dilactone (**1**) from gallic acid[2] and its derivatives (1871);[3] the production of both *para–para* and *ortho–ortho* coupled dimers from 1-naphthol (1873);[4] the synthesis of the diphenoquinone (**2**),[5] in 97% yield, from 2,5-dimethoxyphenol (1878); and the preparation of 2,2′-dihydroxybiphenyl from phenol itself (1878).[6] Reagents used in such early work include iron(III) salts, potassium ferricyanide, oxygen and the halogens; electrochemical methods were also known, and enzyme-catalyzed reactions were reported in, for example, the oxidative dimerization of eugenol (1896).[7] Extensive chemical investigations into this major reaction continued this century and further momentum was gained from the recognition of the role of oxidative coupling in biogenesis, signalled by the important and influential papers of Barton and Cohen,[8] and of Erdtman and Wachtmeister.[9] Subsequent biosynthetic investigations have confirmed the significance of the title reaction in the *in vivo* formation of many aromatic natural products including alkaloids (Battersby[1] estimated that such coupling was involved in *ca.* 10% of known alkaloids), lignans, lignin, tannins, and plant and insect pigments. Many biomimetic studies of oxidative phenolic coupling were made, either for synthetic ends or to demonstrate possibilities in biological processes. Low chemical yields were often reported in such work, particularly in certain well-known alkaloid cases, and attention was turned to new reagents, *e.g.* manganese(III), vanadium(V) and thallium(III), which generally proved more effective. Further, oxidants such as vanadium(V) were found to effect coupling of phenol ethers, and interest was revived in the anodic oxidation of such aromatic substrates. The oxidation of phenol ethers has proved a valuable synthetic process, often more predictable and higher yielding than the corresponding phenol oxidations, and this reaction has been employed in recent years in a number of notable natural product syntheses.

A number of good reviews of the oxidation of phenols have appeared;[1,10–19] the most recent covers the literature to mid-1980. These offer historical perspective and coverage of the biosynthetic aspects of the area, both inappropriate in the present article. This chapter focuses entirely on synthetic uses of the reaction and sets out: (i) to survey the main types of reaction stemming from oxidation of phenols and phenol ethers; and (ii) to offer selected examples of reactions showing satisfactory yield and regioselectivity.

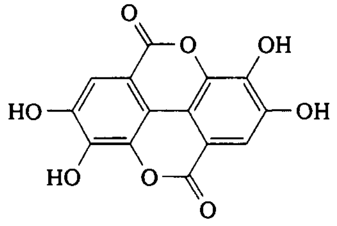

(**1**)

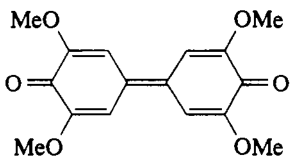

(**2**)

### 2.9.1.2 Mechanistic Possibilities

A wide variety of mechanistic pathways[16,20] present themselves for consideration, and since awareness of these ramifications aids synthetic planning they are outlined here. The major variables are as follows. (i) Substrate — either an un-ionized phenol or a phenolate anion may be oxidized, leading to different intermediates. Also the products after coupling may be new substrates for oxidation. (ii) Reagent — both homogeneous and heterogeneous reagents are employed covering a range of oxidation potential. Metal complexes are often implicated, which sometimes appear to be precipitated. Both inner-sphere and outer-sphere electron transfer processes can be involved. (iii) Pathway — overall two electrons and two protons are removed in a typical oxidation, and various sequences are thus possible. Two single-electron steps may occur, or one two-electron step, leading to radical or ionic processes. Species with carbon–metal or oxygen–metal bonds may intervene. The route may involve oxidation of one phenolic nucleus to quinone or quinone methide followed by a nonoxidative coupling step.

The main reaction pathways thus available for this process are summarized in the following schemes. For an excellent full discussion see ref. 20.

#### *2.9.1.2.1 Coupling of aryloxy radicals*

Scheme 1 illustrates this mechanism, which is the most generally accepted and widely discussed, for the *para–para* self-coupling of a simple phenol. Oxidation to the radical (**3**) may proceed from the phenol or phenolate anion according to pH, *etc.* The formation of such radicals is well attested, for example by ESR,[21-23] and it has been shown[24] that the subsequent dimerization fits a diffusion-controlled model. The coupling step (3) → (4) may be reversible, and in the absence of acid the enolization of (4) to produce biphenyl may be slow and rate determining.

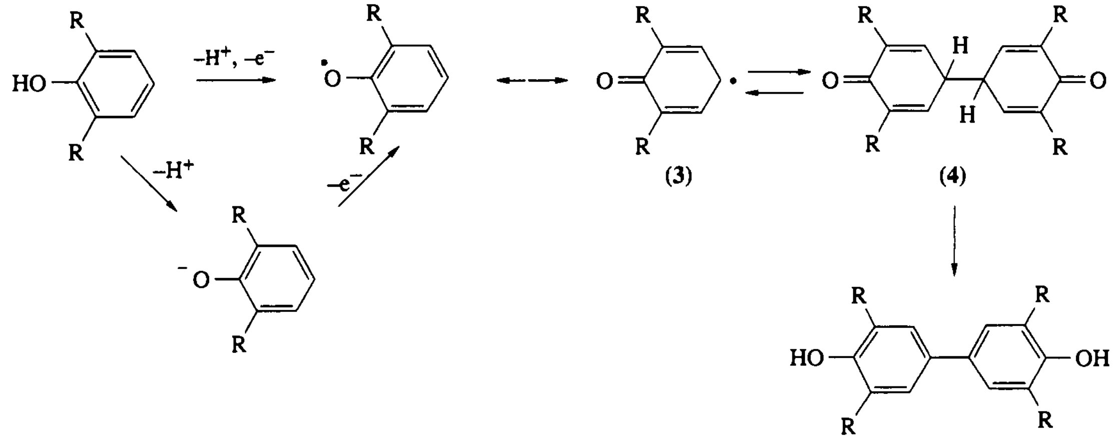

Scheme 1

### 2.9.1.2.2 Radical substitution

While the above mechanism certainly operates in many systems, it is not universal. If each radical is surrounded by unoxidized phenol or phenolate anion molecules, then aromatic substitution becomes possible, and this becomes more likely in intramolecular cases where two units of different reduction potential are held in proximity. Scheme 2 shows the likely pathway with radical insertion into a phenoxide and the second one-electron transfer following coupling, and such a mechanism has been shown to operate in the oxidation of 2,3,4′-trihydroxybenzophenone to 2,6-dihydroxyxanthone (ref. 20, p. 114).

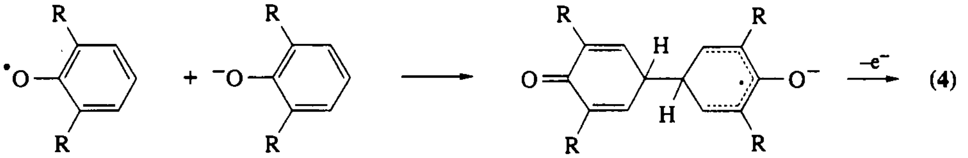

Scheme 2

### 2.9.1.2.3 Heterolytic substitution

Scheme 3 shows that a second one-electron oxidation of an aryloxy radical yields an aryloxonium species, which could lead to a coupled product by electrophilic substitution. Although a less probable reaction course because of the energetics for two successive one-electron transfers, it cannot be discounted, since such transfers have been observed by polarography. Also phenoxy cations have been isolated as fluoroborate salts, and react rapidly with nucleophiles. Alternatively a single two-electron transfer to a suitable metal ion can be envisaged (Scheme 3), also leading to a cation. In this case no radical intermediates are involved. 2,3-Dichloro-2,6-dicyanobenzoquinone is thought to effect phenolic coupling by hydride transfer to an aryloxonium species.[25]

### 2.9.1.2.4 Concerted coupling and electron transfer

Scheme 4 shows the ionic substitution of a phenol by a metal phenolate compound, by a concerted mechanism. Although similar to Scheme 3, a phenoxonium ion is avoided, with probable energetic advantages: thallium(III) oxidations of phenols may follow such a path.

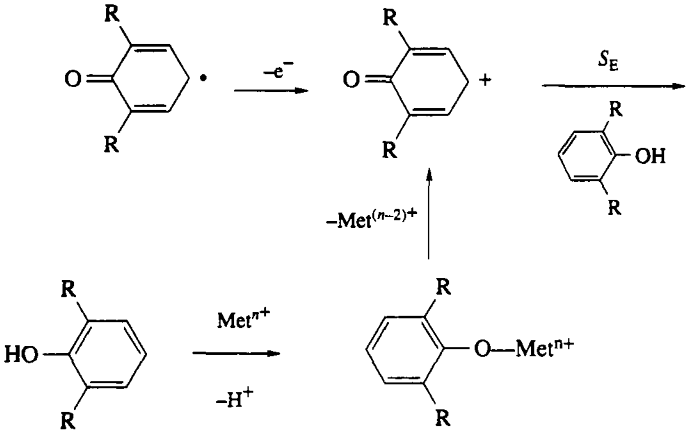

(4)

**Scheme 3**

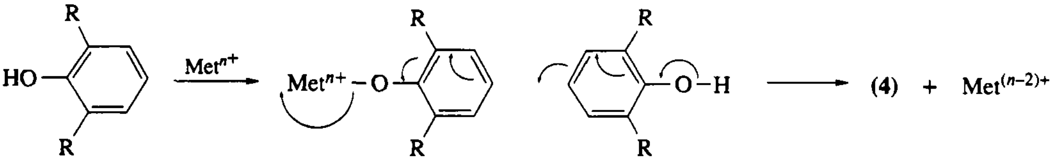

**Scheme 4**

### 2.9.1.2.5 Postoxidative coupling

In some instances it has been demonstrated that oxidation is complete before coupling occurs, the second step thus being nonoxidative. Such cases (Scheme 5) involve oxidation to a quinone or a quinone methide whose further reactions may involve nucleophilic addition, *e.g.* by phenol, or cycloaddition. Examples are given below.

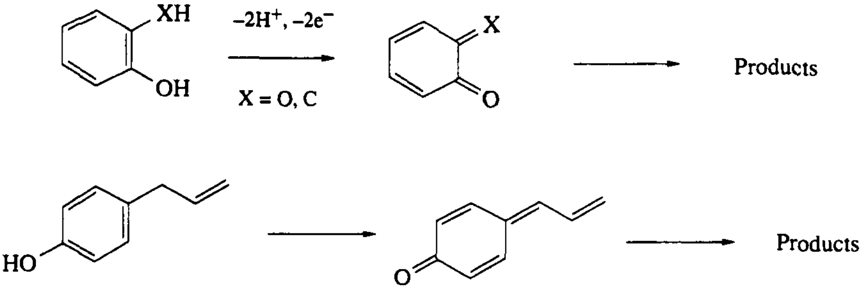

**Scheme 5**

### 2.9.1.2.6 Radical cation reactions

One-electron oxidation of an aryl ether, for example at the anode, gives rise to a radical cation whose fate may be radical coupling (shown as dimerization) or substitution into a neutral phenol ether; both paths are shown in Scheme 6 and converge to a biaryl product. Other products are possible if coupling at a quaternary center takes place. Mechanisms of this type must operate for the important couplings of phenol ethers with phenol ethers, and phenols with phenol ethers; possibly they should not be neglected for phenol–phenol coupling also, in certain cases.

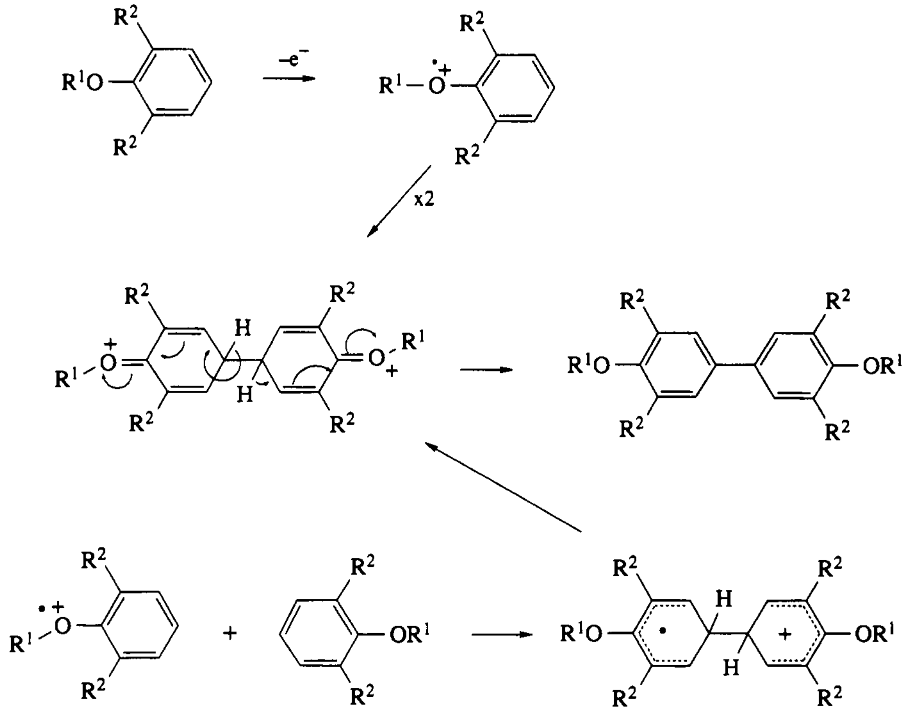

Scheme 6

### 2.9.1.3 Product Types and Chapter Organization

Inter- or intra-molecular carbon–carbon coupling of phenols at two unsubstituted ring carbons leads to the corresponding biaryl. The product may then be further oxidized, for example to a diphenoquinone. Oxygen-unsubstituted ring carbon coupling gives an aryl ether. If coupling involves a substituted ring site then a cyclohexadienone results, which in intramolecular cases will be a spirodienone. Further reactions, for example with nucleophiles, may ensue.

In phenols with *ortho* or *para* unsaturated side chains, coupling reactions may occur outside the aryl ring, and may form new carbon–carbon or carbon–oxygen bonds. Benzylic radicals may also be generated, perhaps by hydrogen atom abstraction, and lead to coupling at this position. Finally the products arising from quinones, quinone ketals, or quinone methides may dominate.

The survey of reactions presented here is divided first into the main product types above. Thus Sections 2.9.2 and 2.9.3 deal with the synthesis of biaryls and spirodienones respectively, by C—C bond formation. Section 2.9.4 covers the preparation of ethers through C—O bond making. The coupling of phenols through side chain sites is dealt with in Section 2.9.5. Section 2.9.6 contains a miscellany; post-oxidative cycloaddition reactions, coupling through benzyl radicals, and some examples of C—N bond forming. Within sections, material is divided firstly by reactant type and secondly by reagent type.

## 2.9.2 SYNTHESIS OF BIARYLS AND RELATIVES

### 2.9.2.1 Phenol–Phenol C—C Coupling

This is the best known and most quoted chemistry in this area. Oxidation of a phenol as in Scheme 7, with loss of one proton and one electron, provides an aryloxy radical, which may dimerize: three modes of C—C union are possible, and two modes of C—O bonding. Spin density is greatest, in general, in the *para* position, but coupling is reversible (before intermediate dienone phenolization) and product ratios depend on pH, temperature, concentration and oxidant, for a given phenol.[26] Mixtures of isomeric dimers may, and often do, result. If different phenols are present then potential products are numerous. A survey of the literature indicates that reasonable chemospecificity is most likely observed either in cases of phenol self-coupling where one or two of the *ortho*/*para* sites are substituted, or in intramolecular examples. The intermolecular coupling of different phenols can also be successful, but often involves a polyhydroxy compound which can be oxidized to a quinone. The coupling step is then nonoxidative, involving addition of phenol to quinone. The feasibility of this reaction is shown by the example in Scheme 8; the initial product is oxidized to a new quinone under the reaction conditions.[27] *o*,*o*-Disubstituted phenols (**5**) give excellent yields of *para–para* coupled products, *e.g.* the formation of (**2**). Essentially quantitative yields of the diphenoquinone (**6**), with R = various alkyl groups, were obtained from the corresponding phenol (**5**) by refluxing in benzene with silver carbonate–celite;[28] conversion of (**5**; R = Bu$^t$) to (**6**; R = Bu$^t$) was also quantitative, and complete in a few minutes at room temperature with hydrogen hexacyanoferrate(III) in methanol;[29] and (**6**; R = Me) was prepared in 92% yield using triphenylbismuth carbonate.[30] Many other oxidants have been investigated,[31] and for (**5**; R = Me) the biphenol (**7**) could be obtained with a silver nitrate–potassium persulfate reagent (27%),[31] or manganese(III) acetylacetonate (45%).[32] Phenol yielded the 4,4′-dihydroxybiphenyl (**7**; R = H; 34%) on oxidation with vanadium tetrachloride,[33] together with the 2,4′-isomer (17%). Vanadium oxytrichloride oxidized 1-naphthol to the *para–para* coupled binaphthyl (**8**; R = H; 56%). The tetrahydroxybinaphthyl (**8**; R = OH), a metabolite of *Daldinia concentrica*, was synthesized[34] by treatment of 1,8-dihydroxynaphthalene with potassium ferricyanide.

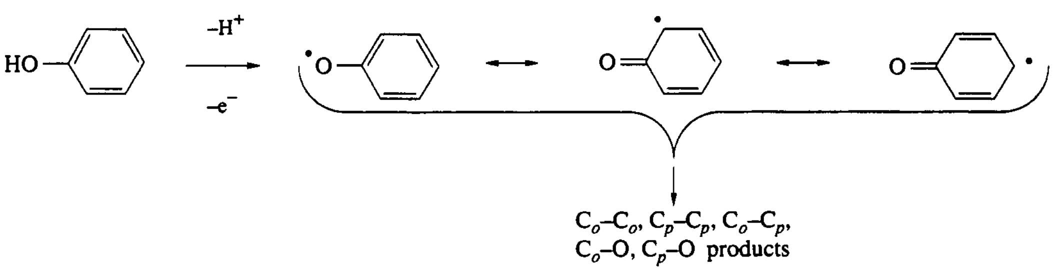
HO
-H⁺
-e⁻
O
O
O
$C_o$–$C_o$, $C_p$–$C_p$, $C_o$–$C_p$,
$C_o$–O, $C_p$–O products

Scheme 7

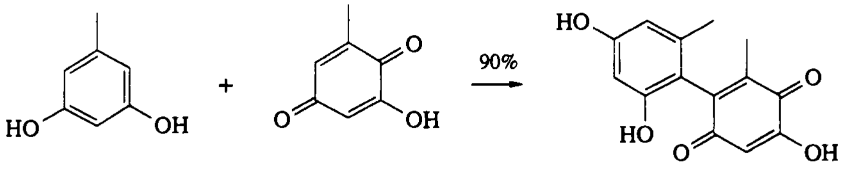

Scheme 8

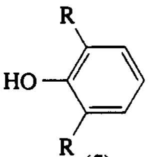

(**5**)

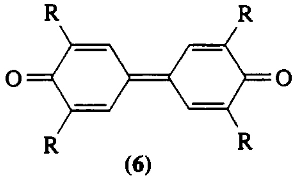

(**6**)

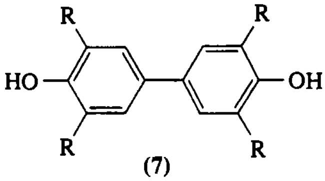

(**7**)

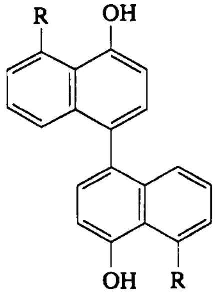

(**8**)

*Para*-substituted phenols may still couple through the *para* position and products may be formed in good yield, especially if stable. Thus *p*-cresol gives Pummerer's ketone (**9**; 63%) on treatment with silver carbonate;[26] only the *o–p* coupled intermediate can cyclize to (**9**), which is then not subject to phenolic oxidation. In contrast *p*-cresol with iron(III) chloride gives at least 10 products including (**9**), and the biphenyl and terphenyl products of *o–o* coupling (**10**) and (**11**).[35] Simple *o–o* linking can be the major pathway, *e.g.* alkaline potassium ferricyanide oxidation of totarol (**12**; R = Me) in benzene–water afforded podototarin (**13**; R = Me) in 43% yield; and ethylmacrophyllate (**13**; R = $CO_2Et$) was the major product from similar oxidation of (**12**; R = $CO_2Et$).[36] An aqueous alkali–organic solvent two-phase system is usually favored for ferricyanide oxidation since the products may be separated from the oxidant. The naphthol (**14**) dimerizes quantitatively on heating (215 °C) in air to the bisnaphthol (**15**; R = H), which contains the gossypol nucleus. *O*-Methylation of (**15**; R = H) gave apogossypol hexamethyl ether (**15**; R = Me).[37] The allylguaiacol (**16**) was oxidized quantitatively at a platinum anode to the biphenol (**17**), using an alkaline electrolyte,[38] although to very different products in neutral media (*vide infra*). The trimethyltetralol (**18**) gave the dimer (**19**) in 46% yield using a copper(II)–amine complex.[39] The oxidation of a similar chiral reactant (**20**) has been examined from the stereochemical viewpoint.[40] The (±)-tetrahydroisoquinoline (**20**) on oxidation with potassium ferricyanide, or with oxygen over platinum, provided three stereoisomers of (**21**); a *meso* (*R*,*S*) form, and two separable rotamers of the (*S*,*S*)/(*R*,*R*) racemate. However, on electrooxidation at a graphite anode only one stereomer was formed (69%), the rotamer shown (**21**) of the (*S*,*S*)/(*R*,*R*) form. Separate oxidations of the (*S*)- and (*R*)-enantiomers of (**20**) afforded only the (*S*,*S*) (62%) and the (*R*,*R*) (66%) isomers, both as a single rotamer.

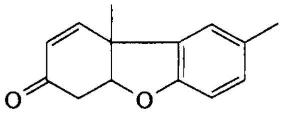

**(9)**

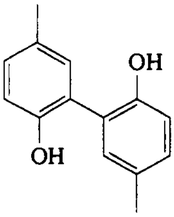

**(10)**

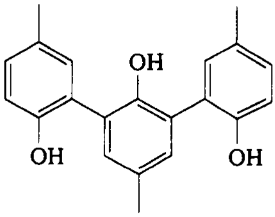

**(11)**

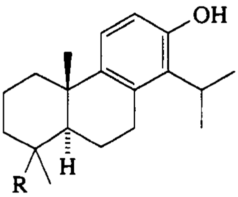

**(12)**

2-Naphthol can successfully be dimerized oxidatively, selectively through the *o*-site to give (**22**) using copper(II)–amine complexes (70%)[39] or manganese(III) acetylacetonate (69%),[32] and *o–o* coupling is the major pathway (90%) on ferricyanide oxidation of the trisubstituted phenol (**23**) to the orthodiphenoquinone (**24**).[41] In this context it is of interest that a compound obtained (74%) on ferricyanide oxidation of

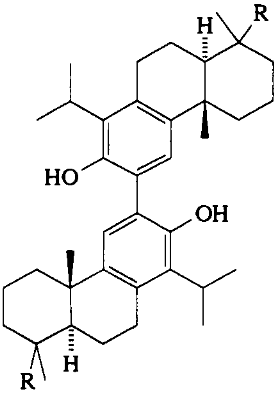

**(13)**

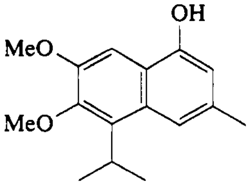

**(14)**

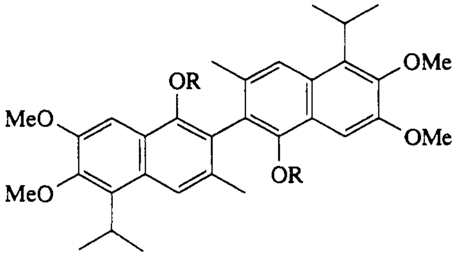

**(15)**

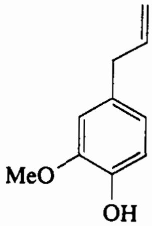

**(16)**

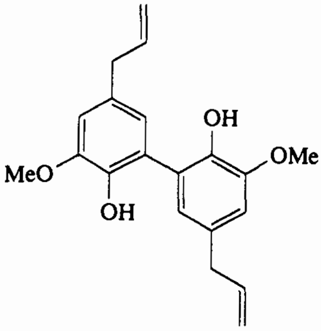
OH
OMe
MeO
OH

**(17)**

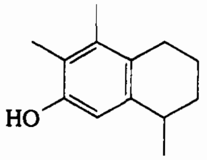

**(18)**

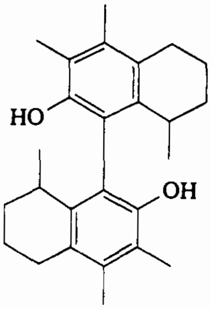

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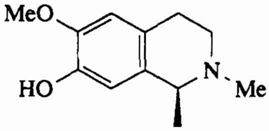

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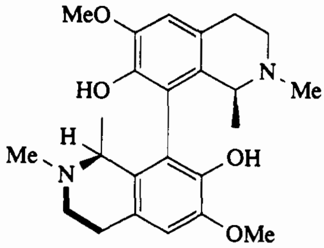
MeO
HO
N
Me
H
Me
N
OH
OMe

**(21)**

the 2,2′-dihydroxybiphenyl (**25**) proved to be the oxepinobenzofuran (**26**)[42] rather than the benzoxete (**27**) as originally formulated.[43] The intermediate orthodiphenoquinone (**28**) rearranges as shown. Another case of *o–o* dimerization is that of the anodic oxidation (graphite anode, acetonitrile–water, 0.3 V) of the sodium salt of the *p*-hydroxybenzyltetrahydroisoquinoline (**29**), which selectively gave product (**30**; 45%).[44] The *N*-ethoxycarbonyl substituent is necessary in this example to prevent oxidation at nitrogen; with NH or NMe analogs fragmentation supersedes coupling, as pictured in (**31**), leading to initial products (**32**) and (**33**).

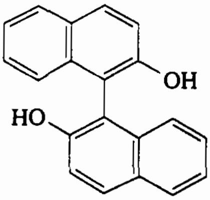

**(22)**

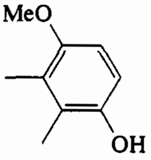

**(23)**

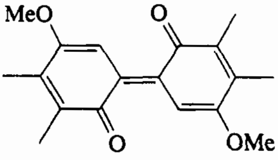

**(24)**

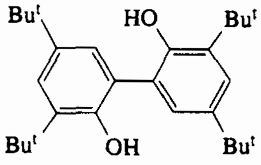
Bu$^t$
HO
Bu$^t$
Bu$^t$
OH
Bu$^t$

**(25)**

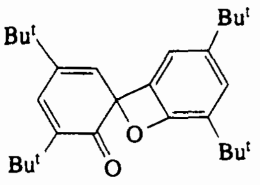
Bu$^t$
Bu$^t$
O
Bu$^t$
O
Bu$^t$

**(27)**

The question of cross-coupling of different phenols was alluded to above. An interesting example[45] of selectivity is shown in Scheme 9; the major product, shown, forms a relatively stable radical anion under the reaction conditions. To what extent this thermodynamic factor controls product ratios is not clear.

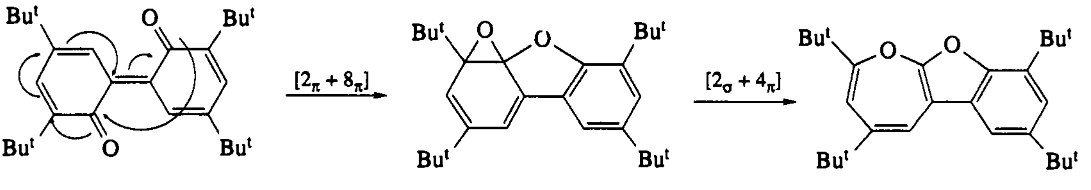

**(28)** **(26)**

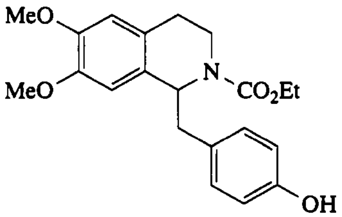

**(29)**

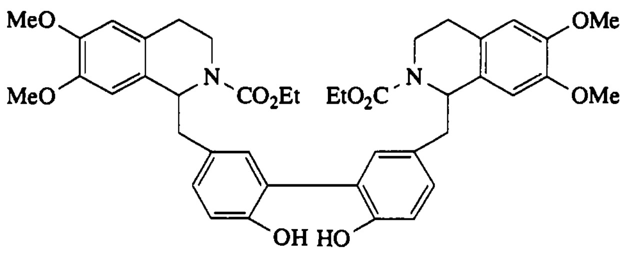

**(30)**

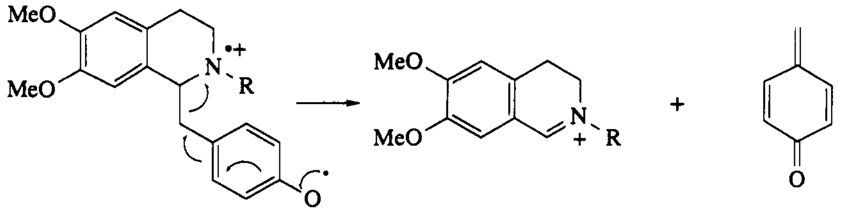

**(31)** **(32)** **(33)**

Few such cases have been described and it does not seem possible to make reliable predictions of such cross-coupling reactions on the basis of present knowledge.

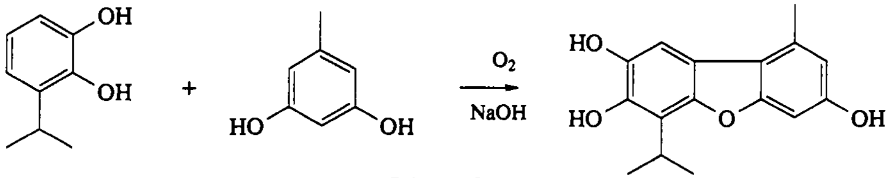

**Scheme 9**

Intermolecular coupling has been displayed in the foregoing reactions. Intramolecular cases are of interest, potentially offering greater product selectivity, and many have been investigated as models of biogenetic significance. A high proportion of these proceed in poor yield and have limited synthetic value. However there are some rewarding examples. Thus laudanosoline methiodide (**34**) underwent preferential *o–p* linking to (**35**; 62%), with aqueous iron(III) chloride at room temperature.[46] Dihydropiceatannol (**36**) was also selectively oxidized to a 9,10-dihydrophenanthrene, isolated (66%) as its tetraacetate (**37**) after reductive acetylation.[47] It is possible but unproven that in both these cases an *o*-benzoquinone intermediate is generated. Such a pathway appears very likely in the following reaction[48] in which the tetrahydroisoquinoline (**38**) was treated with diphenyl selenoxide in methanol at ambient temperature to afford in 80% yield the coupled product (**39**), *N*-trifluoroacetylwilsonirine. This reagent cleanly oxidizes catechols to *o*-quinones *via* an intermediate seleno acetal (**40**). The arylethyltetrahydroisoquinoline (**41**) is similarly intracoupled,[48] forming a new seven-membered ring in product (**42**).

Finally in this section it is worth noting that the oxidative coupling of phenols may be extended to form interesting polymers. Thus electrooxidative polymerization of phenol using basal-plane pyrolytic graphite electrodes gives thin black polymer films which are electrically conducting.[49]

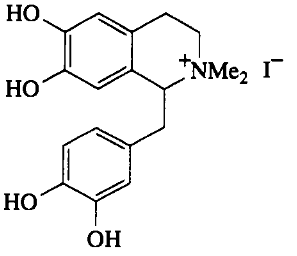

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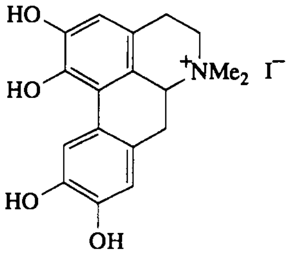

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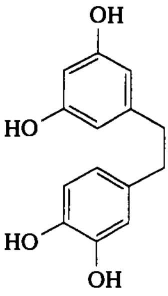

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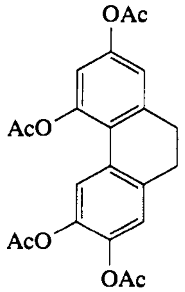

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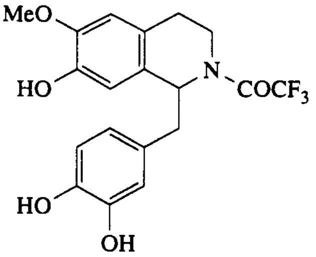

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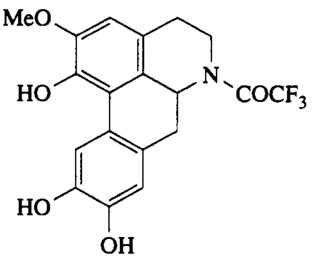

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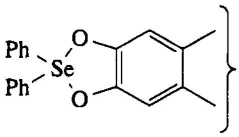

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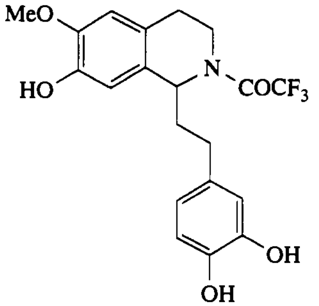

(41)

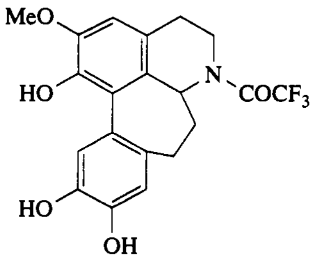

(42)

### 2.9.2.2 Biaryls Formed in Phenol Ether Couplings

This section covers the union of two aryl moieties, one of which is a fully alkylated phenol, and the other is either a free phenol or a phenol ether. Clearly, radical dimerization is not operative in such reactions. An early example is to be found in the work of Fitcher and Dietrich (1924)[50] who showed that 3,3′,4,4′-tetramethoxybiphenyl was among the products of electrolytic oxidation of veratrole in sulfuric acid using a lead dioxide anode; the biaryl was formed in about 20% yield based on reacted veratrole.

The potential of such syntheses was not realized for several decades. (The following account is not historical.)

The intermolecular examples of synthetic value are self-couplings, *e.g.* formation of the dimer (**43**) from benzylsesamol,[51] in 85% yield using vanadium oxytrifluoride; preparation of the biaryl (**44**; 95%), from 4-methylveratrole, employing iron(III) chloride supported on silica;[52] and synthesis of 4,4′-dimethoxybiphenyl (69%) from anisole by oxidation with thallium(III) trifluoroacetate in the presence of catalytic palladium(II) acetate.[53] This approach has been used in a natural product synthesis. The dimers (**45**) and (**46**) were prepared from appropriate derivatives of gallic acid, and transformed into schizandrin C (**47**) and an isomer respectively.[54,55]

Recently the conditions have been defined under which trimerization of some phenol ethers is viable; these require anodic oxidation in a flow cell with porous electrodes, using acetonitrile or trifluoroacetic acid–methylene chloride.[56] Catechol derivative (**48**) and 1,2-methylenedioxybenzene were thus converted into trimers (**49**) and (**50**) respectively, in *ca.* 30% yield.

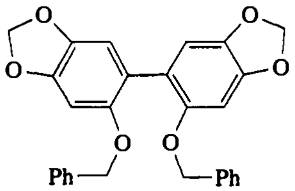

**(43)**

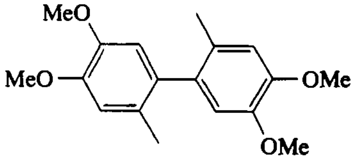

**(44)**

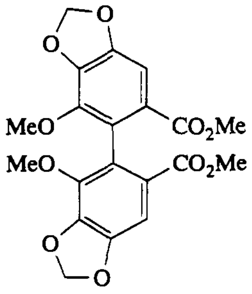

**(45)**

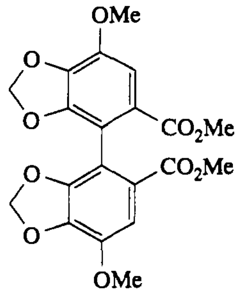

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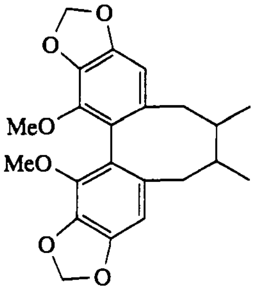

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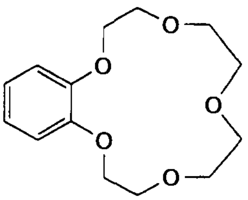

**(48)**

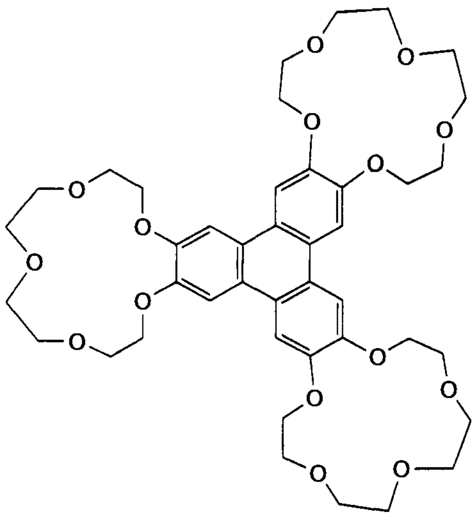

**(49)**

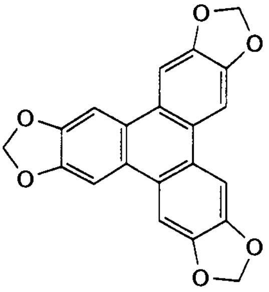

**(50)**

The intramolecular versions of this reaction have been widely exploited particularly for the synthesis of alkaloids and lignans. New six-, seven- and eight-membered rings are readily formed and there are some cases involving macrocycles.[57]

Starting with six-membered ring formation, it has been shown that (±)-laudanosine (**51**; $R^1 = R^2 = Me$) can be oxidized with vanadium oxytrifluoride in trifluoroacetic acid–fluorosulfonic acid to (±)-glaucine (**52**; $R^1 = R^2 = Me$; 43%).[57a] The same oxidant also effected phenol–phenol ether coupling in this alkaloid series, with *N*-trifluoroacetylcodamine (**51**; $R^1 = COCF_3$, $R^2 = H$) yielding the aporphine (±)-*N*-trifluoroacetylwilsonirine (**52**; $R^1 = COCF_3$, $R^2 = H$). The benzyltetrahydroisoquinoline (**53**) was intracoupled to (±)-ocoteine (= thalicmine; **54**) in 46% yield employing thallium trifluoroacetate at –40 °C, with catalytic boron trifluoride.[58]

To exemplify phenol–phenol ether coupling the benzylisoquinoline (**55**) was oxidized with a range of reagents, to form the novel quinonoid oxaporphine (**56**) with generation of the quinone methide after coupling; best yields were obtained with vanadium oxytrifluoride in trifluoroacetic acid (59%) and molybdenum oxytetrachloride (62%).[59] The former reagent was also very effective in converting the (non-natural) system (**57**) to (**58**; 70%); no further product oxidation was observed here, possibly because of reduced thermodynamic drive.[60]

Returning to phenol ether–phenol ether coupling, synthetic septicine (**59**) gave (±)-tylophorine (**60**) on treatment with thallium trifluoroacetate, and the same reagent converted synthetic julandine (**61**) to (±)-cryptopleurine (**62**; 69%).[61] In another synthesis of tylophorine the lactam (**63**) was transformed with va-

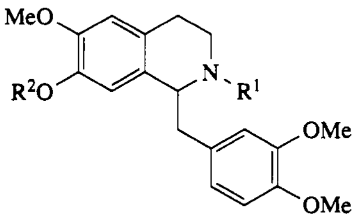

**(51)**

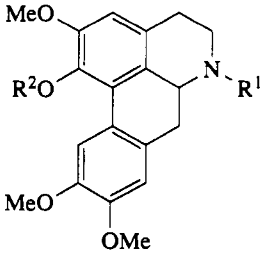

**(52)**

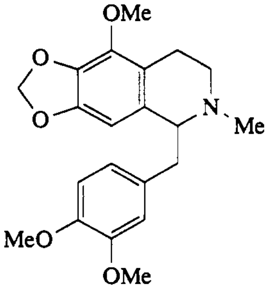

**(53)**

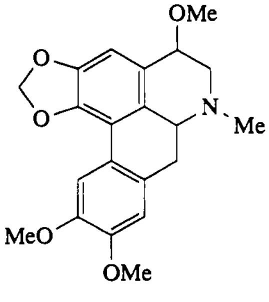

**(54)**

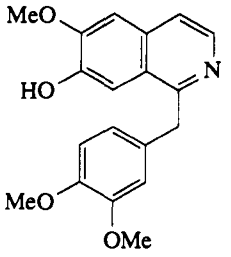
MeO
HO
N
MeO
OMe

**(55)**

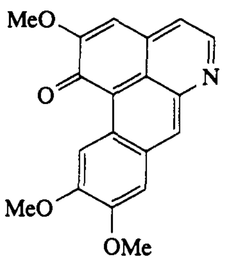
MeO
O
N
MeO
OMe

**(56)**

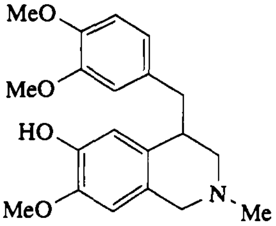
MeO
MeO
HO
MeO
N
Me

**(57)**

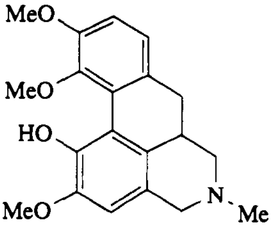
MeO
MeO
HO
MeO
N
Me

**(58)**

nadium oxytrifluoride to (**64**; 59%); reduction with diborane (85%) completed the sequence to tylophorine (**60**).[62]

Electrooxidation is also viable for phenol ether–phenol ether coupling and has been thoroughly investigated. For example a range of compounds (**65**) with R = H or Me, Z = $CH_2$ or O, *n* = 1 or 2, reacted at the anode to give fair yields of the corresponding biaryls (**66**),[63] together with spirodienone products (see Section 2.9.3.2).

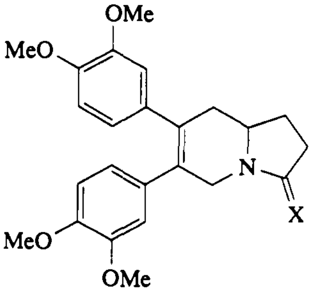
OMe
MeO
N
X
MeO
OMe

**(59)** X = $H_2$
**(63)** X = O

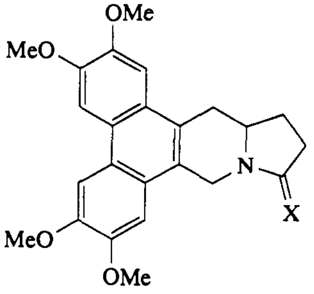
OMe
MeO
N
X
MeO
OMe

**(60)** X = $H_2$
**(64)** X = O

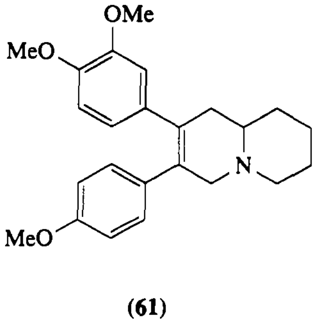
OMe
MeO
N
MeO

**(61)**

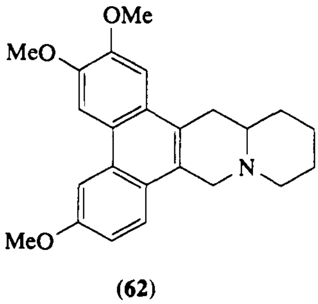
OMe
MeO
N
MeO

**(62)**

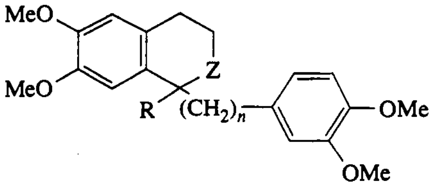

**(65)**

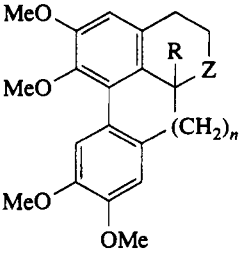

**(66)**

Aryl coupling to a benzylic site has also been observed: the monophenol (**67**) yielded the aryltetralin (**68**; 55%), with thallium trifluoroacetate–boron trifluoride.[64] Probably oxidation to quinone methide precedes the ring closure. Separate oxidation and cyclization steps were employed in the synthesis of (±)-thaliphorphine acetate. (±)-Codamine (**69**) underwent Wessely oxidation with lead tetraacetate to the acetoxycyclohexadienone (**70**), which closed in acetic anhydride–acid to (±)-thaliphorphine acetate (**71**), albeit in modest overall yield (14%).[65]

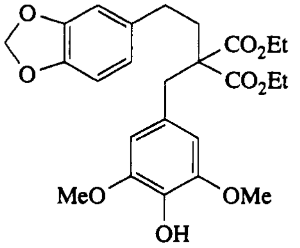

**(67)**

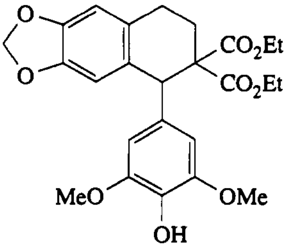

**(68)**

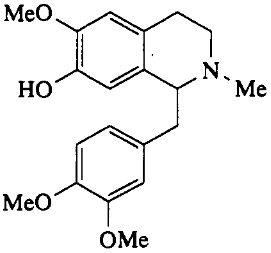

**(69)**

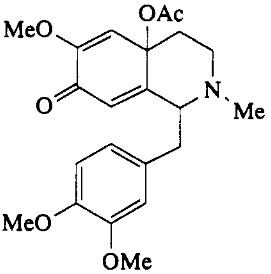

**(70)**

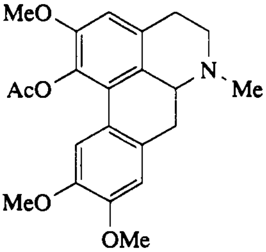

**(71)**

It is worth noting an alternative strategy for intracoupling to biaryls,[66] in which the quinone monoketal (**72**) undergoes addition by a suitable carbanion (**73**); the resulting tertiary alcohols, *e.g.* (**74**) and (**75**), could be cyclized with acid (conditions of low nucleophilicity), to biaryls (**76**; 77%), and (**77**; 61%), respectively. The new C—C bond forms *meta* to methoxy of the new aryl ring, thus complementing the oxidative approach. The formation of a five-membered ring is worthy of note.

Closure to seven-membered rings has been demonstrated a number of times. Thus the 1,3-bisarylpropane (**78**) was oxidized anodically to the bridged biaryl (**79**; 72%). In a thorough study[67] of the effects of

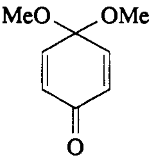

**(72)**

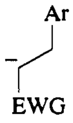

**(73)**

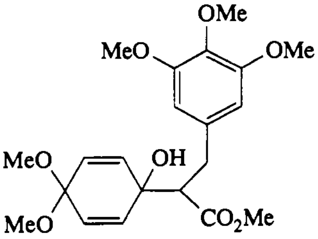

**(74)**

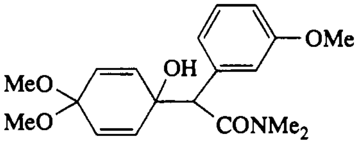

**(75)**

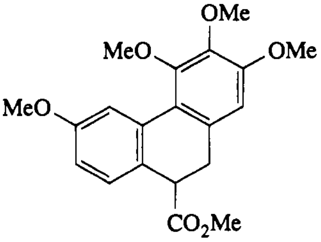

**(76)**

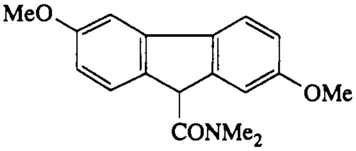

**(77)**

variations in conditions and in substrate structure on the competition between cyclization and dimerization it was concluded that intermolecular processes were favored at low anode potential, and conditions were given for dimerization of the 1,2-bisarylethane (**80**), to (**81**; 61%). It was concluded that, in the full range of examples studied, both cation radical couplings, and electrophilic substitution by cation radicals on unoxidized rings, were operating. Anodic oxidation was used to prepare homoglaucine (**83**) from homolaudanosine (**82**; 34%).[68]

Thallium trifluoroacetate has proved an excellent reagent for similar oxidations, *e.g.* of (**84**) and (**85**) to the bridged biaryls (**86**) and (**87**), 80% and 81%, respectively,[58,69] and this reagent was selected for a crucial step in a total synthesis of (±)-steganone.[70] Thus the (*E*)-2-benzylcinnamate (**88**) provided the bis-

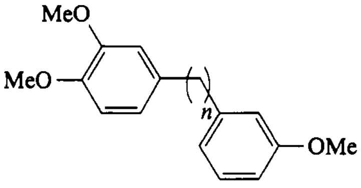

(**78**) $n = 3$
(**80**) $n = 2$

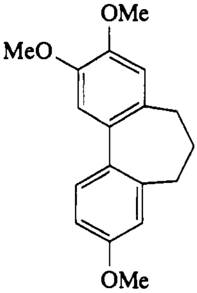

**(79)**

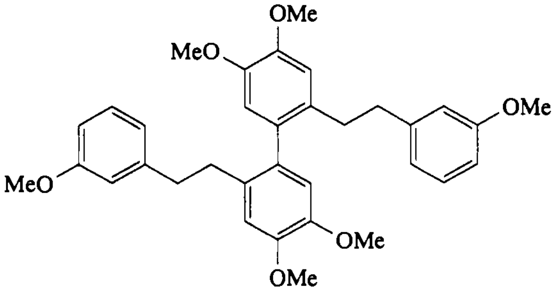

**(81)**

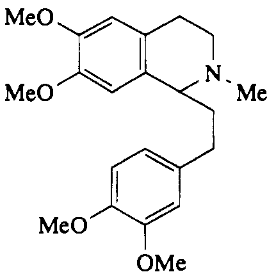

**(82)**

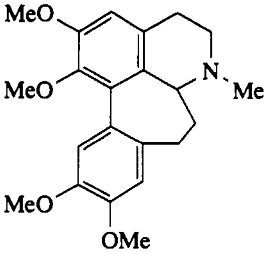

(83)

benzocycloheptatriene (89; 81%), at –18 °C in trifluoroacetic acid. Reduction of the methoxycarbonyl function and Simmons–Smith methylation then generated the cyclopropane (90; R = $CH_2OH$) from which (±)-steganone (91) could be generated *via* ring expansion with the correct biaryl twist, relative to lactone fusion. Alternatively the cyclopropane (92) could be cyclized (45%) to (90; R = $CO_2Me$). Interestingly it was not possible to induce biaryl formation with an eight-membered ring by treatment of (93) with thallium trifluoroacetate.[70b] Much synthetic interest has been shown in steganone and its relatives, induced by the anticancer properties of this group of lignans.

Although the bisarylbutene (93) proved unamenable to oxidative cyclization, eight-membered rings have been constructed successfully using substrates with saturated interaryl links. Several relatives of steganone have been prepared in this way. Thus (±)-steganacin was synthesized[71] using intracoupling of the malonate-derived bisaryl butane (94) to (95), in 45% yield, using vanadium oxytrifluoride at 25 °C,

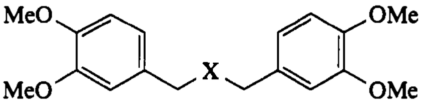

(84) X = O
(85) X = $CH_2$

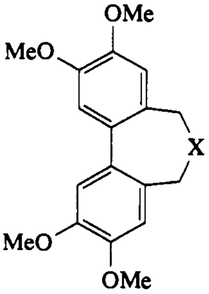

(86) X = O
(87) X = $CH_2$

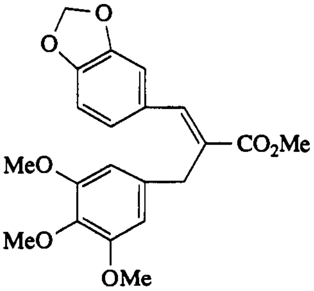

(88)

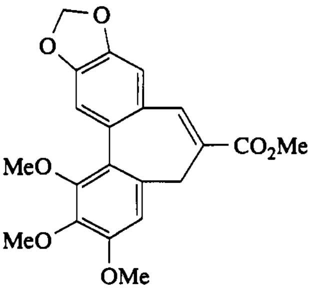

(89)

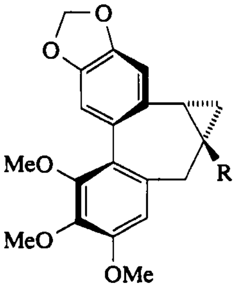

(90)

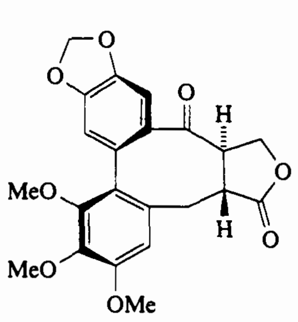
O
O
O
H
O
MeO
H
O
MeO
OMe

**(91)**

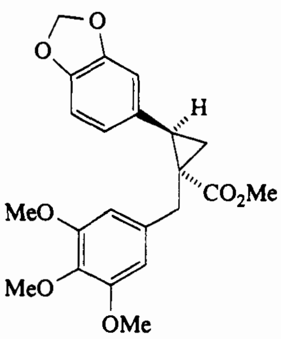
O
O
H
CO2Me
MeO
MeO
OMe

**(92)**

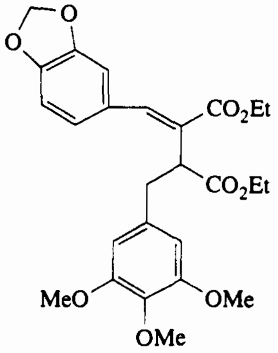
O
O
CO2Et
CO2Et
MeO
OMe
OMe

**(93)**

and (±)-isostegane (**96**) was obtained[72] in good yields (65–70%) by oxidation of the (±)-bisbenzylbutyrolactone (**97**), employing the same reagent at 45 °C. (–)-Isostegane (**96**) was similarly prepared[73] (61%) from (+)-deoxypodorhizone (**97**) (from enantiospecific synthesis), and converted into (+)-stegane and (+)-steganacin (**98**), the enantiomer of natural (–)-steganacin. This sequence demonstrated absolute stereochemistry in the sequence.[73] A related, but not natural, steganane (**99**) was obtained[74] from natural dimethylmatairesinol (**100**), effected by thallium tristrifluoroacetate in methylene chloride at room temperature; the reaction was accelerated by boron trifluoride and yields up to 90% were recorded.

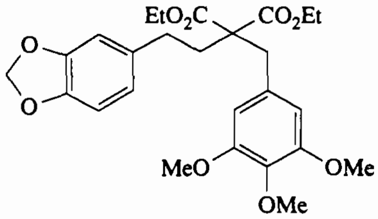
EtO2C
CO2Et
O
O
MeO
OMe
OMe

**(94)**

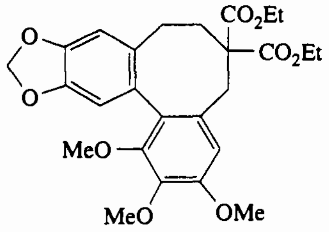
CO2Et
CO2Et
O
O
MeO
MeO
OMe

**(95)**

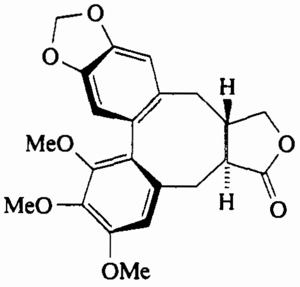
O
O
H
MeO
O
MeO
H
O
OMe

**(96)**

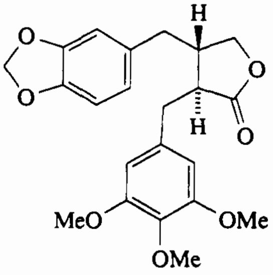
H
O
O
O
H
O
MeO
OMe
OMe

**(97)**

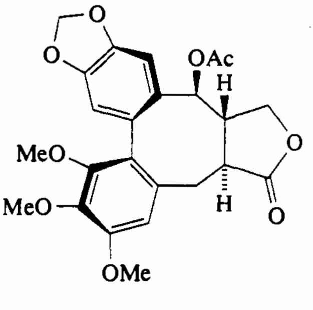
O
O
OAc
H
O
MeO
MeO
H
O
OMe

**(98)**

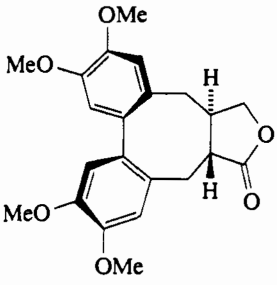
OMe
MeO
H
O
MeO
H
O
OMe

**(99)**

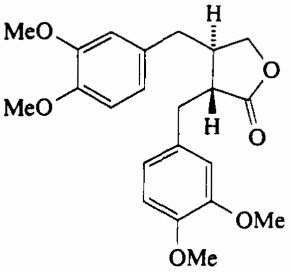
H
MeO
O
MeO
H
O
OMe
OMe

**(100)**

Some simpler lignans of the dibenzocyclooctadiene group have been prepared by related couplings, *e.g.* (±)-deoxyschizandrin (**101**; *ca.* 50%) and (±)-wuweizisu-C (**102**; yield unstated) from precursors (**103**) and (**104**), using low temperature vanadium oxytrifluoride oxidations[75,76] A reinvestigation[77] of the last two syntheses, comparing various reagents, concluded that iron(III) reagents were most effective although the yields reported were only fair, 32% and 46% for (**101**) and (**102**), utilizing iron(III) perchlorate hexahydrate in acetonitrile. Finally the successful formation is worth noting of the eight-membered nitrogen heterocycles (**105**) and (**106**) by anodic oxidations (platinum anode) of the precursor amides (**107**; 45%) and (**108**; 60%).[78]

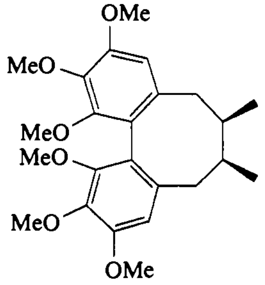

**(101)**

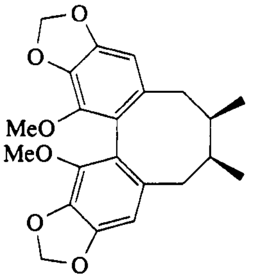

**(102)**

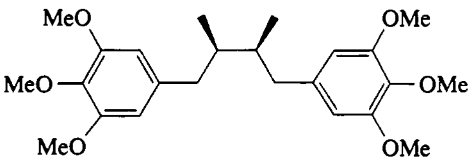

**(103)**

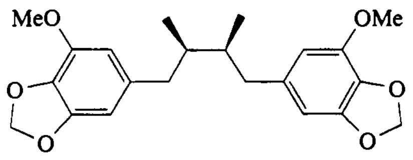

**(104)**

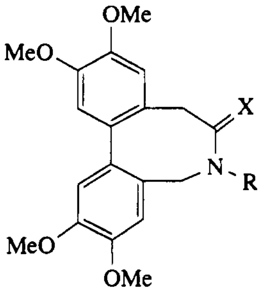

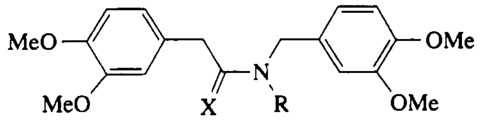

(**105**) X = O, R = Me
(**106**) X = $H_2$, R = Ac

(**107**) X = O, R = Me,
(**108**) X = $H_2$, R = Ac

A few coupling reactions to afford macrocycles have been uncovered.[79] The ester (**109**), on treatment with thallium tristrifluoroacetate for 3 min at room temperature, yielded the 11-membered lactone (**110**; 14%), *via para–para* linking. Longer (10 min) reaction of the related ester (**111**), with water quenching, afforded the 13-membered lactone (**112**), by way of coupling, *para* to a methoxylated site, and loss of a benzylic hydrogen to intermediate (**113**), which was rearomatized in allylic hydrolysis. In studies on anodic oxidations of substrates (**78**), cyclization to biaryls with bridges as long as *n* = 16, *i.e.* 20-membered rings, have been observed, although in low yield.[80]

In concluding this section it is worth noting that in these nonphenolic aryl couplings, the new bond is usually formed between sites *para* to ether oxygen, in accord with electron density calculations on methoxybenzene cation radicals, and with their ESR spectra.

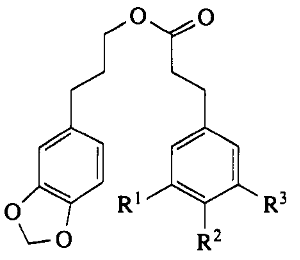

**(109)** $R^1 = H, R^2 = R^3 = OCH_2O$
**(111)** $R^1 = R^2 = R^3 = OMe$

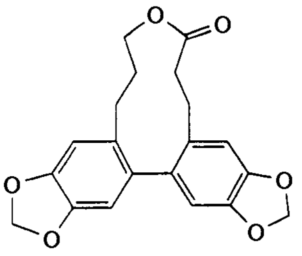

**(110)**

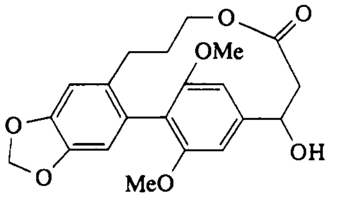

**(112)**

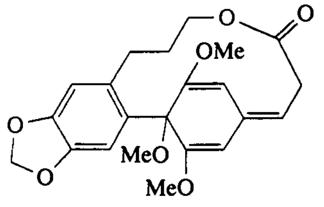

**(113)**

### 2.9.2.3 Biaryls Formed by Aryl Radical Insertion

In the introduction it was pointed out that phenolic coupling may involve addition of a carbon radical to a phenolate anion, and nonphenolic coupling may proceed by way of radical cation attack on an unoxidized aromatic unit. A closely related group of transformations involve generation of an aryl radical which then inserts into a second aryl unit. A few examples are given here, since the process can supplement the direct oxidation approach. A representative reaction is the photochemical transformation,[81] under basic conditions (sodamide–dimethylformamide), of the bromophenol (**114**) into (±)-domesticine (**115**; 31%), with formation of a six-membered ring. The first synthesis[82] of a naphthylisoquinoline alkaloid, *O*-methyltetradehydrotriphyophylline (**116**) used irradiation (254 nm) of bromide (**117**) as the key step, forming the pentacycle (**118**; 15%) for conversion to (**116**). An aryl radical may also be generated by reductive cleavage of halide at the cathode; the bromobenzoylaniline (**119**) gave the biaryl (**120**) in this way.[83] In another example[84] the bromobenzoylnaphthylamine (**121**) afforded the arylnaphthalene (**122**; 44%), by closure and rearrangement through the spiro radical (**123**). Seven-membered rings are amenable to formation in such reactions; irradiation of the iodobenzylamine (**124**) in dilute acid gave the dibenzoazepine (**125**) in 57% yield,[85] and photolysis in dilute alkali of the bromophenol (**126**) yielded the homoaporphine (**127**)[86] albeit in only 55%. Two examples of intracoupling to eight-membered rings complete this brief survey; photolysis of the iodide (**128**)[87] and the bromide (**129**)[85] gave the dibenzoazacyclooctadienes (**130**; 21%) and (**131**; 22%). The former is an apogalanthamine analog.

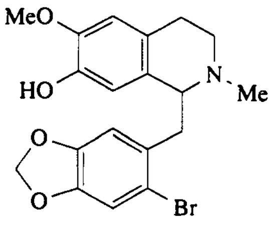

**(114)**

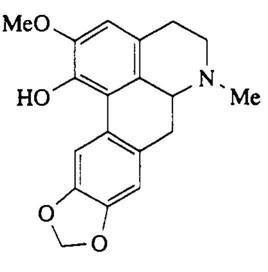

**(115)**

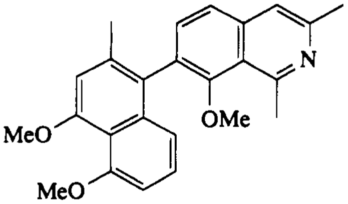
N
OMe
MeO
MeO

**(116)**

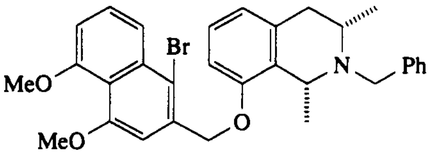
Br
N
Ph
MeO
O
MeO

**(117)**

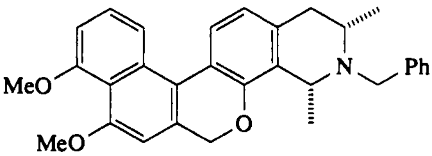
N
Ph
MeO
O
MeO

**(118)**

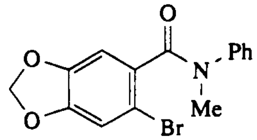
O
N
Ph
Me
O
O
Br

**(119)**

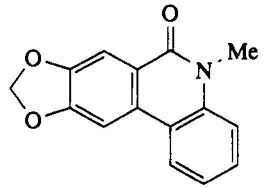

**(120)**

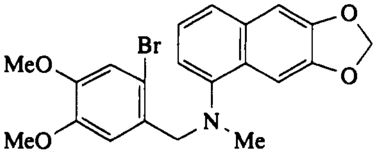
Br
O
MeO
O
MeO
N
Me

**(121)**

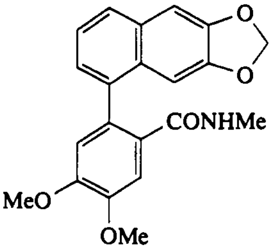
O
O
CONHMe
MeO
OMe

**(122)**

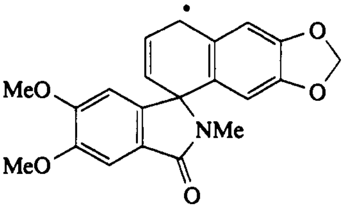
O
MeO
O
NMe
MeO
O

**(123)**

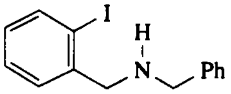

**(124)**

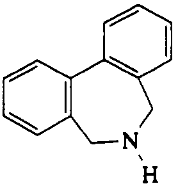

**(125)**

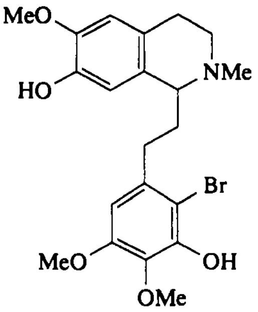
MeO
HO
NMe
Br
MeO
OH
OMe

**(126)**

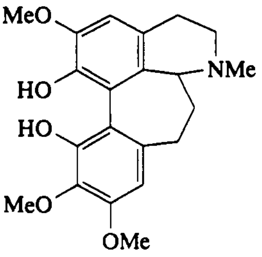
MeO
HO
NMe
HO
MeO
OMe

**(127)**

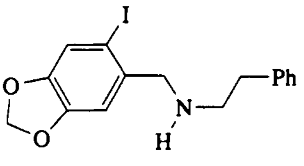

**(128)**

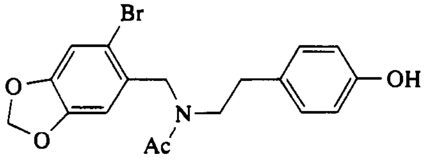

**(129)**

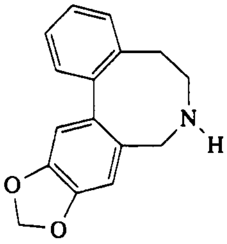

**(130)**

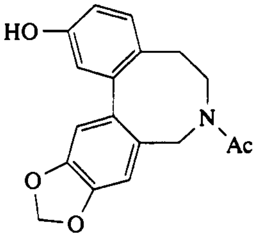

**(131)**

## 2.9.3 SYNTHESIS OF SPIRODIENONES

### 2.9.3.1 Spirodienones *via* Phenol–Phenol C—C Coupling

If, in an intramolecular phenolic coupling process, one of the preferred coupling sites (most usually *para* to OH) is already substituted, then a spirodienone product may form, and may be favored over coupling at another unsubstituted site. In practice good yields of spirodienones have often been isolated in such cases. Spirodienones are prone to undergo dienone–phenol rearrangement (see Chapter 3.5, Whiting, this volume) and occasionally reorganize under the reaction conditions; it is not always clear from products whether or not a dienone has intervened.

The clearest examples are suitably substituted 1,3-diarylpropanes. The 3,4′-dihydroxy compound (**132**) on treatment at –78 °C in ether with vanadium oxytrichloride yielded (75%) the tricyclic dienone (**133**),[88] and the methoxylated relatives (**134**) and (**135**) both cyclized in parallel fashion to (**136**) and (**137**), in 67% yield, using an iron(III) complex reagent.[89] The amide (**138**) formed the spiro-linked benzazepine (**139**; 50%) on oxidation with vanadium oxytrichloride,[90] showing that a seven-membered ring may form. Generation of five-membered rings is also satisfactory, as evidenced by the synthesis of picrolichenic acid (**140**) by manganese dioxide oxidation of the aryl ester (**141**), in 25% (max.) yield.[91]

These couplings are of major importance in the alkaloid area, where they may be biomimetic, and there has been a considerable quantity of work on the 1-benzyl- and 1-phenylethyl-tetrahydroquinoline alkaloids, which has been reviewed.[1,17,19]

One major preoccupation was the realization of a laboratory analogy for the intracoupling of relatives of reticuline (**142**) to the morphine group *via p–o* (4a–3′) linking. In various studies *p–p* coupling (4a–7′) and *o–p* (8–7′) of (±)-reticuline were achieved, leading to (±)-isosalutaridine (**143**) and (±)-isoboldine

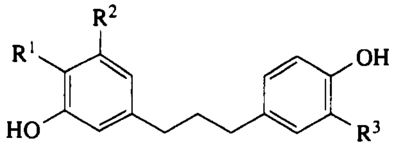

**(132)** $R^1 = R^2 = R^3 = H$
**(134)** $R^1 = R^2 = R^3 = OMe$
**(135)** $R^1 = R^3 = OMe$, $R^2 = H$

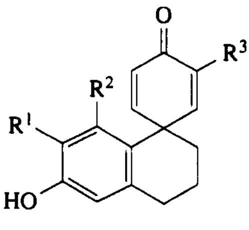

**(133)** $R^1 = R^2 = R^3 = H$
**(136)** $R^1 = R^2 = R^3 = OMe$
**(137)** $R^1 = R^3 = OMe$, $R^2 = H$

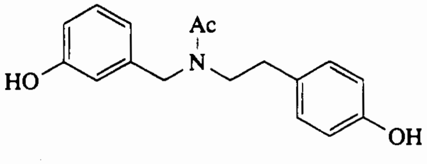

**(138)**

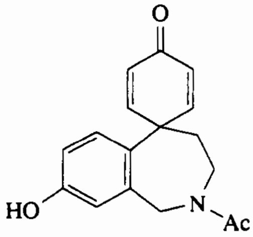

**(139)**

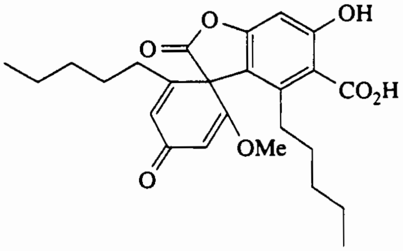
O
O
OH
CO2H
OMe
O

**(140)**

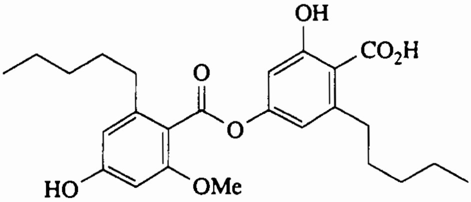
OH
CO2H
O
O
HO
OMe

**(141)**

(**144**) respectively, in reactions of considerable biosynthetic interest, but little preparative value. The long-sought *p–o* linking (4a–3′) was eventually realized using thallium tristrifluoroacetate as oxidant at low temperature; in this way the *N*-ethoxycarbonyl relative (**145**) provided the spirodienone (**146**) in 23% yield.[92] Lithium aluminum hydride reduction gave alcohol (**147**), which closed in acid to (±)-thebaine (**148**).

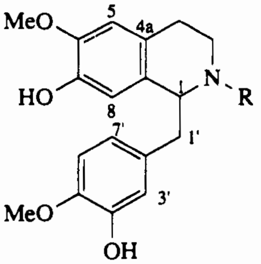
MeO
5
4a
N
R
HO
8
7'
1
1'
3'
MeO
OH

(**142**) R = Me
(**145**) R = $CO_2Et$

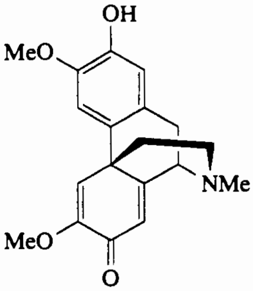
OH
MeO
NMe
MeO
O

**(143)**

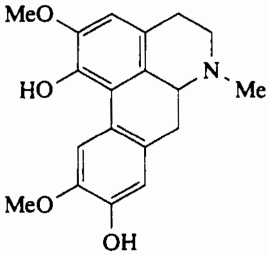
MeO
HO
N
Me
MeO
OH

**(144)**

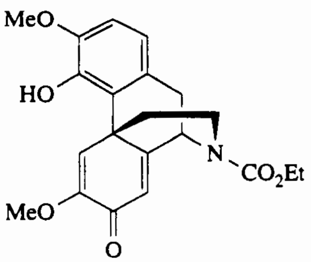
MeO
HO
N
CO2Et
MeO
O

**(146)**

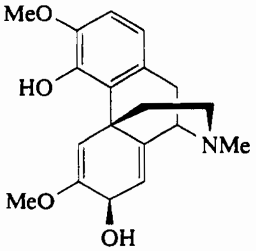
MeO
HO
NMe
MeO
OH

**(147)**

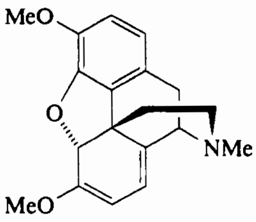
MeO
O
NMe
MeO

**(148)**

The (±)-benzyltetrahydroisoquinoline (**149**), with 3′,7- rather than 4′,7-dihydroxylation as in (**142**), was coupled[93] using potassium ferricyanide to the spiroketone (**150**), as a pair of diastereoisomers (up to 50% yield). One stereoisomer, on reduction of carbonyl and aqueous acid treatment, was converted to the new spirodienone (**151**), the alkaloid orientalone.

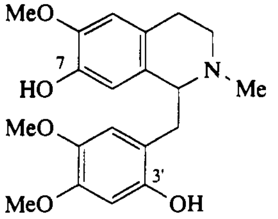

**(149)**

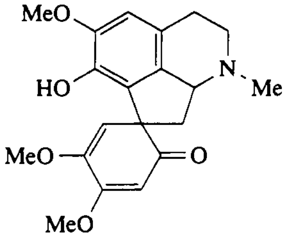

**(150)**

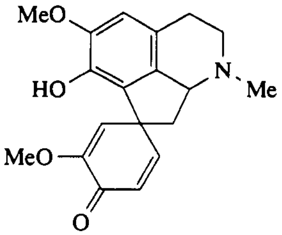

**(151)**

In the 1-arylethyltetrahydroisoquinoline series, the 6′,7-dihydroxy example (**152**) underwent *o–p* coupling (49%) with ferricyanide;[94] the product, (**153**), was rearranged into (±)-multifloramine (see Chapter 3.5, this volume). Similarly the dimethoxy analog (**154**) was oxidized to (±)-(**155**; two diastereomers), in 36% at a graphite anode,[95] and in 68% with vanadium oxytrifluoride;[68] one of the stereoisomers was kreysiginone. With a 6,6′-dihydroxy pattern, as in (**156**), *p–p* coupling was induced by the last named reagent to provide the spiro tetracycle (**157**).[68]

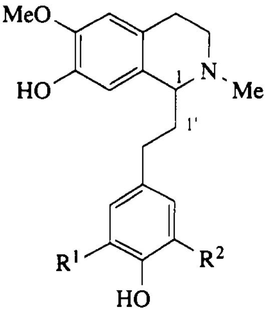

**(152)** $R^1 = R^2 = OMe$

**(154)** $R^1 = H, R^2 = OMe$

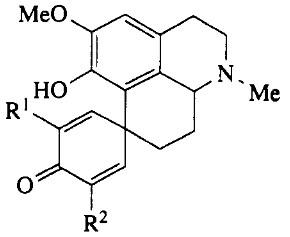

**(153)** $R^1 = R^2 = OMe$

**(155)** $R^1 = H, R^2 = OMe$

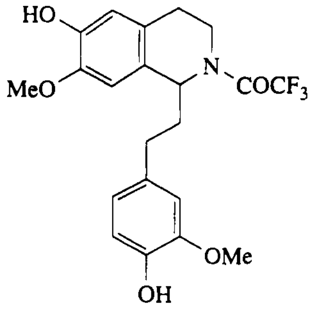

**(156)**

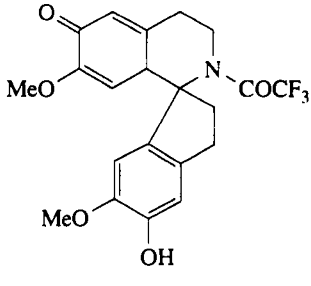

**(157)**

In a biomimetic synthesis of erysodienone (**158**), the bis(arylethyl)amine (**159**) was oxidized with alkaline ferricyanide to give the desired natural product in 35% yield.[96] The reaction probably involves *p–p* coupling, oxidation to the diphenoquinone (**160**), and intra-Michael addition; in support similar oxidation[97] of the bridged biaryl (**161**) also gave erysodienone, 80%. The key intermediate (**161**), both in *in vitro* and *in vivo* formation of (**158**), has also been prepared by oxidative coupling of the benzylisoquinoline (**162**) by vanadium oxytrifluoride at –10 °C. The product dienone (**163**; 40%) fragmented on base deacylation, and reduction of the product imine gave (**161**).[98]

The arylethylbenzylamine derivative (**164**) with one blocked *para* position was smoothly oxidized with alkaline ferricyanide to the spirodienone (**165**),[99] related to the Amaryllidaceae alkaloid system.

In recent work Kende and his coworkers[100] have explored intramolecular oxidative coupling between phenolate and enolate, rather than between two phenolates. This proved a viable process for certain carbonyl enolates, and for nitro-stabilized anions. Thus potassium ferricyanide oxidations of the indandione

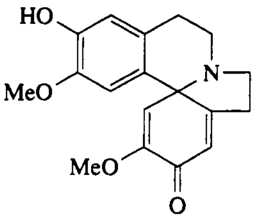
HO
MeO
N
MeO
O

**(158)**

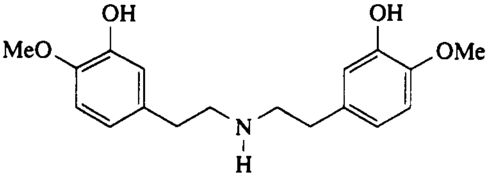
OH
MeO
OH
OMe
N
H

**(159)**

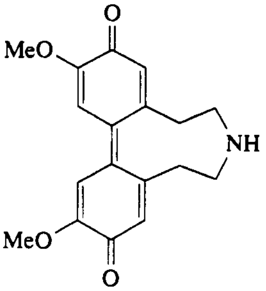
O
MeO
NH
MeO
O

**(160)**

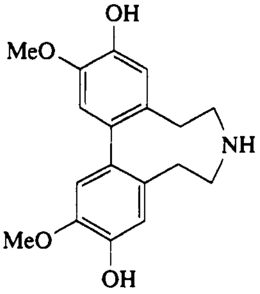
OH
MeO
NH
MeO
OH

**(161)**

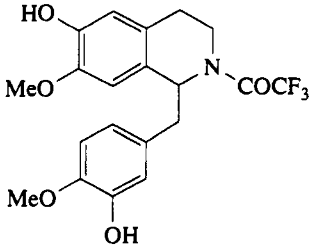
HO
MeO
N
COCF3
MeO
OH

**(162)**

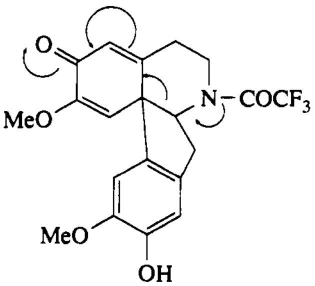
O
MeO
N
COCF3
MeO
OH

**(163)**

derivative (**166**) and 4-(ω-nitropentyl)phenol (**167**) gave the product spirodienones (**168**) and (**169**) in 88% and 83% yields respectively, while reaction of the coumarin (**170**) with dipotassium hexachloroiridate effected cyclization to (**171**; 33%).

For recent examples of intramolecular phenolic coupling to spirodienones, see refs. 164 and 165.

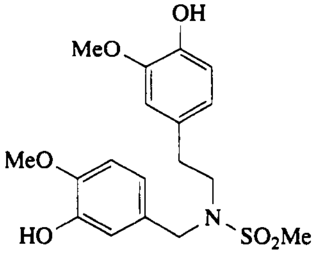
OH
MeO
MeO
HO
N
SO2Me

**(164)**

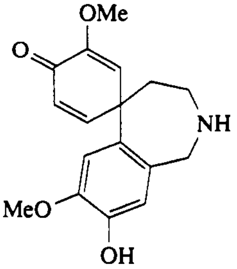
OMe
O
NH
MeO
OH

**(165)**

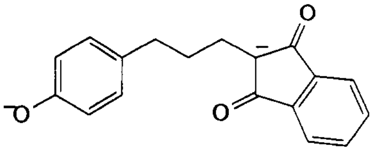

**(166)**

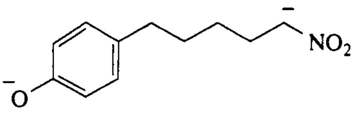

(167)

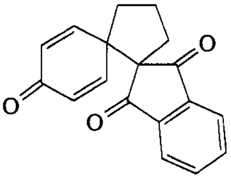

(168)

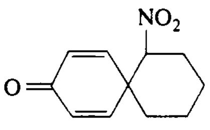

(169)

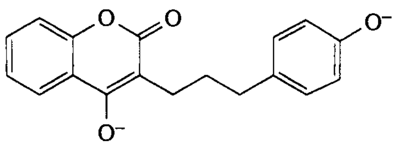

(170)

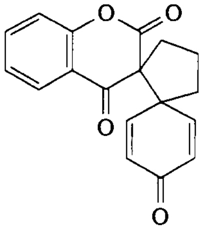

(171)

### 2.9.3.2 Cyclohexadienones *via* Phenol Ether Coupling

A number of interesting and useful reactions involve cyclization, forming six- to eight-membered rings, between the two aryl units separated by a short chain. Thus the bisarylethane (**172**) gave, on anodic oxidation, the tricyclic dienone (**173**) in 90% yield, arising from intracoupling followed by 1,2-shift.[101] Similarly the analog (**174**) afforded dienone (**175**; 98%), using silica-supported iron(III) chloride as oxidant.[52] The 1,2-shift was not observed with the example (**176**) with monooxygenated aryls, which gave the steroidal tricycle (**177**) at the anode (22%) or on reaction with vanadium oxytrifluoride (30%). With suitably substituted diarylpropanes formation of a spirodienone is feasible. Thus vanadium oxytrichloride treatment of (**178**) led to tricyclic spirodienone (**179**; 70%);[90] only 18% of the dibenzocycloheptadiene alternative (**180**) was formed. The parallel monophenolic coupling (**181**) → (**179**)[90] was also effected at −78 °C with the same reagent (97% yield); also, both thallium and silver trifluoroacetates induced the coupling. Such monophenolic coupling, using electrooxidation, was employed for transformation[102] of the biarylpropane (**182**) into the spirodienone (**183**; 80%); the latter was subjected to cyclopropanation, followed by fragmentation and ring expansion to the tropolone (**184**), a key intermediate in a colchicine synthesis. Another example involves monophenolic coupling in the acetal (**185**) using bistrifluoroacetyloxyiodobenzene;[103] the product (**186**), only obtained in 13% yield, was converted on to 6a-epipretazettine.

An original biomimetic synthesis[104] of the Amaryllidaceae alkaloid narwedine involved oxidation of the arylethylbenzylamine (**187**) with lithium tetrachloropalladate to generate the arylpalladium species (**188**); the course of further oxidation with thallium tristrifluoroacetate could be controlled to lead either to the bisspirodienone complex (**189**; 1′–1″ coupling) or to narwedine (**190**; 51%; 1′–2″ coupling). Seven-membered rings were also formed in the monophenolic oxidation of (**191**; vanadium oxytrifluoride–thallium tristrifluoroacetate, 88%)[57b] and in the anodic oxidation (62%) of (**192**),[105] in both cases yielding dienone (**193**). Deacylation of (**193**) leads to spontaneous Michael addition, forming (±)-oxocrinine (**194**).[105]

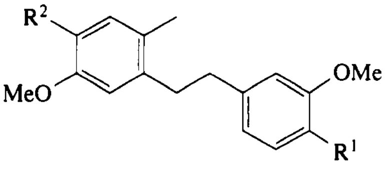

(**172**) $R^1 = R^2 = OMe$
(**174**) $R^1 = OMe$, $R^2 = OEt$
(**176**) $R^1 = R^2 = H$

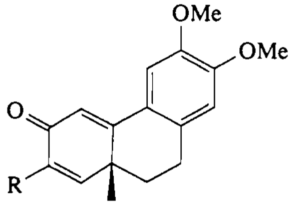

(**173**) R = OMe
(**175**) R = OEt

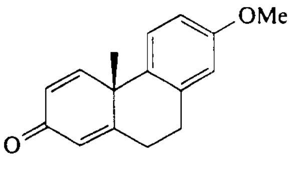

(**177**)

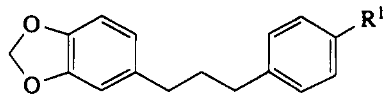

**(178)** R$^1$ = OMe
**(181)** R$^1$ = OH

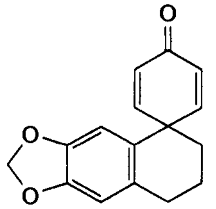

**(179)**

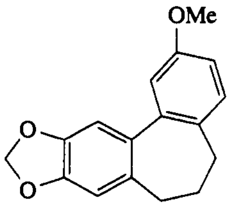

**(180)**

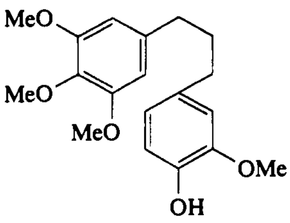
MeO
MeO
MeO
OMe
OH

**(182)**

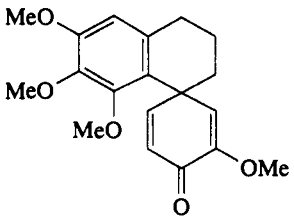
MeO
MeO
MeO
OMe
O

**(183)**

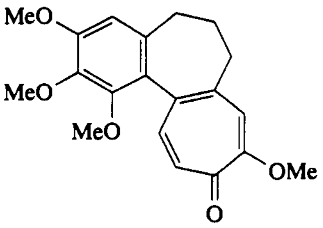
MeO
MeO
MeO
OMe
O

**(184)**

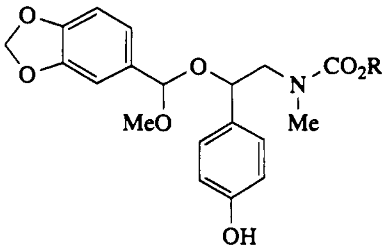
O
N
CO$_2$R
MeO
Me
OH

**(185)**

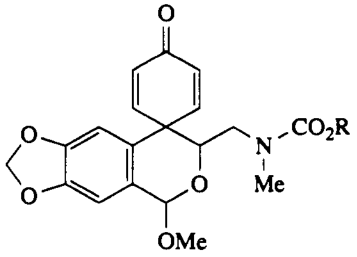
O
N
CO$_2$R
O
Me
OMe

**(186)**

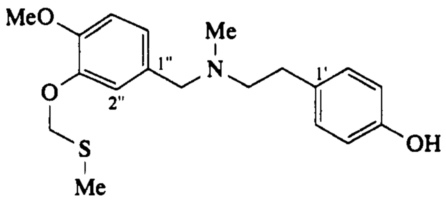
MeO
Me
N
1''
1'
2''
O
S
Me
OH

**(187)**

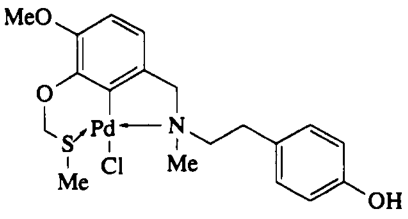
MeO
O
S
Pd
N
Cl
Me
Me
OH

**(188)**

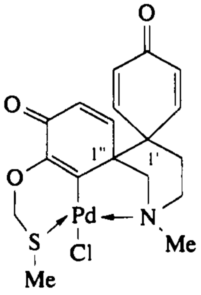
O
O
1''
1'
O
Pd
N
S
Cl
Me
Me

**(189)**

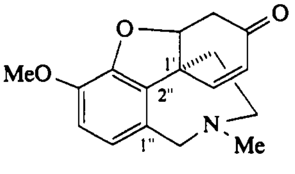
O
O
1'
MeO
2''
N
1''
Me

**(190)**

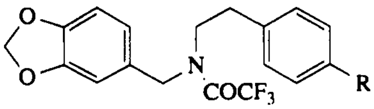

**(191)** R = OH
**(192)** R = OMe

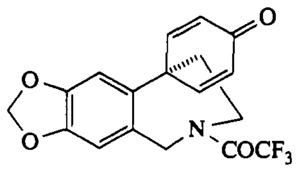

**(193)**

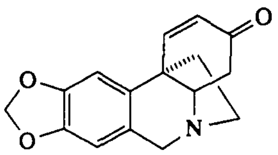

**(194)**

Benzyltetrahydroisoquinolines have been thoroughly investigated for reasons discussed above. (±)-Laudanosine (**195**) was oxidized at a platinum anode to yield methylflavinantine (**196**) in 52% yield[106] (4a–7′ coupling), and a similar reaction proceeds with a number of relatives including 6′,8-dimethoxylaudanosine (**197**), which provided protostephanone (**198**; 35%).[107] An enantioselective synthesis of (*R*)-laudanosine enabled preparation of (*R*)-methylflavinantine by anodic oxidation,[108] with reported yields 70–90%. Various analogs of the benzylisoquinoline system have been examined. Among these, oxidative coupling of the benzyltetralin (**199**) is of interest;[63] varying the conditions of anodic oxidation, *i.e.* solvent, temperature and pH, it was found possible to obtain either the dienone (**200**; 4a–7′ coupling, 71%) or the biaryl (**201**; 7′–8 coupling, 45%). The benzyl lactone (**202**) was electrooxidized to the spirolactone

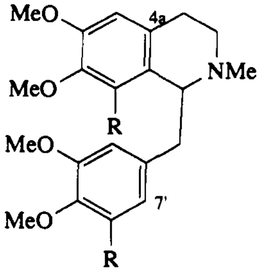
MeO
4a
NMe
MeO
R
MeO
7'
MeO
R

**(195)** R = H
**(197)** R = OMe

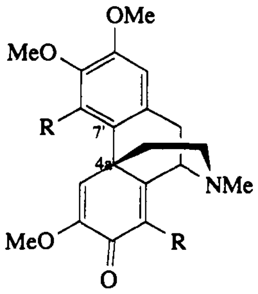
OMe
MeO
R
7'
4a
NMe
MeO
R
O

**(196)** R = H
**(198)** R = OMe

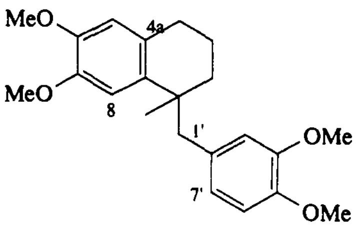
MeO
4a
MeO
8
1'
OMe
7'
OMe

**(199)**

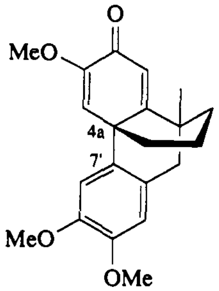
O
MeO
4a
7'
MeO
OMe

**(200)**

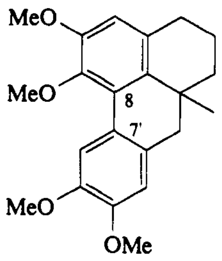
MeO
MeO
8
7'
MeO
OMe

**(201)**

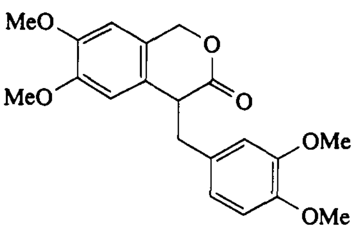
MeO
O
MeO
O
OMe
OMe

**(202)**

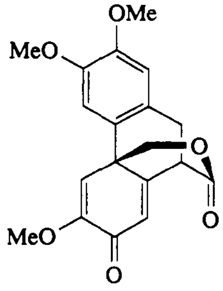
OMe
MeO
O
MeO
O
O

**(203)**

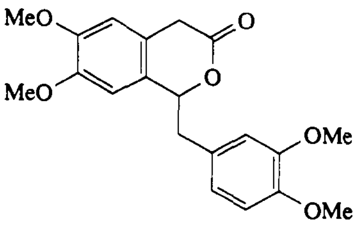
MeO
O
MeO
O
OMe
OMe

**(204)**

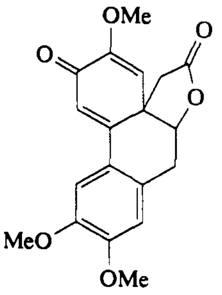
OMe
O
O
O
MeO
OMe

**(205)**

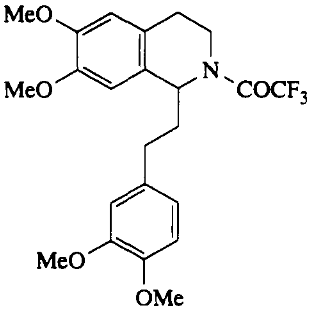

**(206)**

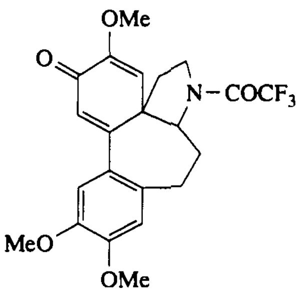

**(207)**

**(203)**,[78] in parallel with the last two cases, but the isomeric lactone (**204**) afforded a rearranged spirolactone (**205**),[109] both with vanadium(V) reagents (59%) and at the anode (33%). The arylethylisoquinoline (**206**) also afforded a similarly rearranged spirodienone (**207**; 64%), on intracoupling, using vanadium oxytrifluoride.[68]

### 2.9.3.3 Spirodienones *via* Aryl Radical Insertion

Two examples suffice to illustrate this reaction type, both involving 1-benzyltetrahydroisoquinolines. The 8-bromo structure (**208**) was photolyzed under alkaline conditions to (±)-mecambrine (**209**), in 10% yield,[81] and the 7′-bromo relative (**210**) afforded dienone (**211**), 34% isolated, on the way to synthesis of (±)-boldine.[110]

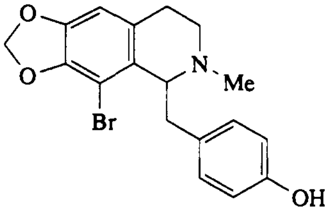

**(208)**

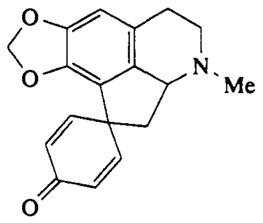

**(209)**

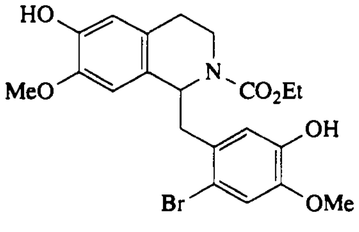

**(210)**

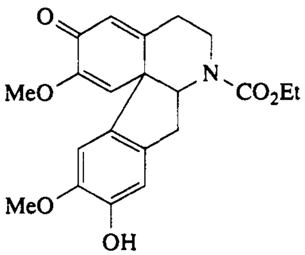

**(211)**

## 2.9.4 FORMATION OF CARBON–OXYGEN BONDS

### 2.9.4.1 Synthesis of Aryl Ethers

An early example[111] was the surprisingly selective oxidation of methoxythymol (**212**) with alkaline ferricyanide to libocedrol (**213**; 49%); further cross-coupling of the latter with more monomer using the same reagent yielded (46%) the trimeric libocedroxythymoquinone (**214**; 46%). Lophocerine (**215**) also formed a dimer, isopilocereine (**216**; 32%), on exposure to ferricyanide, together with traces of the trimeric pilocerine (**217**).[112] Magnocurarine methiodide (**218**) was similarly dimerized (15%) to the model (**219**) for certain dimeric benzylisoquinoline alkaloids;[113] and in the same series, phenol (**220**)[44] was coupled at a graphite anode to a product which was transformed by *O*-protection, reduction, and deprotection to (±)-dauricine (**221**), 8% overall. Yet another benzylisoquinoline (**222**) gave the unusual macrocyclic dehydrodimer (**223**) on treatment with diphenyl selenoxide[48] followed by permethylation.

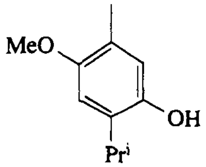

**(212)**

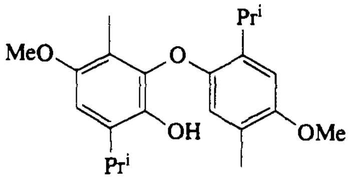
Pr$^i$
MeO
O
OH
OMe
Pr$^i$

**(213)**

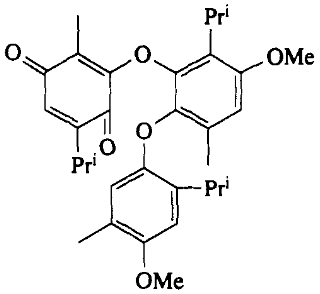
Pr$^i$
O
O
OMe
O
O
Pr$^i$
Pr$^i$
OMe

**(214)**

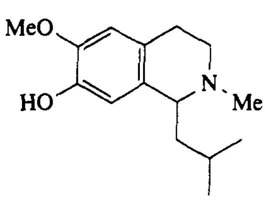

**(215)**

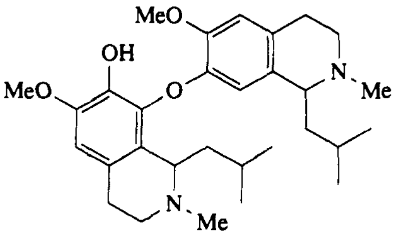
MeO
OH
MeO
O
N
Me
N
Me

**(216)**

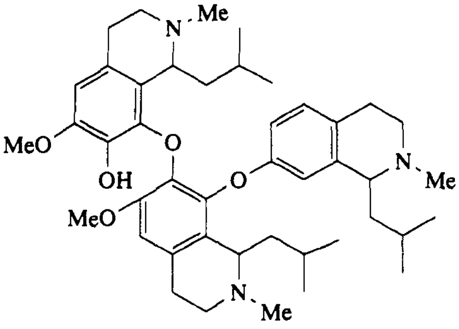
N
Me
MeO
O
OH
O
MeO
N
Me
N
Me

**(217)**

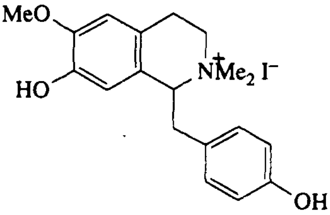
MeO
HO
N$^+$Me$_2$ I$^-$
OH

**(218)**

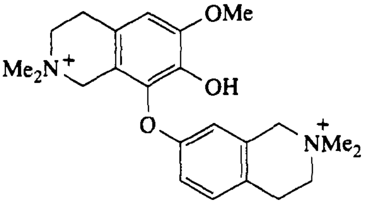
OMe
Me$_2$N$^+$
OH
O
N$^+$Me$_2$

**(219)**

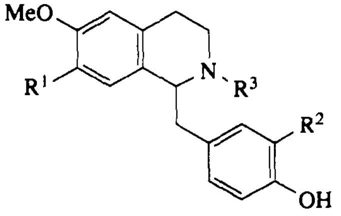
MeO
R$^1$
N
R$^3$
R$^2$
OH

**(220)** $R^1 = OMe, R^2 = H, R^3 = CO_2Et$

**(222)** $R^1 = R^2 = OH, R^3 = COCF_3$

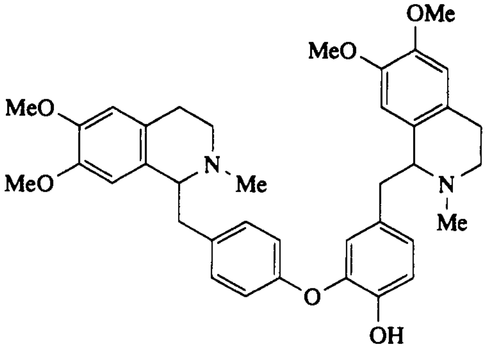
OMe
MeO
MeO
MeO
N
Me
N
Me
O
OH

**(221)**

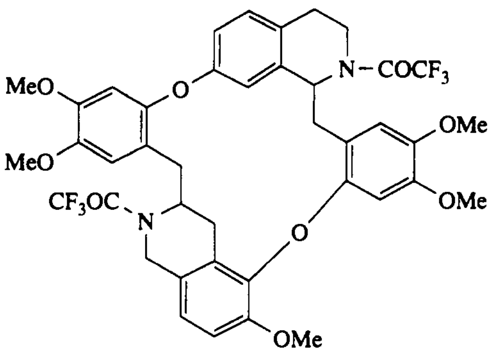
N−COCF3
MeO
O
MeO
OMe
OMe
CF3OC
N
O
OMe

**(223)**

A number of intramolecular variations are documented, some of biogenetic interest. The benzophenone (**224**) was cyclized in good yield (83%) to 2,6-dihydroxyxanthone (**225**) with ferricyanide,[114] and the synthetic depside (**226**) yielded diploicin (**227**) on manganese dioxide oxidation.[115] Finally the diarylheptanoid (**228**) afforded the macrocyclic ether (**229**) on reaction with thallium tristrifluoroacetate; similar ethers, *e.g.* acerogenin, occur naturally.[116]

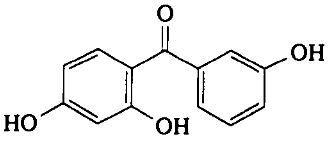

**(224)**

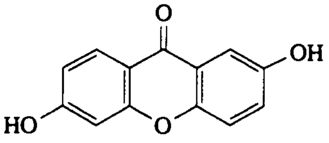

**(225)**

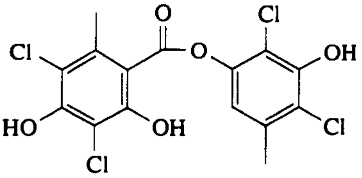
O
Cl
Cl
O
OH
HO
OH
Cl
Cl

**(226)**

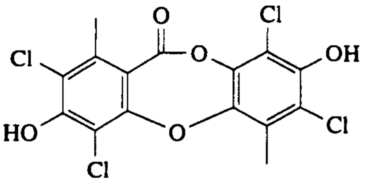
O
Cl
Cl
O
OH
HO
O
Cl
Cl

**(227)**

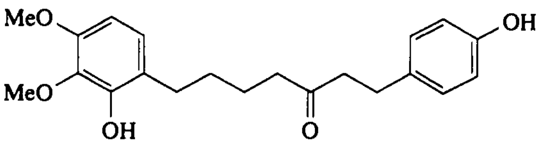
MeO
MeO
OH
O
OH

**(228)**

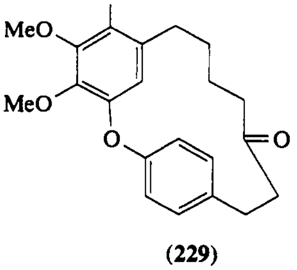
OH
MeO
MeO
O
O

**(229)**

### 2.9.4.2 Spiroethers

Ring systems containing cyclohexadienones spiro-linked to a cyclic ether can be constructed by oxidative C—O bond connection in the intramolecular mode. Five-membered ring formation is well documented, and the reactions may be efficient. For example, the linked bisnaphthols (**230**), (**231**) and (**232**) formed spirodienones (**233**),[117] (**234**)[117] and (**235**)[118] on treatment with sodium hypochlorite (*ca.* 60% yield), alkaline ferricyanide (60%), and dichlorodicyanobenzoquinone ('quantitative'), respectively. A well-known reaction in this area is the oxidation of griseophenone A (**236**) to dehydrogriseofulvin (**237**),[119] which has been induced with various reagents, potassium ferricyanide, lead dioxide and manganese dioxide, and quantitative yields have been reported. Copper(II) salt–amine complexes are also effective[120] and, using (–)-α-phenylethylamine, dehydrogriseofulvin with a small enantiomeric excess was obtained. The oxygen atom participating in C—O bond formation may derive from a function other than phenol. Thus the arylpropanoic acids (**238**) and (**239**) gave the spirodienones (**240**) and (**241**) at a platinum anode, in modest yield, while the acid (**242**) yielded (**243**; 40%), with buffered *N*-bromosuccinimide.[121] In view of the disparity between oxidation potentials of the interacting functions it is unlikely that these reactions involve radical–radical coupling. The same is true for the oxidative cyclization of phenolic oximes, *e.g.* (**244**) to the spirooxazoline (**245**; 62%), using manganese(III) acetylacetonate.[122] The reaction, a model for the biosynthesis of aerothionin, probably proceeds *via* an incipient phenoxonium ion (see Scheme 3).

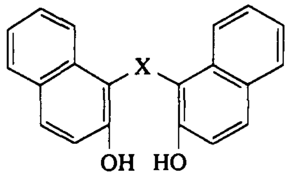

(**230**) X = $CH_2$
(**231**) X = S

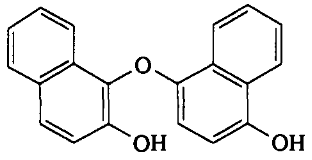

(**232**)

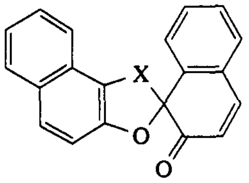

(**233**) X = $CH_2$
(**234**) X = S

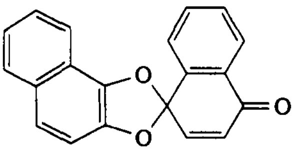

(**235**)

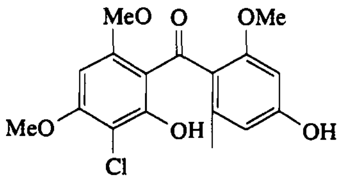

(**236**)

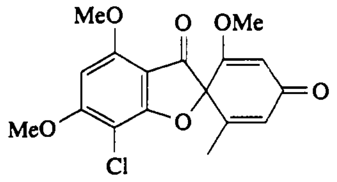

(**237**)

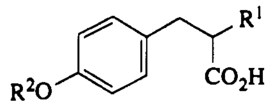

(**238**) $R^1 = R^2 = H$
(**239**) $R^1 = NHCO_2Me$, $R^2 = H$
(**242**) $R^1 = H$, $R^2 = Me$

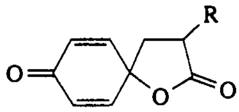

(**240**) R = H
(**241**) R = $NHCO_2Me$

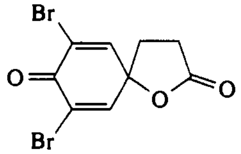

(**243**)

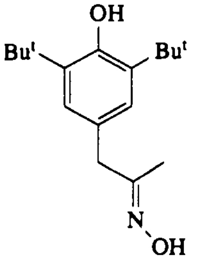

(**244**)

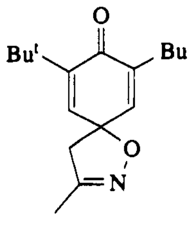

(**245**)

Few examples, in this class, of phenol–phenol coupling generating six-membered rings, are available: the bisarylethane (**246**) gave (**247**) only in 11% yield.[123] However biomimetic oxidation of phenolic acids offers several high yielding examples, *e.g.* the formation of geodoxin (**248**) from geodin (**249**),[124] employing lead dioxide, 88% yield; and the oxidation of the acid (**250**) to dehydrogriseofulvoxin (**251**), 85% with manganese dioxide.[114] A striking case of successful intramolecular coupling[125] is the formation of the 17-membered cyclic ether (**252**) from the phenolic tripeptide (**253**) on oxidation with thallium trinitrate in methanol. Presumably a dibromospirodienone is formed, which suffers allylic displacement of bromine by methanol. Dienone ether (**252**) was transformed into the cyclic bisaryl ether peptide (**254**), an aminopeptidase inhibitor.

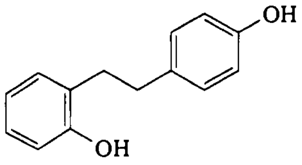

**(246)**

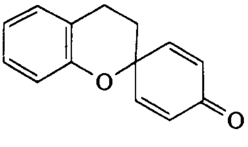

**(247)**

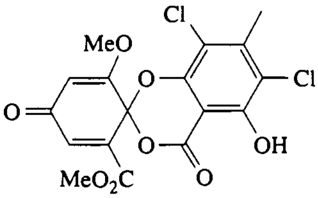
Cl
MeO
O
Cl
O
O
OH
MeO$_2$C
O

**(248)**

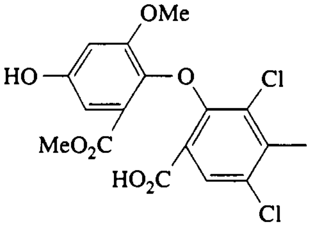
OMe
HO
O
Cl
MeO$_2$C
HO$_2$C
Cl

**(249)**

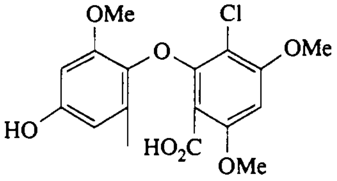
OMe
Cl
O
OMe
HO
HO$_2$C
OMe

**(250)**

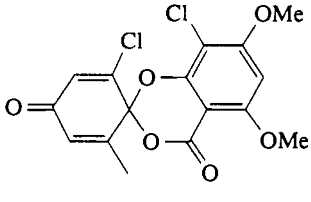
Cl
OMe
Cl
O
O
O
OMe
O

**(251)**

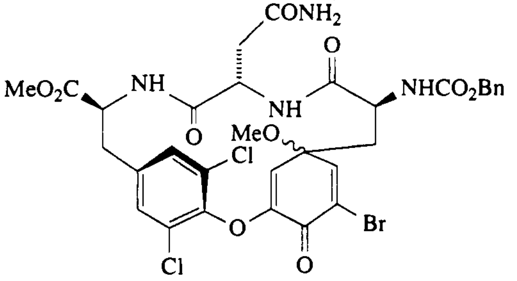
CONH$_2$
O
MeO$_2$C
NH
NHCO$_2$Bn
NH
O
MeO
Cl
O
Br
Cl
O

**(252)**

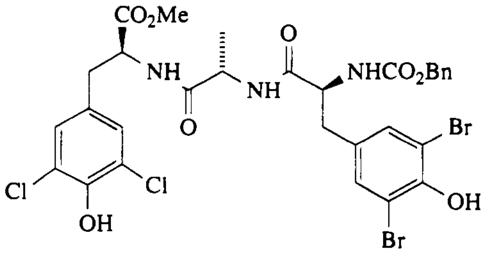
CO$_2$Me
O
NH
NHCO$_2$Bn
NH
O
Br
Cl
Cl
OH
OH
Br

**(253)**

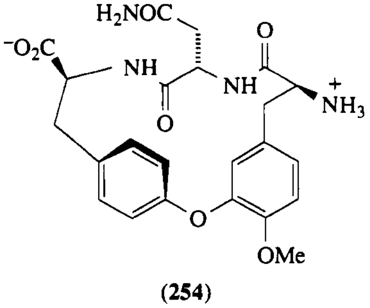
H$_2$NOC
O
$^-$O$_2$C
NH
NH
$\overset{+}{N}H_3$
O
O
OMe

**(254)**

### 2.9.4.3 Aryl Alkyl Ethers *via* C—O Coupling

Two useful groups of related reactions may be discerned here, both of which are observed for propenyl-phenols. The first type is illustrated by the oxidation of isoeugenol (**255**) with aqueous iron(III) chloride,[126] which yields the *threo-* and *erythro-*stereomers (55%) of the hydroxy ether (**256**), presumably by O—C$_\beta$ linking of the initial phenoxyl radical, and addition of water to the resulting intermediate quinone methide. A similar reaction[127] of the phenol (**257**), but using silver oxide, provided (**258**), isolated (62%) as a monomethyl ether; *threo*-(**258**) was (±)-virolin. Cross-coupling is also possible in an efficient manner; thus silver oxide treatment of a mixture of the propenylphenol (**255**) and the allylphenol (**259**; R = Me) yielded[127] an intermediate quinone methide which was reduced *in situ* and methylated to afford the neolignan (**260**), overall in 80% yield. Cross-coupling of (**259**) with (*Z*)-isoeugenol at a platinum anode gave stereoisomers of the ether (**261**; 34%).[128] Related examples are known.[129–131] It has been demonstrated[127] that oxidation of the allylphenol (**259**) with silver oxide in the absence of other phenols or nucleophiles yielded, in solution, the relatively stable quinone methide (**262**); addition of nucleophiles, *e.g.* *p*-methoxyphenol, proceeded smoothly to give ether (**263**), 71% overall.

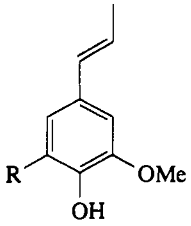

(**255**) R = OMe
(**257**) R = H

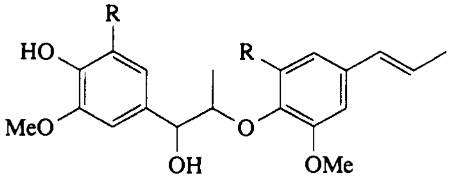

(**256**) R = OMe
(**258**) R = H

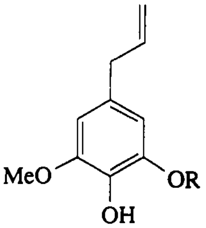

(**259**)

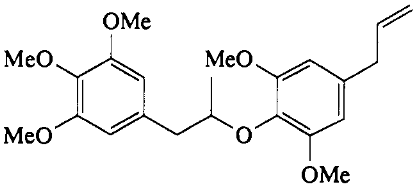

(**260**)

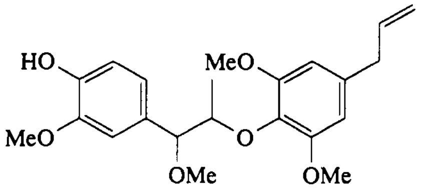

(**261**)

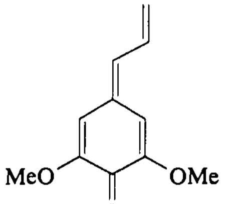

(**262**)

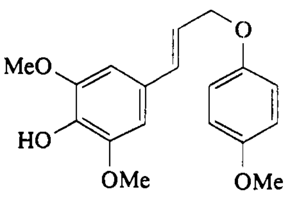

(**263**)

If, in this type of reaction, a suitable catechol component is present, then the major products may be benzodioxanes, *e.g.* silver oxide treatment (benzene, r.t.) of a mixture of propenylphenol (**255**) and allylphenol (**259**; R = H), gave the (±)-product (**264**)[132] in 'good yield', which on methylation formed the neolignan eusiderin. Coumarinolignans have been synthesized in a parallel way, *e.g.* cross-coupling[133] of fraxetin (**265**) with coniferyl alcohol (**266**) using silver oxide or horseradish peroxidase, leads to both cleomiscosin A (**267**) and its regioisomer (**268**), cleomiscosin B. Other members of this class, *i.e.* propacin, aquillochin, and daphneticin were prepared in parallel fashion. The interesting antihepatotoxic flavonolignan silybin (**269**) was obtained from (2*R*,3*R*)-dihydroquercetin (**270**) and coniferyl alcohol; again the regioisomer, isosilybin (**271**), was also produced.[134] These natural products occur as mixtures of stereoisomers, all (2*R*,3*R*) in the chromanone unit but differing in the geometry of the benzodioxane section. The same coupling may be effected enzymically,[135] and peroxidases induce coupling in other vinyl catechols.[136]

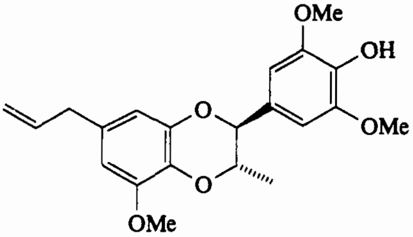

**(264)**

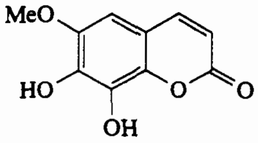

**(265)**

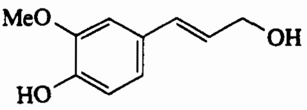

**(266)**

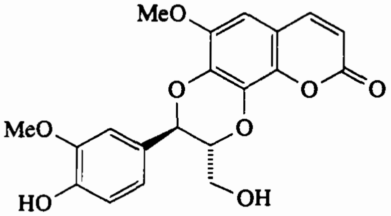

**(267)**

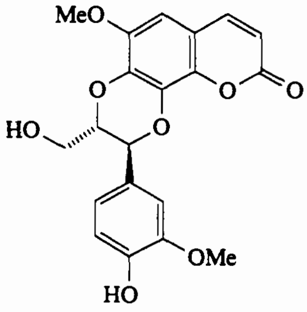

**(268)**

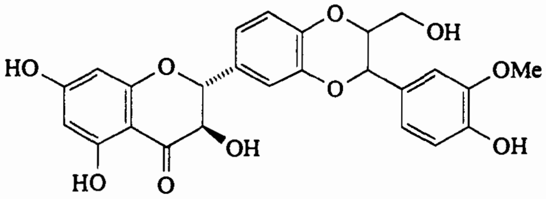

**(269)**

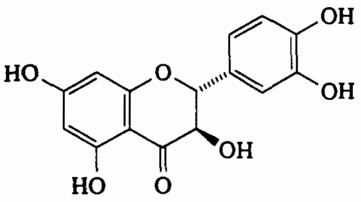

**(270)**

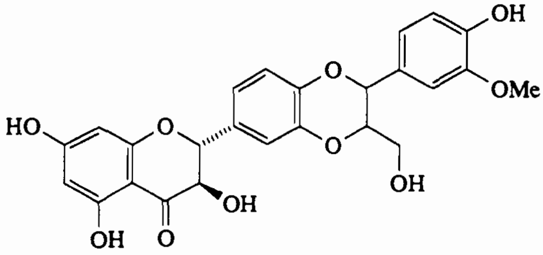

**(271)**

## 2.9.5 C—C COUPLING THROUGH ARYL CONJUGATED DOUBLE BONDS

In structures which contain an *o*- or *p*-hydroxystyryl subunit, the radical from phenolic oxidation is delocalized through the aromatic ring and the side chain (**272**), and couplings may thus involve the β-carbon. The charted reactions which fall into this class can be subdivided into three sets, with products derived from: (i) $C_\beta$—$C_\beta$ coupling; (ii) $C_\beta$—$C_{AR}$ coupling; and (iii) both modes of coupling.

In the first category the best known cases are those in which a hydroxycinnamic acid is dimerized oxidatively to a bisaryldilactone. A range of examples are known.[137] Typical reactions are the oxidation of sinapic acid (**273**) to the dilactone (**274**), in 65% yield using oxygen–iron(III) chloride,[138] and in 60%

yield using a high acid concentration at a glossy carbon anode,[139] and the oxidation of ferulic acid (**275**) to 'dehydrodiferulic acid' (**276**), with iron(III) chloride–air (22%)[140] and with a iron(III) chloride–dimethylformamide reagent.[89] A range of nonphenolic cinnamic acids have been oxidized with thallium tristrifluoroacetate–boron trifluoride to dilactones analogous to (**274**);[141] a nonradical mechanism is preferred whose key step is shown in cipher (**277**). If a *p*-hydroxycinnamate ester is employed, rather than acid, then $C_\beta$—$C_\beta$ coupling can be followed by trapping of quinone methide intermediates with water, as in the formation of the tetrahydrofuran (**278**) from methyl dibromoferulate (**279**), with iron(III) chloride in aqueous acetone.[142] One stereoisomer of the diester (**278**) was obtained, albeit in modest yield; further reduction steps gave the lignan (±)-veraguensin. *p*-Hydroxycinnamyl alcohols can be oxidized to bisaryldioxabicyclo[3.3.0]octanes, *e.g.* syringin (**280**) is both hydrolyzed and oxidized by crude almond emulsion to (±)-syringaresinol (**281**), in up to 68% yield.[143] A cross-coupling between ferulic acid and coniferyl alcohol was used to synthesize, in low yield but in one step, the (±)-natural lactone (**282**).[144] Propenylphenols may also be induced to undergo $C_\beta$—$C_\beta$ coupling, *e.g.* the phenol (**283**) on electrooxidation in methanol[128] afforded the cyclic ether (**284**; 47%), as well as some primary coupled product (**285**; 16%).

The formation of $C_\beta$—$C_{AR}$ bonds is illustrated by the generation of 'dehydrodiisoeugenol' (**286**) from (*E*)-isoeugenol (**257**), enzymically with a mushroom juice[145] (45%) yield, with horseradish peroxidase (65%),[130] with iron(III) chloride[146] (53%), by photooxidation (20%)[129] and by (–)-α-phenylethylamine–copper(II) nitrate (21%). In the last case a low enantiomeric excess was recorded.[120b] Coniferyl alcohol can be oxidized to 'dehydrodiconiferyl alcohol' (**287**) with various enzyme oxidases.[147–149] The *cis*

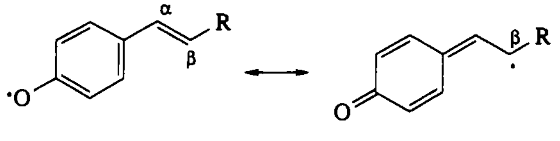

**(272)**

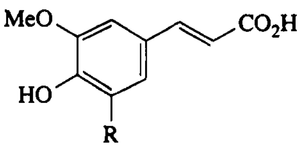

**(273)** R = OMe
**(275)** R = H

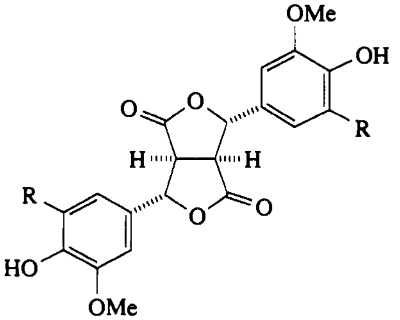

**(274)** R = OMe
**(276)** R = H

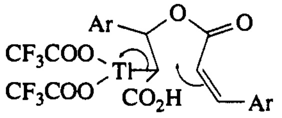

**(277)**

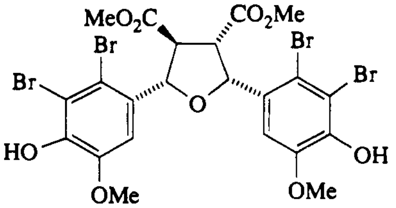

**(278)**

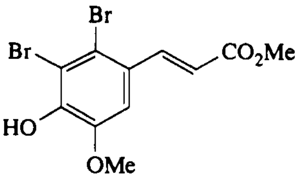

**(279)**

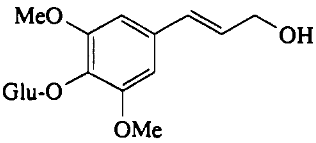

**(280)**

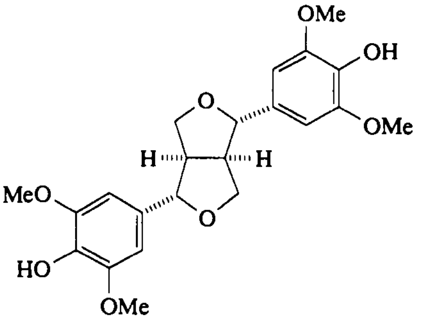

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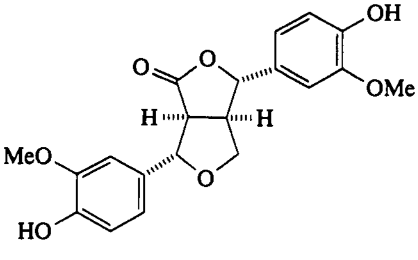

**(282)**

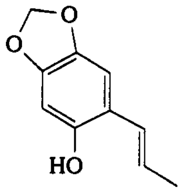

**(283)**

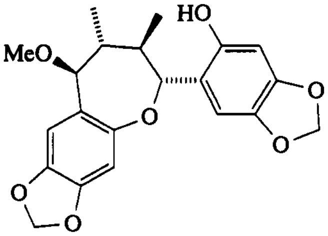

**(284)**

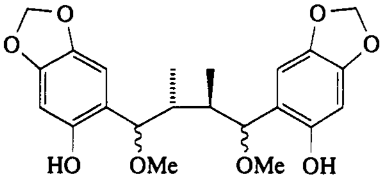

**(285)**

stereochemistry, for the dihydrobenzofuran ring substituents, was specifically formed in one case.[148] When horseradish peroxidase was used in a reaction mixture saturated with β-cyclodextrin, it is claimed[149] that the product was formed enantiospecifically. Sensitized photooxidation of methyl ferulate[150] afforded a related 2-aryldihydrobenzofuran (**288**).[150]

An unusual $C_\beta$—$C_{AR}$ coupling was observed on anodic oxidation, in acetic and trifluoroacetic acids, of a mixture of (*E*)-isosafrole (**289**) and the allylphenol (**290**).[151] Various interesting products were characterized, among them the cyclohexadienone (**291**). Although only formed in 4% yield, this product was readily converted by successive alkali and acid reactions, into the neolignan derivative denudatin A (**292**).

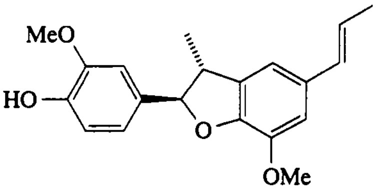

**(286)**

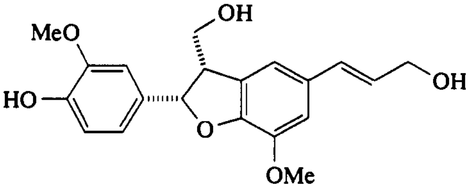

**(287)**

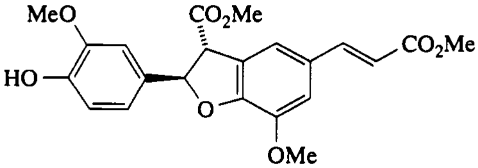

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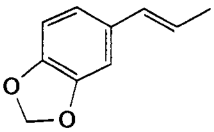

**(289)**

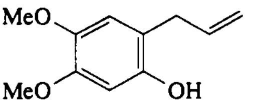

**(290)**

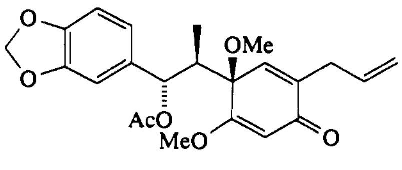

**(291)**

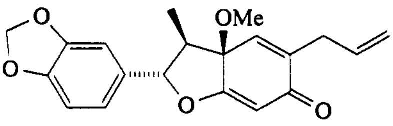

**(292)**

Intramolecular $C_{\beta}$—$C_{AR}$ couplings have been observed in the anodic oxidation of a series of 4-hydroxy-2-vinylbiphenyls, (*e.g.* **293**),[152] which afforded the corresponding spirodienones (*e.g.* **294**; 92% from **293**). Another $C_{\beta}$—$C_{AR}$ linkage resulted from the brief oxidation of the dihydrocinnamyl cinnamate (**295**) with thallium tristrifluoroacetate–catalytic boron trifluoride (water-quench), when the eight-membered lactone (**296**) was formed.[79]

There has been much interest in the synthesis of lignan lactones of the aryl tetralin type, induced by the antitumour activity of podophyllotoxin relatives, and some short oxidative routes into the series have been pursued. In a typical reaction, in which both $C_{\beta}$—$C_{\beta}$ and $C_{\beta}$—$C_{AR}$ couplings occur, the cinnamyl cinnamate (**297**) was treated for 30 s with chromium trioxide–fluoroboric acid in acetonitrile.[153] Three tetracyclic products were obtained, the lactones (**298**; 19%) and (**299**; 7%), and (±)-isopodophyllotoxone

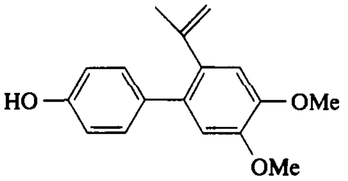

**(293)**

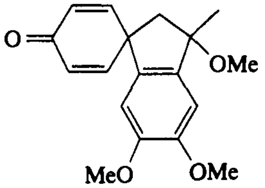
O
OMe
MeO
OMe

**(294)**

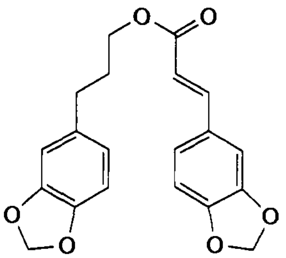

**(295)**

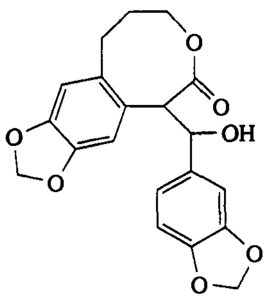

**(296)**

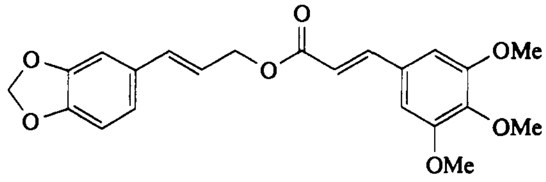
O
O
O
O
OMe
OMe
OMe

**(297)**

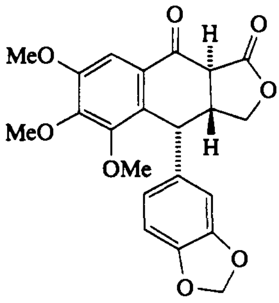
O
H
O
MeO
O
MeO
H
OMe
O
O

**(298)**

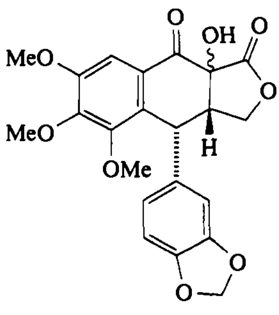
O
OH
O
MeO
O
MeO
H
OMe
O
O

**(299)**

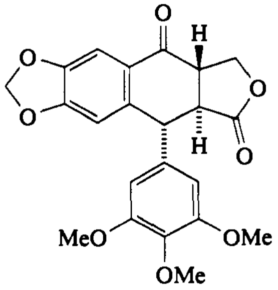
O
H
O
O
O
H
O
MeO
OMe
OMe

**(300)**

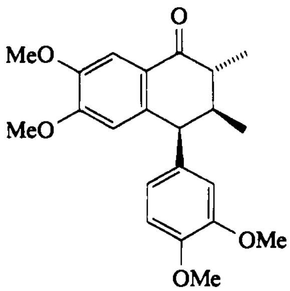
O
MeO
MeO
OMe
OMe

**(301)**

(**300**; 16.3%), which was epimerized (80%) to the *cis* ring fused natural isomer (±)-picropodophyllone. The same reagent converted *O*-methylisoeugenol (3,4-dimethoxyphenyl-1-propene) directly into the tetralone (**301**; 16%), which on deoxygenation gave the lignan (±)-galbulin.[154]

## 2.9.6 MISCELLANEOUS OXIDATIVE COUPLINGS

### 2.9.6.1 Couplings Involving Cycloadditions

The anodic coupling of (*E*)-isosafrole (**289**) and the allylphenol (**290**), in acidic medium was discussed above (see Section 2.9.5). The reaction took a different course under less acidic conditions (methanol–acetic acid) as illustrated in Scheme 10.[151] Two single-electron transfers from the phenol lead to the phenoxonium cation (**302**), which underwent [3 + 2] cycloaddition with the electron-rich alkene; demethylation of the product cation gave the neolignan (**303**; 81%), which occurs naturally in an *Aniba* species. (*E*)-Isosafrole could be replaced by a protected 4-hydroxy-3-methoxyphenylpropene, to form analogous compounds. Using (*Z*)-isosafrole in the reaction, and adding trifluoroacetic acid to the medium, led to isolation of two products, the stereoisomer (**304**) of the *Aniba* neolignan (**303**), and futoene (**305**; 15%), another unusual neolignan. As shown in Scheme 11, the former product arose from *exo* [3 + 2] cycloaddition, while futoene probably was formed by acid-catalyzed rearrangement of the initial *endo* cycloadduct.[151]

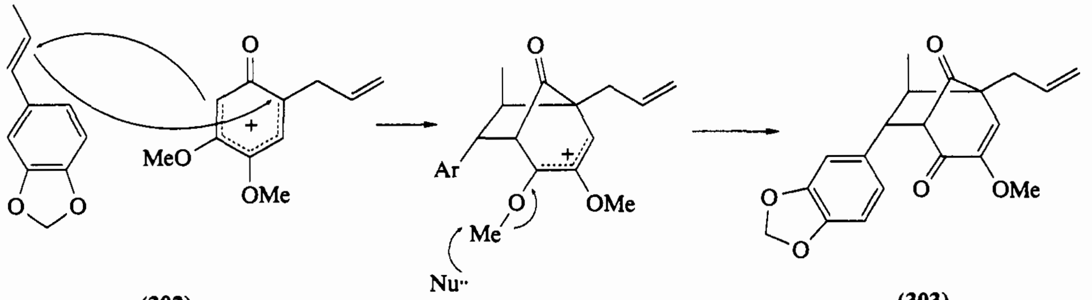

**(302)** **(303)**

Scheme 10

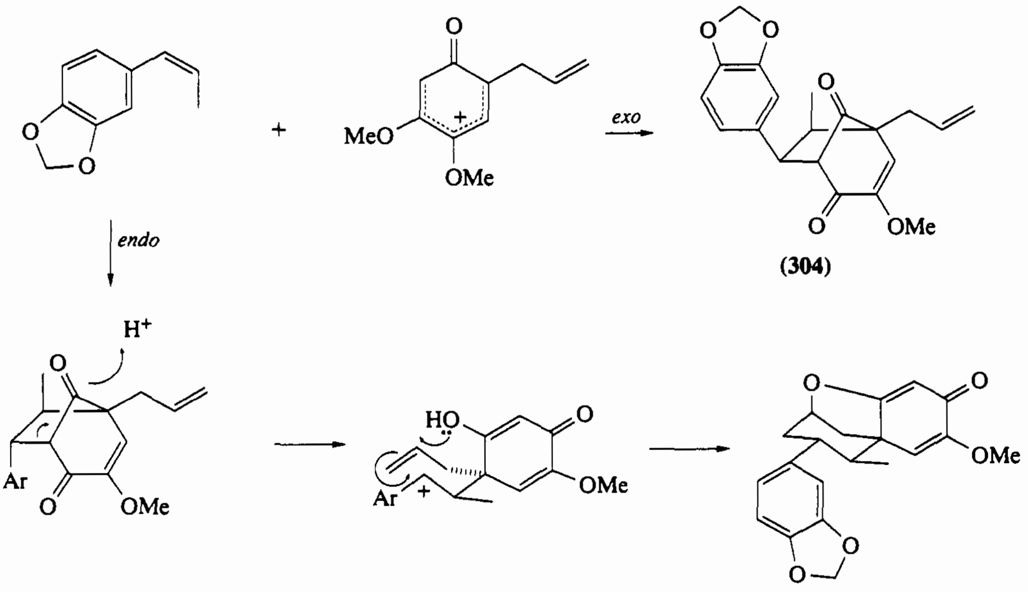

**(304)**

**(305)**

Scheme 11

The electrooxidations of allyl- and propenyl-phenols may follow even more different pathways leading to a rich diversity of products. At a carbon anode in methanol–lithium perchlorate, ferulic acid formed the tricyclic diacid (**306**; *cf.* Section 2.9.5), in a concentration-dependent process[139] probably involving [4 + 2] dimerization of the primary oxidation product, the dienone acetal (**307**).

The allyl phenol (**259**; R = Me) at a platinum anode in methanol–sodium methoxide, gave a C—O coupled major product (see Section 2.9.4.3), but in aqueous methanol–sodium bicarbonate the adduct (**308**; 23%) was formed, by a cycloaddition mechanism whose course is not entirely clear, with a trace of the natural dione asatone (**309**).[131] The constitution of asatone suggests that it originates in [4 + 2] dimerization of the *o*-quinone acetal (**310**), and, in support, electrolysis of (**259**; R = Me) in neutral methanol gave acetal (**310**) which spontaneously dimerized at room temperature to asatone.[155] Further heating together of the quinone acetal (**310**) and asatone (**309**) gave the natural sesquilignans heterotropantrione (**311**) and isoheterotropantrione (**312**) by a further Diels–Alder process.[156] Bisdemethoxyasatone (**313**) can be prepared from 4-allyl-2-methoxyphenol (**16**), and on irradiation in hexane afforded demethoxy-isoasatone (**314**) by [2 + 2] cycloaddition in the mode indicated.[38]

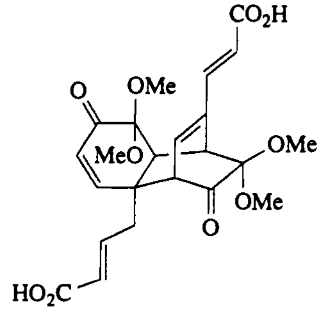

**(306)**

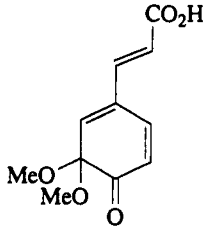

**(307)**

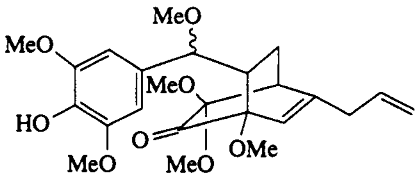

**(308)**

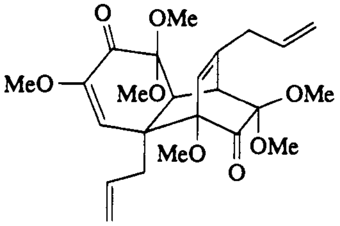

**(309)**

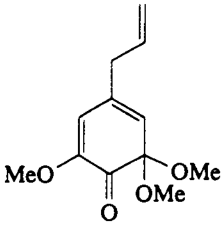

**(310)**

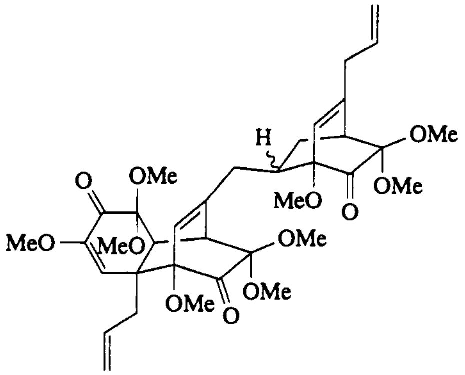

**(311)** β-H
**(312)** α-H

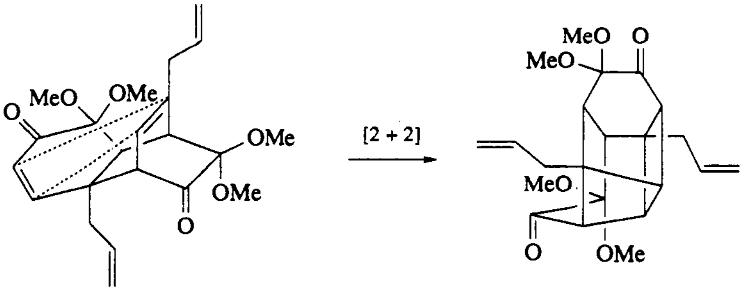

**(313)** **(314)**

The methylenedioxypropenylphenol (**283**) undergoes another form of oxidative dimerization on treatment with palladium(II) chloride in aqueous methanol with sodium acetate. As shown in Scheme 12,

$C_\beta$—$C_\beta$ coupling occurs, probably *via* the first-formed palladium phenolate (**315**) to give the bisquinone methide (**316**), and the latter spontaneously undergoes intramolecular Diels–Alder reaction to the natural lignan carpanone (**317**) in 46% yield, with stereocontrol at five chiral centers.[157a] High yields, up to 94%, have been recorded using oxygen as oxidant with a metal(II)–salen complex as catalyst, *e.g.* cobalt(II) salen.[157b] A low yield of carpanone was also obtained in electrooxidation.[128]

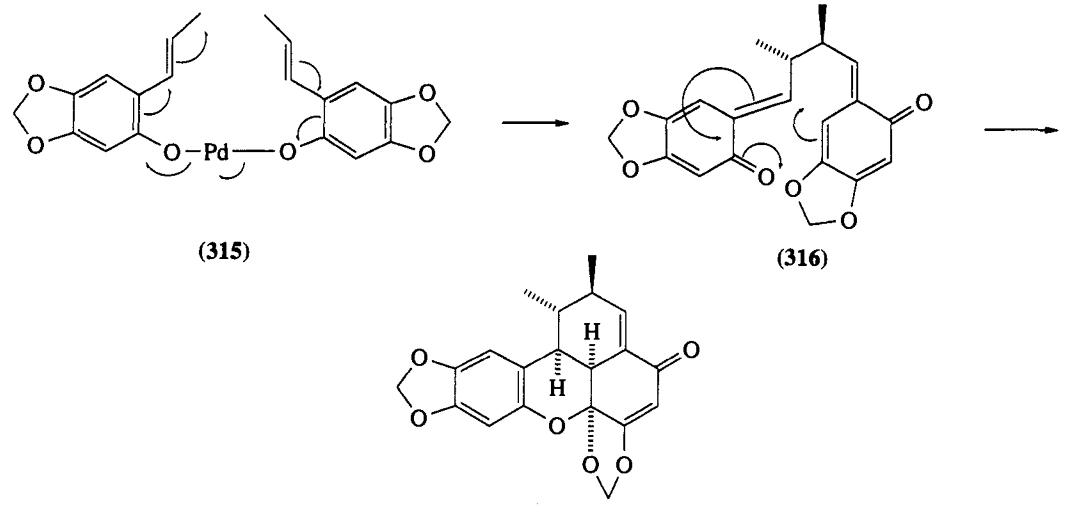

(**315**) (**316**) (**317**)

**Scheme 12**

Another case of oxidative coupling involving [4 + 2] cycloaddition is that of α-tocopherol (**318**). In alkaline ferricyanide the dehydrodimer (**319**) is formed, *ca.* 60%, by the sequence indicated in Scheme 13.[158] The chemistry was elucidated in the model coupling (**320**) → (**321**).[159]

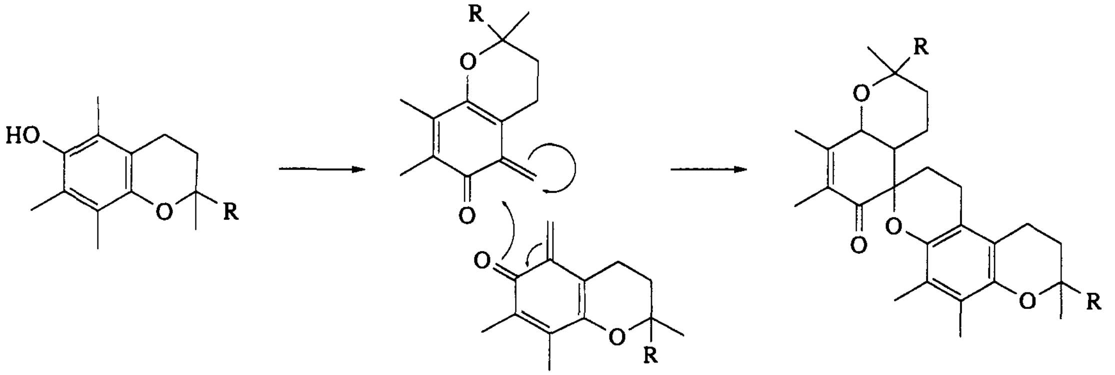

(**318**) R = $C_{16}H_{33}$
(**320**) R = Me

(**319**) R = $C_{16}H_{33}$
(**321**) R = Me

**Scheme 13**

### 2.9.6.2 Coupling at Benzylic Carbon

A minor variant in the oxidative coupling process stems from generation of a benzylic radical and coupling at that site. The mechanistic course remains obscure, although it seems plausible to postulate primary oxidation at phenolic oxygen followed by hydrogen migration from a benzylic site. In practice excellent yields may be obtained, as illustrated by the oxidation of *p*-cresols (**322**) by silver oxide on Celite in refluxing dry benzene, forming the bisquinonemethides (**323**), *e.g.* with $R^1 = R^2 =$ Me, 93% yield.[28] In a biomimetic conversion emodin anthrone (**324**) was oxidized in pyridine by oxygen to form the benzylically coupled dimer (**325**); on further oxidation conventional phenol coupling and dehydrogenation lead through protohypericin (**327**) to the natural pigment hypericin (**328**). Penicillopsin (**326**) also reacted, on exposure to oxygen, by benzylic coupling to give protohypericin and then hypericin, in 50% overall yield.[160] As a final example, the lactone (**204**), the anodic oxidation (acidic medium) of which was discussed in Section 2.9.3.2, could be alternatively oxidized in neutral acetonitrile to the bridged lactone (**329**). Although the yield was only 20%, the reaction represents a novel $C_{AR}$—C benzylic bond formation.[109]

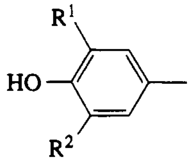

**(322)**

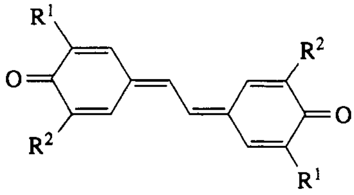
$R^1$
O
$R^2$
$R^2$
O
$R^1$

**(323)**

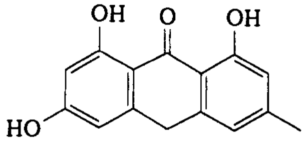

**(324)**

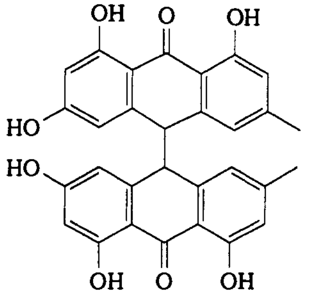
OH
O
OH
HO
HO
OH
O
OH

**(325)**

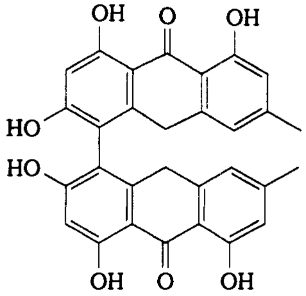
OH
O
OH
HO
HO
OH
O
OH

**(326)**

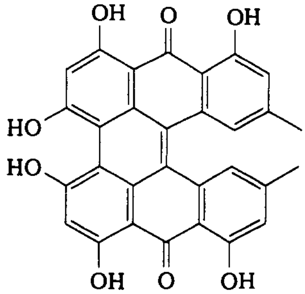
OH
O
OH
HO
HO
OH
O
OH

**(327)**

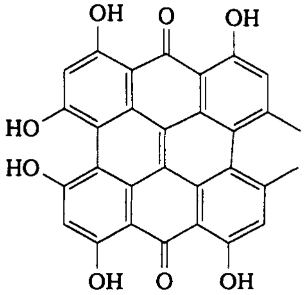
OH
O
OH
HO
HO
OH
O
OH

**(328)**

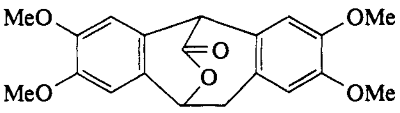
MeO
MeO
O
O
OMe
OMe

**(329)**

### 2.9.6.3 C—N Bond Formation

Coupling between aromatic amines and either phenols or other aromatic amino compounds is known and it is important in the production of azo polymers, and in the formation of azo dyes. Most of this work is outside the scope of this chapter; a number of reviews are cited in ref. 20. One or two examples will suffice here to illustrate the area. Thus anthranilic acid (**330**) forms phenazine-1,6-dicarboxylic acid (**331**) on treatment with manganese dioxide or lead dioxide in dry benzene or chloroform.[161] The mechanistic details are obscure. Excellent yields could be obtained in intramolecular cases,[162] *e.g.* amine (**332**)

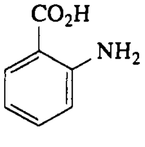

**(330)**

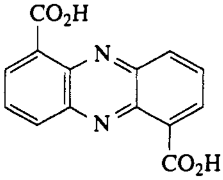
$CO_2H$
N
N
$CO_2H$

**(331)**

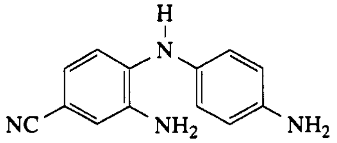
H
N
NC
$NH_2$
$NH_2$

**(332)**

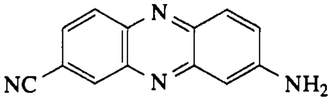

**(333)**

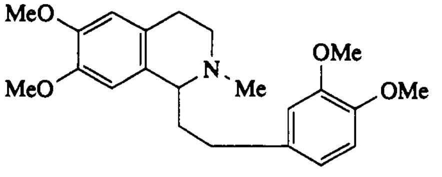

**(334)**

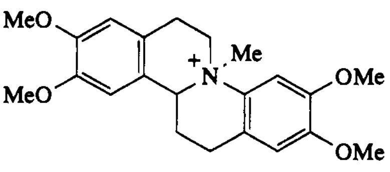

**(335)**

afforded phenazine (**333**) quantitatively on oxidation with iron(III) chloride. These studies comprise models for bacterial phenazine pigments. Lastly N—C (phenolic) linking is exemplified in the anodic conversion of the phenylethyltetrahydroisoquinoline (**334**) to the tetracyclic ammonium salt (**335**).[163]

## 2.9.7 REFERENCES

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# 3.1
# Wagner–Meerwein Rearrangements

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## 3.1.1 INTRODUCTION

Since the initial studies by Wagner at the turn of the century, the Wagner–Meerwein rearrangement has been the subject of almost continuous investigation.[1] The reaction was initially examined in terms of the rearrangement of α-pinene (**1**) to bornyl chloride (**2**; Scheme 1), and of camphene (**3**) *via* camphene hydrochloride (**4**) to isobornyl chloride (**5**).

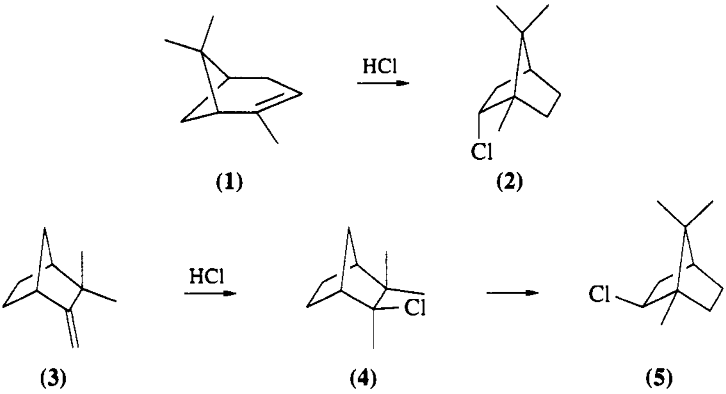

**Scheme 1**

The ionic nature of the rearrangement was first recognized by Meerwein in 1922.[2] These ideas replaced some earlier suggestions by Ruzicka.[3] However, in 1938 Bartlett questioned the intermediacy of the discrete ions proposed by Meerwein.[4] In the following year Wilson, in a remarkable study for the period, suggested the possibility of a mesomeric delocalized carbocationic intermediate.[5] The subsequent controversy between Brown and Winstein in the 1950s and 1960s on the role of classical or nonclassical ions in the norbornyl series meant that the rearrangement and the nature of the intermediates became one of the most widely studied reactions. It is, however, beyond the scope of this chapter to review these mechanistic arguments.[6]

## 3.1.2 DEFINITION OF THE WAGNER–MEERWEIN REARRANGEMENT

The Wagner–Meerwein rearrangement involves the generation of a carbocation on a bicyclic system followed by the 1,2-shift of an adjacent skeletal C—C bond to generate a new carbocation.[7,8] The reaction is thus accompanied by a modification of the bicyclic skeleton. Although the Wagner–Meerwein rearrangement strictly involves the migration of a skeletal bond, the term is sometimes widened to embrace the migration of a substituent such as a methyl group as in the related Nametkin rearrangement. The latter may be exemplified by the conversion of camphenilol (**6**) to santene (**7**; Scheme 2)

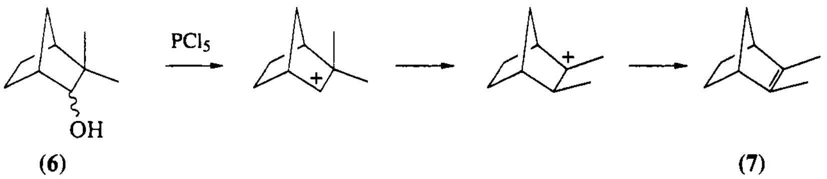

**Scheme 2**

Since its discovery in the context of the reactions of the monoterpenoids, examples of the rearrangement have been found in many other systems. Therefore, for the purposes of this chapter, which is concerned with the synthetic utility of the Wagner–Meerwein type of rearrangement, some reactions involving substituents migrating will be included as well as examples of skeletal rearrangement in polycyclic systems.

## 3.1.3 WAGNER–MEERWEIN PATHWAYS IN BICYCLIC SYSTEMS

The branched chain of the terpenoids and the consequent number of tertiary centers that these natural products contain lead to many cationic rearrangements. Not unexpectedly the majority of the examples

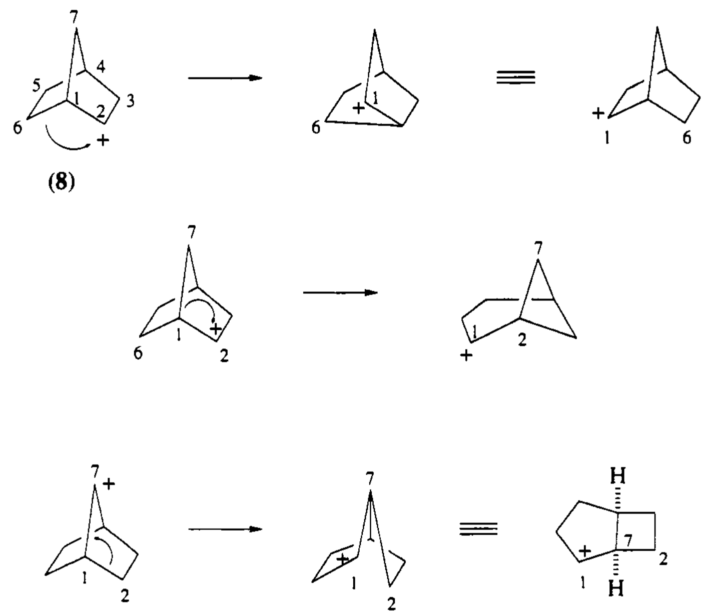

**Scheme 3**

of the Wagner–Meerwein rearrangement come within this area,[9,10] and it is also here that its synthetic utility has been exploited. In the first instance, in order to assess the value of the reaction, it will be helpful to examine the consequences of the rearrangement in terms of the reactions of a simple bicyclo[2.2.1]heptyl (norbornyl) carbocation (**8**; Scheme 3).

These examples illustrate both the utility and the limitations of the rearrangement as part of a synthetic strategy. These may be summarized in the following terms. Firstly, there are many powerful methods with well-established regiospecificity that lead to the bridged ring system of defined stereochemistry, for example the Diels–Alder strategy (Scheme 4).

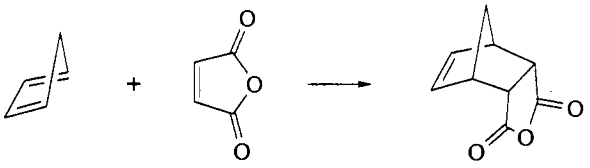

**Scheme 4**

Such reactions may form part of a convergent synthesis and by their very nature place a functional group adjacent to the bridge. Secondly, the rearrangement may lead to the possibility of placing a functional group in a relatively inaccessible position. For example the rearrangement of the epoxide (**9**) affords the primary alcohol (**10**; Scheme 5).

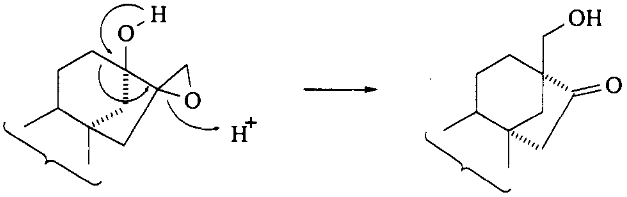

**(9)** **(10)**

**Scheme 5**

However, the existence of many competing pathways as illustrated by Scheme 3 implies significant limitations on the generality of a strategy based on a particular Wagner–Meerwein rearrangement. Indeed the need to build features into a molecule which will drive the rearrangement along a specific pathway is a significant constraint. The tendency is for the carbocation to rearrange to the most stable structure. Thus 1,2-shifts tend to afford five- or six-membered rings rather than three- or four-membered rings. An example is given by the the rearrangement of the cyclobutanone (**11**), obtained from geronic acid, to the bicycloheptenone (**12**).[11] Secondly a bridge carbon bearing a positive charge or a double

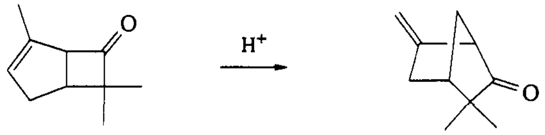

**(11)** **(12)**

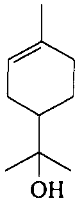

**(13)**

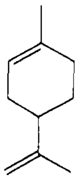

**(14)**

bond is unstable. On the other hand conjugative or hyperconjugative stabilization may favor a particular carbocation. Furthermore a carbocation may collapse by fragmentation rather than by rearrangement as exemplified by the formation of α-terpineol (**13**) and limonene (**14**) from α- and β-pinene in the presence of aqueous mineral acid.[12]

The dehydration of fenchyl alcohol (**15**) demonstrates the many structural possibilities that a Wagner–Meerwein rearrangement may afford (see Scheme 6).[13] The initial carbocation might in principle rearrange by the 1,2-shift of any one of six groups indicated on (**16**). Shift 1 would produce a bridgehead

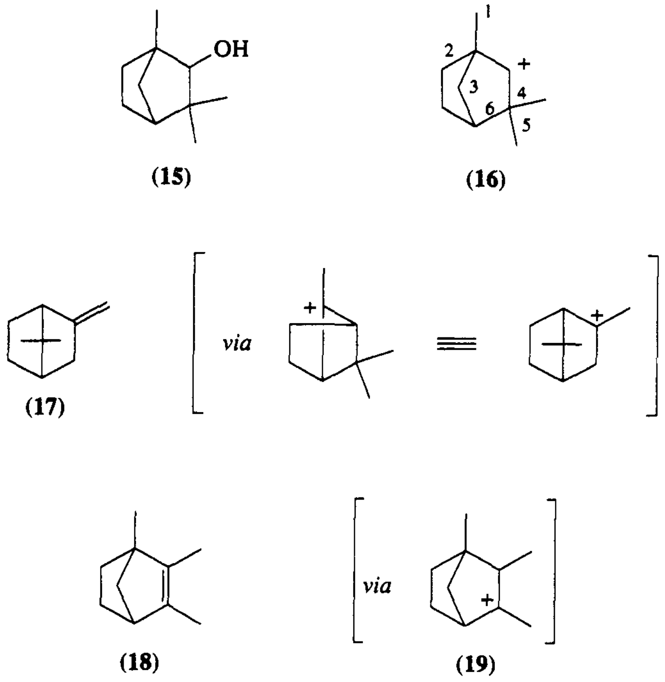

**Scheme 6**

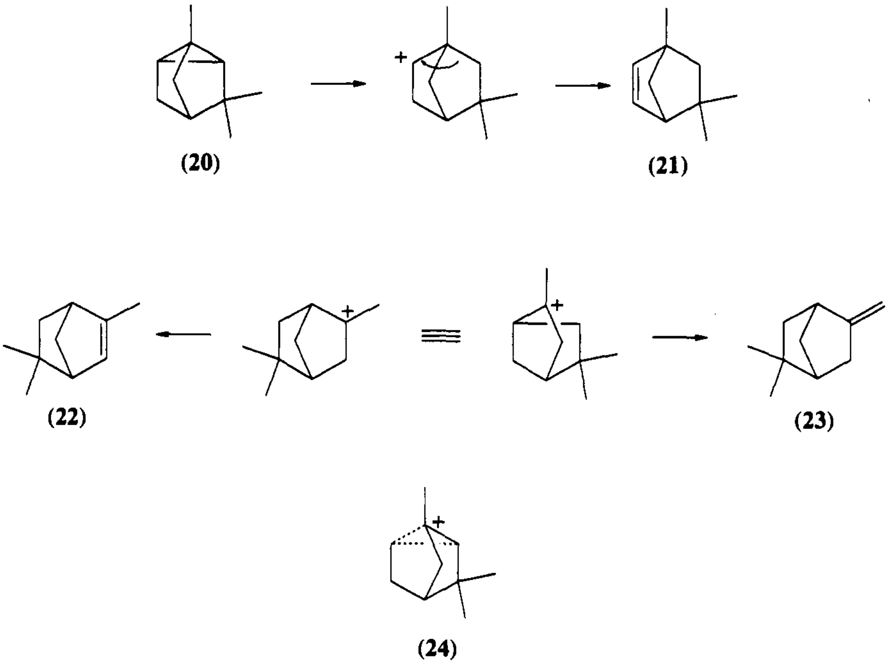

**Scheme 7**

carbocation, whereas shifts 3 or 6 would form less stable rings. On the other hand shifts 2 and 4 are feasible and produce α-fenchene (**17**) and ε-fenchene (**18**).

The ion (**19**) plays an important role in the formation of ε-fenchene; however, the reaction is more complex. In addition to the α- and ε-fenchenes, small amounts of cyclofenchene (**20**), β-fenchene (**23**), γ-fenchene (**22**) and δ-fenchene (**21**) are also formed. Cyclofenchene (**20**) represents the key to the formation of these substances (see Scheme 7). It may arise by the loss of a proton from the carbocation (**24**). Reprotonation of the cyclopropane ring may lead to a new carbocation from which the alkenes may be derived.

This intricacy, whilst revealing the limitations of a Wagner–Meerwein reaction, also indicates another aspect of the rearrangement as part of a synthetic strategy. The cyclopropyl system exemplified by cyclofenchene (**20**) may be accessed by a range of synthetic routes, for example the addition of diazo ketones across alkenes, and the resultant cyclopropane may then be subjected to the conditions of the Wagner–Meerwein rearrangement to afford a more stable ring system.

### 3.1.4 STEREOELECTRONIC FEATURES OF THE WAGNER–MEERWEIN REARRANGEMENT IN SYNTHESIS

The course of the Wagner–Meerwein rearrangement is markedly influenced by stereoelectronic effects.[14,15] In particular for a concerted Wagner–Meerwein rearrangement to occur the leaving and migrating groups should be antiperiplanar — the so-called $sp^3$-alignment factor. The rigid polycyclic triterpenoid and steroidal skeleta often provide a framework for a cascade of Wagner–Meerwein 1,2-shifts in which antiperiplanar groups, typically axially oriented hydrogen atoms and alkyl groups, migrate. These backbone rearrangements have been explored in many systems and are exemplified by the conversion of friedelin (**25**) to olean-13(18)-ene (**26**).[16] Many other examples in which the reaction is initiated by the cleavage of an epoxide or the protonation of a tertiary alcohol are found in the steroid series (*e.g.* a C-5 alcohol, in the Westphalen rearrangement).

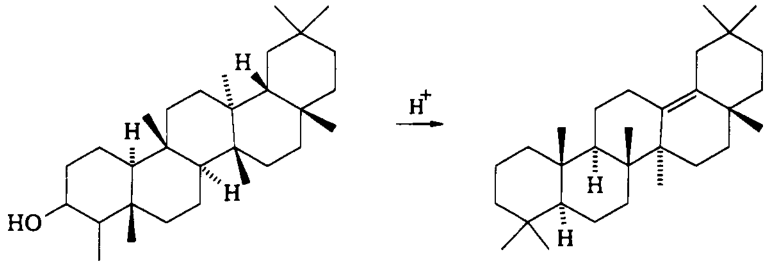

**(25)** **(26)**

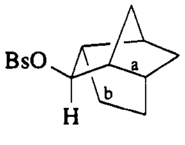

**(27)**

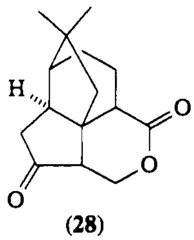

**(28)**

For a nonconcerted rearrangement to a carbocationic site to occur, the migrating group and the receptor *p*-orbital should ideally be in a plane. These features have been explored in the acetolysis of *exo*-twistbrendan-2-ol brosylate (**27**). $sp^3$-Alignment clearly favors the migration of bond 'a', whilst $sp^2$-alignment favors the migration of bond 'b'. Solvolysis in acetic acid buffered with potassium acetate gave products consistent with $sp^3$ bond alignment being the dominant factor.

The importance of stereoelectronic factors in a synthetic context have been examined as part of a program directed at the synthesis of quadrone (**28**). A series of model 4,3,2-propellanols (see Scheme 8) were examined and shown to undergo concerted rearrangements involving initial 1,2-alkyl shift of the best-aligned cyclobutyl bond.[17] However, a number of the reactions were then accompanied by secondary rearrangements, again revealing limitations in the use of the rearrangement in a synthetic strategy. Nevertheless this approach has led to a successful synthesis of quadrone (**28**).[18]

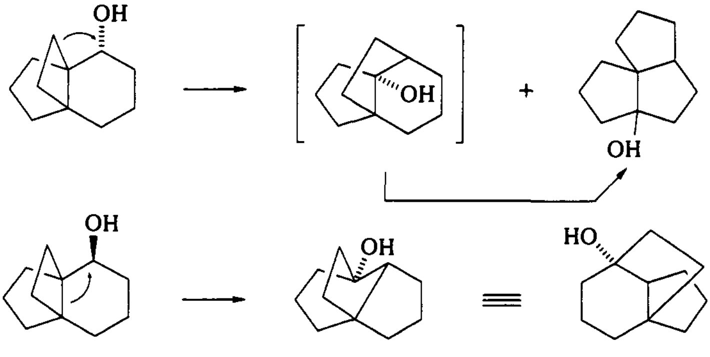

Scheme 8

## 3.1.5 EXAMPLES OF THE USE OF THE WAGNER–MEERWEIN REARRANGEMENT

### 3.1.5.1 Syntheses Based on Camphor

Since α-pinene is a readily available monoterpene, it forms the source of many monoterpenes, including those of the bornane skeleton through a Wagner–Meerwein rearrangement.[19] Camphor (**29**) itself has formed the starting material for a number of syntheses in which Wagner–Meerwein rearrangements have played an important part (for an excellent detailed review see ref. 20). The propensity of this skeleton to undergo Wagner–Meerwein rearrangements enables substituents to be introduced at C-3, C-5, C-8, C-9 and C-10. An example of this is shown in the formation of camphor-10-sulfonic acid (**30**; Scheme 9).[20] A variety of other substituents may then be introduced in place of the sulfonic acid group.

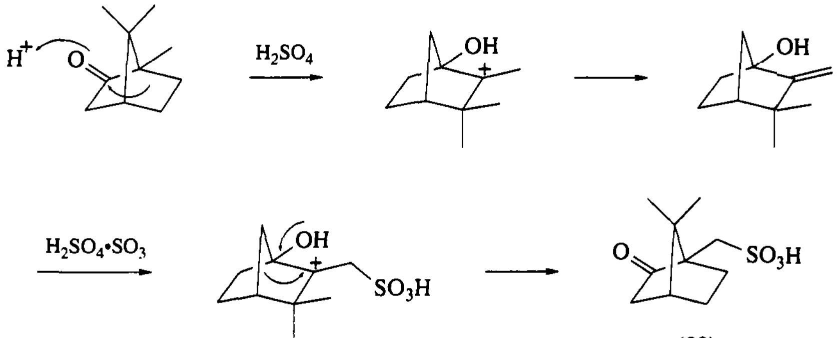

**(30)**

Scheme 9

Functionalization at C-9 (see Scheme 10) in camphor illustrates not only the complexity of the pathways when the possibility of Nametkin (2,3-methyl shift) and 2,6-hydride shifts are taken into account, but also one of the solutions to the simplification of the rearrangement.[21] The product is a mixture of (+)- and (−)-camphor-9-sulfonic acids, *i.e.* the pathway allows for racemization. Indeed camphor itself can be racemized in concentrated sulfuric acid by a similar pathway involving both Wagner–Meerwein and

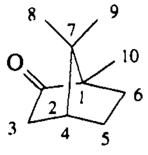

**(29)**

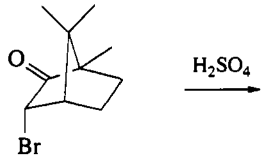

**(31)**

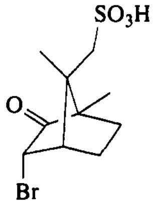

**(32)**

Nametkin rearrangements. A method of avoiding racemization was to use (+)-3-*endo*-bromocamphor (**31**), when only the (+)-3-*endo*-bromocamphor-9-sulfonic acid (**32**) was formed.[22] This problem of racemization has arisen in other situations, for example in syntheses in the alkene series.[23]

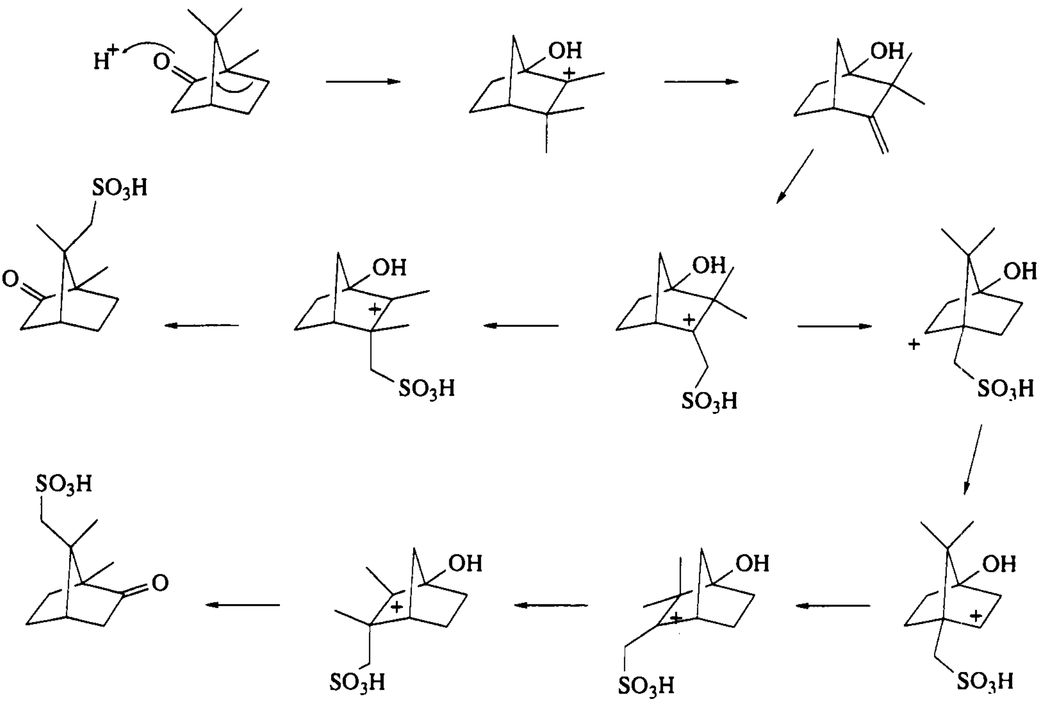

**Scheme 10**

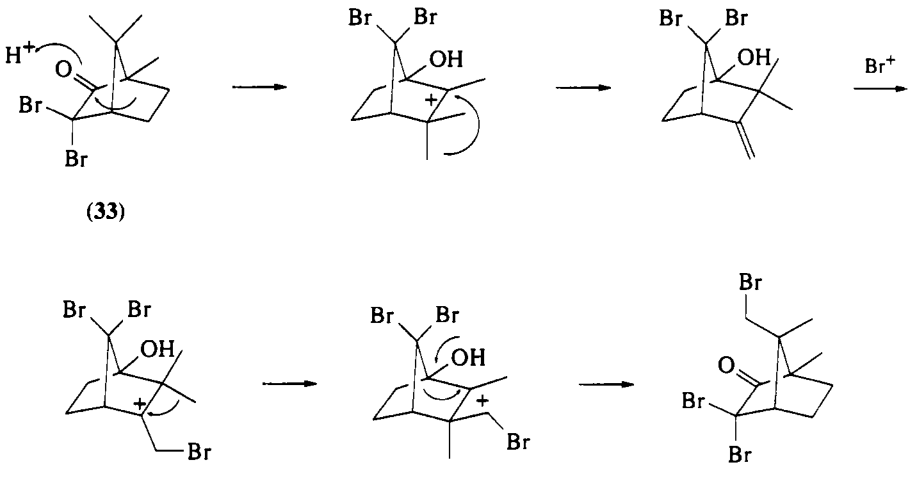

**Scheme 11**

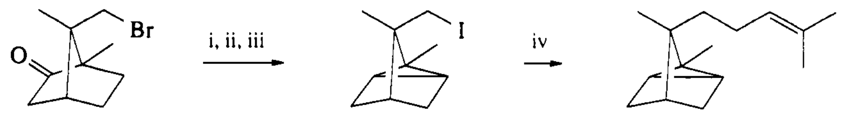

i, $N_2H_4$; ii, HgO, heat; iii, NaI, DMSO; iv, $(Me_2C{=}CHCH_2NiBr)_2$, DMF

**Scheme 12**

The C-8-substituted derivatives of camphor are formed by a route from 3,3-dibromocamphor (**33**) outlined in Scheme 11.[24] This involves a series of Wagner–Meerwein rearrangements.

These variously substituted camphor derivatives have in turn been used in a number of syntheses of natural products, some of which also involve Wagner–Meerwein rearrangements in their later stages. Examples drawn from the syntheses of (+)-α-santalene (**34**),[25] (–)-β-santalene (**35**),[26] (–)-copacamphene (**36**)[26] and (–)-sativene (**37**)[26] are given in Schemes 12–14.

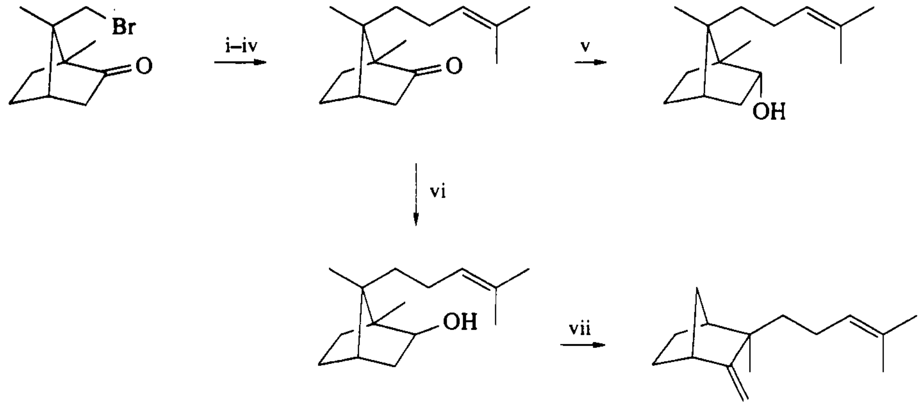

i, NaI, HMPA; ii, $(CH_2OH)_2$, $H^+$; iii, $(Me_2C{=}CHCH_2NiBr)_2$, DMF; iv, $Me_2CO$, HCl; v, Na, $Pr^iOH$; vi, $LiAl(OMe)_3H$, THF; vii, TsCl, pyridine

**Scheme 13**

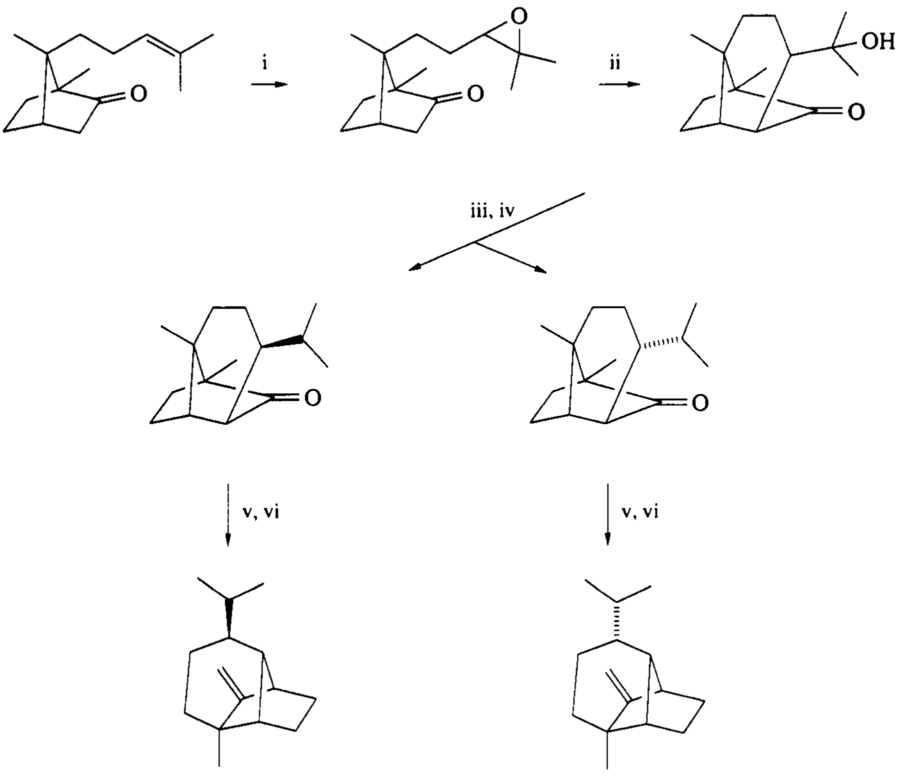

**(36)** **(37)**

i, $ClC_6H_4CO_3H$, benzene; ii, $Bu^tOK$, $Bu^tOH$; iii, $SOCl_2$, pyridine; iv, $H_2$, Pt; v, $LiAlH_4$; vi, $MeSO_2Cl$, pyridine

**Scheme 14**

A number of aspects of longifolene chemistry may be understood in terms of Wagner–Meerwein rearrangements that have their parallel in the camphene series.[27] However, these rearrangements are often of a more deep-seated character, as in the conversion of longifolene (**38**) to isolongifolene (**39**), and have consequently found less application in a purely synthetic context. The intense activity that has surrounded sesquiterpenoid synthesis has involved many other examples of Wagner–Meerwein rearrangements.[28]

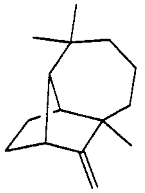

**(38)**

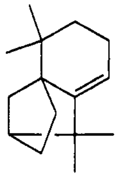

**(39)**

### 3.1.5.2 Ring Expansion Reactions

The ready availability of four-membered rings of defined stereochemistry from enone–alkene photocycloadditions has been the origin of several syntheses which employ Wagner–Meerwein rearrangements in subsequent steps. This is exemplified by a neat and very short synthesis of α-caryophyllene alcohol (**40**) from cyclopentene and 3-methylcyclohexenone which was described some years ago (see Scheme 15).[29] The rearrangement in 40% sulfuric acid proceeded remarkably smoothly. A short synthesis of isocomene (**41**; Scheme 16) also illustrates this strategy.[30]

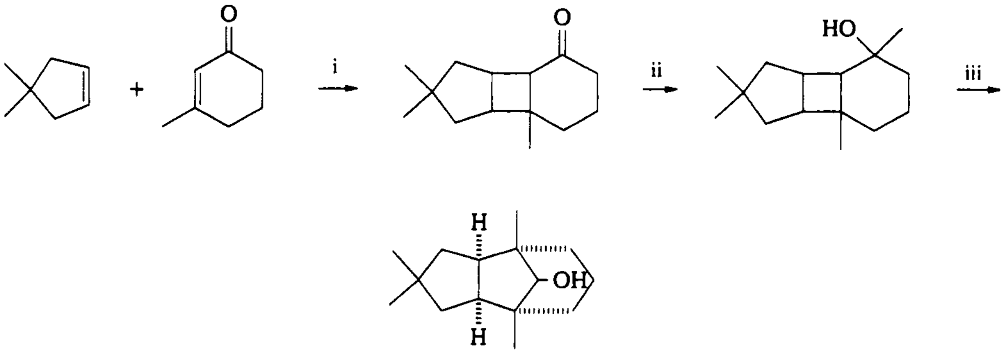

**(40)**

i, *h*ν; ii, MeLi; iii, 40% $H_2SO_4$

**Scheme 15**

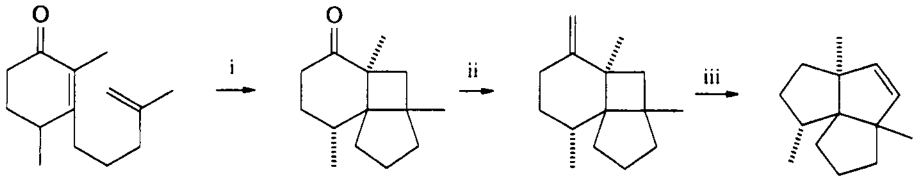

**(41)**

i, *h*ν; ii, $Ph_3\overset{+}{P}\overset{-}{C}H_2$; iii, TsOH, benzene

**Scheme 16**

The defined geometry of these steps has permitted the synthesis of some cycloheptane acids related to terpenoid natural products. The key reaction was the rearrangement of a suitably substituted bicyclo[4.2.0]octane. Thus the photoaddition of ethylene to 3-methylcyclohexenone gave the ketone (**42**), which was converted to the alcohol (**43**). On treatment with HgO and $HBF_4$ this gave the unstable hydroxy aldehyde (**44**), which was readily oxidized to the dicarboxylic acid (**45**; Scheme 17).[31] Ring expansion methodology was also used in an approach to the synthesis of the trichothecenes (see Scheme 18).[32]

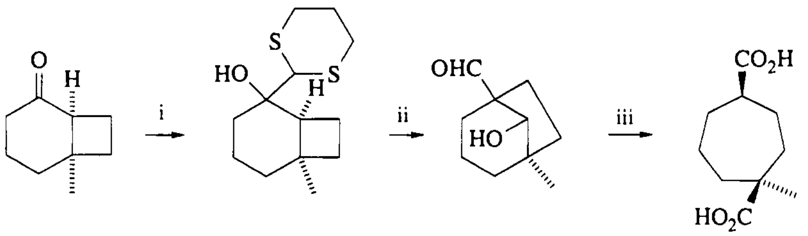

**(42)** **(43)** **(44)** **(45)**

i, 1,3-dithiane, BuLi; ii, HgO, $HBF_4$, aq. THF; iii, $CrO_3$, $H_2SO_4$

**Scheme 17**

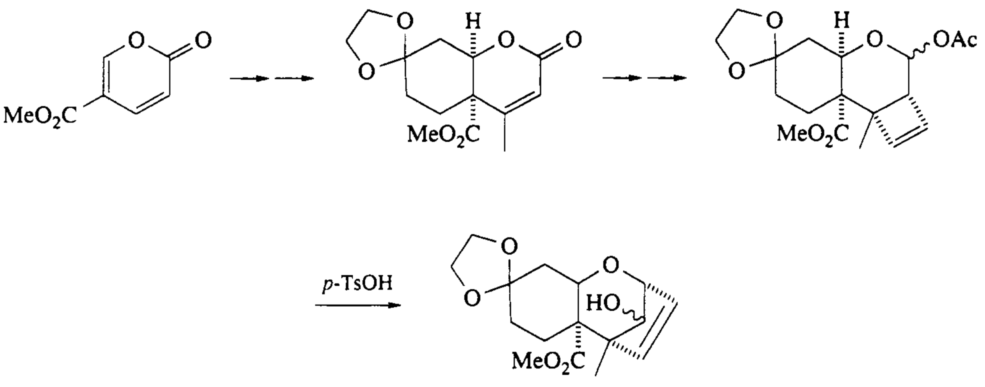

**Scheme 18**

Whereas this synthesis places an oxygen function on a bridge, an oxygen function of this type may also be the source of a ring contraction as exemplified by the conversion of (**46**) to (**47**).[33]

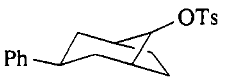

**(46)**

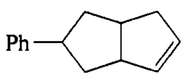

**(47)**

### 3.1.5.3 Biomimetic Syntheses

A number of biomimetic syntheses have included Wagner–Meerwein rearrangements.[34] A chemical conversion of humulene (**48**) to sterpurene (**50**) involved an interesting series of Wagner–Meerwein rearrangements (see Scheme 19).[35] Humulene (**48**) was converted to the cyclooctenol (**51**) and thence to the bromide (**52**) *via* the protoilludyl cation (**49**). Treatment of (**52**) with silver acetate in acetic acid gave racemic sterpurene (**50**). In contrast the epimeric bromide (**53**) gave (**54**).

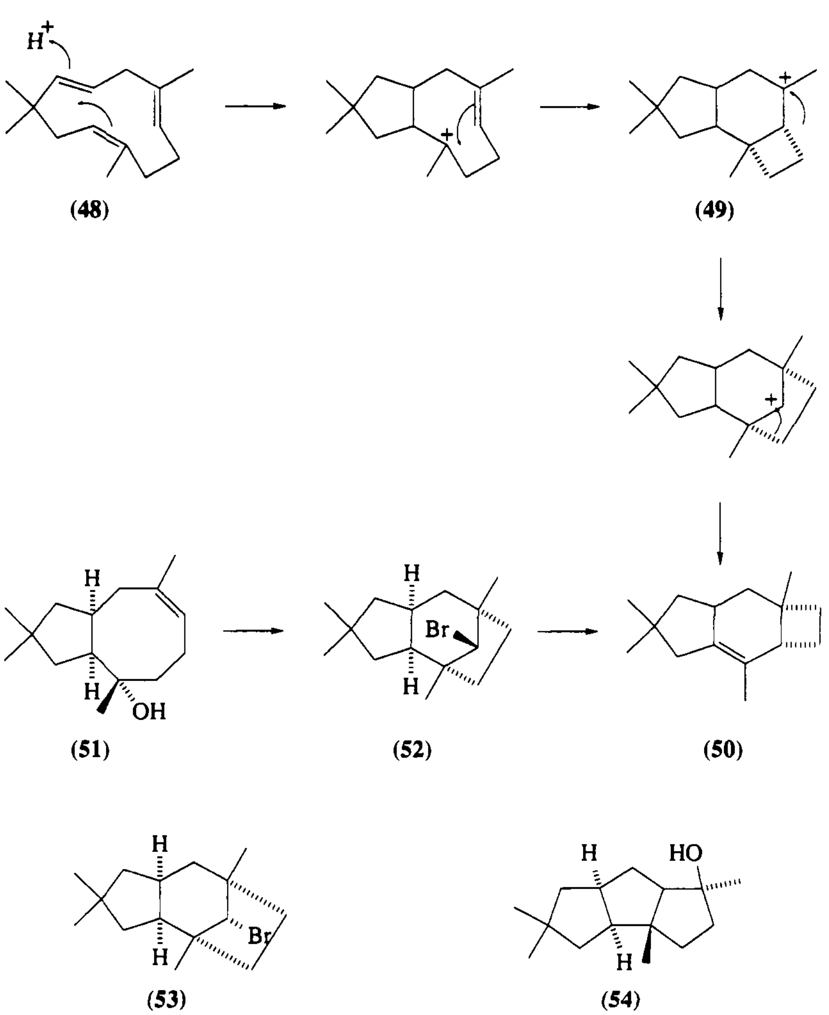

Scheme 19

### 3.1.5.4 Syntheses of the Tetracyclic Diterpenoids

A possible biogenetic relationship between the pimaradienes and the tetra- and penta-carbocyclic diterpenoids was suggested by Wenkert.[36] Implicit in this scheme (see Scheme 20) are a number of rearrangements. There have been many investigations aimed at simulating aspects of this scheme. In particular the beyerene–kaurene rearrangement takes place quite readily. Thus solvolysis of the beyeran-16β-yl toluene-*p*-sulfonate (**55**) affords a mixture of kaurene (**57**), isokaurene (**58**), kauranol (**59**), and beyer-15-ene (**56**; Scheme 21).[37]

An allied rearrangement of the epoxide (**60**) has been used in partial syntheses in both the kaurene and gibberellin series to place oxygen functions at the relatively inaccessible C-14 position (*e.g.* **61**).[38] This type of rearrangement was also used in the final stages of one of the early gibberellin syntheses.[39,40]

The reverse rearrangement, involving the conversion of the kaurene skeleton to that of the beyerene series, is found in the steviol–isosteviol and gibberellin–8,13-isogibberellin rearrangements (see Scheme 22).[41] Apart from their mechanistic interest, these rearrangements were used in partial syntheses directed at structural correlations.

Prior to the advent of simple methods for radical deoxygenation, a double Wagner–Meerwein rearrangement (Scheme 23) was used as a method for removing a bridgehead hydroxy group in this series.[42] The success of this sequence indicates the subtle balance of stabilities in this series.

Interrelationships between the kaurene and atiserene series have also been established by a Wagner–Meerwein rearrangement. For example treatment of isokaurene epoxide (**62**) with acid gave atisiran-15-one (**63**), possibly through the sequence shown in Scheme 24.[43]

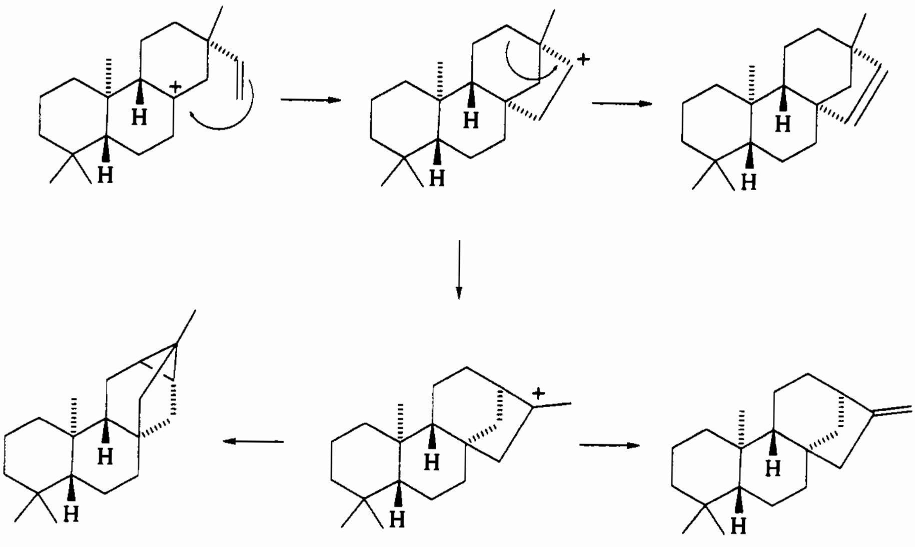

Scheme 20

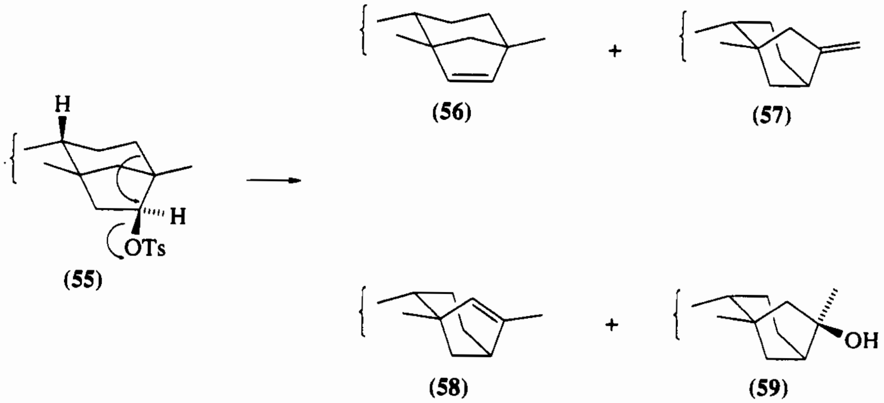

H
H
OTs
(55)
(56)
(57)
(58)
(59)
OH
+

Scheme 21

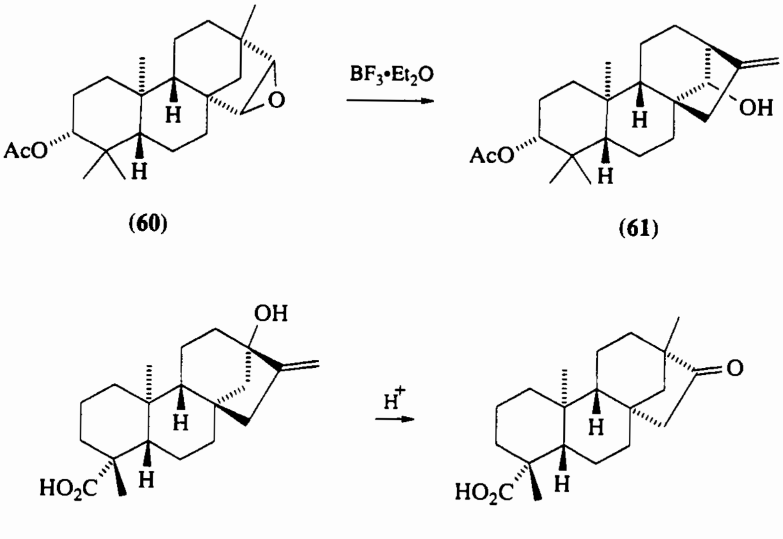

AcO
H
O
(60)
BF₃•Et₂O
(61)
OH
HO₂C
H⁺
O

Scheme 22

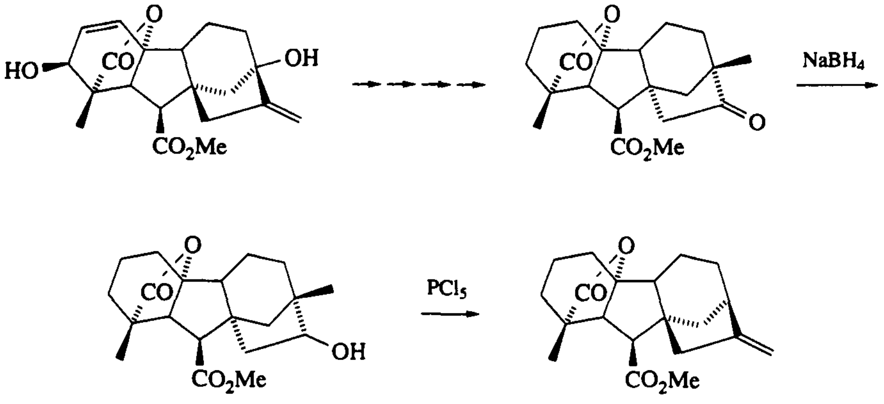

Scheme 23

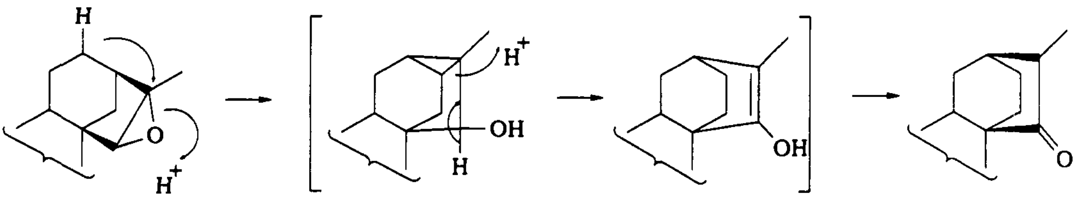

**(62)** **(63)**

Scheme 24

The biologically important diterpenoid aphidicolin (**64**) and its relatives stemodin and maritimol have been the targets of several synthetic studies employing Wagner–Meerwein rearrangements at key steps in the construction of the carbon skeleton. One such strategy involves the solvolytic rearrangement of suitably oriented bicyclo[2.2.2]octenyl methanesulfonates exemplified by Scheme 25.[44] A synthesis of maritimol involved a similar [2.2.2] → [3.2.1] skeletal rearrangement of (**65**) to (**66**).[45] The rearrangement was induced by treatment of the alcohol with excess toluene-*p*-sulfonyl chloride in pyridine.

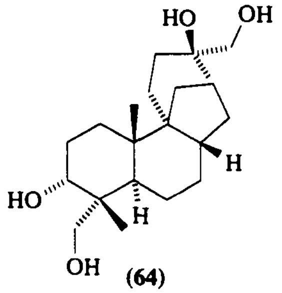

**(64)**

In conclusion, the Wagner–Meerwein rearrangement can be a useful component of a synthetic strategy provided its stereoelectronic requirements can be met and the possible pathways are limited. It has been of particular value in the synthesis of bridged ring systems in which the strategy requires the modification of the skeletal framework.

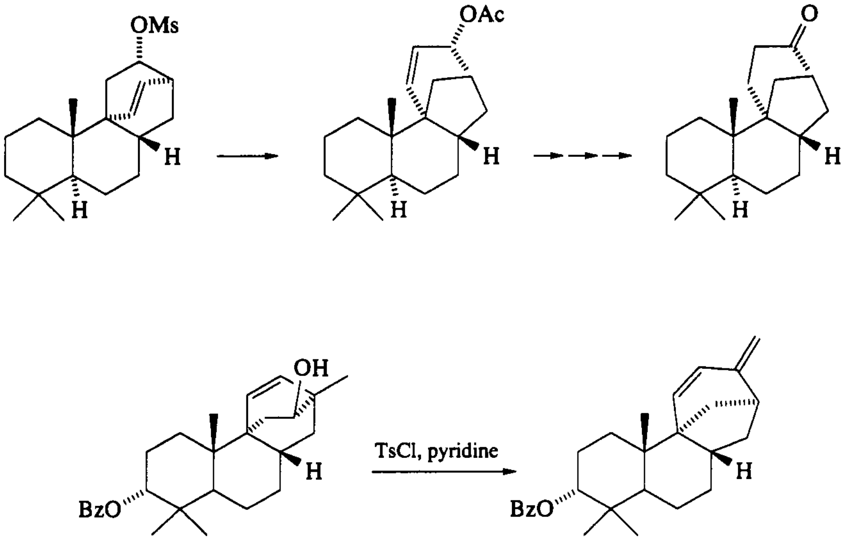

**(65)** **(66)**

Scheme 25

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# 3.2

# The Pinacol Rearrangement

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## 3.2.1 INTRODUCTION

The acid-catalyzed reaction of vicinal diols, which results in dehydration and the migration of an alkyl or aryl group, or a hydrogen atom, to form an aldehyde or ketone is known as the Pinacol rearrangement.[1] The name is derived from the material used in the earliest recorded example. Although the structures of both the starting material and product were unknown when the experiment was published in 1860, Fittig[2] found that treatment of pinacol (**1**) with sulfuric acid gave pinacolone (**2**; equation 1).

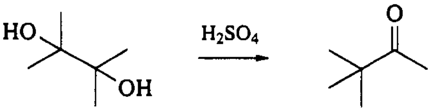

**(1)** **(2)**

(1)

All classes of vicinal diols (primary, secondary, tertiary, alkyl- or aryl-substituted) will undergo the pinacol rearrangement, and many acids and solvents have been used for this purpose. Various procedural modifications have been introduced over the years for particular glycols, but sulfuric acid remains the most commonly employed catalyst. The use of 25% $H_2SO_4$, as recommended in the procedure of Adams,[3] affords pinacolone in essentially quantitative yield. In some instances better results are obtained when cold concentrated acid is used as the solvent. The choice of reagents and conditions is important, and can completely alter the course of the reaction. For example, pinacol also serves as the starting material for the synthesis of 2,3-dimethylbutadiene, formed by slow distillation of a mixture of the diol and catalytic HBr.[4]

The pinacol rearrangement and the acid-catalyzed rearrangement of epoxides (see this volume, Chapter 3.3) may be closely related, depending upon the substrates, reagents and conditions employed. Epoxides have on occasion been isolated from diols under pinacol rearrangement conditions,[5] and they are implicated as reactive intermediates in many other instances. Similarly, the treatment of an epoxide with aqueous acid may cause opening to the vicinal diol either prior to, or in competition with, rearrangement. The two substrates (diol and epoxide) are equivalent for most purposes if the equilibrium shown in Scheme 1 is established more rapidly than rearrangement can occur. The use of strong acids and substrates which bear cation-stabilizing groups will encourage the merger of the two processes shown in Scheme 1 *via* a common carbenium ion intermediate. Conversely, mild acids and good nucleophiles will favor covalent bond-forming reactions, *e.g.* the formation of a halohydrin upon treatment of an epoxide with HX. These covalently bonded materials may be stable and isolable, or may serve as reactive intermediates which lead to rearranged products under the conditions used for their formation. The rearrangement step itself can be regarded as the interaction of an intramolecular nucleophile (the migrating group and its bonding electron pair) with an adjacent electrophilic center. The latter may range from a formal carbocation to a carbon which bears a leaving group suitable for $S_N2$ displacement. These distinctions can be helpful in designing experiments to take advantage of the versatility of epoxides as starting materials.

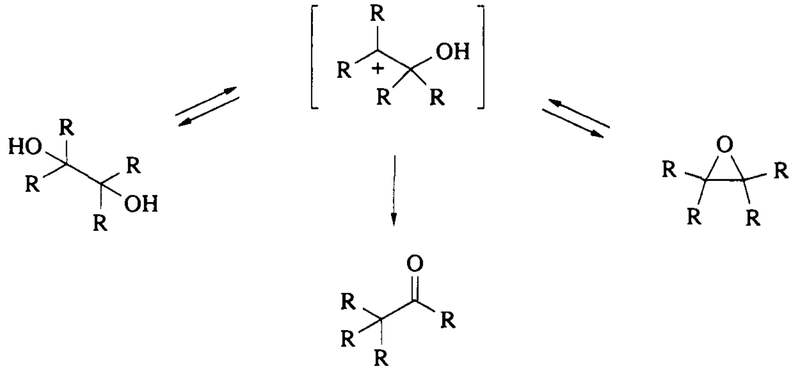

Scheme 1

Other methods of generating β-hydroxy carbocations lead to similar or identical products. The reaction of β-amino alcohols with nitrous acid, one variant of the semipinacol rearrangement (or Tiffeneau–Demjanov ring expansion if used for this purpose), is a familiar example.[6] Another is the so-called α-ketol rearrangement, in which the hydroxy and carbonyl groups of an acyloin exchange positions with concurrent migration of a substituent.[6] Many of the general features described here also apply to these related reactions (see this volume, Chapter 3.4).

## 3.2.2 MECHANISTIC FEATURES

Given the range of substrates and reagents that have been used in pinacol rearrangements, it is not surprising that very few mechanistic conclusions are general for all diols under all conditions. Indeed, the same substrate may give different products when subjected to apparently similar conditions. A classic illustration is provided by the diol (**3**), which gives the ketone (**4**) when treated with concentrated sulfuric acid, but mostly the aldehyde (**5**) when 40% acid is used (equation 2). Close mechanistic examination of this reaction with $^{14}$C-labeled material showed that the kinetically controlled ratio of (**4**) to (**5**) does depend to some extent on the solvent and acid employed, but is further complicated by the conversion of the aldehyde (**5**) to the ketone (**4**) under the reaction conditions.

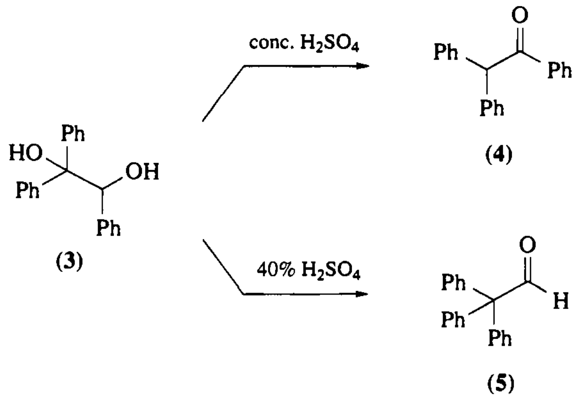

(2)

Other detailed mechanistic examples are described in two reviews by Collins.[6,7] Although published two decades ago, these require little updating in content, and appear to be unchallenged in general mechanistic conclusions, which can be summarized as follows: (i) pinacol rearrangements are exclusively intramolecular; (ii) the course of the pinacol rearrangement usually depends on which OH group is most easily removed, as predicted by consideration of the stability of the intermediate carbenium ion; (iii) the group which preferentially migrates is that which is better able to stabilize a positive charge, although complications may arise due to stereochemical and conformational effects, rapid equilibration of intermediate carbenium ions or interconversion of products; and (iv) either inversion or racemization may be observed at the migration terminus; racemization may occur either at the stage of an intermediate cation or by further reaction of the product.

It appears that the stereochemistry at the migrating center has not been explicitly examined in a pinacol rearrangement but, as seen in related 1,2-migrations, retention of configuration is expected.

Pinacol rearrangements are effectively irreversible in the sense that carbonyl products have not been shown to revert to diols. However, the products may be in equilibrium with the same cationic intermediates that are generated from the diol. This feature emerges clearly under strongly acid conditions, where the 1,2-carbonyl transposition of aldehydes and ketones is observed (*cf.* equation 2). An especially pertinent example comes from the work of Fry,[8] who found that pinacolone itself undergoes the $^{14}C$-label redistribution shown in equation (3). Benzpinacolone, isotopically labeled at the carbonyl carbon, gives material with the label transposed as shown in equation (4).[9] These and related observations can be explained by invoking two or more carbenium ion intermediates connected by 1,2-migrations. The label exchange in equation (4) requires oxygen migration, presumably *via* an epoxide (or protonated epoxide) intermediate.

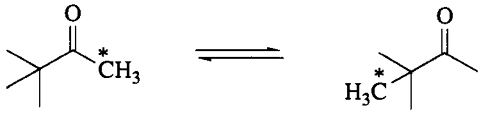

(3)

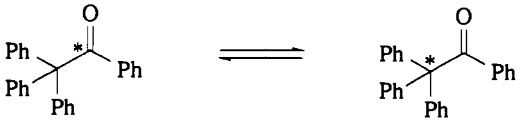

(4)

Many other 1,2-carbonyl transpositions with skeletal rearrangement are known.[6] In general, aldehydes react more rapidly than ketones; the rearrangement of a ketone to form an aldehyde appears to be unknown, but ketones can be converted to other ketones. A few examples from the early work of Venus-Danilova[10] are illustrated. Thus cyclobutane- and cyclopentane-carbaldehyde both gave the simple ring-expanded ketones as shown in equations (5) and (6), upon treatment with concentrated sulfuric acid.

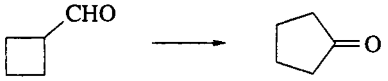

(5)

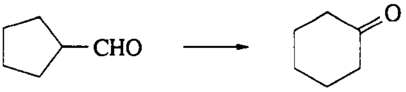

(6)

A more complex sequence, such as that suggested in Scheme 2, must be invoked to explain the formation of the ring-contracted methyl cyclopentyl ketone from cyclohexanecarbaldehyde.[10]

In general, 1,2-carbonyl transpositions require more vigorous conditions (stronger acid, higher temperatures) than pinacol rearrangements in which the same carbenium ion intermediates may be generated. However, harsher conditions than actually required have frequently been used to carry out pinacol rearrangements, and care must be taken to avoid over-interpretation of the mechanism from examination of the products.

The evidence for carbocation intermediates in the pinacol rearrangement is compelling for some substrates and conditions. Bunton[11] found that pinacol itself that was recovered from $^{18}O$-enriched aqueous sulfuric acid had incorporated an appreciable amount of solvent oxygen. Under these conditions the reaction goes to completion, *i.e.* the incorporation cannot be due to reversible formation of diol from pina-

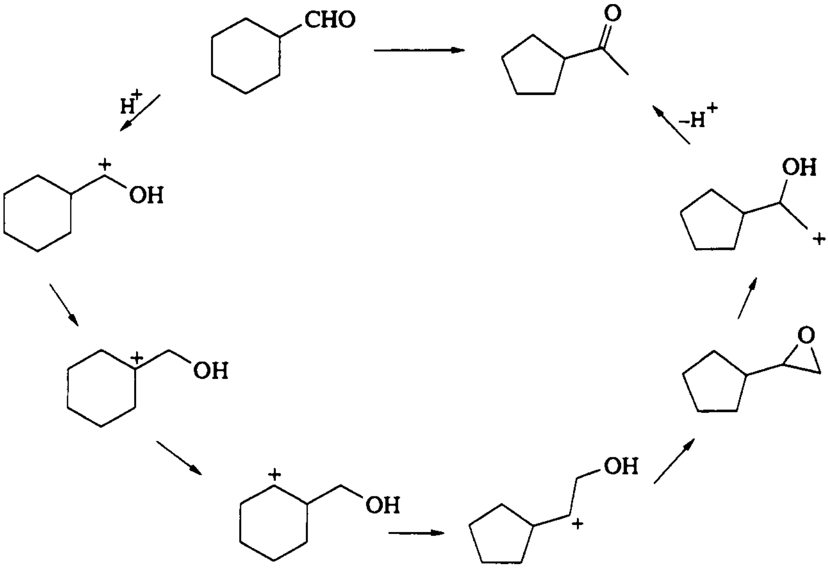

**Scheme 2**

colone. A common carbenium ion intermediate was proposed for both solvent incorporation and rearrangement. Similarly, Collins[12] found that the *threo* and *erythro* isomers of a triaryl-substituted diol, when treated with sulfuric acid in aqueous ethanol, were interconverted more rapidly than either isomer rearranged.

An early report that the *threo* and *erythro* isomers of 1,2-diphenyl-1,2-di(1-naphthyl)ethanediol gave two different products (a ketone and an unidentified substance)[13] could not be substantiated by other workers,[14] who also found that the *threo* and *erythro* isomers of 1,2-bis(2-chlorophenyl)-1,2-diphenylethanediol both gave the same ketone (phenyl migration).[14] Yields were not recorded, precluding substantive mechanistic interpretation.

The *cis* (**6**) and *trans* (**7**) isomers of 1,2-dimethyl-1,2-cyclohexanediol have been examined by several research groups, but a clear understanding of this system did not emerge until modern analytical tools were employed. The very thorough study of Bunton and Carr[15] provides evidence for a carbenium ion intermediate common to both isomers. In *ca.* 1–3 M aqueous perchloric acid at 60 °C the isomeric diols are partially interconverted, and solvent oxygen is incorporated. The ring-contracted ketone (**8**) is the major product from both diols, but a small amount of 2,2-dimethylcyclohexanone (**9**) is also formed (equation 7). A carbenium ion intermediate with sufficient lifetime to undergo chair–chair equilibration would lead to identical product ratios from both diol isomers. The slightly different ratios which were found (from (**6**), (**8**):(**9**) = 93:7; from (**7**), (**8**):(**9**) = 97:3) presumably reflect a small stereochemical memory effect in one or both of the isomers, but the initial stereochemistry of the center which bears the departing hydroxy group clearly does not dominate the stereochemical course of these reactions. Larger differences in reactivity and product composition are found for the five-membered ring analogs.[16]

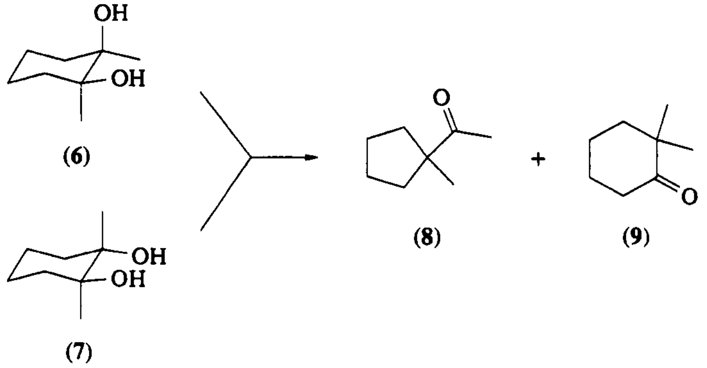

(7)

Earlier studies[17] of these diols, with one exception[18] which was later shown[17b] to be erroneous, differ only marginally in stereochemical conclusions, probably because the minor isomer could not be detected by the analytical methods used.

Another aspect of stereoselectivity has been probed by Berti and coworkers,[19] who used the *t*-butyl group to control the conformational populations of the diols depicted in equations (8) to (11). The results are informative, although atypical conditions ($BF_3{\cdot}OEt_2$ in benzene) for pinacol rearrangement were used, and the generality of the observations is unknown. The products of all four reactions are ascribed to initial loss of the benzylic OH group, with formation of a planar carbenium ion at C-1. The close similarity of the ratios of products for equations (8) and (9), or equations (10) and (11), respectively, supports the view that the departing OH group has at most a very slight influence on the outcome. Formal backside (equation 8) and frontside (equation 9) hydride migrations are involved in the formation of the ketone (**11**). In contrast, the stereochemistry at C-2 plays a controlling role, as shown by the formation of (**11**) as the exclusive ketone from (**10**) and (**13**), while (**15**) is the only ketone formed from the axial 2-hydroxy substrates (equations 10 and 11). The formation of the single stereoisomer of aldehyde (**12**) in all four reactions is in keeping with ring contraction *via* the planar carbenium ion held in the chair conformation of the starting materials.

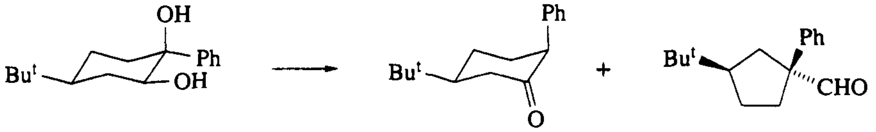

(**10**) (**11**) 93% (**12**) 7% (8)

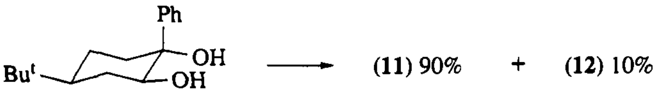

(**13**) (9)

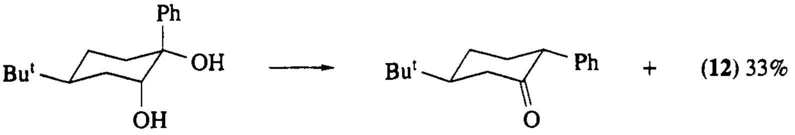

(**14**) (**15**) 67% (10)

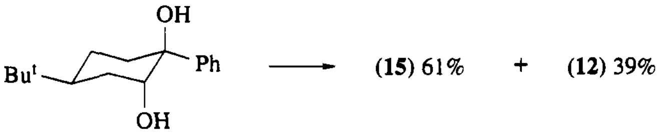

(**16**) (11)

Carbenium ion intermediates are implicated not only for diols in which one or both carbinol centers are tertiary, but also in less-substituted substrates. Alexander and Dittmer[20] found that the *meso* and (±)-isomers of 2,3-butanediol both gave 2-butanone and isobutyraldehyde when refluxed in 60% phosphoric acid, but the ratios were different, ruling out exclusive reaction *via* a single common intermediate. More recently, Herlihy[21] has reported the results of a thorough kinetic analysis of the rearrangement of optically active 1,2-propanediol in aqueous perchloric acid. The rate of racemization exceeded the rate of rearrangement, in keeping with a mechanism involving a carbenium ion intermediate. The rate of exchange of $^{18}O$-enriched substrate was also examined, and found to be half as fast as racemization; a significant memory effect, *e.g.* shielding of one face of the cation by the departing water molecule, can be used to rationalize this rather $S_N2$-like behavior. Arguments against the involvement of an epoxide intermediate were presented, although rigorous exclusion of any role for epoxide is difficult. The ratio of racemization/rearrangement was found to be dependent on the acid concentration, an effect attributed to the influence of acidity on partitioning of the carbocation. The mechanistic conclusions for this system parallel those reached earlier[11] for pinacol itself. The nearly exclusive product from 1,2-propanediol is propanal (which does not survive the reaction conditions), but interestingly, a small amount of acetone is also formed.

Although inversion at the migration terminus has been observed in several pinacol rearrangements, the dramatic rate effects (anchimeric assistance) sometimes associated with neighboring group participation have not been observed or documented. The choice of a proper model to establish a baseline rate for comparison remains a problem. Alcohols are not suitable for this purpose, since diols are significantly less reactive than their monohydroxy analogs, presumably because of the inductive effect of the second OH group.[11,21]

Most detailed studies of pinacol rearrangements support the view that carbenium ion formation precedes migration, but occasionally stereoselectivity is observed when not anticipated from this perspective. The results of three separate labeling and stereochemical experiments carried out by Collins *et al.*[22] are incorporated in the depiction (equation 12) of the rearrangement of diol (**17**) to the ketone (**19**). The course of this reaction can be explained by considering the bridged ion (**18**) as an intermediate, even though the tertiary and benzylic nature of the corresponding classical ion makes it a poor candidate for nonclassical participation.

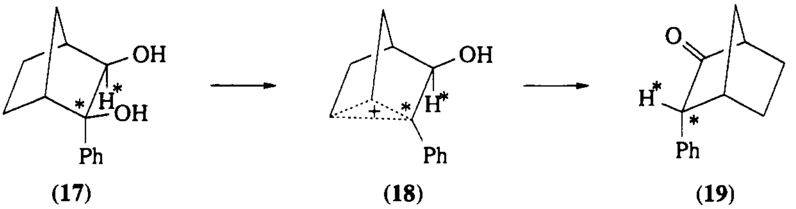

(12)

Aqueous or concentrated acids are the most commonly used catalysts, but several other acidic materials can cause pinacol rearrangement, as noted in a recent review of the dehydration reactions of diols.[23]

Few generalizations can be made about the 'migratory aptitudes' of substituents in pinacol rearrangements, but some observations are worth noting. Phenyl and hydrogen appear to be similar in rate of migration, and hydrogen is some 20 times faster than methyl. The *t*-butyl group has been reported to shift much more rapidly than other simple alkyl groups (*t*-butyl:ethyl:methyl = >4000:17:1).[24] Cyclopropyl substituents migrate more readily than simple alkyl groups, and do so without ring opening, as illustrated in equation (13).[25]

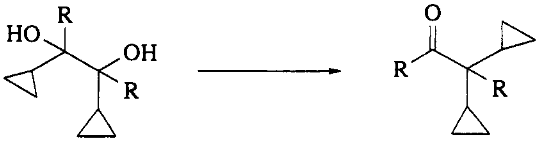

(13)

R = Me, Pr$^i$, cyclopropyl

### 3.2.3 APPLICATIONS

In order to maximize the synthetic utility of pinacol rearrangements, it is necessary to exclude competing processes, and control both regio- and stereo-selectivity. The two factors which influence regioselectivity — which OH is lost, and which adjacent group migrates — are at least marginally predictable and, in favorable circumstances, controllable. Control of stereoselectivity is more problematic, as noted above. Because of these complications and the difficulties associated with the preparation of complex diols, the pinacol rearrangement has not been widely used in multistep syntheses, in spite of its capacity for generating some unusual structural features.

Both ring expansions and contractions are well documented. Ring size can strongly influence the course of the reaction. For example, Vogel[26] found that the diol (**20**), obtained by reductive dimerization of cyclobutanone, cleanly rearranged to the ketone (**21**) on warming in dilute sulfuric acid; (**21**) was subsequently used to prepare the novel pentalene (**22**; equation 14).

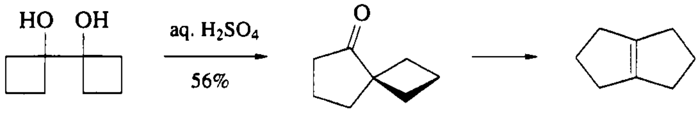

(14)

The symmetrical diols derived from cyclopentanone[27] and cyclohexanone[28] can similarly be converted to ring-expanded ketones in good yield. The diols from reductive coupling of cycloheptanone and cyclooctanone give mainly the corresponding dienes in aqueous acid,[28] especially when heated, but Christol[29] found that pinacol rearrangement is strongly favored even for these materials when cold concentrated sulfuric acid is used as the solvent.

Results which follow the mechanistic generalizations given above have been obtained from examination of similar unsymmetrical diols. The formation of (**24**) as the major product from (**23**) can be explained by more rapid development of the carbenium ion in the five-membered ring (equation 15).

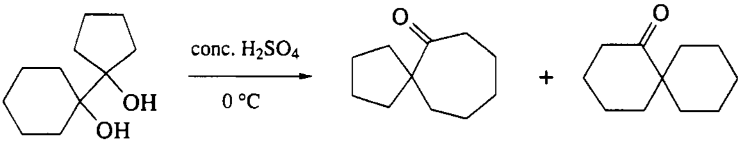

(**23**) (**24**) 60% (**25**) 40% (15)

Other unsymmetrical diols, prepared (inefficiently) by the coupling of mixtures of ketones, have been studied.[28–30] The 'preferred cation' argument is also found to be applicable to mixed medium-ring analogs, *i.e.* the kinetically favored pinacol rearrangement product is that predicted by consideration of the relative stabilities of the two possible, initially formed, carbocations.[30] Earlier work[28] with these compounds may have given misleading results due to product instability. To illustrate, Mundy[30] observed that (**24**) is converted to (**25**) as the temperature is increased.

The *cis*- and *trans*-hydrindandiols (**26**) are both converted exclusively to the spiro ketone (**27**) on brief treatment with cold concentrated sulfuric acid (equation 16).[31] Plausible alternative products, the epoxide and spiro[5.3]nonanone, could not be ruled out as intermediates, since both were prepared by independent routes and found to give (**27**) under the reaction conditions.

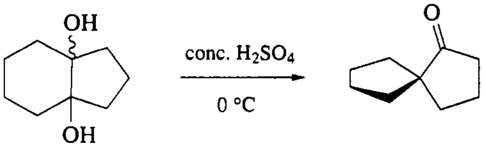

(**26**) (**27**) (16)

The pinacol rearrangements of several cyclobutanediols, mostly induced by $BF_3 \cdot OEt_2$, have been examined by Conia.[32] The reactions of symmetrically substituted materials occurred with high specificity and yield. Both isomers (*cis* and *trans*) gave the same product in instances where this question was examined. As shown in equation (17), for the substituents R = H, alkyl or phenyl, only ring contraction was observed, while equally regiospecific formation of the cyclobutanone product was found for the substituents R = allyl or vinyl.

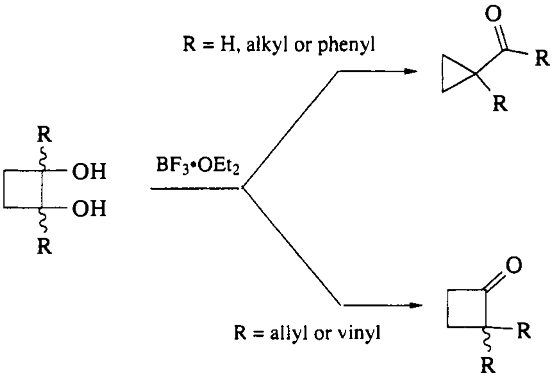

(17)

The strained four-membered ring has been used in a different way by Kuwajima.[33] Bis(trimethylsilyl)succinoin (**28**) when treated with benzaldehyde in the presence of $TiCl_4$ afforded the intermediate (**29**), which gave the ring-expanded product (**30**) on treatment with trifluoroacetic acid (equation 18). An analogous reaction of (**28**) with ketals, catalyzed by $BF_3{\cdot}OEt_2$, led to good yields of 2,2-disubstituted-1,3-cyclopentanediones. These reactions illustrate the facile migration of an acyl group.

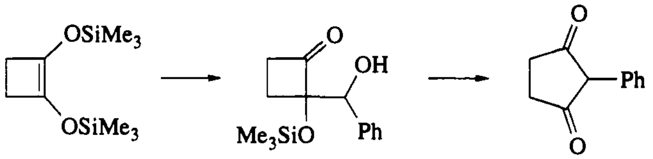

(**28**) (**29**) (**30**) (18)

An unusual observation was made when diol (**31**) was treated with $BF_3{\cdot}OEt_2$. The ring-enlarged terpene karahanaenone (**32**) was formed (along with a double-bond positional isomer); the authors[34] reported that other catalysts gave little or no ring-expanded product (equation 19).

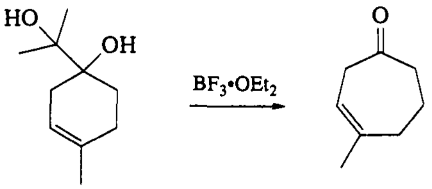

(**31**) (**32**) (19)

When one of the diol centers bears a vinyl group, a preference for initial formation of an allylic carbenium ion is anticipated. Oppolzer and coworkers[35] made use of this feature to develop a cyclohexenone 1,2-carbonyl transposition reaction, illustrated by the sequence shown in equation (20). Oxidation of (**33**) with $Pb(OAc)_4$ was used to introduce the acetoxy group in (**34**); subsequent reduction or addition of an organometallic reagent (*e.g.* R′Li) followed by hydroysis gave the diol (**35**). The pinacol rearrangement was best catalyzed by *p*-toluenesulfonic acid in refluxing benzene, which also caused migration of the double bond into conjugation. Moderate overall yields of the transposed cyclohexenone (**36**) were obtained.

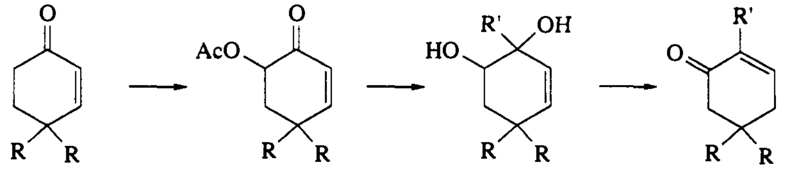

(**33**) (**34**) (**35**) (**36**) (20)

Dana *et al.*[36] examined some similarly unsaturated acyclic diols under pinacol rearrangement conditions. With few exceptions these gave rather complex mixtures of products, and it appears that the synthetic utility of this method is limited.

Some diols of heterocycles have been subjected to pinacol rearrangement. Mundy[37] found that (**37**) gave only (**38**) when treated with cold concentrated sulfuric acid (equation 21). It was noted that (**38**) is *not* the product expected from initial cation stability arguments based on anticipated heteroatom dipole effects. The basis for this selectivity remains unclear. An attempt to detect alternative products at short reaction times failed to shed light on this question.

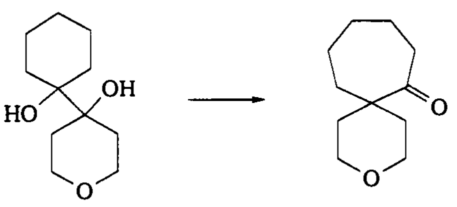

(**37**) (**38**) (21)

Diols obtained by osmium tetroxide treatment of porphyrins constitute some of the more complex structures which have been subjected to pinacol rearrangement.[38] These reactions left the polycyclic framework intact, and the oxochlorin products were formed by rearrangements which followed normal migratory aptitudes (*e.g.* H, Et > Me).

The diol (**39**) gave (**40**; 49%) when treated with $ZnCl_2$ in acetic anhydride (equation 22).[39] Interestingly, the analogous epoxide (**41**) gave the alternative expanded heterocycle azepinone (**42**) when subjected to $BF_3{\cdot}OEt_2$ in benzene (equation 23).

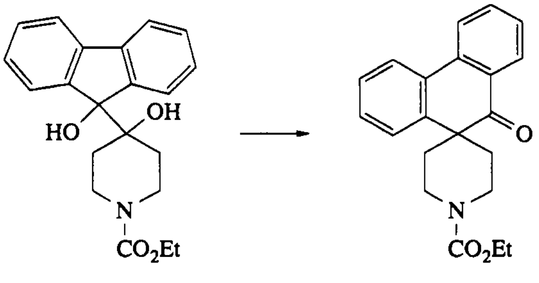

**(39)** **(40)** (22)

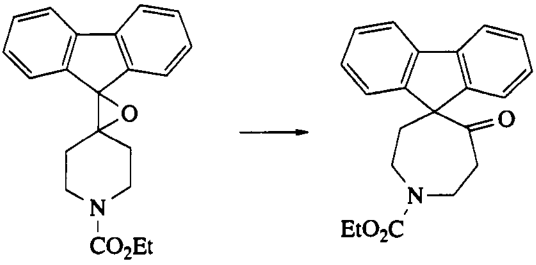

**(41)** **(42)** (23)

The distinction between the pinacol and semipinacol rearrangements is blurred in instances where the starting material is a diol, but steps are taken to form a derivative in order to control the regiochemistry of the reaction. For example, it is sometimes possible to take advantage of differential alcohol reactivity (primary > secondary > tertiary) to form a specific derivative, such that solvolysis will lead to migration to the less-substituted center.[7b] Corey *et al.*[40] used this approach to effect the ring expansion of (**43**) to (**44**) (note the preference for vinyl over alkyl migration), a key step in a synthesis of the sesquiterpene longifolene (equation 24).

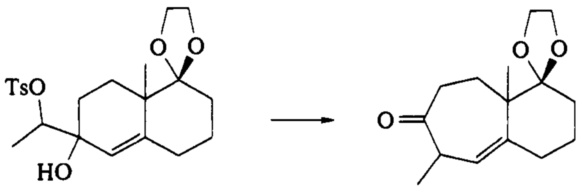

**(43)** **(44)** (24)

Migration to a primary center has also been effected, as shown by the conversion of (**45**) to (**46**; equation 25).[41] Conditions for these reactions are quite mild, consisting of solvolysis in tetrahydrofuran/$LiClO_4$, with $CaCO_3$ present to neutralize the *p*-toluenesulfonic acid that is formed.

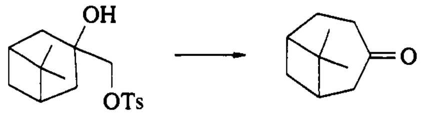

**(45)** **(46)** (25)

Tsuchihashi and coworkers used methanesulfonate esters in a novel variant.[42] An unusual feature is the use of alanes ($Et_3Al$ or $Et_2AlCl$) in $CH_2Cl_2$ solvent at low temperatures to promote the rearrangement. Aryl and vinyl groups migrated more rapidly than alkyl substituents, and the more acidic $Et_2AlCl$ was needed for good results with the latter. Some noteworthy features of this procedure are: (i) migration of vinyl groups with retention of (*E,Z*)-configuration; (ii) clean inversion of configuration at the migration terminus; and (iii) the formation of rather sensitive optically active materials, as illustrated in equation (26).[42b] The authors invoke a 'push–pull' mechanism involving initial formation of an aluminum alkoxide by reaction at the free hydroxy group.

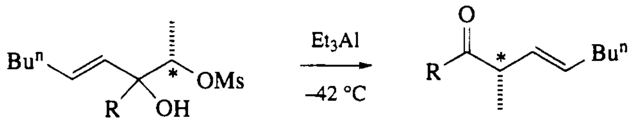

(26)

**(47)** R = alkyl **(48)**

A similar reaction of vicinal diol monoacetates promoted by alanes has been reported.[43] Higher temperatures are needed with these substrates, and in some instances the rearrangement product (ketone) was alkylated (or alkynylated) by the alane promoter. The use of $Et_2AlSPh$ avoided this complication.

Bicyclic systems have provided an interesting framework for examination of stereochemical preferences in the rearrangements of diol monoethers. Monti *et al.*[44] found that the *anti* (double bond and hydroxy group) isomer of the [2.2.2] bicyclic substrate (**49**) gave (**50**) stereospecifically, whereas the *syn* isomer gave a mixture of products (equation 27).

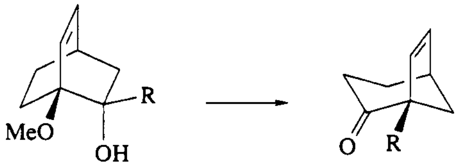

(27)

**(49)** **(50)**

Surprisingly, the [3.2.2] bicyclic analogs gave contrasting results, with the *syn* isomer (**51**; equation 28) rearranging cleanly to (**52**), whereas the *anti* isomer gave a mixture derived from migration of both the saturated and unsaturated two-carbon bridges.[45] The remarkable net retention at the migration terminus in the formation of (**52**) has been ascribed to conformational effects, which also caused the *syn* substrate to react more rapidly that its *anti* counterpart.

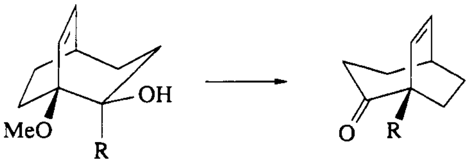

(28)

**(51)** **(52)**

Although its utility appears to be limited, Mukaiyama *et al.*[46] found that the chloropyrimidinium fluorosulfate (**53**) can effect both functionalization and subsequent pinacol rearrangement in a one-pot procedure. Unsymmetrical secondary–tertiary diols give the products expected of derivatization at the secondary hydroxy group. A major side reaction is elimination.

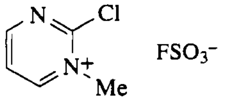

**(53)**

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# 3.3

# Acid-catalyzed Rearrangements of Epoxides

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## 3.3.1 INTRODUCTION

The parallels between acid-catalyzed reactions of epoxides and the pinacol rearrangement are noted in Chapter 3.2 of this volume. Epoxides react more or less readily with acids, but they are at least moderately stable to all but the strongest of bases. It is difficult to find a persuasive instance of epoxide opening, even under basic conditions, that does not involve some probable form of electrophilic assistance, and a case can be made for the view that electrophile bonding/coordination to oxygen is required in order to cleave an epoxide. This electrophilic assistance may be as mild as hydrogen bonding by water in the opening of epoxides with aqueous amines, or as strong as the interactions that occur with concentrated $H_2SO_4$ or powerful Lewis acids.

## 3.3.2 STEREOCHEMISTRY OF EPOXIDE OPENING

The stereochemical outcome is known for many epoxide-opening reactions. Examination of the effects of substituents and conditions on stereochemistry can provide insight into the mechanisms of the rearrangements which are the focus of this section. The words *syn* and *anti* are used here to describe mechanistic features, with the terms *cis* and *trans* retained as structural descriptors. The vast majority of epoxide-opening reactions occur with *anti* stereospecificity, *i.e.* backside displacement of the cleaved C—O bond.[1] *Anti* preference dominates sufficiently to warrant calling this the 'normal' stereochemical outcome.

The stereoelectronic aspects of *anti* opening have been explored in studies of cyclohexene oxides, *e.g.* (**1**; equation 1), including steroidal epoxides.[2] For the few reagents which have been examined in detail, it has been found that an antiperiplanar array of the attacking nucleophile (N in equation 1), the two carbons of the oxirane ring and the epoxy oxygen (bonded to the electrophile E) is very strongly preferred. This antiperiplanar array is feasible with concurrent formation of either a chair (**2**) or twist boat (**4**) cyclohexane skeleton. The appreciable difference in $\Delta\Delta G^{\ddagger}$, which typically favors opening *via* (**2**) over (**4**), suggests that a significant portion of the chair *versus* twist boat energy difference is experienced in the transition states, *i.e.* these reactions are thought to have product-like transition states.

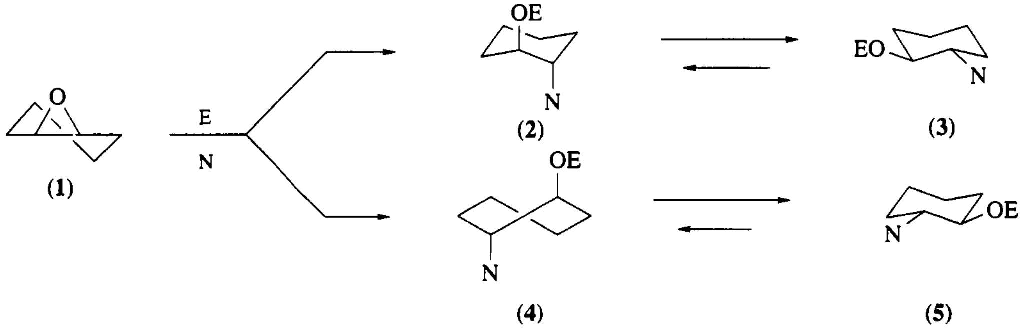

(1)

The chair antiperiplanar mode leads initially to the *trans* diaxial product (**2**), which typically will equilibrate *via* chair–chair interconversion with the *trans* diequatorial conformer (**3**). The twist boat antiperiplanar initial product (**4**) will commonly undergo rotation to form the more stable chair conformer (**5**). Thus both the upper and lower pathways of equation (1) can result in *trans* diequatorial products. Structures (**3**) and (**5**) are enantiomeric; these pathways can be distinguished through the use of an appropriate stereochemical marker (substituent).

Strong preference for chair over twist boat development appears to be general, and is often referred to as the rule of diaxial opening or the Furst–Plattner rule. Twist boat processes can be encouraged by suitable substitution,[3] but in the absence of such special features there are no known examples of cyclohexene oxides which give appreciable amounts of twist boat opened products (sometimes called diequatorial-opening products). The lone apparent exception[4] has been shown[5] to be an artifact caused by an impurity.

Although kinetic control typically favors the *trans* diaxial product, the *trans* diequatorial product is commonly thermodynamically preferred. If the epoxide can be regenerated due to reversibility under particular reaction conditions, a small amount of competing twist boat opening can in principle allow eventual product equilibration. An analogy is found in the classical steroid diaxial to diequatorial dibromide interconversion that is believed to occur *via* reversible formation of a bromonium ion intermediate that slowly drains to the thermodynamically favored product through the kinetically disfavored antiperiplanar twist boat intermediate.[6]

The preference for *anti* opening of epoxides by reagents which function both as an electrophile and a nucleophile is critical to the selectivity observed in some of the rearrangements elaborated below.

*Syn* (abnormal) opening[7] of epoxides appears to be closely associated with the formation of carbenium ion intermediates, and thus is typically observed when substituents, reagents or conditions favor the formation of carbocations. Increasing solvent polarity and acid strength can lead to *syn* opening. Most of the documented examples involve phenyl-substituted epoxides,[8] although an alkyl[9] or alkynyl[10] group at a tertiary center can be sufficient. *Syn* openings of bicyclic alkene oxides have also been observed.[11] The isolation of *syn*-opening products, *e.g.* the *cis*-diol from 1-phenylcyclohexene oxide, requires the use of a solvent, such as water, which is sufficiently nucleophilic to trap the intermediate carbenium ion before pinacol-like rearrangement can occur.

Apparent *syn* opening may also be the result of epimerization after normal *anti* opening. Examples have been identified in the cyanide opening of an anhydro sugar[12] and in the opening of steroidal epoxides by hydrogen fluoride.[13]

## 3.3.3 PROTIC ACID CATALYZED REARRANGEMENTS

The conjugate base of a protic acid is often sufficiently nucleophilic to prevent rearrangements in epoxide-opening reactions. As a consequence, most studies aimed at examining rearrangements have utilized aprotic Lewis acids, especially $BF_3$. Many such studies have compared protic and aprotic acids;

examples in this section are restricted to those in which the protic acid proved superior, or was the sole reagent used.

Acidic treatment of epoxides has provided a wealth of unusual rearrangements, many of which involve participation of a remote substituent with the incipient positive center. Conversely, the oxirane ring itself may function as a neighboring group, although this phenomenon has been little studied. Richey and Kinsman[14] examined the solvolyses of substrates such as (**6**; equation 2), and concluded that conversion to (**7**) was probably accelerated by the oxirane. Similar participation may be involved in the acid-catalyzed rearrangement of (**8**) to (**9**; equation 3).[15] On the other hand, Hornback[16] concluded that there was no anchimeric assistance in the acetolyses of the *cis*- and *trans*-tosylates (**10**; equation 4). Both isomers gave mixtures of products derived mainly from acetolysis of the epoxide ring of inverted acetates (**11**).

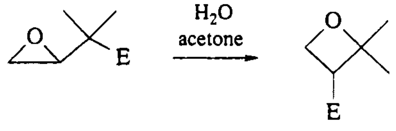

(2)

(**6**) (**7**)

E = 3,5-dinitrobenzoate

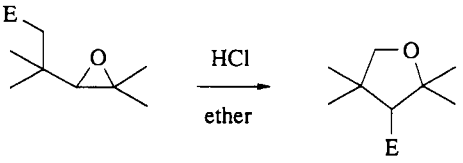

(3)

(**8**) E = isobutyrate (**9**)

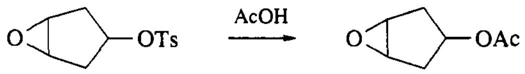

(4)

(**10**) (**11**)

Transannular hydride shifts, first detected by Cope and coworkers[17] in solvolyses of cyclooctene oxide, have subsequently been found in a number of related systems, *e.g.* cyclooctadiene monoepoxides,[18] *exo*-bicyclo[3.3.1]non-2-ene epoxide[19] and 1-oxaspiro[2.6]nonane.[20] In general these reactions do not involve skeletal rearrangements, and they will not be discussed in detail.

Hydroxy groups which are β to the oxirane ring readily participate in opening if the geometrical features are favorable. This, the Payne rearrangement, serves to interconvert two epoxy alcohols with inversion of the central carbon. In the simplest case, that of 2,3-epoxypropan-1-ol, the reaction constitutes a mechanism for racemization. Although usually carried out under basic conditions if the rearranged epoxide is to be isolated, the reaction may also be facile under acidic conditions, as illustrated by an example from the steroid literature (equation 5).[21] In this instance, Payne rearrangement effects the interconversion of (**12**) and (**13**), and normal *anti* opening of the latter by solvent then gives the formal *syn*-opening (from **12**) product, triol (**14**).

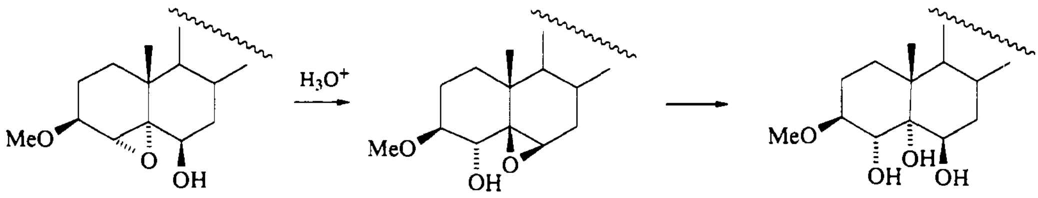

(5)

(**12**) (**13**) (**14**)

When the hydroxy group is further removed from the oxirane it may still participate in opening, but these reactions have been studied mainly under basic[22] conditions or with Lewis acids, as described in the next section.

Remote double bonds often participate in epoxide openings, sometimes with extensive skeletal changes. *exo*-Norbornadiene oxide (**15**; equation 6) provides an interesting example. Meinwald *et al.*[23] found that this very acid-sensitive material rearranged simply on standing to give the *endo*-aldehyde (**17**), presumably *via* the intermediate nortricyclanol ion (**16**).

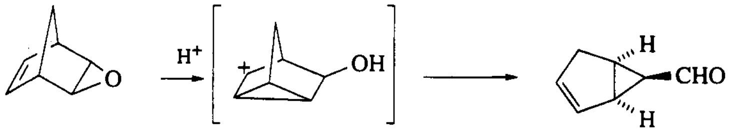

(**15**) (**16**) (**17**)

(6)

Murray and coworkers[24] extended their studies of the novel oxidant dimethyldioxirane (**19**) to the reaction of quadricyclane (**18**; equation 7). The epoxide (**15**) was the nearly exclusive monooxidation product when the acetone solution of the oxidant was carefully dried, but in the presence of water a considerable amount of (**17**) was formed.

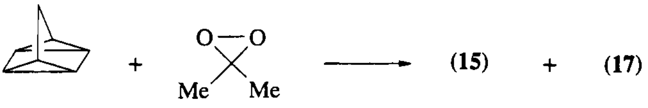

(**18**) (**19**)

(7)

Competition between an alkene and an ether oxygen for participation in epoxide opening is evident in the reactions of trichothecenes (illustrated by the skeletal structure **20**; equation 8). In aqueous acid, participation of the ether oxygen is favored and (**21**) is formed, probably due to preferred cleavage at the tertiary center under the more electrophilic conditions. Under neutral or basic conditions, the diminished role of intermolecular electrophile (water) results in unusual scission of the primary epoxide bond, with formation of (**22**).[25]

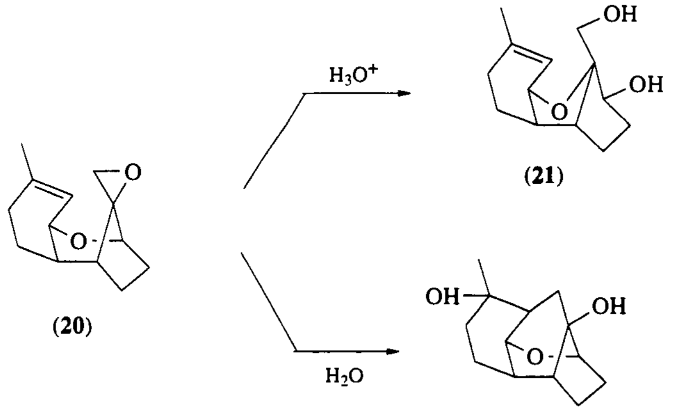

(**20**) (**21**) (**22**)

(8)

Detailed mechanistic studies of epoxide reactions in aqueous acid led Pocker *et al.* to conclude that protonated epoxide is an intermediate, distinguishable from the ring-opened carbocation (the latter leads to pinacol rearrangement),[26] and more recently a neutral solution zwitterion intermediate has been proposed for reactions in solutions of high ionic strength.[27] Solvent hydrogen bonding of the zwitterion would appear to be equivalent to calling upon water as the electrophile in 'spontaneous' openings such as that shown in equation (8).

An interesting approach to the pyrrolizidine ring system was developed by Glass *et al.*,[28] who found that transannular displacement of the epoxide (**23**; equation 9) could be effected simply by heating in ethanol.

Cyclopropanes can also participate in epoxide openings, much like double bonds. The work of Ohloff and Giersch[29] with carene epoxides illustrates this behavior, *e.g.* (**25**; equation 10) is converted to (**26**) and related carbenium ion derived products, and (**27**; equation 11) similarly forms (**28**).

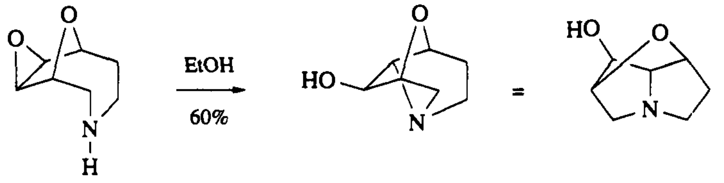

**(23)** **(24)**

(9)

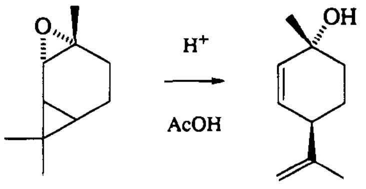

**(25)** **(26)**

(10)

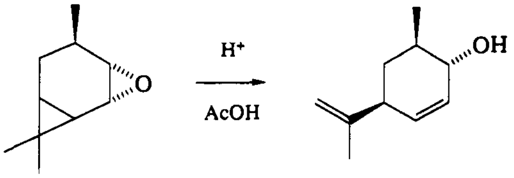

**(27)** **(28)**

(11)

When the carbamazepin epoxide (**29**; equation 12) is treated with *p*-toluenesulfonic acid in chloroform solvent in the presence of methanethiol, the dithioacetal (**30**) is formed.[30] Apparently, rearrangement to ring-contracted aldehyde occurs more rapidly than normal thiol opening of the epoxide.

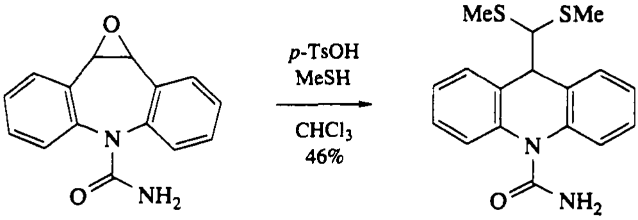

**(29)** **(30)**

(12)

Attempted peroxy acid epoxidation of the bicyclic ketone (**31**; equation 13) gave the lactone (**33**), instead of several possible rational alternatives.[31] The epoxide (**32**) was implicated as an intermediate when it was independently synthesized from the epoxy alcohol, and shown to give (**33**) on treatment with aqueous acid.[32] A mechanism involving scission of the acyl bridgehead bond *via* the hydrated 1,1-diol form of the ketone was proposed to account for the formation of this unexpected product. The rearrangement of the isolongifolene derivative (**34**; equation 14) appears to be mechanistically related. The product (**35**) is formed by brief treatment with dilute $HClO_4$ in dioxane as a mixture of isomers believed to arise by acid-catalyzed epimerization of the carbinol center.[33]

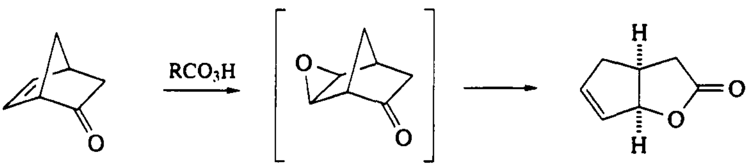

**(31)** **(32)** **(33)**

(13)

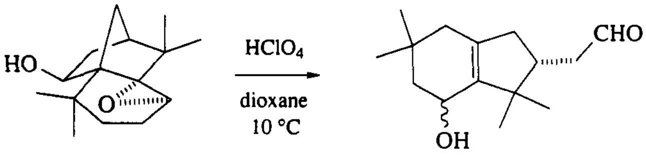

(14)

**(34)** **(35)**

Hart and coworkers[34] used trifluoroacetic acid to catalyze some deep-seated epoxide rearrangements, illustrated by the examples in equations (15) and (16). An unusual mechanism involving scission of the epoxide C—C bond was suggested for the conversion of (**38**) to (**39**), in order to accommodate deuterium-labeling results.

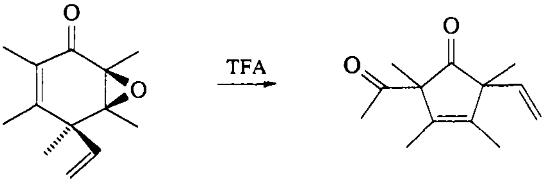

(15)

**(36)** **(37)**

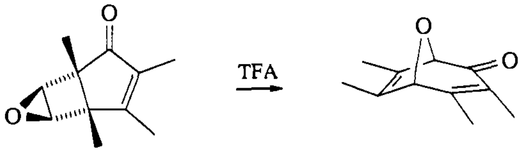

(16)

**(38)** **(39)**

HBr in HOAc has been used to effect the rearrangement/aromatization of the androstenone epoxide (**40**). The use of DBr/DOAc and $^{13}C$ NMR analysis led to the conclusion that the reaction takes place *via* the phenonium ion (**41**) shown in equation (17).[35]

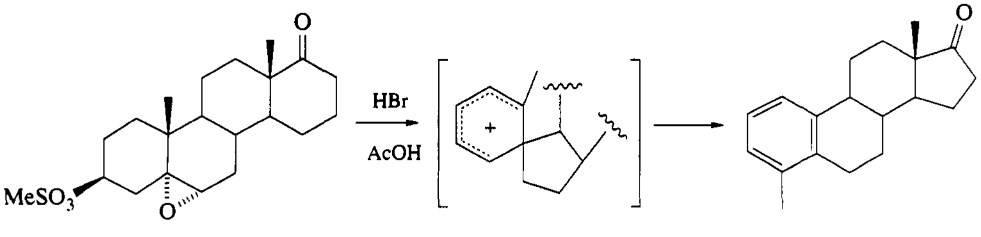

(17)

**(40)** **(41)** **(42)**

One of the few (intentional) applications of HF to epoxide rearrangement is found in an informative study by Audouin and Levisalles,[36] who isolated fluorohydrin and diene products on mild treatment of (**43**; equation 18); these proposed intermediates were converted to the dione (**44**) when resubjected to the reaction conditions.

Some α-substituted epoxides exhibit predictable and synthetically useful behavior when subjected to acids. Others are thermally unstable, and appear to rearrange by different mechanisms in the presence and absence of acids.

Lewis acid induced reactions of α-carbonyl epoxides have been extensively studied, but protic acid reactions in general have not found favor. An exception is shown in equation (19). The protic acid mixture shown was found to be superior to $BF_3$ etherate for the desired rearrangement.[37]

In the Darzens' aldehyde synthesis the α-substituent is a carboxyl(ate) group, which is lost during or subsequent to rearrangement. The normal mode of reaction of glycidic acids generates the new carbonyl group at the point of the original carboxyl group attachment, as shown in equation (20). However, when

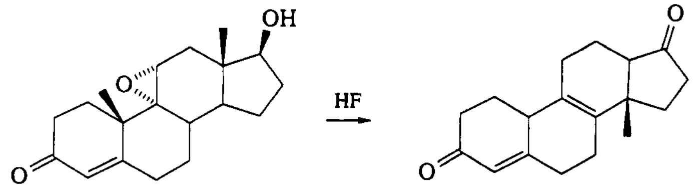

(18)

**(43)** **(44)**

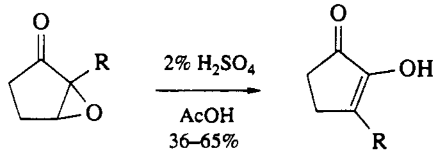

(19)

**(45)** R = alkyl **(46)**

the α-cation is stabilized by phenyl substitution as in (**49**), the product (**50**), derived from abnormal α-opening, may dominate (equation 21), depending upon the β-substituents.[38]

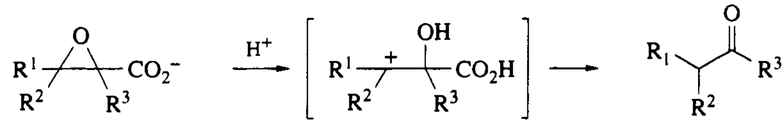

(20)

**(47)** $R^3$ = H or alkyl **(48)**

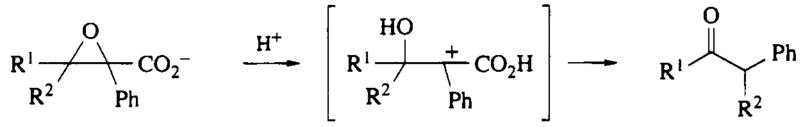

(21)

**(49)** **(50)**

Epoxides derived from vinyl halides and vinyl acetates tend to rearrange readily on heating. McDonald and his coworkers uncovered several mechanistically intriguing examples of thermal rearrangements involving α-chloro epoxides. In some instances the epoxides could not be isolated, but presumably are reactive intermediates, *e.g.* in the peroxy acid reaction of chlorostilbenes.[39] A common intermediate was proposed to account for the formation of the same (chlorine-migrated) product from both geometrical isomers of (**51**; equation 22).

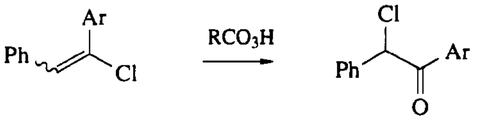

(22)

**(51)** *(E) or (Z)* **(52)**

The *cis* and *trans* isomers of (**53**) both gave (**54**) as the kinetically controlled product (equation 23).[40] These results, and those obtained in a study of (+)-2-chloronorbornene *exo*-oxide,[41] led the authors to conclude that the thermal reaction occurs by way of intermediate α-ketocarbenium–chloride ion pairs; preferential axial attack results in the formation of (**54**) as shown.

The role of acid in some of these rearrangements is not obvious. Kirrmann and coworkers[42] determined that thermal and acid-catalyzed reactions of α-chloro epoxides give different products in some instances. Again, preferred migration of chlorine was observed in thermal reactions.

Different mechanisms for thermal and acid-catalyzed rearrangements of steroidal α-acetoxy epoxides have also been proposed.[43] On heating (**55**; equation 24), intramolecular migration of the acetate group occurs, with stereospecific inversion of the cleaved epoxide center leading to (**56**). Treatment of (**55**)

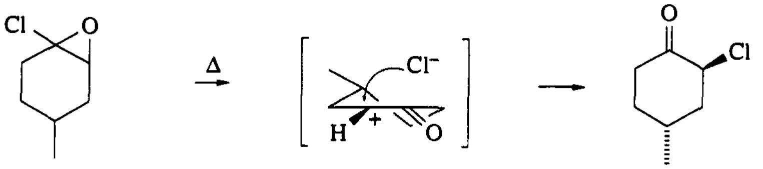

**(53)** *cis* or *trans* **(54)** (23)

with acid results in formation of the more stable equatorial acetate (**57**). From rate studies, it was demonstrated that (**56**) is not an intermediate in the acid-catalyzed formation of (**57**). Although (**56**) does rearrange to (**57**) under the acidic reaction conditions, it does so much more slowly than the direct conversion of (**55**) to (**57**). The acyclic analog (**58**) gave the aldehyde (**59**) both thermally and under acid catalysis (equation 25). Several other reagents and conditions were examined in an effort to clarify the mechanisms of various reactions of (**58**), but some uncertainty remains.[44]

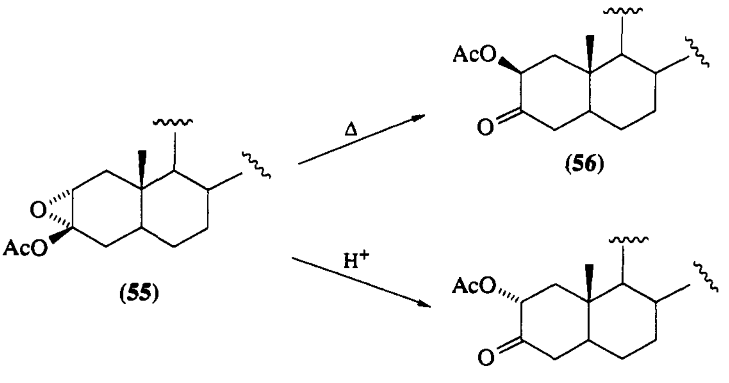

**(55)** **(56)** **(57)** (24)

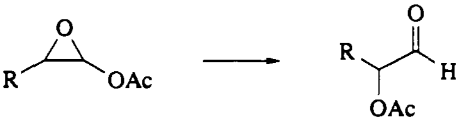

**(58)** R = alkyl, Ph **(59)** (25)

Stevens and Pillai[45] prepared and isolated the azirane (**60**; equation 26), a rare example of an α-amino epoxide. This remarkably stable material required vigorous heating in *o*-dichlorobenzene to effect the ring expansion to (**61**); the remainder was converted to polymeric material.

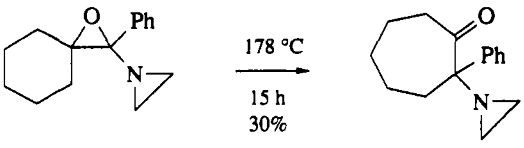

**(60)** **(61)** (26)

Yamamoto *et al.*[46] pointed out potential utility as an 'acyl anion' equivalent for the reaction shown in equation (27). The reaction of (**62**) with *m*-chloroperbenzoic acid was carried out in refluxing $CCl_4$. The presumed intermediate epoxide (**63**) rearranged directly under these conditions to give the product (**64**) in excellent yield.

More remote substituents may also participate in epoxide opening/rearrangement. Christol and coworkers examined several 5,(6)-substituted-2,3-norbornene *exo*-oxides under acidic conditions, and found that certain 5-*endo* substituents played a part in oxirane opening. For example, oxa rings were formed in reactions of substrates bearing 5-*endo*-methoxycarbonyl or -hydroxymethyl groups.[47] A novel 1,4-migration of chloride was also detected (equation 28).[48]

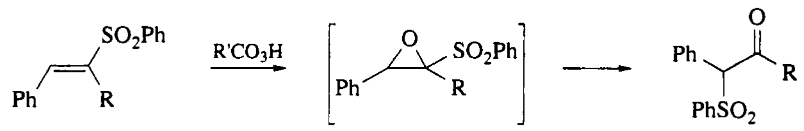

**(62)** **(63)** **(64)** (27)

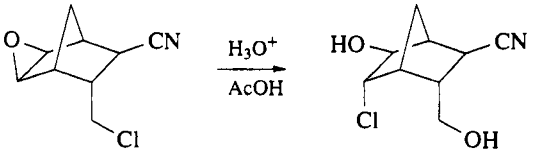

**(65)** **(66)** (28)

Macchia *et al.*[49] observed that the proportion of *syn* opening of 1-benzylcyclohexene oxide increased as the nucleophilicity of the acid/solvent decreased, and became the major pathway when trichloroacetic acid in methylene chloride was employed (equation 29). The relative amount of *syn* opening was greater for (**67**) than for 1-methylcyclohexene oxide under the same conditions. The authors concluded that a phenonium ion intermediate, *i.e.* (**68**), was generated, even though no product involving phenyl migration was detected.

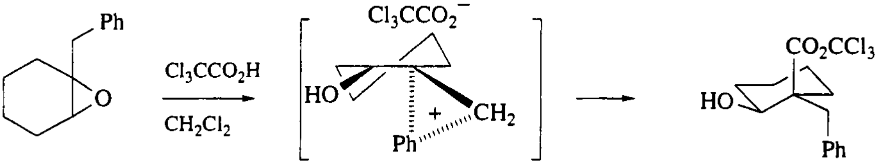

**(67)** **(68)** **(69)** (29)

## 3.3.4 BF$_3$-INDUCED REARRANGEMENTS

Scores of epoxides have been subjected to BF$_3$ (mostly as the etherate), and this appears to be the most widely used Lewis acid for rearrangement. The BF$_3$ is often consumed or altered in the course of these reactions, and is thus a reagent rather than a catalyst, although less than an equivalent is effective in some instances. Steroidal and terpene epoxides have been favorite substrates for study. In spite of the very extensive literature in this area, it is difficult to make product predictions with confidence. Some processes are clean and occur in high yield; many others give low yields and multicomponent mixtures. There is no single recommended standard set of conditions, and many solvent, temperature and time combinations have been described. Products range from simple hydride shift carbonyl isomers to structures formed by multistep rearrangement. Epoxides may also be converted, with or without skeletal rearrangement, to unsaturated alcohols,[50] dienes,[50,51] dimers or oligomers[52] or (very commonly) fluorohydrins.[53] To complicate matters further, the products of several reactions have been shown to rearrange to other materials on longer exposure. Given this context, it is not surprising to find that BF$_3$-induced rearrangements of epoxides are not commonly used in multistep rational syntheses.

On the other hand, no epoxide has been reported to be immune to reaction with BF$_3$, although an interesting example of inertness was noted by Crandall and Machleder.[54] Allene epoxides are usually too sensitive to acids to be isolable from peroxy acid epoxidations, but the bulky *t*-butyl groups on (**70**; equation 30) make it exceptionally unreactive. Several hours of reflux with BF$_3$ in ether were required to effect the conversion to (**71**).

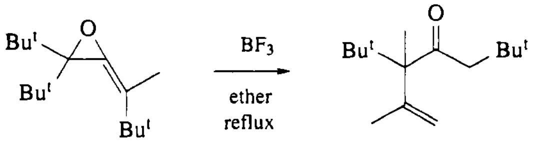

(70) (71) (30)

Steric effects are presumably also responsible for the formation of pivalaldehyde (**73**) when (**72**) is treated with ether-free $BF_3$ in $CCl_4$ (equation 31).[55] Although both isomers (*E* and *Z*) of (**72**) form pivalaldehyde as the major product under these conditions, a sharp distinction between the isomers was noted in ether solvent. The (*E*)-isomer was recovered unchanged from conditions that with the (*Z*)-isomer gave fluorohydrin in good yield.[55]

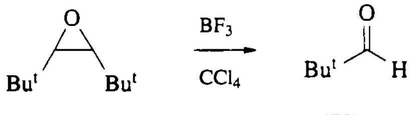

(**72**) (**73**)

(31)

Mechanistic details are rarely obvious in $BF_3$–epoxide reactions, and various views ranging from concerted rearrangement to free carbenium ion intermediate processes have been put forward. The bulk of evidence, especially that obtained in elegant experiments carried out in the laboratory of Coxon and coworkers in New Zealand, supports a general mechanism involving carbenium ions which retain modest stereochemical memories. Coxon has introduced the perspective of relatively slow epoxide opening to give a carbenium ion which is then subject to rapid migration of adjacent groups, at rates which can be somewhat faster than conformer equilibration in the cleaved complex. Preferential direction of rotation to give a conformer which is stereoelectronically suitable for a 1,2-shift is dictated by steric interactions between the $OBF_3$ moiety and groups on the adjacent carbocation center. Rotation towards the smaller of these groups correctly predicts the results obtained with simple aliphatic epoxides. For example, by use of deuterium labeling with corrections for isotope effects, it was found that $H_A$ migrates 1.4 times more readily than $H_B$ in 1,2-epoxyoctane (**74**; equation 32).[56] This outcome was attributed to preferred rotation, as shown in the initial conformer (**75**), towards the smaller group (H *versus* alkyl) at the carbenium ion center. As a conformer with suitable orbital overlap features arises, (**76**), migration of this bond ($H_A$) must take place at a rate greater than or equal to that for continued rotation, in order to account for the formation of (**77**) as the major product. Similar results were obtained with epoxide (**78**; equation 33), which exhibited a preference of $H_A/H_B$ = 1.9 for the formation of the aldehyde (**79**).[57]

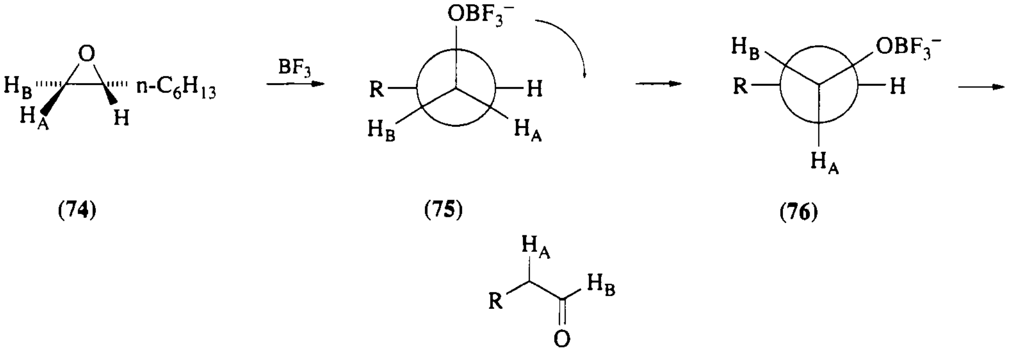

(**74**) (**75**) (**76**)

(**77**)

(32)

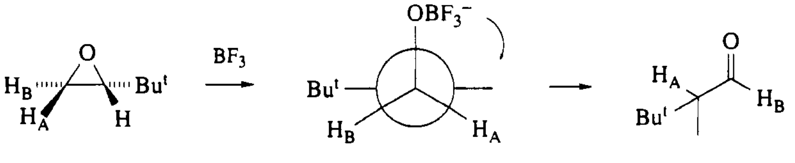

(**78**) (**79**)

(33)

This mechanistic view can be used to rationalize other epoxide rearrangements. For example, the observation[55] that $BF_3$ treatment of (*Z*)-2,3-epoxybutane gives only 2-butanone (equation 34) is nicely accommodated. The (*E*)-isomer gives some isobutyraldehyde (2-butanone:aldehyde = 3:1), which again may be rationalized by this model. Preferred rotation (as in **82**) leads to conformer (**83**), in which the poorer intrinsic migratory aptitude of the methyl group (compared to H) prevents migration from being much faster than further rotation (equation 35).

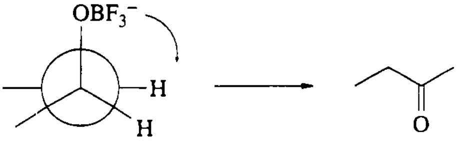

**(80)** **(81)** (34)

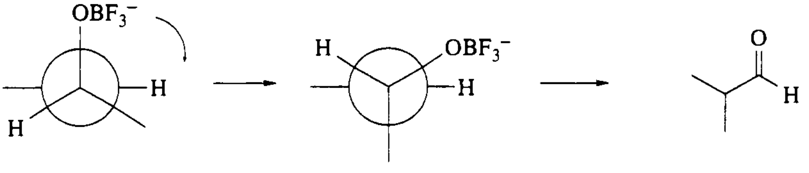

**(82)** **(83)** **(84)** minor product (35)

The important study of Berti *et al.*$^{58}$ (also discussed in the context of the pinacol rearrangement: see equations 8 to 11 of Chapter 3.2 in this volume) included $BF_3$-induced reactions of the *cis*- and *trans*-epoxides (**85**; equation 36) and (**91**; equation 37), respectively. These very informative reactions show that, at least under the particular reaction conditions used in this work (benzene as solvent), the Coxon mechanism must be expanded to include an appreciable antiperiplanar geometrical feature. Unlike the pinacol rearrangements of the related diols, which gave only ketone (**89**) and aldehyde (**90**) under the same conditions, epoxide (**85**) gives, in addition to these same products, a significant amount of aldehyde (**87**). This appears to require the involvement of the twist boat conformer (**86**), which is the expected intermediate if the shown starting material conformer opens at the tertiary benzylic center with antiperiplanar constraints. Subsequent rotation of (**86**) to the chair conformer (**88**) allows formation of the ketone (**89**) and the aldehyde (**90**).

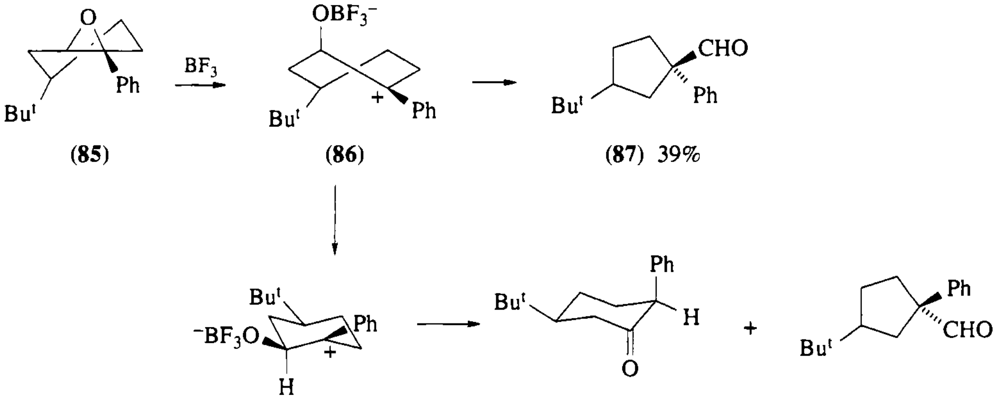

**(85)** **(86)** **(87)** 39%

**(88)** **(89)** 44% **(90)** 17% (36)

This view is reinforced by the reaction of isomer (**91**; equation 37). In this case antiperiplanar opening would occur directly to give a chair (**92**), which can then produce ketone (**93**) and aldehyde (**90**). The striking feature here is the preponderance of aldehyde relative to ketone, not expected based on migratory aptitude considerations, and quite different from the pinacol rearrangement of the related diols. Whatever the cause of this stereocontrol, it signifies fairly strong preference for migration to the back side of the cleaved epoxide center. It should be noted that some possible antiperiplanar-opening intermediates, *e.g.* *trans*-fluorohydrins, will not serve to rationalize this intriguing behavior.

The formation of aldehydes from 1,1-disubstituted epoxides has occasionally found use in synthesis, although simpler aldehydes in particular tend to form dioxolane dimers by $BF_3$-induced reaction with epoxide.$^{57}$ Hill *et al.*$^{59}$ converted the epoxide (**94**), which had been prepared from a β-ionone derivative, into luciferin aldehyde (**95**) by treatment with cold $BF_3$ etherate (equation 38).

Coxon and coworkers$^{60}$ found a small but consistent bias favoring the product involving inversion of the cleaved center when eight epoxides (four pairs of α- and β-isomers) derived from *exo*-methylene steroids were subjected to $BF_3$ etherate in benzene at room temperature. A carbenium ion intermediate was

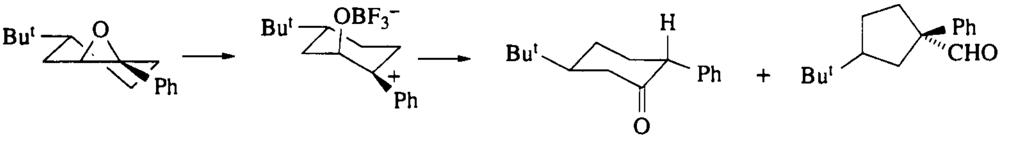

**(91)** **(92)** **(93)** 12% **(90)** 88% (37)

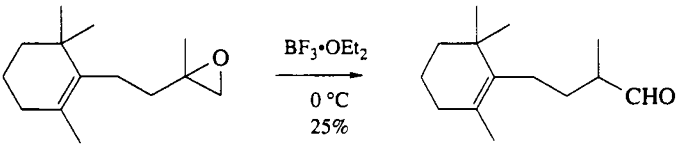

**(94)** **(95)** 25% (38)

proposed, and appears to be required to account for the nearly identical mixtures of epimeric aldehydes obtained from the stereoisomeric pairs of epoxides. This result is not due to equilibration, which would strongly favor the equatorial aldehyde. One isomeric pair is used to illustrate these features (equation 39).

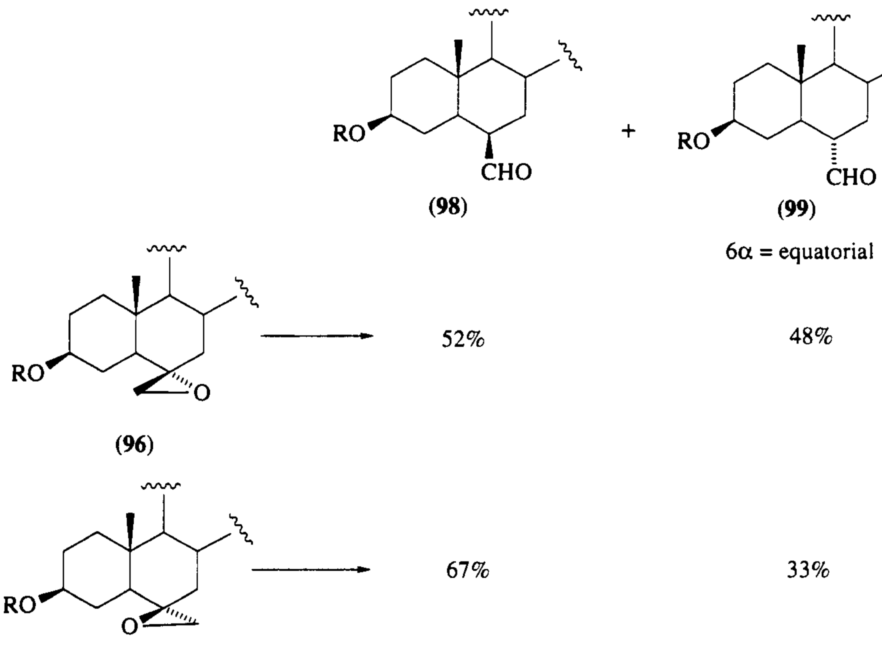

**(98)** **(99)** **(96)** **(97)** (39)

The 1,1-disubstituted epoxide (**100**; equation 40) undergoes ring expansion rather than hydride migration, to afford materials such as (**101**) and related products.[61] It is conceivable that an aldehyde was generated in this instance, which then rearranged to the isolated products. This kind of behavior is seen with (**102**; equation 41) which upon brief treatment with $BF_3$ afforded aldehyde (**103**) and ketone (**104**) in nearly equal amounts. When resubjected to the reaction conditions the aldehyde (**103**) gave a new ketone (**105**). Compound (**103**) was used as a precursor to the hydrocarbon cuparene, which has the structure of (**103**) modified by reduction of CHO to Me; in spite of the modest yield, this proved a convenient approach to a structure with two adjacent quaternary carbons.[62]

Some unsymmetrical tetrasubstituted alkenes (and hence epoxides) have become more available since the advent of McMurry low-valent Ti reductive-coupling procedures and related reactions, but relatively little use has been made of this in epoxide rearrangement studies. An exception involves the cycloheptyl derivative (**106**; equation 42) which was found to rearrange cleanly to ketone (**107**).[63]

Rearrangement of a tetrasubstituted epoxide is a key step (equation 43) in a recent approach to the taxane ring system.[64]

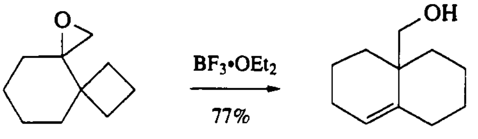

**(100)** **(101)** (40)

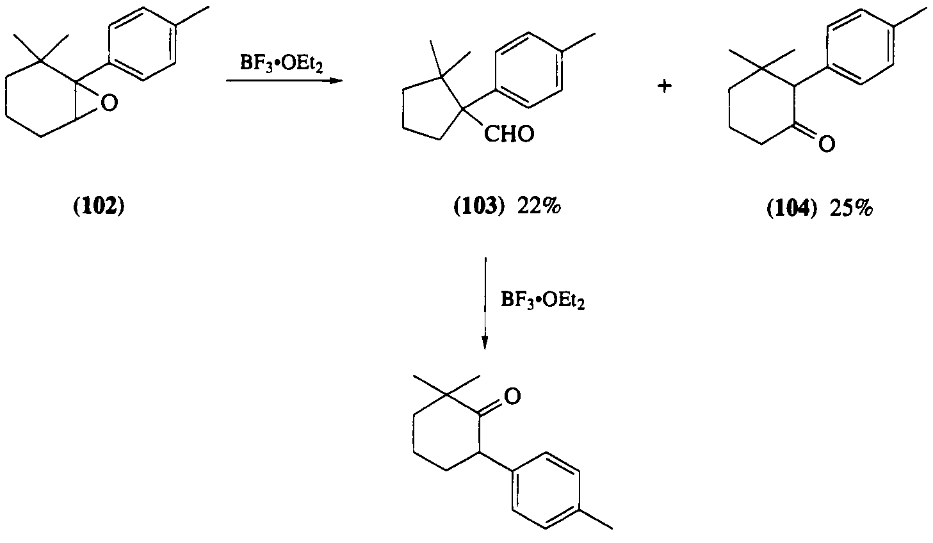
BF3•OEt2
BF3•OEt2

**(102)** **(103)** 22% **(104)** 25%

**(105)** (41)

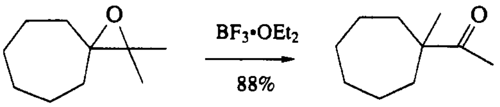

**(106)** **(107)** (42)

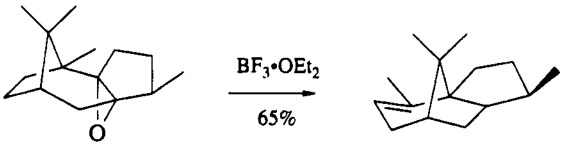

**(108)** **(109)** (43)

Berti *et al.*[65] found that the tetrasubstituted epoxide derivative (**110**; equation 44) of the triterpene hopane gave an efficient rearrangement to the ketone (**111**).

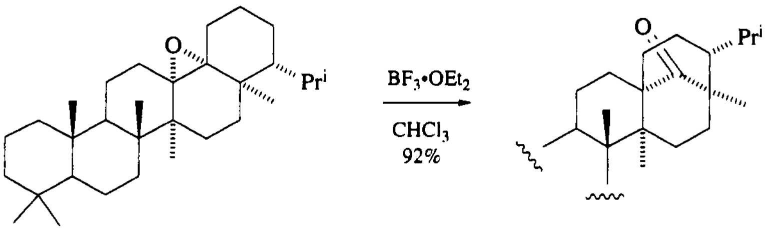
BF3•OEt2
CHCl3
92%

**(110)** **(111)** (44)

The phenyl substituent appears to be a major factor leading to the interesting results displayed in equation (45).[66] The timing needed to obtain the excellent yield of (**113**) is noteworthy, and indicates just how easy it can be to miss interesting chemistry associated with such rapid reactions.

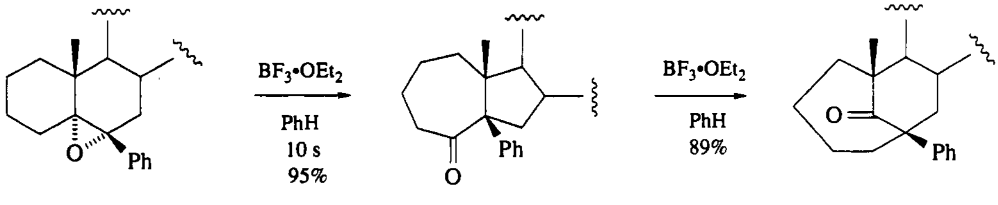

(45)

(**112**) (**113**) (**114**)

Disubstituted epoxides tend to give mixtures of products when treated with $BF_3$. An interesting exception is found in the novel approach to the noradamantane ring developed by Majerski and Hamersak.[67] The epoxide (**115**; equation 46) gives an excellent yield of this ring system with other acids as well, but $BF_3$ in HOAc offers the added advantage of directly differentiating the two alcohol functions in the formation of (**116**).

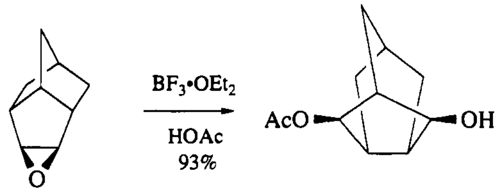

(46)

(**115**) (**116**)

The β-cation-stabilizing influence of the trimethylsilyl group probably assists in the rearrangement of (**117**) to (**118**; equation 47).[68]

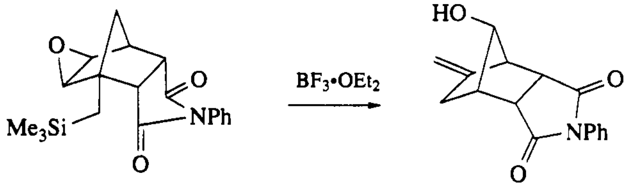

(47)

(**117**) (**118**)

Reactions of $BF_3$ and epoxides bearing an α-electron-withdrawing group (EWG) have been extensively studied. Often the course of such reactions can be predicted by assuming formation of a carbenium ion β to the EWG (avoidance of positive charge adjacent to the EWG dipole). When this occurs, facile migration of the EWG may take place.

House and Reif examined certain heavily substituted acyclic keto epoxides, and found diverse behavior as illustrated by equations (48) to (51).[69]

The reaction of (**119**; equation 48) follows what may be regarded as normal behavior, *i.e.* the product is that predicted by β-cleavage followed by migration of the acyl group. Rearrangement of (**121**; equation 49) can be similarly explained. The formation of (**124**; equation 50) from (**123**) is most expediently regarded as involving β-cleavage, but with aryl migration occurring more rapidly than benzoyl migra-

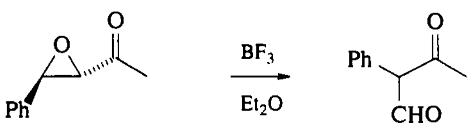

(48)

(**119**) (**120**)

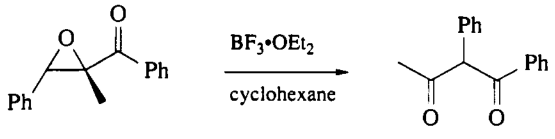

**(121)** **(122)** (49)

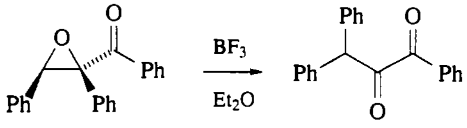

**(123)** **(124)** (50)

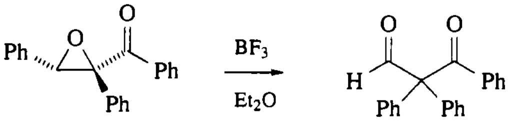

**(125)** **(126)** (51)

tion. This order of migratory aptitude appears to be in keeping with observations in other rearrangements. The (*Z*)-isomer (**125**; equation 51) gave an unexpected product, (**126**). The formation of this aldehyde requires cleavage of the epoxide α to the EWG. These early examples served to frame some of the important mechanistic questions.

Kagan *et al.*[70] examined a series of 3-phenylglycidic esters (EWG = ethoxycarbonyl) and observed migratory preferences which parallel those developed in other studies. However, one important caveat arose from examination of variations in acid, solvent and temperature: the course of the reactions proved to be highly dependent on these variables, leading Kagan to disavow predictability based on structural features alone.

Nonetheless, acyl epoxides and related materials have given useful results when subjected to $BF_3$. The interesting spiro diketone (**128**; equation 52) for example, is readily prepared by $BF_3$ etherate treatment of the epoxide (**127**).[71]

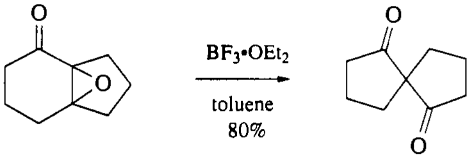

**(127)** **(128)** (52)

When the initially formed rearrangement product is a β-keto aldehyde, facile loss of the formyl group is sometimes observed (retro-aldol). An interesting example is found in the reactions of the quinone derivative (**129**; equation 53) Rearrangement accompanied by deformylation occurred under a variety of acidic conditions, but the $BF_3$-induced reaction was especially efficient.[72]

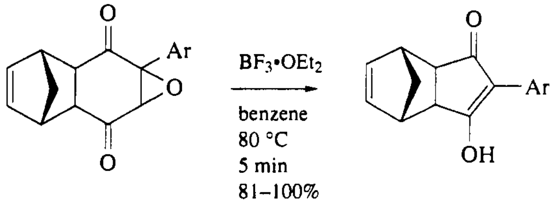

**(129)** **(130)** (53)

An example from the terpene literature[73] is shown in equation (54). The corresponding epoxy alcohol in this instance gave a complex mixture from which no product could be isolated. The formation of a second carbonyl group may help to stabilize the product *via* complex formation, as discussed by House.[69]

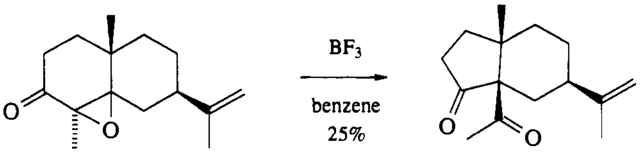

**(131)** **(132)**

(54)

McDonald and Hill[74] found that α-cleavage is a common feature of aromatic epoxynitriles such as (**133**), which gave (**134**) in excellent yield (equation 55). In simpler systems the nitrile group typically leads to β-cleavage, a feature that has been used for the synthesis of fluoro ketones as shown by the example in equation (56).[75]

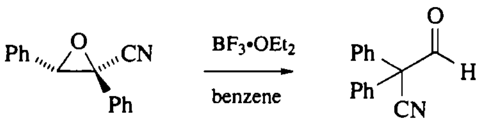

**(133)** **(134)**

(55)

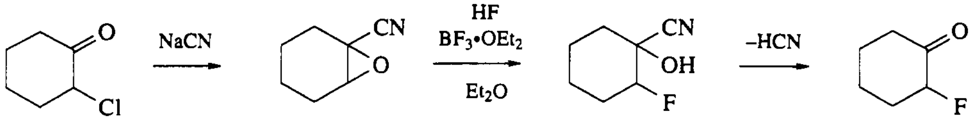

**(135)** **(136)** **(137)** **(138)**

(56)

Other EWG which migrate readily upon β-cleavage of an epoxide include the phosphonate ester[76] (equation 57), sulfoxide (equation 58)[77] and sulfone (equation 59).[78]

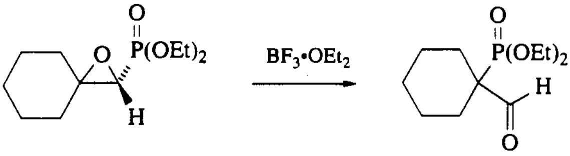

**(139)** **(140)**

(57)

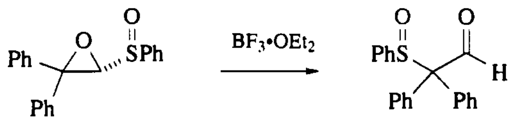

**(141)** **(142)**

(58)

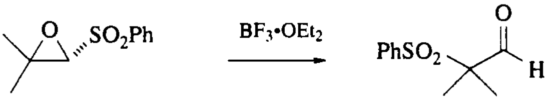

**(143)** **(144)**

(59)

Bach and Domagala have demonstrated that the acyl migrations which occur when diastereomers (**145**; equation 60) and (**147**; equation 61) are treated with BF$_3$[79] (and in the case of (**145**), the analogous thermal[80] reaction) are stereospecific, in each instance taking place with complete inversion at the migration terminus, yielding the enantiomers (**146**) and (**148**), respectively. It was noted that such behavior is more in keeping with a concerted rearrangement than a carbenium ion process. The contrast to the modest levels of inversion discussed previously is appreciable, but it is not clear if this signals a fundamental change in mechanism or some feature of the carbonyl group which allows especially favorable interaction with the developing positive center. Bach suggested that the carbonyl group may have a conformational requirement for migration, and explored this idea with the systems shown below.[81] It was found that fluorohydrin formation occurred very rapidly with (**149**; equation 62) and (**152**; equation 63), although none was detected with (**154**; equation 64) under conditions where rearrangement to (**155**) took place. The fluorohydrins (**150**) and (**153**) both rearranged to diones rapidly in refluxing benzene containing $BF_3$. It was thus established that the fluorohydrins are viable but not necessarily required precursors to the dione product. The authors suggested that fluorohydrin formation occurred because acyl migration was geometrically retarded, and that the fluorohydrin in an appropriate conformation could serve as the immediate precursor to the dione. If the fluorohydrins are formed by normal *anti* opening of the epoxides, one would expect retention at the migration terminus in these reactions, an interesting possibility that remains to be tested on a suitably designed substrate.

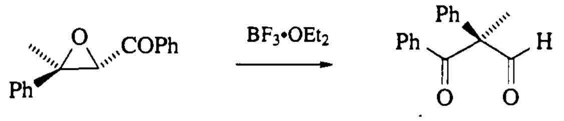

**(145)** **(146)** (60)

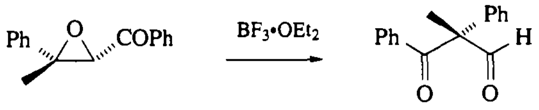

**(147)** **(148)** (61)

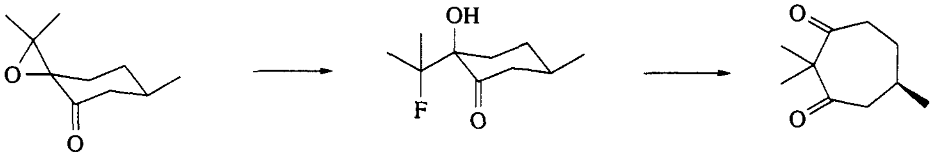

**(149)** **(150)** **(151)** (62)

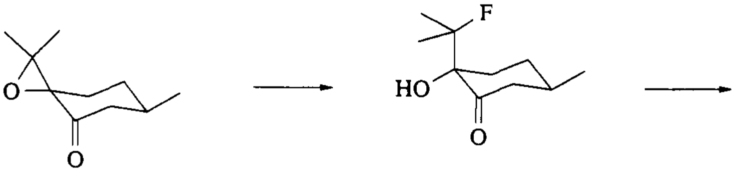

**(152)** **(153)** **(151)** (63)

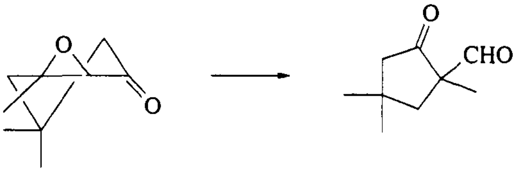

**(154)** **(155)** (64)

Zwanenburg *et al.* examined keto epoxides which contained an acid-sensitive diazomethyl group, *e.g.* (**156**; equation 65), and found conditions for selective initial reaction at both sites. $BF_3$ treatment gave the heterocycle (**157**), presumably by epoxide rearrangement followed by a carbene reaction with the carbonyl group.[82] Pd(OAc)2 catalysis was used to retain the epoxide function while carrying out typical carbenoid reactions, illustrated by the formation of (**158**).[83]

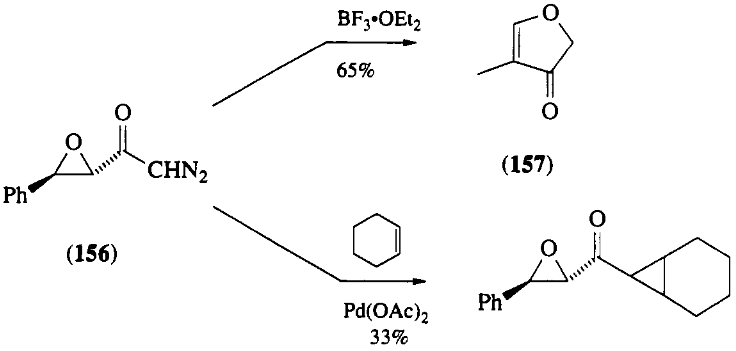
BF3•OEt2
65%
O
O
CHN2
Ph
O
O
Pd(OAc)2
33%
O
O
Ph

(**156**) (**157**) (**158**) (65)

A subtle substituent effect is evident in the reactions of (**159**; equation 66); when the amine (R = alkyl) is subjected to acid-induced rearrangement it gives the hydride migration product (**160**), whereas the amide (R = acyl) reacts almost exclusively by ring contraction.[84]

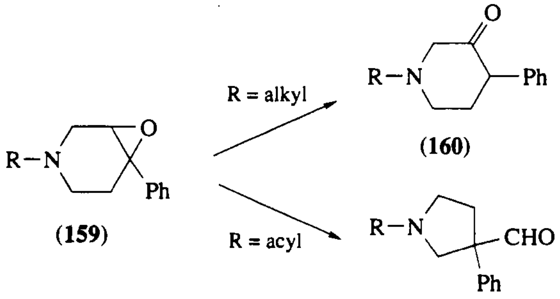
R—N
O
Ph
R = alkyl
R = acyl
O
R—N
Ph
R—N
CHO
Ph

(**159**) (**160**) (**161**) (66)

The epoxy ketal (**162**; equation 67) gave a modest yield of the furan (**163**) along with several other unidentified products.[85]

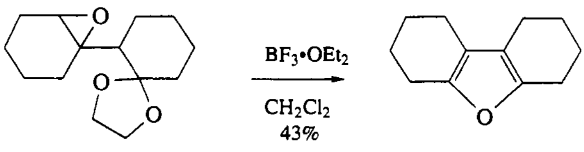
O
O
O
BF3•OEt2
CH2Cl2
43%
O

(**162**) (**163**) (67)

An effort to use an adjacent hydroxy group to force the conversion of a [4.4.0] derivative (**164**; equation 68) to the [5.3.0] ring system was thwarted by an alternative high yield rearrangement to the [4.3.1] bicyclic product (**165**).[86]

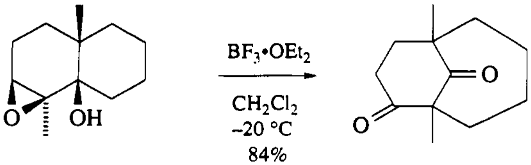
O
OH
BF3•OEt2
CH2Cl2
−20 °C
84%
O
O

(**164**) (**165**) (68)

Another example of a rational synthetic plan going awry occurred with (**166**; equation 69). In this instance the desired reaction was simple methyl migration followed by loss of a proton, but instead contraction of ring A took place. A high yield of oxetane (**167**) was isolated in this example. The stereochemistry of this product was attributed to a mechanism involving opening and reclosure of ring B.[87]

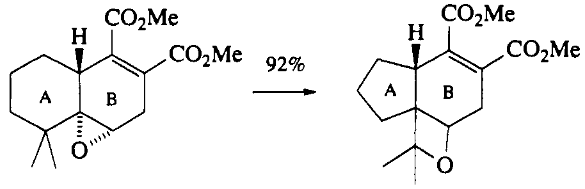

(**166**) (**167**) (69)

The epoxy oxygen reappears in the furanoid rings of (**169**) and (**170**) when (**168**) is subjected to typical rearrangement conditions (equation 70). The stereochemical relationships of these products support a stepwise carbenium ion process.[88]

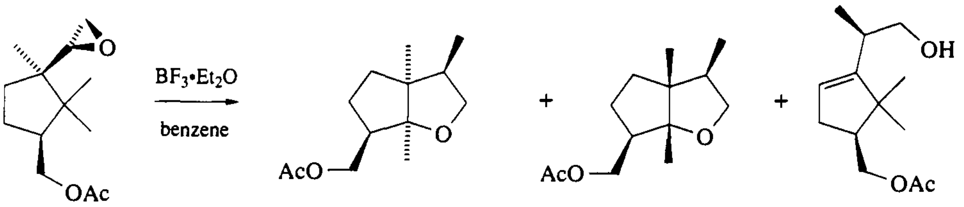

(**168**) (**169**) 38% (**170**) 13% (**171**) 42% (70)

The remarkable, highly symmetrical compound (**173**) is generated when the triepoxide (**172**; equation 71) is treated with $BF_3$ etherate.[89]

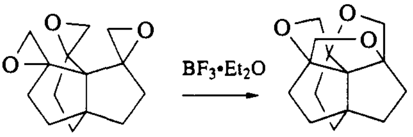

(**172**) (**173**) (71)

Remote hydroxy groups participate in various epoxide openings. Coxon *et al.*[90] observed the formation of cyclic products in the peroxy acid epoxidation of some unsaturated alcohols, and examined the process in greater detail using $BF_3$ in ether. These reactions exhibited a ring size preference: 5 > 6 > 7. The reactions of *cis*- and *trans*-5,6-epoxyheptan-1-ol and *cis*- and *trans*-4,5-epoxyhexan-1-ol appeared to be stereospecific, with inversion of the cleaved center as expected for opening with participation of the hydroxy group. In contrast, the reactions of *cis*- and *trans*-3,4-epoxypentan-1-ol were not stereospecific, in spite of the apparently favored formation of five-membered ring products. Some of these features are illustrated in equations (72) and (73).

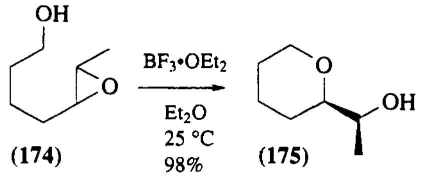

(**174**) (**175**) (72)

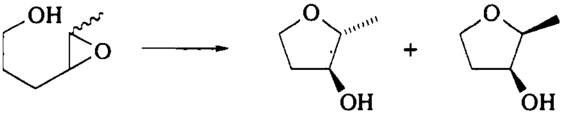

(73)

| (**176**) | (**177**) | (**178**) |
|---|---|---|
| *cis* | 86% | 8% |
| *trans* | 35% | 3% |

A novel mechanism involving an orthoester intermediate was proposed to account for the stereochemical features of reactions like that shown in equation (74), in which the relative configuration of the epoxide is retained.[91]

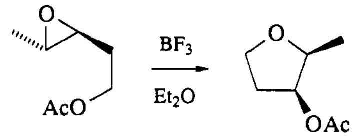

**(179)** **(180)**

(74)

Suitably positioned carbonyl groups may cause ring closure, leading to either five- or six-membered ring lactones. BF$_3$ etherate proved to be more selective than protic acids in a study of unsaturated epoxides, giving exclusively the larger ring size, as illustrated in equation (75).[92]

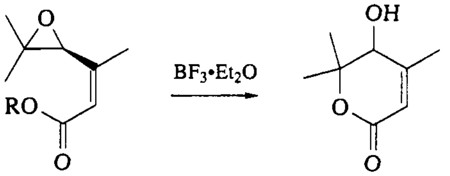

**(181)** **(182)**

(75)

Among the best-known epoxide rearrangements are those which utilize remote double bonds in biomimetic reactions.[93] Two recent syntheses of aphidocolin illustrate variants of this concept. The application described by Van Tamelen *et al.*[94] is outlined in equation (76), while the Tanis *et al.*[95] alternative is shown in equation (77). These reactions tend to be highly stereoselective. Efforts are usually made to avoid nucleophilic gegenions which can disrupt the desired reaction cascade; a wide variety of catalysts in addition to BF$_3$ have been explored. In the conversion of (**185**) to (**186**), for example, an unusual 2:1 ratio of BF$_3$·OEt$_2$ and triethylamine in a three component solvent was found to give the best yield.

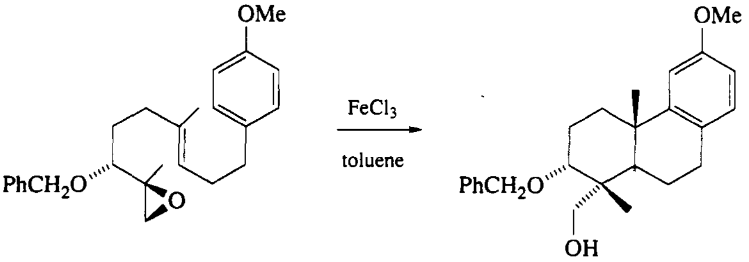

**(183)** **(184)**

(76)

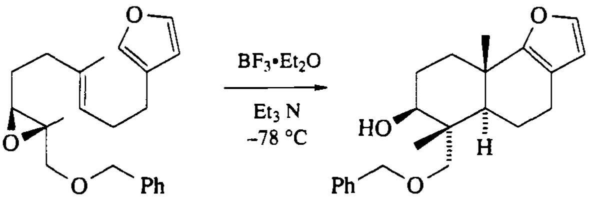

**(185)** **(186)**

(77)

Conacher and Gunstone[96] reported the novel conversion of the diene monoepoxide methyl vernolate (**187**; equation 78) to the cyclopropyl keto isomer (**188**). Later Italian work[97] supported this conclusion, and furnished additional examples of cyclopropane formation.

Excellent yields of bi- or poly-cyclic materials may be obtained if the starting material contains significant portions of the desired product structure. Thus the isogermacrone epoxide (**189**; equation 79) is transformed into (**190**) by brief treatment with BF$_3$ etherate, while longer contact causes further rearrangements.[98] Similarly, epoxide (**191**; equation 80) with two six-membered rings already in place,

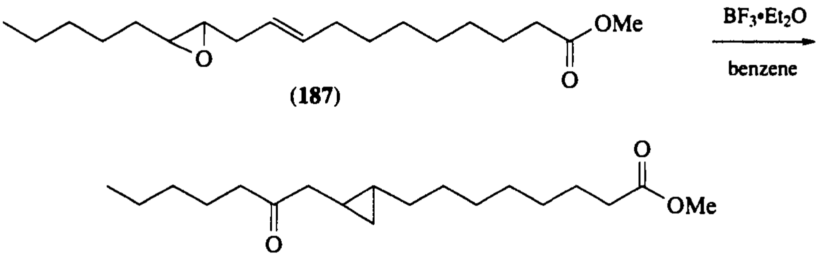

(187)

(188)

(78)

affords a nearly quantitative yield of the hydrophenanthrene derivative (**192**), isolated after hydrolytic work-up as a mixture of the two double-bond isomers.[99]

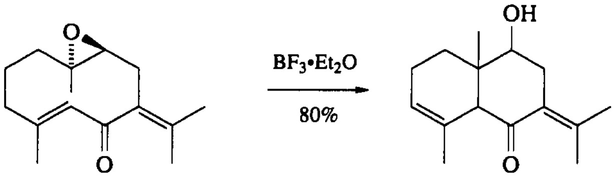

(79)

(**189**) (**190**)

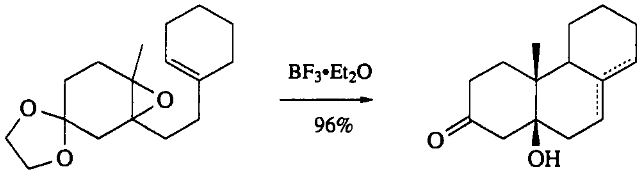

(80)

(**191**) (**192**)

Cyclopropane participation occurs in the reaction of (**193**; equation 81) which rearranges exclusively to the aldehyde (**194**), although the latter is unstable to the reaction conditions. The *endo* (cyclopropyl) isomer was also examined in this study,[100] and gave mostly polymeric product.

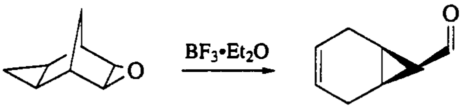

(81)

(**193**) (**194**)

Epoxides may be generated as reactive intermediates when unsaturated materials are treated with $BF_3$/trifluoroperacetic acid, a powerful oxidation/rearrangement mixture developed by Hart.[101] The products from numerous alkenes and aromatic substrates, to the extent that comparisons can be made, are those expected from epoxide/carbenium ion rearrangements.

Although infrequently used, sodium cyanotrihydroborate in the presence of $BF_3$ has been shown to reduce epoxides with interesting regio- and stereo-chemical results.[102] For example, 1-methylcyclohexene oxide is converted in high yield to *cis*-2-methylcyclohexanol contaminated with only small amounts of the *trans* and 1-methylcyclohexanol isomers.

Acyloins are sometimes formed in moderate yield when 1,2-disubstituted epoxides are treated with $BF_3$ in dimethyl sulfoxide solvent.[103] A curious report[104] of highly temperature dependent nonoxidative rearrangement of 2,3-epoxycyclododecanone indicates that a 1,2-dione is formed at 85 °C, whereas a 1,3-dione is the product at 150 °C. All of these applications require heating, since the Lewis acidity of $BF_3$ is strongly attenuated in dimethyl sulfoxide.[105]

### 3.3.5 MAGNESIUM HALIDE CATALYSIS

French work over 60 years ago first led to the recognition that skeletal rearrangement can take place when epoxides are treated with Grignard reagents. By the 1940s the involvement of halohydrin salt intermediates was considered proven, and general stereochemical features were understood, *i.e.* preference for a *trans* relationship between the migrating group and the departing halide.[106] Geissman and Akawie[107] provided additional evidence relating cyclic halohydrin stereochemistry with the course of rearrangement. This work reinforced the view that a *trans* relationship was preferred for rearrangement, but also showed that the same rearrangement product could be formed (in low yield) from the 'wrong' halohydrin stereoisomer. Subsequent studies support the view that epoxide/Grignard and related reactions rarely provide clearcut mechanistic features, and that mixtures of products not explicable by a single pathway are commonly encountered.

Halohydrins are often the major products isolated (after hydrolysis) from epoxide/Grignard reagent mixtures. The magnesiohalide salt of the halohydrin (**196**; equation 82) is assumed to be the species present in solution, formed by reaction of the $MgX_2$ that is present from Schlenk equilibrium. *Anti* opening of the epoxide (**195**) is also usually assumed; there is experimental evidence in several instances to support this conclusion. The alternative (*syn* opening) halohydrin has rarely been ruled out, however, especially as a minor product. The magnesiohalide salts appear to be reasonably stable in ether solutions. Unlike the lithium salt analogs discussed in the next section, (re)closure of (**196**) to the epoxide does not appear to be thermodynamically favorable, and is known to be relatively slow in instances where this question has been addressed.

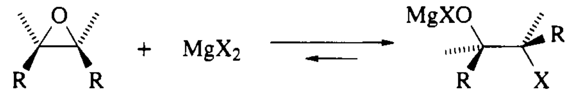

(82)

**(195)** **(196)**

Rearrangements of halohydrin salts usually require prolonged treatment of ether solutions at ambient temperature or heating in a less polar solvent, but there are some interesting exceptions. The 'standard' conditions consist of formation of the magnesiohalide salt in ether, followed by solvent replacement by benzene and short term reflux. House[108] found that residual ether can significantly influence the course of a reaction, and since this variable appears not to have been carefully controlled in most experiments, comparisons may have limited significance.

The reaction of cyclohexene oxide with MeMgX was reexamined in 1969, in work which clearly established the importance of the halide.[109] Standard conditions (1 h at 80 °C) were employed with 1.4 equiv. of the organometallic, to give the yields listed under equation (83). Only minor amounts of the 'normal' displacement product (**200**) are formed from the chloride and bromide, and none from the iodide. The iodide and bromide give extensive rearrangement, with the bromide being more selective in the sense that product (**198**) is expected on the basis of stereoelectronic considerations (backside displacement of halide) from the *trans*-halohydrin. The unusual product from this perspective is (**199**). It must arise either from the *cis*-halohydrin or a process which is not subject to the same stereoelectronic controls, *e.g.* *via* a carbenium ion.

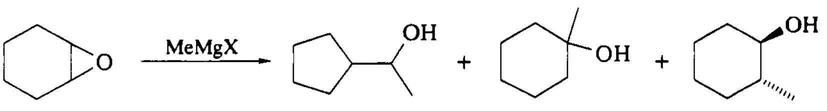

(83)

**(197)** **(198)** **(199)** **(200)**

| *X* | (198) | (199) | (200) |
|---|---|---|---|
| I | 43% | 22% | – |
| Br | 54% | 3% | 5% |
| Cl | 5% | – | 8% |

Treatment of (**197**) with $MgX_2$ ($X = I$ or Br) in ether gave high yields of the corresponding *trans*-halohydrins, with no sign of the *cis* isomers. When heated as in the Grignard reagent experiments, cyclopentanecarbaldehyde and cyclohexanone were formed in ratios of *ca.* 2:1 for the iodide, and 9:1 for the bromide. Based on these observations, the authors suggested that (**199**), or more precisely its precursor cyclohexanone, arises from the carbenium ion generated by loss of halide from the halohydrin salt, and that this process is more favorable with $X = I$ than Br.

House[108] had earlier reached the same conclusion (competing concerted and carbenium ion pathways) from a study of the reactions of *cis*- and *trans*-stilbene oxide with $MgBr_2$ in refluxing benzene. The *cis*-epoxide (**201**; equation 84) gave diphenylacetaldehyde (**202**) with traces of deoxybenzoin (**204**), while the *trans*-epoxide (**203**; equation 85) gave a mixture of (**202**) and (**204**). The significance of these observations follows from the rearrangements of the corresponding independently prepared bromohydrins (**205**; equation 86) and (**206**; equation 87). When treated with RMgBr to form the magnesiobromide salts and then heated as before, *threo*-(**205**) gave only (**202**), while *erythro*-(**206**) gave only (**204**).

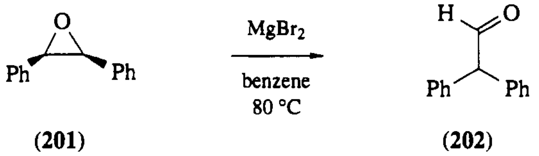

(84)

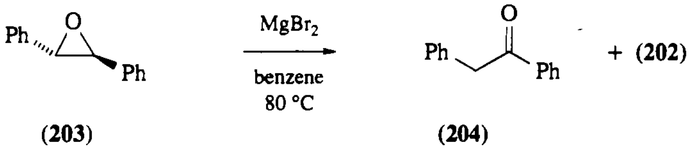

(85)

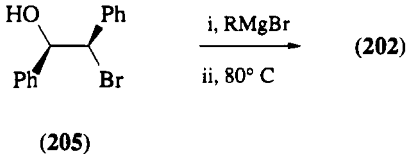

(86)

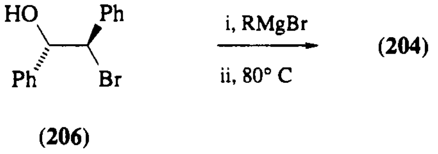

(87)

The cleaner reactions of the halohydrins show that these, if formed by *anti* opening and not subsequently epimerized, cannot account for the product mixtures from the epoxides. House proposed a competing carbenium ion route for both epoxides, leading to the normal pinacol rearrangement (carbenium ion) product, the aldehyde (**202**).

It is by no means obvious why these acyclic halohydrins should give mutually exclusive products. Simple stereoelectronic and steric considerations do not provide explanations. House suggested that the OMgX substituent might have abnormally large spatial requirements. A similar observation was made by Curtin and Meislich, who proposed large differences in solvation for two alternative transition states to rationalize an even more subtle distinction (migration of Ph *versus* $p$-$ClC_6H_4$ in two diastereomers).[110] These suggestions appear reasonable especially when aggregation effects are taken into consideration.

Similar experiments with *cis*- and *trans*-2,3-epoxybutane and the corresponding bromohydrins all gave a single product, 2-butanone.[111] Thus the unusual factors in the aryl-substituted materials failed to appear in the simpler aliphatic materials. Here the product can be rationalized simply by assuming that hydride migration occurs more readily than methyl migration. Of course, this may be true for both concerted and carbenium ion processes, and the existence of a dual mechanism may be hidden in this example. The cyclohexene oxide results cited above suggest that this is plausible, and perhaps probable.

In all of these reactions halohydrin salts were implicated as the reactive species, since no rearrangement occurred when the halohydrins were treated with $MgBr_2$.

House also examined analogous reactions of 2-bromo-3-pentanol (**207**; equation 88) and 3-bromo-2-pentanol (**210**; equation 89), presumed to be mixtures of diastereomers obtained by $NaBH_4$ reduction of the corresponding bromo ketones. Each system gave some of the oxygen-shifted ketone, as shown in equations (88) and (89), presumably *via* the epoxides, with reopening leading to the opposite regioisomer. This work is significant in showing that such interconversions can occur, even though epoxide formation in these systems must be slower than rearrangement. Other examples of oxygen shifts which appear to require formation of an epoxide intermediate are known.[112]

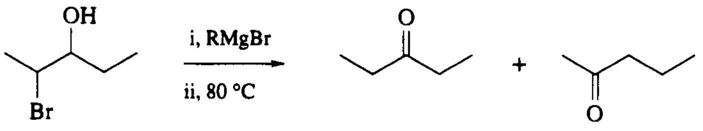

(88)

**(207)** **(208)** 95% **(209)** 5%

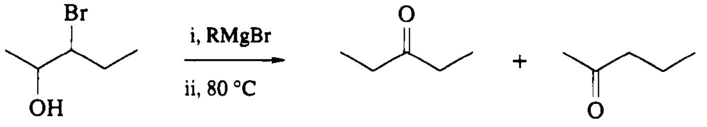

(89)

**(210)** **(208)** 20% **(209)** 80%

Cleavage of an epoxide by $MgX_2$ is only one of several ways by which halohydrins can be made. Other significant methods are reduction of halo ketones, addition of HOX to alkenes, bromination of alcohols and addition of RMgX or RLi to halo ketones. Some offer the advantage of controlling the regiochemistry of the halohydrin. Because of this diversity of approaches, $MgX_2$-catalyzed rearrangements of halohydrins have been studied more extensively than analogous reactions of epoxides.

The addition of Grignard reagents to α-halo ketones can give a variety of products, including enolates generated either by dehalogenation or deprotonation.[113] Substitution of the halide by the organometallic R group has also been known for over half a century. Tiffeneau was the first to recognize that this product resulted from rearrangement of an initially formed halohydrin salt.[114] The halohydrin configuration that produces this skeletally unrearranged material is apparently formed preferentially because of addition to the carbonyl face away from the halide. However, these reactions rarely give pure products or high yields. An angular methylation application developed by Sisti and Vitale[115] illustrates the stereochemical features (equation 90).

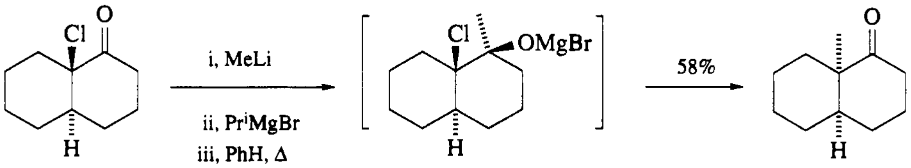

(90)

**(211)** **(212)** **(213)**

Simpler α-chloro ketones have also been examined,[115] and exhibit negligible selectivity. The mixtures of products shown in equations (91) and (92) may be the result of formation of both *cis*- and *trans*-halohydrin isomers in the addition step or, less likely with the chloride, a carbenium ion mechanism. The effect of varying the halide in such reactions has not been systematically investigated.

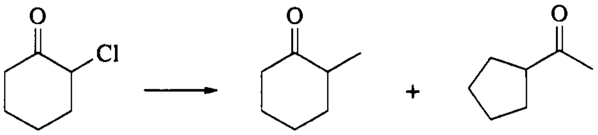

(91)

**(135)** **(214)** 32% **(215)** 22%

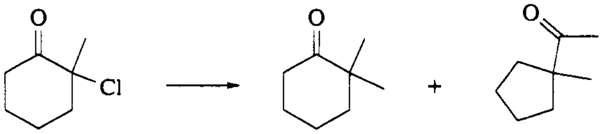

(92)

**(216)** **(217)** 26% **(218)** 40%

Sisti has also explored the potential utility of halohydrin rearrangements for ring expansions. A few examples are outlined. Ring-expanded α-phenyl ketones of product ring size six to nine were prepared in 60–80% yields by the sequence shown in equation (93).[116]

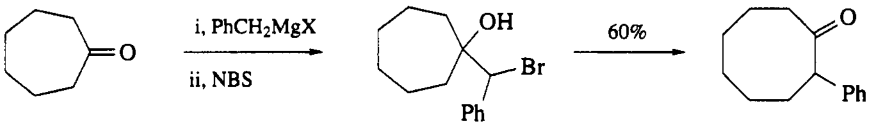

**(219)** **(220)** **(221)** (93)

The reactions of bromohydrins shown in equation (94) to (96) are especially informative. No cycloheptanone was obtained from the primary halide (**222**; equation 94),[117] whereas the secondary (**225**; equation 95)[118] and tertiary (**227**; equation 96)[119] halides both gave good yields of ring-expanded products. These results reinforce the observation made earlier by Geissman[107] that facile rearrangement is associated with ease of carbenium ion formation. It would thus be misleading to view the rearrangement process as a simple $S_N2$-like displacement, in spite of the apparent operation of stereoelectronic control features. More complex halohydrins have also been examined; these tend to give mixtures of products.[120]

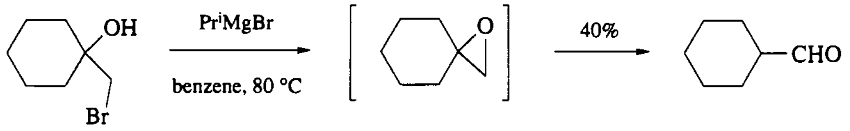

**(222)** **(223)** **(224)** (94)

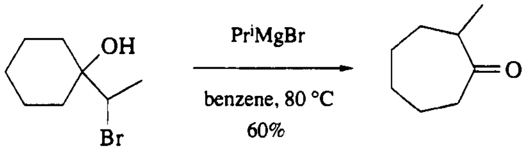

**(225)** **(226)** (95)

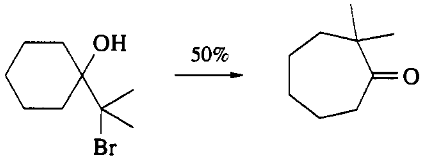

**(227)** **(228)** (96)

Enhanced reactivity associated with a tertiary center appears to be a factor in the observations made by Naqvi *et al.*[121] on treatment of 1-methylcyclohexene oxide (**229**; equation 97) with $MgBr_2$. At 0 °C, conditions which give only halohydrin with cyclohexene oxide, (**229**) was converted into the aldehyde (**230**). Conversely, when (**229**) was added to a solution of $MgBr_2$ at 60 °C, only ketone rearrangement products were isolated. The modest yields prevent mechanistic conclusions.

A striking example of enhanced reactivity is found in the vitamin A related studies of Rosenberger *et al.*[122] The example shown (equation 98) and several other analogous high yield reactions almost certainly proceed *via* the stabilized carbocation (tertiary and dienyl in this instance). Higher temperatures were detrimental to these applications, probably because of product instability.

Matsuda and Sugishita[123] found that cyclooctatetraene monoepoxide (**233**; equation 99) gave only skeletally rearranged products, *e.g.* (**234**), when treated with Grignard reagents. In an effort to isolate the presumed intermediate cycloheptatrienecarbaldehyde, (**233**) was subjected to a catalytic amount of $MgBr_2$, but this resulted in the formation of phenylacetaldehyde.

The stereochemistry of the product obtained when β-2,3-epoxycholestane is treated with MeMgI is in keeping with a mechanism involving initial diaxial opening to form an iodohydrin salt (equation 100), followed by rearrangement with backside displacement of the iodide *via* a twist boat conformer. Addition of MeMgI to the A-norsteroid aldehyde formed in this manner would then result in the two alcohols (epimeric at the carbinol center), which were isolated.[124]

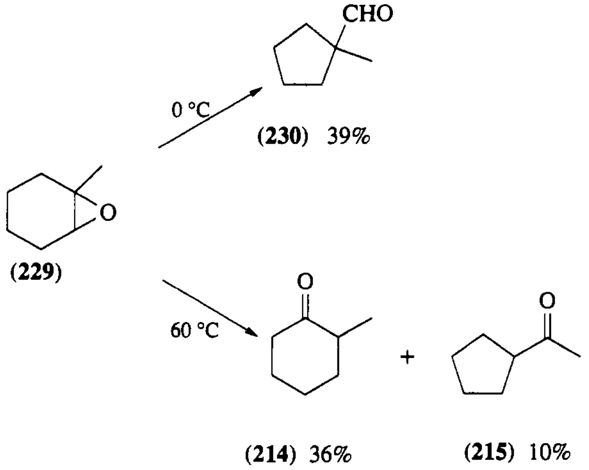
CHO
0 °C
(230) 39%
O
(229)
60 °C
O
+
O
(214) 36%
(215) 10%

(97)

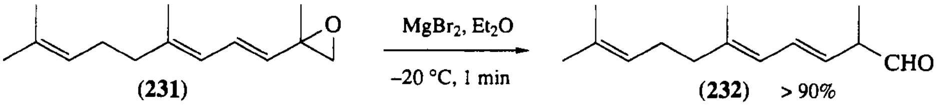
O
(231)
MgBr2, Et2O
-20 °C, 1 min
CHO
(232) > 90%

(98)

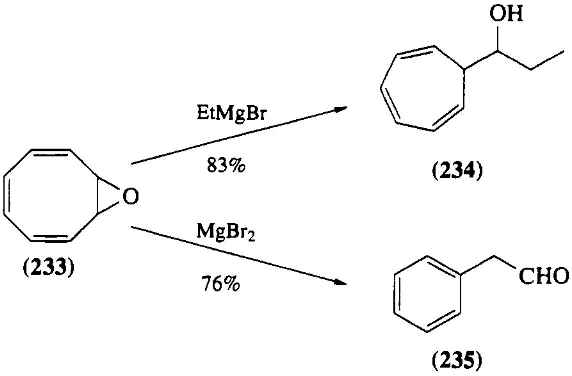
OH
EtMgBr
83%
(234)
O
(233)
MgBr2
76%
CHO
(235)

(99)

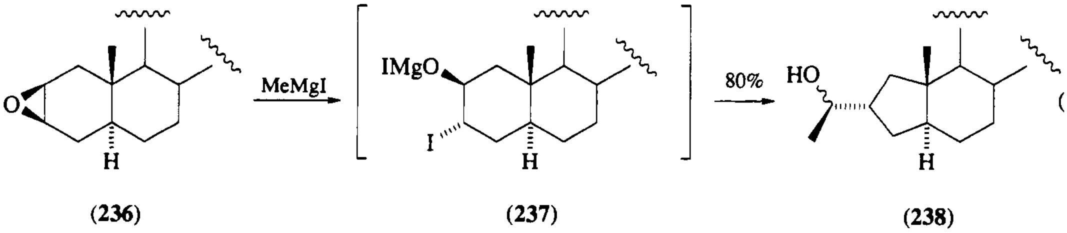
O
H
(236)
MeMgI
IMgO
I
H
(237)
80%
HO
H
(238)

(100)

Although indirectly related to the present topic, a common alternative method of inducing rearrangement of halohydrins utilizes a soluble silver salt. It is interesting that the bromohydrin which is regioisomeric to the intermediate iodohydrin proposed in equation (100), when treated with $AgNO_3$ in refluxing ethanol, delivered the analogous aldehyde (of unknown stereochemistry) in protected form (equation 101).[125]

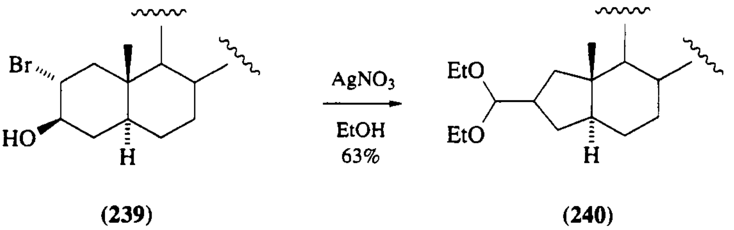
Br
HO
H
(239)
AgNO3
EtOH
63%
EtO
EtO
H
(240)

(101)

An unusual (for $MgX_2$) rearrangement of an epoxide to an allylic alcohol has been described in the terpene literature.[126]

Several epoxides substituted by α-EWG or other substituents have been treated with RMgX and/or $MgX_2$, generally to give products derived from initial β-cleavage. These substituents include chloride,[127] nitrile[128] and chloride/ester combined. The latter easily prepared substrates offer an attractive route to pyruvates and 1,2-diones. Chloro epoxy esters such as (**241**; equation 102) react with Grignard reagents at low temperature at the ester group, without opening the epoxide, to furnish epoxy ketones, *e.g.* (**242**), in modest yield.[129] This outcome is somewhat unusual, since ketones are rarely isolated in significant amounts from ester/Grignard reagent reactions; it appears that the electronegative substituents improve the stability of the initially formed intermediate. Subsequent treatment of (**242**) with $MgI_2$ gave the interesting iododione (**243**; equation 103) which could be reduced to the dione (**244**) by treatment with aqueous $NaHSO_3$.[130] In this sequence, facile loss of chloride from the iodohydrin (salt) intermediate prevents rearrangement from occurring.

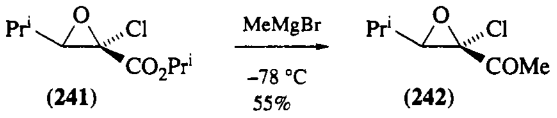

**(241)** **(242)** (102)

**(242)**

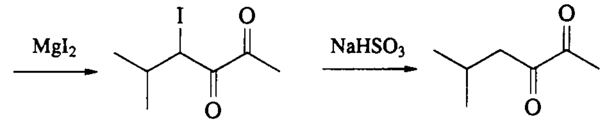

**(243)** **(244)** (103)

Attempts to prepare β-trimethylsilyl epoxides by closure of halohydrins resulted instead in the formation of aldehydes or ketones.[131] Epoxides are thought to be involved as intermediates, and the addition of $MgBr_2$ improved the overall conversion illustrated in equation (104). The potent β-cation-stabilizing capacity of β-trimethylsilyl groups was invoked to explain the high reactivity of the intermediate epoxides. Only hydride migration products were found. Application to tertiary halide halohydrins, which would require carbon migration to effect rearrangement, has apparently not been done.

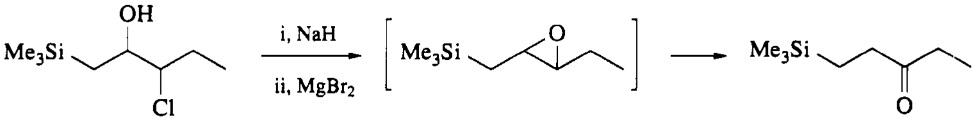

**(245)** **(246)** **(247)** (104)

α-Trimethylsilyl epoxides have been more extensively studied, particularly by Hudrlik and coworkers. Reactions have been carried out with both $MgBr_2$[132] and $MgI_2$.[133] The products obtained arise from nucleophilic attack at the carbon adjacent to the silicon.[132,134] Depending upon the other substituents, the resulting bromohydrin (salt) may be stable and isolable, or rearrangement may occur to form β-keto-(aldehydo)silanes, or enol trimethylsilyl ethers derived from these carbonyl primary products. These features are illustrated in equations (105) to (107).

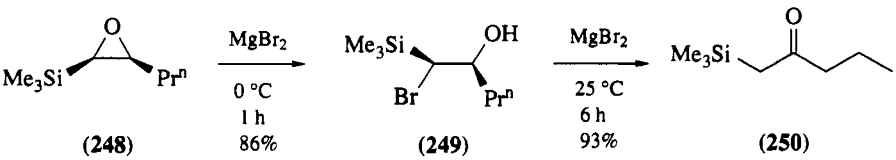

**(248)** **(249)** **(250)** (105)

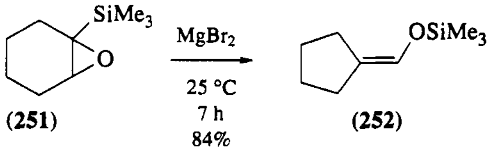

**(251)** **(252)** (106)

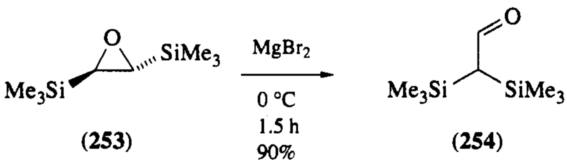

(107)

The stereochemistry shown in the bromohydrin (**249**; equation 105) has been proven (in analogs) by isolation and stereospecific conversion to vinyl bromide.[135] The reaction of (**251**; equation 106) to give exclusively ring-contracted product also supports the intermediacy of a bromohydrin (salt), and suggests the importance of normal stereoelectronic factors in the rearrangement. The preferential migration of a trimethysilyl group (over H) in equation (107) is noteworthy. The ketosilanes (and *in situ* Grignard reagent trapped aldehyde analogs[135]) are useful synthons.

## 3.3.6 LITHIUM SALT CATALYSIS

An attempt[136] to repeat, with presumably a minor modification, an established procedure[137] for the conversion of cyclohexene oxide to the cyclopropane (**255**; equation 108) gave instead the ring-contracted isomer (**256**). This reaction is fairly general and constitutes a convenient method for the preparation of acrylate esters, including some not easily made in other ways.

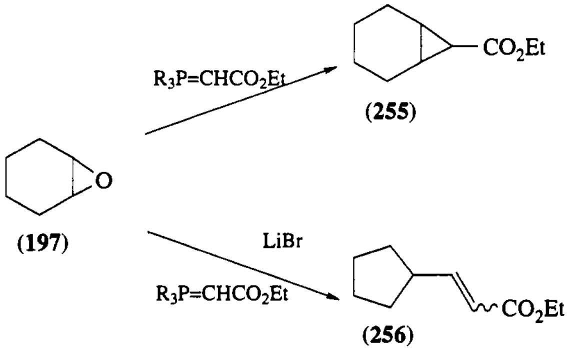

(108)

The key difference between the literature procedure[137] and the acrylate-forming reaction proved to be the use of a phosphonium bromide and BuLi to form the ylide in the latter. This gave a combination of ingredients (LiBr, ylide and/or $R_3PO$) and conditions (benzene solvent, reflux) which caused rapid rearrangement of epoxides to carbonyl compounds. Subsequent study provided the first unequivocal evidence[138] that LiBr as well as some other lithium salts can cause epoxide rearrangements.

In contrast to Grignard reagent/epoxide reactions in which $MgX_2$ (X = Br, I) is clearly responsible for many skeletal or hydride shift rearrangements, organolithium reactions usually do not exhibit these features, although some exceptions are known.[139] Heeren *et al.*[140] found that LiI altered the (complex) product mixture from treatment of cyclohexene oxide with MeLi in refluxing ether. One of the products (1-cyclopentylethanol) formed in the presence of LiI requires skeletal rearrangement. This material was not produced in the reaction with MeLi prepared from MeBr, *i.e.* LiBr did not cause similar rearrangement. We now recognize that this reflects the relative rates of competing reactions, and the dampening effect of ethereal solvents on the rearrangement process.

A systematic study[141] of epoxide/lithium salt reactions established the following general features: (i) LiI[138] is more reactive than LiBr. LiCl does not cause rearrangements, perhaps due to insolubility; (ii) LiBr is insoluble in benzene, and does not cause rearrangement unless a solubilizing agent is present (in controlled amounts). Phosphorus ylides (equation 108), tri-n-butylphosphine oxide and hexamethylphosphoramide (HMPA) will function as solubilizers; and (iii) $LiClO_4$ is insoluble in benzene but is partially solubilized by epoxides. Substrates susceptible to carbenium ion formation rearrange readily. Solubilizers and other Lewis bases diminish the rates of $LiClO_4$ reactions.

The effects of epoxide structure on rates and product distributions indicate that $LiClO_4$ reactions occur by a carbenium ion mechanism. Conversely, the LiBr-catalyzed reactions involve bromohydrin salts as precursors to rearrangement products. These are sharp distinctions, and provide the cleanest examples of the two extreme mechanisms for epoxide–carbonyl rearrangement.

### 3.3.6.1 $LiClO_4$ Catalysis

Certain epoxides rearrange readily in refluxing benzene in the presence of solid $LiClO_4$. When any epoxide (reactive or not) is added, the salt slowly disappears from the bottom of the flask, and is redeposited as a ring at the surface of the boiling liquid.[141] This phenomenon is presumably associated with a strong Lewis acid/base interaction between the lithium cation and ether oxygen. Pocker and Buchholz[142] carried out detailed studies of solutions of $LiClO_4$ in diethyl ether (up to 6 M solutions can be made), which exhibited various phenomena verifying a strong interaction. Solid mono- and di-etherate phases were also identified. It was noted that hydrated $LiClO_4$ has very low solubility in ether, in contrast to the anhydrous material. Hydration is also expected to diminish catalytic activity, although this has not been specifically demonstrated. A relatively simple procedure for purifying and drying $LiClO_4$ (vacuum, 160 °C, 8 h) is described in this work.[142]

The evidence that $LiClO_4$ catalysis involves carbenium ion intermediates arises from consideration of the structures that undergo reaction and the products that are formed. For example, all epoxides with a tertiary oxirane center rearrange readily, and the products are those expected from tertiary carbenium ion formation.[141] Thus 1-methylcyclohexene oxide gives 80% of 2-methylcyclohexanone (hydride migration) and 20% of the ring-contracted product, 1-methylcyclopentanecarbaldehyde. The products from 1,2-dimethylcyclohexene oxide are identical in structure and proportion to those found by Bunton and Carr[143] in the pinacol rearrangement of 1,2-dimethyl-1,2-cyclohexanediol (see equation 7 of Chapter 3.2 in this volume). This is a remarkable outcome given the differences in conditions (particularly solvent, benzene *versus* aqueous perchloric acid), and strongly supports a similar mechanism for both processes. Presumably ions present or generated in the nonpolar medium exist as ion pairs or higher aggregates, but they appear to react in traditional ways.

Facile rearrangement is observed with 1,1-disubstituted epoxides and $LiClO_4$. For example, (**257**; equation 109) gives the aldehyde (**258**) exclusively.[141]

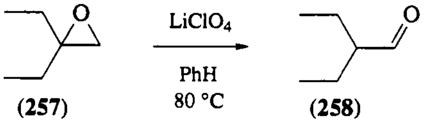

(**257**) (**258**) (109)

Although cyclopentene oxide was unreactive and cyclohexene oxide reacted very slowly to give mostly nonvolatile products, some other 1,2-disubstituted epoxides will rearrange, but at a diminished rate. Cycloheptene oxide provides an interesting illustration; treatment with $LiClO_4$ (equation 110) affords mainly the ring-contracted aldehyde along with some ketone formed by hydride migration.[141]

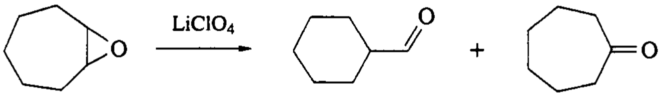

(**259**) (**224**) 83% (**219**) 17% (110)

Norbornene oxide (equation 111) rearranges with apparent nonclassical ion involvement, to give a similar ratio of aldehyde (**261**) and norbornanone (**262**).[141]

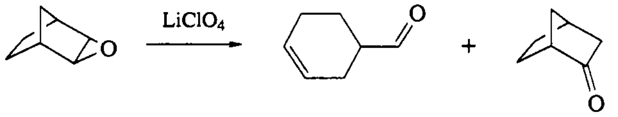

(**260**) (**261**) 83% (**262**) 17% (111)

The reaction of styrene oxide is noteworthy, not because phenylacetaldehyde (only) is formed, but because this reactive product appears to be reasonably stable to the reaction conditions.[141] This illustrates one of the advantages of using a catalyst which is only slightly soluble and contains an especially nonnucleophilic, nonbasic gegenion. Much of the work that has been done using $BF_3$ to catalyze epoxide rearrangements might benefit from reexamination with $LiClO_4$.

Trost and Bogdanowicz[144] examined several acidic catalysts for the rearrangement of oxaspiropentanes to cyclobutanones, and found the $LiClO_4$ method to be the most generally useful for this transformation. The reaction of (**263**), which is converted quantitatively to the ketones as shown in equation

(112), illustrates a tendency for migration with inversion at the cleaved center, reminiscent of some $BF_3$-induced reactions discussed previously.

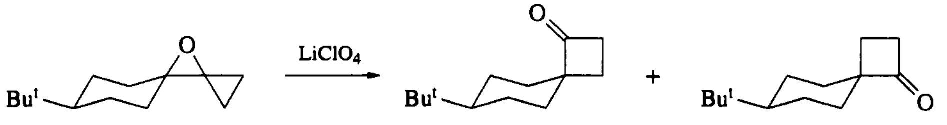

(112)

**(263)** **(264)** 91% **(265)** 9%

Synthetic utility depends upon compatibility with other functional groups, and although $LiClO_4$ has not been extensively tested in this regard, the method appears to be suitable for those groups examined to date. Thus a remote alkene does not interfere (equation 113).[144]

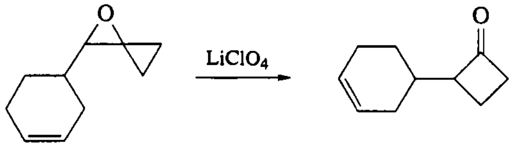

(113)

**(266)** **(267)**

Allylic epoxides seem to behave normally. Stereospecific hydride migrations were observed in the McMurry *et al.* synthesis of eremophilone.[145] Treatment of the isomeric epoxides (**268**) and (**270**) under standard conditions resulted in the exclusive formation of the rearranged ketones, as illustrated in equations (114) and (115).

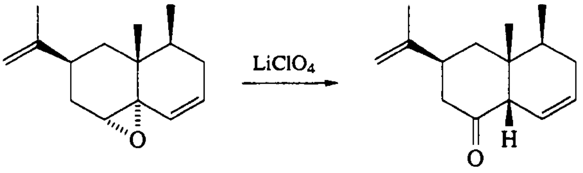

(114)

**(268)** **(269)**

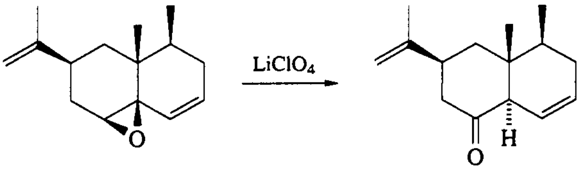

(115)

**(270)** **(271)**

Details are lacking, but the amide group apparently does not interfere with $LiClO_4$-catalyzed rearrangement of compound (**159**; equation 66), which gave the same product as $BF_3$ catalysis.[84]

Two interesting applications show that $LiClO_4$ is compatible with at least some acetal groups. The reaction shown in equation (116) was used in the Corey *et al.* synthesis of aphidicolin.[146]

Burge *et al.*[147] reported that (**274**; equation 117) is cleanly converted to ketone (**275**) by $LiClO_4$ under the standard refluxing benzene conditions. Apparently the ketal group helps to prevent the small amount of ring contraction that accompanies analogous ketone formation in the parent system.[141]

Kennedy and Buse[148] used a $LiClO_4$–$LiClO_3$ eutectic mixture as a molten salt phase in a GLC column at 280 °C for rearrangement of a few model epoxides. Those with tertiary centers gave lower product selectivity than in the typical solution reaction, but the harsher conditions did cause cyclohexene oxide to rearrange, giving cyclopentanecarbaldehyde as the major product.

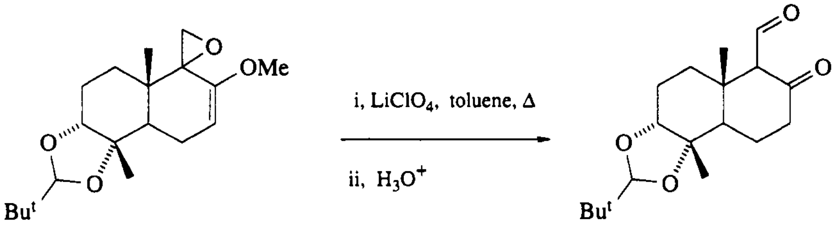

**(272)** **(273)** (116)

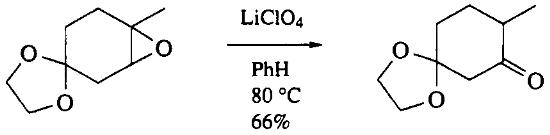

**(274)** **(275)** (117)

### 3.3.6.2 Lithium Halide Catalysis

Both LiBr and LiI have been widely used to effect epoxide–carbonyl rearrangements. These salts differ significantly in reactivity,[138] although no systematic comparison has been made. LiBr in benzene (or toluene) solvent requires a solubilizer (unlike LiClO$_4$, for which the epoxide itself is sufficient). LiI does not require a solubilizer, and has been used in several solvents, most often CH$_2$Cl$_2$; the possible role that solubilizer or solvent may play in LiI reactions has not been addressed. LiI is often employed as a hydrate, but occasionally 'anhydrous' salt is specified, although the purity of this difficult to dry material may be questioned.

Various addends have been used to bring LiBr into solution. Hexamethylphosphoramide (HMPA) has been most widely used, although its reputation as a carcinogen provides interest in identifying alternatives. Magnusson *et al.*[149] found that tetramethylurea (TMU) is a suitable replacement for some highly oxygenated epoxides derived from sugars. It is not yet clear what role the addend plays in the determination of products. Magnusson found that TMU and HMPA gave essentially the same product mixtures, whereas some differences were observed in an earlier comparison of HMPA and Bu$^n_3$PO.[138,141]

Only products which can be attributed to bromohydrin (salt) intermediates are formed when epoxides are treated with LiBr (solubilizer) in refluxing benzene. Any apparent exceptions to this generalization are believed to be due to interconversion of halohydrin stereoisomers, as discussed below. The bromohydrin is formed by traditional *anti* opening (antiperiplanar, probably nearly exclusively *trans* diaxial). It has been established[141] that a model epoxide (1-methylcyclohexene oxide) reacts by a process that is kinetically first order in a 1:1 complex of LiBr–HMPA, but the state of aggregation [$n$ in the formula (LiBr·HMPA)$_n$] is not known.[150] The nature of the epoxide–(LiBr·HMPA)$_n$ interaction that allows bromide to attack (exclusively) in the *anti* mode is not known, but must require fairly extensive ion pair (aggregate) reorganization.

Solid complexes of defined stoichiometry have been prepared for all the lithium halides with HMPA.[151] For LiBr, both [LiBr(HMPA)$_2$] and [LiBr(HMPA)$_4$] have been obtained as solids of defined m.p., but the 1:1 complex, the kinetically active species for epoxide rearrangement, has not been isolated. The rate of epoxide loss and solubility of LiBr increased proportionately with added solubilizer (HMPA), to a maximum rate at a 1:1 ratio of addend:LiBr.[141] Additional HMPA beyond this ratio caused the rate to decrease even though all the LiBr remained in solution. At an addend:LiBr ratio of 2:1, the reaction effectively ceased. These observations allow the conclusions that [LiBr(HMPA)$_2$] is more stable than the reactive 1:1 complex in benzene, and that only the latter is kinetically competent.[141]

1-Methylcyclohexene oxide (equation 118) provides a useful model system for mechanistic discussion. It is important that no 2-methylcyclohexanone is formed, since this rules out carbenium ion pathways. The major product is derived from the bromohydrin (**276**), formed by bromide attack at the tertiary center (followed by chair–chair interconversion), but care must be taken to avoid overinterpretation of this observation. Thus, if the bromohydrins are rapidly interconverting *via* the epoxide, the product distribution would be determined not only by the equilibrium ratio of (**276**) and (**277**), but also by the respective rate constants for rearrangement to (**230**) and (**215**). Although cyclohexene bromohydrin is immediately converted to the epoxide by treatment with Bu$^n$Li in benzene,[138] the possible effect of HMPA on the bromohydrin(salt)/epoxide equilibrium is not known. The rearrangement rates would be Br$^t$ (**276**) > Br$^s$

(**277**) if parallels with $MgX_2$-catalyzed halohydrin–carbonyl rates can be drawn. The rates for the final rearrangement steps rather than the rates of initial bromohydrin formation may thus control the product ratio.

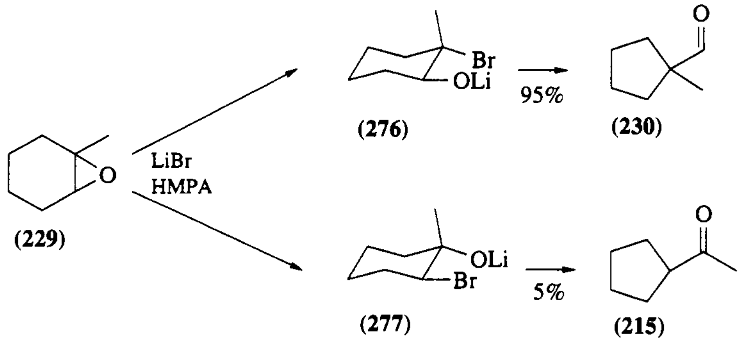

(118)

Rate constants were obtained[141] for rearrangement of a variety of epoxides with LiBr·HMPA in refluxing benzene, and an inverse relationship between degree of epoxide substitution and reactivity is evident. Terminal alkene epoxides are the most reactive, followed by 1,2-disubstituted, which are in turn more reactive than 1,1-disubstituted, while trisubstituted and tetrasubstituted epoxides react even more slowly. While this appears to parallel $S_N2$ reactivity, the expected ease of bromide attack is not reflected in the products of many of these reactions. For example, the terminal epoxide (**278**; equation 119) is among the most reactive examined but it gives a mixture of products, the major one requiring attack of bromide at the secondary center. Both rates and product ratios thus appear to be associated with more subtle features of the actual rearrangement step, as suggested above.

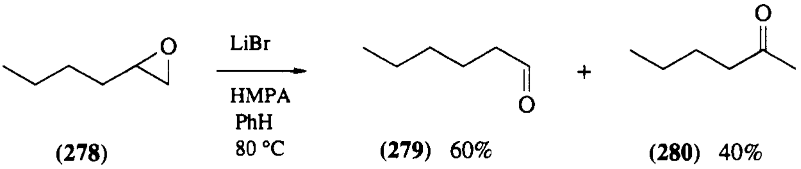

(119)

The reaction of cyclohexene oxide with LiBr·HMPA in refluxing benzene leads exclusively to cyclopentanecarbaldehyde, but, like other enolizable aldehydes, the product is not indefinitely stable to the reaction conditions. The rearrangement of 1,2-dimethylcyclohexene oxide, although much slower, gives only the ketone (**218**) as shown in equation (120). This result is especially difficult to rationalize by any mechanism other than one requiring a bromohydrin intermediate.

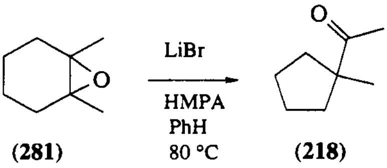

(120)

Styrene oxide reacted rapidly but gave no volatile material, perhaps because of aldol polymerization of phenylacetaldehyde (the probable initial product). Norbornene oxide gave no detectable reaction, either because *endo* attack of bromide is especially unfavorable, or because the bromohydrin salt has no geometrically accessible alternative other than to return to epoxide.

Cyclopentene oxide is very unreactive ($k \leq 10^{-3}k_{\text{cyclohexene oxide}}$), an observation clearly not in accord with expected $S_N2$ reactivity; it gives cyclopentanone as the only observed product. This ketone cannot be formed by antiperiplanar hydride displacement of bromide from the *trans*-bromohydrin, whereas the *cis*-bromohydrin could easily adopt the necessary conformation for hydride migration. Almost certainly the latter is formed by slow, perhaps rate-determining $S_N2$ attack by bromide on the initially formed *trans*-bromohydrin salt, as outlined in equation (121). This secondary reaction may be more important with LiI than with LiBr, although this has not been proven (see also equation 83 and discussion of $MgX_2$-catalyzed reactions).

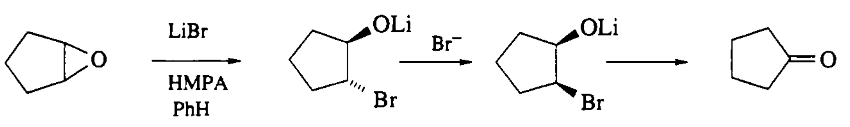

(282) (283) (284) (285) (121)

LiBr solubilized by Bu$^n{}_3$PO (or HMPA) was found[152] to catalyze the formation of 2-oxazolidones from organic isocyanates and terminal alkene epoxides. The epoxide substituent appears at the 5-position of the product as shown in equation (122). This outcome is in keeping with rapid trapping by the isocyanate of the halohydrin salt formed by attack of bromide at the primary center. This interpretation requires that oxazolidone formation be faster than epoxide rearrangement; data are not available to confirm this point.

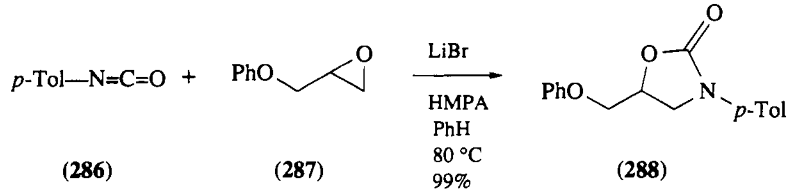

(286) (287) (288) (122)

Rearrangements of epoxides catalyzed by LiBr·HMPA or LiI have figured in a number of natural product syntheses in which ring expansions to cyclopentanones are required. Both salts were earlier shown to effect the especially facile rearrangements of the small ring spiro epoxides which serve as models for these processes. Thus (**289**; equation 123) was found by Salaun and Conia[153] to rearrange rapidly and in excellent yield to cyclobutanone, simply on exposure to commercial hydrated LiI.

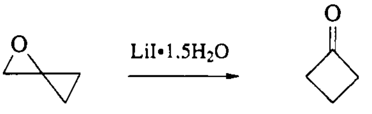

(289) (290) (123)

Conia and coworkers[154] later examined the rearrangements of acylated derivatives such as (**291**; equation 124) which undergo analogous ring expansion to give unstable diones. Rearrangement of (**291**) was effected by LiBr in $CCl_4$, reflecting not only high reactivity but perhaps also the ability of the keto epoxide to solubilize the salt.

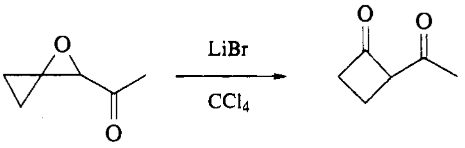

(291) (292) (124)

Leriverend and Leriverend[155] used LiI hydrate in refluxing $CH_2Cl_2$ to examine the conversion of the unsubstituted homolog (**293**; equation 125) into cyclopentanone. Analogs with methyl substituents on the cyclobutane ring reacted more slowly (up to 75 h as opposed to 6 h for **293**) and, interestingly, exhibited a strong preference for migration of the more-substituted carbon. Thus (**294**; equation 126) gave exclusively (**295**).[155] This kind of selectivity appears in a number of spiro epoxide rearrangements discussed below, although usually smaller in magnitude.

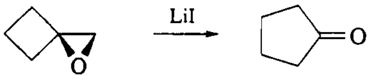

(293) (285) (125)

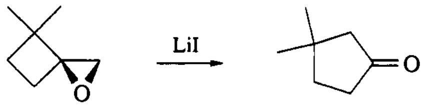

(294) (295) (126)

Halazy and Krief[156] showed that substituents on the epoxide ring are tolerated, and analogous migration selectivity was exhibited by substrates having one substituent on the cyclobutane and one on the epoxide (equation 127). Substrates with more than two substituents at the pertinent positions have apparently not been examined.

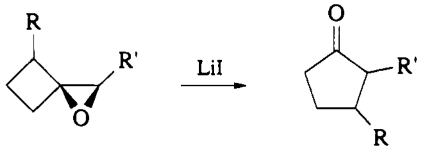

(296) (297) (127)

Trost and Latimer's approach to gibberellins[157] made use of the rearrangement shown in equation (128). Migration of the more-substituted center is evident in the conversion of (**298**) to (**299**; 65%), and even more so in the isomer of (**298**), epimeric at the epoxide center, which gave (**299**) in even higher yield (equation 128).

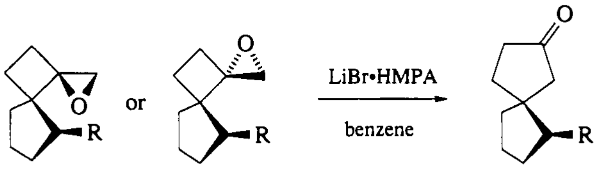

(298) R = $CH_2CH_2OPh_3$ (299) (128)

Related selectivity is also evident in the reaction of (**300**; equation 129), used as an undetermined mixture of epimers at the epoxide center. Ketones (**301**) and (**302**) were formed in a 9:1 ratio.[158] The use of THF solvent for this and some other anhydrous LiI-catalyzed reactions is worth noting, since ethers have been shown to inhibit reactions of LiBr.

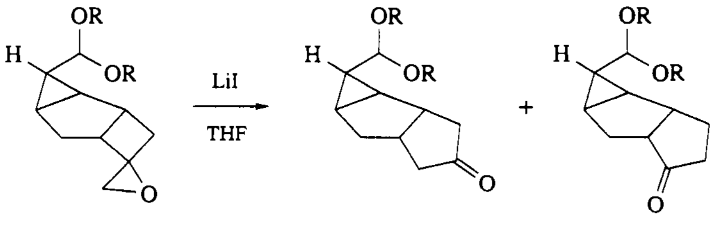

(300) (301) (302) (129)

High migration selectivity is again demonstrated in the efficient conversion of (**303**; equation 130) to (**304**), a key step in a synthesis of a pentalenolactone G.[159]

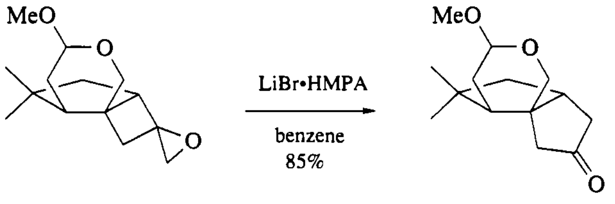

(303) (304) (130)

Only one exception to this otherwise general selectivity feature has been reported. In prostacyclin synthon studies, Hart and Comte[160] separately examined the two epimeric epoxides (**305**) and (**308**). Both gave only modest selectivity when treated with LiI in THF, with (**305**) showing the normal preference for migration of the more highly substituted center. In a slower reaction, (**308**) rearranged with the opposite selectivity, giving mainly the product (**307**) formed by migration of the methylene carbon (equation 131). This 'abnormal' behavior may be associated with an adverse steric interaction between the R group and the iodine in the conformation of the halohydrin needed for migration of the more-substituted center.

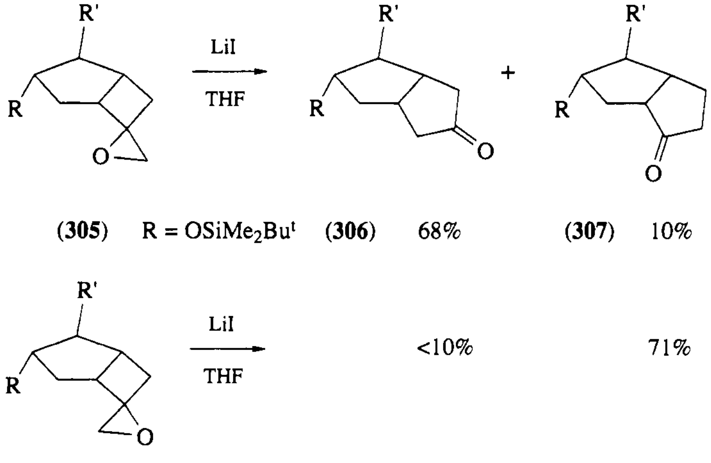

(**305**) R = OSiMe$_2$Bu$^t$ (**306**) 68% (**307**) 10%

(**308**) <10% 71%

(131)

Ring contraction from cyclobutyl to cyclopropyl will also occur if other structural features permit; thus conversion of an epoxide ring to a carbonyl group more than compensates for any free energy cost associated with the change in carbocyclic ring size. Garin's work[161] nicely proves the stereochemical features of this kind of rearrangement, and provides convincing evidence for the intermediacy of a halohydrin. Halohydrins formally derived from cyclobutene are known[162] to undergo facile ring contraction. The slow conversion of the initially formed *endo* aldehyde (**311**) to the more stable *exo*-(**312**) form is typical behavior of enolizable aldehydes under LiX epoxide rearrangement conditions (equation 132). Garin also made the interesting observation that lithium thiocyanate could be used in place of LiI to effect this epoxide rearrangement.[161] There is no record in the literature of LiSCN causing the rearrangement of any other epoxide, so generality remains doubtful.

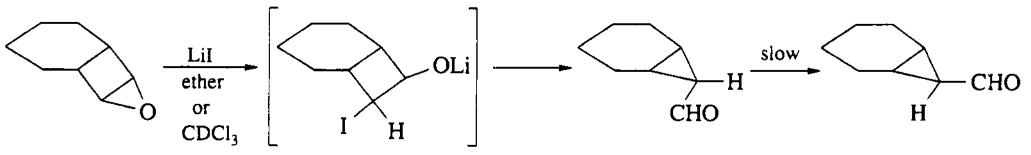

(**309**) (**310**) (**311**) (**312**) (132)

Lin and coworkers[163] used LiBr in acetonitrile to carry out the conversion of the *trans*-diepoxide (**313**) to (**314**); in this instance the enol(ate) generated after the initial aldehyde formation causes aromatization and opening of the other epoxide in an elimination-type reaction (equation 133). The use of BF$_3$ in ether allowed isolation of the dialdehyde (**315**). It is worth noting that the more acidic conditions cause epoxide rearrangement to occur more rapidly than enolization reactions of this sensitive substrate.

Banks and Ziffer[164] used LiBr in both acetonitrile and in benzene/HMPA in attempts to cause carbon migration (ring contraction) of epoxides such as (**316**; equation 134), but in all instances only ketones formed by hydride migration were obtained. The authors noted the lability caused by the tertiary benzylic center, and suggested that this could account for the failure of normal stereoelectronic features with these substrates. Ring contraction was also thwarted in substrates lacking a suitable hydride for migration; instead, relatively slow elimination with loss of a proton from the exocyclic methyl group occurred.

The work of Magnusson and his colleagues[165] with epoxides derived from allylic alcohols has provided important mechanistic insights as well as useful synthetic procedures. These reactions require the

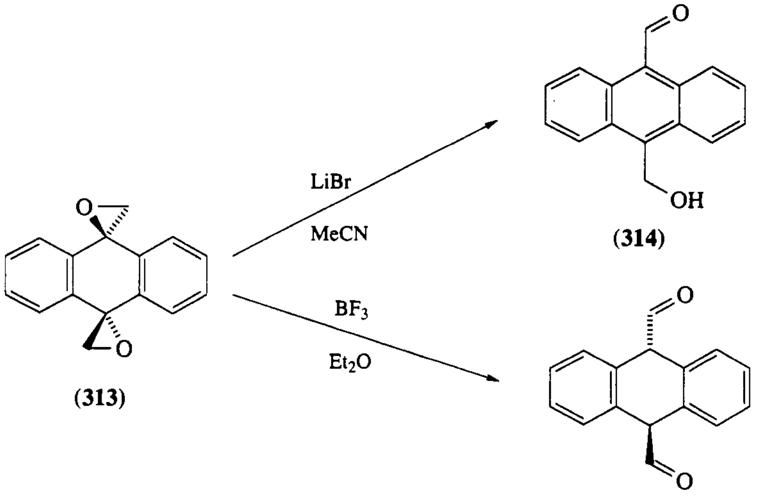

**(313)** **(314)** **(315)**

(133)

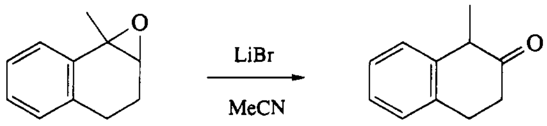

**(316)** **(317)**

(134)

use of stoichiometric or greater amounts of LiBr·HMPA to obtain high yields, presumably because the water that is formed inhibits the catalytic power of the salt. The formation of the two isomeric aldehydes (**320**) and (**321**) from both epoxides (**318**) and (**322**) was shown to occur by interconversion of the bromohydrin salts (**319**) and (**323**), as depicted in equation (135). The fact that the two epoxides give different ratios of the two aldehydes conversely shows that this halohydrin salt interconversion is not rapid compared to rearrangement. Since the interconversion of (**319**) and (**323**) appears to require only proton (and lithium ion) exchange, this is a surprising observation, and suggests that the mechanism may be more complex than depicted here. These intriguing mechanistic points were demonstrated by carrying out the reactions with specifically deuterated substrates.

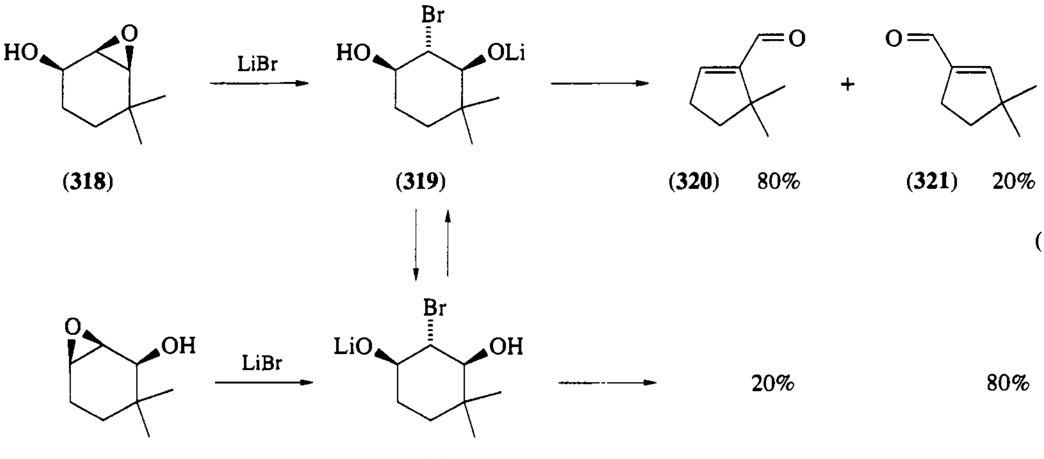

**(318)** **(319)** **(320)** 80% **(321)** 20%

**(322)** **(323)**

(135)

Similar bromohydrin interconversions were demonstrated in sugar-based epoxide rearrangements.[149] The unsaturated aldehydes formed in these reactions are useful for further elaboration, as shown in a recent synthesis of botryodiplodin.[166]

A one-step homologation/ring expansion has been reported,[167] in which a ketone is treated with $CH_2I_2$ and Li metal. The epoxides that could conceivably be generated from the presumed iodohydrin salts formed in this process generally do not ring-expand with other lithium salts. Thus if this reaction involves intermediate iodohydrin salts, rearrangement must take place more rapidly than closure to epoxide. Acyclic aldehydes apparently give isolable homologated epoxides from similar treatment.

Kennedy and Buse[148] examined the rearrangement of a series of epoxides on molten salt (LiBr + RbBr) at 280 °C. At this temperature the epoxides also undergo thermal rearrangement, and it is difficult to separate out the effects of the salt-catalyzed process. In general, these reactions are much less selective than the 80 °C LiBr·HMPA solution analogs, and some of the products appear to require formation of the alternative halohydrin stereoisomer or carbenium ion intermediates.

Another interesting LiBr variant was recently discovered by Suga and Miyake,[168] who reported that LiBr coated on alumina (LiCl and $MgBr_2$ were also effective, as was LiBr on silica gel) is an effective catalyst for use either in the gas phase or as a solid added to refluxing toluene, affording 80% of cyclopentanecarbaldehyde from cyclohexene oxide. This reagent (LiBr–alumina) promises to be useful, especially for the formation of large amounts of volatile aldehydes by a continuous stream gas phase process.

There are many different variations for epoxide–carbonyl rearrangements that utilize lithium salts. Unfortunately, there are very few controlled comparisons of the sort needed to determine the best choice of LiX, solvent, addend and conditions for a particular application.

## 3.3.7 OTHER CATALYSTS

Most common Lewis acids have at one time or another been examined as prospective catalysts for epoxide rearrangements. Relatively few cause skeletal changes, although formal hydride migration leading to ketones is often observed.

Epoxides have occasionally been used in Friedel–Crafts reactions, and some interesting stereochemical observations have been made in this context. Quite unlike secondary alcohols which give almost fully racemized product, it has been shown[169] that optically pure propylene oxide with $AlCl_3$ and benzene gives optically pure 2-phenyl-1-propanol with inversion of configuration at the cleaved center. $AlBr_3$ leads to much lower levels of optical purity; it was demonstrated that both starting material and product are optically stable to the reaction conditions, and therefore partial racemization is intrinsic to the mechanism with $AlBr_3$. It is nonetheless clear from these and other results that even powerful Lewis acids do not assure reaction *via* simple planar carbenium ions.

Strong Lewis acids are often chosen for use with epoxides when the goal is intramolecular addition to an alkene or aromatic system. In an informative study, Sutherland *et al.*[170] compared the effect of different catalysts on the ratio of cyclization (**325**) to ring contraction (**326**) for the system shown in equation (136). A positive correlation between Lewis acid strength and cyclization was noted. Thus $AlCl_3$ was reasonably effective in this regard (ratio (**325**):(**326**) = 3:1) but it was inferior to $TiCl_4$ which gave only cyclized product (55%). Other catalysts (ratio) are: $FeCl_3$ (1.1); $SnCl_4$ (0.6); $BF_3·Et_2O$ (0.8); and $ZnCl_2$ (0.3).

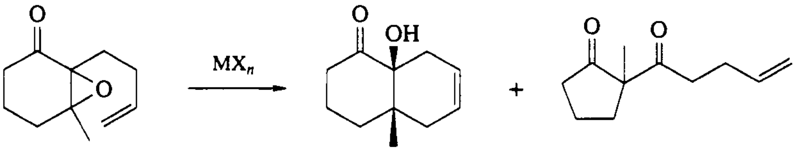

(136)

**(324)** **(325)** **(326)**

$AlCl_3$ in ether has been used to explore intramolecular cyclization of some germacrones, and gives a [5.3.0] bicyclic derivative in one instance, illustrated in equation (137).[171]

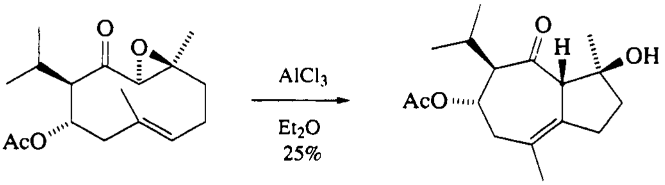

(137)

**(327)** **(328)**

An organoaluminum compound in hydrocarbon solvent caused rearrangement of an acid-sensitive diene monoepoxide, but a change to ether solvent mediated this (undesired) reaction.[172]

The modest Lewis acid properties of $Al(OPr^i)_3$ are needed for the fragmentation reactions of epoxides derived from homoallylic alcohols described recently by Waddell and Ross.[173] Carbonyl groups in the initial fragmentation products are reduced by $Al(OPr^i)_3$ to give the materials shown in equations (138) and (139).

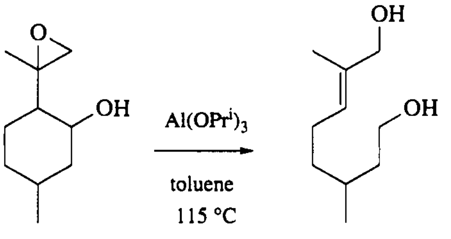

**(329)** **(330)** (*E* + *Z*)

(138)

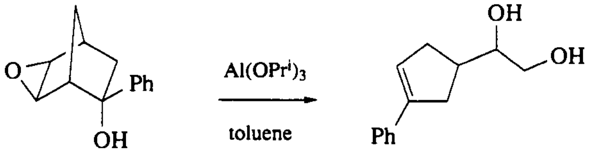

**(331)** **(332)**

(139)

$Al(OPr^i)_3$ was less satisfactory than $Ti(OPr^i)_4$ for the hydroxy-influenced cyclizations examined by Sharpless *et al.*[174] The relative stereochemistry of the hydroxy group and epoxide proved critical for this process, leading to the suggestion that an intramolecular metal alkoxide was the active catalyst (equation 140).

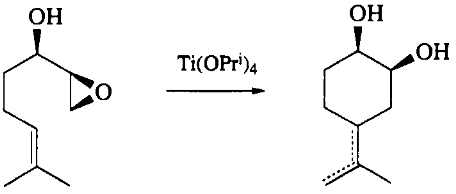

**(333)** **(334)**

(140)

$SnCl_4$ was used with epoxide **(335)**, and resulted in a deep-seated rearrangement. The mechanism proposed by Scovell and Sutherland[175] is shown in equation (141).

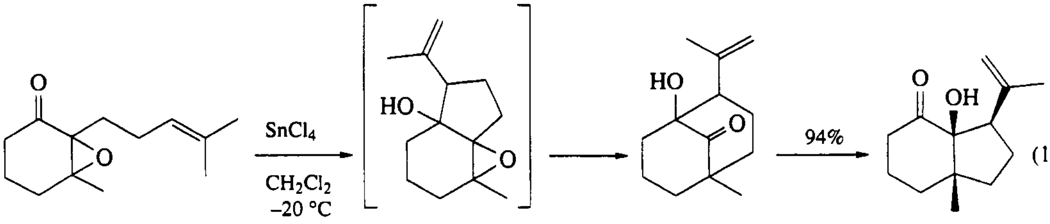

**(335)** **(336)** **(337)** **(338)**

(141)

$FeCl_3$ is infrequently used to initiate epoxide rearrangements. It has been shown to give chlorohydrins rapidly with a range of oxiranes, simply by brief mixing in ether followed by an aqueous wash.[176] Other rarely used reagents for rearrangement are $SbCl_5$,[177] $Me_2SO + Pr^nI$,[178] various clays,[179] $[Rh_2Cl_2(CO)_4]$[180] and $[Mo(CO)_6]$,[181] each of which has either demonstrated or potential Lewis acid properties. Probably not in this category but worthy of note as a useful synthetic method is the $Pd^0$-catalyzed conversion of

2,3-epoxy ketones to 1,3-diones.[182] Some epoxides are rearranged to allylic alcohols by diborane, with subsequent reaction (addition, oxidation) typically leading to diols.[183]

An epoxide has been identified as an intermediate in the copper(I) triflate-catalyzed reaction outlined in equation (142).[184]

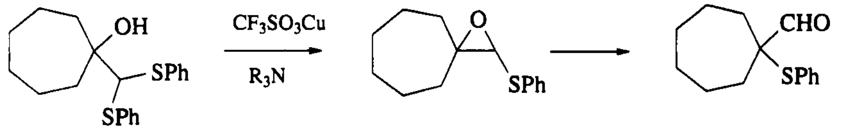

(142)

**(339)** **(340)** **(341)**

The zinc halides have a mixed reputation in the field of epoxide chemistry. $ZnI_2$ is recommended as a catalyst for epoxide opening, without rearrangement, in the addition of thiosilanes[185] and selenosilanes.[186] Conversely, rearrangements catalyzed by zinc salts have been clearly documented for several epoxides. Sutherland's comparison[170] suggests that $ZnCl_2$ should be rated on the weaker end of the strong acid scale.

Terpene oxides have been favorite substrates for $ZnBr_2$-catalyzed reactions, probably because early work indicated that certain reactions afforded high yields of unusual materials. Indeed some of these claims have held up well to later analytical scrutiny. For example, α-pinene oxide (**342**; equation 143) yields essentially pure (**343**; 88%) upon brief treatment with $ZnBr_2$ (catalytic amount) in refluxing benzene.[187]

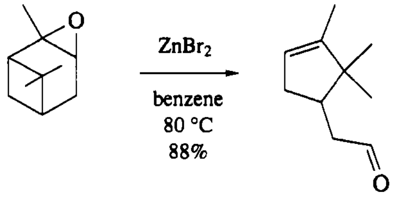

(143)

**(342)** **(343)**

More typically, mixtures of products are formed. Terpene epoxides that have been subjected to $ZnBr_2$-catalyzed rearrangement include the oxiranes derived from limonene,[188] carvomenthene,[188] other pinenes,[189] 2,3-carvene,[190] pulegone[191] and piperitone.[191] $ZnCl_2$ is rarely employed, but has been compared with $AlCl_3$ in a study involving several epoxides.[192] In most instances there appears to be no evidence for special advantages of zinc halides compared with other more commonly used Lewis acids.

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# 3.4
# The Semipinacol and Other Rearrangements

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## 3.4.1 INTRODUCTION

### 3.4.1.1 Semipinacol Rearrangements

The semipinacol rearrangement was originally defined as a special case of the pinacol rearrangement, in which migration occurred towards the secondary center of a tertiary, secondary diol (equation 1), *i.e.* the reverse of the regiochemistry observed in the pinacol rearrangement. However, the term 'semipinacol' is now used generally to describe all such rearrangements which are related to, or reminiscent of, the pinacol rearrangement.[1] The largest class of semipinacol rearrangements are those derived from 2-heterosubstituted alcohols (**1**), such as halohydrins (**1**; X = Cl, Br), 2-amino alcohols (**1**; X = $NH_2$), 2-hydroxy sulfides (**1**; X = SR) and 2-hydroxy selenides (**1**; X = SeR).

The normal pathway for rearrangement of the substrates (**1**) is *via* loss of the heteroatom substituent with migration of an adjacent alkyl (or aryl) group, and concomitant ketone formation (Scheme 1, path a). An alternative migration (path b), is occasionally observed in protic media, *i.e.* protonation of the alcohol (**1**) and migration with loss of water generates the stabilized carbocation (**2**), which is then hydrolyzed.

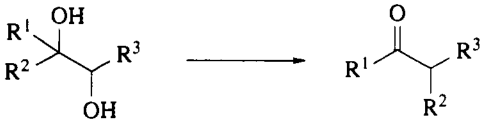
(1)

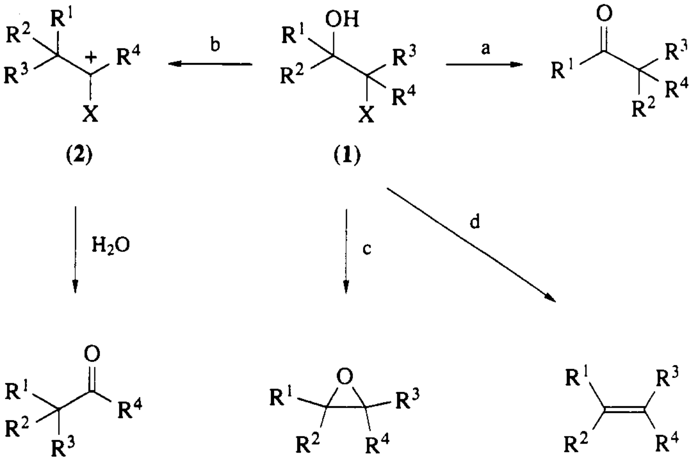

**Scheme 1**

Epoxide formation (path c) is an important side reaction which can become the dominant pathway. For example, the addition of sulfur ylides to ketones (equation 2) constitutes a general synthesis of epoxides,[2] while 2-hydroxy sulfides undergo the semipinacol rearrangement under certain conditions (equation 3).[3] Elimination (path d) is observed in some special cases such as 2-hydroxysilanes (**1**; X = SiR$_3$; the Peterson alkenation)[4] and 2-hydroxyphosphonium species (**1**; X = PR$_3^+$ ; Wittig intermediates).[5]

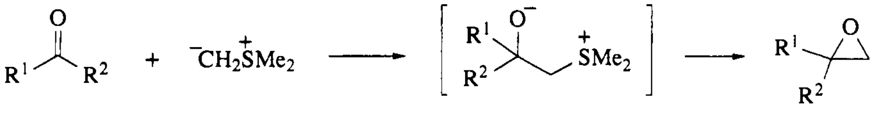
(2)

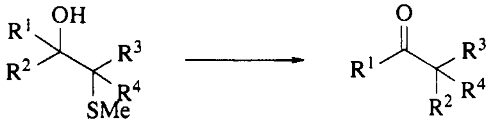
(3)

The semipinacol rearrangement is not restricted to 2-heterosubstituted alcohols. Thus, the addition of diazoalkanes to ketones yields homologated ketones (equation 4), *via* rearrangement of the adduct (**3**). This process is closely related to the rearrangement of 2-amino alcohols on treatment with nitrous acid (equation 5). Similarly, 2-hydroxyimines undergo rearrangement to 2-amino ketones in a related process (equation 6).

The rearrangement of acetals of 2-haloalkyl aryl ketones is a well-documented process yielding esters of 2-arylalkanoic acids by 1,2-aryl shift (equation 7).[6] The mechanism of this rearrangement is reminiscent of other semipinacol rearrangements. Loss of the halogen (usually assisted by Lewis acid), yields a carbocation (**4**), which then undergoes a 1,2-aryl shift with carbonyl group formation.

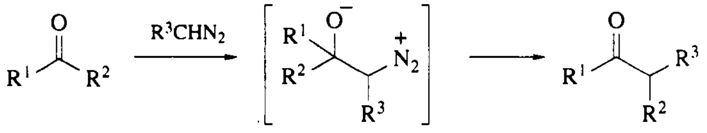

(**3**)

(4)

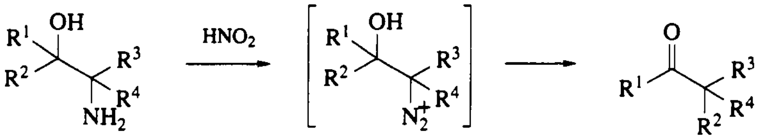

(5)

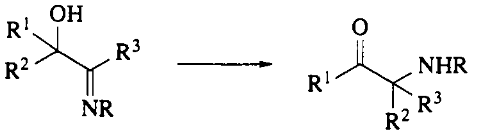

(6)

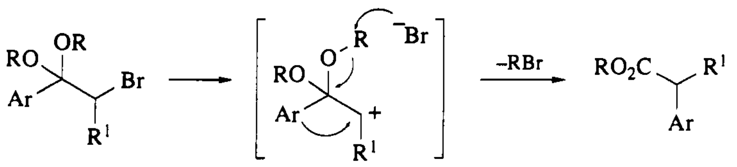

(4)

(7)

A number of tandem cyclization–semipinacol rearrangements have been reported,[7] whereby cyclization is initiated by an acetal and terminated by a semipinacol rearrangement (equation 8).

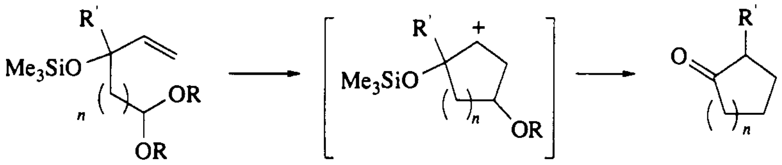

(8)

In general, semipinacol rearrangements are more selective than the classical pinacol rearrangement in terms of regiochemistry and mildness of conditions. Consequently there have been many applications of the semipinacol rearrangement in the formation of carbon–carbon bonds. The carbon atom bearing the migrating group is usually tertiary, while the carbon receiving the migrating group can be primary, secondary or tertiary. Migratory aptitude is not an important factor in semipinacol rearrangements. Electronic factors, the relief of ring strain and the stereochemistry of the substrate all influence the course of migration. Inversion of configuration is observed in most cases, and this feature has been utilized in chiral synthesis. With some exceptions, the mechanism of semipinacol rearrangements has not been examined in detail. Most investigations have centered on the synthetic utility of the rearrangement.

### 3.4.1.2 Boron Rearrangements

Organoboranes undergo rearrangements with the formation of carbon–carbon $\sigma$-bonds. The boron atom plays a pivotal role in the rearrangement by accepting a nucleophile (**5**) to produce an intermediate four-coordinate organoborate species (**6**). Migration from boron to carbon occurs if a leaving group is positioned on the carbon center $\alpha$ to boron (equation 9), yielding a new neutral organoborane. For example, ylides of sulfur (**5**; L = $SMe_2^+$) and nitrogen (**5**; L = $NMe_3^+$) add to triorganylboranes to yield rearranged products; anions of haloalkanes (**5**; L = halogen) effect a similar transformation.

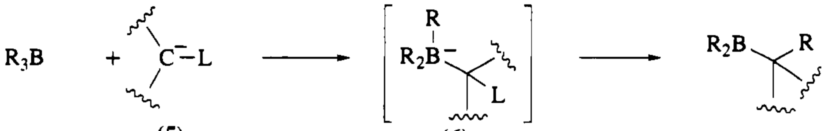

(5) (6)

(9)

The carbonylation of triorganylboranes is well documented,[8] and provides a unique route to tertiary alcohols. Thus, triorganylboranes react with carbon monoxide to yield a trimeric product (**7**) which is readily oxidized to a tertiary alcohol (Scheme 2). The exact mechanism of this process is not clear, but it is known to proceed by three sequential rearrangements from boron to carbon.

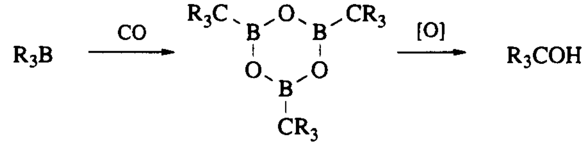

**Scheme 2**

Boronic esters (**8**) react with dichloromethyllithium to form intermediate borate complexes which then undergo rearrangement to form 2-haloboronic esters (**9**). When treated with a Grignard reagent, the 2-haloboronic esters (**9**) rearrange to secondary alkylboronic esters (**10**; Scheme 3).

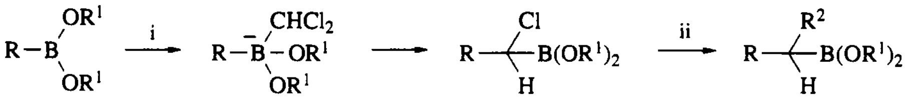

**(8)** **(9)** **(10)**

i, $LiCHCl_2$ ; ii, $R^2MgX$

**Scheme 3**

This iterative procedure has been utilized with great effect in asymmetric synthesis *via* chiral boronic esters derived from chiral alcohols.[9]

Certain tetraorganylborate salts are stable isolable species, and undergo rearrangement by migration from boron to carbon when treated with electrophiles. For example, the cyanoborates (**11**), when treated with acylating agents, yield the heterocyclic intermediate (**12**) by two successive rearrangements (Scheme 4). Oxidation of the intermediate (**12**) yields ketones. Similarly, alkynylborates produce alkynes when treated with iodine, *via* rearrangement and elimination (equation 10).

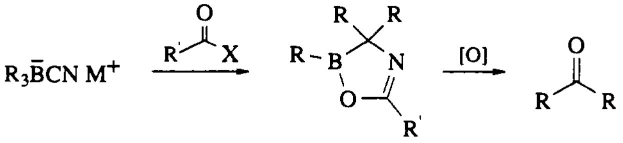

**(11)** **(12)**

**Scheme 4**

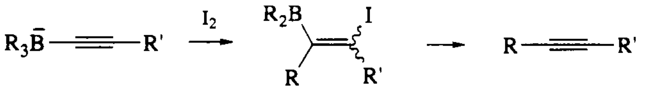

(10)

There are many applications of boron rearrangements in organic synthesis and the subject has been comprehensively reviewed.[10] This methodology offers considerable scope in the formation of carbon–carbon bonds.

A common mechanism involved in these rearrangements is one whereby an organic group migrates from a four-coordinate, electron-rich boron center, to an electron-deficient α-carbon center. In general, primary groups migrate before secondary, which migrate before tertiary. This migratory aptitude can be rationalized by consideration of a partial negative charge on the nucleophilic migrating group (equation 11), and hence reflects the relative stabilization of negative charge.

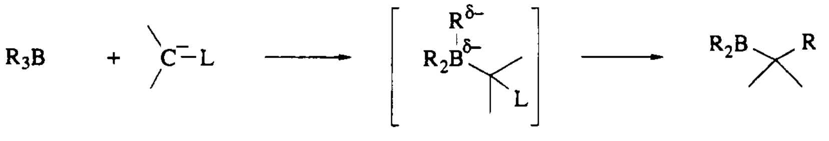

(11)

## 3.4.2 SEMIPINACOL REARRANGEMENTS

### 3.4.2.1 Rearrangements of 2-Amino Alcohols

The semipinacol rearrangement of primary 2-amino alcohols on exposure to nitrous acid is known generally as the Tiffeneau–Demjanov rearrangement. The reaction is well documented and is often associated with ring enlargement[11] and, to a lesser extent, ring contraction. Thus, a cyclic ketone may be homologated in a three-step sequence *via* cyanohydrin formation, followed by reduction to an aminomethylcycloalkanol and rearrangement (Scheme 5). This sequence has been applied to the formation of five- to eight-membered rings, for example in the preparation of cyclooctanone (equation 12).[12] Trimethylsilyl cyanide forms cyanohydrin *O*-silyl ethers of ketones resistant to HCN treatment, and has been recommended for the preparation of 2-amino alcohols.[13]

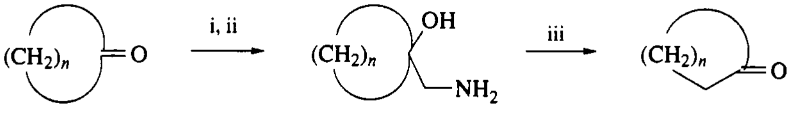

i, HCN; ii, LiAlH$_4$ or PtO$_2$ / H$_2$; iii, HNO$_2$

**Scheme 5**

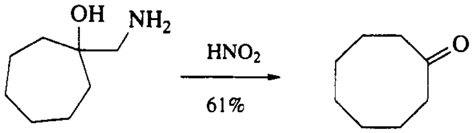

(12)

In general, the rearrangement is most effective when the hydroxy group is tertiary. However, rearrangement is possible with a secondary hydroxy group, as Woodward *et al.*[14] have demonstrated in the ring contraction of the bicyclic acetal (**13**; equation 13), used in a synthesis of prostaglandin F$_{2\alpha}$. The degree of substitution at the carbon bearing the primary amino group is variable, but an aryl group has been shown to inhibit rearrangement.[15]

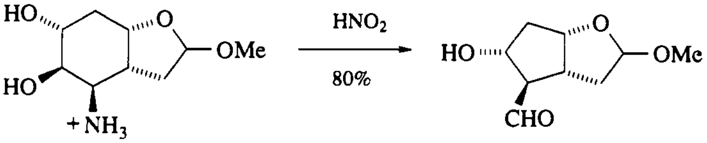

**(13)**

(13)

In ring expansion reactions, the least-substituted group shows a greater tendency to migrate (equations 14 and 15), although the selectivity may be attributable to conformational effects. The importance of conformational effects has been amply demonstrated in the rigid steroidal framework. Thus, the D-ring homosteroid (**14**) rearranges to the ketone (**15**; equation 16),[17] while the alcohol epimer (**16**) does not rearrange under the same conditions, but instead forms the epoxide (**17**; equation 17).[18] In marked contrast, the homosteroid (**18**), which is diastereoisomeric with (**14**) at the amino alcohol function, undergoes ring contraction (equation 18).[19] In these rigid systems it is the group that is *trans* coperiplanar to the amino function which migrates. In the case of the amino alcohol (**16**) the hydroxy group is *trans* coperiplanar, and epoxide formation is favored (Scheme 6).

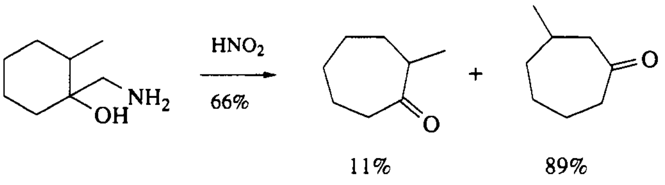

(14)[15]

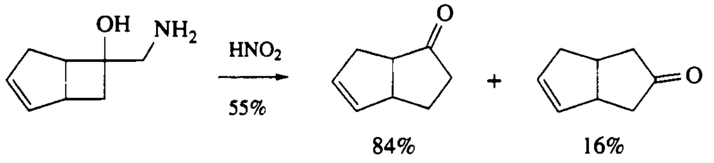
OH
NH2
HNO2
55%
O
+
O
84%
16%

(15)[16]

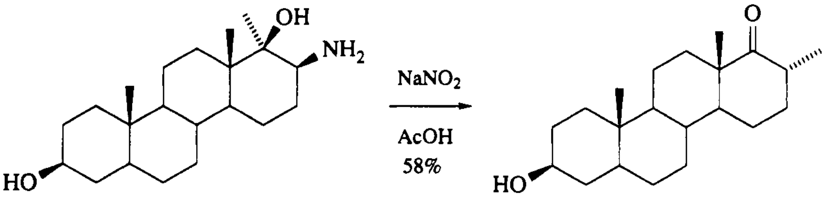
OH
NH2
HO
NaNO2
AcOH
58%
O
HO

**(14)** **(15)** (16)

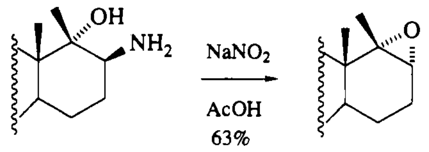
OH
NH2
NaNO2
AcOH
63%
O

**(16)** **(17)** (17)

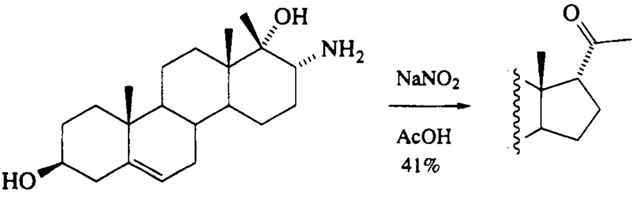
OH
NH2
HO
NaNO2
AcOH
41%
O

**(18)** (18)

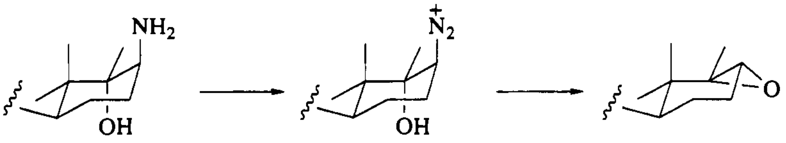
NH2
OH
+
N2
OH
O

**(16)** **(17)**

**Scheme 6**

Inversion of configuration is normally observed on rearrangement of cyclic 2-amino alcohol substrates. Collins *et al.*[20] have examined in detail the stereochemical course of the Tiffeneau–Demjanov rearrangement in acyclic substrates. In a series of 2-amino-1,2-diaryl alcohols studied, variable amounts of inversion were observed, while in some cases retention of configuration predominated (equation 19). This complexity can be attributed to the flexibility of such acyclic substrates where several conformations are possible in the transition states.

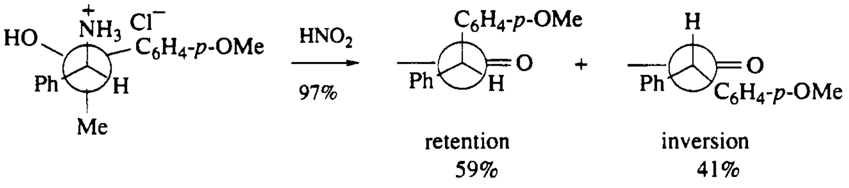
HO
+
NH3 Cl⁻
C6H4-p-OMe
Ph
H
Me
HNO2
97%
C6H4-p-OMe
O
Ph
H
+
H
O
Ph
C6H4-p-OMe
retention
59%
inversion
41%

(19)

### 3.4.2.2 Additions of Diazoalkanes to Ketones

The homologation of ketones by the addition of diazoalkanes complements the Tiffeneau–Demjanov rearrangement. Epoxide formation is a side reaction which can be minimized if polar aprotic solvents are avoided (Scheme 7). Rearrangement (*i.e.* homologation) is maximized in ether solvents or by Lewis acid catalysis.[21] The reaction is most effective in the ring expansion of cyclic ketones.

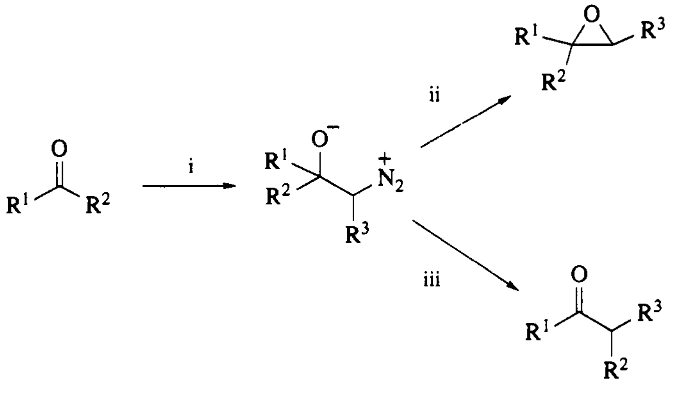

i $R^3CHNH_2$; ii, aprotic solvents; iii, ether solvents or Lewis acid

**Scheme 7**

In the addition of simple diazoalkanes to ketones, the product homologated ketone is often an effective substrate for further homologation. For example, norbornenone (**19**), when treated with an excess of diazomethane, yields a complex mixture of homologated ketones (equation 20).[22] However, high yields of a desired homologated ketone can be obtained, as in the preparation of 5-ethoxycarbonyl-2-methylcycloheptanone from 4-ethoxycarbonylcyclohexanone (equation 21).[23] With unsymmetrical ketones a mixture, due to migration of either group, is obtained (equation 22),[24] and the degree of substitution of either group appears to be of little importance.[25] However, 2-halo ketones undergo rearrangement with exclusive migration of the nonhalogenated group, and this selectivity has been utilized in a regioselective synthesis of ketones (Scheme 8).[26]

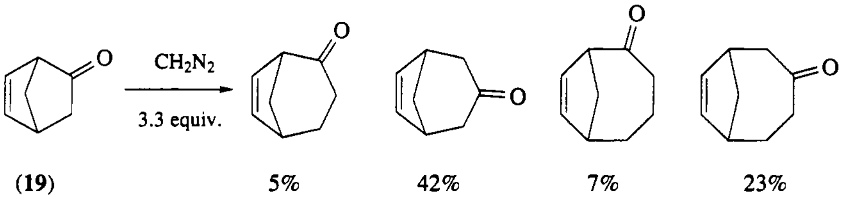

(**19**)

(20)

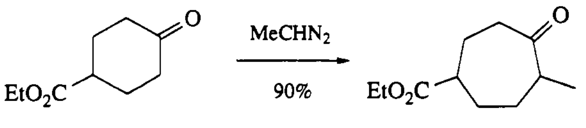

(21)

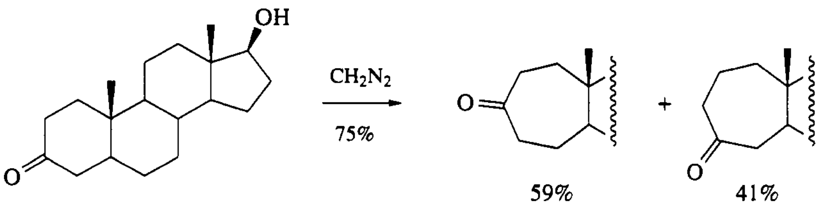

(22)

Ethyl diazoacetate has been used extensively in the homologation of ketones to 3-keto esters. Lewis acid is required for the reaction (equation 23).[105] There is a tendency for the least-substituted group to migrate, particularly if one group is fully substituted (equation 24).[27] In a total synthesis of (±)-aplysin (**20**) this selective rearrangement was applied (Scheme 9),[28] and a similar approach was used in a synthesis of (+)-hirsutic acid.[29] Ethyl diazoacetate has also been used in the homologation of acyclic

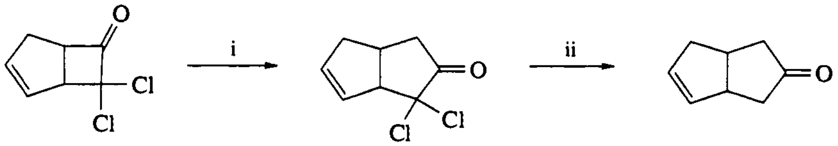
i
ii
O
Cl
Cl
O
Cl
Cl
O

i, $CH_2N_2$; ii, Zn, AcOH, 70% (2 steps)

**Scheme 8**

ketones. The presence of a 2-halogen promotes selective migration of the nonhalogenated group. The halogen 'protection' and the ethoxycarbonyl group can be removed reductively in one operation (Scheme 10).[30] The anion of ethyl diazoacetate adds to ketones to produce isolable 3-hydroxy-2-diazo esters, which rearrange to 3-keto esters when exposed to metal salt catalysis (Scheme 11).[31]

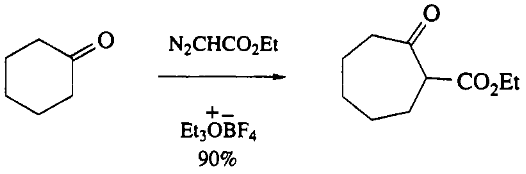
O
$N_2CHCO_2Et$
$Et_3\overset{+}{O}\overset{-}{B}F_4$
90%
O
$CO_2Et$

(23)

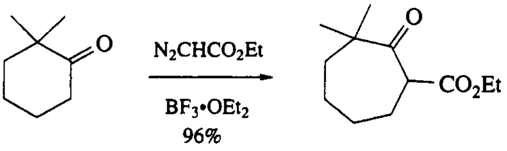
O
$N_2CHCO_2Et$
$BF_3$•$OEt_2$
96%
O
$CO_2Et$

(24)

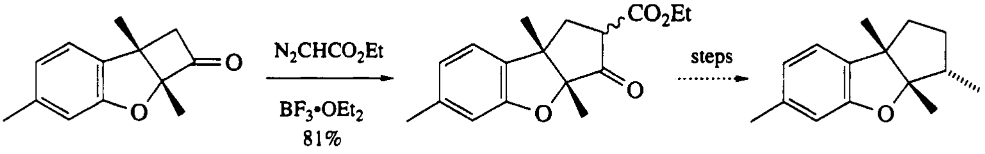
O
O
$N_2CHCO_2Et$
$BF_3$•$OEt_2$
81%
$CO_2Et$
O
O
steps
O

**(20)**

**Scheme 9**

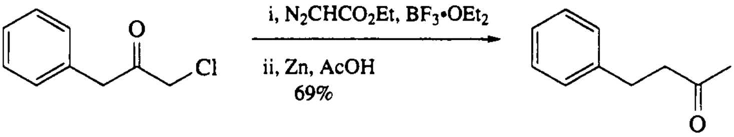
O
Cl
i, $N_2CHCO_2Et$, $BF_3$•$OEt_2$
ii, Zn, AcOH
69%
O

**Scheme 10**

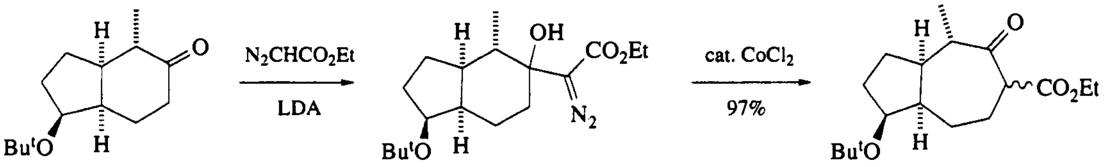
H
O
Bu<sup>t</sup>O
H
$N_2CHCO_2Et$
LDA
H
OH
$CO_2Et$
$N_2$
Bu<sup>t</sup>O
H
cat. $CoCl_2$
97%
H
O
$CO_2Et$
Bu<sup>t</sup>O
H

**Scheme 11**

### 3.4.2.3 Rearrangements of 2-Hydroxy Sulfides

2-Hydroxy sulfides rearrange to ketones under a variety of conditions. In aqueous acid it is the carbon bearing the sulfur group which ultimately becomes the carbonyl carbon. The rearrangement proceeds *via* protonation of the hydroxy group (Scheme 1, path b), and appears to be restricted to the expansion of small rings, particularly cyclopropanes (equation 25).[32] Trost and coworkers have developed this method, whereby the anion of cyclopropyl phenyl sulfide adds to a ketone and the adduct then rearranges to a cyclobutanone.[32,33]

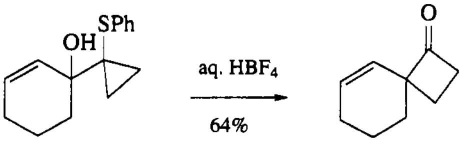

(25)

Two such rearrangements were used in the preparation of the cyclobutanone (**21**), a key intermediate in a synthesis of grandisol (**22**; Scheme 12).[33] A similar rearrangement is observed if the alcohol is allylic to the sulfide (equation 26),[34] and the formation of cyclobutanones from 1-thiophenyl-1-vinylcyclopropanes[35] is a closely related process.

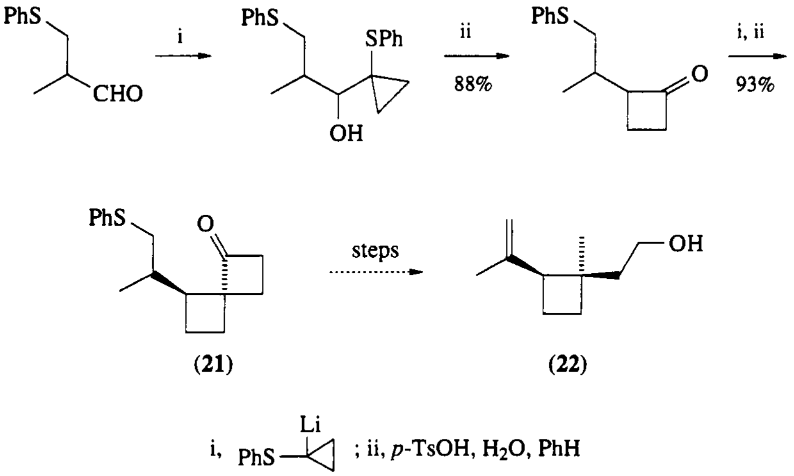

**(21)** **(22)**

i, PhS–Li(cyclopropyl); ii, *p*-TsOH, $H_2O$, PhH

**Scheme 12**

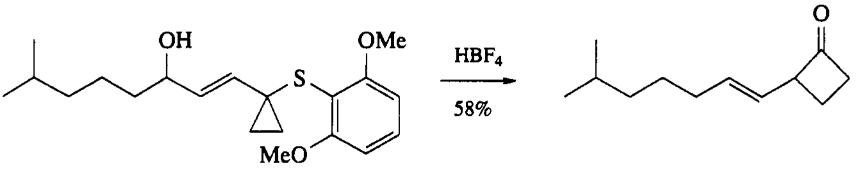

(26)

When exposed to soft electrophiles such as dichlorocarbene (generated *in situ*), 2-hydroxy sulfides rearrange with loss of the sulfur group and ketone formation at the hydroxy-bearing carbon,[3,36] as in the synthesis of cuparenone (**23**; equation 27).[3]

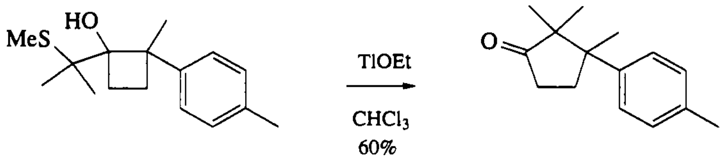

**(23)**

(27)

The anion of 1,1-dithiophenoxymethane adds to cyclic ketones and the adduct then rearranges to a ring-expanded ketone on metal salt catalysis (equation 28).[36a] The least-substituted group migrates in this case, as in the trithioalkyl derivative (**24**; equation 29), which was utilized in a synthesis of coriolin.[36b]

In a similar vein, the adducts derived from the anion of methoxymethyl phenyl sulfone and cyclic ketones rearrange on Lewis acid catalysis (Scheme 13).[37] This rearrangement is quite stereospecific, in that a single diastereoisomer is formed and it is the most substituted group which migrates. Similar results were obtained with adducts derived from phenyl thiomethyl phenyl sulfone (Scheme 14).[37]

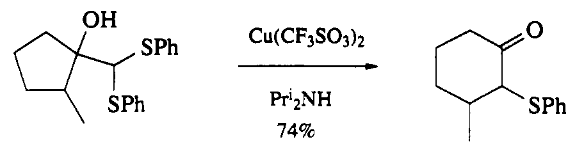
OH
SPh
SPh
Cu(CF3SO3)2
Pri2NH
74%
O
SPh

(28)

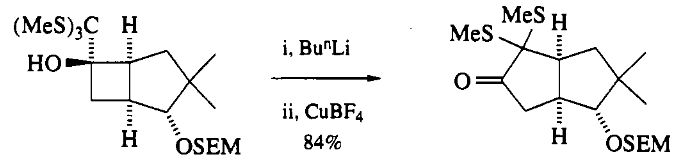
(MeS)3C H
HO
H
OSEM
i, BunLi
ii, CuBF4
84%
MeS
MeS
H
O
H
OSEM

**(24)**

(29)

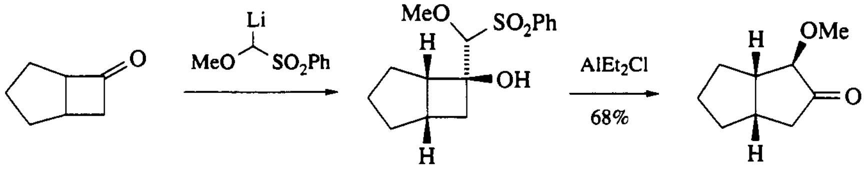
O
Li
MeO SO2Ph
MeO
H
SO2Ph
OH
H
AlEt2Cl
68%
H
OMe
O
H

Scheme 13

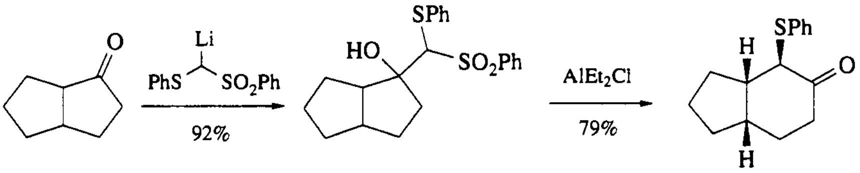
O
Li
PhS SO2Ph
92%
SPh
HO
SO2Ph
AlEt2Cl
79%
H
SPh
O
H

Scheme 14

Rearrangement is sometimes observed on the addition of sulfur ylides to ketones, yielding a homologated ketone rather than the expected epoxide (equation 30).[38] Hydroxy sulfides can undergo elimination to form alkenes, but the conditions are quite specific and require derivatization at oxygen[39] or sulfur.[40]

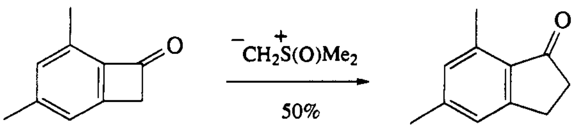
O
⁻CH2S⁺(O)Me2
50%
O

(30)

### 3.4.2.4 Rearrangements of 2-Hydroxy Selenides

The semipinacolic rearrangements of 2-hydroxy selenides are closely related to those of 2-hydroxy sulfides, but they have not been studied as extensively, and the use of selenium does not seem to offer any advantages over sulfur. The rearrangement has been applied mainly to the ring expansion of cyclic ketones *via* the addition of $\alpha$-selenoalkyl anions.

Paquette *et al.*[41] prepared the complex tricyclic ketone (**25**) by a selective rearrangement of a 2-hydroxy selenide (equation 31). In this case, it was the alkyl rather than the vinyl group which migrated. However, this preference is not as marked in a less rigid system.[41] A similar selectivity was noted in a cyclobutene derivative,[42] and Krief *et al.*[43] found that selectivity was highly dependent on ring size and the degree of substitution at the migrating center.

Dichlorocarbene (generated *in situ*), is generally used to induce migration, but silver tetrafluoroborate has also been used, as in the preparation of cuparenone (**23**; equation 32).[44] Rearrangement occurs only if the selenyl moiety is attached to a fully substituted carbon. For example, the hydroxy selenide (**26**) does not rearrange but instead yields the epoxide (**27**; equation 33).[44]

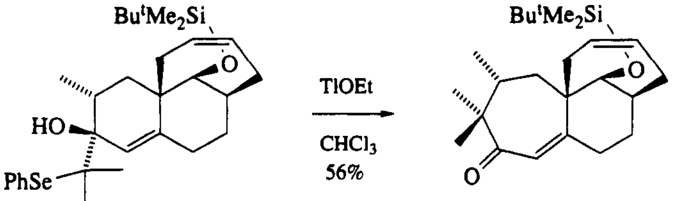

**(25)**

(31)

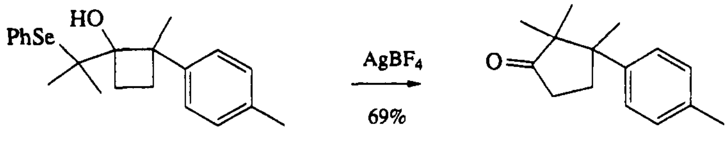

**(23)**

(32)

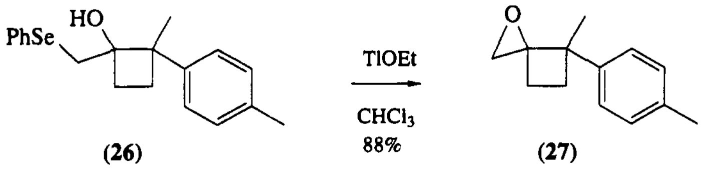

**(26)** **(27)**

(33)

This limitation can be overcome using the anion of alkyl phenyl selenoxides which add to ketones and rearrange *in situ* (equation 34).[45] The amalgam reduction is required to remove the small amount of α-phenyl selenated ketones formed in the reaction.

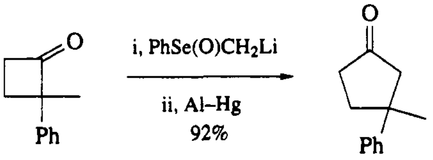

(34)

2-Hydroxy selenides undergo elimination to alkenes when treated with an excess of methanesulfonyl chloride, but elimination is not an important side reaction in rearrangement reactions.[46]

### 3.4.2.5 Rearrangements of Halohydrins

Halohydrins undergo semipinacolic rearrangement when exposed to base. The rearrangement of epoxides with metal halides is a closely related process and both rearrangements have been described in Chapter 3.3. However, the adducts of ketones and polyhalomethyllithium undergo rearrangements analagous to halohydrins, but by a quite different mechanism. The adducts are easily prepared by treating a mixture of polyhalomethane and ketone with an *N*,*N*-disubstituted lithium amide (equation 35).[47] When a dichloromethylcycloalkanol is treated with 2 equiv. of *n*-butyllithium, a dilithiated species (**28**) is formed, which then rearranges to form a homologated 2-chloro ketone (Scheme 15).[48]

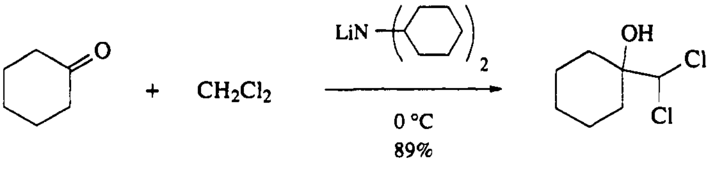

(35)

A dibromomethylcycloalkanol rearranges in a similar fashion, except that a different dilithio intermediate is formed *via* halogen–metal exchange rather than deprotonation (Scheme 16).[48] With unsymmetrical ketones, the more substituted group migrates. This selectivity has been applied to a synthesis of (±)-muscone (**29**; Scheme 17).[48] Substituted polyhalomethyllithium species can be used in the prepara-

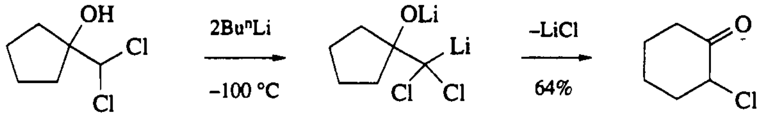

**(28)**

**Scheme 15**

tion of 2-substituted homologated ketones (Scheme 18).[49] The *O*-silyl ethers of dihaloalkylcarbinols do not rearrange when treated with *n*-butyllithium but instead eliminate to form vinyl halides.[50]

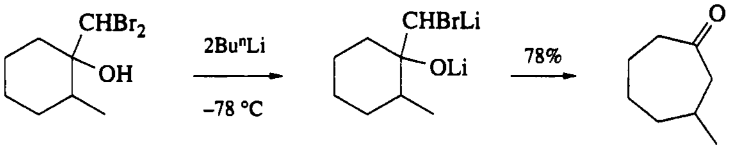

**Scheme 16**

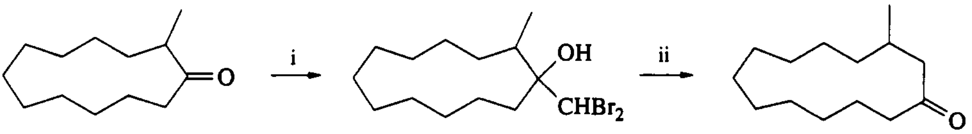

**(29)**

i, $LiCHBr_2$, 78%; ii, Bu$^n$Li, 76%

**Scheme 17**

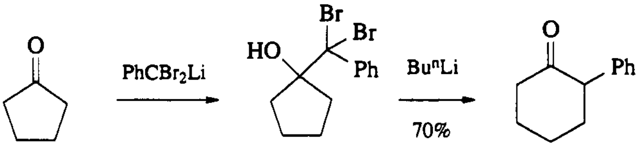

**Scheme 18**

### 3.4.2.6 Rearrangements of 2-Halo Ketones and Acetals

The semipinacolic rearrangement of 2-halo ketones and acetals to esters or acids is a valuable synthetic procedure, and the reaction has attracted considerable interest in the synthesis of 2-arylalkanoic acids,[6] several of which are valuable pharmaceuticals. The rearrangement is related to the Favorskii rearrangement and is sometimes referred to as the 'quasi-Favorskii' rearrangement. Under basic conditions, the semipinacolic mechanism applies with 2-halo ketones where the cyclopropanone intermediate of the Favorskii rearrangement cannot form. Such examples are ketones which do not have an α′-hydrogen (Scheme 19),[51] or certain cyclobutanones (equation 36).[52] Low yields in the base-induced rearrangement are often due to preferential displacement of the halogen by hydroxide ion. However, the rearrangement can be induced under milder conditions, such as silver nitrate in methanol, which was used in the chlorocyclobutanone ring contraction step in a recent synthesis of (±)-sirenin (**30**; Scheme 20).[53] Lewis acid is equally effective in the rearrangement of aryl bromoalkyl ketones (equation 37),[54] which is limited to secondary or tertiary bromides and to an electron-rich aromatic ring.

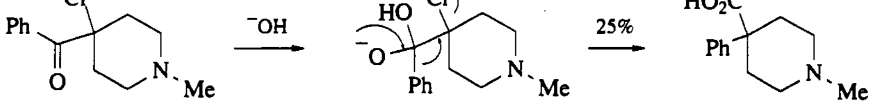

**Scheme 19**

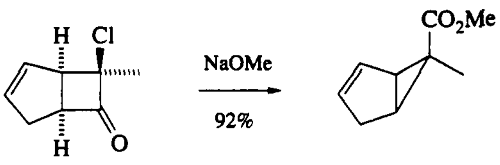
H
Cl
H
O
NaOMe
92%
$CO_2Me$

(36)

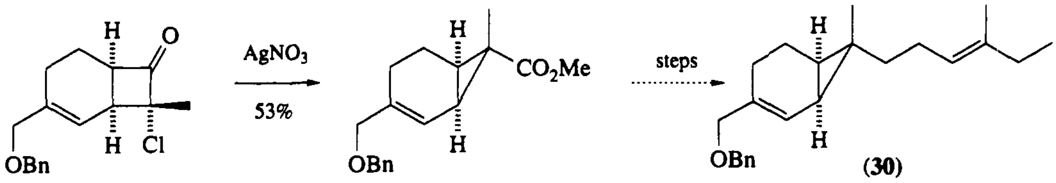
H
O
H
Cl
OBn
$AgNO_3$
53%
H
$CO_2Me$
H
OBn
steps
H
H
OBn
(30)

Scheme 20

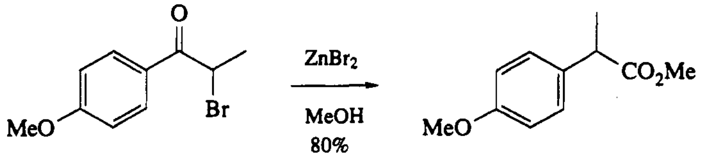
O
MeO
Br
$ZnBr_2$
MeOH
80%
$CO_2Me$
MeO

(37)

The acetals of 2-haloalkyl aryl ketones rearrange to esters of 2-arylalkanoic acids under a wide range of conditions.[6] Simply heating these substrates in aqueous alcohol containing sodium acetate provides the ester in high yield (equation 38).[55] Primary halides or electron-deficient arenes do not rearrange under these conditions. The use of silver salts in alcoholic media is more general (equation 39).[56] The rearrangement proceeds with inversion of configuration and an asymmetric synthesis of (+)-naproxen highlighting this feature has been described (Scheme 21).[57] Thus, the acetal (**31**), derived from (2*R*,3*R*)-tartaric acid, undergoes stereospecific bromination to yield a bromo acetal, which rearranges in high yield to the ester of (+)-naproxen. Yamauchi *et al.*[70] have demonstrated the similarity of these rearrangements by preparing esters of 2-arylalkanoic acids from ketones, acetals or enol ethers, using iodine, iodine monochloride or iodine trichloride in trimethylorthoformate solution (Scheme 22).

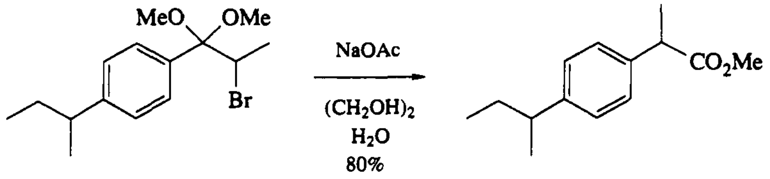
MeO
OMe
Br
NaOAc
$(CH_2OH)_2$
$H_2O$
80%
$CO_2Me$

(38)

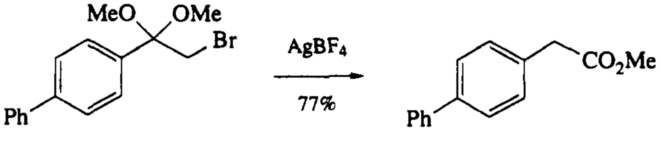
MeO
OMe
Br
Ph
$AgBF_4$
77%
$CO_2Me$
Ph

(39)

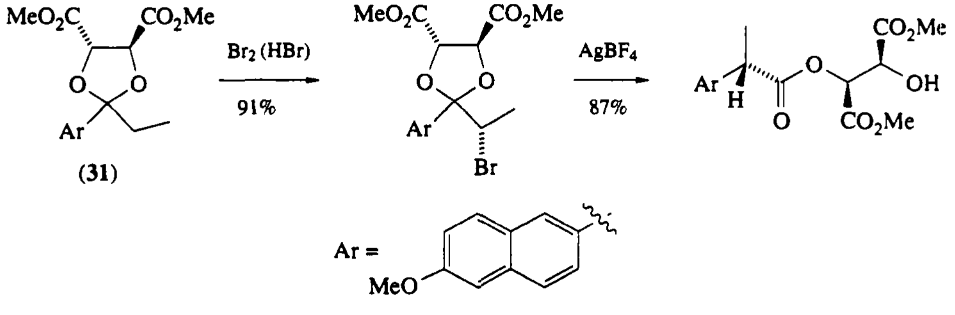
$MeO_2C$
$CO_2Me$
O
O
Ar
(31)
$Br_2$ (HBr)
91%
$MeO_2C$
$CO_2Me$
O
O
Ar
Br
$AgBF_4$
87%
Ar
H
O
O
$CO_2Me$
OH
$CO_2Me$
Ar =
MeO

Scheme 21

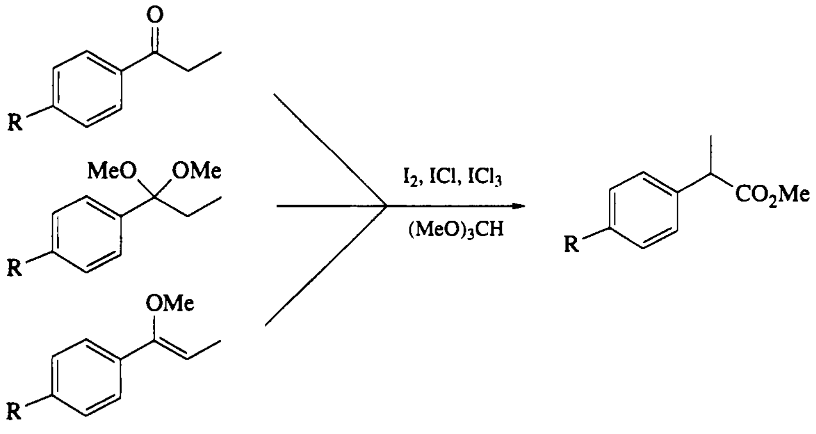
O
R
MeO
OMe
R
OMe
R
I2, ICl, ICl3
(MeO)3CH
CO2Me
R

R = MeO, Bu$^i$, H, Br, F

Scheme 22

### 3.4.2.7 Rearrangements of 2-Amino Ketones and 2-Hydroxyimines

Certain 2-amino ketones undergo rearrangement on thermolysis to produce new 2-amino ketones. The reaction proceeds by an initial 1,2-shift to yield a hydroxyimine, followed by a second 1,2-shift to the observed product (Scheme 23).[58] The amine must be primary or secondary and attached to a tertiary center. As would be expected, 2-hydroxyimines rearrange to 2-amino ketones (equation 40).[58] Similarly, 2-hydroxy ketones when heated with amines form rearranged 2-amino ketones *via* 2-hydroxyimines (equation 41).[58] This reaction has been applied in the synthesis of a D-ring homosteroid (equation 42).[59]

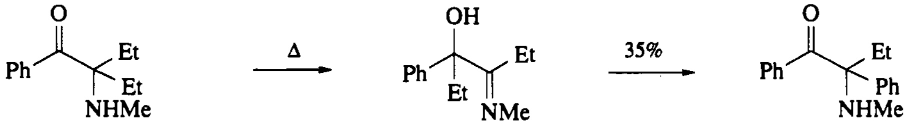
O
Ph
Et
Et
NHMe
Δ
OH
Ph
Et
Et
NMe
35%
O
Ph
Et
Ph
NHMe

Scheme 23

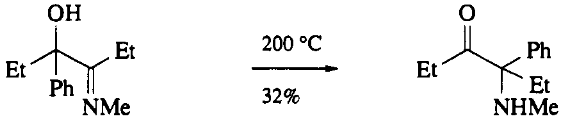
OH
Et
Et
Ph
NMe
200 °C
32%
O
Et
Ph
Et
NHMe

(40)

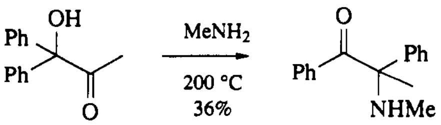
Ph
OH
Ph
O
MeNH2
200 °C
36%
O
Ph
Ph
NHMe

(41)

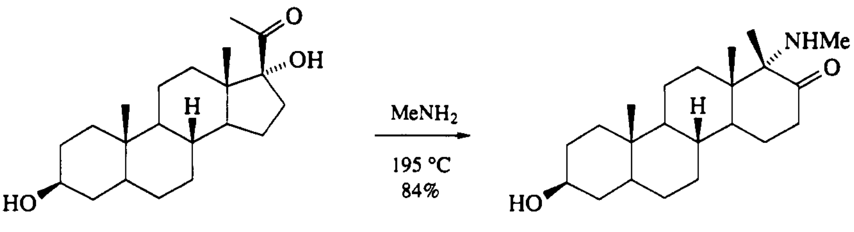
O
OH
H
HO
MeNH2
195 °C
84%
NHMe
O
H
HO

(42)

The semipinacolic rearrangement of 2-hydroxyimines has also been applied to the synthesis of 2-amino ketones which are not easily available by other methods (equation 43).[60] An impressive example is the biomemetic formation of the spiroindoxyl brevianamide A (**32**; equation 44).[61]

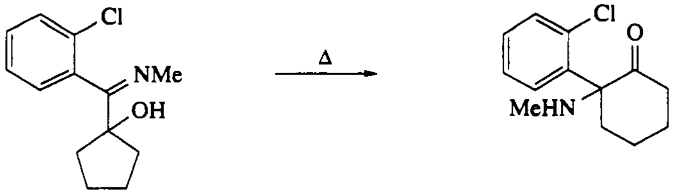
Cl
NMe
OH
Δ
Cl
O
MeHN

(43)

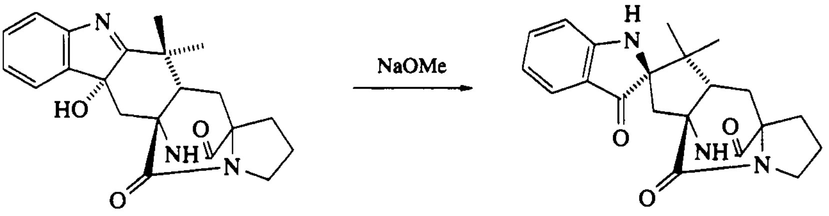
N
HO
O
NH
N
O
NaOMe
H
N
O
O
NH
N
O

(32)

(44)

### 3.4.2.8 Rearrangements of 2-Hydroxy Ketones

The rearrangement of 2-hydroxy ketones is analagous to the rearrangement of 2-hydroxyimines, and is termed the acyloin rearrangement. The reaction is of limited use, however, and has not found wide application. The rearrangement is initiated by base or Lewis acid (Scheme 24).[62] With unsymmetrical ketones it is possible for either group to migrate, depending on the conditions. With 3β,17α-dihydroxy-5α-pregnan-20-one, the more substituted group migrates under basic conditions (equation 45),[63] while Lewis acids promote migration of the least substituted group (equation 46).[62] Ring contraction is also possible, as in the case of the steroidal substrate (**33**; equation 47).[64]

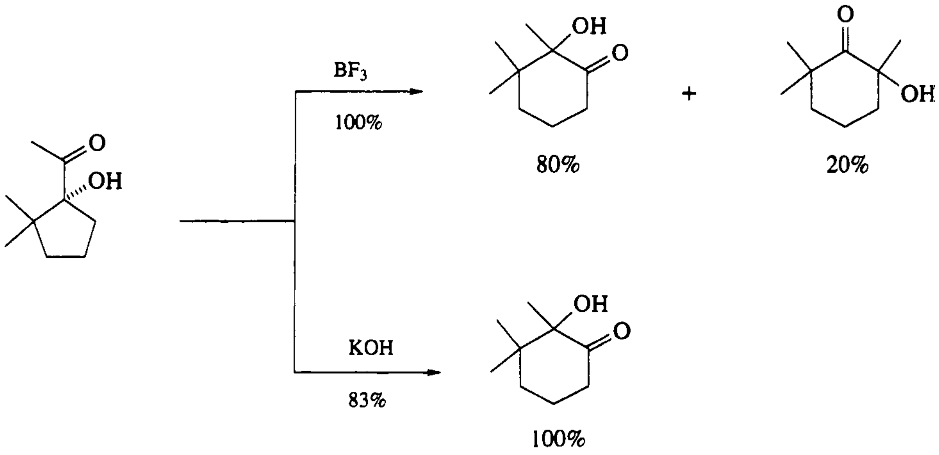
O
OH
BF3
100%
OH
O
+
O
OH
80%
20%
KOH
83%
OH
O
100%

**Scheme 24**

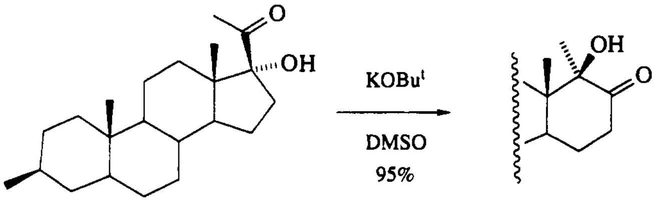
O
OH
KOBu^t
DMSO
95%
OH
O

(45)

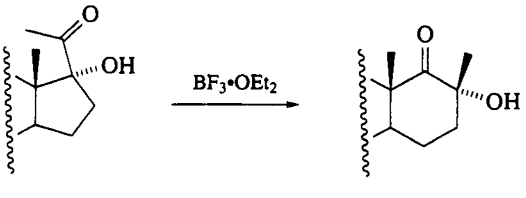
O
OH
BF3•OEt2
O
OH

(46)

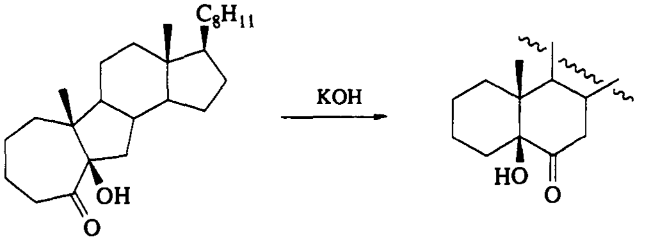

C8H11
OH
O
KOH
HO
O

**(33)**

(47)

### 3.4.2.9 Tandem Cyclization–Semipinacol Rearrangements

A semipinacol rearrangement in tandem with a cyclization has been shown to be a powerful method for the construction of carbocyclic rings. Here the cyclization is initiated by an acetal function and terminated by a semipinacol rearrangement (Scheme 25).[7] In some cases, the cyclization has been found to be stereospecific at the acetal center (equation 48),[65] and up to four chiral centers can be generated in a single step (equation 49).[66] Highly substituted tetrahydrofurans are obtained from cyclic acetals (Scheme 26),[67] and stereoselective tetrahydrofuran annelations are possible using bicyclic acetals (Scheme 27).[68]

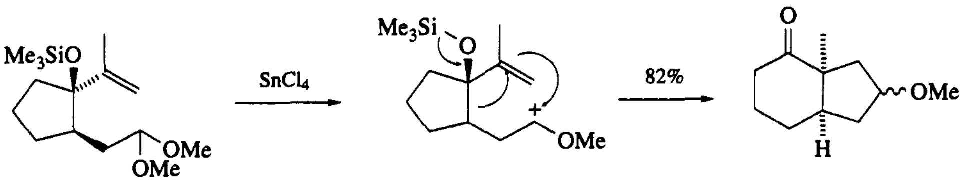

Me3SiO
OMe
OMe
SnCl4
Me3Si
O
+
OMe
82%
O
OMe
H

Scheme 25

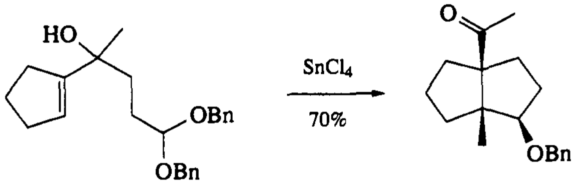

HO
OBn
OBn
SnCl4
70%
O
OBn

(48)

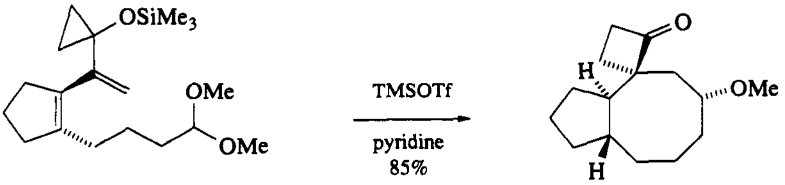

OSiMe3
OMe
OMe
TMSOTf
pyridine
85%
O
H
OMe
H

(49)

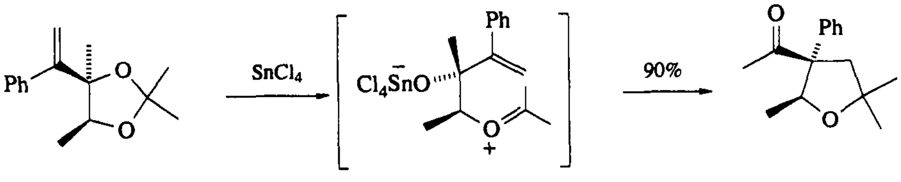

Ph
O
O
SnCl4
Ph
Cl4SnO
O
+
90%
O
Ph
O

Scheme 26

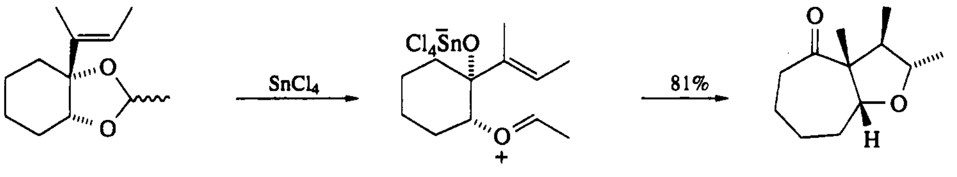

**Scheme 27**

### 3.4.3 ORGANOBORON REARRANGEMENTS

### 3.4.3.1 Rearrangements of Triorganylboranes

Trialkylboranes react with carbon monoxide in the presence of ethylene glycol to yield tertiary alkylboronic esters (Scheme 28), which on oxidation yield trialkylmethanols.[8,69] The presence of ethylene glycol is not necessary for this rearrangement but it greatly facilitates the oxidation reaction. The alkyl groups can be primary, secondary or tertiary, but tertiary groups do not migrate easily and more vigorous conditions are required (Scheme 29).[71]

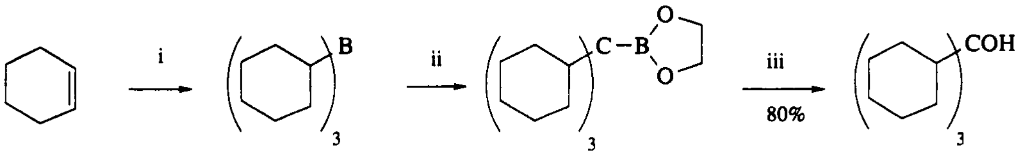

i, $BH_3$ ; ii, CO, $(CH_2OH)_2$, 100 °C; iii, NaOH, $H_2O_2$

**Scheme 28**

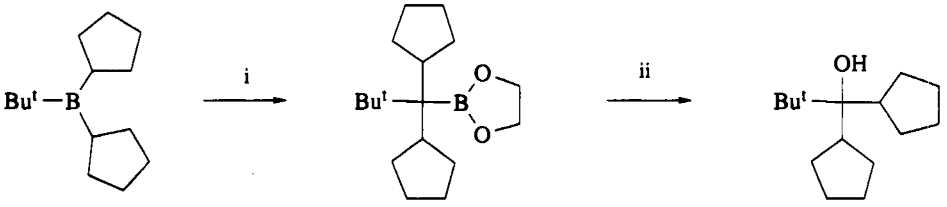

i, CO (70 atm), $(CH_2OH)_2$, 150 °C; ii, NaOH, $H_2O_2$, 60% (2 steps)

**Scheme 29**

If water is present in the carbonylation reaction, rearrangement of the third group is inhibited and ketones instead are obtained on oxidation (Scheme 30).[72] The mechanism of this sequence is not clear but the reaction proceeds *via* the intermediate (**34**). Unsymmetrical ketones are available from thexyldialkylboranes (equation 50),[73] since the thexyl group does not migrate easily. Cyclic ketones are also available by this route (Scheme 31).[74] When the carbonylation is performed in the presence of reducing agents, only one alkyl group migrates. Aldehydes and alcohols are then available by this method.[8,75]

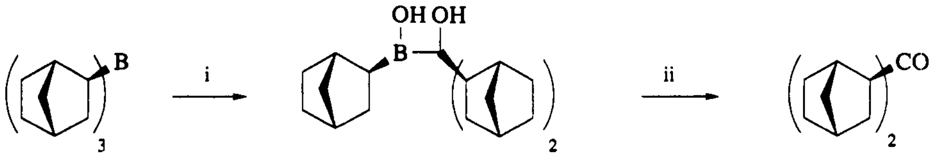

(**34**)

i, CO, $H_2O$, 100 °C; ii, NaOH, $H_2O_2$, 82%

**Scheme 30**

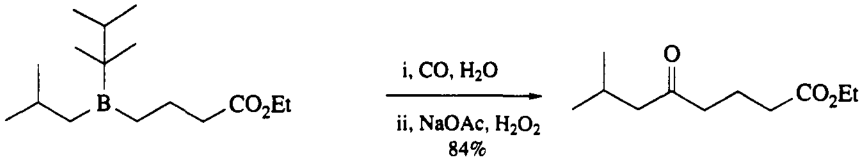
B
CO2Et
i, CO, H2O
ii, NaOAc, H2O2
84%
O
CO2Et

(50)

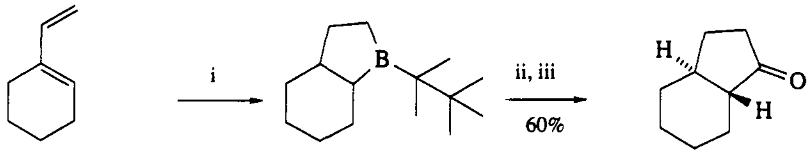
i
B
ii, iii
60%
H
O
H

i, $Me_2CHMe_2CBH_2$; ii, CO, $H_2O$; iii, $H_2O_2$, NaOAc

Scheme 31

There are certain disadvantages to the carbonylation reaction, such as high temperature and pressure. An alternative preparation of trialkylmethanols is the use of the anion of dichloromethyl methyl ether. Addition of this anion to a trialkylborane is followed by three successive migrations to yield the trialkylmethanol on oxidation. The reaction takes place at room temperature, and tertiary groups migrate without difficulty (Scheme 32).[76]

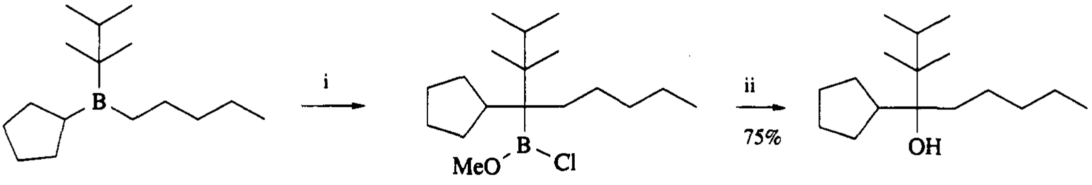
B
i
B
MeO
Cl
ii
75%
OH

i, $CHCl_2OMe$, $Et_3COK$; ii, $(CH_2OH)_2$, NaOH, $H_2O_2$

Scheme 32

2-Halocarbonyl compounds react with triorganylboranes to yield 2-alkylated derivatives. 9-Alkyl- or 9-aryl-borabicyclononane derivatives yield the 9-alkyl/aryl group selectively (equation 51).[77] Sequential dialkylation of dichloroacetonitrile is feasible by this method.[78] Trialkylboranes also react with halo sulfones (equation 52)[79] and diazo ketones (equation 53),[80] in a similar fashion.

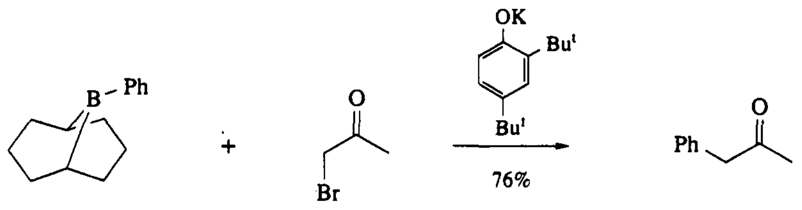
B
Ph
+
O
Br
OK
Bu^t
Bu^t
76%
Ph
O

(51)

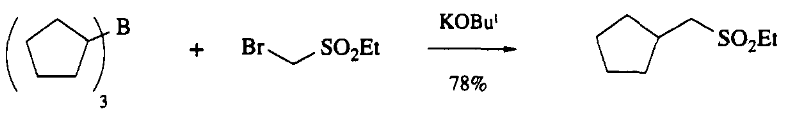
B
3
+
Br
SO2Et
KOBu^t
78%
SO2Et

(52)

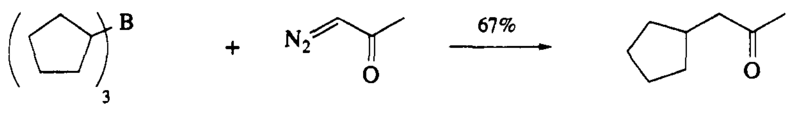

(53)

The reactions between ylides of sulfur and nitrogen, and triorganylboranes have not proved to be synthetically useful. A major side reaction is the competitive reaction between the product and the starting ylide. This complication can be overcome in the case of sulfur, by first reacting the borane with the anion of a sulfide and inducing rearrangement of the tetraorganylborate with an electrophile (Scheme 33), to yield a homologated borane.[81] The rearrangements of alkenylboranes yield either (*E*)- or (*Z*)-alkenes of high geometric purity by the judicious choice of substrate and conditions.

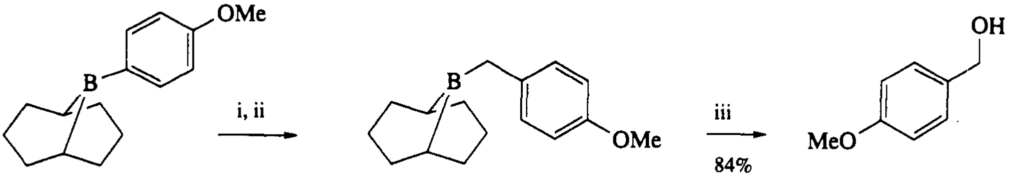

i, $LiCH_2SMe$; ii, MeI; iii, NaOH, $H_2O_2$

**Scheme 33**

Alkylbromoalkenylthexylboranes are available from thexylborane by sequential hydroboration of alkenes and bromoalkynes, and they rearrange to borinic esters when treated with methoxide. Protonation yields (*E*)-alkenes of high purity (Scheme 34).[82] Rearrangement takes place with inversion of configuration at the halogen center, while protonation proceeds with retention of configuration.

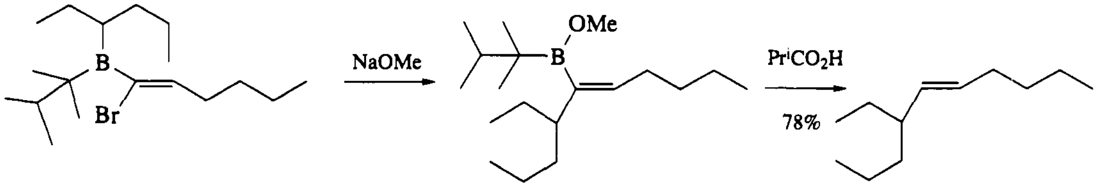

**Scheme 34**

Monoalkylbromoboranes hydroborate terminal alkynes to yield alkylalkenylbromoboranes, which then rearrange to yield (*Z*)-alkenes after protonation; this useful procedure has been applied to the preparation of muscalure (**35**; Scheme 35).[83] (*E*)-Alkenes are available by a similar sequence if 1-bromoalkynes are employed at the hydroboration stage.[84] Similarly, dialkenylthexylboranes yield dienes on rearrangement and protonation.[85]

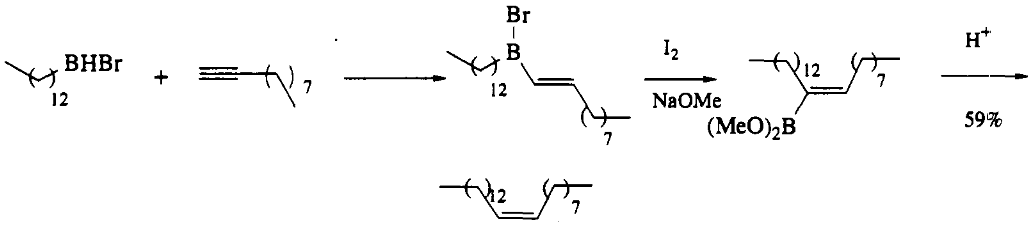

(**35**)

**Scheme 35**

The rearrangements of triorganylboranes have focused on the use of alkyl and alkenyl groups, due to the availability of these substrates by hydroboration. However, aryl groups are equally effective for rearrangement and this aspect warrants further study. There are many variants of the rearrangements of triorganylboranes which constitute a wide and varied methodology,[8,10a,75,86,87] some of which have not been fully exploited in synthesis.

### 3.4.3.2 Rearrangements of Boronic Esters

Boronic esters are not as reactive as triorganylboranes towards nucleophiles; however, rearrangement does take place if the boronic ester is treated with an α-halocarbanion (equation 54).[88] In this case, the 1-chloroethylboronate (**36**) can be obtained in 95% *de* due to the diastereofacial influence of the chiral pinanediol. Similarly, chloro- or bromo-alkylboronic esters react with Grignards reagents, alkyllithiums and enolates leading to rearranged products.[9,88]

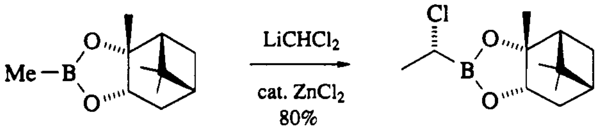

(**36**)

(54)

This methodology has been developed by Matteson and coworkers,[9,87] with particular emphasis on chiral boronic esters derived from pinanediol. Sequential chiral centers can be assembled by an iterative procedure with excellent enantiomeric excess at each step. The two chiral centers in eldanolide (**37**), for example, were assembled in this manner (Scheme 36).[88]

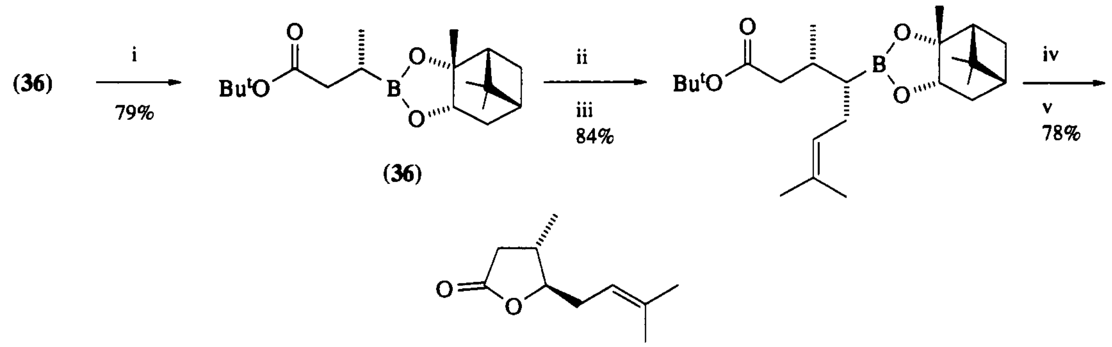

(**37**)

i, $Bu^tO_2CCH_2Li$; ii, $LiCHCl_2$, cat. $ZnCl_2$; iii,$Me_2C{=}CHCH_2MgCl$; iv, $H_2O_2$; v, TFA

**Scheme 36**

L-α-Amino acids can also be prepared by this method. Thus, heteronucleophiles, such as azide ion, react with the chloroalkylboronic ester *via* a four-coordinate boronate, as with carbon nucleophiles (Scheme 37).[89]

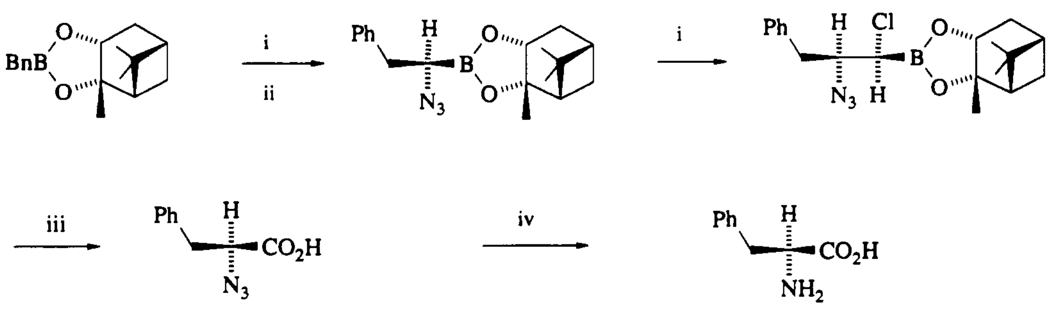

i, $LiCHCl_2$, cat. $ZnCl_2$; ii, $NaN_3$; iii, $NaClO_2$; iv, $H_2$, Pd/C, 63% (5 steps)

**Scheme 37**

The $C_2$ symmetry present in the boronic ester (**38**) derived from (*S*,*S*)-1,2-dicyclohexylethanediol allows the stereoselective displacement of each chlorine atom to yield the chiral pentenylboronic ester

(**39**), a key intermediate which has been used in a synthesis of the macrolide mycinomycin (Scheme 38).[90]

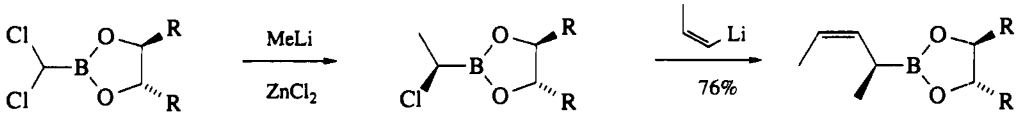

R = cyclohexyl

(**39**)

Scheme 38

(*S,S*)-Diisopropylethanediol and (*R,R*)-2,3-butanediol are also effective chiral 'directors' in boronic ester rearrangements.[9] Both of these vicinal diols are $C_2$ symmetric and the butanediolboronic esters are readily hydrolyzed to boronic acids, which can then be reesterified if a change in chiral direction is required.

Brown and coworkers[75] have described an alternative synthesis of chiral alkylboronic esters. In this synthesis prochiral alkenes are hydroborated with monoisopinocamphenylborane to yield isopinocamphenylalkylboranes which are then readily transformed to chiral alkylboronic esters (Scheme 39).[91] Homologation with dichloromethyllithium, followed by reduction with potassium triisopropoxyborohydride (KIPBH) and oxidation, finally yields β-chiral alcohols (Scheme 40).[92] These alcohols are not easily prepared by other methods. Aldehydes can be prepared by homologation from chiral alkylboronic esters with LiCH(OMe)SPh and oxidation (Scheme 41).[91]

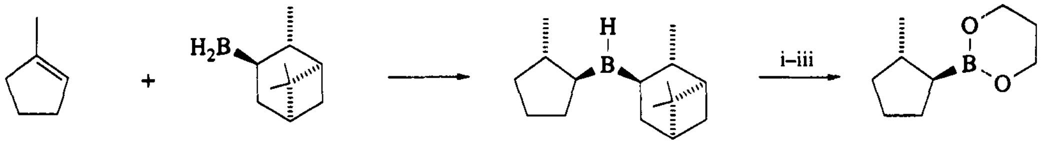

i, MeCHO; ii, NaOH; iii, $HOCH_2CH_2CH_2OH$, 85% (3 steps)

Scheme 39

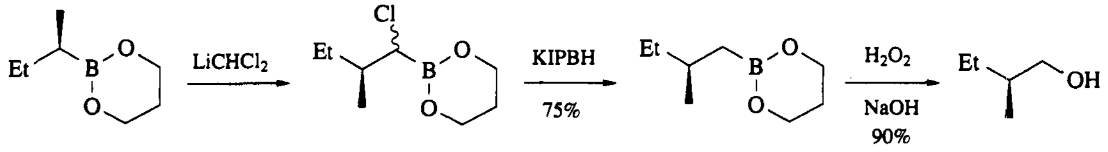

Scheme 40

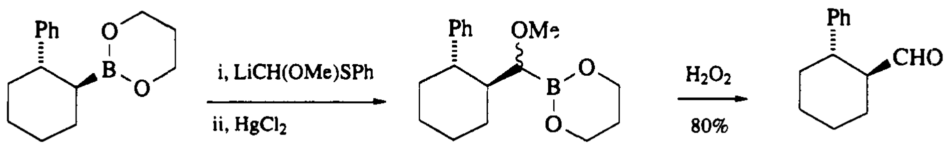

Scheme 41

Chiral boronic esters react with organolithium reagents to form diorganylalkoxyboranes (borinic esters).[93] Subsequent reaction with the anion of dichloromethyl methyl ether then yields chiral ketones by rearrangement of both of the groups on boron (Scheme 42).[93] No racemization is observed in this sequence and alkyl-, aryl-[93] or alkynyl-lithium[94] reagents can be used.

The rearrangements of boronic esters frequently offer advantages over those of triorganylboranes. The presence of only one organic group for migration, for example, contrasts with triorganylboranes where selectivity is often a problem. In addition, the use of boronic esters derived from chiral diols is a powerful technique in chiral synthesis. Finally, the use of alkyl, alkenyl and aryl groups in rearrangements of boronic esters has been demonstrated. All of these features have resulted in the wide application of boronic esters in synthesis.[9,86,87,95]

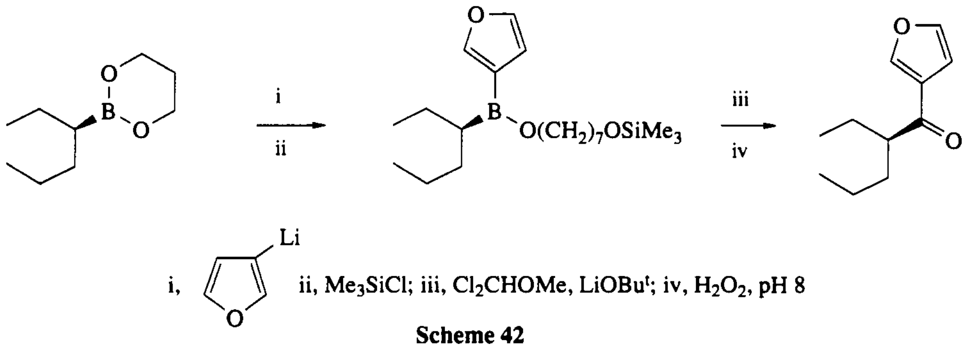
i
ii
B
O(CH$_2$)$_7$OSiMe$_3$
iii
iv
O
Li
i,
ii, Me$_3$SiCl; iii, Cl$_2$CHOMe, LiOBu$^t$; iv, H$_2$O$_2$, pH 8

**Scheme 42**

### 3.4.3.3 Rearrangements of Tetraorganylboronates

Triorganylboranes have been shown to react with certain carbon nucleophiles to produce stable, isolable tetraorganylboronate salts. On exposure to electrophiles, these boronates then rearrange, producing neutral triorganylboranes.[10b,95]

Cyanoboronates are prepared by the treatment of triorganylboranes with cyanide ion. When treated with an excess of TFAA, all three groups in the triorganylborane migrate to the cyanide carbon, leading to tertiary alcohols on oxidation (Scheme 43).[96] This transformation is closely related to the carbonylation of triorganylboranes (see Section 3.4.3.1). In the presence of 1 equiv. of TFAA, the third group does not migrate and ketones are obtained instead (equation 55).[97] Unsymmetrical ketones are available from thexyldialkylcyanoboronates since the bulky thexyl group does not migrate (equation 56);[97] cyclic ketones can also be prepared by this method (Scheme 44).

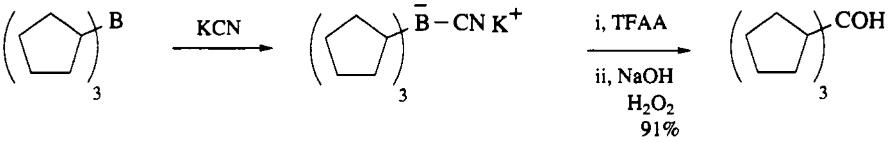
B
3
KCN
$\bar{B}$−CN K$^+$
3
i, TFAA
ii, NaOH
H$_2$O$_2$
91%
COH
3

**Scheme 43**

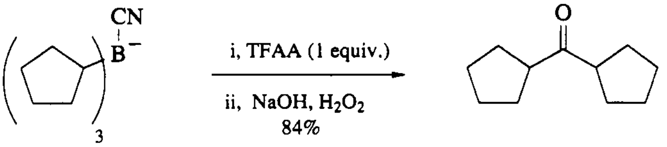
CN
B$^-$
3
i, TFAA (1 equiv.)
ii, NaOH, H$_2$O$_2$
84%
O

(55)

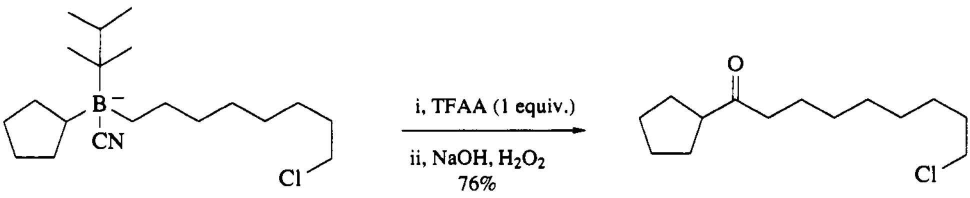
B$^-$
CN
Cl
i, TFAA (1 equiv.)
ii, NaOH, H$_2$O$_2$
76%
O
Cl

(56)

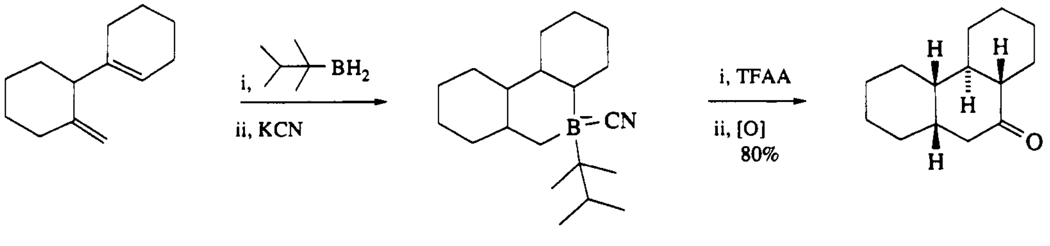
i,
BH$_2$
ii, KCN
B$^-$−CN
i, TFAA
ii, [O]
80%
H
H
H
H
O

**Scheme 44**

Triorganylboranes react with alkynide ion to yield alkynylborates. When exposed to iodine and hydroxide, rearrangement to an alkylated alkyne then takes place (Scheme 45).[98] When alkynylborates are treated with alkylating agents such as dimethyl sulfate, rearrangement and concomitant alkylation takes place. The resulting alkenylborane can then be hydrolyzed to an (*E*)/(*Z*) mixture of alkenes or oxidized to ketones (Scheme 46).[99] This alkylation–rearrangement reaction has been used, for example, in a synthesis of propylure.[100]

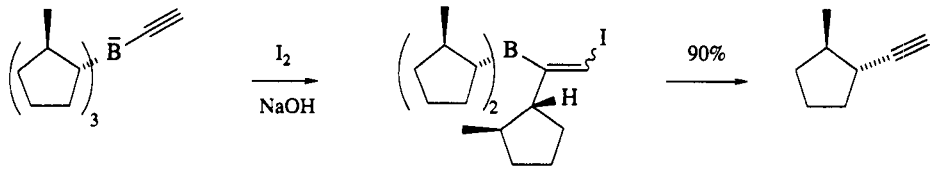
B
3
I₂
NaOH
B
I
H
2
90%

Scheme 45

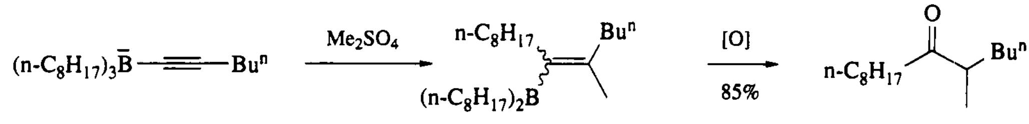
(n-C₈H₁₇)₃B—≡—Buⁿ
Me₂SO₄
n-C₈H₁₇
Buⁿ
(n-C₈H₁₇)₂B
[O]
85%
O
n-C₈H₁₇
Buⁿ

Scheme 46

Alkenylalkynyldi(1,2-dimethylpropyl)boronates, when exposed to iodine and hydroxide, rearrange with selective migration of the alkenyl group to the alkynyl group. The pheromone bombykol (**40**) has been synthesized *via* this key reaction (Scheme 47).[101]

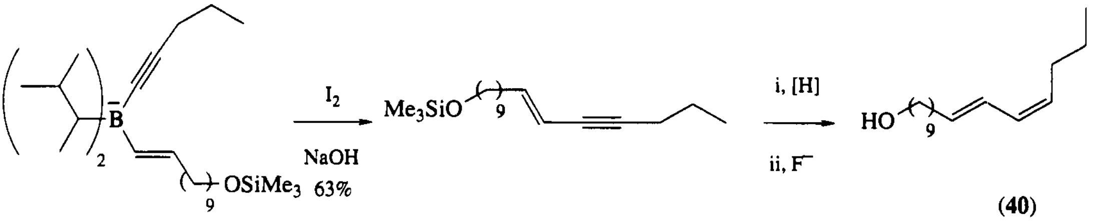
B
2
OSiMe₃
9
I₂
NaOH
63%
Me₃SiO
9
i, [H]
ii, F⁻
HO
9
(40)

Scheme 47

Alkenylalkyldimethoxyboronates have been shown to rearrange with inversion of geometry, leading to substituted alkenes (equation 57),[102] and alkenyltrialkylboronates react with epoxides to yield 1,4-diols after oxidation (Scheme 48).[103]

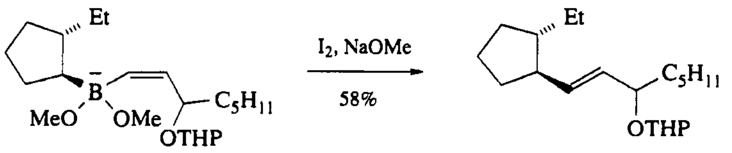
Et
B
MeO
OMe
C₅H₁₁
OTHP
I₂, NaOMe
58%
Et
C₅H₁₁
OTHP

(57)

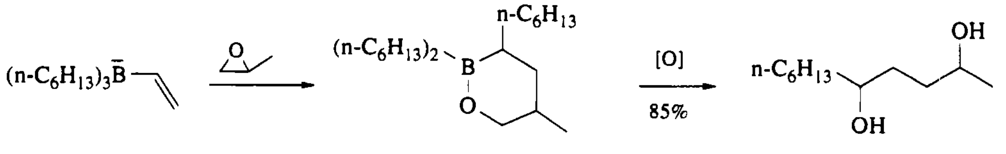
(n-C₆H₁₃)₃B
O
(n-C₆H₁₃)₂
B
O
n-C₆H₁₃
[O]
85%
n-C₆H₁₃
OH
OH

Scheme 48

Tetraorganylboronates offer some advantages over triorganylboranes, particularly in the preparation of ketones from cyanoborates. Where a direct comparison has been made, the cyanoborate method was found to be superior.[104]

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# 3.5

# Dienone–Phenol Rearrangements and Related Reactions

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## 3.5.1 INTRODUCTION

Dienone–phenol rearrangements involve cyclohexadienones in the great majority of cases, although other variations are possible, *e.g.* ring contractions of tropolones to phenols. Cyclohexadienones can be either cross conjugated as in the 2,5-dienones (**1**), or linearly conjugated as in the 2,4-dienones (**2**). These forms are often referred to as the '*para*' and '*ortho*' dienones respectively, and they are available synthetically from a number of reactions, including oxidative coupling of phenols, electrophilic substitution of phenols, oxidation of phenols, other aromatic rearrangements and dehydrogenation of cyclohexanones.

The cross-conjugated structures are generally more stable than their linearly conjugated isomers, but both types rearrange readily to a phenol (**3**) with migration of a substituent X or Y from C-4 (**1**) or C-6 (**2**). Both substituents X and Y may shift. If the migrating group moves to a site on the ring which aromatizes, as in (**3**), the rearrangement is termed 'intracyclic', but if a group migrates to a position outside the ring, as in (**4**), then the reorganization is referred to as 'extracyclic'.

Dienone–phenol rearrangements are mechanistically diverse. They may involve: 1,2-shifts of the Wagner–Meerwein type, or of the benzil–benzilic acid kind; 1,3-shifts by a Claisen–Cope mechanism; 1,5-sigmatropic shifts; Favorskii-like reactions; and other types. They may also be induced photochemically. A number of reviews are available,[1] which discuss mechanistic aspects in detail. In this chapter emphasis is put on preparative aspects of these reactions and the examples are organized on a structural basis, stressing the new bond(s) formed.

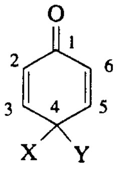

(1)

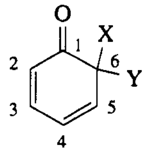

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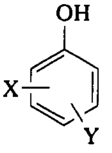

(3)

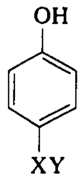

(4)

## 3.5.2 INTRACYCLIC MIGRATION

### 3.5.2.1 Formation of New C—C Bonds

The major ramifications of carbon migration in the dienone–phenol rearrangement are shown in Scheme 1, for a steroid ring A dienone (**5**). Several hundred of such acid-catalyzed reactions have been described[2] and five different pathways can be discerned. Protonation at oxygen in the dienone (**5**) leads to cation (**6**), and three different carbon shifts may follow. C-9 migration to C-5 leads to a new cation (**7**) which can reach an aromatic system either by migration of C-6, leading to phenol (**8**) or by shift of C-9, giving rise to phenol (**9**). Going back to cation (**6**), two courses are possible for a methyl (C-19) shift; 1,2-migration to C-1 yields phenol (**10**), while shift to C-5 affords another cation (**11**). Intermediate (**11**) can undergo either a C-6 → C-10, C-6 → C-1 sequence to arrive at phenol (**12**), or a C-6 → C-10, C-9 → C-1 routine to yield phenol (**13**). Of the five phenol products, (**10**) and (**12**) are structurally identical as shown, but represent different bond reorganizations. All these pathways have been observed. The choice between, for example, the migration of methyl or methine from C-10 is finely balanced and is sensitive to reagents and conditions.[3] The migration of the potentially most stable carbocation is expected to be kinetically preferred, *i.e.* the pathway which leads to (**9**). However, the shifts are reversible, and other factors may intervene, so that although product (**9**) may predominate, phenols of structures (**8**) and (**10**) are often the major products. The reader is referred to mechanistic reviews for a discussion of the controlling features. The examples collected in this chapter are organized on a structural basis, and it should be pointed out that a mechanism cannot always be reliably deduced from product structure.

#### *3.5.2.1.1 Rearrangements forming one new C—C bond*

Alkyl shifts in simple cyclohexadienones can be induced with strong acids at room temperature. Thus 4,4-dimethylcyclohexadienone (**14**) rearranges to 3,4-dimethylphenol (**15**) at 25 °C with 70% perchloric acid, in 90% yield.[4] The 4-methyl-4-ethyl homolog (**16**) smoothly rearranges in trifluoroacetic acid, with preferential ethyl shift, to 3-ethyl-4-methylphenol (**17**).[5,6] Preferred ethyl shift is also seen in the *o*-dienone (**18**), which rearranges to the 3-ethyl-2-methylphenol (**19**) with loss of a *t*-butyl group.[7] In the 4-hydroxy-4-methyldienone (**20**), methyl group shift dominates when boron trifluoride etherate is used as acid (but see Section 3.5.3) to yield methyl hydroquinone (**21**; 55%).[8] Vinyl groups[9] and ethoxycarbonyl groups[5] migrate in preference to methyl. Electron-withdrawing groups adjacent to reacting centers slow down the reaction so that the dichloromethyl-substituted dienone (**22**) requires long treatment at 50 °C with concentrated sulfuric acid for conversion (84%) to 4-hydroxy-2-methylbenzaldehyde (**23**), with methyl migration, and concomitant hydrolysis of the *gem*-dichloride.[10] In the decalindienone group the rearrangement of santonin (**24**) in acid to desmotroposantonin (**25**) is an example of historical interest.[11] The parent ring system (**26**) has been investigated systematically.[3,12] With (**26**; R = Me) fairly good yields (50–60%) of the methyltetralol (**27**) were obtained using aqueous hydrochloric or sulfuric acid as catalyst; a small proportion (10%) of the isomeric tetralol (**28**; R = Me) was also obtained. Apparent 1,2-shift of the methyl is the major pathway. With other angular alkyls, *e.g.* (**26**; R = Pr$^n$), in which both potential migrating centers are methylene, the product of 1,2-shift dominates even more *i.e.* (**27**; R = Pr$^n$):(**28**; R = Pr$^n$) = 98:2, on rearrangement with 10 M sulfuric acid.

In the steroid series the androstadiendione (**29**) reacts slowly with 48% hydrobromic acid at room temperature; after 5 d the main product (55%) is 1-methylestrone (**30**) with its isomer (**31**) in minor amount (11%).[3] The ring bond shifts are inhibited in the 11-ketodienone (**32**) which essentially reacts exclusively by 1,2-methyl shift in perchloric acid–acetic anhydride to provide the 2-methyl steroid (**33**), with parallel peracetylation.[13] An 11-hydroxy function has a different effect (see Section 3.5.2.1.2). The 1,2-methyl

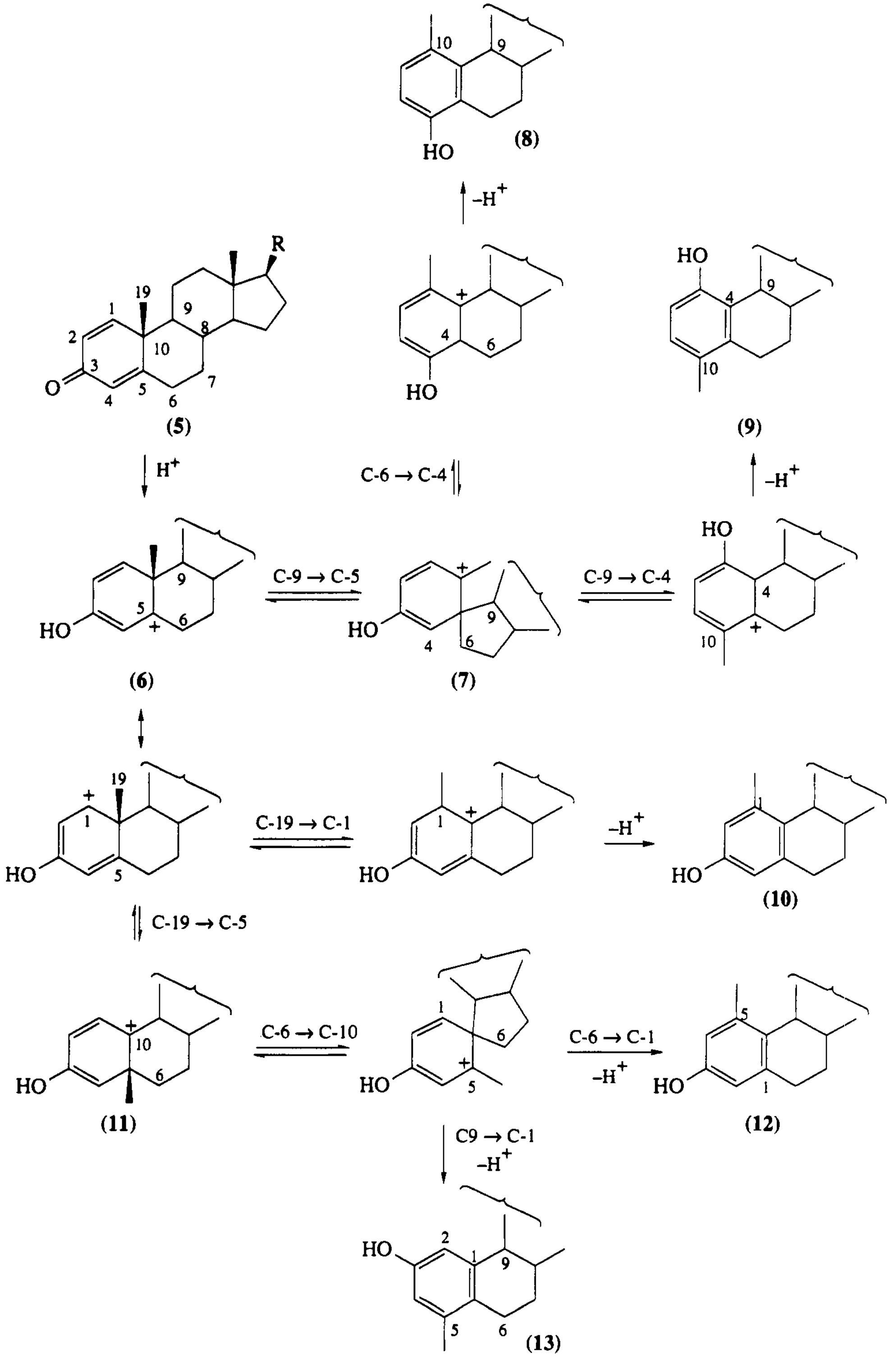

(8)
HO
-H+
R
19
1
2
3
4
5
6
7
8
9
10
O
(5)
H+
C-6 → C-4
HO
(9)
C-9 → C-5
C-9 → C-4
(6)
(7)
C-19 → C-1
-H+
(10)
C-19 → C-5
C-6 → C-10
C-6 → C-1
(11)
(12)
C9 → C-1
(13)

Scheme 1

shift becomes the major pathway when C-4 is blocked, and when C-6 is an $sp^2$-hybrid. Thus the 4-methylandrostadienone (**34**) yields the phenol (**35**; 73%) after saponification with acetic anhydride–*p*-toluenesulfonic acid,[14] and the same reagents effect the parallel conversion of the $\Delta^6$-dienone (**36**) to the phenol acetate (**37**).[15]

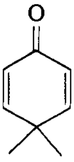
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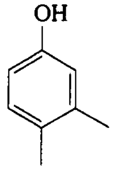
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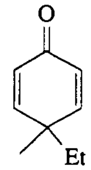
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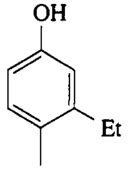
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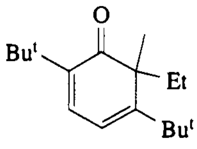
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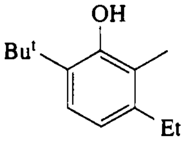
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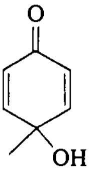
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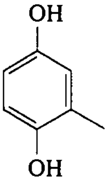
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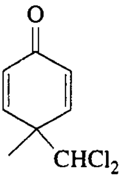
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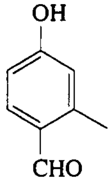
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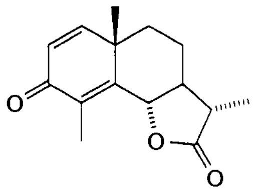
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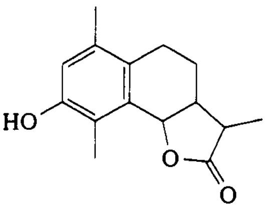
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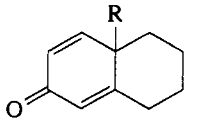
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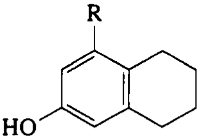
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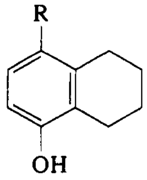
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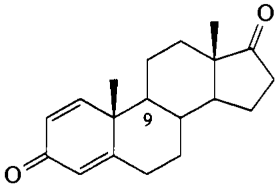
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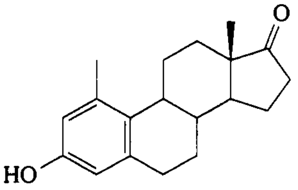
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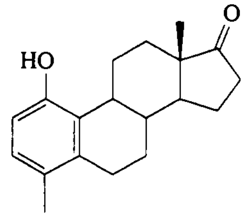
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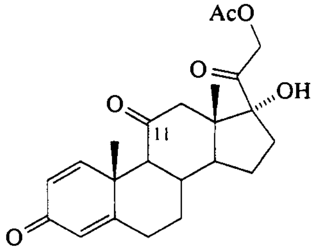
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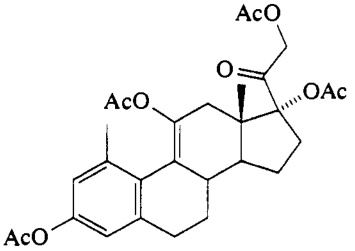
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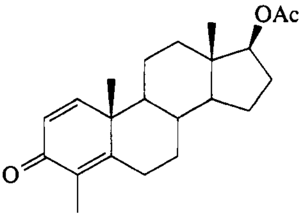
**(34)**

Not all dienone–phenol rearrangements are acid catalyzed. The 4-hydroxy-4-methyl-2,5-cyclohexadienones (**38**; R = H) and (**38**; R = Me) react in refluxing aqueous alkali to afford the methylhydroquinones (**39**; R = H) and (**39**; R = Me; 95%), respectively.[16] This is understandable as migration in an electron-rich, vinylogous α-ketol system (**40**). A different mechanism operates in the rearrangement of the decaladienone (**41**), induced by sodium hydroxide–aqueous methanol, to the tetralindiol (**42**; 76%) which appears to proceed by a retro-aldol–aldol sequence, by way of the aldehyde (**43**).[17]

The acid-catalyzed reactions so far listed in this section all involve shift of an alkyl residue. In bicyclic spirodienones, a related ring bond shift leads to ring expansion, and rearrangement to a fused bicycle. Thus the spirooxetane (**44**) is converted quantitatively into the hydroxydihydrobenzofuran (**45**) on treatment with ethanolic hydrogen chloride (preferred carbon migration),[18] and expansion of a four- to a five-membered ring is also seen in the spontaneous benzylic migration of the lactam (**46**), yielding (**47**; 62%).[19] Five- to six-membered ring size increase is observed in the conversion of the dienone (**48**) to the octahydrophenanthrol (**49**; 95%) with acetic anhydride–sulfuric acid,[20] and in the transformation of the dienone (**50**) to the tetralone derivative (**51**), with migration of the undeactivated methylene.[21] Six- to seven-membered ring expansion occurs in the reaction of the dienone oxime (**52**) with acetic anhydride–sulfuric acid, which yields the phenolic amine diacetate (**53**; 75%). This sequence probably involves addition (of acetate) then elimination to afford a spirodienimine (**54**) which reacts analogously to a dienone.[22] Interestingly the spirodienone (**55**) in aqueous citric acid reacts by a different mode of ring expansion, yielding the tropone (**56**; 80%), presumably through a tricyclic intermediary (**57**).[23]

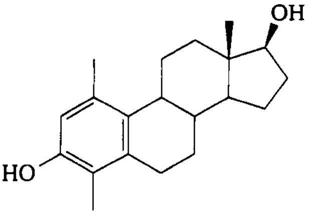

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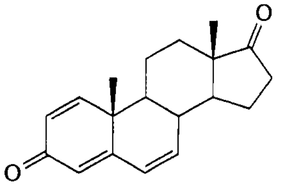

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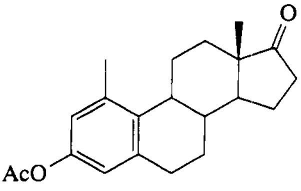

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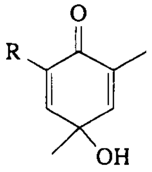

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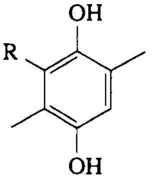

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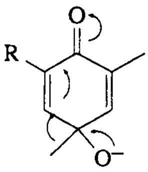

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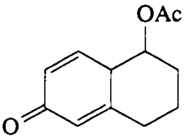

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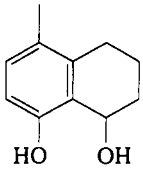

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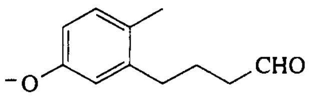

**(43)**

1,2-Aryl shifts are preferred, as expected, to competing alkyl shifts. Thus the 2,4-dienone (**58**) aromatizes quantitatively by phenyl migration, to trimethylphenylphenol (**59**),[24] and the 2,5-dienone (**60**) gives the biaryl (**61**; 51%),[25] in both cases with acetic anhydride–sulfuric acid. Suitable spirodienones react similarly, *e.g.* (**62**) yields the triphenylene derivative (**63**; 83%),[26] and the quinamide (**64**) rearranges sluggishly to the biaryl (**65**), with slow aryl migration in the protonated system.[27] Aryl shifts feature in the best-known applications of the dienone–phenol rearrangement for natural product synthesis, in the alkaloid area. Thus synthetic (±)-orientalinone (**66**) was converted into (±)-corydine (**67**) with dry methanolic hydrogen chloride (through preliminary hemiketalization) and into (±)-isocorytuberine (**68**) with an acetic acid–hydrochloric acid mixture.[28–30] Synthetic spirodienone (**69**) gave (±)-multifloramine (**70**; 45%) with concentrated sulfuric acid,[31] and its relative (**71**) rearranged with boron trifluoride to the homoaporphine (**72**) in 93% yield.[32] The dienone (**73**) also reacts by 1,2-aryl shift to give homoaporphine (**74**),[33] and the demethyl homolog (**75**) is similarly transformed to (**76**; 75%),[34] using boron trifluoride as catalyst in both cases. The homoaporphine series can also be reached from another variation on the spirodienone structure in this series (**77**), which affords (**78**) by boron trifluoride induced ring bond and aryl shifts.[33] Finally, it is worth noting the concurrent fragmentation–aryl migration involved in the transformation of (**79**) to (**80**) in a colchicine synthesis.[35]

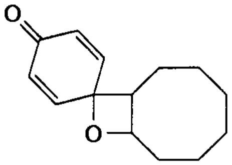

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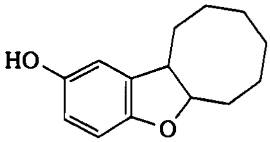

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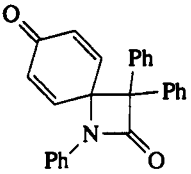

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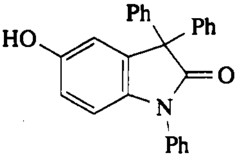
Ph
Ph
HO
O
N
Ph

**(47)**

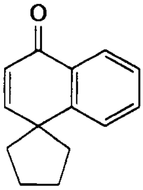

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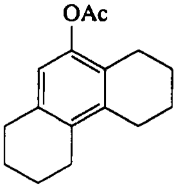

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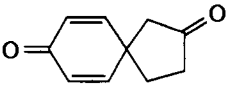

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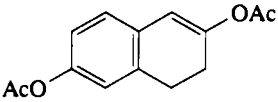

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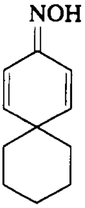

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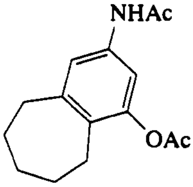

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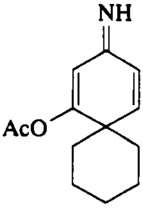

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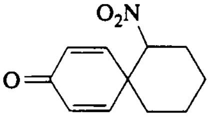

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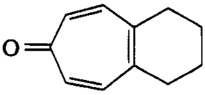

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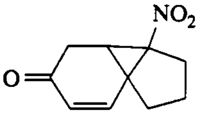

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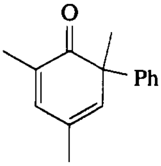

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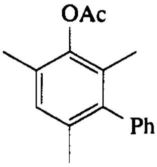

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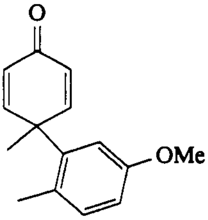

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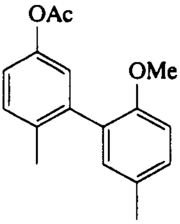

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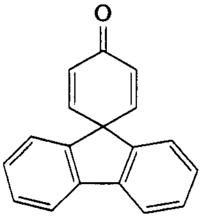

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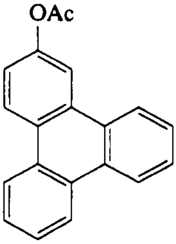

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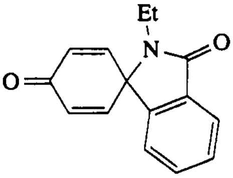

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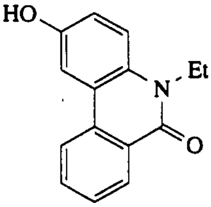

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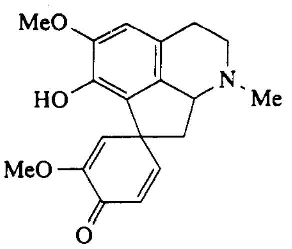
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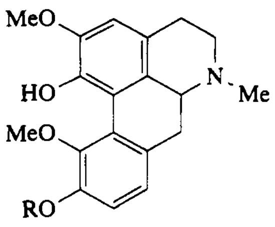
**(67)** R = Me
**(68)** R = H

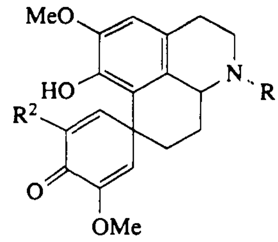
**(69)** $R^1$ = Me, $R^2$ = OMe
**(71)** $R^1$ = $COCF_3$, $R^2$ = H

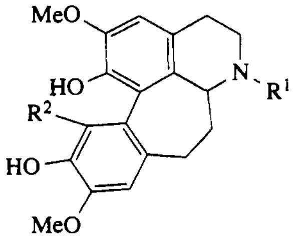
**(70)** $R^1$ = Me, $R^2$ = OMe
**(72)** $R^1$ = $COCF_3$, $R^2$ = H

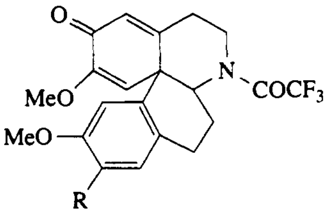
**(73)** R = OMe
**(75)** R = OH

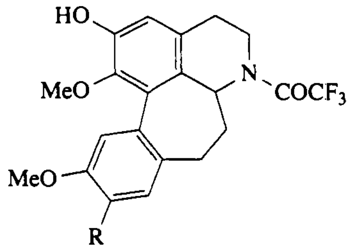
**(74)** R = OMe
**(76)** R = OH

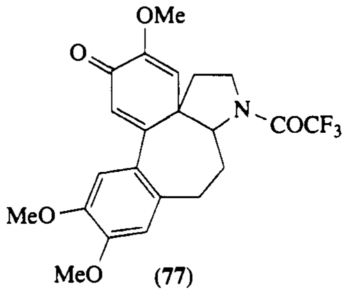
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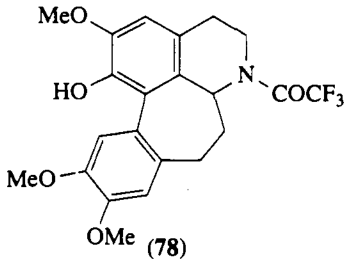
**(78)**

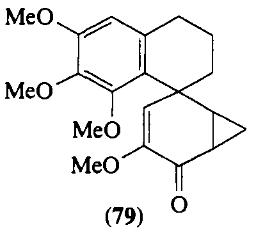
**(79)**

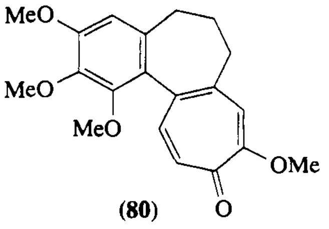
**(80)**

The last topic in this section concerns allyl shifts. This is a mechanistically complex area, in which migrations may proceed by one or more 1,2-shifts to cationic centers, or by 1,3- or 1,5-sigmatropic shifts, thermal or acid catalyzed. It is interesting that carbon–carbon bond formation is generally preferred to carbon–oxygen bond formation, even where the latter would be favored by aromaticity,[1b] as in the thermal reactions of dienones (**81**) and (**82**) which lead at *ca.* 100 °C to the new dienones (**83**) and (**84**), but not detectably to the corresponding *O*-allylphenols, *e.g.* (**85**). The 2,5-dienone (**86**) reacts rapidly in acid to give a mixture of phenols (**87**:**88** = 2:1),[36] the first by an acid-catalyzed Claisen–Cope reaction, and the second *via* a Wagner–Meerwein shift. The 1,3-shift is blocked in the 2,5-dienone (**83**), and 1,2-migration is induced on an acidic clay surface yielding (**89**; 98%).[37] Rearrangement of the 2,5-dienone (**90**) proceeds by two sequential 1,2-shifts, rather than a 1,3, yielding (**91**).[38] 1,3-Shifts are observed in the aromatization of the 2,4-dienone (**92**) in trifluoroacetic acid, yielding (**93**; 63%),[39] with its homolog (**94**) in sulfuric acid–acetic acid, giving (**95**; 83%),[36] and with the androstadienone (**96**),[40] which yields both phenols (**97**:**98** = 3:2), essentially quantitatively and stereospecifically.

In synthetic work towards tetracyclines the tricyclic dienone (**99**) was rearranged at 0 °C using boron trifluoride, to the anthraquinone (**100**; 65%) apparently by a direct 1,5-shift.[41] The quinamine (**101**) undergoes facile reorganization in hydrochloric acid to the biaryl (**102**)[42] in an aza-Claisen-like process.

Lastly, aromatization of the dienone (**103**), in sodium acetate–acetic anhydride at 140 °C, proceeds by a Favorskii-style mechanism, to afford (**104**).[43]

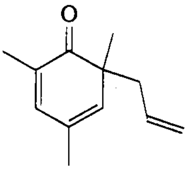

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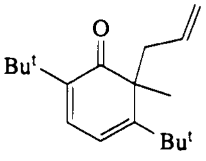

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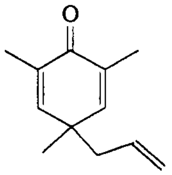

**(83)**

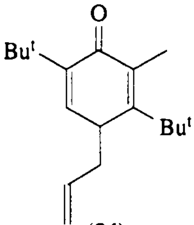

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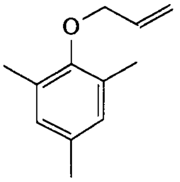

**(85)**

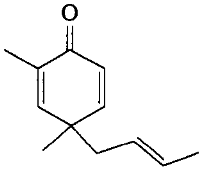

**(86)**

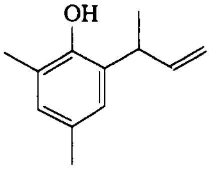

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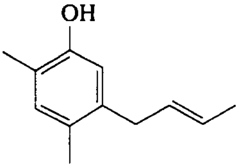

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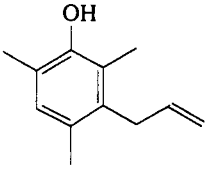

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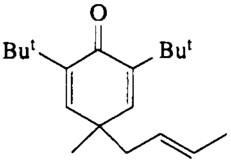

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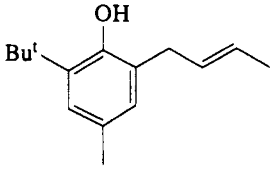

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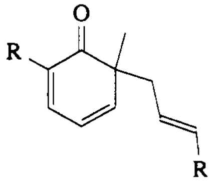

**(92)** R = H
**(94)** R = Me

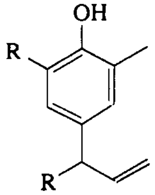

**(93)** R = H
**(95)** R = Me

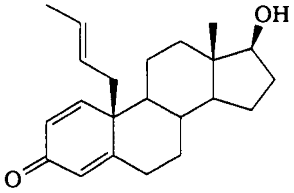

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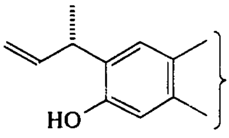

**(97)**

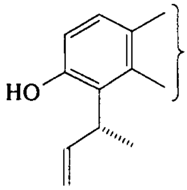

**(98)**

### *3.5.2.1.2 Rearrangements forming more than one new C—C bond*

Aromatization through sequential ring bond shifts is exhibited in the acid-catalyzed conversion of the decaladienone (**105**; R = Me) to the methyltetralol (**106**; R = Me; 57%)[44] at room temperature with acetic anhydride–sulfuric acid; lactone (**107**) very similarly rearranges to (**108**; 69%).[45] Decaladienones with an angular hydroxy, *e.g.* (**105**; R = OH), react in parallel fashion, to give, for example, (**106**; R = OH),[46,47] although their acetyl derivatives undergo oxygen migration, *vide infra*. In the steroid series the androstadienedione (**109**) rearranges in acetic anhydride–zinc chloride, with two shifts of C-9 (methine), to the 1-hydroxyandrosta-1,3,5-trienone (**110**) in 92% yield.[48] A number of similar reactions are cataloged in valuable reviews.[2] 10-Hydroxy steroids can also rearrange in this way, *e.g.* (**111**) to (**112**).[49] Although a 6,7 double bond usually impresses 1,2-methyl shifts, the androstatrienone (**113**) was converted by superacid into the ring bond rearranged product (**114**; 75%).[50] In the tetracycle (**115**) shifts of a methylene from the quaternary center, and then of a benzylic carbon, lead to the phenol acetate (**116**)[51] in 88% conversion.

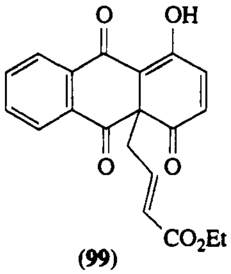
O
OH
O
O
CO2Et

**(99)**

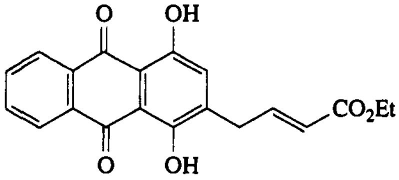
O
OH
CO2Et
O
OH

**(100)**

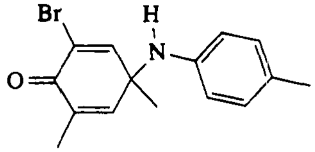

**(101)**

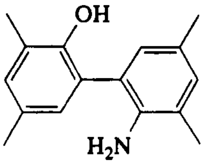

**(102)**

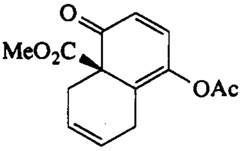

**(103)**

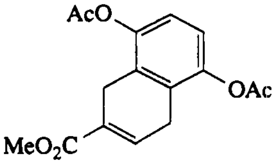
AcO
OAc
MeO2C

**(104)**

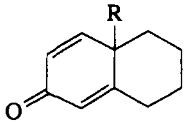

**(105)**

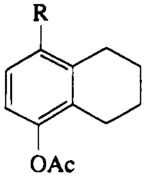

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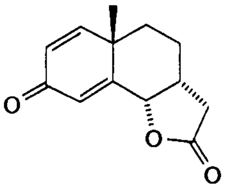

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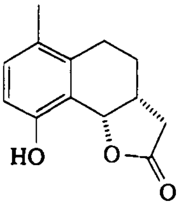

**(108)**

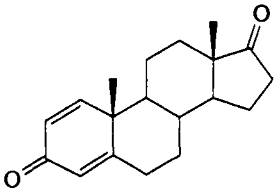

**(109)**

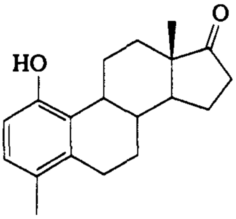

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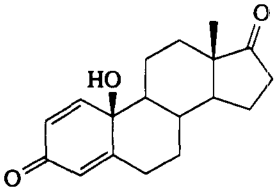

**(111)**

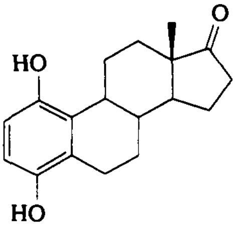

**(112)**

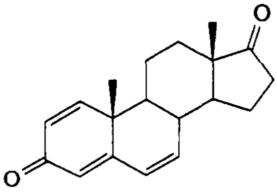

**(113)**

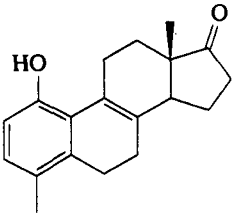

**(114)**

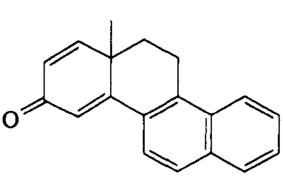

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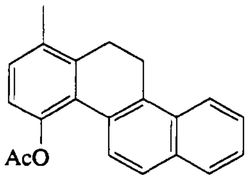

**(116)**

### 3.5.2.2 Formation of a New C—O Bond

The migration of oxygen from a quaternary center in a cyclohexadienone may be preferred to a carbon shift, when present as an ether or ester function rather than free hydroxy. Thus the *p*-quinol acetate (**117**) yields the orcinol monoacetate (**118**; 79%) on treatment at room temperature with trifluoroacetic anhydride,[52] and the *p*-quinol ether (**119**) forms the resorcinol diethyl ether (**120**; 71%) in ethanolic sulfuric acid. In the second case, hemiketalization must intervene; also some methyl shift (12%) is observed.[53] With the quinol (**121**), treatment with acetic anhydride–sulfuric acid leads to the lactone (**122**); acetylation or lactonization probably precedes oxygen shift.[54] A number of related examples can be found in the steroid area.[2,55] Thermal 1,3-shifts of *p*-quinol acetates can also be induced; acetate (**117**) yields catechol acetate (**123**; 50–60%, 45 °C) by way of isomerization of the first-formed acetate (**124**).[56] In the *o*-quinol acetate series, 1,2-acetoxy shift is seen in (**125**) → (**126**; 92%)[57] and in (**127**) → (**128**; 90%),[58] both in acetic anhydride with acid catalyst. In the 2,4-dienone (**129**), two 1,2-acetoxy shifts are required for aromatization, leading to the hydroquinone diacetate (**130**).[54]

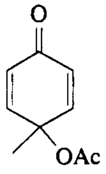

(**117**)

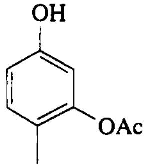

(**118**)

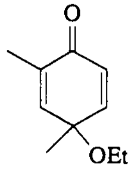

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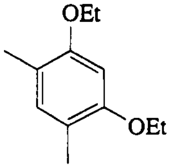

(**120**)

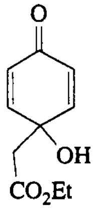

(**121**)

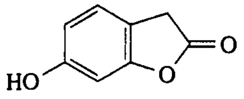

(**122**)

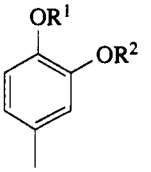

(**123**) R¹ = Ac, R² = H
(**124**) R¹ = H, R² = Ac

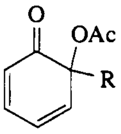

(**125**) R = Et
(**127**) R = Ph

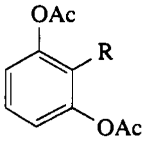

(**126**) R = Et
(**128**) R = Ph

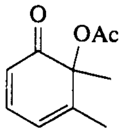

(**129**)

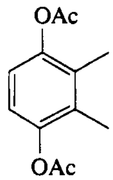

(**130**)

A number of *o*-quinol diacetates have been prepared and they rearrange smoothly to triacetoxybenzenes;[59] *o* → *o*′ migration is preferred unless the latter position is blocked or sterically crowded, when acetoxy shift is directed to another aryl site. The range of possibilities is indicated by the conversions of the *o*-quinol diacetates (**131**)–(**134**) to the 1,2,3- or 1,2,4-triacetoxybenzenes (**135**)–(**138**), in 56–90% yields.

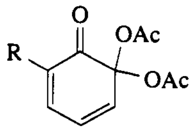

(**131**) R = H
(**132**) R = Me

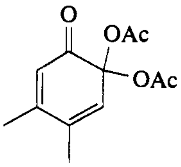

(**133**)

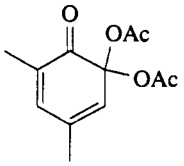

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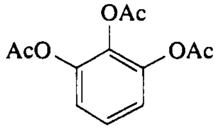

(**135**)

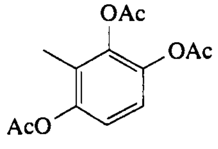

(**136**)

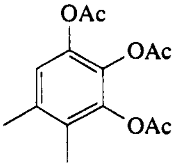

(**137**)

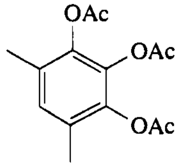

(**138**)

The reactions in this section represent useful ways of introducing oxygen into aromatic rings, for which methodology is limited, and of reaching certain substitution patterns.

Oxygen migration may be observed in spirodienones. Thus the lactone (**139**) affords dihydrocoumarins (**140**) and (**141**) in 90% and 10% yields, respectively, in acetic acid–sulfuric acid; change of reagent to dilute sulfuric acid changes the yields to 5% and 95%, respectively, nicely illustrating the fine balance between pathways in these reactions.[60] The spirodienone (**142**) undergoes *O*-shift in acid, but *C*-shift in alkali, yielding either (**143**) or (**144**).[61]

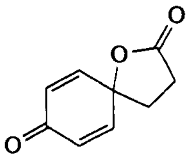

**(139)**

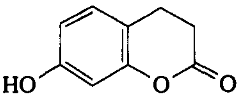

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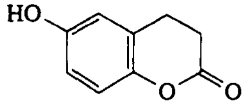

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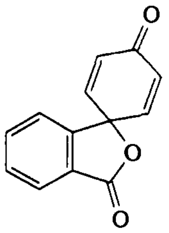

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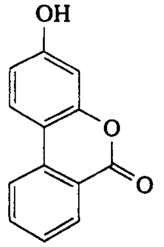

**(143)**

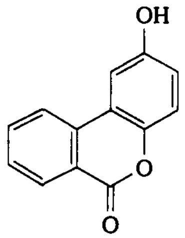

**(144)**

Finally a rare example of C—O bond formation by migration of carbon to oxygen is found in the pyrolysis of the complex spirodienone (**145**) at 205 °C, which affords the depside (**146**; 91%).[62]

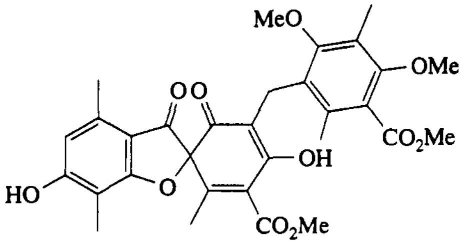

**(145)**

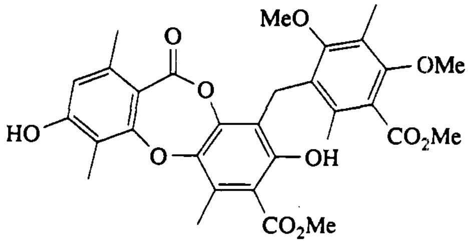

**(146)**

### 3.5.2.3 Formation of New C—C and C—O Bonds

In a number of cyclohexadienone aromatizations both new C—C and C—O bonds are formed, in multistep reactions which may still be high yielding. Thus the tetralenone (**147**) gives the trimethylnaphthol acetate (**148**; 95%) in acetic acid.[63] Both of the spiroketones (**149**) and (**150**) reorganize under acetylating conditions to the tetrahydrophenanthrol acetate (**151**).[64] The allylquinol acetates (**152**; R = H) and (**152**; R = Me) reorganize to the monacetylallylcatechols (**153**) on heating at 180–190 °C, through an initial 1,5-acetyl shift to (**154**), followed by 1,3-allyl shift and acetyl transfer between oxygens.[65]

## 3.5.3 EXTRACYCLIC BOND MIGRATION

The conventional dienone–phenol rearrangements of *o*-quinol acetates are described above. An alternative mode of restructuring to an aromatic system has been observed, exemplified by the quantitative conversion of the 2,4-dienone (**155**) on heating at 110 °C in acetic acid to the benzylic acetate (**156**).[66] The related 2,4-dienone (**157**) rearranges at 70–80 °C in dimethyl sulfoxide–sodium bicarbonate to the

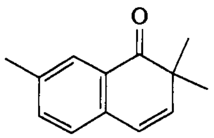

**(147)**

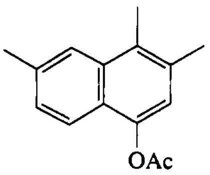

**(148)**

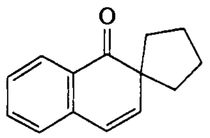

**(149)**

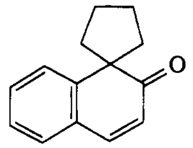

**(150)**

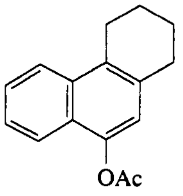

**(151)**

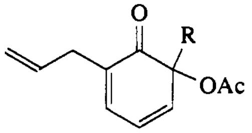

**(152)**

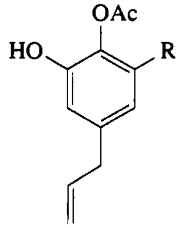

**(153)**

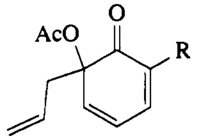

**(154)**

*m*-hydroxybenzaldehyde (**158**), in 45% yield.[67] The mechanisms by which the benzylic positions are oxidized are not known. Interestingly, pyrolysis of (**155**) at 450 °C gave the diarylethane (**159**; 37%), with some of the corresponding stilbene,[68] suggesting formation of benzylic radicals. Similar halogen migrations have been recorded. Thus the *p*-bromodienone (**160**) quantitatively converts to the benzylic bromide (**161**) on standing at 0 °C, and the di-*t*-butyl analog (**162**) similarly rearranges on brief warming, to give (**163**; 70%).[69] Related reactions occur with polyhalomethyl groups. Thus the 2,5-cyclohexadienone (**164**) yields the benzoate (**165**) on heating with benzoyl chloride to 140 °C.[70] If phosphorus pentachloride is used then the product is the trichloroethylaryl chloride (**166**; 89%), but in polyphosphoric acid the acid (**167**) is the major product (56%).[71] Again mechanisms remain obscure.

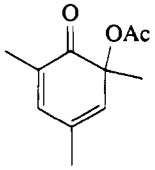

**(155)**

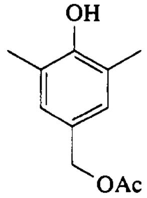

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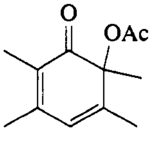

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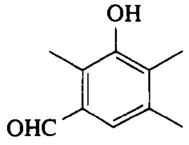

**(158)**

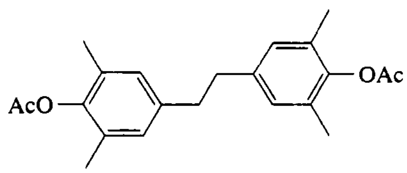

**(159)**

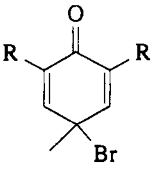

**(160)** R = Me

**(162)** R = Bu$^t$

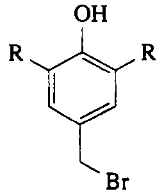

**(161)** R = Me

**(163)** R = Bu$^t$

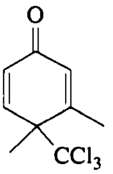

**(164)**

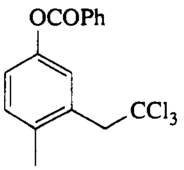

**(165)**

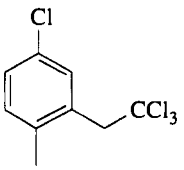

**(166)**

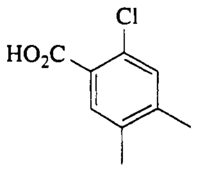

**(167)**

The last example in this section is the facile and quantitative rearrangement of the quinamine (**168**) in $10^{-5}$ M hydrochloric acid, to the aminoaryl ether (**169**), with extracyclic shift of aryl to oxygen.[72] A number of examples are known and the mechanism appears similar to the benzidine rearrangement.

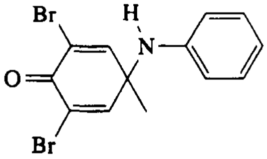

(**168**)

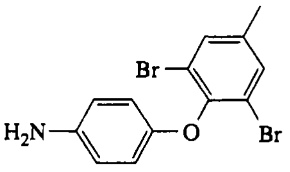

(**169**)

## 3.5.4 PHOTOCHEMICAL AROMATIZATION

The photochemistry of cyclohexadienones is a complex topic, which has been reviewed[73] and is discussed in detail elsewhere in this series. It is only appropriate here to point out that aromatization to a phenol is a possible outcome of such reactions, and indicate a very few synthetically useful examples.

The steroidal dienone (**170**) can be induced to undergo the relatively unusual reorganization to the 2-hydroxy-4-methylandrosta-1,3,5-triene (**171**), by irradiation in refluxing acetic acid;[74] although only 48% of the acetate (**171**) was isolated, the related 17-ketone (36%) was also formed. The *p*-dienones (**172**) and (**173**) are restructured on irradiation in cyclohexane with net relocation of methyl and *t*-butyl groups to afford the phenols (**174**) and (**175**) in 55% and 73% yield, respectively.[75,76] A photo-induced aryl shift in the benzylisoquinoline dienone (**176**) was employed to prepare the aporphine (**177**; 44%) *en route* to (±)-boldine.[77] The *p*-dienones (**178**; X = Cl, X = $N_3$) aromatize on irradiation to yield the alkylated p-hydroxybenzoates (**179**; *e.g.* X = $N_3$, 57%) as well as minor quantities of their isomers (**180**).[78] Mechanistic aspects of these reactions are discussed in the literature cited.

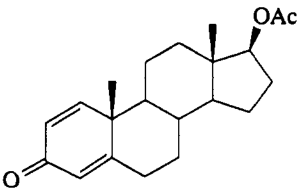

(**170**)

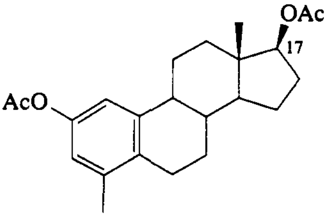

(**171**)

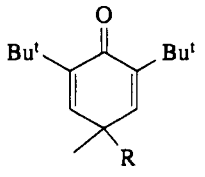

(**172**) R = $CH_2CH{=}CH_2$
(**173**) R = $Bu^t$

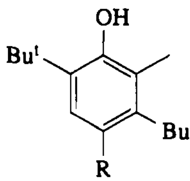

(**174**) R = $CH_2CH{=}CH_2$
(**175**) R = H

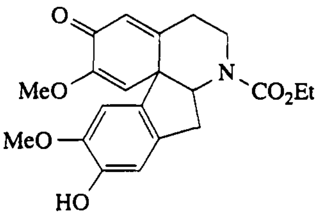

(**176**)

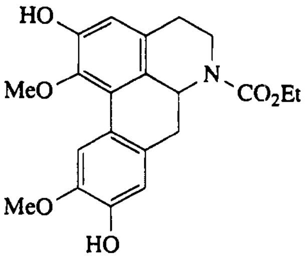

(**177**)

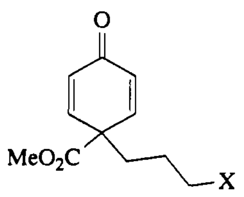

(**178**)

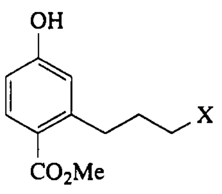

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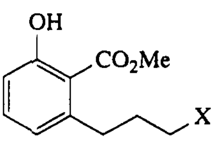

(**180**)

## 3.5.5 MISCELLANEOUS AROMATIZATION

### 3.5.5.1 Dienone Aromatization with Bond Cleavage

A group of predominantly steroid reactions involve a ring A or ring B dienone which aromatizes under reductive conditions with cleavage of a carbon fragment. In most cases[79] the angular A/B methyl is removed, as in the case of the androstatrienedione (**181**) which suffers reductive demethylation to the phenol (**182**) on brief refluxing with zinc in aqueous pyridine,[79a] in 93% yield. Less commonly, fragmentation of the C(9)—C(10) ring bond is engineered, as in the reductive elimination of the 11-hydroxy derivative (**183**) with samarium diiodide to the B-secophenol (**184**; 38%).[80] Fragmentations have also been ingeniously employed in alkaloid syntheses. Thus the spirodienone (**185**) aromatized during alkaline deacylation; *in situ* reduction of the resulting imine gave the *o,o'*-bridged biaryl (**186**; 80%), a key intermediate in both *in vivo* and *in vitro* formation of erysodienone.[81] The ketal (**187**), formed conventionally from the corresponding dienone, fragments (increased *N*-basicity) during reduction of the formamide function with lithium aluminum hydride to the *N*-methyl compound, to yield *O*-methylerybidine (**188**; 81%).[82] In a synthesis of L-tyrosine, the precursor (**189**), from L-glutamic acid was aromatized in dilute alkali, with decarboxylation, to form *N*-BOC-Tyr (**190**; 98%).[83] Outside the natural product area the spirodienone (**191**) achieved aromaticity in acid with C—C cleavage, giving (**192**; 40%),[84] and the epoxide (**193**) rearranged with C—O cleavage to yield naphthaldehyde (**194**; 92%).[85]

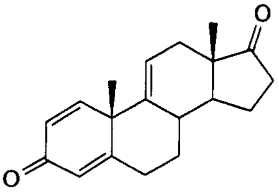

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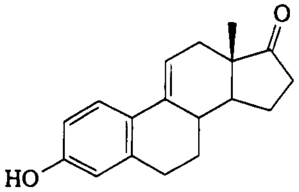

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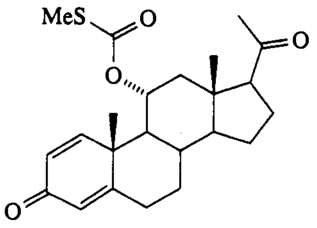

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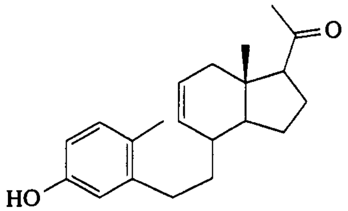

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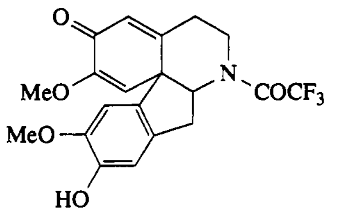

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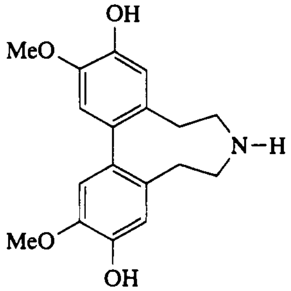

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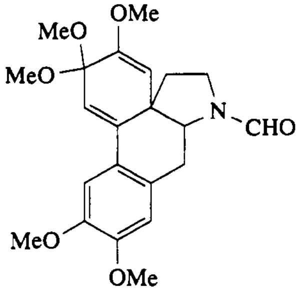

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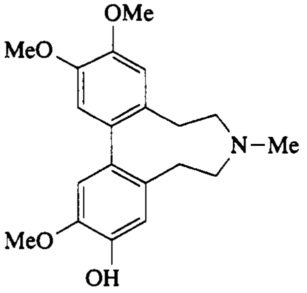

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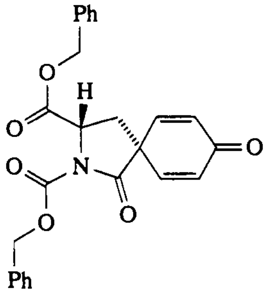

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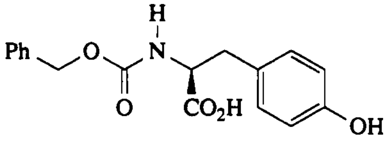

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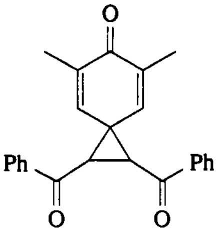

**(191)**

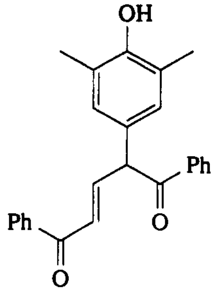

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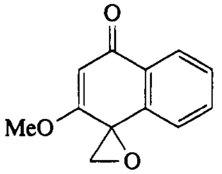

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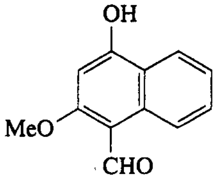

**(194)**

### 3.5.5.2 Rearrangements in Dienone Reactions with Nucleophiles

Cyclohexadienones containing a leaving group, such as *o*- or *p*-quinol acetates, undergo various reactions with nucleophiles, most often involving an addition–elimination sequence to form a phenolic product with nucleophile as a substituent. Thus the *o*-quinol acetate (**195**) reacts with secondary amines, cyanide ion, or diethyl sodiomalonate to give the phenols (**196**; X = $NR_2$),[86] (**196**; X = CN),[87] and (**196**; X = CH $(CO_2Et)_2$);[88] Wittig reagents behave similarly.[89] The site of attack may be modified by other functions, *e.g.* azide ion adds to C-2 in aldehyde (**197**) yielding azidophenol (**198**) as product.[90] Thiols behave in a different fashion from other nucleophiles, for example thiophenol substitutes the dienone acetate (**199**) at C-4 rather than C-3, to afford (**200**) as the major product;[91] various mechanisms are possible, including $S_N2'$ substitution–enolization. More complex sequences occur when the dienone carbaldehydes (**201**) and (**197**) are treated with cyanide. In the first case, methanolic cyanide affords the cyano ester (**202**), but cyanide in dimethylformamide gives the aldehyde (**203**), in good yield in both cases.[92] The isomer (**197**) reacts with cyanide in methanol to provide the ester (**204**; 85%) without incorporating cyanide.[92] For mechanistic discussions see ref. 1b. Related transformations occur with *p*-dienones, *e.g.* (**205**) yields cyanophenol (**206**), on addition–elimination with cyanide ion.[87] Different patterns of reactivity emerge with different nucleophiles; thus (**205**) reacts with phenyl- or methyl-magnesium bromide to afford phenols (**207**; R = Ph and R = Me) respectively. This is a result of 1,2-addition

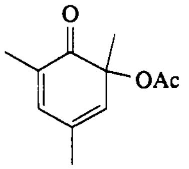

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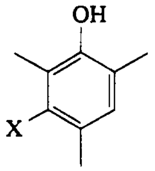

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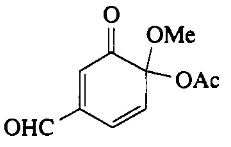

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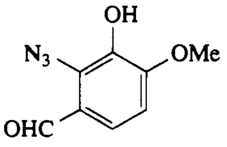

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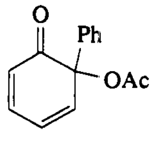

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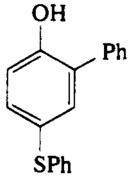

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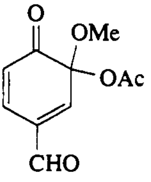

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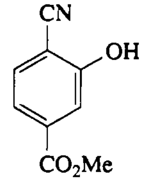

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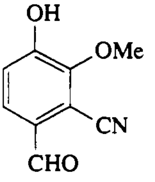

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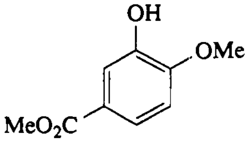

**(204)**

followed by loss of acetate and 1,2-shift of phenyl (or methyl), whereas (**205**) and phenyllithium yield (**208**) *via* 1,2-addition, deacylation, loss of benzylic oxygen function and 1,2-methyl shift.[93] Another interesting conversion occurs when the spirodienone (**209**) is treated with diacetyl sulfide and boron trifluoride, giving rise to the thiolactone (**210**), in a useful C—S bond-forming process.[94] Finally in this section we remark on the curious transformation of the dichloromethyldienone (**211**) into the acid (**212**) by hydroxide ion in ethanol;[95] an intermediate (**213**) is implicated. The conversion (**214**) → (**215**) also requires a bridged intermediate.[96]

### 3.5.5.3 Tropolone–Phenol Rearrangements

A number of cases are known of ring contraction of tropolones to phenols, with extrusion of the carbonyl group as carboxylate or carbon dioxide. Examples are the conversions of the benzotropolone (**216**) to the naphthol ester (**217**; 73%) with methanolic potash;[96] the pyridinotropolone (**218**) to the quinoline (**219**; 50%) in dilute alkali;[97] the aminotropolone (**220**) to the methylsalicyclic acid (**221**; 82%) on diazotization;[98] and the tropolonecarboxylate (**222**) to the dicarboxylic acid (**223**; 78%) on brief alkali fusion.[99]

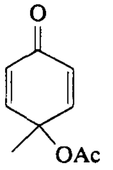

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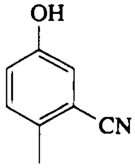

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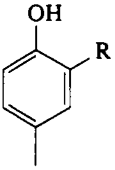

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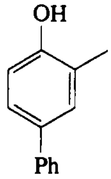

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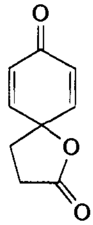

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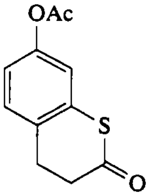

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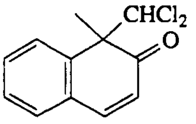

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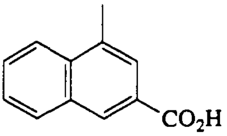

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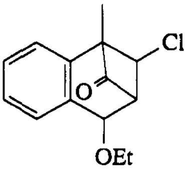

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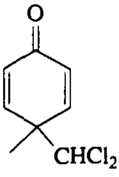

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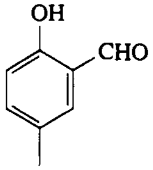

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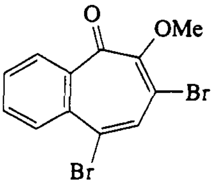

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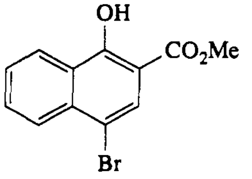

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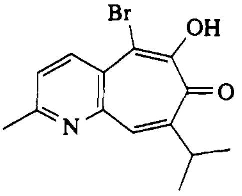

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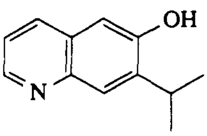

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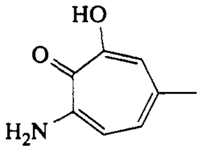

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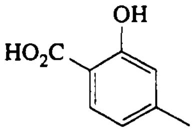

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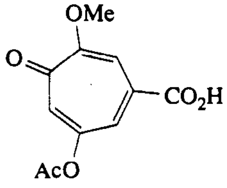

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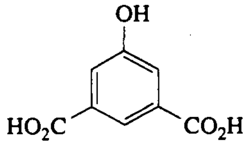

**(223)**

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# 3.6

# Benzil–Benzilic Acid Rearrangements

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## 3.6.1 INTRODUCTION

In 1838 von Liebig[1] described the hydroxide ion induced transformation of an α-diketone, benzil (**1**), into the salt of an α-hydroxy acid, benzilic acid (**2**; equation 1). This process is probably the first molecular rearrangement reaction to be recognized, and hence occupies a special place in both synthetic organic and physical organic chemistry. In its strictest sense the benzil–benzilic acid rearrangement refers to the reaction of bisaryl α-diketones with hydroxide ion leading to aryl migration. Generally, however, the reaction is chronicled in a wider sense to include the migrations of other groups (*e.g.* alkyl, acyl, nitrogen), which result from the treatment of vicinal dicarbonyl systems with hydroxide, methoxide, *t*-butoxide and other bases. This wider interpretation is used in this chapter.

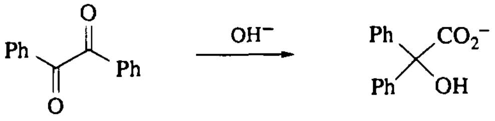

**(1)** **(2)**

(1)

## 3.6.2 SCOPE AND MECHANISM

### 3.6.2.1 Benzilic Acid Type Rearrangements

The prototype reaction is the conversion of glyoxal into glycolic acid (equation 2),[2] and here the benzilic acid rearrangement mechanism coincides with that for an intramolecular Cannizzaro reaction. The reaction is observed with other purely aliphatic α-diketones such as *t*-butyl 2,3-dioxobutyrate[3] and cyclohexane-1,2-dione (equations 3 and 4),[4] but the scope is limited in the aliphatic series by competing (*e.g.* aldol) reactions. Suitably constructed heterocyclic systems also rearrange, and the conversion of alloxan (**3**) into alloxanic acid (**4**) was among the first of the benzilic acid rearrangements to be discovered (equation 5).[5]

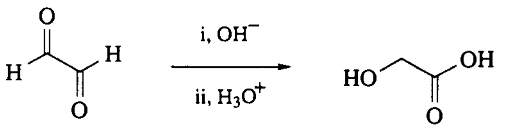

(2)

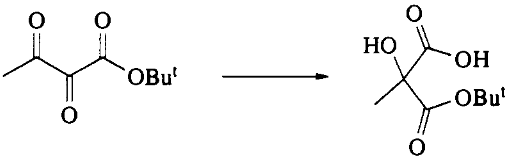

(3)

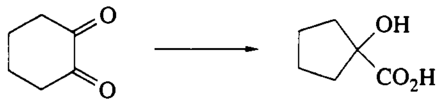

(4)

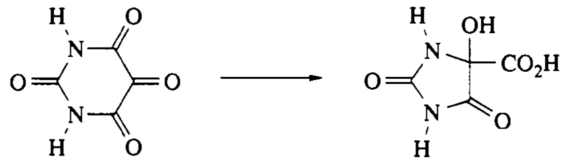

(**3**) (**4**)

(5)

Much of the definitive mechanistic evidence has been provided by studies of the reaction of hydroxide ion with benzil (**1**) and substituted benzils.[6] The presently accepted mechanism is that which was proposed by Ingold[7] as early as 1928, and is shown in Scheme 1; see, however, Section 3.6.2.2. The initial step involves the fast reversible addition of hydroxide to one of the carbonyl groups. In unsymmetrical α-diketones (**5**) the more electrophilic carbonyl (*i.e.* the one with the lower LUMO) is attacked preferentially. Thus, if $R^2$ in (**5**) is more electron withdrawing than $R^1$, the concentration of intermediate (**6**) greatly exceeds that of (**7**), and the rearrangement follows the (**6**) → (**9**) → (**8**) pathway. In physical organic terms, the observed rate constant ($k_{obs}$) is the product of the equilibrium constant ($K$) for the first step, and the rate constant ($k$) for the rate-determining second step. Thus $k_{obs} = Kk$ and, of the two variables, the key term is $K$, since the rate-limiting transition state is not far along the reaction coordinate leading from (**6**) to (**9**). It follows, therefore, that it is the more electron-withdrawing substituent $R^2$ which migrates (in the absence of steric problems).[6,8]

With simple unsymmetrical α-diketones (**5**) it appears to be immaterial which substituent migrates, for the product structure is the same. Much of the information concerning migratory aptitudes has come from studies of benzils possessing one $^{14}C{=}O$ group.[6] Hydroxide ion attack at the labeled center results in the migration of the attached aryl substituent with the production of carboxy-labeled benzilic acid. The rearrangement is irreversible. Similar labeling studies in other α-dicarbonyl systems[3,9-13] have indicated the preferential migration of H over Ph, Ph over Me, $CONH_2$ over Ph, $CO_2R$ over $CO_2^-$, and $CO_2R$ or $CO_2^-$ over cyclopropyl. These results are all consistent with initial hydroxide ion addition to the more electrophilic C=O group.

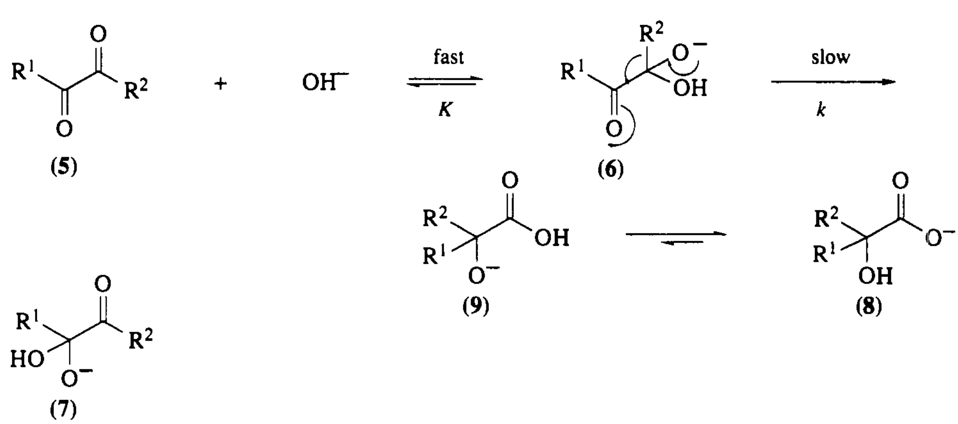

Scheme 1

When $R^1$ and/or $R^2$ in (**5**) possess a chiral center, both the initial attack of hydroxide ion and the subsequent migration can be stereoselective, regioselective and stereospecific. Steroidal α-diketones are suitable vehicles for such studies, and their chemistry is considered later (see Section 3.6.3.5).

The results obtained for alloxan (**3**)[9] and related N-heterocycles[14] are much more complex. The central of the three contiguous C=O groups is the most electrophilic part of the molecule (**3**) and, indeed, alloxan readily forms a stable hydrate through the addition of water to this center. In alkaline solution, and depending on pH, the mono-, di- and tri-anions (**10**)–(**12**) exist; (**10**) is much more stable than the corresponding species for benzil and does not rearrange. Thus, isotopic labeling of this C-5 carbon atom affords, on rearrangement in aqueous alkali, C-4 ring-labeled alloxanic acid. The carboxylic acid group contains none of the isotope, which would be the requirement if (**10**) was involved directly in the rate-determining rearrangement to the anion of (**4**). Furthermore, analysis of the products of alkaline rearrangement of C-4 labeled (**3**), and its methyl- and phenyl-substituted derivatives, is consistent with the exclusive shift of nitrogen over carbon. In the rearrangement of *N*-phenyl[4-$^{14}$C]alloxan the shift of NPh occurs to the exclusion of NH, whereas in the case of *N*-methyl[4-$^{14}$C]alloxan the migration ratio of NMe to NH is about 4:1. Clearly, then, C-5 is the migration terminus, and rearrangement is triggered by hydroxide ion attack at C-4 (or the symmetry related C-6 position). Specific catalysts such as borate, which is ineffective for the benzil–benzilic acid transformation, enhance the electrophilicity of C-4 by coordinating the carbonyl oxygen atom, as shown in formula (**13**).

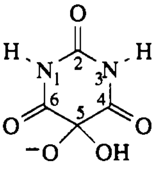

(**10**)

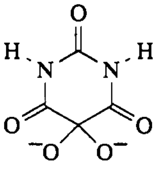

(**11**)

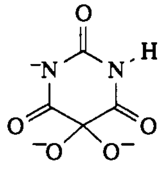

(**12**)

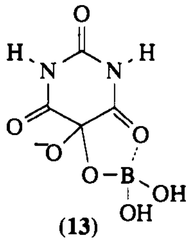

(**13**)

### 3.6.2.2 The Benzilic Ester Rearrangement

A somewhat confusing situation existed in the early literature concerning the precise timing of the migration and proton transfer steps and the apparent specificity of hydroxide ion, because of the failure of alkoxides to give benzilic esters.[6] However, benzil is a good oxidizing agent for alcohols in the presence of their alkoxides,[15] and Doering and Urban showed[16] that the failure of the rearrangement with primary and secondary alkoxide ions was due to competitive hydride transfers (a Meerwein–Ponndorf–Verley–Oppenauer type of reaction). Nevertheless, boiling anhydrous methanolic sodium methoxide gave methyl benzilate (68%), benzoin (9.6%) a product of the above redox reaction, and benzilic acid (9.7%) which probably arose from a *B*AL2 mechanism (*i.e.* *S*N2 attack by methoxide on the methyl carbon atom of methyl benzilate). The reaction of (**1**) with sodium ethoxide in dry ethanol at reflux gave a mixture of rearrangement, oxidation and cleavage products. The reaction of (**1**) with potassium *t*-butoxide in boiling benzene is especially clean, affording *t*-butyl benzilate in 90% yield. The reaction fails with the weakly basic phenoxides, presumably because of an unfavorable equilibrium (*cf.* the formation of **6**) in the initial attack on the α-diketone.

Rearrangement of benzil in nonhydroxylic solvents by nonoxygen bases such as sodium amide[17] or acetylide,[18] followed by mild hydrolytic work-up, afforded not the expected benzilamide or 1,1-diphenyl-2-oxobut-3-yn-1-ol but rather benzilic acid itself. As the mild conditions were insufficient to bring about the hydrolysis of the amide, and the only source of the required oxygen atom was another molecule of benzil, Selman and Eastham[6] suggested the mechanism given in Scheme 2. The consistent recovery of starting material in these reactions is accounted for by the mechanism — which was also suggested as a pathway by which benzilic acid could form in some of the alkoxide-initiated processes (X = OR).

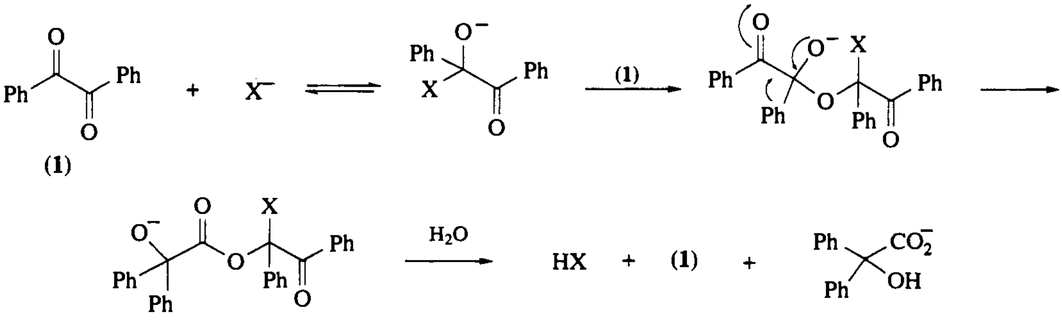

**Scheme 2**

In recent years, single-electron transfer (SET) mechanisms have been suggested for a number of organic processes, including a number of base-catalyzed reactions. These include the Wittig 1,2-rearrangement (see Chapter 3.11, this volume), the Cannizzaro reaction,[19] Meerwein–Ponndorf–Verley reductions,[20] and also the benzilic acid (or ester) rearrangement.[21] Benzil is not rearranged by lithium dialkylamides (Scheme 2; X = $NEt_2$, $NPr^i_2$), but these bases are of low nucleophilicity. Reaction with lithium *t*-butoxide in benzene–THF gives intense violet-colored paramagnetic solutions which exhibit an ESR spectrum consistent with the presence of the lithium semidione of benzil (**14**). On the basis of this evidence the SET mechanism given in Scheme 3 was proposed.[21] Although the $Bu^tOLi$ reaction gave *t*-butyl benzilate in high yield (96%), similar reaction using LiOEt failed to cause rearrangement, but the semidione was detected. In a somewhat related case, the condensation products of 3-amino-2,4-dicyanocrotonic esters with benzils (see Section 3.6.3.2) undergo a benzilic acid type rearrangement in aqueous alkali, and $^1H$ NMR–CIDNP experiments support the assumption of a partial radical character for the processes.[22] Hence, the SET mechanisms do deserve careful consideration, but the problem is that such proposals are highly controversial at the present time,[23] and it is not yet clear if the SET mechanism for benzilic acid rearrangements will achieve general acceptance. The mechanism raises a number of questions on interpretation. For example, the semidione species is a radical anion, four canonical forms of which are shown in formulae (**14a–d**). It is not yet clear if the electron density distribution in (**14a–d**) finds a satisfactory parallel in the experimentally determined migratory aptitudes of the substituents $R^1$ and $R^2$. Likewise, it is not clear why phenoxide anions, which are efficient one-electron transfer agents, fail to promote the rearrangement.

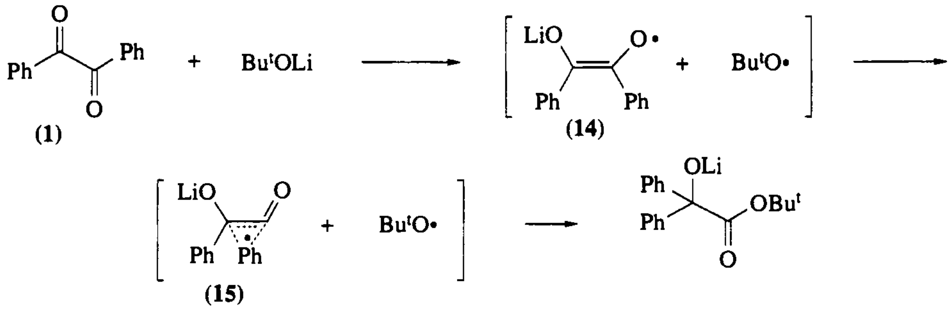

**Scheme 3**

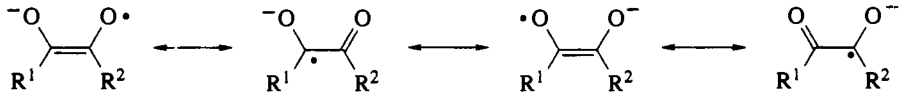

(14a) (14b) (14c) (14d)

Hence, although the presence of radicals has been demonstrated, it has yet to be shown that the SET pathway is more than a minor competitive reaction, and for the remainder of this review the anionic mechanism set out in Scheme 1 will be assumed to apply.

## 3.6.3 THE CHEMISTRY OF BENZILIC ACID REARRANGEMENTS

### 3.6.3.1 Reaction Conditions

The sensitivity, or otherwise, of the α-dicarbonyl substrate determines the reaction conditions. However, variations in conditions are not especially large. Although 1 equiv. of base may be used, more usually an excess is employed — sometimes 10 equiv. or more to accelerate the reaction. Studies on the reaction of hydroxides with benzil indicate that the rate depends to some extent on the cation,[24a] and it can be advantageous to use $Ba(OH)_2$ rather than the more usual NaOH or KOH.[24b] With hydroxide ion, favored solvents are water and aqueous ethanol. Heterogeneous conditions, for example potassium hydroxide and diethyl ether[25] or sodamide and toluene,[17,26] have also been employed. The reactions are conducted at room temperature (sometimes requiring up to 4 d) or under reflux (10 min–24 h). With methoxide or *t*-butoxide the corresponding anhydrous alcohol or benzene are employed as solvents.[16,21]

### 3.6.3.2 Bisaryl α-Diketones

A detailed *Organic Synthesis* procedure is available for the conversion of benzil into benzilic acid.[27a] It is advantageous to isolate the acid as its potassium salt, for this enables the removal of the more soluble potassium benzoate, which results from a competitive cleavage reaction. Benzilic acid is then obtained in 77–79% yield by acidifying an aqueous solution of potassium benzilate. Since benzil is usually obtained by the oxidation of benzoin, both this conversion and rearrangement can be performed in tandem by using alkaline sodium bromate.[27b] Thus, benzilic acid is obtained in 84–90% yield from benzaldehyde *via* benzoin.

The rearrangement of substituted benzils is facilitated by electron-withdrawing substituents in the *meta* or *para* positions (*m* > *p*); steric hindrance retards the rate of rearrangement of *ortho*-substituted aryl groups. Some typical examples of the rearrangement of simple bisaryl α-diketones are summarized in Table 1. The very high reactivity of decafluorobenzil is noteworthy; quite exceptionally the rate of the benzilic acid rearrangement exceeds that for hydride transfer reduction by ethoxide ion (see Section 3.6.2.2) and ethyl decafluorobenzilate is obtained in 90% yield in the benzilic ester rearrangement.[32] The analogous reaction with sodium methoxide was found to occur at –78 °C. The similar reaction of

**Table 1** Rearrangement of Substituted Benzils

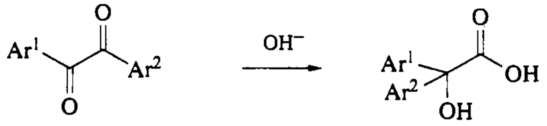

| *Ar*$^1$ | *Ar*$^2$ | *Temperature* (°C) | *Time (h)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| Ph | 4-$ClC_6H_4$ | 25 | 72 | 70 | 28 |
| Ph | 2-$MeC_6H_4$ | 80 | 0.17 | 80 | 29 |
| Ph | 4-$MeOC_6H_4$ | 80 | 0.17 | 60 | 28, 30 |
| 4-$Pr^iC_6H_4$ | 4-$Pr^iC_6H_4$ | 80 | — | 70 | 31 |
| 2-OH-5-$BrC_6H_3$ | 2-OH-5-$BrC_6H_3$ | 100 | 17 | 68 | 24 |
| $C_6F_5$ | $C_6F_5$ | 25 | 0.08 | 83 | 32 |
| 2-Furyl | 2-Furyl | 25 | 24 | 88 | 25 |

decafluorobenzil with pentafluorophenyllithium gave the pentafluorophenyl migration product, $(C_6F_5)_2C(OH)COC_6F_5$, after low temperature hydrolysis (see Section 3.6.3.7).

The generality of the rearrangement is further illustrated by the reaction of 2,2′-furil with hydroxide ion in dry ether (Table 1).[25] Likewise, 2,2′-pyridil is rearranged in hot methanol solution (40 min) to give the sodium salt of 2,2′-pyridilic acid (86%).[33] Acidification, however, affords bis(2-pyridyl)methanol by decarboxylation since 2,2′-pyridilic acid (**16**) is structurally similar to a β-keto acid. Benzilic rearrangement of 2,2′-pyridil with methanolic nickel(II) and cobalt(II) acetates results in the formation of metal complexes of 2,2′-pyridilic acid (**17**; 92%). A plausible mechanism is summarized in Scheme 4.[34] Rearrangement is also observed with 2,2′-quinaldil, but benzil, 2,2′-furil or 1-phenyl-2-(2′-pyridyl)ethane-1,2-dione are not susceptible to these metal template reactions.

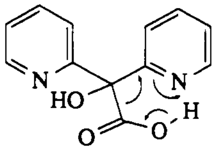

**(16)**

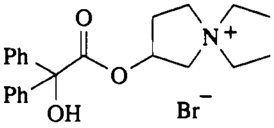

**(18)**

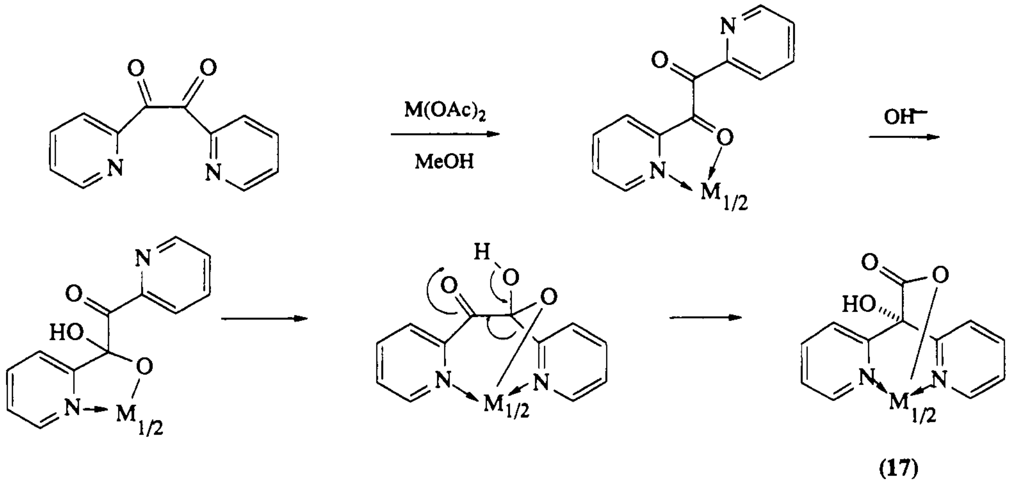

Scheme 4

Simple benzilic acid derivatives frequently show pronounced pharmacological activity.[35] For example, the ester (**18**) is an anticholinergic and spasmolytic agent (Minelsin, Ortyn). The reaction of benzil with urea in ethanol in the presence of potassium hydroxide affords 5,5′-diphenylhydantoin (**22**),[36] the sodium salt of which is the anticonvulsant Dilantin. The probable mechanism is shown in Scheme 5, the function of the hydroxide ion being the deprotonation of the initial adduct (**19a**), thereby triggering the benzilic rearrangement of the anion (**20**). The corresponding reaction with *N*-methylurea gives 3-methyl-5,5-diphenylhydantoin (**21b**; 95%), the regioselectivity resulting from the preferential formation of (**19b**) through the attack by the more nucleophilic nitrogen center. Substituted benzils[37] and ureas[36] or thioureas[38] generally react to give analogous hydantoins; however, condensation reactions without rearrangement compete in some cases.

In somewhat similar chemistry, a one-step synthesis of 4-cyano-3,3-diaryl-5-methyl-2-oxo-2,3-dihydropyrroles (**23**) is available through the reaction of benzils with acetonitrile in the presence of sodium hydride (Scheme 6).[39] Likewise, the base-catalyzed addition of malononitrile to benzil[40] yields 2-benzoyl-2-phenylethylene-1,1′-dicarbonitrile (**24**) which, in the presence of aqueous alkali, undergoes 1,2-aryl migration (Scheme 7) and cyclization, yielding the succinimide (**25**).[41] Condensation of benzils with 3-amino-2,4-dicyanocrotonic esters gives the ylidene cyanoacetates (**26**), which rearrange to the ylidene pyrrolidines (**27**) in the presence of aqueous alkali (Scheme 8); $^1$H NMR–CIDNP experiments indicate that radical intermediates are formed under the rearrangement conditions.[22] The regiochemistry of the initial condensation is determined by the more electrophilic of the two carbonyl groups of the benzil.

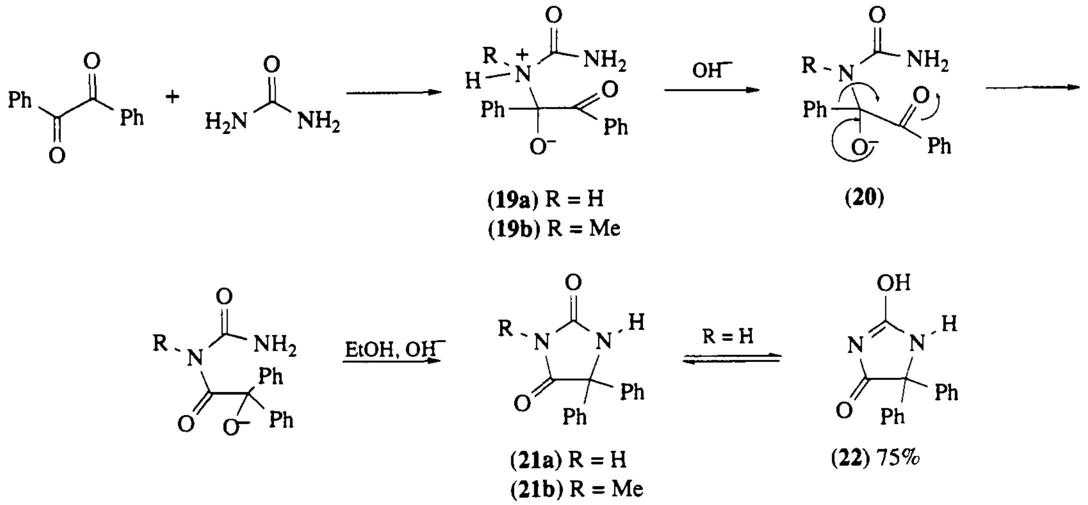

(19a) R = H
(19b) R = Me
(20)
OH⁻
EtOH, OH⁻
R = H
(21a) R = H
(21b) R = Me
(22) 75%

Scheme 5

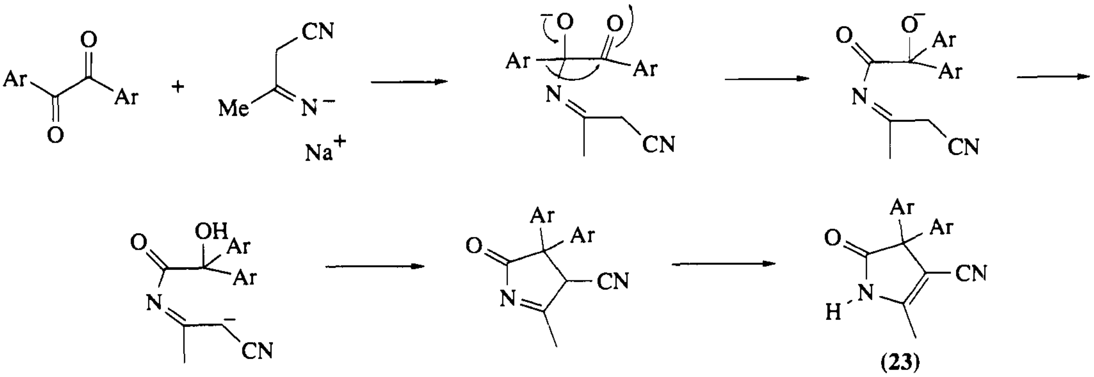

Scheme 6

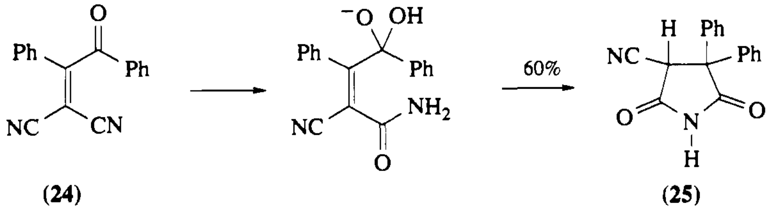

Scheme 7

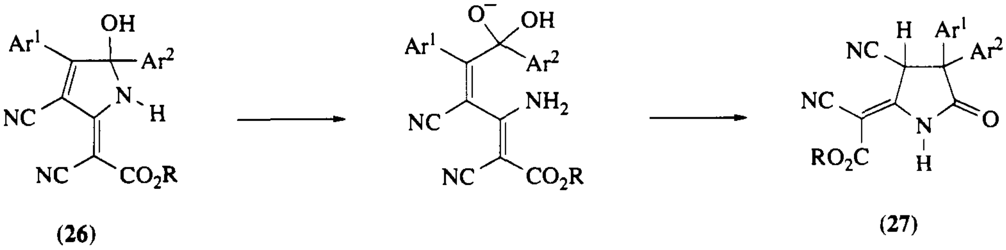

Scheme 8

### 3.6.3.3 Quinones

The benzilic rearrangement of an *o*-quinone results in ring contraction. Among the earliest recorded examples is the synthetically useful conversion of phenanthroquinones into 9-hydroxyfluorenecarboxylic acids (equation 6).[42–46] As with the benzilic acids, compounds such as (**28**) are susceptible to oxidative decarboxylation, especially under acidic conditions. Simply boiling a solution of (**28**) in oxygenated water gives the 9-fluorenone derivative.[44] The phenanthroquinones are readily prepared through the chromium(VI) oxidation of phenanthrenes. When phenanthrene derivatives are oxidized with alkaline permanganate, oxidation to the quinone and benzilic acid rearrangement occur in tandem; furthermore, permanganate cleaves α-hydroxy acids, and the 9-fluorenone is thus obtained directly.[45]

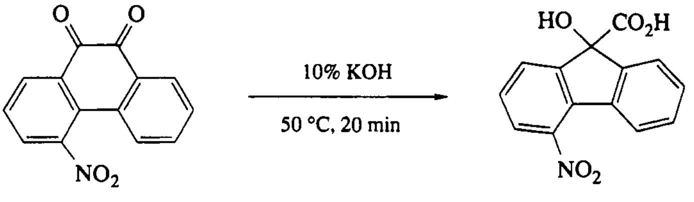

(**28**)

(6)

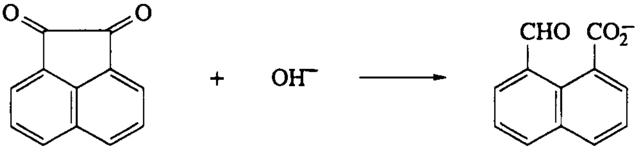

(7)

The outcome of the reaction of acenaphthoquinone with hydroxide ion is quite different. Benzilic rearrangement, which would lead to a highly strained four-membered ring, is not observed. Instead, simple cleavage occurs to give naphthaldehyde-9-carboxylate (equation 7).[24a] Despite the fact that the benzilic acid and ester rearrangements have been shown to be irreversible, they apparently cannot be employed routinely in the construction of strained rings (see Section 3.6.3.5). This contrasts with the semibenzilic mechanism (*e.g.* Scheme 9)[47] which operates in certain base-induced rearrangements of α-halo ketones when the conventional Favorskii mechanism is not possible (see Section 3.6.3.7).

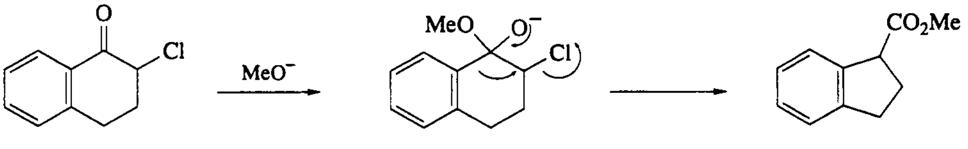

**Scheme 9**

Annelated quinones such as phenanthroquinone are best regarded simply as bisaryl α-diketones. The benzilic acid rearrangement mechanism does not figure large in the chemistry of the simpler benzoquinones, presumably because there are too many other opportunities for reaction, such as oxidation and reduction, condensation, Michael addition and retro-aldol cleavage. However, benzilic rearrangements do occur, and may not be uncommon in the oxidative rearrangements of hydroxyquinones.[48] The Hooker oxidation of 2-hydroxy-3-alkyl-1,4-naphthoquinones by alkaline permanganate gives the next lower homolog, and it has been shown[49] that the alkyl and hydroxy groups exchange places. The mechanism shown in part in Scheme 10 has been proposed for the Hooker oxidation (and the related $H_2O_2/OH^-$ oxidation),[49,50] and contains a benzilic acid ring contraction step. The R group in (**29**) is usually saturated, but examples in which R contains unsaturation, alcohol, ether or carboxylic acid functionality have also been studied. When R is a large group (*t*-butyl or cyclohexyl), treatment with 5% aqueous alkali in the absence of oxygen leads to the formation of 2-alkylindenone-3-carboxylic acids (**31**) in high yield *via* the benzilic acids (**30**), which may be isolated under buffered conditions.[51,52] An analogous transformation is involved in the base-promoted rearrangement of the natural pigment dunnione (**32**) into allodunnione (**33**).[53]

The rearrangements of hydroxy-1,4-benzoquinones in alkali are more complex.[48] Under conditions in which polyporic acid (**34**) is converted, by way of retro-aldol ring cleavage and benzilic rearrangement, into α-benzyl-β-phenylsuccinic acid, *cis*- and *trans*-α-benzylcinnamic acid and oxalic acid, atromentin

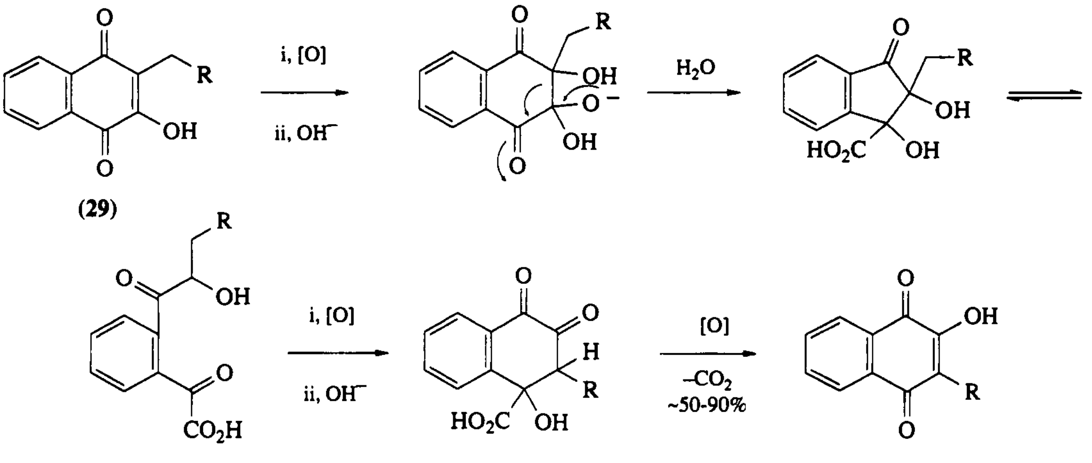

Scheme 10

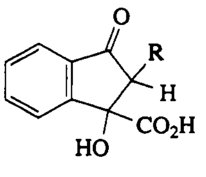

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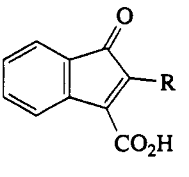

(31)

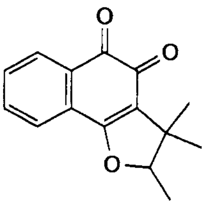

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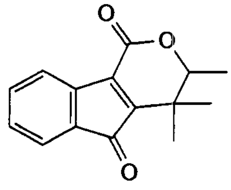

(33)

(35) gives the lactone (36), which affords the analogous cinnamic acid only on boiling in 50% alkali.[54,55] Analogously, 4-hydroxycyclopentane-1,3-diones are available in good yield from 2,6-dihydroxy-1,4-benzoquinones by base-induced benzilic rearrangement followed by decarboxylation; equation (8) is fairly typical.[48,55]

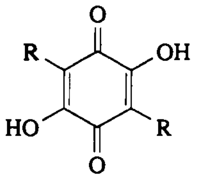

(34) R = Ph
(35) R = 4-HOC$_6$H$_4$

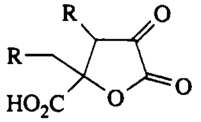

(36) R = 4-HOC$_6$H$_4$

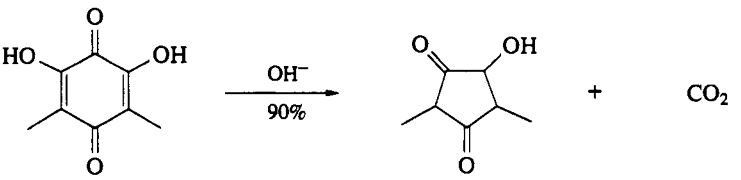

(8)

### 3.6.3.4 1-Alkyl-2-aryl-1,2-dicarbonyl Systems

The simplest of such systems is phenylglyoxal (PhCOCHO), which undergoes H migration to give mandelic acid (PhCHOHCO$_2$H; 72.5%) on reaction with barium hydroxide.[13,56] Likewise, the reaction of α-(4-isobutylphenyl) β-methyl diketone with 10% aqueous sodium hydroxide–xylene mixture at 100 °C for 5 h affords a 96% yield of α-(4-isobutylphenyl)-α-hydroxypropionic acid (4-Me$_2$CHCH$_2$C$_6$H$_4$C(Me)OHCO$_2$H) on work-up.[57] The rearrangement of both methyl phenyl diketone and α,α-dibromopropiophenone (PhCOCBr$_2$Me) occurs with 100% phenyl migration;[10] the yield of atrolactic acid (PhC(Me)OHCO2H) is rather low since aldol condensation competes. It is essential, therefore, to keep the concentration of the diketone low to limit the rate of the competing bimolecular reaction.

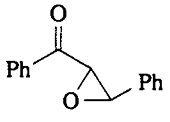

**(37)**

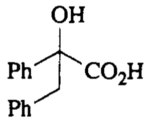

**(38)**

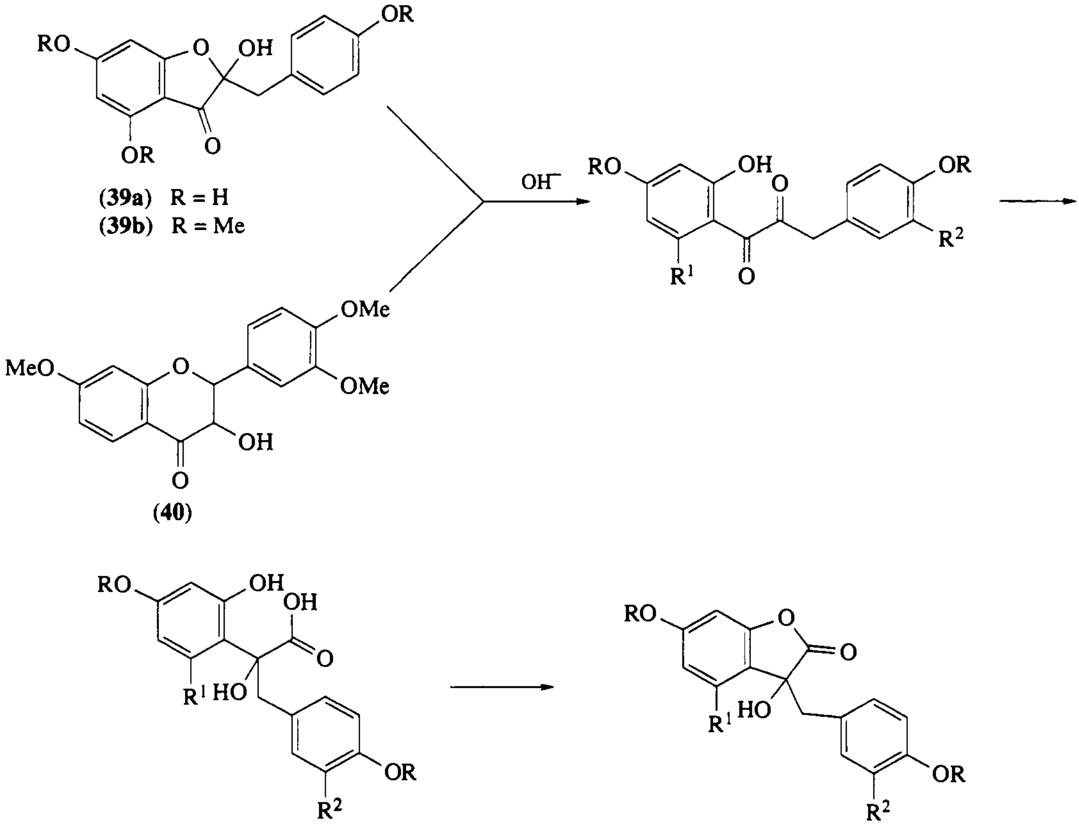

**(39a)** R = H
**(39b)** R = Me

**(40)**

**(41)** $R = R^2 = H; R^1 = OH$
**(42)** $R = Me; R^1 = H; R^2 = OMe$
**(43)** $R = Me; R^1 = OMe; R^2 = H$

**Scheme 11**

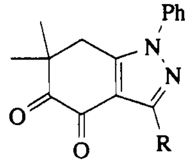

**(44)**

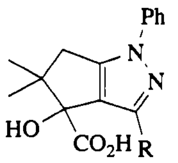

**(45)**

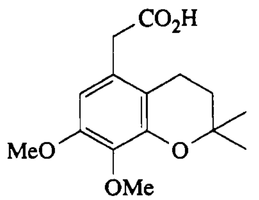

**(46)**

The reaction of benzylideneacetophenone oxide (**37**) with aqueous sodium hydroxide in ethanol at reflux for 1.5 h affords, on work-up, a 72% yield of the acid (**38**). The reaction proceeds *via* benzyl phenyl diketone, and isotopic labeling indicates that exclusive benzyl migration occurs.[58] Benzyl 2-hydroxyphenyl diketones are available through the base-promoted ring scission of 2-benzyl-2-hydroxy-2*H*-benzo[*b*]furan-3-ones (*e.g.* the hardwood extract maesopsin **39a**)[59] and 3-hydroxyflavanones (*e.g.* **40**).[60] Hence, under alkaline conditions rearrangement products are formed (*i.e.* 3-benzyl-3-hydroxy-3*H*-benzo[*b*]furan-2-ones, respectively **41** and **42**) as shown in Scheme 11. A photochemical equivalent of the benzilic acid rearrangement has also been observed in this series. Thus, irradiation of 4,4′,6-tri-*O*-methylmaesopsin (**39b**) in THF–water at 350 nm afforded the rearrangement product (**43**) in modest yield.[61]

The cyclopentapyrazoles (**45**; R = H, Me) are obtained in 67% and 54% yields, respectively, by benzilic acid rearrangement of the corresponding indazolediones (**44**).[62] This ring contraction has many analogs in the next section, and may occur during alkaline permanganate oxidations of suitable substrates. For example, oxidation of fuscinic acid dimethyl ether (**46**) affords (**48**) and (**49**), implicating the α-diketone (**47**) as a common intermediate.[63]

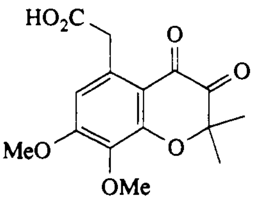

(**47**)

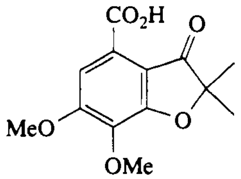

(**48**)

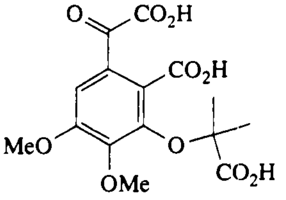

(**49**)

### 3.6.3.5 Aliphatic and Alicyclic α-Diketones

Glyoxal is the simplest member, and is readily rearranged in aqueous alkali to glycolic acid (equation 2).[2] This and similar rearrangements of simple aliphatic α,β-dicarbonyl and α,β,γ-tricarbonyl systems are of mechanistic rather than synthetic interest and importance. However, in handling such compounds for other synthetic purposes it is necessary to recognize their lability to base. In the rearrangement of *t*-butyl α,β-dioxobutyrate, which exists in aqueous solution as the hydrate $MeCOC(OH)_2CO_2Bu^t$, exclusive 1,2-shift of the $CO_2Bu^t$ group occurs (equation 3).[3] Likewise, in alkaline medium ethyl cyclopropane-2,3-dioxopropionate is transformed into $Pr^nC(OH)(CO_2H)_2$ by rearrangement only of $CO_2Et$ or $CO_2^-$ (not cyclopropyl)[12] and only $CONH_2$ migration occurs with the compounds $ArCH_2COC(OH)_2CONH_2$.[12]

Compounds which are converted into α-diketones by base are susceptible to benzilic acid rearrangement. Especially common is the base-catalyzed dehydration of α,β-dihydroxycarbonyl compounds, and the transformation of glyceraldehyde into lactic acid (Scheme 12) is a simple example of α-hydroxy acid formation by this route.[64] The higher carbohydrates also undergo similar alkali-induced degradative rearrangements,[65] but here an α-ketol rearrangement (see Section 3.6.3.7), for example (**50**) → (**51**) in Scheme 13,[66] precedes the formation and benzilic rearrangement of the α-diketone. α,β-Dihydroxy ketones are also formed in the ring opening of α,β-epoxy ketones by hydroxide, and hence produce the rearranged α-hydroxy acids by way of the intermediate α-diketone; an example, (**37**) → (**38**), was given earlier.[58]

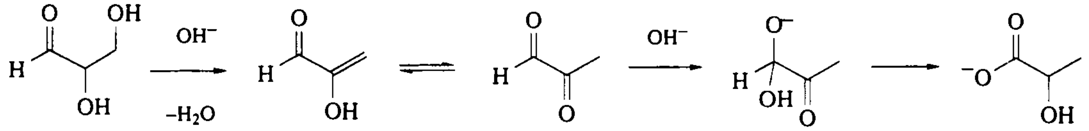

**Scheme 12**

The ring contraction rearrangement of alicyclic α-diketones is much more valuable from the synthetic viewpoint (*e.g.* equation 4). There are several routes available for the synthesis of α-diketones from monoketones. These include: direct oxidation using selenium dioxide; permanganate or osmium tetroxide addition across the double bond of an enone followed by base-promoted elimination of water; bromination to give the dibromo ketone followed by hydrolysis; condensation with 4-nitroso-*N*,*N*-dimethylaniline followed by acidic hydrolysis — but there are many others. The bromination–hydrolysis route has been extensively studied by Wallach.[4] The conversion of menthone into 1-hydroxy-

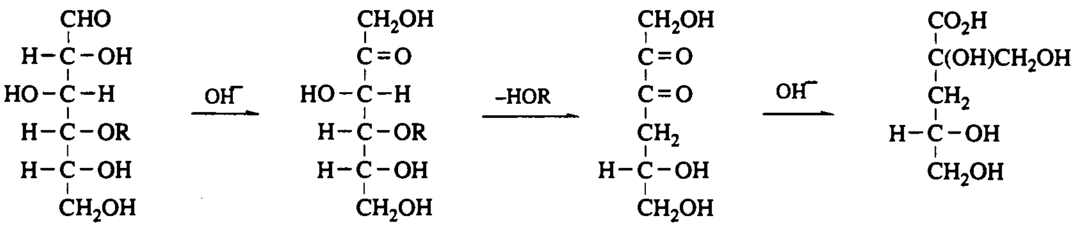

(50) (51)

Scheme 13

2-isopropyl-5-methylcyclopentanecarboxylic acid (**56**) is fairly typical. In the dibromination of menthone it was proven that the bromine atoms are not attached to the same carbon atom, but rather the dibromide has the structure (**52**). The dihydroxy ketone formed in the initial hydrolysis step (**53**) presumably is transformed (*cf.* ref. 4) into the necessary α-diketone (**55**; shown in a monoenolic form, a diosphenol) by sequential α-ketol rearrangement (**53**) → (**54**) and dehydration (**54**) → (**55**; Scheme 14). The same acid (**56**) is formed in the cognate reaction of carvomenthone, the reaction also proceeding *via* α-diketone (**55**).

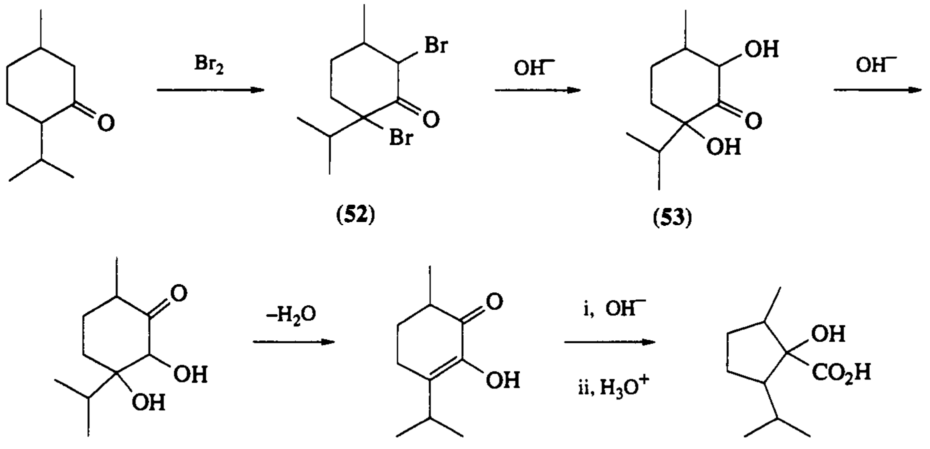

(52) (53)

(54) (55) (56)

Scheme 14

The general strategy for ring contraction also works well with more elaborate molecules. Regiospecific sulfenylation of the diketone (**57**) followed by acetoxylation afforded the α-acetoxy sulfide (**58**; 68%).[67] Hydrolysis and *in situ* rearrangement was effected with aqueous potassium hydroxide, and oxidative cleavage of the crude α-hydroxy acid (**59**) gave the perhydroindanone (**60**; 50%), a potential intermediate in the synthesis of taxanes. Relatively unstrained cage ketones can also be ring-contracted by employing the benzilic acid rearrangement strategy (for example equation 9).[68a] There are few examples of the production of strained rings. However, cyclobutane-1,2-diones have been shown to undergo ring contraction to α-hydroxycyclopropanecarboxylic acids and derivatives.[68b] Relatively little attention has been paid to the use of other bases for promoting rearrangement. Cyclohexane-1,2-dione reacts in this manner with arylbiguanides (**61**) and with *N*-amidino-*O*-alkylisoureas (**62**) to give the heterocyclic derivatives (**63**) in fair yield (*cf.* Scheme 5).[69]

Considerable interest has been shown in the rearrangement of the α-diketones of steroids and of di- and tri-terpenoids. Of particular interest is the abutment of the reaction center to a chiral system of rigid stereochemistry. This allows an examination of the regiochemistry and the stereospecificity and stereoselectivity of the reaction with alkali. The isomeric diosphenols (**64**) and (**65**), respectively 3-hydroxy-5α-cholest-3-en-2-one and 2-hydroxy-5α-cholest-1-en-3-one, are interconvertible in the presence of acid or base. On reaction of either with potassium hydroxide in propanol a single benzilic acid rearrangement

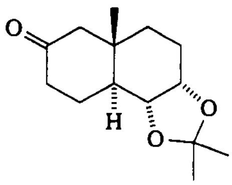

**(57)**

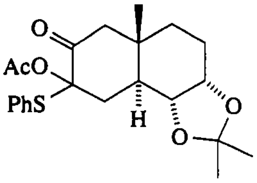

**(58)**

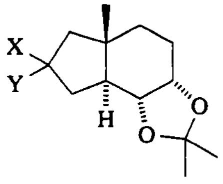

**(59)** X = OH; Y = $CO_2H$
**(60)** X = Y = O

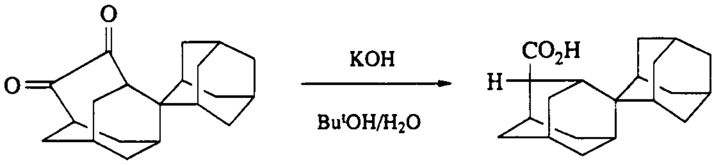

(9)

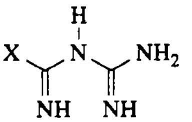

**(61)** X = 4-$RC_6H_4NH$
**(62)** X = RO

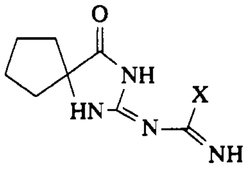

**(63)**

product, A-nor-5α-cholestan-2-ol-2-carboxylic acid, was obtained.[70] The necessary common intermediate is presumably the α-diketone (**66**; Scheme 15) which can yield four possible hydroxide addition products arising from α- or β-attack at either of the two carbonyl groups. It was thought that of these (**67**) should be the most stable through the minimization of 1,3-diaxial interactions and oxygen–oxygen dipolar repulsions, and by stereospecific rearrangement should give 2β-hydroxy-2α-carboxy-A-nor-5α-cholestane (**68**). However, the configuration of the single product was not determined. Likewise, the diosphenol (**69**), 5α-pregn-1-en-2-ol-3,20-dione, was rearranged by treatment with potassium hydroxide in ethanol or propanol to give a single product, A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid (90%).[71] The configuration of the substituents at C-2 in the hydroxy acid (**70**) was tentatively assigned as 2β-hydroxy-2α-carboxy on the basis of similar reasoning to the above. There have been several other reports in this area of benzilic acid rearrangements in which only a single α-hydroxycarboxylic acid was isolated.[70]

Reaction of a solution of 3α,17β-diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one (**71**) in aqueous propanol with potassium hydroxide, followed by an acidic work-up, afforded the lactone (**75**; 76%). Three events are involved in this transformation (Scheme 16), namely retro-aldol equilibration to give the *cis*-fused C–D-ring system (**72**) → (**73**), stereoselective benzilic acid rearrangement (**73**) → (**74**) to

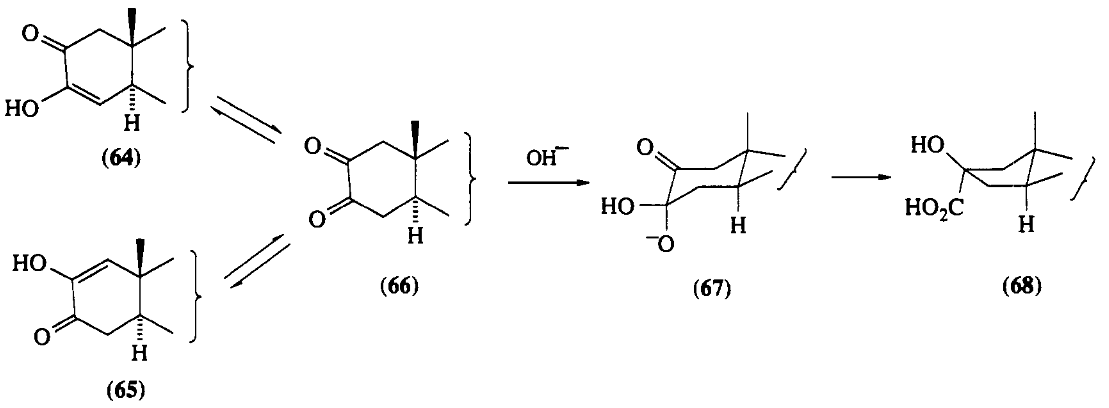

Scheme 15

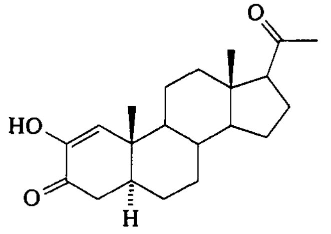

**(69)**

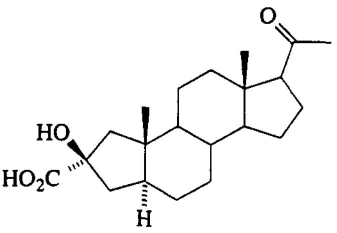

**(70)**

provide the 11β-carboxylic acid function, and finally lactonization (**74**) → (**75**).[72] Since the benzilic acid rearrangement has been shown to be irreversible,[6,73] the formation of the lactone (**75**) indicates that the transformation (**73**) → (**74**) is a highly stereoselective process.

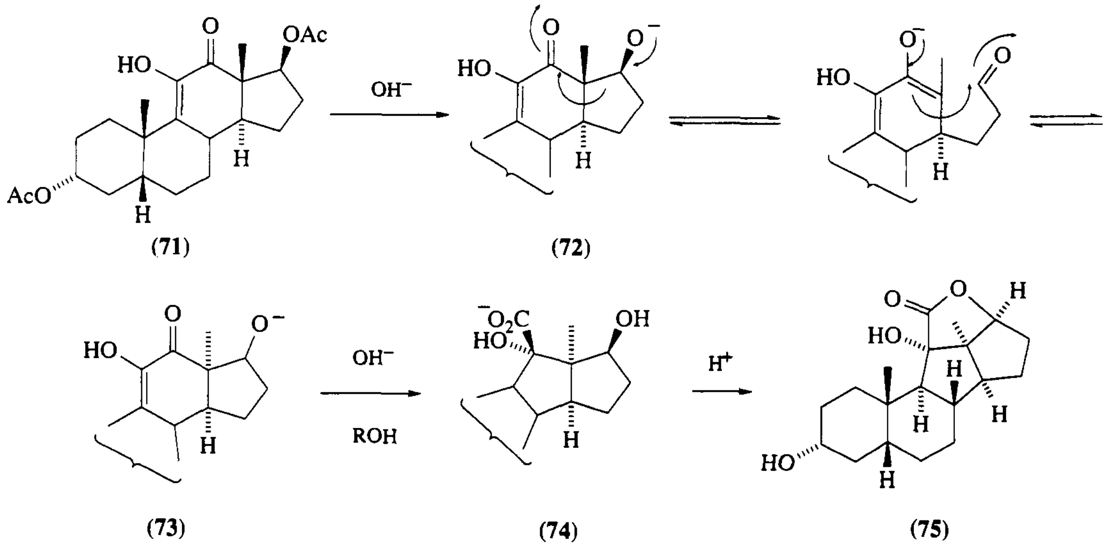

**Scheme 16**

The major product of the rearrangement of 5α-cholestane-3,4-dione (**76**) was shown to be 3α-carboxy-A-nor-5α-cholestan-3β-ol (**78**). By using (**76**) labeled with $^{14}C$ at C-4, it was shown that the carboxy group of (**78**) arose from C-3 of (**76**). The evidence, and the steric constraints imposed by the steroidal system, favors stereo- and regio-specific α-attack by hydroxide to give (**77**) and stereoselective rearrangement *via* a chair-like transition state to give the product (**78**; Scheme 17).[11] Rearrangement of 4,4-dimethyl-5α-cholestane-2,3-dione (**79**) gave only the hydroxy acid (**81**) with the carboxy group α. Labeling experiments indicated that 94% of the benzilic rearrangement resulted from attack at the C-3 carbonyl through a quasi-chair transition state. The remaining 6% of the rearrangement resulted from attack at the C-2 carbonyl through a quasi-boat transition state.[74] The similar reaction of 5α-cholestane-2,3-dione (**80**) gave the two hydroxy acids (**82**; 85%) and its epimer at C-2 (15%). Labeling studies reveal a more complex regio- and stereo-chemical situation than for the conversion of (**79**) into (**81**).[75]

The stereochemistry of the hydroxy diacid obtained by the rearrangement of the dioxo ester (**83**), itself derived from (–)-abietic acid, has been determined unequivocally, and is as shown in (**84**).[76] Other stereospecific benzilic acid rearrangements have been reported, including ring contraction of a D-homo-17,17a-dione,[77] and contraction of ring A in ursolinic acid[78] and betulinic acid.[79]

### 3.6.3.6 Heterocyclic Systems

Relatively little attention has been paid to this important area, and much of the definitive work has centered upon studies of the rearrangement of alloxan[5] and substituted alloxans[9] (equation 5). The essen-

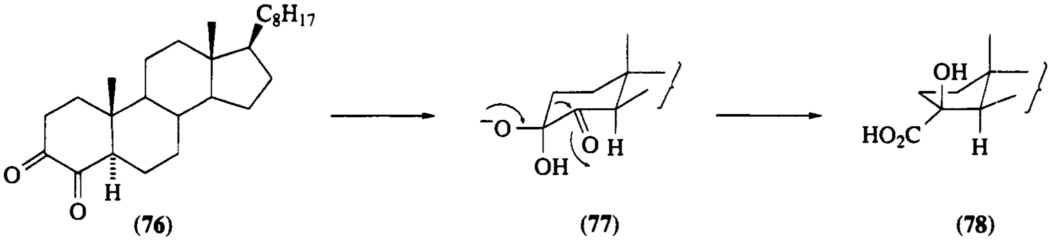

**Scheme 17**

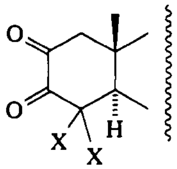

**(79)** X = Me
**(80)** X = H

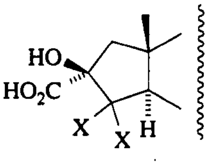

**(81)** X = Me
**(82)** X = H

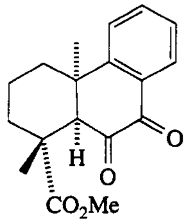

**(83)**

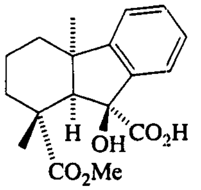

**(84)**

tial features concerning mechanism and regiochemistry were covered in Section 3.6.2.1. These studies indicated the exclusive shift of nitrogen over carbon. A similar situation is found in the reactions of the phthalonimides (**85**) and (**86**) with aqueous alkali to give 3-hydroxyphthalimidine-3-carboxylic acids (**87**).[14] Indeed, the ring-shrinking process can be conducted on the 1,3(2,4)-isoquinolinediones (**88**) or their monothio analogs (**89**), and their substituted derivatives, by the expedient of using excess hydrogen peroxide in aqueous alkali at room temperature (*ca.* 3 h or less). The phthalonimide intermediates (**85**) and (**86**) are converted rapidly under the reaction conditions into the hydroxy acids (**87**). These can be isolated provided that the excess peroxide is destroyed before acidification (46–81%), otherwise oxidative decarboxylation occurs and the corresponding phthalimides are formed. Kinetic measurements on the amide quinisatine (**90**) have also revealed that the rearrangement involves the shift of the carboxyamide group.[12b] The base-promoted conversion of 2-phenylindolone (**91**) into 3-phenyldioxindole (**92**), which occurs readily, may also be classified as a benzilic acid type rearrangement.[24,80]

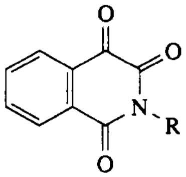

**(85)** R = H
**(86)** R = Me

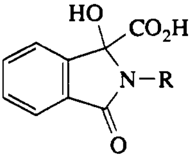

**(87)**

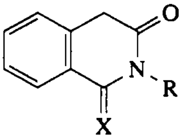

**(88)** R = H, Me; X = O
**(89)** R = H, Me; X = S

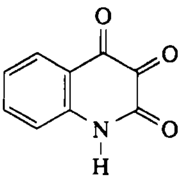

**(90)**

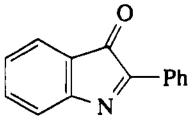

**(91)**

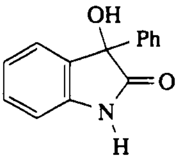

**(92)**

### 3.6.3.7 Related Rearrangements

The key steps in several additional rearrangements can be represented as in equations (10) and (11), and they are effectively the 'back-end' and the 'front-end' respectively of the benzilic acid rearrangement itself. Selman and Eastham[6] and others[8,81] have provided a brief analysis of such processes, and their scope. These reactions are referred to by a variety of names; for equation (10) Selman and Eastham suggest they be called 'α-oxo alcohol rearrangements', but the 'tertiary α-ketol rearrangement' or 'acyloin rearrangement'[81] are more common labels. Equation (11) differs from a benzilic acid rearrangement only inasmuch as the displacement occurs on a $\sigma$-bonding electron pair rather than the $\pi$-bonding electron pair of a carbonyl group, and has been referred to earlier as a 'semibenzilic rearrangement' (see Scheme 9). $Z^-$ is a stable anion such as halide or tosylate, and the reaction may operate when the Favorskii mechanism is not possible. The subsequent loss of the carboxylate proton from (**93**; R = H) under the basic conditions of equation (11) renders the process irreversible. However, even with alkoxides as bases (*e.g.* **93**; R = Me) the inherent stability of the carboxylic ester function and the lack of electron pressure on the α-carbon atom, makes the reaction irreversible in the general sense. No such situation exists for equation (10), and its reversible nature frequently leads to the formation of mixtures of products. The tertiary α-ketol rearrangement occurs upon treatment of a tertiary alcohol containing an α-oxo group with base, or by reaction of an α-diketone with 1 equiv. of a Grignard reagent. The base-catalyzed reactions of α-hydroxyketosteroids have been especially well-studied. The reader is referred to the above-mentioned review articles for further insights into this area.

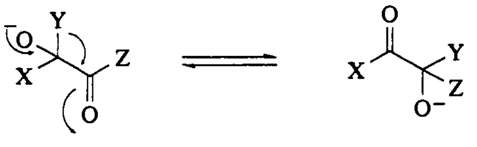

(10)

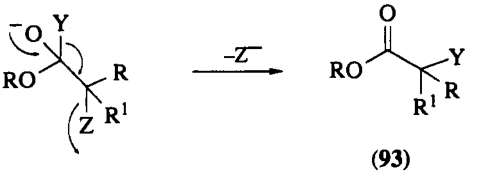

(**93**)

(11)

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# 3.7
# The Favorskii Rearrangement

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## 3.7.1 INTRODUCTION

The rearrangement of α-halo ketones under the influence of base was first described by Favorskii in 1892,[1,2] and the general scope of the reaction and the mechanistic implications have been the subject of a number of reviews.[3–12] In its most generally useful form, α-halo ketones undergo skeletal rearrangement when treated with a nucleophilic base (hydroxide, alkoxide or amine) to produce salts, esters and amides respectively (Scheme 1). With polyhalogenated ketones unsaturated acid derivatives are produced, as shown in Scheme 2.

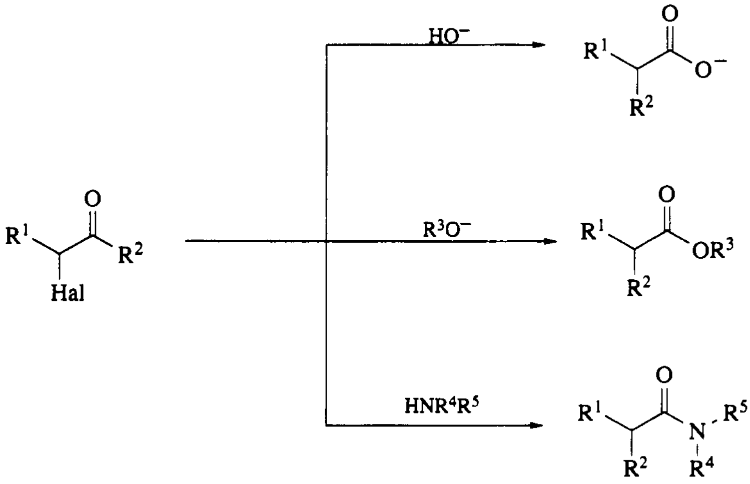

**Scheme 1**

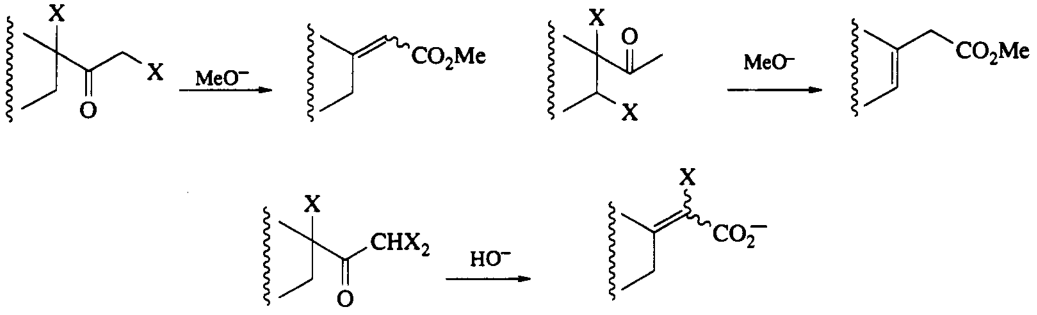

**Scheme 2**

The reactions are usually carried out by adding the halo ketone to a solution or suspension of the base in either a protic solvent (water, alcohols) or an ether (diethyl ether, dioxane, dimethoxyethane). The bases employed include: hydroxides of Group I and Group II metals; alkoxides, carbonates and hydrogen-carbonates of Group I metals; ammonia, and amines. There is no one recommended set of experimental conditions, because both the mechanism of the reactions and the type of products obtained depend upon the initial choice of α-halo ketones. In addition, since the halo ketones are highly reactive molecules, side products are inevitably obtained; those most commonly produced are shown in Scheme 3.

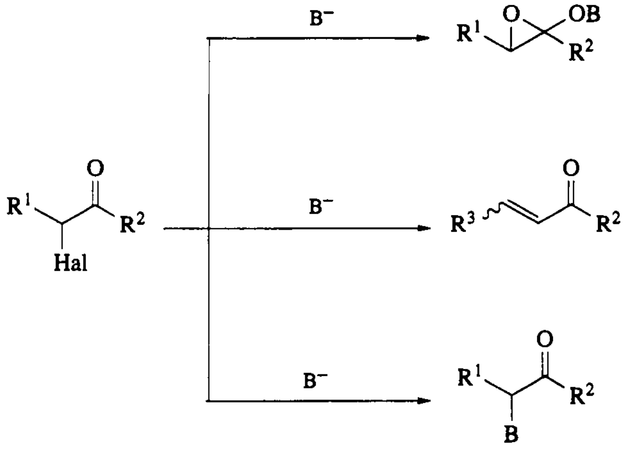

**Scheme 3**

## 3.7.2 MECHANISM

The various mechanisms that have been proposed for the rearrangement have been discussed in full,[12] and only a brief summary will be given here. Two main reaction mechanisms have been established: (i) a symmetrical mechanism, also known as the cyclopropanone pathway; and (ii) an unsymmetrical mechanism or semibenzylic pathway (Schemes 4 and 5).

The symmetrical mechanism necessitates an acidic hydrogen at the α′-center, and the intermediacy of a cyclopropanone or zwitterion/oxyallyl cation (Scheme 4). The likely existence of a symmetrical intermediate was first suggested by McPhee and Klingsberg[13] when they showed that the two ketones (**1**) and (**3**) rearranged to yield the same ester (**2**; Scheme 6). More cogent experimental support was provided by Loftfield[14] who reacted [1,2-$^{14}C_2$]-2-chlorocyclohexanone with sodium pentylate and obtained two ring-contracted products. These had an identical isotope distribution to the starting ketone (Scheme 7).

Numerous more recent experiments (reviewed in ref. 12) have confirmed the general accuracy of the mechanism shown in Scheme 4, and the actual intermediate involved depends upon the relative stabilities of the zwitterions/oxyallyl cations and the corresponding cyclopropanones. These will be affected by the choice of solvent and structural features of the starting ketone, such as the degree of substitution and ring strain (in cyclic halo ketones). A recent example in which an oxyallyl intermediate and a cyclopropanone intermediate were both intercepted is shown in Scheme 8.[15]

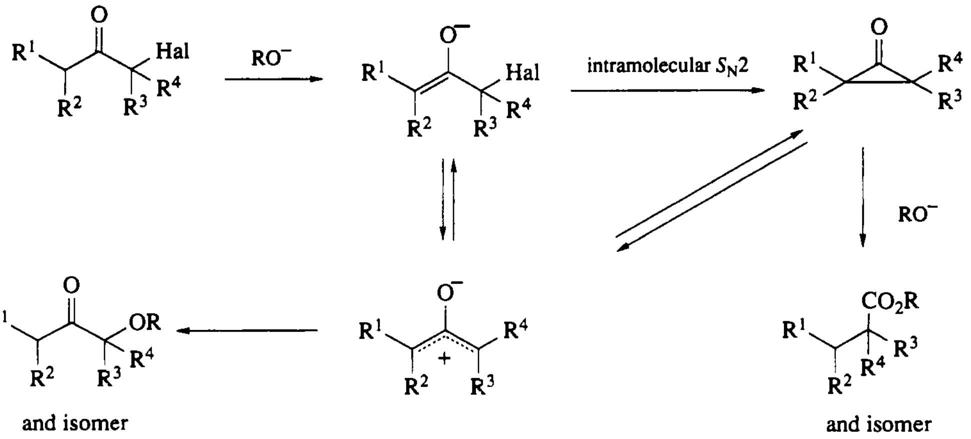
RO⁻
intramolecular $S_N2$
RO⁻
Hal
$R^1$
$R^2$
$R^3$
$R^4$
OR
$CO_2R$
and isomer
and isomer

Scheme 4

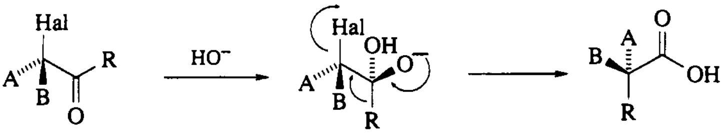
Hal
A
B
R
O
HO⁻
OH
O⁻
OH

Scheme 5

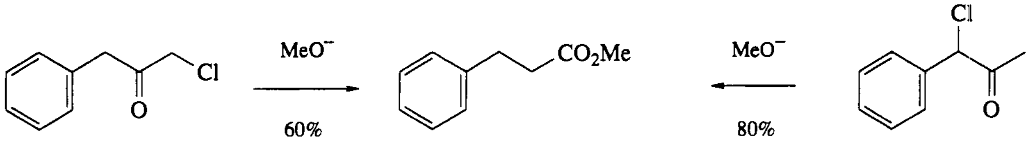
Cl
MeO⁻
60%
$CO_2Me$
MeO⁻
80%

(1) (2) (3)

Scheme 6

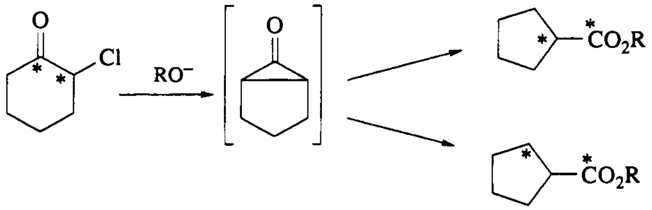
Cl
RO⁻
*
$CO_2R$
$CO_2R$

Scheme 7

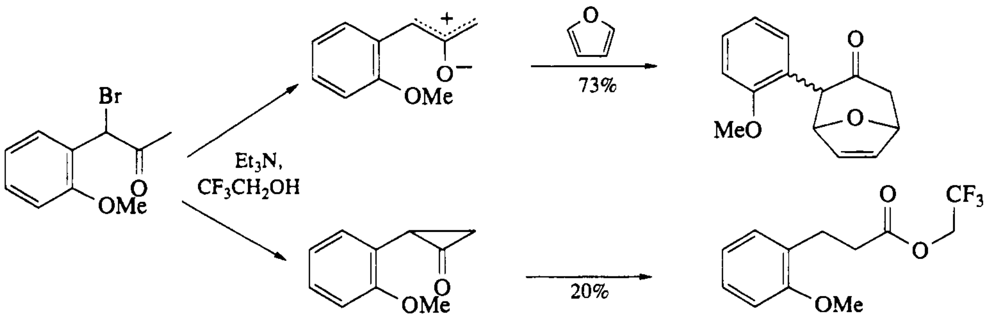
Br
OMe
$Et_3N$,
$CF_3CH_2OH$
OMe
73%
MeO
20%
OMe
OMe
$CF_3$

Scheme 8

In the semibenzylic pathway there is a nucleophilic attack by the base at the carbonyl carbon, followed by a concerted 1,2-migration of a carbanionic moiety with concomitant expulsion of halide. Implicit in this mechanism is the requirement for an antiparallel arrangement of the C—C bond that is broken and the carbon–halogen bond. This further requires an inversion of configuration at the carbon center initially bonded to the halogen atom, and an elegant demonstration of this feature has been provided by Charpentier and coworkers (Scheme 9).[16]

In cyclic systems where ring strain may be large for the cyclopropanone pathway, the semibenzylic pathway is preferred, and a good example of this is shown in Scheme 10.[17] Even when the ring strain is less severe, the semibenzylic pathway will be favored if there is a pseudo-equatorial halogen, thus allowing the new C—C bond to form from the pseudo-axial direction.

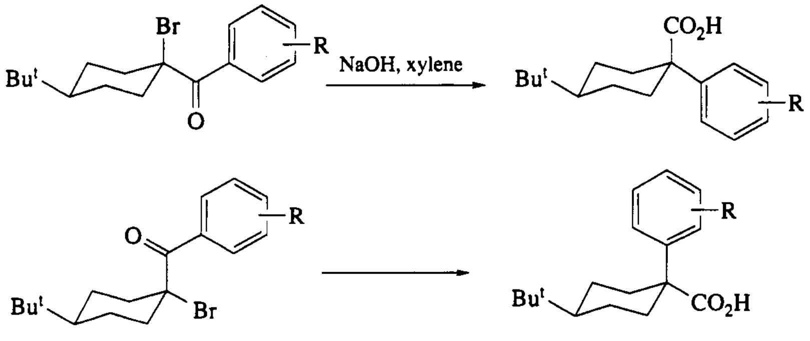

**Scheme 9**

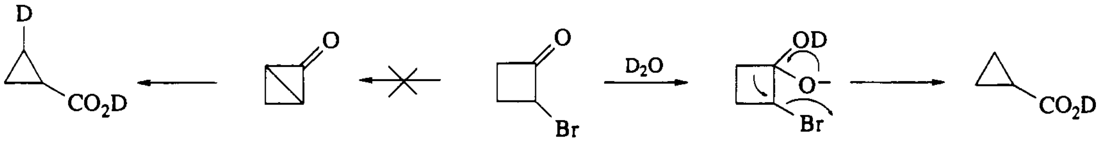

**Scheme 10**

### 3.7.3 SYNTHETIC UTILITY

### 3.7.3.1 Acyclic α-Halo Ketones

The Favorskii rearrangement of α-monohalo ketones is of primary utility for the synthesis of branched-chain aliphatic acid derivatives, and a typical example is shown in equation (1).[18,19] With increasing substitution at the α-carbon center, the rearrangement is favored since competing side reactions are suppressed; increasing the substitution at the α′-carbon center disfavors the rearrangement due to steric hindrance.

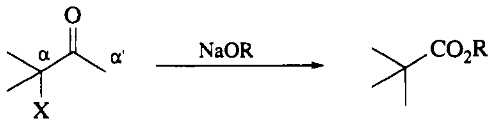

(1)

| *R* | Me | Et | Pr$^i$ | Ph |
|---|---|---|---|---|
| *X* | Br | Br | Br | Cl |
| % | 39 | 61 | 64 | 47 |

The structural equivalence of the starting materials with respect to their common rearrangement product has already been mentioned, and two further examples are illustrated in Scheme 11.[20,21] In practice this often means that the ketone can be halogenated, and the mixture of halo ketones used directly in the Favorskii rearrangement.

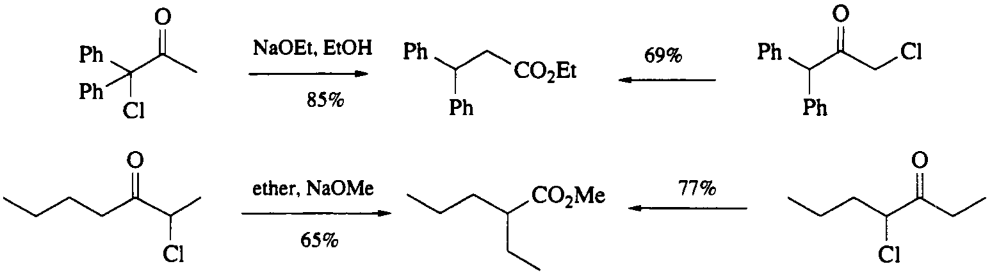

Scheme 11

Aryl groups generally have a labilizing effect on the substrate, and the rearrangements are particularly facile, often requiring only weak bases for their initiation. However, if aryl groups are present on both $\alpha$- and $\alpha'$-centers, alkoxy epoxides are formed in preference to the Favorskii products (equation 2).[22,23] Complications can also arise if an alkyl group is present at the $\alpha$-center, of which the results shown in Scheme 12[24] are examples. It appears that the rearrangements are subject to the competitive influences of carbanion stability (secondary more stable than tertiary) and steric factors. The proportions of the two products also vary with the steric bulk of the base.

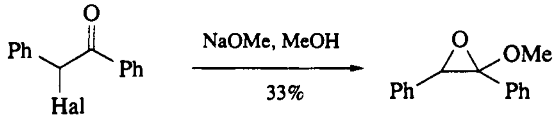

(2)

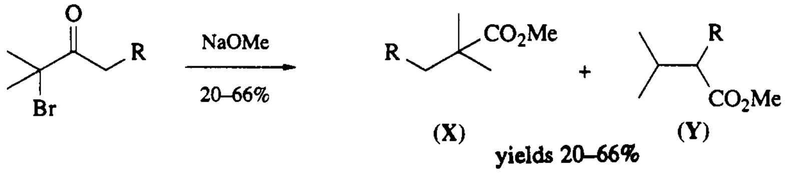

percentage of (Y) in the product mixture increases from 16 to 80% as R changes from Me to Et to $Pr^i$

Scheme 12

When the Favorskii rearrangement is carried out on a substrate which contains an internal nucleophile, this can attack the cyclopropanone intermediate to yield cyclic products. The reaction shown in Scheme 13[25] provides a route to polysubstituted $\gamma$-butyrolactones by this kind of mechanism.

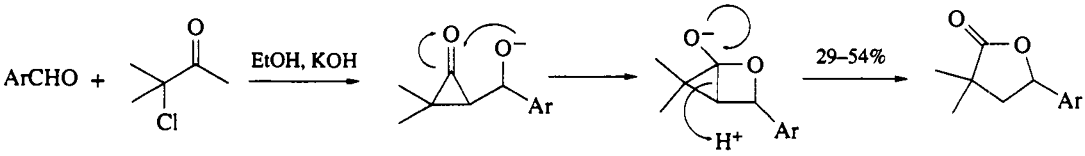

Scheme 13

The reaction of a polyhalo ketone with base (equation 3)[26] was described several years before Favorskii described a similar rearrangement (equation 4).[27] Simple $\alpha,\alpha$- and $\alpha,\alpha'$-dihalo ketones yield the same product (Scheme 14),[28] so dibromination can be followed by Favorskii rearrangement without purification. These rearrangements are usually stereospecific, though subsequent *cis* to *trans* isomerization, under the influence of base, often obscures this feature. Various explanations have been provided for this stereospecificity, but the one due to Rappe (illustrated in Scheme 15) seems most plausible.[29]

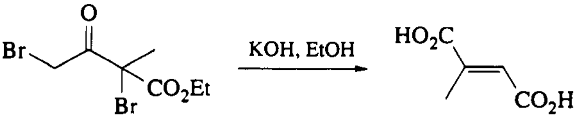

(3)

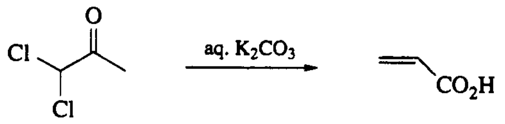
O
Cl
Cl
aq. $K_2CO_3$
$CO_2H$

(4)

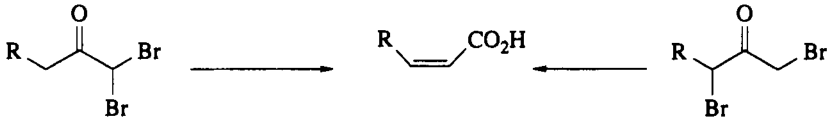
O
R
Br
Br
R
$CO_2H$
O
R
Br
Br

Scheme 14

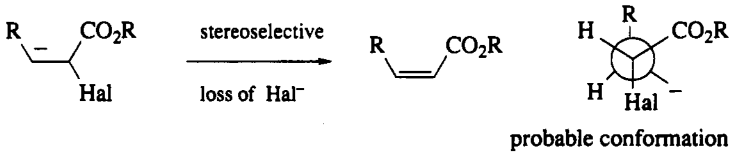
R
$CO_2R$
Hal
stereoselective
loss of $Hal^-$
R
$CO_2R$
H
R
$CO_2R$
H
Hal
probable conformation

Scheme 15

The reactions of polyhalo ketones often proceed in good yield, and the examples shown in equations (5) and (6) are typical.[30,31] Favorskii-type rearrangements of α,α′-dihalo ketones with enolates of diethoxyphosphinylacetic esters[32] or with sodiomalonates,[33] have provided useful routes to divinyl ketones and conjugated enones respectively (Scheme 16). Most of this chemistry is of a general nature, but a reaction that provides a key intermediate for the elaboration of an analog of obtusilactone (**4**) is shown in Scheme 17.[34] These analogs are of interest because the parent lactone (R = H) has antitumor activity. Finally, the tribromo ketones (**5**) undergo base-induced rearrangement and elimination to yield conjugated dienes (**6**) with a high (*Z*)-stereoselectivity (Scheme 18).[35]

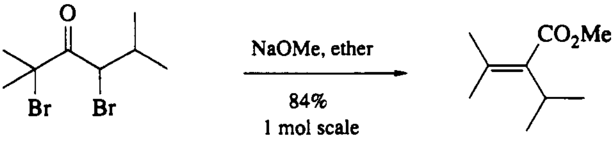
O
Br
Br
NaOMe, ether
84%
1 mol scale
$CO_2Me$

(5)

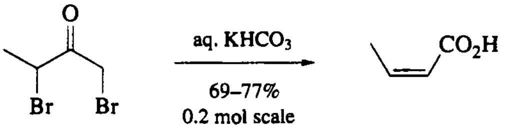
O
Br
Br
aq. $KHCO_3$
69–77%
0.2 mol scale
$CO_2H$

(6)

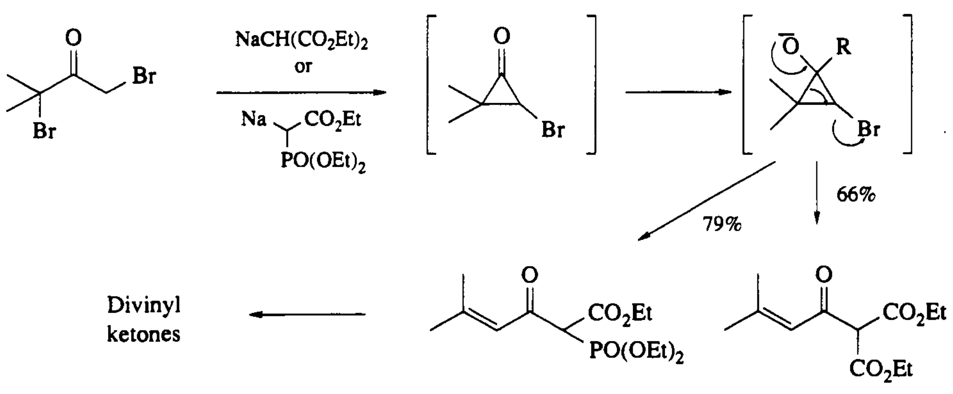
O
Br
Br
$NaCH(CO_2Et)_2$
or
Na
$CO_2Et$
$PO(OEt)_2$
O
Br
O
R
Br
79%
66%
Divinyl ketones
O
$CO_2Et$
$PO(OEt)_2$
O
$CO_2Et$
$CO_2Et$

Scheme 16

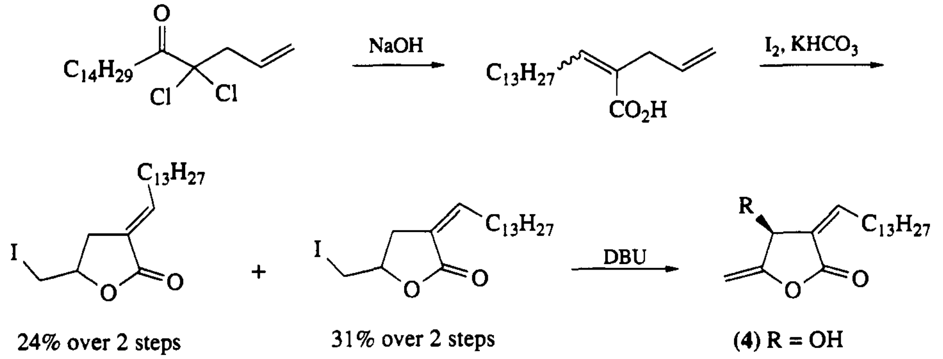
$C_{14}H_{29}$
Cl
Cl
O
NaOH
$C_{13}H_{27}$
$CO_2H$
$I_2$, $KHCO_3$
$C_{13}H_{27}$
I
O
O
+
DBU
R
24% over 2 steps
31% over 2 steps
(4) R = OH

Scheme 17

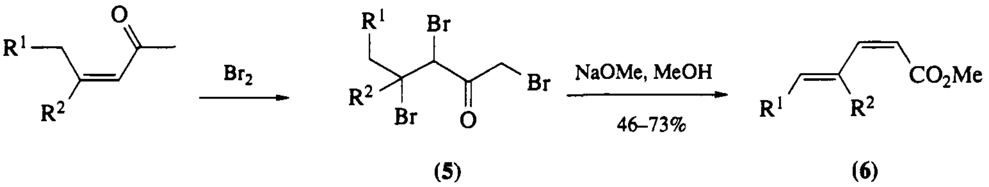
$R^1$
$R^2$
O
$Br_2$
Br
NaOMe, MeOH
46–73%
$CO_2Me$
(5)
(6)

Scheme 18

### 3.7.3.2 α-Halocycloalkyl Ketones

The reactions of monohalocycloalkyl ketones are of considerable interest because they allow access to cycloalkylcarboxylic acids; the rearrangements shown in Scheme 19 are examples. When pure stereoisomers were employed, complete racemization resulted, suggesting the intermediacy of ion pairs.[36] This methodology has been used for the synthesis of the potent analgesic pethidine (**8**) from the piperidyl ketone (**7**).[37] The lack of products from bromomethyl cyclohexyl ketone (**9**) was ascribed to a slow (rate-determining) removal of hydrogen to produce a tertiary carbanion, thus allowing competing side reactions to occur.[38]

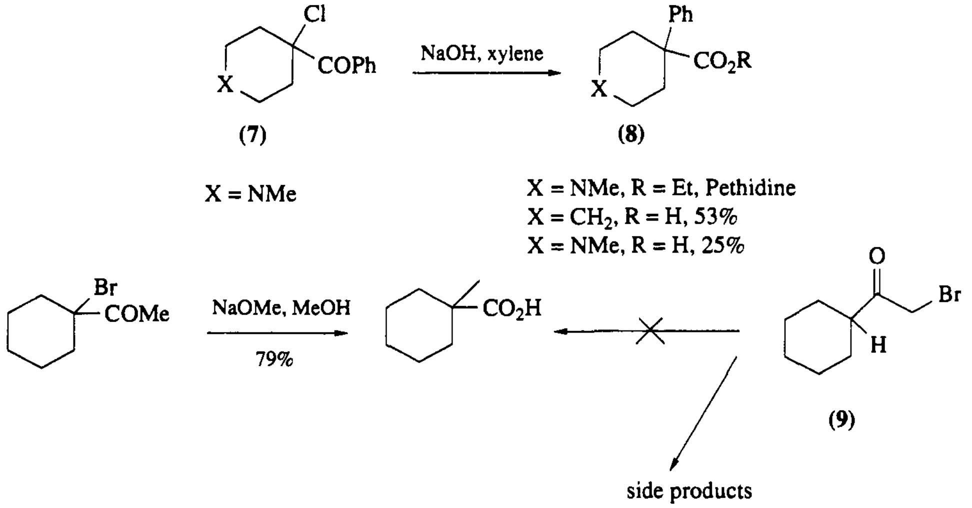
Cl
COPh
X
NaOH, xylene
Ph
$CO_2R$
X
(7)
(8)
X = NMe
X = NMe, R = Et, Pethidine
X = $CH_2$, R = H, 53%
X = NMe, R = H, 25%
Br
COMe
NaOMe, MeOH
79%
$CO_2H$
O
Br
H
(9)
side products

Scheme 19

Relatively inaccessible cycloalkylcarboxylic acids can be produced *via* these Favorskii rearrangements (for example equation 7),[39] and they have been especially useful for the introduction of alkyl groups at C-17 of the steroid nucleus. Thus the pregnenolones (**10**) and (**11**) can be converted into mixtures of rearrangement products (**12**) and (**13**), with the latter usually predominating in polar, protic solvents (Scheme

20).[40] The potent progestin (**14**) and the relatively inactive cortisone analog (**15**) have been prepared *via* this strategy.[41,42]

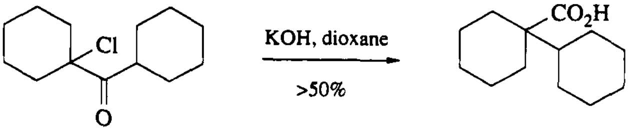

(7)

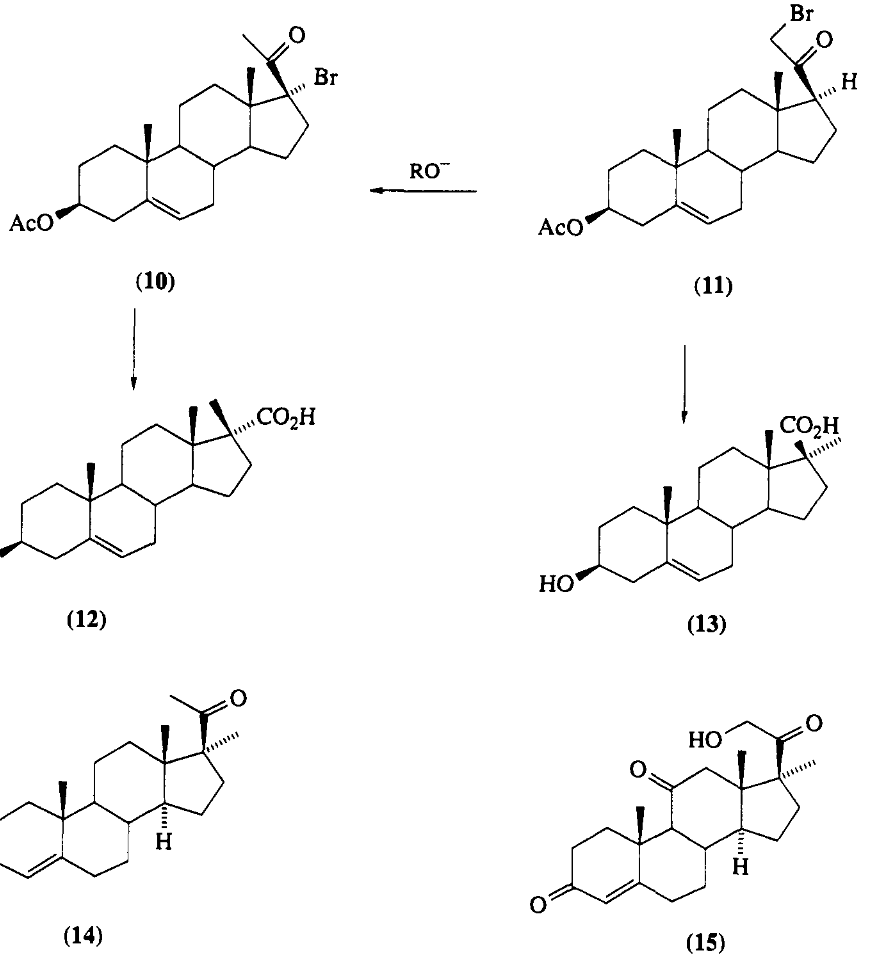

Scheme 20

When a nonprotic, though relatively polar, solvent, such as dimethoxyethane, was employed, the 17-α-bromopregnenolone yielded primarily the 17-β-methyl product; these results have been rationalized as shown in Scheme 21.[43] The 17-α-bromo steroid and the 21-bromo steroid are converted *via* separate concerted processes into discrete stereoisomeric cyclopropanones; these transformations are in competition with the formation of the common dipolar species which can yield both stereoisomers. However, one of these will usually be favored on steric grounds, and the rearrangement can thus proceed with a high degree of stereoselectivity. The steric effect of having a 12-α-substituent or substituents at C-16 has been probed, and the result is a lowering of stereoselectivity observed in polar aprotic solvents.[44,45]

With dihalogenated analogs of these steroids, rearrangement yields the anticipated products in high yield (Scheme 22),[46] and these unsaturated acids are appropriately substituted for elaboration of the steroid side chain.

Finally, the related trihalogenated steroids produce α-bromo acids, and the example shown in equation (8) is representative.[47]

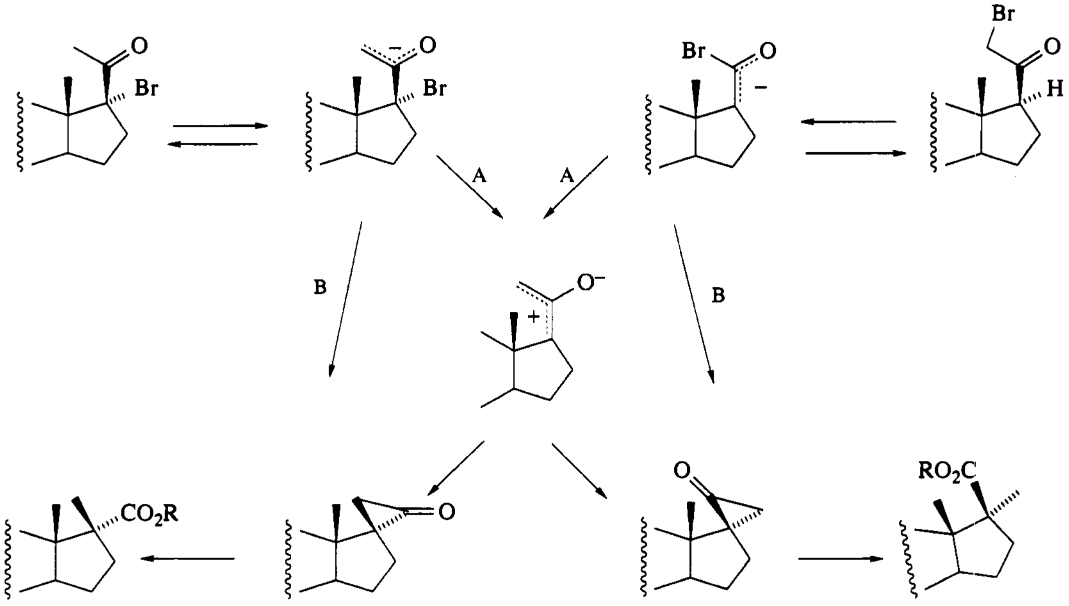
O
Br
A
B
O⁻
+
CO₂R
RO₂C
H

A is a polar, protic solvent; B is an aprotic, medium polarity solvent

Scheme 21

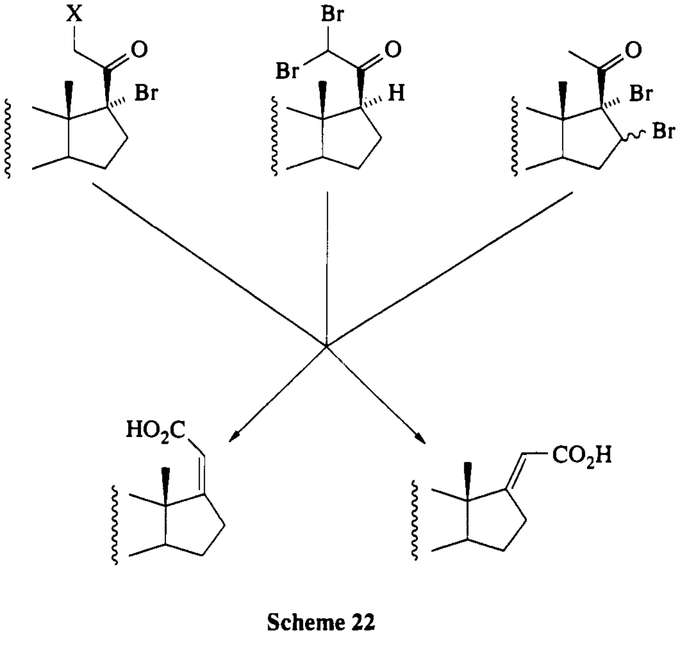
X
O
Br
H
HO₂C
CO₂H

Scheme 22

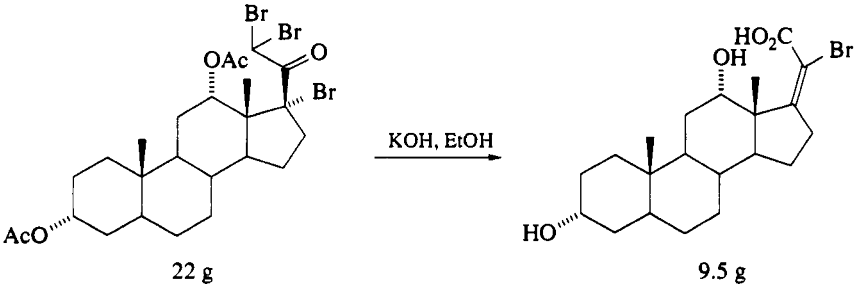
Br
OAc
O
AcO
KOH, EtOH
HO₂C
OH
HO

22 g

9.5 g

(8)

### 3.7.3.3 Monocyclic Halo Ketones

Favorskii rearrangements have been reported with alicyclic and heterocyclic bromocycloalkanones containing 4–13 (but not 5) atoms in the rings. The important mechanistic studies with 2-bromocyclobutanone have already been mentioned (Scheme 10),[17] and Scheme 23 contains a summary of other results obtained by Conia and coworkers.[17,48] Of particular note is the fact that the rearrangement will even proceed with water as reagent, and that the stereospecificity observed is consistent with a mechanism involving (as expected) inversion of configuration at the carbon center initially attached to the bromine atom.

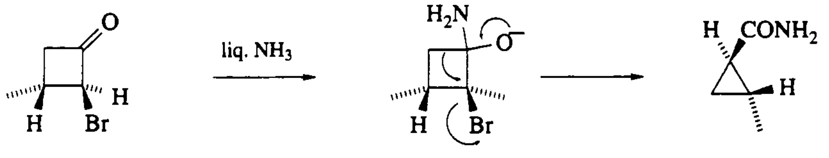

Scheme 23

Reactions of this type have been much employed for the construction of cyclopropane carboxylic acids that are appropriately functionalized for elaboration into the commercially important pyrethroid insecticides (Scheme 24 and equation 9).[49,50] The stereospecificity observed in the second report is of particular note given the superior potency of the *cis*-pyrethroids.

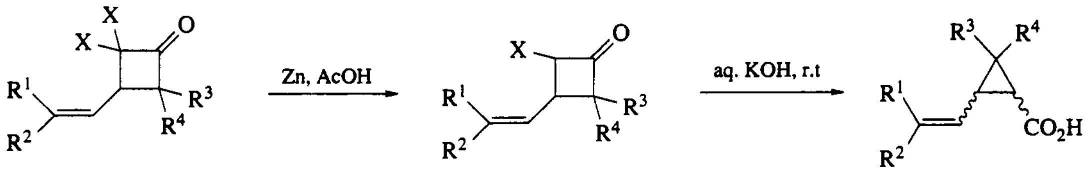

all R = Me, 73%
*cis*:*trans* = 1:3

Scheme 24

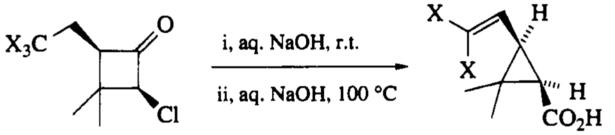

(9)

| *X* | % | *cis*:*trans* |
|---|---|---|
| Cl | 86 | 83:17 |
| Br | 84 | 85:15 |

No Favorskii rearrangement products are produced when α-halocyclopentanones are treated with base, and products of aldol, substitution and dehydrohalogenation reactions are produced. However, when an α-halocyclopentanone is part of certain condensed systems, cubane derivatives may be obtained (see Section 3.7.3.5).

The reactions of α-halocyclohexanones have been most thoroughly studied, and the reaction shown in equation (10),[51] carried out on the molar scale, is an example. In general the chloro compounds provide larger yields than the bromo and fluoro analogs, and branched-chain aliphatic alkoxides are claimed to be the most effective bases.[7]

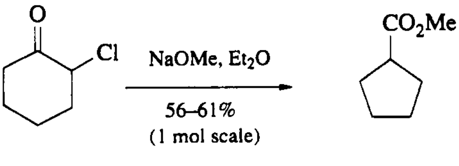

(10)

The synthetic potential of these reactions can be illustrated by their use for the construction of polyfunctionalized cyclopentanecarboxylic acids and derivatives (Scheme 25).[52–54a] The Michael-induced

Favorskii rearrangement is of note, as is the use of carvone as a chiral starting material,[54b] and the annelation procedure that follows the rearrangement shown in Scheme 26.[55]

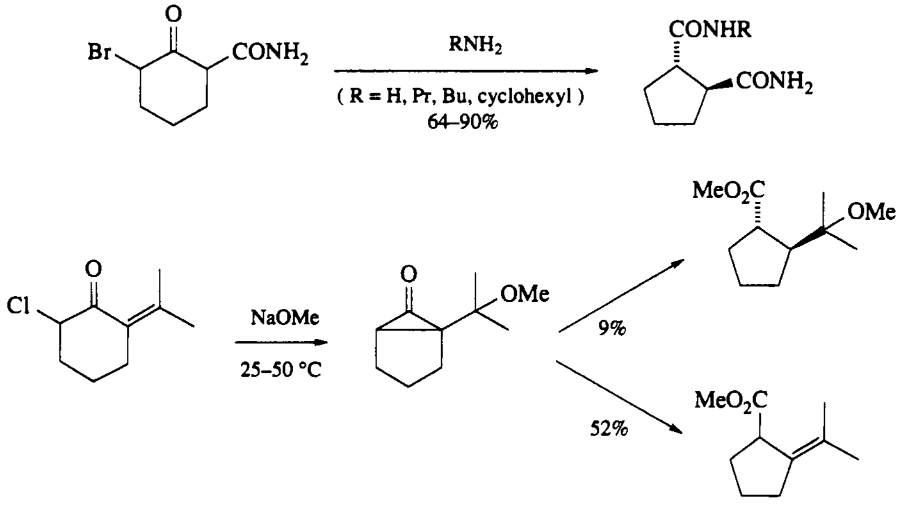
Br
O
CONH$_2$
RNH$_2$
( R = H, Pr, Bu, cyclohexyl )
64–90%
CONHR
CONH$_2$
Cl
O
NaOMe
25–50 °C
O
OMe
9%
52%
MeO$_2$C
OMe
MeO$_2$C

**Scheme 25**

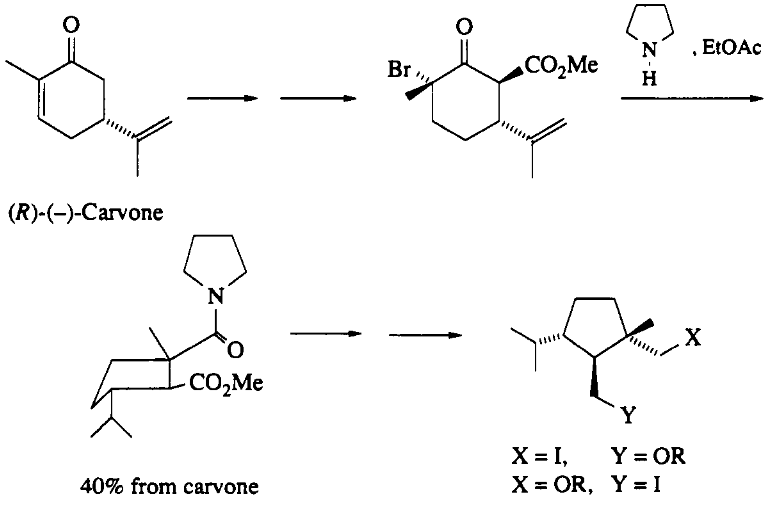
O
(R)-(–)-Carvone
Br
O
CO$_2$Me
N
H
, EtOAc
N
O
CO$_2$Me
40% from carvone
X
Y
X = I, Y = OR
X = OR, Y = I

**Scheme 26**

The corresponding rearrangements of higher homologs are also well documented (*e.g.* 2-chlorocyclododecadienone[56] and 2-bromocycloundecanone)[57] as are the base-induced rearrangements of heterocyclic haloalkanones, such as the conversion of halolactams into proline and homologs (equation 11).[58] In addition, the rearrangement of 2-chlorocaprolactam has been reported on the 3.5 mol scale.[59]

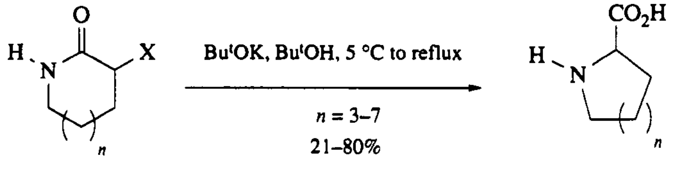
O
H
N
X
n
Bu$^t$OK, Bu$^t$OH, 5 °C to reflux
n = 3–7
21–80%
CO$_2$H
H
N
n

(11)

When polyhalocycloalkanones are employed the anticipated products are almost invariably obtained, and the reactions of polybromomonoterpenes are of particular synthetic value. Dibromination of pulegone produced dibromo ketone (**16**), and reaction of this (on a 0.3 mol scale) produced the results shown in Scheme 27.[60] The *trans*-acid usually predominates because there are steric constraints to the hydrolysis of the *cis*-ester. The related tribromomonoterpene (**17**) provides access to carvenolide (**18**;

Scheme 28)[61] and both rearrangement processes have potential utility for the construction of cyclopentanoid monoterpenes, *e.g.* the iridolactones which are important as constituents of insect defensive secretions.

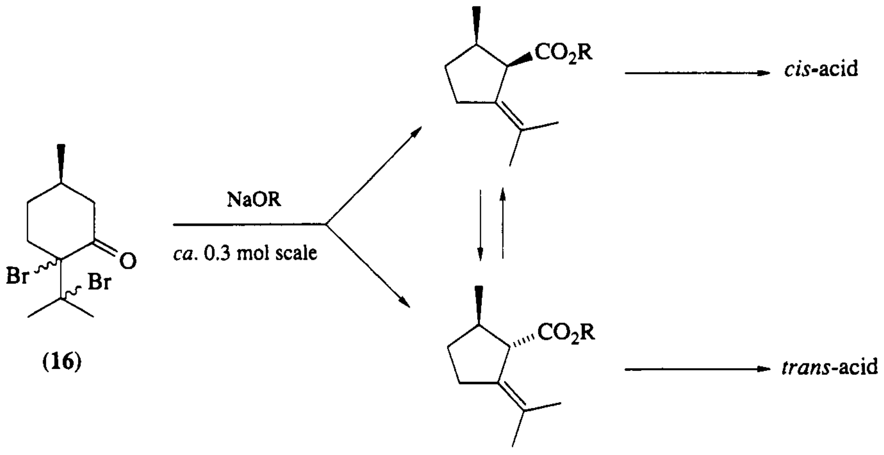
Br
Br
O
(16)
NaOR
ca. 0.3 mol scale
CO2R
cis-acid
CO2R
trans-acid

aq. NaOH, *cis*:*trans* ≈ 1:1; NaOEt, EtOH, *cis*:*trans* ≈ 0:100

Scheme 27

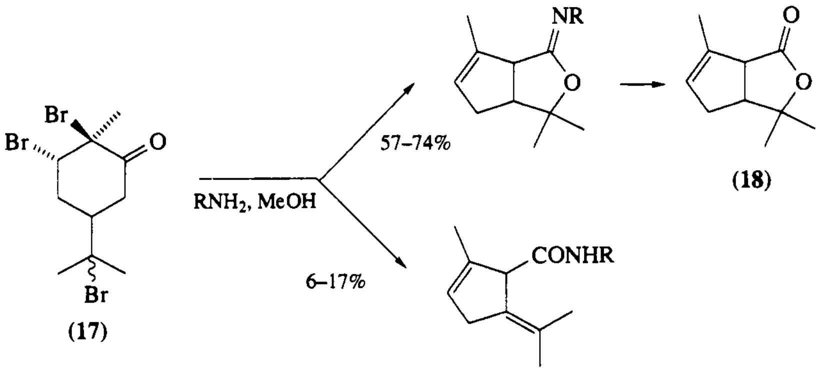
Br
Br
O
Br
(17)
RNH2, MeOH
57–74%
6–17%
NR
O
O
O
(18)
CONHR

R = Et, Pr$^i$, Pr$^n$, allyl, cyclohexyl

Scheme 28

Larger ring polyhalocycloalkanones behave in a predicatable fashion. Thus 2,8-dibromocyclooctanone yields cyclohept-1-enecarboxylic acid in 96% yield when treated with aqueous NaOH, and 2,2,8-tribro-

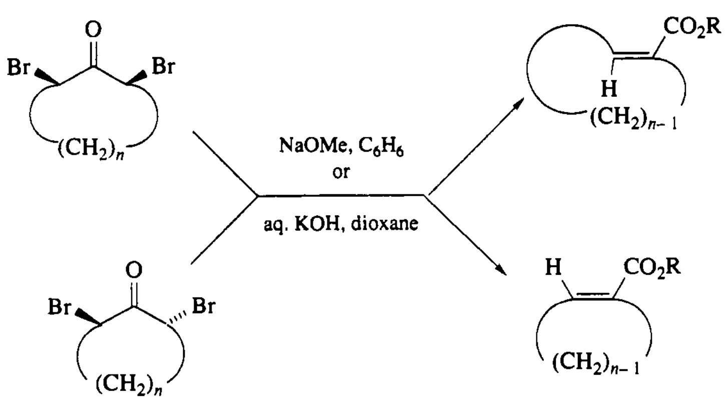
O
Br
Br
(CH2)n
O
Br
Br
(CH2)n
NaOMe, C6H6
or
aq. KOH, dioxane
CO2R
H
(CH2)n-1
H
CO2R
(CH2)n-1

$n = 9$
from *cis*-dibromo
*cis*:*trans* ≈ 0:100
from *trans*-dibromo
*cis*:*trans* ≈ 86:14
$n = 8$; similar values

Scheme 29

mocyclooctanone when treated with ethanolic sodium ethoxide yields 2-bromocyclohept-1-enecarboxylic acid in 83% yield.[62] The results obtained with dibromo- undecanones and -dodecanones are shown in Scheme 29.[63] Finally, when various dibromomonochlorocycloalkanones are treated with sodium methoxide, there is an almost exclusive preference for displacement of bromide rather than chloride (equation 12).[64]

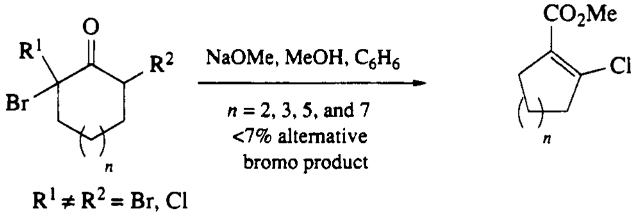
O
R1
Br
R2
n
R1 ≠ R2 = Br, Cl
NaOMe, MeOH, C6H6
n = 2, 3, 5, and 7
<7% alternative
bromo product
CO2Me
Cl
n

(12)

### 3.7.3.4 Bicyclic Halo Ketones

*Cis*-fused 5,6- and *cis*-fused 6,6-bicyclic halo ketones undergo Favorskii rearrangements to produce 5,5- and 6,5-bicyclic ring systems, respectively. The *trans*-5,6-bicyclic system does not yield rearranged products, presumably due to steric constraints. Representative examples are shown in Schemes 30 and 31,[65,66] and the high degree of retention of stereochemistry at the bridging centers is noteworthy.

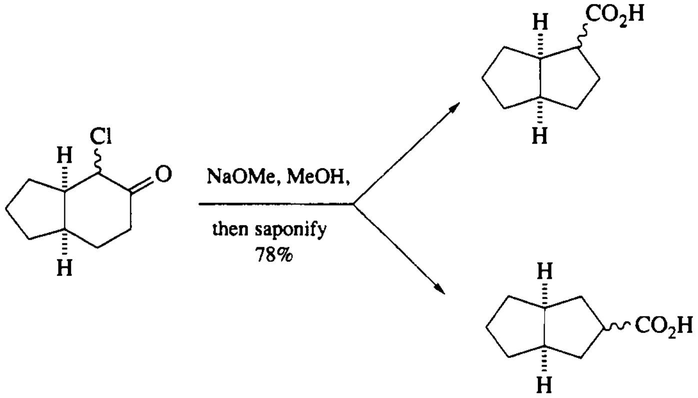
Cl
H
O
H
NaOMe, MeOH,
then saponify
78%
H
CO2H
H
H
CO2H
H

Scheme 30

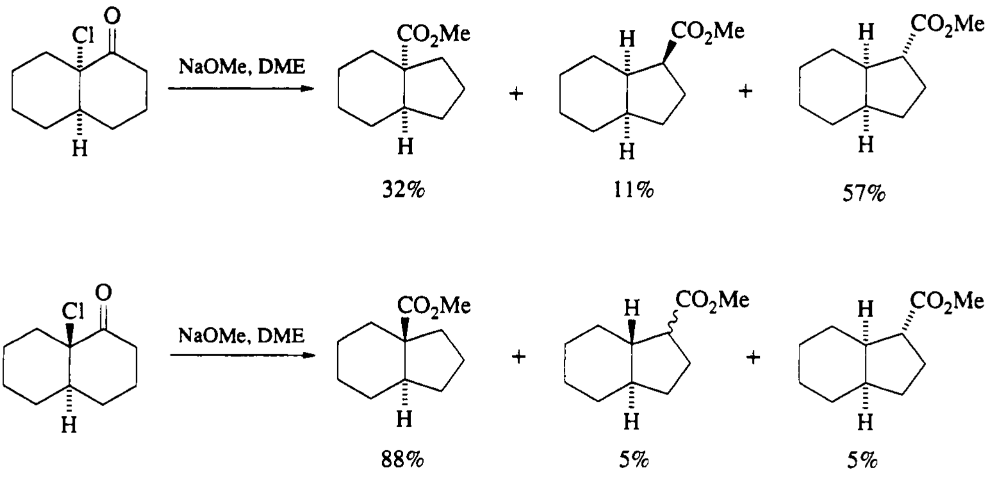
Cl
O
H
NaOMe, DME
CO2Me
H
32%
+
H
CO2Me
H
11%
+
H
CO2Me
H
57%
Cl
O
H
NaOMe, DME
CO2Me
H
88%
+
H
CO2Me
H
5%
+
H
CO2Me
H
5%

Scheme 31

An interesting syn thesis of bicyclo[$n$.1.0] systems is shown in equation (13),[67] though the yields for $n = 6$ are rather poor. Of more preparative use is the chemistry illustrated in Scheme 32,[68] by which bicyclic analogs of proline may be prepared. These were required as components of potential inhibitors of angiotensin-converting enzyme. Once again a high degree of diastereoselectivity was observed.

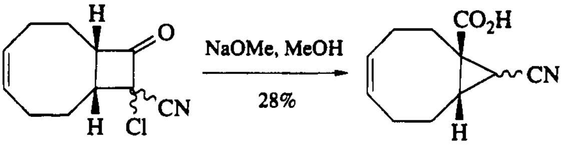
H
O
CN
H
Cl
NaOMe, MeOH
28%
CO2H
CN
H

(13)

Saturated 6,4-system, 62%
Saturated 8,4-system, 12%

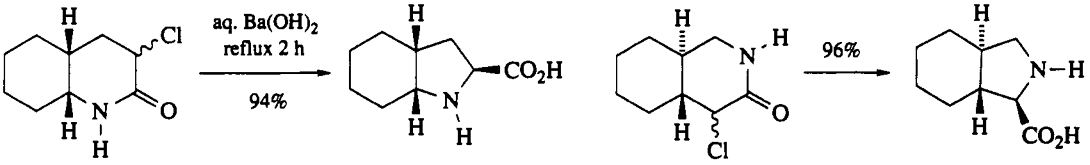
H
Cl
N
O
H
H
aq. Ba(OH)2
reflux 2 h
94%
H
CO2H
N
H
H
H
N
H
O
H
Cl
96%
H
N–H
H
CO2H

Scheme 32

With nonfused bicyclic systems, most reactions have been carried out with compounds containing a bridgehead halogen; though the chemistry of 2-bromobicyclo[3.2.1]octan-3-ones has provided interest-

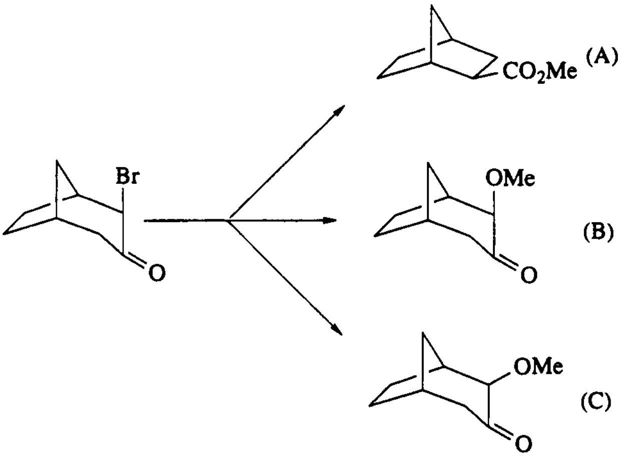
CO2Me
(A)
Br
O
OMe
(B)
O
OMe
(C)
O

NaOMe, MeOH, A, 10%, B, 5%, C, 74%; NaOMe, DME, A, 76%, *endo* ester, 24%

Scheme 33

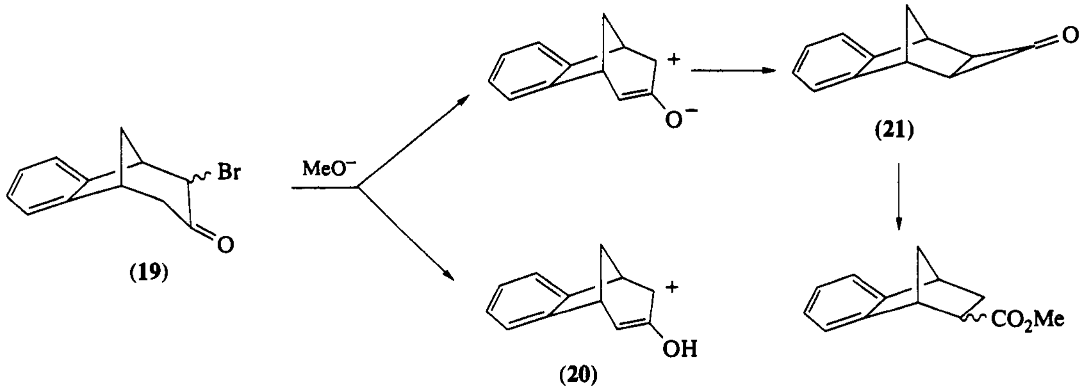
Br
O
(19)
MeO⁻
+
O⁻
O
(21)
+
OH
(20)
CO2Me

Scheme 34

ing mechanistic results (Scheme 33).[69,70] A preponderance of the solvolysis products is obtained when methanol is used as solvent, whilst dimethoxyethane favors the Favorskii rearrangement. Protonation of the intervening enolate or zwitterion would disfavor formation of a cyclopropanone, and favor attack at the carbocation by methoxide. Interestingly, both equatorial and axial bromides of the related fused benzobicyclo[3.2.1]octanone (**19**) react with sodium methoxide to provide good yields of Favorskii rearrangement products (Scheme 34).[71] The greater facility of this reaction has been attributed to the inherent instability of the bishomoantiaromatic carbocation (**20**), which would favor the alternative formation of the cyclopropanone (**21**), and resultant Favorskii rearrangement.

A mixture of the 2-bromobicyclo[3.3.1]nonan-3-ones (**22**) rearranges with great stereoselectivity and good yield to the *exo*-ester (**23**; equation 14).[72]

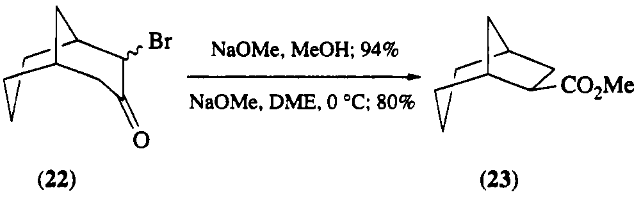

(14)

Most other systems studied have bridgehead halogens, and special attention has been paid to the reactions of the kind shown in Scheme 35. The yields of rearrangement products are uniformly good, and deuterium incorporation results imply that the semibenzilic mechanism operates for the smaller ring

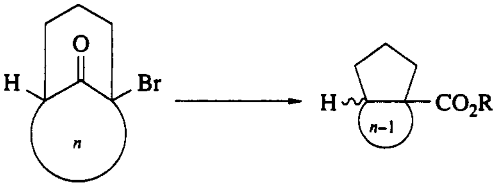

i, $n = 6$, Bu$^t$OK, Bu$^t$OD; R = Bu$^t$, 94%, 0.026 atoms D incorporated
ii, $n = 7$, NaOMe, MeOD; R = Me, 96%, 0.00 atoms D incorporated
$n = 7$, Bu$^t$OK, Bu$^t$OD; R = Bu$^t$, 67%, 0.83 atoms D incorporated
iii, $n = 8$, NaOD, EtOD, $D_2O$; R = H, 88%, 0.90 atoms D incorporated

**Scheme 35**

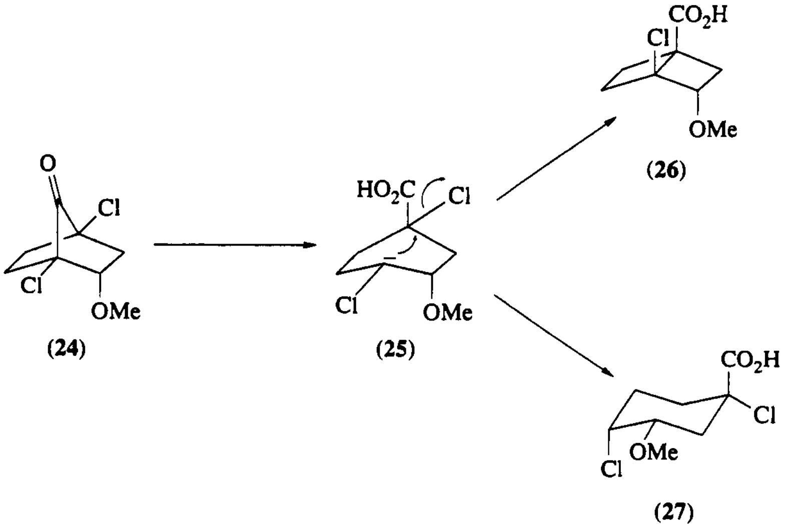

NaOH, THF, (**26**):(**27**) = 89:11
aq. NaOH, (**26**):(**27**) = 64:36

**Scheme 36**

sizes, whilst a cyclopropanone is implicated for the larger ring size (*cf.* Schemes 4 and 5). This is reasonable since Bredt's rule would suggest a difficult enolization for the ring systems with $n = 6$ and 7. When stronger base (*t*-butoxide) was employed, the cyclopropanone pathway apparently also operates for the system with $n = 7$.[73]

Compound (**24**), with two bridgehead chlorines, yields the bicyclo[2.2.0] acid (**26**) and the cyclohexanecarboxylic acid (**27**). The relative proportion of the latter was increased when water was present, presumably because there was more quenching of the intermediate anion (**25**; Scheme 36).[74]

The related dihalo ketone (**28**) rearranges smoothly at 0 °C, whilst bromo ketone (**29**) requires prolonged heating at 155 °C (Scheme 37).[75] This is anticipated, since formation of the intermediate (**30**) required for the semibenzilic mechanism is sterically disfavored.

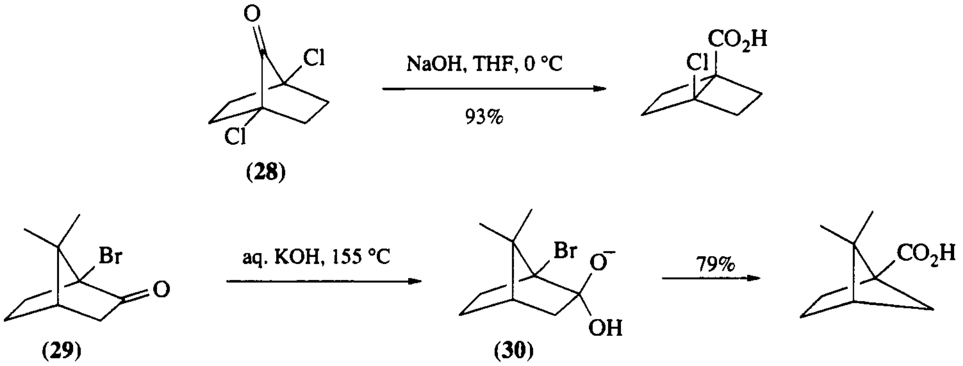

Scheme 37

### 3.7.3.5 Polycyclic Halo Ketones

In terms of synthetic utility these rearrangements fall into two major classes: (i) reactions of halo steroids and related systems; and (ii) reactions that yield cage-like structures. Reactions of the first type are exemplified by the rearrangements illustrated in Scheme 38.[76–78]

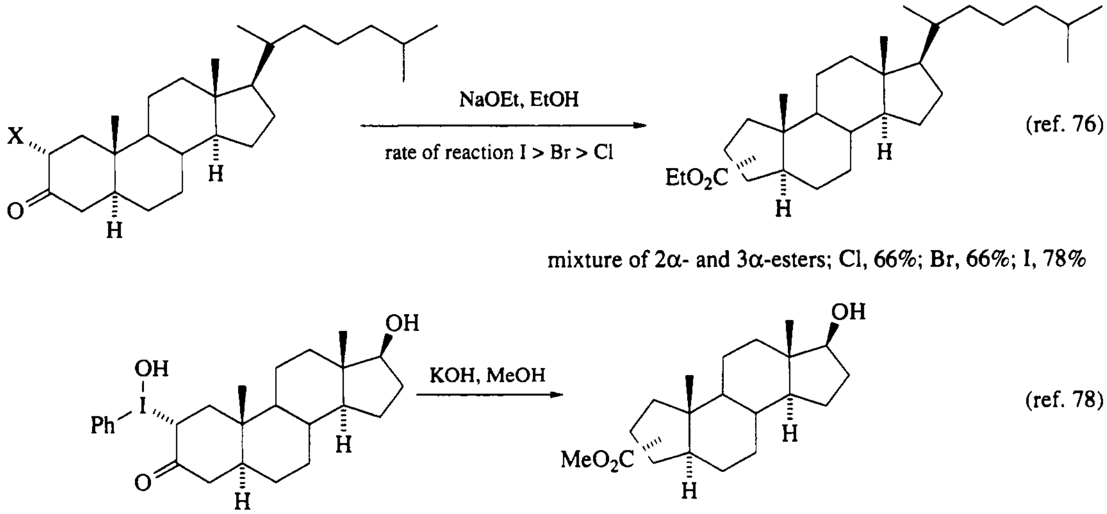

mixture of 2α- and 3α-esters; Cl, 66%; Br, 66%; I, 78%

mainly 2α-ester (65%) and some 3α-ester

Scheme 38

The rearrangements of cage-like structures have been discussed in some detail in refs. 11 and 12, and can be divided into three main classes: (i) homocubane to cubane; (ii) adamantane to noradamantane; and (iii) homoadamantane to twist-brendane; and these are depicted (together with strain energy estimations from ref. 79) in Scheme 39. It can be seen that in each case rearrangement provides a system with greater strain, and the Favorskii reaction thus allows access to strained structures that would be otherwise inaccessible. Typical examples are shown in Scheme 40.[80–85]

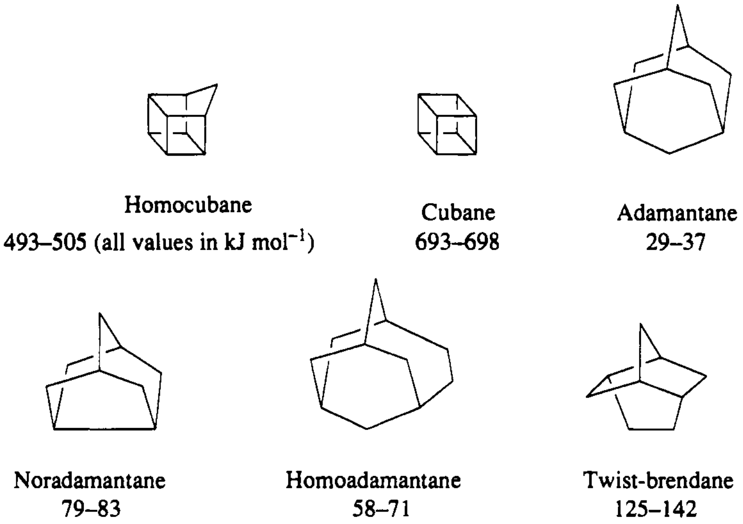
Homocubane
493–505 (all values in kJ mol$^{-1}$)
Cubane
693–698
Adamantane
29–37
Noradamantane
79–83
Homoadamantane
58–71
Twist-brendane
125–142

Scheme 39

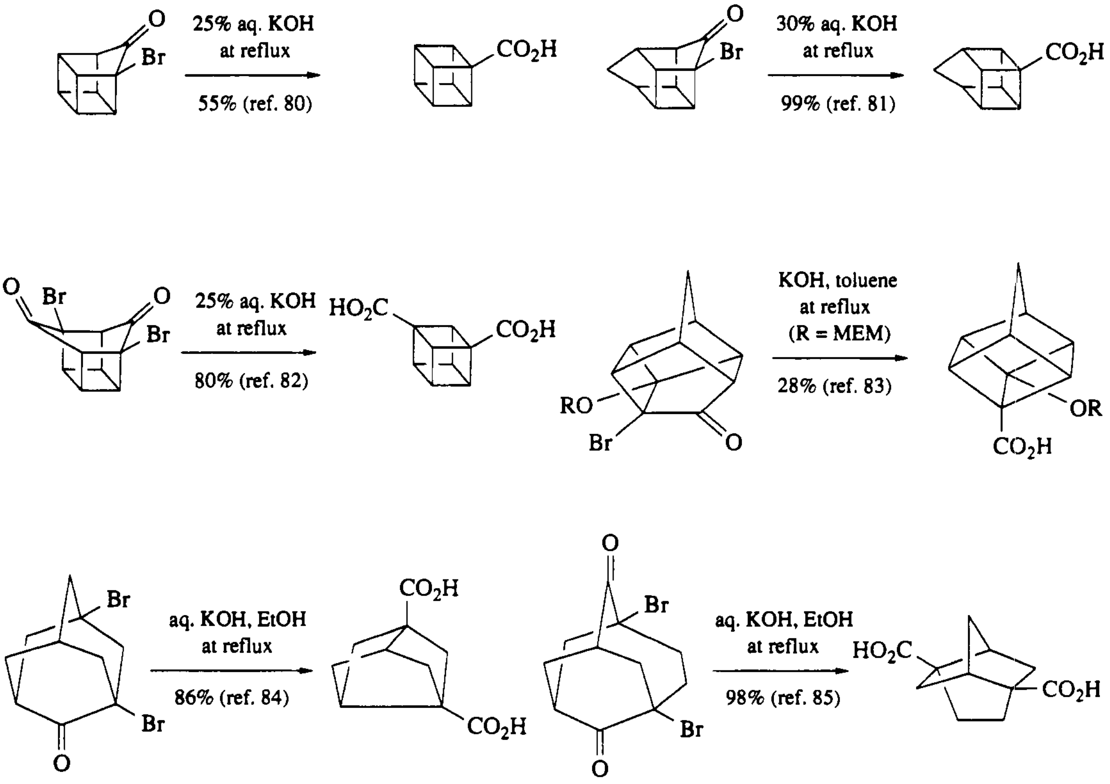
O
Br
25% aq. KOH
at reflux
55% (ref. 80)
CO₂H
O
Br
30% aq. KOH
at reflux
99% (ref. 81)
CO₂H
O
Br
O
Br
25% aq. KOH
at reflux
80% (ref. 82)
HO₂C
CO₂H
RO
Br
O
KOH, toluene
at reflux
(R = MEM)
28% (ref. 83)
OR
CO₂H
Br
Br
O
aq. KOH, EtOH
at reflux
86% (ref. 84)
CO₂H
CO₂H
O
Br
Br
O
aq. KOH, EtOH
at reflux
98% (ref. 85)
HO₂C
CO₂H

Scheme 40

It is interesting to note that with the homocubane derivatives it is the cyclopentanone ring that contracts, whilst this process has never been observed in simple halocyclopentanones. A semibenzilic mechanism probably operates in most cases, since the requisite cyclopropanones are unlikely to be produced. Ring-opened products are not infrequent side products, and they are favored products when highly halogenated precursors are employed (Scheme 41).[86] The intermediate carbanions are stabilized by the electron-withdrawing halogens, and these lead to products that are less strained than the usual cage products.

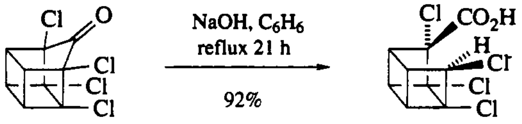
Cl
O
Cl
Cl
Cl
NaOH, C6H6
reflux 21 h
92%
Cl
CO2H
H
Cl
Cl
Cl

**Scheme 41**

### 3.7.3.6 Miscellaneous

All of the examples described thus far have involved the use of bases to initiate the Favorskii rearrangements. However various Lewis acids have also been used for this purpose. An early example of this methodology is shown in Scheme 42.[87] The Lewis acid promoted ring contractions depicted in Scheme 43[88] and Scheme 44[89] are also Favorskii-type rearrangements.

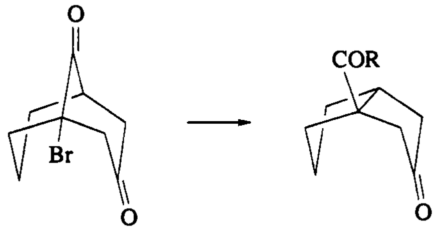

KOH, $Et_2O$, R = OH, 34%; Na, liq. $NH_3$, R = $NH_2$, 68%; $AgNO_3$, aq. EtOH, R = Et, 11%; R = OH, 61%; $Hg(OAc)_2$, EtOH, R = Et, 71%

**Scheme 42**

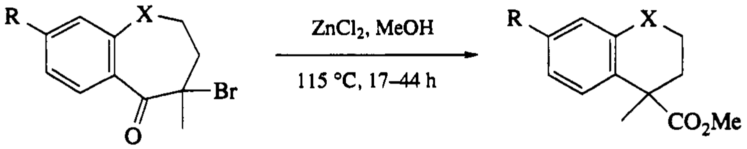
R
X
Br
O
ZnCl2, MeOH
115 °C, 17–44 h
R
X
CO2Me

| *R* | OMe | H | OMe | H |
|---|---|---|---|---|
| *X* | $CH_2$ | $CH_2$ | O | O |
| % | 61 | 91 | 44 | 22 |

**Scheme 43**

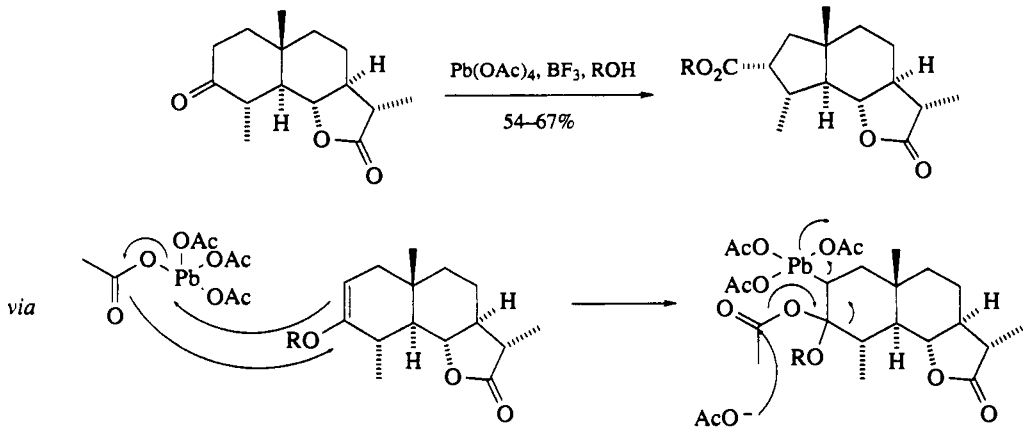
H
O
H
O
O
Pb(OAc)4, BF3, ROH
54–67%
RO2C
H
H
O
O
via
O
O
OAc
OAc
Pb
OAc
RO
H
H
O
O
AcO
OAc
Pb
AcO
O
O
RO
H
H
O
O
AcO

**Scheme 44**

The Favorskii-type rearrangements of chloroenamines such as (**31**) have received some investigation, and key results are presented in Scheme 45.[90] Finally, the so-called homo-Favorskii rearrangement has been probed, and an example from the original work of Wenkert and coworkers is illustrated in Scheme 46.[91] A partially successful homo-Favorskii rearrangement carried out on the diterpenoid (**32**; a derivative of virescenol A) is shown in Scheme 47,[92] but the synthetic potential of this variant of the Favorskii rearrangement remains to be established.

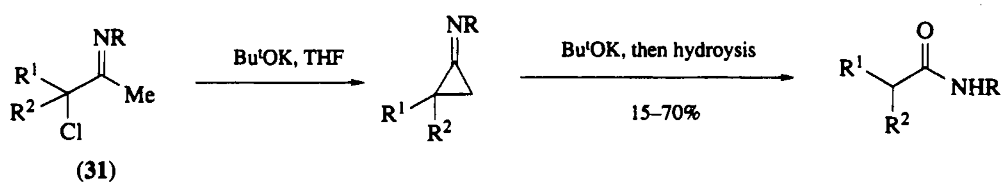
NR
R1
R2
Me
Cl
(31)
Bu^tOK, THF
NR
R1
R2
Bu^tOK, then hydroysis
15–70%
O
R1
R2
NHR

$R^1$ = Me, Ph; $R^2$ = H, Me; R = $Pr^i$, $Bu^t$, Ph, cyclohexyl

**Scheme 45**

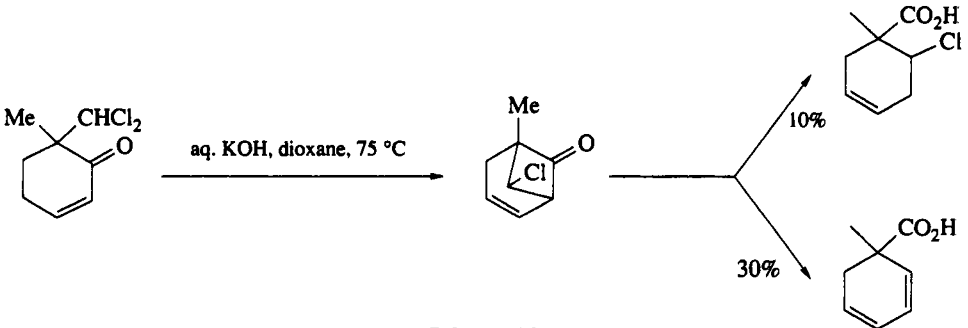
Me
CHCl2
O
aq. KOH, dioxane, 75 °C
Me
Cl
O
10%
CO2H
Cl
30%
CO2H

**Scheme 46**

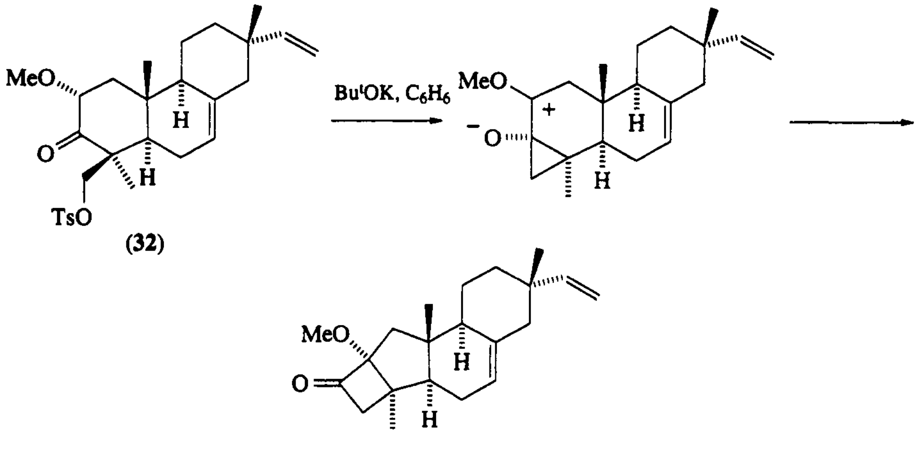
MeO
O
TsO
H
H
(32)
Bu^tOK, C6H6
MeO
+
–O
H
H
MeO
O
H
H

**Scheme 47**

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# 3.8

# The Ramberg–Bäcklund Rearrangement

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## 3.8.1 INTRODUCTION

In 1940, Ramberg and Bäcklund reported a new and surprising reaction, *i.e.* that on treatment with an excess of aqueous KOH, α-bromoethyl ethyl sulfone was converted in high yield into 2-butene (equation 1).[1] α-Chloroethyl ethyl sulfone reacts in the same way, although more slowly. Also surprising was the stereoselectivity of this reaction; bromination of the 2-butene was found to give racemic 2,3-dibromobutane, showing that the (*Z*)-isomer predominated. Since that time, this transformation, now known as the Ramberg–Bäcklund rearrangement, or simply as the Ramberg–Bäcklund reaction, has been used to synthesize a wide variety of alkenes. It is now understood to take place *via* 1,3-elimination of halide from the sulfone α-anion, and loss of $SO_2$ from the resulting thiirane 1,1-dioxide (Scheme 1).

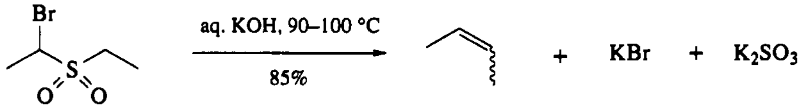

(1)

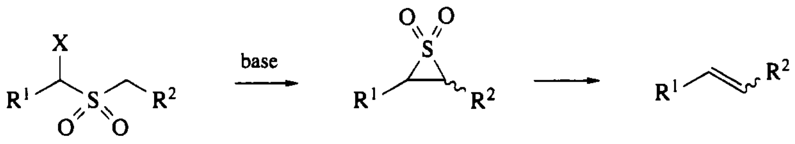

**Scheme 1**

The Ramberg–Bäcklund reaction has been reviewed several times previously,[2] and brief reviews have appeared as recently as 1988.[3] The classic and most comprehensive review was written by Paquette in 1977[4] and, though still extremely useful, particularly with respect to mechanism and the preparation of the α-halo sulfone precursors, it is now, of course, rather out of date. Two older reviews[5,6] are still worth citing because they discuss the mechanism of the reaction in great detail.

## 3.8.2 SCOPE AND IMPORTANT USES OF THE REACTION

The Ramberg–Bäcklund reaction can be used to synthesize mono-, 1,1- or 1,2-di-, tri- and tetra-substituted alkenes, including alkenes substituted with a variety of functional groups. Despite the (*Z*)-stereoselectivity obtained with acyclic α-halo sulfones under the original conditions of Ramberg and Bäcklund, the reaction is most useful where stereoisomeric alkenes cannot occur because high stereocontrol is not a general feature. Nevertheless, very high (*E*)-stereoselectivity can be achieved in favorable circumstances, especially with functionalized alkenes.

One of the great strengths of the reaction is that there is no ambiguity about the position of the newly introduced double bond; it is fixed by the position of the sulfone group in the precursor, and never migrates under the reaction conditions. Good examples are shown in equations (3) and (29), and in Scheme 20.

The reaction is extremely useful for preparing strained cycloalkenes, particularly cyclobutenes. The success of such reactions stems from the fact that they are not ring forming, but involve contraction of a less-strained saturated ring.

Thiols may be converted into alkenes with one extra carbon atom by successive chloromethylation, oxidation at sulfur, and Ramberg–Bäcklund rearrangement. If the original thiol is prepared by free radical addition of $H_2S$ to an alkene, the sequence constitutes a one-carbon homologation of alkenes. Although these transformations were at one time important applications of the Ramberg–Bäcklund reaction,[4,5] they have hardly been used in recent years.

Incorporation of deuterium at the vinylic positions of alkenes can be carried out very efficiently by performing the Ramberg–Bäcklund reaction in $D_2O$. Finally, the recently developed 'Michael-induced' and 'vinylogous' modifications of the Ramberg–Bäcklund reaction offer useful approaches to conjugated dienes and polyenes.

## 3.8.3 PREPARATION OF PRECURSORS: α-HALO SULFONES

α-Halo sulfones are most commonly prepared by successive oxidation and halogenation (or *vice versa*) of the corresponding sulfides. These, and other methods, have been described in detail by Paquette,[4] while more recent reviews give numerous ways to prepare sulfones[7] and α-halo sulfides.[8] Representative pathways to α-halo sulfones are shown in the schemes throughout this review.

## 3.8.4 REACTION CONDITIONS

The first rearrangements of α-halo sulfones were performed using aqueous hydroxide, and these conditions are still frequently used. However, the rearrangement takes place in a wide variety of base–solvent systems and the yield and stereochemical outcome are often strongly dependent on the conditions chosen. The work of Scholz, in which he uses the reaction to prepare a variety of alkenes with remote carboxy groups, usefully illustrates this point. Examples are shown in Schemes 2[9] and 3.[10,11] In each case, treatment of a cyclic β-keto sulfone with a hypohalite produces a ring-opened α-halo sulfone bearing a carboxy group; Ramberg–Bäcklund rearrangement then furnishes the unsaturated carboxylic acid.

A systematic survey showed that the stereochemical outcome of these Ramberg–Bäcklund reactions is highly dependent on both the base and the solvent used, while the temperature is relatively unimportant.[11] Whereas aqueous hydroxide favors the (*Z*)-alkenes, very high (*E*)-stereoselectivity can be achieved in favorable circumstances using Bu$^t$OK in DMSO. Scholz has also reported reactions analogous to those shown in Scheme 3 involving five- or seven-membered cyclic substrates.[12] An acyclic version gives simple alkenes as products, since the carboxy group is lost during halogenation.[13]

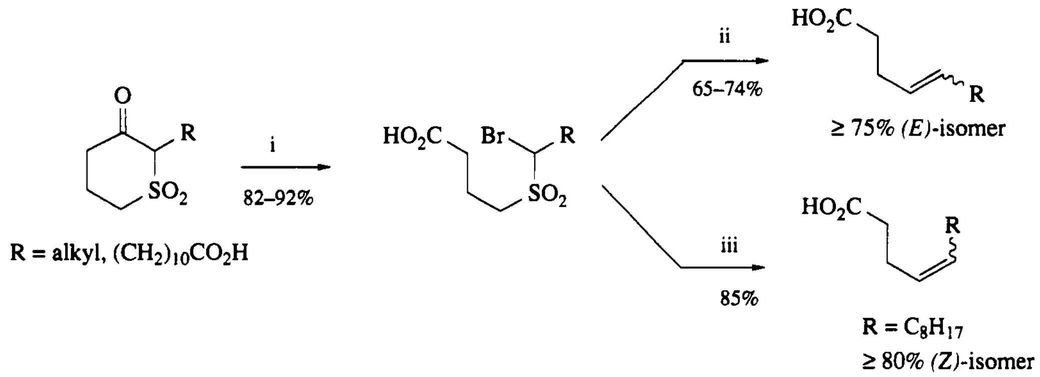

R
SO2
R = alkyl, (CH2)10CO2H
i
82–92%
HO2C
Br
R
SO2
ii
65–74%
HO2C
R
≥ 75% (E)-isomer
iii
85%
HO2C
R
R = C8H17
≥ 80% (Z)-isomer

i, $Br_2$, aq. NaOH, 0 °C, 2 h; ii, Bu$^t$OK, Bu$^t$OH, reflux, 4 h; iii, aq. KOH, 100 °C, 3 h

**Scheme 2**

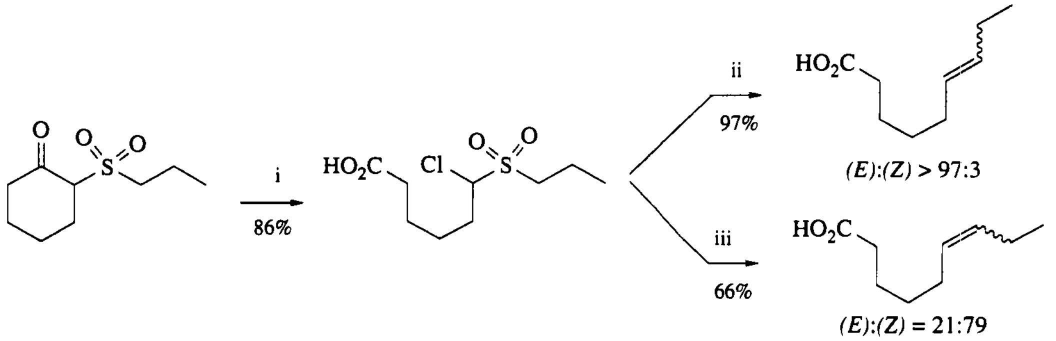

O
O
S
O
i
86%
HO2C
Cl
O
S
O
ii
97%
HO2C
(E):(Z) > 97:3
iii
66%
HO2C
(E):(Z) = 21:79

i, NaOCl, NaOH, aq. EtOH, 0 °C to r.t., 15 h; ii, Bu$^t$OK, DMSO, r.t., 12 h; iii, 0.5 M aq. NaOH, 100 °C, 18 h

**Scheme 3**

The Ramberg–Bäcklund reaction using hydroxide as base can also be performed under phase-transfer conditions, the rate of reaction varying markedly from one substrate to another (equations 2 and 3).[14] One advantage of using these conditions is that ester groups are not hydrolyzed (equation 4; compare equation 46).

Without doubt, the most important modification of the Ramberg–Bäcklund reaction is the result of the work of Meyers. In 1969, he reported that a suspension of powdered KOH in a mixture of $CCl_4$ and Bu$^t$OH is a powerful chlorinating system for a variety of compounds with acidic methylene groups.[15]

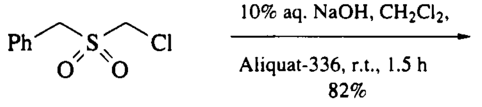

Ph
S
Cl
O
O
10% aq. NaOH, CH2Cl2,
Aliquat-336, r.t., 1.5 h
82%
Ph

(2)

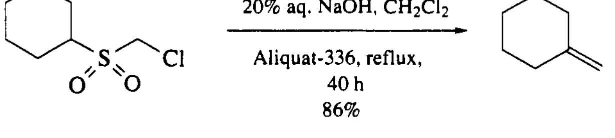

S
Cl
O
O
20% aq. NaOH, CH2Cl2
Aliquat-336, reflux,
40 h
86%

(3)

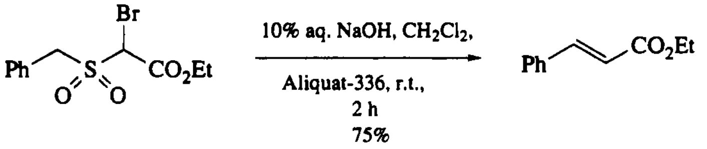

(4)

Sulfones with α-hydrogens, for example, are converted into α-chloro sulfones on treatment with this mixture of reagents. More interesting, however, is the observation that α-chloro sulfones are formed but cannot be isolated from reactions of sulfones with both α- and α′-hydrogens; instead, further reaction, often Ramberg–Bäcklund rearrangement, takes place in the basic reaction medium. Clearly, the ability to convert sulfones into alkenes in one operation, circumventing a separate halogenation step, is extremely useful. Furthermore, the reagents required for this reaction are easy to handle, readily available and are easily separated from the reaction products. For these reasons, Meyers' variant of the Ramberg–Bäcklund reaction has been used with great frequency, and many examples appear later in this chapter. Meyers himself has written two excellent reviews on this subject.[16,17]

Numerous experiments support the following mechanism for the chlorination of sulfones under Meyers' conditions. Reaction takes place at the surface of the KOH, where a small concentration of Bu$^t$OK is maintained and is responsible for converting the sulfone into its α-anion. This anion transfers an electron to a molecule of $CCl_4$ to form an intimate 'caged' radical/radical anion pair in which transfer of a chlorine atom is effected by nucleophilic attack of the substrate radical on a chlorine of the $CCl_4$ radical anion. The by-product of this process is the trichloromethyl anion, which can eject chloride to give dichlorocarbene. If the α-chloro sulfone has an α′-hydrogen, further reaction takes place, the course of which depends on the relative rates of 1,3-elimination (which leads *via* a thiirane 1,1-dioxide to the Ramberg–Bäcklund alkenes) and further chlorination (which leads *via* an α,α-dichloro sulfone to the salt of an alkenesulfonic acid).[18] With dibenzyl sulfones, 1,3-elimination clearly predominates since they are converted in high yield into stilbenes (equation 5).[15,19] Di-*s*-alkyl sulfones give tetrasubstituted alkenes, although these often react further with dichlorocarbene to give dichlorocyclopropanes (equation 6).[15] Fortunately, this side reaction can be suppressed by the addition of a suitable carbene trap such as phenol or an inexpensive nucleophilic alkene. Simple acyclic di-primary-alkyl sulfones normally give alkenesulfonates rather than the Ramberg–Bäcklund products (equation 7),[17,20] although branching at the β-position can divert the course of the reaction to give alkenes (Scheme 4).[21] Primary- or *s*-alkyl benzhydryl sulfones give 1,1-diarylalkenes very efficiently, while primary-alkyl benzyl sulfones give mixtures of β-alkylstyrenes and alkenesulfonates.[22] Whichever type of sulfone is used as substrate, carbonyl and primary or secondary hydroxy groups must be protected since they are reactive under Meyers' chlorinating conditions.[15,16,23]

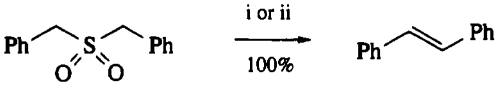

(5)

i, KOH, $CCl_4$, Bu$^t$OH, $H_2O$, 60–80 °C, 10–60 min (ref. 15); ii, KOH, $CCl_4$, $CH_2Cl_2$, $H_2O$, cat. $(PhCH_2)Et_3N^+Cl^-$, 24 h (ref. 24)

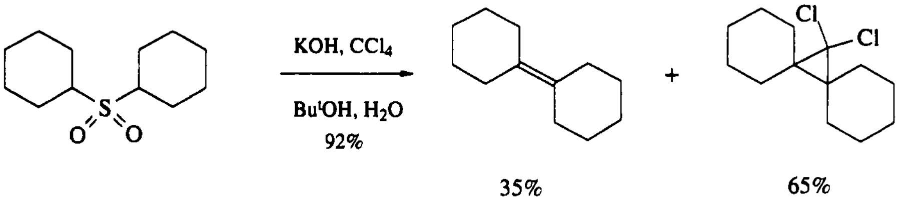

(6)

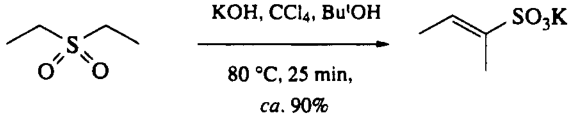

(7)

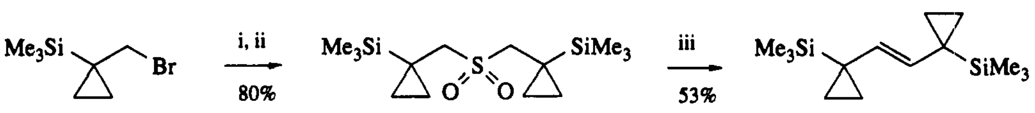

i, $Na_2S{\bullet}9H_2O$, EtOH, heat; ii, MCPBA, $NaHCO_3$, $CHCl_3$; iii, KOH, $CCl_4$, $Bu^tOH$, 50 °C

Scheme 4

Meyers' method has been modified to allow it to be operated under phase-transfer conditions.[14,24] This is a convenient way of converting dibenzyl sulfones directly into (*E*)-stilbenes (equation 5), but it is not so useful for less reactive substrates.

Vedejs has developed a method for the conversion of α-substituted-α-alkoxycarbonyl sulfones directly into α,β-unsaturated esters, whereby chlorination and Ramberg–Bäcklund rearrangement occur consecutively in the same reaction vessel (equation 8).[25] The α-substituent is crucial; without it, the reaction stops after chlorination, presumably because formation of the wrong anion is so strongly favored (equation 9).[25] Cyclic α-alkoxycarbonyl sulfones are particularly good substrates for this reaction (equation 10)[25] and several examples have been reported.[26] In some cases, the rearrangement is slow, and yields are improved if the α-alkoxycarbonyl-α-chloro sulfone is isolated and treated with $Bu^tOK$ in a separate step.[25,27] Although similar to Meyers' variant of the Ramberg–Bäcklund reaction, Vedejs' method is not applicable to simple unactivated sulfones, which are recovered unchanged.

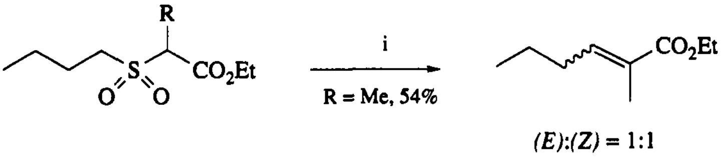

(8)

i, excess NaH, $Cl_3CCCl_3$, DME, 20 °C

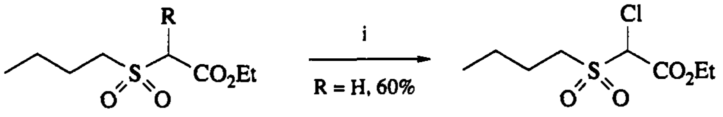

(9)

i, excess NaH, $Cl_3CCCl_3$, DME, 20 °C

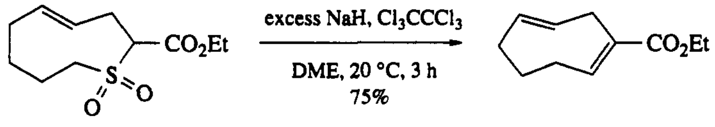

(10)

Sulfones may also be converted directly into alkenes by oxidation of their α,α′-dianions with copper(II) chloride; the intermediate thiirane 1,1-dioxides extrude $SO_2$ under the reaction conditions (equation 11; compare equation 47).[28]

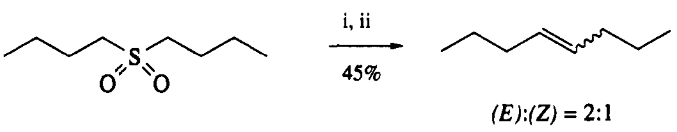

(11)

i, 5 equiv. $Bu^nLi$, DME, 0 °C or below; ii, 5 equiv. $CuCl_2$, r.t.

## 3.8.5 COMPATIBILITY OF FUNCTIONAL GROUPS

Ramberg–Bäcklund reactions are always performed under basic conditions, and sulfones containing incompatible functional groups must obviously be protected. Carbonyl groups, for example, may be protected as acetals (*e.g.* Scheme 21). Certain functional groups may undergo 1,2-elimination under the reaction conditions (*e.g.* equation 24), and if this affects the α-halo sulfone, Ramberg–Bäcklund rearrangement may be prevented from taking place (Scheme 5[29] and equation 12[30]). Further examples of undesirable competing 1,2-elimination are shown in Scheme 18 and equation (25). The α-chloro sulfone (**1**) undergoes 1,2-elimination when treated with an excess of KOH, but with 1 equiv. an intriguing Ramberg–Bäcklund-like rearrangement involving a 1,7- (instead of the usual 1,3-) elimination step takes place (Scheme 6).[16,17,31]

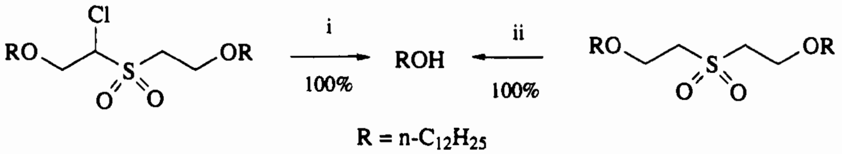
Cl
RO
OR
S
O
O
i
100%
ROH
ii
100%
RO
OR
S
O
O

R = n-$C_{12}H_{25}$

i, $\mathrm{Bu^tOK}$ or NaOMe or NaOH in THF, 0 °C; ii, $\mathrm{Bu^tOK}$, $CCl_4$, THF

Scheme 5

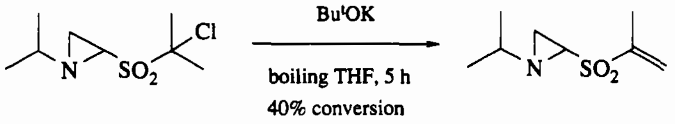
N
$SO_2$
Cl
$\mathrm{Bu^tOK}$
boiling THF, 5 h
40% conversion
N
$SO_2$

(12)

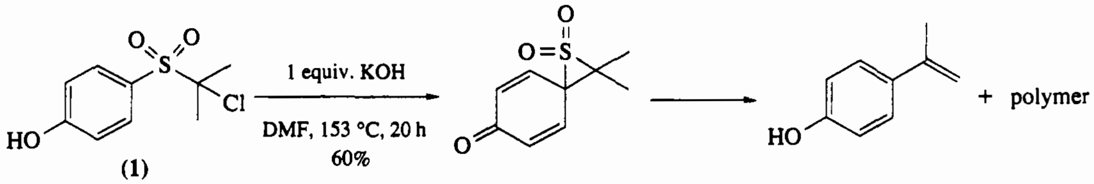
O
O
S
Cl
HO
(1)
1 equiv. KOH
DMF, 153 °C, 20 h
60%
O
O=S
O
HO
+ polymer

Scheme 6

## 3.8.6 MECHANISM OF THE REACTION

It is now widely accepted that α-halo sulfones are converted into alkenes under the basic conditions of the Ramberg–Bäcklund reaction *via* intermediate thiirane 1,1-dioxides (Scheme 7). Experimental data in support of this mechanism were first put forward by Bordwell in 1951,[32] and extensive studies carried out since that time, particularly by Bordwell and Paquette in the late 1960s and early 1970s, have substantiated this overall scheme and have provided further insight into the mechanisms of the individual steps. Very little additional work concerning the mechanism of the reaction has been published since 1975. Consequently, only a summary of the essential features is presented here, and readers are referred to the detailed reviews, written by the leaders of the key research groups themselves, for the full data which support the following broad outline.[4–6]

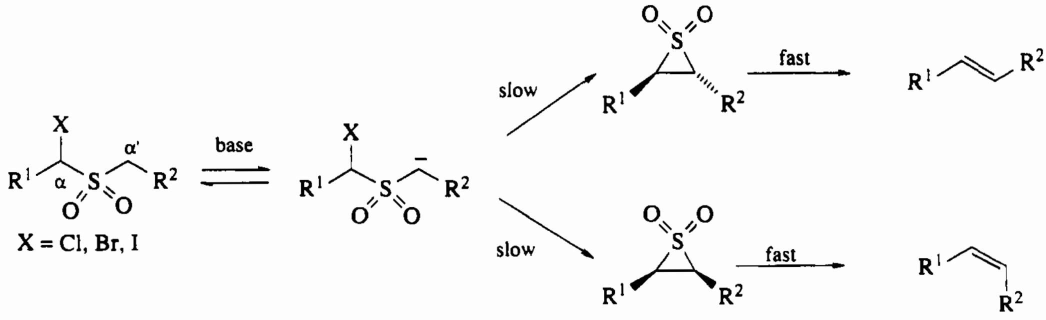
X
$R^1$
α
S
α'
$R^2$
O
O
X = Cl, Br, I
base
X
$R^1$
S
−
$R^2$
O
O
slow
O
O
S
$R^1$
$R^2$
fast
$R^1$
$R^2$
slow
O
O
S
$R^1$
$R^2$
fast
$R^1$
$R^2$

Scheme 7

The transformation of an α-halo sulfone into an alkene takes place in three steps (Scheme 7). Step 1 involves reversible formation of the α′-anion. Under the basic reaction conditions, there is a rapid equilibration of the α-halo sulfone with its α- and α′-anions. Only the α′-anion leads to step 2 which is intramolecular displacement of a halide ion to give a thiirane 1,1-dioxide, generally as a mixture of *cis* and *trans* isomers. This is the rate-limiting step. Finally, in step 3, the thiirane dioxides lose $SO_2$ to give the stereoisomeric alkenes. This transformation can take place *via* two distinct pathways; one is thermal, while the other involves base catalysis. Both pathways are stereospecific; *trans*- or *cis*-thiirane 1,1-dioxides give only (*E*)- or (*Z*)-alkenes, respectively. Consequently, the stereochemical outcome of the overall reaction is determined at the ring-forming step 2.

Strongest evidence for a rapid equilibration of the α-halo sulfone with its α- and α′-anions comes from reactions performed in $D_2O$. If such reactions are interrupted before they are complete, the recovered α-halo sulfones are almost fully deuterated at both the α- and α′-positions. Furthermore, the alkene products are also essentially fully deuterated, this time at the vinylic positions. When allowed to run to completion, this forms the basis of a very useful preparative method for deuterium-labeled alkenes (Scheme 8[33] and equation 24). Not only is a high percentage incorporation possible, but the source of deuterium is very cheap.

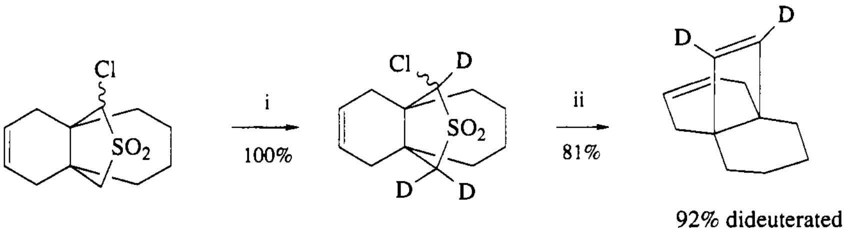

i, NaOD, $D_2O$, dioxane, reflux, 72 h; ii, Bu$^t$OK, THF, reflux, 4 h

**Scheme 8**

Halogens of α-halo sulfones are remarkably resistant to intermolecular nucleophilic substitution due to a combination of steric effects and the large negative field of the oxygen atoms of the sulfonyl group.[34] However, during the Ramberg–Bäcklund reaction, displacement of halide occurs in an intramolecular sense, leading to diastereomeric thiirane 1,1-dioxides. These intermediates are not normally deprotonated under the reaction conditions. However, if one or both of the groups $R^1$ or $R^2$ (Scheme 7) stabilizes an adjacent negative charge, or if a very strong base is used, reversible deprotonation and hence equilibration of the diastereoisomeric thiirane dioxides can occur. Under such circumstances, the ratio of (*E*)- to (*Z*)-alkenes does not reflect the ratio of first-formed thiirane dioxides. Instead, (*E*)-stereoselectivity can be rather high, the simple result of the greater stability of the *trans*-thiirane dioxide intermediate. For example, α,β-unsaturated ketones, sulfones and acids of (*E*)-configuration are formed when the appropriate sulfone precursors are successively brominated and treated with alkoxide (equations 13–15).[35]

The precise mechanisms by which thiirane 1,1-dioxides are converted stereospecifically into alkenes and $SO_2$ (or products derived from $SO_2$) are not clear.[6,36,37] In typical Ramberg–Bäcklund reactions both thermal and base-catalyzed mechanisms are likely to be in operation, with the latter generally predominating. The importance of the base-catalyzed pathway accounts for the fact that thiirane 1,1-dioxides

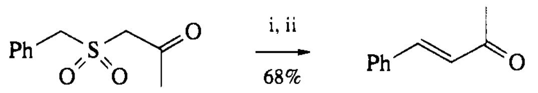

(13)

i, $Br_2$, aq. $K_2CO_3$, $CHCl_3$; ii, NaOMe, MeOH, reflux, 0.5 h

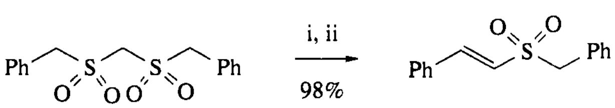

(14)

i, $Br_2$, aq. $K_2CO_3$, $CHCl_3$; ii, NaOMe, MeOH, reflux, 0.5 h

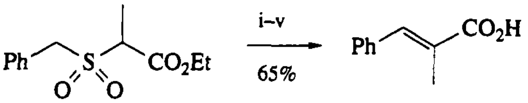

(15)

i, NaH, benzene, reflux, 10 min; ii, $Br_2$, benzene, 10 °C; iii, NaOEt, EtOH, reflux, 0.5 h;
iv, KOH, EtOH, reflux, 10 min; v, $H_3O^+$

have never been isolated from Ramberg–Bäcklund reactions. Nevertheless, they can be prepared by quite independent methods,[38] and it is samples obtained in this way which have allowed their properties, such as the stereospecificity of their decomposition to alkenes, to be established.

Finally, no definitive mechanistic explanation has been given for one of the most intriguing aspects of the Ramberg–Bäcklund reaction, the fact that acyclic α-halo sulfones consistently give products rich in the (*Z*)-isomer.[4,6]

## 3.8.7 RELATED REACTIONS

### 3.8.7.1 Replacement of the Halide

Variations of the Ramberg–Bäcklund reaction have been described in which the usual halide ion is replaced by *p*-toluenesulfonate or *p*-toluene-, alkane- or trifluoromethane-sulfinate leaving groups. For example, Meyers has described a single transformation of the Ramberg–Bäcklund type of an α-tosyloxy sulfone (Scheme 9).[39] The reaction is surprisingly slow, nearly 1000 times slower than that of the corresponding α-chloro sulfone under the same conditions, and this, of course, limits its value in synthesis. Another problem is the fact that the precursors are not easy to prepare.

An example of sulfinate functioning as a leaving group is shown in equation (16),[40] while another forms the basis of a useful synthesis of 3-cyclopentenones (Scheme 22). Zwanenburg has reported a transformation related to the Ramberg–Bäcklund reaction in which the halide leaving group is replaced by sulfinate and, in addition, the usual sulfone is replaced by sulfoxide.[41]

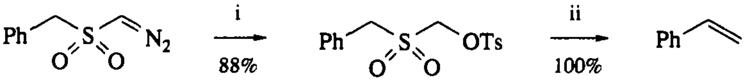

i, *p*-TsOH, $ClCH_2CH_2Cl$, 25 °C, 2 h; ii, $Bu^tOK$, $Bu^tOH$, 25 °C

Scheme 9

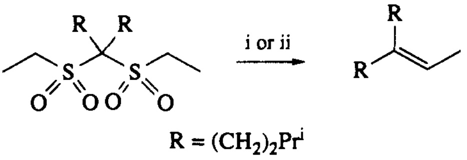

(16)

i, 10% aq. NaOH, 250 °C, 24 h (33%); ii, $LiAlH_4$, $Et_2O$, 24 h (61%)

More useful from a synthetic point of view than any of these variations is the discovery by Hendrickson that trifluoromethanesulfinate ('triflinate') is a very effective leaving group in Ramberg–Bäcklund reactions.[42–44] The reaction succeeds only if the precursors, α-triflyl sulfones, are fully substituted at the α-position; if they are not, simple deprotonation occurs under the basic reaction conditions because the triflyl group is so strongly electron withdrawing. Consequently, this approach is applicable only to the synthesis of 1,1-di-, tri- and tetra-substituted alkenes.

The precursors for this reaction can be prepared by multiple alkylations of mesyltriflone (**2**); this can be carried out with a high degree of regiocontrol and, in fact, is facile enough to allow several successive operations in one vessel (Scheme 10).[44] The α-proton of mesyltriflone is so acidic that treatment with

1 equiv. of base (*e.g.* $K_2CO_3$) leaves an α-monoanion which is very stable and difficult to alkylate. Interestingly, a second equivalent of base (usually $\mathrm{Bu^nLi}$) abstracts the second α-hydrogen in preference to an α′-hydrogen to give an α,α-dianion which can be monoalkylated without danger of over reaction. If required, further successive treatments with $\mathrm{Bu^nLi}$ and alkyl halides can be used to introduce either one or two alkyl groups at the α′-position, the α-anion protecting the molecule from premature Ramberg–Bäcklund rearrangement when the α′-anions are formed. Alternatively, the α,α′-dianions can be acylated at the α′-position in high yield by reaction with acid chlorides, anhydrides, esters or chloroformates. (In these reactions, an extra equivalent of base, typically LDA, is added since the β-keto sulfone products are more acidic than the starting sulfones.) Finally, the second α-position is alkylated (this can be performed only with very reactive alkylating agents and requires elevated temperatures), and treatment with another equivalent of base triggers the Ramberg–Bäcklund rearrangement. Optimum conditions depend on the nature of the substrate. For simple alkylated compounds, $\mathrm{Bu^tOK}$ is generally the base of choice (equation 17). Formation of cyclic disulfones as by-products can be a problem, especially with trialkyl compounds (equation 18).[44] For α′-acylated substrates, the reaction proceeds smoothly on heating with $K_2CO_3$ (*e.g.* Scheme 11, which shows a synthesis of dihydrojasmone),[43] or on treatment with sodium hydroxide under phase-transfer conditions (*e.g.* Scheme 12, which shows the simplest reported synthesis of artemisia ketone).[44]

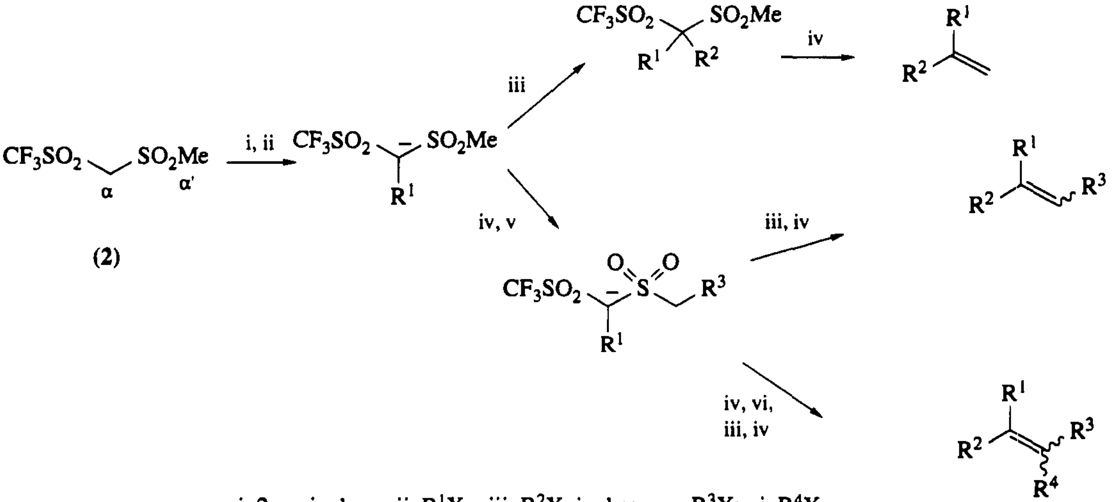
CF3SO2 SO2Me
α α'
(2)
i, ii
CF3SO2 SO2Me
R1
iii
CF3SO2 SO2Me
R1 R2
iv
R1
R2
iv, v
CF3SO2 S R3
R1
iii, iv
R1
R2 R3
iv, vi,
iii, iv
R1
R2 R3
R4

i, 2 equiv. base; ii, $R^1X$; iii, $R^2X$; iv, base; v, $R^3X$; vi, $R^4X$

Scheme 10

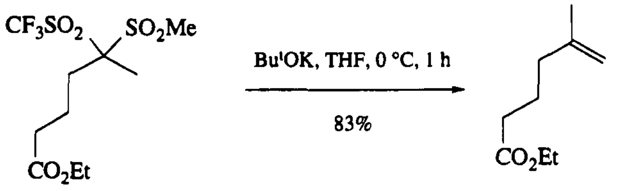
CF3SO2 SO2Me
CO2Et
Bu'OK, THF, 0 °C, 1 h
83%
CO2Et

(17)

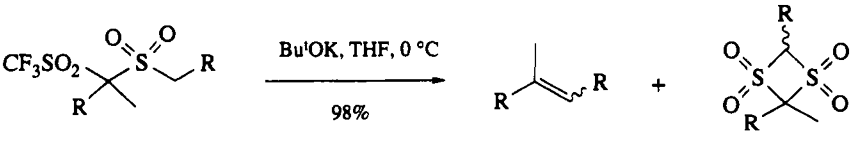
CF3SO2 S R
R
Bu'OK, THF, 0 °C
98%
R R
+
R
R
R = n-pentyl
(E):(Z) = 2.2:1; 46%
trans:cis = 3:2; 54%

(18)

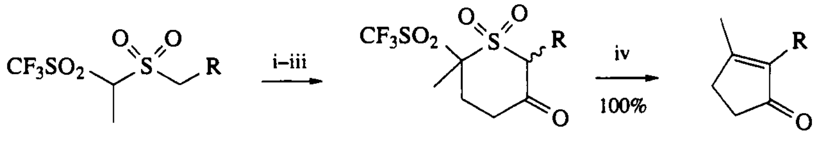

R = *n*-pentyl

i, 2 equiv. $Bu^nLi$, THF, –78 °C; ii, $H_2C{=}CHCHO$; iii, $CrO_3$, aq. acetone, 0 to 5 °C; iv, 2 equiv. $K_2CO_3$, THF, reflux, 3 to 5 h

**Scheme 11**

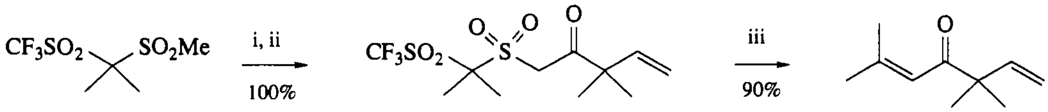

i, 2LDA, THF, –78 °C; ii, 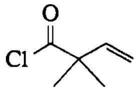 ; iii, 10% aq. NaOH, $CH_2Cl_2$, $Bu_4N^+HSO_4^-$, r.t., overnight

**Scheme 12**

As usual, no significant stereocontrol is observed with these transformations. The alkylation of the mesyltriflone (**2**), although highly regioselective, generally gives diastereoisomeric mixtures of products, which are converted during the Ramberg–Bäcklund reaction into (*E*)/(*Z*)-mixtures of alkenes. Consequently, the sequence is most useful for the synthesis of compounds where stereoisomers are not possible, such as 1,1-disubstituted alkenes and five- or six-membered cycloalkenes.

### 3.8.7.2 Replacement of the Sulfone Group

In simple terms, the function of the sulfone group in Ramberg–Bäcklund reactions is first to stabilize an α-anion and then, following 1,3-elimination of halide, to be extruded efficiently from the intermediate thiirane 1,1-dioxide to yield an alkene. In fact, the sulfone group is not unique in its ability to perform these tasks: transformations related to the Ramberg–Bäcklund reaction have been described in which sulfide, sulfoxide, sulfoximine, phosphine oxide,[45] or phosphinate[46] groups replace the familiar sulfone group. On occasions, even α-halo ketones can be diverted from their usual Favorskii rearrangement to give alkenes instead of carboxylic acids. Reactions which are useful for the synthesis of alkenes are discussed in more detail in the following paragraphs.

Mitchell has reported that benzyl α-chlorobenzyl sulfides are cleanly converted into stilbenes on successive treatment with $PPh_3$ and $Bu^tOK$ (Scheme 13).[47] Desulfurization of an intermediate thiirane by $PPh_3$ is a likely pathway for this reaction. Benzyl α,α-dichlorobenzyl sulfides are converted into diphenylacetylenes under the same conditions.[48] Viehe has reported that pyrolysis of α-halo-α-alkylthio esters, ketones and nitriles under reduced pressure furnishes α,β-unsaturated esters, ketones and nitriles respectively; it is probable that these reactions also take place *via* intermediate thiiranes.[49] α-Chlorophenacyl phenacyl sulfide is converted into (*E*)-dibenzoylethylene on treatment with $Et_3N$.[50]

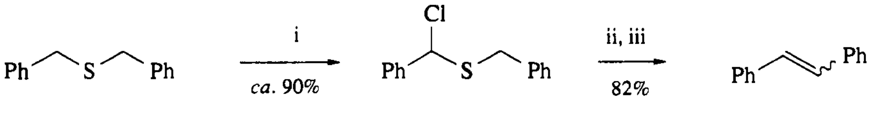

(*E*):(*Z*) = 10:1

i, $SO_2Cl_2$, $CCl_4$; ii, $PPh_3$, THF; iii, $Bu^tOK$, THF, reflux, 24 to 36 h

**Scheme 13**

Cyclobutenes can sometimes be prepared more efficiently from five-membered cyclic α-chloro sulfoxides rather than from the corresponding sulfones (*e.g.* Scheme 17).

Johnson has shown that α-halo-*N*-tosylsulfoximines with an α′-hydrogen atom, on treatment with KOH in refluxing methanol, undergo rearrangement to alkenes by analogy with the Ramberg–Bäcklund reaction.[51] Surprisingly, alkenes are not formed from the corresponding *N*-H- or *N*-methyl-sulfoximines under these conditions. Two types of *N*-tosylsulfoximine were examined. The first, alkyl-α-chloroalkylsulfoximines, give alkenes as approximately 1:1 mixtures of geometric isomers (equation 19). By contrast, alkyl- or benzyl-α-bromobenzylsulfoximines give predominantly (*Z*)-alkenes, together with significant quantities of sulfoximines resulting from debromination (equation 20). This (*Z*)-stereoselectivity probably stems from equilibration *via* deprotonation of the intermediate 2-phenylepisulfoximines in favor of the isomer in which substituents at the 2- and 3-positions are both *trans* to the bulky tosyl group.

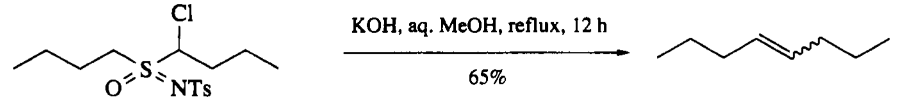

(19)

single unidentified diastereoisomer

(*E*):(*Z*) = 52:48

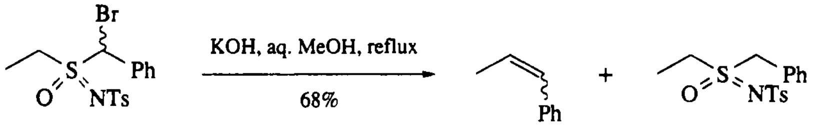

(20)

1:1 mixture of diastereoisomers

72% (*E*):(*Z*) = 8:92 28%

Under basic conditions, α-halo ketones with an α′-hydrogen atom generally undergo Favorskii rearrangement *via* cyclopropanones to carboxylic acids. It is clear that while the ring closure step of this transformation resembles that of the Ramberg–Bäcklund reaction, the subsequent ring-opening step does not. However, under certain conditions and with particular substrates, α-halo ketones can be redirected to give alkenes *via* (in some cases formal) loss of carbon monoxide from the intermediate cyclopropanones. An isolated example is shown in equation (21).[52] In this case, the intermediate cyclopropanone reacts with hydroperoxide anion to form an adduct which collapses to the alkene with loss of carbon dioxide and hydroxide ion; the Favorskii acid is a by-product. Far more useful is a preparative method for 2-cyclopentenones based on the ring contraction of 2-chloro-1,3-cyclohexanediones which was discovered by Büchi (Scheme 14)[53] and has since been applied on numerous occasions.[54] The success of this reaction depends on the use of a non-nucleophilic base, which avoids simple dechlorination of the substrate; a systematic survey showed that $Na_2CO_3$ is the reagent of choice.

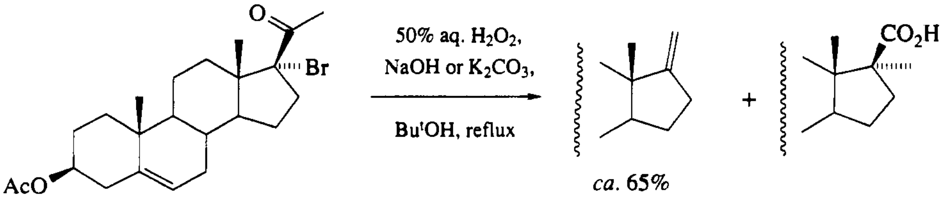

(21)

*ca.* 65%

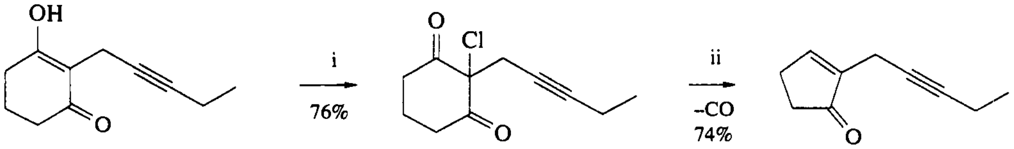

i, $Bu^tOCl$, $CHCl_3$, −15 °C; ii, $Na_2CO_3$, boiling xylene, 12 h

**Scheme 14**

## 3.8.8 SYNTHESIS OF CYCLOALKENES

### 3.8.8.1 Cyclobutenes

In spite of an unpromising early report,[55] the Ramberg–Bäcklund rection has been applied with great success since the early 1970s to the synthesis of cyclobutenes, particularly by Paquette and Weinges. Although yields are often only moderate or low, the reaction still compares favorably with other possible approaches to these strained compounds.

The following general remarks may be made concerning the use of the Ramberg–Bäcklund reaction to prepare cyclobutenes. It is usually performed by treating α-chloro sulfones with an excess of Bu$^t$OK in THF or, less commonly, in dioxane. These precursors are almost always prepared by successive chlorination and oxidation of the corresponding substituted tetrahydrothiophenes. Since the intermediate α-chloro sulfides and α-chloro sulfones are frequently formed as mixtures of regio- and stereo-isomers, it is convenient to use them in a crude form, and to withhold purification until after the Ramberg–Bäcklund reaction itself. The reaction is particularly suitable for the synthesis of cyclobutenes which are unsubstituted at the vinylic positions and fully substituted at the 3- and 4-positions, and the products of the reactions in the following examples are mostly compounds of this type. Meyers' method for the direct conversion of sulfones into alkenes appears not to have been applied to the synthesis of cyclobutenes.[24]

A Diels–Alder reaction with a substituted maleic anhydride followed by a Ramberg–Bäcklund rearrangement are key steps in a reaction sequence which Paquette has used frequently for the synthesis of fused cyclobutenes.[56–58] An example is shown in Scheme 15.[58] Weinges has prepared 1,4-bridged Dewar benzenes using double Ramberg–Bäcklund reactions which introduce both double bonds simultaneously (Scheme 16).[59] Although yields are low, these compounds are difficult to prepare by other methods. The interesting tetracyclic hydrocarbon pterodactyladiene was prepared for the first time using another double Ramberg–Bäcklund reaction (equation 22).[60]

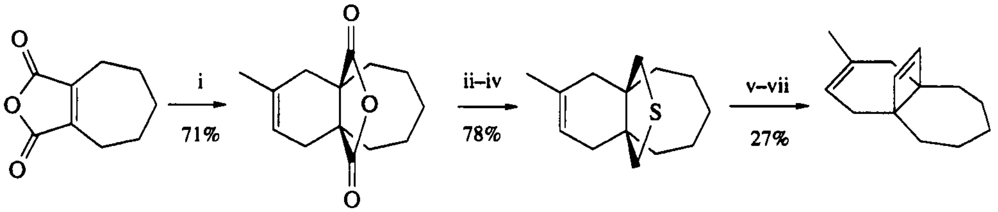

i, isoprene, hydroquinone, dioxane, 170 °C, 68 h; ii, LiAlH$_4$, THF; iii, MeSO$_2$Cl, Py, 0 °C; iv, Na$_2$S, HMPA, 130 °C, 20 h; v, NCS, CCl$_4$, reflux, 1 h; vi, monoperphthalic acid, Et$_2$O, –78 to 0°C; vii, Bu$^t$OK, THF, –78 to 0 °C

**Scheme 15**

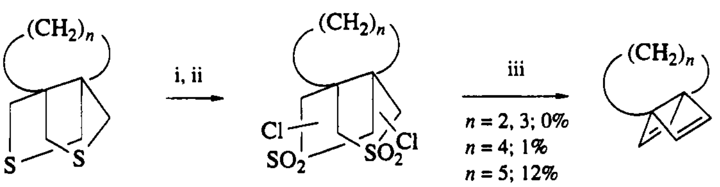

i, NCS, CCl$_4$, 0 °C, 4 h; ii, monoperphthalic acid, Et$_2$O, r.t., 2 to 3 d; iii, Bu$^t$OK, THF: for $n$ = 4, –15 °C, 24 h; for $n$ = 5, r.t., 18 h, then reflux, 2 h

**Scheme 16**

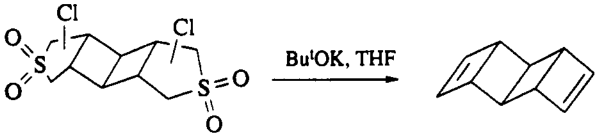 (22)

Pterodactyladiene

Weinges has discovered that, on occasions, cyclobutenes can be prepared far more efficiently using α-chloro sulfoxides rather than the conventional α-chloro sulfones as precursors (Scheme 17).[61] The course of these reactions is analogous to the usual Ramberg–Bäcklund reaction, proceeding *via* base-catalyzed or thermal elimination of sulfur monoxide from thiirane 1-oxide intermediates.[37] In fact, Weinges was able to isolate such intermediates from some reactions and these were converted into cyclobutenes by treatment with Bu$^t$OK in refluxing THF[62] or with LAH in THF at 55 °C.[63] It is not clear why sulfoxides give better yields than sulfones in these reactions.

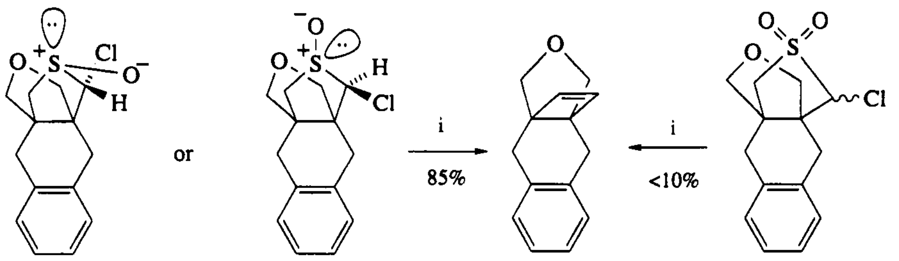

either pure stereoisomer

i, Bu$^t$OK, THF, –70 °C to r.t. over 2 h, then 55 °C, 2 h

**Scheme 17**

As the preceding examples illustrate, most successful applications of the Ramberg–Bäcklund reaction to the synthesis of cyclobutenes involve as precursors 2-halotetrahydrothiophene 1,1-dioxides which are fully substituted at the 3- and 4-positions. Where this is not the case, simple 1,2-elimination of hydrogen halide can compete with the required 1,3-elimination. For example, the simple substrate (**3**) is converted into 1,2-dimethylenecyclobutane (**4**), the product of 1,2-elimination of HCl, rather than the product expected from Ramberg–Bäcklund rearrangement (Scheme 18).[64] Nevertheless, on treatment with Bu$^t$OK, either of the epimeric α-bromo sulfones (**5**) and (**6**) are converted with surprising efficiency into the highly strained cyclobutene (**7**). It is postulated that competing 1,2-elimination of HBr does not occur in these instances because of unfavorable dihedral angles.[65]

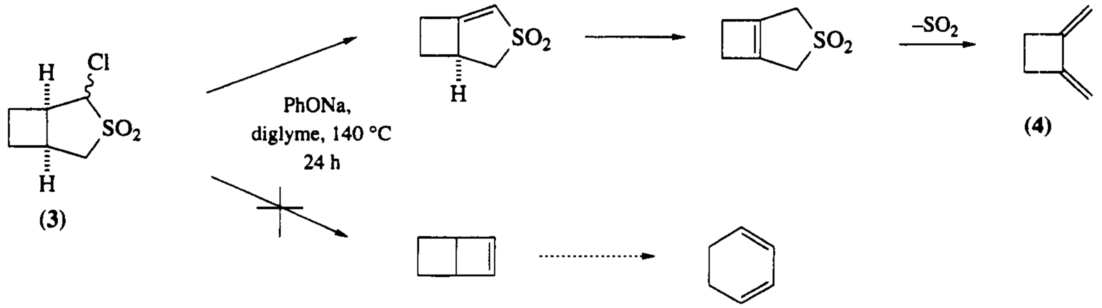

**Scheme 18**

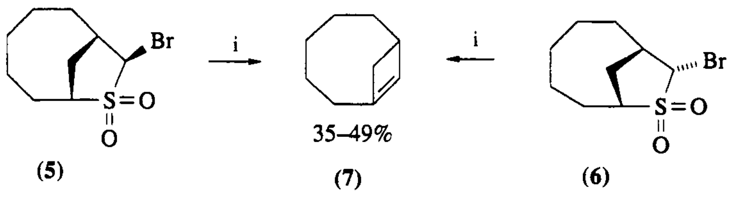

i, Bu$^t$OK, THF, 5 h at –75 °C then warm to room temperature

Cyclobutenes prepared by the Ramberg–Bäcklund reaction are almost always unsubstituted at the vinylic positions. In 1974, Paquette introduced a related and complementary ring contraction which is particularly suitable for the synthesis of 1,2-dialkylcyclobutenes.[33,57,66,67] The reaction takes place when carbanions of five-membered cyclic sulfones are treated with LAH in refluxing dioxane (Scheme 19).[66] The mechanism of the reaction is not clear. Good yields are obtained only when the sulfone is 2,5-dialkylated; in the absence of these groups, simple reduction of sulfone to sulfide becomes a serious side reaction. Dibenzyl sulfone is converted into a mixture of stereoisomeric stilbenes (56%) and dibenzyl sulfide (23%) under the same conditions.[66]

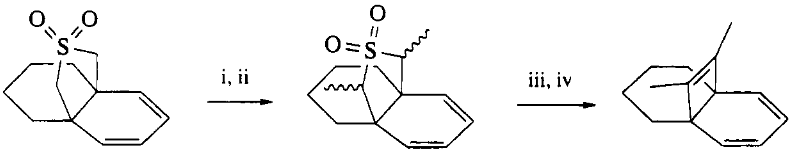

57% overall yield

i, 2 equiv. Bu$^n$Li, THF, –80 °C; ii, excess MeI; iii, Bu$^n$Li, dioxane, 0 °C; iv, LiAlH$_4$, dioxane, reflux, 6 h

**Scheme 19**

### 3.8.8.2 Cyclopentenes, Cyclopentadienes and Cyclopentenones

Since the late 1970s, the Ramberg–Bäcklund reaction has been used to convert a wide variety of six-membered cyclic α-halo sulfones into cyclopentenes, often in high yield; and useful regioselective syntheses of both 2- and 3-cyclopentenones, using sequences in which the Ramberg–Bäcklund reaction is the key step, have also been reported. Bu$^t$OK in THF, diethyl ether or DME are the preferred conditions for these reactions and, in addition, Meyers' method has been used to convert six-membered cyclic sulfones directly into cyclopentenes. Examples of these reactions follow.

Weinges has used the reaction to prepare the stereochemically pure intermediates (**8**), which are useful for the synthesis of cyclopentenoid natural products (equation 23).[68] In contrast to his observations when preparing cyclobutenes (*e.g.* Scheme 17), he found that in these cases, α-chloro sulfoxides give only low yields of cyclopentenes and numerous by-products on treatment with Bu$^t$OK. The Ramberg–Bäcklund reaction has been used to prepare (–)-(*S*)-3-methylcyclopentene (**9**; Scheme 20) as well as its enantiomer.[69] Although the yield is low, this method is very attractive because the product is free from double bond regioisomers. Paquette treated the trihalo sulfone (**10**) with an excess of Bu$^t$OK at low temperatures in a mixture of THF and $D_2O$ to perform a remarkable simultaneous double dehydrobromination and Ramberg–Bäcklund reaction with deuterium incorporation to give the unstable tricyclodecatriene (**11**; equation 24).[70] Bicyclo[2.1.1]hexenes, which, though less elaborate, are related compounds, can be made from 1,3-cyclobutanedicarboxylic acids in a sequence incorporating the Ramberg–Bäcklund reaction.[71] In rigid fused-ring systems, unfavorable geometry can lead to 1,2-elimination of hydrogen halide to give a vinyl sulfone (equation 25) instead of the Ramberg–Bäcklund alkene (equation 26).[65]

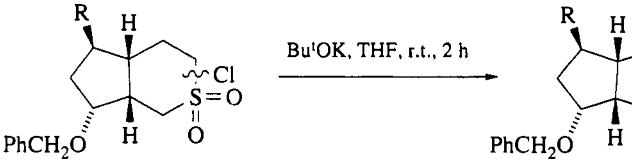

(23)

R = H; 66%; R = PhCH$_2$O; 71% (**8**)

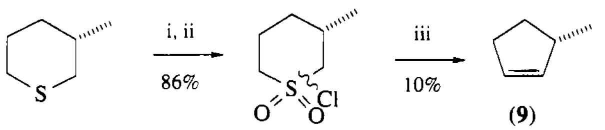

(**9**)

i, NCS, CCl$_4$, heat, 1 h; ii, MCPBA, Et$_2$O, 12 h; iii, Bu$^t$OK, Et$_2$O, 0 °C, 2 h, then reflux, 6 h

**Scheme 20**

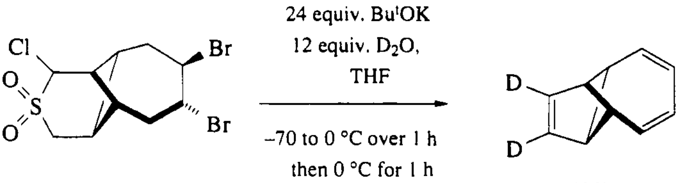

(**10**) (**11**)

(24)

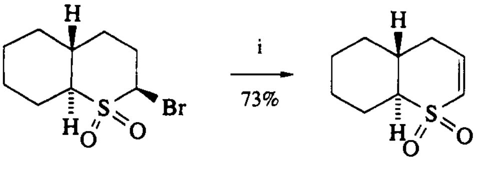

(25)

i, $\mathrm{Bu^tOK}$, THF, –15 °C, 6 h, then r.t., 18 h

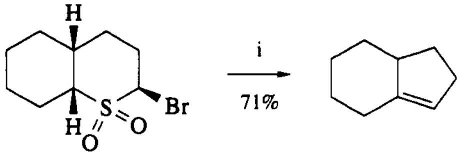

(26)

i, $\mathrm{Bu^tOK}$, THF, –15 °C, 6 h, then r.t., 18 h

The Ramberg–Bäcklund reaction has also been applied to the synthesis of cyclopentadienes. For example, the α-chloro sulfone (**12**), a single unidentified diastereoisomer, was converted regiospecifically into the cyclopentadiene (**13**).[72] In principle, the acidity of the product requires the use of at least 2 equiv. of base for optimum yields, but, in practice, more than 1 equiv. of $\mathrm{Bu^nLi}$ causes appreciable polymerization.

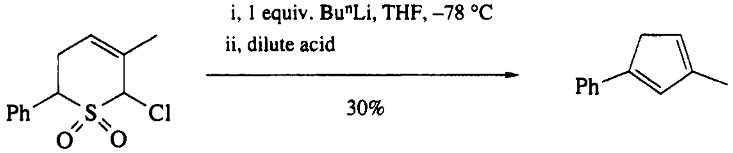

i, 1 equiv. $\mathrm{Bu^nLi}$, THF, –78 °C
ii, dilute acid

**(12)** **(13)**

Matsuyama and Taylor have reported that the Ramberg–Bäcklund reaction may be used to prepare a variety of 2-substituted-3-cyclopentenones (Scheme 21),[73,74] 3-substituted-3-cyclopentenones (Scheme 22)[74,75] and 2,3-disubstituted-2- or -3-cyclopentenones (Scheme 23).[76] De Waard has applied similar chemistry to the synthesis of the D-ring of a steroid.[77] In each case, the carbonyl group is protected as an acetal during the ring contraction, and careful hydrolysis is essential if migration of the carbon–carbon double bond into conjugation with the carbonyl group is to be avoided. If 2-cyclopentenones are required, hydrolysis and migration can be performed simultaneously under more strongly acidic conditions (Scheme 23). Other noteworthy features of these reactions are the use of sulfones with Meyers' one-pot basic chlorination conditions in the synthesis of 2-substituted-3-cyclopentenones (Scheme 21) and the use of 4-toluenesulfinate instead of the usual halide leaving group during the synthesis of 3-substituted-3-cyclopentenones (Scheme 22). 2-Cyclopentenones, as well as cyclopentenes, can be prepared very efficiently using Hendrickson's variant of the Ramberg–Bäcklund reaction in which trifluoromethanesulfinate functions as the leaving group (*e.g.* Scheme 11). Furthermore, 2-cyclopentenones can be prepared by ring-contraction of 2-chloro-1,3-cyclohexanediones (*e.g.* Scheme 14).

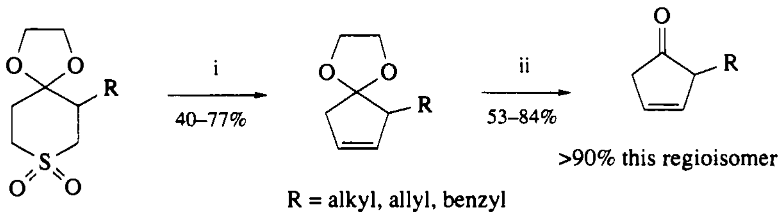

i, $\mathrm{Bu^tOK}$, $\mathrm{CCl_4}$, $\mathrm{Bu^tOH}$, 50 °C, 20 h; ii, *p*-TsOH•Py, aq. acetone, reflux, 22 h

**Scheme 21**

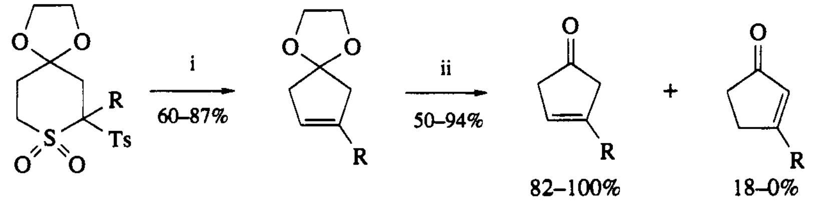

R = alkyl

i, 2.5 to 3.0 equiv. NaH, 0.1 equiv. KH, DMSO, 20 to 30 °C, 24 h; ii, *p*-TsOH•Py, aq. acetone, reflux

Scheme 22

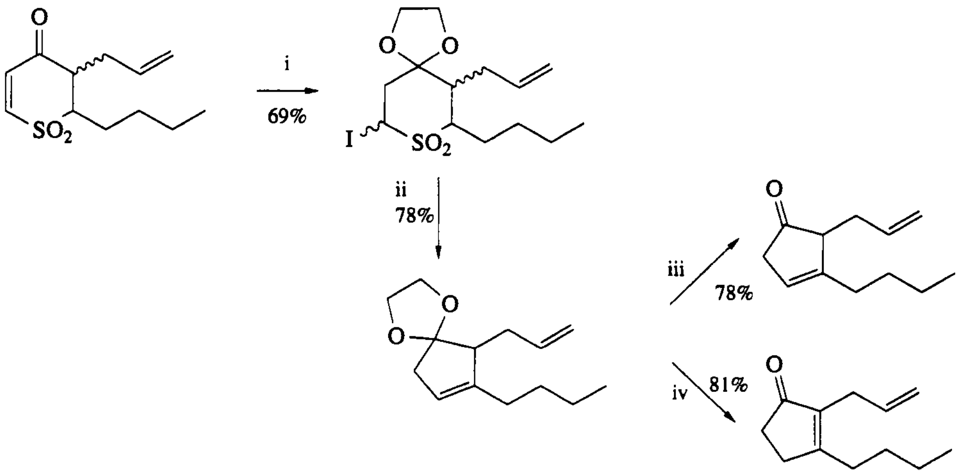

i, $Me_3SiI$, $HOCH_2CH_2OH$; ii, Bu$^t$OK, –78 °C, 0.5 h; iii, *p*-TsOH•Py, aq. acetone; iv, 5% aq. HCl

Scheme 23

### 3.8.8.3 Cyclohexenes and Phenanthrenes

The Ramberg–Bäcklund reaction has not been applied frequently to the synthesis of six-membered rings, but it has nevertheless proved useful where the target compounds are strained. Gassman chose to use the reaction to prepare *trans*-bicyclo[4.1.0]hept-3-ene (**14**), a strained hydrocarbon which slowly isomerizes to the more stable *cis* isomer at 120 °C (Scheme 24).[78] The 7-methyl[79] and 7,7-dimethyl derivatives[80] were prepared by similar methods (with yields of 20% and 45% respectively at the Ramberg–Bäcklund reaction step). Cyclohexenes can be prepared by Hendrickson's variant of the Ramberg–Bäcklund reaction in which trifluoromethanesulfinate functions as the leaving group.[44]

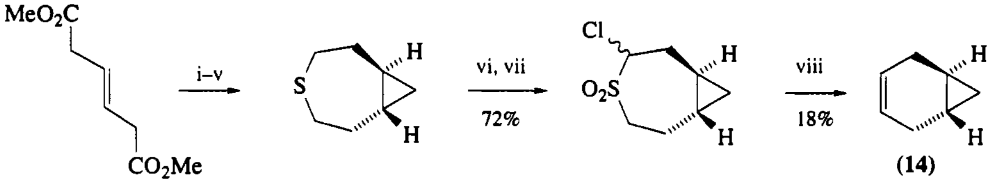

(**14**)

i, Zn–Cu, $CH_2I_2$; ii, $LiAlH_4$; iii, TsCl, Py; iv, LiBr; v, $Na_2S$, high dilution; vi, NCS, $CCl_4$, reflux; vii, MCPBA, $CH_2Cl_2$, 0 to 25 °C; viii, Bu$^t$OK, $Et_2O$, 0 °C

Scheme 24

In 1964, Paquette reported that although the 9,10-double bond of simple phenanthrenes can be formed using the Ramberg–Bäcklund reaction (NaOH in aqueous dioxane), the sterically crowded 4,5-dimethylphenanthrene cannot be made by this method.[81] Staab has now shown that the highly strained 'proton sponge' 4,5-bis(dimethylamino)phenanthrene (**15**) can be prepared using Meyers' modification of the reaction, although over-chlorination under these conditions necessitates an extra reduction step (Scheme 25).[82]

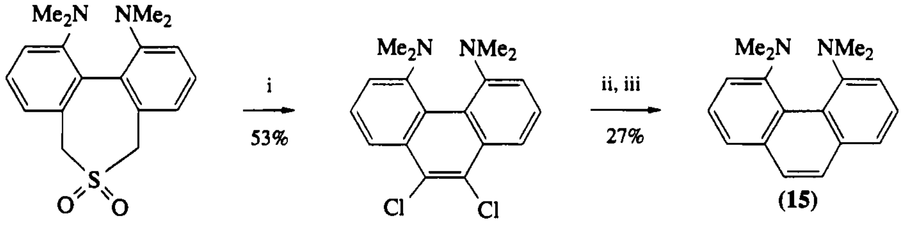

i, KOH, $CCl_4$, Bu$^t$OH, 0 to 20 °C, 1 h; ii, Li, THF, –55 to –35 °C, 1.5 h; iii, MeOH

Scheme 25

### 3.8.8.4 Large Ring Systems

The Ramberg–Bäcklund reaction has been used to synthesize unsaturated cyclophanes and related bridged systems. However, it does not always compare favorably with the alternative methods for the conversion of similar precursors into the same products, namely: (i) the Wittig rearrangement of sulfides followed by repeated methylation and Hofmann elimination;[83] (ii) the Stevens rearrangement of sulfur ylides followed by quaternization and Hofmann elimination;[84] or (iii) the benzyne–Stevens rearrangement of sulfides followed by oxidation and pyrolysis.[85] The major problem with this application of the Ramberg–Bäcklund reaction is the preparation of the appropriate α-halo sulfones; the precursors are frequently benzylic sulfones and it has proved difficult to oxidize these to α-halo sulfones without over-halogenation. When α-halo sulfones can be obtained, the Ramberg–Bäcklund reaction itself takes place in moderate yield (Schemes 26[86] and 27[87]). One way of circumventing these problems is to allow sulfones to react under Meyers' conditions (equation 27).[88] Yields are sometimes low, and over-chlorination can still occur (leading, for example, after dehydrochlorination, to alkynes; equation 28),[89] but despite these drawbacks, the ability of the reaction to introduce a double bond regiospecifically can be extremely valuable. For example, the [3.3]paracyclophanediene (**16**), prepared in just 2% yield by the

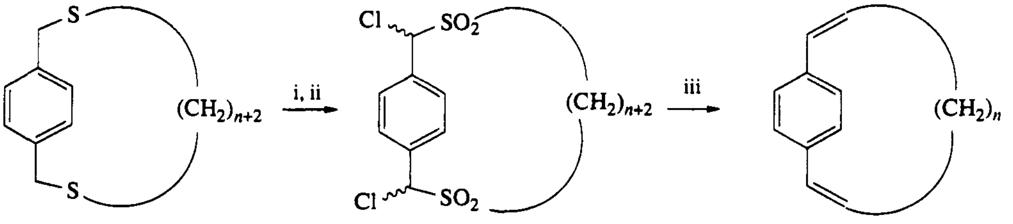

yield from disulfide: $n = 5$; 29%
$n = 7$; 55%

i, NCS, $CCl_4$; ii, MCPBA, $CH_2Cl_2$; iii, 4 equiv. Bu$^t$OK, DME

Scheme 26

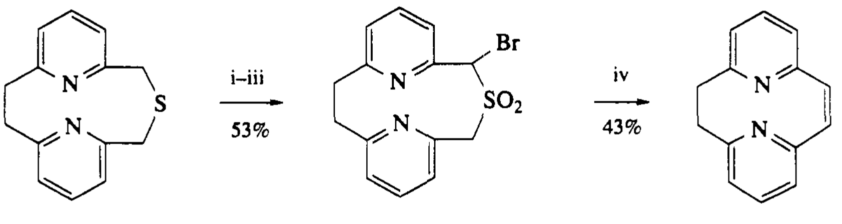

i, $H_2O_2$, cat. tungstic acid, aq. THF, 50 to 60 °C, 1 h; ii, Bu$^n$Li, THF, –78 °C; iii, $Br_2$, –78 °C;
iv, NaOH, aq. dioxane, r.t., 2 h

Scheme 27

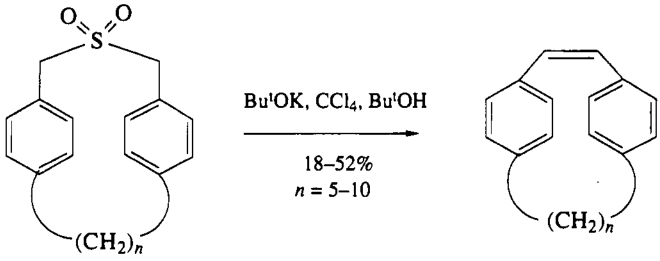

(27)

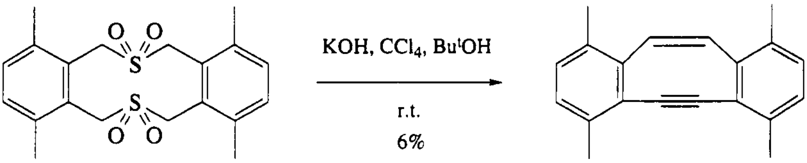

(28)

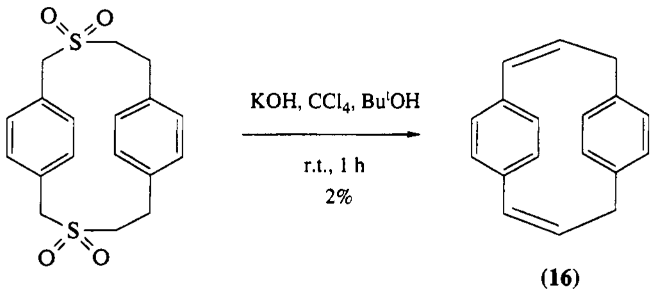

(29)

**(16)**

Ramberg–Bäcklund reaction (equation 29),[90] can be prepared in higher yield using the benzyne–Stevens rearrangement, but, when this approach is used, it is always contaminated with an equal amount of the inseparable regioisomeric [3.3]paracyclophanediene.

## 3.8.9 SYNTHESIS OF CONJUGATED DIENES, ENYNES AND POLYENES

In 1975, it was reported that treatment of each of the stereoisomeric α,β-unsaturated γ-bromo sulfones (**17**) and (**18**) with $Bu^tOK$ leads *via* a vinylogous Ramberg–Bäcklund reaction to the same mixture of stereoisomeric 1,3-dienes (**19**).[91] More recently, Block has demonstrated that α,β-unsaturated α′-bromo sulfones are alternative and versatile precursors for vinylogous Ramberg–Bäcklund reactions, and he has developed this concept into an extremely useful method for the synthesis of dienes and polyenes. Examples are shown in equations (30)–(32).[92–95] The (*Z*)-stereoselectivity of the transformation shown in equation (30) stems from an attractive interaction between the developing negative charge at the α-position and the methylene group at the δ-position of the (*E*)-sulfone (**20**), which favors the transition state leading to the (*Z*)-isomer. With the corresponding (*Z*)-sulfone (**21**); steric effects disfavor the transition state which leads to the (*Z*)-isomer and the (*E*)-diene is the predominant product (equation 31). In a more extreme case (equation 32), the (*E*)-isomer is the exclusive product.

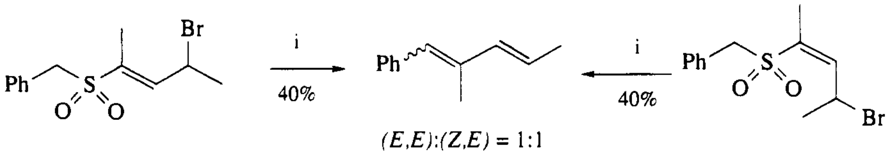

**(17)** **(19)** **(18)**

i, $Bu^tOK$, $Bu^tOH$, r.t., 12 h

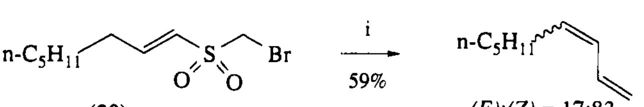

**(20)** $(E)$:$(Z)$ = 17:83 (30)

i, 2.5 equiv. Bu$^t$OK, Bu$^t$OH:THF (7:3), –20 °C, 1 h

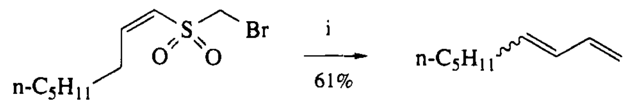

**(21)** $(E)$:$(Z)$ = 94:6 (31)

i, 2.5 equiv. Bu$^t$OK, Bu$^t$OH:THF (7:3), –20 °C, 1 h

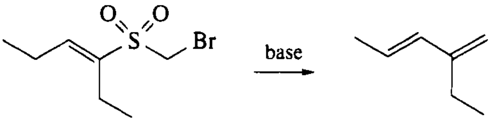

(32)

>99% $(E)$-isomer
[58% yield from $(E)$-3-hexene]

An attractive feature of Block's vinylogous Ramberg–Bäcklund reaction is that the precursors are easily prepared by the addition of α-haloalkanesulfonyl bromides to alkenes followed by elimination of the elements of HBr (Scheme 28). The addition, which takes place for a wide range of alkenes, is almost certainly a free radical chain reaction and is regiospecific for mono-, 1,1-di- and tri-substituted alkenes, with the formation of products consistent with the addition of the sulfonyl radical first to give the more stabilized radical intermediate. Even unsymmetrical 1,2-disubstituted alkenes show a high degree of regioselectivity, and in the case of compounds with both 1,1-di- and tri-substituted double bonds, addition occurs exclusively at the less-hindered disubstituted double bond. The general procedure involves treatment of the crude addition product with $Et_3N$ in $CH_2Cl_2$ at 0 °C, which gives α,β-unsaturated α′-bromo sulfones as stereoisomeric mixtures in which the (*E*)-isomer predominates.[92,94] Taken sequentially, these addition and elimination steps and the vinylogous Ramberg–Bäcklund reaction allow an alkene to be converted into a 1,3-diene. Due to incomplete stereocontrol, during both the elimination and the rearrangement, the sequence is most useful where geometric isomers cannot occur, or for specific classes of compounds where high stereoselectivity has been observed. Several examples are shown in equations (33)–(38).[93,94] In each case, the initial alkene was treated in three successive steps with $BrCH_2SO_2Br$, $Et_3N$ and Bu$^t$OK without separating stereoisomeric intermediates. Particularly noteworthy are the transformations shown in equations (33) and (34), which illustrate how the sequence allows a methylene group to be attached to interior atoms in chains or rings. 1-Methylcyclohexene gives 1,2-dimethylenecyclohexane as the predominant product (equation 36),[96] indicating that Bu$^t$OK preferentially abstracts a proton from the methyl rather than the methylene position of the intermediate unsaturated sulfone. Block has studied the regioselectivity of this deprotonation with Bu$^t$OK and Bu$^t$OLi for a selection of substrates. His results can be rationalized in terms of two effects: (i) abstraction at the less-hindered position is favored with both bases; and (ii) coordination of the cations by sulfonyl oxygen favors deprotonation *syn* to the sulfonyl group, and this effect is far more significant with lithium than potassium. Examples are shown in equations (39) and (40).[94,97]

Conjugated trienes can also be synthesized *via* the vinylogous Ramberg–Bäcklund reaction (Scheme 29).[94] However, it is not possible to convert conjugated trienes into conjugated tetraenes using Block's procedure: conjugated trienes fail to give adducts with $BrCH_2SO_2Br$, probably because the intermediate

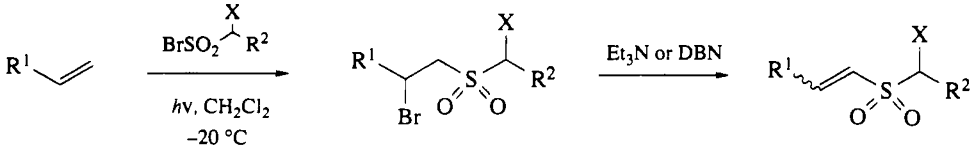

mainly $(E)$-isomer

X = Cl, Br, I; R$^1$ = alkyl, allyl, benzyl, *etc.*; R$^2$ = H, Me

**Scheme 28**

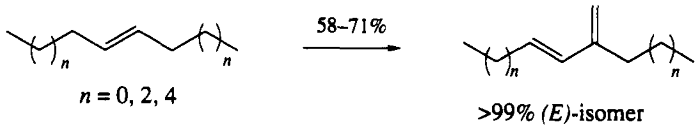
n = 0, 2, 4
58–71%
n
n
>99% (E)-isomer

(33)

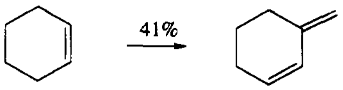

(34)

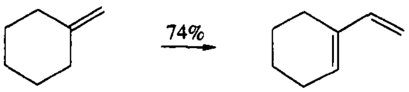

(35)

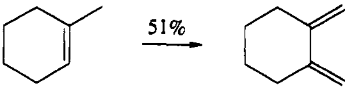

(36)

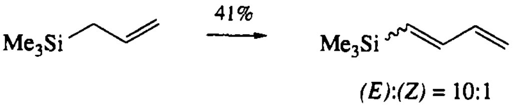
Me3Si
41%
Me3Si
(E):(Z) = 10:1

(37)

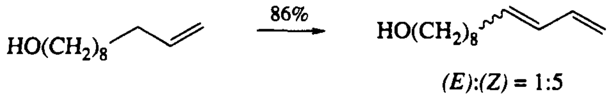
HO(CH2)8
86%
HO(CH2)8
(E):(Z) = 1:5

(38)

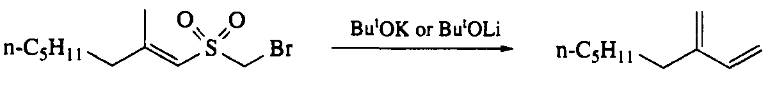
n-C5H11
O
O
S
Br
BuᵗOK or BuᵗOLi
n-C5H11

(39)

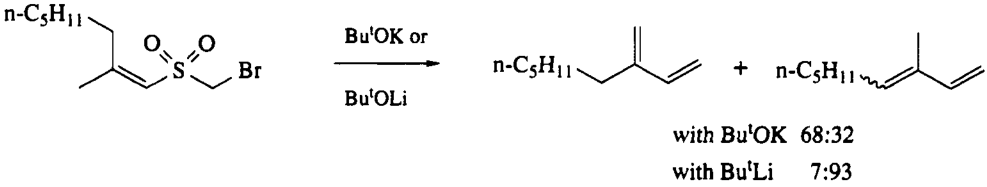
n-C5H11
O
O
S
Br
BuᵗOK or
BuᵗOLi
n-C5H11
+
n-C5H11
with BuᵗOK 68:32
with BuᵗLi 7:93

(40)

pentadienyl radical is too stable to abstract a bromine atom from $BrCH_2SO_2Br$. Nevertheless, conjugated tetraenes can be made by the alternative procedure shown in Scheme 30, a process which involves a Ramberg–Bäcklund rearrangement through three intervening double bonds! Furthermore, terminal or internal alkynes are converted into 1,3-enynes under appropriate conditions (equations 41 and 42).[94]

Block has described a further use for α-haloalkanesulfonyl bromides; radical addition to silyl enol ethers followed by simple Ramberg–Bäcklund rearrangement yields α,β-unsaturated ketones (Scheme 31).[94,98] Ethylene oxide, an acid scavenger, is used as solvent for the radical addition to prevent hydrolysis of the silyl enol ether.

De Waard has developed a modification of the Ramberg–Bäcklund rearrangement in which the intermediate α-sulfonyl carbanion is generated by 1,4-addition of a nucleophile to a vinyl sulfone: the 'Mi-

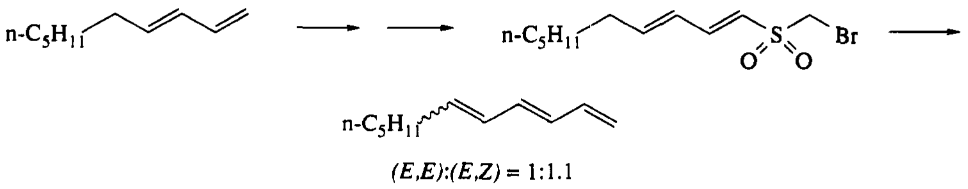
n-C5H11
n-C5H11
S
Br
O
O
n-C5H11
(E,E):(E,Z) = 1:1.1

**Scheme 29**

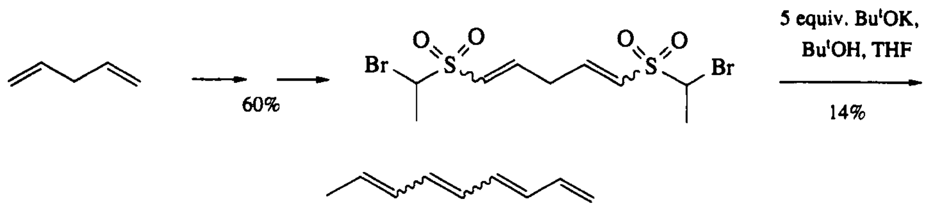
60%
5 equiv. Bu$^t$OK, Bu$^t$OH, THF
14%
Br
Br

**Scheme 30**

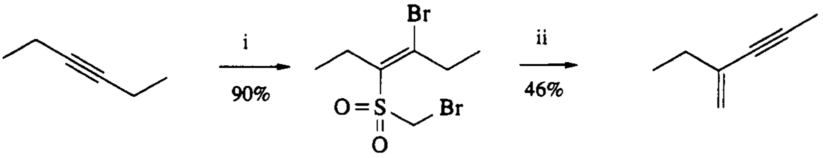
i
90%
ii
46%
Br
Br

(41)

i, 0.5 equiv. $BrCH_2SO_2Br$, *h*ν, $CH_2Cl_2$, –20 °C; ii, 4 equiv. Bu$^t$OK, Bu$^t$OH, THF

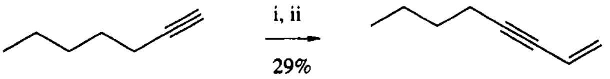

(42)

i, 0.5 equiv. $BrCH_2SO_2Br$, *h*ν, $CH_2Cl_2$, –20 °C; ii, 4 equiv. Bu$^t$OK, Bu$^t$OH, THF

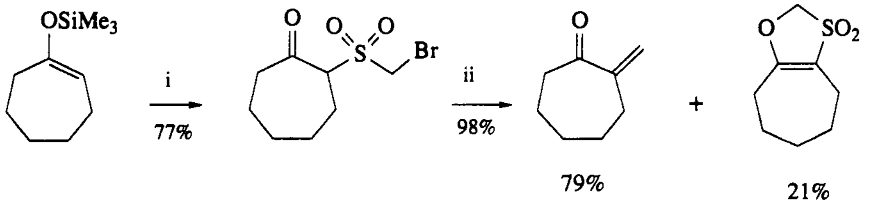
OSiMe$_3$
i
77%
Br
ii
98%
+
79%
21%

i, $BrCH_2SO_2Br$, ethylene oxide, *h*ν, –15 °C; ii, DBN, $CH_2Cl_2$, –78 °C, 2 h, then 23 °C, 0.5 h

**Scheme 31**

chael-induced Ramberg–Bäcklund reaction'.[99] Scheme 32 shows this transformation in its simplest form, though in practice it appears that butadienyl sulfones have been used universally, perhaps because the equilibrium shown does not favor the sulfone α-anion with simple vinyl sulfones (compare Scheme 5). Examples from de Waard[99] and from Block[94] are shown in equations (43) and (44), respectively.

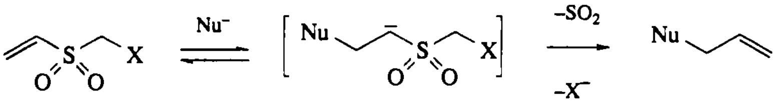
Nu$^-$
Nu
X
–SO$_2$
–X$^-$
Nu

X = Cl, Br; Nu$^-$ = $RSO_2^-$, RO$^-$

**Scheme 32**

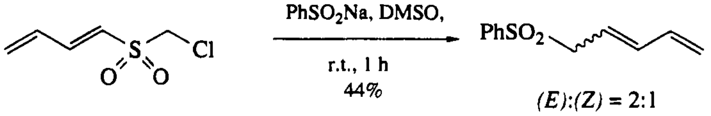
Cl
$PhSO_2Na$, DMSO,
r.t., 1 h
44%
$PhSO_2$

(*E*):(*Z*) = 2:1

(43)

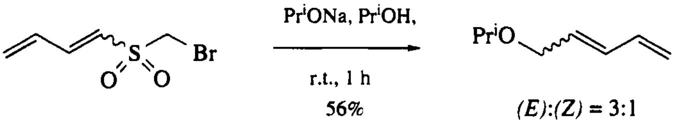
Br
Pr$^i$ONa, Pr$^i$OH,
r.t., 1 h
56%
Pr$^i$O

(*E*):(*Z*) = 3:1

(44)

De Waard has focused on the use of the reaction for the synthesis of conjugated isoprenoids (Scheme 33);[100] the regioisomeric sulfinates (**22**) and (**23**) or their stereoisomers function as the key five-carbon building blocks. Reaction of the sulfinate (**22**) with prenyl chloride followed by chlorination[101] gives the α-chloro sulfone (**24**), precursor for the Michael-induced reaction. Further treatment with the sulfinate (**22**) then gives the stereoisomeric 'head-to-tail' linked pentaenes (**25**), ready for rechlorination and for the cycle to be repeated. Use of the alternative isoprene synthon (**23**) results in 'tail-to-tail' coupling of the isoprene units. When the polyisoprenoid chain reaches the required length, phenylsulfinate is allowed to trigger the rearrangement and gives an allyl phenyl sulfone, *e.g.* the conversion of (**24**) into the stereoisomeric trienes (**26**), from which the phenylsulfonyl group may be removed by reduction.

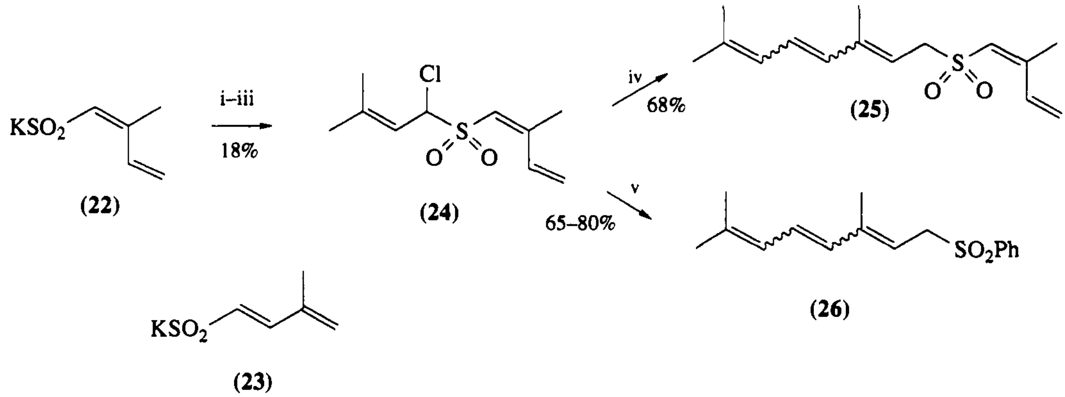

i, prenyl chloride, DMSO, r.t., 40 h; ii, LDA, THF, –78 °C; iii, $Cl_3CCCl_3$, –78 °C to r.t.; iv, (**22**), DMSO, r.t., 68 h; v, $PhSO_2Na$, DMSO, r.t., 0.5 h

**Scheme 33**

The least attractive feature of the Michael-induced Ramberg–Bäcklund reaction is the absence of any useful stereocontrol; where several isomeric products are possible, they are all formed. In fact, both stereoisomers of the α-chloro sulfone (**24**) give the same mixture of trienes (**26**) on treatment with sodium phenylsulfinate.[100] The reaction is presumably most useful if the required isomer can be obtained by equilibration of the complex mixture in a subsequent step.

Bisallylic sulfones are converted into conjugated trienes under Meyers' conditions;[102–104] an example is shown in equation (45).[102] Although experiments with isomerically pure substrates have not been performed, there are indications that the geometry of the allyl groups is conserved during the rearrangement while the newly introduced double bond has mainly the (*E*)-configuration.[104] Meyers' conditions also allow unsaturated β-sulfonyl esters such as (**27**) to be converted into (*E,E*)-dienoic acids, hydrolysis accompanying the rearrangement (equation 46; compare equation 4). An all-(*E*)-trienoic acid was made by the same method.[105]

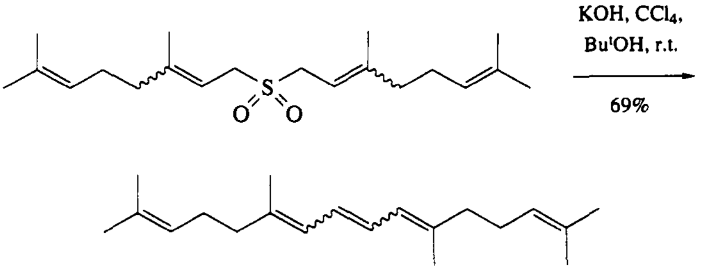

(45)

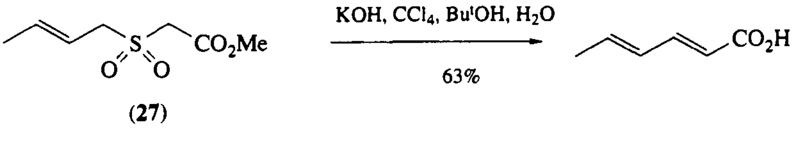

(46)

β-Carotene has been prepared by treatment of an appropriate sulfone α,α′-dianion with bromine or iodine (equation 47).[102] This transformation may be regarded either as proceeding through a conventional α-halo sulfone α′-anion, or *via* a two-electron oxidation to the intermediate thiirane 1,1-dioxide (compare equation 11).

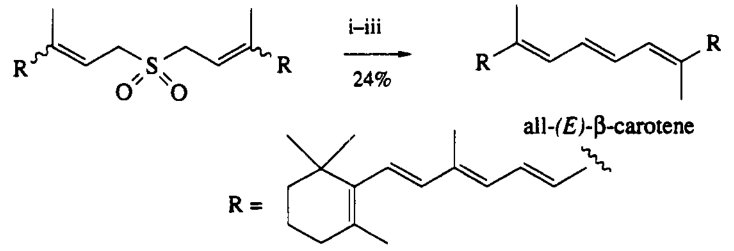

(47)

i, 2 equiv. $Bu^nLi$, THF, 0 °C; ii, $I_2$ or $Br_2$; iii, thermal or $I_2$–catalyzed stereomutation

The reactive cyclodecenediyne ring system found in the calicheamicins has recently been synthesized for the first time, together with a homologous series of larger (11- to 16-membered) rings containing the same enediyne unit.[106] The synthesis of the first derivative (**28**) with DNA-cleaving properties by the same approach (equation 48) was reported soon afterwards.[107]

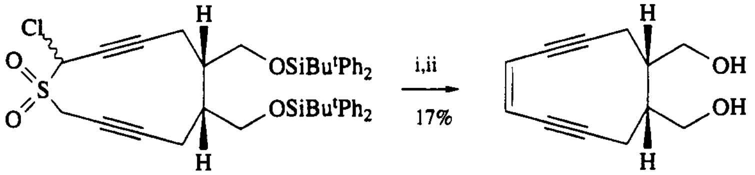

(**28**)

(48)

i, 1.2 equiv. MeLi, $Et_2O$, −78 °C, 15 min (20% yield); ii, $Bu^n{}_4NF$, THF, 1 h (84% yield)

### 3.8.10 SYNTHESIS OF ALKYNES

On treatment with appropriate tertiary amines, both α,α-[108] and α,α′-dihalodibenzyl sulfones[109] are converted into diphenylthiirene 1,1-dioxides which, although far more stable than the corresponding thiirane dioxides, extrude $SO_2$ on heating to give diphenylacetylenes (Scheme 34).[37] The highly strained alkyne acenaphthyne, isolated in the form of its trimer, has been prepared in this way.[110] α-Chloroneopentyl neopentyl sulfone reacts under Meyers' basic chlorinating conditions (KOH, $CCl_4$, $Bu^tOH$) at above 40 °C to give di-*t*-butylacetylene in yields of up to 90%.[16,17]

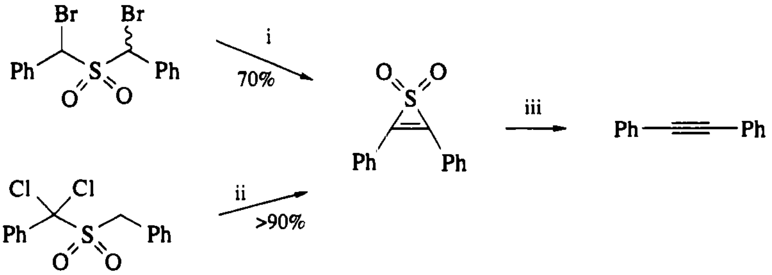

i, $Et_3N$, $CH_2Cl_2$, reflux, 3 h; ii, triethylenediamine, DMSO, r.t.; iii, boiling benzene, several hours, or melt

**Scheme 34**

## 3.8.11 REFERENCES

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# 3.9
# The Wolff Rearrangement

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## 3.9.1 INTRODUCTION

### 3.9.1.1 Historical

During a study of the chemistry of α-diazo ketones at about the turn of the century, Wolff found, for example, that treatment of diazoacetophenone ($PhCOCHN_2$) with water and silver oxide gave not the hydroxy ketone ($PhCOCH_2OH$), but rather the rearrangement product phenylacetic acid ($PhCH_2CO_2H$).[1a] When aqueous ammonia was present in the reaction medium, the corresponding amide ($PhCH_2CONH_2$) was formed in good yield, even in the cold. A few years later, but independently of Wolff, Schröter[1b] published his results of an analogous study. Occasionally, therefore, such transformations of α-diazo ketones are also called the Wolff–Schröter rearrangement.

In a sense the discoveries of Wolff and Schröter were ahead of their time, for over 20 years were to pass before convenient methods for the preparation of the diazo ketones became available. Hence, synthetic applications largely date from the early 1930s. Periodically since then a number of substantial reviews of the Wolff rearrangement have been published,[2-11] testifying to the importance that the reaction has achieved in preparative organic chemistry. Diazo ketone chemistry has achieved modern commercial importance in the photolithography industry.[12]

### 3.9.1.2 Preparative Routes to α-Diazo Ketones

Several methods are now available for the preparation of α-diazo ketones. Of these, the Arndt–Eistert procedure is the most versatile and popular.[2–4,8,10,13,14] In essence, the method involves the *C*-acylation of a primary diazoalkane ($RCHN_2$), usually diazomethane (*i.e.* R = H), with acid chlorides or, less commonly, with acid anhydrides.[15] In practice, it is essential to realize that diazo ketones are decomposed by acid. Hence, the acid chloride should be freshly purified and distilled, and precautions taken to exclude moisture. Any carboxylic acid present is converted by diazomethane into the methyl ester which contaminates the product, reducing the yield. In the classical Arndt–Eistert procedure the diazo ketones are formed in nearly quantitative yield by the slow addition of the acid chloride (1 equiv.) to an ice-cold dry ethereal (or $CH_2Cl_2$) solution of diazomethane (2 equiv.; for higher homologs, see below). The second equivalent of diazomethane combines with the hydrogen halide formed in the first step to give the gaseous by-products methyl chloride and nitrogen (equations 1 and 2). In the absence of the second equivalent of diazomethane,[16] the HCl protonates the diazo ketone and an α-chloro ketone is then formed by the $S_N2$ displacement of nitrogen (equation 3).[3] Triethylamine may frequently be used to take on the role of the second molecule of diazomethane in neutralizing the HCl.[17] With acid anhydrides the reaction produces equimolar quantities of the diazo ketone and the methyl ester (equation 4). The addition of a mixture of a carboxylic acid (1 equiv.) and dicyclohexylcarbodiimide (1 equiv.) in ether to ice-cold ethereal diazomethane (1.25 equiv.) or diazoethane (1.25 equiv.) affords the corresponding diazoketones (max. yield 50%) by way of acid anhydride intermediates (Scheme 1).[18] This route may be applicable in thoses cases where the conventional Arndt–Eistert method fails.

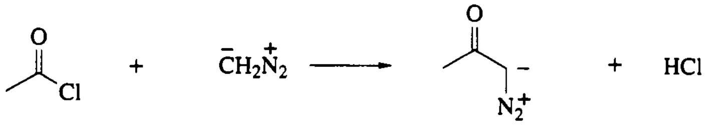
(1)

$$HCl + \bar{C}H_2\overset{+}{N}_2 \longrightarrow MeCl + N_2 \qquad (2)$$

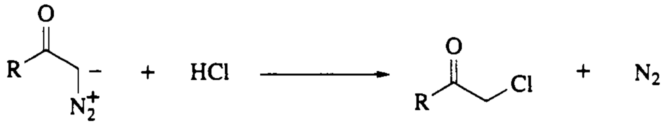
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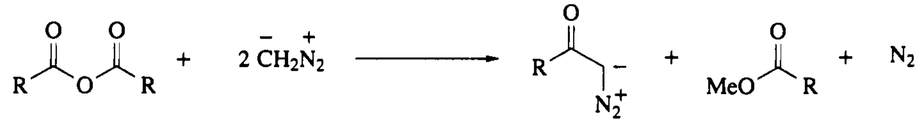
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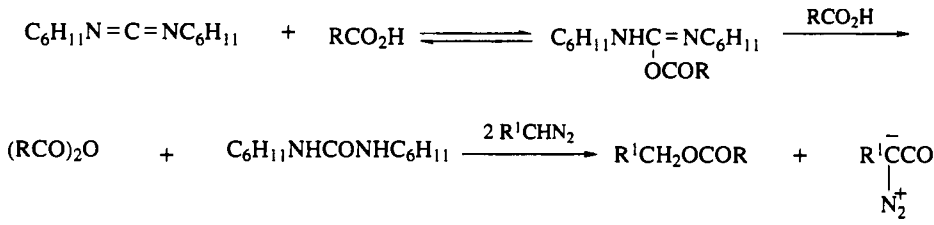

$$C_6H_{11}N{=}C{=}NC_6H_{11} + RCO_2H \rightleftharpoons \underset{\textstyle OCOR}{C_6H_{11}NHC{=}NC_6H_{11}} \xrightarrow{RCO_2H}$$

$$(RCO)_2O + C_6H_{11}NHCONHC_6H_{11} \xrightarrow{2\,R^1CHN_2} R^1CH_2OCOR + \underset{\textstyle \overset{+}{N}_2}{R^1\bar{C}COR}$$

**Scheme 1**

Reaction conditions for the acylation of higher diazoalkanes by acid chlorides are more critical.[19,20] Since azo coupling of the diazo ketone with the diazoalkane can occur to give azines (equation 5),[21] it is essential to avoid an excess of the diazoalkane and to carry out the acylation at lower temperatures. Typically, the acid chloride (1 equiv.) in ether is added to a stirred solution of the diazoalkane (1 equiv.) and triethylamine (1 equiv.) in ether at –40 °C. Yields of the diazoketones are then *ca.* 74–91%, and equation (6) is fairly representative.[20]

There are a few, mainly obvious, limitations to the Arndt–Eistert acylation procedure, in that other functional groups in the acid chloride which react with the diazoalkane require suitable protection. Be-

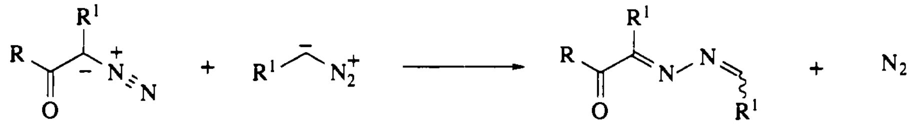
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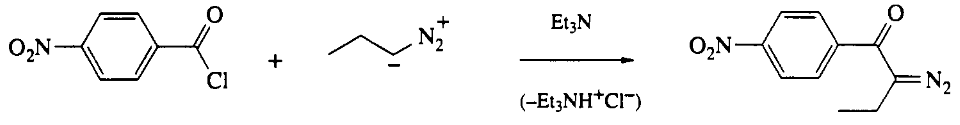
(6)

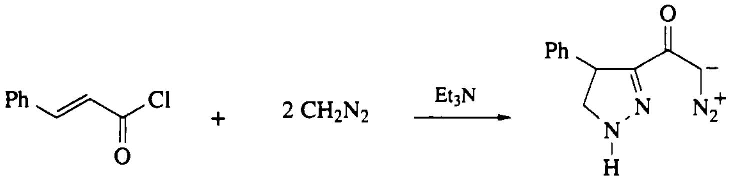
(7)

cause diazomethane is a fairly reactive 1,3-dipole, activated alkenes (dipolarophiles) afford cycloaddition products. Hence, α,β-unsaturated acid chlorides react with diazomethane at both the carbonyl carbon atom and at the double bond (*e.g.* equation 7).[22,23] A more remote, unactivated double bond does not usually inhibit diazo ketone formation. On the whole, therefore, the *C*-acylation of primary diazo compounds is a widely applicable procedure.[6,10]

The Dakin–West reaction[24] provides a source of *N*-acyl-α-amino ketones (*e.g.* **1**), which Franzen[20] has exploited for the synthesis of secondary diazo ketones, thereby avoiding the need to use the higher homologs of diazomethane (Scheme 2). The ketoamide (**1**) is first nitrosated using $N_2O_3$ in glacial acetic acid. The oily *N*-nitroso derivative is separated and then decomposed with sodium methoxide in methanol to give the diazo ketone (**2**); yields are about 50–60%.

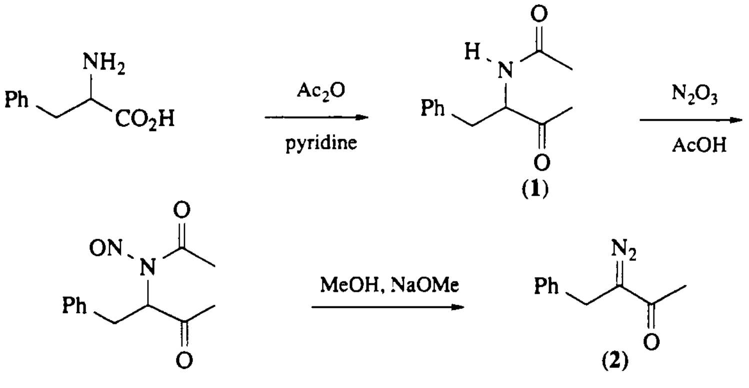

**Scheme 2**

The synthesis of α-diazocarbonyl compounds by the transfer of a diazo group from an organic azide to a suitable substrate containing an active methylene group was studied extensively in the 1960s and 1970s, but the origins of the basic reaction are much older.[10,25] Tosyl azide is now used almost exclusively as the diazo group transfer agent since it is stable and easily prepared, and because tosyl amide (a coproduct) is readily removed. The presence of a base is necessary, for it is the enolate anion which reacts with the tosyl azide. Commonly used solvent/base combinations are ethanol and potassium hydroxide, triethylamine, or potassium ethoxide; methanol and sodium methoxide; acetonitrile and triethylamine; and dichloromethane and piperidine. The choice of the base is, of course, dictated by the p$K_a$ of the active methylene group in the substrate; hence the presence of two Z-groups (*i.e.* COR, $CO_2R$, CN, $NO_2$, $SO_2R$, *etc.*) is essential. The preparation of ethyl acetodiazoacetate (**4**) is illustrated in Scheme 3.[26] Since α-diazo-β,β′-dicarbonyl compounds such as (**4**), but more especially those formed from β-diketones, have a highly electrophilic diazo group, it can be difficult to completely suppress azo coupling with the enolate ion (**3**).[25] The yields of the α-diazocarbonyl compounds can be improved by employing phase-transfer catalysis. Thus, reaction of ethyl acetoacetate with tosyl azide in a mixture of pentane and saturated aqueous sodium carbonate containing tetrabutyl ammonium bromide, afforded (**4**) in 90% yield.[27]

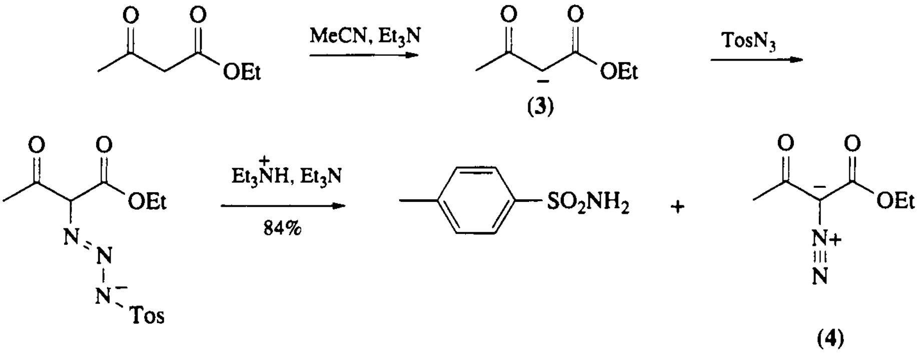

Scheme 3

The diazo-transfer reaction strategy has to be modified for the preparation of simple diazo monoketones (*e.g.* **8**). The presence of only one activating Z-group is circumvented by the temporary introduction of a formyl group by means of a Claisen reaction (Scheme 4; **5** → **6**).[28] The formyl derivative is either preformed and then treated with tosyl azide and a tertiary amine, or the initial ketone is reacted with ethyl formate and sodium ethoxide in ethanol and then the tosyl azide is added to the Claisen adduct. Yields are generally in the range 55–90%,[25] and deformylative group transfer renders a wide range of α-diazocarbonyl compounds accessible; even α,β-unsaturated diazo ketones can be prepared by this route.[29]

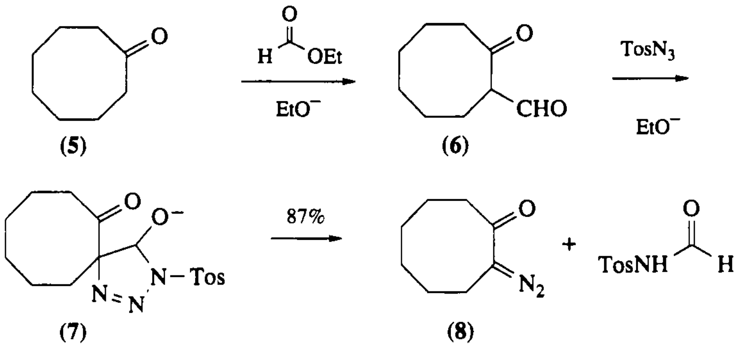

Scheme 4

The need for proton-activating Z-groups may be dispensed with by employing diazo group transfer to enamines of suitable structure. The initial addition is regiospecific (*cf.* **7**), and the triazoline so-formed decomposes spontaneously to give the diazo compound and a tosyl amidine. Although α-diazo ketones can be prepared in this manner, the other routes outlined above are generally superior. However, the method is useful for α-diazoaldehydes, and an example is given in equation (8).[30]

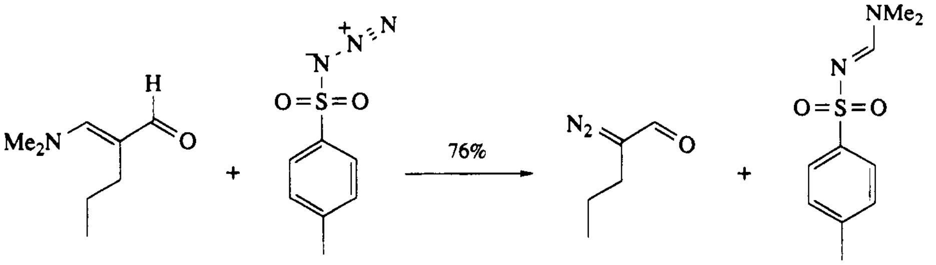

(8)

Various other procedures have been developed for the synthesis of α-diazo ketones and, although less popular in modern organic chemistry, may occasionally be valuable for the preparation of specific compounds.[7,10,25] These routes include the oxidation of α-ketoximes with chloramine,[31] the oxidation of α-ketohydrazones with yellow mercury(II) oxide[32] or manganese dioxide,[33] the hydroxide ion assisted decomposition of tosylhydrazones,[34] and the diazotization of α-amino ketones.[1,35]

### 3.9.1.3 Methods for Initiating the Wolff Rearrangement

The Wolff rearrangement may be initiated thermally, by transition metal catalysts, or by photolysis. Thermolysis is used less frequently than the other two procedures since solution temperatures in the region of 180 °C are often required, and this can be counter-productive if the rearrangement results in the formation of a strained ring. Additionally, under thermal control nucleophiles can displace the diazo group without causing rearrangement.[1,36] Nevertheless, the ketene intermediate produced by the rearrangement (see Section 3.9.2.1) can often be intercepted efficiently by employing a high boiling point amine or alcohol as solvent (*e.g.* aniline[1,37] and benzyl alcohol[19] which, respectively, afford the anilide and benzyl ester).

The use of transition metal species can lower appreciably the decomposition temperature of α-diazocarbonyl compounds; they can also alter the reactivity of the carbene intermediate (resulting from the initial nitrogen elimination; see Section 3.9.2.1) by complex formation. Hence, the Wolff rearrangement may occur with difficulty or, usually, not at all. Thus, some copper species (excepting, for example, CuI),[38] or Rh and Pd catalysts are inappropriate. Freshly prepared silver(I) oxide has been used most frequently, but silver salts (especially silver benzoate) are sometimes preferred.[1,2,37,39] Silver-based catalysts are usually employed in combination with an alkaline reagent (*e.g.* sodium carbonate or a tertiary amine). Even under silver catalysis competing reactions may be observed, and sometimes the products of Wolff rearrangement may not be obtained (see Section 3.9.2.3).

Photolysis[40] is often successful when the thermal or catalytic procedures fail and, increasingly, has become the method of choice. The UV spectra of simple diazo ketones show two absorption bands; one in the 240–270 nm region, and a lower intensity (forbidden) band in the 270–310 nm region. Protic solvents diminish the intensity of the first band relative to the second.[41a] Excitation of this second band accesses the lowest energy excited singlet state ($^1S$) of the diazo ketone by way of a $\pi \rightarrow \sigma^*$ overlap-forbidden transition.[41b] This may be achieved by use of a medium-pressure mercury arc. Since $^1S$ is only moderately reactive it may be necessary to excite the higher intensity, higher energy $\pi \rightarrow \pi^*$ band by use of a low-pressure mercury arc, but this may lead to increased amounts of by-products. The photochemical procedure fails if the reaction product itself is photolabile under the reaction conditions. Since moderately low temperatures are usual (*e.g.* 0 °C), problems of thermal lability can be avoided. The presence of triplet sensitizers tends to suppress the Wolff rearrangement but other, carbene-mediated, processes may occur. Rearrangements of α-diazo ketones have also been observed under electron impact in the mass spectrometer.[42]

## 3.9.2 MECHANISM, STEREOCHEMISTRY AND COMPETING REACTIONS

### 3.9.2.1 Mechanism

Even after more than 75 years, theoretical and mechanistic interest in the Wolff rearrangement continues unabated.[43] There is as yet no general agreement on all of the mechanistic detail connecting reactant to product, and it is probable that there is not a single mechanistic description for all Wolff rearrangements. Scheme 5 summarizes the main features; most of the disagreements concern the exact placement of the interconnecting arrows and the participation of the reactive intermediates (**11**)–(**13**).

Two features of the mechanism are regarded as secure. Firstly, an acyclic α-diazo ketone exists as an equilibrium mixture of the *s*-(*Z*) and *s*-(*E*) forms (**9**) and (**10**), respectively. The central C—C bond possesses double bond character, and the rotational barrier is approximately 9–18 kcal mol$^{-1}$ (1 kcal = 4.18 kJ).[44] The substituents $R^1$ and $R^2$ influence the balance of the equilibrium, and it is possible to favor entirely the *s*-(*Z*) form (*e.g.* $R^1$,$R^2$ = small ring) or the *s*-(*E*) form (*e.g.* $R^1 = R^2 =$ *t*-butyl). Secondly, the rearrangement leads to the ketene intermediate (**14**),[1b,40] which is usually trapped by a weak acid RXH (*e.g.* water, alcohols and amines) to give the product (**15**); stronger acids protonate the diazo ketone, and nucleophilic displacement of nitrogen occurs without rearrangement to give the product (**16**).

In the *s*-(*Z*) form (**9**) the leaving group ($N_2$) and the migrating group ($R^2$) are deployed in an ideal antiperiplanar geometry for concerted extrusion/rearrangement (*i.e.* **9** → **14**). Indeed, the concerted mechanism has been proposed to account for the conformational control observed in the photolysis and thermolysis of some α-diazo ketones.[44] Product ratios obtained in direct and triplet-sensitized photolyses have led to the proposal of a concerted component from (**9**) and a nonconcerted (carbenic) component from (**10**).[45] Likewise, CIDNP studies indicate that the photochemical rearrangement of diazoacetone is concerted.[46] However, the observation of conformational control in the Wolff rearrangement is not

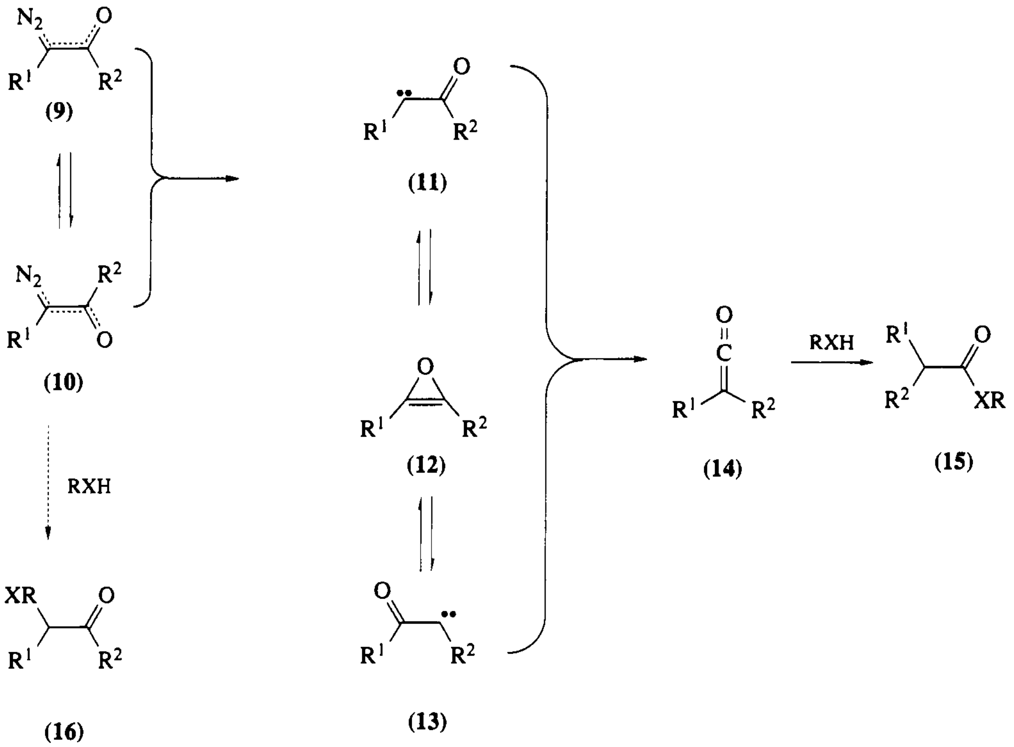

Scheme 5

regarded[47] as proof *per se* for a concerted mechanism, and compelling evidence for the intermediacy of α-ketocarbenes[43] and for the oxirene (**12**)[48] has been advanced. The oxirene appears neither to be formed directly from the diazo ketone nor to rearrange directly to the ketene, but a 'symmetrical' species is needed to explain the scrambling of isotopic label which has been observed in some reactions. A wide variety of groups $R^1$ or $R^2$ in the carbenes (**11**) or (**13**) are able to migrate. For thermal reactions the migratory aptitudes fall in the series: H > Ph > Me > $NR_2$ > OR. Under photochemical control Ph and Me exchange places.[11]

There are undoubtedly appreciable mechanistic differences in the transition metal catalyzed reactions.[7,11] For example, Newman and Beal have suggested that a radical chain process is involved in the silver benzoate/triethylamine-promoted rearrangement of diazomethyl ketones.[39]

### 3.9.2.2 Stereochemistry

The Wolff rearrangement, irrespective of the method employed for initiation, appears to occur by the intramolecular transfer of the migrating group. By and large, all stereochemical information at the migrating center is conserved. Thus, studies with optically active diazo ketones have shown predominant or complete retention of configuration of the migrating group.[49-51] The loss, or partial loss, of stereochemical integrity has only been observed when the migrating center is a secondary carbon atom. This centre is adjacent to the C=O group of the diazo ketone, and hence partial racemization through enolization could result during diazo ketone synthesis or storage, or under the conditions of the Wolff rearrangement, as well as during the rearrangement itself. From their results on the rearrangement of *s*-butyldiazomethyl compounds ($RCH_2CH(Me)COCHN_2$; R = H, Ph) photochemically or by a variety of silver ion catalyzed methods, Wiberg and Hutton[51] concluded that either the diazo ketone was partially racemized under the reaction conditions, or racemization occurred during the rearrangement. An alternative explanation for the racemization based on a minor pathway involving C—H insertion by the carbene intermediate (Scheme 6) seems unattractive in view of the known chemistry of cyclopropanones (*i.e.* cleavage requires a strong base and takes place in the direction towards the less-substituted carbon atom).[52]

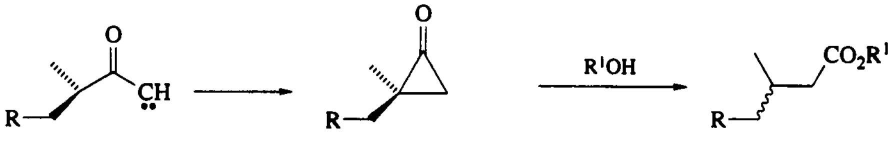

Scheme 6

### 3.9.2.3 Competing Reactions

Diazo ketones are reactive substances. The problems of compatibility towards functional groups in the same molecule are discussed in Section 3.9.1.2. Clearly, there will be a similar incompatibility in intermolecular processes if certain other compounds are present in the reaction medium during Wolff rearrangement. α-Diazo ketones are 1,3-dipoles but, according to Huisgen's index of reactivity for diazo compounds (*i.e.* $CH_2N_2$ > $Ph_2CN_2$ > $EtO_2CCHN_2$ > $RCOC(N_2)R^1$ > $RCOC(N_2)CO_2Et$), they are only moderately reactive.[53a] Since dipolarophile reactivity of Z-group-activated alkenes falls in the series $CO_2Ph$ > $CO_2Et$ > CN > COMe > $C_6H_4NO_2$ > Ph,[53b] then loss of diazo ketone through 1,3-dipolar cycloaddition is generally only important for the more electron-deficient alkenes and alkynes. Thus, for example, cycloaddition of 2-diazo-3-oxobutane to diethyl acetylenedicarboxylate affords 5-acetyl-3,4-diethoxycarbonyl-5-methyl-5*H*-pyrazole (**16**; equation 9).[54] Analogous intramolecular cycloaddition occurs across the nitrile group in (**17**) under alkaline conditions; on acidification the initial adduct undergoes prototropic rearrangement to give the triazole (**18**; equation 10).[55] The triazole (**18**) is converted by acidic hydrolysis into 2-diazoindane-1,3-dione (80%).

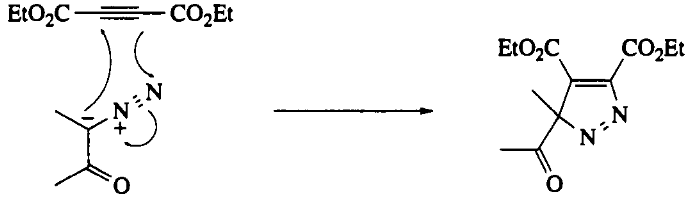

(9)

(**16**)

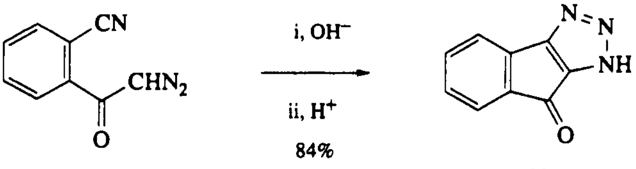

(**17**) (**18**)

(10)

Diazo ketones also possess an electrophilic diazo group, and hence are susceptible to diazo-coupling reactions with suitable soft nucleophiles. Examples are given in equations (11)[1a] and (12).[56] Phosphazines such as (**19**) are useful synthetic intermediates in their own right. The carbon terminus of the 1,3-dipole possesses nucleophilic properties and can participate in aldol-type reactions with the particularly electrophilic carbonyl groups in 1,2-di- and 1,2,3-tri-carbonyl compounds.[25] Intramolecular condensations occur with greater ease (equation 13).[57] Reaction of diazo ketones of the type summarized in equations (9)–(12) have been thoroughly reviewed.[4,6,8]

Prevention of the Wolff rearrangement is much more likely to occur through alternative reactions of the ketocarbene intermediate (**11**; Scheme 5). Lack of rearrangement to the ketene (**14**) may be due to a structural feature present in the ketocarbene (*e.g.* functional groups α to the C=O interfere with the Wolff rearrangement, or lead to secondary reactions)[7–11] but, not infrequently, it can be the result of an

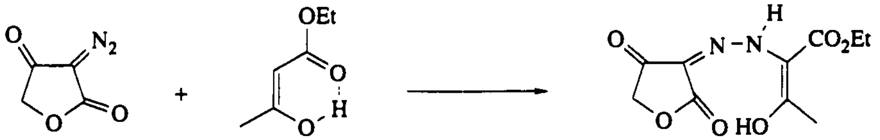

(11)

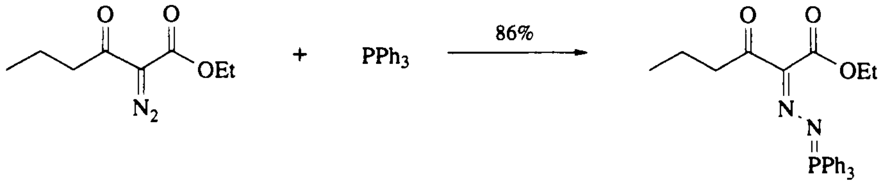

(12)

**(19)**

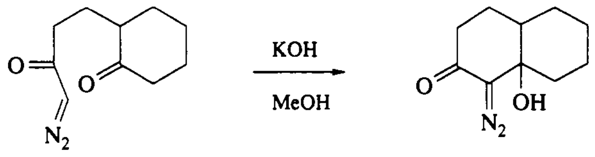

(13)

inappropriate choice of reaction conditions. Hence, it is often worthwhile investigating the photochemical decomposition of the α-diazocarbonyl compound if the thermal or transition metal catalyzed procedures fail to effect rearrangement. Likewise, changes in temperature, solvent or coreactants should be considered.

Ketocarbenes of type (**21**) obtained from acyclic and medium to large ring alicyclic α-diazo ketones (**20**) are prone to react by way of an intramolecular [1,2] H-shift, especially under catalytic conditions, to afford α,β-unsaturated ketones (**22**).[1,20,58–60] Franzen[20] has shown that the Wolff rearrangement of diazo ketones (**20**) is favored if temperatures in excess of 100 °C are used in the photochemical or Ag$_2$O-promoted decompositions. Related [1,2] methyl shifts can also occur, and this pathway is the principal decomposition route of 4-diazo-2,2,5,5-tetramethyl-3-hexanone.[61]

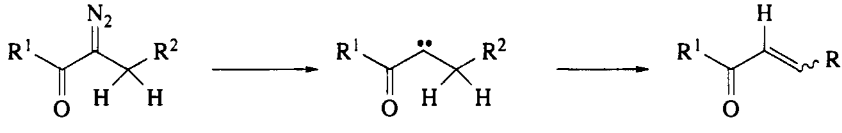

**(20)** **(21)** **(22)**

The transient ketocarbene is also able to effect both intramolecular and intermolecular H-abstraction. The fact that a triplet state of the carbene is often implicated follows from observations that sensitized photolyses frequently enhance the abstraction pathway.[6,9] Abstraction and radical combination results in the formal insertion of the carbene into the C—H (or S—H, N—H, *etc.*) bond. Insertions may also occur into C—C, C—O, C—S, C—Hal, *etc.* bonds; the mechanisms are often not known, but a singlet state of the ketocarbene is probably involved in many cases. Reactions at soft basic centers (*e.g.* —S: or —Br:) generally proceed by the preliminary formation of an ylide. The multiplicity of the possible pathways is illustrated in Scheme 7,[58] equation (14) (photolysis in dioxane affords only **27**, 57% and **28**, 43%),[62] and Scheme 8.[63]

The electron deficiency in the ketocarbene intermediate can be satisfied through various types of addition reactions. Cyclopropane derivatives are the result of inter- or intra-molecular cycloaddition to alkenic double bonds. In the case of Z-group-activated C═C, the initial reaction of the diazo ketone is usually a 1,3-dipolar cycloaddition to give a pyrazoline derivative (see equation 9); on heating these decompose with nitrogen elimination, resulting in cyclopropane formation (*e.g.* **29** → **30** → **31**).[64] The electrophilic ketocarbenes generated by photolysis or under thermal control normally undergo the Wolff rearrangement with too great a rapidity to allow trapping by a nucleophilic double bond, even in the same molecule. Hence, the formation of the tricyclo[1.1.1.0$^{4,5}$]pentane skeleton by this means (equation 15) is quite exceptional.[65] Silver benzoate catalysis, however, affords only the Wolff rearrangement product (**32**). The production of cyclopropanes is of some importance in synthesis, and hence there have been a number of studies directed towards inhibition of the rearrangement pathway.[9] Photolysis of diazo esters affords alkoxycarbonylcarbenes which rearrange relatively slowly and, accordingly, cyclopropanation reactions have been observed in both direct and sensitized irradiations.[6] The *exo* addition route is favored (*e.g.* equation 16).[66] Similar results may be achieved by copper-catalyzed decomposition of the

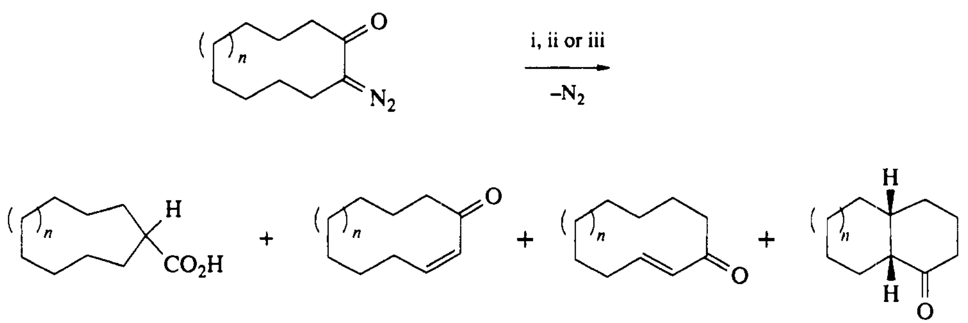
i, ii or iii
$-N_2$

(23) (24) (25) (26)

| | | (23) | (24) | (25) | (26) |
|---|---|---|---|---|---|
| (i) | $n = 1$ | 62% | – | – | – |
| | $n = 2$ | 35% | – | – | – |
| (ii) | $n = 1$ | 5% | 57% | – | – |
| | $n = 2$ | 2% | 30% | 30% | – |
| (iii) | $n = 1$ | – | 39% | – | 13% |
| | $n = 2$ | – | 20% | 15% | – |

i, $h\nu$, THF/$H_2O$; ii, $Ag_2O$, THF/$H_2O$; iii, CuO, Δ, hexanes

**Scheme 7**

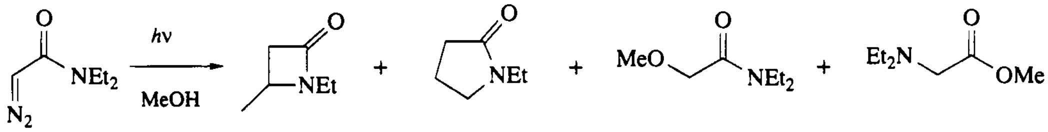

(14)

(27) 43% (28) 5% 34% 18%

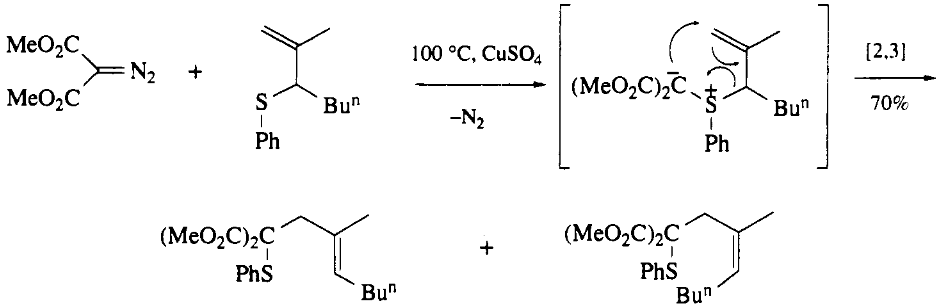
100 °C, CuSO₄
−N₂
[2,3]
70%

90:10

**Scheme 8**

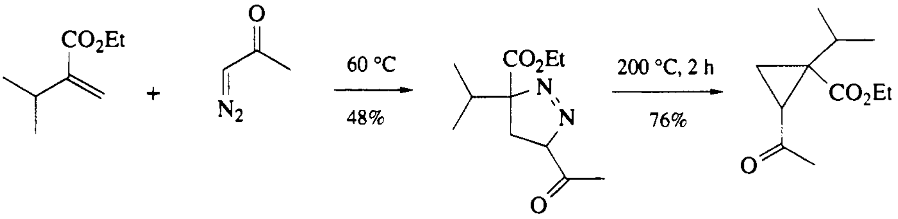
60 °C
48%
200 °C, 2 h
76%

(29) (30) (31)

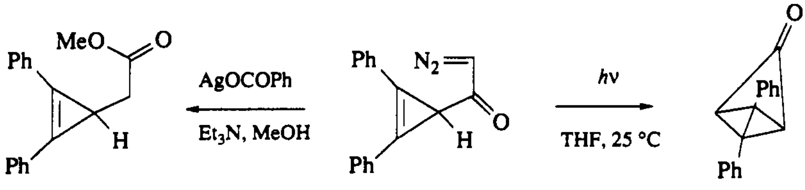
MeO
O
Ph
Ph
H
AgOCOPh
Et3N, MeOH
Ph
N2
H
O
Ph
hν
THF, 25 °C
O
Ph
Ph

(32)

(15)

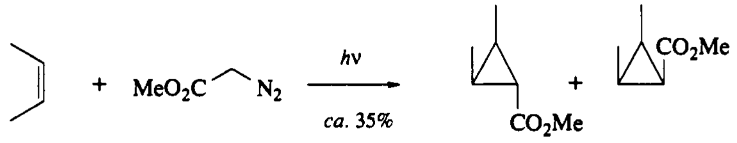
+
MeO2C
N2
hν
ca. 35%
+
CO2Me
CO2Me

(33) 71.4:28.6 (34)

(16)

diazo ester,[67] but loss of the metallocarbene can occur through dimerization (*e.g.* to form dimethyl fumarate as well as **33** and **34**).[66] The rearrangement of ketocarbenes is greatly inhibited through complexation by copper. Copper powder and anhydrous copper(II) sulfate are the favored catalysts, and intramolecular trapping of the metallocarbene is relatively efficient. Equations (17) ($w$ = 1–4, $x$ = 0–2, y = 0–1; yields *ca.* 50%)[68] and (18) (R = H, Me; X = Me, OEt; yields 30–50%)[69] hopefully indicate the scope.[9] Allylic C—H insertion may occur in competition with cyclopropanation and Wolff rearrangement, but by the appropriate choice of the transition metal catalyst (and its ligands), a degree of control may be achieved.[9,70] Similar reactions occur with other multiple bonds, but with nitriles, for example, formal 1,3-dipolar cycloaddition occurs to give oxazoles; yields are improved by copper catalysts (*e.g.* equation 19).[71] In the absence of such trapping agents, and the use of inert solvents and copper(II) oxide as catalyst, symmetrical diacylethylenes are obtained by dimerization of the carbenone.[6,7,72] Sometimes azines (*e.g.* RCOCH=N—N=CHCOR) are obtained by the reaction of the carbene with the original diazo compound.[7]

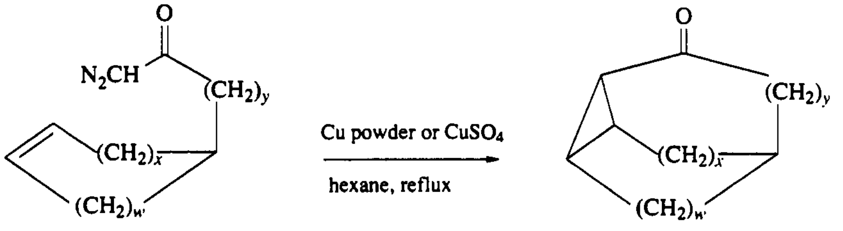
O
N2CH
(CH2)y
(CH2)x
(CH2)w
Cu powder or CuSO4
hexane, reflux
O
(CH2)y
(CH2)x
(CH2)w

(17)

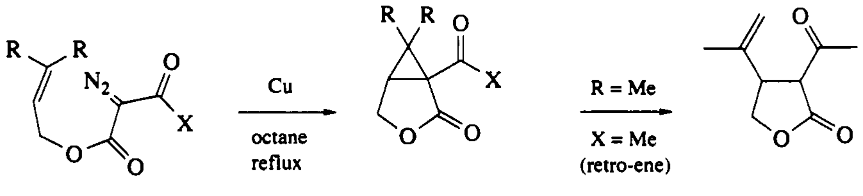
R
R
N2
O
X
O
O
Cu
octane
reflux
R R
O
X
O
O
R = Me
X = Me
(retro-ene)
O
O
O

(18)

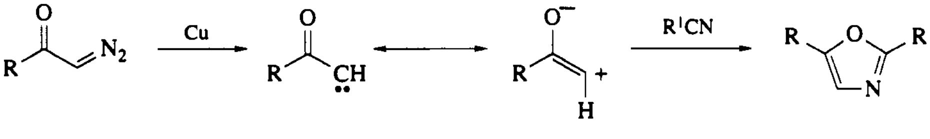
O
R
N2
Cu
O
R
CH
O⁻
R
+
H
R¹CN
R
O
R¹
N

(19)

In the light of the large number of ways in which the reaction of α-diazocarbonyl compounds can be deflected away from the Wolff rearrangement pathway to give the ketene intermediate, it is clear that, in practice, careful thought has to be given to the choice of reaction conditions. Nevertheless, the Wolff rearrangement is a synthetic tool of very wide scope, and in the following sections only a flavor of a large body of chemistry can be given.

## 3.9.3 THE CHEMISTRY OF WOLFF REARRANGEMENTS

The essence of the Wolff rearrangement is the production of the ketene intermediate (**14**; Scheme 5). The fate of the ketene is determined by its structure and the reaction conditions. Usually the ketene is trapped *in situ* with a weak acid (RXH) to give the addition product (**15**). A variety of weak acids can be employed, but water, alcohols, ammonia, or primary or secondary amines are the most popular reagents (*i.e.* XR = OH, OR, $NH_2$, NHR, NHOH, $NR_2$, SR). The structure of the carboxylic acid or derivative (**15**) thus formed is inevitably linked to the nature of the groups $R^1$ and $R^2$ in the original α-diazocarbonyl compound (**9**). If $R^1$ = H, then the overall transformation is, in effect, a one-carbon homologation (*i.e.* $R^2CO_2H \rightarrow R^2COCl \rightarrow R^2COCHN_2 \rightarrow R^2CH_2COXR$). This is the Arndt–Eistert synthesis,[2–11,73] and is the principal application of the Wolff rearrangement, since it represents a rapid, efficient and economical method, of wide scope, for effecting homologation. When $R^1 \neq$ H, then the ultimate product (**15**) is an α-substituted carboxylic acid or derivative, and the overall change represents an extension to the Arndt–Eistert synthesis. However, the Wolff rearrangement, (**11**) → (**14**), may be less efficient here because of competing decomposition pathways for the carbene intermediate (**11**); see Section 3.9.2.3. Hence, very much less attention has been focused on the case $R^1 \neq$ H. These two aspects of the Arndt–Eistert synthesis are covered in Section 3.9.3.1.

A third possibility arises when $R^1$ and $R^2$ are directly linked such that (**9**) is a cyclic α-diazo ketone. Rearrangement to (**14**) therefore represents a ring contraction, and trapping by RXH affords the ring-contracted carboxylic acid derivative (**15**). This area is covered in Section 3.9.3.2.

Occasionally the ketene (**14**) is sufficiently stable to allow its isolation in the absence of the coreactant RXH (*e.g.* $R^1 = R^2$ = aryl).[1b] In hydrocarbon solvents, however, the ketene is usually lost through self-dimerization or through inter- or intra-molecular cycloaddition reaction with alkenic double bonds. This aspect of the Wolff rearrangement is covered in Section 3.9.3.3. Extensions to the Wolff rearrangement strategy are covered in the concluding sections.

### 3.9.3.1 Homologations and Related Reactions

In the usual Arndt–Eistert homologation strategy, (**9**) → (**14**) → (**15**), the nonmigrating group $R^1$ is a hydrogen atom and the starting material is an α-diazomethyl ketone or ester. In principle, the ketene (**14**) could also be generated from an α-diazo aldehyde ($R^1C(N_2)CHO$) in which the migrating group ($R^2$ in **9**) is a hydrogen atom. However, the lack of such examples is indicative of the greater reactivity and poorer accessibility of α-diazo aldehydes.[30] Table 1 and the accompanying formulae provide a short summary of the many hundreds of examples of the Arndt–Eistert synthesis that have been published. Silver ion catalysis or photolysis are the favored methods for effecting the reaction. In the preparation of carboxylic acids (*i.e.* RXH = $H_2O$), solubility problems usually dictate the use of water as a diluant rather than as the main solvent. Hence, it can be more efficient to trap the ketene with an alcohol or amine, and subsequently hydrolyze the ester or amide obtained. The preparation of the peptides (**52**) and (**55**) indicates that the trapping agent RXH can be a fairly sophisticated molecule in its own right. In several of these examples it can be seen that migration of $R^2$ occurs with complete retention of configuration.

The migratory aptitude of $R^2$ in (**11**) varies widely with its structure (see Section 3.9.2.1), the shift of an alkoxy group being among the slowest. The formation of alkoxyketenes in the photolysis of alkyl diazoacetates is a fairly recent discovery.[9] The major competing reactions of the carbene precursor are insertions into the C—H and O—H bonds of alcohols employed as solvents and ketene traps. The extent of Wolff rearrangement varies with structure: ethyl diazoacetate (20–25%), phenyl diazoacetate (45–60%), and *N*-methyldiazoacetamide (30%).[94] These reactions are of limited synthetic interest at present.

The value of the Arndt–Eistert method in synthesis rests with the versatility of the products obtained, and there have been a number of developments which increase the overall appeal. One of these allows the direct synthesis of homologous aldehydes by the reduction of the *N*-methylanilide with lithium aluminum hydride, or the thiol ester using Raney nickel (Scheme 9).[4,76]

Table 2 surveys some of the results of the Arndt–Eistert method for higher order α-diazocarbonyl systems (*i.e.* **9**; $R^1, R^2 \neq$ H). The mildness of the photochemical procedure under neutral conditions is nicely demonstrated by the isolation of β-keto acids from the photolysis of α-diazo-β-keto thiol esters in the presence of water (entry 6).[73,91] This work indicates that the migratory aptitude of RS is greater than RO, and occurs exclusively. Likewise, it has been shown that in the rearrangement of methyl 3-diazo-2,4-dioxopentanoate (*i.e.* $MeCOC(N_2)COCO_2Me$) the migratory aptitudes fall in the series Me > $MeCO_2$ > MeO.[92] Hence, although the decomposition of an unsymmetrical 2-diazo-1,3-dicarbonyl compound can give two different ketenes, one pathway usually predominates and the procedure shows sufficient selectivity to be of value in synthesis.[11] The reactions in which $R^1$ represents a sulfonyl or phosphonate group are also of interest in this respect.

**Table 1** Arndt–Eistert Homologations

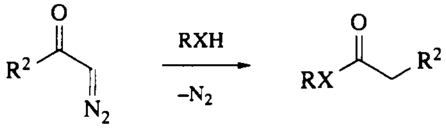

| *Diazo ketone* | *RXH* | *Activation* | *Solvent/conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| (**35a**) | EtOH | $Ag_2O$ | EtOH, reflux, 18 h | (**35b**) | 40 | 74 |
| (**36a**) | $NH_3$ | $AgNO_3$ | aq. $NH_3$, reflux, 2 h | (**36b**) | 33 | 75 |
| (**37a**) | $Bu^tOH$ | AgOCOPh | $Bu^tOH$, reflux, 1.25 h | (**37b**) | 57 | 39 |
| (**38a**) | EtSH | *hν* | $Et_2O$, 8 h | (**38b**) | 67 | 76 |
| (**38a**) | PhNHMe | *hν* | PhH, 3 d | (**38c**) | 45 | 76 |
| (**39a**) | $H_2O$ | $Ag_2O$ | aq. dioxane, 65 °C, 2.5 h | (**39b**) | 64 | 77 |
| (**40a**) | EtOH | AgOCOPh | EtOH, reflux, 1 h | (**40b**) | 88 | 78 |
| (**41a**) | $H_2O$ | $Ag_2O$ | aq. dioxane, 25 °C, 1 h | (**41b**) | 33 | 79 |
| (**42a**) | $H_2O$ | $Ag_2O$ | $H_2O$, 50 °C | (**42b**) | 68 | 49 |
| (**43a**) | MeOH | AgOCOPh | MeOH, 25 °C, 15 min | (**43b**) | 55 | 80 |
| (**44a**) | $H_2O$ | $Ag_2O$ | aq. dioxane, reflux, 2 h | (**44b**) | 33 | 81 |
| (**45a**) | EtOH | $Ag_2O$ | EtOH, reflux, 1 h | (**45b**) | 68 | 82 |
| (**46a**) | $H_2O$ | $Ag_2O$ | aq. dioxane, 70 °C, 1.5 h | (**46b**) | 81 | 83 |
| (**47a**) | $H_2O$ | *hν* | aq. dioxane, 2.75 h | (**47b**) | 58 | 84 |
| (**48a**) | MeOH | $Ag_2O$ | MeOH, 100 °C, 13 h | (**48b**) | 65 | 85 |
| (**49a**) | MeOH | *hν* | MeOH, 6–8 h | (**49b**) | 70 | 86 |
| (**50**) | (**51**) | $Ag_2O$ | dioxane, 60 °C | (**52**) | 62 | 87 |
| (**53**) | (**54**) | $Ag_2O$ | dioxane, 65 °C, 10 min | (**55**) | 45 | 88 |

$F_3C-X$

(**35a**) X = $COCHN_2$
(**35b**) X = $CH_2CO_2Et$

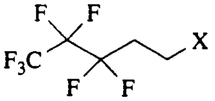

(**36a**) X = $COCHN_2$
(**36b**) X = $CH_2CONH_2$

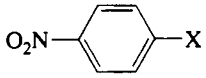

(**37a**) X = $COCHN_2$
(**37b**) X = $CH_2CO_2Bu^t$

$Me-X$

(**38a**) X = $COCHN_2$
(**38b**) X = $CH_2COSEt$
(**38c**) X = $CH_2CON(Me)Ph$

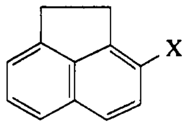

(**39a**) X = $COCHN_2$
(**39b**) X = $CH_2CO_2H$

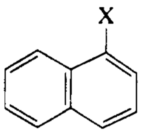

(**40a**) X = $COCHN_2$
(**40b**) X = $CH_2CO_2Et$

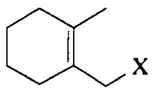

(**41a**) X = $COCHN_2$
(**41b**) X = $CH_2CO_2H$

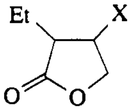

(**42a**) X = $COCHN_2$
(**42b**) X = $CH_2CO_2H$

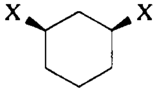

(**43a**) X = $COCHN_2$
(**43b**) X = $CH_2CO_2Me$

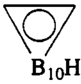

**(44a)** X = $COCHN_2$
**(44b)** X = $CH_2CO_2H$

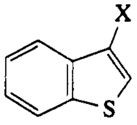

**(45a)** X = $COCHN_2$
**(45b)** X = $CH_2CO_2H$

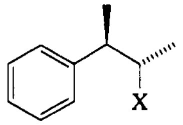

**(46a)** X = $COCHN_2$
**(46b)** X = $CH_2CO_2H$

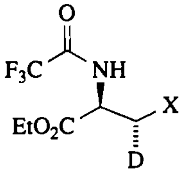

**(47a)** X = $COCHN_2$
**(47b)** X = $CH_2CO_2H$

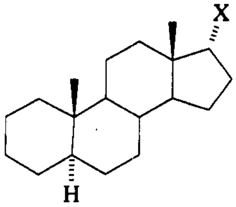

**(48a)** X = $COCHN_2$
**(48b)** X = $CH_2CO_2Me$

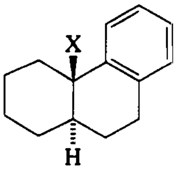

**(49a)** X = $COCHN_2$
**(49b)** X = $CH_2CO_2Me$

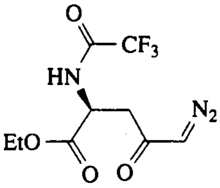

**(50)**

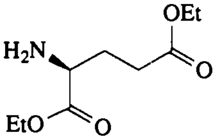

**(51)**

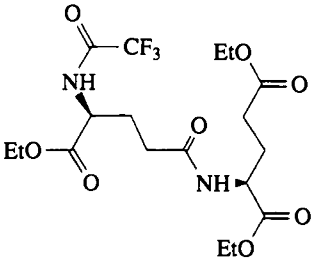

**(52)**

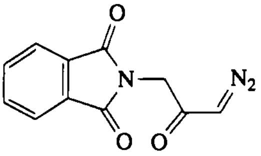

**(53)**

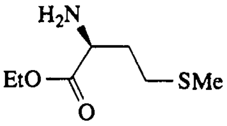

**(54)**

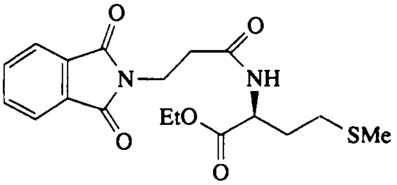

**(55)**

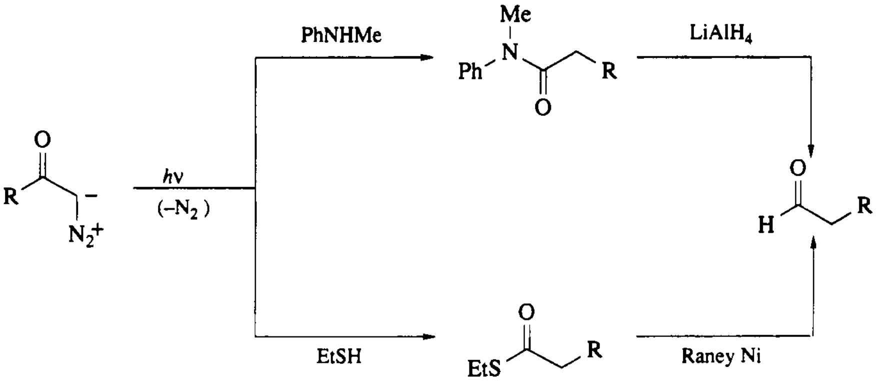
PhNHMe
LiAlH$_4$
$h\nu$
$(-N_2)$
EtSH
Raney Ni

Scheme 9

**Table 2** Rearrangements Leading to α-Substituted Carboxylic Acids and Derivatives

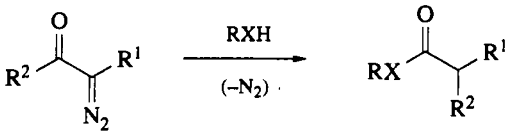

| *R²* | *R¹* | *RXH* | *Activation* | *Solvent/conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 4-$ClC_6H_4$ | Me | $PhCH_2OH$ | 190 °C | $PhCH_2OH$, isoquinoline, 5 min | 87 | 19 |
| $PhCH_2$ | Et | $NH_3$ | $AgNO_3$ | aq. $NH_3$, 80 °C, 2 h | 60 | 89 |
| Ph | $(CH_2)_3CO_2Me$ | $PhNH_2$ | 150 °C | $PhNH_2$, 5 min | 55 | 59 |
| $Me_2CH$ | $SO_2CH_2Ph$ | $PhCH_2OH$ | 110 °C | PhMe, 2 h | 86 | 90 |
| Ph | $SO_2CH_2Ph$ | $PhCH_2OH$ | 110 °C | PhMe, 4 h | 92 | 90 |
| $H_2C{=}CHCH_2S$ | $CO_2Me$ | $H_2O$ | *hv* | PhH, 3 h | 70 | 91 |
| $MeO_2C$ | $CO_2Me$ | MeOH | *hv* | PhH, 4 h | 83 | 92 |
| Me | $COCO_2Me$ | MeOH | *hv* | PhH, 6 h | — | 92 |
| 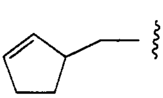 | $PO(OMe)_2$ | EtOH | *hv* | $CH_2Cl_2$, 2–3 h | 81 | 93 |
| 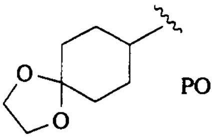 | $PO(OMe)_2$ | EtOH | *hv* | $CH_2Cl_2$, 2–3 h | 66 | 93 |

### 3.9.3.2 Ring Contractions

When the groups R[1] and R[2] of (**9**; Scheme 5) are directly linked to give a cyclic α-diazocarbonyl system, then Wolff rearrangement results in ring contraction (Scheme 10). It is in this area especially that the photochemical method comes into its own. In processes involving thermal control or transition metal catalysis, competing reaction pathways are frequently a serious problem. Application of the Wolff rearrangement to ring contraction is relatively recent, and post-dates Horner's pioneering work on the photochemical method.[40] Thus, although diazocamphor (**56**) yields the tricyclic ketone (**57**) upon heating,[1a] photolysis in aqueous dioxane affords *exo*-1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (**59**) through kinetically controlled hydration of the ketene intermediate (**58**) at its least-hindered *endo* face (Scheme 11).[95] This study laid the groundwork for a protocol in synthesis which has since been widely exploited, especially for the construction of strained rings since ring size imposes few restrictions on the Wolff rearrangement. This area has been reviewed previously.[4–11,96]

There are very few examples of ring contraction from cyclobutyl to cyclopropyl. Irradiation of a benzene solution of 2-diazo-3,4-bis(diphenylmethylene)cyclobutanone (**60**) in the presence of water, methanol, 2-propanol or aniline afforded the carboxylic acid derivatives (**61**) in 13, 87, 75 and 45% yield respectively. Thermolysis of an aqueous dioxane solution of (**60**) surprisingly gave (**61**; XR = OH) in higher yield (52%; equation 20).[97]

α-Diazocyclopentanones are much easier to prepare, and consequently much more attention has been given to the contraction of cyclopentanes to cyclobutanes. Several bicyclo[2.1.1]hexane derivatives have been prepared from α-diazobicyclo[2.2.1]heptanones following similar chemistry to the transformation (**56** → **59**; Scheme 11).[98] Frequently the 5-carboxylate derivatives are formed as a mixture of *endo* and

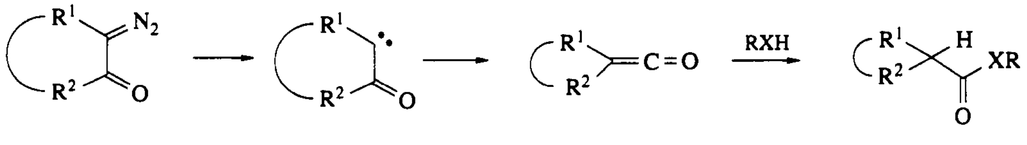

**Scheme 10**

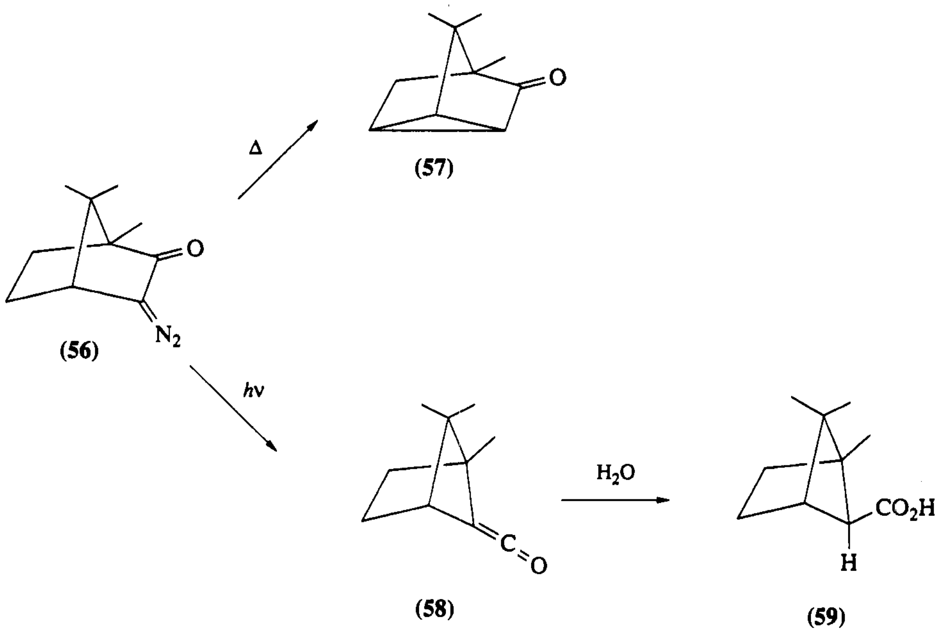

Scheme 11

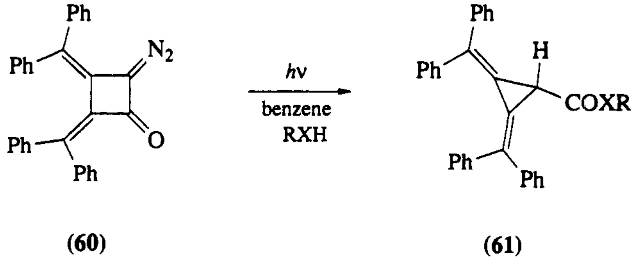

(20)

*exo* isomers as a result of kinetically controlled addition of RXH to each of the two faces of the ketene intermediates. The *endo*:*exo* ratio reflects the ease of access on steric grounds. When XR represents a large grouping, however, thermodynamic control may apply and the least-hindered carboxylic acid derivative is then formed predominantly. The derivatives (**62**)–(**66**) have been prepared by the photolysis of the analogous α-diazo ketones in the presence of the appropriate trapping agent RXH. Product ratios, where given, are in the sense *endo*:*exo*.

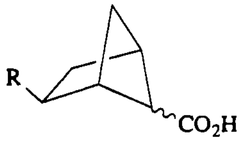

(**62a**) R = H (ref. 99)
(**62b**) R = OAc; 90:10 (ref. 100)

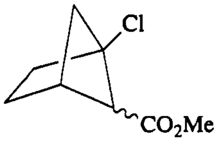

(**63**) (ref. 101)

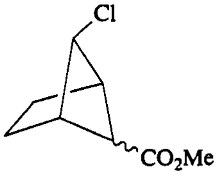

(**64a**) XR = OH; 20:80 (ref. 102)
(**64b**) XR = NHBu$^t$; 16.7:83.3 (ref. 102)

Similar procedures are also successful in the construction of cyclobutane rings in other stereochemical environments, including the formation of bicyclo[3.1.1]heptane (**67**)[105] and bridged tricyclic systems such as (**68**),[106] (**69**)[107] and (**70**).[108] A variety of annelated cyclobutanes have been prepared by the photochemical procedure; as above, yields are sometimes poor or only moderate. Examples include bicyclo[2.1.0]pentanes (**71**),[109] bicyclo[2.2.0]hexanes (**72**)[110] and cyclobuteno aromatics (*e.g.* **73**),[111] D-norsteroids (*e.g.* **74**),[112] A-bisnorsteroids[113] and triterpenes[114] as well as the highly strained tricyclo[4.2.0.0$^{1,4}$]octane system (**75**),[115] and the [4.4.4.5]fenestrane (**76**).[116]

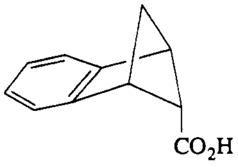

**(65)** (ref. 103)

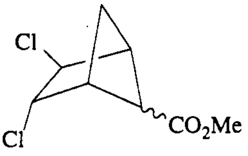

**(66)** 85:15 (ref. 104)

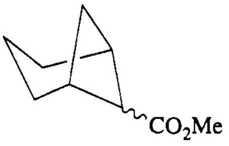

**(67)** 96:4, 75%

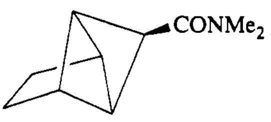

**(68)** 3%

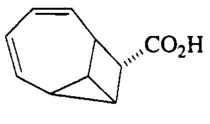

**(69)** 43%

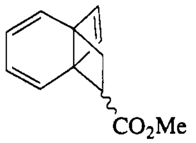

**(70)** 11%

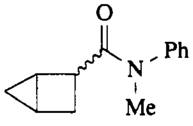

**(71)** 80:20

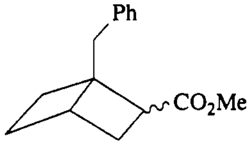

**(72)** 75:25, 68%

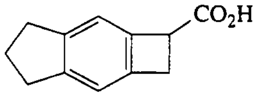

**(73)** 46%

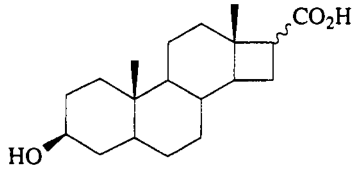

**(74)** 75%

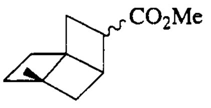

**(75)** 84.6:15.4, 80%

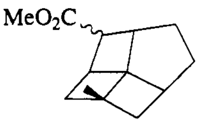

**(76)** 75:25, 20%

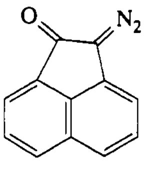

**(77)**

The ring contraction of 2-diazo-1-oxonaphthenes is very difficult because of a large increase in in-plane strain. The parent compound (**77**) failed to undergo Wolff rearrangement on thermolysis, instead giving the ketazine (81%; *cf.* equation 5).[117] Chapman and coworkers[43a] have observed the photochemical extrusion of nitrogen from (**77**) and related compounds in an argon matrix at 10–15 K. The α-ketocarbenes were characterized spectroscopically and by trapping; excitation ($T_0$–$T_1$) led to ring contraction, the rates paralleling the increase in strain of ketene formation. In solution-phase preparative chemistry such α-ketocarbenes are, presumably, simply too reactive to survive encounters with the solvent or unreacted diazoketone.

Applications of the Wolff rearrangement in the synthesis of four-membered heterocycles have been much more limited, and have largely been directed towards the simpler mono- and bi-cyclic systems. Ring contraction of 3-diazopyrrolidine-2,4-diones affords a relatively simple route to β-lactams;[118] carbon migrates in preference to nitrogen (*e.g.* equation 21).[118a] The photochemical decomposition of 4-diazopyrazolidine-3,5-diones analogously yields aza-β-lactams. Unsymmetrically substituted substrates give rise to a mixture of regioisomers (equation 22).[119] Relative migratory aptitudes fall in the series NPh > $NCHPh_2$ ≈ $NCH_2Ph$ ≈ NMe > $NCH_2CO_2Et$; yields were in the range 30–72% and regioselectivities varied from *ca.* 1:1 to 2.8:1. Earlier work on 2,2,5,5-tetraalkyl-4-diazotetrahydro-3-oxofurans had shown that rearrangement to oxetane-3-carboxylates occurred in good yield under photochemical, thermal or $Ag_2O$-promoted conditions.[7]

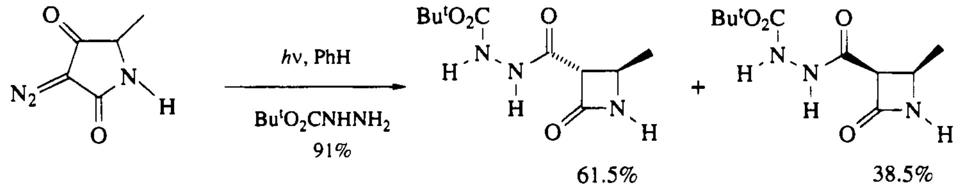

(21)

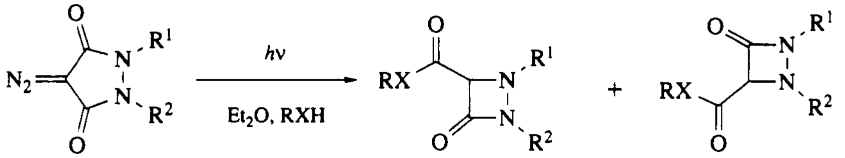

(22)

There are a considerable number of examples of great variety for the construction of cyclopentane rings by ring contraction.[4–11,96] Six-membered rings in highly strained polycyclic systems are amenable to contraction, as shown by the synthesis of homocubanecarboxylic acid (**78**),[120] but there have been few applications in this area. Among bicyclic systems, photolysis of the appropriate diazo ketones resulted in efficient conversion into the bicyclo[2.1.1]hexane-2-carboxylic acid (**79**)[99] and bicyclo[2.2.1]heptane-7-carboxylic acid (**80**).[121] In view of the earlier discussion concerning diazo ketone (**77**), the very low yield of ring-contracted product from photolysis of the phenanthrene derivative (**81**; equation 23), is not too surprising. A dihydrobenzofuran is the major product, resulting from an unprecedented reaction of the ketocarbene (or 1,3-dipole) with the aromatic solvent. On the other hand, Wolff rearrangement of 9-diazo-10-oxophenanthrene itself proceeds efficiently.[122]

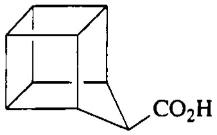

(**78**) 47%

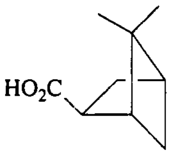

(**79**) 68%

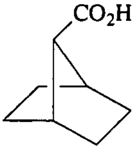

(**80**) 82%

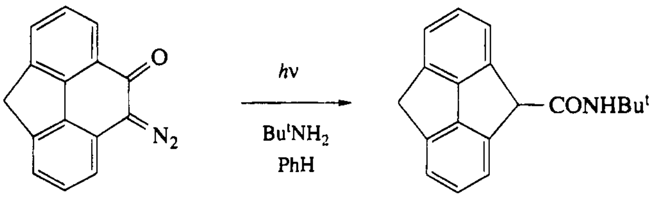

(23)

(**81**)

2%

Simple 2-diazocyclohexanones are readily converted by photolysis in methanol, for example, into methyl cyclopentanecarboxylates.[123] However, the Favorskii method for ring contraction (see Volume 3, Chapter 3.7) is usually more convenient in these systems since the necessary starting materials are more readily prepared. Applications have been found in the synthesis of A-norsteroids[113,124] and A-nortriterpenes. For example, photolysis of 2-diazoallobetulone (**82**) in the presence of weak acids RXH affords mainly the 2β-carboxy-A-nor derivative (**83**).[114] The 3,12-cycloiceane esters (**84**) are obtained in 52% yield from the photolysis of the diazo ketone (**85**) in methanol.[125] Wolff rearrangement of cyclic 2-diazo-1,3-dicarbonyl systems gives ring-contracted β-keto carboxylic acid derivatives.[126,127] The predominant or exclusive product of rearrangement of an unsymmetrical diazo compound can be predicted from the relative migratory aptitude data discussed previously (see Sections 3.9.2.1 and 3.9.3.1). Thus, for example, exclusive carbon migration occurs in the conversion of the spirocyclic diazo compound (**86**) into (**87**; 69%).[128]

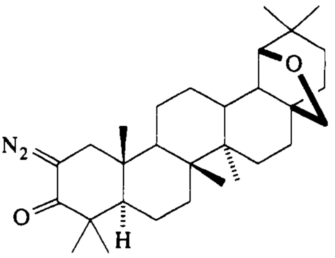

(**82**)

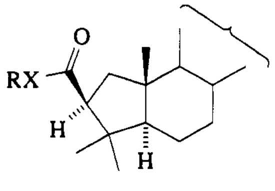

(**83**)

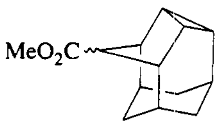

(**84**)

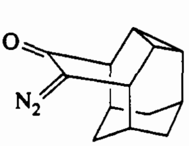

**(85)**

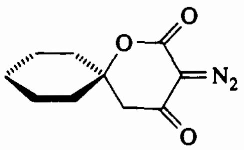

**(86)**

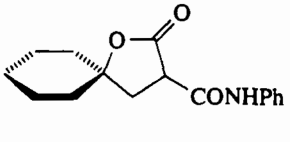

**(87)**

The photochemical decomposition of *o*-diazo oxides ('*o*-quinone diazides') is of both preparative and commercial interest and importance. Wolff rearrangement with ring contraction gives access to the cyclopentadiene system (including heterocyclic analogs). Since the *o*-diazo oxides are usually prepared from *o*-aminophenols, the process is remarkable in that it represents the shrinking of a benzene ring. However, the products are prone to undergo diazo coupling with unreacted starting material (*e.g.* **88** → **89** → **90**),[129] but this chemistry has been exploited in the Diazotype offset photocopying process.[130] Reduction of pH inhibits the coupling process, hence the photolyses for preparative ring contraction are often conducted in acidic solvents (*e.g.* aq. AcOH). Reaction of benzene derivatives is decidedly more difficult than for *o*-diazo oxides based on naphthalene and higher aromatics where stabilization is not so great. Thermolysis can be used for the latter systems, but an intense UV source is necessary for benzenoid *o*-diazo oxides to enhance the rate of rearrangement. An indication of the variety of the synthetic applications is given in equations (24),[131] (25),[131] (26)[132,133] and (27).[133] The migration of $sp^2$ nitrogen (equation 25) is particularly noteworthy. Similar routes have been used for the synthesis of a variety of indenecarboxylic acids (yields *ca.* 20–60%),[131] related systems[134] and pentalenes such as (**105**; 75%).[135]

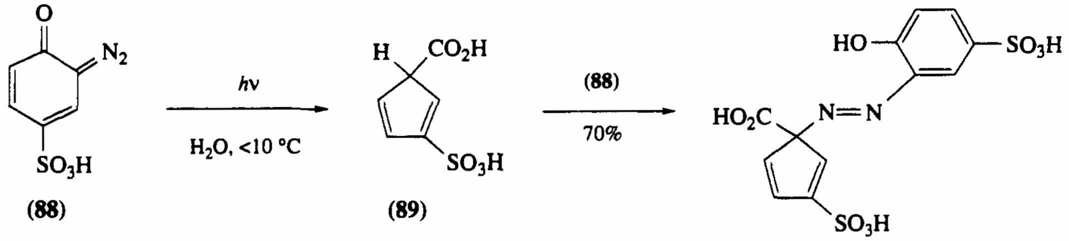

**(88)** **(89)** **(90)**

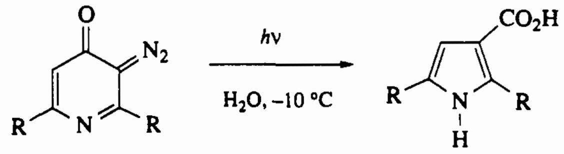

**(91)** R = H, Me **(92)** R = H, Me

(24)

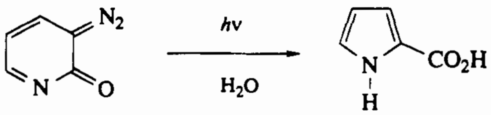

**(93)** **(94)**

(25)

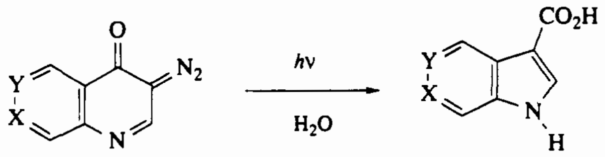

(26)

| | | |
|---|---|---|
| **(95)** | X = Y = CH | **(96)** |
| **(97)** | X = CH, Y = CCl | **(98)** |
| **(99)** | X = N, Y = CH | **(100)** |
| **(101)** | X = CH, Y = N | **(102)** |
| **(103)** | X = CMe, Y = CH | **(104)** |

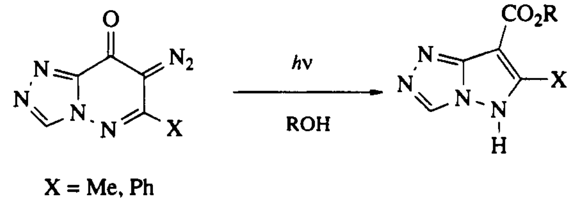

(27)

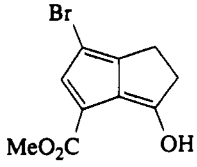

**(105)**

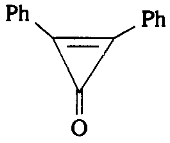

**(106)**

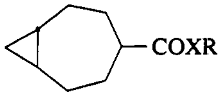

**(107)**

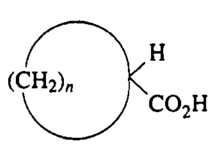

**(108)**

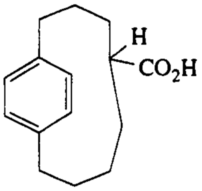

**(109)**

Irradiation of 1,3-bisdiazocyclohexan-2-ones in hydroxylic solvents affords cyclopentene-1-carboxylic acids and esters; regiochemical control is only moderate.[9,136] Although the course of the reactions could be accommodated by sequential Wolff rearrangement and [1,2] H-shift, studies on 1,3-bisdiazo-1,3-diphenylpropan-2-one indicate the formation of the cyclopropenone intermediate (**106**).[137]

There have been relatively few applications to the contraction of larger rings. Irradiation of solutions of 4-diazo-*trans*-bicyclo[6.1.0]nonan-5-one afforded the strained carboxylate derivatives (**107**; XR = OH, OMe) in *ca.* 22–45% yield.[138] Small to medium ring diazo ketones afford the ring-contracted carboxylic acids (**108**; *n* = 4–10) in 25–95% yield on photolysis in dioxane–$H_2O$[139] or THF–$H_2O$.[58] Thermolysis of the diazo ketones in aniline at 150–160 °C gave the anilides of (**108**) in 78–91% yield.[28] Transannular reactions of the ketocarbene intermediates can be a complication under some conditions.[28,139] 4-Carboxy[8]paracyclophane (**109**) has been prepared (25%) by the photochemical method.[140]

### 3.9.3.3 Cycloaddition Reactions

When the Wolff rearrangement is conducted in inert solvents (*i.e.* in the absence of weak acids, RXH) it is possible, in principle, to intercept the ketene intermediate; stabilized ketenes can be isolated.[1b] Their [2 + 2] cycloadditions to activated alkenes and dienes is a valuable synthetic procedure.[141] However, such reactions are relatively slow, and the generation of ketenes from α-diazo ketones provides a number of other species capable of acting as trapping agents. Thus, the rather labile aldoketenes react with intact α-diazo ketone to give butenolides or pyrazoles (equation 28).[7,9,11] The *o*-diazo oxides on thermolysis afford dioxofulvalenes, resulting from the formal [1,3] dipolar cycloaddition of the ketocarbene intermediate to the ketene (equation 29).[9,11] Nevertheless, trapping the ketene by cycloaddition to C═C, C═N, N═N and the C═O bonds of *o*-quinones has been achieved frequently.[9,11] but such reactions have been studied mainly from a general interest viewpoint rather than for specific purposes in synthesis. Various

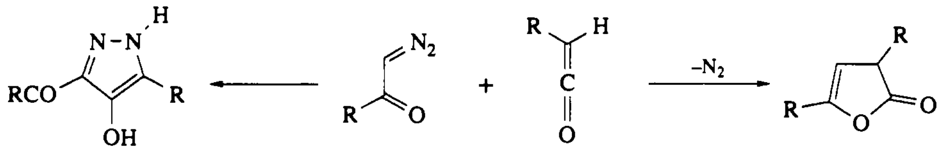

(28)

examples of intramolecular trapping by a strategically located C=C in the molecule are also known. A particularly remarkable case is shown in equation (30).[142] The major product of decomposition of diazo ketone (**110**) is 6,7,7-trimethyltricyclo[3.2.1.$0^{3,6}$]octan-4-one (**111**), even in boiling aqueous dioxane. On the other hand, decomposition of the more rigid diazo ketone (**112**) partitions between intramolecular trapping of the carbene to give (**113**) and the ketene to give (**114**) by way of a Cope rearrangement.[143] The pathway to (**114**) *via* the ketene is favored in the photolytic reaction, whereas copper-catalyzed decomposition affords (**113**) preferentially. By-and-large, therefore, this area of diazo ketone chemistry has scarcely been over-exploited.

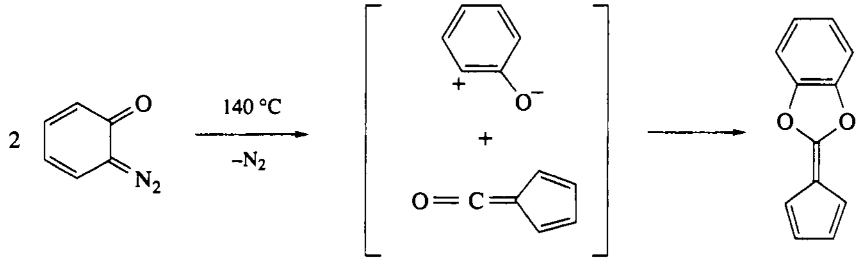

(29)

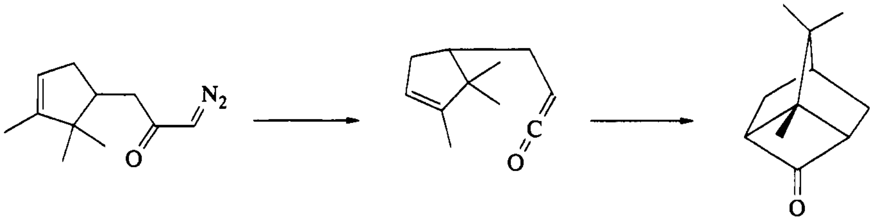

(30)

**(110)** **(111)**

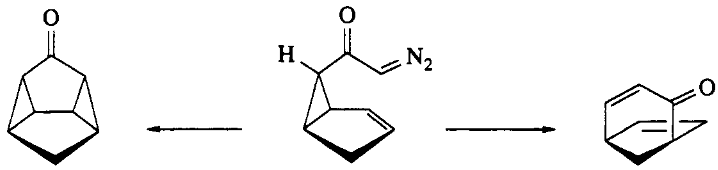

**(113)** **(112)** **(114)**

### 3.9.3.4 The Vinylogous Wolff Rearrangement

This name has been applied[144] to the decomposition of β,γ-unsaturated diazo ketones (**115**) by copper salts in the presence of alcohols, leading to skeletally rearranged γ,δ-unsaturated esters, and is a comparatively recent discovery.[144,145] The transformation represents a synthetic alternative to Claisen type rearrangements (compare equations 31 and 32). The allylic transposition of the acetate residue is thought to occur by way of a bicyclo[2.1.0]pentan-2-one (**116**), which is formed by intramolecular trapping of the ketocarbenoid (Scheme 12). Fragmentation of the bicyclo[2.1.0]pentan-2-one gives rise to a β,γ-unsaturated ketene (**117**), which is captured by the added nucleophile to afford the observed γ,δ-unsaturated carboxylic acid derivative (**118**). Similar decomposition of (**115**) by thermolysis, photolysis or by silver ion catalysis gives mixtures of rearranged product and the normal Wolff product, respectively (**118**) and (**119**); mixture compositions vary, but the normal product (**119**) generally predominates. In contrast, copper(II) ion catalysis affords mainly rearranged products (**118**), and $Cu(OTf)_2$ and benzyl alcohol give the best results. Although the initial insertion step leading to (**116**) seems to be stereoselective, the fragmentation reaction appears to proceed with loss of this initial stereoselectivity, hence mixtures of stereoisomers are usually produced. Illustrative examples of the reaction are given in equations (33)–(35);[144] the reactions were carried out in boiling cyclohexane for 4 h. In equation (35) it can be seen that the vinylogous Wolff rearrangement leading to (**121**), a 1:1 mixture of stereoisomers, competes effectively with cyclopropanation of the γ,δ-double bond, giving a 1:1 mixture of the stereoisomers of (**120**), when the β,γ-double bond is at least equally activated.

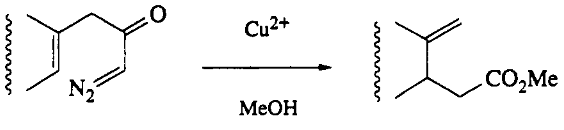

O
$N_2$
$Cu^{2+}$
MeOH
$CO_2Me$

**(115)**

(31)

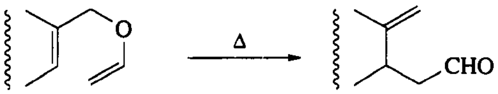

(32)

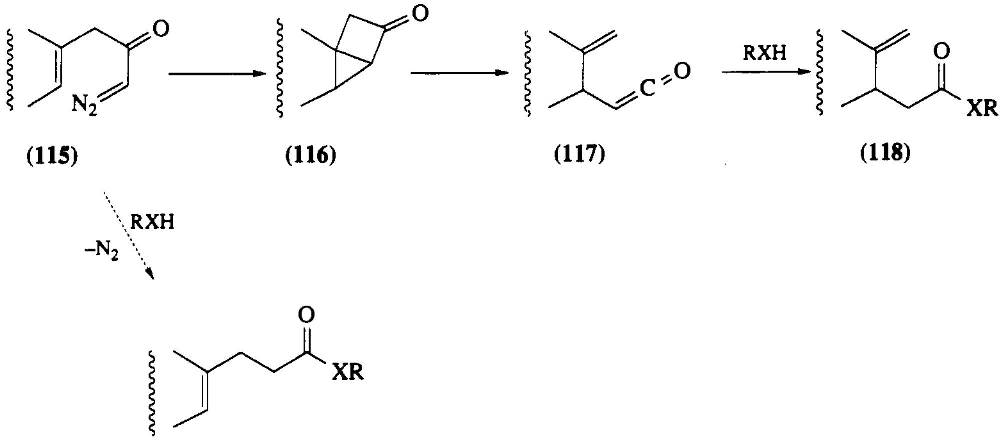

O
$N_2$
O
C=O
RXH
O
XR
RXH
$-N_2$
O
XR

**(115)** **(116)** **(117)** **(118)**

**(119)**

**Scheme 12**

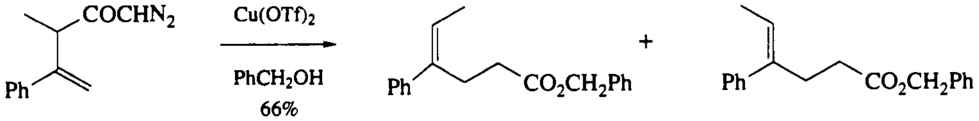

$COCHN_2$
Ph
$Cu(OTf)_2$
$PhCH_2OH$
66%
Ph
$CO_2CH_2Ph$
+
Ph
$CO_2CH_2Ph$

20% 80%

(33)

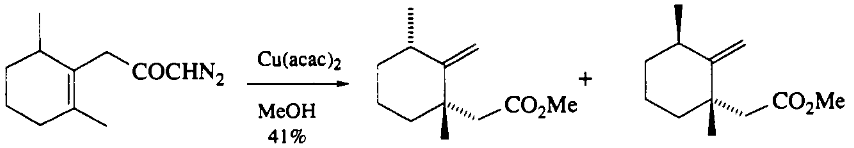

$COCHN_2$
$Cu(acac)_2$
MeOH
41%
$CO_2Me$
+
$CO_2Me$

10% 90%

(34)

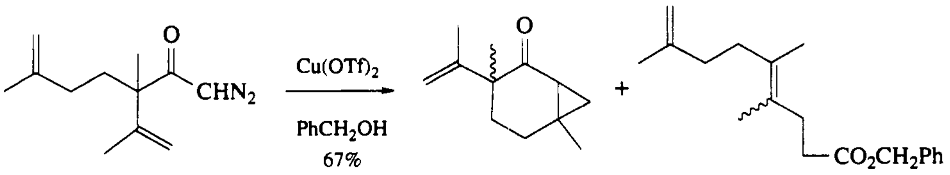

O
$CHN_2$
$Cu(OTf)_2$
$PhCH_2OH$
67%
O
+
$CO_2CH_2Ph$

**(120)** 25% **(121)** 75%

(35)

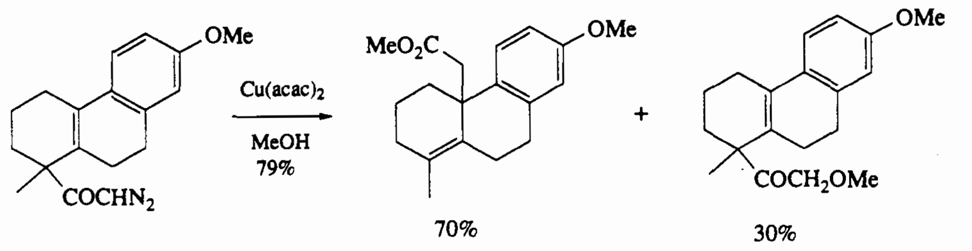
OMe
COCHN$_2$
Cu(acac)$_2$
MeOH
79%
MeO$_2$C
OMe
70%
+
OMe
COCH$_2$OMe
30%

(36)

In a recent application, the vinylogous Wolff rearrangement has been used to provide angular functionalization in annelated polycyclic systems (*e.g.* equation 36).[146]

### 3.9.3.5 Related Reactions

The Wolff rearrangement has much broader horizons than the decomposition pathway for α-diazocarbonyl compounds, and a generalized mechanistic route is given in Scheme 13. This allows for both a stepwise pathway (a) and concerted decomposition (b). Thus, although sometimes α-diazo ketones (**122a**) appear to give the ketene (**124**) by path b, in the majority of reactions there is strong evidence for a ketocarbene intermediate (**123**) preceding the ketene. Acyl azides (**122c**), on the other hand, suffer concerted rearrangement to isocyanates (**124**) on thermolysis (Curtius rearrangement); there is no evidence for nitrene intermediates in the rearrangement pathway.[147,148] The related Schmidt, Lossen and Hofmann

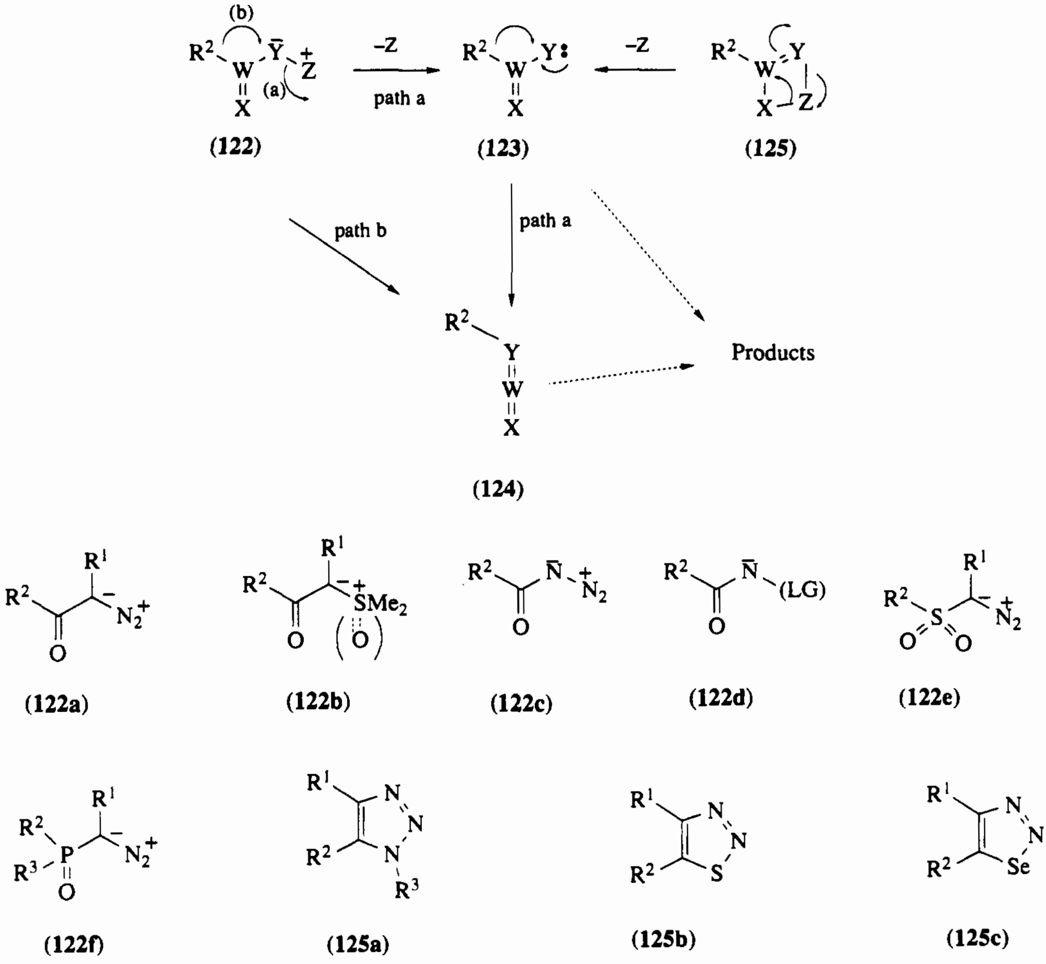
(b)
(a)
-Z
path a
-Z
(122)
(123)
(125)
path b
path a
(124)
Products
(122a)
(122b)
(122c)
(122d)
(LG)
(122e)
(122f)
(125a)
(125b)
(125c)

Scheme 13

reactions, which proceed *via* (**122c**; Schmidt) or (**122d**; LG = leaving group such as Br or OAc) also follow path b but, because of the reaction conditions, products derived from the isocyanate, rather than the isocyanate itself, are isolated.[147]

The electronic make-up of the assemblage WXYZ of (**122**) can be fulfilled in a number of other ways, as indicated by the selection of structures (**122b**)–(**122f**). Although in simple α-diazo ketones there does not appear to be a strong direct electronic interaction between the carbonyl oxygen atom (X in **122**) and the terminal diazo nitrogen atom (Z in **122**), when X is a softer base (*e.g.* NR, S, Se) the cyclic form (**125**) is more stable. Thus, the intermediate (**123**) can be accessed from (**125a**)–(**125c**), further broadening the scope. Studies on these other variants of (**122**) and (**125**) have been much more limited. Reaction pathways are determined by reaction conditions, but products arising from Wolff-type rearrangements have been observed in the thermolysis or pyrolysis of acylsulfonium ylides,[149] β-ketosulfoxonium ylides (**122b**),[150] α-diazosulfones (**122e**),[151] α-diazophosphine oxides (**122f**),[152,153] 1,2,3-triazoles (**125a**),[154] 1,2,3-thiadiazoles (**125b**),[155] and 1,2,3-selenadiazoles (**125c**).[156]

## 3.9.4 REFERENCES

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# 3.10

# The Stevens and Related Rearrangements

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## 3.10.1 INTRODUCTION

Nitrogen and especially sulfur ylides are used extensively in synthetic organic chemistry. Our understanding of the sigmatropic rearrangements of these ylidic intermediates has matured over the last few decades. These rearrangements, which often proceed with high regio-, stereo- and enantio-selectivities, have become a powerful synthetic tool.

In 1928, T. S. Stevens reported the first example of a reaction which was later to be called the Stevens rearrangement.[1] He found that, upon treatment with aqueous alkali, phenacylbenzyldimethylammonium bromide (**1**) was converted into 1-benzoyl-2-benzyldimethylamine (**2**) in high yield (Scheme 1, equation a). Soon after, in 1932, Stevens reported the analogous rearrangement of the corresponding sulfonium derivative.[2] The sulfonium bromide (**3**) was smoothly transformed into a sulfide, which was initially formulated as structure (**4**), when (**3**) was treated with hot alkali (Scheme 1, equation b). Subsequent work, however, established that the correct structure of the rearranged material was (**84**) (Scheme 19).

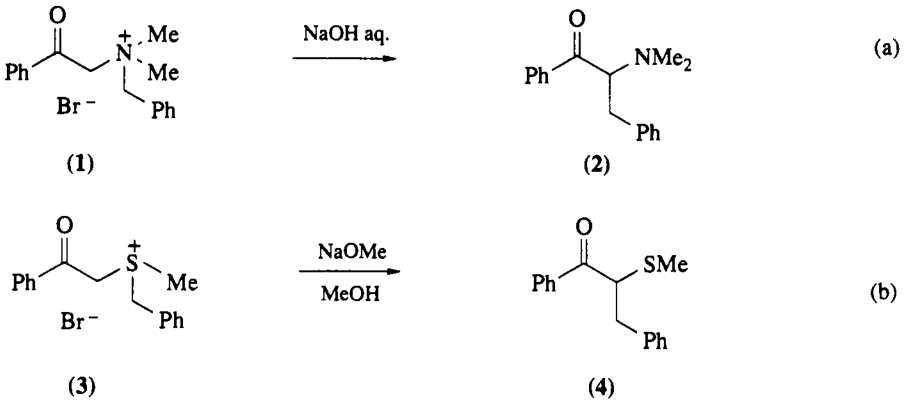

**Scheme 1**

A variety of groups, including allyl, propargyl and phenacyl, were also shown to be good migrating groups in ylidic rearrangements.[3] Mechanistic investigations, using $^{14}$C-labeled starting material, as well as cross-over experiments, demonstrated the reaction to be intramolecular.[4] Subsequent studies of the effect of substituents on the phenyl ring on the migrating ability of the benzyl group in reactions of (**1**) gave the order $p$-NO$_2$ > $p$-Hal > $p$-Me > $p$-MeO.[5] This observation led Stevens to postulate that the reaction proceeded by initial formation of an ylidic intermediate (**5**) which, by heterolysis, yielded a benzylic anion and an iminium ion. This ion pair could then lead to the observed product (Scheme 2). Later, Kenyon showed that the migrating group retained its configuration during the course of the rearrangement.[6] The optically-active ammonium salt (**7**), for example, was converted into an optically-active amine (**9**) with retention of chirality at the benzylic chiral carbon atom. Wittig[7] and Hauser[8] then proposed that the reaction was a concerted intramolecular displacement of the migrating group by the carbanionic center of the ylidic intermediate (**8**; Scheme 3).

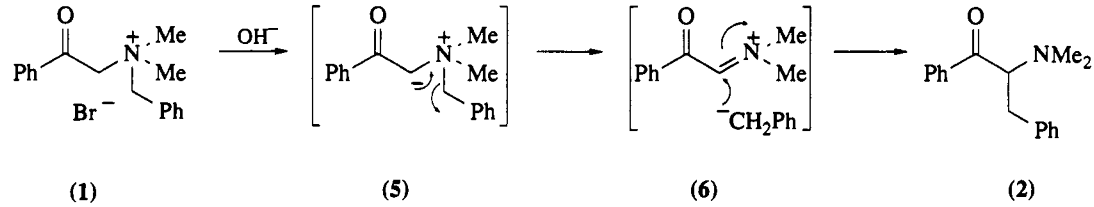

**Scheme 2**

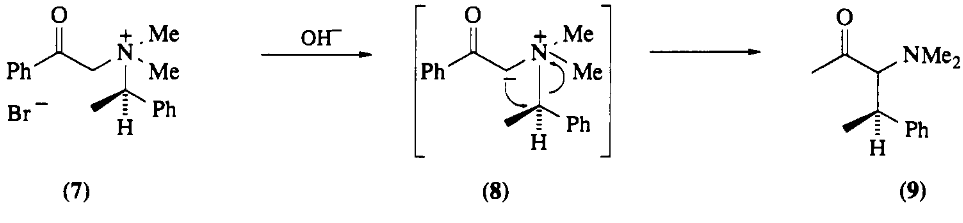

**Scheme 3**

If the Stevens rearrangement is a concerted reaction, then the Woodward and Hoffmann rules of conservation of orbital symmetry demonstrate that it is a symmetry-forbidden reaction.[9] Later on, Ollis reinvestigated the reaction and demonstrated, in a very elegant manner, that the Stevens rearrangement proceeds by radical pair intermediates.[10] These radicals recombine quickly while being held within a solvent cage, a fact that explains the high intramolecularity and stereoselectivity observed in these rearrangements (Scheme 4).

Another type of ylidic rearrangement, the Sommelet–Hauser rearrangement, was discovered later, in 1937, by Sommelet and studied extensively by Sommelet and by Hauser.[11,12] This transposition involves the base-promoted rearrangement of non stabilized ammonium and sulfonium ylides. Thus, the ammonium salt (**11**), when heated with alkali, gave cleanly the substituted diphenylmethane derivative (**12**; Scheme 5). Wittig found that the dibenzyl ammonium salt (**13**) reacted with phenyllithium giving two

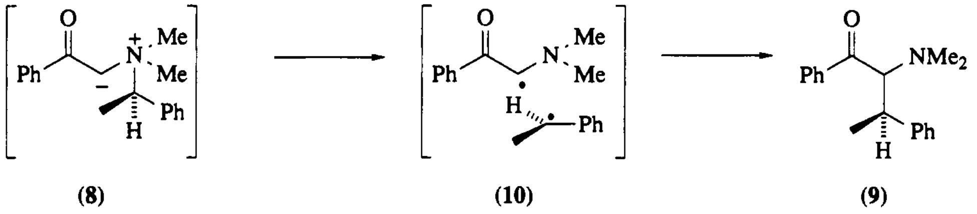
Ph
O
Me
N
Me
Ph
H
Ph
O
N
Me
Me
H
Ph
Ph
O
NMe2
Ph
H

**(8)** **(10)** **(9)**

Scheme 4

products, (**14**) and (**15**).[13] The product (**15**) is produced by a competing Stevens rearrangement. Subsequent work led to the proposed mechanism for the Sommelet–Hauser rearrangement as depicted in Scheme 6.[14] The ylide (**17**), formed upon base treatment of the ammonium salt (**16**), attacks the aromatic ring, leading to the unstable intermediate (**19**), which may be isomerized into the substituted aromatic derivative (**20**). It was also shown later that the two equilibrating ylides (**17**) and (**18**) were involved in these reactions; the ylide (**18**) being associated with the Sommelet–Hauser rearrangement.[15]

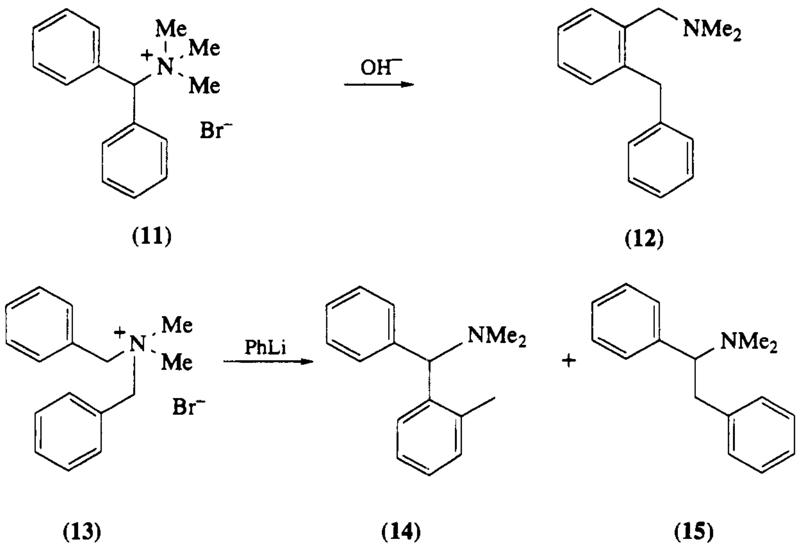
Me
N
Me
Me
Br⁻
OH⁻
NMe2
N
Me
Me
Br⁻
PhLi
NMe2
+
NMe2

**(11)** **(12)**

**(13)** **(14)** **(15)**

Scheme 5

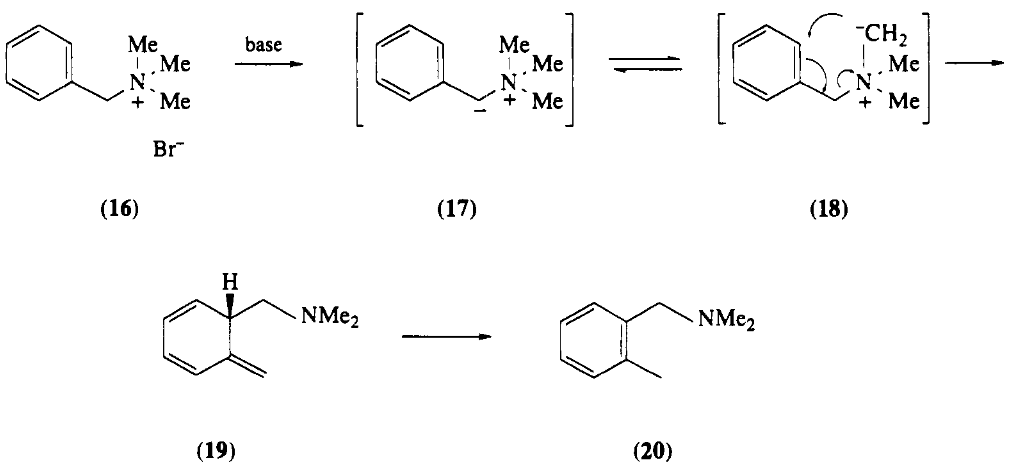
Me
Me
N
Me
Br⁻
base
Me
Me
N
Me
⁻CH2
Me
N
Me
H
NMe2
NMe2

**(16)** **(17)** **(18)**

**(19)** **(20)**

Scheme 6

In 1969, Ollis recognised that the rearrangement of allylic ammonium and sulfonium ylides was a facile process of considerable synthetic interest,[16] and Baldwin reported his generalization of the sigmatropic rearrangement processes.[17] Since then, numerous examples of the synthetic utility of ylidic rearrangements have been recorded in the chemical literature and this number is growing continuously.

## 3.10.2 DEFINITIONS

With some substrates, several types of ylidic rearrangements can occur simultaneously, though by judicious choice of experimental conditions, this competition can be controlled. This is of paramount importance in the utilization of these rearrangements in synthesis. The two examples described below illustrate this point.

When the hypothetical ylide (**21**) is generated, then, in principle, a 1,2-, 3,2- or 5,2-rearrangement can occur, leading to the three products (**22**), (**23**) and (**24**) respectively (Scheme 7). [The 3,2-rearrangement is often reported in the literature as a 2,3-sigmatropic rearrangement. The author believes that, if the other reactions in Scheme 7 are called 1,2- and 5,2-sigmatropic rearrangements respectively, then logic would dictate that this reaction is a 3,2-sigmatropic rearrangement. We would like to encourage the use of the 'correct' 3,2 nomenclature rather than the 'incorrect', but popular, 2,3 one.] Similarly, when examining ylide (**25**), four different products (**26**), (**27**), (**28**) and (**29**) can, in principle, be identified: they are those derived from 1,2-, 1,4-, 3,2- and 3,4-sigmatropic rearrangement respectively (Scheme 8).

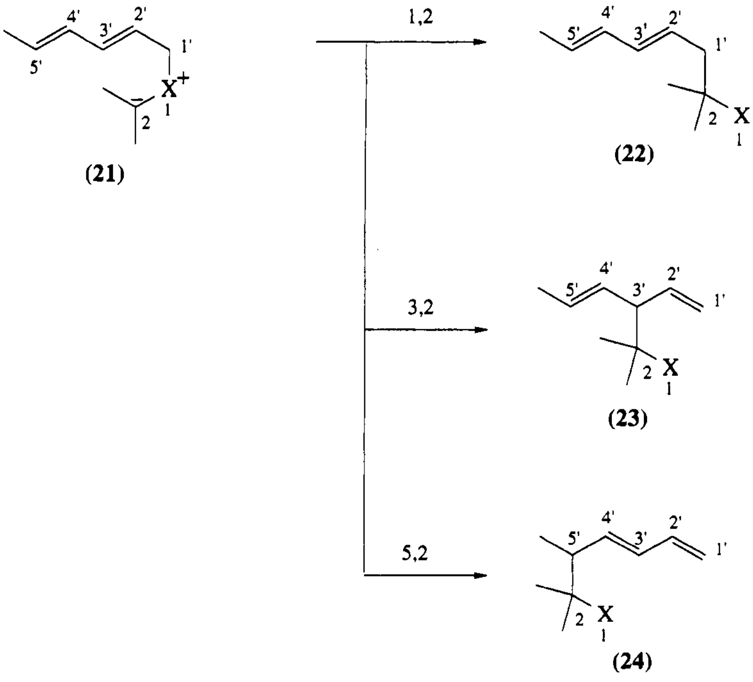

Scheme 7

The 1,4- and 3,2-rearrangements are thermal, concerted, orbital symmetry allowed processes possessing suprafacial–suprafacial characteristics. They are facile reactions, occurring readily and under mild conditions. The 3,2-rearrangement will take place with allylic inversion, as demanded by orbital symmetry control. Thus, the sulfonium salt (**30**) gave the allylic sulfide (**31**), whereas (**32**) gave the isomerically pure (**33**; Scheme 9).[18]

The 1,4-rearrangement, though symmetry-allowed, is rarely observed.[19] The 1,2-, 5,2- and 3,4-rearrangements are symmetry-forbidden processes which would have to take place *via* a suprafacial–antarafacial mode. They have been shown to proceed by radical pair intermediates.[20]

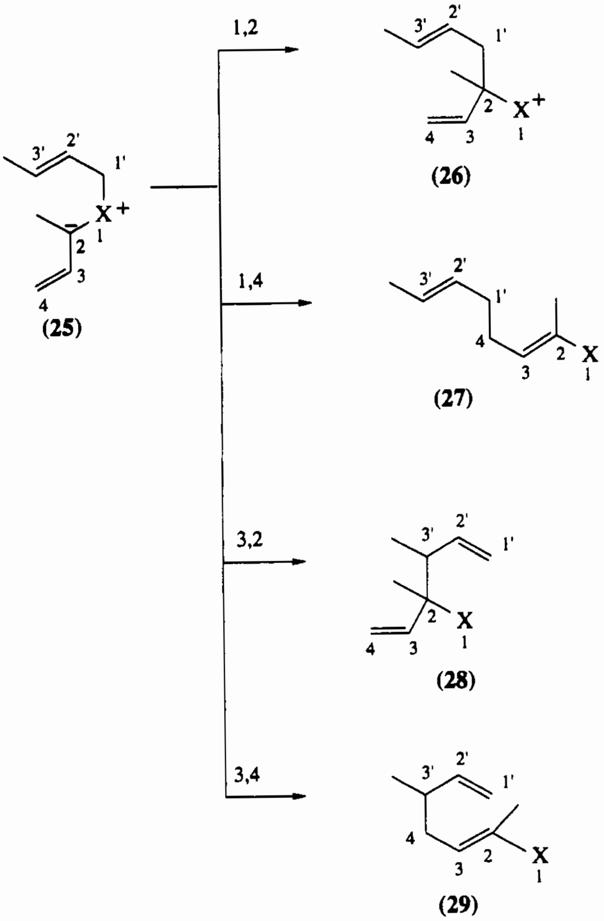
1,2
1,4
3,2
3,4
X+
X
1
2
3
4
1'
2'
3'

(25) (26) (27) (28) (29)

Scheme 8

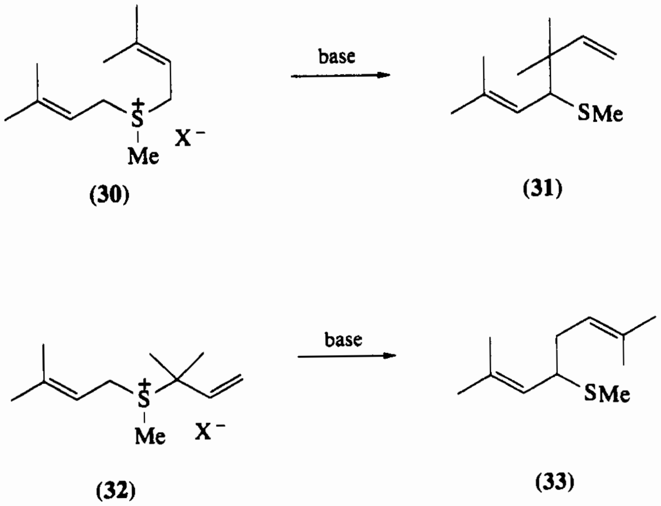
base
base
S+
Me
X−
SMe

(30) (31) (32) (33)

Scheme 9

## 3.10.3 PREPARATION OF NITROGEN AND SULFUR YLIDES

### 3.10.3.1 Indirect Methods

The oldest and most commonly used method for ylide preparation is the so-called 'salt-method', where a sulfonium or ammonium cation, generated by alkylation of the corresponding sulfide or amine, is deprotonated by a strong base (Scheme 10, path a). In general, an active alkylating agent is required. Primary allylic and benzylic halides, as well as α-halocarbonyl derivatives,[21] produce the ammonium or sulfonium salts fairly readily. A serious side reaction, which characterizes this method, is the competitive dealkylation of the salt by any nucleophilic halide ion produced (Scheme 10, path b).[22] Therefore, exchange of the halide ion for a non-nucleophilic counterion employing a metal salt, *e.g.* $Ag^+$, is performed routinely. Alternatively, the use of Meerwein salts,[23] *e.g.* $Me_3O^+BF_4^-$ (Scheme 11, equation a), or the more recently introduced triflate methodology[24] (Scheme 11, equation b) give directly the stable ammonium or sulfonium salts. The counterions in these cases, are poor nucleophiles unable to dealkylate the cations (Scheme 11).

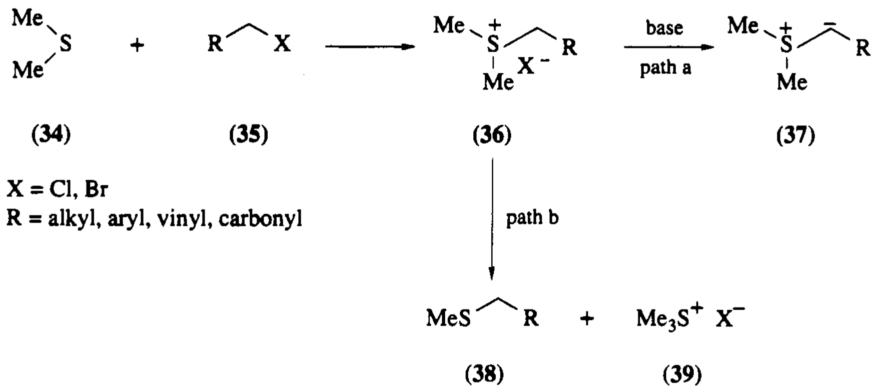

X = Cl, Br
R = alkyl, aryl, vinyl, carbonyl

Scheme 10

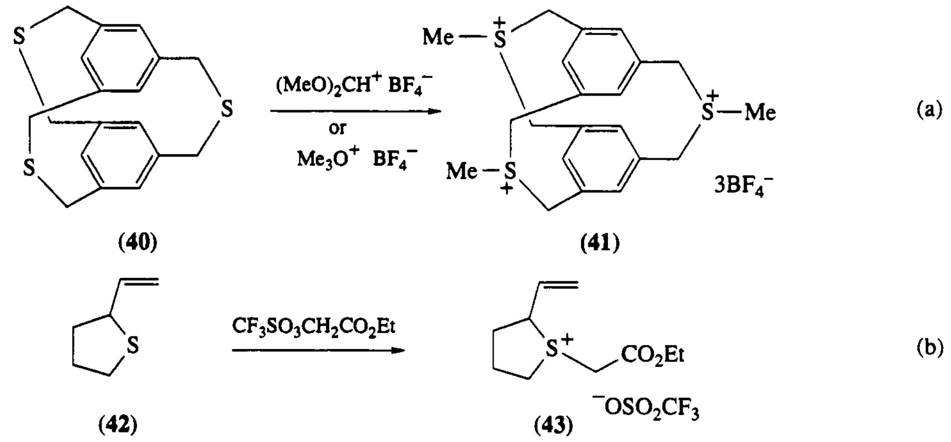

Scheme 11

A second side reaction using this approach is the Hoffmann elimination of the sulfide or amine, during attempted deprotonation of the sulfonium or ammonium salt. This reaction is especially important in the case of ammonium ylides. Finally, another problem which surfaces during the deprotonation step is the formation of a mixture of ylides, *e.g.* (**45**) and (**46**) from (**44**), which undergo competing rearrangements to give (**47**) and (**48**; Scheme 12).[25]

An elegant solution to these problems was proposed independently by Vedejs[26] and Sato.[27] They generated ylides regiospecifically, under nonbasic conditions, using fluoride-catalyzed desilylation of

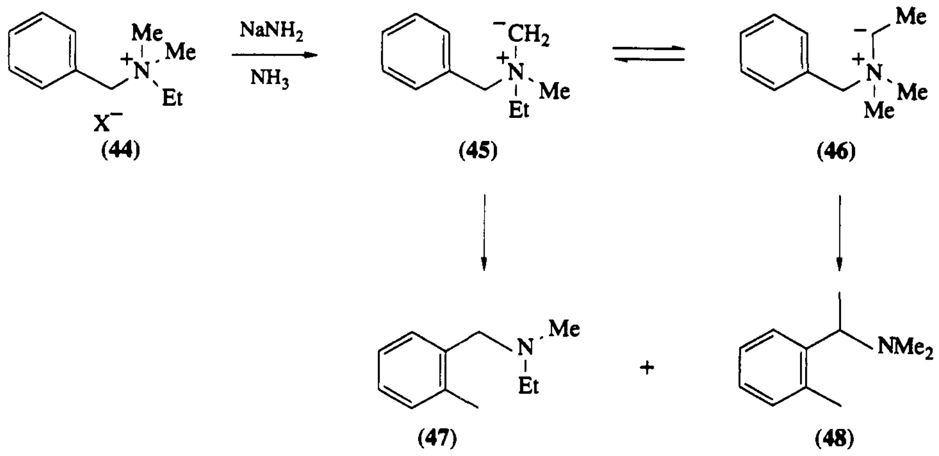

Scheme 12

trimethylsilyl ammonium or sulfonium salts. Not only is the extent of elimination considerably reduced, but also one reaction pathway predominates easily over the other one (Scheme 13).

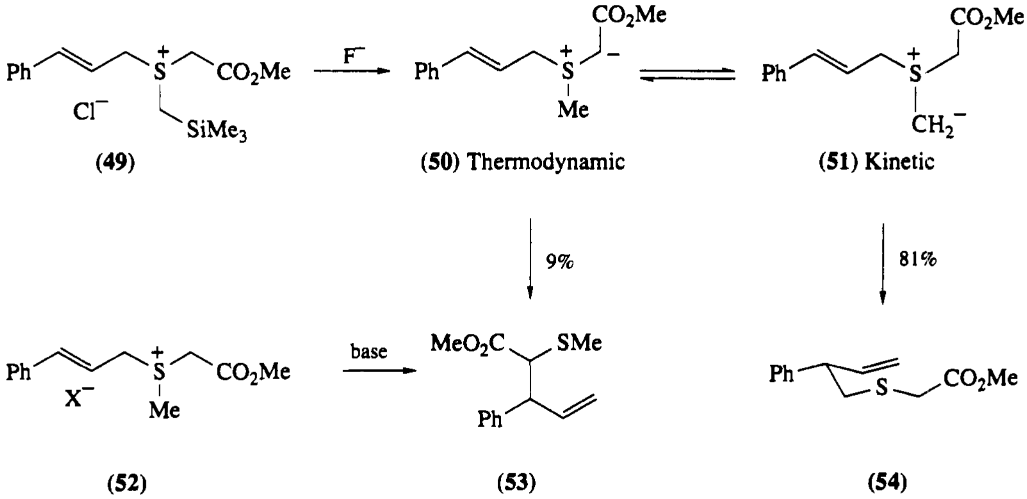

Scheme 13

### 3.10.3.2 Direct Formation of Ylides

The addition of a carbene or benzyne to a sulfide, and to a lesser extent to an amine, provides a direct route to ylides. Enormous progress has been realized with this approach, mainly as a result of the efforts of Ando[28] and Doyle.[29] Most noteworthy amongst examples using benzyne is the squalene synthesis reported by Ollis, in which the sulfide (**55**) was transformed by a 3,2-rearrangement into the squalene precursor (**58**) and eventually into squalene itself (Scheme 14).[30]

The stereospecific rearrangement of *exo*-methylenecyclohexane derivatives discovered by Evans employed dichlorocarbene, generated under phase transfer conditions (Scheme 15).[31]

An extremely versatile approach to ylides involves the light-promoted or metal-catalyzed generation of carbenes from diazonium salts. In most cases, metal-catalyzed reactions give better yields and cleaner reaction mixtures than do corresponding photolytic techniques (Scheme 16, equation a).[32] A classical example is to be found in penicillin chemistry (Scheme 16, equation b).[33] However, copper catalysts have their limitations in the generation of carbenoid intermediates. These limitations can be largely over-

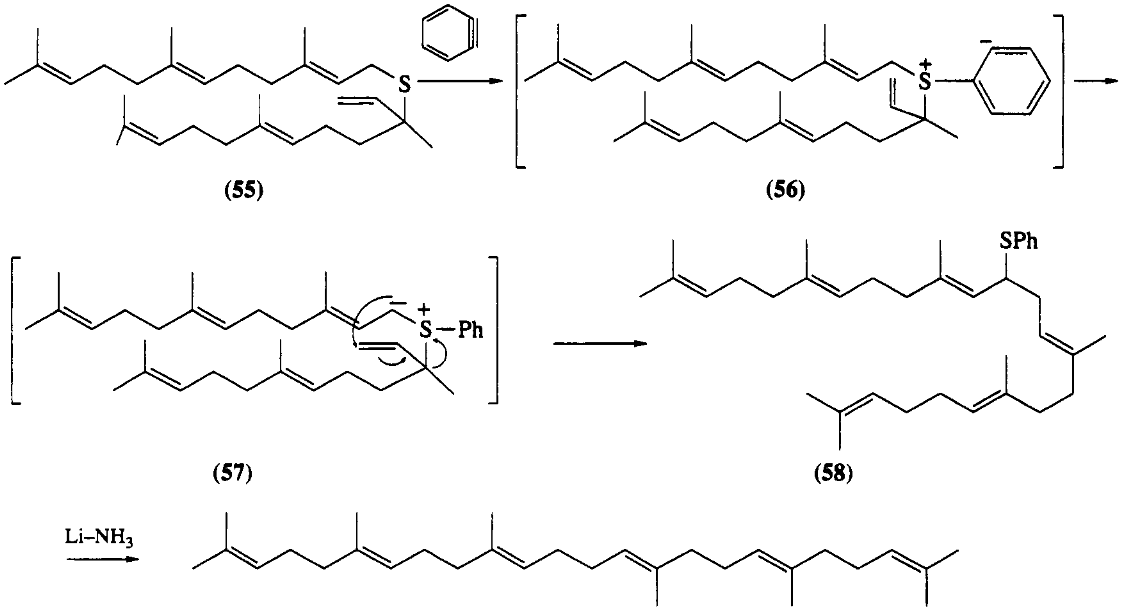
S
(55)
+
S
(56)
+
S—Ph
(57)
SPh
(58)
Li-NH3
(59) Squalene

**Scheme 14**

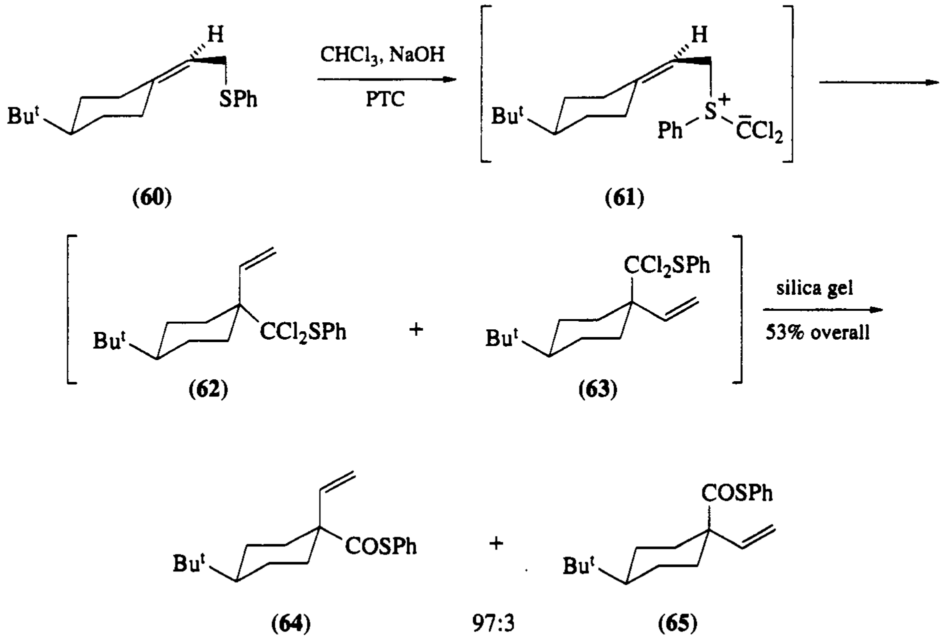
H
SPh
Bu^t
(60)
CHCl3, NaOH
PTC
H
Bu^t
Ph
S+
CCl2
(61)
Bu^t
CCl2SPh
(62)
+
CCl2SPh
Bu^t
(63)
silica gel
53% overall
Bu^t
COSPh
(64)
+
97:3
COSPh
Bu^t
(65)

**Scheme 15**

come by employing rhodium catalysts that not only afford the desired material when the copper catalysts fail to react, but also allow the reactions to be performed under much milder conditions. It is quite remarkable that rhodium catalysts allow the preparation and reaction of some oxonium and halonium ylides.[34] It is only recently that their synthetic use has started to be fully appreciated (Scheme 17).

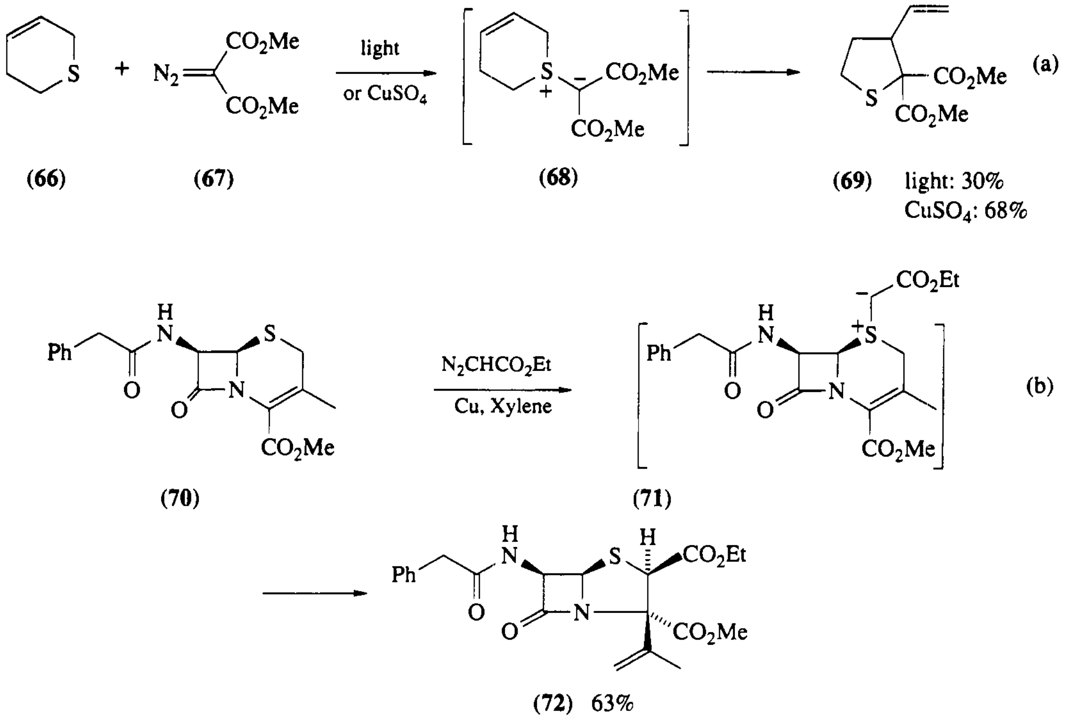

(66)
(67)
light
or CuSO4
(68)
(69) light: 30%
CuSO4: 68%
(a)
(70)
N2CHCO2Et
Cu, Xylene
(71)
(b)
(72) 63%

Scheme 16

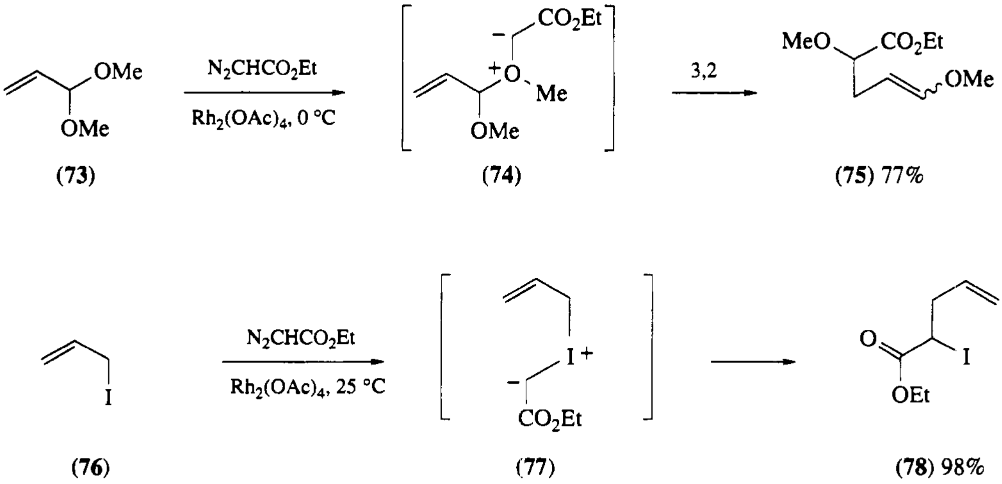

(73)
N2CHCO2Et
Rh2(OAc)4, 0 °C
(74)
3,2
(75) 77%
(76)
N2CHCO2Et
Rh2(OAc)4, 25 °C
(77)
(78) 98%

Scheme 17

## 3.10.4 1,2-SIGMATROPIC REARRANGEMENTS

### 3.10.4.1 Synthetic Applications of the Stevens Rearrangement

Although studied at great length from a mechanistic point of view, the Stevens reactions of nitrogen and sulfonium ylides have, so far, been applied in synthesis only to a limited extent. The details of the earlier work by Stevens have been summarized elsewhere,[35] and some excellent reviews on ylide chemistry mention a few synthetic uses of this rearrangement.[36] One of the classical problems associated with the 1,2-rearrangement is the co-ocurrence of competing reactions, including other rearrangements, *i.e.* 1,3 and 1,2 as well as elimination reactions (more frequent for nitrogen ylides than for sulfur ones). For example, rearrangement of the ylide (**79**) gives the 1,2- and 3,2-products in 1:3 ratio, indicating the greater propensity for the concerted, symmetry-allowed 3,2-rearrangement to occur, in relation to the forbidden 1,2-rearrangement (Scheme 18).[37]

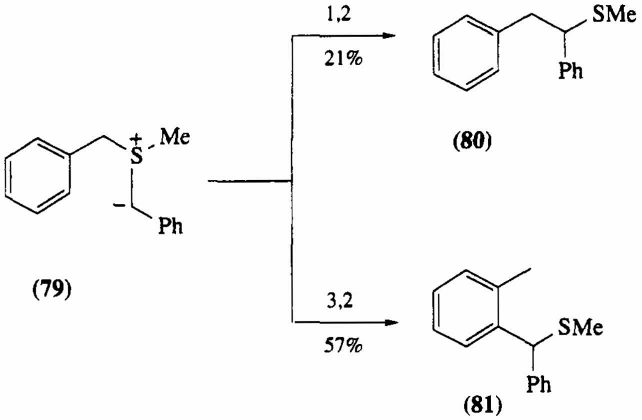

**Scheme 18**

An important breakthrough was the discovery that the ratio 1,2:3,2 was highly dependent upon the nature of the solvent and the concentration of the base. Under aprotic conditions, the Stevens rearrangement of ylide (**82**) takes place nearly exclusively,[35a,38] whereas the 3,2-rearrangement is favored under protic basic conditions (Scheme 19).[37,39] Not only can the 1,2:3,2 ratio be controlled, but the relative proportion of the 3,2-products (**83**) and (**84**) has been shown to depend strongly on the concentration of the base employed in these reactions.[37] This striking result can be understood if one looks at the fate of the primary product (**85**) obtained in the Sommelet–Hauser reaction. This intermediate can participate in two different pathways. Aromatization requires a 1,3-prototropic shift and, therefore, the presence of a proton source or protic solvent. In aprotic solvent, this transformation cannot take place and a competing homolysis will occur followed by a radical recombination giving the 1,2-product (Scheme 20).

Intermediates such as (**85**) have been isolated and reacted under different conditions to give the expected rearrangement products.[37] A few examples of simple Stevens rearrangements are presented in Table 1.

More complex and synthetically useful applications of the Stevens rearrangement have been reported. Kondo, for example, has shown that the ylide (**89**), formed from (**88**) by an intramolecular carbene re-

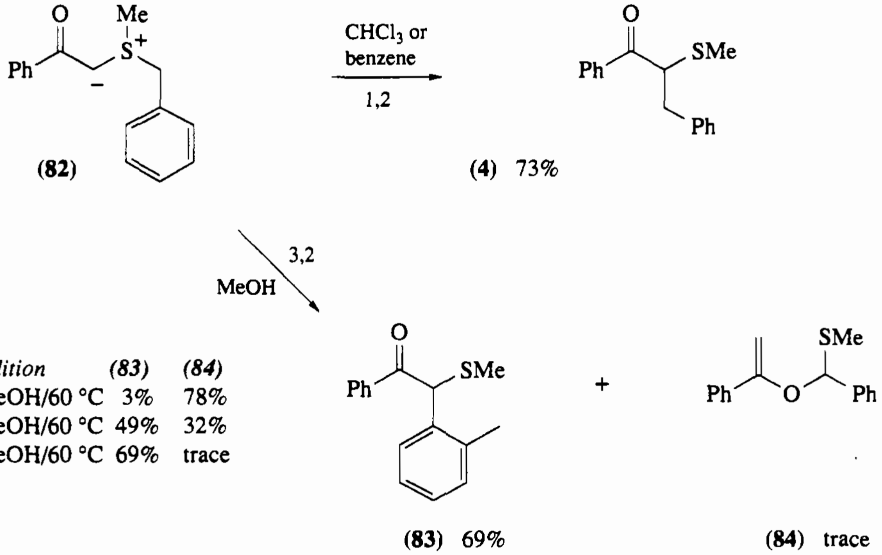

| *Condition* | *(83)* | *(84)* |
|---|---|---|
| 5% Na/MeOH/60 °C | 3% | 78% |
| 10% Na/MeOH/60 °C | 49% | 32% |
| 15% Na/MeOH/60 °C | 69% | trace |

**Scheme 19**

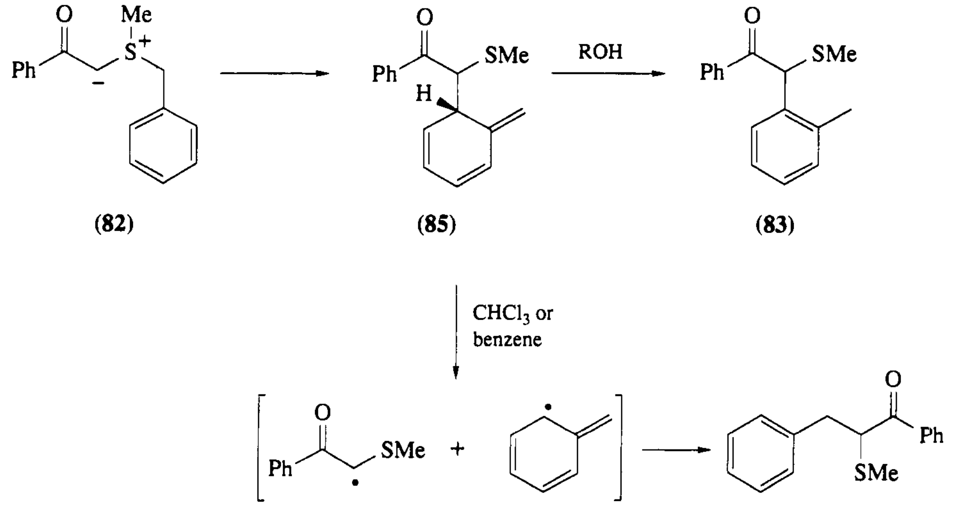

(82) (85) (83)

(86) (87) (4)

**Scheme 20**

action, undergoes a 1,2-sigmatropic shift to give the five-membered ring (**90**) in 51% yield.[42] Even smaller ring compounds, *e.g.* (**94**), can be prepared following this route (Scheme 21). When two ylides of similar stability can be formed and rearranged, poor selectivity is often observed. Thus, irradiation of (**95**) leads to the equilibrating ylides (**96**) and (**97**). It is therefore not too surprising that two Stevens products (**98** and **99**) are obtained from this reaction (Scheme 22).

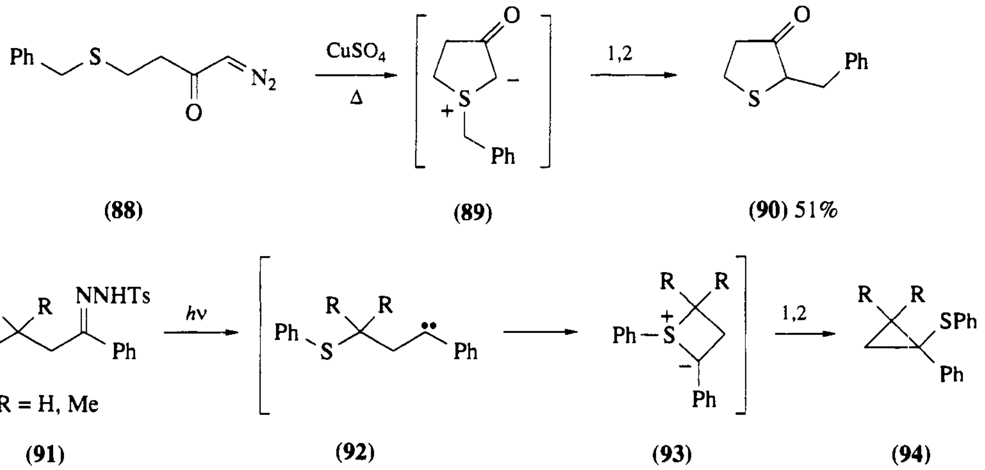

(88) (89) (90) 51%

(91) (92) (93) (94)

**Scheme 21**

In some cases, the Stevens rearrangement can be used to form ring-expanded products. Thus, thietane (**100**) reacts with dimethyl diazomalonate in the presence of a copper catalyst to provide the functionalized tetrahydrothiophene (**102**).[43] A similar and most remarkable example, where a possible competing 3,2-rearrangement is not observed, is the ring expansion of dihydrothiophene (**103**) to (**105**; Scheme 23).[44] Clearly, the increase in strain in the transition state (**106**), which would lead to the 3,2-rearrangement product (**107**) is responsible for this interesting selectivity. In general, nitrogen ylides behave in an analogous manner though sometimes they can supersede sulfur ylides (Scheme 24).

Ollis has demonstrated that the successful transformation of the dihydropyrrole (**110**) into the tetrahydropyridine (**111**) is a fairly easy process.[45] In sharp contrast, the analogous sulfonium salt (**112**) does not form the expected Stevens product (**113**) but rather (**114**), a product of dimerization.

Recent and interesting examples of Stevens reactions were reported by Doyle who reacted dithianes with ethyl diazoacetate in the presence of a rhodium catalyst.[34b] Seven-membered ring bissulfides were

**Table 1**

| *Entry* | *Salt* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 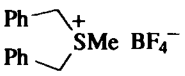 | NaOH, $H_2O$ | 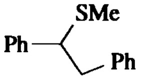 | 21 | 37 |
| 2 | 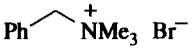 | PhLi | 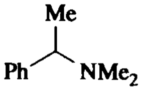 | 32 | 7 |
| 3 | 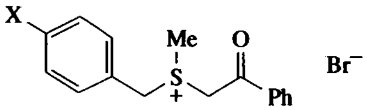 | Δ, THF or acetone | 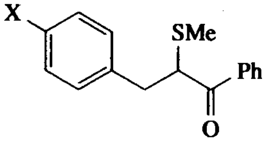<br>X = F, Cl or Br | 70–80 | 35a |
| 4 | 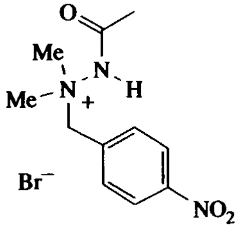 | 180 °C | 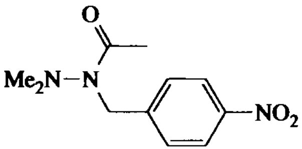 | 50 | 40 |
| 5 | 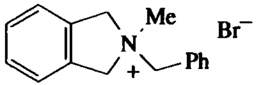 | 3% Na, EtOH | 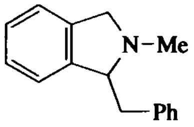 | 75 | 41 |

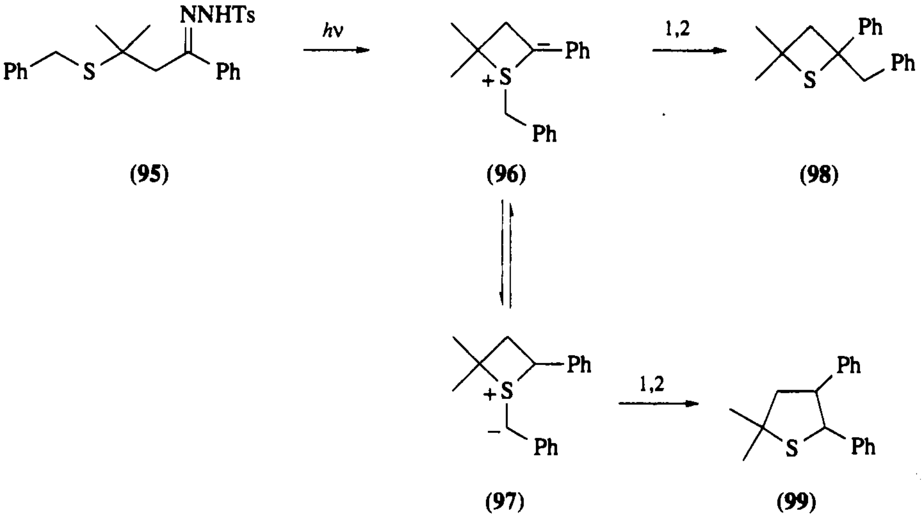
NNHTs
Ph
S
Ph
hν
+S
Ph
Ph
1,2
Ph
S
Ph
(95)
(96)
(98)
+S
Ph
Ph
1,2
Ph
S
Ph
(97)
(99)

Scheme 22

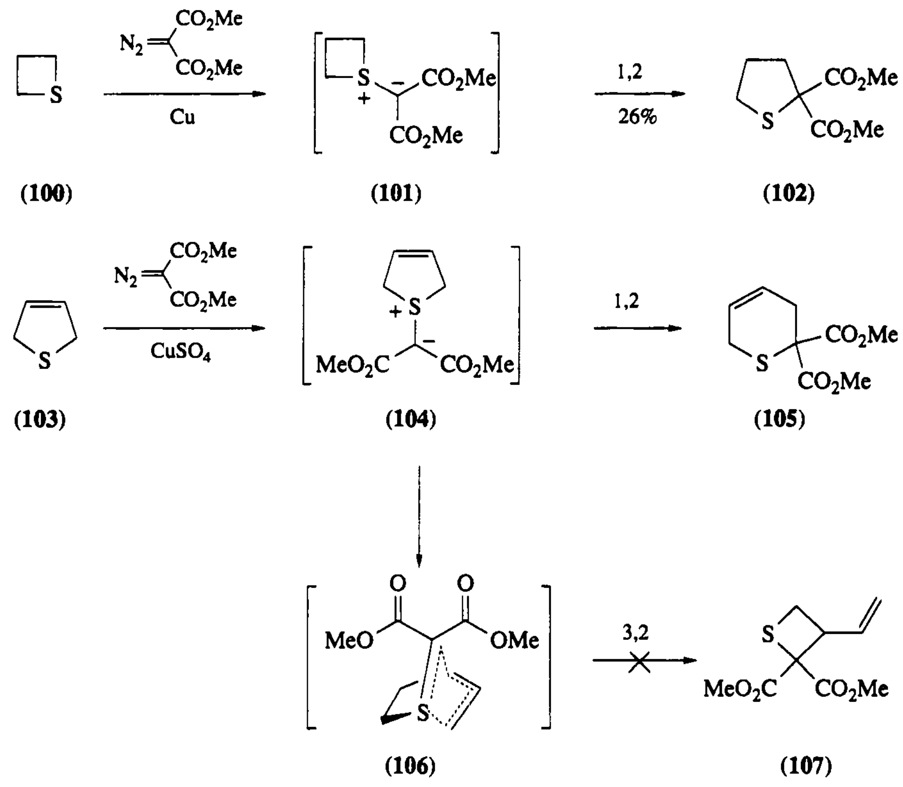
S
$N_2$
$CO_2Me$
$CO_2Me$
Cu
S
+
$CO_2Me$
$CO_2Me$
1,2
26%
S
$CO_2Me$
$CO_2Me$
(100)
(101)
(102)
S
$N_2$
$CO_2Me$
$CO_2Me$
$CuSO_4$
+S
$MeO_2C$
$CO_2Me$
1,2
S
$CO_2Me$
$CO_2Me$
(103)
(104)
(105)
O
O
MeO
OMe
S
3,2
S
$MeO_2C$
$CO_2Me$
(106)
(107)

Scheme 23

obtained in variable yields, depending on the substituents present in the starting dithianes (Scheme 25). With 2-phenyl-1,3-dithiane (**115**), smooth Stevens 1,2-rearrangement gave (**116**). However, with 2-phenyl-2-methyl-1,3-dithiane (**117**), elimination becomes a competing process. In this case, the Stevens 1,2-rearrangement product (**119**) is the minor component of the reaction.

A most remarkable result is obtained when allylic halides are reacted with ethyl diazoacetate in the presence of metal catalysts.[34a] The 1,2-rearrangement product (**122**) and the 3,2-rearrangement product (**121**) can be isolated and their relative proportions shown to be related to the nature of the catalyst em-

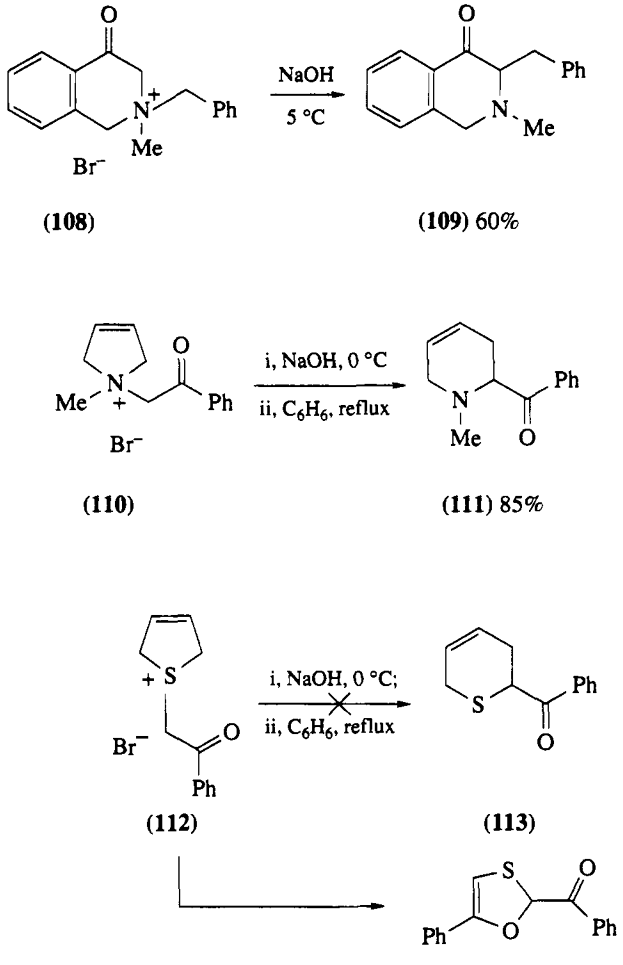
NaOH
5 °C
i, NaOH, 0 °C
ii, $C_6H_6$, reflux
i, NaOH, 0 °C;
ii, $C_6H_6$, reflux

**(108)** **(109)** 60%

**(110)** **(111)** 85%

**(112)** **(113)**

**(114)** 60%

Scheme 24

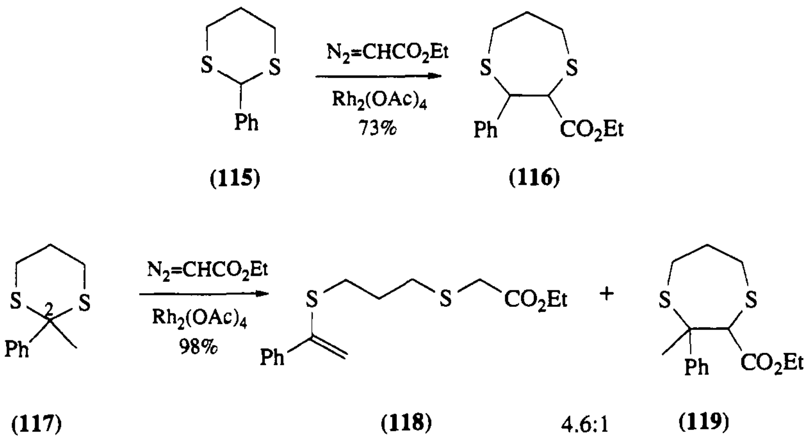
$N_2$=$CHCO_2Et$
$Rh_2(OAc)_4$
73%
$N_2$=$CHCO_2Et$
$Rh_2(OAc)_4$
98%
4.6:1

**(115)** **(116)**

**(117)** **(118)** **(119)**

Scheme 25

ployed (Scheme 26, equation a). A competing side reaction, cyclopropanation, is dependent upon the nature of the halogen atom (X) and it can be totally suppressed when X is iodide (Scheme 26, equation b).

Stevens rearrangements are not limited only to heteroatom to carbon migrations; heteroatom to heteroatom shifts are also observed frequently. Two such examples are given in Scheme 27.[46,47] In this case

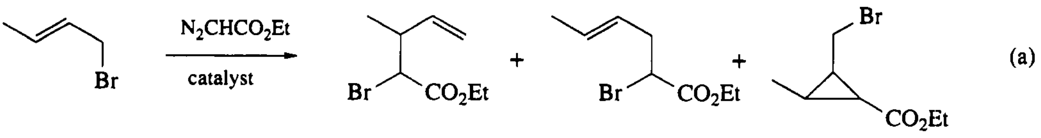

**(120)** **(121)** **(122)** **(123)**

| *Catalyst* | *(121)* | *(122)* | *(123)* | *Yield (%)* |
|---|---|---|---|---|
| $Rh_2(OAc)_4$ | 76 | 0 | 24 | 82 |
| $CuCl{\bullet}P(OPr^i)_3$ | 32 | 53 | 6 | 68 |

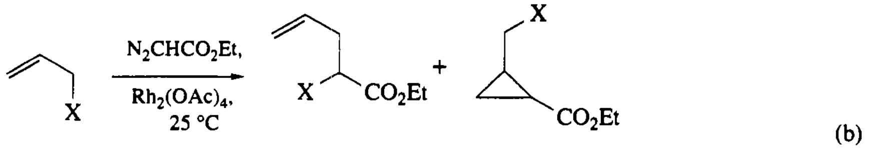

**(124)** **(125)** **(126)**

| *X* | *(125)* | *(126)* | *Yield (%)* |
|---|---|---|---|
| I | 100 | 0 | 98 |
| Br | 28 | 72 | 76 |
| Cl | 5 | 95 | 95 |

**Scheme 26**

too, the 1,2- and 3,2-rearrangements are competing but their relative importance has been shown to be substituent dependent.

Despite extensive mechanistic investigations, the Stevens 1,2-rearrangement has found only a few applications in synthesis. Standing out, however, as a landmark in this area is the beautiful work of Boekelheide, who utilized the 1,2-rearrangement of sulfur-containing macrocycles in an elegant and general approach towards cyclophanes (Scheme 28).[48] This brilliantly conceived strategy has been applied in numerous cases and two recent examples are shown in Scheme 29.[49,50]

### 3.10.4.2 Transfer of Chirality

If the 1,2-rearrangement is a concerted process, then it is a disfavored one. As a consequence, there has been considerable interest in determining the stereochemistry of the migrating group. If the reaction proceeds *via* a suprafacial–antarafacial mode, inversion of configuration at the migrating center should result. In fact, a high degree of retention of configuration was observed by Kenyon[6] and Brewster[51] as early as 1952 (Scheme 30, equation a). Schollkopf[52] and Stevens[53] reinvestigated the reaction and found it to proceed with at least 95% *ee*. The same conclusion was reached by Lown several years later using optically active benzylamine (Scheme 30, equation b).[54] In 1962, Jenny and Bruey showed that retention of configuration was also very high for the analogous allylic system (Scheme 30, equation c).[55] Mislow reported the fascinating case where total transmission of configuration, from a center of chirality involving a nitrogen atom into a center of chirality involving a carbon atom, took place (Scheme 31).[56]

When the optically active diazepinium salt (**151**) was treated with phenyllithium, only the (*S*)-amine (**152**) was obtained. However, the (*S*)-amine (**152**) consists of an equilibrating mixture of (+) and (–) diastereomeric amines which interconvert by mutarotation upon heating. Similarly, Brewster demonstrated that the pure (*R*)-isomer of the spiro ammonium salt (**153**) was transformed into the alkaloid (**155**) having an (*S*) absolute configuration (Scheme 32).[57]

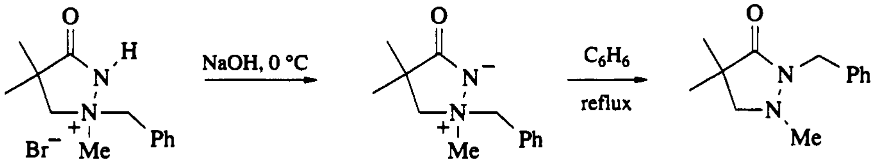
NaOH, 0 °C
$C_6H_6$
reflux

**(127)** **(128)** **(129)**

(ref. 46)

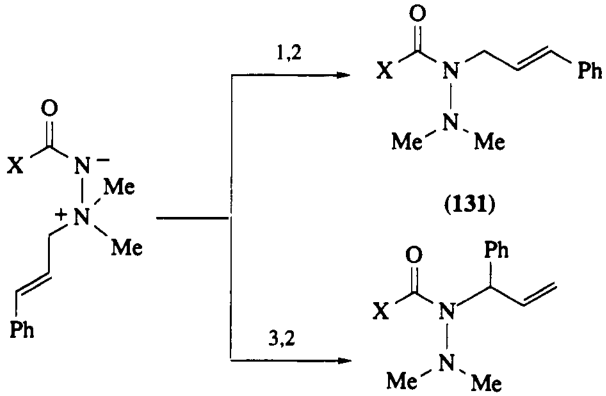

**(130)** **(131)** **(132)**

(ref. 47)

| *X* | (*131*) | (*132*) |
|---|---|---|
| Ph | 88 | 12 |
| OEt | 45 | 55 |
| NHMe | 40 | 60 |

**Scheme 27**

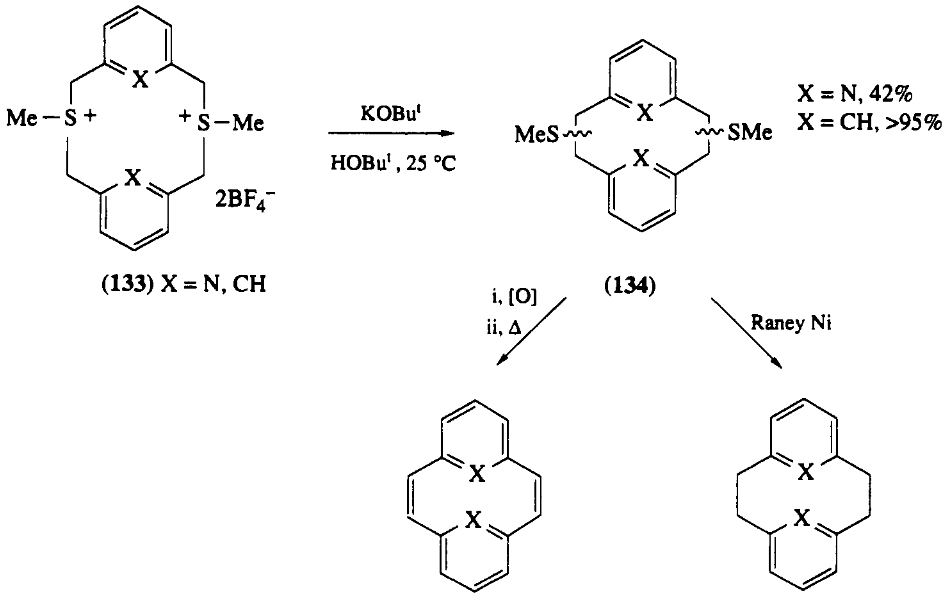
KOBu$^t$
HOBu$^t$, 25 °C
i, [O]
ii, Δ
Raney Ni

X = N, 42%
X = CH, >95%

**(133)** X = N, CH

**(134)**

**(135)** **(136)**

**Scheme 28**

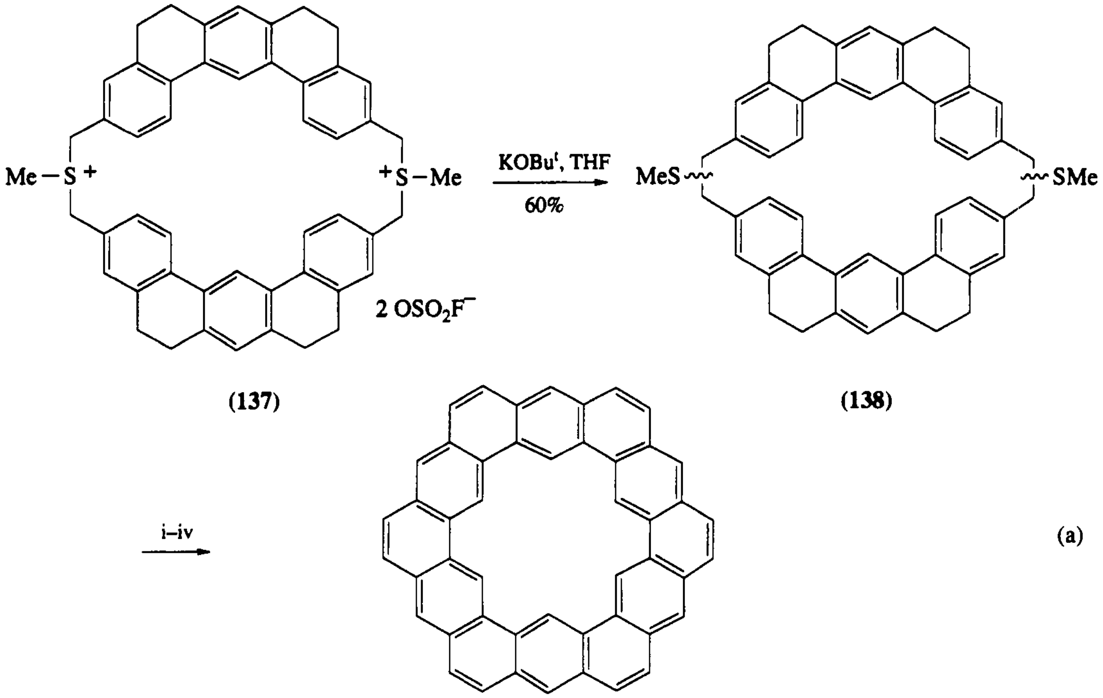
Me−S+
+S−Me
2 OSO₂F⁻
KOBu^t, THF
60%
MeS
SMe
(137)
(138)
i–iv
(a)

(139) Kekulene i, $MeOSO_2F$; ii, $KOBu^t$; iii, *h*ν; iv, DDQ

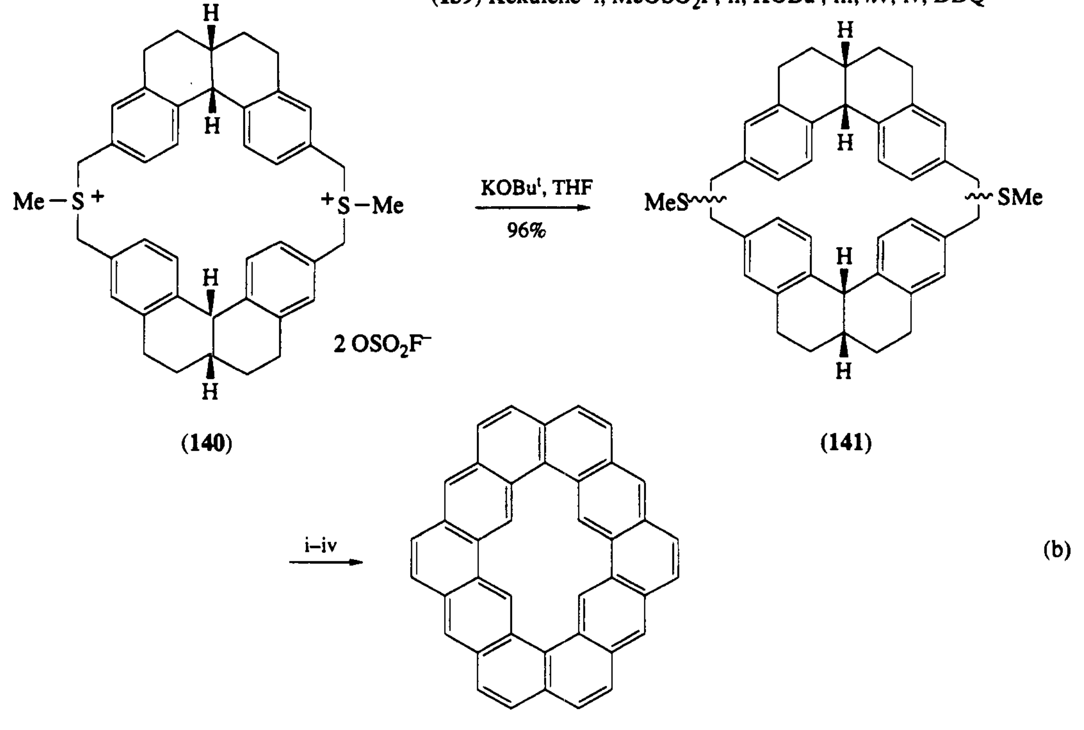
H
H
H
H
Me−S+
+S−Me
2 OSO₂F⁻
KOBu^t, THF
96%
MeS
SMe
(140)
(141)
i–iv
(b)

(142) i, MCPBA, $CH_2Cl_2$; ii, 170 °C; iii, *h*ν; iv, DDQ

**Scheme 29**

Chan and Hill have studied the transmission of configuration in ammonium salts where the only chiral center is the quaternary nitrogen atom.[58] The Stevens rearrangement proceeded in poor yield; a competing 1,4-rearrangement product being surprisingly formed as the major product, and gave the amine (**157**) with 58% *ee* (Scheme 33).

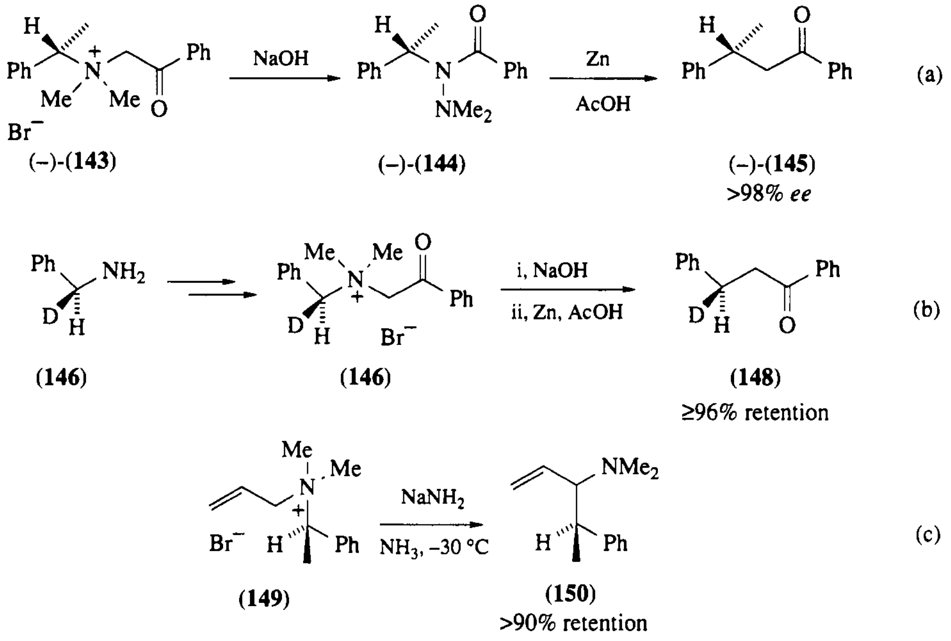
NaOH
Zn
AcOH
(a)
(−)-(143)
(−)-(144)
(−)-(145)
>98% ee
i, NaOH
ii, Zn, AcOH
(b)
(146)
(146)
(148)
≥96% retention
NaNH2
NH3, −30 °C
(c)
(149)
(150)
>90% retention

Scheme 30

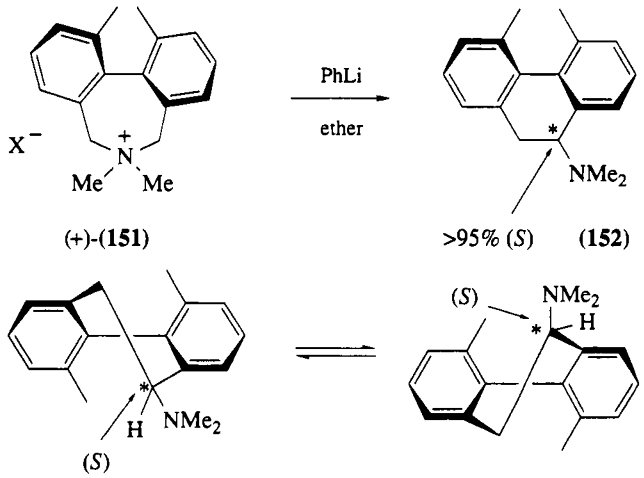
PhLi
ether
(+)-(151)
>95% (S) (152)
(S)
(S)

Scheme 31

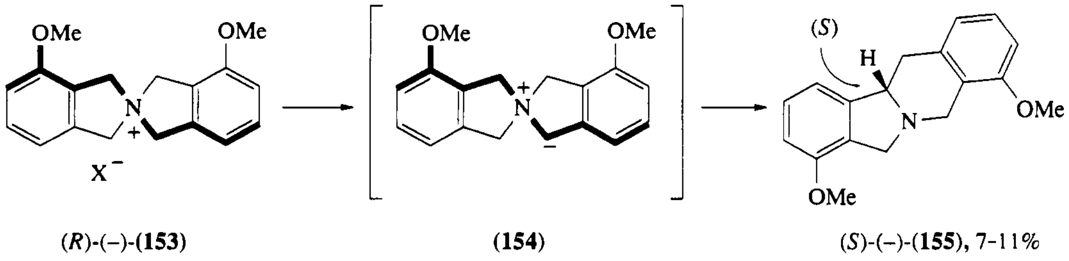
(R)-(−)-(153)
(154)
(S)-(−)-(155), 7-11%

Scheme 32

Ollis and coworkers reinvestigated the stereochemical outcome of the Stevens rearrangement and provided a detailed understanding of the mechanism of this reaction.[10,59] Rearrangement of the optically pure ammonium salt (**143**) gave three products, (**144**), (**159**) and (**160**) in a ratio of 80:11:5 (Scheme 34). The amine (**144**) was optically active and degradation studies proved that migration occurred with more than 95% retention of the stereochemistry at the terminus of the migrating group. The diamine (**159**) (and similarly the alkane **160**) was a mixture of the racemate and the meso compound. Clearly, these products (**159**) and (**160**) arose from coupling of radicals which have escaped from the solvent cage. A few related examples are represented in Table 2.[10]

In all the cases discussed so far, retention of configuration at the terminus of the migrating group has been observed. The degree of retention was influenced strongly by the nature of the substituents present on the migrating group (Table 2, entries 1–3). It is also worth noting that the extent of retention of configuration in the case of sulfonium ylides (entry 4) is substantially lower than in the case of the ammonium analog. Comparison between entry 1 and entry 5 demonstrates how the nature of the substituent influences the enantiomeric excess. All these results can be explained by the mechanism, involving diastereomeric radical pairs, proposed by Ollis for the Stevens rearrangement and summarized in Scheme

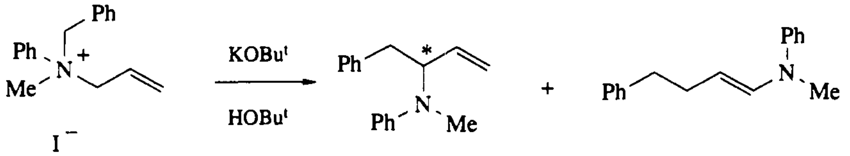

(+)- (**156**) (*S*)-(–)-(**157**) 15% yield, 58% *ee* (**158**) 35% yield

**Scheme 33**

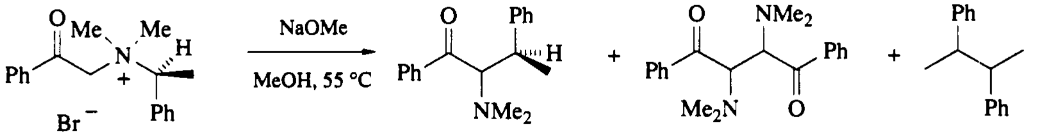

(*R*)-(+)-(**143**) (**144**) 80% yield, >95% *ee* (**159**) 11% (**160**) 5%

**Scheme 34**

**Table 2**

| *Entry* | *Reactant* | *Product* | *ee (%)* |
|---|---|---|---|
| | 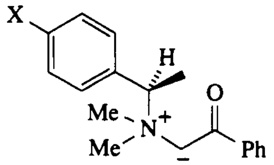 | 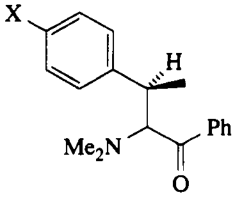 | |
| 1 | X = H | | >95 |
| 2 | X = OMe | | 87 |
| 3 | X = $NO_2$ | | 66 |
| 4 | 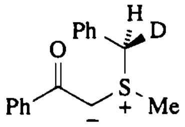 | 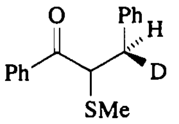 | 36 |
| 5 | 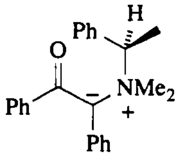 | 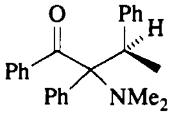 | 32 |

35.[60] Homolytic fission of the chiral ammonium ylide (**143**) generates two diastereomeric radical pairs which evolve by two different routes: (a) cage recombination leads to the two diastereomeric ketoamines (**161**) and (**162**), where the migrating center has retained its absolute stereochemistry; (b) radical escape gives achiral free radicals that combine to yield racemic products (Scheme 35).

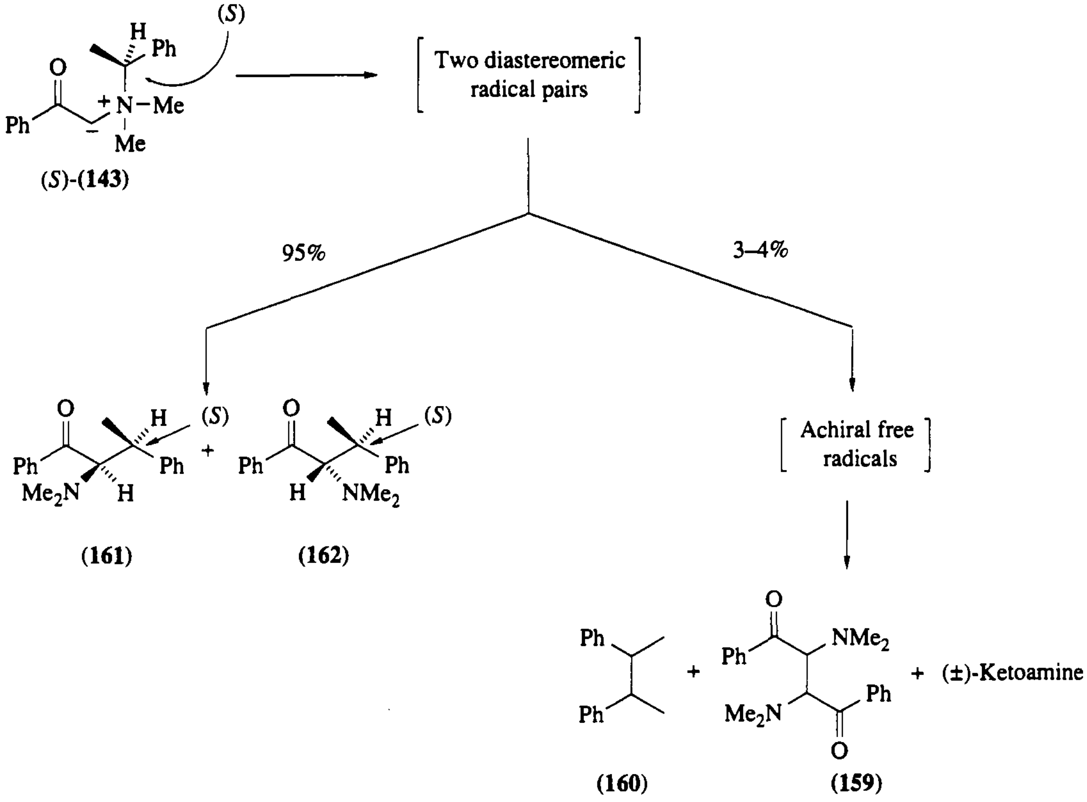

Scheme 35

The radical pair recombination is a very fast process. This explains the high intramolecularity of the Stevens 1,2-rearrangement as well as the high stereoselectivity observed. Retention of configuration is ensured by the absence of rotation of the radicals in the solvent cage. The formation of the two diastereoisomeric amines (**161**) and (**162**) can be explained by the presence of an equilibrium mixture of conformational isomers of the starting ylide.[60] Indeed, the ylide (**143**) exists in the planar cisoid conformation **C**, which is in equilibrium with the two orthogonal conformational isomers **A** and **B**. These are the conformations from which migration will occur, since the $\sigma$-bond to be broken is parallel to the $\pi$-system of the enolate, ensuring maximum stabilization of the radicals as they are formed. Conformation **A** will lead to the radical pair (**163**), which eventually collapses to form the diastereoisomer (**162**). The same process involving co nformation **B** leads to the diastereoisomer (**161**; Scheme 36).

## 3.10.5 3,2-SIGMATROPIC REARRANGEMENTS

### 3.10.5.1 Introduction

In sharp contrast with the Stevens 1,2-rearrangement, the 3,2-sigmatropic rearrangement of ylidic intermediates has been used extensively in organic synthesis. These rearrangements, being concerted symmetry-allowed processes, show high regio-, diastereo- and enantio-selectivities. It is, therefore, not too surprising that they have become rapidly accepted synthetic tools, since Baldwin published his important papers on the generalization of sigmatropic rearrangements.[17]

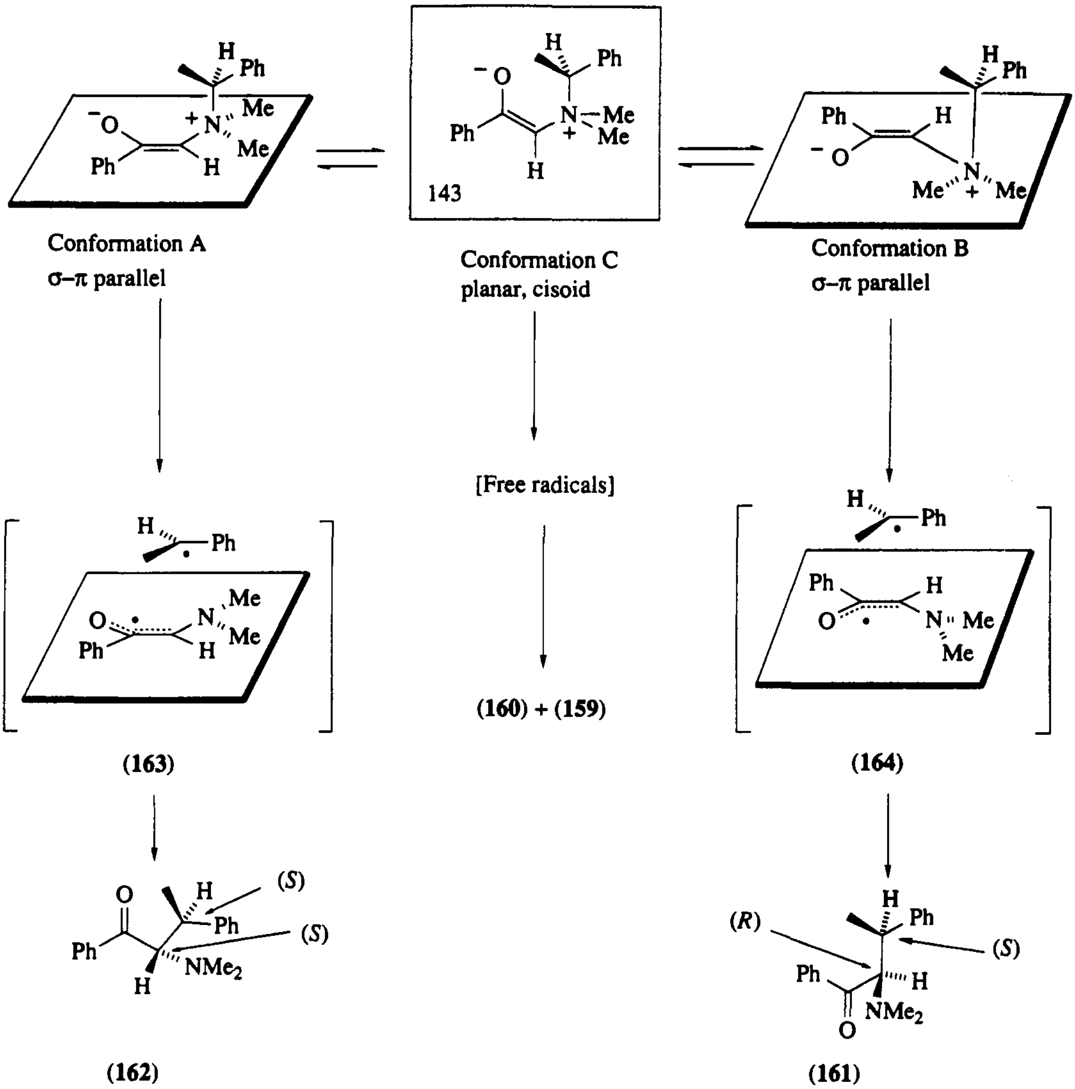
Conformation A
σ–π parallel
143
Conformation C
planar, cisoid
Conformation B
σ–π parallel
[Free radicals]
(160) + (159)
(163)
(164)
(*S*)
(*S*)
(*R*)
(*S*)
(162)
(161)

Scheme 36

### 3.10.5.2 Synthetic Applications in Alicyclic Systems

3,2-Rearrangements of ylidic intermediates proceed with allylic transposition. This useful property is the key feature of one of the best preparations of 1,5-dienes (Scheme 9). Trost has used this approach to synthesize yomogi alcohol (**165**) in a particularly simple way by *S*-alkylation of sulfide (**31**) and solvolysis of the resulting sulfonium ion (Scheme 37).[61]

One of the landmarks in the early use of the 3,2-rearrangement of sulfur ylides is the squalene synthesis reported by Ollis and already discussed in Section 3.10.4.[30] This approach used benzyne to generate the ylidic intermediate. Frequently, however, benzyne produces a mixture of products (Scheme 38).[62] The sulfide (**168**) may be formally regarded as the expected 3,2-sigmatropic rearrangement product, whereas (**169**) results from a competitive 1,4-rearrangement. Use of carbenes instead of benzyne gener-

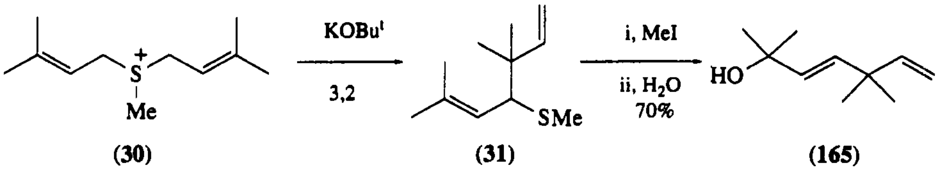
KOBu$^t$
3,2
i, MeI
ii, H$_2$O
70%
(30)
(31)
(165)

Scheme 37

ally gives higher yields of 3,2-rearrangement products. Ando has shown that crotyl phenyl sulfide (**170**) forms mainly the sulfide (**171**) when the carbene is generated using $CuSO_4$.[44,63] In contrast, the light-induced reaction affords the desired material in much lower yield (Scheme 39). Evans also used carbenes to generate sulfonium ylides of rigid systems in order to study the diastereoselectivity of the 3,2-rearrangement (Scheme 40).[31]

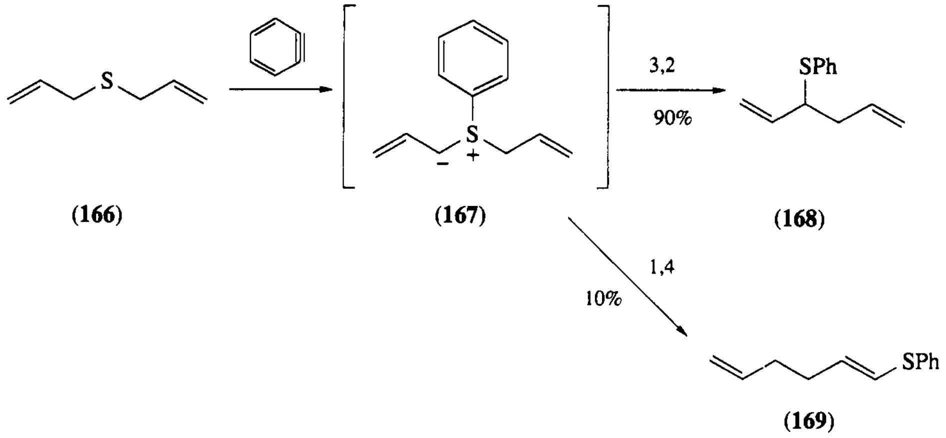

Scheme 38

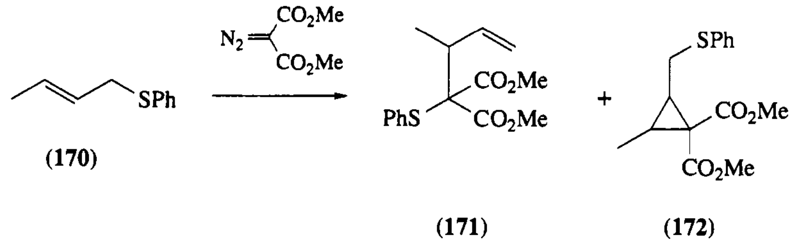

| | (171) | (172) |
|---|---|---|
| *hν* | 47% | 10% |
| $CuSO_4$ | 90% | – |

Scheme 39

John has investigated the $BF_3$–etherate and copper-catalyzed rearrangement of diazopenicillins in the presence of allylic sulfides and selenides.[64] The results are presented in Scheme 41. The reaction is believed to involve the initial formation of ylide (**177**) followed by a 3,2-sigmatropic rearrangement. Support for this mechanism came from utilization of substituted allylic sulfides which were shown to rearrange with net allylic transposition, a result expected on the basis of orbital symmetry considerations (Scheme 42). A similar rearrangement involving nitrogen ylides has been reported by Baldwin (Scheme 43).[65]

Doyle has shown that the rhodium-catalyzed reaction of allylic sulfides and amines with ethyl diazoacetate produced smoothly the products of 3,2-rearrangement.[34] In contrast with the copper-catalyzed reaction, allylic amines can be used and the yields are good to high (Scheme 44); virtually no cyclopropanation is observed. These observations demonstrate the superiority of rhodium catalysts compared with either copper ones or the use of light.

Vedejs has also discussed the inefficiency of copper catalysts in ylidic 3,2-sigmatropic processes.[66] Optimization of ring expansion reactions using diazomalonates were found to be unsatisfactory and analogous reactions using diazoketones were totally unsuccessful. Takano has taken advantage of a rhodium-promoted ylide formation followed by a 3,2-rearrangement, in a useful synthesis of γ,δ-unsaturated carbonyl compounds (Scheme 45).[67]

Julia, in a very elegant approach, has used sulfur ylidic 3,2-rearrangements to produce β,γ-unsaturated aldehydes (Scheme 46).[68] Following the same idea, Kociensky also used ylidic 3,2-sigmatropic rearrangements to prepare β,γ-unsaturated aldehydes; he employed sulfur ylides in conjunction with silicon substituents (Scheme 47).[69] In contrast, Mander used the nitrogen ylidic 3,2-rearrangement as an easy route towards the synthesis of β,γ-unsaturated aldehydes (Scheme 48).[70] It is noteworthy that better

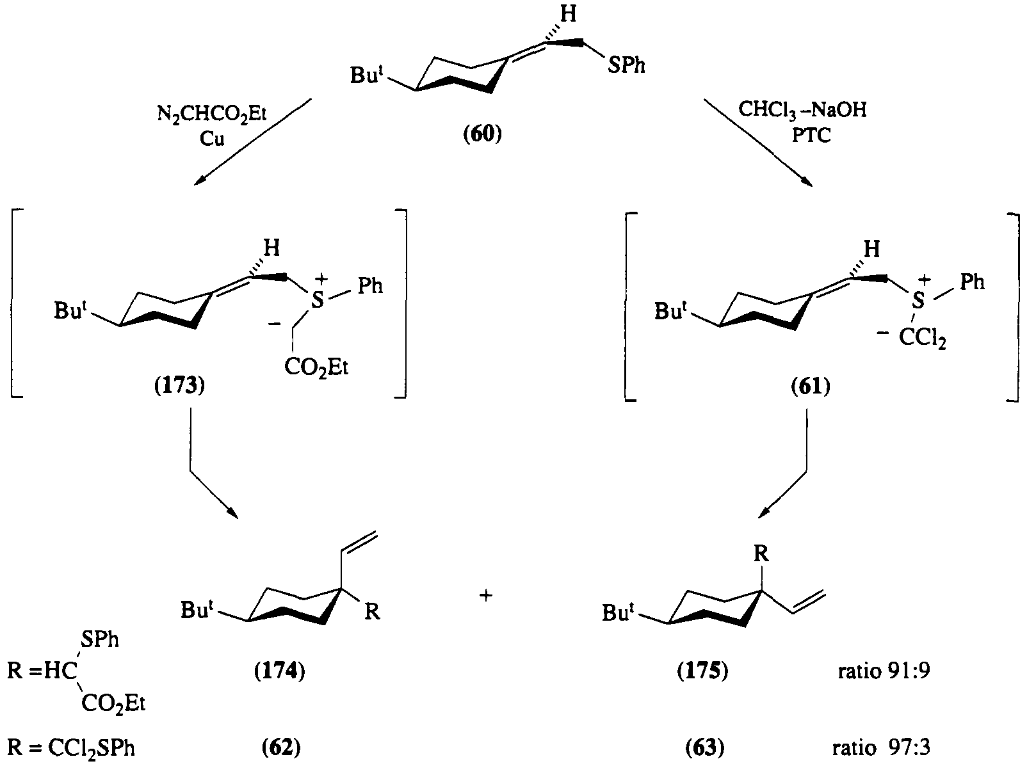
(60)
N$_2$CHCO$_2$Et
Cu
CHCl$_3$-NaOH
PTC
(173)
(61)
(174)
(175)
R =HC(SPh)CO$_2$Et
R = CCl$_2$SPh
(62)
(63)
ratio 91:9
ratio 97:3

Scheme 40

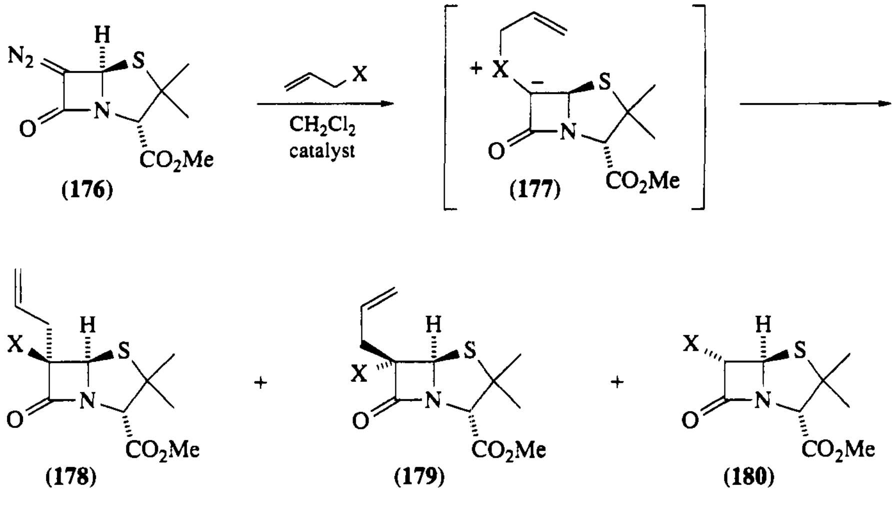
(176)
CH$_2$Cl$_2$
catalyst
(177)
(178)
(179)
(180)

| Entry | X | Catalyst | (178)+(179) (%) | (178):(179) | (180) (%) |
|---|---|---|---|---|---|
| 1 | PhS | $BF_3{\bullet}Et_2O$ | 47 | 56:44 | 5 |
| 2 | MeS | $BF_3{\bullet}Et_2O$ | 49 | 80:20 | 16 |
| 3 | PhSe | $BF_3{\bullet}Et_2O$ | 48 | 66:34 | 15 |
| 4 | PhS | $Cu(acac)_2$ | 65 | 87:13 | 0 |
| 5 | MeS | $Cu(acac)_2$ | 60 | 80:20 | 0 |
| 6 | PhSe | $Cu(acac)_2$ | 64 | 50:50 | 0 |

Scheme 41

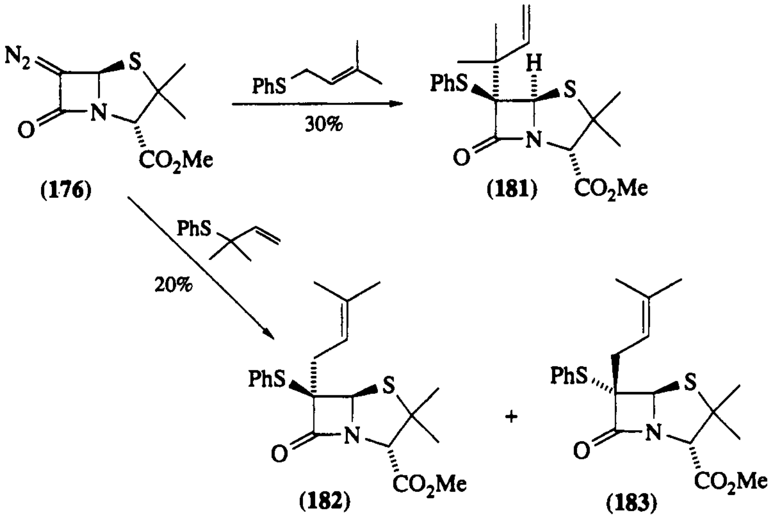

**(176)** **(181)** **(182)** **(183)**

**(182)**:**(183)** = 3:2

**Scheme 42**

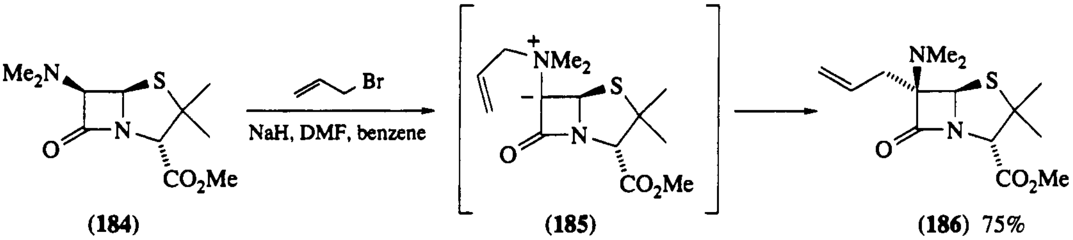

**(184)** **(185)** **(186)** 75%

**Scheme 43**

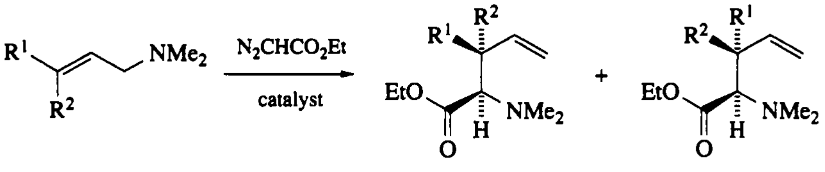

**(187)** **(188)** **(189)**

| *R*$^1$ | *R*$^2$ | *Catalyst* | *Yield (%)* | *(188):(189)* |
|---|---|---|---|---|
| H | H | $Rh_2(OAc)_4$ | 82 | - |
| Me | Me | $Rh_6(CO)_{16}$ | 49 | - |
| Me | H | $Rh_2(OAc)_4$ | 79 | 75:25 |
| Ph | H | $Rh_2(OAc)_4$ | 78 | 72:28 |

**Scheme 44**

overall yields are obtained using ammonium rather than sulfonium ylides. Following the same theme, Lythgoe has used 1,3-dithiane as the masked aldehydic equivalent.[71] *S*-Alkylation of dithiane using allylic halides followed by a sulfur ylidic 3,2-rearrangement gave the homoallylic dithiane (**209**), which was hydrolyzed smoothly to the β,γ-unsaturated aldehyde (**199**; Scheme 49).

Büchi has used Mander's approach as a key step in his synthesis of α-sinensal (**212**; Scheme 50),[72] and Corey has applied the ylidic 3,2-rearrangement to the efficient preparation of 3-cyclopentenones.[73] Thus, base treatment of the sulfonium salt (**213**) first gave the rearranged product (**215**). Thermal vinylcyclopropane ring expansion then produced the spiro compound (**216**). Deprotection finally gave the nonconjugated cyclopentenone (**217**; Scheme 51).

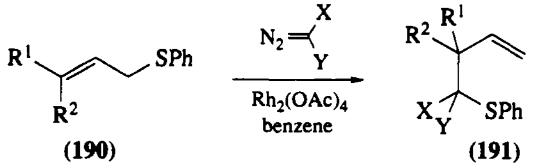

| *Entry* | *R¹* | *R²* | *X* | *Y* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Me | Me | $CO_2Et$ | $CO_2Et$ | 84.3 |
| 2 | Me | Me | 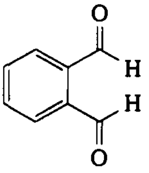 |  | 62.8 |
| 3 | Me | Me | $CO_2Et$ | $O{=}P(OEt)_2$ | 81.1 |
| 4 | $CH_2OBn$ | H | $CO_2Et$ | $CO_2Et$ | 83.4 |
| 5 | $CH_2OBn$ | H | 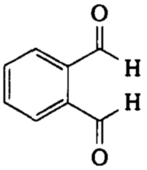 |  | 61.1 |
| 6 | $CH_2OBn$ | H | $CO_2Et$ | $O{=}P(OEt)_2$ | 100 |
| 7 | 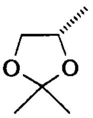 | H | $CO_2Et$ | $CO_2Et$ | 63 |
| 8 | 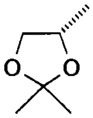 | H | 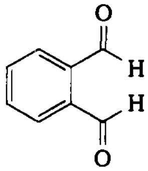 |  | 82.7 |
| 9 | 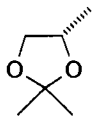 | H | $CO_2Et$ | $O{=}P(OEt)_2$ | 80.3 |

**Scheme 45**

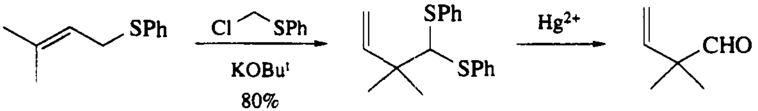

(190) (192) (193)

**Scheme 46**

Cohen has used a soluble version of the Simmons–Smith reagent to promote the 3,2-rearrangement of allylic sulfides (Scheme 52).[74] He has also applied this methodology to the synthesis of sarkomycin (**225**).[75] The allylic sulfide (**221**), easily available *via* a Petrow reaction, was first alkylated and the sulfonium ylide was then generated by a fluoride-promoted desilylation. Rearrangement of the ylide (**223**) gave the homoallylic sulfide (**224**) which was eventually transformed into sarkomycin (Scheme 53).

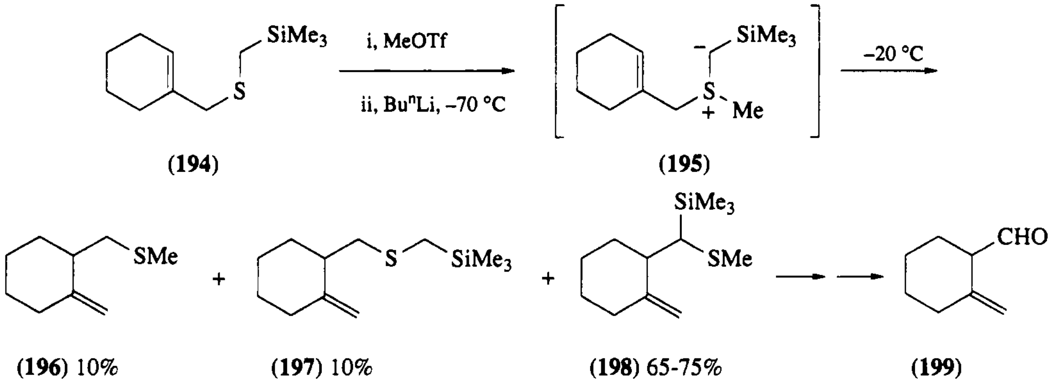
SiMe3
S
i, MeOTf
ii, BunLi, -70 °C
SiMe3
S
Me
-20 °C
(194)
(195)
SMe
S
SiMe3
SiMe3
SMe
CHO
(196) 10%
(197) 10%
(198) 65-75%
(199)

Scheme 47

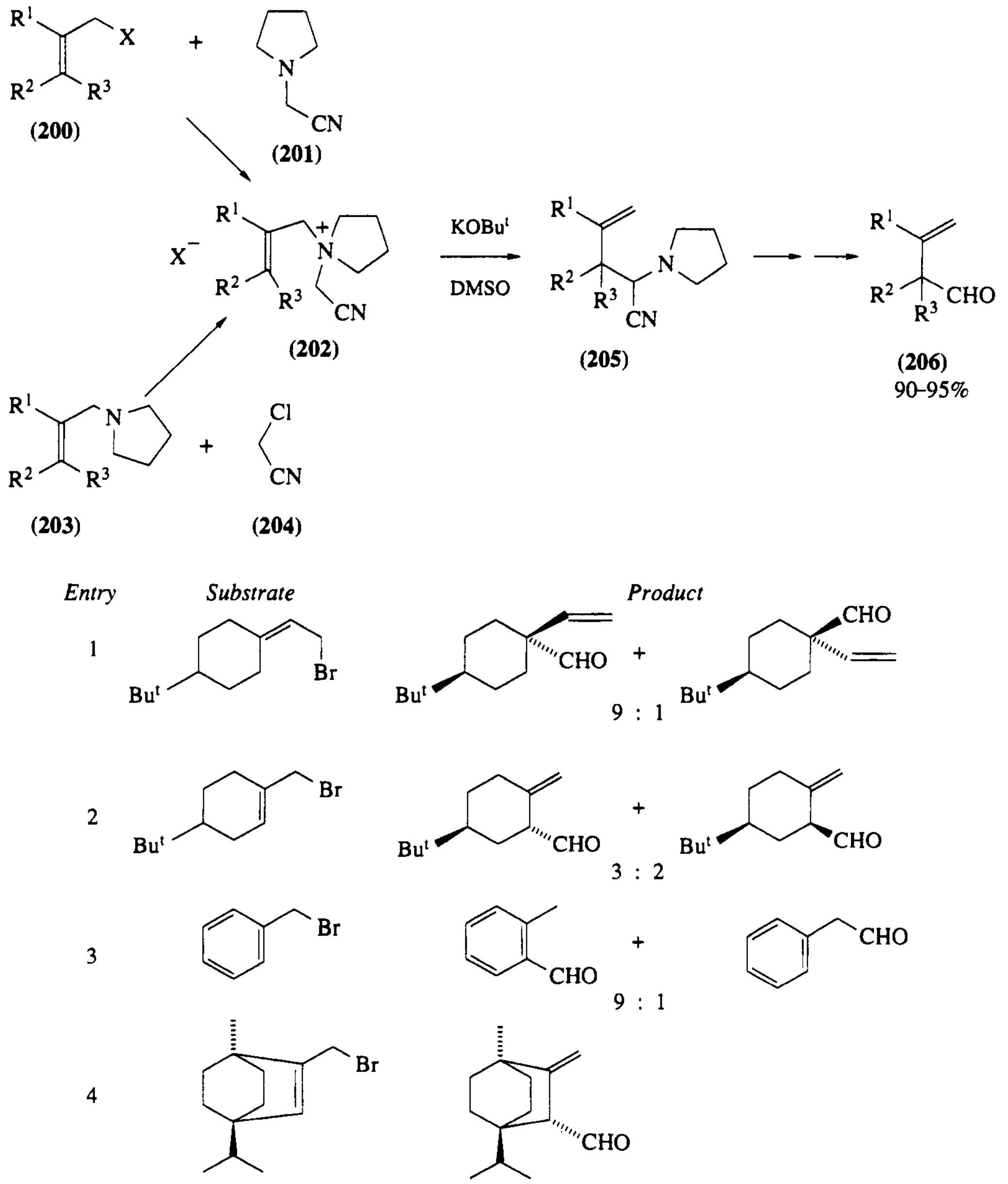
R1
X
R2
R3
(200)
N
CN
(201)
X−
N
CN
(202)
KOBut
DMSO
N
CN
(205)
CHO
(206)
90-95%
Cl
CN
(203)
(204)
Entry
Substrate
Product
1
Br
But
CHO
CHO
9 : 1
2
Br
CHO
CHO
3 : 2
3
Br
CHO
CHO
9 : 1
4
Br
CHO

Scheme 48

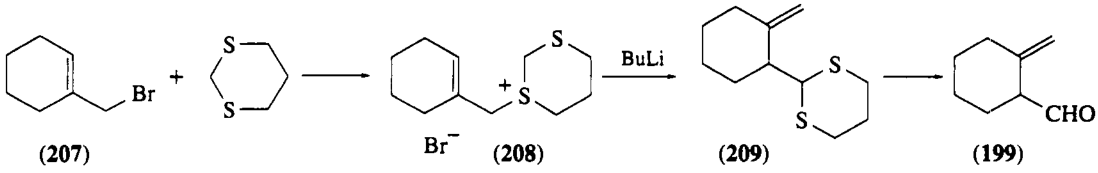

Scheme 49

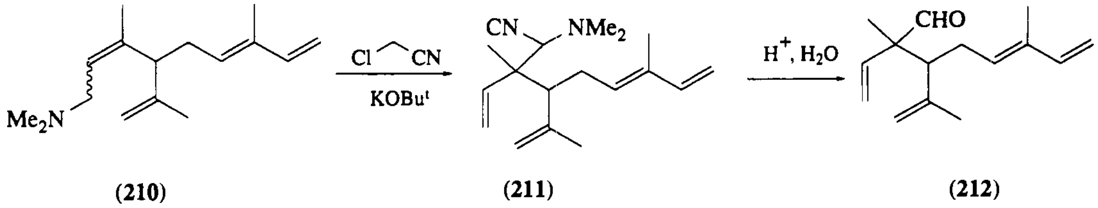

Scheme 50

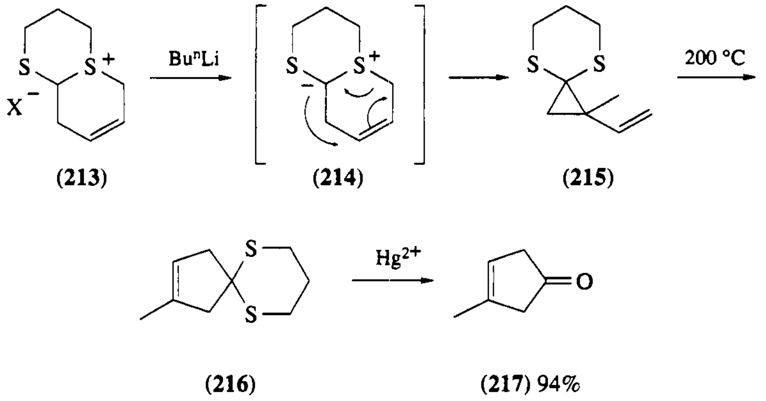

Scheme 51

The formation and 3,2-sigmatropic rearrangement of sulfonium and ammonium ylides, generated by fluoride-promoted desilylation, has also been actively investigated by Vedejs. He showed that ylides, produced under kinetic control, could be prepared using this technique and rearranged by a 3,2-sigmatropic process. This rearrangement can take place before equilibration to the thermodynamically more stable ylide occurs (Scheme 13). In yet another version, Zbiral has used silyl-stabilized ylides to produce homoallylic sulfides.[76] An initial Peterson reaction between the ylide (**227**) and a carbonyl compound (**228**) is followed by a deprotonation to generate another ylide (**229**). Equilibration of the thermodynamically more stable ylide (**229**) gives a small amount of the isomer (**230**), which undergoes rapid 3,2-sigmatropic rearrangement, leading to the observed reaction product (Scheme 54).

Ratts and Yao reported a particularly interesting preparation of enol ethers by a 3,2-sigmatropic transposition in which the carbonyl function of stabilized ylides participates in the rearrangement (Scheme 55).[39] The same starting sulfonium ylide is well known to give Stevens rearrangement products. The competition between the 1,2- and 3,2-pathways is strongly dependent on the reaction conditions and good yields of either product can be obtained by carefully selecting the base concentration (Scheme 56).

During his generalization of 3,2-sigmatropic rearrangements, Baldwin observed the interesting transformation depicted in Scheme 57.[77] Base treatment of the tosylhydrazone (**236**) generates, after loss of nitrogen, the carbene (**237**), which rearranges to the dithioester *via* a 3,2-sigmatropic transposition. A most elegant application of this reaction has been reported by Evans in his bakkenolide synthesis (Scheme 58).[78] Thus, base-promoted rearrangement of the tosylhydrazone (**239**) occurred from the less hindered face of the hydrindane system and gave stereospecifically the dithioester (**241**), which was subsequently transformed into bakkenolide (**242**).

Sulfoxonium ylides also undergo 3,2-sigmatropic rearrangements.[79] A useful preparation of conjugated dienes is based on a 3,2-rearrangement followed by spontaneous elimination of methanesulfenic acid (Scheme 59, equation a). In some cases, the reaction proceeds without isolation of the intermediate ylide (Scheme 59, equation b).

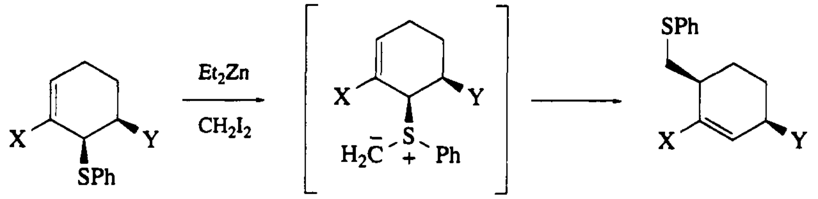
$Et_2Zn$
$CH_2I_2$
X
Y
SPh
$H_2\bar{C}$
S
+
Ph

**(218)** **(219)** **(220)**

| *Entry* | *Substrate* | *Reagent* | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 1 | 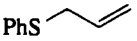 | $Et_2Zn\text{-}CH_2I_2$ | 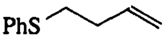 | 55 |
| 2 | 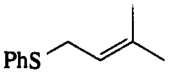 | $Et_2Zn\text{-}CH_2I_2$ | 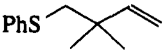 | 80 |
| 3 | 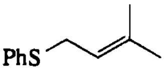 | $Et_2Zn\text{-}EtCHI_2$ | 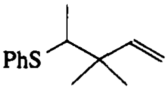 | 70 |
| 4 | 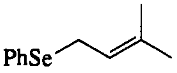 | $Et_2Zn\text{-}CH_2I_2$ | 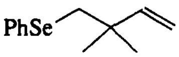 | 75 |
| 5 | 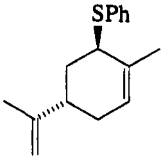 | $Et_2Zn\text{-}CH_2I_2$ | 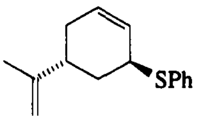 | 78 |
| 6 | 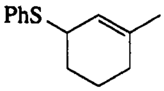 | $Et_2Zn\text{-}CH_2I_2$ | 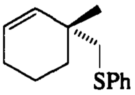 | 72 |

**Scheme 52**

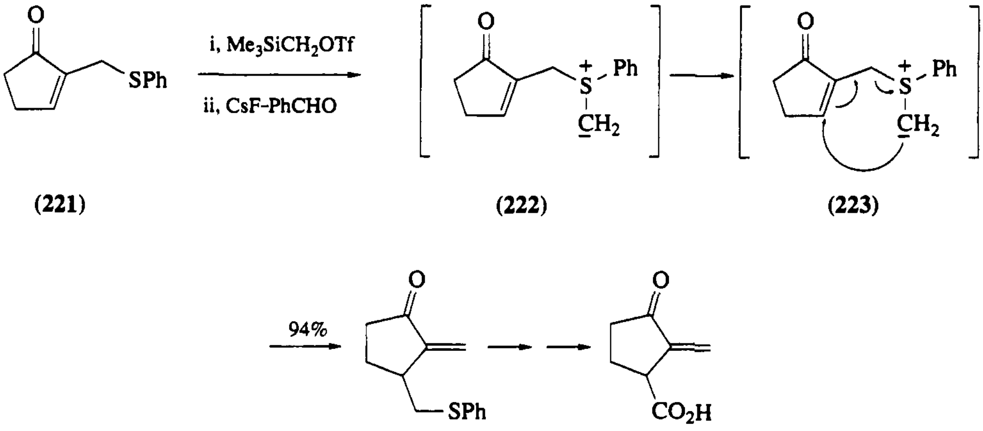
O
SPh
i, $Me_3SiCH_2OTf$
ii, CsF-PhCHO
+
S
Ph
$\underline{C}H_2$
94%
SPh
$CO_2H$

**(221)** **(222)** **(223)**

**(224)** **(225)**

**Scheme 53**

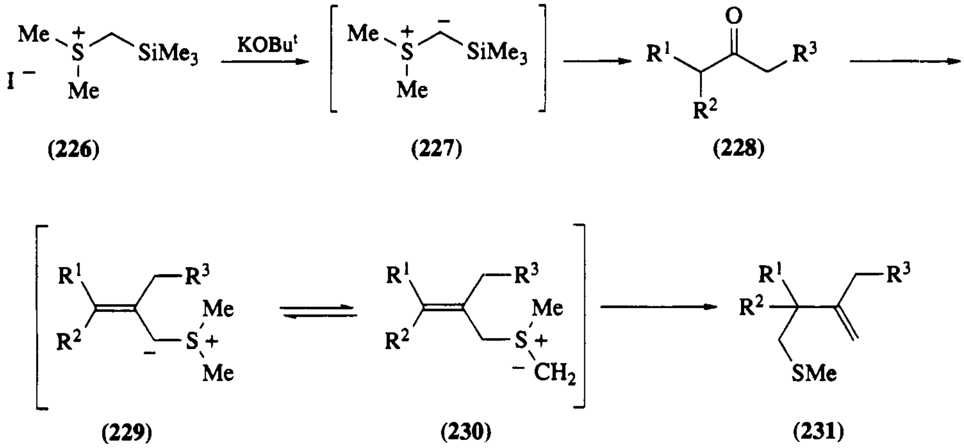
KOBu^t
(226)
(227)
(228)
(229)
(230)
(231)

| *Entry* | *R¹* | *R²* | *R³* | *Yield (%)* |
|---|---|---|---|---|
| 1 | Me | H | H | 49 |
| 2 | Pr$^i$ | H | H | 60 |
| 3 | Me | Me | H | 20 |
| 4 | H | –(CH$_2$)$_2$– | | 20 |
| 5 | H | –(CH$_2$)$_3$– | | ~20 |

**Scheme 54**

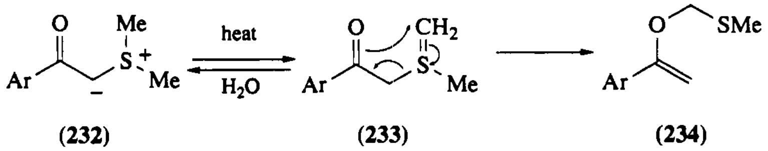
heat
H₂O
(232)
(233)
(234)

| *Entry* | *Ar* | *Yield (%)* |
|---|---|---|
| 1 | Ph | 66 |
| 2 | 4-BrC$_6$H$_4$ | 50 |
| 3 | 4-ClC$_6$H$_4$ | 64 |
| 4 | 2-Naphthyl | 57 |

**Scheme 55**

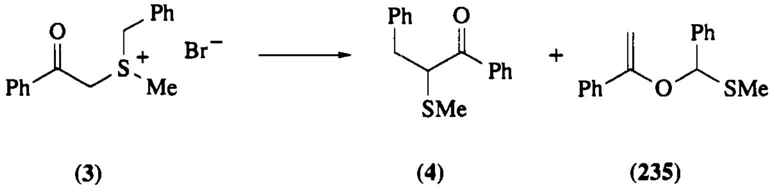

| | (4) | (235) |
|---|---|---|
| 5% Na, MeOH, 60 °C : | 3% | 78% |
| 10% Na, MeOH, 60 °C : | 48% | 32% |
| 15% Na, MeOH, 60 °C : | 69% | trace |

**Scheme 56**

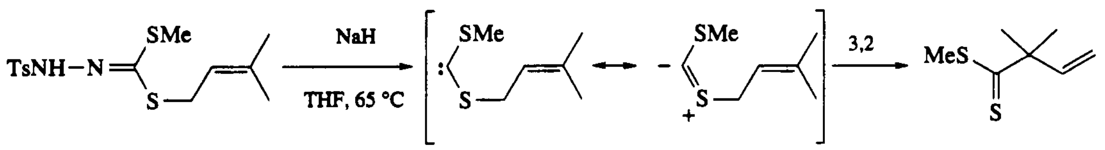
SMe
TsNH–N
S
NaH
THF, 65 °C
SMe
S
SMe
S
+
3,2
MeS
S

**(236)** **(237)** **(237)** **(238)**

Scheme 57

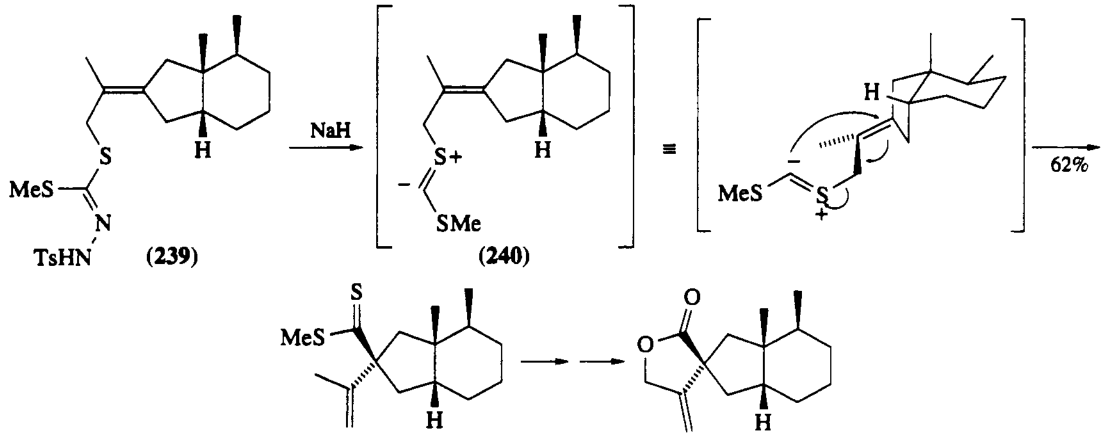
NaH
H
S
MeS
N
TsHN
S+
SMe
H
≡
H
MeS
S
+
62%
S
MeS
H
O
O
H

**(239)** **(240)** **(241)** **(242)**

Scheme 58

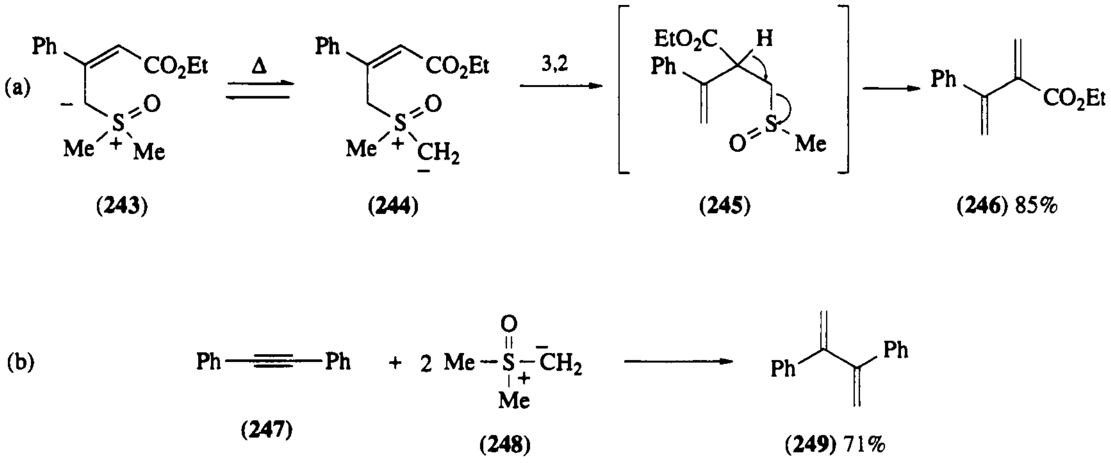
(a)
Ph
CO2Et
S
O
Me
+
Me
Δ
Ph
CO2Et
S
O
Me
+
CH2
3,2
EtO2C
H
Ph
O
S
Me
Ph
CO2Et
(b)
Ph
Ph
+ 2 Me–S–CH2
O
+
Me
Ph
Ph

**(243)** **(244)** **(245)** **(246)** 85%

**(247)** **(248)** **(249)** 71%

Scheme 59

Despite the pioneering work of Ando and Doyle, few synthetic applications of oxonium ylidic rearrangements have been reported. However, three examples of synthetic relevance appeared recently (Schemes 60 to 62). When α-allyloxyacetic esters are reacted with trimethylsilyl triflate and a base, the transposed material (**252**), resulting from a 3,2-sigmatropic rearrangement of the transient ylide (**251**), could be isolated in good yields.[80] The same product ratio was also obtained upon treatment of the ketene acetal (**253**) with trimethylsilyl triflate. This second variant involves the direct formation of ylide (**251**) followed by its transformation into (**252**; Scheme 60).

Almost at the same time, Pirrung[81a] and Johnson[81b] independently described the rearrangement of oxonium ylides prepared by intramolecular rhodium-catalyzed carbene addition. The reaction appears to have a broad scope and gives an easy entry into complex oxygenated polycycles (Scheme 61). When the possibility arises, high levels of diastereocontrol are exercised (Scheme 62).

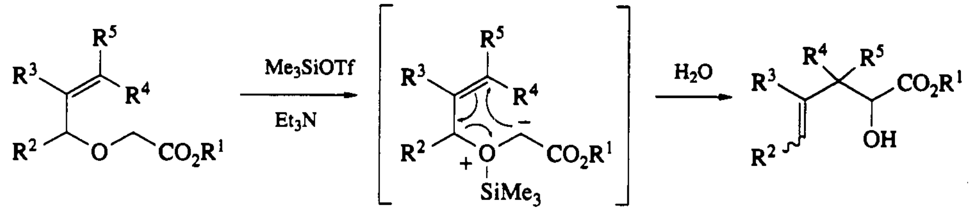

**(250)** **(251)** **(252)**

| *Entry* | *R1* | *R2* | *R3* | *R4* | *R5* | *(E)* | *(Z)* | *Syn:anti* | *Yield (%)* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | Me | H | H | H | 31 | 69 | | 93 |
| 2 | Me | Me | Me | H | H | 31 | 69 | – | 98 |
| 3 | Me | H | H | H | Me | – | – | 92:8 | 83 |
| 4 | Me | H | H | Me | H | – | – | 53:47 | 86 |
| 5 | H | Me | H | H | H | 43 | 57 | | 85 |
| 6 | H | H | H | H | Me | – | – | 88:12 | 92 |
| 7 | Pr$^i$ | H | H | H | Me | – | – | 95:5 | 86 |
| 8 | Bu$^t$ | H | H | H | Me | – | – | 88:12 | 56 |

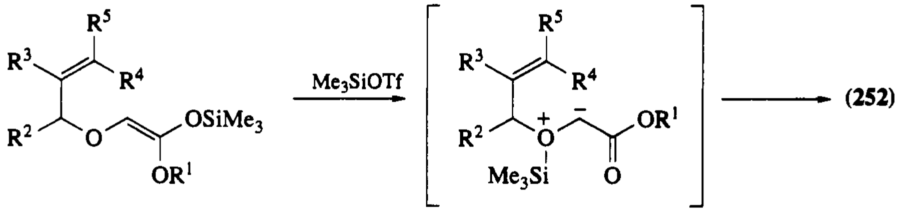

**(253)** **(251)**

**Scheme 60**

### 3.10.5.3 Configuration of the Newly Formed Double Bond

The 3,2-sigmatropic rearrangement of ylides proceeds in general with high stereocontrol at the newly formed carbon–carbon double bond. In the synthesis of squalene by Ollis for example, the sulfur ylide (**57**) rearranged into the sulfide (**58**) with a *trans* (*E*) double bond (Scheme 14). Grieco has also shown that rearrangement of the sulfide (**262**) gave a 9:1 ratio of (*E*)- to (*Z*)-alkenes (Scheme 63, equation a).[82] Hill demonstrated that ammonium ylide rearrangements proceed with >95% (*E*)-stereoselectivity (Scheme 63, equation b),[83] and Julia found that the sulfur ylide (**267**) gave the sulfide (**268**) as the pure (*E*)-isomer (Scheme 63, equation c).[84]

By analogy with the chair conformation invoked for the transition state of the 3,3-rearrangement, the transition state geometry of the 3,2-sigmatropic rearrangement could be analyzed in terms of the 'folded envelope', or puckered, conformation of cyclopentane.[85] This well-defined conformation should result in a high degree of stereocontrol of the alkene geometry and a high level of stereospecificity in the generation of chiral centers. In the absence of particular effects, examination of these puckered conformations for the transition states of the 3,2-sigmatropic rearrangement suggests that a substituent located on carbon C-1′ of the ylide (**269-T**, Scheme 64) would prefer to be pseudo-equatorial. This should lead preferentially to the formation of (*E*)-alkenes (Scheme 64).

Model studies have been carried out in order to compare the stereospecificity of different types of 3,2-rearrangements (Scheme 65). From these results, it appears that, in the absence of any special effect, the 3,2-ylidic rearrangement is (*E*)-selective. The Wittig rearrangement shows a greater tendency for (*Z*)-stereochemistry.[89] However, the energy difference between the cisoid (**270-C**) and transoid (**270-T**) transition states in a 3,2-sigmatropic rearrangement (Scheme 64) is not very large. These rearrangements will

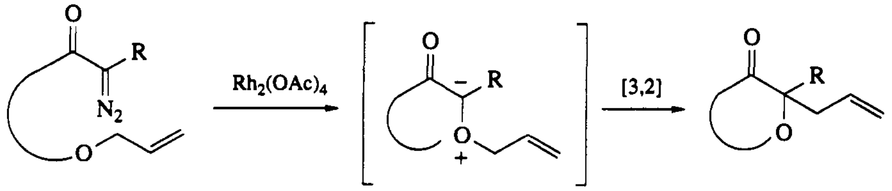

**(254)** **(255)** **(256)**

| *Entry* | *Substrate* | *Product* | *Yield (%)* | | |
|---|---|---|---|---|---|
| | | | *R = H* | *R = CO$_2$Me* | *R = CO$_2$Et* |
| 1 | 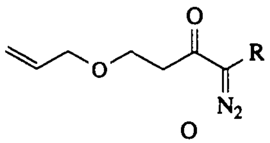 | 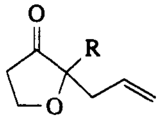 | 70 | 91 | - |
| 2 | 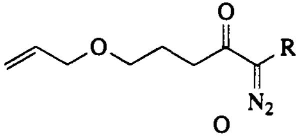 | 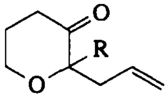 | 33 | 53 | - |
| 3 | 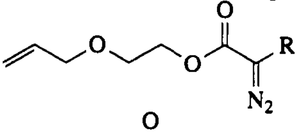 | 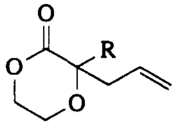 | 0 | - | 51 |
| 4 | 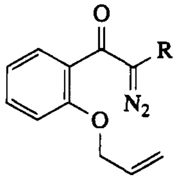 | 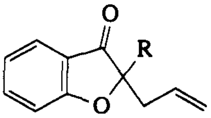 | 71 | - | 95 |
| 5 | 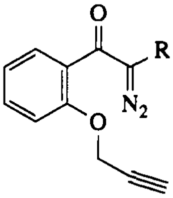 | 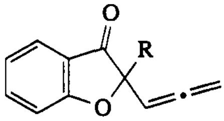 | 33 | 53 | - |
| 6 | 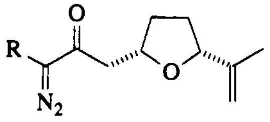 | 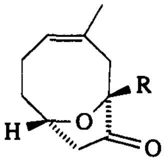 | 81 | 67 | - |

Scheme 61

occur readily even if they have to proceed *via* the less favored cisoid transition state (**270-C**). This is observed when the reacting double bond is incorporated into a ring, as shown in Scheme 66. However, if the ring size allows it, the products of the favored transoid transition state will be observed. The increase in strain associated with the formation of an (*E*)-alkene in a cyclic system might sometimes disfavor the transoid transition state (Scheme 67).[90]

Rearrangement of the five-membered ring sulfonium ylide (**278**) gives the (*Z*)-sulfide (**279**) accompanied by a small amount of (*E*)-isomer. The homologous six-membered ring sulfonium ylide (**280**) reacts smoothly to give diastereomerically pure (*E*)-(**281**). In the formation of the sulfide (**279**), the transition state (**278-C**) leading to the (*Z*)-alkene suffers from an H–H steric interaction. However, the steric strain arising from the incipient *trans* double bond, in what will eventually become an eight-membered ring, is far more important and transition state (**278-C**) is preferred over (**278-T**; Scheme 68). The reverse holds true for the reaction of the ylide (**280**) where the transition state (**280-C**) leading to the (*Z*)-alkene is the more sterically encumbered one because of a severe H–H interaction (Scheme 69).

By placing substituents at suitable positions on the starting ylide, it may become possible to alter the stereochemical course of these reactions. Fava has actually been able to reverse completely the normal stereochemical trend in these 3,2-sigmatropic rearrangements (Scheme 70).[91] Ylide (**282**) rearranges

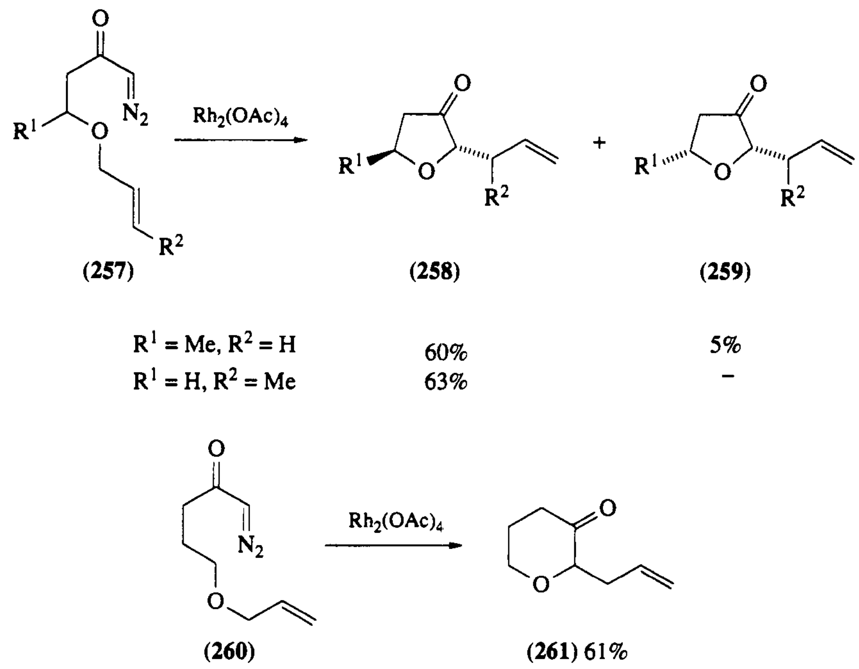

(257) (258) (259)

| | (258) | (259) |
|---|---|---|
| $R^1 = Me, R^2 = H$ | 60% | 5% |
| $R^1 = H, R^2 = Me$ | 63% | - |

(260) (261) 61%

Scheme 62

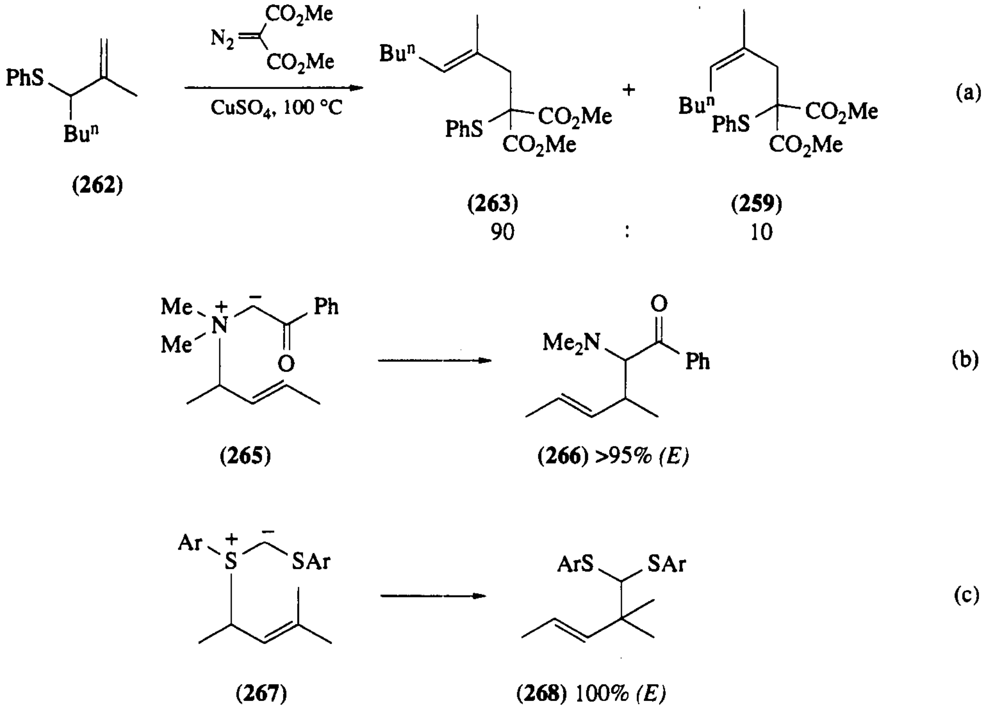

(262) (263) 90 : (259) 10

(265) (266) >95% *(E)*

(267) (268) 100% *(E)*

Scheme 63

smoothly to the (*E*)-sulfide (**283**), which is contaminated by less than 2% of the (*Z*)-alkene. In the transition state (**282-C**) leading to the (*Z*)-product, a severe steric interaction can be observed between an axial hydrogen and one of the alkenic methyl groups. This interaction will destabilize transition state (**282-C**) relative to (**282-T**) and a product with (*E*)-stereochemistry will be obtained. Similarly, the ylide (**284**) rearranges to the (*Z*)-alkenic nine-membered sulfide (**285**; Scheme 71).

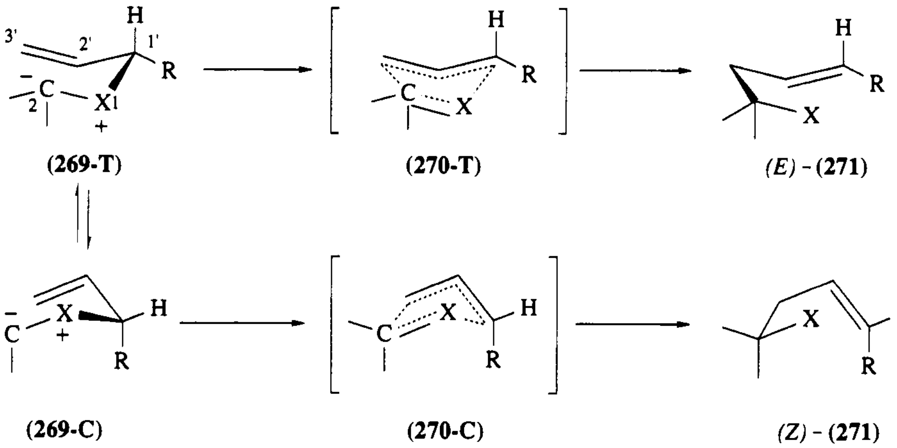
3'
2'
1'
H
R
C
2
X
+
(269-T)
H
R
C
X
(270-T)
H
R
X
(E)-(271)
X
C
+
H
R
(269-C)
C
X
H
R
(270-C)
X
H
R
(Z)-(271)

Scheme 64

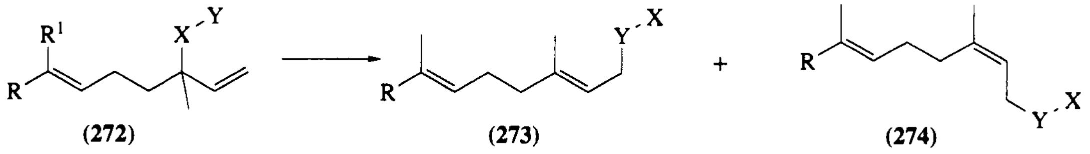
R1
X
Y
R
(272)
Y
X
R
(273)
+
R
Y
X
(274)

| *R* | *R'* | *X* | *Y* | *(E)* | *(Z)* | *Ref.* |
|---|---|---|---|---|---|---|
| 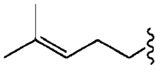 | Me | $PhS^+$ | 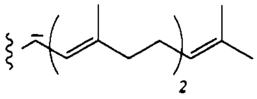 | 100 | 0 | 30 |
| Me | H | $PhS^+$ | $-O^-$ | 9 | 1 | 86 |
| Me | H | S | 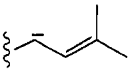 | 3 | 2 | 87 |
| Me | H | O | 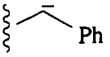 | 1 | 1 | 88 |

Scheme 65

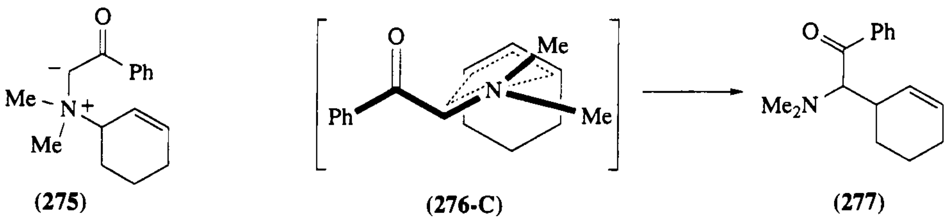
O
Ph
Me
N+
Me
(275)
O
Ph
N
Me
Me
(276-C)
O
Ph
Me2N
(277)

Scheme 66

Transition state (**284-T**) reveals clearly a particularly destabilizing methyl–methyl interaction. It is therefore strongly disfavored compared with transition state (**284-C**), which shows only an axial methyl–methyl interaction. This approach has been used by Fava in a highly imaginative route to betweenanenes.[92] The sulfonium salt (**286**) is transformed by a stereospecific 3,2-sigmatropic rearrangement into the (*E*)-macrocycle (**287**). A Ramberg–Backlund reaction followed by catalytic hydrogenolysis then leads to betweenanene (**289**; Scheme 72, equation a). The epimeric sulfonium salt (**290**) rearranges smoothly to the (*Z*)-macrocycle. An identical methodology has been used by Nickon to prepare betweenanenes with enol sulfide functionalities.[93]

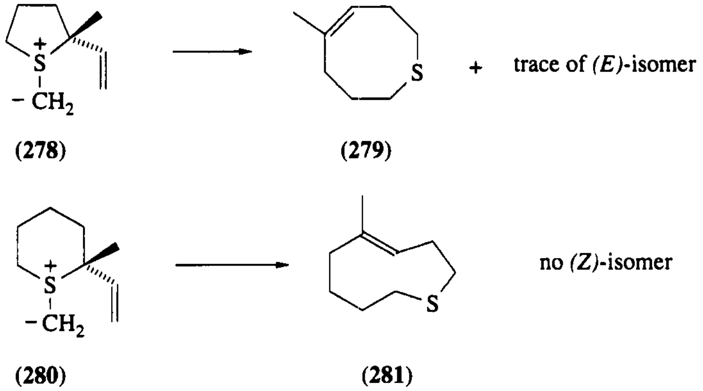
S
$^+$
$^-CH_2$
(278)
S
(279)
+ trace of (E)-isomer
S
$^+$
$^-CH_2$
(280)
S
(281)
no (Z)-isomer

Scheme 67

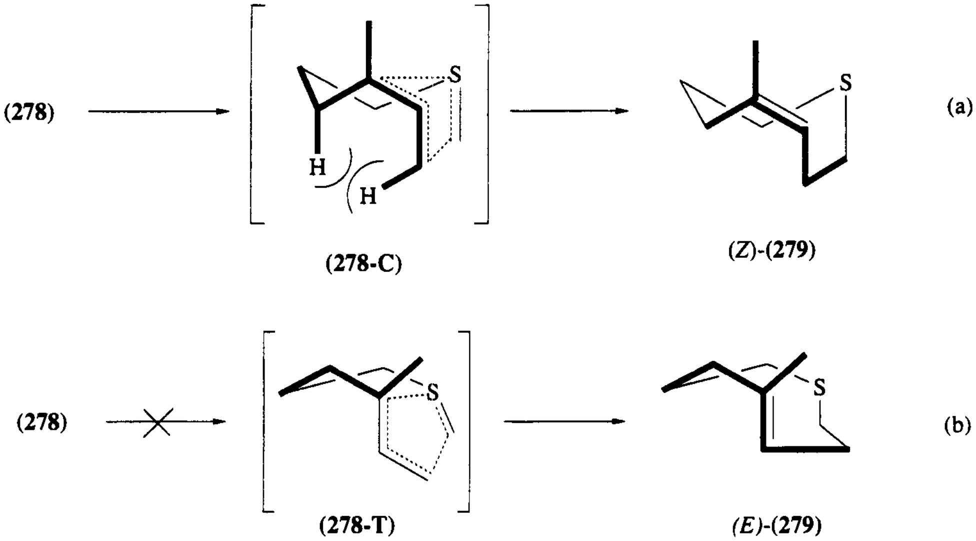
(278)
S
H
H
(278-C)
S
(Z)-(279)
(a)
(278)
S
(278-T)
S
(E)-(279)
(b)

Scheme 68

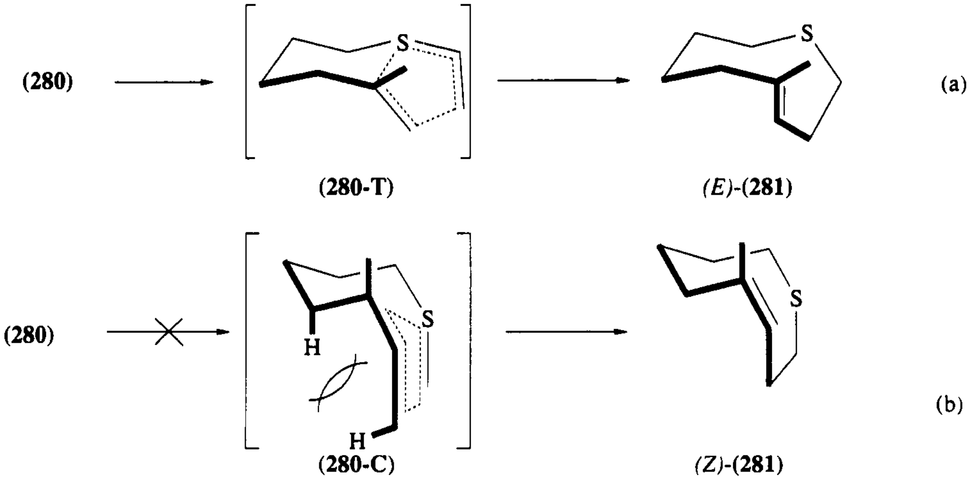
(280)
S
(280-T)
S
(E)-(281)
(a)
(280)
S
H
H
(280-C)
S
(Z)-(281)
(b)

Scheme 69

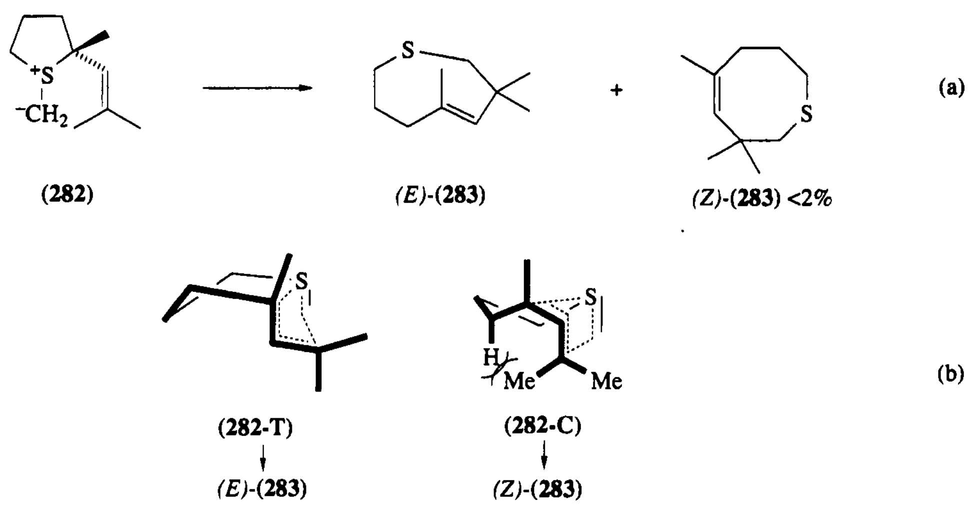
(282)
(E)-(283)
(Z)-(283) <2%
(a)
(282-T)
(E)-(283)
(282-C)
(Z)-(283)
(b)

**Scheme 70**

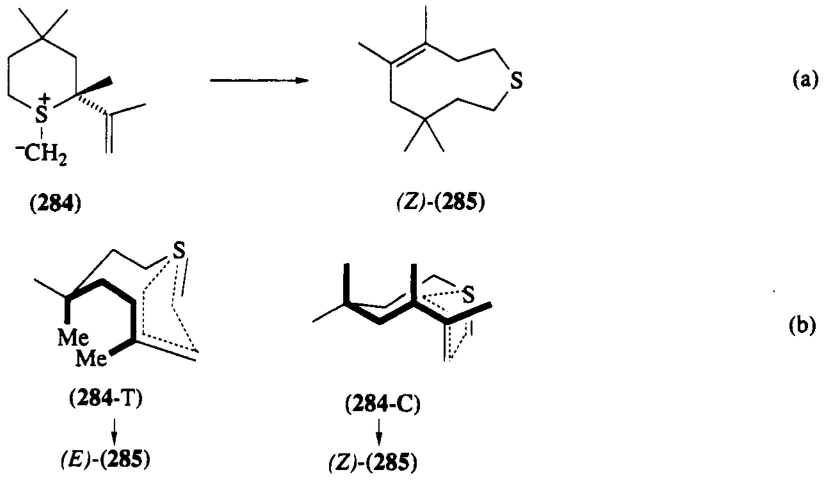
(284)
(Z)-(285)
(a)
(284-T)
(E)-(285)
(284-C)
(Z)-(285)
(b)

**Scheme 71**

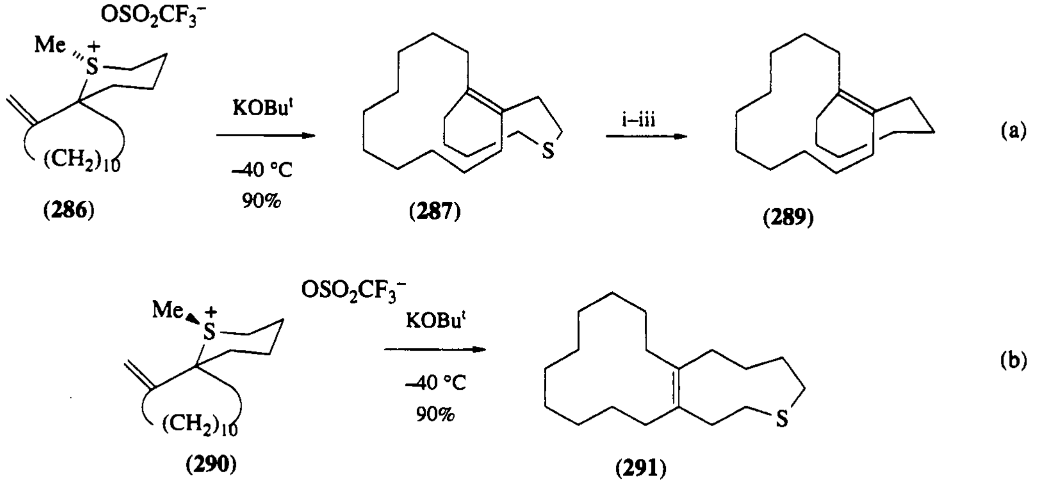
OSO2CF3−
KOBut
−40 °C
90%
i–iii
(286)
(287)
(289)
(a)
KOBut
−40 °C
90%
(290)
(291)
(b)

i, MCPBA; ii, NaH; iii, $H_2$–Pd–C

**Scheme 72**

### 3.10.5.4 The Erythro–Threo Ratio

In 3,3-sigmatropic rearrangements, the ratio of diastereoisomers is controlled by the energy difference between boat and chair conformations. In general, this energy difference represents a significant quantity. For 3,2-sigmatropic rearrangements the diastereoisomeric ratio will be dependent upon the preference of a substituent to be located on the *exo* or *endo* position in the transition state. These are often only small energy differences and, therefore, mixtures occur frequently (Scheme 73).

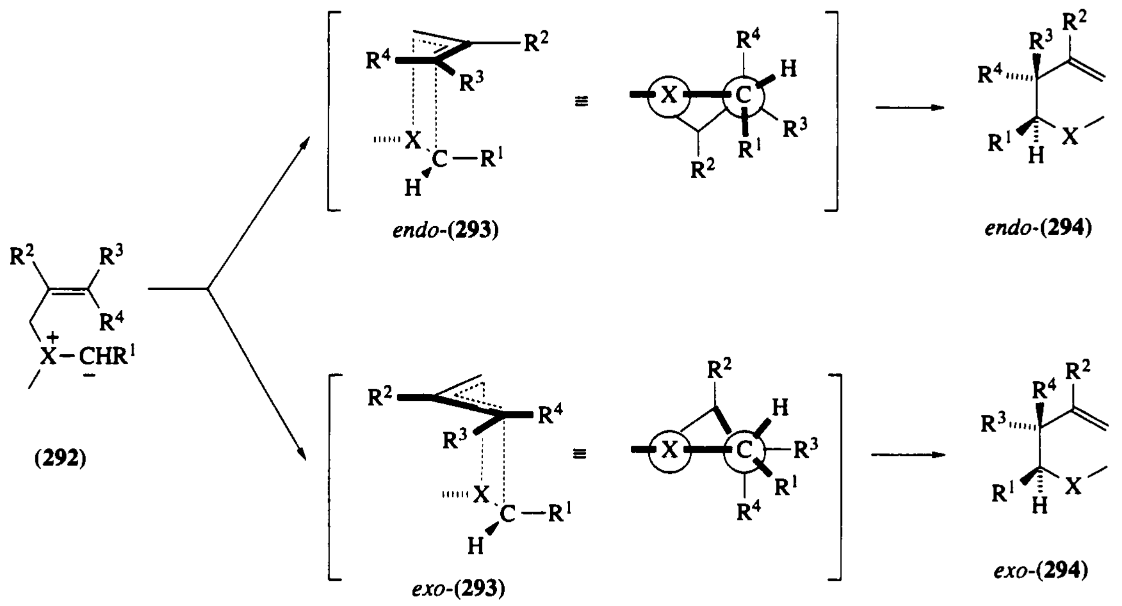

**Scheme 73**

When sterically feasible, an *endo* transition state will however be favored.[94] Some examples are collected in Table 3.[94–97] From the results indicated in the table, a general pattern seems to emerge. Sulfur ylides and propargylic ammonium ylides undergo preferential 3,2-rearrangement *via* an *endo* transition state and the diastereoisomeric control is good to excellent. Acyclic, nonpropargylic ammonium ylides give a mixture of diastereoisomers and, in some cases, a strong *exo* preference is displayed (Table 4).[98] Examination of the envelope transition states reveals that the *exo* transition state is the least sterically congested and should, therefore, be the preferred one in these cases (Scheme 74).

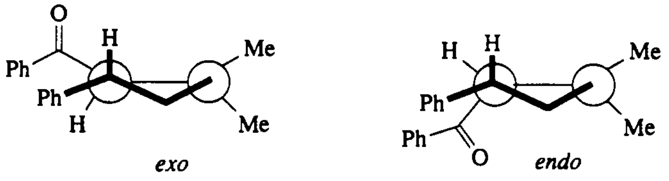

**Scheme 74**

It can also be seen that an increase in the steric bulk of the ketone substituent (Ph replaced by $\mathrm{Bu^t}$) should favor the *exo* transition state even more. This is indeed observed, since the *endo*:*exo* ratio rises from 1:5 to 1:9. It is, however, difficult to make some predictions since subtle effects which could be present could favor either one or the other of the transition states (compare entry 5 in Table 3 with entry 1 in Table 4). Sometimes, steric hindrance in one of the transition states is so overwhelming that prediction can be made rather safely.[99] This is the case for the ylide (**295**) which rearranges exclusively *via* an *exo* transition state *exo*-(**296**), the *endo* transition state *endo*-(**296**) being much too hindered to be attained (Scheme 75). Similarly, the ylide (**299**) gives the amine (**300**) as a single isomer in 88% yield (Scheme 76).[99]

Table 3

| *Entry* | *Substrate* | *Products* | *Ratio* | *Transition state* |
|---|---|---|---|---|
| 1 | 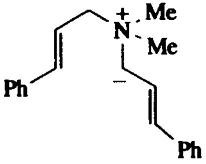 | 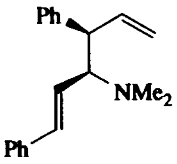<br>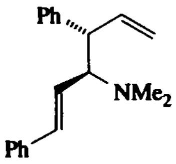 | 10:1 | *Endo* |
| 2 | 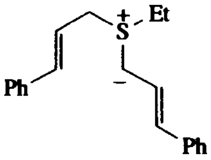 | 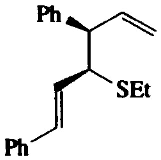<br>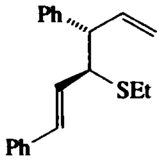 | — | *Endo* |
| 3 | 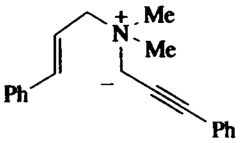 | 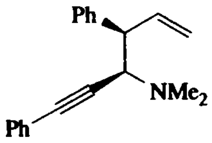<br>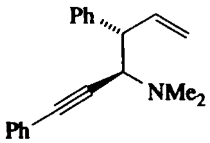 | 86:14 | *Endo* |
| 4 | 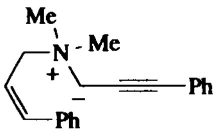 | 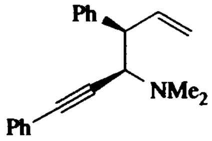<br>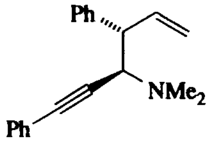 | 10:90 | *Endo* |
| 5 | 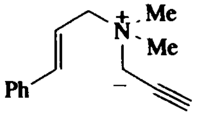 | 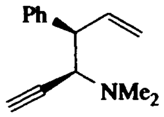<br>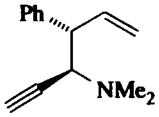 | 100:0 | *Endo* |

**Table 3** *(continued)*

| *Entry* | *Substrate* | *Products* | *Ratio* | *Transition state* |
|---|---|---|---|---|
| 6 | 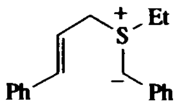 | 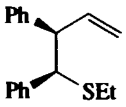 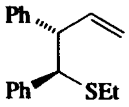 | 60:40 | *Endo* |
| 7 | 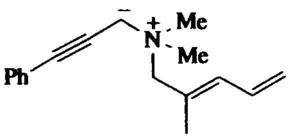 | 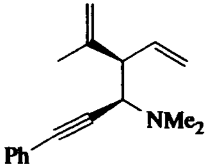 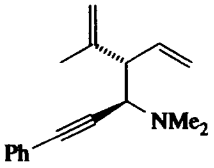 | 60:10 | *Endo* |

**Table 4**

| *Entry* | *Substrate* | *Products* | | *Ratio* | *Transition state* |
|---|---|---|---|---|---|
| 1 | 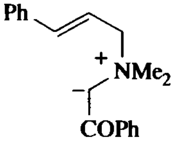 | 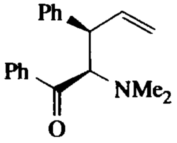 | 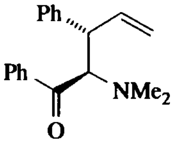 | 1:5 | *Exo* |
| 2 | 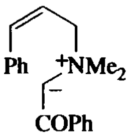 | 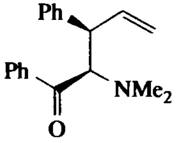 | 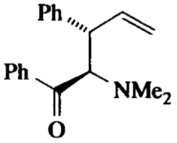 | 2:1 | *Endo* |
| 3 | 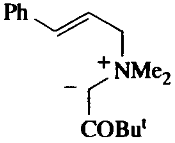 | 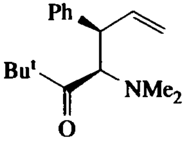 | 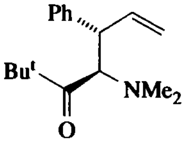 | 1:9 | *Exo* |
| 4 | 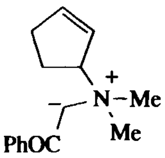 | 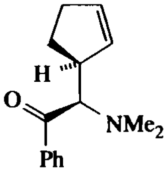 | 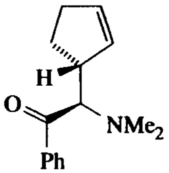 | 2:1 | *Endo* |

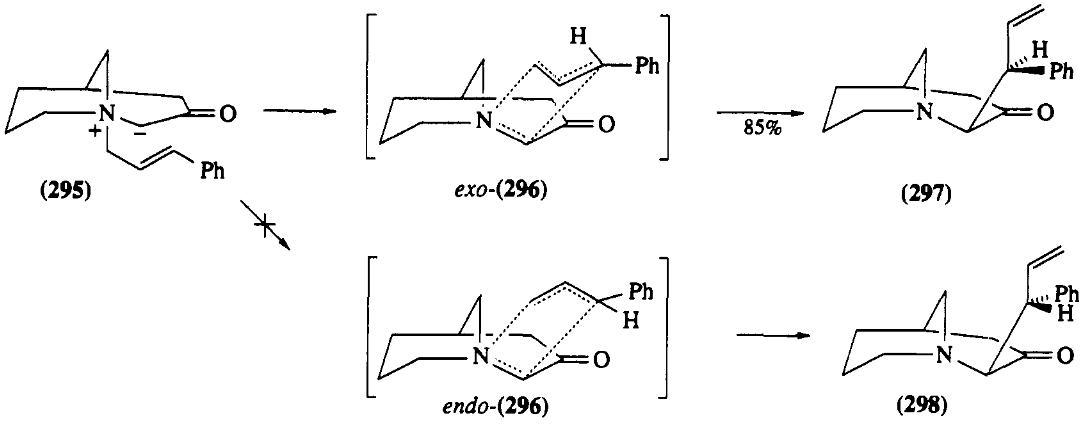

Scheme 75

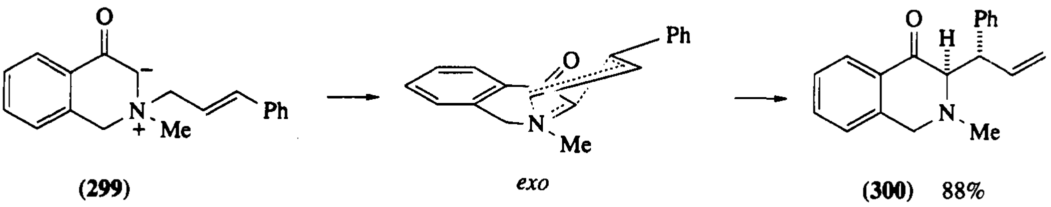

Scheme 76

### 3.10.5.5 Transfer of Configuration

In a way similar to 3,3-rearrangements, the configuration of C-1 of the allylic group can be transferred to C-3 by a 3,2-sigmatropic rearrangement. The original chiral center and the double bond configuration will control, *via* the envelope transition state, the chirality and configuration of the product; an (*R*)-(*E*)-starting material usually leads to an (*S*)-(*E*)-product, whereas the use of a (*Z*)-substrate gives the opposite result: (*R*)-(*Z*). Hill has studied the chirality transfer of simple acyclic ammonium ylides and observed that transposition of the ylide (**301**), followed by reductive cleavage, gave the ketone (**304**; 88% *ee*).[83,100] The configuration of the carbon–carbon double bond is, as expected, retained. Similarly, the ylide (**305**) leads to the (*R*)-(–)-cyclic ketone (**307**; Scheme 77). In an analogous manner, rearrangement of the (*S*)-(*E*)-allylic alcohol (**308**) using the 'Buchi method' gives the (*Z*)-amide (**310**) of >99% *ee*, accompanied by ~13% of the (*S*)-(*Z*)-isomer resulting from the other envelope conformation.[101] In sharp contrast, the (*R*)-alcohol (**308**) gives only the (*R*)-(*E*)-amide (**310**; Scheme 78).

An interesting transfer of asymmetry from a chiral heteroatom to the newly formed carbon–carbon bond has been reported by Trost.[102] The sulfonium salt (**311**) gives the 3,2-rearrangement product (**312**) with 94% *ee* (Scheme 79, equation a). The high asymmetric induction obtained in this case can be rationalized by preferential rearrangement *via* transition state (**313**), containing a minimum of nonbonded interactions, rather than the more congested transition state (**315**; Scheme 79, equation b). This is, however, a rather exceptional example and, in general, the asymmetric induction remains low (Scheme 80).[103–105]

Asymmetric induction arising from remote chiral centers present in the ylide is yet another way of transferring chirality. Although only a few examples are known, an outstanding one has been described by Baldwin and Kaiser, who obtained the α-allyl penam derivative (**186**) as a single isomer upon rearrangement of the nitrogen ylide (**185**; Scheme 43).[65] Sulfonium and selenonium ylides proved to be much less efficient, as demonstrated by John (Scheme 41).[64]

The last, and probably most interesting, example of the approach towards chiral products derived from ylidic 3,2-rearrangements, involves the generation of a chiral ylide by enantioselective deprotonation of a prochiral sulfonium (ammonium) salt using a chiral base. Few attempts have been reported so far, the most noteworthy coming from the laboratory of Trost and involving the reaction of the sulfonium salt (**321**) with the chiral base (**322**; Scheme 81).[103] The asymmetric induction is rather poor and represents the extent of prochiral recognition by the chiral base.

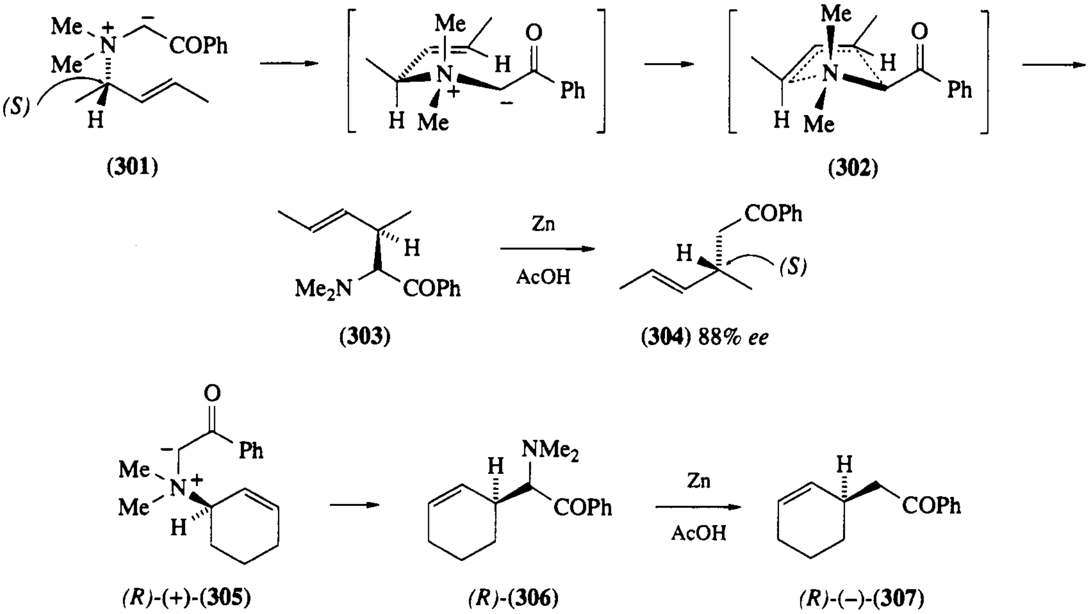

Scheme 77

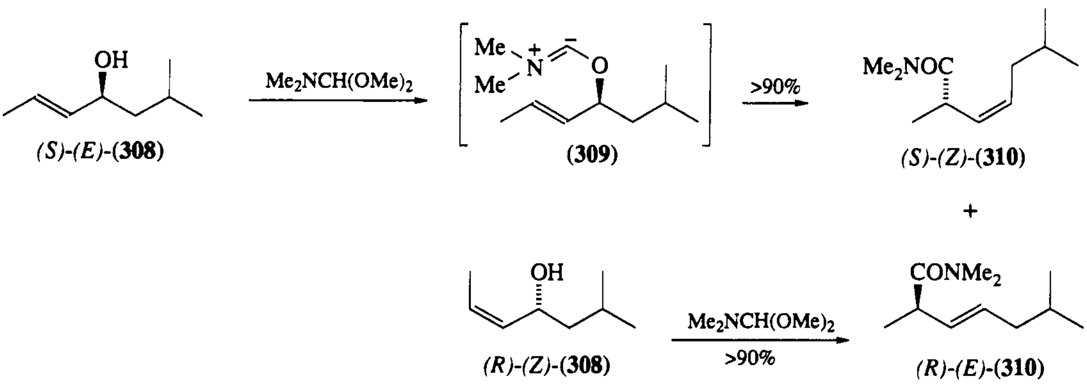

Scheme 78

### 3.10.5.6 Ring Contraction Reactions

Ylidic 3,2-sigmatropic rearrangements have quite recently been used to promote ring contraction reactions, generally with high selectivity. One of the most famous examples involves the transformation of the cephalosporin derivative (**70**) into the penicillin derivative (**72**; Scheme 82).[33] A similar ring contraction was observed by Ando when the unsaturated sulfide (**66**) was reacted with diazomalonate under photolytic conditions.[44] The stable ylide (**68**) underwent 3,2-rearrangement only upon heating (Scheme 83, equation a).

In sharp contrast, the ylide (**325**) rearranges spontaneously above −5 °C to give a mixture of *cis*- and *trans*-sulfides (**326**) and (**327**) in a 25:1 ratio.[98] The fact that the stereochemistry of the reaction products is under kinetic control was demonstrated by the base-catalyzed epimerization of (**326**) and (**327**) to a thermodynamic 1:19 ratio. Ammonium ylides also undergo ring contraction but with complete *cis* diastereoselectivity (Scheme 84).[98] Base-catalyzed equilibration affords some *trans* isomer. The high diastereoselectivities displayed in these reactions contrasts with the poor and rather unpredictable ones observed for acyclic ylide rearrangements (*cf.* Section 3.10.5.4). In all of the cases examined, the *endo* transition state *endo*-(**325**) is highly favored over the *exo* transition state *exo*-(**325**) (Scheme 85). A

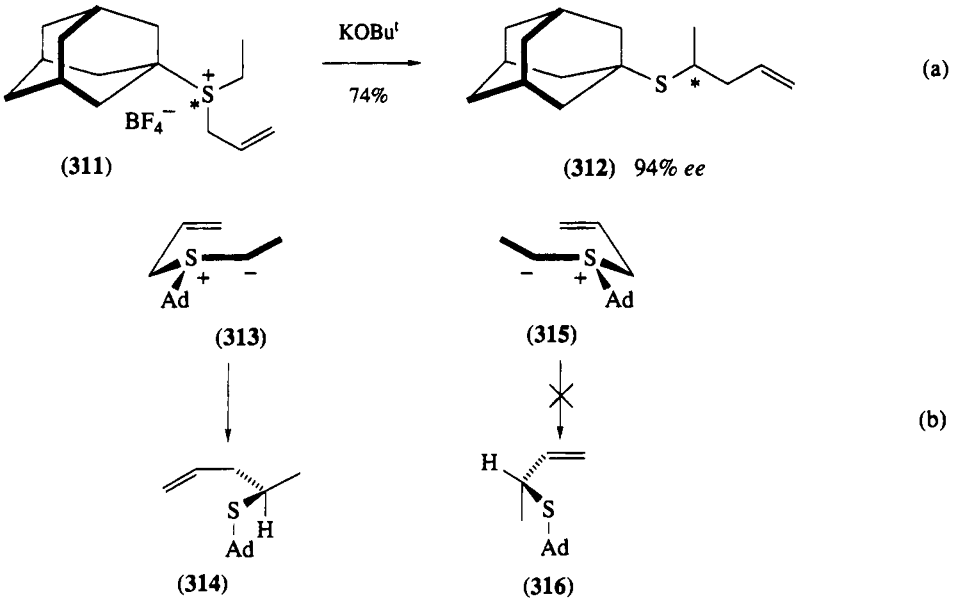
KOBu$^t$
74%
$BF_4^-$
(311)
(312) 94% ee
(a)
Ad
(313)
(315)
(314)
(316)
(b)

Scheme 79

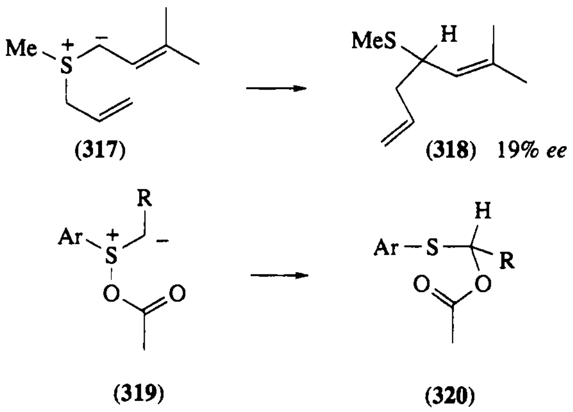
Me
MeS
H
(317)
(318) 19% ee
R
Ar
(319)
(320)

Ar = $p$-MeC$_6$H$_4$, R = CN 29% *ee*
Ar = $p$-MeC$_6$H$_4$, R = P(O)(OEt)$_2$ 24% *ee*

Scheme 80

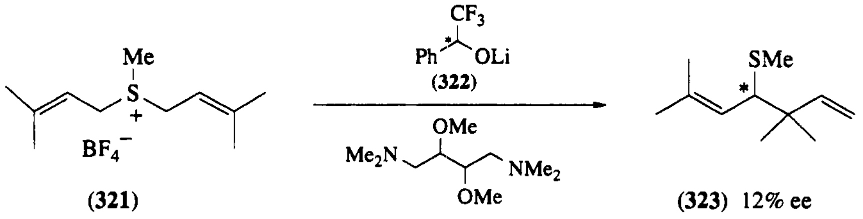
Me
$BF_4^-$
(321)
$CF_3$
Ph
OLi
(322)
OMe
$Me_2N$
$NMe_2$
OMe
SMe
(323) 12% ee

Scheme 81

possible explanation invokes secondary orbital interactions, which can take place between the *endo* carbonyl group and the carbon–carbon double bond only in the *endo* transition state (**328**; Scheme 86).

Once again, ammonium ylides display higher diastereoselectivities than their sulfur counterparts. This observation formed the basis of a recent synthetic approach towards the alkaloid makomakine (**331**; Scheme 87) where the key step was the ring contraction of the azepine (**329**) into the *cis*-substituted piperidine ring (**330**).[106]

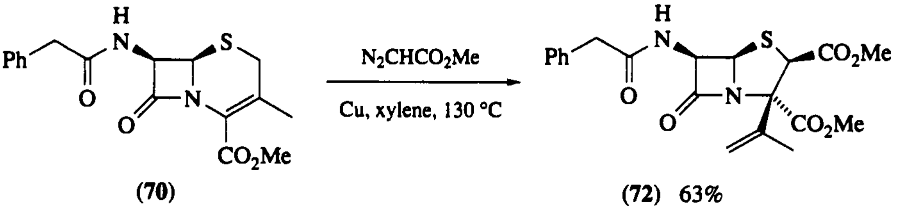
(70)
N₂CHCO₂Me
Cu, xylene, 130 °C
(72) 63%

**Scheme 82**

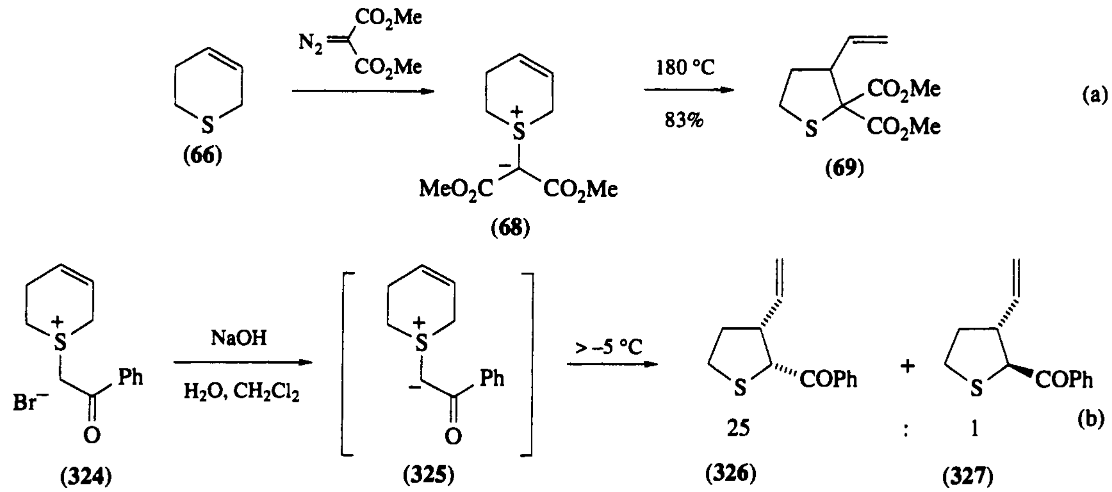
(66)
(68)
180 °C
83%
(69)
(a)
NaOH
H₂O, CH₂Cl₂
> -5 °C
(324)
(325)
(326)
(327)
25 : 1
(b)

**Scheme 83**

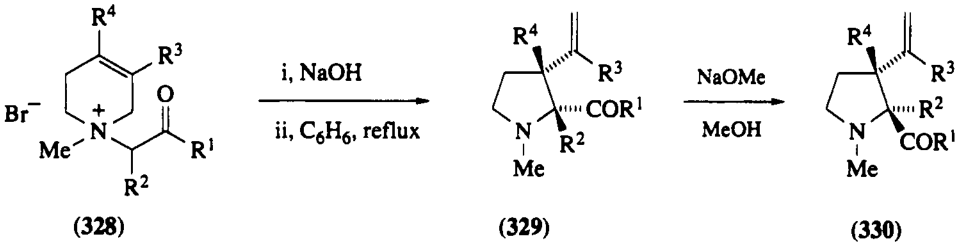
(328)
i, NaOH
ii, C₆H₆, reflux
(329)
NaOMe
MeOH
(330)

| *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *(329):(330)* |
|---|---|---|---|---|
| Ph | H | H | H | 100:0 |
| Ph | H | Me | Me | 100:0 |
| Ph | H | H | Et | 100:0 |
| Ph | H | H | $Bu^t$ | 100:0 |
| Ph | Ph | H | H | 100:0 |
| $Bu^t$ | H | H | H | 100:0 |

**Scheme 84**

Yoshikoshi has explored a novel strategy directed towards the enantioselective preparation of highly substituted butyrolactones, based on the 3,2-sigmatropic rearrangement of sulfur ylides (Scheme 88).[107] Intramolecular carbene trapping generated the eight-membered ring sulfur ylide (**334**), which then underwent ring contraction to give the complex lactone (**335**) as a single stereoisomer.

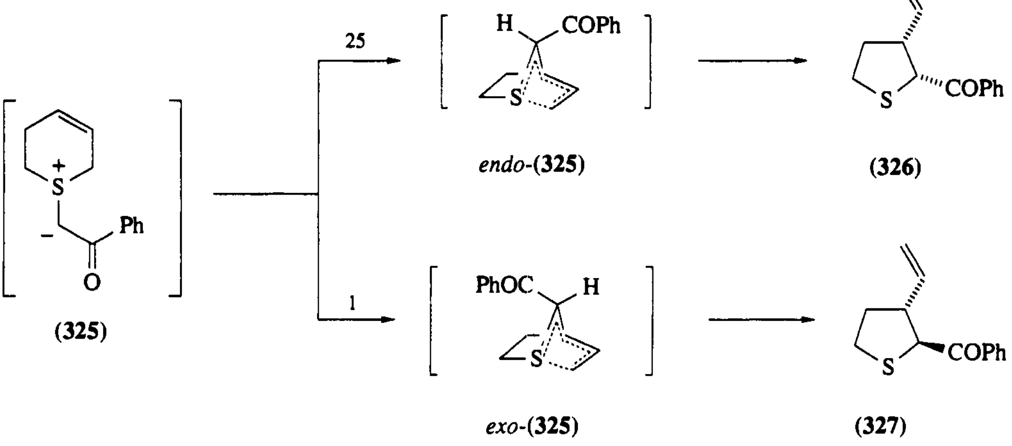

Scheme 85

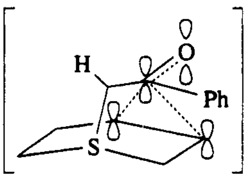

(328)

Scheme 86

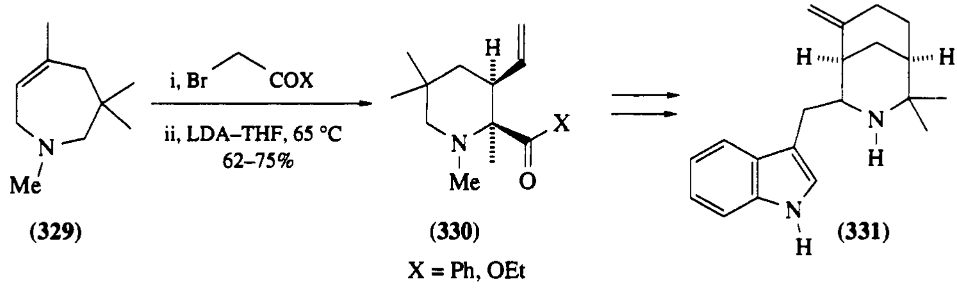

Scheme 87

### 3.10.5.7 Ring Expansion Reactions

One of the first ring expansion reactions of an ylidic intermediate was reported by Hauser and involves the Sommelet–Hauser reaction (see Section 3.10.5.9) of the nitrogen ylide (**336**; Scheme 89).[108] However, the recognition of the synthetic potential of ylidic 3,2-rearrangements for controlled ring expansions is due to Vedejs, who published in 1975 a novel 'ring-growing' reaction.[109] This was to be the beginning of a remarkable synthetic methodology, which eventually culminated in the preparation of numerous natural and non-natural products. The general strategy is summarized in Scheme 90.[110] Transformation of a cyclic α-vinyl sulfide (**338**) into a stabilized ylide (**340**) is followed by a 3,2-sigmatropic rearrangement to give the eight-membered ring sulfide (**341**) as a mixture of (*Z*) (major) and (*E*) (minor) isomers. Separation and Wittig reaction regenerates an α-vinyl sulfide (**343**) ready to undergo another ring expansion reaction. The original approach used stabilized ylides but required an extra Wittig reaction in order to become an iterative process. However, by using a nonstabilized allylic ylide such as (**346**), the ring expansion product (**347**) contains an exocyclic vinylic moiety and the process can be repeated again (Scheme 91).[111]

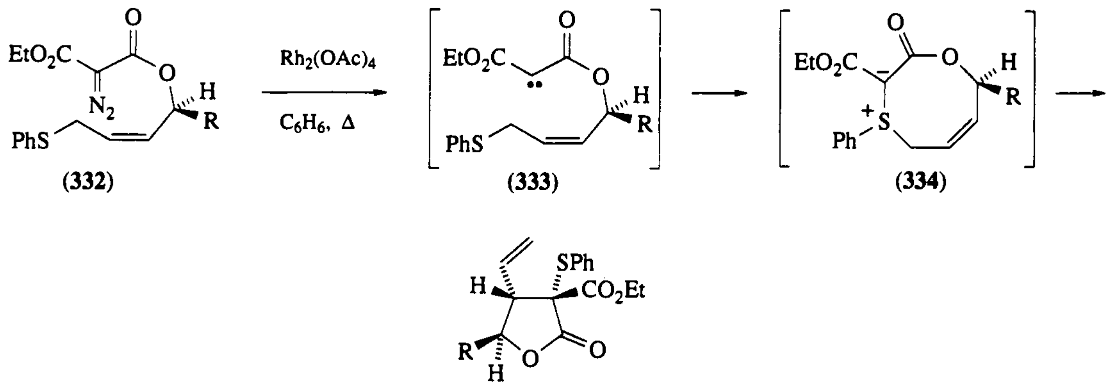

**(332)** **(333)** **(334)** **(335)**

| *R* | *Yield* (%) |
|---|---|
| Me | 53 |
| $Pr^n$ | 68 |
| $Pr^i$ | 70 |
| Pentyl | 66 |
| $PhCH_2$ | 63 |

**Scheme 88**

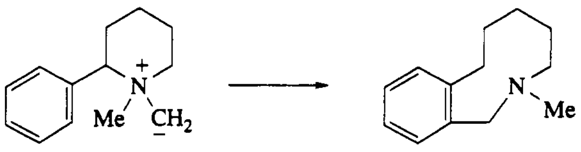

**(336)** **(337)**

**Scheme 89**

When comparing the examples described in Scheme 90 and 91, several important considerations surface. When employing nonstabilized ylides, the stereochemistry at the sulfur atom of the starting sulfonium salt can no longer be ignored. This is a real problem since the sulfonium salt, and therefore the ylide, has the vinyl group and alkyl group *trans* to each other, a result of kinetically-controlled alkylation at sulfur. The formation of (*Z*)-alkenes by a concerted 3,2-sigmatropic rearrangement requires a *cis* relationship between these two groups in order for it to take place. Fava has contributed extensively to the solving of this crucial problem.[112] He has shown that, with nonstabilized ylides, equilibration of the *cis* and *trans* sulfonium ions takes place more rapidly than deprotonation of the group present on sulfur (Scheme 92). The formation of *cis* sulfonium ylide by equilibration of the *trans* material then allows the concerted 3,2-rearrangement to take place. By blocking the epimerizable center, only the *cis* isomer rearranges smoothly, the *trans* one giving mostly the elimination product (**354**; Scheme 93).[90]

The expected high preference for (*E*)-alkenes (as compared with acyclic precursors) is conserved in the formation of the nine (and higher) membered rings,[66] but the formation of eight-membered rings, as already discussed in Section 3.10.5.3, is (*Z*)-selective. However, ammonium ylides behave differently in these reactions than their sulfur counterparts.[113] Both of the ylide isomers (**358**) and (**359**), derived from the ammonium salt (**357**) give smoothly the nine-membered ring amine (**360**; Scheme 94). Transition states (**358-C**) and (**358-T**) have been invoked to rationalize this result. If the piperidine ring is locked in a conformation in which the ylidic carbon center has to adopt an axial orientation, then only a *cis* macrocycle will be obtained (Scheme 95).[113]

Transition states (**363**) and (**364**) can be considered, with (**363**) possessing a correct bonding distance between the alkenic terminus and the ylidic carbon. In (**364**) this distance is too long for bonding and a conformational change to a boat form would be required for reaction to ensue. This is energetically too

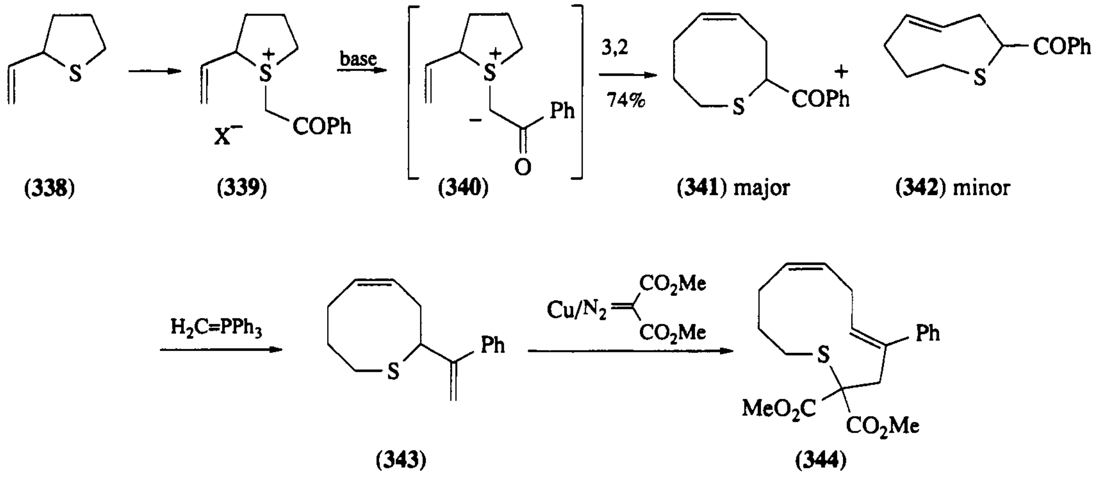
(338)
(339)
X⁻
COPh
base
(340)
Ph
O
3,2
74%
(341) major
COPh
+
(342) minor
COPh
H₂C=PPh₃
(343)
Ph
Cu/N₂=C(CO₂Me)₂
(344)
Ph
MeO₂C
CO₂Me

Scheme 90

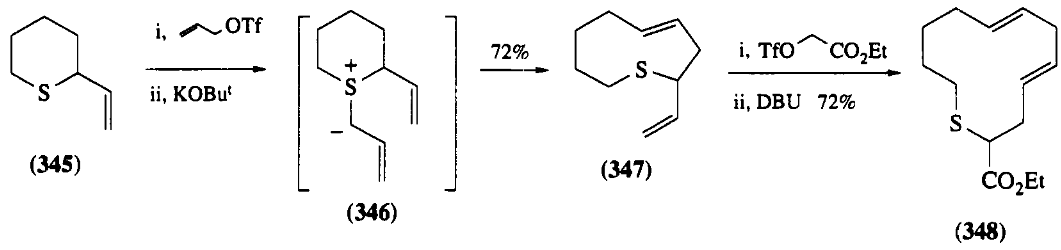
(345)
i, allyl OTf
ii, KOBuᵗ
(346)
72%
(347)
i, TfO CO₂Et
ii, DBU 72%
(348)
CO₂Et

Scheme 91

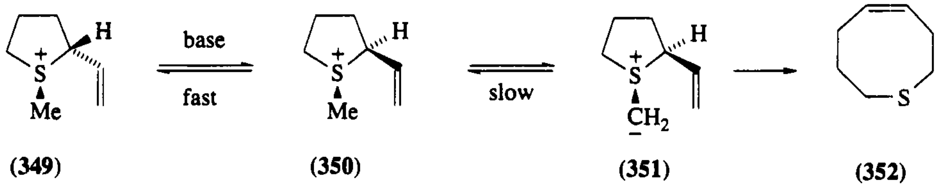
(349)
H
Me
base
fast
(350)
H
Me
slow
(351)
H
CH₂
(352)

Scheme 92

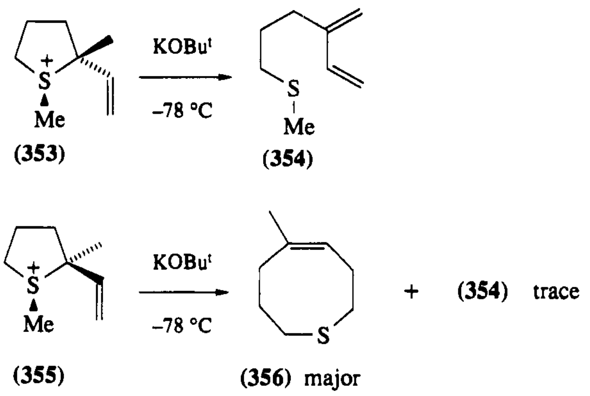
(353)
Me
KOBuᵗ
–78 °C
(354)
S
Me
(355)
Me
KOBuᵗ
–78 °C
(356) major
+ (354) trace

Scheme 93

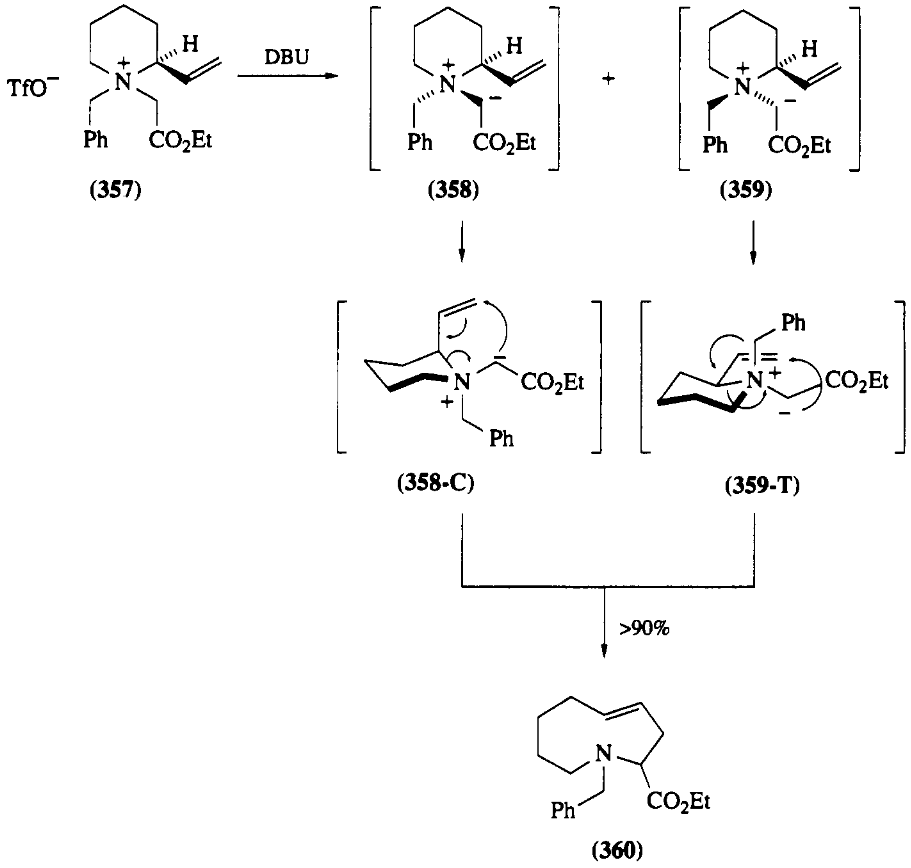

Scheme 94

costly and no *trans*-alkene is observed. Vedejs has used this ring expansion methodology in the preparation of macrocyclic lactones and a typical example is recorded in Scheme 96.[114]

Intramolecular *S*-alkylation of (**366**) is followed by deprotonation to form the ylide (**367**), which rearranges to the sulfide (**368**). A few more steps are then required to obtain the nine- and ten-membered ring lactones, including a particularly interesting *S*- to *O*-acyl transfer. The efficient stereocontrol usually observed for 3,2-sigmatropic rearrangements was utilized in the synthesis of the C-1 to C-9 fragment (**373**) of the erythromycin family (Scheme 97).[115] This methodology was also used in a repetitive manner for methynolide synthesis (Scheme 98).[116] Thus, the 3,2-sigmatropic rearrangement of the ylide (**376**) initially gave the (*Z*)-sulfide (**377**) in 40% yield. This low yield is attributed to the impossibility for the second diastereoisomeric ylide to rearrange. In this case, equilibration through the usual proton transfer is prevented by the C-4 methyl group. Six more steps are then necessary to transform (**377**) into (**378**), ready to undergo another ring expansion reaction. The 3,2-rearrangement proceeded this time uneventfully and gave the 11-membered ring (**379**) in 80–85% yields. Only the (*E*)-alkene was obtained, as expected. More surprising was the kinetic 16:1 mixture of C-10 epimers isolated, even though (**378**) consisted of a 1:1 mixture of diastereoisomers. The strong conformational preference for the transoid vinyl rotamers of ylides (**381**) and (**382**) accounts for this observation.

Particularly outstanding examples of the high degree of stereocontrol that can be exercised using ylidic 3,2-sigmatropic rearrangements are demonstrated in the cytochalasin (**387**)[117] and zygosporin (**388**)[118] syntheses (Scheme 99). The allylic halide (**384**) was obtained with high regio- and stereo-selectivity from the lactam (**383**). The key 3,2-sigmatropic rearrangement was performed by heating the chloride (**384**) with sodium iodide and $K_2CO_3$. A 1.3:1 mixture of epimeric sulfides (**386**) was obtained in 60% yield. Both isomers have the crucial (*E*)-double bond geometry. The rest of the synthesis then involved desulfurization and allylic transposition. The preparation of the highly elaborated zygosporin (**388**) followed essentially the same route.

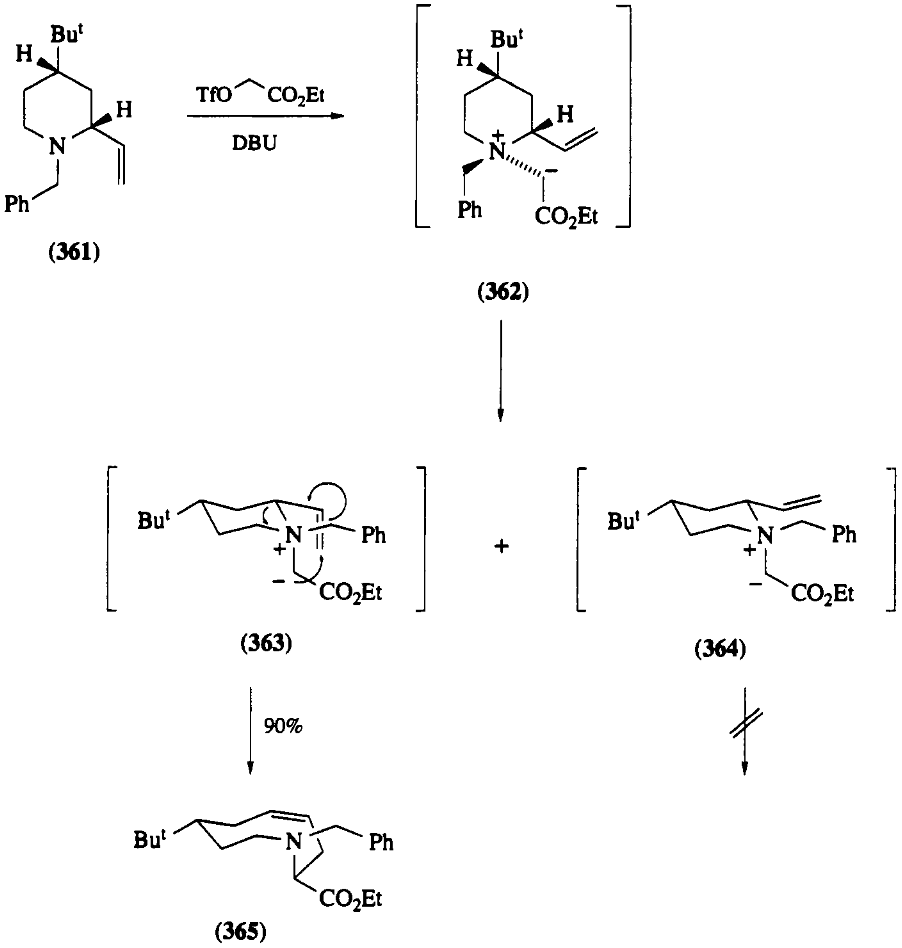
(361)
TfO⁀CO2Et
DBU
(362)
(363)
(364)
90%
(365)
Bu^t
Ph
CO2Et

Scheme 95

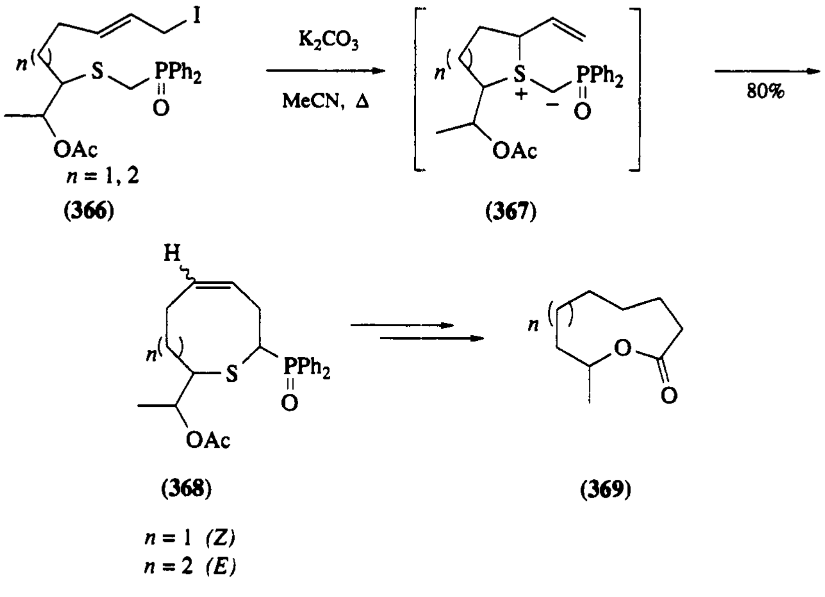
K2CO3
MeCN, Δ
80%
(366)
n = 1, 2
(367)
(368)
n = 1 (Z)
n = 2 (E)
(369)
PPh2
OAc

Scheme 96

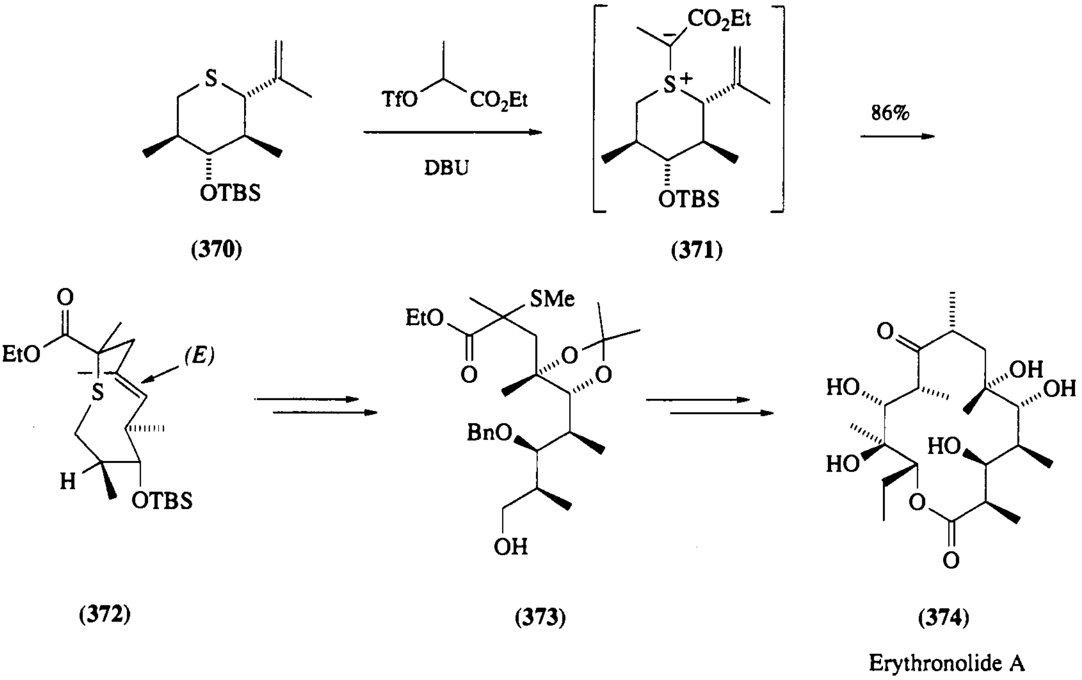
TfO CO2Et
DBU
86%
OTBS
(370)
(371)
EtO
O
(E)
SMe
BnO
OH
HO
(372)
(373)
(374)
Erythronolide A

**Scheme 97**

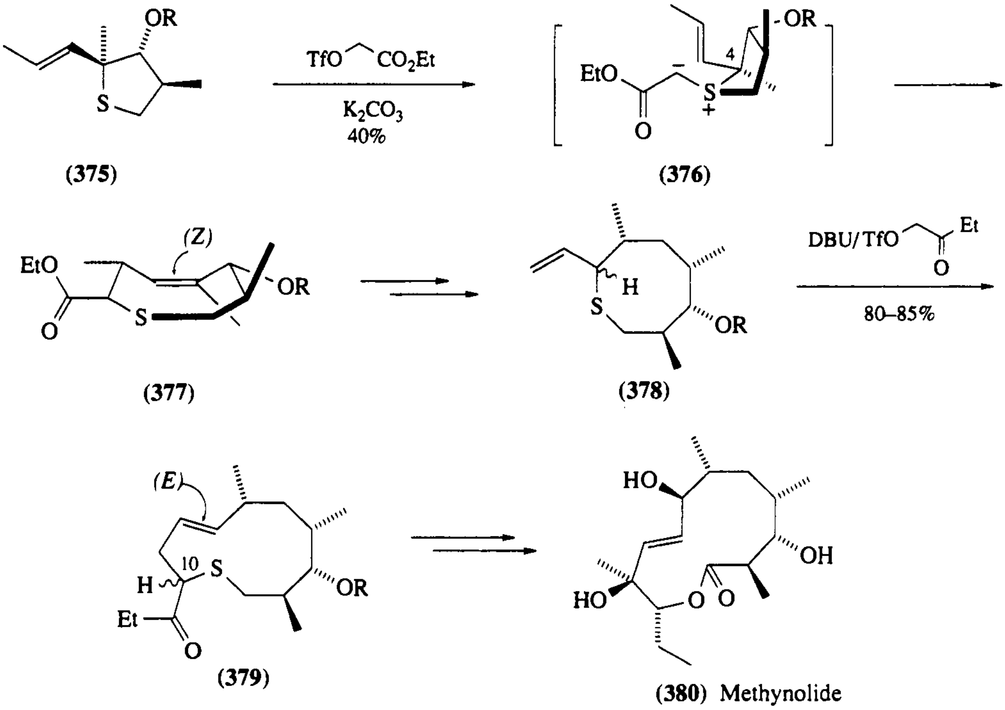
OR
TfO CO2Et
K2CO3
40%
EtO
4
(375)
(376)
(Z)
DBU/TfO Et
80–85%
(377)
(378)
(E)
10
H
Et
(379)
HO
OH
(380) Methynolide

**Scheme 98**

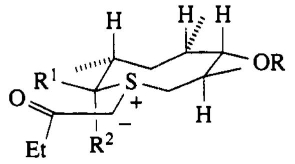

**(381)**: $R^1$ = –CH=CH$_2$, $R^2$ = H
**(382)**: $R^1$ = H, $R^2$ = –CH=CH$_2$

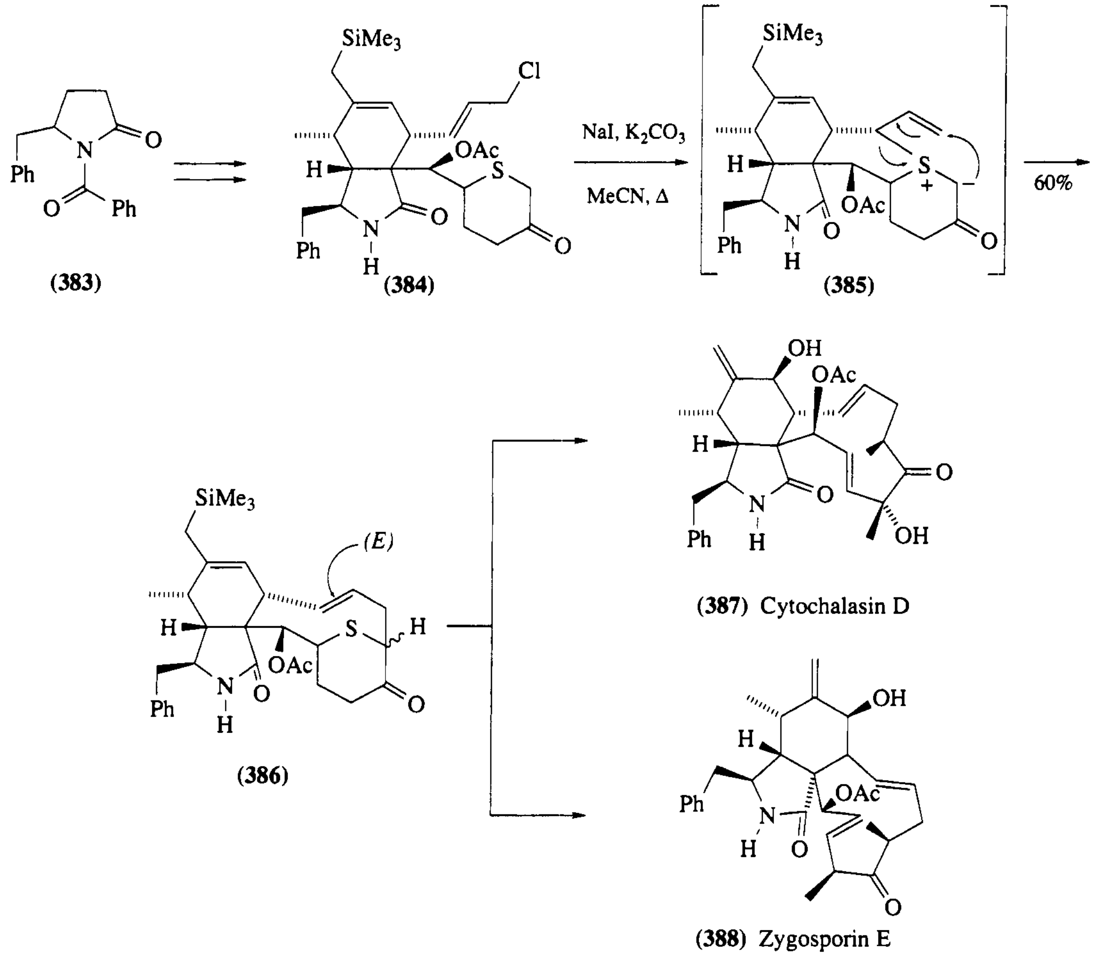

**(383)** **(384)** **(385)** **(386)**

**(387)** Cytochalasin D

**(388)** Zygosporin E

**Scheme 99**

### 3.10.5.8 Ylidic Rearrangements Involving Alkynes and Allenes

Allenes can be easily prepared using the 3,2-sigmatropic rearrangement of ylidic intermediates. This methodology also provides a general route towards the synthesis of cumulenes. Some examples using sulfonium and ammonium ylides are collected in Table 5.[119–122]

Ketene dithioacetals have been prepared by Julia by isomerization of the initially formed allene (Scheme 100),[123] and Viehe has utilized this approach to obtain capto-datively substituted dienes (Scheme 101).[124] The latter reaction can be stopped before isomerization is complete and the allene can be detected along with some diene. The analogous cyanodienes are also easily accessible *via* this route (Scheme 102).

The striking difference in behavior between nitrogen and sulfur ylides is illustrated once again with the examples collected in Scheme 103.[124] In most of the cases involving the rearrangement of propargylic ammonium ylides, the allene (initial reaction product) can be isolated or identified as a component of the

**Table 5**

| *Ylide* | *Product* | | | | *Yield (%)* |
|---|---|---|---|---|---|
| 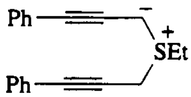 | 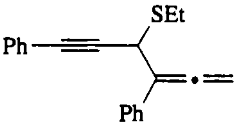 | | | | — |
| 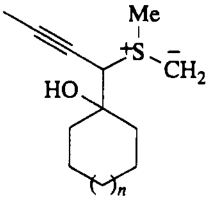 | 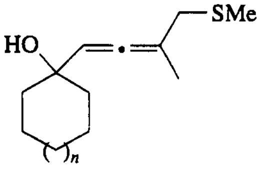 | $n = 0$<br>$n = 1$ | | | 61<br>43 |
| 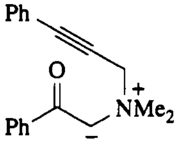 | 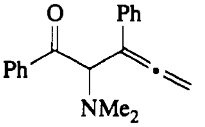 | | | | 83 |
| 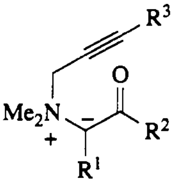 | 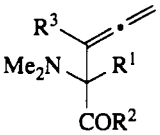 | | | | |
| | | *$R^1$* | *$R^2$* | *$R^3$* | |
| | | H | Bu$^t$ | Ph | 60 |
| | | H | OMe | Ph | 56 |
| | | H | Me | Ph | 80 |
| | | Ph | Ph | H | 19 |
| | | Ph | Ph | Ph | 7 |
| 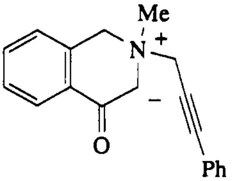 | 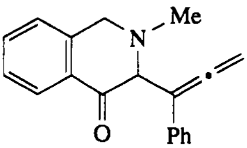 | | | | 86 |
| 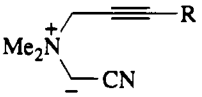 | 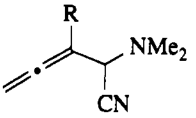 | R = H<br>R = Me | | | 50<br>54 |

reaction mixture. When the substituent at C-2 is an amino group, the allene (**400**) is the only isolable product. Its isomerization to the diene does not occur under the reaction conditions (Scheme 103, equation a). However, in the case of the sulfur ylides, the allene cannot be detected, even after a very short period of time (Scheme 103, equation b).[125]

Very few synthetic applications have appeared in this area, the most noteworthy being the extremely short synthesis of artemesia ketone (**408**) starting from the allyl sulfide (**404**; Scheme 104).[123] If an alkyne unit can replace a carbon–carbon double bond without apparent deleterious effect on the 3,2-rearrangement, so also can an allene unit. Dienes are then produced (Scheme 105).[126]

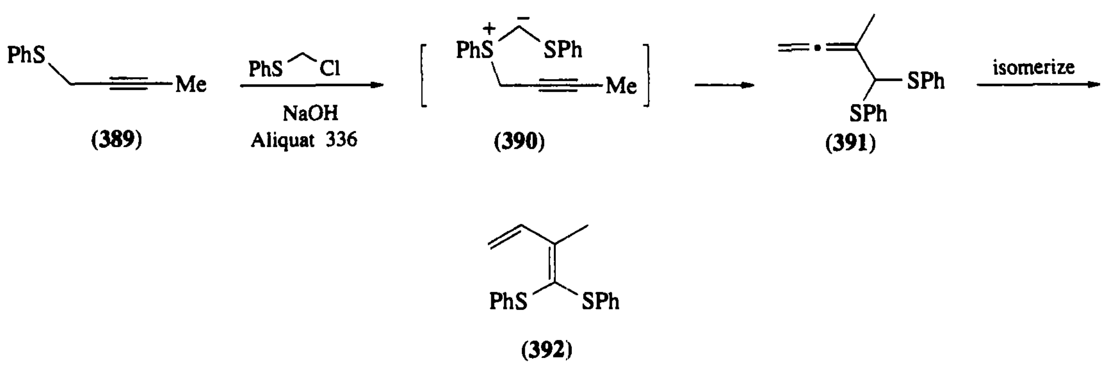
PhS
Me
(389)
PhS
Cl
NaOH
Aliquat 336
PhS
SPh
Me
(390)
SPh
SPh
(391)
isomerize
PhS
SPh
(392)

Scheme 100

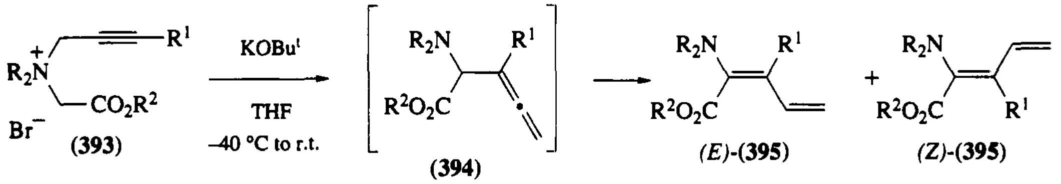
R¹
R₂N
CO₂R²
Br⁻
(393)
KOBuᵗ
THF
–40 °C to r.t.
R₂N
R¹
R²O₂C
(394)
R₂N
R¹
R²O₂C
(E)-(395)
+
R₂N
R²O₂C
R¹
(Z)-(395)

| *R, R* | *$R^1$* | *$R^2$* | *Yield (%)* | *(E)* | *(Z)* |
|---|---|---|---|---|---|
| Me, Me | H | Me | 87 | – | 100 |
| Me, Me | Me | Me | 80 | 55 | 45 |
| Me, Me | H | Et | 79 | – | 100 |
| Me, Me | Me | Et | 79 | 45 | 55 |
| $-(CH_2)_2O(CH_2)_2-$ | H | Me | 62 | – | 100 |
| $-(CH_2)_4-$ | H | Me | 48 | 85 | 15 |
| $-(CH_2)_4-$ | Me | Me | 57 | – | – |

Scheme 101

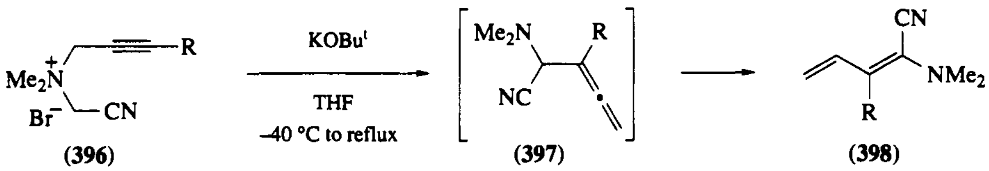
R
Me₂N
Br⁻
CN
(396)
KOBuᵗ
THF
–40 °C to reflux
Me₂N
R
NC
(397)
CN
NMe₂
R
(398)

| *R* | *Yield (%)* | *(E)* | *(Z)* |
|---|---|---|---|
| H | 60 | 100 | 0 |
| Me | 64 | 25 | 75 |

Scheme 102

### 3.10.5.9 Sommelet–Hauser Rearrangement

In 1930, Ingold and Jessop reported the rearrangement of the fluorenyl ylide (**412**).[127] Compound (**414**) was obtained in what can be considered as the first example of a Sommelet–Hauser reaction (Scheme 106). In 1937, Sommelet described the base-catalyzed transformation of the benzhydryl ammonium bromide (**415**) into the substituted benzylic amine (**416**; Scheme 107, equation a).[11] Wittig found later that reacting the salt (**417**) with phenyllithium produced two amines, (**418**) and (**419**).[13] The former is derived from a Sommelet–Hauser 3,2-rearrangement, whereas the latter comes from a Stevens

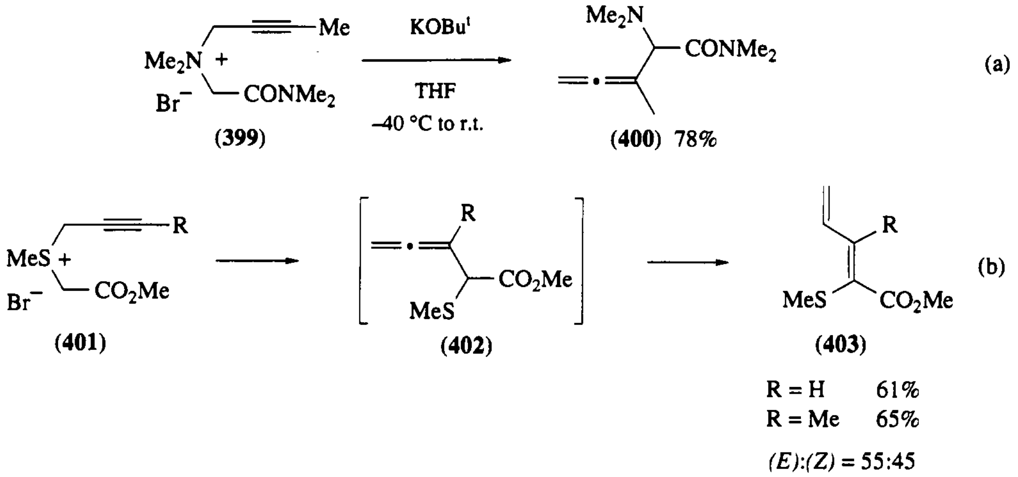
Me
Me$_2$N +
Br$^-$
CONMe$_2$
(399)
KOBu$^t$
THF
–40 °C to r.t.
Me$_2$N
CONMe$_2$
(400) 78%
(a)
R
MeS +
Br$^-$
CO$_2$Me
(401)
R
CO$_2$Me
MeS
(402)
R
MeS
CO$_2$Me
(403)
(b)
R = H 61%
R = Me 65%
*(E)*:*(Z)* = 55:45

Scheme 103

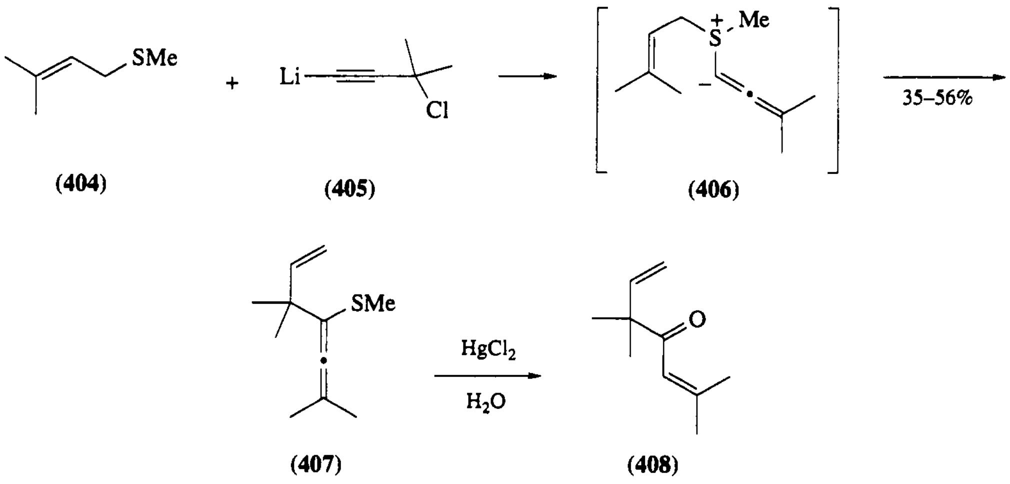
SMe
(404)
+
Li
Cl
(405)
+ Me
S
–
(406)
35–56%
SMe
(407)
HgCl$_2$
H$_2$O
O
(408)

Scheme 104

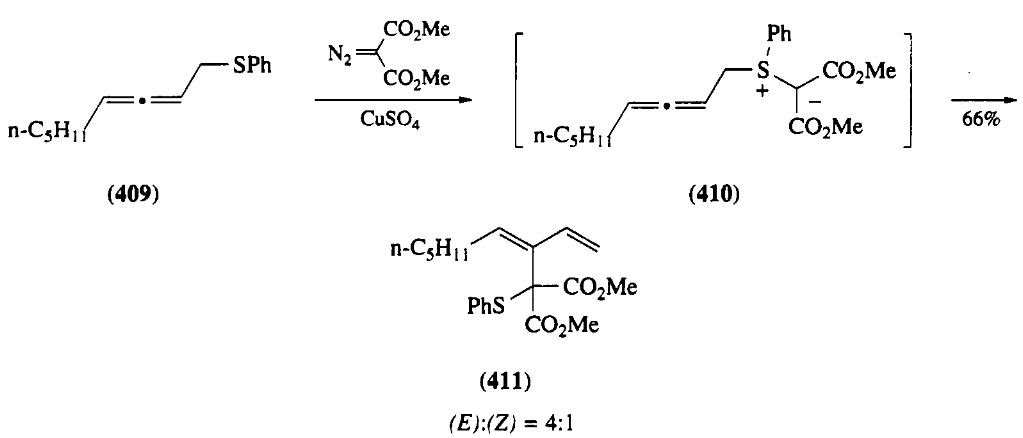
n-C$_5$H$_{11}$
SPh
(409)
CO$_2$Me
N$_2$
CO$_2$Me
CuSO$_4$
Ph
S
+
CO$_2$Me
–
CO$_2$Me
n-C$_5$H$_{11}$
(410)
66%
n-C$_5$H$_{11}$
PhS
CO$_2$Me
CO$_2$Me
(411)
*(E)*:*(Z)* = 4:1

Scheme 105

1,2-rearrangement (Scheme 107, equation b). The Stevens rearrangement often competes with the Sommelet–Hauser rearrangement. However, in protic solvents, Sommelet–Hauser rearrangements usually predominate.

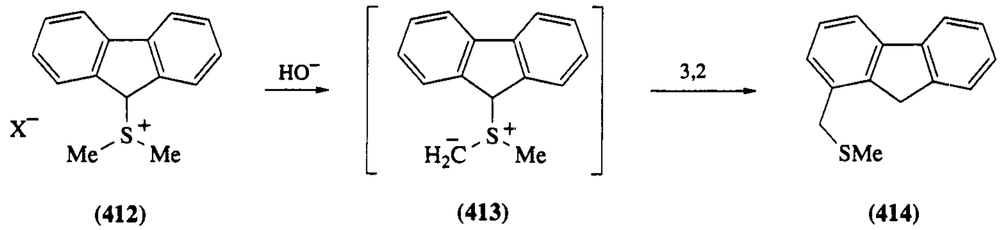
X⁻
Me S+ Me
HO⁻
H₂C S+ Me
3,2
SMe
(412)
(413)
(414)

Scheme 106

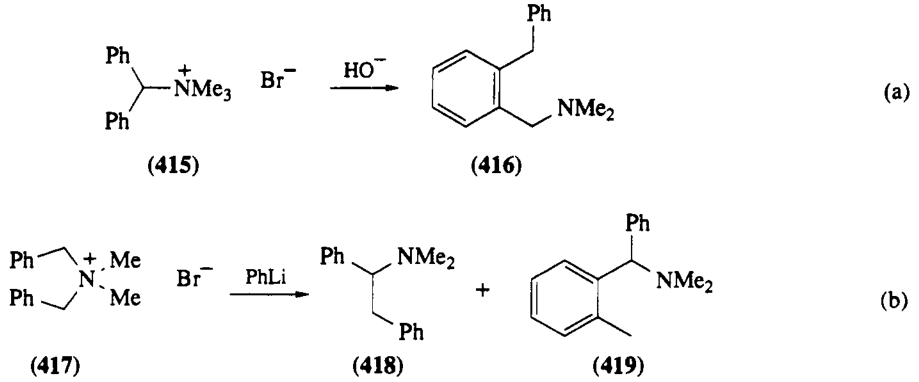
Ph
Ph
NMe₃
Br⁻
HO⁻
Ph
NMe₂
(a)
(415)
(416)
Ph
Ph
N
Me
Me
Br⁻
PhLi
Ph
NMe₂
Ph
+
Ph
NMe₂
(b)
(417)
(418)
(419)

Scheme 107

Initial work on the Sommelet–Hauser rearrangement was mechanistically inspired. Hauser and Kantor provided a major contribution to the understanding of this transformation.[14] They showed that two ylides were involved in the rearrangement. The more stable ylide (**421**) is initially generated but equilibrates with the less stabilized one (**422**). The latter ylide then undergoes a concerted, symmetry-allowed 3,2-sigmatropic shift, giving the triene (**423**). Aromatization finally affords the *ortho*-substituted benzylic amine (**424**; Scheme 108).

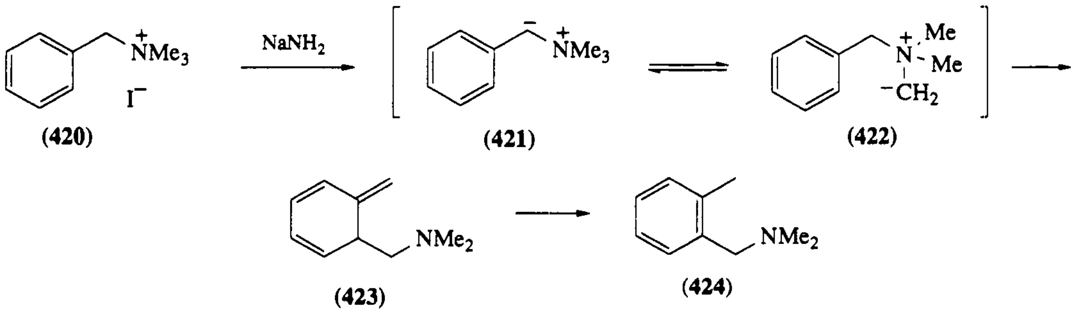
NMe₃
I⁻
NaNH₂
NMe₃
N
Me
Me
CH₂
(420)
(421)
(422)
NMe₂
NMe₂
(423)
(424)

Scheme 108

Similar rearrangements also occur in the case of sulfur analogs. Since the product of a Sommelet–Hauser rearrangement is a benzylic tertiary amine (or sulfide), just as the starting material was a benzylic amine (or sulfide), the process can be repeated and is a unique method to move substituents around the periphery of aromatic rings (Scheme 109).

Several limitations of this base-promoted rearrangement are worthy of mentioning: (a) when structurally feasible, both Stevens and Sommelet–Hauser reactions will compete; (b) certain substituents on the aromatic ring, *e.g.* Cl, CN, $NO_2$, prevent the formation of the ylide and no rearrangement takes place; (c) if a β-hydrogen is present on the ammonium salt, elimination becomes yet another undesirable side reaction. In an attempt to overcome these limitations, Sato has utilized the fluoride-induced desilylation of

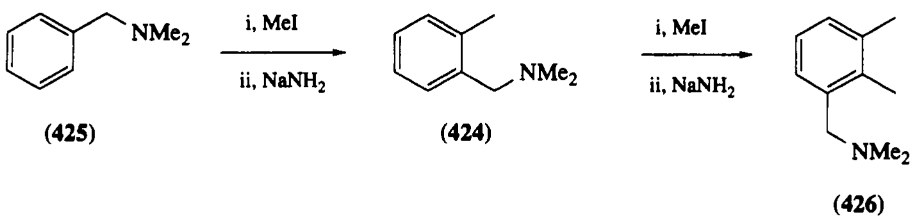
NMe₂
i, MeI
ii, NaNH₂
NMe₂
i, MeI
ii, NaNH₂
NMe₂
(425)
(424)
(426)

**Scheme 109**

triorganosilylmethyl ammonium salts (**427**).[128] This provided a new route for effecting the Sommelet-Hauser rearrangement under non-basic conditions (Table 6). Remarkably, the Stevens product was obtained in small amounts in most cases, except when strong electron-withdrawing groups (COR, NO$_2$, CN) were present on the aromatic substituent. Sato also found that, under the fluoride-induced desilylation conditions, minimum competitive Hoffmann elimination was observed (Table 7).[129] The lack of elimination products can be rationalized by the absence of ylide equilibration under fluoride-induced Sommelet–Hauser reaction conditions as compared with the base-promoted rearrangement. Desilylation affords ylide (**435**) which undergoes the 3,2-sigmatropic rearrangement faster than equilibration with the other ylides (**434**) and (**436**; Scheme 110).

**Table 6**

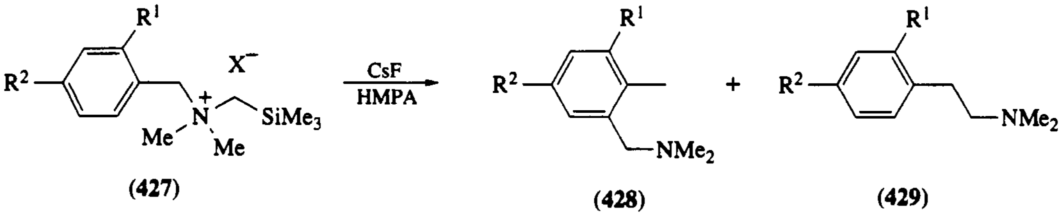
R¹
R²
X⁻
N
SiMe₃
Me
Me
CsF
HMPA
R¹
R²
NMe₂
+
R¹
R²
NMe₂
(427)
(428)
(429)

| *Entry* | *R*$^1$ | *R*$^2$ | *Yield (%)* | *(428):(429)* |
|---|---|---|---|---|
| 1 | H | H | 84 | 97:3 |
| 2 | Me | H | 84 | 96:4 |
| 3 | H | Me | 77 | 96:4 |
| 4 | H | OAc | 72 | 99:1 |
| 5 | Cl | H | 69 | 94:6 |
| 6 | H | Cl | 84 | >99:<1 |
| 7 | CoMe | H | 54 | 42:58 |
| 8 | No$_2$ | H | 80 | <1:>99 |

**Table 7**

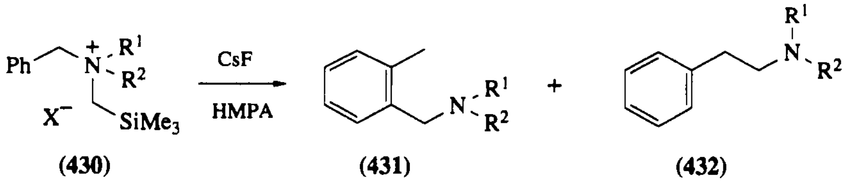
Ph
N
R¹
R²
X⁻
SiMe₃
CsF
HMPA
N
R¹
R²
+
R¹
N
R²
(430)
(431)
(432)

| *Entry* | *R*$^1$ | *R*$^2$ | *(431):(432)* |
|---|---|---|---|
| 1 | Me | Et | 97:3 |
| 2 | Pr$^i$ | Me | 93:7 |
| 3 | Bu$^t$ | Me | 65:35 |
| 4 | Cyclohexyl | Me | 89:11 |
| 5 | Et | Et | 91:9 |
| 6 | —(CH$_2$)$_4$— | | 98:2 |
| 7 | —(CH$_2$)$_5$— | | 97:3 |

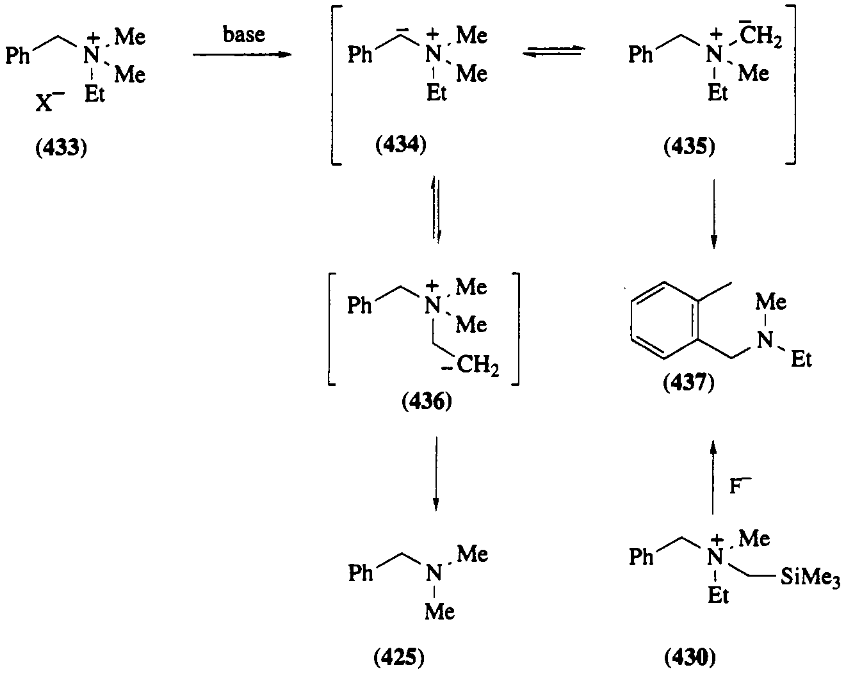

Scheme 110

The Sommelet–Hauser rearrangement has been mostly employed for aromatic functionalization and ring expansion. Julia for example has reported an elegant formylation using a sulfonium ylide rearrangement (Scheme 111).[130] The reaction provides an easy entry into orthoformylation of aromatics. It is interesting to note that alkylation of the thioacetal (**432**) followed by hydrolysis could lead to ketone preparation. Gassman has used a similar approach to formylate aniline derivatives (Scheme 112, equation a),[131] and has extended his method to the useful preparation of substituted oxindoles (Scheme 112, equation b).[132] Gammill, in his synthetic approach towards khellin, used the sulfonium ylide 3,2-sigmatropic rearrangement to transfer functionality from C-6 to C-7 in the key intermediate (**441**; Scheme 113).[133] Warpehoski employed Gassman's procedure as an important step in his synthetic route towards the indole alkaloid CC-1065 (Scheme 114).[134]

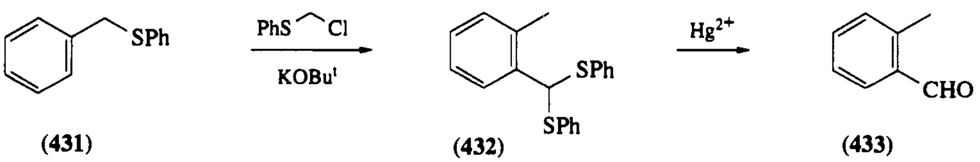

Scheme 111

Aromatic functionalization coupled with ring expansion has also been applied to produce macrocyclic amines. Lednicer and Hauser for example reported the Sommelet–Hauser rearrangement of ammonium salt (**336**) to give the macrocycle (**337**; Scheme 89).[108] Sato reinvestigated this reaction and was able, using his silicon methodology, to isolate the intermediate triene (**446**).[135] Surprisingly enough, compound (**446**) is fairly stable and can be stored for several weeks. It reacts readily with dienophiles to provide interesting adducts (Scheme 115).

Finally, attempts have been made to induce asymmetry in the Sommelet–Hauser rearrangement, but with limited success. Campbell rearranged the optically active sulfonium salt (**449**) and obtained a mixture of the two Sommelet–Hauser products (**450**) and (**451**).[136] The chiral product (**451**) displayed only low optical activity (Scheme 116).

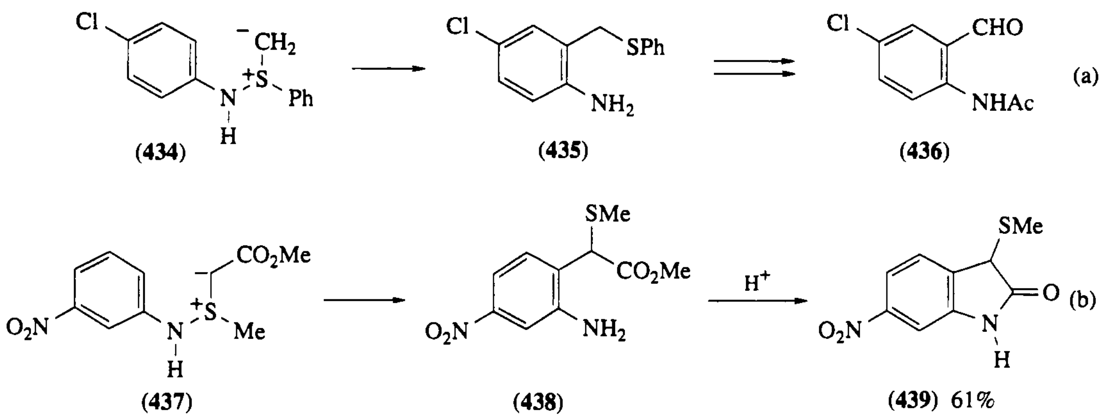
(434)
(435)
(436)
(a)
(437)
(438)
H+
(439) 61%
(b)

Scheme 112

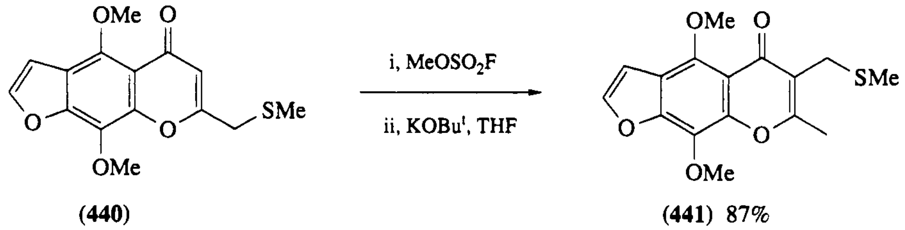
i, MeOSO2F
ii, KOBut, THF
(440)
(441) 87%

Scheme 113

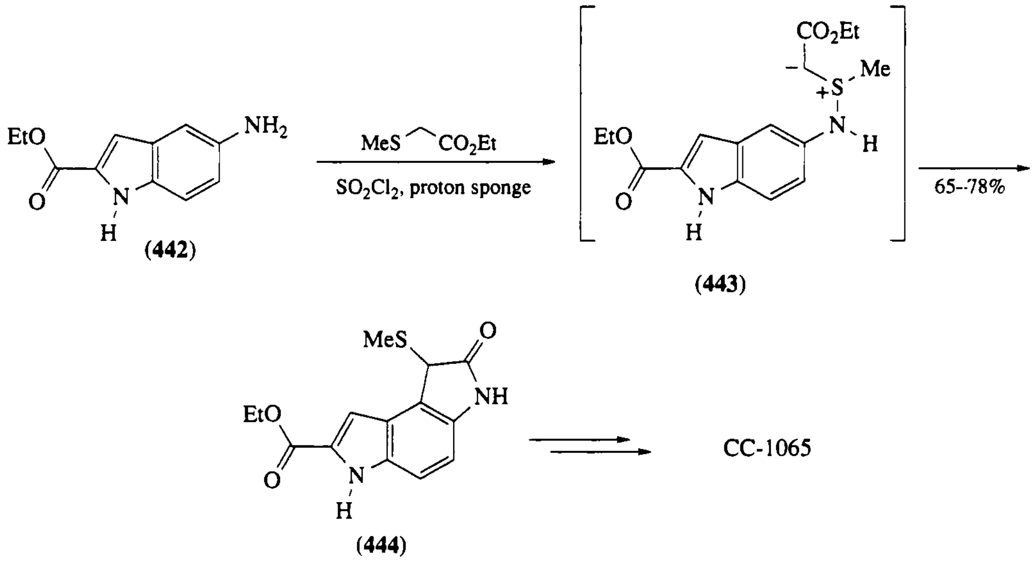
MeS CO2Et
SO2Cl2, proton sponge
(442)
(443)
65–78%
(444)
CC-1065

Scheme 114

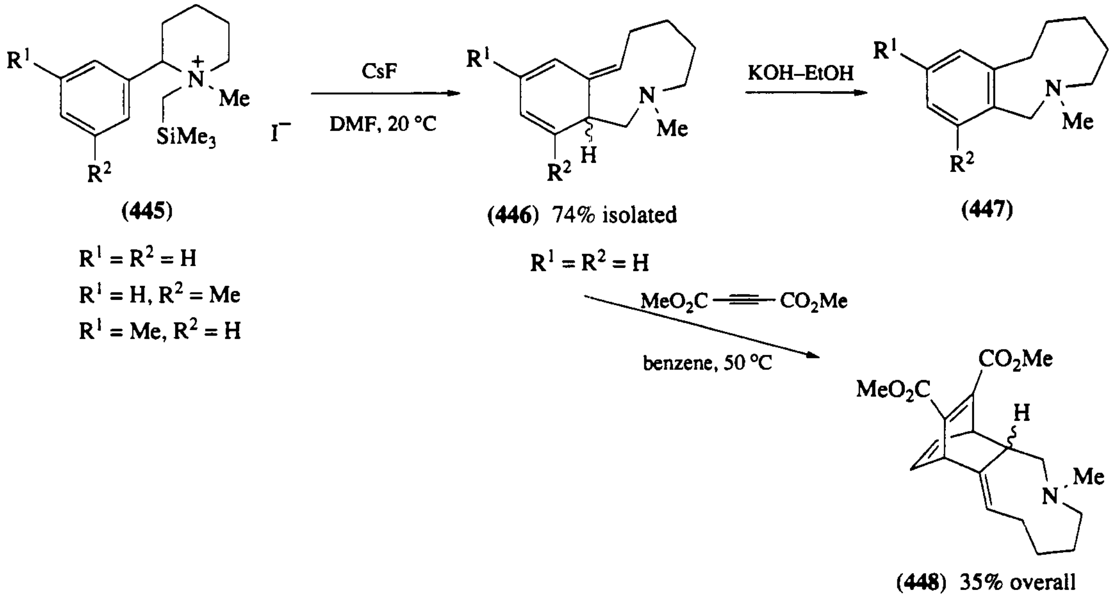

**Scheme 115**

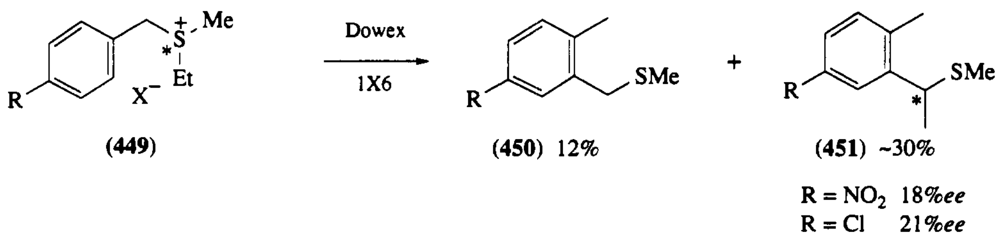

**Scheme 116**

## 3.10.6 CONCLUSIONS

Enormous progress has been realized in the last two decades both in the preparation of ylidic intermediates and in the mechanistic understanding of ylidic sigmatropic rearrangements. The Stevens 1,2-sigmatropic rearrangement has been shown to proceed *via* radical pair intermediates, whereas the 3,2-sigmatropic rearrangements have been demonstrated to be concerted processes. Unfortunately, competition between these and other related rearrangements often takes place, and this has always placed a severe limitation on the use of ylidic rearrangements in synthesis. However, as a result of contemporary mechanistic insights, suitable experimental conditions have been defined that allow one of these processes to predominate largely, if not solely, over the other one. The 3,2-sigmatropic rearrangement of ylidic intermediates has been shown to be a particularly efficient and versatile synthetic tool, mainly because of the remarkable contributions by Vedejs and his group. In sharp contrast, the Stevens 1,2-sigmatropic rearrangement has, so far, led to very few synthetic applications.

## ACKNOWLEDGEMENTS

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# 3.11

# The Wittig Rearrangement

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## 3.11.1 INTRODUCTION

### 3.11.1.1 Historical Development

In 1942 Wittig and Löhmann described the isomerization of α-lithiated ethers (**2**; R = Me or $CH_2Ph$) to skeletally rearranged lithio alkoxides (**3**; equation 1).[1] Subsequent work by Wittig and others established that a variety of ethers undergo the Wittig rearrangement, provided the α-anion is stabilized by an aryl substituent. Of the several mechanisms proposed for this reaction a sequence involving homolysis of the anion intermediate (**5**), followed by recombination of the radical and radical anion fragments (equation 2) best accommodates the experimental findings.[1–4]

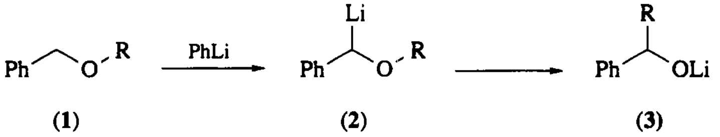

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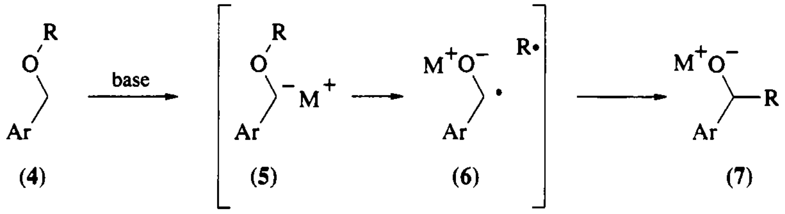
R
O
Ar
base
R
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$^-$M$^+$
Ar
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Ar
M$^+$O$^-$
R
Ar

**(4)** **(5)** **(6)** **(7)** (2)

Hauser noted that diallyl ether (**8**) also undergoes Wittig rearrangement upon base treatment and suggested that product formation could involve either a 1,2-shift or a 'cyclic mechanism' (equation 3).[2] Later studies by Schöllkopf[5] and Makisumi[6] with substituted allylic ethers (**10**, **11** and **14**–**16**; equations 4 and 5) pointed to a cyclic ($S_Ni'$) mechanism; a process allowed by the Woodward–Hoffmann rules.[7] The diastereoselectivity of the reaction was not determined in these cases, but Schöllkopf subsequently found that benzyl *trans*-crotyl ether (**20**; equation 6) affords mainly the *anti* products upon rearrangement of ether (**20**) with BuLi in THF.[8] Rautenstrauch observed a 1:1 mixture of *syn* and *anti* products upon rearrangement of ether (**20**) in the presence of TMEDA, whereas the *cis* isomer (**23**) gave only the *syn* product (**22**; equation 7).[9]

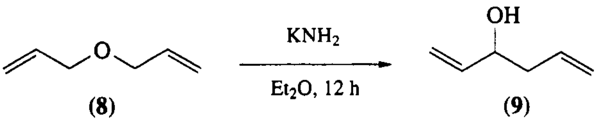
O
$KNH_2$
$Et_2O$, 12 h
OH

**(8)** **(9)** (3)

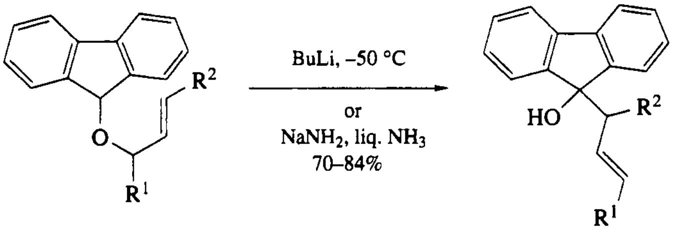
R$^2$
O
R$^1$
BuLi, –50 °C
or
$NaNH_2$, liq. $NH_3$
70–84%
HO
R$^2$
R$^1$

(4)

**(10)** R$^1$ = Me, R$^2$ = H

**(11)** R$^1$ = H, R$^2$ = Me

**(12)** R$^1$ = Me, R$^2$ = H >99% *(E)*

**(13)** R$^1$ = H, R$^2$ = Me

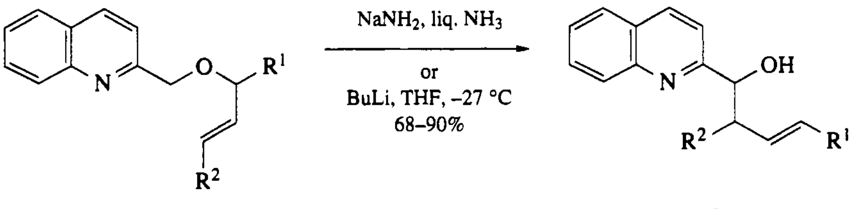
N
O
R$^1$
R$^2$
$NaNH_2$, liq. $NH_3$
or
BuLi, THF, –27 °C
68–90%
N
OH
R$^2$
R$^1$

(5)

**(14)** R$^1$ = R$^2$ = H

**(15)** R$^1$ = H, R$^2$ = Me

**(16)** R$^1$ = Me, R$^2$ = H

**(17)** R$^1$ = R$^2$ = H

**(18)** R$^1$ = H, R$^2$ = Me

**(19)** R$^1$ = Me, R$^2$ = H

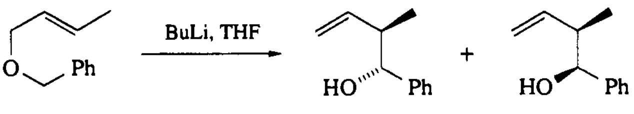
O
Ph
BuLi, THF
HO
Ph
+
HO
Ph

(6)

**(20)** **(21)** 66% **(22)** 33%

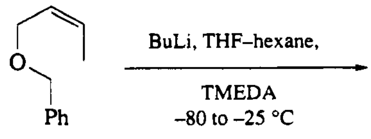
O
Ph
BuLi, THF–hexane,
TMEDA
–80 to –25 °C

**(21)** 0% **(22)** 100% (7)

**(23)**

### 3.11.1.2 Rearrangement Pathways

Rearrangements of allylic ethers can follow several pathways (Scheme 1). The 2,3- and 1,4-routes are symmetry allowed concerted processes, whereas the 1,2- and 3,4-rearrangements proceed in a stepwise manner through radical dissociation and recombination (equation 2). In fact, all four pathways have been experimentally observed with bis-γ,γ-(dimethyl)allyl ether (**24**; equation 8).[9] Anions derived from allyl vinylcyclopropylmethyl ethers (*e.g.* **i**) rearrange by competing, 1,2, 1,4, homo-2,5, homo-4,5 and radical dissociation–recombination pathways.[9a] Nakai has shown that 1,4-rearrangement proceeds with retention of stereochemistry in the cyclohexenyl system (**29**; equation 9), as required by orbital symmetry considerations.[10]

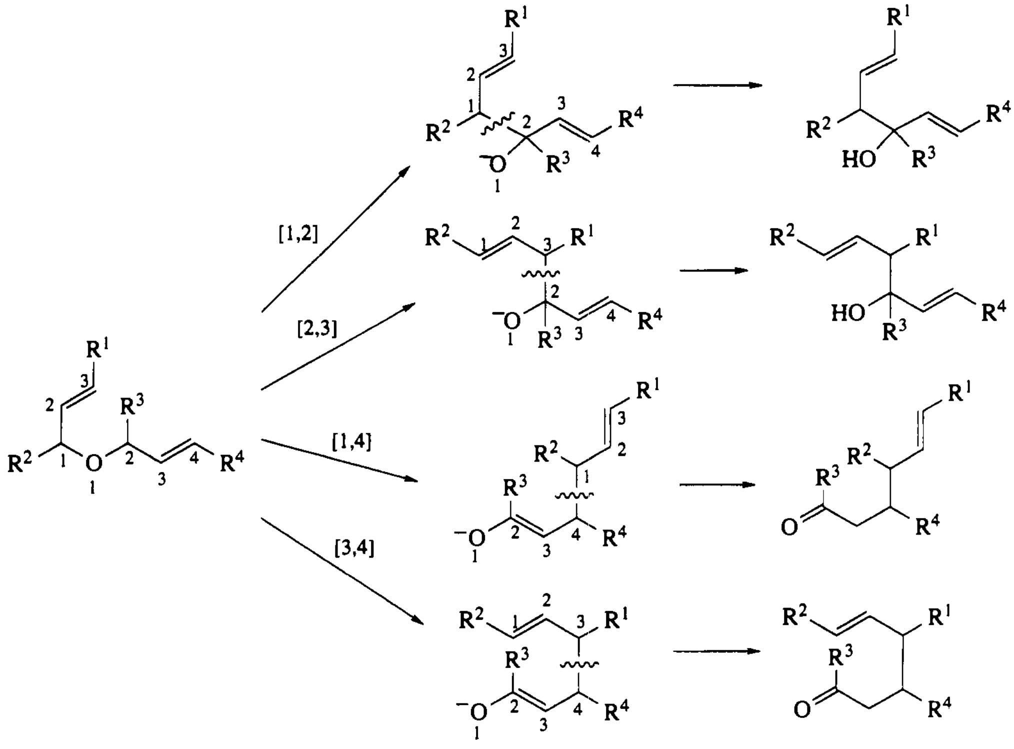

**Scheme 1** Rearrangement pathways for allylic ether anions

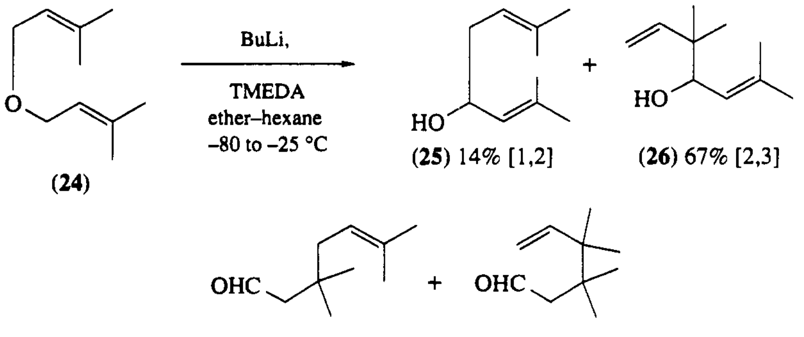

**(24)** **(25)** 14% [1,2] **(26)** 67% [2,3] **(27)** 8% [1,4] **(28)** 10% [3,4]

(8)

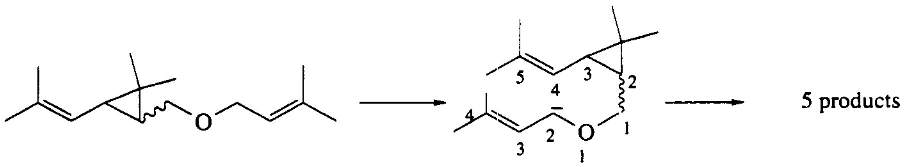

**(i)** **(ii)**

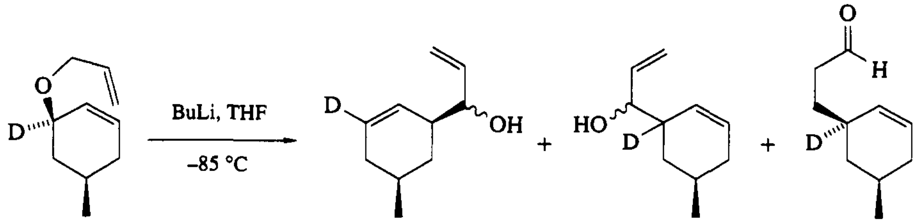

(9)

**(29)** **(30)** 41% [2,3] **(31)** 20% [1,2] **(32)** 14% [1,4]

### 3.11.1.3 Heterologs

Sulfides undergo 2,3-Wittig rearrangement, but at a slower rate than their oxygen counterparts (equation 10). This rate retardation has been attributed to a decrease in the energy of the anion HOMO as a consequence of the greater stabilizing influence of sulfur.[7c] Snider prepared the α-thiomethylcyanomethyl sulfides (**36**) through ene reaction of alkenes with methyl cyanodithioformate, and observed facile 2,3-rearrangement upon treatment with BuLi or LDA in THF–HMPA (equation 11).[11] In the absence of HMPA the α-cyano anions are stable and can be readily C-methylated with iodomethane. Representative examples are shown in Table 1.

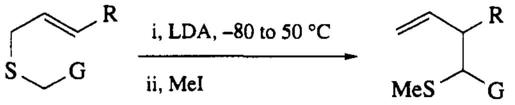

(10)

**(33)** **(34)**

G = Ph, $CO_2Li$, CN, $CO_2Et$, COMe; R = Ph, H, Me

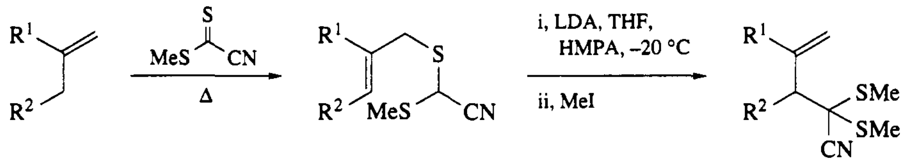

(11)

**(35)** **(36)** **(37)**

**Table 1** Formation and 2,3-Rearrangement of Sulfides

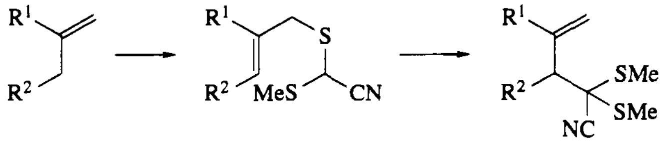

**(35)** **(36)** **(37)**

| *Alkene (35)* | *R*¹ | *R*² | *Yield (%)* (36) | (37) |
|---|---|---|---|---|
| (**35a**) | Et | Me | 72 | 86 |
| (**35b**) | H | Pr | 43 | 56 |
| (**35c**) | $(CH_2)_4$ | | 76 | 70 |
| (**35d**) | a | | 22 | 77 |
| (**35e**) | 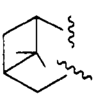 | | 83 | 72 |

[a] $(CH_2)_2CH(CH_2OCO_2Me)CH_2$.

The amine α-anions (**38a–c**) failed to rearrange under conditions employed for the analogous ethers.[2] The corresponding ammonium salts, on the other hand, readily isomerize *via* the derived ylides (Stevens rearrangement) in a process analogous to the 1,2-Wittig rearrangement.[12]

The *N*-benzyl β-lactams (**39**) and (**40**) undergo facile rearrangement upon base treatment.[13] In the former case only the 2,3-product (**41**) is observed, whereas the latter affords a mixture of 2,3- and 1,2-products (**42**) and (**44**; equation 12). The methyl substituent of (**40**) evidently facilitates homolysis of the intermediate benzylic anion. The phenyl-substituted β-lactams (**45**) and (**46**) yield the 1,2-rearrangement products (**47**) and (**48**) exclusively under comparable conditions (equation 13). These rearrangements undoubtedly derive considerable driving force from relief of ring strain. Thus *N*,*N*-allylbenzylbenzamide, an acyclic counterpart of lactam (**39**), is recovered unchanged upon exposure to strong base.

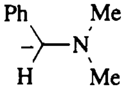

**(38a)**

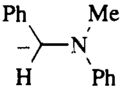

**(38b)**

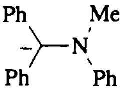

**(38c)**

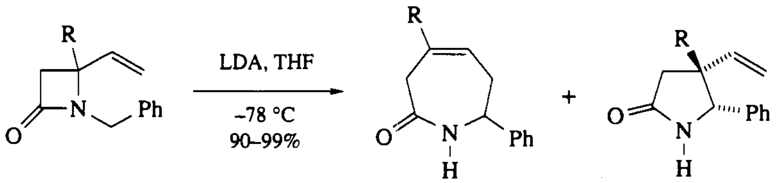

(12)

(**39**) R = H
(**40**) R = Me

(**41**) R = H; 100%
(**42**) R = Me; 60%

(**43**) R = H; 0%
(**44**) R = Me; 40%

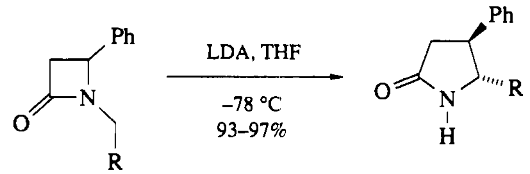

(13)

(**45**) R = Ph
(**46**) R = CH=CH$_2$

(**47**) R = Ph
(**48**) R = CH=CH$_2$

## 3.11.2 1,2-REARRANGEMENTS

Early work on the 1,2-Wittig rearrangement was mechanistically inspired. As indicated in Table 2, yields of products tended to be moderate and harsh conditions were often employed. The effects of structural variation on reaction rates and product composition can be accommodated by a pathway involving homolysis of an α-anion intermediate and recombination of the radical and radical anion fragments (equation 2). In a more recent study, Schöllkopf found that the optically active benzyl ethers (**51**) and (**52**) afford the alcohols (**53**) and (**54**) of predominately retained configuration in 20% and 80% enantiomeric excess (equation 14). This finding further supports a dissociative mechanism.[4] A concerted one-step rearrangement should proceed with inversion of the migrating center according to orbital symmetry considerations.

In the first purely synthetic application of the reaction, Schreiber employed the 1,2-Wittig rearrangement to synthesize 1,3-diol monoethers (equation 15).[14] The *syn* products (**56**) were obtained in 14–32% yield with 90–95% diastereoselectivity (Table 3). The 1,4-product (**57**) was found to predominate at low temperature, whereas at 0 °C the 1,2-product was favored but the absolute yield did not increase.

The nonracemic secondary ethers (**58**) and (**60**) rearrange with over 90% retention of stereochemistry at the migrating center (equations 16 and 17). A lithium-bridged diradical species (**63**; Scheme 2) is postulated to account for the observed diastereoselectivity. Recombination of the radical pair must occur more rapidly than inversion of the radical center, judging from the high degree of retention observed with (**58**) and (**60**). A two-directional application of this rearrangement was used to prepare the *syn*-skipped polyols (**66**) and (**68**; Scheme 3).

**Table 2** 1,2-Wittig Rearrangement of Benzyl Ethers

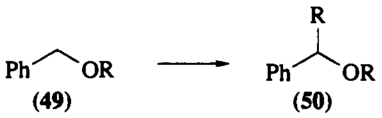
Ph
OR
(49)
R
Ph
OR
(50)

| *R* | *Conditions* | *Time* (h) | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| $PhCH_2$ | a | 15 | 61–67 | 2 |
| $CH_2{=}CHCH_2$ | a | 15 | 65 (mixture) | 2 |
| $Bu^s$ | a | 140 | 27 | 2 |
| Ph | a | 18 | 0 (recovered ether) | 2 |
| Et | a | 19 | 0 (40% $PhCH_2OH$) | 2 |
| $CH_2{=}CH(CH_2)_2$ | b | 24 | 67 | 3 |
| c-$C_4H_7$ | b | 24 | 68 | 3 |
| $Bu^t$ | c | 48 | 50 | 3 |
| 1-Adamantyl | c | 48 | 54 | 3 |

[a] 2KNH$_2$, Et$_2$O, reflux. [b] 2MeLi, THF, r.t. [c] 5MeLi, THF, r.t.

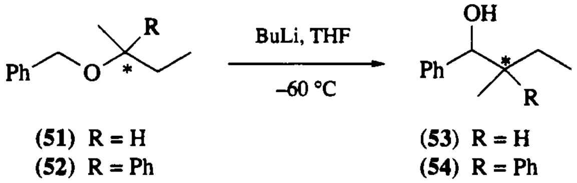
Ph
O
*
R
BuLi, THF
–60 °C
OH
Ph
*
R
(51) R = H
(52) R = Ph
(53) R = H
(54) R = Ph

(14)

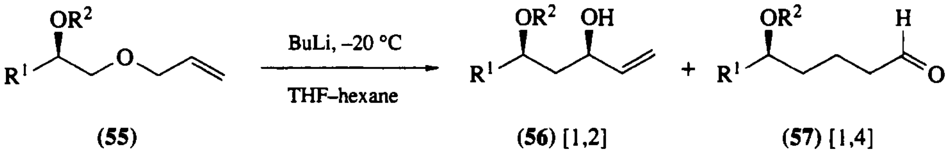
OR2
R1
O
(55)
BuLi, –20 °C
THF–hexane
OR2
OH
R1
(56) [1,2]
+
OR2
H
R1
O
(57) [1,4]

(15)

**Table 3** 1,2-Wittig Rearrangement of Glyceryl Allyl Ethers

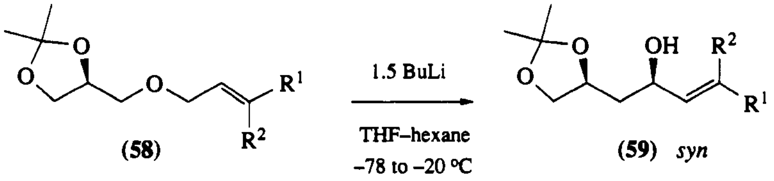
O
O
O
R1
R2
(58)
1.5 BuLi
THF–hexane
–78 to –20 °C
O
O
OH
R2
R1
(59) syn

| *R*$^1$ | *R*$^2$ | *Syn/anti* | *Yield* (%) |
|---|---|---|---|
| H | H | 92:8 | 32 |
| Me | H | 91:9 | 30 |
| Ph | H | 90:10 | 25 |
| Me | Me | 90:10 | 14 |

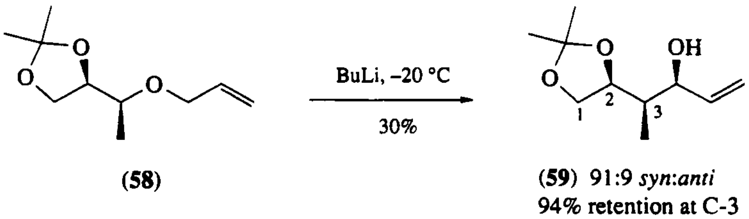
O
O
O
(58)
BuLi, –20 °C
30%
O
O
OH
1
2
3
(59) 91:9 syn:anti
94% retention at C-3

(16)

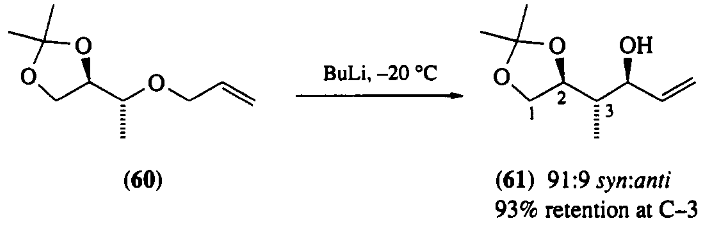
BuLi, –20 °C
OH
1
2
3
(60)
(61) 91:9 syn:anti
93% retention at C-3

(17)

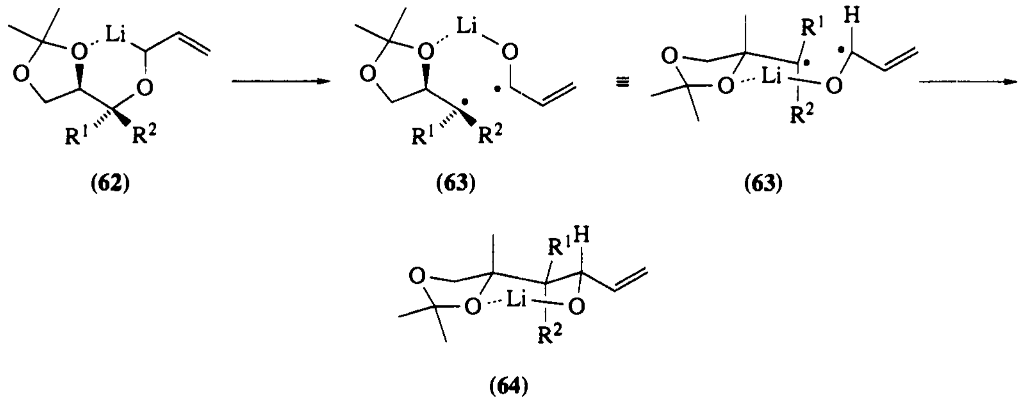
Li
R1
R2
(62)
(63)
(63)
H
(64)

**Scheme 2** Chelation-controlled 1,2-rearrangement of glyceryl allyl ethers

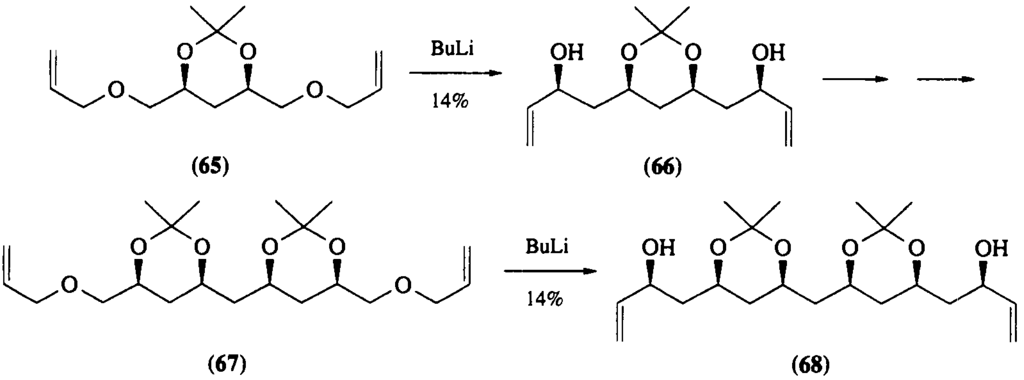
BuLi
14%
OH
(65)
(66)
(67)
(68)

**Scheme 3**

## 3.11.3 2,3-REARRANGEMENTS

### 3.11.3.1 Overview

The 2,3-Wittig rearrangement (equation 18) proceeds under milder conditions and gives higher yields of products than its 1,2-counterpart. Furthermore, a greater degree of structural variation is possible in the starting ether. For these reasons, the 2,3-rearrangement offers considerable promise as a synthetic method. The reaction effects an interchange of $sp^2$ and $sp^3$ stereochemistry such that both (*E*)/(*Z*) and *syn*/*anti* isomerism are possible in appropriately substituted systems. Furthermore, in nonracemic ethers

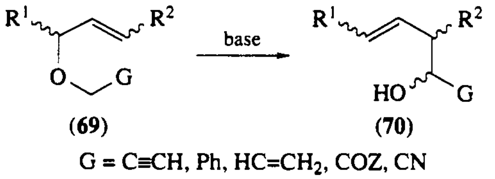
R1
R2
base
G
HO
(69)
(70)

(18)

G = C≡CH, Ph, HC=CH$_2$, COZ, CN

the concerted nature of the rearrangement allows for control of absolute stereochemistry. In most applications, various functional groups (G) are employed to promote formation of the intermediate anion. In principle, propargylic ethers could undergo 2,3-rearrangement analogously leading to allenes (equation 19). In practice such rearrangements have infrequently been observed.

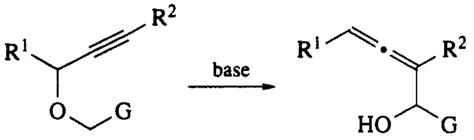

(71) (72) (19)

### 3.11.3.2 2,3-Rearrangements of Allyl Lithiomethyl Ethers

A unique variant of the 2,3-Wittig rearrangement employs an unstabilized lithiomethyl allylic ether generated *in situ* through lithiation of a (trialkylstannyl)methyl allylic ether (equation 20). This version, first introduced by Still,[15] has proven exceedingly useful owing to its efficiency and potential for high stereoselectivity. Applications to acyclic systems are summarized in Table 4. The rearrangement proceeds under mild conditions to give high yields of products. Interestingly, the stereochemistry of the rearranged double bond depends upon the substitution pattern of the allylic ether. In rearrangements of secondary allylic ethers R$^2$-substituents favor (*Z*)-products (**76**) whereas R$^4$-substituents are highly (*E*)-directing. These trends are accommodated by the envelope transition states (**A**) and (**B**) in Scheme 4. Unfavorable steric interactions between R$^1$ and R$^2$ in (**A**) are alleviated in (**B**), thereby favoring formation of the (*Z*)-alkenic product. Transition state (**B**), on the other hand, imposes unfavorable 1,3-*syn* steric strain on substituents R$^1$ and R$^4$. This strain is lacking in (**A**). When 1,2- and 1,3-interactions are both present, or when they are both absent (R$^2$ = R$^3$ = R$^4$ = H), a mixture of (*Z*)- and (*E*)-rearranged products is obtained.

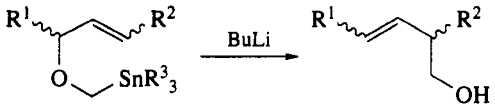

(73) (74) (20)

**Table 4** 2,3-Wittig Rearrangement of Lithiomethyl Allyl Ethers

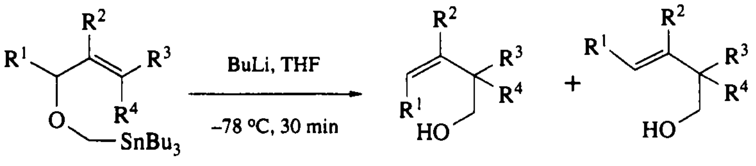

(75) (76) (*Z*) (77) (*E*)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *Yield* (%) | (*Z*):(*E*) |
|---|---|---|---|---|---|
| $n$-C$_7$H$_{15}$ | H | H | H | 95 | 60:40 |
| $n$-C$_7$H$_{15}$ | H | Me | H | 96 | 65:35 |
| $n$-C$_7$H$_{15}$ | H | H | Me | 91 | 0:100 |
| Bu$^n$ | Me | H | H | 95 | 97:3 |

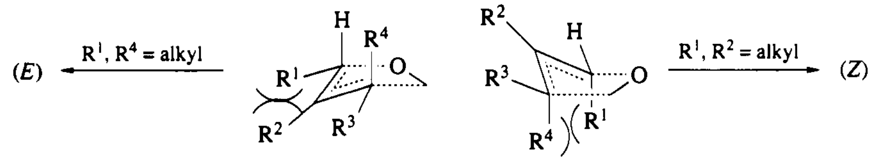

(**A**) (**B**)

**Scheme 4** Transition states for lithiomethyl allyl ether rearrangements

An additional example of such geometric control was recently observed by Midland and Kwon in the isomeric allylic ethers (**78**) and (**79**; equation 21).[16] The (*Z*)-isomer (**78**) gave the (*E*)-rearranged alcohol (**80**) exclusively, in accord with transition state (A), whereas the (*E*)-allylic ether (**79**) yielded a 53:47 mixture of (*E*)- and (*Z*)-products (**81**) and (**83**). In both cases rearrangement proceeded with retention of $sp^3$ stereochemistry, as expected for a concerted suprafacial process. In related work, 2,3-rearrangement of the steroidal (23*R*)-ether (**86**) afforded (25*R*)-26-hydroxycholesterol (**88**), an important intermediate in bile acid biosynthesis (Scheme 5). Again, the key rearrangement step proceeded with complete (>120:1) 1,3-*syn* stereoselectivity.[17] A similar application led to the 25,28-dihydroxylated ergosterol derivatives (**91**) and (**92**; equation 22).[18]

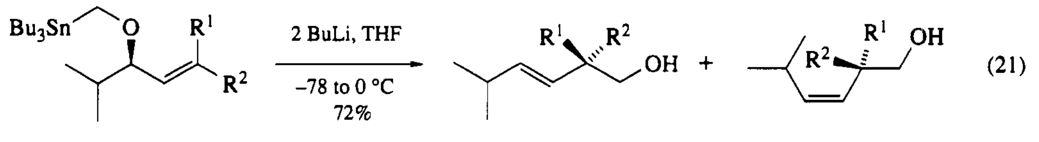
Bu$_3$Sn
O
R$^1$
R$^2$
2 BuLi, THF
–78 to 0 °C
72%
R$^1$
R$^2$
OH
+
R$^1$
OH
R$^2$
(21)

(**78**) $R^1 = Me, R^2 = H$

(**79**) $R^1 = H, R^2 = Me$

(**80**) $R^1 = Me, R^2 = H$ (100%)

(**81**) $R^1 = H, R^2 = Me$ (53%)

(**82**) $R^1 = Me, R^2 = H$ (0%)

(**83**) $R^1 = H, R^2 = Me$ (47%)

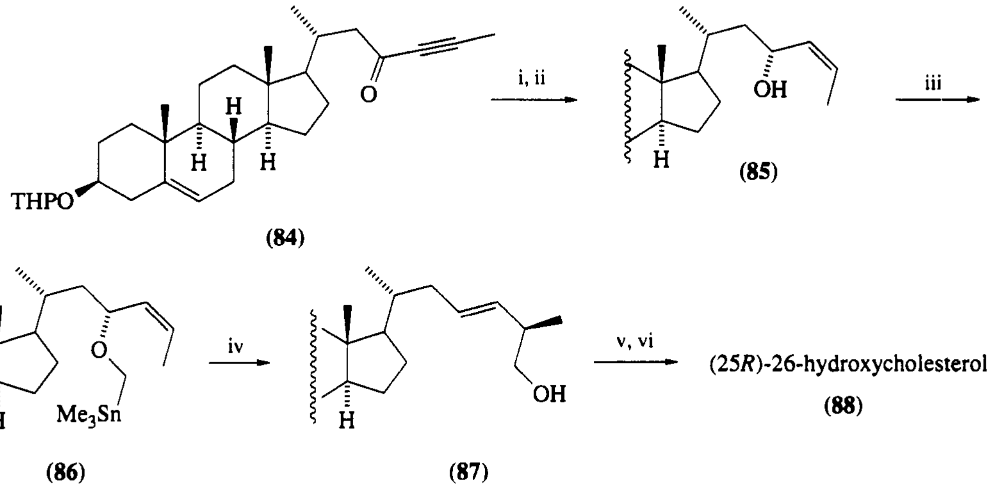
THPO
H
H
H
O
i, ii
OH
H
iii
O
Me$_3$Sn
H
iv
OH
H
v, vi
(25*R*)-26-hydroxycholesterol

(**84**) (**85**) (**86**) (**87**) (**88**)

i, (*R*)-alpine borane, 92%, 92% *ee*; ii, $H_2$, Lindlar catalyst; iii, NaH, $Me_3SnCH_2I$, 62%; iv, 2.3 BuLi, THF, –78 to 0 °C, 80%; v, $H_2$/Pd–C; vi, AcOH, $H_2O$, THF

**Scheme 5**

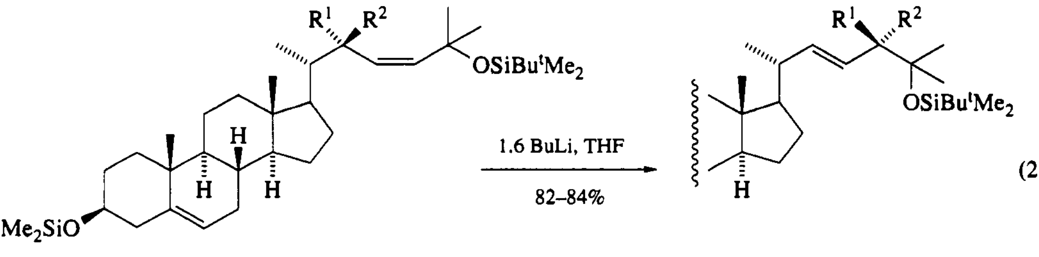
R$^1$
R$^2$
OSiBu$^t$Me$_2$
H
H
H
Bu$^t$Me$_2$SiO
1.6 BuLi, THF
82–84%
R$^1$
R$^2$
OSiBu$^t$Me$_2$
H
(22)

(**89**) $R^1 = H, R^2 = OCH_2SnMe_3$

(**90**) $R^1 = OCH_2SnMe_3, R^2 = H$

(**91**) $R^1 = H, R^2 = CH_2OH$

(**92**) $R^1 = CH_2OH, R^2 = H$

Still–Wittig rearrangement of the (*E*)- and (*Z*)-17-ethylidene-16α ethers (**93**) and (**94**) afforded the 20α- and 20β-methyl steroids (**95**) and (**96**) with complete stereochemical control (equation 23).[19] As in other examples, $sp^3$ stereochemistry depends upon double bond geometry in the starting allylic ether.

Still–Wittig rearrangements have been used to introduce an allylic hydroxymethyl substituent to a cyclohexene ring (equations 24 and 25).[20,21] These reactions proceed with retention of stereochemistry. Al-

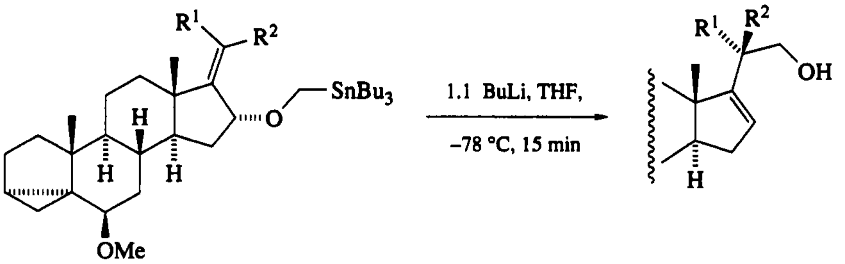

(23)

(93) $R^1$ = Me, $R^2$ = H

(94) $R^1$ = H, $R^2$ = Me

(95) $R^1$ = Me, $R^2$ = H (83%)

(96) $R^1$ = H, $R^2$ = Me (70%)

cohol (98) was employed in the total synthesis of (–)-punctatin A, a sesquiterpene antibiotic.[20] Alcohol (100) is a precursor of a synthetic intermediate for 1α, 25-dihydroxy vitamin $D_3$.[21]

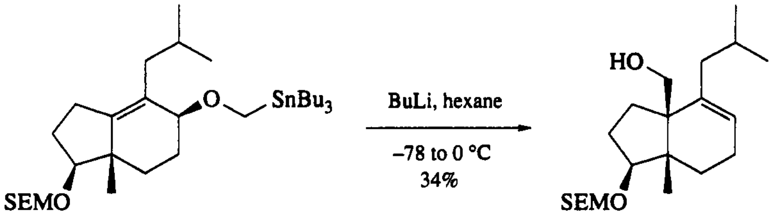

(97) (98)

(24)

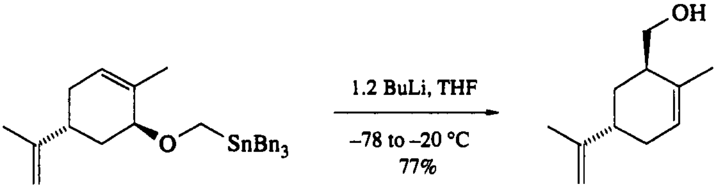

(99) (100)

(25)

Still–Wittig rearrangement of the nonracemic (*R*)-propargylic ethers (**100a**) and (**100b**) has been found to give the (*R*)-allenes (**100c**) and (**100d**) with complete asymmetric transfer (equation 25a).[21a] The stereochemistry is consistent with a five-membered cyclic transition state.

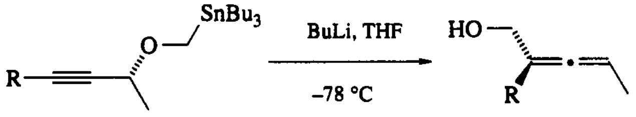

(25a)

(100a) R = Bu

(100b) R = $C_7H_{15}$

(100c) R = Bu

(100d) R = $C_7H_{15}$

### 3.11.3.3 2,3-Wittig Rearrangement of Allyl Propargyl Ethers

Allyl propargyl ethers are selectively deprotonated at the propargylic position to give anions which readily undergo 2,3-rearrangement. Typically *n*-butyllithium is employed as the base in THF or THF–hexane at –85 to 0 °C. In substituted allylic systems a high degree of diastereoselectivity is often seen, particularly with (*Z*)-allylic ethers (Table 5). In general, (*E*)-allylic ethers afford *anti* homoallylic alcohols (**102**), and (*Z*)-allylic ethers rearrange to *syn* homoallylic alcohols (**103**) as major 2,3-products. The TMS-propargyl (*E*)-allylic ethers (entries 3 and 4) are exceptional, giving rise to a predominance of *syn* products.[22,23] However, the TMS-propargyl (*Z*)-allylic ether (entry 12) behaves normally to give the rearranged *syn* alcohol.[22] When allylic substituents are present, as in (**101**; $R^1 \neq H$), (*E*)/(*Z*)-isomerism is possible in the rearranged products. The examples in Table 5 (entries 5–9 and 13–15) afford only the (*E*)-products within the limits of detection.

**Table 5** 2,3-Wittig Rearrangement of Allyl Propargyl Ethers

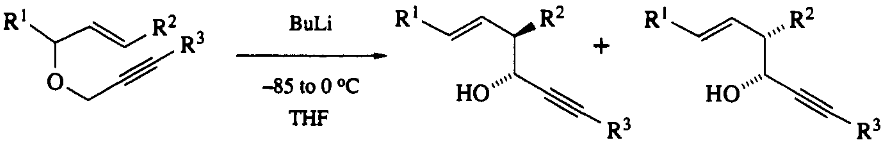

**(101)** *(E)* or *(Z)* **(102)** *anti* **(103)** *syn*

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *(E)/(Z)* | *Anti:syn* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | Me | H | (*E*) | 99:1 | 72 | 22 |
| 2 | H | Me | Me | (*E*) | 99:1 | 65 | 22 |
| 3 | H | Me | TMS | (*E*) | 27:73 | 72 | 22 |
| 4 | H | TMS | TMS | (*E*) | 3:97 | 91 | 23 |
| 5 | Me | Me | H | (*E*) | 91:9 | 62 | 22 |
| 6 | Me | Me | H | (*E*) | 88:12[a] | b | 22 |
| 7 | Me | TMS | TMS | (*E*) | 96:4 | 85 | 23 |
| 8 | Et | TMS | TMS | (*E*) | 97:3 | 80 | 23 |
| 9 | Bu | TMS | TMS | (*E*) | 89:11 | 61 | 23 |
| 10 | H | Me | H | (*Z*) | 10:90 | 56 | 22 |
| 11 | H | Me | Me | (*Z*) | 0:100 | 55 | 22 |
| 12 | H | Me | TMS | (*Z*) | 0:100 | 74 | 22 |
| 13 | Me | Me | TMS | (*Z*) | 1:99 | 64 | 22 |
| 14 | Me | Bu | TMS | (*Z*) | 1:99 | 96 | 24 |
| 15 | Bu$^i$ | Me | TMS | (*Z*) | 1:99 | b | 25 |
| 16 | H | OTBS | TMS | (*Z*)[c] | 98:2 | 79 | 25a |
| 17 | H | OTBS | TMS | (*Z*)[d] | 95:5 | 66 | 25a |

[a] 1:1 THF–hexane. [b] Not reported. [c] 65:35. [d] 95:5.

An envelope transition state in which the alkynyl grouping assumes an equatorial-like orientation has been proposed to accommodate these observations (Scheme 6).[26a] The orientation of R$^2$ is fixed by the (*E*)/(*Z*)-geometry of the starting allylic ether. When allylic (R$^1$) substituents are present they likewise adopt an equatorial position as in (**C**) and (**D**), thereby favoring the (*E*)-double bond geometry in the rearrangement product.[26b]

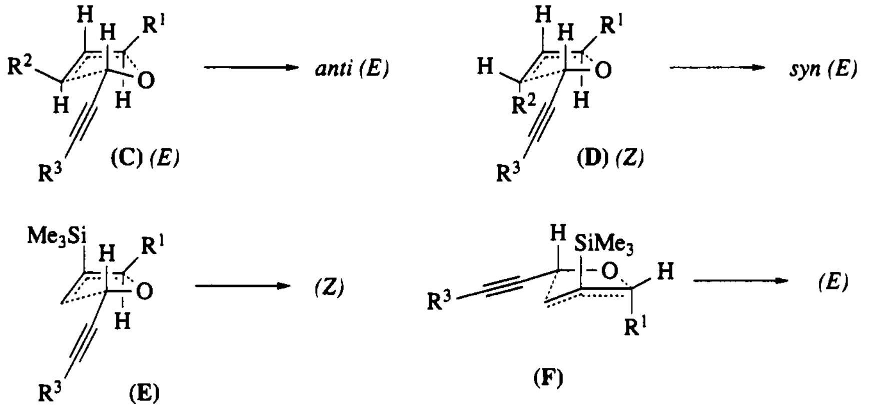

**Scheme 6** Envelope transition states for 2,3-Wittig rearrangements of propargyl allyl ethers

The TMS-propargyl ether (**104**) rearranges to an 80:20 mixture of the (*E*)- and (*Z*)-isomers (**106**) and (**108**) in an apparent violation of this transition state proposal (equation 26).[27] (Note that because of the stereochemical descriptor rules the sense of (*E*) and (*Z*) is inverted by the TMS substituent.) However, replacement of the vinylic TMS grouping by hydrogen led 'almost exclusively' to the (*E*)-product (**109**). Evidently, the normally favored transition state (**E**) is destabilized by steric interactions between the vinylic TMS substituent and the *n*-pentyl grouping (R$^1$). The alternative conformation (**F**) lacks this interaction. The situation is analogous to that noted by Still in the rearrangement of lithiomethyl allyl ethers (Scheme 4).

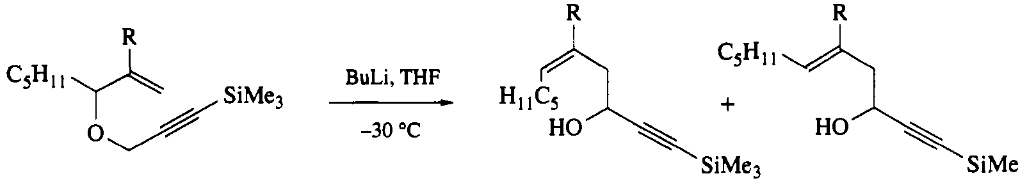
R
$C_5H_{11}$
SiMe3
O
BuLi, THF
-30 °C
R
$H_{11}C_5$
HO
SiMe3
+
R
$C_5H_{11}$
HO
SiMe3

(26)

**(104)** R = $SiMe_3$
**(105)** R = H

**(106)** R = $SiMe_3$ (80%)
**(107)** R = H

**(108)** R = $SiMe_3$ (20%)
**(109)** R = H (~100%)

The 2,3-rearrangement of nonracemic propargylic ethers proceeds enantioselectively, as might be expected considering the concerted nature of the reaction and its high diastereoselectivity. Nakai examined the (*S*)-2-butenyl propargyl ethers (**110**; Table 6).[28] In each case a rearranged product of high stereochemical integrity was obtained in near quantitative yield. The stereochemistry of these rearrangements reflects the equatorial preference of substituents in the envelope transition state (**G**; $R^1$ = Me, $R^2$ = H) as depicted in Scheme 7.

**Table 6** 2,3-Wittig Rearrangement of Chiral Allyl Propargyl Ethers

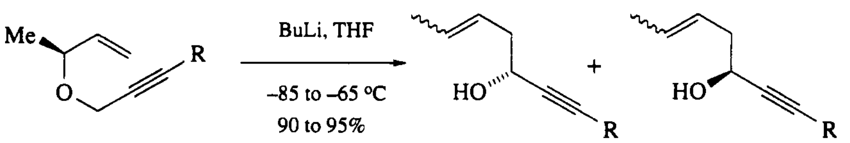
Me
R
O
BuLi, THF
-85 to -65 °C
90 to 95%
HO
R
+
HO
R

**(110)**

**(111)** *(R) (E)/(Z)*

**(112)** *(S) (E)/(Z)*

| *R* | *(E)/(Z)* | *(R)/(S)*[a] |
|---|---|---|
| H | 98:2 | 96:4 |
| TMS | 93:7 | 90:10 |
| Me | 97:3 | 94:6 |

[a]Major isomer.

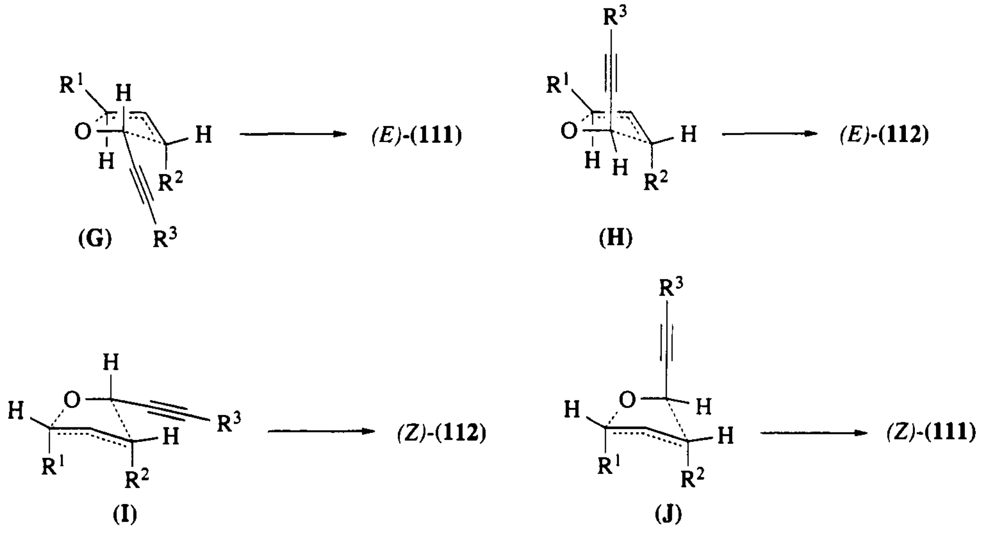
$R^1$
H
O
H
H
$R^2$
(G)
$R^3$
(E)-(111)
$R^3$
$R^1$
O
H
H
H
$R^2$
(H)
(E)-(112)
H
H
O
$R^3$
H
$R^1$
$R^2$
(I)
(Z)-(112)
$R^3$
H
O
H
H
$R^1$
$R^2$
(J)
(Z)-(111)

**Scheme 7** Transition states for 2,3-Wittig rearrangements of chiral propargyl allyl ethers

Nonracemic (*Z*)-allylic propargyl ethers likewise rearrange with excellent enantioselectivity (Table 7). In these examples the configuration of the starred center in (**114**) and (**115**) should be opposite for (*E*)- and (*Z*)-products owing to the concerted suprafacial nature of the rearrangement. The stereochemistry at the carbinyl center is related to the equatorial/axial preference of the alkynyl grouping (Scheme 7). It should be noted that the (*E*)-products (**114**) and (**115**) are greatly favored because of repulsive *syn*-1,3 interactions between R$^1$ and R$^2$ in the transition states (**I**) and (**J**) leading to (*Z*)-products (Scheme 7). The (*E*)-allylic ether (**116**), lacking this 1,3-interaction, rearranges with complete chirality transfer but yields a mixture of *syn*/*anti* and (*E*)/(*Z*)-isomers (equation 27).[29]

**Table 7** 2,3-Wittig Rearrangement of Chiral (*Z*)-Allyl Propargyl Ethers

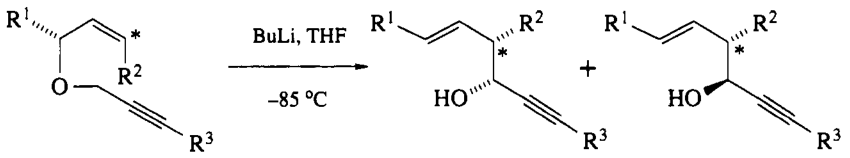

(**113**) (**114**) *syn* (**115**) *anti*

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *Yield (%)* | *Syn:anti* | *Enantioselectivity* | *Ref.* |
|---|---|---|---|---|---|---|
| Pr$^i$ | Me | H | 89 | 91:9 | 100 | 29 |
| Pr$^i$ | Me | TMS | 62 | 98:2 | 100 | 29 |
| Pr$^{i a}$ | CH$_2$OTBS | TMS | b | 98:2$^a$ | 100 | 30 |
| Me | Bu | TMS | 96 | 99:1 | 100 | 24 |
| Me$^a$ | Me | TMS | 64 | 99:1$^a$ | 100 | 31 |

$^a$The enantiomer of the depicted compound was employed. $^b$Not reported.

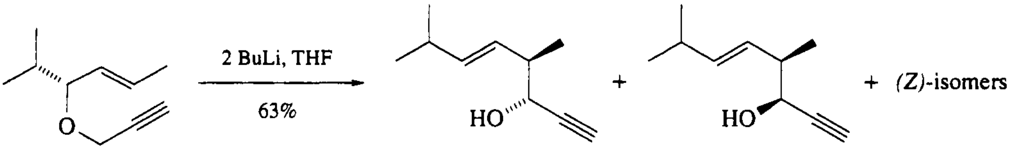

(27)

(**116**) (**117**) 82% (**118**) 10% 8%

Nakai has employed the propargylic 2,3-Wittig rearrangement for elaboration of side chains in steroidal systems. The (*E*)-17-ethylidene-16α ether (**119**) rearranges to the expected alcohol (**120**) on base treatment (equation 28).[32] Remarkably, the TMS derivative (**121**) of ether (**119**) rearranges with even greater facility to give the diastereomeric alcohol (**122**; equation 29).[33] The isomeric (*Z*)-17-ethylidene-16β TMS-propargyl ether (**123**) yields the same alcohol (equation 30). These results indicate that attack by the propargylic anion derived from the 16α ether (**121**) takes place with orientation of the TMS-ethynyl grouping toward the C-ring of the steroid as in (**K**; Scheme 8). In the 16β-(*Z*)-isomer (**123**) the TMS-

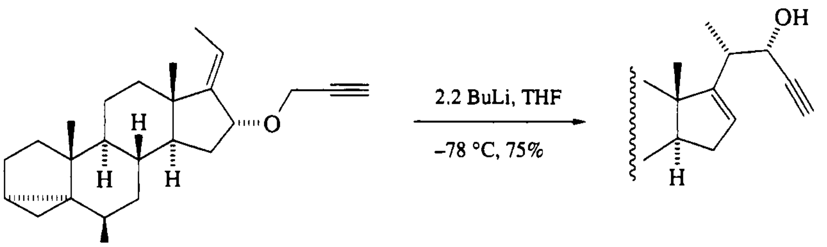

(28)

(**119**) (**120**)

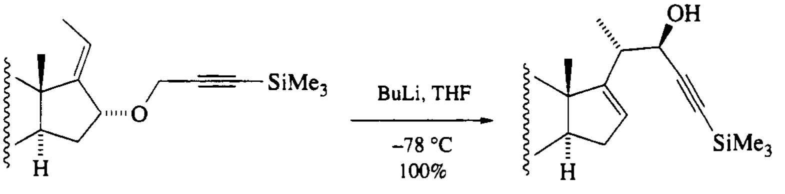

(29)

(**121**) (**122**)

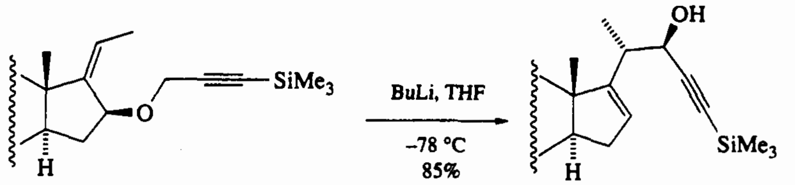
SiMe$_3$
O
H
BuLi, THF
–78 °C
85%
OH
SiMe$_3$
H

**(123)** **(122)**

(30)

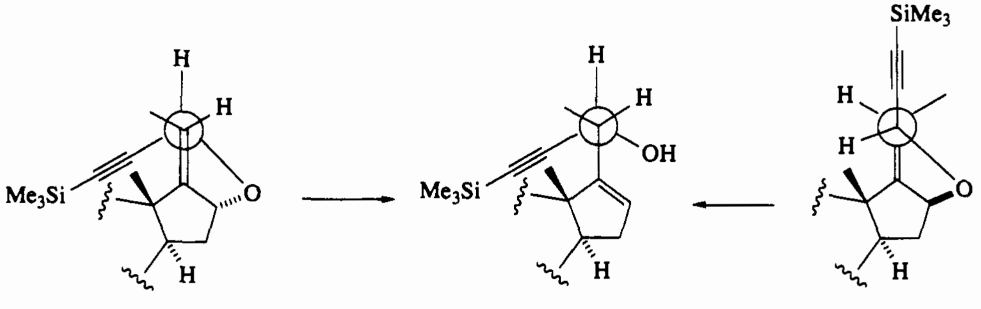
H
H
Me$_3$Si
O
H
H
H
OH
Me$_3$Si
H
SiMe$_3$
H
H
O
H

**(K)** **(122)** **(L)**

**Scheme 8** 2,3-rearrangment of steroial 17-ethylidene-16-trimethylsilyl-propargyl ethers

ethynyl grouping adopts the opposite orientation (**L**), also leading to the (22*R*)-alcohol (**122**). The ethynyl anion must assume the same relative orientation as in (**L**) but on the α-face of the double bond *en route* to the (22*S*)-alcohol (**120**).

The effect of a stereocenter at the δ-allylic position of allyl propargyl ethers has been examined by Nakai.[33a] The (*Z*)-ethers show particularly high 3,4-diastereoselectivity (Tables 7a and 7b).

The high asymmetric induction of these rearrangements is explained by transition states (**La**) and (**Lb**) as shown in Scheme 8a. The allylic oxygen substituents adopt an orientation perpendicular to the plane of the double bond to minimize allylic 1,3-repulsion. The propargylic anion attacks the double bond preferentially *anti* to these oxygens.

**Table 7a** 2,3-Wittig Rearrangement of Nonracemic Allylic Propargylic Ethers Derived from (*S*)-Lactaldehyde.

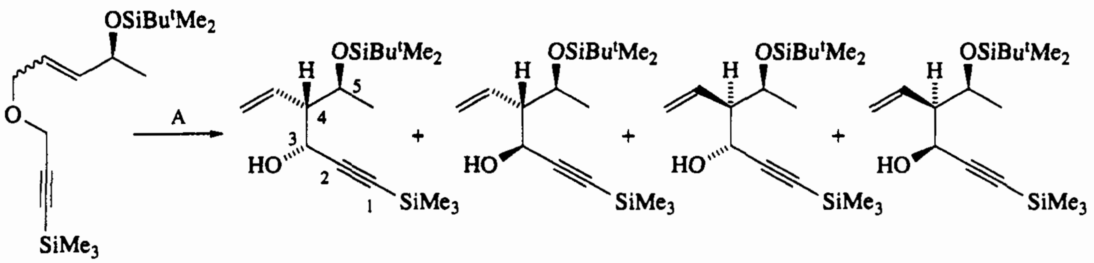
OSiBu$^t$Me$_2$
O
SiMe$_3$
A
H
OSiBu$^t$Me$_2$
5
4
3
HO
2
1
SiMe$_3$
+
H
OSiBu$^t$Me$_2$
HO
SiMe$_3$
+
H
OSiBu$^t$Me$_2$
HO
SiMe$_3$
+
H
OSiBu$^t$Me$_2$
HO
SiMe$_3$

**(123a)** **(123b)** **(123c)** **(123d)** **(123e)**

| *(123a)* | *A* | *Yield (%)* | *Product distribution*<br>*(123b)* | *(123c)* | *(123d)* | *(123e)* |
|---|---|---|---|---|---|---|
| (*Z*) | BuLi, THF, –78 °C | 77 | 94 | 1 | 4 | 1 |
| (*E*) | BuLi, THF, –78 °C | 93 | 10 | 21 | 80 | 19 |
| (*E*) | LDA ,THF–HMPA | 74 | 3 | 3 | 87 | 7 |

**Table 7b** 2,3-Wittig Rearrangement of Nonracemic Allylic Propargylic Ethers Derived from (*R*)-Glyceraldehyde Acetonide

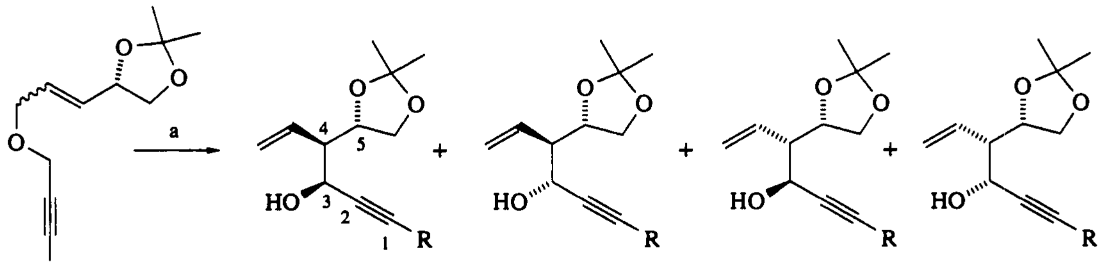

(123f) (123g) (123h) (123i) (123j)

| (123f) | R | Yield (%) | Product distribution<br>(123g) | (123h) | (123i) | (123j) |
|---|---|---|---|---|---|---|
| (*Z*) | TMS | 77 | >99 | 0 | 0 | 0 |
| (*Z*) | Me | 62 | 98 | 0 | 0 | 2 |
| (*E*) | TMS | 86 | 12 | 81 | 3 | 4 |
| (*E*) | Me | 73 | 7 | 77 | 16 | 0 |

[a] $Bu^nLi$, THF, −78 °C, 5 h.

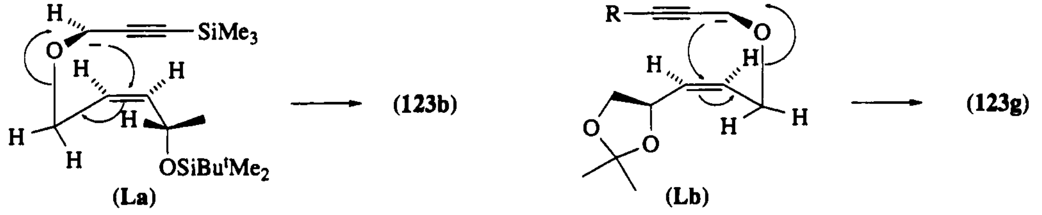

Scheme 8a

### 3.11.3.4 2,3-Wittig Rearrangement of Allyl Benzyl Ethers

As noted in Section 3.11.1, some of the earliest mechanistic work on the 2,3-Wittig rearrangement was carried out with allyl benzyl ethers. Selective benzyl deprotonation is typically effected with *n*-butyllithium in THF or THF–TMEDA at low temperature. Rautenstrauch's studies, summarized in Table 8, clearly showed that lower temperature favors 2,3- over 1,2-rearrangement, and established the potential

**Table 8** 2,3-Wittig Rearrangement of Allyl Benzyl Ethers

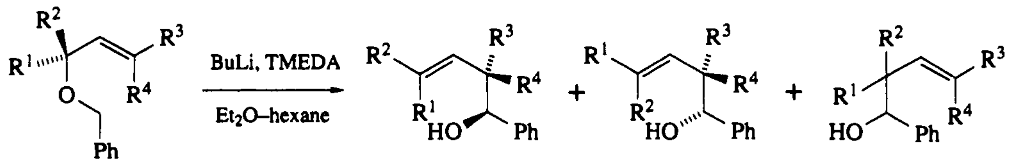

(124) (125) (126) (127)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *T* (°C) | (125):(126):(127) | Ref. |
|---|---|---|---|---|---|---|
| H | H | Me | H | −80 to −25 | 50:50:0 | 9 |
| H | H | H | Me | −80 to −25 | 100:0:0 | 9 |
| Me[a] | H | H | H | −80 to −25 | 0:100:0 | 9 |
| H | H | Me | Me | −80 to −25 | (89)[b]:11 | 9 |
| H | H | Me | Me | 23 | (86)[b]:14 | 9 |
| Me | Me | H | H | −25 | (60)[b]:40 | 9 |
| H | H | H | OTBS[c] | −65 | 18:82[d] | 25a |
| H | H | H | OTBS[e] | −65 | 23:77[d] | 25a |

[a] Racemic. [b] (125) = (126). [c] 71:29 (*Z*):(*E*). [d] (125):(126). [e] 93:7 (*Z*):(*E*).

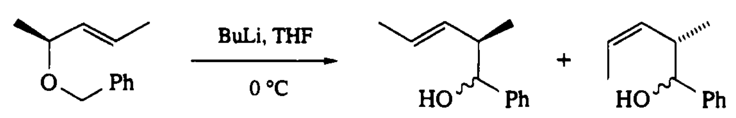

**(128)** **(129)** 83% 72% *ee* **(130)** 17% 62% *ee* (31)

for (*E*)/(*Z*) and *syn*/*anti* stereoselectivity in the former.[9] Baldwin and Patrick examined the chiral (*S*)-(*E*)-1-methyl-2-butenyl ether (**128**) and concluded that the 2,3-rearrangement is 100% suprafacial (equation 31).[34] A second pathway, involving nonconcerted homolysis and supported by deuterium labeling studies, was proposed to account for some 28% of racemic (*E*)-product (**129**). The configuration of the carbinyl center was not determined.

In connection with studies on chirality transfer in 2,3-Wittig rearrangements, Tsai and Midland examined the (*E*)- and (*Z*)-(*R*)-1-isopropyl-2-butenyl benzyl ethers (**131**; equation 32) and (**135**; equation 33).[29] Both ethers rearranged with essentially complete suprafaciality, but the (*Z*)-isomer (**135**) showed considerably higher (*E*)/(*Z*) and *syn*/*anti* selectivity in accord with transition state considerations previously discussed for the analogous propargylic ethers (Scheme 7).

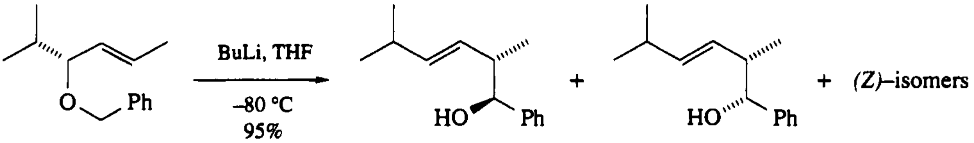

**(131)** **(132)** 62% **(133)** 20% **(134)** 18% (32)

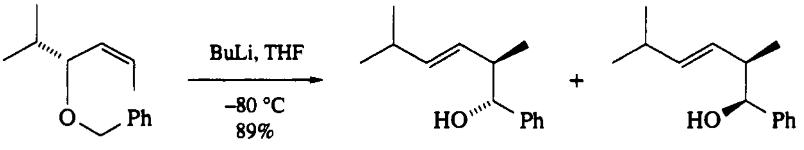

**(135)** **(136)** 7% **(137)** 93% (33)

A novel approach to stereocontrol in 2,3-Wittig rearrangements involves the use of chiral chromium tricarbonyl complexes (Table 8a).[34a] The reactions, which were carried out with racemic ethers, show excellent diastereoselectivity as a consequence of a preferred transition state in which the benzylic oxygen and the $R^3$-substituent and the vinylic grouping and $Cr(CO)_3$ grouping adopt *anti* orientations (**Lc**).

**Table 8a** 2,3-Wittig Rearrangement of $Cr(CO)_3$-complexed Benzyl Allyl Ethers

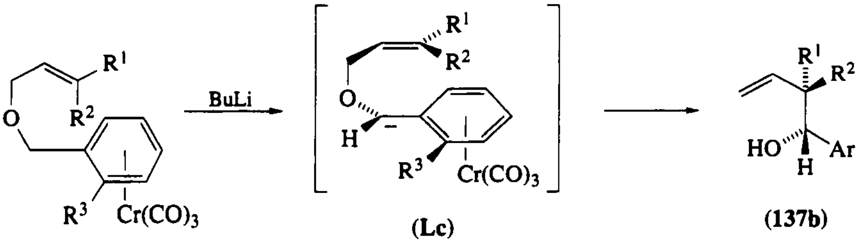

**(137a)** **(Lc)** **(137b)**

| $R^1$ | $R^2$ | $R^3$ | *Yield* (%) |
|---|---|---|---|
| H | H | H | 98 |
| H | H | Me | 82 |
| Me | H | Me | 90[a] |
| H | Me | H | 90[a] |
| Me | Me | Me | 88 |

[a] An 80:20 mixture of (*E*) and (*Z*) ethers yielded an 80:20 mixture of *syn* and *anti* products.

### 3.11.3.5 2,3-Rearrangement of Dipropargyl Ethers

As noted in Section 3.11.3.3, allyl propargyl ethers undergo highly selective 2,3-rearrangement through the propargylic anion intermediate. Allenic products (**138**) arising from 2,3-rearrangement of the allylic anion are not observed (equation 34). This regioselectivity may result from preferred formation of the propargylic anion or from the unfavorable geometry associated with a five-membered allenic transition state. Dipropargylic ethers lack this ambiguity. In fact, such ethers afford mixtures of 2,3- and 1,2-rearrangement products on base treatment (Table 9).[35] A methyl substituent at the propargylic position significantly retards 2,3- in favor of 1,2-rearrangement whereas geminal substituents defeat both processes. Neither the mono- nor the di-methylated propargyl allyl ethers (**144**) and (**145**) gave an allenic rearrangement product (**147**). In the former case only the propargyl alcohol (**146**) and traces of aldehyde were isolated, whereas the latter yielded no rearranged products (equation 35).

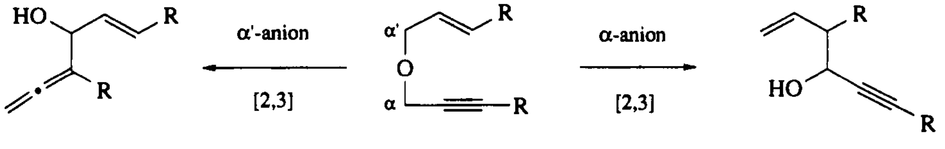

(**138**) (**139**) (**140**)

(34)

**Table 9** Wittig Rearrangement of Dipropargylic Ethers

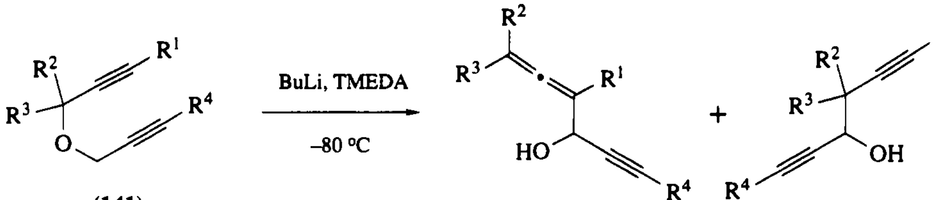

(**141**) (**142**) [2,3] (**143**) [1,2]

| *R*¹ | *R*² | *R*³ | *R*⁴ | (**142**) (%) | (**143**) (%) |
|---|---|---|---|---|---|
| H | H | H | H | 10 | 0 |
| Me | H | H | Me | 64 | 0 |
| TMS | H | H | TMS | 52 | 0 |
| Me | Me | H | Me | 9 | 31 |
| Me | Me | Me | H | 0 | 0 |
| H | Me | Me | H | 0 | 0 |

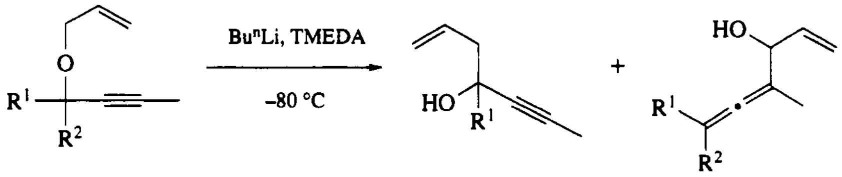

(35)

(**144**) $R^1$ = Me, $R^2$ = H

(**145**) $R^1$ = $R^2$ = Me

(**146**) $R^1$ = Me

(**147**)

Allenic products are formed in the anion-initiated rearrangement of cyanohydrin propargylic ethers (**148**; Table 10).[36] The intermediate cyanohydrins (**149**) are converted to allenyl ketones (**150**) upon work-up.

### 3.11.3.6 2,3-Rearrangement of Diallyl Ethers

Unsymmetrical diallyl ethers, like their propargyl allyl counterparts, can theoretically yield isomeric 2,3-rearrangement products depending upon the site of deprotonation. In the first systematic study of

**Table 10** 2,3-Wittig Rearrangement of Cyanohydrin Propargylic Ethers

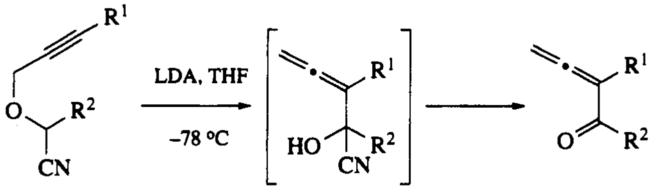
R1
O
R2
CN
LDA, THF
-78 °C
HO
R1
R2
CN
O
R1
R2

**(148)** **(149)** **(150)**

| *R*$^1$ | *R*$^2$ | *LDA* (equiv.) | *Yield* (%) |
|---|---|---|---|
| H | Bu$^n$ | 3.5 | 48 |
| H | Bu$^i$ | 4 | 51 |
| Me | Bu$^n$ | 2.2 | 54 |
| Et | Bu$^n$ | 2.2 | 61 |

such reactions, Nakai and coworkers found that the regioselectivity of the rearrangement is related to the stability of the presumed allylic anion intermediate (Table 11).[37] Thus allyl or methallyl are deprotonated more readily than crotyl or 1-methyl-2-propenyl (Table 11, entries 1 and 3–7). Allyl and methallyl, on the other hand, are deprotonated with comparable ease (entry 2). In general the less-substituted allylic anion is preferred (equation 36). (*Z*)-Allylic ethers afford *syn* products with high diastereoselectivity (Table 11, entries 4 and 7), whereas (*E*)-allylic ethers yield *anti* products, but less selectively (entries 3 and 6). Ethers with α′-substituents rearrange to (*E*)-products nearly exclusively (entries 1 and 5). Further investigations by Nakai and coworkers confirmed and extended these findings (Table 12).[38]

**Table 11** 2,3-Wittig Rearrangement of Unsymmetrical Diallylic Ethers

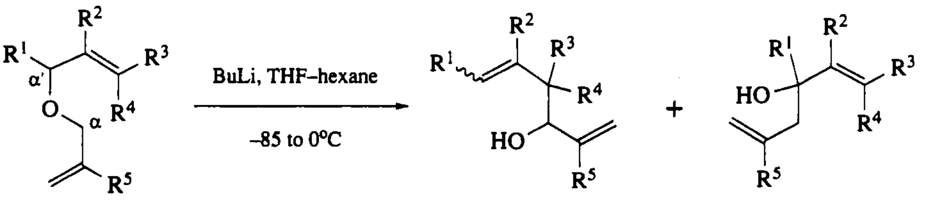
R2
R1
R3
α′
O
α
R4
R5
BuLi, THF–hexane
–85 to 0°C
R2
R1
R3
R4
HO
R5
+
R2
R1
HO
R3
R4
R5

**(151)** **(152)** α-anion **(153)** α′-anion

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *R*$^5$ | *Yield* (%) | α:α′ | *Anti:syn* | *(E):(Z)* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | H | H | 79 | 100:0 | | >95:5 |
| 2 | H | Me | H | H | H | 77 | 55:54 | | |
| 3 | H | H | Me | H | H | 81 | 100:0 | 84:16 | |
| 4 | H | H | H | Me | H | 88 | 100:0 | 8:92 | |
| 5 | Me | H | H | H | Me | 60 | 100:0 | | >95:5 |
| 6 | H | H | Me | H | Me | 70 | 100:0 | 72:28 | |
| 7 | H | H | H | Me | Me | 71 | 100:0 | 5:95 | |

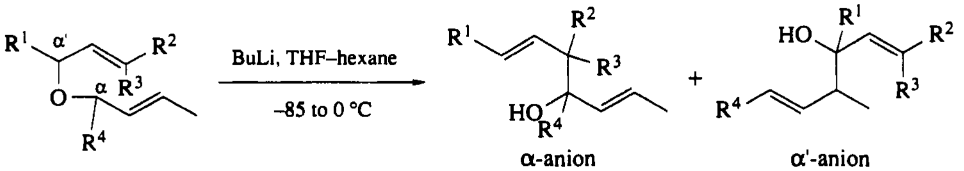
R1
α′
R2
O
α
R3
R4
BuLi, THF–hexane
–85 to 0 °C
R1
R2
R3
HO
R4
+
HO
R1
R2
R4
R3

(36)

α-anion α′-anion

**(154a)** R$^1$ = Me, R$^2$ = R$^3$ = R$^4$ = H **(155a)** 33% **(156a)** 66%

**(154b)** R$^1$ = R$^4$ = H, R$^2$ = R$^3$ = Me **(155b)** 100% **(156b)** 0%

**(154c)** R$^1$ = H, R$^2$ = R$^3$ = R$^4$ = Me **(155c)** 100% **(156c)** 0%

**Table 12** Diastereoselectivity in 2,3-Wittig Rearrangement of Diallylic Ethers

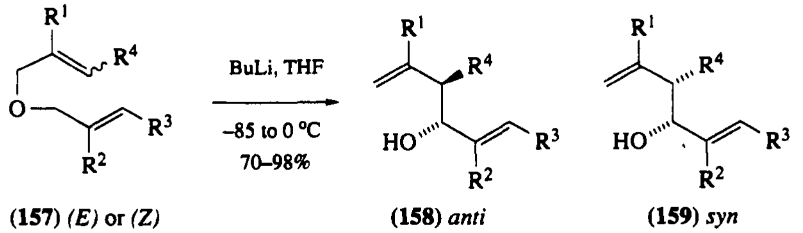

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *(E)or(Z)* | *Anti:syn* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | Me | (*E*) | 84:16 | 38 |
| 2 | H | Me | H | Me | (*E*) | 72:28 | 38 |
| 3 | TMS | Me | H | Me | (*Z*)[a] | 91:9 | 38 |
| 4 | H | TMS | H | Me | (*E*) | 70:30 | 38 |
| 5 | H | H | Ph | Me | (*E*) | 74:26 | 38 |
| 6 | H | H | H | Me | (*Z*) | 8:92 | 38 |
| 7 | H | Me | H | Me | (*Z*) | 5:95 | 38 |
| 8 | H | H | Ph | Me | (*Z*) | 28:72 | 38 |
| 9 | H | H | H | OTBS | (*Z*)[b] | 95:5 | 25a |
| 10 | H | Me | H | OTBS | (*Z*)[b] | 91:1 | 25a |

[a] Artefact of sequence rule priority change. [b] 70:30 (*Z*):(*E*).

A transition state model was formulated (Scheme 9) in which the anion-stabilizing vinyl substituent adopts the lower energy equatorial orientation in the envelope conformation (**M**) for the (*E*)-allylic ether and (**N**) for the (*Z*)-allylic ether.[38] The alternative higher energy axial disposition of this grouping as in (**O**) and (**P**) would lead to the *syn* and *anti* products, respectively. [It should be noted that these products are enantiomers of the *syn* and *anti* products derived from (**N**) and (**M**).] Presumably, interactions between the vinyl substituent and the equatorial (Me) grouping at the migration terminus raises the energy of this transition state slightly in the (*E*)-allylic ethers, resulting in lower diastereoselectivity. R$^1$-substituents destabilize the axial vinylic grouping in transition state (**O**) in favor of (**M**) leading to an enhanced *anti:syn* ratio (Table 12, entry 3). The lower *syn:anti* ratio seen in entry 8 for the (*E*)-3-phenylallyl ether may stem from unfavorable interactions between the Me grouping at the migration terminus and the R$^3$-phenyl substituent in transition state (**N**).

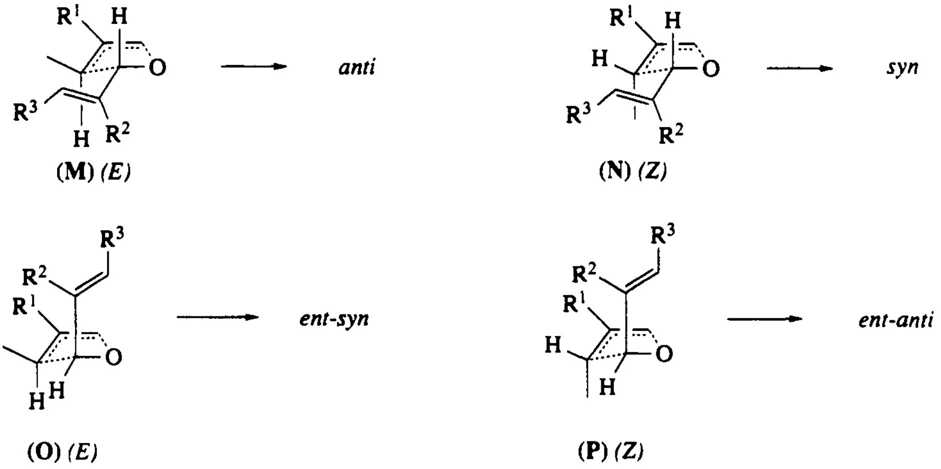

**Scheme 9** Envelope transition states for 2,3-Wittig rearrangements of diallylic ethers leading to diastereomeric and enantiomeric products

The question of conformational preferences at the nonmigrating carbinyl center was addressed by Tsai and Midland (Table 13).[29] Their results are consistent with the previously described transition state picture for lithiomethyl and propargyl allyl ethers (Schemes 4 and 6). Accordingly, (*Z*)-allylic ethers rearrange to *syn* (*E*)-products with high diastereoselectivity and (*E*)-allylic ethers favor *anti* (*E*)-products. The rearrangement proceeds with complete 1,3-*syn* stereocontrol as expected for a concerted suprafacial process. The Nakai transition state (Scheme 6) with an equatorial-like isopropyl substituent ($R^1$) accommodates these results.

**Table 13** Stereoselectivity of 2,3-Wittig Rearrangement of Chiral Diallylic Ethers

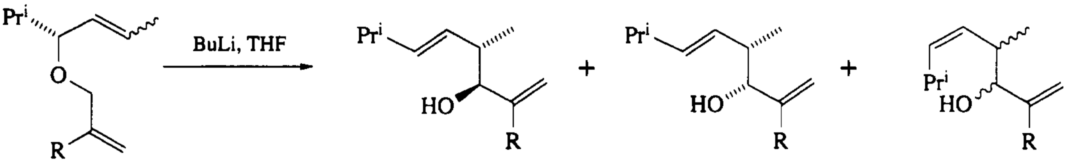

**(160)** **(161)** *anti* **(162)** *syn* **(163)** *(Z)*

| *R* | *(E) or (Z)* | *Yield (%)* | *Anti:syn:(Z)* |
|---|---|---|---|
| H | (*E*) | 75 | 60:40:0 |
| Me | (*E*) | 89 | 50:40:10 |
| H | (*Z*) | 84 | 8:92:0[a] |
| Me | (*Z*) | 93 | 7:93:0[a] |

[a] *ent*-(**161**)/(**162**).

Studies on the nonracemic methylenecyclododecyl ethers (**164**; equation 37) led to similar conclusions.[39] With HMPA as a cosolvent the secondary allylic ether (**164a**) afforded mainly (86:14) the (*E*)-homoallylic alcohol (**165a**) of 95% *ee*. The tertiary ether (**164b**) yielded a 98:2 (*E*):(*Z*) mixture, but the major product (**165b**) was 40% racemic. A dissociative rearrangement process could account for this result. Without HMPA both ethers rearranged in poor yield (5–30%) to nearly 1:1 mixtures of (*E*)- and (*Z*)-cycloalkenes.

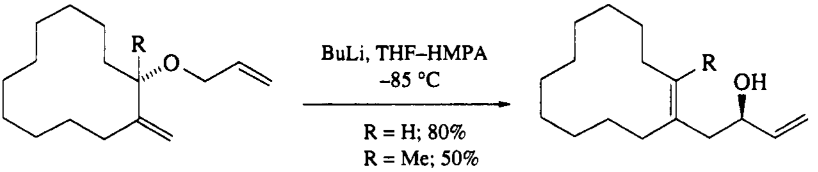

(37)

**(164a)** R = H
**(164b)** R = Me

**(165a)**
**(165b)**

### 3.11.3.7 Tandem and Sequential 2,3-Wittig–3,3-Sigmatropic Rearrangements

The 1,5-dien-3-ols produced by 2,3-Wittig rearrangement of diallylic ethers can serve as pivotal intermediates for further elaboration through tandem or sequential 3,3-sigmatropic reactions.[40,41] The three sequences examined to date are summarized in Scheme 10.

2,3-Wittig rearrangement of the (*E*)- and (*Z*)-diallylic ethers (**166a**) and (**166b**) afforded mixtures of the 1,5-dienes (**167a**) and (**167b**) enriched in the *anti* [from (*E*)] and *syn* [from (*Z*)] isomers, respectively. Subsequent oxy-Cope rearrangement of these dienes gave the enals (**168a**) and (**168b**) as mixtures of (*E*)- and (*Z*)-isomers whose composition depended upon the oxy-Cope reaction conditions, but not the *syn:anti* ratios of the precursor 1,5-dienes (**167**).[42] Best results were obtained in refluxing decane, whereupon (*E*)-enals (**168**) of 90–95% isomeric purity were produced.

Allylation of the 2,3-Wittig products (**167**) leads to diallylic ethers (**171**) in which one of the allylic double bonds is part of a 1,5-diene system. These ethers undergo 3,3-oxy-Cope rearrangement to afford vinyl allyl ethers (**170**), which rearrange *in situ* by a 3,3-Claisen process to yield the (*E*)-dienals (**169**).[43] Some typical results are summarized in Table 14. The cyclopentanols (**175**) were shown to arise from aldehydes (**169**) by an intramolecular thermal ene reaction.[44]

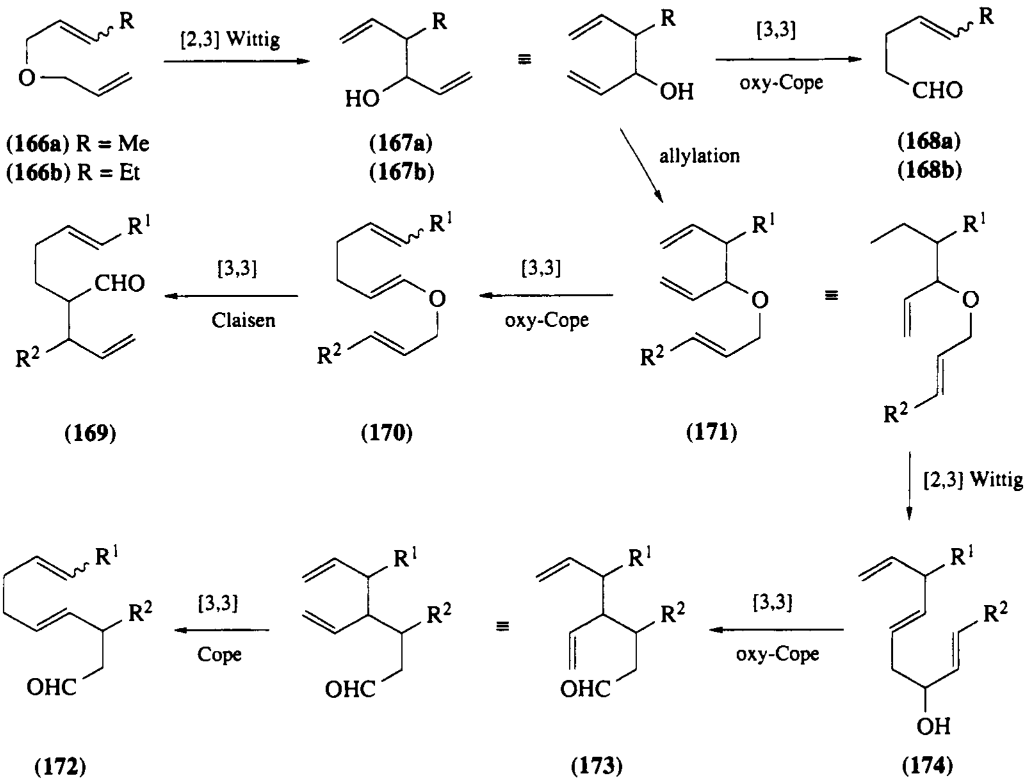
[2,3] Wittig
[3,3]
oxy-Cope
allylation
Claisen
Cope
(166a) R = Me
(166b) R = Et
(167a)
(167b)
(168a)
(168b)
(169)
(170)
(171)
(172)
(173)
(174)
R
R$^1$
R$^2$
HO
OH
O
CHO
OHC

**Scheme 10** Tandem and sequential 2,3-Wittig–3,3-sigmatropic rearrangements

**Table 14** Tandem Oxy-Cope–Claisen Rearrangements of 1,5-Dien-3-ol Allylic Ethers

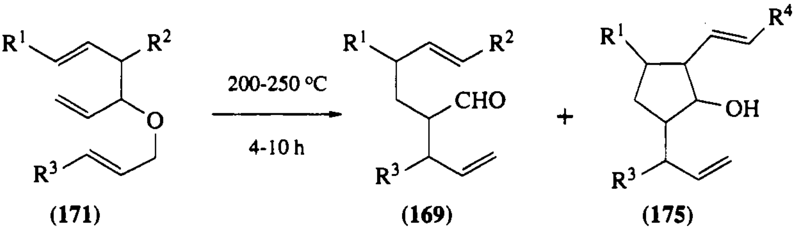
200-250 °C
4-10 h
(171)
(169)
(175)
R$^1$
R$^2$
R$^3$
R$^4$
O
CHO
OH
+

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *(171) Anti:syn* | *(169) (%)* | *(175) (%)* |
|---|---|---|---|---|---|---|
| H | Me | Me | H | 79:21 | 36 | 20 |
| H | $CH_2{=}CH(CH_2)_3$ | Me |  | 80:20 | 45 | 0 |
| H | $CH_2{=}CH(CH_2)_3$ | H | a | 80:20 | 45 | 13 |
| Me | H | H |  |  | 41 |  |

[a] $(CH_2)_2CH{=}CH_2$.

A third variant of tandem rearrangements employs the dienyl allylic ether (**171**) in a second regioselective 2,3-Wittig rearrangement leading to the 1,5-dienol (**174**), which undergoes sequential oxy-Cope–Cope rearrangement to the dienal (**172**). Examples of the latter steps of this sequence are collected in Table 15. In the oxy-Cope rearrangement of the methyl derivative (**174**; R$^1$ = Me) the silyl ether proved superior to the free alcohol (entries 1 *versus* 2). No such improvement was realized with the geranyl-derived silyl ether (**174**; entries 3 *versus* 4). The ratio of isomeric products (**172**) was independent of the diastereomeric composition of the starting allylic ethers (**171**).

**Table 15** Tandem Oxy-Cope–Cope Rearrangements

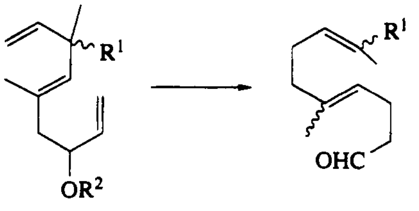

**(174)** **(172)**

| *Entry* | *R*1 | *R*2 | *Temperature* (°C) | *Yield* (%) | *(E):(Z)* (**172**) |
|---|---|---|---|---|---|
| 1 | Me | H | 202 (NMP) | 41 | 67:33 |
| 2 | Me | TMS | 250 (neat) | 86 | a |
| 3 | $CH_2CH{=}CMe_2$ | H | 202 (NMP) | 46 | b |
| 4 | $CH_2CH{=}CMe_2$ | TMS | 250 (neat) | 46 | b |

[a] Not determined. [b] Mixture of all four geometric isomers.

### 3.11.3.8 Rearrangement of α-Allyloxy Enolates

The anion that initiates a 2,3-Wittig rearrangement can be derived from α-allyloxy or α-propargyloxy ketones, nitriles (cyanohydrins), acids, esters and amides. Such anions have the virtue of being more easily formed under milder conditions than their methyl, benzyl, propargyl and allyl counterparts. In addition, they lead to more highly functionalized products with greater potential for synthetic applications. Furthermore, through changes in counterion or incorporation of chiral auxilliary groupings, better control of relative and absolute stereochemistry can often be realized.

#### *3.11.3.8.1 α-Allyloxy ketones*

One of the earliest observations of ketone enolate 2,3-rearrangement was made in connection with attempts to add Grignard reagents to the tetrahydrofurfuryl ketone (**176**).[45] Instead of the expected adduct, the hydroxy ketone (**177**) was obtained (equation 38). Both *cis* and *trans* ketones (**176a**) and (**176b**) rearranged to this product. Concordant with a concerted 2,3-process, the nonracemic ketone (**177**) was produced from optically active ether (**176**). The acyclic ether (**178**) also underwent 2,3-rearrangement upon base treatment (equation 39). An analogous α-allyloxy ketone (**180**) was found to follow a 3,3-rearrangement pathway[43] exclusively with KOMe–KH or NaOMe–NaH in toluene or THF (Scheme 11).[46] With LiOMe–LiH as the base an 80:20 mixture of the 3,3- and 2,3-products (**183**) and (**182**) was produced.

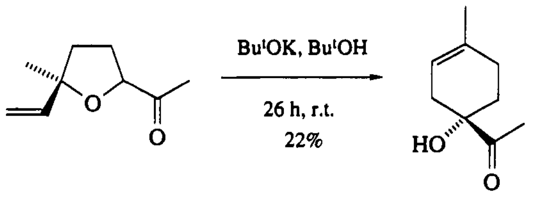

(38)

(**176a**) *cis*
(**176b**) *trans*
(**177**)

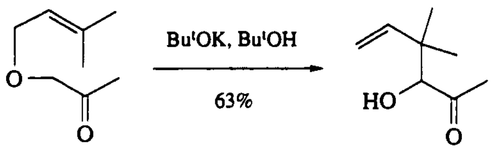

(39)

(**178**) (**179**)

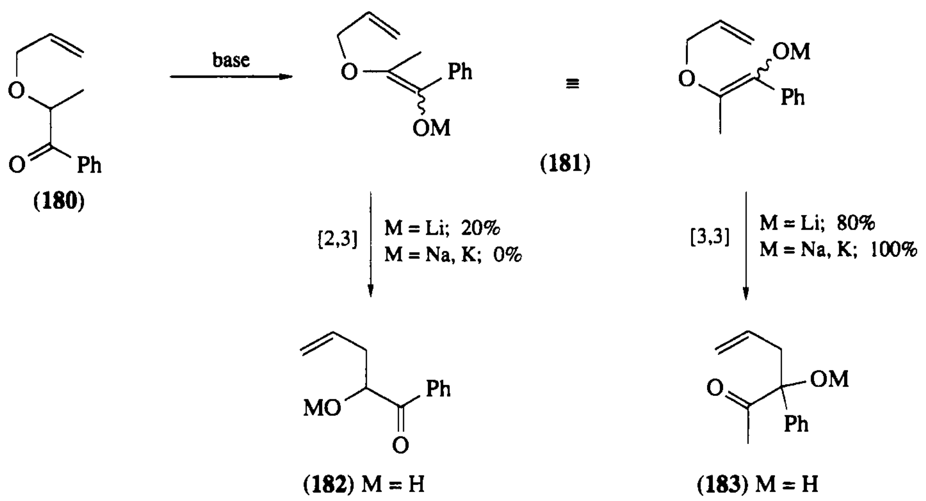
base
Ph
OM
≡
OM
Ph
O
(180)
(181)
[2,3]
M = Li; 20%
M = Na, K; 0%
[3,3]
M = Li; 80%
M = Na, K; 100%
MO
Ph
O
OM
Ph
(182) M = H
(183) M = H

**Scheme 11** Competing 3,3- and 2,3-rearrangement pathways for a ketone enolate

The dimethylhydrazone derivatives of α-allyloxy ketones undergo exclusive 2,3-Wittig rearrangement upon deprotonation with excess KH in *t*-butyl alcohol (equation 39a).[46a] The lack of competing 3,3-rearrangement is ascribed to the higher charge density on carbon in the anion as a result of the diminished electronegativity of the hydrazone nitrogen. In the case of (**183b**) only the (*E*)-hydrazone isomer rearranged. The apparent unreactivity of the (*Z*)-isomer is thought to stem from greater steric hindrance to deprotonation.

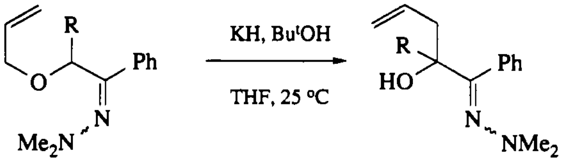
R
Ph
O
N
$Me_2N$
KH, Bu$^t$OH
THF, 25 °C
R
HO
Ph
N
$NMe_2$

(39a)

(**183a**) R = H (*E*:*Z* = 1:3) (**183c**) 95% yield

(**183b**) R = Me (*E*:*Z* = 2.9:1) (**183d**) 73% yield

The cyclohexanone hydrazones (**183e**) rearrange similarly (Table 15a). The *cis* isomers (entries 2 and 4) required elevated temperatures for deprotonation owing to the stereoelectronically disfavored equatorial disposition of the α-proton (H-2). The diastereofacial selectivity of the rearrangement was high in all cases examined but the diastereoselectivity at the allylic center was poor (entries 3–5).

**Table 15a** 2,3-Wittig Rearrangement of Cyclohexanone Hydrazone Derivatives

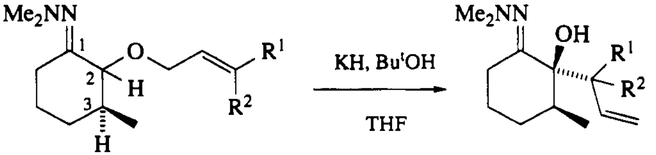
$Me_2NN$
1
2
3
O
H
H
$R^1$
$R^2$
KH, Bu$^t$OH
THF
$Me_2NN$
OH
$R^1$
$R^2$

(**183e**) (**183f**)

| *Entry* | $R^1$ | $R^2$ | *(E)/(Z)* | *H-2/H-3* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | H | H | >50:1 | *Trans* | 91 |
| 2 | H | H | 4:1 | *Cis* | 92 |
| 3 | Me | H | >50:1 | *Trans* | 88 (1.4:1) |
| 4 | Me | H | 6:1 | *Cis* | 45 (1.1:1) |
| 5 | H | Me | >50:1 | *Trans* | 81 (1.25:1) |

The complimentarity of hydrazone and ketone enolate rearrangements is illustrated in equation (39b).

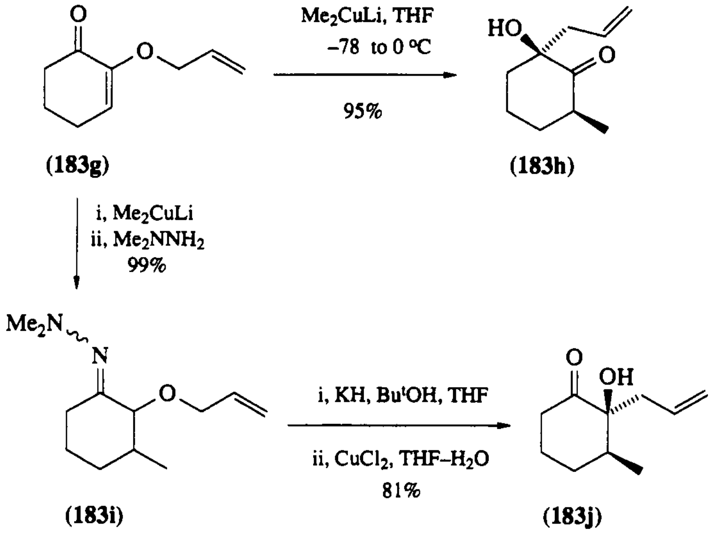
Me$_2$CuLi, THF
−78 to 0 °C
95%
HO
O
i, Me$_2$CuLi
ii, Me$_2$NNH$_2$
99%
Me$_2$N
N
O
i, KH, Bu$^t$OH, THF
ii, CuCl$_2$, THF–H$_2$O
81%
OH

(183g) (183h) (183i) (183j)

(39b)

### 3.11.3.8.2 *O-Allyl cyanohydrins*

Allylic ethers of cyanohydrins are easily prepared through phase transfer allylation.[47] Deprotonation of these ethers with LDA in THF at −78 °C effects 2,3-rearrangement to transient β,γ-unsaturated ketone cyanohydrins, which are transformed during work-up to the ketones (Table 16).[48] In an extension of this work, the mixed acetal cyanohydrin ethers (**187**), prepared by mild acid treatment of the cyanohydrins with 2-methoxy-1,3-butadiene or 1-*t*-butoxyallene, rearranged to the keto enol ethers (**189**; equation 40).[49] Hydrolysis of the enol ethers (**189**) leads to 1,4-dicarbonyl compounds, which can be cyclized to cyclopentenones.

**Table 16** 2,3-Rearrangement of *O*-Allyl Cyanohydrins

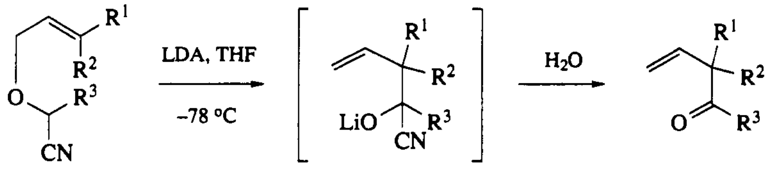
R$^1$
R$^2$
R$^3$
O
CN
LDA, THF
−78 °C
R$^1$
R$^2$
LiO
R$^3$
CN
H$_2$O
R$^1$
R$^2$
O
R$^3$

(184) (185) (186)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *Yield (%)* (*184*) | (*186*) |
|---|---|---|---|---|
| H | H | Bu$^i$ | 46 | 76 |
| Me$^a$ | H | Bu$^i$ | 45 | 65 |
| Me | Me | Bu$^i$ | 57 | 75 |
| Me | Me | Me | 32 | 36 |
| b | Me$^c$ | Bu$^i$ | 48 | 58 |
| b | Me$^c$ | Me | 15 | 36 |

$^a$85:15 (*E*):(*Z*). $^b$Me$_2$C ═ CHCH$_2$CH$_2$. $^c$90:10 (*E*):(*Z*).

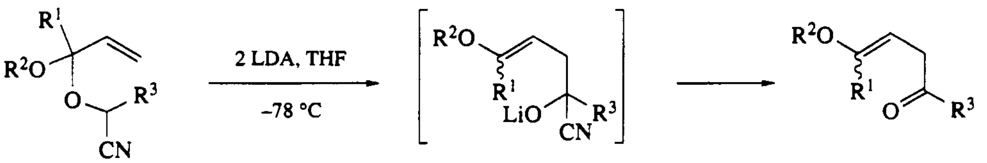
R$^1$
R$^2$O
O
R$^3$
CN
2 LDA, THF
−78 °C
R$^2$O
R$^1$
LiO
R$^3$
CN
R$^2$O
R$^1$
O
R$^3$

(40)

(**187a**) R$^1$ = H, R$^2$ = Bu$^t$, R$^3$ = Bu$^i$; 84%
(**187b**) R$^1$ = H, R$^2$ = Bu$^t$, R$^3$ = n-C$_6$H$_{13}$; 80%
(**187c**) R$^1$ = Me, R$^2$ = Me, R$^3$ = n-C$_6$H$_{13}$; 63%

(**188**)

(**189a**) 90%
(**189b**) 89%
(**189c**) 83%

Base treatment of the cyanoisopentyl β-furfurylmethyl ether (**190**; equation 41) affords Elsholtzia ketone (**192**), a naturally occurring monoterpene.[50] Even though it disrupts the aromatic furan ring, this rearrangement proceeds readily, illustrating the potency of cyanohydrin anions as 2,3-Wittig initiators.

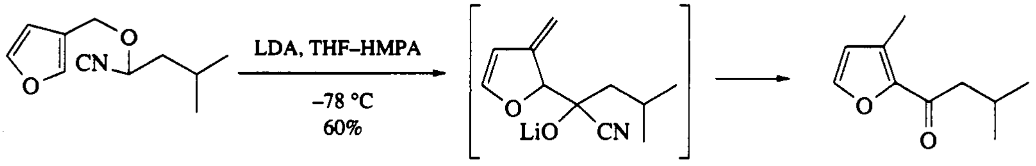
CN
O
LDA, THF–HMPA
-78 °C
60%
LiO
CN
O

(41)

**(190)** **(191)** **(192)**

### 3.11.3.8.3 α-Allyloxycarboxylic acids

2,3-Wittig rearrangement of α-allyloxycarboxylic acid dianions and allyl propargylic dianions (Section 3.11.3.3) might be expected to proceed analogously. In fact, the same high preference for (*E*)-products is observed, but the diastereoselectivity is reversed (Table 17, entries 5 *versus* 6).[51] A chelated bicyclo [3.3.0] transition state readily explains the *anti* selectivity of (*Z*)-allylic ethers [Scheme 12, compare (**R**) with (**T**)]. The basis for *syn* selectivity observed with (*E*)-allylic ethers (**Q**) *versus* (**S**) is less clear.

**Table 17** 2,3-Wittig Rearrangement of α-Allyloxycarboxylic Acids

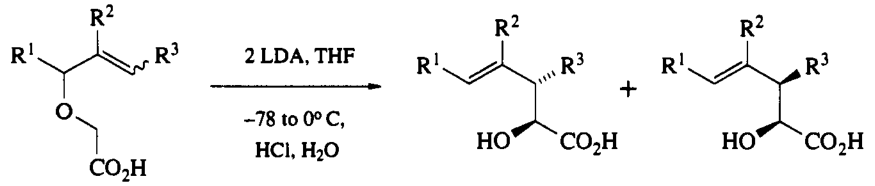
R2
R1
R3
O
CO2H
2 LDA, THF
-78 to 0° C,
HCl, H2O
R2
R1
R3
HO
CO2H
+
R2
R1
R3
HO
CO2H

**(193)** **(194)** *anti* **(195)** *syn*

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *(E) or (Z)* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | n-$C_7H_{15}$ | H | H | | 80[a] |
| 2 | n-$C_5H_{11}$ | H | H | | 64[a] |
| 3 | Me | H | H | | 87[a] |
| 4 | n-$C_5H_{11}$ | Me | H | | 74[a] |
| 5 | H | H | Me | (*E*) | 60[b] |
| 6 | H | H | Me | (*Z*) | 73[c] |

[a] >95% (*E*). [b] 92:8 *syn*:*anti*. [c] 79:21 *anti*:*syn*.

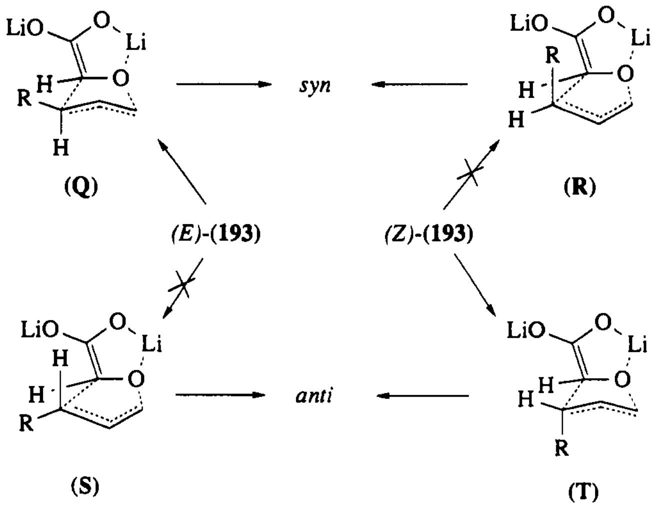
LiO
O
Li
O
H
R
H
(Q)
syn
LiO
O
Li
R
O
H
H
(R)
(E)-(193)
(Z)-(193)
LiO
O
Li
H
O
H
R
(S)
anti
LiO
O
Li
O
H
H
R
(T)

**Scheme 12** Envelope transition states for 2,3-rearrangement of α-allyloxycarboxylic acid dianions

The carboxylic acid variant of the 2,3-Wittig rearrangement has been used in steroidal systems to elaborate the 22-hydroxy substituent found in ecdysone and brassinolide natural products (equation 42).[52] Whereas the ethyl ester (**196**; R = Et) gave a mixture of products, acid (**196**) was cleanly converted to the (22*S*)-alcohol (**197**) at –78 °C *via* the dianion followed by acidification and esterification.[53] The stereochemistry of this rearrangement is analogous to that observed for the corresponding propargylic ether (**119**) and opposite to that of the acyclic *trans* crotyl analog (Table 17, entry 5). The preference for (**197**) can be clearly seen by comparison of transition states (**U**) and (**V**) in Scheme 13.

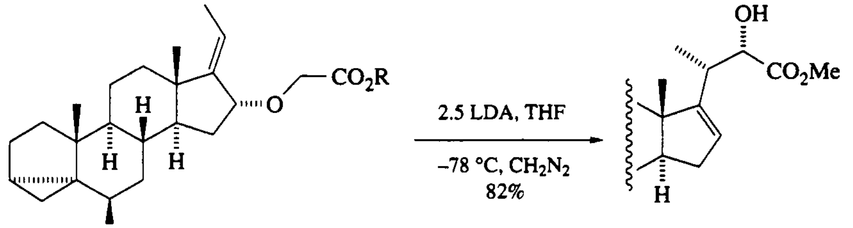

(**196**) R = H

(**197**)

(42)

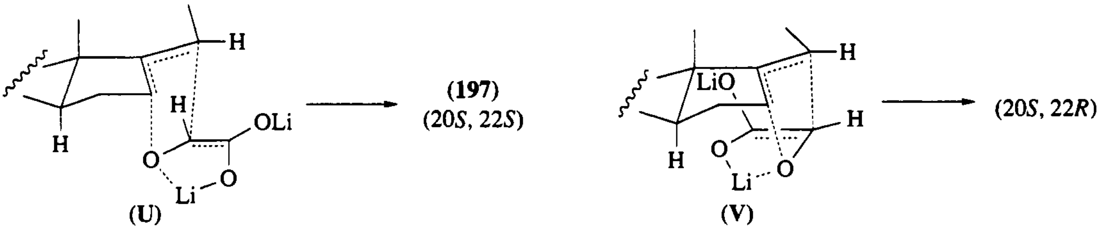

**Scheme 13** Diastereomeric transition states for carboxylic acid dianion 2,3-rearrangement of a steroidal 17-ethylidene-16α ether

2,3-Wittig rearrangement of the nonracemic (*R*)-propargylic glycolic acid ethers (**197d**) and (**197e**) to the (*R*,*S*)-α-hydroxy acids (**197f**) and (**197g**) proceeds with complete chirality transfer and 94% diastereoselectivity (equation 42a).[51b]

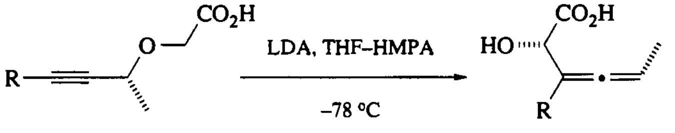

(**197d**) R = Bu
(**197e**) R = $C_7H_{15}$

(**197f**)
(**197g**)

(42a)

### *3.11.3.8.4 α-Allyloxycarboxylic esters*

It was previously noted that enolates of α-allyloxy ketones were capable of either 2,3- or 3,3-rearrangement, depending upon counterion, reaction conditions and substituents.[46] Ester enolates show a greater propensity for the 2,3-pathway, as illustrated by the geraniol-derived alkoxyacetate (**198**) which afforded hydroxy ester (**200**) as the sole product upon treatment with LDA in THF at –78 to 0 °C.[54] The 3,3-product (**201**) could be obtained by addition of TBDMS-Cl and HMPA to the enolate at –78 °C and thermal rearrangement of the TBS enol ether (**199b**; Scheme 14).[43]

Zirconium enolates offer a number of advantages in the 2,3-Wittig rearrangement of α-allyloxyacetic esters. Although both lithium and zirconium enolates afford predominantly *syn* (*Z*)-products, regardless of initial allyl geometry, reactions of the latter tend to be more efficient and more selective (Table 18, entries 1, 3 and 5 *versus* 2, 4 and 6).[55] In addition, nonracemic secondary allyloxyacetates rearrange with high 1,3-suprafaciality (entries 6–9). These trends reflect steric interactions between the coordinated metal and the substituent R in a bicyclo [3.3.0] folded transition state (Scheme 15). Of the four possible arrangements, (**U**) offers the best steric environment for an R-substituent. When the allylic position is primary (R = H), then (**U**) and (**X**) are enantiomeric, as are (**V**) and (**W**).

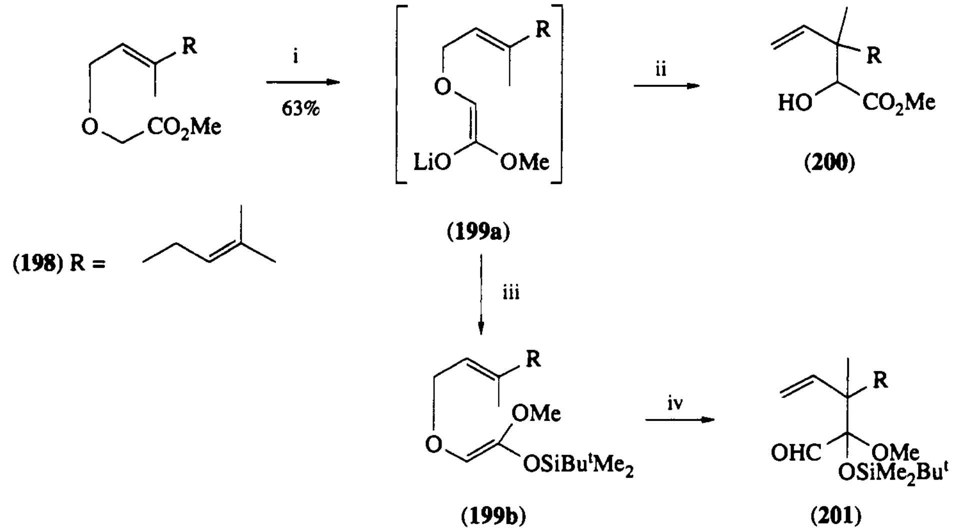

i, LDA, THF, –78 °C; ii, –78 to 0 °C, $H_2O$; iii, –78 °C, THF, HMPA, $Bu^tMe_2SiCl$; iv, 110 °C

Scheme 14

**Table 18** 2,3-Wittig Rearrangement of α-Allyloxyacetic Ester Enolates

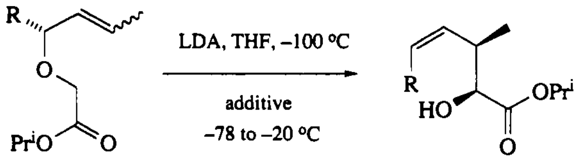

(202) (203) *syn (2S,3R)*

| *Entry* | *R* | *(E)/(Z)* | *Additive* | *Yield (%)* | *Syn:anti* | *ee (%)* |
|---|---|---|---|---|---|---|
| 1 | H | (*Z*) | None | 20 | 67:33 | |
| 2 | H | (*Z*) | $Cp_2ZrCl_2$ | 15 | 86:12 | |
| 3 | H | (*E*) | None | 14 | 82:18 | |
| 4 | H | (*E*) | $Cp_2ZrCl_2$ | 47 | 98:2 | |
| 5 | Me | (*E*) | None | 72 | 80:20 | |
| 6 | Me[a] | (*E*) | $Cp_2ZrCl_2$ | 91 | 99:1 | >96[a] |
| 7 | $Bu^n$ | (*E*) | $Cp_2ZrCl_2$ | 81 | 98:2 | >96 |
| 8 | n-$C_8H_{17}$ | (*E*) | $Cp_2ZrCl_2$ | 70 | 99:1 | >96 |
| 9 | $Pr^i$ | (*E*) | $Cp_2ZrCl_2$ | 26 | 98:2 | >96 |
| 10 | $CH_2OBn$ | (*E*) | $Cp_2TiCl_2$ | 72 | 98:2[b] | |
| 11 | $CH_2OBn$ | (*E*) | $Cp_2HfCl_2$ | 37 | 97:3[b] | |
| 12 | $(CH_2)_2OBn$ | (*E*) | $Cp_2ZrCl_2$ | 62 | 98:2 | |
| 13 | $(CH_2)_3OBn$ | (*E*) | $Cp_2ZrCl_2$ | 57 | 98:2 | |
| 14 | $(CH_2)_3OBn$ | (*E*) | $Cp_2TiCl_2$ | 37 | 79:21[c] | |

[a] Enantiomer of depicted structure. [b] The (*E*) product formed predominantly. [c] *Ca.* 2:1 mixture of (*E*) and (*Z*).

The presence of a benzyloxymethyl substituent at the allylic position of ester (**202**) leads to a predominance of the (*E*)-*syn* rearranged product with Hf and Ti enolates (Table 18, entries 10 and 11). In these cases favorable chelation between the ester enolate and the benzyloxy oxygen stabilizes transition state (**X**; Scheme 15). When the benzyloxy substituent is more remote (Table 18, entries 12–14) such chelation is less favorable and the reaction proceeds through transition state (**U**).

2,3-Rearrangement of the γ-TMS-allyloxy system (**204**) gave the (*Z*)-*syn*-β-TMS-α-hydroxy esters (**205a–c**) as single isomers.[56] These were transformed through reduction and basic elimination to the (*Z,E*)-dienols (**206a–c**). Lewis acid promoted elimination converted ester (**205c**) to the (*Z,Z*)-dienoate (**207**; Scheme 16).

Chiral auxilliaries have been employed to direct stereochemistry in 2,3-rearrangements of ester enolates. The (–)-8-phenylmenthyl α-allyloxyacetates (**208**) rearrange *via* their lithium enolates to the *syn*

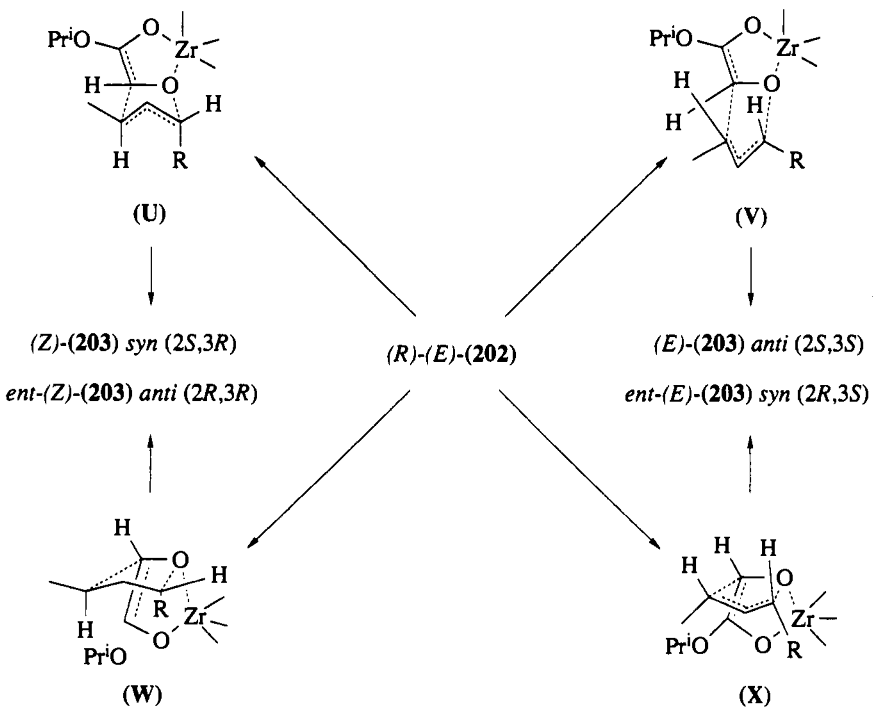

**Scheme 15** Envelope transition states for 2,3-rearrangement of α-allyloxyacetate zirconium enolates

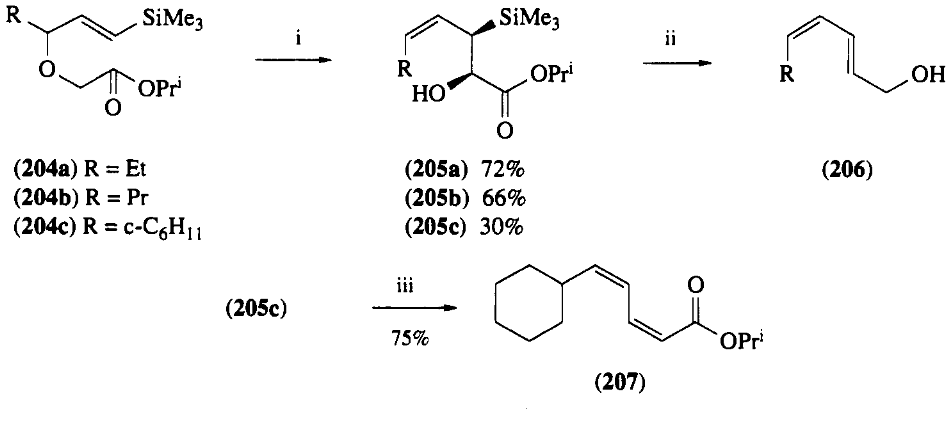

i, LDA, $Cp_2ZrCl_2$, THF; ii, DHP, PPTS, $LiAlH_4$, PPTS, MeOH, NaH; iii, $Et_2O{\bullet}BF_3$, $CH_2Cl_2$

**Scheme 16**

(2*S*, 3*R*)-hydroxy esters (**209**) with generally high diastereo- and enantio-selectivity (Table 19).[57] Best results are obtained with allylic ethers possessing substituents at the γ-position (compare entries 1–4 with 5 and 6). The observed enantioselectivity is in accord with the envelope transition state (**Y**) in which the double bond approaches the enolate from the *si* face to avoid steric confrontation with the bulk of the 8-phenylmenthyl grouping (Scheme 17). Substituents ($R^1$, $R^2$) on the allylic double bond accentuate this steric interaction, thereby enhancing the enantioselectivity.

Substituents at the δ-position of the allylic ether have also been found to influence diastereoselectivity in α-allyloxyacetate enolate 2,3-rearrangements. The acetonide (**211**) afforded the α-hydroxy ester (**212**) containing less than 2% of isomeric rearrangement products (equation 43).[58] In a closely related example, an analog of (**211**), R = $Bu_3Sn$, but with an (*E*) double bond, rearranged upon lithiation to an 86:14 mixture of diastereoisomers. These results can be explained by transition state (**AA**) in which the oxygen of the acetonide aligns perpendicular to the double bond, thereby lowering the LUMO of the allylic system through π*/σ*-orbital overlap (equation 44).

**Table 19** 2,3-Wittig Rearrangement of (–)-8-Phenylmenthyl α-Allyloxyacetates

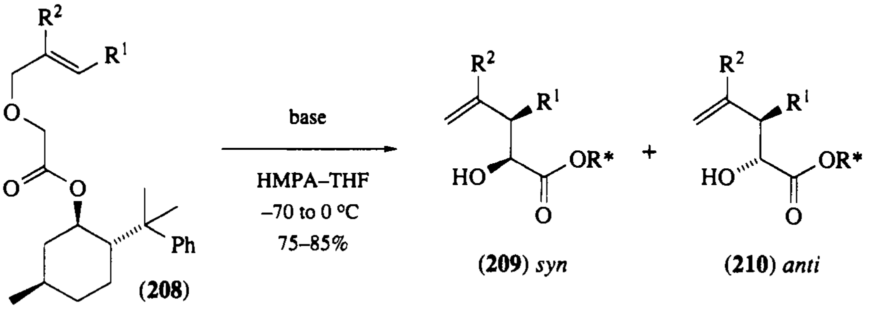

R2
R1
O
O
O
Ph
base
HMPA–THF
–70 to 0 °C
75–85%
HO
OR*
+

**(208)** **(209)** *syn* **(210)** *anti*

| *Entry* | *R*$^1$ | *R*$^2$ | *Base* | *Syn:anti* | *ee (%)*[a] |
|---|---|---|---|---|---|
| 1 | Me | H | LDA | 90:10 | 97 |
| 2 | Me | H | LHDS | 93:7 | 96 |
| 3 | Me | H | LTMP | 92:8 | 97 |
| 4 | Bu | H | LDA | 92:8 | 95 |
| 5 | H | H | LDA | | 11 |
| 6 | H | Me | LDA | | 4 |

[a] Major isomer.

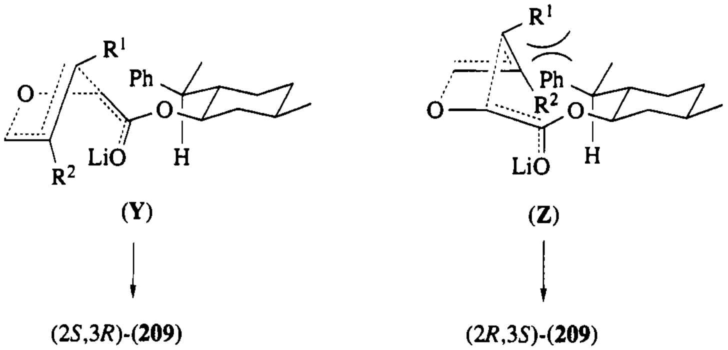

R1
O
Ph
O
LiO
H
R2
(Y)
(Z)
(2S,3R)-(209)
(2R,3S)-(209)

**Scheme 17** Diastereomeric transition states for 2,3-rearrangement of (–)-8-phenylmenthyl α-allyloxyacetates

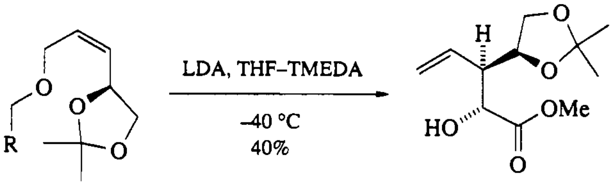

O
R
LDA, THF–TMEDA
–40 °C
40%
H
HO
OMe

**(211)** R = $CO_2Me$ **(212)** (43)

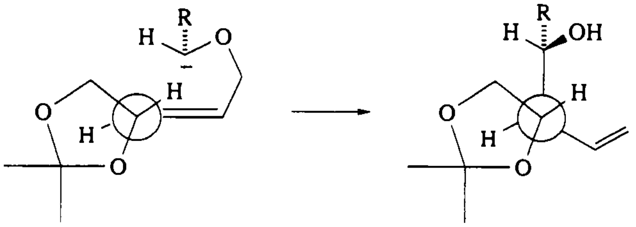

**(AA)** **(212)** R = $CO_2Me$ (44)

### *3.11.3.8.5 α-Allyloxycarboxamides*

The 2,3-rearrangement of α-allyloxyacetamide enolates proceeds readily. (*E*)-Crotyl ethers (**213**) show high *syn* diastereoselectivity (Table 20) in accord with acid and ester analogs (**193**) and (**208**). Amides of homochiral pyrrolidines derived from (*S*)-proline undergo moderately enantioselective rearrangement (entries 5–8).[59] 2,5-Disubstituted pyrrolidine amides, on the other hand, rearrange with appreciably higher enantioselectivity but with generally lower diastereoselectivity.[60] The (*E*)-allylic ether zirconium enolate (Table 21, entry 3) gives the best overall result. In contrast, rearrangement of the isomeric (*Z*)-allylic ether zirconium enolate is unselective (entry 5). The diastereomeric cyclohexyl-substituted allylic ethers (**215**; $R^1 = c\text{-}C_6H_{11}$, $R^2 = H$) exhibit double stereodifferentiation. At low conversion (Table 21, entry 7) product of 87% *ee* is isolated, indicating preferential rearrangement of one diastereomeric amide enolate over the second. At 70% conversion (entry 8) rearrangement of the mismatched diastereoisomer results in a product of lower *ee*.

**Table 20** 2,3-Rearrangement of α-Crotyloxyacetamides

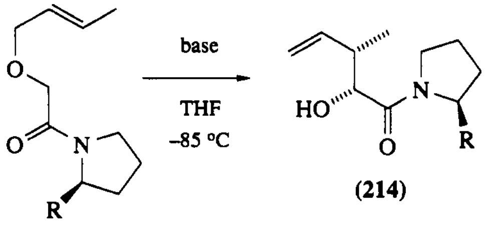

**(213)**

**(214)**

| *Entry* | *R* | *Base* | *Yield (%)* | *Syn:anti* | *ee (%)*[a] |
|---|---|---|---|---|---|
| 1 | H | LDA | 98 | 96:4 | |
| 2 | H | LHMDS | 96 | 96:4 | |
| 3 | H | LDA[b] | 98 | 96:4 | |
| 4 | H | KHMDS | 88 | 96:4 | |
| 5 | $CH_2OH$ | LDA | c | 95:5 | 52 |
| 6 | $CH_2OH$ | LHMDS | c | 95:5 | 20 |
| 7 | $CH_2OMEM$ | LDA | c | 97:3 | 20 |
| 8 | $CH_2OMEM$ | d | c | 95:5 | 12[e] |

[a]Major isomer. [b]THF–HMPA solvent. [c]'70–80%'. [d]LDA, –100 °C; $Cp_2ZrCl_2$. [e]Enantiomer at C-2,C-3 of depicted structure.

**Table 21** 2,3-Rearrangement of Chiral α-Allyloxyacetamides

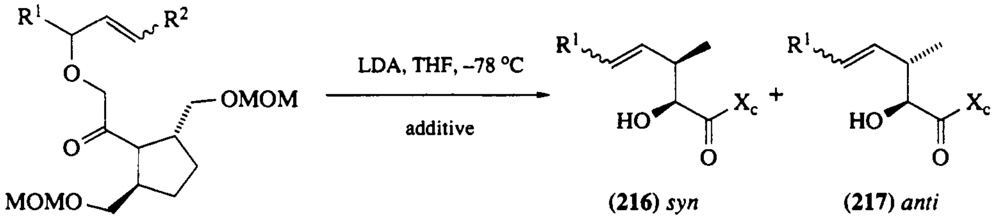

**(215)**

**(216)** *syn*

**(217)** *anti*

| *Entry* | *R*[1] | *R*[2] | *(E)/(Z)* | *Additive* | *Yield (%)* | *Syn:anti* | *ee (%)*[a] |
|---|---|---|---|---|---|---|---|
| 1 | H | H | | None | 61 | | 96 |
| 2 | H | Et | (*E*) | None | 75 | 67:33 | 92 |
| 3 | H | Et | (*E*) | $Cp_2ZrCl_2$ | 65 | 97:3 | 96 |
| 4 | H | Et | (*Z*) | None | 33 | 22:78 | 90 |
| 5 | H | Et | (*Z*) | $Cp_2ZrCl_2$ | 7 | 50:50 | 92 |
| 6 | $n\text{-}C_7H_{15}$ | H | | None | 82 | | 67[b] |
| 7 | $c\text{-}C_6H_{11}$ | H | | $Cp_2ZrCl_2$ | 25 | | 87[b] |
| 8 | $c\text{-}C_6H_{11}$ | H | | $Cp_2ZrCl_2$ | 70 | | 41[b] |

[a]Major isomer. [b](*E*):(*Z*) ratio not determined.

These results are consistent with the chelated transition states depicted in Scheme 18. Steric interactions between the substituent $R^3$ and the carboxamide favor (**AC**) for (*E*)-allylic ethers. The $R^4$-substituent of a (*Z*)-allylic ether, though less affected by this interaction, still experiences a certain degree of steric strain in the *anti* transition state (**AB**) thus diminishing *anti* selectivity. Enantioselectivity is controlled by the substituents $R^1$ and $R^2$ on the pyrrolidine ring. As pictured in Scheme 18, bonding occurs preferentially on the face of the enolate *anti* to $R^1$. For the diastereomeric secondary allylic ethers (Table 21, entries 6–8) transition state (**AB**) represents the matched arrangement for $R^5$ = H and $R^6$ = alkyl, whereas (**AC**) is matched for $R^5$ = alkyl and $R^6$ = H. The former arrangement would lead to an (*E*)-product and the latter to a (*Z*)-product.

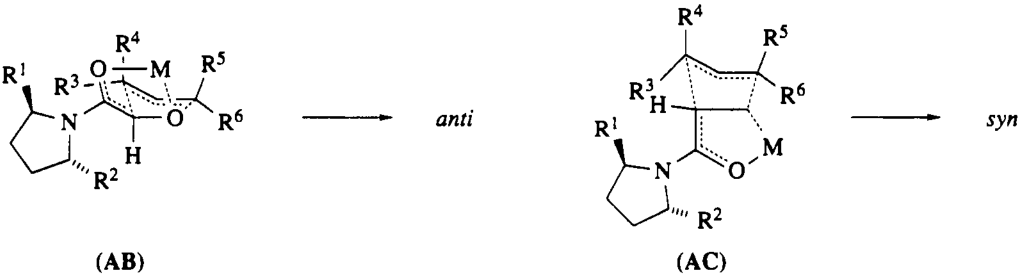

**Scheme 18** Diastereomeric transition states for 2,3-rearrangement of α-allyloxyacetamide enolates

### 3.11.3.8.6 *Allyloxymethyl-oxazolines and -1,3-oxazines*

2-Oxazolines (**218a**) and 5,6-dihydro-1,3-oxazines (**218b**) with C-2 allyloxymethyl substituents, readily undergo 2,3-rearrangement *via* their imino-stabilized anions (Table 22).[61] The (*E*)-crotyl ethers afford the *syn* products (**219a**) and (**219b**) and the oxazoline ether (*Z*)-(**218a**) yields mainly the *anti* product (**220a**). Surprisingly, the 1,3-oxazine analog (*Z*)-(**218b**) gives the *syn* product (**219b**) predominantly.

**Table 22** 2,3-Rearrangement of Oxazoline and 1,3-Oxazine Crotyloxymethyl Anions

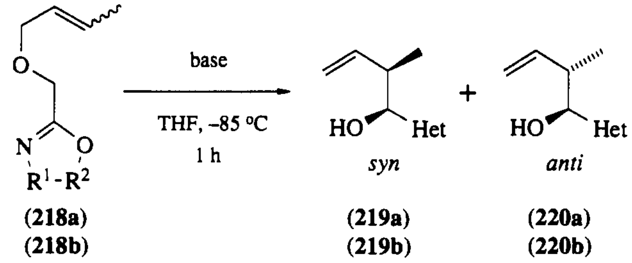

| *Entry* | *System* | *(E)/(Z)* | *Base* | *Yield (%)* | *Syn:anti* |
|---|---|---|---|---|---|
| 1 | (**218a**)[a] | (*E*) | BuLi | 98 | 66:34 |
| 2 | (**218a**)[a] | (*E*) | LDA | 80 | 84:16 |
| 3 | (**218a**)[a] | (*Z*) | LDA | 80 | 22:78 |
| 4 | (**218b**)[b] | (*E*) | BuLi | 92 | 98:2 |
| 5 | (**218b**)[b] | (*E*) | LDA | 86 | 96:4 |
| 6 | (**218b**)[b] | (*Z*) | LDA | 82 | 65:35 |

[a] $R^1$—$R^2$ = $Me_2C$—$CH_2$. [b] $R^1$—$R^2$ = $Me_2C$—$CH_2CHMe$.

These findings have been extended to nonracemic oxazolines (**221**; Table 23).[62,63] The methoxymethyl-substituted derivatives (entries 1–3) rearrange with moderate enantioselectivity and high *syn* diastereoselectivity (entries 2 and 3). The hydroxymethyl analogs, on the other hand, rearrange with excellent enantioselectivity when KH is used as the base (entries 4, 6 and 8–10). However, the crotyl ethers show poor diastereoselectivity (entries 6, 9 and 10).

The foregoing results for the most part parallel those observed with carboxamides (Section 3.11.3.8.5) and an analogous chelated transition state has been proposed (Scheme 19). Accordingly (**AD**) represents the lowest energy rearrangement pathway for (*E*)-allylic ethers. The alternative (**AF**) places the $R^1$-sub-

**Table 23** 2,3-Rearrangement of Chiral Oxazoline Allyloxymethyl Anions

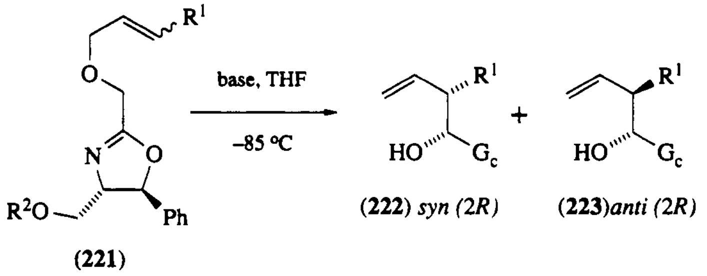
R1
O
N
O
R2O
Ph
(221)
base, THF
−85 °C
R1
HO
Gc
+
R1
HO
Gc
(222) syn (2R)
(223) anti (2R)

| *Entry* | *R*$^1$ | *R*$^2$ | *(E)/(Z)* | *Base* | *Syn:anti* | *ee (%)* | *Configuration* |
|---|---|---|---|---|---|---|---|
| 1 | H | Me | | BuLi | | 38 | (2*R*) |
| 2 | Me | Me | (*E*) | BuLi | 90:10 | 78$^a$ | (2*R*) |
| 3 | Me | Me | (*E*) | LDA | 84:16 | 64$^a$ | (2*R*) |
| 4 | H | H | | KH | | 84 | (2*S*) |
| 5 | H | H | | BuLi | | 8 | (2*R*) |
| 6 | Me | H | (*E*) | KH | 41:59 | 74$^a$ | (2*S*) |
| 7 | Me | H | (*E*) | BuLi | 89:11 | 0$^b$,<br>0$^a$ | |
| 8 | H | H | | KH–18-crown-6 | | 96 | (2*R*) |
| 9 | Me | H | (*E*) | KH–18-crown-6 | 46:54 | 84$^a$<br>86$^b$ | (2*R*)$^a$<br>(2*R*)$^b$ |
| 10 | Me | H | (*Z*) | KH–18-crown-6 | 54:46 | 86$^a$<br>86$^b$ | (2*R*)$^a$<br>(2*R*)$^b$ |

$^a$Major isomer. $^b$Minor isomer.

stituent closer to the oxazoline ring. Interactions between the R$^1$-substituent and the oxazoline ring must also exist to a degree in (**AD**) as evidenced by the lower enantioselectivity of rearrangements in systems lacking this substituent (Table 23, entries 1 *versus* 2). Evidently the methoxymethyl- and hydroxymethyl-substituted oxazoline systems (**221**; R$^2$ = Me or H) rearrange through different transition states. The potassium counterion plays a major role in the latter cases (Table 23, compare entries 4 and 6 with 5 and 7). The possibility of a preferred (*Z*)-enolate has been suggested to explain the enantioselectivity of rearrangements carried out with KH–18-crown-6 (Table 23, compare entries 4 with 8 and 6 with 9).

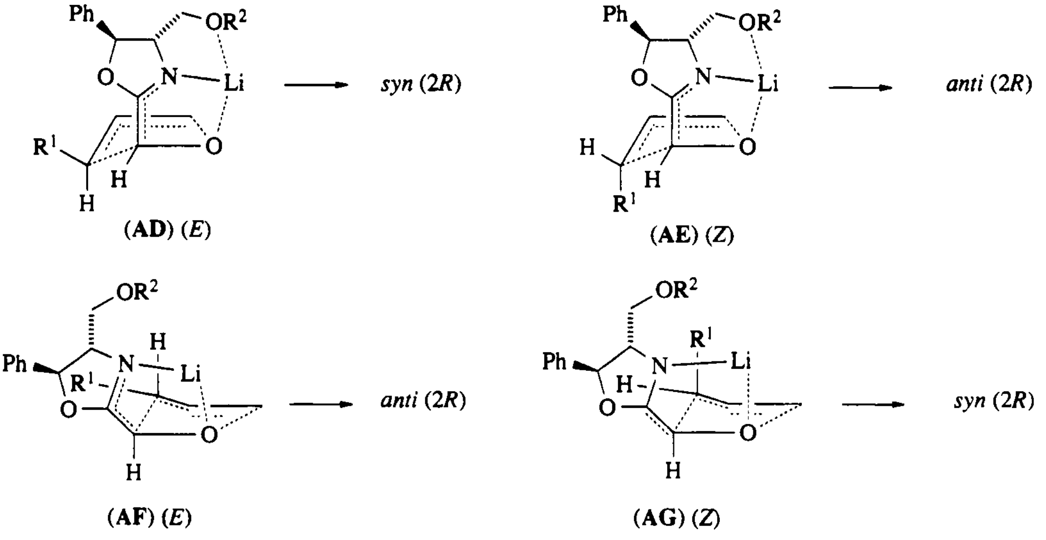
Ph
OR2
O
N
Li
R1
O
H
H
(AD) (E)
syn (2R)
Ph
OR2
O
N
Li
H
O
H
R1
(AE) (Z)
anti (2R)
OR2
Ph
H
N
Li
R1
O
O
H
(AF) (E)
anti (2R)
OR2
R1
Ph
N
Li
H
O
O
H
(AG) (Z)
syn (2R)

**Scheme 19** Transition states for 2,3-rearrangement of oxazoline allyloxy anions

The role of chelation by lithium cations in 2,3-rearrangements of oxazoline allyloxymethyl anions is exemplified by the contrasting behavior of the two tertiary ethers (**224**; equation 45) and (**227**; equation

46).[64] Rearrangement of the former affords a 72:28 mixture of (*Z*)- and (*E*)-products (**225**) and (**226**), whereas the methoxymethoxy analog (**227**) yields the (*E*)-isomer (**229**) as the sole product. The epimeric tertiary allylic methoxymethoxy-substituted ether (**231**; equation 47), on the other hand, gives rise to a 64:36 mixture of rearranged products favoring the (*E*)-isomer (**233**).

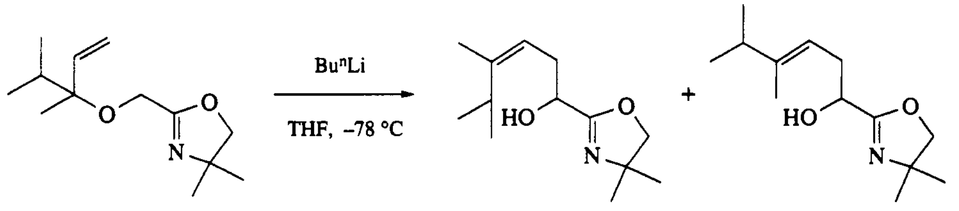

(**224**) (**225**) (72%) (**226**) (28%) (45)

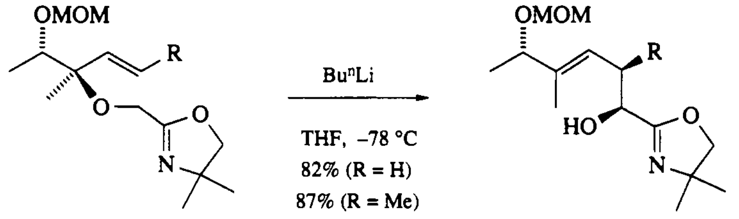

(**227**) R = H
(**228**) R = Me

(**229**) R = H (100%)
(**228**) R = Me (98.5%)

(46)

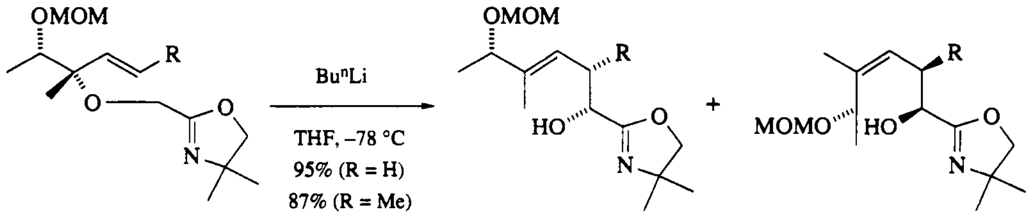

(**231**) R = H
(**232**) R = Me

(**233**) R = H (64%)
(**234**) R = Me (69%)

(**235**) R = H (36%)
(**236**) R = Me (31%)

(47)

The high (*E*)-preference observed with ether (**227**) can be accounted for by the chelated transition state (**AH**) in which the oxazolidine enamide is held in close proximity to the allylic double bond terminus in the *s-trans* conformation (Scheme 20). The analogous transition state (**AI**) for the epimer (**231**) suffers from an eclipsing interaction between the two adjacent carbinyl methyl groupings. Accordingly, the rearrangement of (**231**) takes place, in part, *via* a nonchelated *s-cis* conformer to give a mixture of (*E*)- and (*Z*)-products. The crotyl ether (**228**) likewise rearranges with high (*E*)-selectivity, whereas the epimeric ether (**232**) gives rise to a mixture of isomers favoring the (*E*)-product (**234**). Selectivity for the cooperative diethers (**227**) and (**228**) decreases dramatically (to 90:10 and 55:45, respectively) in the presence of HMPA, owing to competitive coordination of the lithium cation with this cosolvent.

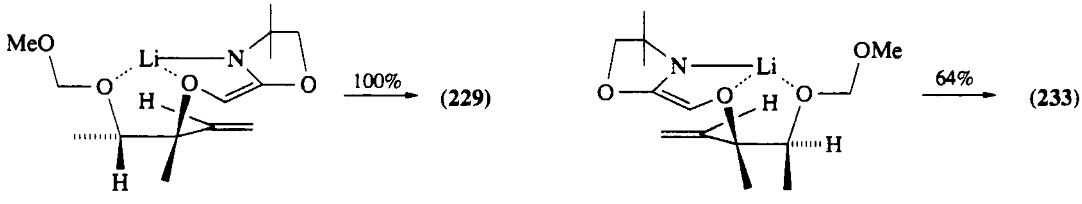

(**AH**) (**AI**)

**Scheme 20** Chelated transition states for 2,3-rearrangement of epimeric tertiary alkoxyallyl oxazolines

Greatly enhanced ratios of the (*E*)/(*Z*)-products (**234**):(**236**) (>99:1) can be realized by using MeMgBr as the base for rearrangement of the uncooperative diether (**232**), but the yield is only 20%. Presumably, chelation is strong with a Mg counterion, but the anionic character of the resulting enamide is relatively weak.

An application of this chemistry to the synthesis of the nargenicins has recently been reported.[64a]

### 3.11.3.9 Oxonium Ylide Rearrangements

The 2,3-rearrangement of α-allyloxyacetic esters can be effected with TMSOTf and $Et_3N$ (Table 24).[65–71] A pathway involving the trimethylsilyloxonium ylide (**240**; equation 48) has been proposed. Accordingly, treatment of the TMS ketone acetals (**239**; $R^1$ = Me, $R^2 = R^3$ = H; $R^1 = R^2$ = Me, $R^3$ = H; $R^1 = R^2$ = H, $R^3$ = Me) with 20 mol % of TMSOTf yields rearranged products (**241**) in ratios comparable to those obtained directly from the corresponding esters (**237**). The enhanced formation of (*Z*)-products is thought to reflect a preference for the *anti* (**AJ**) *versus syn* (**AK**) $R^1/Me_3Si$ orientation in the oxonium intermediates (Scheme 21).

**Table 24** Trimethylsilyl Triflate Promoted 2,3-Rearrangement of α-Allyloxyacetic Esters

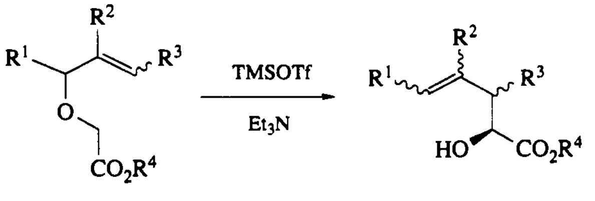

(**237**) (**238**)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *(E) or (Z)* | *Yield (%)* | *(E):(Z)* | *Syn:anti* |
|---|---|---|---|---|---|---|---|
| Me | H | H | Me | | 93 | 31:69 | |
| Me | H | H | H | | 85 | 43:57 | |
| Me | Me | H | Me | | 98 | 31:69 | |
| H | H | Me | Me | (*E*) | 83 | | 92:8 |
| H | H | Me | H | (*E*) | 92 | | 88:12 |
| H | H | Me | Me | (*Z*) | 86 | | 53:47 |
| H | H | Me | $Pr^i$ | (*E*) | 86 | | 95:5 |
| H | H | Me | $Bu^t$ | (*E*) | 56 | | 88:12 |

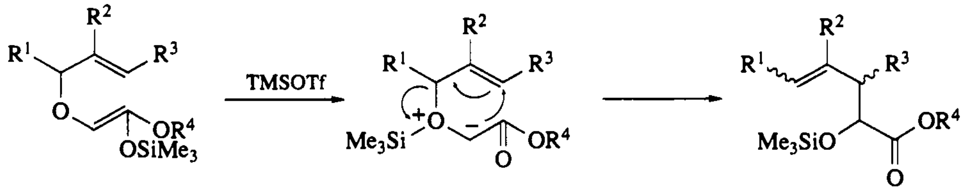

(**239**) (**240**) (**241**) (48)

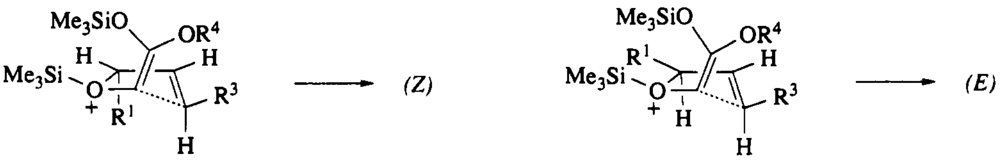

(**AJ**) *anti* (**AK**) *syn*

**Scheme 21** Transition state orientations for trimethylsilyloxonium rearrangements

### 3.11.3.10 Cyclic 2,3-Rearrangement–Ring Contractions

In 1986 the groups of Takahashi[72] and Marshall[73] independently and simultaneously announced a new application of the 2,3-Wittig rearrangement for the construction of medium and large ring carbocycles (Scheme 22). The incorporation of the allylic ether into a cyclic structure (**AL**) ensures favorable proximity of the reacting centers, as in (**AM**), thereby lowering the activation energy of the rearrangement considerably.

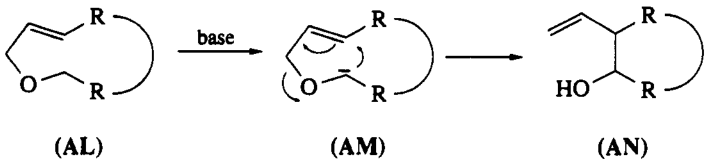

**Scheme 22** 2,3-Wittig ring contraction

Thus, for example, the cyclic propargylic allylic ether (**242**; equation 49) rearranges completely within 30 min upon treatment with Bu$^n$Li in THF–hexane at –20 °C, whereas the acyclic analog (**244**; equation 50) requires 12 h under comparable conditions. Alcohol (**243**) serves as a useful intermediate for the synthesis of cembranoid diterpenes.[74]

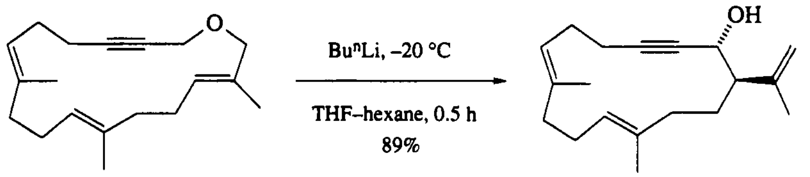

(49)

(**242**) (**243**) 80:20 *trans*:*cis*

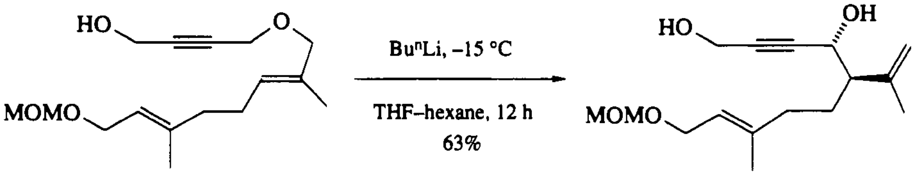

(50)

(**244**) (**245**) 67:33 *trans*:*cis*

Takahashi and coworkers studied 2,3-Wittig ring contractions of the isomeric 13-membered diallylic ethers (**246**), (**248**) and (**250**).[72] The (*E*,*E*)-diallylic ether (**246**; equation 51) rearranges to the (*E*)-*trans*-cyclodecenol (**247**). Interestingly, the (*Z*,*Z*)-ether (**248**; equation 52) yields the (*Z*)-*trans*-cyclodecenol (**247**) with the opposite relative stereochemistry from that observed with acyclic (*Z*)-allylic ethers (Table 12). The (*Z*,*E*)-diallylic ether (**250**; equation 53) is converted with high regioselectivity to a 9:91 mixture of (*E*)- and (*Z*)-products (**247**) and (**249**). The latter consists of a 50:41 mixture of *trans* and *cis* isomers. The contrasting diastereoselectivity of acyclic (*E*)-allylic ethers is again noteworthy (Table 12). Evidently, conformational factors in these cyclic diallylic ethers attenuate or override intrinsic transition state preferences of the acyclic analogs (Scheme 9).

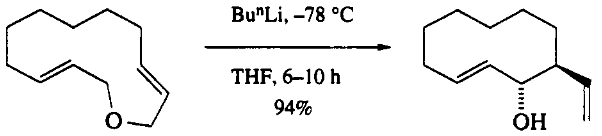

(51)

(**246**) (**247**)

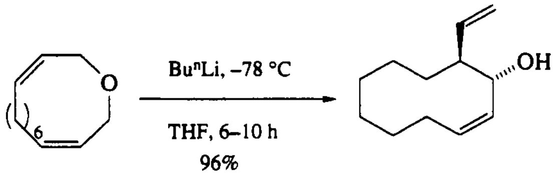

(52)

(**248**) (**249**)

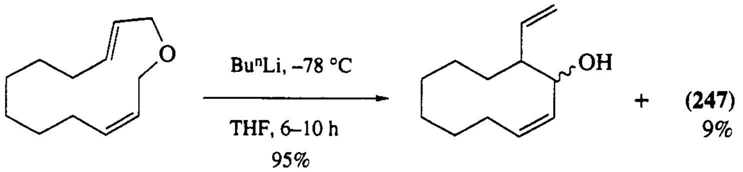

(250) (249) *trans*; 50% (251) *cis*; 41% (247) 9% (53)

The isoprenoid (*E,E*)-diallylic ether (**252**; equation 54) affords a 75:25 mixture of the regioisomeric products (**253**) and (**254**) in 98% yield. The major isomer (**253**) was employed in a synthesis of racemic costunolide, a medium ring sesquiterpene. In a related application the TBS ether (**255**; equation 55) was converted to a 48:52 mixture of regioisomers (**256**) and (**257**) in 90% yield.[75] The former consists of a 81:19 mixture of diastereoisomers (**256a**) and (**256b**). Alcohol (**256a**) was converted to the sesquiterpene (±)-haagenolide, along lines developed in the costunolide synthesis.[72]

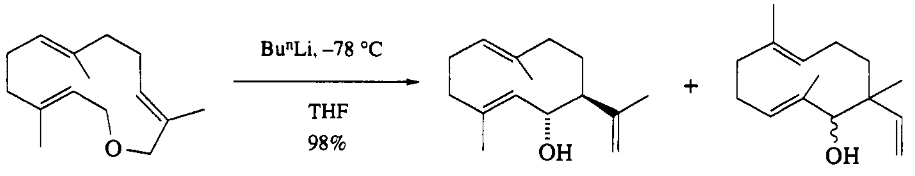

(252) (253) 75% (254) 25% (54)

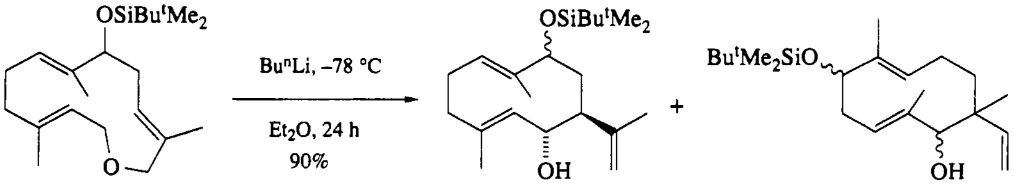

(255) (55)

(256a) β-Bu$^t$Me$_2$SiO; 39% (257) 52%

(256b) α-Bu$^t$Me$_2$SiO; 9%

In contrast to the foregoing diallylic examples, the 13-membered allylic propargylic ether (**258**) rearranges to a single regioisomer (**259**).[74] The apparent preference for propargylic anion formation is in accord with analogous acyclic systems. In the first application of nonracemic chiral bases for 2,3-Wittig rearrangements, treatment of the allylic propargylic ether (**258**) with the lithio amide (+)-(**260**), prepared from (*R*)-(+)-1-phenylethylamine, afforded the (–)-alcohol (**259**) in 78% yield and 70% *ee*.[76] The enantiomeric base (–)-(**260**) gave rise to (+)-(**259**) in comparable yield and *ee*. These alcohols were converted to the germacranolide sesquiterpene aristolactone (+)-(**261**) and its enantiomer (Scheme 23). The bases (+)- and (–)-(**260**) also effect 2,3-Wittig rearrangement of the 17-membered allyl propargyl ether (**242**) to the cembranoid precursor (**243**) with an *ee* of 20–30%. The nine-membered diallylic ether (**262**; equation 56) afforded the optically active alcohol isopiperitenol (**263**) of 25% *ee* upon treatment with (–)-(**260**).[77] This rearrangement was considerably slower than those of the 13- and 17-membered ethers (**246**), (**252**), (**258**) and (**242**), indicative of a more highly strained transition state. The preferential formation of the *cis* diastereoisomer from the (*E*)-allylic ether moiety is contrary to results obtained with acyclic (*E*)-allylic ethers (Table 12). It should be noted that the diallylic ether (**262**) is incapable of rearranging to the regioisomeric product derived from α′-deprotonation because of the strain associated with a *trans*-cyclohexene product.

The acyclic ethers (**264a–c**; equation 57) failed to give optically active rearrangement products with the nonracemic amide base (–)-(**260**). Accordingly, the asymmetric induction observed in the rearrangements of ethers (**242**), (**258**) and (**262**) appears to depend upon the chiral environment provided by the cyclic array.

Macrocyclic ethers with remote *sp*$^3$ stereocenters can undergo diastereoselective 2,3-Wittig ring contractions. Thus, the alcohol (**266a**; equation 58) and several of its ether derivatives (**266b**) and (**266c**) upon treatment with Bu$^n$Li in pentane–THF–TMEDA afforded the four diastereomeric rearrangement

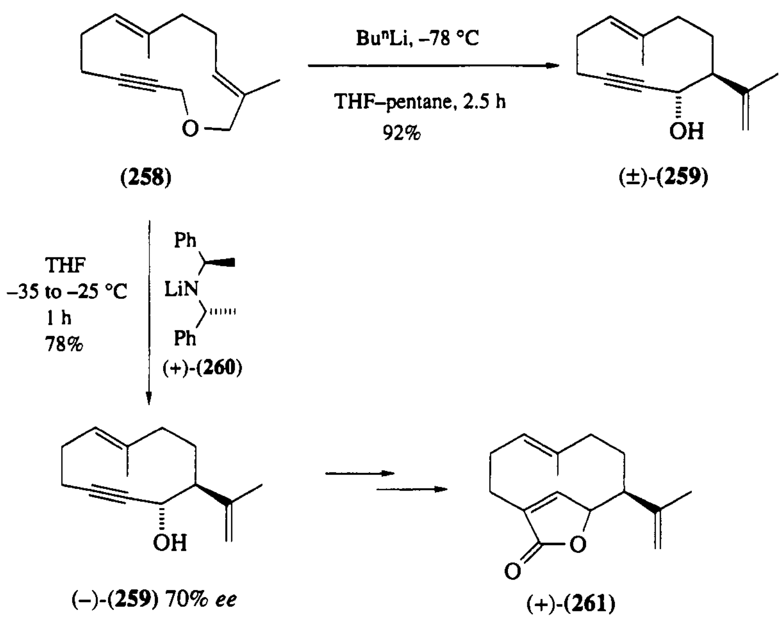
Bu$^n$Li, –78 °C
THF–pentane, 2.5 h
92%
(258)
OH
(±)-(259)
THF
–35 to –25 °C
1 h
78%
Ph
LiN
Ph
(+)-(260)
OH
(–)-(259) 70% *ee*
O
O
(+)-(261)

Scheme 23

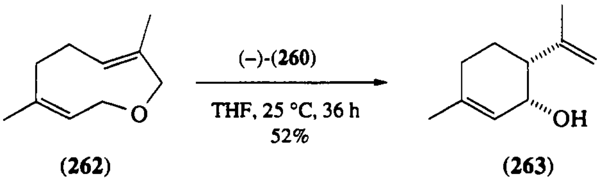
O
(–)-(260)
THF, 25 °C, 36 h
52%
OH
(262)
(263)

(56)

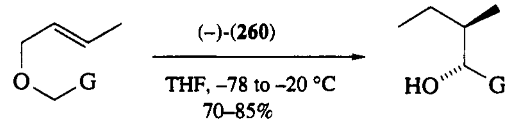
O
G
(–)-(260)
THF, –78 to –20 °C
70–85%
HO
G

(57)

**(264a)** G = C≡CH

**(264b)** G = $CO_2H$

**(264c)** G = $CON(CH_2)_4$

(±)-**(265)**

products (**267**)–(**270**) in varying ratios (Table 25), depending upon the nature of the substituent OR.[78] Presumably, bulkier OR groupings tend to fix the conformation of the macrocyclic ether, thereby enhancing the diastereoselectivity of deprotonation and ensuing 2,3-rearrangement. Because the controlling substituent is well removed from the reaction center, this type of directing effect is referred to as remote

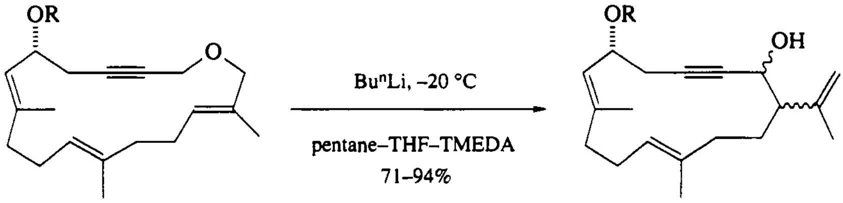
OR
O
Bu$^n$Li, –20 °C
pentane–THF–TMEDA
71–94%
OR
OH

(58)

**(266a)** R = H

**(266b)** R = THP

**(266c)** R = $SiBu^tMe_2$

(**267**)–(**270**)

diastereocontrol. A similar effect may be operational in the rearrangement of the 13-membered ether (**255**), although in this example the substituent is closer to one of the reacting centers and could therefore exert a direct steric effect.

**Table 25** Remote Diastereocontrol in Macrocyclic 2,3-Wittig Ring Contraction

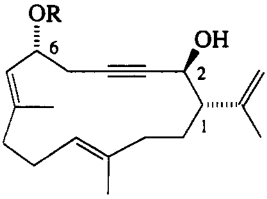

**(267a)** R=H
**(267b)** R=THP
**(267c)** R=TBS

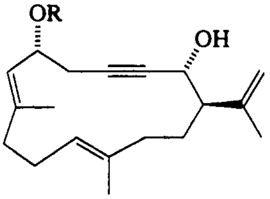

**(268)**

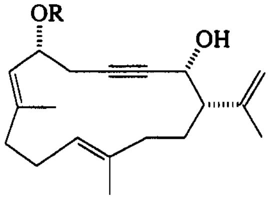

**(269)**

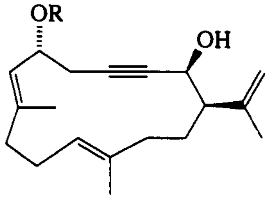

**(270)**

| *R* | *Yield (%)* | *(**267**)* | *(**268**)* | *(**269**)* | *(**270**)* | *Trans/cis*[a] | *Syn/anti*[b] |
|---|---|---|---|---|---|---|---|
| H (a series) | 71 | 20 | 29 | 39 | 12 | 49:51 | 59:41 |
| THP (b series) | 90 | 81 | 7 | 6 | 6 | 88:12 | 87:13 |
| TBS (c series) | 94 | 74 | 8 | 14 | 4 | 82:18 | 88:12 |

[a] C-1/C-2 relationship. [b] C-1/C-6 relationship.

Remote diastereocontrol can be used to effect chirality transfer in these macrocyclic systems. Thus ring contraction of the nonracemic propargyl ether (+)-(**266c**), followed by Swern oxidation, afforded the ketone (**271**) as a 9:1 mixture of *syn* and *anti* isomers in over 70% yield (Scheme 24). Further transformations led to α- and β-CBT (**274**) and (**275**), two tumor inhibitory constituents of tobacco.[79] The former was prepared in nonracemic form starting from (+)-(**266c**) of the indicated (*R*)-configuration.[80] The β-isomer (**275**) was obtained as the racemate starting from racemic (**266c**).

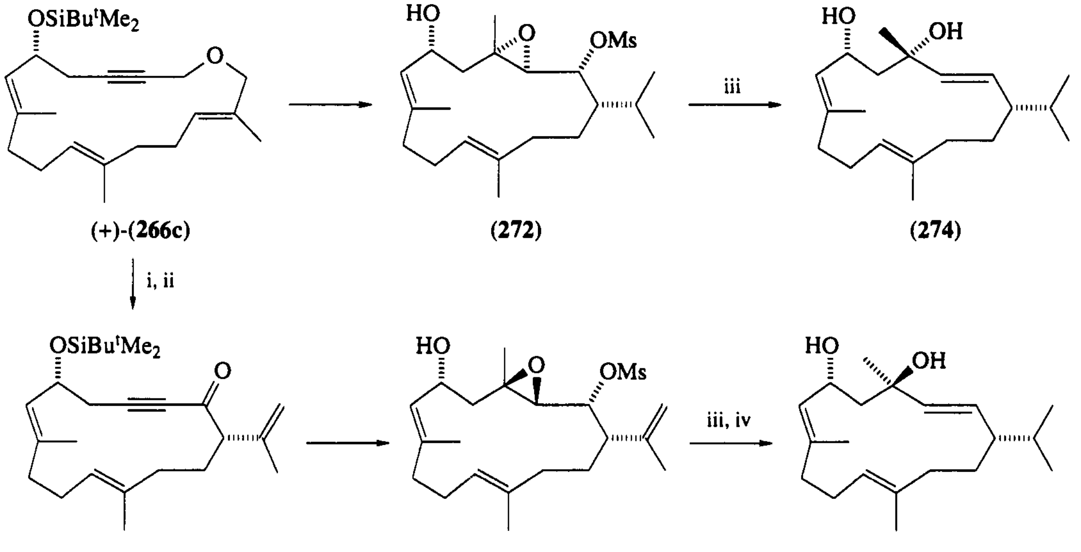

i, Bu$^n$Li, pentane, –78 °C; ii, $(COCl)_2$, $Et_3N$, DMSO; iii, Na, $NH_3$, THF; iv, $(PPh_3)RhCl$, $H_2$, $C_6H_6$, EtOH

**Scheme 24**

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# 4.1

# Carbonylation and Decarbonylation Reactions

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## 4.1.1 INTRODUCTION

Fifty years ago the first well-defined carbonylation reaction was discovered by Otto Roelen.[1] Whilst studying the high pressure, cobalt-catalyzed Fisher–Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen, he observed that addition of ethylene to the $CO/H_2$ feed gas led to formation of 1-propanal in high yield. This reaction, subsequently named hydroformylation, as it results in the addition of hydrogen to one end of the $C{=}C$ double bond and a formyl group at the other, has been intensively studied over the years[2] and has formed the basis of several industrial processes, for example the synthesis of 1-butanal from propene, and acrylic acid from acetylene. Unfortunately, the reaction generally requires the use of high temperatures (100–300 °C) and pressures (100–1000 bar; 1 bar = 100 kPa), expensive autoclave equipment and the use of large quantities of toxic or unstable catalysts such as $[Ni(CO)_4]$, $[Fe(CO)_5]$ or $[HCo(CO)_4]$.

Subsequently, up until the early 1960s carbonylation chemistry was little considered as a synthetic method for the preparation of fine organic chemicals. In recent years, however, there has been a dramatic change in this picture, mostly brought about by the discovery of stable but extremely active catalysts based on organophosphine complexes of palladium and rhodium. Many carbonylations can now be carried out below 100 °C at atmospheric pressure, using very small quantities of involatile, air-stable catalyst precursors, such as $[Pd(PPh_3)_2Cl_2]$ or $[RhCl(CO)(PPh_3)_2]$, which are converted to the active catalytic species *in situ*. Moreover, the scope and understanding of carbonylation has grown to such an extent that it can now be regarded, like catalytic hydrogenation, as one of the more generally useful techniques of synthetic organic chemistry, with a well-developed set of guidelines for choice of catalyst and reaction conditions. In most cases the functional group tolerances of catalysts and reaction conditions have been examined and selectivities between different functional groups established, so that reactions using new substrates can be carried out with a degree of confidence impossible a few years ago.

Even after 50 years of continuous development carbonylation chemistry has still not achieved its full potential and new reactions are still being discovered, a good recent example being double carbonylation leading to α-keto carboxylic acids, α-keto esters and α-keto amides.[3]

Whilst a large number of transition metal complexes have been studied for carbonylation reactions, most transformations can be carried out by selection from a relatively small number of accessible metal complexes (Table 1). Wherever possible, reactions described later in this chapter will avoid the use of volatile and toxic metal carbonyls, particularly $[Ni(CO)_4]$, and will concentrate on the use of readily available metal complex catalysts or reagents which can be used in apparatus familiar to the synthetic organic chemist.

**Table 1** Transition Metal Complexes Used in Carbonylation Reactions

| *From*<br>*To* | *Aryl halide* | *Alkyl, vinyl halide* | *Alkene* | *.Alkyne* |
|---|---|---|---|---|
| Aldehyde | a, b | d, f | d, e, g | — |
| Ketone | a, b, j | a, f | a, d, g | g |
| Carboxylic acid | a, h | f, g | g, h | g, h |
| Ester | a, h | a, f, g | g, h | c, h |
| Lactone | a, g | a, b, h | c, e | c |
| Lactam | a, g | a | e | — |
| Amide | a, g | a, h | — | — |

[a] $[Pd(PPh_3)_2Cl_2]$. [b] $[Pd(PPh_3)_4]$. [c] $PdCl_2$. [d] $[PtCl_2(PPh_3)_2]$. [e] $[HRhCO(PPh_3)_3]$. [f] $[Fe(CO)_5]$, $Na_2[Fe(CO)_5]$. [g] $[Co_2(CO)_8]$, $Na[Co(CO)_4]$. [h] $[Ni(CO)_4]$. [j] $[Ni(CO)_2(PPh_3)_2]$.

## 4.1.2 CARBONYLATION MECHANISMS

Despite the presence of a formally divalent carbon atom, CO is not in fact a particularly reactive molecule and much of its chemistry depends on the use of either extreme conditions, energetic reagents or some form of catalysis. Perhaps the simplest examples of such catalysis are found in the reactions of carbon monoxide with protic reagents such as alcohols or secondary amines, affording esters or amides of formic acid. These reactions are catalyzed by alkoxide or amide anions, respectively, and, as shown in Scheme 1, the key step is nucleophilic attack on CO by the catalyst to give a strongly basic alkoxyacyl or aminoacyl anion which is immediately trapped by proton transfer from the alcohol or amine, so generating the catalytic species.

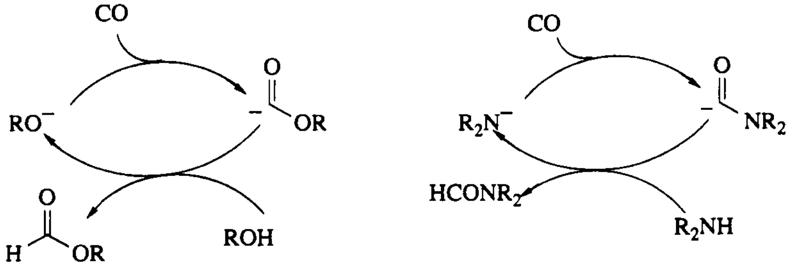

Scheme 1

The aminoacyl anions can also be generated as stoichiometric reagents in the form of lithium derivatives which are stable at –75 °C and react with a variety of electrophiles, including alkyl halides, aldehydes and ketones (Scheme 2).[4]

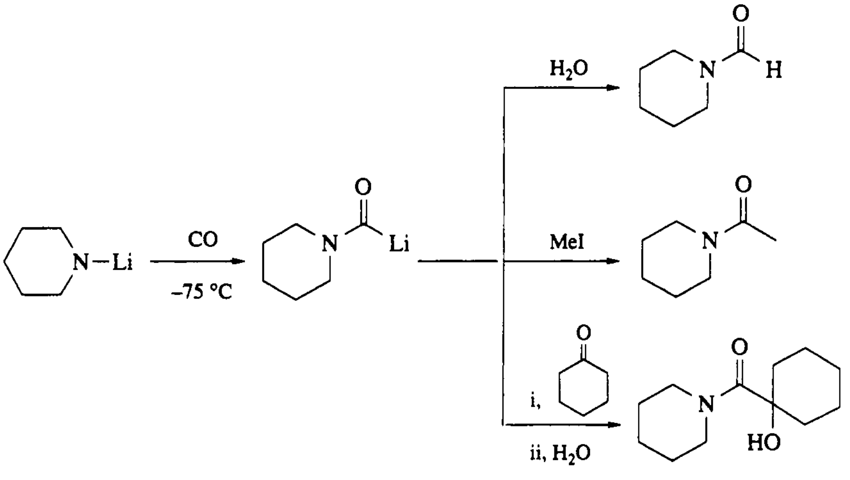

**Scheme 2**

Organolithium reagents, like lithium amides, also react with carbon monoxide at low temperature (–100 °C) *via* a formal nucleophilic attack to give acyllithium species which can be trapped cleanly by reaction with alkyl or silyl halides. Other trapping agents can also be used; aldehydes and ketones afford α-hydroxy ketones, whereas esters give good yields of α-diketones (Scheme 3). In the absence of such trapping agents, however, complex mixtures of products tend to be obtained on hydrolytic work-up, so that although reaction of phenyllithium with CO yields benzophenone as the major product, appreciable quantities of benzoin, benzil, benzpinacol and benzhydrol are also formed.[5]

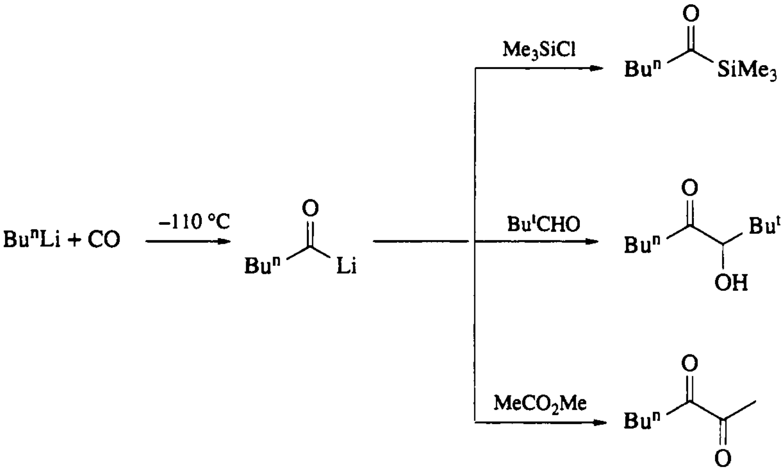

**Scheme 3**

Since the highest filled molecular orbital in carbon monoxide is the weakly antibonding carbon-centered 5σ-orbital, it would be reasonable to expect electrophilic reagents to attack CO at carbon and, indeed, powerful electrophiles such as carbenium ions do react to give acylium ions $[R_3CCO]^+$, which can be hydrolyzed to carboxylic acids *in situ* (the Koch reaction).[6] However, carbon monoxide is an extremely weak σ-donor and does not form stable complexes with more conventional Lewis acids such as $BF_3$ or $AlCl_3$, though there is good evidence for a transient protonated species (solvated $[HCO]^+$) in acid-catalyzed reactions of CO with aromatics (Gatterman–Koch synthesis, Scheme 4).[7]

In contrast, transition metals form a vast array of complexes containing coordinated CO. The effect of the metal coordination is to increase the susceptibility of CO towards nucleophilic attack, either by another ligand or by a noncoordinated nucleophile. A detailed description of the various transition metal catalyzed reactions is not appropriate here, especially as excellent reviews are available.[8] However, it is

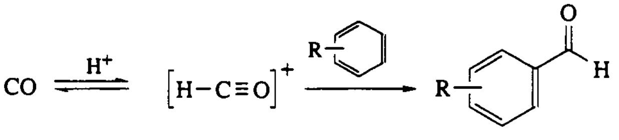

Scheme 4

worthwhile to outline the five major types of carbonylation which will describe nearly all the reactions to be detailed later.

### 4.1.2.1 Direct Carbonylation

This is the simplest of all carbonylations and is best illustrated by the conversion of iodomethane to acetyl iodide,[9] a reaction crucial to the success of the low pressure Monsanto process for acetic acid production from methanol (equation 1).

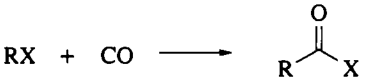

(1)

### 4.1.2.2 Substitutive Carbonylation

Direct carbonylation of an organic halide is a rather rare synthetic process and systems in which halide ion is replaced by a nucleophile (equation 2) are much more frequently encountered. This is a particularly versatile type of reaction providing a wide range of 'acyl anion equivalents', which allow the synthesis of many carboxylic acid derivatives from organic halides. As an example, the elementary steps involved in the palladium-catalyzed carbonylation of a bromoarene are shown in Scheme 5, where oxidative addition is followed by CO insertion and reductive cleavage by whichever nucleophile (Nu = OH, OR, $NR_2$ or F) is present in the system. Substitutive carbonylation of aliphatic halides is also possible, but generally requires more vigorous conditions and the use of platinum–phosphine complexes, such as $[Pt(PPh_3)_2Cl_2]$.[10]

$$RX + CO + Nu^- \longrightarrow RCONu + X^- \qquad (2)$$

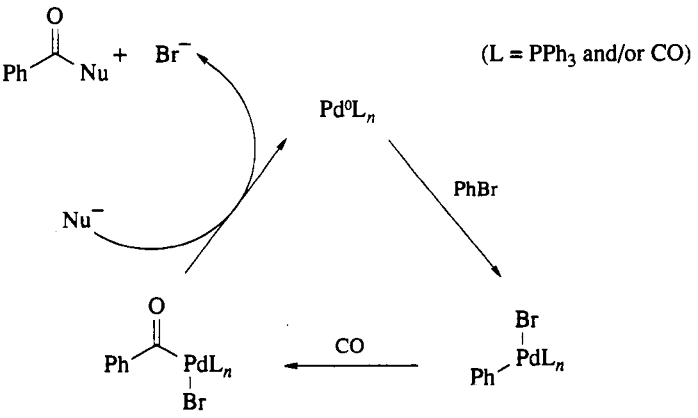

Scheme 5

A rather different approach to carbonylation of aliphatic halides involves the carbonyl anion $[Co(CO)_4]^-$ which, being a kinetically stable 18-electron species, attacks the halide by nucleophilic displacement rather than by undergoing oxidative addition. A probable catalytic cycle for cobalt-catalyzed carbonylation of benzyl chloride is shown in Scheme 6.[11]

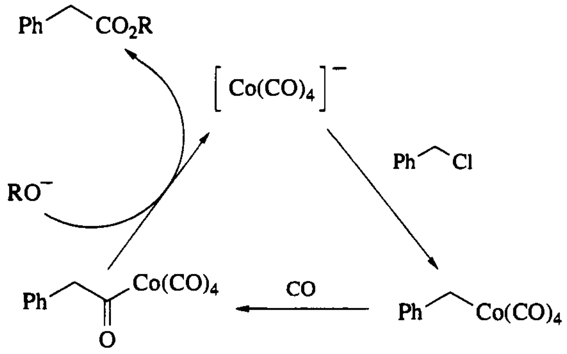
Ph CO2R
[Co(CO)4]⁻
Ph Cl
RO⁻
Ph Co(CO)4 O
CO
Ph Co(CO)4

Scheme 6

### 4.1.2.3 Additive Carbonylation

As noted in the introduction this class of reaction includes hydroformylation (Y = H; equation 3), the first carbonylation to be discovered. Replacing hydrogen by water or an alcohol yields carboxylic acids (hydrocarboxylation) or esters (hydroesterification), respectively, and although different catalysts may be required the general mechanistic pattern is very similar in all three cases. The reaction is initiated by alkene insertion into a metal–hydride bond and the resulting alkyl ligand migrates to coordinated CO. In cobalt-catalyzed hydroformylation, oxidative addition of hydrogen to the metal is followed by reductive elimination of aldehyde, and the original metal hydride complex is thus regenerated (Scheme 7).

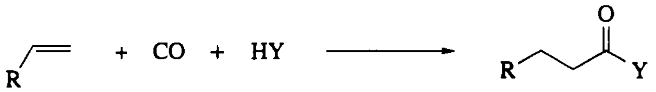

(3)

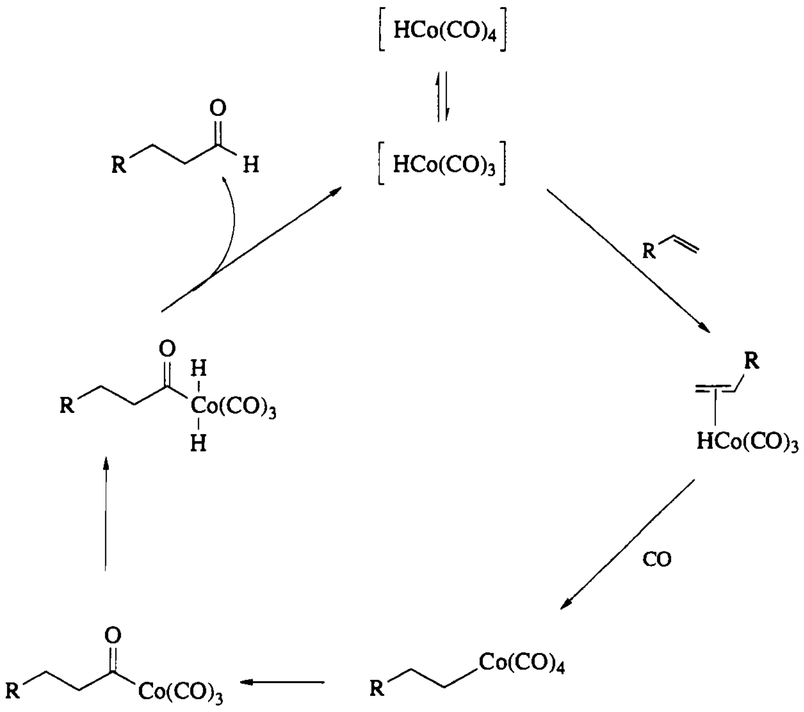
[HCo(CO)4]
[HCo(CO)3]
O
R H
R
R
HCo(CO)3
O H
R Co(CO)3
H
CO
O
R Co(CO)3
R Co(CO)4

Scheme 7

### 4.1.2.4 Multicomponent Carbonylations

One of the best illustrations of the ability of homogeneous catalysts to assemble complex organic molecules by sequential insertions is the hydroxybutenolide synthesis shown in Scheme 8, where no fewer than five separate molecules (MeI, HC≡CR, $H_2O$ and 2CO) combine under ambient conditions with high selectivity.[12]

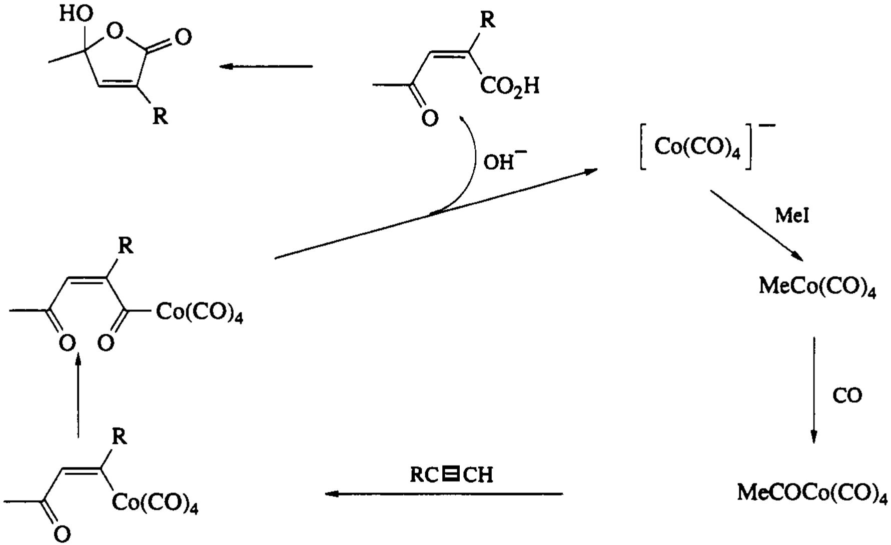
HO
O
O
R
R
CO2H
O
OH⁻
[Co(CO)4]⁻
MeI
MeCo(CO)4
CO
MeCOCo(CO)4
RC≡CH
R
Co(CO)4
O
R
Co(CO)4
O O

Scheme 8

### 4.1.2.5 Decarbonylation

Since most of the elementary reactions involved in carbonylation chemistry are readily reversible (equation 4), it is not surprising that metal complexes which catalyze carbonylation also catalyze decarbonylation under certain conditions. The catalytic decarbonylation of aldehydes by [RhCl(CO)($PPh_3$)$_2$], for example, is shown in Scheme 9.

$$\mathrm{RCOX} \longrightarrow \mathrm{RX} + \mathrm{CO} \qquad (4)$$

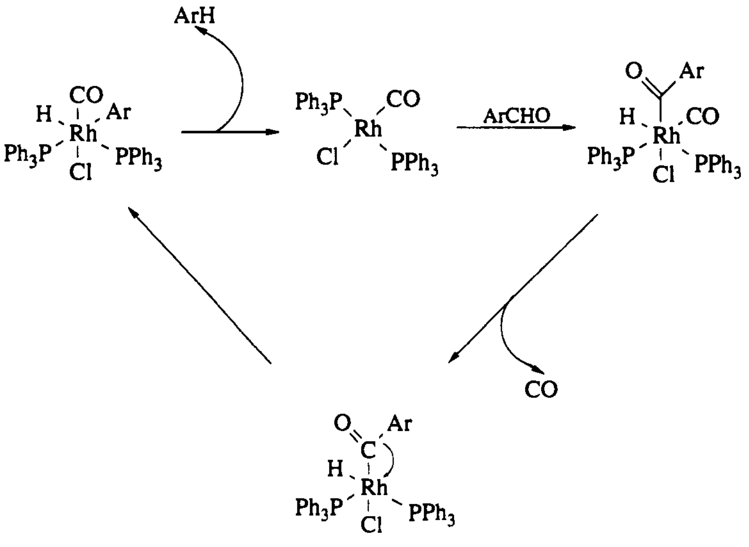
ArH
CO
H
Ar
Rh
Ph3P
PPh3
Cl
Ph3P
CO
Rh
Cl
PPh3
ArCHO
O
Ar
H
CO
Rh
Ph3P
Cl
PPh3
CO
O
Ar
C
H
Rh
Ph3P
Cl
PPh3

Scheme 9

### 4.1.3 FORMATION OF ALDEHYDES

The direct catalytic carbonylation of halides to aldehydes is not readily achieved. Aryl, heterocyclic and vinyl halides, for example, in the presence of $[Pd(PPh_3)_2Cl_2]$, a stoichiometric quantity of tertiary amine and synthesis gas ($CO/H_2$), are converted to aldehydes, but the conditions are somewhat drastic (80–100 bar, 80–150 °C).[13] Alkyl halides are even less suitable for this reaction as they tend to undergo dehydrohalogenation to form alkenes, rather than carbonylation. However, using the platinum catalyst $[PtCl_2(PPh_3)_2]$, primary alkyl iodides can be successfully carbonylated to aldehydes in good yield under moderate conditions (equation 5).[10]

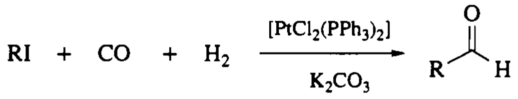

(5)

Using poly(methylhydrosiloxane) (PMHS) as the hydrogen donor, aryl and benzyl halides can be carbonylated to aldehydes in the presence of $[Pd(PPh_3)_4]$ under mild conditions (3 bar, 80 °C).[14] The reaction only works for iodides; 4-bromophenyl iodide, for example, is converted to 4-bromobenzaldehyde in 95% yield (equation 6).

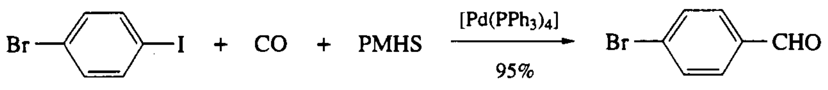

(6)

A more versatile palladium-catalyzed formylation of organic halides takes place using tributyltin hydride and carbon monoxide (equation 7).[15] The reaction works for a variety of substrates — aryl, benzyl and vinyl iodides, vinyl triflates and allyl halides. Reaction conditions are mild (1–3 bar CO, 50 °C), and a variety of functional groups can be tolerated. With unsymmetrical allyl halides formylation is regioselective, taking place at the less-substituted allylic position with retention of geometry at the allylic double bond.

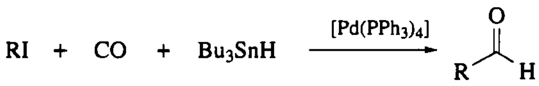

(7)

Carbonylferrate salts, such as $K^+[HFe(CO)_4]^-$, which is readily prepared from $[Fe(CO)_5]$ and ethanolic KOH, react with alkyl bromides or iodides to form alkyliron complexes. Under ambient conditions these complexes undergo insertion of CO and, in the presence of excess CO, aldehyde is eliminated and $[Fe(CO)_5]$ is regenerated (Scheme 10).[16] Unfortunately, the reaction is not catalytic and the hydridocarbonylferrate salt must be prepared in a separate step. Using the commercially available salt $Na_2[Fe(CO)_4]$ a similar reaction takes place, but in this case the intermediate acyl complex is anionic and acid treatment is necessary to liberate the aldehyde (Scheme 11).[17]

$$KHFe(CO)_4 \xrightarrow{RX} R(H)Fe(CO)_4 \xrightarrow{CO} RCOFe(H)(CO)_4 \xrightarrow{CO} RCHO + [Fe(CO)_5]$$

**Scheme 10**

$$Na_2Fe(CO)_4 \xrightarrow{RX} Na^+[RFe(CO)_4]^- \xrightarrow{CO} [RCOFe(CO)_4] \xrightarrow{H^+} RCHO + [Fe(CO)_5]$$

**Scheme 11**

The cobalt-catalyzed reaction of carbon monoxide and hydrogen with an alkene, hydroformylation, is an extremely important industrial process, but it occurs under vigorous conditions (200–400 bar, 150–200 °C) and is not a particularly selective reaction. In the presence of ligand-modified rhodium catalysts, however, hydroformylation can be carried out under extremely mild conditions (1 bar, 25 °C). The catalytic activity of such rhodium complexes is in fact $10^3$–$10^4$ times greater than that of cobalt complexes and side reactions, such as hydrogenation, are significantly reduced. The reactivity of alkenes in hydroformylation follows a similar pattern to that observed in other carbonylation reactions, *i.e.* linear terminal alkenes react more readily than linear internal alkenes, which in turn are more reactive than branched alkenes. An interesting review describes the application of rhodium-catalyzed hydroformylation to the synthesis of a number of vitamins, terpenes and pharmacologically active compounds.[18] Hydroxycitronnellal (**1**), for example, can be produced by hydroformylation of 2,6-dimethyl-6-hepten-2-ol.

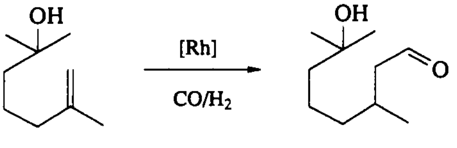

(**1**)

Rhodium complexes of the ligand α,α-TREDIP (**2**) give very high iso regioselectivity in the hydroformylation of styrene under mild conditions, and this has been extended to the synthesis of 2′-(2-methoxy-6-naphthyl)propanal (**3**), a precursor of the antiinflammatory drug naproxen.[19]

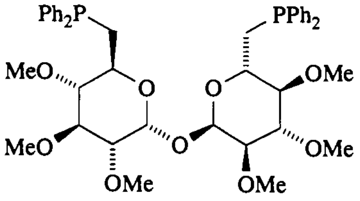

(**2**)

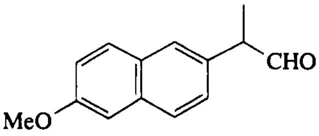

(**3**)

Using phosphite-modified rhodium catalysts, otherwise unreactive alkenes, such as 2-methyl-1-hexene, limonene and cyclohexene, are hydroformylated under mild conditions.[20] 2-Methyl-1-hexene, for example, yields almost exclusively 3-methylheptaldehyde, which is in contrast to the result of cobalt catalysis where a compound with a quaternary carbon is formed (Scheme 12).

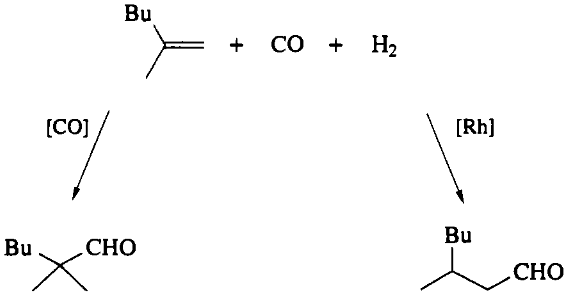

**Scheme 12**

Optically active aldehydes can be obtained by hydroformylation of prochiral alkenes, but few successful results have been obtained. One major problem appears to be that the product aldehydes are susceptible to racemization and hence the optical yield deteriorates as the reaction proceeds. Most progress has been made with rhodium catalysts, but platinum-catalyzed reactions have also shown promise. Hydroformylation of styrene, for example, using $PtCl_2/SnCl_2$ in the presence of the chiral ligand (–)-BPPM (**4**) and triethyl orthoformate gives the enantiomerically pure acetal of 2-phenylpropanal, together with the acetal of 3-phenylpropanal (equation 8).[21] A number of other chelating biphosphines, for example DIOP

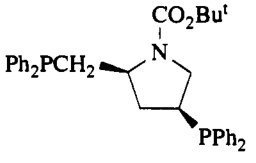

(**4**)

and CHIRAPHOS, have been used with rhodium and platinum systems but generally optical yields do not exceed 50%.[22]

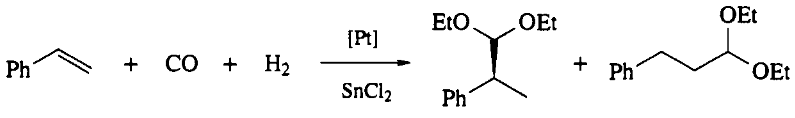

(8)

## 4.1.4 FORMATION OF KETONES

To date, only a limited number of methods for the synthesis of unsymmetrical ketones under carbonylation conditions have been described. Aryl iodides in the presence of stoichiometric amounts of a zinc–copper couple and a catalytic amount of [Pd(PPh$_3$)$_4$] react with alkyl iodides in an atmosphere of CO to give unsymmetrical ketones in good yield (equation 9).[23] The reaction works best for aryl halides containing electron-donating substituents and can be applied to either primary or secondary alkyl halides.

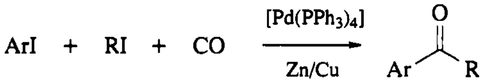

(9)

The palladium-catalyzed carbonylative coupling reaction of organic halides with organotin compounds is a potentially useful route to unsymmetrical ketones (equation 10).[24] Diallyl ketones are synthesized by the reaction of allyl chlorides and allyltin reagents in the presence of CO and a palladium catalyst under mild conditions. This reaction has been used for the high yield synthesis of egomaketone from prenyl chloride and 3-furanyltrimethyltin (equation 11).[24] Vinyl iodides and vinyl triflates also react with vinyl-, alkenyl-, alkynyl- and phenyl-tin compounds in the presence of CO and a palladium catalyst to yield the corresponding ketone (equation 12).[24] The reaction tolerates carbonyl groups in both reagents as well as alkynic groups in the tin reagents. The (*E*)-configurations of the double bonds in the vinyl iodide and the stannate are retained in the product. The (*Z*)-configuration of the double bond in the stannate, however, is lost under the usual reaction conditions and the (*E*)-isomer of the product predominates. With vinyl triflates the presence of lithium chloride is essential to ensure that the reaction proceeds smoothly. This palladium-catalyzed coupling reaction of triflates with organostannates has been extended to aryl triflates,

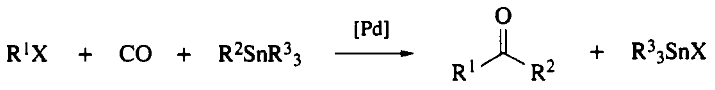

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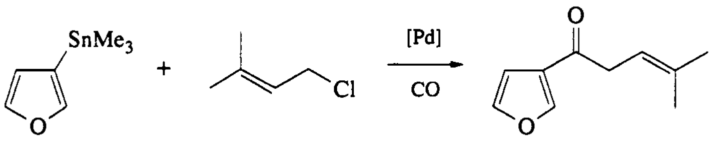

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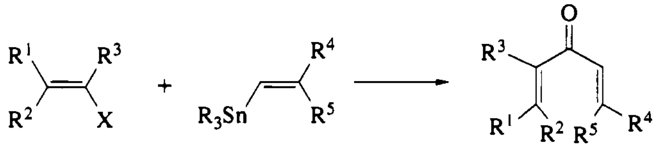

(12)

X = I, OTf

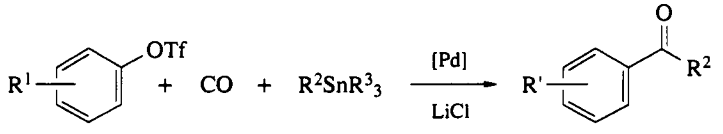

(13)

which react under mild conditions to give good yields of aryl ketones (equation 13).[25] The coupling takes place in the presence of functional groups such as alcohol, aldehyde and ester in the coupling reagents.

Methyl aryl ketones can be synthesized *via* carbonylation of aryl iodides and tetramethyltin in the presence of a nickel catalyst (equation 14).[26] Unfortunately the reaction cannot be extended to the synthesis of unsymmetrical diaryl ketones since tetraphenyltin does not react under these conditions.

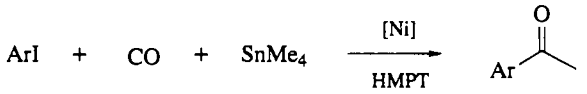

(14)

Reaction of alkyl halides or tosylates with the commercially available $Na_2[Fe(CO)_4]$ gives anionic alkyliron complexes, $[RFe(CO)_4]^-$, which can then react further with alkylating agents to give ketones in good yield (Scheme 13).[27] Whereas primary bromides, iodides and tosylates or secondary tosylates can be used in the first alkylation, only more reactive alkylating agents such as benzyl halides or primary iodides can be used in the second stage. Activated alkenes such as acrylonitrile or ethyl acrylate can also be used in the second step.[28]

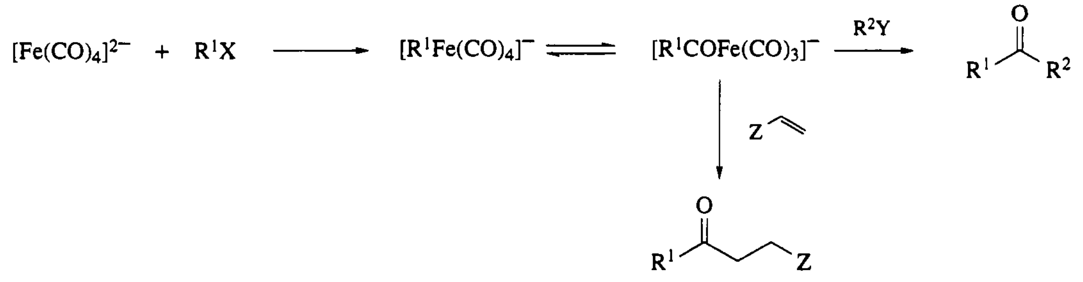

**Scheme 13**

Acyl dienes can be prepared in good yield by reaction of alkyl or acyl halides with conjugated dienes and CO in the presence of catalytic quantities of $[Co(CO)_4]^-$ and a stoichiometric quantity of base (equation 15). By using a phase transfer method increased yields can be obtained under milder conditions (1 bar, 25 °C).[29] The reaction is highly stereo- and regio-specific since the acyl group is normally added to the least-substituted carbon atom of the least-substituted double bond, with exclusive formation of the *trans*-acyldiene. The (acyl-π-allyl)cobalt complex (**5**), an intermediate in this reaction, can also be reacted with stabilized carbanions resulting in alkylation of the unsubstituted π-allyl terminus to give the product (**6**).[30] In all cases studied the alkylation only took place at the unsubstituted π-allyl terminus.

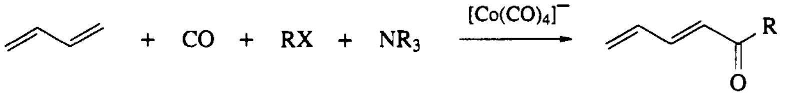

(15)

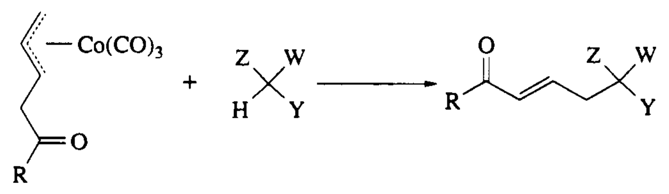

(**5**) Y, W = $CO_2Me$, COMe; Z = H, Me (**6**)

Carbonylation of the cuprate reagent, $R_2(CN)CuLi_2$, prepared from copper(I) cyanide and an alkyllithium, gives a product which can be used for the direct nucleophilic 1,4-acylation of α,β-unsaturated aldehydes and ketones (equation 16).[31] The reaction works particularly well with cyclic α,β-unsaturated ketones to give high yields of the expected 1,4-diketone.

A particularly useful synthesis of cyclopentanones involves the coupling of an alkene, an alkyne and carbon monoxide in the presence of dicobalt octacarbonyl (equation 17). The reaction proceeds *via* an alkyne–cobalt complex (**7**) and with relatively unreactive alkenes such as cyclopentene it is preferable to synthesize the complex in a separate step.[32] With highly strained alkenes such as norbornadiene, how-

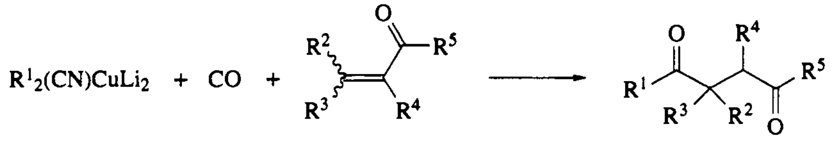

(16)

ever, only catalytic quantities of $[Co_2(CO)_8]$ are required. Very volatile or gaseous alkenes require the use of an autoclave, but since the reaction proceeds at 1 bar pressure of CO/acetylene less volatile alkenes may be used in hydrocarbon solvents. Fused ring systems are equally readily synthesized by this route and the reaction has been extended to the synthesis of a number of natural products and oxygen heterocycles.[33] 3-Oxabicyclo[3.3.0]octa-6-en-7-ones, for example, are synthesized in moderate yields by intramolecular cyclization of the cobalt complexes of substituted allyl propargyl ethers (equation 18).[33a]

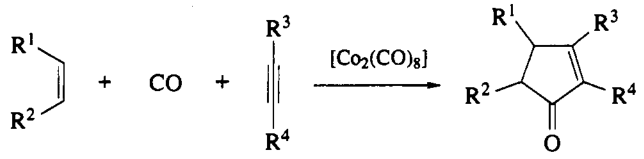

(17)

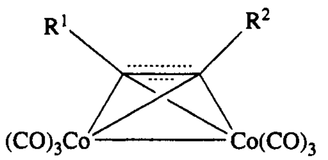

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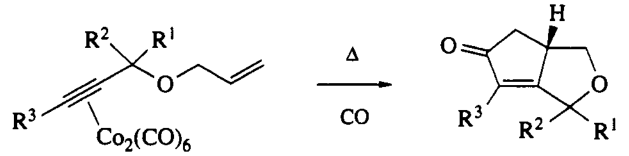

(18)

One major problem associated with this type of reaction is the formation of regioisomeric cyclopentenones when unsymmetrically substituted alkenes are used, although unsymmetrically substituted alkynes prefer an orientation which places the larger substituent in the α-position of the cyclopentenone.[33c] Several examples have been published which show that steric interactions can bias the regiochemical outcome of the intermolecular cycloaddition. Substituents in the allylic position, for example, exert a modest to excellent degree of regiocontrol (equation 19).[34] In this case the larger of the two ring fusion substituents becomes β to the new enone carbonyl.

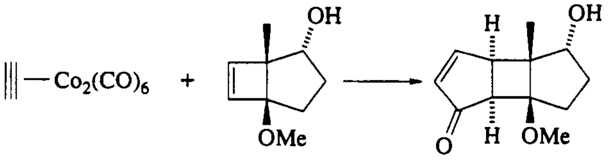

(19)

1-Iodo-1,4-dienes undergo carbonylation in the presence of stoichiometric amounts of $[Pd(PPh_3)_4]$ to give α-methylenecyclopentenones (**8**).[35] By varying the conditions the reaction can be made catalytic in palladium, but the reaction has to be performed in methanol and the product in this case is the methyl ester (**9**). The reaction is also applicable to the formation of cyclohexenones and spiro compounds, with good yields being obtained in all cases.

Alkenic tosylates undergo cyclization with concomitant carbonylation when treated with $Na_2[Fe(CO)_4]$ (equation 20).[36] The reaction is particularly effective for the synthesis of five- and six-membered rings but seven-membered rings can also be prepared, although in the latter case the reaction is not regiospecific and a mixture of products is obtained. The reaction appears to be limited to monosub-

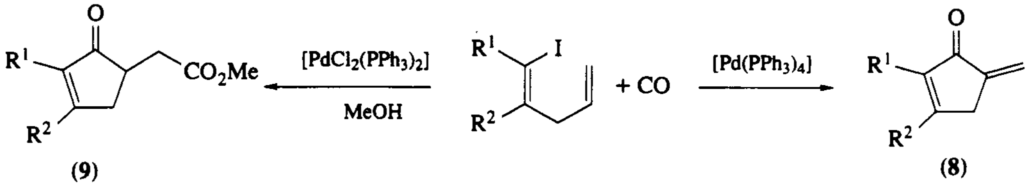

stituted alkenes since addition of a second substituent on either carbon of the double bond prevents cyclization.

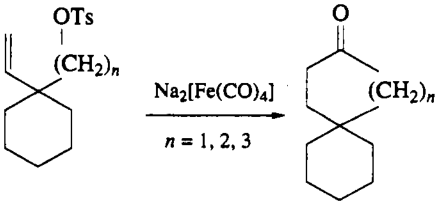

(20)

### 4.1.5 FORMATION OF CARBOXYLIC ACIDS

Early work on the conversion of aryl halides to carboxylic acids was mostly concerned with the use of nickel tetracarbonyl, and although the reaction proceeds under mild conditions more effective and less hazardous syntheses can be achieved using palladium catalysts. In particular, aryl, benzyl, vinyl and heterocyclic halides can be converted to carboxylic acids under mild conditions in two-phase systems.[37] The carbonylation reaction is carried out by addition of the organic halide, triphenylphosphine, $[PdCl_2(NCPh)_2]$ and a phase transfer catalyst, such as $Bu^n{}_4N^+I^-$, to a two-phase system consisting of *p*-xylene and 50% aqueous sodium hydroxide, followed by stirring for several hours under CO at a pressure of 1–10 bar. A great advantage of this system is that continuous extraction of the product acid into the aqueous phase leaves the catalyst and any residual starting material in the organic layer, allowing easy product separation and effectively making heterogeneous the homogeneous catalyst. This procedure also allows selective monocarbonylation of polyhalogenated aromatic substrates such as 1,4-dibromobenzene, since transformation of the first C—X group to carboxy enables the product to be rapidly removed from the organic to the aqueous phase where it is no longer in contact with the catalyst.

A related biphasic synthesis uses $[Co(CO)_4]^-$ as the catalyst, but in this case the reaction is limited to substrates such as benzyl and naphthylmethyl halides which are susceptible to attack by the metal carbonyl anion.[38]

Iron pentacarbonyl is also an effective catalyst precursor allowing high yield carbonylation of alkyl and aralkyl halides under relatively mild biphasic conditions (equation 21).[39] This represents a very interesting and useful development of the earlier procedure which used stoichiometric quantities of the preformed reagent $Na_2[Fe(CO)_4]$. The reaction works equally well for bromides and chlorides.

$$RX + CO \xrightarrow[\text{base}]{[Fe(CO)_5]} RCO_2H \qquad (21)$$

Under conditions of photostimulation $[Co_2(CO)_8]$ in aqueous alkali will catalyze carbonylation of aryl and vinyl halides, including the normally less reactive aryl chlorides, at low pressures and with high efficiency. The active catalyst under these conditions is $[Co(CO)_4]^-$ and this can be generated *in situ* from simple cobalt salts such as $CoCl_2{\cdot}6H_2O$, thus avoiding any need to handle the highly air sensitive $[Co_2(CO)_8]$ or its derived anion (equation 22).[40]

$$ArX + CO + NaOH \xrightarrow[h\nu]{CoCl_2} ArCO_2Na \qquad (22)$$

Arenediazonium salts react stoichiometrically with nickel and iron carbonyls to give aromatic carboxylic acids in moderate yield, but a more reliable procedure involves direct, catalytic carbonylation in the presence of palladium acetate.[41] The reaction proceeds at room temperature under CO pressure (9 bar) and gives a mixed anhydride as the initial product. Hydrolytic work-up produces the aromatic acid in 50–90% yield (Scheme 14).

$$ArN_2^+ + CO + MeCO_2K \xrightarrow{Pd(OAc)_2} ArCO_2COMe \longrightarrow ArCO_2H + MeCO_2H$$

**Scheme 14**

Addition of carbon monoxide and water to an alkene, *i.e.* hydrocarboxylation, is catalyzed by a variety of transition metal complexes, including $[Ni(CO)_4]$, $[Co_2(CO)_8]$ and $[H_2PtCl_6]$. Unfortunately this reaction usually leads to mixtures of products due to both metal-catalyzed alkene isomerization and the occurrence of both Markownikov and anti-Markownikov addition of the metal hydride intermediate to the alkene. The commercially available zirconium hydride $[(C_5H_5)_2Zr(H)Cl]$ can be used as a stoichiometric reagent for conversion of alkenes to carboxylic acids under mild conditions (equation 23).[42] In this case the reaction with linear alkenes gives exclusively terminal alkyl complexes even if the alkene double bond is internal. Insertion of CO followed by oxidative hydrolysis then leads to linear carboxylic acids in very good yield.

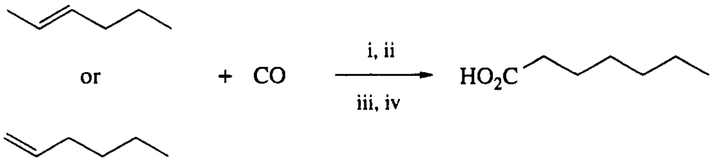

(23)

i, $Cp_2ZrHCl$; ii, CO; iii, NaOH; iv, $H_2O_2$

Alkynes react readily with stoichiometric quantities of $[Ni(CO)_4]$ under essentially ambient conditions to give, in the presence of aqueous acid, good yields of *cis*-α,β-unsaturated carboxylic acids (equation 24).[2] With monosubstituted alkynes the reaction rate decreases with increasing size of the substituent group and with alkyl substituents the branched product isomer usually predominates.

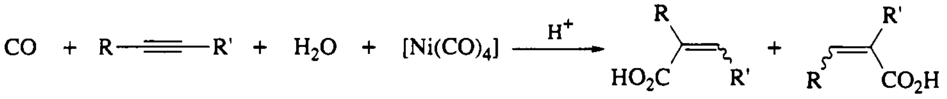

(24)

The nickel-catalyzed carbonylation of allyl halides in the presence of alkynes and water produces 2,5-dienoic acids in good yields under very mild conditions (equation 25).[43] This remarkable four-component reaction probably involves oxidative addition of the allyl chloride to the catalyst, followed by successive insertions of alkyne and CO, and finally hydrolysis. The carbon–carbon double bond derived from alkyne insertion is thus conjugated with the carbonyl group and generally has the (*Z*)-configuration.

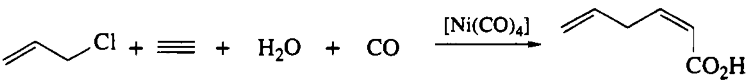

(25)

An interesting reaction discovered by Wakamatsu involves the cobalt-catalyzed carbonylation of aldehydes in the presence of primary amides to give *N*-acylamino acids in high yield (equation 26).[44] By combining this reaction with known catalytic routes to aldehydes, for example isomerization of allyl alcohols or hydroformylation of alkenes, it is possible to achieve the direct synthesis of *N*-acylamino acids from precursors other than aldehydes.[45]

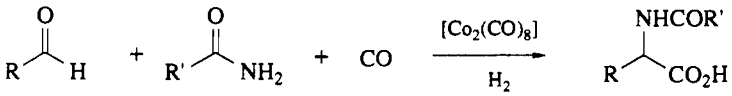

(26)

By using a two-phase benzene/aqueous sodium hydroxide medium and a palladium catalyst, allyl chlorides can be converted into 3-butenoic acids in high yield at atmospheric pressure and room temperature (equation 27).[46] The reaction appears to go equally well using either water soluble or water insoluble catalysts, but in the latter case some α,β-unsaturated acid is also produced. In the absence of a two-phase system the reaction requires high pressures of CO.

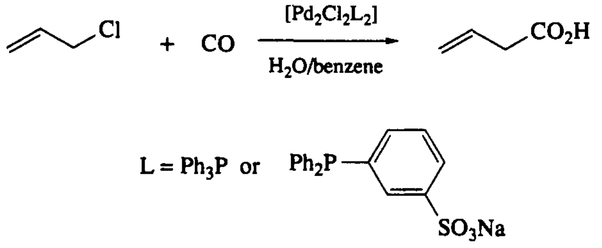

(27)

## 4.1.6 FORMATION OF ESTERS

Nickel tetracarbonyl is an efficient catalyst for the carboalkoxylation of aryl or vinyl halides, but a much better and safer route is *via* palladium-catalyzed synthesis. Bromides and iodides in the presence of 1–2 mol % $[Pd(PPh_3)_2Cl_2]$, the reactant alcohol as solvent and a tertiary amine as acid acceptor react at 60–100 °C and atmospheric pressure to produce the corresponding ester in good yield (equation 28).[47] With iodo compounds even palladium acetate, without any added phosphine, may be used as catalyst. The reaction is unaffected by the presence of a variety of functional groups (ester, ether, nitrile), and strong electron-donating or -withdrawing substituents do not affect the yield of aromatic esters to any significant extent. A more recent application of this reaction indicates that by conducting the reaction in benzyl alcohol aryl iodides are readily converted to the benzyl ester, which can then be easily cleaved to the acid by catalytic hydrogenation.[48]

$$RX + CO + R'OH \xrightarrow{[Pd]} RCO_2R' + HX \qquad (28)$$

At 60–80 °C vinyl halides can be carbonylated with almost complete retention of stereochemistry. For example, carbonylation of (*E*)-3-iodo-3-hexene in *n*-butanol gives 74% of the corresponding (*E*)-carbobutoxylated product (**10**), with only 6% of the (*Z*)-isomer.[47]

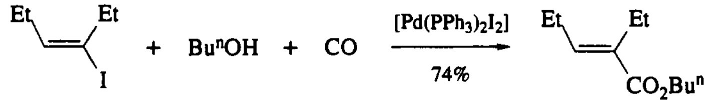

**(10)**

Iodoalkanes tend to undergo dehydrohalogenation rather than carbonylation, but more recently it has been shown that primary, secondary and even tertiary alkyl halides can be efficiently carbonylated to esters in the presence of platinum catalysts, under mild conditions, if the reaction takes place under UV irradiation (equation 29).[49] Alkyl bromides and chlorides are not carbonylated under these conditions and in the presence of visible light irradiation the reaction is very slow. Other transition metal carbonyls, such as $[Co_2(CO)_8]$, $[Ru_3(CO)_{12}]$, $[Os_3(CO)_{12}]$, $[Mn_2(CO)_{10}]$ and $[Re_2(CO)_{10}]$, also catalyze the reaction.

$$RI + R'OH + CO \xrightarrow[h\nu]{[Pt(CO)_2(PR_3)_2]} RCO_2R' \qquad (29)$$

Benzyl halides can be catalytically carbonylated to esters in the presence of $[Rh_2(CO)_4Cl_2]$[50] and $[Ni(PPh_3)_2(CO)_2]$.[47] Esters can also be obtained from alkyl and benzyl halides using stoichiometric quantities of $Na_2[Fe(CO)_4]$ (Scheme 15).[51] Although aryl halides do not react with this reagent, initial

$$RX + Na_2[Fe(CO)_4] \longrightarrow Na^+[RFe(CO)_4]^- \xrightarrow{I_2} RCOI \xrightarrow{R'OH} RCO_2R'$$

**Scheme 15**

preparation of a Grignard reagent, followed by reaction with $[Fe(CO)_5]$, produces an acyliron intermediate which on subsequent treatment with alcoholic halogen yields the ester (Scheme 16).[52]

$$ArX + Mg \longrightarrow ArMgX \xrightarrow{Fe(CO)_5} ArCOFe(CO)_4 \xrightarrow[ROH]{I_2} ArCO_2R$$

**Scheme 16**

Alkyliron complexes, $[(C_5H_5)Fe(CO)_2R]$, undergo carbonyl insertion on treatment with donor ligands, such as triphenylphosphine, to give iron acyls which are configurationally asymmetric. When resolved into their isomers such complexes allow extensive elaboration of the acyl ligand with essentially complete control of the stereochemistry at any new chiral center which may be formed (Scheme 17).[53] Moreover, chirality is almost invariably retained when the organic product (ester, acid or amide) is liberated by oxidative cleavage of the iron–acyl bond. Both enantiomers of the acetyl complex $[(C_5H_5)Fe(PPh_3)(CO)(COMe)]$ are now commercially available.

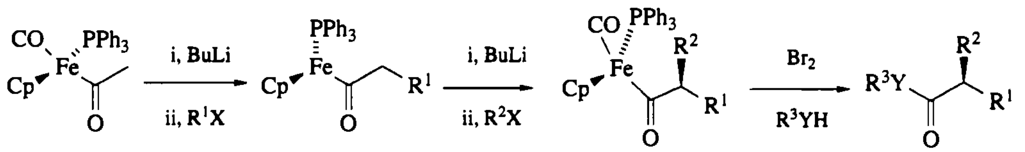

Cp = $C_5H_5$; Y = N, O

**Scheme 17**

Organohalides, such as iodoalkanes, alkyl chloroacetates and benzyl halides, which are highly susceptible to nucleophilic attack, are readily converted to esters by reaction with carbon monoxide and an alcohol in the presence of a base using $Na[Co(CO)_4]$ as catalyst (equation 30).[54] Reactions proceed under mild conditions (25 °C, 1 bar CO) and very good yields and selectivities can be obtained. With less reactive halides, however, higher temperatures are required leading to isomerization of the intermediate alkylcobalt complex and hence to a mixture of carbonylated products.

$$RX + CO + R'OH \xrightarrow{Na[Co(CO)_4]} RCO_2R' + HX \qquad (30)$$

By careful selection of the palladium catalyst, aryl trifluoromethanesulfonates can be converted directly to benzoate esters under mild conditions (70 °C, 1 bar CO; equation 31).[55] The best catalyst appears to be $Pd(OAc)_2$–1,3-bis(diphenylphosphino)propane and the best solvent DMF. With aromatic compounds bearing electron-withdrawing substituents carbonylations can be carried out under even milder conditions.

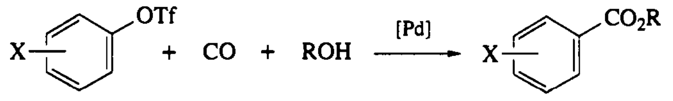

(31)

The synthesis of an ester by addition of carbon monoxide and an alcohol to an alkene, *i.e.* hydroesterification, has a fairly obvious relationship to the hydrocarboxylation described in Section 4.1.5, where water replaces the alcohol and a carboxylic acid is formed. Not surprisingly, therefore, the same types of catalysts, $[Co_2(CO)_8]$, $[H_2PtCl_6]$ and $[Pd(PPh_3)_2Cl_2]$, are effective for both reactions. Unfortunately, the reaction usually requires very high pressures (200 bar) and necessitates the use of an autoclave. By varying the catalyst and reaction conditions a variety of linear, branched and cyclic alkenes can be carbonylated under these conditions to give the product in good yield (equation 32).[56] Improved selectivity to the linear ester can be obtained by addition of $SnCl_2$ to the catalyst system.

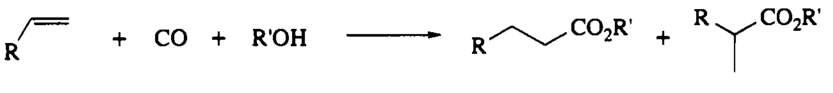

(32)

Stoichiometric hydroesterification can be carried out using the zirconium complex $[(C_5H_5)_2Zr(H)Cl]$, as described in Section 4.1.5 in the context of carboxylic acid synthesis, and, apart from the use of alcoholic rather than aqueous bromine in the final cleavage reaction, the same procedure is applicable (equation 33).[42]

$$(C_5H_5)Zr(R)Cl \xrightarrow[\text{iii, R'OH}]{\text{i, CO; ii, Br}_2} RCO_2R' \qquad (33)$$

Palladium-catalyzed hydroesterification of styrene gives predominantly the branched ester, in which a new chiral center has been created at the 2-position (equation 34). Carrying out this reaction at low pressure (1–2 bar) in the presence of the bulky chiral phosphine neomenthyldiphenylphosphine and trifluoroacetic acid leads to significant asymmetric induction (50% *ee*);[57] this work seems to represent the only significant advance towards stereocontrol of catalytic hydroesterification reactions.

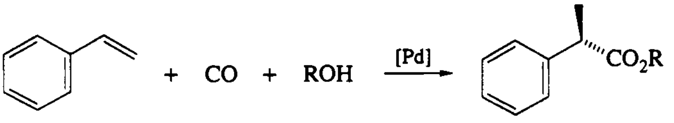

(34)

Palladium salts can bring about oxidative carbonylation of alkenes in the presence of copper(II) salts which can reoxidize $Pd^0$ to $Pd^{II}$. Oxidative carbonylation is favored over simple hydroesterification by the presence of bases and by low temperatures (25 °C) and low pressures (3–15 bar). The products can be α,β-unsaturated esters, dicarboxylic acid esters or β-alkoxy esters. By careful optimization of the conditions (25 °C, 4 bar CO, methanol solvent, $CuCl_2$ reoxidant and sodium butyrate buffer) high yields of diesters can be obtained (equation 35).[58]

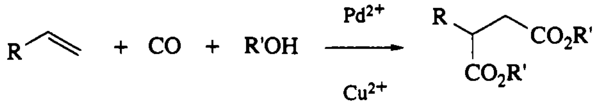

(35)

The carbonylation of 1-iodo-1,4-dienes in the presence of homogeneous palladium catalysts provides a good example of the ability of such catalysts to promote a complex sequence of metal-centered reactions yielding a single product with a high degree of specificity. Two carbonylation steps are involved, the first leading to formation of a cyclic ketoalkyl ligand and the second to the introduction of an ester function and release of the product from the metal (Scheme 18).[35]

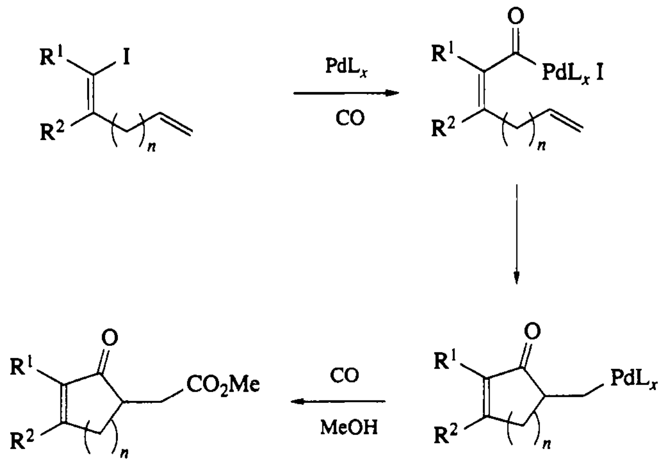

**Scheme 18**

Alkynes undergo simple hydroesterification under mild conditions to give α,β-unsaturated esters. Addition of the ester function to terminal alkynes frequently occurs at the substituted carbon atom to give branched products, but linear esters may be obtained with high selectivity using palladium–tin catalysts (equation 36).[59] Under oxidative carbonylation conditions *cis*-diesters are formed.[60]

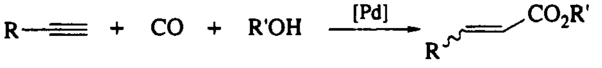

(36)

### 4.1.7 FORMATION OF LACTONES

β-Lactones can be obtained by oxidative carbonylation of alkenes in the presence of water. Ethylene, for example, is converted to β-propiolactone by carbonylation in aqueous acetonitrile at –20 °C using a catalytic amount of $PdCl_2$ and a stoichiometric quantity of copper(II) chloride (equation 37).[61] Palladium-catalyzed carbonylation of halides can also be used to prepare β-lactones under mild conditions. The reaction takes place at room temperature and pressure in the presence of $[PdCl_2(PPh_3)_2]$ and has been applied to both bromides and chlorides (equations 38 and 39).

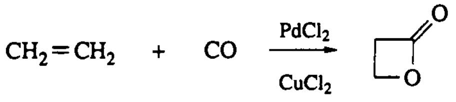

(37)

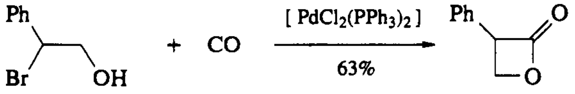

(38)

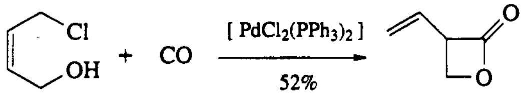

(39)

In recent years, one of the most useful and best-studied areas of transition metal mediated carbonylation reactions is the formation of γ-lactones. Carbonylation of ethynyl alcohols is a very attractive route to α-methylene-γ-lactones. Earlier methods used nickel carbonyl but a more recent method uses a palladium/thiourea catalyst (equation 40).[63] A further improvement in the catalytic system is to use $PdCl_2$ with 1 equiv. of anhydrous $SnCl_2$ and 2 equiv. of a tertiary phosphine in dry acetonitrile.[64] Using either of these methods a variety of α-methylenelactones have been synthesized in good yield, including fused ring products. Both *trans*- and *cis*-ethynyl alcohols readily give fused-ring methylenelactones of the corresponding stereochemistry (equation 41).

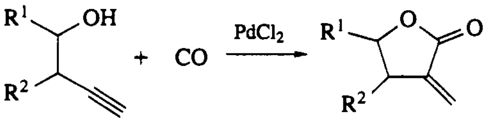

(40)

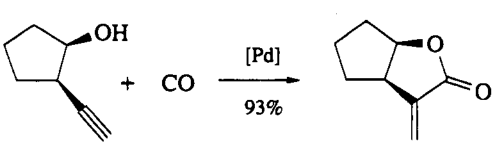

(41)

α-Methylenebutyrolactones can also be synthesized from homoallylic alcohols in the presence of a base (equation 42). Early work used $[Ni(CO)_4]$, but more recently the reaction has been shown to proceed in the presence of $[Ni(CO)_2(PPh_3)_2]$ and triethylamine.[65] Unfortunately neither of these reactions are catalytic but the homoallylic alcohol method has been used in the synthesis of the sesquiterpene frullanolide (**11**).[65b]

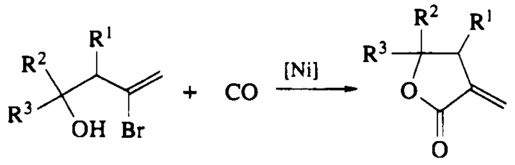

(42)

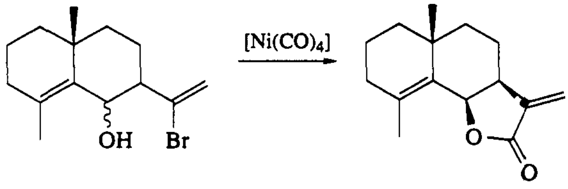

**(11)**

The conversion of hydroxy-substituted vinyl halides into α-methylenebutyrolactones can be performed catalytically in the presence of [Pd(PPh$_3$)$_4$].[66] The starting materials for this reaction are prepared from epoxides and α-silylated vinyl Grignard reagents followed by the substitution of the silyl substituent by bromine. Due to the regio- and stereo-specific nature of the ring-opening reaction of the epoxide by the vinyl Grignard reagent, and the noninvolvement of asymmetric carbons in the carbocyclization reaction, the reaction can be extended to the synthesis of optically active lactones from the corresponding optically active epoxides (Scheme 19).

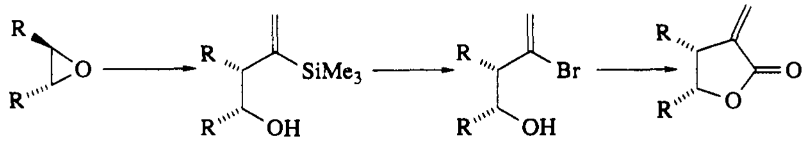

**Scheme 19**

A further variation on this reaction is the cyclocarbonylation of hydroxy-substituted vinyl halides using a palladium acetate/triphenylphosphine catalyst system. Using this procedure five-, six- and seven-membered α-methylenelactones can be prepared (equation 43).[67]

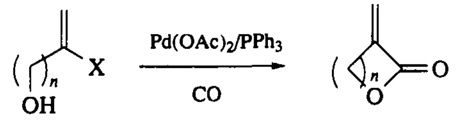

(43)

$n = 2, 3, 4$

Acylcobalt tetracarbonyl complexes, formed from Na[Co(CO)$_4$] and alkyl or acyl halides, react with alkynes to give 2,4-pentadieno-4-lactones (Scheme 20).[68] The reaction is catalytic in cobalt and yields are around 60% for a variety of substituted alkynes and alkyl halides.

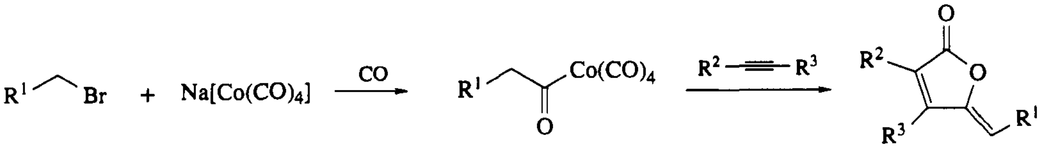

**Scheme 20**

Five-membered ring lactones are formed from the reaction of primary, secondary or tertiary allyl alcohols with carbon monoxide in the presence of a catalytic amount of PdCl$_2$/CuCl$_2$ (equation 44).[69] The reaction proceeds at room temperature under 1 bar of CO and yields are generally in the range 40–60%.

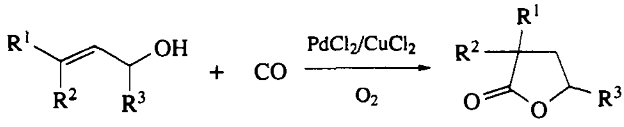

(44)

Dilactones can be synthesized by a palladium-catalyzed stereospecific intramolecular double cyclization of 3-hydroxy-4-pentenoic acids (Scheme 21).[70] The *cis* stereochemistry of the reaction is rationalized by assuming that attack of Pd$^{II}$ on the alkene is directed by the allylic OH group, forming the intermediate (**12**).

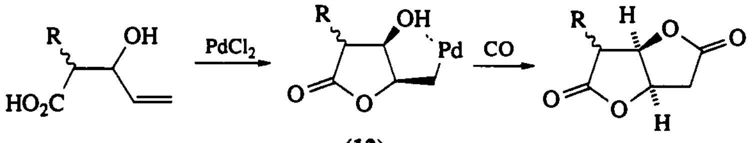

**(12)**

**Scheme 21**

*cis*-3-Hydroxytetrahydrofuranacetic acid lactones have been prepared in high yield by intramolecular palladium-catalyzed oxycarbonylation of 4-pentene-1,3-diols under mild conditions (equation 45).[71] A wide range of 4-pentene-1,3-diols can be prepared in essentially quantitative yield by the sequential aldol condensation (reaction of enolates, ketones, esters or lactones with unsaturated aldehydes in THF) and reduction with LiAlH$_4$ in ether at room temperature, thus allowing the ready synthesis of a number of lactones.

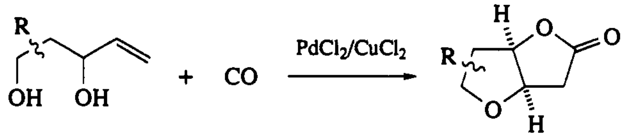

(45)

The catalytic carbonylation of halides can also be used to synthesize phthalides (equation 46). The reaction will proceed both in the presence of palladium[62] and cobalt[72] catalysts.

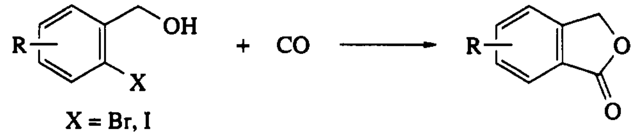

(46)

The direct carbonylation of arylthallium compounds usually requires high temperatures and pressures, but in the presence of palladium catalysts the reaction proceeds in high yield at room temperature and atmospheric pressure (equation 47).[73]

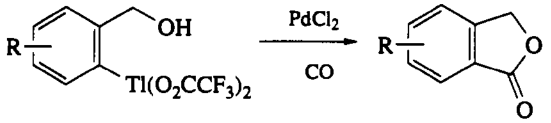

(47)

Compared with the synthesis of five-membered rings relatively little has been done on the synthesis of δ-lactones. Homoallylic alcohols can be converted into δ-lactones by rhodium-catalyzed hydroformylation followed by oxidation (equation 48).[74] The thallation and subsequent palladium-catalyzed carbonylation described earlier can also be used for the synthesis of six-membered rings (equation 49).[73]

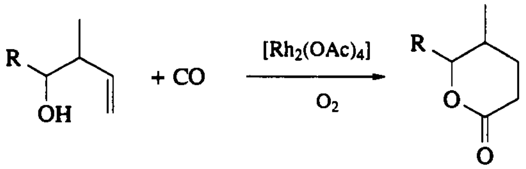

(48)

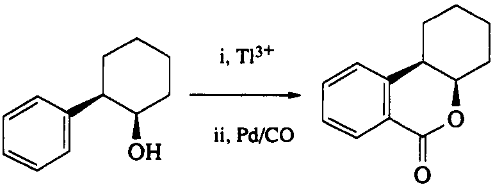

(49)

Palladium-catalyzed carbonylation of halides has been applied to the synthesis of natural products such as zearalenone (**13**; Scheme 22)[75] and curvulin (**14**; Scheme 23).[76] In both cases the yields for the carbonylation steps are 70%.

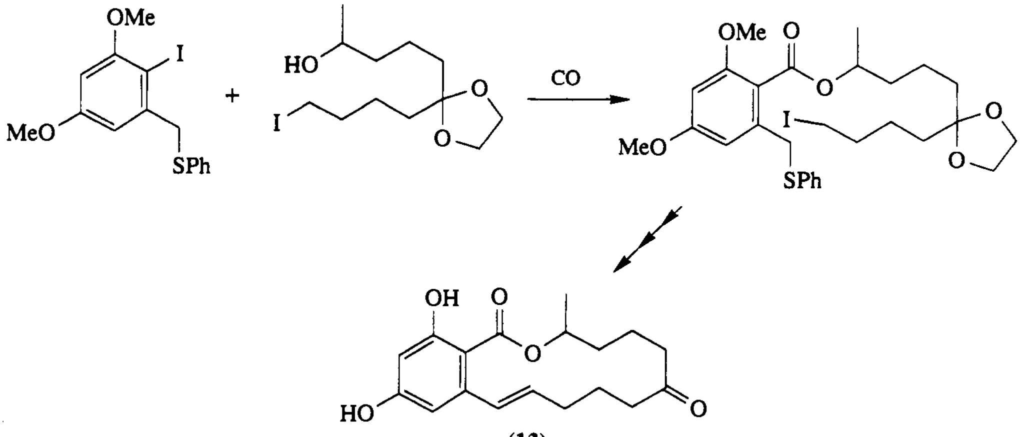

(13)

Scheme 22

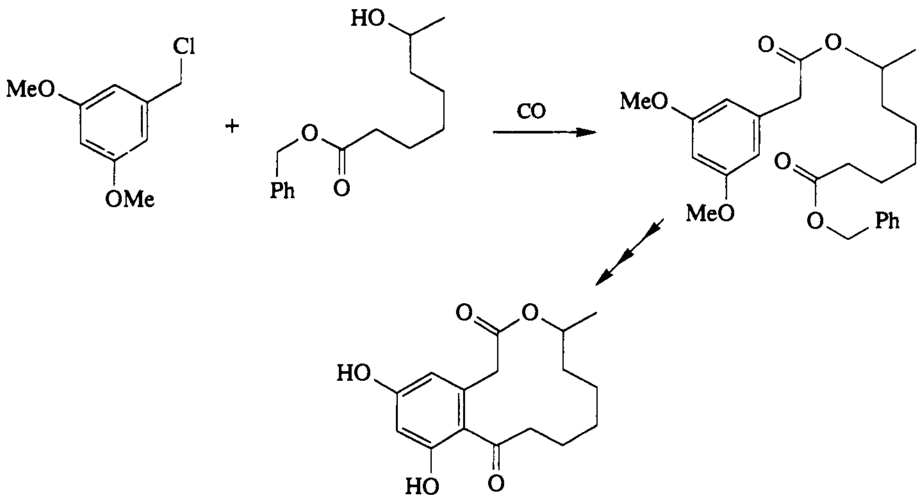

(14)

Scheme 23

Whereas most carbonylation studies have focused on the use of transition metal catalysts, one recent report describes the facile synthesis of 4-hydroxycoumarins using sulfur-assisted carbonylation (equation 50).[77] Yields are good for a variety of substrates while reaction conditions are relatively mild.

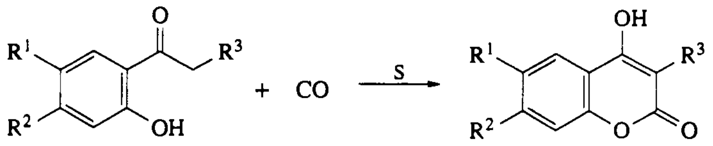

(50)

## 4.1.8 FORMATION OF AMIDES

Reaction of organic halides with CO and amines using stoichiometric quantities of [Ni(CO)$_4$] or Na[Co(CO)$_4$] indicate that metal-promoted amidation is a feasible route to carboxylic amides, but of more use is a palladium-catalyzed synthesis (equation 51).[78] Aryl, vinyl or heterocyclic halides react with primary or secondary amines in the presence of [Pd(PPh$_3$)$_2$Cl$_2$] under mild conditions (60–100 °C; 1 bar CO) to give high yields of the appropriate amide. The amidation reaction proceeds much more rapidly than the corresponding ester synthesis (Section 4.1.6) so that bromobenzene, for example, reacts with benzylamine and CO to give *N*-benzyl benzamide about 17 times faster than with 1-butanol under the same conditions. Amidation also shows greater stereoselectivity than carboalkoxylation with *cis*- and *trans*- vinyl halides, giving amides with essentially complete retention of configuration.

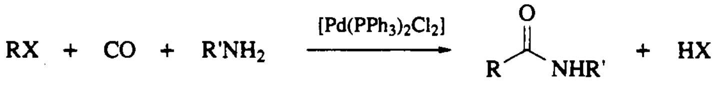

$$\mathrm{RX} + \mathrm{CO} + \mathrm{R'NH_2} \xrightarrow{[\mathrm{Pd(PPh_3)_2Cl_2}]} \mathrm{RC(=O)NHR'} + \mathrm{HX} \qquad (51)$$

Vinyl and aryl esters of trifluoromethanesulfonic acid are readily converted to amides using a palladium–phosphine catalyst (equation 52).[79] The reaction proceeds under mild conditions (60 °C; 1 bar CO) to produce amides in excellent yield, but often appears to need the use of the exotic ligand 1,1′-bis(diphenylphosphino)ferrocene (DPPF).

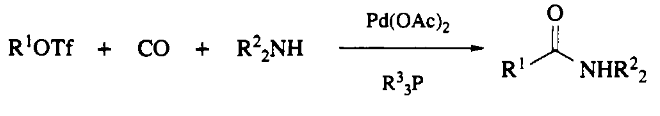

$$\mathrm{R^1OTf} + \mathrm{CO} + \mathrm{R^2{}_2NH} \xrightarrow[\mathrm{R^3{}_3P}]{\mathrm{Pd(OAc)_2}} \mathrm{R^1C(=O)NHR^2{}_2} \qquad (52)$$

## 4.1.9 FORMATION OF LACTAMS AND RELATED *N*-HETEROCYCLES

The synthesis of β-lactams has been achieved using a variety of transition metal mediated reactions, many of which are specific to this type of compound. The vinyl epoxide (**15**) reacts with $[\mathrm{Fe_2(CO)_9}]$ to

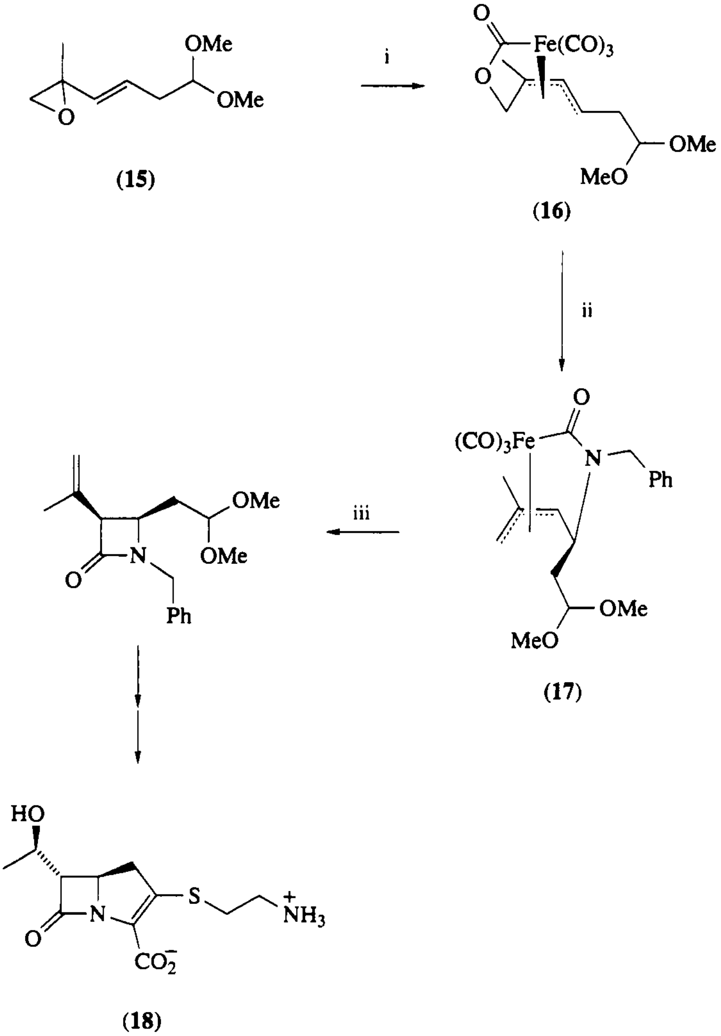

i, $\mathrm{Fe_2(CO)_9}$; ii, $\mathrm{PhCH_2NH_2}$; iii, $\mathrm{Ce^{4+}}$

**Scheme 24**

give the lactone complex (**16**), which then reacts with benzylamine to give the complex (**17**). Oxidation with cerium(IV) ammonium nitrate produces the β-lactam, in 64% yield, which can be further elaborated into the antibiotic thienamycin (**18**; Scheme 24).[80]

Iron–alkene complexes have also been used for the synthesis of β-lactams (Scheme 25).[81] The alkene complex (**19**) is transformed into the pyrroline complex (**20**) on exposure to ammonia. Reduction with $NaBH_4$ gives a mixture of stereoisomeric pyrrolidine complexes which are then converted on heating to the diastereomeric chelate (**21**). Oxidation with air or silver oxide produces the lactam (**22**).

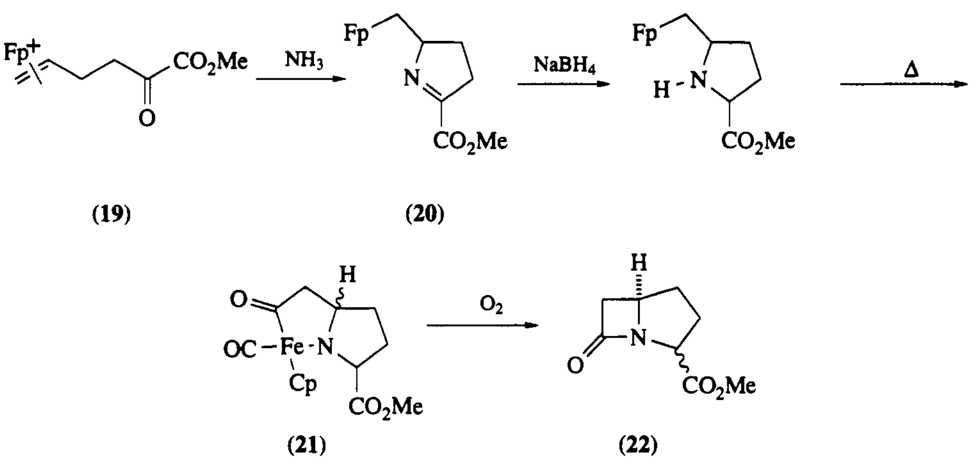

**(19)** **(20)**

**(21)** **(22)**

Fp = $C_5H_5Fe(CO)_2$

**Scheme 25**

A more conventional carbonylation route to β-lactams involves the palladium-catalyzed conversion of various 2-bromo-3-aminopropene derivatives into the corresponding α-methylene-β-lactams (equation 53).[82]

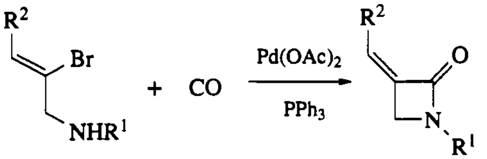

(53)

Exposure of an azirine to carbon monoxide in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ gives the bicyclic β-lactam (**23**) in reasonable yield.[83] Attempts to synthesize monocyclic β-lactams from azirines has so far failed, but aziridines can be carbonylated to β-lactams. Depending on the organometallic reagent used two different products can be obtained (Scheme 26). Using catalytic quantities of $[Rh_2(CO)_4Cl_2]$ carbon monoxide inserts selectively into the more-substituted C—N bond,[84] whereas using a stoichiometric amount of $[Ni(CO)_4]$ it is the less-substituted C—N bond that is carbonylated.[85]

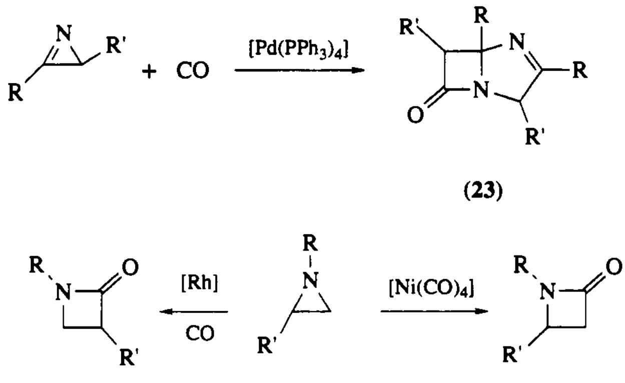

**(23)**

**Scheme 26**

Azetidine-2,4-diones can be prepared in good yield from aziridinones by carbonylation in the presence of a rhodium catalyst (equation 54).[86] This conversion can also be brought about using $[Co_2(CO)_8]$, but in this case the reaction is not catalytic.

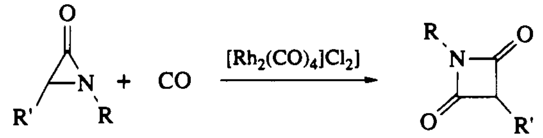

(54)

A somewhat different approach to the synthesis of mono- and bi-cyclic β-lactams involves the reaction of pentacarbonyl(methoxymethyl)chromium complexes with amines under sunlight irradiation (Scheme 27).[87] The chromium complexes are readily made by reaction of $[Cr(CO)_6]$ with alkyl- or aryl-lithium reagents, followed by alkylation with trimethyloxonium tetrafluoroborate. Sunlight photolysis is required for β-lactam formation, with the product being isolated in 40–76% yield. The reaction is applicable to a wide variety of imines and proceeds with high stereoselectivity. However, the reaction is sometimes limited by the stability of the alkoxycarbene complex and to overcome this the reaction has been extended by using the more stable aminocarbene complex (**24**). Photolytic reaction of these complexes with imines, oxazines, oxazolines, imidates, thiazines and thiazolines produces β-lactams in fair to good yield, with *trans* stereochemistry being observed in most cases (equation 55).

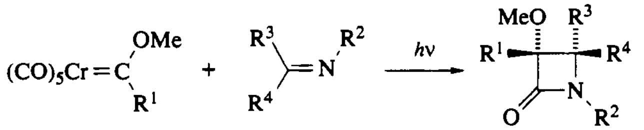

**Scheme 27**

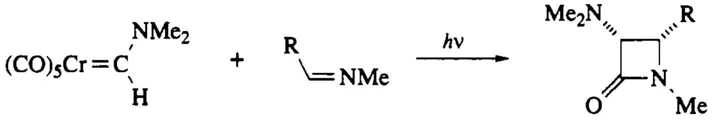

(**24**)

(55)

Carbonylation of allylamines can produce pyrrolidones, although relatively high pressures of CO are usually required. Homogeneous rhodium catalysts are preferred and, using similar catalysts, the pyrrolidones can be obtained from allylic halides, CO and ammonia (Scheme 28).[88]

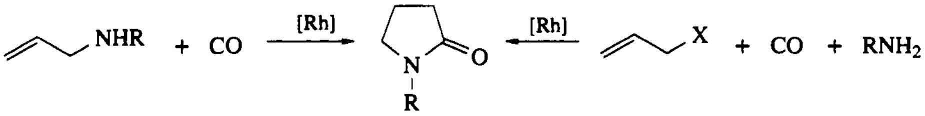

**Scheme 28**

The formation of *ortho* palladium products from α-aryl nitrogen derivatives and palladium salts is well known.[89] Complexes formed from azobenzene, Schiff bases, tertiary benzylamines and oximes readily undergo insertion of CO into the metal–carbon bond to give, after work-up, a variety of heterocyclic compounds. Unfortunately, such reactions use expensive palladium salts in stoichiometric quantities. However, a number of related reactions have been shown to proceed in the presence of only catalytic quantities of palladium. Isoindolinones, for example, can be synthesized in good yield by reaction of *o*-bromoaminoalkylbenzenes with CO (100 °C, 1 bar) in the presence of catalytic amounts of $Pd(OAc)_2$, $PPh_3$ and $Bu^n{}_3N$ (equation 56).[90]

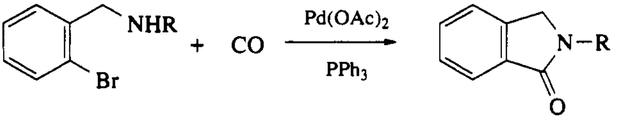

(56)

Cyclization of *N*-substituted-*o*-allylanilines in the presence of carbon monoxide, methanol and a palladium catalyst gives the dihydroindoleacetic acid ester (**25**) in 70% yield.[91]

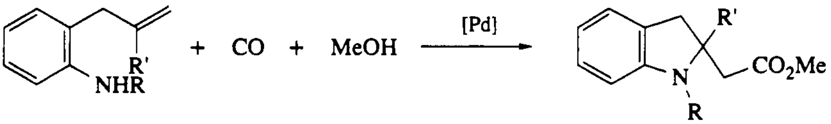

**(25)**

*N*-Substituted-1,2,3,4-tetrahydroisoquinolin-1-ones (**26**) can be prepared in good yield by carbonylation of *N*-alkyl-*o*-bromophenethylamines in the presence of catalytic amounts of $Pd(OAc)_2/PPh_3$.[90] Similarly substituted 2-(2-bromoanilino)pyridines undergo carbonyl insertion to produce pyrido[2,1-*b*]quinazoline derivatives in good yield (equation 57).[92]

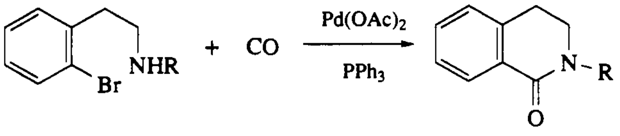

**(26)**

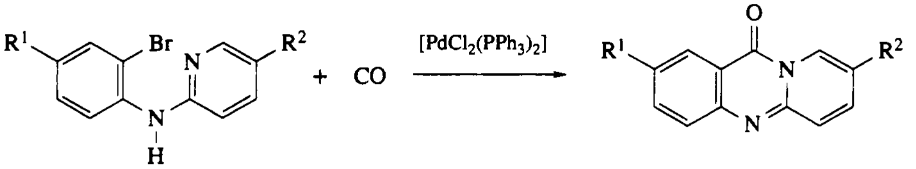

(57)

A number of berbin-8-ones have been synthesized from 2′-halogeno-1-benzylisoquinolines by reaction with metal carbonyls.[93] In order to optimize the yield of the required product and suppress the main side reaction, dehalogenation, it is important to choose the right metal carbonyl. In some cases $[Co_2(CO)_8]$ appears to be the right reagent (equation 58), whereas in other cases $[Fe_3(CO)_{12}]$ is more suitable (equation 59). The latter reaction can also be brought about by palladium-catalyzed carbonylation of the same starting material in 52% yield.[94]

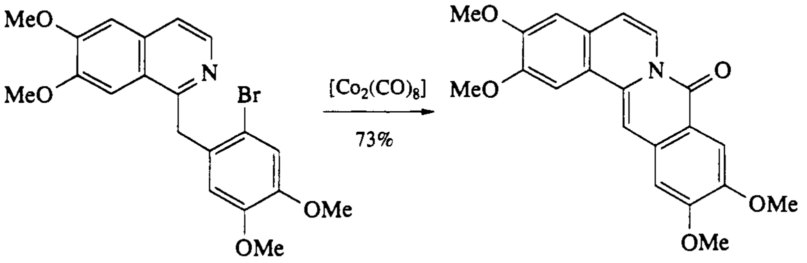

(58)

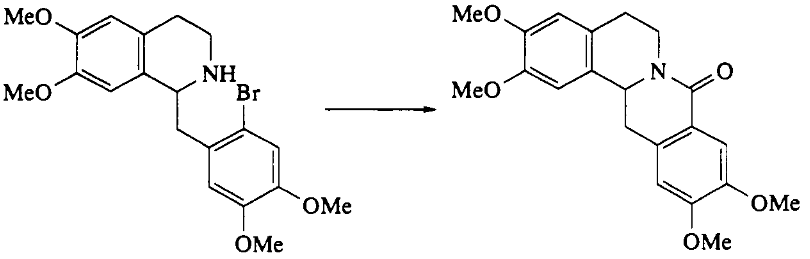

(59)

Using the same procedure as for the synthesis of the related five- and six-membered benzolactams, the benzoazepinone derivatives (**27**) have been synthesized in good yield.[90] This palladium-catalyzed procedure has more recently been extended to the synthesis of a number of antibiotics.[95] A key step in the synthesis of anthramycin, for example, is the palladium-catalyzed insertion of CO into the amine (**28**).[95b]

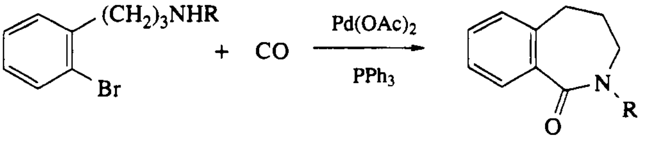

**(27)**

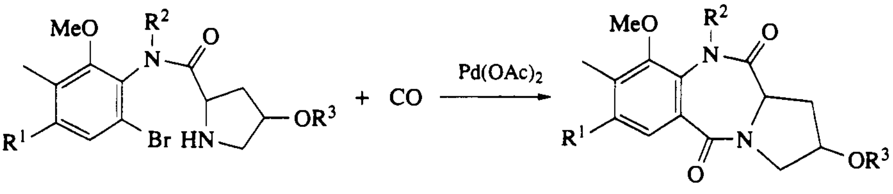

**(28)**

### 4.1.10 FORMATION OF ISOCYANATES

Aromatic nitro compounds can be carbonylated to isocyanates in the presence of palladium catalysts such as $PdCl_2$/pyridine (equation 60).[96] Although high conversions can be obtained the reaction conditions are somewhat vigorous (200 °C, 150 bar CO). Rhodium catalysts have also been shown to be active for this transformation.[97] From an industrial point of view, however, the simplicity of the reaction offers an attractive route to isocyanates, which are important intermediates for polyurethanes.[98]

$$ArNO_2 + 3CO \longrightarrow ArNCO + 2CO_2 \qquad (60)$$

2-Arylazirines are carbonylated under very mild conditions (5 °C, 1 bar CO) in the presence of $[Rh_2(CO)_4Cl_2]$ to give arylvinyl isocyanates in high yield (equation 61).[99] These products can be isolated or more conveniently converted to carbamates or ureas by reaction with alcohols or amines, respectively.

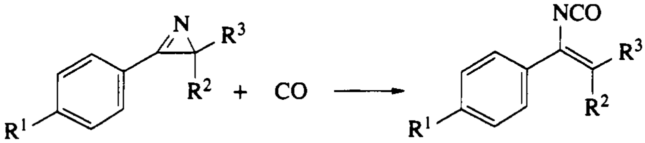

(61)

### 4.1.11 DOUBLE CARBONYLATION

The realization that doubly carbonylated products can be formed in carbonylation reactions has only emerged in the last ten years, but specific syntheses of many α-keto acids, amides, esters and related products are being developed rapidly. Although many such syntheses depend on the use of CO pressures well above ambient, variation of other parameters such as catalyst, solvent and base can lead to efficient double carbonylation even at relatively low pressures. Selective, cobalt-catalyzed formation of phenylpyruvic acid (97% selectively at 85% yield) from benzyl chloride was thus achieved at 50 bar pressure of CO in propan-2-ol, but more recent work has shown that similar selectivity and an even higher yield can be obtained at less than 2 bar when 1,2-dimethoxyethane is used as solvent (equation 62).[100]

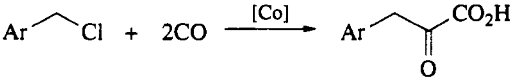

(62)

Palladium-catalyzed double carbonylations of aromatic halides have also been studied (equation 63).[101] As might be expected, higher pressure is favorable for both reaction rate and selectivity. Selectivity for the formation of keto esters is also maximized by the use of sterically hindered alcohols and solvents of low polarity.

The above reactions take place in the presence of an organic tertiary amine as base, but in the presence of calcium hydroxide reductive double carbonylation takes place with the formation of α-hydroxy acids (equation 64).[102] To maximize the yield of hydroxy acid it is necessary to use isopropyl alcohol as

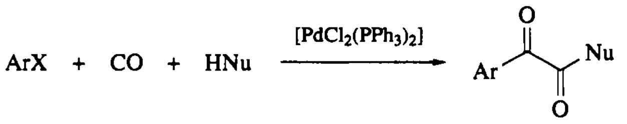

(63)

HNu = $R_2NH$, $RNH_2$, ROH, $H_2O$

solvent and a basic phosphine ligand, such as $PMe_3$, in combination with calcium hydroxide as the base. Formation of the α-hydroxy acid is rationalized in terms of a double carbonylation followed by Meerwein–Ponndorf-type reduction of the resulting α-keto acid by the isopropyl alcohol/calcium hydroxide mixture.

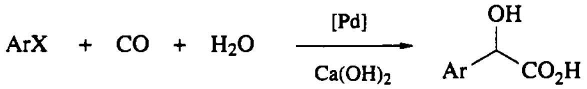

(64)

By careful selection of the reaction conditions 3-butenols undergo efficient dialkoxycarbonylation to produce γ-butyrolactone 2-acetic acid esters under 1 bar of CO (equation 65).[103] Although the roles of the additives are not fully understood, the presence of propylene oxide and ethyl orthoacetate is essential to ensure high selectivity to the double carbonylation product.

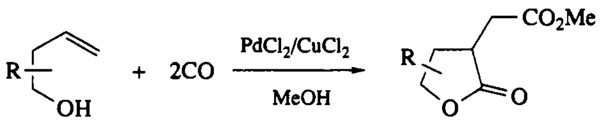

(65)

In the presence of catalytic amounts of $[PdCl_2(NCMe)_2]$/CuI under CO and $O_2$, amines react with alcohols to form oxamates (equation 66).[104] The reaction proceeds at room temperature and with β-amino alcohols the corresponding cyclic oxamate is produced (equation 67).

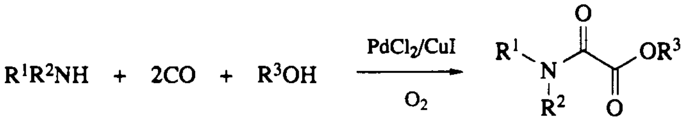

(66)

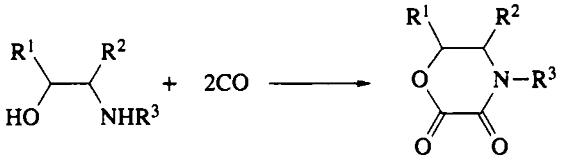

(67)

## 4.1.12 DECARBONYLATION

Since most of the elementary steps in carbonylation reactions are reversible, it is not surprising that transition metals and their complexes promote the decarbonylation of organic compounds in either a stoichiometric or a catalytic manner.[105] In stoichiometric reactions carbon monoxide removed from the organic compound is retained by the metal complex, as in equation (68), whereas for catalytic behavior this CO must be released, a reaction that often occurs only at high temperatures (>200 °C).

$$\mathrm{RCHO} + [\mathrm{RhCl(PPh_3)_3}] \longrightarrow \mathrm{RH} + \mathrm{PPh_3} + [\mathrm{RhCl(CO)(PPh_3)_2}] \qquad (68)$$

The rhodium complex $[RhCl(PPh_3)_3]$ readily brings about stoichiometric decarbonylation of aldehydes, acyl halides and diketones. A typical aldehyde decarbonylation is illustrated by equation (69).[106] α,β-Unsaturated aldehydes are decarbonylated stereospecifically (equation 70), while with chiral aldehydes the stereochemistry is largely retained (equation 71).[107]

Acyl halides are decarbonylated under mild conditions, but halides containing β-hydrogens also undergo dehydrohalogenation and alkenes rather than alkanes are obtained.[108] Early reports suggested that aromatic acyl chlorides, bromides and fluorides could be decarbonylated, but more recent work indicates that the reaction is not as simple as first thought and variable results have been obtained.[109]

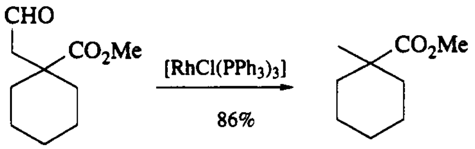

(69)

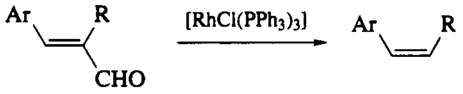

(70)

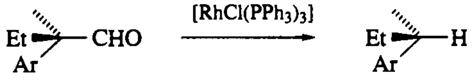

(71)

By heating above 200 °C catalytic decarbonylation is possible using $[RhCl(PPh_3)_3]$, and is particularly suitable for aromatic aldehydes since aliphatic aldehydes tend to dehalogenate under these conditions to form alkenes (equation 72). Cationic rhodium complexes, for example $[Rh(Ph_2P(CH_2)_2PPh_2)_2]^+$, are much more active catalysts and hence reactions can be carried out at below 100 °C.[110] Because of the milder conditions aliphatic aldehydes can be decarbonylated to the alkane using this catalyst system. Rhodium catalysts can also be used to decarbonylate α- and β-diketones and keto esters (equations 73 and 74).[111]

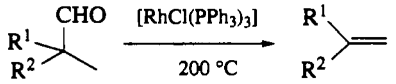

(72)

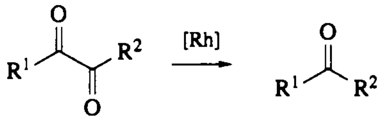

(73)

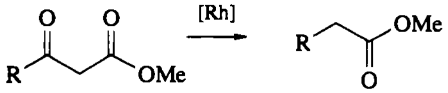

(74)

The palladium-catalyzed decarbonylation of aromatic acyl cyanides proceeds at 120 °C to give the corresponding nitriles in excellent yield.[112] Since acyl cyanides are readily prepared by the ruthenium-catalyzed oxidation of cyanohydrins with Bu$^t$OOH this represents a good method for the conversion of aldehydes to nitriles under mild conditions (Scheme 29).

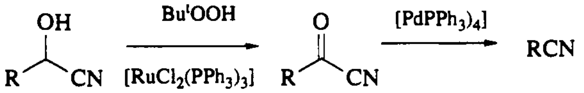

**Scheme 29**

Decarbonylation of the tricyclic bridgehead acid chloride (**29**) with a palladium catalyst at 130 °C in the presence of tri-*n*-butylamine gives exclusively the disubstituted alkene (**30**) in essentially quantitative yield.[113] Under these conditions none of the bridgehead alkene is obtained, but it is assumed that this is an intermediate in the reaction.

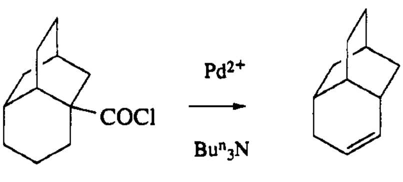

(**29**) (**30**)

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# 4.2

# Carbon–Carbon Bond Formation by C—H Insertion

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## 4.2.1 INTRODUCTION

Traditionally, carbon–carbon bond forming processes have required that both organic fragments be specifically activated. This approach is exemplified by the alkylation of an enolate anion (**1**) with an alkyl halide (**2**; equation 1).

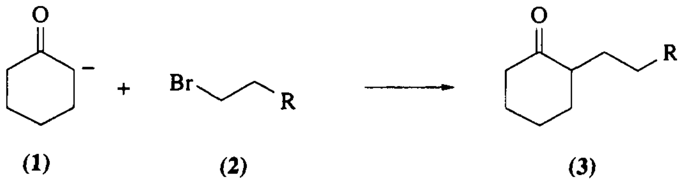

(1)

There are isolated reports of an alternative approach, in which the carbon–carbon bond is formed by direct insertion into an unactivated C—H bond. Often, these are special cases. The conditions under which carbonylation of adamantane (**4**; equation 2) is observed, for instance, would not be expected to be equally efficacious for cyclohexane.[1]

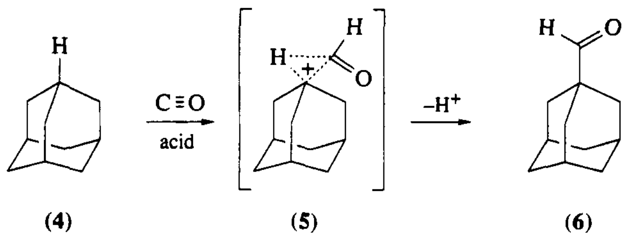

(2)

The purpose of this chapter is to review those methods for constructing C—C bonds from unactivated C—H bonds that appear to have some synthetic generality. Both intermolecular and intramolecular reactions will be considered.

## 4.2.2 INTERMOLECULAR C—H INSERTION

### 4.2.2.1 Abstraction–Recombination

The most common strategy for laboratory-scale hydrocarbon functionalization is hydrogen atom abstraction followed by free radical recombination. This approach is exemplified by the method of Tanner for cyanation of hydrocarbon (**7**) to give (**8**; equation 3).[2]

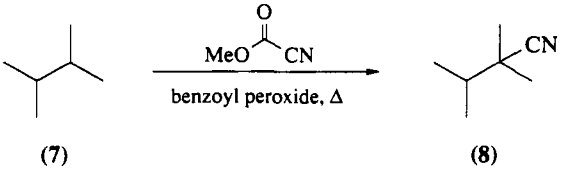

(3)

It is possible to achieve some selectivity using this method. As illustrated above, tertiary C—H sites are much more reactive than primary C—H sites. Radical-stabilizing functional groups also impart selectivity, as illustrated by the regioselective functionalization of (**9**; equation 4).[3]

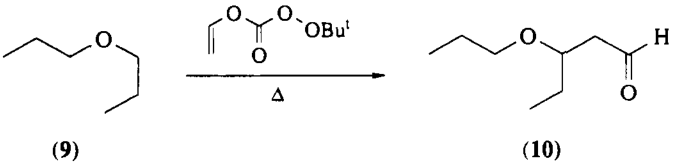

(4)

Crabtree, by combining ease of free radical generation with the site selectivity imparted by functional groups that stabilize adjacent free radicals, has developed a very practical approach to hydrocarbon carbafunctionalization, as illustrated by the conversion of cyclohexane to (**13**; equation 5).[4] The real elegance of this method is that it does not require highly reactive reagents. This photochemically initiated dimerization of hydrocarbons proceeds efficiently in the presence of even a very low concentration of mercury vapor.

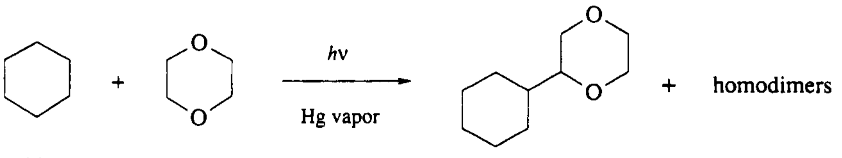

(5)

(**11**) (**12**) (**13**)

Hill has shown that the nature of the product formed in such an insertion reaction can vary with the substrate (equations 6 and 7).[5] It is thought that bond formation using the procedure he has developed also proceeds *via* a free radical intermediate. A secondary radical, as from (**14**), will react directly with acetonitrile to form a new carbon–carbon bond. A tertiary radical, as from (**16**), on the other hand, will be oxidized to the corresponding carbocation before reacting with acetonitrile.

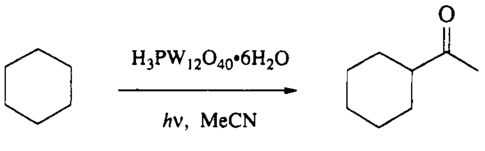

(6)

(**14**) (**15**)

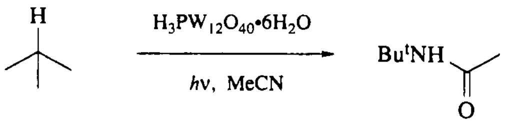

(7)

(**16**) (**17**)

### 4.2.2.2 Carbenoid Insertion

Intermolecular insertion of free carbenes or carbenoids into C—H bonds is not, in general, an efficient process. However, if the C—H is especially activated, as with an alkoxide such as (**18**; equation 8), the reaction can be preparatively useful.[6]

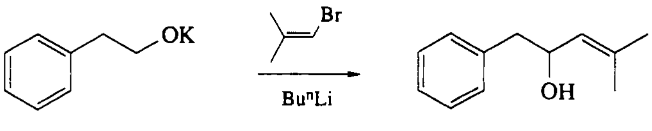

(8)

(**18**) (**19**)

### 4.2.2.3 Metallocarbene Insertion

In 1981, Noels reported that rhodium(II) carboxylates, originally developed as cyclopropanation catalysts, smoothly catalyze the addition of ethyl diazoacetate (**21**; equation 9) to a variety of alkanes.[7,8] While some differentiation between possible sites of insertion is observed, selectivity is not as high for this carbenoid process as it is for the free radical processes illustrated above.

Rhodium-mediated intermolecular C—H insertion is thought to proceed *via* oxidative addition of an intermediate rhodium carbene into the alkane C—H bond. Evidence that the rhodium and its ligands are directly associated with the product-determining transition state has been put forward by Callot, who ob-

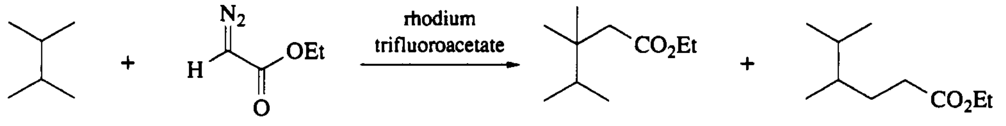

(9)

**(20)** **(21)** **(22)** 88% **(23)** 12%

served that the differential selectivity observed for C—H insertion into (**24**) is a function of the rhodium complex employed (equation 10).[9]

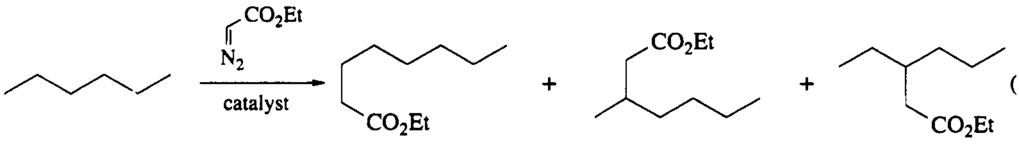

(10)

**(24)** **(25)** **(26)** **(27)**

| | (25) | (26) | (27) |
|---|---|---|---|
| Rh pivalate | 5 | 62 | 33 |
| Rh tetraphenylporphyrin | 8 | 71 | 21 |
| Rh tetra(trimethylphenyl)porphyrin | 25 | 61 | 14 |

## 4.2.3 INTRAMOLECULAR C—H INSERTION: CARBACYCLES

### 4.2.3.1 Introduction

Unlike the intermolecular examples of C—H insertion mentioned above, most of which are relatively recent, intramolecular C—H insertion has long been recognized. In a late stage of the biosynthesis of cycloartenol (**29**), for instance, the cyclopropane ring is formed by such a process (equation 11).[10]

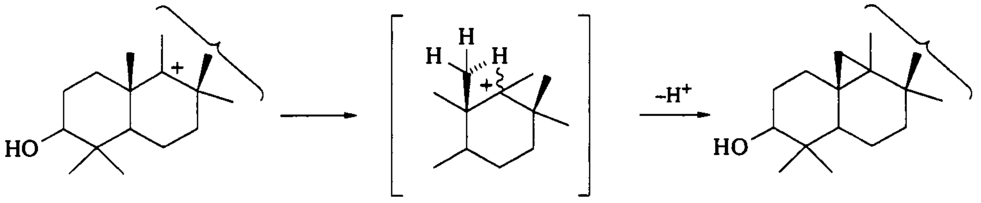

(11)

**(28)** **(29)**

### 4.2.3.2 Photochemical

Photochemical C—H insertion of a ketone (**30**) will proceed by initial photoexcitation to give an excited state that can usefully be considered to be a 1,2-diradical. Intramolecular hydrogen atom abstraction then proceeds, to give a 1,4- or 1,5-diradical, which can collapse to form the new bond. This approach has been used to construct both four- and five-membered rings (equations 12–14).[11–13] Photochemically mediated cyclobutanol formation is known as the Norrish type II reaction.

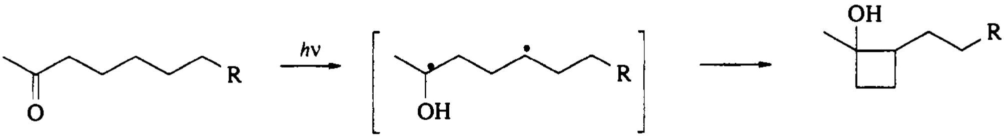

(12)

**(30)** **(31)**

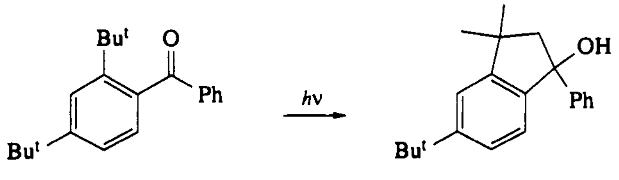

(32) (33)

(13)

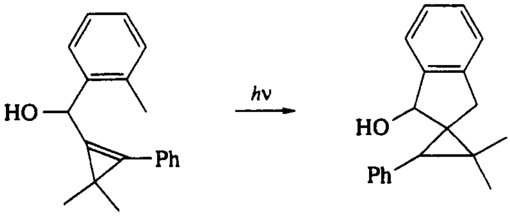

(34) (35)

(14)

## 4.2.3.3 Alkylidene Carbenes

### *4.2.3.3.1 Alkynone pyrolysis*

The first preparative use of intramolecular C—H insertion in organic synthesis was developed by Dreiding, who reported in 1979 that, on flash vacuum pyrolysis, a conjugated alkynyl ketone such as (**36**) is smoothly converted to a mixture of the cyclized enones (**37**) and (**38**) (equation 15).[14] This elegant reaction apparently proceeds *via* isomerization of the alkyne to the corresponding alkylidene carbene.

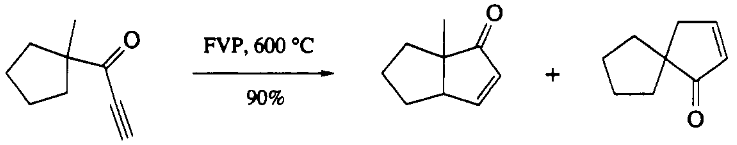

(**36**) (**37**) 92% (**38**) 8%

(15)

It should be noted that despite a 3:2 statistical predominance of primary C—H bonds over secondary C—H bonds, a marked preference for insertion into the latter is observed.

In subsequent work, Dreiding demonstrated that the straight chain conjugated alkynone (**39**) cyclizes smoothly to the corresponding cyclopentenone (**40**; equation 16).[15]

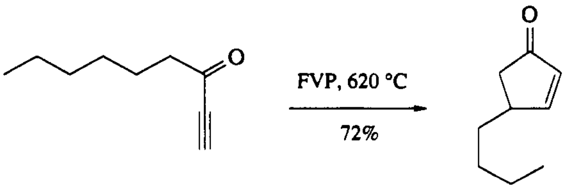

(**39**) (**40**)

(16)

### *4.2.3.3.2 Diazaalkenes*

In 1982, Gilbert reported that an aliphatic ketone or aldehyde on exposure to dimethyl (diazomethyl)phosphonate is converted to the corresponding cyclopentene (**41** → **42** and **43**; equation 17).[16]

This reaction apparently proceeds by way of the normal phosphonate condensation product, the diazoalkylidene, which then spontaneously loses nitrogen to form the transient alkylidene carbene.

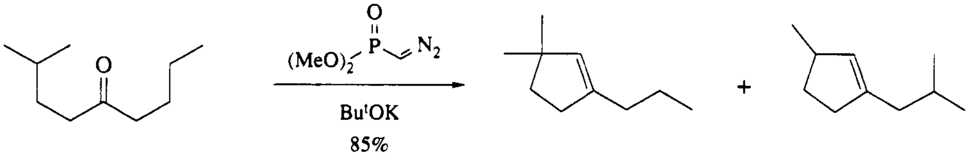

(17)

**(41)** **(42)** 90% **(43)** 10%

Careful work showed that, after statistical corrections were applied, the reactivity of a C—H bond toward insertion was approximately —$CH_3$ = 0.003; —$CH_2$— = 1.0; Ph—$CH_2$— = 7.5; $R_3C$—H = 18.6. These relative reactivities are very similar to those previously observed by Wolinsky for intramolecular C—H insertion by an alkylidene carbenoid generated from a vinyl bromide.[17]

In subsequent work, Gilbert showed that the alkylidene carbene insertion reaction proceeds with retention of absolute configuration.[18] Using this approach, cyclopentene (**45**) and cyclohexene (**46**) were prepared in high enantiomeric purity (equation 18).

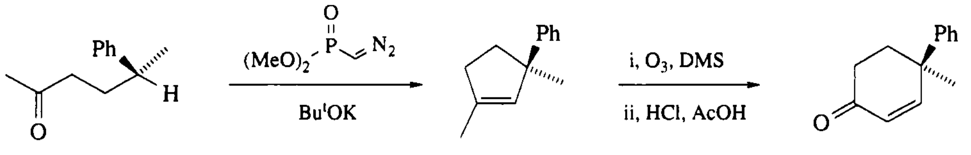

(18)

**(44)** **(45)** **(46)**

### 4.2.3.3.3 *Alkylidene carbenoids*

The insertion reactions described above probably proceed *via* the free alkylidene carbenes. The analogous alkylidene carbenoids also insert efficiently into remote C—H bonds. Ochiai has demonstrated that such alkylidene carbenoids are conveniently generated from the corresponding iodinium tosylates.[19] Depending on the substitution pattern employed, either [5 + 0] cyclization to give (**49**; equation 19), or [2 + 3] cyclization to give (**52**; equation 20), can be obtained.

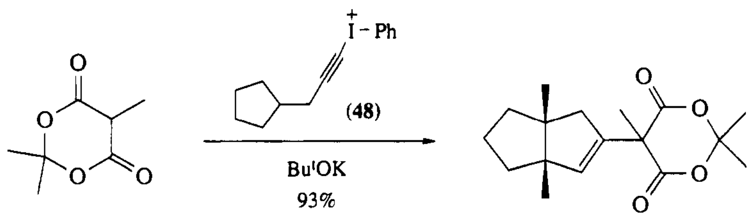

(19)

**(47)** **(49)**

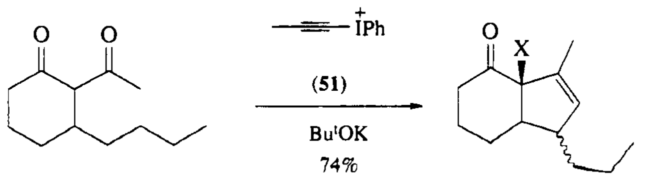

(20)

**(50)** **(52)** X = COMe

### 4.2.3.4 Alkyl Carbenoids

#### *4.2.3.4.1 Thermal insertions*

The simple thermal insertion of an unsubstituted alkyl carbene or carbenoid into a remote C—H bond is, in general, not a useful synthetic method. Activation of the C—H bond by an α-alkoxy group, as with the cyclization of (**53**) to (**54**) reported by Cohen, makes this process more efficient (equation 21).[20]

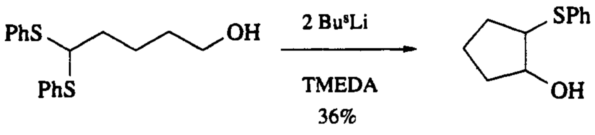

**(53)** **(54)**

(21)

#### *4.2.3.4.2 Copper-catalyzed diazo insertions*

There are several isolated examples of conformationally constrained α-diazo ketones that, under catalysis by Cu salts, smoothly undergo intramolecular C—H insertion.[21] This cyclization was investigated in some detail by Wenkert, who found that it was not, in the acyclic series, a preparatively useful synthetic method (equation 22).[22]

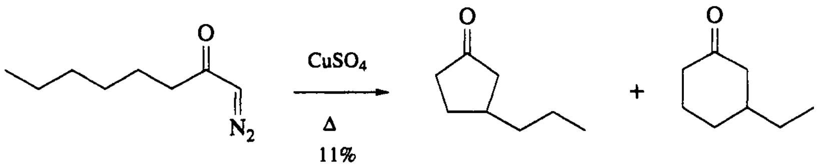

**(55)** **(56)** 82% **(57)** 18%

(22)

#### *4.2.3.4.3 Rhodium-catalyzed diazo insertions*

*(i) Initial cyclization studies*

Hubert in 1976 reported that rhodium acetate efficiently catalyzes diazo insertion into an alkene, to give the cyclopropane.[8] In 1979, Southgate and Ponsford reported that rhodium acetate also catalyzes diazo insertion into a C—H bond.[23] Prompted by these studies, Wenkert then demonstrated that cyclization of (**58**) to (**59**) proceeded much more efficiently with the rhodium carboxylates than it had with copper salt catalysis (equation 23).[22]

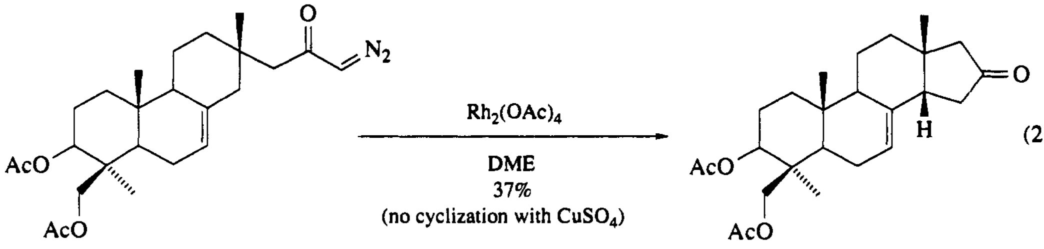

**(58)** **(59)**

(23)

Concurrently, Noels had reported that rhodium carboxylates smoothly catalyze the intermolecular C—H insertion of ethyl diazoacetate into alkanes.[7] Following up on this report, Taber demonstrated that the open chain α-diazo β-keto ester (**60**) cyclizes smoothly under rhodium acetate catalysis to give the corresponding cyclopentane (**61**; equation 24).[24] In contrast to the copper-mediated cyclization cited above (equation 22), the six-membered ring product is not observed. The insertion shows significant electronic selectivity. Although there is a 3:1 statistical preference for methyl C—H, only the methylene C—H insertion product (**61**) is observed (equation 24).

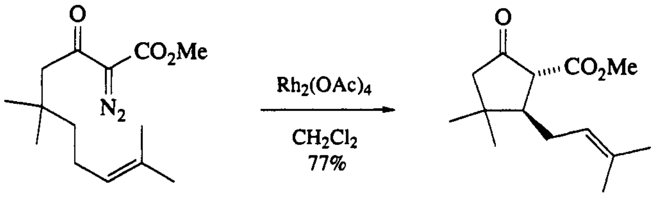

(24)

**(60)** **(61)**

In a direct comparison, it has been found that with the same substrate (**62**), $Rh_2(OAc)_4$ directs the reaction toward C—H insertion, to give (**63**), whereas Cu bronze favors alkene insertion, to make the cyclopropane (**64**; Scheme 1).[24,25]

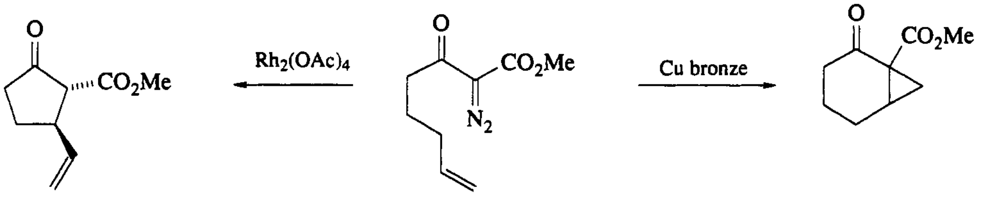

**(63)** **(62)** **(64)**

**Scheme 1**

Other electron-withdrawing groups are compatible with both diazo transfer and cyclization. Both the β-keto sulfone (**65**) and the β-keto phosphonate (**67**) have been cyclized using rhodium acetate catalysis (equations 25 and 26).[26,27] The cyclized keto phosphonate (**68**) can be further reacted with formaldehyde to make the α-alkylidenecyclopentanone (**69**; equation 26).[27]

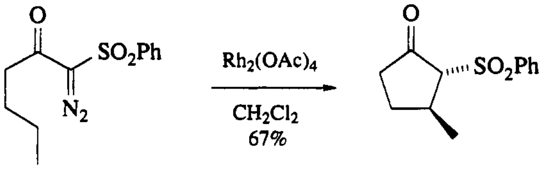

(25)

**(65)** **(66)**

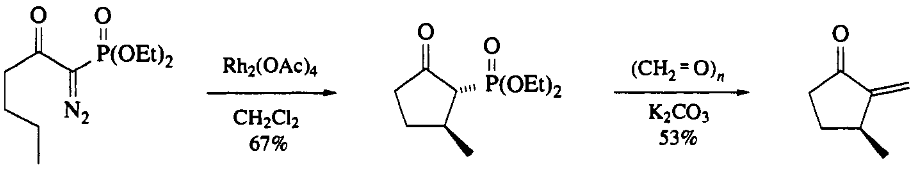

(26)

**(67)** **(68)** **(69)**

### *(ii) Selectivity*

Steric and electronic selectivity in the C—H insertion process has been studied in some detail.[28] The cyclization of (**70**) was shown to give (**71**) with high diastereoselectivity (equation 27).

Wenkert demonstrated that cyclization of the diazomethyl ketone corresponding to (**72**)[22] proceeds to give predominantly the *trans*-hydrindan (equation 28).[22] Taber showed that the degree of diastereoselectivity in the cyclization of (**72**) to (**73**) and (**74**) is affected by the ligands on rhodium (equation 28).[28]

As with the work of Gilbert cited above, electronic selectivity can also be observed.[28] It is striking that cyclization of (**75**) proceeds to give preferentially (**76**) rather than (**77**; equation 29). The observation that

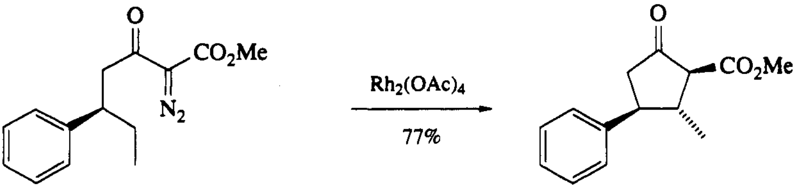

(27)

**(70)** **(71)** only product observed

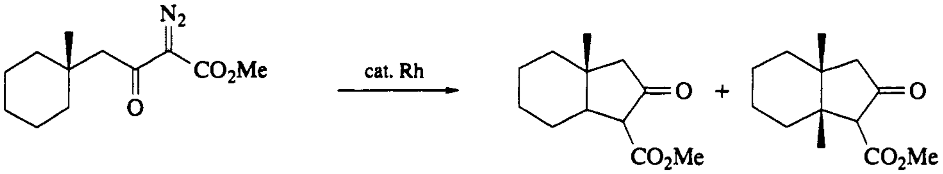

(28)

**(72)** acetate 3:1, octanoate 5:1 **(73)** **(74)**

a benzylic —$CH_2$— is significantly less reactive than an aliphatic —$CH_2$—, in direct contrast to the 'free carbene' work of Gilbert and others,[16] led to the suggestion that the reaction is proceeding by complexation of a coordinatively unsaturated rhodium carbene complex with the electron density in the target C—H bond.[28] The phenyl substituent, being inductively electron-withdrawing, might then be expected to deactivate the benzylic methylene.

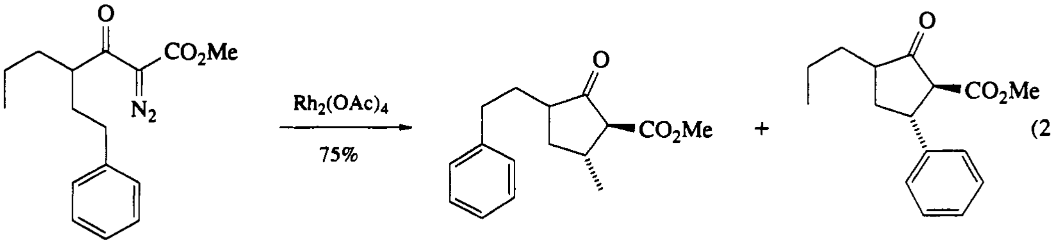

(29)

**(75)** **(76)** 77% **(77)** 23%

## (iii) Mechanism

While the detailed mechanism of the rhodium-mediated cyclization is not known, a working hypothesis that accommodates all of the observations to date is that it proceeds *via* a $Rh^I$ carbene complex such as (**82**; Scheme 2). Oxidative addition of the rhodium carbene into a remote C—H bond would give a metallacycle such as (**83**). Carbene rearrangement could then give (**84**), which could undergo reductive elimination to give the product (**85**), along with the regenerated catalyst (**79**).

This mechanistic hypothesis led to two predictions.[28] The first was that, since the product-determining step would seem to be oxidative addition of an electron deficient Rh center into the C—H bond, a C—H bond near an electron-withdrawing group should be less reactive than an isolated C—H bond. This prediction was borne out remarkably well by the work of Stork and Nakatani.[29] They demonstrated that cyclization of (**86**) proceeds to give exclusively (**87**; equation 30). Thus, a C—H bond even β to the electron-withdrawing carboxyl group is much less reactive toward rhodium-mediated C—H insertion than is an isolated aliphatic C—H bond.

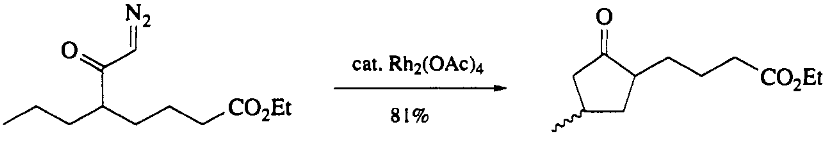

(30)

**(86)** **(87)** only product observed

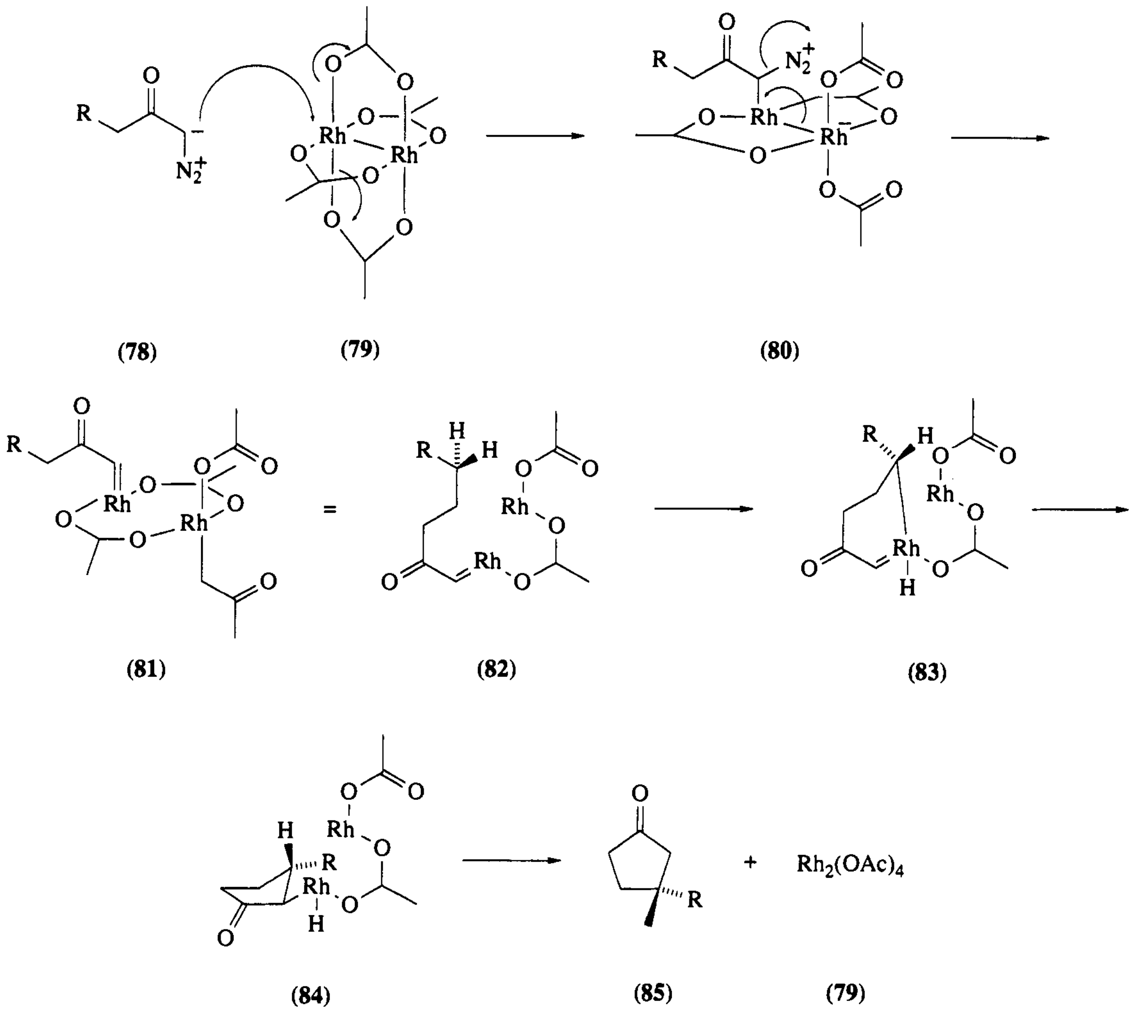

Scheme 2

The other prediction stemmed from the expectation that in the transition state leading to C—H insertion, the forming ring would adopt a lowest energy, staggered, chair-like conformation. It followed that it might be possible to design an enantiomerically pure ester that would destabilize one of the two enantiomeric transition state conformations and thus direct the absolute stereochemistry of the cyclization. Indeed, even though the nearest stereogenic center in the directing alcohol is eight atoms removed from the C—H insertion site, cyclization of (**88**) to (**89**) and (**90**) proceeds with reasonably good selectivity (equation 31).[30] The cyclized esters are diastereomers and can be separated chromatographically.

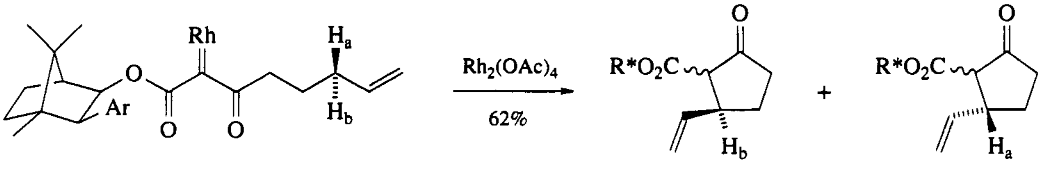

(31)

(**88**) Ar = 1-naphthyl (**89**) 92% (**90**) 8%

*(iv) Simple α-diazo ketones and esters*

It could be expected that if a simple α-diazo ketone with β-C—H bonds were exposed to the rhodium catalyst, metallocarbene formation would proceed as usual, but that β-hydride elimination would compete with the desired 1,5-insertion. Such a β-hydride elimination could, in fact, be viewed as a 1,2-insertion (**91** → **93**; equation 32).

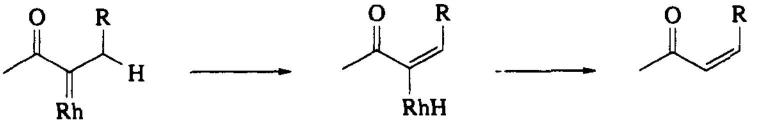

**(91)** **(92)** **(93)** (32)

In recent work, Taber and Hennessy have found that simple α-diazo ketones and esters can, in fact, be induced to undergo 1,5-insertion in preparatively useful yields.[31] It was already known[28] that, in the rhodium-mediated insertion process, methyl C—H is electronically less reactive than methylene C—H or methine C—H. It therefore seemed likely that competing β-hydride elimination would be least likely with a diazoethyl ketone. In fact, on cyclization of (**94**), only a trace of the enone product from β-hydride elimination is observed (equation 33). The main side reaction competing with 1,5-insertion is dimer formation.

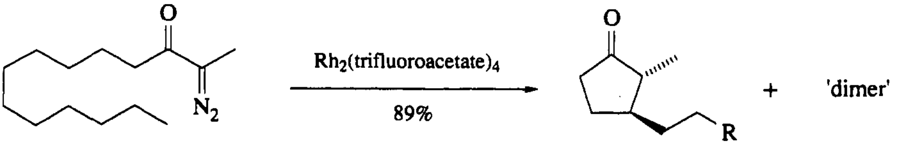

**(94)** **(95)** 77% **(96)** 23% (33)

In a direct competition between 1,2- and 1,5-insertion into methylene C—H, the relative proportion of products depends on the rhodium carboxylate used. Rhodium benzoate is the most efficient catalyst so far found for the cyclization of α-diazo ester (**97**) to (**98**) (equation 34).[31]

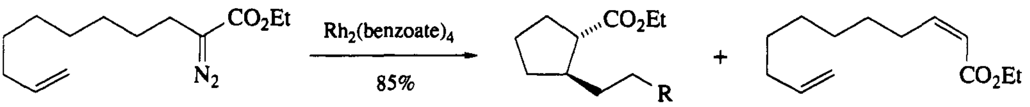

**(97)** **(98)** 77% **(99)** 23% (34)

With the long chain α-diazo ketone (**100**), 1,5-insertion could proceed to put the carbonyl outside the ring or to include it in the ring. In fact, only the product (**101**) from the first of these two cyclization modes is observed (equation 35).[31] The alternative cyclopentane (**103**) is not formed. As with the α-diazo ester, the relative proportion of 1,2- and 1,5-products depends on the rhodium carboxylate used. Throughout these studies, it has been observed that the alkene (**102**) obtained from 1,2-elimination is cleanly *cis*.[31,32]

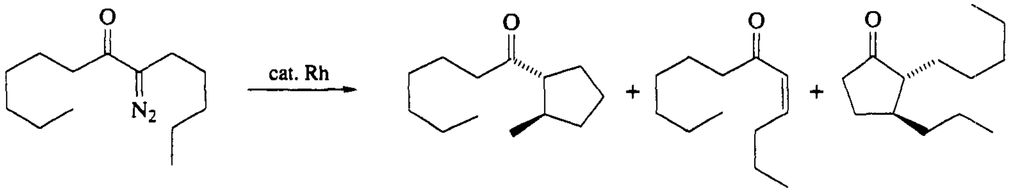

**(100)** **(101)** **(102)** **(103)** (35)

| | | | |
|---|---|---|---|
| acetate (86%) | 70% | 30% | 0% |
| trifluoroacetate (87%) | 38% | 62% | 0% |

The complete absence of the cyclopentanone product (**103**) in the reaction above suggests that, in the intermediate rhodium carbenoid, there is a significant preference for the conformation (**104**), in which the ketone carbonyl and the rhodium center are *syn* to one another (equation 36).

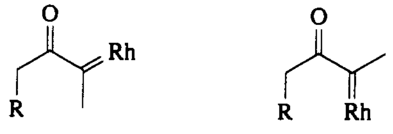

(36)

*syn* (**104**) *anti* (**105**)

## 4.2.4 INTRAMOLECULAR C—H INSERTION: HETEROCYCLES

### 4.2.4.1 Rhodium-mediated Cyclization

#### 4.2.4.1.1 *β-Lactam synthesis*

The first observation of rhodium-mediated intramolecular C—H insertion was by Southgate and Ponsford at Beecham Pharmaceuticals, who reported that (**106**) on exposure to a catalytic amount of rhodium acetate cyclizes cleanly to the β-lactam (**107**; equation 37).[23] This approach to thienamycin derivatives has been developed further by the Beecham group.[33,34]

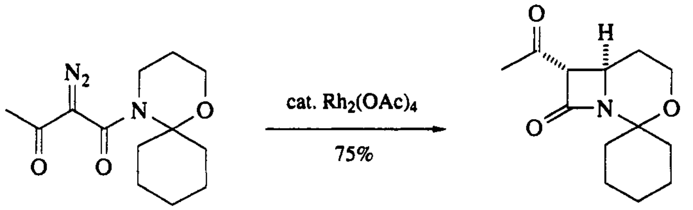

(37)

(**106**) (**107**)

More recently, Doyle has shown that even an acyclic amide such as (**108**) can cyclize smoothly to the β-lactam (**109**; equation 38).[35] β-Lactam formation in these cases is surprising, since the electron-withdrawing heteroatom should direct insertion away from the α-C—H bond. It may be that in this situation, overlap between the filled orbital on the nitrogen atom and the C—H orbital can increase the electron density in the latter, thus making it more reactive. It may be pertinent that as (**108**) becomes more product-like, amide resonance decreases and the electron-donating ability of the nitrogen atom could increase.

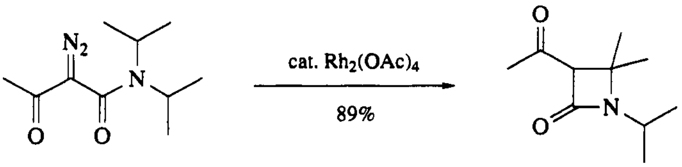

(38)

(**108**) (**109**)

#### 4.2.4.1.2 *Furanone synthesis*

The cyclization of (**110**) to (**111**) reported by Adams is a particularly striking example of C—H activation by an adjacent heteroatom (equation 39).[36] Although the ring size would be the same, and conformational differences in the transition states leading to the two products should be minimal, none of the alternative bicyclic ketone (**112**) was observed.

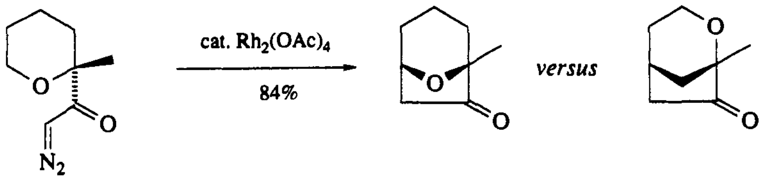

(39)

**(110)** **(111)** 100% **(112)** 0%

#### *4.2.4.1.3 Pyrrole synthesis*

Rhodium-catalyzed intramolecular insertion into aromatic C—H bonds proceeds smoothly.[28,37] For instance, (**113**) cyclizes to a mixture of the heterocyclic product (**114**) and the carbacyclic product (**115**; equation 40).[37] From the product ratios observed, one could conclude that the substituent on the aromatic ring can accelerate or decelerate C—H insertion. As with the results cited above (Section 4.2.3.4.3), the differences in reactivity observed can be ascribed to greater or lesser electron density in the target C—H bond.

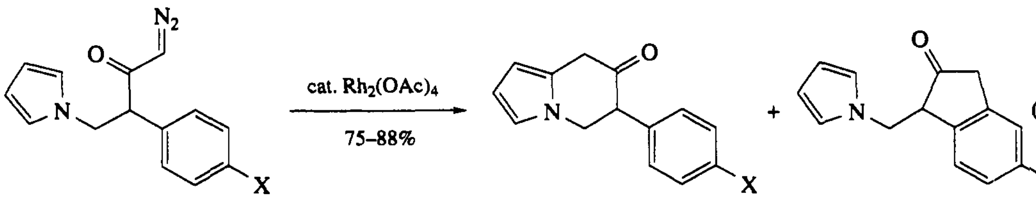

(40)

**(113)**

| X | (114) | (115) |
|---|---|---|
| $-NO_2$ | 100% | 0% |
| -H | 83% | 17% |
| -OMe | 77% | 22% |

### 4.2.4.2 Photochemical Cyclization

#### *4.2.4.2.1 γ-Lactam synthesis*

Photochemical C—H insertion, by abstraction–recombination, can also be used to construct heterocyclic rings. In the example illustrated, 1,5-hydrogen atom abstraction leads to the six-membered lactam (**117**; equation 41).[38]

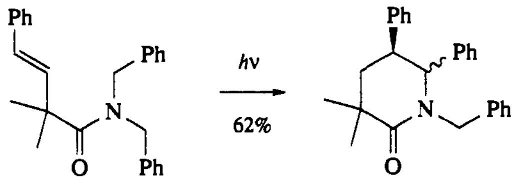

(41)

**(116)** **(117)**

#### *4.2.4.2.2 Macrolactam synthesis*

In some cases, abstraction–recombination can lead to still larger rings. In the example illustrated, 1,8-hydrogen atom extraction leads to the formation of a seven-membered ring product (**119**; equation 42).[39] The 1,7-diradical would be thermodynamically favored because of the radical-stabilizing ability of the two sulfur atoms. The reaction may not, however, proceed by direct 1,8-abstraction. A 1,5-abstraction followed by a subsequent 1,4-abstraction would give the same product and would be sterically more reasonable.

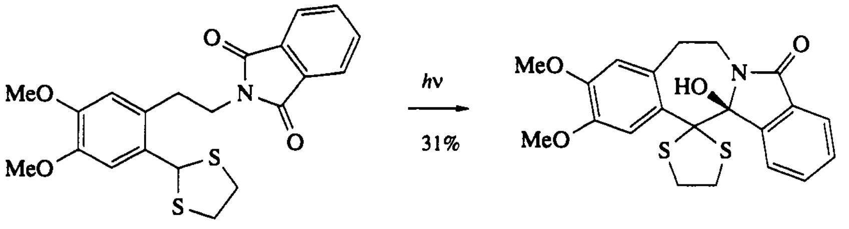

(42)

**(118)** **(119)**

#### *4.2.4.2.3 Macrolide synthesis: remote functionalization*

In sterically constrained cases, hydrogen atom abstraction over long distances has been unequivocally established. In the steroid functionalization work of Breslow, for instance, irradiation of (**120**) leads, by 1,13-abstraction, to clean formation of the 12-membered macrolide (**121**; equation 43).[40] The chapter on 'Remote Functionalization' (Volume 7, Chapter 1.3) contains a full discussion of this family of reactions.

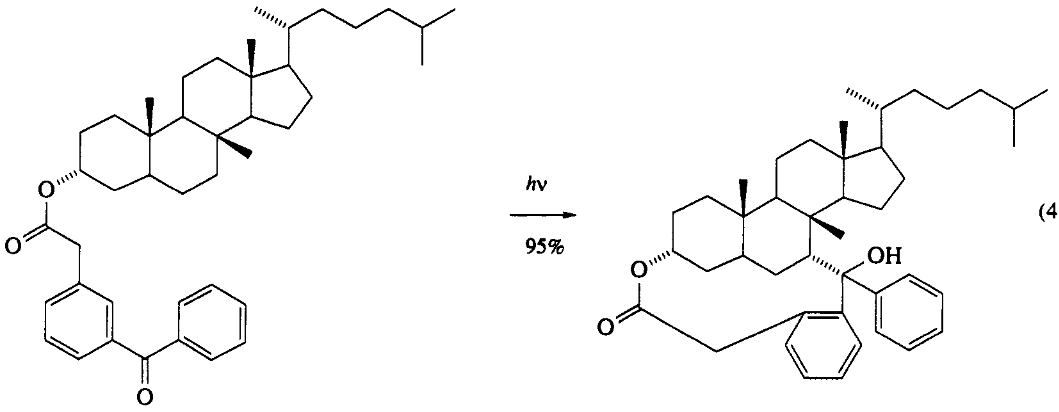

(43)

**(120)** **(121)**

### 4.2.5 APPLICATIONS TO NATURAL PRODUCT SYNTHESIS

#### 4.2.5.1 Photochemical: (–)-Punctatin A

The elegant route to (–)-punctatin A (**125**) developed by Paquette nicely illustrates the synthetic utility of photochemically mediated intramolecular C—H insertion (Scheme 3).[41] The excellent stereoselectivity observed in the four-membered ring forming process (**123**) → (**124**) was, in fact, predicted. The intermediate 1,4-diradical could cyclize to the equatorially fused *trans*-cyclobutane, as illustrated. The alternative cyclization mode, leading to the *cis*-fused cyclobutane, has a bad steric interaction with the angular alkoxymethyl group, and so is less favored.

#### 4.2.5.2 Alkylidene Carbene: Clovene

Dreiding has used the conjugated alkynone flash vacuum pyrolysis he developed (Section 4.2.3.3) as the key step in several elegant natural product syntheses. The considerations that lead to regio- and stereo-chemical control are nicely illustrated by his approach to clovene (**130**; Scheme 4).[42] Thermolysis of the (symmetrical) alkynone (**126**) could lead to three different enones, two of which (**127** and **128**) are illustrated. In fact, only (**127**) is isolated, in 80% yield. The structure and stereochemistry of this product enone was confirmed by straightforward conversion to the tricyclic hydrocarbon clovene (**130**). The outcome of the thermolysis was anticipated, on the basis of previous observations that insertion is most

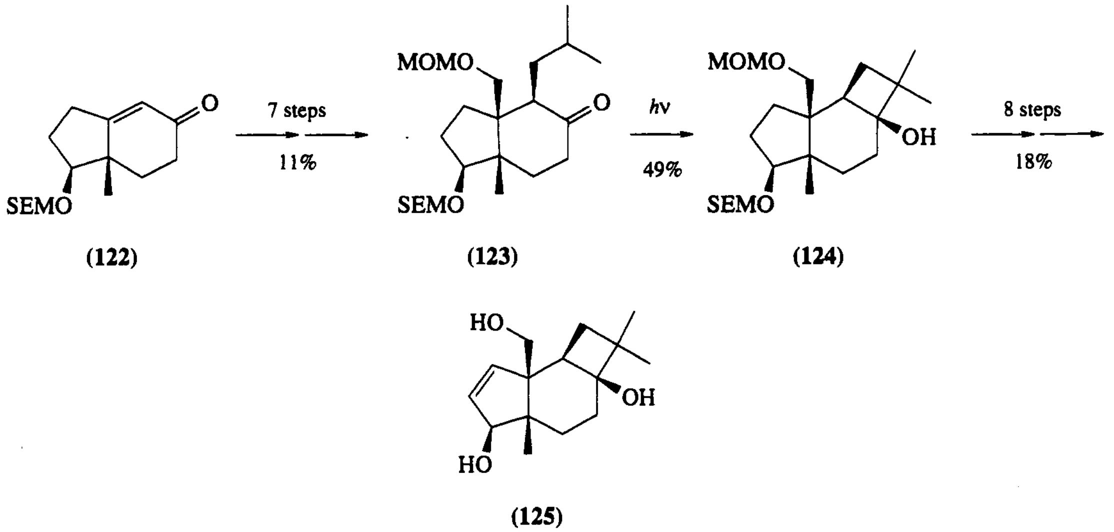
MOMO
SEMO
7 steps
11%
*hν*
49%
OH
8 steps
18%
HO
(122)
(123)
(124)
(125)

**Scheme 3**

facile when the intermediate alkylidene carbene can achieve coplanarity with the target C—H bond. In this system, such coplanarity is easily achieved only by insertion into the boat conformation of the more flexible of the two rings.

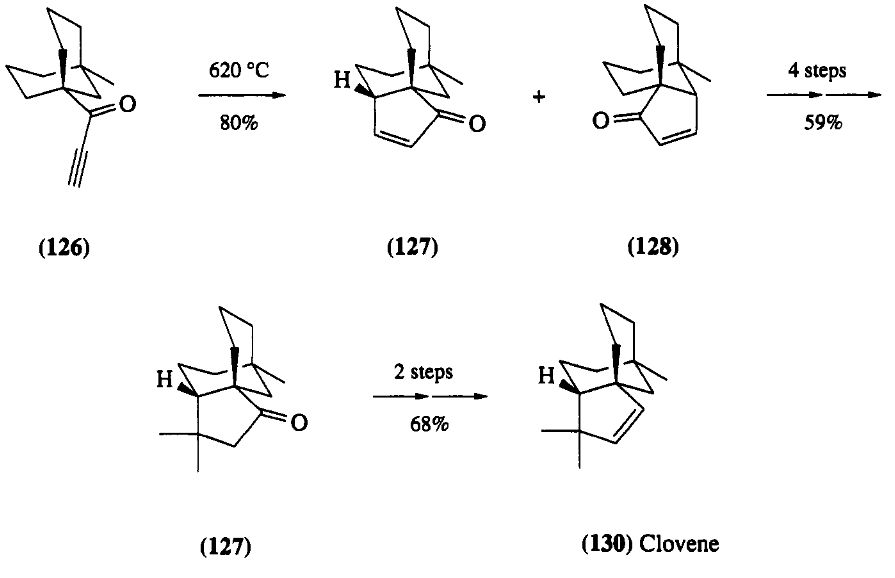
O
620 °C
80%
H
+
4 steps
59%
(126)
(127)
(128)
2 steps
68%
(127)
(130) Clovene

**Scheme 4**

### 4.2.5.3 Rhodium-mediated C—H Insertion

#### *4.2.5.3.1 Pentalenolactone E (Cane)*

After the initial observation by the Beecham group, the first detailed exploration of rhodium-mediated intramolecular C—H insertion in natural product synthesis was by Cane (Scheme 5).[25,43] Starting from the symmetrical bicyclooctanone (**131**), he elaborated the corresponding diazo ester (**132**). Rhodium-mediated methine insertion to give (**133**) then proceeded smoothly. The tricyclic lactone (**133**) so produced had already been converted, by Paquette, to pentalenolactone E (**134**). In the same article (not illustrated here), Cane also reported that rhodium-mediated cyclization provides a viable route to substituted bicyclo[3.3.0]octanones.[43]

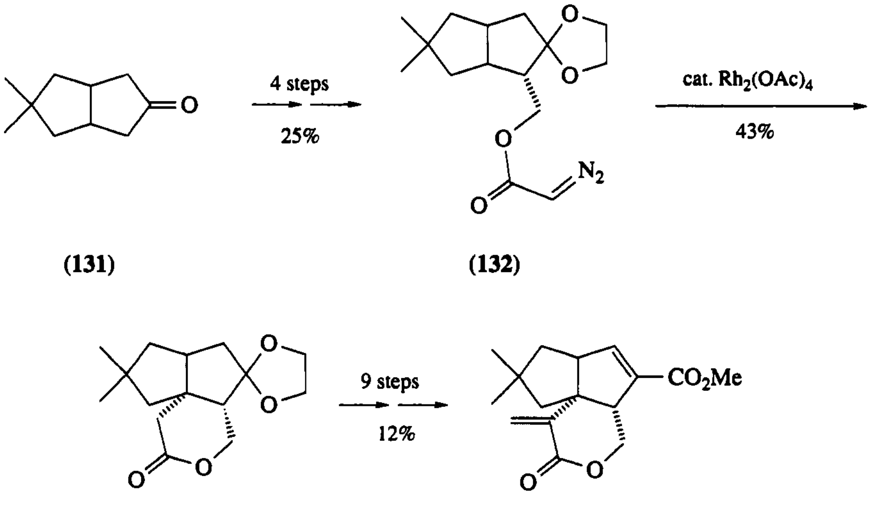

**(131)** **(132)**

**(133)** **(134)** Pentalenolactone E methyl ester

**Scheme 5**

### *4.2.5.3.2 (+)-α-Cuparenone*

A powerful feature of intramolecular C—H insertion is the inherent ability to transform an acyclic ternary stereogenic center into a cyclic quaternary stereogenic center.[18] Taber has demonstrated that the rhodium-mediated cyclization of (**135**) to (**136**) indeed proceeds with retention of absolute configuration (Scheme 6).[44] The absolute stereochemistry of (**136**) was confirmed by conversion to the sesquiterpene (+)-α-cuparenone (**137**).

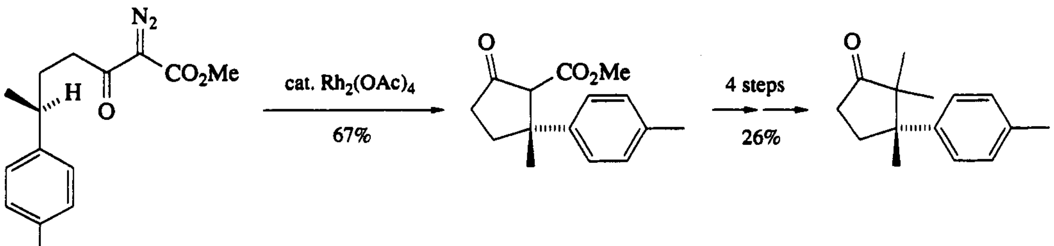

**(135)** **(136)** **(137)** (+)-α-Cuparenone

**Scheme 6**

### *4.2.5.3.3 Pentalenolactone E (Taber)*

Intramolecular C—H insertion is, essentially, a method for specific remote functionalization of hydrocarbons. An important implication of this for synthetic strategy is that the C—H insertion process can dissolve symmetry, thus leading from a simple precursor to a much more complex product. Both the clovene synthesis, by Dreiding, and the pentalenolactone E synthesis, by Cane, take advantage of this idea. It is further illustrated by the pentalenolactone E synthesis reported by Taber (Scheme 7).[45] In the key step, β-keto ester (**139**), which has a single stereogenic center, is transformed into the tricyclic ketone (**140**), which has four stereogenic centers.

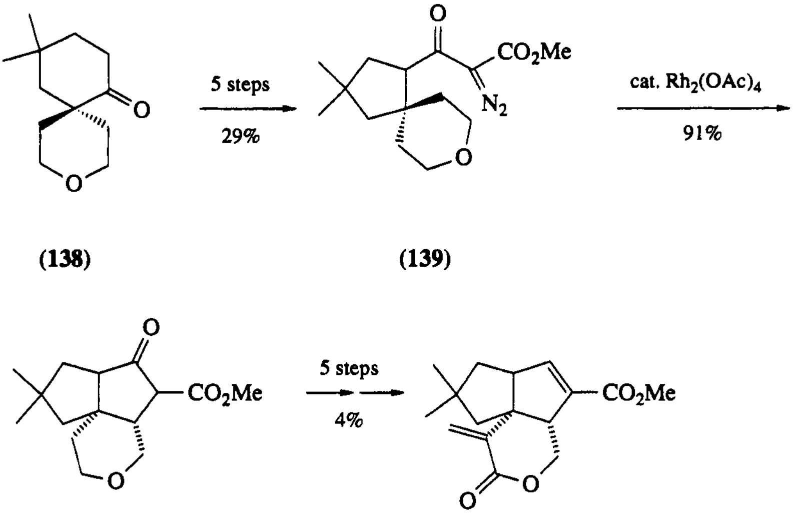

**(138)** **(139)**

**(140)** **(134)** Pentalenolactone E methyl ester

Scheme 7

#### 4.2.5.3.4 (+)-Estrone methyl ether

The key step in the enantioselective synthesis of a polycyclic target is the establishment of the first cyclic stereogenic center. Further construction can then be directed by that initial center. This principle is nicely illustrated by a synthesis of (+)-estrone methyl ether (**145**), reported by Taber (Scheme 8).[46] The specifically designed naphthylbornyl ester (**141**) is used to direct C—H insertion selectively toward one of the two diastereotopic C—H bonds. The new ternary center so created then directs the formation of the adjacent quaternary center in the course of the alkylation. Finally, the chiral skew in the product cyclopentanone (**144**) directs the relative and absolute course of the intramolecular cycloaddition, to give the steroid carbon skeleton.

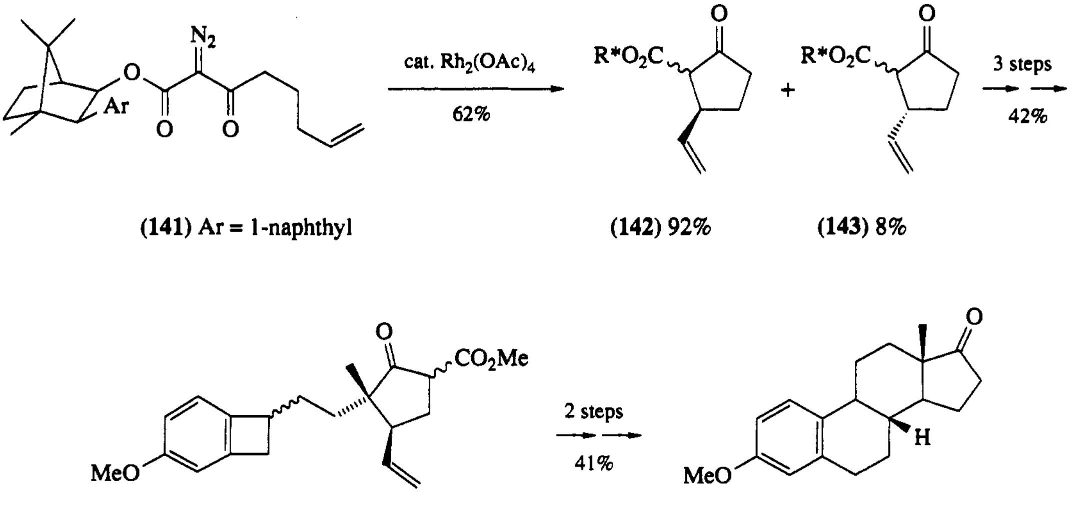

**(141)** Ar = 1-naphthyl **(142)** 92% **(143)** 8%

**(144)** **(145)** (+)-Estrone methyl ether

Scheme 8

## 4.2.6 DIRECTIONS FOR THE FUTURE

It is apparent that intermolecular C—C bond formation by C—H insertion can be effective for the preparative functionalization of hydrocarbons. A drawback to this approach is the substantial cost of the reagents, as compared to the relatively low value of the products. These factors are perhaps best balanced in the mercury-catalyzed photochemical process developed by Crabtree.[4]

Intramolecular C—H insertion, on the other hand, is already a practical alternative for the construction of cyclobutanols,[41] β-lactams[23,33–35] and of cyclopentane-containing targets. With regard to the latter, diazo transfer can be effected on a large scale with the inexpensive methanesulfonyl azide.[47] The rhodium carboxylate catalysts are effective at very low concentration (<1 mol %) and can easily be recovered from the reaction mixture, if desired.[31]

In the rhodium carboxylate catalyzed process, the transition state leading to C—H insertion is highly ordered.[30,46] Rhodium-mediated C—H insertion has further been shown to proceed with retention of absolute configuration.[44] It may likely be possible, therefore, to design enantiomerically pure ligands for rhodium that would direct the absolute course of insertion into a target methylene.

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# Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

Abbott, D. E., 6[12,12c], 10[40], 573[53,54]

The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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*Stanford University, CA, USA*

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## Volume 4

## ADDITIONS TO AND SUBSTITUTIONS AT C—C π-BONDS

Volume Editor
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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N′*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1′-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Stabilized Nucleophiles with Electron Deficient Alkenes and Alkynes

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## 1.1.1 OVERVIEW

### 1.1.1.1 History

The addition of stabilized nucleophiles to activated π-systems is one of the oldest and most useful constructive methods in organic synthesis, dating back more than a hundred years. In 1887 Michael, after whom the most well-known example of this reaction was named, published the first of a series of papers on this reaction describing the addition of the sodium salt of both diethyl malonate (**1**) and ethyl acetoacetate (**2**) to ethyl cinnamate (**3**) to give the products (**4**) and (**5**), respectively (equation 1).[1] This Michael reaction, in which a carbanion stabilized by one or usually two electron-withdrawing groups adds to the β-carbon of an α,β-unsaturated carbonyl derivative, represents one of the earliest and most highly utilized methods for carbon–carbon bond formation. In that same 1887 paper,[1a] Michael also reported the synthesis of triethyl cyclopropane-1,1,2-tricarboxylate (**9**) from (**1**) and ethyl α-bromoacrylate (**6**) *via* the intermediates (**7**) and (**8**), a synthetic route to cyclopropanes used often today (Scheme 1). In 1894 he showed that an alkynic ester could also function as the electrophilic component in these reactions, *e.g.* (**1**) and (**10a**) or (**10b**) giving (**11a**) or (**11b**), respectively (equation 2).[2] This reaction and its variants were in wide use around the turn of the century to prepare straight chain polycarboxylates, *e.g.* the reaction of (**12**) to give (**13**; equation 3) and cyclohexane-1,3-diones, *e.g.* (**15**; equation 4) (*via* Knoevenagel and Claisen condensations).[3] The combination of Michael addition followed by intramolecular aldol condensation and decarboalkoxylation furnishes cyclohexenones, *e.g.* isophorone (**17**; equation 5), from enones such as mesityl oxide (**16**) and the salt of ethyl acetoacetate (**2**).[4] This process of annulation was made much more general in the 1930s by Robinson and his coworkers,[5] who showed that vinyl ketones and their derivatives, *e.g.* Mannich bases, could be used with simple ketone enolates to produce cyclohexenones of a wide variety, *e.g.* (**20**; equation 6), a process which has come to be known as the Robinson annulation.[6]

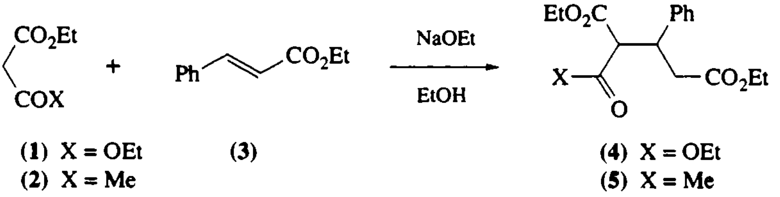
CO2Et
COX
+
Ph
CO2Et
NaOEt
EtOH
EtO2C
Ph
X
O
CO2Et
(1) X = OEt
(2) X = Me
(3)
(4) X = OEt
(5) X = Me

(1)

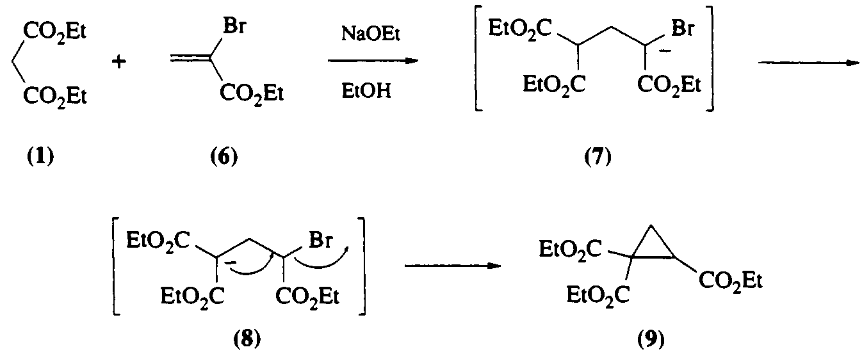
CO2Et
CO2Et
+
Br
CO2Et
NaOEt
EtOH
EtO2C
Br
EtO2C
CO2Et
(1)
(6)
(7)
EtO2C
Br
EtO2C
CO2Et
(8)
EtO2C
EtO2C
CO2Et
(9)

**Scheme 1**

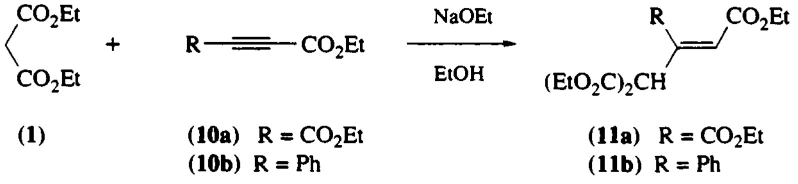
CO2Et
CO2Et
+
R
CO2Et
NaOEt
EtOH
R
CO2Et
(EtO2C)2CH
(1)
(10a) R = CO2Et
(10b) R = Ph
(11a) R = CO2Et
(11b) R = Ph

(2)

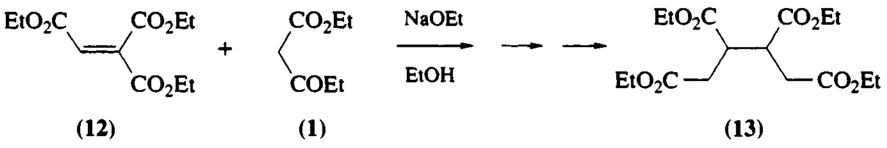
EtO2C
CO2Et
CO2Et
+
CO2Et
COEt
NaOEt
EtOH
EtO2C
CO2Et
EtO2C
CO2Et
(12)
(1)
(13)

(3)

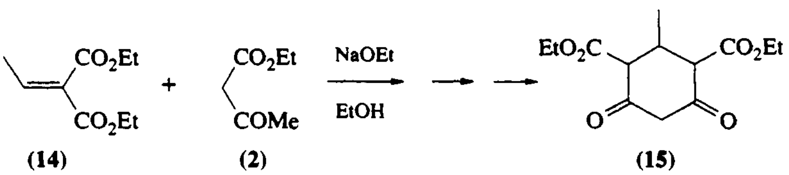
CO2Et
CO2Et
+
CO2Et
COMe
NaOEt
EtOH
EtO2C
CO2Et
O
O
(14)
(2)
(15)

(4)

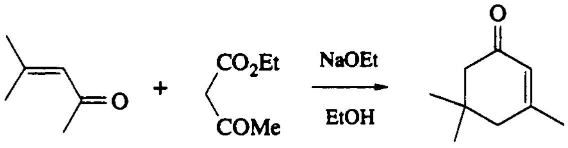

**(16)** **(2)** **(17)** (5)

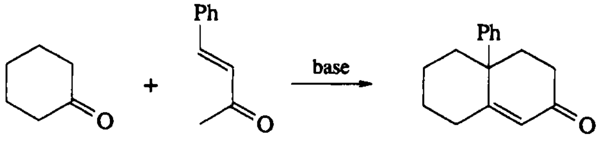

**(18)** **(19)** **(20)** (6)

These early results paved the way for a myriad of applications of this process in organic synthesis, as described in detail in this chapter. It should be pointed out that only additions of stabilized nucleophiles are included here, with the addition of reactive nucleophiles (organolithiums, Grignards, cuprates, *etc.*), Lewis acid promoted additions and asymmetric nucleophilic additions, among others, being covered in Chapters 1.3 and 1.5, respectively, in this volume.

### 1.1.1.2 Other Reviews

The literally thousands of examples involving the addition of stabilized nucleophiles to activated alkenes and alkynes have spawned many reviews over the years. The Michael reaction has been discussed in detail several times[7] and reviews on other related topics, such as annulation[8] and Mannich base methiodides,[9] have also appeared, as have several reviews on nucleophilic additions to activated alkynes.[10]

It is not the goal of this chapter to present a complete or comprehensive view of these nucleophilic additions, but rather a selective and illustrative one. In particular, emphasis will be given to those methods with real potential for organic synthesis.

## 1.1.2 ALKENIC π-SYSTEMS

### 1.1.2.1 Carbon Nucleophiles

This section describes the additions of stabilized carbon nucleophiles, such as cyanide, malonate, ketone enolates, enamines, *etc.*, to alkenic π-systems. These reactions are highly useful in organic synthesis since they are all carbon–carbon bond-forming reactions, and therefore have been used extensively in organic chemistry.

#### *1.1.2.1.1 Intermolecular additions*

The original work of Michael[1] showed that highly stabilized carbanions from diactivated methylenes, such as malonate or acetoacetate, could add in a conjugate or 1,4-fashion to α,β-unsaturated esters in good yield. Over the years, innumerable variations on this theme have been exploited in organic synthesis. A typical example involves the condensation of ethyl acetoacetate (**2**) with methyl acrylate (**21**) in the presence of sodium ethoxide to give the product (**22**) in 73% yield (Scheme 2).[11] The mechanism of the reaction involves the formation of the stabilized anion (**23**) (from **2** and ethoxide), which can then add in a reversible fashion to the Michael acceptor (**21**) to give the stabilized anion (**24**). In hydroxylic solvents this anion is converted to the more stable anion (**25**) which is eventually protonated to give (**22**).

Several points arise from consideration of this mechanism: (i) unlike alkylation of stabilized enolates, the Michael reaction regenerates a basic species and thus usually catalytic quantities of base can be utilized;[7a,7c,12] (ii) the high acidity of the doubly activated methylene permits the use of weaker bases, *e.g.* simple amines (piperidine, triethylamine *etc.*) or hydroxides (Triton B, *i.e.* benzyltrimethylammonium hydroxide); (iii) it was recognized early that, when a full equivalent of base was used, the final more

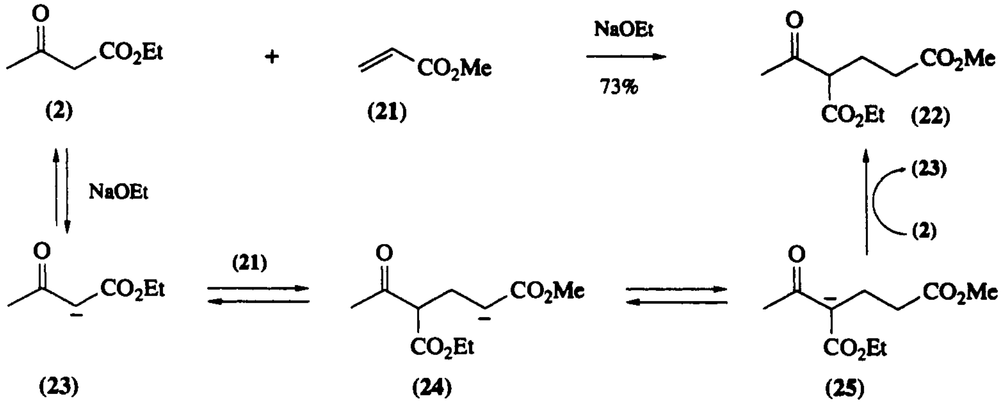

**Scheme 2**

stable anion, *e.g.* (**25**), could be utilized synthetically and alkylated to give the product of overall addition and alkylation, *e.g.* the formation of (**29**; Scheme 3) by alkylation of (**28**), which is formed from (**26**) and (**27**);[13] (iv) multiple Michael addition is a potential side reaction, *e.g.* formation of (**32**) from (**1**) and (**30**), as is a Michael reaction followed by a subsequent Claisen or aldol condensation of the resultant 1,5-dicarbonyl compound,[14] both of which are shown (formation of **34** and **35**) in Scheme 4;[14a] (v) a rearrangement is often observed, the abnormal Michael reaction, resulting in transfer of an activating group from the nucleophilic species to the α-carbon of the Michael acceptor, *e.g.* formation of (**37**; equation 7);[15] and (vi) the key carbon–carbon bond formation step is reversible, so that starting materials and unusual products can sometimes result,[16] *e.g.* the products of arylmethylene transfer (**40**; equation 8)[16a] or malononitrile transfer (**43**; equation 9).[16b]

A large part of the usefulness of the Michael reaction in organic synthesis derives from the fact that almost any activated alkene can serve as an acceptor[7]—α,β-unsaturated ketones, esters, aldehydes, amides, acids, lactones, nitriles, sulfoxides, sulfones, nitro compounds, phosphonates, phosphoranes, quinones,

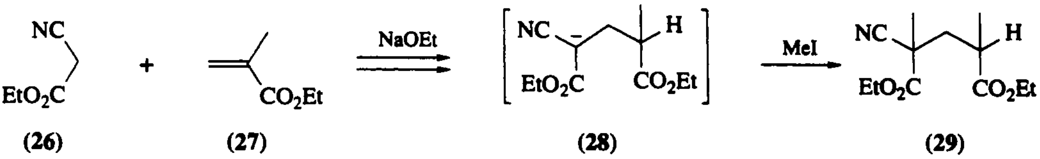

**Scheme 3**

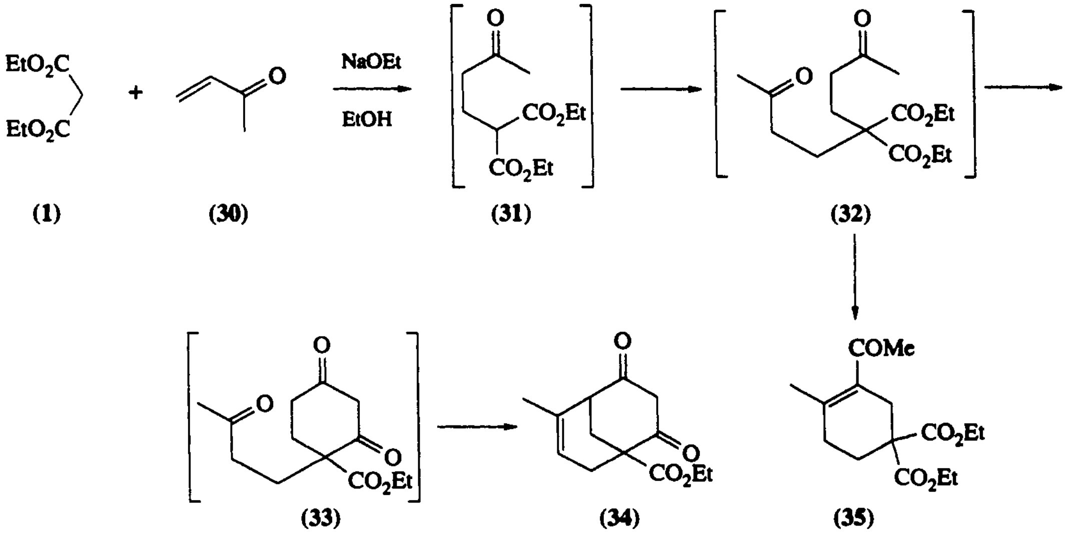

**Scheme 4**

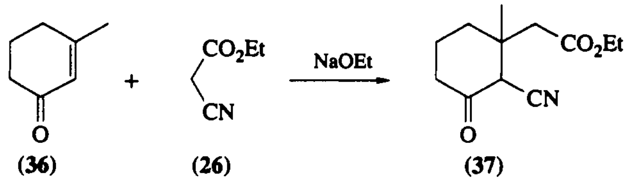
CO2Et
CN
NaOEt
(36)
(26)
(37)

(7)

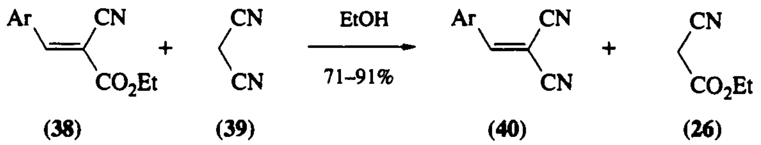
Ar
CN
CO2Et
EtOH
71–91%
(38)
(39)
(40)
(26)

(8)

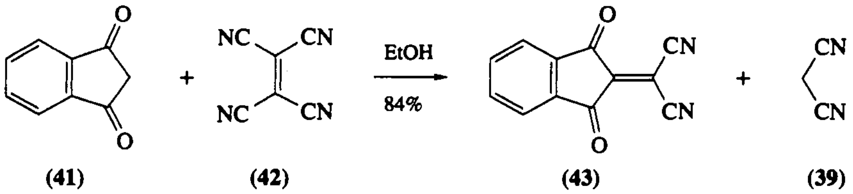
NC
CN
EtOH
84%
(41)
(42)
(43)
(39)

(9)

coumarins, vinylpyridines, *etc.* Since good compilations of these reactions have appeared in various reviews, only a few typical examples are given in equations (10) to (14).[17] Not only is 1,4-addition possible but also 1,6- and 1,8-addition to dienyl and trienyl systems, such as (**58a,b**; equation 15) giving (**59a,b**).[18] Some 1,4-addition is also observed as a minor reaction pathway. The use of enamines leads to a final cyclization of the intermediate zwitterion, resulting in a six-membered ring (equation 16).[19] The use of a simple enamine of a cyclic ketone (**64**) with (**61**) followed by distillation causes loss of the amine and production of the cross-conjugated dienoate system (**65**; equation 17).[19e] A similar process is seen with 2-formylcycloalkanones.[19g]

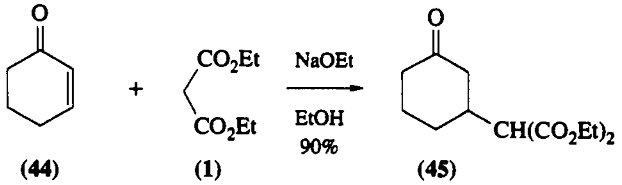
CO2Et
NaOEt
EtOH
90%
CH(CO2Et)2
(44)
(1)
(45)

(10)

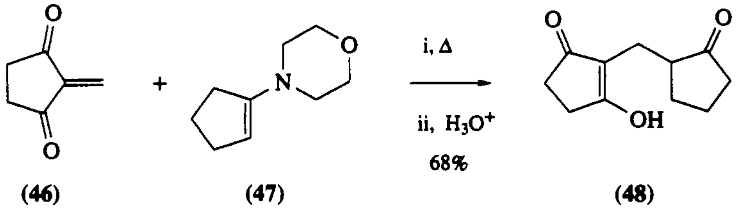
O
N
i, Δ
ii, H3O+
68%
OH
(46)
(47)
(48)

(11)

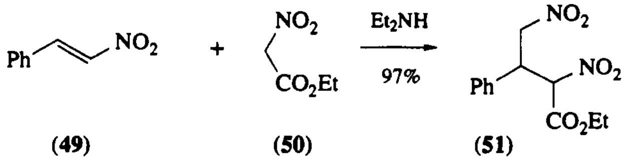
Ph
NO2
CO2Et
Et2NH
97%
(49)
(50)
(51)

(12)

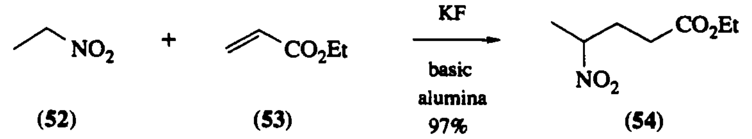
NO2
CO2Et
KF
basic alumina
97%
CO2Et
NO2
(52) (53) (54) (13)

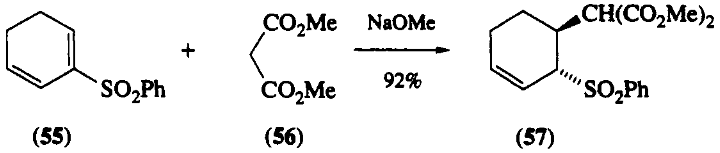
SO2Ph
CO2Me
CO2Me
NaOMe
92%
CH(CO2Me)2
SO2Ph
(55) (56) (57) (14)

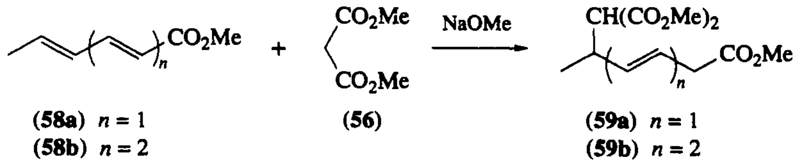
CO2Me
n
CO2Me
CO2Me
NaOMe
CH(CO2Me)2
CO2Me
n
(58a) $n = 1$
(58b) $n = 2$
(56)
(59a) $n = 1$
(59b) $n = 2$
(15)

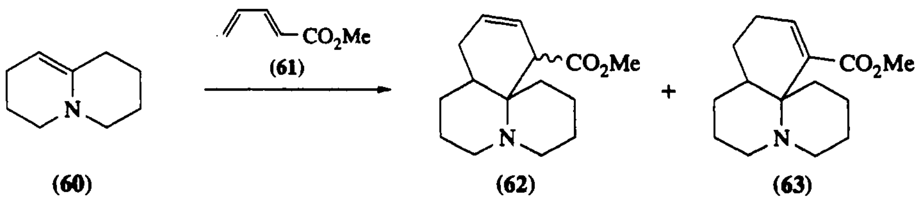
N
CO2Me
(61)
CO2Me
N
CO2Me
N
(60) (62) (63) (16)

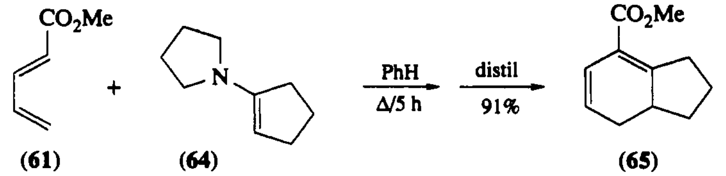
CO2Me
N
PhH
Δ/5 h
distil
91%
CO2Me
(61) (64) (65) (17)

Michael additions of unsymmetrical ketones usually give the products of addition at the more-substituted α-carbon,[20] *e.g.* the reaction of 2-methylcyclohexanone (**66**; equation 18) to give (**67**) in preference to (**68**) (the ratio is solvent dependent)[20a] and reaction of 2-butanone (**69**; equation 19) at the substituted carbon to give (**71**).[14f] This preference is reversed by using enamines,[21] namely the enamine (**72**) of 2-methylcyclohexanone (**66**) reacts with acrylonitrile (**70**) to give, after hydrolysis, the 2,6-disubstituted product (**73**) in 55% yield (Scheme 5).[21a] The combination of a Michael addition followed by a Claisen condensation permits the easy construction of cyclic ketone derivatives,[22] *e.g.* dimedone (**75**; Scheme 6) from mesityl oxide (**16**) and malonate (**1**) *via* the diketo ester (**74**), and 4-pentylcyclohexane-1,3-dione (**78**; Scheme 7) from 2-heptanone (**76**) and ethyl acrylate (**53**) *via* the keto ester (**77**).[20c] Other further cyclizations are also possible,[23] *e.g.* the production of cyclooctane[23a] or cycloheptane[23b] systems (Scheme 8) *via* an initial Michael reaction, aldol-type ring closure, quaternization of the amine and deacylative elimination.

A much more generally useful process was developed by Robinson to prepare cyclohexenones from ketones and methyl vinyl ketone or its derivatives. Again, because good compilations of the Robinson annulation exist,[8] only a few examples are given here. The first step of this process, the Michael addition, is carried out by normal base catalysis, while the second step, the aldol condensation, is best accomplished by the use of a secondary amine to form the enamine of the acyclic ketone, which then cyclizes

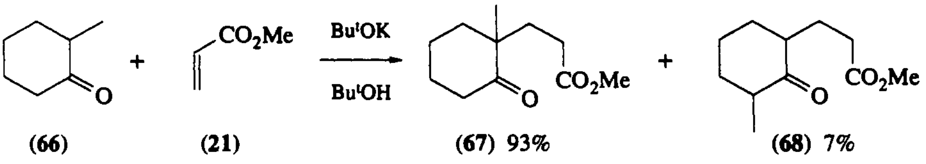
O
CO2Me
Bu$^t$OK
Bu$^t$OH
O
CO2Me
O
CO2Me
(66) (21) (67) 93% (68) 7% (18)

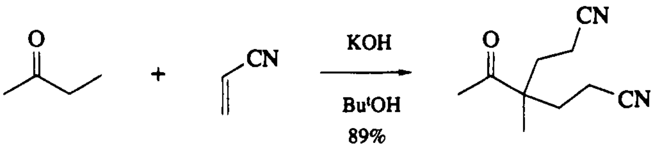
KOH
Bu$^t$OH
89%
CN
CN
CN

**(69)** **(70)** **(71)**

(19)

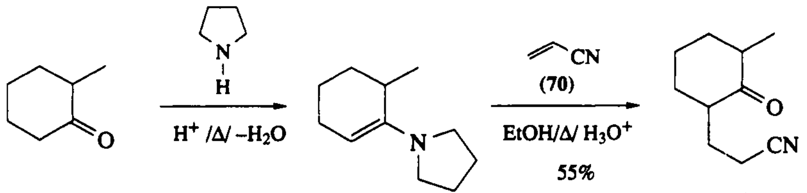
N
H
H$^+$ /Δ/ -H$_2$O
CN
(70)
EtOH/Δ/ H$_3$O$^+$
55%
CN

**(66)** **(72)** **(73)**

**Scheme 5**

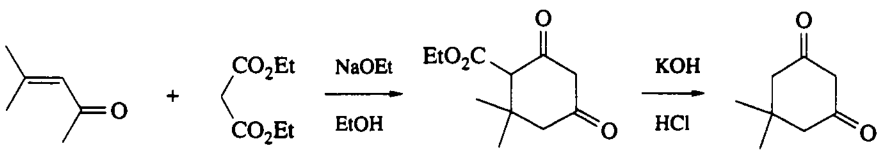
CO$_2$Et
CO$_2$Et
NaOEt
EtOH
EtO$_2$C
KOH
HCl

**(16)** **(1)** **(74)** **(75)**

**Scheme 6**

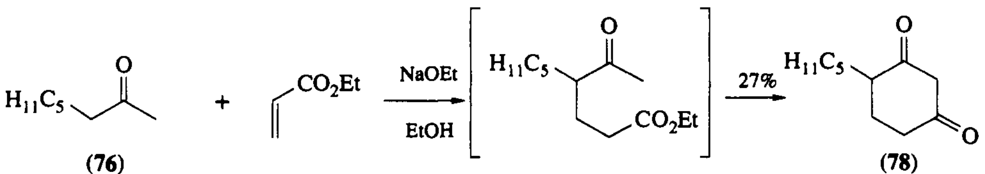
H$_{11}$C$_5$
CO$_2$Et
NaOEt
EtOH
H$_{11}$C$_5$
CO$_2$Et
27%
H$_{11}$C$_5$

**(76)** **(53)** **(77)** **(78)**

**Scheme 7**

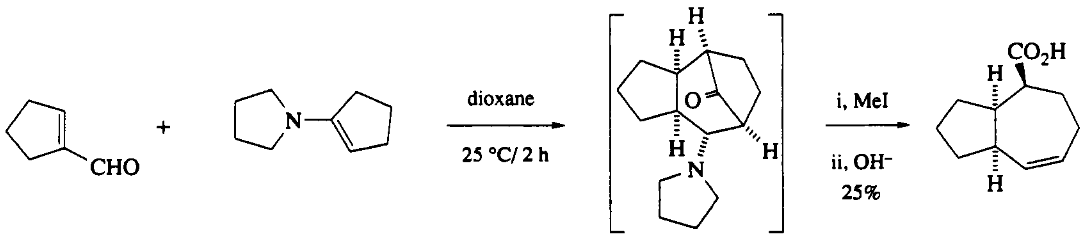
CHO
N
dioxane
25 °C/ 2 h
H
H
O
H
H
N
i, MeI
ii, OH$^-$
25%
CO$_2$H
H
H

**(79)** **(64)** **(80)** **(81)**

**Scheme 8**

and dehydrates (Scheme 9).[24] When β-keto esters are used, all of the key steps (Michael, aldol and decarboalkoxylation) can be done in one pot.[24c] The use of optically active amines in either of these two steps affords products of very high enantiomeric excess (equations 20 and 21).[25] Simple Robinson annulations can be carried out under acidic as well as basic conditions (equation 22).[26] The use of enamines of 2-substituted ketones such as (**72**) permits the production of the isomeric octalone (**91**; equation 23).[21a]

For years most Michael reactions were carried out under protic conditions so that rapid proton transfer was possible. However, in the early 1970s several groups performed Michael reactions under aprotic conditions and these processes are now quite common. Early attempts at trapping a kinetic enolate in aprotic solvents with simple enones such as methyl vinyl ketone or an α,β-unsaturated ester such as acrylate led to a scrambling of the enolate (using the Michael product as proton source).[8a] However, the introduction of an α-trialkylsilyl group in the enone (**93**; Scheme 10) permitted the trapping of kinetic

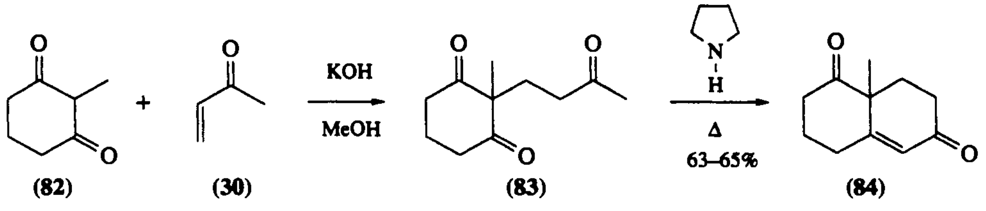

**Scheme 9**

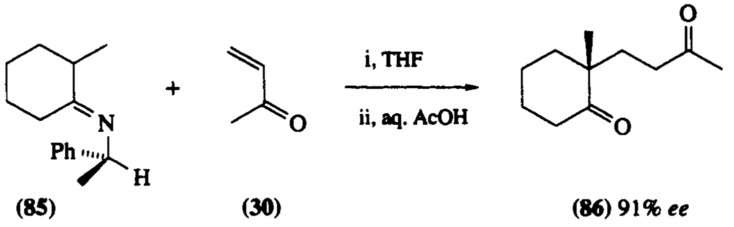

(20)

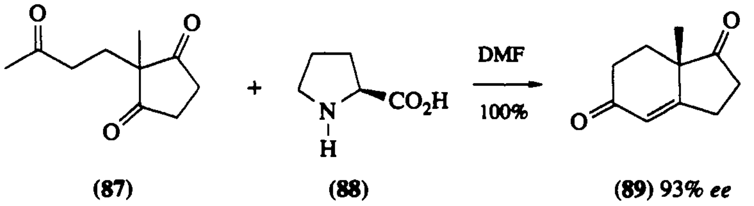

(21)

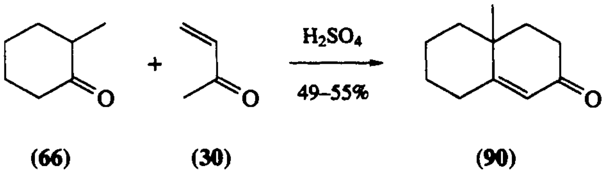

(22)

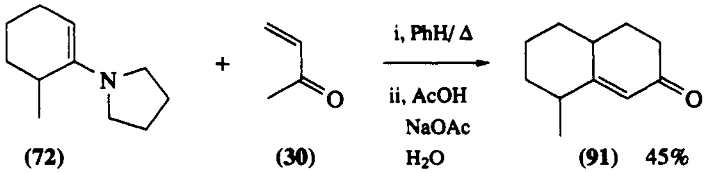

(23)

enolates such as (**92**).[27] Further treatment of (**94**) with base caused both aldol condensation and removal of the α-silyl group to give the desired enone (**95**).[27a]

As in simple Michael additions, dienones and trienones can be used in the Robinson annulation with an initial 1,6- or 1,8-addition.[8a] Dienoates can also be used,[28] *e.g.* (**82**; equation 24) and (**96**) give an 11:1 mixture of isomers (**97a,b**) in 47% yield.[28a]

Bicyclic keto esters can easily be prepared by a process called α,α′-annulation.[29] Thus, treatment of the enamine of cyclopentanone (**64**) with ethyl α-(bromomethyl)acrylate (**98**) affords, after work-up, the bicyclic keto ester (**99**) in 80% yield (equation 25).[29b] The mechanism probably involves an initial Michael addition and elimination (or a simple $S_N2$ or $S_N2'$ alkylation) followed by an intramolecular Michael addition of the less-substituted enamine on the acrylate unit. The use of the enamine of 4,4-bis(ethoxycarbonyl)cyclohexanone (**100**; equation 26) with (**98**) gives a 45% yield of the adamantanedione diester (**101**) (yield based on **100**; 70% when based on **98**) *via* α,α′-annulation followed by Dieckmann condensation.[29e] Enamines of heterocyclic ketones can also serve as the initial nucleophiles, *e.g.* (**102**) and (**103**) give (**105**) *via* (**104**), formed *in situ*, in 70% yield (Scheme 11).[29g]

The use of α-thiophenyl enones (**106**; Scheme 12) allows the preparation of phenols such as (**107**) from cyclic ketones (**18**).[30a] The same product can also be obtained by normal Robinson annulation of methyl vinyl ketone (**30**) and the β-keto sulfoxide (**108**).[30b] Acceptors other than α,β-unsaturated carbonyls have been used in both the Michael reaction and the Robinson annulation process. For example, nu-

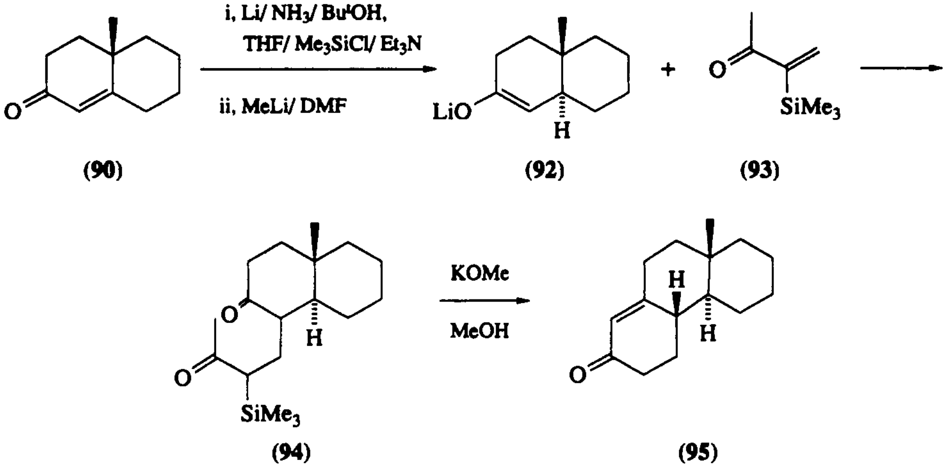
i, Li/ NH3/ ButOH, THF/ Me3SiCl/ Et3N
ii, MeLi/ DMF
LiO
H
O
SiMe3
+
(90)
(92)
(93)
KOMe
MeOH
(94)
(95)

Scheme 10

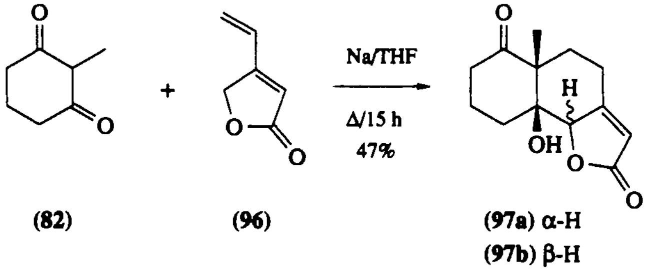
Na/THF
Δ/15 h
47%
OH
H
(82)
(96)
(97a) α-H
(97b) β-H

(24)

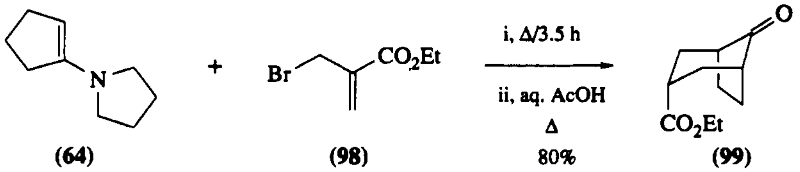
N
Br
CO2Et
i, Δ/3.5 h
ii, aq. AcOH
Δ
80%
(64)
(98)
(99)

(25)

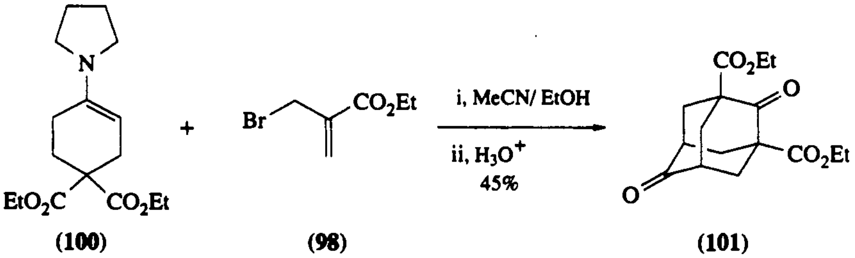
N
EtO2C
CO2Et
Br
i, MeCN/ EtOH
ii, H3O+
45%
(100)
(98)
(101)

(26)

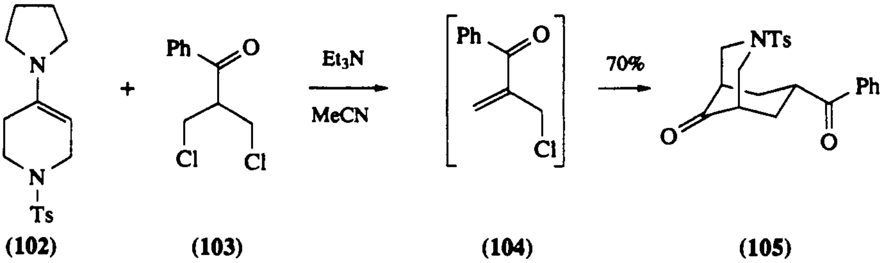
N
Ts
Ph
O
Cl
Et3N
MeCN
70%
NTs
(102)
(103)
(104)
(105)

Scheme 11

cleophiles have been added to 2- or 4-vinylpyridines in high yield;[31] a specific example is shown in equation (27).[31b] The use of 6-methyl-2-vinylpyridine (**112**) with the enamine of cyclohexanone (**113**) gives a product (**114**) which could be used in a diannulation procedure, as shown in Scheme 13, to give the dienone (**116**).[31c]

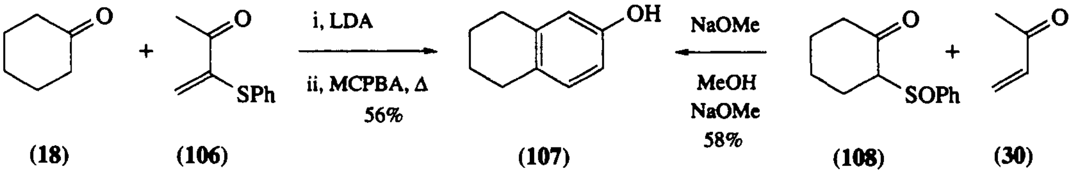

Scheme 12

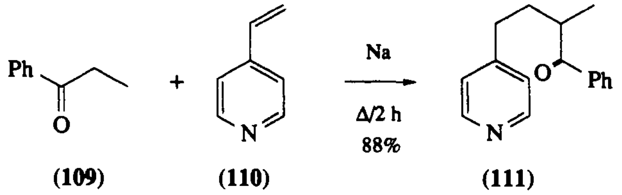

(27)

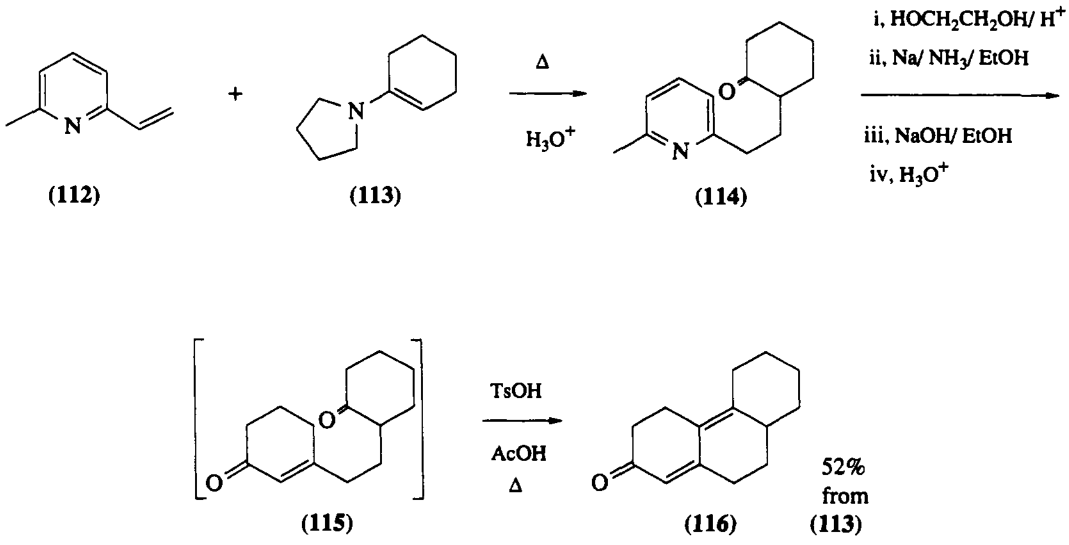

Scheme 13

In 1973, a series of papers from Schlessinger's group showed that Michael additions could be carried out in high yield under aprotic conditions.[32] In particular, alkyl (dithioalkyl)acetate enolates (Scheme 14) gave high yields of 1,4-addition products and, after hydrolysis, α-keto esters[32a–32d] (and is thus the 1,4-addition of an acyl anion equivalent), while α-(thiomethyl)acrylate as an acceptor resulted in high yields of the corresponding Michael adducts.[32c] A second acyl anion equivalent was also developed for use in Michael additions, the thioacetal monoxide; thus the anion of (**120**; Scheme 15) adds to MVK (**30**) to give a 96% yield of (**121**) which is easily hydrolyzed to (**122**).[32d,32e] The corresponding unsaturated compounds, namely ketene thioacetal monoxides (**124**), were developed as α-formyl cation synthons (Scheme 16). Addition of an enolate to (**124**) gave in high yield the expected adduct (**125**) which, on hydrolysis, produced the 1,4-dicarbonyl system (**126**).[32f,32g] This process has found further use,[33] *e.g.* in an efficient synthesis of allethrolone[33a] and also for trapping a kinetically formed enolate in a prostaglandin synthesis.[33b]

A large number of workers have examined the effects of temperature, solvent and reaction times on the ratio of the products of 1,4-addition *versus* 1,2-addition of dithiane and other α-thioalkyl carbanions.[34] Their results show that in general 1,2-addition is kinetically favored and therefore predominates at low temperatures and in less polar solvents,[34a,34b] whereas 1,4-addition is thermodynamically favored and predominates at 25 °C and in THF containing HMPA,[34c–34g] as the examples in equations (28) and (29) indicate. If a chiral ligand is used in these additions, fair enantiomeric excess (32–67%) can be obtained.[34f] It is possible to trap the enolates so generated with electrophiles,[32e,35] as shown in Scheme 17. The alkoxycarbonyl anion equivalent (**136**; Scheme 18) has also been added 1,4- and hydrolyzed to the ester (**138**).[36]

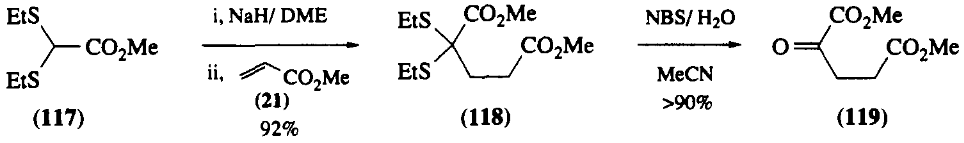
EtS
EtS
CO2Me
(117)
i, NaH/ DME
ii, CO2Me
(21)
92%
EtS
EtS
CO2Me
CO2Me
(118)
NBS/ H2O
MeCN
>90%
O
CO2Me
CO2Me
(119)

**Scheme 14**

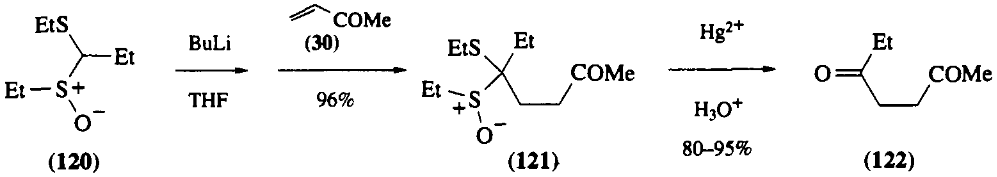
EtS
Et
Et—S+
O−
(120)
BuLi
THF
COMe
(30)
96%
EtS
Et
COMe
Et
+S
O−
(121)
Hg2+
H3O+
80–95%
O
Et
COMe
(122)

**Scheme 15**

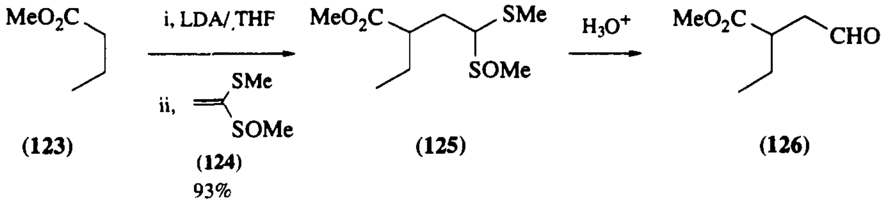
MeO2C
(123)
i, LDA/ THF
SMe
ii,
SOMe
(124)
93%
MeO2C
SMe
SOMe
(125)
H3O+
MeO2C
CHO
(126)

**Scheme 16**

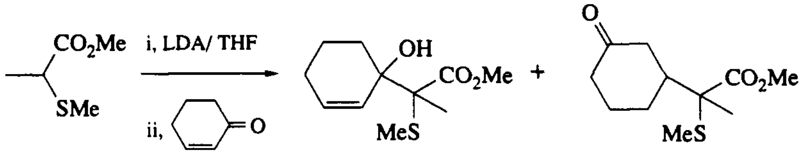
CO2Me
SMe
i, LDA/ THF
ii,
O
OH
CO2Me
MeS
+
O
CO2Me
MeS

(28)

| (127) | (44) | (128a) | (128b) |
|---|---|---|---|
|  | −78 °C | 63% | 7% |
|  | 25 °C | 0% | 85% |

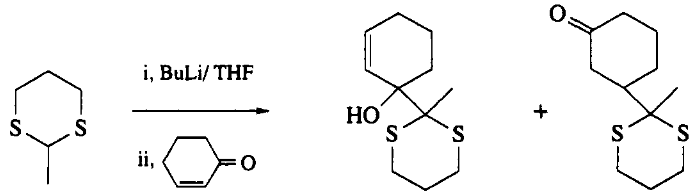
S
S
i, BuLi/ THF
ii,
O
HO
S
S
+
O
S
S

(29)

| (129) | (44) | (130a) | (130b) |
|---|---|---|---|
|  | no HMPA | 99% | 0% |
|  | 1 equiv. HMPA | 7% | 93% |
|  | 2 equiv. HMPA | 3% | 97% |

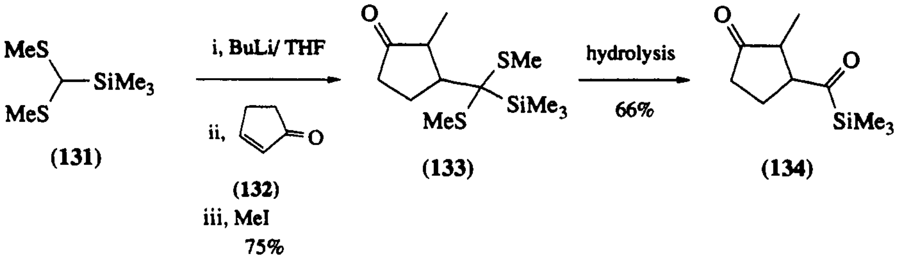

MeS
MeS
SiMe$_3$
(131)
i, BuLi/THF
ii,
O
(132)
iii, MeI
75%
O
SMe
MeS
SiMe$_3$
(133)
hydrolysis
66%
O
O
SiMe$_3$
(134)

Scheme 17

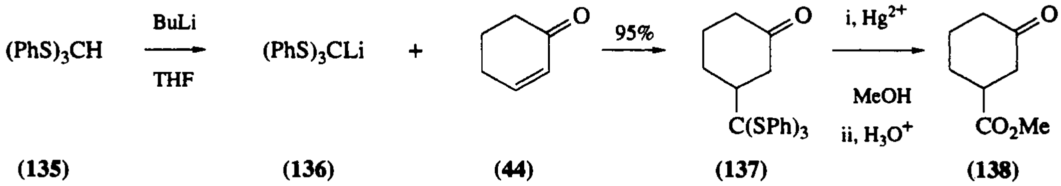

(PhS)$_3$CH
BuLi
THF
(PhS)$_3$CLi
+
O
95%
O
C(SPh)$_3$
i, Hg$^{2+}$
MeOH
ii, H$_3$O$^+$
O
CO$_2$Me
(135)
(136)
(44)
(137)
(138)

Scheme 18

An interesting difference in regiochemistry of addition has been observed with sulfur-substituted allyl anions.[37] The anion of the sulfide (**139**; equation 30) adds to cyclopentenone (**132**) in THF/HMPA (without HMPA 1,2-addition predominates, as expected from the above arguments) to give mainly the product of α-addition (**140a**) rather than that of γ-addition (**140b**).[37a,37b] However, addition of the anion of the corresponding sulfoxide (**141**) affords only the product of γ-addition, namely (**142b**).[37c] The use of the corresponding optically active allyl sulfoxides[37d–37f] causes the new carbon–carbon bond to be formed with virtually complete diastereoselectivity, *e.g.* (**143**; equation 31) gives (**144**) with 96% *de*.[37f]

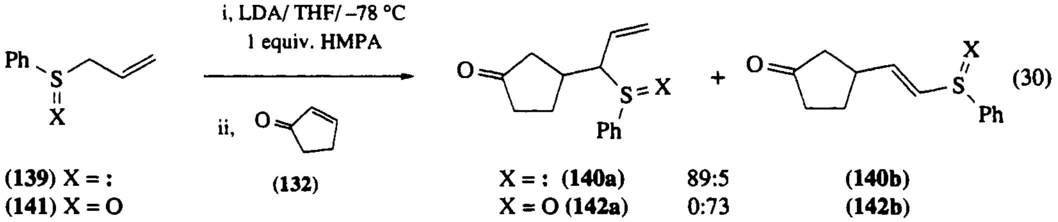

Ph
S
X
i, LDA/THF/–78 °C
1 equiv. HMPA
ii, O
(132)
O
S=X
Ph
+
O
X
S
Ph
(30)
(139) X = :
(141) X = O
X = : (140a)
X = O (142a)
89:5
0:73
(140b)
(142b)

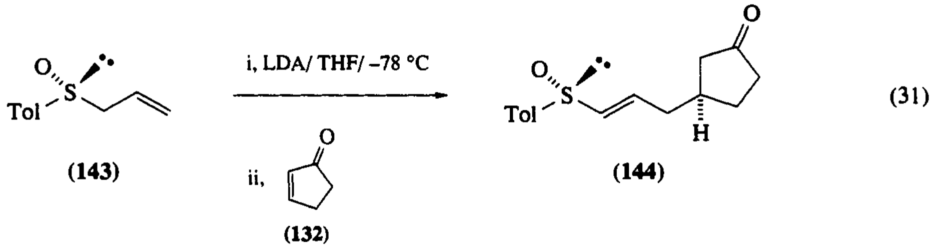

O
S
Tol
i, LDA/THF/–78 °C
ii,
O
O
S
Tol
O
H
(31)
(143)
(132)
(144)

In addition to dithiane and thioacetal monoxide anions, several other acyl anion equivalents[35b,35c] have been added in a Michael fashion. For example, Stork has shown that protected cyanohydrins of aldehydes, especially α,β-unsaturated aldehydes (**145**; Scheme 19), give high yields of 1,4-addition and, after two-step removal of the cyanohydrin ether, the 1,4-diketone (**147**).[38] Stetter has published more than a score of papers showing that both cyanide ion and *N*-alkylthiazolium salts (equation 32) catalyze the 1,4-addition of aldehydes to α,β-unsaturated carbonyl compounds in good yields.[39] Steglich has shown that oxazolones (**152**; Scheme 20) will add in a Michael fashion to acrylonitrile (**70**) under very mild conditions to give, after hydrolysis, the β-cyano ketone (**153**) in good overall yield.[40] Finally, McMurry and others have added the anions of nitroalkanes to enones (Scheme 21) and then converted the nitro group to a carbonyl by reduction and hydrolysis.[41]

Since nitro groups are readily converted to carbonyls by various procedures,[41,42] nitroalkenes can serve as α-carbonyl cation equivalents in Michael reactions.[43] For example, addition of the amide enolate (**158**; Scheme 22) to the nitroalkene (**157**) affords, in 60% yield, the Michael adduct (**159**), which can be con-

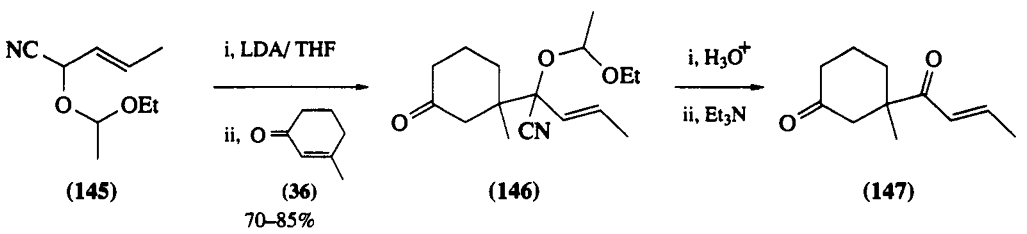
i, LDA/ THF
ii, O=
(145)
(36)
70–85%
(146)
i, $H_3O^+$
ii, $Et_3N$
(147)

Scheme 19

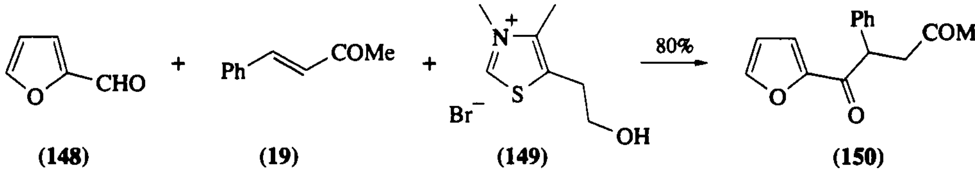
(148)
(19)
(149)
80%
(150)

(32)

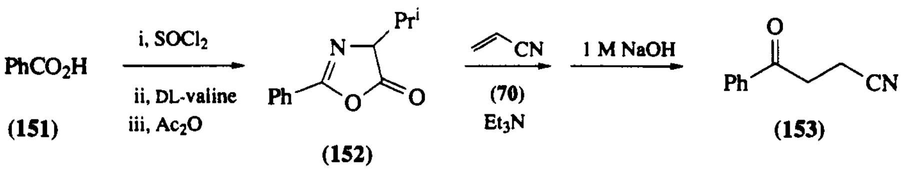
i, $SOCl_2$
ii, DL-valine
iii, $Ac_2O$
(151)
(152)
(70)
$Et_3N$
1 M NaOH
(153)

Scheme 20

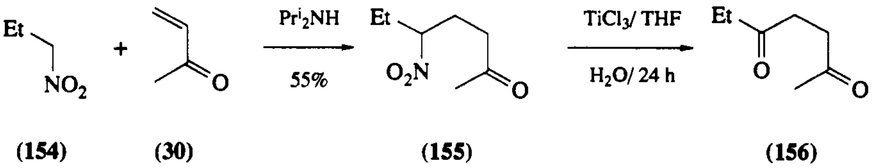
$Pr^i_2NH$
55%
$TiCl_3$/ THF
$H_2O$/ 24 h
(154)
(30)
(155)
(156)

Scheme 21

verted to the ketone (**160**) in 90% yield.[43a,43b] The highly stabilized anions of nitroalkanes are useful in Michael additions not only as acyl anion or α-carbonyl cation equivalents (*via* conversion to carbonyls) but also, *via* reductive removal of the nitro group, as alkyl anion equivalents or as alternatives to simple alkyl halides to give overall alkylation *via* a Michael addition process.[44] For example, treatment of a simple nitroalkane (**161**; Scheme 23) with DBU or tetramethylguanidine (TMG) in the presence of a Michael acceptor, such as MVK (**30**), affords the Michael adduct (**162**) which can be readily reduced with tributylstannane and AIBN to the ketone (**163**).[44b] Likewise, a vinylnitro compound can serve as a surrogate alkylating agent. Thus the nitroalkene (**164**; equation 33) can be used to trap the enolate (**165**, generated by cuprate addition to the corresponding cyclopentenone) to give the Michael adduct (**166**), the nitro group of which is removed reductively to give (**167**), a protected form of prostaglandin $E_1$.[44c]

In a like manner, vinyl sulfoxides and sulfones can serve as the equivalents of vinyl and alkenyl cations *via* a process involving a Michael addition followed by an elimination.[45] For example, addition of the enolate of the β-keto ester (**168**; Scheme 24) to phenyl vinyl sulfoxide (**169**) furnished, in 50% yield,

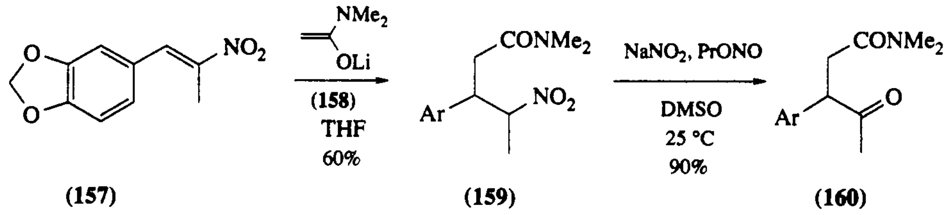
(158)
THF
60%
NaNO$_2$, PrONO
DMSO
25 °C
90%
(157)
(159)
(160)

Scheme 22

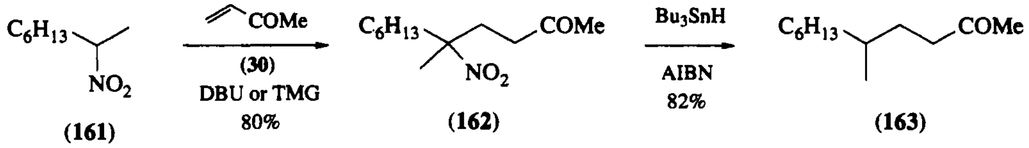
C6H13
NO2
(161)
COMe
(30)
DBU or TMG
80%
C6H13
COMe
NO2
(162)
Bu3SnH
AIBN
82%
C6H13
COMe
(163)

**Scheme 23**

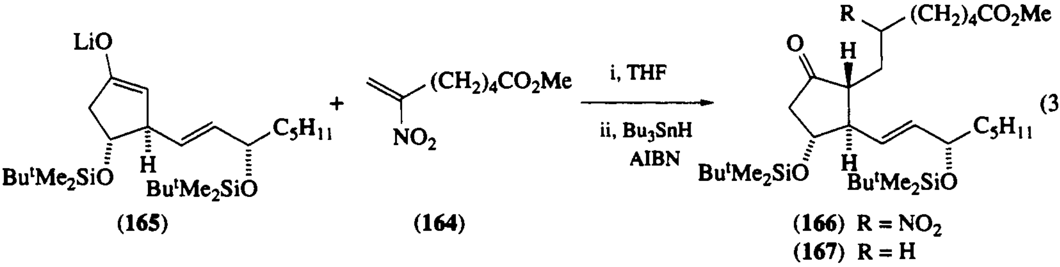
LiO
C5H11
ButMe2SiO
H
ButMe2SiO
(165)
+
(CH2)4CO2Me
NO2
(164)
i, THF
ii, Bu3SnH
AIBN
R
(CH2)4CO2Me
O
H
C5H11
ButMe2SiO
H
ButMe2SiO
(166) R = NO2
(167) R = H

(33)

the Michael adduct (**170**) which lost phenylsulfenic acid on pyrolysis to give the vinyl-substituted β-keto ester (**171**) in 60% yield, the vinyl sulfoxide (**169**) being a vinyl cation equivalent in this process.[45a] In a similar addition–elimination process, treatment of alkenyl sulfones (**172**) with cyanide and a crown ether in refluxing *t*-butyl alcohol afforded the α-methylene nitrile (**173**) in good yield *via* Michael addition, proton transfer and elimination of phenylsulfinic acid (equation 34).[45b]

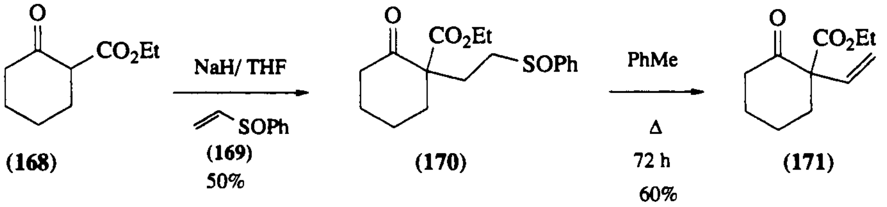
O
CO2Et
(168)
NaH/ THF
SOPh
(169)
50%
O
CO2Et
SOPh
(170)
PhMe
Δ
72 h
60%
O
CO2Et
(171)

**Scheme 24**

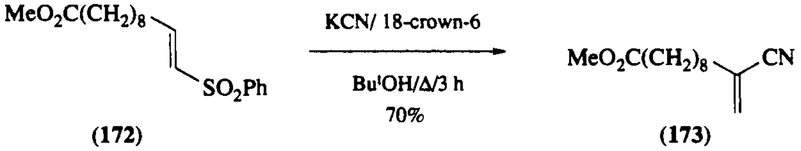
MeO2C(CH2)8
SO2Ph
(172)
KCN/ 18-crown-6
ButOH/Δ/3 h
70%
MeO2C(CH2)8
CN
(173)

(34)

Michael additions followed by intramolecular acylation of the enolate so generated have been used often in organic synthesis to generate cycloalkanones.[46] For example, treatment of the dianion of the diester (**174**; equation 35) with 2,6-dichlorophenyl acrylate (**175**) affords the product of Michael addition–Dieckmann condensation (**176**) in 67% yield.[46a] Similarly, the anion (**178**; equation 36) of the carbonate ester produces a high yield of the lactone (**179**) when added to the unsaturated lactam (**180**).[46b] This process has been widely used in anthracycline and other polyketide aromatic syntheses.[47] The addition of a phthalide anion bearing a good leaving group that is also acidifying (arylsulfonyl or cyano) to a cyclohexenone or quinone monoketal affords the polycyclic hydroquinone (**182**; equation 37) or (**185**; equation 38) in one step *via* addition, intramolecular acylation, loss of the cyano or arylsulfonyl anion and final aromatization.[47a–47m] When the anion of the *o*-toluate (**186**) is added to the β-methoxy enone system (**187**), the *o*-acylphenol (**188**; equation 39) is obtained *via* a Michael addition, elimination and intramolecular Claisen condensation.[47o] The simple Michael addition of a naphthylacetonitrile (**189**; equation 40) to a cyclohexenecarboxylate (**190**) has also been used to produce intermediates, like (**191**), for anthracycline synthesis.[48]

Several other procedures for trapping the initially generated enolate of the Michael addition have also been used synthetically. Foremost among them is elimination of a good leaving group,[49] an overall addition–elimination process, illustrated by a specific example in equation (41).[49a] Using the 2-nitropropenyl pivalate (**195**; Scheme 25) Seebach[49c] was able to carry out a double Michael process, an initial addi-

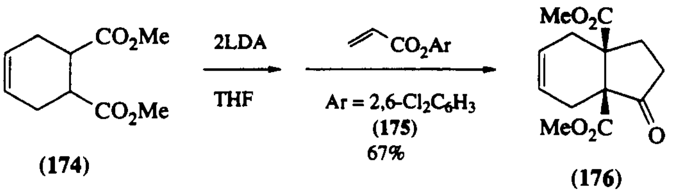
CO2Me
CO2Me
(174)
2LDA
THF
CO2Ar
Ar = 2,6-Cl2C6H3
(175)
67%
MeO2C
MeO2C
O
(176)

(35)

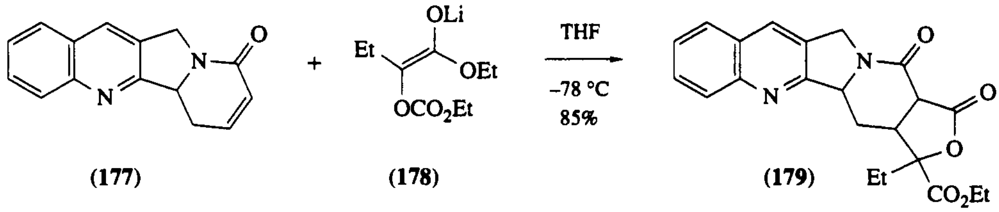
N
N
O
(177)
+
OLi
Et
OEt
OCO2Et
(178)
THF
−78 °C
85%
N
N
O
O
O
Et
CO2Et
(179)

(36)

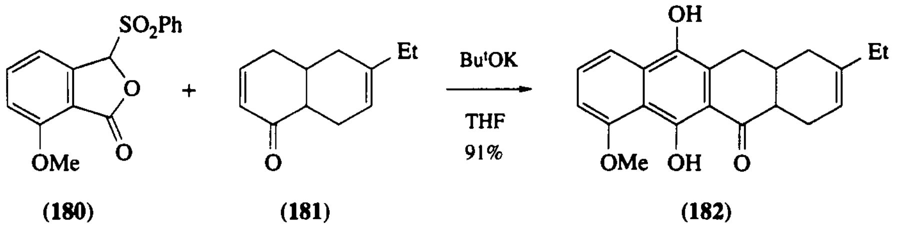
SO2Ph
O
OMe
O
(180)
+
Et
O
(181)
Bu^tOK
THF
91%
OH
Et
OMe
OH
O
(182)

(37)

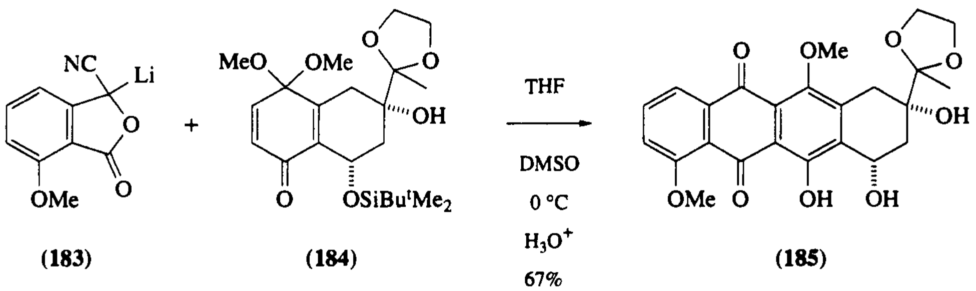
NC
Li
O
OMe
O
(183)
+
MeO
OMe
O
O
OH
O
OSiBu^tMe2
(184)
THF
DMSO
0 °C
H3O+
67%
O
OMe
O
O
OH
OMe
O
OH
OH
(185)

(38)

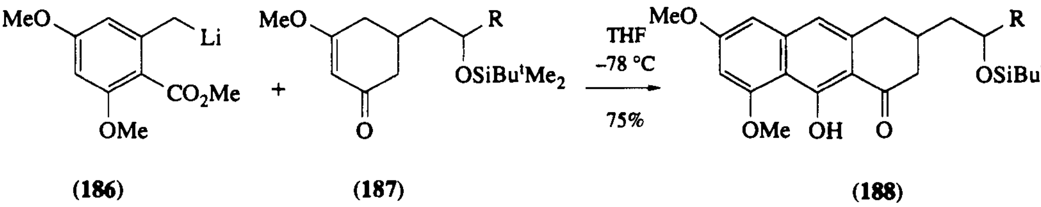
MeO
Li
CO2Me
OMe
(186)
+
MeO
R
OSiBu^tMe2
O
(187)
THF
−78 °C
75%
MeO
R
OSiBu^tMe2
OMe
OH
O
(188)

(39)

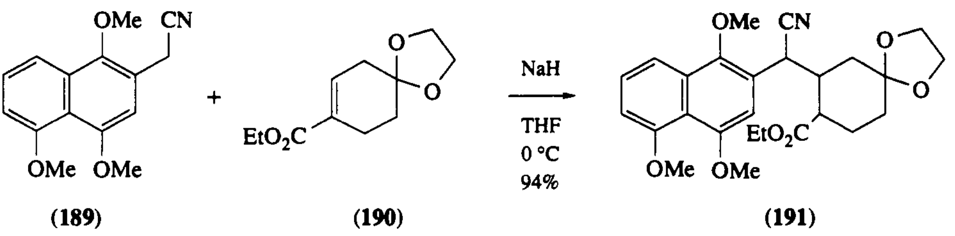
OMe
CN
OMe
OMe
(189)
+
O
O
EtO2C
(190)
NaH
THF
0 °C
94%
OMe
CN
O
O
EtO2C
OMe
OMe
(191)

(40)

tion–elimination followed by a simple Michael addition, to give (**197**). If a vinyl phosphonate or phosphonium salt is used as the Michael acceptor, the anionic intermediate can be trapped by an intramolecular Wittig reaction with a nearby ketone to give (**199**; equation 42) or (**202**; equation 43).[50] In certain cases, this process can lead to cyclohexenone products which are structurally transposed from those of the normal Robinson annulation (Scheme 26).[50c] An interesting variant on this approach uses the anion of a formylphosphorane (**207**; equation 44) as the nucleophile in a 1,6-addition to (**208**), followed by an aldol of the enolate on to the aldehyde and loss of triphenylphosphine oxide to give (**209**) in fair yield.[50e] Other intramolecular aldol-trapping reactions (not leading to Robinson annulation) have also been reported,[51] *e.g.* formation of the hindered enedione (**213**; Scheme 27).[51a] It is also possible to trap the initial enolate with an allylic leaving group or an isonitrile to produce cyclopentenes (**215**; Scheme 28),[52a,b] pyrrolines (**217**; Scheme 29)[52c] or pyrroles (**220**; Scheme 30).[52d]

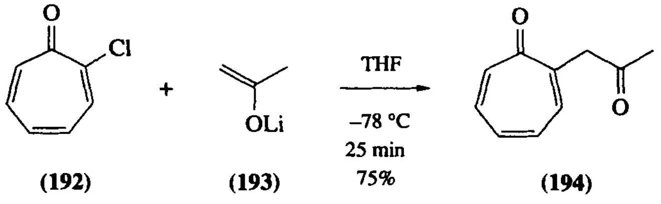
O
Cl
+
OLi
THF
–78 °C
25 min
75%
O
O
(192)
(193)
(194)

(41)

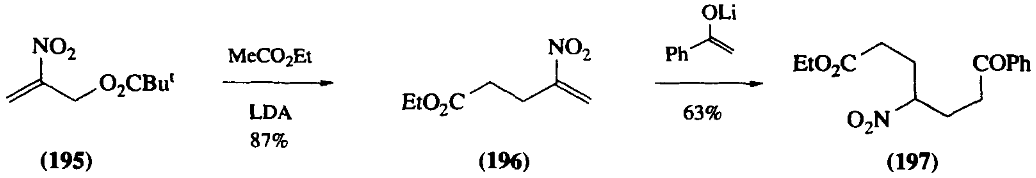
NO2
O2CBut
MeCO2Et
LDA
87%
NO2
EtO2C
OLi
Ph
63%
EtO2C
COPh
O2N
(195)
(196)
(197)

**Scheme 25**

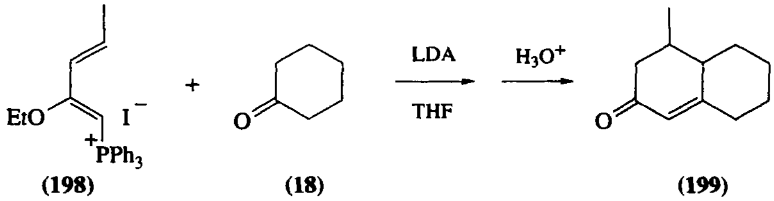
EtO
I⁻
+PPh3
+
O
LDA
THF
H3O+
O
(198)
(18)
(199)

(42)

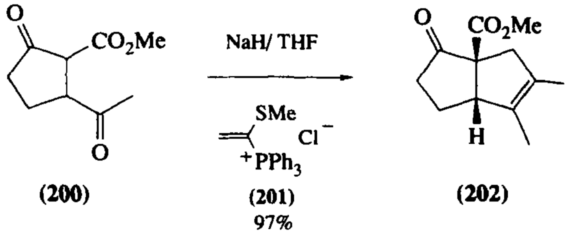
O
CO2Me
O
NaH/ THF
SMe
Cl⁻
+PPh3
(201)
97%
O
CO2Me
SMe
H
(200)
(202)

(43)

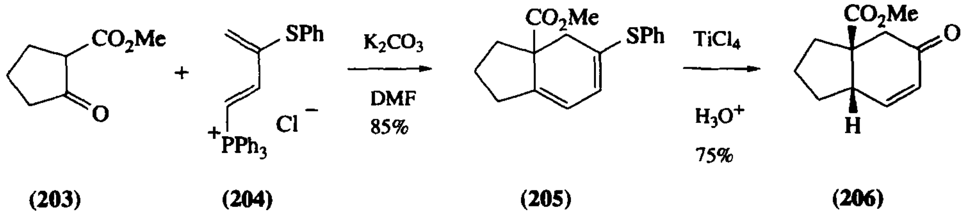
CO2Me
O
+
SPh
Cl⁻
+PPh3
K2CO3
DMF
85%
CO2Me
SPh
TiCl4
H3O+
75%
CO2Me
O
H
(203)
(204)
(205)
(206)

**Scheme 26**

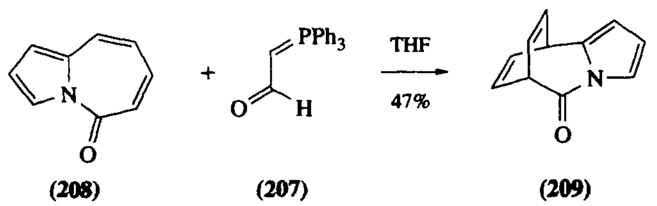
N
O
+
PPh3
O
H
THF
47%
N
O
(208)
(207)
(209)

(44)

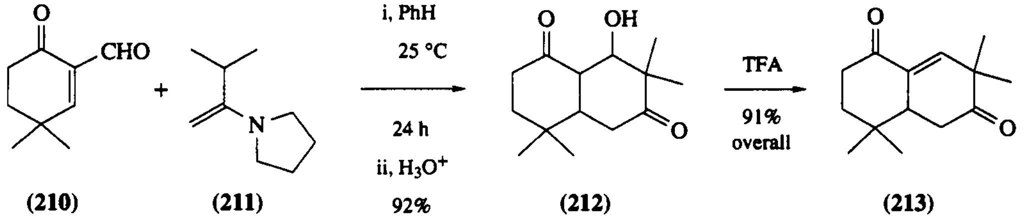
CHO
+
N
i, PhH
25 °C
24 h
ii, $H_3O^+$
92%
O
OH
TFA
91%
overall
(210)
(211)
(212)
(213)

Scheme 27

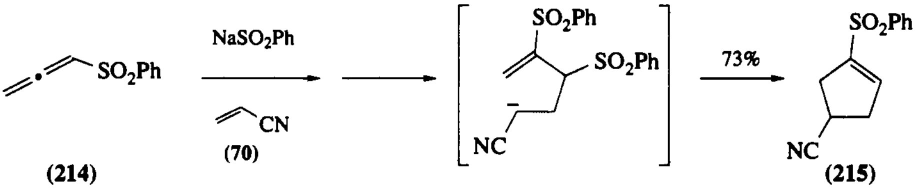
$SO_2Ph$
$NaSO_2Ph$
CN
(70)
$SO_2Ph$
$SO_2Ph$
NC
73%
$SO_2Ph$
NC
(214)
(215)

Scheme 28

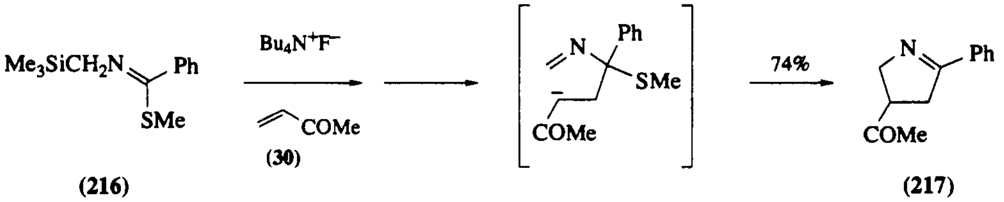
$Me_3SiCH_2N$
Ph
SMe
$Bu_4N^+F^-$
COMe
(30)
N
Ph
SMe
COMe
74%
N
Ph
COMe
(216)
(217)

Scheme 29

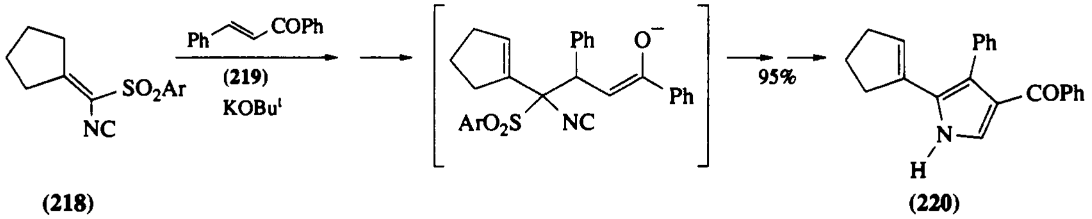
$SO_2Ar$
NC
Ph
COPh
(219)
$KOBu^t$
Ph
$O^-$
Ph
$ArO_2S$
NC
95%
Ph
COPh
N
H
(218)
(220)

Scheme 30

With certain exceptions, simple intermolecular Michael additions often proceed in poor yield when the acceptor is a β,β-disubstituted enone or ester, presumably due to steric hindrance of nucleophilic attack. However, this lack of reactivity can be overcome by two techniques. The first one involves the use of high pressures, which can greatly increase the yields of these hindered additions.[53] Thus, addition of diethyl malonate (**1**) to 3-methylcyclohexenone (**36**) in the presence of DBN at 15 kbar (1 bar = 100 kPa) affords the desired addition product (**221**; equation 45) in 71% yield.[53a] Alternatively, if the acceptor is sufficiently activated (usually with two strongly electron-withdrawing groups), then normal Michael addition is possible, even when contiguous quaternary centers are being formed. Holton has used this process to prepare very hindered compounds (**224**; equation 46) in high yield.[54]

The anion generated by a Michael addition can also be trapped by another Michael addition. Obviously, continued repetition of this process produces polymeric esters, nitriles, *etc.*, in a typical anionic poly-

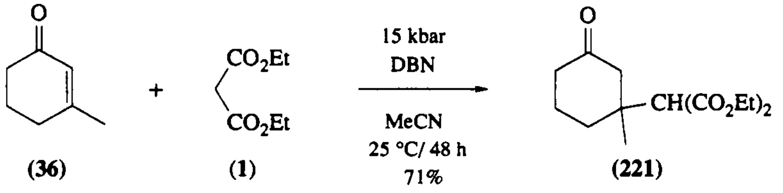
O
+
$CO_2Et$
$CO_2Et$
15 kbar
DBN
MeCN
25 °C/ 48 h
71%
O
$CH(CO_2Et)_2$
(36)
(1)
(221)

(45)

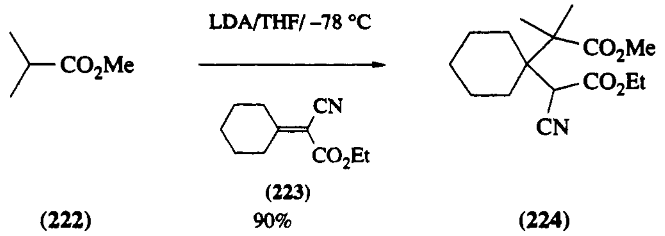

(46)

merization process. However, in certain cases, other chain-terminating steps can intervene to produce quite useful nonpolymeric material from these multi-Michael processes. Since an excellent review of these multicomponent one-pot annulations has recently appeared,[55] only a few key examples are noted here. Addition of excess lithium dimethylcuprate (**225**; Scheme 31) in THF to methyl crotonate (**226**) at 10 °C afforded the single stereoisomer of the keto diester (**227**) in 49% yield *via* cuprate addition, two Michael additions and final Dieckmann condensation.[56] Cyclopentanones and their bicyclic derivatives (**228**; equation 47) and (**230**; equation 48) are available from acrylates using cyanide as the initial nucleophile, again *via* two Michael additions followed by Dieckmann-like condensation.[57] A similar process using the thiomethyl sulfone (**231**; equation 49) and acrylate gives the β-keto ester (**232**) in 81% yield.[58] When the activating group of the Michael acceptor is also a good leaving group, as in nitroalkenes or vinylphosphonium salts, an $S_N2$ reaction is the final step. For example, treatment of the anion of isophorone (**17**) with 1-nitropropene (**233**) gave the tricyclooctanones (**236a,b**; Scheme 32) in 63% yield, by way of the intermediates (**234**) and (**235**).[59] A synthetically useful example of these one-pot annulations involves the condensation of an enolate ion with an enone bearing an α-bromoacrylate unit.[60] Treatment of (**237a,b**; Scheme 33) with (**238**) gives rise to the tricyclic compounds (**239a,b**), which are converted into the enals (**240a,b**). Curiously, the major products obtained in the parent and methyl-substituted cases have the opposite stereochemistry at one of the new ring junctions.[60a,60b] Posner has explored extensively the synthetic utility of these multi-Michael reactions.[61] The reaction of the enolate of cyclohexanone (**18**; Scheme 34) with α-substituted acrylates (**241**) or (**242**) gave rise to the cyclohexanol products (**243**) and (**244**), respectively, in good yield.[61a] The dibromo compound (**244**) could be converted easily into the aromatic diester (**245**). When vinyltriphenylphosphonium bromide (**247**; equation 50) is used as the acceptor with the enol borate from benzoylcyclopentane (**246**), the phosphine oxide (**248**) is produced *via* two Michael additions and a final Wittig reaction.[61b] Other multiple Michael reactions, especially those involving intramolecular Michaels, are discussed in the section on intramolecular additions.

Finally, a discussion of the relative stereochemistry of such reactions completes this section on intermolecular Michael additions. It should be pointed out that Chapter 1.5, this volume, is devoted wholly to asymmetric induction in Michael reactions and thus this topic is not covered here.

The diastereoselectivity of intermolecular Michael additions was first examined in two areas: the Robinson annulation using (*E*)-3-penten-2-one (**249**; equation 51)[62] and the reaction of enamines of cyclic

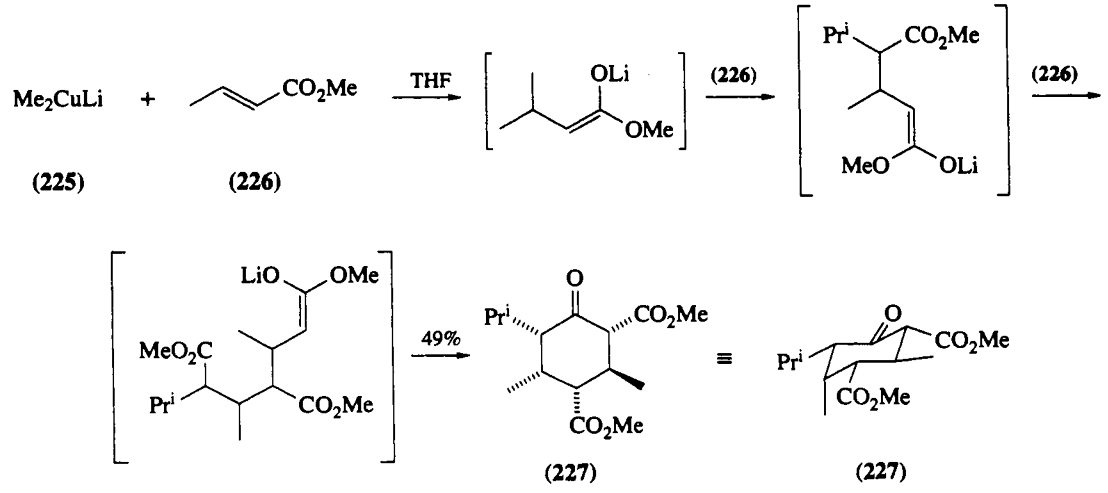

Scheme 31

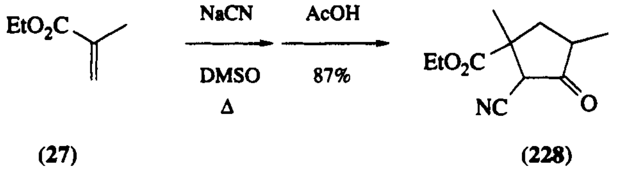

$EtO_2C$
NaCN
DMSO
Δ
AcOH
87%
$EtO_2C$
NC
O
(27)
(228)

(47)

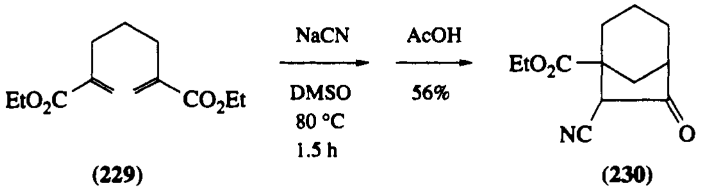

$EtO_2C$
$CO_2Et$
NaCN
DMSO
80 °C
1.5 h
AcOH
56%
$EtO_2C$
NC
O
(229)
(230)

(48)

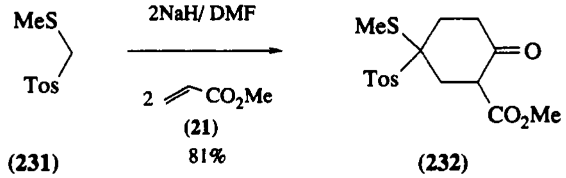

MeS
Tos
2NaH/ DMF
2 $CO_2Me$
(21)
81%
MeS
Tos
O
$CO_2Me$
(231)
(232)

(49)

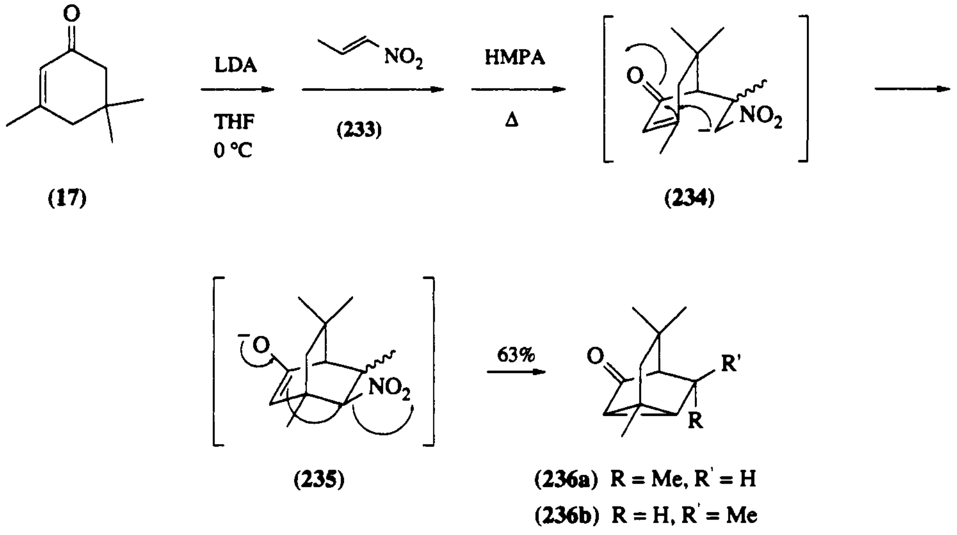

O
LDA
THF
0 °C
$NO_2$
(233)
HMPA
Δ
O
$NO_2$
O
$NO_2$
63%
O
R'
R
(17)
(234)
(235)
(236a) R = Me, R' = H
(236b) R = H, R' = Me

**Scheme 32**

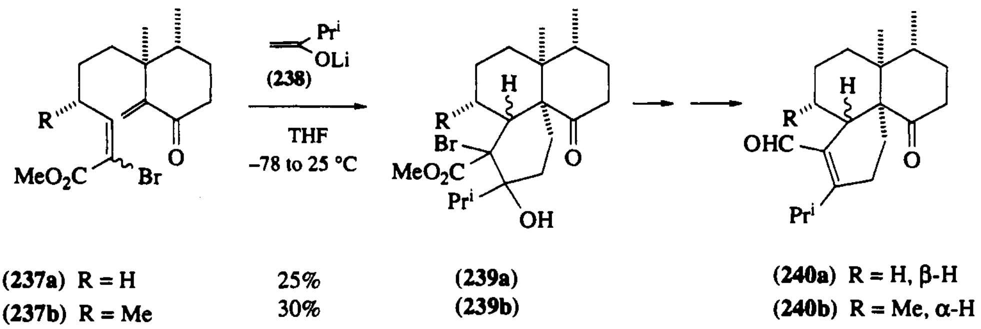

R
$MeO_2C$
Br
O
$Pr^i$
OLi
(238)
THF
−78 to 25 °C
H
R
Br
$MeO_2C$
$Pr^i$
OH
O
H
R
OHC
$Pr^i$
O
(237a) R = H
(237b) R = Me
25%
30%
(239a)
(239b)
(240a) R = H, β-H
(240b) R = Me, α-H

**Scheme 33**

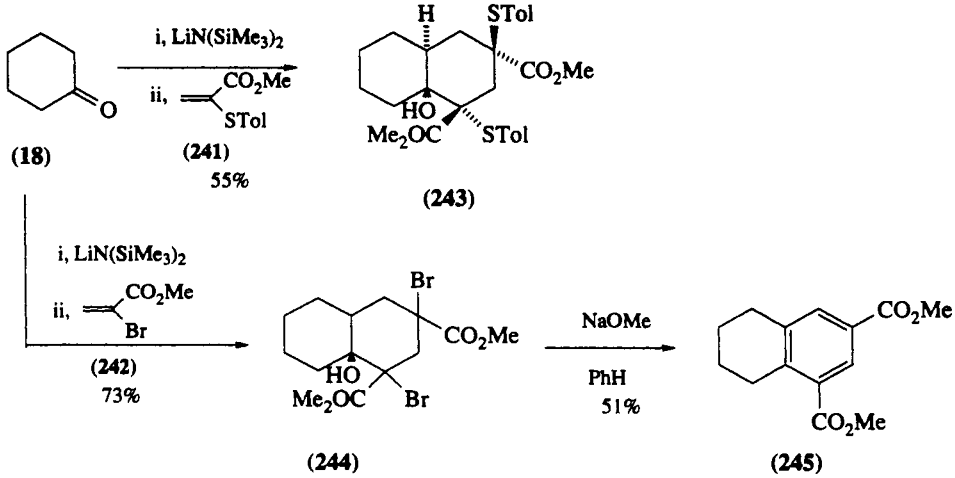
i, LiN(SiMe3)2
ii, CO2Me STol
(18)
(241)
55%
H STol
CO2Me
HO
Me2OC STol
(243)
i, LiN(SiMe3)2
ii, CO2Me Br
(242)
73%
Br
CO2Me
HO
Me2OC Br
(244)
NaOMe
PhH
51%
CO2Me
CO2Me
(245)

Scheme 34

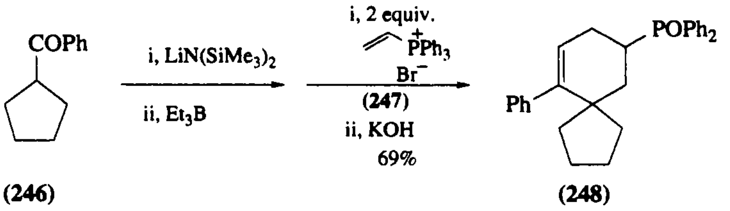
COPh
(246)
i, LiN(SiMe3)2
ii, Et3B
i, 2 equiv.
PPh3 Br−
(247)
ii, KOH
69%
POPh2
Ph
(248)

(50)

ketones with β-substituted-α,β-unsaturated nitro compounds and sulfones.[63,64] Several groups have reported the stereoselective Michael additions of 2-substituted cyclohexanone enolates (**250**) and (**66**) with (**249**) to give, after aldol and dehydration, the corresponding *cis*- or *trans*-substituted octalones, (**251a**, **251b**) and (**252a**, **252b**), respectively (equation 51). In general, the use of apolar or alcoholic solvents affords a mixture in which the *cis* isomer (**251a**) predominates while the *trans* isomer (**252a**) is major in DMSO.[62a–62c,62f,62h,62i] The best example of this solvent dichotomy involves the production of only the *cis*-(**252a**) or only the *trans*-(**252b**) octalones from 2-methylcyclohexanone (**66**) and (**249**) in dioxane or DMSO, respectively.[62g] With 2-methylcyclohexane-1,3-dione (**82**) or its enamine (**253**) the *trans* isomer

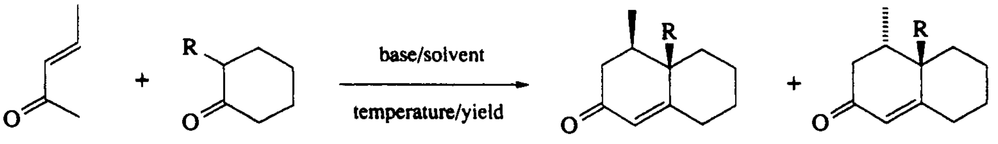
R
base/solvent
temperature/yield
O
R
R

(51)

(**249**) (**250**) R = $CO_2Me$ KOt-$C_5H_{11}$/t-$C_5H_{11}$OH/−15 °C/65% (**251a**) 3.08:1 (**252a**)
NaOMe/DMSO/29 °C/72% 0.61:1

(**66**) R = Me NaH/dioxane/25 °C/65% (**251b**) >95:<5 (**252b**)
NaH/DMSO/25 °C/72% <5:>95

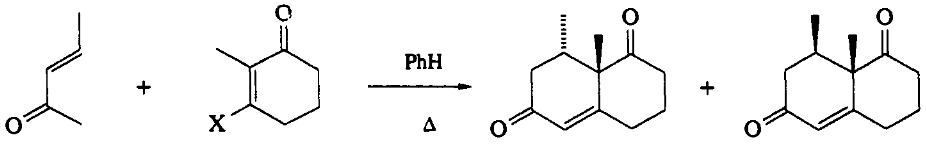

(52)

(**249**) (**82**) X = OH KOH/EtOH/pyrrolidine/71% (**254a**) 6:1 (**254b**)

(**253**) X = N AcOH/NaOAc/59% 10:1

(**254a**) is the major product in benzene with ethanol or acetic acid, while in DMF a 1:1 mixture results (equation 52).[62d,62e]

The reaction of the morpholine enamine of cyclohexanone (**255**; equation 53) with β-nitrostyrene (**49**) or 1-nitropropene (**233**) followed by hydrolysis affords the *erythro* products (**256a,b**) almost exclusively; similar selectivity was also seen for the corresponding sulfones.[63] Seebach has extended these results to enamines of acyclic ketones and various enolates with little or no loss in selectivity and has proposed a 'topological rule' for such carbon–carbon bond-forming processes, as well as others.[64] As applied to the Michael addition, the best approach of the two reagents is represented by transition structure (**258**; equation 54) which has three important features: (i) all of the existing bonds are staggered; (ii) the donor (enolate, enamine) and acceptor (α,β-unsaturated system) units are in a *gauche* arrangement; and (iii) the actual donor and acceptor atoms, *e.g.* X and Z in (**258**), are situated close to each other (to minimize charge separation or to allow for chelation of metal ions). This approach, using a so-called closed transition state, predicts that the *erythro* product (**259**) would be formed preferentially, and thus correctly rationalizes most of the experimental results. For instance, Mulzer[65] reported that reaction of the lithium enolate of various β-lactones (**260a–260d**) with dimethyl maleate (**261**; equation 55) gives predominantly the corresponding diastereomer (**262a–262d**) rather than (**263a–263d**), which conforms to Seebach's topological rule *via* (**264**). However, the stereochemical results with ester and amide enolates are less easily rationalized by this model.[66,67] For example, Yamaguchi reported that the lithium enolates of simple esters (**266**; equation 56) react with β-substituted acrylates (**3**) in THF–HMPA at –78 °C to afford high yields of the *erythro*-glutarates (**267a**).[66a] The *threo* product was favored even when the HMPA was added after the lithium enolate was formed or when no HMPA was used at all! The lithium enolate of *t*-butyl propionate (**268**; equation 57) in THF without HMPA adds to ethyl crotonate (**269**) to give mainly the *threo* product (**270b**).[66a] It is hard to correlate these results with those of Heathcock,[67b] who showed that reaction of the (*E*)- and (*Z*)-enolates (**272**; Scheme 35) of *t*-butyl propionate (**268**) with the enone (**273**) gave stereospecifically the *threo*-glutarate (**274a**) from the (*E*)-enolate and the *erythro*-glutarate (**274b**) from the (*Z*)-enolate (results in accord with the Seebach model). The results with amide enolates are even harder to explain. Yamaguchi reports high *threo* selectivity in the addition of the enolate of the amide (**275**; equation 58) to ethyl crotonate (**269**),[66c] while Heathcock reports very low selectivity for reaction of the same enolate with a series of enones like (**273**).[67a] With very hindered amides (**277**; equation 59), Yamaguchi reports high *erythro* selectivity and good diastereomeric excess.[66c] Heathcock could achieve high *erythro* selectivity by using the cyclic amide (**279**; equation 60).[67a] These results and others[68] are not consistent with the Seebach model. Heathcock suggests an 'open transition state' model (Scheme 36) in which the interaction between the alkenic methyl and the pyrrolidine ring causes (**281b**) to be destabilized relative to (**281a**).[67a] Furthermore, when a halide is present on the alkyl group of the β-alkylacrylate moiety, as in (**282**; equation 61) a stereospecific alkylation of the kinetically generated enolate occurs to give high yields of the *trans*-substituted products, with only (**283a**; *threo* Michael adduct) being formed in the absence of HMPA and only (**283b**; *erythro* Michael adduct) being formed in the presence of HMPA.[66b]

Whatever the explanation for the stereocontrol, these processes are quite useful synthetically, enabling one to prepare nearly pure *erythro* or *threo* diastereomers in high yield. A number of groups have shown that by using a chiral auxiliary in the enamine, ester or amide unit, products of very high enantiomeric excess can be obtained.[69]

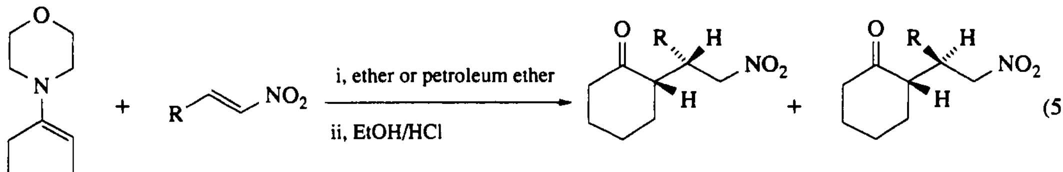

(53)

(**255**)

(**49**) R = Ph
(**233**) R = Me

(**256a**) 95:5 (**257a**)
(**256b**) 99:1 (**257b**)

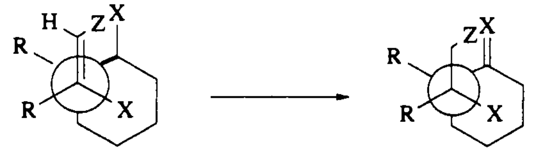

(54)

(**258**) (**259**)

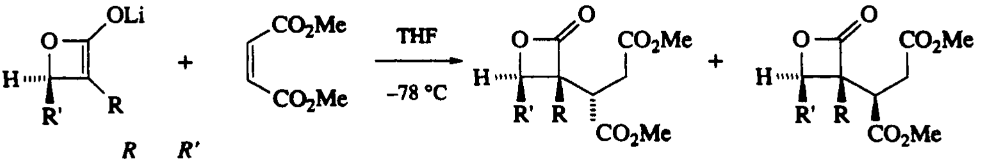
OLi
O
H
R'
R
+
CO2Me
CO2Me
THF
–78 °C
O
O
H
R'
R
CO2Me
CO2Me
+
O
O
H
R'
R
CO2Me
CO2Me

(55)

| | *R* | *R'* | | | | | |
|---|---|---|---|---|---|---|---|
| **(260a)** | Ph | $Bu^t$ | **(261)** | 73% | **(262a)** | 89:11 | **(263a)** |
| **(260b)** | Ph | $Pr^i$ | | 68% | **(262b)** | 82:18 | **(263b)** |
| **(260c)** | Ph | Me | | 56% | **(262e)** | 85:15 | **(263e)** |
| **(260d)** | Me | $Bu^t$ | | 45% | **(262d)** | 100:0 | **(263d)** |

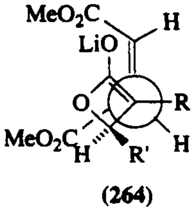
MeO2C
H
LiO
O
R
MeO2C
H
R'
H

**(264)**

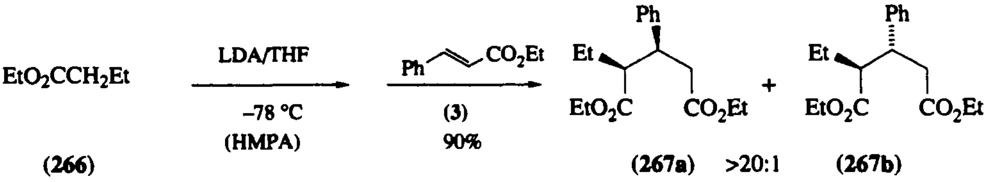
EtO2CCH2Et
(266)
LDA/THF
–78 °C
(HMPA)
Ph
CO2Et
(3)
90%
Ph
Et
EtO2C
CO2Et
+
Ph
Et
EtO2C
CO2Et
(267a)
>20:1
(267b)

(56)

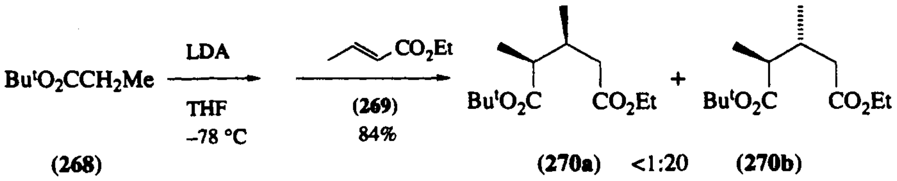
Bu'O2CCH2Me
(268)
LDA
THF
–78 °C
CO2Et
(269)
84%
Bu'O2C
CO2Et
+
Bu'O2C
CO2Et
(270a)
<1:20
(270b)

(57)

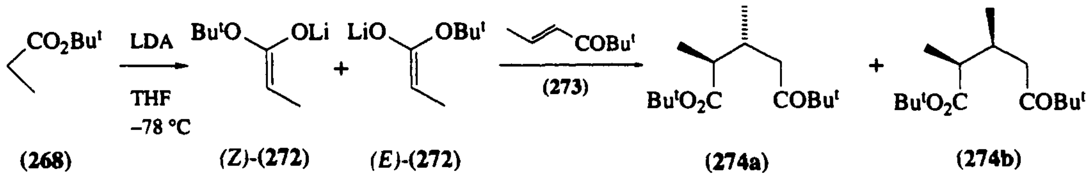
CO2Bu'
(268)
LDA
THF
–78 °C
Bu'O
OLi
+
LiO
OBu'
(Z)-(272)
(E)-(272)
COBu'
(273)
Bu'O2C
COBu'
+
Bu'O2C
COBu'
(274a)
(274b)

| | | | |
|---|---|---|---|
| with HMPA | 88:12 | 73% | 13:87 |
| no HMPA | 6:94 | 85% | 95:5 |

**Scheme 35**

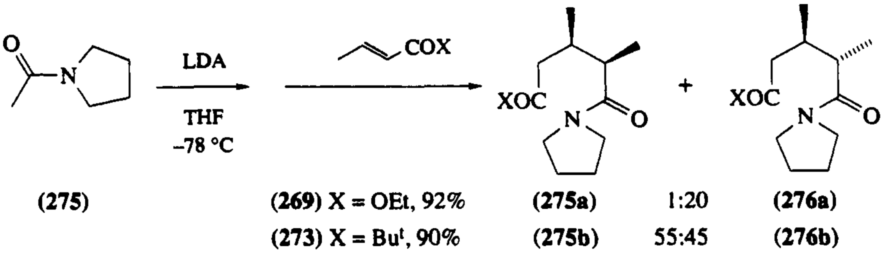
O
N
(275)
LDA
THF
–78 °C
COX
XOC
N
O
+
XOC
N
O
(269) X = OEt, 92%
(273) X = Bu', 90%
(275a)
(275b)
1:20
55:45
(276a)
(276b)

(58)

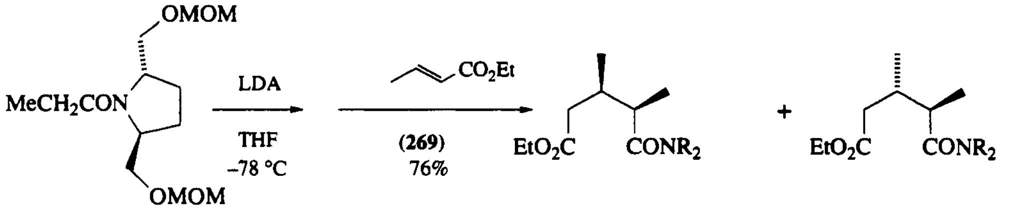

**(277)** **(278a)** 15:1 **(278b)** (59)

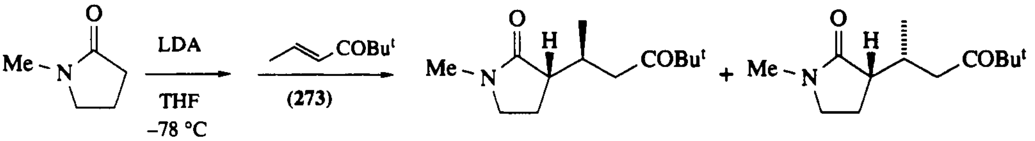

**(279)** **(280a)** 90:10 **(280b)** (60)

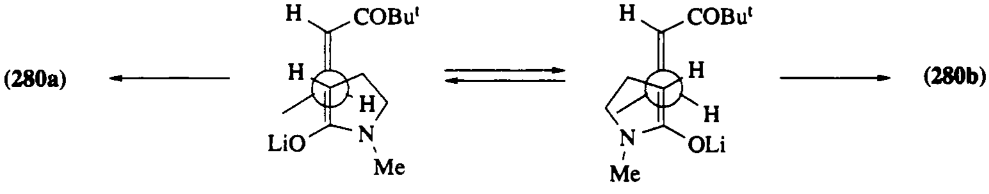

**(281a)** **(281b)**

Scheme 36

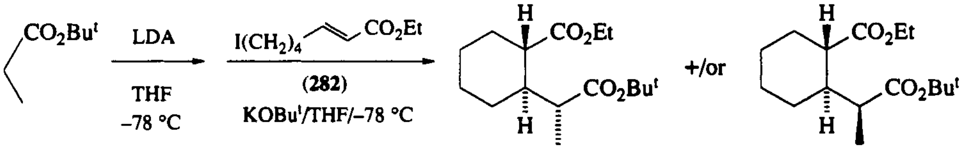

**(268)** **(283a)** **(283b)** (61)

| | **(283a)** | **(283b)** |
|---|---|---|
| no HMPA | 100% | 0% |
| with HMPA | 0% | 100% |

With cyclic Michael acceptors, *e.g.* cycloalkenones and unsaturated lactones, the relative stereochemistry is determined by other substituents on the ring. Generally an allylic substituent causes the addition to occur from the opposite face for steric reasons, giving the *trans* product (equation 62).[33d] The addition to cyclohexenone systems (equation 63) generally occurs in an antiparallel sense to give the axial product.[70] In the reaction of cyanide with octalones such as (**90**; equation 64) under basic conditions, a mixture of *cis* and *trans* products (**289a**,**289b**) is obtained which can be made to favor the *cis* isomer (**289a**).[71] However, the use of Nagata's reagent (HCN/Et$_3$Al) affords the *trans* isomer (**289b**) as the major product.[71a] This reagent has been used in several steroid syntheses to give predominately the desired *trans* C/D-ring juncture (**291b**; equation 65).[71a]

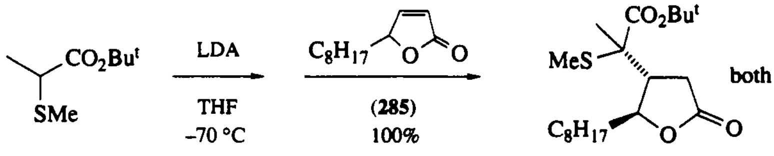

both diastereomers (62)

**(284)** **(286)**

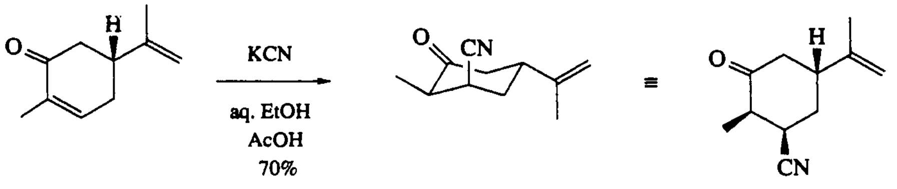

**(287)** **(288)** **(288)** (63)

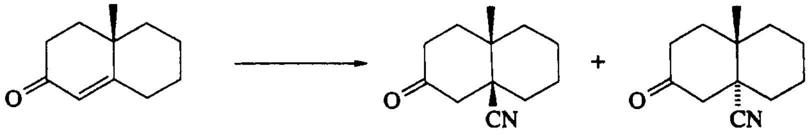

(64)

| **(90)** | | |
|---|---|---|
| $KCN/NH_4Cl$ | **(289a)** 43:57 **(289b)** |
| $Me_2C(OH)CN/KCN/18\text{-crown-}6$ | 68:17 |
| $HCN/Et_3Al$ | 29:71 |

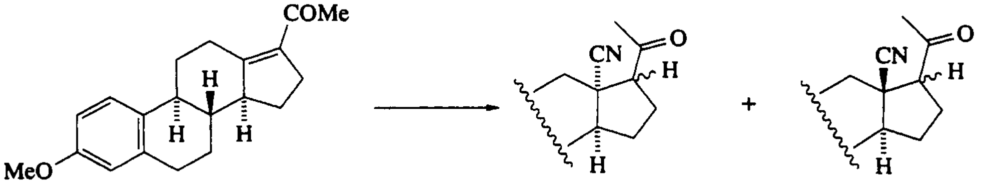

(65)

| **(290)** | | |
|---|---|---|
| $KCN/NH_4Cl$ | **(291a)** 57:22 **(291b)** |
| $HCN/Et_3Al$ | 9:67 |

### *1.1.2.1.2 Intramolecular additions*

*(i) Five-membered rings*

Several groups have prepared cyclopentane systems by intramolecular Michael addition.[72] Reaction of the triester (**292**; Scheme 37) with phenyl vinyl ketone (**293**) and base produces the cyclopentane (**295**) in good yield *via* an intermolecular (giving **294**) and subsequent intramolecular Michael addition.[72a] When the Michael acceptor is a cyclohexenone (Scheme 38), the *cis*-fused hydrindanone is produced (**298** or **297**).[72b–72f] Spiro systems can also be formed by these reactions (**300a,b**; equation 66) in which the Michael addition gives a spiro ring fusion.

Stork reported excellent stereochemical control in the intramolecular Michael addition to produce methyl-substituted cyclopentane systems.[73] For example, base-catalyzed conjugate addition of (**301a,b**; equation 67) followed by intramolecular aldol condensation affords the hydrindenones (**302a,b**) in high yields with excellent stereoselectivity.[73a] The corresponding β-keto esters (**304a,b**; equation 68) are cyclized with sodium hydride in benzene to give again predominantly the *trans*-cyclopentanes (**305a,b**).[73b] The use of chiral esters permits high absolute stereocontrol.[73c] This work has been extended to systems with allylic substituents, *e.g.* (**307**; equation 69) gives mainly (**308**).[73d]

The introduction of heteroatoms in the chain connecting the nucleophile and the acceptor does not affect the reaction. Bicyclic butyrolactones, which are of interest in the forskolin area, have been prepared by this approach, *e.g.* (**314**; Scheme 39) and (**317**; Scheme 40).[74] Pyrrolidines such as (**319**; equation 70) are also easily formed by an internal Michael reaction.[75] This chemistry has been used by Büchi in the

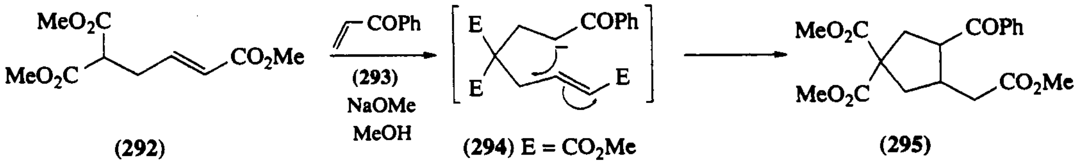

**(292)** **(294)** **(295)**

Scheme 37

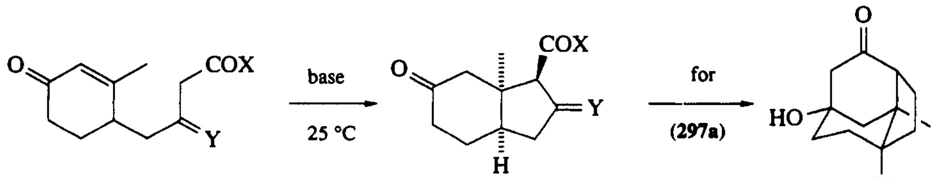
COX
Y
base
25 °C
COX
Y
H
for
(297a)
O
HO
H

| | | | | |
|---|---|---|---|---|
| **(296a)** | X = Me | $Bu^tOK$ | **(297a)** | |
| | Y = $H_2$ | $Bu^tOH$/0.5 h | | **(298)** 75% |
| **(296b)** | X = OEt | $K_2CO_3$ | **(297b)** 45% | |
| | Y = O | EtOH/40 h | | |

**Scheme 38**

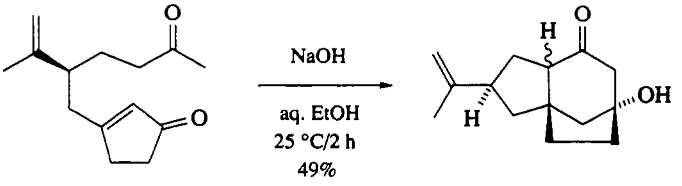
O
NaOH
aq. EtOH
25 °C/2 h
49%
H
O
OH
H

(66)

**(299)** **(300)** α-H 38%
β-H 11%

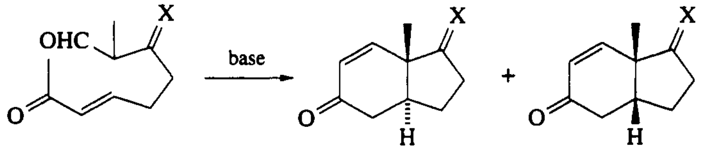
OHC
X
O
base
X
O
H
+
X
O
H

(67)

| | | | | |
|---|---|---|---|---|
| **(301a)** X = $H_2$ | NaOMe | **(302a)** | 3:1 | **(303a)** |
| | $Zr(OPr)_4$ | | 40:1 | |
| **(301b)** X = O | LiOH | **(302b)** | 4:1 | **(303b)** |
| | $Zr(OPr)_4$ | | 25:1 | |

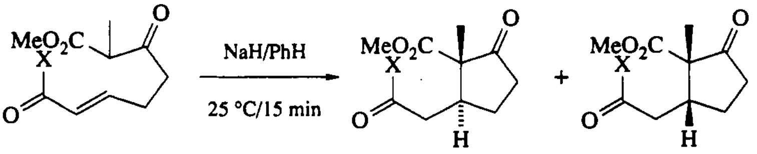
$MeO_2C$
X
O
O
NaH/PhH
25 °C/15 min
$MeO_2C$
X
O
O
H
+
$MeO_2C$
X
O
O
H

(68)

| | | | | |
|---|---|---|---|---|
| **(304a)** X = Me | 90% | **(305a)** | 100:0 | **(306a)** |
| **(304b)** X = OMe | 90% | **(305b)** | 22:1 | **(306b)** |

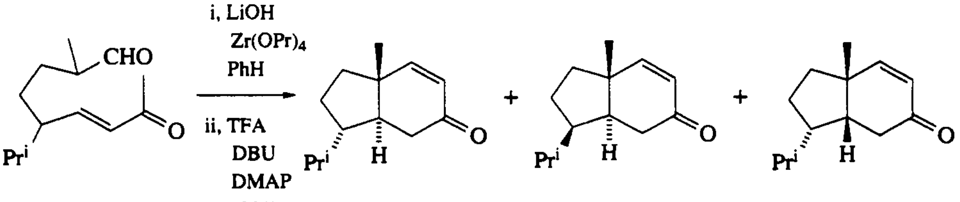
CHO
O
$Pr^i$
i, LiOH
$Zr(OPr)_4$
PhH
ii, TFA
DBU
DMAP
80%
O
$Pr^i$
H
+
O
$Pr^i$
H
+
O
$Pr^i$
H

(69)

**(307)** **(308)** **(309)** **(310)**

10 : 1 : 1

synthesis of pentacyclic indole alkaloids such as vindoline and vindorosine, in which an acid-catalyzed Michael addition is followed by trapping of the spiroindolenium ion to give the products of an overall annulation process (**321a,b**; equation 71).[75a,75b] Finally, an intramolecular version of the thiazolium salt catalyzed Michael addition of an aldehyde has been used to generate a cyclopentanone system (**323**; equation 72) in a synthesis of hirsutic acid C.[76]

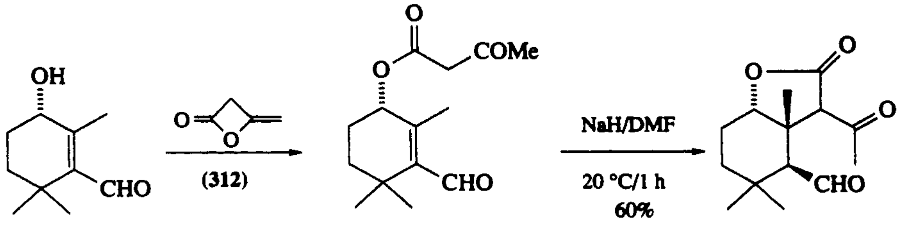
OH
CHO
(312)
O
COMe
CHO
NaH/DMF
20 °C/1 h
60%
O
O
CHO

**(311)** **(313)** **(314)**

**Scheme 39**

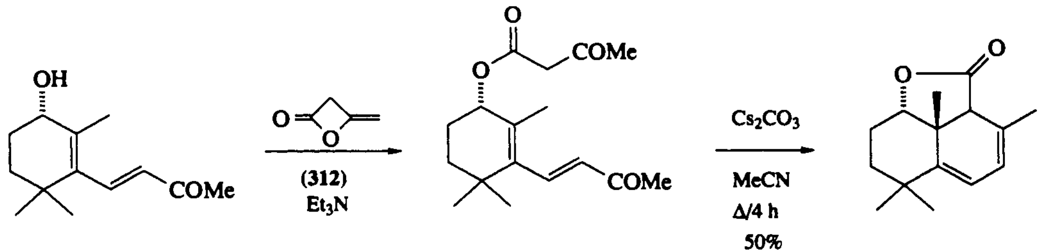
OH
COMe
(312)
Et3N
O
COMe
COMe
Cs2CO3
MeCN
Δ/4 h
50%
O

**(315)** **(316)** **(317)**

**Scheme 40**

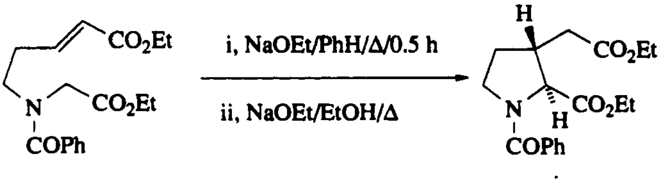
CO2Et
N
CO2Et
COPh
i, NaOEt/PhH/Δ/0.5 h
ii, NaOEt/EtOH/Δ
H
CO2Et
N
H
CO2Et
COPh

**(318)** **(319)** (70)

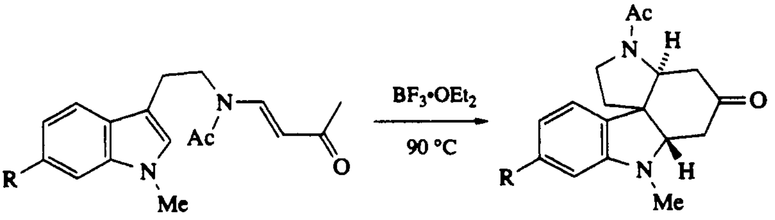
R
N
Me
N
Ac
O
BF3•OEt2
90 °C
Ac
N
H
O
R
N
H
Me

(71)

**(320a)** R = H 27 min, 38% **(321a)**
**(320b)** R = OTs 16 min, 89% **(321b)**

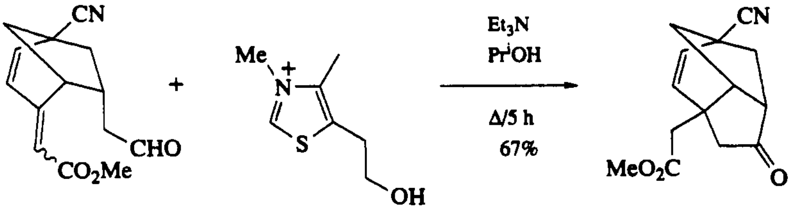
CN
+
CHO
CO2Me
Me
+
N
S
OH
Et3N
PriOH
Δ/5 h
67%
CN
MeO2C
O

**(322)** **(323)** (72)

*(ii) Six-membered rings*

4,4-Disubstituted cyclohexanones (**325**; equation 73) are easily prepared by a double Michael process, in which the intramolecular addition forms the six-membered ring.[77] Either the *cis* or *trans* compound can be obtained selectively. The enamines of cyclic ketones produce similar products.[77b] By using enynones 4,4-disubstituted cyclohexenones can be prepared by this route, *e.g.* griseofulvin (**328**; equation 74) (and its analogs) from the benzofuranone (**326**) and the enynone (**327**).[78] In fused systems, the *cis* ring juncture is again usually favored,[79] (**329**; equation 75) giving (**330**).[79a] The trione (**332**; Scheme 41) prepared by acidic hydrolysis of (**331**), also gives the *cis*-decalindione (**333**).[79c] Ivie showed that an intermediate similar to (**332**), namely (**336**; Scheme 42), could be prepared by intermolecular Michael addition to the dienone (**334**) and could then undergo intramolecular addition to give the *cis*-fused product (**337**).[79d,79e] The use of β-keto amides or esters as the nucleophilic components does not change the stereospecificity, the *cis* ring juncture again being preferred (equation 76).[80] However, there is a recent report of the opposite stereoselectivity, namely the formation of the *trans*-decalone (**341**; equation 77) from the keto triester (**340**).[81] Cyclization of the acyclic keto ester (**342**; equation 78), *via* its chiral enamine, gives exclusively the *trans*-substituted piperidine (**343**) in 80–83% yield and up to 90% *ee*.[82] This process of forming cyclohexane systems *via* an intramolecular Michael addition has been used often to form the A-ring in anthracycline syntheses (equations 79 and 80).[83] In these cases, the Michael acceptor is formed *in situ* by prototropic rearrangement; the products revert to anthraquinones by either loss of nitrous acid or air oxidation.

Bridged systems can also be prepared in high yield by this process.[84] For example, treatment of the keto diester (**348**; Scheme 43) with (**61**) in basic DMSO gave a 41% yield of the diketo diester (**352**) by way of the intermediates (**349**) to (**351**), involving two Michael additions and final Dieckmann condensation.[84a] Similar processes have also been used to make other bicyclo[3.3.1]nonanes and related com-

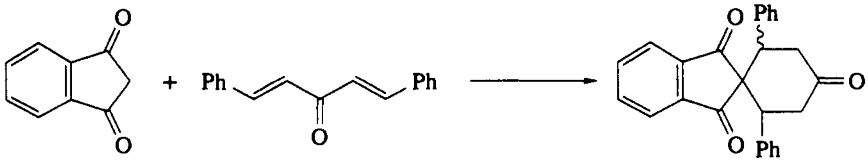

(73)

**(41)** **(324)** AcOH/Δ/1 h 63% NaOEt/EtOH 86% **(325a)** *trans* **(325b)** *cis*

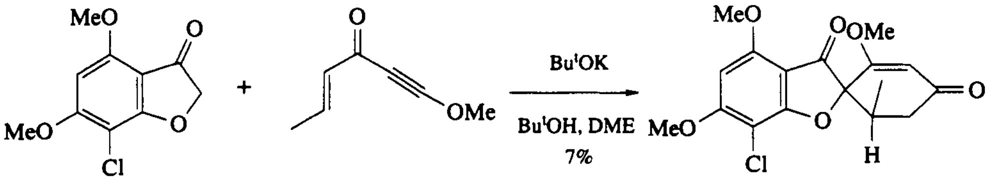

(74)

**(326)** **(327)** **(328)**

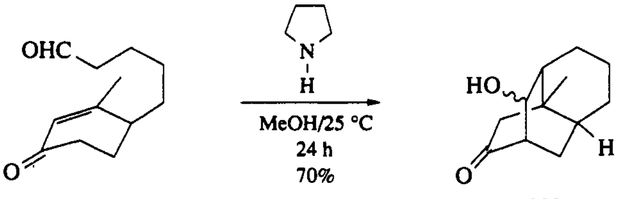

(75)

**(329)** **(330)**

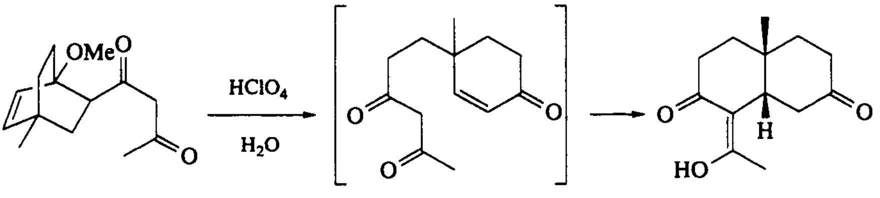

**(331)** **(332)** **(333)**

Scheme 41

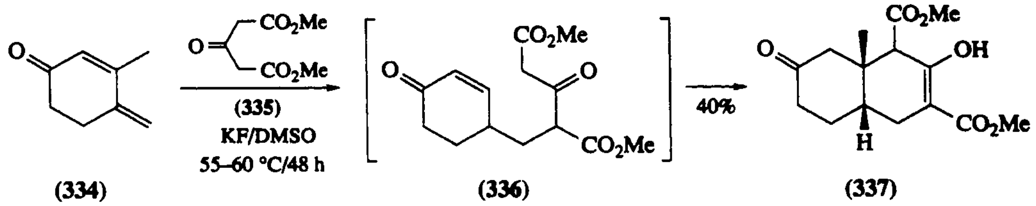
(334)
(335)
KF/DMSO
55–60 °C/48 h
(336)
40%
(337)

**Scheme 42**

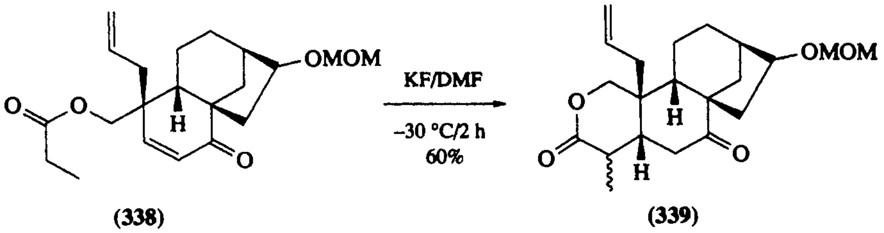
OMOM
KF/DMF
–30 °C/2 h
60%
(338)
(339)

(76)

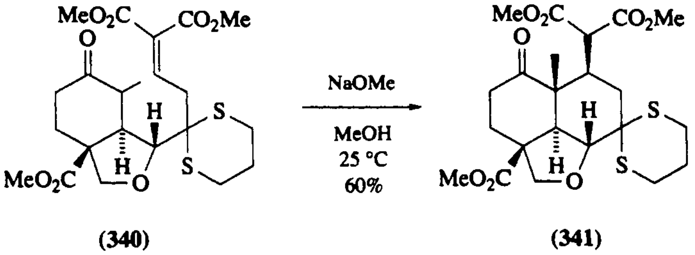
NaOMe
MeOH
25 °C
60%
(340)
(341)

(77)

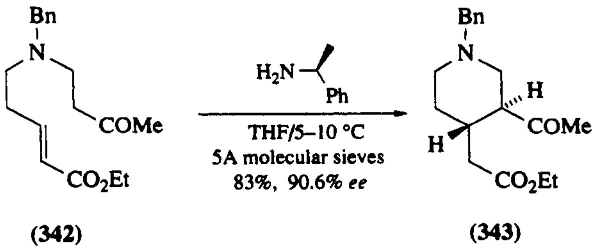
THF/5–10 °C
5A molecular sieves
83%, 90.6% ee
(342)
(343)

(78)

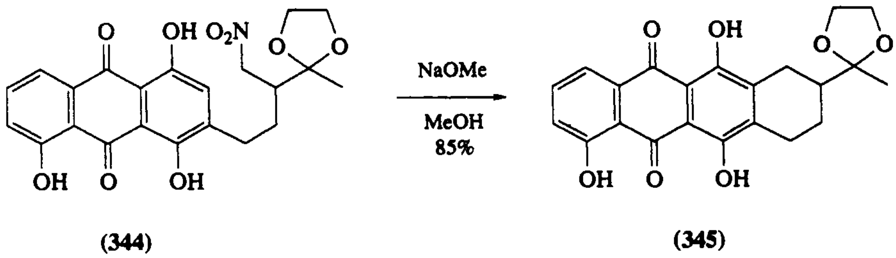
NaOMe
MeOH
85%
(344)
(345)

(79)

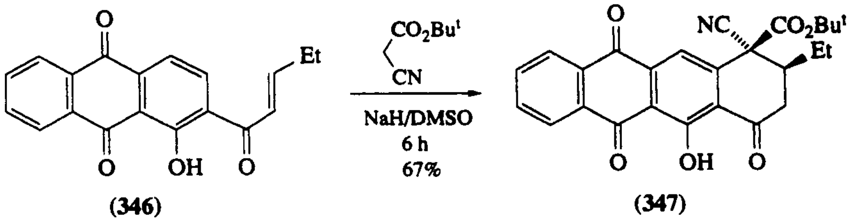
NaH/DMSO
6 h
67%
(346)
(347)

(80)

pounds.[84b,84c] A synthesis of adrene used an intermolecular Michael to produce, after conversion of nitro to carbonyl, the key intermediate (**356**; Scheme 44) for an intramolecular Michael addition to afford the tricyclic dione (**357**).[84d] Deslongchamps showed that only *cis*-fused products were formed in cyclizations to give six-, seven- and eight-membered rings (equation 81), with poor acyclic stereocontrol except for the seven-membered case.[85] Finally, it is perhaps instructive to point out the failure of a simple internal Michael addition, namely the reluctance of the amide (**360**; equation 82) to cyclize to (**361**).[86]

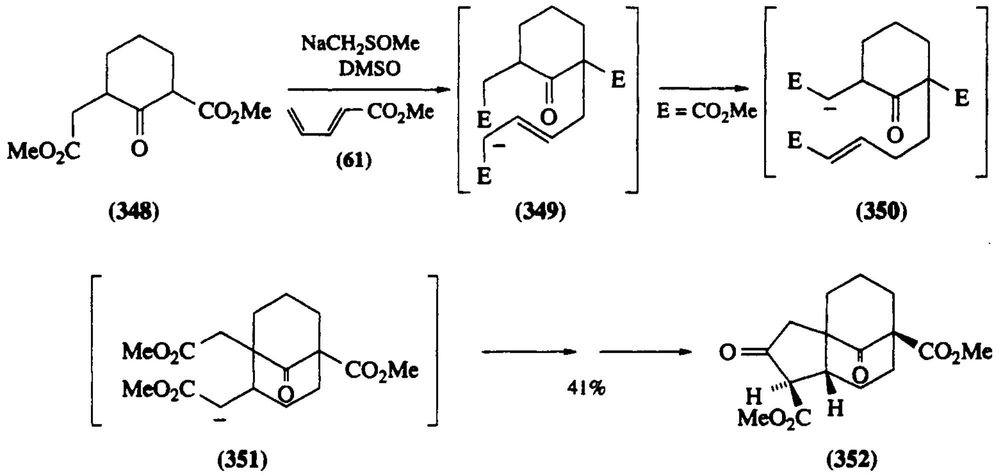
NaCH$_2$SOMe
DMSO
CO$_2$Me
(61)
E = CO$_2$Me
41%
MeO$_2$C
CO$_2$Me
(348)
(349)
(350)
(351)
(352)

**Scheme 43**

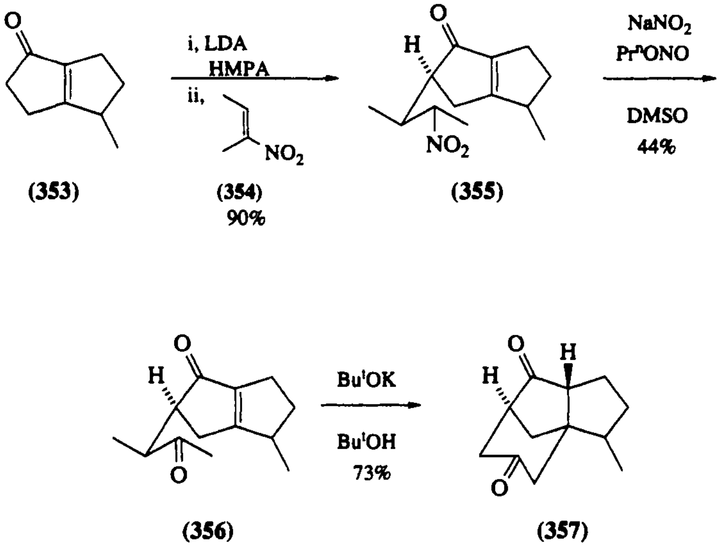
i, LDA
HMPA
ii,
NO$_2$
NaNO$_2$
Pr$^n$ONO
DMSO
44%
Bu$^t$OK
Bu$^t$OH
73%
(353)
(354)
90%
(355)
(356)
(357)

**Scheme 44**

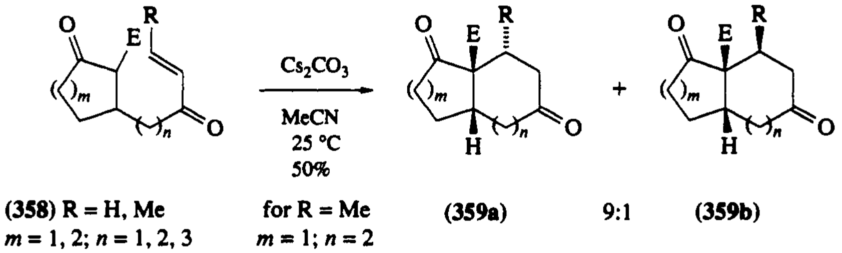
Cs$_2$CO$_3$
MeCN
25 °C
50%
9:1
(358) R = H, Me
m = 1, 2; n = 1, 2, 3
for R = Me
m = 1; n = 2
(359a)
(359b)

(81)

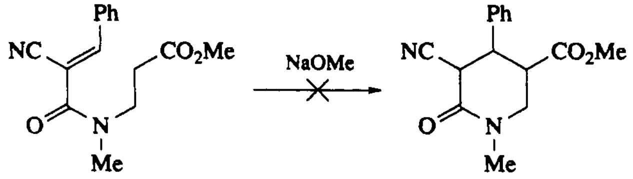

(360) (361)

(82)

*(iii) Dienolate double Michael additions*

In the 1960s and early 1970s, a highly useful synthetic technique was developed, for the formation of cyclohexanones with an electron-withdrawing substituent in the 4-position, and their bicyclic analogs, by a simple double Michael process using a dienolate ion as the initial nucleophile and a normal unsaturated system as Michael acceptor.[87] For instance, treatment of isophorone (**17**; Scheme 45) with lithium isopropyl(cyclohexyl)amide (LICA) in THF at –23 °C followed by addition of methyl acrylate (**21**) afforded the *endo*-bicyclo[2.2.2]octanone ester (**365**) as a single diastereomer in 98% yield.[87g] The reaction proceeds by addition of the dienolate (**362**) to the acrylate to give the ester enolate (**363**) which adds back *via* an internal Michael to the enone to generate the enolate (**364**); protonation gives the product (**365**). The *endo* stereochemistry is determined in the intramolecular Michael addition of (**363**) to give (**364**), and is presumably due to minimization of charge separation or partial chelation of the lithium cation by the oxygen atoms, as proposed earlier in the intermolecular additions. This reaction sequence has since been used many times to prepare compounds of use in natural product synthesis,[88] a few examples of which are given here. A substituent on the dienolate unit causes the initial Michael addition to occur *trans* to that substituent, thus setting an additional stereochemical center, *e.g.* (**366a,b**; equation 83) gave only (**367a,b**) when reacted with the acrylates (**269**) or (**223**).[88g,88h] Likewise, a substituent on the acceptor can also cause the initial Michael addition to be highly stereoselective (equation 84).[88e] The use of a pentenoate bearing an allylic chiral center as the acceptor affords the expected product with high diastereoselectivity.[88j] The initial dienolate can be generated by other reactions, *e.g.* a Michael reaction, so that a triple Michael process is observed, *e.g.* (**371**) and (**372**; Scheme 46) generate the dienolate (**373**) which adds to methyl acrylate (**21**) to give (**374**) in good yield.[88p] Finally, an intramolecular version of this process has been used in the synthesis of steroids and steroidal alkaloids.[88k–88o] For example, treatment of the enone (**375**; equation 85), bearing an appropriately positioned acrylate unit, with base in ether–hexane at low temperature produced, in 43% yield, the desired polycyclic keto ester (**376**), which was then taken on to atisine.[88o] It should be pointed out that these reactions could be formally viewed as Diels–Alder reactions of the dienolate ion and the Michael acceptor, since cycloadditions of similar cross-conjugated dienolate derivatives are known.[89] However, they are almost certainly correctly considered as double Michael additions since: (i) in certain cases the reaction can be carried out stepwise, by isolating the first Michael product and cyclizing it under similar conditions;[88q] (ii) the TLC of the reaction mixture under silylating conditions shows that the cyclization precedes silylation and thus the reaction does not involve the silyloxydiene;[88m,88n] and (iii) the reluctance of similar Diels–Alder reactions to proceed well.[88g,88q,90] Finally, it should be pointed out that by using a different set of conditions for dienolate formation, one can produce a through-conjugated dienolate, *e.g.* (**377**; Scheme 47) from (**36**), and effect a different double Michael process,[91] as shown, to give a product isomeric to that expected from the above references, namely (**380**).[91a]

### 1.1.2.2 Heteronucleophiles

The addition of heteroatomic nucleophiles, *e.g.* oxygen, nitrogen, sulfur, halogen, phosphorus, *etc.*, to activated alkenes is covered in this section.

#### *1.1.2.2.1 Intermolecular additions*

The conjugate addition of heteronucleophiles to activated alkenes has been used very often in organic synthesis to prepare compounds with heteroatoms β to various activating functional groups, *e.g.* ketones, esters, nitriles, sulfones, sulfoxides and nitro groups. As in the Michael reaction, a catalytic amount of a weak base is usually used in these reactions (with amines as nucleophiles, no additional base is added).

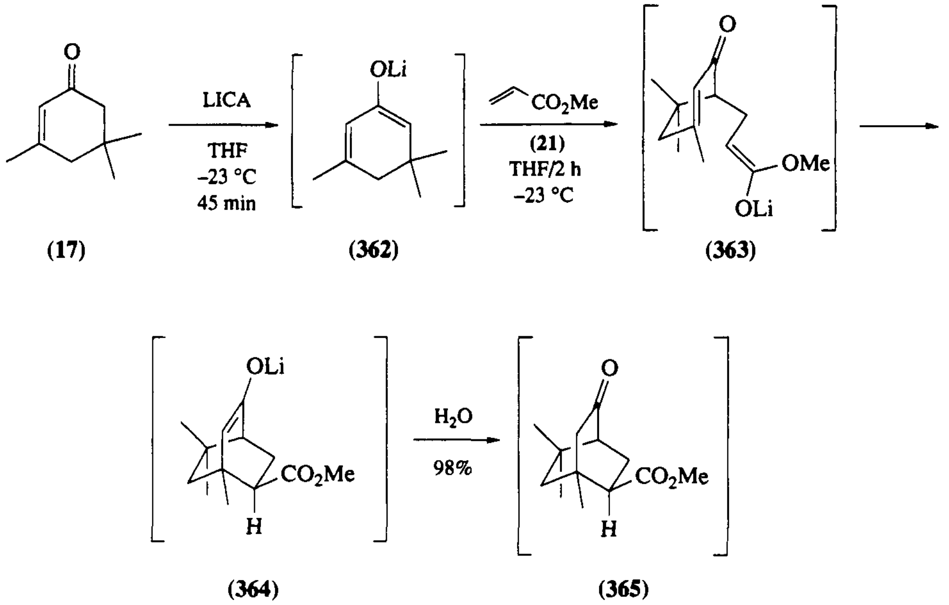

**Scheme 45**

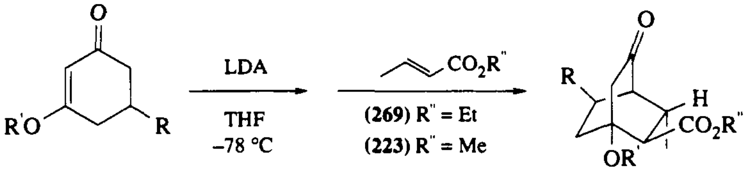

(83)

| | | |
|---|---|---|
| **(366a)** $R = Me, R' = MOM$ | 94% | **(367a)** $R = Me, R' = MOM, R'' = Et$ |
| **(366b)** $R = CH_2OMOM, R' = SiMe_3$ | 74% | **(367b)** $R = CH_2OMOM, R' = SiMe_3, R'' = Me$ |

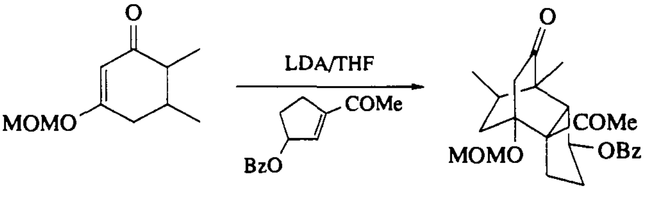

(84)

**(368)** **(369)** 62% **(370)**

Several representative examples of this large class of reactions are given in equations (86) to (89) and Scheme 48.[92] The reaction works quite well with good acceptors such as acrylonitrile (**70**; equation 86)[7f,92c,92f,92g] or nitroethylene (**387**; Scheme 48)[92i–92k] and with good nucleophiles such as thiols or amines.[92a,92b,92d,92e] As with Michael additions, the initially formed adduct can add a second time to give dialkylated products (**384**; equation 88), sometimes in excellent yield.[92b] Even with α-amidoacrylates as acceptors (equation 90), good yields of addition are obtained.[93]

This addition of a heteronucleophile to an enone has often been used as evidence for the formation of strained alkenes such as anti-Bredt's bridgehead enones.[94] Treatment of the β-chloro ketone (**393**; Scheme 49) with basic methanol produced the β-methoxy ketone (**395a**) in 91% yield by way of the bridgehead enone (**394**).[94a] Trapping with a thiol or amine also proceeded in excellent yield to give (**395b**) or (**395c**), respectively. The bicyclic enones can also be prepared by an intramolecular Wittig reaction and trapped *in situ* with alcohols.[94d] An intramolecular version of this process has been used in a clever synthesis of lycopodine (**400**; Scheme 50).[94e] Treatment of the β-bromo ketone (**396**) with the amine (**397**) in the presence of DBU afforded the desired tricyclic amino ketone (**399**) in quantitative

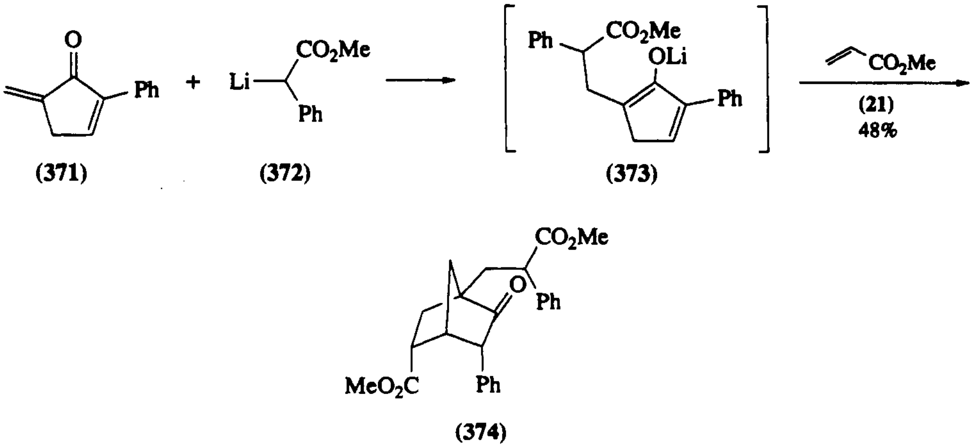
O
Ph
+
Li
CO2Me
Ph
Ph
CO2Me
OLi
Ph
CO2Me
(21)
48%
CO2Me
O
Ph
MeO2C
Ph
(371)
(372)
(373)
(374)

Scheme 46

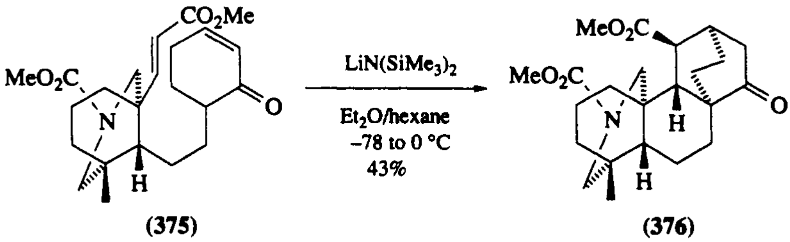
CO2Me
MeO2C
N
H
O
LiN(SiMe3)2
Et2O/hexane
−78 to 0 °C
43%
MeO2C
MeO2C
N
H
H
O
(375)
(376)

(85)

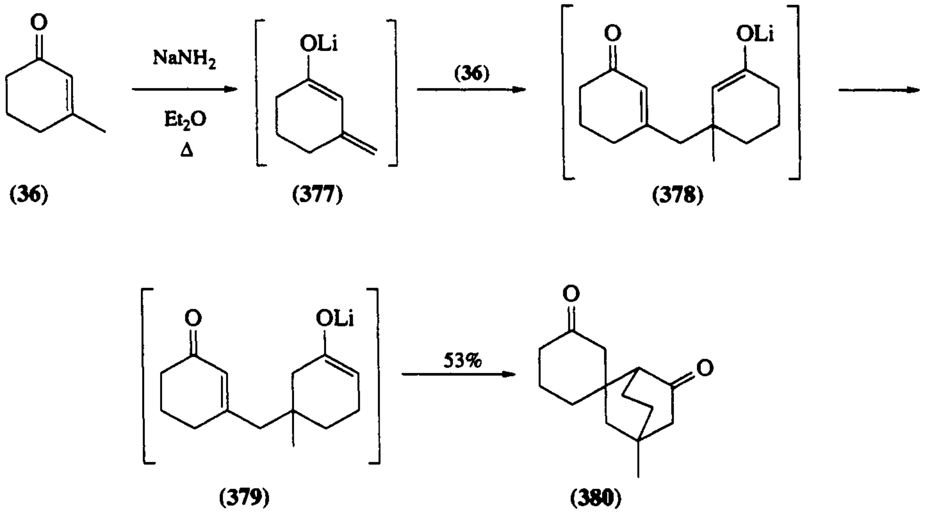
O
NaNH2
Et2O
Δ
OLi
(36)
O
OLi
(36)
(377)
(378)
O
OLi
53%
O
O
(379)
(380)

Scheme 47

yield by way of the amino enone (**398**). The final conversion of (**399**) to lycopodine (**400**) was carried out in only two steps by Heathcock's route.[94f]

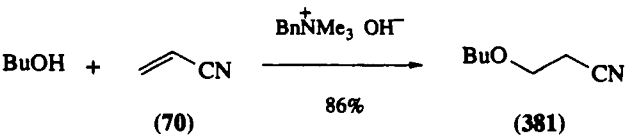
BuOH
+
CN
BnN⁺Me3 OH⁻
86%
BuO
CN
(70)
(381)

(86)

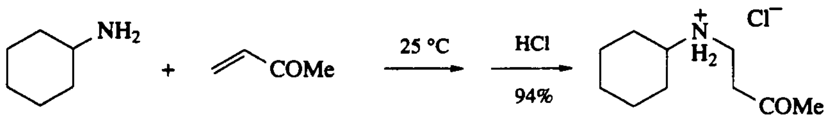

NH2
+
COMe
25 °C
HCl
94%
Cl⁻
COMe

**(382)** **(30)** **(383)** (87)

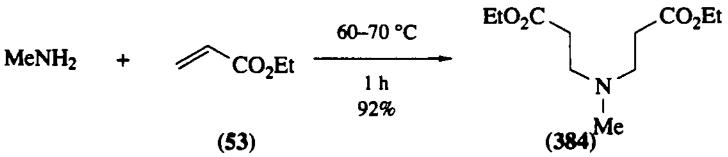

MeNH2
+
CO2Et
60–70 °C
1 h
92%
EtO2C
CO2Et
N
Me

**(53)** **(384)** (88)

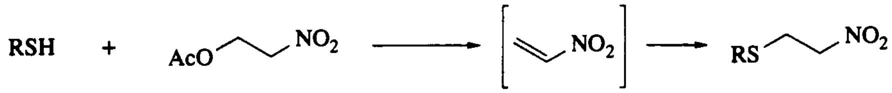

RSH
+
AcO
NO2
NO2
RS
NO2

**(385a)** R = Ph  **(386)** $Et_3N$ 96% **(387)** **(388a)**

**(385b)** R = 3-cycloheptenyl  EtOH/0 °C/3 h 99% **(388b)**

**Scheme 48**

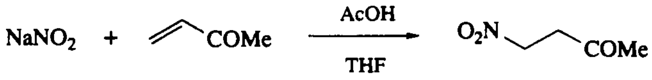

NaNO2
+
COMe
AcOH
THF
82%
O2N
COMe

**(30)** **(389)** (89)

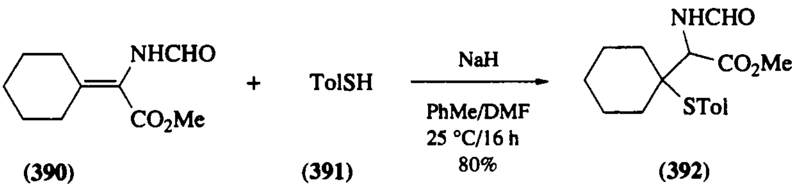

NHCHO
CO2Me
+
TolSH
NaH
PhMe/DMF
25 °C/16 h
80%
NHCHO
CO2Me
STol

**(390)** **(391)** **(392)** (90)

As in the Michael reaction, various methods for trapping the stabilized anion of the initial adduct have been developed. If, for example, there is a leaving group (thioalkyl, halogen), then an addition–elimination process occurs readily to regenerate the alkene.[95] The sequential addition of two different amines to the β,β-disubstituted nitro compound (**401**; Scheme 51) gives the disubstituted nitroalkene (**403**) and finally the pyrrole (**404**).[95a] The addition of a tertiary amine such as (**405**; Scheme 52) to a β-chloroacrylate (**406**) produces the alkenylammonium salt (**407**) which can undergo cycloaddition to give (**408**).[95b]

Another common trapping method is an intramolecular aldol reaction of the initially formed anion, as shown in equation (91) and Schemes 53 and 54.[96] In the first case, an aldol-like trapping of the iminium salt produced (**411**; equation 91).[96b] The initial heteronucleophile in the other two cases is ultimately lost from the product by oxidation and elimination, so that the overall process is C—C bond formation at the α-center of an enone. Thus, treatment of the formyl enone (**412**; Scheme 53) with an aluminum thiolate afforded in 60% yield the trapped product (**413**) which could be oxidized and eliminated to give (**414**).[96c] Addition of the corresponding aluminate species to the ketoacrylate (**415**; Scheme 54) produced only one diastereomer of the aldol product (**416**) which was converted into the alkene (**417**) in excellent yield.[96d]

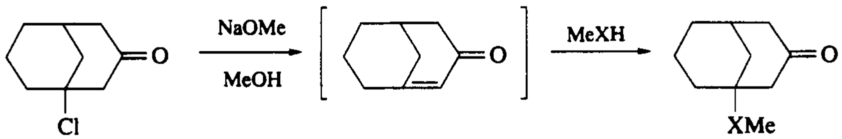

O
Cl
NaOMe
MeOH
O
MeXH
O
XMe

**(393)** **(394)** **(395a)** X = O, 91%

**(395b)** X = S, 86%

**(395c)** X = NMe, 92%

**Scheme 49**

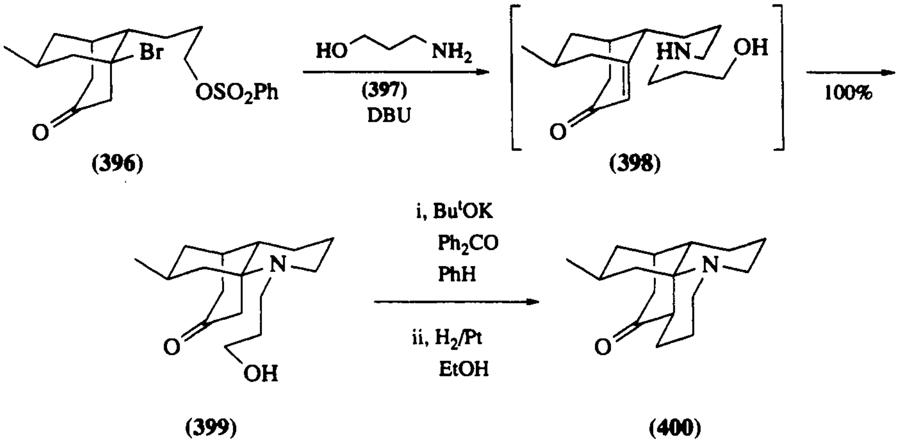
Br
OSO2Ph
O
HO NH2
(397)
DBU
HN
OH
100%
i, Bu'OK
Ph2CO
PhH
ii, H2/Pt
EtOH
N
OH

(396) (398) (399) (400)

**Scheme 50**

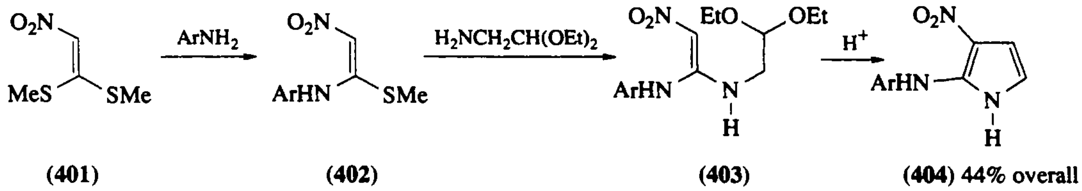
O2N
MeS
SMe
ArNH2
ArHN
H2NCH2CH(OEt)2
EtO
OEt
N
H
H+

(401) (402) (403) (404) 44% overall

**Scheme 51**

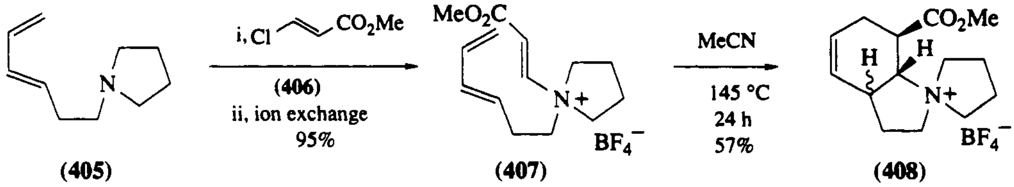
N
i, Cl CO2Me
(406)
ii, ion exchange
95%
MeO2C
N+
BF4−
MeCN
145 °C
24 h
57%
CO2Me
H
H

(405) (407) (408)

**Scheme 52**

This method of forming the oxahydrindene ring system was later applied to an elegant total synthesis of avermectin $A_{1a}$.[96e]

This C—C bond-forming process has been used very often in the intermolecular case[97] to produce α-hydroxyalkyl-α,β-unsaturated esters, ketones, nitriles, sulfones, *etc.* by treatment of the activated alkene

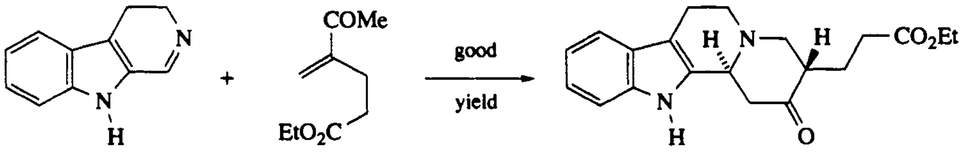
N
N
H
+
COMe
EtO2C
good
yield
H
N
H
CO2Et
O

(409) (410) (411) (91)

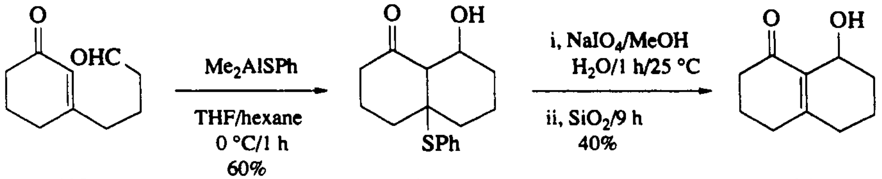
O
OHC
Me2AlSPh
THF/hexane
0 °C/1 h
60%
O
OH
SPh
i, NaIO4/MeOH
H2O/1 h/25 °C
ii, SiO2/9 h
40%
O
OH

(412) (413) (414)

**Scheme 53**

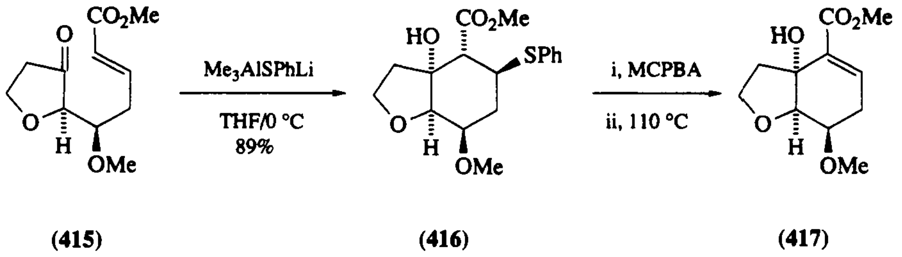
CO2Me
O
H
OMe
Me3AlSPhLi
THF/0 °C
89%
HO
CO2Me
SPh
H
OMe
i, MCPBA
ii, 110 °C
HO
CO2Me
H
OMe
(415)
(416)
(417)

Scheme 54

with a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) and any aldehyde (or even imine).[97d] The mechanism involves addition of DABCO to the activated alkene to form the zwitterion (**420**) which reacts with the aldehyde to give the alkoxide (**421**; Scheme 55). Proton transfer produces the zwitterion (**422**) which then eliminates DABCO to give the observed products (**419a–419e**) in high yields under mild conditions.[97] This process has also been catalyzed by tricyclohexylphosphine.[97i] Another interesting process for trapping the initial anion is an intramolecular proton transfer (Scheme 56), as in the formation of the ylides (**424a**) and (**424b**) from the addition of triphenylphosphine to maleic anhydride (**423a**) or maleimide (**423b**).[98a–98e] These stabilized ylides, and the esters derived from them, have been used in synthesis,[98f–98j] both in Wittig reactions and alkylations.

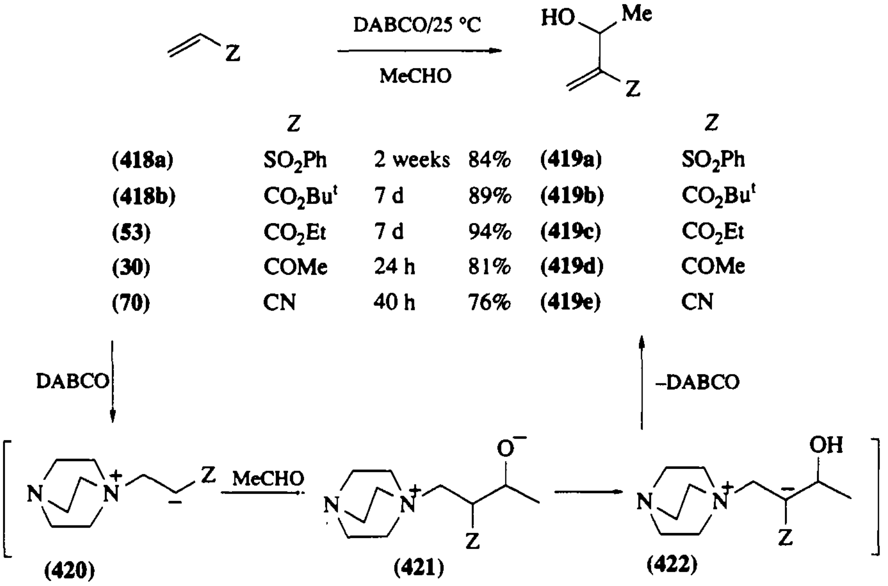
Z
DABCO/25 °C
MeCHO
HO
Me
Z
DABCO
-DABCO
Z
MeCHO
O⁻
OH
Z
Z
(420)
(421)
(422)

| | Z | | | | Z |
|---|---|---|---|---|---|
| (**418a**) | $SO_2Ph$ | 2 weeks | 84% | (**419a**) | $SO_2Ph$ |
| (**418b**) | $CO_2Bu^t$ | 7 d | 89% | (**419b**) | $CO_2Bu^t$ |
| (**53**) | $CO_2Et$ | 7 d | 94% | (**419c**) | $CO_2Et$ |
| (**30**) | COMe | 24 h | 81% | (**419d**) | COMe |
| (**70**) | CN | 40 h | 76% | (**419e**) | CN |

Scheme 55

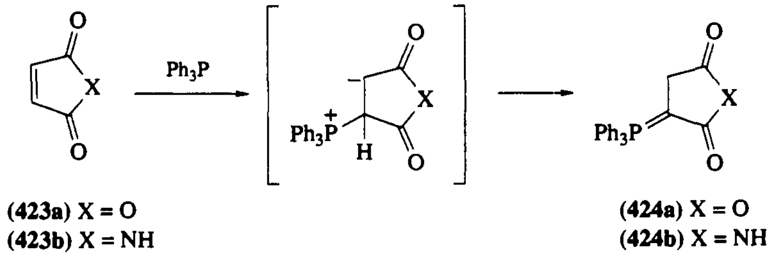
O
X
O
Ph3P
O
X
Ph3P
H
O
O
X
Ph3P
O

(**423a**) X = O
(**423b**) X = NH

(**424a**) X = O
(**424b**) X = NH

Scheme 56

Epoxidation of enones on treatment with basic hydrogen peroxide or *t*-butyl hydroperoxide, or with bleach, might be viewed as another form of trapping the initially produced anion.[99] In this case the enolate, *e.g.* (**425**; Scheme 57), attacks the oxygen of the hydroperoxide to eject hydroxide and yield the epoxy ketone (**426**).[99a] Finally, the initial anion can also be trapped by a sigmatropic rearrangement, as in the production of the azepines (**429a,b**; Scheme 58) from the vinylaziridine (**427**), *via* the zwitterion (**428**).[100]

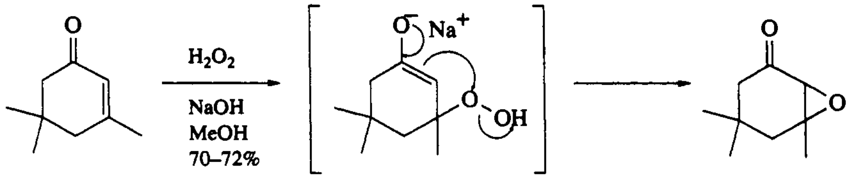

(**17**) (**425**) (**426**)

**Scheme 57**

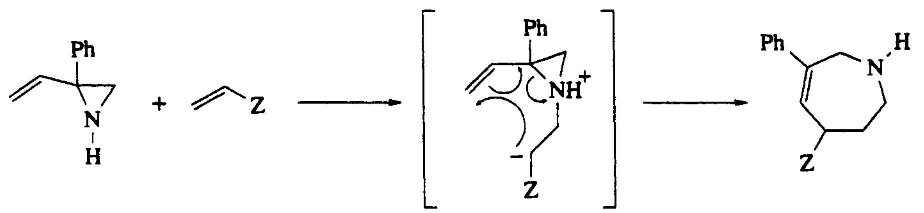

(**427**) (**70**) Z = CN (**428**) (**429a**) Z = CN 70%
(**21**) Z = $CO_2Me$ (**429b**) Z = $CO_2Me$ 55%
(**418a**) Z = $SO_2Ph$ (**429c**) Z = $SO_2Ph$ 50%

**Scheme 58**

A discussion of the relative stereochemistry of these additions completes this section on intermolecular heteronucleophile additions.

In cyclic cases, the normal rules for relative stereocontrol described earlier for carbon nucleophiles apply to heteronucleophiles as well. An allylic substituent usually causes the addition to occur from the opposite face for steric reasons, resulting in the *trans* product (equation 92).[101] Addition of heteronucleophiles to cyclohexenone or dihydropyrone systems generally occurs in an antiparallel sense[102] to give the axial product (equation 93).[102a] This kinetic axial product is often easily rearranged to the thermodynamically more stable equatorial adduct when subjected to the reaction conditions for an extended period.[102b,102c,102e] The use of alkoxide as the nucleophile causes the lactone to be opened and, in certain cases, allows further base-catalyzed processes to occur (equation 94).[102g]

In acyclic systems, high diastereoselectivity can often be achieved.[103] Additions of amines or alkoxides to the (*Z*)-enoate (**436**; equation 95) at low temperature afforded mainly the single diastereomer (**437a,b**) in good yield.[103a,103b] Similar results were obtained with the enone corresponding to (**436**).[103c]

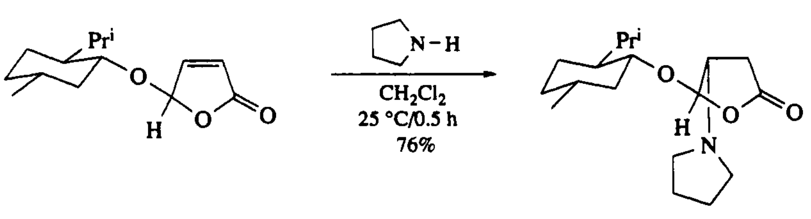

(**430**) (**431**) (92)

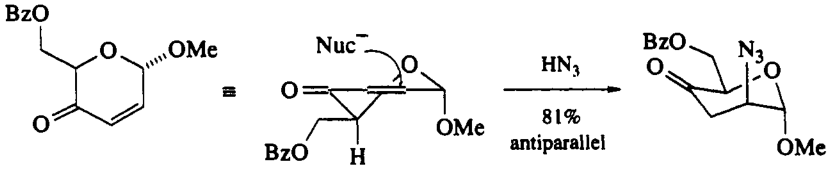

(**432**) (**432**) (**433**) (93)

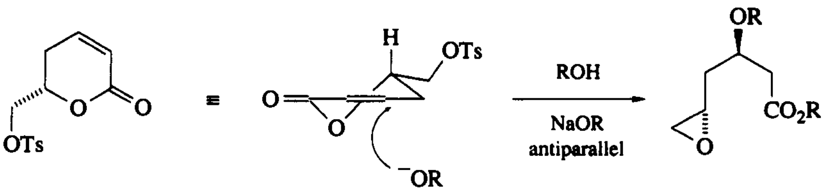

**(434)** **(434)** **(435)** R = allyl, 87% (94)

Chiral α,β-unsaturated sulfoxides also produce predominately one diastereomer on addition of heteronucleophiles (equation 96).[104] Kinetic protonation of the anion (**440**; Scheme 59), generated by addition of thiophenoxide to the nitroalkene (**233**), followed by trapping with formaldehyde, produced a 87:13 mixture of diastereomers favoring (**441**).[105] Finally, the use of high pressure can increase the diastereoselectivity of the addition of amines to chiral crotonates.[106a]

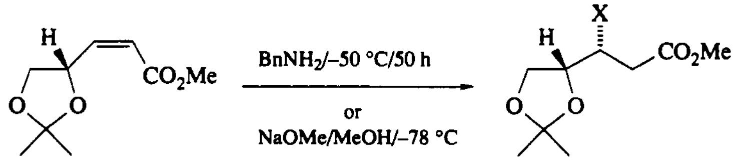

**(436)** (95)

**(437a)** X = NHBn
**(437b)** X = OMe

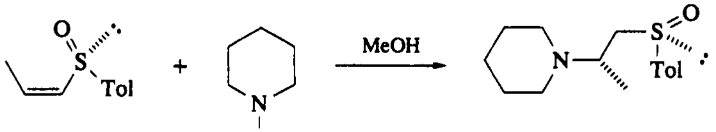

**(438)** **(439)** (96)

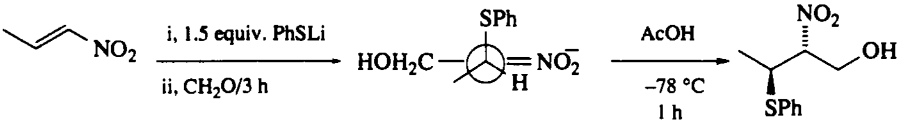

**(233)** **(440)** **(441)**

**Scheme 59**

### *1.1.2.2.2 Intramolecular additions*

#### *(i) Baldwin's rules for ring closure*

Many intramolecular versions of heteronucleophilic additions have been published. However, a major contribution in this area is due to Baldwin who, in 1976, published a paper describing the rules for ring closure.[107a] In that paper and the succeeding ones,[107] he showed that 5-endo-trigonal cyclizations of hydroxy enones and unsaturated esters, such as (**442a**; equation 97) and (**442b**; equation 98), do not occur under basic conditions to give the expected products, (**443a**) and (**443b**), respectively (although the former reaction proceeds well under acidic conditions).[107b,107c] In order to demonstrate conclusively that the reluctance of the anion of (**442a**) to cyclize was not due to an unfavorable equilibrium, Baldwin treated (**443a**) (prepared *via* acid-catalyzed cyclization of **442a**) with NaOMe in MeOD. The α-protons of (**443a**) were exchanged for deuterium but none of the retro-Michael product (**442a**) was produced. The rule that 5-endo-trigonal cyclizations are disfavored has generally been followed, with few exceptions, *e.g.* the thiol (**442c**; equation 98) cyclizes in warm basic methanol to give (**443c**).[107b] The other favored cyclizations—5-exo, 6-endo, 6-exo, *etc.*—have been reported often, as described below. There are obviously many examples of each class, but due to space limitations only a few recent representative examples of each are presented.

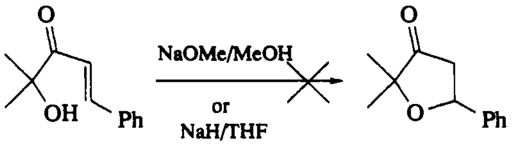

(442a) (443a)

(97)

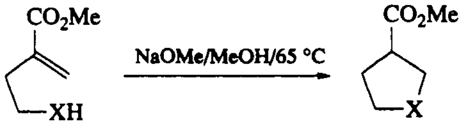

(442b) X = O no reaction
(442c) X = S good yield
(443b) X = O
(443c) X = S

(98)

### *(ii) 5-Exo-trigonal cyclizations*

Baldwin showed that oxidation of the allylic alcohol (**444**; Scheme 60) gave the five-membered ring (**446**) in quantitative yield by way of the unisolable hydroxy enone (**445**).[107e] A useful 5-exo-trig cyclization has been reported often in the synthesis of carbohydrates from protected aldoses by a Wittig condensation followed by an intramolecular conjugate addition of the alkoxide.[108] As an example, reaction of the aldose (**447**; Scheme 61) with the stabilized Wittig reagents (**448a,b**) afforded a 3:1 mixture of β:α anomers of (**450a,b**), in which the key step is an intramolecular addition of the alkoxide of (**449**) to the enoate.[108a] The corresponding fully protected arabinose analog gave predominately the α-anomer.[108c] Hirama has used a similar cyclization of carbamates to give good 1,2- and 1,3-diastereoselectivity.[109a] For example, cyclization of either the (*E*)- or (*Z*)-allylic carbamate esters (**451a,b**; equation 99) gave the *trans*-oxazolidinones (**452a,b**) as the major products.[109a] The corresponding homoallylic carbamate, (**453**; equation 100) gave mainly the *cis* six-membered ring (**454**).[109a] Finally, an interesting example of a 5-exo-trig cyclization[109b] followed by a retro-Mannich reaction has been reported in the synthesis of a series of isoindole systems.[110] Treatment of the bromide (**455**; Scheme 62) with methylamine gave the pyrrolothiophene (**459**), the mechanism of which involves a 5-exo-trig cyclization of the amine (**456**) to (**457**), which undergoes a retro-Mannich reaction to give (**458**) and finally (**459**).[110]

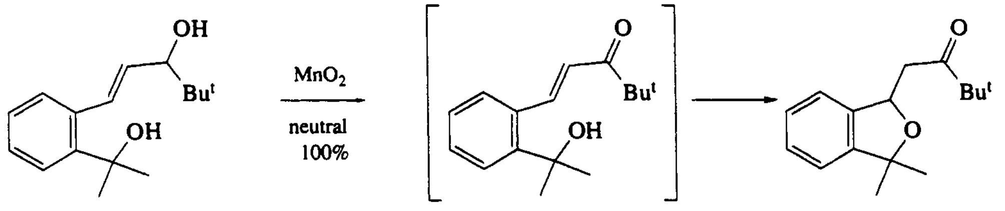

(444) (445) (446)

**Scheme 60**

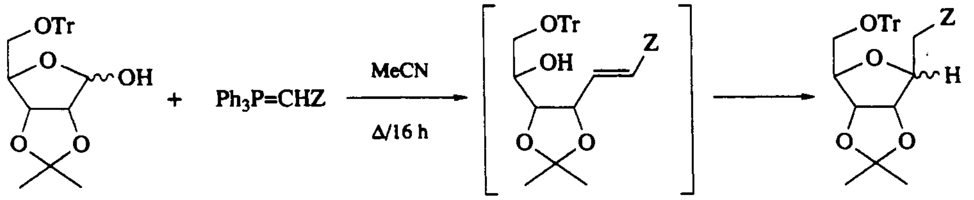

(447) (448a) Z = $CO_2Me$ 98% (449a, b) (450a, b)
(448b) Z = CN 92%

**Scheme 61**

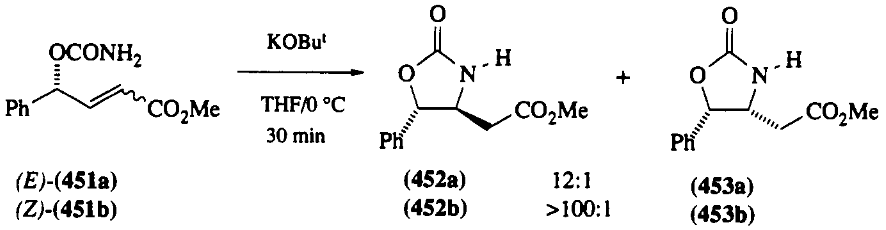
OCONH$_2$
Ph
CO$_2$Me
KOBu$^t$
THF/0 °C
30 min
O
O
N
H
CO$_2$Me
Ph
+
(*E*)-(451a)
(*Z*)-(451b)
(452a)
(452b)
12:1
>100:1
(453a)
(453b)

(99)

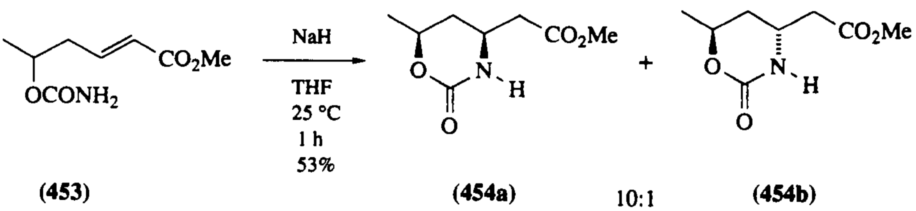
CO$_2$Me
OCONH$_2$
NaH
THF
25 °C
1 h
53%
O
N
H
+
(453)
(454a)
10:1
(454b)

(100)

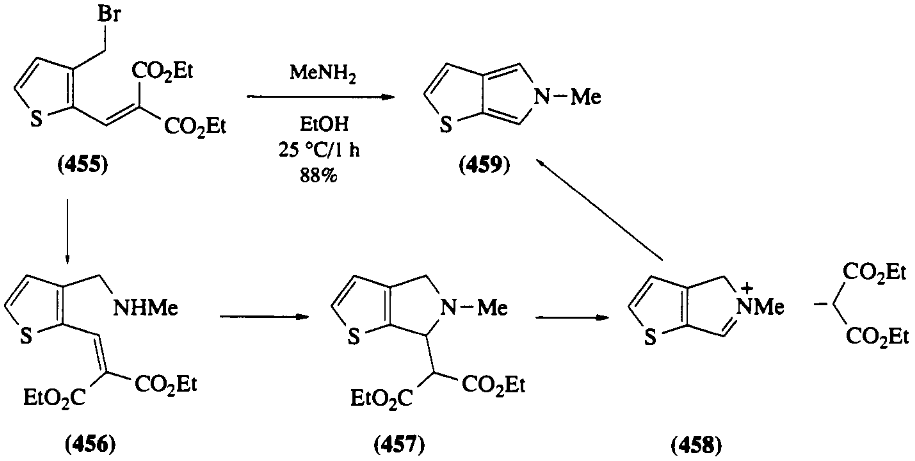
Br
CO$_2$Et
CO$_2$Et
S
(455)
MeNH$_2$
EtOH
25 °C/1 h
88%
N–Me
(459)
NHMe
EtO$_2$C
(456)
(457)
NMe
(458)

**Scheme 62**

## (iii) 6-Exo-trigonal cyclizations

Baldwin has shown that the 6-exo-trig process is a favorable one,[107c,107e] *e.g.* cyclization of the phenolic enone (**459**; equation 101) in base furnished (**460**) in good yield.[107e] An intramolecular addition of an amine to a chiral vinyl sulfoxide, a 6-exo-trig process, was used in the synthesis of canadine.[111] Reaction of (**461**; equation 102) produced a 3–4:1 mixture of (**462a**) and (**462b**), in which the former predominated.[111c] An interesting 6-exo-trig cyclization was thought to be responsible for the racemization of the chiral hydroxy acid (*R*)-(**463**) under base-catalyzed alkylation conditions to give (±)-(**464**).[112] It was suggested that the dianion (**465**; Scheme 63) racemized *via* a 6-exo-trig cyclization to give the bridged acid dianion (**466**) which opened up to a mixture of (**465**) and (**467**) and was then alkylated to give racemic (**464**).

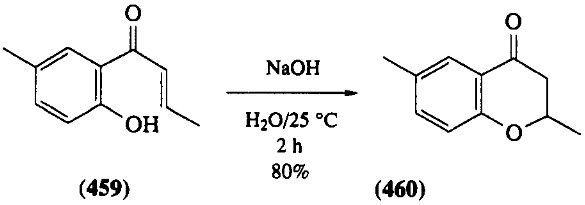
O
OH
(459)
NaOH
H$_2$O/25 °C
2 h
80%
O
O
(460)

(101)

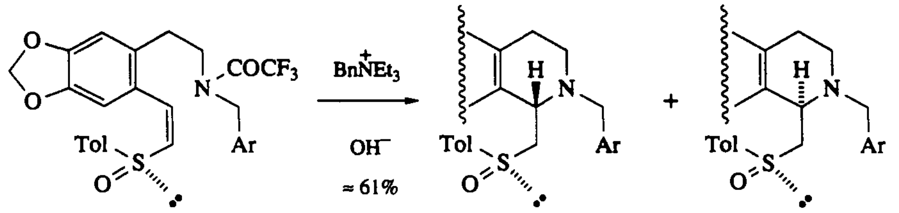

(102)

**(461)** **(462a)** 3–4:1 **(462b)**

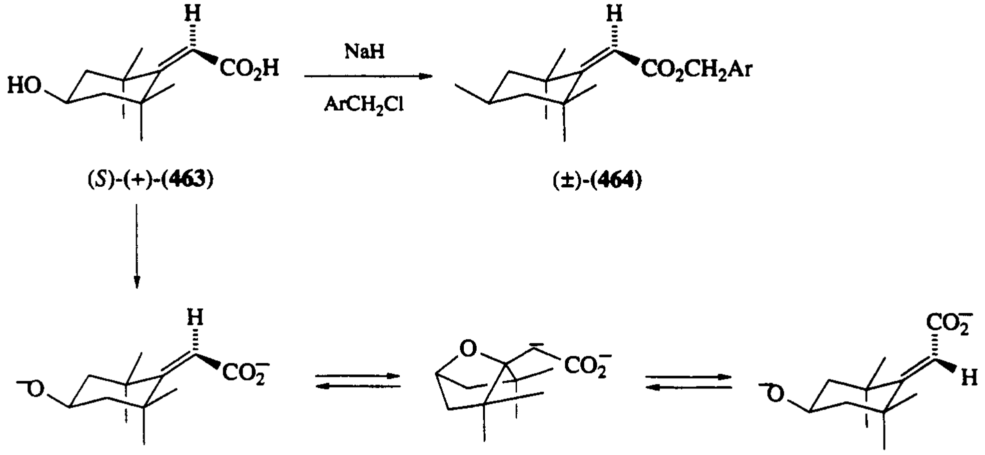

(*S*)-(+)-**(463)** (±)-**(464)**

**(465)** **(466)** **(467)**

Scheme 63

*(iv) 6-Endo-trigonal cyclizations*

These cyclizations are somewhat less common than those presented above but they are occasionally reported. In a recent forskolin synthesis, Ziegler reported the cyclization of (**468**; Scheme 64) to give (**470**) *via* a 6-endo-trig addition–elimination process involving the β-methoxy enone (**469**) as an intermediate.[113] A second 6-endo-trig addition–elimination process involves cyclization of (**471**; equation 103) with loss of benzenesulfinic acid to give (**472**).[114] Finally, a retro-6-endo-trig process was used to prepare a silyloxy diene for an intramolecular Diels–Alder reaction.[115] Treatment of *N*-methylpiperidone (**473**; Scheme 65) with acryloyl chloride and then Hünig's base produced the enone acrylamide (**474**), *via* a retro-6-endo-trig reaction. Silylation and thermal cyclization then afforded (**475**) in 72% yield.

*(v) 5-Endo-trigonal cyclizations*

Finally, it might be of interest to present one example of a formal violation of Baldwin's rules (since Baldwin uses the terms 'favored' and 'disfavored', there can be no violations of these rules, but only normally 'disfavored' reactions which proceed). We have reported[116] the formation of the cyclic keto alk-

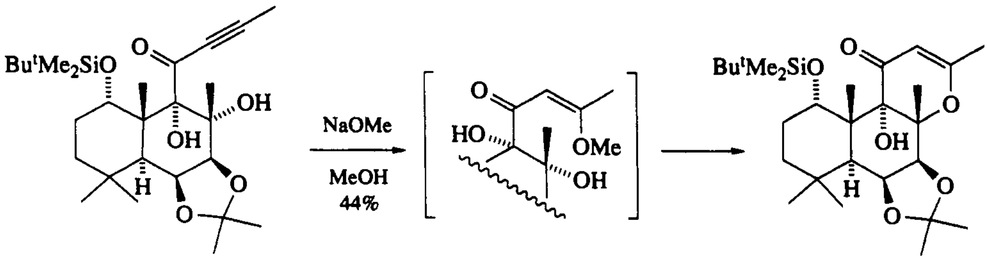

**(468)** **(469)** **(470)**

Scheme 64

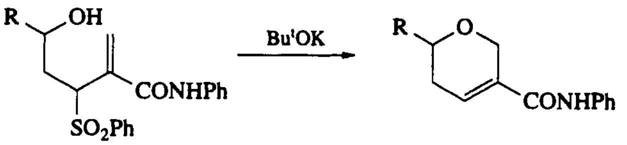

**(471)** **(472)**

(103)

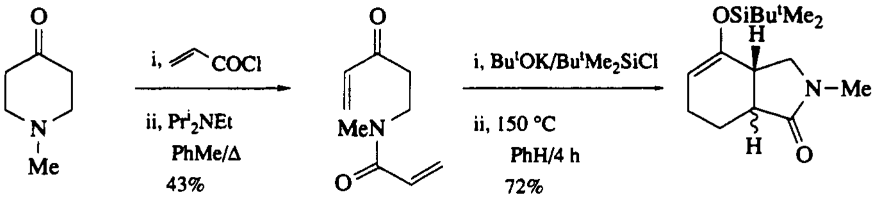

**(473)** **(474)** **(475)**

**Scheme 65**

enylammonium salt (**478**; Scheme 66) by treatment of the β-keto aldehyde anion (**476**) with tosyl (or mesyl) chloride in acetonitrile, a reaction that we suggest proceeds *via* the tosylate (**477**), which undergoes a 5-endo-trig cyclization and then elimination of the tosylate. The exact mechanism has not yet been proven.

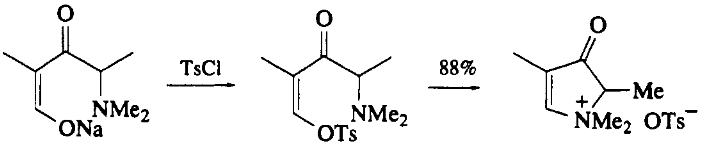

**(476)** **(477)** **(478)**

**Scheme 66**

## 1.1.3 ALKYNIC π-SYSTEMS

The addition of stabilized nucleophiles—both carbon and heteronucleophiles—to activated alkynes has been used far less often in organic synthesis than the corresponding addition to activated alkenes. Since several excellent reviews on nucleophilic additions to alkynes appeared in the 1960s and 1970s,[10] this section includes only a few representative examples from the early literature and some more recent applications.

### 1.1.3.1 Carbon Nucleophiles

#### *1.1.3.1.1 Intermolecular additions*

As mentioned early in this chapter, the first example of an addition of a stabilized carbon nucleophile to an activated alkyne was published by Michael in 1894 (see equation 2).[2] The addition of a β-keto ester (**2**) or β-diketone (**479**) to the alkynic ester (**10b**; equation 104) afforded the pyrone (**480a**) or (**480b**), respectively, by cyclization of the initial adduct.[117] Similarly, the addition of diethyl malonate (**1**) to an alkynic ketone (**481**; equation 105) afforded the pyrone-3-carboxylate (**482**) in good yield.[118] The yields of additions to alkynes are generally lower than with the corresponding alkenes, although in certain cases quite high yields of the initial Michael adduct can be obtained,[119] *e.g.* the cyanoacrylate (**485**; equation 106) is obtained from the addition of diphenylacetonitrile (**483**) to ethyl propiolate (**484**) in 92% yield[119a] and the ketoacrylate (**487**; Scheme 67) is produced from the tetrahydrophenanthrenone (**486**) and ethyl propiolate (**484**) in 83% yield.[119b] On heating in acid, the ketoacrylate (**487**) cyclizes to the pyrone (**488**). Depending on the reaction conditions, either the *cis* (kinetic) or *trans* (thermodynamic) enones can be obtained. For example, addition of the anion of the oxazolone (**152**; Scheme 68) to phenyl ethynyl ketone (**489**) produces initially the (*Z*)-product (*Z*)-(**490**), which can be isomerized thermally to the (*E*)-isomer (*E*)-(**490**).[120] The corresponding trifluoromethyl oxazolone (**491**; equation 107) adds to (**489**) at the aminal carbon rather than at the α-keto carbon to give (*Z*)-(**492**), which might find use as a method for the 1,4-addition of a trifluoroacetyl anion equivalent.[120] Dichloroacetylene (**493a**) (either preformed or formed *in situ* by reaction of trichloroethylene **493b** with base) is also sufficiently activated to react with stabilized nucleophiles, *e.g.* diethyl ethylmalonate (**494**), to give the dichlorovinyl product (**495**; Scheme 69).[121] Treatment with *t*-butyllithium affords the alkynic product (**496**), thus allowing for α-ethynylation of stabilized anions. The ethynyl iodonium salt (**498a**) reacts similarly with the enolate of β-diketone (**497**) to give the ethynylated product (**499**) in good yield (equation 108).[122a] However, a quite different product, namely (**500**; Scheme 70) has been obtained in 84% yield by the reaction of the corresponding 1-decynylphenyliodonium salt (**498b**) with (**497**) under similar conditions.[122b] In this latter reaction the initial addition occurs at the alkyl-substituted carbon to give the anion (**501**), which α-eliminates to the alkylidene carbene (**502**); insertion into the C—H bond then gives the cyclopentene (**500**). The reaction of the phenylsulfonylacetophenone (**503**; equation 109) with (**498b**) under the same conditions afforded the furan (**504**) in 67% yield *via* an analogous mechanism.[122b] The formation of (**499**) has now been shown to occur *via* the corresponding alkylidene carbene which undergoes a 1,2-phenyl migration.[122b]

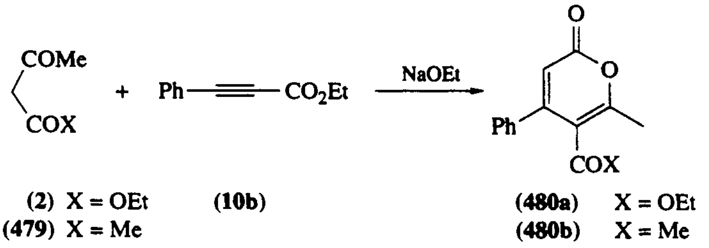
COMe
COX
+
Ph—≡—CO2Et
NaOEt
O
O
Ph
COX
(2) X = OEt
(479) X = Me
(10b)
(480a) X = OEt
(480b) X = Me

(104)

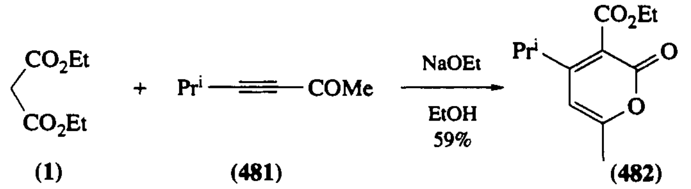
CO2Et
CO2Et
+
Pri—≡—COMe
NaOEt
EtOH
59%
CO2Et
Pri
O
O
(1)
(481)
(482)

(105)

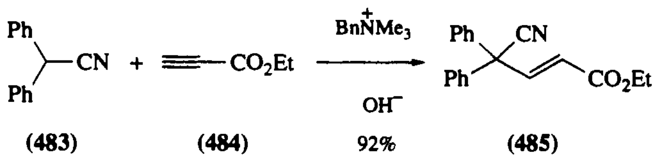
Ph
Ph
CN
+
≡—CO2Et
BnN+Me3
OH−
92%
Ph
Ph
CN
CO2Et
(483)
(484)
(485)

(106)

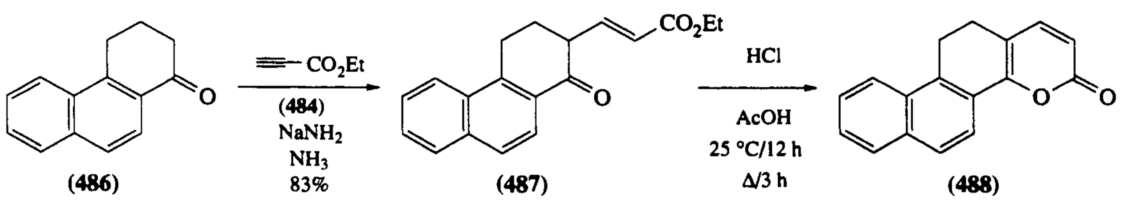
O
≡—CO2Et
(484)
NaNH2
NH3
83%
CO2Et
O
HCl
AcOH
25 °C/12 h
Δ/3 h
O
O
(486)
(487)
(488)

Scheme 67

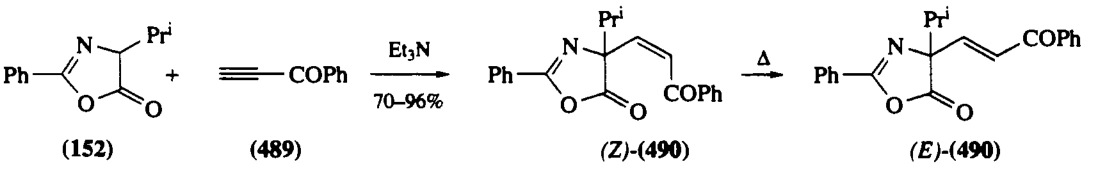
Ph
N
Pri
O
O
+
≡—COPh
Et3N
70–96%
Ph
N
Pri
O
O
COPh
Δ
Ph
N
Pri
O
O
COPh
(152)
(489)
(Z)-(490)
(E)-(490)

Scheme 68

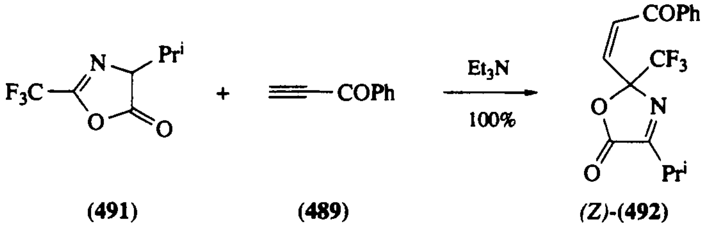
F3C
N
Pri
O
O
+
COPh
Et3N
100%
COPh
CF3
O
N
O
Pri
(491)
(489)
(Z)-(492)

(107)

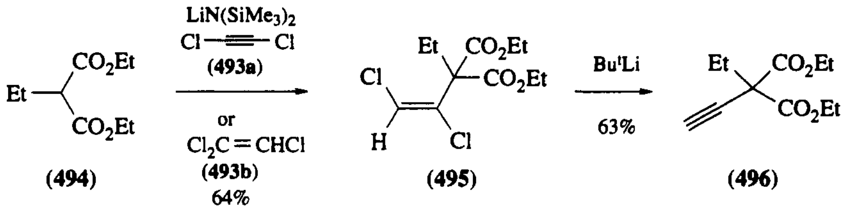
CO2Et
Et
CO2Et
(494)
LiN(SiMe3)2
Cl—≡—Cl
(493a)
or
Cl2C=CHCl
(493b)
64%
Et
CO2Et
Cl
CO2Et
H
Cl
(495)
ButLi
63%
Et
CO2Et
CO2Et
(496)

Scheme 69

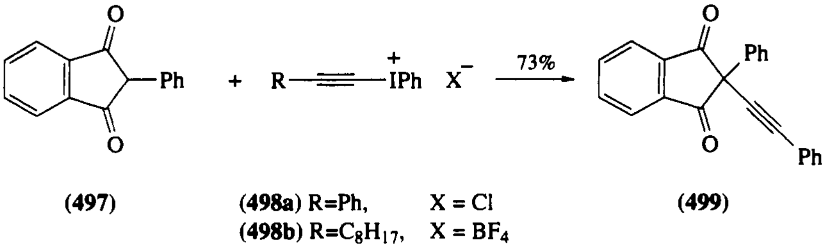
O
Ph
O
(497)
+
R—≡—IPh X
+
−
(498a) R=Ph, X = Cl
(498b) R=C8H17, X = BF4
73%
O
Ph
O
Ph
(499)

(108)

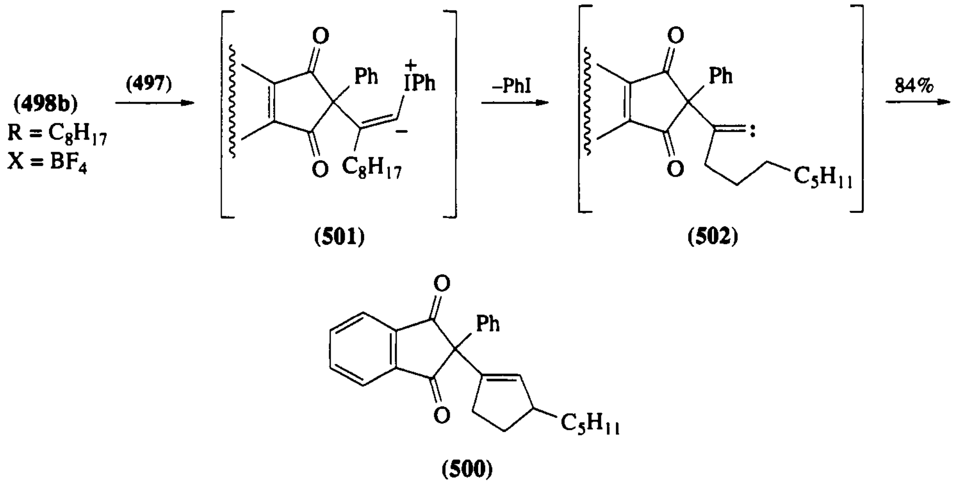
(498b)
R = C8H17
X = BF4
(497)
O
Ph
+
IPh
−
O
C8H17
(501)
-PhI
O
Ph
O
C5H11
(502)
84%
O
Ph
O
C5H11
(500)

Scheme 70

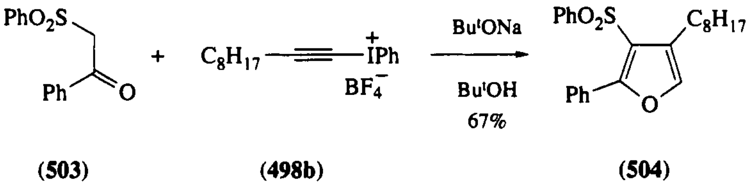
PhO2S
Ph
O
(503)
+
C8H17—≡—IPh
+
BF4−
(498b)
ButONa
ButOH
67%
PhO2S
C8H17
Ph
O
(504)

(109)

As with Michael additions to activated alkenes, the initial adducts with activated alkynes can be trapped by various processes. An aldol reaction can occur if a carbonyl is properly situated in the starting material (Scheme 71).[123] However, the use of methyl ethynyl ketone (**509**) and its homologs in the Robinson annulation process to give cyclohexadienones (**510**; equation 110) usually proceeds in poor yield,[124] presumably due to the fact that the enedione intermediate may be largely the (*E*)-isomer.[124b] However, alkoxyethynyl vinyl ketones (**511**; Scheme 72) give good yields of cyclic β-alkoxy enones (**513**) when reacted with diethyl malonate (**1**) in base, *via* internal trapping by proton transfer and an intramolecular Michael addition of the intermediate (**512**).[78a] This process was used in a synthesis of griseofulvin, as described earlier. A Dieckmann condensation can also serve as an internal trapping step. For example, reaction of dimethyl acetylenedicarboxylate (DMAD) (**514**; equation 111) with malononitrile (**39**) or ethyl cyanoacetate (**26**) in the presence of pyridine and acetic acid affords the salts (**515a**) or (**515b**), respectively, in good yield *via* an alkynic multiple Michael process followed by Dieckmann condensation.[125] However, the analogous condensation of (**514**) with dimethyl malonate (**56**; equation 112) under the same conditions afforded the seven-membered rings (**516a**) and (**516b**) in 63% and 4% yield, respectively.[125] These compounds are presumably formed by three consecutive intermolecular Michael additions followed by an intramolecular Michael addition to give the seven-membered rings (the last Michael addition being a 7-endo-trig cyclization).

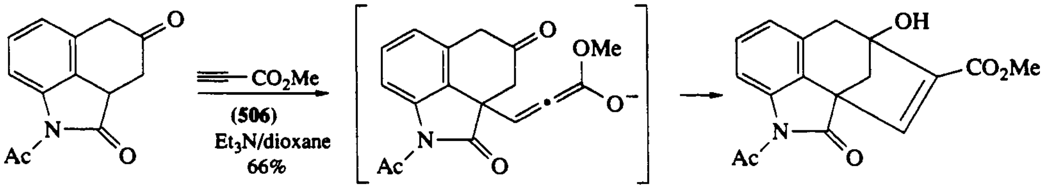
O
N
Ac
O
CO2Me
(506)
Et3N/dioxane
66%
O
OMe
O−
N
Ac
O
OH
CO2Me
N
Ac
O

(**505**) (**507**) (**508**)

Scheme 71

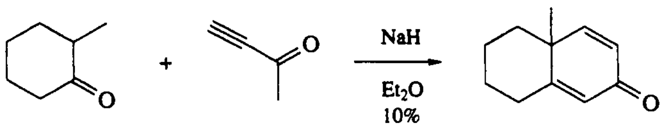
O
O
NaH
Et2O
10%
O

(**66**) (**509**) (**510**) (110)

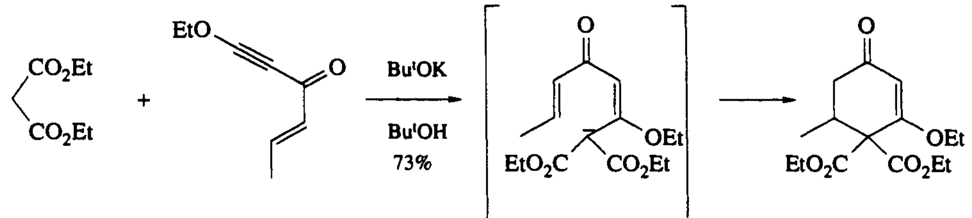
CO2Et
CO2Et
EtO
O
ButOK
ButOH
73%
O
OEt
EtO2C
CO2Et
O
OEt
EtO2C
CO2Et

(**1**) (**511**) (**512**) (**513**)

Scheme 72

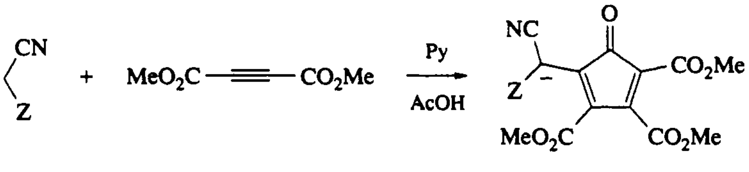
CN
Z
MeO2C
CO2Me
Py
AcOH
NC
Z
−
O
CO2Me
MeO2C
CO2Me

(111)

(**39**) Z = CN (**514**) 60% (**515a**) Z = CN

(**26**) Z = CO$_2$Et 68% (**515b**) Z = CO$_2$Et

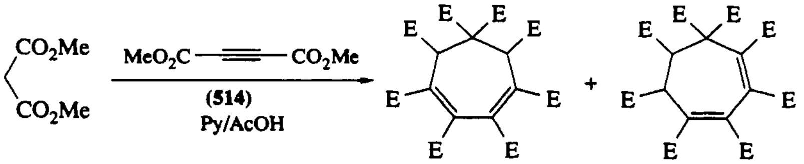
CO2Me
CO2Me
MeO2C
CO2Me
(514)
Py/AcOH
E
E
E
E
E
E
E
E
E
E
E
E
E
E
E
E

(112)

(**56**) (**516a**) 63% E = CO$_2$Me (**516b**) 4%

The reaction of enamines with alkynic esters has been used often in organic synthesis.[126] Enamines of aldehydes (**517**; Scheme 73) react with methyl or ethyl propiolate to give the 1-aminobutadiene-2-carboxylates (**519a,b**) by way of the cyclobutenes (**518a,b**).[126a] A similar reaction pathway is followed in the reaction of (**517**) with DMAD (**514**).[126b] Even enamines of β-diketones (β-amino enones) undergo this reaction to give analogous products which can then undergo further reactions.[126c] The reaction of enamines of cyclic ketones (**64**; Scheme 74) with methyl propiolate (**506**) or DMAD (**514**) at 90–110 °C affords the cyclic dienoates (**521a,b**), in which the ring has undergone a two-carbon expansion *via* the bicycloheptene intermediates (**520a,b**).[126a,126c,126e] By carrying out the addition at lower temperatures, the intermediate (**520a**) can be isolated.[126c,126e] Enamines of heterocyclic ketones, *e.g.* 3-piperidinoindole (**522a**; equation 113)[127a] or the 3-pyrrolidinodihydrothiophene (**522b**; equation 114),[127b] afford the corresponding seven-membered rings, (**523a**) and (**523b**), respectively, in excellent yields when heated with DMAD.[127] This type of two-carbon ring expansion of cyclic ketones has been used quite often in natural product synthesis.[128] It has also been applied to a variety of heterocyclic amino compounds to give products derived from similar reaction pathways.[129] Moreover, other nucleophilic alkenes can be used in place of enamines.[130] For example, the ynamine (**524**; equation 115) reacts with two equivalents of DMAD to give the aromatic product (**525**).[130a] The alkenic iminophosphoranes (**526**; equation 116), also, react with methyl propiolate or DMAD to give the ring-enlarged product (**527**).[130c,130d] Finally, the iminophosphoranes of certain ring systems, *e.g.* uracils, can give either simple Michael adducts or structurally rearranged products.[130e]

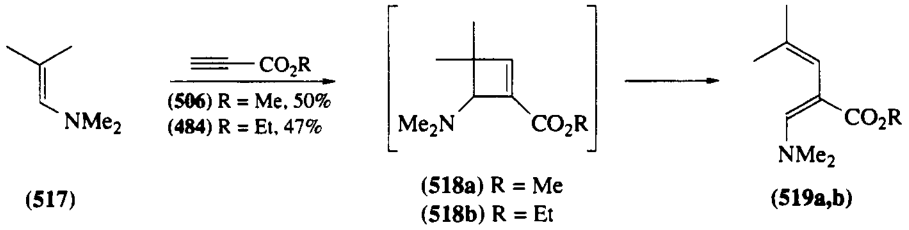

NMe$_2$
CO$_2$R
(**506**) R = Me, 50%
(**484**) R = Et, 47%
Me$_2$N
CO$_2$R
CO$_2$R
NMe$_2$
(**517**)
(**518a**) R = Me
(**518b**) R = Et
(**519a,b**)

**Scheme 73**

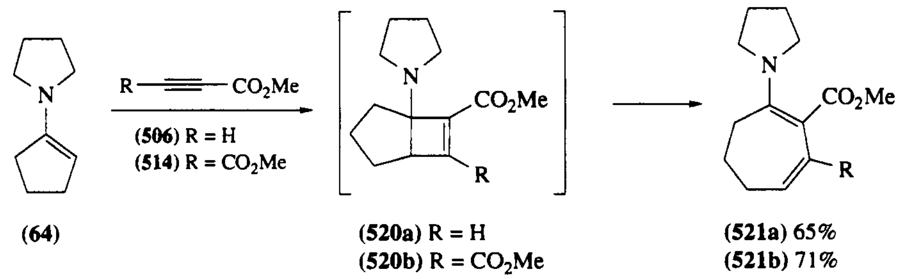

N
R
CO$_2$Me
(**506**) R = H
(**514**) R = CO$_2$Me
N
CO$_2$Me
R
N
CO$_2$Me
R
(**64**)
(**520a**) R = H
(**520b**) R = CO$_2$Me
(**521a**) 65%
(**521b**) 71%

**Scheme 74**

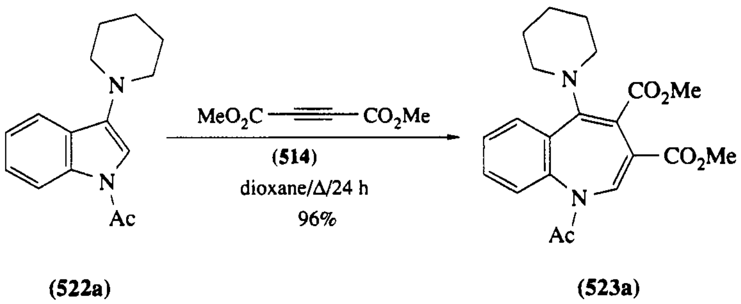

N
N
Ac
MeO$_2$C
CO$_2$Me
(**514**)
dioxane/Δ/24 h
96%
N
CO$_2$Me
CO$_2$Me
N
Ac
(**522a**)
(**523a**)

(113)

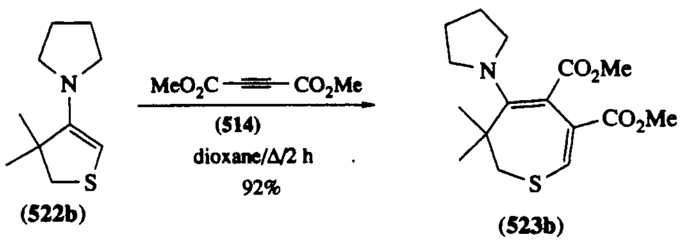
MeO2C≡CO2Me
(514)
dioxane/Δ/2 h
92%
N
S
CO2Me
CO2Me

(522b) (523b) (114)

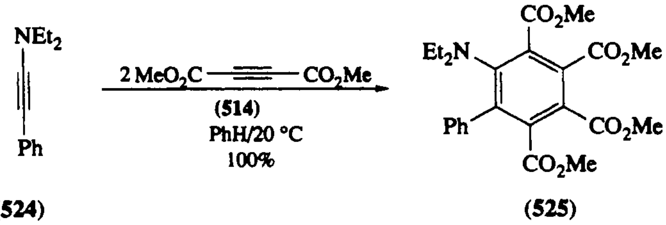
NEt2
Ph
2 MeO2C≡CO2Me
(514)
PhH/20 °C
100%
Et2N
Ph
CO2Me
CO2Me
CO2Me
CO2Me

(524) (525) (115)

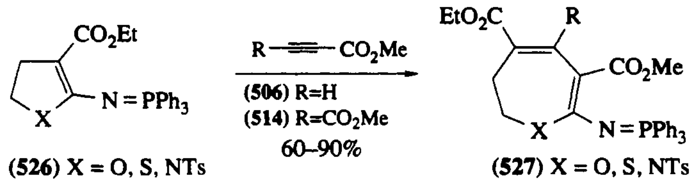
CO2Et
N = PPh3
X
R≡CO2Me
(506) R=H
(514) R=CO2Me
60–90%
EtO2C
R
CO2Me
N = PPh3

(526) X = O, S, NTs (527) X = O, S, NTs (116)

### 1.1.3.1.2 Intramolecular additions

There are only a few examples of intramolecular addition of a stabilized carbon nucleophile to an activated alkyne, one of these being in Trost's synthesis of hirsutic acid C, where basic treatment of the ketopropiolate (**528**; equation 117) at 110 °C resulted in a 65–70% yield of the bicyclic ketoacrylate (**529**), *via* a 5-exo-digonal cyclization.[76] Even though 5- and 6-endo-digonal cyclizations would be expected to be disfavored because of the inhibition of resonance stabilization of the enolate, due to angle strain (an allenic system in a five- or six-membered ring), under the right conditions they can be made to occur in high yields (*via* the vinyl anion not stabilized by resonance). For example, Deslongchamps has reported the formation of the hydrindenediones and the octalinediones, (**531a**) and (**531b**), respectively, from the corresponding β-keto ester ynones (**530a,b**) in very high yields (equation 118).[131] The reaction works poorly for the formation of the corresponding seven- and eight-membered systems.[131] However, this type of *endo* cyclization has not generally been seen in other systems. For instance, treatment of the ester ynamide (**532**; Scheme 75) with base did not afford the desired Michael adduct (**533a**) but rather the so-called 'anti-Michael' product (**533b**) and its endocyclic double-bonded isomer (**533c**).[86] Likewise, treatment of bis(phenylethynyl) ketone (**534**; equation 119) with ethyl acetoacetate (**2**) under basic conditions affords the 'anti-Michael' product (**535**) in 68% yield *via* a normal intermolecular Michael addition followed by an intramolecular 'anti-Michael' addition.[132]

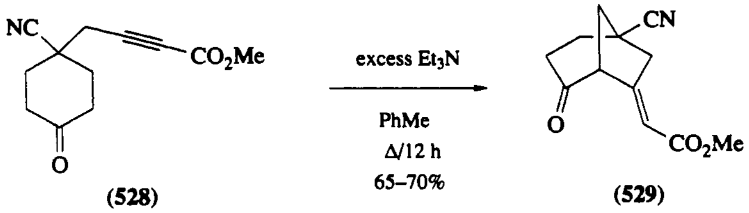
NC
CO2Me
O
excess Et3N
PhMe
Δ/12 h
65–70%
CN
O
CO2Me

(528) (529) (117)

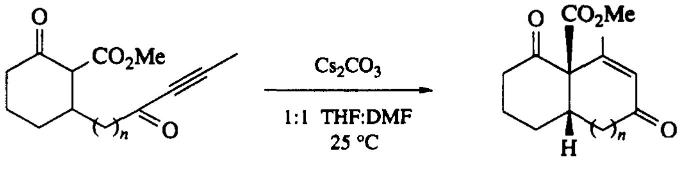

(118)

**(530a)** *n* = 0 82% **(531a)**
**(530b)** *n* = 1 89% **(531b)**

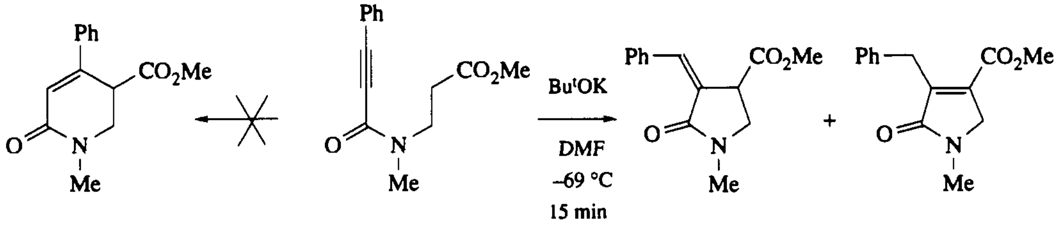

**(533a)** **(532)** **(533b)** 4% 48% **(533c)**

**Scheme 75**

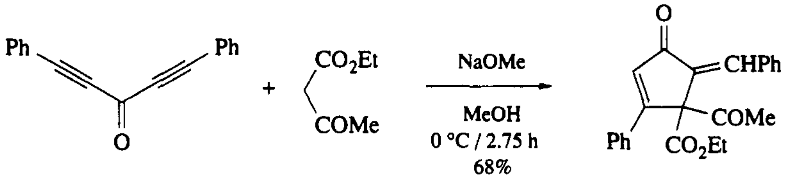

(119)

**(534)** **(2)** **(535)**

## 1.1.3.2 Heteronucleophiles

Since several excellent reviews summarize the literature in this area up to about 1970,[10] only a few representative examples from the older literature and some more recent applications are presented here.

### *1.1.3.2.1 Intermolecular additions*

Michael was to first report, in 1896, the 1,4-addition of a heteronucleophile, namely the addition of ethoxide to diethyl acetylenedicarboxylate (**10a**) to give (**536**; equation 120).[133] As with the Michael addition, many electron-withdrawing groups have been used to activate the alkyne for addition—esters, aldehydes, ketones, nitriles, sulfones and so on. The number of heteronucleophiles used is quite extensive, including alcohols, amines (primary, secondary and tertiary), thiols, selenols, tellurols, halides, phosphines, phosphites, hydrazines and so on. The addition can be highly stereoselective or nearly stereorandom depending on the reaction conditions. The best mechanistic explanation for the large body of stereochemical results is as follows. Initial attack of the nucleophile on an activated alkyne (**A**; Scheme 76) occurs in an *anti* fashion to give the (*Z*)-vinyl anion (**B**) in preference to the (*E*)-vinyl anion (**C**).[134] If protonation is faster under the reaction conditions than equilibration, this compound leads to the (*Z*)-isomer (**D**) *via* overall *anti* addition.[135] This initially formed (*Z*)-vinyl anion (**B**) can isomerize to the (*E*)-vinyl anion (**C**) by way of the linear *sp*-hybridized anion (**E**) and its various resonance contributors (*e.g.* for Z = CO$_2$R, COR, *etc.*). If protonation is slow compared to equilibration, the more stable of the two products will be obtained—usually (**F**) when the nucleophile is alkoxide or a secondary or tertiary amine, but (**D**) when the nucleophile is a primary amine (due to internal hydrogen bonding). The relative rates of isomerization versus protonation will be directly dependent on the ability of the activating group Z to stabilize by resonance (*i.e.* to stabilize the linear anion E)[134d] and on the ability of the solvent to donate a proton to the anion. Thus, additions carried out in protic solvents tend to give a higher proportion of *anti* addition than those done in aprotic solvents, and alkynes activated by inductively stabilizing groups (sulfonyl, cyano) tend to give more *anti* addition. Finally, there is a second equilibration mechanism possible in certain cases, namely the direct isomerization of (C) and (F) *via* the intermediacy of the zwitterionic form (G) which can rotate about the central C—C single bond to lead to either product. A good discussion of this process for the addition of trialkylamines to various activated alkynes has recently been published.[136] This mechanistic picture can readily explain otherwise somewhat contradictory results.

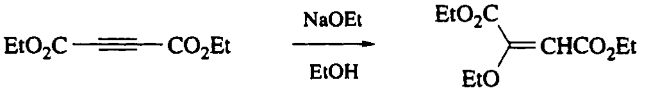

(120)

**(10a)** **(536)**

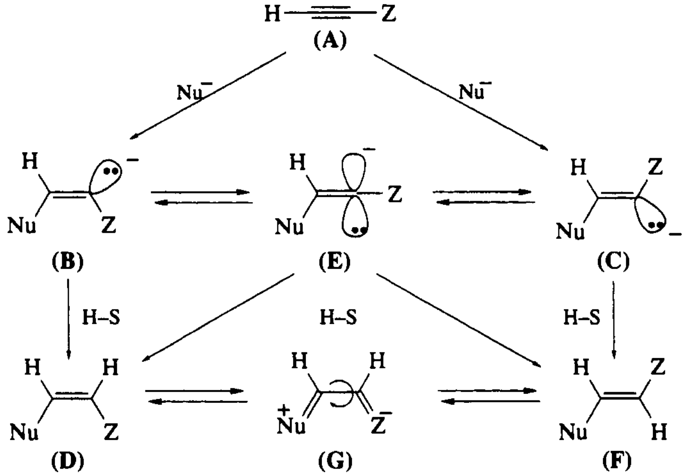

Scheme 76

Base-catalyzed addition of an alcohol[137] to methyl propiolate (**506**; equation 121) usually gives nearly exclusively the (*E*)-isomer (*E*)-(**537**),[137a] although under very weakly basic conditions a 2:1 mixture favoring the (*Z*)-isomer has been obtained.[137c] However, with DMAD (**514**) under certain conditions the (*Z*)-isomer (*Z*)-(**538**) predominates.[137a] An interesting rearrangement was initiated by addition of the alkoxide of the 3-hydroxy-*N*-phenylpyridine betaine (**539**; Scheme 77) with DMAD to give the furan (**543**), *via* the initial 1,4-adduct (**540**).[137g]

The addition of amines to activated alkynes leads to either the (*E*)- or (*Z*)-isomer with fairly high stereoselectivity based on the substitution pattern of the amine.[138] Primary amines add to alkynic ketones and propiolates (equation 122) to give an equilibrium mixture favoring the (*Z*)-isomer,[138a,138c] although there are reports of selective formation of the (*E*)-isomers.[138f] Secondary amines also afford an equilibrium mixture of (*E*)- and (*Z*)-isomers, but greatly favoring the (*E*)-isomer often to the exclusion of the (*Z*)-isomer (equation 123).[139] Addition of the chiral C(2)-symmetric pyrrolidine (**550**; Scheme 78) to the ester (**551**) gave in essentially quantitative yield the (*E*)-isomer which was cyclized with fluoride to furnish the lactone (**552**) in 94% overall yield. Alkylation of the anion of (**552**) proceeded with very high diastereoselectivity to give (**553**) as the major isomer.[139f] The use of aziridine[140] in protic solvents furnishes a higher proportion of the (*Z*)-isomer (*Z*)-(**554**), due to inhibition of the isomerization of the kinetic (*Z*)-isomer into the (*E*)-isomer *via* a zwitterionic intermediate (equation 124). With alkynic sulfones the proportion of the (*Z*)-isomer can be very high (equation 125).[138d] The addition of the 2-vinylaziridine (**427**; Scheme 79) to DMAD (**514**) at –20 °C produced the dihydroazepine (**558**) in 95% yield,

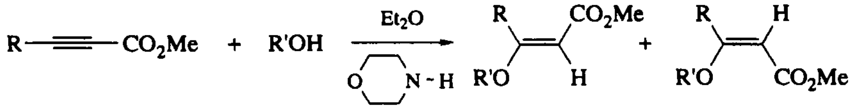

(121)

| | | | | | |
|---|---|---|---|---|---|
| (**506**) R = H | R' = Pr$^i$ | 87% | (*E*)-(**537**) | 100:0 | (*Z*)-(**537**) |
| (**514**) R = CO$_2$Me | R' = Me | 92% | (*E*)-(**538**) | 10:90 | (*Z*)-(**538**) |

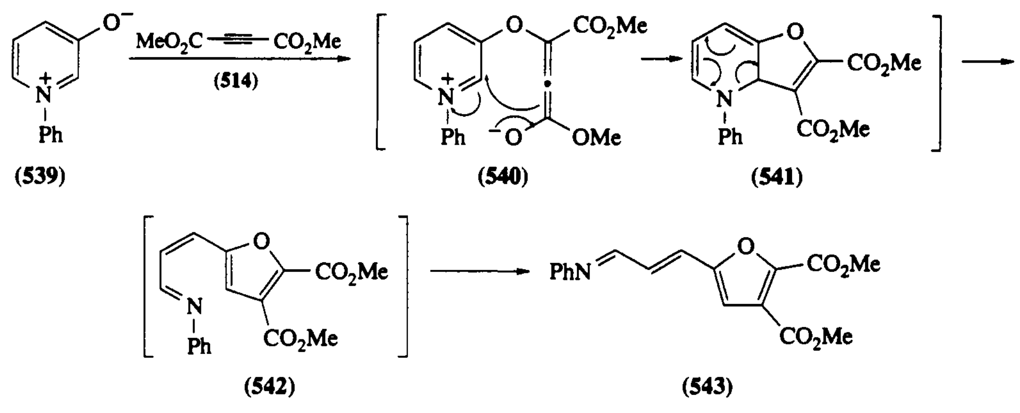

Scheme 77

presumably *via* a [3,3] sigmatropic rearrangement of the initially formed zwitterion (**557**) from 1,4-addition.[100a] The addition of trialkylammonium salts[141] to activated alkynes in methanol can give either exclusive (*E*)- or (*Z*)-isomers or a mixture, depending on the activating group. With the ketone (**509**; equation 126) only the (*E*)-isomer (*E*)-(**560**) is formed, while with the nitrile (**559**), only the (*Z*)-isomer (*Z*)-(**561**) is produced. With propiolate (**506**), a nearly 1:1 mixture of (*E*)- and (*Z*)-(**562**) is obtained.[136] These results are easily explained by analysis of the ability of the activating group to stabilize the linear form of the initially formed Zq(*Z*)-vinyl anion.[134d] Thus the inductively stabilizing nitrile group isomerizes slowly and is directly protonated before equilibration to give the (*Z*)-isomer, while the resonance-stabilizing ketone allows rapid and complete equilibration and only the (*E*)-isomer is formed. The ester lies between these two extremes. This work[136] furnishes the best experimental evidence for the theoretical calculations of vinyl anion stability.[134d]

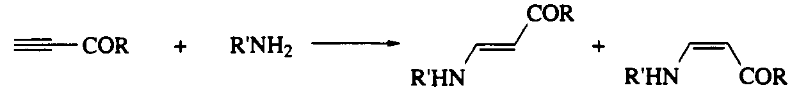

(122)

| | | | | | |
|---|---|---|---|---|---|
| (**506**) R = OMe | R' = Bu$^t$ | 64% | (*E*)-(**544**) | 0:100 | (*Z*)-(**544**) |
| (**506**) R = OMe | R' = *c*-hexyl | | (*E*)-(**545**) | 15:85 | (*Z*)-(**545**) |
| (**489**) R = Ph | R' = Bn | 98% | (*E*)-(**546**) | 0:100 | (*Z*)-(**546**) |

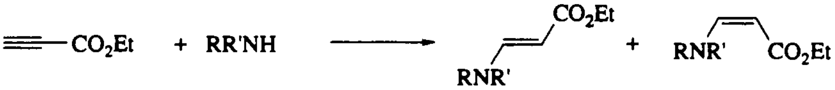

(123)

| | | | | | |
|---|---|---|---|---|---|
| (**484**) | R = R' = $(CH_2)_4$ | >95% | (*E*)-(**547**) | 100:0 | (*Z*)-(**547**) |
| | R = R' = Pr$^i$ | 90% | (*E*)-(**548**) | 100:0 | (*Z*)-(**548**) |
| | R = Me, R' = $CH_2CO_2Et$ | 90% | (*E*)-(**549**) | 100:0 | (*Z*)-(**549**) |

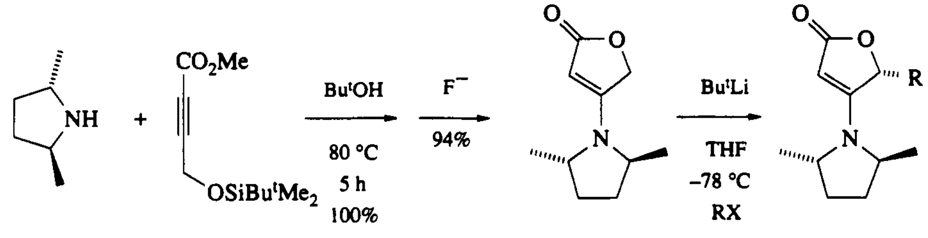

(**550**) (**551**) (**552**) (**553**)

R = Me, 97:3

Scheme 78

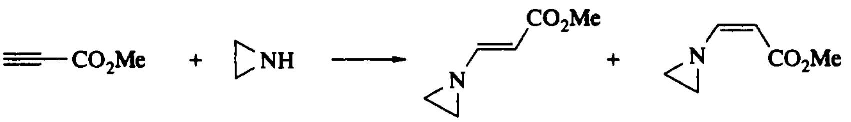

(124)

| | | | | |
|---|---|---|---|---|
| **(506)** | DMF | (*E*)-**(554)** | 97:3 | (*Z*)-**(554)** |
| | MeOH | | 47:53 | |

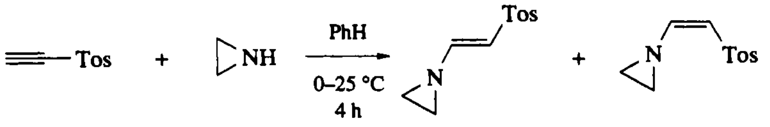

(125)

**(555)** (*E*)-**(556)** 5:95 (*Z*)-**(556)**

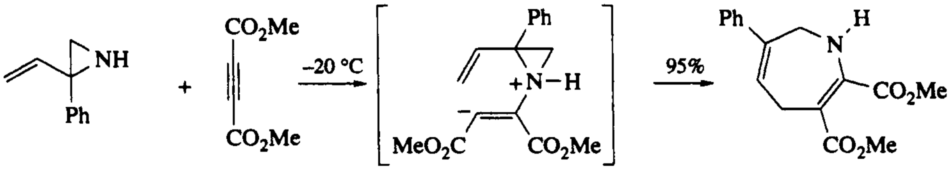

**(427)** **(514)** **(557)** **(558)**

**Scheme 79**

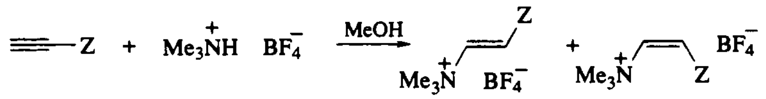

(126)

| | | | | |
|---|---|---|---|---|
| **(509)** Z = COMe | 25 °C/8 h | (*E*)-**(560)** | 100:0 | (*Z*)-**(560)** |
| **(559)** Z = CN | 25 °C/18 h | (*E*)-**(561)** | 0:100 | (*Z*)-**(561)** |
| **(506)** Z = $CO_2Me$ | 65 °C/24 h | (*E*)-**(562)** | 57:43 | (*Z*)-**(562)** |

The additions of thiol anions, selenides and tellurides are all highly selective for the (*Z*)-isomers, exclusively so for the selenides and tellurides.[142] For example, addition to (**10b**) gives primarily the (*Z*)-isomer (equation 127).[142a,142e,142l] The addition of dithiolate, dithiocarbamate and dithiocarbonate salts also occurs with high (*Z*)-selectivity in acetic acid/acetonitrile[142p] to give (*Z*)-(**566**; equation 128), but dithioic acids give mixtures enriched in the (*E*)-isomer (*E*)-(**567**) in carbon tetrachloride.[142g] The addition of thiols to activated alkynes has been used in a clever stereospecific trisubstituted alkene synthesis.[142b] Addition of thiophenoxide to the alkynic ester (**568**; Scheme 80) gives exclusively the (*Z*)-isomer (**569**), which is converted into the (E)-trisubstituted alkene (**570**) *via* copper-promoted Grignard addition. The kinetic (*Z*)-vinyl anion initially produced can be trapped with benzaldehyde to afford mainly the product of *anti* addition (*Z*)-(**571**; equation 129).[142k]

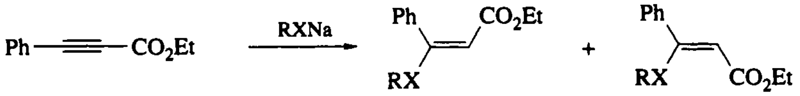

(127)

| | | | | | |
|---|---|---|---|---|---|
| **(10b)** | RX = PhS | 85% | (*E*)-**(563)** | 1:5 | (*Z*)-**(563)** |
| | TolS | 33% | (*E*)-**(564)** | 0:100 | (*Z*)-**(564)** |
| | PhSe | 85% | (*E*)-**(565)** | 0:100 | (*Z*)-**(565)** |

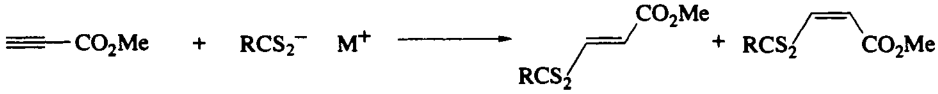

(128)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **(506)** | R = Ph | M = $Et_3NH$ | AcOH/MeCN | 88% | (*E*)-**(566)** | 0:100 | (*Z*)-**(566)** |
| | R = Me | M = H | $CCl_4/\Delta$ | | (*E*)-**(567)** | 95:5 | (*Z*)-**(567)** |

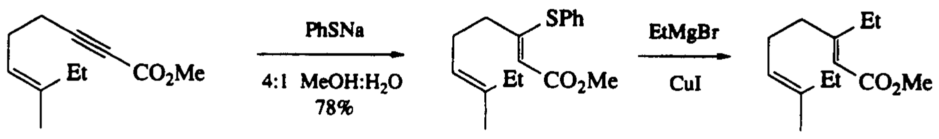
PhSNa
4:1 MeOH:H₂O
78%
EtMgBr
CuI
Et
CO₂Me
SPh

**(568)** **(569)** **(570)**

**Scheme 80**

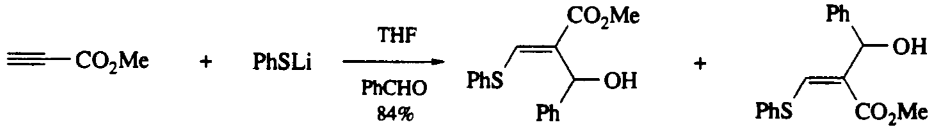
CO₂Me
PhSLi
THF
PhCHO
84%
PhS
OH
Ph

**(506)** *(E)*-**(571)** 17:83 *(Z)*-**(571)** (129)

The addition of hydrogen halides to propiolic acid (**572**; equation 130) occurs by overall *anti* addition to furnish cleanly the (*Z*)-isomer of (**573**).[143] This product can also be formed in 80% yield by refluxing the acid (**572**) with methylmagnesium iodide in THF and quenching with glacial acetic acid.[143c] *N*,*N*-Dialkylhydrazines add to propiolic acid (**572**) to give the betaine (**574**),[144a] but when added to methyl propiolate (**506**) or DMAD (**514**) afford the cyclic betaines (**575**; equation 131).[144b] Hydrazine and *N*-alkylhydrazines produce the corresponding pyrazolin-5-one.[144c]

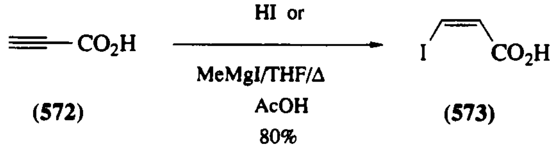
HI or
MeMgI/THF/Δ
AcOH
80%
CO₂H
I

**(572)** **(573)** (130)

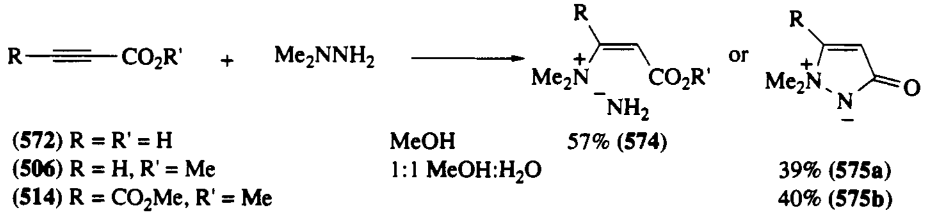
R
CO₂R'
Me₂NNH₂
Me₂N
NH₂
or
O
N
MeOH
1:1 MeOH:H₂O
57% (574)
39% (575a)
40% (575b)

(131)

(**572**) R = R' = H

(**506**) R = H, R' = Me

(**514**) R = $CO_2Me$, R' = Me

Trialkylphosphines add *via anti* addition to give the expected salts (**577**; Scheme 81) which decompose upon work-up to products (**578**) not containing phosphorus.[145a] Triethyl phosphite (equation 132) reacts with propiolic acid (**572**) or methyl propiolate (**506**) to give predominately (>90%) the β-phosphono ester (**579**) with the (*E*)-configuration.[145b]

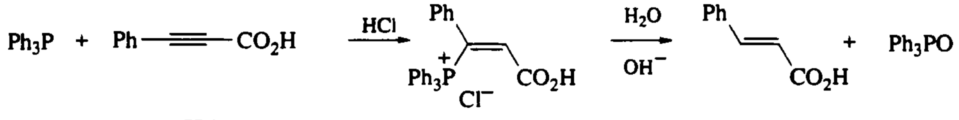
Ph₃P
Ph
CO₂H
HCl
Cl⁻
H₂O
OH⁻
Ph₃PO

**(576)** **(577)** **(578)**

**Scheme 81**

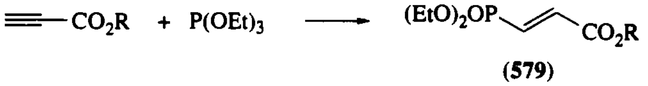
CO₂R
P(OEt)₃
(EtO)₂OP

(132)

(**579**)

(**572**) R = H R = H

(**506**) R = Me R = Me

Finally, a recent paper reports that under kinetic conditions (25 °C/6 h) phenoxide and thiophenoxide add to benzoyl(trifluoromethyl)acetylene (**580**; equation 133), 1,4 to the trifluoromethyl group rather than 1,4 to the benzoyl group (so-called 'anti-Michael' addition), to give the (*Z*)-addition products (**581**) in high yields. Under thermodynamic conditions (150 °C/24 h) a nearly 1:1 mixture of the regioisomeric adducts is produced.[146]

The initial vinyl anion produced can be trapped in several ways. One particularly useful intramolecular trapping involves the condensation of an α-amino, α-hydroxy or α-mercapto ketone with an activated alkynes to produce the heterocyclic aromatic compounds in one or two steps in good yield.[147] For example, condensation of the anilino ketone (**582**; equation 134) with methyl propiolate or DMAD produces the pyrroles (**583a,b**) in good yield.[147b] Similar processes in which the vinyl anion condenses on a ketone to form the C(3)–C(4) bond have been described often in the literature.[147a,147c,147d] However, the condensation of methyl *N*-ethylglycinate (**584**; equation 135) and DMAD affords the 3-hydroxypyrrole (**585**) *via* a Dieckmann condensation to form the C(2)–C(3) bond rather than the C(3)–C(4) bond.[147e] In this case and the following, one of the DMAD ester groups serves as the electrophile in the subsequent cyclization process. Quinolones (**588**; Scheme 82) can also be formed in two steps by condensing the anthranilate (**586**) with DMAD to give the anilinofumarate (**587**), which on pyrolysis affords the quinolone (**588**).[147c] Condensation of the enamino ketone (**589**; Scheme 83) with DMAD gives the amino fumarate (**590**) which on heating in methanol produces the pyrrolone (**591**).[147a] Furans can also be prepared by this general route. Condensation of benzoin (**592**; Scheme 84) with DMAD in the presence of potassium carbonate yields the hydroxydihydrofuran (**593**) which can be dehydrated to the furan (**594**) in 90% yield on heating with acidic methanol.[147a] The formation of thiophenes by this process shows this dichotomy of cyclization modes. Treatment of mercaptoacetone (**595**; Scheme 85) with methyl propiolate and molar quantities of potassium *t*-butoxide in DMSO furnishes only 2-acetyl-3-hydroxythiophene (**597**) by way of a Dieckmann-like condensation of the (*Z*)-isomer (*Z*)-(**596**). The use of catalytic quantities of base, however, gives a very different mixture of products in which the (*E*)-isomer of the initial adduct (*E*)-(**596**) and its condensation product (anion α to ester condensing on to the ketone) (**598**) predominate.[147f] Several other heterocyclic systems have been produced by similar chemistry.[147g]

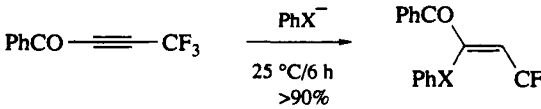

(133)

(**580**) (**581**) X = O, S

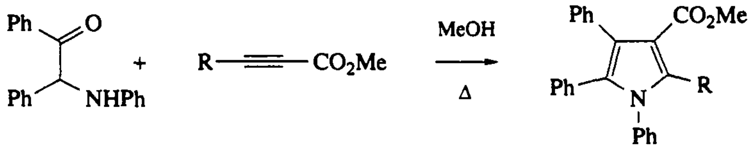

(134)

(**582**)

(**506**) R = H 2 h/79% (**583a**) R = H

(**514**) R = CO$_2$Me 16 h/70% (**583b**) R = CO$_2$Me

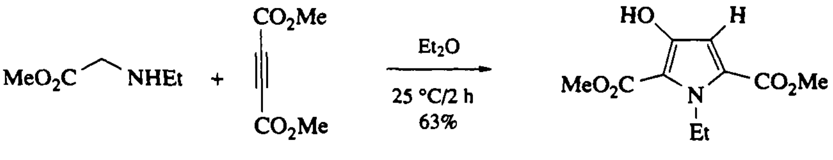

(135)

(**584**) (**514**) (**585**)

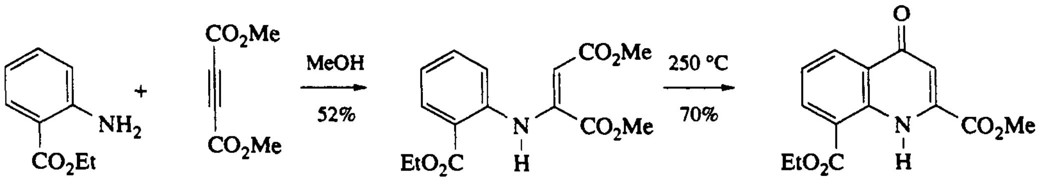

(**586**) (**514**) (**587**) (**588**)

**Scheme 82**

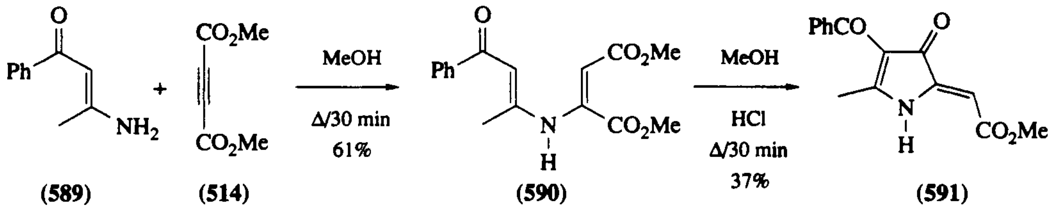
Ph
NH2
CO2Me
CO2Me
MeOH
Δ/30 min
61%
CO2Me
CO2Me
N
H
MeOH
HCl
Δ/30 min
37%
PhCO
O
N
H
CO2Me
(589)
(514)
(590)
(591)

Scheme 83

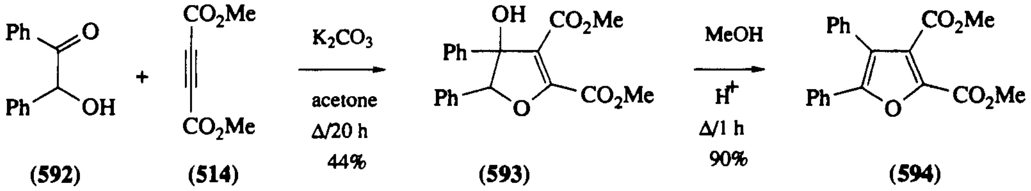
Ph
O
Ph
OH
CO2Me
CO2Me
K2CO3
acetone
Δ/20 h
44%
OH
CO2Me
Ph
Ph
O
CO2Me
MeOH
H+
Δ/1 h
90%
Ph
CO2Me
Ph
O
CO2Me
(592)
(514)
(593)
(594)

Scheme 84

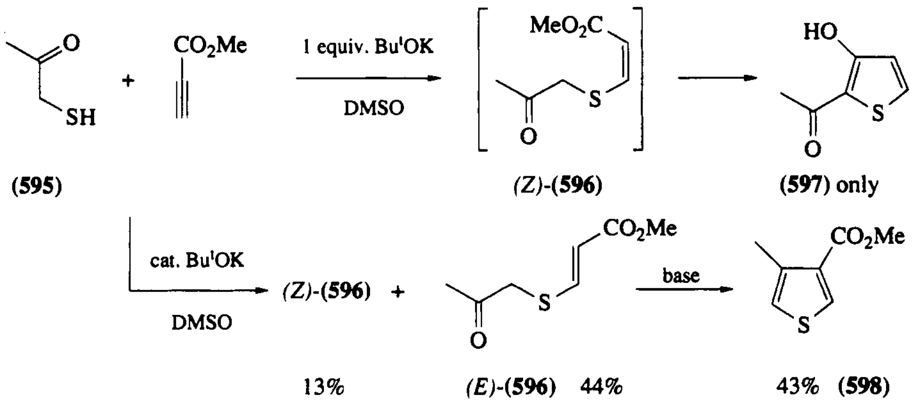
O
SH
CO2Me
1 equiv. BuᵗOK
DMSO
MeO2C
S
O
HO
S
O
(595)
(Z)-(596)
(597) only
cat. BuᵗOK
DMSO
(Z)-(596) +
CO2Me
S
O
base
CO2Me
S
13%
(E)-(596) 44%
43% (598)

Scheme 85

### *1.1.3.2.2 Intramolecular additions*

A number of intramolecular additions of heteronucleophiles to activated alkynes have been reported to give heterocyclic systems. For example, the addition of water, hydrogen sulfide or primary amines to the disubstituted diethynyl ketones (**598**; equation 136) furnish the pyrones (**599**) in good yields, *via* a 6-endo-digonal cyclization.[132,148] In certain cases (especially when R = Ph), the 'anti-Michael' products (**600**) can predominate.[132a] Reaction of the ethynyl amide or ketone, (**601a**) or (**601b**), respectively, with isothiocyanate or carbon disulfide (quenching with methyl iodide) gives exclusively the 'anti-Michael' products (**602a**) and (**602b**) from the amide (**601a**) but mainly the Michael products (**603**), rather than (**604**), from the ketone (**601b**; Scheme 86).[149] Treatment of the dihydroxy alkynic ketone (**605**; equation 137) with cesium carbonate in acetonitrile gives exclusively the furanone (**606**) *via* a 5-endo-digonal cyclization, rather than the product of the 6-endo-digonal cyclization (**607**).[113] An interesting 8-endo-digonal cyclization of an alkoxide is a key step in the formation of the oxocenone (**610**; Scheme 87) from the lactone (**608**), which presumably proceeds *via* the anion (**609**).[150]

## 1.1.4 ALLENIC π-SYSTEMS

Nucleophilic additions to activated allenes have been reported fairly often. Since there are several good recent reviews of this area,[151] only a brief overview is given here.

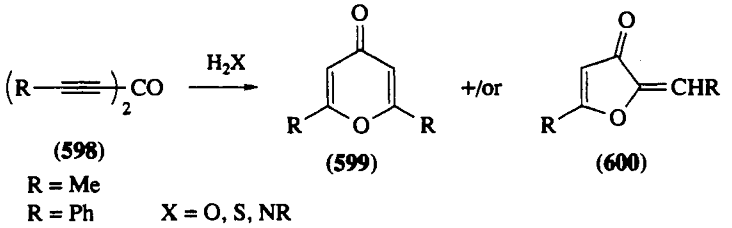
(598)
R = Me
R = Ph
H2X
X = O, S, NR
(599)
+/or
(600)
CHR

(136)

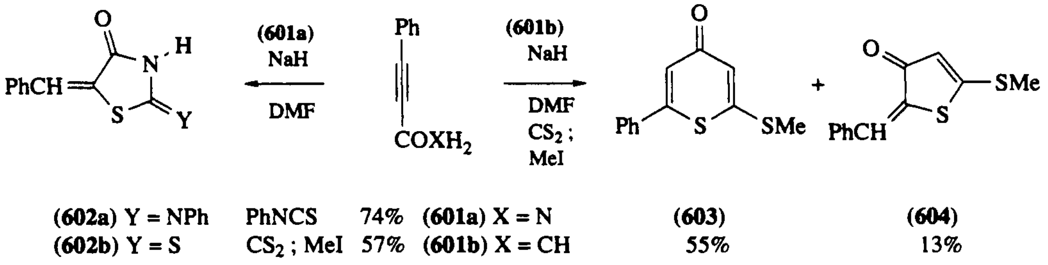
(601a)
NaH
DMF
(601b)
NaH
DMF
CS2 ; MeI
COXH2
SMe
PhCH
(602a) Y = NPh PhNCS 74% (601a) X = N
(602b) Y = S CS2 ; MeI 57% (601b) X = CH
(603) 55%
(604) 13%

Scheme 86

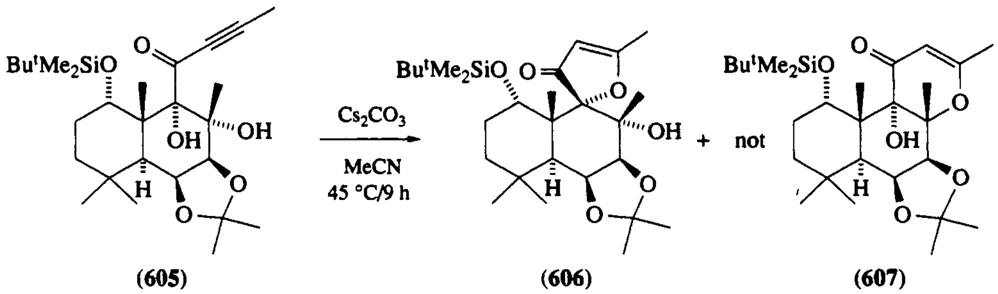
Bu^tMe2SiO
Cs2CO3
MeCN
45 °C/9 h
not
(605)
(606)
(607)

(137)

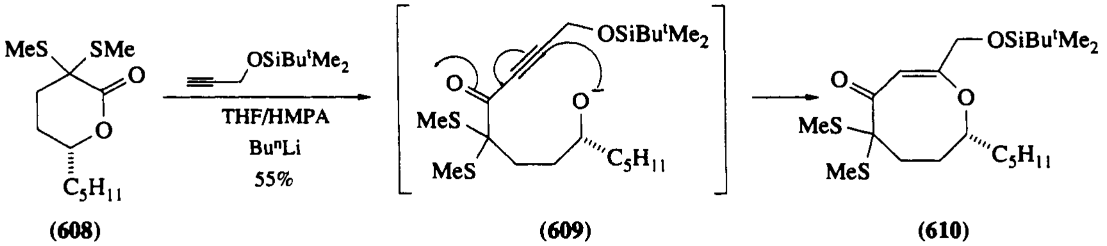
MeS
SMe
OSiBu^tMe2
THF/HMPA
Bu^nLi
55%
C5H11
(608)
(609)
(610)

Scheme 87

### 1.1.4.1 Carbon Nucleophiles

Stabilized carbon nucleophiles add to the central carbon of activated allenes.[152] For example, addition of the enamine (**611**; Scheme 88) to diethyl allenedicarboxylate (**612**), followed by heating with acetic acid, affords the pyridone (**614**) in 70% yield *via* the intermediate (**613**).[152a] A more substituted fumarate was used in this process in the key step of a synthesis of camptothecin.[152b] A second approach to camptothecin used a pyridone synthesis based on the reaction of an imine of pyruvate (**615**; equation 138) with dimethyl allenedicarboxylate (**616**) to give (**617**).[152c] The addition of simple nucleophiles also works well, *e.g*. the formation of (**619**; equation 139) in 71% yield from (**1**) and (**618**).[153a] The additions of acylaminomalonates (**620**; equation 140) to the nitrile (**618**) or the ester (**621**) afford the unconjugated products (**622**) in very high yields.[153b] Addition of β-keto esters or β-diketones to the allenic dimethylsulfonium salt (**623**; equation 141) (prepared *in situ* from the corresponding propargylic salt) affords 4-methylfurans with electron-withdrawing substituents in the 3-position (**624a,b**).[154] However, malonates and substituted malonates (Scheme 89) react with (**623**) to give the rearranged α-alkenylmalonates (**628a**) and (**628b**), *via* a [2,3] sigmatropic shift of the sulfur ylides (**627a**) and (**627b**), formed from the initial Michael adducts (**626a**) and (**626b**). Finally, it has been reported that phosphonium ylides add to activated allenes to give new vinyl ylides and further products.[155]

### 1.1.4.2 Heteronucleophiles

Many heteronucleophiles have been added to allenic ketones, esters, nitriles, sulfones, *etc.*[156] In general, the product is the α,β-unsaturated system, as the following examples show (equation 142, Schemes 90 to 92). The β,γ-unsaturated system is formed first (and can sometimes be isolated)[156c,156g] and then rearranges to the α,β-unsaturated system.[156c] In general, the thermodynamically more stable alkene isomer is produced in this process, although mixtures are common. With dimethyl allenedicarboxylate (**616**), addition of alcohols and secondary amines is reported to give only the (*E*)-isomers (**635**), while addition of cyclohexylamine gives mainly the (*Z*)-isomer (*Z*)-(**636**) due to internal H-bonding (Scheme 93).[156n]

Cyclization of the initial acyclic adducts is also possible and several heterocyclic ring systems can be formed.[157] Addition of hydrazine or hydroxylamine to the nitrile (**618**; equation 143) produces the ami-

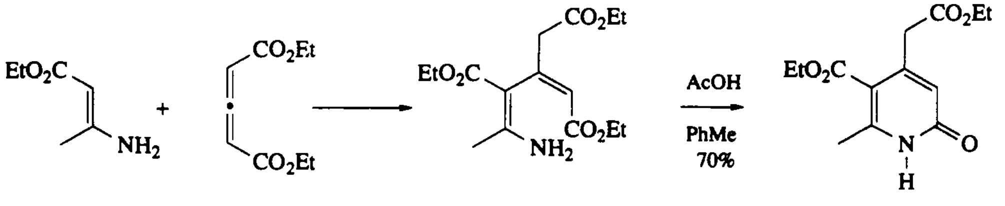
EtO2C
NH2
+
CO2Et
CO2Et
EtO2C
CO2Et
CO2Et
NH2
AcOH
PhMe
70%
EtO2C
CO2Et
N
H
O

**(611)** **(612)** **(613)** **(614)**

Scheme 88

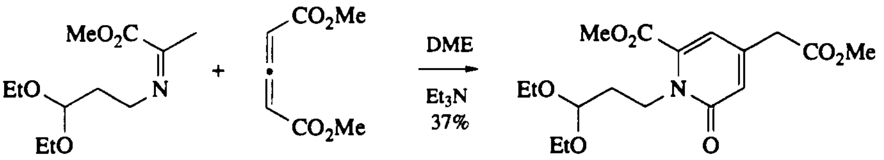
MeO2C
EtO
N
EtO
+
CO2Me
CO2Me
DME
Et3N
37%
MeO2C
CO2Me
EtO
N
EtO
O

(138)

**(615)** **(616)** **(617)**

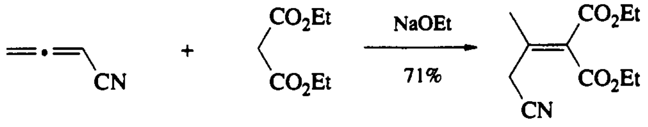
CN
+
CO2Et
CO2Et
NaOEt
71%
CO2Et
CO2Et
CN

(139)

**(618)** **(1)** **(619)**

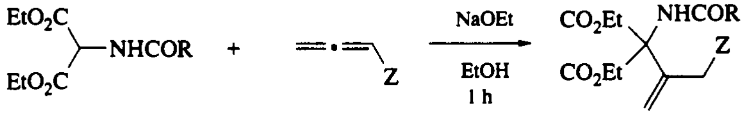
EtO2C
NHCOR
EtO2C
+
Z
NaOEt
EtOH
1 h
CO2Et
NHCOR
Z
CO2Et

(140)

**(620)** **(622)**

R = Bu$^t$O (**618**) Z = CN 89% R = Bu$^t$O, Z = CN

R = Me (**621**) Z = $CO_2Et$ 94% R = Me, Z = $CO_2Et$

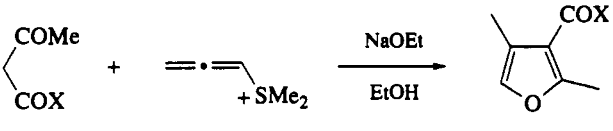
COMe
COX
+
+SMe2
NaOEt
EtOH
COX
O

(141)

**(2)** X = OEt (**623**) 86% (**624a**) X = OEt

**(479)** X = Me 89% (**624b**) X = Me

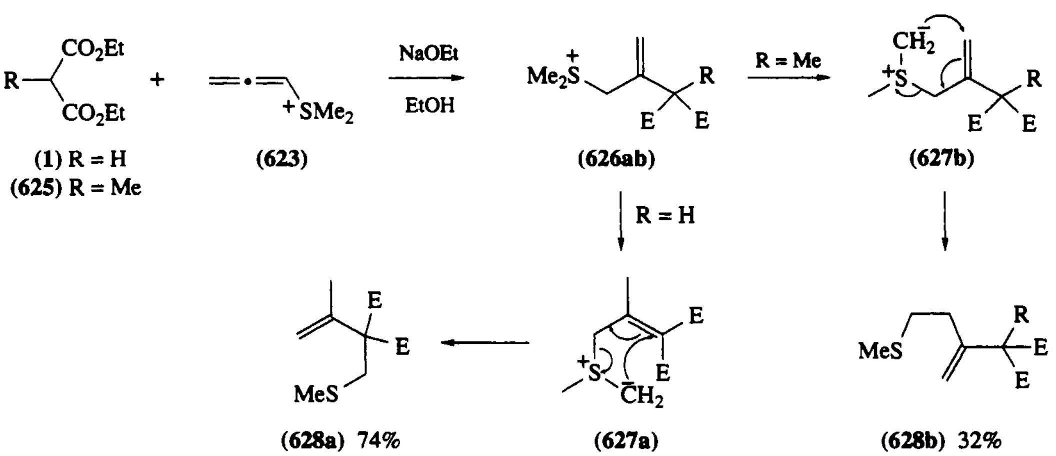
CO2Et
R
CO2Et
+
+SMe2
NaOEt
EtOH
Me2S
R
E E
R = Me
CH2
+S
R
E E
(1) R = H
(625) R = Me
(623)
(626ab)
(627b)
R = H
E
E
MeS
+S
E
E
CH2
MeS
R
E
E
(628a) 74%
(627a)
(628b) 32%

Scheme 89

nopyrazole or isoxazole, (**637a**) or (**637b**) in good yield.[153a,157a] A synthetically quite useful process involves the addition of an *N*-acylarylhydroxylamine (**638**; Scheme 94) to an activated allene (**639**) under basic conditions to give the anion (**640**), which undergoes a [3,3] sigmatropic rearrangement to afford in high yield the 2-alkylated aniline (**642**) by way of the intermediate (**641**).[158] Heating (**642**) with formic acid produces the indole in this oxygen analog of the Fischer indole synthesis.[158] Addition of ethyl *N*-

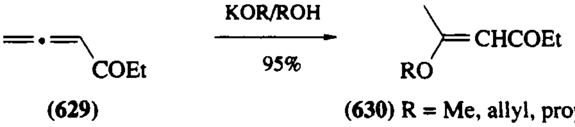
COEt
KOR/ROH
95%
=CHCOEt
RO
(629)
(630) R = Me, allyl, propargyl

(142)

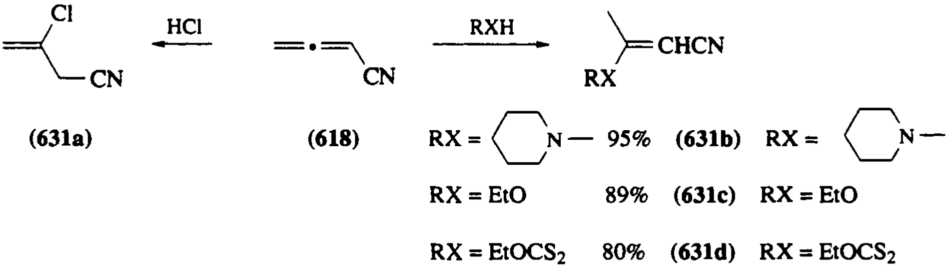
Cl
CN
HCl
CN
RXH
=CHCN
RX
(631a)
(618)
RX = N— 95% (631b) RX = N—
RX = EtO 89% (631c) RX = EtO
RX = EtOCS2 80% (631d) RX = EtOCS2

Scheme 90

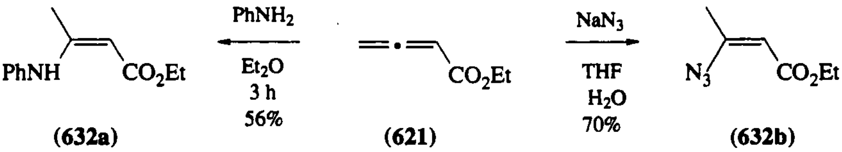
PhNH
CO2Et
PhNH2
Et2O
3 h
56%
CO2Et
NaN3
THF
H2O
70%
N3
CO2Et
(632a)
(621)
(632b)

Scheme 91

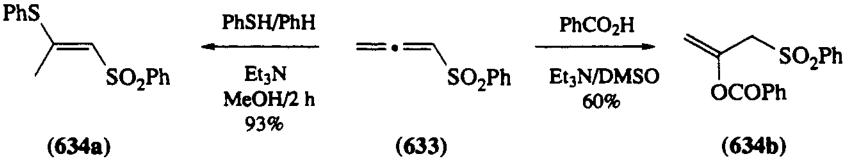
PhS
SO2Ph
PhSH/PhH
Et3N
MeOH/2 h
93%
SO2Ph
PhCO2H
Et3N/DMSO
60%
SO2Ph
OCOPh
(634a)
(633)
(634b)

Scheme 92

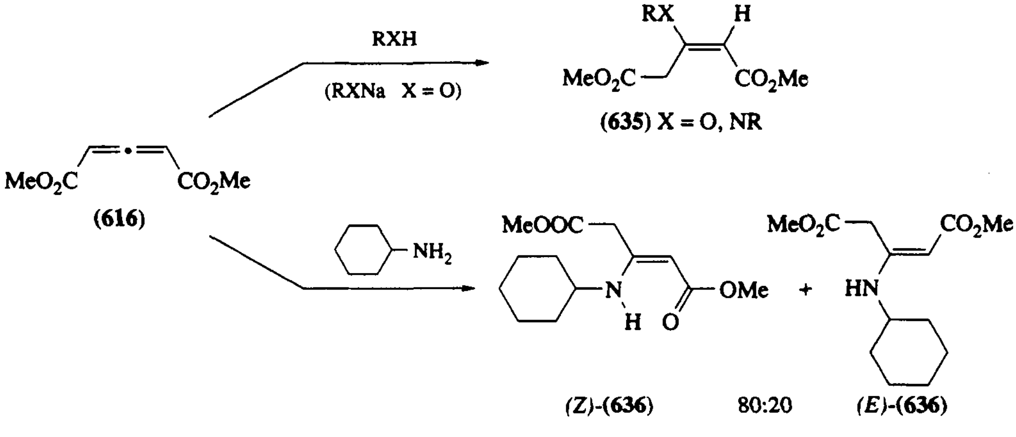
RXH
(RXNa X = O)
RX
H
MeO$_2$C
CO$_2$Me
(635) X = O, NR
MeO$_2$C
CO$_2$Me
(616)
NH$_2$
MeOOC
N
H
O
OMe
+
MeO$_2$C
CO$_2$Me
HN
(Z)-(636)
80:20
(E)-(636)

Scheme 93

methylglycinate (**643a**) or methyl α-mercaptoacetate (**643b**) to the allenic nitrile (**644**; equation 144) affords in good yield the corresponding heterocycle (**645a**) or (**645b**).[157f] Similarly, reaction of the salicylate (**646a**), thiosalicylate (**646b**) and anthranilate (**646c**) with diethyl allenedicarboxylate (**612**) produces the corresponding heterocycle (equation 145) in moderate yield.[157h] The addition of ethylenediamine to the nitrile (**644**; equation 146) produces the imidazole (**648**) *via* two Michael additions and loss of acetonitrile.[157c] Similar reaction of ethylene glycol with cyanoallene gives the ethylene ketal of cyanoacetone.[157o] Reaction of *o*-phenylenediamine (**649a**) or 2-aminothiazole (**649b**) with dimethyl allenedicarboxylate (**616**) produces the corresponding heterocycle (Scheme 95) in moderate yield.[157b,157d,157j] Several other heterocyclic systems have been prepared by analogous applications of this general scheme.[157j] Finally, additions of trialkyl phosphites to allenic ketones (**629**; equation 147) give the methyleneoxaphospholenes in high yield (**651**).[157k,157l]

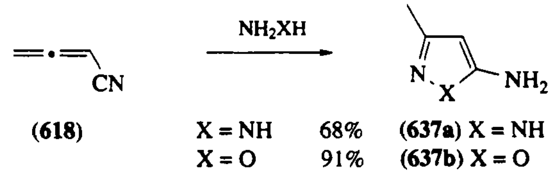
CN
(618)
NH$_2$XH
X = NH 68%
X = O 91%
N
X
NH$_2$
(637a) X = NH
(637b) X = O

(143)

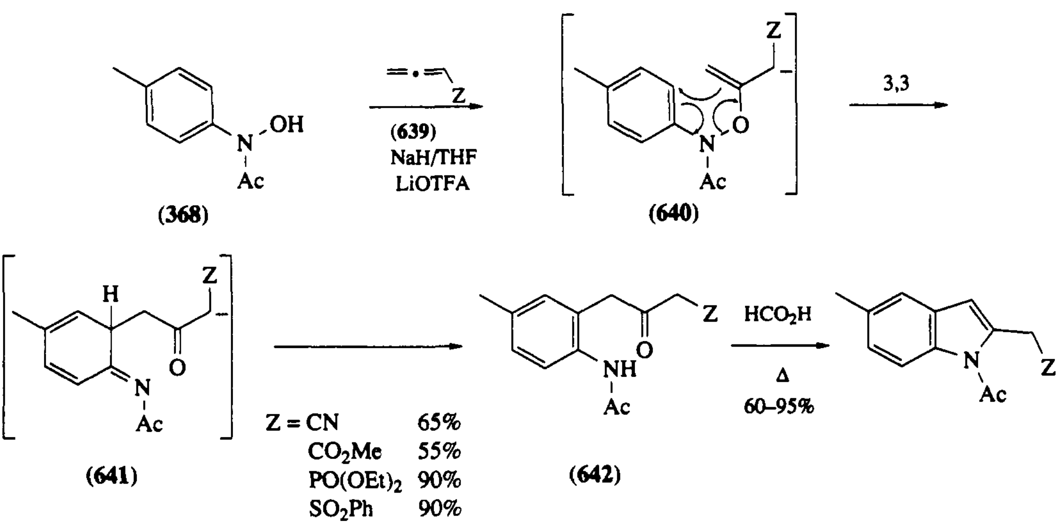
OH
N
Ac
(368)
Z
(639)
NaH/THF
LiOTFA
Z
N
O
Ac
(640)
3,3
H
Z
O
N
Ac
(641)
Z = CN 65%
CO$_2$Me 55%
PO(OEt)$_2$ 90%
SO$_2$Ph 90%
Z
O
NH
Ac
(642)
HCO$_2$H
Δ
60–95%
N
Ac
Z

Scheme 94

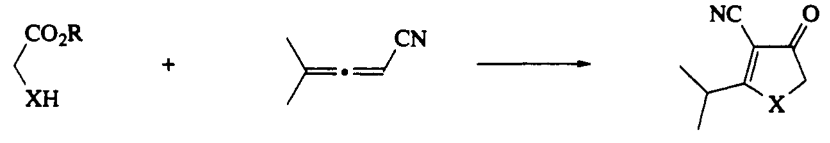
CO2R
XH
+
CN
NC
O
X

(144)

**(643a)** R = Et, X = NMe
**(643b)** R = Me, X = S

**(644)**

100 °C/2 h/84%
NaOEt/EtOH/89%

**(645a)** X = NMe
**(645b)** X = S

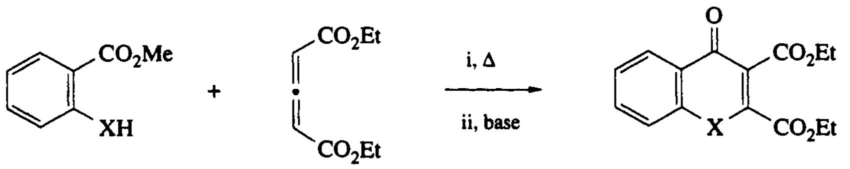
CO2Me
XH
+
CO2Et
CO2Et
i, Δ
ii, base
O
CO2Et
X
CO2Et

(145)

**(646a)** X = O
**(646b)** X = S
**(646c)** X = NMe

**(612)**

29%
66%
65%

**(647a)** X = O
**(647b)** X = S
**(647c)** X = NMe

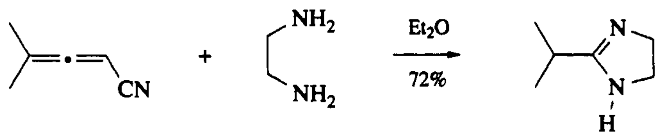
CN
+
NH2
NH2
Et2O
72%
N
N
H

(146)

**(644)** **(648)**

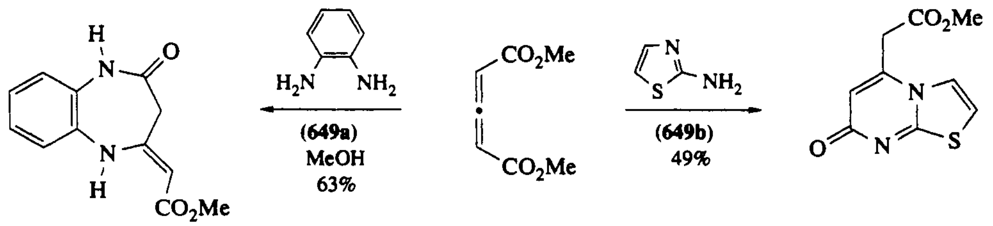
H
N
O
N
H
CO2Me
H2N
NH2
(649a)
MeOH
63%
CO2Me
CO2Me
N
S
NH2
(649b)
49%
CO2Me
N
O
N
S

**(650a)** **(616)** **(650b)**

**Scheme 95**

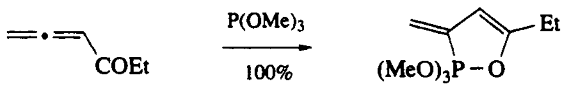
COEt
P(OMe)3
100%
Et
(MeO)3P – O

(147)

**(629)** **(651)**

## 1.1.5 CONCLUSION

The addition of stabilized nucleophiles to activated π-systems is one of the most widely used constructive methods in organic synthesis. This chapter has provided a selective overview of this still burgeoning area where further progress continues, especially in the area of stereocontrol.

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# 1.2

# Conjugate Additions of Reactive Carbanions to Activated Alkenes and Alkynes

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## 1.2.1 INTRODUCTION

The 1,4-conjugate addition of stabilized carbanions (1,3-dicarbonyl class) to α,β-unsaturated carbonyl compounds was reported by Michael in 1887 and quickly became established as an efficient method for carbon–carbon bond formation.[1] Numerous stabilized nucleophiles (donors) have been found to participate efficiently in 1,4-conjugate additions to other activated alkenes (acceptors).[2] In general, the reactivity of acceptors ($a^3$-synthons) towards various stabilized carbanions follows: α,β-unsaturated aldehydes >> α,β-unsaturated ketones > α,β-unsaturated nitriles > α,β-unsaturated esters > α,β-unsaturated amides.[3] Although the basic synthetic principles and reactivity were investigated in early years, limitations to this versatile form of carbon–carbon bond formation were observed. For example, the addition of organolithiums or organomagnesium halides to α,β-unsaturated aldehydes affords exclusive 1,2-addition, while additions to α,β-unsaturated ketones afford predominant 1,2-addition. During the last four decades intensive research in the use of unstabilized carbon nucleophiles for 1,4-conjugate additions was stimulated by three events. First, Kharasch and Tawney reported that preferential 1,4-conjugate addition of alkylmagnesium halides to isophorone was effected by catalytic amounts of copper(I) chloride,[4] and second, House, Respess and Whitesides showed that the actual reactive species in the earlier work was an organocopper species.[5] Third, Gilman and Kirby reported a comparative study of the addition of various aryl metallics to benzalacetophenone (1,3-diphenylpropene-1-one) in which several Group II ($R_2Cd$ and $R_2Zn$) and Group III ($R_3Al$) organometallics afforded exclusive 1,4-conjugate addition.[6]

The ever-expanding application of 1,4-conjugate additions and, more recently, the tandem 1,4-conjugate addition–electrophile trapping protocol (triple convergent syntheses), especially with prostaglandin syntheses, and the Michael initiated ring closure protocol (MIRC)[7,8] has prompted the development and characterization of additional organometallic reagents for accomplishing these transformations (equation 1). In contrast to the robust organolithiums and Grignard reagents, more selective organometallic reagents have been introduced that are permissive of additional functionalities on either the acceptor or donor. Alternatively, modified $a^3$-synthons, *e.g.* α-silylvinyl carbonyl species and α,β-unsaturated thioamides, have been introduced in order to minimize undesirable carbanion-catalyzed processes, namely polymerization. Methods have been developed for the conjugate addition of organometallics to alkenes ($a^2$-synthons) with functionality capable of carbanion stabilization, *e.g.* $NO_2$, $R_3P^+$, $R_2S^+$. For example, 2-(*N*-methylanilino)acrylonitrile, ketene thioacetal monoxide, α-nitroalkenes, vinyl sulfoxides, vinyl sulfones and vinyl phosphonates serve as α-carbonyl cation or (and) vinyl cation equivalents. In this survey, the 1,4-conjugate addition of various organometallic reagents to activated alkenes and alkynes will be discussed and, where appropriate, the synthesis of these reagents will be discussed. In addition, sections will be devoted to (a) enolate and homoenolate additions, (b) acyl anion (and equivalents) additions, (c) multiple conjugate additions and (d) heteroconjugate additions, *i.e.* carbometallation. Where appropriate, asymmetric and diastereoselectivity aspects will also be discussed. This survey is not intended to be comprehensive, but the transformations cited are illustrative of their synthetic potential. Lewis acid promoted additions and stoichiometric organocopper reagents will be reviewed separately (Volume 4, Chapters 1.3 and 1.4, respectively).

A survey of the 1,4-conjugate addition of organometallic reagents should include a discussion of the interdependence of (a) electronegativity of various metals, (b) hard and soft acid and base (HSAB) theory, (c) the structure of the acceptor and (d) reaction conditions and solvent effects. The difference in electronegativity between a metal and carbon is reflected in the degree of ionic character imparted to the carbon–metal σ-bond and the direction of polarization.[9] Thus the highly ionic Group IA and IIA organometallics (RK, RNa, RLi and RMgX) are extremely reactive in contrast to the less ionic Group IIB organometallics ($R_2Cd$ and $R_2Zn$) with the Group IB (RCu) and Group IIIB organometallics ($R_3Al$ and $R_3B$) being intermediate. However with the Group IB and IIIB organometallics, carbon–carbon bond formation is mediated by either carbanion, free radical or electron-transfer processes. Typically, the nucleophilicity of the Group IIB and Group IIIB organometallics is enhanced by conversion to the corresponding stable 'ate' complexes which comprise of a Lewis acid (electron-deficient organometallic) and a Lewis base (organolithium) (Volume 4, Chapter 1.3).[10]

Chemoselectivity can also be partially explained by a hard and soft acid and base (HSAB) theory.[11] From HSAB theory, the lithium cation is a harder acid than the magnesium cation and, with α,β-unsaturated ketones, C-1 (carbonyl carbon) is a harder base than C-3; thus reactions of organolithiums are preferred at the the hard site, C-1, affording 1,2-addition products. The structure of the carbanion is also

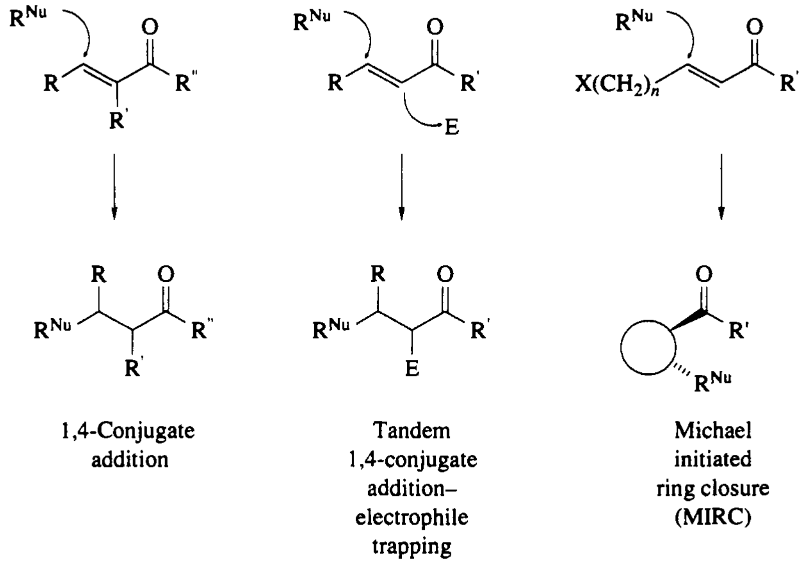
1,4-Conjugate addition
Tandem 1,4-conjugate addition–electrophile trapping
Michael initiated ring closure (MIRC)

(1)

a determinant in additions to α,β-unsaturated carbonyl acceptors; for example, benzylic lithiums[12] and lithio-2-phenyl-1,3-dithiane[13] undergo preferential, but not exclusive, 1,4-addition to α,β-unsaturated ketones, while alkyllithiums and lithio-1,3-dithiane[13b] show preferential 1,2-addition mode. The additional phenyl stabilization affords softer carbanions and thus higher preference for C-3; in addition, the higher the degree of substitution or bulkiness on the carbanion, the greater the tendency for 1,4-addition. It is instructive to note that the additions of *t*-butyllithium (–78 °C, ether)[14] and *t*-butylmagnesium chloride (25 °C, ether)[15] to 2-cyclohexen-1-one afford exclusively the 1,2- and 1,4-addition products (**1**) and (**2**), respectively (Scheme 1).

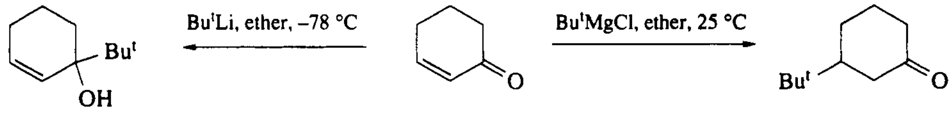

**(1)** **(2)**

**Scheme 1**

The electronics and structure of the acceptors, especially α,β-unsaturated ketones, is also a determinant in 1,2- *vs.* 1,4-addition processes. In general, substitution of aryl or large groups at the carbonyl unit increases the preference for 1,4-addition,[16a,b] while α,β-unsaturated aldehydes afford exclusive 1,2-addition and β,β-disubstitution suppresses 1,4-addition,[16c] presumably due to steric hinderance. House and Seyden-Penne have established good correlations between chemoselectivity and either the half-wave electrolytic reduction potentials,[17a] or the energy levels of the LUMO of various α,β-unsaturated ketones.[17b]

Finally, the effect of reaction conditions and solvents on chemoselectivity should also be considered.[18] Empirically, polar, more basic solvents, *e.g.* HMPA, DMF, serve to minimize counterion effects by formation of solvent-separated ion pairs and promote electron-transfer processes which are conducive for 1,4-additions,[14,19] while low polarity solvents afford contact ion pairs.[20] Numerous researchers have studied the effects of reaction conditions and solvents on the addition of α-thiosubstituted carbanions to α,β-enones;[21] in general, low polarity solvents afford kinetic 1,2-addition products while at higher temperatures the thermodynamic 1,4-addition products predominate. However, by using highly polar solvents, *e.g.* HMPA, and low temperatures, 1,4-adducts are formed predominantly and further warming to 25 °C results in exclusive formation of 1,4-adducts; thus the intermediate allylic alkoxide undergoes rearrangement to the more stable enolate (Scheme 2). In contrast, the addition of *t*-butyllithium to 2-cyclohexen-1-one affords a thermally noninterconvertible mixture of 1,2- and 1,4-addition products (**1** and **2**), but increasing quantities of 1,4-adduct are obtained with increasing amounts of HMPA in the reaction mixture.[14] In the absence of HMPA, low reaction temperatures (<–50 °C) also favor kinetic 1,4-addition of sulfur-stabilized organolithiums to α,β-enones.[20]

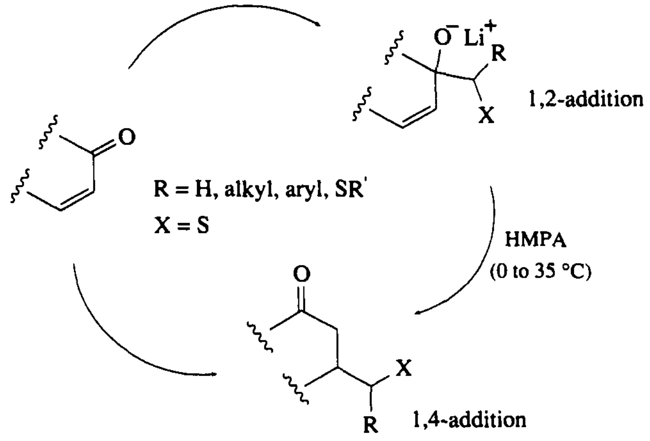

**Scheme 2**

Where applicable in this survey, emphasis will be given to the mode of synthesis of various organometallic reagents and optimal reaction conditions. Four general methods are employed for the synthesis of organometallic reagents: (a) oxidative metallation of organic halides, (b) metal–halogenation exchange, (c) metal–hydrogen exchange and (d) transmetallation.[22] Of these synthetic methods, the transmetallation protocol involving exchange of an organolithium (or Grignard reagent) with anhydrous metal halides, especially Group II metals, generates byproduct lithium halides (or magnesium halides) which modify the chemoselectivity of the newly formed organometallic reagent. The reactivity of the Group IIB organometallics ($R_2Cd$ and $R_2Zn$) is highly influenced by the presence of magnesium halides ($MgI_2 > MgBr_2 > MgCl_2$) and lesser so with lithium halides (LiI > LiBr).[23] Where appropriate data exist, the differential reactivity of 'salt-free' organometallics *vs.* 'salt-containing' organometallics will be presented.

## 1.2.2 ADDITIONS TO ALKENIC π-SYSTEMS

### 1.2.2.1 Additions of Alkyl, Aryl, Alkenyl and Alkynyl Groups

### *1.2.2.1.1 Organolithiums*

The reaction of organolithiums with α,β-unsaturated aldehydes, α,β-unsaturated ketones and α,β-unsaturated esters generally affords 1,2-addition products, which is attributed to the high ionicity of the organolithiums.[24] However, 1,4-chemoselectivity is attained when the acceptor carbonyl group is sterically hindered or deactivated towards 1,2-addition, as exemplified by the trityl enones (**3**; equation 2),[25] the $N^1,N^2,N^2$-(trimethyl)acrylhydrazides (**4**; equation 3),[26] hindered tertiary acrylamides (**5**; equation 4),[27] BHA (2,6-di-*t*-butyl-4-methoxyphenol) acrylates (**6**)[28] or BHT (2,6-di-*t*-butyl-4-methylphenol) acrylates (**7**; Scheme 3).[29] The tandem 1,4-conjugate addition–electrophile trapping protocol (aldehydes, alkyl halides, allylic halides, benzylic halides and dialkyl disulfides) has been extended to (**5**)[27,30] and (**6**) and (**7**).[31] In contrast to the other acceptors, the enones (**3**) also undergo 1,4-addition with lithium acetylides (–45 to 25 °C, THF) to afford the tritylalkynones.[25b]

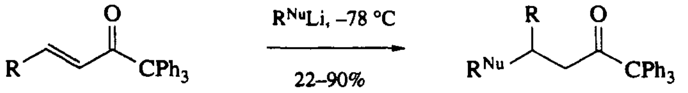

(**3**)

(2)

R = H, Me, Ph

$R^{Nu}$ = Me, Bu$^n$, Bu$^t$, Ph, RC≡C

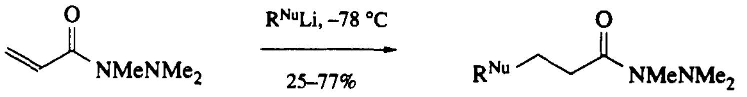

$R^{Nu}Li$, –78 °C
25–77%
NMeNMe2
$R^{Nu}$

(**4**)

$R^{Nu}$ = Me, $Bu^n$, $Bu^t$

(3)

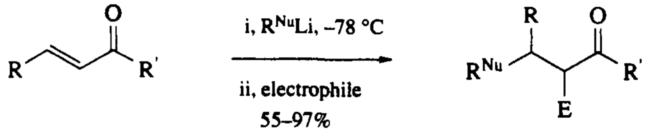

i, $R^{Nu}Li$, –78 °C
ii, electrophile
55–97%
R
R'
$R^{Nu}$
E

(**5**) R' = $Me_2N$, piperidino

$R^{Nu}$ = $Bu^n$, $Bu^t$, Ph, 4-$MeC_6H_4$, dithiane, enolates
E = H, alkyl, allyl, R"CH(OH), $EtO_2C$, PhS

(4)

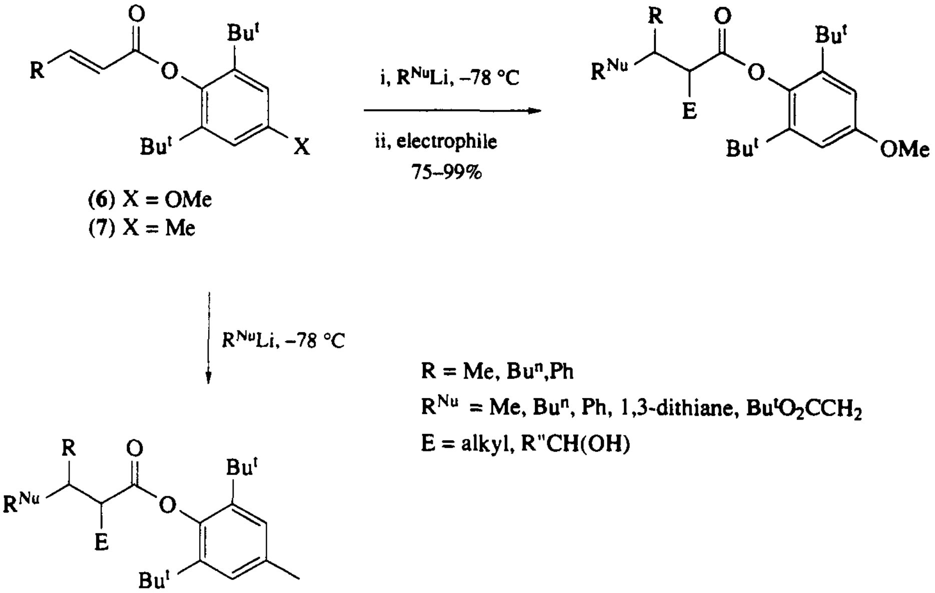

$Bu^t$
X
i, $R^{Nu}Li$, –78 °C
ii, electrophile
75–99%
$R^{Nu}$
E
OMe
$R^{Nu}Li$, –78 °C

(**6**) X = OMe
(**7**) X = Me

R = Me, $Bu^n$,Ph
$R^{Nu}$ = Me, $Bu^n$, Ph, 1,3-dithiane, $Bu^tO_2CCH_2$
E = alkyl, R"CH(OH)

**Scheme 3**

In general, β,β-disubstituted α,β-unsaturated carbonyl systems are poor acceptors for carbanions, due to steric hinderance, and the above acceptors are no exception;[16c,32] in contrast, for intramolecular cyclizations, the substituent limitations are not as stringent.[33] For example, Cooke reports that the intramolecular cyclization of *t*-butyl ω-iodo-α,β-unsaturated esters (**8**) to *t*-butyl cycloalkylacetates (**10**) *via* the ω-lithio-α,β-unsaturated esters (**9**) is highly efficient (equation 5).[34] However, the corresponding lower alkyl esters, ω-iodo-α,β-unsaturated tertiary amides or ω-iodo-α,β-unsaturated ketones afforded low yields of cyclized product. The reaction conditions necessary for optimal yields include *n*-butyllithium as the lithiation reagent and reaction temperatures of –100 °C. Similarly, Rodrigo reports that the intramolecular cyclization of ethyl (*o*-iodophenoxy)crotonates (**11**) affords dihydrobenzofurans (**12**; equation 6).[35]

In contrast, chemoselectivity can be attained by a 'charge directed conjugate addition' strategy in which 1,2-additions are suppressed, not by steric constraints, but by the presence of an adjacent negative

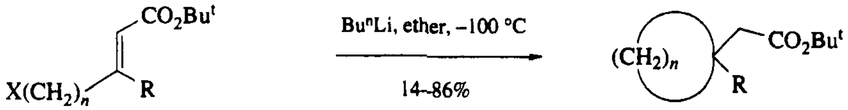

$CO_2Bu^t$
$X(CH_2)_n$
R
$Bu^nLi$, ether, –100 °C
14–86%
$(CH_2)_n$

(5)

(**8**) X = I; *n* = 3–5
(**9**) X = Li; *n* = 3–5

(**10**) R = H, Me; *n* = 3–5

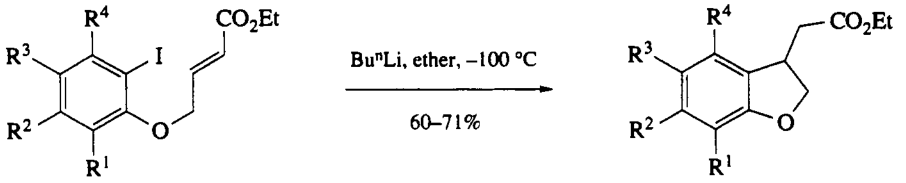

(6)

**(11)** **(12)**

$R^1$ = OMe, $R^2$ = $R^3$ = H, $R^4$ = Me
$R^1$ = OMe, $R^2$ = $R^3$ = $R^4$ = H
$R^1$ = $R^2$ = H, $R^3$ + $R^4$ = $OCH_2O$
$R^1$ = $R^4$ = H, $R^2$ = $R^3$ = Me
$R^1$ = OMe, $R^3$ = Me, $R^2$ = $R^4$ = H
$R^1$ = $R^2$ = H, $R^3$ = $R^4$ = $(CH{=}CH)_2$

charge (on either carbon or nitrogen), which deactivates the carbonyl group to either initial or secondary reactions with organometallic reagents.[36] Typical acceptors are the secondary amides (**13**)[27] or anilides (**14**)[37] and the acryl(alkoxycarbonyl)methylenetriphenylphosphoranes (**15**; Scheme 4);[38a] the latter are obtained by acylation of (alkoxycarbonyl)methylenetriphenylphosphoranes.[38b] The adducts (**16**) are conveniently transformed in high yields to the corresponding carboxylic acids,[39a] esters[39b] or methyl ketones[39c] under mild conditions.

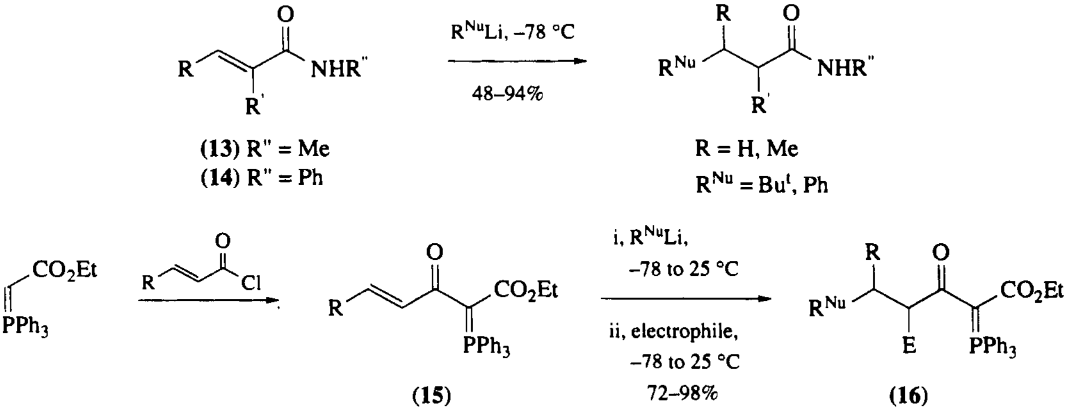

R = H, alkyl, $CH_2{=}CH$; $R^{Nu}$ = alkyl, Ph, $CH_2{=}CH$, $Me_3SiC{\equiv}CCH_2$, 1,3-dithiane, $Bu^tO_2CCH_2$
E = H, alkyl, R''CH(OH)

**Scheme 4**

It should be noted with (**3**), (**4**), (**13**) and (**14**) only hard lithium nucleophiles are tolerated, while for (**5**), (**6**), (**7**) and (**15**) the range of useful lithium nucleophiles, *e.g.* including lithio-1,3-dithianes and lithium enolates, is broader. In addition, none of these Michael acceptors react with organocuprates, Grignard reagents or stabilized carbanions.

Two intramolecular variants of the 'charge directed conjugate addition' strategy are reported to afford high yields of precursors of cycloalkylacetic esters (**20**),[40a] *trans*-2-substituted cycloalkylcarboxylate esters (**21**) and 2-cycloalkenylacetic esters (**22**).[40b,c] Both processes involve identical carbon skeletons, but different leaving groups at the ω-position. Low temperature lithiation (–100 °C, *n*-butyllithium) or oxidative metallation (Mg) of ω-iodides (**17**) and (**18**) affords the intramolecular 1,4-addition esters (**20** or **22**). Alternatively, the MIRC protocol for cyclization of a ω-chloride (or ω-bromide) (**19**) requires an initial intermolecular 1,4-addition of a carbanionic species, *e.g.* organolithium or lithium enolate, followed by ring closure to ester (**21**; Scheme 5).

In a variant of the 'charge directed conjugate addition' strategy, the incorporation of an α-trimethylsilyl unit in an acceptor serves to stabilize the intermediate carbanion and minimize anionic polymerizations.[41] This is exemplified by the highly efficient 1,4-conjugate addition of organolithiums (or Grignard reagents) to α-(trimethylsilyl)-α,β-unsaturated carboxylic acids (**23**); in contrast, α,β-unsaturated carb-

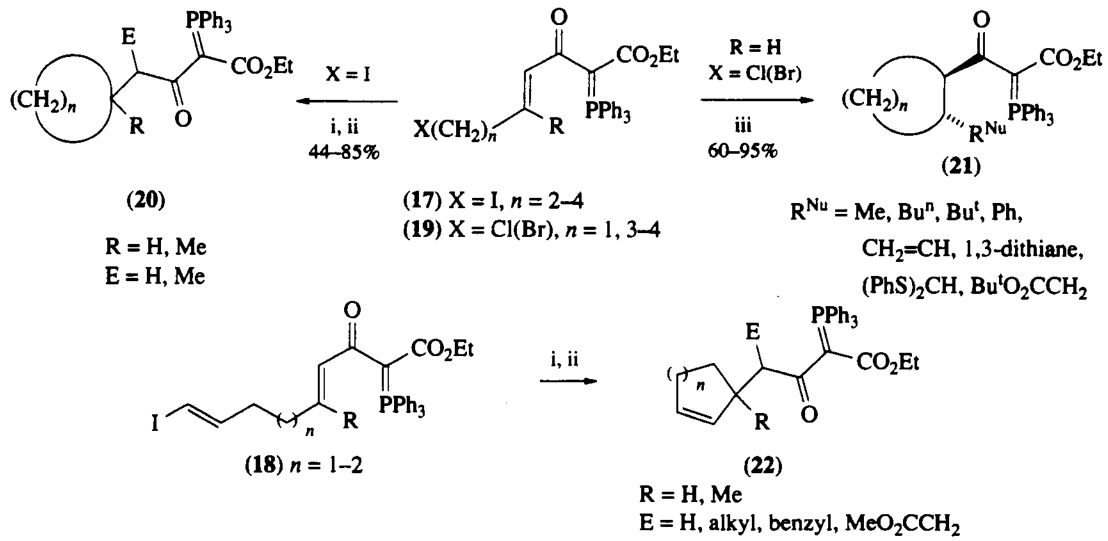

E
PPh3
CO2Et
(CH2)n
R
O
X = I
i, ii
44–85%
O
CO2Et
PPh3
X(CH2)n
R
R = H
X = Cl(Br)
iii
60–95%
O
CO2Et
(CH2)n
PPh3
RNu
(20)
R = H, Me
E = H, Me
(17) X = I, n = 2–4
(19) X = Cl(Br), n = 1, 3–4
(21)
RNu = Me, Bun, But, Ph,
CH2=CH, 1,3-dithiane,
(PhS)2CH, ButO2CCH2
O
CO2Et
I
n
R
PPh3
i, ii
E
PPh3
CO2Et
n
R
O
(18) n = 1–2
(22)
R = H, Me
E = H, alkyl, benzyl, MeO2CCH2

i, Bu$^n$Li (Bu$^t$Li), –100 to –78 °C; ii, electrophile; iii, R$^{Nu}$Li, –78 °C

**Scheme 5**

oxylic acids typically afford exclusive 1,2-addition products in low yields. The resultant α-(trimethylsilyl)carboxylic acids (**24**) are desilylated with sodium hydroxide; thus, this is the equivalent of the 1,4-conjugate addition of an organometallic reagent to an α,β-unsaturated carboxylic acid.[42a] Two aspects of the reaction conditions should be highlighted: (a) excellent yields of (**24**) are obtained when acid (**23**) is added to the organometallic donor (–78 °C) and (b) in contrast to the intermediate lithium dianions, the intermediate magnesium dianions react with aldehydes to yield α,β-unsaturated acids (**25**; Scheme 6).[42b]

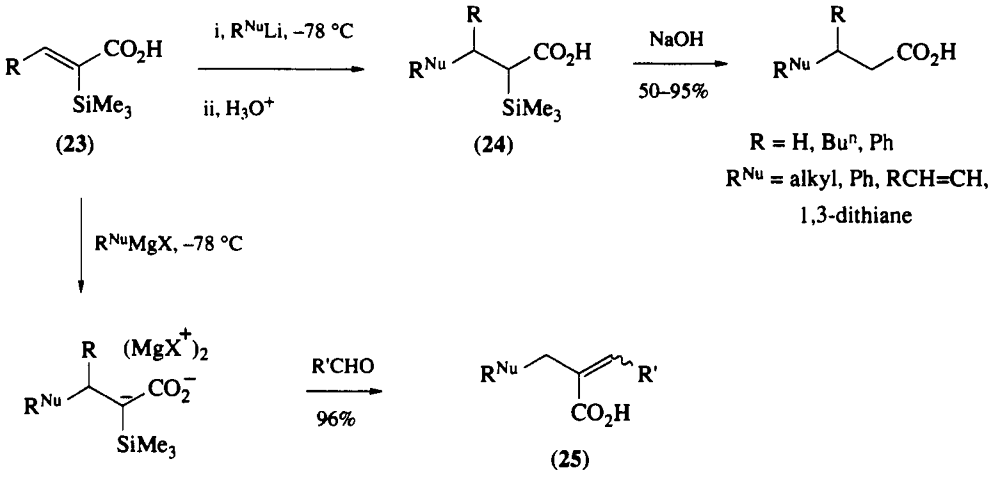

R
CO2H
SiMe3
(23)
i, RNuLi, –78 °C
ii, H3O+
R
RNu
CO2H
SiMe3
(24)
NaOH
50–95%
R
RNu
CO2H
R = H, Bun, Ph
RNu = alkyl, Ph, RCH=CH,
1,3-dithiane
RNuMgX, –78 °C
R (MgX+)2
RNu
CO2−
SiMe3
R'CHO
96%
RNu
R'
CO2H
(25)

R$^{Nu}$ = Bu$^t$; R' = n-$C_8H_{17}$

**Scheme 6**

Similarly, organolithiums (or Grignard reagents) add to ester (**26**) to afford silyl enolates which are intercepted with aldehydes and ketones to give α,β-unsaturated esters (**27**),[43a] while addition of the bifunctional aryllithium (**28**) (MIRC protocol) affords the 2-(trimethylsilyl)tetrahydronaphthoate ester (**29**; Scheme 7).[43b]

The addition of organolithiums to α,β-unsaturated *s*-thioamides (**30**) occurs exclusively in a 1,4-mode which is a consequence of the high stability of the intermediate thioimidate anion.[44a,b] The thioamide acceptors are obtained by the reaction of an alkyl (or aryl) isothiocyanate with a vinylic lithium (or vinylic Grignard reagent) or an allylic Grignard reagent followed by a base-catalyzed conjugation. Typically, hard organolithiums add to afford the corresponding thioamide dianion which can be α-alkylated effi-

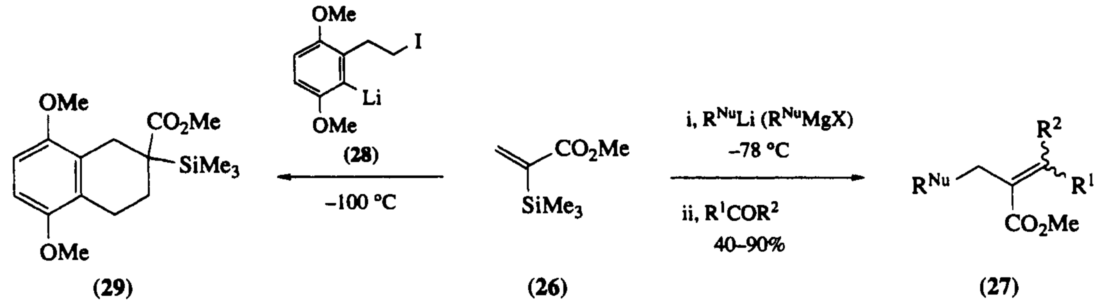
OMe
I
Li
OMe
(28)
-100 °C
OMe
CO2Me
SiMe3
OMe
(29)
CO2Me
SiMe3
(26)
i, RNuLi (RNuMgX)
-78 °C
ii, R1COR2
40–90%
R2
RNu
R1
CO2Me
(27)

$R^{Nu}$ = Ph, MeS–CH–SOMe,
$CH_2{=}CH{-}C{=}CH_2$
$R^1$ = alkyl, $R^3CH{=}CH$ ($R^3$ = Me, Ph)
$R^2$ = H, alkyl

**Scheme 7**

ciently; while with the α,β-unsaturated *N*-(trimethylsilyl)thioamides (**31**), both soft lithium anions, *e.g.* enolates, and hard lithium anions and Grignard reagents add efficiently (Scheme 8). Similarly, the corresponding α,β-unsaturated *t*-thioamides (**32**), including *N,N*-dimethylthiosorbamide, undergo exclusive 1,4-conjugate additions with organolithiums to afford an intermediate (*Z*)-enethiolate, which is a softer anion and thus not subject to further organometallic attack, but can undergo further α-alkylation or α-phenylsulfenylation.[44c]

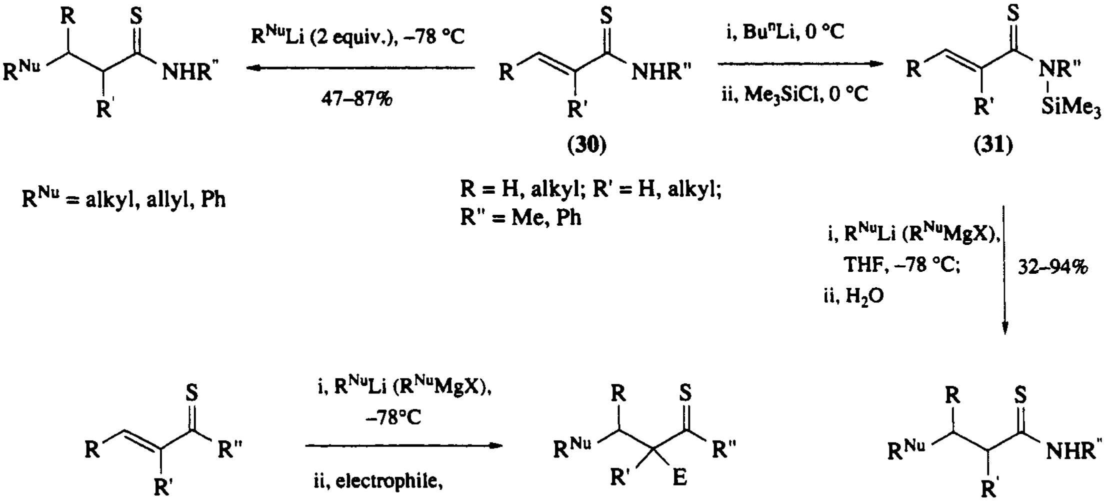
R
S
RNu
NHR"
R'
RNuLi (2 equiv.), -78 °C
47–87%
S
R
NHR"
R'
(30)
i, BunLi, 0 °C
ii, Me3SiCl, 0 °C
S
R
NR"
R'
SiMe3
(31)
i, RNuLi (RNuMgX),
THF, -78 °C;
ii, H2O
32–94%
S
R
R"
R'
(32)
i, RNuLi (RNuMgX),
-78°C
ii, electrophile,
50–97%
R
S
RNu
R"
R'
E
R
S
RNu
NHR"
R'

$R^{Nu}$ = alkyl, allyl, Ph

R = H, alkyl; R' = H, alkyl;
R" = Me, Ph

R = H, Me, MeCH=CH
$R^1$ = H, Me
R" = $Me_2N$, pyrrolidine

$R^{Nu}$ = alkyl, Ph, $CH_2{=}CH$,
1,3-dithiane, $MeSOCH_2$
E = H, allyl, $CH_2{=}CBrCH_2$, PhS

$R^{Nu}$ = $Pr^i$, $Bu^n$, $CH_2{=}CH$,
Ph, 2-furyl,
$Bu^tO_2CCH_2$

**Scheme 8**

While α,β-unsaturated aldehydes react exclusively with organolithiums in the 1,2-mode, the corresponding imines or imidates, *e.g.* α,β-unsaturated azomethines, are excellent surrogates for '—CH═CH—CHO' [$^+CH_2CH_2CHO$ synthon] that undergo exclusive 1,4-additions. For example, the 2-styryldihydro-1,3-oxazines (**33**; equation 7),[45] 2-vinylbenzothiazoles (**34**; equation 8),[46] 2-alkenyl-2-imidazolines (**35**; equation 9)[47] and α-(phenylthio)vinyloxazolines (**36**; equation 10)[48] afford addition products that can be converted to the corresponding aldehydes, ketones or carboxylic acids (or esters). Similarly, Meyers has reported that *N*-cyclohexylnaphthylimines (**37**) are transformed to the corresponding 1,2-dihydronaphthalene aldehydes, as shown in Scheme 9.[49]

Notable is the general enantioselective addition of organolithiums to chiral vinyloxazolines (**38**) in which the intermediate azaenolate (**39**) can be further alkylated with high diastereoselectivity (Scheme

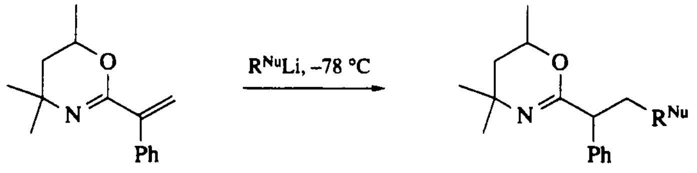

(7)

**(33)**

$R^{Nu}$ = c-$C_6H_{11}$, $Bu^s$, $Bu^i$, $Bu^t$

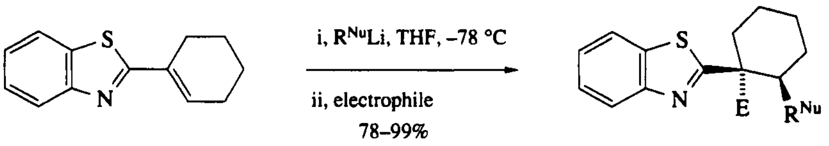
i, $R^{Nu}Li$, THF, –78 °C
ii, electrophile
78–99%

(8)

**(34)**

E = H, allyl
$R^{Nu}$ = Me, $Bu^n$, $Bu^t$, Ph, $CH_2$=$CHCH_2$, $CH_2$=CH, $HC(NNMe_2)CH_2$

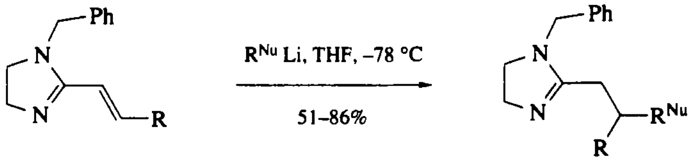
$R^{Nu}$ Li, THF, –78 °C
51–86%

(9)

**(35)**

R = Et, $Pr^n$, Ph; $R^{Nu}$ = $Bu^n$, Ph

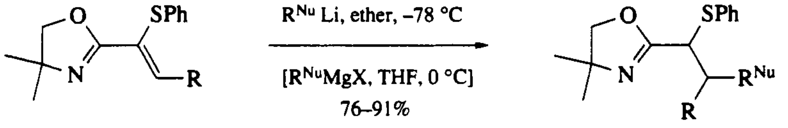
$R^{Nu}$ Li, ether, –78 °C
[$R^{Nu}MgX$, THF, 0 °C]
76–91%

(10)

**(36)**

R = Me, Ph; $R^{Nu}$ = alkyl, Ph, RC≡C

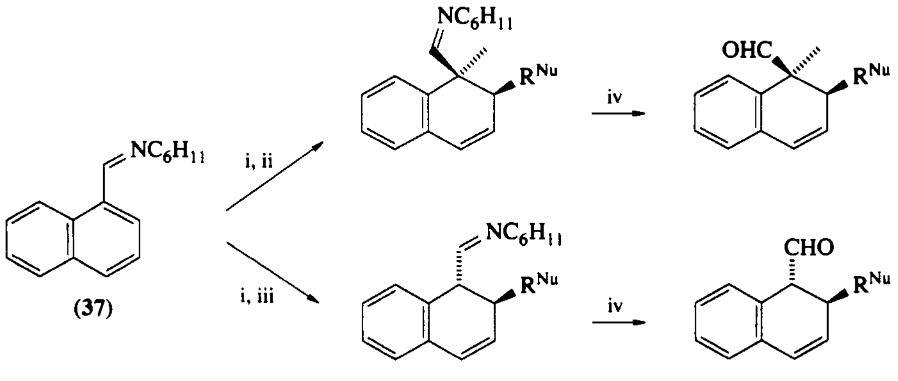
**(37)**
i, ii
i, iii
iv
iv

$R^{Nu}$ = alkyl, benzyl, MeC=$CH_2$

i, $R^{Nu}$ Li, –78 °C; ii, MeI; iii, $Pr^nOH$; iv, $H_3O^+$

**Scheme 9**

10).[50] The initial selectivity is attributed to coordination of the organolithium to the methyl ether substituent followed by delivery of the ligand to the *syn* face of the alkene.

The low temperature (–110 to –78 °C)[51] addition of organolithiums to β-substituted-α-nitroalkenes (**40**) affords intermediate nitronate anions which can be quenched with either a proton source or tetra-

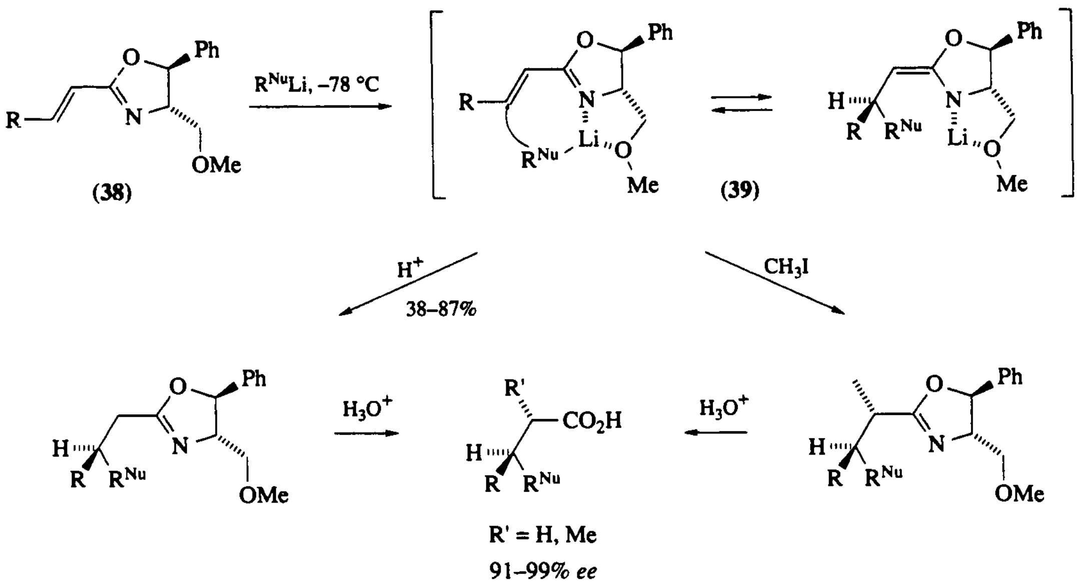

R = alkyl ($C_1$–$C_3$), $Pr^i$, $Bu^t$, c-$C_6H_{11}$, Ph, 2-$MeOC_6H_4$, $MeOCH_2CH_2$
$R^{Nu}$ = alkyl ($C_2$–$C_6$), Ph, 4-$MeC_6H_4$

**Scheme 10**

nitromethane to afford nitroalkanes[52a] or geminal dinitroalkanes,[52b] respectively (Scheme 11). This process is the cornerstone to the synthesis of (+)-lycoricidine in which the addition of aryllithium (**41**) (–100 °C) to α-nitroalkene (**42**) affords both the *ido*- (**43**) and *gluco*-configured (**44**) addends (equation 11).[52c]

Seebach has shown that the nitroallylating reagent, 2-nitroallyl pivalate (**45**, NPP) can be used for triply convergent Michael coupling of dissimilar organometallic reagents.[53] As shown in Scheme 12, various organometallics add efficiently to reagent (**45**) to afford new α-nitroalkenes.

Conjugate additions of organolithiums to cycloalkenyl sulfones have become a pivotal point in various synthetic strategies.[54] Due to the sulfone activation, competing β- (primarily) and γ-deprotonation occurs; however, γ-deprotonation is suppressed by a γ-heteroatom (N or O) substituent, while β-deprotonation is retarded by the use of either *t*-butyl (preferably) or phenyl sulfones. The γ-heteroatom substituent also influences the addition of the ligand to the β-position so that either of two orientations are obtained by the expedient use of protecting groups.[54c] Typically the sulfonyl activating group is re-

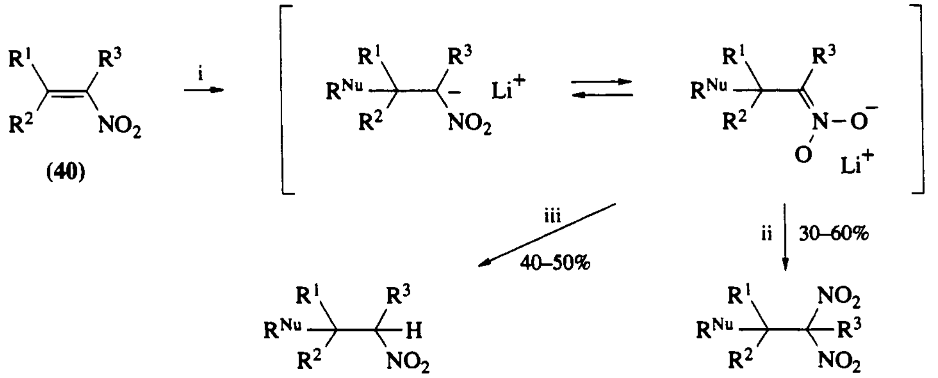

$R^1$ = Ph; $R^2$ = H; $R^3$ = Me
$R^{Nu}$ = alkyl

$R^1$ = Ph; $R^1$ = $R^3$ = H
$R^{Nu}$ = alkyl, allyl, 1,3-dithiane, enolates

i, $R^{Nu}Li$, THF, –100 to –78 °C; ii, $C(NO_2)_4$; iii, $H_3O^+$

**Scheme 11**

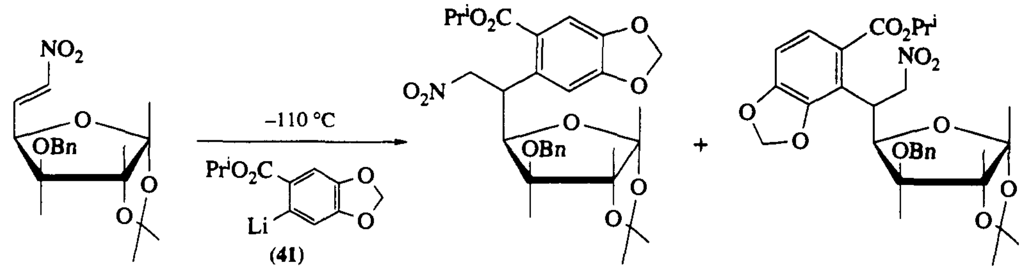

(42) (43) (44) (11)

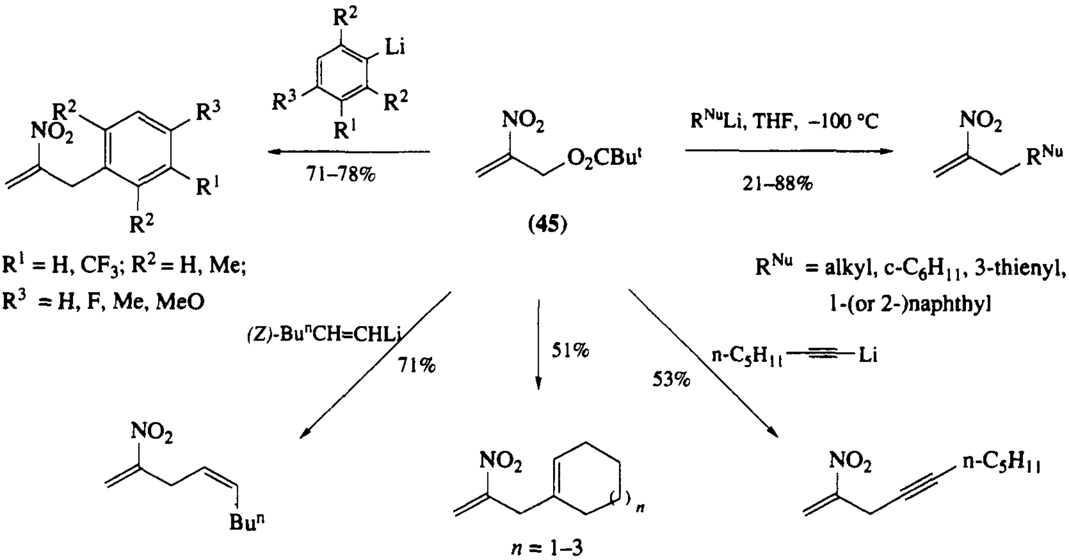

**Scheme 12**

ductively removed in a subsequent step; thus, the additions are the equivalent of adding to an unactivated alkene. The elaboration of cycloalkenyl sulfones, by an intermolecular tandem 1,4-conjugate addition–intramolecular (or intermolecular) electrophile trapping protocol, results in the formation of three (or four) contiguous asymmetric centers. Examples are shown in Scheme 13 for the conversion of sulfones (**46** and **47**) to (–)-PGE$_2$[55a] and (+)-carbacyclin (MIRC protocol).[55b] (±)-Morphine was synthesized by a tandem intramolecular 1,4-conjugate addition–intramolecular electrophile trapping protocol on the cyclohexenyl sulfone (**48**; Scheme 14).[56]

Eisch and Isobe have reported that open-chain vinyl sulfones (*e.g.* **49**) undergo exclusive α-deprotonation with organolithiums;[57] however, with α-(trimethylsilyl)vinyl phenyl sulfones (**50**), 1,4-conjugate addition occurs exclusively (Scheme 15). Desilylation is readily accomplished with anhydrous potassium fluoride. In contrast, the diastereoselective (>99% *threo*) addition of alkyllithiums to γ-hydroxy-(*Z*)-α-(trimethylsilyl)vinyl phenyl sulfones (**51**) occurs with concomitant desilylation, while the corresponding (*E*)-isomer (**52**) affords exclusive 1,4-silyl migration with no conjugate addition.[58a] Both (*E* and *Z*) γ-MEM ether isomers (**53** and **54**) afford *threo* (>99%) addition products (Scheme 16).[58b] The high diastereoselectivity is attributed to initial coordination of the organolithium to the γ-oxygen substituent (**55** and **56**) followed by delivery of the ligand to the *syn* face of the alkene; however, with (**52**), the intermediate alkoxide (**57**) undergoes 1,4-silyl transfer. As shown in Scheme 17, numerous organolithium reagents add to α-(trimethylsilyl)vinyl phenyl sulfones and the sequence of addition and trapping may be reversed to afford opposite diastereomers.[59a,b] Similarly, asymmetric induction is attained with organolithium additions to the chiral hemithioacetal α-(trimethylsilyl)vinyl phenyl sulfone (**58**) in the presence of lithium bromide (Scheme 18).[59c]

In spite of the high reactivity of the organolithiums, other compatible acceptors have also shown synthetic utility. For example, select organolithium reagents add exclusively to 2-(*N*-methylanilino)acrylonitrile (**59**), an α-carbonyl cation equivalent, to afford an intermediate α-aminonitrile anion (Section

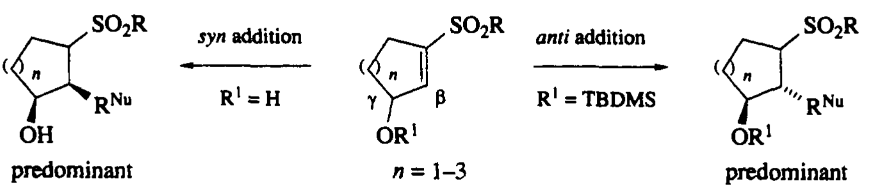
syn addition
R¹ = H
anti addition
R¹ = TBDMS
predominant
n = 1–3
predominant

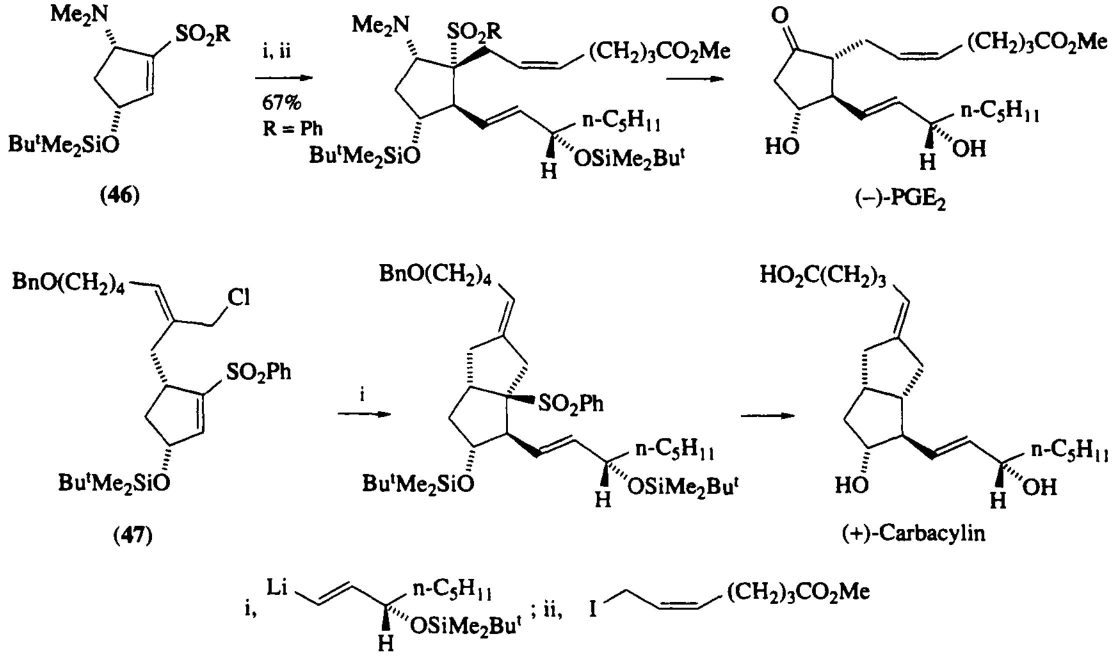
i, ii
67%
R = Ph
i
i, ; ii,

(46)

(–)-PGE$_2$

(47)

(+)-Carbacylin

Scheme 13

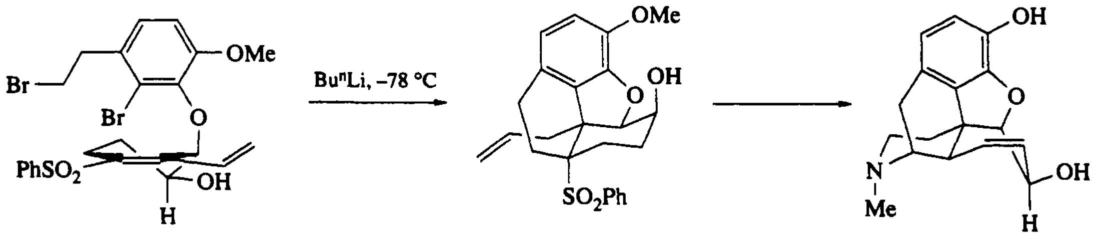

(48)

(±)-Morphine

Scheme 14

1.2.2.3.1), which is quenched with either a proton source or further alkylated. Hydrolysis of the resultant α-aminonitrile (**60**) affords aldehydes or ketones (Scheme 19).[60]

Recently, $\eta^6$-arenechromium complexes and α,β-unsaturated iron acyls have shown utility as acceptors for organolithiums; in both examples, the role of the organometallic ligand is to stabilize the inci-

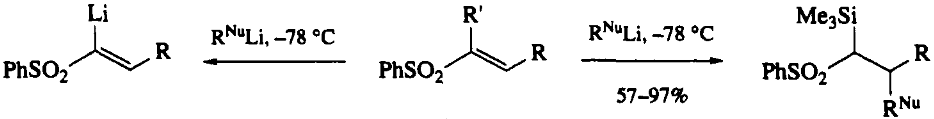
R$^{Nu}$Li, –78 °C
R$^{Nu}$Li, –78 °C
57–97%

(**49**) R = Bu$^t$, Pr$^i$, Ph; R' = H

(**50**) R = Bu$^t$, Pr$^i$, Ph; R' = Me$_3$Si

Scheme 15

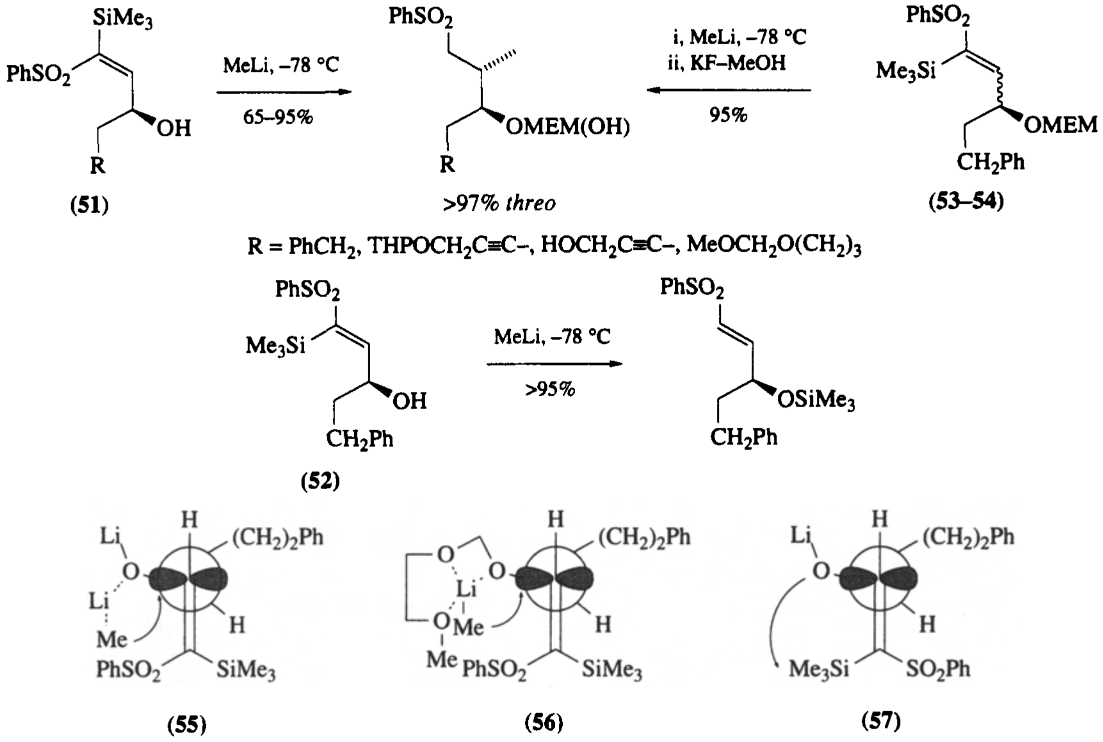
(51)
MeLi, −78 °C
65–95%
>97% threo
i, MeLi, −78 °C
ii, KF–MeOH
95%
(53–54)
R = PhCH2, THPOCH2C≡C–, HOCH2C≡C–, MeOCH2O(CH2)3
(52)
MeLi, −78 °C
>95%
(55)
(56)
(57)

**Scheme 16**

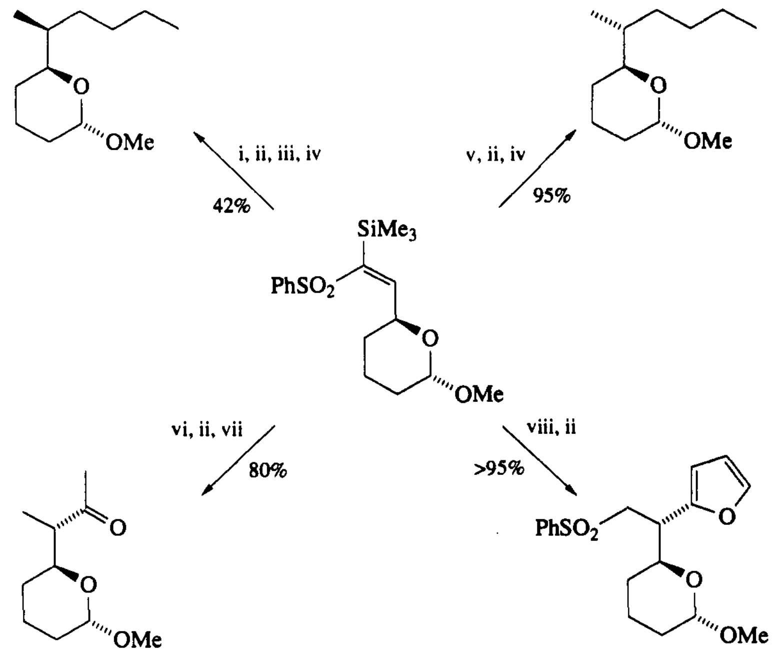
i, ii, iii, iv
42%
v, ii, iv
95%
vi, ii, vii
80%
viii, ii
>95%

i, MeLi, −78 °C; ii, KF–MeOH, 58 °C; iii, $\mathrm{Bu^nLi}$, $\mathrm{Pr^nBr}$, −78 °C; iv, Na–Hg; v, $\mathrm{Bu^nLi}$, −78 °C; vi, $\mathrm{CH_2{=}C(Li)\text{-}OEt}$, −78 °C; vii, $\mathrm{H_3O^+}$; viii, 2-furyllithium, −78 °C

**Scheme 17**

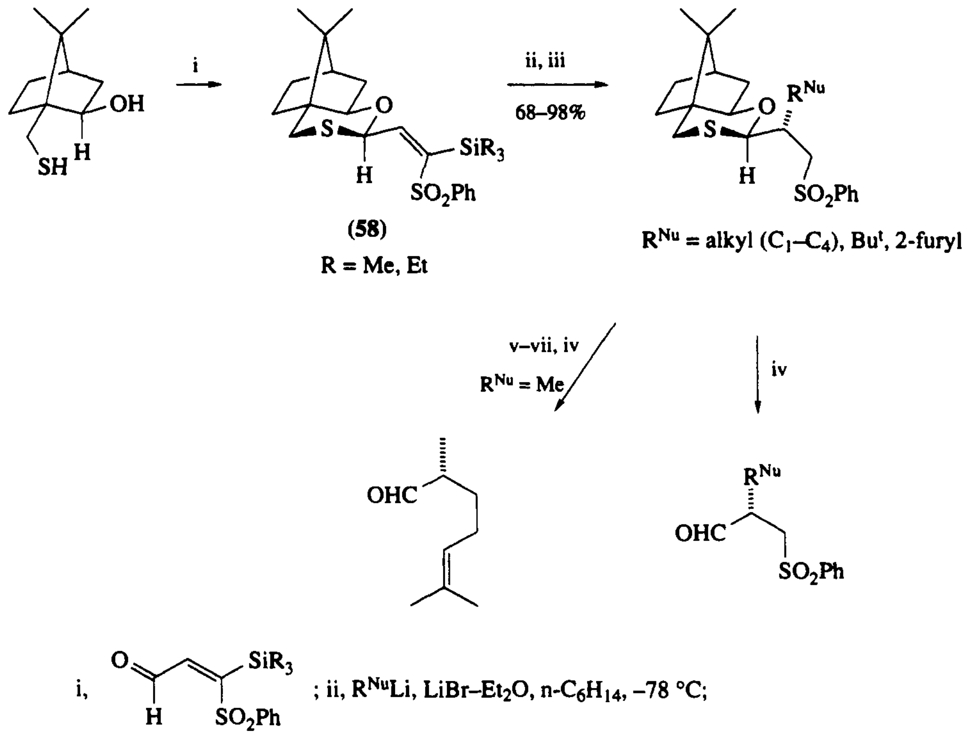
OH
SH
H
i
O
S
SiR₃
H
SO₂Ph
ii, iii
68–98%
O
R^Nu
S
H
SO₂Ph
v–vii, iv
R^Nu = Me
iv
OHC
R^Nu
OHC
SO₂Ph
O
SiR₃
H
SO₂Ph

**(58)**
R = Me, Et

$R^{Nu}$ = alkyl ($C_1$–$C_4$), $Bu^t$, 2-furyl

i, ; ii, $R^{Nu}Li$, LiBr–$Et_2O$, n-$C_6H_{14}$, –78 °C;
iii, $Bu^n{}_4NF$; iv, $HgCl_2$; v, $Bu^nLi$, –78 °C; vi, prenyl bromide; vii, Na–Hg

Scheme 18

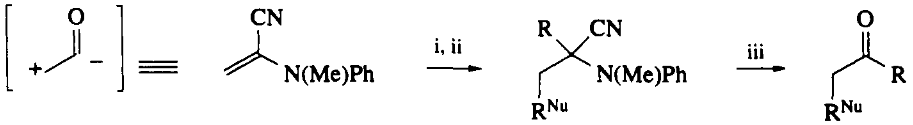
O
+
-
CN
N(Me)Ph
i, ii
R
CN
N(Me)Ph
R^Nu
iii
O
R
R^Nu

**(59)** **(60)**

$R^{Nu}$ = $Bu^t$, Ph
R = alkyl ($C_1$–$C_3$), benzyl, $H_2O$

i, $R^{Nu}Li$, THF, –78 °C; ii, RX (or $H_2O$); iii, 3N HCl

Scheme 19

pient benzylic carbanion or enolates. Knox and Semmelhack have shown that the regiospecific β-alkylation (arylation) of isolated styrene units is readily accomplished with complexes (**61**; Scheme 20).[61] Davies and Liebeskind have independently reported that the addition of organolithiums (–78 °C, THF) to chiral (*E*)-α,β-unsaturated iron acyls (**62** and **63**) and alkylation of the resultant enolate occurs with high diastereoselectivity (Scheme 21).[62a–f] The selectivity is attributed to a preferred *anti* conformation of the carbon monoxide ligand and acyl carbonyl and steric shielding of one face of the alkene by the triphenylphosphine ligand.[62g]

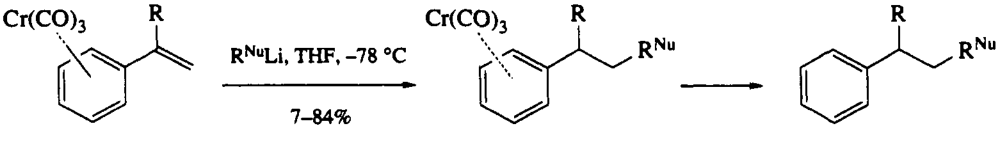
Cr(CO)₃
R
R^NuLi, THF, –78 °C
7–84%
Cr(CO)₃
R
R^Nu
R
R^Nu

**(61)**

R = H, Me, MeCO, SEt

$R^{Nu}$ = Me, Ph, $Bu^n$, 1,3-dithiane, $Me_2CCN$, $Me_2CCO_2Bu^t$

Scheme 20

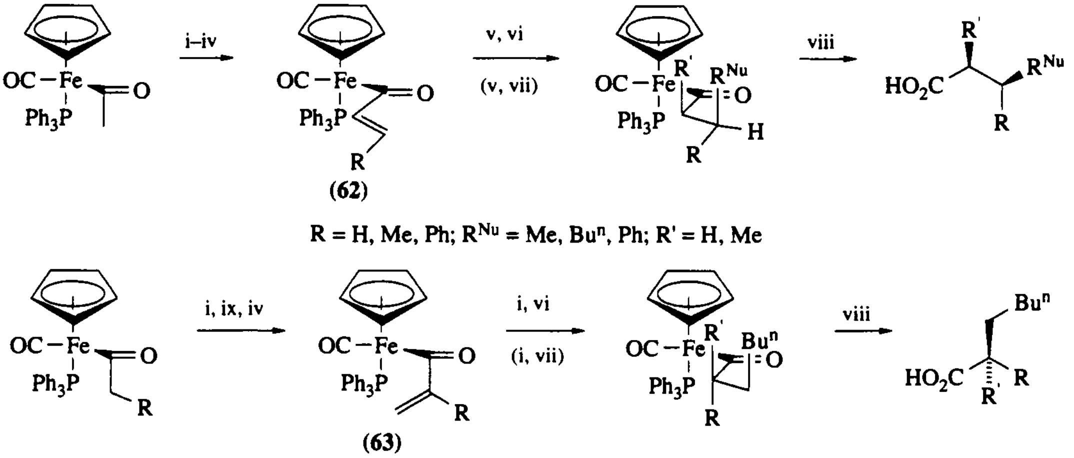

R = H, Me, Ph; $R^{Nu}$ = Me, $Bu^n$, Ph; R' = H, Me

i, $Bu^nLi$, THF, −78 °C; ii, RCHO, −40 °C; iii, NaH, MeI, THF, 50 °C; iv, NaH, THF; v, $R^{Nu}Li$, THF, −78 °C; vi, R'X; vii, MeOH; viii, $Br_2$, $H_2O$; ix, $ClCH_2OR''$ (R" = Me, menthyl), −40 °C

Scheme 21

### *1.2.2.1.2 Organomagnesiums*

The Grignard reagents have shown prevalent usage in carbon–carbon bond formation due to their ease of formation,[63] but some Grignard reagents are reported to be inaccessible because of synthetic complications, namely coupling. However, with newer methods for activation of magnesium, numerous sensitive Grignard reagents can be prepared quantitatively.[64] In addition, the greater tendency of Grignard reagents *vs.* organolithiums to form cyclic complexes with suitably juxtaposed unshared electron pairs on either nitrogen or oxygen, on a chiral auxiliary, is advantageous for diastereoselective additions.

The addition of Grignard reagents to α,β-unsaturated ketones generally affords 1,2-addition products, but examples of exclusive 1,4-additions to α,β-enones, with unique structural characteristics, are precedented. For example, the addition of *m*-methoxybenzylmagnesium chloride to α-methylene ketones (**64** and **65**) and subsequent acetylation affords the enol acetates (**66**) and (**67**) exclusively (Scheme 22);[65a–c] the absence of 1,2-addition products is due to severe 1,3-diaxial interactions of the incoming ligand with the axial juncture methyl.[65d] Similarly, as shown in Scheme 23, the anomalous 1,4-addition of Grignard reagents to sterically hindered aromatic ketones (**68**) affords *ortho*-alkylated ketones.[66]

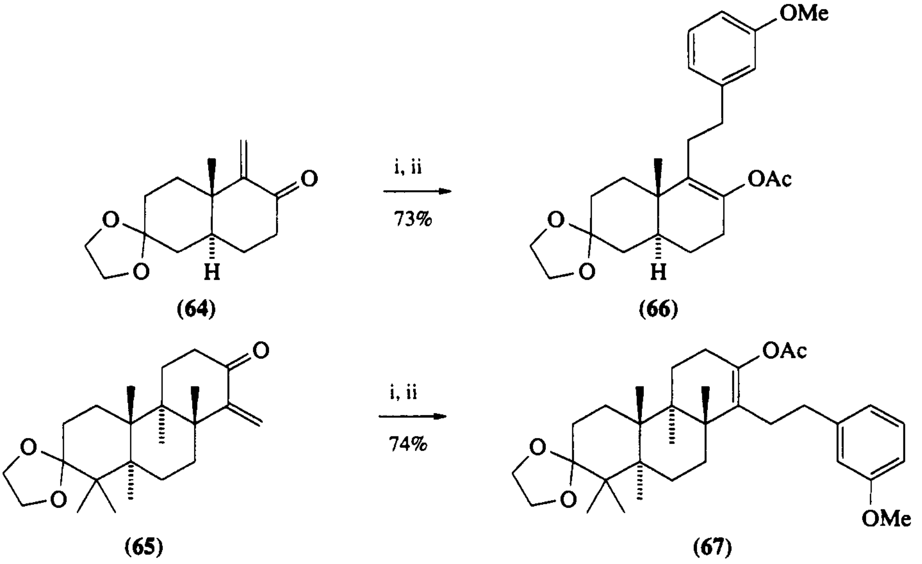

i, $3\text{-}MeOC_6H_4CH_2MgCl$; ii, $(MeCO)_2O$

Scheme 22

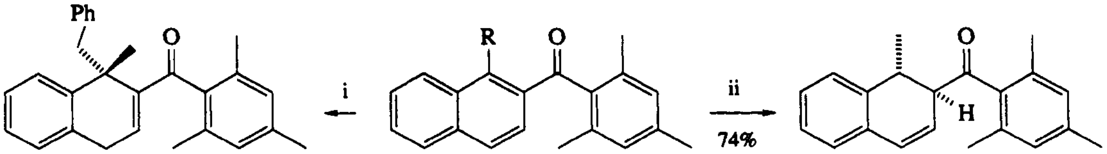
Ph
O
R
O
i
ii
74%
O
H

**(68)** R = H or Me

i, $PhCH_2MgCl$, $Et_2O$, 38 °C; ii, MeMgBr, $Et_2O$, 38 °C

**Scheme 23**

The 1,4-conjugate addition of Grignard reagents to *N*,*N*-disubstituted cinnamamides (**69**) was reported by Kohler in 1905;[67] subsequently numerous examples of Grignard conjugate additions to *N*,*N*-dialkylcrotonamides (**70**; Scheme 24),[68a] *N*,*N*-dialkylsorbamides (**71**)[68b] and higher analogs were reported. Notable is the exclusive 1,4-addition of Grignard reagents to amide (**71**), while organocuprates add exclusively in a 1,6-addition mode.[68b] The addition of allylic Grignard reagents affords allylic transposition adducts (**72**) exclusively, while both allenic and isomeric propargylic Grignard reagents afford predominantly allenic adducts (**73**; Scheme 25).[68c,d] In contrast, Grignard reagents add to *trans*-β-aroyl-*N*-alkylpropionamides (**75**) to afford exclusively β-aroyl-α-alkyl-*N*-alkylpropionamides (**76**; equation 12).[69]

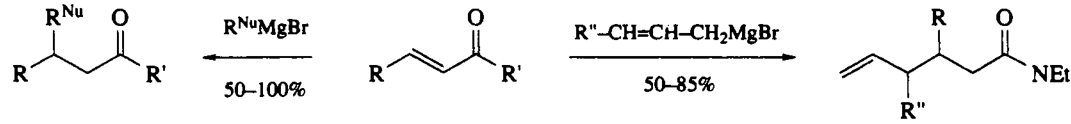
$R^{Nu}$
O
R
R'
$R^{Nu}MgBr$
50–100%
O
R
R'
R"–CH=CH–$CH_2$MgBr
50–85%
R
O
$NEt_2$
R"

R' = $Me_2N$, $Et_2N$, piperidino, $(c\text{-}C_6H_{11})_2N$
$R^{Nu}$ = Et, $Pr^n$, Ph

**(69)** R = Ph
**(70)** R = Me (Et)
**(71)** R = MeCH=CH

**(72)** R" = H, Me, Et

**Scheme 24**

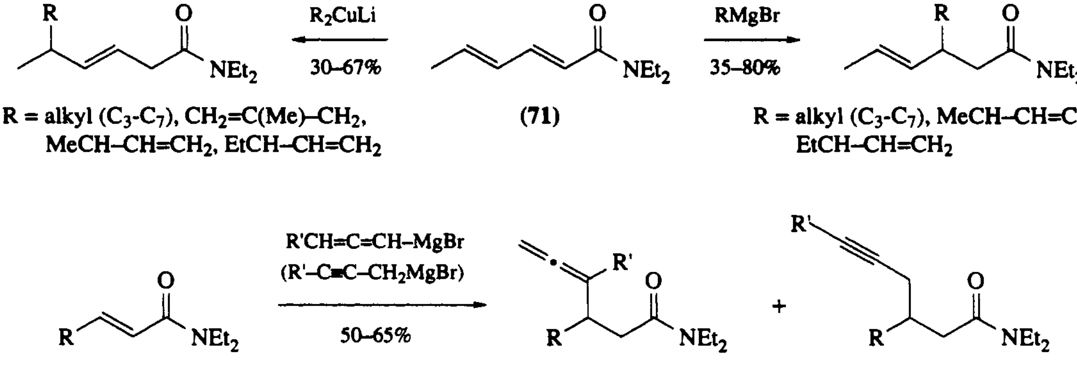
R
O
$NEt_2$
$R_2CuLi$
30–67%
O
$NEt_2$
RMgBr
35–80%
R
O
$NEt_2$
O
R
$NEt_2$
R'CH=C=CH–MgBr
(R'–C≡C–$CH_2$MgBr)
50–65%
R'
O
R
$NEt_2$
+
R'
O
R
$NEt_2$

R = alkyl ($C_3$-$C_7$), $CH_2$=C(Me)–$CH_2$, MeCH–CH=$CH_2$, EtCH–CH=$CH_2$

**(71)**

R = alkyl ($C_3$-$C_7$), MeCH–CH=$CH_2$, EtCH–CH=$CH_2$

**(70)** R = Me, Et

**(73)** 81–90%

**(74)** 10–19%

**Scheme 25**

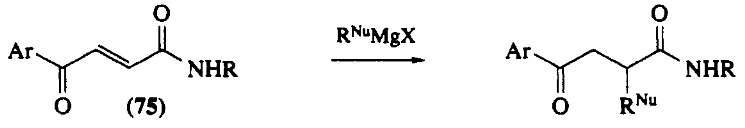
O
Ar
NHR
O
$R^{Nu}MgX$
O
Ar
NHR
O
$R^{Nu}$

**(75)**

(12)

Ar = Ph, 4-$MeC_6H_4$, 4-$ClC_6H_4$
R = $Bu^n$, $Bu^s$, $Bu^t$, benzyl

**(76)** $R^{Nu}$ = Me, Et, Ph

Variable levels of asymmetric induction or diastereoselectivity have been found with additions of organometallics to α,β-unsaturated chiral amides (chiral auxiliary). For example, as shown in Scheme 26, Mukaiyama reports that the diastereoselective addition of Grignard reagents to β-substituted α,β-unsaturated *N*-methyl-(–)-ephedrine amides (**77**) occurs in moderate yields with >85% *ee*, while the use of either organolithiums or strong coordinating solvents negates the intramolecular ligand effects.[70] Similarly, Soai reports that Grignard reagents add to α,β-unsaturated (*S*)-prolinol amides (**78**; R′ = H) or α,β-unsaturated (*S*)-2-(1-hydroxy-1-methylethyl)pyrrolidine amides (**78**; R′ = Me) with 50–89% *ee* in the presence of a tertiary amine, *e.g.* DBN, DBU, (–)-sparteine or TMEDA.[71] The selectivity is attributed to a combination of the intrinsic aggregative properties and chelation of the Grignard reagent with the carbinol and carbonyl functionality. Similarly, Oppolzer reports that alkylmagnesium chlorides add to *N*-enoylsultams (**79** and **80**) with high diastereoselectivity (Scheme 27) which is attributed to initial chelation of the alkylmagnesium chloride to both the sultam and carbonyl groups followed by facial selective delivery of a second chelated alkylmagnesium chloride to the β-alkenic carbon (**81**).[72]

The addition of Grignard reagents to α,β-unsaturated *N*,*N*-dialkylthioamides (**32**) affords an intermediate (*Z*)-enethiolate which is a soft anion and resistant to further organometallic attack. Thus, in a tandem conjugate addition–electrophile trapping protocol with aldehydes, the enethiolate affords primarily *threo* aldols (**82**). The 1,4-conjugate addition of Grignard reagents to *N*,*N*-dimethyl-α-methacrylothioamide (**83**) affords the intermediate (*Z*)-enethiolate which undergoes aldol condensation to afford either the corresponding *erythro* aldols (**84**) or *threo* aldols (**85**) depending on the steric bulk of the aldehyde (Scheme 28).[73]

The α,β-unsaturated *N*-phenylthioimidates (**86**) have also shown utility as acceptors for nonallylic Grignard reagents (–5 to –10 °C) and alkyllithiums (–78 °C) while allylic Grignard reagents add exclusively in a 1,2-mode (equation 13). These adducts (**87**) can be converted quantitatively to the corresponding dithioesters with hydrogen sulfide. In contrast, α,β-unsaturated dithioesters (**88**) react with allylic Grignards in a 1,4-mode exclusively with allylic transposition (equation 14).[74]

Koga reports that α,β-unsaturated aldimines (**89**), derived from L-*t*-leucine *t*-butyl esters, undergo asymmetric additions with Grignard reagents which is due to formation of a highly ordered magnesium chelate (Scheme 29).[75]

The addition of Grignard reagents to α-nitroalkenes occurs in moderate to excellent yields with byproducts, from overreaction, being hydroxylamines and oximes.[76] In contrast to the optimal reaction temperatures of <–78 °C for organolithium additions, the optimal reaction temperature for Grignard reagent additions is <15 °C.[77a–c] The addition of phenylethynylmagnesium bromide to α-nitroalkenes (**40**) affords the intermediate magnesium nitronates (**90**) which can be hydrolyzed or halogenated to afford γ-alkynic nitroalkanes (**91**) or γ-alkynic α-bromonitroalkanes (**92**), respectively (Scheme 30).[77d] Vinylmagnesium bromide adds to the α-nitroalkenes (**93**) to afford exclusively the L-*ido*-furanosides (**94**; equation 15) (*cf.* **42** → **43** and **44**).[77e]

In contrast to the α-nitroalkenes, Grignard reagents add to mononitroarenes in a bimodal manner,[78a] with alkyl Grignard reagents adding efficiently in 1,4- (predominant) and 1,6-addition modes to afford

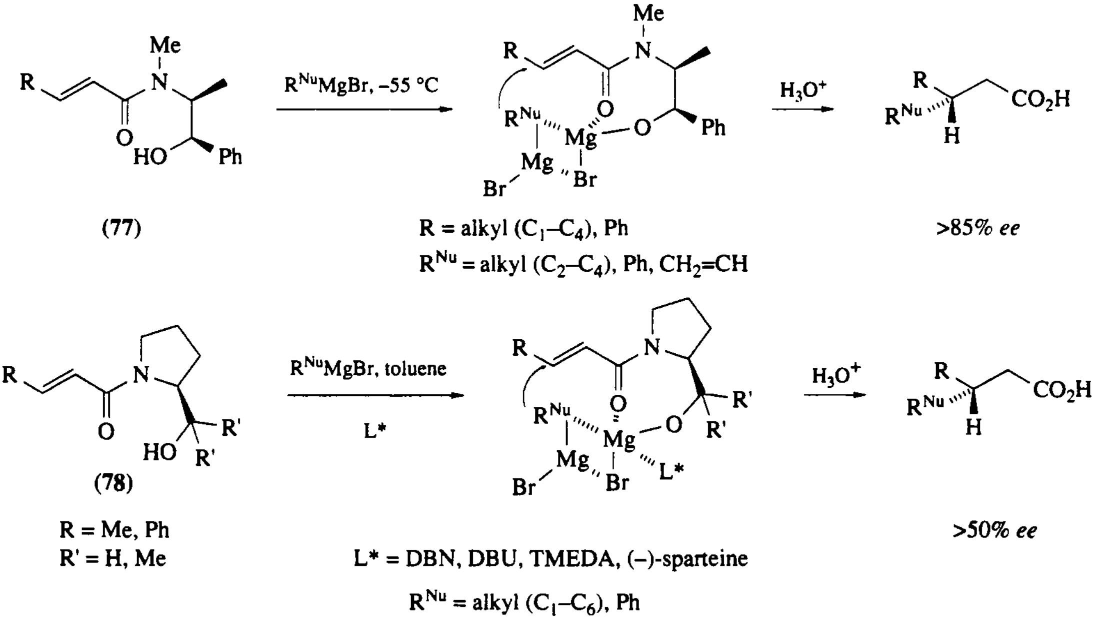

(77)
$R^{Nu}MgBr$, –55 °C
$H_3O^+$
R = alkyl ($C_1$–$C_4$), Ph
$R^{Nu}$ = alkyl ($C_2$–$C_4$), Ph, $CH_2$=CH
>85% *ee*
(78)
R = Me, Ph
R' = H, Me
$R^{Nu}MgBr$, toluene
L*
$H_3O^+$
>50% *ee*
L* = DBN, DBU, TMEDA, (–)-sparteine
$R^{Nu}$ = alkyl ($C_1$–$C_6$), Ph

**Scheme 26**

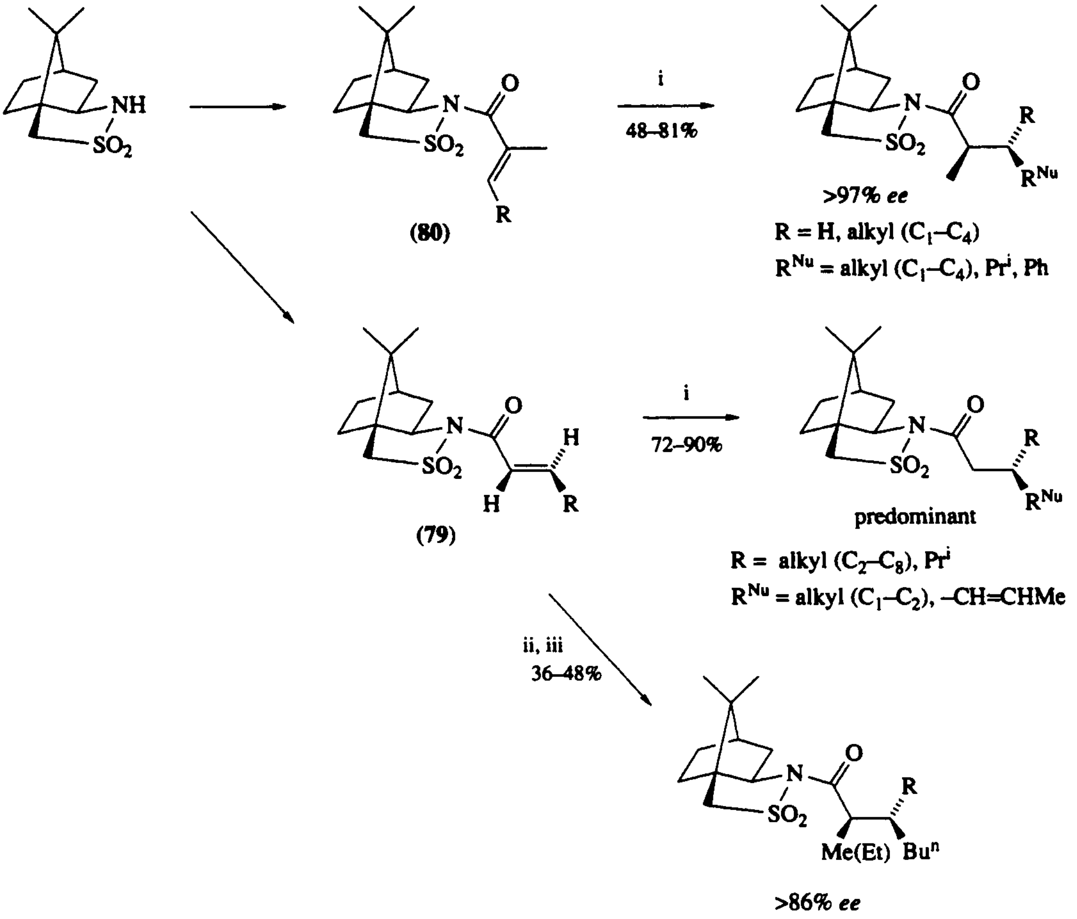
NH
SO2
N
SO2
O
R
(80)
i
48–81%
R
RNu
>97% ee
R = H, alkyl (C1–C4)
RNu = alkyl (C1–C4), Pri, Ph
H
H
R
(79)
i
72–90%
predominant
R = alkyl (C2–C8), Pri
RNu = alkyl (C1–C2), –CH=CHMe
ii, iii
36–48%
Me(Et)
Bun
>86% ee

i, $R^{Nu}MgCl$; ii, $Bu^nMgCl$; iii, MeI (EtI)

**Scheme 27**

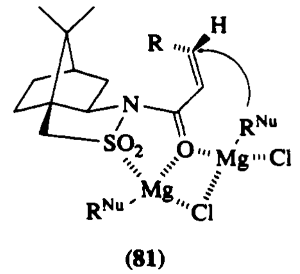
R
H
N
SO2
O
RNu
Mg
Cl
Mg
RNu
Cl

**(81)**

the intermediate nitronate salts,[78b,c] while aryl Grignard reagents add in a 1,2-addition mode to afford *N,N*-diarylamines and *N,N*-diarylhydroxylamines.[78d,e] The intermediate nitronate salts are subsequently oxidized with dichlorodicyano-1,4-benzoquinone (DDQ) or potassium permanganate,[79a] or treated with boron trifluoride to afford the *ortho*-alkylated nitroarenes or *ortho*-alkylated nitrosoarenes, respectively (Scheme 31).[79b]

Examples of Grignard reagent or other organometallic additions to α,β-unsaturated sulfoxides are rare, typically kinetic α-deprotonation occurs;[54b] however, the addition of methylmagnesium bromide to methylenecephem sulfoxide (**95**) affords the epimeric C-2 ethylcephems (**96**) in moderate yields (equation 16).[80] In contrast, Posner reports that Grignard reagents add to enantiomerically pure 2-(arylsulfinyl)-2-cycloalkenones with chirality transfer from the sulfoxide sulfur atom to the β-carbon; coupled with reductive removal of the sulfinyl group, this is equivalent to the enantioselective conjugate addition of Grignard reagents to α,β-enones.[81] The simple expedient of reacting (*S*)-(+)-(**97**) with an alkylmagnesium chloride or dialkylmagnesium, followed by reductive cleavage of the sulfinyl group affords the 3-

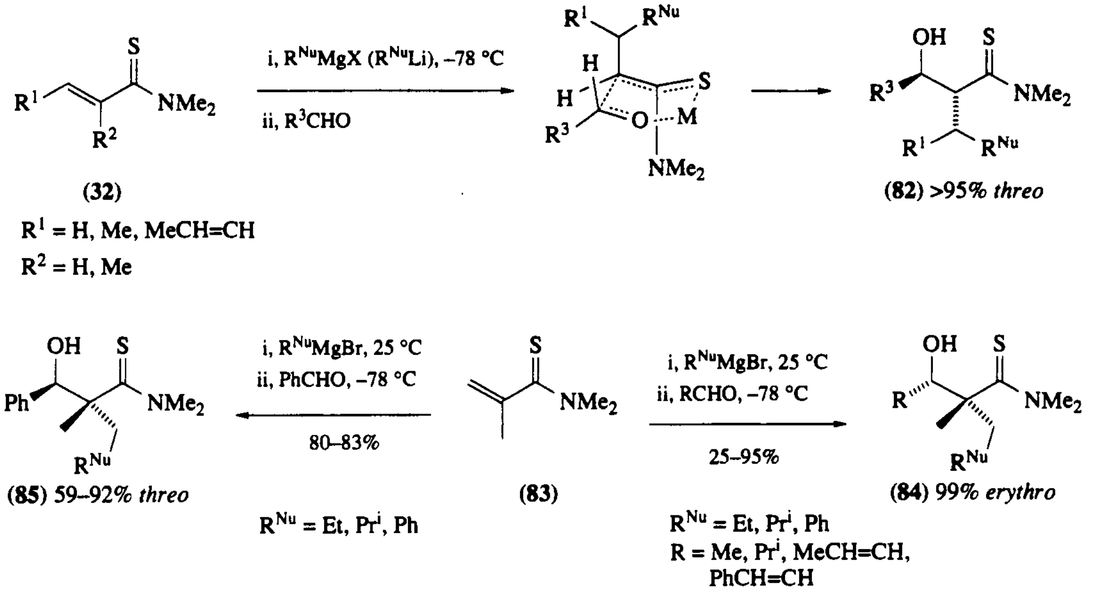
(32)
R¹ = H, Me, MeCH=CH
R² = H, Me
i, RNuMgX (RNuLi), -78 °C
ii, R³CHO
(82) >95% threo
(85) 59–92% threo
i, RNuMgBr, 25 °C
ii, PhCHO, -78 °C
80–83%
RNu = Et, Pri, Ph
(83)
i, RNuMgBr, 25 °C
ii, RCHO, -78 °C
25–95%
(84) 99% erythro
RNu = Et, Pri, Ph
R = Me, Pri, MeCH=CH, PhCH=CH

**Scheme 28**

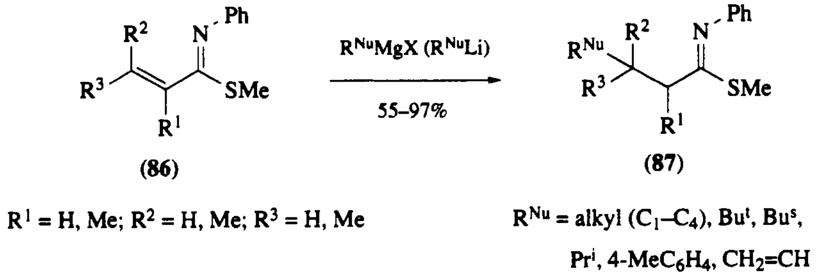
(86)
RNuMgX (RNuLi)
55–97%
(87)
R¹ = H, Me; R² = H, Me; R³ = H, Me
RNu = alkyl (C1–C4), But, Bus, Pri, 4-MeC6H4, CH2=CH

(13)

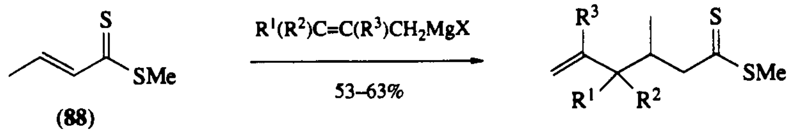
(88)
R¹(R²)C=C(R³)CH2MgX
53–63%

(14)

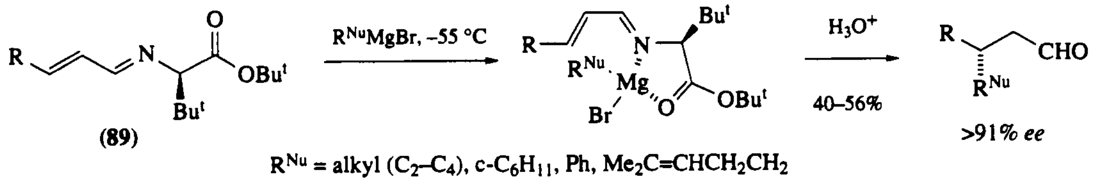
(89)
RNuMgBr, -55 °C
H3O+
40–56%
>91% ee
RNu = alkyl (C2–C4), c-C6H11, Ph, Me2C=CHCH2CH2

**Scheme 29**

substituted cycloalkenones, (*R*)-(+)-(**99**) and (*S*)-(–)-(**100**), respectively. Similarly, 6-methoxy-2-naphthylmagnesium bromide reacts with (*S*)-(+)-(**97**) to afford the steroidal intermediate (**101**, >98% *ee*; Scheme 32).

The stereoselectivity of addition is a consequence of the intrinsic differences in chelation tendencies between various alkylmagnesium halides and dialkylmagnesium reagents and the preferred *anti*-conformation of the sulfoxide and carbonyl groups. Organometallic reagents with low Lewis acidity or low chelation tendency, *i.e.* less electrophilic (RMgI or $R_2Mg$), add to the more accessible face of the enone double bond (**97**). In contrast, higher Lewis acidity organometallics (RMgCl or RMgX–$ZnBr_2$) form an initial chelate (**98**) with both the sulfoxide and carbonyl groups, followed by addition to the double bond *anti* to the aryl group.[82]

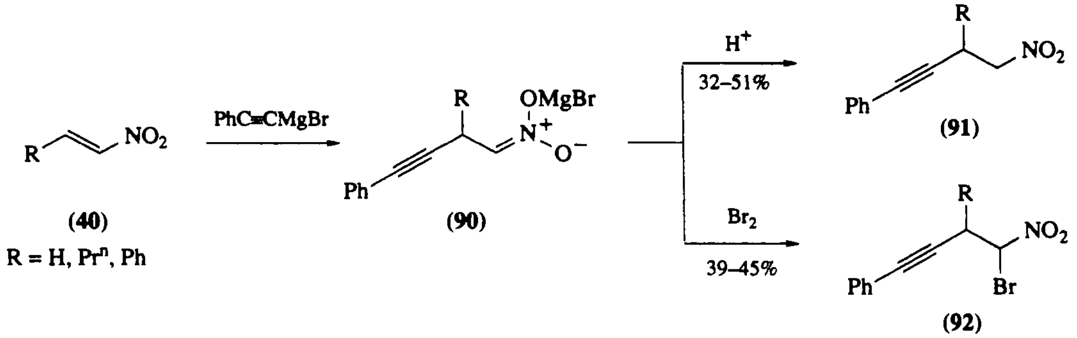
PhC≡CMgBr
(40)
R = H, Prⁿ, Ph
(90)
H⁺
32–51%
Br₂
39–45%
(91)
(92)

Scheme 30

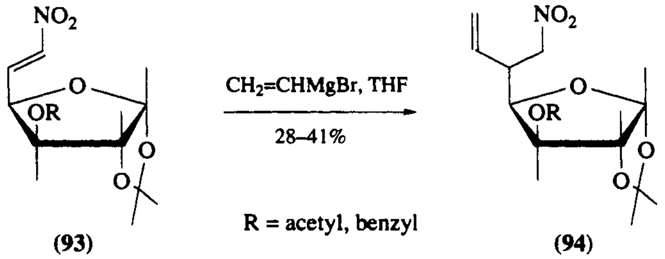
CH₂=CHMgBr, THF
28–41%
R = acetyl, benzyl
(93)
(94)

(15)

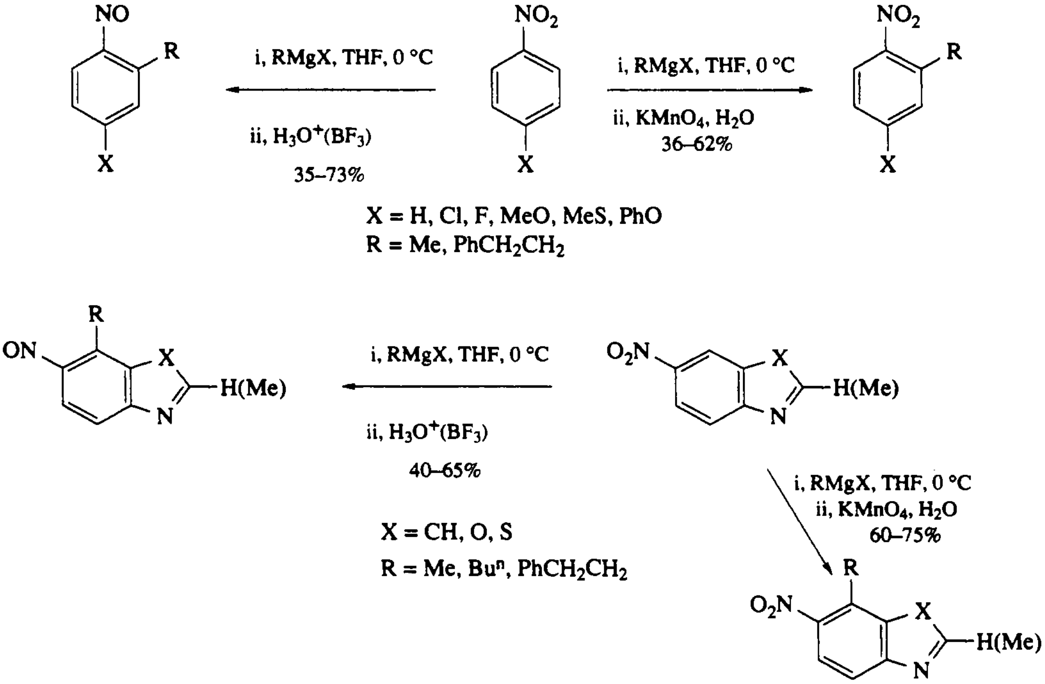
i, RMgX, THF, 0 °C
ii, H₃O⁺(BF₃)
35–73%
i, RMgX, THF, 0 °C
ii, KMnO₄, H₂O
36–62%
X = H, Cl, F, MeO, MeS, PhO
R = Me, PhCH₂CH₂
i, RMgX, THF, 0 °C
ii, H₃O⁺(BF₃)
40–65%
X = CH, O, S
R = Me, Buⁿ, PhCH₂CH₂
i, RMgX, THF, 0 °C
ii, KMnO₄, H₂O
60–75%

Scheme 31

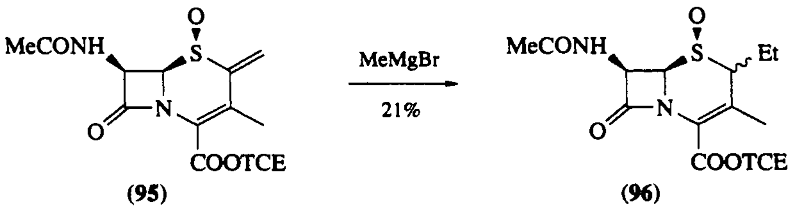
MeMgBr
21%
(95)
(96)

(16)

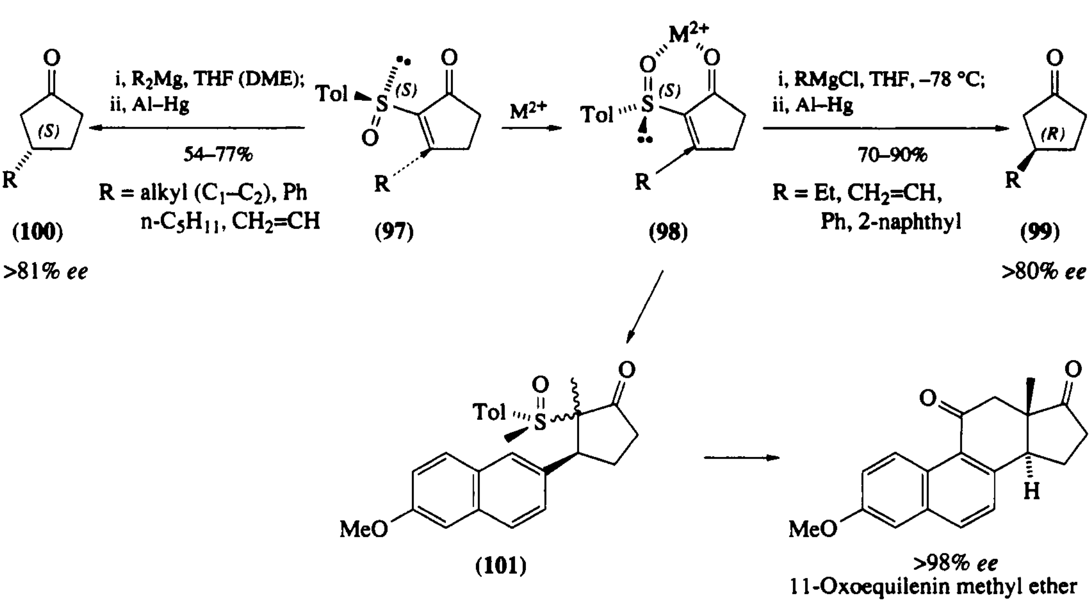
i, $R_2Mg$, THF (DME);
ii, Al–Hg
54–77%
R = alkyl ($C_1$–$C_2$), Ph
n-$C_5H_{11}$, $CH_2$=CH
(100)
>81% ee
(97)
$M^{2+}$
$M^{2+}$
(98)
i, RMgCl, THF, –78 °C;
ii, Al–Hg
70–90%
R = Et, $CH_2$=CH,
Ph, 2-naphthyl
(99)
>80% ee
Tol
MeO
H
(101)
>98% ee
11-Oxoequilenin methyl ether

**Scheme 32**

Eisch has reported that alkyl Grignard reagents add to γ-hydroxy-α,β-unsaturated phenyl sulfones (**102a**) to afford γ-hydroxysulfones (**103**) (*cf.* **49**) while nonalkyl Grignard reagents add to γ-bromo-α,β-unsaturated phenyl sulfones (**102b**) to afford *trans*-(phenylsulfonyl)cyclopropanes (**104**; Scheme 33).[83]

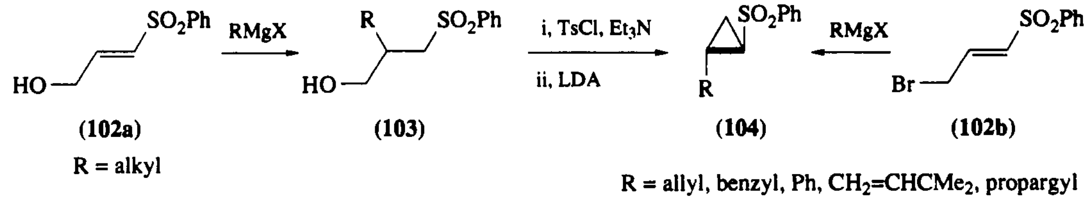
RMgX
(102a)
R = alkyl
(103)
i, TsCl, $Et_3N$
ii, LDA
(104)
RMgX
(102b)
R = allyl, benzyl, Ph, $CH_2$=$CHCMe_2$, propargyl

**Scheme 33**

The addition of Grignard reagents to 1,1-doubly activated alkenes, *e.g.* alkylidenemalonates (**105**),[68a,84a–d] alkylidenecyanoacetates (**106**),[84e,f] alkylideneisocyanatoacetates (**107**),[84g] alkylidenephosphonoacetates (**108**),[84h] isopropylidenemethylenemalonates (**109**)[84i,j] and their arylidene analogs, occurs in a 1,4-addition mode exclusively (Schemes 34 and 35). Similarly, as shown in Scheme 36, Mukaiyama reports that the addition of Grignard reagents to chiral oxazepines (**110**) and (**111**) affords an enantioselective synthesis of β-substituted carboxylic acids.[85]

Few comparative studies of the 1,4-addition capabilities of organomagnesium halides *vs.* diorganomagnesiums are available, although substrate and ligand variability is observed. Ethylmagnesium bromide shows a tendency to afford 1,4-addition products with 2-cyclohexen-1-one and *trans*-3-pentenone while diethylmagnesium affords exclusive 1,2-addition products.[86a] The addition of the homoenolate equivalent Grignard reagent (**112**) to alicyclic α,β-enones shows a temperature dependency in the ratios of 1,4-addition:1,2-addition, which varies from 1:1, at 0 °C, to 20:1, at –78 °C. The reversal of selectivity is attributed to low temperature alterations in the Schlenk equilibrium in which magnesium halides precipitate (or crystallize) from the reaction mixture, thus enriching the concentration of diorganomagnesium (**113**) in solution (Scheme 37).[86b]

### *1.2.2.1.3 Copper-catalyzed organomagnesium additions*

The first example of a copper(I)-catalyzed Grignard conjugate addition was that described by Kharasch and Tawney;[4] subsequently this protocol was the cornerstone for various natural products syntheses, but it lacked predictability and dependability.[87] Experimental aspects that affect the efficiency of copper(I)-catalyzed Grignard additions are the type of catalyst used and the order of addition; these factors should be determined experimentally. Numerous sources of copper(I) have been employed, among them are the copper(I) halides, copper(I) acetate, copper(I) *t*-butoxide, copper(I) cyanide, copper(I) thiophenolate and copper(I) bromide–dialkyl sulfide complexes.[87d] Some of the conflicting experimental results from earlier studies were due to contamination with copper(II) species which oxidize

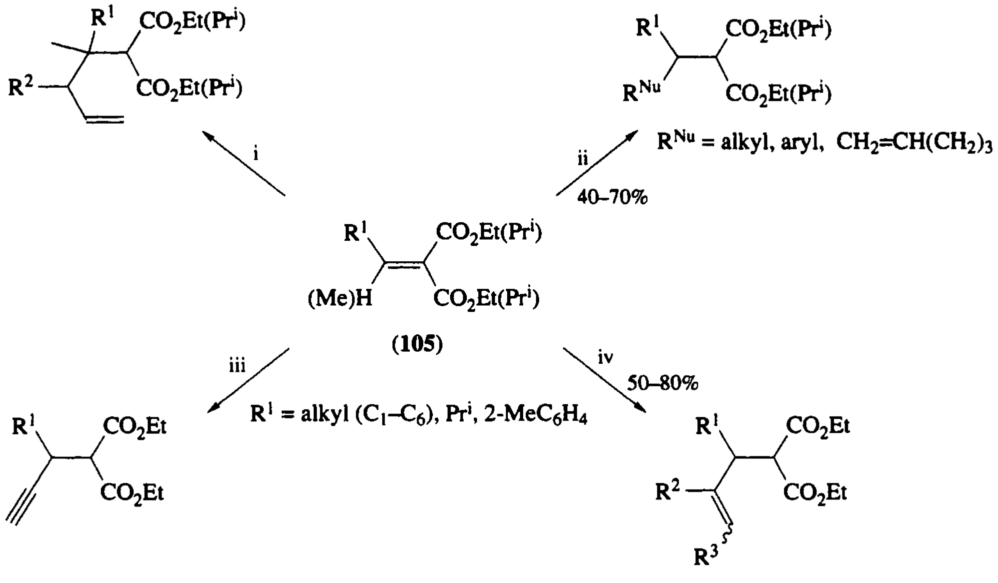

$R^1$
$CO_2Et(Pr^i)$
$R^2$
$CO_2Et(Pr^i)$
i
ii
$R^{Nu}$ = alkyl, aryl, $CH_2$=$CH(CH_2)_3$
40–70%
$(Me)H$
(105)
iii
iv
50–80%
$R^1$ = alkyl ($C_1$–$C_6$), $Pr^i$, 2-$MeC_6H_4$
$CO_2Et$
$R^3$

$R^2$ = H, alkyl; $R^3$ = H, alkyl

i, $R^2CH$=$CHCH_2MgBr$; ii, $R^{Nu}MgX$; iii, $HC{\equiv}CMgBr$; iv, $R^3CH$=$C(R^2)MgBr$

Scheme 34

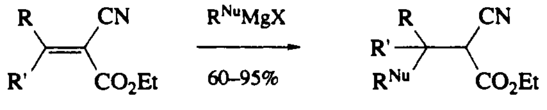

R
CN
R'
$CO_2Et$
$R^{Nu}MgX$
60–95%
$R^{Nu}$

(106)

R = alkyl, aryl, $CCl_3$; R' = alkyl, Ph, $CH_2$=$C(Me)CH_2$; $R^{Nu}$ = alkyl, allyl

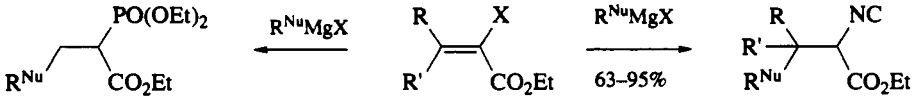

$PO(OEt)_2$
$R^{Nu}$
$CO_2Et$
$R^{Nu}MgX$
R
X
R'
63–95%
NC

(107) X = NC
(108) X = $PO(OEt)_2$

R = H, alkyl, aryl; R' = alkyl, Ph, 3,4-$(MeO)_2C_6H_3$; $R^{Nu}$ = alkyl, Ph

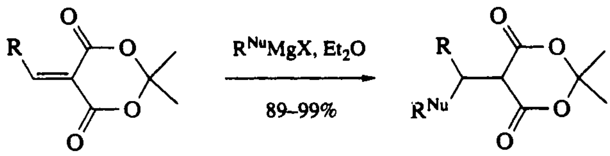

O
R
$R^{Nu}MgX$, $Et_2O$
89–99%
$R^{Nu}$

(109)

R = Ph, 2-thienyl, 1-naphthyl, (*E*)-PhCH=CH; $R^{Nu}$ = alkyl, Ph

Scheme 35

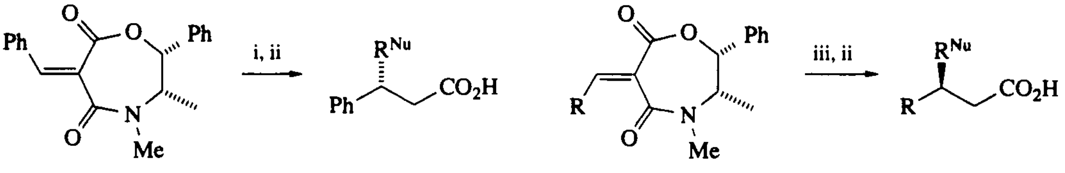

*(Z)*-**(110)** >99% *ee* *(E)*-**(111)** >58% *ee*

$R^{Nu}$ = alkyl ($C_1$–$C_4$)

R = alkyl ($C_1$–$C_4$), $Pr^i$, Ph

$R^{Nu}$ = alkyl ($C_1$–$C_4$), $Pr^i$, Ph

i, $R^{Nu}MgBr–NiCl_2$; ii, $H_3O^+$; iii, $R^{Nu}MgBr$

**Scheme 36**

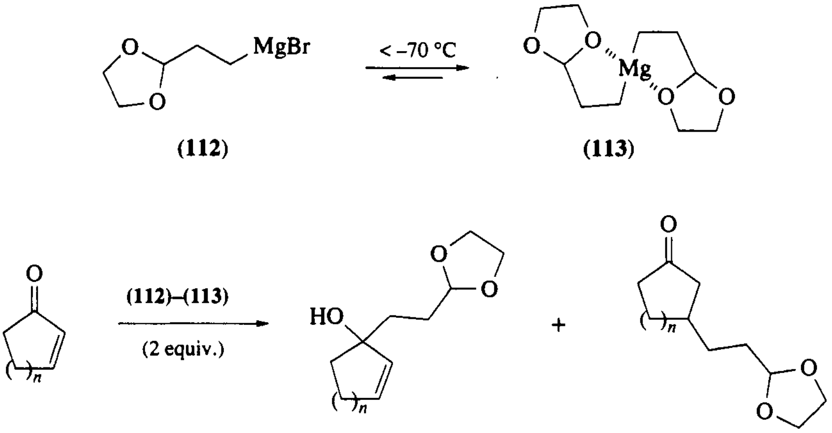

**(112)** **(113)**

| *n* | *Temp.* (°C) | *Yield* (%) | *1,2 vs. 1,4* |
|---|---|---|---|
| 1 | -78 | 73 | 5:95 |
| 1 | 25 | 69 | 78:22 |
| 2 | -78 | 80 | 13:87 |
| 2 | 25 | 98 | 88:12 |

**Scheme 37**

the reactive intermediates, and the low solubility of the copper(I) salts which lead to heterogeneous reactions. Because of the advent of the stoichiometric organocopper reagents (Volume 4, Chapter 1.4), this method of C—C bond formation is rarely employed; however, under certain conditions the copper(I)-catalyzed Grignard additions offer advantages over the stoichiometric organocuprates. The stereoselectivity of copper-catalyzed Grignard additions is similar to that found with stoichiometric organocopper reagents. The examples highlighted have been arbitrarily chosen where the catalyst comprises <25 mol %.

Copper-catalyzed Grignard additions to α,β-enones, α,β-unsaturated esters and 1,1-doubly activated alkenes have been extensively studied. For example, catalyzed additions of alkyl, aryl and vinylic Grignard reagents to alkylidenecycloalkanones and cycloalkenones proceed in excellent yields (Scheme 38).[88a–e] As exemplified in Scheme 39, the conjugate addition of the homoenolate equivalent Grignard reagent (**112**) and bishomoenolate equivalent Grignard reagent (**114**) to cycloalkenones is the basis of general cyclopentenocycloalkanone and cyclohexenocycloalkanone syntheses.[88f] Similarly, the synthesis of a prototypical prostaglandin (**115**) was accomplished by a copper(I)-catalyzed conjugate addition of a Grignard reagent to an appropriate cyclopentenone.[88g] The presence of a proximal nitrogenous functionality on an α,β-enone acceptor is not detrimental to catalyzed Grignard additions, as shown in Scheme 40, by the use of basic alkaloid intermediates and β-enaminones.[89]

The catalyzed conjugate addition of Grignard reagents to α,β-enones affords, in principle, regiospecific enolates which can be intercepted with electrophiles under non-equilibrating, kinetically controlled conditions; however, few examples have been reported.[90] The conjugate addition of Grignard reagents to

2-cyclohexen-1-one and 3-methyl-2-cyclohexen-1-one affords the intermediate cyclohex-1-enolates which can undergo *C*-acylation,[90b] alkylation[90c,d] or aldol condensation (Scheme 41).

Ethyl acrylate reacts efficiently under the copper-catalyzed Grignard addition protocol, in which the combination of low temperatures (–20 → –50 °C) and catalytic copper(I) chloride (2.6%) was necessary to afford moderate to excellent yields of 1,4-addition products, while elaboration of complex α,β-unsaturated esters is not predictable.[91a] In contrast, addition to the α,β-unsaturated ester (**116**) affords the

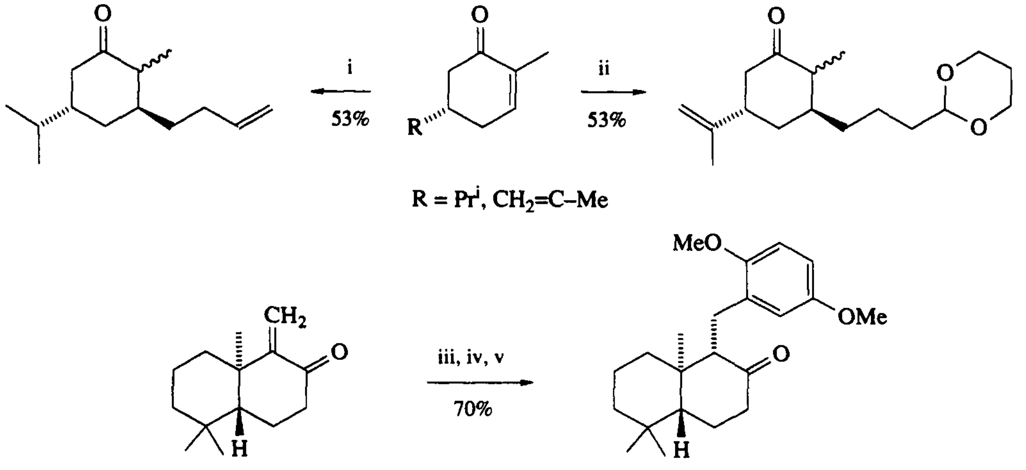
O
i
53%
R
ii
53%
R = Pr$^i$, CH$_2$=C–Me
CH$_2$
O
H
iii, iv, v
70%
MeO
OMe
O
H

i, $CH_2=CHCH_2CH_2MgBr$, CuI (5%), THF, 0 °C; ii, 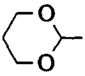 $-(CH_2)_3MgCl$, CuI (5%), THF, 0 °C;
iii, 2,5-$(MeO)_2C_6H_3MgBr$, CuI (20%), DME, 0 °C; $(MeCO)_2O$; v, $HO^-$

**Scheme 38**

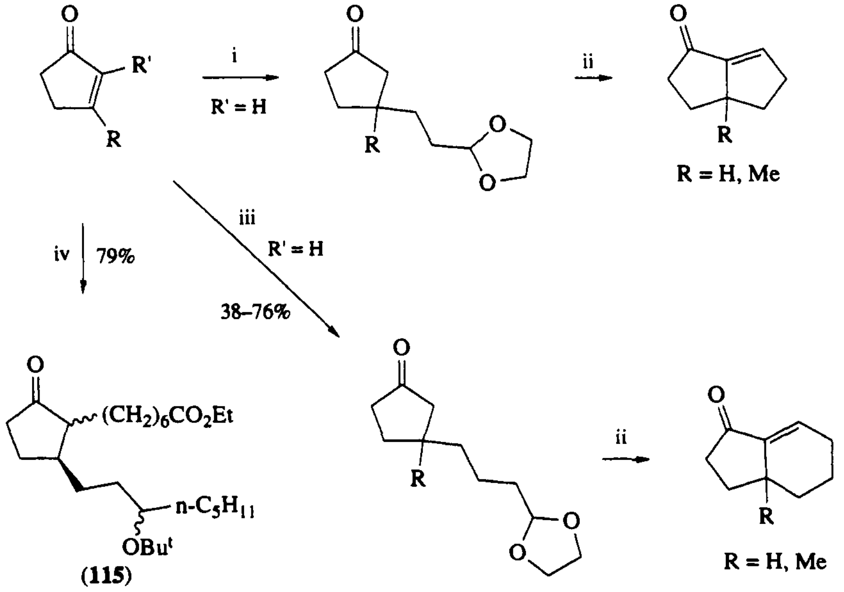
O
R'
R
i
R' = H
O
R
ii
R = H, Me
iv
79%
iii
R' = H
38–76%
(CH$_2$)$_6$CO$_2$Et
n-C$_5$H$_{11}$
OBu$^t$
(115)
ii
R = H, Me

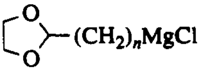

(**112**) $n = 2$
(**114**) $n = 3$

i, (**112**), $CuBr-Me_2S$ (25%), THF, –78 °C; ii, $H_3O^+$;
iii, (**114**), $CuBr-Me_2S$ (25%), THF, –78 °C;
iv, n-$C_5H_{11}CH(OBu^t)CH_2CH_2MgBr$, CuI–$(Bu^n)_3P$ (5%), THF, 0 °C

**Scheme 39**

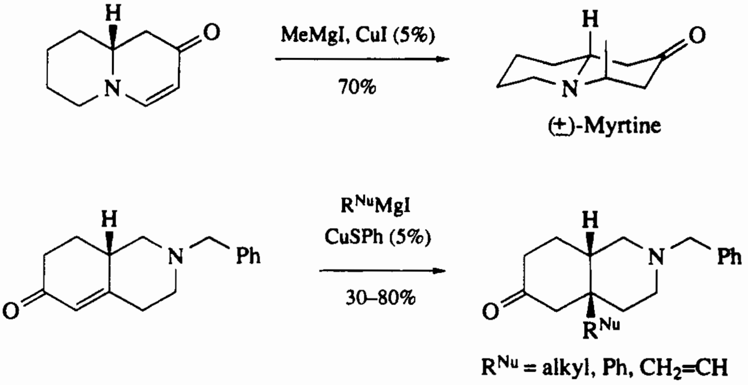

**Scheme 40**

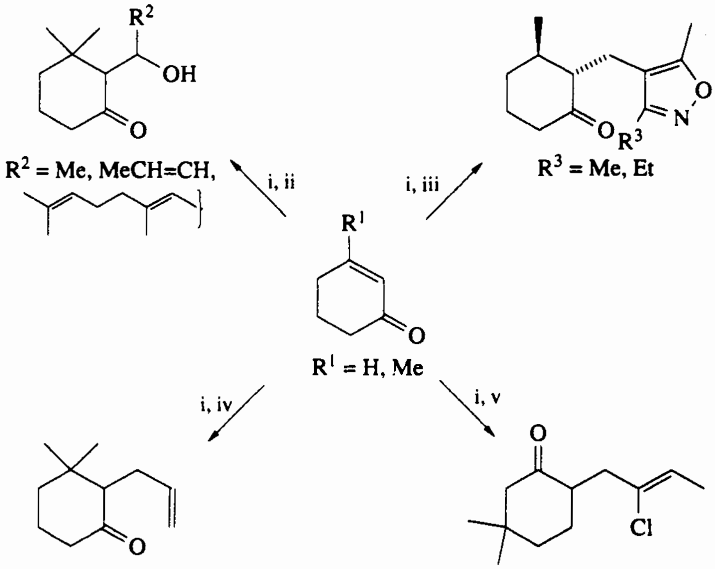

i, MeMgX, CuCl (5%); ii, $R^2CHO$; iii, chloromethylisoxazole;
iv, $CH_2{=}CHCH_2Br$; v, $CH_2{=}C(Cl)CH_2Cl$

**Scheme 41**

*manno* adduct (**117**) exclusively (Scheme 42).[91b] Asami and Mukaiyama have reported that enantioselective catalyzed Grignard additions to the chiral β-aminal-α,β-unsaturated ester (**118**) affords 3-alkylsuccinaldehydic methyl esters in >85% *ee* and moderate yields (Scheme 43).[92]

The catalyzed addition of Grignard reagents to 1,1-doubly activated alkenes (**105–108**) is a highly efficient process;[93a–c] notable are additions to *N*-acyldehydroamino acid ester (**119**), which cannot be accomplished with lithium dialkylcuprates (Scheme 44).[93d]

Itoh reports that copper-catalyzed Grignard additions to *N*-tosyl-*N*-alkyl-α,β-unsaturated amides and *N*-tosyl-α,β-unsaturated lactams proceed efficiently while deprotonation occurs exclusively with the corresponding *N*-alkyl-α,β-unsaturated lactams (Scheme 45).[94]

### *1.2.2.1.4 Organozincs*

The organozincs were one of the first organometallic reagents synthesized, but interest in these reagents waned with the discovery of the more reactive and easier to handle Grignard reagents.[95] Within this class of organometallics there are four groups: (a) diorganozincs (**120**), (b) organozinc halides (**121**), (c) lithium triorganozincates ('ate' complex) (**122**) and (d) α-(alkoxycarbonyl)alkylzinc halides (**123**),

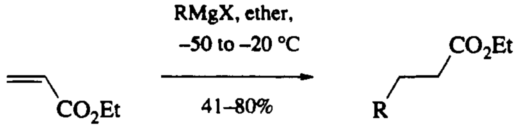
RMgX, ether,
–50 to –20 °C
41–80%
$CO_2Et$
$CO_2Et$
R

R = n-$C_5H_{11}$, c-$C_6H_{11}$, Ph, $CH_2$=$CH(CH_2)_4$, $CH_2$=CH, $PhCH_2$

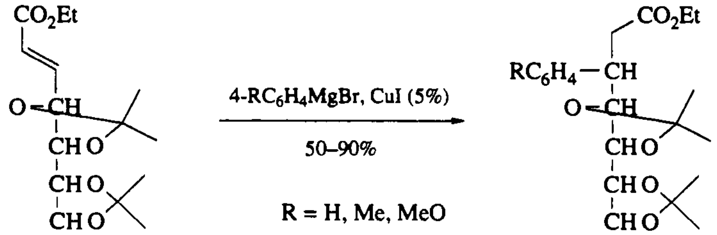
$CO_2Et$
O–CH
CHO
CHO
CHO
4-$RC_6H_4MgBr$, CuI (5%)
50–90%
R = H, Me, MeO
$CO_2Et$
$RC_6H_4$–CH
O–CH
CHO
CHO
CHO

**(116)** **(117)**

Scheme 42

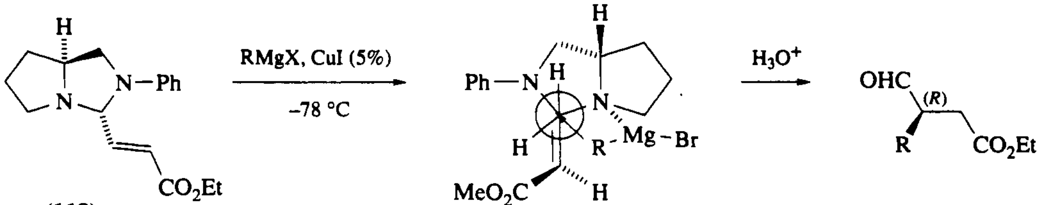
H
N–Ph
N
$CO_2Et$
RMgX, CuI (5%)
–78 °C
H
Ph–N
H
N
Mg–Br
H
R
$MeO_2C$
H
$H_3O^+$
OHC
(R)
R
$CO_2Et$

**(118)**

R = alkyl ($C_2$–$C_5$), $Pr^i$
>85% *ee*

Scheme 43

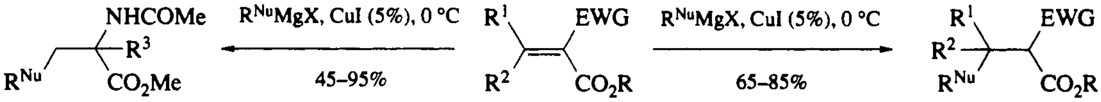
NHCOMe
$R^3$
$R^{Nu}$
$CO_2Me$
$R^{Nu}MgX$, CuI (5%), 0 °C
45–95%
$R^1$
EWG
$R^2$
$CO_2R$
$R^{Nu}MgX$, CuI (5%), 0 °C
65–85%
$R^1$
EWG
$R^2$
$R^{Nu}$
$CO_2R$

$R^{Nu}$ = alkyl ($C_2$–$C_4$), $Pr^i$, $Bu^t$,
phenyl, naphthyl
$R^3$ = H, Me

**(105)** EWG = $CO_2R$
**(106)** EWG = CN
**(107)** EWG = NC
**(108)** EWG = $PO(OEt)_2$
**(119)** EWG = NHCOMe

$R^{Nu}$ = alkyl, phenyl

Scheme 44

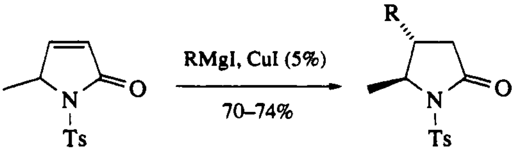
O
N
Ts
RMgI, CuI (5%)
70–74%
R
O
N
Ts

R = Me, Ph, 4-$MeOC_6H_4$

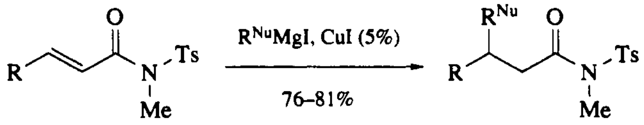
O
R
N
Ts
Me
$R^{Nu}MgI$, CuI (5%)
76–81%
$R^{Nu}$
O
R
N
Ts
Me

R = Me, Ph; $R^{Nu}$ = Me, Ph

Scheme 45

*i.e.* Reformatsky reagents. In general, the organozincs and organocoppers have similar reactivity profiles, but the organozincs are tolerant of higher reaction temperatures.

$R_2Zn$ **(120)**

$RZnX$ **(121)**

$LiR_3Zn$ **(122)**

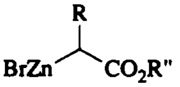

$BrZnCH(R)CO_2R''$

**(123)**

The diorganozincs are classified into two subgroups based on contrasting reactivity profiles: (a) the dialkylzincs and the diarylzincs and (b) the allylic, benzylic and propargylic zincs. The dialkylzincs (diarylzincs) are characterized by their low reactivity towards carbonyl groups[96] and other unsaturated species, while the allylic (benzylic or propargylic) zincs are highly reactive. Traditionally, they are prepared by several routes: (a) thermal recombination of organozinc halides or (b) transmetallation of organolithiums (or Grignard reagents) with an anhydrous zinc halide. The transmetallation process affords byproduct magnesium halides (or lithium halides) which modify the reactivity of the diorganozincs ($MgX_2 \gg LiX$).[23,97] Recent developments in ultrasonic reaction methodology[98] have permitted rapid, quantitative one-pot syntheses of diverse diorganozinc reagents from alkyl bromides (iodides), allylic or benzylic bromides (iodides), or vinyl bromides (iodides) with minimal competing Wurtz coupling. The dialkylzincs (diarylzincs) react easily with α,β-enones (0–25 °C) and α,β-unsaturated aldehydes (–40 °C) in the presence of nickel acetylacetonate [$Ni(acac)_2$] (1%), as shown in Scheme 46;[99a,b] further alkylation of the intermediate zinc enolates is readily accomplished. In contrast to the stoichiometric organocuprates or the copper(I)-catalyzed Grignard reagents, these reagents add efficiently to β,β-disubstituted enones, as shown for two syntheses of (±)-β-cuparenone (**124**).[99c]

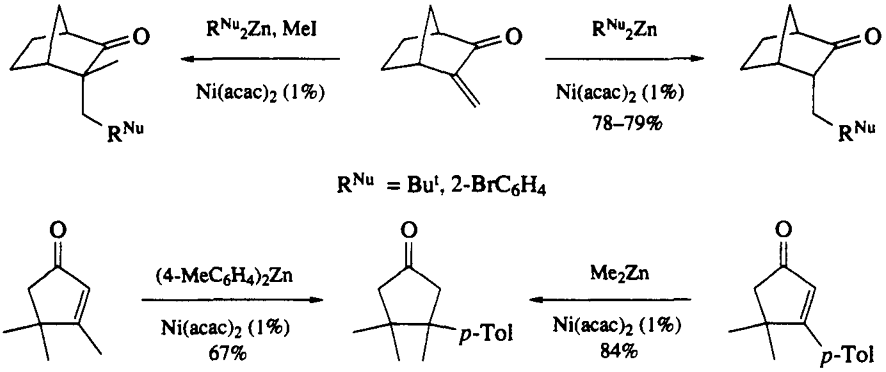

$R^{Nu} = Bu^t$, $2\text{-}BrC_6H_4$

**(124)**

**Scheme 46**

The organozinc halides are prepared by either of two processes: (a) selective transmetallation between an organolithium (or Grignard reagent) (1 equiv.) and an anhydrous zinc halide or (b) oxidative metallation of an organic halide. Typically these reagents are generated *in situ* because of thermal instability, which affords the less reactive diorganozincs and zinc halides. Few examples of syntheses with alkylzinc halides are known, but they retain their inertness towards various functionalities and are characterized by their exclusive 1,4-addition chemistry. A prime example, as shown in Scheme 47, is an alkylzinc halide promoted tandem 1,4-conjugate addition to α-halo-α,β-unsaturated esters to afford exclusively 1-alkyl-2-halo-*cis*-cyclopropanedicarboxylate esters (**125**).[100] Another variation is exemplified by the zinc-promoted three component coupling of alkyl halides, activated alkenes and ketones to afford β-hydroxyesters (nitriles) (**126**).[101] This process, in essence, is the equivalent of coupling a nitrile (or ester) with a carbonyl species (Scheme 47).

The addition of allylic (or benzylic) zinc halides to alkylidenemalonates (**105**),[102a–c] alkylidenecyanoacetates (**106**),[102d,e] alkylidenephosphonoacetates (**108**),[84h] alkylidene barbiturates[102f] and their arylidene analogs occurs exclusively in a 1,4-addition mode. However, the addition of allylic zinc halides to alkylidenemalonates (**105**) is temperature dependent; at low temperatures (–15 °C), the homoallylic malonate (**128**) is obtained, while at higher temperatures (68 °C) the isomeric 2-cyclopentenedicarboxylate esters (**129**) are obtained by a zinc halide promoted electrocyclic closure of the intermediate ester (**127**; Scheme 48).[102g]

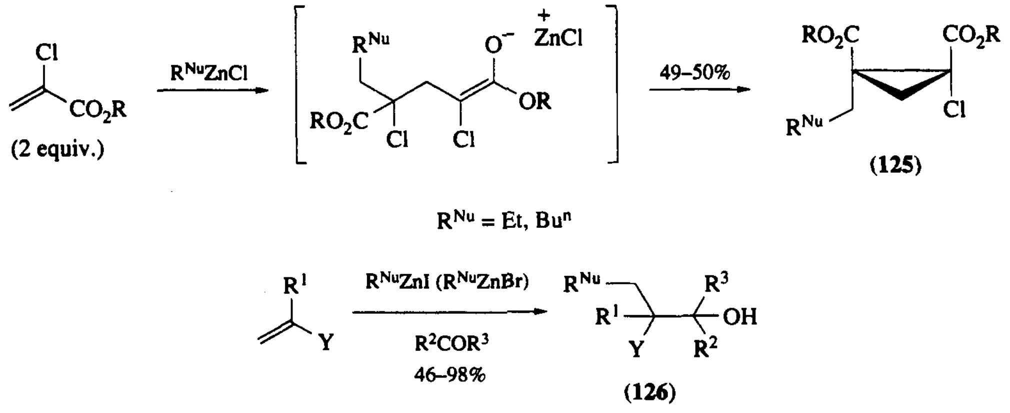

$R^{Nu}$ = Et, $Bu^n$

$R^1$ = H, Me; $R^2$ = alkyl, Ph; $R^3$ = H, alkyl; $R^{Nu}$ = alkyl, c-$C_6H_{11}$, benzyl; Y = CN, $CO_2Me$

**Scheme 47**

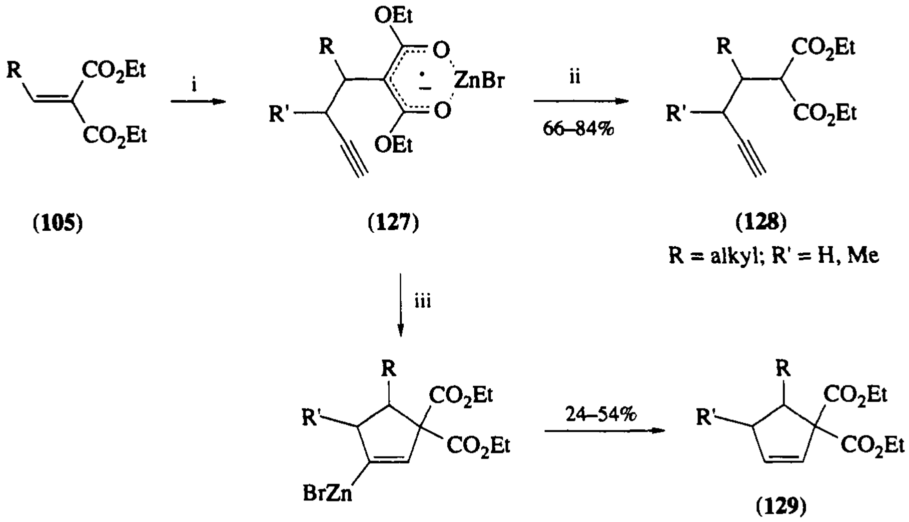

R = alkyl; R' = H, Me

R = alkyl; R' = H, Me

i, R'CH(Br)C≡CH, Zn, THF; ii, −15 °C, 48 h; iii, 65 °C, 48 h

**Scheme 48**

In contrast to the parent diorganozincs, the lithium triorganozincates (**122**) are more reactive, but few examples of their use in synthesis are available. The first lithium triorganozincates, lithium triphenylzincate and lithium diethyl(1,1-diphenyl-*n*-hexyl)zincate, were prepared by the reaction (1:1) of an organolithium with a symmetrical diorganozinc (Method A) and characterized by either reaction with benzalacetophenone or spectroscopically.[103a,b] Subsequently, two expedient syntheses of lithium and magnesium triorganozincates were reported in which either anhydrous zinc chloride–*N*,*N*,*N'*,*N'*-tetramethylethylenediamine complex ($ZnCl_2 \cdot$TMEDA) (Method B)[104] or anhydrous zinc chloride (Method C) is treated with an alkyllithium or Grignard reagent (3 equiv.). The symmetrical triorganozincates effect 1,4-additions to α,β-enones with indiscriminate transfer of ligands, but with unsymmetrical triorganozincates, alkynyl and aryl ligands transfer slowly due to stabilized covalent carbon–zinc bonds. Method A is the method of choice for the synthesis of 'salt-free' unsymmetrical organozincates[103c] while method B affords zincates complexed with TMEDA. In general, organozincates made by method B afford higher yields of conjugate addition products.

By analogy to the mixed cuprates, unsymmetrical organozincates (**130**) have been introduced to overcome the ligand wastage in which methyl groups do not transfer as readily as other alkyl ligands.[105] The unsymmetrical organozincates exhibit selectivity for ligand transfer with the lithium (or magnesium) alkyldimethylzincates, $RMe_2ZnLi$, being optimal with the order of ligand transfer preferences being:

$\mathrm{PhMe_2Si} \gg \mathrm{CH_2{=}CH}$, Et, $\mathrm{Bu^n}$, $\mathrm{Pr^i} > \mathrm{Bu^i}$, Ph > Me, $\mathrm{Bu^t} \gg \mathrm{Bu^tCH_2}$. This is exemplified in Scheme 49 by an expedient prostaglandin synthesis in which the preferential transfer of vinyl ligands *vs.* methyl groups occurs with zincate (**132**).[105b] In contrast to the diorganozincs, the triorganozincates are sensitive to β-substitution on the α,β-enones and transition metal catalysis has negligible effect on either the chemoselectivity or the rate of reaction of these reagents.

$$\mathrm{ZnCl_2{-}TMEDA} \xrightarrow[\text{(Method B)}]{\text{RLi (RMgX) (3 equiv.)}} \underset{\textbf{(122)}}{\mathrm{LiR_3Zn}} \xleftarrow[\text{(Method C)}]{\text{RLi (RMgX) (3 equiv.)}} \mathrm{ZnCl_2}$$

$$\mathrm{R_2Zn} \xrightarrow[\text{(Method A)}]{\text{R'Li}} \underset{\textbf{(130)}}{\mathrm{LiR_2R'Zn}} \xleftarrow[\text{(Method B)}]{\text{i, RLi (2 equiv.); ii, R'Li (1 equiv.)}} \mathrm{ZnCl_2{-}TMEDA}$$

$$\mathrm{ZnCl_2{-}TMEDA} \xrightarrow{\text{i, KOBu}^t\text{ (1 equiv.) ii, RMgX (2 equiv.)}} \underset{\textbf{(131)}}{\mathrm{R_2(Bu^tO)ZnMgBr{-}TMEDA}}$$

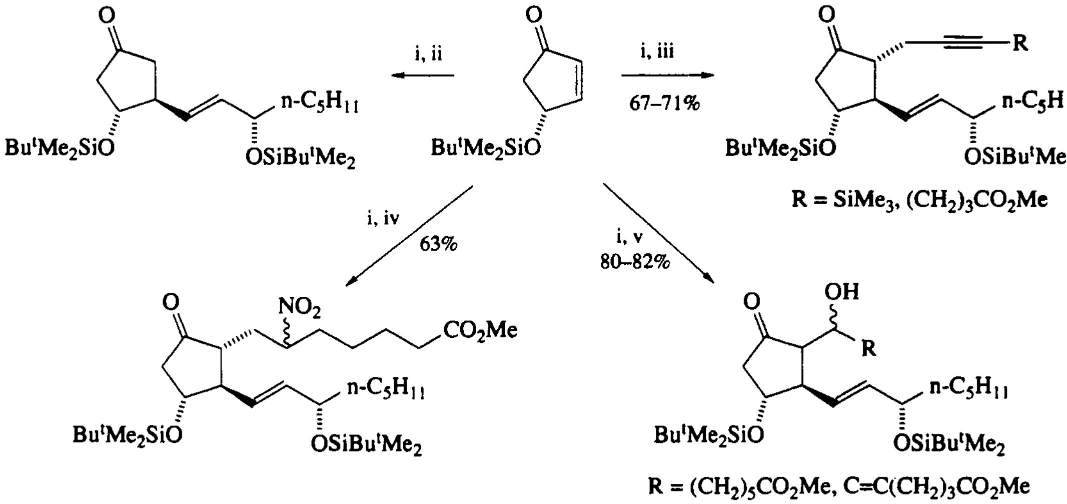

i, Li $(E)$-$\mathrm{Me_2ZnCH{=}CHCH(OSiBu^tMe_2)}$-n-$\mathrm{C_5H_{11}}$ (**132**); ii, $\mathrm{H_3O^+}$; iii, $\mathrm{BrCH_2C{\equiv}CR}$, HMPA, –78 to –40 °C; iv, $\mathrm{CH_2{=}C(NO_2)(CH_2)_3CO_2Me}$; v, RCHO, $\mathrm{Et_2O{\bullet}BF_3}$

**Scheme 49**

Feringa reports that alkyl heterozincates (**131**), made from zinc chloride·TMEDA complex, potassium *t*-butoxide and alkyl Grignard reagents in ether (or tetrahydrofuran), are highly effective in 1,4-additions to α,β-enones (>85%) while the aryl heterozincates are less efficient (<50%).[106]

Reformatsky first introduced electron-withdrawing substituents on the α-carbon of an organozinc halide, leading to the more reactive and thermally stable α-(alkoxycarbonyl)alkylzinc halides (**123**).[107a] Typically these reagents react with aldehydes or ketones to afford β-hydroxy esters while nitriles afford β-keto esters (Blaise reaction),[107b,c] but 1,4-conjugate additions to select α,β-unsaturated ketones are precedented (Section 1.2.2.2.2).

### 1.2.2.1.5 Organocadmiums

The reactivity of the organocadmiums has been the subject of numerous conflicting reports.[108a] Many of these organocadmium reagents are typically prepared by transmetallation of a Grignard reagent with anhydrous cadmium chloride (or bromide) in ether which generates byproduct magnesium halides which enhance ('activate') the nucleophilicity of the organocadmiums *via* a four-centered complex.[108b–d] Removal of the incipient magnesium halides is accomplished in two ways: (a) distillation or sublimation of the reagent or (b) precipitation of the salts with dioxane.

The reactivity of the 'salt-free' diorganocadmiums can be divided into two groups, (a) alkyl- and arylcadmiums and (b) allylic and benzylic cadmiums, with the latter group being more reactive. The 'salt-free' alkyl- or aryl-cadmiums participate in 1,4-conjugate additions to α,β-unsaturated ketones,[103a,109a–e] α-nitroalkenes (**40**),[109f] alkylidenemalonates (**105**),[109g] alkylideneacetoacetates[109b] and alkylidenecyanoacetates (**106**).[109g,h] In contrast, the allylic and benzylic cadmiums react exclusively in a 1,2-mode.[110]

### 1.2.2.1.6 Organomanganese

Organomanganese reagents were first reported to undergo exclusive 1,4-addition to benzalacetophenone, but interest in these reagents was minimal.[6] Depending on the stoichiometry, the transmetallation of organolithiums (or Grignard reagents) with anhydrous manganese(II) iodide affords organomanganese halides (RMnX), diorganomanganese ($R_2Mn$) or manganate complexes ($R_3MnLi$ or $R_3MnMgX$) which are poor reactants for the conjugate addition process. However, in the presence of copper(I) iodide (<5.0%), conjugate additions of organomanganese halides to α,β-enones occur efficiently. Even β,β-disubstituted-α,β-enones, *e.g.* 4-methyl-3-penten-2-one, which react with difficulty with organocopper reagents and copper-catalyzed Grignard reagents, undergo conjugate additions efficiently (Scheme 50).[111]

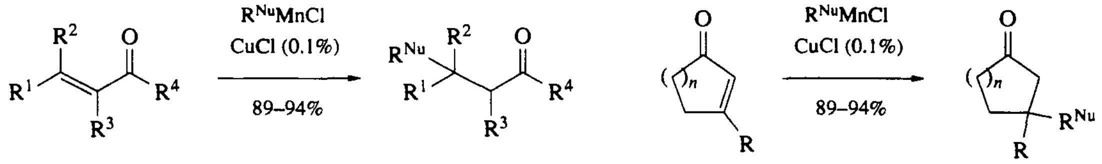

$R^1$ = H, Me, $Pr^n$
$R^2$ = H, $Bu^n$, n-$C_5H_{11}$
$R^3$ = H, Me
$R^4$ = $Bu^n$, n-$C_5H_{11}$

$R^{Nu}$ = $Bu^n$, n-$C_5H_{11}$

R = H, Me
*n* = 1, 2

$R^{Nu}$ = alkyl ($C_1$-$C_4$), $Bu^t$,
Ph, $Me_2C{=}CH$, PhCH=CH

Scheme 50

### 1.2.2.1.7 Organosilanes

The cleavage of organosilanes to form anionic species was first reported by Brook;[112] subsequently, Sakurai and coworkers reported that the fluoride ion mediated desilylation of allyltrimethylsilane in the presence of α,β-enones afforded mixtures of 1,2-addition (predominant) and 1,4-addition products.[113] Less electrophilic Michael acceptors, *e.g.* α,β-unsaturated nitriles, α,β-unsaturated esters or α,β-unsaturated *N*,*N*-dialkylamides, were found to afford exclusive 1,4-addition by the fluoride ion mediated desilylation of allyltrimethylsilanes, benzyltrimethylsilanes or heteroaryltrimethylsilanes.[114] The use of either cesium fluoride or tetra-*n*-butylammonium fluoride in HMPA affords optimal yields of 1,4-adducts (Scheme 51). This allylation procedure complements the original Lewis acid catalyzed procedure (Volume 4, Chapter 1.3) of α,β-enones which fails with the above substrates.[113b] Typically, fluoride-mediated conjugate allylation yields are comparable to those obtained by the addition of lithium diallylcuprate.[114b] Data point towards the reactive species being an intermediate hypervalent fluorosilicon species (**133**). Similarly, Panek found that the fluoride ion catalyzed addition of 1-acyloxy-2-propenyltrimethylsilanes (**134**) to α,β-enones affords exclusive $1,4_{(\alpha)}$-addition of the 1-acyloxy-2-propenyl moiety with moderate diastereoselectivity (Scheme 52).[115]

Majetich reports that the fluoride ion catalyzed carbocyclization of allyl anion equivalents to α,β-enones is sensitive to the structure of the α,β-enone in which competing 1,2- and 1,4-addition processes occur.[116] For example, α,β-enones (**135**) afford predominantly the *syn*-bicyclo[4.3.0]nonan-3-ones (**136**)

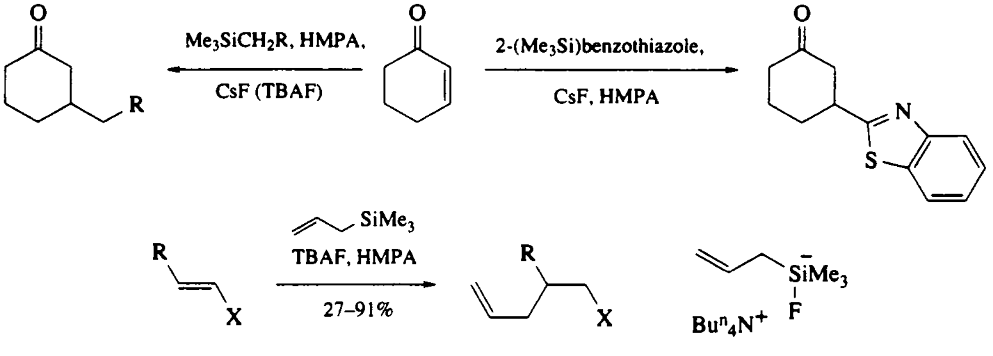

(133)

R = H, Bu$^t$, $CO_2Me$, Ph, 3-furyl, PhCH=CH; X = CN, $CO_2Me$, $CO_2CH_2Ph$, $CONEt_2$

Scheme 51

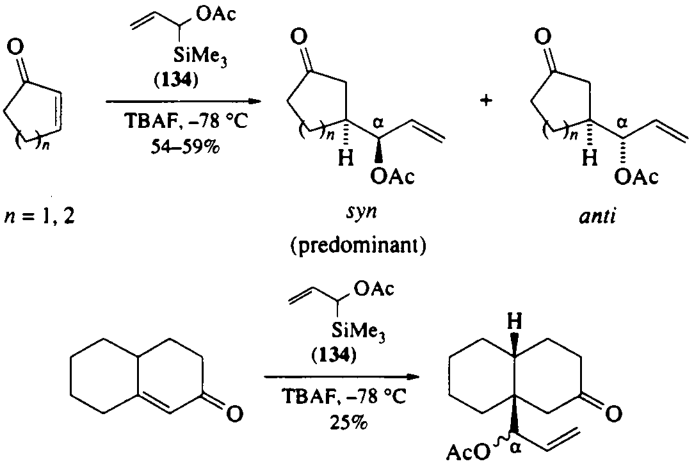

Scheme 52

while vinyl enones (**138**) afford both bicyclo[6.4.0]dodecen-3-ones (**139**) and bicyclo[2.2.2]octenes (**140**). In contrast, the vinyl enones (**141**) afford both bicyclo[6.3.0]undecen-3-ones (**142**) and vinylbicyclo[4.3.0]nonene-3-ones (**143**; Scheme 53).

### 1.2.2.2 Additions of Enolates, Azaenolates and α-Nitrile Anions

The conjugate addition of unstabilized enolates to various acceptors was conceptually recognized by early researchers; however, complications were encountered depending on the enolates and acceptors employed. Reexamination of this strategy was made possible by the development of techniques for kinetic enolate formation. This discussion is divided into three enolate classes (a) aldehyde and ketone enolates, azaenolates or equivalents, (b) ester and amide enolates, dithioenolates and dienolates and (c) α,*O*-carboxylic dianions and α-nitrile anions, in order to emphasize the differential reactivity of various enolates with various acceptors.[117] The α-nitrile anions are included because of their equivalence to the hypothetical α-carboxylic acid anion.

#### *1.2.2.2.1 Aldehyde and ketone enolates, azaenolates and equivalents*

The 1,4-conjugate addition of ketones to α,β-unsaturated ketones, under protic conditions, was reported by Stobbe in 1912;[118a] further developments afforded protocols for the synthesis of fused cyclohexenones, *i.e.* Robinson annulation.[118b–d] Robinson also reported that aprotic 1,4-conjugate additions of select reagents, *e.g.* sodiocyclohexanone with styryl methyl ketone,[119] was preferable to the protic addi-

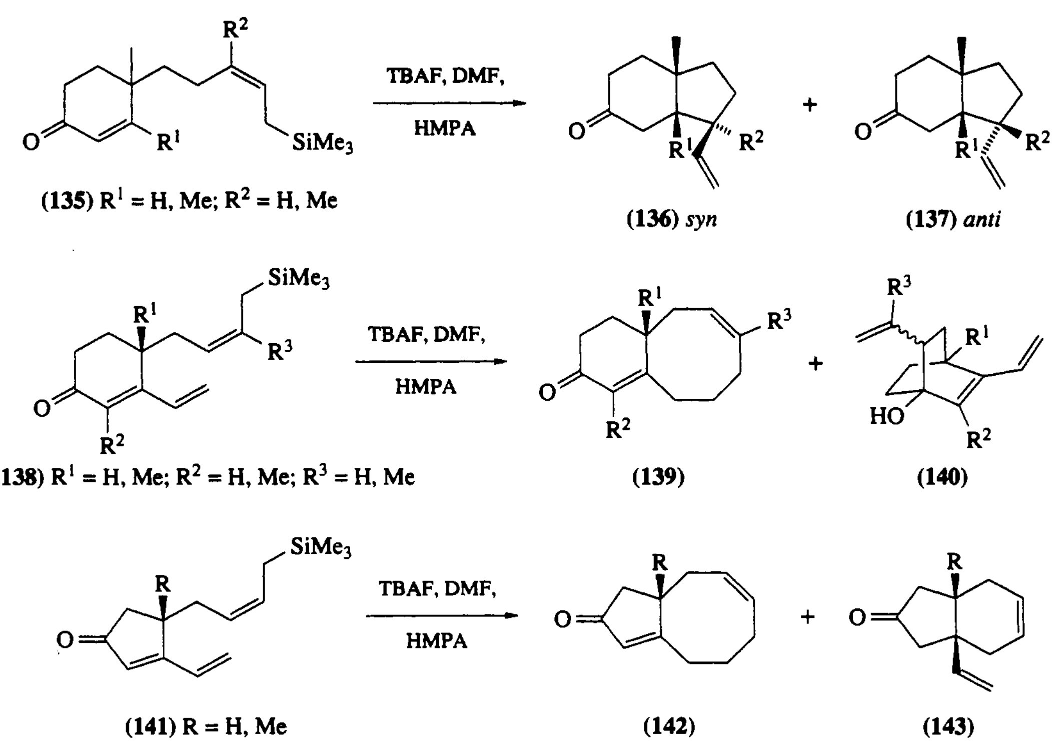

Scheme 53

tion protocol. However, complications with kinetic enolate additions include (a) enolate scrambling during addition of the acceptor, (b) self-aldolization and (c) polymerization of certain acceptors, *e.g.* acrylonitrile or methyl vinyl ketone. Enolate equivalents and modified acceptors, primarily a$^3$-synthons, have been introduced that obviate these complications. For example, azaenolates, *e.g.* metallated alkylidene amines, *N*,*N*-dimethylhydrazones and oximes (oxime ethers), do not suffer from anion scrambling or self-aldolization,[120] while the modified a$^3$-synthons, *e.g.* α-silyl vinyl ketones,[41,121] α-silylacrylate esters[43] and α,β-unsaturated thioamides,[122] are characterized by the presence of functionalities that stabilize an intermediate anion without proton transfer.

Gorrichon and Heathcock have reported that three factors affect the chemoselectivity of kinetic ketone enolate additions to α,β-enones. These factors are (a) enolate geometry and substitution pattern, (b) the cation and (c) reaction conditions. In general, under kinetic reaction conditions (–78 °C), lithium enolates and magnesium dienolates afford preferential 1,4-addition products while halomagnesium enolates afford substantial amounts of 1,2-addition products, but the intermediate allylic halomagnesium alkoxides undergo 1,2 to 1,4 equilibration at higher temperatures. In addition, increasing substitution on the enolates enhances the formation of 1,4-addition products.[123]

Heathcock[123b] and Seebach[124] have shown that the diastereoselectivity of the conjugate additions is highly dependent on both the lithium enolate geometry and geometry of the acceptor. For example, with (*E*)-acceptors, the (*Z*)-enolates (**144**) afford high *anti*-selectivity while the (*E*)-enolates (**145** and **146**) afford high *syn*-selectivity (Scheme 54). In contrast, Mukaiyama reports that tin(II) enolates of alicyclic ketones, *e.g.* (**147**), with (*E*)-β-nitrostyrene, afford predominant *anti*-selectivity (Scheme 55).[125]

Corriu and coworkers have reported an alternative procedure for the conjugate addition of ketones to α,β-unsaturated acceptors which employs CsF–(RO)$_4$Si (Scheme 56);[126] this procedure affords adducts with α,β-enones, α,β-unsaturated esters and α,β-unsaturated amides. Mechanistically, silyl enol ether formation occurs initially, followed by fluoride ion catalyzed enolate formation.

Stork and Boeckmann have reported that enolates react with α-(trialkylsilyl)vinyl ketones (**148**) without proton scrambling to afford adducts in excellent yields; subsequent alcoholysis affords the desilylated ketone (Scheme 57).[41,121] Yoshida reports that various enolates undergo conjugate additions efficiently with α,β-unsaturated *N*,*N*-dialkylthioamides (**32**; Scheme 58),[122] while preferential 1,4-addition to *N*,*N*-dimethylthiosorbamide is observed (*cf.* Schemes 8 and 28).

The adducts of ketone enolates to various a$^2$-synthons, *e.g.* α-nitroalkenes (**40**), vinyl sulfoxides, 2-(*N*-methylanilino)acrylonitrile (**59**) and ketene dithioacetal monoxide (**151**), are versatile synthetic inter-

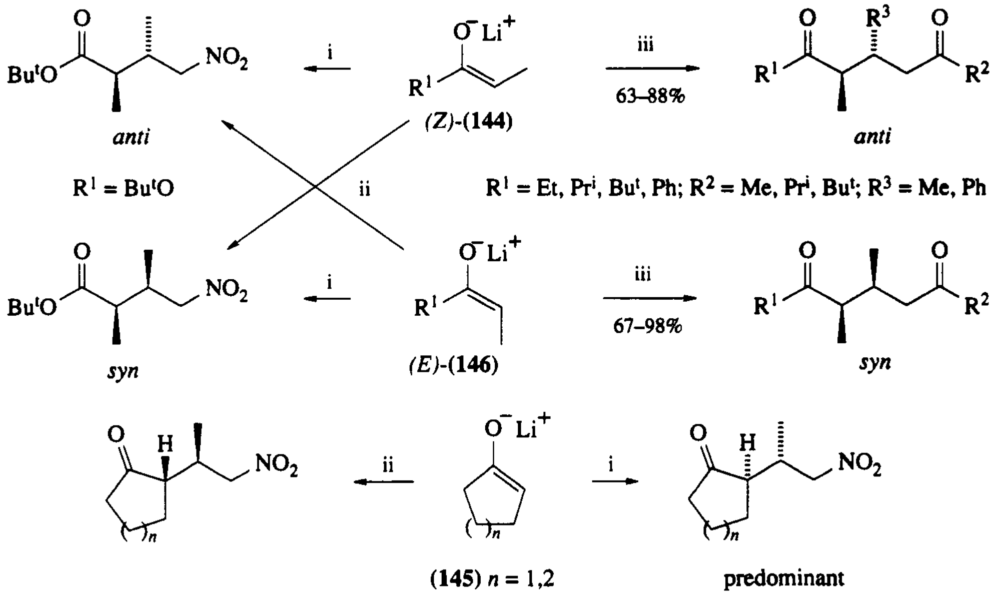
anti
R¹ = BuᵗO
syn
(Z)-(144)
(E)-(146)
63–88%
67–98%
anti
syn
R¹ = Et, Prⁱ, Buᵗ, Ph; R² = Me, Prⁱ, Buᵗ; R³ = Me, Ph
(145) n = 1,2
predominant

i, (*E*)-$MeCH=CHNO_2$; ii, (*Z*)-$MeCH=CHNO_2$; iii, (*E*)-$R^2COCH=CHR^3$

**Scheme 54**

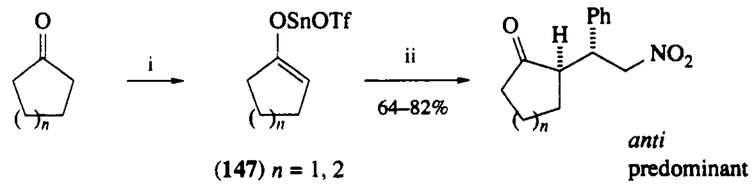
(147) n = 1, 2
64–82%
anti
predominant

i, $Sn(OTf)_2$, *N*-ethylpiperidine, −78 °C; ii, (*E*)-$PhCH=CHNO_2$

**Scheme 55**

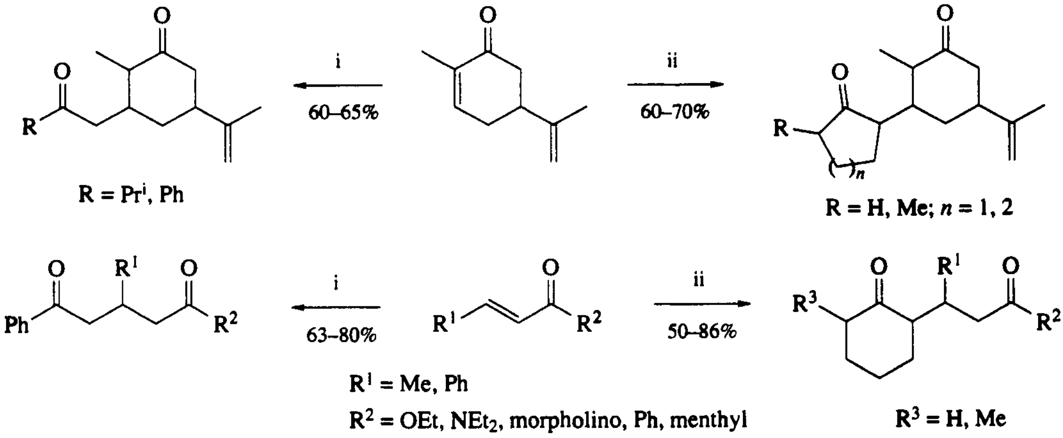
60–65%
60–70%
R = Prⁱ, Ph
R = H, Me; n = 1, 2
63–80%
50–86%
R¹ = Me, Ph
R² = OEt, NEt₂, morpholino, Ph, menthyl
R³ = H, Me

i, $R^1COMe$, CsF–$Si(OMe)_4$, 25–80 °C; ii, cycloalkanone, CsF–$Si(OMe)_4$, 25–100 °C

**Scheme 56**

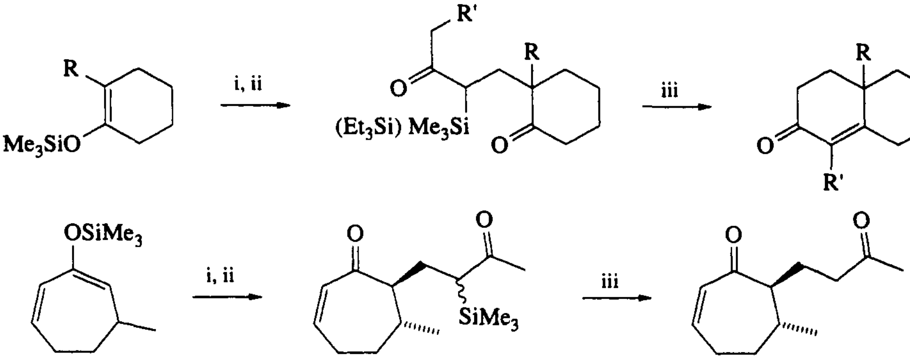

i, MeLi, –78 °C; ii, R'CH$_2$COC(Me$_3$Si)=CH$_2$ [(**148**), R' = H, Me]; iii, NaOEt, EtOH

**Scheme 57**

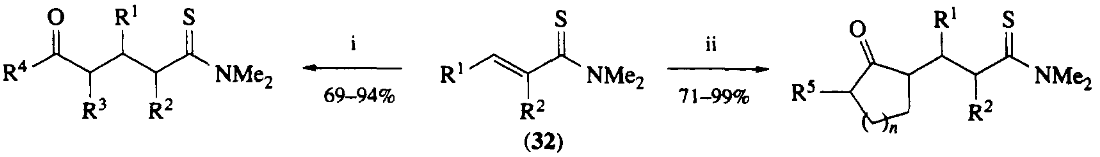

R$^3$ = H, Me
R$^4$ = Pr$^i$, Bu$^t$, Ph, NMe$_2$
Bu$^t$O, EtO$_2$CCH$_2$

R$^1$ = H, Me, Ph, MeCH=CH
R$^2$ = H, Me

R$^5$ = H, Me
$n$ = 1, 2

i, R$^3$CH$_2$COR$^4$, LDA, –78 °C; ii, cycloalkanone, LDA, –78 °C

**Scheme 58**

mediates. Notable are the α-nitroalkenes which serve as α-carbonyl cations (*via* Nef reaction), β-aminocations (*via* reduction) or vinyl cation equivalents (*via* elimination).[127] For example, Pattenden reports that the addition of the bicyclo[3.3.0]octenone (**149**) to 2-nitrobut-2-ene and subsequent oxidation affords the 1,4-diketone (**150**).[127b] Similarly, adducts with either 2-(*N*-methylanilino)acrylonitrile (**59**)[128a–c] or ketene dithioacetal monoxide (**151**),[128d] α-formyl cation equivalents, afford 1,4-diketones (Scheme 59).

In contrast to the paucity of citations concerning additions of organolithiums or Grignard reagents to vinyl sulfoxides, ketone enolate additions are highly precedented. Vinyl sulfoxides and vinyl sulfones are considered as equivalent a$^2$-synthons; however, further transformation of the sulfone unit is restricted to reductive cleavage. With the sulfoxide moiety, additional transformations are permissive, *i.e*. Pummerer rearrangement and eliminations. Jones has reported several prototypical prostaglandin syntheses in which ketone enolates and ethyl acetoacetate dianion are added to vinyl sulfoxides (**152** and **153**; Scheme 60).[129] Further, additions to chiral β-substituted vinyl sulfoxides result in chirality transfer from sulfur. For example, Yamazaki and Ishikawa report that the addition of ketone and ester enolates to (*R*,*E*)-3,3,3-trifluoroprop-1-enyl *p*-tolyl sulfoxide (**154**) occurs with high diastereoselectivity (equation 17).[130]

Takaki reports that ketone enolates add to dimethylstyryl sulfonium perchlorate (**155**) or methyl styryl sulfone (**156**) in a Robinson-type annulation sequence to afford the corresponding β-hydroxythiadecalin (**157**) or *S*-dioxide (**158**), respectively; subsequent reductive desulfonation of (**158**) affords diene (**159**).[131] However, additions to acceptor (**155**) suffer from competing cyclopropanation which is dependent on the electrophilicity of the carbonyl group and the ring size of the ketone (Scheme 61). As an aside, DeLucchi reports that 1,1-bis(benzenesulfonyl)ethylene (**160**) adds to ketones at the more substituted α-carbon *under neutral conditions* in refluxing acetonitrile (equation 18).[132]

In contrast to α,β-unsaturated phosphonium salts, α,β-unsaturated phosphonates (**161**)[133a] alkylate alicyclic ketone enolates efficiently, while the homologous diethyl butadiene phosphonate (**162**)[133b,c] undergoes 1,6-addition exclusively at the exclusion of intramolecular cyclization. Heathcock reports that

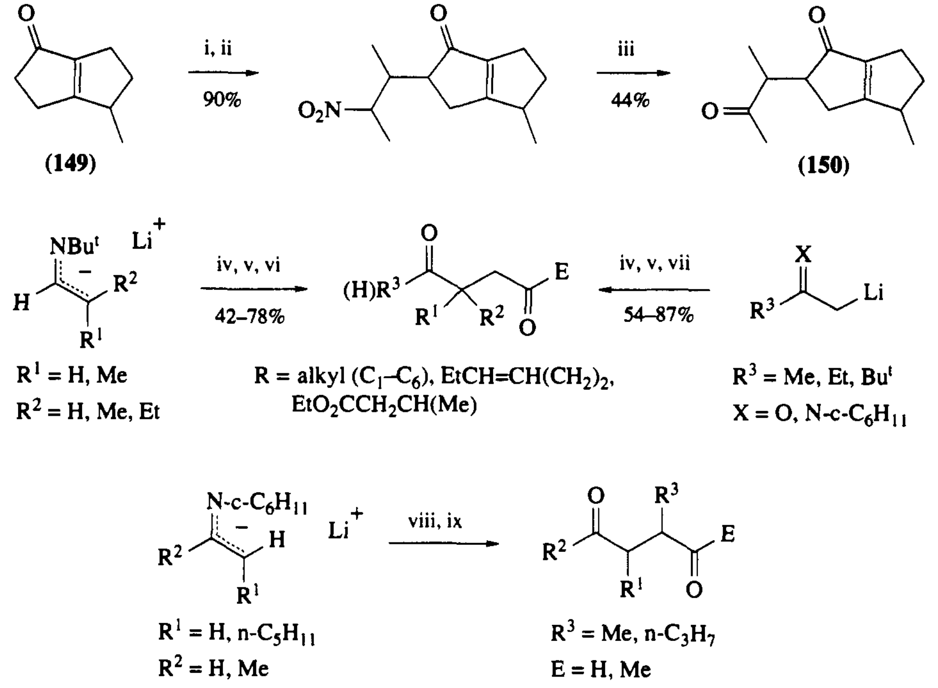
(149)
i, ii
90%
$O_2N$
iii
44%
(150)
NBu$^t$ Li$^+$
$R^2$
H
$R^1$
$R^1$ = H, Me
$R^2$ = H, Me, Et
iv, v, vi
42–78%
(H)$R^3$
E
$R^1$ $R^2$
R = alkyl ($C_1$–$C_6$), $EtCH{=}CH(CH_2)_2$, $EtO_2CCH_2CH(Me)$
iv, v, vii
54–87%
X
$R^3$
Li
$R^3$ = Me, Et, Bu$^t$
X = O, N-c-$C_6H_{11}$
N-c-$C_6H_{11}$
Li$^+$
$R^2$
H
$R^1$
$R^1$ = H, n-$C_5H_{11}$
$R^2$ = H, Me
viii, ix
$R^3$
$R^2$
E
$R^1$
$R^3$ = Me, n-$C_3H_7$
E = H, Me

i, LDA, HMPA, –78 °C; ii, $NO_2(Me)C{=}CHMe$; iii, $NaNO_2$, Pr$^n$ONO, DMSO; iv, $CH_2{=}C(CN)[N(Me)Ph]$ **(59)**; v, electrophile; vi, $CuSO_4$, $H_2O$; vii, $H_2SO_4$ (3N); viii, $R^3CH{=}C(SMe)SOMe$ **(151)**; ix, Amberlite IR-120, 18–50 °C

**Scheme 59**

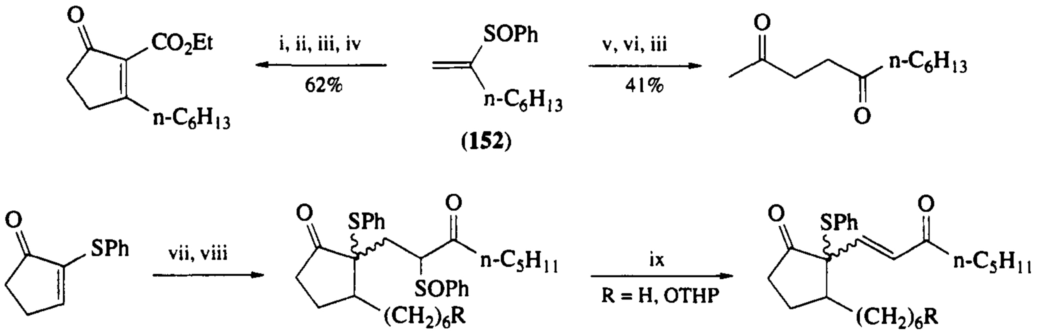
$CO_2Et$
n-$C_6H_{13}$
i, ii, iii, iv
62%
SOPh
n-$C_6H_{13}$
(152)
v, vi, iii
41%
n-$C_6H_{13}$
SPh
vii, viii
SPh
n-$C_5H_{11}$
SOPh
$(CH_2)_6R$
ix
R = H, OTHP
SPh
n-$C_5H_{11}$
$(CH_2)_6R$

i, $LiCH_2COCH(Li)CO_2Et$; ii, MeSSMe; iii, $CF_3CO_2H$; iv, NaOH; v, acetone, LiTMP, –78 °C; vi, TFAA, pyridine; vii, $R(CH_2)_6MgBr$, CuCl (1%); viii, $CH_2{=}C(SOPh)CO$-n-$C_5H_{11}$ **(153)**; ix, $(MeO)_3P$

**Scheme 60**

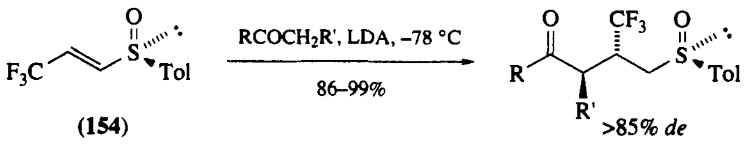
$F_3C$
S
Tol
(154)
$RCOCH_2R'$, LDA, –78 °C
86–99%
$CF_3$
R
S
Tol
R'
>85% *de*

(17)

R = Et, Bu$^t$, Ph, OEt; R' = H, Me, $CO_2Et$

ester and ketone enolates add to ethyl 2-(diethylphosphono)acrylate (**163**) to afford the intermediate keto ester phosphonates which can react with aldehydes or ketones to afford α,β-unsaturated esters (Scheme 62).[134]

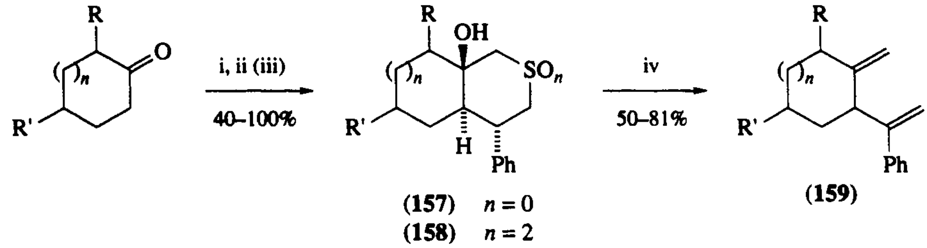

**(157)** $n = 0$

**(158)** $n = 2$

**(159)**

$R = H, Me; R' = H, Bu^t; n = 0 - 2$

i, LDA, –78 °C; ii, $PhCH{=}CH\overset{+}{S}Me_2\ ClO_4^-$ (**155**), DMF, 80 °C; iii, $PhCH{=}CHSO_2Me$ (**156**), DMF, 80 °C;
iv, Na, EtOH, THF

**Scheme 61**

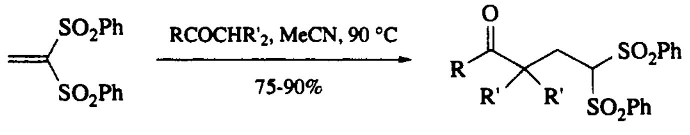

(18)

**(160)**

$R = Me, Ph; R' = H, Me$

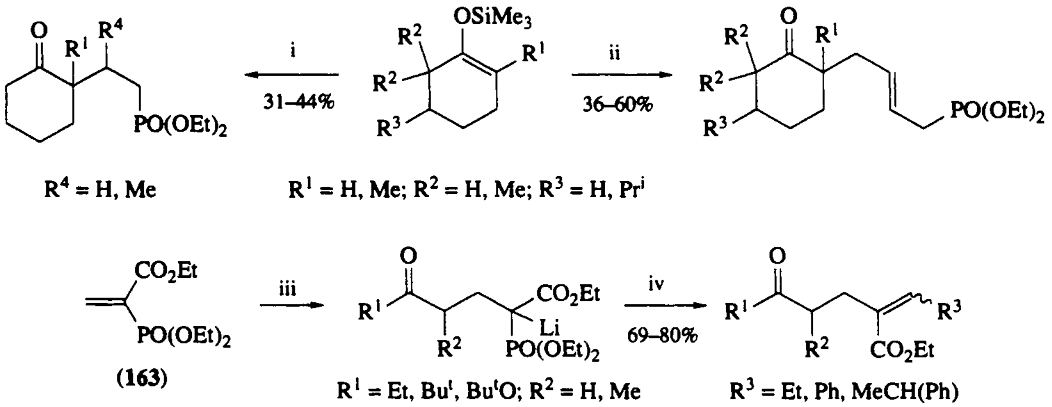

$R^4 = H, Me$

$R^1 = H, Me; R^2 = H, Me; R^3 = H, Pr^i$

**(163)**

$R^1 = Et, Bu^t, Bu^tO; R^2 = H, Me$

$R^3 = Et, Ph, MeCH(Ph)$

i, $R^4CH{=}CHPO(OEt)_2$ (**161**), $PhCH_2\overset{+}{N}Me_3\ \overset{-}{F}$ ; ii, $CH_2{=}CH{-}CH{=}CHPO(OEt)_2$ (**162**), $PhCH_2\overset{+}{N}Me_3\ F^-$ ;
iii, $R^1COCH_2R^2$, LDA, –78 °C; iv, $R^3CHO$

**Scheme 62**

Casey and coworkers have shown that ketone enolates add efficiently to α,β-unsaturated vinyl carbene complexes (**164**), irrespective of β,β-disubstitution on the complex or high substitution on the enolate;[135a] thus, contiguous β and γ quaternary centers are easily assembled. When coupled with the ease of release of the carbene ligand from the complexes by either oxidation to the ester functionality[135b–d] or elimination to the corresponding enol ether,[135a] the vinyl carbene complexes are synthetic equivalents for α,β-unsaturated esters or α,β-unsaturated aldehydes, respectively (Scheme 63).

The use of aldehyde enolates for conjugate additions is precluded by competing polymerization and aldolization processes; however, introduction of the 'CH2CHO' moiety is accomplished with aldehyde enolate equivalents. For example, dianions of nitroethanes, *e.g.* β-phenylnitroethane (**165**) or methyl β-nitropropionate (**166**), add exclusively in the 1,4-mode to α,β-enones.[136a,b] Similarly, the dianion of 4-nitro-1-butene (**167**) adds in a 1,4-mode exclusively; unlike typical dienolates (Section 1.2.2.2.2) which react at the α-position, this dianion is formally equivalent to the crotonaldehyde γ-enolate (Scheme 64).[136c]

The introduction of a chiral auxiliary on the nitrogen of an azaenolate offers the capability to perform asymmetric conjugate additions of chiral nucleophiles to achiral acceptors. This is in contrast to the typical asymmetric conjugate addition of achiral nucleophiles to chiral acceptors.[137] For example, the con-

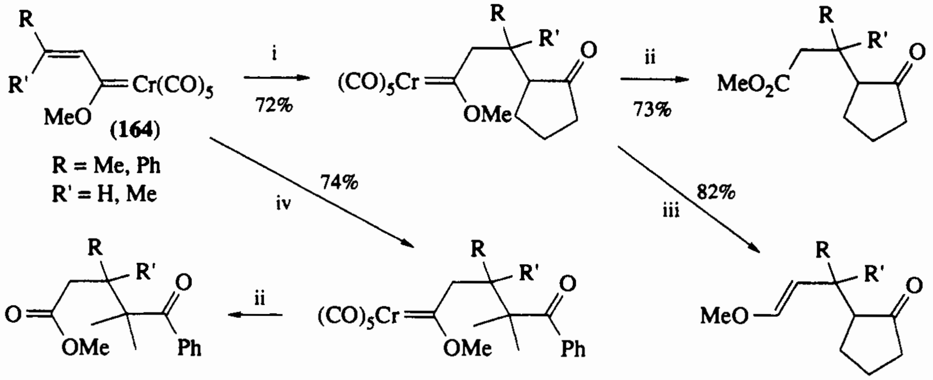
(164)
R = Me, Ph
R' = H, Me
i
72%
ii
73%
iv
74%
iii
82%
ii

i, lithium cyclopent-1-enolate; ii, $(NH_4)_2Ce(NO_2)_6$; iii, pyridine; iv, $PhC(OLi){=}CMe_2$

**Scheme 63**

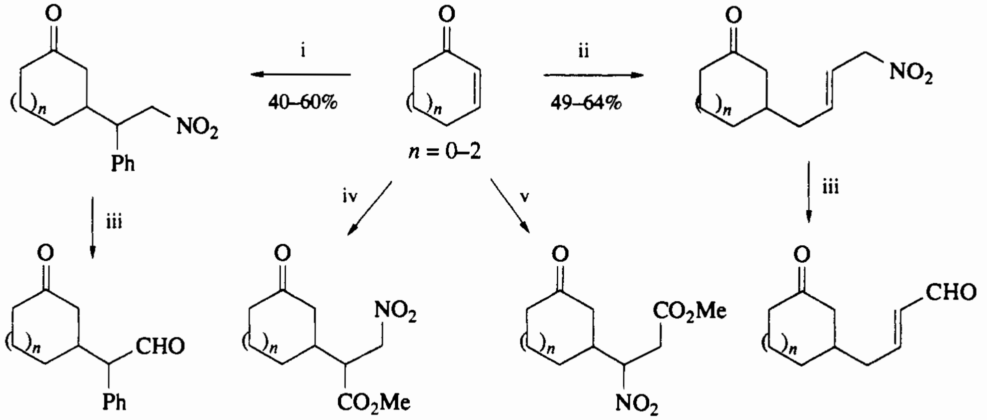
i
40–60%
ii
49–64%
n = 0–2
iii
iv
v
iii

i, $PhCH_2CH_2NO_2$ (**165**), Bu$^n$Li, HMPA, –90 °C; ii, $CH_2{=}CH(CH_2)_2NO_2$ (**167**), Bu$^n$Li, HMPA, –90 °C; iii, $TiCl_3$; iv, $MeO_2CCH_2CH_2NO_2$ (**166**); LDA, –78 °C; v, $MeO_2CH_2CH_2NO_2$ (**166**), DBU, 25 °C

**Scheme 64**

jugate addition of lithiated SAMP/RAMP hydrazones (**168**) of ketones to β-substituted-α,β-unsaturated esters occurs with excellent asymmetric induction (Scheme 65).

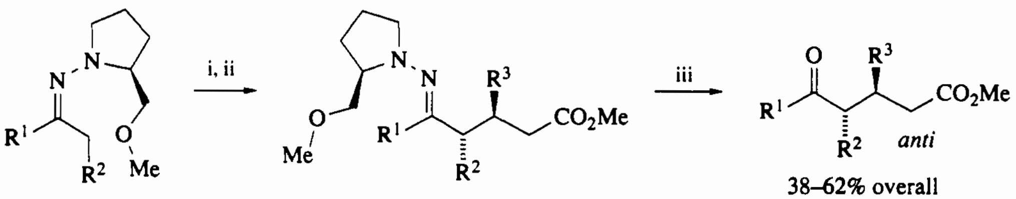
i, ii
iii
anti

(**168**)

38–62% overall
$R^2 \neq H$: >90% *de*, >92% *ee*
$R^2 = H$: >96% *ee*

$R^1$ = H, alkyl ($C_1$–$C_6$), Ph; $R^2$ = H, alkyl ($C_1$–$C_3$), benzyl; $R^3$ = alkyl ($C_1$–$C_3$), Ph

i, LDA, THF, –78 °C; ii, (*E*)-$R^3CH{=}CHCO_2Me$; iii, $O_3$, $CH_2Cl_2$, –78 °C

**Scheme 65**

### *1.2.2.2.2 Amide enolates, ester enolates, dithioenolates and dienolates*

The 1,4-conjugate addition of ester enolates to α,β-enones was first reported by Kohler in 1910,[138a–c] as an anomalous Reformatsky reaction, but chemoselectivity was dependent on the structure of the α,β-enone and restricted to bromozinc enolates obtained from either α-bromoisobutyrate or bromomalonate esters (Scheme 66).[138d,e] Further evaluation, with lithio ester enolates and lithio amide enolate additions, has resulted in identification of four factors that affect the chemoselectivity and diastereoselectivity of additions to α,β-enones.[139] These factors are (a) enolate geometry, (b) acceptor geometry, (c) steric bulk of the β-substituent on the acceptor enone and (d) reaction conditions. In general, under kinetic reaction conditions (–78 °C), (*E*)-ester enolates afford preferential 1,2-addition products while (*Z*)-ester enolates afford substantial amounts of 1,4-addition products; however, 1,2 to 1,4 equilibration occurs at 25 °C in the presence of HMPA. The stereostructure of the 1,4-adducts is dependent on the initial enolate structure; for example, with (*E*)-enones, (*Z*)-ester enolates afford *anti* adducts, while (*E*)-ester enolates afford *syn* adducts (Scheme 54). In contrast, amide enolates show a modest preference for *anti* diastereomer formation.

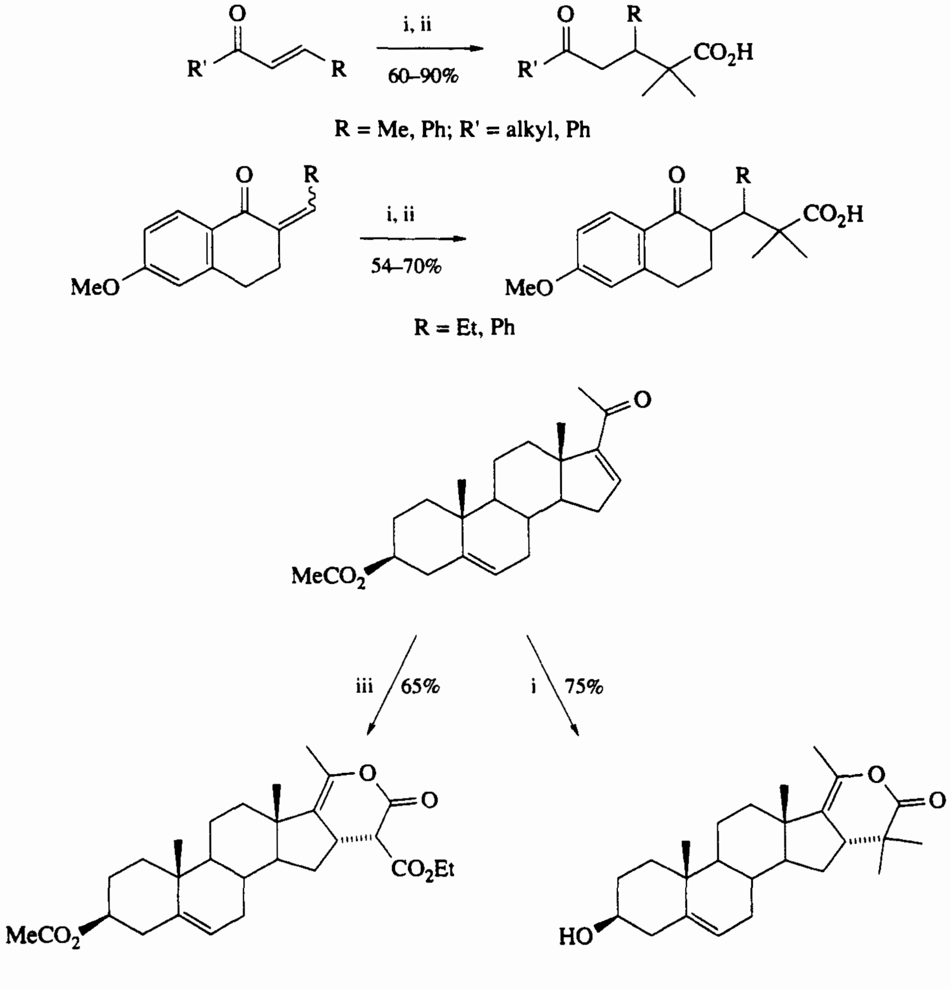

i, BrZnC(Me)$_2$CO$_2$Et, THF, 68 °C; ii, HO$^-$, H$_3$O$^+$; iii, BrZnHC(CO$_2$Et)$_2$, THF, 68 °C

**Scheme 66**

Various groups have reported that additions of α-hetero substituted ester enolates to α,β-enones are temperature dependent,[140a–c] but, in general, the 1,2 to 1,4-equilibration of α-seleno and α-thio substituted ester adducts occurs at lower temperature than the α-oxo substituted ester adducts. In contrast to the simple ester enolates, the α-hetero substituted ester enolates are extremely useful for functionalization of alicyclic α,β-enones with the tandem conjugate addition–electrophile trapping protocol, as shown in Scheme 67.[141] However, α-silyl ester enolates undergo conjugate additions to cyclopentenones only. Yamamoto reports that conjugate additions of α-thio substituted esters (or nitriles) can be achieved with catalytic 18-crown-6- potassium *t*-butoxide complex (5%) in toluene, while modest enantioselectivity is obtained with chiral crown ethers (>41% *ee*).[140d] McMurry and coworkers have reported that the conjugate addition of magnesium monoethyl malonate (**169**) to β-substituted-α,β-enones and β-substituted nitroalkenes introduces an acetic acid ester moiety which complements the above lithium enolate procedures which are not reliable for simple ester enolates.[142]

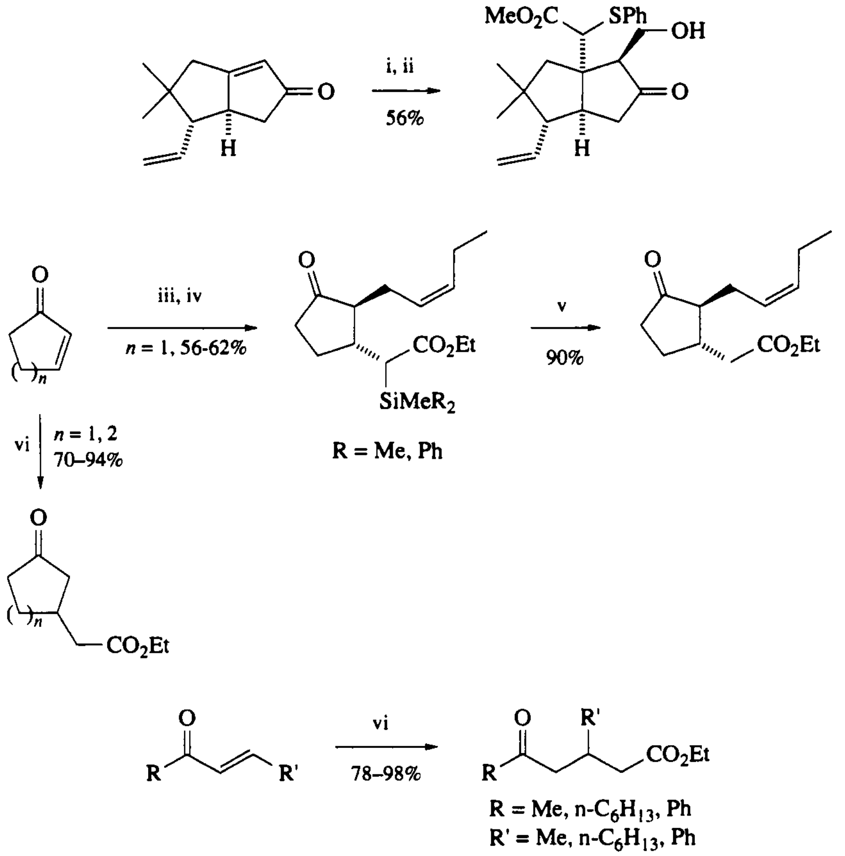

i, $PhSCH_2CO_2Me$, LDA, THF, –60 to –35 °C; ii, $CH_2O$; iii, $MeR_2SiCH_2CO_2Et$, LDA, THF, –20 °C; iv, $EtCH{=}CHCH_2Br$, –40 °C; v, KF, MeOH, 25 °C; vi, $Mg^{2+}(EtO_2CCHCO_2)^{2-}$ (**169**)

**Scheme 67**

Metzner reports that lithium dithioenolates, which are softer nucleophiles than the corresponding carbonyl enolates, add kinetically in a 1,4-mode exclusively to α,β-enones and the diastereoselectivity preferences are similar to that for ester enolate additions.[143a–d] Typically, kinetic deprotonation of dithioesters affords predominantly the (*Z*)-enethiolate (**170**) which is opposite to that for esters;[139] thus, with (*E*)-enones, *anti* adducts (**172**) are obtained. In contrast, the addition of methyl dithioacetate to α,β-disubstituted enones affords predominantly *syn* adducts (**174** and **175**) which is a consequence of intramolecular protonation of the resultant enolate (Scheme 68).[143e]

Few examples exist for the conjugate addition of ester enolates to α,β-unsaturated esters; typically the incipient enolate undergoes decomposition and secondary reactions. The first examples, described by Schlessinger,[144] are the addition of *t*-butyl lithioacetate and *t*-butyl α-lithio-α-(methylthio)propionate to butenolide (**176**; Scheme 69). Similarly, Normant reported that cyclopropanes are obtained from α-haloesters (**177**) and ethyl acrylate or acrylonitrile.[145]

The addition of ester enolates to α,β-unsaturated esters occurs with identical diastereoselectivity as shown for α,β-enones; this is exemplified by the diastereoselective synthesis of *erythro*- and *threo*-2,3-disubstituted glutarate esters (**178** and **179**).[146a–c] Similarly, Yamaguchi reports a general synthesis of *trans*-2-alkoxycarbonyl-1-cycloalkanepropionates (**181–184**) from ω-halo-α,β-unsaturated esters (**180**),

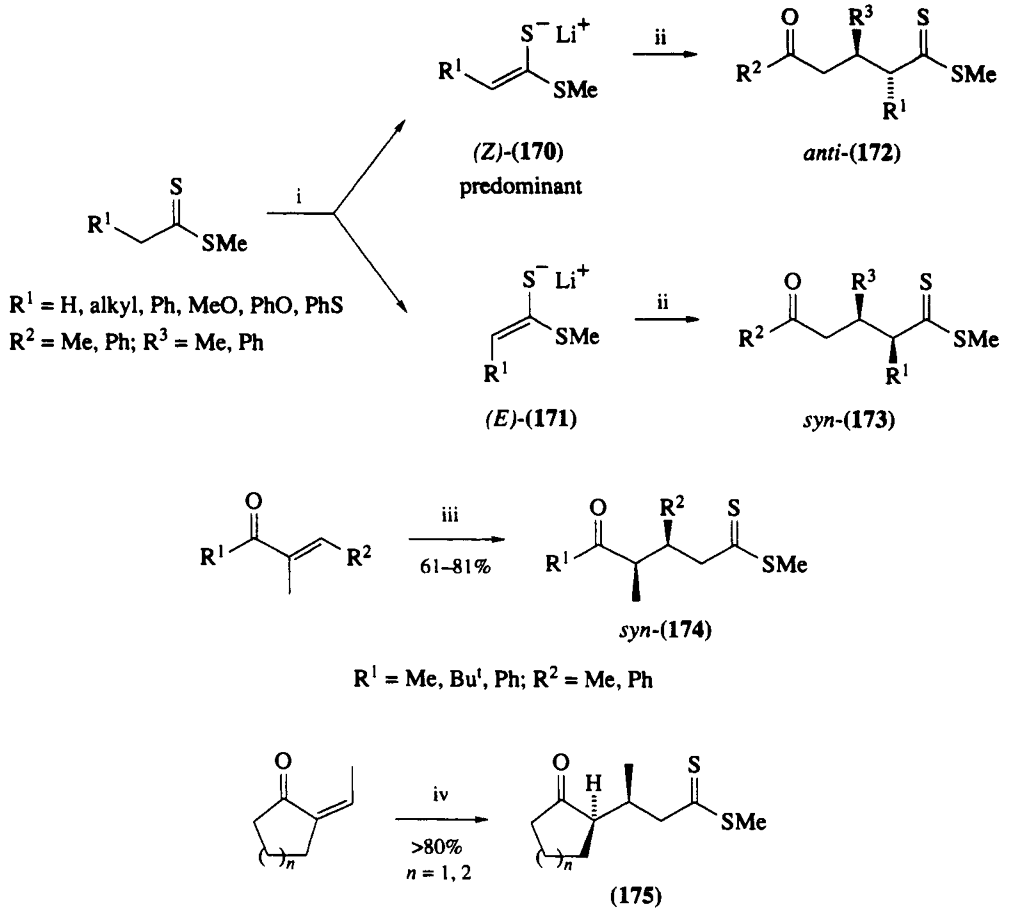
i
ii
ii
iii
61–81%
iv
>80%
n = 1, 2
SMe
S
O
R1
R2
R3
H
n

(Z)-(170) predominant

anti-(172)

R1 = H, alkyl, Ph, MeO, PhO, PhS
R2 = Me, Ph; R3 = Me, Ph

(E)-(171)

syn-(173)

syn-(174)

R1 = Me, Bu$^t$, Ph; R2 = Me, Ph

(175)

i, LDA, THF, –78 °C; ii, (E)-$R^2COCH{=}CHR^3$; iii, $MeCS_2Me$, LDA, THF, –5 to 0 °C;
iv, $MeCS_2Me$, LDA, THF, –45 to –25 °C

Scheme 68

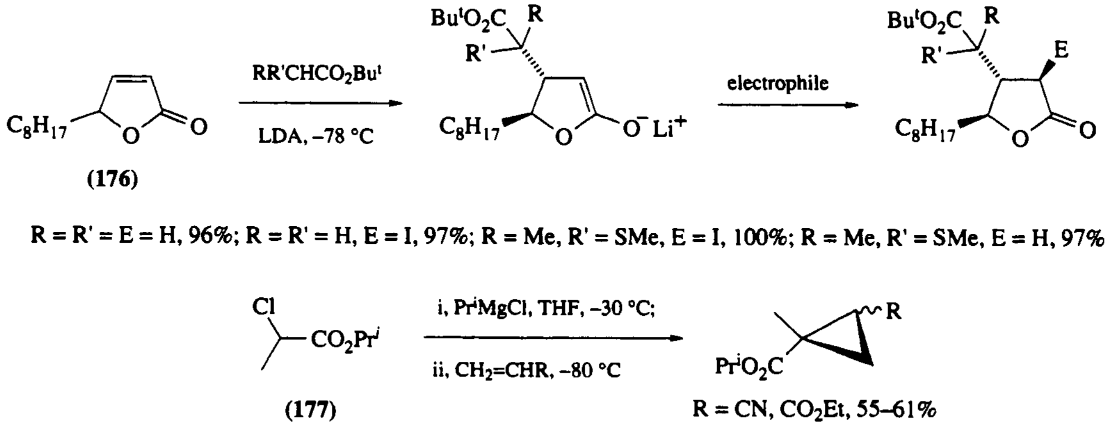
RR'CHCO2Bu$^t$
LDA, –78 °C
electrophile
i, Pr$^i$MgCl, THF, –30 °C;
ii, CH2=CHR, –80 °C
Bu$^t$O2C
R
R'
E
C8H17
O
O⁻ Li⁺
Cl
CO2Pr$^i$
Pr$^i$O2C

(176)

R = R' = E = H, 96%; R = R' = H, E = I, 97%; R = Me, R' = SMe, E = I, 100%; R = Me, R' = SMe, E = H, 97%

(177)

R = CN, $CO_2Et$, 55–61%

Scheme 69

in a MIRC protocol, in which three contiguous asymmetric centers are formed (Scheme 70) (*cf.* **17**→**21**).[146d–h]

Posner has shown that ester enolates add to enantiomerically pure 2-(arylsulfinyl)-α,β-unsaturated lactones (**185**) and 2-(arylsulfinyl)cycloalkenones (**97**) to afford β-(carboxymethyl)lactones or β-(carboxy-

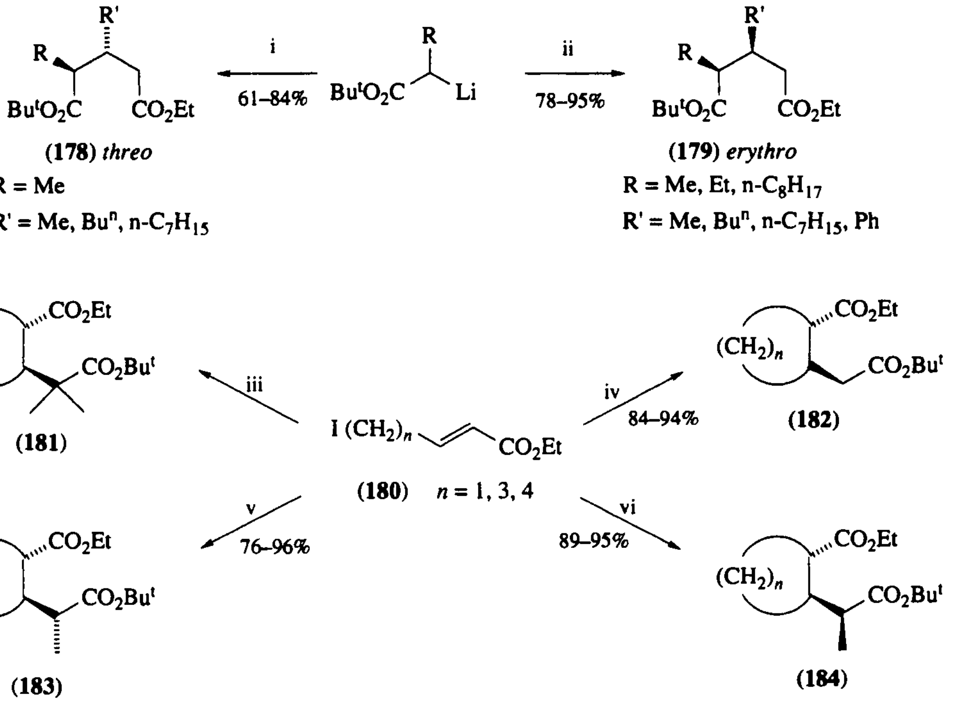
i
61–84%
ii
78–95%
Bu$^t$O$_2$C
Li
CO$_2$Et
(178) *threo*
R = Me
R' = Me, Bu$^n$, n-C$_7$H$_{15}$
(179) *erythro*
R = Me, Et, n-C$_8$H$_{17}$
R' = Me, Bu$^n$, n-C$_7$H$_{15}$, Ph
(CH$_2$)$_n$
CO$_2$Bu$^t$
(181)
(182)
(183)
(184)
iii
iv
84–94%
v
76–96%
vi
89–95%
I (CH$_2$)$_n$
(180) *n* = 1, 3, 4

i, (*Z*)-R'CH=CHCO$_2$Et, THF, –78 °C; ii, (*E*)-R'CH=CHCO$_2$Et, THF, HMPA, –78 °C; iii, Pr$^i$CO$_2$Bu$^t$, LDA, Bu$^t$OK, THF, –78 °C; iv, MeCO$_2$Bu$^t$, LDA, Bu$^t$OK, THF, –78 °C; v, EtCO$_2$Bu$^t$, LDA, Bu$^t$OK, THF, –78 °C; vi, EtCO$_2$Bu$^t$, LDA, Bu$^t$OK, HMPA, THF, –78 °C

**Scheme 70**

methyl)cycloalkanones, respectively, after reductive cleavage of the sulfinyl unit. The best enantiomeric selectivity was obtained with α-thio substituted ester enolates (Scheme 71).[147]

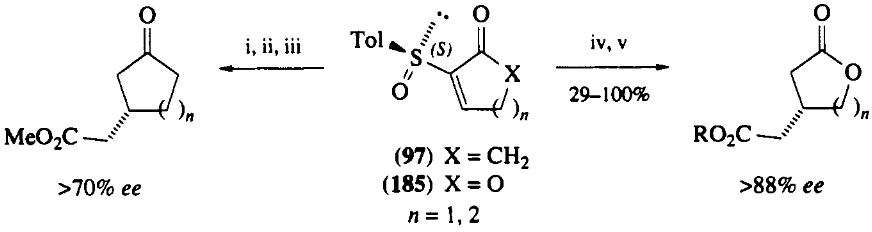
i, ii, iii
iv, v
29–100%
MeO$_2$C
>70% *ee*
Tol
*(S)*
X
(97) X = CH$_2$
(185) X = O
*n* = 1, 2
RO$_2$C
>88% *ee*

i, Me$_3$SiCH$_2$CO$_2$Me, LDA, –78 °C; ii, Al–Hg; iii, KF; iv, YCH$_2$CO$_2$R (Y = H, PhS, 4-MeC$_6$H$_4$S); v, Raney Ni

**Scheme 71**

Schlessinger has shown that the addition of ester enolates to sulfur stabilized acceptors, *e.g.* ketene dithioacetal monoxide (**151**) and methyl α-(methylthio)acrylate (**187**), is highly efficient for the synthesis of γ-ketoesters.[148] Similarly, Ahlbrecht and Seebach have reported that amide and ester enolate additions to nitrogen stabilized acceptors, *e.g.* nitroalkenes (**40**) and 2-(*N*-methylanilino)acrylonitrile (**59**; Scheme 72), are highly efficient.[149]

Masked chiral α-hetero substituted carboxylic acid enolates have also shown utility in diastereoselective additions to nitroalkenes. For example, derivatives of α-hydroxycarboxylic acids, *e.g.* 1,3-dioxolan-4-ones (**187**); α-amino acids, *e.g.* 1,3-imidazolidin-4-ones (**188**); and α-amino-β-hydroxycarboxylic acids, *e.g.* methyl 1,3-oxazolidin-4-carboxylates (**189**) and methyl 1,3-oxazolin-4-carboxylates (**190**), have been employed.[150a] Further, diastereoselective additions of chiral β-hydroxyesters (**191**), *via* the enediolates, to nitroalkenes (**40**) afford predominant *anti*-β-hydroxyesters (**192**; Scheme

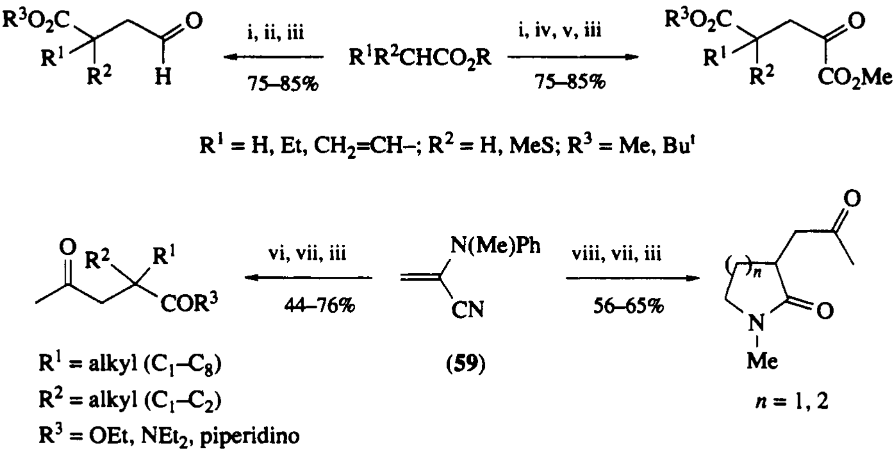
i, ii, iii
75–85%
R¹R²CHCO₂R
i, iv, v, iii
75–85%
R¹ = H, Et, CH₂=CH–; R² = H, MeS; R³ = Me, Buᵗ
vi, vii, iii
44–76%
N(Me)Ph
CN
(59)
viii, vii, iii
56–65%
R¹ = alkyl (C₁–C₈)
R² = alkyl (C₁–C₂)
R³ = OEt, NEt₂, piperidino
n = 1, 2

i, LDA, THF, –78 °C; ii, $CH_2{=}C(SOMe)SMe$ (**151**); iii, $H_3O^+$; iv, $CH_2{=}C(SMe)CO_2Me$ (**187**); v, LDA, MeSSMe, –78 °C; vi, amide or ester enolate, THF, –78 °C; vii, MeI; viii, lactam enolate, THF, –78 °C

**Scheme 72**

73).[150b] Hanessian reports a carbapenem synthesis in which intramolecular cyclization of the β-lactam nitroalkene (**193**) affords β-lactams (**194** and **195**; Scheme 74).[151]

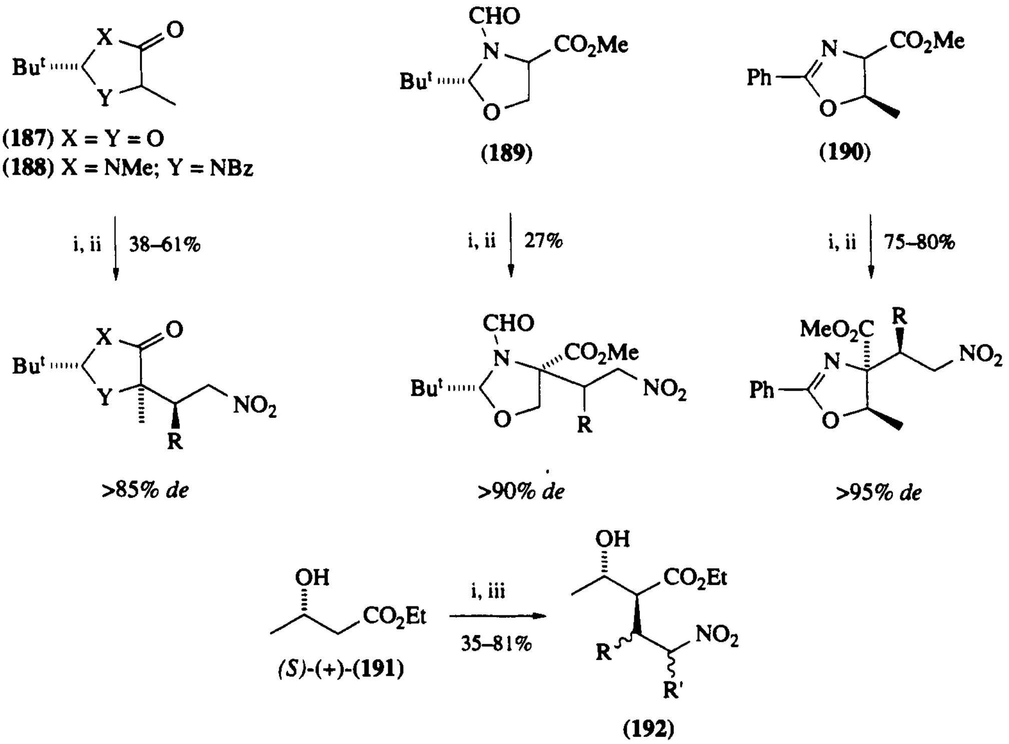
(187) X = Y = O
(188) X = NMe; Y = NBz
(189)
(190)
i, ii
38–61%
i, ii
27%
i, ii
75–80%
>85% de
>90% de
>95% de
(S)-(+)-(191)
i, iii
35–81%
(192)

R = H, Me, Ph; R' = H, Me, $BrCH_2$, Ph, 3,4-$(OCH_2)C_6H_3$

i, LDA, –78 °C; ii, (*E*)-$RCH{=}CHNO_2$; iii, (*E*)-$RCH{=}C(R')NO_2$

**Scheme 73**

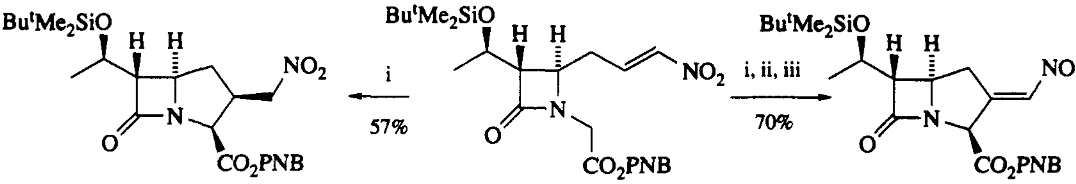

(194) (193) (195)

i, LiHMDS, THF, –100 °C; ii, PhSeCl; iii, $H_2O_2$

Scheme 74

Alternatively, enantioselective additions of chiral Schiff base glycine anion equivalents can also be used, as illustrated in Scheme 75. (+)-Phosphinothricin (**199**) and (+)-2-amino-4-phosphonobutyric acid (**200**) are obtained by the conjugate addition of the chiral *N*-alkylideneglycinate (**196**) to the phosphorus acceptors (**197**) and (**198**),[152a–c] while addition of the dihydropyrazine glycine equivalent (**201**)[152d] to α,β-unsaturated esters affords an asymmetric synthesis of glutamic acids and pyroglutamate esters.[152e]

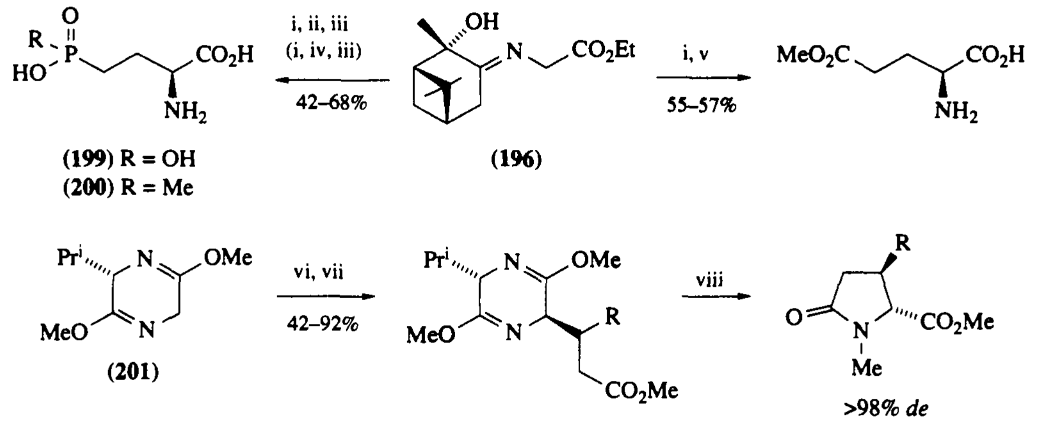

(199) R = OH
(200) R = Me
(196)
(201)

i, Bu$^t$OK, THF, –78 °C; ii, $(EtO)_2P(O)CH{=}CH_2$ (197); iii, 6N HCl, Δ; iv, $Me(MeO)P(O)CH{=}CH_2$ (198); v, $CH_2{=}CHCO_2Me$; vi, Bu$^n$Li, THF, –78 °C; vii, $RCH{=}CHCO_2Me$, –78 to 0 °C; viii, 0.25 N HCl, 25 °C

Scheme 75

The addition of lithium alkoxydienolates to α,β-enones occurs exclusively in the 1,4$_{(\alpha)}$-mode. For example, alkoxydienolate (**202**), obtained from ethyl senecioate, adds efficiently, in a tandem conjugate addition–allylation protocol, to cyclopentenone to afford the α,β-functionalized cyclopentanone (**203**).[153] In contrast, the lithium dienolate (**204**), from 5-methylbutenolide, affords exclusive γ-alkylation,[154a,b] while the analogous phthalide enolates (**206**) can be exploited to accomplish regiospecific polynuclear aromatic syntheses (Scheme 76).[154c–g]

### *1.2.2.2.3 α,O-Carboxylic dianions and α-nitrile anions*

In contrast to the ester enolates, the α,*O*-carboxylic dianions are intrinsically more reactive and their use in conjugate reactions is thus limited. Typically, α-substituted-α,*O*-carboxylic dianions add exclusively to α,β-unsaturated esters[155a] and nitroalkenes,[155b] while additions to α,β-enones are sensitive to the substitution pattern of the enones.[155c,d] Notable is the conjugate addition of dihydrobenzoic acid dianions (**207**), from Birch reduction of benzoic acids, to α,β-unsaturated esters (Scheme 77).[155e]

The addition of unstabilized α-nitrile carbanions to α,β-unsaturated carbonyl acceptors affords predominantly 1,2-addition products,[156] while lithiated acetonitrile derivatives having α-alkoxy, α-aromatic, α-dialkylamino, α-phenylselenyl, α-phenylthio or α-trimethylsilyl substituents afford 1,4-adducts. However, some of these are acyl anion equivalents (Section 1.2.2.3.2) so this discussion is limited to α-stabilized nitriles in which the nitrile function is retained after removal of the activating group. Notable examples are trimethylsilylacetonitrile (**208**),[157] phenylthioacetonitriles (**209**),[158a,b] phenylselenylacetoni-

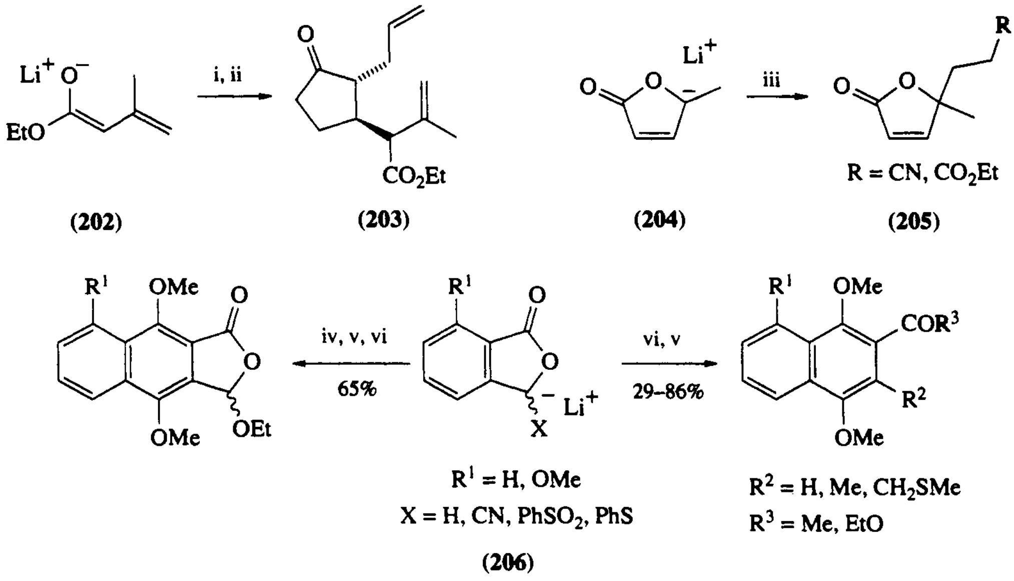

i, ii
iii
iv, v, vi
65%
vi, v
29–86%
R = CN, CO$_2$Et
(202)
(203)
(204)
(205)
R$^1$ = H, OMe
X = H, CN, PhSO$_2$, PhS
R$^2$ = H, Me, CH$_2$SMe
R$^3$ = Me, EtO
(206)

i, 2-cyclopenten-1-one, THF, –78 °C; ii, $CH_2{=}CHCH_2Br$; iii, $CH_2{=}CHR$, THF, –78 °C; iv, 5-ethoxy-2(5*H*)-furanone; v, $(MeO)_2SO_2$, $K_2CO_3$, acetone; vi, (*E*)-$R^2CH{=}CHCOR^3$

Scheme 76

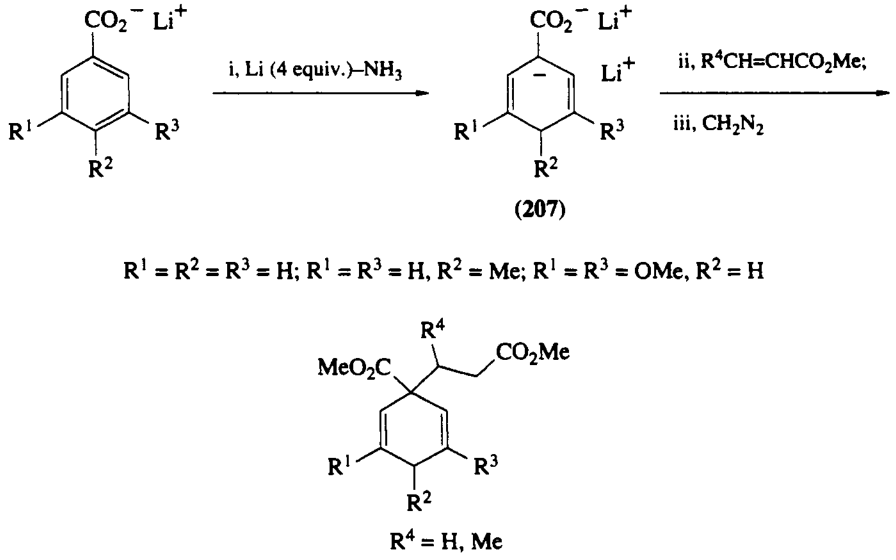

i, Li (4 equiv.)–NH$_3$
ii, R$^4$CH=CHCO$_2$Me;
iii, CH$_2$N$_2$
(207)
R$^1$ = R$^2$ = R$^3$ = H; R$^1$ = R$^3$ = H, R$^2$ = Me; R$^1$ = R$^3$ = OMe, R$^2$ = H
R$^4$ = H, Me

Scheme 77

trile (**210**)[158c] and phenylsulfonylacetonitrile (**211**).[158d] Seyden-Penne has reported that α-arylacetonitriles (**212**) add to α,β-cycloalkenones in a tandem conjugate addition–alkylation protocol to afford *trans* 2,3-disubstituted cycloalkanones (Scheme 78).[159] In contrast, Ahlbrecht has reported a versatile γ-ketonitrile synthesis in which unstabilized α-nitrile carbanions add to acceptor (**59**; equation 19).[160]

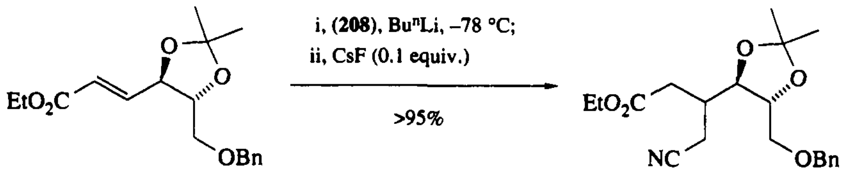

R(X)CHCN

**(208)** X = SiMe$_3$; R = H
**(209)** X = PhS; R = H, alkyl
**(210)** X = PhSe; R = n-C$_4$H$_9$
**(211)** X = PhSO$_2$; R = H
**(212)** X = aryl; R = H

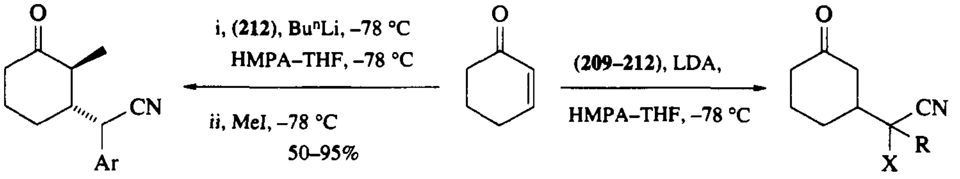

**Scheme 78**

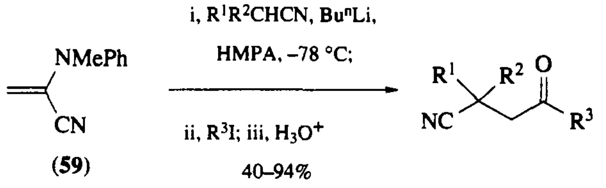

(19)

R$^1$ = alkyl (C$_1$–C$_4$); R$^2$ = H, Me; R$^3$ = alkyl (C$_1$–C$_4$), allyl, benzyl

### 1.2.2.3 Additions of Acyl Anion Equivalents

#### *1.2.2.3.1 Masked acyl anion equivalents*

The realization of the principle of 'umpolung', in which reactivity at a normally electrophilic site is inverted to that of a nucleophilic species,[161] has resulted in the development of numerous masked acyl anion equivalents for carbon–carbon bond formation.[162] The use of masked acyl anion equivalents for conjugate additions was made possible by several observations. First, Stork reported that protected cyanohydrins afforded preferential kinetic 1,4-addition with α,β-enones[16b] and second, Brown reported that preferential kinetic 1,4-addition of 1,3-dithianes was effected by the use of HMPA.[163]

The masked acyl anion equivalents discussed in this section are divided into two classes, based on their unmasked functional groups, *i.e.* acyl and carboxylate. Representative acyl group synthons include the 1,3-dithianes (**214**),[164] bis(arylthio)acetals (**215**), [165] bis(arylseleno)acetals (**216**),[165] di(ethylthio)acetal monoxides (**217**),[166] α-silyl sulfides (**218**),[167] α-(dialkylamino)nitriles (**219**),[168] protected cyanohydrins (**220** and **221**)[16b,159b,168d–e,169] and *t*-butylhydrazone aldimines (**222**).[170] The carboxylate group synthons include the trithioorthoformates (**223**),[171] α-(trialkylmetallo)dithioacetals (**224** and **225**),[172] α-cyanodithioacetals (**226**),[173] methoxy(phenylthio)(trimethylsilyl)methane (**227**)[174] and the benzothiazoles (**228**; Scheme 79).[46,114,175] Numerous groups have reported additions of (**214–228**) to α,β-enones, α,β-unsaturated esters and α,β-unsaturated nitriles. The addition of the protected cyanohydrin (**229**),[169c] carboxylate synthon (**223**)[171e–i] or 1,3-dithiane (**230**)[176] to butenolides in a tandem conjugate addition–electrophile trapping protocol is representative of their synthetic versatility (Scheme 80).

### 1.2.2.3.2 *Formal acyl anion equivalents*

The use of masked acyl anion equivalents in a synthetic protocol requires additional steps to unmask the carbonyl unit. Sometimes the deprotection procedures are incompatible with sensitive compounds; thus, a direct nucleophilic acylation protocol is desirable. While C-nucleophilic carbonyl groups do not

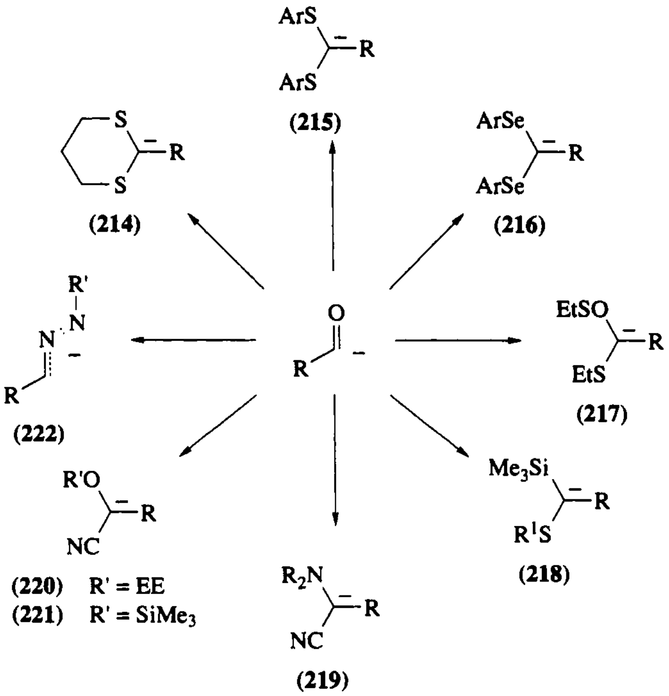
(214)
(215)
(216)
(217)
(218)
(219)
(220) R' = EE
(221) R' = SiMe₃
(222)

*Acyl Anion Equivalents*

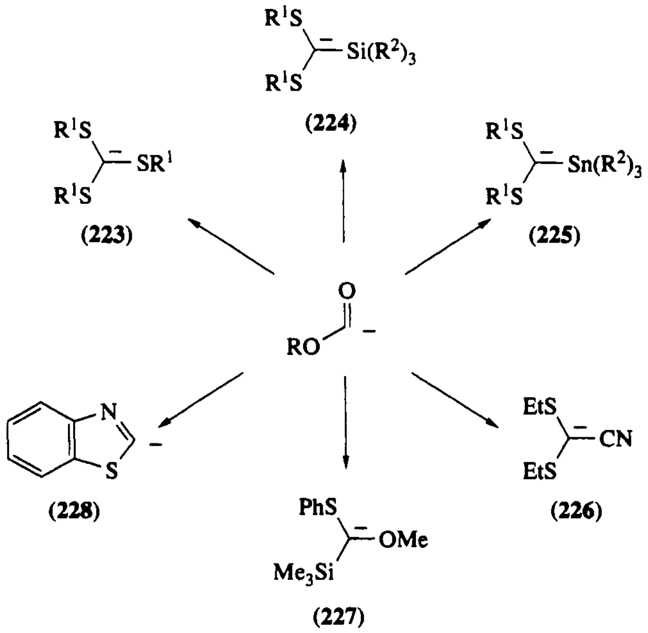
(223)
(224)
(225)
(226)
(227)
(228)

*Carboxylate Equivalents*

**Scheme 79**

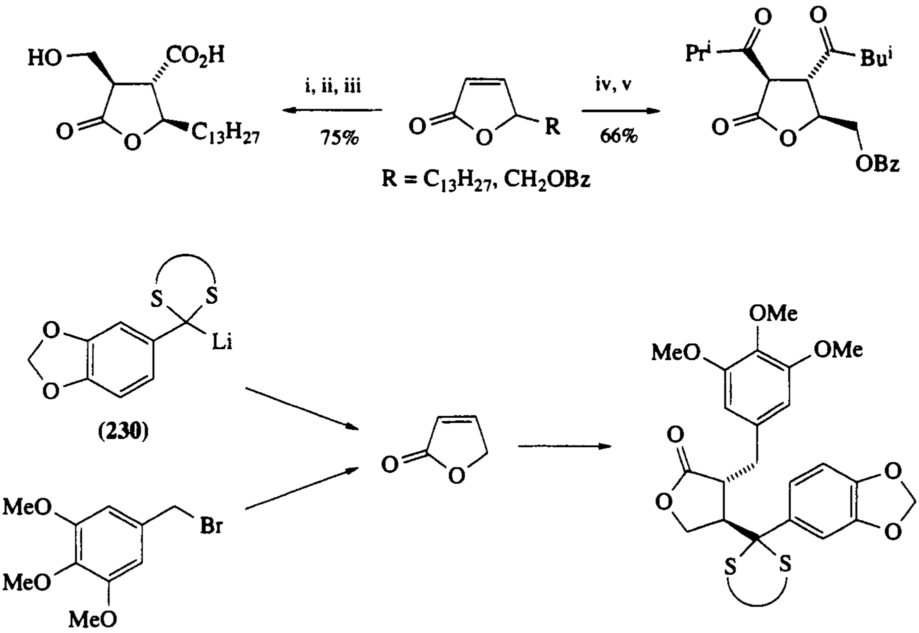

i, $(MeS)_3CH$ (223), LDA, THF, HMPA, −78 °C; ii, $CH_2O$, −40 °C; iii, HgO, $BF_3$–$Et_2O$; iv, $Pr^iCH_2CH(OEE)CN$ (229), LDA, THF, HMPA, −78 °C; v, $Pr^iCOCl$, −78 to 25 °C

**Scheme 80**

exist *per se*,[177] the organotetracarbonylferrates (**231**) or acylnickel complexes (**232**) afford formal 1,4-addition of β-acyl units to α,β-unsaturated esters, α,β-enones or α,β-unsaturated nitriles. The two reagents differ mechanistically and in synthetic versatility; for example, the organoferrate system is sensitive to steric effects on the acceptor and tandem trapping at the α-position is not effective.[178] In contrast, the acyl nickel complexes are insensitive to steric effects on the acceptor and amenable to tandem electrophilic trapping protocols,[179a] as reported by Semmelhack, in an efficient synthesis of pyranonaphthoquinone antibiotic intermediates from quinone monoketals (**233**; Scheme 81).[179b]

Variations to the above processes have been introduced to obviate handling of the volatile and toxic metal carbonyls. For example, the tricarbonyl(α,β-enone)iron complexes (**234**),[180a–c] on treatment with organolithiums (or Grignard reagents), afford the corresponding 1,4-diketones[180d,e] or γ-ketoamides.[180f] The highly stable cobalt complex, $Co(NO)(CO)_2(Ph_3P)$,[181a] on reaction with alkyllithiums, affords an intermediate carbonylate complex which adds exclusively to α,β-enones; however, data is lacking as to the applicability of this complex in a tandem conjugate addition–electrophile trapping protocol.[181b]

Alternatively, the expedient cyanide (or fluoride) ion desilylation of acylsilanes (**235**), in the presence of α,β-enones or α,β-unsaturated esters, affords γ-dicarbonyl adducts;[182] even bis(trimethylsilyl)ketone (**236**), a formyl anion equivalent, adds to 2-cyclohexen-1-one to afford 3-formylcyclohexanone in moderate yields.[182e]

## 1.2.2.4 Additions of α-Heteroatom-stabilized Carbanions (Non-acyl Anion Equivalents)

### *1.2.2.4.1 Phosphorus- and sulfur-stabilized carbanions*

The synthetic utility of α-phosphorus- and α-thio-stabilized carbanions is the subject of numerous reviews.[21] Notable are additions of phosphonium ylides (**237**),[183] sulfonium ylides (**238**),[184a–c] oxosulfonium ylides (**239**)[184a–c] and sulfoximine ylides (**240**)[184d] to electron-deficient alkenes which afford nucleophilic cyclopropanation products. In contrast, with α-(phenylthio)-stabilized carbanions, which are not acyl anion equivalents, either nucleophilic cyclopropanation or retention of the hetero substituent occurs, depending on the acceptor and reaction conditions used. For example, carbanion (**241**) adds to 1,1-

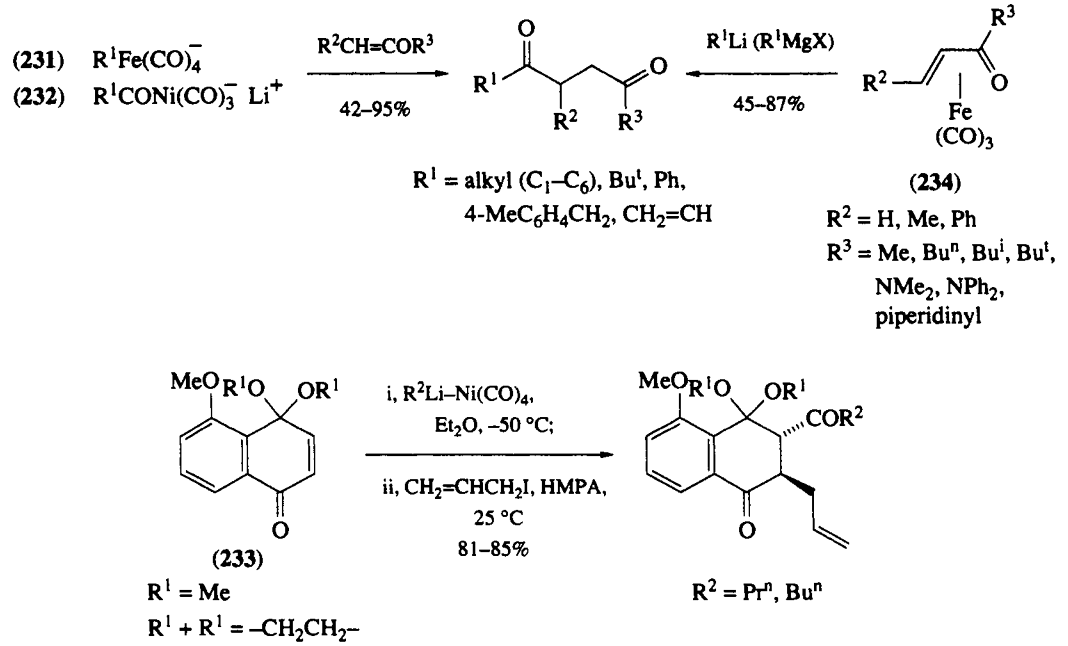
(231) R¹Fe(CO)₄⁻
(232) R¹CONi(CO)₃⁻ Li⁺
R²CH=COR³
42–95%
R¹Li (R¹MgX)
45–87%
R¹ = alkyl (C₁–C₆), Buᵗ, Ph, 4-MeC₆H₄CH₂, CH₂=CH
(234)
R² = H, Me, Ph
R³ = Me, Buⁿ, Buⁱ, Buᵗ, NMe₂, NPh₂, piperidinyl
i, R²Li–Ni(CO)₄, Et₂O, –50 °C;
ii, CH₂=CHCH₂I, HMPA, 25 °C
81–85%
(233)
R¹ = Me
R¹ + R¹ = –CH₂CH₂–
R² = Prⁿ, Buⁿ

(235) $RCOSiMe_3$
(236) $Me_3SiCOSiMe_3$

Scheme 81

doubly stabilized a²-synthons, *e.g.* *N*-(methylanilino)acrylonitrile (**59**),[185a] α-TMS vinyl phenyl sulfide (**242**),[185b] 1,1-bis(phenylthio)ethylene (**243**),[185c] with concomitant $S_N2$ displacement, while normal addition occurs with α,β-enones (Scheme 82).[185d] The initial products can be further desulfurized as shown for adduct (**244**).[186]

In contrast, few examples of conjugate additions of nonallylic α-sulfinyl (or α-sulfonyl) carbanions have been reported (for allylic α-sulfinyl carbanion additions, see Section 1.2.2.5.1). Notable is the diastereoselective addition of alkyl *t*-butyl sulfoxides (**245**) to α,β-unsaturated esters (equation 20)[187] which is complementary to the diastereoselective addition of enolates to β-substituted-α,β-unsaturated sulfoxides (equation 20).

### *1.2.2.4.2 Oxygen- and silicon-stabilized carbanions*

While there are few examples of conjugate additions of either α-oxygen- or α-silyl-stabilized carbanions, Tamao and Posner have reported two hydroxymethyl synthons [$^-CH_2OH$] (**246** and **247**) which show synthetic promise. Additions with the silicon-based synthon (**246**) is restricted to 2-cyclohexen-1-ones and work-up requires a successive acid and base procedure that is incompatible with sensitive molecules,[188a,b] while the tin-based synthon (**247**) is more versatile and the hydroxyl group is obtained under neutral conditions (Scheme 83).[188c]

### *1.2.2.4.3 Nitrogen-stabilized carbanions*

Aside from the nitronates, cyanide anion and acyl anion equivalents, *e.g.* (**219**), examples of conjugate additions of α-aza-stabilized carbanions are rare. The aminomethyl synthon [$^-CHRNH_2$] is typically introduced with either nitronates or cyanide; however, α-metallomethyl isocyanides (**248**) also show synthetic promise in conjugate additions. In addition, depending on hydrolytic conditions employed, they also serve as equivalents for the *N*-formamidomethyl anion [$^-CHRNHCHO$] or the isocyanatomethyl anion [$^-CHRN{=}C{:}$] (Scheme 84).[189]

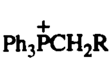

$Ph_3\overset{+}{P}CH_2R\ X^-$

**(237)**

$R'_2\overset{+}{S}CH_2R\ X^-$

**(238)**

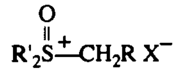

$R'_2\overset{\overset{O}{\|}}{S^+}{-}CH_2R\ X^-$

**(239)**

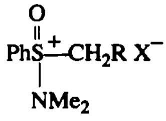

$Ph\underset{NMe_2}{\overset{\overset{O}{\|}}{S^+}}{-}CH_2R\ X^-$

**(240)**

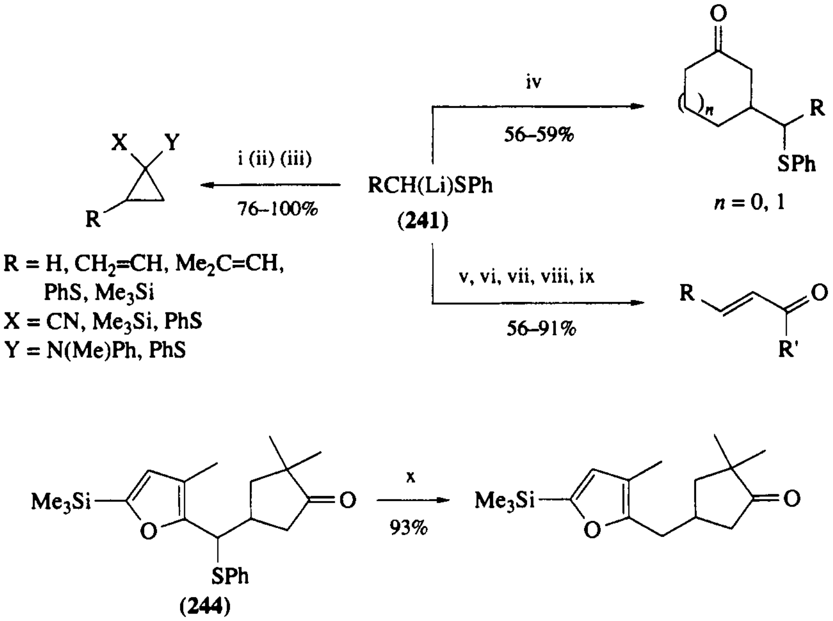
X
Y
R
i (ii) (iii)
76–100%
RCH(Li)SPh
(241)
iv
56–59%
O
( )n
R
SPh
n = 0, 1
v, vi, vii, viii, ix
56–91%
R
O
R'
R = H, CH2=CH, Me2C=CH,
PhS, Me3Si
X = CN, Me3Si, PhS
Y = N(Me)Ph, PhS
Me3Si
O
O
SPh
(244)
x
93%
Me3Si
O
O

i, $CH_2{=}C(CN)N(Me)Ph$ (**59**), 25 °C, 30 h; ii, $CH_2{=}C(SiMe_3)SPh$ (**242**), TMEDA, –25 to 25 °C; iii, $CH_2{=}C(SPh)_2$ (**243**), TMEDA; iv, cycloalkenones, –78 °C; v, $CH_2{=}C(CN)N(Me)Ph$ (**59**), –78 °C; vi, R'X; vii, 3N HCl; viii, MCPBA; ix, Δ, $CCl_4$; x, Raney Ni

**Scheme 82**

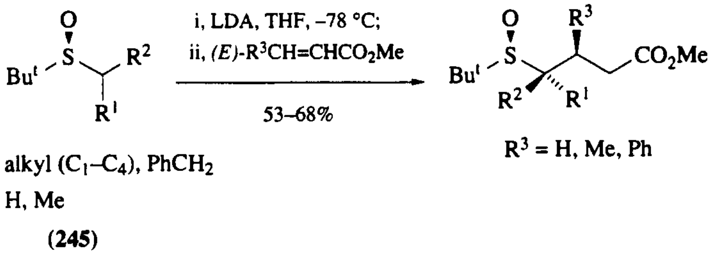
O
Bu$^t$
S
R$^2$
R$^1$
i, LDA, THF, –78 °C;
ii, (E)-R$^3$CH=CHCO$_2$Me
53–68%
O
R$^3$
Bu$^t$
S
CO$_2$Me
R$^2$
R$^1$
R$^1$ = alkyl (C$_1$–C$_4$), PhCH$_2$
R$^2$ = H, Me
(245)
R$^3$ = H, Me, Ph

(20)

### 1.2.2.5 Additions of Homoenolates or Homoenolate Equivalents

#### *1.2.2.5.1 Homoenolate equivalents*

The concept of homoenolization was recognized by Nickon in the 1960s but attempts at direct formation of homoenolates were frustrated by cyclopropanolate formation. This lack of success has prompted the development of homoenolate equivalents[190] of which the first example, the β-propionaldehyde anion equivalent (**112**), was previously discussed (Sections 1.2.2.1.2 and 1.2.2.1.3). Ghosez has shown that α-cyanoenamines (**249** and **250**) add preferentially in the $1,4_{(\gamma)}$-mode to cycloalkenones. The versatility of (**250**) which serves as either a β-carboxyvinyl anion equivalent [$^-CH{=}CHCO_2R$] or β-propionate anion equivalent [$^-CH_2CH_2CO_2R$] (Scheme 85) is notable.[191]

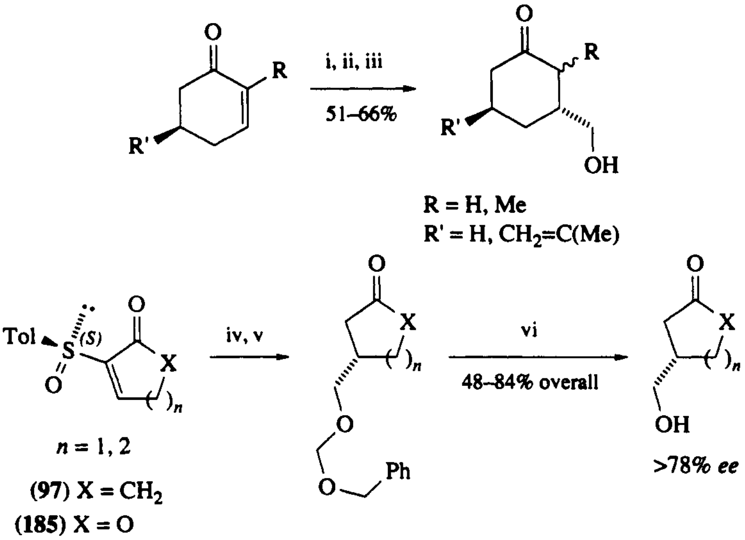
i, ii, iii
51–66%
R = H, Me
R' = H, CH2=C(Me)
iv, v
vi
48–84% overall
n = 1, 2
(97) X = CH2
(185) X = O
>78% ee

i, $(CH_2{=}CHCH_2)Me_2SiCH_2MgCl$ **(246)**, $Et_2O$, CuI (10%), 25 °C; ii, $KHF_2$ (2 equiv.), $CF_3CO_2H$, 50 °C; iii, 30% $H_2O_2$, $NaHCO_3$, MeOH, THF, 68 °C; iv, $PhCH_2OCH_2OCH_2SnBu^n_3$ **(247)**, $Bu^nLi$ (2 equiv.), −78 °C; v, Raney Ni, EtOH; vi, $H_2$, 10% Pd–C

**Scheme 83**

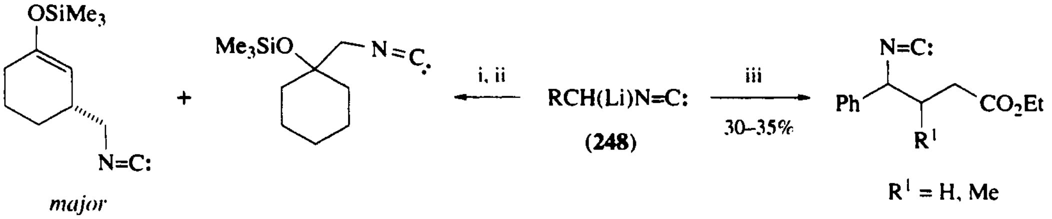
i, ii
RCH(Li)N=C:
(248)
iii
30–35%
R1 = H, Me
major

i, cyclohexenone, −78 °C; ii, $Me_3SiCl$; iii, (*E*)-$R^1CH{=}CHCO_2Et$

**Scheme 84**

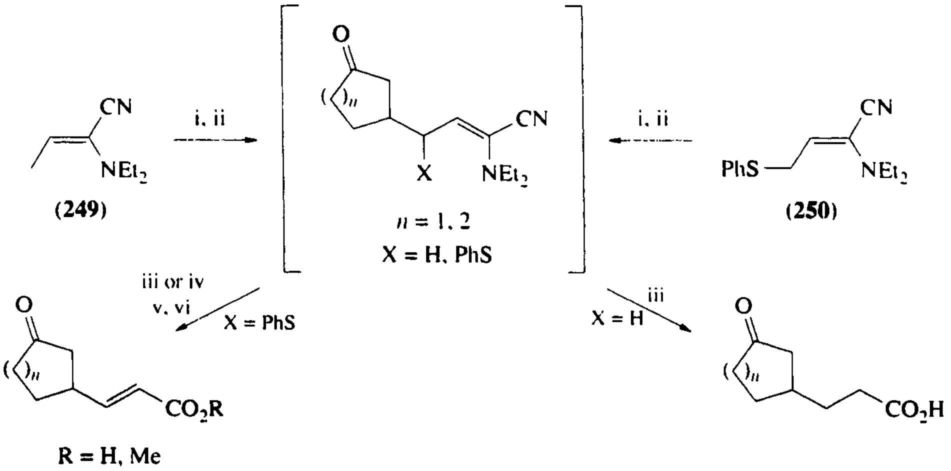
(249)
(250)
i, ii
i, ii
n = 1, 2
X = H, PhS
iii or iv
v, vi
X = PhS
iii
X = H
R = H, Me

i, LDA, THF, −60 to −30 °C; ii, cycloalkenones; iii, 3N HCl, Δ; iv, HCl, MeOH; v, MCPBA; vi, Δ, $CCl_4$

**Scheme 85**

Alternatively, the ambident α-hetero substituted allyl anions have been utilized as homoenolate equivalents. For example, in the presence of HMPA, allyl phenyl sulfides (**251**),[192a] allyl phenyl sulfones (**252**)[192b,c] and allyl phenyl selenides (**253**)[192d,e] add to α,β-enones in a $1,4_{(\alpha)}$-mode, while allyl phenyl sulfoxides (**254**) and allyl phosphine oxides (**255**) afford $1,4_{(\gamma)}$-addition exclusively, irrespective of solvent used.[193] Hua has shown that additions of either chiral sulfoxide (**254**; $R^1 = R^2 = R^3 = R^4 = H$, $R^5$ = *p*-tolyl) or allyl oxazaphospholidine oxide (**256**) occur with excellent enantioselectivity (>95% *ee*).[194] Similarly, Ahlbrecht reports that the α-azaallyl (**257**) adds exclusively in a $1,4_{(\gamma)}$-mode to acceptor (**59**) to afford 1,5-diketones (Scheme 86).[195]

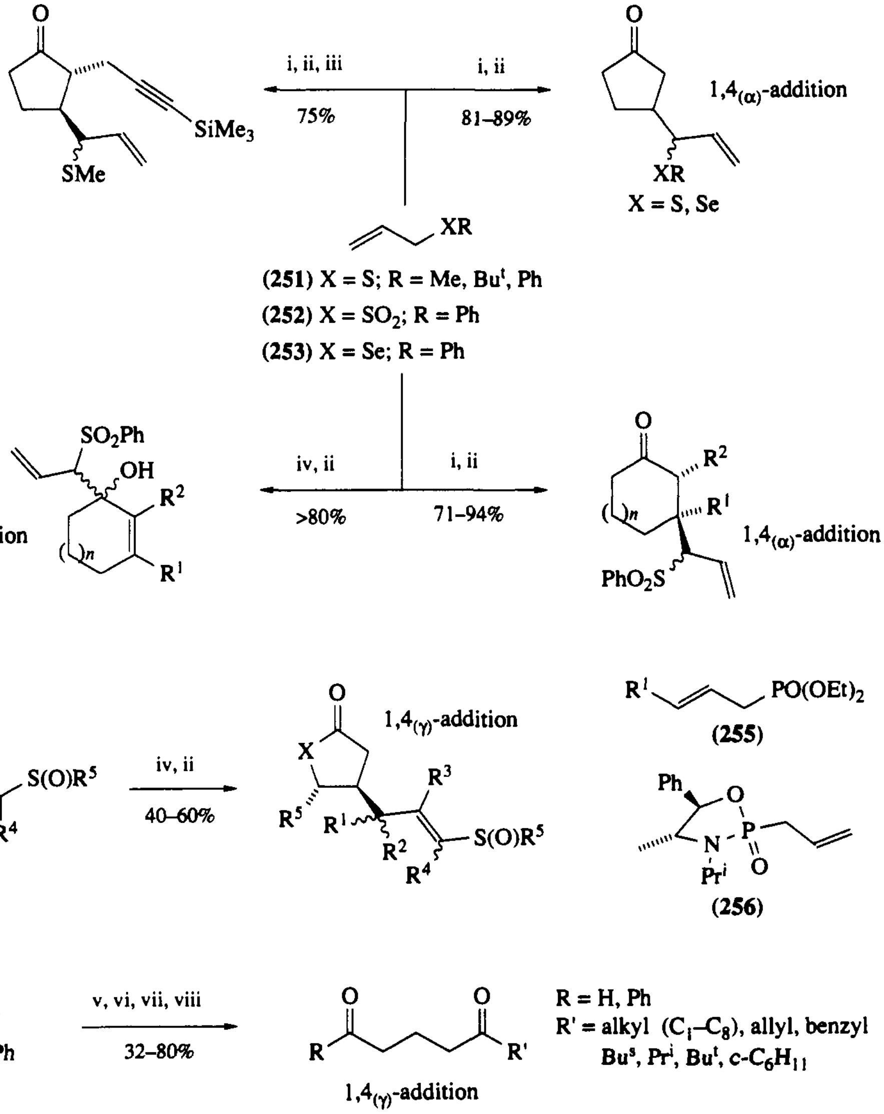
SiMe3
SMe
i, ii, iii
75%
i, ii
81–89%
1,4(α)-addition
XR
X = S, Se
XR
(251) X = S; R = Me, Bu^t, Ph
(252) X = SO2; R = Ph
(253) X = Se; R = Ph
SO2Ph
OH
R2
R1
1,2(α)-addition
iv, ii
>80%
i, ii
71–94%
R2
R1
PhO2S
1,4(α)-addition
R3
R1
S(O)R5
R2
R4
(254)
iv, ii
40–60%
X
1,4(γ)-addition
R3
R5
R1
R2
R4
S(O)R5
R1
PO(OEt)2
(255)
Ph
O
P
N
Pr^i
O
(256)
R
N(Me)Ph
(257)
v, vi, vii, viii
32–80%
R
R'
1,4(γ)-addition
R = H, Ph
R' = alkyl (C1–C8), allyl, benzyl
Bu^s, Pr^i, Bu^t, c-C6H11

i, Bu$^s$Li (Bu$^n$Li), HMPA, −78 °C to −50 °C; ii, cycloalkenone or α,β-unsaturated lactone; iii, $BrCH_2C{\equiv}CSiMe_3$; iv, Bu$^n$Li, THF, −78 °C; v, Bu$^n$Li, TMEDA, THF, 0 °C; vi, $CH_2{=}C(CN)N(Me)Ph$ (**59**), −78 °C; vii, R'Br (R'I); viii, 3N HCl

**Scheme 86**

### *1.2.2.5.2 Formal homoenolates*

Marino has reported that the fluoride-induced ring cleavage of 1-silyloxy-2-carboalkoxycyclopropanes affords γ-oxo-α-ester enolates, modified homoenolates, which add to Michael acceptors to afford cyclopentanes and cyclopentenes, *e.g.* (**258**→**259**);[196] alternatively, a carboannulation procedure affords octalin-1-ones (**260**→**261**; Scheme 87) (note the intramolecular enolate addition to the α,β-unsaturated sulfone).

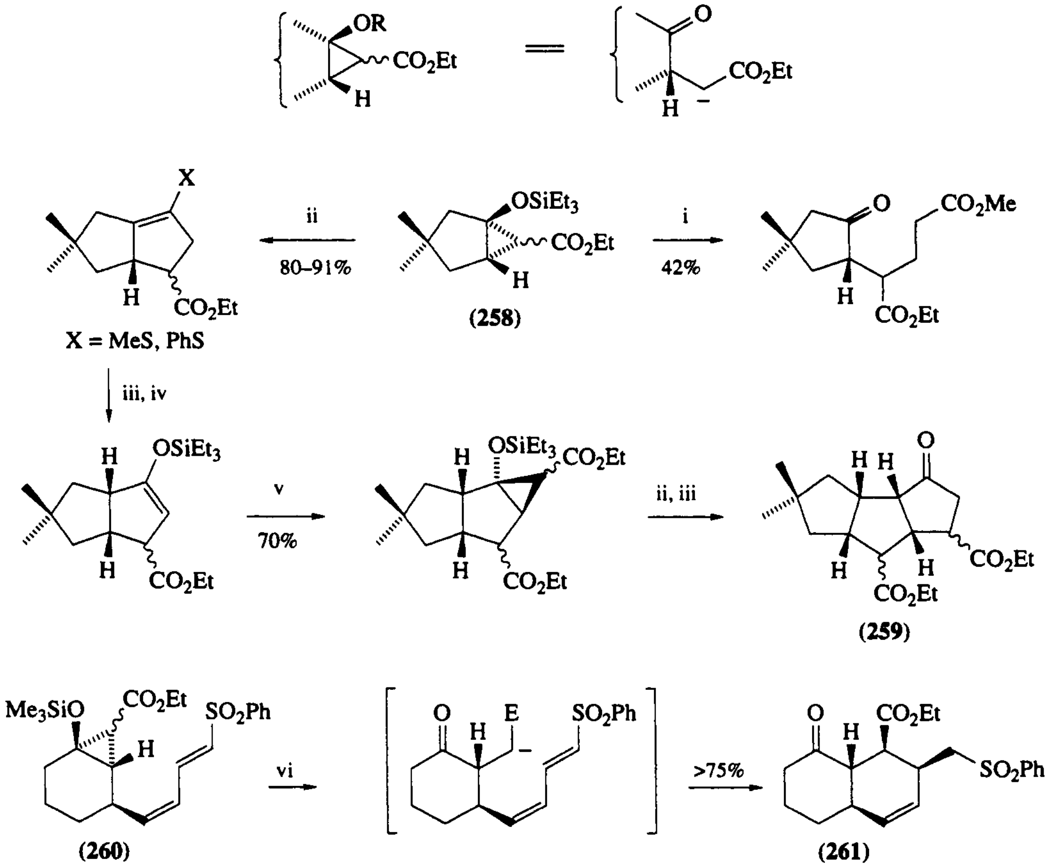

OR
$CO_2Et$
H
O
$CO_2Et$
H
X
H
$CO_2Et$
X = MeS, PhS
ii
80–91%
$OSiEt_3$
$CO_2Et$
H
(258)
i
42%
O
$CO_2Me$
H
$CO_2Et$
iii, iv
H
$OSiEt_3$
H
$CO_2Et$
v
70%
H
$OSiEt_3$
$CO_2Et$
H
$CO_2Et$
ii, iii
H H
O
H
H
$CO_2Et$
$CO_2Et$
(259)
$Me_3SiO$
$CO_2Et$
$SO_2Ph$
H
(260)
vi
O
H
E
$SO_2Ph$
>75%
O
H
$CO_2Et$
$SO_2Ph$
(261)

i, $CH_2=CHCO_2Me$, CsF; ii, $CH_2=CX-\overset{+}{P}Ph_3\ BF_4^-$; iii, TFA; iv, LDA–THF, –78 °C, $Et_3SiCl$;

v, $N_2=CHCO_2Et$, $CuSO_4$; vi, CsF, DMF, 60 °C

Scheme 87

## 1.2.2.6 Heteroconjugate Additions (Carbometallation)

During the last three decades, the addition of organolithiums or Grignard reagents to vinyl derivatives of either second row (P, S or Si) or third row (Se) elements in their normal oxidation state has been recognized as an important procedure for the *in situ* generation of α-heteroatom stabilized carbanions. Carbometallation was initially recognized with vinylsilanes (**262**)[197] and subsequently for vinyl diarylphosphines (**263**),[198] aryl vinyl sulfides (**264**),[199] aryl vinyl selenides (**265**)[200] and 2-methylene-1,3-dithianes (**266**).[201] The driving force for these carbometallation reactions arises from the adjacent heteroatom stabilization of the incipient carbanion which is attributed to either charge dispersion or *d*-orbital interactions,[202] but it is not the role of this survey to discuss the issue.

Intermolecular carbometallations are typically accomplished with organolithiums; however, diastereocontrolled intramolecular carbometallation can be attained with appropriate Grignard reagents, as exemplified in Scheme 88, the suprafacial and 5-*exo*-trig closure of (*E*)-6-bromo-3-methyl-1-trimethylsilyl-1-hexene (**267**) to *trans*-1-methyl-2-(trimethylsilyl)methylcyclopentane (**268**).[203]

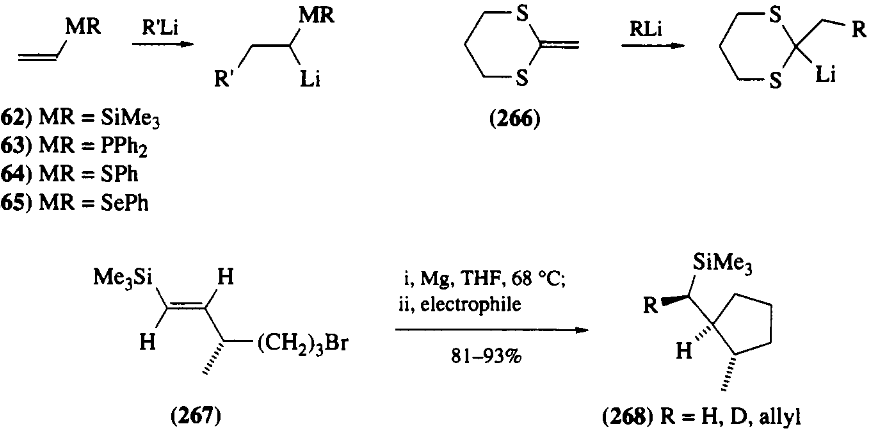
MR
R'Li
MR
R'
Li
S
S
RLi
S
S
R
Li
Me$_3$Si
H
H
(CH$_2$)$_3$Br
i, Mg, THF, 68 °C;
ii, electrophile
81–93%
SiMe$_3$
R
H

**(262)** MR = SiMe$_3$
**(263)** MR = PPh$_2$
**(264)** MR = SPh
**(265)** MR = SePh

**(266)**

**(267)**

**(268)** R = H, D, allyl

Scheme 88

## 1.2.3 ANNULATIONS AND MULTIPLE CONJUGATE ADDITIONS (TANDEM MICHAEL REACTIONS)

Examples of the intermolecular tandem conjugate addition–electrophile trapping protocol with simple electrophiles have been cited earlier in this review, but the initial nucleophile can also possess a suitably juxtaposed electrophilic site, *e.g.* either a carbonyl group or Michael acceptor.[204] For example, the reaction of β-oxo-stabilized vinyllithiums, derived from β-heteroatom functionalized α,β-unsaturated esters or β-heteroatom vinyl ketones, *e.g.* **(269)**, respectively, with α,β-unsaturated esters affords cyclopentenones (Scheme 89).[205a–c] Alternatively, Beak reports that (2-carbamoylallyl)lithiums [β'-lithiomethacrylate synthon] **(270)** react with Michael acceptors to afford cyclopentenecarboxamides **(271)**;[205d–f] formally this would be a [3 + 2] anionic cycloaddition, but data show that this occurs in discrete stages: (a) initial conjugate addition, (b) 5-*endo*-trig cyclization and (c) sulfinate elimination. The α'-dienolates, derived from α,β-enones, are also excellent tandem Michael donor-acceptors and have been used extensively for the synthesis of complex bicyclo[2.2.1]heptanones **(272)**,[206] bicyclo[2.2.2]octan-2-ones **(273)**[207] and tricyclo[3.2.1.0$^{2,7}$]octan-6-ones (**274**; Scheme 90).[208]

Examples of intramolecular transformations[209] include dienone–α,β-unsaturated ester cyclizations, *e.g.* (**275**→**276**),[209a,b] and ester–α,β-unsaturated ester annulations, *e.g.* (**277**→**278**; Scheme 91).[209c] Pertinent to the success of these multibond formation protocols is the selective use of the initiating carbanion (or enolates), the counter cation and the initial acceptor.

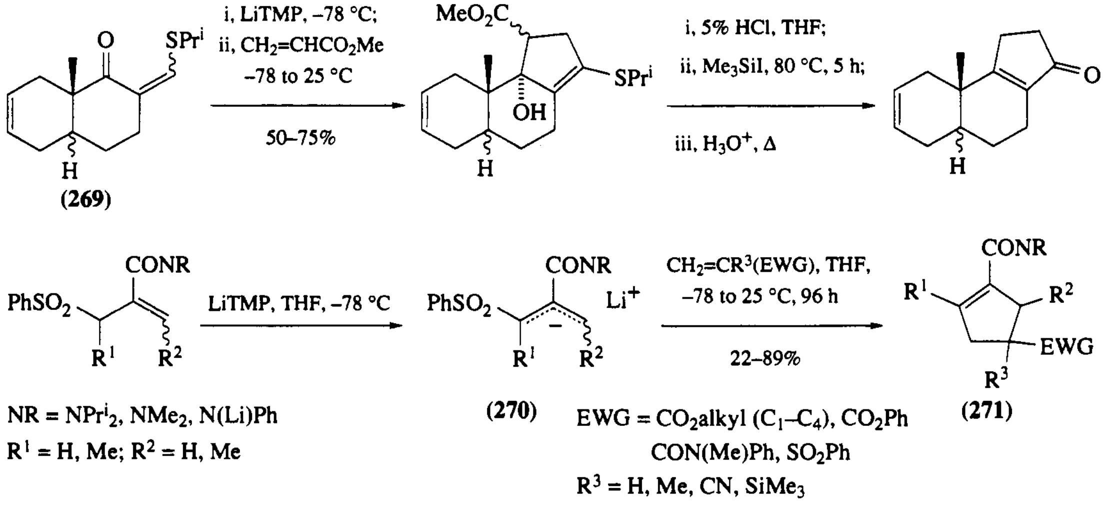
O
SPr$^i$
H
i, LiTMP, –78 °C;
ii, CH$_2$=CHCO$_2$Me
–78 to 25 °C
50–75%
MeO$_2$C
SPr$^i$
OH
H
i, 5% HCl, THF;
ii, Me$_3$SiI, 80 °C, 5 h;
iii, H$_3$O$^+$, Δ
O
H
CONR
PhSO$_2$
R$^1$
R$^2$
LiTMP, THF, –78 °C
CONR
PhSO$_2$
Li$^+$
R$^1$
R$^2$
CH$_2$=CR$^3$(EWG), THF,
–78 to 25 °C, 96 h
22–89%
CONR
R$^1$
R$^2$
EWG
R$^3$

**(269)**

NR = NPr$^i_2$, NMe$_2$, N(Li)Ph
R$^1$ = H, Me; R$^2$ = H, Me

**(270)** EWG = CO$_2$alkyl (C$_1$–C$_4$), CO$_2$Ph
CON(Me)Ph, SO$_2$Ph
R$^3$ = H, Me, CN, SiMe$_3$

**(271)**

Scheme 89

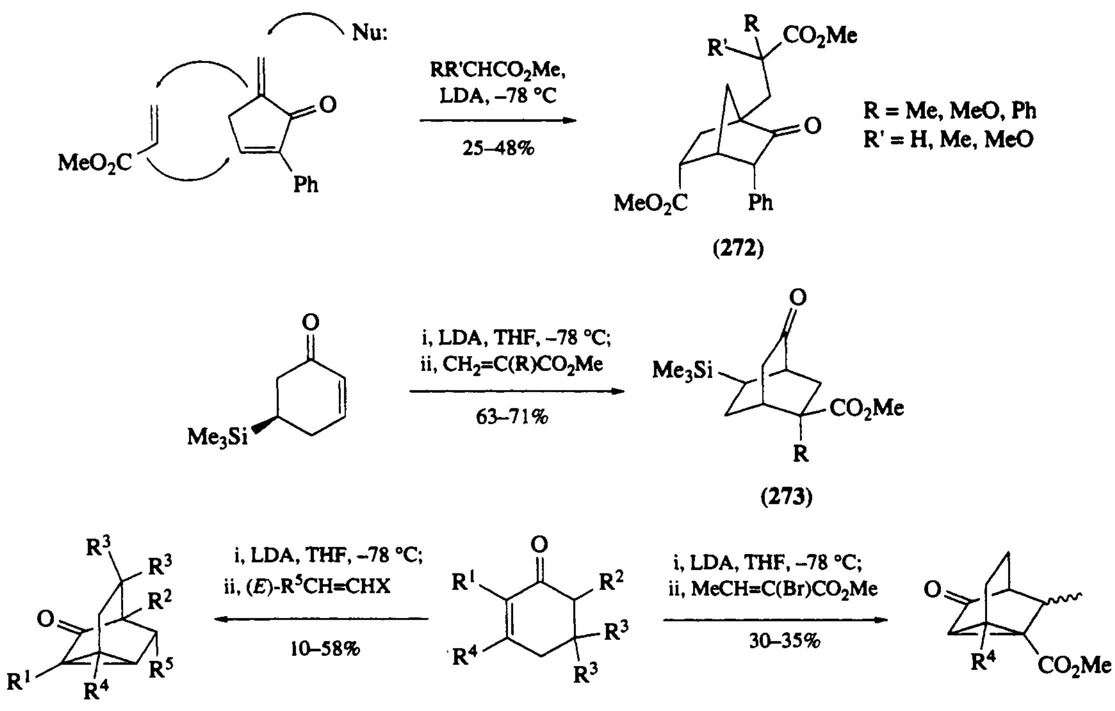
Nu:
MeO2C
O
Ph
RR'CHCO2Me,
LDA, –78 °C
25–48%
R
R'
CO2Me
O
MeO2C
Ph
R = Me, MeO, Ph
R' = H, Me, MeO
O
Me3Si
i, LDA, THF, –78 °C;
ii, CH2=C(R)CO2Me
63–71%
O
Me3Si
CO2Me
R
R3
R3
R2
O
R1
R4
R5
i, LDA, THF, –78 °C;
ii, (E)-R5CH=CHX
10–58%
O
R1
R2
R4
R3
R3
i, LDA, THF, –78 °C;
ii, MeCH=C(Br)CO2Me
30–35%
O
R4
CO2Me

**(272)**

**(273)**

$R^1$ = H, Me; $R^2$ = H, Me; $R^3$ = H, Me; $R^4$ = H, Me; $R^5$ = alkyl

**(274a)** X = $NO_2$, $PhSO_2$, $Ph_3P^+Br^-$

**(274b)**

**Scheme 90**

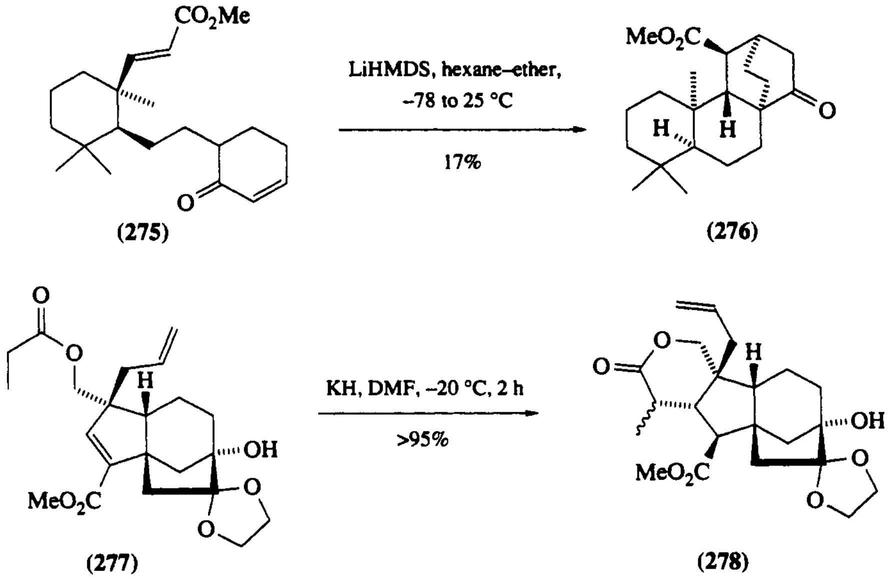
CO2Me
O
LiHMDS, hexane–ether,
–78 to 25 °C
17%
MeO2C
H
H
O
O
O
H
OH
O
O
MeO2C
KH, DMF, –20 °C, 2 h
>95%
O
O
H
OH
O
O
MeO2C

**(275)**

**(276)**

**(277)**

**(278)**

**Scheme 91**

### 1.2.4 ADDITIONS TO 'PUSH–PULL' ALKENES

The addition of organometallic reagents to 'push–pull' alkenes is a synthetically important process in which retention of an alkenic unit in the product occurs; this process complements the direct conjugate addition of organometallic reagents to activated alkynes (Section 1.2.5) which is complicated primarily by multiple additions. 'Push–pull' alkenes, which are formally vinyl cation equivalents, are characterized by the presence of an electron-withdrawing functionality on one terminus of an alkene and an electron-donating functionality at the other terminus. Examples of 'push–pull' alkenes include enaminones (**279**), β-amino-α,β-unsaturated esters (**280**), β-nitroenamines (**281**), β-halovinyl ketones (**282**), β-halo-α,β-unsaturated esters and amides (**283**), β-alkoxy-α,β-unsaturated ketones (**284**), β-alkoxy-α,β-unsaturated esters (**285**), β-(alkylthio)enones (**286**), β-(alkylthio)-α,β-unsaturated esters (**287**) and β-halovinyl sulfones and sulfoxides (**288**). In contrast to additions to activated alkynes additions of organometallics to enaminones and nitroenamines are free of overaddition because the initial adducts do not eliminate the secondary amine functionality until work-up. Even select α,α-difluoroalkenes (**289**) react with organometallic reagents to afford fluoroalkenes.

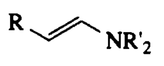
**(279)** R = COR"
**(280)** R = $CO_2R$"
**(281)** R = $NO_2$

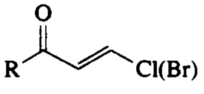
**(282)** R = alkyl, aryl
**(283)** R = alkoxy

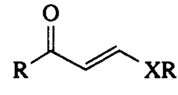
**(284)** R = alkyl, aryl; X = O
**(285)** R = alkoxy; X = O
**(286)** R = alkyl, aryl; X = S
**(287)** R = alkoxy; X = S

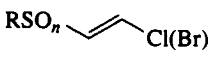
**(288a)** $n$ = 2
**(288b)** $n$ = 1

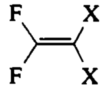
**(289)**

### 1.2.4.1 Enaminones

The addition of Grignard reagents[210a] and organolithium[210b] to enaminones (**279**) is an efficient process for the synthesis of α,β-unsaturated esters and α,β-enones. Typically, the enaminones are obtained by the treatment of activated methylene or methyl groups with dialkylformamide dialkyl acetals.[211] A variety of organolithiums have been added to enaminones, while Grignard reagents have been utilized

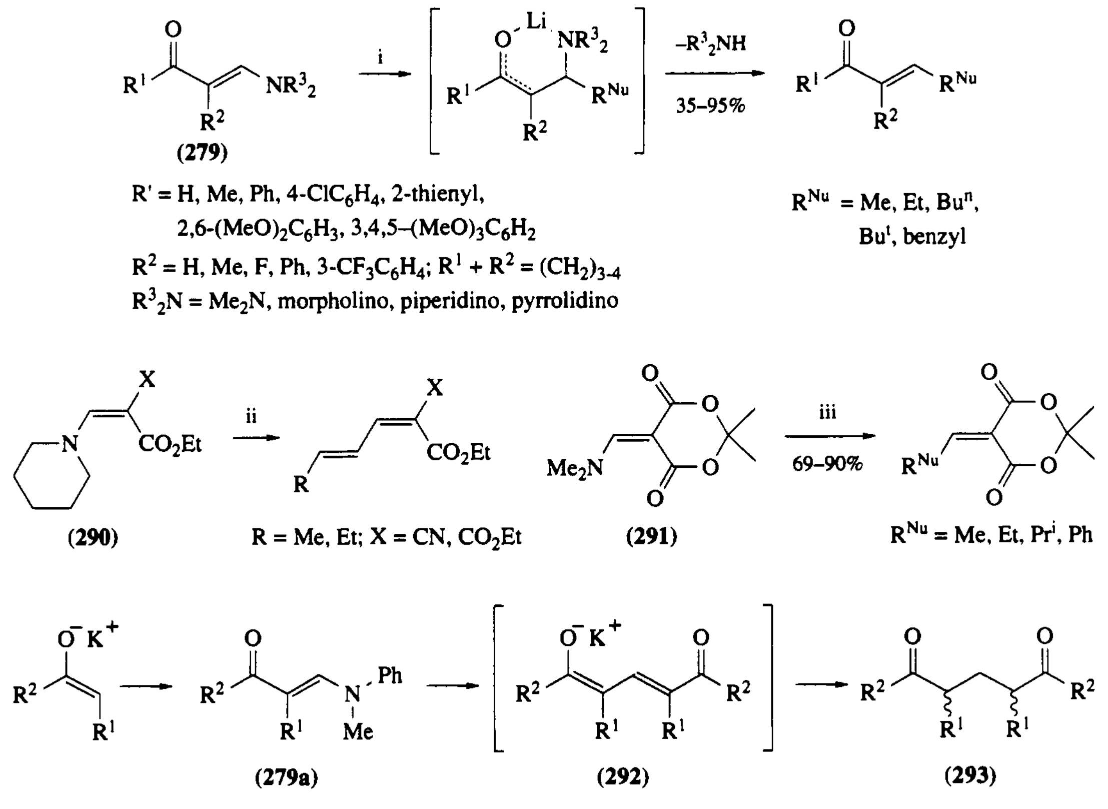

R' = H, Me, Ph, 4-$ClC_6H_4$, 2-thienyl, 2,6-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$
$R^2$ = H, Me, F, Ph, 3-$CF_3C_6H_4$; $R^1$ + $R^2$ = $(CH_2)_{3-4}$
$R^3_2N$ = $Me_2N$, morpholino, piperidino, pyrrolidino

$R^{Nu}$ = Me, Et, Bu$^n$, Bu$^t$, benzyl

R = Me, Et; X = CN, $CO_2Et$

$R^{Nu}$ = Me, Et, Pr$^i$, Ph

i, $R^{Nu}Li$, ether (THF), –30 to 0 °C; ii, (*Z*)-RCH=CHMgX, THF, 25 °C; iii, $R^{Nu}MgX$, THF, 25 °C

**Scheme 92**

for additions to doubly activated enaminones (**290** and **291**; Scheme 92). While numerous examples of direct additions of organometallics to enaminones have been discussed, few examples of enolate additions to enaminones are reported. Recently, Kiyooka reported a synthesis of symmetrical 1,5-diketones permits a ketone (2 equiv.), *N*-methyl-*N*-phenylformamide (1 equiv.) and potassium metal (3 equiv.) react at 25 °C (THF). The enolate adds to enaminone (**279a**) to afford intermediate (**292**) and subsequent reduction affords the symmetrical 1,5-diketone (**293**); however, with preformed *N*-methyl-*N*-phenylenaminones (**279a**), cross-coupling with ketones permits the synthesis of unsymmetrical 1,5-diketones (Scheme 92).[212]

### 1.2.4.2 Nitroenamines

The addition of Grignard reagents or organolithiums (alkenyl, alkyl, alkynyl, allyl or aryl) to nitroenamines (**281**)[213] was reported by Severin to afford β-substituted-α-nitroalkenes.[214a,b] Similarly, ketone enolates (sodium or potassium), ester enolates (lithium) and lactone enolates (lithium) react to afford *aci*-nitroethylidene salts (**294**) which, on hydrolysis with either silica gel or dilute acid, afford γ-keto-α,β-unsaturated esters or ketones (**295**)[214c,d] or acylidene lactones (**296**).[214e] Alternatively, the salts (**294**, X = $CH_2$) can be converted to γ-ketoketones (**297**) with ascorbic acid and copper catalyst.

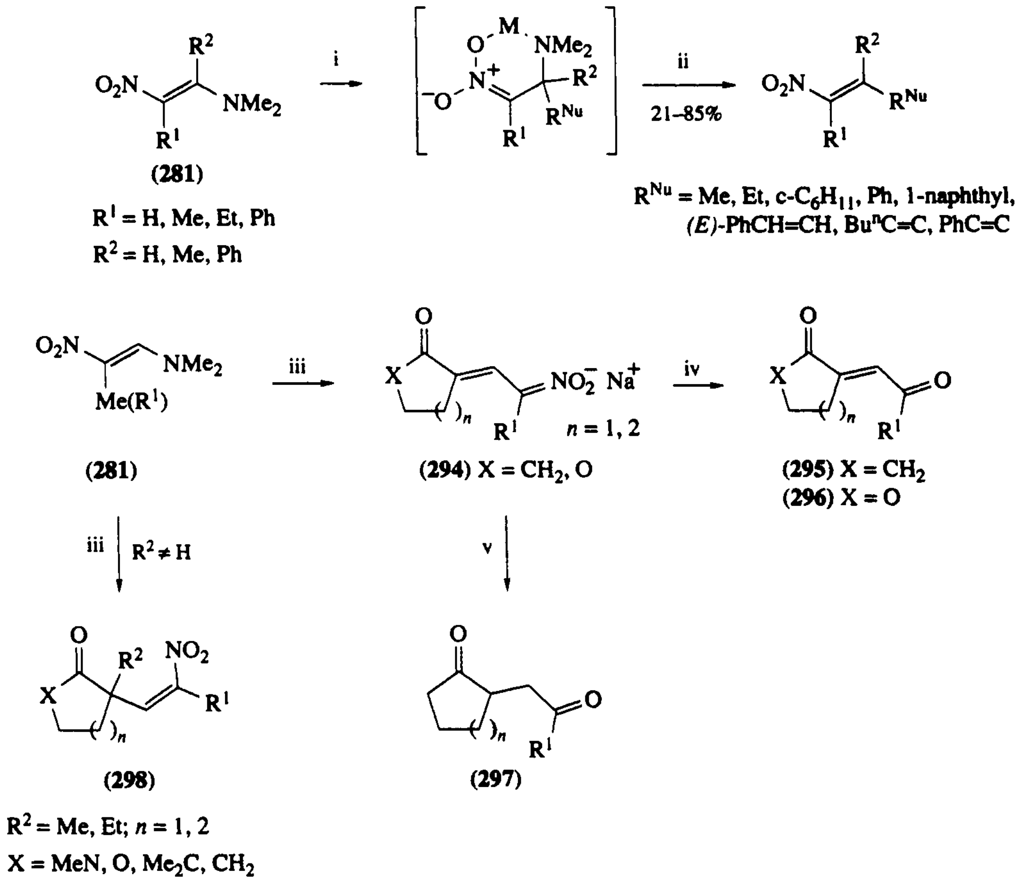
R2
O2N
NMe2
R1
(281)
R1 = H, Me, Et, Ph
R2 = H, Me, Ph
i
M
O
NMe2
N+
-O
R2
RNu
R1
ii
21–85%
O2N
R2
RNu
R1
RNu = Me, Et, c-C6H11, Ph, 1-naphthyl,
(E)-PhCH=CH, BunC≡C, PhC≡C
O2N
NMe2
Me(R1)
(281)
iii
O
X
NO2− Na+
R1
n = 1, 2
(294) X = CH2, O
iv
O
X
O
R1
(295) X = CH2
(296) X = O
iii
R2≠H
v
O
R2
NO2
X
R1
(298)
R2 = Me, Et; n = 1, 2
X = MeN, O, Me2C, CH2
O
O
R1
(297)

i, $R^{Nu}MgX$ (Li), ether (THF), 0 °C; ii, $H_3O^+$; iii, lactone enolate or ketone enolate; iv, $SiO_2$; v, ascorbic acid, $Cu^{II}$

**Scheme 93**

In contrast, α-nitroalkenation adducts (**298**) are obtained with thermodynamic enolates of α-substituted ketones or esters; in addition, Fuji reports that enantioselective addition of α-substituted lactone enolates to chiral nitroenamines is cation dependent with zinc affording maximum enantioselectivity.[215]

### 1.2.4.3 β-Haloenones and β-Halo-α,β-unsaturated Esters (Amides)[216]

Rupe and Iselin reported in 1916 the first example of an addition–elimination reaction in which Grignard reagents added to chloromethylenecamphor (**299**) to afford ketones (**300**).[216a] Subsequently, additions of dialkylcadmiums,[210b,216b] sodium dimsyl,[216c,d] allylidenetriphenylphosphorane (**303**),[216e] acyl anion equivalents, *e.g.* (**304**),[216f] and enolates, *e.g.* (**305**),[216g,h] to β-chloroenones and β-halo-α,β-unsaturated esters, *e.g.* (**301** and **302**), have been reported. The allylidenetriphenylphosphorane adducts afford a new Wittig reagent for polyene syntheses (Scheme 94).

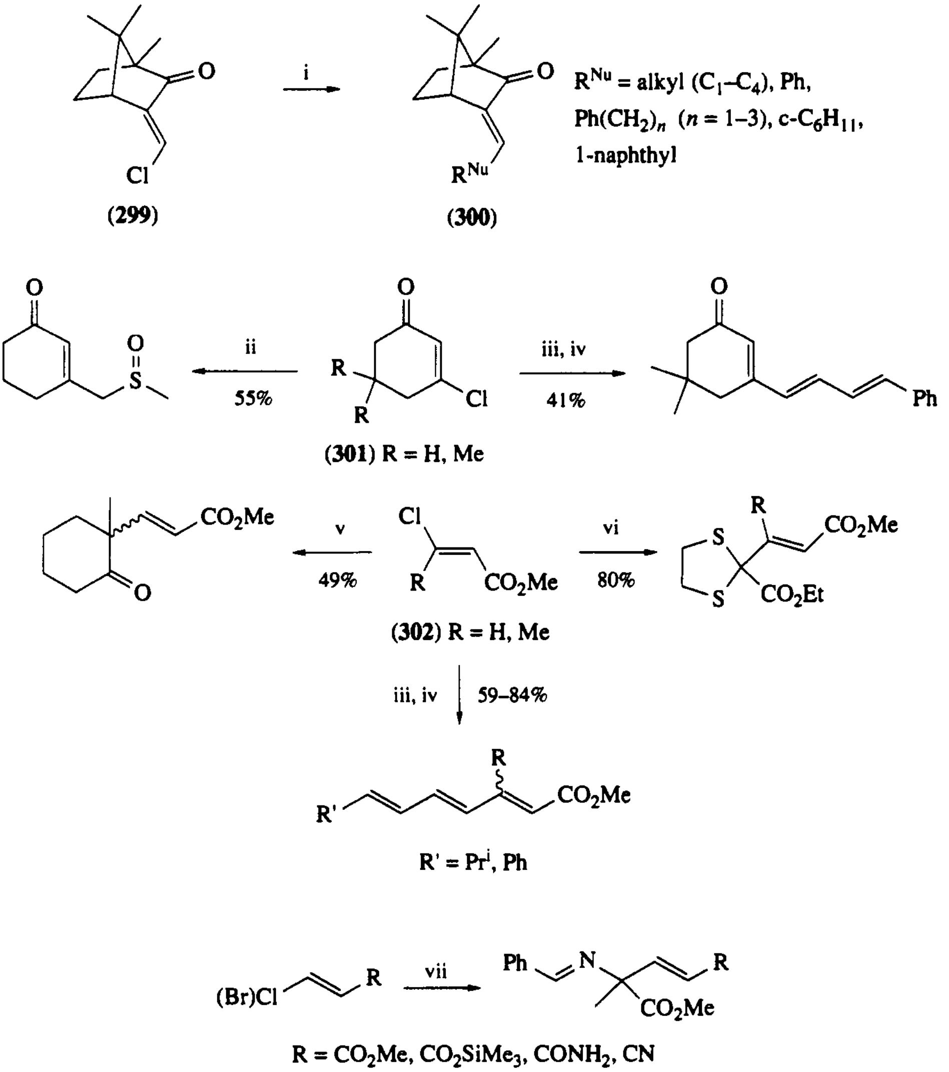
i
$R^{Nu}$ = alkyl ($C_1$–$C_4$), Ph, $Ph(CH_2)_n$ ($n$ = 1–3), c-$C_6H_{11}$, 1-naphthyl
(299)
(300)
ii
55%
iii, iv
41%
(301) R = H, Me
v
49%
vi
80%
(302) R = H, Me
iii, iv
59–84%
R' = $Pr^i$, Ph
vii
R = $CO_2Me$, $CO_2SiMe_3$, $CONH_2$, CN

i, $R^{Nu}MgBr$, ether, 25 °C; ii, $NaCH_2SOMe$, THF; iii, $CH_2{=}CH{-}CH{=}PPh_3$ (**303**); iv, PhCHO (R'CHO); v, lithium 2-methylcyclohexen-1-olate, THF, −78 °C; vi, glyoxylate anion equivalent (**304**), THF, −78 °C; vii, $PhCH{=}NCH(Li)CO_2Me$ (**305**), THF, −78 °C

**Scheme 94**

### 1.2.4.4 β-Alkoxy-α,β-unsaturated Esters

Kraus has shown that organolithiums add to diethyl alkoxymethylenemalonate in excellent yields to afford diethyl alkylidenemalonates; similarly, *ortho*-lithiated phenol ethers and ketone enolates afford alkoxy-carbonyl coumarins (**306** and **307**).[217a,b] In contrast, the treatment of diethyl alkoxymethylenemalonates with alkynyllithiums affords the adduct diesters (**308**) in which loss of the alkoxy group does not occur, but alkaline hydrolysis affords ylidenemalonic acids (**308**; Scheme 95).[217c,d]

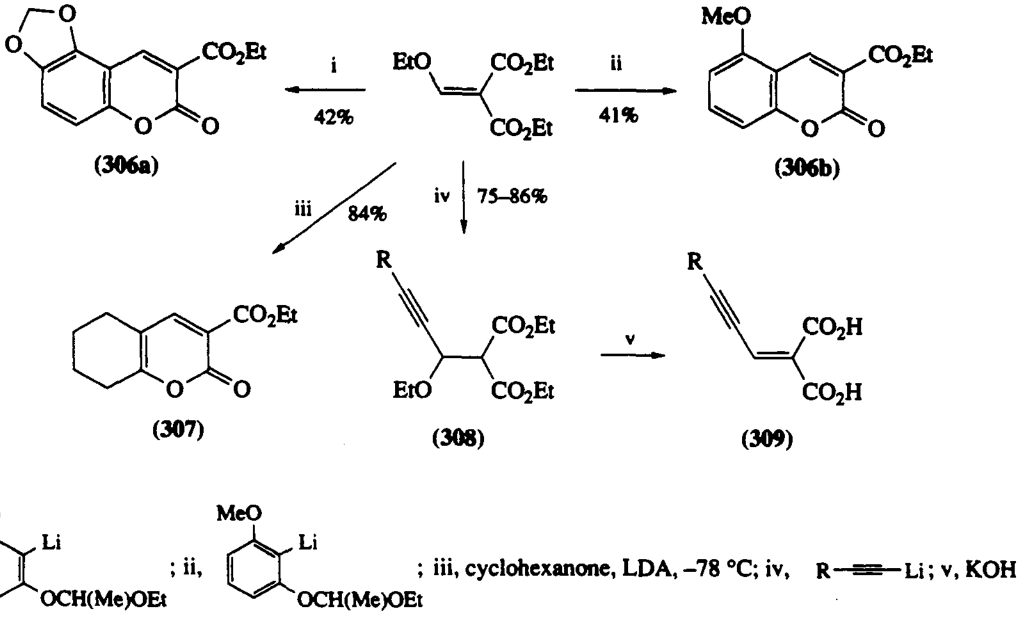
CO2Et
(306a)
i
42%
EtO
CO2Et
CO2Et
ii
41%
MeO
CO2Et
(306b)
iii
84%
iv
75–86%
CO2Et
(307)
R
CO2Et
EtO
CO2Et
(308)
v
R
CO2H
CO2H
(309)
i,
Li
OCH(Me)OEt
; ii,
MeO
Li
OCH(Me)OEt
; iii, cyclohexanone, LDA, –78 °C; iv, R—≡—Li; v, KOH

Scheme 95

### 1.2.4.5 β-(Alkylthio)enones, β-(Alkylthio)-α,β-unsaturated Esters and β-(Alkylthio)nitroalkenes

The copper(I)-catalyzed addition of Grignard reagents to β-(alkylthio)-α,β-unsaturated esters is the preferred protocol for substitution of the alkylthio substituent, *e.g.* (**310** → **311**),[218a] while potassium enolates add to α-ketoketene dithioacetals, *e.g.* (**312** → **313**), without dialkylation (Scheme 96).[218b,c] Further, Hanessian reports an expedient synthesis of penam (**315**) *via* intramolecular cyclization of the β-lactam nitroalkene (**314**), but loss of the methylthio moiety does not occur spontaneously (Scheme 97).[219]

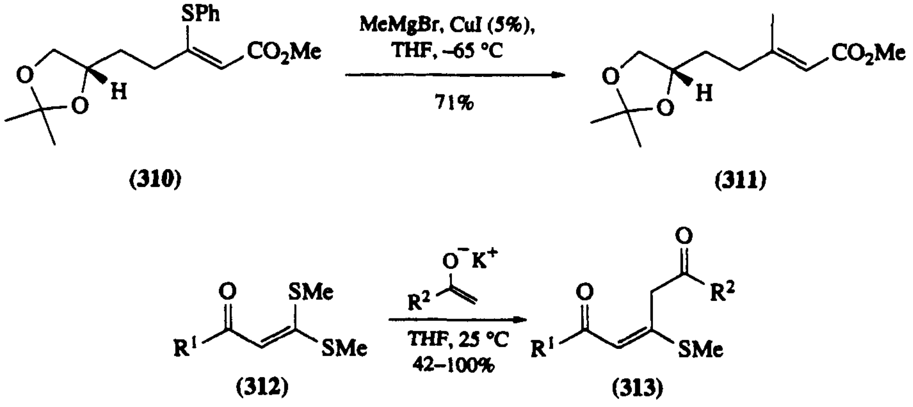
SPh
CO2Me
O
O
H
(310)
MeMgBr, CuI (5%),
THF, –65 °C
71%
CO2Me
O
O
H
(311)
O
SMe
R1
SMe
(312)
O⁻K⁺
R2
THF, 25 °C
42–100%
O
R2
O
R1
SMe
(313)

Scheme 96

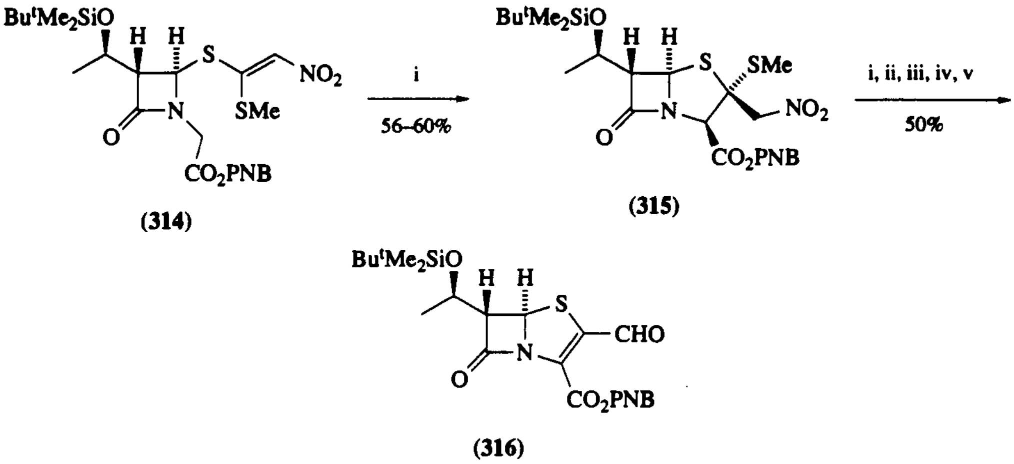

i, LiHMDS, THF, –78 °C; ii, MeI; iii, $O_3$; iv, MCPBA; v, $NaHCO_3$ (aq.)

Scheme 97

### 1.2.4.6 β-Halovinyl Sulfones

Enolate additions to β-halovinyl sulfones (**289a**) show synthetic promise; notable is the procedure, by Metcalf, for vinylation of α-amino acid derivatives, *e.g.* (**289a** → **317** → **318**).[220a] Recently, Ban reported that alicyclic ketone enolates add to the acetyl cation equivalent (**319**) to afford 1,3-diketones (Scheme 98).[220b] In general, β-halovinyl sulfones are synthetically superior to the β-halovinyl sulfoxides.

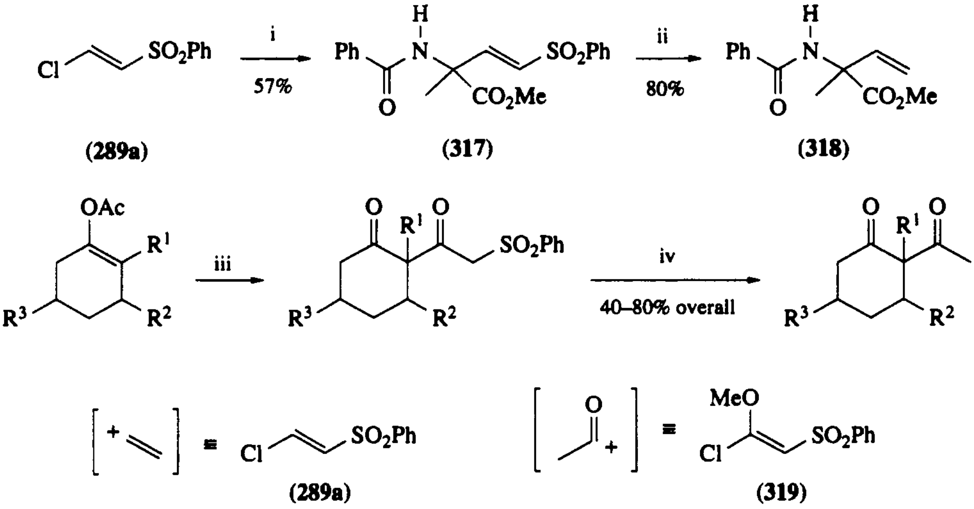

i, $PhCONHCH(Me)CO_2Me$, LDA, THF, –78 °C; ii, Al–Hg; iii, (**319**), HMPA, THF, –78 °C; iv, Raney Ni

Scheme 98

### 1.2.4.7 α,α-Difluoroalkenes

The reaction of organolithiums with vinyl halides generally results in metal–halogen exchange; however, with fluoroalkenes, $S_NV$ (nucleophilic vinylic substitution) processes occur. For example, organolithiums (or Grignard reagents) add to 1,1-dichloro-2,2-difluoroethylene (**290a**) and difluoroketene dithioacetals (**290b**) to afford α,α-dichloro-β-fluoroalkenes (**320a**) and fluoroketene thioacetals (**320b**), respectively; however, further treatment of **(320a)** with *n*-butyllithium affords lithium acetylides **(321)**. In an iterative process, **(321)** also reacts with **(290a)** to afford dienynes. Similarly, 1,1,1-trifluoroethyl ethers (or sulfides) **(324)** react with organolithiums in a three-step process (**324** → **290c–d** → **320c–d** → **325**) to afford alkynic ethers (or sulfides) (Scheme 99).[221]

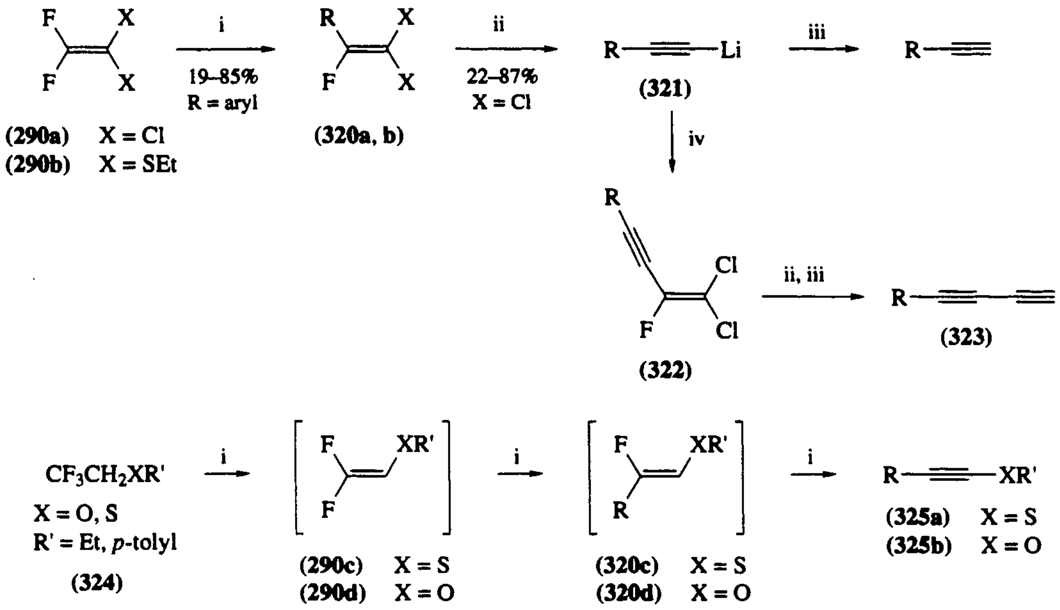
i
19–85%
R = aryl
ii
22–87%
X = Cl
iii
iv
ii, iii
(290a) X = Cl
(290b) X = SEt
(320a, b)
(321)
(322)
(323)
CF3CH2XR'
X = O, S
R' = Et, p-tolyl
(324)
(290c) X = S
(290d) X = O
(320c) X = S
(320d) X = O
(325a) X = S
(325b) X = O

i, RLi, ether, –78 to 38 °C; ; ii, Bu$^n$Li (2 equiv.), –78 to 40 °C; iii, $H_3O^+$; iv, **(290a)**, 20 to 38 °C

**Scheme 99**

### 1.2.5 ADDITIONS TO ALKYNIC π-SYSTEMS

In contrast to the well documented conjugate addition of carbon nucleophiles to activated alkenes, similar intermolecular attempts with activated alkynes with non-cuprate reactants are typically non-productive due to competing multiple addition processes.[87a,b] However, protic intramolecular conjugate additions of ketones as shown for the syntheses of griseofulvin and hirsutic acid,[222] are successful. Recently, several aprotic intramolecular conjugate additions to activated alkynes have been reported, as

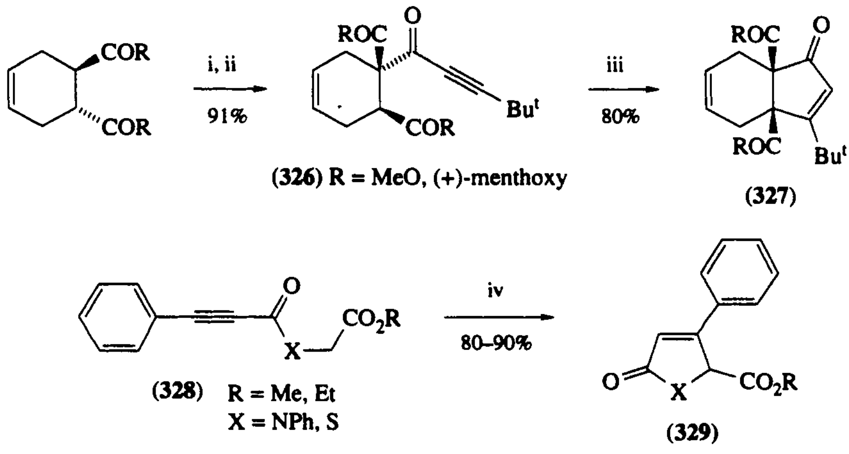
i, ii
91%
iii
80%
(326) R = MeO, (+)-menthoxy
(327)
iv
80–90%
(328) R = Me, Et
X = NPh, S
(329)

i, LDA, THF, –78 °C; ii, Bu$^t$C≡CCO$_2$Ph; iii, KHMDS, THF, –45 °C; iv, LiH (NaH)

**Scheme 100**

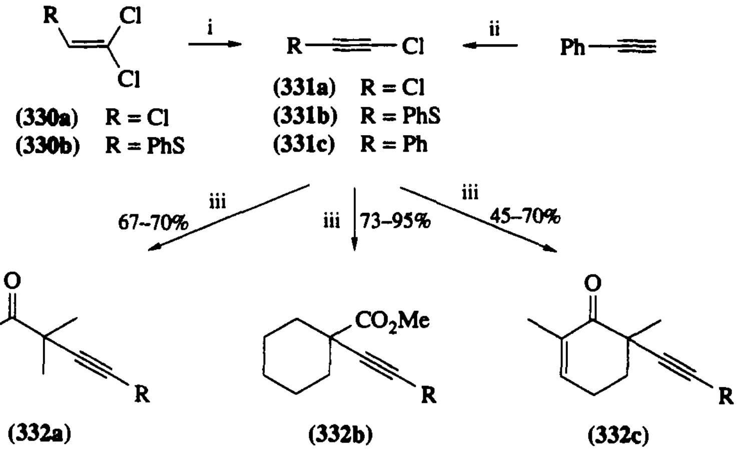
(330a) R = Cl
(330b) R = PhS
(331a) R = Cl
(331b) R = PhS
(331c) R = Ph
i
ii
iii
67–70%
iii 73–95%
iii 45–70%
CO$_2$Me
(332a)
(332b)
(332c)

i, LiHMDS, ether, –78 to 25 °C; ii, NaOH, $Cl_2$; iii, ester or ketone enolate, –78 to 25 °C

**Scheme 101**

shown for (**326** → **327**)[223a] and (**328** → **329**; Scheme 100).[223b] In contrast, Kende reports that α-disubstituted enolates add efficiently to chloroacetylenes (**331**) to afford α-ethynylated ketones (and esters) (**332**; Scheme 101).[224]

## 1.2.6 ELECTROCHEMICAL MEDIATED ADDITIONS

Electrochemical techniques in organic synthesis have become a burgeoning research area.[225] Several of the synthetically promising electrochemical intramolecular and intermolecular conjugate addition processes, catalyzed by either vitamin $B_{12a}$ or CoHDP, are mediated by either [Co–R] complexes or [acyl–

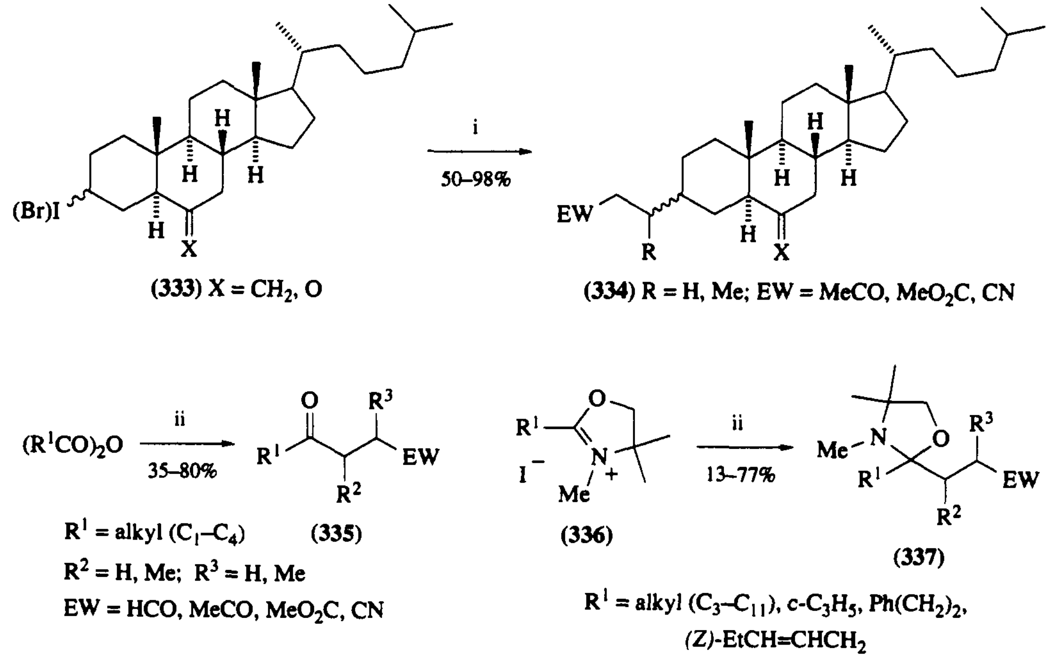
(Br)I
i
50–98%
EW
(333) X = CH$_2$, O
(334) R = H, Me; EW = MeCO, MeO$_2$C, CN
(R$^1$CO)$_2$O
ii
35–80%
(335)
R$^1$ = alkyl (C$_1$–C$_4$)
R$^2$ = H, Me; R$^3$ = H, Me
EW = HCO, MeCO, MeO$_2$C, CN
(336)
ii
13–77%
(337)
R$^1$ = alkyl (C$_3$–C$_{11}$), c-C$_3$H$_5$, Ph(CH$_2$)$_2$,
(*Z*)-EtCH=CHCH$_2$

i, (*E*)-RCH=CH(EW), e$^-$; ii, $R^2CH=CR^3(EW)$, e$^-$

**Scheme 102**

Co(III)] complexes. For example, the coupling of 3-halocholestanes (**333**) and Michael acceptors affords epimeric mixtures of the 3-homologated steroids (**334**). The electrochemical nucleophilic acylation of α,β-unsaturated aldehydes, α,β-unsaturated ketones and α,β-unsaturated nitriles with acyl anhydrides affords adducts (**335**) in moderate yields.[226a,b] Similarly, the reduction of *N*-methyloxazolinium salts (**336**) affords the *N,O*-acetal intermediates (**337**) which are readily hydrolyzed (Scheme 102).[226c]

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# 1.3

# Conjugate Additions of Carbon Ligands to Activated Alkenes and Alkynes Mediated by Lewis Acids

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## 1.3.1 INTRODUCTION

The conjugate addition of stabilized carbanions, nonstabilized carbanions and heteroanions to activated alkenes and alkynes has been discussed extensively in previous chapters in this volume (Chapters 1.1 and 1.2). In summary, the regioselectivity of carbanion additions is sensitive to: (i) the electronegativity of the metal center;[1] (ii) the Hard and Soft Acid–Base (HSAB) characteristics of the metal center and the transferring ligand;[2] (iii) the structure of the acceptor;[3] and (iv) reaction conditions and solvent effects.[4] The difference in electronegativity between a metal and carbon is reflected in the degree of ionic character imparted to the carbon–metal σ-bond and the direction of polarization.[5] Thus the highly ionic Groups IA and IIA organometallics (RK, RNa, RLi and RMgX; Volume 4, Chapter 1.2) are extremely reactive, in contrast to the less ionic Group IIB organometallics ($R_2Cd$ and $R_2Zn$; Volume 4, Chapter 1.2).

In contrast to the robust organolithiums and Grignard reagents, more selective and less basic organometallic reagents effective in transferring carbon ligands in a 1,4-mode have been introduced that are compatible with additional functionalities on either the acceptors or donors. These reagents are characterized by metal centers either with electron deficient *p*-orbitals which enhance their Lewis acidity, *e.g.* $R_3Al$ or $R_3B$ (Group IIIB), or that are electropositive *vis-à-vis* carbon, *e.g.* $R_4Si$ or $R_4Sn$ (Group IVB). Typically, carbon ligand transferrals with the latter class of organometallics are facilitated with a Lewis acid catalyst. However, with the Group IB organometallics, *e.g.* RCu (Volume 4, Chapter 1.4), and Group IIIB organometallics, carbon–carbon bond formation is mediated by either carbanion, free radical or electron transfer processes. For example, trialkylborane additions to α,β-enones are free radical mediated, while similar alkenylborane additions are not. The nucleophilicity of the Group IIB and Group IIIB organometallics is also enhanced with the corresponding stable 'ate' complexes which consist of a Lewis acid (electron deficient organometallic) and a Lewis base (organolithium).[6] In this chapter, the conjugate addition of carbon ligands to activated alkenes and alkynes mediated by Lewis acidic reagents will be discussed.

## 1.3.2 ADDITIONS TO ALKENIC π-SYSTEMS

### 1.3.2.1 Additions of Alkyl, Aryl, Alkenyl and Alkynyl Groups

#### *1.3.2.1.1 Organoaluminums*

The reactivity of the organoaluminums was described by Gilman[7a] and Wittig[7b] during the 1940s and subsequently they have become a widely used class of reagents in organic synthesis. In spite of the Lewis acid characteristics of the organoaluminums, their carbon–carbon bond formation reactions with electrophiles is similar to that of the organolithiums or organomagnesium halides. Fundamental to the chemistry of the organoaluminums is their heterophilic character in which the formation of coordination complexes with Lewis bases, *e.g.* carbonyl or ether groups, enhances the nucleophilicity of the attached ligands or moderates the reaction rates.[8] For example, trimethylaluminum, in either aromatic or hydrocarbon solvents, adds in a 1,2-mode to α,β-enones. In diethyl ether, both 1,2-additions and 1,4-additions are suppressed, but with catalytic nickel(II) acetylacetonate [Ni(acac)$_2$ (3%)] 1,4-addition products predominate. The trimethylaluminum reduces the nickel(II) to nickel(0), which undergoes oxidative addition to trimethylaluminum to afford the aluminum–nickel reagent MeNiAlMe$_2$ (**1**). The aluminum–nickel reagent undergoes initial addition to the carbonyl to afford an allylic methylnickel complex (**2**), which disproportionates to the corresponding 1,2- and 1,4-addition products (Scheme 1).[9] Alternatively, Kabalka reports that tri-*n*-propylaluminum reacts with α,β-enones (**3**; Scheme 1) at –78 °C in 1,4-mode by radical initiation, *e.g.* photochemically or with oxygen; in the absence of radical initiation, addition products are not observed.[10]

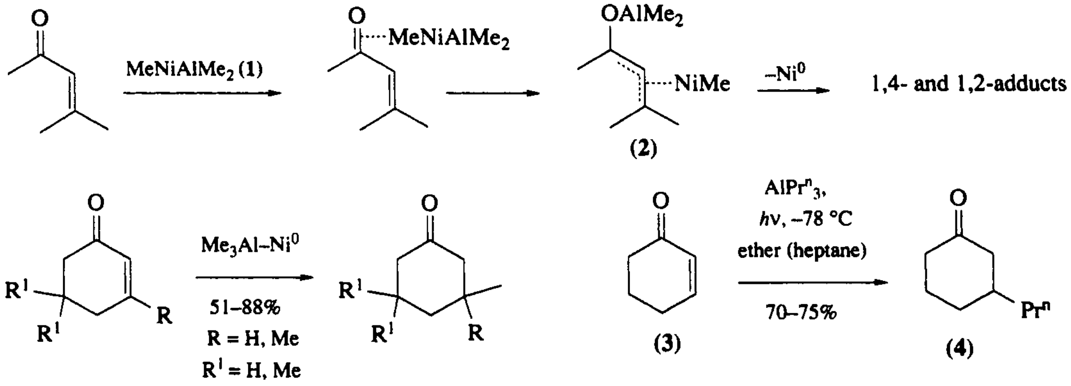

**Scheme 1**

While α,β-unsaturated aldehydes react exclusively with triorganoaluminums in the 1,2-mode, the identical reaction of the corresponding chiral α,β-unsaturated acetals (**5**), obtained from (*R*,*R*)-(+)-*N*,*N*,*N'*,*N'*-tetramethyltartaric acid amides, is solvent dependent.[11] For example, in 1,2-dichloroethane, preferential γ-addition ($S_N2'$) occurs (**5** giving **7**; Scheme 2), while in dichloromethane, preferential α-addition occurs (**5** giving **8**; Scheme 2). Subsequent hydrolysis of (**7**) affords the β-substituted aldehydes in high enantiomeric purity (Scheme 2); thus the acetals (**5**) serve as effective surrogates for '—CH═CH—CHO' ($^+$CH$_2$CH$_2$CHO).

Recently, Kunz reported that dialkylaluminum chlorides add in a 1,4-mode to *N*-(α,β-unsaturated acyl)oxazolidones (**9**; Scheme 3),[12] while high enantioselectivity is obtained with the chiral *N*-(α,β-unsaturated acyl)oxazolinone (**11**). Typically, higher dialkylaluminum halides (R* = ethyl, isobutyl) do not

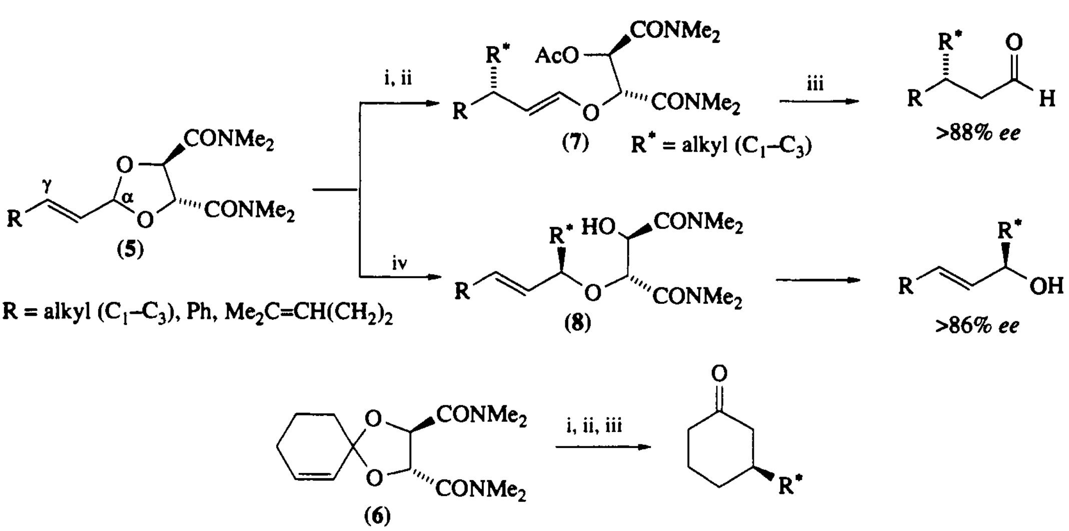

R = alkyl ($C_1$–$C_3$), Ph, $Me_2C{=}CH(CH_2)_2$

i, $R^*{}_3Al$, $ClCH_2CH_2Cl$; ii, $(MeCO)_2O$, pyridine; iii, $H_3O^+$; iv, $R^*{}_3Al$, $CHCl_3$

**Scheme 2**

add, but in combination with dimethylaluminum chloride, ligand transfer occurs exclusively with the higher alkyl ligand. These additions are specific for the described substrates, while *N,N*-disubstituted acrylamides do not react (Scheme 3).

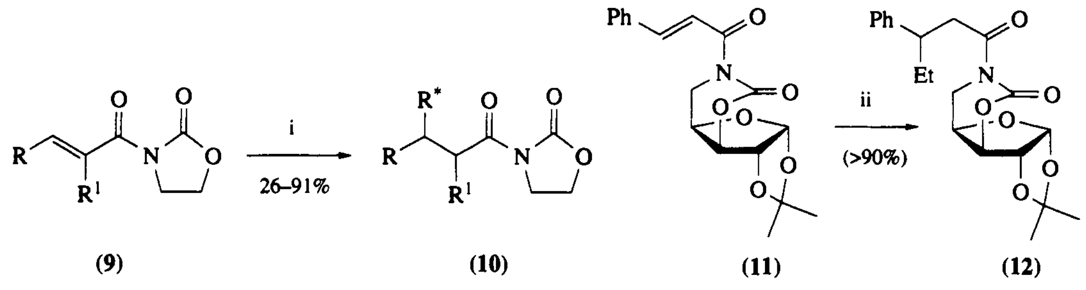

$R^1$ = H; $R^2$ = Me, $Bu^i$, Ph, 2-$MeOC_6H_4$
$R^1 + R^2 = (CH_2)_4$

(3*S*):(3*R*) = 87:13

i, $Me_2AlCl$–$R^*{}_2AlCl$ (1:1); ii, $Et_2AlCl$ (2 equiv.)

**Scheme 3**

The conjugate addition of vinyl groups to α,β-enones is the cornerstone of various synthetic challenges, especially with prostaglandin syntheses. These transformations are typically effected with organocuprates which necessitate initial formation of stereochemically defined precursor vinyllithiums;[13] alternatively, the alkenylalanes effect alkenyl transfer to *s-cis* α,β-enones exclusively with retention of alkene stereochemistry.[14] The alkenylalanes are prepared by the regioselective and stereoselective hydroalumination of alkynes with dialkylaluminum hydrides, generally diisobutylaluminum hydride. Remote substituents on the alkynes may impact the hydroalumination process; for example, the hydroalumination of 1-octyn-3-ol ethers (**13**) to (**15**) affords the *cis*-octenylalanes (**17**) to (**19**), while the sterically encumbered trityl ether (**16**) affords *trans*-octenylalane (**20**) in moderate yields (Scheme 4). The unfavorable yield of alane (**20**) is attributed to competing Lewis acid catalyzed reactions, *i.e.* reductive propargylic ether cleavage (*cf.* alane **24**).[15] The specificity for 1,4-additions of alkenylalanes to *s-cis* α,β-enones (**22**) infers a highly ordered cyclic transition state.[14b] In contrast, the addition of either (*E*)-1-hexenyldiisobutylalane (**21**; Scheme 5) or (*E*)-6-triphenylmethoxy-1-heptenyldiisobutylalane (**24**) to hydroxyenone

(**25**) occurs exclusively *anti* to the hydroxy group, but isomeric at the acetyl position.[16] Thus, the initially formed alane alkoxide shields the *syn* face of the alkene.

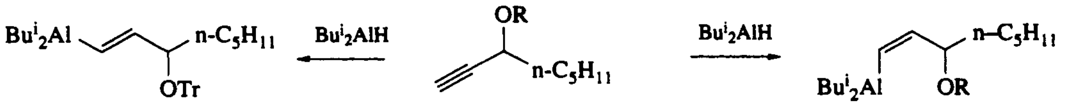
$Bu^i_2Al$
$n\text{-}C_5H_{11}$
OTr
$Bu^i_2AlH$
OR
$n\text{-}C_5H_{11}$
$Bu^i_2AlH$
$n\text{-}C_5H_{11}$
$Bu^i_2Al$
OR

(**20**)

(**13**) R = $Bu^t$ (**14**) R = Me
(**15**) R = 1-methylcyclohexyl
(**16**) R = $Ph_3C$

(**17**) R = $Bu^t$
(**18**) R = Me
(**19**) R = 1-methylcyclohexyl

Scheme 4

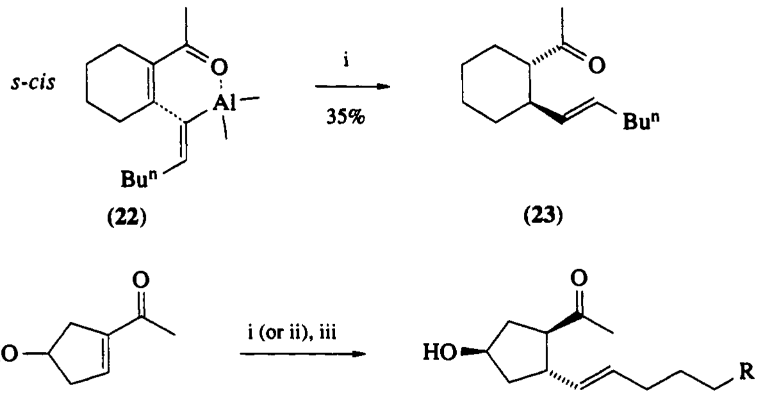
*s-cis*
O
Al
$Bu^n$
i
35%
O
$Bu^n$
HO
O
i (or ii), iii
HO
O
R

(**22**) (**23**)

(**25**)

(**26**) R = Me
(**27**) R = CH(OTr)Me

i, (*E*)-$Bu^i_2AlCH{=}CH(CH_2)_3Me$ (**21**); ii, (*E*)-$Bu^i_2AlCH{=}CH(CH_2)_3CH(OTr)Me$ (**24**); iii, NaOMe

Scheme 5

Irrespective of the stereochemistry of the α,β-enones, lithium alkenyltrialkylalanates, *e.g.* (**28**) and (**29**), obtainable by treatment of alkenylalanes with methyllithium (or *n*-butyllithium), are also excellent 1,4-conjugate alkenyl transfer reagents. The cornerstone of a general prostaglandin synthesis, as exemplified in Scheme 6, employs the alanate conjugate addition process exclusively.[15]

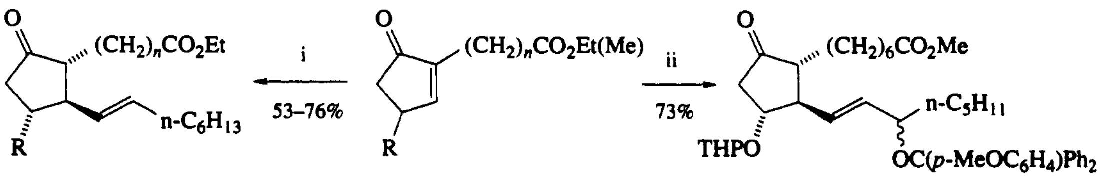
O
$(CH_2)_nCO_2Et$
$n\text{-}C_6H_{13}$
R
i
53–76%
O
$(CH_2)_nCO_2Et(Me)$
R
ii
73%
O
$(CH_2)_6CO_2Me$
$n\text{-}C_5H_{11}$
THPO
$OC(p\text{-}MeOC_6H_4)Ph_2$

(**31**) (**30**) (**32**)

R = H, $MeCO_2$, THPO; *n* = 1 or 6

i, $Li^+$ (*E*)-$Me(CH_2)_5CH{=}CHAlMeBu^i_2{}^-$ (**28**); ii, $Li^+$ (*E*)-$Me(CH_2)_4(MTrO)CHCH{=}CHAlMeBu^i_2{}^-$ (**29**)

Scheme 6

Pecunioso reports that trialkylaluminums, alkenyldialkylalanes and alkynyldialkylalanes add efficiently to α-nitroalkenes (**33**) to (**35**) to afford nitroalkanes,[17a] γ-nitroalkenes[17b] and γ-nitroalkynes,[17c] respectively (Scheme 7). This method complements the organolithium and Grignard reagent mediated processes in which terminal α-nitroalkenes do not undergo efficient addition (*cf.* Volume 4, Chapter 1.2, Sections 1.2.2.1.1 and 1.2.2.1.2). Depending on the work-up conditions employed, either the nitroalkanes or the corresponding ketones (Nef reaction) are obtained. The latter work-up procedure affords an efficient synthesis of cyclopenten-3-ones (**36**), as shown in Scheme 7.[17b]

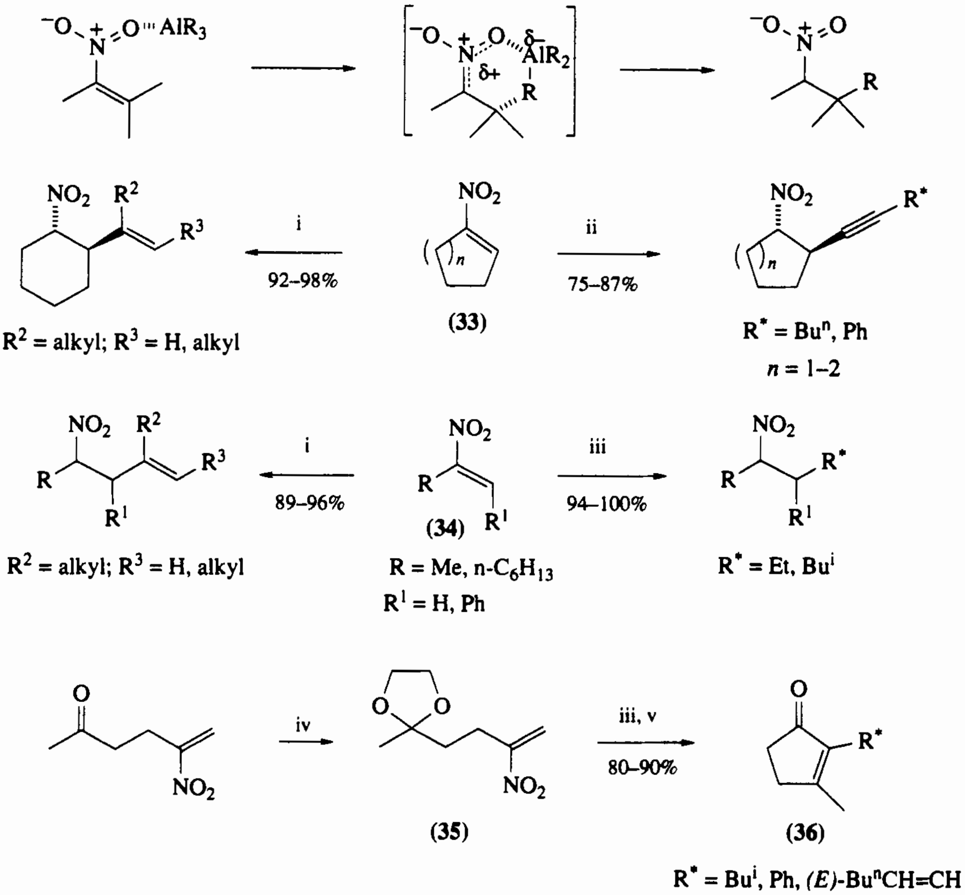

i, $Bu^i_2AlC(R^2)$=$CHR^3$; ii, $R^*C{\equiv}CAlEt_2$; iii, $R^*_3Al$; iv, $HOCH_2CH_2OH$, *p*-TsOH; v, 3 M HCl

**Scheme 7**

The direct conjugate addition of alkynyl groups to α,β-unsaturated systems is a synthetic challenge since virtually all alkynylmetallic reagents are ineffective at introducing alkynic moieties. The more popular stoichiometric organocuprates or copper-catalyzed Grignards do not transfer alkynyl ligands because of the strong alkynyl–copper bond. Typically, introduction of an alkynyl moiety is accomplished with a precursor functionality, *e.g.* (tri-*n*-butylstannyl)vinylcuprate.[18] The alkynyldialkylalanes transfer alkynyl ligands effectively to all α,β-enones in the presence of a nickel(0) catalyst, like $Ni(acac)_2$·DIBAL-H (1:1) (Scheme 8);[19] in the absence of the catalyst, only *s-cis* α,β-enones (**22**) are alkynylated, while fixed *s-trans* α,β-enones undergo 1,2-addition. Thus, a cyclic transition state is inferred for the noncatalyzed conjugate addition reactions. In contrast, the noncatalyzed conjugate addition of the trialkynylaluminum (**39**) to the 4-hydroxycyclopentenone (fixed *s-trans* configuration) (**40**) necessitates prior coordination to the 4-hydroxy group in order to direct the alkynyl ligand *syn* to the β-position.[20] Protection of the 4-hydroxy group, *e.g.* with THP, retards this conjugate addition process (equation 1).

While conjugate additions with organoaluminums typically occur *via* intramolecular ligand transferral from the aluminum coordination complexes, intermolecular ligand transferral from the more basic, nucleophilic reagents, *e.g.* RLi or RMgX, can be accomplished with unusual chemoselectivity and stereoselectivity in the presence of oxophilic organoaluminum reagents possessing bulky nontransferable ligands. For example, the bis(2,6-di-*t*-butyl-4-alkylphenoxy)methylaluminums (MAD **42** and MAT **43**; Scheme 9) facilitate conjugate additions of organolithiums to select cycloalkenones, quinone monoketals (**44**) and quinol ethers (**45**).[21]

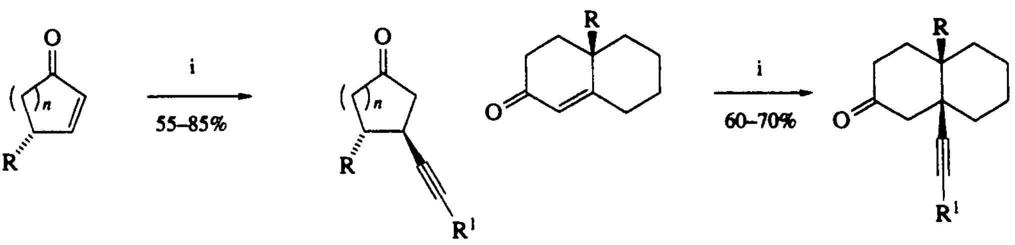

**(37)** R = H, PhCMe$_2$O; *n* = 1–2 **(38)** R = H, Me; R$^1$ = Bu$^n$, Bu$^t$, SiMe$_3$

i, Me$_2$AlC≡CR$^1$, Ni$^0$ catalyst

**Scheme 8**

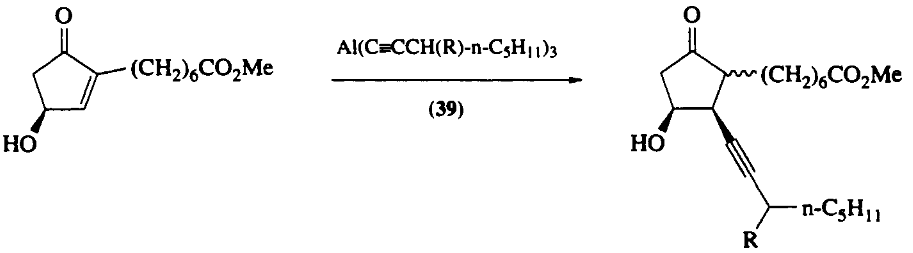

(1)

**(40)** **(41)** R = H, OTHP

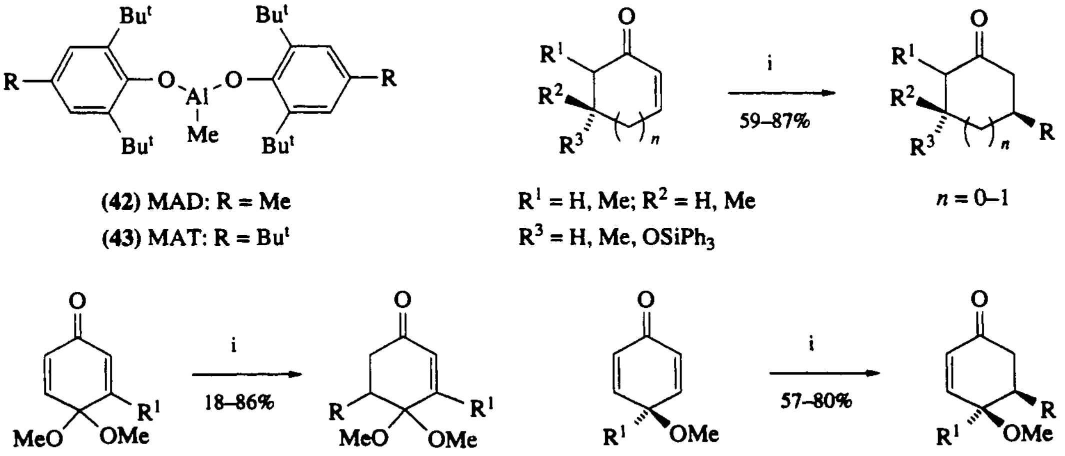

**(42)** MAD: R = Me
**(43)** MAT: R = Bu$^t$

R$^1$ = H, Me; R$^2$ = H, Me
R$^3$ = H, Me, OSiPh$_3$

*n* = 0–1

**(44)** R$^1$ = H, Me, Cl

**(45)** R$^1$ = Ph, CH$_2$=CH, 4-Bu$^t$Me$_2$SiOC$_6$H$_4$

i, MAD **(42)** 2 equiv., RLi 2 equiv., PhMe, –78 °C
[R = alkyl (C$_1$–C$_4$), Ph, 1,3-dithiane, Me$_3$SiC≡C, ester enolate]

**Scheme 9**

### *1.3.2.1.2 Organoboranes*

The Lewis acidic organoboranes, on the other hand, are electrophilic in their chemical behavior.[22] This is attributed to the high degree of covalent character in the boron–carbon bond, which results in the low reactivity of organoboranes *versus* organolithiums towards electrophiles. In spite of the low reactivity of the triorganoboranes with simple aldehydes and ketones, formal conjugate addition of alkyl (or aryl) groups occurs with α,β-unsaturated aldehydes and α,β-unsaturated ketones to afford the alkenyloxydialkylboranes (vinyloxyboranes, **46**; Scheme 10) regiospecifically.[23] The ease of addition is dependent on the substituents on the α,β-unsaturated aldehyde or ketone; in the absence of β-substituents spontaneous addition occurs, while with β-substituted systems a radical initiator is required. Initiators include diacyl peroxides, light or oxygen.[24] Similar additions to α-nitroalkenes,[25] α,β-unsaturated imines,[26] α,β-unsaturated nitriles[27] (secondary alkyls only) and 1,4-benzoquinones (naphthoquinones)[28] also occur efficiently (equation 2). The free radical nature of these additions is shown by the inhibition of these reactions with galvinoxyl, a highly efficient free radical scavenger,[29a] and secondary product formation arising from solvents capable of radical formation, *e.g.* tetrahydrofuran and 2-propanol.[29b]

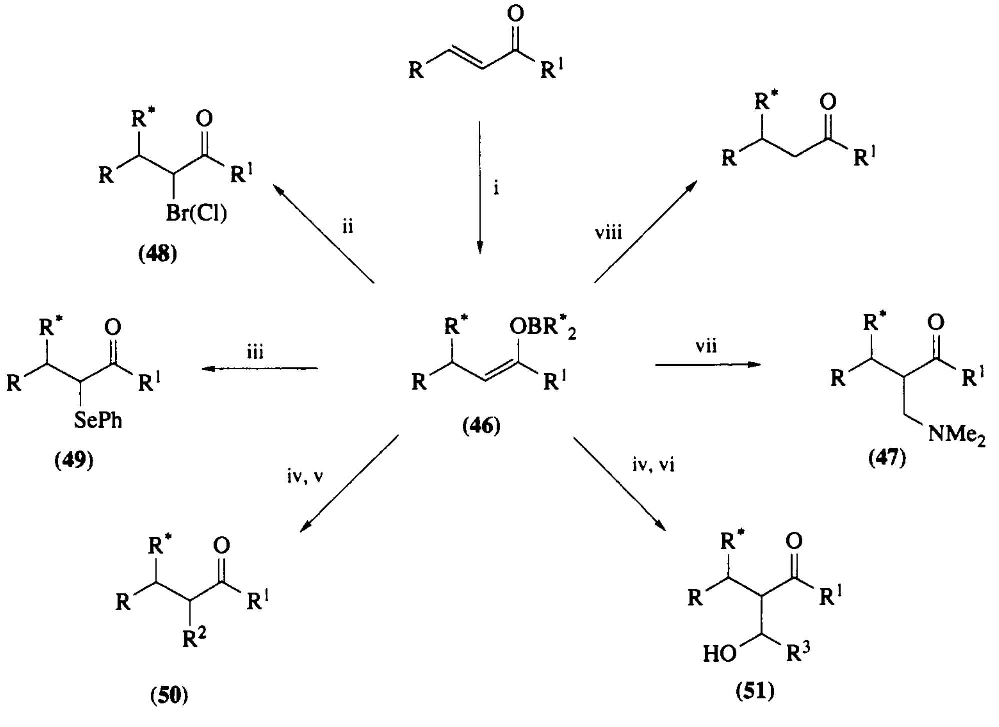

i, $R^*_3B$; ii, NBS (NCS); iii, PhSeCl; iv, $Me_2NCH_2CH_2OLi$; v, $R^2X$;
vi, $R^3CHO$; vii, $CH_2{=}NMe_2^+ I^-$; viii, $H_3O^+$

**Scheme 10**

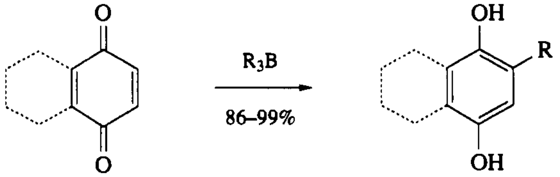

(2)

R = alkyl ($C_1$–$C_6$), c-$C_6H_{11}$, c-$C_8H_{15}$, $PhCH_2$

Further transformations of the intermediate alkenyloxydialkylboranes (**46**), as shown in Scheme 10, include: aqueous hydrolysis to the homologated aldehydes or ketones;[30] electrophilic additions to afford the corresponding α-dialkylaminomethyl aldehydes and ketones (**47**),[31] and α-halogenated (**48**)[32] or α-arylselenylated aldehydes or ketones (**49**);[33] transmetallation–alkylation to afford α-substituted aldehydes or ketones (**50**);[34] and aldol condensations with aldehydes (**51**).[35] These reagents offer the equivalent of the tandem 1,4-conjugate addition–electrophile-trapping protocol. A prototypical prostaglandin synthesis by an organoborane-mediated double Michael addition protocol is shown in Scheme 11.[36]

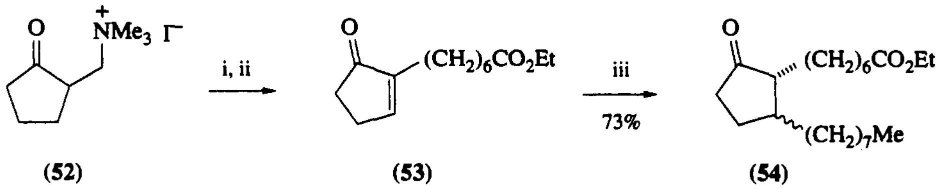
i, ii
iii
73%
(52)
(53)
(54)
NMe3 I−
(CH2)6CO2Et
(CH2)7Me

i, $B\{(CH_2)_5CO_2Et\}_3$, $K_2CO_3$; ii, $Br_2$, base; iii, $B\{(CH_2)_7Me\}_3$

Scheme 11

However, conjugate additions with trialkylboranes are inefficient in that only one of the three organic groups is transferred. The inefficiencies of group transfer are surmounted by the use of either the *B*-alkylboracyclanes (**55**)[37a,37b] or *B*-alkyldiphenylboranes (**56**),[37c] in which the *B*-alkyl groups are preferentially transferred under radical conditions. The *B*-alkylboracyclanes are obtained by sequential

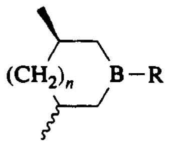

(**55**) $n$ = 1–2

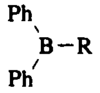

(**56**)

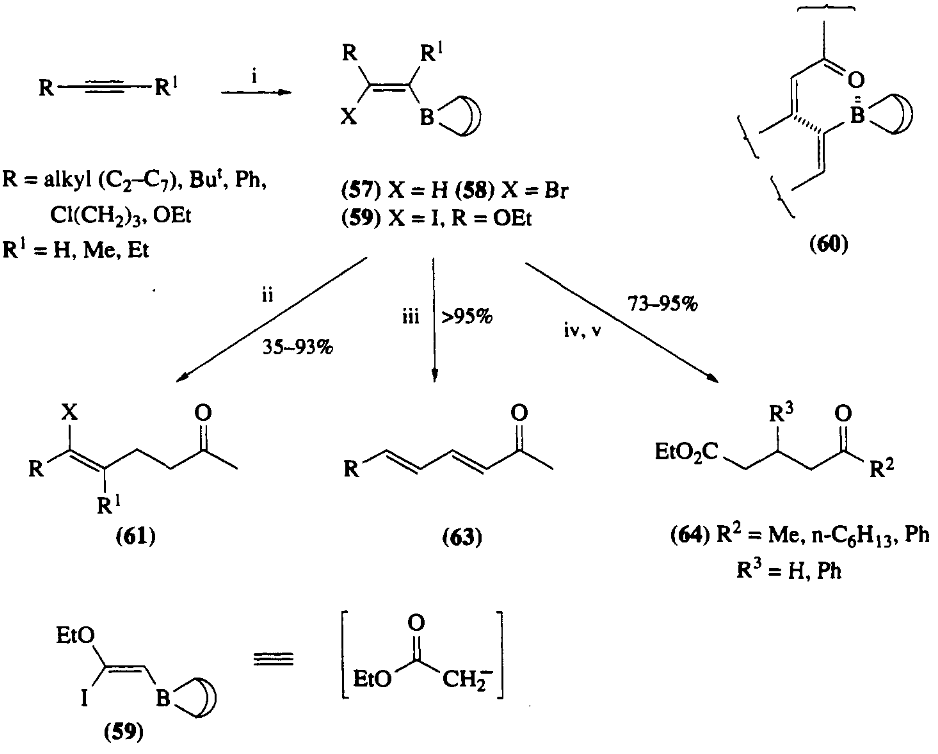
R———R1
i
R = alkyl (C2–C7), But, Ph,
Cl(CH2)3, OEt
R1 = H, Me, Et
(57) X = H (58) X = Br
(59) X = I, R = OEt
(60)
ii
35–93%
iii
>95%
iv, v
73–95%
(61)
(63)
(64) R2 = Me, n-C6H13, Ph
R3 = H, Ph
EtO2C
EtO
I
(59)
EtO
CH2−

i, 9-BBN (*B*-Br-9-BBN) (*B*-I-9-BBN); ii, $CH_2{=}CHCOMe$; iii, $MeOCH{=}CHCOMe$ (**62**); iv, $R^3CH{=}CHCOR^2$; v, EtOH

Scheme 12

hydroboration of either 2,4-dimethyl-1,4-pentadiene or 2,5-dimethyl-1,5-hexadiene followed by addition to appropriate alkenes. Hydroborations with the boracyclanes occur with high regioselectivity which is crucial for the subsequent conjugate additions in which the minor hydroboration isomers (Markownikov) will transfer preferentially with respect to the major hydroboration isomers (*anti*-Markownikov isomer).

In contrast, the *B*-1-alkenyl-9-borabicyclo[3.3.1]nonanes, (**57**) to (**59**) and (**65**), and *B*-1-alkynyl-9-borabicyclo[3.3.1]nonanes (**72**) effect alkenyl and alkynyl transfer, respectively, to *s-cis* α,β-enones exclusively *via* a cyclic transition state (**60**), with the 9-BBN moiety serving as a nontransferable ligand. Thus, the alkenylation of α,β-enones and β-methoxy-α,β-unsaturated ketones (**62**) affords γ,δ-enones (**61**) and α,β,δ,γ-dienones (**63**), respectively (Scheme 12). The *B*-(*E*)-1-alkenyl-9-borabicyclo[3.3.1]nonanes (**57**) to (**59**) are prepared by the regioselective and stereoselective hydroboration (9-BBN)[38a] or haloboration (*B*-X-9-BBN; X = Br, I)[38b] of alkynes, while the *B*-(*Z*)-1-alkenyl-9-borabicyclo[3.3.1]nonanes (**65**) and *B*-1-alkynyl-9-borabicyclo[3.3.1]nonanes (**72**) are prepared from *B*-methoxy-9-BBN and (*Z*)-lithio-1-alkenes (Scheme 13)[39] and lithium alkynides (Scheme 15),[40] respectively. Suzuki reports that *B*-1-(2-ethoxy-2-iodovinyl)-9-borabicyclo[3.3.1]nonane (**59**), an acetate ester enolate equivalent, adds to α,β-enones to afford δ-keto esters (**64**).[41] In contrast, α,β-enone alkenylations with the more stable *B*-(1-alkenyl)dialkoxyboranes (**68**) and (**71**) are facilitated by the presence of boron trifluoride etherate which generates *in situ* the reactive *B*-(1-alkenyl)alkoxyfluoroboranes (**69**). This procedure allows for the introduction of alkenyl groups which are not accessible by direct hydroboration, *e.g.* 1,2- or 2,2-disubstituted-1-alkenyl substituents, irrespective of alkene stereochemistry (Scheme 14).[42]

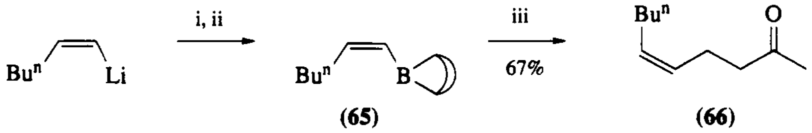

i, *B*-MeO-9-BBN; ii, $BF_3{\bullet}Et_2O$; iii, $CH_2{=}CHCOMe$

**Scheme 13**

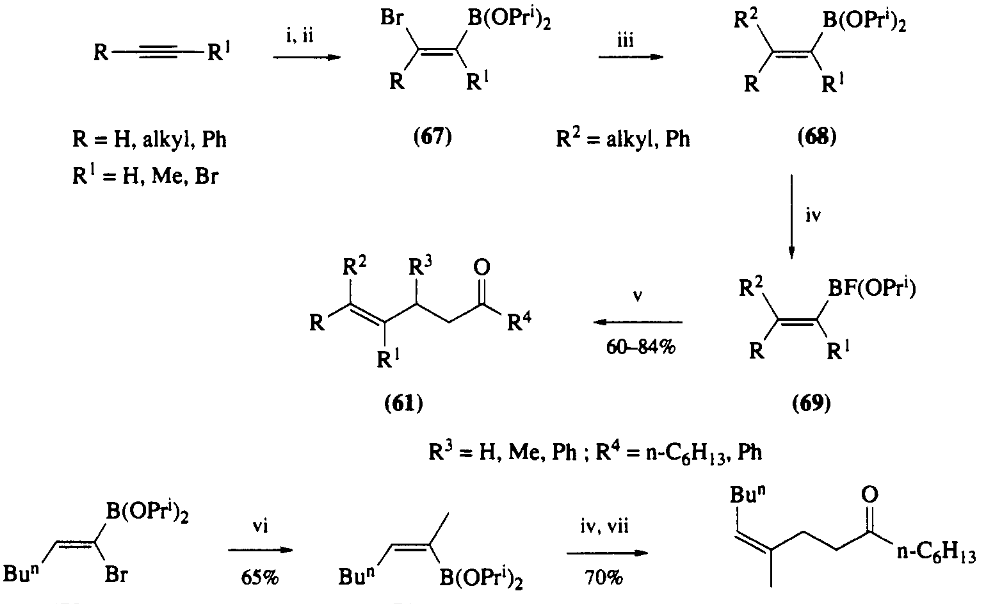

i, $BBr_3$; ii, $Pr^i{}_2O$; iii, $R^2ZnCl$, $Pd^0$ catalyst; iv, $BF_3{\bullet}Et_2O$; v, $R^3CH{=}CHCOR^4$; vi, MeLi;
vii, $CH_2{=}CHCO\text{-}n\text{-}C_6H_{13}$

**Scheme 14**

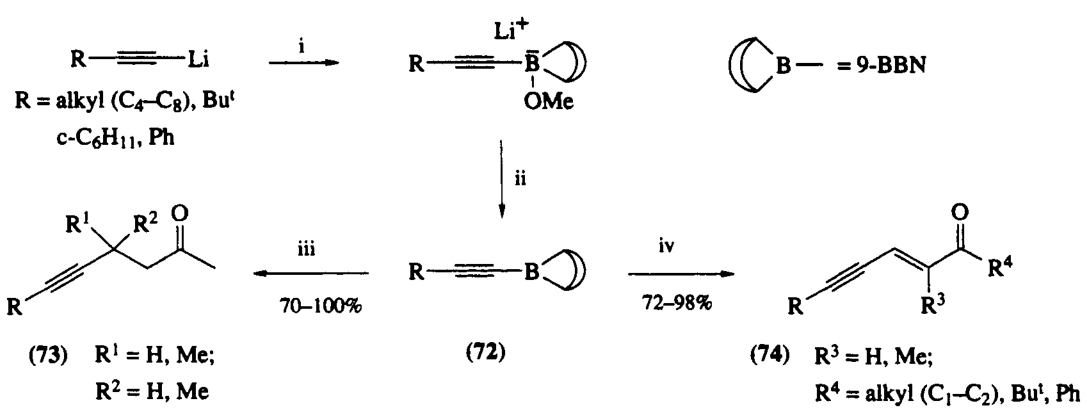

i, *B*-OMe-9-BBN; ii, $BF_3 \cdot Et_2O$, –78 °C; iii, $R^1R^2C{=}CHCOMe$; iv, $MeOCH{=}C(R^3)COR^4$

**Scheme 15**

The reactivity profiles of the boronate complexes are also diverse.[43] For example, the lithium methyltrialkylboronates (**75**) are inert, but the more reactive copper(I) methyltrialkylboronates (**76**) afford conjugate adducts with acrylonitrile and ethyl acrylate (Scheme 16).[44] In contrast, the lithium alkynylboronates (**77**) are alkylated by powerful acceptors, such as alkylideneacetoacetates, alkylidenemalonates and α-nitroethylene, to afford the intermediate vinylboranes (**78**) to (**80**), which on oxidation (peracids) or protonolysis yield the corresponding ketones or alkenes, respectively (Scheme 17).[45a] Similarly, titanium tetrachloride-catalyzed alkynylboronate (**77**) additions to methyl vinyl ketone afford 1,5-diketones (**81**).[45b] Mechanistically, the alkynylboronate additions proceed by initial β-attack of the electrophile and simultaneous alkyl migration from boron to the α-carbon.

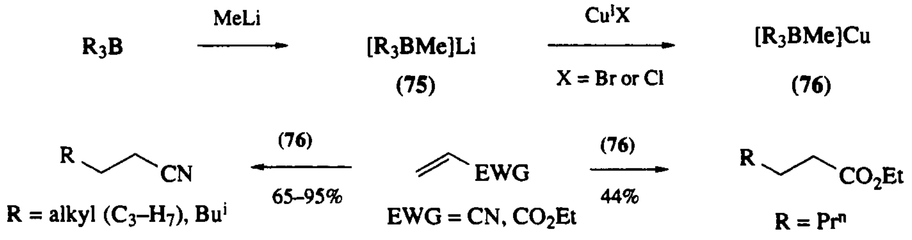

**Scheme 16**

### *1.3.2.1.3 Lewis acid modified organocoppers and organocuprates*

Enhancement of the chemoselectivity in the reaction of Grignard reagents with α,β-enones, in the presence of copper(I) salts, was first described by Kharasch and Tawney.[46] Subsequently, this conjugate addition protocol became the cornerstone for various natural products syntheses, but it lacked predictability and dependability. House and coworkers demonstrated that an organocopper (RCu, **82**) was the reactive species;[47a] independently, Gilman had reported on the synthesis and reactivity of lithium dimethylcuprate.[47b] With the development of general procedures for the synthesis of stoichiometric organocoppers and homocuprates ($R_2CuM$, **83**), their synthetic utility was soon established, but limitations on their thermal stability, ligand transfer efficiencies and acceptor reactivity profiles were soon recognized.[48] Additional copper-based reagents, *e.g.* mixed homocuprates ($RR^1CuM$, **84**), heterocuprates (RCuMX, **85**) and higher order cuprates ($R_3CuLi$, **86**),[49] were developed in order to address the above deficiencies. Some interesting variants are the Lewis acid modified organocoppers ($RCu{\cdot}MX_n$, **87**), Lewis acid modified organocuprates ($R_2CuLi{\cdot}MX_n$, **88**) and Lewis acid modified cyanocuprates ($R_2Cu(CN)Li_2{\cdot}MX_n$, **89**).

Yamamoto[50] and Ibuka[51] have reported that ligand transferrals from organocoppers to a broad range of acceptors are facilitated in the presence of aluminum trichloride or boron trifluoride, at –78 °C, with high

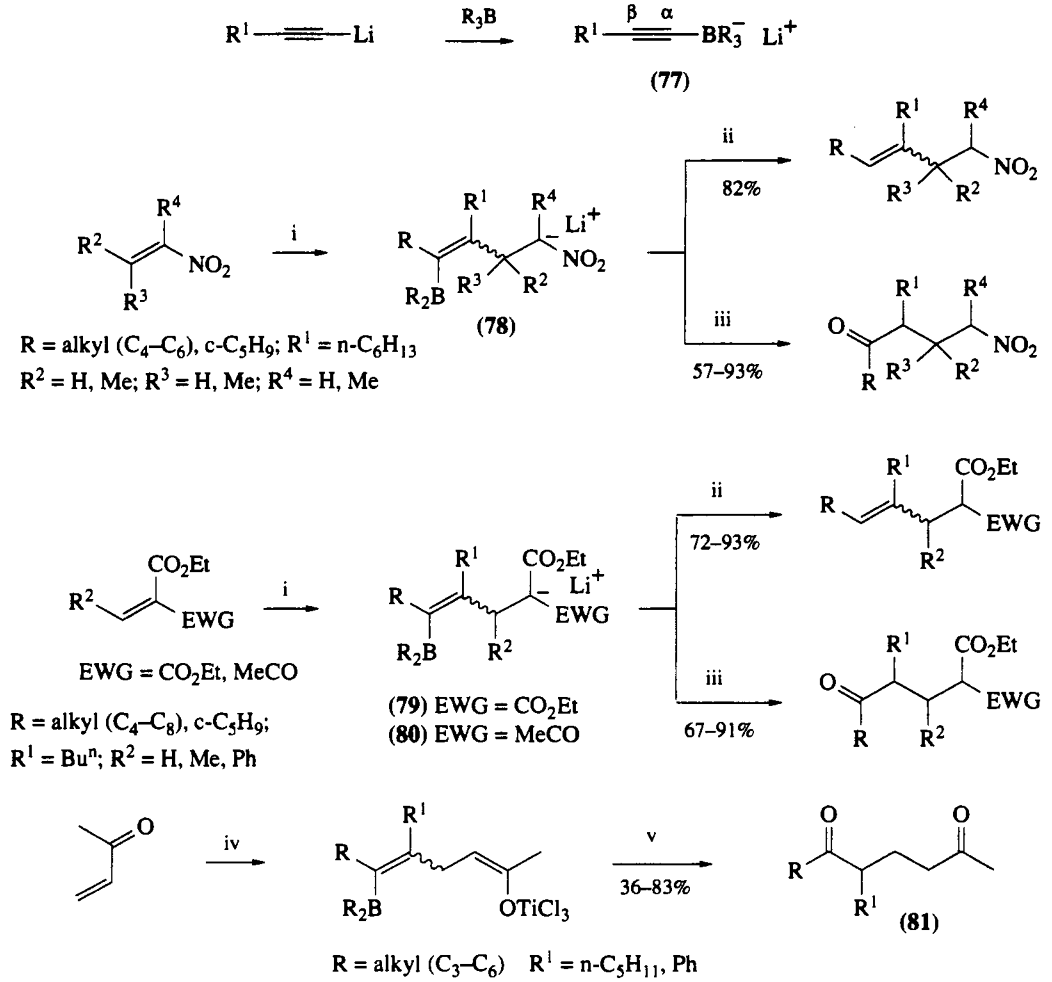
$R^1$—≡—Li
$R_3B$
$R^1$—≡—$BR_3^-$ $Li^+$
β α
(77)
i
ii
82%
iii
57–93%
(78)
$R_2B$
$NO_2$
Li+
R = alkyl ($C_4$–$C_6$), c-$C_5H_9$; $R^1$ = n-$C_6H_{13}$
$R^2$ = H, Me; $R^3$ = H, Me; $R^4$ = H, Me
$CO_2Et$
EWG
EWG = $CO_2Et$, MeCO
R = alkyl ($C_4$–$C_8$), c-$C_5H_9$;
$R^1$ = $Bu^n$; $R^2$ = H, Me, Ph
(79) EWG = $CO_2Et$
(80) EWG = MeCO
72–93%
67–91%
iv
v
36–83%
$OTiCl_3$
(81)
R = alkyl ($C_3$–$C_6$) $R^1$ = n-$C_5H_{11}$, Ph

i, $RC{\equiv}CBR^1{}_3{}^-$ $Li^+$ (77); ii, $EtCO_2H$; iii, MCPBA; iv, (77), $TiCl_4$, $CH_2Cl_2$, −78 °C; v, $H_2O_2$

**Scheme 17**

| | | | | |
|---|---|---|---|---|
| $RCu$ | $R_2CuM$ | $RR^1CuM$ | $RCuMX$ | $R_3CuLi$ |
| **(82)** | **(83)** | **(84)** | **(85)** | **(86)** |

| | | |
|---|---|---|
| $RCu{\bullet}MX_n$ | $R_2CuLi{\bullet}MX_n$ | $R_2Cu(CN)Li_2{\bullet}MX_n$ |
| **(87) a–c** | **(88)** | **(89)** |

chemoselectivity and stereoselectivity. The acceptors include α,β-disubstituted-α,β-unsaturated esters, β,β-disubstituted-α,β-unsaturated esters, α,β-disubstituted-α,β-enones, β,β-disubstituted-α,β-enones, α,β,β-trisubstituted-α,β-enones and α,β-unsaturated carboxylic acids, which typically do not react with organocoppers or lower order organocuprates. However, characterization of the organocopper–Lewis acid complexes is lacking. It is instructive to compare the reactivity of the organocopper–Lewis acid complexes (**87**) *vis-à-vis* the homocuprates (**83**); for example, organocopper–aluminum trichloride (**87b**; Scheme 18) is highly effective in conjugate additions to γ-*t*-butyldimethylsilyloxy-α,β-enones, (**94**) and (**96**) (exclusive *anti* addition to the silyl ether), and γ-cyclopropyl-α,β-enones, (**98**) and (**100**).[51] In contrast, with the homocuprates (**83**) competing $S_N2'$ reaction processes, reduction processes or cyclopropane cleavage typically occurs. The lack of cyclopropane cleavage with (**87b**) implies that carbon–carbon bond formation does not involve an electron transfer process. Chemoselectivity differences are also observed with methyl sorbate (**102**), where (**87b**, R = $Bu^n$) affords predominantly 1,4-adduct (**103**),[50b] while (**83**, R = $Bu^n$) affords 1,6-adduct (**104**; Scheme 18).[52] Other subtle differences include the diastereoselective addition of (**87a**) to γ-benzyloxy-α,β-unsaturated esters (**105**) and (**106**). For example, the (*E*)-ester (**105**) affords predominantly the *anti* adduct (**109**), while the (*Z*)-ester (**106**) affords the *syn* adduct (**110**; Scheme 19). In contrast, the corresponding homocuprate additions proceed exclusively in an $S_N2'$ mode.[53]

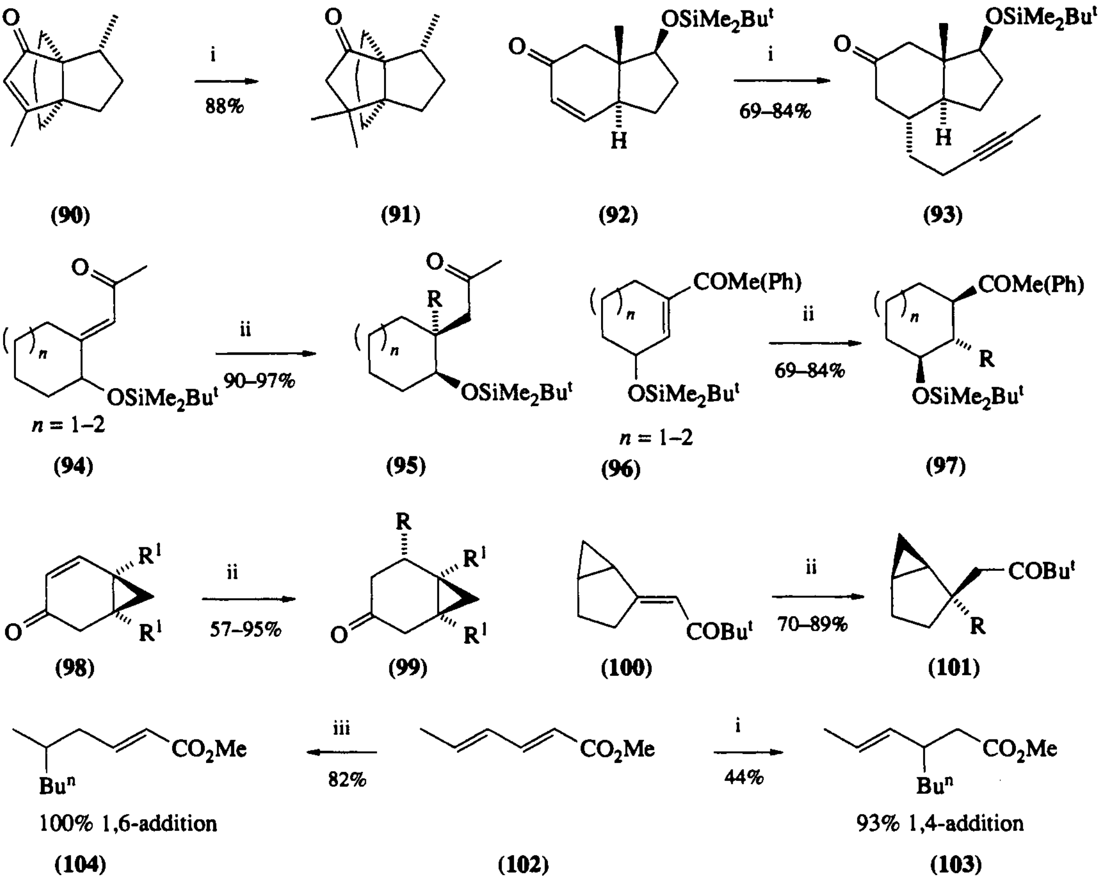
(90)
i
88%
(91)
(92)
OSiMe₂Buᵗ
i
69–84%
(93)
(94)
n = 1–2
ii
90–97%
(95)
(96)
COMe(Ph)
ii
69–84%
(97)
(98)
ii
57–95%
(99)
(100)
ii
70–89%
COBuᵗ
(101)
iii
82%
(102)
i
44%
100% 1,6-addition
(104)
93% 1,4-addition
(103)

i, $RCu{\bullet}BF_3$ (**87a**), $Et_2O$, –78 to –25 °C; ii, $RCu{\bullet}AlCl_3$ (**87b**), $Et_2O$, –78 to –25 °C; iii, $Bu^n{}_2CuLi$ (**83**)

**Scheme 18**

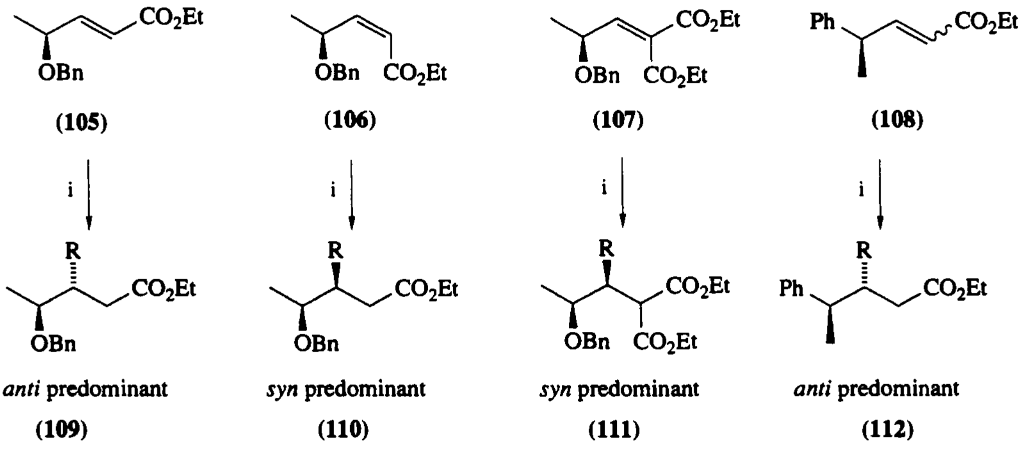
(105)
(106)
(107)
(108)
i
i
i
i
anti predominant
(109)
syn predominant
(110)
syn predominant
(111)
anti predominant
(112)

i, $RCu{\bullet}BF_3$ (**87a**)

**Scheme 19**

Oppolzer reports that similar additions of the ether soluble organocopper–boron trifluoride–tri-*n*-butylphosphine complexes (**87c**) to chiral α,β-unsaturated esters (Scheme 20) proceed with high diastereoselectivity. Subsequent hydrolysis or reduction of the chiral adducts, *e.g.* (**115**) and (**116**), affords

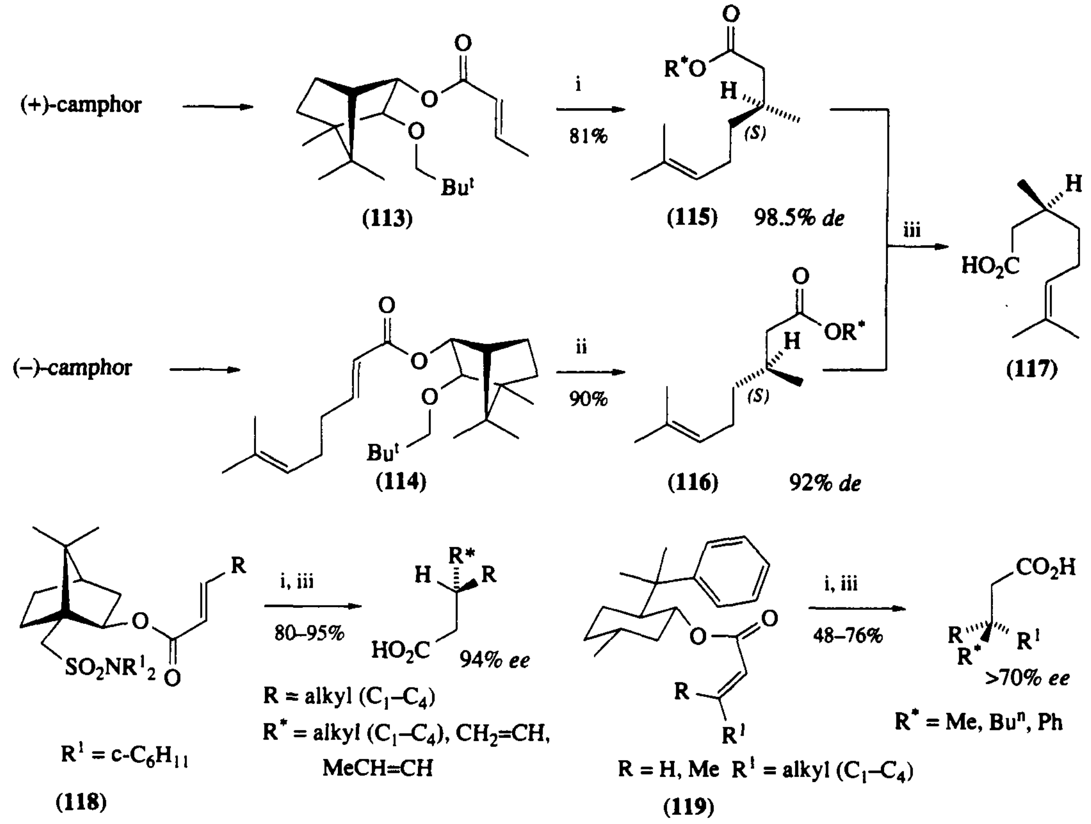

(+)-camphor
(−)-camphor
O
Bu$^t$
(113)
(114)
i
81%
ii
90%
R*O
OR*
H
(S)
(115) 98.5% *de*
(116) 92% *de*
iii
HO$_2$C
H
(117)
SO$_2$NR$^1{}_2$
R
R$^1$ = c-C$_6$H$_{11}$
(118)
i, iii
80–95%
R*
HO$_2$C
94% *ee*
R = alkyl (C$_1$–C$_4$)
R* = alkyl (C$_1$–C$_4$), CH$_2$=CH, MeCH=CH
i, iii
48–76%
R$^1$
R = H, Me R$^1$ = alkyl (C$_1$–C$_4$)
(119)
CO$_2$H
>70% *ee*
R* = Me, Bu$^n$, Ph

i, MeLi (R*Li), CuI, Bu$^n_3$P, BF$_3$, −78 °C; ii, Me$_2$C=CHCH$_2$CH$_2$Li, CuI, Bu$^n_3$P, BF$_3$, −78 °C;
iii, NaOH (MeONa), MeOH

**Scheme 20**

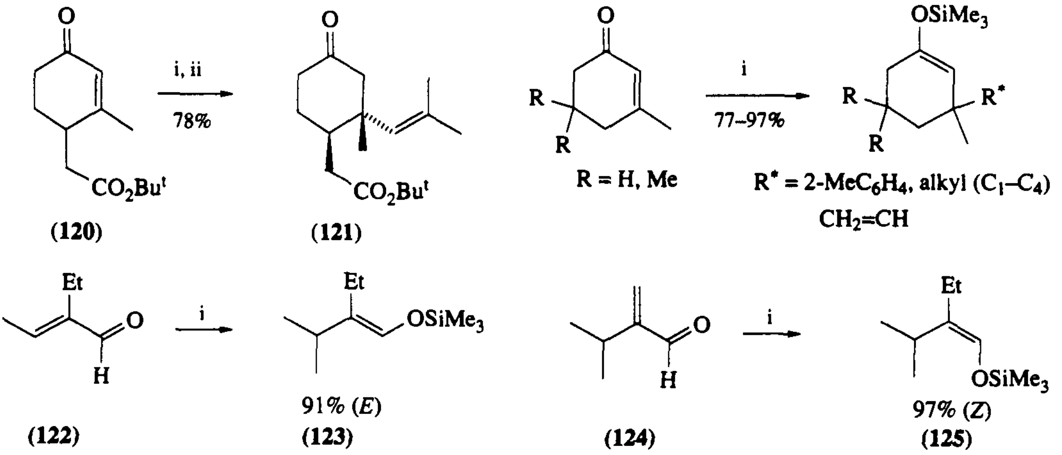

O
CO$_2$Bu$^t$
(120)
i, ii
78%
(121)
R
R = H, Me
i
77–97%
OSiMe$_3$
R*
R* = 2-MeC$_6$H$_4$, alkyl (C$_1$–C$_4$) CH$_2$=CH
Et
H
(122)
i
91% (*E*)
(123)
(124)
i
97% (*Z*)
(125)

i, RMgBr, CuBr•SMe$_2$ (3%), HMPA, −78 °C, TMSCl; ii, H$_3$O$^+$

**Scheme 21**

chiral β-substituted carboxylic acids or β-substituted alcohols, respectively.[54] As exemplified in Scheme 20, for the synthesis of (*S*)-citronellic acid (**117**), several combinations of enoate acceptor unit and chiral auxiliary will result in identical chiral products.

The combinations of chlorotrimethylsilane–hexamethylphosphoramide (HMPA) or chlorotrimethylsilane–4-(dimethylamino)pyridine (DMAP) are also powerful accelerants for copper(I)-catalyzed Grignard conjugate additions,[55] and stoichiometric organocopper and homocuprate additions (Scheme 21).[56] However, these reactions must be performed in tetrahydrofuran instead of ether.[57] These procedures are noted for their high yields with stoichiometric quantities of Grignard reagents, excellent chemoselectivity and efficiency with α,β-unsaturated amides and esters and enals.[58] Typically, additions to enals proceed *via* the *S-trans* conformers to afford stereo-defined silyl enol ethers; for example, enals (**122**) and (**124**) give the (*E*)-silyl enol ether (**123**) and (*Z*)-silyl enol ether (**125**), respectively.

Alternatively, as exemplified in Scheme 22, Normant reports that the chiral α,β-unsaturated acetals (**126**) and (**127**), obtained from (*R*,*R*)-2,3-butanediol, undergo exclusive γ-addition ($S_N2'$) by complex (**87c**) with high diastereoselectivity. For example, (*E*)-acetals (**126**) and (*Z*)-acetals (**127**) afford (*S*)-β-substituted aldehydes and (*R*)-β-substituted aldehydes, respectively (*cf.* Scheme 2).[59]

Dramatic reactivity enhancements have also been reported for the Lewis acid modified cyanocuprates (**89**);[60] for example, additions of the α-hydroxyalkyl synthon ($^-$CH(R)OH) reagents, (**89a**) and (**89b**), to

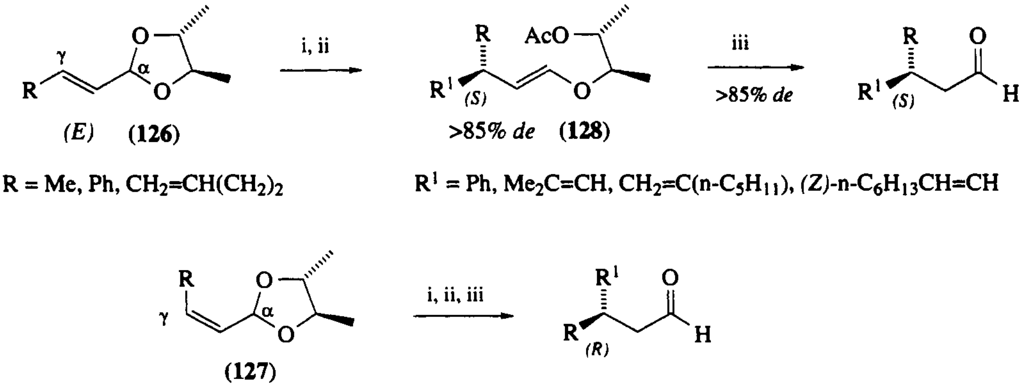

R = Me, Ph, $CH_2{=}CH(CH_2)_2$

R$^1$ = Ph, $Me_2C{=}CH$, $CH_2{=}C(n\text{-}C_5H_{11})$, (*Z*)-n-$C_6H_{13}CH{=}CH$

i, $R^1Cu{\cdot}R^*{}_3P{\cdot}BF_3$ (**87c**); ii, $(MeCO)_2O$, $C_5H_5N$, DMAP; iii, $H_3O^+$

**Scheme 22**

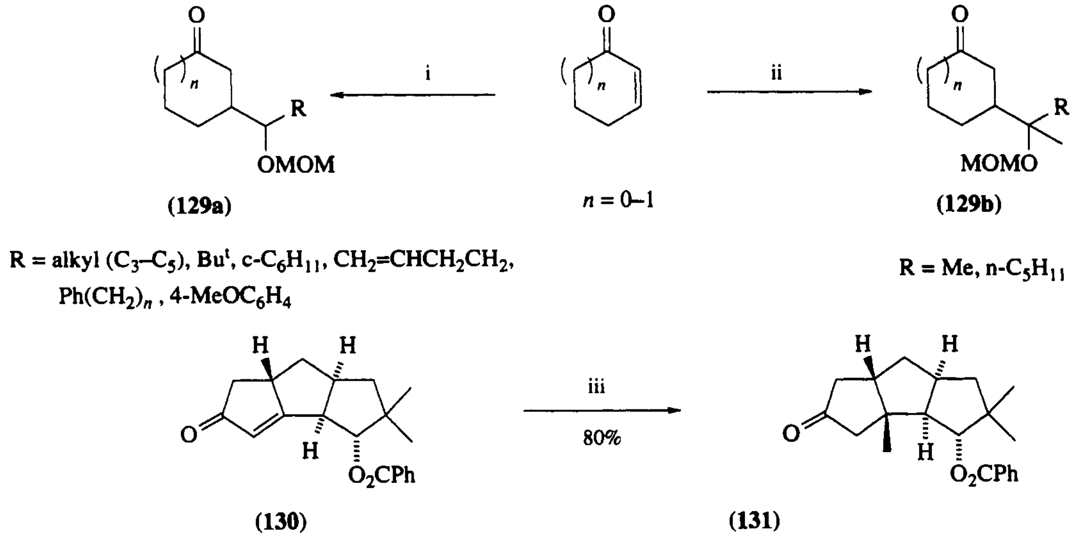

R = alkyl ($C_3$–$C_5$), Bu$^t$, c-$C_6H_{11}$, $CH_2{=}CHCH_2CH_2$, $Ph(CH_2)_n$, 4-$MeOC_6H_4$

R = Me, n-$C_5H_{11}$

i, $[RCH(OMOM)]_2Cu(CN)Li_2{\cdot}Me_3SiCl$ (**89a**), –78 °C; ii, $[RMeC(OMOM)]_2Cu(CN)Li_2{\cdot}Me_3SiCl$ (**89b**), –78 °C; iii, $Me_2Cu(CN)Li_2{\cdot}BF_3$ (**89c**), –78 °C

**Scheme 23**

α,β-cycloenones proceed efficiently to afford homoaldol products (**129**).[61a–61d] Similarly, additions to sterically congested β,β-disubstituted-α,β-enones (**130**) proceed in the 1,4-mode exclusively, at low temperatures (Scheme 23).[61e]

### *1.3.2.1.4 Organozirconiums*

The use of organozirconium reagents in synthesis was prompted by Wailes' discovery that alkynes and alkenes undergo hydrozirconation efficiently with bis($\eta^5$-cyclopentadienyl)chlorohydridozirconium, $[(\eta^5\text{-}C_5H_5)_2Zr(H)Cl]$.[62a,62b] Terminal alkynes undergo regiospecific *cis* addition, while unsymmetrically substituted alkynes show good regioselectivity.[62c] The alkenylzirconiums (**132**) are notable for their compatibility with various functionalities without masking; for example, the alkenylzirconium (**134**) is prepared in the presence of an ester functionality. In the presence of catalytic amounts of nickel acetylacetonate [Ni(acac)$_2$], excellent yields of 1,4-addition products with α,β-enones are obtained (Scheme 24).[63a] By-product dienes arising from alkene dimerization are minimized when a prereduced catalyst

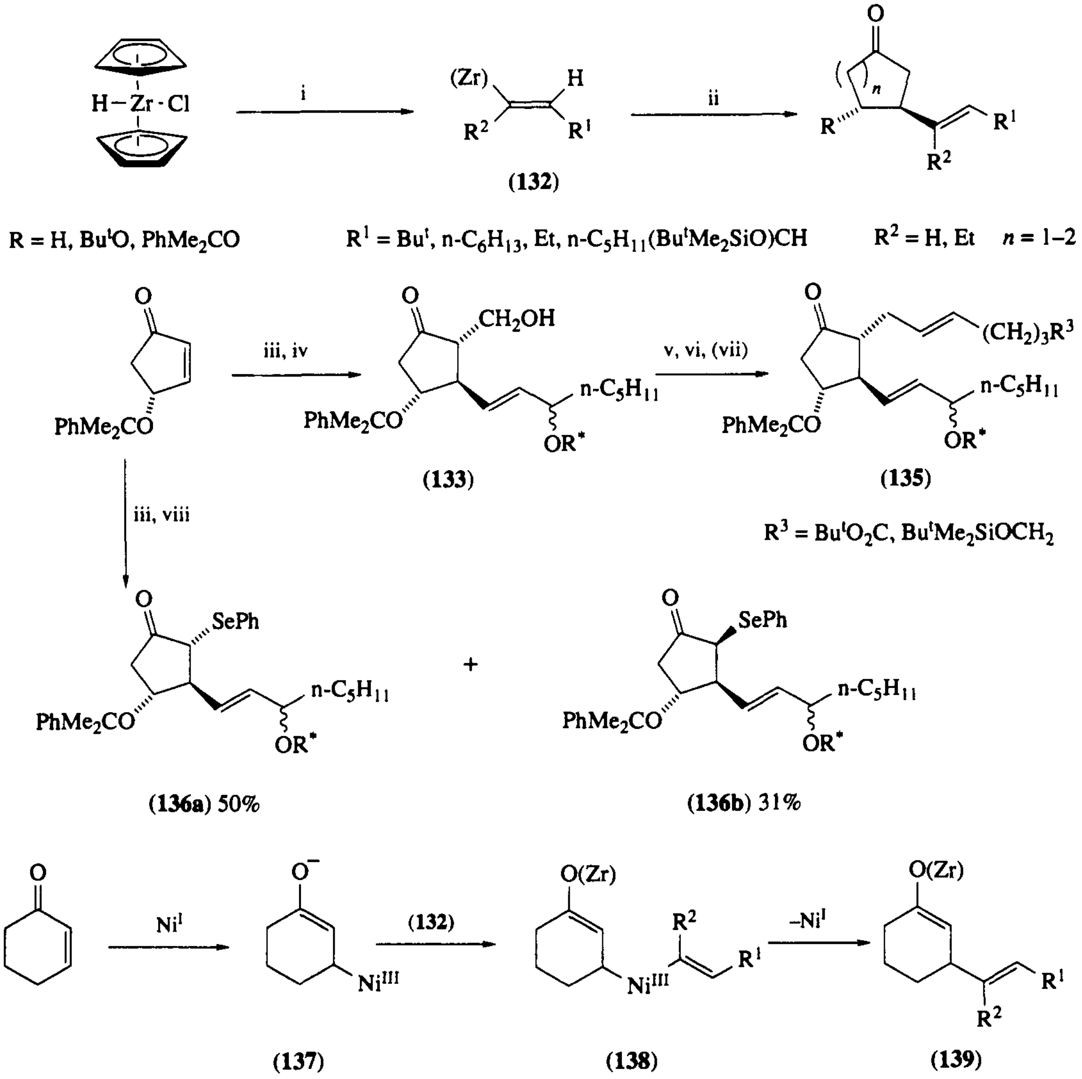
H–Zr·Cl
i
(Zr)
H
$R^2$
$R^1$
ii
O
n
R
$R^1$
$R^2$
(132)
R = H, Bu$^t$O, PhMe$_2$CO
$R^1$ = Bu$^t$, n-C$_6$H$_{13}$, Et, n-C$_5$H$_{11}$(Bu$^t$Me$_2$SiO)CH
$R^2$ = H, Et  n = 1–2
O
PhMe$_2$CO
iii, iv
CH$_2$OH
n-C$_5$H$_{11}$
OR*
(133)
v, vi, (vii)
(CH$_2$)$_3$R$^3$
n-C$_5$H$_{11}$
OR*
(135)
$R^3$ = Bu$^t$O$_2$C, Bu$^t$Me$_2$SiOCH$_2$
iii, viii
SePh
n-C$_5$H$_{11}$
OR*
PhMe$_2$CO
+
SePh
n-C$_5$H$_{11}$
OR*
(136a) 50%
(136b) 31%
O
Ni$^I$
O$^-$
Ni$^{III}$
(132)
O(Zr)
$R^2$
$R^1$
Ni$^{III}$
-Ni$^I$
O(Zr)
$R^1$
$R^2$
(137)
(138)
(139)

i, $R^1C{\equiv}CR^2$; ii, cycloalkenone, Ni$^{II}$ catalyst; iii, (*E*)-(Zr)CH=CHCH(OR*)-n-C$_5$H$_{11}$, Ni$^{II}$ catalyst; iv, CH$_2$O (g); v, MeSO$_2$Cl, Et$_3$N; vi, (*E*)-(Zr)CH=CH(CH$_2$)$_3$CO$_2$Bu$^t$ (**134**), Ni$^{II}$ catalyst; vii, (*E*)-(Zr)CH=CH(CH$_2$)$_4$OSiMe$_2$Bu$^t$, Ni$^{II}$ catalyst; viii, PhSeCl

**Scheme 24**

complex of nickel acetylacetonate and diisobutylaluminum hydride (DIBAL-H) is utilized. In contrast to the nickel acetylacetonate catalyzed dialkylalkenylalane conjugate additions (*cf.* Section 1.3.2.1.1), the alkenylzirconium transfers are highly efficient with terminal alkenylzirconiums and moderate yielding with internal alkenylzirconiums. The latter may be due to steric hindrance of the intermediate complex to conjugate addition and subsequent destruction of the nickel catalyst. Quenching of the intermediate zirconium enolates with either anhydrous formaldehyde or phenylselenyl chloride affords α-hydroxymethyl ketones (**133**)[64a] or α-phenylselenyl ketones (**136**),[64b] respectively; dehydration of ketol (**133**) and further alkenylzirconium conjugate addition affords the corresponding prostaglandin analogs (**135**). Similar conjugate additions have been successfully accomplished with α,β-unsaturated esters and α,β-enynones.

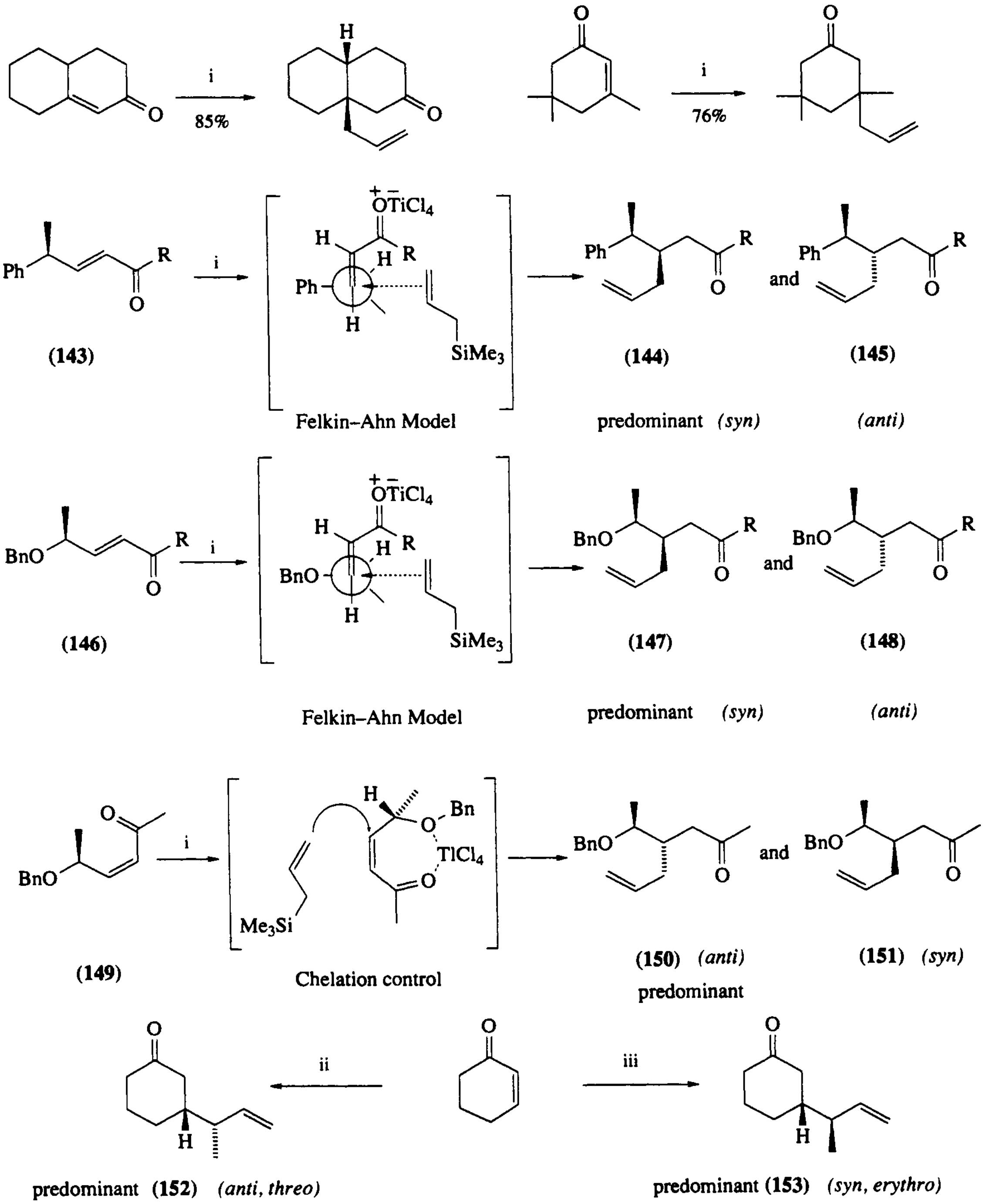
i
85%
i
76%
(143)
i
Felkin–Ahn Model
(144)
(145)
predominant (syn)
(anti)
(146)
i
Felkin–Ahn Model
(147)
(148)
predominant (syn)
(anti)
(149)
i
Chelation control
(150) (anti)
predominant
(151) (syn)
ii
iii
predominant (152) (anti, threo)
predominant (153) (syn, erythro)

**Scheme 25**

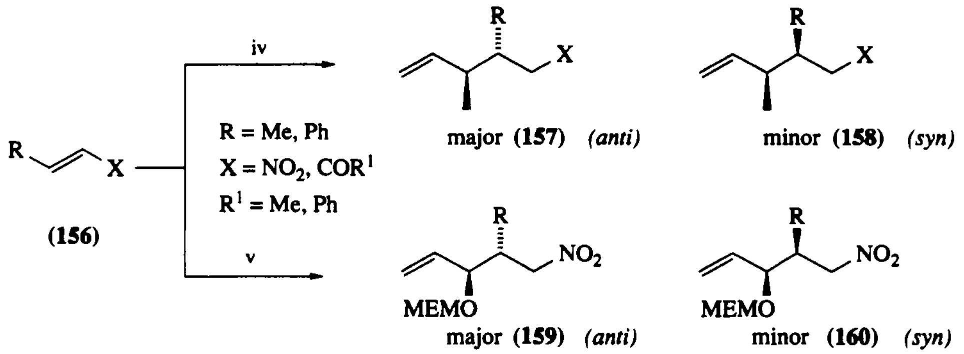

i, $CH_2=CHCH_2SiMe_3$ (**140**), $TiCl_4$, $CH_2Cl_2$, −78 °C; ii, (*Z*)-$MeCH=CHCH_2SiMeR^1R^2$ (**141**), $TiCl_4$, $CH_2Cl_2$, −78 to −40 °C; iii, (*E*)-$MeCH=CHCH_2SiMeR^1R^2$ (**142**), $TiCl_4$, $CH_2Cl_2$, −78 °C; iv, (*E*)-$MeCH=CHCH_2SnBu^n_3$ (**153**), $(Et_2Al)_2SO_4$, $C_6H_6$, 80 °C; v, (*Z*)-$MOMOCH=CHCH_2SnBu^n_3$ (**155**), $(Et_2Al)_2SO_4$, $C_6H_6$, 80 °C

**Scheme 25** *(continued)*

Mechanistically, the addition of a nickel(I) species to an α,β-enone generates a nickel(III) enolate (**137**) which undergoes transmetallation with an alkenylzirconium (**132**) and reductive elimination of nickel(I) to afford a zirconium enolate (**139**).[63b]

### *1.3.2.1.5 Organosilanes and organostannanes*

The reactivity of the organosilanes[65] and organostannanes[66] towards electrophiles is dependent on the characteristics of the organic ligands. Typically, the alkylsilanes and alkylstannanes are unreactive, which is a consequence of the weakly polarized carbon–silicon and carbon–tin σ-bonds ($C^{\delta-}$—$M^{\delta+}$). However, allylsilanes[67] and allylstannanes are highly reactive to electrophiles because of extensive σ–π (C—Si or C—Sn) conjugation in the allyl metals and the β-carbonium ion stabilization effect of the metal center. Consequently, electrophiles add exclusively with allylic transposition.

The Lewis acid catalyzed conjugate addition of allylsilanes (**140**) to (**142**) and allylstannanes (**154**) and (**155**) to α,β-enones, described by Sakurai,[68a,68b] is highly efficient and experimentally simple in contrast to the allylcuprate additions. Various substituents can be incorporated into the allylsilanes (allylstannanes), *e.g.* alkoxy, alkoxycarbonyl and halogen, some of which are incompatible with cuprate reagents.[69] In addition, Heathcock and Yamamoto report that diastereoselectivity is correlated to the alkene geometry of both the allylmetals and the acceptor units; for example, allylation of (*E*)-enones (**143**) and (**146**) affords predominantly the *syn* adducts (**144**) and (**147**), while (*Z*)-enone (**149**) gives predominantly the *anti* adduct (**150**; Scheme 25).[68c] On the other hand, with cyclohexen-2-one the (*Z*)-silane (**141**) affords predominantly the *threo* adduct (**152**), while (**142**) affords *erythro* adduct (**153**).[68d] The more reactive allylstannanes (**154**) and (**155**) also afford similar diastereoselectivity.[68e,f]

Typically, α,β-unsaturated esters, α,β-unsaturated aldehydes and α,β-unsaturated nitriles are poor acceptors for the Lewis acid catalyzed silylallylation procedure, but they are excellent acceptors for the complementary fluoride ion mediated allylation procedure (*cf.* Volume 4, Chapter 1.2, Section 1.2.2.1.7). Other suitable acceptors include 1,4-quinones,[70] α,β-unsaturated acyl cyanides (**162**),[71a] silyl α,β-enoates (**163**)[71b] and nitroalkenes (Scheme 26);[72] reduction (titanium(III) trichloride) of the intermediate nitronates arising from nitroalkene allylation affords γ,δ-enones (**166**).

Majetich reports a general intramolecular Lewis acid allylation protocol for the synthesis of bicyclo[5.4.0]undecen-3-ones (**168**) and bicyclo[4.4.0]decen-3-ones (**170**), which are 1,6-addition products (Scheme 27). The same precursors, (**167**) and (**169**), when submitted to the fluoride ion cyclization protocol, also afford 1,2- and 1,4-addition products.[73] Typically, ethylaluminum dichloride, a 'proton sponge' Lewis acid, is used in order to minimize adventitious protonic desilylation. Other β,γ-unsaturated silanes also undergo similar intramolecular Lewis acid catalyzed additions; for example, the silylpropargylic enones (**171**) undergo intramolecular cyclization to the allenylspiro system (**172**).[74]

Subtle reactivity differences are reported for the reaction of allenylsilanes *vis-à-vis* the allenylstannanes with α,β-cycloalkenones. The stannane (**175**) affords the alkynic ketone (**176**)[75] exclusively, while

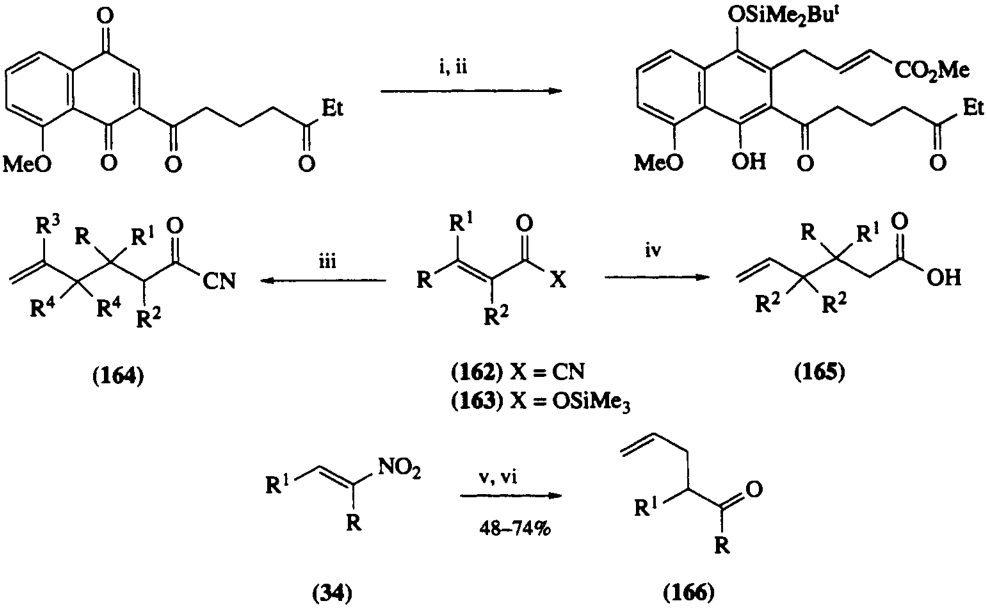
i, ii
iii
iv
v, vi
48–74%
(164)
(162) X = CN
(163) X = OSiMe3
(165)
(34)
(166)

$R = Me, Et; R^1 = n\text{-}C_{10}H_{21}, Ph, 4\text{-}ClC_6H_4, 4\text{-}MeOC_6H_4, PhCH_2CH_2$

i, $CH_2{=}CHCH[SiMe_2Ph]CO_2Me$ (**161**), $SnCl_4$, $CH_2Cl_2$, −78 to −30 °C; ii, $Bu^tMe_2SiCl$, imidazole, DMF; iii, $R^4{}_2C{=}C(R^3)CH_2SiMe_3$, $TiCl_4$, $CH_2Cl_2$, −78 °C; iv, $R^2{}_2C{=}CHCH_2SiMe_3$, $TiCl_4$, $CH_2Cl_2$, −78 °C; v, $CH_2{=}CHCH_2SiMe_3$ (**140**), $AlCl_3$, −20 °C; vi, $TiCl_3$

**Scheme 26**

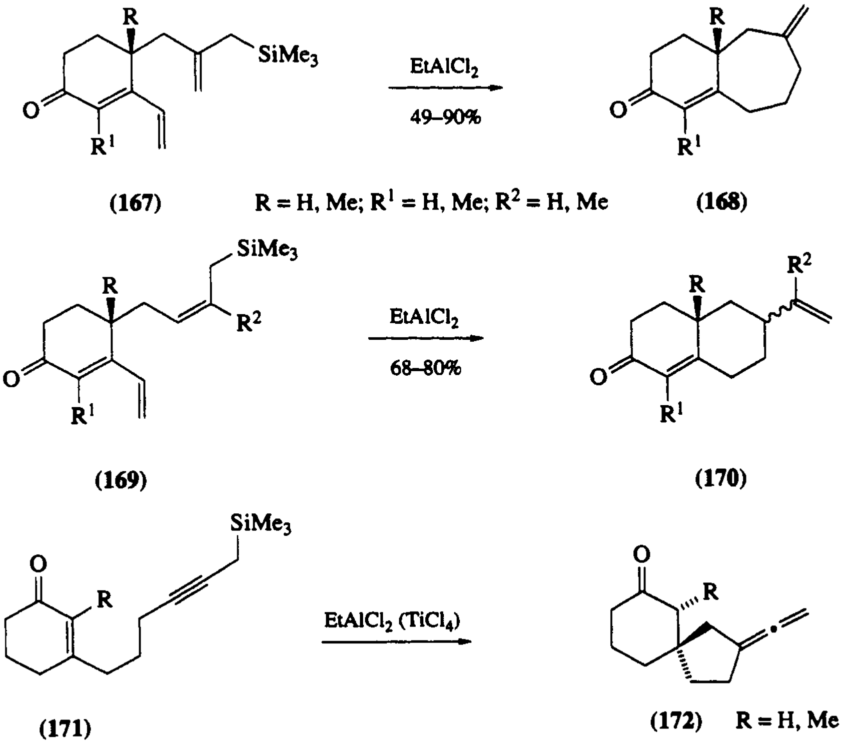
EtAlCl2
49–90%
(167)
R = H, Me; R1 = H, Me; R2 = H, Me
(168)
EtAlCl2
68–80%
(169)
(170)
EtAlCl2 (TiCl4)
(171)
(172) R = H, Me

**Scheme 27**

the silane (**173**) affords the bicyclo[4.3.0]nonenylsilane (**174**; Scheme 28). The initial step, *i.e.* Lewis acid activated enone addition of the allenylmetallic, is identical for both reactions, but the subsequent

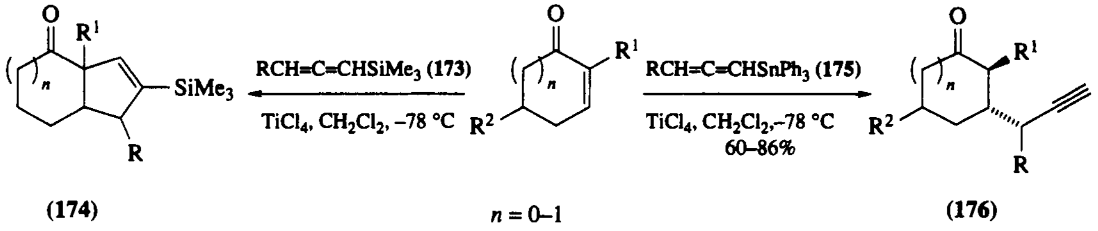

O
R¹
n
SiMe₃
R
RCH=C=CHSiMe₃ (173)
TiCl₄, CH₂Cl₂, -78 °C
O
R¹
n
R²
RCH=C=CHSnPh₃ (175)
TiCl₄, CH₂Cl₂, -78 °C
60–86%
O
R¹
n
R²
R
(174)
n = 0–1
(176)

R = H, Me; R² = H, Me; R¹ = H, Me

Scheme 28

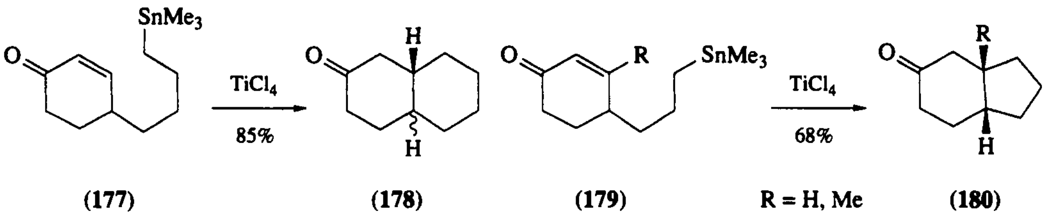

SnMe₃
O
TiCl₄
85%
H
O
H
O
R
SnMe₃
TiCl₄
68%
R
O
H
(177)
(178)
(179)
R = H, Me
(180)

Scheme 29

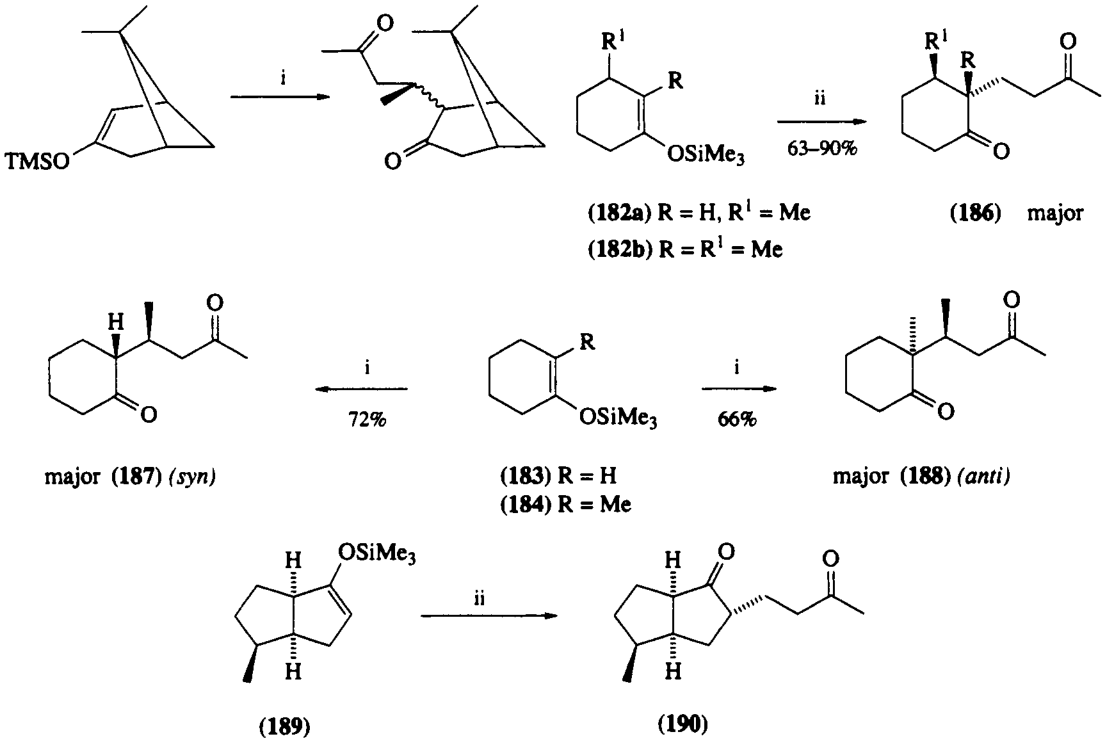

TMSO
i
O
O
R¹
R
OSiMe₃
ii
63–90%
R¹
R
O
O
(182a) R = H, R¹ = Me
(182b) R = R¹ = Me
(186) major
H
O
O
i
72%
R
OSiMe₃
i
66%
O
O
major (187) (syn)
(183) R = H
(184) R = Me
major (188) (anti)
H
OSiMe₃
H
ii
H
O
O
H
(189)
(190)

i, (*E*)-MeCH=CHCOMe (**181**), $TiCl_4$, $CH_2Cl_2$, −78 °C;
ii, $H_2C{=}CH\text{-}C(OCH_2CH_2O)Me$ (**185**), $TiCl_4\text{-}Ti(OPr^i)_4$, $CH_2Cl_2$, −80 to −95 °C

Scheme 30

step differs. The intermediate vinylstannane cation collapses to the alkyne, while the trimethylsilylvinyl cation undergoes a 1,2-shift to form an isomeric vinyl cation followed by titanium enolate capture.[76]

In contrast to the numerous examples of conjugate allyl transfers, the analogous alkyl transfers mediated by either alkylsilanes or alkylstannanes are scarce. However, in the presence of a β-electrophilic center cleavage of stereoproximate carbon–tin σ-bonds is facilitated; for example, the Lewis acid catalyzed carbocyclization of select 2-cyclohexenones with alkylstannane appendages, *e.g.* (**177**) or (**179**), affords bicyclic systems (Scheme 29).[77]

### 1.3.2.2 Additions of Enol Silyl Ethers and Silyl Ketene Acetals

The titanium(IV) chloride-catalyzed conjugate addition of enol silyl ethers (**182**) to (**184**) and (**189**; Scheme 30), and silyl ketene acetals, (**191**) to (**194**), to α,β-enones is the key feature in various synthetic strategies (Mukaiyama–Michael) (Scheme 31).[78,79] In contrast to the earlier described enolate addition

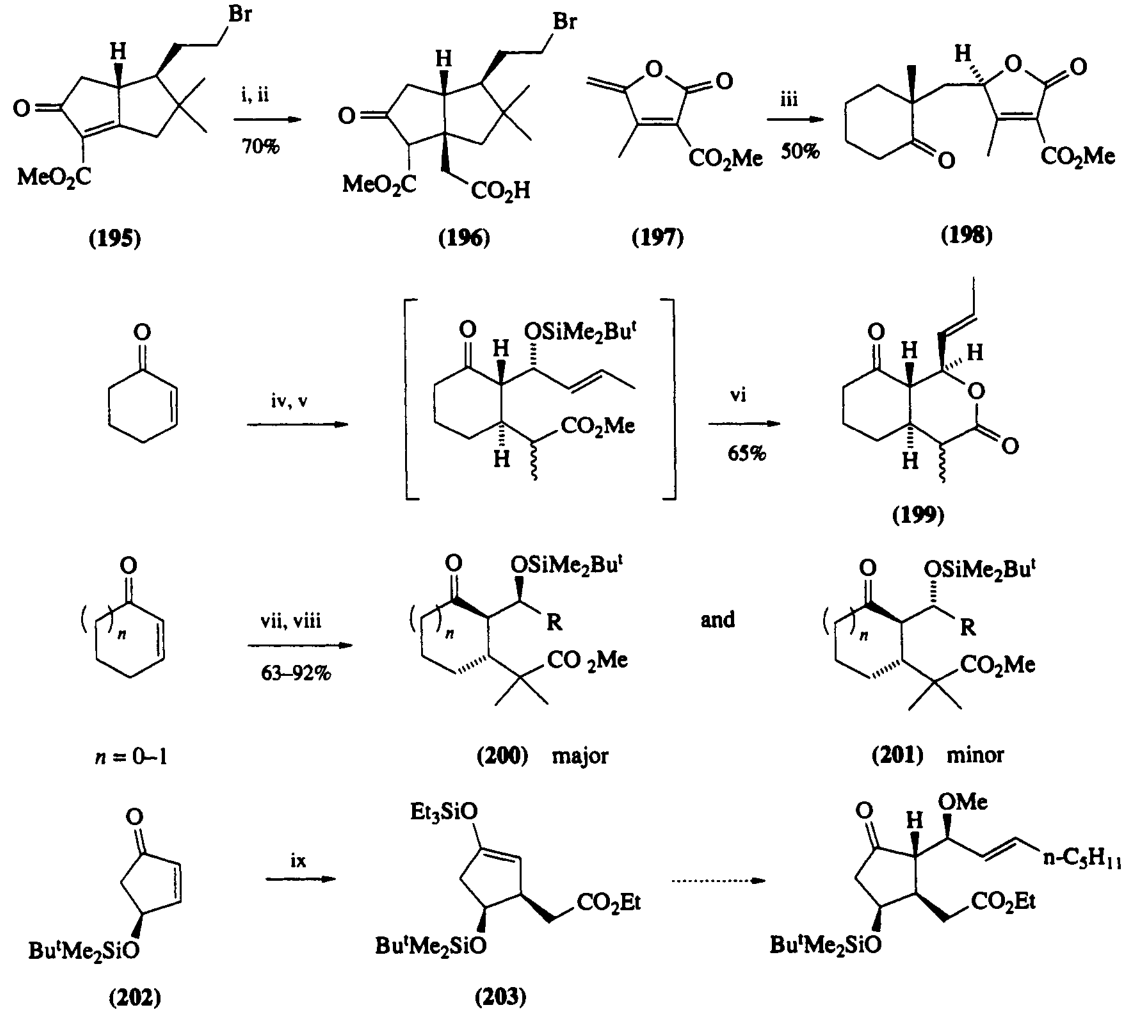
Br
H
O
MeO2C
i, ii
70%
Br
H
O
MeO2C
CO2H
O
O
CO2Me
iii
50%
H
O
O
O
CO2Me
(195)
(196)
(197)
(198)
O
iv, v
O
H
OSiMe2Bu^t
CO2Me
H
vi
65%
O
H
H
O
O
H
(199)
O
n
vii, viii
63–92%
O
OSiMe2Bu^t
n
R
CO 2Me
and
O
OSiMe2Bu^t
n
R
CO2Me
n = 0–1
(200) major
(201) minor
O
Bu^tMe2SiO
ix
Et3SiO
CO2Et
Bu^tMe2SiO
O
H
OMe
n-C5H11
CO2Et
Bu^tMe2SiO
(202)
(203)

i, $CH_2{=}C(OSiMe_2Bu^t)OBu^t$ (**191a**), $TiCl_4$, $CH_2Cl_2$; ii, $Bu^n{}_4N^+F^-$; iii, 2-methylcyclohexanone trimethylsilyl enol ether (**186**), $TiCl_4$, $CH_2Cl_2$; iv, $MeCH{=}C(OSiMe_2Bu^t)OMe$ (**192**), $Ph_3C^+ClO_4^-$ (5 mol%), $CH_2Cl_2$, −78 °C; v, (*E*)-$MeCH{=}CHCHO$; vi, $MeCO_2H$, THF; vii, $Me_2C{=}C(OSiMe_2Bu^t)OMe$ (**193**), $Ph_3C^+ClO_4^-$ (5 mol%), $CH_2Cl_2$, −78 °C; viii, RCHO; ix, $CH_2{=}C(OSiEt_3)OEt$ (**194**), $HgI_2$

**Scheme 31**

procedures (*cf.* Volume 4, Chapter 1.2, Section 1.2.2.2), this protocol is synthetically advantageous; for example, base sensitive acceptors may be used, β-quaternary centers are assembled in high yields (**196**; Scheme 31)[80] and by-products due to 1,2-addition or proton transferrals, *i.e.* enolate scrambling, are nonexistent. Thus enol silyl ethers arising from either kinetic or thermodynamic enolates do not undergo scrambling. However, the highly Lewis acidic nature of these reactions precludes the use of methyl vinyl ketone (MVK) as an acceptor, while the corresponding ethylene ketal (**185**) is an excellent acceptor with bis(isopropoxy)titanium dichloride catalysis, *e.g.* the conversion of (**189**) to (**190**) in Scheme 30.[81]

The choice of catalyst determines the range of suitable acceptors and work-up procedures employed. For example, trityl cation promoted additions of acetals (**192**) and (**193**) to α,β-enones typically afford regiochemically pure enol silyl ethers that can be utilized *in situ* for aldol condensations (Tandem Michael–aldol) (Scheme 31).[82] With similar reaction conditions, additions of silyl thioketene acetals (**204**) to α,β-cycloenones and α-substituted-α,β-cycloenones afford *anti* (**205**) and *syn* adducts (**206**), respectively. The diastereoselectivity differences are attributed to a highly ordered transition state (Scheme 32).[83] Danishefsky reports that mercury(II) iodide catalyzes the exclusive *syn* addition of silyl ketene acetals (**194**) to enone (**202**) (*cf.* the formation of **203**; Scheme 31),[84] while the corresponding carbanion additions give exclusive *anti* addition.[85]

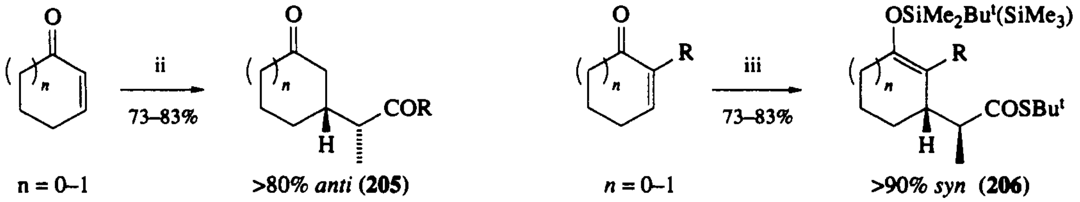

>80% *anti* (**205**)

>90% *syn* (**206**)

R = Ph, EtS, Bu$^t$S

R = Me, PhS, $MeO_2C$

i, $MeCH{=}C(OSiMe_3)R$ [$MeCH{=}C(OSiMe_2Bu^t)R$], $Ph_3CCl–SnCl_2$ (5–10 mol %), $CH_2Cl_2$, –78 °C;

ii, $MeCH{=}C(OSiMe_2Bu^t)SBu^t$ [$MeCH{=}C(OSiMe_3)SBu^t$] (**204**), $2\text{-}(C_5H_4N)CH_2OH$, $Ph_3C^+SbCl_6^-$, –78 °C

**Scheme 32**

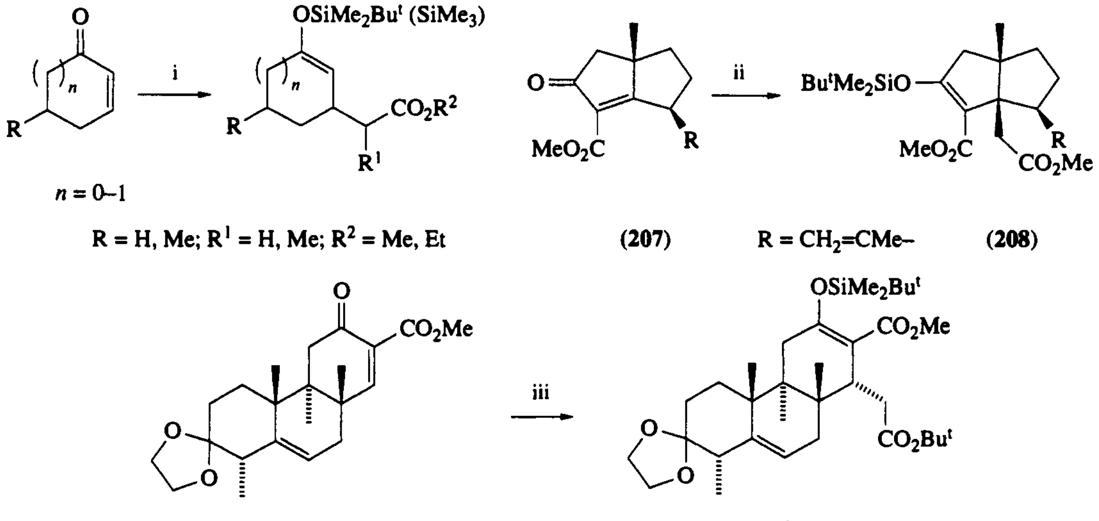

R = H, Me; R$^1$ = H, Me; R$^2$ = Me, Et

(**207**) R = $CH_2{=}CMe$– (**208**)

(**209**) (**210**)

i, $R^1CH{=}C(OSiMe_2Bu^t)OR^2$ [$R^1CH{=}C(OSiMe_3)OR^2$] (**191**) and (**192**), MeCN, 55 °C;

ii, $CH_2{=}C(OSiMe_2Bu^t)OMe$, (**191b**), 15kbar; iii, $CH_2{=}C(OSiMe_2Bu^t)OBu^t$ (**191a**), 15 kbar

**Scheme 33**

Remarkable solvent effects have been reported for select silyl ketene acetal–enone additions; for example, acetonitrile suffices to promote additions in the absence of a Lewis acid.[86a] Alternatively, addi-

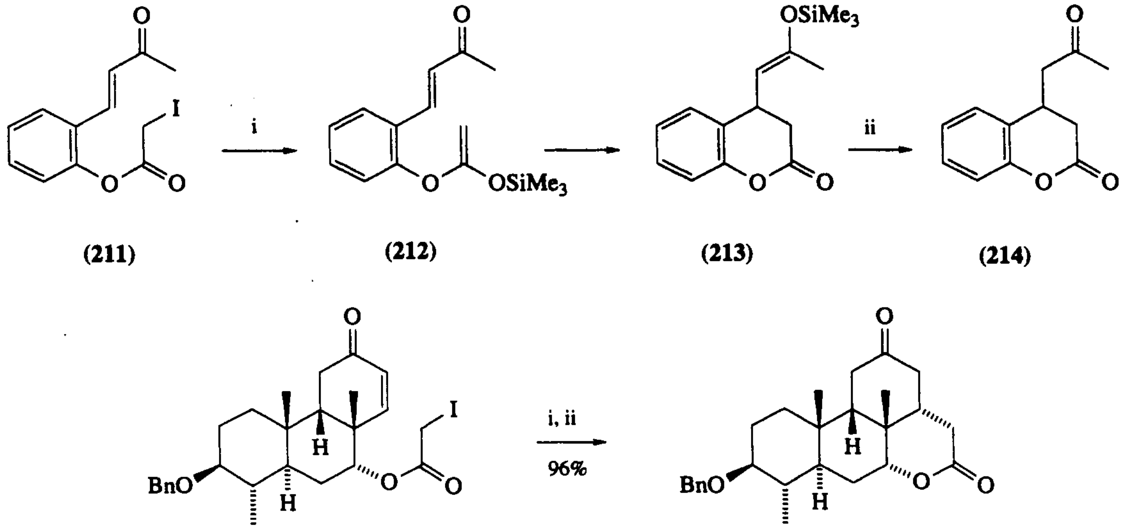
(211)
(212)
(213)
(214)
i
ii
i, ii
96%

i, $Me_3SiI$; ii, $H_3O^+$

Scheme 34

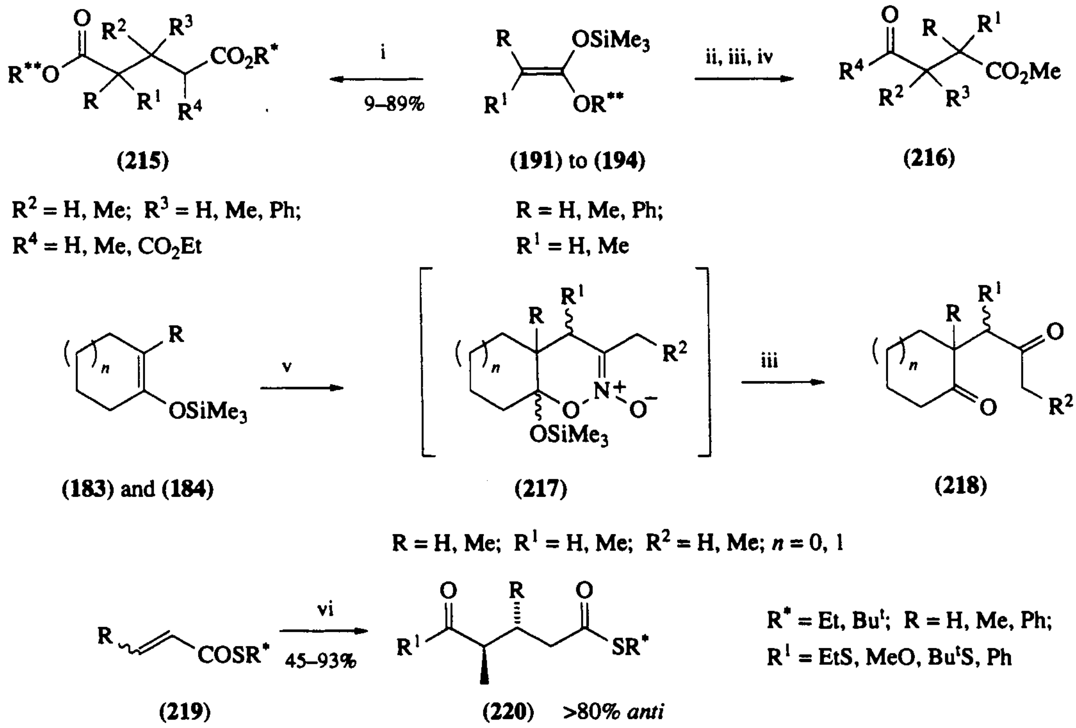
(215)
(191) to (194)
(216)
(183) and (184)
(217)
(218)
(219)
(220) >80% *anti*
i
9–89%
ii, iii, iv
v
iii
vi
45–93%

$R^2$ = H, Me; $R^3$ = H, Me, Ph; $R^4$ = H, Me, $CO_2Et$

R = H, Me, Ph; $R^1$ = H, Me

R = H, Me; $R^1$ = H, Me; $R^2$ = H, Me; *n* = 0, 1

$R^*$ = Et, $Bu^t$; R = H, Me, Ph; $R^1$ = EtS, MeO, $Bu^tS$, Ph

i, $R^2R^3C{=}C(R^4)CO_2R^*$, $Al(SO_3CF_3)_3$ or Al–montmorillonite; ii, $R^2R^3C{=}C(NO_2)R^4$, $TiCl_4$–$Ti(OPr^i)_4$; iii, $H_2O$; iv, $CH_2N_2$; v, $R^1CH{=}C(NO_2)CH_2R^2$, $TiCl_4$ ($SnCl_4$), $CH_2Cl_2$; vi, $MeCH{=}C(OSiMe_3)R^1$ [$MeCH{=}C(OSiMe_2Bu^t)R^1$], $SbCl_5$–$Sn(OTf)_2$ (5 mol %), –78 °C

Scheme 35

tions of silyl ketene acetals to sterically encumbered doubly activated α,β-enones, (**207**) or (**209**), which are not amenable to Lewis acid catalysis, proceed under high pressure (15 kbar, 1 bar = 100 kPa) (Scheme 33).[86b,c]

Few examples of intramolecular enol silyl ether or silyl ketene acetal cyclizations to α,β-enones have been reported. Notable, as exemplified in Scheme 34, is the iodotrimethylsilane-mediated intramolecular cyclization of δ-(iodoacetoxy)-α,β-enones (**211**) to δ-lactones (**214**). These cyclizations proceed with *in situ* generated silyl ketene acetals (**212**) arising from iodotrimethylsilane reduction of the iodoacetoxy moiety.[87]

In contrast to titanium(IV) tetrachloride, which causes polymerization of α,β-unsaturated esters, aluminum triflate[88] or aluminum-impregnated montmorillonite[87b] are excellent promoters of silyl ketene acetal additions to α,β-unsaturated esters (Scheme 35). Similarly, the addition of silyl ketene acetals and enol silyl ethers to nitroalkenes, followed by Nef-type work-up, affords γ-keto esters (**216**) and γ-diketones (**218**), respectively (Scheme 35).[89a,89b] Mechanistically, the γ-diketones (**218**) arise from Nef-type hydrolysis of an initial nitronate ester (**217**).[89c,89d] Mukaiyama reports that $SbCl_5$–$Sn(OTf)_2$ catalyzes diastereoselective *anti* additions of silyl ketene acetals, silyl thioketene acetals and enol silyl ethers to α,β-unsaturated thioesters (**219**).[90]

Vinyl sulfoxides (**221**), which are aldehyde α-cation equivalents, and vinylthiolium ions (**230**), which are α,β-unsaturated carbonyl β-cation equivalents, are also suitable acceptors for silyl ketene acetals and enol silyl ethers (Scheme 36). Kita reports that the bulky *t*-butyldimethylsilyl ketene acetals and trimethylsilyl ketene acetals form 1:1 adducts (**224**) and 1:2 adducts (**225**) with (**221**), respectively;[91] mechanistically, these additions proceed *via* an initial Pummerer rearrangement. The vinylthiolium ion additions are notable for their synthetic flexibility; for example, additions to the ketene dithioacetal (**229**) proceed with higher diastereoselectivity than the corresponding enolate additions to α,β-unsaturated esters.[91c,91d]

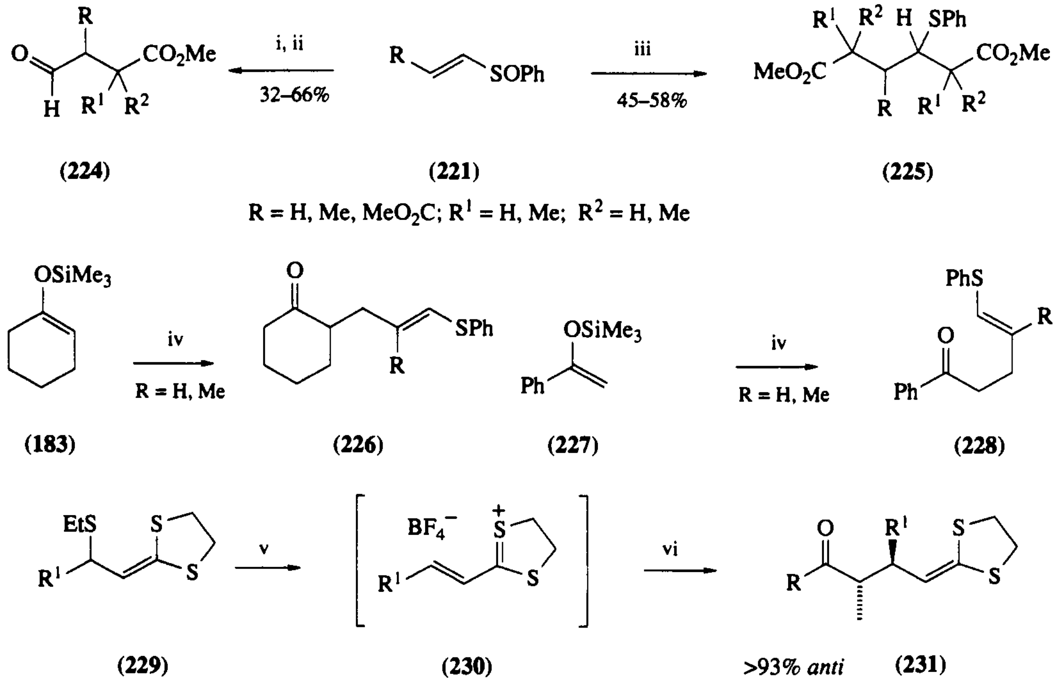

R = Ph, Bu$^t$, EtO, MeO; R$^1$ = alkyl ($C_1$–$C_3$), Ph

i, $R^1R^2CH{=}C(OSiMe_2Bu^t)OMe$, $ZnI_2$, MeCN, 0 °C; ii, TBAF; iii, $R^1R^2CH{=}C(OSiMe_3)OMe$, $ZnI_2$, MeCN; iv, (*E*)-$Me(R)C{=}CHSOPh$ (**222**), $Me_3SiOTf$, $Pr^i_2NEt$; v, $Ph_3C^+BF_4^-$; vi, $MeCH{=}C(OSiMe_2Bu^t)R$

Scheme 36

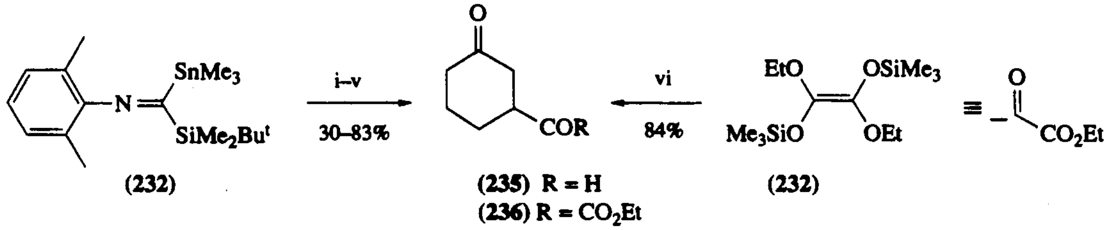
SnMe3
N
SiMe2Bu$^t$
(232)
i–v
30–83%
O
COR
(235) R = H
(236) R = CO2Et
vi
84%
EtO
OSiMe3
Me3SiO
OEt
(232)
≡
O
CO2Et

i, Bu$^n$Li, THF, –78 °C; ii, CuBr–DMS; iii, $Me_3SiCl$ (Bu$^t$Me$_2$SiCl); iv, cycloalkenone; v, $H_3O^+$;
vi, cycloalkenone, $ZnCl_2$

Scheme 37

### 1.3.2.3 Additions of Acyl Anion Equivalents

Except for the well-documented conjugate additions of diethylaluminum cyanide,[92] triethylaluminum–hydrogen cyanide and Lewis acid–tertiary alkyl isonitriles,[93] examples of Lewis acid catalyzed conjugate additions of acyl anion equivalents are scant. Notable examples are additions of copper aldimines (**233**),[94a,94b] prepared from (**232**), and silyl ketene acetals (**234**)[94c] to α,β-enones which afford 1,4-ketoaldehydes (**235**) and 2,5-diketo esters (**236**), respectively (Scheme 37). The acetal (**234**) is considered a glyoxylate ester anion equivalent.

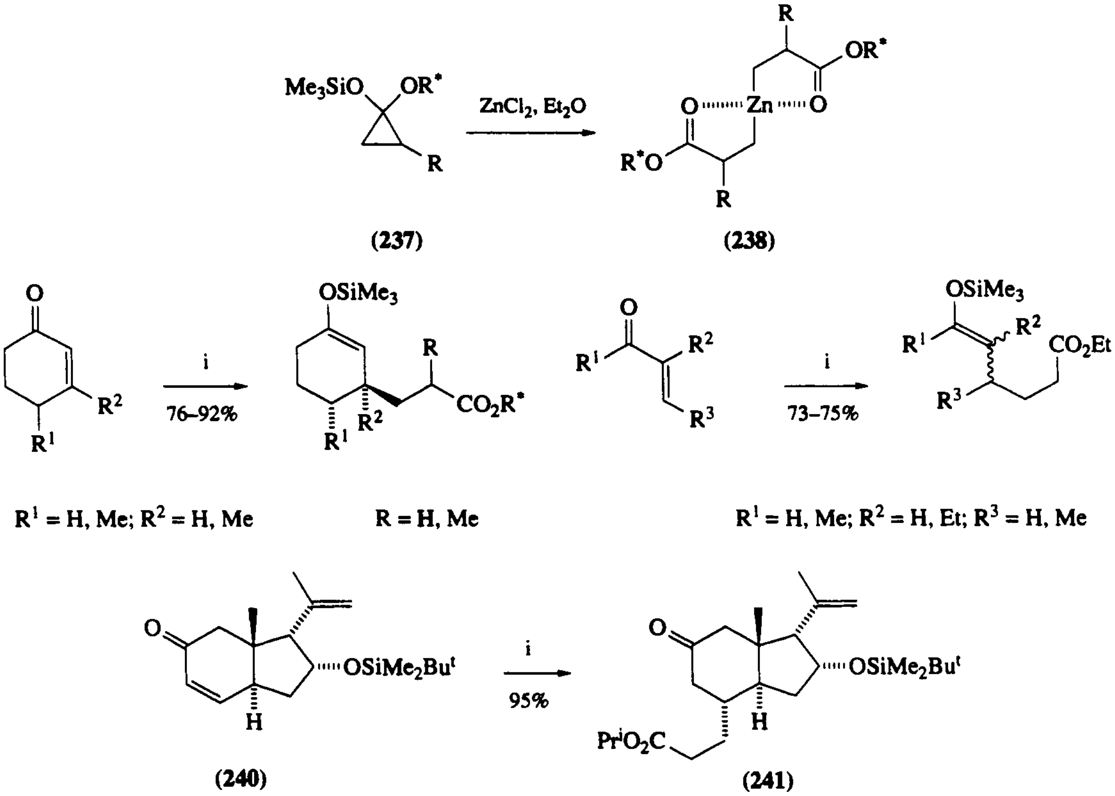
Me3SiO
OR*
R
ZnCl2, Et2O
R
OR*
O
Zn
O
R*O
R
(237)
(238)
O
R$^2$
R$^1$
i
76–92%
OSiMe3
R
CO2R*
R$^2$
R$^1$
R$^1$ = H, Me; R$^2$ = H, Me
R = H, Me
O
R$^1$
R$^2$
R$^3$
i
73–75%
OSiMe3
R$^1$
R$^2$
CO2Et
R$^3$
R$^1$ = H, Me; R$^2$ = H, Et; R$^3$ = H, Me
O
OSiMe2Bu$^t$
H
(240)
i
95%
O
OSiMe2Bu$^t$
H
Pr$^i$O2C
(241)

i, (**238**), $CuBr{\bullet}SMe_2$ (0.5 mol %), HMPA, 0 °C

Scheme 38

### 1.3.2.4 Additions of Homoenolates

The concept of homoenolization was recognized during the 1960s. However, attempts at direct formation of homoenolates were complicated by their spontaneous cyclopropanolate formation. *In lieu* of direct methods, various groups have focussed on the development of homoenolate equivalents.[95] Kuwajima reports that the treatment of cyclopropanone silyl hemiketals (**237**) with zinc chloride, in the presence of HMPA, affords a convenient source for homoenolates (**238**). *In situ* transmetallation with a copper bromide–dimethyl sulfide complex affords the low reactivity copper homoenolate (**239**) which on activation with chlorotrimethylsilane–HMPA undergoes conjugate additions with α,β-enones and enals (Scheme 38).[96] Recently, Yoshida reported a versatile procedure for *in situ* generation of zinc homoenolates and homologous carbanions *via* a zinc–copper couple in the presence of HMPA (Scheme 39).[97] As an aside, the trimethylsilyl triflate catalyzed addition of γ-triphenylphosphorylidene *t*-butyldimethylsilyl enol ether (**248**), an α,β-enone β-anion equivalent, to activated alkenes affords β-substituted cycloalkenones (**249**).[98] Conceptually, this protocol is equivalent to the addition–elimination of a homoenolate or equivalent to a β-halo-α,β-enone (*cf.* Volume 4, Chapter 1.2, Section 1.2.4.3).

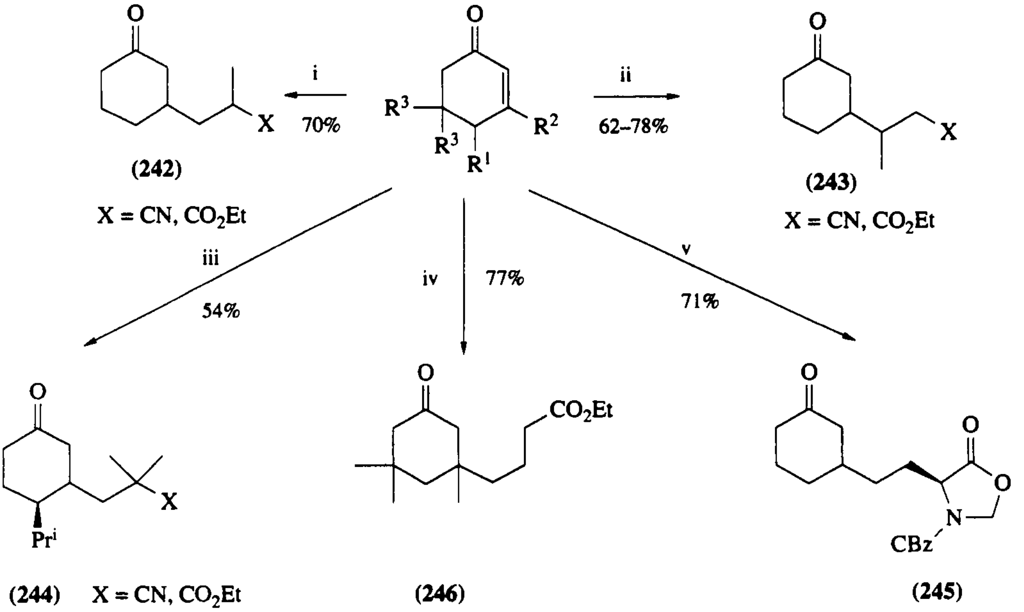

i, $ICH_2CH(Me)X$, Zn–Cu; ii, $MeCHICH_2X$, Zn–Cu; iii, $ICH_2CMe_2CN$, Zn–Cu; iv, $I(CH_2)_3CO_2Et$, Zn–Cu; v, $ICH_2CH_2Het$, Zn–Cu

**Scheme 39**

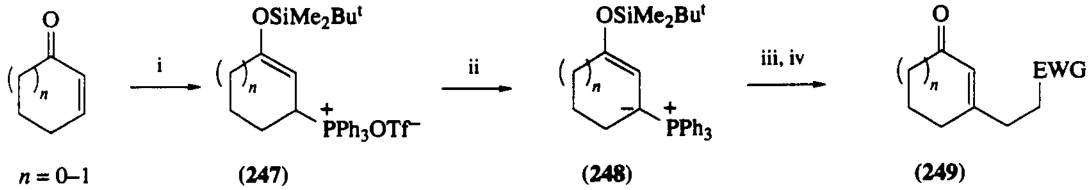

EWG = COEt, COPh, $CO_2Et$, $SO_2Ph$, CN

i, TMSOTf, $Ph_3P$; ii, $Bu^nLi$, THF, −78 °C; iii, $CH_2{=}CH\text{-}EWG$, TMSOTf, −78 °C; iv, TBAF

**Scheme 40**

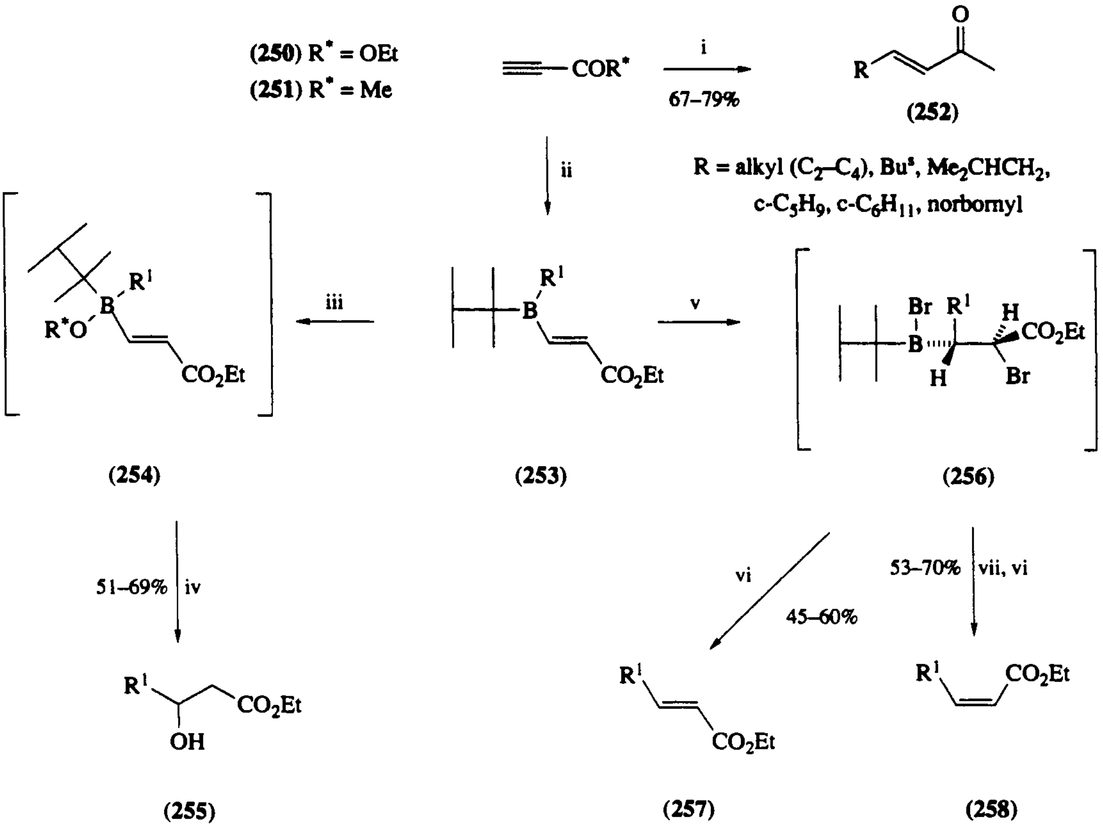

$R^1$ = c-$C_6H_{11}$, norbornyl, (*E*)-2-methylcyclopentenyl, $Me_2CHCHMe$

i, $R_3B$, catalytic $O_2$; ii, $R^1$(thexyl)BH; iii, $R^*ONa$; iv, NaOH, $H_2O_2$; v, $Br_2$; vi, $H_2O_2$, $MeCO_2Na$; vii, $MeCO_2Na$, −78 °C

**Scheme 41**

### 1.3.3 ADDITIONS TO ALKYNIC π-SYSTEMS

The intermolecular conjugate addition of carbon ligands to activated alkynes is typically accomplished with organocopper reagents,[48,96] while similar additions with Lewis acids are rare. Notable examples are the organoborane[99] and silyl ketene acetal additions[100] to propynoate esters. The addition of trialkylboranes, catalyzed by oxygen, to butyn-3-one proceeds directly to afford (*E*)-enones (**252**). On the other hand, alkynes are functionalized *via* alkenylboronates or alkenylborates (**254**) which have a propensity to undergo alkyl migration from boron to α-carbon. For example, the hydroboration of ethyl propynoate with alkyl(thexyl)boranes (Scheme 41) affords the intermediate (*E*)-boraenoates (**253**), which can be transformed to either β-hydroxy esters (**255**),[99a] (*E*)-enoates (**257**) or (*Z*)-enoates (**258**).[99b,99c]

Further versatility of this approach has been realized with contrasting Lewis acid promoted additions of silyl ketene acetals, (**191**) to (**194**), to ethyl propynoate (Scheme 42). In fact, the tandem 1,4-conjugate addition–electrophile trapping protocol is feasible when titanium(IV) tetrachloride is employed. *In situ* functionalization of the intermediate titanate enoate (**259**), with select electrophiles, affords α-substituted enoates (**260**) to (**262**). On the other hand, the zinc iodide and zirconium(IV) tetrachloride protocols afford directly γ-alkoxycarbonyl-α-trimethylsilylenoates (**263**) and [2 + 2] adducts (**264**), respectively.[100]

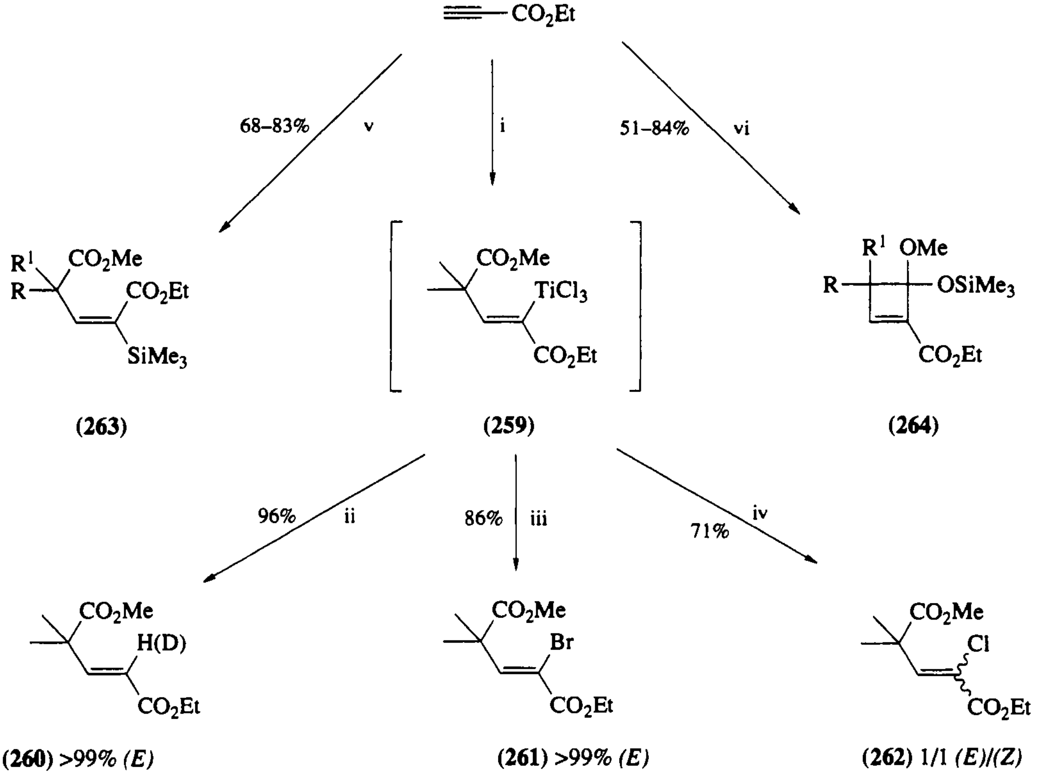

R = H, Me $R^1 = n\text{-}C_5H_{11}$, $c\text{-}C_6H_{11}$, Me $R\text{-}R^1 = \text{-}(CH_2)_5\text{-}$

i, $Me_2C{=}C(OSiMe_3)OMe$ (**193**), $TiCl_4$, $CH_2Cl_2$, –78 °C; ii, $H_2O(D_2O)$; iii, NBS; iv, NCS;
v, (**191**)–(**194**), $ZnI_2$, $CH_2Cl_2$, 20 °C; vi, (**191**)–(**194**), $ZrCl_4$, $CH_2Cl_2$, 20 °C

**Scheme 42**

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# 1.4

# Organocuprates in the Conjugate Addition Reaction

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## 1.4.1 INTRODUCTION

One of the distinguishing features of the reaction of organocuprates with α,β-unsaturated carbonyl compounds is the overwhelming preference for the 1,4 *versus* the 1,2 mode of addition.[1] Dramatic changes in chemoselectivity are often observed when a copper(I) salt is added to a solution of an organomagnesium or organolithium reagent and an enone. For example, when *trans*-3-penten-2-one is treated with MeLi, a selective 1,2-addition takes place (99% 1,2). Use of methylmagnesium bromide leads to a mixture of 1,4- and 1,2-addition products (30:70). However, if the same enone is treated with $Me_2CuLi$, prepared from 2MeLi and CuI, only the conjugate addition product is formed (99% 1,4).[2]

$$\mathrm{RLi} + \mathrm{CuX} \longrightarrow \mathrm{RCu} + \mathrm{LiX} \qquad (1)$$

Typically organocuprates are formed by the addition of either an organolithium or organomagnesium reagent to a copper(I) salt under an inert atmosphere, where the relative stoichiometry is important in determining the type of reagent formed.[1,3,4] Monoorganocopper species, RCu (equation 1), are ether-insoluble compounds which tend to be thermally unstable. They can be solubilized with additives such as tributylphosphine[1] and are used successfully with Lewis acids such as boron trifluoride etherate ($BF_3{\cdot}Et_2O$).[5]

$$2\,RLi \;+\; CuX \longrightarrow R_2CuLi \;+\; LiX \qquad (2)$$

Diorganocuprates are ether-soluble reagents which react with a wide range of substrates.[1,6–10] These reagents can be prepared directly from a copper(I) salt (equation 2), or from a monoorganocopper species by addition of 1 mol equiv. of an RLi species.

Triorganocuprates are ether-soluble reagents which are often referred to as 'higher order cuprates'. Generally prepared from copper(I) cyanide, these reagents undergo the same reactions as diorganocuprates but offer a different reactivity profile (equation 3).[3,4]

$$2RLi \;+\; CuCN \longrightarrow R_2Cu(CN)Li_2 \qquad (3)$$

The many uses of organocuprates have been the subject of numerous reviews,[1,3,4,6–10] especially the conjugate addition reaction which has received the most attention[1] and is the subject of this discussion.

## 1.4.2 MECHANISTIC CONSIDERATIONS

Diorganocuprates such as dimethylcopperlithium are routinely written as $R_2CuLi$ (R = Me), but this is simply a stoichiometric representation of the reagent and is not indicative of its actual structure or aggregation state. Common structural probes[11] such as X-ray crystallography have been hampered by difficulties in growing and maintaining a crystal of the cuprate. Although several X-ray structures of cuprate clusters have been reported which indicate a dimeric form,[12,13] characterization of the monomeric complexes $[Cu(DPPE)_2]\,[Cu(C_6H_2Me_3)_2]$[14] and $[Li(THF)_4]\,[Cu(C(SiMe_3)_3)_2]$[15] have also been noted. Discrepancies concerning the nature of bonding between copper, lithium and the alkyl group further complicate the issue.[12,16,17] An unequivocal picture of the structure and aggregation state of organocuprates does not exist.

Two general mechanisms are considered for the conjugate addition of organocuprates: (i) an electron-transfer process[9] or (ii) direct nucleophilic addition.[18] Both mechanisms are seen as proceeding through an oxidative addition to give a $Cu^{III}$ species,[19] followed by reductive elimination. There is, however, no direct evidence for the $Cu^{III}$ intermediate, and the direct transfer of the alkyl group cannot be ruled out. Attempts to discover free radicals in the conjugate addition have failed,[20–22] and the two mechanistic schemes differ only in the sequence or mode by which the oxidative addition occurs (Scheme 1).

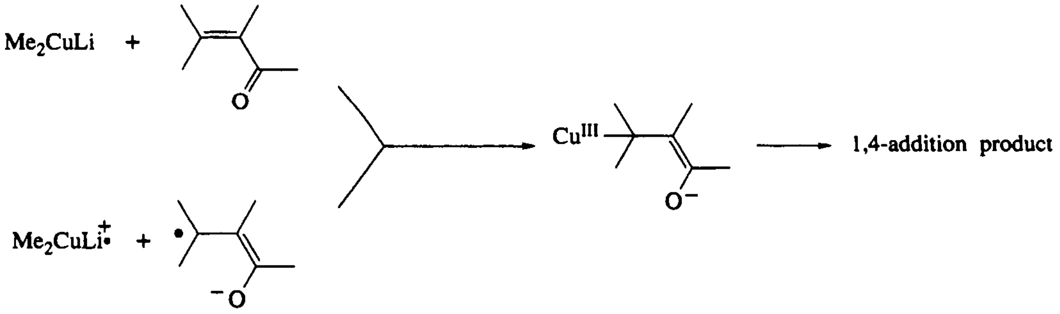

Scheme 1

Support for the electron-transfer pathway has been reported[9,23] where a strong correlation was found between the reactivity of enones toward conjugate addition of cuprates and their one-electron polarographic reduction potential. However, the one-electron electrochemical oxidation of cuprates has not been observed polarographically.[24] Critics of the electron-transfer mechanism have argued that the reduction potential of an enone is simply a measure of electron affinity, which would correlate with both a one-electron (electron-transfer) and/or two-electron (nucleophilic addition) process.[18] In countering this argument House has pointed out that there is no obvious correlation between the reduction potentials of enones and reactivity in the Michael addition, and that β-substituents play a major role in carbanion conjugate addition.[9]

Further support for the electron-transfer argument was seen in the reaction of the γ-acetoxy enone (**1**) and $Me_2CuLi$.[25] This compound underwent elimination of acetoxy while reaction of the tetrahydropyranyl analog (**2**), with $Me_2CuLi$, resulted in the conjugate addition product (Scheme 2).[25] These results have been interpreted as arising from an electron-transfer step, which produces a radical anion intermediate that can undergo either a 1,2-elimination if the leaving group is good (*i.e.* acetoxy), or continue down the conjugate addition pathway if the leaving group is poor.

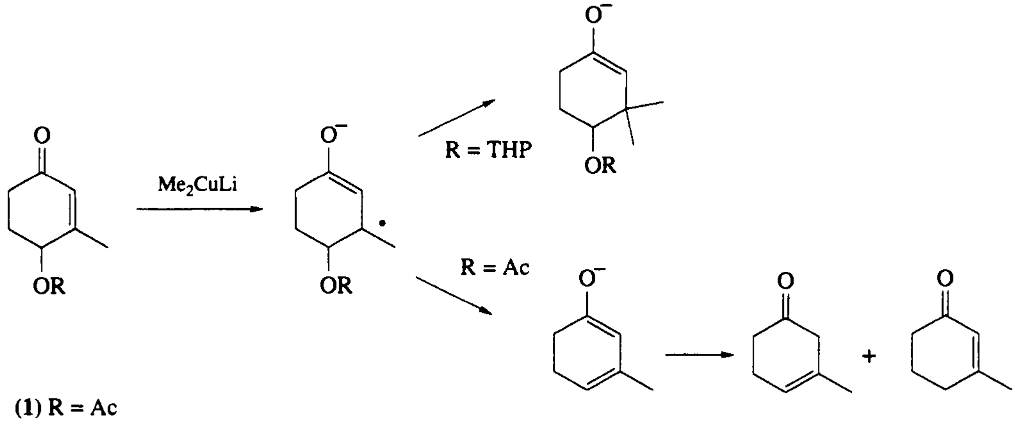

(**1**) R = Ac
(**2**) R = THP

Scheme 2

Two spectroscopic investigations support an enone–cuprate complex as an early intermediate in the conjugate addition mechanism. When cinnamate esters were treated with $Me_2CuLi$ at temperatures where conjugate addition is slow (–70 °C), shifts in both the $^{13}C$ and $^{1}H$ signals of the π-system were observed.[26,27] An alkene–copper π-complex was proposed as an explanation. In a separate account, stopped flow spectroscopy was utilized to identify an intermediate complex in reactions of enones with $Me_2CuLi$.[28] The data were consistent with equilibrium formation of an intermediate alkene–copper complex which unimolecularly rearranges to a $Cu^{III}$ intermediate (Scheme 3). Reductive elimination gives the β-alkylated ketone. Further evidence of an intermediate alkene–copper complex arose from the study of the reaction of the bicyclic enone (**3**) with $Me_2CuLi$. (Scheme 4).[29] It was reported that an ether solution of the two reagents gave a yellow precipitate, which was collected by centrifugation. The precipitate was then shown to be transformed into the β-substituted product by the addition of THF and TMS-Cl. This is the first example of an isolated complex, presumed to be a cuprate–enone complex, which was later converted to the conjugate addition product. An equilibrium between the *cis* and *trans* complexes, (**4**) and (**5**), was proposed to explain the observed isomeric mixture. In a THF solution, the *trans* complex (copper and oxygen of furan) was assumed to be favored, and was offered as an explanation for the formation of a single isomer.

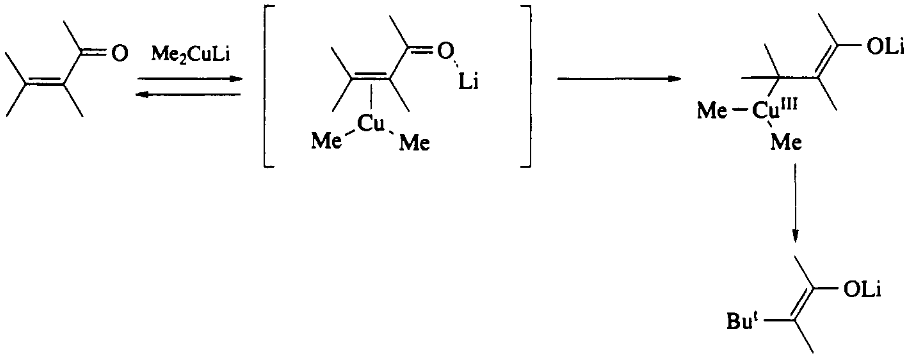

Scheme 3

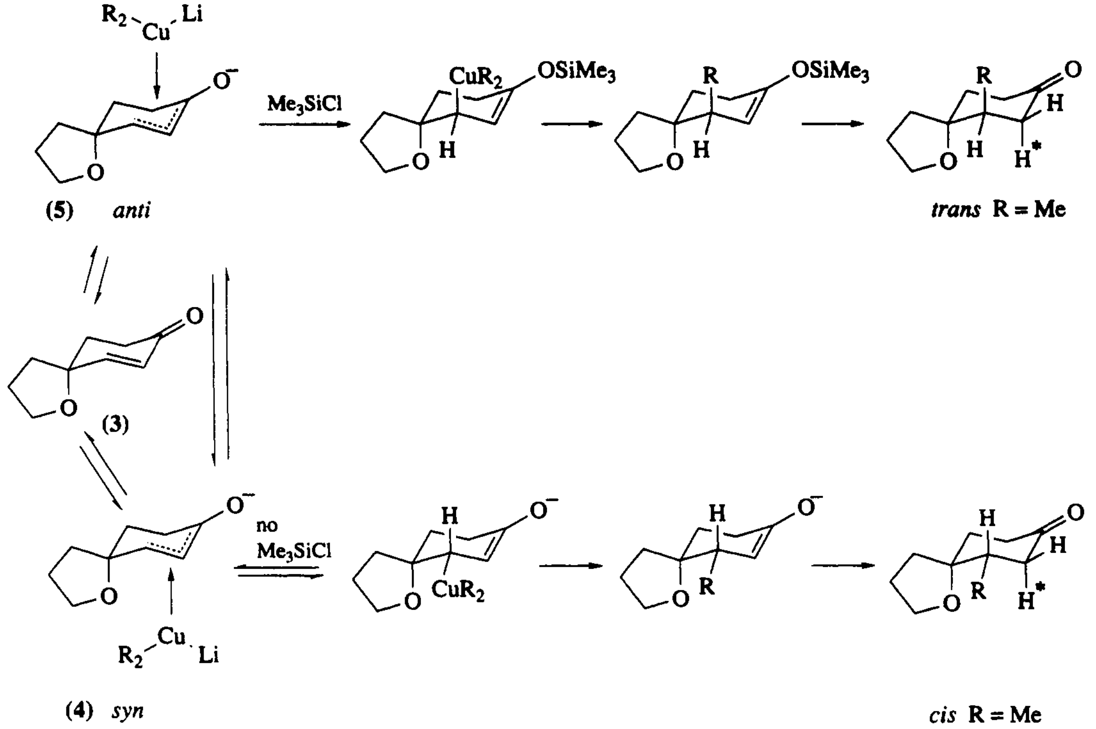

**Scheme 4**

The idea of a reversible alkene–copper complex had been used to explain the enantioselective alkylation of 2-cyclohexenone using a chiral auxilliary ligand.[30] Interaction of the cuprate with the *re* face of C-3 in 2-cyclohexenone was presumed to be favored over complexation with the *si* face of C-3 for steric reasons (equation 4).

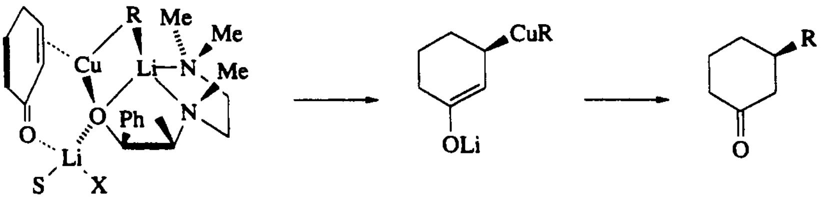
(4)

$X = I^-$ or THF; S = THF; R = Et, $Bu^n$ or $Bu^tOCH_2$

## 1.4.3 STOICHIOMETRIC *VERSUS* CATALYTIC REAGENTS

An impressive feature of the copper-catalyzed reaction of organomagnesium and organolithium compounds is the wide range of conjugate additions achieved. Several reviews have documented these results,[1,31] and the reaction is considered to be catalytic when less than 10 mol % of a copper(I) salt is used. The solubility of the copper(I) salt influences the yield of conjugate addition, with more soluble copper(I) salts giving higher yields. For example, the yield in conjugate addition of isopropylmagnesium bromide to enoate (**6**; equation 5) was found to vary with the copper catalyst: CuCl (29–48%, least soluble); CuBr (46%); CuI (56%). Attempts to solubilize the copper(I) salt led to the use of copper(I) halides complexed with phosphines or sulfides ($Me_2S$), and good success has been achieved with this method.[1,31]

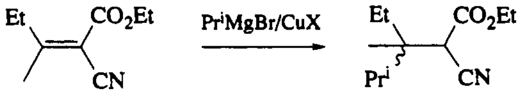
(5)

(**6**)

The order of addition of reagents has a significant impact on the yield of conjugate addition.[1] Commonly the substrate is added to a mixture of the copper(I) salt and the organo-magnesium or -lithium reagent, but inverse addition can often be beneficial (inverse refers to adding the organo-lithium or -magnesium reagent to a mixture of the substrate and copper catalyst). Enoate (**7**), for example,[1] reacts with Bu$^n$MgBr and CuCl to give (**8**) in 42% yield by the normal route and 89% yield by the inverse mode (equation 6).

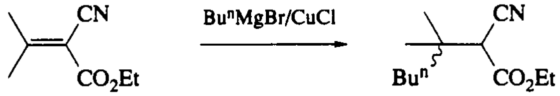

(6)

(**7**) (**8**)

In spite of the good success achieved in catalytic organocopper reactions, recent developments have emphasized the stoichiometric reagents. Presumably this is due to a greater reproducibility in results, with higher yields and greater stereoselectivity reported.[1,31]

## 1.4.4 VARIATIONS IN THE REAGENT

There is a wide tolerance for variations in the transferable R-group of organocuprates. Many of the early examples involved commercially available or easily synthesized (*i.e.*, methyl, phenyl, butyl) organolithium reagents. Organocuprates are usually formed by the addition of 2 mol equiv. of an RLi to a copper(I) salt, and a commercially available RLi simplifies the process. In spite of the limited variation of R for much of the early work, the methodology became accepted and established in the synthetic community. The deliveries of phenyl, methyl, or benzyl to enone (**9**; equation 7) were all shown to proceed in good yield.[1] Further scope of the methodology was demonstrated with cyclopropyl[32] and alkenyl[33] ligands (the alkenyl stereochemistry is retained).[34] These were also observed to be transferred in high yield as demonstrated by the reaction of 2-cyclohexenone with $R_2CuLi$ (equation 8).

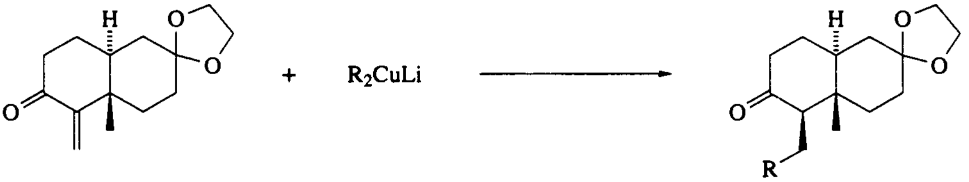

(7)

(**9**) R = Ph, 84%; Me, 68%; $CH_2Ph$, 45%

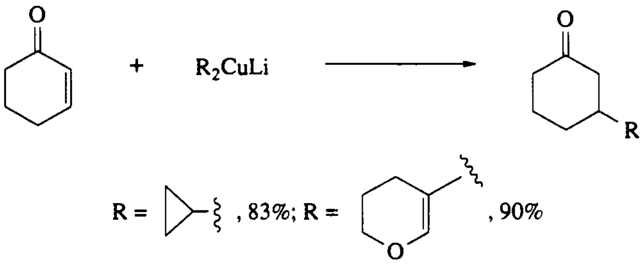

(8)

Interesting and useful variations in R involve more complex alkyllithium reagents. For example, the treatment of β-iodoenone (**10**) with lithium phenylthio(2-vinylcyclopropyl)cuprate gave the conjugate addition product (**11**) as an intermediate *en route* to the bicyclic dienone (**12**; 82%; equation 9).[35] The ability of a cuprate to deliver a functionalized group to the enone was a definite advantage in this synthetic scheme.

Heteroatoms were also tolerated in the cuprate, as demonstrated by the reaction of methyl vinyl ketone with (**13**; equation 10).[36] A good yield of the conjugate addition product was reported (85%), without evidence of competing side reactions.

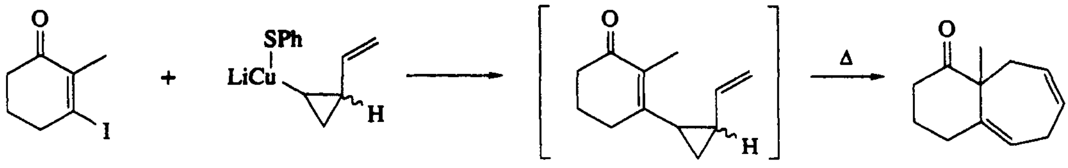

**(10)** **(11)** **(12)**

(9)

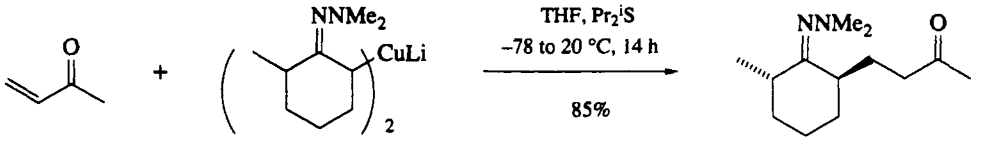

**(13)**

(10)

In a special example of the tolerance of R, Seyferth and Hui described a procedure for the direct nucleophilic β-acylation of α,β-unsaturated carbonyl compounds by the combination of CO with higher order organocuprates (formed from 2RLi and CuCN).[37] This methodology was successful with primary, secondary, and tertiary alkyllithium reagents, producing high yields of the corresponding β-acylated ketones (equation 11). Surprisingly, the methodology was not successful when primary alkyls and the traditional lower order reagents were examined.[38] Conjugate addition without acylation was found to occur. These cases necessitated use of the higher order cuprates to obtain the desired acylated product (equation 12).

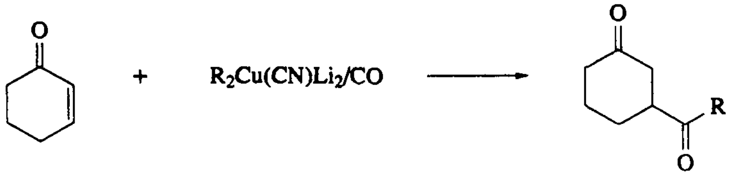

(11)

R = Bu$^n$, 86%; R = Bu$^s$, 75%; R = Bu$^t$, 78%

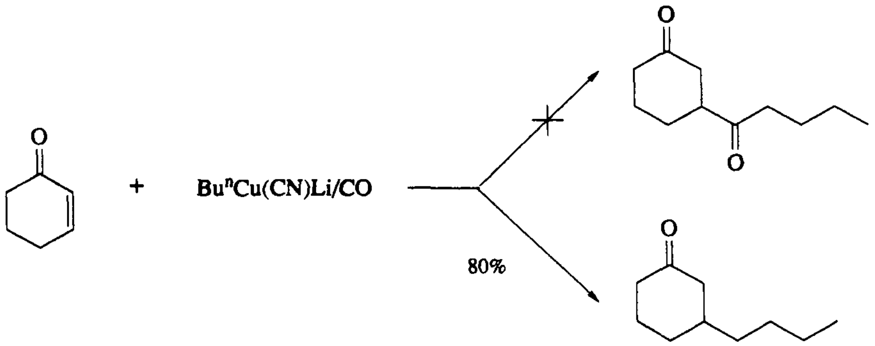

(12)

Although a similar methodology was reported earlier,[39] in which an excess of the 1:1 RLi/Ni(CO)$_4$ reagent was used, the organocuprate method is advantageous in that it avoids use of the highly toxic Ni(CO)$_4$.

Triorganotin groups can also be transferred from the cuprate. β-Iodoenones are transformed into β-trimethylstannylenones by reaction of a cuprate prepared from Me$_3$SnLi and PhSCu (equation 13).[40]

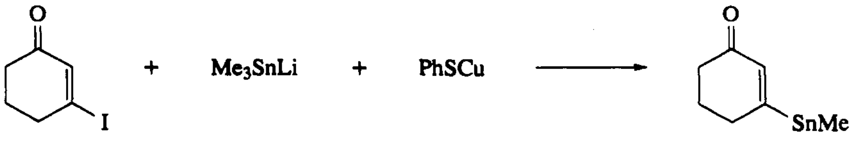

(13)

The direct formation of functionalized organocuprates by oxidative addition of activated zerovalent copper, prepared from the lithium naphthalide reduction of $\mathrm{CuIPR_3}$ complexes, into carbon–halogen bonds was found to be a mild method for the generation of cuprates.[41] Since formation of the cuprate by this method does not involve prior formation of an organolithium species, the range of R can be expanded to include functional groups which are sensitive to these highly basic reagents (equation 14). To date, organocuprates containing ester, nitrile, and chloride functionalities have been prepared directly from the corresponding alkyl bromide.[41]

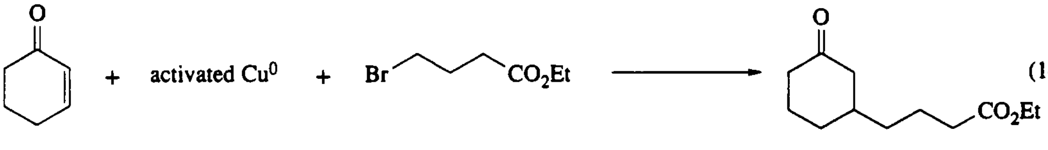

(14)

Similarly compatible are organozinc compounds, RCu(CN)ZnI, which are formed under mild conditions.[42] The organozinc compounds were prepared from the corresponding primary and secondary iodides by treatment with zinc (activated by treatment with 4 mol % of 1,2-dibromoethane and 3 mol % TMS-Cl). Formation of the cuprate follows by addition of the soluble copper salt CuCN–2LiX (X = Cl, Br) to the zinc organometallic (equation 15). Functional groups such as ester and nitrile are stable to this reagent and the presence of TMS-Cl is necessary for the conjugate addition reaction to occur (equation 16).

$$\mathrm{RI}\ \xrightarrow[\text{THF, 25–40 °C, 4–12 h}]{\text{activated Zn}}\ \mathrm{RZnI}\ \xrightarrow[0\ \text{°C, 10 min}]{\text{CuCN–2LiX}}\ \mathrm{RCu(CN)ZnI} \qquad (15)$$

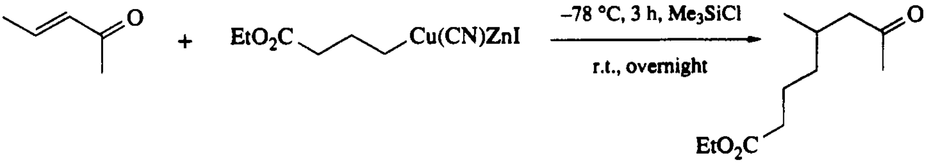

(16)

A novel mode of formation of higher order cuprates has been reported *via* transmetallation between the cuprate and a vinylstannane.[43] Since vinyltin reagents are prepared directly from alkynes, a vinyllithium intermediate is bypassed. The mixed higher order cuprate is formed from the admixture of $\mathrm{Me_2Cu(CN)Li_2}$ and a vinylstannane (equation 17). The exchange is quantitative, and is suggested to be driven by the preferential release of a vinyl group from tin.[43,44] The transfer of vinyl over methyl from the cuprate was highly selective, and the generality of the method was demonstrated with several substrates (equation 18).

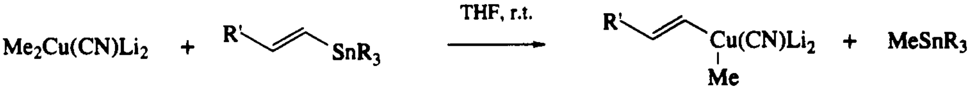

(17)

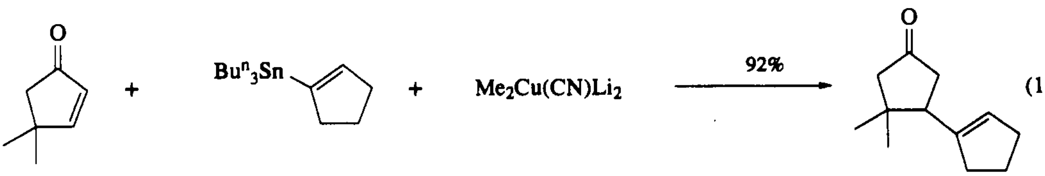

(18)

## 1.4.5 NONTRANSFERABLE LIGANDS

The preparation of traditional organocuprates such as $\mathrm{R_2CuLi}$ necessitates use of 2 mol equiv. of an RLi and 1 mol equiv. of a copper(I) salt. In the normal course of reaction only 1 equiv. of R is consumed in transfer, thereby leaving 1 equiv. unused in the form of RCu. Generally the second equivalent is lost in work-up as the product of reduction, RH. With respect to the R-group, the maximum efficiency for this process can only be 50%. If the RLi is commercially available (*e.g.* butyl, methyl, phenyl, vinyl), then this issue is usually not of concern. However, when one considers an organolithium which is not readily available, such as the chiral vinyllithium intermediate used by Corey *en route* to aplasmomycin,[45] the concept of ligand conservation becomes significant (equation 19). Rarely has an effort been made to recover the reduced ligand RH, but considerable attention has been given to the pursuit of a convenient nontransferable ligand $R_R$ for the cuprate.

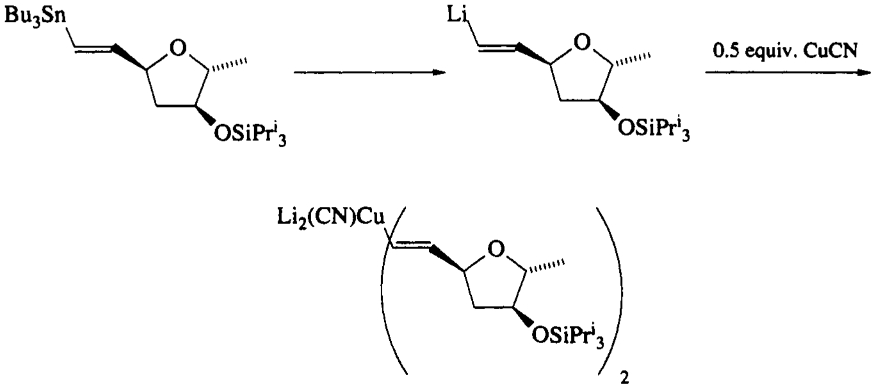

(19)

Various R-groups differ in their ease of transfer from copper. For example, reaction of the mixed cuprate $Bu^n(Ph)CuLi$ with methyl vinyl ketone gave a 89:11 ratio of $Bu^n$ to Ph transfer.[46] An improvement in the ratio of the transferable ligand, $R_T$, to the residual ligand, $R_R$, was realized by use of 1-pentynyllithium as $R_R$ which led to a >97:3 ratio of *n*-butyl to 1-pentynyl transfer (equation 20).[46] An improved version of the alkyne scheme, which avoids the solubility problems associated with pentynylcopper, was reported[47] using 3-methyl-3-methoxy-1-butynyllithium as $R_R$. In spite of the many practical applications of alkynes as $R_R$ ligands in organocuprates, they have been hampered by the lower reactivity which they impart to the reagent. As Whitesides has pointed out, 'The reactivity of organometallic groups in mixed cuprates is qualitatively intermediate between the reactivity of the constituent components'.[46]

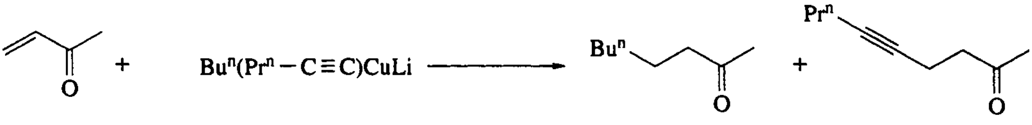

(20)

>97:3

The commercial availability of copper(I) cyanide has also provided an attractive alternative to the *in situ* preparation of copper alkynides, as cyanide functions very well as a nontransferable ligand (equation 21).[48] Unfortunately, the cyanocuprates (**14**) suffer from a diminished reactivity, similar to alkynylcuprates, and have not been widely used.[3] Other useful residual ligands are SPh,[49] $Bu^tS$,[49] and $Bu^tO$.[49]

$$\text{RLi} \quad + \quad \text{CuCN} \longrightarrow \underset{\textbf{(14)}}{\text{RCu(CN)Li}} \qquad (21)$$

The low reactivity associated with cyanocuprates was solved by introduction of the higher order reagents $R_2Cu(CN)Li_2$.[3,4] A dramatic increase in reactivity over the lower order organocuprates, RCu(CN)Li, was observed in applications of these reagents, but the higher order reagents are also subject to the same problem of selective ligand transfer. A satisfactory solution is the use of 2-lithiothiophene as the nontransferable ligand (equation 22).[50,51] A stoichiometric amount of reagent is generally required and good reactivity is observed with most substrates. For example, the transfer of phenyl, which is normally slow, is completely selective from the mixed thienylcuprate (**15**; equation 23). The high selectivity of ligand transfer[52] was attributed to stabilizing *d*–π* and *d*–*d* backbonding between copper and the thiophene ligand. That stabilizing interaction is also possible in $Me(Ph)Cu(CN)Li_2$, but phenyl transfer was observed.[53] The 2-furyl ligand couples smoothly with various substrates[54] which suggests that sulfur plays a key role in the selective retention of thiophene. This reagent combination has met with such success that (2-thienyl)Cu(CN)Li (**16**) is now commercially available.[55] To form the active reagent, all that is required is the addition of 1 mol equiv. of $R_T$ to (**16**).

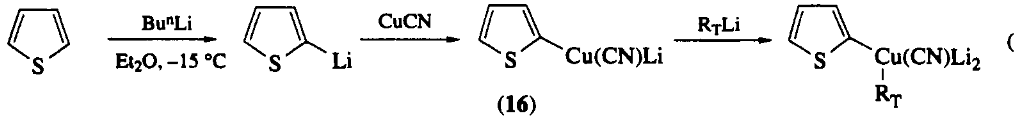
(22)

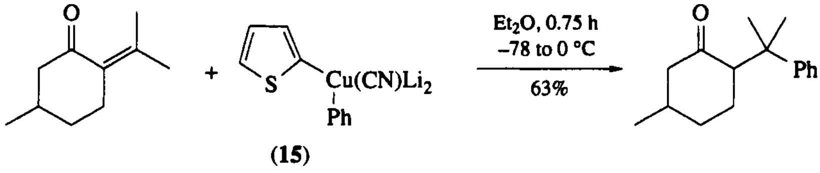
(23)

An unusual result was noted with this reagent. If steric demands are pushed to a severe level, then 1,2-addition of the thienyl group is observed.[50] The reasons are not clear, but a solution to the problem is the addition of $BF_3{\cdot}Et_2O$ to the reagent.[56]

Another class of sulfur-containing residual ligands utilized the dimethyl sulfoxide anion as the $R_RLi$ (Table 1).[57] While the procedure is simple and general, 2 mol equiv. of the reagent and/or the addition of $BF_3{\cdot}Et_2O$ is necessary to obtain a good yield of β-alkylated product. Increased yields were obtained when the dimethyl sulfoxide anion was used in conjunction with the higher order cyanocuprate.[57] For example, the β-alkylation of enone (17) occurred in 95% yield with the higher order reagent and in 78% yield with the lower order cuprate. If only a single mole equivalent of reagent was used, then the disparity in yield was even greater; 22% for the lower order, and 67% for the higher order reagent (Table 1).

**Table 1** Reaction of Isophorone (17) with Various Organometallic Reagents

| *Reagent* | *Product yield (%)* |
|---|---|
| 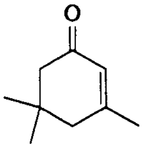<br>(17) | 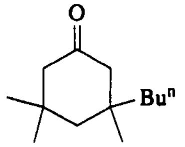 |
| $Li(MeSOCH_2)Cu(Bu^n)$ | 22 (1 equiv.)<br>78 (2.3 equiv.) |
| $Li(MeSOCH_2)Cu(CN)(Bu^n)$ | 67 (1 equiv.)<br>95 (2 equiv.) |
| $Bu^n(Ph_2P)CuLi$ | 75–88 |
| $Bu^n(Cy_2N)CuLi$ | 29 |
| $Bu^nCu/LiI/5$ equiv. $Bu^n{}_3P$ | 80–100 |

Cuprates based upon diphenylphosphidocopper(I) and dicyclohexylamidocopper(I) as $R_RCu$ have also been introduced in the literature.[58] Addition of a mole equivalent of $R_TLi$ is necessary to form the active reagents $R_T(Ph_2P)CuLi$ and $R_T(Cy_2N)CuLi$ respectively. These cuprates are reported to show enhanced thermal stability, and display a moderate reactivity with enones, but have not yet seen widespread use (Table 1). The handling and preparation of $^-PPh_2$ may detract from their appeal, and there is no clear advantage in reactivity over the reagents discussed above.

Phosphine-complexed cuprates, formed from copper(I) iodide, 1 mol equiv. of $R_TLi$, and 2–5 mol equiv. of tri-*n*-butylphosphine, show good reactivity in conjugate addition reactions with enones (Table 1).[59] The hazards surrounding the use of excess $Bu^n{}_3P$, and the availability of other methodologies lower the popularity of this method, but efficiency can be realized with this methodology.

### 1.4.6 SOLVENT EFFECTS

Good general success is observed with diethyl ether as solvent[1] for the reaction of $Me_2CuLi$, and other cuprates, with α,β-unsaturated carbonyl compounds. Many other solvents have been examined with variable success,[23,60] including tetrahydrofuran (THF), pyridine, acetonitrile, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). Additives such as hexamethylphosphoramide (HMPA) and dimethyl sulfide are also common.[23] Generally these solvents are analyzed with regard to their ability as donor ligands (*e.g.* HMPA is a good donor) and it is recognized that while good donor solvents enhance reaction rates of cuprates with alkyl halides, they generally retard or inhibit the reaction of cuprates with enones.[23,49,61] The effect can be dramatic as demonstrated by the reaction of isophorone with the higher order vinylcuprate (equation 24), and of the higher order phenyl reagent with enone (**18**; equation 25).[62]

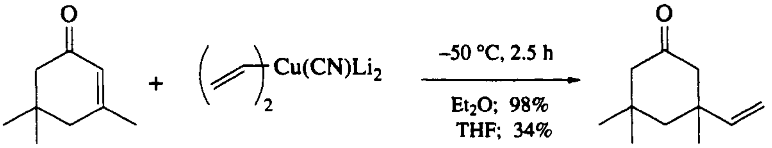

(24)

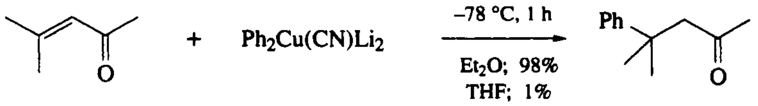

**(18)**

(25)

The inhibiting effects of THF (or other donor solvents) can often be used to advantage.[3] When a highly reactive enone such as 2-cyclopentenone is treated with $(vinyl)_2Cu(CN)Li_2$ in $Et_2O$, the yield is *ca.* 80%, while in THF the reaction is slower and more selective, giving the product in 90% yield. The chemoselectivity of organocuprates can be controlled by the choice of reaction medium (Scheme 5).[63] When bromoenone (**19**) was treated with $Me_2CuLi$ in a $Et_2O–Me_2S$ solution, the conjugate addition product (**20**) formed. Indeed this was not surprising as conjugate addition reactions of cuprates often proceed at a rate much faster than the displacement reaction of alkyl halides. However, when HMPA was included in the solvent mixture, the selectivity reversed and the methylated enone (**21**) was formed without a trace of the conjugate addition product.

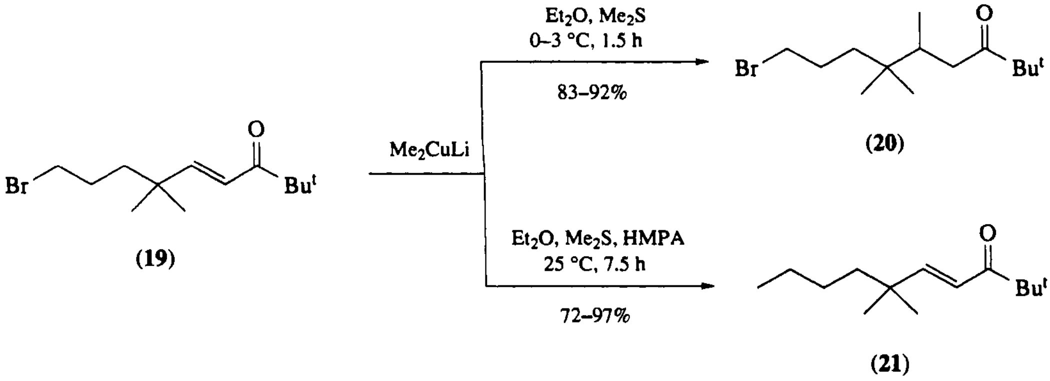

**(19)** **(20)** **(21)**

**Scheme 5**

Donor solvents might participate in at least two ways: complexation with $Li^+$, from LiI or LiBr; or complexation to the cuprate itself. Equal amounts of conjugate addition products were formed from the reaction of an enone with an $Et_2O$ solution of $Me_2CuLi$ + LiBr, or from an $Et_2O$ solution of $Me_2CuLi$ from which 95% of the LiBr had been removed. It was concluded that a good donor ligand would compete with the enone for coordination sites on the cuprate, and thus reduce the concentration of an enone–cuprate complex (a prerequisite for reaction in House's mechanism). A similar conclusion was reached in a separate study where fast conjugate addition reactions in hydrocarbon solvents (dichloromethane and $Et_2O$) were observed, while the rates were retarded in better coordinating solvents (THF, pyridine, acetonitrile).[60]

## 1.4.7 LEWIS ACID EFFECTS

Although organocuprates have seen great success as reagents for conjugate addition reactions, there are substrates encountered for which reagent reactivity is not sufficient. Poor results are often obtained in the reaction of cuprates with β,β-disubstituted acrylic esters, α,β-unsaturated nitriles, highly hindered enones, and α,β-unsaturated carboxylic acids. The reactivity can be increased by redesigning the reagent (*e.g.* higher order *versus* lower order cuprates), or by an additive such as a Lewis acid.[5] The additive must be chosen carefully to avoid direct reaction with the cuprate.

Good success has been reported with $BF_3{\cdot}Et_2O$. The combination of an organocopper species and $BF_3{\cdot}Et_2O$ gave a new complex,[64] $RCu{\cdot}BF_3$, which was far superior to RCu in its reactivity profile, and in many instances was also superior to $R_2CuLi$ (equation 26).[5] There are many other examples of Lewis acid activation in the literature, with the details discussed in Volume 1, Chapter 1.12 and Volume 4, Chapter 1.3.

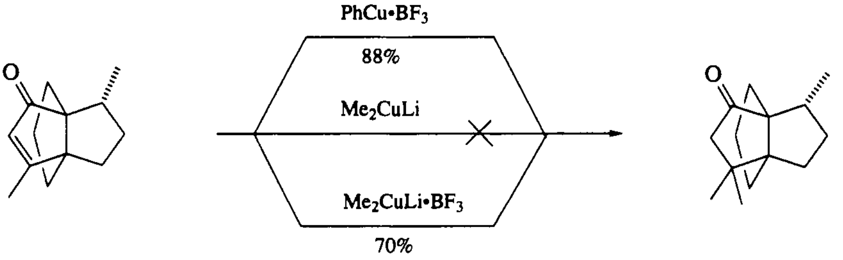

(26)

## 1.4.8 THE α,β-UNSATURATED CARBONYL COMPOUND AS A SUBSTRATE

### 1.4.8.1 γ-Alkoxy-α,β-unsaturated Ketones

The reaction of organocuprates with enones is often described as being generally applicable and easily carried out. With reactive enones such as cyclopentenone, cyclohexenone, or similar acyclic enones, this is the case; it is difficult to find an organocuprate which will not add effectively to these substrates. However, there are many enone substrates for which little or no organocuprate conjugate addition occurs. For example, the reaction of γ-acetoxy-α,β-unsaturated ketones with cuprates results in reduction of acetoxy (*vide supra*) and not conjugate addition. Although this example provided some interesting mechanistic data, the class of substrates has potential synthetic application and a methodology to allow β-alkylation without reduction would be of value. Such a methodology was realized with the alkylcopper·$AlCl_3$ system (Scheme 6).[65] Use of 5–7 mol equiv. of an equimolar mixture of methylcopper and aluminum trichloride, in ether, was found to produce good yields of the conjugate addition product with no indication of reduction. The methodology was also found to be general, and was demonstrated with several substrates.

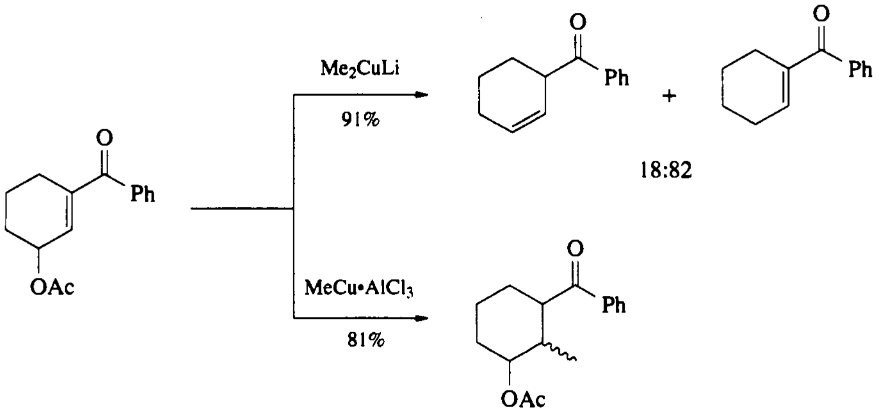

Scheme 6

### 1.4.8.2 β-Cyclopropyl-α,β-unsaturated Ketones

β-Cyclopropyl-α,β-unsaturated ketones are another class of compounds for which simple conjugate addition is not the major pathway in reaction with conventional cuprates such as $R_2CuLi$. Generally a mixture of conjugate addition and cyclopropane ring-opened products are formed. When either geometrical or steric constraints cause the cyclopropyl group to be approximately perpendicular to the plane of the enone, the ring-opening reaction may dominate.[66] Again, use of an $RCu{\cdot}AlCl_3$ combination disfavors the process characteristic of electron transfer (ring opening) and the conjugate addition product appears in high yield (equation 27).[67] A marked increase in reactivity of $MeCu{\cdot}AlCl_3$ over $Me_2CuLi$ was also noted. $Me_2CuLi$ was found to be unreactive with the bicyclic enone (**22**) at –70 to –25 °C while the $MeCu{\cdot}AlCl_3$ complex readily underwent conjugate addition to give β-alkylated product in high yield (Scheme 7).

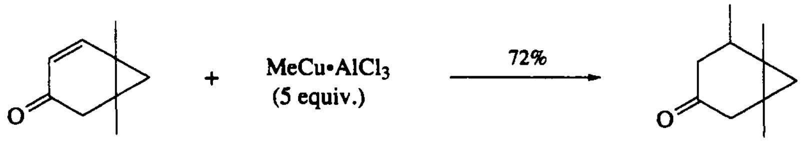

(27)

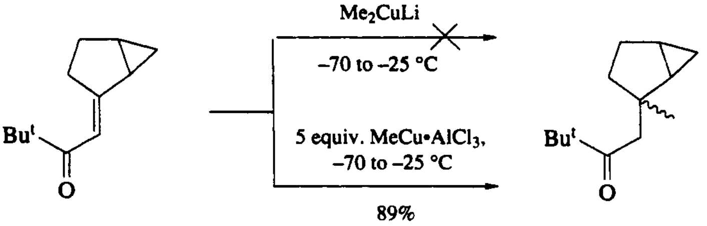

Scheme 7

### 1.4.8.3 β-Substituted-α,β-unsaturated Ketones

The simple substrates which are often chosen to demonstrate new methodologies often give an incomplete picture of the reactivity profile of the reagents. It is the more difficult cases which highlight the similarities and differences among cuprates. Enones which are either β,β-disubstituted or sterically congested may be troublesome in conjugate addition reactions. Treatment of isophorone (Scheme 8) with $(vinyl)_2CuLi{\cdot}Bu^n{}_3P$ (0 °C, 1 h) led to the conjugate addition product in 60% yield.[68] The higher order reagent $(vinyl)_2Cu(CN)Li_2$ gave the same product (–50 °C, 2.5 h) in 98% yield without the need for $Bu^n{}_3P$, and at a reaction temperature which was 50 °C lower.[62] Vinyldicyclohexylamido- and vinyldiphenylphosphido-cuprates were found to be similar to or less reactive than $R_2CuLi$, and both gave lower yields of the 1,4-addition product with isophorone compared to the higher order reagent (Scheme 8).[58a]

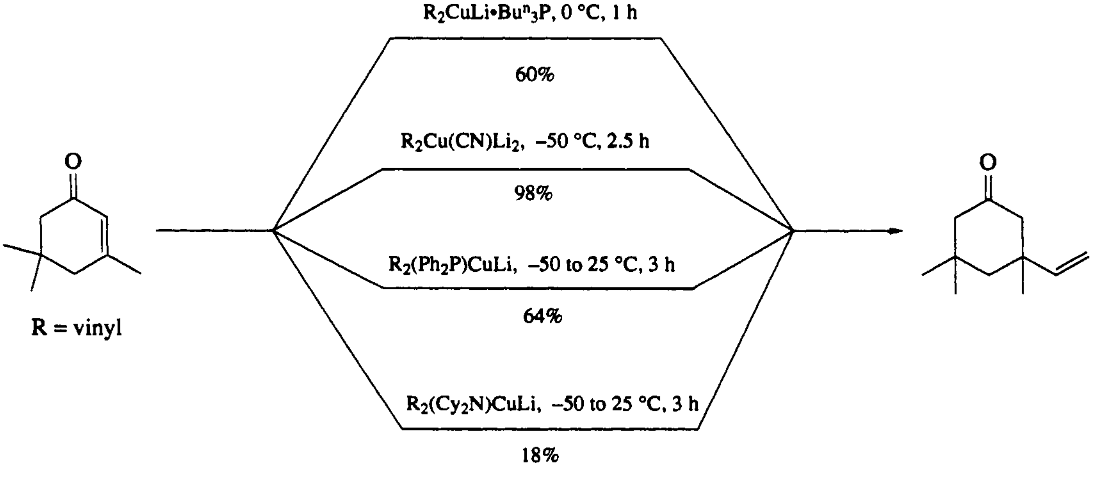
R2CuLi•Bun3P, 0 °C, 1 h
60%
R2Cu(CN)Li2, –50 °C, 2.5 h
98%
R2(Ph2P)CuLi, –50 to 25 °C, 3 h
64%
R2(Cy2N)CuLi, –50 to 25 °C, 3 h
18%
O
O
R = vinyl

Scheme 8

### 1.4.8.4 Polycyclic α,β-Unsaturated Carbonyl Compounds

Bicyclic or polycyclic enones may give slow or inefficient reaction with organocuprates. In particular, it is those enones which contain substituents arranged so as to create a steric hindrance on the carbon β to the carbonyl that see the greatest effect. The yields are often low to moderate, unless additional activation is provided. For example, when the bicyclic enone (**23**) was treated with $R_2CuLi$ (R = 3-pentynyl), the β-substituted product was formed in only 46% yield,[69] while exposure of the same enone to $RCu{\cdot}BF_3$ (R = 3-pentynyl) gave the same β-alkylated product in 76% yield (Scheme 9).[70]

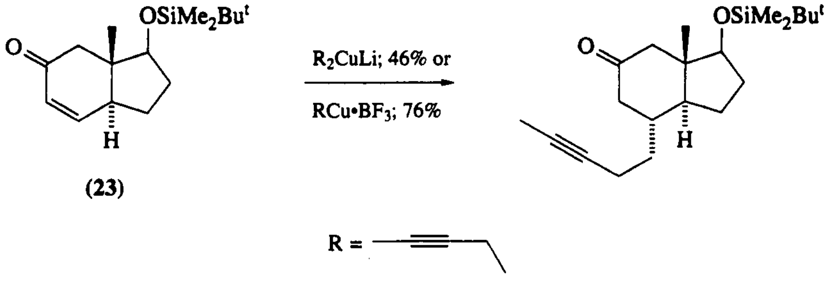

**Scheme 9**

In many cases a Lewis acid has been added to a cuprate to enhance its reactivity with an enone, but there are also examples for which the Lewis acid–organocopper reagents do not work well, (Scheme 10). Reaction of the bicyclic enonate (**24**) with $Me_2CuLi$ led to smooth conjugate addition,[71] but the use of either $Me_2CuLi{\cdot}BF_3$ or $MeCu{\cdot}BF_3$ resulted in formation of a dark resinous material. It is often difficult to predict when the reaction will go astray, but it should be recognized that a Lewis acid–cuprate complex is not always an effective solution to a reactivity problem.

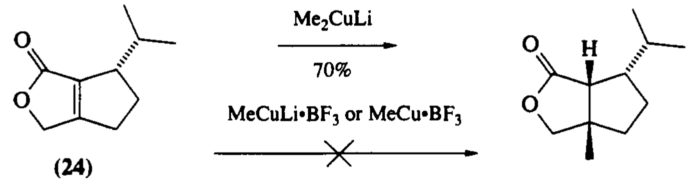

**Scheme 10**

### 1.4.8.5 Polyalkenic α,β-Unsaturated Carbonyl Compounds

The conjugate addition of organocopper reagents to polyalkenic carbonyl compounds presents an opportunity in which either 1,4-, 1,6- and sometimes 1,8-addition can occur. Much of the early work in this area was conducted in the study of the reaction of a dienoate or dienone with an alkylcuprate or a catalytic copper/organomagnesium combination. The predominant mode of addition for the reaction of a dienoate and a copper-based organomagnesium reagent was found to be 1,6 not 1,4.[72] If the opportunity of 1,8-addition was present, then this mode prevailed.[73] However, a truly systematic study has not been carried out with the various reagents.

The reaction of a conjugated dienone and a catalytic copper/organomagnesium reagent produced a mixture of 1,2-, 1,4-, and 1,6-addition products.[1,74] In contrast, the stoichiometric cuprates showed a marked preference for 1,6- over 1,4-addition (equation 28).[1,75] However, both reagents are sensitive to steric demands, and the selectivity is often affected (Scheme 11).[1]

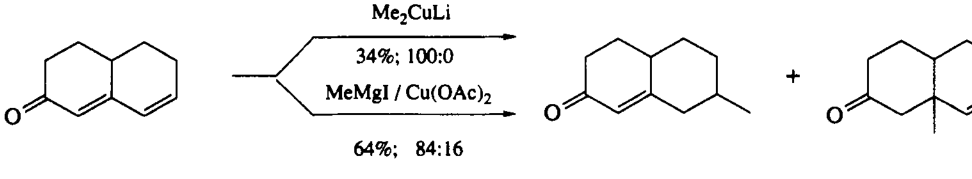

(28)

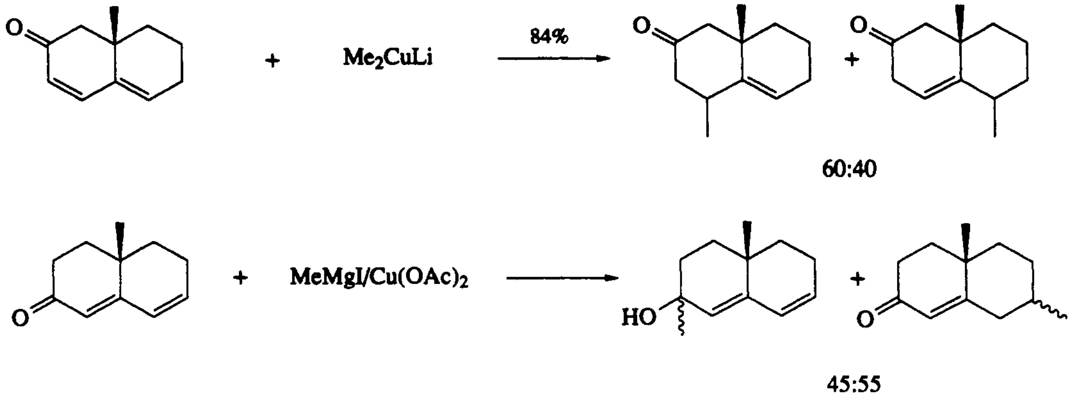
+
$Me_2CuLi$
84%
+
60:40
+
$MeMgI/Cu(OAc)_2$
HO
+
45:55

**Scheme 11**

An interesting competition experiment was conducted on the steroid trienone (**25**), where the possibility for conjugate addition existed in three separate sites in the same molecule, C-1, C-5, and C-7 (equation 29). The catalytic reagent, MeMgI/CuI, gave only addition at C-1.[76]

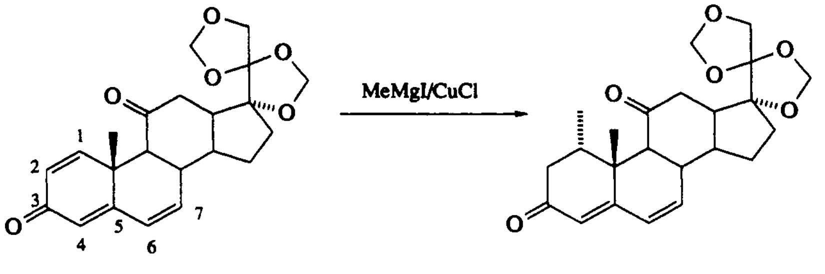
MeMgI/CuCl
1
2
3
4
5
6
7

(29)

**(25)**

With Lewis acid–organocopper complexes, the question of chemoselectivity in polyalkenic carbonyl systems was further investigated. The reaction of $BuCu{\cdot}BF_3$ with dienoate (**26**) led to selective 1,4-addition.[64a] This result was in contrast with the diorganocuprate, where 1,6-addition was reported (equation 30).[64c]

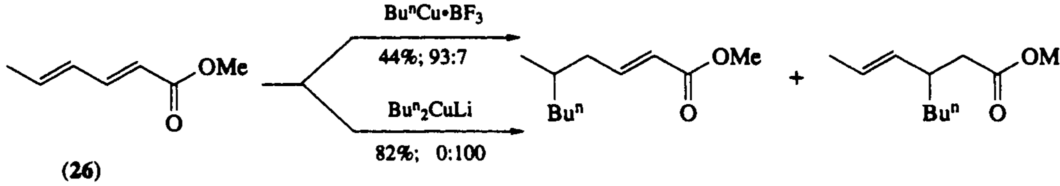
OMe
$Bu^nCu{\cdot}BF_3$
44%; 93:7
$Bu^n{}_2CuLi$
82%; 0:100
OMe
$Bu^n$
+
OMe
$Bu^n$

(30)

**(26)**

The corresponding methyl ketone showed a similar trend[77] but the selectivity was not as high. Use of $Bu^nCu{\cdot}BF_3$ gave 1,4- and 1,6-addition products in a ratio of 60:40, while the diorganocuprate selectivity remained high at 100% 1,6-addition. It was intriguing to see a change in selectivity with $Bu^nCu{\cdot}BF_3$ when the free acid was chosen as substrate (equation 31).[64a,c] The 14:86 ratio of 1,4 to 1,6 was a significant reversal from the 93:7 ratio seen with the ester.

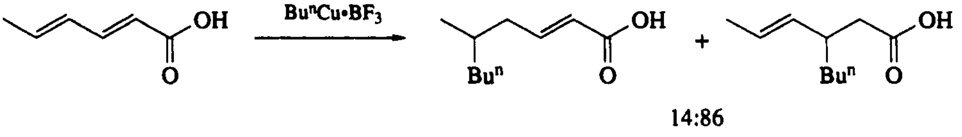
OH
$Bu^nCu{\cdot}BF_3$
OH
$Bu^n$
+
OH
$Bu^n$
14:86

(31)

The conjugate addition of organomagnesium reagents to *N,N*-diethylsorbamide led to only 1,4-addition (equation 32).[78] Yields for the addition were good (35–60%) with alkylmagnesium compounds, and higher with allylic magnesium reagents (60–80%). With organocuprates, only the 1,6-addition was observed, in yields similar to those of the organomagnesium reagents.

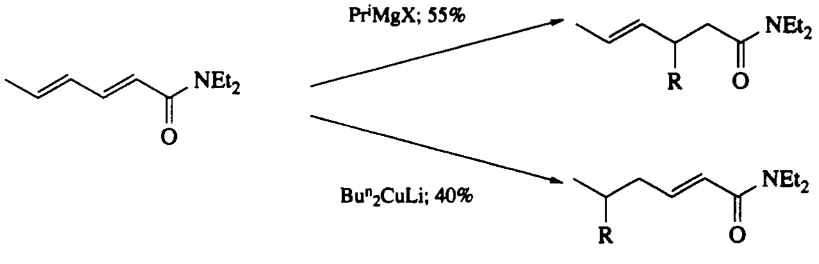

(32)

### 1.4.8.6 α,β-Unsaturated Aldehydes

The first observations of reaction of lithiocuprates with α,β-unsaturated aldehydes indicated 1,2-addition was competing with 1,4-addition to a significant degree.[79] For example, lithium dimethylcuprate adds to enals to give a mixture of 1,2- and 1,4-addition products.[80] More recently, the addition of TMS-Cl to the reaction mixture was found to give the 1,4-addition product in reproducibly high yield (equation 33).[81] Good results were reported with acrolein and β-monosubstituted acroleins; however, lower ratios of 1,4- to 1,2-selectivity were observed with α,β,β-trisubstituted enals. For the more highly substituted enal, $Me_5Cu_3Li_2$ was used in place of $Me_2CuLi$ to improve the conjugate addition selectivity to an acceptable 78:22 ratio (equation 34). Good results with other less-substituted substrates are also reported for this reagent.[80]

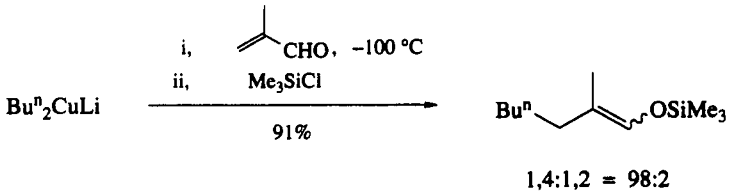

(33)

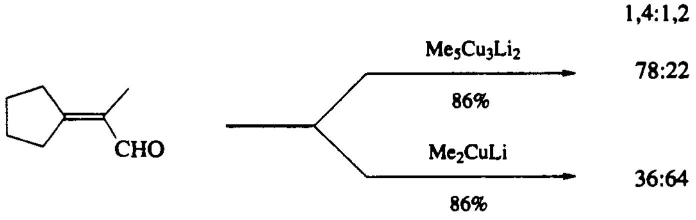

(34)

Significant solvent effects have also been reported for the reaction of organocuprates with enals.[81] Less polar solvents are preferable, and a dramatic difference in the 1,4- to 1,2-selectivity was reported (equation 35).

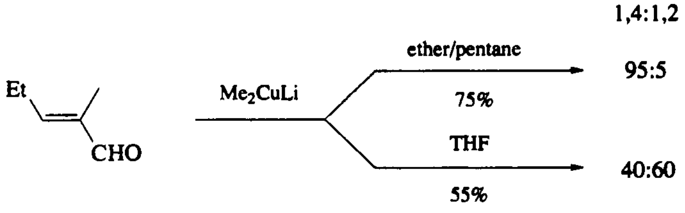

(35)

Cuprates formed from organomagnesium reagents are acceptable reagents for the conjugate addition reaction with α,β-unsaturated aldehydes.[81] However, these cuprates are highly dependent upon the choice of copper(I) salt. With $CuBr{\cdot}Me_2S$, a dramatic increase in 1,4-:1,2-selectivity was reported over

CuBr (equation 36). This result must be taken with caution as the effects of using $CuBr{\cdot}Me_2S$ are not easily generalized.[82]

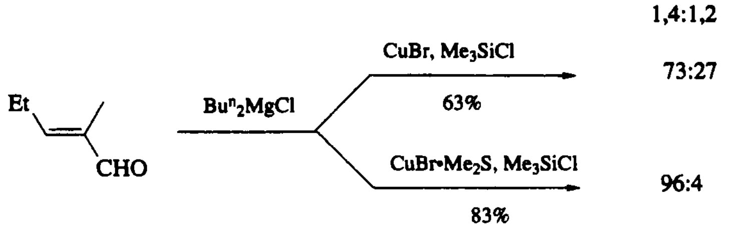

(36)

The direct nucleophilic acylation of enals by organocuprates is also successful.[37,38] With either the lower order $RCuCNLi/CO$ or higher order $R_2CuCNLi_2/CO$ reagents, high yields of the β-acylated product were observed (equation 37). A wide variation in R was also reported to be tolerated. Unfortunately, only β-monosubstituted enals were examined, so the extent to which substitution in the enal can be tolerated has yet to be determined.

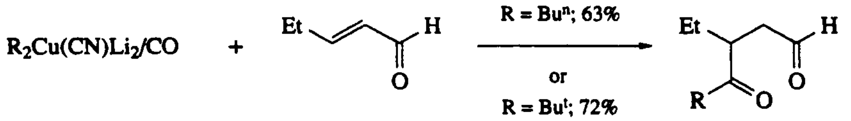

(37)

### 1.4.8.7 α,β-Unsaturated Esters

Relative to the reaction of cuprates with enones, the reaction of organocuprates with enoates has not been extensively studied.[64a,c,83–85] The lack of attention may be related to the unavailability of a reagent which could consistently produce high yields of the 1,4-addition product due to slow reactions and competition from 1,2-addition. Esters of hindered alcohols were prepared and bulky magnesiocuprates were employed, but without general success. An effective solution to this problem was realized with the introduction of $Bu^nCu{\cdot}BF_3$ as a reagent.[64a,b] Enoates with β-mono-, α,β-di-, and β,β-di-substituted structures underwent conjugate addition with this reagent while the corresponding diorganocuprates produced the dialkylation product (1,2- then 1,4-addition to the enone; equation 38). The success of $RCu{\cdot}BF_3$ in the conjugate addition reaction of enoates is well documented,[5] and for enoates such as (27) these appear to be the reagents of choice (equation 39).

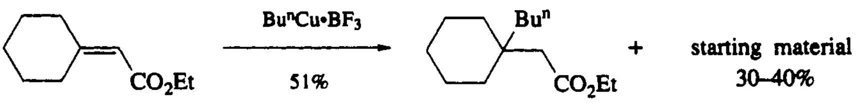

(38)

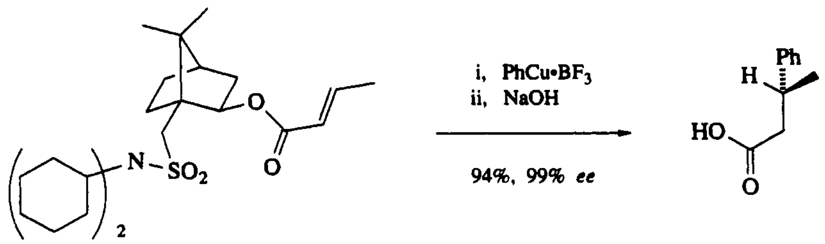

(39)

(27)

Higher order cuprates were also found to be effective in the conjugate addition reaction of α,β-unsaturated esters.[84] Primary alkyl, allyl, phenyl, vinyl, and trialkylsilyl reagents have all been used successfully with β-monosubstituted enoates. An increase in yield of the higher order reagent over the diorganocuprates order was demonstrated by the reaction of ethyl crotonate (equation 40). Under identical conditions, the 1,4-adduct was obtained in 75% yield with the higher order cuprate while the other diorganocuprate could only muster 38%.

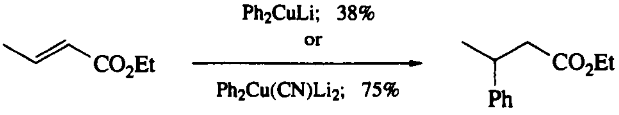

$Ph_2CuLi$; 38%
or
$Ph_2Cu(CN)Li_2$; 75%
$CO_2Et$
$CO_2Et$
Ph

(40)

It was found that with increasing substitution about the enoate, the efficiency of higher order reagents is lower due to competing side reactions. For example, treatment of ethyl tiglate with $Bu^n{}_2CuCNLi_2$ led to formation of a dialkylated ketone from 1,2- then 1,4-addition of the cuprate. Fortunately, we have already seen that good results can be obtained with enoates of this type if $RCu{\cdot}BF_3$ is employed (Scheme 12).

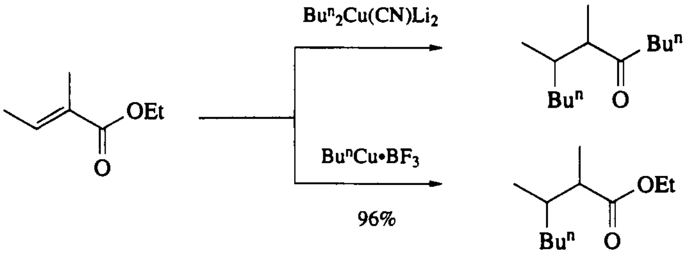

$Bu^n{}_2Cu(CN)Li_2$
$Bu^nCu{\bullet}BF_3$
96%
OEt
O
$Bu^n$
$Bu^n$
O
OEt
$Bu^n$
O

**Scheme 12**

Good chemoselectivity was demonstrated with the higher order reagent in the reaction of epoxy enoate (**28**) with $Bu^n{}_2CuCNLi_2$. Conjugate addition was reported[84] to occur in high yield without disturbing the epoxide (equation 41).

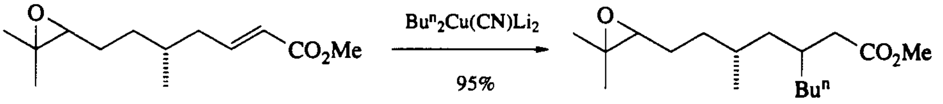

O
$CO_2Me$
$Bu^n{}_2Cu(CN)Li_2$
95%
O
$CO_2Me$
$Bu^n$

(**28**)

(41)

Cuprates derived from copper thiophenoxide and 3 mol equiv. of organomagnesium reagent were also shown to undergo conjugate addition with β-monosubstituted enoates.[86] The large molar excess of RMgX is necessary and ether is the preferred solvent for the reaction (equation 42). The results with disubstituted enoates have not been reported, and should provide a further test of the utility of this reagent.

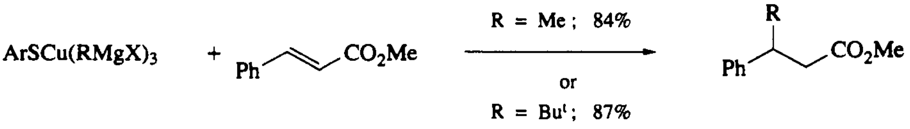

$ArSCu(RMgX)_3$
+
Ph
$CO_2Me$
R = Me ; 84%
or
R = $Bu^t$; 87%
R
Ph
$CO_2Me$

(42)

Ar = Ph, *o*-MeOPh

## 1.4.8.8 α,β-Alkynic Carbonyl Compounds

The conjugate addition of organocopper reagents to α,β-alkynic esters, ketones, aldehydes and acids is a useful method for the preparation of various tri- and tetra-substituted alkenes,[87] although addition to aldehydes is less common.[88] Use of a vinylcuprate results in the formation of a conjugated dienone, which further highlights the importance of this methodology (equation 43).[87]

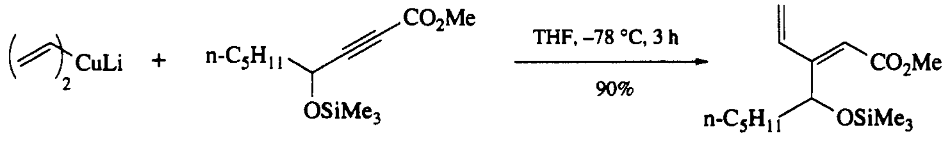

CuLi
2
+
$n\text{-}C_5H_{11}$
$CO_2Me$
$OSiMe_3$
THF, –78 °C, 3 h
90%
$CO_2Me$
$n\text{-}C_5H_{11}$
$OSiMe_3$

(43)

Early work in this area[89,90] established that the conjugate addition of cuprates to alkynic esters, in THF, occurred stereoselectively at –78 °C *via cis* addition. If the reaction is carried out at 0 °C, a mixture of (*E*)- and (*Z*)-isomers results. The change in stereoselectivity at higher temperatures was attributed to configurational equilibration of the copper enolates (**29**) and (**30**; equation 44). Quenching experiments[90,91] confirmed that the equilibration was temperature sensitive (Scheme 13) and also demonstrated that prolonged stirring at room temperature, followed by protonolysis, led to a predominance of the *trans* isomer (**31**). The *trans* configuration is defined according to the relative orientation of the carbonyl and the phenyl group in (**31**). In diethyl ether as solvent,[91] the addition was again *cis*, but the enolates were reported to equilibrate more rapidly (even at −78 °C).

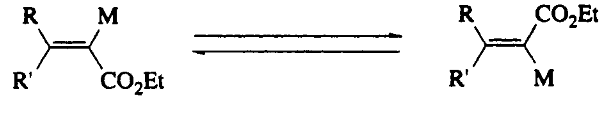

(44)

(**29**) (**30**)

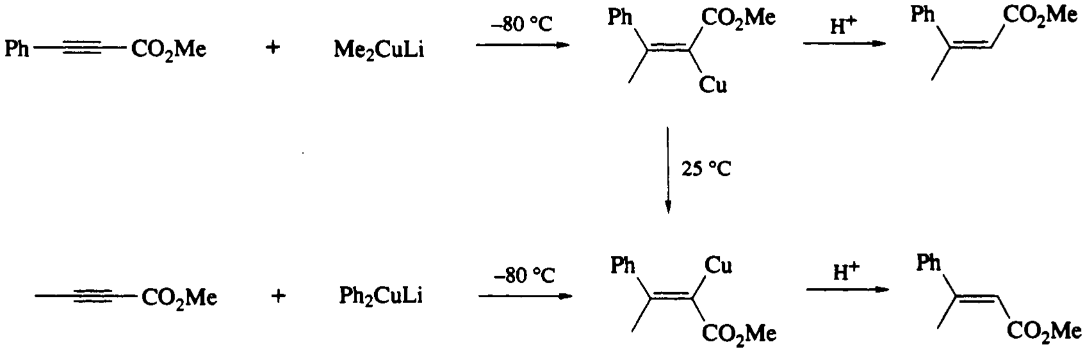

(**31**)

**Scheme 13**

Higher order cuprates have also been used in the addition to alkynic esters with good success. For example, ethyl tetrolate was found to react with $(Me_3Si)_2CuCNLi_2$ selectively to give the (*E*)-alcohol in 90% yield after reduction (equation 45).[92,93] Other organocopper reagents such as $Me_3SiCu{\cdot}Me_2S{\cdot}LiI$ and the cyanocuprate, $Me_3SiCuCNLi$, gave mixtures of (*E*)- and (*Z*)-isomers.[92]

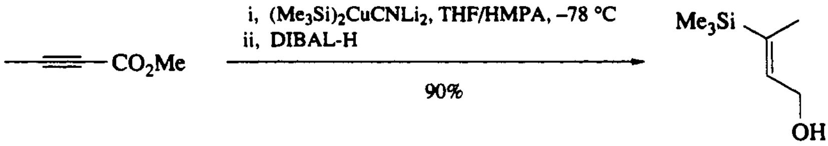

(45)

**Table 2** Reaction of (**32**) with Organocopper Reagents

| *Substrate* | *Reagent* | *Products* | | | *Yield (%)* |
|---|---|---|---|---|---|
| $MeO_2C-\equiv-CO_2Me$<br>(**32**) | | 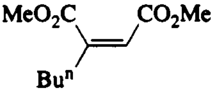 | | 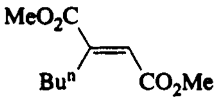 | |
| | $Bu^nCu{\cdot}BEt_3$ | >99 | : | <1 | 93 |
| | $Bu^nCu{\cdot}BF_3$ | 87 | : | 13 | 85 |
| | $Bu^n{}_2CuLi$ | 60 | : | 40 | 98 |
| | $Bu^nCu{\cdot}9\text{-}BBN$ | ~100 | : | 0 | 92 |

Highly stereoselective *cis* additions of organocuprates to alkynic esters have also been reported with alkylcopper–Lewis acid complexes.[5] The choice of the proper Lewis acid was found to be important in determining the stereoselection as was demonstrated with enyne (**32**; Table 2).[5,88] While both the diorganocuprate and the alkylcopper·$BF_3$ complex gave mixtures of stereoisomers, the $Bu^nCu{\cdot}BEt_3$ provided much higher stereoselectivity and a good chemical yield as well. The use of $Bu^nCu{\cdot}9\text{-}BBN$ gave selectivity results similar to $Bu^nCu{\cdot}BEt_3$ (100% *cis*).[5]

## 1.4.9 STEREOSELECTIVITY

The 1,4-addition of a cuprate or organomagnesium reagent to an α,β-unsaturated ketone differs from the traditional Michael addition in that it is an irreversible process.[94] As a consequence, the products should be governed by kinetic control,[94] which has stereochemical implications. For example, the reaction of methylmagnesium iodide/catalytic copper(I) chloride with 5-methyl-2-cyclohexenone produces a mixture of *trans*:*cis* 3,5-dimethylcyclohexenone in the ratio 95:5 (equation 46),[95] consistent with attack of the nucleophile from the less-hindered face of the enone.[96] Alternatively, reactions of this type can be analyzed in terms of the relative energies of the transition states.[95] As Allinger has pointed out, each of the two conformations of the 5-methyl-2-cyclohexenone has two possible reaction paths available to it, which leads to four transition states and two products.[95] Since the methyl group offers an obvious hindrance in only one of four pathways, the least-hindered face argument is an incomplete explanation. Of the two modes of attack available to each cyclohexenone, one leads to a chair and the other to a boat conformation, with the chair expected to be favored by 2–3 kcal $mol^{-1}$ (1 cal = 4.18 J). Since pathway D is disfavored due to a 1,3-interaction of the methyl groups, the preferred route is pathway A, which leads to the *trans* product in agreement with the experimental result (Scheme 14).

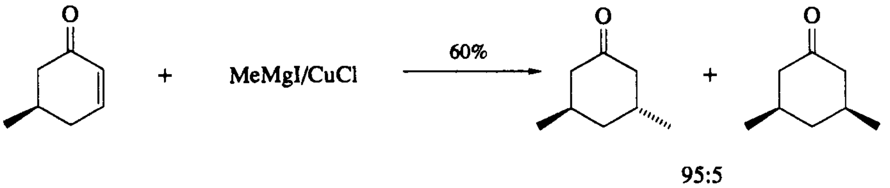

(46)

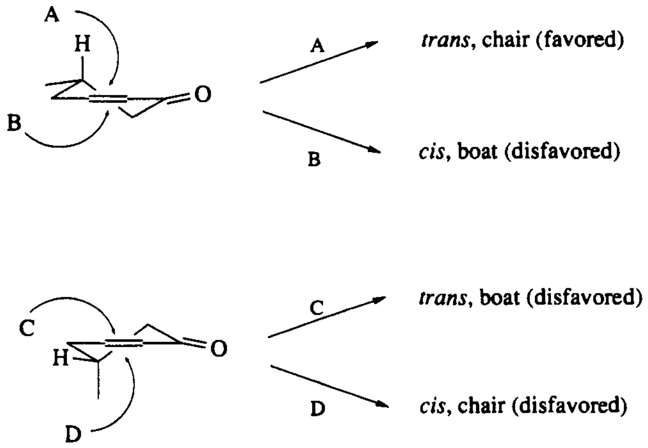

**Scheme 14**

In a similar experiment, enone (33) reacted with the diorganocuprate formed from copper(I) chloride and vinylmagnesium bromide to produce (34) and (35) as a 80:20 mixture.[97] The preference is consistent with a 1,2-interaction (*gauche*) of vinyl with ethoxycarbonyl, being of lower energy than a 1,3-interaction (diaxial) of vinyl with methyl (Scheme 15).

When a cuprate undergoes conjugate addition to an enone containing an α-substituent, a preference for the 2,3-*trans* product is generally observed.[1,98] If the α-substituent is 'large', as in (36), the preference is strong (>95:5; equation 47). If another electrophile is substituted for the proton,[99] the same stereoselectivity is observed. This important phenomenon has often been used to advantage in the synthesis of prostaglandins.[100]

In substrates where the carbonyl is exocyclic to the ring, a *cis* preference is reported for the 1,2-stereoselectivity.[5] The protonolysis has been reasoned to be the determining feature of the stereoselectivity. For example, when enone (37) was treated with dimethylcopperlithium, a *ca.* 70:30 *cis*:*trans* preference

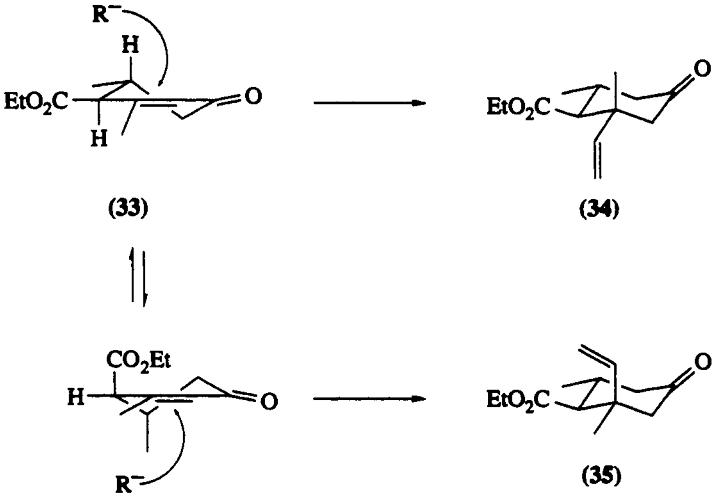
R⁻
H
EtO2C
H
O
(33)
EtO2C
O
(34)
CO2Et
H
O
R⁻
EtO2C
O
(35)

**Scheme 15**

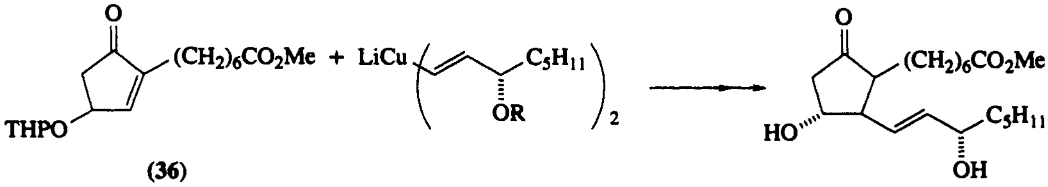
O
(CH2)6CO2Me + LiCu
C5H11
OR
2
THPO
(36)
O
(CH2)6CO2Me
C5H11
HO
OH

(47)

was observed (equation 48). The proton was believed to arrive from axial direction on the preferred conformer (**40**; Scheme 16). Addition of $MeCu{\cdot}BF_3$ led to an 86:14 *cis*:*trans* ratio, not greatly different from the above example.

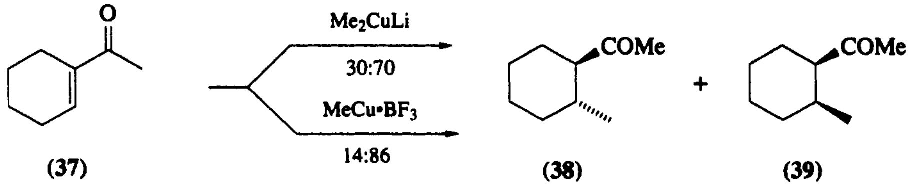
O
(37)
Me2CuLi
30:70
MeCu•BF3
14:86
COMe
(38)
+
COMe
(39)

(48)

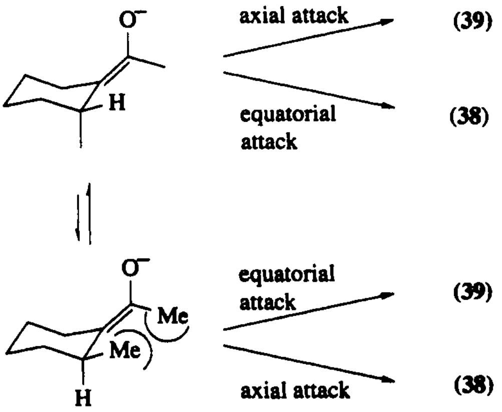
O⁻
H
axial attack
(39)
equatorial attack
(38)
O⁻
Me
Me
H
equatorial attack
(39)
axial attack
(38)

**Scheme 16**

A stereoselectivity dependence on the cuprate was also reported in the β-alkylation of γ-substituted acyclic enoates (Scheme 17).[101] The *trans* isomer (**41**) gave preferential formation of the *anti* isomer (**42**), regardless of the organocopper reagent employed. When the *cis* isomer (**43**) was treated with

$Bu^nCu{\cdot}BF_3$, compound **(42)** was formed with similar selectivity. However, if the *cis* compound **(43)** was treated with a $BF_3$-complexed diorganocuprate, then the *syn* isomer **(44)** was formed. The diastereoselectivities were explained in terms of a modified Felkin–Anh model, and electron transfer from the cuprate was used to account for the different stereochemical preferences of RCu and $R_2CuLi$ with **(43)**.[101]

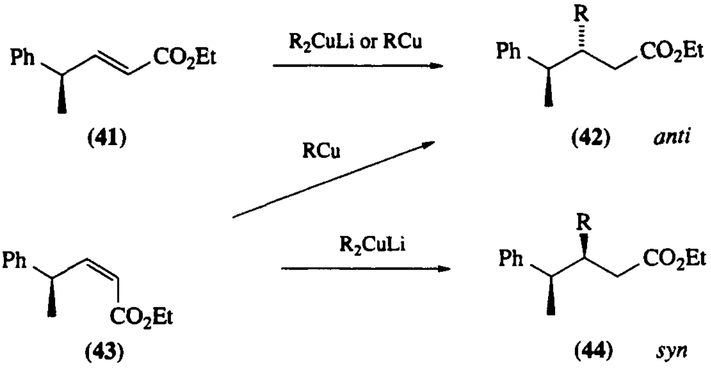

| *Reagent* | *Substrate* | *Yield (%)* | *Anti:syn* |
|---|---|---|---|
| $Bu^nCuLi{\bullet}BF_3$ | (41) | 90 | 70:30 |
| $Bu^nCuLi{\bullet}BF_3$ | (43) | 89 | 30:70 |
| $Bu^nCu{\bullet}BF_3$ | (41) | 82 | 88:12 |
| $Bu^nCu{\bullet}BF_3$ | (43) | 84 | 74:26 |

**Scheme 17**

With acyclic substrates such as **(45)**, simple steric arguments are a suitable rationale for the observed stereoselectivity.[85a] For example, in the reaction of $PhCu{\cdot}BF_3$ with enoate **(45)**, acid **(46)** was obtained, after hydrolysis, in 99.5% *ee*. This preference is consistent with an attack of the reagent from the least sterically encumbered side of the carbon–carbon double bond (shown by the arrow; equation 49).

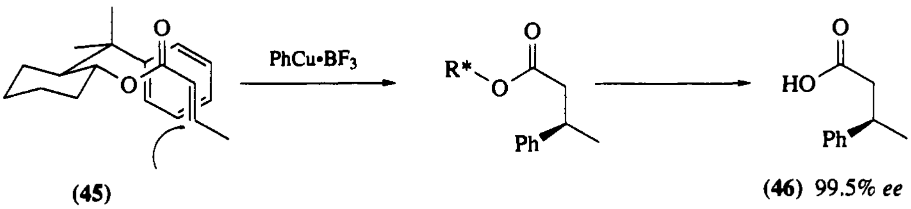

(49)

**(45)** **(46)** 99.5% *ee*

A stereoselectivity question also arose during addition/elimination of enones and enoates containing a good leaving group at the β-carbon.[102] A wide range of cuprates and leaving groups (L = halide,[103] acetate,[104] alkoxy,[105] alkylthio[106] *etc.*) have been used successfully, and this transformation constitutes a versatile synthesis of β-substituted enones and enoates with some obvious stereochemical implications (equation 50).

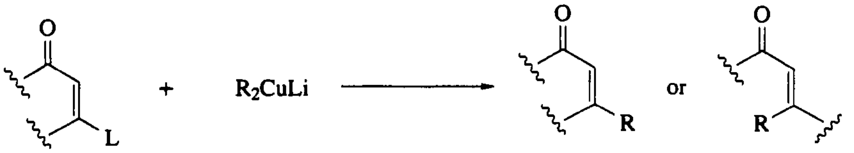

(50)

In many of the early reports, ester derivatives were extensively studied[105a,106b,107] and a preference for retention *versus* inversion was observed, where retention refers to introduction of the nucleophile to the same side of the carbon–carbon double bond as the leaving group it replaced (Scheme 18).

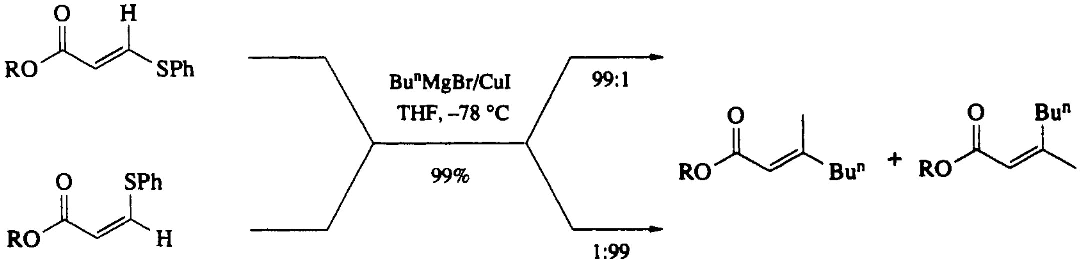
O
H
RO
SPh
O
SPh
RO
H
Bu^nMgBr/CuI
THF, –78 °C
99%
99:1
1:99
O
RO
Bu^n
+
O
Bu^n
RO

**Scheme 18**

The stereoselectivity in reactions of β-alkylthio-α,β-enones with organocuprates is dependent upon both the solvent and bulk of the ligand in the cuprate. Ether solutions favor inversion, while THF solutions favor retention (Scheme 19). It was proposed that in coordinating solvents such as THF, a more reactive enolate is formed, which eliminates before rotation occurs, thereby giving retention of configuration.[108]

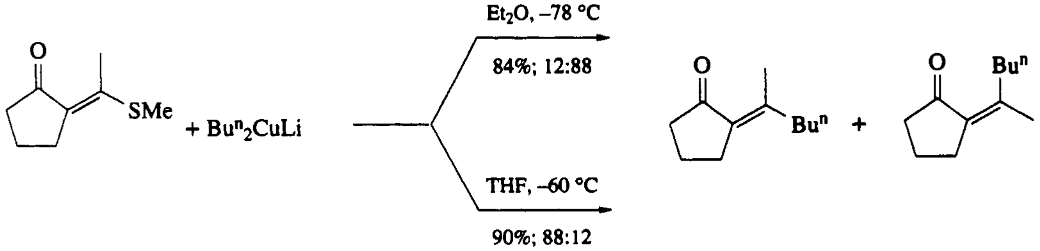
O
SMe
+ Bu^n₂CuLi
Et₂O, –78 °C
84%; 12:88
THF, –60 °C
90%; 88:12
O
Bu^n
+
O
Bu^n

**Scheme 19**

Bulky ligands (*e.g. t*-butyl) end up preferentially *anti* to the carbonyl, which is independent of the configuration of the β-alkylthio enone reactant (Scheme 20).

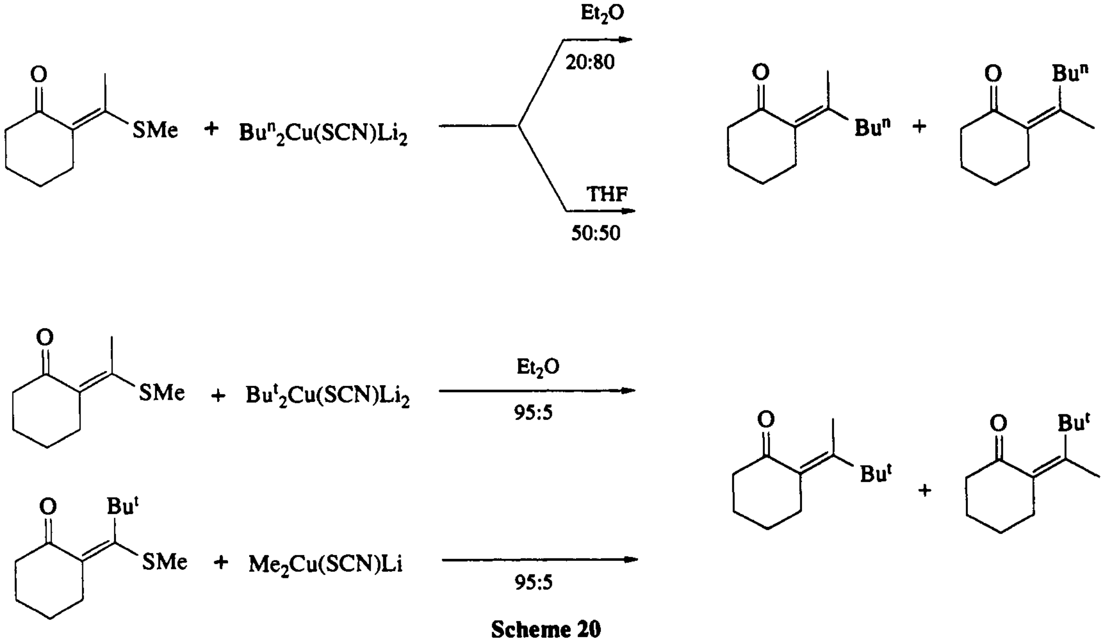
O
SMe
+ Bu^n₂Cu(SCN)Li₂
Et₂O
20:80
THF
50:50
O
Bu^n
+
O
Bu^n
O
SMe
+ Bu^t₂Cu(SCN)Li₂
Et₂O
95:5
O
Bu^t
SMe
+ Me₂Cu(SCN)Li
95:5
O
Bu^t
+
O
Bu^t

**Scheme 20**

Use of α-oxoketene dithioacetals and organocuprates provided a stereoselective synthesis of tri- and tetra-substituted alkenes.[109] In fact, it was reported that either the (*E*)- or (*Z*)-alkene could be prepared by the proper choice of cuprate and of the sequence of addition (Scheme 21).

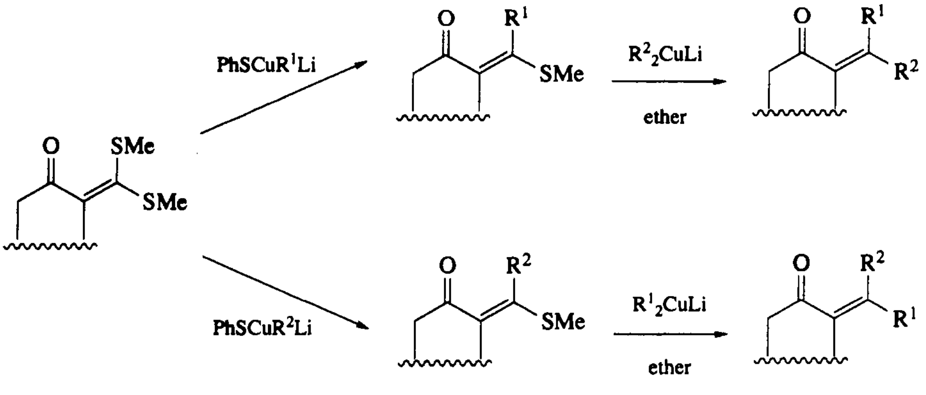

**Scheme 21**

## 1.4.10 APPLICATIONS

Conjugate addition of organocuprates has seen many applications in complex synthesis. For example, in the preparation of an opiate alkaloid it was necessary to introduce a methyl group at a late stage of the synthesis.[110] The transformation of (**47**) to (**48**) was successfully carried out with $Me_2CuLi$ in a stereoselective manner (equation 51).

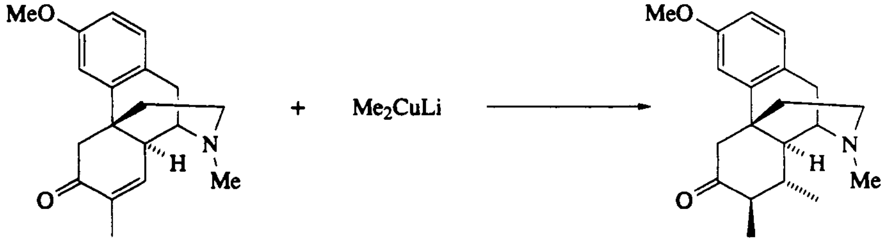

(51)

(**47**) (**48**)

The synthesis of pipitzol[111] also called for conjugate addition of a methyl group to a highly substituted enone. Good stereoselectivity (>95:5) was observed in the conversion of (**49**) to (**50**) with $Me_2CuLi$ where attack was reasoned to occur from the less-hindered α-face (equation 52).

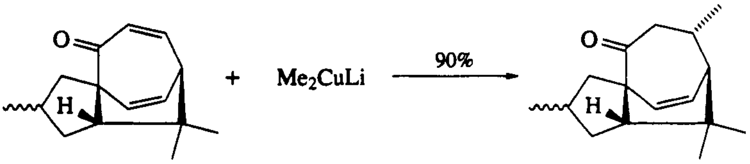

(52)

(**49**) (**50**)

Ligands other than methyl are also routinely delivered as organocuprates. For example, the transfer of vinylsilanes provided a methodology for conjugate addition of an enolate anion equivalent (equation 53).[113] Vinylsilanes are transformed to carbonyl groups by epoxidation followed by acid treatment.[112] There are no examples of simple enolates which undergo conjugate addition *via* cuprate formation, and simple enolates are generally poor nucleophiles for Michael reactions.[114]

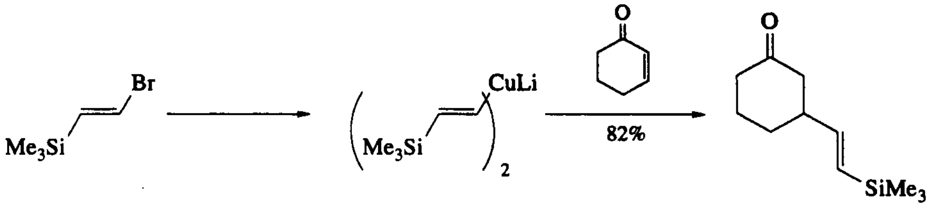

(53)

Ligands functioning as acyl anion equivalents also proceed efficiently in the conjugate addition to enones, producing the β-substituted product in high yield (equation 54).[113] Removal of the protecting group results in the free keto unit, and provides an alternative to the direct acylation (*vide supra*).[37,38]

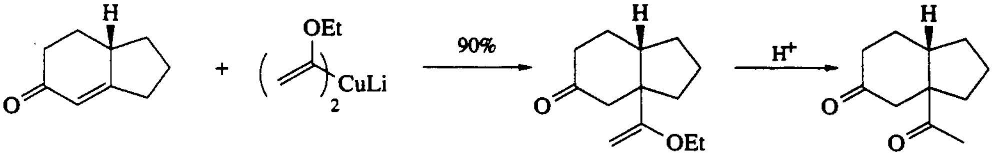

(54)

A synthesis of α-pyrones has been reported where a key step involved the chemoselective addition of an organocuprate to an α-oxoketene dithioacetal.[115] The methodology requires four steps and is quite general since the cuprate can deliver a range of ligands in a selective manner (Scheme 22).

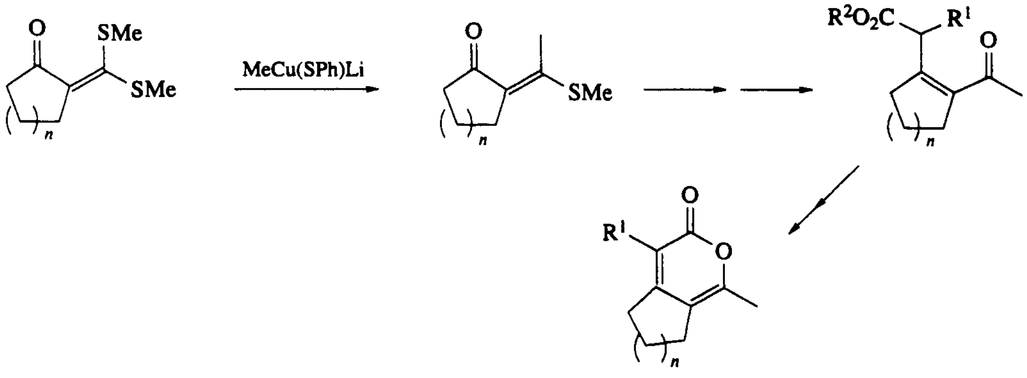

Scheme 22

The presence of a leaving group at the β-position of an enone provides the opportunity for double addition and creation of a quarternary carbon. If 2 mol equiv. of cuprate are employed, then the β,β-dialkylated product is expected. However, if a bisorganocuprate is used as the nucleophile, then a spiroannulation results.[116] Scheme 23 shows an example of a spiroannulation procedure with a biscuprate which formed spiro[4,4], [4,5] and [5,5] ring systems.[116] The bisorganocuprate was prepared from an organodilithium and copper thiophenoxide, with the obvious restriction being the limited range of dilithium species which can be prepared. Several such species were reported to undergo the spiroannulation, which provided for the rapid assembly of some interesting products in high yield (equation 55).

A nontransferable ligand is used to advantage in the above spiroannulation, and is generally important when a highly valued ligand must be transferred. In the synthesis of a steroid nucleus, the nucleophilic addition of a cuprate to enone (51) was one of two key steps (equation 56).[117] A good yield of the β-alkylated product was obtained, and a high stereochemical preference was reported as well.

From a study of the addition of organometallic reagents to β-substituted cyclopentyl sulfones, the reactivity of cuprates and organolithium species was compared (Scheme 24).[118] Organolithium reagents add to amine (**52**) to produce the *trans* adduct (**53**) in high stereoselectivity, while the cuprate adds to (**52**) (amine directed) to produce only the *cis* adduct (**55**). The amine was subsequently removed by quaternization and elimination, leaving the *cis*- or the *trans*-vinyl sulfones. Substrate (**52**) is apparently a special case since in earlier work vinyl sulfones were reported to be poor substrates for the reaction with organocuprates.[119,120] The ammonium ion is critical to the success of the addition; a related substrate with no amine present failed to give smooth addition.[118b]

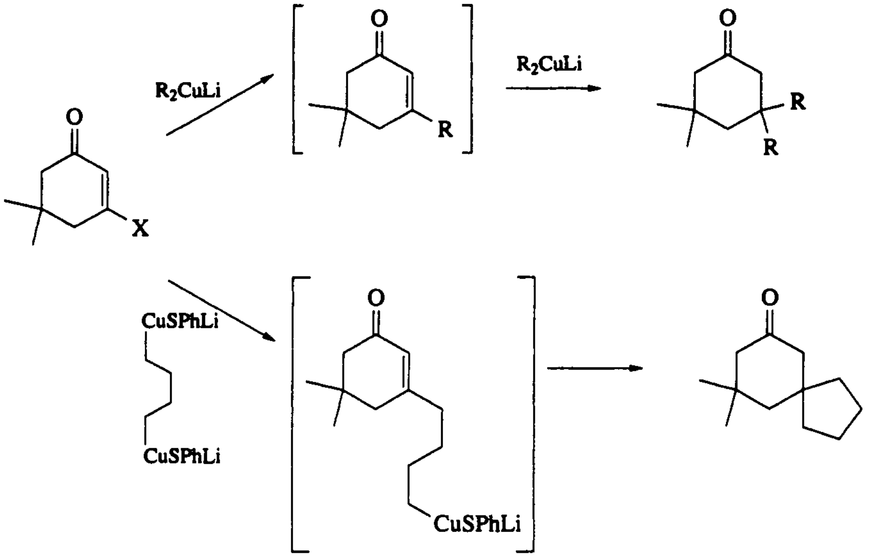

R2CuLi
R2CuLi
X
R
R
R
CuSPhLi
CuSPhLi
CuSPhLi

**Scheme 23**

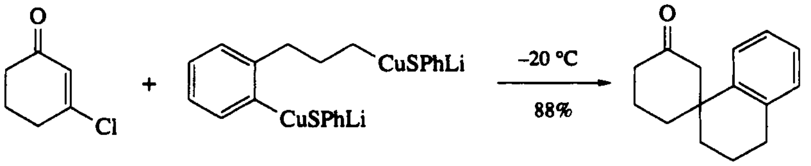

Cl
CuSPhLi
CuSPhLi
–20 °C
88%

(55)

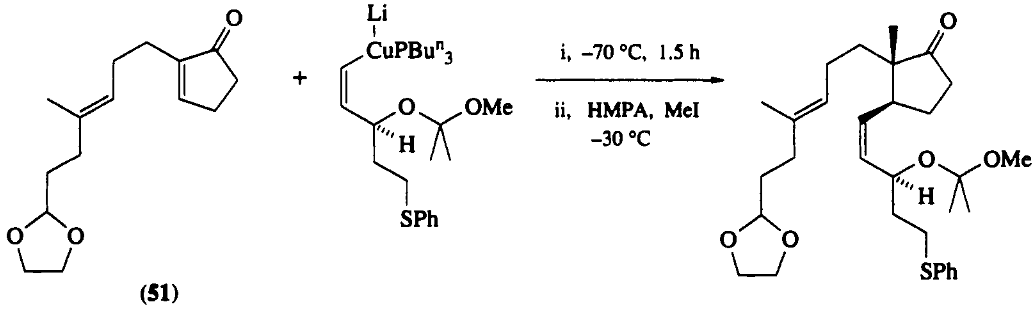

Li
CuPBun3
OMe
SPh
i, –70 °C, 1.5 h
ii, HMPA, MeI
–30 °C
OMe
SPh

(56)

(51)

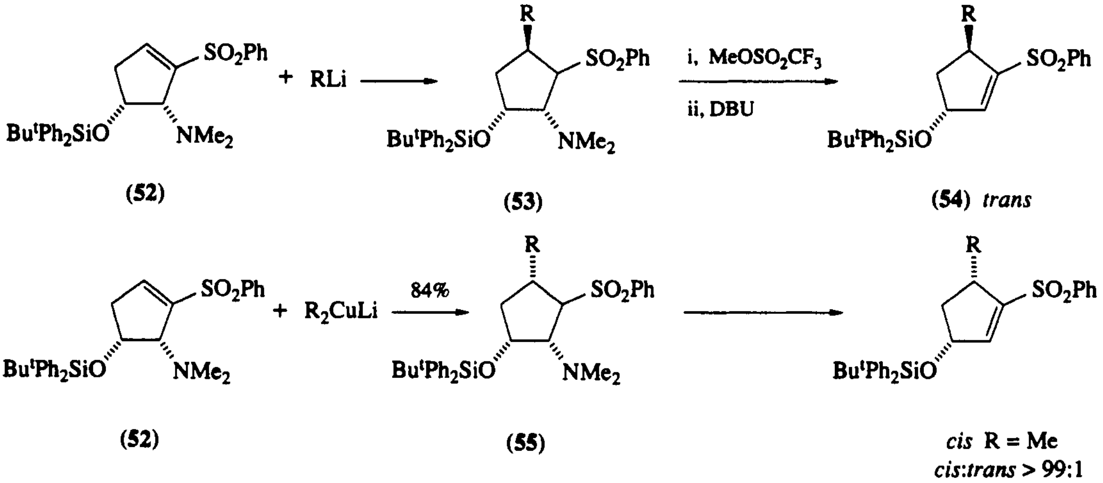

SO2Ph
Bu^tPh2SiO
NMe2
+ RLi
R
SO2Ph
NMe2
i, MeOSO2CF3
ii, DBU
(52)
(53)
(54) trans
+ R2CuLi
84%
(52)
(55)
cis R = Me
cis:trans > 99:1

**Scheme 24**

In a formal total synthesis of coriolin,[121] an unactivated cuprate, $Me_2CuLi$, failed in a conjugate addition (Scheme 25). It was reasoned that enone (**56**) was especially hindered at the β-carbon due to the β,β-substitution, and the methine hydrogen at C-11 of the c-ring. The low reactivity was overcome by use of the higher order reagent–$BF_3$ complex, $Me_2Cu(CN)Li_2{\cdot}BF_3$, which produced the β-alkylated product in an isolated yield of 80%. The advantage in reactivity realized by addition of a Lewis acid can be substantial.

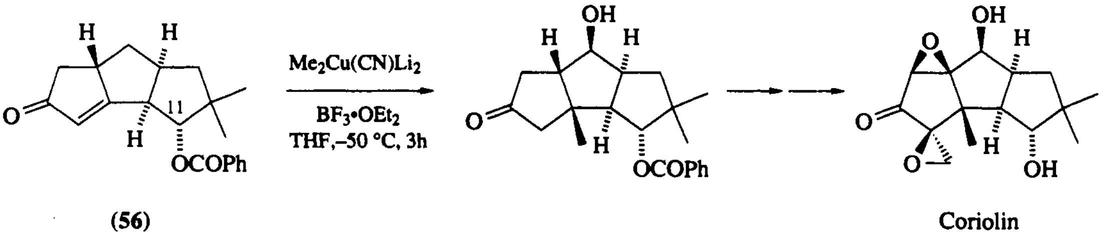

**Scheme 25**

In the total synthesis of mevinolin,[122] a stereoselective conversion of (**57**) into (**58**) was called for. Several organocopper reagents were examined, but it was $MeCu{\cdot}BF_3$ which exhibited the highest selectivity (Scheme 26). The reason for the selectivity is not obvious, but the results do indicate that there can be significant differences between the reactivity profile of the various organocopper reagents available.

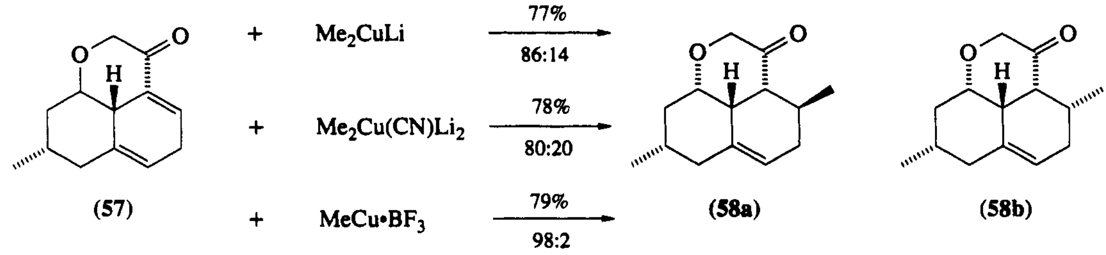

**Scheme 26**

In a good test of the regioselectivity of organocuprates, addition to trifluoromethyl alkynyl ketones was examined.[123] The methodology was used to provide a simple route to α,β-unsaturated trifluoromethyl ketones, and due to the electrophilic character of the fluoro ketone, 1,2-addition was expected to be a competing reaction. Surprisingly good 1,4-/1,2-selectivity was reported with the organocuprates, with cyanocuprates (higher and lower order) demonstrating the highest ratios (Scheme 27). In all cases the (*E*)-isomer prevailed, which indicated that isomerization of the products had occurred under the reaction conditions.

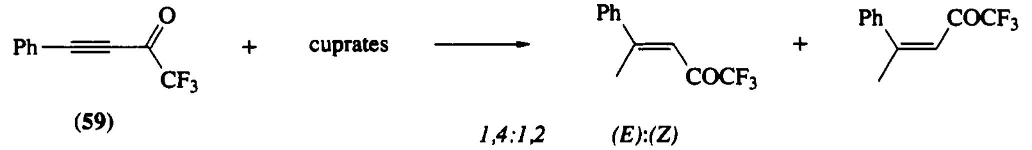

| | *1,4:1,2* | *(E):(Z)* | |
|---|---|---|---|
| $Me_2CuLi$ | 88:12 | 76:24 | |
| $MeCu(CN)Li_2$ | 100:0 | 53:47 | (75%) |
| $Me_2Cu(CN)Li_2$ | 100:0 | 71:29 | (93%) |

**Scheme 27**

Two highly unusual reactions were noted in this study which merit attention. First, the treatment of (**59**) with cuprate (**60**) gave rise to 1,2-addition of the alkyne as the only product (67%; equation 57). Second, when trifluoromethyl ketone (**59**) was treated with either the higher or lower order methylcuprates, the cyanohydrin (**61**) was isolated in addition to the normal 1,4-addition product (equation 58).

This may be a rare example of CN transfer from the cuprate to a substrate, but more likely is a result of HCN addition formed from the acidic work-up.[124]

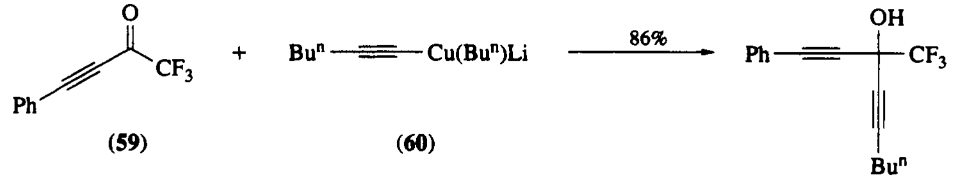

(57)

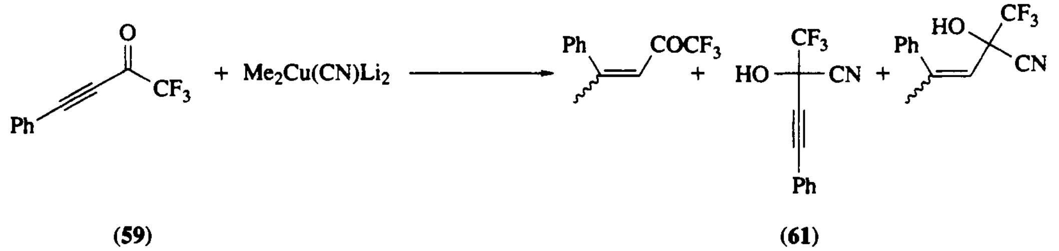

(58)

A Michael-initiated ring closure, begun by the conjugate addition of a cuprate to an alkyne, has also been reported.[125] Use of the higher order reagent was crucial to the success of this transformation as the lower order reagent led only to conjugate addition. It is likely that addition to the alkyne was followed by isomerization (facile at 0 °C) to attain a conformation suitable for ring opening of the epoxide (Scheme 28). The intermediacy of a vinylcuprate (**62**) is consistent with the reactivity difference between the lower and higher order reagents, where different species would undoubtedly be present.

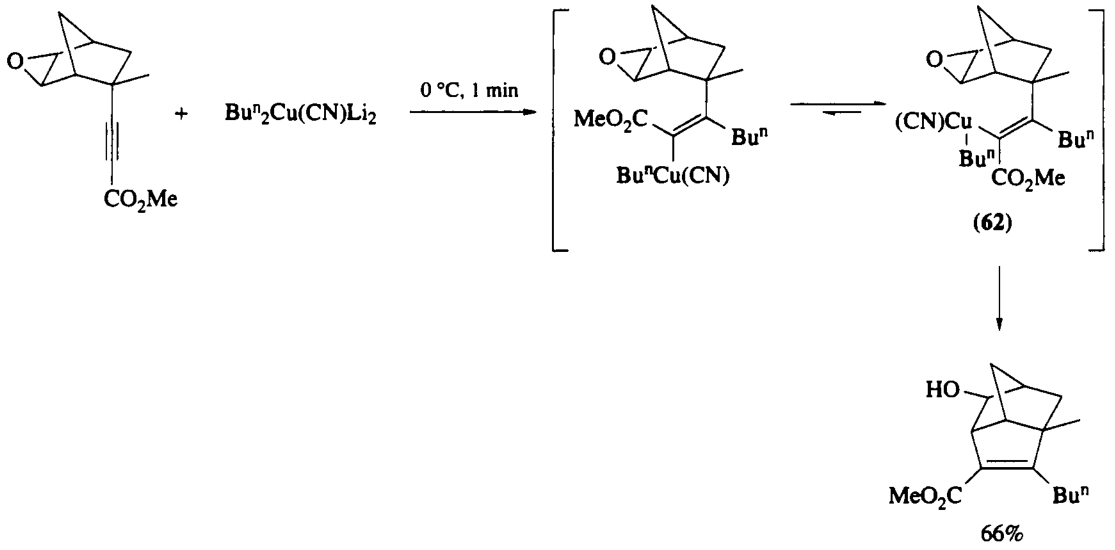

**Scheme 28**

## 1.4.11 CONCLUDING REMARKS

Organocuprates are easily prepared and undergo conjugate addition with a wide spectrum of substrates. A large variation in the R-group of $R_2CuLi$ is tolerated and alternative modes of formation are available for ligands which contain sensitive functional groups. The emergence of technology which permits the selective transfer of a single equivalent of an R-group from the cuprate has increased the efficiency of the conjugate addition. Lewis acid additions have dramatically increased the reactivity of many cuprates, and transformations are now possible which were previously unattainable. Some mechanistic aspects are still unresolved but a more unified picture has emerged. The structure and aggregation state of the reagent is a topic which is also unsettled, and future work will undoubtedly be carried out here.

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# 1.5

# Asymmetric Nucleophilic Addition to Electron Deficient Alkenes

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## 1.5.1 INTRODUCTION

Additions of nucleophiles to electron-deficient double bonds, *e.g.* the classical Michael addition or the $Cu^I$-mediated 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds (see previous chapters of this volume), constitute some of the very valuable items in the toolbox of the synthetic organic chemist. No wonder that they have found widespread application in organic synthesis. While early interest in these reactions was based particularly on their reliable chemo- and regio-selectivity, in recent years much progress has been made in the development of highly diastereo- and even enantio-selective methods, allowing the control of absolute stereochemistry.[1–4]

It is the aim of this chapter to survey these latter methods, independent of the special type of reagent (nucleophile) or substrate (electron-deficient alkene). The treatise will mainly focus on C—C bond-forming reactions, and will be restricted to such methods which: (i) allow the preparation of optically active, and, if possible, of enantiomerically pure (homochiral) compounds (EPC-synthesis);[5] (ii) involve the formation of at least one new stereogenic center during the addition step with a significant degree of asymmetric induction; and (iii) in general, give products containing only those stereogenic centers which are generated during the nucleophilic addition and, eventually, during subsequent alkylation steps (occasionally after removal of a chiral auxiliary group). Synthetic applications will be emphasized.

Most of the reactions which will be discussed lead to carbonyl compounds with a stereogenic center in the β-position. This is illustrated in Scheme 1: a substrate molecule (**1**; X = heteroatom or heteroatom-based functional group), having an electron-deficient double bond, is attacked by a nucleophilic reagent (possibly in the presence of a coordinating ligand or a catalyst) to form an anionic intermediate (**2**), which is then converted to the product (**3**) on hydrolytic work-up.

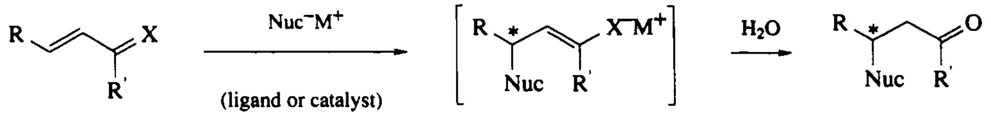

(**1**) (**2**) (**3**)

**Scheme 1**

To achieve the desired asymmetric induction, chirality must be introduced. There are essentially three ways to do this. One can employ: (i) chirally modified substrates; (ii) chirally modified nucleophiles; or (iii) a chiral reaction medium (chiral coordinating cosolvents, ligands or catalysts). This chapter is organized according to these three approaches.

## 1.5.2 DIASTEREOSELECTIVE ADDITIONS OF ACHIRAL CARBON NUCLEOPHILES TO CHIRAL SUBSTRATES

### 1.5.2.1 Additions to Chiral Derivatives of α,β-Unsaturated Carboxylic Acids

### *1.5.2.1.1 Additions to chiral esters*

The conjugate addition of (achiral) nucleophiles to α,β-unsaturated esters of chiral alcohols (**4**) generally produces optically active β-branched acids, (**7**):(*ent*-**7**) ≠ 1, after saponification of the diastereomeric ester intermediates (**5**) and (**6**; Scheme 2).[6]

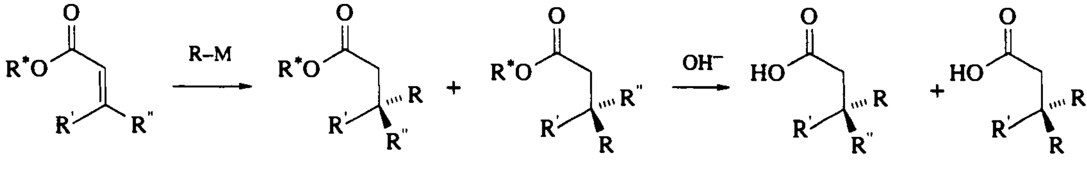

(**4**) (**5**) (**6**) (**7**) (*ent*-**7**)

**Scheme 2**

Following this concept, the 1,4-addition of phenylmagnesium bromide to (–)-menthyl crotonate was investigated, however with quite disappointing results.[7] By using sugar-derived chiral auxiliaries, somewhat better selectivities were obtained,[8] but the results could not be reproduced.[9] Attempts to alkylate enamines with menthyl crotonate led also to unsatisfying yields and selectivities.[10]

The introduction of RCu/$BF_3$-type reagents[11] prompted investigation of the conjugate addition of these reagents to chiral enoates prepared from (–)-8-phenylmenthol (**8**).[12] While additions to the (*E*)-crotonate (**9**) were highly selective (Scheme 3) and proceeded in reasonable yields, (*Z*)-configured or tri- and tetra-substituted enoates gave only moderate results. These difficulties could be overcome by employing the $Bu_3P$-stabilized RCu/$BF_3$ reagents, which lead to increased reaction rates, improved yields and, most important, generally high selectivities.[13–16] Addition of these reagents to the enoates (**11**), accessible from the camphor-derived alcohol (**10**), gave carboxylic acids (**13**) of high enantiomeric purity, after hydrolysis of the initially formed esters (**12**; Scheme 4). The even more practical auxiliary (**14**), available in only two steps from camphor-10-sulfonyl chloride, also gave rise to high diastereoselectivities during 1,4-addition to its enoates (**15**). The results, summarized in Table 1, demonstrate the broad scope of this highly useful methodology. The chiral auxiliary alcohols are available in both enantiomeric forms and can efficiently be recycled.

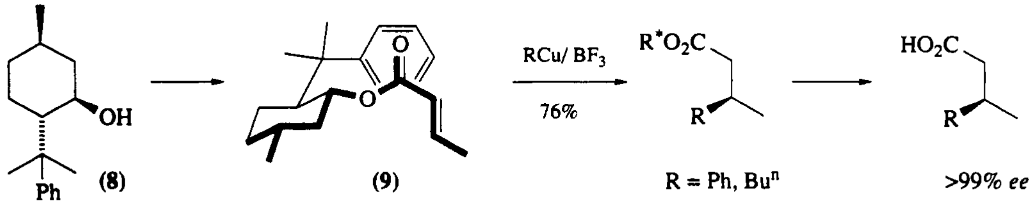

Scheme 3

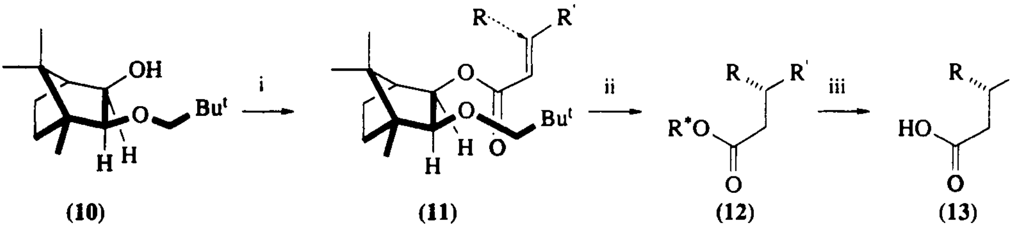

i, acid chloride, AgCN, benzene, reflux, 4 h; ii, add excess of an equimolar mixture of RLi, CuI, $Bu_3P$ and $BF_3{\cdot}OEt_2$, –78 to –35 °C; iii, NaOH, aq. EtOH, reflux

Scheme 4

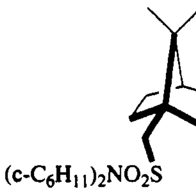

(**14**)

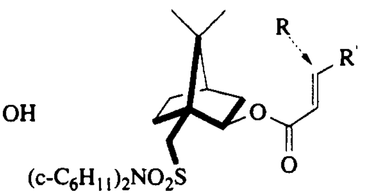

(**15**)

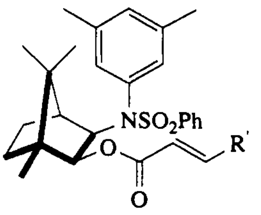

(**16**)

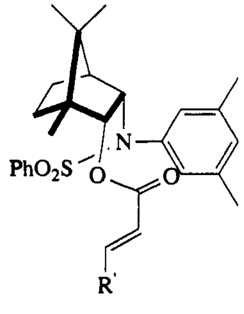

(**17**)

**Table 1** Preparation of Chiral Carboxylic Acids (13) or (*ent*-13) *via* Ester Intermediates by Addition of $Bu_3P$-Stabilized $RCu/BF_3$ Reagents to Chiral Enoates Followed by Hydrolysis (Scheme 4)

| *Enoate* | *R′* | *R* | *Ester yield (%)* | *Carboxylic acid* | *ee (%)* | *Configuration* | *Ref.* |
|---|---|---|---|---|---|---|---|
| (11) | Bu$^n$ | Me | 82 | (13) | 94 | (*R*) | 13 |
| (11) | Et | Me | 85 | (13) | 92 | (*R*) | 13 |
| (11) | Me | 4-Methyl-3-pentenyl | 81 | (13) | 98 | (*S*) | 13 |
| (11) | Me | Vinyl | 85 | (13) | 94 | (*R*) | 14 |
| (11) | Me | 2-Propenyl | 86 | (13) | 99 | (*R*) | 14 |
| (11) | 1,5-Hexadien-2-yl | 2-Propenyl | 89 | (13) | 98 | (*R*) | 14 |
| (*ent*-11) | n-$C_8H_{17}$ | Me | 90 | (*ent*-13) | 98 | (*S*) | 13 |
| (*ent*-11) | 4-Methyl-3-pentenyl | Me | 90 | (*ent*-13) | 92 | (*S*) | 13 |
| (15) | Me | Pr | 98 | (13) | 97 | (*S*) | 15 |
| (15) | Me | Bu$^n$ | 89 | (13) | 97 | (*S*) | 15 |
| (15) | Me | Vinyl | 80 | (13) | 98 | (*R*) | 15 |
| (15) | Me | 2-Propenyl | 84 | (13) | 94 | (*R*) | 15 |
| (15) | Pr | Me | 89 | (13) | 94 | (*R*) | 15 |
| (15) | Bu$^n$ | Me | 93 | (13) | 97 | (*R*) | 15 |

A related approach involves the diastereomeric chiral enoates (**16**) and (**17**), which are both prepared from (+)-camphor, but behave like pseudo-enantiomers, leading to products of opposite absolute configuration at the newly formed stereogenic center.[17] Conjugate addition of $RCu/BF_3$ reagents to these substrates at low temperatures generally proceeds with almost complete diastereoselectivity (>99:1). The right choice of the solvent, depending on the metal species involved, is crucial: while THF works well for the copper compounds prepared from Grignard reagents, the alkyllithium-derived species show best results in ether.

In all cases where secondary alcohols are used as chiral auxiliaries, one can understand (and predict) the stereochemical outcome of these reactions, if one takes into account: (i) that esters of secondary alcohols always try to adopt a conformation with a coplanar (horseshoe-type) arrangement of the carbonyl group, the ether oxygen and the alkoxy C—H bond;[18,19] and (ii) that in the presence of Lewis acids, (*E*)-enoates appear to prefer the *s-trans* conformation (antiplanar position of the carbonyl group and the C═C double bond).[20] Depending on the structure of the chiral auxiliary, one of the two (diastereotopic) faces of the double bond will now be more or less shielded, forcing the nucleophile to attack on the opposite face.

The homochiral β-branched carboxylic acids (**13** or *ent*-**13**; Table 1) have been used for the synthesis of a variety of natural products[21] such as California red scale pheromone,[14] α-skytanthine,[22] the southern corn rootworm pheromone,[15] and norpectinatone.[16] Pure (*S*)-3-trichloromethylbutyric acid (a structural subunit of some sponge metabolites) was prepared *via* conjugate addition of $Cl_3CMgCl$ to the chiral crotonate (**16**) followed by hydrolysis (Scheme 5).[23]

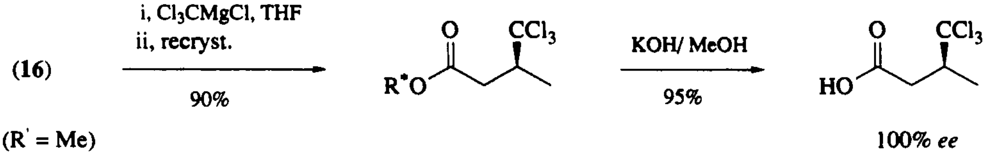

**Scheme 5**

In an isolated case, a tertiary alcohol was used as chiral auxiliary: the crotonate (**19**), prepared from the (+)-camphor-derived alcohol (**18**), undergoes highly diastereoselective 1,4-addition of a cuprate reagent (Scheme 6).[24]

### *1.5.2.1.2 Additions to chiral amides and imides*

Analogous to the use of chiral enoates (see previous section), α,β-unsaturated carboxylic amides, prepared from chiral amines, may be utilized in asymmetric 1,4-additions. When Grignard reagents are added to unsaturated amides (**21**), derived from (–)-ephedrine (**20**),[25] highly optically active β-substituted alkanoic acids (**22**; R and R′ = alkyl or phenyl) are obtained in a variety of cases, after hydrolysis of the initially formed adducts (Scheme 7). This method was used for the synthesis of the antibiotic (–)-malyngolide and its stereoisomers.[26] Recrystallization of the intermediate (saturated) amide was necess-

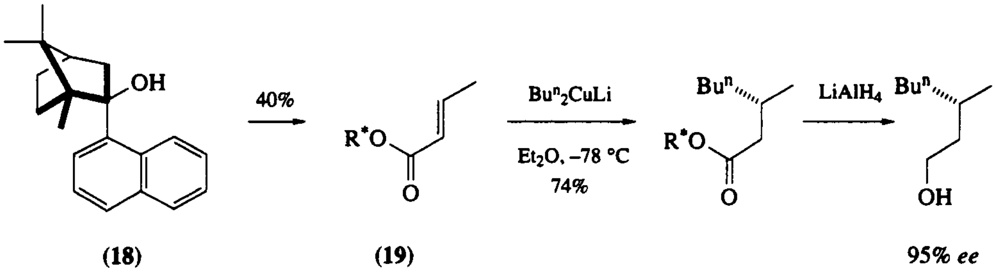
OH
40%
R*O
O
Bu$^n{}_2$CuLi
Et$_2$O, -78 °C
74%
Bu$^n$
R*O
O
LiAlH$_4$
Bu$^n$
OH
(18)
(19)
95% ee

**Scheme 6**

ary in this case to raise the enantiomeric excess (*ee*) of the hydrolysis product from 87 to 97%. A closely related approach involves addition of organometallic reagents to chiral (proline-derived) unsaturated amides in the presence of certain tertiary amines.[27–30] Best results are obtained with Grignard reagents in toluene in the presence of DBU, and when amino alcohol (**23**) is used as the chiral auxiliary (Scheme 8). The method was applied to the preparation of (*S*)-(–)-citronellol, however with only 63% *ee*.[30] With the lactam (**24**) as chiral auxiliary, conjugate addition of dialkylcuprates to the corresponding unsaturated imide (**25**) gives, after hydrolysis, carboxylic acids (**26**) with predictable absolute configuration and with reasonably high *ee* (Scheme 9).[31] In contrast to the reactions of chiral esters, these methods (based on chiral carboxylic amides or imides) seem to rely on rigid substrate conformations, which are due to chelation with a metal ion.

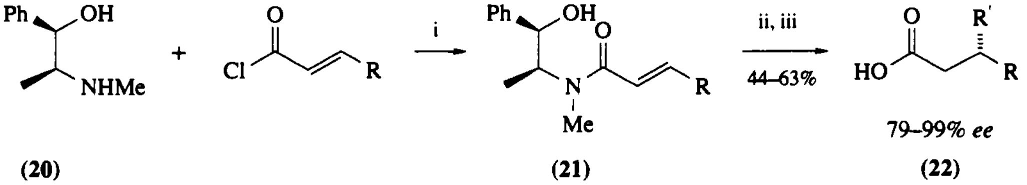
Ph
OH
NHMe
+
O
Cl
R
i
Ph
OH
O
N
Me
R
ii, iii
44–63%
O
R'
HO
R
79–99% ee
(20)
(21)
(22)

i, proton sponge; ii, 6 equiv. of R'MgBr, ether, –40 °C, 48 h, then add buffer pH 7; iii, AcOH, 3 M $H_2SO_4$, reflux, 3 h

**Scheme 7**

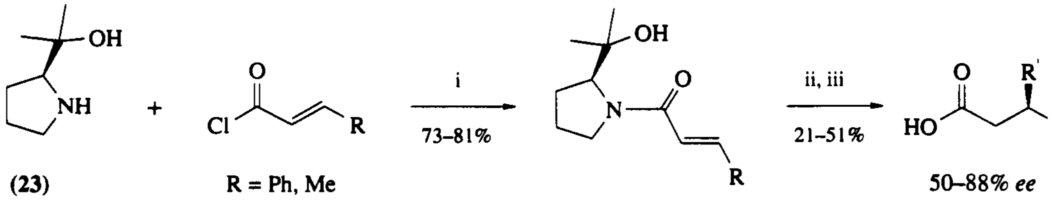
OH
NH
+
O
Cl
R
i
73–81%
OH
N
O
R
ii, iii
21–51%
O
R'
HO
R
(23)
R = Ph, Me
50–88% ee

i, 1 M aq. NaOH, ether, 1.5 h, r.t.; ii, R'MgBr, DBU, toluene, –40 °C to r.t.; iii, 3 M HCl, dioxane, reflux, 40 h

**Scheme 8**

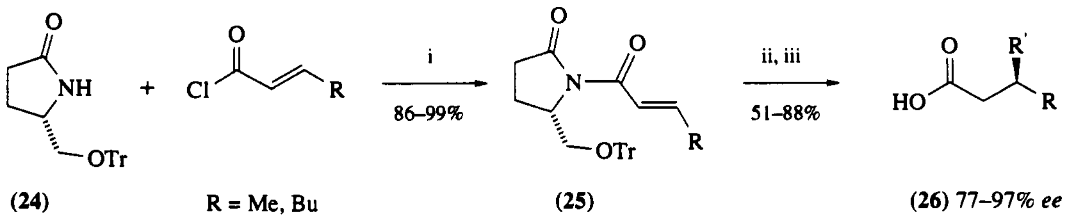
O
NH
OTr
+
O
Cl
R
i
86–99%
O
N
O
OTr
R
ii, iii
51–88%
O
R'
HO
R
(24)
R = Me, Bu
(25)
(26) 77–97% ee

i, Bu$^n$Li, THF, then add acid chloride; ii, R'$_2$CuLi, THF, –23 °C; iii, HCl, MeOH, then aq. KOH

**Scheme 9**

### *1.5.2.1.3 Additions to chiral* N*-enoylsultams*

Another type of chiral auxiliary is the bornane-10,2-sultams (**27**) and (*ent*-**27**), which are quite easily accessible from the (+)-and (–)-camphor-10-sulfonyl chlorides.[21,32] They are readily converted into the corresponding *N*-enoylsultams (**28**) by successive treatment with sodium hydride and acyl chlorides. These substrates smoothly undergo 1,4-addition when treated with 2 mol equiv. of alkylmagnesium chlorides.[33] The β-substituted derivatives (**28**; R″ = H) lead predominantly to isomers (**29**) with reasonably high diastereoselectivity (Scheme 10). The diastereomeric purity of the products can be dramatically enhanced in most cases by simple recrystallization. Mild hydrolysis affords the free carboxylic acids (**30**) under recovery of the chiral auxiliary (**27**). The method also allows the diastereo- and enantioselective preparation of α,β-disubstituted alkanoic acids in two different ways: (A) conjugate addition to β-substituted derivatives (**28**; R″ = H) followed by *in situ* alkylation of the intermediate enolate leads preferentially into the same diastereomeric series (**31**) as does (B) the 1,4-addition to α,β-disubstituted derivatives (**28**; R″ ≠ H) with subsequent (kinetically controlled) protonation (Scheme 11). The steric course of the conjugate addition of Grignard reagents to *N*-enoylsultams (**28**) can be explained by the assumption of a reactive conformation as shown in (**32a**). A similar topological picture applies when β-silyl-substituted-*N*-enoylsultams are treated with $PBu_3$-stabilized RCu reagents in the presence of ethylaluminum dichloride (Scheme 12).[34] Methanolysis of the adducts (**33**) followed by successive fluorodephenylation and oxidation of the C—Si bond leads to homochiral β-hydroxy esters (**34**). Gilman reagents also smoothly add to (**28**),[35] leading preferentially to isomers (**35**; Scheme 13). The steric course of the addition step can be attributed in this case to a reactive conformation as shown in (**32b**). Addition of $Me_2CuLi$ to the 1-cyclohexenoylsultam (**36**) and subsequent protonation gave the *cis* compound (**37**) as the sole product, which was then hydrolyzed to the homochiral acid (**38**; Scheme 14). An application of this methodology for the synthesis of β-necrodol (**39**)[36] is outlined in Scheme 15.

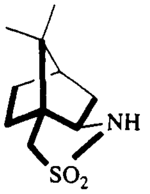

(**27**)

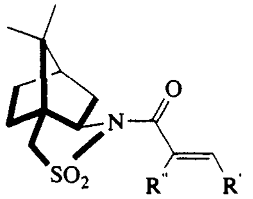

(**28**)

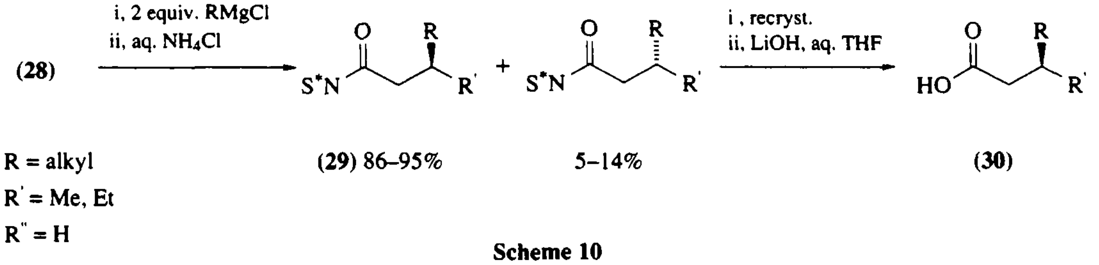

Scheme 10

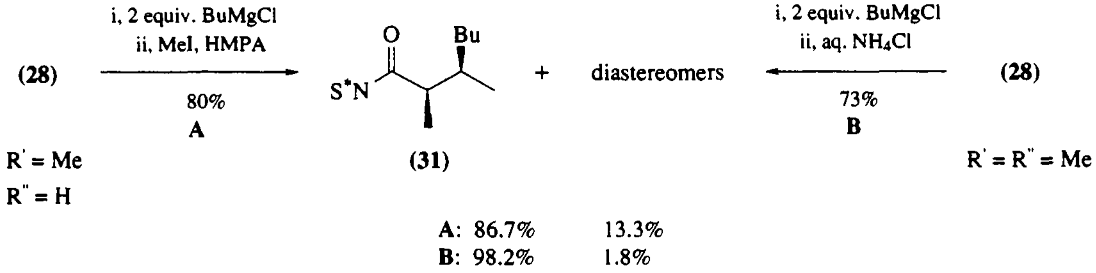

Scheme 11

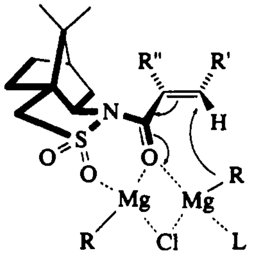
R''
R'
N
S
O
H
O
O
R
Mg
Mg
R
Cl
L

**(32a)**

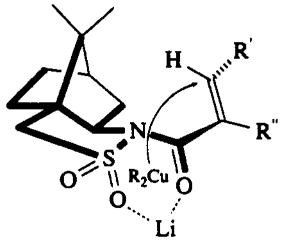
H
R'
R''
N
S
O
R2Cu
O
O
Li

**(32b)**

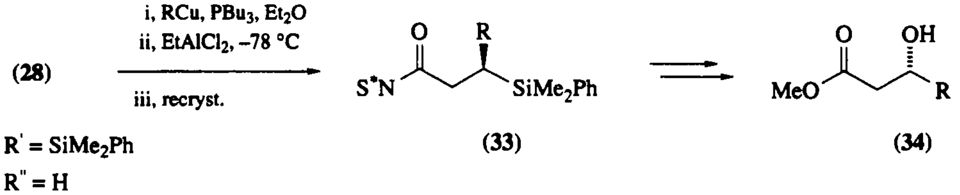
(28)
i, RCu, PBu3, Et2O
ii, EtAlCl2, –78 °C
iii, recryst.
R' = SiMe2Ph
R'' = H
O
R
S*N
SiMe2Ph
(33)
O
OH
MeO
R
(34)

Scheme 12

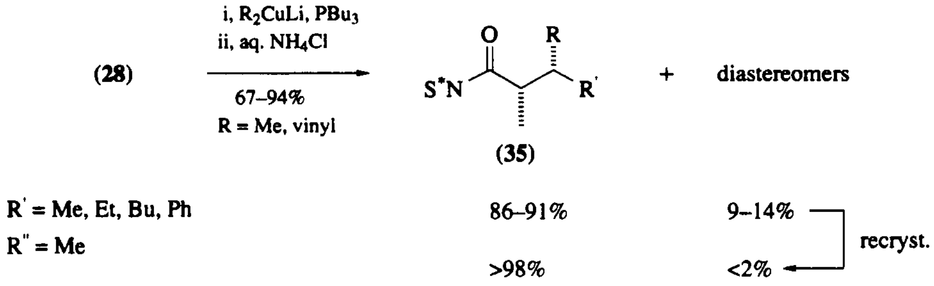
(28)
i, R2CuLi, PBu3
ii, aq. NH4Cl
67–94%
R = Me, vinyl
O
R
S*N
R'
(35)
+ diastereomers
R' = Me, Et, Bu, Ph
R'' = Me
86–91%
>98%
9–14%
<2%
recryst.

Scheme 13

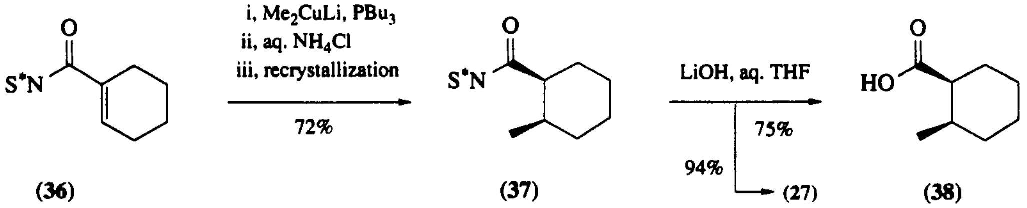
O
S*N
(36)
i, Me2CuLi, PBu3
ii, aq. NH4Cl
iii, recrystallization
72%
O
S*N
(37)
LiOH, aq. THF
75%
94%
(27)
O
HO
(38)

Scheme 14

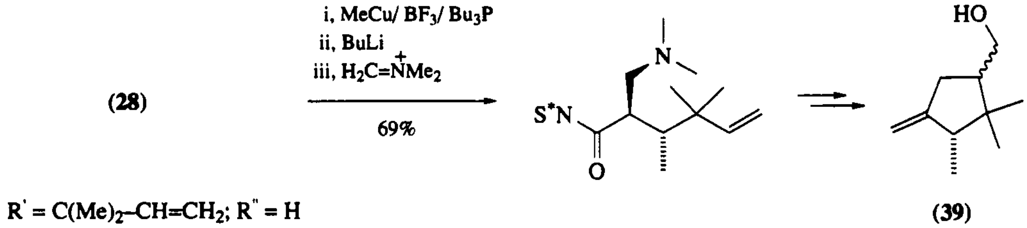
(28)
i, MeCu/ BF3/ Bu3P
ii, BuLi
iii, H2C=N⁺Me2
69%
R' = C(Me)2–CH=CH2; R'' = H
N
S*N
O
HO
(39)

Scheme 15

### *1.5.2.1.4 Additions to chiral oxazolines*

The first general method allowing the preparation of optically active β,β-dialkylpropionic acids *via* asymmetric synthesis is based on chiral oxazolines.[37–41] The α,β-unsaturated derivatives (**41**), accessible as pure (*E*)-isomers from (**40**) and the respective aldehydes (RCHO), undergo highly selective 1,4-additions in a variety of cases (Scheme 16) when treated with alkyl- or aryl-lithium reagents. The products

(**42**) are hydrolyzed to β-substituted alkanoic acids (**43**) of generally high enantiomeric purity (>90% *ee*). The method has been applied to the synthesis of (+)-*ar*-turmerone.[42] Substituted dihydropyridines[43,44] and chiral 1,2-dihydronaphthalins[45–48] are also accessible by this methodology. The lignane, (+)-phyltetralin (**44**), was thus synthesized as outlined in Scheme 17.[49]

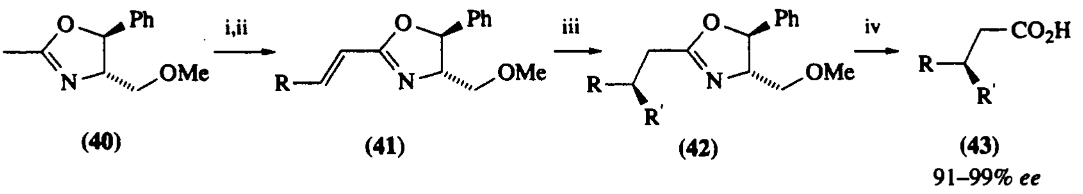

i, LDA, $(Pr^iO)_2POCl$, THF, −78 °C; ii, $Bu^tOK$, RCHO; iii, R′Li, THF, −78 °C, 3 h; iv, 1.5 M $H_2SO_4$, reflux, 24–36 h

**Scheme 16**

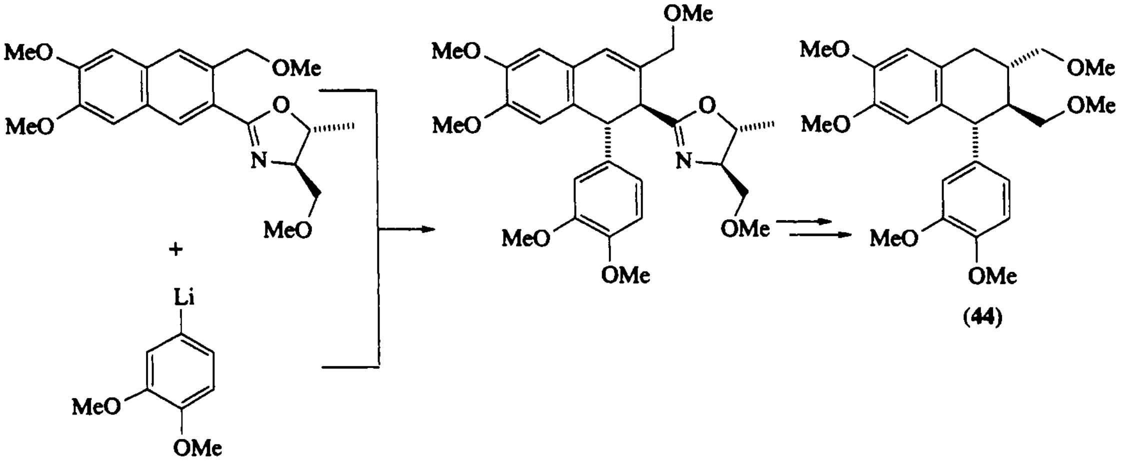

**Scheme 17**

The stereochemical outcome of all these reactions was rationalized in terms of a chelate complex formed between the reactants, from which the R′-group is then transferred to the alkene as drawn in (**45**). Nevertheless, in the case of substrates containing additional stereogenic centers and other coordinating functional groups, a reliable prediction of the product configuration is not always possible.[50]

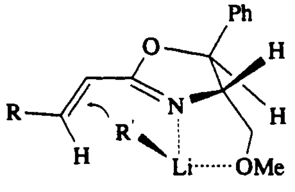

**(45)**

### *1.5.2.1.5 Additions to other chiral derivatives*

Another type of chiral Michael acceptor, the oxazepine derivatives (**47**), is prepared by condensation of the (−)-ephedrine-derived malonic acid derivative (**46**) with aldehydes (Scheme 18).[51,52] Treatment of (**47**) with a variety of Grignard reagents in the presence of $NiCl_2$ affords, after hydrolysis and decarboxylation, the 3-substituted carboxylic acids (**48**), in most cases with more than 90% *ee*. Diastereoselective Michael additions to (**47**) were also used for the preparation of optically active cyclopropane derivatives (**49**)[53] and β-substituted-γ-butyrolactones (**50**; Scheme 18).[54] A total synthesis of indolmycin is based on this methodology.[55]

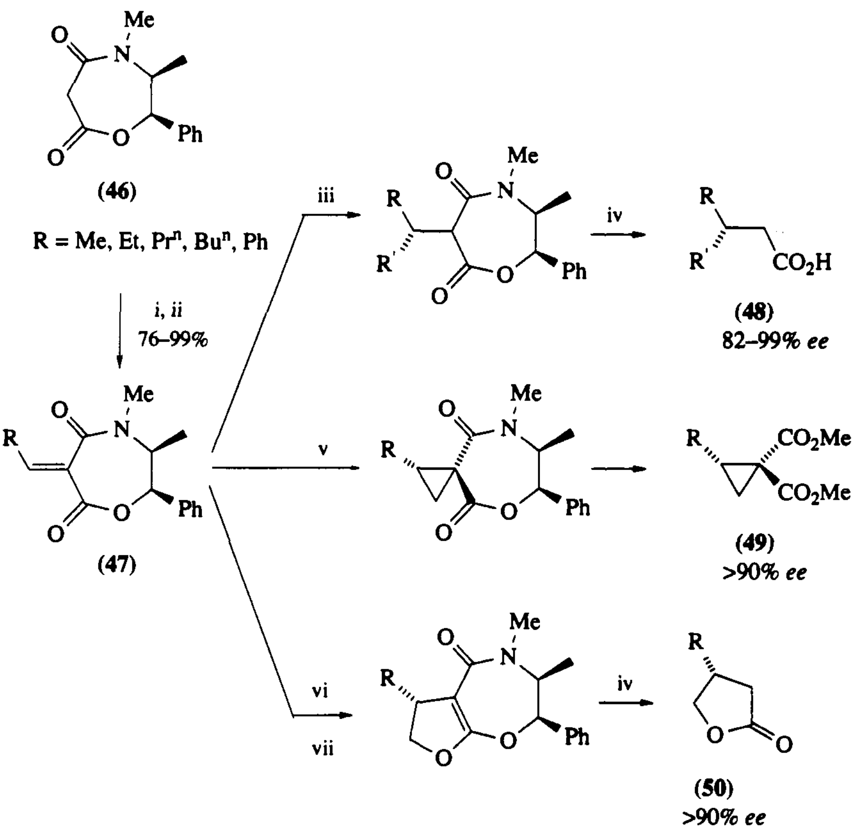

i, RCHO, $TiCl_4$, pyridine, THF, –78 °C to r.t., 12 h; ii, recryst.; iii, R′MgBr, $NiCl_2$, THF, –78 °C, 3 h; iv, 3 M $H_2SO_4$, AcOH, reflux, 6 h; v, $CH_2{=}SOMe_2$; vi, $PhSCH_2Li$, $NiCl_2$, THF/ toluene, –78 °C, 2 h; vii, $Me_3O^+BF_4^-$, $CH_2Cl_2$, 0 °C to r.t., 12 h

**Scheme 18**

A method for the preparation of 3-substituted succinaldehydic esters (**53**) involves conversion of the methyl ester of fumaraldehydic acid into the corresponding imidazoline (**52**) by reaction with the proline-derived chiral diamine (**51**; Scheme 19).[56] Cu$^I$-catalyzed conjugate addition of alkyl Grignard reagents and subsequent acidic hydrolysis yields the products (**53**), generally with high *ee*. A very closely related method uses a norephedrine-derived chiral auxiliary (Scheme 20).[57,58] Another related approach employs the chiral imidazoline (**54**), which on treatment with $R_2CuLi$ reagents (R = Me, Bu, Ph, 1-butenyl) followed by hydrolysis gives chiral aldehydic esters (**55**; Scheme 21).[59]

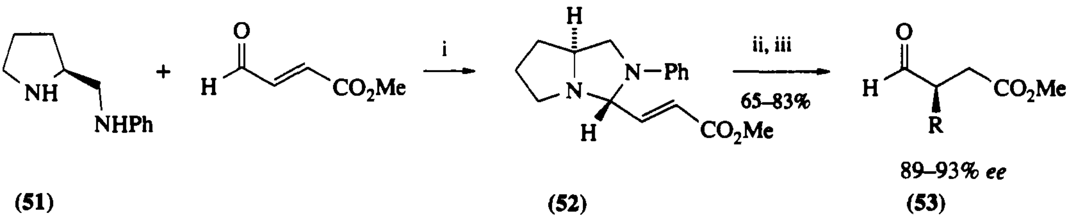

i, cat. $H^+$; ii, RMgBr, CuI, THF; iii, $H_3O^+$

**Scheme 19**

Conjugate addition of dialkylcuprates to the homochiral dioxinone (**57**), prepared from (*R*)-3-hydroxybutyric acid (**56**), produces single diastereomers (**58**), which can be hydrolyzed to the homochiral products (**59**).[60,61] The overall process (Scheme 22) constitutes an example for 'self-regeneration of a stereogenic center'. Interestingly, the high stereoselectivity can not be attributed to simple steric effects.

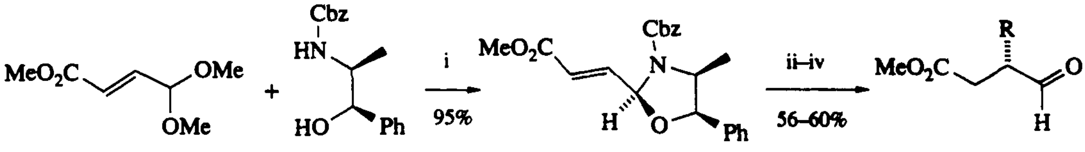
MeO2C
OMe
OMe
+
Cbz
HN
HO
Ph
i
95%
MeO2C
Cbz
N
H
O
Ph
ii–iv
56–60%
R
MeO2C
O
H

(R = Me, Et, Bu, Vinyl) 78–93% *ee*

i, $BF_3{\bullet}Et_2O$, benzene; ii, $R_2CuLi$, $Et_2O$, −25 °C; iii, $HSCH_2CH_2SH$, $BF_3{\bullet}Et_2O$, $CH_2Cl_2$; iv, MeI, $CaCO_3$, $H_2O$

Scheme 20

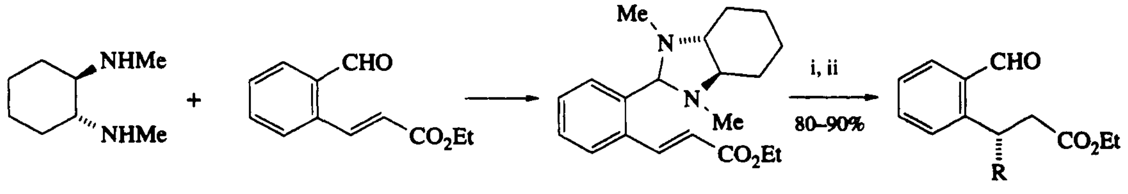
NHMe
NHMe
+
CHO
CO2Et
Me
N
N
Me
CO2Et
i, ii
80–90%
CHO
CO2Et
R

i, $R_2CuLi$, ether, 0 °C; ii, $H_3O^+$ (54) (55) 90–96% *ee*

Scheme 21

The pyramidalization of the trigonal centers (a common feature found in the X-ray structures of several related dioxinones) is probably responsible for the high selectivity.[61] The nucleophile preferentially attacks the electrophilic center from that (convex) face into which it is pyramidalized, in accordance with the principle of minimization of torsional strain. A related example for asymmetric 1,4-addition to chiral dioxinones was reported.[62]

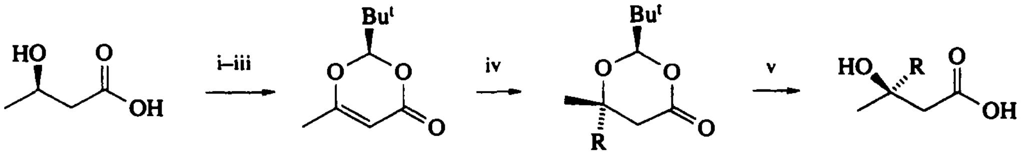
HO
O
OH
i–iii
Bu$^t$
O
O
O
iv
Bu$^t$
O
O
R
O
v
HO
R
O
OH

(56) (57) (58) (59) >99% *ee*

i, Bu$^t$CHO, $CH_2Cl_2$, Dowex 50 W, azeotropic removal of water; ii, LDA, THF, PhSeCl, −75 °C; iii, $H_2O_2$, pyridine, $CH_2Cl_2$, 0 °C; iv, $R_2CuLi$, ether, −75 °C, 2 h; v, 1 M HCl, THF, r.t., 45 min

Scheme 22

### 1.5.2.2 Additions to Chiral Derivatives of α,β-Unsaturated Aldehydes and Ketones

#### *1.5.2.2.1 Additions to chiral acetals and ketals*

The conversion of an α,β-unsaturated aldehyde or ketone into an allylic acetal or ketal, followed by $S_N2'$-type attack of a nucleophile, leads, after hydrolysis of an initially formed enol ether, to a β-substituted carbonyl compound. The overall sequence (Scheme 23) is equivalent to a direct conjugate addition, but has the advantage that it allows the temporary introduction of a chiral auxiliary group: if a chiral ($C_2$-symmetric) diol is used in the acetalization step, the subsequent nucleophilic addition leads to a mix-

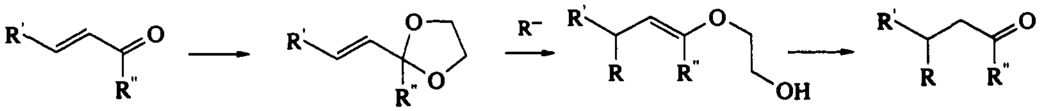
R'
O
R''
R'
O
O
R''
R⁻
R'
O
R
R''
OH
R'
O
R
R''

Scheme 23

ture of two diastereomeric enol ethers (generally in unequal amounts) which may be hydrolyzed to give the product in optically active form.

As a first (isolated) example of such a transformation, some asymmetric induction (26% *ee*) was observed during the addition of $Me_2CuLi/BF_3$ to the chiral ketal, derived from cyclohexenone and (*R*,*R*)-butane-2,3-diol.[63] The addition of trialkylaluminum compounds to α,β-unsaturated ketals and acetals derived from (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (**60**) or its enantiomer (*ent*-**60**), leads to much better results.[64–66] The initially formed enol ethers are first isolated as their corresponding acetates and then hydrolyzed to the actual β-substituted carbonyl compounds. While the ketals, *e.g.* (**61**), react cleanly and with reasonable diastereoselectivities to (**62**; Scheme 24), the acetals (**63**) generally lead to mixtures of regioisomers (**64**) and (**65**), however with an excellent degree of asymmetric induction (Scheme 25). The choice of the solvent is crucial: the desired isomer (**64**) is formed predominantly in less polar solvents like toluene or 1,2-dichloroethane, while more polar solvents (*e.g.* chloroform) strongly favor the direct $S_N2$ attack at the acetal center, leading to the (undesired) allylic ether derivative (**65**). The usefulness of this methodology is demonstrated by the synthesis of the alcohol (**66**), a structural subunit of vitamins K and E (Scheme 26).[65]

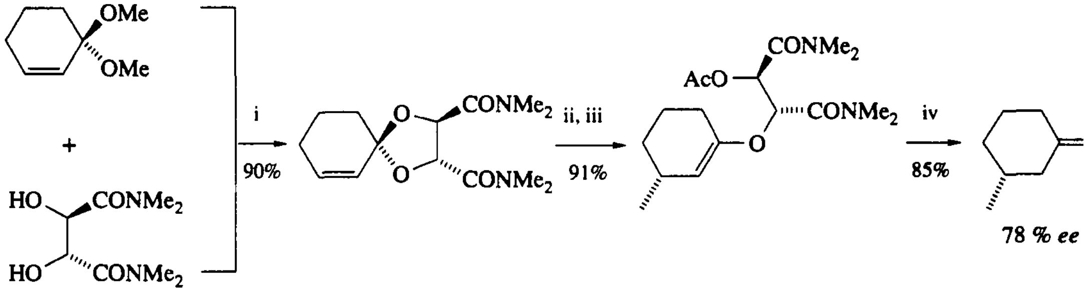

**(60)** **(61)** **(62)**

i, cat. TsOH; ii, 5 equiv. $Me_3Al$, toluene, 3.5 h, r.t.; iii, $Ac_2O$, pyridine, DMAP, 1 h, r.t.; iv, 6 M HCl, dioxane

Scheme 24

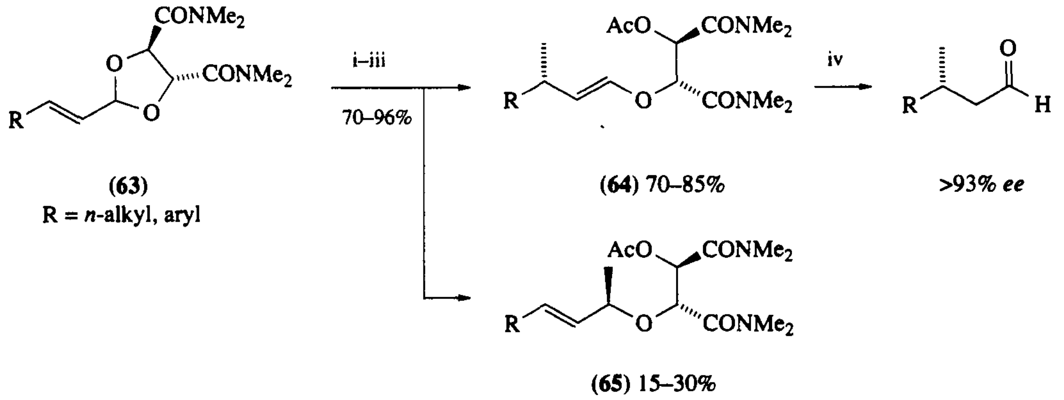

**(63)**
R = *n*-alkyl, aryl

**(64)** 70–85%

>93% *ee*

**(65)** 15–30%

i, 5 equiv. $Me_3Al$, 1,2-dichloroethane or toluene, 0 °C to r.t., 12 h; ii, $Ac_2O$, pyridine, DMAP, 1 h, r.t.; iii, separation of isomers by chromatography; iv, 6 M HCl, dioxane

Scheme 25

The stereochemical outcome of all these reactions may be explained in terms of a stereoelectronically assisted *syn* $S_N2'$ process, assuming a substrate conformation as shown in (**67a**), and a preferred coordination of the Lewis acid to the less hindered acetal oxygen.[67]

In contrast, the corresponding reactions of $RCu/BF_3$ reagents (R = phenyl or alkenyl) with allylic acetals obviously proceed in an *anti* $S_N2'$ fashion, as shown in (**67b**). The unsaturated acetals (**68**), prepared from (*R*,*R*)-butane-1,2-diol, are opened by the $PBu_3$-stabilized reagents to give, after hydrolysis, the β-substituted aldehydes (**69**) with high *ee* (Scheme 27).[68,69] The method has been applied to the preparation of a key intermediate (85% *ee*) for the synthesis of the California red scale pheromone.[69]

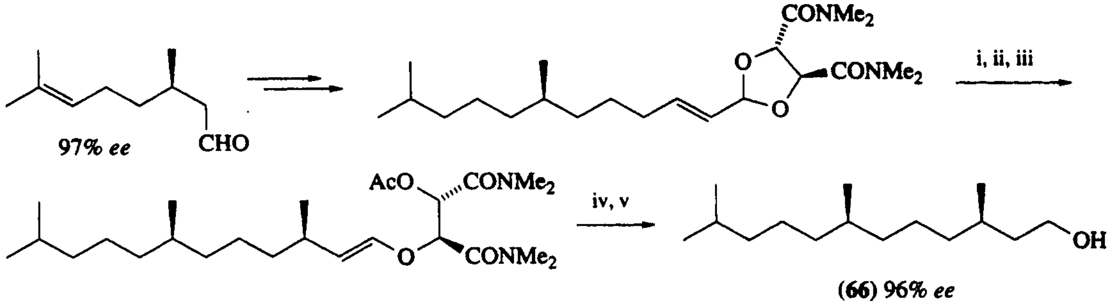

i, $AlMe_3$, toluene; ii, $Ac_2O$, pyridine; iii, chromatography; iv, 6M HCl, dioxane; v, $NaBH_4$

Scheme 26

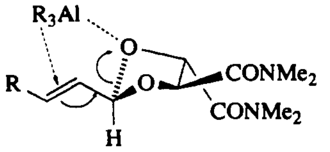

(67a)

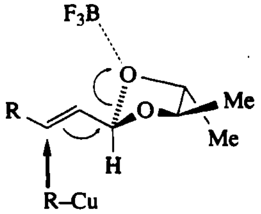

(67b)

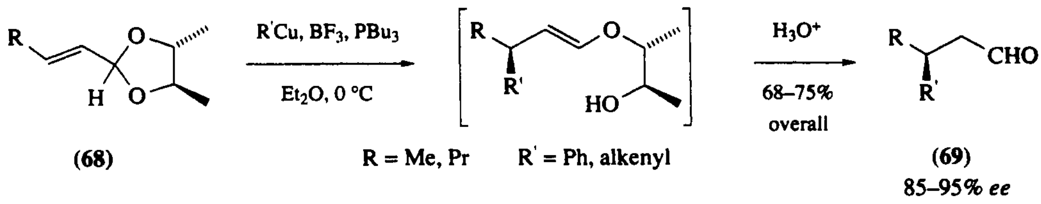

Scheme 27

### 1.5.2.2.2 Additions to chiral N,O-acetals

Analogous to the use of chiral acetals one can employ chiral *N*,*O*-acetals, accessible from α,β-unsaturated aldehydes and certain chiral amino alcohols, to prepare optically active β-substituted aldehydes *via* subsequent $S_N2'$ addition and hydrolysis. However, the situation is more complicated in this case, since the *N*,*O*-acetal center constitutes a new stereogenic center which has to be selectively established. The addition of organocopper compounds to α,β-ethylenic oxazolidine derivatives prepared from unsaturated aldehydes and ephedrine was studied.[70–78] The (diastereo) selectivities were rather low (<50% *ee* after hydrolysis) in most cases, the highest value being 80% *ee* in a single case.[75] There is a strong solvent effect in these reactions, *e.g.* in the addition of lithium dimethylcuprate to the (*E*)-cinnamaldehyde-derived oxazolidine (**70**; Scheme 28):[73] the (*R*)-aldehyde (**71**) is formed preferentially in polar solvents, while the (*S*)-enantiomer (*ent*-**71**) is the major product in nonpolar solvents like hexane. This approach was utilized in the preparation of citronellal (80% *ee*) from crotonaldehyde (40% overall yield).[78]

### 1.5.2.2.3 Additions to chiral imines

The 1,4-addition of carbon nucleophiles to chiral α,β-unsaturated aldimines gives optically active β-substituted aldehydes.[79–86] Best results are obtained with imines prepared from *t*-leucine *t*-butyl ester (**72**). Addition of Grignard reagents to the acyclic imines (**73**) followed by acidic hydrolysis and reduction gives the alcohols (**74**) with high *ee* (Scheme 29).[80,83] The potassium salt of diethyl malonate also adds smoothly to (**73**), however providing a product of opposite configuration (48% yield, up to 86% *ee*).[81,84] Addition of Grignard reagents to cyclic compounds of type (**75**) leads initially to the intermedi-

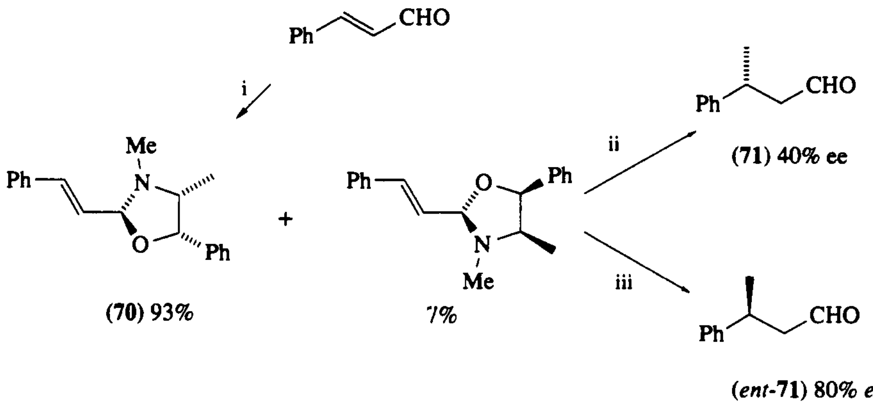

i, (+)-ephedrine, 4 Å mol. sieve, r.t.; ii, $Me_2CuLi$, $Et_2O$–HMPA (1:1), –42 °C, $H_3O^+$;
iii, $Me_2CuLi$, hexane, –42 °C, $H_3O^+$

**Scheme 28**

ate (*Z*)-enamides (**76**), which can either be (kinetically) protonated or alkylated (possibly after isomerization to the thermodynamically more stable (*E*)-isomer), allowing a selective entry into each class of compounds (**77**), (**78**) or (**79**; Scheme 30).[82,85] The products are obtained reliably with high *ee* (82–93%). The method was applied in a synthesis of (+)-ivalin (**80**; Scheme 31).[87]

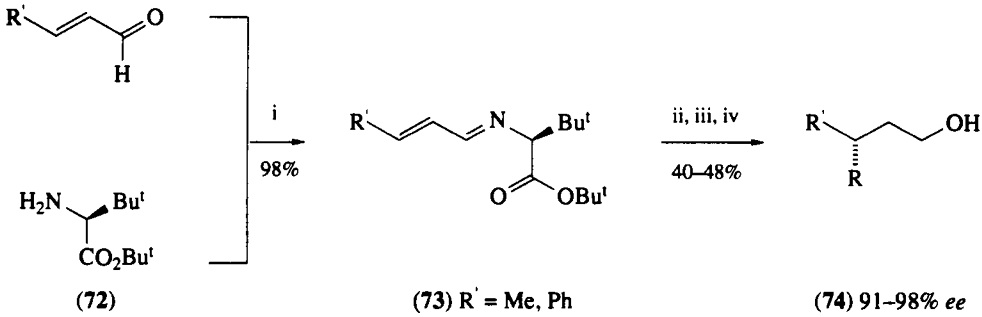

i, 4 Å mol. sieve, hexane, 0 °C to r.t.; ii, 2 equiv. RMgBr (R = Ph, c-$C_6H_{11}$, $Bu^n$, Et, $Me_2C{=}CH(CH_2)_2$), $Et_2O$–THF (5:1), –55 °C, 1.5 h; iii, 2 M HCl; iv, $NaBH_4$

**Scheme 29**

### *1.5.2.2.4 Additions to other chiral derivatives*

Although desirable, the recovery of a chiral auxiliary is not always crucial. Some techniques employ α,β-unsaturated carbonyl compounds containing a 'disposable' stereogenic center, which is removed after the (asymmetric) conjugate addition step has been performed. This concept appears to be useful only if the chiral substrate is easily accessible in high enantiomeric purity.

Conjugate additions to 4-oxo-2-cyclopentenyl acetate (**81**), a compound readily available in both enantiomeric forms,[90] lead (after elimination of the acetoxy group) to substituted cyclopentenones (**82**) (Scheme 32).[88,89] For instance, this methodology was used, though employing (*rac*-**81**), in a synthesis of brefeldin A.[91] The chiral aldehyde (**83**), which is accessible from arabinose, was used in syntheses of botryodiplodin (**84**) and of lignans like (–)-burseran (**85**; Scheme 33).[92,93] In both syntheses, the conjugate addition constitutes a key step and proceeds with high diastereoselectivity. The preparation of homochiral 5-substituted cyclohexenones is possible *via* copper-catalyzed addition of Grignard reagents to 5-trimethylsilyl-2-cyclohexenone (**86**; or *ent*.-**86**) followed by oxidative elimination of the TMS group.[94–96] Multigram amounts of both enantiomers of (**86**) may be prepared in essentially pure form quite easily from anisole. According to Scheme 34, the method was used for the synthesis of (+)-α-curcumene (**87**) and of (–)-β-vetivone (**88**). Additions of Gilman reagents to 5-methoxy-2-cyclopentenone

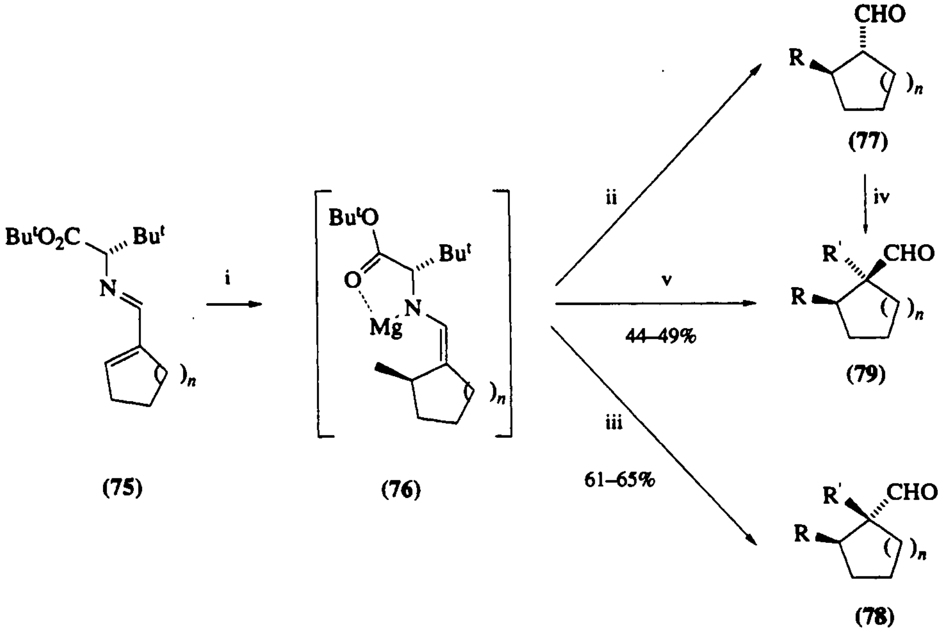

$n$ = 1 or 2 R = Ph, vinyl R' = Me, Et, benzyl, allyl, MOM

i, RMgBr, THF, –23 °C; ii, $H_3O^+$; iii, R'X, HMPA, THF, –23 °C to r.t., 15 h, then $H_3O^+$; iv, KH, R'X, THF, –23 °C; v, reflux for 3 to 6 h, then R'X, HMPA, THF, –23 °C to r.t., 15 h, then $H_3O^+$

Scheme 30

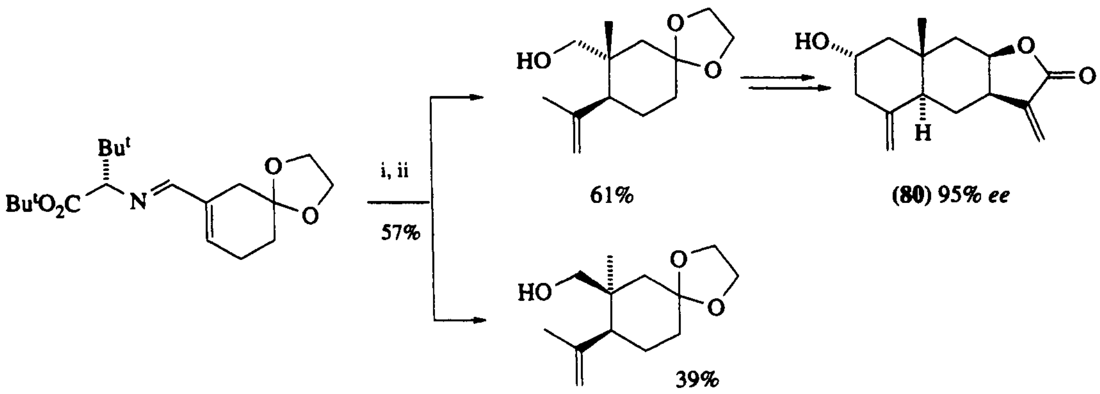

i, 2-propenylMgBr, THF, then MeI, HMPA, then $H_3O^+$; ii, $NaBH_4$, MeOH

Scheme 31

(**89**) also proceed with high diastereoselectivity to give 1,4-adducts, from which the methoxy group can be removed by treatment with samarium iodide to afford 3-substituted cyclopentanones of high enantiomeric purity (Scheme 35).[97,98] Another method, which does not seem to be of high preparative value though, involves diastereoselective complexation of the (enantiomerically pure) enone (**90**) by treatment with tricarbonyl($\eta^4$-benzylideneacetone)iron to give a single complex (**91**). Reaction with α-lithioisobutyronitrile leads (after TFA quench) to compound (**92**), which is subsequently subjected to periodate cleavage to afford the pure carboxylic acid (**93**; Scheme 36).[99]

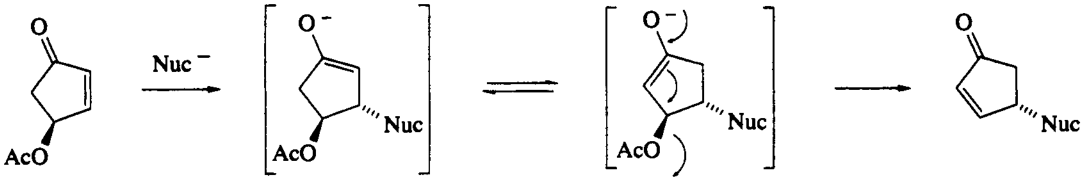

(81) (82)

Scheme 32

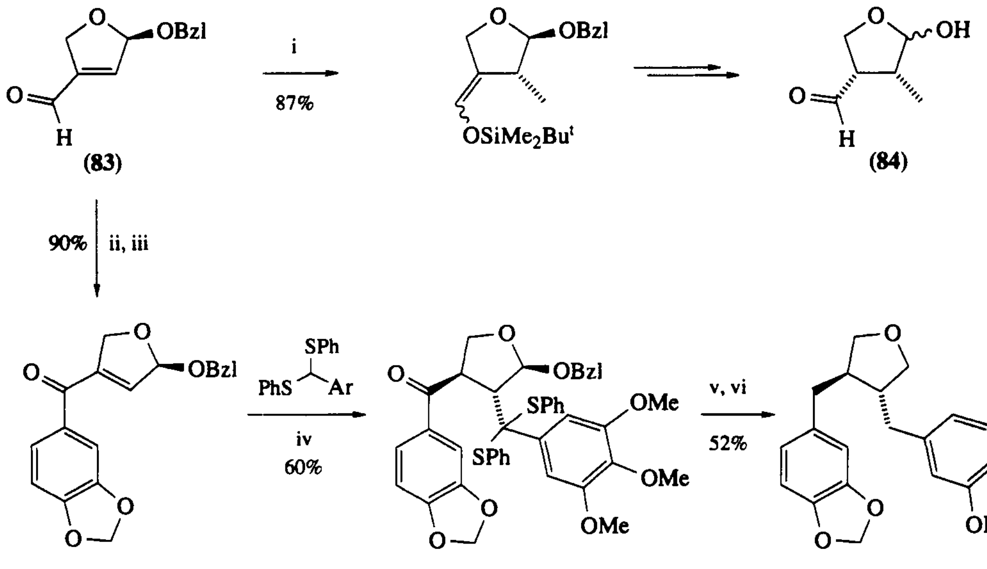

(83) (84) (85) >98% *ee*

i, LiMeCNCu, $Bu^tMe_2SiCl$, THF, –78 °C to r.t.; ii, ArMgBr, THF, 0 °C; iii, $CrO_3$/pyridine, $CH_2Cl_2$, r.t., 15 min.; iv, $Bu^nLi$, THF, –78 °C to r.t.; v, Raney Ni, DME, 0 °C; vi, $H_2$, Pd/C, $AcOH/H_2O$, 6.5 h

Scheme 33

### 1.5.2.3 Additions to Chiral Vinylic Sulfur Compounds

Since early investigations about the asymmetric addition of diethyl sodiomalonate to optically active vinylic sulfoxides,[100,101] Posner and his coworkers[102-117] have developed a highly useful methodology based on the conjugate addition of carbon nucleophiles to homochiral α-arylsulfinyl-α,β-unsaturated carbonyl compounds. While acyclic derivatives still lead only to moderate results,[105] the strength of this method is for cyclic systems. For example, the 2-sulfinyl-2-cycloalkenones (**94**) and (**95**), the 2-sulfinyl-2-alkenolides (**96**) and (**97**), as well as their respective enantiomers are excellent substrates. All these compounds are quite readily accessible in enantiomeric purities of >98% and are configurationally stable, at least for several months at 0 °C.

Reaction of a variety of organometallic reagents (RM) with (**94**) or (**95**) leads diastereoselectively to addition products of type (**98**), which are then desulfurized yielding 3-substituted cycloalkanones (**99**) of reasonable to high enantiomeric purities (Scheme 37 and Table 2).[106,107,110] The steric course of these addition reactions can be understood in terms of an intermediate chelate, which is attacked by the nucleophile from the less hindered face, as shown in (**100a**). In contrast, dialkylmagnesium[108] and dialkylcuprate[109] reagents afford products with an absolute configuration opposite to that obtained with other reagents. This in turn can be rationalized as the result of an attack on the nonchelated substrate molecule, which should prefer the conformation shown in (**100b**). The role of the metal in controlling the stereochemistry of these reactions (chelate *versus* nonchelate mode) was the subject of a recent theoretical study.[119,120] Ester enolates may also be added as donors to these substrates (attack in the nonchelate addition mode),[115] especially with α-substituted derivatives leading to extraordinary high levels of asymmetric induction in some cases (*e.g.* Scheme 39).

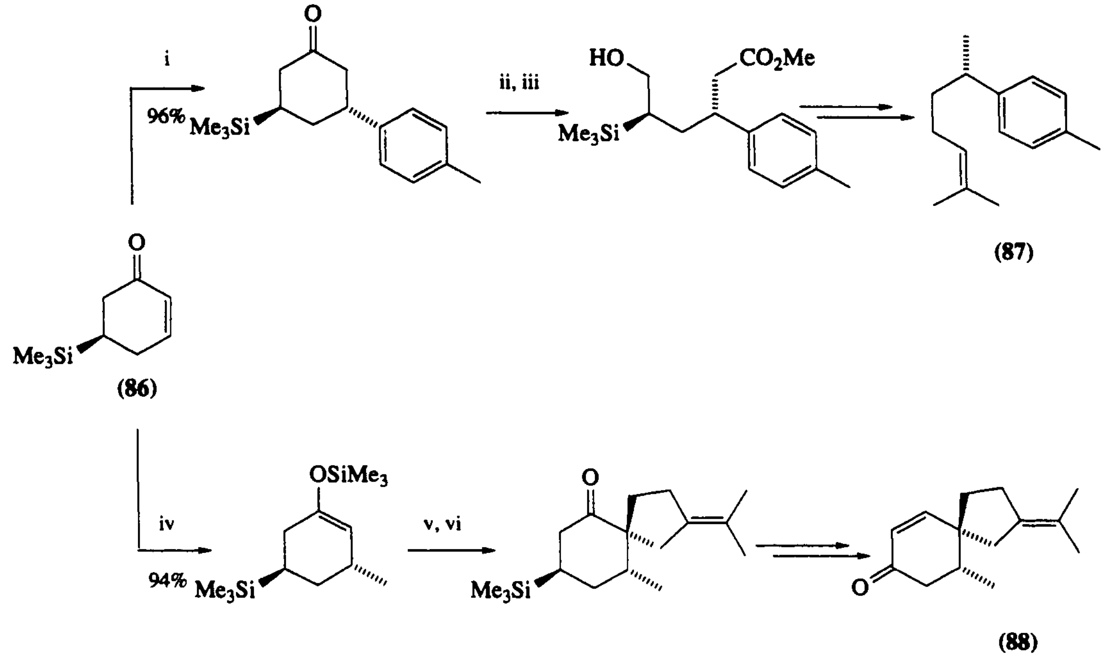
i
96%
Me3Si
HO
CO2Me
ii, iii
(87)
(86)
iv
94%
OSiMe3
v, vi
(88)

i, *p*-TolMgBr, CuBr•Me$_2$S, Me$_3$SiCl, HMPA; ii, MCPBA; iii, NaOMe, MeOH; iv, MeMgI, CuBr•Me$_2$S, Me$_3$SiCl, HMPA; v, 1,4-dibromo-2-isopropylidenebutane, ZnBr$_2$; vi, NaOMe, THF, r.t. to 50 °C, 2.5 h

**Scheme 34**

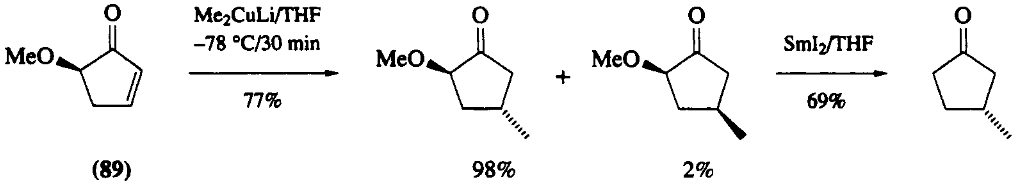
MeO
Me2CuLi/THF
−78 °C/30 min
77%
(89)
98%
2%
SmI2/THF
69%

**Scheme 35**

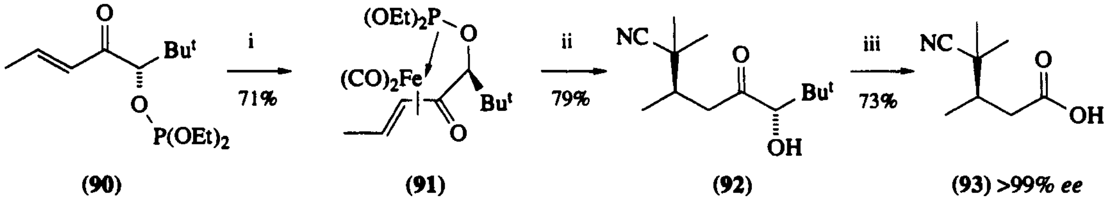
Bu^t
P(OEt)2
i
71%
(OEt)2P
(CO)2Fe
ii
79%
NC
OH
iii
73%
(90)
(91)
(92)
(93) >99% ee

i, tricarbonyl(benzylideneacetone)iron, THF, 60–65 °C, 20 h; ii, α-lithioisobutyronitrile, THF, HMPA, −78 °C, then TFA; iii, H$_5$IO$_6$, MeOH, H$_2$O

**Scheme 36**

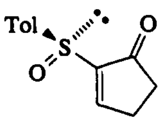

**(94)**

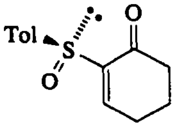

**(95)**

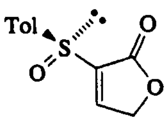

**(96)**

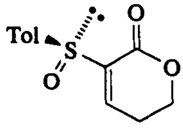

**(97)**

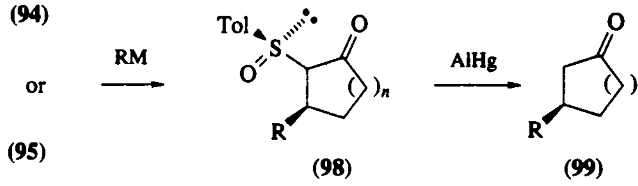

Scheme 37

**Table 2** Preparation of Cyclic β-Substituted Carbonyl Compounds (**99**) *via* Addition of Organometallic Reagents to Unsaturated Sulfoxides (**94**) or (**95**) Followed by Desulfurization of the Intermediates (**98**; Scheme 37)

| *Starting material* | *RM* | *R* | *Overall yield (%)* | *ee of (99) (%)* |
|---|---|---|---|---|
| (**94**) | ZnBr$_2$/MeMgBr | Me | 89 | 87 |
| (**94**) | MeTi(Pr$^i$O)$_3$ | Me | 90 | 90 |
| (**94**) | MeMgCl | Me | 91 | 95–100 |
| (**95**) | ZnBr$_2$/MeMgBr | Me | 95 | 62 |
| (**95**) | MeTi(Pr$^i$O)$_3$ | Me | 85 | 86 |
| (**94**) | ZnBr$_2$/EtMgCl | Et | 90 | 80 |
| (**94**) | EtTi(Pr$^i$O)$_3$ | Et | 67 | >98 |
| (**94**) | ZnBr$_2$/VinylMgBr | Vinyl | 75 | 92 |
| (**94**) | ZnBr$_2$/PhMgCl | Ph | 70 | >98 |
| (**94**) | 2-NaphthylMgBr | 2-Naphthyl | 90 | >98 |

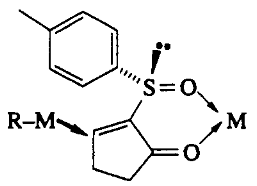

**(100a)**

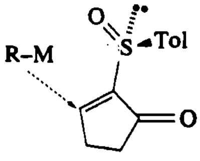

**(100b)**

Several applications in total syntheses exemplify the value of this methodology; 11-oxoequilenin methyl ether (**101**; Scheme 38),[105,107] (+)-α-cuparenone,[109] (–)-podorhizon,[112] (–)-methyl jasmonate (**102**; Scheme 39),[114] (+)-estrone methyl ether,[116] and the so called (+)-A-factor (**103**; Scheme 40)[117] were all prepared in high enantiomeric purity. Other applications constitute preparations of 2-alkylchroman-4-ones,[118] and of 3-vinylcyclopentanones, highly valuable intermediates for steroid total synthesis.[106,107]

In the course of a total synthesis of aphidicolin (**107**), the conjugate addition of the dienolate (**104**) to the chiral butenolide derivative (**105**) serves as a key step. A 7.4:1 mixture of diastereomeric products is obtained, from which the major isomer (**106**) can be isolated in pure form after recrystallization (Scheme 41).[121] The selectivity of this remarkable reaction, in which two quaternary stereogenic centers are simultaneously generated in a highly selective manner, can be explained by the assumption that the reactants approach each other in the chelate-mode indicated in (**108**).

Another application of additions to chiral vinylic sulfoxides constitutes the Hantzsch-type reaction of methyl 3-aminocrotonate with compound (**109**), yielding the dihydropyridine derivative (**110**) as a single

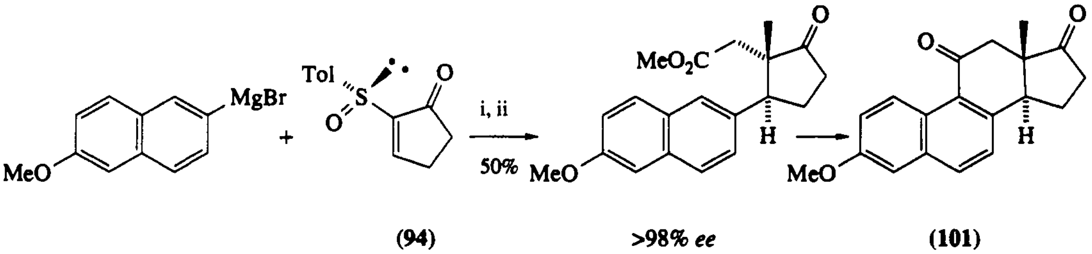

i, THF, –78 °C, then MeI, HMPA; ii, 3 equiv. Me$_2$CuLi, Et$_2$O, THF, 0 °C, 2 h, then BrCH$_2$CO$_2$Me, 25 °C

Scheme 38

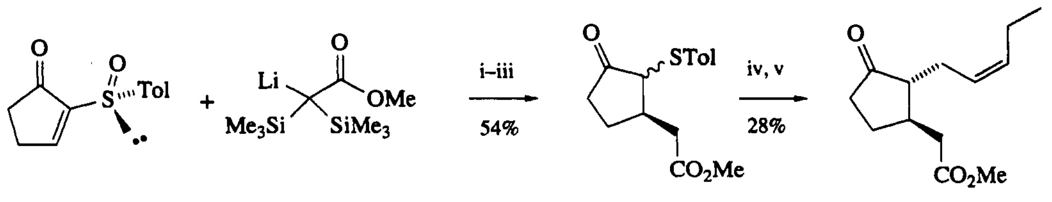

(*ent*-94) (**102**) >98% *ee*

i, THF, –78 °C, 5 min; ii, $P_2I_4$; iii, KF, iv, NaH, (*Z*)-2-pentenyl bromide; v, Raney Ni

**Scheme 39**

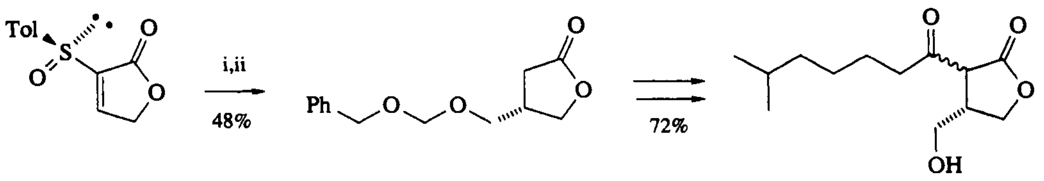

(**96**) 87% *ee* (**103**)

i, $PhCH_2OCH_2OCH_2Li$, 2,5-dimethyl-THF, –78 °C, 10 min; ii, Raney Ni, acetone

**Scheme 40**

(detectable) diastereomer, which was then oxidized to give the sulfone (**111**) with high *ee* (Scheme 42).[122]

Optically active organic compounds, bearing a trifluoromethyl substituent at a stereogenic center, are accessible *via* addition of enolates to the chiral sulfoxides (**112**) or (**113**).[123] Ephedrine-derived sulfoximines of type (**114**) also undergo diasteroselective addition of organometallic reagents, allowing the preparation of 3-alkylalkanoic acids with high *ee*.[124,125] The chirally modified vinylic sulfone (**115**) was utilized in the asymmetric preparation of α-substituted aldehyde derivatives (Scheme 43).[126]

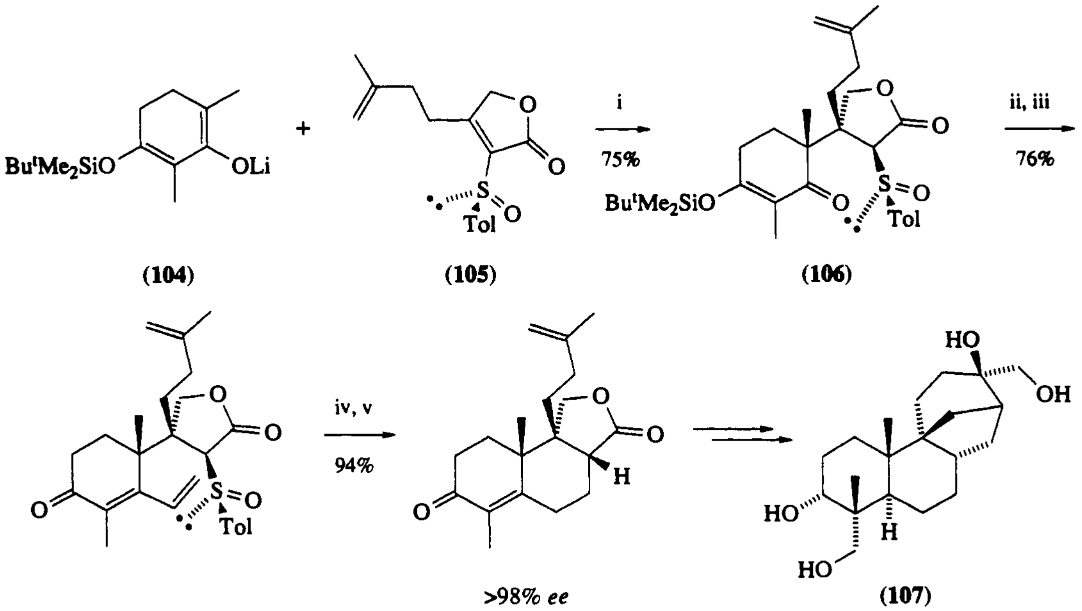

(**104**) (**105**) (**106**)

>98% *ee* (**107**)

i, THF, –95 °C, 2 h; ii, vinylLi, toluene, r.t., 20 min; iii, HF in MeOH, r.t., 20 min; iv, NaOMe, MeOH, 0 °C, 2.5 h; v, Zn, aq. $NH_4Cl$

**Scheme 41**

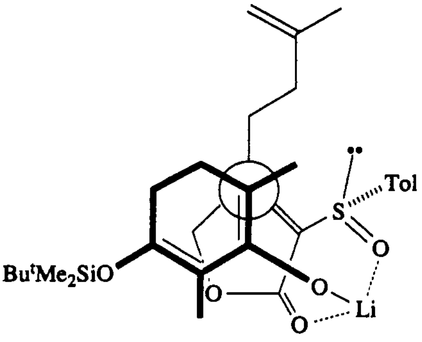
Bu$^t$Me$_2$SiO
Tol
S
O
O
Li
O
O

**(108)**

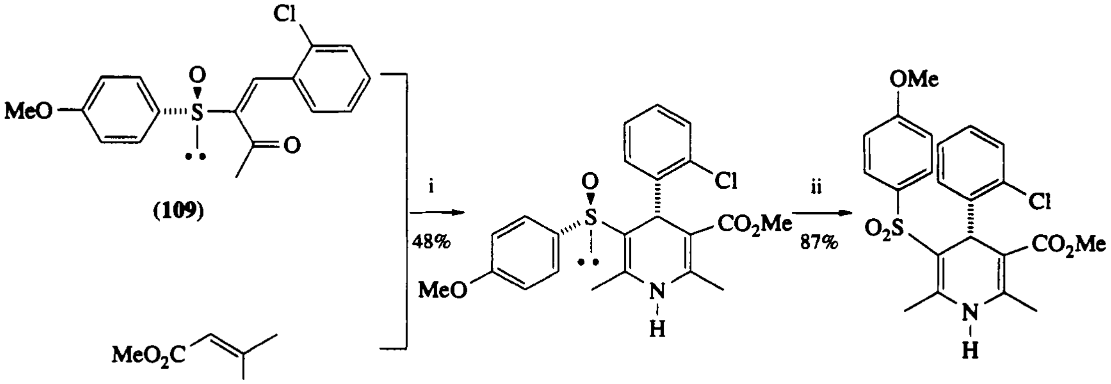
MeO
O
S
Cl
O
MeO$_2$C
NH$_2$
i
48%
O
S
Cl
CO$_2$Me
MeO
N
H
ii
87%
OMe
O$_2$S
Cl
CO$_2$Me
N
H

**(109)**

**(110)**

**(111)** 94.5% *ee*

i, MeOH, reflux; ii, Bu$^t$O$_2$H, 18-crown-6, KOH, EtOH

**Scheme 42**

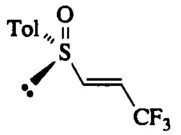

**(112)**

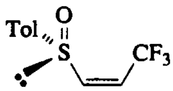

**(113)**

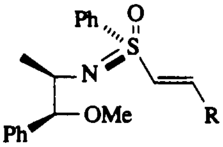
Ph
O
S
N
OMe
Ph
R

**(114)**

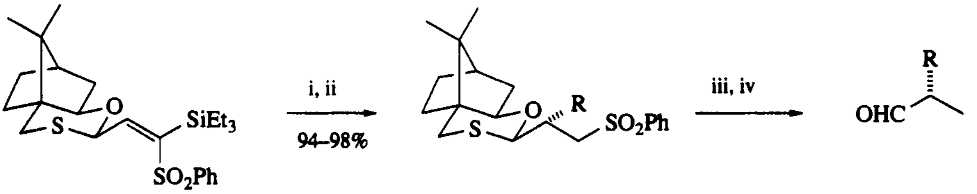
O
S
SiEt$_3$
SO$_2$Ph
i, ii
94–98%
O
R
S
SO$_2$Ph
iii, iv
R
OHC

**(115)**

96–98% *ee*

i, RLi, LiBr–Et$_2$O, hexane, –78 °C; ii, Bu$^n{}_4$F; iii, Na–Hg; iv, HgCl$_2$

**Scheme 43**

### 1.5.2.4 Additions to α,β-Unsaturated Acyl Ligands Bound to a Chiral Metal Center

Addition of organolithium compounds to chiral (*E*)-configured α,β-unsaturated iron acyl complexes (**116**) proceeds with an exceptionally high degree of asymmetric induction.[127–132] The initially formed anionic intermediates (**117**) were either protonated or trapped with methyl iodide yielding diastereomerically pure products (**118**; Scheme 44). Since the starting complexes are configurationally stable under ambient conditions and accessible in enantiomerically pure form, this method allows (after cleavage of the metal–carbon bond) the preparation of a variety of homochiral organic compounds. The selectivity observed for these reactions can be explained in terms of a quite rigid substrate conformation as indicated in Scheme 44, where the acyl C=O group is *anti* with respect to the carbonyl ligand. It was proposed that more than simple steric effects are responsible for this conformational preference of the acyl group, since the diastereoselectivity of the conjugate addition reaction does not change much with the steric bulk of the phosphine ligand.[133]

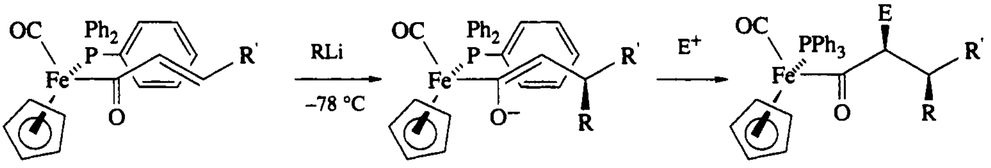

(**116**) R' = alkyl, Ph (**117**) R = Me, Bu (**118**) E = H, Me

Scheme 44

## 1.5.3 DIASTEREOSELECTIVE ADDITIONS OF CHIRAL CARBON NUCLEOPHILES TO ACHIRAL SUBSTRATES

### 1.5.3.1 Reactions of Chiral Enolates

The chiral, nonracemic oxazepine derivative (**46**; Scheme 18) was studied as donor in the Michael addition to prochiral α,β-unsaturated carbonyl compounds.[134,135] The products were obtained with 44–55% *ee* after removal of the chiral auxiliary group. With 1-nitrocyclohexene as acceptor, somewhat better selectivities (62% *ee*) were observed.[136]

A double π-face selective aprotic Michael addition of the lithium dienolate, derived from the chiral senecioate (**119**), to cyclopentenone served for the total synthesis of (–)-kushimone (**120**; Scheme 45).[137,138] The selectivity of the key reaction was rationalized by the assumption of a transition state as shown in (**121a**). A related approach involves the Michael addition of enolates, derived from chiral propionates, to methyl (*E*)-crotonate (Scheme 46).[139] The formation of the '*threo*' isomer (**122**) as the major product indicates a transition state structure as shown in (**121b**). This method was utilized in the synthesis of the marine natural product 7,20-diisocyanoadociane (**123**; Scheme 47).[140]

The intramolecular Michael reaction of chiral acetoacetate derivatives (**124**) proceeds with excellent selectivity when the alcohol (**125**) is used as the chiral auxiliary (Scheme 48),[141] leading to valuable intermediates for the synthesis of homochiral 11-keto steroids.[142] The stereochemical outcome suggests a reactive conformation as shown in (**126**).

Diastereoselective Michael additions of enolates, prepared from the chiral amides (**127**) and (**128**), to prochiral α,β-unsaturated esters were utilized in the synthesis of (+)-dehydroiridodiol (**129**) and its isomer (**130**; Scheme 49).[143]

When Michael additions of chiral enolates to nitroalkenes were studied, it was found that lithium enolates (**132**) of 1,3-dioxolan-4-ones (**131**), derived from the corresponding α-hydroxy acids, afford the adducts (**133**) with high diastereoselectivity (Scheme 50).[144] Recrystallization leads, in general, to diastereomerically pure products, which in turn can efficiently be converted to homochiral compounds like (**134**), (**135**) or (**136**). A number of other chiral enolates (**137**)–(**140**) were also shown to undergo highly selective additions to nitroalkenes; however, product configurations were not determined in these cases.

Mukaiyama–Michael addition of a chiral ketene acetal to nonprochiral vinyl ketones gives products of 72–75% *ee*.[145] A chirally modified glycine derivative (Schiff-base) adds to vinylic phosphorus compounds to yield, after hydrolysis, products with 54–85% *ee*.[146] Another chiral glycine equivalent was used for the preparation of homochiral proline derivatives *via* diastereoselective addition to α,β-unsaturated aldehydes and ketones.[147,148]

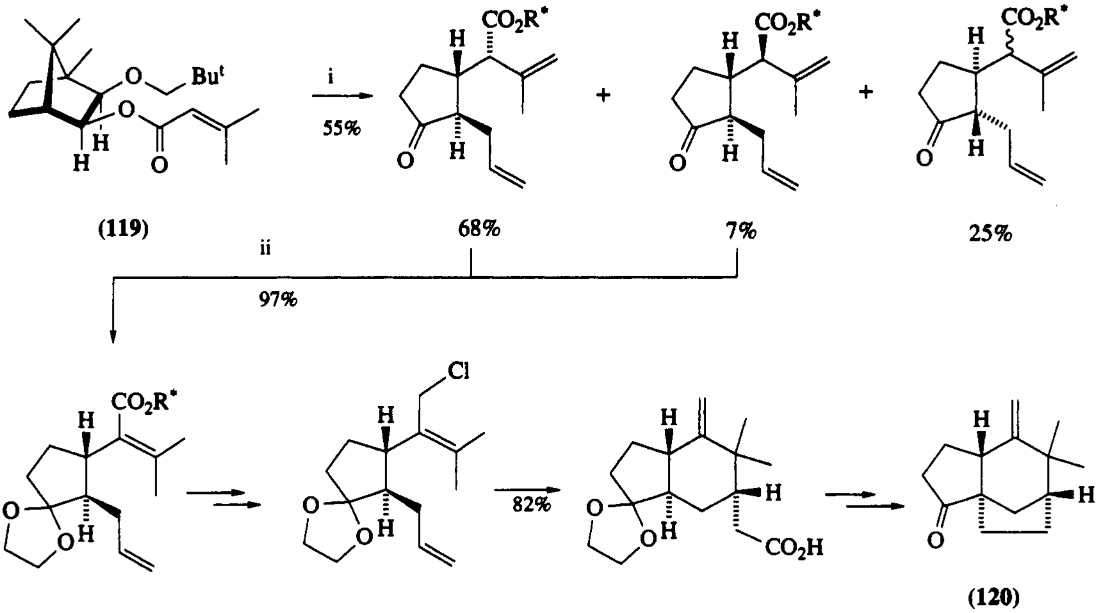
(119)
i
55%
68%
7%
25%
ii
97%
82%
(120)

i, LDA, THF, −78 °C, then cyclopentenone, 5 min, then allyl bromide; ii, ethylene glycol, cat. TsOH, $C_6H_6$, reflux

Scheme 45

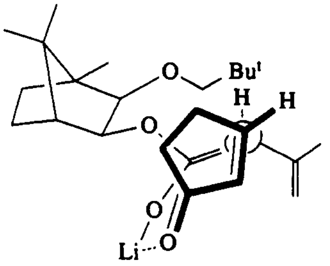

(121a)

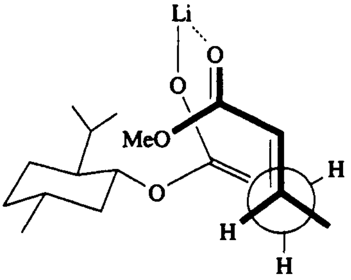

(121b)

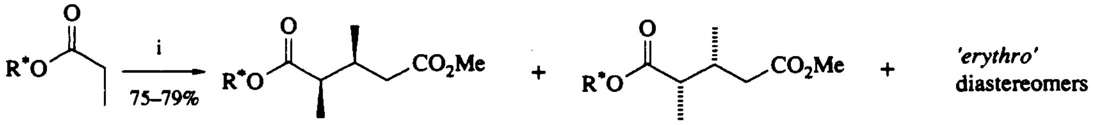
i
75–79%
'erythro' diastereomers

(122)

| | | | |
|---|---|---|---|
| R*OH = (−)-8-Ph-menthol | 86% | 4% | 10% |
| R*OH = (−)-menthol | 69% | 19% | 12% |

i, LDA, THF, −78 °C, 30 min, then (*E*)-methyl crotonate, −100 °C, 3 h, then AcOH quench

Scheme 46

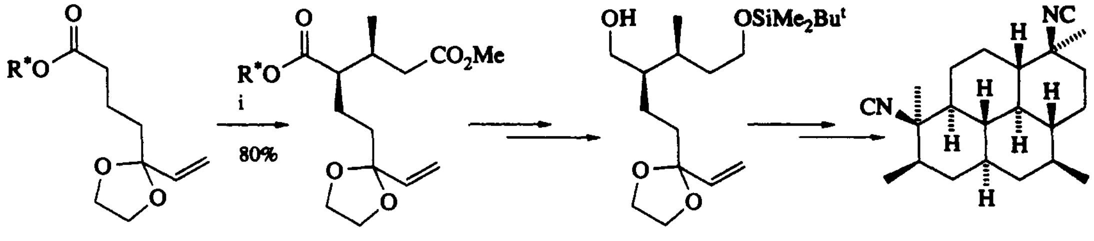
i
80%
OSiMe$_2$Bu$^t$
CO$_2$Me

R$^*$OH = (–)-menthol + diastereomers 60% *ee* **(123)**

i, LDA, THF, –78 °C, 30 min, then (*E*)-methyl crotonate, –78 °C, 1 h, then AcOH quench

**Scheme 47**

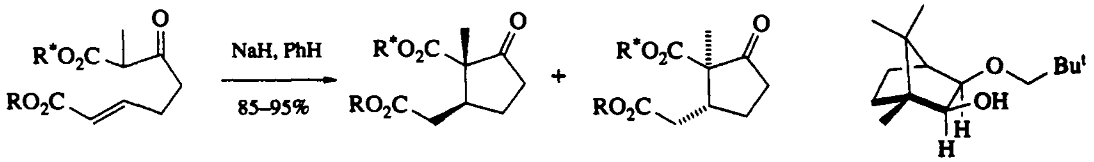
NaH, PhH
85–95%

**(124)** R = Me 94% 6% **(125)**

R = Bu$^t$ >98% <2%

**Scheme 48**

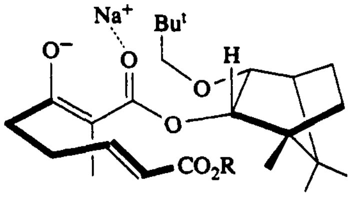

**(126)**

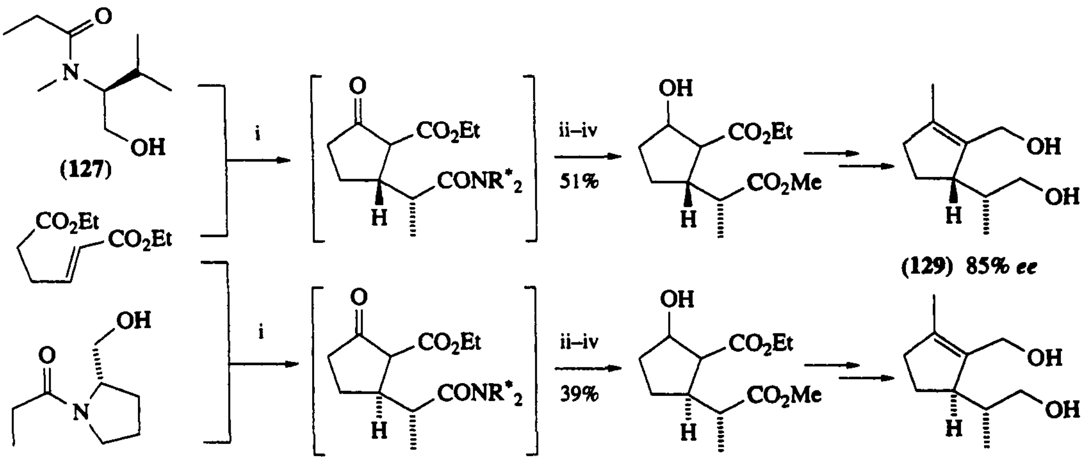
i
ii–iv
51%
i
ii–iv
39%

**(127)** **(128)** **(129)** 85% *ee* **(130)** 79% *ee*

i, LDA, THF, Bu$^t$OK, –78 °C; ii, NaBH$_4$, EtOH, 0 °C, 30 min; iii, 2 M HCl, reflux, 2 h; iv, CH$_2$N$_2$, Et$_2$O, 0 °C, 30 min

**Scheme 49**

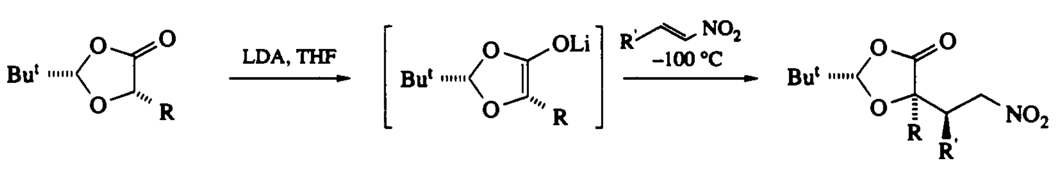

(131) (132) (133) 85 to >98% *ee*

R = Me, Ph, $CH_2CO_2Li$ R' = Me, Et, Ph

Scheme 50

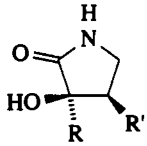

(134)

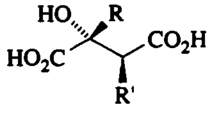

(135)

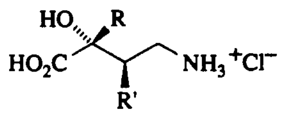

(136)

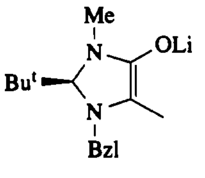

(137)

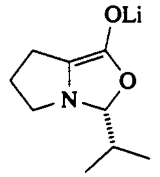

(138)

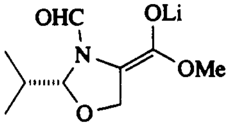

(139)

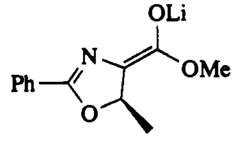

(140)

## 1.5.3.2 Reactions of Chiral Azaenolates and Enamines

Early investigations have demonstrated that aldehydes and ketones can be enantioselectively α-alkylated *via* Michael reactions of the corresponding enamines, prepared from proline-derived secondary amines.[149–156] However, optical purities of the products were generally low and never exceeded 59% *ee*.[157] This kind of asymmetric α-alkylation could later be improved, allowing for example the preparation of compound (141) with high *ee* (Scheme 51).[158–160]

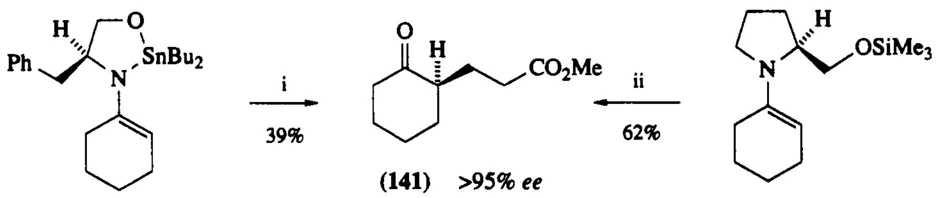

(141) >95% *ee*

i, $H_2C{=}CHCO_2Me$, pentane, 20 °C, 2.5 h; ii, $H_2C{=}CHCO_2Me$, $MgCl_2$, THF, 0 °C, 24 h, r.t., 24 h

Scheme 51

A method, based on a Michael-type (deracemizing) alkylation reaction, allows the enantioselective generation of quaternary carbon centers (Scheme 52).[161] The chiral imine (143), prepared in good yield from racemic (142) and (*S*)-(–)-1-phenylethylamine, smoothly reacts with (nonprochiral) methyl vinyl ketone to give, with quantitative recovery of the chiral auxiliary, the valuable diketone (144) in high yield and high enantiomeric purity. This technique was applied to the synthesis of steroid intermediates[162,163] and to the preparation of optically active oxa-spiro compounds.[164] Whereas 'normal' β-substituted Michael acceptors do not react with (143), (*E*)-crotyl cyanide (145) was shown to be a sufficiently strong acceptor.[165] Reaction of (*ent*-143) with (145) in cyclohexane leads diastereoselectively to a mixture of the bicyclic compounds (147) and (148), both secondary products of the initially formed Michael adduct (146; Scheme 53). The selectivity can be rationalized in terms of a transition state as drawn in (149a). An intramolecular application of this method involves the cyclization of

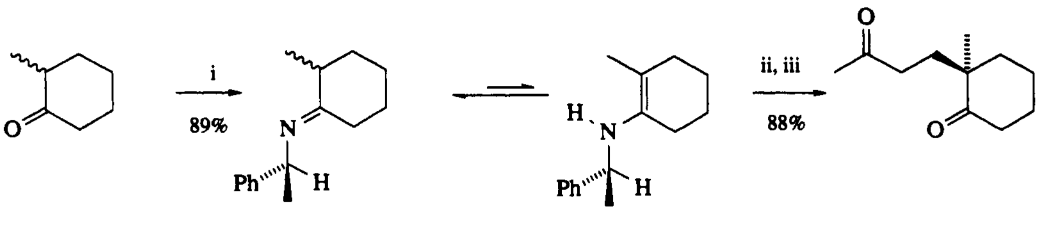

**(142)** **(143)** **(144)** 91% *ee*

i, (*S*)-(–)-1-phenylethylamine, TsOH, toluene, $-H_2O$; ii, MVK, THF, r.t., 3 d; iii, 10% aq. AcOH, r.t., 1 h

Scheme 52

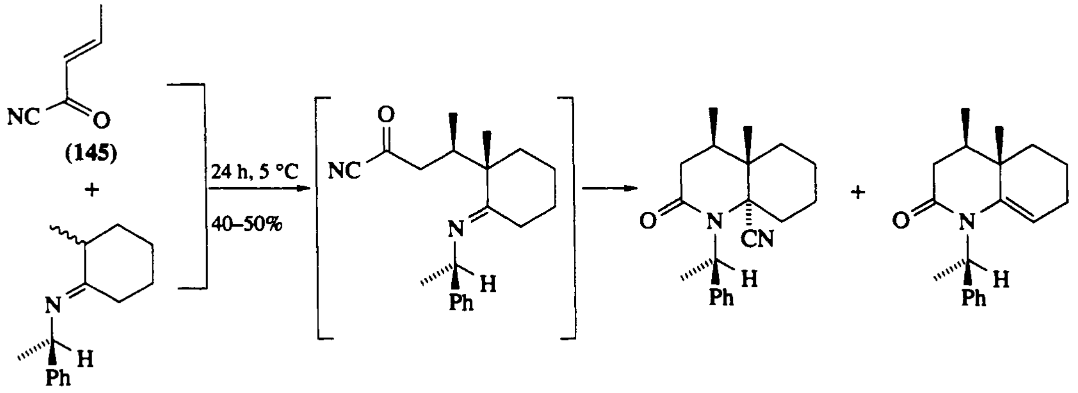

**(145)** + (*ent*-**143**) **(146)** **(147)** + **(148)**

Scheme 53

compound (**150**) in a highly enantioselective manner (Scheme 54).[166] The product (**151**) can be transformed into the piperidine derivative (**152**), which in turn serves for the preparation of valuable intermediates for alkaloid total synthesis. The observed selectivity is in accordance with a transition state structure as drawn in (**149b**).

A highly selective method for the preparation of optically active β-substituted or β,γ-disubstituted-δ-keto esters and related compounds is based on asymmetric Michael additions of chiral hydrazones (**156**), derived from (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) or its enantiomer (RAMP), to unsaturated esters (**154**).[167–172] Overall, a carbonyl compound (**153**) is converted to the Michael adduct (**155**) as outlined in Scheme 55. The actual asymmetric 1,4-addition of the lithiated hydrazone affords the adduct (**157**) with virtually complete diastereoselection in a variety of cases (Table 3). Some of the products were used for the synthesis of pheromones,[169] others were converted to δ-lactones.[170] The Michael acceptor (**158**) also reacts selectively with SAMP hydrazones.[171] Tetrahydroquinolindiones of type (**159**) are prepared from cyclic 1,3-diketones *via* SAMP derivatives like (**160**), as indicated in Scheme 56.[172]

Michael reactions of chiral lithioenamines of β-oxo esters with dimethyl alkylidenemalonates were studied.[173–175] Especially the α-alkyl-substituted compounds (**161**) and (**163**), derived from L-valine *t*-butyl ester, afford, after hydrolysis, the adducts (**162**) and (**164**), respectively, diastereoselectively and with high *ee* (Scheme 57).[175] In the presence of TMS-Cl, even weaker acceptors like acrylates or MVK were shown to react.[176] A somewhat related diastereoselective 1,4-addition, followed by a Pictet–Spengler-type cyclization, allows the preparation of compound (**165**; Scheme 58),[177] a central intermediate for the synthesis of several alkaloids.[177,178]

The anion of the bislactim ether (**166**) successfully acts as a chiral donor in Michael additions to prochiral substrates.[179–181] With methyl enoates, the reaction proceeds generally with high diastereoselectivity producing the isomer (**167**) as the major, and (**168**) as the minor product (Scheme 59).[179] This allows the preparation of virtually enantiomerically pure (*R*)-glutamic acid derivatives, since complete stereocontrol is usually obtained at the newly formed ring–stereogenic center. Conjugated dienoates are attacked under the same conditions in a 1,6-fashion with even higher selectivities to produce, after hydrolysis of the bislactim ether moiety, the adducts (**169**) as single isomers, however with unknown relative configuration (Scheme 60).[180] Enones, especially cyclic ones, are also suitable substrates

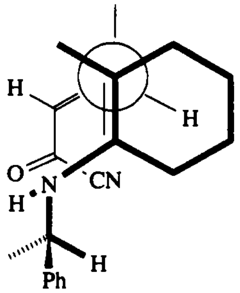
H
H
O
N
CN
H
H
Ph

**(149a)**

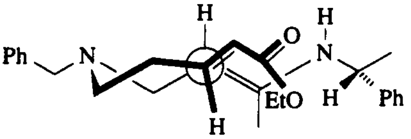
Ph
N
H
O
H
N
EtO
H
Ph
H

**(149b)**

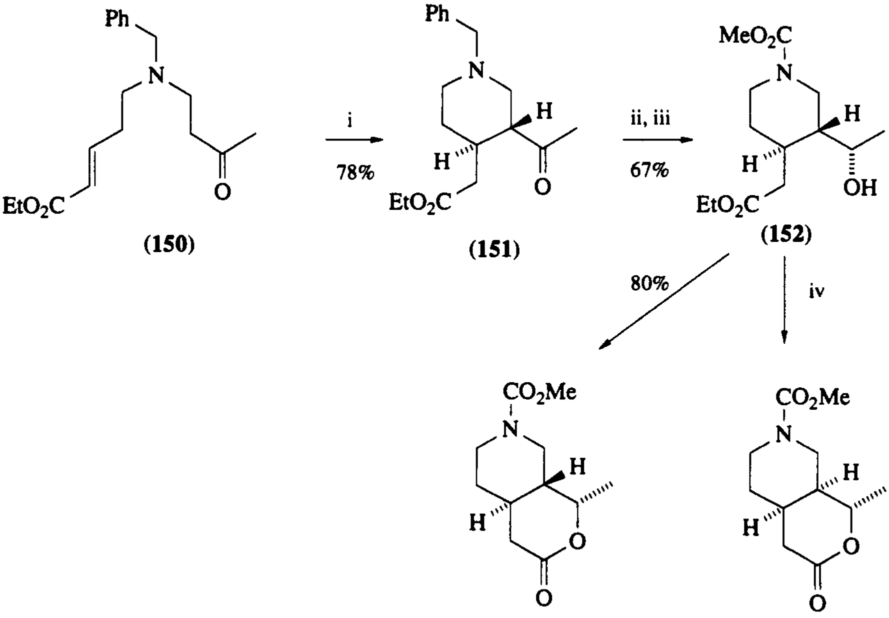
(150)
i
78%
(151)
ii, iii
67%
(152)
80%
iv

i, 1 equiv. (*R*)-(+)-1-phenylethylamine, 5 Å molecular sieve, THF, 5–10 °C; ii, $ClCO_2Me$, benzene, 60 °C; iii, $NaBH_4$, MeOH, –10 °C; iv, 5 steps

**Scheme 54**

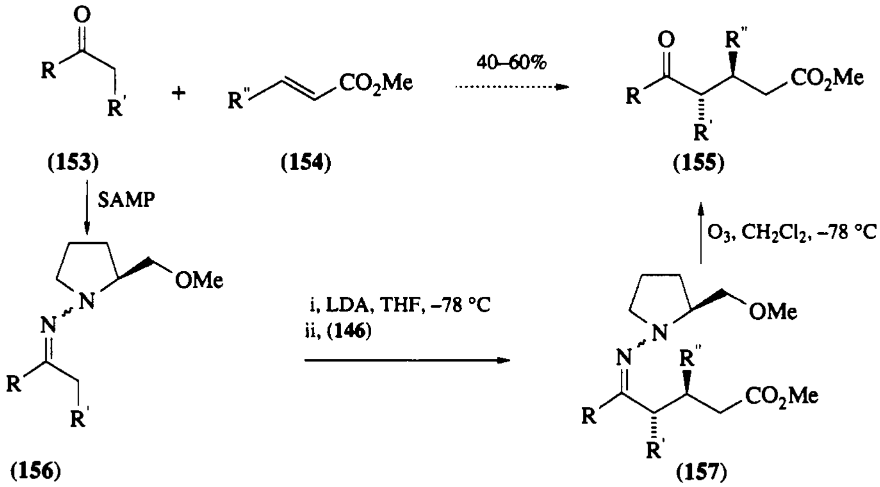
(153)
(154)
40–60%
(155)
SAMP
(156)
i, LDA, THF, –78 °C
ii, (146)
O3, CH2Cl2, –78 °C
(157)

**Scheme 55**

**Table 3** Preparation of Optically Active Substituted 5-Oxoalkanoates (**155**; Scheme 55)

| *R* | *R'* | *R"* | *Overall yield (%)* | *ee (%)* | *Ref.* |
|---|---|---|---|---|---|
| Me | H | Me | 50 | >96 | 167 |
| $Pr^i$ | H | Me | 46 | >96 | 167 |
| n-$C_6H_{13}$ | H | Me | 53 | >99 | 167 |
| Ph | H | Me | 55 | >96 | 167 |
| Me | H | Ph | 62 | >99 | 167 |
| n-$C_5H_{11}$ | H | Ph | 59 | >99 | 167 |
| H | Me | Me | 58 | >96 | 168 |
| Et | Me | Me | 45 | 92 | 168 |
| Ph | Me | Ph | 43 | >99 | 168 |
| $Bu^n$ | $Pr^n$ | Ph | 40 | >96 | 168 |
| H | H | Me | 43 | >96 | 170 |
| H | H | Et | 37 | 90 | 170 |
| H | H | Ph | 51 | >96 | 170 |
| H | H | *p*-MeOPh | 30 | 93 | 170 |

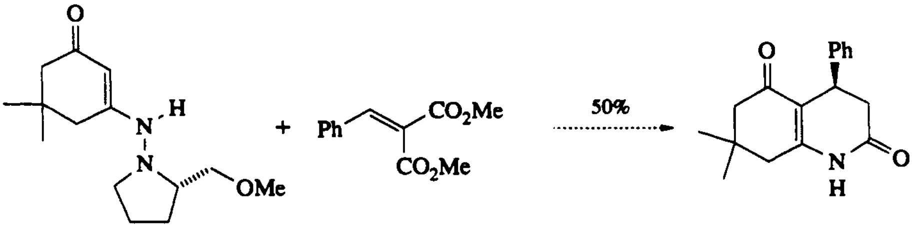

**(160)** **(158)** **(159)** >98% *ee*

Scheme 56

if the lithiated bislactim ether is first converted to the corresponding dialkylcuprate reagent (**170**).[181] The reaction with cyclopentenone, for instance, allows the preparation of compound (**171**) in pure form (Scheme 61).

The alkylation of the chiral enamine (**172**) by β-nitrostyrenes gives diastereomerically pure Michael adducts (**173**) with high *ee* (Scheme 62).[182] Comparable selectivities were observed with α-(methoxycarbonyl)cinnamates as substrates.[183] The same method was used for the enantioselective alkylation of β-tetralones in the 3-position by β-nitrostyrenes.[184]

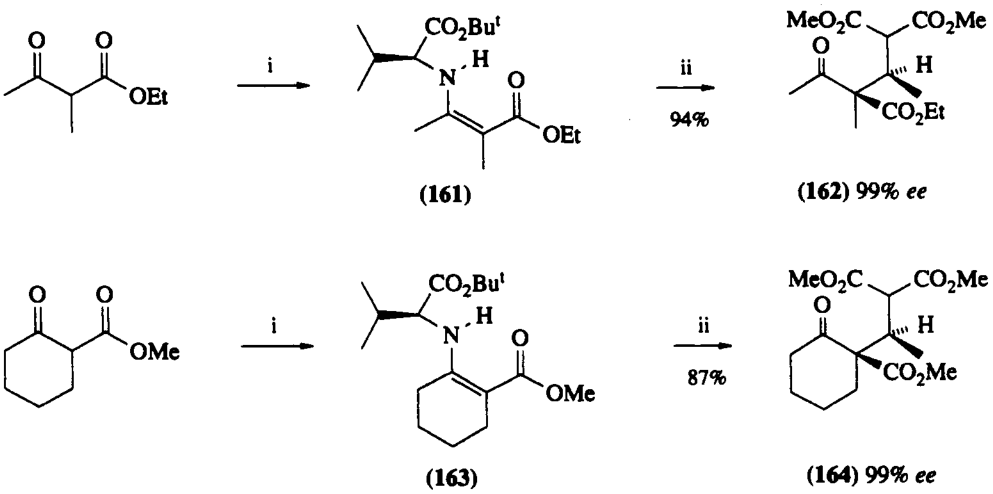

i, L-valine *t*-butyl ester; ii, LDA, then dimethyl ethylidenemalonate, toluene, 2 equiv. HMPA, –78 °C

Scheme 57

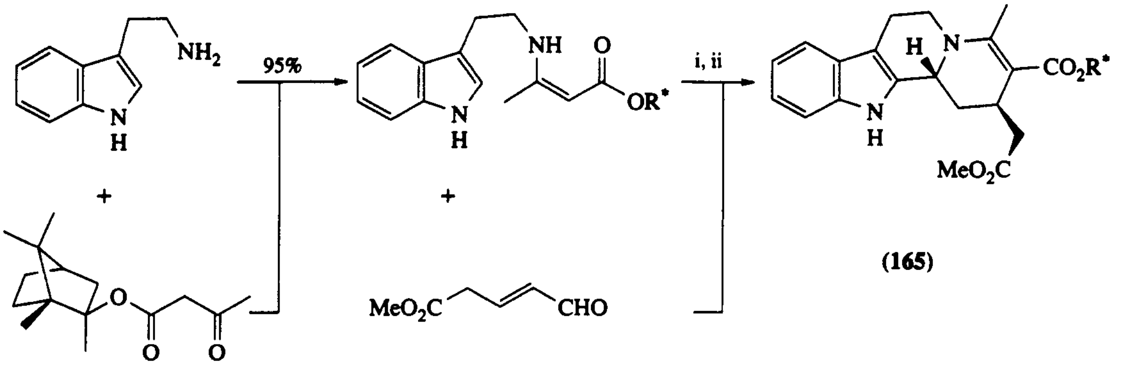

(165)

i, $CH_2Cl_2$, –78 °C; ii, TFA, $CH_2Cl_2$, –78 °C, 24 h, –20 °C, 14 d

Scheme 58

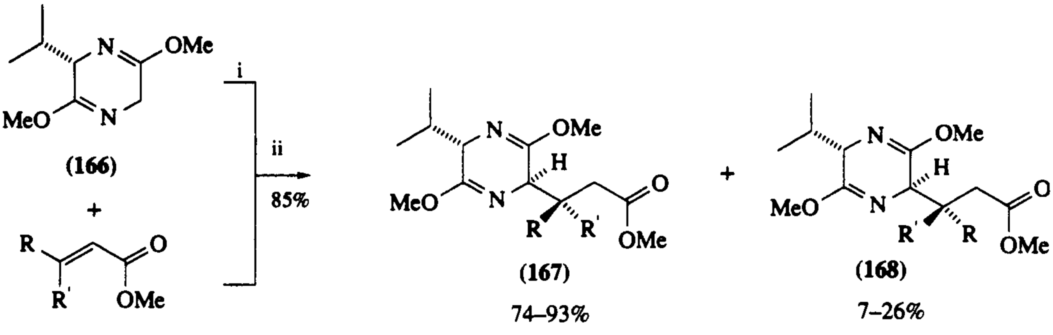

(166) (167) 74–93% (168) 7–26%

R = H, Me, Ph; R' = H, Ph

i, $Bu^nLi$, THF, –78 °C, 10 min; ii, –70 °C, 2–3 h, then 1 equiv. AcOH, –70 °C to r.t.

Scheme 59

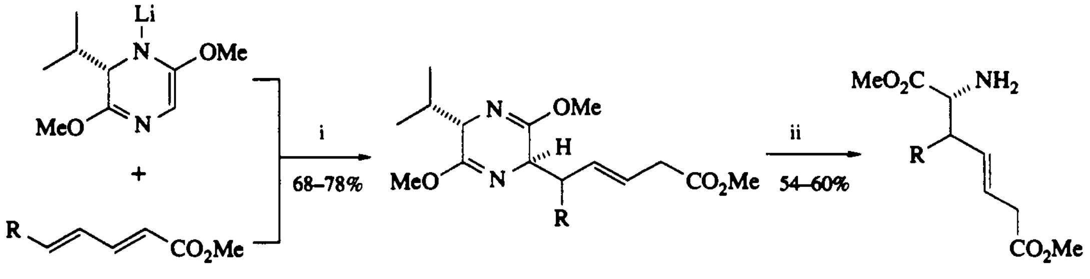

i
68–78%
ii
54–60%

R = Me, Ph, 4-pyridyl

(169) >98% *ee*

i, THF, –70 °C, 2–3 h, then 1 equiv. AcOH, –70 °C to r.t.; ii, 0.25 M aq. HCl, r.t., 4 d

Scheme 60

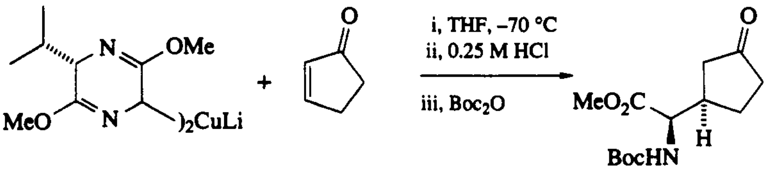

i, THF, -70 °C
ii, 0.25 M HCl
iii, $Boc_2O$

(170) (171) >99% *ee*

Scheme 61

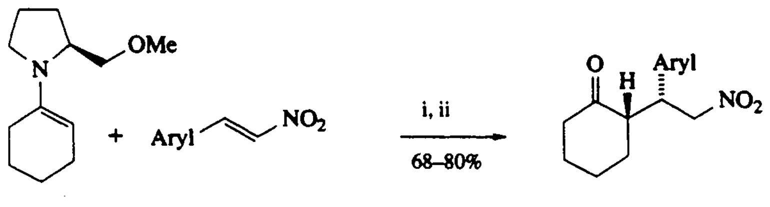

**(172)** **(173)** >90% *ee*

i, $Et_2O$, –80 °C, 30 min, r.t., 5–6 h; ii, aq. HCl, EtOH, 60 °C, 30 min

**Scheme 62**

### 1.5.3.3 Reactions of Chiral Sulfinyl and Phosphonyl Anions

In the first attempts to use a chiral α-sulfinyl ester enolate as donor in Michael additions to α,β-unsaturated esters, only low selectivities were observed.[185,186] Better results are obtained when the α-lithio sulfoxide (**174**), a chiral acyl anion equivalent, is employed. Conjugate addition of (**174**) to cyclopentenone derivatives occurs with reasonably high degrees of asymmetric induction, as exemplified by the preparation of the 11-deoxy prostanoid (**175**; Scheme 63).[187,188] Chiral oxosulfonium ylides and chiral lithiosulfoximines can be used for the preparation of optically active cyclopropane derivatives (up to 49% *ee*) from α,β-unsaturated carbonyl compounds.[189]

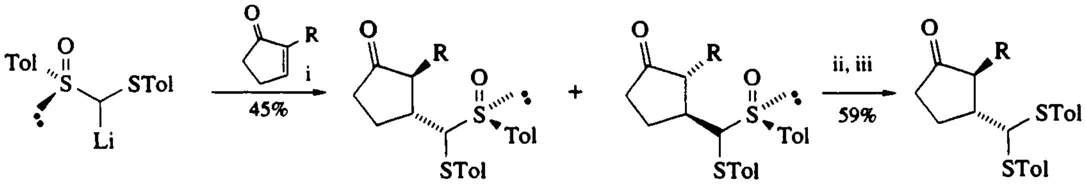

**(174)** 98 : 2 **(175)** >99%*ee*

i, THF, HMPA, 30 min, –78 °C; ii, separation of diastereomers; iii, $I_2$, $(Me_2N)_3P$, MeCN, 45 °C, 5 h

**Scheme 63**

The diastereoselective addition of chiral allylsulfinyl anions to cyclic enones was investigated in terms of diastereoselectivity and mechanism (working with racemic material),[190–195] and allows the preparation of homochiral products if homochiral anions are employed.[196–201] For example, the lithiated allylic sulfoxide (**176**) reacts with 2-cyclopentenone in a highly diastereoselective manner yielding the adduct (**177**), which can be converted to the optically active keto acid (**178**; Scheme 64). Application of this methodology allows the synthesis of cyclopentanoid natural products like (+)-hirsutene (**179**), which was prepared from (*ent*-**176**) according to Scheme 65.[196,199] The synthesis of (+)-pentalene (**182**; Scheme 66) utilizes two kinetic resolution steps:[197] at first, compound (*rac*-**180**) is (partially) resolved by treatment with 0.5 equiv. of lithiated (**176**); subsequent reaction of (**180**) with 2 equiv. of a racemic lithiated allyl sulfoxide affords the intermediate (**181**) diastereoselectively and in high yield. All these reactions are believed to proceed *via* a 10-membered '*trans*-decalyl'-like or '*trans*-fused chair–chair'-like transition state as shown in (**183**).

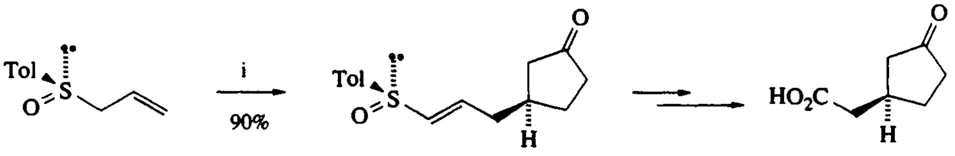

**(176)** **(177)** **(178)** 96% *ee*

i, LDA, THF, HMPA, –78 °C, 1 h, then 1 equiv. of 2-cyclopentenone, –78 °C, 5 min

**Scheme 64**

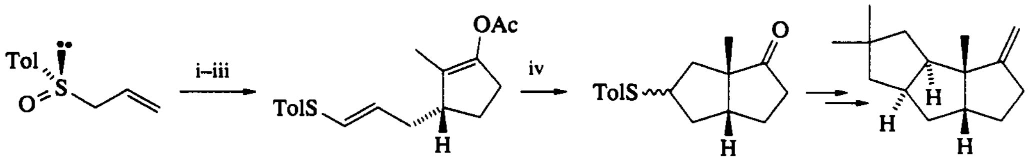

(*ent*-**176**) 94% *ee* (**179**)

i, LDA, THF, HMPA, –78 °C, 1 h, then 2-methyl-2-cyclopentenone, –78 °C, 5 min; ii, $Ac_2O$; iii, Zn, AcOH, r.t., 24 h: iv, 1 equiv. $TiCl_4$, AcOH, $H_2O$, r.t.

**Scheme 65**

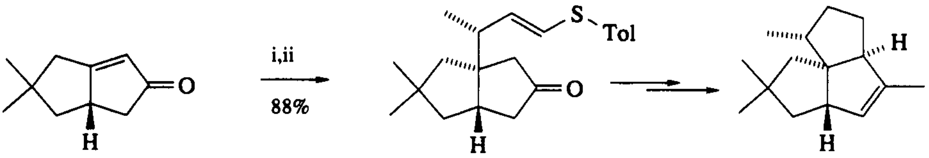

(**180**) 82% *ee* (**181**) (**182**)

i, 2 equiv. rac-(*Z*)-2-butenyl phenyl sulfoxide anion, THF, –78 °C, 45 min; ii, Zn, AcOH, r.t., 24 h

**Scheme 66**

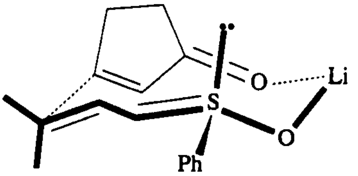

(**183**)

Since allyl sulfoxides may quite easily undergo racemization at the sulfur atom *via* a reversible [2,3] sigmatropic process, the configurationally more stable chiral allylic phosphine oxides were also investigated.[201] Compounds (**184**) and (**185**), prepared as a 1:1 mixture from allylphosphonyl dichloride and (–)-ephedrine, were shown to add to cycloalkenones with reasonably high diastereoselectivities. Ozonolysis of the initially formed 1,4-adducts affords the respective optically active ketoaldehydes (Scheme 67). With a *N*-isopropyl-substituted derivative even higher selectivities (88–98% *ee*) could be obtained.

### 1.5.3.4 Reactions of Organocopper Compounds Prepared from Chiral Carbanions

The chiral organocopper compound (**186**) adds diastereoselectively to 2-methyl-2-cyclopentenone, allowing the preparation of optically active steroid CD-ring building blocks (Scheme 68).[202–204] A related method was applied to a synthesis of the steroid skeleton *via* an intramolecular (transannular) Diels–Alder reaction of a macrocyclic precursor.[205] Chiral acetone anion equivalents based on copper azaenolates derived from acetone imines were shown to add to cyclic enones with good selectivity (60–80% *ee*, after hydrolysis).[206–208] Even better *ee* values are obtained with the mixed zincate prepared from (**187**) and dimethylzinc (Scheme 69). Other highly diastereoselective but synthetically less important 1,4-additions of chiral cuprates to prochiral enones were reported.[209,210]

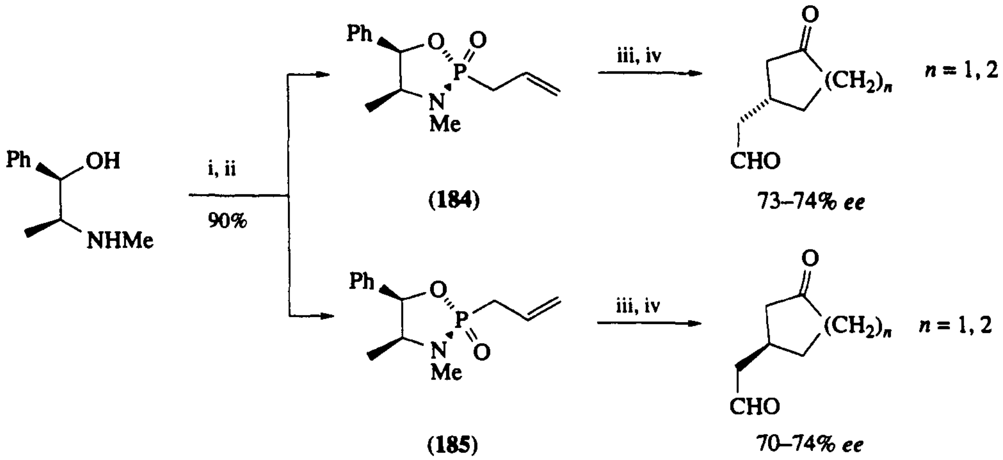
Ph
OH
NHMe
i, ii
90%
Ph
O
O
P
N
Me
(184)
iii, iv
O
(CH2)n
CHO
n = 1, 2
73–74% ee
Ph
O
P
N
O
Me
(185)
iii, iv
O
(CH2)n
CHO
n = 1, 2
70–74% ee

i, allyl-$POCl_2$, 2 equiv. $Et_3N$, toluene, –40 °C to r.t., 12 h; ii, column chromatography; iii, $Bu^nLi$, THF, –78 °C, then cycloalkenone, THF, –78 °C, 30 min; iv, $O_3$, $CH_2Cl_2$, –78 °C

Scheme 67

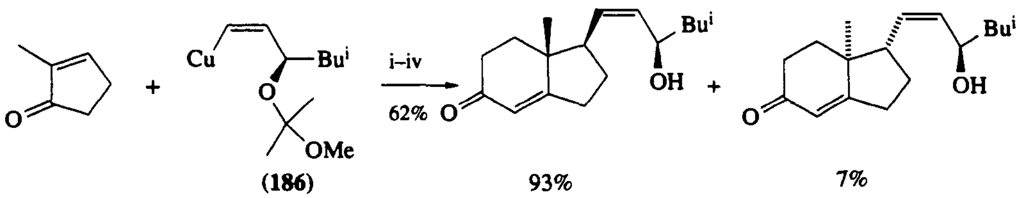
O
+
Cu
Bu$^i$
O
OMe
(186)
i–iv
62%
O
Bu$^i$
OH
+
93%
O
Bu$^i$
OH
7%

i, $Bu_3P$, $Et_2O$, –78 °C to –20 °C, 2 h, then add $H_2C{=}C(SiMe_3)COMe$, $Et_2O$, –20 °C, 2 h; ii, NaOMe, MeOH, reflux, 3 h; iii, 3 M HCl, 0 °C, 5 min; iv, chomatography

Scheme 68

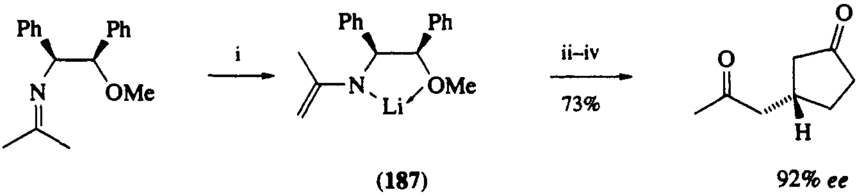
Ph
Ph
N
OMe
i
Ph
Ph
N
Li
OMe
(187)
ii–iv
73%
O
O
H
92% ee

i, $Bu^nLi$, THF, –40 °C, 30 min; ii, add $ZnMe_2$, –78 °C; iii, add 2-cyclopentenone, THF, –78 °C, 5 h, iv, $H_3O^+$

Scheme 69

## 1.5.4 ENANTIOSELECTIVE ADDITIONS OF ACHIRAL CARBON NUCLEOPHILES TO ACHIRAL SUBSTRATES

### 1.5.4.1 Reactions Employing Stoichiometric Amounts of Chiral Ligands or Coordinating Cosolvents

### *1.5.4.1.1 Reactions of organocopper compounds*

Asymmetric induction in the conjugate addition of achiral residues to α,β-unsaturated carbonyl compounds can be achieved with chiral ligand-modified organocuprate reagents. Early experiments, employing a variety of chiral homo- and hetero-cuprates, gave very low enantioselectivities (<6% *ee*),[211–219] only in some cases were somewhat better *ee* values (15–34%) obtained.[220–223] A reasonably high asymmetric induction (68% *ee*) was observed with (*S*)-*N*-methylprolinol as the chiral (nontransferable) ligand in the copper-mediated addition of methyl Grignard reagents to 1,3-diphenyl-2-propene-1-one (chalcone).[224] Proline-derived ligands were also employed in other studies on the addition of magnesium- and lithium-cuprates to (mainly) the same substrate, leading to up to 94% *ee*.[225–229] It was found that the selectivity (up to 50% *ee*) during the addition of chiral organo(hetero)cuprates to 2-cyclohexenone depended upon virtually all experimental variables like the ligand, the solvent, the temperature, the counterion in the $Cu^I$ precursor, and the cation ($Li^+$ or $Mg^{2+}$).[230] Stoichiometric amounts of the tridentate chelate (**188**) effect high asymmetric induction in conjugate additions of alkylcuprate reagents to cyclohexenone, allowing, for instance, the preparation of 3-butylcyclohexanone with 92% *ee* (Scheme 70).[231] Optical yields of 41–83% were obtained in the addition of alkyl(hetero)cuprates to cyclic and acyclic alkenones, the extent of asymmetric induction being a complex function of all experimental parameters.[232] Only a single example exists for the enantioselective transfer of an alkenyl residue from a chirally modified cuprate reagent: (**189**), a chiral building block for the synthesis of the pseudoguaianolide (+)-confertin (**190**),[235,236] was prepared from 2-methyl-2-cyclopentenone according to Scheme 71.[233,234]

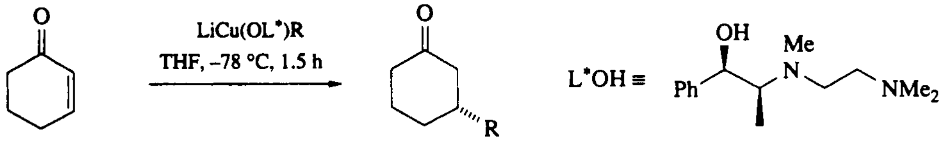

85–92% *ee* (**188**)

**Scheme 70**

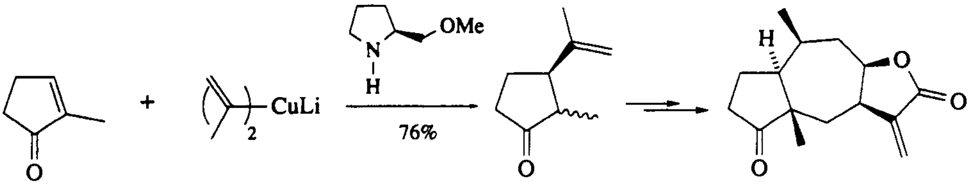

(**189**) 76% *ee* (**190**)

**Scheme 71**

### *1.5.4.1.2 Reactions of organolithium and organozinc compounds*

Asymmetric induction in the 1,4-addition of organometallic compounds to prochiral electron-deficient alkenes can be achieved in the presence of chiral coordinating cosolvents.[237] With the tartaric acid-derived amino ether (**191**), addition of achiral Li-, Cu-, and Zn-organic compounds to α,β-unsaturated aldehydes, ketones, nitro compounds and ketene thioacetals led to adducts with 10 to 26% *ee*, and, in a single case, with 43% *ee*. The related chiral amino ether (**192**) effected the addition of BuLi to nitropropene with even higher enantioselectivity (58% *ee*).[238] Comparable selectivities (32 to 67% *ee*) were obtained in the conjugate addition of lithiated dithioacetals to prochiral unsaturated esters mediated by the chiral ligands (**193**) and (**194**; Scheme 72).[239] The conjugate addition of Grignard reagents to enones mediated by chiral diamine zinc(II) monoalkoxides gave the adducts with low *ee* (<15%).[240]

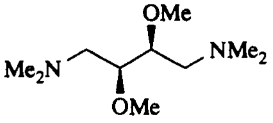

(**191**)

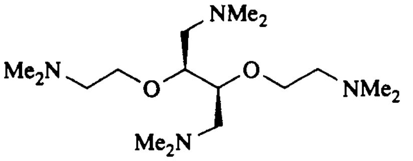

(**192**)

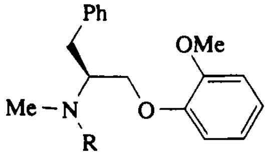

(**193**) R = Me
(**194**) R = $(CH_2)_2NMe_2$

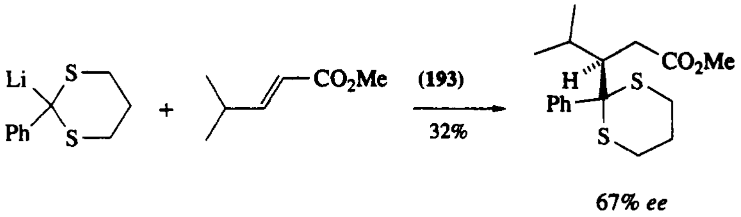

Scheme 72

### 1.5.4.2 Reactions Mediated by Chiral Catalysts

#### *1.5.4.2.1 Reactions of CH-acidic compounds*

Chinchona alkaloids catalyze asymmetric alkylations of highly CH-acidic compounds with (nonprochiral) Michael acceptors.[241-243] For instance, the quinine-mediated reaction of methyl 1-oxo-2-indancarboxylate (**195**) with MVK affords the adduct (**196**) with high *ee* (Scheme 73). A polymer-bound catalyst may also be used without loss of selectivity.[244] The same reaction is catalyzed by a chiral $Co^{II}$ diamine complex (66% *ee*).[245] Chiral crown ether complexed potassium bases catalyze the Michael addition of phenyl acetic esters and β-keto esters (*e.g.* **195**) to MVK and to methyl acrylate, yielding products with up to 99% *ee*.[246] Other chiral cation complexants were also tested.[247,248] Chiral phase-transfer catalysts in the Michael reaction were used to achieve high asymmetric inductions (up to 92% *ee*) in related alkylations of (less acidic) 2-alkyl-1-indanone derivatives.[249-251] The enantioselectivity of such reactions appears to be generally lower at higher pressures.[252]

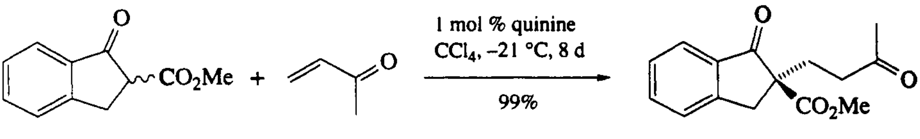

(**195**) (**196**) 76% *ee*

Scheme 73

#### *1.5.4.2.2 Reactions of organometallic compounds*

There are three techniques for true catalytic enantioselective 1,4-addition of organometallic reagents to prochiral α,β-unsaturated carbonyl compounds available so far: (i) the reaction of Grignard reagents with 2-cyclohexenone, mediated by catalytic amounts of the chiral binuclear $Cu^{I}$ complex derived from the tropocoronand ligand H[CHIRAMT] (**197**) leads to rather low *ee* (4–14%); however, the authors mention in a footnote that substantially higher selectivities (up to 80% *ee*) can be obtained with use of an improved catalyst system;[253] (ii) the asymmetric conjugate addition of dialkylzinc compounds to certain enones is catalyzed by a chiral Ni complex prepared *in situ* from a nickel(II) salt and *N,N*-dibutylnorephedrine (**198**) and leads to moderate selectivities (<50% *ee*; Scheme 74);[254,255] (iii) the addition of tin(II) enethiolates, generated *in situ* from trimethylsilyl enethiolates (**199**) with catalytic amounts of $Sn(OTf)_2$ and the bidentate ligand (**200**), to enones yields chiral dithioesters (**201**) with up to 70% *ee* (Scheme 75).[256,257]

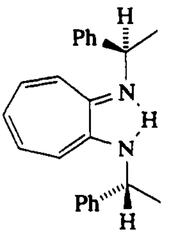

(**197**)

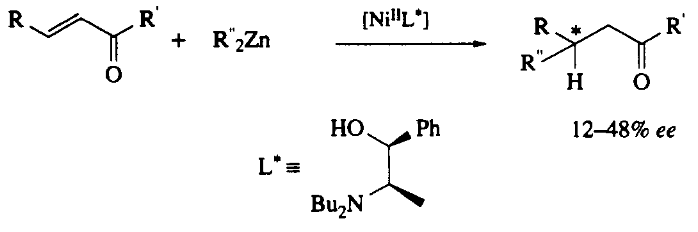

**(198)**

**Scheme 74**

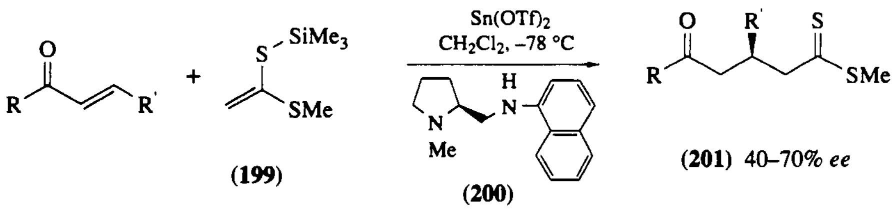

**Scheme 75**

## 1.5.5 ADDITIONS OF NONCARBON NUCLEOPHILES

The (diastereoselective) conjugate addition of silylcuprate reagents to a variety of chiral derivatives of α,β-unsaturated carboxylic acids can be used to prepare optically active β-silyl esters.[258,259] Best results are obtained with substrates of type (**25**). The (related) β-silyl ketones, which also constitute valuable building blocks for (acyclic) stereoselective synthesis, are now accessible in high *ee via* palladium-catalyzed enantioselective 1,4-disilylation of α,β-unsaturated ketones (Scheme 76).[260]

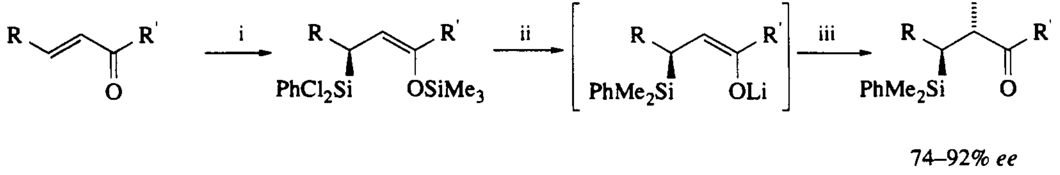

i, PhCl$_2$SiSiMe$_3$, benzene, 0.005 mol % PdCl$_2$-(+)-BiNAP; ii, MeLi, Et$_2$O; iii, MeI, THF

**Scheme 76**

Thiols may be enantioselectively added in a conjugate fashion to α,β-unsaturated carbonyl compounds in the presence of chiral hydroxyamine catalysts (*e.g.* chinchona alkaloids).[242,244,249,252,261–269] In some cases *ee* of up to >80% were achieved (*e.g.* Scheme 77).[242,261,262] This methodology was utilized for the kinetic resolution of compound (*rac*-**86**; Scheme 34) in a multigram scale.[94] Related enantioselective 1,4-additions of thioacetates[270,271] and selenophenols[272] to enones are also known. Epoxidations, based on the asymmetric nucleophilic addition of peroxide anions to enones, are discussed separately.[273]

While sluggish under thermal conditions,[274,275] the asymmetric conjugate addition of amines to alkyl crotonates is achieved at room temperature under high pressure (15 kbar).[276] Thus, benzylamine can be added to the crotonate derived from 8-β-naphthyl menthol, with virtually complete diastereoselectivity. A related intramolecular 1,4-addition of an amine to a chiral enoate was used in a total synthesis of the alkaloid (−)-tylophorine.[277] Additions of amines to chiral iron complexes of type (**116**) proceed with excellent selectivity and allow the preparation of homochiral β-lactams.[127,128,130,132] In contrast, the addition of amine nucleophiles to chiral vinylic sulfoxides[278–280] and to chiral vinylsulfoximines[281] proceeds with comparably low selectivities.

Asymmetric conjugate addition of hydride to *N*-enoylbornane-10,2-sultams (**28**) was used to prepare homochiral β-branched alkanoic acids.[282,283] Another method involves the preparation of such compounds *via* a catalytic enantioselective 1,4-reduction:[284] in the presence of only 1 mol % of a chiral cobalt semicorrin ligand (readily available from pyroglutamic acid), β-methyl-2-alkenoic acids were reduced by $NaBH_4$ in high yields and with up to 96% *ee*.

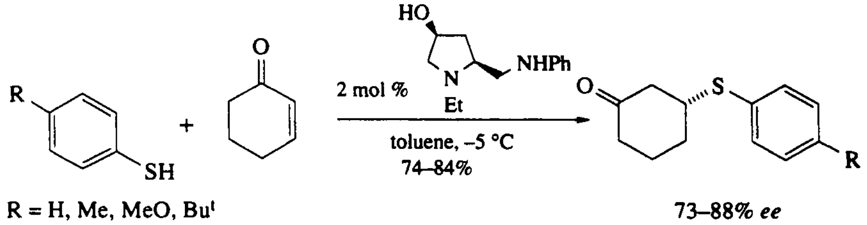

**Scheme 77**

## 1.5.6 CONCLUSIONS

A number of techniques are now available allowing the preparation of enantiomerically pure (or at least enriched) compounds *via* asymmetric nucleophilic addition to electron-deficient alkenes. Some of these transformations have already been successfully applied in total synthesis. In most cases, the methods are based on diastereoselective reactions, employing chirally modified substrates or nucleophiles. There are only very few useful enantioselective procedures accessible so far. The search for efficient enantioselective methods, especially for those which are catalytic and do not require the use of stoichiometric amounts of chiral auxiliaries, remains a challenging task for the future.

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# 1.6

# Nucleophilic Addition–Electrophilic Coupling with a Carbanion Intermediate

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## 1.6.1 INTRODUCTION

Vicinal difunctionalization reactions have been extensively exploited in synthetic organic chemistry providing rapid, convergent access to complex structures in a stereocontrolled fashion. Examples of these reactions are numerous;[1] classical reactions such as Diels–Alder, [2 + 2] and 1,3-dipolar cycloadditions (Volume 5), epoxidation–functionalization of alkenes,[2] carbenoid additions to alkenes[3] and the additions of acyl[4] and alkyl[5] halides to alkenes, using Friedel–Crafts catalysts, have been joined by many new reactions of considerable synthetic potential, including, for instance, inverse electron demand Diels–Alder reactions[6] and radical cyclization–trapping (Volume 4, Part 4).

### 1.6.1.1 Tandem Vicinal Difunctionalization

Over the past 25 years, a specific vicinal difunctionalization sequence referred to as tandem vicinal difunctionalization has been developed.[7–10] The process consists of two reactions, one enabling the other to proceed. An initial Michael-type addition (also referred to as a conjugate or 1,4-addition) of a nucleophile, NuM, to a substrate (**1**), the 'Michael acceptor', which usually is an α,β-unsaturated carbonyl-containing compound, transforms both the α- and β-carbons. The β-carbon, changing from an *sp*$^2$- to an *sp*$^3$-hybridization state, becomes further substituted, and the α-carbon takes on nucleophilic character, usually as the carbanionic center of an ambident enolate ion (**2**), the 'conjugate enolate' (Scheme 1). The conjugate enolate ion subsequently can be trapped *in situ* using an appropriate electrophile, EX, thus further substituting the α-carbon. Conceptually, the process can be envisaged as a vinylogous substitution reaction; by means of a 'third party' two-carbon extension, nucleophile and electrophile react, forming two vicinal σ-bonds.

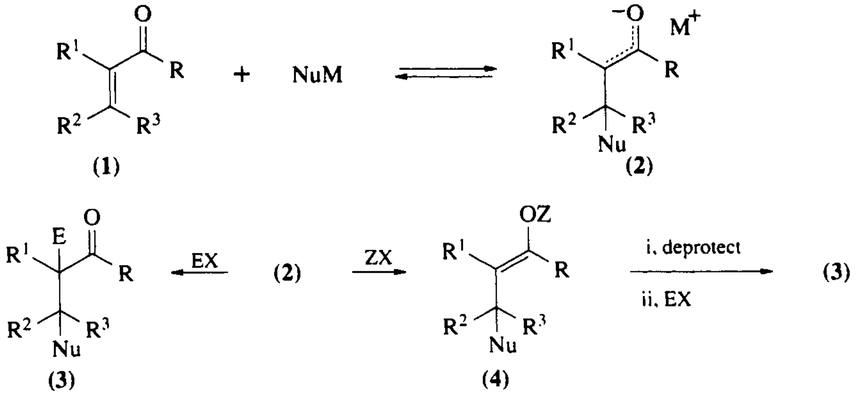

**Scheme 1**

The enolate ion generated by the conjugate addition process need not be α-functionalized *in situ*. It is an ambident anion and can be isolated as a neutral, uncharged species (**4**), an 'enolate equivalent', by straightforward *O*-functionalization using an appropriate protecting reagent, ZX, or by simple protonation. Isolation of enolate equivalent (**4**) allows two courses of action. The most frequently followed is regeneration of the enolate, with subsequent functionalization at the α-carbon to give the vicinally disubstituted product, (**3**). Alternatively, extensive chemical manipulation of the intervening species (**4**) is possible; a series of chemical transformations can be performed between initial β-functionalization and the ultimate α-functionalization.

The general reaction sequence has been named more specifically as tandem vicinal dialkylation, nucleophilic–electrophilic carbacondensation,[11] dicarbacondensation[12,13] or conjugate addition–enolate trapping,[14] usually in reference to the fact that most of the reaction examples available create two new vicinal carbon–carbon bonds. Many noncarbon nucleophiles and electrophiles also are known, resulting in vicinal carbon–heteroatom bonds in the products of the reaction sequence. For this reason, the broader term used here is more descriptive.

Tandem vicinal difunctionalizations by nucleophilic addition–enolate trapping sequences have developed into tools of considerable utility in the total synthesis of natural products, including various terpenoids,[15] steroids,[16,17] prostaglandins,[9] anthraquinones[18] and lactones.[19–21] The method can be used as a cyclization strategy to form cyclopropanes, cyclobutanes[22] and complex polycyclic products,[23] as well as to append new rings onto a substrate molecule.[24] Other applications of the reaction include the preparation of useful intermediates such as 1,3- and 1,5-diones, stereoisomerically pure α,β-unsaturated esters, γ,δ-unsaturated ketones and a variety of heterocyclic systems.[25–27] The methodology continues to widen in scope: an umpolung version, for instance, is available, allowing addition of the nucleophile to occur at the α-carbon and that of the electrophile to occur at the β-carbon.[28]

### 1.6.1.2 Historical Background

Early research optimizing reaction conditions for the 1,2-addition of Grignard reagents to α,β-unsaturated ketones noted the formation of undesired secondary products unless a large excess of the Grignard reagent was used.[29] Recognition that an alternate 1,4-addition pathway was possible, generating a conjugate enolate[30] capable of reacting with the starting ketone when present in significant concentrations, led to the identification of the observed secondary products as dimers formed by a tandem conjugate addition–aldol condensation process.[31]

The synthetic implications of this discovery were slow to be exploited. Base-initiated dimerizations of 2-cycloalkenones, known to give crystalline solids,[32,33] remained puzzling for some time before conjugate additions were suggested to account for some of the possible products;[34] indeed, the product of base-catalyzed dimerization of 4,4-dimethyl-2-cyclopentenone, which proceeds *via* a double Michael addition sequence, was not identified until 1969 (Scheme 2).[35] An unanticipated cyclopropanation reaction of acrylaldehyde[36,37] using ethyl bromomalonate and proceeding by means of a similar Michael addition–$S_Ni$ enolate alkylation represents an early synthetic use of tandem vicinal difunctionalization.

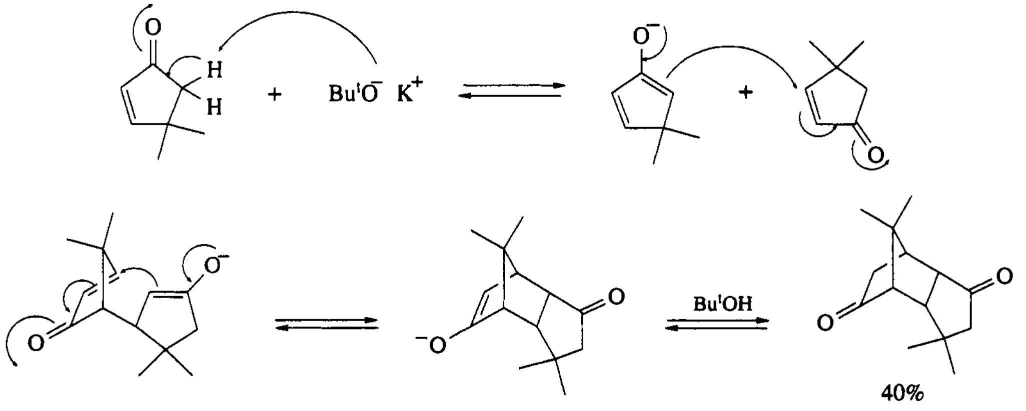

Scheme 2

As the synthetic value[38] of regiospecifically generated enolates became apparent in the 1960s, new methods were discovered and developed to prepare them. Dissolving metal conjugate reduction of α,β-

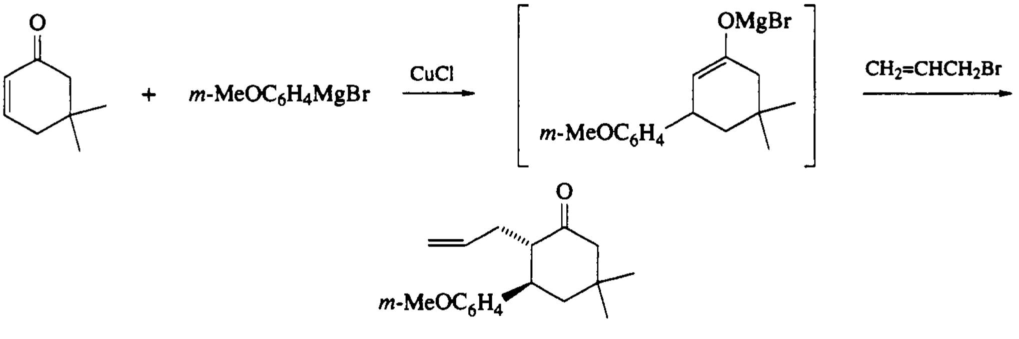

Scheme 3

unsaturated ketones to produce enolates, which could be *C*-alkylated using appropriate electrophiles,[39] comprises the first exploitation of a one-pot, three-component tandem vicinal difunctionalization reaction. The method was extended to conjugate additions of nucleophiles in aprotic media and applied to natural product synthetic strategy, the initial example being a key step in the total synthesis of lycopodine (Scheme 3).[40]

## 1.6.2 MECHANISM AND STEREOCHEMISTRY

The two distinct bond-forming steps in tandem vicinal difunctionalization have been studied extensively. The first step consists of a nucleophilic addition to a π-system; the nucleophile is almost invariably an organometal. 1,4-Addition to an α,β-unsaturated carbonyl substrate concomitantly generates a new σ-bond at the β-carbon and an enolate ion. The second step constitutes *C*-functionalization of the enolate intermediate, forming a new σ-bond between the nucleophilic α-carbon of the enolate and an electrophilic reagent.

The mechanism of the inital conjugate addition step undoubtedly varies according to the identity of the nucleophile.[41,42] The most common nucleophiles used are organocopper reagents. The fundamental aspect of organocopper conjugate additions to α,β-unsaturated carbonyl substrates is agreed[43] to be oxidative addition of a $d^{10}$ cuprate, producing a transient copper(III) ($d^8$) intermediate. Reductive elimination follows to generate a new chemical bond at the β-carbon of the substrate, a conjugate enolate and a copper(I) species (Scheme 4). Copper(I)–π-bond coordination clearly precedes bond formation;[44] an alternative pathway involving carbocupration[45] instead of a copper(III) intermediate has been proposed and the specific nature of the reaction continues to be investigated.

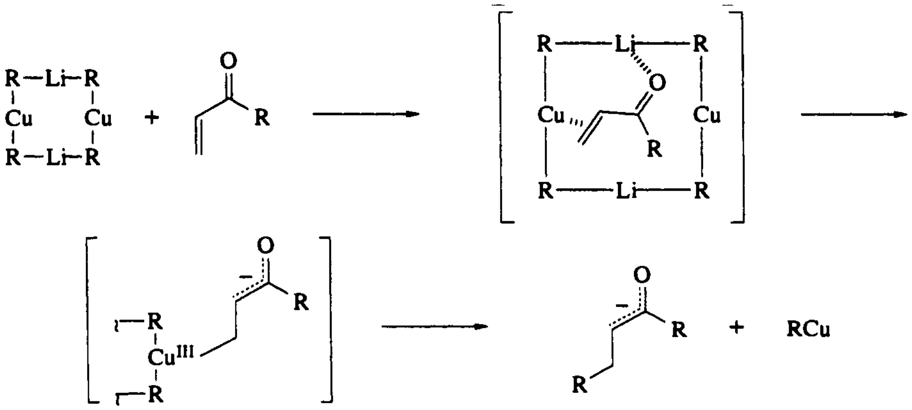

Scheme 4

The mechanistic details of conjugate additions of less common noncopper(I)-containing nucleophiles have not received as much attention.[46–48] Grignard reagents which undergo conjugate additions with specific α,β-unsaturated substrates appear to do so by means of a single-electron transfer mechanism, whereas Michael additions of enolate anions may proceed by either single-electron transfer or a traditional nucleophilic addition to the carbon–carbon multiple bond of the substrate.[49]

The second step of the tandem vicinal difunctionalization sequence, a substitution reaction of an enolate with an electrophile, is mechanistically identical to the *C*-alkylation of regiospecifically generated enolates.[38] For electrophiles of relatively low reduction potentials,[50] such as alkyl iodides, the substitution reaction appears to proceed *via* a single-electron transfer mechanism. Electrophiles with higher reduction potentials such as alkyl bromides, on the other hand, appear to undergo bond formation according to an $S_N2$ mechanism (Scheme 5).[51,52] Often it is found that the identity of the counterion profoundly influences the reactivity of the enolate towards the electrophile.[53,54] The counterion typically is predetermined by the first step of the tandem vicinal difunctionalization and can be a limiting factor in reactivity of the enolate towards reaction with an electrophilic reagent.

As with mechanism, the stereochemical outcome of tandem vicinal difunctionalization is dependent upon the individual bond-forming steps in the sequence. The conjugate addition reaction is quite sensitive to the steric environment of the α,β-unsaturated substrate, so that the bond-forming process at the β-carbon adheres to steric approach control factors: the 5-methoxycarbonyl substituent of (**5**) directs axial attack of a bis(dimethylphenylsilyl)copperlithium reagent so that only the 3,5-*trans* adduct is formed

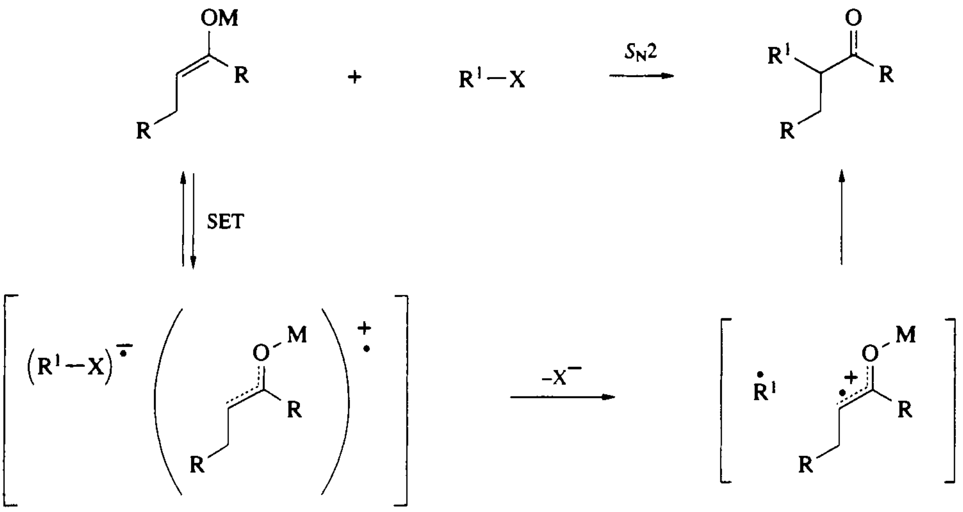
OM
R
R
+
R¹–X
SN2
O
R¹
R
R
SET
(R¹–X)·⁻
O⁻M
R
R
+
•
–X⁻
•
R¹
O⁻M
+
R
R

Scheme 5

(equation 1);[55] smaller substituents have essentially the same effect (equation 2).[56] Subsequent α-functionalization of the conjugate enolate does not always proceed with such high stereoselectivity, as these two examples indicate. Thermodynamically more stable *trans* products usually predominate, as predicted both by steric approach and product development control factors,[57,58] but a complex combination of other factors (the enolate counterion, the nature of the enolate itself, the reaction conditions, the nature of the electrophile) make predictions difficult and occasionally unreliable. When (**5**) undergoes conjugate addition with diphenylcopperlithium and the resulting adduct is α-methylated, the *cis* and not the *trans* product predominates (equation 3).[59] A relatively stereochemically remote substituent on an electrophile clearly influences the stereoselectivity of α-functionalization during tandem vicinal difunctionalization of cyclopentenone (**6**; equation 4).[60]

If the product of α-functionalization has a tertiary α-carbon, equilibration can occur under the conditions of tandem vicinal difunctionalization, as in equation (2). The equilibration process can proceed at

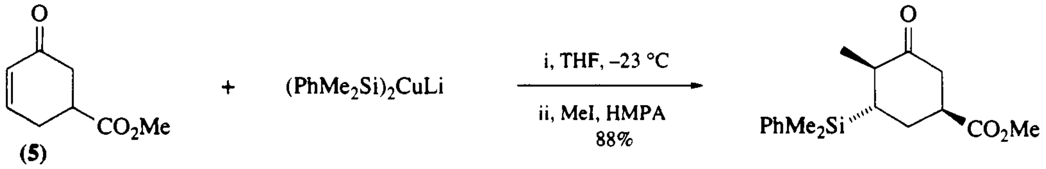
O
CO₂Me
(5)
+
(PhMe₂Si)₂CuLi
i, THF, –23 °C
ii, MeI, HMPA
88%
O
PhMe₂Si
CO₂Me

(1)

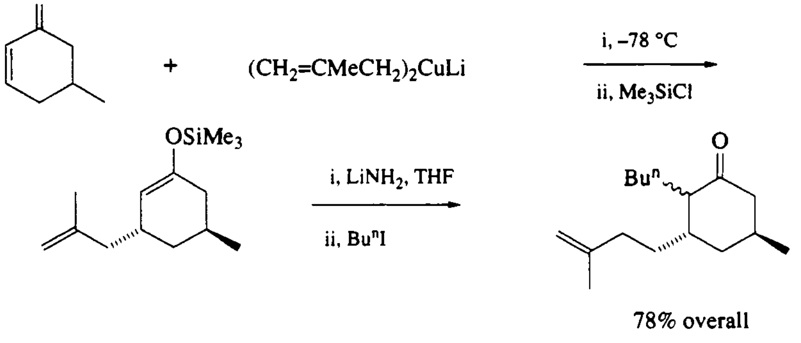
O
+
(CH₂=CMeCH₂)₂CuLi
i, –78 °C
ii, Me₃SiCl
OSiMe₃
i, LiNH₂, THF
ii, Buⁿl
O
Buⁿ
78% overall

(2)

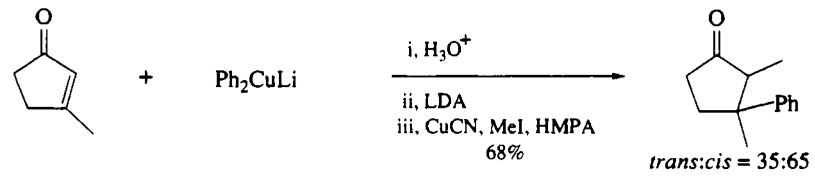
O
+
Ph₂CuLi
i, H₃O⁺
ii, LDA
iii, CuCN, MeI, HMPA
68%
O
Ph
trans:cis = 35:65

(3)

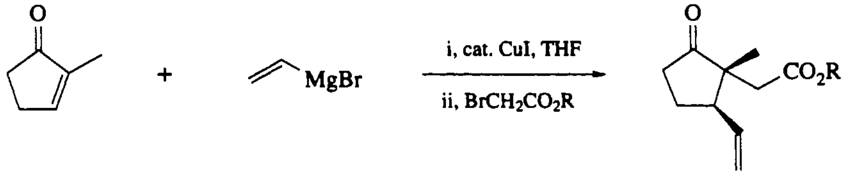

(4)

(6)

R = Et, *trans*:*cis* = 88:12
R = Bu$^t$, >99% *trans*

rates sufficiently fast to obscure the original stereopreference of the α-bond-forming step: methylenecyclohexane annulation of cycloalkenones provides the expected kinetic *cis*-fused adducts after intramolecular α-alkylation of the conjugate addition products, but if there is no 2-substituent on the starting cycloalkenone, the kinetic product equilibrates to give substantial quantities of the thermodynamically more stable *trans* adducts (equation 5).[61]

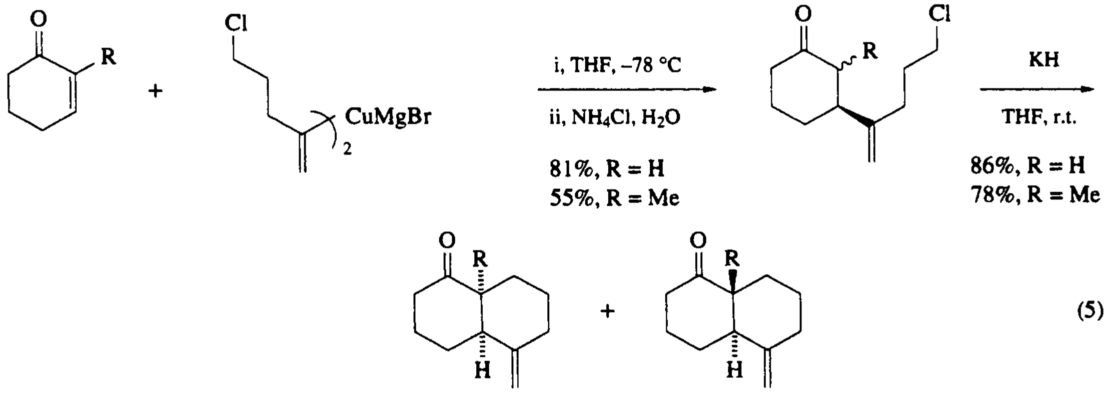

(5)

| | | |
|---|---|---|
| R = H | 33% | 66% |
| R = Me | 100% | 0% |

## 1.6.3 THE α,β-UNSATURATED SUBSTRATE

The variety of conjugated unsaturated substrate types that can be used in tandem vicinal difunctionalization sequences allows considerable latitude in substrate choice. Generally, the only strict requirements that a potential substrate must meet are that the α-carbon of the α,β-unsaturated carbon–carbon bond moiety be substituted with an electron-withdrawing group, usually a carbonyl-containing group or some other unsaturated group capable of making the β-carbon electrophilic, and that there be no functional groups present in the substrate that would be incompatible with the nucleophile to be added. The latter requirement usually precludes the use of unprotected, relatively acidic functional groups in the substrate, such as carboxylic acid, hydroxy, thiol or β-keto ester groups. Exceptions to the former requirement are possible; especially noteworthy is the ability to use alkynes as substrates. A synthesis of spirovetevanes exploits tandem vicinal difunctionalization of a fulvene (equation 6).[62]

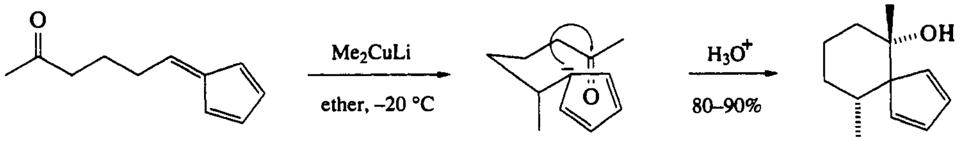

(6)

### 1.6.3.1 Aldehydes and Ketones

Ketones, specifically 2-alkenones and 2-cycloalkenones, have been used extensively as substrates for tandem vicinal difunctionalization, allowing delineation of various reactivity patterns based upon the structural elements present in the enone. Aldehyde substrates have been used less widely; comparison with analogous enone substrates indicates that they may be less effective Michael acceptors, resulting in lower isolated yields of reaction sequence products.[63]

### *1.6.3.1.1 Acyclic aldehydes and ketones*

Aldehyde substrates behave in a manner similar to the analogous ketone substrates in organocopper-initiated 1,4-addition–conjugate enolate alkylation reactions (equation 7);[64] yields are comparable and the diastereoselectivity of the reaction sequence resulting from overall *trans* difunctionalization is good. In some cases, such as in the synthesis of a degradation product of chlorothricin,[65] complete regio- and stereo-control is possible. Cyclopropanations are possible using bromomalonates as Michael donors to α,β-unsaturated aldehydes,[37] as noted earlier; aldimine derivatives of α,β-unsaturated aldehydes serve as aldehyde functional group equivalents and permit naphthaldehydes to undergo organometal 1,4-addition–α-alkylation sequences.[66]

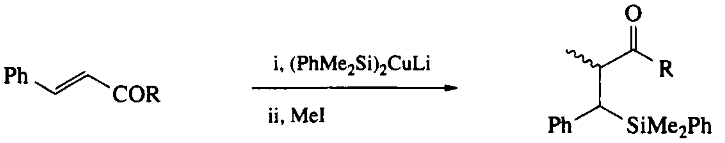

(7)

74%, R = H    *threo*:*erythro* = 12:1
57%, R = Me    *threo*:*erythro* = 49:1
70%, R = Ph    *threo*:*erythro* = 100:0

Acyclic enone substrates have been studied in detail: as with most reactions involving 1,4-addition, substrate substitution has a large influence on reaction outcome. Substituents on the α′-position of the enone act as steric directors, shielding the carbonyl carbon from the nucleophile and thereby promoting the 1,4-addition mode. Understandably, the degree of influence exhibited by an α′-substituent will vary, depending upon the identity of the nucleophile. For organocopper nucleophiles, phenyl and benzyl vinyl ketones are superior Michael acceptors compared to methyl vinyl ketones[67] (equation 7).[64] Methyl vinyl ketones are also the poorest substrates for enolate and acyl anion nucleophiles; interestingly, the homologous ethyl vinyl ketones are best, as illustrated by equation (8).[68,69]

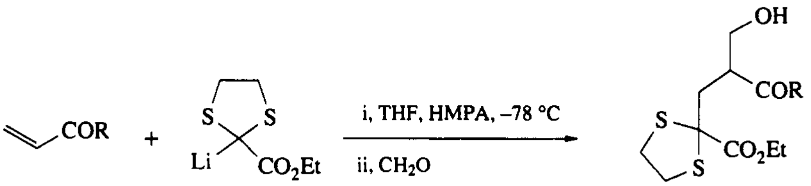

(8)

71%, R = Me
79%, R = Et
54%, R = Pr$^n$

Large steric requirements and charge at the α′-position of the enone substrate are combined in highly effective charge-directed conjugate addition–enolate functionalization reactions.[70] Michael acceptor acylphosphoranes such as (**7**; equation 9) react with a wide range of nucleophiles, including many alkyllithium reagents that normally add to enone substrates by 1,2- and not 1,4-addition;[71] the intermediate conjugate enolates are α-functionalized easily to give acylphosphorane adducts such as (**8**).[72] Conversion of compounds such as (**8**) to ketones can be accomplished by decarboxylation and hydrolysis; the method can be used to initiate intramolecular cyclizations leading to three-, five- and six-membered rings. In a related vein is the use of α,β-unsaturated acyliron complexes as Michael acceptors in tandem vicinal difunctionalization reactions (equation 10).[73,74] The [($\eta^5$-C$_5$H$_5$)Fe(CO)PPh$_3$] moiety of (*E*)-crotonyl complex (**9**) activates the substrate towards 1,4-addition and provides excellent diastereoselectivity during the reaction sequence,[75] resulting in completely diastereospecific and usually rare *cis* dialkylation.[76] The substrate has been used in the synthesis of β-lactams and a single enantiomer of the pseudo-octahedral complex can be used in the difunctionalization sequence: (*R*)-(**9**) yields (2*R*,3*S*)-acids, -amides and -esters after decomplexation.

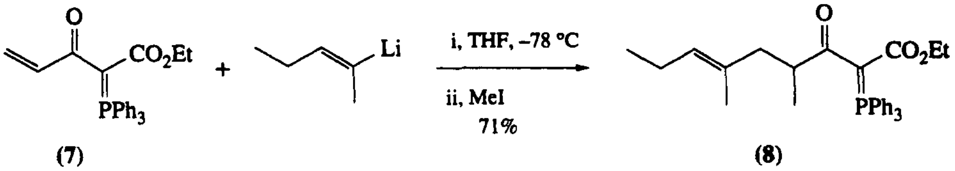
CO2Et
PPh3
(7)
Li
i, THF, -78 °C
ii, MeI
71%
CO2Et
PPh3
(8)

(9)

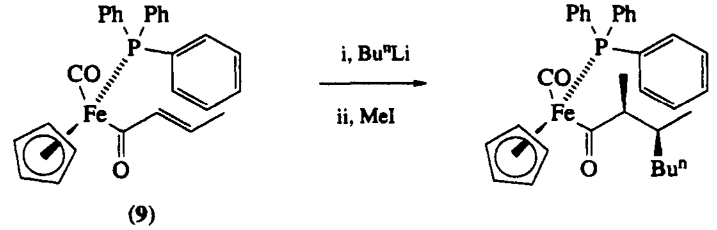
Ph Ph
P
CO
Fe
O
(9)
i, Bu$^n$Li
ii, MeI
Ph Ph
P
CO
Fe
O
Bu$^n$

(10)

Enhancements of the chemical yields of tandem vicinal difunctionalizations are realized when the substrate enone bears an α-substituent. Replacement of the α-hydrogen of an α,β-unsaturated enone with a methyl group almost always provides such enhancement (equation 11)[77] by stabilizing the conjugate enolate, thereby reducing the amount of equilibration before α-functionalization occurs. Larger substituents, especially those that are able to stabilize the conjugate enolate by inductive or resonance effects, should provide similar results, although cycloalkenone difunctionalization examples indicate that this may not always be the case.

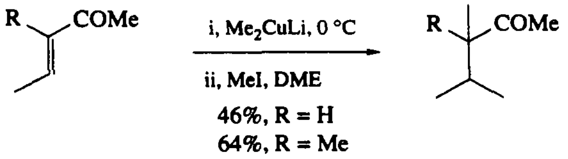
R
COMe
i, Me2CuLi, 0 °C
ii, MeI, DME
46%, R = H
64%, R = Me
R
COMe

(11)

The sensitivity of the conjugate addition reaction to steric factors would indicate that β-substitution of the α,β-unsaturated substrate leads to lower overall reactivity of a prospective Michael acceptor towards tandem vicinal condensation. In the absence of Lewis acids[78,79] this prediction is borne out: β,β-disubstituted enones usually are poor substrates for difunctionalizations using bulky, stabilized Michael donors. Intermediate combinations of steric bulk in the initial nucleophile and the substrate are not as discriminating, especially when the nucleophile is an organocopper reagent or a simple enolate, as illustrated in equations (12)[67] and (13).[80] The combination of steric and electronic factors that deactivate the Michael acceptor towards conjugate addition can substantially reduce chemical yields of the difunctionalized product (equation 14).[69]

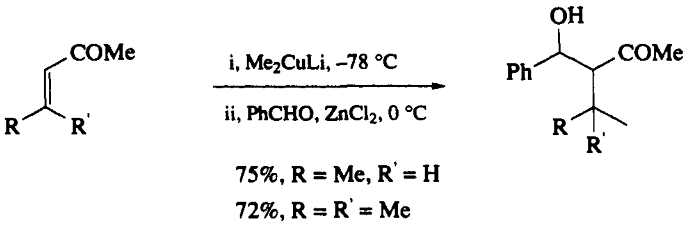
COMe
R
R'
i, Me2CuLi, -78 °C
ii, PhCHO, ZnCl2, 0 °C
75%, R = Me, R' = H
72%, R = R' = Me
OH
Ph
COMe
R
R'

(12)

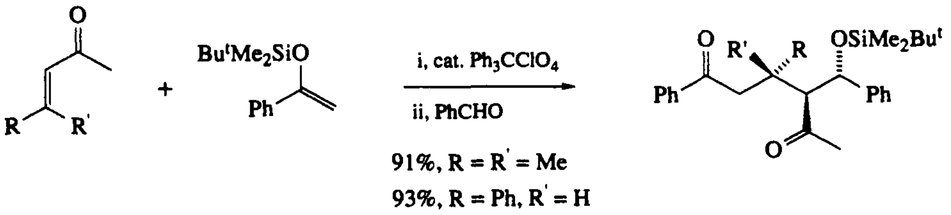
O
R
R'
+
Bu$^t$Me2SiO
Ph
i, cat. Ph3CClO4
ii, PhCHO
91%, R = R' = Me
93%, R = Ph, R' = H
O
Ph
R'
R
OSiMe2Bu$^t$
Ph
O

(13)

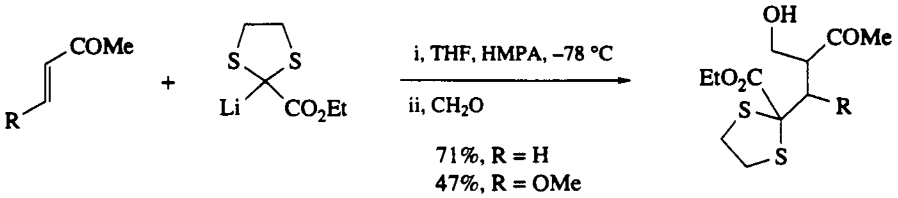

(14)

For the most part, alkynic and allenic ketones have found limited use in conjugate addition–enolate trapping sequences;[69,81–83] their analogous esters have been used with far greater frequency (*vide infra*). Alkynic ketones, in particular, have found use in development of a new anionic polycyclization method consisting of intramolecular Michael addition followed by intramolecular alkylation (equation 15).[84]

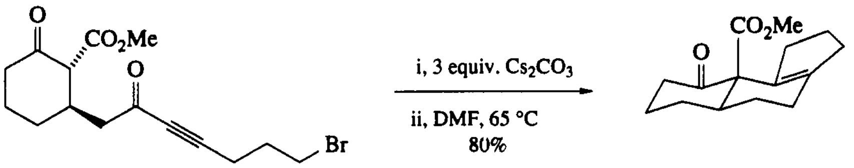

(15)

### 1.6.3.1.2 Cyclic ketones

The prevalence of α,β-disubstituted cycloalkanones and substituted cycloalkanone substructures in nature has resulted in the use of a large number of moderate (5–8) ring size 2-cycloalkenones in total syntheses exploiting a tandem vicinal difunctionalization strategy. Equation (16) provides a representative example for a total synthesis of glycinoeclepin A,[11] in which (*R*)-carvone undergoes diastereospecific *trans* dialkylation to yield the 2,2,3,5-tetrasubstituted cyclohexanone (**10**); the method also has found extensive use in three-component coupling syntheses of prostaglandins.[9,85] General trends, especially for cyclopentenones and cyclohexenones, are discernable. On the whole, cyclopentenones are more reactive substrates than higher homologous cycloalkenones. Isolated yields usually are better, as illustrated by equation (17).[86] The rate of equilibration of the conjugate enolate intermediate varies with ring size, cyclopentanone enolates equilibrating more rapidly than cyclohexenone enolates.[87] Often, α-substituents must be employed to prevent equilibration: thus, 2-methyl-2-cyclopentenone is superior to 2-cyclopentenone as a substrate for difunctionalization. Arylhetero α-substituents which both stabilize the conjugate enolate toward equilibration and enhance subsequent α-functionalization can be used as substrate auxiliaries, resulting in 2-cyclopentenone synthetic equivalents which exhibit superior stereo- and regiochemical results in the difunctionalization sequence. Common examples include 2-phenylthio-[88] and 2-phenylselenyl-2-cyclopentenone.[89] Enantiomerically pure 2-arylsulfinyl-2-cycloalkenones offer additional, directable diastereofacial bias during difunctionalization to produce cycloalkanones of high enantiomeric purities (equation 18; NMP, *N*-methyl-2-pyrrolidone).[90] Substituents at the α-position of the substrate which activate it toward conjugate addition can promote regiospecific attack of the Michael donor when other competing modes of conjugate addition are possible (equation 19).[91]

Cycloalkenones are intrinsically less reactive than non-β-substituted acyclic enones. Cycloalkenones with β-substituents often undergo reaction with Michael donors quite slowly; a lower degree of stereo- and regio-control as well as lower chemical yield result.[92] These observations can be synthetically useful, allowing discrimination between two possible Michael acceptor sites in a molecule.[93,94] Lewis acid catalysis[78,79] of the conjugate addition process usually can greatly enhance the rate at which β-substituted cycloalkenones react.[95] Substituents at positions other than the α- and β-positions typically neither promote nor interfere with difunctionalization. In the case of particularly bulky α′-substitution, it is reasonable to assume that 1,4-addition might be enhanced when using nucleophiles that otherwise would show some

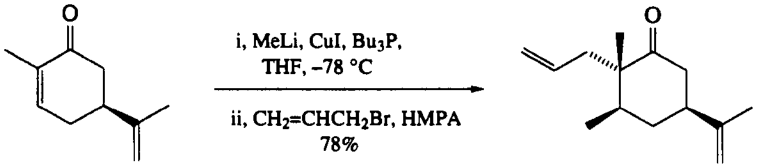

**(10)**

(16)

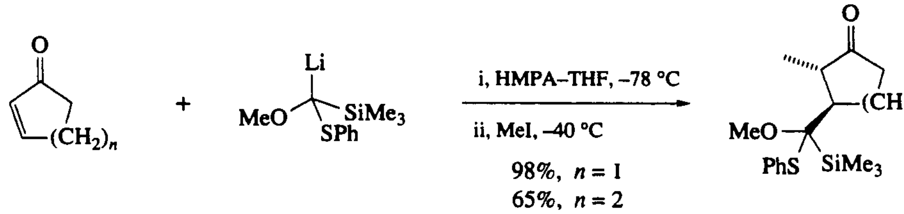

i, HMPA–THF, –78 °C
ii, MeI, –40 °C
98%, n = 1
65%, n = 2

(17)

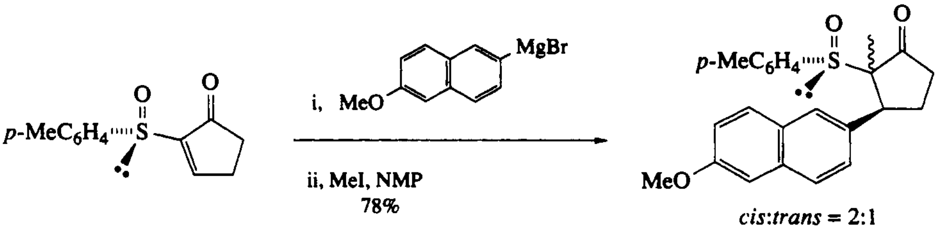

i,
ii, MeI, NMP
78%
cis:trans = 2:1

(18)

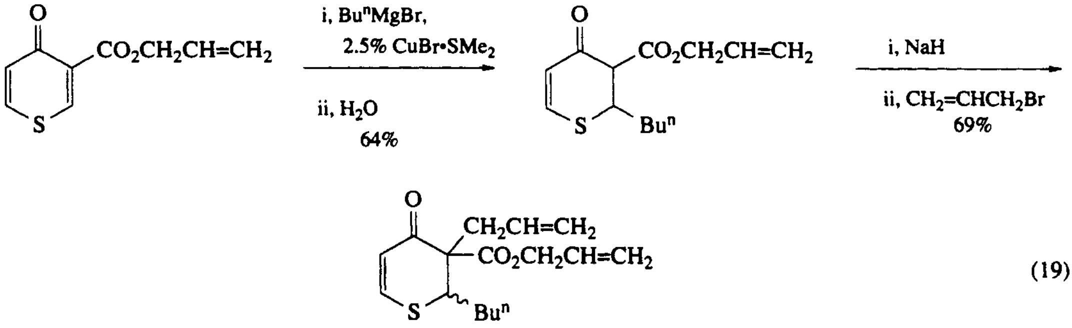

i, Bu$^n$MgBr, 2.5% CuBr•SMe$_2$
ii, H$_2$O
64%
i, NaH
ii, CH$_2$=CHCH$_2$Br
69%

(19)

preference for 1,2-addition; similarly, α′-disubstitution would eliminate any problems arising from equilibration of the conjugate enolate.

It is possible to use α,β-disubstituted cycloalkenone substrates for the construction of vicinal, quaternary carbon centers. Equation (20)[96] illustrates such a successful application; typically, however, enolate equilibration and steric congestion prevent straightforward application of the method.

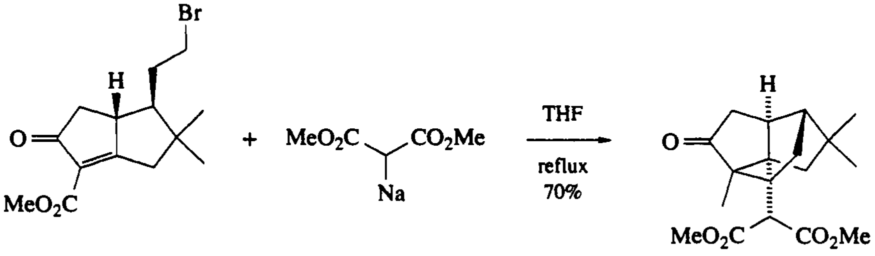

THF
reflux
70%

(20)

### 1.6.3.2 Esters and Amides

Conjugated, carbonyl-containing unsaturated compounds bearing a carbonyl carbon of oxidation state III are very good substrates for tandem vicinal difunctionalization and have been used widely. Anionic polymerization of acrylates, providing high molecular weight addition polymers, such as poly(methyl acrylate) and poly(methyl methacrylate), is an iterative tandem vicinal difunctionalization sequence consisting of sequential Michael additions and is indicative of the broad utility of the technique in applied chemistry.

### *1.6.3.2.1 Acyclic esters and amides*

Alkenoates and alkenamides most commonly are prepared from the respective carboxylic acids or carboxylic acid halides, so it is interesting to inquire as to the suitability of these later compounds as substrates in difunctionalization reaction sequences. Under most reaction conditions, unsaturated acids and acid halides will react with the initial Michael donor to give either a salt or will result in acylation instead of the desired 1,4-adduct. A few rare examples demonstrate successful difunctionalization using such substrates, however. In equation (21), acrylic acid equivalent (**11**) undergoes 1,4-addition with *tert*-butylmagnesium chloride; the intermediate dianion undergoes regiospecific α-alkylation in excellent yield.[70] In equation (22), transient acylsilane (**12**) undergoes a 1,4-addition-initiated dimerization to give lactone (**13**).[97]

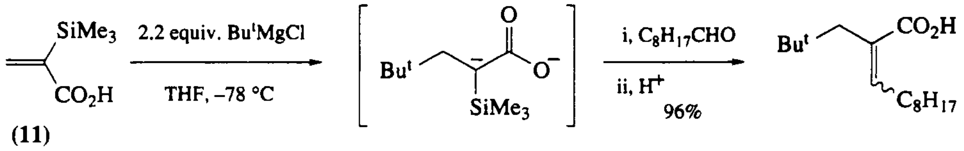

(21)

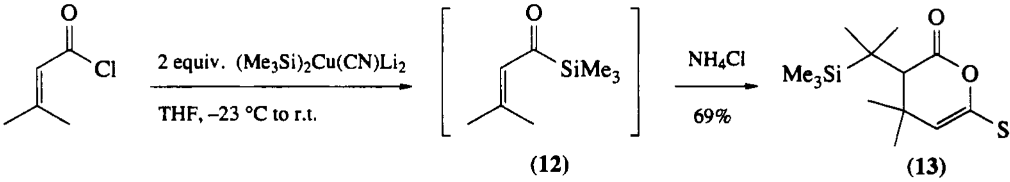

(22)

In most cases[98] conjugate addition–enolate alkylation reaction sequences do not exhibit particular sensitivity with respect to the identity of the alkyl group present in the alkyl alkenoate substrate. When a Michael donor has been chosen that reacts in both the 1,4- and 1,2-addition modes, it may be possible to choose an alkyl group for the ester substrate that forces the Michael donor to undergo exclusive 1,4-addition by sterically shielding the carbonyl carbon from attack by the nucleophile (equation 23).[99]

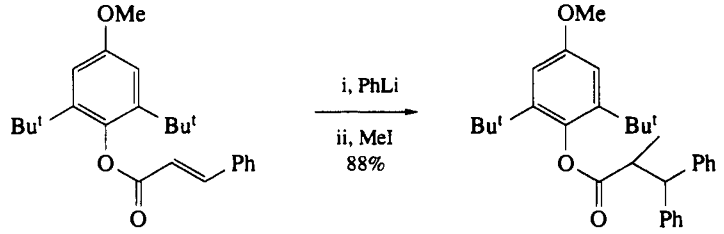

(23)

Simple substitution at the α-carbon of the enoate substrate also does not appear to have much effect on the course of the reaction: methyl acrylate and methyl methacrylate both function well as substrates in the reaction sequence and isolated yields of the products are similar.[100] In certain sterically demanding reaction sequences, α-substitution does reduce the chemical yields of the products but the presence of an α-substituent appears to be of greater importance than the particular identity of the substituent.[101] As with ketones, enoate substrates are activated towards tandem vicinal difunctionalization when electron-withdrawing α-substituents are present.[102–104]

Enoate β-substitution and β-disubstitution cause a decrease in the rate of the initial conjugate addition step of the reaction sequence that is directly related to the steric bulk of the substituent.[103,105] Equation (24) provides a representative case in the α-alkylation of enoates by means of conjugate amination–enolate alkylation followed by dehydroamination.[106] When β-substitution results in stereoisomeric (*E*)- and (*Z*)-alkenoate substrates, tandem difunctionalization typically proceeds with greater facility for (*E*)-isomers.[64,103] Obviously, when the double bond of the ester is part of a medium-sized ring, an (*E*)-alkenoate geometry is mandated; in such cases, tandem vicinal difunctionalization proceeds with uniformly excellent results (equation 25).[25]

When alkynic esters are used as substrates in the reaction sequence, activated alkenes of good isomeric purity can be prepared. Initiation of the difunctionalization usually is by means of organocopper-mediated 1,4-addition, which proceeds *via* carbometallation of the alkynyl moiety of the ester to give a vinylcopper intermediate, (**14**). Trapping by an electrophile affords *cis*-difunctionalized alkenoates

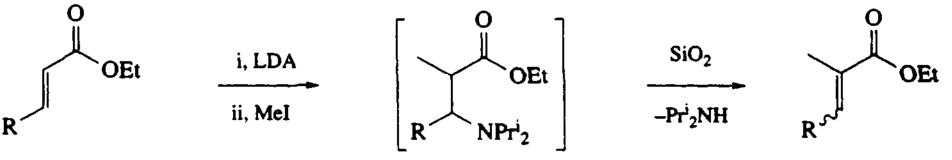
OEt
i, LDA
ii, MeI
R
NPr$^i_2$
SiO$_2$
-Pr$^i_2$NH

(24)

69%, R = n-$C_7H_{15}$ (*E*):(*Z*) = 88:12

33%, R = Pr$^i$ (*E*):(*Z*) = 95:5

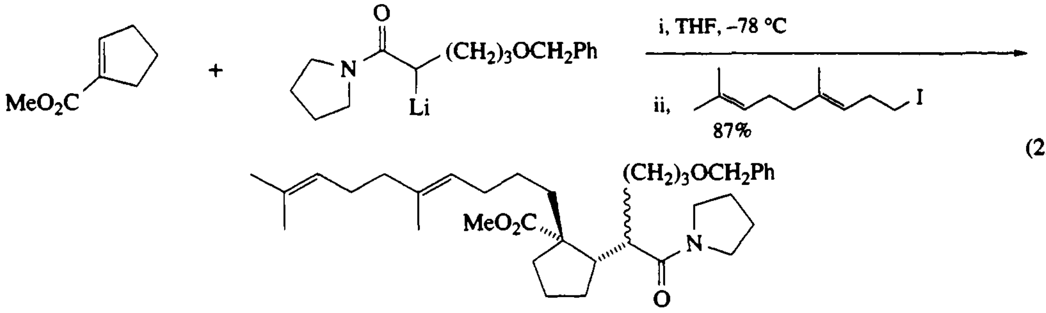
MeO$_2$C
N
(CH$_2$)$_3$OCH$_2$Ph
Li
i, THF, -78 °C
ii,
I
87%
MeO$_2$C
N
O

(25)

(Scheme 6). Alternatively, (**14**) may equilibrate *via* an allenolate species, (**15**),[107] in which case the stereochemistry of the resulting alkenoate can be (*Z*) or (*E*), depending upon the steric interactions experienced between the electrophile and (**15**) during α-functionalization.[108] Loss of the stereointegrity of intermediate (**14**) is common[82,108–110] and clearly temperature- and reagent-dependent;[111,112] ester substrates appear to be somewhat less prone to equilibration than their corresponding ketones. Reactive electrophiles, such as acid chlorides, compete with equilibration effectively[111] to result in net *cis* difunctionalization, whereas less reactive or bulky electrophiles result in net *trans* difunctionalization. Equations (26)[113] and (27)[111] are indicative of the degree of control that can be obtained over the stereochemical outcome of the reaction.

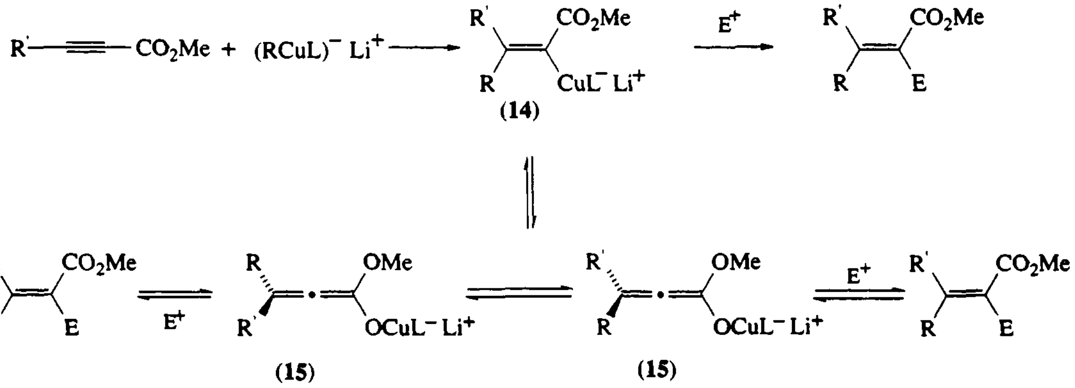
R'—≡—CO$_2$Me + (RCuL)$^-$ Li$^+$
R'
CO$_2$Me
R
CuL$^-$ Li$^+$
(14)
E$^+$
E
OMe
OCuL$^-$ Li$^+$
(15)
(15)

**Scheme 6**

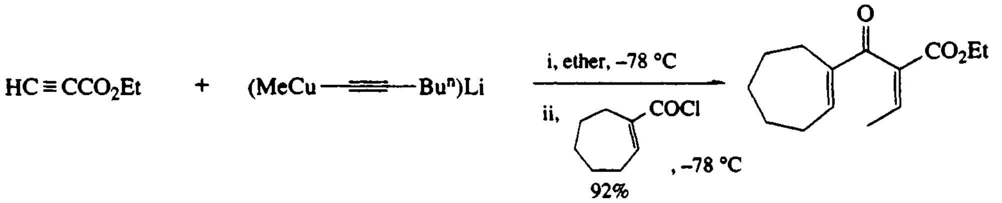
HC≡CCO$_2$Et + (MeCu—≡—Bu$^n$)Li
i, ether, -78 °C
ii, COCl, -78 °C
92%
CO$_2$Et

(26)

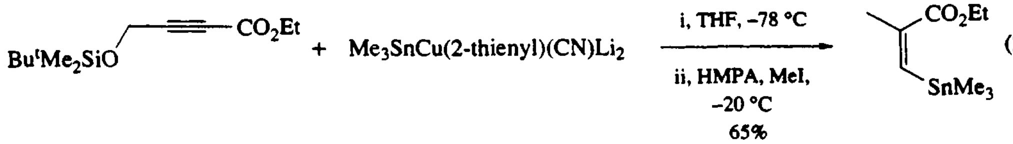
Bu$^t$Me$_2$SiO
CO$_2$Et
+ Me$_3$SnCu(2-thienyl)(CN)Li$_2$
i, THF, -78 °C
ii, HMPA, MeI, -20 °C
65%
CO$_2$Et
SnMe$_3$

(27)

Allenic esters react as enoates in tandem difunctionalization reactions using organocopper reagents as Michael donors; β,γ-unsaturated esters result (equation 28).[81] These substrates have found application in the synthesis of a variety of heterocyclic systems.[114]

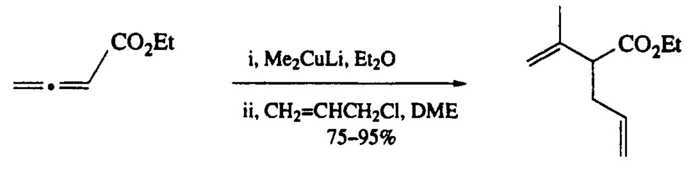

(28)

Secondary and tertiary enamides and tertiary thioenamides undergo conjugate addition–α-functionalization reactions initiated by alkyllithium and Grignard reagent nucleophiles.[115–118] Secondary amides must be protected before the reaction by trimethylsilylation[118] or by amination;[119] alternatively, 2 equiv. of the organometal Michael donor can be employed, the first to deprotonate the amide before conjugate addition proceeds with the second equivalent of donor reagent.[115] Enantiomerically pure enoylsultams, such as (**16**) in equation (29), serve as very effective substrates for chelation-controlled, diastereodiscriminating 1,4-addition–enolate alkylation;[120,121] isolated yields and percent asymmetric induction usually are excellent. Conjugated, alkynic amides also have been noted to serve as substrates in a conjugate stannylation–α-alkylation sequence.[122,123]

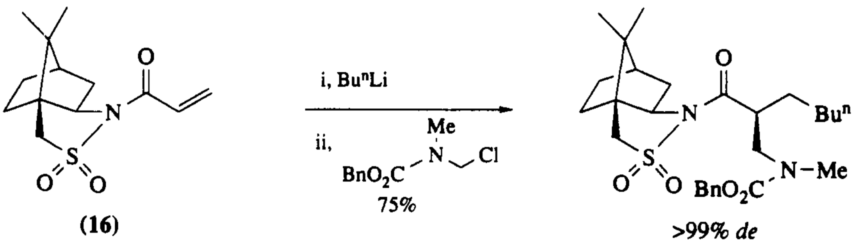

**(16)**

(29)

### *1.6.3.2.2 Cyclic esters and amides*

While α,β-unsaturated lactams have not been exploited as substrates in tandem vicinal difunctionalization, the corresponding lactones serve as key substrates in the convergent preparation of lignans,[124–127] analogs of prostaglandins,[128,129] anthraquinone-derived antibiotics[18] and macrolides.[130] γ-Butenolides and 4-substituted γ-butenolides have found the most frequent use and react with a variety of combinations of Michael donor and electrophilic reagents to give uniformly high yields of *trans* α,β-disubstituted lactone adducts. Equation (30) is illustrative of the use of γ-butenolide in the synthesis of lignans related to the podophyllotoxins.[127]

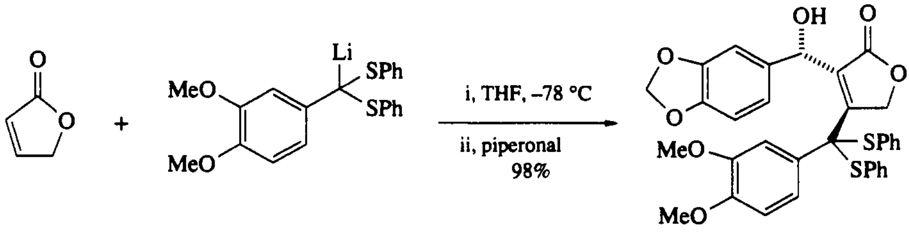

(30)

## 1.6.3.3 Alkynes

Alkynes are unusual in that they are able to undergo vicinal, nucleophilic addition–electrophilic coupling reactions without prerequisite activation of the triple bond by substitution with an electron-withdrawing group on one or both of the *sp*-hybridized carbons. Such tandem difunctionalization reactions proceed by carbometallation,[10,131–133] producing a vinylic organometal intermediate by *syn* Markovnikov addition of a nucleophilic organometal reagent across the triple bond. Highly stereoselective *syn* difunctionalization occurs after subsequent reaction with an electrophile (*cf.* Scheme 6 and Volume 4, Chapter

4.4). In particular, when the nucleophilic reagent is carbanionic in nature, the method serves as an eminently satisfactory way to prepare stereoisomerically pure di-, tri- and tetra-substituted alkenes. Most commonly, the nucleophilic organometal of choice is an organocopper reagent[10] or an organozinc reagent;[133] usually, terminal alkynes are used in the reaction, but some internal alkynes are reactive as well. There is considerable tolerance to a variety of functional groups in the substrate; again, the only cautions to be observed are that highly acidic or otherwise electrophilically reactive groups are not present. Equation (31) provides a typical example resulting in (*E*)-enyne (**17**);[134] iterative use of the method (Scheme 7) results in the rapid synthesis of a variety of insect pheromones, such as the codling moth constituent (**18**).[135] While heteroatom-containing substituents that are distant to the triple bond have no effect on the course of the reaction sequence, proximal heteroatoms can alter its regiochemistry, presumably through chelation-controlled attack of the nucleophile (equation 32).[136]

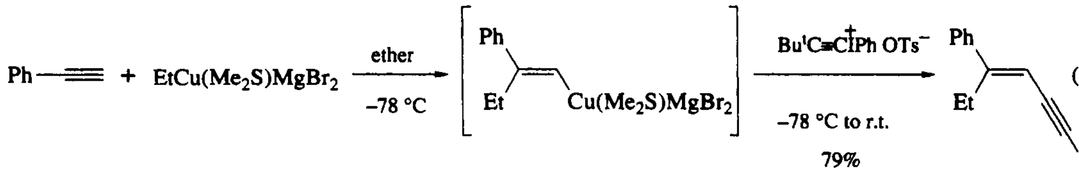

(31)

(**17**) (*E*) >98%

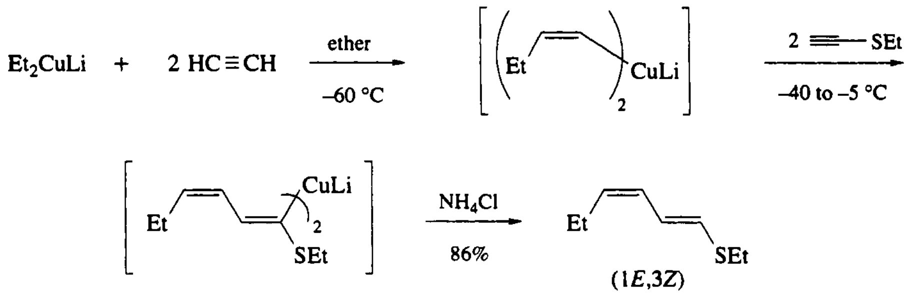

(32)

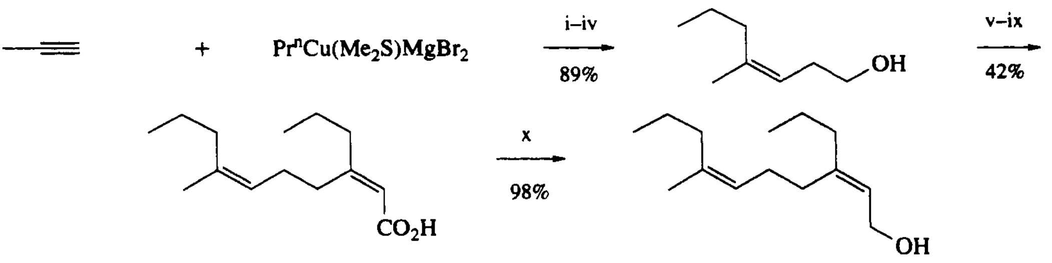

(**18**)

i, –23 °C, 2 h; ii, $Pr^nC{\equiv}CLi$, HMPA, –78 °C, 1 h; iii, ethylene oxide, –78 to 20 °C; iv, aq. $NH_4Cl$; v, TsCl; vi, NaI; vii, Mg; viii, $CuBr{\bullet}Me_2S$; ix, $Pr^nC{\equiv}CH$; x, $LiAlH_4$

**Scheme 7**

A similar but conceptually distinct approach to difunctionalization of terminal alkynes consists of sequential carboboration–palladium-catalyzed cross-coupling;[137] equation (33) illustrates that this method also provides alkenes of high stereochemical purity by net *syn* Markovnikov addition. Benzyne-containing molecules can act as highly activated substrates for vicinal difunctionalizations initiated by nucleophiles;[138–140] thus, nucleophilic addition–electrophilic trapping can serve as an alternative to sequential directed metallation for the production of 1,2-disubstituted and 1,2,3-trisubstituted aromatic systems (equation 34).[141]

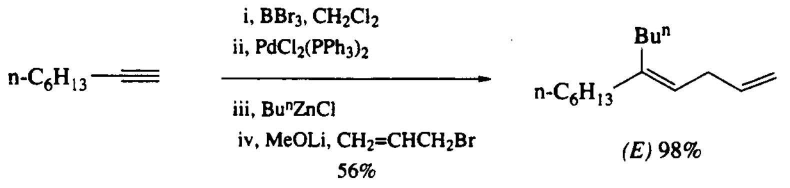

(33)

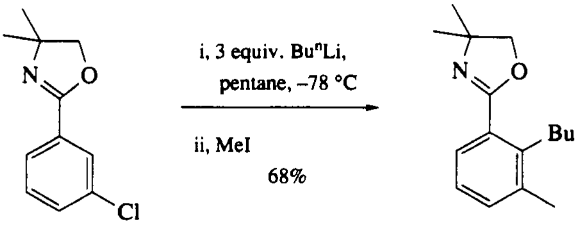

(34)

## 1.6.3.4 Other Substrates

Most substrates that do not contain a carbonyl moiety conjugated with an alkene or alkyne fall into two reactant types: those bearing a masked carbonyl equivalent, in conjugation with the alkene through a carbon atom of oxidation state II or III, and those bearing other activating substituents conjugated or coordinated with the alkene through a heteroatom.

### *1.6.3.4.1 Nitriles*

As carboxylic acid synthetic equivalents, α,β-unsaturated nitriles provide an alternative to esters for use in carboxylic acid synthesis by tandem difunctionalization. Use of these substrates has been limited, however: when alkylzinc halides are used as Michael donors, difunctionalization proceeds well and products can be isolated in high yields;[142] sodium enolates also serve as Michael donors.[143] Alkylidenemalononitriles react with alkoxides[26] and thiolates[144] to initiate cyclizations, leading to tetrahydrothiofurans, pyrones and pyridines. In a related difunctionalization sequence, allenic and alkynic nitriles undergo conjugate addition reactions with *o*-aminobenzyl alcohol; subsequent dehydration of the conjugate adducts produce *o*-xylylene intermediates which undergo cyclization to give quinolines.[145]

### *1.6.3.4.2 Sulfoxides and sulfones*

Vinylic sulfoxides are utilized in asymmetric synthesis; their role as Michael acceptors has been the topic of considerable study.[146] Only a limited number of Michael donor reagents can be used to initiate the conjugate addition–conjugate anion trapping sequence, and usually special reaction conditions are employed. The addition of dialkylcopperlithium reagents to *p*-chlorophenyl vinyl sulfoxide is successful at –60 °C in a mixed solvent system of ether and dimethyl sulfide; electrophilic trapping provides the vicinally dialkylated adducts in fair to good yield.[147] The reaction conditions appear to be specific for the particular substrate. A related vicinal difunctionalization of a vinylic sulfoxide has been used in the total synthesis of (*R*)-(+)-canadine,[148] consisting of an intramolecular 1,4-addition of an amine nucleophile; the conjugate adduct subsequently is subjected to cyclization *via* intramolecular Pummerer rearrangement, thereby alkylating the sulfoxide at the α-carbon.

Vinylic sulfones are much more reactive as Michael acceptors in tandem difunctionalization reactions and consequently have less stringent requirements as to initiating Michael donor and reaction conditions, as shown in equation (35).[149] They have been used to prepare polycyclic hydrocarbons[150] and heterocycles,[151] as well as a considerable number of prostaglandin analogs.[152,153] Uncommon stereochemically constrained *syn* conjugate addition–conjugate anion alkylation of a phenyl cyclohexenyl sulfone provides an important ring-forming step in a synthesis of morphiene (equation 36).[154]

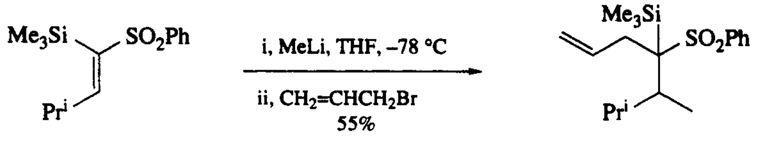
Me$_3$Si
SO$_2$Ph
Pr$^i$
i, MeLi, THF, –78 °C
ii, CH$_2$=CHCH$_2$Br
55%
Me$_3$Si
SO$_2$Ph
Pr$^i$

(35)

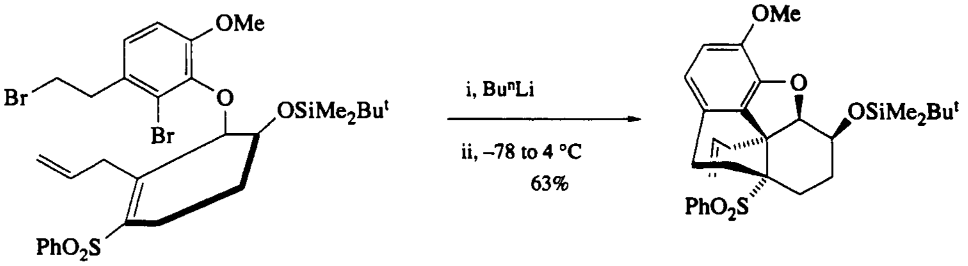
OMe
Br
O
Br
OSiMe$_2$Bu$^t$
PhO$_2$S
i, Bu$^n$Li
ii, –78 to 4 °C
63%
OMe
O
OSiMe$_2$Bu$^t$
PhO$_2$S

(36)

#### 1.6.3.4.3 Phosphorus-containing substrates

Vinylphosphonium salts and dialkyl vinylphosphonates generate Wittig-type conjugate anions upon 1,4-addition of a nucleophile; they, therefore, serve as substrates for tandem vicinal nucleophilic addition–Wittig alkenation when reacted with a Michael donor and a carbonyl-containing electrophile, resulting in net allylation of the donor reagent upon completion of the reaction sequence (equation 37).[102,155–157] The substrates can be used to prepare a variety of heterocycles[158] and carbocycles[159] when Wittig alkenation proceeds intramolecularly; 1,2-vinylenebisphosphonium salts function similarly.[160,161] The conjugate anions are reactive towards other electrophilic reagents as well, enabling, for instance, the production of relatively complex phosphonates,[162] cyclopropanes and cyclohexanes.[23]

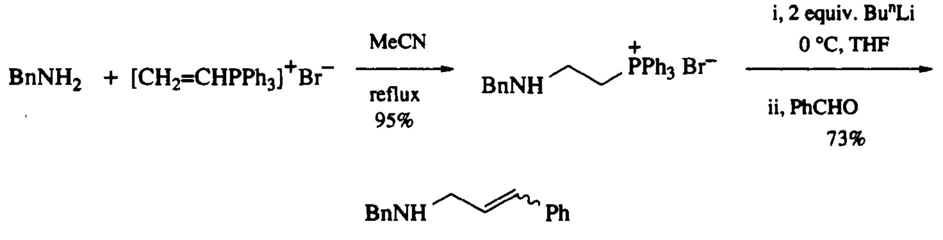
BnNH$_2$ + [CH$_2$=CHPPh$_3$]$^+$Br$^-$
MeCN
reflux
95%
BnNH
+PPh$_3$ Br$^-$
i, 2 equiv. Bu$^n$Li
0 °C, THF
ii, PhCHO
73%
BnNH
Ph

(37)

(*E*):(*Z*) = 71:29

#### 1.6.3.4.4 Imine-containing substrates

α,β-Unsaturated aldehydes protected as imines by reaction with primary amines undergo tandem vicinal dialkylation;[163] when enantiomerically pure amino acid esters are used to generate these imines, the reaction sequence can proceed with good levels of asymmetric induction from the diastereodifferentiating effects of the imino moiety upon the constituent carbon–carbon bond-forming reactions.[164] Similarly, conjugated carboxylic acids protected as benzothiazoles act as substrates for conjugate addition–conjugate anion trapping reactions.[165] Perhaps the most synthetically useful imine-containing substrates are oxazolines prepared from 1- and 2-naphthoic acids.[166,167] These compounds allow direct introduction of vicinal substituents into the naphthalene π-system by addition of organolithium reagents followed by electrophilic trapping (equation 38). Imines of the corresponding 1-naphthaldehyde behave similarly.[66]

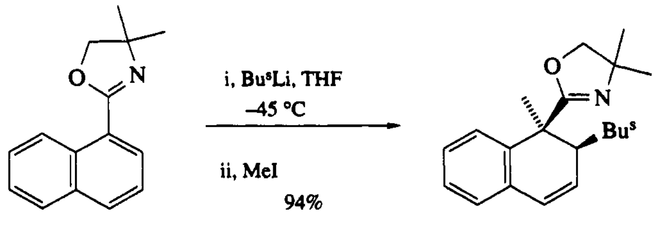
O
N
i, Bu$^s$Li, THF
–45 °C
ii, MeI
94%
O
N
Bu$^s$

(38)

### *1.6.3.4.5 Miscellaneous substrates*

As previously illustrated in equation (6), fulvenes can undergo Michael donor-initiated tandem difunctionalization.[62] Nitroalkenes, superior heterodienes in [4 + 2] cycloaddition reactions,[168] would appear to be very good candidates for nucleophilic addition–conjugate anion trapping reactions. These substrates do undergo Michael additions[169] but so far have found scant use,[170] likely because the Nef-type[315] conjugate anion intermediates that form are not inherently nucleophilic at the α-carbon. (η-Arene) tricarbonylchromium complexes[171] offer a synthetic alternative to oxazoline-mediated vicinal dialkylation of arenes, undergoing nucleophilic addition to give an alkylchromium intermediate; carbonyl insertion into the chromium–carbon bond and subsequent alkylation affords ketones (equation 39).[172] Allenes undergo effective silylcupration–alkylation reactions.[173] Lastly, polyunsaturated ketones and esters, capable of undergoing 'extended' 1,(4 + 2*n*)-addition reactions, have received limited attention as substrates for conjugate addition–enolate trapping sequences.[65,105,174,175] 1,4-Addition-initiated vicinal difunctionalizations generally predominate, as exemplified in equation (40).[174] Related substrates (**19**) and (**20**), wherein one of the two double bonds in a conjugated alkadienoate is replaced by a cyclopropyl moiety, undergo net 2,6-dialkylation and 2,3-dialkylation, respectively (equations 41 and 42).[176]

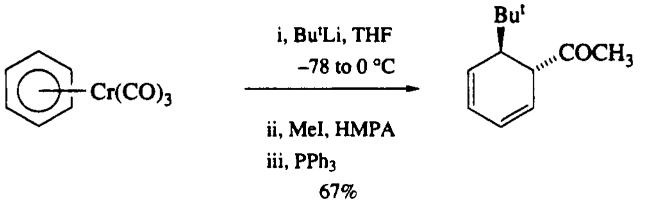
Cr(CO)$_3$
i, Bu$^t$Li, THF
-78 to 0 °C
ii, MeI, HMPA
iii, PPh$_3$
67%
Bu$^t$
COCH$_3$

(39)

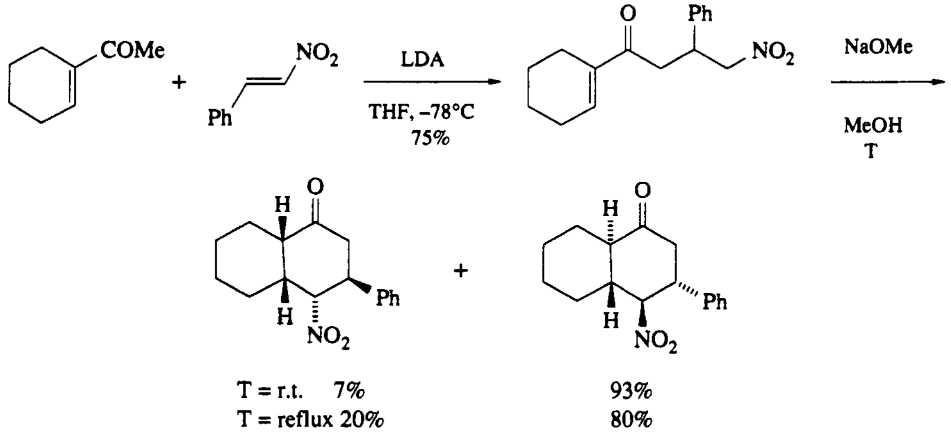
COMe
+
NO$_2$
Ph
LDA
THF, -78°C
75%
O
Ph
NO$_2$
NaOMe
MeOH
T
H
O
Ph
H
NO$_2$
+
H
O
Ph
H
NO$_2$
T = r.t. 7%
T = reflux 20%
93%
80%

(40)

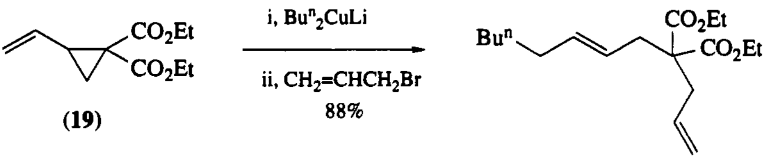
CO$_2$Et
CO$_2$Et
(19)
i, Bu$^n{}_2$CuLi
ii, CH$_2$=CHCH$_2$Br
88%
Bu$^n$
CO$_2$Et
CO$_2$Et

(41)

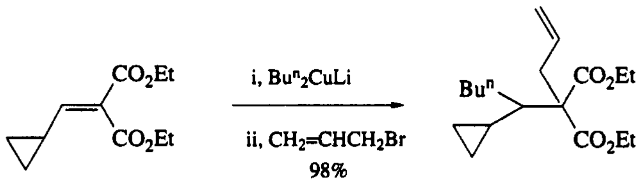
CO$_2$Et
CO$_2$Et
i, Bu$^n{}_2$CuLi
ii, CH$_2$=CHCH$_2$Br
98%
Bu$^n$
CO$_2$Et
CO$_2$Et

(42)

## 1.6.4 THE NUCLEOPHILE

A wide range of nucleophilic reagents has been used to initiate tandem vicinal difunctionalizations of α,β-unsaturated carbonyl-containing substrates. Dominant among these reagents are organocopper (Gilman) reagents[8–10,43] and, to a lesser extent, enolates;[7,38] their use reflects the normally high regioselectivity of these reagents for 1,4- *versus* 1,2-addition as well as their reliably high relative nucleophilicities compared to their basicities.

### 1.6.4.1 Hydrides

As previously mentioned, the first exploitation of a one-pot, three-component tandem vicinal difunctionalization reaction employed a dissolving metal conjugate reduction of α,β-unsaturated ketones to produce enolates, which were *C*-alkylated using various electrophiles.[39] Such dissolving metal conjugate reduction–enolate trapping remains the most popular route to prepare α-alkylated ketones from enones. Other reagents have been developed to act as regioselective, 1,4-hydride donor reagents,[177] including potassium triphenylborane,[178] complex copper hydrides and stoichiometric and catalytic copper(I)–metal hydride mixtures,[179] DIBAL-H–HMPA with methylcopper[180] and 1,3-dimethyl-2-phenylbenzimidazoline;[181] applications to difunctionalizations are rare, however.[182] Reductive alkylation of enones and enoates is possible using lithium and potassium tri-*s*-butylbororanes (equation 43)[183] and the copper hydride cluster (Ph$_3$PCuH)$_6$;[184] copper hydride[185] and copper-containing sodium hydride[186] cause hydrodimerizations of enoates and alkynes, respectively. In general, such hydrodimerizations should be considered as possible products, especially when highly reactive intermediate enolates are generated. Related regioselective hydrosilylation of α,β-unsaturated carbonyl compounds results in silyl enol ethers, from which an enolate may be regenerated.[187]

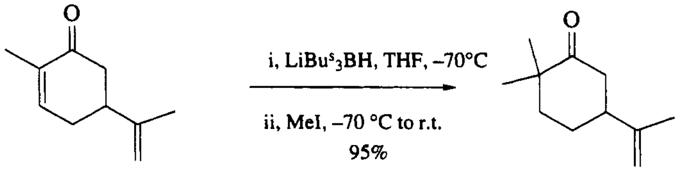

(43)

### 1.6.4.2 Unstabilized Anions

Relatively simple carbon $sp^3$- and $sp^2$-hybridized organometals are frequently used to initiate conjugate alkylation–enolate trapping sequences by carbon–carbon σ-bond formation at the β-carbon of the substrate. While organocopper reagents have proven to be the most versatile of these reagents, many other organometals also can be used, depending upon the nature of the substrate.

#### *1.6.4.2.1 Organocopper reagents*

The first example of a three-component tandem vicinal dialkylation reaction employed copper(I) chloride-catalyzed 1,4-addition of a Grignard reagent to a cyclohexenone (Scheme 3).[40] Catalytic organocopper protocols are used occasionally (*e.g.* equations 4[60] and 19[91]), but usually an improvement in the yield of the conjugate adduct produced can be realized when stoichiometric organocopper reagents are employed. Copper(I)-catalyzed conjugate addition can be very convenient; typically, a Grignard reagent is used as nucleophile and copper(I) halides such as copper(I) iodide, copper(I) bromide or their dimethyl sulfide or trialkylphosphine complexes are present in amounts ranging from 2–10 mol %. In one instance, copper(I) catalysis was imperative for the success of a difunctionalization, the concentration of copper(I) present being able to effect both the reactivity and selectivity of the ambident conjugate enolate towards the electrophilic reagent.[188] In a complementary manner, activation of the substrate with an α-electron-withdrawing substituent can make copper(I) catalysis superfluous.[189]

In spite of the fact that one type of stoichiometric organocopper reagent may display chemical behavior very different from that of another, a variety of the reagents find common use in initiation of vicinal difunctionalizations. The more common of these reagents are: alkylcopper(I) reagents, with and without ligating agents that can be essential to their reactivity; dialkylcopper(I)metal reagents, with both alkyl groups identical; mixed dialkylcopper(I)metal reagents, wherein both alkyl groups are not identical; alkyl(alkylhetero)copper(I)metal reagents containing one copper–heteroatom bond; and the higher order organocopper reagents, exemplified by the cyanodialkylcopper(I)dilithium reagents. The choice of the appropriate reagent for the substrate is compounded by the fact that the reactivity and selectivity of the organocopper reagent is affected by the identity of the metal of the oganometal used to form it. The initial counterion of the copper(I) salt chosen to generate the organocopper species also can influence the outcome of the reaction.[190,191]

Simple alkylcopper(I) reagents are less reactive than their corresponding dialkylcopper(I)metals; this comparitive lack of reactivity in 1,4-addition reactions results in relatively rare use in vicinal difunctionalizations of α,β-unsaturated carbonyl substrates. Equation (44) illustrates that vinylcopper initiates dialkylation of a cyclopentenone,[192] but most organocoppers in fact are inert. In part, this inertness may be explained to the lack of solubility of the copper reagents in common solvents for conjugate addition–enolate trapping reactions, such as THF or diethyl ether. Indeed, when putatively solubilized *via* ligation with organophosphorus or organosulfur ligands, alkylcopper(I) reagents are activated towards 1,4-addition (*e.g.* equation 16).[11] Solubilizing ligands include trialkyl phosphites,[88] boron trifluoride,[193] dimethyl sulfide[194] and trialkylphosphines.[195,196] The latter reagent finds efficient use in three-component coupling syntheses of prostaglandins (equation 45).[197]

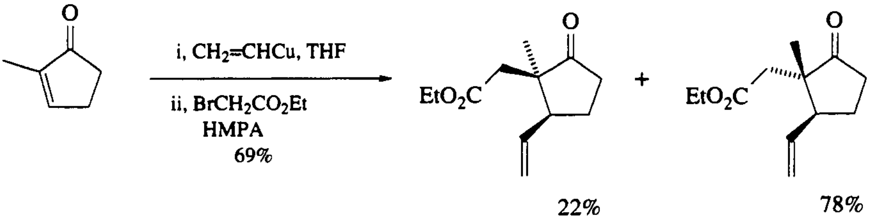

(44)

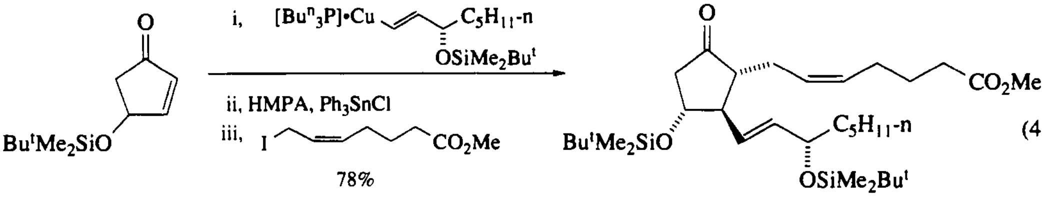

(45)

When terminal alkynes are used as substrates, alkylcoppermagnesium dihalides prepared from a copper(I) bromide–dimethyl sulfide complex typically are used (*e.g.* equation 31[134] and Scheme 7).[135] The choice of a Grignard reagent, from which the alkylcopper(I) species is prepared, is important; in this instance, alkyllithium-derived alkylcopper reagents usually are less satisfactory.[10]

Dialkylcopper(I)metal reagents, also referred to as homocuprates,[43] are the most popular Michael donors for tandem vicinal difunctionalization reactions of α,β-unsaturated carbonyl substrates. The alkyl groups are derived from 2 equiv. of an alkyllithium or Grignard reagent (*e.g.* equations 2,[56] 3,[59] 5,[61] 11[77] and 41[176]); the alkyl group can be methyl, primary or secondary alkyl, alkenyl, allyl, benzyl or aryl. Instances of tertiary dialkylcopper(I)metal conjugate addition–enolate trapping are rare. The reagents can possess additional, even complex functionality: in addition to the example of equation (5),[61] homocuprates have been generated with ether moieties present, including acetal groups;[198] trialkylsilyl groups[199] and imines[200] can be accomodated. Trialkylsilylmetal-derived homocuprate reagents are excellent Michael donors (*e.g.* equations 1[55] and 7[64]). As is the case with alkylcopper(I) reagents, solubilizing ligands can be used to facilitate difunctionalization. Often, these additional ligands do not appear essential for the success of the reaction sequence; occasionally, however, they are mandatory (equation 46).[201]

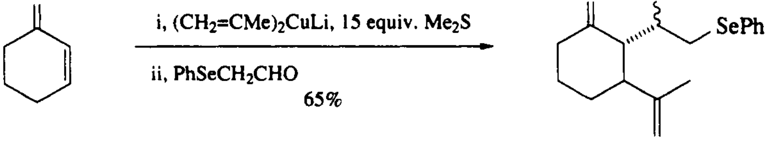

(46)

Enhanced yields result when a Lewis acid catalyst is used during addition of a dialkylcopper(I)metal reagent to a substrate.[78,79] In particular, boron trifluoride etherate has been used as an activating catalyst for conjugate addition in 1,4-addition–enolate trapping sequences.[78,202,203] Halotrimethylsilane-modified organocopper reagents can cause remarkable enhancements in the rates of conjugate additions to normally unreactive substrates:[204] trimethylsilyl enol ethers are the primary products, which can be employed in a subsequent α-functionalizing step.

Mixed or unsymmetrical dialkylcopper(I)metal reagents possess two chemically distinct alkyl groups, only one of which exhibits nucleophilicity and acts as a Michael donor. The two groups almost always differ in the formal hybridizations of the carbon atoms bonded to the copper nucleus and that group whose carbon–copper bond contains the lesser *s*-character is the group that acts as the nucleophile,[205] although a few exceptions to this rule have been noted.[206,207] Generally, the reagents are generated from an alkynylcopper(I) species and an alkylmetal (*e.g.* equation 26),[113] with pentynyl- and hexynyl-copper(I) being the reagents of choice; the net 1:1 nucleophile to electrophile stoichiometry of the Michael donor and substrate is preferable to that of a homocuprate reagent when the parent alkylmetal is difficult to obtain. For this reason, the reagents compete with the previously discussed trialkylphosphine–alkylcopper(I) complexes as preferred reagents with which to introduce the β-chain in conjugate addition–enolate trapping syntheses of prostanoids.[208] Normally alkylalkynylcopper(I)metal reagents are less reactive than their corresponding dialkylcopper(I)metal reagents. Rarely, the opposite can prove to be the case, as in equation (47):[209] the corresponding diarylcopper(I)magnesium halide of (**21**) fails to undergo 1,4-addition with the substrate. Mixed dialkylcopper(I)metal reagents also can serve as interesting and novel synthons: organocopper (**22**; equation 48) functions as a methyl acrylate synthetic equivalent which effectively undergoes vicinal dialkylation in a reverse order, α-bond formation preceding β-bond formation.[113]

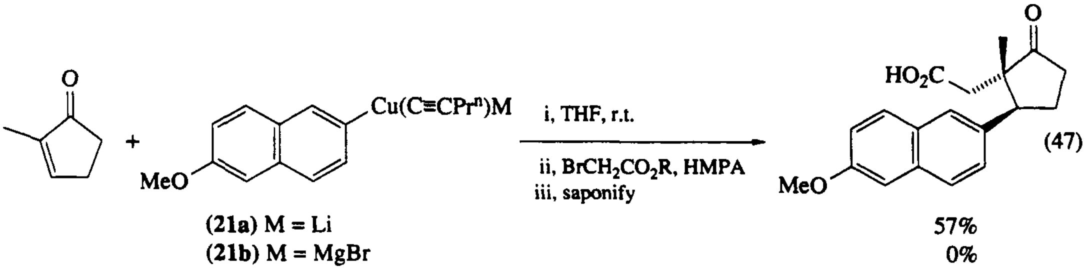

(**21a**) M = Li
(**21b**) M = MgBr

(47)

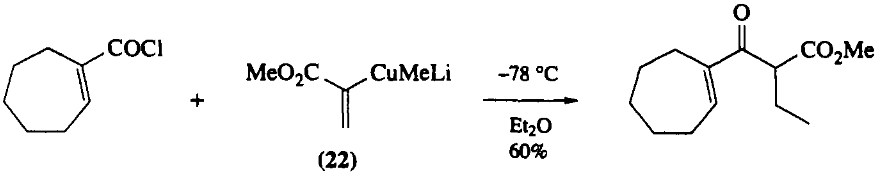

(**22**)

(48)

Alkyl(heteroalkyl)copper(I)metal reagents are much like mixed dialkylcopper(I)metal reagents in that they contain only one alkyl group that is active as a nucleophile. The other group, bonded to the copper nucleus through a heteroatom, is retained by the copper complex almost without exception.[210] Most common among this class of reagents are those derived from addition of an alkylmetal reagent to phenylthiocopper at low temperature. The resulting reagents are thermally labile[211] but usually are as reactive as their corresponding dialkylcopper(I)metal reagents. A comparison between alkyl(phenylthio)- and alkylpentynyl-copper(I)metal reagents indicate that neither may offer particular advantage over the other.[212]

The increasingly popular higher order organocopper reagents[213] have been considered unsuitable for use in direct tandem vicinal difunctionalization reactions.[214,215] These reagents can be exploited by utilization of an indirect conjugate addition–enolate trapping sequence,[216] as illustrated by the synthesis of spiroketone (**23**) for a total synthesis of ginkolide B (equation 49);[21] examples of direct difunctionalization recently have been reported using trialkylsilylmetal- (*e.g.* equation 22)[97] and trialkylstannylmetal-derived (equation 27)[111] higher order organocoppers as well. Occasionally, these reagents offer unique

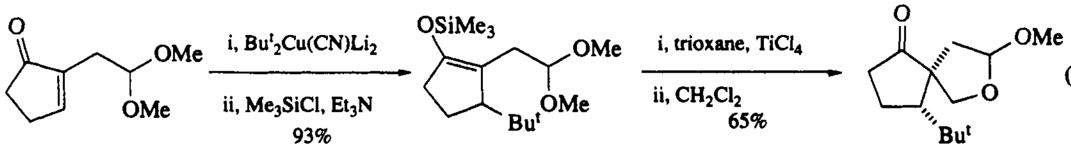

(49)

(**23**)

reactivities unavailable using other Michael donor species, as evidenced by silylcupration–functionalization of alkynes[217] and allenes[173] using cyanobis(dimethylphenylsilyl)copperdilithium.

### *1.6.4.2.2 Other organometal reagents*

Organometallic reagents can be used directly or with a transition metal catalyst in tandem vicinal difunctionalization reactions. Relatively basic reagents find greater use with substrate molecules that are not enolizable so that competitive α-deprotonation is avoided and with substrates that have been activated towards conjugate addition by an electron-withdrawing α-substituent.

A wide variety of Grignard reagents can be used as Michael donors without complication, including primary, secondary, tertiary, vinyl- and aryl-magnesium halides. These nucleophiles have been used most often with activated enoates and enones possessing α-alkoxylcarbonyl[189] or α-arylsulfinyl (*e.g.* equation 18)[90] substituents. Salts of unsaturated carboxylic acids with α-trimethylsilyl substituents also undergo Grignard reagent-initiated difunctionalization (equation 21).[70] *N*,*N*-dialkylthioenamides[118] and *N*,*N*-dialkylenamides[115] are quite reactive towards Grignard reagents, as illustrated in equation (50);[115] such amides have no acidic α-hydrogens and cannot be deprotonated by the organomagnesium reagent. Presumably, substituents on the amide nitrogen also hinder attack of the nucleophile at the carbonyl carbon.

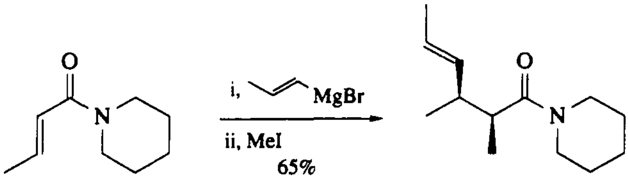

(50)

Alkyllithium reagents are used more frequently than their organomagnesium analogs; they exhibit the same reactivity trends. They also initiate tandem difunctionalizations of α,β-unsaturated amides[115,119] (*e.g.* equation 29)[121] and thioamides.[117] Alkyllithium reagents are preferred for use in charge-directed difunctionalizations[70,72–74] (*e.g.* equations 9[72] and 10[75]), additions to vinyl sulfones (equations 35[149] and 36[154]) and vicinal dialkylations of aryloxazolines (equation 38).[167] The latter application illustrates that the method by which the alkyllithium reagent is prepared can be important: 1-naphthyloxazolines undergo well-behaved dialkylation reactions initiated by commercially available butyllithium reagents, but allylic, benzylic and vinylic organolithiums are suitable only if generated by transmetallation[218] of tetraalkylstannanes with methyllithium. The explanation of this effect may lie in a change of the state of the aggregation of organolithium reagents, making them much more reactive.[219] Only rarely do simple organolithium reagents undergo 1,4-addition–enolate trapping reactions with substrates that otherwise would be anticipated to undergo nearly exclusive 1,2-addition, as illustrated in the synthesis of a tetralone by a benzyllithium-initiated conjugate addition–Dieckmann cyclization of methyl crotonate (equation 51).[18]

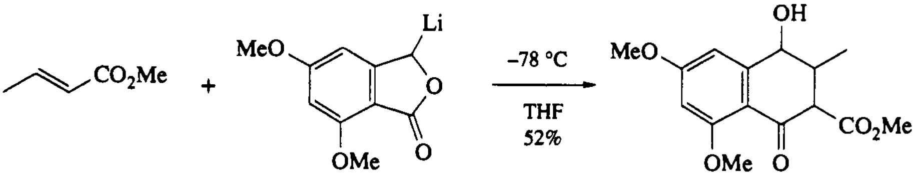

(51)

Less common carbanionic Michael donors include organoaluminum and organozirconium reagents, which react with enones using nickel(II) catalysis[220–223] and acylate–nickel complexes.[224] Noncarbanionic organometal reagents that have been used in difunctionalization sequences include alkoxides,[26,98,114,225] sulfides,[100,114,144,225–227] trimethylsilyllithium,[47] trialkylstannyllithium reagents[130,228] and alkyl-[227] and aryl-selenides.[229,230] Perhaps the most commonly used heteroatom nucleophiles are metal amide reagents such as LDA (*e.g.* equation 24).[27,105,106,115]

### 1.6.4.3 Stabilized Anions

Many carbanionic nucleophiles that would be considered too 'hard' to react as Michael donors can be made into effective reagents for conjugate addition reactions by appending resonance or inductively stabilizing groups to 'soften' their intrinsic Lewis basicity. Such stabilized anionic Michael donors include enolates, alkylthio-substituted carbanions, ylides and nitro-substituted carbanions.

#### *1.6.4.3.1 Enolates*

Michael addition frequently is used as a generic descriptor of 1,4- or conjugate addition, but in fact refers to specific 1,4-addition of an enolate anion to an α,β-unsaturated carbonyl substrate, resulting in a 1,5-dione adduct.[231] Classical Michael additions are conducted in protic media; for tandem vicinal difunctionalization reaction sequences, this dictates that the α-functionalizing reagent be intramolecular in order to compete with proton capture by the conjugate enolate from the solvent,[232] or that the Michael adduct be isolated and α-functionalized under a different set of reaction conditions.[233,234] Generally, these reaction sequences suffer from side reactions. Amongst the undesired reactions are those with the base catalysts used, self-condensation of the substrate and the possiblility of 'retro-Michael' reaction; for these reasons, enolate-initiated difunctionalization sequences invariably are run in aprotic solvents.

Enolates are excellent Michael donor reagents, the initial step in difunctionalization proceeding with ease at low temperatures. The enolate can be generated directly from reaction with a hindered base such as LDA (*e.g.* equation 40)[175] or some other base (equation 15).[84] Alternatively, it can be generated from a neutral enolate synthetic equivalent, such as a silyl enol ether species, by ether cleavage using methyllithium,[235] fluoride,[236] trityl perchlorate (equation 13),[80,237,238] titanium(IV) tetrachloride,[239] alkylaluminum(III) dichlorides[240] and other Lewis acids.[241] Enol triflates may also serve this purpose.[242] The enolate can be derived from esters, especially β-keto esters and malonates (*e.g.* equation 20),[96] ketones or amides (*e.g.* equation 25).[25] An interesting extension of enolate addition–Dieckmann cyclization (equation 52) uses the *o*-xylylenolate (**24**) in a synthesis of tetralones, thereby mimicking a [2 + 4] cycloaddition reaction.[24]

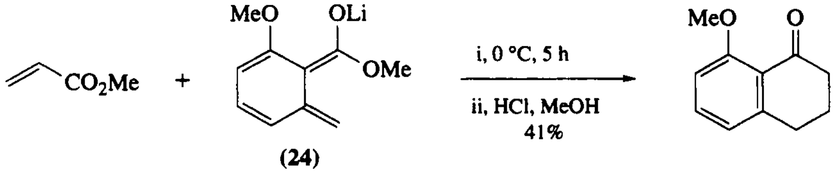

(52)

#### *1.6.4.3.2 Sulfur-containing anions*

The synthesis of 4-alkyl thioketones is possible by exploiting the stabilizing effect of a sulfur atom upon an adjacent carbanionic center. Ambident allylic anions react so that conjugate addition proceeds exclusively with the α-carbon of the nucleophile,[129,243,244] as illustrated in equation (53);[245] arylsulfinyl and arylsulfonyl groups normally[246] behave similarly.[247-249] Sulfur-stabilized vinylic carbanions can be prepared and function as Michael donors in difunctionalization sequences.[250]

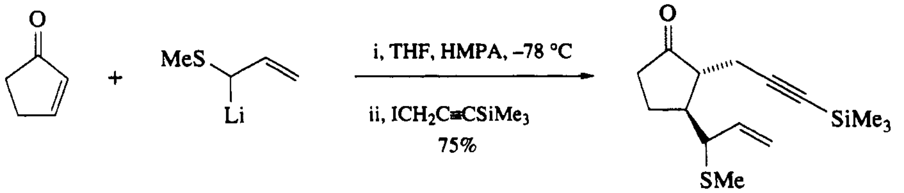

(53)

Organosulfur substituents can play dual roles when sulfur ylides are used as nucleophiles in conjugate addition–enolate trapping reactions; the conjugate enolate undergoes intramolecular displacement of the trialkylsulfonium moiety, resulting in net cyclopropanation.[251,252] Metallated dithianes, containing two geminal sulfur atoms to stabilize the adjacent negative charge, act as acyl anion equivalents to provide a route to 1,4-diketones.[253] As previously shown in equation (30),[127] these Michael donors have been used to prepare a number of lignan antibiotics.[20,124-126,254,255] The dithiane precursor can be further acidified by substitution with an electron-withdrawing group, such as the alkoxycarbonyl group present in equations (8) and (14).[69] Vinylogous dithianylidene anions can react by either an α-1,4- or a γ-1,4-addition mode, selectable by appropriate choice of counterion or by use of HMPA as a solvent adjuvant.[256] Metallated dithianes with one or both of the sulfur atoms oxidized to the sulfoxide or sulfone level also are efficient Michael donors.[102,257]

Orthothioformates[258,259] and their analogs[86,260] function as masked carboxylic acid Michael donors: methoxy(phenylthio)(trimethylsilyl)methyllithium, as illustrated in equation (17), can be used in a simple 1,4-addition–enolate trapping synthesis of sarkomycin.[86] A particularly interesting example[258] of difunctionalization using tri(phenylthio)methyllithium demonstrates umpolung of its carbanionic center, that carbon acting both as nucleophile and electrophile in the cyclopropanation of cyclohexenone (equation 54).

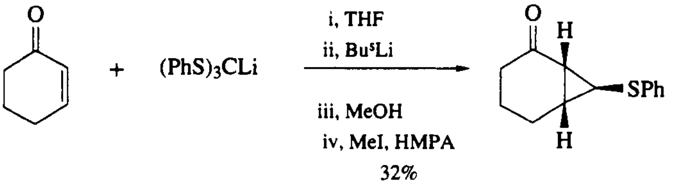

(54)

### *1.6.4.3.3 Other anions*

A limited number of other anionic species have been employed as Michael donors in tandem vicinal difunctionalizations. In a manner similar to sulfur ylides described above, phosphonium ylides can be used as cyclopropanating reagents by means of a conjugate addition–α-intramolecular alkylation sequence. Phosphonium ylides have been used with greater frequency[261–263] than sulfur ylides and display little steric sensitivity.[264] Phosphorus-stabilized allylic anions can display regiospecific γ-1,4-addition when used as Michael donors.[265]

The relative acidity of the α-hydrogens of nitroalkanes allows their conjugate bases to be formed easily and to be used as nucleophiles to initiate difunctionalizations of activated α,β-unsaturated esters[104,266] and amides[226] as well as 2-cyclopentenone.[267] Cyanide has been used as a Michael donor;[226,268,269] cyano-[270–272] and trimethylsilyl-stabilized[273] benzylic anions are very good Michael donors and allow the opportunity for further elaboration of the 1,5-difunctionalized adduct molecule.[274,275] *p*-Toluenesulfonylacetonitrile acts as a double Michael donor in equation (55)[276] to afford a cyclohexanone intermediate; subsequent γ-elimination of the sulfonyl group results in the product ketonitrile. Some very good Michael donors are incompatible with the difunctionalization strategy: enolates of thioesters yield conjugate enolates upon addition to α,β-unsaturated ketones, but the conjugate enolates readily equilibrate so that when an electrophile is added exclusive sulfur–electrophile bond formation is observed.[277]

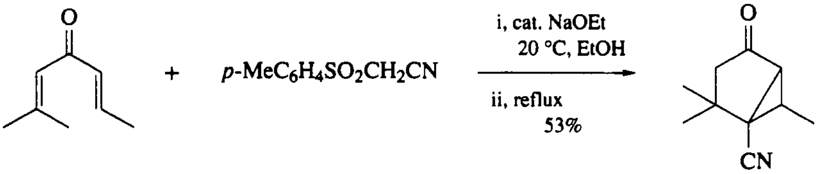

(55)

## 1.6.5 THE ELECTROPHILE

Many different types of electrophilic α-functionalizing reagents are used in tandem vicinal difunctionalization reactions. The most common classes are alkyl iodides, allyl and propargyl bromides, aldehydes, ketones and to a lesser extent, nitroalkenes. Generally, in the case of difunctionalizations of α,β-unsaturated carbonyl substrates, softer, more polarizable electrophiles[278] show the best reactivity and highest *C*-regioselectivity when adding to conjugate enolate intermediates;[38] difunctionalizations of alkynes use the standard electrophiles of organocopper chemistry.[279] When organocopper reagents are used to initiate the reaction sequence for unsaturated carbonyl substrates, α-functionalization can be (and often is) sluggish[8,197] and an astute selection of electrophile, solvent or solvent adjuvant and counterion may be required for satisfactory adduct formation.

### 1.6.5.1 Reactive Alkyl Halides

The most common alkyl halide used is methyl iodide, illustrated by equations (7),[64] (9),[72] (10),[75] (23),[99] (24),[106] (38),[166] (43)[183] and (50).[115] Other alkyl halides that are reliable α-alkylating electrophiles include *n*-alkyl iodides (*e.g.* equation 25),[25] allyl bromide (equation 35),[149] propargylic bromides and iodides (equation 53),[245] benzylic halides and α-halo esters (equation 4);[60] other alkyl halides, especially secondary and tertiary alkyl halides, are far less reactive. When simple, more reactive alkyl halides are compared directly (equation 56), methyl and propargylic halides are better electrophiles than allylic and primary alkyl halides.[86] In many cases of organocopper-initiated dialkylation, the intermediate conjugate enolates do not α-alkylate at sufficient rates to compete with enolate equilibration or other side reactions;[280] often, the rate and amount of α-alkylation can be enhanced by addition of a polar aprotic adjuvant such as HMPA. The adjuvant can be present at the onset of the reaction sequence, as in equation (56), but more frequently it is added subsequent to the conjugate addition step (*e.g.* equations 16,[11] 27[111] and 44).[192] Organocopper 1,4-additions preferentially occur in relatively nonpolar aprotic solvents; a complete change of solvents[77,92,281] after the initial step of a difunctionalization sequence also can be effective (*e.g.* equations 11[77] and 18).[90] In difficult cases, the conjugate enolate can be trapped as a neutral intermediate, usually by simple protonation or by addition of chlorotrimethylsilane to generate a trimethylsilyl enol ether. Regeneration of the conjugate enolate to provide a copper(I)-free lithium, sodium or (rarely) potassium enolate that is much more reactive and is α-alkylated smoothly to give the dialkylated adduct in greater yield than direct tandem difunctionalization would provide (*e.g.* equations 2,[56] 3,[59] 5[61] and 53).[245] This effective transmetallation of the conjugate enolate also can be accomplished directly by addition of the appropriate metal salt to the reaction before adding the electrophile: excellent results have been achieved using triphenyltin(IV) chloride, for instance (*e.g.* equation 45).[197] Alkenyl and alkynyl halides normally do not function as electrophiles in tandem vicinal difunctionalizations; an exception is the alkynylphenyliodonium tosylate[134] reagent class (equation 31).

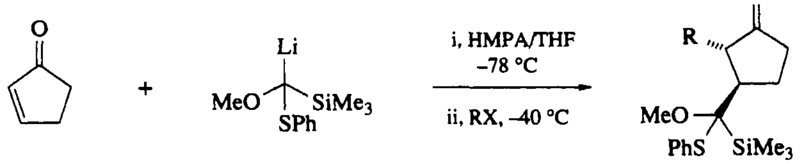

(56)

98%, RX = MeI

48%, RX = EtI

95%, RX = $CH{\equiv}CCH_2Br$

82%, RX = $CH_2{=}CHCH_2Br$

The alkyl halide electrophile can be intramolecular in nature, causing ring formation upon α-alkylation of the conjugate enolate. Such *M*ichael *r*ing *c*losure (MIRC) reactions[282] have become a valuable addition to the repertoire of annulation reactions available in organic synthesis. The alkyl halide-containing moiety may originate either as part of the substrate (*e.g.* equations 15[84] and 20)[96] or, more commonly, may be present as part of the Michael donor (equation 5).[61] When both the Michael donor and the alkyl halide are present as substituents of the substrate molecule, double annulation occurs (equation 36).[154] The chemical yields of adducts from MIRC reactions usually are quite good, due to rate acceleration and decreased by-product formation inherent in the intramolecular nature of the process.

### 1.6.5.2 Carbonyl-containing Electrophiles

Aldehydes and ketones typically are superior electrophiles in conjugate addition–enolate trapping sequences when compared to alkyl halides. Aldehydes are the more reactive reagent class: formaldehyde (*e.g.* equation 14), *n*-alkyl aldehydes (equations 21 and 46) and aromatic aldehydes (equation 13 and 30) all are equally reactive. Branching α to the carbonyl moiety has a detrimental effect: as equation (57) illustrates, chemical yields of adducts can be significantly lowered.[67] This α-branching effect is clearly substrate and reaction condition dependent.[100] Ketones are less reactive electrophilic reagents and have been used less often. Nonetheless, they are quite efficient as α-alkylating reagents for conjugate enolate intermediates. Acetone and cyclohexanone are representative of the class.[100,108,142] As with the alkyl halide reagents, MIRC reactions are observed when a carbonyl moiety is present in the conjugate enolate (*e.g.* equation 6);[62] if the carbonyl moiety is masked as an acetal, the conjugate adduct can be isolated as a trimethylsilyl enol ether and ring closure accomplished[283] by a Mukaiyama reaction (equation 49).[21]

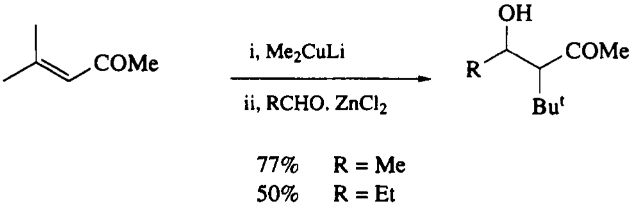

(57)

Esters are far less reactive as electrophiles when compared to aldehydes and ketones. Successful tandem vicinal dialkylations are possible using alkyl formates,[67] but most esters lack the needed reactivity. More reactive thioesters can serve as electrophiles in these sequences.[208] Presence of a potentially electrophilic ester group as a substituent in the conjugate enolate permits very efficient Dieckmann cyclization to take place as the second step of a MIRC sequence (*e.g.* equations 51[18] and 52).[24] Ortho esters are far more reactive, giving β-keto esters as adducts when used in sequences that employ enones as substrates.[230]

Acyl halides have been investigated extensively as α-functionalizing reagents in conjugate addition–enolate trapping sequences.[8] Equation (26)[113] indicates that they can be highly effective trapping agents. It is not unusual for *O*-acylation to compete with *C*-acylation; the ratio of products depends upon the acyl halide itself,[113,284] the substrate chosen[285,286] and the reaction conditions.[188,287,288] Sometimes *O,C*-diacylated products are obtained,[289] an observation which has been used to synthetic advantage.[287,290] Acyl cyanides have been used as α-acylating reagents in a tandem difunctionalization sequence leading to heterocycles.[291]

In addition to the simple one-carbon electrophile formaldehyde, carbon dioxide[67,292] and carbonyl sulfide[273] also are excellent one-carbon electrophiles for use in conjugate enolate trapping.

### 1.6.5.3 Michael Acceptors

The addition of conjugate enolate anions derived from initial reaction between a nucleophile and an unsaturated substrate to a new Michael acceptor molecule should follow trends similar to those already discussed for the initial reaction in Sections 1.6.3 and 1.6.4.3.1. Indeed this is the case for these double Michael or sequential Michael reactions. An appropriate combination of Michael acceptor and conjugate anion is required for sequential Michael addition to take place; otherwise, Michael addition–aldol-type condensation is observed. Thus, with conjugate enolates derived from initial 1,4-addition of an organocopper nucleophile or a simple enolate to an α,β-unsaturated ketone or ester substrate, α-functionalization occurs by means of 1,4-addition to ambident electrophiles such as enoates[293–295] and enones.[296–298] Only 1,2-addition is observed when enals are used as electrophiles,[13,227,248,287,295] as can be seen when equations (58) and (59) are compared.[295] Sequential Michael addition reactions can be used in MIRC-type processes (equation 59). Typically, the initial nucleophile is a conjugated enolate which transfers its nucleophilicity upon 1,4-addition to the substrate, either intermolecularly[170,238,240] or intramolecularly.[17,27,299–301] The newly generated conjugate enolate then reaches back to the nascent enone, cyclization

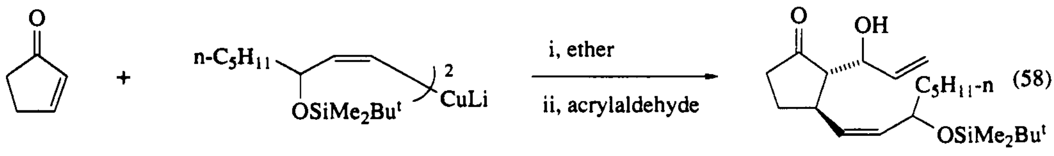

(58)

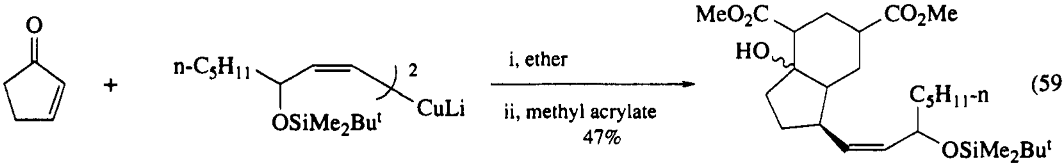

(59)

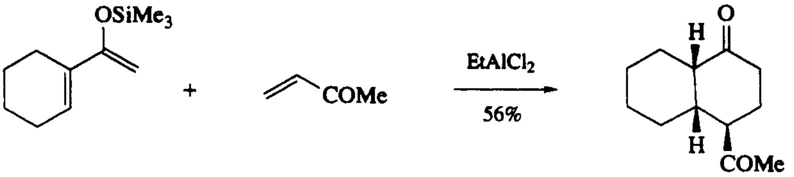

(60)

ensues and the second, cyclized conjugate enolate can be quenched with a proton source. An example is given in equation (60).[240]

In a similar manner, alkynes can undergo sequential carbometallation reactions, previously illustrated in equation (32).[136] It is possible to combine carbocupration of alkynes with the use of a Michael acceptor as electrophile; when that electrophile is a vinylphosphonium salt, carbocupration can be coupled to Wittig alkenation to result in a stereospecific synthesis of dienes *via* a one-pot, four-component, four carbon–carbon bond-forming reaction sequence.[302]

### 1.6.5.4 Other Reagents

A limited number of other electrophile types have been used in difunctionalization reaction sequences. Disulfides,[105,212] sulfenyl chlorides[268,212] and sulfinyl chlorides[303] permit α-thiolation of the conjugate anion; selenyl halides behave similarly.[105,222,304] Molecular bromine[59,305] and iodine[82,110,306,307] trap conjugate enolates to give α-halo ketones, which may be used as electrophiles in other reactions or can be used to regenerate the conjugate enolate regiospecifically. Nitroalkenes appear to be quite reactive Michael-type acceptors;[308] also, unusual uses of lead tetraacetate[309] and an iminium triflate[310] have been reported. Lastly, when tandem vicinal difunctionalizations of acrylates or crotonates are mediated by their corresponding tetracarbonyliron complexes, their intermediate conjugate iron enolates undergo carbonyl insertion into the α-carbon–iron enolate bond; subsequent alkylation affords β-keto esters.[311]

## 1.6.6 SEQUENTIAL MICHAEL RING CLOSURE REACTIONS

A powerful modification of the Michael addition–enolate functionalization sequence involves use of a second Michael acceptor as the electrophilic α-functionalizing reagent. By way of example, ketone (**25**) in Scheme 8 undergoes 1,4-addition of the lithium enolate of methyl 2-methylpropanoate; the conjugate enolate that results then is *C*-methylated to generate adduct (**26**).[94] If methyl acrylate is substituted as the electrophilic reagent, α-functionalization generates a new conjugate ester enolate, (**27**), which undergoes yet a third conjugate addition reaction with the 2-phenyl-2-cyclopentenone moiety remaining from the original substrate (**25**). Norbornanone (**28**) is generated in 40% overall yield, the equivalent of 74% chemical yield per carbon–carbon bond-forming step in the sequence.[93] An analogous process determines the formation of the product diester of equation (59).[295] One-pot, multibond-forming, multiple tandem vicinal difunctionalization sequences with ultimate ring closure compose a reaction class referred to as *s*equential *Mi*chael *r*ing *c*losure (SMIRC) reactions.[23] Controlled anionic codi-, cotri- and cotetrapolymerization reactions like these can proceed in notably high yields and with excellent control of stereochemistry to generate complex polycyclic structures.

Both inter- and intra-molecular cyclopropanations are possible using SMIRC methodology,[98,312,313] but cyclohexane-forming sequences by sequential reaction of three- or four-components with ultimate 1,6-bond closure are more common.[23,101,207,314] Usually, the initial conjugate anion reacts in such a way that it is α-functionalized exclusively; in this way it acts as a two-carbon fragment in the annulation process. Equation (61) illustrates a four-component, tri-*n*-stannyllithium-initiated SMIRC sequence that yields a γ-hydroxystannane in 53% overall chemical yield, equivalent to a yield of 85% per chemical bond formed. Oxidative dehydrostannylation results in a macrolide.[130] By varying the identity of the various components in this sequential Michael–aldol ring closure reaction, various naphthalenes, benzothiophenes, benzofurans and quinolines can be generated.

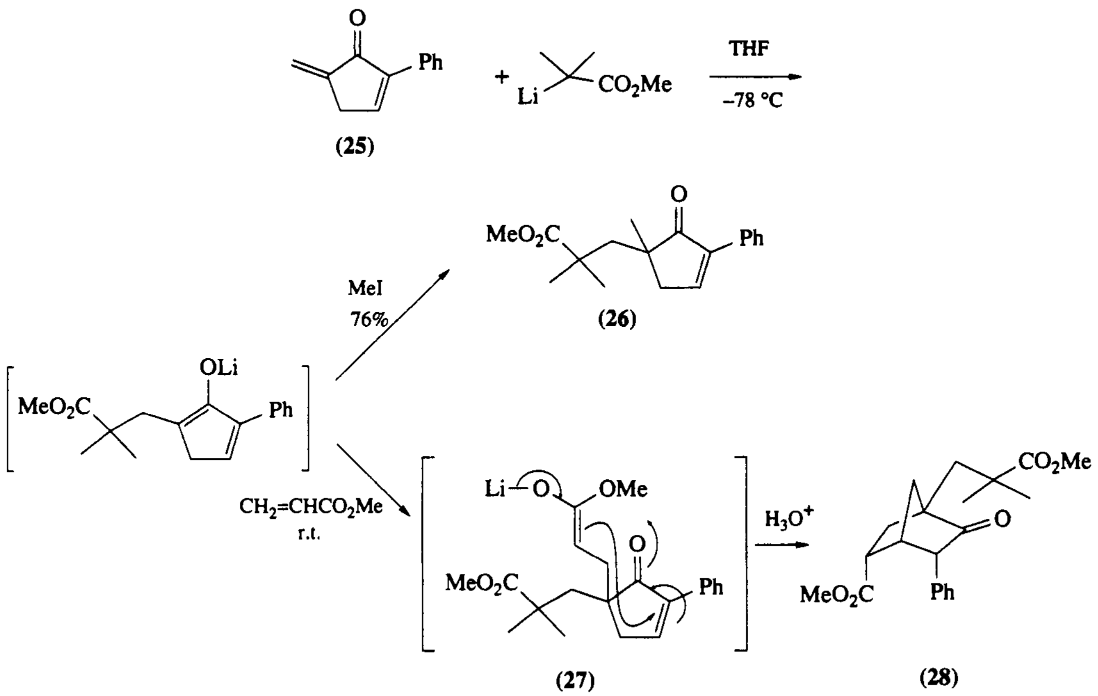

(25) (26) (27) (28)

Scheme 8

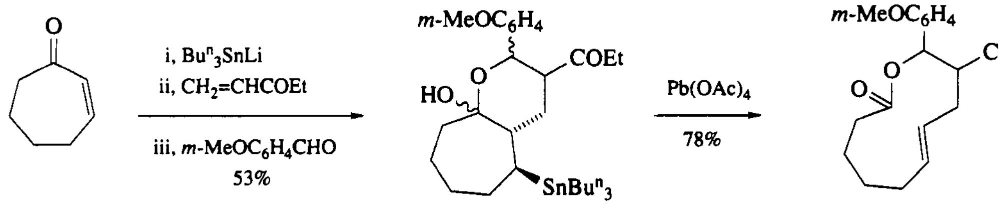

(61)

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# 1.7

# Addition of H—X Reagents to Alkenes and Alkynes

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## 1.7.1 INTRODUCTION

The direct electrophilic addition of the elements H—X to alkenes, dienes and alkynes, where X = halogen, nitrogen, oxygen, sulfur and selenium, is among the oldest known and most important synthetic methods used to prepare the corresponding addition compounds. Unfortunately, much of the early literature from the late 1800s and early 1900s tends to be more confusing than helpful. Rather surprisingly though, relatively little in the way of major new synthetic advances have occurred since that time. However, a number of alternative, indirect procedures, such as solvomercuration–demercuration, have more recently been developed that offer important advantages in chemo-, regio- or stereo-selectivity. These processes are the focus of this chapter.

## 1.7.2 HYDROGEN HALIDE ADDITION

### 1.7.2.1 Introduction

The addition of H—X, where X = F, Cl, Br and I, to alkenes, dienes and alkynes has been extensively studied from both mechanistic[1–3] and synthetic standpoints. While it is one of the earliest methods employed for the synthesis of organic halides, it can often lead to mixtures of products, and the direct conversion of the corresponding alcohols is more commonly used nowadays. The early literature abounds with examples of this reaction in which either mixtures of products are formed, or the products are not well characterized. Few major advances have been reported in more recent times which overcome the synthetic disadvantages of this direct process. It can nevertheless be the method of choice for the synthesis of certain substrates.

In general, the ease of addition of H—X to simple alkenes follows their relative acidity, HI > HBr > HCl, but HF addition is often surprisingly easy. A diversity of mechanisms appear to be involved in these processes, ranging from relatively pure carbocation processes to those more reminiscent of four-center addition. Markovnikov addition is commonly observed when precautions are taken to exclude peroxide or other possible free radical initiators. Though strong acids are involved and rearrangements are not uncommon, the reaction conditions are otherwise quite mild and yields can be high.

### 1.7.2.2 H—F Addition

The addition of HF to alkenes to form alkyl fluorides is difficult to effect in the laboratory, because of the low reactivity of aqueous HF, the difficulties in handling anhydrous HF, the need for pressure equipment, the ease of polymerization of alkenes by HF, and the instability of the resulting alkyl fluorides, especially where secondary, or particularly tertiary, fluorides are concerned.[4–6]

While aqueous HF is unreactive towards alkene addition, anhydrous HF is surprisingly reactive. The addition of HF to simple alkenes, such as ethylene, propene and cyclohexene, has been effected by mixing the reagents in an appropriate metal container at temperatures of –78 to –45 °C, and gradually heating the mixture from room temperature to 90 °C.[7–9] Representative yields are 60–80%. Catalysts are unnecessary. Markovnikov addition is observed, but the stereochemistry of addition to norbornene is not clear.[10] With bornylene[11] and camphene,[12] HF addition gives excellent yields of a mixture of products.

With the great commercial interest in chlorofluorocarbons, the addition of HF to unsaturated organic chlorides, particularly vinylic chlorides has received considerable industrial attention.[4,5,13–19] While these reactions are more difficult to effect than those of simple alkenes and increasing halogen substitution about the C—C double bond decreases the alkene reactivity, the reactions of simple monochloroalkenes proceed at temperatures from –23 to +120 °C and can give good yields. Trichloroethylene or 1,1,2-trichloropropene, on the other hand, require temperatures in excess of 200 °C, and tetrahaloethylenes fail to react in the absence of a catalyst.[5] However, substitution of fluorine for chlorine tends to facilitate HF addition.[5]

While HF addition can on occasion efficiently produce addition products as in equation (1),[13] mixtures of halogen exchange products are often observed (equation 2).[18]

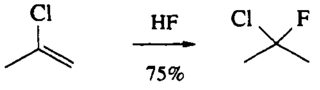

(1)

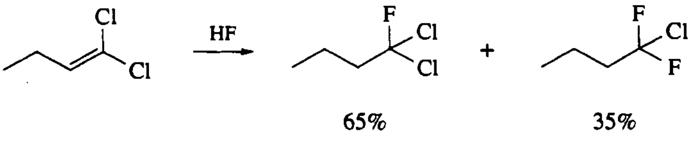

(2)

Indeed, the exchange product can sometimes be obtained directly in high yield (equation 3),[15] or be favored by the addition of excess HF and $SbCl_5$, or $SbF_3$ plus $Cl_2$ (equation 4).[5,16] With the more highly halogenated starting materials, the higher reaction temperatures required lead to increasing halogen exchange.

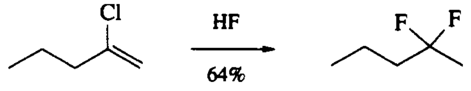

(3)

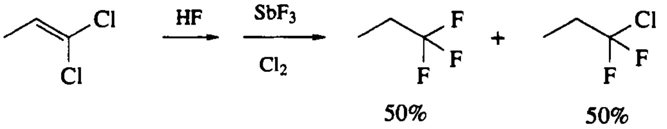

(4)

Unsaturated fatty acids and steroids also react with HF, but the structure of the products has not always been clearly established.[4–6]

While procedures other than those described above, including the use of a variety of catalysts, have apparently been explored industrially, few experimental details are readily available.[5] It is known that $BF_3$ facilitates HF addition, but it also promotes alkene decomposition and halogen exchange and is, therefore, limited to the less reactive polyhaloalkenes.[17,19]

A significant, recent advance in this area involves the use of HF–pyridine or HF–trialkylamine reagents.[20] These stable poly(hydrogen fluoride) reagents react with simple alkenes at atmospheric pressure and room temperature in polyethylene containers using THF as the solvent to give secondary and tertiary alkyl fluorides in yields of 35–90% (equation 5).

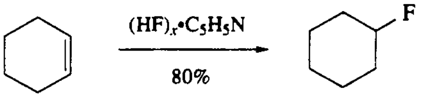

(5)

There appear to be only two reports in the literature of the reaction of HF with dienes (equation 6).[21,22] The yields are quite low probably due to polymerization.

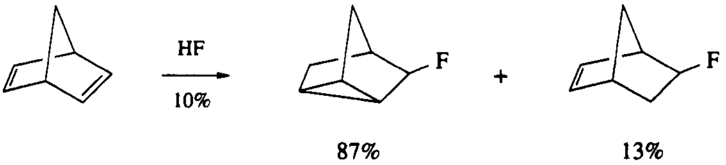

(6)

There are, however, several publications which describe the addition of HF to alkynes to form either vinylic fluorides or difluoroalkanes.[4,23–26] Only the addition of HF to acetylene,[23,24] vinylacetylene[23] and 3,3,3-trifluoropropyne[25] have been reported to form vinylic fluorides (equations 7–9).

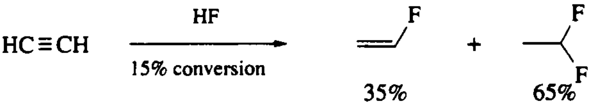

(7)

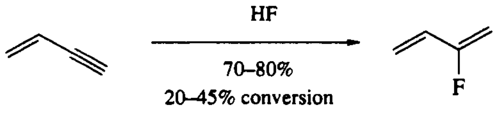

(8)

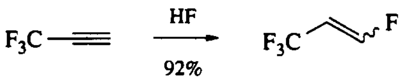

(9)

While the direct reaction of HF and acetylene requires high pressure, proceeds in only low conversion and gives mixtures, a number of catalyst systems have been reported to give improved results.[23] Addition of boron trifluoride, however, favors the formation of 1,1-difluoroethane. Similar results are reported for vinylacetylene. On the other hand, 3,3,3-trifluoropropyne reacts readily to afford the anti-Markovnikov vinylic fluoride in 92% yield.[25]

The reaction of alkynes and HF more commonly gives geminal difluoroalkanes, usually in high yield. Terminal alkynes afford 2,2-difluoroalkanes (equation 10) and internal alkynes yield geminal difluorides (equation 11).[4,23,24,26]

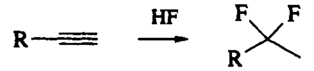

(10)

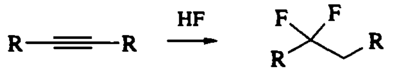

(11)

These reactions are generally carried out at temperatures of –70 to +15 °C using either liquid HF,[24] or HF in ether or acetone.[26] The latter process affords regioisomeric mixtures of geminal difluorides when unsymmetrical internal alkynes, such as 2-pentyne, are employed.

Yields of geminal difluorides of 70–75% are also obtained from the reaction of terminal or internal alkynes with the $(HF)_x{\cdot}C_5H_5N$ reagent.[21]

On the other hand, the use of tetra-*n*-butylammonium or polymer-supported dihydrogentrifluoride at temperatures of 60–120 °C affords 57–90% yields of vinylic fluorides when alkynes activated by the presence of one or two strong electron-withdrawing groups (Ph, CHO, COR, $CO_2R$, CN) are employed (equation 12).[27,28] The (*Z*)-isomer tends to predominate. These reagents are substantially more reactive towards addition to these electron-deficient alkynes than $(Bu^n{}_4N)HF_2$, pyridine–HF, or $Et_3N{\cdot}3HF$. It has been suggested that these reactions actually proceed by nucleophilic attack of fluoride anion.

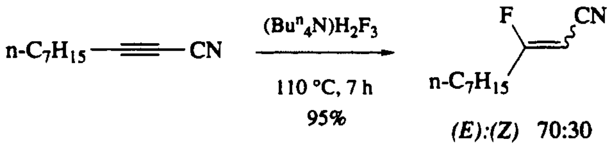

(12)

## 1.7.2.3 H—Cl Addition

There are numerous examples of the direct addition of HCl to alkenes, even though HCl is less reactive than HBr or HI.[29,30] Several different experimental procedures have been employed. Most useful of these involves the passage of dry HCl gas into the alkene either neat or in an inert solvent such as pentane, dichloromethane or diethyl ether. Most successful of these reactions are those which generate tertiary and/or benzylic alkyl chlorides (equations 13–17).[31–35]

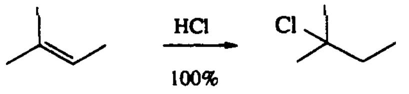

(ref. 31) (13)

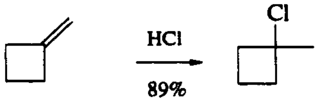

(ref. 32) (14)

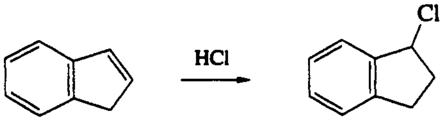

(ref. 33) (15)

Since these addition reactions appear to proceed through carbocation intermediates, carbon skeleton rearrangements can be expected (equations 18 and 19).[36–39]

The stereochemistry of HCl or DCl addition to a wide variety of alkenes has been examined. Addition of HCl to *cis*-2,3-dideutero-2-butene affords a mixture of *erythro* and *threo* 2-chlorobutanes.[40] 1-Methylcyclopentene[37] and 1,2-dimethylcyclopentene[41] give almost exclusively tertiary chlorides formed by *anti*

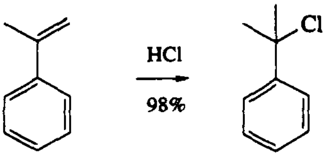

(ref. 34) (16)

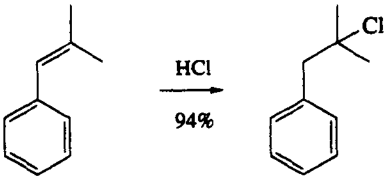

(ref. 35) (17)

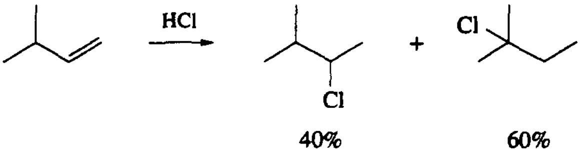

(refs. 36, 37) (18)

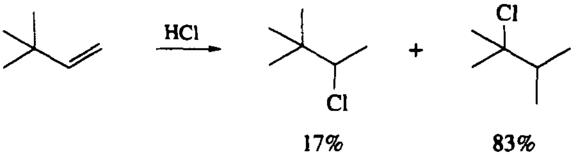

(refs. 37–39) (19)

addition. With cyclohexene[42] and the tetrasubstituted alkenes (**1**)–(**3**),[43,44] products of both *syn* and *anti* addition are observed and the ratio can be dramatically reversed simply by changing the solvent and temperature of the reaction (equation 20).[44]

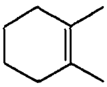

**(1)**

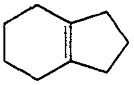

**(2)**

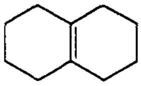

**(3)**

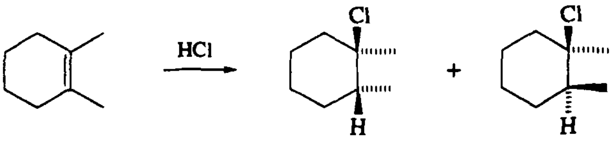

(20)

| | | |
|---|---|---|
| $CH_2Cl_2$ (–98 °C) | 88% | 12% |
| $Et_2O$ (0 °C) | 5% | 95% |

With acenaphthene[45] and 4-*t*-butyl-1-phenylcyclohexene,[46] HCl or DCl addition in nonpolar solvents affords predominantly the products of *syn* addition.

Numerous bicyclic alkenes have been allowed to react with HCl to generate the corresponding *exo* chlorides.[47–53] Skeletal rearrangements, either during addition or soon thereafter, are observed in a number of these additions (equation 21).[47]

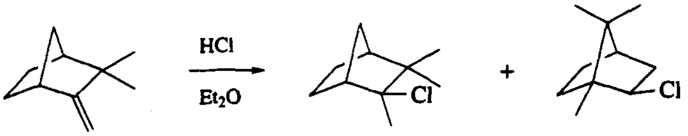

(21)

Electron-rich alkenes, such as vinylic esters and ethers, undergo HCl addition in high yields (equations 22 and 23).[29]

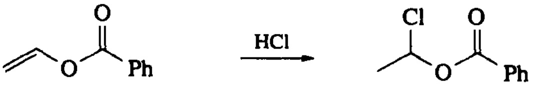

(22)

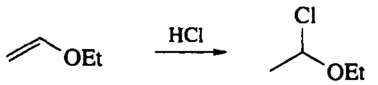

(23)

The addition of HCl to alkenes bearing electron-withdrawing groups also provides a useful approach to functionalized organic chlorides (equations 24–31).[29] Predominant *anti* addition has been observed in all of these examples where stereochemistry can be observed.[54–60]

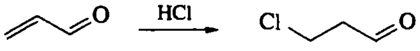

(ref. 54) (24)

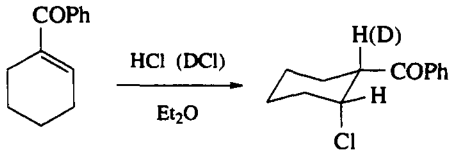

(ref. 55) (25)

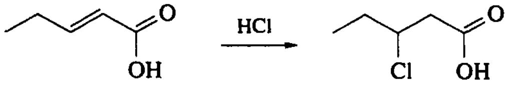

(ref. 56) (26)

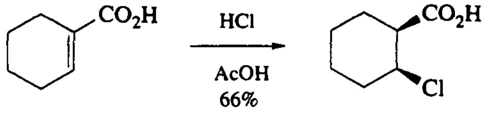

(ref. 57) (27)

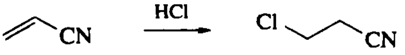

(ref. 58) (28)

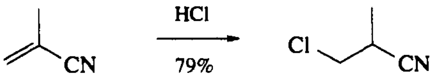

(ref. 59) (29)

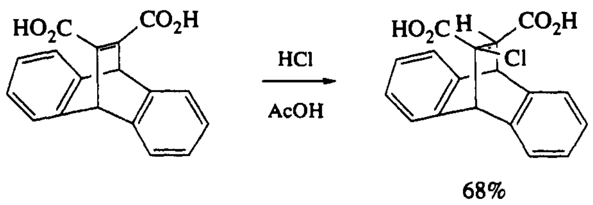

(ref. 57) (30)

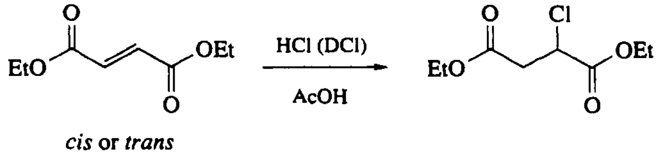

(ref. 60) (31)

With less reactive alkenes, particularly those bearing one or more halogens, it is often advisable to add a Lewis acid catalyst to the reaction (equations 32–41).[61–66] The metal halides $AlCl_3$, $FeCl_3$, $SnCl_4$ and $BiCl_3$ have been most commonly employed as catalysts.[29]

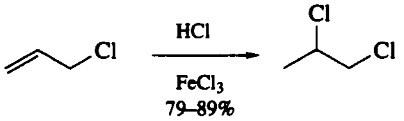
HCl
FeCl3
79–89%

(ref. 61) (32)

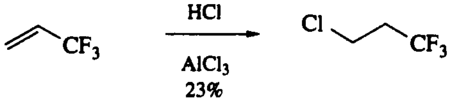
HCl
AlCl3
23%

(ref. 62) (33)

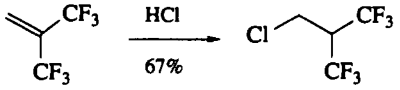

(ref. 63) (34)

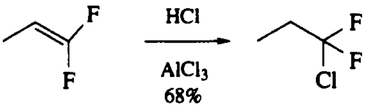
HCl
AlCl3
68%

(ref. 63) (35)

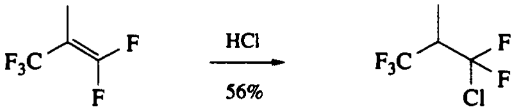

(ref. 63) (36)

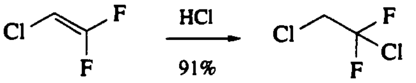

(ref. 64) (37)

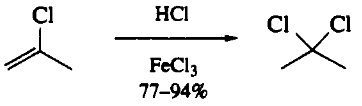
HCl
FeCl3
77–94%

(ref. 61) (38)

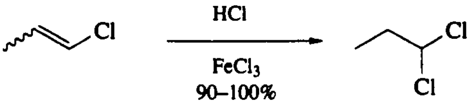
HCl
FeCl3
90–100%

(ref. 65) (39)

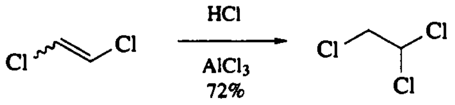
HCl
AlCl3
72%

(ref. 66) (40)

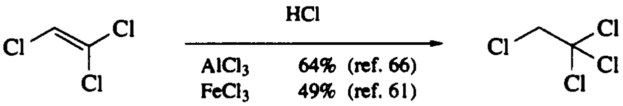
HCl
AlCl3 64% (ref. 66)
FeCl3 49% (ref. 61)

(41)

Occasionally aqueous solutions of HCl have been employed in the hydrochlorination of alkenes (equations 42 and 43).[67,68] The latter procedure appears quite general and avoids the difficulties of working with gaseous HCl.

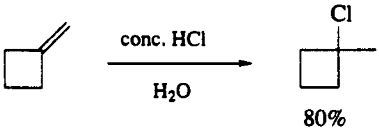
conc. HCl
$H_2O$
80%

(ref. 67) (42)

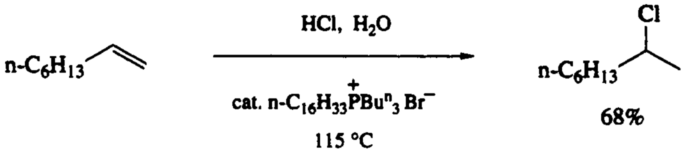

(ref. 68) (43)

Very little work on the addition of HCl to nonconjugated dienes has been reported. The reaction of divinyl sulfide with HCl can be controlled to give either the mono- or di-chloride (equation 44).[69,70]

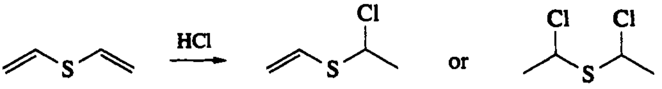

(44)

Norbornadiene affords chiefly the alkenyl chloride, but significant amounts of nortricyclyl product are observed (equation 45).[71]

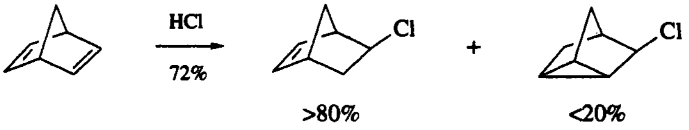

(45)

A few examples of HCl addition to conjugated dienes have been reported.[29] 1,3-Butadiene[29,72] and isoprene[29,73] produce allylic chloride mixtures of 1,2- and 1,4-addition, while 1,3-cyclopentadiene[74] affords 3-chlorocyclopentene in excellent yield (equation 46).[74]

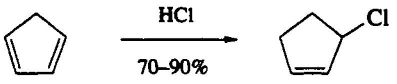

(46)

Considerably more work has been reported on the addition of HCl to allenes.[75,76] Bismuth trichloride has frequently been added to catalyze these reactions. 1,2-Propadiene affords mixtures of 2-chloro-1-propene, 2,2-dichloropropane, propyne, and 1,3-dichloro-1,3-dimethylcyclobutane.[75–77]

Monosubstituted allenes afford predominantly 2-chloro-2-alkenes (equation 47),[73,75,76,78] although 1-phenyl-1,2-propadiene forms exclusively cinnamyl chloride (equation 48).[79]

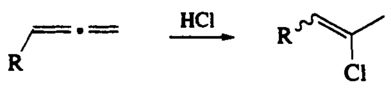

(47)

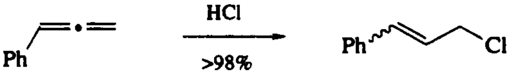

(48)

1,3-Disubstituted allenes generally produce mixtures of vinylic and allylic chlorides (equation 49),[75,76,80,81] although 1,2-cyclononadiene forms the allylic chloride exclusively (equation 50).[80]

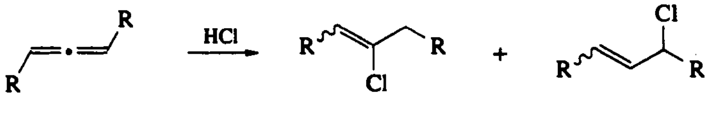

(49)

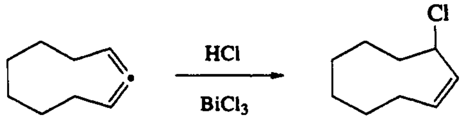

(50)

1,1-Disubstituted[73,76] and trisubstituted[76,82] allenes give rise to mixtures of regioisomeric allylic chlorides (equations 51 and 52).

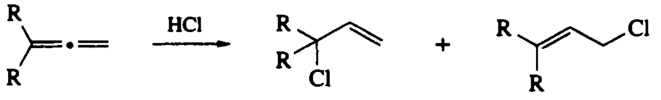

(51)

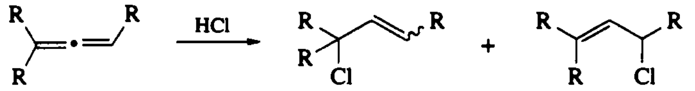

(52)

A few functionally substituted allenes have been reported to undergo HCl addition. Tetrafluoroallene and tetrachloroallene produce allylic chlorides (equation 53), while hydrochlorination of $\mathrm{Bu^tCMe{=}C{=}CCl_2}$ and $(p\text{-}\mathrm{ClC_6H_4})_2\mathrm{C{=}C{=}CCl_2}$ yields $\mathrm{Bu^tCMeClCH{=}CCl_2}$ and $(p\text{-}\mathrm{ClC_6H_4})_2\mathrm{C{=}CHCCl_3}$ respectively.[83]

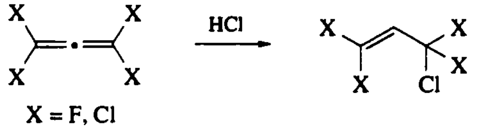

(53)

Allenic nitriles and esters provide nonconjugated products (equations 54 and 55).[76]

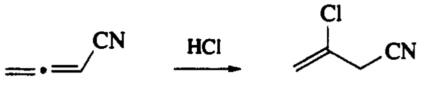

(54)

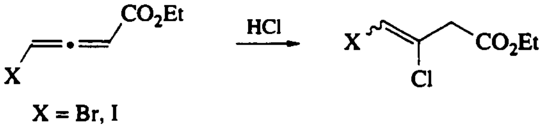

(55)

The addition of HCl to alkynes has received considerable attention.[29] Numerous procedures, usually involving a metal chloride catalyst, have been developed for the industrially important conversion of acetylene to vinyl chloride.[29] The addition of HCl or DCl to terminal alkylalkynes generally produces 2-chloro-1-alkenes plus 2,2-dichloroalkanes (equation 56).

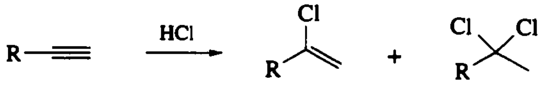

(56)

The reaction has been carried out using HCl either neat or in acetic acid,[84] or in the presence of $\mathrm{HgCl_2}$,[85] $\mathrm{BiCl_3}$[86] or $\mathrm{Me_4NCl}$.[84] In acetic acid, mixtures of *syn* and *anti* adducts are produced,[84] but reactions catalyzed by $\mathrm{HgCl_2}$ proceed by stereospecific *anti* addition.[85,87] The reaction of *t*-butylacetylene affords the expected vinylic chloride, plus a mixture of isomeric dichloride adducts.[84,88] The hydrochlorination of phenylacetylene produces mixtures of *syn* and *anti* adducts in which the ratio is significantly affected by the solvent and catalyst used.[84,89,90]

Symmetrical dialkylalkynes react with HCl in acetic acid to produce *anti* addition products plus ketone (equation 57).[30,91,92] The *anti* adducts are favored by higher HCl concentrations, or the addition of water or $\mathrm{Me_4NCl}$.

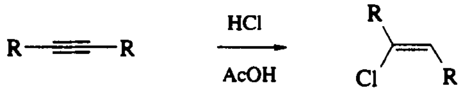

(57)

Unsymmetrical dialkylalkynes react with HCl in acetic acid plus $\mathrm{Me_4NCl}$ to give regioisomeric *anti* adducts,[84] while 1-phenyl-1-alkynes afford predominantly *syn* adducts (equation 58).[84,90–93]

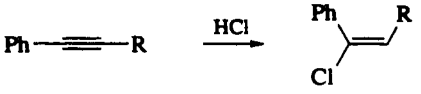

(58)

Vinylacetylene reacts with HCl, CuCl and NH$_4$Cl to give 2-chloro-1,3-butadiene.[29,94] Halogenated alkynes also undergo HCl addition (equations 59 and 60).[25]

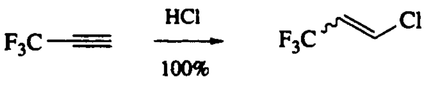

(59)

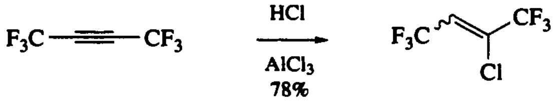

(60)

A wide variety of functionally substituted alkynes react with HCl to produce vinylic chlorides (equations 61–65).[29,95,96] Both *syn*[29] and *anti*[97,98] adducts have been reported to predominate in the reaction of alkynoic acids.

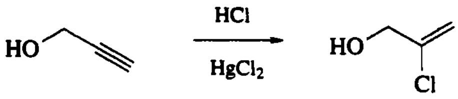

(ref. 29) (61)

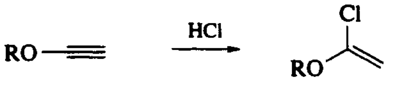

(ref. 29) (62)

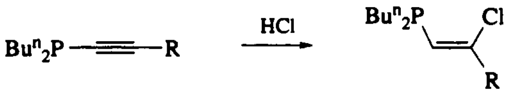

(ref. 95) (63)

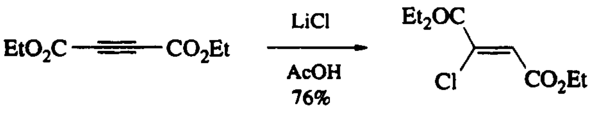

(ref. 96) (64)

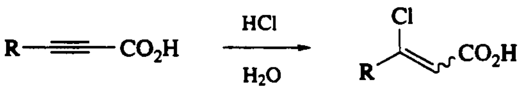

(65)

A wide variety of alkynes have also been reported to react with (Et$_3$NH)HCl$_2$ either neat or in chloroform (equation 66).[99] *Anti* adducts predominate (R$^1$, R$^2$ = CO$_2$Me, CO$_2$Me; CH$_2$Cl, H; Ph, H; Ph, Me), except when R$^1$ = Ph and R$^2$ = Bu$^t$.

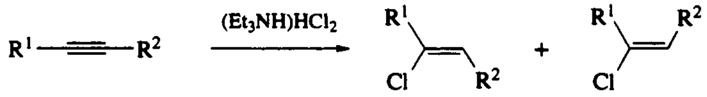

(66)

The addition of HCl across the triple bond of $PhC\equiv CX$ (X = Cl, Br) can even be effected using Et$_4$NCl in aqueous DMSO (equation 67).[100]

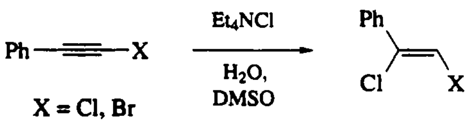

(67)

### 1.7.2.4 H—Br Addition

The electrophilic addition of HBr to alkenes has been extensively studied.[30,101] The reaction is quite facile, but care must be taken to avoid competing anti-Markovnikov free radical chain processes by omitting light and free radical initiators such as peroxides.[102–104] The addition of HBr to alkenes is exothermic and considerably more rapid than HCl addition. Hydrobromination has usually been carried out neat, in inert solvents, or in water or acetic acid. Recently, good results have also been reported using excess aqueous HBr at 115 °C in the presence of a catalytic amount of $n$-$C_{16}H_{33}PBu^n{}_3Br$.[68] Catalysts are generally unnecessary except with the less reactive alkenes, where Lewis acids might be added.

The literature prior to the observation of competitive free radical processes initiated by peroxides and/or light is often contradictory. When the reaction is properly carried out, however, high yields of Markovnikov addition products can be achieved from a wide variety of simple alkenes (equations 68–71).[61,101,105–111] Unsymmetrical alkenes such as 2-pentene give mixtures of regioisomers.[112–114]

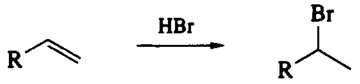

(68)

| *R* | *Yield (%)* | *Ref.* | *R* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| Me | 89–98 | 61 | $Ph(CH_2)_2$ | 80–85 | 108 |
| Et | 100 | 105 | $PhCH_2$ | 92 | 108 |
| $Pr^n$ | ≥84 | 106 | Ph | 65–85 | 109 |
| $Me_3CCH_2$ | 100 | 107 | | | |

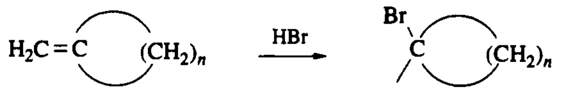

(69)

| *n* | *Yield (%)* | *Ref.* |
|---|---|---|
| 3 | 61, 72 | 67, 110 |
| 4 | 53 | 110 |
| 5 | 65 | 110 |
| 6 | 63 | 110 |

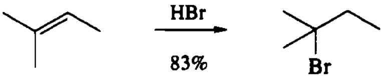

(ref. 31) (70)

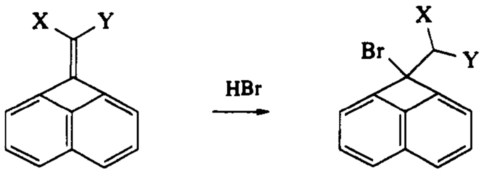

(ref. 111) (71)

| *X* | *Y* | *Yield (%)* |
|---|---|---|
| H | H | 100 |
| Me | H | 89 |
| Me | Me | 79 |
| Ph | H | 91 |

On occasions rearrangements have been observed during hydrobromination (equations 72 and 73).[31,48,115]

The stereochemistry of HBr addition to alkenes has been thoroughly studied. The reaction of *cis*- or *trans*-2-butene with DBr in DOAc gives a mixture consisting of 60% *threo* and 40% *erythro* products.[116] While cyclohexene[117] and alkene (**1**)[118] undergo predominant *anti* addition, the alkenes (**4**)–(**6**) give

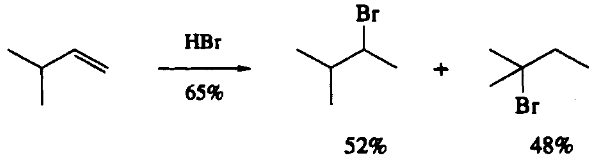

(ref. 31) (72)

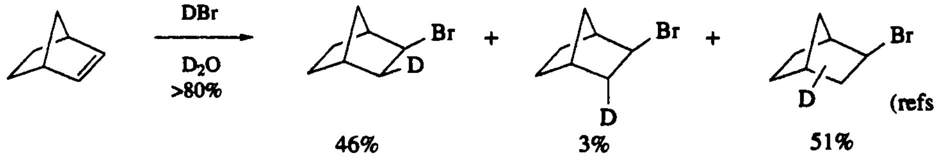

(73)

(refs. 48, 115)

stereoisomeric mixtures. Acenaphthalene,[45] indene,[119] and *cis*- or *trans*-1-phenyl-1-propene[120] undergo 74–90% *syn* addition of DBr, while 1-phenyl-4-*t*-butylcyclohexene gives a mixture of stereoisomers.[46]

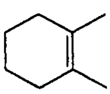

(1)

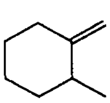

(4) (ref. 118)

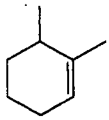

(5) (ref. 118)

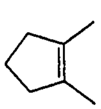

(6) (ref. 41)

The hydrobromination of a number of halogenated alkenes has been examined. Allyl bromide reacts with HBr in the absence of peroxides, or upon addition of antioxidants[121] or $FeCl_3$,[61] or in acetic acid,[122] to produce primarily 1,2-dibromopropane (equation 74). Allyl chloride behaves similarly.[123]

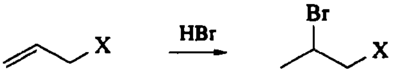

X = Cl, Br

(74)

On the other hand, 3,3,3-trifluoro-1-propene,[62,101] 3,3,3-trifluoro-2-trifluoromethyl-1-propene[63] and 3,3,4,4,5,5,5-heptafluoro-1-pentene[124] react with HBr to afford exclusively the terminal bromides (equations 75–77).

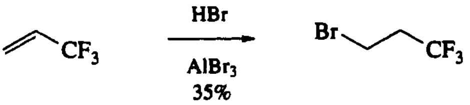

(75)

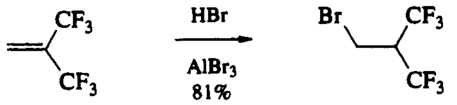

(76)

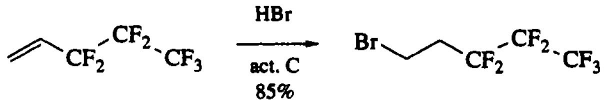

(77)

Vinylic halides are less reactive than simple alkenes, but generally afford clean addition products. The addition of HBr to vinyl chloride[125] or vinyl bromide[61,122,126,127] in the presence of iron(III) chloride or bromide affords primarily the geminal dihalides (equation 78).

With other vinylic halides, the substitution pattern determines the direction of HBr addition (equations 79–83).[61,65,128–130]

Polyhalogenated alkenes also undergo HBr addition (equations 84–87).[61,63,131] Even tetrahaloethylenes undergo HBr addition in a continuous flow reactor in the presence of a catalyst.[132]

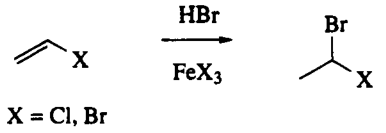
X
HBr
FeX$_3$
Br
X
X = Cl, Br

(78)

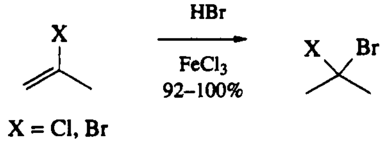
X
HBr
FeCl$_3$
92–100%
X
Br
X = Cl, Br

(refs. 61, 65) (79)

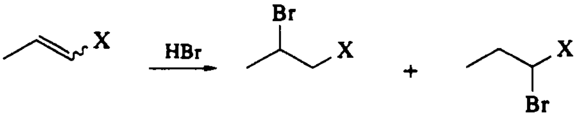
X
HBr
Br
X
+
X
Br

(7) (8)

(refs. 61, 65) (80)

| *X* | *Additive* | *Yield* (%) | *(7)*:*(8)* |
|---|---|---|---|
| Cl | – | 60–100 | ≥98:≤2 |
| Cl | FeCl$_3$ | 90 | ≥90:≤10 |
| Br | – | 70 | ≥92:≤8 |
| Br | FeCl$_3$ | 61–95 | ~66:~34 |

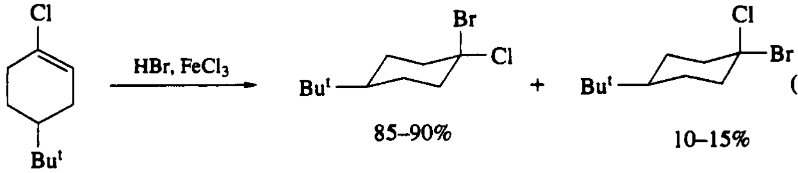
Cl
Bu$^t$
HBr, FeCl$_3$
Br
Cl
Bu$^t$
85–90%
+
Cl
Br
Bu$^t$
10–15%

(ref. 128) (81)

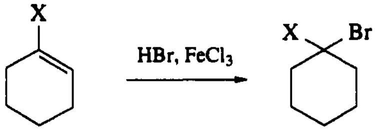
X
HBr, FeCl$_3$
X
Br

(ref. 129) (82)

| *X* | *Yield* (%) |
|---|---|
| Cl | 69–90 |
| Br | 75–80 |

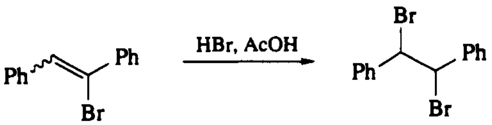
Ph
Ph
Br
HBr, AcOH
Br
Ph
Ph
Br

(ref. 130) (83)

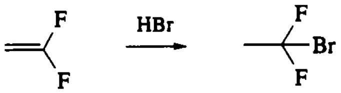

(ref. 131) (84)

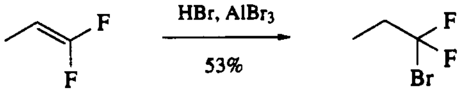
F
F
HBr, AlBr$_3$
53%
F
F
Br

(ref. 63) (85)

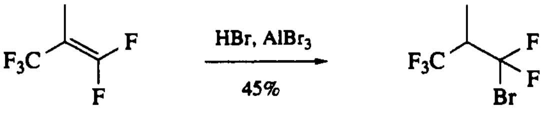
F$_3$C
F
F
HBr, AlBr$_3$
45%
F$_3$C
F
F
Br

(ref. 63) (86)

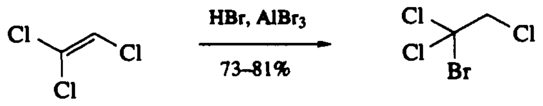

(ref. 61) (87)

A number of functional groups including sulfones, ethers and even alcohols (occasionally) can be accommodated during hydrobromination. Functional groups in close proximity to the C—C double bond can have an important directing effect (equations 88 and 89).[133,134]

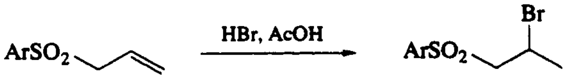

(ref. 133) (88)

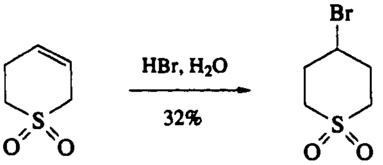

(ref. 134) (89)

α,β-Unsaturated aldehydes,[101] ketones[101] and esters[109,135,136] afford β-bromo carbonyl products, often in excellent yield (equation 90). Even tribenzoylethylene reacts in fair yield (equation 91).[137]

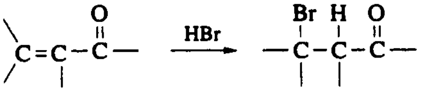

$$\mathrm{C{=}C{-}\overset{O}{\overset{\|}{C}}{-}} \xrightarrow{HBr} \mathrm{{-}\overset{Br}{C}{-}\overset{H}{C}{-}\overset{O}{\overset{\|}{C}}{-}}$$

(90)

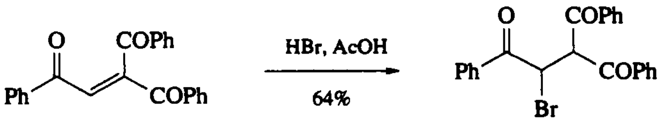

(91)

A wide variety of unsaturated carboxylic acids have been allowed to react with HBr.[101] Carboxylic acids with remote C—C double bonds react as simple alkenes.[138,139] 4-Pentenoic acid reacts with HBr neat or in a polar solvent to give exclusively 4-bromopentanoic acid, but the reaction in nonpolar solvents affords only 5-bromopentanoic acid.[136] On the other hand, 5-methyl-4-hexenoic acid produces only the 5-bromo acid. A similar pattern is followed by 3-butenoic, 3-pentenoic and 4-methyl-3-pentenoic acids. No matter what the substitution pattern, 2-alkenoic acids always favor the 3-bromo acid.[113,136,140,141] Addition of HBr to cyclic α,β-unsaturated acids initially forms predominantly the product of *trans* diaxial addition which upon longer reaction time or higher temperature isomerizes to the *trans* product (equation 92).[57,141,142] Similar observations have been made on bicyclic α,β-unsaturated acids.[141]

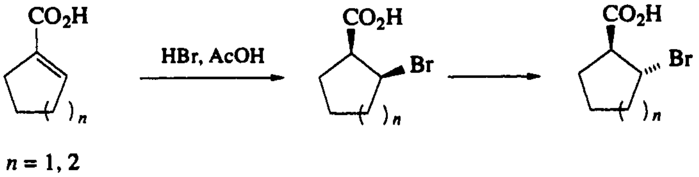

(92)

The stereochemistry of addition to unsaturated dicarboxylic acids has also been examined (equations 93 and 94).[130,143]

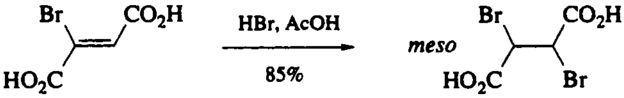

(ref. 130) (93)

Addition of HBr to unsaturated nitriles can also proceed in good yield (equation 95).[59]

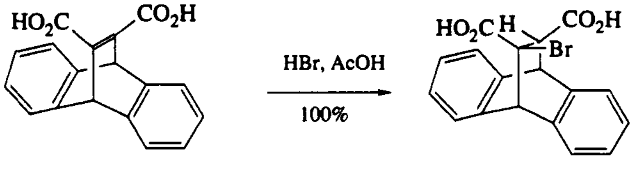
HO2C
CO2H
HBr, AcOH
100%
HO2C
H
CO2H
Br

(ref.143) (94)

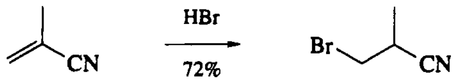
CN
HBr
72%
Br
CN

(95)

Nonconjugated dienes react as expected to give mono- or di-addition products (equations 96–98).[70,144,145] Norbornadiene also produces nortricyclyl product (equation 99).[71]

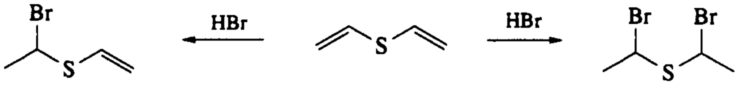
Br
S
HBr
S
HBr
Br
Br
S

(ref. 70) (96)

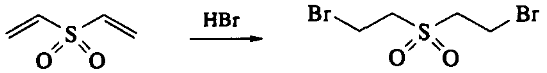
S
O
O
HBr
Br
S
Br
O
O

(ref. 144) (97)

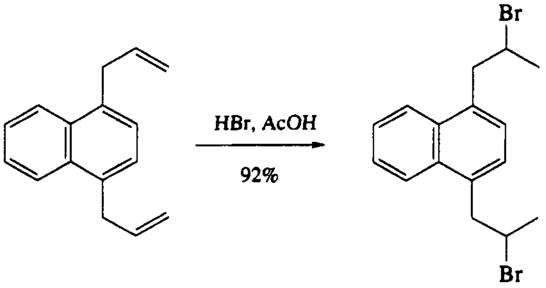
HBr, AcOH
92%
Br
Br

(ref. 145) (98)

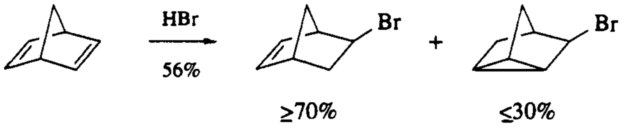
HBr
56%
Br
+
Br
≥70%
≤30%

(99)

Conjugated dienes generally produce mixtures of 1,2- and 1,4-addition compounds.[101] 1,3-Butadiene reacts rapidly with HBr even at low temperatures and gives mixtures in which either 1-bromo-2-butene or 3-bromo-1-butene predominate, depending on the reaction conditions (equation 100.)[72,146,147] Further HBr addition gives mixtures of 1,3-dibromobutane and 2,3-dibromobutane.[147]

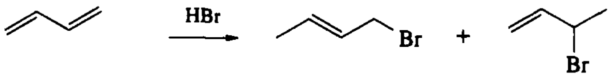

(100)

Isoprene initially forms 3-bromo-3-methyl-1-butene, which rapidly rearranges to 1-bromo-3-methyl-2-butene (equation 101).[148,149]

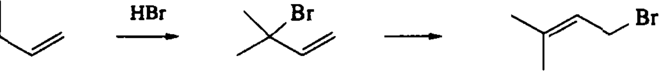

(101)

2,3-Dimethyl-1,3-butadiene cleanly affords 1-bromo-2,3-dimethyl-2-butene,[150] but further HBr addition produces a mixture of dibromides (equation 102).[151]

The addition of HBr to 2-methyl-1,3-pentadiene, 1-bromo-1,3-butadiene, 1-phenyl-1,3-butadiene and 2,4-hexadiene produces 2,4-dibromo-2-methylpentane, 1,3-dibromo-1-butene, 3-bromo-1-phenyl-1-

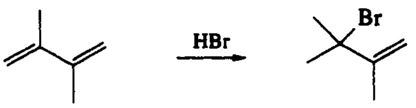

(102)

butene and 2-bromo-3-hexene plus 4-bromo-2-hexene, respectively.[101] The addition of DBr to 1,3-cyclohexadiene provides allylic bromide in 85% yield; both 1,4-*syn* and 1,2-*anti* addition are suggested to occur, followed by stereospecific rearrangement.[152]

Numerous studies of the addition of HBr to allenes have been reported.[75,76] The low temperature addition of HBr to allene produces a mixture of products (equation 103).[77] However, gas phase photocatalyzed addition generates only the vinylic bromide, in near quantitative yield.[153]

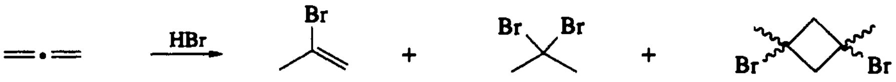

(103)

Terminal monosubstituted allenes afford primarily (*E*)- and (*Z*)-2-bromo-2-alkenes using either approach (equation 104).[153–155] However, terminal disubstituted allenes give quite different products (equation 105).[82,153,155]

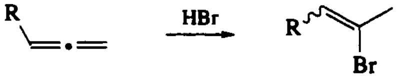

(104)

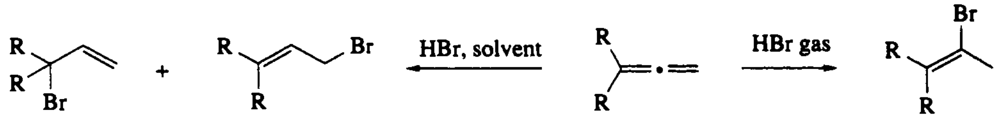

(105)

Symmetrical 1,3-disubstituted allenes give predominantly vinylic bromide or allylic bromide depending upon reaction conditions (equation 106).[82,153,154] Analogous unsymmetrical allenes give mixtures of all four possible bromides.[81,82]

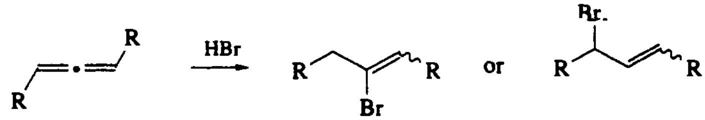

(106)

Totally different products are observed from aqueous[82] and gas phase[153] HBr addition to tetrasubstituted allenes (equation 107).

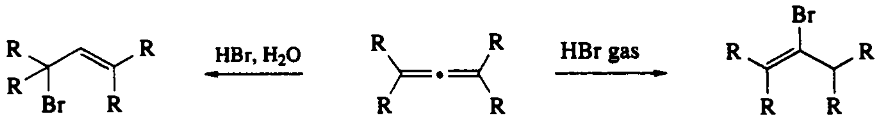

(107)

The products of addition of HBr to cyclic allenes is highly dependent on the size of the ring and the solvent used (equation 108).[154,156] 1,2-Cyclononadiene affords rather selectively either product.

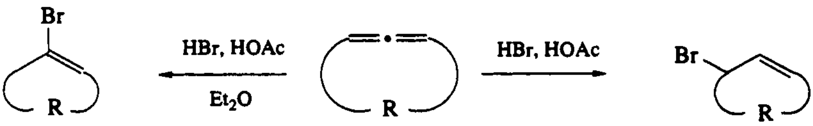

(108)

1,2-Cyclodecadiene and 1,2,6-cyclononatriene have been converted to the corresponding allylic bromide and vinylic bromide respectively, while 1,2-cyclotridecadiene reacts with HBr in HOAc to give a mixture of bromides.

The hydrobromination of functionally substituted allenes has received little attention. Vinylic allenes generate mixtures of bromides,[76] while tetrafluoroallene affords the allylic bromide,[83] and allenic acids produce 3-bromo-3-alkenoic acids (equation 109).[157,158]

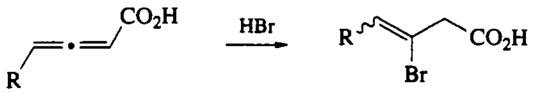

(109)

There are numerous examples of the addition of HBr to alkynes.[101] Addition to acetylene is difficult, tends to produce mixtures of bromide products, and requires a catalyst.[94,101,122] Simple terminal alkynes react with HBr in the absence of peroxides to produce mixtures of 2-bromo-1-alkenes and geminal dibromides (equation 110).[85,159] The latter can be produced in high yield when excess HBr is used.[160]

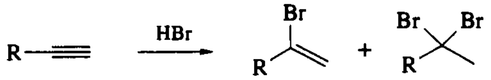

(110)

Mercury(II) bromide[85] and iron(III) bromide[159] have been employed as catalysts in these reactions. The former catalyst affords stereospecific *trans* adducts.[85]

In the presence of peroxides, 1-bromo-1-alkenes or 1,2-dibromoalkanes are produced depending on the amount of HBr employed (equation 111).[85,159,160]

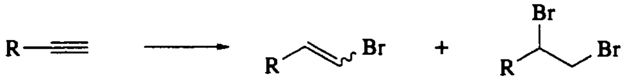

(111)

The hydrobromination of arylalkynes in acetic acid produces good yields of vinylic bromides in which *syn* addition is favored over *anti* addition by ~3 to 1 (equation 112).[90,161,162]

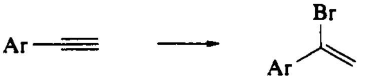

(112)

3,3,3-Trifluoro-1-propyne readily adds HBr in an anti-Markovnikov fashion (equation 113).[25,163]

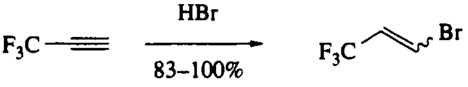

(113)

The stereochemistry of HBr addition to 1-alkyn-3-ones can be controlled by proper choice of reagents (equation 114).[164]

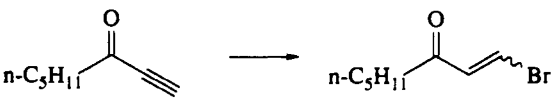

(114)

| | *% cis* | *% trans* |
|---|---|---|
| LiBr, $CF_3CO_2H$ (30 min) | 1 | 89 |
| LiBr, $CH_3CO_2H$ (overnight) | 68 | 12 |

Alkynoic acids in which the C—C triple bond is far removed from the acid moiety behave like simple alkynes.[165,166] Propiolic acid, on the other hand, adds HBr to form almost exclusively (*Z*)-3-bromopropenoic acid (equation 115).[98]

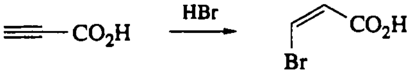

(*Z*)

(115)

Surprisingly, no work has apparently been carried out on the addition of HBr to simple dialkylalkynes. Hexafluoro-2-butyne readily adds HBr in the presence of $AlBr_3$ (equation 116).[25]

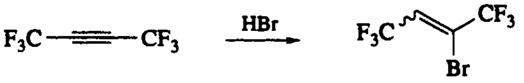

(116)

Diarylalkynes add HBr in an *anti* fashion (equation 117).[130]

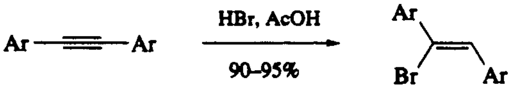

(117)

1-Halo-1-alkynes react with HBr–HOAc[167] or HBr–$Cu_2Br_2$[168,169] to afford primarily *anti* adducts (equation 118).

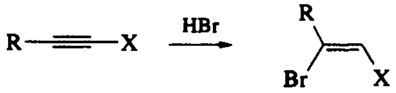

X = Cl, Br

(118)

Even aqueous $Et_4NBr$ will hydrobrominate PhC≡CX, where X = Cl or Br, although the yield is low (equation 119).[100]

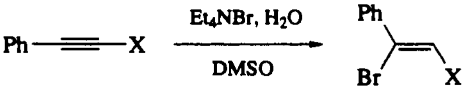

X = Cl, Br

(119)

*Anti* addition products have also been reported for a wide variety of functionally substituted alkynes (equations 120 and 121).[95,97,170,171]

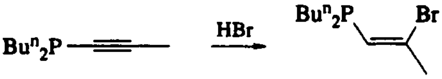

(ref. 95) (120)

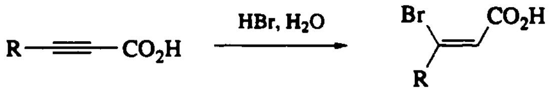

R = H, Me, Ar, $CO_2H$

(refs. 97, 170, 171) (121)

However, HBr addition to tetrolic acid and phenylpropiolic acid in benzene is reported to afford the opposite regioisomers (equation 122),[170] and the stereochemistry of HBr addition to $PhC{\equiv}CCO_2Et$[171] and NCC≡CCN[172] is unclear.

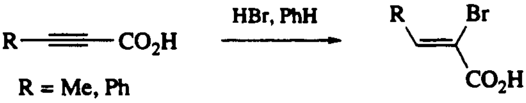

R = Me, Ph

(122)

Recently, two very useful procedures for the conversion of terminal alkynes to 2-bromo-1-alkenes have been reported (equations 123 and 124).[173,174] Both procedures accommodate alcohol groups as well.

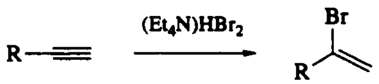

(ref. 173) (123)

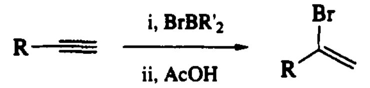

(ref. 174) (124)

The addition of HBr to alkynes *via* hydrometallation–halogenation is another important approach to vinylic halides which will be discussed elsewhere in this series (see Volume 8, Chapters 3.9–3.12).

### 1.7.2.5 H—I Addition

Although HI addition to alkenes and alkynes is faster than that of the other hydrohalides and free radical anti-Markovnikov additions are not a problem, this reaction has received less attention than the others.[175] The hydroiodination of alkenes is most commonly run using concentrated HI in water or acetic acid at or below room temperature. While the early literature suggests that simple terminal alkenes afford small amounts of anti-Markovnikov products, only Markovnikov products have been reported in the more recent literature (equations 125–129).[67,176–179]

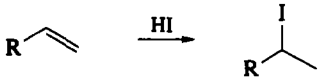

(125)

| *R* | *Yield (%)* | *Ref.* |
|---|---|---|
| Me | 79, >90 | 176, 177 |
| Et | 73 | 176 |
| Bu$^n$ | 94 | 178 |
| Me$_3$CCH$_2$ | 92 | 176 |

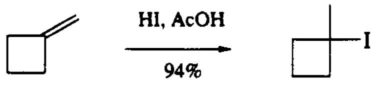

(ref. 67) (126)

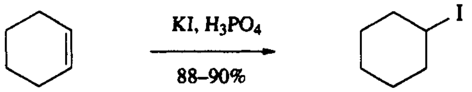

(ref. 178) (127)

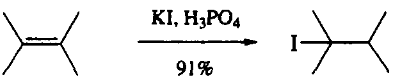

(ref. 178) (128)

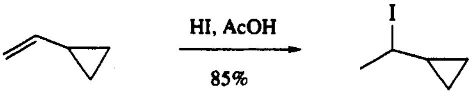

(ref. 179) (129)

While cyclopropylethylene is reported not to rearrange,[179] this appears questionable since other alkenes prone to rearrangements have been reported to do so (equation 130).[31,38,39,180]

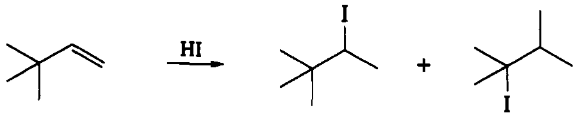

(130)

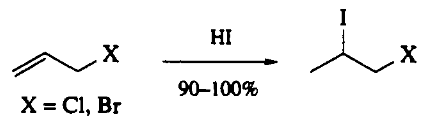

X = Cl, Br

(131)

Allyl chloride and bromide afford high yields of HI addition products (equation 131).[176,177]

Even vinylic halides add HI readily, though 1-bromo-1-propene gives a mixture of products (equations 132–135).[125,131,177] However, perfluoroalkenes have proven unreactive towards HI addition.

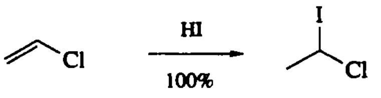

(ref. 125) (132)

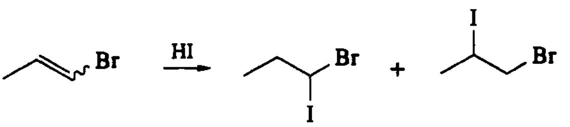

(ref. 177) (133)

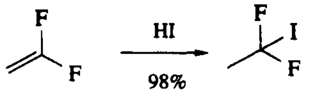

(ref. 131) (134)

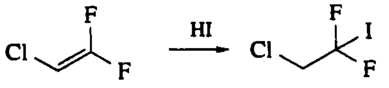

(ref. 131) (135)

Certain functional groups can be accommodated during HI addition. While alcohols are converted to alkyl iodides under the usual reaction conditions,[181] sulfones present no problems.[133,134] Remote carboxylic acid functionality has no effect on the addition of HI,[182] and α,β-unsaturated carboxylic acids produce good yields of exclusively the 3-iodocarboxylic acids, no matter what the substitution pattern about the C—C double bond (equation 136).[114,140,183–186]

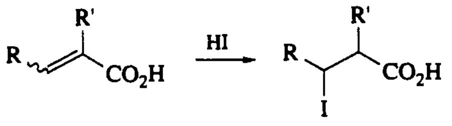

(136)

The addition of ammonium and phosphonium salts as catalysts for HI addition to alkenes has been recommended as a useful alternative procedure.[68]

While the reaction of alkenes with $I_2$ at temperatures of 125–130 °C reportedly produces regioisomeric mixtures of iodoalkanes,[187] in the presence of dehydrated alumina in refluxing petroleum ether, this reaction gives low to reasonable yields of Markovnikov adducts.[188,189] This approach does not appear very general, however, and rearrangement has been observed.

There are very few examples of the addition of HI to dienes (equations 137–139).[72,77,144]

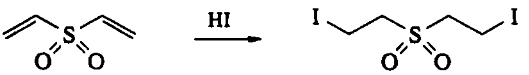

(ref. 144) (137)

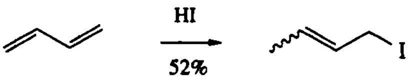

(ref. 72) (138)

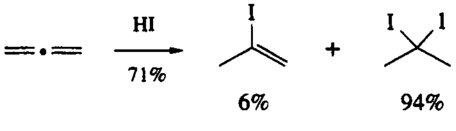

(ref. 77) (139)

Relatively little work has also been reported on the addition of HI to alkynes. 1-Propyne affords a mixture of iodides (equation 140).[77,85]

The reaction of 3,3,3-trifluoro-1-propyne requires a temperature of 100 °C or the addition of $AlI_3$ to produce the terminal vinylic iodide (equation 141).[25]

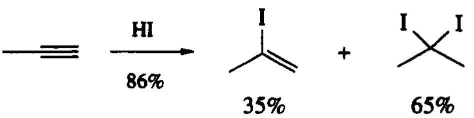
HI
86%
I
35%
I I
65%

(ref. 77) (140)

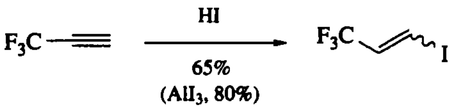
$F_3C$
HI
65%
($AlI_3$, 80%)
$F_3C$
I

(141)

A variety of haloenynes react with HI and $Cu_2I_2$ to afford products of *anti* addition (equation 142).[168,169]

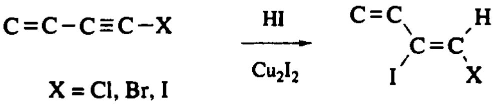
C=C−C≡C−X
X = Cl, Br, I
HI
$Cu_2I_2$
C=C
H
C=C
I
X

(142)

A variety of functionally substituted alkynes also undergo facile HI addition (equations 143–145).[95,164,190]

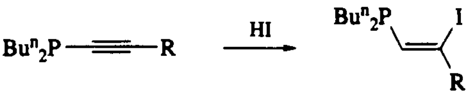
$Bu^n{}_2P$
R
HI
$Bu^n{}_2P$
I
R

(ref. 95) (143)

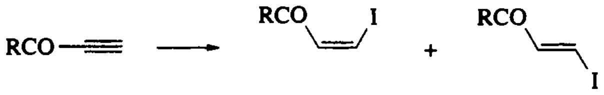
RCO
RCO
I
RCO
I

(ref. 164) (144)

| | | |
|---|---|---|
| NaI, $CF_3CO_2H$ | 0% | 95% |
| NaI, $CH_3CO_2H$ | 70% | 17% |

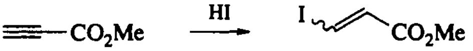
$CO_2Me$
HI
I
$CO_2Me$

(ref. 190) (145)

While 4-pentynoic acid reportedly yields the geminal diiodide (equation 146),[165] 2-alkynoic acids generally produce almost exclusively the 3-iodo-2-alkenoic acids of *anti* addition (equation 147).[97,98,191]

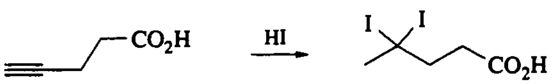
$CO_2H$
HI
I I
$CO_2H$

(146)

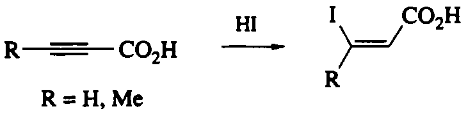
R
$CO_2H$
R = H, Me
HI
I
$CO_2H$
R

(147)

3-Bromo- and 3-iodo-propiolic acids are also reported to give the corresponding 3,3-dihalo-2-propenoic acids of unknown stereochemistry.[191]

Alkynes bearing two strong electron-withdrawing groups are still capable of undergoing HI addition at or below room temperature (equation 148).[172,192,193]

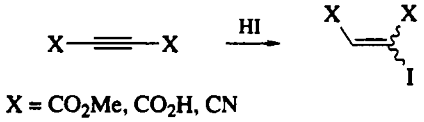
X
X
X = $CO_2Me$, $CO_2H$, CN
HI
X
X
I

(148)

Terminal alkynes also undergo HI addition in good yields upon reaction with $I_2$ and dehydrated alumina (equation 149),[189] or by iodoboron addition followed by protonolysis (equation 150).[174] These methods appear quite useful.

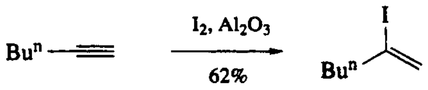

(149)

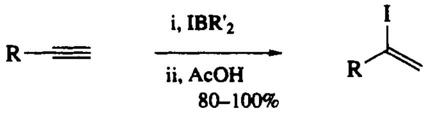

(150)

## 1.7.3 H—N ADDITION

### 1.7.3.1 Introduction

There are several methods available for the electrophilic addition of hydrogen and nitrogen to alkenes, dienes and alkynes. While the direct electrophilic addition of amines to these substrates is not feasible, aminomercuration–demercuration affords a very useful indirect approach to such amines. The addition of amides to C—C multiple bonds can be effected directly through the Ritter reaction or by the less direct, but equally useful, amidomercuration–demercuration process using either nitriles or amides. Similarly, H—$N_3$ addition to alkenes can be carried out directly or *via* mercuration to produce organic azides.

### 1.7.3.2 Aminomercuration–Demercuration

There do not appear to be any direct approaches for electrophilic addition of amines across C—C double or triple bonds. However, aminomercuration–demercuration affords a very useful process to effect this transformation (equation 151). This reaction has been thoroughly reviewed recently.[194]

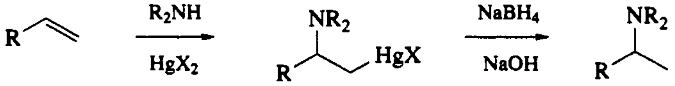

(151)

Although the relative reactivity of mercuric salts is $Hg(ClO_4)_2 \approx Hg(NO_3)_2 \gg Hg(OAc)_2 > HgCl_2$,[195] the latter two salts have been used in almost all examples of this reaction reported to date. The reaction can be reversible or irreversible depending on the mercury salt employed.[196]

Most work on aminomercuration has employed secondary aliphatic amines, or primary or secondary anilines. Primary amines have been successfully employed using mercuric perchlorate or mercuric nitrate.[197] No reactions utilizing ammonia have been reported. While excess amine or various ether solvents can be used, it is sometimes desireable to add water.[198,199]

A wide variety of alkenes have been shown to undergo aminomercuration–demercuration, including alkenes bearing alcohol, ester, acid, amide, imide, urea, urethane, ether, sulfide and aryl groups.[194]

Although Markovnikov addition is generally observed, little work on the regio- or stereo-selectivity of this reaction has been reported. Both *cis*- and *trans*-2-pentene afford mixtures of the 2- and 3-substituted amines.[199] $\alpha,\beta$-Unsaturated esters yield $\beta$-amino esters.[200] The aminomercuration of *cis*- and *trans*-2-butenes gives $\geq 97\%$ of the *anti* adducts.[201]

While reductive demercuration of the intermediate $\beta$-aminomercurials can usually be carried out *in situ* using alkaline sodium borohydride,[202,203] regeneration of the starting alkene or nitrogen migration can be a problem. Alkene formation can often be circumvented by adding 10% NaOH prior to reduction[197] and using a phase transfer catalyst.[204] This reducing system also cuts down on the problem of nitrogen migration.

The intramolecular solvomercuration of unsaturated amines provides a very useful route to a variety of nitrogen heterocycles.[194,205] This reaction is particularly useful for the preparation of pyrrolidines and piperidines and their heteroatom-substituted analogs (equation 152).

Bicyclic[206] and spirocyclic[207] amines are also readily prepared by intramolecular aminomercuration–demercuration (equations 153 and 154).

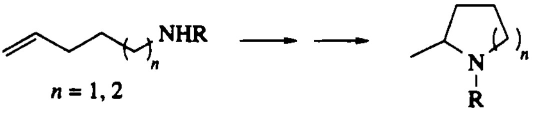

(152)

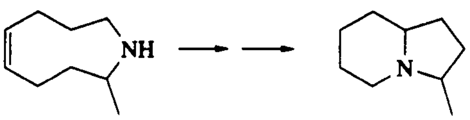

(153)

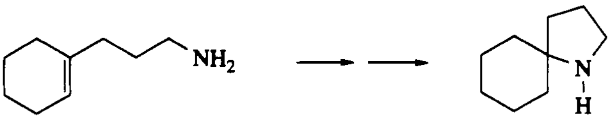

(154)

Analogous cyclic amines can also be prepared by aminomercuration–demercuration of unsaturated organic halides (equation 155).[208]

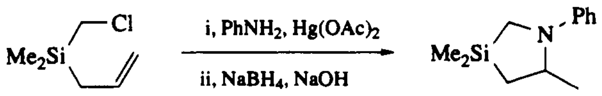
Cl
Me2Si
i, PhNH2, Hg(OAc)2
ii, NaBH4, NaOH
Me2Si
N
Ph

(155)

High stereoselectivity is frequently observed in these types of cyclization.

These cyclic aminomercurials are particularly prone to alkene formation and rearrangement during reduction. However, alkaline sodium borohydride under phase transfer conditions usually works well.[209,210]

Nonconjugated dienes also undergo aminomercuration–demercuration to generate pyrrolidines, piperidines and their heterocyclic analogs (equations 156–158).[211-218]

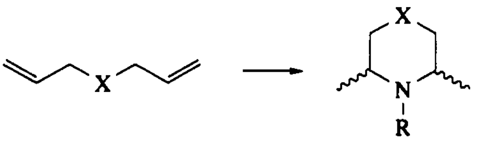

$X = CH_2, O, S, NR, SiMe_2$

(refs. 211–214) (156)

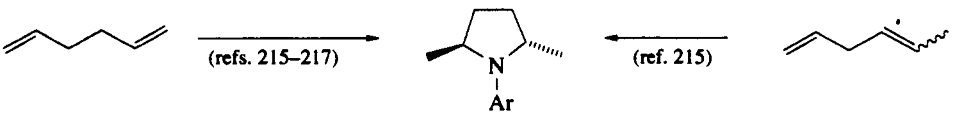
(refs. 215–217)
N
Ar
(ref. 215)

(157)

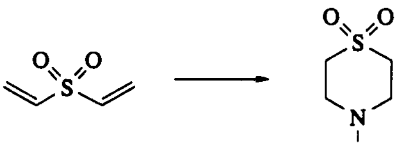

(ref. 218) (158)

Conjugated dienes afford either allylic amines or saturated diamines (equation 159).[204,219] When mercury(II) oxide plus tetrafluoroboric acid is employed, dihydropyrroles are formed instead (equation 160).[220]

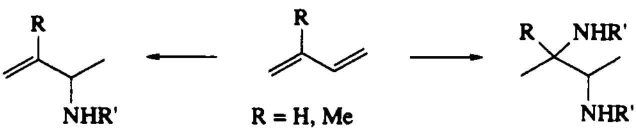
R
NHR'
R
R = H, Me
R
NHR'
NHR'

(159)

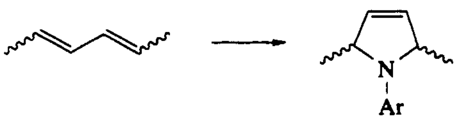

(160)

Allylic amines are usually obtained from the aminomercuration of allenes (equation 161),[204,221] while allenes with amino groups in a side chain produce the corresponding heterocycles (equation 162).[222]

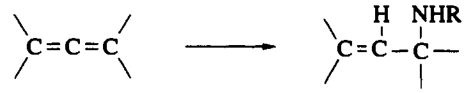

(161)

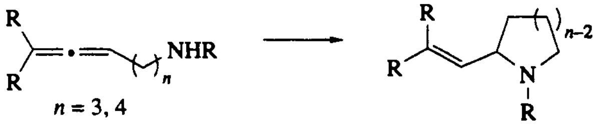

(162)

The aminomercuration–demercuration of alkynes affords a variety of nitrogen-containing products. Most commonly imines are formed,[194] though there are a few examples of enamines being produced (equation 163).[223–228]

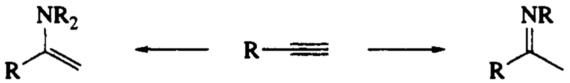

(163)

### 1.7.3.3 Amide Addition

#### *1.7.3.3.1 Ritter reaction*

The preparation of amides by the addition of hydrogen cyanide or alkyl nitriles to alkenes in the presence of acids, known as the Ritter reaction, has been reviewed.[229–232] The reaction may be considered simplistically as nucleophilic attack of a nitrile on a carbocation formed by the protonation of an alkene. Subsequent hydrolysis of the nitrilium intermediate gives the amide product (equation 164). The overall result is addition of a molecule of H—NHCOR to a C—C double bond.

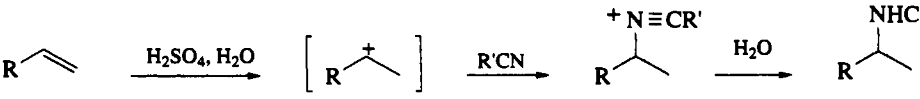

(164)

Although terminal alkenes provide the best yields, the Ritter reaction is also successful when using trisubstituted alkenes and haloalkenes. Markovnikov addition is generally observed. Rearranged products arise occasionally, especially with alkenes that are prone to cationic rearrangements (equation 165).[233]

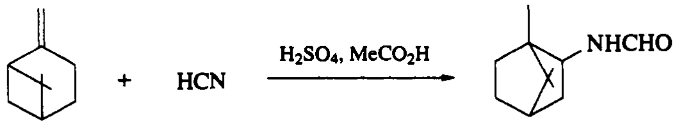

(165)

The Ritter reaction of internal alkenes may yield mixtures of regioisomers, and on occasion, small amounts of rearranged products (equation 166).[234]

The acid used in the Ritter reaction is usually sulfuric acid, although other acids such as perchloric, phosphoric, polyphosphoric, formic and sulfonic acids have been used. Lewis acids such as aluminum trichloride and boron trifluoride are also occasionally used. However, high yields are generally best obtained with sulfuric acid. The choice of solvents varies among sulfuric acid, glacial acetic acid, acetic an-

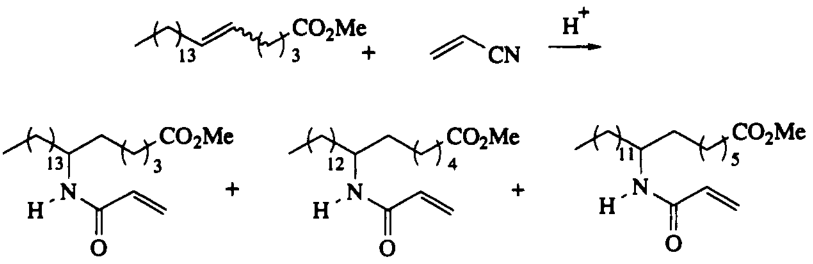

(166)

hydride, di-*n*-butyl ether, some chlorinated solvents, hexanes and nitrobenzene. Reaction times and temperatures are variable, but generally the reaction conditions are very mild.

The synthetic utility of the Ritter reaction is evident from surveying the literature. An early example of the Ritter reaction is found in the synthesis of *in vivo* metabolites of the drug mephentermine (equation 167).[235]

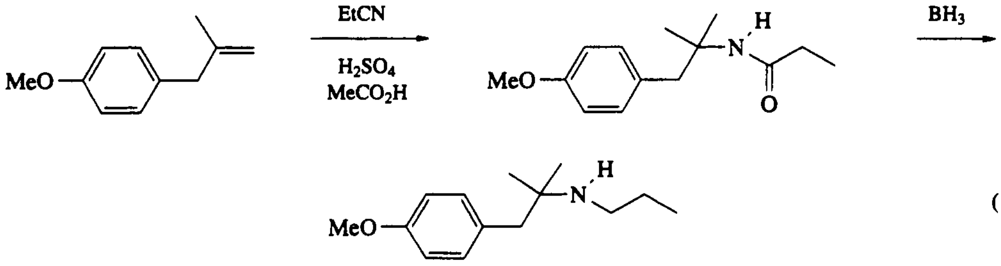

(167)

The synthesis of heterocycles is another common application of the Ritter reaction. Equations (168)–(170) illustrate the preparation of a lactam,[236] oxazoline[237] and dihydroisoquinoline,[235] respectively.

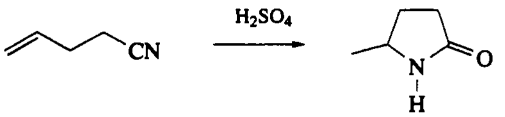

(168)

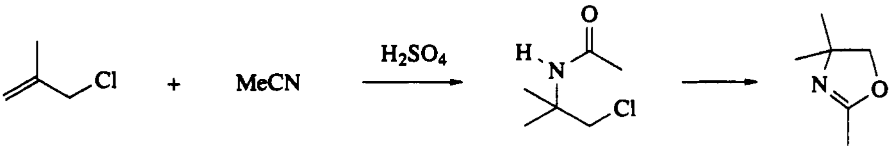

(169)

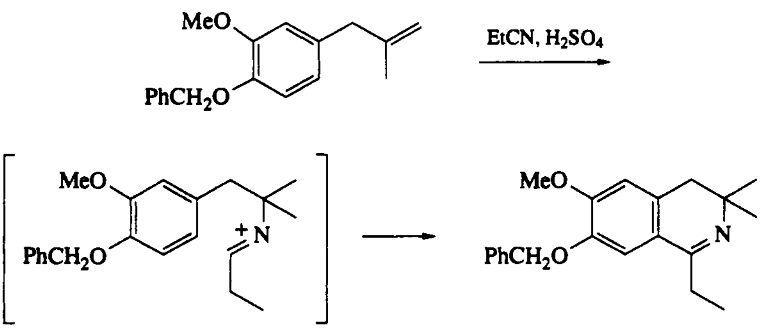

(170)

Recently, nonconjugated dienes have been successfully used in the Ritter reaction for the preparation of bridgehead amides[238] and azatricycloundecane amides (equations 171 and 172).[239]

Extension of the Ritter reaction to conjugated dienes, however, has been less successful. The reaction is often met with competing Diels–Alder reactions or extensive polymerization. The polymerization that occurs during the reaction of 1,3-dienes and nitriles has been used in the synthesis of linear

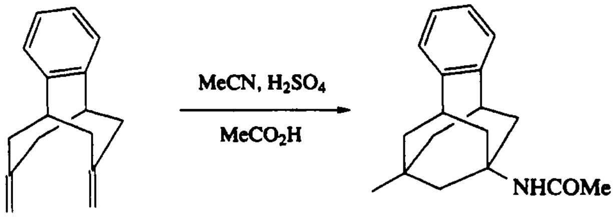

(171)

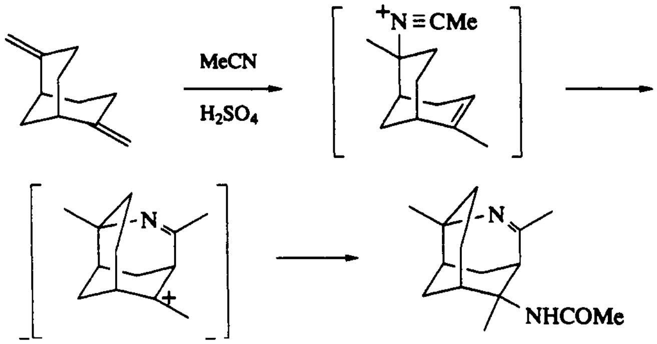

(172)

polyamides.[240] However, satisfactory Ritter reactions with conjugated dienes can provide pyrroline derivatives (equation 173).[241]

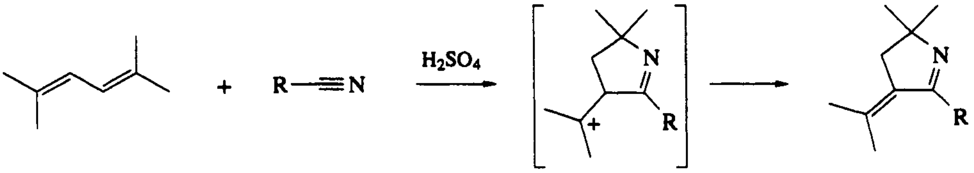

(173)

### 1.7.3.3.2 Amidomercuration–demercuration

The reaction of alkenes or dienes, mercuric salts, and either nitriles or amides generates β-amidomercurials, which can be easily reduced to the corresponding amides (equation 174). This reaction effects H—NHCOR addition to alkenes and dienes, and has been thoroughly reviewed recently.[242]

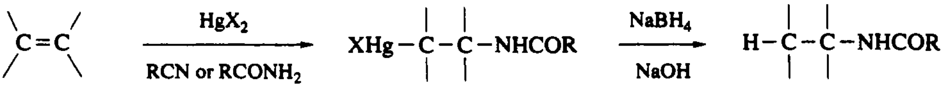

$$\mathrm{>C{=}C<} \xrightarrow[\mathrm{RCN\ or\ RCONH_2}]{\mathrm{HgX_2}} \mathrm{XHg{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}NHCOR} \xrightarrow[\mathrm{NaOH}]{\mathrm{NaBH_4}} \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}NHCOR} \qquad (174)$$

Amidomercuration using nitriles has received the most attention. This reaction commonly employs mercury(II) nitrate with the nitrile as solvent. Acetonitrile is the most widely used nitrile, but RSCN and $R_2NCN$ can also be employed.[243]

A variety of alkenes undergo successful amidomercuration, but alkenes of the type $R_2C{=}CH_2$ and $R_2C{=}CHR$ fail to react in the anticipated fashion.[243–245] While rearrangements have been observed with α- and β-pinene,[245] 3,3-dimethyl-1-butene reacts normally.[244]

Most useful of the demercuration procedures reported is the use of alkaline sodium borohydride[244] or sodium–mercury amalgam.[243,246] Reduction with $LiAlH_4$ affords the corresponding amines.[243]

There appears to be only one example of intramolecular amidomercuration using an unsaturated nitrile (equation 175),[247] and no examples of the amidomercuration of dienes or alkynes using nitriles.

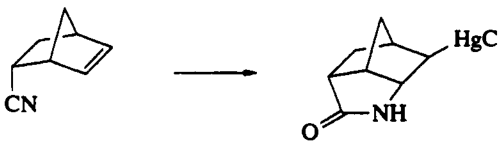

(175)

Amides can also be utilized for amidomercuration.[242,248,249] The reaction is usually run using equivalent amounts of the alkene and $Hg(NO_3)_2$, plus 10 equiv. of amide in refluxing dichloromethane (equation 176).

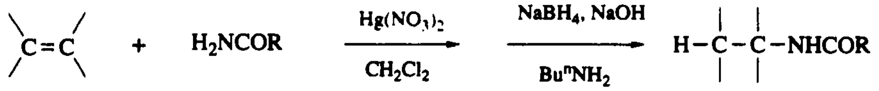

(176)

The reaction may be subject to limitations in the alkene structure similar to those of the nitrile process. Besides simple amides, one can also utilize urea and urethanes in this reaction. Demercuration is best effected by using alkaline sodium borohydride in the presence of a primary amine such as $Bu^nNH_2$.

Intramolecular amidomercuration of unsaturated amides and subsequent reduction is a very useful approach to cyclic amides (equations 177 and 178).[242] Mercuric acetate has been employed in all such reactions to date. The reaction is often highly regio- and stereo-selective.[250–253]

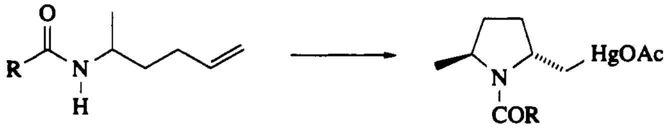

(refs. 250–252) (177)

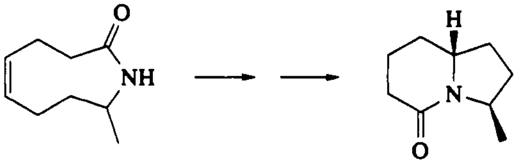

(ref. 253) (178)

Sulfonamides can also be employed in amidomercuration when mercury(II) nitrate is utilized as the mercury salt (equation 179).[254]

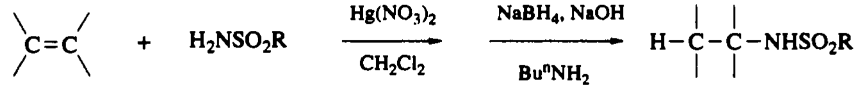

(179)

While no intramolecular examples of this reaction exist, dienes undergo reaction to generate *cis*-pyrrolidines (equation 180).

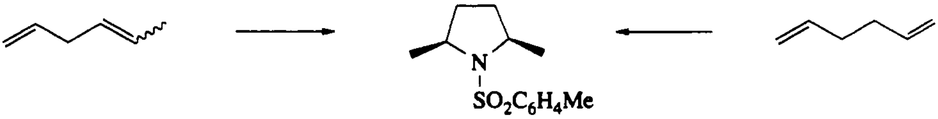

(180)

## 1.7.3.4 Azide Addition

### *1.7.3.4.1 Direct H—N₃ addition*

The chemistry of alkyl and alkenyl azides has been well summarized in several recent reviews.[255–257] The azides can be prepared *via* numerous methods, of which the addition of hydrazoic acid to C—C multiple bonds is one. With the exception of cyclopropenes,[258] most alkenes are unreactive towards hydrazoic acid itself. However, the addition can be catalyzed by acids (phosphoric acid,[259] sulfuric acid[260] or trifluoroacetic acid[261]) or Lewis acids (aluminum trichloride, boron trifluoride or titanium tetrachloride).[262]

The acid-catalyzed reactions proceed through a carbocation intermediate formed by protonation of the double bond, followed by nucleophilic attack of $HN_3$ and subsequent loss of a proton (equation 181).

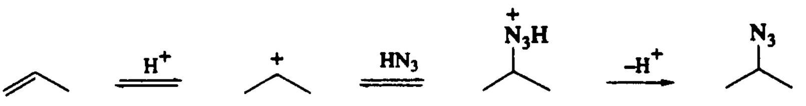

(181)

This reaction works well for simple alkenes and cycloalkenes. Attempts to add hydrazoic acid to diarylalkenes in the presence of sulfuric acid, however, leads to considerable decomposition due to Schmidt rearrangement.[260]

The addition of $HN_3$ to alkenes in the presence of Lewis acids also involves carbocationic intermediates. This is nicely illustrated by the boron trifluoride-catalyzed addition of $HN_3$ to α- or β-pinene in which carbocation rearrangements are observed (equation 182).[263]

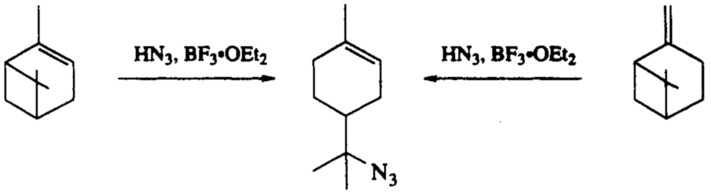

(182)

The combination of hydrazoic acid and boron trifluoride has also been used to convert 5β-hydroxypregnane into the corresponding azido compound (equation 183).[264] This reaction is presumed to involve elimination of water to form a $\Delta^5$-pregnene which then adds $HN_3$.

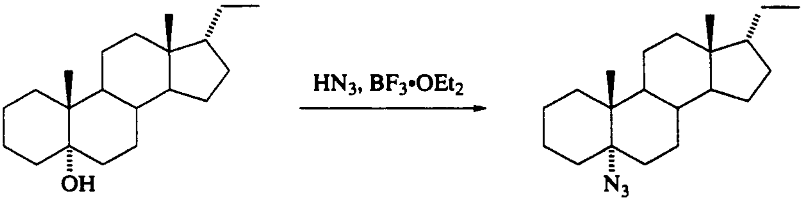

(183)

The addition of hydrazoic acid to numerous acyclic and cyclic alkenes also proceeds well in the presence of titanium tetrachloride or aluminum trichloride.[262] Dichloromethane or chloroform are ideal solvents for these catalysts. The addition is regiospecific and tolerates the presence of primary and secondary alcohols, as well as esters (equation 184).

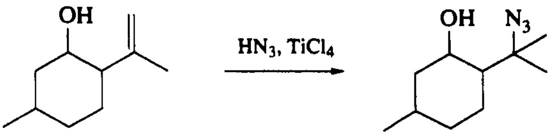

(184)

These Lewis acids may also be used to catalyze additions of hydrazoic acid to enol ethers and silyl enol ethers (equation 185). In an earlier report, the addition of $HN_3$ to enol ethers was accomplished with trifluoroacetic acid.[261] Curiously, the same additions are observed in comparable yields even in the absence of a catalyst.[262]

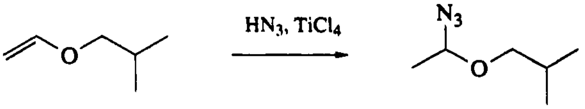

(185)

The reaction of hydrazoic acid with alkynes generally provides triazoles instead of azides (equation 186).[265]

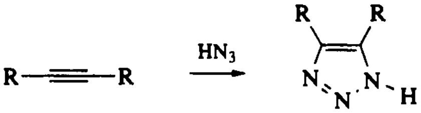

(186)

Alkoxyalkynes are an exception, but unfortunately they undergo further additions to yield geminal diazides as the only product (equation 187).[266]

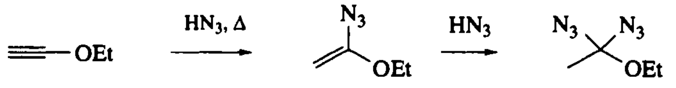

(187)

### *1.7.3.4.2 Azidomercuration–demercuration*

The formal addition of H—N$_3$ across C—C double bonds can also be brought about *via* azidomercuration–demercuration, a process recently reviewed.[267] In the presence of NaN$_3$, Hg(OAc)$_2$, Hg(O$_2$CCF$_3$)$_2$ or Hg(NO$_3$)$_2$, in aqueous THF, methanol or DMF, alkenes undergo azidomercuration (equation 188).[268–274]

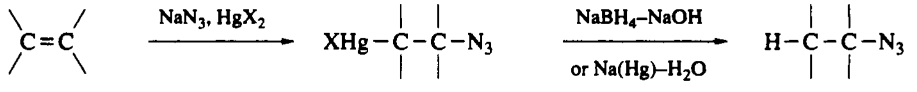

$$\text{>C=C<} \xrightarrow{\text{NaN}_3,\ \text{HgX}_2} \text{XHg}-\overset{|}{\underset{|}{\text{C}}}-\overset{|}{\underset{|}{\text{C}}}-\text{N}_3 \xrightarrow[\text{or Na(Hg)–H}_2\text{O}]{\text{NaBH}_4\text{–NaOH}} \text{H}-\overset{|}{\underset{|}{\text{C}}}-\overset{|}{\underset{|}{\text{C}}}-\text{N}_3 \qquad (188)$$

While highly substituted alkenes react poorly, strained alkenes like cyclopropene[268] and norbornene[270] undergo a facile reaction. 3,3-Dimethyl-1-butene does not rearrange during addition.[270] The reaction conditions are mild enough that unsaturated carbohydrates can be utilized.[271–274]

Alkaline sodium borohydride is the preferred demercuration reagent, but sodium–mercury amalgam in D$_2$O is best for stereospecific reduction with retention.[268]

Only two dienes, and no alkynes, have been subjected to azidomercuration (equations 189 and 190).[275–277]

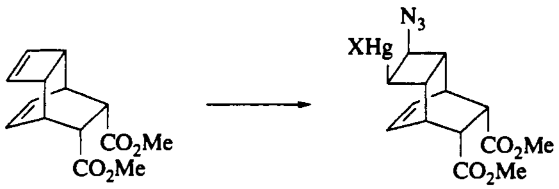

(refs. 275, 276) (189)

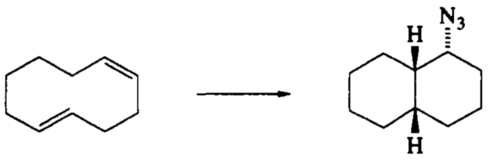

(ref. 277) (190)

## 1.7.4 H—O ADDITION

### 1.7.4.1 H—OH Addition

### *1.7.4.1.1 Direct hydration*

The addition of H—OH to alkenes is a well studied reaction for the synthesis of alcohols with important industrial applications.[278,279] It is seldom used as a laboratory procedure. The hydration is commonly achieved under acid or metal catalysis, but may also be accomplished photochemically under acidic or neutral conditions. The acid-catalyzed addition of water to the C—C double bond occurs in a Markovnikov fashion, and is typically carried out using sulfuric acid, phosphoric acid or perchloric acid. Yields are highly variable and depend on exact reaction conditions. The large number of mechanistic studies reported concerning this reaction has convincingly provided evidence for an $A_{SE}2$ mechanism involving a cationic species (Scheme 1). As anticipated, rearrangements of the cationic species are observed.

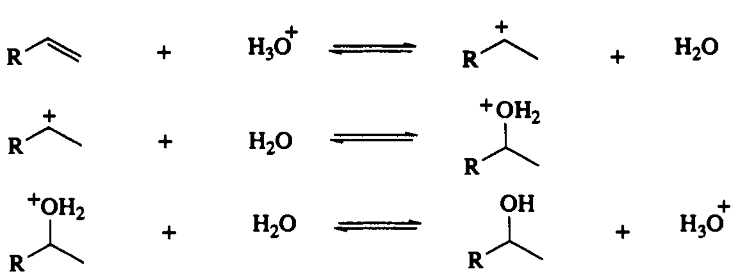

Scheme 1

The rate of hydration is dependent on the substitution and hence the nucleophilicity of the C—C double bond.[280] In general, trisubstituted alkenes are hydrated faster than terminal alkenes. Thus, the reaction is most commonly applied to the preparation of tertiary alcohols (equation 191).[281]

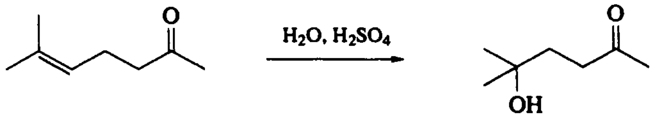

(191)

Furthermore, *cis* isomers are more easily hydrated than their *trans* counterparts, although exceptions are known. Thus, the hydration of *cis*-1,2-dicyclopropylethylene is 2.5 times faster than its *trans* isomer.[282] Strain introduced into a ring by the incorporation of a *trans* double bond reverses the trend, thereby making the hydration of *trans*-cyclooctene more rapid than the *cis* compound.[283] Smaller ring alkenes are also rather sluggish towards hydration.[284]

Recently, there have been many new catalysts developed for the hydration of alkenes, although most are more suited for industrial purposes. These catalysts include zeolites such as pentasil,[285] mordenite[286] and ferrierite,[185] as well as those containing heavy metals,[287] heteropolyacids[288] and sulfonic acid exchange resins.[289] It is reported that some of these new catalysts perform as high as 99.6% conversions and 99.4% selectivity, as illustrated in the hydration of propene into 2-propanol (equation 192).[290]

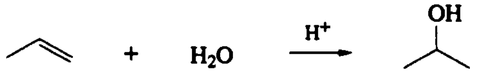

(192)

Hydration by synthetic zeolites is also applicable to structurally more complicated alkenes (equation 193).[291]

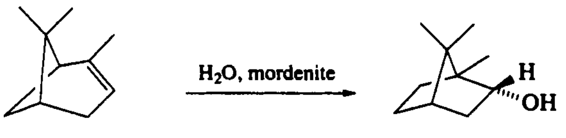

(193)

The metal ion promoted hydration of alkenes that mimic biochemical reactions has also received attention.[292]

The rate of acid-catalyzed hydration of styrenes can be enhanced photochemically (Scheme 2).[293,294] Except for nitro-substituted styrenes, such photohydrations undergo exclusive Markovnikov addition.

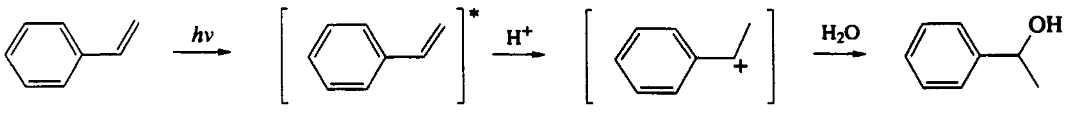

Scheme 2

The products obtained *via* the acid-catalyzed hydration of conjugated dienes are dependent on the structure of the diene. Thus, through the use of deuterated reagents, the sulfuric acid-catalyzed hydration of 1,3-cyclohexadiene was shown to proceed exclusively by a 1,2 addition (equation 194).[295]

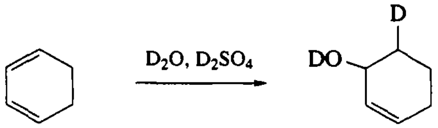

(194)

On the other hand, the hydration of acyclic dienes such as 1- or 2-substituted 1,3-butadienes affords an equilibrium mixture of allylic alcohols resulting from both 1,2- and 1,4-addition (equation 195).[296]

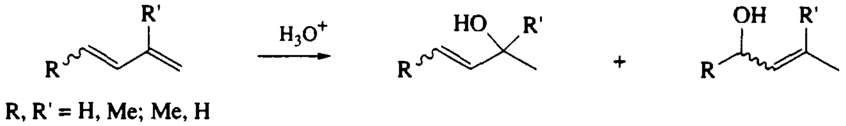

(195)

Interestingly, stereochemistry also plays a role in the mode of addition.[297] Thus, hydration of *cis*-1-ethoxy-1,3-butadiene shows deuterium incorporation at both the 2 and 4 positions (equation 196), while the *trans* isomer incorporates deuterium only at the 4 position (equation 197).

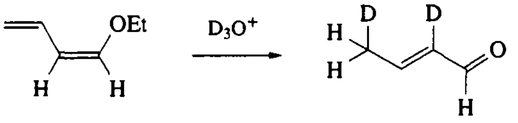

(196)

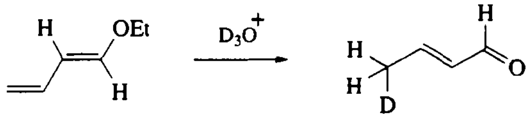

(197)

The addition of water to allenes has been reviewed recently.[298,299] The product obtained from the acid-catalyzed hydration of allene, alkylallenes and 1,3-dialkylallenes is usually the ketone. The intermediate is a vinyl cation formed by protonation on the terminal carbon of the allene moiety (equation 198).

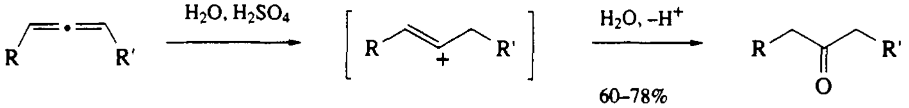

(198)

However, the site of protonation changes to the central carbon when electron-donating substituents such as acetates, alkoxides, arenes and fluoride are attached to the allene moiety. Thus, the hydration of allenyl ethers provides unsaturated aldehydes showing deuterium incorporation at the central carbon (equation 199).[300]

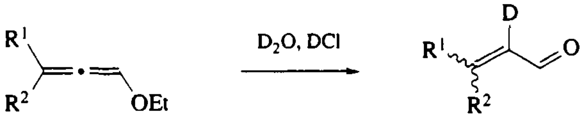

(199)

Carboxylic acids are obtained when water is added to the carbon–carbon double bond of ketenes (equation 200).[301] The addition is acid catalyzed, and involves protonation at the β-carbon.

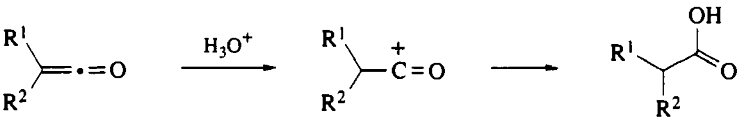

(200)

The direct hydration of a C—C triple bond has been recently reviewed.[302,303] Hydration is possible under acid or metal catalysis, as well as by photohydration. Hydration under acid catalysis is generally done with sulfuric acid, although other acid systems such as phosphoric acid/boron trifluoride have been reported.[304] It is established that acid catalysis occurs by a vinyl cationic intermediate which reacts with water to form an enol, followed by tautomerism into a ketone. The addition of water to terminal alkynes is governed by Markovnikov's rule (equation 201).

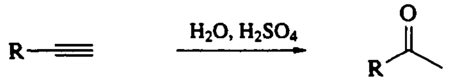

(201)

Except for very reactive alkynes, acid-catalyzed hydrations are usually sluggish. This slow hydration can be overcome by the addition of catalytic amounts of mercury(II) salts. Such hydrations are generally mild and will tolerate the presence of other functional groups. Specific examples of mercury-catalyzed hydrations are discussed in the next section.

The hydration of alkynes is also accomplished by use of catalytic amounts of palladium and gold salts.[305] The mildness of this reaction is demonstrated by the preparation of 5-oxo-prostaglandin derivatives (equation 202). In this connection, it should be noted that attempted use of other metal salts to catalyze C—C triple bond hydrations has met with little success.[306]

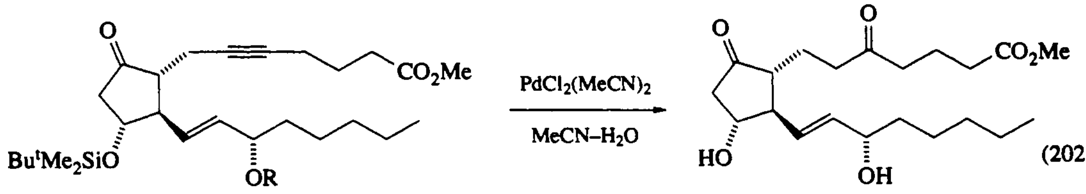

(202)

Analogous to the photohydration of styrenes, the acid-catalyzed hydration of phenylalkynes is also possible photochemically.[293,294,307] Except for nitro-substituted arylalkynes, the reaction follows Markovnikov's rule. This reaction has thus far received limited synthetic attention.

The hydration of heteroatom-substituted alkynes proceeds well under general acid catalysis. This reaction provides a convenient synthesis of amides,[308] esters[309] and thioesters.[308] Equation (203) illustrates the utility of this reaction for the regiospecific synthesis of 3-alkenamides.

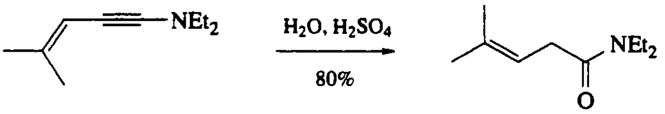

(203)

The hydration of conjugated diynes readily affords 1,3-diketones. The hydration may be acid- or mercuric sulfate-catalyzed. The Rupe rearrangement is observed under general acid catalysis (equation 204).[310]

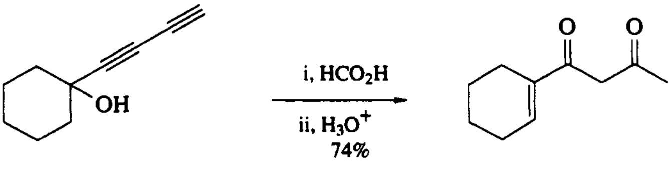

(204)

### 1.7.4.1.2 Hydroxymercuration–demercuration

In view of the many limitations inherent in the direct acid-catalyzed hydration of alkenes, indirect hydration *via* hydroxymercuration–demercuration has become a very valuable method for the preparation of alcohols. This process has recently been thoroughly reviewed.[311]

While many different procedures have been reported for the hydroxymercuration–demercuration of alkenes, the most useful procedure uses mercury(II) acetate in aqueous THF, followed by *in situ* alkaline sodium borohydride reduction (equation 205).[312,313] Virtually all substitution patterns about the C—C double bond are accommodated.

The following relative rates have been observed: $R_2C{=}CH_2 > RCH{=}CH_2 > (Z)\text{-}RCH{=}CHR > (E)\text{-}RCH{=}CHR$. Only certain aryl-substituted alkenes, tetrasubstituted alkenes or sterically hindered alkenes

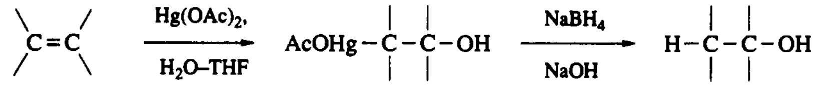

$$\mathrm{C{=}C} \xrightarrow[\mathrm{H_2O\text{–}THF}]{\mathrm{Hg(OAc)_2,}} \mathrm{AcOHg{-}C{-}C{-}OH} \xrightarrow[\mathrm{NaOH}]{\mathrm{NaBH_4}} \mathrm{H{-}C{-}C{-}OH} \qquad (205)$$

fail to react. The reaction rate is increased by electron donation and decreased by electron withdrawal, as expected for an electrophilic process.

The overall process is generally highly regiospecific. Mono- or di-substituted terminal alkenes and tri-substituted alkenes afford >99% of the Markovnikov adduct (equation 206).[312–314]

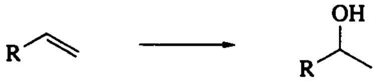

(206)

The direction of hydration is disubstituted internal alkenes is controlled by steric factors (equation 207).[312]

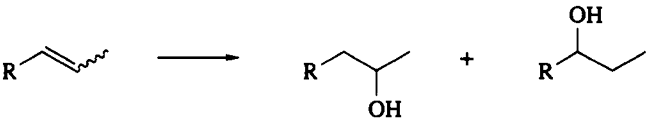

(207)

| *R* | % | % |
|---|---|---|
| Et | 64 | 36 |
| Pr$^i$ | 91 | 9 |
| Bu$^t$ | 98 | 2 |

Functional groups in the vicinity of the C—C double bond can also have a substantial effect on the regiochemistry of hydration (equations 208 and 209).[315–317]

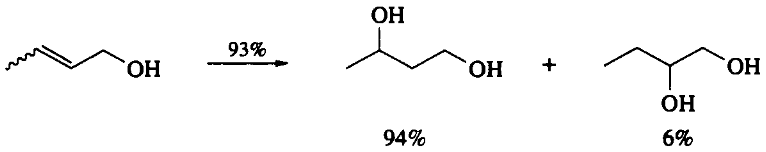

(ref. 315) (208)

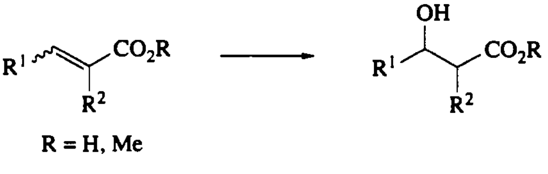

(refs. 316, 317) (209)

The regio- and stereo-selectivity of various substituted cycloalkenes have been examined (equations 210–212).[318–324]

Unfortunately, these reactions tend to afford mixtures. Similar mixtures are observed when using 2-cyclohexen-1-ol,[315] 3-cyclohexen-1-ol,[315,325] or the corresponding ethers or esters.[326,327]

The regio- and stereo-selectivity of the hydration of bicyclic alkenes has also been carefully examined (equation 213).[328–330]

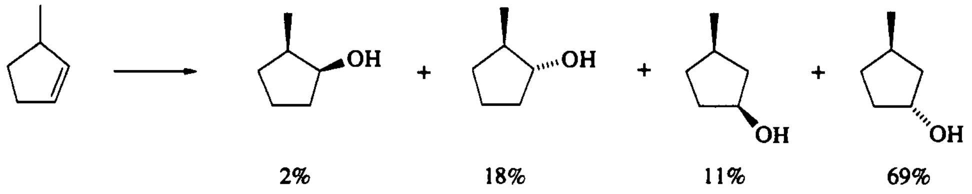

(210)

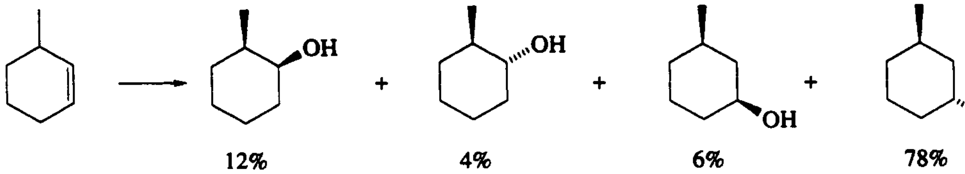

(211)

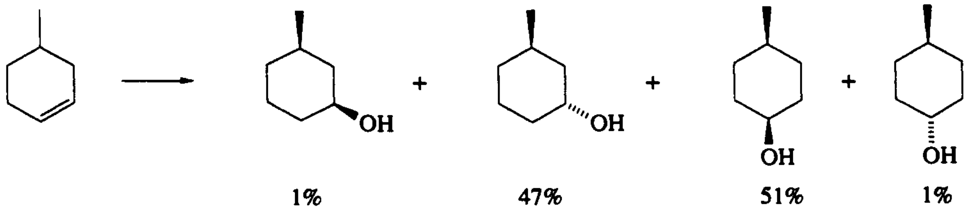

(212)

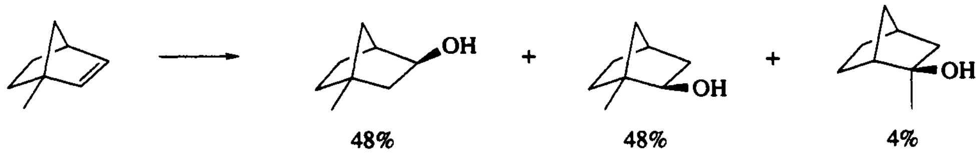

(213)

The stereoselectivity of this hydration process has been studied on a number of alkenes. Acyclic alkenes and most cyclic alkenes give exclusively *trans* addition (equations 214 and 215).[331,332] However, some strained cyclic alkenes, such as *trans*-cyclooctene and *trans*-cyclononene, give *cis* adducts.[332]

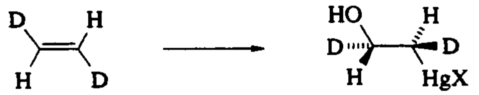

(ref. 331) (214)

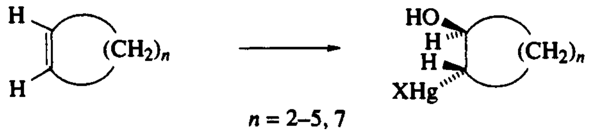

(ref. 332) (215)

Various substituted cyclic alkenes have been reported to give mixtures of stereoisomers (equations 216 and 217).[319,320,322,323,333–336]

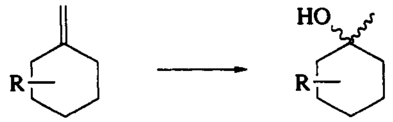

(refs. 323, 333–335) (216)

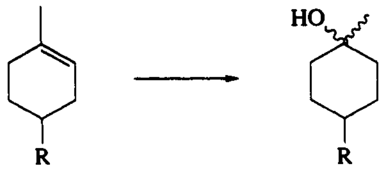

(refs. 319, 320, 322, 336) (217)

As noted earlier, many bicyclic and polycyclic alkenes undergo hydroxymercuration–demercuration. Norbornene and derivatives[328] give *cis* adducts, but less strained alkenes afford the expected *trans* adducts.

Attempts at asymmetric induction using mercury salts of optically active carboxylic acids have met with limited success.[337,338]

Relatively few functional groups have been reported to interfere in the reaction, and rearrangements during hydroxymercuration or reduction are rare.

While reduction is usually best carried out using alkaline sodium borohydride, this reaction proceeds by free radicals and is not stereospecific. By employing Na(Hg) in $D_2O$, reduction with retention is observed. However, the stereospecific reduction of β-hydroxymercurials in which the mercury moiety is α to a carbonyl group has been reported using alkaline $NaBH_4$–EtOH,[316] alkaline $H_2S$[317] and $HS(CH_2)_3SH$ (equation 218).[316]

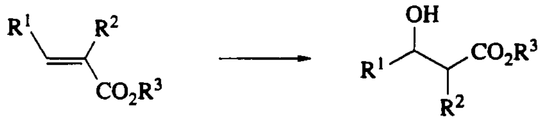

(218)

| | |
|---|---|
| $NaBH_4$–EtOH | *threo* |
| $HS(CH_2)_3SH$ | *erythro* |

Numerous dienes and polyenes have been subjected to hydroxymercuration–demercuration.[311] With nonconjugated dienes, the products can usually be predicted by applying what one has learned from the corresponding simple alkenes. Isolated double bonds are more reactive than conjugated double bonds and frequently one of the double bonds is sufficiently more reactive than the others that monohydroxylated products can be obtained. Improvements in selectivity have been reported by using mercury(II) trifluoroacetate[339] or by adding sodium lauryl sulfate.[340]

When five- or six-membered ring ethers can readily be formed by intramolecular alkoxymercuration of the initially formed alkenol, cyclic ethers are often the observed product (equation 219).[341] This process has recently proven useful in the synthesis of spirocyclic acetals (equation 220).[342]

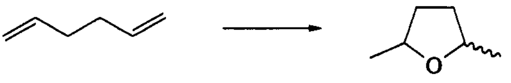

(219)

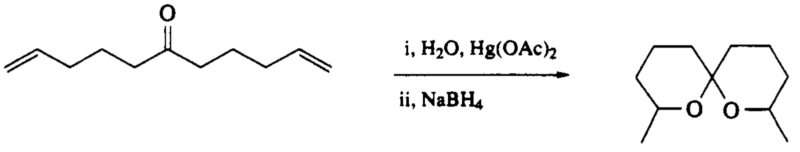

(220)

Carbon–carbon bond formation is another side reaction occasionally observed (equation 221).[343]

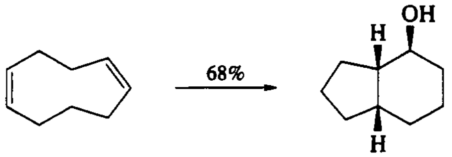

(221)

Carbon skeleton rearrangements during either hydroxymercuration or demercuration are also more common with dienes.

The hydroxymercuration–demercuration of conjugated dienes generally does not afford monohydration products selectivity, but diols can sometimes be obtained in reasonable yield. The direction of addition of H—OH is that expected by extrapolation from simple alkenes and allylic alcohols.

Allenes undergo mercury-catalyzed hydration to give a variety of products depending upon the substituents and the substitution pattern (equations 222 and 223).[344–347]

Alkynes undergo mercury-catalyzed hydration to afford ketones (equation 224).[311,348–350]

A wide variety of mercury(II) salts have been employed as catalysts, though mercury(II) sulfate is the most widely used.[351] Phenylmercury(II) hydroxide is useful for the selective conversion of terminal al-

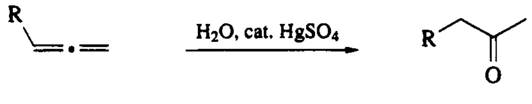

(refs. 344, 345) (222)

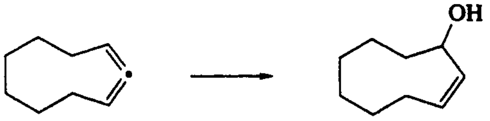

(refs. 346, 347) (223)

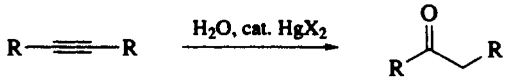
R
R
H2O, cat. HgX2
O
R
R

(224)

kynes to methyl ketones (equation 225).[352] Internal alkynes or conjugated alkynes fail to react in this process.

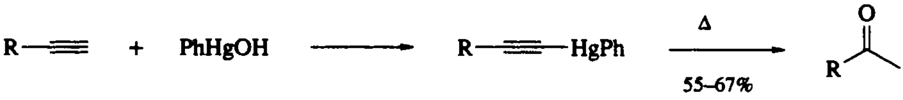
R
+
PhHgOH
R
HgPh
Δ
55–67%
O
R

(225)

Mercury-impregnated polymeric resins have also proven valuable for the hydration of alkynes.

These mercury-catalyzed processes are commonly effected in water, aqueous sulfuric acid, acetic acid or alcohol solutions.

The hydration of terminal alkynes produces methyl ketones. Simple unsymmetrical internal alkynes generally afford mixtures of regioisomeric ketones, but alkynes bearing certain functional groups exhibit high regioselectivity (equations 226 and 227).[353–355]

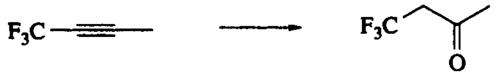

(ref. 353) (226)

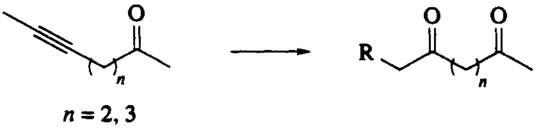

(refs. 354, 355) (227)

While many functional groups are accommodated by this process, acid-promoted rearrangements and eliminations are not uncommon (equations 228–231).[356–360] In fact, the hydration of certain unsaturated alkynes produces oxygen heterocycles (equations 232 and 233).[361,362]

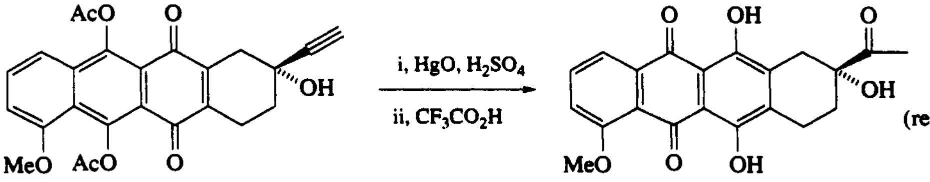
AcO
O
OH
MeO
AcO
O
i, HgO, H2SO4
ii, CF3CO2H
O
OH
O
OH
MeO
O
OH

(228)
(ref. 356)

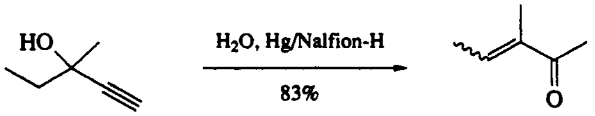
HO
H2O, Hg/Nalfion-H
83%
O

(ref. 357) (229)

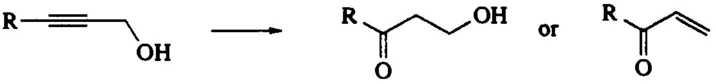
R
OH
R
OH
O
or
R
O

(230)
(refs. 358, 359)

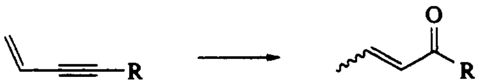

(ref. 360) (231)

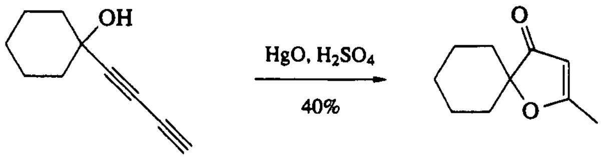

(ref. 361) (232)

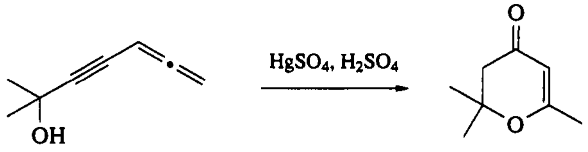

(ref. 362) (233)

### 1.7.4.2 H—$O_2$H and H—$O_2$R Additions

#### *1.7.4.2.1 Acid-catalyzed addition*

There are very few examples in the literature of electrophilic additions of hydrogen peroxide or alkyl hydroperoxides to C—C multiple bonds. The products of these additions, alkyl hydroperoxides or dialkyl peroxides respectively, can be explosively unstable[363] and are more commonly obtained by peroxymercuration–demercuration methods (*vide infra*).

Early work on the electrophilic addition of hydrogen peroxide to alkenes was performed in the presence of an acid catalyst, usually sulfuric acid[364] or *p*-toluenesulfonic acid.[365] The reaction proceeds *via* Markovnikov-directed protonation of the double bond (Scheme 3). Subsequent nucleophilic attack of hydrogen peroxide on the carbocation, followed by loss of a proton, furnishes the alkyl hydroperoxide.[366]

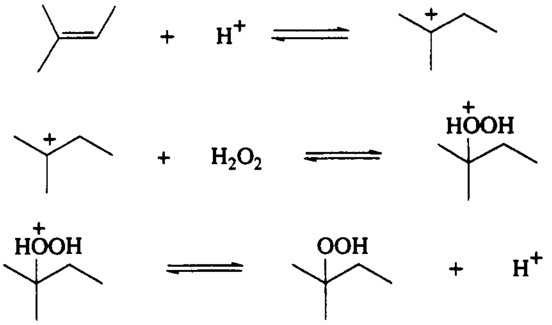

Scheme 3

Since the reaction involves a carbocation, it is subject to the normal substituent effects. Hence, the addition of hydrogen peroxide to a mixture of 3-methyl-2-hexene and 3-methyl-3-hexene yields the tertiary alkyl hydroperoxide as the only product (equation 234).[367] On the other hand, cyclohexene does not react under similar conditions.

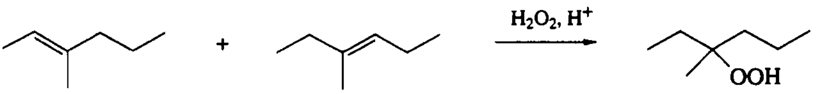

(234)

Hydrogen peroxide also adds well to alkenes with heteroatom substituents on the double bond, as exemplified by the reactions of vinyl ethers (equation 235)[368,369] and enamines (equation 236).[370]

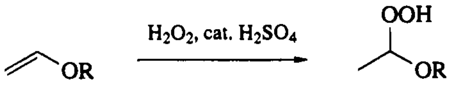

(235)

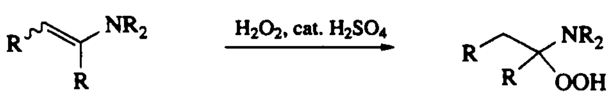

(236)

Recently, it has been proposed that alkyl hydroperoxides are formed from the $Co^{III}$-catalyzed Markovnikov addition of hydrogen peroxide to alkenes.[371] The alkyl hydroperoxides thus formed are immediately decomposed into ketones and alcohols under the reaction conditions (equation 237).

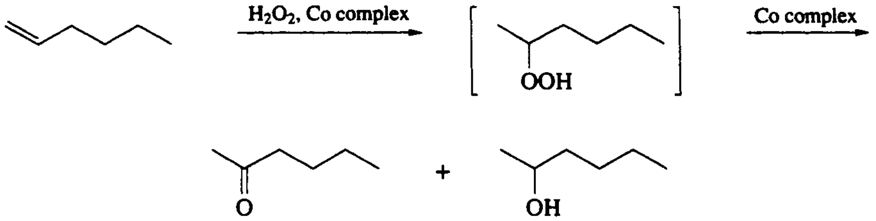

(237)

In a manner analogous to the acid-catalyzed addition of hydrogen peroxide, dialkyl peroxides are formed by the addition of alkyl hydroperoxides to alkenes (equation 238).[366]

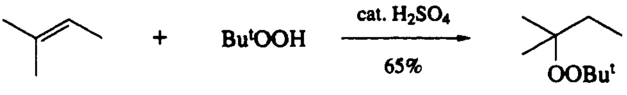

(238)

Surprisingly, there is no literature precedent for the addition of either hydrogen peroxide or alkyl hydroperoxides to dienes, polyenes or alkynes.

### 1.7.4.2.2 *Peroxymercuration–demercuration*

The peroxymercuration–demercuration of alkenes provides a more versatile approach to the corresponding hydroperoxides or dialkyl peroxides than direct acid-catalyzed addition (equation 239).[372–374]

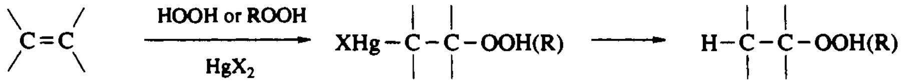

$$\mathrm{>C{=}C<} \xrightarrow[\mathrm{HgX_2}]{\mathrm{HOOH\ or\ ROOH}} \mathrm{XHg{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OOH(R)} \longrightarrow \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OOH(R)} \qquad (239)$$

The most widely used mercury salts for this transformation are $Hg(OAc)_2$ in the presence of catalytic amounts of $HClO_4$[375] or $Hg(O_2CCF_3)_2$.[376] While hydrogen peroxide itself can be used, mono- and dimercuration products have been observed.[377] Alkyl hydroperoxides generally give cleaner reactions. Dichloromethane is commonly employed as the solvent.

A wide variety of alkenes undergo Markovnikov peroxymercuration. Even α,β-unsaturated carbonyl compounds afford peroxymercurials whose regiochemistry is dependent on the substitution pattern about the C—C double bond.[378–381] Selective *anti* addition to the double bond of simple alkenes is the general rule.[375,382]

While successful demercuration using alkaline sodium borohydride has been reported, this process can also give rise to epoxides (equation 240).[383] Tri-*n*-butyltin hydride often gives improved results.[384]

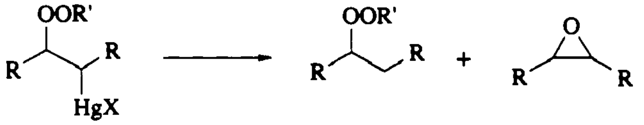

(240)

Several alkenyl hydroperoxides have been successfully cyclized to five-, six- and seven-membered ring peroxides (equation 241).[385–388] Alkaline sodium borohydride reduction of these mercurials is frequently accompanied by epoxide or cyclic ether formation.

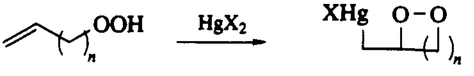

(241)

Dienes can afford either mono- or di-mercurated products (equations 242 and 243).[385,389–391] Mercury(II) trifluoroacetate or mercury(II) nitrate are the reagents of choice for this latter reaction. Alkaline sodium borohydride reduction is often accompanied here by formation of unsaturated alcohols.

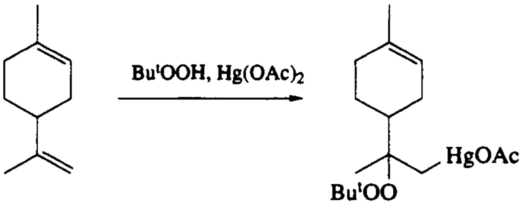

(ref. 389) (242)

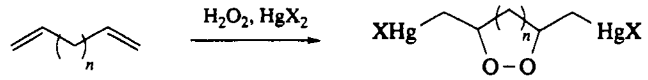

(243)
(refs. 385, 390, 391)

### 1.7.4.3 H—OR Addition

#### *1.7.4.3.1 Direct H—OR addition*

Alcohols add directly to alkenes under acid or metal catalysis, or under photoinitiated conditions to give dialkyl ethers. Although these additions provide certain ethers under rather mild conditions, alkoxymercuration–demercuration is generally a superior method.

As in the hydration of alkenes, sulfuric acid is the preferred catalyst. The reaction occurs in accordance with Markovnikov's rule (equation 244).

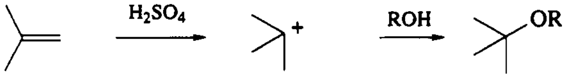

(244)

As might be anticipated, isomeric products resulting from cationic rearrangements have been observed. The yield of ether is dependent on the amount of the catalyst used, the strength of the acid, and the reaction temperature.[392] Optimum conditions generally involve trace amounts of acid catalyst and room temperature reaction. Acids with weakly nucleophilic conjugate bases are recommended so as not to compete with the alcohols for the cationic intermediate.[393]

The addition of alcohols to alkenes is also catalyzed by boron trifluoride–hydrogen fluoride, but the reaction proceeds only under vigorous conditions and the yields are generally low.[394] Recently, the etherification of alkenes has also been achieved industrially by using acidic montmorillonite[395] and macroporous sulfuric acid resins (ion-exchange resins).[396]

Alcohol addition to alkenes can also be achieved photochemically under neutral conditions (equation 245).[397] This reaction appears to be a photochemically induced ionic addition to the double bond. An arene photosensitizer is required. Unfortunately, this reaction is limited to cyclic alkenes and double bond isomerization is significant.

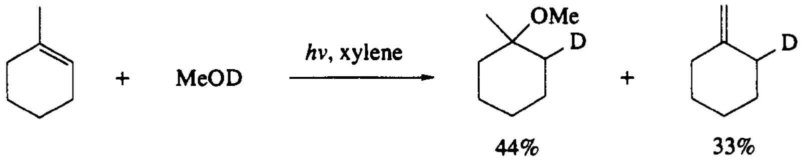

(245)

The presence of electron-donating groups on an alkene enhances the nucleophilicity of the double bond. Thus, the addition of alcohols to vinylic ethers proceeds rapidly by either acid[398] or mercury(II) acetate catalysis.[399] Equation (246) illustrates the addition of an allylic alcohol to 2-methoxypropene, followed by a Claisen rearrangement which affords good yields of γ,δ-unsaturated ketones.

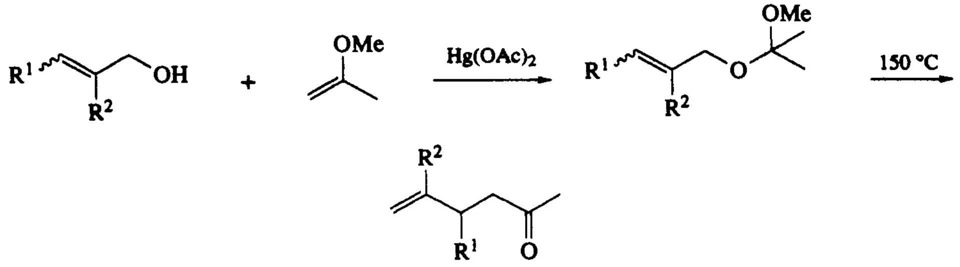

(246)

Under acidic conditions, dihydropyran will undergo additions with alcohols at room temperature to form 2-tetrahydropyranyl ethers (equation 247).[398] This reaction constitutes an important method for the protection of primary and secondary alcohols.[400]

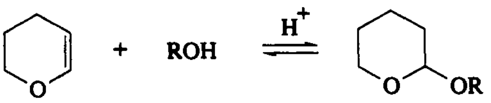

(247)

Alcohols will add to allenes in the presence of trace amounts of acids to give vinyl ethers (or acetals) or allylic ethers.[401] Analogous to the hydration of allenes, protonation occurs on the terminal carbon of the allenic functionality in 1,2-propadiene, 3-alkyl-1,2-propadienes and 1,3-dialkyl-1,2-propadienes (equation 248).[402] Addition of an alcohol to the resulting vinylic cation produces a vinylic ether, which may on further reaction form an acetal of the corresponding ketone.

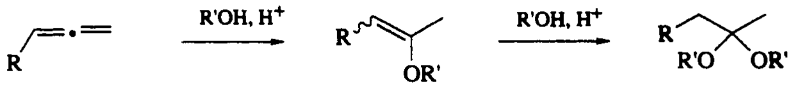

(248)

On the other hand, allylic ethers are obtained from 3,3-dialkyl-1,2-propadienes and tetraalkyl allenes (equation 249).[403]

When treated with catalytic amounts of acid,[404,405] silver salts[406–410] or mercury salts,[409,410] allenic alcohols will cyclize to ethers (equations 250–253). By proper choice of reaction conditions, the yields of products obtained in these cyclizations are generally high. Interestingly, the stereoselectivity observed in equation (253) is proposed to arise from a chair conformation of the intermediate.[408]

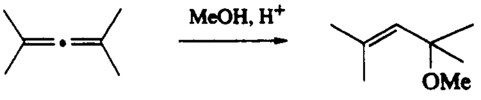

(249)

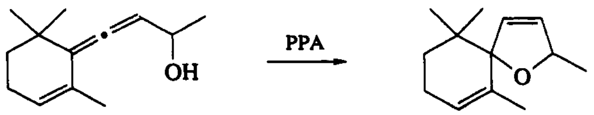

(250)

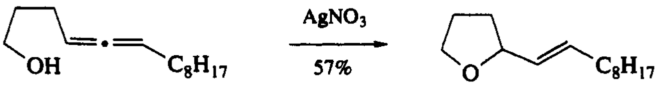

(251)

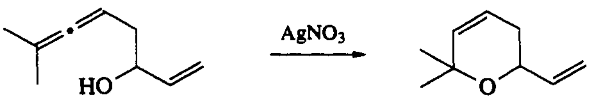

(252)

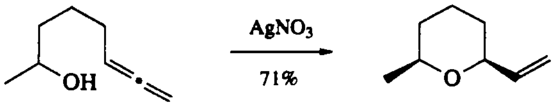

(253)

The addition of alcohols to alkynes is catalyzed by bases,[411,412] or salts of palladium,[413] silver[414] or mercury[413] (equations 254–256). The mercury-catalyzed processes are summarized in the following section.

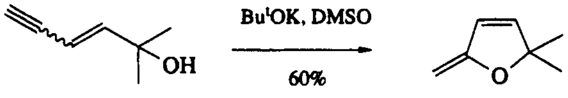

(ref. 412) (254)

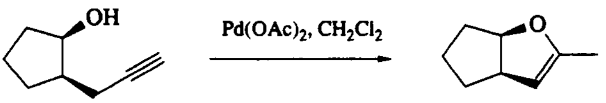

(255)

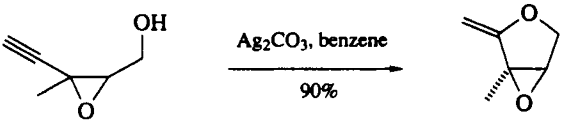

(256)

### *1.7.4.3.2 Alkoxymercuration–demercuration*

The alkoxymercuration–demercuration of alkenes, dienes and alkynes in the presence of alcohols provides an even more versatile approach to the corresponding ethers than the acid-catalyzed process. This reaction has been extensively studied and thoroughly reviewed recently.[415] The reaction of alkenes is best carried out using mercury(II) acetate or, for more highly substituted alcohols or alkenes, mercury(II) trifluoroacetate (equation 257).[416,417]

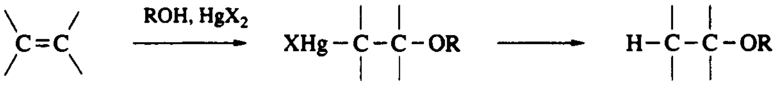

$$\mathrm{>C{=}C<} \xrightarrow{\mathrm{ROH,\ HgX_2}} \mathrm{XHg-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OR} \longrightarrow \mathrm{H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OR}$$

(257)

The reaction is commonly run at room temperature using the alcohol as the solvent. For hindered alcohols, better results can sometimes be obtained at 0 °C.[417] There are few examples in which other solvents or only stoichiometric amounts of alcohols have been employed (equation 258).[418]

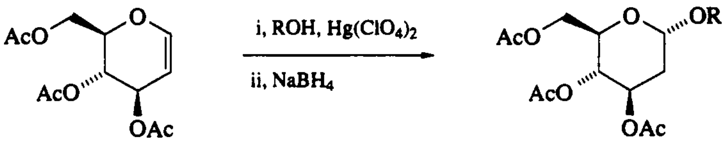

(258)

A wide variety of alcohols and alkenes can be utilized in this process. Numerous functional groups in either the alcohol or the alkene can be accommodated during alkoxymercuration. For example, alkenes differing in their nucleophilicity as much as vinylic ethers[419] and α,β-unsaturated aldehydes or ketones[420,421] react smoothly (equations 259 and 260).

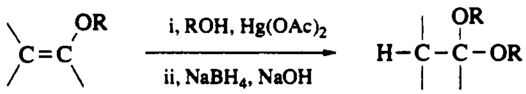

$$\mathrm{>C{=}C<^{OR}} \xrightarrow[\mathrm{ii,\ NaBH_4,\ NaOH}]{\mathrm{i,\ ROH,\ Hg(OAc)_2}} \mathrm{H-\overset{|}{\underset{|}{C}}-\overset{OR}{\underset{|}{C}}-OR}$$

(259)

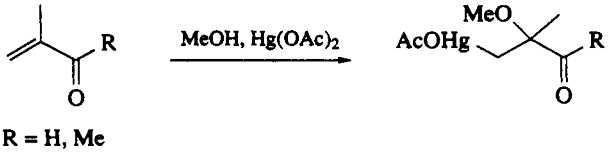

(260)

The reaction is extremely versatile with regard to the substitution pattern of the alkene. All but the most hindered of alkenes tend to react and very few functional groups interfere. The regio- and stereo-selectivity is very similar to that reported for hydroxymercuration (see Section 1.7.4.1.2). The reaction is generally highly regioselective in the Markovnikov sense. Carbonyl groups (acids, esters, aldehydes and ketones) can, however, reverse the direction of addition depending on the substitution pattern about the C—C double bond (equation 261). The more remote the functional group, the less its influence.[422–424]

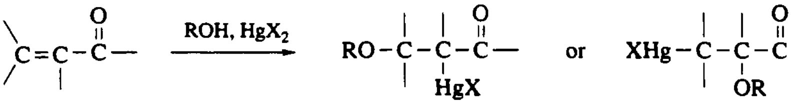

$$\text{>C=C}-\overset{\text{O}}{\overset{\|}{\text{C}}}- \xrightarrow{\text{ROH, HgX}_2} \text{RO}-\overset{|}{\underset{|}{\text{C}}}-\overset{|}{\underset{\text{HgX}}{\text{C}}}-\overset{\text{O}}{\overset{\|}{\text{C}}}- \quad \text{or} \quad \text{XHg}-\overset{|}{\underset{|}{\text{C}}}-\overset{|}{\underset{\text{OR}}{\text{C}}}-\overset{\text{O}}{\overset{\|}{\text{C}}}- \qquad (261)$$

The stereochemistry of addition to acyclic, cyclic and polycyclic alkenes is essentially identical to that of hydroxymercuration wherever the two processes have been compared. Fewer data have been accumulated for alkoxymercuration however.

One major advantage of the alkoxymercuration–demercuration approach to ethers over the acid-catalyzed process is the fact that carbon skeleton rearrangements are seldom observed. Only unsaturated cyclopropanes,[425,426] or aryl-substituted alkenes[427,428] in the presence of highly electrophilic mercury salts afford rearranged products.

The kinetics of alkoxymercuration have received considerable attention.[415] The relative reactivity of various alkenes parallels that reported for hydroxymercuration.

The demercuration of β-alkoxymercurials is usually best effected using alkaline sodium borohydride. Few rearrangements during this free radical reduction process have been observed.[429] When the mercury moiety is positioned α to a carbonyl group, alkaline $H_2S$[430,431] or 1,3-propanedithiol[316] provide alternatives that afford complementary stereochemical results (equation 262). The use of sodium–mercury amalgam is also useful for stereospecific reduction.[432,433]

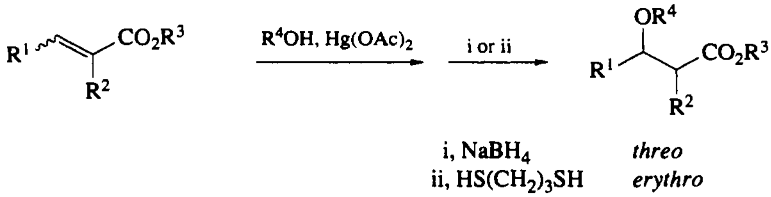

i, $NaBH_4$ *threo*
ii, $HS(CH_2)_3SH$ *erythro*

(262)

The intramolecular alkoxy- or phenoxy-mercuration of unsaturated alcohols or phenols, respectively, provides an exceptionally useful process for the formation of cyclic ethers, particularly those bearing a five- or six-membered ring (equation 263).[415]

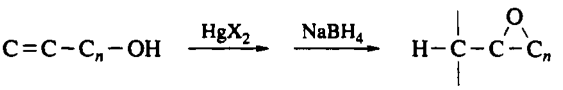

$$\text{C=C}-\text{C}_n-\text{OH} \xrightarrow{\text{HgX}_2} \xrightarrow{\text{NaBH}_4} \text{H}-\overset{|}{\underset{|}{\text{C}}}-\text{C}\overset{\text{O}}{\frown}\text{C}_n \qquad (263)$$

The choice of mercury salt for this reaction appears to be less critical than intermolecular variants and many salts (X = Cl, OAc, $NO_3$, $SO_4$, $ClO_4$, $CF_3CO_2$) have been successfully utilized. The electrophilicity of the salt can effect the regio- and stereo-chemistry of addition.[434–438] The regioselectivity is also determined by the substitution pattern of the unsaturated alcohol. For cycloalkenes, steric factors, ring strain, and other reaction variables become important (equation 264). High regio- and stereo-selectivity are often encountered in these intramolecular processes.

The demercuration of these cyclic mercurials is fraught with more problems than analogous mercurials formed by intermolecular processes. Alkaline sodium borohydride is once again the most common reducing agent, but elimination to the starting unsaturated alcohol is not unusual. The extent of elimination varies with the mercury ligand, the pH and the solvent used.[434] Phase transfer approaches offer advant-

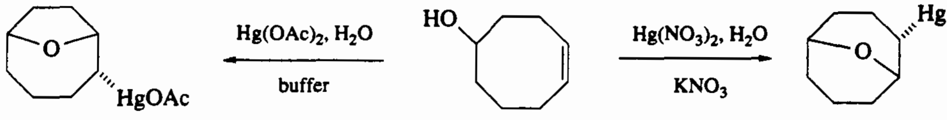

(264)
(ref. 434)

ages here.[439–441] Sodium trithiocarbonate reduction of cyclic alkoxymercurials bearing a neighboring carboxylic acid moiety provides stereoselectivity complementary to $NaBH_4$.[442]

The alkoxymercuration of dienes and polyenes has been extensively studied. Mono-, di- or poly-mercurated adducts are formed as expected based on results from the alkoxymercuration of analogous alkenes, but the product distribution varies depending on the nature of the diene or polyene.

Nonconjugated dienes or polyenes can be monomercurated if the diene or polyene is employed in excess, but more frequently these compounds are allowed to react with an excess of the mercury salt and di- or poly-mercurated products are obtained. The relative reactivity of isolated double bonds is basically that expected from studies on simple alkenes.

The alkoxymercuration of conjugated dienes is more complex since these compounds are less reactive than simple alkenes and the products often react further to afford dimercurated products whose regio- or stereo-chemistry is strongly affected by the initial product. For example, 1,3-butadiene, 1,3-pentadiene, 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene react with mercury(II) acetate in methanol to produce 1,2-adducts (equation 265).[443–446] These adducts sometimes rearrange with time.[446] 1,3-Butadiene reacts further to afford primarily the *meso* adduct of double 1,2-additions.[447] Surprisingly, little additional work has been reported on reactions of conjugated dienes.

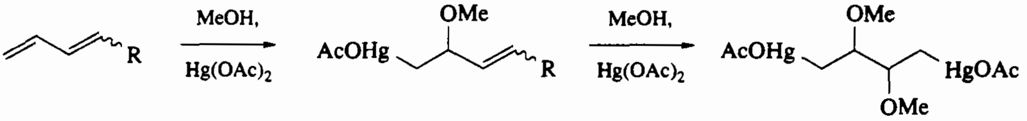

(265)

Considerable work on the alkoxymercuration of allenes has been reported.[415] Mono- or di-mercuration products are observed depending on the substitution pattern of the allene. While allene and 1,2-butadiene afford dimercurated acetals, more highly substituted allenes produce vinylmercurials (equations 266 and 267).[448] Cyclic allenes also afford vinylmercurials.[449,450] Alkaline sodium borohydride reduction of these vinylmercurials produces the expected allylic ethers.

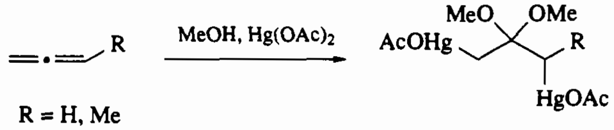

(266)

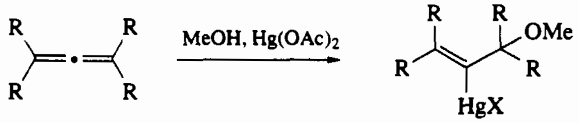

(267)

Nonconjugated dienols undergo intramolecular cyclization in the same manner as simple dienols (equation 268).[451]

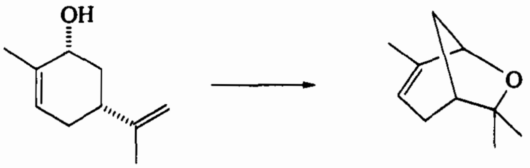

(268)

The alkoxymercuration of conjugated dienols does not appear to have been examined, while allenic alcohols provide unsaturated ethers (equation 269).[452]

The alkoxymercuration of alkynes generally provides vinylic ethers[453] or acetals[454] depending on the reaction conditions (equations 270 and 271). Only catalytic amounts of mercury salts are generally

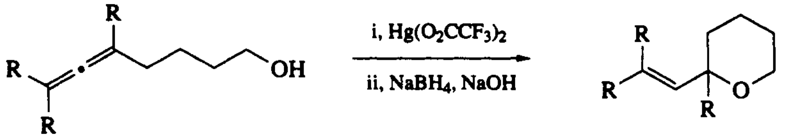
R
R
R
OH
i, Hg(O2CCF3)2
ii, NaBH4, NaOH
R
R
O
R

(269)

necessary in these reactions. Internal alkynes usually afford acetals exclusively. However, the intramolecular alkoxymercuration of alkynols can be stopped at the vinyl ether stage (equation 272).[455]

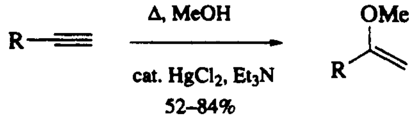
R
Δ, MeOH
cat. HgCl2, Et3N
52–84%
OMe
R

(270)

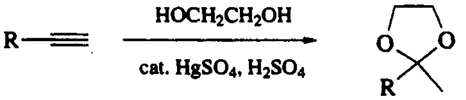
R
HOCH2CH2OH
cat. HgSO4, H2SO4
O
O
R

(271)

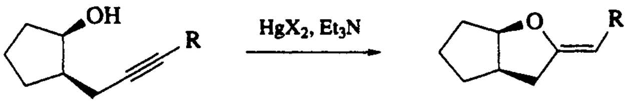
OH
R
HgX2, Et3N
O
R

(272)

## 1.7.4.4 H—O$_2$CR Addition

### *1.7.4.4.1 Direct addition of H—O$_2$CR*

Although a seldom used laboratory method, the addition of carboxylic acids to alkenes provides carboxylic esters. The addition is catalyzed by protic acids or Lewis acids and obeys Markovnikov's rule (equation 273).[456–458]

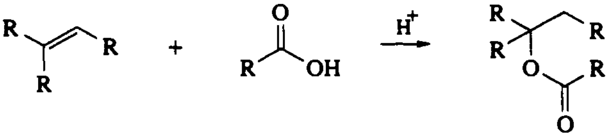
R
R
R
+
O
R
OH
H+
R
R
R
O
R
O

(273)

The best yields of ester are generally obtained with alkenes which provide highly stabilized carbocations. This reaction is particularly effective for the preparation of hindered esters (equation 274).[459]

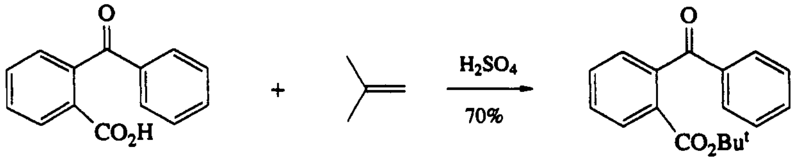
O
CO2H
+
H2SO4
70%
O
CO2Bu^t

(274)

To obtain high yields from the esterification of terminal alkenes, boron trifluoride–hydrogen fluoride is reported to be more effective than sulfuric acid as a catalyst (equation 275).[456]

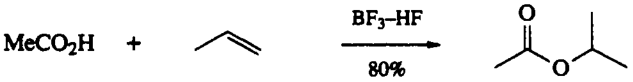
MeCO2H
+
BF3-HF
80%
O
O

(275)

In the presence of a strong acid as catalyst, alkenoic acids will add internally to furnish a valuable route to lactones (Scheme 4).[460] Regardless of the position of the double bond in the chain, the product obtained is always the γ- and/or δ-lactone due to acid-catalyzed double bond migration to a position favorable for ring closure.[461] The choice of catalyst and the reaction temperature are important in minimizing the amount of cycloalkenone side product that usually accompanies lactone formation.[462]

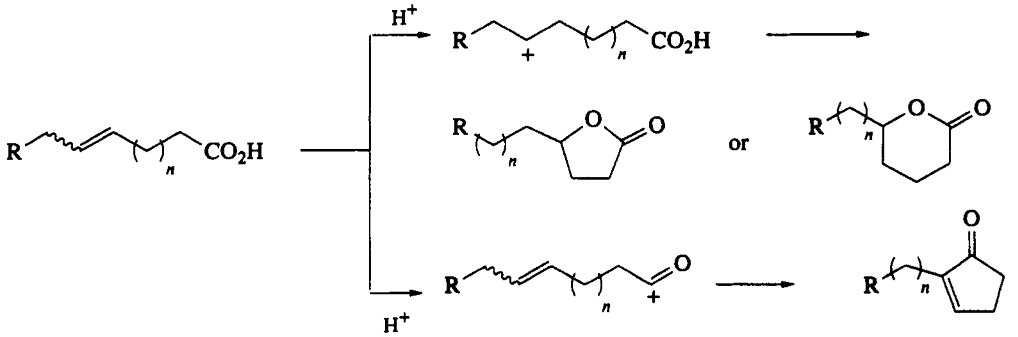

**Scheme 4**

In an earlier study, interesting stereochemical aspects of this lactonization reaction were demonstrated, as illustrated in the synthesis of (±)-ambreinolide (equation 276).[463]

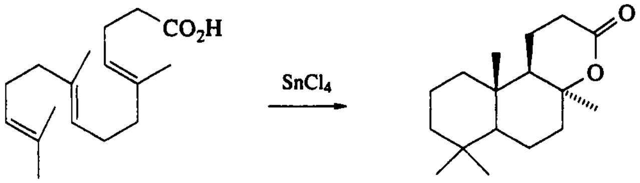

(276)

The intermolecular addition of carboxylic acids to dienes is not very efficient. Conjugated dienes generally form polymeric products,[456] whereas nonconjugated dienes tend to give polycyclic products (equation 277).[464] The addition to allenes, on the other hand, is marred by regio- or stereo-isomerism (equation 278).[465]

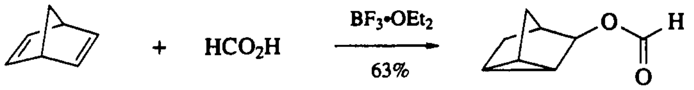

(277)

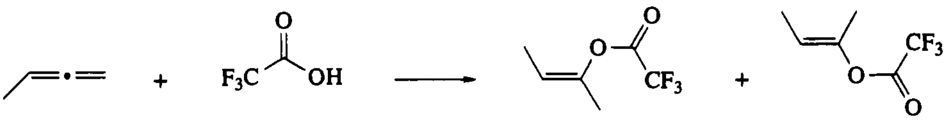

(278)

More recently, interest in the addition of carboxylic acids to alkenes has focused on the development of new catalytic systems such as clay,[466] sheet silicate (montmorillonites),[467] wofatit[468] and zeolites.[469]

The addition of carboxylic acids to alkynes affords enol esters which are useful as intermediates in organic synthesis.[470] As in the addition to alkenes, a catalyst is usually required for high conversions of alkynes to enol esters. Simple acid catalysis has been employed (equation 279),[471] but the more common catalysts are Lewis acids, such as boron trifluoride etherate,[472] silver nitrate,[473] zinc acetate[474] and zinc oxide (equations 280 and 281).[475,476]

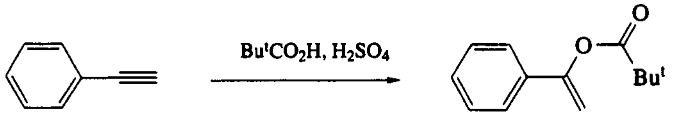

(279)

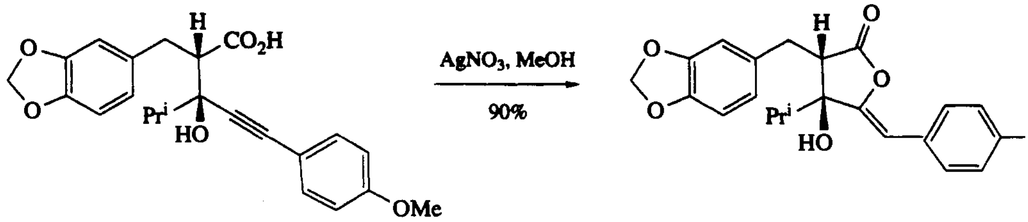

(280)

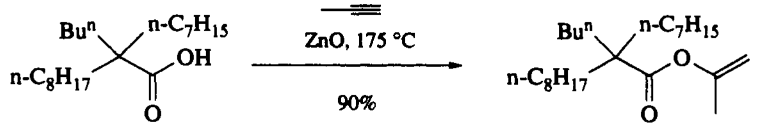

(281)

Mercury(II) salts and transition metals are also important catalysts for this reaction. Mercury catalysis will be discussed in the next section, while transition metal catalysis is discussed elsewhere in this series.

### 1.7.4.4.2 *Acyloxymercuration–demercuration*

The acyloxymercuration–demercuration of alkenes provides an alternative route to esters which is probably less prone to carbon skeleton rearrangements than the direct addition of carboxylic acids to alkenes (equation 282). This reaction has recently been reviewed.[477] The reaction is most commonly run using mercury(II) acetate in acetic acid, though other mercury salts may be used and aprotic solvents can also be employed. Equilibria have been measured for the reaction of mercury(II) trifluoroacetate and alkenes in tetrahydrofuran, and were found to be solvent dependent.[478]

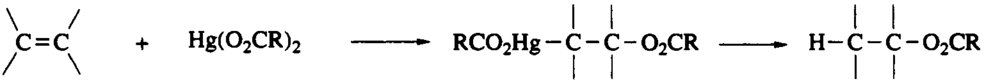

$$>C=C< + Hg(O_2CR)_2 \longrightarrow RCO_2Hg-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-O_2CR \longrightarrow H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-O_2CR \qquad (282)$$

Acyloxymercuration follows Markovnikov's rule and involves *anti* addition with most cyclic alkenes.[479–482] However, certain strained bicyclic alkenes, such as norbornene, afford *cis exo* adducts.[483] With substituted cyclic alkenes, the regio- and stereo-selectivity of acetoxymercuration is very similar to hydroxy- and methoxy-mercuration.[484,485] While simple alkenes, and vinylic ethers[486,487] and esters[488–491] undergo acetoxymercuration, there does not appear to be any example of alkenes bearing electron-withdrawing groups undergoing this reaction (equation 283).

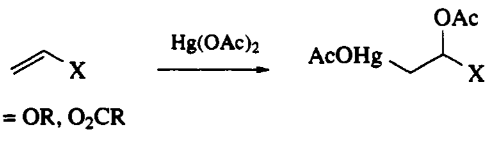

(283)

The reaction accommodates halides, esters, ethers, nitriles, cyclopropanes, epoxides, alcohols and nitro groups. Even carbohydrates can be used.[492–494] However, vinylic halides afford aldehydes and ketones (equation 284).[495–498]

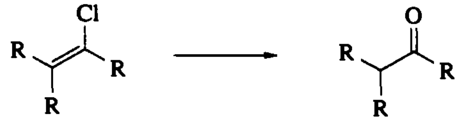

(284)

Mercury(II) salts also catalyze the transesterification of vinylic esters (equation 285).[477]

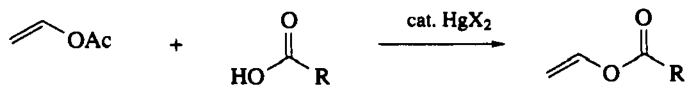

(285)

While the demercuration of β-acyloxymercurials has not received much attention, sodium borohydride or alkaline sodium borohydride have been most widely employed for this task. Hydrolysis to the corresponding alcohol or reversion to alkene are significant side reactions, however, and they are sensitive to the solvent used.[499,500] Sodium amalgam and tri-*n*-butyltin hydride[501] have also been utilized as reducing agents.

A number of alkenoic acids undergo intramolecular acyloxymercuration when treated with mercury(II) acetate or mercury(II) chloride (equations 286 and 287).[477]

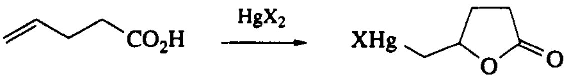

(286)

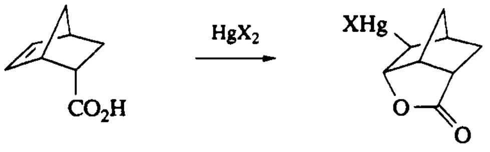

(287)

It appears that all but one[502] (eleven-membered ring) of the examples of this reaction in the literature involve the synthesis of monocyclic or tricyclic five-membered ring lactones.[503-507] Sodium borohydride,[508,509] sodium trimethoxyborohydride[510] and sodium amalgam[483] have been employed for demercuration of these substrates.

Dienes and polyenes undergo acyloxymercuration. Nonconjugated dienes afford either mono- or dimercurated species, depending on the stoichiometry of the reaction (equation 288).[511-513] Products involving carbon–carbon bond formation are occasionally observed during this process.[512] Allenes afford vinylmercurials (equation 289).[514,515]

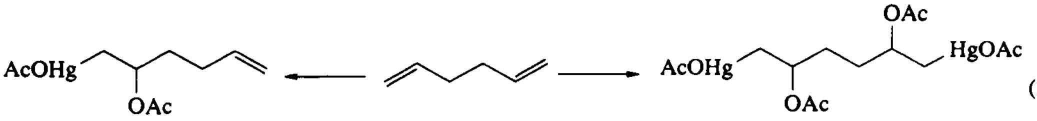

(288)

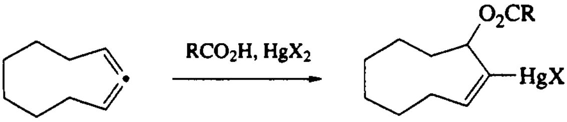

(289)

The acyloxymercuration of alkynes has been reported to produce a wide variety of products. Terminal alkynes afford either dialkynylmercurials[516,517] or polymercurated products whose structures have not been well established (equation 290). Internal alkynes usually afford vinylic mercurials in which the mercury(II) salt has added in an *anti* fashion (equation 291).[518-520] Only sodium borohydride has been used to demercurate a few of these mercurials.[520]

$$2\,R{-}{\equiv} \;+\; Hg(OAc)_2 \longrightarrow R{-}{\equiv}{-}Hg{-}{\equiv}{-}R \qquad (290)$$

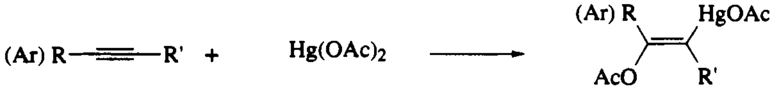

(291)

Mercury salts, such as mercury(II) acetate,[521-525] mercury(II) oxide,[524,526-528] mercury(II) trifluoroacetate,[529,530] mercury(II) sulfate[524,531] and mercury(II) phosphate[531] catalyze the addition of carboxylic acids to alkynes. Acetic anhydride in the presence of boron trifluoride etherate can also be effectively used in this reaction (equation 292).[521,522] Alkynoic acids undergo mercury-catalyzed cyclization to lactones (equation 293).[523,532,533]

Applications of the lactonization reaction are illustrated in the syntheses of obtusilactones,[530] benzamidopyranone,[529] oxaspirolactone,[527] diaxospirodione,[528] and morphohinones[526] (equations 294–298).

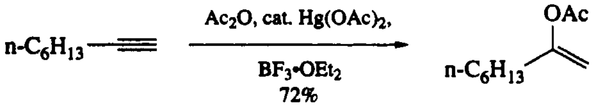
n-C6H13
Ac2O, cat. Hg(OAc)2,
BF3•OEt2
72%
OAc
n-C6H13

(292)

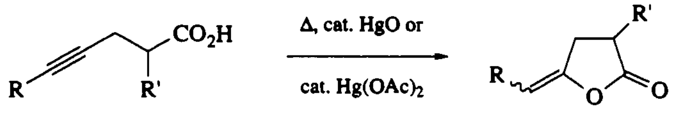
CO2H
R
R'
Δ, cat. HgO or
cat. Hg(OAc)2
R'
R
O
O

(293)

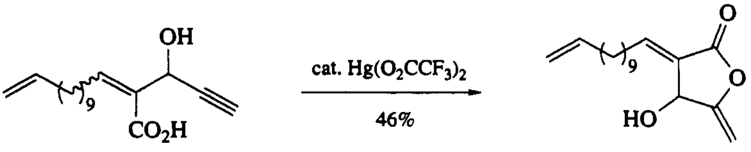
OH
9
CO2H
cat. Hg(O2CCF3)2
46%
O
9
O
HO

(294)

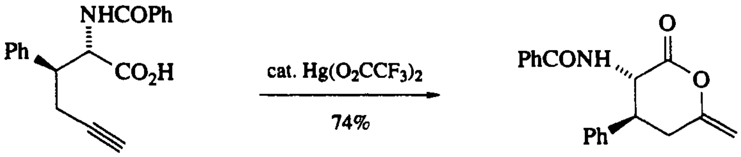
NHCOPh
Ph
CO2H
cat. Hg(O2CCF3)2
74%
O
PhCONH
O
Ph

(295)

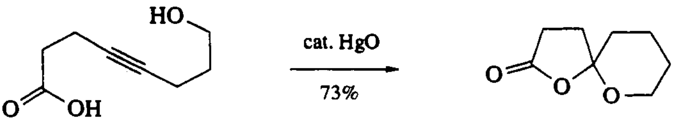
HO
O
OH
cat. HgO
73%
O
O
O

(296)

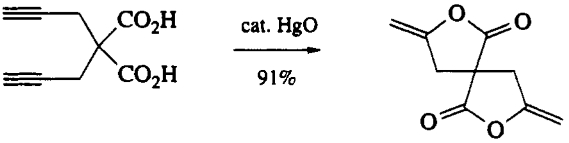
CO2H
CO2H
cat. HgO
91%
O
O
O
O

(297)

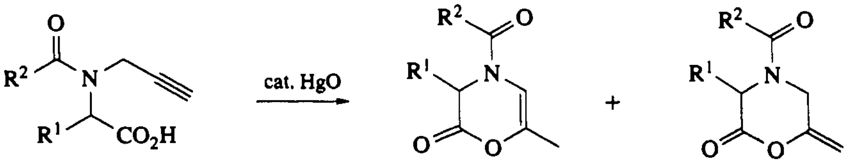
O
R2
N
R1
CO2H
cat. HgO
R2
O
R1
N
O
O
+
R2
O
R1
N
O
O

(298)

## 1.7.5 H—SR ADDITION

The addition of thiols to C—C multiple bonds may proceed *via* an electrophilic pathway involving ionic processes or a free radical chain pathway. The main emphasis in the literature has been on the free radical pathway, and little work exists on electrophilic processes.[534–537] The normal mode of addition of the relatively weakly acidic thiols is by the electrophilic pathway in accordance with Markovnikov's rule (equation 299). However, it is established that even the smallest traces of peroxide impurities, oxygen or the presence of light will initiate the free radical mode of addition leading to anti-Markovnikov products. Fortunately, the electrophilic addition of thiols is catalyzed by protic acids, such as sulfuric acid[538] and *p*-toluenesulfonic acid,[539] and Lewis acids, such as aluminum chloride,[540] boron trifluoride,[536] titanium tetrachloride,[540] tin(IV) chloride,[536,540] zinc chloride[536] and sulfur dioxide.[541]

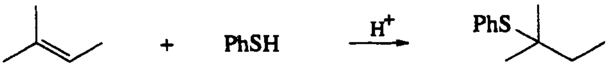

(299)

More acidic H—SR reagents, such as dialkyldithiophosphoric acids, may add to alkenes without the aid of a catalyst to yield exclusively the product of Markovnikov addition (Scheme 5).[542] The anti-Markovnikov product is obtained if the alkene used contains even slight amounts of peroxide impurities.[543]

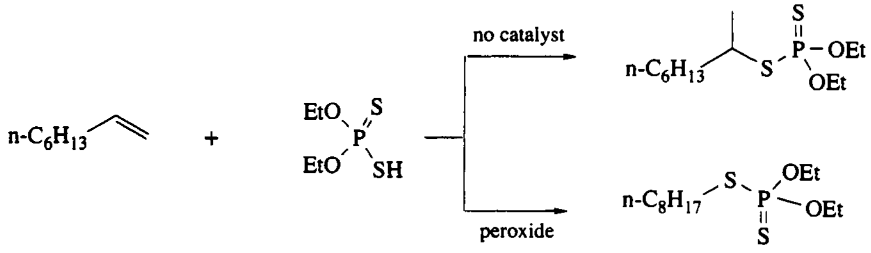

**Scheme 5**

The reaction of H—SR compounds with vinylic ethers and vinylic sulfides occurs more readily than with unactivated alkenes (equations 300 and 301).[544–547] An application of this reaction is found in the synthesis of organophosphorus insecticides.[548]

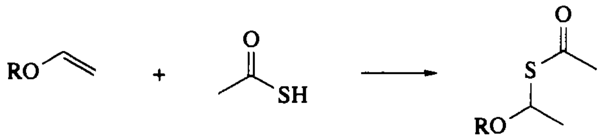

(300)

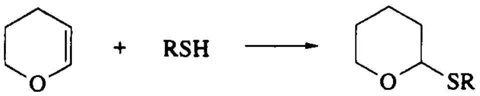

(301)

The intramolecular addition of thiols to alkenes provides a novel entry into heterocycles. One example of this is the reaction of hydrogen sulfide with various nonconjugated dienes to form six-membered rings (equation 302).[549,550]

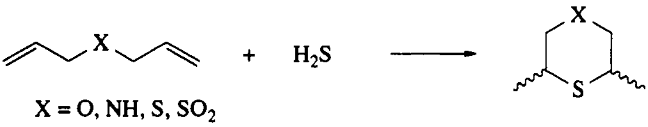

(302)

An unusual example of intramolecular thiol addition to double bonds is illustrated in the synthesis of spirothiazines.[551] The key step is described as an acid-catalyzed Markovnikov addition of a thiol to a double bond (Scheme 6).

The thiylation of conjugated dienes and allenes proceeds as expected. Thus, the acid-catalyzed reaction of thiols with 1,3-dienes affords the 1,4-addition product,[552] whereas the nucleophilic addition to allene provides the product arising from sulfur attack at the central carbon (equations 303 and 304).[553]

In contrast to the reaction of alkenes, the addition of H—SR reagents to alkynes generally requires higher temperatures and the presence of a base.[534] Terminal alkynes generally react to give anti-Markovnikov products. Substituted alkynes, however, will provide terminal alkenes if the reaction is carried out in sodium and liquid ammonia (equation 305).[554] Polyynes react with $H_2S$ to produce thiophenes (equation 306).[555]

Recently, it has been reported that sulfenic acids add readily to 1-alkynes to give α,β-unsaturated sulfoxides,[556] themselves useful for the synthesis of various cyclopentenones (equation 307).[557]

## 1.7.6 H—SeR ADDITION

There are several reviews that enumerate the many methods that effect the addition of H—SeR to C—C multiple bonds.[558,559] Of these, only a few methods involve true electrophilic additions of selenols to C—C multiple bonds. High yields of the Markovnikov product are reported when the relatively acidic

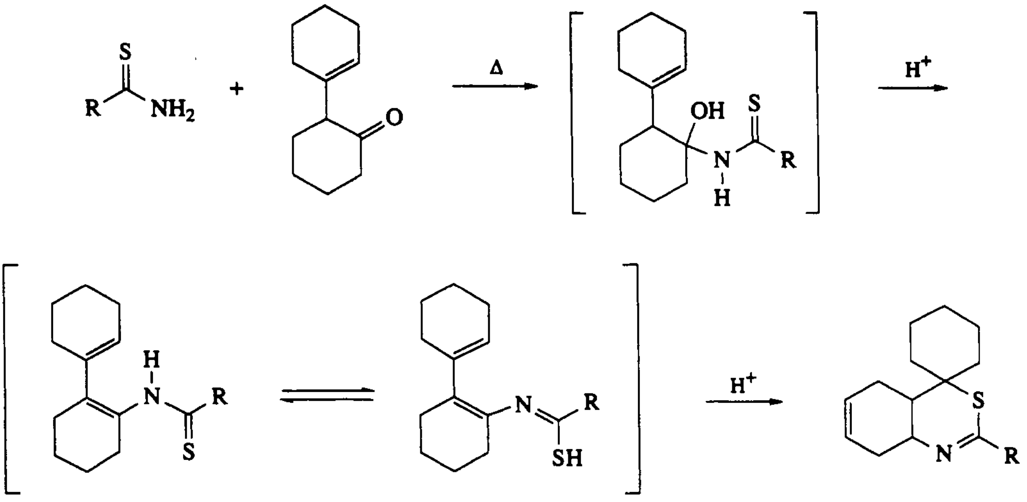

Δ
OH
N
H
R
S
NH₂
O
H⁺
SH

Scheme 6

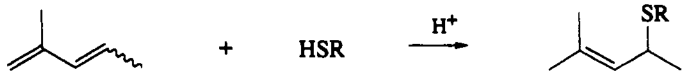

(303)

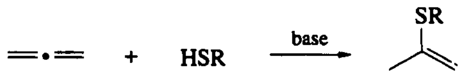

(304)

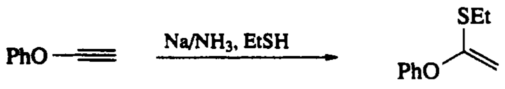

PhO
Na/NH₃, EtSH
SEt
PhO

(305)

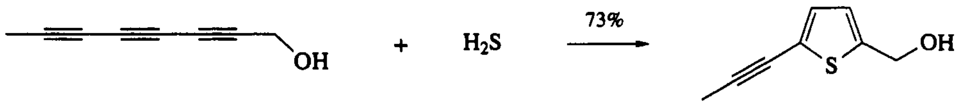

OH
+ H₂S
73%
S
OH

(306)

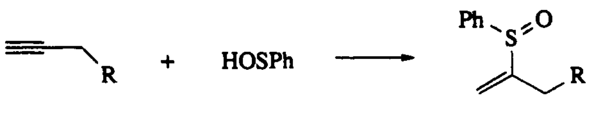

R
+ HOSPh
Ph
S
O
R

(307)

selenophenol reacts with vinylic sulfides, vinylic ethers or vinylic selenides (equation 308).[560] In the reaction with vinylic selenides, $BF_3{\cdot}OEt_2$ is required as a catalyst, because of the relatively nonnucleophilic double bond. Recently, it has been reported that the acid-catalyzed intramolecular selenol addition to double bonds affords spiroimino selenides (equation 309).[561]

An example of adding selenols to triple bonds in a Markovnikov fashion is the reaction of selenophenol and 1-hexyne (equation 310).[562]

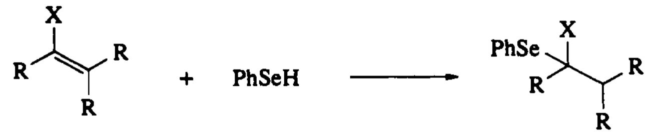

X
R
R
R
+ PhSeH
PhSe
X
R
R
R

X = OR, SR, SeR

(308)

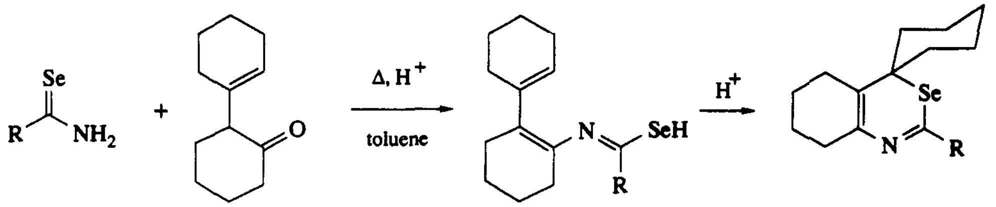

(309)

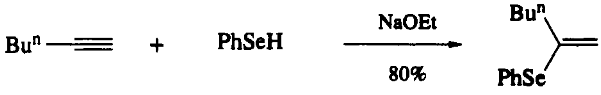

(310)

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# 1.8

# Electrophilic Addition of X—Y Reagents to Alkenes and Alkynes

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## 1.8.1 INTRODUCTION

Electrophilic addition of the halogens and related X—Y reagents to alkenes and alkynes has been a standard procedure since the beginning of modern organic chemistry.[1] *Anti* electrophilic bromination of such simple compounds as cyclohexene and (*E*)- and (*Z*)-2-butene, and variants of this reaction when water or methanol are solvents (formation of halohydrin or their methyl ethers, respectively), are frequently employed as prototype examples of stereospecific reactions in elementary courses in organic chemistry. A simple test for unsaturation involves addition of a dilute solution of bromine in $CCl_4$ to the compound in question: alkenes and alkynes discharge the color. Prior to the development of modern analytical methods, quantitative analysis of alkenes was performed by titration with bromine, thiocyanogen or related interhalogens. Spurred by interest in biologically active organofluorine compounds, methods have recently been developed for controlled addition of highly reactive elemental fluorine and fluorine-containing interhalogens to alkenes and alkynes. Regio- and stereo-specific addition of sulfenyl halides and reagents with nitrogen–halogen bonds to alkenes and alkynes have been used for many years for controlled introduction of sulfur and nitrogen, respectively, as well as for other more general synthetic purposes. More recently, electrophiles containing selenium and tellurium have been added to the list of synthetically useful reagents that undergo stereocontrolled addition to π-bonds.

Mechanistic details for these electrophilic addition reactions have been determined by Ingold, Bartlett, Tarbell, Roberts, Kimball, Grob and Winstein among others; these studies represent an important chapter in the history of organic chemistry.[1a,c,d,2] All of the above electrophilic reagents contain a polar or polarizable bond which is cleaved during the addition so that the rate-determining transition state has a net positive charge. The electrophile can add in a one-step process or in a two-step process involving a discrete cationic intermediate. Bond formation in the adduct can be preceded by formation of complexes of various types. Thus, reaction of adamantylideneadamantane ($Ad_2$) with bromine has been shown to involve formation of an initial charge-transfer complex ($Ad_2 \rightarrow Br_2$), followed by formation of two bromonium–polybromide complexes ($Ad_2Br^+ Br_n^-$; $n = 3$ or 5).[3] Regioselection in attachment of X—Y to an alkene can be described as Markovnikov or anti-Markovnikov (with reference to the more electrophilic part of X—Y) while stereoselection can be described as *syn* (X and Y add to the same side of the plane of the double bond) or *anti*. When the π-system has two distinct faces, configurational selectivity is also possible. In the case of a bicyclic alkene such as bicyclo[2.2.1]hept-2-ene the attack of the electrophile from the less hindered *exo* face is favored; on the other hand bicyclo[2.2.1]hepta-2,5-diene shows a preference for *endo* attack (Scheme 1).[4]

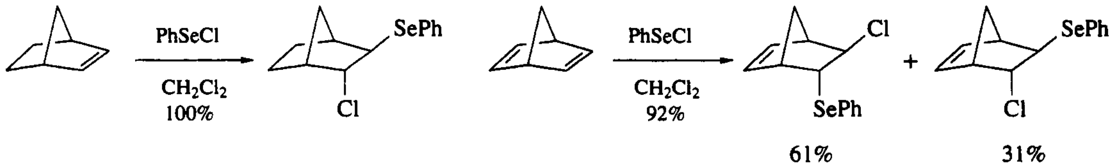

Scheme 1

The major focus in this chapter will be on synthesis, with emphasis placed on more recent applications, particularly those where regiochemistry and stereochemistry are precisely controlled. The reader is referred to the earlier reviews for full mechanistic information and details of historic interest. Electrophilic addition of X—Y to an alkene, where X is the electrophile, gives products with functionality Y β to the heteroatom X. Further transformations of X and/or Y provide the basis for diverse synthetic applications. These transformations include replacement of Y by hydrogen, elimination to form a π-bond (either including the carbon bonded to X or β to that carbon so that X is now in an allylic position), and nucleophilic or radical substitution. Representative examples of these synthetic methods will be given below. This chapter will include examples of heterocycles formed in one-pot reactions where the the initial alkene–electrophile adduct contains an electrophilic group that can react further. Examples of heterocycles formed in several steps from alkene–electrophile adducts will also be considered. Cases in which activation by an external electrophile directly results in addition of an internal heteroatom nucleophile are treated in Chapter 1.9 of this volume.

## 1.8.2 ELECTROPHILIC SULFUR, SELENIUM AND TELLURIUM

### 1.8.2.1 Sulfenyl Halides and Related Compounds

Early work on electrophilic addition of sulfur halides to alkenes stems from the development of bis(β-chloroethyl) sulfide ('mustard gas') as a chemical warfare agent. The original synthesis of mustard gas involved addition of sulfur dichloride (or $S_2Cl_2$) to ethylene according to the equation $2CH_2{=}CH_2 + SCl_2 \rightarrow (ClCH_2CH_2)_2S$. Electrophilic addition of sulfenyl compounds to alkenes and alkynes, which has been widely studied from a mechanistic standpoint,[1c,d,5] finds considerable utility in organic synthesis due to the regio- and stereo-selectivity of the addition, as well as the numerous options for subsequent replacement of the sulfur or vicinal substituent with other functional groups. The most common type of agents for electrophilic addition of sulfur to carbon–carbon multiple bonds are sulfenyl halides (RS—X, X = halogen). Other possibilities include RS—OY and RS—$NR_3^+$, discussed following the halides, Y—S—X (Y is also a leaving group), and $R_2S^+$—X, discussed under the heading 'sulfonium salts' in Section 1.8.2.2.

Representative examples of addition of sulfenyl halides to alkenes include the *anti* addition of ethanesulfenyl chloride to cyclopentene and dihydropyran (Scheme 2)[6] and the diastereoselective addition of benzenesulfenyl chloride to optically active bornyl propenoates as in equation (1).[7] The chlorine can be replaced with retention of stereochemistry by other nucleophiles such as nitrogen (see below), hydrogen (as hydride), oxygen or carbon. Examples of the latter process, termed carbosulfenylation, are shown in Scheme 3,[8] where the regioselectivity is 85% and the diastereofacial selectivity is >99%, and Scheme 4.[9] In this latter sequence, acetonylation and allylation are accomplished using a silyl enol ether or allyltrimethylsilane as the carbon nucleophiles using catalytic zinc bromide. White and coworkers used the carbosulfenylation procedure in an enantioselective total synthesis of (–)-monic acid C (Scheme 5).[10] Here the triphenylmethanesulfenyl group undergoes spontaneous elimination. Replacement of the chlorine by oxygen is used in the synthesis of a 2α-glycoside of *N*-acetylneuraminic acid (Scheme 6).[11] In the final step the phenylthio group is removed by treatment with tri-*n*-butyltin hydride.

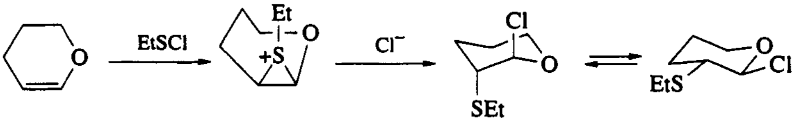

**Scheme 2**

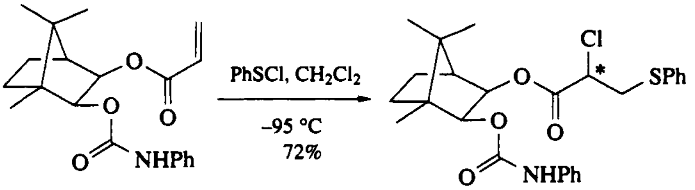

(1)

93:7 ratio of diastereomers

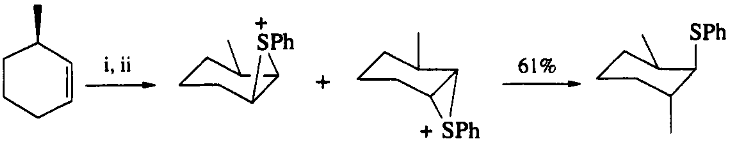

i, PhSCl; ii, $Me_2Zn$, 0.2 equiv. $TiCl_4$, $CH_2Cl_2$

**Scheme 3**

Thiiranes can be formed directly and stereospecifically from 1,2-disubstituted alkenes by addition of trimethylsilylsulfenyl bromide, formed at –78 °C from reaction of bromine with bis(trimethylsilyl) sulfide (Scheme 7).[12] A two-step synthesis of thiiranes can be achieved by addition of succinimide-*N*-sulfenyl chloride or phthalimide-*N*-sulfenyl chloride to alkenes followed by lithium aluminum hydride cleavage of the adducts (Scheme 8).[13] Thiaheterocycles can also be formed by intramolecular electrophilic addition of sulfenyl chlorides to alkenes, *e.g.* as seen in Schemes 9[14] and 10.[15] Related examples involving sulfur dichloride are shown in Schemes 11[16] and 12.[17] In the former case addition of sulfur dichloride to 1,5-cyclooctadiene affords a bicyclic dichloro sulfide *via* regio- and stereo-specific intramolecular addition of an intermediate sulfenyl chloride. Removal of chlorine by lithium aluminum hydride reduction affords 9-thiabicyclo[3.3.1]nonane, which can be further transformed into bicyclo[3.3.0]oct-1,5-ene.[16]

Addition of a sulfenyl chloride to an alkene in the presence of silver fluoride affords β-fluoro sulfides, as shown in equation (2).[18] The same *trans* adducts can also be prepared from the sulfenyl chloride adducts and silver fluoride. An alternative procedure for the formal addition of methanesulfenyl fluoride to alkenes involves the use of dimethyl(methylthio)sulfonium tetrafluoroborate and triethylamine tris(hydrofluoride) as in equation (3).[19]

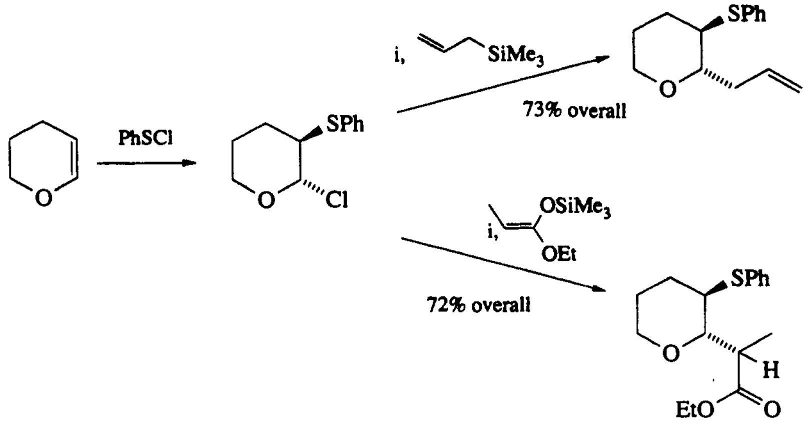
PhSCl
SPh
Cl
O
i,
SiMe$_3$
73% overall
SPh
O
i,
OSiMe$_3$
OEt
72% overall
SPh
O
H
EtO
O

i, $ZnBr_2$ (0.05 equiv.), $CH_2Cl_2$, 20 °C

Scheme 4

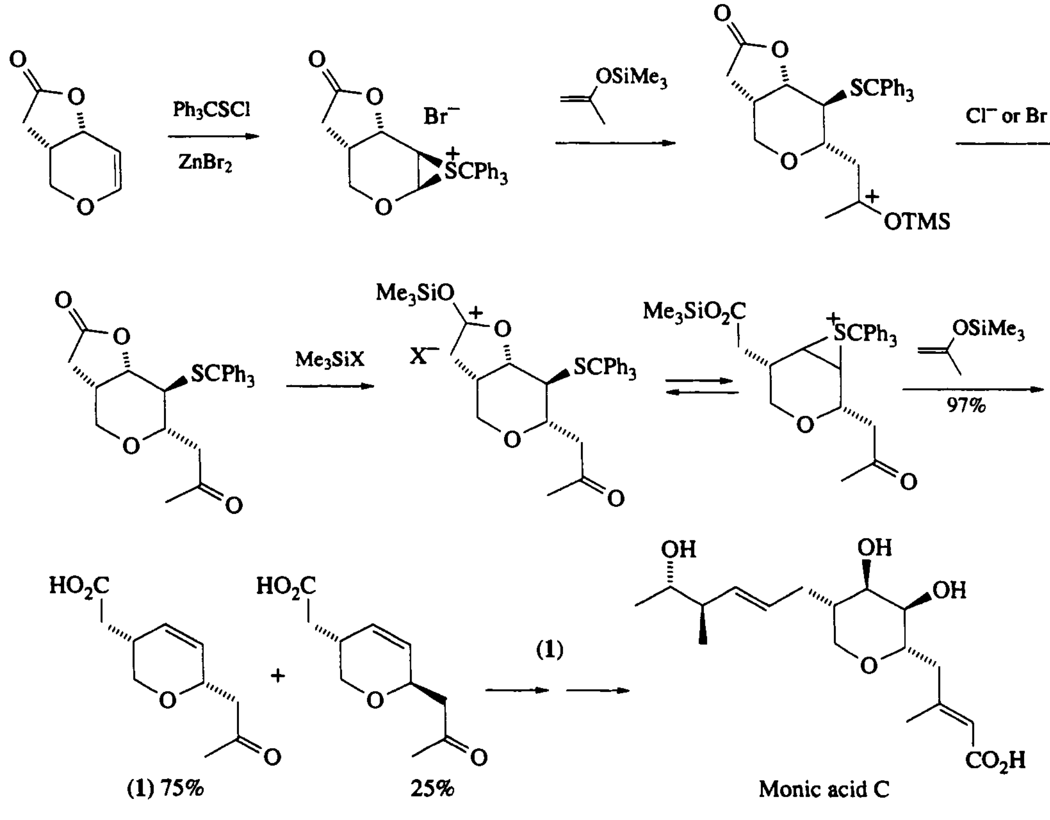
O
O
O
Ph$_3$CSCl
ZnBr$_2$
O
O
Br$^-$
+
SCPh$_3$
O
OSiMe$_3$
O
O
SCPh$_3$
O
+
OTMS
Cl$^-$ or Br$^-$
O
O
SCPh$_3$
O
O
Me$_3$SiX
Me$_3$SiO
+
O
X$^-$
SCPh$_3$
O
O
Me$_3$SiO$_2$C
+
SCPh$_3$
O
O
OSiMe$_3$
97%
HO$_2$C
O
O
+
HO$_2$C
O
O
(1)
OH
OH
OH
O
CO$_2$H
(1) 75%
25%
Monic acid C

i, overall, $Ph_3CSCl$, $CH_2{=}C(Me)OSiMe_3$, cat. $ZnBr_2$, $CH_2Cl_2$, −78 °C, 15 h

Scheme 5

The groups of Trost and coworkers and Caserio and coworkers independently developed procedures for azasulfenylation. Caserio reported that when alkenes are treated with a sulfenamide such as $MeSNMe_2$ in the presence of the Meerwein reagent trimethyloxonium tetrafluoroborate, azasulfenylation of the alkene is observed, presumably *via* the thioammonium ion $MeSNMe_3^+$ (equation 4).[20] Boron trifluoride etherate can also serve as a catalyst for addition of sulfenamides to alkenes. The adduct stereochemistry is strictly *anti* as established by treatment of the dihydropyran methanesulfenyl chloride adduct (see Scheme 2) with $AgBF_4$ followed by trimethylamine.

Cycloazasulfenylation (or 'sulfenocycloamination') can be achieved by addition of benzenesulfenyl chloride to an alkene containing a remote nitrogen followed by treatment of the β-chloro sulfide adduct

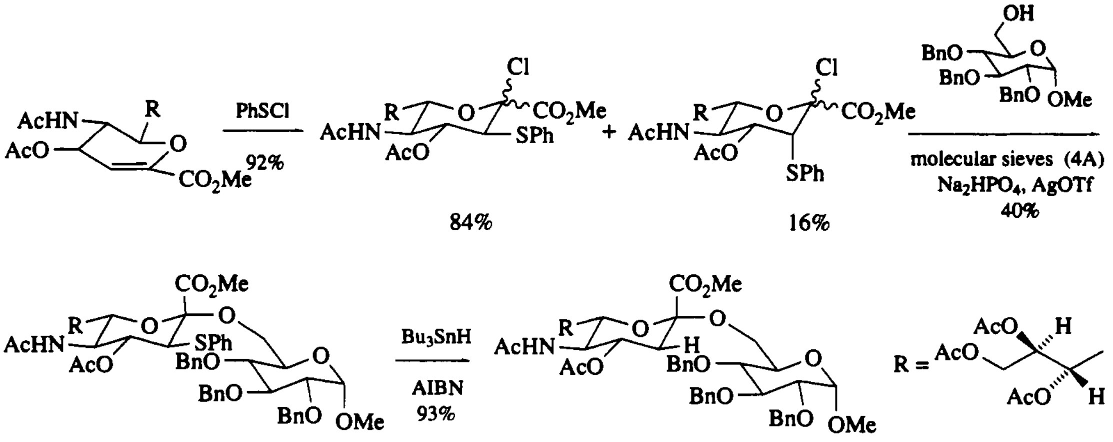
PhSCl
92%
84%
16%
molecular sieves (4A)
Na₂HPO₄, AgOTf
40%
Bu₃SnH
AIBN
93%
R =

**Scheme 6**

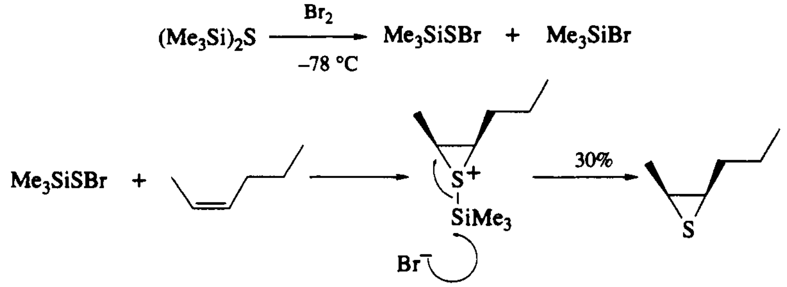
(Me₃Si)₂S
Br₂
−78 °C
Me₃SiSBr + Me₃SiBr
Me₃SiSBr +
SiMe₃
Br⁻
30%

**Scheme 7**

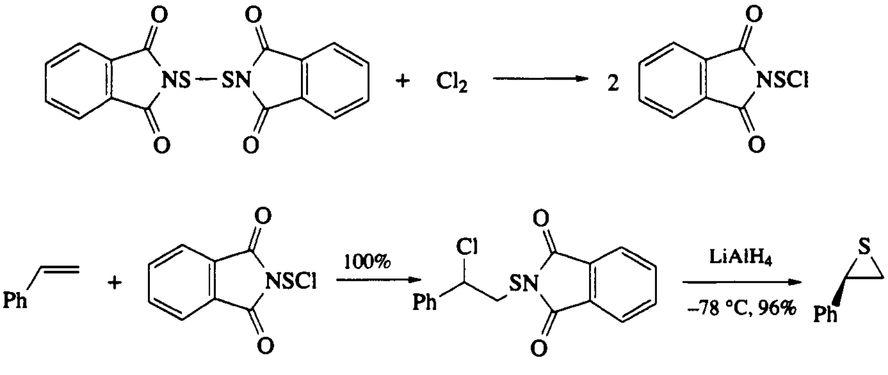
+ Cl₂
2
100%
LiAlH₄
−78 °C, 96%

**Scheme 8**

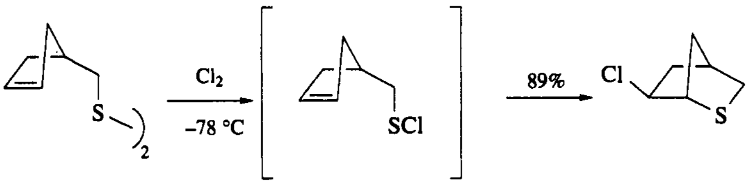
Cl₂
−78 °C
SCl
89%
Cl

**Scheme 9**

with potassium carbonate/sodium iodide (Scheme 13).[21] The phenylthio group can be replaced with hydrogen using Raney nickel, or can be oxidized to a sulfoxide and benzenesulfenic acid eliminated by heating. These overall procedures have been used in the synthesis of the pyrrolizidine alkaloids retronecine and turneforcidine (Scheme 14)[22] as well as β-lactam antibiotics (Scheme 15).[23] If alkenes containing a remote nitrogen are treated with the methylsulfenylium equivalent bis(methylthio)methylsulfonium

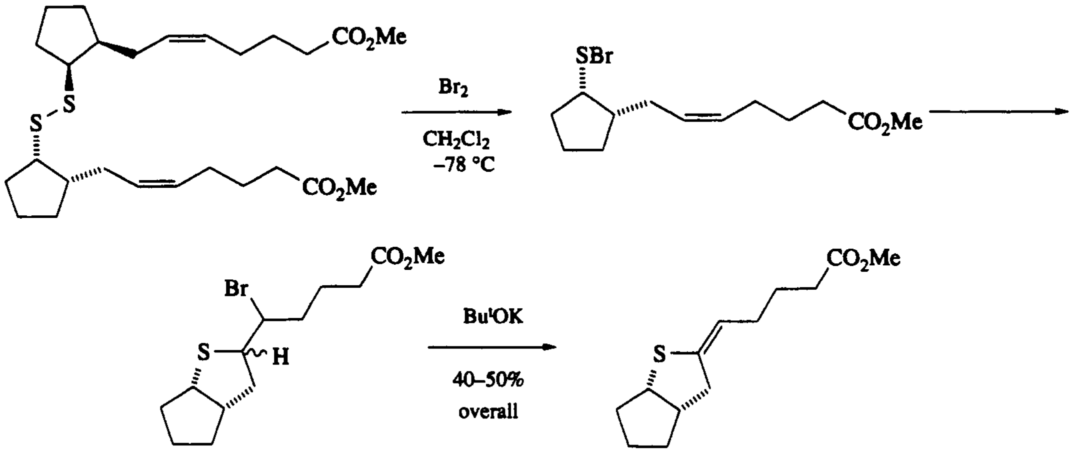
CO2Me
CO2Me
Br2
CH2Cl2
–78 °C
SBr
CO2Me
CO2Me
Br
H
ButOK
40–50%
overall
CO2Me

**Scheme 10**

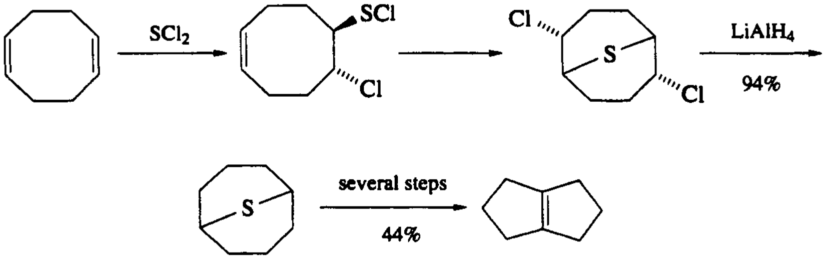
SCl2
SCl
Cl
Cl
Cl
LiAlH4
94%
several steps
44%

**Scheme 11**

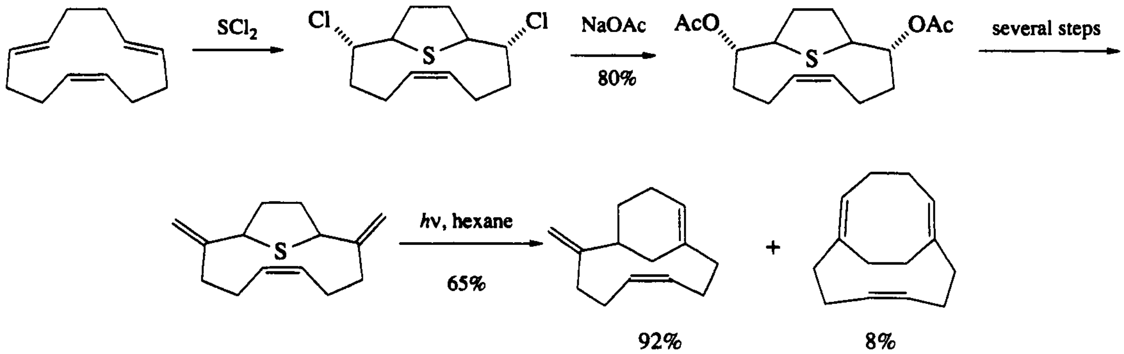
SCl2
Cl
Cl
NaOAc
80%
AcO
OAc
several steps
hv, hexane
65%
92%
8%

**Scheme 12**

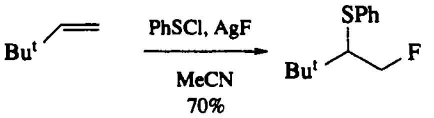
But
PhSCl, AgF
MeCN
70%
SPh
But
F

(2)

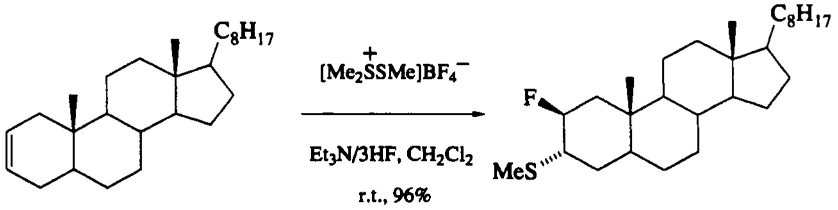
C8H17
[Me2S+SMe]BF4−
Et3N/3HF, CH2Cl2
r.t., 96%
F
MeS
C8H17

(3)

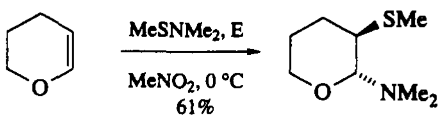
MeSNMe2, E
MeNO2, 0 °C
61%
SMe
NMe2
O

(4)

$E = Me_2O{\bullet}BF_3, Me_3O^+BF_4^-$

tetrafluoroborate [$(MeS)_2SMe^+$ $BF_4^-$], instead of benzenesulfenyl chloride, nitrogen heterocycles can be isolated in one step;[24] these types of reactions are treated in Chapter 1.9 of this volume.

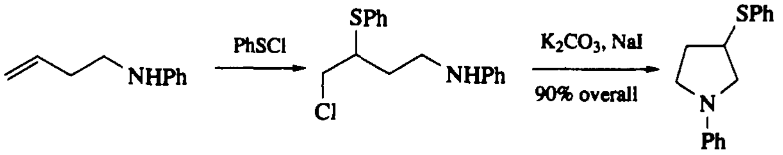
NHPh
PhSCl
SPh
Cl
NHPh
K2CO3, NaI
90% overall
SPh
N
Ph

Scheme 13

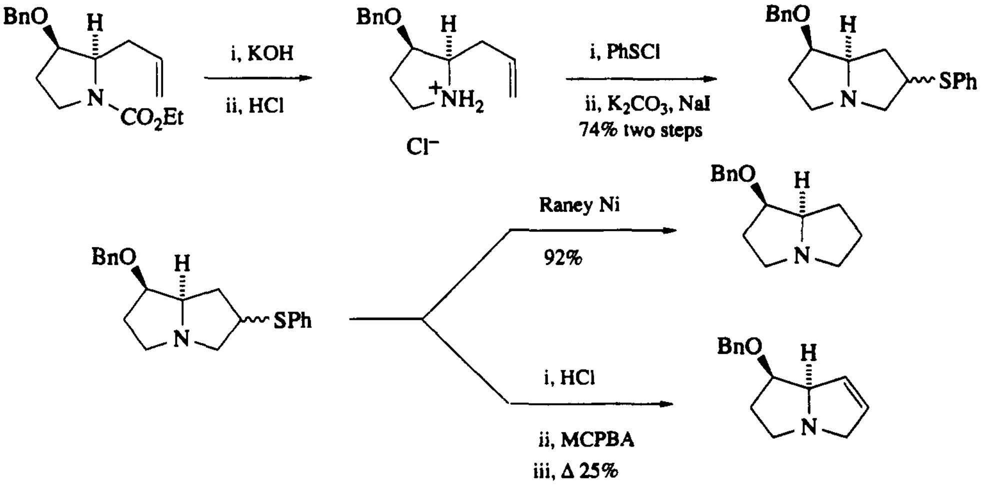
BnO
H
N
CO2Et
i, KOH
ii, HCl
+NH2
Cl−
i, PhSCl
ii, K2CO3, NaI
74% two steps
SPh
Raney Ni
92%
i, HCl
ii, MCPBA
iii, Δ 25%

Scheme 14

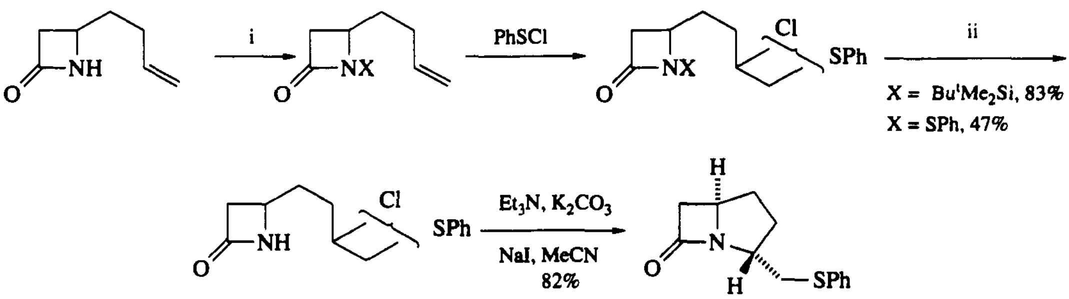
O
NH
i
NX
PhSCl
Cl
SPh
ii
X = Bu<sup>t</sup>Me2Si, 83%
X = SPh, 47%
Et3N, K2CO3
NaI, MeCN
82%
H
N
SPh

X = SPh: i, PhSCl; ii, $NaBH_4$, MeOH

X = $Bu^tMe_2Si$: i, $Et_3N$, $Bu^tMe_2SiCl$, DMF; ii, TBAF

Scheme 15

Intramolecular electrophilic addition of a sulfenate ester (RS—OR′) to a carbon–carbon double bond (intramolecular oxosulfenylation) is indicated in the work of Block and Wall (Scheme 16).[25] Zefirov and coworkers find that arenesulfenamides can be activated with sulfur trioxide to give arenesulfenyl sulfamates, which react with alkenes such as cyclohexene giving good yields of the oxosulfenylated *trans* 1,2-adducts, as shown in Scheme 17.[26] Sulfenyl trifluoro- or trichloro-acetates, prepared from reaction of thiosulfinates with the corresponding trihaloacetic anhydrides, give *trans* 1,2-diadducts with a variety of alkenes (Scheme 18).[27]

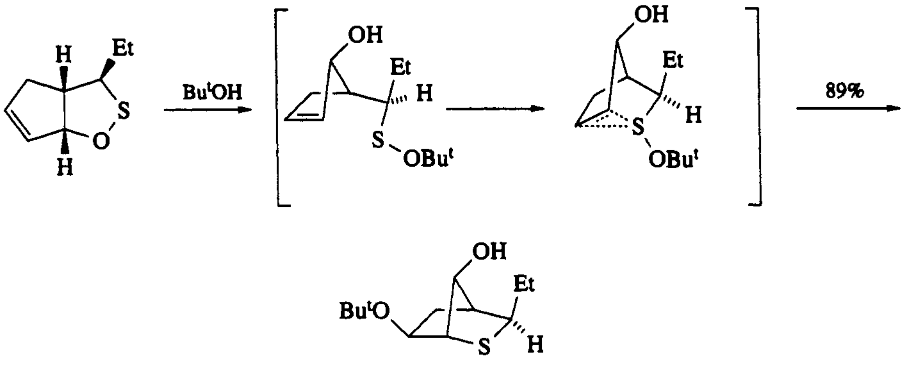

**Scheme 16**

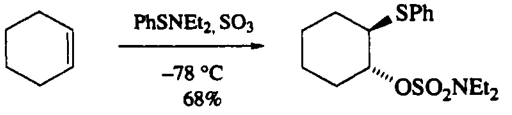

$PhSNEt_2 + SO_3 \longrightarrow PhSOSO_2NEt_2$

**Scheme 17**

$3\,MeS(O)SMe + (CX_3CO)_2O \longrightarrow 2\,MeSSMe + 2\,MeS(O)OC(O)CX_3$ *via* $MeSOC(O)CX_3$

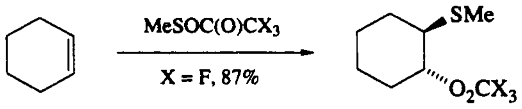

**Scheme 18**

An example of addition of sulfenyl halides to an alkyne is shown in Scheme 19[28] where the initial *trans* adduct of 1,4-dichlorobut-2-yne is further transformed by treatment with base or aluminum amalgam. Another example involves boron trifluoride-catalyzed addition of an arenesulfenamide to alkynes in the presence of acetonitrile, giving β-acetamidinovinyl sulfides (Scheme 20),[29] which can be hydrolyzed to β-keto phenyl sulfides.[30]

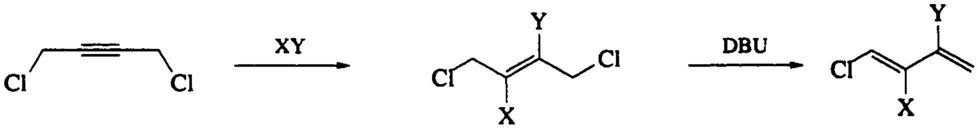

| *XY* | (2) | |
|---|---|---|
| PhSCl | 98 % | 85% |
| PhSBr | 80 | 63 |
| PhSeCl | 100 | 46 |
| PhSeBr | 93 | 68 |
| $Br_2$ | 97 | 85 |
| $I_2$ | 86 | 81 |

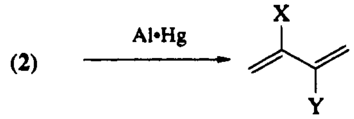

| *XY* | *Yield* (%) |
|---|---|
| PhSCl | 68 |
| PhSBr | 40 |
| PhSeCl | 75 |
| PhSeBr | 76 |

**Scheme 19**

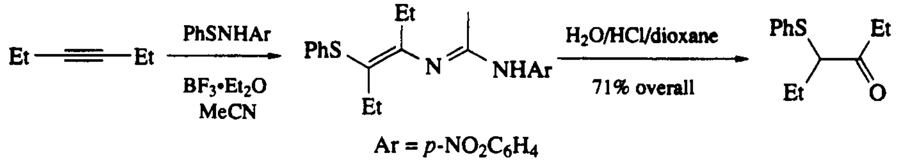

Scheme 20

## 1.8.2.2 Sulfonium Salts

As seen above, β-chloroalkyl sulfides are generally prepared by addition of sulfenyl chlorides to alkenes. A new procedure involves reaction of alkenes with dimethyl sulfoxide activated with phenyl dichlorophosphate or phosphorus oxychloride (Scheme 21).[31] In this latter reaction the addition proceeds in a completely regiospecific manner with the methylthio group being added to the carbon bearing the greater number of hydrogen atoms. Exclusive *trans* addition is observed with simple cycloalkenes. It is suggested that the active electrophile is the oxysulfonium salt $[Me_2SOPO(R)Cl]^+$ $Cl^-$ (R = OPh or Cl). When the double bond is conjugated with a benzene ring, double addition of the methylthio group occurs (Scheme 21); dimethyl sulfide is suggested to be the source of the second methylthio group. In the above procedures chlorotrimethylsilane may be used in place of the phosphorus reagents to activate dimethyl sulfoxide.[32] Double addition of the methylthio (or other alkylthio groups) to unactivated alkenes can be achieved using the combination of dimethyl disulfide (or other dialkyl disulfides) and boron trifluoride etherate (equation 5).[33] Chlorosulfonium salts have been found to add to alkenes, giving the β-chloroalkylsulfonium salt adducts in good yield (Scheme 22).[34]

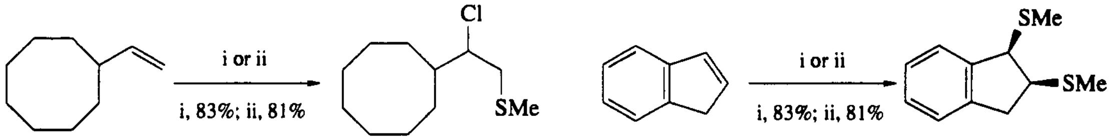

i, $Me_2SO$ (10 equiv.), $PhOP(O)Cl_2$ (5 equiv.), $CH_2Cl_2$, –20 to 20 °C; ii, $Me_2SO$ (6 equiv.), $POCl_3$ (3 equiv.), $CH_2Cl_2$, –20 to 20 °C

Scheme 21

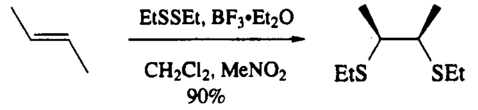

(5)

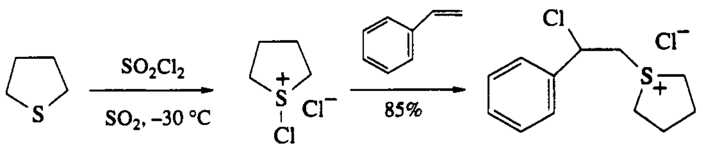

Scheme 22

An alternative route from alkenes to 2-azasulfides reported by the groups of Caserio and Trost involves addition of a thiosulfonium salt, *e.g.* dimethyl(methylthio)sulfonium tetrafluoroborate ($MeSSMe_2^+$ $BF_4^-$), followed by treatment of the resultant thiosulfenylated adduct with an amine or other nitrogen nucleophiles (Schemes 23[20] and 24).[35] Trost reports that the addition of the thiosulfonium salt can be followed by addition of an oxygen nucleophile, such as acetate, or a carbon nucleophile, such as cyanide, effecting oxosulfenylation and cyanosulfenylation, respectively (Scheme 25).[36]

The dimethyl sulfide–sulfur trioxide complex also functions as a thiosulfenylating agent, *e.g.* converting 1,5-cyclooctadiene into a single adduct, presumably of *trans* stereochemistry (Scheme 26),[37] giving the *trans* adduct of 2-butyne (equation 6),[38] and 1,4-adducts with acyclic 1,3-dienes (Scheme 26).[37] With cyclopentadiene both 1,2- and 1,4-addition occurs (Scheme 26).[37]

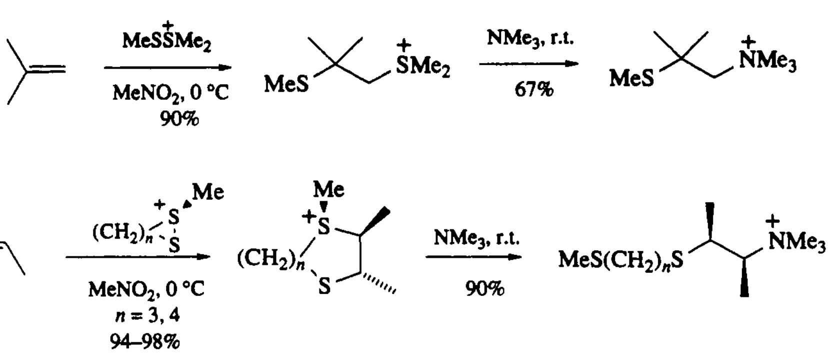
MeS$\overset{+}{S}$Me$_2$
MeNO$_2$, 0 °C
90%
MeS
$\overset{+}{S}$Me$_2$
NMe$_3$, r.t.
67%
MeS
$\overset{+}{N}$Me$_3$
(CH$_2$)$_n$
Me
MeNO$_2$, 0 °C
$n$ = 3, 4
94–98%
NMe$_3$, r.t.
90%
MeS(CH$_2$)$_n$S
$\overset{+}{N}$Me$_3$

**Scheme 23**

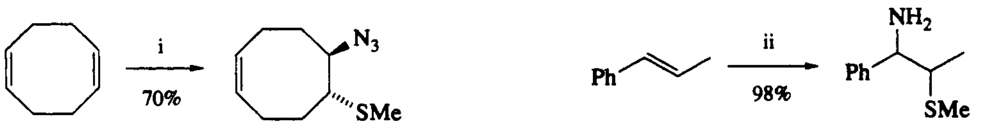
i
70%
N$_3$
SMe
Ph
ii
98%
NH$_2$
Ph
SMe

i, $Me_2\overset{+}{S}(SMe)\ BF_4^-$, $NaN_3$, $MeNO_2$, $Me_2S$; ii, $Me_2\overset{+}{S}(SMe)\ BF_4^-$, $NH_3$, $CH_2Cl_2$, $Me_2S$

**Scheme 24**

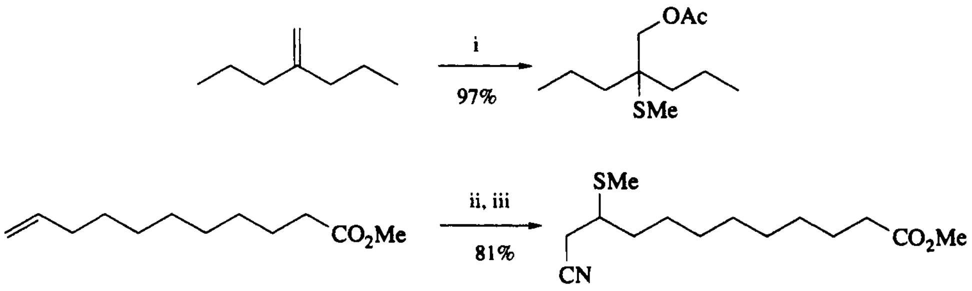
i
97%
OAc
SMe
CO$_2$Me
ii, iii
81%
SMe
CN
CO$_2$Me

i, $Me_2\overset{+}{S}(SMe)\ BF_4^-$, KOAc, MeCN; ii, $Me_2\overset{+}{S}(SMe)\ BF_4^-$, NaCN, $HBF_4$, $MeNO_2$; iii, MeOH

**Scheme 25**

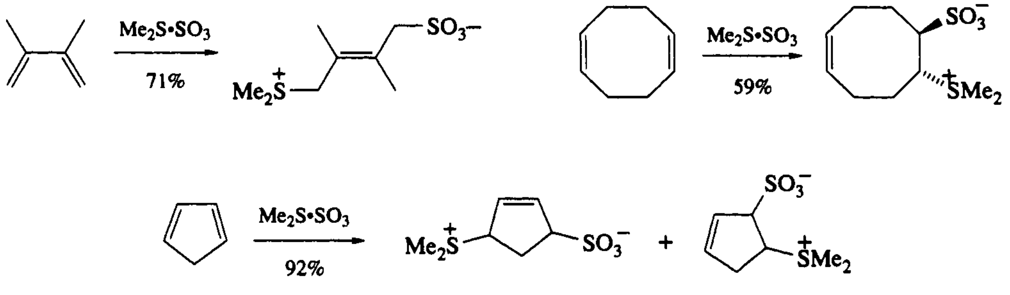
Me$_2$S•SO$_3$
71%
SO$_3^-$
Me$_2\overset{+}{S}$
Me$_2$S•SO$_3$
59%
SO$_3^-$
$\overset{+}{S}$Me$_2$
Me$_2$S•SO$_3$
92%
Me$_2\overset{+}{S}$
SO$_3^-$
+
SO$_3^-$
$\overset{+}{S}$Me$_2$

**Scheme 26**

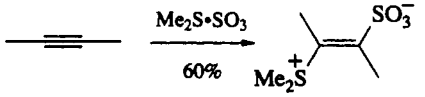 (6)
Me$_2$S•SO$_3$
60%
SO$_3^-$
Me$_2\overset{+}{S}$

### 1.8.2.3 Selenenyl Halides, Pseudohalides and Related Compounds.

The reaction of electrophilic selenium reagents with alkenes and alkynes is the subject of several recent reviews[39,40] and mechanistic studies.[41] The majority of electrophilic selenium reactions involve selenenic ($Se^{II}$) compounds. Reactions of $Se^{IV}$ electrophiles, which have been less studied than their $Se^{II}$ counterparts, are considered in Section 1.8.2.4. Aryl, rather than alkyl, selenium derivatives are favored for electrophilic reactions because of the less offensive odors, increased stability, lower volatility and, in general, greater ease of handling of the former, compared to the latter, compounds. Diphenyl diselenide (PhSeSePh), a commercially available crystalline solid, can be readily converted into benzeneselenenyl bromide (PhSeBr) or chloride (PhSeCl) by treatment with bromine or chlorine, respectively. These latter two reagents can in turn be converted to such useful $Se^{II}$ electrophiles such as PhSeOAc, PhSeSCN, $PhSeN_3$, PhSeCN and $PhSeSO_2Ar$. Addition of selenenyl halides to alkenes forming β-halo selenides bears a superficial resemblance to addition of sulfenyl halides to alkenes, although there are significant differences in the reactivity, nature of the intermediates and the regioselectivity of product formation. The 1,2-additions of ArSeX to alkenes are generally highly *anti* stereospecific, consistent with the intermediacy of selenium-bridged intermediates (episelenuranes and seleniranium or episelenonium ions). The regiochemistry of addition varies with the temperature and solvent with anti-Markovnikov adducts favored at low temperatures (–78 °C) where kinetic control predominates and the Markovnikov adducts favored at room temperature under thermodynamic control. When ArSeX reacts with alkenes in the presence of other nucleophiles the latter are often incorporated in the β-position, instead of the halide ion. In cases where there exist two distinct faces of the π-system, attack of ArSeX is favored from the less sterically congested side of the double bond (configurational selectivity, *e.g. exo versus endo* attack in bicyclic systems; Scheme 1).

Regio- and stereo-specific addition of methaneselenenyl bromide in acetic acid to estra-1,3,5(10),16-tetraen-3-ol gave 17α-(methylseleno)estra-1,3,5(10)-triene-3,16β-diol 16-acetate in 80% yield (equation 7).[42] The latter compound and related seleno analogs of estradiol are of interest for biological studies using radioactive $^{75}Se$. Regiospecific addition of benzeneselenenyl bromide to ethyl vinyl ether followed by treatment of the adduct with an allylic alcohol affords mixed acetals (Scheme 27).[43] These on oxidation and heating then give esters of δ,γ-unsaturated acids by sequential selenoxide elimination and Claisen rearrangement. A related alkoxyselenation process involving regiospecific addition of benzeneselenenyl bromide to 3,4-dihydro-2*H*-pyrans in the presence of alcohols followed by oxidative deselenation gives cyclic α,β-unsaturated acetals, which can be further transformed into hexopyranose derivatives or the C-glycoside pseudomonic acid C.[44] The phenylseleno group in 3,4-dihydro-2*H*-pyran alkoxyselenation adducts can also be removed by reductive deselenation with triphenyltin hydride. This latter procedure has been successfully employed in efficient syntheses of β-2-deoxyglycosides.[45] The useful homologating reagent phenylselenoacetaldehyde can be prepared by regiospecific addition of phenylselenenyl bromide to ethyl vinyl ether in the presence of ethanol, followed by hydrolysis (Scheme 28).[46]

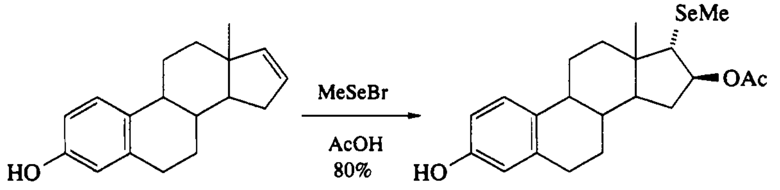

(7)

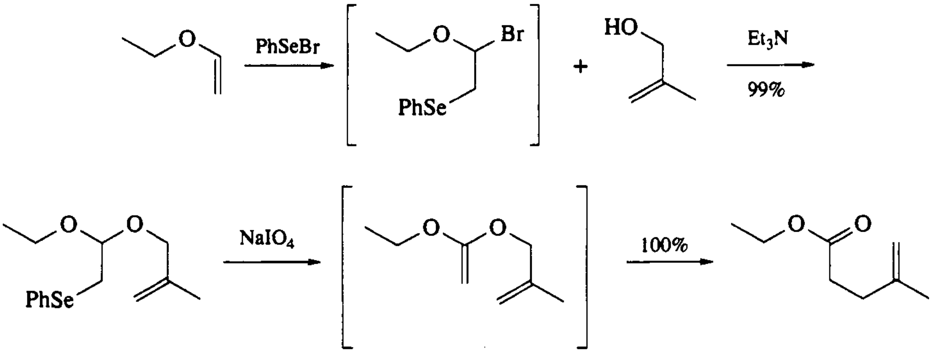

Scheme 27

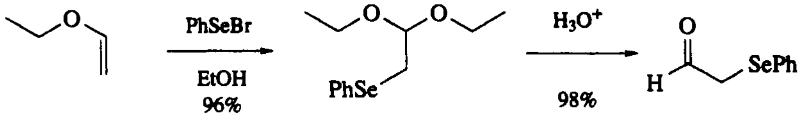

Scheme 28

Addition of benzeneselenenyl chloride to conjugated dienes in methanol as solvent followed by treatment of the resultant methoxyselenation product with LDA affords 1-phenylseleno-1,3-dienes.[47] Regiospecific addition of benzeneselenenyl chloride to allylic alcohols is the key step in a 1,3-enone transposition sequence (Scheme 29).[49] *cis*-Vicinal dichlorides can be prepared from the corresponding alkenes by a process involving *trans* addition of phenylselenenyl chloride followed by treatment with chlorinating agents, ultimately leading to *trans* displacement of the seleno moiety (Scheme 30).[50] Chlorination with $SO_2Cl_2$ of the β-chloroalkyl phenyl selenides derived from terminal alkenes, followed by hydrolysis to selenoxide, followed by elimination leads instead to 2-chloro-1-alkenes (Scheme 31).[51] Arylselenenyl chloride, generated *in situ* from aryl diselenides and NCS, are effective as catalysts for chlorination of alkenes with NCS to give principally a rearranged allylic chloride (Scheme 32).[52] Addition of phenylselenenyl chloride and silver trifluoroacetate to nitroalkenes results in regiospecific formation of the phenylseleno–trifluoroacetoxy adducts which can be converted to nitroallylic alcohols (Scheme 33).[53] In a related example, successive addition of phenylselenenyl chloride and silver crotonate to alkenes or cycloalkenes affords β-phenylseleno crotonates which give γ-lactones upon reaction with triphenyltin hydride (Scheme 34).[54]

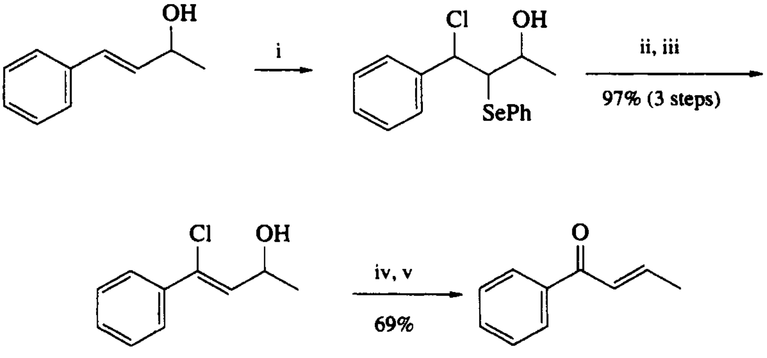

i, PhSeCl, $CH_2Cl_2$, −78 °C; ii, $O_3$, $CH_2Cl_2$; iii, $Et_2NH$, $CH_2Cl_2$, Δ; iv, AcCl, pyridine, $Et_2O$; v, $Hg(OAc)_2$, TFA

Scheme 29

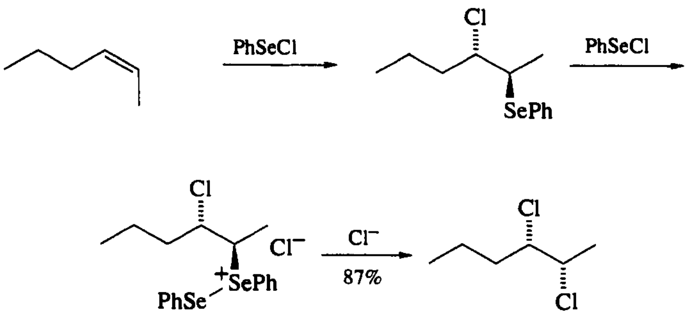

Scheme 30

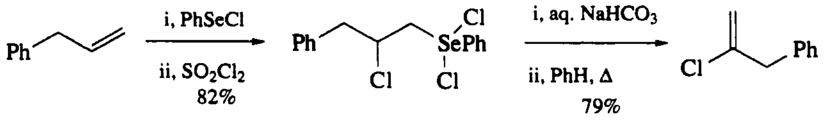

Scheme 31

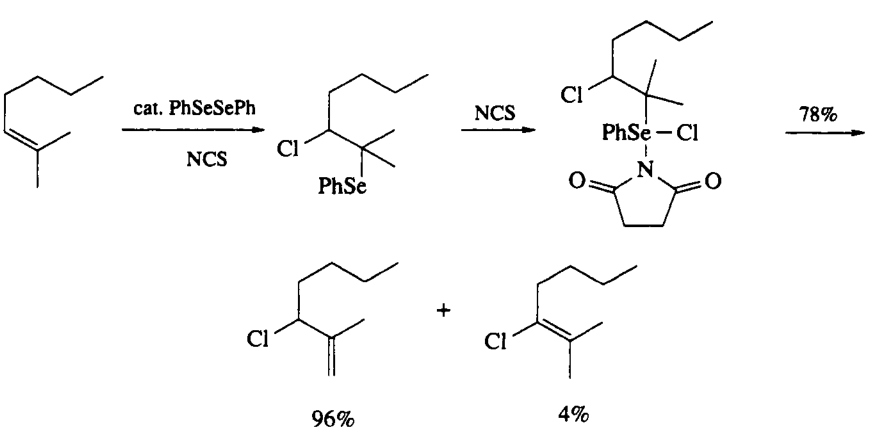
cat. PhSeSePh
NCS
Cl
PhSe
NCS
Cl
PhSe – Cl
N
O
O
78%
Cl
+
Cl
96%
4%

Scheme 32

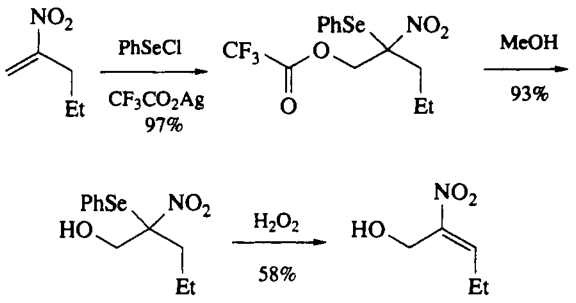
NO2
Et
PhSeCl
CF3CO2Ag
97%
PhSe
NO2
CF3
O
O
Et
MeOH
93%
PhSe
NO2
HO
Et
H2O2
58%
HO
NO2
Et

Scheme 33

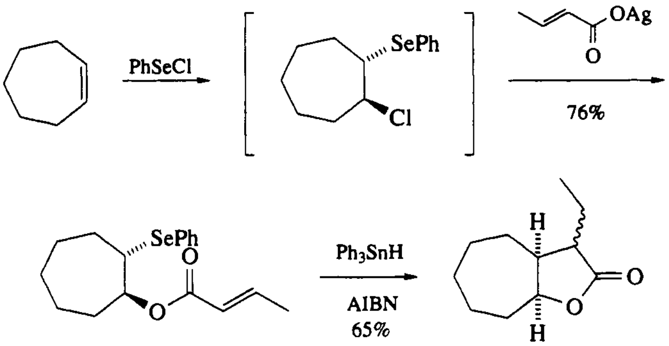
PhSeCl
SePh
Cl
OAg
O
76%
SePh
O
O
Ph3SnH
AIBN
65%
H
O
O
H

Scheme 34

Phenyl selenocyanate, PhSeCN, adds regio- and stereo-specifically to nucleophilic alkenes such as enamines and ketene acetals giving β-phenylselenocarbonitriles by a process termed vicinal cyanoselenenylation.[55] Phenyl selenocyanate also adds to simple alkenes in the presence of Lewis acids.[55] In alcohol in the presence of metal salts β-alkoxyalkyl phenyl selenides are formed.[56] Benzeneselenenyl thiocyanate, PhSeSCN, undergoes Markovnikov addition to alkenes affording either the β-phenylseleno thiocyanate or isothiocyanate, depending on the alkene.[57] Isothiocyanate formation dominates when mercury(II) salts are present.[58]

*Se*-Phenyl areneselenosulfonates, $PhSeSO_2Ar$, add to alkenes to give β-phenylseleno sulfones (selenosulfonation). The reaction may be conducted in the presence of a Lewis acid such as $BF_3{\cdot}Et_2O$ to give regioselectivity or regiospecifically the adduct of Markovnikov orientation arising from stereospecific ionic *anti* addition. Alternatively, the addition may be thermally induced to afford anti-Markovnikov products generated by a nonstereospecific free radical reaction.[59] Reaction of alkenes such as cyclooctene with phenylselenenyl chloride in the presence of sodium azide leads to the formation of phenylselenenyl azide which adds stereospecifically to the double bond (equation 8).[60] In a similar manner alkenes can be nitroselenated using a mixture of phenylselenenyl chloride and silver nitrite[53] or cyanamidoselenated using *N*-phenylselenophthalimide and cyanamide.[61]

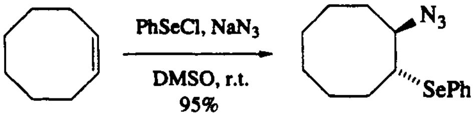
PhSeCl, $NaN_3$
DMSO, r.t.
95%
$N_3$
SePh

(8)

Addition of a selenenyl halide to an alkyne takes a course analogous to that of the sulfenyl halide, as seen in the reaction of 1,4-dichlorobut-2-yne with PhSeCl or PhSeBr (Scheme 19).[28,62] Selenenyl halides also undergo facile addition to allenes with exclusive attack by selenium occurring at the central allenic carbon.[63]

### 1.8.2.4 Tetravalent Selenium

Brief reviews of electrophilic addition reactions of tetravalent selenium have appeared.[39,64] Alkenes react with selenium tetrabromide ($SeBr_4$) and tetrachloride ($SeCl_4$) to afford 2:1 adducts (Scheme 35 and equation 9)[65,66] with *anti* stereospecificity and Markovnikov regioselectivity. Dienes undergo intramolecular double addition with $SeX_4$ (Scheme 36).[67] Monoadducts are formed with alkyl- or aryl-selenium trichloride ($RSeCl_3$) and $R_2SeCl_2$ with *anti* stereospecificity (equation 10).[68,69] The $RSeCl_3$ adducts can be hydrolyzed with aqueous bicarbonate to selenoxides which spontaneously eliminate, affording vinylic or allylic chlorides depending on the regiochemistry of elimination (compare Scheme 31).[70] Methylselenium trichloride, $MeSeCl_3$, adds *anti* stereoselectively to disubstituted alkynes.[71]

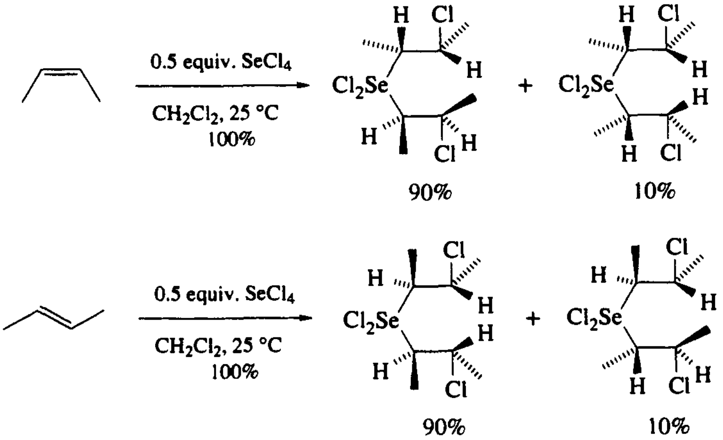
0.5 equiv. $SeCl_4$
$CH_2Cl_2$, 25 °C
100%
H
Cl
$Cl_2Se$
H
Cl
90%
+
10%
0.5 equiv. $SeCl_4$
$CH_2Cl_2$, 25 °C
100%
90%
10%

**Scheme 35**

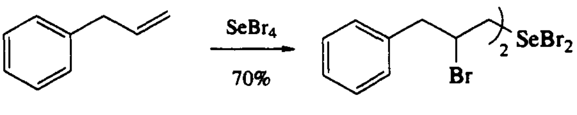
$SeBr_4$
70%
Br
$SeBr_2$
2

(9)

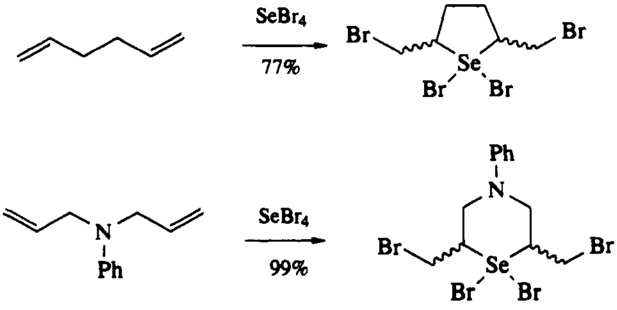
$SeBr_4$
77%
Br
Se
Br
Br
Br
N
Ph
$SeBr_4$
99%

**Scheme 36**

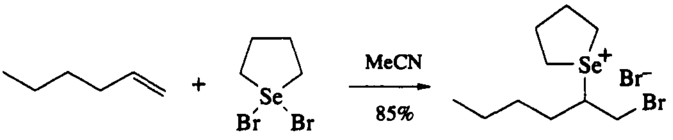
MeCN
85%
Se
Br
Br
Se+
Br−
Br

(10)

### 1.8.2.5 Tellurium Compounds

Electrophilic addition reactions of tetravalent tellurium compounds have been reviewed.[64] 2-Naphthyltellurium trichloride ($ArTeCl_3$) adds to alkenes in an *anti* stereospecific manner (equation 11), whereas tellurium tetrachloride gives mixtures of 2:1 adducts with both *syn* and *anti* addition.[72] A one-pot alkene inversion procedure has been developed, based upon $TeCl_4$ addition to alkenes followed by treatment of the β-chloroalkyltellurium trichloride adduct with aqueous $Na_2S$ (Scheme 37).[73] Tellurium compounds such as tellurinyl acetates, ArTe(O)OAc, prepared *in situ* through reaction of tellurinic acid anhydrides with acetic acid, can be employed in oxytelluration and aminotelluration procedures (Schemes 38 and 39).[74] In the oxytelluration reaction intermediate triacetates of the type $RCH_2Te(OAc)_2Ph$ are reduced with hydrazine to the corresponding tellurides.

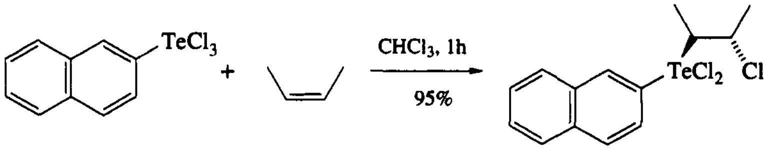
TeCl3
+
CHCl3, 1h
95%
TeCl2
Cl

(11)

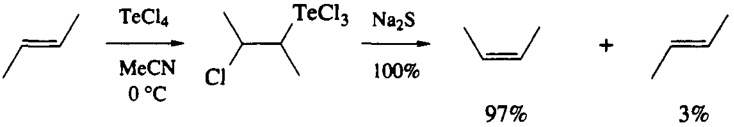
TeCl4
MeCN
0 °C
TeCl3
Cl
Na2S
100%
+
97%
3%

Scheme 37

$$[ArTe(O)]_2O + AcOH \longrightarrow ArTe(O)OAc + H_2O$$

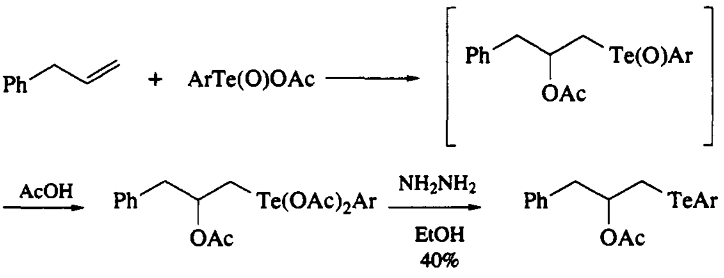
Ph
+ ArTe(O)OAc
Ph
Te(O)Ar
OAc
AcOH
Ph
Te(OAc)2Ar
OAc
NH2NH2
EtOH
40%
Ph
TeAr
OAc

Scheme 38

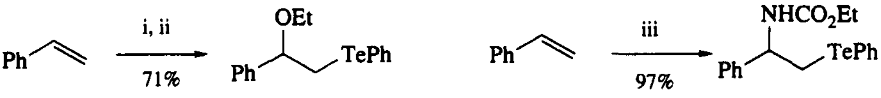
Ph
i, ii
71%
OEt
Ph
TePh
Ph
iii
97%
NHCO2Et
Ph
TePh

i, PhTe(O)OAc, $SnCl_4$; ii, $NH_2NH_2$, EtOH; iii, PhTe(O)OAc, $BF_3 \cdot OEt_2$, $NH_2CO_2Et$

Scheme 39

## 1.8.3 HALOGENS

### 1.8.3.1 Fluorine

Until recently there have been few examples reported of the controlled addition of fluorine to alkenes and alkynes.[75] Many elementary texts dismiss the utility of $F_2$ in organic chemistry with statements such as 'fluorine is so reactive that it not only adds to the double bond but also rapidly replaces all the hydrogens with fluorines, often with considerable violence.'[76] Because of the weak F—F bond (37.7 kcal $mol^{-1}$, 1 kcal = 4.18 kJ) reactions of fluorine at ambient temperatures tend to be homolytic in nature, frequently leading to extensive decomposition. However by working at −78 °C with a 1% stream of fluorine in nitrogen in $CHCl_3$–$CFCl_3$ in the presence of a proton source such as ethanol to suppress radical processes, ionic addition of $F_2$ in a stereospecific *syn* manner is observed, as shown in Scheme 40.[77] The exclusive *syn* addition, which is opposite to the stereochemistry observed with other halogen additions, is characteristic of all electrophilic fluorination processes (*e.g.* with $FOCF_3$, $FOCF_2CF_3$, $FOCOCF_3$, FOCOMe) and is considered as a good criterion for their existence.[77] Rapid collapse of the tight ion pair involving the α-fluorocarbocation is believed to account for the stereospecificity. Fluorination of enones by the above procedure also proceeds without complications (Scheme 41).[77] Dehydrofluorination of the initial *syn* difluoro adduct affords α-fluoroenones.

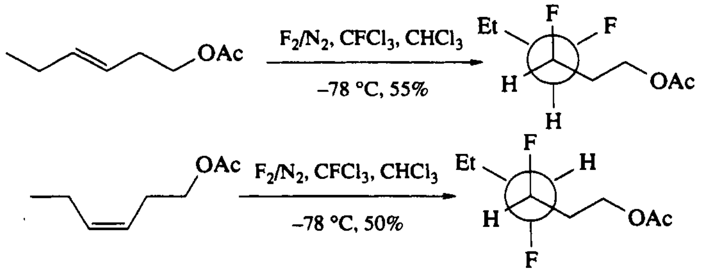

Scheme 40

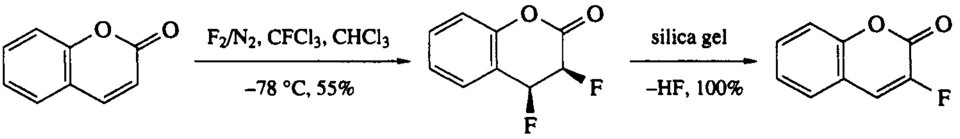

Scheme 41

### 1.8.3.2 Chlorine

Few recent studies have appeared on electrophilic addition reactions of chlorine which significantly update the earlier literature.[1,2] While simple alkenes react readily with elemental chlorine it is possible to carry out chlorinations of such groups as sulfur–sulfur bonds in the presence of C=C functions without competition from chlorination of the C=C bond (Scheme 9).[14] Alkenes have been chlorinated in good yield under mild conditions using chlorine incorporated into an anion-exchange resin.[78a] Isomerically pure vinyl silanes on low temperature chlorination followed by desilicohalogenation give vinyl chlorides with inverted geometry in good yield with high stereoselectivity.[78b] A comparative study of the chlorination, bromination and iodination of 1,5-cyclooctadiene is described in Section 1.8.3.4 below.

### 1.8.3.3 Bromine

What is the precise mechanistic process by which bromine (and by extension chlorine) adds to alkenes? Studies designed to probe this question are generally difficult to conduct due to the very fast product-forming steps. By applying stopped-flow spectrokinetics to sterically crowded alkenes such as adamantylideneadamantane ($Ad_2$), where steric hindrance retards the final addition step by hampering rearside nucleophilic attack of the counterion at the bromonium carbons of the intermediate ion pairs, it is possible to obtain useful mechanistic information on the initial steps in the interaction of bromine with a π-bond. Bellucci and coworkers[3] present a mechanism for the $Ad_2$–bromine reaction involving a sequence of multiple equilibria involving 1:1 and 1:2 $Ad_2$–$Br_2$ molecular charge-transfer complexes and bromonium–bromide, –tribromide and –pentabromide salts arising from solvent-assisted, $Br_2$-assisted or unassisted ionization of the molecular complexes and from the tribromide–pentabromide equilibrium. Charge-transfer complexes have already been indicated in the ionic bromination of cyclohexene.[79] It is concluded from these studies that a large part of the increase in bromination rate resulting from increasing substitution on the double bond (*e.g.* for mono-:di-:tri-:tetra-substituted double bonds the relative rate constants for bromine addition are 1:60:2000:20 000)[80] must be due to an increase in the alkene–$Br_2$ charge-transfer complex formation constant.

Another approach in the study of the mechanism and synthetic applications of bromination of alkenes and alkynes involves the use of crystalline bromine–amine complexes such as pyridine hydrobromide perbromide ($PyHBr_3$), pyridine dibromide ($PyBr_2$), and tetrabutylammonium tribromide ($Bu_4NBr_3$) which show stereochemical differences and improved selectivities for addition to alkenes and alkynes compared to $Br_2$ itself.[81] The improved selectivity of bromination by $PyHBr_3$ forms the basis for a synthetically useful procedure for selective monoprotection of the higher alkylated double bond in dienes by bromination (Scheme 42).[80] The less-alkylated double bonds in dienes can be selectively monoprotected by tetrabromination followed by monodeprotection at the higher alkylated double bond by controlled-potential electrolysis (the reduction potential of vicinal dibromides is shifted to more anodic values with increasing alkylation; Scheme 42).[80] The question of which diastereotopic face in chiral allylic alcohols reacts with bromine has been probed by Midland and Halterman as part of a stereoselective synthesis of bromo epoxides (Scheme 43).[82]

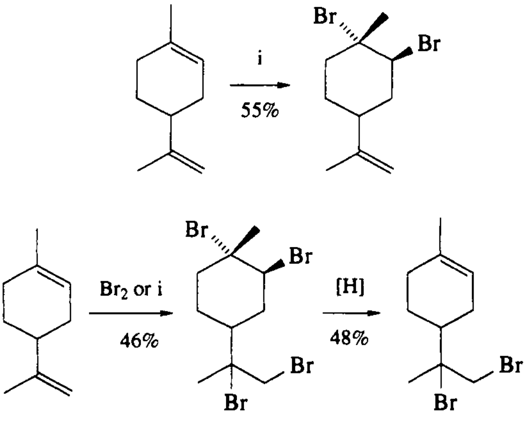

i, pyridinium hydrobromide perbromide

**Scheme 42**

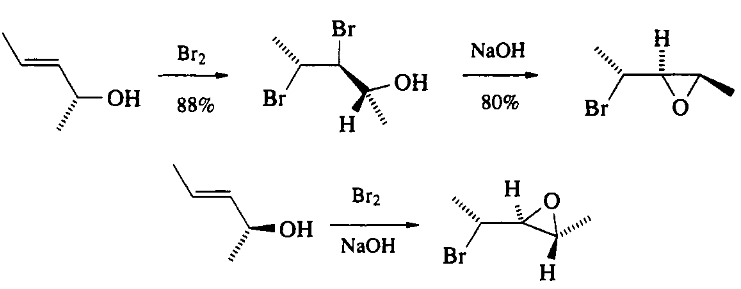

**Scheme 43**

White and coworkers used *trans* Addition of bromine and (–)-1-borneol to 3,4-dihydro-2*H*-pyran to afford the stereoisomeric bornyl bromotetrahydropyranyl ethers (**3**) and (**4**; Scheme 44) which are employed in an enantioselective total synthesis of (–)-monic acid C (Scheme 5).[10] A simple synthesis of 4-methylthio-1,2-dithiolane, the photosynthesis inhibitor of the green alga *Chara globularis* (Scheme 45),[83] exploits the observation that allylic sulfides undergo rearrangement on addition of bromine.[84] Block and Naganathan employed the *trans* addition of bromine to 4-thioacetoxycyclopentene as a key step in the synthesis of 2-bromo-5-thiabicyclo[2.1.1]hexane (Scheme 46).[85] *trans* Addition of bromine to 1,4-dichlorobut-2-yne followed by base- or aluminum amalgam-induced elimination is employed in the synthesis of halo-1,3-butadienes (Scheme 19).[28]

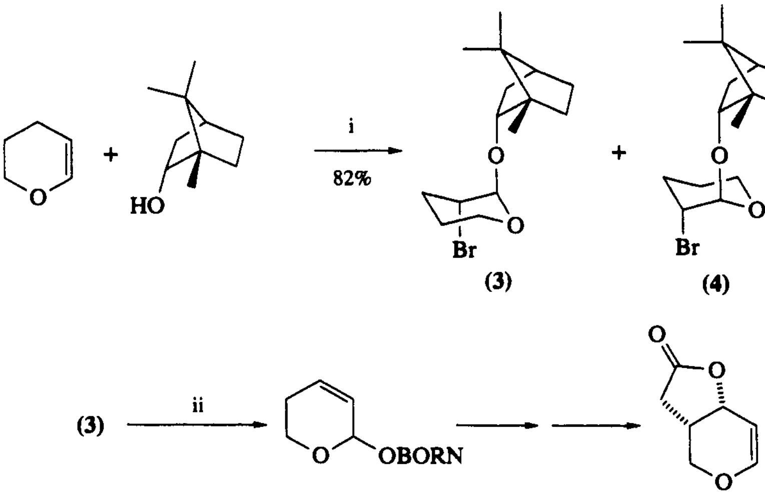

i, $Br_2$, $PhNMe_2$, $CH_2Cl_2$, −78 to 0 °C; ii, DBU, 95 °C, 20 h

Scheme 44

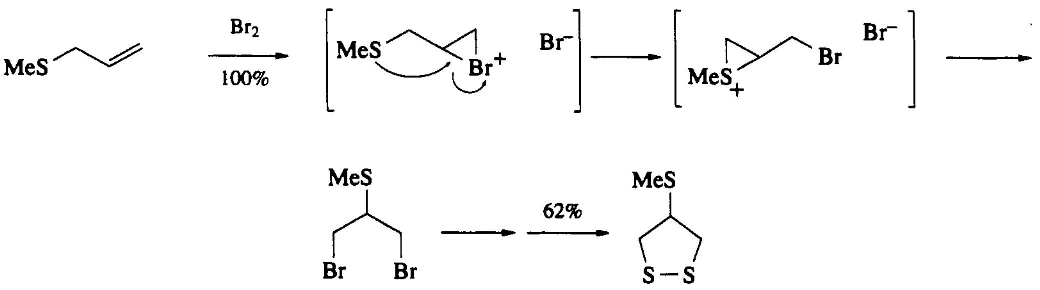

Scheme 45

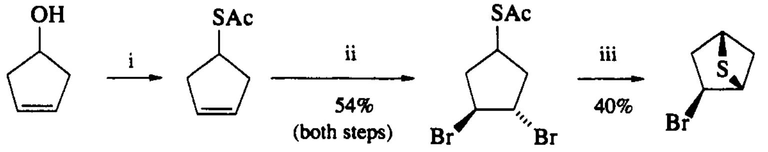

i, diisopropylazodicarboxylate, $PPh_3$, THF, MeC(O)SH, 0 °C to r.t., 3 h; ii, $Br_2/CCl_4$, 0 °C, 1 h; iii, KOH, $EtOH/H_2O$, reflux, 90 h

Scheme 46

### 1.8.3.4 Iodine

Iodine, less reactive than bromine, is best added to alkenes by use of ICl and IBr (see Section 1.8.3.5). Iodine itself adds rapidly but reversibly to alkenes forming diiodides by mechanisms that can be either ionic or radical. The position of the equilibrium depends upon the structure of the alkene, the solvent and the temperature. Simple vicinal diiodides survive distillation in the dark, but are unstable toward iodine or radicals. In the presence of functions containing free OH groups, such as alumina, HI generated from $I_2$ adds to alkenes irreversibly with the result that the HI adduct, rather than the $I_2$ adduct, is the exclusive product.[86a] A comparison of the reaction of 1,5-cyclooctadiene with chlorine, bromine and iodine in $CH_2Cl_2$ reveals that chlorine gas at −50 °C gives a 93:7 mixture of *trans*- and *cis*-5,6-dichlorocyclooctene, bromine gives *trans*-5,6-dibromocyclooctene in 95%, while iodine gives a 1:1 mixture of *endo,exo*- and *endo,endo*-2,6-diiodobicyclo[3.3.0]octanes in 70% yield.[87] Significant differences in product composition are seen in all cases with changes in solvent. Addition of iodine to terminal (*E*)-vinylsilanes in the presence of Lewis acids (iodesilylation) gives different ratios of (*E*)- and (*Z*)-vinyl iodides depending on the amount of Lewis acid.[88]

Unlike alkenes, which react reversibly with $I_2$, alkynes react in solution irreversibly with $I_2$, forming (*E*)-1,2-diiodoalkenes.[89] The reaction may involve radicals rather than ionic species.[90] Ordinary alumina appears to promote the addition, forming electrophilic species.[86b] The addition of iodine to 1,4-dichlorobut-2-yne is analogous to the addition found with bromine cited above (Scheme 19).[28]

### 1.8.3.5 Interhalogens

Halofluoridation has been reviewed.[91] Iodine fluoride, IF, and bromine fluoride, BrF, formed from the elements in $CFCl_3$ at −78 °C, are highly reactive toward π-systems, reacting at −75 °C in the dark in a matter of seconds. Additions to alkenes are regiospecific in the Markovnikov sense ($X^+$ $F^-$) and *anti* stereospecific, affording vicinal fluoro iodides or bromides.[92] Other sources of these two interhalogens, which have been added to alkenes and alkynes, include $I^+(collidine)_2BF_4^-$, $I^+(py)_2BF_4^-$, $I_2$/AgF, *N*-iodosuccinimide/HF–pyridine, and $BrF_3$.[93] Addition of IF or BrF to terminal alkynes gives adducts of type $RCF_2CX_2$ (equation 12).[94] A variety of mechanistic studies have appeared on the addition of BrCl, ICl, IBr and related reagents to alkenes and alkynes.[95]

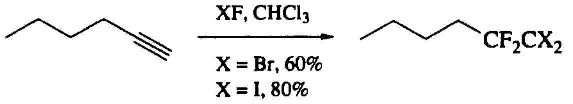

(12)

### 1.8.3.6 Reagents with O—X Bonds

Electrophilic addition of hypohalites, HOX, formed through reaction of halogens with water, has been known for many years.[96] Even hypofluorous acid, HOF, will add to alkenes and alkynes.[97] A variety of other types of reagents with oxygen–halogen bonds are also known to add to alkenes and alkynes. Examples of such reagents, capable of undergoing low-temperature addition to alkenes, include acyl hypohalites, XOC(O)R (equations 13[48] and 14[98] and Scheme 47),[99] perchlorates $XOClO_3$,[100] sulfates, $XOSO_2Y$ (Scheme 48),[101] triflates, $XOSO_2CF_3$[102,103] and trifluoromethyl hypofluorite, $CF_3OF$ (equation 15).[104,105] A related reagent, cesium fluoroxysulfate $FOSO_3Cs$, has also been found to add to alkenes under mild conditions, affording vicinal fluoroalkyl sulfates (Scheme 49).[103] The latter reactions exhibit low regio- and stereo-selectivities, with a preference for anti-Markovnikov and *syn* addition.

Zefirov and coworkers have developed procedures for chlorosulfamation of alkenes and alkynes using reagents of the type $R_2NSO_2OCl$ formed by insertion of sulfur trioxide into the nitrogen–chlorine bond in *N*-chloroamines ($R_2NCl$).[106]

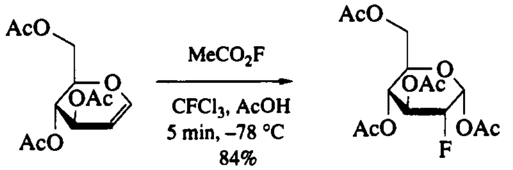

(13)

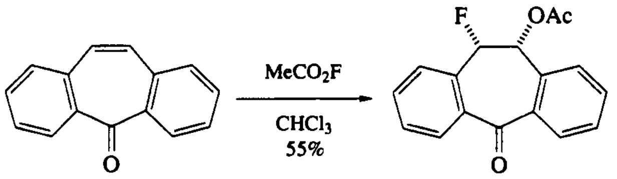

(14)

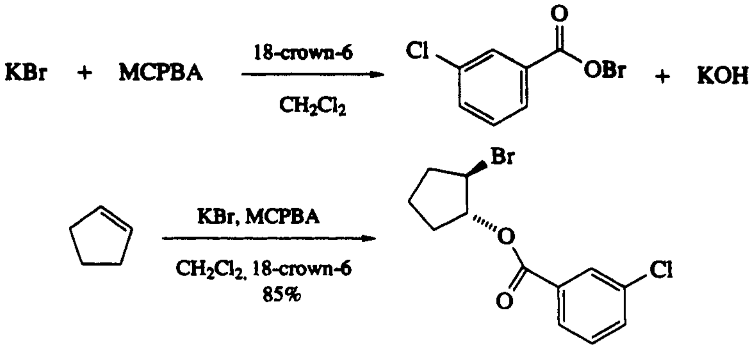
KBr + MCPBA
18-crown-6
CH2Cl2
Cl
O
OBr
+ KOH
KBr, MCPBA
CH2Cl2, 18-crown-6
85%
Br
O
O
Cl

Scheme 47

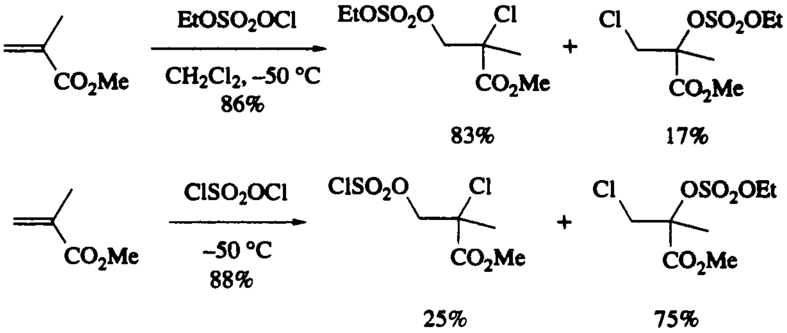
CO2Me
EtOSO2OCl
CH2Cl2, –50 °C
86%
EtOSO2O
Cl
CO2Me
+
Cl
OSO2OEt
CO2Me
83%
17%
CO2Me
ClSO2OCl
–50 °C
88%
ClSO2O
Cl
CO2Me
+
Cl
OSO2OEt
CO2Me
25%
75%

Scheme 48

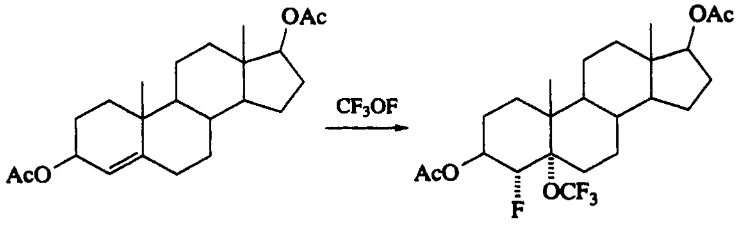
OAc
AcO
CF3OF
OAc
AcO
F
OCF3

(15)

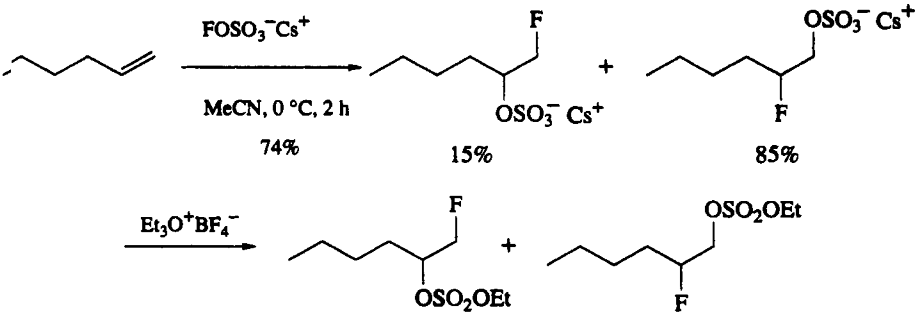
FOSO3⁻Cs⁺
MeCN, 0 °C, 2 h
74%
F
OSO3⁻ Cs⁺
15%
+
OSO3⁻ Cs⁺
F
85%
Et3O⁺BF4⁻
F
OSO2OEt
+
OSO2OEt
F

Scheme 49

## 1.8.4 PSEUDOHALOGENS

### 1.8.4.1 Thiocyanogen

The addition of thiocyanogen[107] to unsaturated compounds[108] forms the basis of a classical analytical method for determination of the unsaturation in fats and oils.[108a] The addition has been found to afford both α,β-dithiocyanates as well as isomeric α-isothiocyanato-β-thiocyanates in ratios dependent on solvent and catalysts.[108b] Metals such as iron[108b] or tin[108c] favor the α,β-dithiocyanate form by coordinating to the harder (HSAB concept) nitrogen terminus of NCS; in related studies use of mercury salts (a softer metal) favors isothiocyanate formation.[58] Thiocyanogen[108a] addition has been utilized in the inversion of alkene geometry (Scheme 50).[108b] More recently thiocyanogen addition to a silylated alkene has been used in the synthesis of various silylated thiols, unsaturated thiocyanates and *trans*-2,3-bis(trimethylsilyl)thiirane (Scheme 51).[109] (*E*)-1,2-Dithiocyanatoalkenes can be prepared by addition of thiocyanogen, formed *in situ* from $Hg(SCN)_2/I_2$, to alkynes (equation 16).[110]

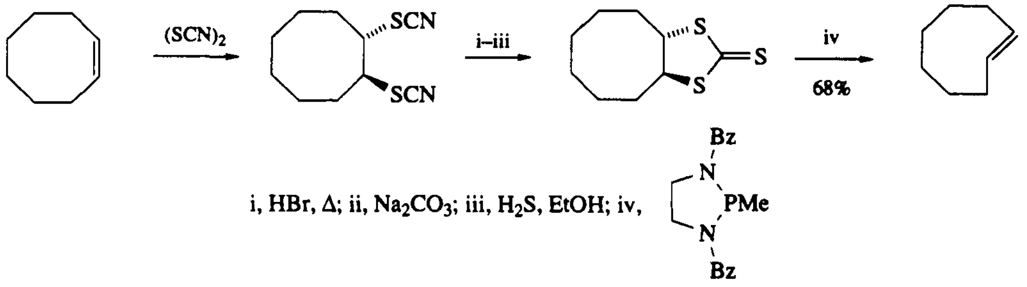
(SCN)₂
SCN
SCN
i–iii
S
S
=S
iv
68%
i, HBr, Δ; ii, Na₂CO₃; iii, H₂S, EtOH; iv,
Bz
N
PMe
N
Bz

**Scheme 50**

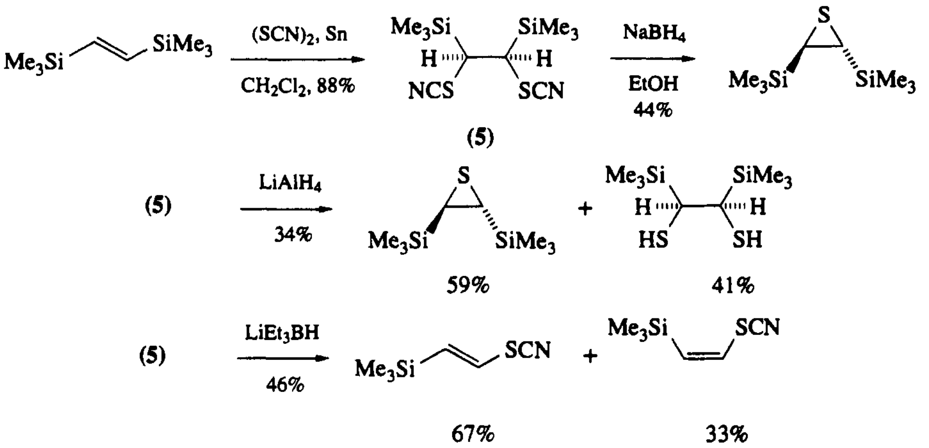
Me₃Si
SiMe₃
(SCN)₂, Sn
CH₂Cl₂, 88%
Me₃Si
SiMe₃
H
H
NCS
SCN
(5)
NaBH₄
EtOH
44%
S
Me₃Si
SiMe₃
(5)
LiAlH₄
34%
S
Me₃Si
SiMe₃
+
Me₃Si
SiMe₃
H
H
HS
SH
59%
41%
(5)
LiEt₃BH
46%
Me₃Si
SCN
+
Me₃Si
SCN
67%
33%

**Scheme 51**

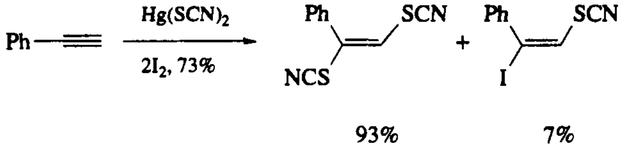 (16)
Ph
Hg(SCN)₂
2I₂, 73%
Ph
SCN
NCS
+
Ph
SCN
I
93%
7%

### 1.8.4.2 Halogen Azides

Some of the most useful procedures for the stereospecific introduction of nitrogen functionalities into the carbon skeleton are based on reagents with a N—X bond such as halogen azides, nitrates and isocyanates together with haloamines and haloamides. Hassner has published an excellent overview of applications of the reagent, $XN_3$.[111] Special procedures must be used to prepare the explosive iodine azide, $IN_3$, *in situ* in organic solvents;[112] $BrN_3$ and $ClN_3$ can be prepared using a two-phase system (water–pentane) by the interaction of $Br_2$ or $Cl_2$ with $NaN_3$ in the presence of acid.[111] More recently $BrN_3$ has been prepared *in situ* from NBS and $NaN_3$ in the presence of the alkene in $DME/H_2O$. The $BrN_3$ adducts can be converted to aziridines by treatment with lithium aluminum hydride (Schemes 52[113] and 53).[114]

Iodine azide adds stereo- and regio-specifically to 2-cholestene giving a *trans*-diaxial adduct with azide at the 2-position, a consequence of attack by $I^+$ from the less hindered face of the steroid. With 1-hexene the addition proceeds regiospecifically to yield the secondary azide, most likely *via* a three-membered iodonium ion intermediate.[111] With (*Z*)-2-octene, $BrN_3$ addition gives a single adduct in 71% yield

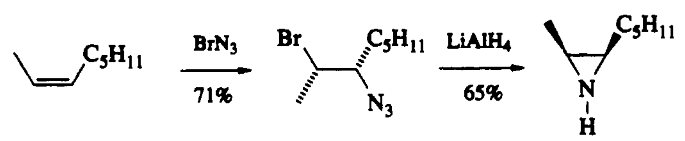

**Scheme 52**

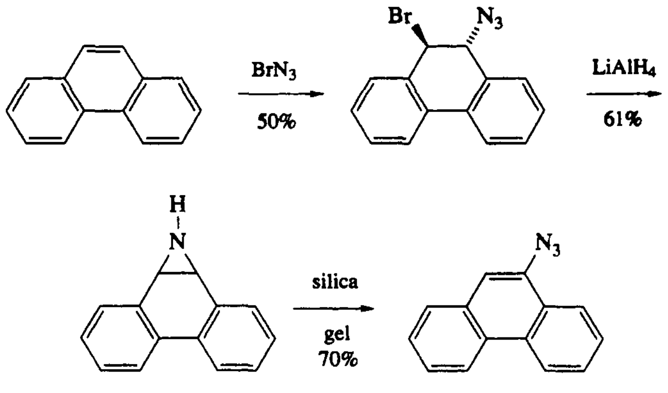

**Scheme 53**

in a process termed directiospecific.[113] A notable exception to the rule that azide is preferentially attached to the center best stabilizing a positive charge is seen with $IN_3$ addition to 3,3-dimethyl-1-butene, $Me_3CCH{=}CH_2$. The adduct has the structure $Me_3CCHICH_2N_3$. It is suggested that the sterically bulky *t*-butyl group forces the azide ion to attack at the primary carbon (compare equation 2). Another example in which steric effects dominate over polar effects is seen in the addition of $IN_3$ to 1-arylcyclohexenes; in this example addition of $IN_3$ is followed by HI elimination to afford an allylic azide (Scheme 54).[115] Addition of $IN_3$ to vinyl sulfones affords single regioisomers which eliminate either HI, giving β-azidovinyl sulfones, or $HN_3$, giving α-iodovinyl sulfones (Scheme 55).[116] The halogen in halogen azide adducts can also be displaced intermolecularly by nucleophiles (including azide ion), as in Schemes 56[117] and 57,[118] or removed using a tin hydride, as in the elegant synthesis of the alkaloid (±)-*O*-methylorantine by Wasserman and coworkers (Scheme 58).[119]

Addition of halogen azides to allenes affords a variety of useful products by regioselective processes (Scheme 59).[120] In the addition of $BrN_3$ and $ClN_3$ and even $IN_3$ to alkenes, both ionic and free radical addition are possible. Thus in polar solvents such as nitromethane, $BrN_3$ adds to 2-cholestene giving a single diaxial adduct. Under free radical conditions (pentane, light, peroxides) two stereoisomers are formed (Scheme 60).[111] Similar results have been reported for $IN_3$ (Scheme 61).[121]

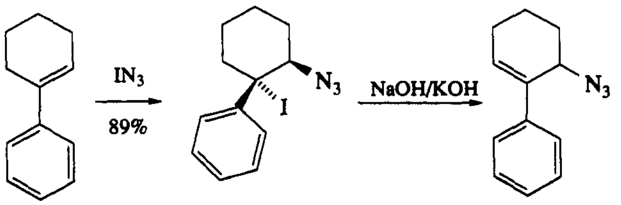

**Scheme 54**

### 1.8.4.3 Halogen Nitrates

The work of Lown and coworkers[122] on iodonium nitrates has been reviewed.[1] Addition of these reagents proceeds in a *trans* stereospecific manner, but with mediocre regiospecificity. The Lown group has also studied $BrNO_3$ and found it to be a more regiospecific reagent.[123]

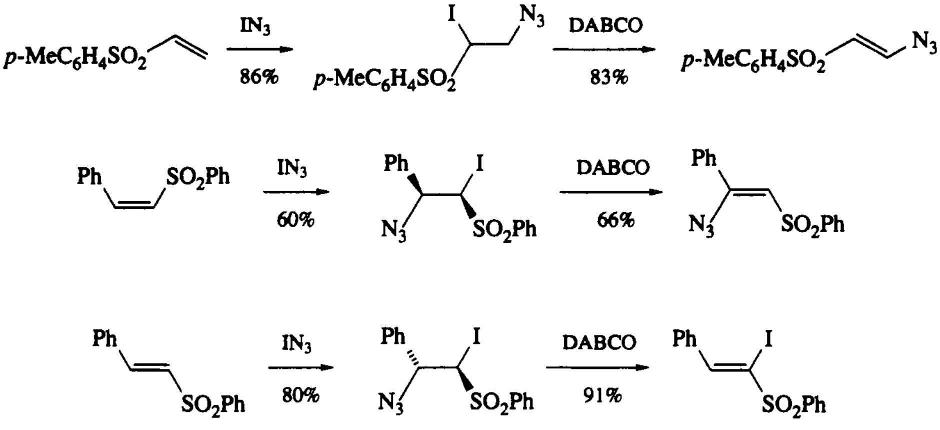
p-MeC6H4SO2
IN3
86%
I
N3
p-MeC6H4SO2
DABCO
83%
p-MeC6H4SO2
N3
Ph
SO2Ph
IN3
60%
Ph
I
N3
SO2Ph
DABCO
66%
Ph
N3
SO2Ph
Ph
SO2Ph
IN3
80%
Ph
I
N3
SO2Ph
DABCO
91%
Ph
I
SO2Ph

**Scheme 55**

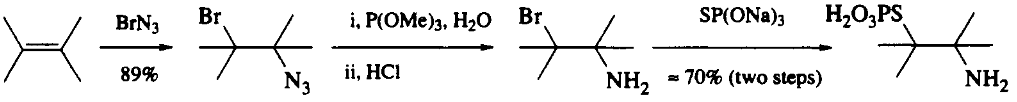
BrN3
89%
Br
N3
i, P(OMe)3, H2O
ii, HCl
Br
NH2
SP(ONa)3
≈ 70% (two steps)
H2O3PS
NH2

**Scheme 56**

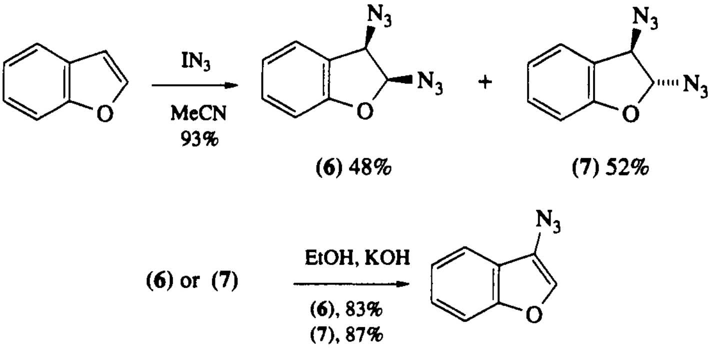
O
IN3
MeCN
93%
N3
N3
O
+
N3
N3
O
(6) 48%
(7) 52%
(6) or (7)
EtOH, KOH
(6), 83%
(7), 87%
N3
O

**Scheme 57**

Barluenga has introduced a new reagent for the addition of $XNO_3$ across double bonds. Thus, $Hg(NO_3)_2{\cdot}X_2$, where X = Br or I, is a good reagent for the efficient generation of 1,2-halonitrates (Scheme 62).[124] Unfortunately this mercury reagent, like simple $INO_3$ or $BrNO_3$, is inert toward alkynes.

### 1.8.4.4 Halogen Isocyanates

The chemistry of halogen isocyanates and the mode by which they interact with double bonds has been reviewed.[1] The addition to alkenes has *anti* stereospecificity, but displays limited regiospecificity. Halogen isocyanates have received little attention in recent years, but there are two examples worth noting. An INCO addition was employed in an important step in the synthesis of methyl α-D-tetronitroside (Scheme 63).[125] The preparation allowed for a confident structural assignment relating to tetronitrose, one of the sugar components of the antibiotics tetrocarcins A and B, and kijanimicin. Barluenga's $I(py)_2^+$ $BF_4^-$ reagent, introduced in Section 1.8.3.5,[93c] has been utilized with the $OCN^-$ ion to afford 1-iodo-2-isocyanatoalkanes.[93c]

### 1.8.4.5 Halogen Thiocyanates

The chemistry of the XSCN reagents has been reviewed briefly.[1] When X = Br or Cl, the reagent is polarized $X^-(SCN)^+$, while when X = I the polarization is $I^+(SCN)^-$.[126] Examples using ISCN or its equivalents dominate the recent literature on XSCN reagents. Thiocyanate is often introduced as an ionic

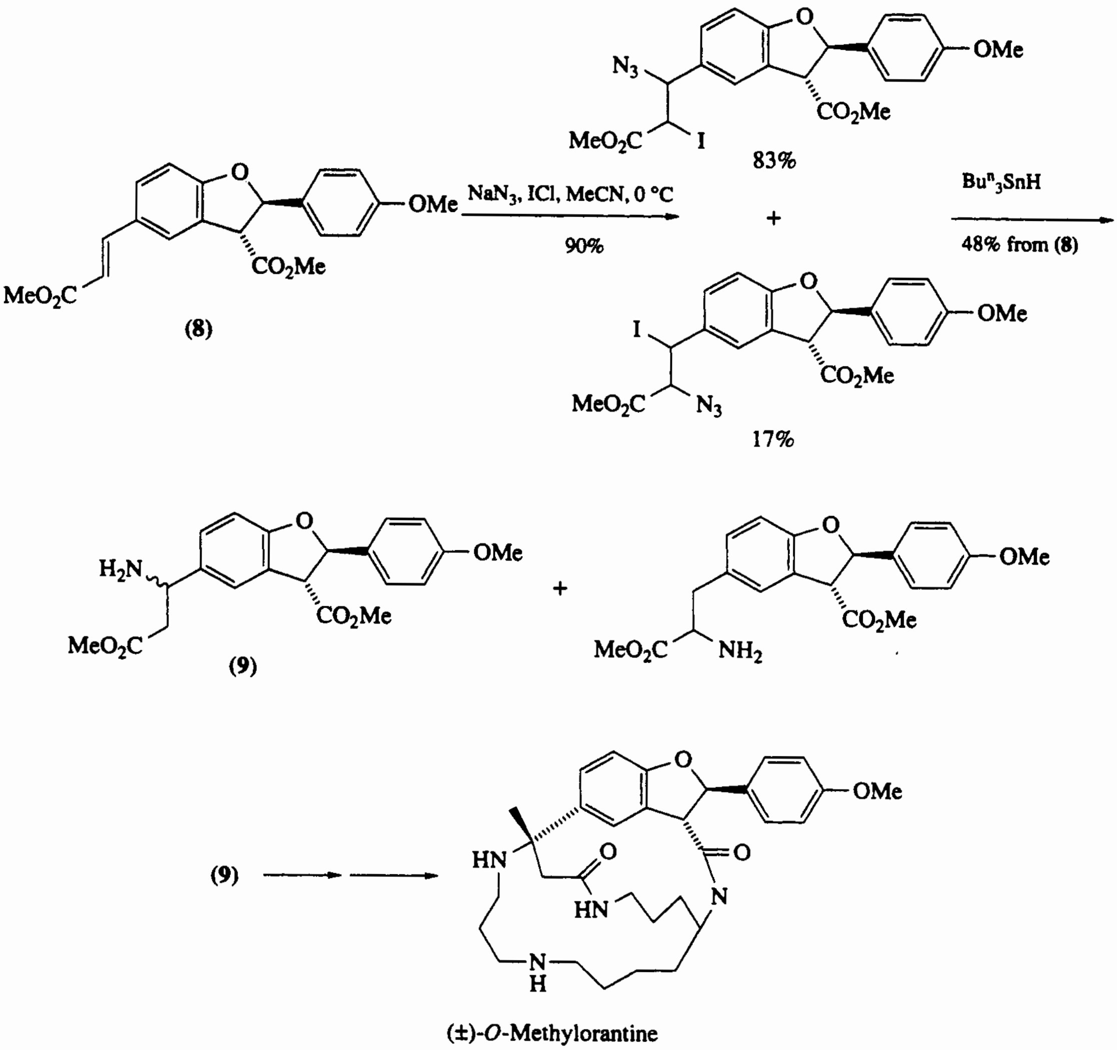
(8)
NaN₃, ICl, MeCN, 0 °C
90%
83%
+
17%
Buⁿ₃SnH
48% from (8)
(9)
+
(9)
(±)-O-Methylorantine

Scheme 58

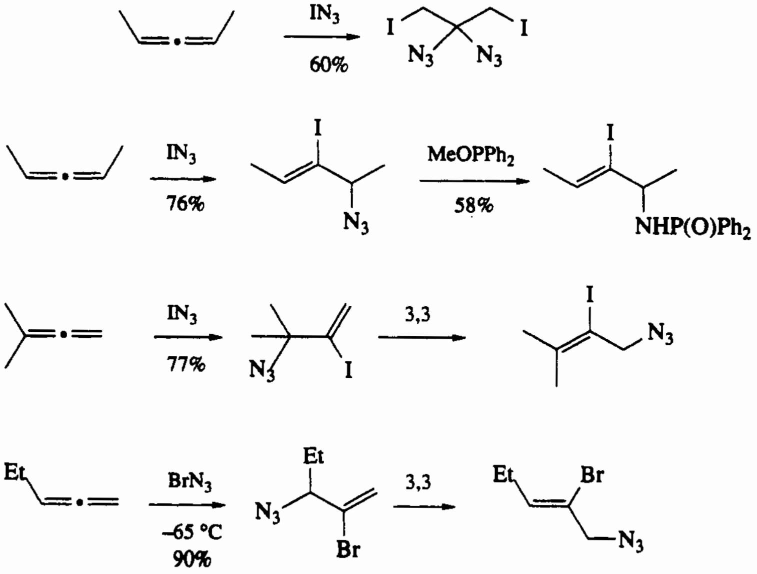
IN₃
60%
IN₃
76%
MeOPPh₂
58%
IN₃
77%
3,3
BrN₃
−65 °C
90%
3,3

Scheme 59

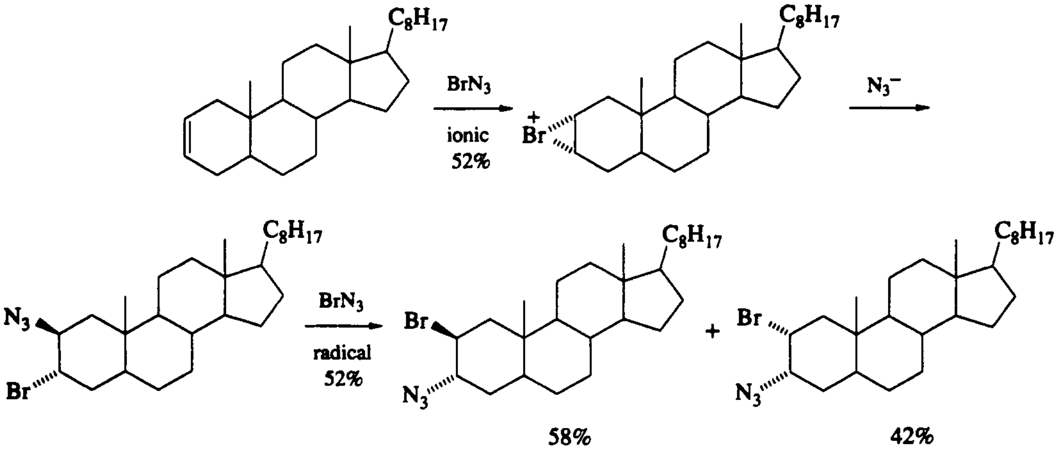
C8H17
BrN3
ionic
52%
Br+
N3−
N3
Br
BrN3
radical
52%
58%
42%

Scheme 60

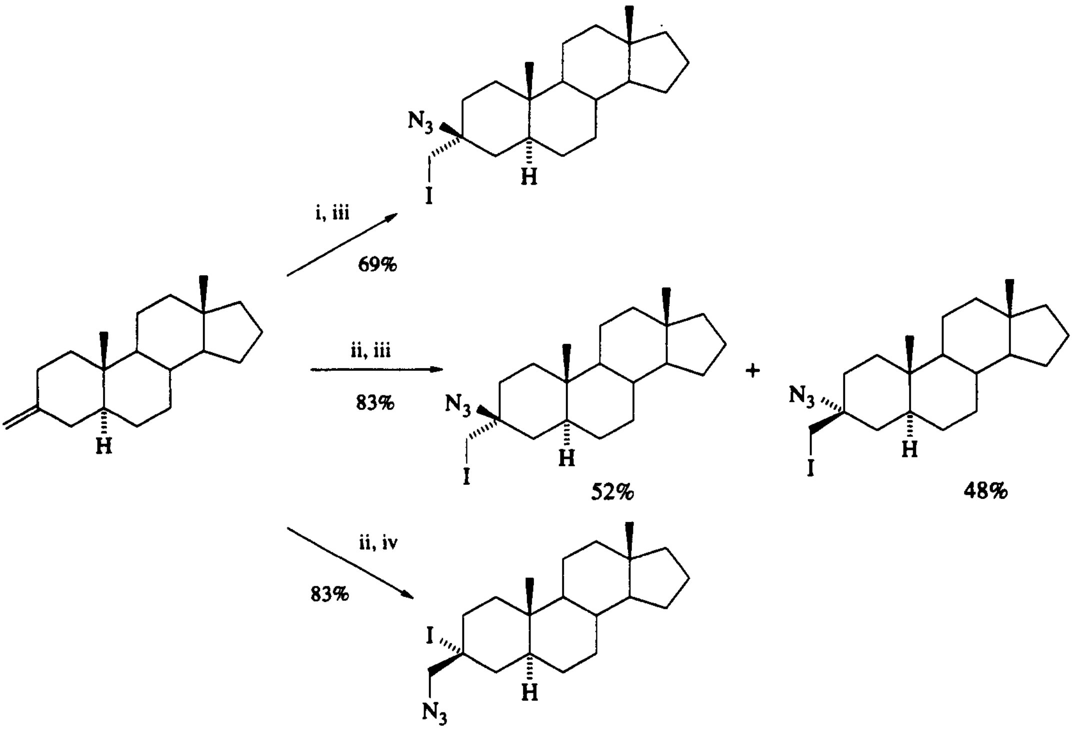
N3
I
H
i, iii
69%
ii, iii
83%
52%
48%
ii, iv
83%

i, *N*-iodosuccinimide•$HN_3$, $CH_2Cl_2$; ii, $NaN_3$•ICl, MeCN; iii, no removal of $O_2$ from reaction solution; iv, displacement of $O_2$ in reaction solution with $N_2$

Scheme 61

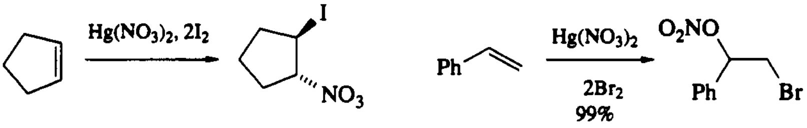
Hg(NO3)2, 2I2
I
NO3
Ph
Hg(NO3)2
2Br2
99%
O2NO
Ph
Br

Scheme 62

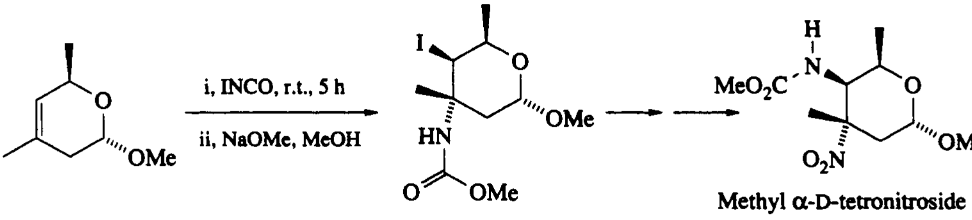
i, INCO, r.t., 5 h
ii, NaOMe, MeOH
Methyl α-D-tetronitroside

**Scheme 63**

salt. Addition product distribution is usually sensitive to the identity of the counterion of the thiocyanate salt. Another problem sometimes incurred is that the *vic*-halothiocyanates often isomerize to the thermodynamically more stable *vic*-haloisothiocyanates (Scheme 64).[127] Some of the factors governing this isomerism have been evaluated.[128] Adducts of BrSCN do not suffer from the problem of isomerism.[126]

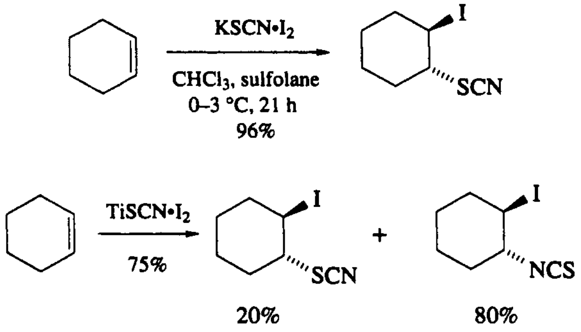
KSCN•I2
CHCl3, sulfolane
0–3 °C, 21 h
96%
TiSCN•I2
75%
20%
80%

**Scheme 64**

Grayson and Whitham have found the regiochemistry of addition of ISCN (from LiSCN and $I_2$) to vinyl silanes to be consistent with the intermediacy of an iodonium ion which is particularly stabilized at one of the carbons due to the β-silicon effect.[129] The products were a thiocyanate in one case and an isothiocyanate in the other (Scheme 65).[129]

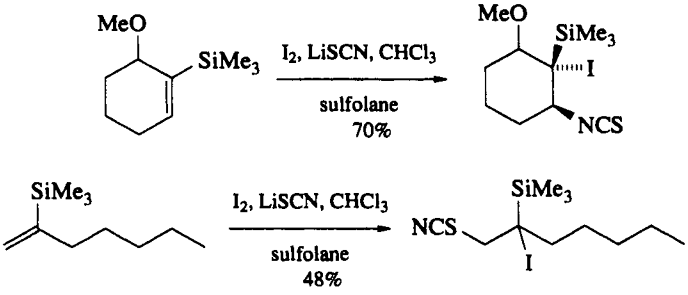
I2, LiSCN, CHCl3
sulfolane
70%
I2, LiSCN, CHCl3
sulfolane
48%

**Scheme 65**

The $I(py)_2^+ BF_4^-$ reagent of Barluenga (see Sections 1.8.3.5 and 1.8.4.4) is a useful reagent for introduction of ISCN as well as other pseudohalides. The reagent was used for the iodothiocyanation of 3-hexyne.[93d] Other efficient iodothiocyanations include the use of $Hg(SCN)_2{\cdot}I_2$[110] (see Section 1.8.4.3) and the use of inorganic solid supported KSCN, as indicated by equation (17).[130]

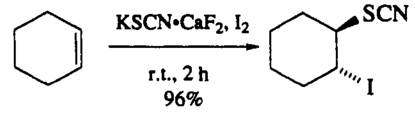
KSCN•CaF2, I2
r.t., 2 h
96%

(17)

### 1.8.4.6 Haloamides

Currently the most popular of the pseudohalides are *N*-haloamides. These reagents are used in conjunction with the solvent or an added nucleophilic reagent to give overall 1,2-addition of a halogen and a nucleophile to the alkenic substrate. The amides of choice seem to be *N*-halosuccinimides. The low nucleophilicity of the succinimdyl anion allows for a variety of nucleophiles to attack the initially formed halonium ion.

Alcohols have been shown to be suitable nucleophiles. Thus unsymmetrical ketene acetals can be prepared by treating vinyl ethers with *N*-iodosuccinimde (NIS) in the presence of functionalized alcohols (Scheme 66).[131] In an elegant example, McDougal *et al.* treated the 2-phenylthio-7-oxa[2.2.1]hept-2-ene (**10**) with NCS in MeOH to effect *syn, exo* chloromethoxylation of the double bond (Scheme 67).[132] Presumably the phenylthio group can bridge to form a thiiranium ion as the initial intermediate. This cation is then attacked on the *exo* face by MeOH. The preparation of a key intermediate along the pathway to the tricyclo[5.4.0.0$^{2,8}$]undecane ring system employs NBS in the presence of MeOH or NaOAc (equation 18).[133] The authors use molecular models and force-field calculations to help account for the high degree of regio- and stereo-selectivity of the addition.

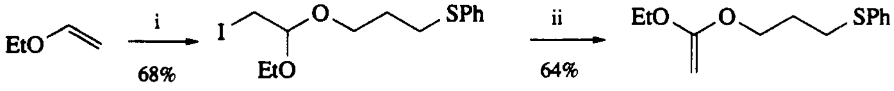
EtO
i
68%
I
O
SPh
EtO
ii
64%
EtO
O
SPh

i, *N*-iodosuccinimide, HO(CH$_2$)$_3$SPh; ii, Bu$^t$OK, THF

Scheme 66

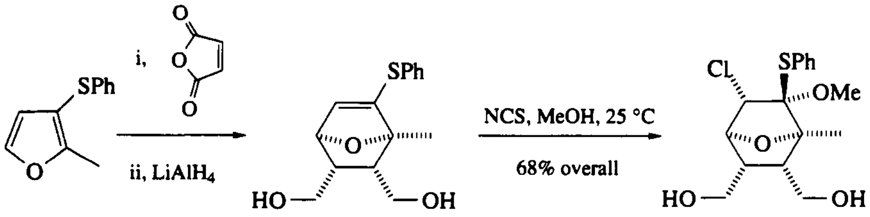
SPh
O
i, O (maleic anhydride)
ii, LiAlH4
SPh
O
HO
OH
NCS, MeOH, 25 °C
68% overall
Cl
SPh
OMe
O
HO
OH

(**10**)

Scheme 67

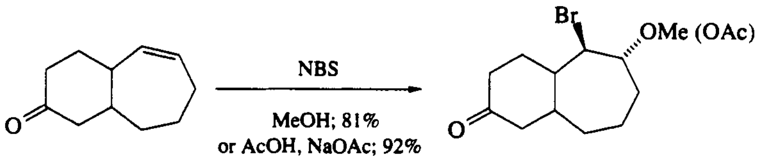
O
NBS
MeOH; 81%
or AcOH, NaOAc; 92%
Br
OMe (OAc)
O

(18)

Jung and Kohn have demonstrated the use of an external nitrogen nucleophile. Haloamination of alkenes with NBS and cyanamide, followed by further manipulation, results in vicinal diamines in high yield (Scheme 68).[134]

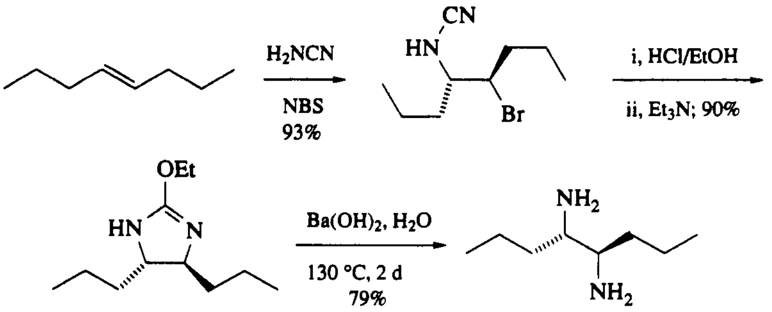
H2NCN
NBS
93%
CN
HN
Br
i, HCl/EtOH
ii, Et3N; 90%
OEt
HN
N
Ba(OH)2, H2O
130 °C, 2 d
79%
NH2
NH2

Scheme 68

*N*-Bromoacetamide (NBA) is also a useful positive bromine equivalent. Thus NBA in the presence of $H_2O$ or LiOAc/HOAc has resulted in the functionalization of 11,12-dihydrobenzo[*e*]pyrene (Scheme 69).[135] NBA has also been employed in conjunction with $H_2O$ for the regio- and stereo-selective hydrobromination of the 10,11 double bond of avermectin B1a, a complex antibiotic containing *five* double bonds.[136]

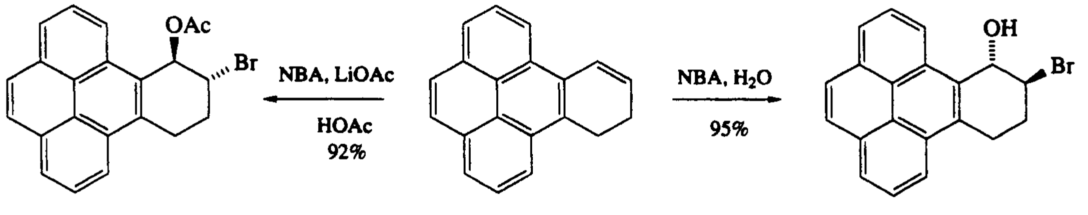

NBA = *N*-bromoacetamide

Scheme 69

Several groups have employed *N*-halosuccinimdes for the halofluorination of alkenes. Laurent and coworkers have found that triethylamine tris(hydrofluoride) is a suitable fluoride source for the halofluorination of a number of alkenes (Scheme 70).[137] Other examples of halofluorinations include NBS and tetrabutylammonium fluoride as the halogen sources for the formal addition of BrF across funtionalized cyclohexenes[138] and the halofluorination of alkenes and alkynes by all three *N*-halosuccinimides and polymer-supported HF.[139]

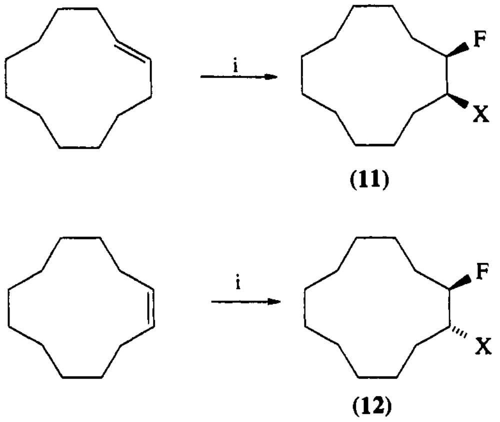

| *Product* | *X* | *Yield (%)* |
|---|---|---|
| (11) | Cl | 96 |
| (11) | Br | 95 |
| (11) | I | 82 |
| (12) | Cl | 92 |
| (12) | Br | 91 |
| (12) | I | 76 |

i, $Et_3N/3HF$, $CH_2Cl_2$ or ether, *N*-halosuccinimide, 0 to 20 °C

Scheme 70

## 1.8.5 ELECTROPHILIC NITROGEN

### 1.8.5.1 Nitronium Tetrafluoroborate

Like *N*-haloamides, nitronium tetrafluoroborate ($NO_2BF_4$) is employed with a nucleophile to effect overall addition of a nitro group and the nucleophile to the double bond of an alkene. The nature of the cation resulting from the attack of an alkene on $NO_2^+$ is addressed in a recent review by Smit.[140] One solvent commonly used for trapping the initially formed cations is acetonitrile. The reaction of alkenes with $NO_2BF_4$ in dichloromethane/acetonitrile followed by aqueous work-up affords good yields of products of nitroacetamidation (equation 19).[141,142] Nitration in the presence of trifluoroacetic anhydride and subsequent elimination of trifluoroacetic acid is an effective method for the preparation of 1-nitro-1,3-dienes (equation 20).[143] It has also been found that nitration using $NO_2BF_4$ in the presence of lithium perchlorates and fluoride sources leads to 1,2-nitroperchlorates[144] and 1,2-nitrofluorides,[145] respectively.

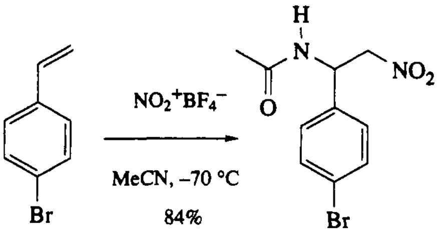

(19)

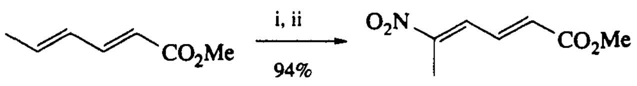

(20)

i, $NH_4^+NO_3^-$, TFAA, $HBF_4$, $CH_2Cl_2$; ii, KOAc, ether

### 1.8.5.2 Nitryl and Nitrosyl Halides

The nitrosochlorination of alkenes has been reviewed.[146] The products of nitrosochlorination are often dimers due to the propensity of nitroso groups to couple with one another. For this reason, and because of the advent of newer reagents, modern synthetic uses of NOCl are scarce. Instances where NOCl has proven to be a useful reagent include the preparation of α-oximinocarbonyl compounds (Scheme 71)[147] and the synthesis of precursors of insect growth regulators (Scheme 72).[148]

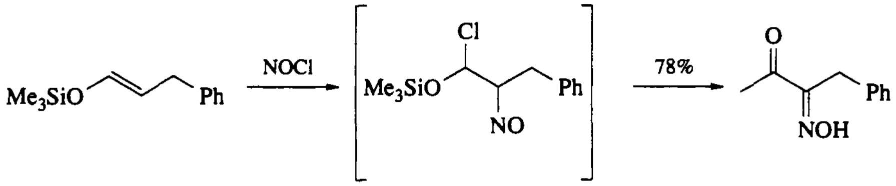

Scheme 71

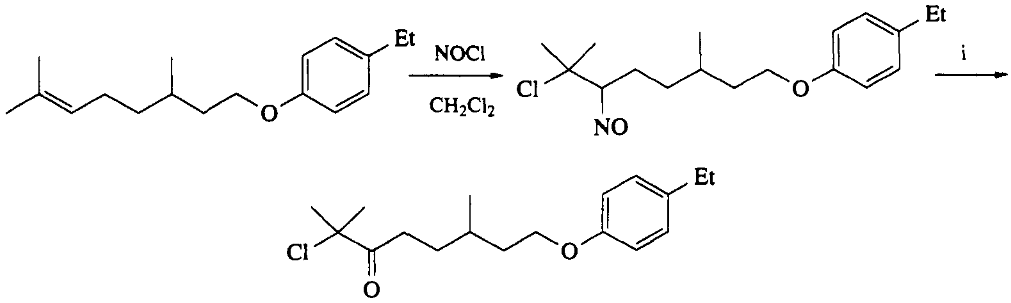

i, levulinic acid, acetone

Scheme 72

Nitryl halides have been more popular reagents. Treatment of substituted styrenes with iodine and sodium nitrite leads to Markovnikov addition of $NO_2I$ (electropositive $NO_2$) to the double bond. Elimination of HI affords β-nitrostyrenes[149,150] as shown in Scheme 73.[149] (*E*)-2-nitro-1-(trimethylsilyl)ethylene has been prepared by addition of nitryl chloride to trimethylsilylethylene, followed by elimination of HI. The author advertises the use of $NO_2Cl$ and the other reagents involved as more economical than some of the other approaches to the nitroalkene (Scheme 74).[151]

## 1.8.6 ELECTROPHILIC BORON

The electrophilic addition of hydrogen-bearing boranes to alkenes (hydroboration), now recognized as a vital component of organic synthesis, is covered in Chapter 1.7 of this volume. The boron compounds that do fall under the realm of this chapter are boron bromides. Suzuki and coworkers have demonstrated

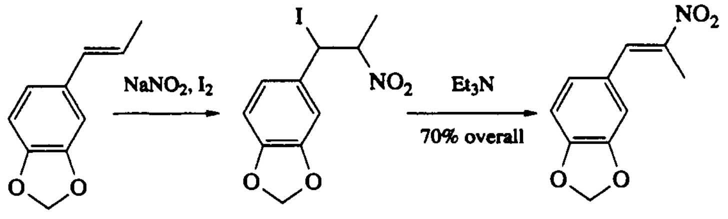
NaNO2, I2
I
NO2
Et3N
70% overall
NO2
O
O

Scheme 73

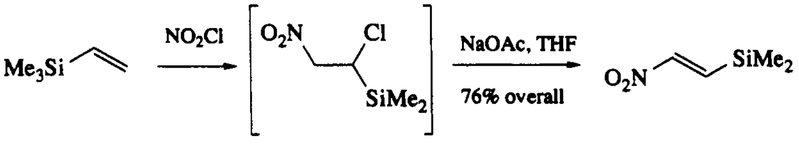
Me3Si
NO2Cl
O2N
Cl
SiMe2
NaOAc, THF
76% overall
O2N
SiMe2

Scheme 74

that these species are synthetically useful X—Y addition reagents for the functionalization of terminal alkynes and allenes.[152] Addition of B-bromo- or B-iodo-9-borabicyclo[3.3.1]nonane (B-X-9-BBN) and $BBr_3$ was found to proceed in a Markovnikov manner to afford *cis* alkenes. The reagents are chemoselective for terminal alkynes and allenes, while internal alkynes and simple alkenes of either type remain unaffected.[152]

The synthetic utility of the products of haloborane addition, β-halovinylboranes, gives this chemistry its great value. For instance, the products of addition of $BBr_3$ can be treated with phenyl isocyanate or a positive halogen source to provide *N*-phenyl-β-bromo-α,β-unsaturated amides[153] or (*Z*)-1-halo-2-bromoalkenes,[154] respectively (Scheme 75). The vinyl boranes can also be oxidized under buffered conditions as a means of preparing α-bromoaldehydes (Scheme 75).[155] Alternatively, organozinc nucleophiles, when used along with a palladium catalyst, have been shown to displace the bromine of the bromovinyl boranes.[156] The boron substituent remains intact under these conditions.[156]

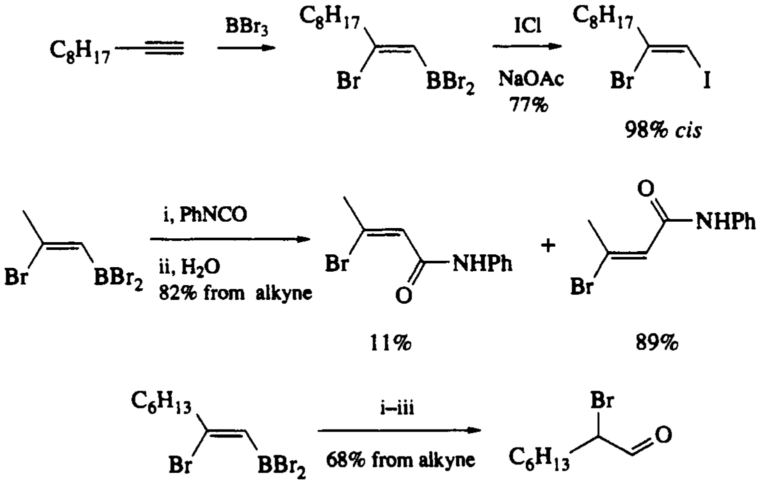
C8H17
BBr3
C8H17
Br
BBr2
ICl
NaOAc
77%
C8H17
Br
I
98% cis
Br
BBr2
i, PhNCO
ii, H2O
82% from alkyne
Br
NHPh
O
+
O
NHPh
Br
11%
89%
C6H13
Br
BBr2
i–iii
68% from alkyne
Br
C6H13
O

i, pH 5 buffer; ii, KOAc; iii, $H_2O_2$

Scheme 75

The synthetic utility of the alkyne/B-X-9-BBN adducts has also been explored.[152] (*Z*)-1-Alkynyl-2-halo-1-alkenes are the result of lithium alkynide action on these latter boranes (Scheme 76).[157] The adducts resulting from the treatment of alkynes with B-X-9-BBN have been shown to be labile under protic conditions. However the decomposition has been harnessed and is an efficient preparation of 2-halo-1-alkenes.[158]

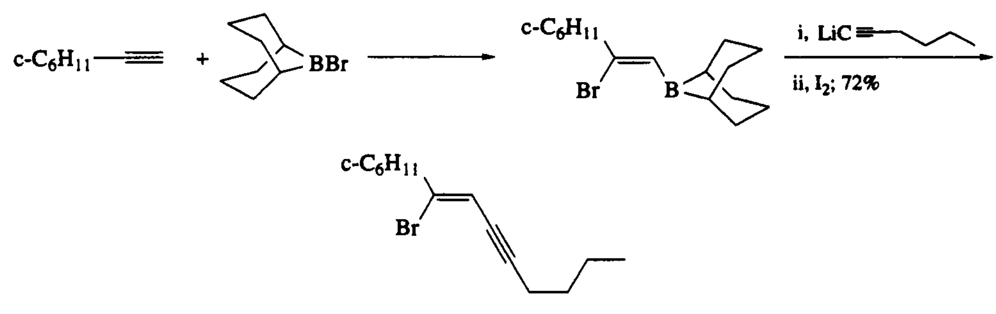

Scheme 76

## 1.8.7 REAGENTS THAT ADD *VIA* ELECTROPHILIC AND RADICAL MECHANISMS

In the course of reaction with an alkene or alkyne many reagents of type X—Y can be dissociated into radical pairs X· Y· as well as, or instead of, ionic species $X^+Y^-$. In some cases the radical pair can add to the π-bond(s) (see Chapter 4.1 of this volume). Furthermore, in some cases both ionic and radical behavior can be observed in the same reaction. For example, while the sulfonyl bromide bromomethanesulfonyl bromide, $BrCH_2SO_2Br$, adds to alkenes and alkynes by processes that most likely involve free radicals (equation 21),[159] mechanisms are less clear cut in other related cases, (equation 22[160] and Scheme 77).[161]

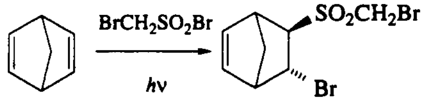

(21)

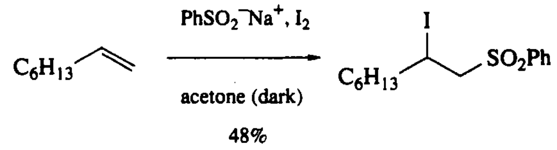

(22)

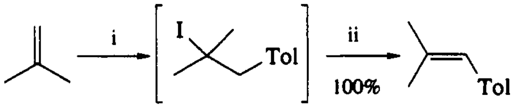

i, $Ts^-Na^+\cdot H_2O/I_2$, MeOH; ii, $Et_3N/MeCN$

Scheme 77

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# 1.9
# Electrophilic Heteroatom Cyclizations

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## 1.9.1 INTRODUCTION

### 1.9.1.1 Coverage

This chapter on electrophilic heteroatom cyclizations covers reactions of carbon–carbon π-bonds in which activation by an *external* electrophilic reagent results in addition of an *internal* heteroatom nucleophile. The general reaction is illustrated in Scheme 1. These cyclization reactions generate heterocyclic products, but many synthetic applications involve subsequent cleavage of the newly formed heterocyclic ring.

The above definition excludes a number of types of heteroatom cyclofunctionalization reactions from discussion in this chapter. Examples include: neighboring group participation in which the cyclic structure is only a transient intermediate; cyclization reactions where the C—C π-bond is internally activated

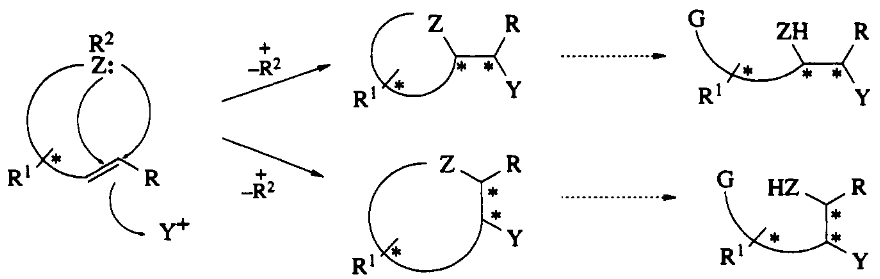

Z = O, N, S

Y = $H^+$, $M^{n+}$ (Hg, Ag, Pd, Tl, Te, Fe), $RSe^+$, $RS^+$

Scheme 1

(conjugation with another functionality) *and* the reaction is best considered as an acid- or base-initiated Michael reaction; cationic π-cyclization where the cyclofunctionalization is the termination step; and reactions in which the heterocyclization involves the heteroatom acting as an electrophile or reactive radical.

Several recent reviews have included specific types of electrophilic cyclofunctionalization reactions.[1] Important areas covered in these reviews are: halolactonization;[1a] cyclofunctionalization of unsaturated hydroxy compounds to form tetrahydrofurans and tetrahydropyrans;[1b] cyclofunctionalization of unsaturated amino compounds;[1c] cyclofunctionalization of unsaturated sulfur and phosphorus compounds;[1d–1f] electrophilic heterocyclization of unconjugated dienes;[1g] synthesis of γ-butyrolactones;[1h] synthesis of functionalized dihydro- and tetrahydro-furans;[1j] cyclofunctionalization using selenium reagents;[1k,1m] stereocontrol in synthesis of acyclic systems;[1n] stereoselectivity in cyclofunctionalizations;[1p] and cyclofunctionalizations in the synthesis of α-methylenelactones.[1q] Previous reference works have also addressed this topic.[2]

### 1.9.1.2 Synthetic Considerations

The identity of the heteroatom present in a target molecule dictates the identity of the nucleophilic atom (Z) to be used in an electrophilic heteroatom cyclization reaction of the type shown in Scheme 1. However, successful application of this strategy to the synthesis of specific target molecules also requires selection of appropriate combinations of nucleophilic functionality (Z–R) and activating electrophile. Therefore, major subdivisions within this chapter are based on the identity of the heteroatom, although comparisons between results observed for the different heteroatoms will be made.

These heterocyclization reactions provide initial products with a functionality β to the heteroatom, except for cases where a proton is the electrophile. Synthetic applications often depend upon further transformation of this functionality. Useful transformations include: replacement by hydrogen, elimination to form a π-bond, nucleophilic substitution, and substitution *via* radical intermediates. These reactions will be discussed only when understanding the cyclization step requires inclusion of the functional group transformation.

Although these cyclofunctionalization reactions have been used extensively to generate specific heterocyclic structures in target molecules, they can also be used to control the introduction of functional groups which are not part of a heterocyclic system. Cyclofunctionalization followed by ring cleavage (see Scheme 1) has been used to introduce functionality into existing ring systems or acyclic systems with control of regiochemistry and stereochemistry, to control conformational mobility and to serve as a means for protecting the double bond and/or nucleophilic functional group against other reagents in a synthesis. The most recent extensions of this synthetic strategy involve the synthesis and cyclization of substrates in which the nucleophilic Z group is attached to the substrate by a transient 'tether', which is added to an initial substrate and removed after cyclization to generate the final product (Scheme 2).

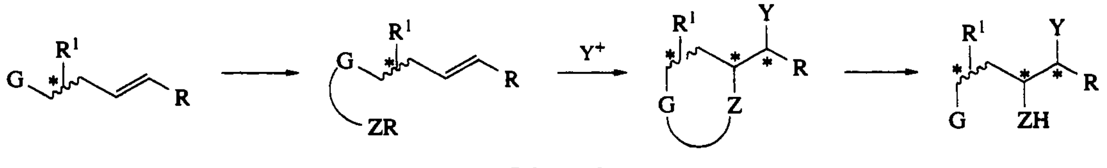

Scheme 2

## 1.9.1.3 Mechanistic Considerations

### 1.9.1.3.1 General mechanism

A generalized mechanism for electrophile-initiated cyclofunctionalization is shown in Scheme 3. (To simplify this initial discussion, factors affecting regioselectivity will not be considered until later.) The specific mechanistic pathway may vary from system to system, but it is generally considered that an activated intermediate must be involved. Reaction of the π-system with an electrophile can generate several potential intermediates for the cyclization (a π-complex **B**, a cyclic 'onium' ion **C**, an addition product **D**, a carbocation **E** or an intermediate with an electrophile–Z bond **F**), each of which could undergo attack by the internal nucleophile to give cyclic products. Each type of intermediate has been considered to be involved in some examples of cyclofunctionalization, but most cyclofunctionalizations are best rationalized with intermediates (**B**) and/or (**C**). Although Scheme 3 shows each intermediate being generated from the starting alkene, interconversions between intermediates (**B**) to (**F**) are expected in some cases.

All mechanistic pathways that generate product (**H**) represent examples of neighboring group participation, but anchimeric assistance is observed only if the rate-limiting step is that of ring closure.[3] Since each of the steps may be readily reversible under the conditions of the reaction, it is not always clear whether a given reaction was conducted under conditions of kinetic or thermodynamic control, which step was rate-limiting, or which step controlled the stereochemistry.

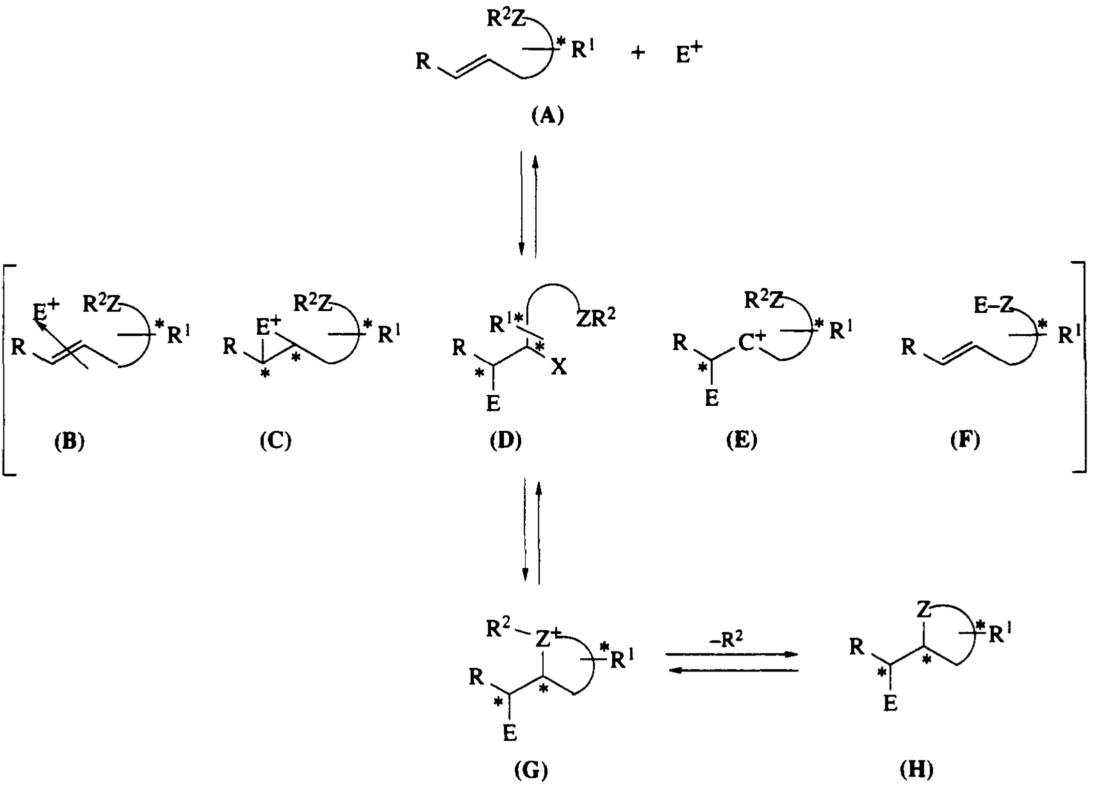

Scheme 3

Most of the types of cyclofunctionalization reaction discussed in this chapter have been shown to result in stereospecific *anti* addition across the π-bond. This result suggests that the important intermediates are π-complexes (**B**) or 'onium' ions (**C**) rather than carbocations (**E**). In the case of cyclofunctionalization with some electrophiles, such as phenylselenenyl chloride, it has been shown that the formation of addition products such as (**D**) occurs faster than the cyclization.[4] Stereospecific *trans* addition in these reactions then requires conversion to intermediates (**B**) or (**C**) before nucleophilic attack, since nucleophilic attack on intermediate (**D**) and substitution of X with inversion would result in *syn* addition. Thus, in the discussions below, intermediates (**B**) and/or (**C**) are considered to be the key cyclization precursors in most reactions. It should be noted that cyclization of intermediate (F) by alkene insertion would be expected to lead to stereospecific *syn* addition also.

In a few cases, detailed mechanistic studies have shown that the cyclization step is rate limiting.[5,6,7] One method has been to demonstrate that the overall rate of reaction is a function of the nucleophilicity of the ZR group or of the formed ring size.[5,6] However, the cyclization step need not be the rate-limiting step in all electrophilic heteroatom cyclizations.[8] The uncertainty about which step is rate limiting complicates attempts to derive general rationales for predicting the stereochemical results of these reactions.

### *1.9.1.3.2 Stereoselectivity*

When the cyclization substrate (A; Scheme 3) contains stereogenic centers, and the formation of the C—Z bond generates a new stereogenic center, two diastereomers of the cyclization product (H) can be formed (stereospecific *anti* addition assumed). The factors which lead to high stereoselectivity in this process are of considerable importance and have been the subject of numerous studies in recent years. This reaction mechanism shows that all pathways leading to cyclic products are potentially reversible; thus, the ratios of products in these reactions may be the result of thermodynamic rather than kinetic control. Unfortunately, many studies have not determined which type of control was operating under the reaction conditions used.

The stereoselectivity of cyclization reactions conducted under conditions of thermodynamic control can often be reliably predicted by estimation or calculation of the energy differences between the diastereomers of the cyclization product (H) or its immediate precursor (G). It has been shown that, even in cases where the (G) to (H) step is not reversible, thermodynamic control of the diastereomer ratio can be influenced through the use of cyclization substrates in which the neutralization step (G to H) is the slow step, thus allowing for equilibration of the diastereomers of (G). Thermodynamic equilibration of diastereomeric products will occur only if the reaction reverses to starting materials (A), or interconversion of the diastereomers of the intermediates (B) or (C) occurs in some other way (*e.g.* the C to D interconversion can equilibrate diastereomers if E = X).

The factors controlling product stereochemistry under conditions of kinetic control depend upon which step of the reaction is rate limiting. The initial reaction of an electrophile with (A) leads to diastereomers of intermediates (B) and/or (C). If the formation of these intermediates is the slow step of the reaction, stereoselectivity will be determined by the diastereofacial discrimination in the attack of the electrophile on the π-system. The stereoselectivity of the reaction will be controlled in the cyclization step *only* if the ring closure is rate limiting and the diastereomeric precursor intermediates are interconverting rapidly. In any case, it is apparent that high stereoselectivity will be observed only if the chiral elements present in the starting substrate result in significant energy differences between the diastereomeric transition states in the product-determining step.

The most successful examples of stereochemical control in electrophilic heteroatom cyclizations are those in which the substitution pattern constrains the substrate so that the two diastereofaces of the π-system are significantly different. The most straightforward prediction of stereochemistry involves incorporating both the π-system and the directing chiral center into a ring such that rotation about the vinylic bond that attaches the nucleophile to the double bond is highly restricted. Comparison of equations (1) and (2) illustrates this difference. For this reason, in the sections on cyclizations to form five- and six-membered rings, examples with constrained C═C—C bonds will be discussed separately.

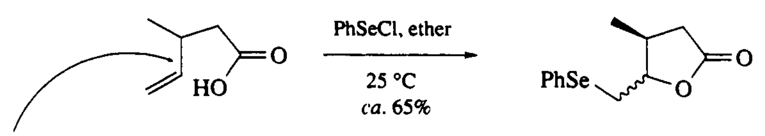

(1)

variety of conformations possible

1:1 mixture of isomers

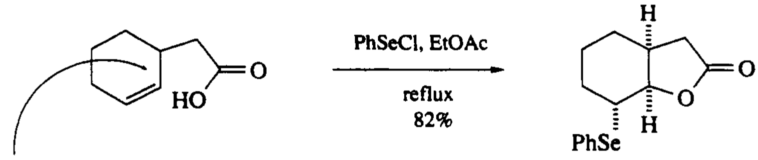

(2)

bond rotation severely restricted

single diastereoisomer

### *1.9.1.3.3 Regioselectivity*

While the regiochemistry of simple electrophilic additions to double bonds is controlled by a combination of electronic (Markovnikov rule), stereoelectronic (*trans* diaxial addition to cyclohexenes) and steric factors,[9] the intramolecular nature of electrophilic heteroatom cyclizations introduces additional conformational, stereoelectronic and entropic factors. The combination of these factors in cyclofunctionalization reactions results in a general preference for *exo* cyclization over *endo* cyclization (Scheme 4).[3,10] However, *endo* closure may predominate in cases where electronic or ring strain factors strongly favor that mode of cyclization. The observed regiochemistry may differ under conditions of kinetic control from that observed under conditions of thermodynamic control.

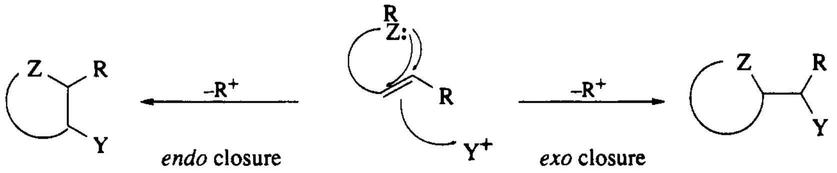

**Scheme 4**

The stereochemistry and regiochemistry of cyclofunctionalization reactions in the following sections are discussed in terms of the above mechanistic concepts. Emphasis is placed on the relationship between the products and the heteroatom-substituted substrates; thus, examples of electrophilic heterocyclization involving two sequential additions to nonconjugated dienes are not discussed. These reactions have been covered in a recent review.[1g]

## 1.9.2 OXYGEN NUCLEOPHILES

Cyclofunctionalization reactions involving oxygen nucleophiles have been studied more extensively than reactions involving any other heteroatom. Examples of functional groups used as oxygen nucleophiles are shown in Figure 1.

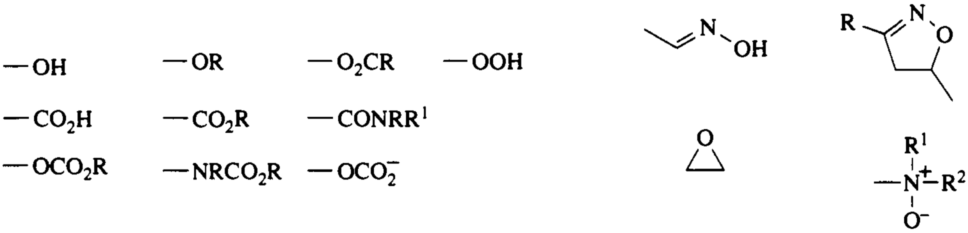

**Figure 1**

### 1.9.2.1 Small Rings

The formation of strained three- and four-membered rings by electrophile-initiated cyclization requires that the reaction be conducted under conditions which minimize the possibility of simple addition of the activating reagent across the double bond or reversal of the cyclization product to intermediates that can be trapped by external nucleophiles.

Cyclization of allylic alcohols to form epoxides has been particularly problematical, and the reactions have been more of mechanistic than of synthetic interest. For reactions conducted under basic conditions, it is possible that epoxide formation involves initial halogen addition followed by nucleophilic displacement to form the epoxide. Early examples of direct formation of epoxides from allylic alcohols with sodium hypobromite,[11] bromine and 1.5 M NaOH,[12] and *t*-butyl hypochlorite[13] have been reviewed previously.[1p] Recently it has been shown that allylic alcohols can be cyclized effectively with bis(*sym*-collidine)iodine(I) perchlorate (equation 3).[14] An unusual example of epoxide formation competing with other cyclization types is shown in equation (4).[15] In this case, an allylic benzyl ether competes effectively with a γ-hydroxyl group as the nucleophile.

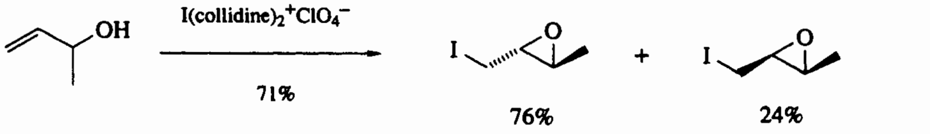

(3)

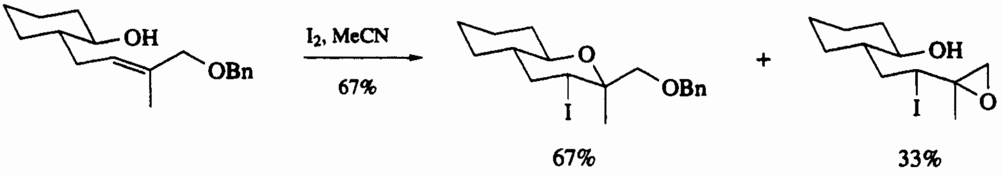

(4)

Cyclofunctionalization of homoallylic alcohols with bis(*sym*-collidine)iodine(I) perchlorate produces oxetanes in good yield if the 4-*exo* mode of cyclization is favored electronically by the alkene substitution pattern (Table 1).[14] Geminal substitution at the carbinol carbon also favors this mode of cyclization (compare entries 2 and 3 with entry 1). Substitution at C-3 leads to reaction only by the 4-*exo* mode (entry 4), while substitution at C-4 leads to cyclization only *via* the 5-*endo* mode (entry 5).

**Table 1** Cyclization of Homoallylic Alcohols with I(collidine)$_2$$^+$ ClO$_4$$^-$

| *Entry* | *Reactant* | *Yield (%)* | *Product(s) (% of total)* | |
|---|---|---|---|---|
| 1 | 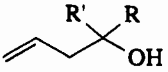 | | 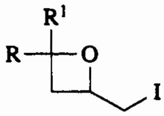 | 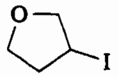 |
| | R = R' = H | | 50 | 50 |
| 2 | R = R' = Me | 62 | 100 | |
| 3 | R, R' = (CH$_2$)$_5$ | 64 | 100 | |
| 4 | 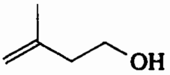 | 67 | 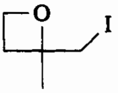 | |
| 5 | 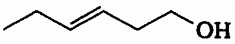 | 70 | 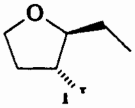 | |

One example of oxetane formation proceeding by an intramolecular *syn* addition of a sulfenate ester intermediate has been reported (equation 5).[16] This mode of cyclofunctionalization appears to fail unless the substrate enforces the correct alignment of the sulfenate ester.[16b] However, related 7-oxanorbornen-2-ols give oxetane products with an *exo* phenylsulfenyl group.[17]

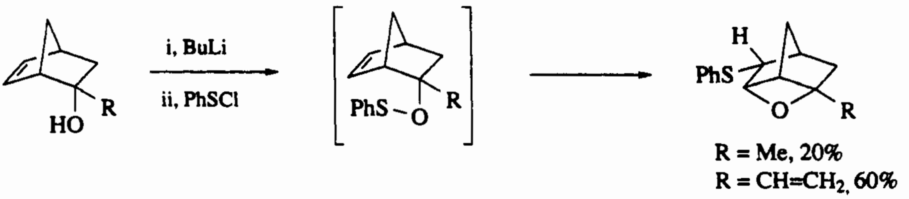

(5)

Cyclizations of β,γ-unsaturated acids form β-lactones (4-*exo* cyclization) when the reactions are conducted under conditions of kinetic control.[1a,1p] The most common procedure for β-lactone formation, developed by Barnett, involves halolactonization in a two-phase system using an aqueous solution of the carboxylate salt of the substrate with the halogen (Br$_2$ or I$_2$) added in an organic solvent.[18] Cyclization with bis(*sym*-collidine)iodine(I) perchlorate provides a higher yield than the Barnett procedure in cases where cyclization is not favored by geminal α-substitution (Table 2, entries 1 and 2).[14] Iodo- and bromolactonization of thallium salts of the carboxylic acids have also been shown to be useful procedures for formation of β-lactones.[21,22] It should be noted that the initially formed β-lactone products may be readily rearranged to thermodynamically more stable γ-lactones.[19,23,24]

**Table 2** Cyclization of β,γ-Unsaturated Acids to β-Lactones

| *Entry* | *Reactant* | *Conditions* | *Yield (%)* | *Product(s) (% of total)* | | *Ref.* |
|---|---|---|---|---|---|---|
| | 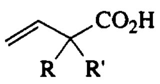 | | | 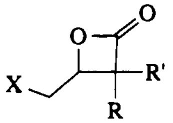 | | |
| 1 | R = R' = H | aq. $NaHCO_3$, $I_2$, $Et_2O$ | 25 | | | 18b |
| 2 | R = R' = H | $I(collidine)_2^+ ClO_4^-$ | 75 | | | 14 |
| 3 | R = R' = H | $Tl_2CO_3$, $Br_2$, $CH_2Cl_2$ | 51 | | | 21 |
| 4 | R = R' = Me | aq. $NaHCO_3$, $I_2$, $Et_2O$ | 75 | | | 18b |
| | 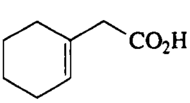 | | | 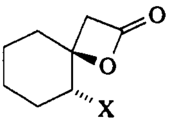 | 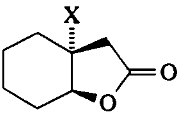 | |
| 5 | | NBS/DMF | 53 | 100 | 0 | 21 |
| 6 | | aq. $NaHCO_3$, $Br_2$, $CH_2Cl_2$ | 66 | 67 | 33 | 21 |
| | 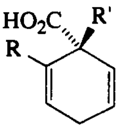 | | | 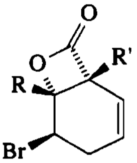 | | |
| 7 | R = R' = H | aq. $NaHCO_3$, $Br_2$, $CH_2Cl_2$ | 42–94 | | | 19,20 |

Formation of β-lactones by 4-*endo* cyclization has been observed in very few cases. Examples of such halolactonization reactions proceeding by stereospecific *anti* addition have been discussed in previous reviews.[1p,2b]

### 1.9.2.2 Five- and Six-membered Rings

The lack of significant ring strain and favorable entropic factors results in facile cyclofunctionalization to form five- or six-membered rings. Emphasis in this review is placed on examples which illustrate general principles of regiochemical and stereochemical control.

#### *1.9.2.2.1 Cyclizations with C═C—C constrained by existing ring*

Electrophile-initiated cyclizations of substrates where an existing ring constrains rotation of the vinylic bond which attaches the nucleophile to the double bond generally occur with quite predictable stereochemical and regiochemical control. These reaction types have been used extensively in synthesis and only representative examples and leading references will be presented here.

*(i) Synthesis of fused ring lactones and ethers*

The cyclization of 2-cycloalkeneacetic acids leads to *cis*-fused γ-lactones arising from *anti* addition across the double bond (equation 6 and Table 3). This type of reaction, effected with a wide variety of electrophiles and substrate substitution patterns, has been used both for generation of γ-lactone target molecules and selective introduction of a hydroxy group onto the original ring by cleavage of the lactone cyclization product. As shown in equation (7), the 5-*exo* mode of cyclization is preferred even when this mode of addition is anti-Markovnikov.[1q,37] However, one example of iodolactonization to a tricyclic product produced a mixture of a γ-lactone and a bridged ring δ-lactone (6-*endo* cyclization).[38]

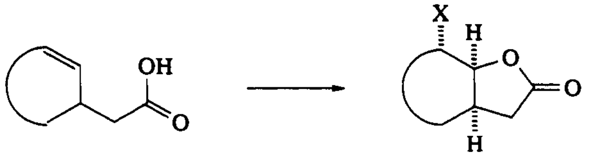

(6)

Table 3 Fused Ring γ-Lactones from Cyclization of 2-Cycloalkenylacetic Acids (Equation 6)

| *X* | *Refs.* | *X* | *Refs.* |
|---|---|---|---|
| I | 22, 25–28 | RS | 16b, 32, 35 |
| Br | 21, 25a, 29, 30 | H | 1q, 33 |
| PhSe | 4, 31, 36 | $ArCl_2Te$ | 34 |

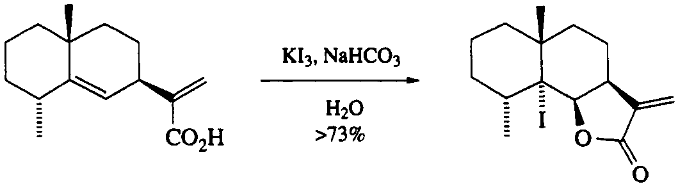

(7)

Cyclization to yield fused ring γ-lactones has also been effected using *N*,*N*-dialkylamide derivatives as the nucleophile, as shown in equation (8).[29,39,40] Isolation of the fused ring iminolactone from cyclization of an *N*-monoalkylamide derivative with phenylselenenyl chloride has been reported also.[41]

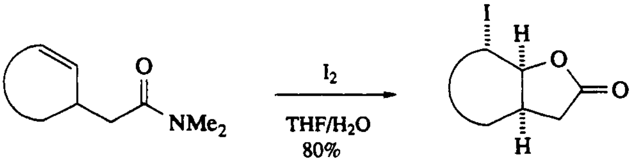

(8)

Cyclizations with some electrophiles generate products in which the C—E bond is solvolyzed under the reaction conditions. Cyclization of 2-cyclopenteneacetic acid with lead tetraacetate forms the acetoxy-substituted lactone from solvolysis of the plumbolactonization intermediate (equation 9).[42] When the substrate contains a second suitably located carboxylate group, bislactones are generated (equation 10).[43,44] Similar cyclizations to form ether–lactones have been reported.[45] Unsaturated fused ring lactones have been obtained from 2-cyclopenteneacetic acid upon treatment with hydroxy(tosyloxy)-iodobenzene or hydroxybis(phenyloxy)phosphoryloxyiodobenzene, as shown in equation (11).[46]

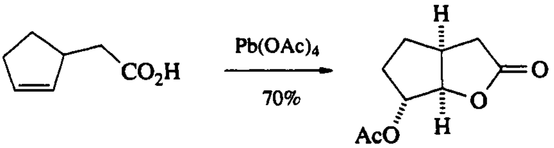

(9)

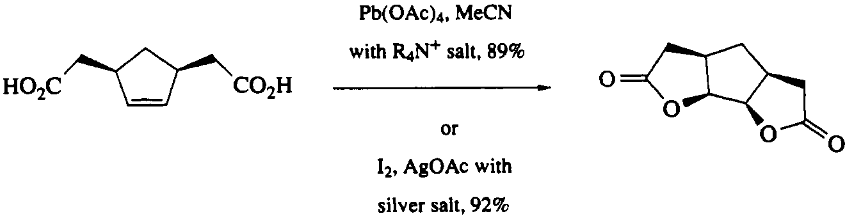

(10)

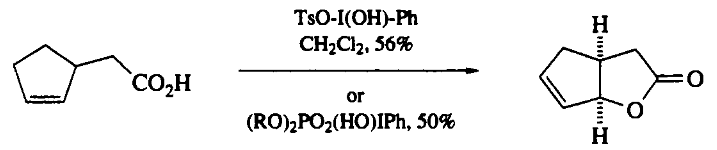

(11)

Fused ring γ-lactones may also be formed by cyclizations of 1-cycloalkeneacetic acids under equilibrating conditions. Nicolaou obtained evidence for the presence of an unstable β-lactone in the phenylselenolactonization of 1-cyclohexeneacetic acid, but rearrangement occured readily at room temperature to the more stable γ-lactone (equation 12).[32] An example of a one-step conversion of a 2-methyl-1-cyclohexeneacetic acid to a fused butenolide by use of diphenyldiselenide and electrochemical oxidation has been reported.[47] Recent studies by Rutledge showed that simultaneous addition of bromine and thallium carbonate to 1-cyclohexeneacetic acid gave the γ-lactone as the exclusive product (compare to Table 2); however, the mechanism of this reaction may differ from other cyclofunctionalizations.[21]

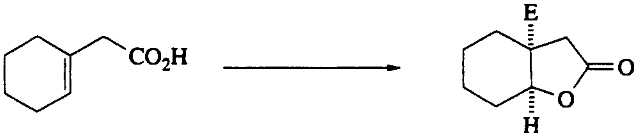

(12)

| | | |
|---|---|---|
| PhSeCl or PhSCl | E = PhSe or PhS | (ref. 32) |
| $Tl_2CO_3$ and $Br_2/CH_2Cl_2$ | E = Br | (ref. 21) |

The cyclofunctionalization of cyclohexa-2,4-dieneacetic acids results in 1,4-addition to form *cis*-fused γ-lactones, as shown in equation (13) and Table 4. Most reaction conditions gave products with the electrophile *trans* to the lactone ring (entries 1–4), but the stereochemistry of the palladium-catalyzed reaction was reversed if an excess of a complexing ligand was added to the reaction (entries 5 and 6).[49,50] Results of lactonization in cyclohepta-2,4-dieneacetic acid systems were similar, but selenolactonization produced 1,2-addition products under some conditions.[51] It is possible that these products result from a 1,3-rearrangement of the initial allyl selenide.[52]

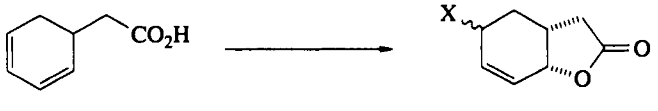

(13)

**Table 4** Cyclofunctionalization of Cyclohexa-2,4-dieneacetic Acid (Equation 13)

| *Entry* | *Conditions* | *Yield (%)* | *X* | *Ref.* |
|---|---|---|---|---|
| 1 | PhSeCl, $Et_3N$, $CH_2Cl_2$ | 70 | β-SePh | 48 |
| 2 | $I_2$, MeCN | 60 | β-I | 48 |
| 3 | $Hg(OAc)_2$, $BF_3$/MeOH | 60 | β-HgOAc | 48 |
| 4 | 5 mol % $Pd(OAc)_2$, HOAc, acetone, benzoquinone | 77 | β-OAc | 49 |
| 5 | Entry 4 plus 2 equiv. LiOAc and 0.5 equiv. LiCl | 57 | α-OAc (76%) | 49 |
| 6 | Entry 4 plus 2 equiv. LiOAc and 2 equiv. LiCl | 75 | α-Cl (>95%) | 49 |

*Cis*-fused tetrahydrofurans are produced when 2-cycloalkenyl-substituted ethanol derivatives are cyclized *via* 5-*exo* ring closure (equation 14 and Table 5). The related 1-cycloalkenyl alcohol systems also yield *cis*-fused tetrahydrofurans upon reaction with phenylselenyl reagents, similar to their carboxylic acid analogs (see equation 12).[60] A sulfoetherification to a fused ring tetrahydrofuran from a system with an exocyclic methylene provided an 86:14 ratio of *cis*- and *trans*-fused isomers.[61]

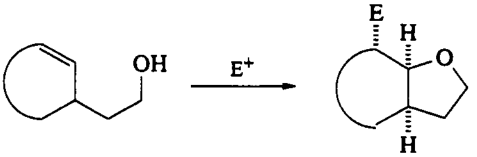

(14)

**Table 5** Cyclization to Fused Ring Tetrahydrofurans (Equation 14)

| *Entry* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| 1 | $I_2$, $Na_2CO_3$, MeCN | >78 | 53 |
| 2 | $I^-$ or $Br^-$ + MCPBA | 85 and 78 | 30 |
| 3 | NBS, acetone | 85 | 54 |
| 4 | PhSeCl | 86–90 | 55, 57 |
| 5 | PhSeNPht | 83 | 31,60 |
| 6 | $Hg(OAc)_2$ | >66 | 59 |
| 7 | $(ArTe{=}O)_2O$, HOAc | 42–53 | 58 |
| 8 | $ArTeCl_3$, $CHCl_3$, Δ | 90 | 56 |

A recent study of group selectivity in iodocyclizations which could form either *cis*-fused tetrahydrofuran or γ-lactone products (equation 15) has shown that the observed selectivity correlates with the conformational bias of each isomeric substrate.[62] One isomer, with no significant conformational bias, produced a mixture of the products upon cyclization of the ester, but gave only the γ-lactone upon cyclization of the carboxylic acid.

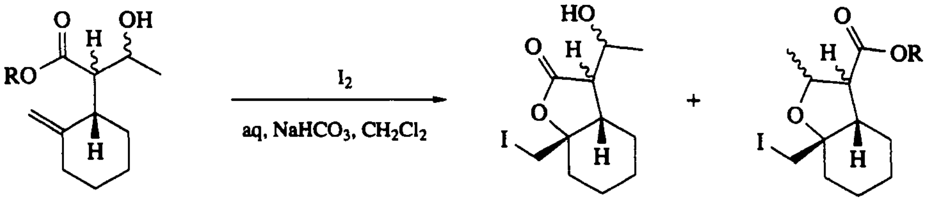

(15)

In cyclofunctionalization of some substituted cyclohexadienylethyl alcohols, products of 1,4-addition were observed (equation 16).[63] However, the stereochemistry of the addition to the diene functionality depended upon the choice of electrophile.

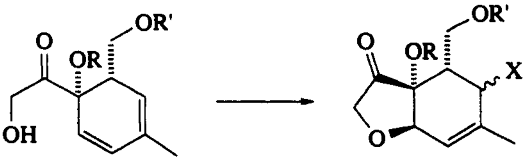

(16)

| *Conditions* | *Yield* | *X* |
|---|---|---|
| PhSCl, $CH_2Cl_2$ | | α-SPh |
| PhSeCl, $NaHCO_3$, $CH_2Cl_2$ | >70% | α-SePh |
| NBS, $CH_2Cl_2$ | 94% | β-Br |

Few applications of cyclizations to form fused ring δ-lactones or tetrahydropyrans are found. Two consecutive bromolactonizations were used to effect stereoselective dihydroxylation of a cyclohexadienone system in a total synthesis of erythronolide B (Scheme 5).[64a] Iodolactonization of an *N,N*-diethylbenzamide derivative to form a *cis*-fused benzolactone was a key step in a recent synthesis of pancratistatin.[64b] A *cis*-fused tetrahydropyran was produced in good yield by intramolecular oxymercuration as shown in equation (17),[59] although attempts to cyclize a more highly functionalized system have been reported to fail.[65] Formation of a fused ring tetrahydropyran *via* an anti-Markovnikov 6-*endo* selenoetherification has been reported in cases where steric and stereoelectronic factors disfavor a 5-*exo* cyclization to a spirocyclic structure.[38]

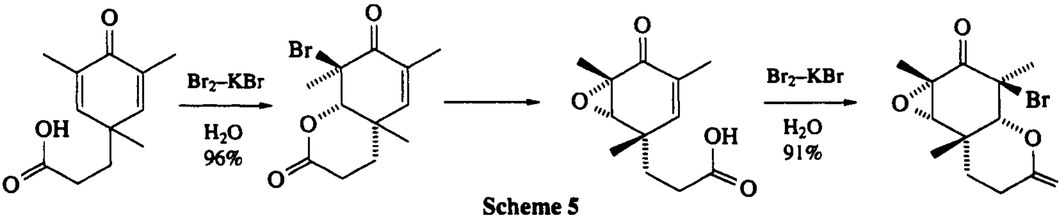

Scheme 5

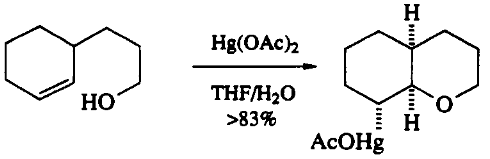

(17)

### (ii) Synthesis of bridged ring lactones and ethers

Cyclofunctionalization of cycloalkenyl systems to form bridged ring systems under kinetically controlled conditions generally results in products formed from *exo* cyclization. This type of cyclization has been applied to the synthesis of a variety of natural products and novel unnatural products including twistane,[66] dodecahedrane,[67] reserpine,[68] picrotoxin,[69] gibberellins[70] and antheridiogens,[71] kessanol,[72] incensole,[73] the quassinoid ring system,[74] isolineatin,[75] actinobolin,[76] aklavinone and ε-pyrromycinone,[77] shikimic acid derivatives,[78] *exo*-brevicomin and the *Mus musculus* pheromone,[79,80,81] compactin and mevinolin[82] and glycinoeclipin A.[83,84] Many examples have been covered in earlier reviews of halolactonization,[1a] intramolecular oxymercuration,[85] phenylselenoetherification and lactonization[1k,1m] and cyclizations to form tetrahydrofurans and tetrahydropyrans.[1b] Syntheses of diheterotricyclodecanes by a variety of cyclofunctionalization reaction types have been included in an earlier review (see Scheme 6).[86]

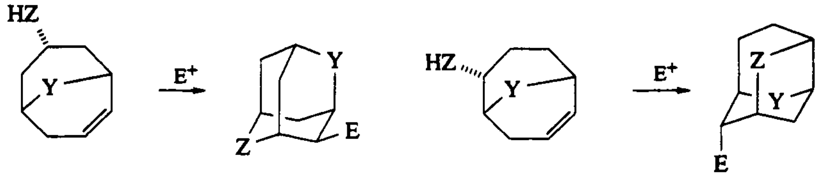

2,6-diheteroadamantane

2,7-diheteroisotwistane

**Scheme 6**

Some unusual nucleophile functional groups that have been utilized in cyclofunctionalizations to form bridged ring systems include cyclic hemiacetals (equation 18)[75] and epoxides (equation 19).[87] The cyclizations in equation (20) involve a cyclic enol ether as the reactive π-system and have been used in syn-

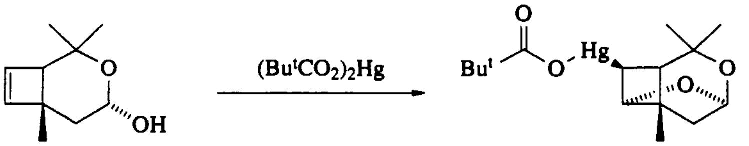

(18)

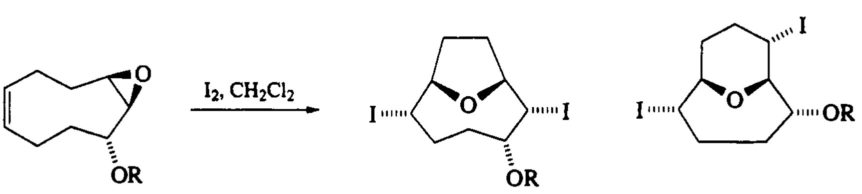

(19)

R = OAc, >94% 40% 60%
R = SiBu$^t$Me$_2$, >89% 0% 100%

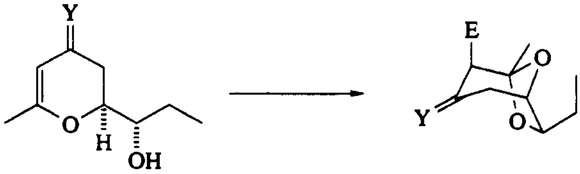

(20)

| | | | |
|---|---|---|---|
| Y = H, H | PhSeCl, Et$_3$N | 91% | E = PhSe |
| Y = O | Hg(OAc)$_2$ | | E = HgOAc |
| Y = H, OH | Hg(OAc)$_2$ | | E = HgOAc |

theses of *exo*-brevicomin and the *Mus musculus* pheromone.[79,80,81] Bridged spiroacetals have also been synthesized by palladium(II)-mediated cyclization of ω-unsaturated diols, as shown in equations (21) and (22).[88,89,90] These bis-heterocyclizations result from the facile β-hydrogen elimination of the initially formed σ-alkylpalladium intermediate to form an enol ether that serves as the substrate for the second cyclization.[50]

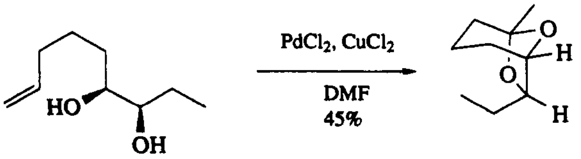

(21)

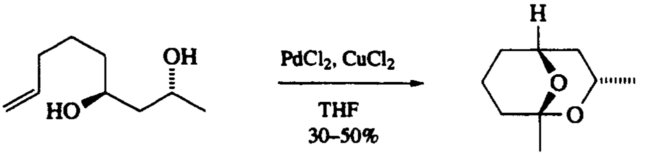

(22)

As mentioned earlier in the discussion of cyclizations leading to β-lactones, the β-lactones formed from halolactonization of 1,4-dihydrobenzoic acids readily rearrange to produce bridged ring γ-lactones.[19] In some cases, the substitution pattern favors formation of the γ-lactone even under conditions of kinetic control (equation 23).[20] Synthesis of a variety of γ-lactones by iodolactonization of dihydrobenzoic acid derivatives has been reported recently by Hart (equation 24).[91] Attempted iodolactonization of the acid in the case where R′ = H resulted primarily in an oxidative decarboxylation; however, iodolactonization was effected using the amide derivative.

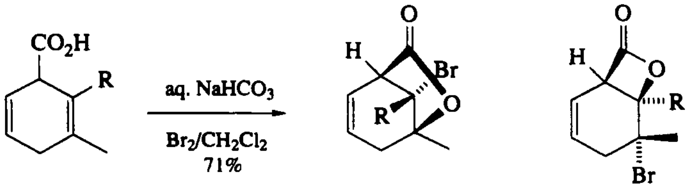

(23)

| | | |
|---|---|---|
| R = H | 93% | 7% |
| R = Me | >80% | <20% |

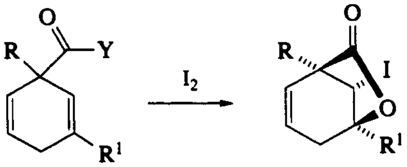

(24)

| | | |
|---|---|---|
| R = alkenyl, $R^1$ = Me, Y = OH | aq. $NaHCO_3$, ether | 61% |
| R = alkenyl, $R^1$ = OMe, Y = OH | aq. $NaHCO_3$, ether | >66% |
| R = alkenyl, $R^1$ = $SPr^i$, Y = OH | aq. $NaHCO_3$, ether | 67% |
| R = alkyl, $R^1$ = H, Y = $NR_2$ | THF, water | 70–94% |

The effect of conformational control on the regiochemistry of cyclizations in steroid systems has been studied extensively by Kočovsky. A cyclization which proceeds both in an anti-Markovnikov and 6-*endo* mode is shown in equation (25).[92]

### *(iii) Cyclization of heteroatom-tethered cyclic systems*

The cyclofunctionalization strategy involving a transient 'tether' attached to a preexisting functional group, as outlined in Scheme 2, has been used to introduce a new oxygen functionality onto a ring with

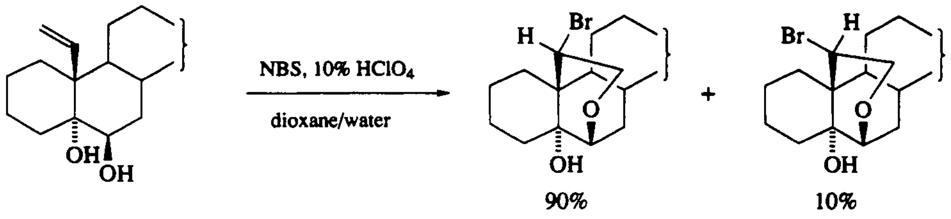
NBS, 10% HClO$_4$
dioxane/water
OH
OH
H
Br
O
OH
90%
+
Br
H
O
OH
10%

(25)

stereochemical and regiochemical control. This strategy has been particularly useful in stereoselective synthesis of amino sugars and aminocyclitols. Examples of cyclizations of derivatives of cyclic allyl alcohols and amines are given in Table 6. The attachment of the tether to an allylic functional group generally leads to *cis*-fused products upon cyclization. Exceptions are found in the cyclizations of the

**Table 6** *O*-Cyclization of Derivatives of Cyclic Allylic Alcohols and Amines

| *Entry* | | | | | *Ref.* |
|---|---|---|---|---|---|
| 1 | 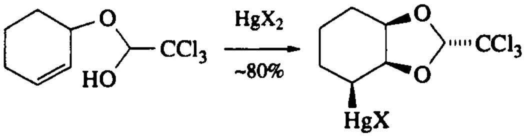  O<br>HO<br>CCl$_3$<br>HgX$_2$<br>~80%<br>O<br>O<br>CCl$_3$<br>HgX | | | | 93 |
| 2 | 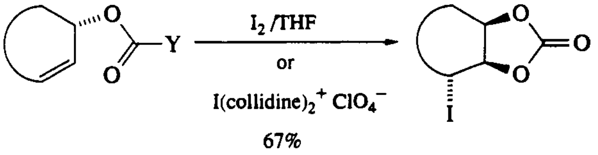  O<br>O<br>Y<br>I$_2$/THF<br>or<br>I(collidine)$_2^+$ ClO$_4^-$<br>67%<br>O<br>O<br>O<br>I | | | | 94 |
| | 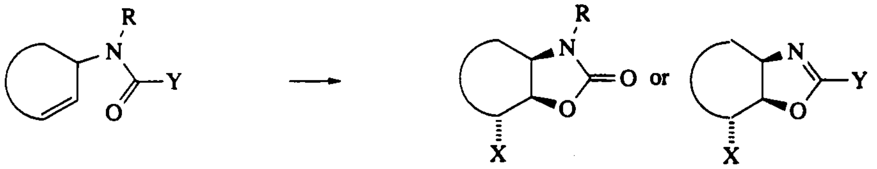  R<br>N<br>O<br>Y<br>R<br>N<br>O<br>O<br>X<br>or<br>N<br>Y<br>O<br>X | | | | |
| 3 | R = alkyl<br>Y = OMe | I$_2$, aq. NaSO$_3$/THF | 96% (X = I) | | 96b, 96c |
| 4 | R = alkyl<br>Y = OMe | i, Br$_2$, AgBF$_4$<br>ii, H$_2$O, NaHCO$_3$ | 79% (X = Br) | | 96a |
| 5 | R = H<br>Y = OEt | I(collidine)$_2^+$ClO$_4^-$<br>CH$_2$Cl$_2$ | | 61% (X = I) | 95a |
| 6 | R = Me<br>Y = OEt | I(collidine)$_2^+$ClO$_4^-$<br>dioxane, Δ | 71% (X = I) | | 95b |
| 7 | R = H<br>Y = OEt | NBS/CH$_2$Cl$_2$, 0 °C | | 60% (X = Br) | 97 |
| 8 | R = H<br>Y = NH$_2$ | PhSeCl, CH2Cl$_2$<br>silica gel, 25 °C | | 76–92% | 98a |
| | 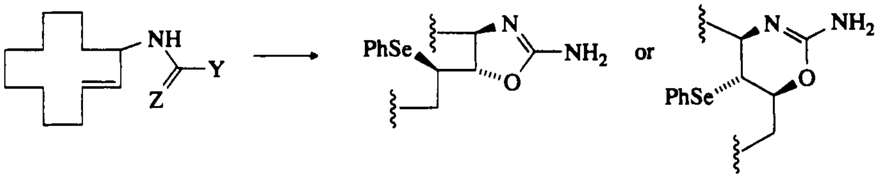  NH<br>Y<br>Z<br>PhSe<br>N<br>NH$_2$<br>O<br>or<br>N<br>NH$_2$<br>O<br>PhSe | | | | |
| 9 | Y = NH$_2$<br>Z = O | PhSeCl, CH$_2$Cl$_2$ | 91% | | 98a |
| 10 | Y = OMe<br>Z = NH$_2$ | PhSeCl, CF$_3$SO$_3$Ag<br>CF$_3$SO$_3$H, silica gel | | 65% | 98b |

*trans*-cycloalkene derivatives shown in entries 9 and 10. Cyclization to a bridged ring product has been observed in the bromocyclization of the phthalimide derivative of cyclohexenylamine.[98c,98d] Cyclic amines which are allylic to an exocyclic methylene also generate *cis*-fused ring systems as shown by equation (26).[96b] The cyclization of carbamate derivatives of cyclic homoallylic amines generates bridged ring systems which are derivatives of 1,3-amino alcohols (equation 27).[99] Preparation of 1,3- and 1,4-diol derivatives *via* cyclofunctionalization of 19-carbamoyloxysteroids has been studied by Kočovsky.[9]

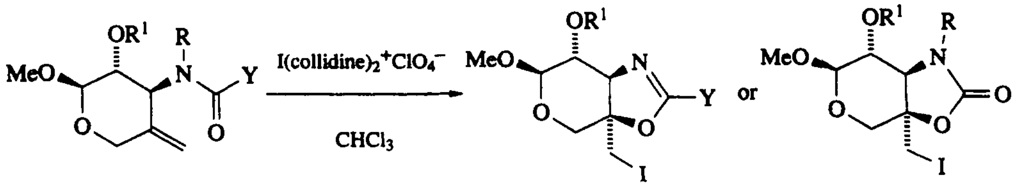

(26)

93–100% (R = H, Y = Ph) 82% (R = Me, Y = OEt)

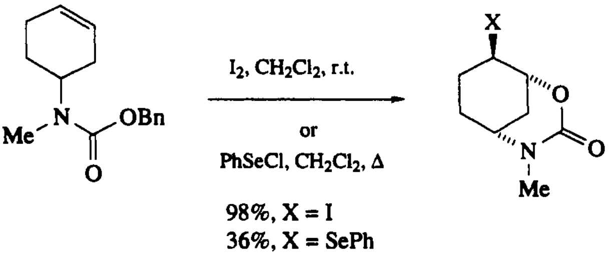

(27)

### 1.9.2.2.2 Other C═C cyclizations

The discussion of 'unconstrained' cyclization substrates in this section includes not only acyclic structures but also cyclic structures in which the vinylic bond which connects the nucleophile to the double bond is not constrained by the ring system. The factors which control the stereochemistry and regiochemistry in cyclizations of this type are much less obvious than those for the cases discussed in the previous section. The major synthetic utility of these reactions, however, comes from cases in which stereochemistry and regiochemistry can be predictably controlled. Thus, the initial discussion in this section will examine these two types of selectivity.

#### (i) Regioselectivity

A number of cyclizations of acyclic substrates illustrate that a balance of electronic and stereoelectronic factors control the regiochemical course of the reactions. Examples of such balance are found in cases where the preference for *exo* cyclization is opposed by ring strain or by electronic factors (Markovnikov rule). The ring strain generated in 4-*exo* ring closure often results in 5-*endo* cyclization predominating. The 4-*exo* mode of cyclization is normally found only when the substitution pattern also favors this mode and equilibration does not occur. Some examples of cyclizations of homoallylic alcohols are found in Table 1. Cyclizations of acyclic $\beta,\gamma$-unsaturated acids normally result in formation of $\gamma$-lactones *via* the 5-*endo* mode (equation 28 and Table 7). Attempts to effect selenolactonization of substrates with substitution heavily favoring 4-*endo* closure ($R^3$ = alkyl, $R^1 = R^2$ = H) resulted only in the formation of allyl selenides *via* a decarboxylative elimination from the acyclic addition product.[102] The cyclization of 2-vinylcyclohexanols with thallium triacetate produced tetrahydrofuran products of the 5-*endo* type (equation 29).[103]

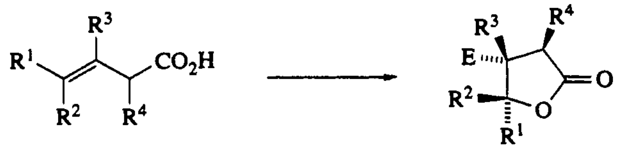

(28)

**Table 7** Cyclofunctionalization of β,γ-Unsaturated Carboxylic Acids (Equation 28)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *E* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| Me | Me | H | H | I | TlOAc, $I_2$ | 65 | 22 |
| Me | Me | H | H | Br | $Tl_2CO_3/Br_2/CH_2Cl_2$ | 74 | 21 |
| Me | Me | H | H | I | $NaHCO_3/I_2/MeOH/H_2O$ | 95 | 100 |
| Me | Me | H | H | Br | $TlX/Br_2/CH_2Cl_2$ | 85–90 | 100 |
| Ph | H | H | H | I | $NaHCO_3/I_2$/ether | Only product | 101 |
| Me | H | Me | H | PhSe | PhSeCl, silica gel | 86 | 102 |
| Et | H | H | H | PhSe | PhSeCl, silica gel | 95 | 102 |

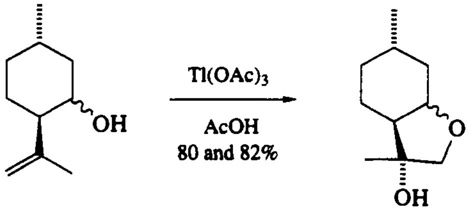
OH
Tl(OAc)3
AcOH
80 and 82%
O
OH

(29)

The 5-*exo* and 6-*endo* modes of cyclization are more closely balanced since ring strain is not a factor. Thus, in cyclizations of simple 4-alkenyl systems with a disubstituted internal double bond, the *exo* cyclization mode appears to be favored slightly when there is no Markovnikov preference (equation 30). In some systems, the ratio of 6-*endo* to 5-*exo* products has been found to vary with substrate structure (*e.g.* double-bond geometry), the electrophilic reagent used and reaction conditions (kinetic or thermodynamic control).[104,124b,145a] The 6-*endo* mode can be made to predominate by significantly increasing the electronic bias. The introduction of a strongly stabilizing group at the 6-position leads to preferential 6-*endo* cyclization, as shown in equations (31),[104a,105a] (32)[105b] and (33).[105c]

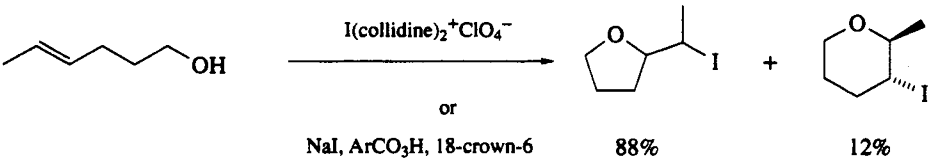
OH
I(collidine)2+ClO4−
or
NaI, ArCO3H, 18-crown-6
O
I
+
O
I
88%
12%

(30)

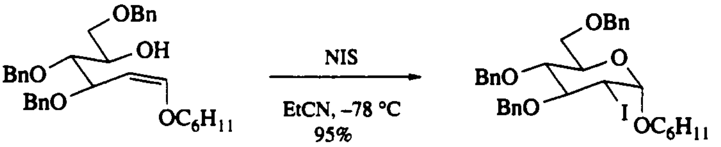
OBn
OH
BnO
BnO
OC6H11
NIS
EtCN, −78 °C
95%
OBn
O
BnO
BnO
I
OC6H11

(31)

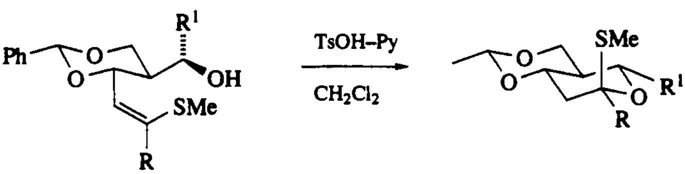
R1
Ph
O
O
OH
SMe
R
TsOH–Py
CH2Cl2
SMe
O
O
O
R1
R

(32)

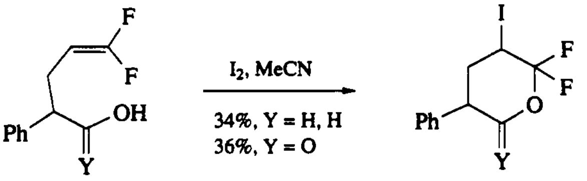
F
F
OH
Ph
Y
I2, MeCN
34%, Y = H, H
36%, Y = O
I
F
F
O
Ph
Y

(33)

For systems in which 6-*endo* cyclization is favored only by alkyl substitution, the ratio of 5-*exo* to 6-*endo* cyclization appears to be sensitive to both reaction conditions and substrate structure. Cyclizations of a variety of 5,5-dimethyl-4-pentenols (equation 34) are shown in Table 8. Although the use of 2,4,4,6-

tetrabromocyclohexa-2,5-dienone (TBCD) promoted the 6-*endo* cyclization in some systems (Table 8, entries 4 and 5),[104a,104b,108] recent cyclization studies directed toward synthesis of oxacyclic squalenoids found 5-*exo* cyclization to predominate under all conditions examined (entries 6 and 7).[109,110]

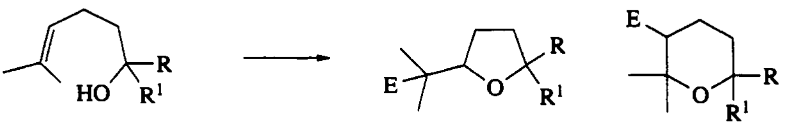

(34)

Table 8 Cyclization of Some 4-Pentenols (Equation 34)

| *Entry* | *R, R*$^1$ | *Conditions* | *Product yield (5-ring:6-ring) (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | Me, CH=CH$_2$ | NBS/CCl$_4$ | 85 | 106 |
| 2 | Me, steroid | NBS/CCl$_4$ | Only product | 107 |
| 3 | Me, C≡C | NBS/CCl$_4$ | Major:minor | 108 |
| 4 | Me, C≡C | TBCD | 20:80 | 108 |
| 5 | H, alkyl | TBCD | 20:58 | 104a |
| 6 | Me, pyranopyran | TBCD/MeNO$_2$ | 61:31 | 109 |
| 7 | Me, pyranopyran | NBS/CH$_2$Cl$_2$ | 62:22 | 110 |
| 8 | H, phenyl | Pd(OAc)$_2$, Cu(OAc)$_2$ | Trace:45 | 104f |
| 9 | H, Me | PhSCl, Pr$^i_2$NEt | 42:42 | 16b |

An interesting method for the generation of anti-Markovnikov products has been described by Bartlett.[111] Cyclization of γ-alkenyl alcohols of the type shown in equation (35) with thallium triacetate in a nucleophilic solvent generates *trans*-2,5-disubstituted tetrahydrofurans. The reaction is considered to proceed *via* an initial 6-*endo* cyclization to a tetrahydropyran, which undergoes heterolytic dethallation with concomitant 1,2-oxygen migration through a bridged oxonium ion.[104a,111] The products from this type of cyclization are equivalent to those expected from use of 'RO$^+$' as electrophile. Examples of *exo* mode cyclization followed by ring expansion have been described also.

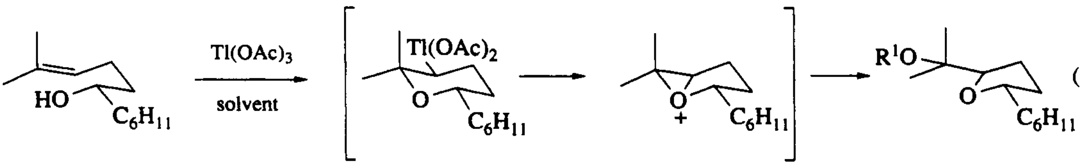

(35)

72% (solvent = AcOH, R$^1$O = AcO)

73% (solvent = acetone/H$_2$O, R$^1$O = HO)

The lactonization of 5,7-dienoic acids with selenium and sulfur electrophiles generates δ-lactones by regioselective 1,4-addition to the diene (equation 36).[52a] With substitution at the 8-position, reaction with PhSeCl or PhSCl gave a 1:1 mixture of rapidly interconverting 1,2- and 1,4-addition products. This interconversion, presumably *via* a 1,3-rearrangement,[52b] was not observed with the alkylthio adduct. An example of conjugate cyclization of an enyne system to form an allenyl product has also been reported (equation 37).[112]

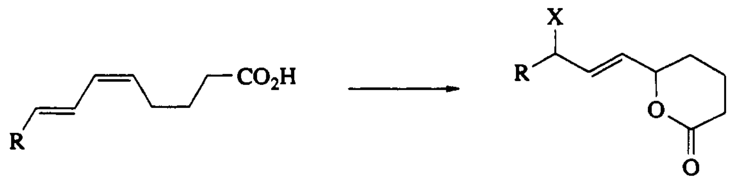

(36)

| *R* | *Conditions* | *X* | *Yield (%)* |
|---|---|---|---|
| H | PhSeCl, –78 °C, dark | PhSe | 95 |
| H | PhSCl, 25 °C | PhS | 82 |
| Me | MeO$_2$CCH$_2$CH$_2$SCl | RS | 69–72 |

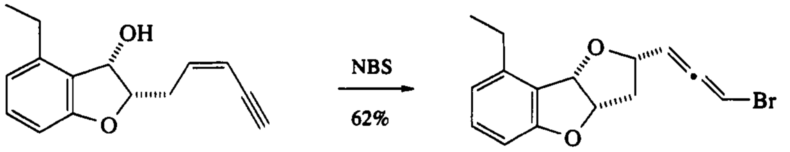

(37)

### *(ii) Stereoselectivity*

The major use of cyclofunctionalization in stereochemical control has been in the area of relative asymmetric induction; that is, control of stereochemistry in the introduction of a new stereogenic center by stereogenic center(s) present in the substrate. Several types of structural features have been found to provide high levels of stereocontrol in cyclofunctionalizations to five- and six-membered rings.

Perhaps the most important structural feature that has been used extensively in recent times for controlling stereochemistry is the allylic oxygen functionality. Cyclization of derivatives of the type shown in equation (38) with a variety of electrophiles leads to stereoselective formation of the '*cis*' five- and six-membered ethers and lactones (Table 9).[113] Although different theoretical approaches have been taken to rationalize these examples of 1,2-relative asymmetric induction,[113,115e,117] each analysis leads to the conclusion that the cyclizations involve a transition state conformation with the allylic oxygen functionality oriented toward the alkene bond, either fully eclipsed (**2**; OR-in-plane conformation)[113,115e] or slightly staggered (**3**; inside alkoxy conformation),[117] and that electrophilic attack occurs from the side opposite the alkyl chain. The same *cis* stereoselectivity is found in the iodolactonizations of *N,N*-dimethylamide derivatives related to (**1**) ($n = 1$).[114b] Recent results have shown that an allylic fluorine substituent exerts even higher stereochemical control in this type of cyclization, a result consistent with calculations that the major control factor is orientation of the electronegative substituent in the plane of the alkene.[115e] Selectivity of the same type has been found in mercuricyclizations of substrates with an allylic *N*-benzylamine substituent, forming α-*C*-glucosides of *N*-benzyl-D-glucosamine.[118]

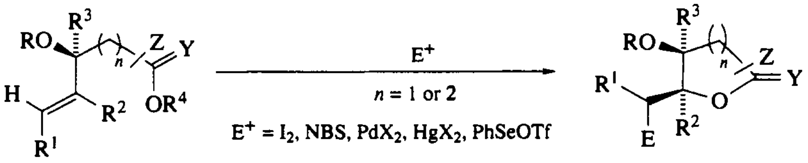

(38)

R = H, alkyl, $SiR_3$, Ac; $R^1$ = H, alkyl, $CO_2R$; $R^2$ and $R^3$ = H or alkyl; $R^4$ = H, alkyl, benzyl; Y = H,H or O

**Table 9** Control of Stereochemistry by Allylic Oxygen Substituents (Equation 38)

| *Product type* | *Leading refs.* |
|---|---|
| γ-Lactones | 104j, 114 |
| Tetrahydrofurans and *C*-furanosides | 104e, 115 |
| Tetrahydropyrans and *C*-pyranosides | 104e, 116 |

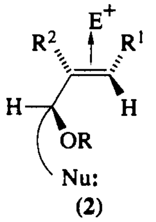

(**2**)
OR-in-plane conformation

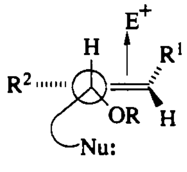

(**3**)
'inside alkoxy' conformation

The stereochemical control exerted by the allylic oxygen functionality generally dominates control by other stereogenic centers in the ring, although substitution at other centers may affect reaction rate, the level of stereocontrol or regioselectivity.[115b,115e] One example of a dramatic lack of stereocontrol is found in the 2,4-dimethyl-3-hydroxy-4-pentenoic acid system with the 2-methyl group *syn* to the allylic hydroxy group (*cis*:*trans* = 42:58).[114a,115e] Although stereoselectivity in some systems is not affected by the change of the allylic substituent from OH to OR, some cyclizations with palladium salts show lower selectivity with the ethers. This change could be a result of direct complexation of the electrophilic metal with the hydroxy group.[116c]

Several studies indicate that the level of stereocontrol is greater when $R^1$ is an electron-withdrawing group,[104d,104e] and can vary with the electrophile used.[104e,115h] In particular, the variable selectivity observed with phenylselenyl reagents appears to depend upon reaction conditions and substrate structure.[104d,104e,115g,115h]

Stereocontrol opposite to that shown in Table 9 occurs when the double bond contains a nonhydrogen substituent *cis* to the carbinol carbon (equation 39). In this system the OR-in-plane conformation is disfavored by $A^{1,3}$ strain. In cases with a secondary allylic oxygen substituent, cyclization through an H-in-plane conformation gives the *trans* product with high selectivity.[113a,115e] Several examples demonstrating this type of stereocontrol have been described.[104e,114a,115b,115h,119]

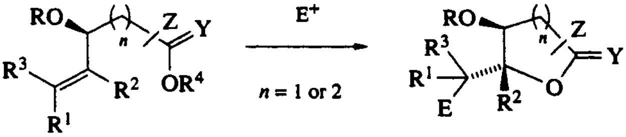

(39)

$R^1$ and $R^2$ = H or alkyl; $R^3$ = alkyl, OR, $CO_2Et$

The stereochemistry of products from cyclizations of systems with an allylic alkyl group and a *cis* substituent on the alkene is also controlled by steric interactions. Cyclization through an H-in-plane conformation generates the new stereogenic center *trans* to the allylic group (equation 40).[1n,115h,120,124b] An exception has been reported in a cyclization effected with phenylseleneny chloride.[121] If the *cis* alkene substituent ($R^2$) is hydrogen, $A^{1,3}$ steric interactions are absent; the stereoselectivity in kinetically controlled cyclizations is generally low with electrophiles such as halogen, mercury(II) ion or phenylselenenyl chloride, and the *cis* isomer predominates in many cases (*cis*:*trans* ratios varying from 3.8:1 to 2:3).[4,104j,115e,115h,115j,120b,122] Exceptions include the iodolactonizations of some 2-alkyl-3-methylpentenoic acids, which have been found to proceed with very high *cis* 1,2-relative asymmetric induction (7.9–30:1) irrespective of the configuration at C-2.[123]

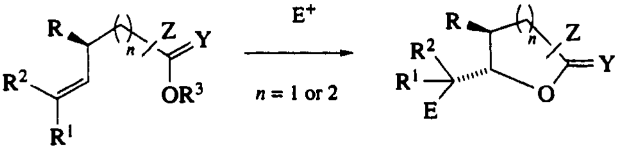

(40)

R and $R^2$ = alkyl; $R^1$ = H or alkyl; Y = O or H, H

The effect of the nature of the electrophile on the stereoselectivity of reactions with substrates containing a terminal alkene and an allylic substituent is dramatically illustrated by some recent results with palladium electrophiles.[124] Cyclizations of 3-methyl- or 3-phenyl-5-hydroxyalkenes with palladium catalysts proceed with high selectivity (≥9:1) for the 2,3-*trans* isomer (equation 41).[50,124] It is suggested that the steric interactions of the palladium–alkene complex affects the stereochemistry of these cyclizations. In some related cyclizations to form tetrahydropyran products (equation 42 and Table 10), reaction with iodine in the presence of sodium bicarbonate gives a different major diastereomer from cyclization with mercury(II) trifluoroacetate or palladium chloride.[125]

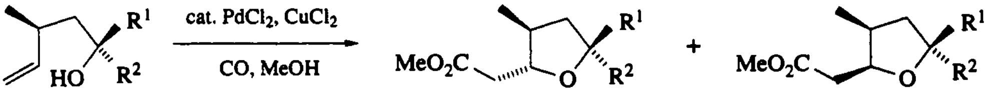

(41)

| | | |
|---|---|---|
| 90% ($R^1$ = Me, $R^2$ = H) | 90% | 10% |
| 88% ($R^1$ = H, $R^2$ = Me) | 87% | 13% |
| 87% ($R^1$ = $R^2$ = H) | only isomer observed | |

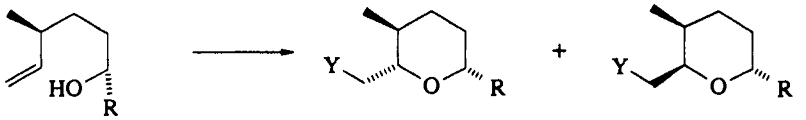

(42)

**Table 10** Stereoselectivity in Cyclizations to 2,3,5-Trisubstituted Tetrahydropyrans (Equation 42)

| *Entry* | *Reagent* | *Y* | *Product ratio* | *Ref.* |
|---|---|---|---|---|
| 1 | $PdCl_2$, $CuCl_2$, MeOH, CO | $CO_2Me$ | 7.9:1 | 125a |
| 2 | $Hg(OTFA)_2$, MeCN, $PdCl_2$, LiCl, $CuCl_2$, CO, MeOH | $CO_2Me$ | 2.5–3.0:1 | 125a |
| 3 | $I_2$, $NaHCO_3$ | I | 1:2.9 | 125b |

One general solution to low levels of 1,2-asymmetric induction in iodolactonization reactions of unsaturated acids with an allylic methyl group was developed by Bartlett, who demonstrated that cyclization in a nonbasic solvent ($CH_3CN$) and in the absence of a proton scavenger allowed for equilibration to the thermodynamically favored *trans* product (equation 43).[1p,120b,122a] The *trans* isomers of both γ- and δ-lactones are generally preferred under these conditions by ratios of greater than 10:1. Similar equilibration has been effected with mercury(II) salts,[120b] phenylselenenyl triflate[126a] and *N*-(phenylseleno)phthalimide in the presence of $TiCl_4$.[126b] The low stereoselectivity in cyclizations with other phenylselenenyl reagents (*e.g.* equation 1) may be due to rapid nonselective addition of electrophile to the starting alkene combined with a lack of reversal of intermediates (**D**) or (**C**) back to starting alkene (Scheme 3).[4,120b] Cyclization of the ester derivatives (Scheme 7) with iodine also generates the thermodynamically more stable product even though the final lactone product would not be considered to be in equilibrium with starting ester.[8a] In this case, equilibration is achieved since the dealkylation of the cyclic intermediate (**4**) is the slow step, and equilibration of all prior intermediates can occur (*cf.* **G** to **H** in Scheme 3). Numerous examples of this strategy have been reported in previous reviews,[1p,127] and the method has found widespread use in synthesis.

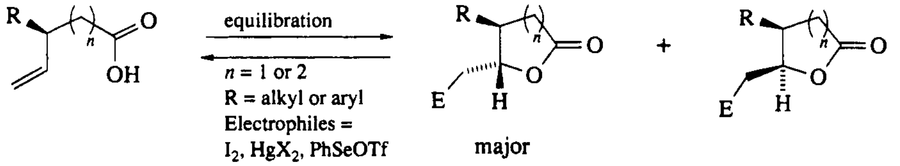

(43)

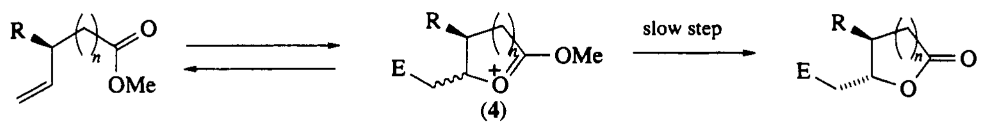

**Scheme 7**

Steric effects similar to those shown in equations (39) and (40) are found when the substitution pattern leads to tetrahydropyran systems through 6-*endo* cyclization. Cyclizations of systems with an allylic oxygen and a *syn* alkene substituent give products rationalized by cyclization through H-in-plane conformations as shown earlier in equations (31) and (32).[105,128] Examples with allylic methyl substitution have been reported also.[104a]

A few examples of high 1,3-asymmetric induction under kinetically controlled conditions have been reported.[1p] A recent study has shown that iodoetherification proceeds with high stereoselectivity on systems with an α,β-unsaturated ester as the π-participant and an electronegative homoallylic substituent (equation 44 and Table 11).[129] When the homoallylic substituent was a methyl group, the major diastereomer was the *cis* isomer. These results were rationalized using AM1 calculations of chair-like transition state models. The calculations predict an H-in-plane conformation for the iodonium ion or π-complex and either an *anti* or *gauche* conformation between the substituent, Y, and the hydroxy group (structures **5** and **6**). The normal preference for an equatorial methyl leads to cyclization through transition state (**5**) to produce the *cis* product (Table 11, entry 6). However, when Y is an electronegative substituent, the calculations predict a preference for the conformation where the substituent is *gauche* to the hydroxy group, which acquires positive charge as the C—O bond is formed (**6**; Table 11, entries 1–5). A selenoetherification of a related system with an internal (*Z*) double bond, but without an ester functionality, showed moderate stereoselectivity (3:1) for the product predicted by transition state (**6**).[130] Iodocyclizations to 2,3,5-trisubstituted tetrahydrofurans of systems with a homoallylic hydroxy group and a terminal double bond have shown little stereoselectivity,[115k,115m] but mercuricyclizations with a terminal double bond and a homoallylic fluorine have shown good stereoselectivities (4.5:1 to 20:1).[131a] The effect of a homoallyic sulfoxide substituent on the stereochemistry in mercuricyclizations of secondary alkenols has been reported recently.[131b]

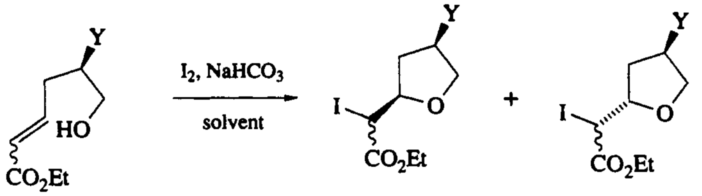

(44)

Table 11 Relative Asymmetric Induction by Homoallylic Substituent (Equation 44)[129]

| *Entry* | *(E) or (Z)* | *Y* | *Solvent* | *Product ratio* |
|---|---|---|---|---|
| 1 | *E* | OH | THF | 1:4.5 |
| 2 | *E* | OH | $Et_2O$ | 1:8.6 |
| 3 | *Z* | OH | $Et_2O$ | 1:11 |
| 4 | *E* | OMe | THF | 1:4.6 |
| 5 | *E* | F | THF | 1:6.3 |
| 6 | *E* | Me | THF | 3.6:1 |

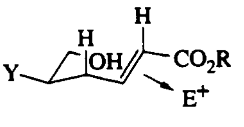

**(5)**

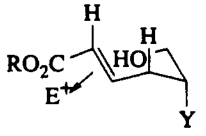

**(6)**

Iodolactonizations of *N*-acyl derivatives of 2-amino-4-pentenoic acids produce the *cis* γ-lactones selectively (equation 45).[132] These lactonizations have been proposed to result from thermodynamic control,[129] although chelation of the bromonium ion by the nitrogen has been proposed also.[132b] Formation of δ-lactones by 6-*exo* iodolactonization of 3-(*N*-acylamino)-5-hexenoic acids proceeds with little selectivity.[133]

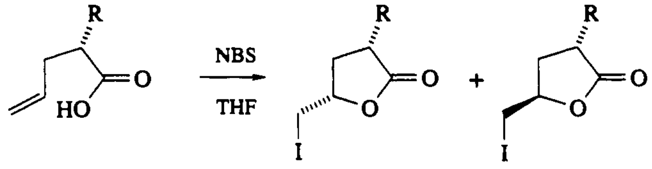

(45)

R = $NHCO_2R$, NPht, NHTs 6–8.8:1

High levels of 1,3-asymmetric induction also have been obtained in some cyclizations to γ-lactones under conditions of thermodynamic control (equation 46 and Table 12).[114b,134] Cyclizations of carboxylic acid esters result in equilibration related to that shown in Scheme 7, and *cis* products predominate (Table 12, entry 1). Alternatively, cyclizations of *N,N*-dimethylamide derivatives produce the *trans* isomer with very high selectivity (entries 2–4).[114b,134a] A related cyclization of an *N*-acyloxazolidinone derivative has been reported to proceed with high stereoselectivity.[134b] The *trans* selectivity is attributed to equilibration of the initial cyclic product, with the steric interactions between an amide methyl group and the β-substituent ($A^{1,3}$ strain) disfavoring the *cis* isomer. Phenylselenenyl triflate and iodine cyclizations of the carboxylic acids gave low selectivity (entries 5 and 6).[114b,126]

Examples of 1,3-asymmetric induction in cyclizations to δ-lactones have been observed. Iodolactonization of 3-methyl-5-hexenoic acid to a δ-lactone under equilibrating conditions showed reasonable stereoselectivity (6:1 *cis:trans*).[120b] Recent studies have examined the formation of δ-lactones from cyclization of 5-hexenoic acids with a homoallylic oxygen substituent at C-3.[135] Selenolactonization of 3-hydroxy-5-hexenoic acid under conditions of kinetic control provided the *trans* lactone in modest yield (40%) and high stereoselectivity.[135b] Equilibrating conditions led to a slight preponderance of the *cis*

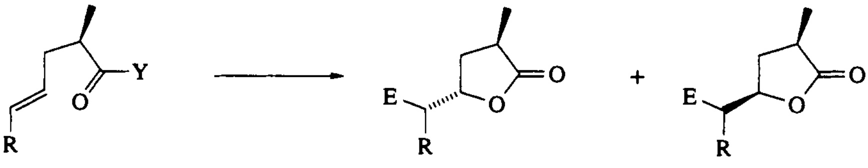

(46)

Table 12 Stereoselectivity in Cyclizations to α-Methyl-γ-lactones

| *Entry* | *R* | *Y* | *Conditions* | *Yield (%)* | *trans:cis* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Alkyl | OMe | 3 equiv. $I_2$, MeCN | | 1:9 | 134a |
| 2 | Alkyl | $NMe_2$ | 3 equiv. $I_2$, MeCN | | *Trans* only | 134a |
| 3 | H | $NMe_2$ | NBS | 75 | >99:1 | 114b |
| 4 | Me | $NMe_2$ | NBS | 74 | 94:6 | 114b |
| 5 | H | OH | 3 equiv. $I_2$, MeCN | 92 | 32:68 | 114b |
| 6 | H | OH | PhSeOTf | 85 | 3:4 or 4:3 | 126 |

isomer in higher yields (65%). Iodolactonizations of the corresponding 3-silyloxy derivatives under kinetic control were also selective (5.5:1 *trans:cis* with a triisopropylsilyl derivative). Selenolactonization of a related system with an internal double bond (*Z* configuration) showed little selectivity.[135a]

Examples of high levels of 1,4-asymmetric induction in kinetically controlled cyclofunctionalizations are rare. Cyclizations of 5-hydroxyalkenes to form 2,5-disubstituted tetrahydrofurans (equation 47) proceed with low selectivity in most cases.[1p] Exceptions shown in Table 13 are the palladium-catalyzed cyclization to a *trans* 2-vinyl system (entry 1)[50,104f] and cyclization of a 2-phenyl system with mercury(II) chloride to give a preponderance of the *cis* isomer (entry 2), presumably through equilibration.[136] Equilibration with substituents other than phenyl (Me or *t*-butyl) resulted in much lower selectivity.[136,138]

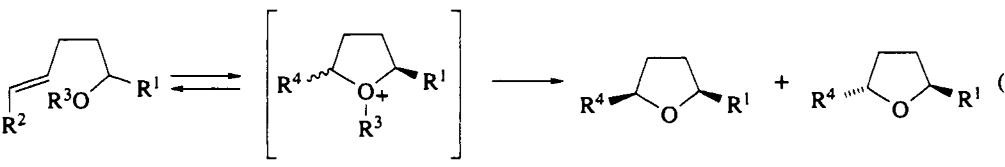

(47)

Table 13 Stereoselectivity in Cyclofunctionalization to 2,5-Dialkyltetrahydrofurans (Equation 47)

| *Entry* | *$R^1, R^2, R^3$* | *Conditions* | *$R^4$* | *Yield (%)* *cis* | *Yield (%)* *trans* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Ph, Me, H | $Pd(OAc)_2$, $Cu(OAc)_2$ | $CH{=}CH_2$ | 0 | 40 | 104f |
| 2 | Ph, H, H | $HgCl_2$ | $CH_2HgX$ | 56 | 4 | 136 |
| 3 | $CHMe_2$, H, H | $I_2$, MeCN | $CH_2I$ | 18 | 70 | 137 |
| 4 | $CHMe_2$, H, DCB | $I_2$, MeCN | $CH_2HgX$ | 95 | 0 | 137 |

Bartlett developed a strategy for the highly stereoselective synthesis of *cis* 2,5-disubstituted tetrahydrofurans involving the use of bulky ether derivatives for the cyclization, such that dealkylation of the oxonium ion is the slow step.[137] This strategy results in a large *cis:trans* ratio (compare Table 13, entries 3 and 4) because steric interactions between the bulky substituent on oxygen and the substituents at C-2 and C-5 cannot be avoided in the *trans* intermediate.[137] The success of this strategy requires a substituent which is bulky, but does not prevent cyclization, and which is cleaved faster than either of the ring groups in the dealkylation step. The 2,6-dichlorobenzyl (DCB) group has been found to be useful in a number of such reactions.[115h,137,139] Application of the slow dealkylation strategy to stereoselective syntheses of *trans* 2,5-disubstituted tetrahydropyrans was not successful.[15] Also, cyclizations of 2-alkyl-5-hexenoic acids to δ-lactones proceed with very low levels of 1,4-asymmetric induction under conditions of either kinetic or thermodynamic control.[134a,140]

An interesting example of the apparent dependence of stereoselectivity on the rate of breakdown of the initial cyclization intermediate has been observed in cyclizations with isoxazolines as the nucleophilic functionality (equation 48 and Table 14).[141] The stereochemistry of products from cyclizations to form tetrahydrofuran products varies significantly upon changing the 3-substituent of the isoxazoline ring (Table 14, entries 1–3). The exact factors controlling these variations have not been determined, but the stereoselectivity may be synthetically useful. Particularly noteworthy is the high selectivity for the less stable *trans* isomer of 2,3-disubstituted tetrahydropyrans; this type of selectivity is not obtainable by other strategies.[15] Some cyclizations with $Br_2$ and PhSeBr also have been reported.[141a]

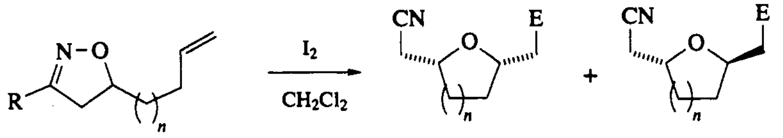

(48)

**Table 14** Cyclic Ethers from Cyclofunctionalization of Unsaturated Isoxazolines (Equation 48)[141]

| *Entry* | *n* | *R* | *Yield (%)* | *Ratio (cis:trans)* |
|---|---|---|---|---|
| 1 | 1 | $Ph_3C$ | 60 | 1:4 |
| 2 | 1 | $Me_3C$ | 59 | 1:1 |
| 3 | 1 | $Me_3Si$ | 40 | 6.6:1 |
| 4 | 2 | $Ph_3C$ | 82 | 1:9 |
| 5 | 3 | $Ph_3C$ | 80 | 1:3 |

The stereoselectivity in cyclizations of vinyl ether systems to form furanosyl disaccharides is controlled by both the side chain substituent (1,4-asymmetric induction) and the configuration of the existing pyranoside linkage (equation 49).[142] Substrates with no side chain substituent show no stereoselectivity.

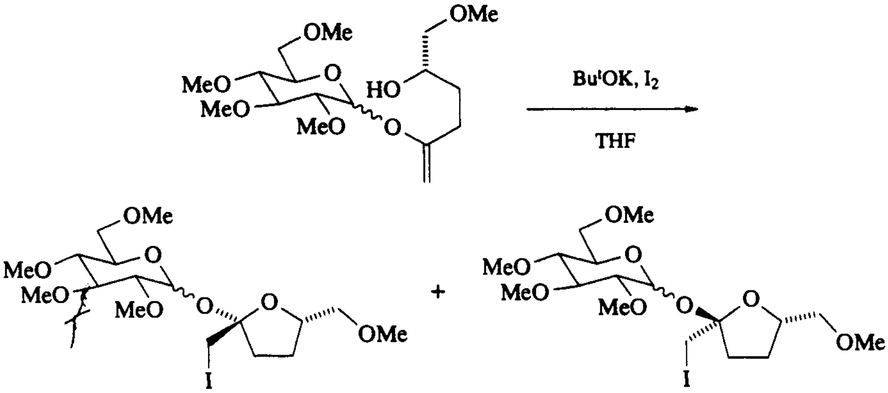

(49)

β-anomer 8:1
α-anomer ≥40:1

Formation of tetrahydropyran ring systems through 6-*endo* or 6-*exo* cyclization of substrates which lack 1,2-interactions of the type shown in equations (39) and (40), generally proceed with moderate selectivity for the diastereomer that would result from cyclization through chair conformations with equatorial substituents.[7,110,131b,142,143]

The levels of 1,5-asymmetric induction in the palladium-catalyzed alkoxy-carbonylations of alkenols to form 2,6-disubstituted tetrahydropyrans have been shown to be quite reasonable (Table 10 and equation 50).[144] Recent studies have shown that cyclization with palladium(II) acetate in DMSO in the absence of CO results in controlled β-hydride elimination to form vinyl-substituted tetrahydropyrans with high levels of 1,4- and 1,5-asymmetric induction (equation 51).[144b]

Although several of the stereoselective cyclizations discussed above have more than one chiral center which could affect the diastereoselectivity of the reaction, they have been discussed in terms of the factor which seems the most important. High stereoselectivity in cyclizations of some highly substituted systems results from cooperative effects of the substituents. Some examples of high stereoselectivity in cyclizations used in syntheses of macrolide antibiotics appear to result from a combination of substitution pattern *and* the (*Z*)-alkene configuration of the substrate. Examples include the formation of a 2,3,5-trisubstituted tetrahydrofuran in a synthesis of monensin[145a] and of a 2,2,5-trisubstituted tetrahydrofuran in a synthesis of ionomycin.[145b] Studies[7] on intramolecular oxymercuration to form substituted tetrahydropyrans (equation 52), conducted as part of a total synthesis of antibiotic X-206, demonstrated that formation of a mercuronium ion was reversible, and that extremely high levels of stereocontrol can result from additive contributions of several control elements, including extraannular allylic oxygen substituents.[113b]

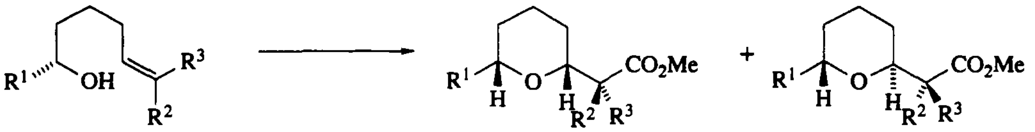
R1
OH
R3
R2
R1
O
H
CO2Me
R3
+
R1
O
H
CO2Me
R2
R3

(50)

| $R^1$ | $R^2$ | $R^3$ | *cis:trans ratio* |
|---|---|---|---|
| Me | H | H | ≈20:1 |
| $Bu^tCH_2$ | H | H | 6:1 |
| $Bu^i$ | Me | H | 83:10 |
| $Bu^i$ | H | Me | ≥97:3 |

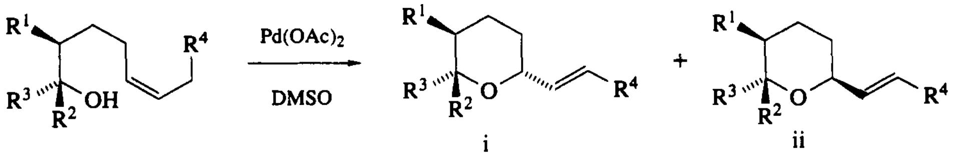
R1
R4
R3
OH
R2
Pd(OAc)2
DMSO
R1
R3
O
R2
R4
i
+
R1
R3
O
R2
R4
ii

(51)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *Ratio (i:ii)* |
|---|---|---|---|---|
| H | Me | H | Me | 90:5 |
| Me | H | H | Me | 98:2 |
| Me | H | Me | Me | 94:3 |

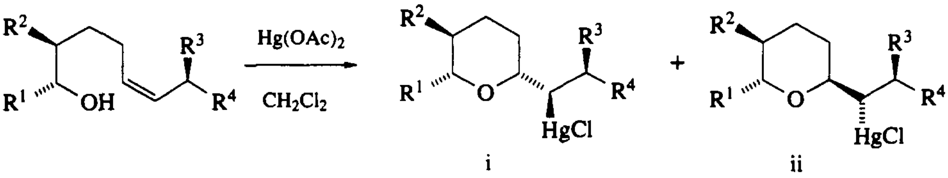
R2
R3
R1
OH
R4
Hg(OAc)2
CH2Cl2
R2
R3
R1
O
R4
HgCl
i
+
R2
R3
R1
O
R4
HgCl
ii

(52)

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *Ratio (i:ii)* |
|---|---|---|---|---|
| H | Me | Me | Me | 85:15 |
| secondary alkyl | Me | Me | Me | >97:3 |
| H | H | OBn | secondary alkyl | 95:5 |
| H | Me | OBn | secondary alkyl | >97:3 |

Examples of 5-*exo* cyclizations in which the hydroxy group is constrained by a five-membered ring are shown by equation (53). The stereoselectivity in these cyclizations ranges from quite high in iodocyclization (9:1 in $H_2O$ and >20:1 in $CH_2Cl_2$) to only moderate (2–3:1) with mercury and phenylselenenyl chloride.[1p] This type of cyclization has been widely applied to synthesis of prostacyclins.[146] Similar cyclizations with dimethyl(methylthio)sulfonium fluoroborate have been reported recently.[35]

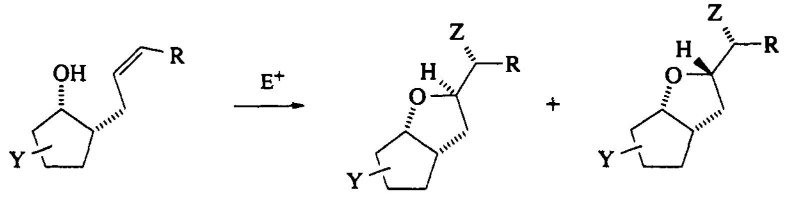
OH
R
Y
E+
Z
H
R
O
Y
+
Z
H
R
O
Y

(53)

$E^+$ = $I_2$, $Hg(OAc)_2$, NBS, PhSeCl, DBDMH (1,3-dibromo-5,5-dimethylhydantoin)

### *(iii) Cyclization of heteroatom-tethered systems*

Cyclizations of substrates in which internal oxygen nucleophiles have been attached to unsaturated alcohols provide a method for stereoselective formation of acyclic 1,2- and 1,3-diol functionalities, as outlined in Scheme 2.

Cyclizations of chloral hemiacetal derivatives of cyclic allyl alcohols were regio- and stereo-selective (Table 6, entry 1), but a mixture of regioisomers was obtained from analogous derivatives of acyclic allyl alcohols with a nonterminal double bond.[93] Hemiacetal derivatives of allyl alcohols with a terminal vinyl group have been cyclized with mercury(II) acetate to give acetal derivatives of *threo* 1,2-diols with moderate selectivities (equation 54 and Table 15, entries 1 and 2).[147] Moderate to excellent stereoselectivity has been observed in the iodocyclizations of carbonate derivatives of allyl alcohols (entries 3–5).[94a] The currently available results do not provide a rationale for the variation in observed stereoselectivity.

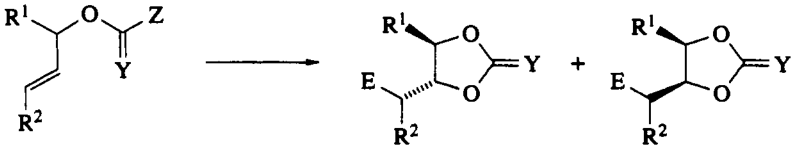

(54)

**Table 15** *O*-Cyclizations of Derivatives of Acyclic Allylic Alcohols (Equation 54)

| *Entry* | *R$^1$, R$^2$* | *Y* | *Z* | *Conditions* | *E* | *Ratio (trans:cis)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Et, H | H, CCl$_3$ | OH | i, Hg(OAc)$_2$; ii, NaBH$_4$ | H | 81:19 | 147 |
| 2 | Bu$^t$, H | H, CCl$_3$ | OH | i, Hg(OAc)$_2$; ii, NaBH$_4$ | H | 91:9 | 147 |
| 3 | Pr, H | O | OLi | I$_2$/THF, 12 h | I | 60:40 | 94a |
| 4 | Pr, H | O | O | I$_2$/THF, 12 h | I | 80:20 | 94a |
| 5 | Bu$^n$, Me | O | OLi | I$_2$/THF/ 12 h | I | 93:7 | 94a |

Cyclizations of derivatives of homoallylic alcohols have proven useful for 1,3-asymmetric induction (equation 55 and Table 16). This approach was initially examined with phosphate esters,[8b,151] but the resistance of the cyclic phosphate ester functionality to hydrolytic removal has limited the applications of this approach. Cyclic carbonates, which are readily cleaved, can be prepared by cyclization of *t*-butyl carbonate[148a,149] lithium carbonate,[94a,148b,148c] and carbamate derivatives of homoallylic alcohols,[125a,150] although the stereoselectivity is somewhat higher in the phosphate cyclizations.[148a] In most systems, the stereoselectivities obtained from the two types of carbonate derivatives did not differ significantly, although the *t*-butyl carbonate reactions were significantly slower, and the stereoselectivity of the lithium carbonate reaction was greatest at low temperature (Table 16, entries 1 and 3).[148c] Although the stereoisomer ratio did not change with time in cyclizations of *t*-butyl carbonate systems with a terminal vinyl group, cyclization of a *t*-butyl carbonate derivative of a 2-alkyl-4-hydroxyalkene was shown to give an extremely high stereoisomer ratio (>50:1) under mild conditions, but reaction for long periods at higher temperature (equilibration) resulted in a significantly lower selectivity (5:1; Table 16, entries 5 and 6).[149]

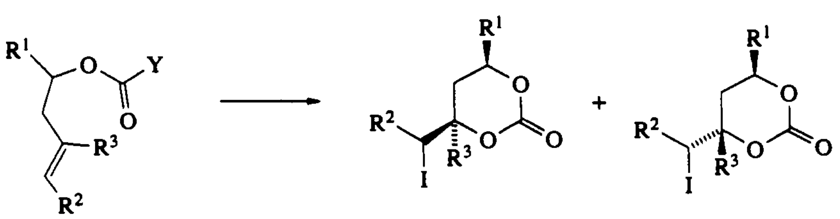

(55)

The synthesis of amino alcohol derivatives by cyclization of derivatives of allylic and homoallylic amines has received considerable attention recently. Early studies by McManus and Pittman[152a] demonstrated that allylic amides could be converted into 2-oxazolines by treating them with concentrated sulfuric acid and drowning the reaction mixture in cold dilute base. The results suggested that reaction occurred through carbocation intermediates, and cyclizations of allylic systems with substitution favoring 6-*endo* cyclization gave tetrahydrooxazine products.[152b] Allylic amides (equation 56) have also been cyclized with halogen,[153] selenium,[154] tellurium,[155] and sulfur[156] electrophiles. The halogen electrophile of choice appears to be *N*-iodosuccinimide.[153a,157] The regiochemistry is predicted by the Markovnikov rule, with 1,2-disubstituted alkene systems giving a mixture of oxazoline and tetrahydrooxazine products.[153b] The stereoselectivity of cyclization is variable, with 4,5-dialkyloxazolines obtained in *trans:cis*

**Table 16** *O*-Cyclizations of Derivatives of Acyclic Homoallylic Alcohols (Equation 55)

| *Entry* | $R^1, R^2, R^3$ | *Y* | *Conditions* | *Ratio (cis:trans)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | Alkyl, H, H | OLi | $I_2$/THF/$CO_2$, –78 °C to r.t. | 19:1 | 94a, 148 |
| 2 | Alkyl, H, H | $OBu^t$ | $I_2$/MeCN, –20 °C | 10:1 | 148a |
| 3 | Et, Me, H | OLi | $I_2$/THF/$CO_2$, 0 °C | 4:1 | 148a |
| 4 | Et, Me, H | $OBu^t$ | $I_2$/MeCN, –20 °C | 4:1 | 148a |
| 5 | Alkyl, H, Me | $OBu^t$ | $I_2$/EtCN, –40 °C, 30 min | 50:1 | 149 |
| 6 | Alkyl, H, Me | $OBu^t$ | $I_2$/EtCN, –10 °C, 14 h | 5:1 | 149 |
| 7 | Alkyl, alkyl, H | $NH_2$ | $I_2$/ether/saturated $NaHCO_3$, r.t. | 10–17:1 | 150, 125a |
| 8 | Alkyl, alkyl, H | $NMe_2$ | $I_2$/ether/aq. $NaHCO_3$, r.t. | >20:1 | 125a |

ratios varying from 80:20 to 24:76 (equation 57).[153a,157] Examples of tetrahydrooxazine formation by 6-*exo* cyclization of homoallylic *N*-acylamines have also been reported.[156,158] The product from an iodocyclization in aqueous THF was shown to result from rearrangement of the initial product (equation 58).[158b] A related cyclization of the amide from a symmetrical homoallylic amine (R = allyl) and a chiral acid gave the pyrrolidine derivative in only 7–26% *ee*.[159] A synthesis of 5-methylene-2-oxazolines by cyclization of amide derivatives of propargylamine has been reported also (equation 59).[160]

The cyclization of carbamate derivatives of unsaturated amines has proven synthetically useful. Cyclizations of carbamates of allylamines containing a terminal vinyl group give oxazolidinone products (equation 60 and Table 17, entries 1 and 2).[99,161] Bromocyclizations of systems with a di- or tri-substituted alkene often give mixtures of oxazolidinones and tetrahydrooxazinones,[163a] while cyclization of an *N*-cinnamyl carbamate with phenylsulfenyl chloride gave only the oxazolidinone product.[163b,163c] The stereochemistry of the cyclization of primary carbamates of either allylic or homoallylic amines is low

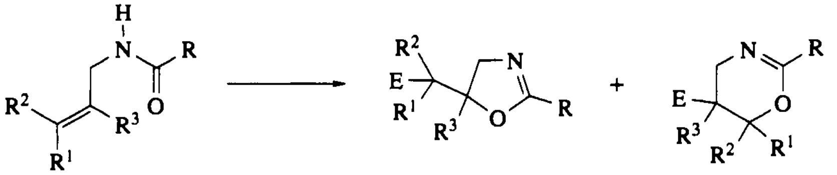

(56)

E = H, Cl, Br, I, PhSe, PhS, $TeX_4^-$

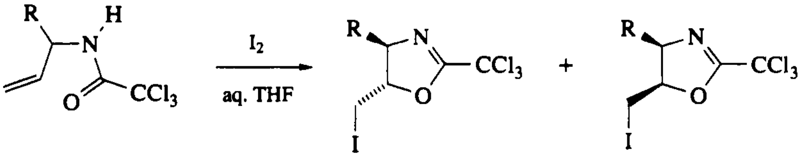

(57)

| *R* | *Ratio* (trans:cis) | *Ref.* |
|---|---|---|
| $CH_2OBn$ | 80:20 | 157b |
| $C_{15}H_{31}$ | 55:45 | 153a |
| $Pr^n$ | 66:30 | 157a |
| Ph | 24:76 | 157a |

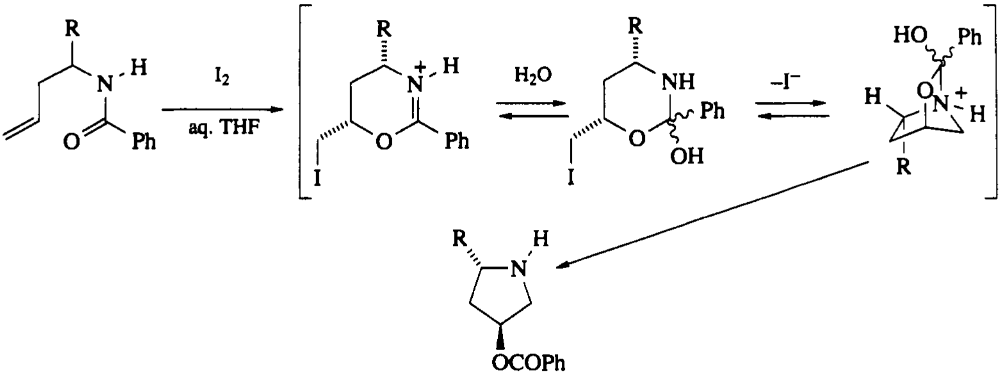

(58)

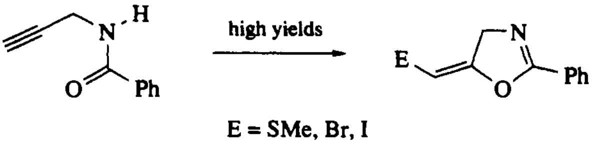

(59)

(Table 17), but cyclization of *N*-substituted carbamates is highly selective (entries 2, 4 and 5), presumably by insuring reversible formation of the intermediate prior to benzyl cleavage and steric interactions between the *N*-substituent and the alkyl substituent favoring the axial orientation (equation 61). Cyclizations of this type, where R = H and Y = α-phenethyl, result in little asymmetric induction. However, the diastereomeric products can be separated and used for the synthesis of chiral nonracemic amino alcohol derivatives.[164]

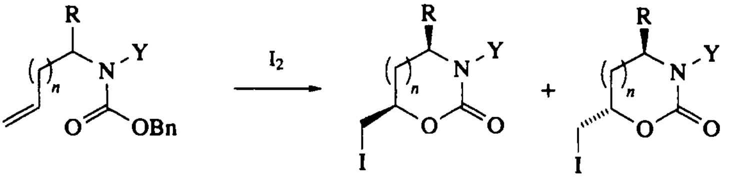

(60)

**Table 17** Stereoselectivity in *O*-Cyclizations of Carbamate Derivatives of Unsaturated Amines

| *Entry* | *n* | *Y* | *Ratio (cis:trans)* | *Ref.* |
|---|---|---|---|---|
| 1 | 0 | H | 1:1.5 | 161 |
| 2 | 0 | $CO_2Bn$ | 1:6.6 | 161 |
| 3 | 1 | H | 2.3:1 | 133 |
| 4 | 1 | $CO_2Bn$ | 1:2.3 | 133 |
| 5 | 1 | TBDMS | 1:14 | 133, 162 |

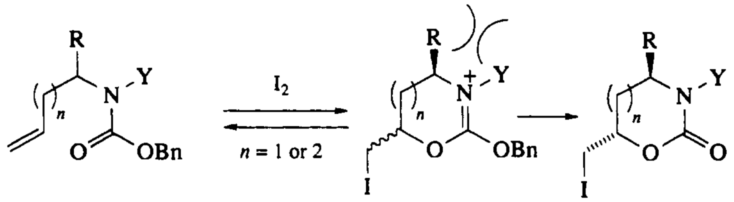

(61)

Cyclizations of urea derivatives of allylamines with selenium reagents have been examined recently (equation 62 and Table 18).[98] Cyclization of the allylic ureas produces *trans*-2-oxazoline derivatives with high stereoselectivity when the double bond is internal (Table 18, entry 2). Although *O*-methylisourea derivatives can be cyclized to dihydroimidazoles [see Section 1.9.3.2.2(ii)], cyclization with phenylselenenyl trifluoromethanesulfonate and trifluoromethanesulfonic acid produces 5,6-dihydro-1,3-oxazines (6-*endo* products), even when the double bond is monosubstituted (entry 3).

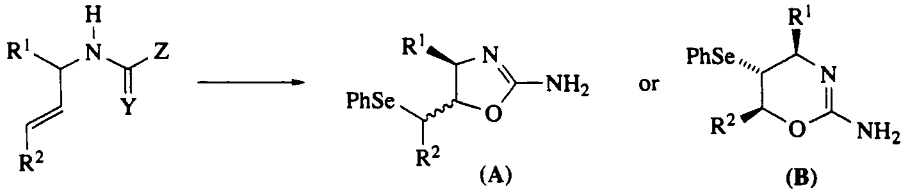

(62)

**Table 18** *O*-Cyclization of Urea Derivatives of Acyclic Allylic Amines.

| *Entry* | | *Conditions* | *Yield (%) (A)* | *Yield (%) (B)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | $Z = NH_2$, $Y = O$<br>$R^1 = Ph$, $R^2 = H$ | PhSeCl, $CHCl_3$<br>Silica gel, 25 °C | 96% (*trans:cis* = 2:1) | | 98a |
| 2 | $Z = NH_2$, $Y = O$<br>$R^1 = Bu^n$, $R^2 = Pr^n$ | PhSeCl, $CHCl_3$<br>Silica gel, 25 °C | 81% (*trans* only) | | 98a |
| 3 | $Z = OMe$, $Y = NH$<br>$R^1 = Ph$, $R^2 = H$ | PhSeCl, $CF_3SO_3Ag$<br>Silical gel, $CF_3SO_3H$ | | 66% | 98b |
| 4 | $Z = OMe$, $Y = NH$<br>$R^1 = Bu^n$, $R^2 = Pr^n$ | PhSeCl, $CF_3SO_3Ag$<br>Silical gel, $CF_3SO_3H$ | | 62% | 98b |

The cyclization of carbamate derivatives of 2-alkenylpyrrolidines has been examined (equation 63 and Table 19). Cyclization to oxazolidinones proceeds with high stereoselectivity through an H-in-plane transition state for systems with a terminal double bond. With phenyl substitution, the only product is the tetrahydrooxazinone (Table 19, entry 4). However, when the phenyl group contained an electron-withdrawing substituent *and* the alkene had (*Z*)-geometry, the major product was the oxazolidinone (entry 6). Thus, the regioselectivity is affected by small changes in substrate structure.

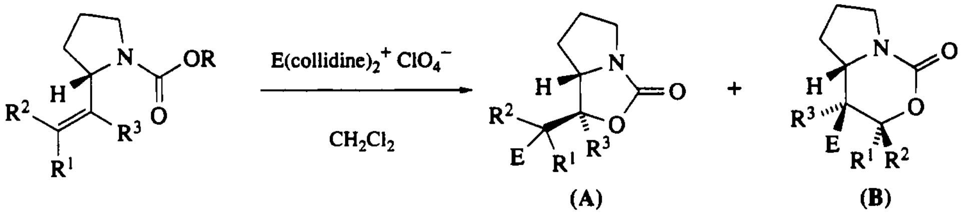

(63)

**Table 19** Cyclization of 2-Alkenylpyrrolidine Derivatives (Equation 63)

| *Entry* | *R* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *E* | *Yield (%) (A)* | *Yield (%) (B* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | H | Br | 80 | | 104g |
| 2 | Bn | H | H | Me | Br or I | 83 | | 165 |
| 3 | Bu$^t$ | H | Ph | H | I | | 73 | 104g |
| 4 | Bu$^t$ | Ph | H | H | I | | 60 | 104g |
| 5 | Bu$^t$ | *p*-NO$_2$Ph | H | H | Br | | 60 | 104g |
| 6 | Bu$^t$ | H | *p*-NO$_2$Ph | H | Br | 58 | 12 | 104g |

Allylamines may be converted directly to oxazolidinones through condensation with CO$_2$, to form carbamate salts, and treatment with iodine (equation 64 and Table 20).[166] High stereoselectivity was obtained only in cases where the α-substituent was hydroxymethyl (entry 5) or the amine was secondary and the substituent was phenoxymethyl (entry 4). The results with primary amines are comparable to those for amide cyclizations shown in equation (57).

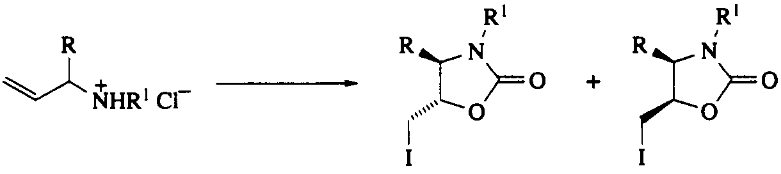

(64)

**Table 20** Cyclization to 2-Oxazolidinones from Allylic Amines and Carbon Dioxide (Equation 64)

| *Entry* | *R* | *R*$^1$ | *Conditions* | *Ratio (cis:trans)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Pr | H | Amberlyst A26 (CO$_3^{2-}$ form), I$_2$, CHCl$_3$, r.t. | 45:55 | 95 | 166a |
| 2 | Pr | CH$_2$Ph | Same as entry 1 | 70:30 | 95 | 166a |
| 3 | CH$_2$OPh | H | Same as entry 1 | 70:30 | 94 | 166a |
| 4 | CH$_2$OPh | CH$_2$Ph | Same as entry 1 | 99:1 | 90 | 166a |
| 5 | CH$_2$OH | H | Same as entry 1 | 93:7 | 80 | 166a |
| 6 | H | H | CO$_2$, MeOH, I$_2$ | | 60 | 166b |

One example of the cyclization of a hemiaminal adduct of a homoallylic β-lactam has been reported to proceed with high 1,3-asymmetric induction (equation 65).[167]

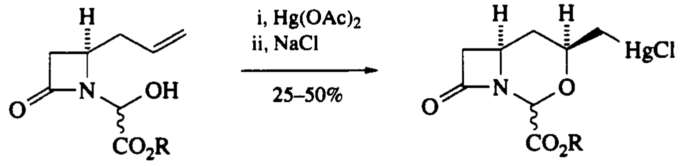

(65)

### *(iv) Miscellaneous*

The cyclofunctionalization of cycloalkenyl systems where the chain containing the nucleophilic functionality is attached at one end of the double bond leads to spirocyclic structures. Cyclizations of cyclic and acyclic enol ethers to generate spiroacetals are shown in equations (66)[168] and (67).[169] These reactions generate the thermodynamically more stable products based on anomeric and steric factors.[170] Spiroacetal products have also been obtained using isoxazolines as the nucleophilic functionality (*cf.* Table 14).[141b] Studies of steric and stereoelectronic control in selenoetherification reactions which form spirocyclic tetrahydrofurans have been reported.[38] An interesting example of stereoelectronic control in the formation of a spirocyclic lactone has been reported in a recent mevinolin synthesis (equation 68).[171]

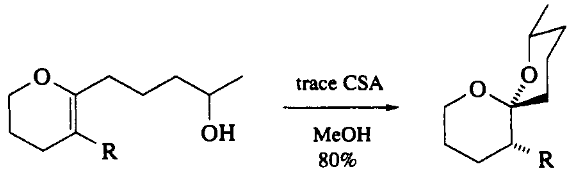

(66)

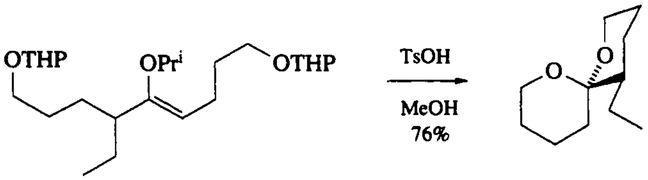

(67)

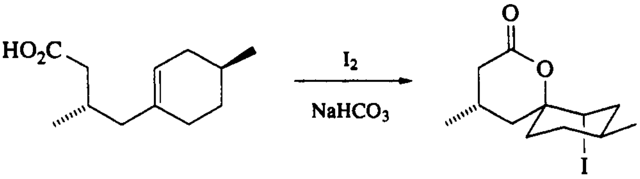

(68)

Early studies on mercuricyclization of hydroperoxides have been summarized by Bartlett.[1p] Recent applications include the generation of endoperoxide intermediates (7) for use in biomimetic syntheses of prostaglandins (equation 69).[172] These results, and others,[173a,173b] show that *cis*-3,5-dialkyl-1,2-dioxolanes are the predominant products from both 5-*exo* and 5-*endo* cyclizations. As shown in equation (70), where 5-*endo* cyclization involves electrophilic attack on a diene system, the ratio of the 5-*exo* and 5-*endo* modes of cyclization could be varied by changing the mercury(II) salt used. Studies on 6-*exo* cyclizations by Porter and Bartlett have shown that *trans*-3,6-disubstituted-1,2-dioxanes predominate (equation 71),[1p,173c] but 6-*exo* cyclizations of related tertiary hydroperoxides are not selective.[104b] Halocyclization of unsaturated hydroperoxides has also been reported.[173a,174] Recent studies have shown that cyclization of homoallylic hydroperoxides with NIS proceeds through a radical chain mechanism, whereas cyclization with NBS is mainly a polar process.[174a] A recent study of competition between 5-*exo* and 6-*exo* peroxycyclizations showed little regioselectivity.[174c]

Several examples of uncommon oxygen nucleophiles should be mentioned. Cyclizations with selenium electrophiles where the nucleophile is an OH group of a hemiacetal function have been used to generate monocyclic[104h] and spirocyclic[175a] acetals (equation 72). Related cyclizations to generate spirocyclic acetals with substituents on both rings using mercury(II) salts[175b] or NIS[175c] have been found to show significant stereoselectivity. Selenocyclization of dialkenyl ketones to fused and spirocyclic acetals

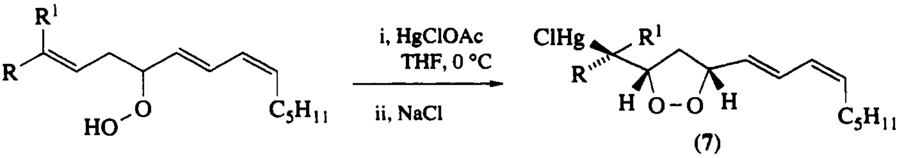

(69)

80% [R = H, $R^1 = CH_2CH(OMe)_2$]; 93% [$R = CH_2CH(OMe)_2$, $R^1$ = H]

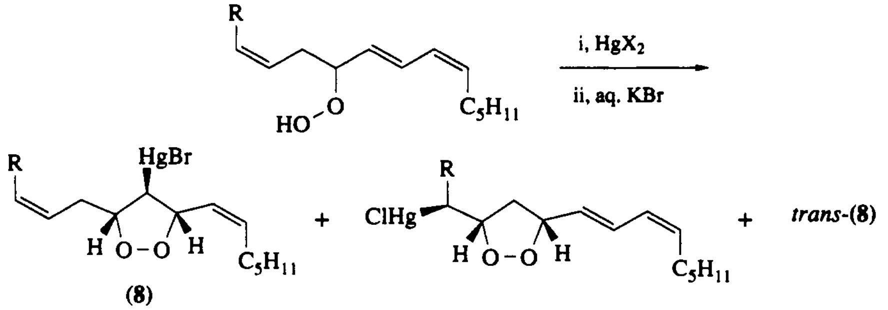

(8) (70)

| | (8) | | trans-(8) |
|---|---|---|---|
| $Hg(O_2CBu^t)_2$ | 36% | 55% | 9% |
| $Hg(TFA)_2$ | 76% | 21% | 3% |
| $Hg(OMs)_2$ | trace | 85% | 15% |

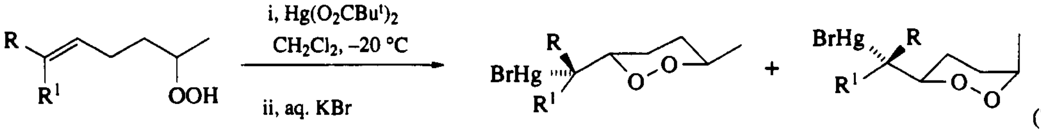

(71)

| | | |
|---|---|---|
| $R = R^1 = H$ | 90% | 10% |
| $R = H, R^1 = Et$ | 88% | 12% |
| $R = Et, R^1 = H$ | 79% | 21% |

using photooxidative (single electron transfer) cleavage of diphenyldiselenide has been reported recently.[175d]

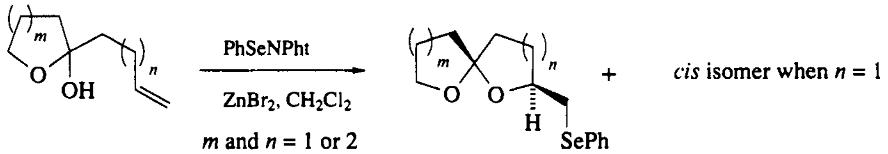

(72)

Heterocyclizations involving the oxygen of enolizable β-dicarbonyl groups[115g,176] and of epoxides[177] as the nucleophile have also been reported. Iodocyclizations of unsaturated *N*-oxides of tertiary amines to form substituted tetrahydro-1,2-oxazines,[178a,178b] and iodocyclizations of *N*,*N′*-dimethyl-*N′*-allylbenzohydrazides to form substituted 4*H*-1,3,4-oxadiazinium salts[178c] have been reported.

Alkyl ethers can act as nucleophiles in cyclofunctionalization reactions,[179] and recently acetal oxygens have been shown to be excellent nucleophiles for participation in heteroatom cyclizations (Scheme 9). This reaction has been used as a nonhydrolytic procedure for unraveling complex acetals (conversion of **9** to **10**),[180] for specific liberation of an anomeric center (conversion of **11** to **12**),[181a] for preparation of glycosyl bromides[181b] and for saccharide coupling (reaction of **13** and **14** to give **15**).[182]

The selective activation of a mixture of (**13**) and (**14**) requires that iodonium ion formation be reversible. Then, the rate of cyclization to the activated intermediate is dependent upon the nucleophilicity of the glycosidic oxygen, which is found to be a function of the protecting group present on the C-2 oxygen. The method has also been used for the synthesis of oligosaccharides and for the synthesis of 2-deoxyglycosides with a 2-bromo group used to deactivate the *n*-pentenyl protecting group.[182a] Further studies have also demonstrated the utility of *n*-pentenyl acetals as a general protecting groups for alcohols and carbonyl groups (equations 73 and 74).[183]

### *1.9.2.2.3 Asymmetric induction with chiral auxiliaries*

The asymmetric halolactonization reactions of unsaturated L-proline amides, developed by Terashima and coworkers,[184] has been extended to α-alkyl acrylic acid derivatives (equation 75 and Table 21).[185] This allows for the synthesis of either enantiomer of an α-methyl-α-hydroxy acid using L-proline as the auxiliary. Less successful approaches to asymmetric induction with a chiral auxiliary include iodolac-

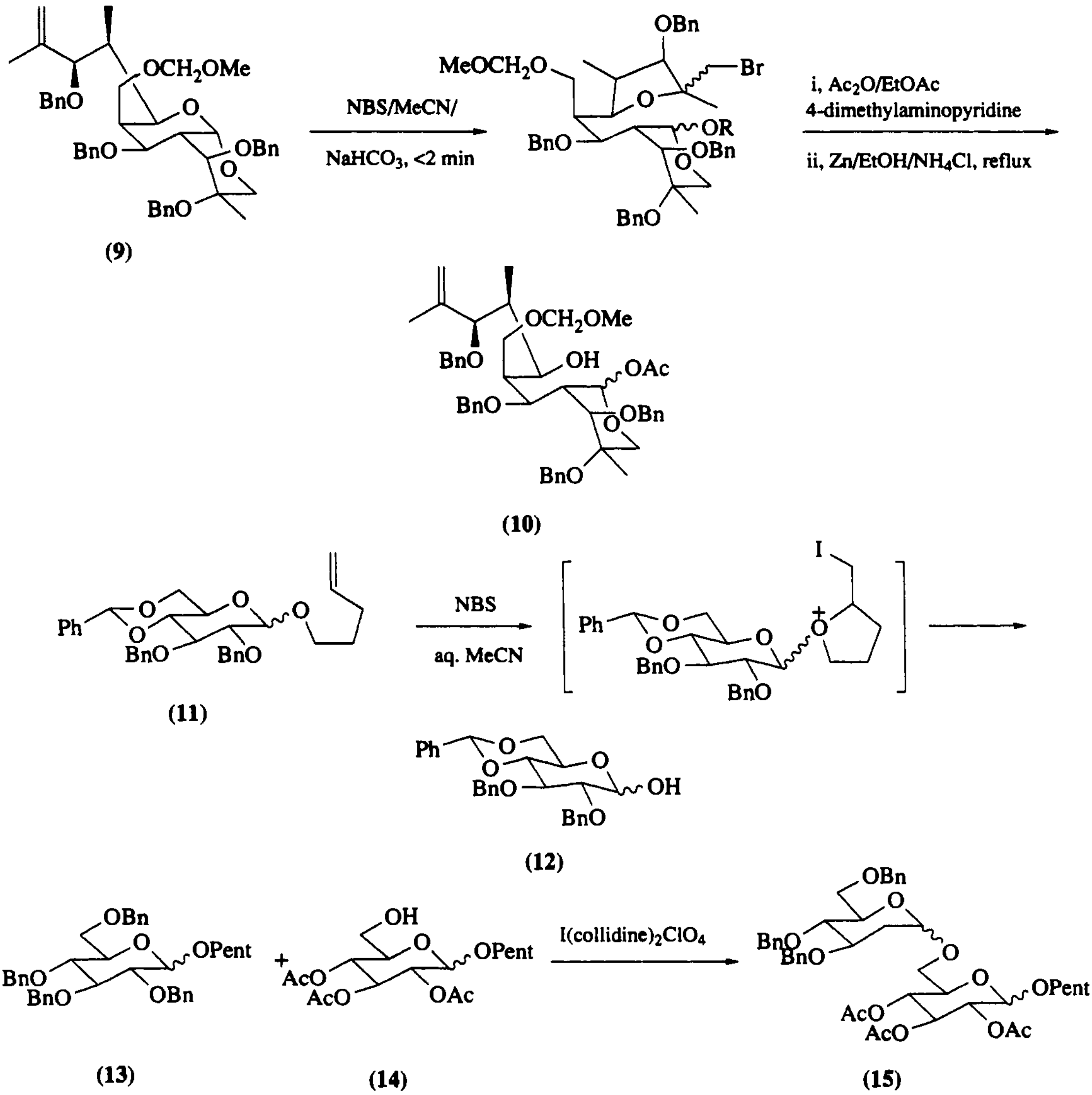
OCH$_2$OMe
BnO
BnO
OBn
BnO
(9)
NBS/MeCN/
NaHCO$_3$, <2 min
OBn
MeOCH$_2$O
Br
OR
BnO
OBn
BnO
i, Ac$_2$O/EtOAc
4-dimethylaminopyridine
ii, Zn/EtOH/NH$_4$Cl, reflux
OCH$_2$OMe
BnO
OH
OAc
BnO
OBn
BnO
(10)
Ph
BnO
BnO
(11)
NBS
aq. MeCN
I
Ph
BnO
BnO
Ph
BnO
OH
BnO
(12)
OBn
OPent
BnO
BnO
OBn
(13)
OH
OPent
AcO
AcO
OAc
(14)
I(collidine)$_2$ClO$_4$
OBn
BnO
BnO
OPent
AcO
AcO
OAc
(15)

**Scheme 9**

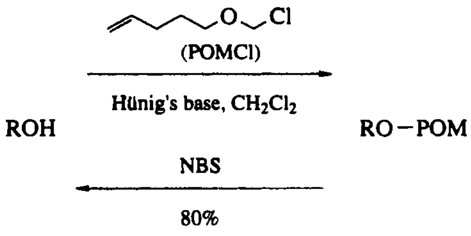
(POMCl)
Hünig's base, CH$_2$Cl$_2$
ROH
RO−POM
NBS
80%

(73)

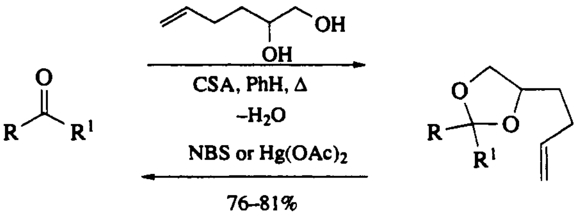
OH
OH
CSA, PhH, Δ
−H$_2$O
NBS or Hg(OAc)$_2$
76–81%
R
R$^1$
R
R$^1$

(74)

tonization of amides from symmetrical *bis*-γ,δ-unsaturated acids and chiral amines (<17% *ee*),[186] cyclization of amides of symmetrical homoallylic amines and chiral acids (<26% *ee*),[159] cyclization of carbamates of allylic amines with a chiral *N*-alkyl substituent,[164a,164c] use of mercury salts of chiral carboxylic acids (<5% *ee*)[187] and intramolecular oxypalladation with chiral palladium(II) complexes (<30% *ee*).[50,188] It is interesting to note that the one successful approach (Table 21) incorporates the chiral center of the auxiliary into the newly formed ring system.

**Table 21** Asymmetric Bromolactonization of Proline Amides

| *Entry* | | *Conditions* | *Yield (%)* | *Diastereomer ratio* | *Crystalline yield (major isomer) (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 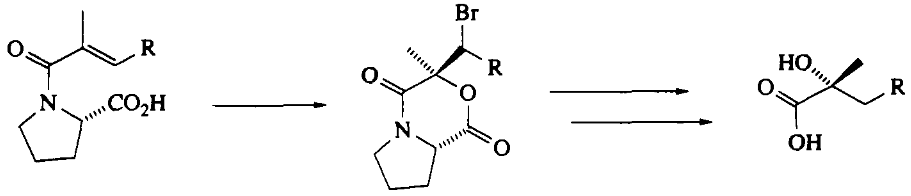 | | | | | | (75) |
| 1 | R = Me | NBS/DMF | 84 | 94:6 | 64 | 184a |
| 2 | R = Me (Z-isomer) | NBS/Bu$^t$OK/DMF | 76 | 61:39 | | 184b |
| 3 | R = Pr$^n$ | NBS/CCl$_4$ | | | 76 | 185 |
| 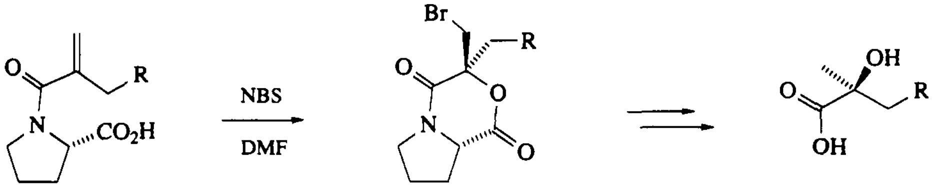 | | | | | | |
| 4 | R = Pr$^n$ | | | | 76 | 185 |
| 5 | R = H | | | | 64 | 185 |

### *1.9.2.2.4 Cyclizations with alkynes and allenes*

Electrophilic heteroatom cyclizations of systems involving alkyne and allene π-systems have attracted significant attention. A major difference from alkene cyclizations is that the electrophilic group in the initial product may be a vinyl substituent, and, in the case of metal electrophiles, possess different reactivity patterns than when attached to a saturated carbon.

The cyclofunctionalization of 4-alkynoic and 5-alkynoic acids generates γ-alkylidene-γ-lactones and δ-alkylidene-δ-lactones, respectively (equation 76 and Table 22). The initial products from the reactions catalyzed by mercury or silver salts undergo protiodemetallation under the reaction conditions. The vinylpalladium intermediates undergo either protiodemetallation or coupling with an added allyl halide. The palladium(II)-catalyzed cyclization of 3-alkynoic acids proceeds by 5-*endo* closure to give 3-buten-4-olides (Table 22, entry 2).[50,190]

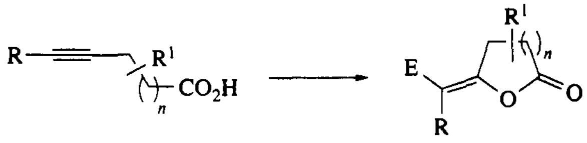

(76)

Several cyclofunctionalization reactions of alkynic alcohols are synthetically useful. Metal ion-promoted cyclofunctionalization of *cis*-2-propargylcyclopentanol systems proceeds by the 5-*exo* mode (equation 77 and Table 23).[197] Protiodemetallation or reductive demetallation provides the cyclic enol ether in high yields. This method has been used by Noyori in the synthesis of prostacyclin (PGI$_2$).[197b,197c] Reactions with catalytic amounts of mercury(II) or palladium(II) salts gave the endocyclic enol ether as the major product.[197a,198] A related cyclization with Ag$_2$CO$_3$ has been reported by Chuche.[191] Schwartz

**Table 22** Lactonization of Acyclic Alkynic Acids (Equation 76)

| *Entry* | *Reagent* | *n* | *E* | *Ref.* |
|---|---|---|---|---|
| 1 | Mercury(II) salts | 1 or 2 | H | 189 |
| 2 | $[PdCl_2(PhCN)_2]$, $Et_3N$ | 1 or 2 | H | 190 |
| 3 | $AgCO_3$, PhH | 1 | H | 191 |
| 4 | Li carboxylate, $[PdCl_2(MeCN)_2]$, $CH_2{=}CHCH_2Cl$ | 1 or 2 | Allyl | 192 |
| 5 | NCS, NIS or NBS, $KHCO_3$, $CH_2Cl_2$ | 1 or 2 | Cl, I, Br | 189b, 189c, 193 |
| 6 | PhSeNPhth | 1 | PhSe | 194 |
| 7 | PhSCl, $Et_3N$ | 1 | PhS | 195 |
| 8 | $I_2$, KI, $H_2O$ | 1 or 2 | I | 196 |

found that the organomercury intermediate could be intercepted by NBS or NIS to give the β-halo enol ether, and that the *trans*-cyclopentanol isomer cyclized *via* the 6-*endo* mode to give a fused dihydropyran.[197a]

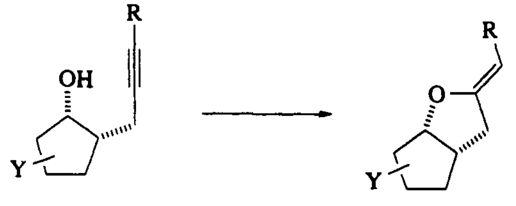

(77)

**Table 23** Cyclization of Propargyl-substituted Cyclopentanols (Equation 77)

| *Reagent* | *Yield (%)* | *Ref.* |
|---|---|---|
| i, $Hg(TFA)_2$, $Et_3N$, –78 °C<br>ii, LiI, ether | 45 | 197a |
| i, $Hg(TFA)_2$, $Et_3N$, –78 °C<br>ii, $NaBH_4$, NaOMe, MeOH | 67 | 197b |
| i, $[PdCl_2(PhCN)_2]$<br>ii, $NH_4^+HCO_3^-$ | 71 | 197c |

Successive intramolecular oxypalladation of dihydroxyalkynes has been used for the synthesis of spirocyclic and bridged acetals. Equations (78) to (80) show the syntheses of some insect pheromones by this method.[198] The results from several diols suggest that preferred modes for initial cyclization are 5-*endo* > 5-*exo* > 6-*endo*. A related conversion of 8-hydroxyoct-4-ynoic acid to an oxaspirolactone with mercury(II) oxide has been reported.[199]

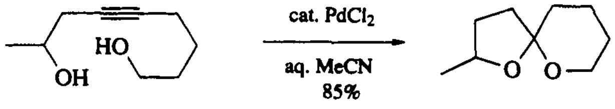

(78)

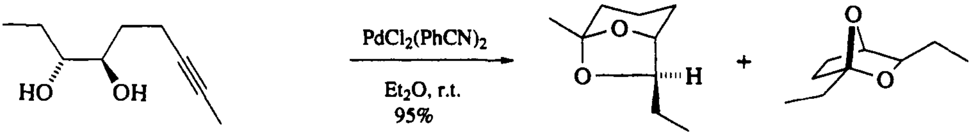

(79)

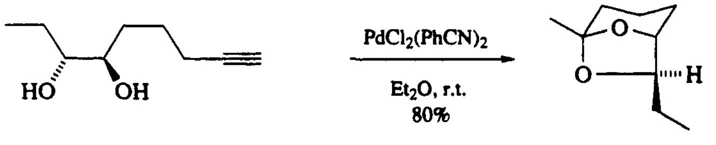

*exo*-Brevicomin

(80)

Several examples of intramolecular solvomercuration of arylalkynes have been reported (equations 81 to 83).[200] The mercury moiety can be removed by protiodemetallation or converted to a variety of other functional groups. The use of a methyl ether as the nucleophilic functionality is noteworthy, as is the change in the regioselectivity (equation 82 *versus* equation 83). A bromocyclization related to equation (83) using a phenylethynylbenzoate ester also gives an isocoumarin derivative *via* 6-*endo* cyclization.[201] Palladium-catalyzed cyclizations of β,γ-alkynic ketones or 2-methyl-3-alkyn-1-ols to form substituted furans are discussed in Chapter 1.4, Section 3.1.3 in this volume.

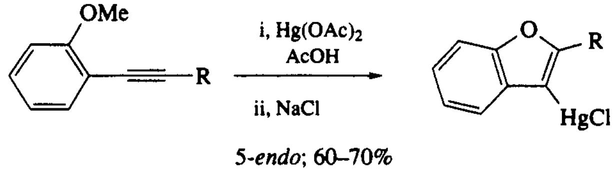

(81)

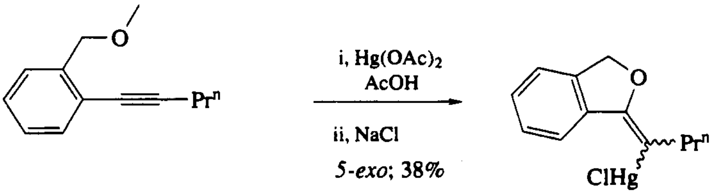

(82)

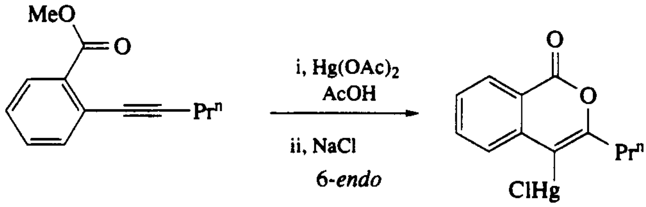

(83)

Allenes can also act as the π-participant in electrophilic heteroatom cyclizations. Reviews of electrophilic additions to allenes discuss early examples of this type of cyclization.[1d,1e,202] Numerous examples of cyclizations of α-functionalized allenes, including carboxylic acids, phosphonates, sulfinates and alcohols, to form five-membered heterocycles (equation 84) are cited in these reviews. The silver nitrate-mediated conversion of α-allenic alcohols to 2,5-dihydrofurans[203] has recently been applied to trimethylsilyl-substituted systems.[204]

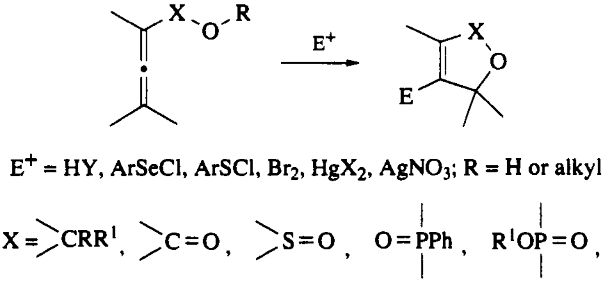

(84)

$E^+$ = HY, ArSeCl, ArSCl, $Br_2$, $HgX_2$, $AgNO_3$; R = H or alkyl

X = $\rangle$CRR$^1$, $\rangle$C=O, $\rangle$S=O, O=PPh, R$^1$OP=O,

Most cyclizations of β-allenic alcohols have produced six-membered ring products *via* a 6-*endo* process (equation 85).[168e,205] The exception is found with terminally unsubstituted allenes as shown in equation (86).[205d] The bicyclic acetal results from a 5-*exo* cyclization to an enol ether, which undergoes a second cyclization to form the acetal.

Cyclization of a variety of γ-allenic alcohols with silver nitrate proceeds by 5-*exo* cyclization to form 2-alkenyltetrahydrofurans (equation 87).[205c,206] Little stereoselectivity is seen in cyclizations of secondary alcohols. Cyclization by intramolecular oxypalladation/methoxycarbonylation or oxymercuration followed by transmetallation and methoxycarbonylation also showed no stereoselectivity (equation 88 and Table 24, entries 1 and 2).[50,207a] However, cyclization of the corresponding *t*-butyldimethylsilyl ether derivatives with mercury(II) trifluoroacetate followed by transmetallation/methoxycarbonylation pro-

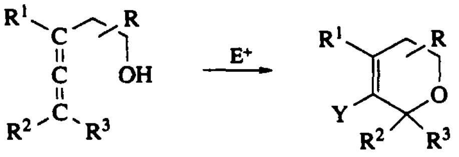

(85)

$E^+$ = HY, ArSeCl, $BF_3$, $HgCl_2$, $AgNO_3$; $R^1$ = H, alkyl or SPh; $R^2$ and $R^3$ = alkyl, H or alkyl, alkyl

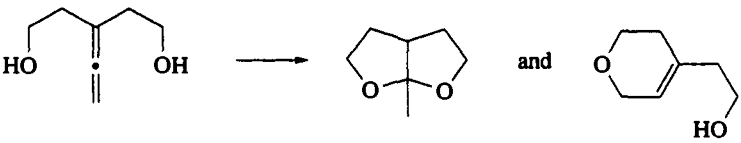

(86)

| *Reagent* | *Yield* | *Product ratio* | |
|---|---|---|---|
| cat. $HgCl_2$, $CH_2Cl_2$, r.t. | 90% | 100% | 0% |
| 1.1 equiv. $AgNO_3$, aq. acetone | 80% | 60% | 40% |

ceeds with high stereoselectivity (entries 3 and 5).[207a,207b] This selectivity is presumed to derive from equilibrium control brought about by slow desilylation and the steric effect of the silyl group. Two exceptions to 5-*exo* cyclizations of systems with the allene γ to the nucleophilic atom are the mercury(II) oxide cyclization of 4,5-hexadienoic acid to a δ-lactone (equation 89)[189d] and the cyclization of β-allenic oximes to dihydro-1,2-oxazepines (equation 90).[208]

δ-Allenic alcohols with a variety of allene substitution patterns form 2-alkenyltetrahydropyrans by a 6-*exo* ring closure upon cyclization with silver or mercury salts (equation 91).[209] The organosilver intermediate undergoes protiodemetallation under the reaction conditions, while the vinylmercury

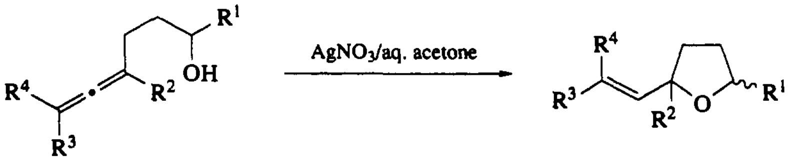

(87)

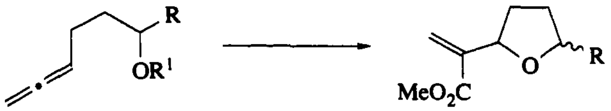

(88)

**Table 24** Effect of *O*-Silylation on Stereoselectivity of Cyclization of γ-Allenic Alcohols (Equation 88)

| *Entry* | *R, R*¹ | *Reagents* | *Yield (%)* | *cis:trans* |
|---|---|---|---|---|
| 1 | Me, H | i, $Hg(OAc)_2$, $CH_2Cl_2$;<br>ii, cat. $PdCl_2$, $CuCl_2$, MeOH, CO (1 atm) | 55 | 50:50 |
| 2 | Me, H | Cat. $PdCl_2$, $CuCl_2$, MeOH, CO (1 atm) | 72 | 50:50 |
| 3 | Me, $SiMe_2Bu^t$ | i, $Hg(TFA)_2$, $CH_2Cl_2$;<br>ii, cat. $PdCl_2$, $CuCl_2$, MeOH, CO (1 atm) | 53 | 94:6 |
| 4 | Me, $SiMe_2Bu^t$ | Cat. $PdCl_2$, $CuCl_2$, MeOH, CO (1 atm) | 60 | 50:50 |
| 5 | Pr, $SiMe_2Bu^t$ | i, $Hg(TFA)_2$, $CH_2Cl_2$;<br>ii, cat. $PdCl_2$, $CuCl_2$, MeOH, CO (1 atm) | 89 | >98:2 |

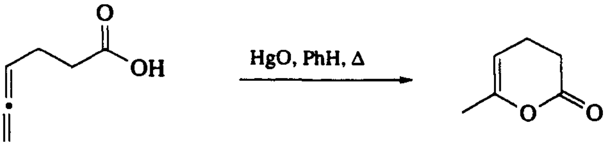

(89)

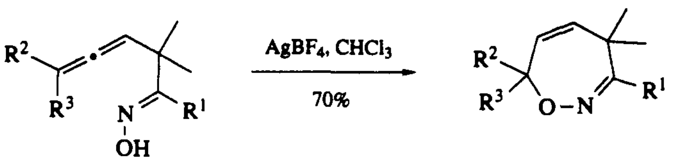
R2
R3
N
OH
R1
AgBF4, CHCl3
70%
R2
R3
O–N
R1

(90)

intermediate is stable and mercury is removed by subsequent reduction with sodium borohydride. In cyclizations of analogous secondary alcohols or of 3-alkyl-substituted systems, the *cis*-fused isomer predominates (equation 92).[209,210] The predominant formation of the *cis* isomer is rationalized in terms of a chair-like transition state. Enolizable γ- and δ-allenic ketones have been converted to 2-alkenyl-substituted dihydrofuran and dihydropyran structures in moderate yield using catalytic amounts of mercury(II) oxide and *p*-TsOH in refluxing cyclohexane.[211]

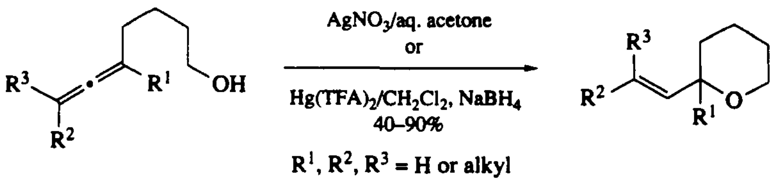
R3
R2
R1
OH
AgNO3/aq. acetone
or
Hg(TFA)2/CH2Cl2, NaBH4
40–90%
R1, R2, R3 = H or alkyl
R3
R2
R1
O

(91)

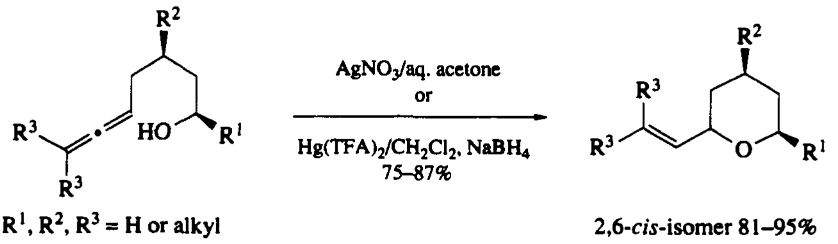
R2
R3
R3
HO
R1
R1, R2, R3 = H or alkyl
AgNO3/aq. acetone
or
Hg(TFA)2/CH2Cl2, NaBH4
75–87%
R2
R3
R3
O
R1
2,6-cis-isomer 81–95%

(92)

### 1.9.2.3 Large Rings

Electrophilic heteroatom cyclizations have been rarely applied to the synthesis of large rings. Although isolated examples of cyclization to seven-membered rings (*e.g.* equation 90) are known,[9,58,141b,184b,208] applications to synthesis have been limited. A selenoetherification of a vinyl ether to an eight-membered acetal has been reported.[212] Examples of phenylselenolactonizations to form 14- and 16-membered rings are shown in equation (93).[31] Reagents such as phenylselenenyl chloride lead to simple addition across the double bond with no cyclization.

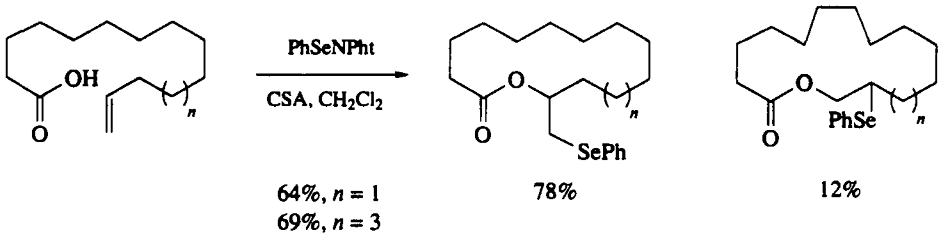
OH
O
n
PhSeNPht
CSA, CH2Cl2
64%, n = 1
69%, n = 3
O
O
n
SePh
78%
O
O
PhSe
n
12%

(93)

## 1.9.3 NITROGEN NUCLEOPHILES

The generation of nitrogen heterocycles by electrophilic heterocyclization has been reviewed recently.[1c] Examples of functional groups used as nitrogen nucleophiles are shown in Figure 2.

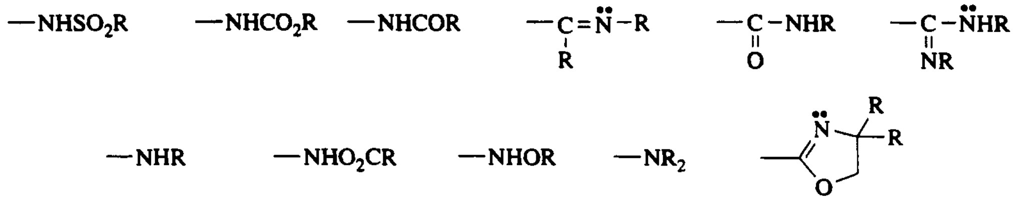

**Figure 2**

### 1.9.3.1 Small Rings

Few examples of cyclization to small ring nitrogen compounds are known. Cyclization of alkenic amides normally results in nucleophilic attack by the carbonyl oxygen and formation of lactone products (see Section 1.9.2, Oxygen Nucleophiles). However, cyclizations of some β,γ-unsaturated amide derivatives to β-lactams have proven successful (equation 94 and Table 25). Ganem demonstrated that the use of *N*-sulfonyl derivatives with a more acidic carboxamide nitrogen proton resulted in preferential cyclization to β-lactam derivatives.[213] Similar results were obtained from cyclization of *O*-acylhydroxamate derivatives.[214] The formation of β-lactams by cyclization of amides with phenylsulfenyl chloride is reported to result from rapid addition of the chalcogenide to the double bond, with cyclization resulting from subsequent *N*-deprotonation and attack of the amide anion on the episulfonium ion intermediate.[215]

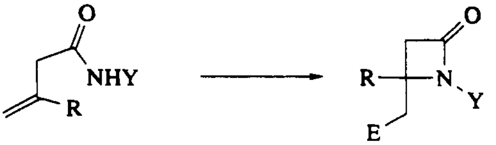

(94)

**Table 25** *N*-Cyclization of Amide Derivatives to Form β-Lactams (Equation 94)

| *Entry* | *R* | *Y* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | H or alkyl | $SO_2Ar$ or $SO_2OR^1$ | $I_2$, $CH_2Cl_2$/aq. $NaHCO_3$ | 77–95 | 213 |
| 2 | H | $O_2CR^1$ | $Br_2$, $K_2CO_3$/10% aq. MeCN | 75–90 | 214 |
| 3 | H or alkyl | $CH_2Ar$ | i, PhSCl; ii, KOH, $Bu_4NBr$ | 45–97 | 215 |

### 1.9.3.2 Five- and Six-membered Rings

#### *1.9.3.2.1 Cyclizations with C=C—C constrained by existing ring*

Cyclizations of substrates in which an existing ring constrains rotation of the vinylic bond that attaches the nucleophile to the double bond form fused ring nitrogen heterocycles with highly predictable regiochemistry and stereochemistry. Examples include cyclizations to fused ring pyrrolidines[216] and pyrrolidones[217] (equation 95 and Table 26).

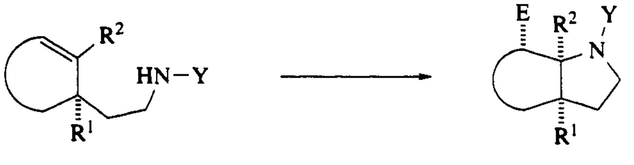

(95)

Fused ring products also may be formed from the transannular cyclization of medium ring unsaturated amine derivatives, as shown in Table 27.[218] A transannular cyclization to the loline ring system was reported by Wilson (entry 4).[218c] Cyclization of a tertiary amine to a pyrrolizidine perchlorate has also been reported.[219]

One example of the formation of a bridged ring product *via* 6-*endo* closure has been reported using phenylselenenyl chloride (equation 96).[220] The regioselectivity is presumably controlled by conjugation of the alkene with the thiazole ring. Cyclizations to form bridged ring systems from monocyclic sub-

**Table 26** Cyclization to Fused-ring Pyrrolidine Derivatives

| *Entry* | *$R^1$, $R^2$* | *Y* | *Conditions* | *E* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | H | $CO_2R$ | PhSeBr, $AgO_2CCF_3$ | PhSe | 59 | 216a |
| 2 | H | $CO_2R$ | NPhSeNPht, $CH_2Cl_2$ | PhSe | >82 | 216b |
| 3 | $(CH_2)_4$ | H | $Br_2$, $CH_2Cl_2$ | Br | 72 | 216d |
| 4 | alkyl, H | $CO_2R$ | $I_2$, $K_2CO_3$ | I | 76 | 216e |
| 5 | | | 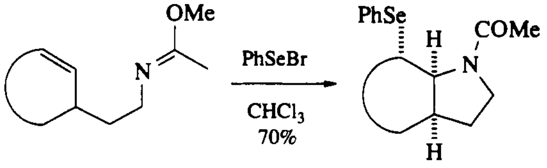 OMe<br>N<br>PhSeBr<br>CHCl3<br>70%<br>PhSe<br>H<br>COMe<br>N<br>H | | | 216e |
| | | | 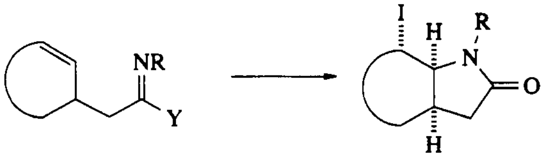 | | | |
| 6 | $CH_2Ph$ | SMe | $I_2$ | | 63 | 217b |
| 7 | $SiMe_3$ | $OSiMe_3$ | $I_2$ | | 86–88 | 217a |

For entries 1–4, see equation (95).

**Table 27** Cyclization with Nitrogen Nucleophiles

| *Entry* | *Y* | *X* | *Yield (%)* | *Product(s) (% of total)* | | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | | 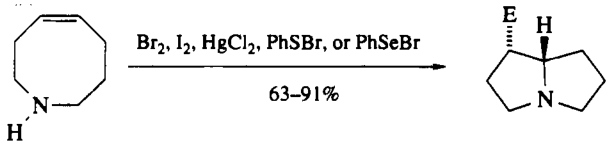 N<br>H<br>Br2, I2, HgCl2, PhSBr, or PhSeBr<br>63–91%<br>E<br>H<br>N | | | | 218a |
| | | 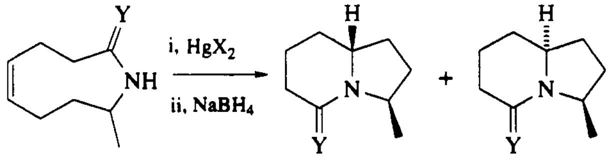 Y<br>NH<br>i, HgX2<br>ii, NaBH4<br>H<br>N<br>Y<br>+<br>H<br>N<br>Y | | | | |
| 2 | O | OAc | 83 | 100 | 0 | 218b |
| 3 | H, H | Cl | 68 | 70 | 30 | 218c |
| 4 | | 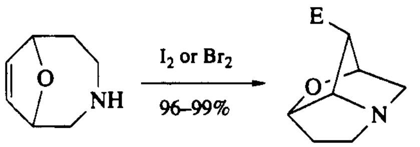 | | | | 218c |

strates (equation 97)[221] as well as from bridged ring substrates (equation 98)[222] have been covered in previous reviews.[1c,86] In equation (98) the organomercury intermediate undergoes substitution in the highly polar solvent with participation of the neighboring nitrogen. The bridged lactam (**16**), prepared by bromolactamization of a silyl imidate derivative,[223] was used in a recent synthesis of an aminouronic acid (Scheme 10).[217a] The synthesis of bridged ring systems from monocyclic dienes has been discussed in recent reviews.[1c,224]

Examples of highly stereoselective iodocyclizations of δ-aminocyclohexenes to generate azaspirocycles are shown in equations (99)[225a] and (100).[225b] The stereocontrol in these examples is attributed to the effect of the *t*-butyldimethylsilyloxy substituent.[225]

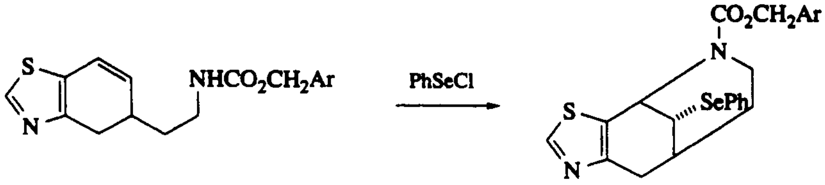
NHCO2CH2Ar
PhSeCl
CO2CH2Ar
N
SePh
S
N

(96)

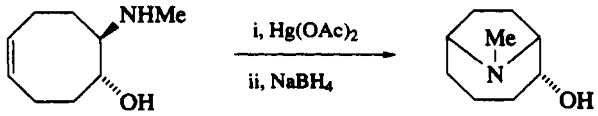
NHMe
OH
i, Hg(OAc)2
ii, NaBH4
Me
N
OH

(97)

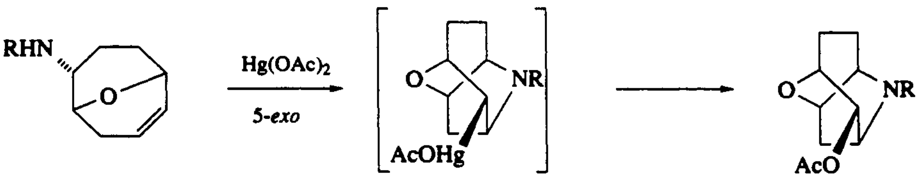
RHN
O
Hg(OAc)2
5-exo
O
NR
AcOHg
O
NR
AcO

(98)

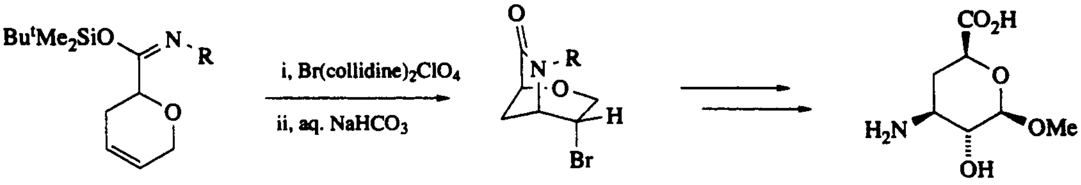
ButMe2SiO
N
R
O
i, Br(collidine)2ClO4
ii, aq. NaHCO3
O
N - R
O
H
Br
CO2H
O
H2N
OMe
OH

**(16)**

**Scheme 10**

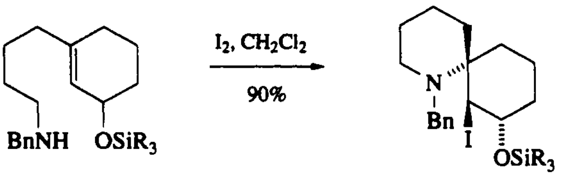
BnNH
OSiR3
I2, CH2Cl2
90%
N
Bn
I
OSiR3

(99)

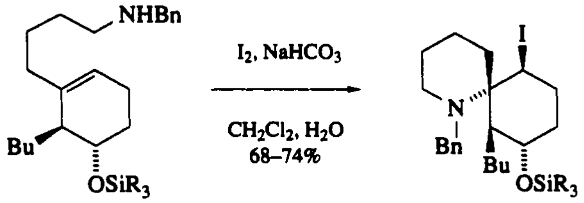
NHBn
Bu
OSiR3
I2, NaHCO3
CH2Cl2, H2O
68–74%
I
N
Bn
Bu
OSiR3

(100)

Fused ring heterocycles, prepared by cyclization of substrates with a 'tethered' nitrogen nucleophile, have been used in the synthesis of amino sugars and aminocyclitols. The examples shown in Table 28 make use of imidate-type functionality (equation 101) to insure nucleophilic attack by nitrogen. The bromocyclization of *N*,*N*-dialkylaminomethyl ethers of 2-cyclohexen-1-ol to form bicyclic oxazolidine derivatives has been reported also.[228b]

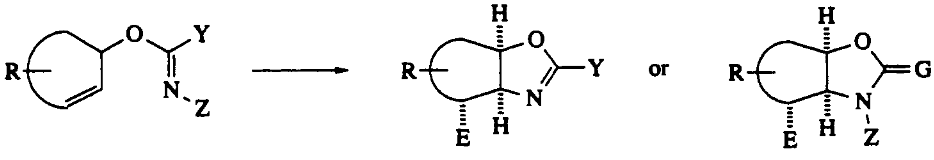
R
O
Y
N
Z
H
O
Y
N
E
H
or
H
O
G
N
E
H
Z

(A) (B)

(101)

**Table 28** *N*-Cyclization of Derivatives of Cyclic Allylic Alcohols

| *Entry* | *Y* | *Z* | *Conditions* | *Yield (%) (A)* | *Yield (%) (B)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | $CCl_3$ | H | NBS or NIS or $I(\textit{sym}\text{-collidine})_2BF_4$ | 70–95 | | 94c, 226 |
| 2 | SMe | Alkyl | $Br(coll)_2ClO_4$ or $I_2$ | | 61–90 (O) | 96b,227 |
| 3 | Ph | COPh | NBS | | >85 (OR, Ph) | 226d,228a |
| 4 | $NMe_2$ | H | $Hg(O_2CCF_3)_2$; $NaBH_4$ | 80 | | 228c, 228d |

### *1.9.3.2.2 Other C=C cyclizations*

#### *(i) Regioselectivity and stereoselectivity*

Most cyclizations to form five-membered rings involve the 5-*exo* mode of cyclization. An exception has been reported in the intramolecular sulfenoamination of β-alkenylamines used in the synthesis of pyrrolidine alkaloids (equation 102).[215a,229] Other examples include the aminomercurations of *N*-substituted-1-amino-3-butenes[162a,230] and the methylsulfenilium ion-initiated cyclization of *O*-(2-propenyl)-*N*-tosylaniline.[231]

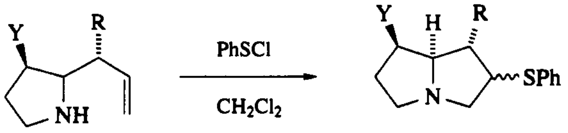

(102)

Y, R = H, H or OBn, $CH_2OBn$

Systems which can react by either 5-*exo* or 6-*endo* cyclization normally produce the five-membered ring system. Exceptions result when equilibration of the initially formed five-membered ring is facile and substitution electronically favors the 6-*endo* mode of cyclization. Several examples have been found in amidoselenation reactions.[41,158c,216a,216e,232] For example, halocyclization of thioimidate (**17**) produced only the pyrrolidone product,[217b,217c,233] while selenocyclization of amide (**18**) produced only the piperidone product.[232a] Note that the cyclization of (**18**) to a piperidone also involves regioselectivity in the cyclization of an amide functionality to a lactam rather than an imidate. Both the ring size and type of product can be explained by equilibration.

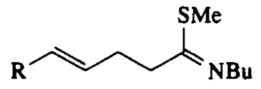

R= Ph or alkyl

(**17**)

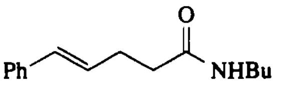

(**18**)

The regiochemistry of the palladium-catalyzed cyclizations of some alkenic sulfonamides was found to vary with the amount of palladium used (Scheme 11).[50,234a] The regioselectivity in cyclizations of ammonium salts of 1-amino-4-hexene with palladium chloride[234b] (5-ring:6-ring = 80:20) was significantly different from cyclizations of the same amine promoted with platinum salts[234b] (5-ring:6-ring = 9:91).

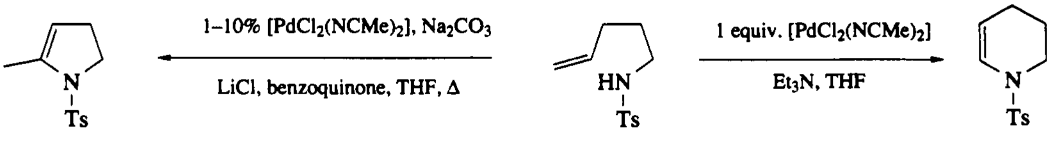
N
Ts
1–10% $[PdCl_2(NCMe)_2]$, $Na_2CO_3$
LiCl, benzoquinone, THF, Δ
HN
Ts
1 equiv. $[PdCl_2(NCMe)_2]$
$Et_3N$, THF
N
Ts

**Scheme 11**

Another aspect of regioselectivity with many nitrogen nucleophiles is the ambident nature of the nucleophile, which can lead to products of the same ring size through either *N*-cyclization or *O*-cyclization (see Scheme 12 for an example). As shown by entries 1 and 2 in Table 25, preferential *N*-cyclization to β-lactams has been effected by use of sulfonyl or acyloxy substitution on nitrogen. However, these substituents do not lead to *N*-cyclization in substrates which generate five- or six-membered products. Although isolated examples of the cyclization of amides to lactams have been observed (*cf.* cyclization of **18** described above), most examples of lactam formation have involved amide derivatives which direct the cyclization to nitrogen (see below). A recent study has shown that *N*-heterocyclic α-alkyl γ,δ-unsaturated amides form lactam products upon bromocyclization (equation 103 and Table 29).[235] No explanation for the anti-Markovnikov 6-*endo* cyclization in entry 3 is given.

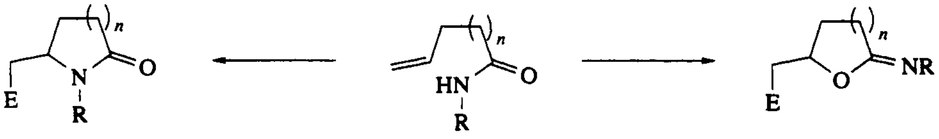

Scheme 12

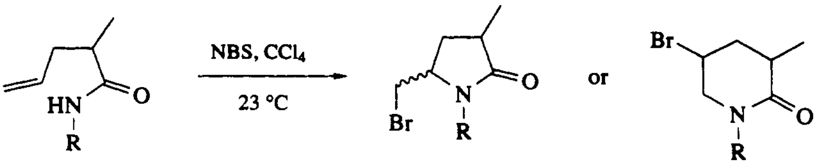

(103)

Table 29 *N*-Cyclization of γ,δ-Unsaturated Amides (Equation 103)[235]

| *Entry* | *R* | *Yield* |
|---|---|---|
| 1 | 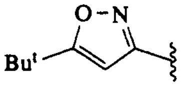 | 30% |
| 2 | 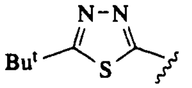 | 73% |
| 3 | 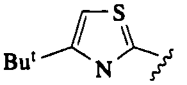 | 43% |

Many of the factors controlling stereochemistry in cyclizations with a nitrogen nucleophile are analogous to those discussed earlier with oxygen as nucleophile. One example is found in the strong directing effect of an allylic hydroxy group, as shown in equation (104)[236] (compare with the results for oxygen cyclizations, shown in Table 9). The *cis* isomer (resulting from OH-in-plane cyclization) was formed with high selectivity in a variety of substituted systems. In particular, the configuration of a C-4 (homoallylic) alkyl group had little effect on stereoselectivity. The tosylamide system cyclized more readily than the carbamate system, which required higher temperatures and did not cyclize with NBS.

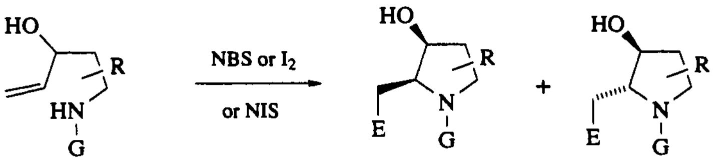

(104)

| *G* | *Product ratio (cis:trans)* |
|---|---|
| $O_2STos$ | 93:7–97:3 |
| $CO_2Me$ | 90:10–95:5 |

Similar stereochemical results have been reported in iodolactamizations of thioimidates (equation 105)[217b,217c] and the palladium(II)-catalyzed aminocarbonylation reaction (equation 106).[50,237] In some cases, the stereoselectivity in the aminocarbonylation reaction varied considerably with changes in the group on nitrogen or reaction conditions.

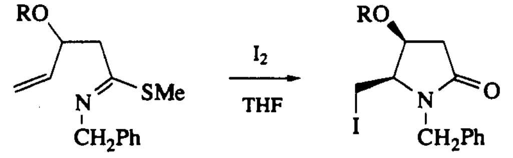

R = H or $SiMe_2Bu^t$ 7–12:1 *(cis:trans)* (105)

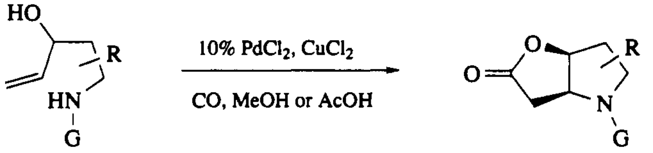

G = $CO_2Me$ or CONHPh or $SO_2Tol$ (106)

As found in oxygen cyclizations (equations 36 and 37), steric interactions result in a strong preference for the generation of *trans* isomers from the cyclization of systems with an allylic substituent and a double bond with the (*Z*)-configuration (equation 107).[238]

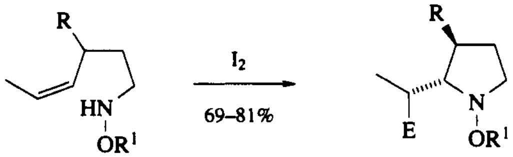

R = alkyl or OR (107)

The stereochemistry of cyclizations involving a terminal double bond or an internal double bond with an (*E*)-configuration and an allylic alkyl group depends upon the substrate and reaction conditions. Iodocyclizations of *N*,*O*-bis(trimethylsilyl)imidates containing allylic substituents provide iodolactams with a small preference for the *cis* stereoisomers (equation 108).[223] Cyclization of 3-methyl-4-pentenylamine with $[PtCl_4]^{2-}$ in aqueous acid produced the *trans*- and *cis*-dimethylpyrrolidine in 85% yield and an 88:12 ratio, although the reaction required 21 d for completion.[239] Iodocyclization with an oxazoline as the nucleophile gave a slight preference for the *cis* isomer with R = Me, but a large preference for the *trans* isomer when R was the much more sterically demanding *t*-butyl group (equation 109).[240] Selenoamination of some arylamine systems with an (*E*) double bond and an allylic substituent to generate mitosane ring systems proceeded with a moderate (80:20) to high (>95:5) preference for the *trans* isomers.[241]

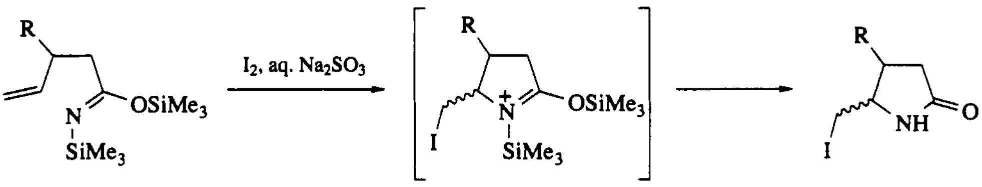

(108)

R = Me, *cis:trans* = 3:1
R = Ph, *cis:trans* = 2:1
R = $BnOCH_2$, *cis:trans* = 1:1

High asymmetric induction has been observed in some cyclizations to 2,5-disubstituted pyrrolidines. The selectivity in these cases appears to be a function of the nitrogen derivative used and the reaction conditions (equation 110 and Table 30). Cyclization of carbamate derivatives with mercury salts or I(col-

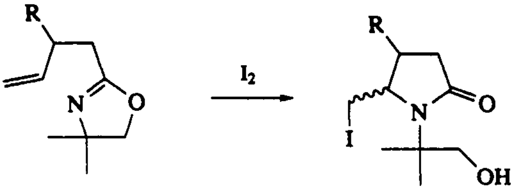

(109)

R= Me, *trans*:*cis*= 1:1–2; R= Bu$^t$, *trans*:*cis*= 9:1

lidine)$_2$ClO$_4$ provides *trans* products with high stereoselectivity.[242] The high selectivity in the mercuration reactions has been shown to be a result of kinetic control; equilibration of the products results in a predominance of the *cis* isomer.[246] Cyclization with *N*-phenylselenophthalamide (PhSeNPht) produced a 1:1 mixture of the two isomers (Table 30, entry 3).[216b] Cyclizations of substrates in which the C-5 substituent is part of a β-lactam ring have been reported to give only the *trans* isomer (entry 4).[243]

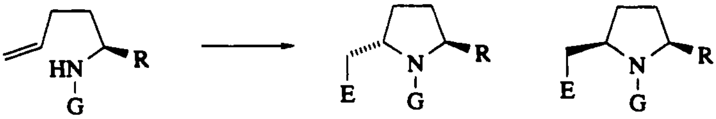

(110)

**Table 30** Cyclization to 2,5-Disubstituted Pyrrolidine Derivatives (Equation 110)

| *Entry* | *G* | *R* | *Electrophile* | *E* | *Ratio (trans:cis)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | $CO_2R$ or COMe | Me or Pr | $Hg(OAc)_2$ | HgOAc | 98:2 | 242a, 242b |
| 2 | $CO_2R$ | Me | $I(coll)_2ClO_4$ | I | >95:5 | 83a, 242b, 242c |
| 3 | $CO_2R$ | Me | PhSeNPht | SePh | ≈1:1 | 216b |
| 4 | G, R = —$COCH_2$— | | $Hg(OAc)_2$ or $I_2$ | HgOAc or I | >95:5 | 243 |
| 5 | OEt | Me | $I_2$ | I | ≤75:25 | 244 |
| 6 | Me | Me | $HgCl_2/H_2O$–THF | HgCl | 93:7 | 245 |
| 7 | Me | Me | $HgCl_2$/THF | HgCl | 36:64 | 245 |
| 8 | H | Me | $PtCl_4^{2-}$/aq. HCl | H | 60:40 | 239 |

In contrast, cyclizations of *N*-alkoxy derivatives with iodine are much less selective (Table 30, entry 5), and similar results are observed with systems containing internal double bonds of either (*E*)- or (*Z*)-configuration.[238] The stereoselectivity of the aminomercuration reaction of *N*-methyl derivatives has been reported to be controlled by the choice of mercury(II) salt and solvent (entries 6 and 7).[244] Cyclization with platinum salts showed little selectivity (entry 8).[239] An iodocyclization of a complex *N*-alkyl system has been used in a recent synthesis of (+)-croomine.[238]

High stereoselectivity has been observed in the cyclizations to γ-lactams of thioimidate systems with a homoallylic substituent (equation 111).[217b,217c] The selectivity is considered to arise from A$^{1,2}$ strain favoring a quasiaxial orientation of the homoallylic substituent in (**17**; see above). In comparison, the cyclizations to γ-lactams shown in Table 29 were not stereoselective.[235]

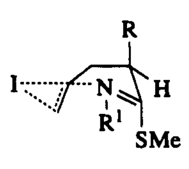

(**17**)

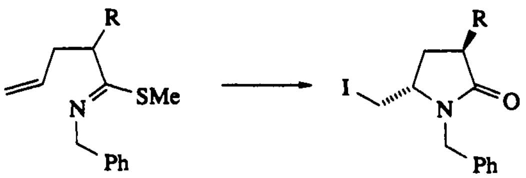

(111)

R = Me, $C_6H_{11}$, Ph

*trans*:*cis* = 12–14:1

Few examples of stereoselectivity in 6-*exo* cyclizations to piperidine derivatives have been reported. The aminocarbonylation reactions of systems with an allylic hydroxy substituent that are quite stereoselective in cyclization to pyrrolidine systems (equation 106) are nonselective in cyclizations to piperidine systems.[237] Cyclizations with mercury(II) acetate also proceed with low selectivity (59–69% *cis* isomer).[237] A series of aminoalditols have been synthesized by aminomercuration of oxygen-substituted 6-(*N*-benzylamino)hexenes. The stereochemistry of these cyclizations (equation 112)[247] does not appear to be controlled solely by the stereochemistry of the allylic oxygen substituent. Cyclization of the aminoalkene (**18**) derived from galactose (entry 1) with mercury(II) trifluoroacetate under conditions of kinetic control did give a predominance of the equatorial product after reductive oxygenation.[247b] Cyclization with mercury(II) bromide (thermodynamic control) gave a 1:1 mixture of the stereoisomeric organomercury compounds. Cyclization of the aminoalkene (**18**) derived from mannose (entry 2) with mercury(II) trifluoroacetate also gave predominantly the product with the hydroxymethyl *cis* to the allylic benzyloxy substituent.[247a] Iodocyclization gave the same ratio of stereoisomers. However, cyclization of the aminoalkene (**18**) derived from glucose (entry 3) produced the *trans* isomer as the predominant product.[247a]

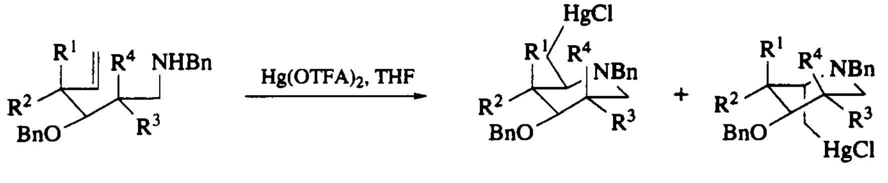

(112)

(**18**) i ii

| *Entry* | *R¹* | *R²* | *R³* | *R⁴* | *Ratio (i:ii)* |
|---|---|---|---|---|---|
| 1 | OBn | H | OBn | H | 75:10 |
| 2 | H | OBn | H | OBn | 1:7 |
| 3 | H | OBn | OBn | H | 61:39 |

Intramolecular amidomercuration of carbamate derivatives to generate 2,6-disubstituted piperidine systems (equation 113 and Table 31) proceeds with low selectivity under conditions of kinetic control (*cis:trans* = 40:60),[246,248] but cyclization under conditions of thermodynamic control highly favors the *cis* isomer (*cis:trans* ≥ 98:2).[246] Interestingly, only the *cis* isomer was isolated from cyclization with phenylselenenyl chloride in the presence of silica gel.[216a]

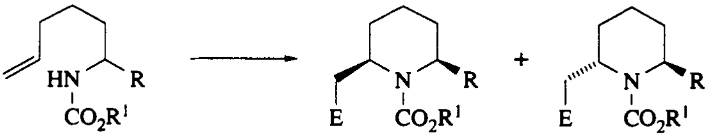

(113)

**Table 31** Cyclization of Carbamates to 2,6-Disubstituted Piperidine Derivatives (Equation 113)

| *Entry* | *R* | *R¹* | *Conditions* | *Yield (%)* | *cis:trans* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Me | Bn | $Hg(OAc)_2$, THF |  | 40:60 | 246 |
| 2 | Me | Bn | $Hg(O_2CCF_3)_2$, $CH_3NO_2$ | 93 | >98:2 | 246 |
| 3 | Me | Me | $Hg(OAc)_2$, THF | >62 | ~40:60 | 248 |
| 4 | $C_{11}H_{23}$ | Me | PhSeCl, silica | 84 | *cis* only | 216a |

Lower stereoselectivity has been observed with other nitrogen nucleophiles (equation 114 and Table 32). Iodocyclization of *N*-alkoxyamine derivatives gave a slight preponderance of the *trans* products with terminal vinyl groups (Table 32, entry 1), but the *cis* isomers predominated when the double bond was disubstituted with a (*Z*)-configuration (entry 2).[238] Aminomercuration of a related primary amine with the double bond an (*E*)/(*Z*) mixture provided a moderate excess of the *cis* isomer (entry 3).[249] The cyclization of a similar system with a homoallylic alkoxy substituent was also only moderately selective.[250a] However, the cyclization of a conformationally constrained system proceeded with quite high selectivity (equation 115).[250b] Aminomercuration reactions to form *N*-aryl-1-aza-4-silacyclohexanes showed variable stereoselectivities (*cis:trans* = 30:70 to 58:42).[251]

A stereoselective 6-*exo* selenoamination to form a tetrahydroisoquinoline ring system is probably a result of the specific substitution pattern.[252] Selenocyclizations which generate piperidine systems by 6-*endo* cyclization give products predicted by reaction through the more stable chair conformation (equation 116).[41,158c,216e,232a]

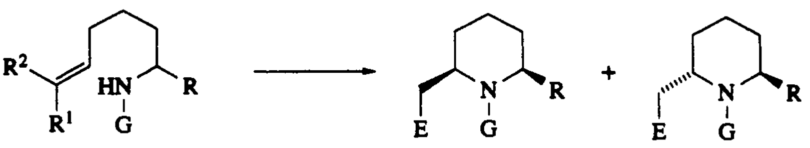
R2
R1
HN
G
R
N
E
G
R
+
N
E
G
R

(114)

**Table 32** Cyclization of Amines and *N*-Alkoxyamines to 2,6-Disubstituted Piperidine Derivatives (Equation 114)

| *Entry* | *$R^1, R^2$* | *R* | *G* | *Conditions* | *Yield (%)* | *cis:trans* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H, H | Alkyl | $OCH_2OCH_3$ | $I_2/CH_2Cl_2$, $Et_2O$ | ~82 | ~36:64 | 238 |
| 2 | H, alkyl | Alkyl | $OCH_2OCH_3$ | $I_2/CH_2Cl_2$, $Et_2O$ | 80 | 67:33 | 238 |
| 3 | alkyl, H | Alkyl | H | i, $Hg(OAc)_2$<br>ii, $NaBH_4$ | 52 | 79:21 | 249 |

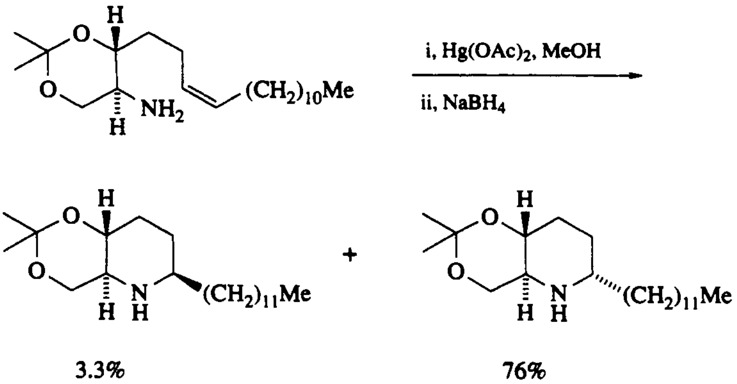
H
O
O
H
NH2
(CH2)10Me
i, Hg(OAc)2, MeOH
ii, NaBH4
H
O
O
N
H H
(CH2)11Me
+
H
O
O
N
H H
(CH2)11Me
3.3%
76%

(115)

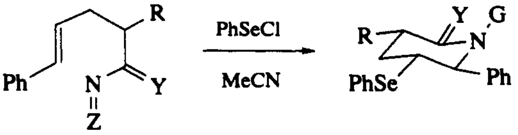
R
Ph
N
Y
Z
PhSeCl
MeCN
Y
G
R
N
PhSe
Ph

(116)

| *Y* | *Z* | *G* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| O | H, Bu | Bu | 73 | 232a |
| H, H | H, COMe | COMe | 79 | 41, 158c |
| H, H | =C(OR)Me | COMe | 30–40 | 216e |

### *(ii) Cyclization of heteroatom-tethered systems*

Cyclizations of systems in which nitrogen nucleophiles have been tethered to the oxygen atoms of unsaturated alcohols have been used for stereo- and regio-selective syntheses of 1,2- and 1,3-amino alcohols. A variety of nitrogen nucleophiles have been examined.

Bromocyclization of the thiocarbamidate generated from *t*-butylisothiocyanate and 3-buten-2-ol gave oxazolidinone products with slight selectivity for the *cis* isomer (*cis:trans* ≤ 1.9:1),[227a] while iodocyclizations of *N*-sulfonylated carbamates gave somewhat higher stereoselectivity (equation 117).[253]

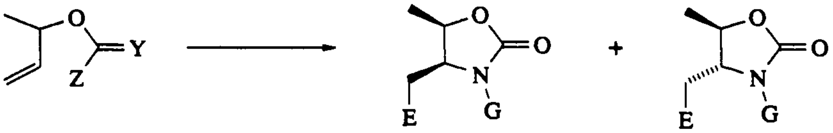
O
Y
Z
O
O
N
E
G
+
O
O
N
E
G

(117)

| *Y* | *Z* | *Conditions* | *Yield (%)* | *Ratio (c:t)* | *Ref.* |
|---|---|---|---|---|---|
| $NBu^t$ | SMe | $Br(coll)_2ClO_4$, $CH_2Cl_2$, −78 °C | 68 | 1.4:1 | 227a |
| O | $NHSO_2C_6H_4Me$ | $I_2$, ether/$K_2CO_3$ | 78 | 2.7:1 | 253 |

Iodocyclization of trichloroacetimidates forms *trans*-1,3-oxazolines with moderate to good stereoselectivity (equation 118).[254] Cyclizations of systems with internal double bonds (equation 119) generate 5-*exo* products *only* if the double bond has a (*Z*)-configuration (entries 2 and 3) *or* an oxygen substituent is attached to the allylic carbon (entries 3 and 4).[104c,153a,157b,254c]

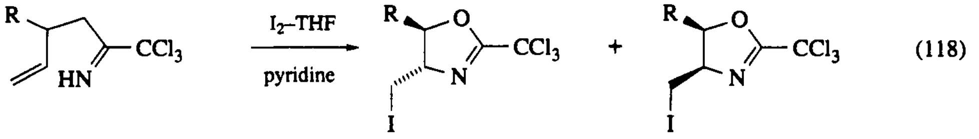

*Ratio* (*trans*:*cis*)
75:25 (R = $C_5H_{11}$)
95:5 (R = $Pr^i$)

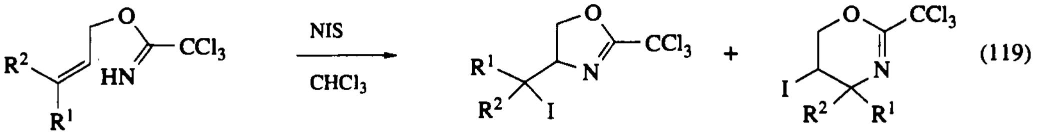

| *Entry* | *R¹* | *R²* | *Yield* | |
|---|---|---|---|---|
| 1 | alkyl or aryl or alkenyl | H | | |
| 2 | H | alkyl | 88–90% | 80–90% |
| 3 | H | $CH_2OR$ | 81–98% | |
| 4 | $CH_2OR$ | H | 55–75% | 18–38% |

The bromocyclization of *N*,*N*-dialkylaminomethyl ethers of allyl and propargyl alcohols to form oxazolidinium salts has been reported, but not used in synthesis.[255] The heterocyclization of *N*-acylaminomethyl ethers with mercury salts has been used for stereoselective synthesis of a variety of 1,2-amino alcohol systems. These cyclizations form *trans*-4,5-dialkyloxazolidine products with good to excellent stereoselectivities (equation 120 and Table 33). As shown by entry 5, 6-*endo* cyclization predominates (6:3) with an internal double bond of (*E*)-configuration, but this mode of cyclization is reduced with substrates containing a (*Z*) double bond and/or allylic oxygen substitution (Table 33, entries 6–9).

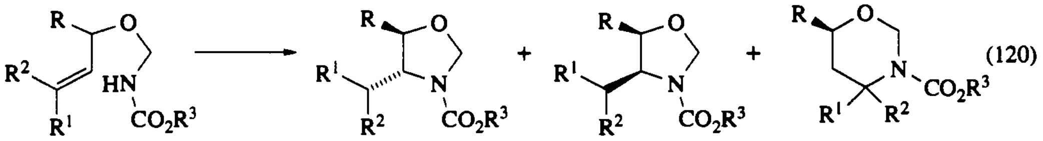

**Table 33** *N*-Cyclization of *N*-Acylaminomethyl Ether Derivatives of Allylic Alcohols (Equation 120)

| *Entry* | *R* | *R¹* | *R²* | *Conditions* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Me | H | H | i, $Hg(OAc)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | 75:25:0 | 256a |
| 2 | $(CH_2)_3OBn$ | H | H | i, $Hg(OAc)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | 81:19:0 | 256d |
| 3 | $CHMe_2$ | H | H | i, $Hg(OAc)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | >95:5:0 | 256a |
| 4 | Ph | H | H | i, $Hg(OAc)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | >95:5:0 | 256a |
| 5 | Me | Me | H | i, $Hg(OTFA)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | 2:1:6 | 256b |
| 6 | Me | H | Me | i, $Hg(OTFA)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | 10:1:5.5 | 256b |
| 7 | $(CH_2)_2NPht$ | H | $CH_2OBn$ | i, $Hg(OTFA)_2$, EtOAc;<br>ii, $NaBH_4$, $^-OH$ | 65:0:17 | 256c |
| 8 | H | H | $CH_2OBn$ | i, $Hg(NO_3)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | Oxazolidine only | 256b |
| 9 | H | $CH_2OBn$ | H | i, $Hg(NO_3)_2$, MeCN;<br>ii, $NaBH_4$, $^-OH$ | Oxazolidine only | 256b |

Quite recently, new methods for stereocontrol in cyclizations of *N*-acylaminomethyl ethers have been developed. *N*,*O*-acetals of type (**19**; Scheme 13) were prepared from the corresponding secondary allyl alcohol and the diastereomers were separated by chromatography and/or crystallization. Cyclization with mercury(II) salts and reduction of the organomercury intermediate proceeded with high stereocontrol exerted by the amidal stereogenic center, *not* the stereogenic center on the original alcohol.[257a]

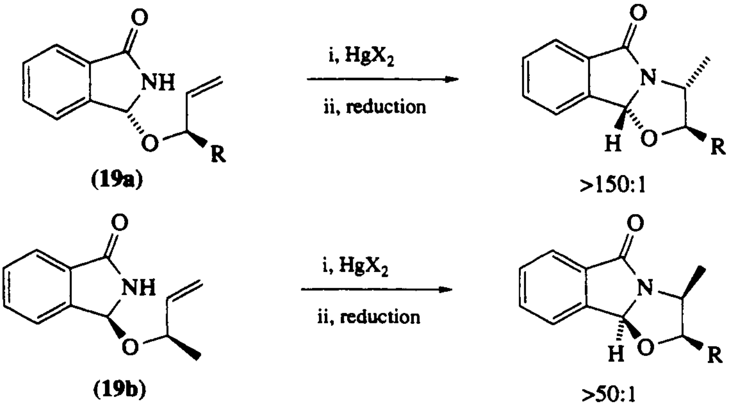

**Scheme 13**

A related strategy provides for control of absolute stereochemistry through the use of a chiral auxiliary (Scheme 14).[257b] Generation of the amidal (**20**) proceeds with reasonable stereoselectivity (87:13), and chromatography provides a pure diastereomer. Cyclization of either diastereomer gives an oxazolidine product in which the configuration of the new C—N bond is controlled solely by the configuration of the stereogenic center containing the —$CCl_3$ group. Interestingly, the product is a *trans*-2,5-disubstituted oxazolidine, while the cyclizations shown in Scheme 13 give products with a *cis* relationship between the groups at C-2 and C-5. Cyclization of a system similar to that shown in Scheme 14, but with stereocenters only on the chiral auxiliary (H replacing the —$CCl_3$ group) gave only a 60:40 ratio of diastereomers.

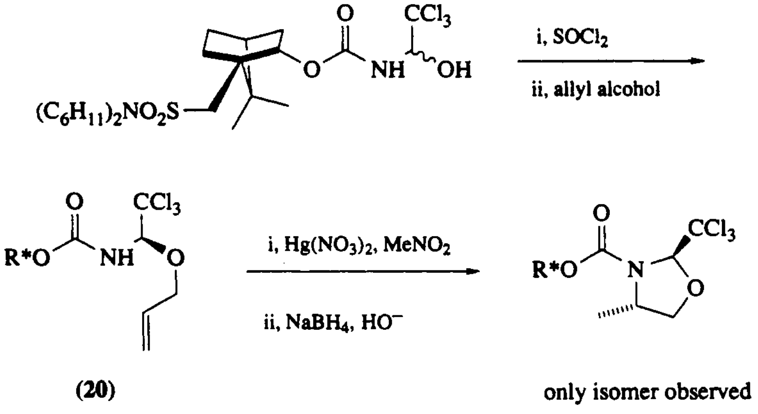

**Scheme 14**

Studies on tethered derivatives of homoallylic alcohols are fewer in number. Iodocyclization of trichloroacetimidate derivatives of 4-penten-2-ol (**21**) gave *cis*- and *trans*-dihydrooxazines in an 80:20 ratio,[254a,254b] while cyclization of the *N*-benzenesulfonylcarbamate derivatives (**22**) provided an 86:14 ratio of cyclic carbamates.[253] Cyclization of the *N*-acylaminomethyl derivatives (**23**) with mercury(II) trifluoroacetate under conditions of kinetic control gave a 75:25 ratio of *cis*- and *trans*-tetrahydrooxazine derivatives, but cyclization under conditions which allowed for equilibration of the organomercury intermediates produced a 6:94 ratio.[258]

A variety of nitrogen nucleophiles have been tethered to the nitrogen of allylic and homoallylic amines. Examples include halocyclizations of amidines (equation 121),[259a,259b] *O*-substituted isoureas (equations 122[259a,259c] and 123[98b]) and *S*-alkylisothioureas (equation 124),[259e,259f] aminopalladation/methoxycarbonylation of alkylurea derivatives (equation 125)[259d] and bromocyclization of substituted urea derivatives (equation 126).[235] Bromocyclization of an isothiourea has also been reported.[1c,259e] Although most studies have resulted in cyclization to five-membered rings, halocycliza-

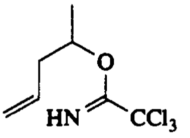

**(21)**

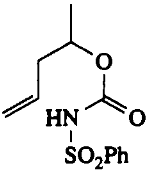

**(22)**

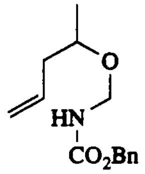

**(23)**

tion of amidine derivatives[259b] and selenocyclization of urea derivatives[98a] of cinnamylamine give products of 6-*endo* cyclization.

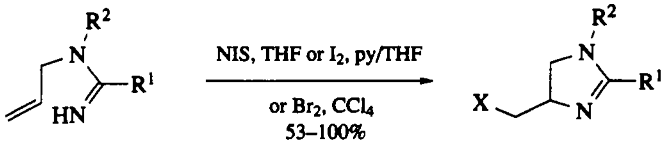
R2
N
R1
HN
NIS, THF or I2, py/THF
or Br2, CCl4
53–100%
R2
N
R1
X
N

(121)

$R^1$ = Ph or $CCl_3$, $R^2$ = H or Ph

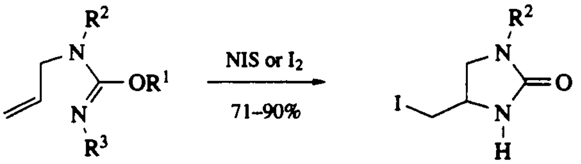
R2
N
OR1
N
R3
NIS or I2
71–90%
R2
N
O
I
N
H

(122)

$R^1 = R^3 = SiMe_3$, $R^2$ = Me or Ph; $R^1$ = Et, $R^3$ = H, $R^2$ = Ph(Me)CH

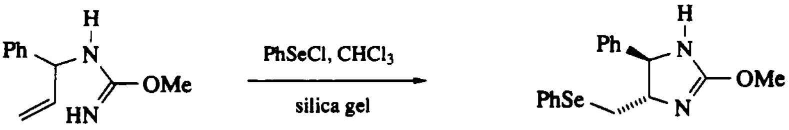
H
Ph
N
OMe
HN
PhSeCl, CHCl3
silica gel
H
Ph
N
OMe
PhSe
N

(123)

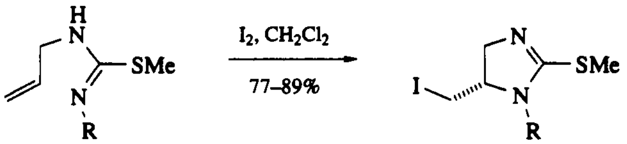
H
N
SMe
N
R
I2, CH2Cl2
77–89%
N
SMe
I
N
R

(124)

R = Ph or Ac

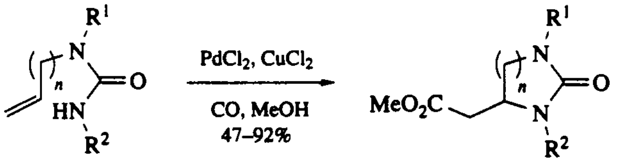
R1
N
n
O
HN
R2
PdCl2, CuCl2
CO, MeOH
47–92%
R1
N
n
O
MeO2C
N
R2

(125)

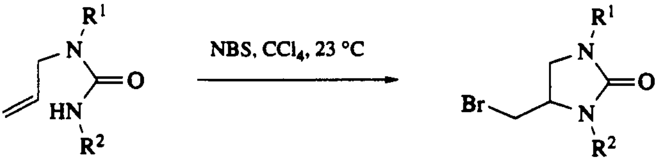
R1
N
O
HN
R2
NBS, CCl4, 23 °C
R1
N
O
Br
N
R2

(126)

$R^1$ = aryl, aroyl, or $EtO_2CCH_2$; $R^2$ = Me or Ph

Related intramolecular aminomercurations of cyclic guanidine derivatives have been studied in some detail,[260a] but are primarily useful for the synthesis of bicyclic heterocycles (equations 127 and 128). Cyclizations of allylic isothiouronium salts have also been reported (equation 129).[260b,260c]

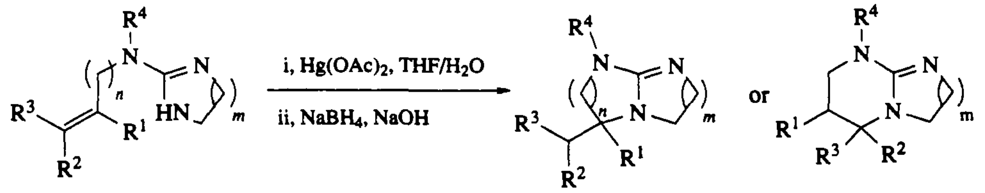

(127)

$n$ = 1 or 2; $m$ = 1, 2 or 3

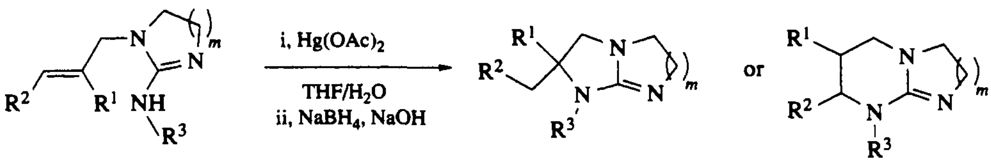

(128)

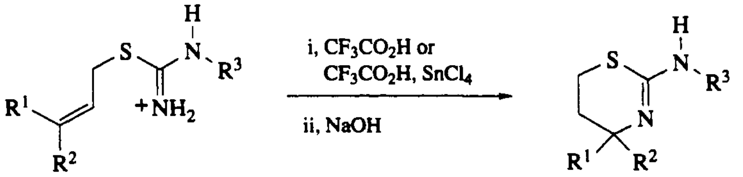

(129)

R$^1$, R$^2$ = alkyl or aryl, R$^3$ = H or aryl

*(iii) Miscellaneous*

Some synthetically useful reactions not covered in the above sections should be mentioned. An unusual heterocyclization to form indole derivatives is found in the aminomercuration of allylenaminones (equation 130).[261] Palladium(II)-catalyzed cyclizations of *o*-allyl- and *o*-vinyl-anilines and aminoquinones are discussed elsewhere.[50] Other electrophiles used to form dihydroindole derivatives include phenylselenenyl chloride[216a] and methyl(bismethylthio)sulfonium salts.[231]

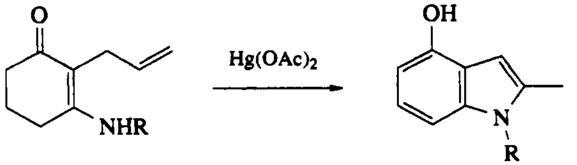

(130)

Cyclizations of alkenic amines and imines using organoiron complexes to generate bicyclic β-lactams are discussed in Chapter 3.1 of this volume. Examples of heterocyclizations of alkenic *N*,*N*-dialkylamine and pyridine derivatives to form cyclic quaternary ammonium salts are cited in the Staninets review.[1c] A cyclization of an enol thioether has been used to generate a thiazolidine intermediate used in cephalosporin synthesis (equation 131).[262]

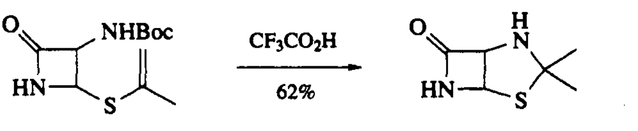

(131)

Examples of cyclization through alkene insertion of a metal–nucleophile intermediate (Scheme 3, intermediate F) using organolanthanide catalysts, (Cp′$_2$LaH)$_2$, have been reported recently (equation 132), although turnover numbers rather than synthetic yields were reported.[263]

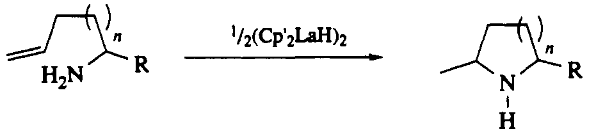
½(Cp'₂LaH)₂
H₂N
R
n
N
H

(132)

$n = 1, R = H$
$n = 1$, $R = Me$ (*trans*:*cis* = 5:1 at 25 °C or 8:1 at 0 °C)
$n = 2, R = H$

### 1.9.3.2.3 Cyclizations with alkynes and allenes

Cyclizations with nitrogen nucleophiles involving alkynes and allenes have received little attention until recently. The cyclizations of several α-aminoallenes to 3-pyrrolines with silver tetrafluoroborate was reported by Claesson and coworkers (equation 133).[264] A similar cyclization to form $\Delta^1$-carbapenems has been reported (equation 134).[265a] Diastereomeric allenes ($R^1 \neq R^2$) were shown to cyclize with complete stereocontrol. Cyclization with palladium chloride in the presence of allyl bromide or electrophilic alkenes allowed for the intermediate vinylpalladium species to be trapped by the electrophile.[265b] A related product was obtained by cyclization of an alkynic substrate (equation 135).[265a] Other examples of 5-*endo* cyclization of β-aminoalkynes[50] include the formation of indoles by cyclization of 2-alkynylanilines with mercury salts[200] or palladium chloride,[266a,266b,266c] formation of 1-pyrrolines with catalytic palladium chloride (equation 136)[198] and formation of pyrroles by cyclization of hydroxy-substituted β-aminoalkynes.[198,266d]

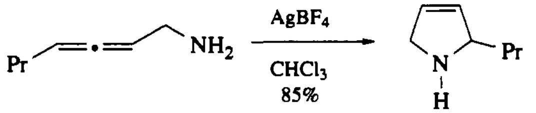
Pr
NH₂
AgBF₄
CHCl₃
85%
N
H
Pr

(133)

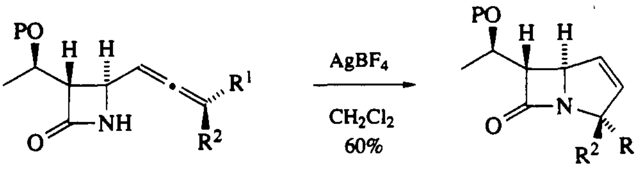
PO
H H
R¹
NH
O
R²
AgBF₄
CH₂Cl₂
60%
PO
H H
O
N
R² R¹

(134)

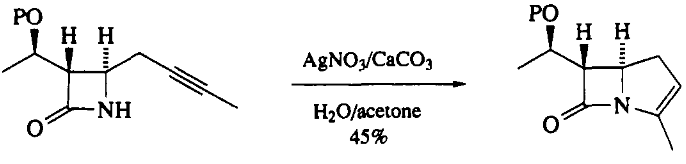
PO
H H
NH
O
AgNO₃/CaCO₃
H₂O/acetone
45%
PO
H H
O
N

(135)

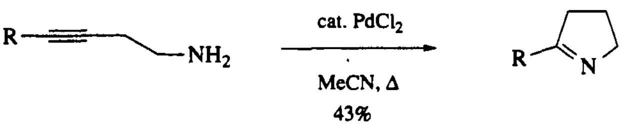
R
NH₂
cat. PdCl₂
MeCN, Δ
43%
R
N

(136)

Cyclization of β-allenylamine systems to six-membered ring products has been observed recently. Cyclization of terminally substituted β-allenylamides with silver tetrafluoroborate produced lactam products (equation 137).[267a] The cyclization shown in equation (138) was used to generate the indolizidine ring system of allopumiliotoxin alkaloids.[267b]

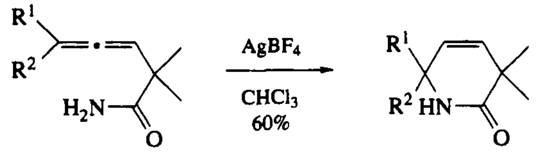
R¹
R²
H₂N
O
AgBF₄
CHCl₃
60%
R¹
R² HN
O

(137)

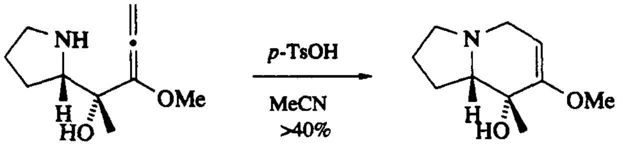

(138)

A number of cyclizations of γ-allenylamines have been reported. Cyclization studies of *N*-alkyl and *N*-aryl systems with mercury and silver salts to form 2-alkenylpyrrolidines[268a] were followed by studies of stereoselectivity in the formation of 2,5-disubstituted pyrrolidines (equation 139 and Table 34).[268b] Although cyclization of the primary amine was nonselective, only the *cis* product could be observed with *N*-substituted amines. This reaction has been used in a stereoselective synthesis of anatoxin-a.[268d] Interestingly, the aminopalladation/methoxycarbonylation reaction provides a modest excess of the *trans* isomer (Table 34, entry 3).[268c] Recently, it has been demonstrated that reasonable stereochemical control can be exerted by a chiral group attached to nitrogen if a coordinating group is present on the *N*-substituent (equation 140).[268e]

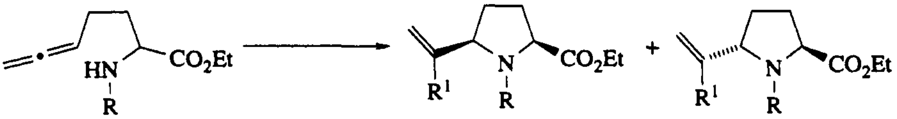

(139)

**Table 34** Cyclization of γ-Allenylamine Derivatives (Equation 139)

| *Entry* | *R* | *Conditions* | *Cis:trans ratio* | *R*¹ | *Ref.* |
|---|---|---|---|---|---|
| 1 | H | $AgBF_4$, $CH_2Cl_2$ | 1:1 | H | 268d |
| 2 | $CO_2Bn$ or $CH_2Ph$ or $SO_2PhMe$ | $AgBF_4$, $CH_2Cl_2$ | >50:1 | H | 268d |
| 3 | $CH_2Ph$ or $SO_2PhMe$ | $PdCl_2$, $CuCl_2$ MeOH, CO | 1:3 | $CO_2Me$ | 268c |

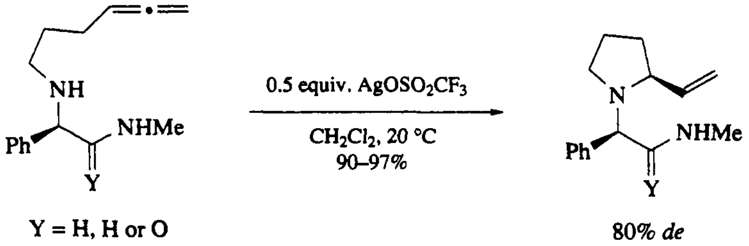

(140)

Cyclization of δ-allenylamines is successful also. Synthesis of 2-alkenylpiperidines can be effected with mercury(II) or silver salts, with silver salts giving higher yields (equation 141 and Table 35).[268a] The significant asymmetric induction found in the cyclization of a chiral allene (78% *ee*, entry 2) suggests that the low stereoselectivity observed in the synthesis of the 2,6-disubstituted system (entry 3)[269] may be a result of starting with a diastereomeric mixture. Aminopalladation/methoxycarbonylation has been effected in moderate yield also (entry 4).

Silver ion catalysis has also been used with allenic oximes to generate cyclic nitrones, which are trapped by 1,2-dipolarophiles (equation 142).[270] This reaction was used in a synthesis of pyrrolizidine alkaloids.[270b]

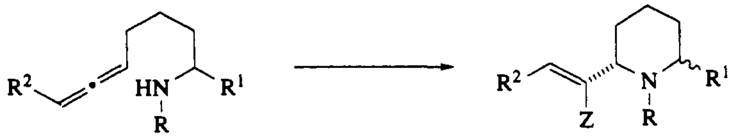

(141)

**Table 35** Cyclization of δ-Allenylamine Derivatives (Equation 141)

| *Entry* | $R^1$ | $R^2$ | *R* | *Z* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | H or alkyl | Pr or Bn | H | $AgNO_3$, $H_2O$/acetone | 76–95 | 268a |
| 2 | H | Me | Bn | H | $AgBF_4$, $CH_2Cl_2$, 20 °C | 86 (78% *ee*) | 269b |
| 3 | Me | Me | Bn | H | $AgNO_3$, $H_2O$/acetone | ~100 (62:38) | 269a |
| 4 | H | H or Me | Bn | $CO_2Me$ | $PdCl_2$, MeOH/CO | 42–52 | 268c |

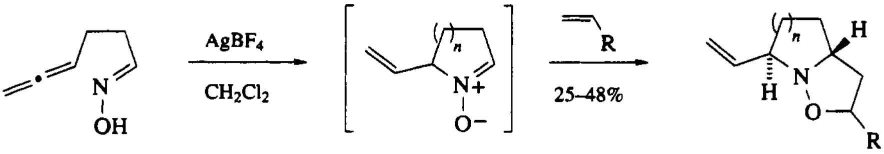

(142)

## 1.9.4 SULFUR NUCLEOPHILES

Reviews which cover heterocyclization of unsaturated sulfur compounds have been published recently.[1d,1f] Cyclizations of sulfur systems can also be effected by radical chain mechanisms or by reactions in which the sulfur acts as an electrophile. Examples of nucleophilic sulfur functional groups used in heterocyclization reactions are shown in Figure 3.

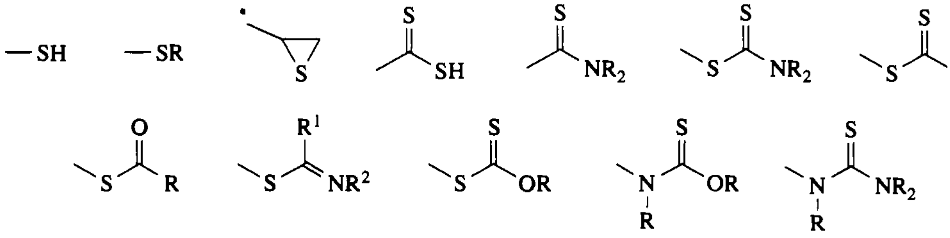

**Figure 3**

Sulfur heterocyclization reactions have been used to provide sulfur heterocycles of many types, but few examples have been used as general synthetic methods. One exception is found in the synthesis of thiaprostacyclins.[146] The key step in the synthesis of the thiaprostacyclins (**25**) was the cyclization of 9-thia-$PGF_{2\alpha}$ derivatives with phenylselenenyl chloride (Scheme 15).[271a] The cyclization reaction was shown to proceed with either the thiol (R = H) or thioacetate (R = COMe) as nucleophile and with high stereoselectivity (the (*Z*)-isomer gave only the *endo* product, while the (*E*)-isomer gave only the *exo* product).[271a,271b] The stereoselectivity is much higher than found in the corresponding selenoetherification reactions with oxygen as nucleophile.[272] Thiaprostacyclins have also been prepared by cyclization with halogens, but reactions of this type are considered to proceed through the sulfenyl halide with electrophilic addition of the sulfur to the alkene.[273] 9-Thiaprostacyclins have also been prepared by nucleophilic addition of a thiolate to an alkyne analog of (**24**).[274]

Cyclization of either of the thiols (**24**) with acid provided the saturated thia-$PGI_1$ analogs (**26**) as a 2.7:1 mixture of the *exo* and *endo* isomers.[271a] Although many addition reactions of thiols to alkenes are radical reactions catalyzed by light, oxygen, or other radical initiators, conversion to (**26**) was not effected under photolytic conditions or with AIBN. A radical chain mechanism for selenothiolactonization has also been reported recently.[275]

A recent paper[276] has shown that some halocyclizations involving sulfur functionalities other than thiols (*e.g.* thiazolidinones) may involve initial reaction at sulfur to generate a sulfenyl halide which cyclizes *via* attack of the electrophilic sulfur. This type of reaction would be an alternative to the nucleophilic heterocyclization mechanism previously proposed for a synthesis of a biotin intermediate from a vinylthiazolidine.[1p,277]

One recent study (Scheme 16) has shown that the iminothiolactones generated from iodocyclization of γ,δ-unsaturated thioamides can be converted to 2-acetamidothiophenes[278a,278b] in addition to thiolactones, as previously reported.[114b,278c] Iodocyclizations of allylic or homoallylic thioureas to generate dihydrothiazoles and dihydrothiazines (equation 143) have been reported recently.[259e]

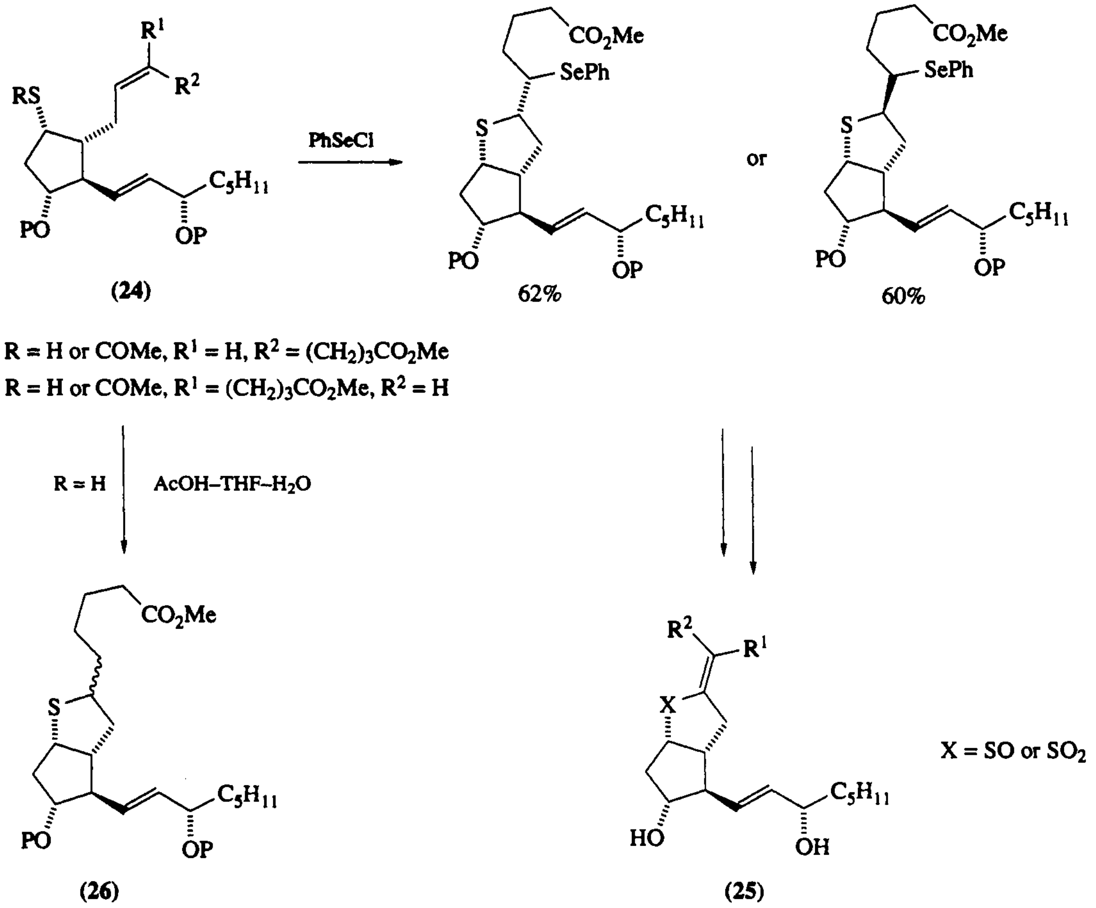
RS
R1
R2
PO
OP
C5H11
(24)
PhSeCl
CO2Me
SePh
S
62%
or
60%
R = H or COMe, R1 = H, R2 = (CH2)3CO2Me
R = H or COMe, R1 = (CH2)3CO2Me, R2 = H
R = H
AcOH–THF–H2O
(26)
X
HO
OH
(25)
X = SO or SO2

**Scheme 15**

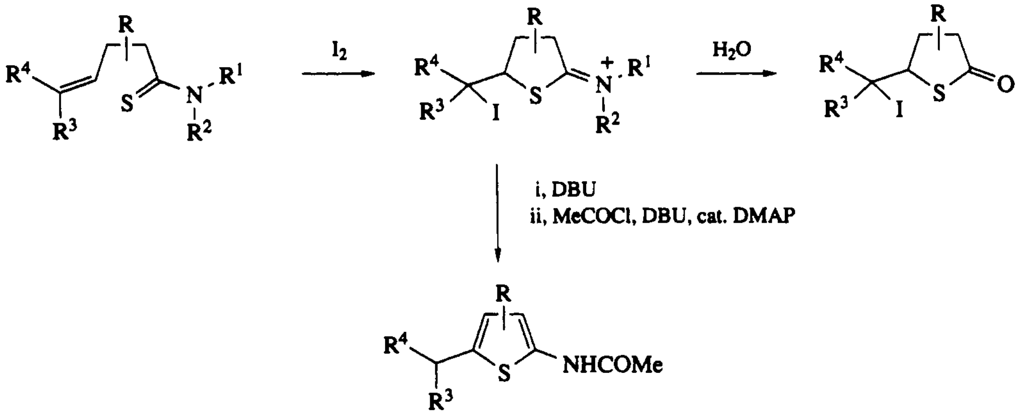
R
R4
R3
S
N
R1
R2
I2
I
+
H2O
O
i, DBU
ii, MeCOCl, DBU, cat. DMAP
NHCOMe

**Scheme 16**

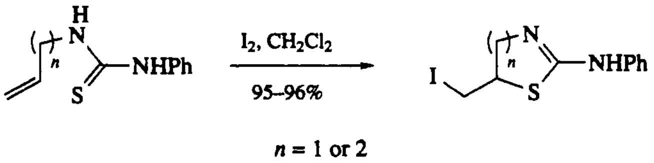
H
N
n
S
NHPh
I2, CH2Cl2
95–96%
I
n = 1 or 2

(143)

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# 2.1

# Arene Substitution *via* Nucleophilic Addition to Electron Deficient Arenes

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## 2.1.1 INTRODUCTION

This chapter reviews those reactions of nucleophiles with electrophilic aromatic systems which proceed *via* formation of a covalently bound intermediate ($\sigma$-adduct), and result in the substitution of either a nucleofugal ring substituent or of a ring hydrogen. A few different processes are classified in this category. In the $S_NAr$ reaction the nucleophile attacks, in what is often the rate-limiting step, the carbon carrying the nucleofugal substituent, Y, and the substitution product forms *via* expulsion of $Y^-$ from the $\sigma$-adduct.[1–4] When nucleophilic attack occurs at a ring carbon other than that bearing the leaving group, *cine* (*e.g.* the Von Richter reaction)[1] and/or *tele* substitution can take place.[5] The reaction of 2,3-dinitroaniline with piperidine, shown in equation (1), serves as a remarkable example since it gives the products of $S_NAr$ (**1**), of *cine* (**2**) and of *tele* substitution (**3**) in comparable yields.[5]

Significant advances have recently been made in the development of synthetically useful procedures to achieve formal nucleophilic displacement of hydrogen.[6,7] The hydride ion being such a poor leaving group, processes other than $H^-$ expulsion are effective in most cases. A common approach involves oxidation of the $\sigma$-adduct by inorganic (*e.g.* $H_2O_2$, halogens, $KMnO_4$, hypohalites) and organic (*e.g.* NBS, chloranil, DDQ, *p*-benzoquinone) reagents.[8] In the absence of an added oxidant 'spontaneous' oxidation[1] of the $\sigma$-adduct may occur *via* reduction of the substrate itself,[8–10] or *via* disproportionation of the $\sigma$-ad-

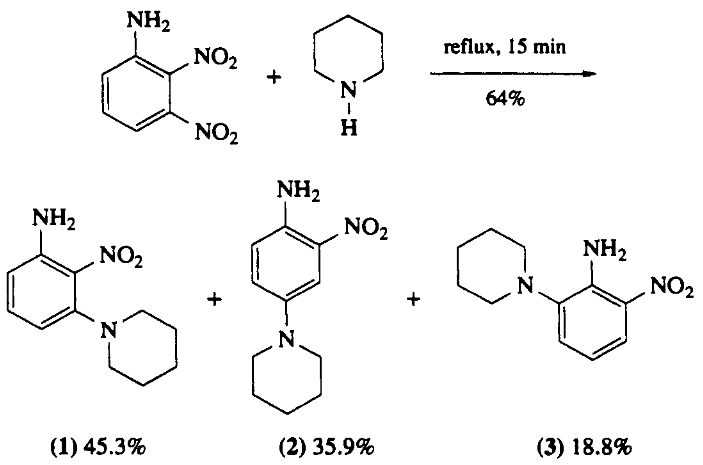

(1)

duct.[11,12] In these cases the substitution product is normally obtained in poor yield (Scheme 1).[12] Special cases of 'spontaneous' oxidation have been observed in which rearomatization of the $\sigma$-adduct is accomplished *via* $NO_2 \rightarrow NO$ reduction in what can be formally viewed as an intramolecular redox process.[13,14] The reaction of 1,2,4-triazines with nitronate anions produces oximes in good yields, according to the mechanism proposed in Scheme 2.[14]

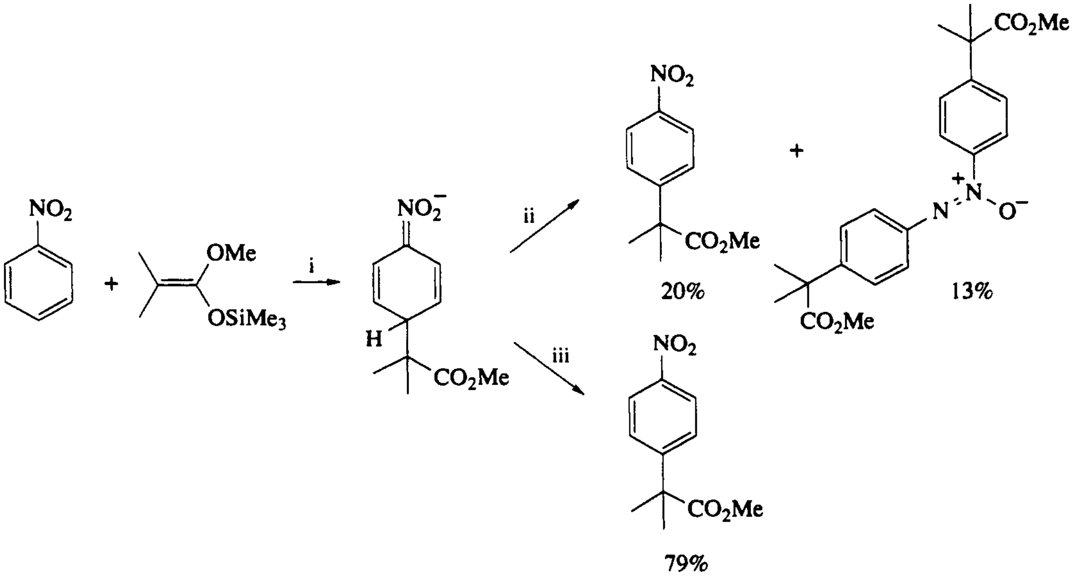

i, TASF, THF; ii, HCl; iii, $Br_2$ or DDQ

**Scheme 1**

When the attacking atom of the nucleophile carries a leaving group, replacement of hydrogen can take place *via* the VNS (vicarious nucleophilic substitution) reaction,[15] as shown in Scheme 3.[16] The key feature of this reaction is the rate-limiting base-induced $\beta$-elimination from the $\sigma$-adduct.

Other processes, limited to heteroaromatic systems, include the $S_N$(ANRORC) reaction (Scheme 4),[17,18] and ring transformation reactions.[18,19] Reactions which proceed *via* $\sigma$-adduct intermediates, but do not lead to substitution on the aromatic nuclei, such as the $S_N$(AEAE) reaction,[20] or give nonaromatic products, are not included. Also not covered are processes involving aryl–metal intermediates, such as most copper-catalyzed aromatic substitutions.

Activation of the aromatic ring towards nucleophilic attack is required for all these reactions to proceed at reasonable rates and is commonly provided by strongly electron-withdrawing substituents. Reactivity also strongly depends on the leaving group and on the nucleophile. Scales of activating power of

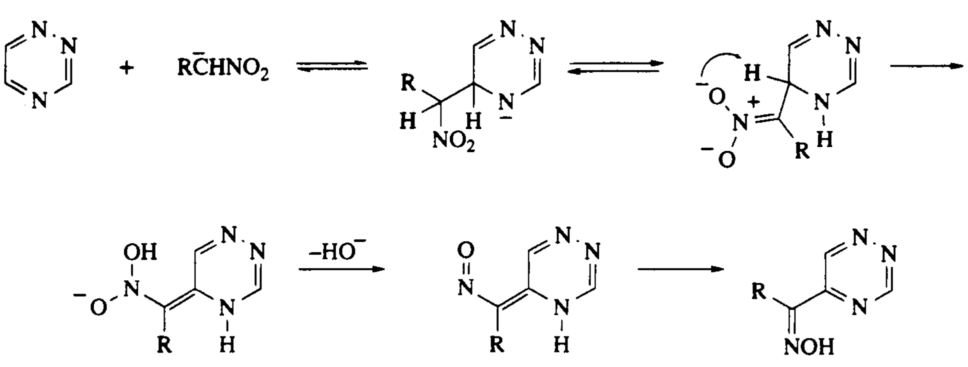

**Scheme 2**

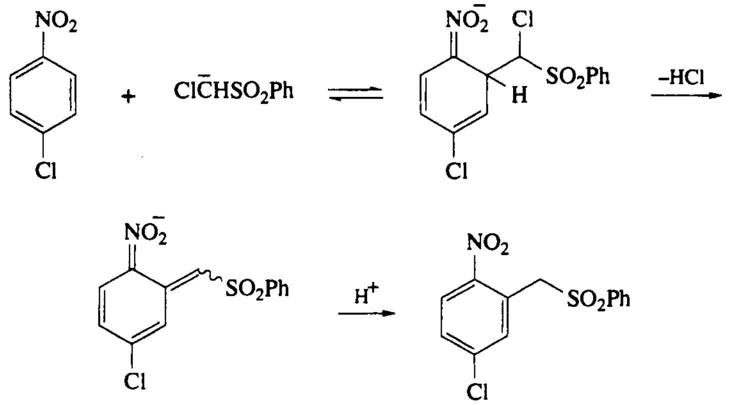

**Scheme 3**

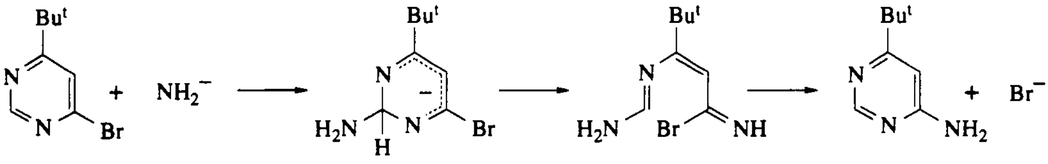

**Scheme 4**

substituents, of leaving group ability and of nucleophilicity, compiled in earlier reviews[1,2] on nucleophilic aromatic substitution, can serve as guidelines in predicting reactivity and selectivity. A partial listing is reported below for the reader's convenience. Ability as: (i) activating substituent, $N_2^+$ > $^+NR$ (heterocyclic) > NO > $NO_2$ > N (heterocyclic) > $SO_2R$ > $^+NR_3$ > $CF_3$ > CN > CHO, COR > $CO_2H$ > $SO_3^-$ > Br, Cl, I; (ii) leaving group, F > $NO_2$ > OTs > SOPh > Cl, Br, I > $N_3$ > $^+NR_3$ > OAr, OR, SR, $SO_2R$, $NH_2$; (iii) nucleophile, $RS^-$ > $R_3C^-$ > $RO^-$ > $RNH_2$ > $ArO^-$ > $HO^-$ > $ArNH_2$ > $NH_3$ > $I^-$ > $Br^-$ > $Cl^-$.

The use of oxazoline units to activate *ortho* positions has lately found many applications and has been reviewed.[21] Other activating groups recently employed include aryliodonium,[22] azopyridinium,[23] and, for nitrogen heterocycles, 2,6-dimethyl-4-oxopyridin-1-yl[24,25] and pyridinium[26] units. A rather extreme case of activation was reported in the reaction of polynitroarenes with HX (X = Cl, Br), which results in nucleophilic displacement of $NO_2^-$ by $X^-$, and which proceeds *via* the highly electrophilic nitro-protonated form of the substrate.[27] Activation of the substrate towards nucleophilic attack is also achieved by $\pi$-complexing with transition metal ligands, a subject covered in Chapter 2.4 of this volume. Among the leaving groups, $NO_2$ has recently been exploited with success in many applications.[28-30]

Reference is also made to computer programs potentially useful in the prediction of reactivity/selectivity.[31] It is now well established that nucleophilic reactivity[32] is the result of a complex interplay of substrate–nucleophile–solvent interactions, with solvation[32,33] and steric effects[34,35] playing major roles. The relative abilities of leaving groups, for example, have been found to vary depending on the nucleophile.

Thus, nitrite displays enhanced reactivity as leaving group when the nucleophile is thiophenoxide.[36,37] Since the nucleophilic reactivity of anions is greatly reduced in solvents of low polarity, due to ionic association, or in protic solvents, due to solvation or H-bonding, the use of polar aprotic solvents (mostly DMF, DMSO and HMPA) and of phase transfer catalysis has become common practice in synthetic applications. PTC has proved of great value, especially in large-scale applications where the alternative use of polar aprotic solvents would be prohibitively expensive and product recovery and purification more difficult. Despite the considerable body of fundamental studies on micellar catalysis[38,39] and related molecular host–guest systems[40,41] in nucleophilic aromatic substitution, synthetic applications are lacking. The reasons probably include limited substrate solubilization and temperature range, as well as the difficulty of separating the products from the surfactants.

For any of the nucleophilic aromatic reactions covered in this chapter, regioselectivity, when more than one activated position is available, depends in most cases on the selectivity of attack by the nucleophile. However, when the conversion of the $\sigma$-adduct to product is the rate-limiting step, as in the VNS reaction, the final product distribution may differ from that expected, based on the relative electrophilic reactivity of the possible reaction sites.[15] Important roles are played by deactivating steric effects and by stabilizing specific interactions such as those, for example, between an ion-paired nucleophile and a nitro activating group, which favor attack at the *ortho* position.

Diastereo- and enantio-selectivity in nucleophilic aromatic substitution is limited to atropisomerism in binaphthyl- and biaryl-forming reactions.[21,42]

Nucleophilic attack is faster at unsubstituted ring positions than at similarly activated but substituted ring positions.[8,15,43–45] Since the addition is in most cases reversible, the opportunity exists for competing reactions. Indeed an extremely varied spectrum of reactivities is found in these systems, depending on reactants and reaction conditions. Examples are known of competing $S_NAr$ and *cine* substitution,[46] $S_NAr$ and *tele* substitution,[47] $S_NAr$ and *cine* and *tele* substitution (equation 1),[5] $S_NAr$ and VNS,[16] and $S_NAr$ and $S_N$(ANRORC).[48]

Moreover, reactions at side chain centers, such as $S_N2$ displacement[49–51] and attack on an ester carbonyl,[50,52,53] may compete or prevail. Further complexity may result from the presence of ambident nucleophiles.[54,55]

A more intriguing type of competition is due to radical processes, which usually involve the substrate radical anion. These can fragment, if they carry a suitable substituent, *via* anion expulsion.[56] The resulting aryl radical, Ar·, can form the reduced product, ArH, by hydrogen abstraction[57] or the product of substitution *via* reaction with the nucleophile according to the $S_{RN}1$ mechanism, discussed in Chapter 2.2 of this volume. Examples of competition between $S_NAr$ and radical processes of this type have been reported.[57–59]

In the case of nitro-substituted arenes, the formation of radical anions usually leads, in protic solvents, to products of nitro reduction, mostly azoxyarenes.[60] The challenge of avoiding reduction is commonly encountered, since the nitro group is a favorite activating substituent, easily introduced and readily transformed into a variety of functionalities. Early attempts to perform nucleophilic aromatic substitution on nitroaryl halides with alkoxides[61] and thiolate[62] ions, failed because of this complication. The presence of molecular oxygen[63] or other radical traps, such as azobenzene,[57] di- or tri-nitrobenzene[64] or excess thiol,[65] is often sufficient to inhibit reduction.

Ion-pairing effects may be crucial in determining the competition between radical and nonradical reactions. Recent investigations have shown that ion pairing accelerates the reduction of nitroarenes in alcoholic media.[60] Therefore, the higher yields of substitution products often obtained in the absence of ion pairing are due, at least in some cases, not only to the promotion of substitution, but also to the depression of radical pathways.

The material is organized in sections grouped according to the central atom of the attacking nucleophile. The coverage is not exhaustive, but hopefully representative of recent developments and trends.

## 2.1.2 CARBON NUCLEOPHILES

During the last decade the use of carbon nucleophiles in aromatic substitution reactions has increased greatly. Important advances concern particularly the alkylation of unsubstituted ring positions by formal nucleophilic displacement of hydrogen, according to the addition/oxidation sequence in its many variants and to the VNS reaction. In the following sections some of the most significant applications are described, grouped according to the nucleophile rather than to the reaction type.

### 2.1.2.1 Organometallics

A convenient route to biaryls involves nucleophilic displacement of *o*-methoxy, *o*-fluoro, or *o*-bromo in 2-aryloxazolines[21] and oxazoles[66] by ArLi or ArMgBr. Chiral binaphthyls have been obtained as a result of asymmetric induction by a chiral *o*-alkoxy leaving group[42] or by a chiral oxazoline *ortho*-activating substituent.[67] The latter method has also been applied to the synthesis of chiral biphenyls with moderate success.[68] Among the chiral leaving groups employed, derived from the naturally occurring alcohols 1-menthol, quinine, quinidine, α-fenchol and borneol, (–)-menthoxy gave the highest chiral transfer efficiencies (defined as % chemical yields × % optical yield), which ranged from 41% to 65% (Scheme 5).[42] The use of a chiral oxazoline *ortho*-activating group, exemplified in Scheme 6, led to a mixture of diastereomeric products, which upon acidic hydrolysis and LAH reduction yielded (hydroxymethyl)binaphthyls of enantiomeric excess in the range 87.4–96%.[67]

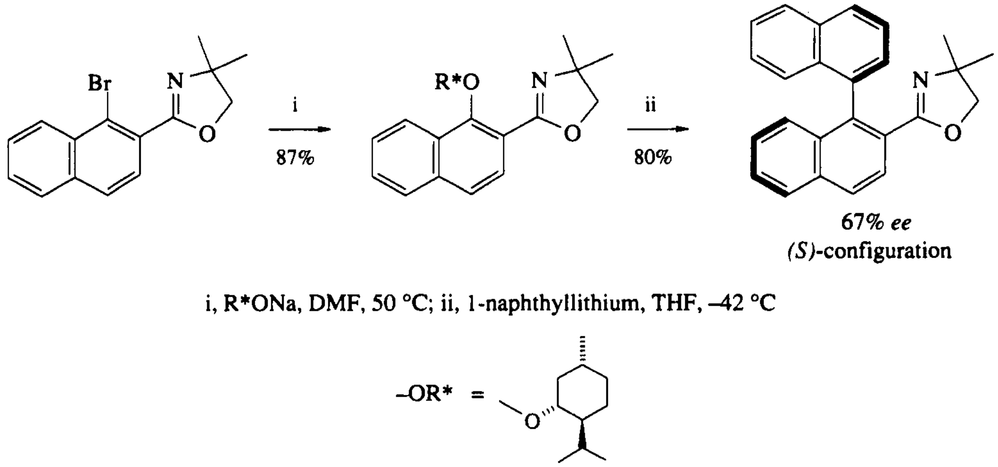

i, R*ONa, DMF, 50 °C; ii, 1-naphthyllithium, THF, –42 °C

**Scheme 5**

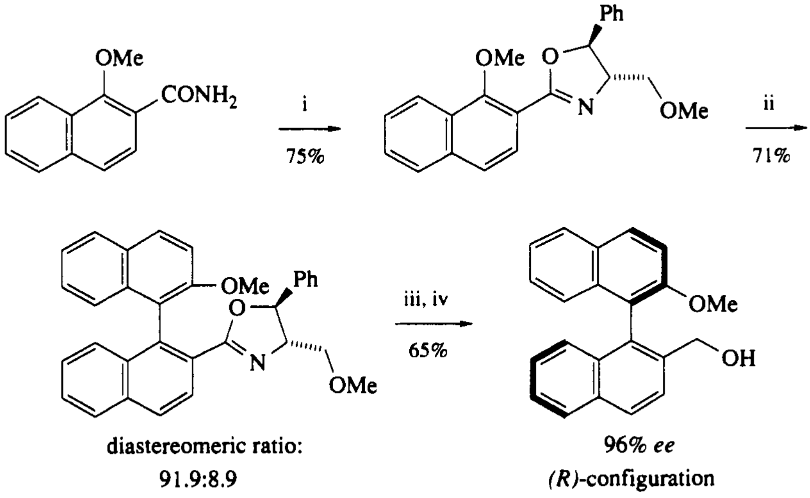

i, $Et_3O{\bullet}BF_4$, DCE, 30 h, r.t, then (+)-1-MeO-2-$NH_2$-3-phenyl-3-hydroxypropane, reflux, 48 h; ii, 2 equiv. 2-MeO-naphthylMgBr, THF; iii, HCl, EtOH, reflux; iv, $LiAlH_4$, THF, 25 °C, 6 h

**Scheme 6**

Nucleophilic displacement of $RSO_2^-$ (R = alkyl, aryl) by RMgX and ArMgX is a convenient route to alkylate the 2-position of pyridines.[69] The method is not applicable to the 4-isomers which give sluggish reactions and radical-derived products.[69]

Grignard and lithium reagents have also been reported to effect nucleophilic displacement of hydrogen. Treatment of 3-pyridyloxazoline with a variety of lithium and Grignard reagents gave the products of addition to the 4-position of the pyridine ring in good yields.[70,71] The dihydropyridines so obtained are readily oxidized to pyridines, as in the example of Scheme 7.[70] In contrast, treatment of the isomeric 4-pyridyloxazoline with lithium reagents gave *ortho* metallation.[21] The addition/oxidation sequence has been used to prepare optically active (*S*)-4-naphthylquinoline derivatives from a chiral 3-quinolinyloxazoline precursor.[72] The addition of Grignard reagents to 1-carboxy-[73,74] and 1-alkoxycarboxy-pyridinium salts,[75] the latter unstable species being generated *in situ* (*e.g.* **4**; Scheme 8), provides an alternative convenient route to alkylated pyridines. With 1-carboxypyridines, a catalytic amount of copper(I) iodide was required to attain regioselectivity and form the product of 1,4-addition almost exclusively.[73,74] 1-(2,6-Dimethyl-4-oxopyridin-1-yl) pyridinium cation reacted with aryl and heteroaryl Grignard reagents to give regiospecifically the corresponding 4-arylpyridines.[24]

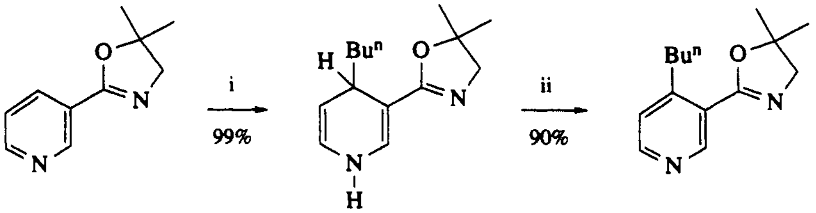

i, $Bu^nLi$, THF, –78 °C, 1 h; ii, chloranil, toluene, 2 h

**Scheme 7**

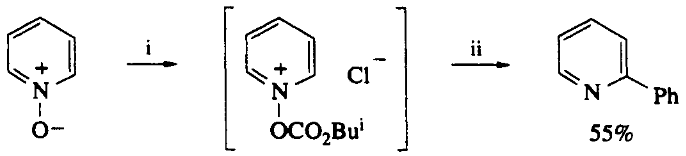

(4)

i, $ClCO_2Bu^i$, THF, 20 °C; ii, PhMgCl, –78 °C, 30 min

**Scheme 8**

Aromatic nitro compounds can be alkylated in *ortho* or *para* positions by treatment with alkyllithium or alkyl Grignard reagents followed by oxidation.[76] Thus, for example, the reaction of 2-methyl-1-nitronaphthalene with BuLi gave 3-butyl-2-methyl-1-nitronaphthalene in 70–75% yield when the adduct was oxidized with $Br_2$ or DDQ in ether.[76] Interesting redox processes have been identified in the reaction of nitroarenes with 2-lithium-1,3-dithiane.[11] A unified mechanism has been proposed for these reactions, comprising an initial single electron transfer step to form a radical anion–radical pair, followed by geminate radical combination to form the $\sigma$-adduct, or by diffusion from the solvent cage to give the radical anion and products derived therefrom.[11,77,78]

Alkyl (but not aryl) Grignard reagents add irreversibly[79] to activated unsubstituted positions of nitroarenes, including polycyclic and heterocondensed systems.[78] Reactive positions are pointed by the arrows in (**5**)–(**7**) (X = S, NR), and (**8**) and (**9**) (A = thiazole, oxazole, thiophene, pyrrole, pyridine, benzene).[78] The resulting nitronate intermediates can be: oxidized to alkylated nitroarenes with DDQ in THF, LTA in $CH_2Cl_2$, or $KMnO_4$ in alkaline acetone–water;[76,78] converted to alkylnitrosoarenes with HCl (37%) $BF_3{\cdot}Et_2O$,[78] or reduced to alkylanilines with $LiAlH_4$ or $NaBH_4$, Pd/C in THF.[79] At low temperatures high chemoselectivity was observed: keto, cyano and ester functions were not attacked by the

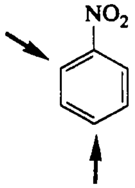

(**5**)

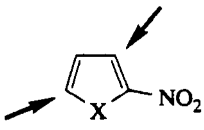

(**6**)

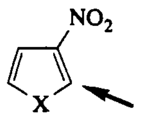

(**7**)

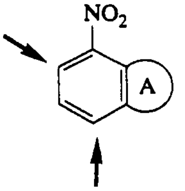

(**8**)

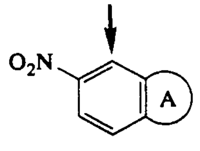

(**9**)

Grignard reagent.[80] Competition by nucleophilic aromatic substitution was not observed unless the only active position(s) was (were) substituted with a leaving group, as in the reaction of 1-methoxy-2-nitronaphthalene which gave 1-alkyl-2-nitronaphthalenes in 73–95% yields.[81] The use of $Me_3SiCH_2MgCl$ (Peterson reagent) provides an entry to nitro-substituted benzyl anion intermediates, as shown in the example of Scheme 9.[82]

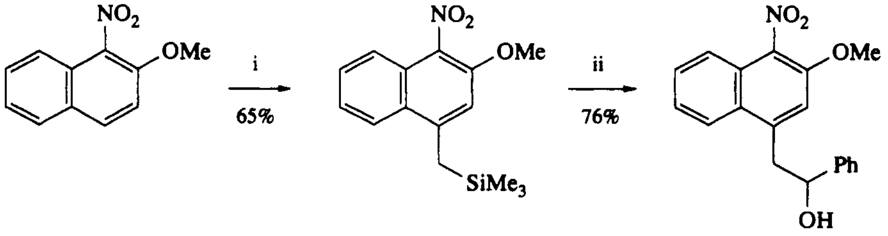

i, $Me_3SiCH_2MgCl$, THF, –30 °C, 1 h, then DDQ, –30 to 0 °C, 1 h;
ii, PhCHO, TBAF, THF, r.t., 30 min

**Scheme 9**

### 2.1.2.2 Active Hydrogen Compounds

Activated nitro and halo substituents have been efficiently replaced by a variety of alkyl groups *via* $S_NAr$ reaction with carbanions. Examples include the displacement of the nitro group in compounds (**10**; X = 4-PhCO, 4-MeOCO, 4-CN, 4-$NO_2$, 4-$PhSO_2$, 3,5-$(CF_3)_2$) by the anion of 2-nitropropane in HMPA at room temperature (equation 2),[83] and the reaction of *p*-dinitrobenzene with several ketones, esters and nitriles (RH; equation 3) in Bu$^t$OK/liquid $NH_3$ at –70 °C.[84] Interestingly, under the latter reaction conditions, *p*-chloronitrobenzene gave the product of alkylation rather than of $S_NAr$ displacement of chloride, as in equation (4).[85] Further examples include the dehalogenation of *p*-halonitrobenzenes by 9-fluorenyl anions in DMSO at room temperature,[34] and dehalogenation and denitration reactions by the carbanions of phenyl- and diphenyl-acetonitrile in DMSO or under PTC conditions.[86]

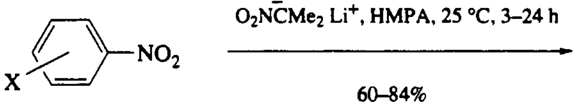

(**10**)

(2)

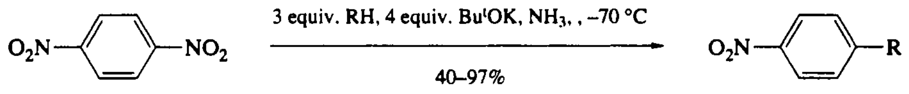

(3)

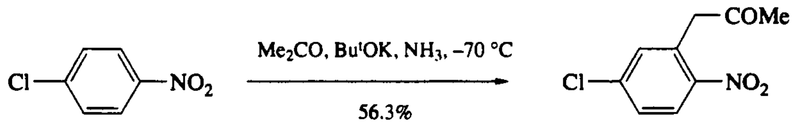

(4)

Unsymmetrical biphenyls have been prepared in good yields by the $S_NAr$ reaction of nitroarenes, bearing a leaving group *ortho* or *para* to the nitro group, with the anion of 2,6-di-*t*-butylphenol, which behaves as a carbon nucleophile.[9] Reaction conditions and scope are summarized in equation (5; X = 2-F, 2-Cl, 2-Br, 2-I, 2-$NO_2$, 2-$SO_2Ph$, 4-$NO_2$, 4-$SO_2Ph$). Arylation took place at activated unsubstituted ring positions in substrates lacking a suitably located leaving group, such as *m*-dinitrobenzene, according to an addition/oxidation sequence.[9] Bis- and tris-(dialkylamino)benzenes also behave as carbon nucleophiles in displacing chloride from activated arenes. In this case, however, greater activation of the electrophile was required, such as that provided by at least two nitro groups.[87]

The reaction of nitroarenes with silyl enol ethers and ketene silyl acetals in MeCN/THF with 1 equiv. of TASF, followed by *in situ* oxidation with $Br_2$ or DDQ, provides an easy route to α-nitroaryl carbonyl compounds (Scheme 1).[12] The use of these compounds as reagents for the synthesis of arylacetic acids, propionic acids, indoles, 2-indolinones and other heterocyclic compounds has recently been described.[88]

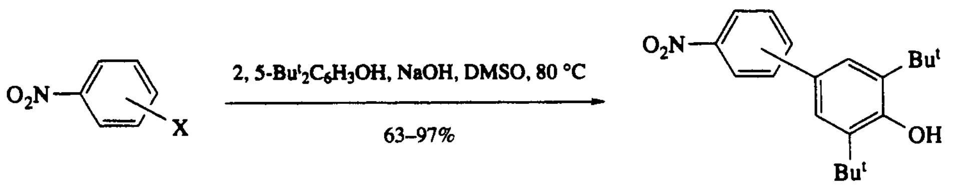

(5)

The alkylation reaction is limited to nitro-substituted arenes and heteroarenes and is highly chemoselective; nucleophilic displacement of activated halogens, including fluorine, was not observed. The regioselectivity is determined by the bulkiness of the silicon reagent. With unhindered silyl derivatives a strong preference for *ortho* addition was observed, as in the example of equation (6). With bulkier reagents attack took place exclusively at the *para* position (Scheme 1). The success of this reaction, which could not be reproduced with alkali enolates, was attributed at least in part to the essentially nonbasic reaction conditions under which side processes due to base-induced reactions of nitroarenes can be effectively eliminated.[12]

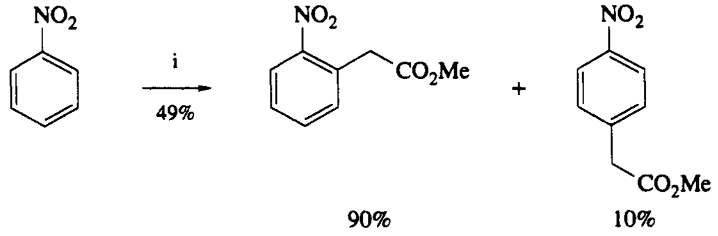

(6)

i, $CH_2{=}C(OMe)OSiMe_3$, TASF, THF, –78 °C, 18–21 h; $Br_2$

Base-catalyzed rearrangement of *N*-(aryloxy)pyridinium salts (**11**) leads to 2-arylpyridines (**12**) *via* intramolecular attack on the *ortho* position of the aryloxy ring by the 2-pyridyl carbanion. When X was 3-$CO_2Me$, pyrido[3,2-*d*]coumarins (**13**; R = $NO_2$, CN) were directly obtained in useful yields from this reaction. When in (**11**) X was 3-COMe and R was 4-$NO_2$, 10-hydroxy-10-methyl-6-nitropyrido[2,3-*d*]benzopyran (**14**) was obtained in 10.8% yield.[89]

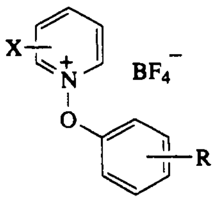

**(11)**

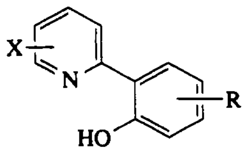

**(12)**

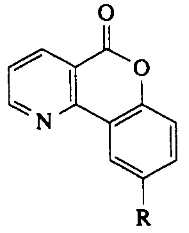

**(13)**

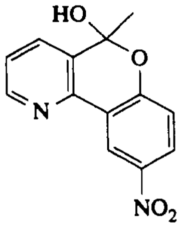

**(14)**

The *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts (**15**)[24] have proved to be versatile intermediates for the regiospecific synthesis of 4-substituted pyridines (**17**) *via* attack by the appropriate carbon nucleophiles, *e.g.* ionized ketones,[90] nitroalkanes,[91] esters and nitriles,[92] and α-diketones, α-keto esters, α-diesters, disulfones *etc.* (Scheme 10).[93] Aromatization of the intermediate 1,4-dihydro adduct (**16**) was generally achieved under free radical conditions.

Selective *ortho* alkylation of anilines and phenols can be carried out *via* the sequence of Scheme 11, which involves as the key step a Sommelet–Hauser-type [2,3] sigmatropic rearrangement of ylides (**19**).[94,95] The success of these reactions depends on the effective generation of the intermediate aza- and phenoxy-sulfonium salts (**18**). Conversion rates ranged from 37% to 82% for anilines (yields, based on unrecovered starting material, were 41–90%)[94] and were somewhat lower for the reactions of phenols.[95] High conversion rates have recently been reported for phenol alkylations using alkyl isopropyl sulfide, $SO_2Cl_2$ and triethylamine.[96] Useful elaborations of the alkyl side chain in the product have been reported, including desulfurization *via* Raney nickel reduction,[94,95] cyclization to heterocyclic compounds (*e.g.* indoles when sulfides with β-carbonyl groups are used,[97] chromans, chromenes and coumarins[96]) and hydrolysis of —CHR′SR″ to —CHO when R′ is an alkylthio group.[95,98]

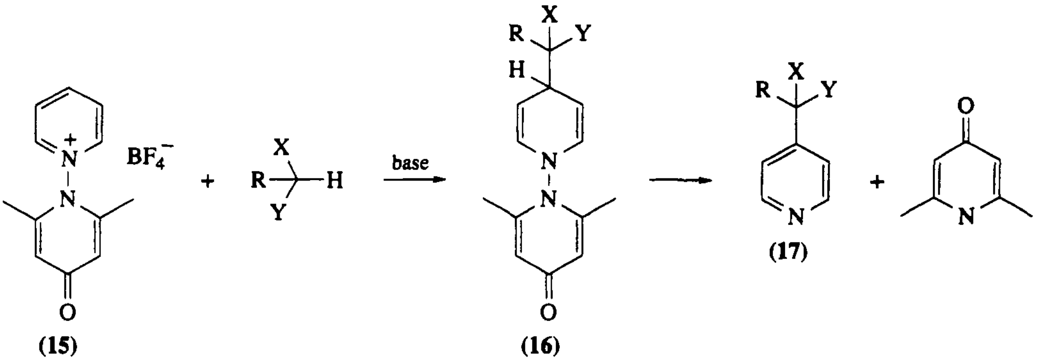

**Scheme 10**

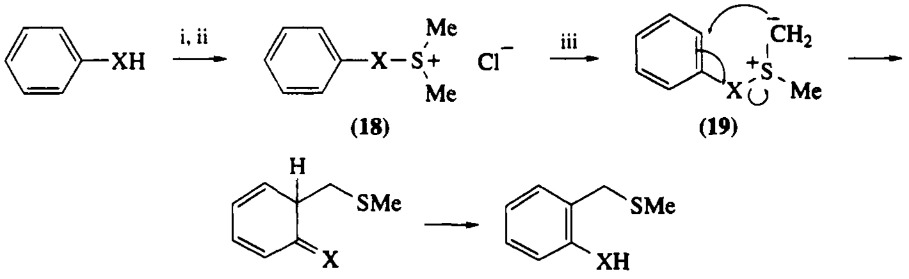

X = NH: i, $\mathrm{Bu^tOCl}$, $CH_2Cl_2$, –65 °C; ii, 3 equiv. MeSMe; iii, MeONa, MeOH

X = O: i–ii, 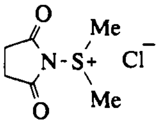 $Cl^-$ (prepared *in situ* from NCS and $Me_2S$), $CH_2Cl_2$, –25 °C,

or $Me_2\overset{+}{S}Cl\ Cl^-$ (prepared *in situ* from $Me_2S$ and $Cl_2$), $CH_2Cl_2$, –60 °C; iii, $Et_3N$

**Scheme 11**

A related process involves fluoride-induced desilylation in HMPA at room temperature of benzyldimethyl(trimethylsilylmethyl)ammonium halides (**20**) to (**21**; 62–84% yields; R = H, 2-Me, 4-Me, 2-Cl, 4-Cl, 4-OAc; X = Cl, Br).[99,100] Compunds (**20**) were prepared by reaction of the corresponding benzyl halide derivatives with (dimethylaminomethyl)trimethylsilane, $Me_3SiCH_2NMe_2$. The product of Stevens rearrangement (**22**) formed competitively and predominantly from precursors (**20**) having strong electron-withdrawing substituents (R = 2-COMe, 2-CN, 4-CN, $2\text{-}NO_2$, and $4\text{-}NO_2$).[100]

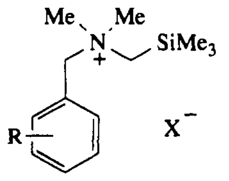

**(20)**

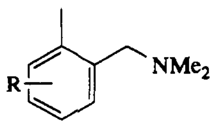

**(21)**

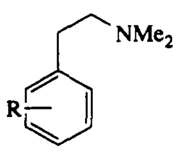

**(22)**

Several α-functionalized alkyl substituents can be introduced, often with good regioselectivity, into unsubstituted positions of nitro-substituted arenes by means of the VNS reaction (Scheme 3).[15,101] Useful nucleophiles are of the type RCHXY, where X is a leaving group (Cl, PhS, $Me_2NCS_2$, PhO, MeO), Y is an electron-withdrawing substituent ($SO_2Ph$, $\mathrm{SO_2Bu^t}$, $SO_2OPh$, $\mathrm{SO_2CH_2Bu^t}$, SOPh, $POPh_2$, $P(OEt)_2$, CN, $CO_2R'$, PhS, Cl), and R is H, alkyl, aryl, PhS, or Cl.[15] The corresponding carbanions are relatively inert towards oxidation and self-condensation.[15] The nucleophile of greatest applicability appears to be the anion of chloromethyl phenyl sulfone. Most substituents on the aromatic ring do not interfere with the VNS reaction. Nitrophenols, present as nitrophenoxides under the reaction conditions, do not react, but nitrobenzoates, in which the negative charge does not conjugate with the ring, do.[102] Activation by a nitro substituent is a requisite to enter the VNS reaction also for electrophilic arenes, such as pyridine. The only reported exceptions are 1,2,4-triazines[103] and benzothiazoles.[104] The following nitro-substituted heteroarenes were found to undergo the VNS reaction: nitropyridines and 4-nitropyridine *N*-oxide (but not the 2- and 3-$NO_2$ isomers);[105] nitrothiophenes and nitro-*N*-alkylpyrroles (but not nitrofurans);[106] and 5-, 6- and 8-nitroquinolines.[107] Studies on nitrobenzene derivatives showed that in the absence of steric effects attack at *ortho* is favored. However, steric and ion-pairing effects are of major consequence in determining the reaction selectivity. In DMSO, DMF or $NH_3$, solvents in which the carbanions are not strongly associated with the cation, steric effects dominate and the product of *para* alkylation was obtained exclusively with tertiary carbanions and preferentially even with relatively unhindered secondary carbanions like the anion of bromo- and iodo-methyl phenyl sulfone.[16] With $Bu^tOK$ in THF[108] and in DMF[109] at low temperatures, however, *ortho* alkylation appears to be favored, as a result of specific stabilizing interactions of the ion-paired $K^+Nu^-$ with the nitro group, which favors approach and attack at the *ortho* position.

The VNS reaction generally proceeds only to the stage of monoalkylation since the products are anions (Scheme 3), inert towards attack by the nucleophile. In the presence of two or three nitro groups, however, products of di- and tri-substitution were obtained.[110] The products of VNS were obtained selectively also in the presence of activated leaving groups, as shown in the example of equation (7).[111] In other instances, like in the reaction with chloromethyl phenyl sulfone in DMSO/KOH, competing $S_NAr$ displacement of $F^-$ and $NO_2^-$ was found in 4-F-, 2-$NO_2$- and 4-$NO_2$-substituted nitrobenzene.[16] In these cases, however, low combined yields of $S_NAr$ and VNS products were obtained. In the reaction of chloromethyl phenyl sulfone with nitro-substituted benzophenones VNS ring alkylation is accompanied by Darzens' condensation (equation 8).[112] It has been pointed out that in these cases the VNS reaction can be promoted by increasing the concentration of the base, which has an effect on the rate-determining β-elimination step of the VNS reaction, but no effect on either the Darzens' or the $S_NAr$ reactions.[15] The products of bisannulation rather than of VNS substitution were obtained from the reaction of chloromethyl phenyl sulfone with quinoxaline, several naphthyridines, and 1-cyano- and 1-(methylsulfonyl)-naphthalene.[15]

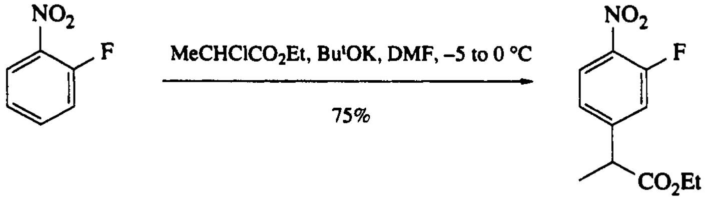

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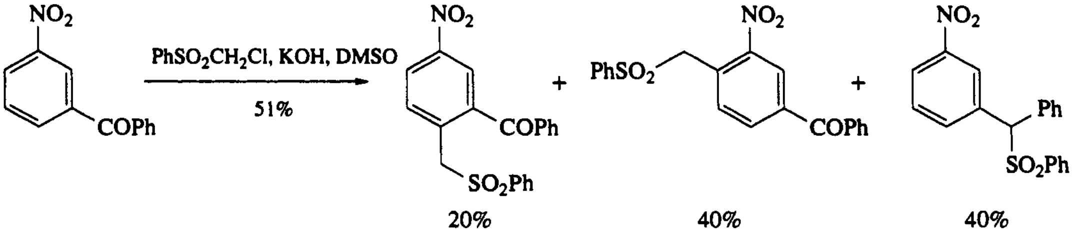

(8)

Some useful elaboration of the initially introduced nucleophiles has also been reported.[113] Thus, formylation of nitro aromatic rings was achieved *via* VNS reaction of the nitroarene with the anions of trisphenylthiomethane[114] and chloroform,[115] followed by hydrolysis, as in the example of Scheme 12.

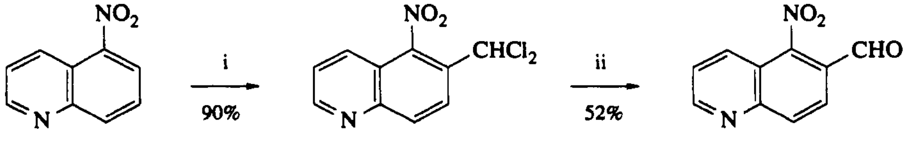

i, $CHCl_3$, $Bu^tOK$, THF/DMF; ii, $HCO_2H$, $H_2O$

**Scheme 12**

Some synthetic applications involving an intramolecular VNS reaction have been developed.[116-118]

### 2.1.2.3 Cyanides

1-Cyanoisoquinolines and 2-cyanoquinolines were recently prepared *via* the reaction of isoquinolines and quinolines with *p*-TsCl/KCN.[119] The reaction proceeds in two steps, as shown in the example of Scheme 13, and involves Reissert intermediates, which upon treatment with base give the cyano aromatic products in good overall yields.[119]

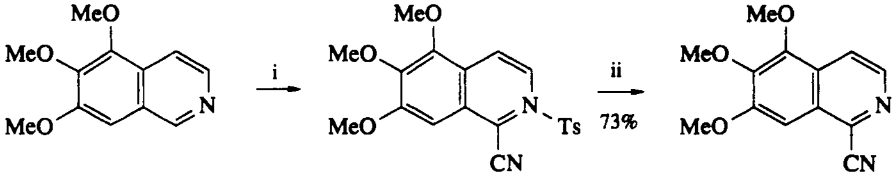

i, 1.5 equiv. *p*-TsCl, 6 equiv. KCN, THF, 25 °C, 12 h; ii, 1.2 equiv. DBU, THF, 25 °C, 1 h

Scheme 13

Regioselective cyanation in the α-position of pyridines and quinolines was achieved by treatment of the corresponding *N*-oxides with trimethylsilyl cyanide in the presence of triethylamine.[120] The silyl reagent could also be generated *in situ* by the reaction of chlorotrimethylsilane with KCN, as in the example reported in equation (9). In the presence of catalytic amounts of $Bu^n{}_4NF$ the reactions could be carried out at 5 °C in THF. The method has been extended to pyrimidine *N*-oxides, which underwent cyanation at the 2- and 6-position, attack at C-2 being generally favored.[121] Thus, 4-methoxypyrimidine 1-oxide gave the 2-carbonitrile as the sole product in 86% yield.[121]

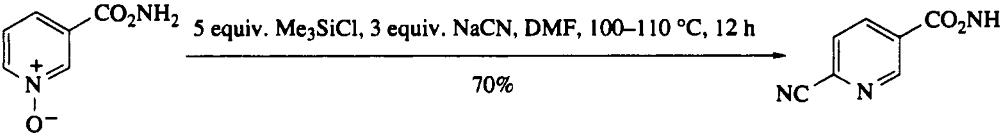

(9)

### 2.1.3 NITROGEN NUCLEOPHILES

Mechanistic features of $S_NAr$ displacement reactions involving amino nucleophiles have been the object of many investigations, a major point of interest being the occurrence of base-catalyzed paths. Strongly activated aryl halides react readily with ammonia and with primary and secondary amines to give the corresponding arylamines. Thus, for example, 2,4-dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain.

Some of these reactions are characterized by high negative activation volumes.[122] Recently, high pressure conditions have been employed to activate some $S_NAr$ reactions involving primary and secondary amines and activated aryl halides[123] and halopyridines.[124] The reaction of 4-chloronitrobenzene with $Bu^nNH_2$ in THF, for example, gave 4-*N*-butylnitroaniline in 76% yield after 20 h at 7.2 kbar and 50 °C (equation 10).[123] By contrast, at 1 atm and 80 °C no reaction took place during the same time.[123] The promotion of reactivity was much less pronounced with secondary amines, with the exception of cyclic ones, and absent with tertiary and aromatic amines.[123]

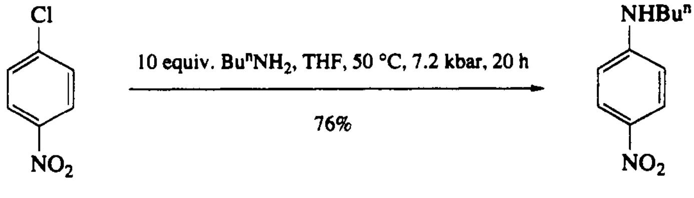

(10)

Ammonolysis of aryl halides has been performed under PTC conditions.[125] The reaction of 2,4-dinitrochlorobenzene with $NH_3$ (g) in toluene at ambient temperature and pressure gave, in the presence of 10% TBAB and after 3 h, 2,4-dinitroaniline in 16% yield (0.6% in the absence of TBAB). The reaction was complete after 24 h but the product final yield was not reported.[125]

The use of formamide as solvent in the ammonolysis of activated aryl chlorides has been recommended when the substrate carries cyano ring substituents which can undergo hydrolysis in water.[126]

Anilines (**23**; R = 2-Pr, $PhCH_2$; X = Cl, Br, I) have been obtained in high yields (40–95%) from the reaction of the primary amines 2-propylamine and benzylamine with the ethers (**24**; R′ = Me, $CH_2{=}CHCH_2$, $CH_2$-oxirane) in EtOH at room temperature.[127] With secondary amines dealkylation of the aromatic ether to the corresponding phenol took place rather than $S_NAr$ dealkoxylation.

Diarylamines are readily obtained from the reaction of activated fluoroarenes with arylamines containing electron-releasing groups.[128] Anilines carrying electron-withdrawing substituents require deprotonation to enter $S_NAr$ or nucleophilic hydrogen displacement reactions. Diarylamines (**25**; R′, R″ = *o*- or *p*-$NO_2$, CN, PhCO, $PhSO_2$) have been obtained in fair to good yields *via* defluorination or denitration of activated fluorobenzenes[129] and nitrobenzenes[130] respectively, using an excess of the aniline reagent and $Bu^tOK$ in DMSO at 20–25 °C or $K_2CO_3$ in DMSO or DMF at 120–130 °C. Under the latter conditions ($K_2CO_3$ in DMF at 120–130 °C) the reaction of 4-cyanoaniline with 4-fluoronitrobenzene gave the triarylamine (**26**) in 64% yield whereas, with *p*-dinitrobenzene (**26**) only formed as a minor product (3% yield), the major product (50% yield) being the diamine (**25**; R′ = 4-CN; R″ = 4-$NO_2$). The difference in reactivity was attributed to the greater bulk of the nitro substituent with respect to fluorine.[129]

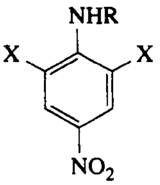

**(23)**

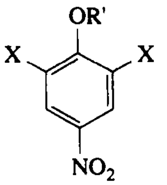

**(24)**

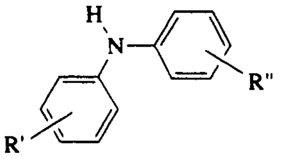

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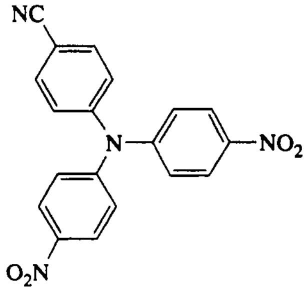

**(26)**

Treatment of the salicylic acid derivatives, dinitrolactone (**27**) and dinitro ester (**28**), with aqueous amines ($NH_3$, $MeNH_2$, $Me_2NH$) afforded salicylamides (**29**; R, R′ = H, Me) in quantitative yields.[131]

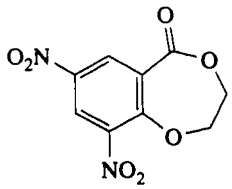

**(27)**

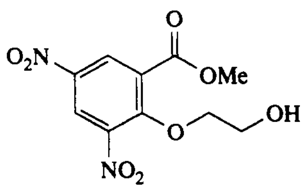

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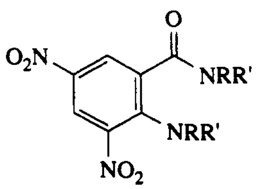

**(29)**

Nitroanions derived from phenothiazenes readily displace the halide in 4-halonitrobenzenes in DMSO at room temperature (equation 11).[34] On the other hand nucleophilic displacement of hydrogen as well as $S_NAr$ displacement of a leaving group were observed in the reaction of nitrobenzene derivatives with *p*-nitroaniline and $Bu^tOK$ in HMPA.[132] The oxidation with potassium permanganate of adducts formed from nitrogen heterocycles, such as pyridazines and 4-nitropyridazine 1-oxide, with liquid ammonia or with $KNH_2$ has been widely applied to the synthesis of aminoaza aromatics.[133]

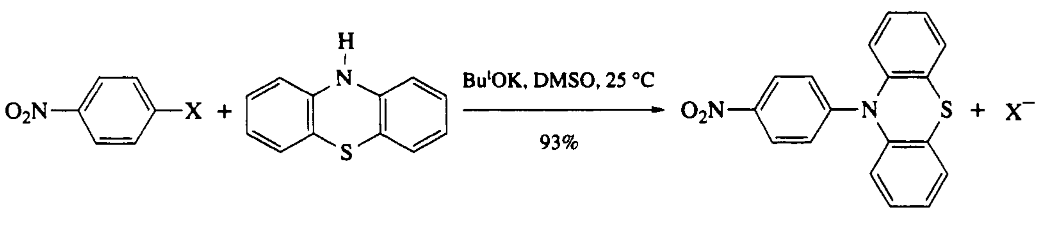

(11)

Amine–amine exchange reactions have recently been performed with high yields and under mild conditions (DMSO at 30 °C[134] or MeCN at room temperature[135]) on activated naphthylamines with primary amines or pyrrolidine. Equation (12), where R′, R″ = H, H; Me, H; Et, H; Pr$^i$, H; Bu$^t$, H; PhCH$_2$, H; 4-MeOC$_6$H$_4$, H; —(CH$_2$)$_4$—, summarizes the reactions of *N*,*N*-dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine.[135]

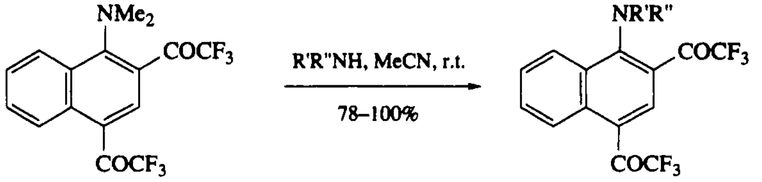

(12)

Several useful syntheses of polycondensed systems have been reported, based on an intramolecular displacement involving an amino nucleophile. Phenazine-1-carboxylic acids (**30**) have been prepared *via* reaction of *N*-phenyl-3-nitroanthranilic acids (**31a**; X = H; R = 6′-MeO, 3′-MeO) with NaBH$_4$ under alkaline conditions, a process involving reduction of NO$_2$ to NH$_2$, followed by intramolecular nucleophilic attack and aromatization.[136] An improved procedure utilizes *N*-(2-fluorophenyl)-3-nitroanthranilic acids (**31b**; X = F; R = H, 3′-F, 5′-F, 6′-F, 5′-Cl, 6′-Cl, 5′-Me) with the advantage that no ambiguity as to the carbon attacked exists in this case since ring closure occurs *via* $S_{\rm N}$Ar displacement of fluoride.[137] Reactions were conducted in H$_2$O, MeOH or EtOH and gave (**30**) in 47–92% yield.

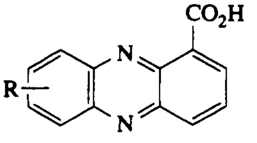

**(30)**

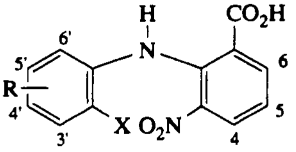

**(31a–b)**

A large number of 5-deazaflavins (**32**; R$^1$, R$^2$ = H, alkyl, aryl; R$^3$, R$^4$ = H, Cl, NO$_2$, OH; 48 examples in all), have been prepared in good yields *via* condensation of 6-substituted aminouracils with *o*-halobenzaldehydes in DMF under reflux. The mechanism shown in Scheme 14 was proposed for this reaction.[138] Several bis(5-deazaflavin-10-yl)alkanes (**33**; *n* = 6, 8, 10, 12) have also been prepared *via* the same route using bis(uracil-6-ylamino)alkanes.[138] By an analogous reaction the substituted quinolines (**34a**) and (**34b**) were obtained in 87% and 50% yield, respectively, from enaminones (**35a**; X = Y = NMe; Z = O) and (**35b**; X = Y = CH$_2$; Z = Me$_2$) and pentafluorobenzaldehyde in glacial acetic acid at reflux.[139]

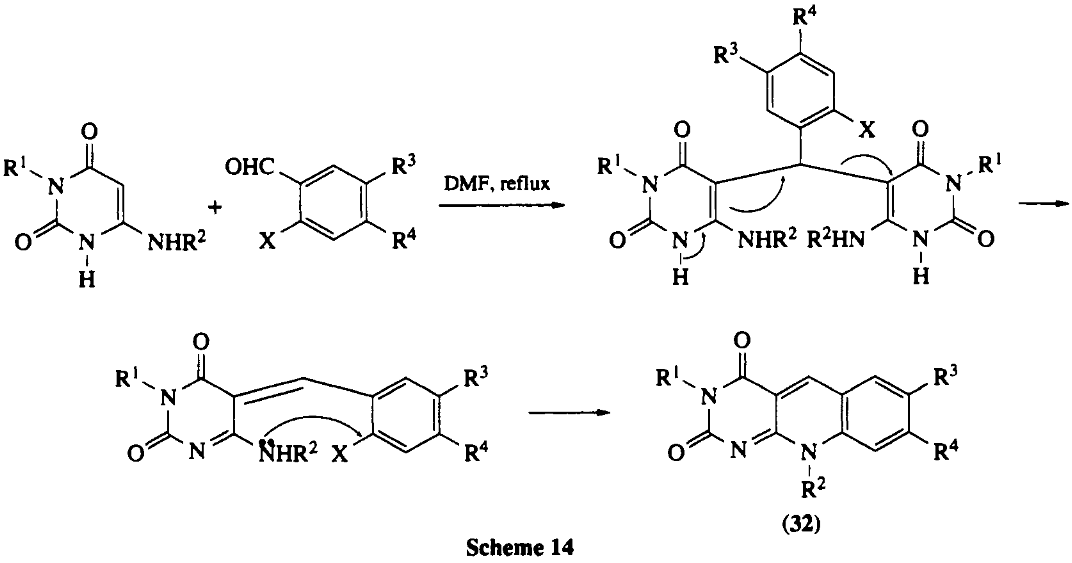

**Scheme 14**

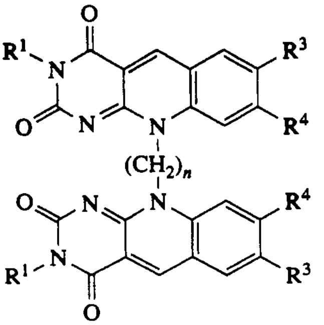

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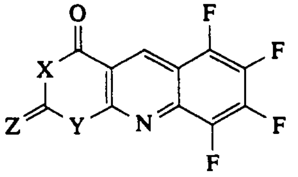

(34a–b)

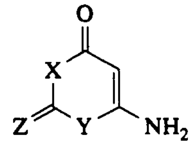

(35a–b)

Several 3-aryl-2-methylimidazo[4,5-*b*]pyridines (**36**; X = H, R = H, 4-F, 4-Et; X = Cl, R = H, 4-F, 3-$CF_3$, 2,4-$Me_2$, 2,4-$Cl_2$, 2-Me-6-Et, 3-$CF_3$-4-Cl) with pesticidal activity have been prepared in moderate yields by the reaction of *N*-(2-chloro-3-pyridyl)acetamides (**37**) with aromatic amines in the presence of $P_2O_5$ and $Et_3N{\cdot}HCl$ at 150 °C.[140] With X = H the cyclized products were isolated directly, whereas with X = Cl treatment of the intermediate amidines (**38**) with $K_2CO_3$ in DMF was required to arrive at the final cyclized product.

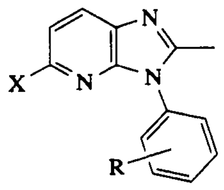

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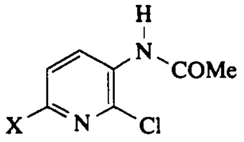

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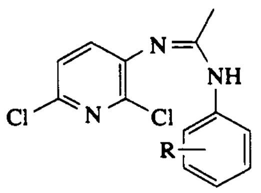

(38)

A one-pot synthesis of 3-amino-2,1-benzisoxazoles (**39**) has been reported, based on the initial $S_NAr$ displacement of halogen by hydroxylamine in the precursor *o*-halobenzonitriles (**40**; X = F, Cl; R = 3-CN, 5-$NO_2$, 5-CN, 3,5-$(NO_2)_2$, 3-$NO_2$-5-CN, 5-$NO_2$-6-Cl), followed by cyclization and aromatization (Scheme 15).[141]

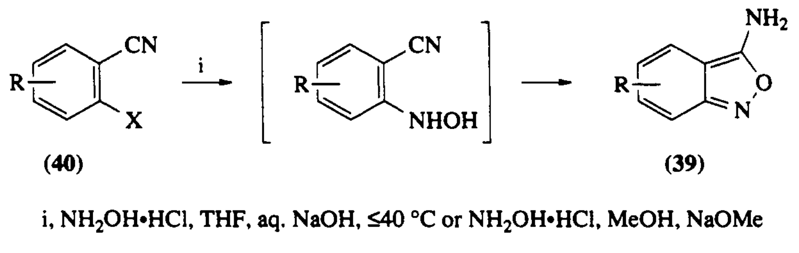

(40) (39)

i, $NH_2OH{\cdot}HCl$, THF, aq. NaOH, ≤40 °C or $NH_2OH{\cdot}HCl$, MeOH, NaOMe

**Scheme 15**

The one-pot conversion of pyrimidinediones (**41**; $R^1 = R^2$ = Me; $R^1$ = Me, $R^2$ = Ph; $R^1$ = H, $R^2$ = Me, Et, Ph, 2,6-$Me_2C_6H_3$) to isoalloxazines (**42**) has been reported to proceed in good yield *via* oxidative cyclization in DMF at 120 °C under oxygen.[142] The reaction was completely inhibited by degassing. The precursors (**41**) were in turn prepared in high yield *via* $S_NAr$ debromination by anilines on the appropriate 5-Br-6(alkyl- or aryl-amino)pyrimidinediones (**43**).[143]

A clever application of the VNS reaction was recently reported to afford direct amination of nitrobenzenes, an otherwise prohibitive process, using 4-amino-1,2,4-triazole (Scheme 16).[144] Exclusive attack at position 4 was observed in all cases studied (R = H, Me, Cl, $CO_2H$, OMe, F, I, CN) with yields in the range 22–91%.

Several activated aryl and heteroaryl halides were converted into the corresponding *N*,*N*-dimethylamino derivatives by treatment with HMPA at 150 °C.[145] Chlorobenzenes activated by *o*- and/or *p*-$NO_2$, CN, and 4-$ClC_6H_4SO_2$ groups gave this reaction with 62–94% yields. Chlorine on pyrazine, tetrazole, thia-

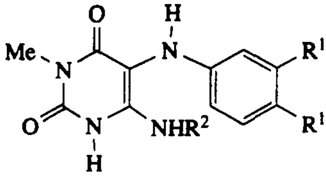
**(41)**

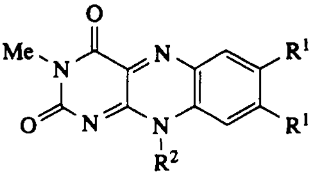
**(42)**

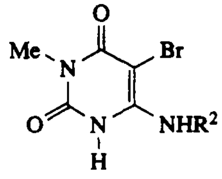
**(43)**

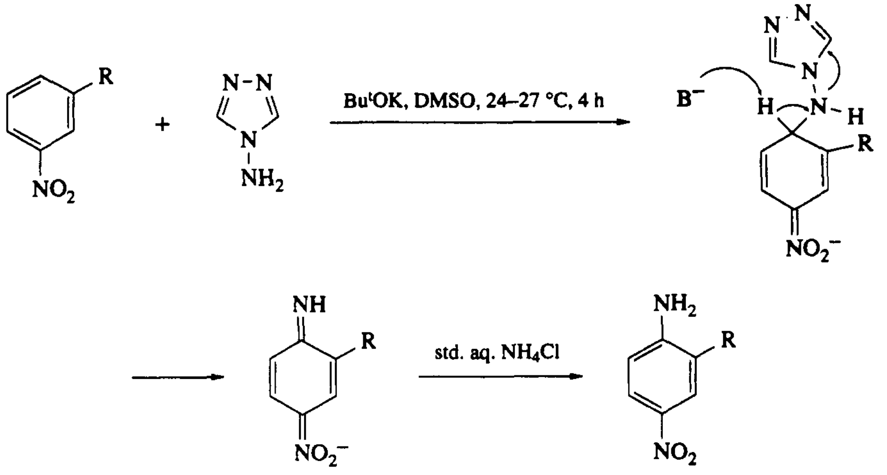
**Scheme 16**

zole, as in the example of equation (13), and quinoline rings, was sufficiently reactive to produce a clean substitution. It was proposed that the reaction proceeds *via* SNAr displacement of the suitably activated leaving groups (halide and also nitrite) by *N,N*-dimethylamide formed by the solvent at elevated temperatures.[145]

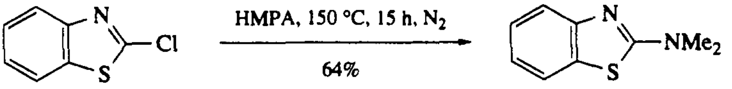 (13)

## 2.1.4 OXYGEN NUCLEOPHILES

The great majority of synthetic applications with oxyanions involve SNAr displacement of leaving groups other than hydrogen. Nucleophilic displacement of hydrogen by oxyanions has been observed, as, for example, in the reaction of nitrobenzene with Bu$^t$OK in THF to give 4-Bu$^t$O-nitrobenzene and potassium nitrobenzenide,[10] but has not found as yet general application in synthesis. In one example alkoxy-dehydrogenation *via* addition/oxidation has been proposed to be a step in the synthesis of 2-alkoxy-5,10,15,20-tetraphenylporphyrins from the corresponding 2-nitro derivative *via* a multistep *cine* substitution sequence.[146]

The use of solvents like HMPA has found many applications in SNAr displacements by alkoxides since the report by Shaw and collaborators on the ability of this solvent to promote methoxylation *via* chloride displacement in unactivated aryl chlorides, including chlorobenzene.[147] Due to the deactivating effect of the OMe group, bissubstitution did not take place on the dichlorobenzenes even under prolonged reaction times and with a large excess of MeONa. SN2 demethylation of chloroanisoles to the corresponding chlorophenols was instead observed.[51] The reaction of tri- and tetra-chlorobenzenes with 1 equiv. of MeONa is not regioselective, with the exception of 1,2,4-trichlorobenzene which gave 2,5-dichloroanisole (88%) as the sole product. When an excess of nucleophile was used, mixtures resulting from monosubstitution, bissubstitution and demethylation were obtained.[51] An analogous survey showed that in DMF methoxydehalogenation takes place regioselectively in dichloro- and dibromo-pyridines (equation 14).[148] Substitution of the second halide was more difficult with these substrates, and bisethers could be obtained in fair yields only from the 2,6- and 3,5-dihalopyridines using 8 equiv. of MeONa. In contrast, the reaction with MeSNa or 2-PrSNa afforded in all cases the bissulfides in good yields.[148]

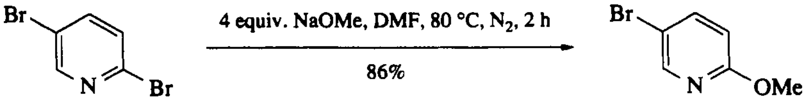

(14)

Aryl fluoroalkyl ethers have been prepared from the reaction, at room temperature in HMPA, of fluoro-substituted alkoxides with activated fluoro-,[149] nitro-,[149] and, at 150 °C, also chloro-arenes[150,151] and some chloro-substituted pyrazines (equation 15), pyrimidines, quinolines,[150,152] and pyridines.[152] Disubstitution was observed in the presence of comparably activated leaving groups such as in 2,4- and 2,6-dichloronitro- or cyano-benzenes, whereas regiospecific substitution took place at position 4 in 3,4-dichloronitro- or cyano-benzene and at position 2 in 2-fluoro-6-chlorocyanobenzene.[151] Steric hindrance and the number of fluorine substituents in the alkoxide pose limits to the reactivity. Thus, tertiary alkoxides, or alkoxides containing more than four fluorine substituents, displace activated nitro and fluoro, but not chloro substituents.[149,150] The secondary hexafluoro-2-propoxide anion does not react even with the more reactive nitro and fluoro derivatives.[149]

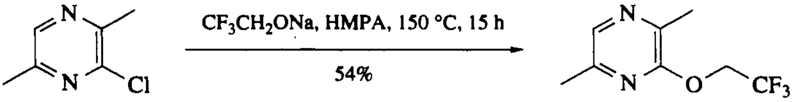

(15)

A convenient one-step conversion of moderately activated nitroarenes to phenols was achieved in DMSO *via* nucleophilic nitrite displacement by the anion of an aldoxime.[153] The resulting *O*-arylaldoxime is rapidly cleaved to the phenol derivative under the reaction conditions. The reaction is also applicable to activated fluorides and even to 2-chloropyridine which, at 110 °C, is converted to 2-pyridone in 72% yield.[153] A somewhat related process concerns the synthesis, in 82–92% yield, of 4-alkoxybenzonitriles (**45**; R = Me, $CH_2$-oxirane, $CH_2Ph$, $CHMeCH_2Me$ from *O*-alkyl-4-nitrobenzaldoximes (**44**) *via* hydride-induced elimination of the alkoxide followed by alkoxy denitration (Scheme 17).[154]

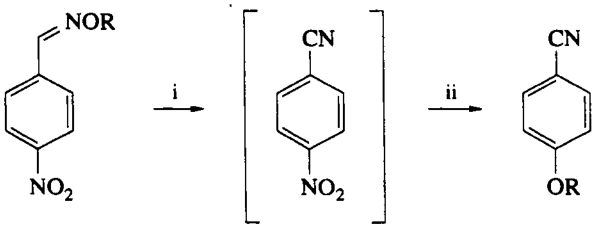

(**44**) (**45**)

i, NaH (excess), DMF, r.t., 1–4 h; ii, RONa (formed in i)

**Scheme 17**

The use of PTC conditions has proved beneficial in several cases and the method of choice in large scale operations. *m*-Dinitrobenzene was converted to *m*-nitroanisole in 81% yield on the mole scale by treatment for 2 h with MeONa in chlorobenzene at 80 °C in the presence of a catalytic amount of trioctylmethylammonium chloride (Aliquat 336).[155] No reaction occurred in the absence of the onium salt catalyst.[155] Analogous results were obtained by performing the reaction in HMPA.[83]

4-Nitrophenyl ethers (**46**; R = 2-Pr, 2-Bu, *n*-$C_8H_{17}$, Ph) were prepared in good yields from the reaction of 4-chloronitrobenzene in the appropriate alcohol (chlorobenzene for R = Ph) with KOH in the presence of TBAB.[156] Without the onium salt, the substitution products formed in poor yields due to reduced $S_NAr$ rates and to competing nitro reduction. Reagents capable of complexing the $K^+$ cation (glymes, high molecular weight polyethers and, best of all, 18-crown-6) could be used in place of the onium salt.[156] Reflux conditions were found unsuitable for these reactions because of the removal of oxygen, a powerful inhibitor of the reduction process.

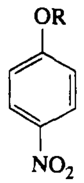

**(46)**

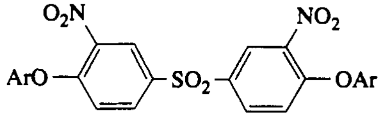

**(47)**

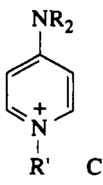

**(48)**

Potassium hydroxide in DMSO has proved a useful reagent to promote the reaction of activated aryl and heteroaryl chlorides with long chain primary alcohols, to form the corresponding ethers (equation 16).[157] The procedure failed with secondary alcohols.

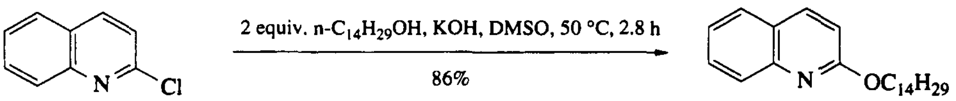

(16)

Perfluorotoluene and pentafluoropyridine have been proposed as reagents for protecting alcohols and phenols as perfluoroaryl ethers, a reaction which takes place under mild PTC conditions. Deprotection involves demethoxylation with NaOMe in DMF at 60 °C (Scheme 18; R = phenyl, steroidal).[158]

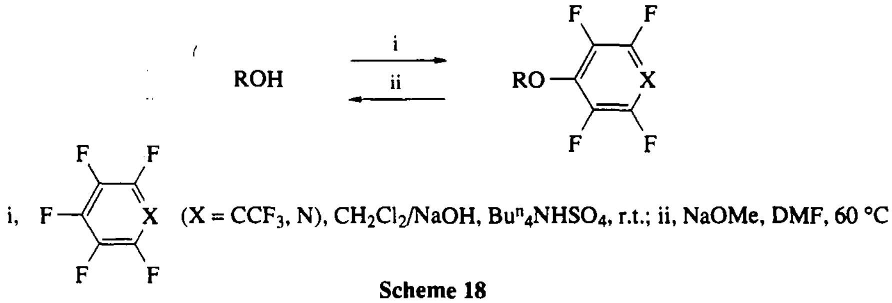

(X = $CCF_3$, N), $CH_2Cl_2$/NaOH, $Bu^n{}_4NHSO_4$, r.t.; ii, NaOMe, DMF, 60 °C

**Scheme 18**

PTC with onium salts (TBAB or TBPB) in a two-phase system ($H_2O$/NaOH/$CH_2Cl_2$) afforded bis(aryloxynitrophenyl) sulfones (**47**) in good yields at room temperature, from the reaction of the corresponding chlorides with several phenols.[159]

More elaborate catalysts have also been used, like tris(3,6-dioxaheptyl)amine (TDA-1) in dechlorinations of chloropyridines by benzyl alcohol[160] and of 4-chloronitrobenzene, 4-chlorobenzonitrile, and 2-chloro-5-(trifluoromethyl)nitrobenzene by phenols and methanethiol.[161]

In the reaction of activated aryl halides with phenoxide and thiophenoxide in chloro- or *o*-dichlorobenzene at reflux, pyridinium salts (**48**; R, R = —$CH_2CH_2CHMeCH_2CH_2$—; R = Me, $Bu^n$, *n*-$C_6H_{13}$; R′ = $CH_2CHEtBu$, $CH_2Bu^t$) proved to be superior catalysts to simpler onium salts, like TBAB, due mainly to their greater thermal stability.[162]

Electrochemical reduction of phenol and thiophenol in the presence of a suitable support electrolyte has been proposed as a method to produce solutions of reactive $PhX^{-}\,{}^{+}NR_4$ (X = O, S) to be used in $S_NAr$ reactions.[163]

Investigations on the use of ionic fluorides as bases in organic synthesis have led to the interesting observation that fluoride hydrogen-bonds to a variety of H-bond electron-acceptor (protic) compounds and that such H-bound complexes may actually be more effective nucleophilic reagents than the salt of the protic.[164] Examples of fluoride-promoted nucleophilic aromatic substitutions range from the synthesis of aromatic polyethers *via* polycondensation of bis(4-chloro-3-nitrophenyl) sulfone with 2,2-bis(4-hydroxyphenyl)propane (equation 17),[165] to the synthesis of aryl-4-cyanophenyl ethers obtained from the reaction of activated nitro- or chloro-arenes with the hydrogen-bonded complex of 4-cyanophenol with KF (equation 18).[166] In the latter case, H-bonding results in charge localization on the oxygen, thus presumably increasing the selectivity of the nucleophile. However, no data were supplied to allow a comparison of the H-bonded complex and the phenoxide salt.

One method of synthesis of 1,2-benzisoxazoles involves cyclization of *o*-halo- or *o*-nitro-benzoyl oximes *via* intramolecular $S_NAr$.[167,168] A recently reported variant, which gives access to sterically constrained 3-phenyl-1,2-benzisoxazoles, employs a reversed sequence of steps, *e.g.* nucleophilic

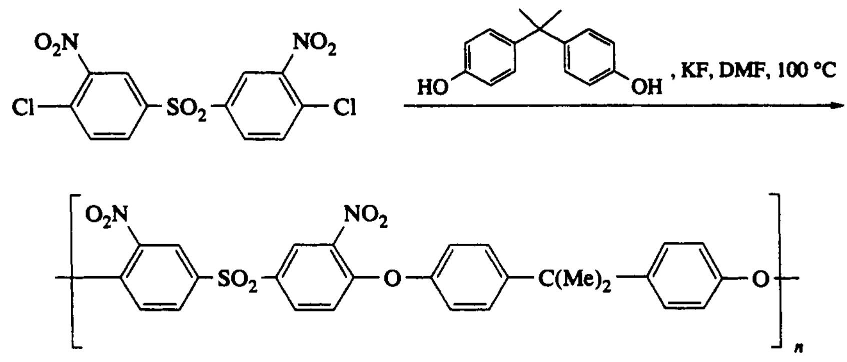

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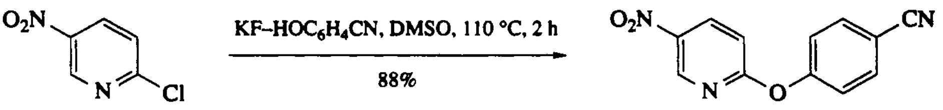

(18)

displacement by the anion of acetone oxime of an *o*-fluoro substituent in the precursor benzophenone, followed by cyclization *via* acid-induced transoxymation (Scheme 19; R = H; 2,3-$Cl_2$-4-MeO; 2,6-$Me_2$; 2,6-$Cl_2$).[169] In contrast to the intramolecular $S_NAr$ route, which is not selective (Cl and F are displaced at comparable rates, so that mixtures of 3-(2-chlorophenyl)- and 3-(2-fluorophenyl)-1,2-benzisoxazoles were obtained from 2-chloro-2′-fluorobenzophenone oximes), the intermolecular $S_NAr$ reaction is highly selective. Thus only 3-(2,3-dichloro-4-methoxyphenyl)-1,2-benzisoxazole (**49**; R = 2,3-$Cl_2$-4-OMe) was obtained in 73% overall yield from 2,3-dichloro-2′-fluoro-4-methoxybenzophenone.[169]

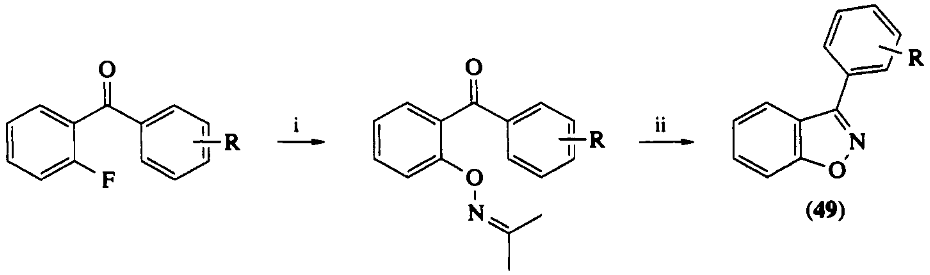

i, $Me_2C{=}NOH$, Bu$^t$OK, THF, reflux, 3 h; ii, aq. HCl, EtOH

**Scheme 19**

A convenient one-pot conversion of alkyl halides into thiols under mild conditions is based on the sequence shown in Scheme 20.[170] It involves quaternarization of 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione (**50**) followed by an intramolecular $S_NAr$ displacement.

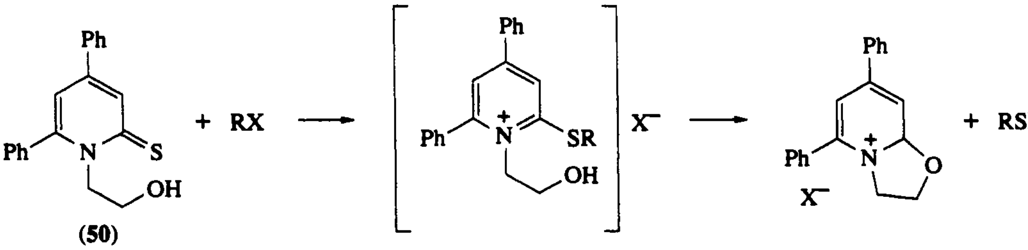

(**50**)

**Scheme 20**

2-Alkoxy- and 2-aryloxy-4-amino-5-pyrimidinecarbonitriles (**51**; X = MeO, EtO, PhO, 4-$MeOC_6H_4O$, 4-$ClC_6H_4O$, 4-$BrC_6H_4O$, 4-$CNC_6H_4O$) were prepared in good yields from the corresponding chloro or bromo derivatives (X = Cl, Br) by the reaction with RONa in refluxing acetone.[171] 2-Amino derivatives (**51**; X = $NH_2$, NHR, $NR_2$) were prepared in analogous fashion.[171]

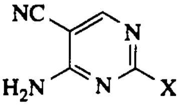

(51)

## 2.1.5 SULFUR NUCLEOPHILES

Sulfur anions are generally good nucleophiles, more powerful than their oxygen analogs. While the nucleophilic displacement of hydrogen by thioanions has not been frequently observed,[6] the $S_NAr$ displacement of nitrite, halides and other leaving groups constitutes a common and often easily accomplished step in synthesis. However, undesired redox processes occur frequently with thioanions due to their low oxidation potentials. To avoid oxidation of the nucleophile, reactions with thioanions are best carried out under an inert atmosphere. Under these conditions, however, simple nitrobenzene derivatives like 4-chloronitrobenzene readily undergo reduction. Thus, complex mixtures resulting from reduction of the nitro group were obtained from the reaction of 4-chloronitrobenzene with MeSNa in DMF[172] and with MeSNa and EtSNa in HMPA,[173] under conditions which with more substituted arenes or with secondary thioanions lead to the products of substitution in high yields.[173] 4-Chloromethylthiobenzene was instead obtained in 92% yield from the reaction in MeOH of 4-chloronitrobenzene with an excess of MeSH upon the dropwise addition of methanolic KOH.[65]

Displacement of the nitro group of moderately activated nitroarenes by thioanions occurs readily in polar aprotic solvents.[174–176] Kornblum and collaborators found that nitrobenzenes carrying one electron-withdrawing group react with thioanions, in HMPA at 25 °C, to give the products of nitrite displacement (**52**) in good to excellent yields (equation 19; RS = MeS, $PhCH_2S$, PhS, $PhSO_2$; W = 2-, 3-, and 4-$NO_2$, 4-CN, 4-PhCO, 4-EtOCO, 4-$PhSO_2$, 3,5-$(CF_3)_2$).[83]

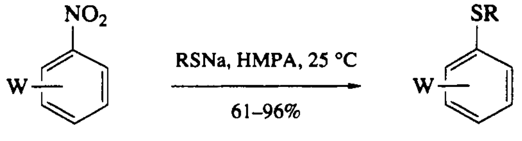

(19)

(52)

Thiol anions in polar aprotic solvents are also effective in displacing chloride in activated and even weakly activated arenes. In substrates with more than one replaceable chlorine regioselective displacement of one chlorine was seldom observed, the reaction usually yielding mixtures of mono- and polysubstituted products. It was thus concluded that alkylthio substituents exert an activating effect roughly comparable to that of a chlorine.[172,173] Exhaustive substitution was often observed when the thiolate reagent was used in excess.[172,173,177–179] Several bis-, tris-, tetrakis- and pentakis-(methylthio)benzoic acids and derivatives,[178] and poly(alkylthio)benzenes,[179] were prepared in good yields in DMF and HMPA, respectively. The extent of substitution could be controlled in some cases by proper choice of the reaction conditions, *e.g.* the amount of nucleophile and/or the temperature. Thus, the reaction of 4-chloro-3,5-dinitrotoluene (**53**) with excess methanethiolate in DMF at ice bath temperature for 15 min produced (**54**) in 78% yield, whereas the tris(sulfide) (**55**) was isolated in 60% yield when the reaction mixture was allowed to stand for 4.5 h at room temperature.[172] In the examples of Scheme 21, advantage was taken of the different rates of the alkylthio denitration and alkylthio dechlorination processes to prepare the isomeric tris(sulfides) (**56**) and (**57**) in 70% and 65.5% yield, respectively.[173] In contrast, the reaction of 1-chloro-2,4-dinitrobenzene with 1 and 2 equiv. of $Me_2CHSNa$ gave mixtures of mono- and di-, and di- and tri-substitution products, respectively.[173] Reactions of polychloroarenes in HMPA with EtSNa, and, even more so, with MeSNa, proceed *via* $S_NAr$ displacement of chloride followed by dealkylation *via* $S_N2$ displacement of thiophenoxides by the thiolate anion. The reaction has been developed into a one-pot synthetic route to thiophenols from aryl chlorides and bromides, as exemplified in equation (20).[180] Mercaptopyridines and mercaptoquinolines were prepared by the same procedure in DMF.[181] Alkoxyaryl alkyl sulfides were obtained from dichlorobenzenes and dichlorotoluenes by sequential treatment with RSNa and R′ONa in HMPA.[182]

Treatment of activated diaryl sulfides with $Na_2S$ in DMF at 130 °C results in the cleavage of the sulfide and in the formation of sodium aryl sulfides which can be used *in situ* to prepare mixed diaryl or alkyl aryl sulfides.[183] An example is reported in Scheme 22.

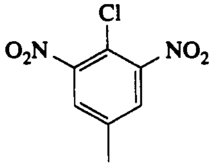

**(53)**

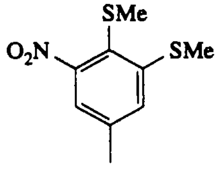

**(54)**

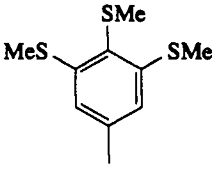

**(55)**

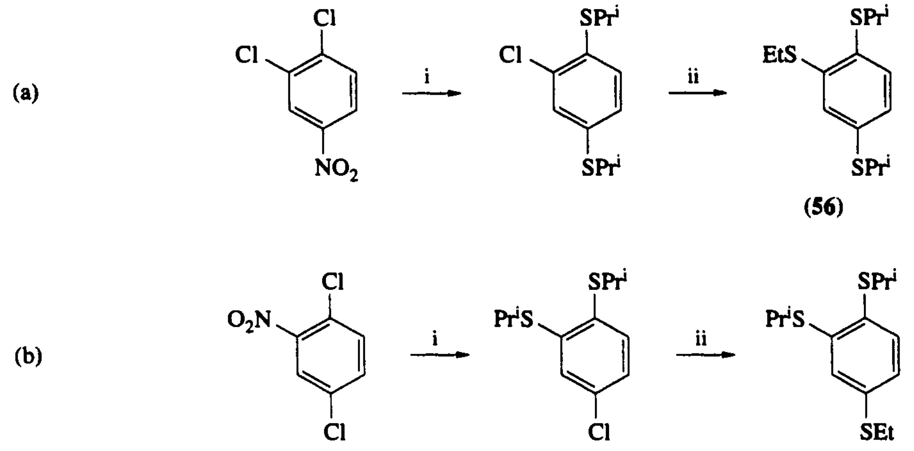

**(56)**

**(57)**

i, 2 equiv. Pr$^i$SNa, HMPA, r.t.; ii, 1 equiv. EtSNa, 80 °C

**Scheme 21**

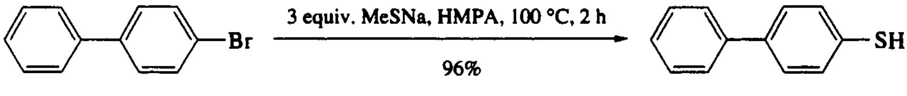

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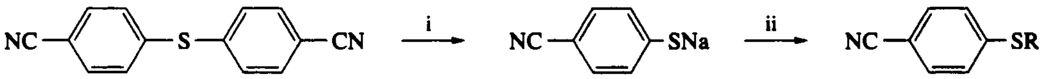

i, $Na_2S$, DMF, 130 °C, 12–18 h; ii, RX (alkyl or aryl halide)

**Scheme 22**

The reaction of EtSLi with the isomeric dinitrotoluenes (**58**) in HMPA at 20 °C gave regiospecific displacement of the nitro group adjacent to the alkyl group in excellent yields (equation 21).[184] With a bulky *o*-alkyl substituent, like in 2,4-dinitro-*t*-butylbenzene, regiospecificity was lost, the two nitro groups being displaced in equal proportions. Notably, when the same substrate was allowed to react with Bu$^t$Li slow displacement of the nonadjacent nitro group took place, accompanied by redox processes: azoxy and hydrazo compounds and di-*t*-butyl disulfide (80%) were isolated from the reaction mixture.

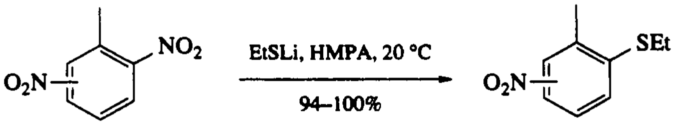

(21)

**(58)**

Dichloropyridines were converted in good yield to the corresponding bis(alkylthio)pyridines *via* reaction with sodium thiolates in DMF at 140 °C.[185] Room temperature oxidation of the sulfides with chlorax solution gave bis(alkylsulfonyl)pyridines in high yields.[185]

The convenient preparation of 2,7-dinitrothianthrene (**59**) *via* base-induced cyclization of 2-chloro-5-nitrobenzenethiol in acetone at room temperature (equation 22), provides an easy access to a number of 2,7-substituted thianthrenes *via* elaboration of the nitro groups in (**59**).[186]

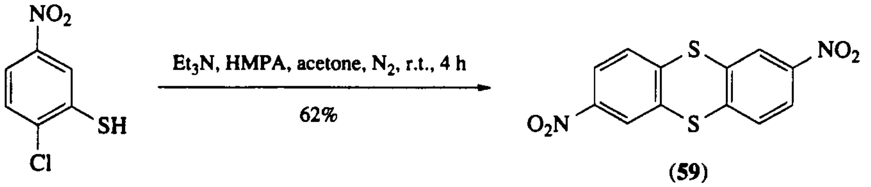

(**59**)

(22)

Polyglymes offer a viable alternative as solvents to the potentially carcinogenic HMPA.[187,188] Alkyl and phenyl sulfides were prepared from the reaction of suitable aryl halide precursors and an excess of sodium thiolates in tetraglyme.[188] By the same procedure 2-(alkylthio)-substituted (alkyl = $Me(CH_2)_n$; *n* = 3, 15, 17) quinolines, pyrimidines and pyrazines were prepared from the corresponding chlorides.[187]

Halide displacement by thioanions such as thioalkoxides, thiocyanate and sulfite, can be readily carried out under PTC conditions in activated arenes. The reaction of nitro- and dinitro-aryl halides with thiophenol and NaOH in the presence of an ammonium or phosphonium salt catalyst proceeds readily in toluene at room temperature to give the phenyl aryl sulfides in nearly quantitative yield.[189] Excellent yields of thiocyanoarenes were obtained from the reaction of the 2,4-dinitrohalobenzenes with KSCN in toluene at 90 °C with a tetraalkyl onium salt PTC catalyst.[190]

Protonated tertiary amines ($(Me(CH_2)_n)_3N$ (*n* = 2, 3, 4, 5 and 7) were found to be better catalysts than tetraalkyl ammonium salts for the sulfodechlorination of 1-chloro-2,4-dinitrobenzene.[191]

Unsymmetrical diaryl sulfides (**60**; R = 2-$NO_2$, 4-$NO_2$, 2,4-$(NO_2)_2$; R′ = H, 4-$NMe_2$) were obtained in 80–97% yields from the reaction under PTC conditions of nitro-activated aryl halides with arenethiolates generated *in situ* from the reduction of the corresponding diaryl disulfides with aminoiminomethanesulfinic acid (**61**).[192] Arylthiolates carrying electron-withdrawing substituents were not sufficiently reactive. The reaction could also be applied to the synthesis of diaryl selenides, but not of ditellurides.

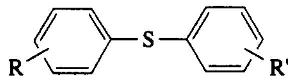

(**60**)

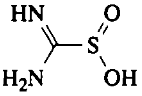

(**61**)

Symmetrical diaryl sulfides were produced in fair yield from the PTC reaction of sodium sulfide with molten aryl chlorides activated by a cyano, nitro, phthalimido or anhydrido group.[193] Typical conditions require use of a 3:1 mole ratio of aryl chloride to $Na_2S$ and 10% of catalyst (crown ethers and onium salts) at 200 °C for 24 h.

Thioiminium salts (**62**; R′ = H, Me; R = H, Ph, CH=$CH_2$) can be used to generate *in situ* thiolates $RCH_2S^-$ which under PTC conditions in $CHCl_3$, at room temperature, react with aryl halides to give the alkyl aryl sulfides (**63**; R = H, Ph, CH=$CH_2$; R″ = H, $CO_2H$, Cl, $NO_2$).[194] Yields are best with activated aryl halides. With an excess of (**62**), *p*-dichlorobenzene gave products of disubstitution (**63**; R″ = $CH_2SR$).

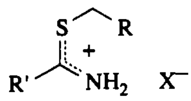

(**62**)

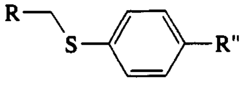

(**63**)

Catalysts of greater thermal stability have also been used, such as *N*-alkyl salts of 4-dialkylaminopyridines (**48**)[162] and tris(polyoxaheptyl)amine (TDA-1).[161]

Displacement of chloride has also been accomplished on moderately activated substrates, such as $C_6H_nCl_{6-n}$ (*n* = 2, 3, 4), under PTC conditions at temperatures which depend on the number of chlorine substituents. The dichlorobenzenes react with aliphatic thiols at 110 °C in a heterogeneous mixture with concentrated aq. KOH containing dicyclohexano–18-crown-6 as PTC catalyst.[195] Reaction times were long, ranging from 14 h with primary thiols to >200 h with tertiary ones. The reactivity of the first chlorine atom followed the order 1,2- > 1,3- > 1,4-dichlorobenzenes. The reaction of 1,2-dichlorobenzene with secondary and tertiary thiolates was selective and gave exclusively the product of monosubstitution. With Bu$^n$SH some disulfide (5% by GC) was also formed. The reaction of 1,3- and 1,4-dichlorobenzene gave in all cases mixtures of mono- and di-sulfides of variable composition.

Several alkyl aryl sulfides in which the alkyl group is a linear primary $C_nH_{2n}$ chain ($n$ = 7, 8, 12), have been prepared from the corresponding thiols and di-, tri-, and tetra-chlorobenzenes under PTC conditions with KOH and a catalyst in toluene.[196] Ammonium and phosphonium salts, 18-crown-6, and polyethylene glycols were used, (tricyclohexyl-*n*-dodecyl)phosphonium bromide being the most efficient catalyst. The regioselectivity is determined by the prevalent influence of the –*I*-activating effect of the chloro substituent, *ortho* > *meta* > *para*. Thus the reaction of 1,2,4,5-tetrachlorobenzene (**64**; X = H, Y = Cl) gave disulfide (**65**; X = H, Y = SR) in 89% yield, and 1,2,4,6-tetrachlorobenzene (**64**; X = Cl, Y = H) gave monosulfide (**65**; X = Cl, Y = H) in 88% yield. The reaction of 3-chlorobromobenzene with *n*-heptanethiol gave exclusively the product of bromide displacement in 86% yield.

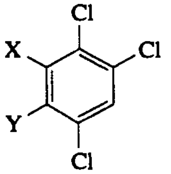

**(64)**

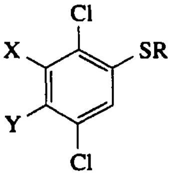

**(65)**

A one-pot synthesis of benzothiazolones from 2-halonitrobenzenes has been reported (equation 23).[197] The proposed mechanism involves the displacement of halide by some sulfide species ($H_2S$ or $HS_n^-$, $n$ = integer) generated *in situ*, followed by nitro reduction and condensation with SCO.

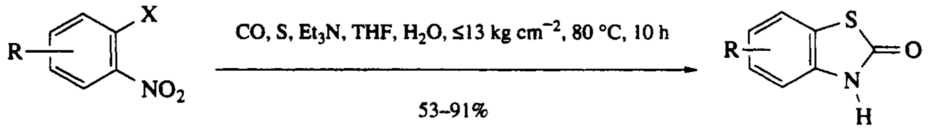

(23)

Mercaptobenzoic acids (*ortho*, *meta* and *para* isomers) were prepared in fair to good yields from the reaction of the chlorobenzoic acids with elemental sulfur and molten NaOH–KOH (1:1 molar ratio) at 270 °C for 3 min. Both 2- and 4-chloropyridine gave the mercaptopyridines by an analogous procedure.[198] Use of selenium instead of sulfur gave poor yields and mixtures of isomeric products.

## 2.1.6 OTHER NUCLEOPHILES

### 2.1.6.1 Hydride

Anionic σ-adducts with the hydride ion have been detected and some also isolated as stable salts.[8,43] A few examples of nucleophilic displacement by hydrogen have been reported. Displacement of $NO_2^-$, $Cl^-$ and $Br^-$ by hydride, *via* σ-adduct intermediates, was observed in DMSO solutions of $XC_6H_4NO_2$ (X = 2-Br, 2-Cl and 4-$NO_2$) and of 1-X-2,4-dinitrobenzene (X = Br, Cl) with $NaBH_4$.[199] Another example is the reaction of arene diazonium salts carrying an electron-withdrawing substituent with formamide and $Et_3N$ to form arenes in moderate to good yields. The mechanism of this proto dediazoniation was shown to involve transfer of the formyl hydrogen as hydride within a 1-aryl-3-formyltriazene intermediate (Scheme 23).[200]

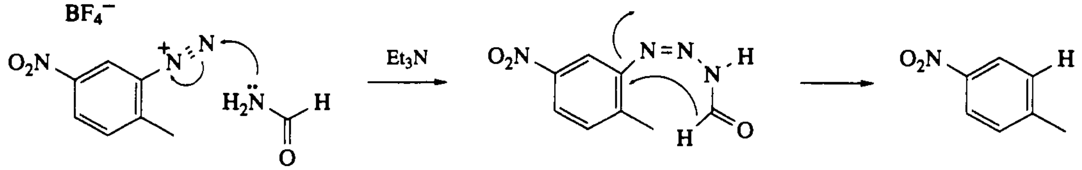

Scheme 23

### 2.1.6.2 Halides

Great effort has been given in the last decade to the synthesis of fluoro aromatics due to their growing importance as pesticides and pharmaceuticals.[201,202] One of the most useful reactions to introduce a fluorine or other halogen substituent into an arene is nucleophilic displacement by fluoride (halide) of an activated leaving group. Special areas of research deal with the selective introduction of fluorine into biologically active molecules and with the synthesis of radiopharmaceuticals labeled with short-lived radionuclides, particularly with the positron-emitting nuclides $^{18}$F ($t_{1/2}$ = 110 min) and $^{122}$I ($t_{1/2}$ = 3.6 min).

$^{18}$F-labeled aromatics have been prepared most efficiently from activated arenes in DMSO *via* displacement of nitrite with $Rb^{18}F$[203,204] and with $Cs^{18}F$,[204] and of fluoride ($^{19}F \rightarrow {}^{18}F$ exchange), chloride, and bromide with $Cs^{18}F$,[204] of iodide with $H^{18}F$–$K_2CO_3$,[205] and of $Me_3N$ with $Cs^{18}F$.[206] The temperatures needed to obtain high conversions in the required short reaction times (<20 min) depend on the leaving group ability as well as on the activating group and range from 80–150 °C for the displacement of nitrite,[203] to 180 °C for the displacement of iodide.[205] The use of rapid heating in microwave ovens has been reported to significantly reduce the reaction times in these and related systems.[207] The use of polar aprotic solvents like DMSO can be avoided in these reactions by the choice of better nucleophiles like anhydrous tetrabutylammonium fluoride (TBAF) which can be used in THF at room temperature (equation 24).[35] The convenience of using the KF–$Ph_4PBr$ system has also been pointed out, rate enhancements being especially significant in less polar solvents (1,2-dimethoxyethane, acetonitrile).[208]

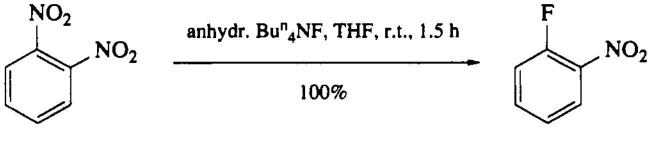

(24)

Fluorodesulfonylation reactions on arylfluorosulfonyl fluorides, carried out with KF in sulfolane or DMF, or without solvent in the presence of 18-crown-6, have shown that the $FSO_2^-$ is a good activating group and a good leaving group (equation 25).[209]

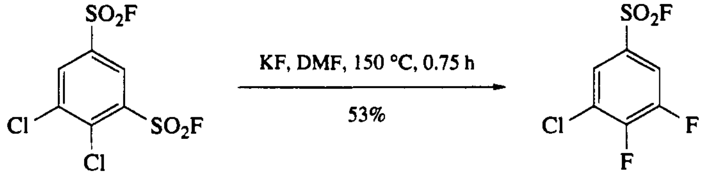

(25)

The synthetic potential of 'solid-state' nucleophilic aromatic substitutions has been pointed out in a report on the displacement of *o*-nitro groups in arene diazonium ions by chloride from the chlorozincate counterion in the salt.[210] The reaction is selective for the *ortho* position. Chloroarenes and heteroarenes have been synthesized in good yields from the corresponding nitro compounds upon treatment with phenyltetrachlorophosphorane (PTCP) in phenylphosphonic dichloride at 170 °C for 5 h. Reactive substrates ranged from nitrobenzene to nitropyridines and nitropyrimidines, yields being in the range 66–94%. An

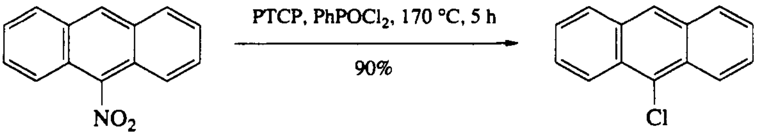

(26)

example is shown in equation (26). A stepwise mechanism (Scheme 24), involving in the final stage an intramolecular chlorine attack to displace NOCl from intermediate (**66**), was proposed for this reaction.[211]

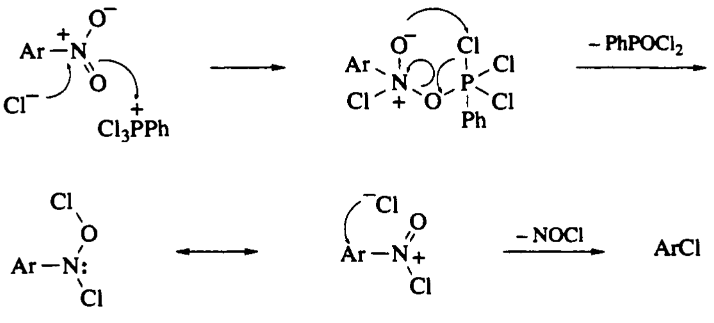

Ar
Cl⁻
Cl₃PPh
Cl
Ph
- PhPOCl₂
- NOCl
ArCl

(**66**)

**Scheme 24**

### 2.1.6.3 Phosphorus Nucleophiles

Attack by phosphorus nucleophiles on pyridinium salts is well established, and is the basis for a method for the regioselective synthesis of 4-alkylpyridines,[212] and of 1-alkylisoquinolines.[213] Although the phosphonate adducts (**67**) were obtained in high yields in all cases examined (R = Me, Et, $CH_2{=}CHCH_2$, Bu, $PhCH_2$), the final step gave satisfactory yields only in the case R = Bu (Scheme 25).

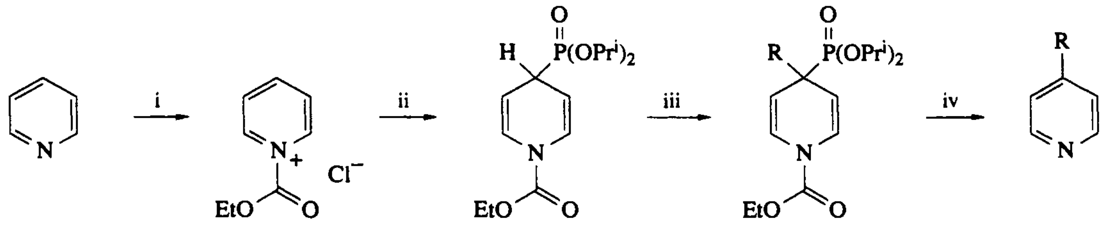

i
ii
iii
iv
H
R
P(OPr^i)₂
EtO
Cl⁻

(**67**)

i, EtOCOCl; ii, $P(OPr^i)_3$; iii, BuLi, THF, −78 °C, RBr; iv, BuLi

**Scheme 25**

The reaction of nitronaphthalenes and nitroisoquinolines with dimethyl phosphite in MeONa/MeOH (equation 27), proceeded *via* nucleophilic substitution of hydrogen according to a redox stoichiometry and gave substituted dimethyl naphthalene- and isoquinoline-phosphonates and benzazepines.[214]

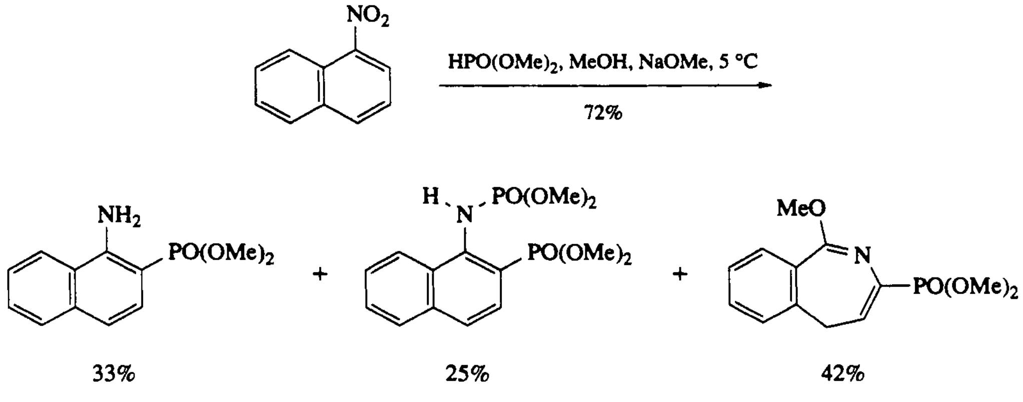

NO₂
HPO(OMe)₂, MeOH, NaOMe, 5 °C
72%
NH₂
PO(OMe)₂
PO(OMe)₂
MeO
33%
25%
42%

(27)

### 2.1.6.4 Selenium and Tellurium Nucleophiles

The methods of synthesis of diaryl and aryl alkyl selenides have been recently reviewed.[215] 4-Nitrophenyl methyl selenide was obtained in 93% yield from the reaction of 4-chloronitrobenzene in DMF with a suspension of MeSeLi in THF, prepared from powdered Se and MeLi.[216] Other mixed RSeAr selenides were synthesized *via* alkylation with RI of $ArSe^-$ resulting from the nucleophilic substitution of unactivated haloarenes ArCl with MeSeLi in DMF at 120 °C, followed by $MeSe^-$-induced demethylation.[217]

Diaryl selenides (**68**; X = Z = H, Y = $NO_2$; X = Y = H, Z = $NO_2$; X = H, Y = Z = $NO_2$; X = Cl, Y = $NO_2$, Z = H) were prepared in 75–95% yields from diaryl diselenides and chloro- or bromo-nitrobenzenes under PTC conditions, by the procedure already described in Section 2.1.5.[192]

The synthesis of aromatic tellurides has been performed *via* the reaction of iodoarenes (*o*-, *m*- and *p*-iodonitrobenzene, and di- and tri-methyliodonitrobenzenes) with phenyltelluride in HMPA at 80–90 °C, preferably in the presence of CuI. Yields range between 53 and 95%.[218] Symmetrical diaryl tellurides (**69**; R = 3-Me, 4-Me, 2,4-$Me_2$, 2,4,6-$Me_3$, 4-MeO) were prepared in good yields from reaction of nonactivated aryl iodides with $Na_2Te$ in DMF at 60 °C.[219] The mechanisms of these reactions, which are limited to the iodoarenes, have not been discussed.

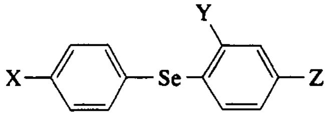

**(68)**

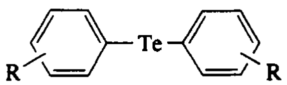

**(69)**

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# 2.2
# Nucleophilic Coupling with Aryl Radicals

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## 2.2.1 INTRODUCTION

Electrophilic substitution allows replacement of a proton or another electrofuge with a different group and is the most-used process for functionalizing aromatic rings, whereas nucleophilic substitution is often considered to be more difficult or to require special substituents or reaction conditions. Prior to 1970, only two significant classes of nucleophilic substitution processes on aromatic rings had been identified. The first, formally termed the $S_NAr$ reaction, requires the presence of one or more electron-withdrawing groups on the aromatic ring, and is a two step addition–elimination process (see Chapter 2.1 of this volume), whereas the second proceeds through the intermediacy of arynes in a two-step elimination–addition sequence and often is accompanied by *cine* substitution (see Chapter 2.3 of this volume). It was during a study of the latter reaction type involving treatment of 5- and 6-iodopseudocumenes with potassium amide in liquid ammonia that Kim and Bunnett[1] observed that more of the respective *ipso* substitution products were being formed than could be explained on the basis that the reaction was proceeding through a common aryne intermediate. It was shown that the *ipso* substitution reaction was radical in nature and involved single-electron transfer steps, being inhibited by radical scavengers and promoted by one-electron donors, such as potassium. The reaction was recognized as being an aromatic analog of substitution processes at the aliphatic carbon in *p*-nitrobenzylic and α-nitroalkyl halides, independently identified in 1966 by the research groups of Kornblum[2] and Russell.[3] Bunnett[1,4] suggested the term '$S_{RN}1$', standing for substitution, radical nucleophilic, unimolecular, for these reactions and this widely adopted description will be used throughout this chapter.

The utility of the $S_{RN}1$ process from a synthetic viewpoint was very quickly recognized. It allows substitution of nucleofugic substituents on *unactivated* aromatic rings (*cf.* the $S_NAr$ reaction) and does not give rise to rearranged products (*cf. cine* substitution in the aryne mechanism). Detailed mechanistic studies have identified the nature of the individual steps occurring in $S_{RN}1$ reactions (see Section 2.2.2.1), but from a synthetic viewpoint, the key process is the trapping of an aryl radical by a nucleophile, establishing a new aryl carbon to carbon or heteroatom bond, depending on the nature of the nucleophile. The generality of trapping of radicals by nucleophiles was recognized in the late 1960s and an overview by Russell[5] in 1970 summarizes the early observations. The mechanistic and synthetic work performed on the $S_{RN}1$ reaction since that time, however, has served as the most useful source of information on the chemo- and regio-selectivity of this key step.

The $S_{RN}1$ reaction has been the subject of numerous reviews. The very comprehensive review by Kornblum[6] principally deals with the aliphatic version, in which the new bond is formed between an aliphatic carbon and a nucleophile,[6] whereas other more general reviews treat both the aliphatic and aromatic reactions[7–12] or discuss the reaction in the context of electron transfer processes and/or electrochemical processes.[13–15] Among the reviews principally dealing with the aromatic version, one by Bunnett[4] deals with the discovery and initial work on the aromatic $S_{RN}1$ reaction, the review by Wolfe and coworkers[16] summarizes the early synthetic uses of the reaction, and a later review by Beugelmans discusses the application of the reaction to heterocyclic synthesis.[17] The monograph by Rossi and Rossi[18] details many aspects of the aromatic version, with particular emphasis on the mechanistic intricacies of the reaction. The discussion of the $S_{RN}1$ reaction in this chapter will be restricted to the aromatic version of the reaction, except for a brief mention of reaction with vinylic substrates. (*i.e.* it is limited to trapping of nucleophiles by $sp^2$-hybridized radical sites). Reactions which are catalyzed by or involve electron transfer to transition metal ions, *e.g.* the Sandmeyer reaction or the recently discovered cobalt carbonyl catalyzed carbonylation of aryl and vinyl halides,[19] also will be omitted.

## 2.2.2 THE $S_{RN}1$ REACTION

### 2.2.2.1 Mechanistic Considerations

The steps in the general $S_{RN}1$ reaction as applied to aromatic systems are given in equations (1)–(4), where $X^-$ is a nucleofuge. Equation (1) represents the generalized initiation step. The single electron necessary for initiating the whole reaction sequence has been shown to arise from the nucleophile (equation 5) in either photostimulated or thermal (spontaneous) processes, added nonparticipant nucleophiles or radical anions (entrainment), or from solvated electrons and/or dissolving alkali metals. Numerous possibilities exist for both the nature of the photostimulation of the $S_{RN}1$ reaction and the way in which electron transfer from nucleophile to substrate takes place. These are discussed at length in Chapter 7 of ref. 18, but some points are further elaborated below.

An example of transfer of electron from nucleophile to substrate is seen in the formation of the radical anions (observable by ESR) of 5-halo-2*H*,3*H*-benzo[*b*]thiophene-2,3-diones on treatment with nucleophiles.[20] It has been proposed in some cases, that this single-electron transfer step takes place through a charge transfer complex between the nucleophile and the aromatic substrate.[21,22] Some reactions occur spontaneously, *i.e.* without any catalysts or reagents other than the substrate and the nucleophile, but the initiation process is usually, although not invariably, photostimulated (near-ultraviolet radiation, 300–

$$ArX + e^{-} \longrightarrow ArX^{\bullet -} \qquad (1)$$

$$ArX^{\bullet -} \longrightarrow Ar^{\bullet} + X^{-} \qquad (2)$$

$$Ar^{\bullet} + Nu^{-} \longrightarrow ArNu^{\bullet -} \qquad (3)$$

$$ArNu^{\bullet -} + ArX \longrightarrow ArNu + ArX^{\bullet -} \qquad (4)$$

$$ArX + Nu^{-} \longrightarrow ArX^{\bullet -} + Nu^{\bullet} \qquad (5)$$

400 nm). Indeed, the catalytic effect of irradiation has been used extensively as a mechanistic probe for the occurrence of aromatic substitution by the $S_{\mathrm{RN}}1$ mechanism. It should be noted, however, that some powerful nucleophiles, such as the phenylated anions of the Group IVA elements[23–25] do not need photostimulation to bring about reaction. In similar fashion, reactions between the enolate ion from pinacolone ($^{-}CH_2COBu^t$) and iodobenzene or bromobenzene also proceed spontaneously in DMSO in the absence of irradiation, although irradiation certainly increases the reaction rate.[26]

A practical disadvantage of using dissolving alkali metals, first noted by Bunnett and Kim in their initial discovery of the aromatic $S_{\mathrm{RN}}1$ reaction,[1] is formation of reduction products, *i.e.* replacement of the nucleofuge by a hydrogen atom (equation 6; Solv-H is solvent). The first example of an electrochemically induced aromatic substitution of the $S_{\mathrm{RN}}1$-type was reported in 1970,[27] when it was demonstrated by cyclic voltammetry that the substitution of iodide by cyanide in *p*-iodonitrobenzene could be accomplished. In 1974, Pinson and Savéant[28] carried out the substitution of the bromine in *p*-bromobenzophenone with $PhS^{-}$ ion under electrocatalytic conditions (0.2 F $mol^{-1}$) and since this beginning, electrochemically induced $S_{\mathrm{RN}}1$ processes have been extensively studied, mainly by French chemists. In 1980 Savéant[13] reviewed the earlier literature, which principally consisted of mechanistic studies. In more recent work, especially since 1985, electrochemically initiated reactions have been used in preparative procedures and these would appear to be an important addition to the synthetic use of the $S_{\mathrm{RN}}1$ reaction, particularly with some nucleophiles which fail to react or react very poorly under other conditions. These nucleophiles include phenoxides, $CN^{-}$ and *aci*-nitronic ions (see Sections 2.2.3.1.4–6 respectively). In some cases these reactions only take place under electrochemical conditions with stoichiometric amounts of current (*i.e.* are noncatalytic processes) and are not really chain processes (*e.g.* reaction of iodobenzene with 2-nitropropan-2-ide ion).[29]

$$Ar^{\bullet} + e^{-} \longrightarrow Ar^{-} \xrightarrow{\text{Solv-H}} ArH \qquad (6)$$

The propagation steps in the $S_{\mathrm{RN}}1$ sequence are the dissociative step (equation 2), the associative step (equation 3), and the single-electron transfer step (equation 4). These processes are discussed extensively in Chapter 8 of ref. 18. The nature of the nucleofuge is critical in that poor nucleofuges retard the dissociation of the intermediate radical anion, $ArX^{-\cdot}$ (equation 2), and prevent the reaction from proceeding at a reasonable rate or stop it completely (see Section 2.2.2.3).

The associative step (equation 3) determines the nature of the product, since in this step the synthetically important bond formation between the aromatic moiety and the nucleophile takes place. The rates for the association of a number of nucleophiles with a variety of aryl and heteroaryl radicals has been measured in electrochemical studies[29–31] and competitive product studies.[32–35] The range of nucleophiles, classified according to the atom which becomes directly bonded to the aromatic ring, and, where the nucleophile is ambident, the regiochemistry of the association reaction shown in equation (3) are detailed in Section 2.2.3. The final propagating step (equation 4), that returns the chain-propagating electron from product radical anion to another molecule of substrate, is essential if a chain reaction is to continue.

Several alternative processes can impede or dramatically alter the overall substitution reaction. First, if the product radical anion, $ArNu^{-\cdot}$, is significantly more stable than the radical anion of the substrate, $ArX^{-\cdot}$, then the electron transfer step in equation (4) can become rate limiting and the reaction may become very sluggish. This may be one of the contributing factors towards the absence of examples of nitrite ion acting as a nucleophile in aromatic $S_{\mathrm{RN}}1$ reactions. It is known from other studies that $NO_2^{-}$ is readily trapped by aryl radicals,[36,37] so failure of the associative step, (equation 3; with $Nu^{-} = NO_2^{-}$) cannot account for lack of reaction. The nitroarene radical ion, $ArNO_2^{-\cdot}$, formed is relatively too stable and so propagation of the chain is stopped. Second, the radical anion, $ArNu^{-\cdot}$, can fragment (*i.e.* dissociate with breaking of a bond other than the newly formed Ar—Nu bond), rather than transferring an electron to ArX. The mode of fragmentation depends on the nature of the aryl group, including the attached substituents, and the nature of the group Nu. Radical ions bearing a second nucleofugic group can dissociate to give new aryl radicals whose subsequent reaction leads to overall disubstitution, whereas dissociation within the Nu substituent can give rise to alternative aryl radicals or to unproductive radicals that terminate the radical chain. Two examples will suffice to show how poor yields of the desired products result when these processes take place. The reaction of *p*-iodoanisole with $PhSe^-$ ion in liquid ammonia, in addition to the desired product (**1**) gives the selenides (**2**) and (**3**; equation 7). This mixture of products is explicable in terms of the reversible association/dissociation sequence given in equation (8), in which two different cleavages of the aryl–Se bond compete with the electron transfer propagation step.[35] This phenomenon, leading to 'aryl scrambling' also occurs with arsenic, antimony and tellurium derivatives (see Sections 2.2.3.2.5 and 2.2.3.3.2). As the result of a quite different cleavage, reaction of bromobenzene with $^-CH_2CN$ provoked by potassium metal, gives a poor yield of phenylacetonitrile, and gives rise to appreciable amounts of 1,2-diphenylethane (**4**; equation 9).[38] When the same reaction was carried out under photostimulation (less reducing reaction conditions), (**4**) is still the major product, phenylacetonitrile remains a minor product, and small amounts of 1,1,2-triphenylethane and 1,1,2,2-tetraphenylethane are detected.[39,40] Fragmentation of the initially formed radical anion of phenylacetonitrile to give cyanide ion and benzyl radicals (equation 10) explains the formation of (**4**) (by dimerization) and toluene (electron transfer/protonation). Similar behavior is shown by the intermediate radical anions formed in reaction of aryl radicals with *aci*-nitronate and alkanethiolate ions. The occurrence of alternative fragmentation processes in $S_{\mathrm{RN}}1$ reactions has been reviewed by Rossi.[41]

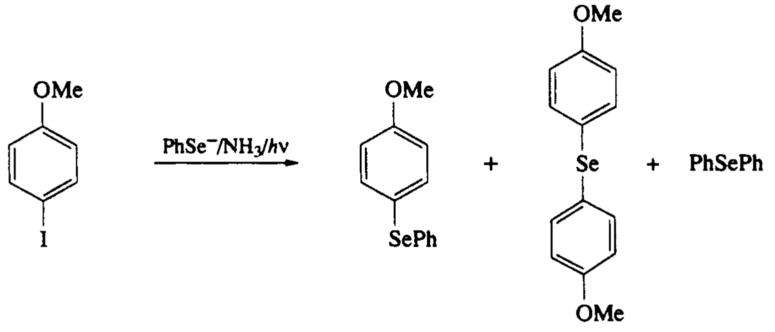

(7)

(**1**) 25% (**2**) 19% (**3**) 20%

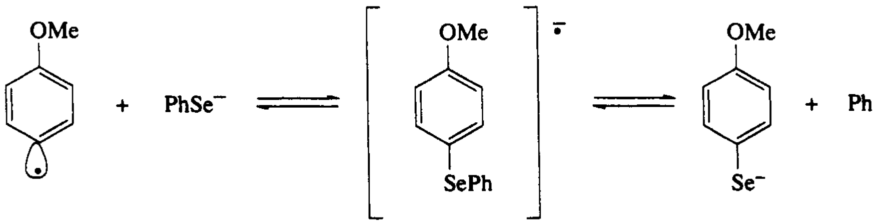

(8)

$$PhBr + {}^-CH_2CN \xrightarrow{K/NH_3} \underset{5\%}{PhCH_2CN} + \underset{(4)\ 14\%}{(PhCH_2)_2} + \underset{3\%}{Ph_2CH_2} + \underset{26\%}{PhMe} + \underset{43\%}{PhH} \qquad (9)$$

$$Ph\bullet + {}^-CH_2CN \longrightarrow [\,PhCH_2CN\,]^{\bar{\bullet}} \longrightarrow PhCH_2\bullet + CN^- \qquad (10)$$

Termination steps in $S_{\mathrm{RN}}1$ reactions compete with the propagation steps and, although these processes have aroused considerable mechanistic and theoretical speculation (see Chapter 9 in ref. 18), their effects, with several important exceptions, are not significant. For example the self-coupling of aryl radicals (equation 11) does not appear to occur under the conditions used for the $S_{\mathrm{RN}}1$ reaction. One potentially disruptive termination step is reduction of the intermediate aryl radical (equation 6). The source of the reducing electron can be a dissolving metal (or solvated electron), one of the radical anion intermediates in the reaction ($ArNu^{-\bullet}$ or $ArX^{-\bullet}$), an electrode, or the nucleophile itself. These termination processes can normally be minimized by suitable choice of reaction conditions. In the rare cases of reduction of the intermediate radical by the nucleophile (equation 12) competing successfully with the associative propagating step (equation 3) the $S_{\mathrm{RN}}1$ reaction is doomed to failure. This phenomenon was used to explain the failure of *p*-nitrophenyl and *p*-cyanophenyl radicals to couple with *aci*-nitronic ions.[36] Another termination reaction is abstraction of a hydrogen from solvent (Solv-H; equation 13) to give an aromatic hydrocarbon and a solvent-derived radical, which invariably is nonchain propagating. Although rate constant data for abstraction of hydrogen atoms from DMSO, DMF and acetonitrile indicated that these solvents might lead to interference with the successful operation of $S_{\mathrm{RN}}1$ reactions,[42] the abstraction of hydrogen from these dipolar aprotic solvents, or from the much poorer hydrogen atom donor liquid ammonia, most commonly used in these reactions, does not appear to interfere significantly. One process, which sometimes limits the scope of the $S_{\mathrm{RN}}1$ reaction, involves the reaction of aryl radicals with enolate ions having abstractable β-hydrogens. The classic example of this side reaction occurs in the reaction of phenyl radical (from iodobenzene) with the enolate ion (**5**) from diisopropyl ketone, as outlined in Scheme 1. Hydrogen abstraction from the enolate ion by the phenyl radical competes with association of the phenyl radical with (**5**), and gives the relatively stable (and hence chain-terminating) radical anion (**6**). Disproportionation of (**6**) into the dianion (**7**) and the α,β-unsaturated ketone (**8**), followed by protonation of (**7**) by the solvent, regenerates the enolate ion (**5**). Michael addition of (**5**) to (**8**) gives the by-product (**9**) in yields as high as 20%.[43] Similar abstraction processes occur in intramolecular reactions, and the work of Semmelhack and coworkers with the deuterated ketone (**10**) showed that β-hydrogen (deuterium) abstraction was occurring by isolation of the deuterated α,β-unsaturated ketone (**11**).[44,45] Another significant termination phenomenon is fragmentation of the radical anion of the intended product, $(\text{ArNu}^{-}\cdot)$, to give an unproductive (nonchain-propagating) radical, *e.g.* the benzyl radical (equation 10).

$$2\text{Ar}\bullet \longrightarrow \text{Ar—Ar} \tag{11}$$

$$\text{Ar}\bullet + \text{Nu}^{-} \longrightarrow \text{Ar}^{-} + \text{Nu}\bullet \tag{12}$$

$$\text{Ar}\bullet + \text{Solv-H} \longrightarrow \text{ArH} + \text{Solv}\bullet \tag{13}$$

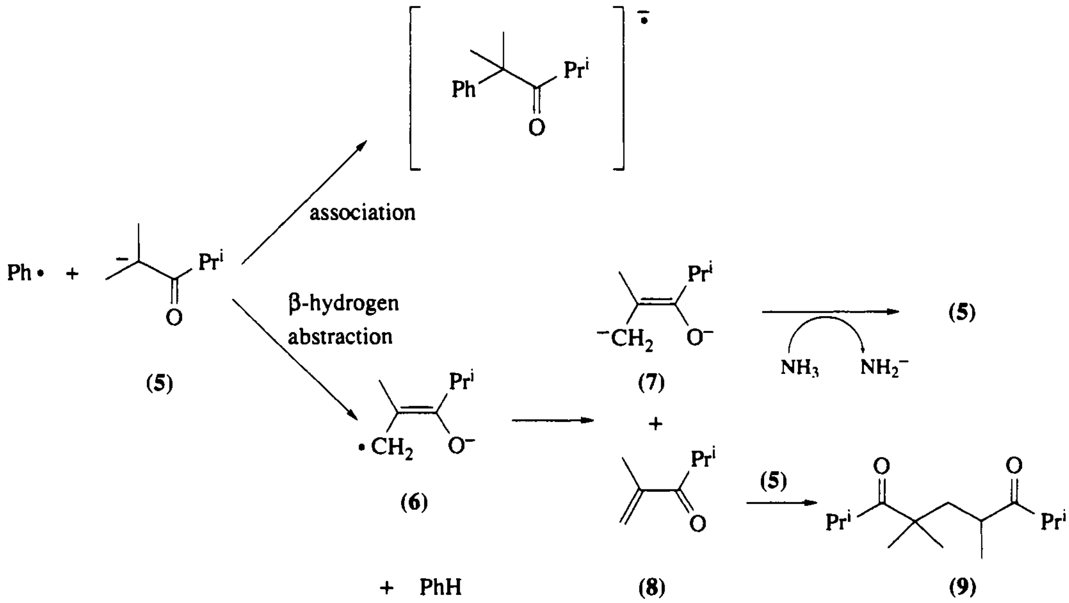

**Scheme 1**

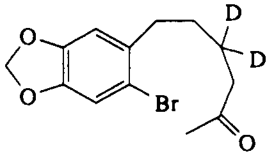

(**10**)

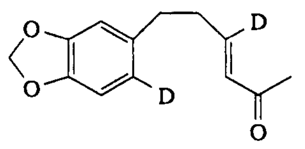

(**11**)

Inhibition of the $S_{RN}1$ reaction by a number of substances such as 2-methyl-2-nitrosopropane, tetraphenylhydrazine, oxygen, di-*t*-butyl nitroxide, and *m*- and *p*-dinitrobenzene has been demonstrated, but clearly for synthetic purposes all such substances must be excluded from the appropriate reactions. One important practical consequence is that all $S_{RN}1$ reactions should be carried out under an inert atmosphere to avoid inhibition by oxygen; nitrogen or argon are generally used. Anomalous cases are known, however, where oxygen did not affect the reaction rate or in fact, accelerated the reaction. Coupling of phenyl radicals with $(EtO)_2PO^-$ appears to be too rapid to be affected by oxygen.[21] The reaction of iodobenzene with $K^+ \ ^-CH_2COBu^t$ in DMSO in the dark was actually accelerated by oxygen, but no useful yield of the expected $S_{RN}1$ product was obtained since it was destroyed by oxygen under the reaction conditions.[26]

### 2.2.2.2 Choice of Solvents

The number of solvents that have been used in $S_{RN}1$ reactions is somewhat limited in scope, but this causes no practical difficulties. Characteristics that are required of a solvent for use in $S_{RN}1$ reactions are that it should dissolve both the organic substrate and the ionic alkali metal salt ($M^+Nu^-$), not have hydrogen atoms that can be readily abstracted by aryl radicals (*cf.* equation 13), not have protons which can be ionized by the bases (*e.g.* $NH_2^-$ or $Bu^tO^-$ ions), or the basic nucleophiles ($Nu^-$) and radical ions ($RX^{-\cdot}$ or $RNu^{-\cdot}$) involved in the reaction, and not undergo electron transfer reactions with the various intermediates in the reaction. In addition to these characteristics, the solvent should not absorb significantly in the wavelength range normally used in photostimulated processes (300–400 nm), should not react with solvated electrons and/or alkali metals in reactions stimulated by these species, and should not undergo reduction at the potentials employed in electrochemically promoted reactions, but should be sufficiently polar to facilitate electron transfer processes.

A comparison of the suitability of solvents for use in $S_{RN}1$ reactions was made in benzenoid systems[46] and in heteroaromatic systems.[47] The marked dependence of solvent effect on the nature of the aromatic substrate, the nucleophile, its counterion and the temperature at which the reaction is carried out, however, often make comparisons difficult. Bunnett and coworkers[46] chose to study the reaction of iodobenzene with potassium diethyl phosphite, sodium benzenethiolate, the potassium enolate of acetone, and lithium *t*-butylamide. From extensive data based on the reactions with $K^+ \ (EtO)_2PO^-$ (an extremely reactive nucleophile in $S_{RN}1$ reactions and a relatively weak base) the solvents of choice (based on yields of diethyl phenylphosphonate, given in parentheses) were found to be liquid ammonia (96%), acetonitrile (94%), *t*-butyl alcohol (74%), DMSO (68%), DMF (63%), DME (56%) and DMA (53%). The powerful dipolar aprotic solvents HMPA (4%), sulfolane (20%) and NMP (10%) were found not to be suitable. A similar but more discriminating trend was found in reactions of iodobenzene with the other nucleophilic salts listed above.[46] Nearly comparable suitability of liquid ammonia and DMSO have been found with other substrate/nucleophile combinations. For example, the reaction of *p*-iodotoluene with $Ph_2P^-$ (equation (14) gives 89% and 78% isolated yields (of the corresponding phosphine oxide) in liquid ammonia and DMSO respectively.[48]

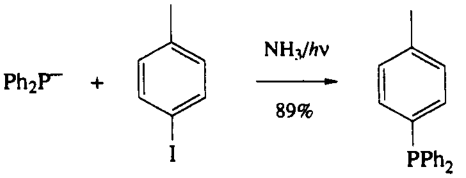

(14)

As an example of the dangers associated with interpreting solvent effects in these reactions, it was found in reactions involving $K^+ \ ^-CH_2COMe$ with 2-chloroquinoline, that liquid ammonia gave the most rapid reaction and the best yields (at –33 °C) and that the rate of consumption of 2-chloroquinoline at ambient temperature increased with solvent in the order benzene ≈ ether << DME < THF < DMF < DMSO. Moon and Wolfe wrote that, 'however, for preparative purposes, the more polar solvents DMF and especially DMSO, appear to offer no advantages over THF, in which substitution proceeds at very respectable rates with a minimum of side reactions'.[47] These same authors found in the same study, however, that iodobenzene failed to react in THF with $K^+ \ ^-CH_2COMe$. The reaction of bromobenzene with $K^+ \ ^-CH_2COBu^t$, as shown in equation (15), after 80 min gave the substitution product (**12**) in yields of 96% (liquid ammonia, –33 °C), 84% (DMSO, 35 °C) and 57% (DMF, 35 °C) and failed completely in

THF.[45] To confuse the situation further, THF is found to be a quite appropriate solvent for cyclization reactions in which the enolate ion from an amide attacks a benzene ring intramolecularly.[49,50]

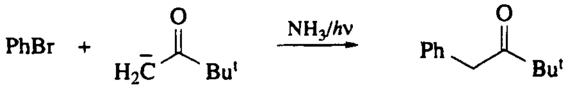

**(12)**

(15)

Aprotic solvents, such as DMSO and acetonitrile generally give good results, and the latter appears to be the solvent of choice (with appropriate supporting electrolytes) in electrochemically initiated reactions.

Protic solvents (other than ammonia) are generally unsuitable on account of their high acidity relative to that of most nucleophiles used in $S_{RN}1$ reactions. Water was found to be unsuitable, even with water-soluble substrates and weakly basic nucleophiles.[46] The reported reaction of halobenzenes with $PhO^-$ in 50% aqueous $Bu^tOH$, catalyzed by sodium amlagam,[51] was shown to be unreproducible.[52] Methanol was used as solvent in an unusual reaction, believed to be occurring by the $S_{RN}1$ mechanism and catalyzed by $MeO^-$ at 147 °C, in which $PhS^-$ replaces the bromine in 3-bromoisoquinoline.[53] Other protic solvents have been reported to give acceptable yields in $S_{RN}1$ reactions, but on the whole these involve substrates which give good yields in other solvents as well.

In general, from among the protic solvents, only liquid ammonia (the first used)[1] is particularly useful, and is still used more than any other solvent despite the low temperature at which reactions have to be carried out (b.p. −33 °C) and the fact that solubilities of some aromatic substrates and salts ($M^+Nu^-$) are poor. Ammonia has the added advantage of being easily purified by distillation, being an ideal system for production of solvated electrons, and has very low reactivity with basic nucleophiles and radical anions, and aryl radicals. Also, poor solubilities can sometimes be ameliorated by use of cosolvents such as THF. In addition it can be used as a solvent for the *in situ* reductive generation of nucleophiles such as $ArSe^-$ and $ArTe^-$ ions, *e.g.* the formation of $PhTe^-$ from diphenyl ditelluride (equation 16).[54,55]

$$PhTePh + 2Na \xrightarrow[>80\%]{NH_3} 2Na^+PhTe^- \qquad (16)$$

### 2.2.2.3 Nature of the Nucleofuge

Practical considerations, namely the ready availability of halogenated aromatic compounds, normally lead to the use of a halogen as the nucleofuge (X) in aromatic $S_{RN}1$ reactions (see equation 2). Other leaving groups have been used, however, and the best comparative lists are given by Rossi and Bunnett, who studied the reductive cleavage of various aromatic substrates (ArX) with potassium metal in liquid ammonia, in the presence of the enolate from acetone.[56,57] The suitability of groups as nucleofuges was measured by the overall production of phenylacetone (**13**), together with its reduction product (**14**) and 1,1-diphenylacetone (**15**; equation 17). Unsuitable nucleofuges gave predominant formation of benzene, formed by the alternative cleavage/protonation sequence (equation 18), failed to react or formed other products. In addition to the halogens, other nucleofuges used in the above study[56,57] and other work, with varying degress of success, include: the $(EtO)_2(P{=}O)O$,[33,38,58,59] PhO,[1,58] $Me_3N^+$,[38,60] $Ph_2S^+$,[58] and $PhI^+$ groups. Although ArS and ArSe groups were used as nucleofuges in the earlier studies,[56–58,61] the use of these groups is not recommended since fragmentation of radical anions of the form $Ar—Y—Ar^{-\cdot}$ (Y = Se, Te) can introduce the problem of aryl scrambling (*e.g.* equation 8).[41] The reactions of arenediazonium ions with some nucleophiles almost certainly occur by a mechanism which has many of the characteristics of the $S_{RN}1$ reaction. These reactions will not be discussed in detail here, but two recent synthetic routes which present convenient preparations of arenecarbonitriles[62] and diaryl sulfides[63,64] and involve intermediacy of arenediazo sulfides, are summarized in Scheme 2. The radical anion of the diazo sulfide is believed to be formed and to dissociate as shown in equations (19) and (20)[62,64] to give aryl radicals which are trapped by either $CN^-$ and/or arenethiolate ions.

The reactivity sequence in the the aryl halides, in decreasing order, has been found to be ArI > ArBr > ArCl >> ArF (with the same aryl group) and this is believed to result, among other factors, from the well-known greater nucleofugicity of the halogens in the sequence $I^- > Br^- > Cl^- >> F^-$, differences in reduction potentials of the corresponding substrates, and solvation effects (see Chapter 8 in ref. 18). Typical examples confirming the above reactivity order are found in the reaction of the halobenzenes with

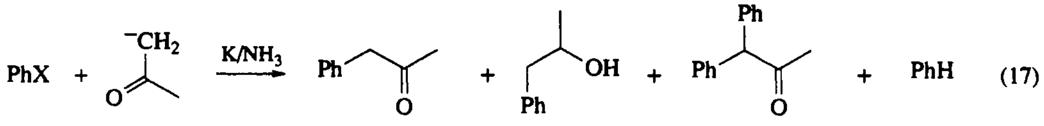

**(13)** **(14)** **(15)** (17)

$$\mathrm{PhX} \xrightarrow{\mathrm{K/NH_3}} \mathrm{PhX}^{-\bullet} \longrightarrow \mathrm{Ph}^- + \mathrm{X}^\bullet \xrightarrow{\mathrm{NH_3}} \mathrm{PhH} \tag{18}$$

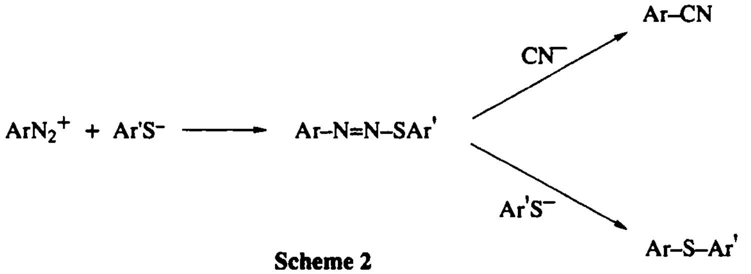

**Scheme 2**

$$\mathrm{Ar{-}N{=}N{-}S{-}Ar'} + \mathrm{Nu}^- \longrightarrow [\mathrm{Ar{-}N{=}N{-}S{-}Ar'}]^{-\bullet} + \mathrm{Nu}^\bullet \tag{19}$$

$$[\mathrm{Ar{-}N{=}N{-}S{-}Ar'}]^{-\bullet} \longrightarrow \mathrm{Ar}^\bullet + \mathrm{N_2} + \mathrm{Ar'{-}S}^- \tag{20}$$

$^-CH_2COMe$,[58] $^-CH_2CN$[40] or, in competitive studies, with $^-CH_2COBu^t$ and $(EtO)_2PO^-$,[32] and in reactions of $^-CH_2COMe$ with 2-bromo-, 2-chloro- and 2-fluoro-pyridine.[65] Bunnett and coworkers have identified a peculiar leaving group effect in the reaction of halobenzenes with the enolate ion of acetone, in reactions stimulated by solvated electrons. They found that both the ratio of (**13**):(**14**) and the amount of benzene formed in the reaction given in equation (17) depended on the halogen, and both decreased as the halogen was changed from fluorine through chlorine and bromine to iodine. This phenomenon was interpreted as resulting from competition between rate of advance of solvated electrons through the solvent to the reactive intermediates and the rate of decomposition of the intermediate radical anions, $ArX^{-\cdot}$ (X = halogen).[66,67] This observation is of more than mechanistic interest, since it indicates that the aryl iodides (or bromides) are usually the substrates of choice in benzene derivatives because, not only are the reactions faster, but, in the case of reactions stimulated by solvated electrons, production of by-products is minimized. On account of the greater degree of reactivity in some heteroaromatic and polycyclic aromatic substrates, the use of aryl chlorides usually gives quite satisfactory results.

An exception to the above generalizations appears to be in reactions which are induced by electrochemical means. In cases where the intermediate radical anion, $ArX^{-\cdot}$, decomposes so rapidly that the aryl radical produced is still near the reducing electrode, a second electron transfer can take place with production of the aryl anion (see equation 6). Clearly a less nucleofugic halogen is preferable under these conditions. As confirmation of this principle, in the reaction of 2-halogenoquinolines with $PhS^-$ and $PhCOCH_2^-$ ions the best electrochemically induced substitution reactions take place when the halogen is chlorine, less substitution occurs with bromine and significant, if not predominant reduction to give quinoline, occurs with the iodo compound.[68] The special selectivity problems which arise when a substrate has two nucleofuges attached is discussed in Section 2.2.2.4.2.

### 2.2.2.4 Nature of the Aromatic Substrate

The generalizations in the following discussion are based on reports of reactions carried out under ideal conditions, *i.e.* liquid ammonia or DMSO as solvent, photostimulation rather than 'dark' reactions, most appropriate nucleofuge, *etc.* The range of nucleophiles which can be used are itemized in Section 2.2.3, which also contains several extensive tables in which the range of substrates can be clearly seen. It must be noted, however, that reactions which proceed in high yield with one nucleophile may fail or proceed inefficiently with another if the nucleophile is incompatible with substituents on the aromatic substrate.

### 2.2.2.4.1 Benzene rings with one nucleofuge

The $S_{RN}1$ on benzene rings with only one nucleofuge, the best normally being either iodine or bromine, is an excellent method for replacing the nucleofuge without interference from *cine* substitution processes. The unsubstituted benzene ring reacts readily with most nucleophiles, but there are now sufficient examples of reactions which fail with the unsubstituted ring, but succeed when the ring has particular substituents, to modify the earlier generalization that there is no requirement for activation by substituents.[4] Bunnett and coworkers have summarized the effect of *ortho* substituents on $S_{RN}1$ reaction with $Bu^tCOCH_2^-$ and $(EtO)_2PO^-$ ions.[69] They showed that a wide range of *o*-substituents and, in an earlier study,[70] a large number of substituents in general, can be tolerated without deleterious effect. Beugelmans and coworkers, have more recently observed that *o*-, *m*- or *p*-cyano, *o*-carbonyl, *o*-methoxy or *o*-amino functions have a substantial facilitating effect on the reaction of halobenzenes with nucleophiles such as phenoxides, or the enolate ions of aldehydes and β-dicarbonyl compounds and that reactions with these nucleophiles generally fail to give substitution products without these specific substituents.[71–75]

In general, electron-donating groups such as alkyl, alkoxy or aryloxy groups do not interfere, with good results being obtained even with two *o*-methyl groups (equation 21).[70] Moderate steric hindrance does not impede substitution, but one $Bu^t$ or two $Pr^i$ groups *ortho* to the nucleofugic halogen reduce reactivity of the aromatic substrate and lead to substantial replacement of the halogen by hydrogen.[70] Ionized phenolic groups ($—O^-$) do prevent reaction,[70] but, contrary to the earlier report,[70] the dimethylamino group does not interfere.[76] *o*-Amino groups have the special facilitating effect discussed above, but *m*- and *p*-iodoanilines also react readily with $(EtO)_2PO^-$ ion.[77]

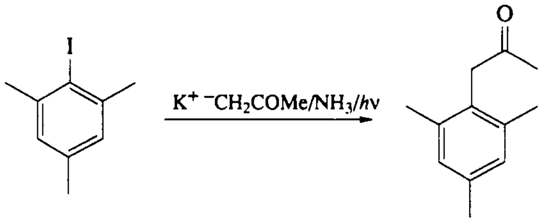

(21)

Electron-withdrawing groups, on the whole, do not interfere with the reaction as long as they do not react with the nucleophile, and, as mentioned above, facilitate the reactions with certain nucleophiles. This is also apparent in reactions carried out under electrochemical stimulation. Examples of substitution reactions on benzene rings bearing ionized carboxy ($—CO_2^-$), carbonylamino, acetyl, benzoyl, formyl and cyano groups are to be found in the references cited and the tables presented in Sections 2.2.3 and 2.2.4. There are also numerous examples of electrochemically stimulated reactions where benzoyl,[28,29,31,78–81] cyano[30,78,80,82–86] and *p*-acetyl groups[87] are present on the benzene ring.

The nitro group, which most successfully facilitates both the $S_NAr$ reaction and the aliphatic version of the $S_{RN}1$ reaction, appears to prevent the aromatic $S_{RN}1$ reaction under nucleophile-initiated conditions,[39,70,77] with the possible exception of the reaction of *o*-iodonitrobenzene with $^-CH_2COBu^t$.[69]

Aromatic substrates with a $CF_3$ group either *ortho* or *para* to the halogen, on reaction with the the enolates from acetone or pinacolone, undergo reactions in which HF is eliminated from the initially formed $S_{RN}1$ product.[88] The normal substitution product is obtained, however, on treatment of *m*-$CF_3$-iodobenzene with ketone enolates[70,88] or on reaction of *o*-$CF_3$-iodobenzene with $(EtO)_2PO^-$ ion.[88]

### 2.2.2.4.2 Benzene rings with two nucleofuges

When the aromatic ring bears two nucleofugic groups, the decision as to which of the two is replaced or whether both are replaced depends on the nature of the two groups, their relative positions (*ortho, meta* or *para*) and the reaction conditions. The dependence on the above factors is best explained in terms of dissociation of the intermediate anion radical, $X—Ar—Y^{-\cdot}$, with two nucleofuges X and Y, and the subsequent reactions shown in equations (22)–(26). Initially, the better nucleofuge ($Y^-$), departs from the first-formed radical anion, as shown in equation (22), and consideration of all reactions with dihalobenzenes results in affirmation of the reactivity sequence $I^- > Br^- > Cl^- >> F^-$. In cases where one of the two halogens is fluorine only monosubstitution occurs (*e.g.* equation 27).[70,89–92] These results show that the C—F bond does not cleave in either equation (22) or (24). With the other halogens, the sequence of reactions in equations (22), (23) and (24) and (26) lead to disubstituted products, whereas the reactions in equations (22), (23) and (25) lead to monosubstituted products. The product distribution is determined by the relative rates of the reactions in equations (24) and (25).

For diiodo compounds the dissociation of the radical anion $\mathrm{IArNu}^{-\bullet}$ appears always to be faster than the electron transfer step (equation 25) and disubstitution invariably takes place.[89,91,92] Bromoiodo and dibromo compounds behave similarly to the diiodo derivatives, with trace amounts of the monosubstituted monobromo compounds being found among the reaction products, but only when the halogens are in a *meta* relationship.[91,93] *o*-Dibromobenzene, for example, reacts readily with $^{-}\mathrm{CH_2COBu^t}$ to give the disubstituted product (**16**) in 62% yield with no evidence of formation of the monosubstituted product.[94] Similarly, with $\mathrm{MeCOCH_2^-}$, no monosubstituted product is isolated, but the initially formed disubstituted product (**17**) undergoes an internal aldol condensation to give a 64% yield of a mixture of the compounds (**18**) and (**19**) and also undergoes a further $S_{\mathrm{RN}}1$ reaction with *o*-dibromobenzene to give (**20**) in 5% yield.[94]

$$\mathrm{XArY}^{-\bullet} \longrightarrow \mathrm{XAr}\bullet + \mathrm{Y}^- \tag{22}$$

$$\mathrm{XAr}\bullet + \mathrm{Nu}^- \longrightarrow \mathrm{XArNu}^{-\bullet} \tag{23}$$

$$\mathrm{XArNu}^{-\bullet} \longrightarrow \bullet\mathrm{ArNu} + \mathrm{X}^- \tag{24}$$

OR

$$\mathrm{XArNu}^{-\bullet} + \mathrm{XArY} \longrightarrow \mathrm{XArNu} + \mathrm{XArY}^{-\bullet} \tag{25}$$

$$\bullet\mathrm{ArNu} + \mathrm{Nu}^- \longrightarrow \mathrm{ArNu_2}^{-\bullet} \tag{26}$$

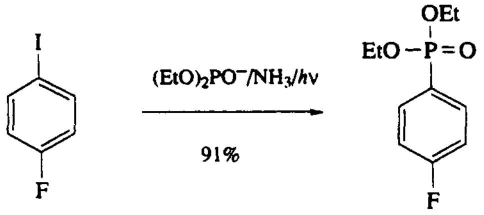

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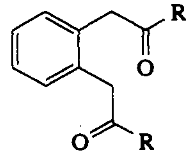

(**16**) R = Bu$^t$

(**17**) R = Me

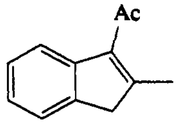

(**18**)

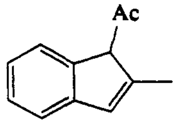

(**19**)

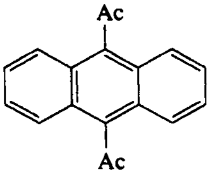

(**20**)

Chloroiodo compounds give disubstituted products when the halogens are in an *ortho* or *para* relationship, with trace amounts of monosubstituted products,[89,90,92] whereas with *m*-chloroiodobenzene the ratio of monosubstituted to disubstituted product depends on the nucleophile. With $\mathrm{(EtO)_2PO^-}$ ion, the monosubstituted product (**21**) can be isolated in 89% yield[91,92] and the disubstituted product (**22**) is formed in only 4% yield, whereas with $\mathrm{PhS^-}$ the disubstituted product (**23**; 91%) is by far the major product.[90] This difference in behavior has been attributed to stabilization, by the electron-withdrawing $\mathrm{P(O)(OEt)_2}$ group, of the intermediate radical anion formed in the reaction with $\mathrm{(EtO)_2PO^-}$, allowing the intermediate to undergo the electron transfer process in equation (25) in preference to the fragmentation reaction in equation (24).[92] By way of contrast, the *m*-chloroiodo relationship in some 5-chloro-7-iodoquinolines (both of the halogens are on the benzene rather than the pyridine ring), results in initial, almost exclusive substitution of the iodine by sulfur-, carbon- and phosphorus-based nucleophiles.[95–97] *o*-Dihalobenzenes (**24**) and (**25**) when treated with the dithiolate (**26**) give good yields of cyclic product (**27**; equation 28), and no monosubstituted product could be detected.[98]

Other substrates, in which one of the two nucleofuges is not a halogen, have been studied. Haloarenediazo sulfides on treatment with arenethiolate ions give substantial formation of bis(arylthio)arenes except that the monofluorophenyl sulfide is produced when the halogen is fluorine,[64] and *p*-iodophenyltrimethylammonium ion, on treatment with benzenethiolate ion in liquid ammonia, gives *p*-bis(phenylthio)benzene in 95% yield.[90]

Benzene derivatives with two nucleofuges have been used in the preparation of polymeric materials with varying degrees of success. Poly(1,4-phenylene sulfide) has been prepared by condensation of *p*-dichlorobenzene with sodium sulfide,[99,100] and in a related process, diazonium ions have been shown to initiate the polymerization of *p*-halobenzenethiolate ions.[101] In a preliminary study, poorly characterized polymers were obtained from reaction of equimolar amounts of *p*-dihalobenzenes and the enolate ions from ketones in the presence of excess base. When an excess of the ketone enolates was used, the normal *p*-disubstituted derivatives were formed.[102]

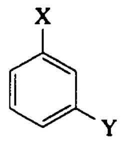

(21) $X = Cl$ ; $Y = P(O)(OEt)_2$
(22) $X = Y = P(O)(OEt)_2$
(23) $X = Y = SPh$

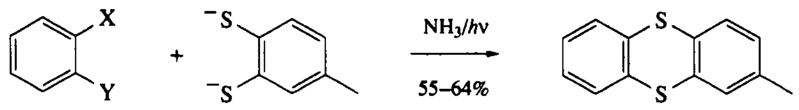

(24) $X = Cl, Y = Br$
(25) $X = Y = I$
(26)
(27)

(28)

### 2.2.2.4.3 Polycyclic arenes

The extension of the $S_{RN}1$ reaction to polycyclic aromatic substrates has been limited almost entirely to the simple halogenated derivatives (see tables and references in Section 2.2.3). The substrates used include 4-halobiphenyls, 1- and 2-halonaphthalenes, 9-bromoanthracene and 9-bromophenanthrene. There appears to be only one report on the effect of additional substituents on these ring systems; the ionized phenolic group in 1-bromo-2-naphthoxide causes substitution of the bromine by $^-CH_2CN$ to be completely supplanted by a reductive process.[39]

The increased stability of the radical anions of the products ($ArNu^{-\cdot}$), when the aryl moiety is a polycyclic system, has important practical consequences in that intermediates, which in the benzene series dissociate and give fragmented or rearranged products, are now sufficiently stable to allow chain-propagating electron transfer to take precedence.[41] The successful reaction of 4-chlorobiphenyl with $^-CH_2CN$ (equation 29),[39] for example, contrasts with that of bromobenzene (see equations 9 and 10),[38] and other halobenzenes.[38–40] Similar reduction in the occurrence of fragmentation processes and 'aryl scrambling' is seen when the benzene ring is replaced by polycyclic systems in reactions with alkanethiolate,[103] $ArSe^-$ and $ArTe^-$ ions,[54] and $Ph_2As^-$ and $Ph_2Sb^-$ ions.[25] Thus, butanethiolate gives a poor yield of substitution product (14%) with iodobenzene, but the reaction in the naphthalene system proceeds well (equation 30).[103]

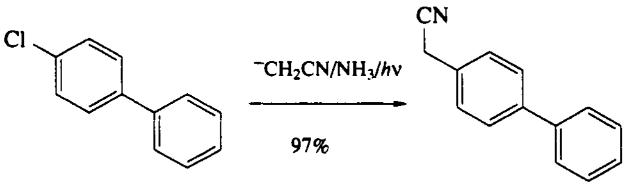

(29)

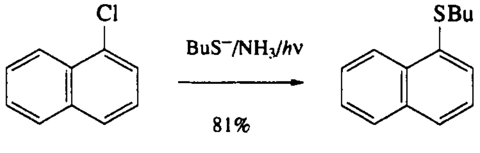

(30)

### 2.2.2.4.4 Heteroaromatic compounds

Numerous halogenated heteroaromatic substrates undergo $S_{RN}1$ reactions with a variety of nucleophiles (see tables and references in Section 2.2.3 for specific examples). The substrates used to date include all four 2-halopyridines, 3-bromo- and 3-iodo-pyridine, 4-bromopyridine, 2-chloro-, 2-bromo- and 2-iodo-quinoline, 3-bromoquinoline, 3-bromoisoquinoline, 2-chloropyrimidine, 2-chloropyrazine, 2-chloroquinoxaline, 4-chloroquinazoline, 2-chloro-, 2-bromo- and 2-iodo-thiophene, 3-bromothiophene, 2-chlorothiazole, 2-bromothiazole and 9-alkyl-6-iodopurines. Although the earlier studies were restricted to these monosubstituted derivatives (2-chloroquinoline often being used as a model system), more recent studies indicate that a similar range of substituents to that tolerated in the benzene system can be situated on the heteroaromatic ring. *o*-Substituents such as aryl, alkyl, alkoxy, fluoro, amino and functionalized amino, acyl, cyano and carbonylamino groups do not interfere. Alkyl and alkoxy groups in other positions similarly do not have a deleterious effect on reactivity. It would appear that the nitrogen-containing, π-deficient heterocycles give the best results, with yields from π-excessive substrates (*e.g.* halothiophenes) generally being poor. 2-Halothiazoles (π-excessive substrates) do react but $S_NAr$ processes take place with some nucleophiles. Dihalopyridines behave in similar fashion to the benzene derivatives. Disubstituted derivatives are formed in good yields in the reaction of the 2,3-, 2,5-, 2,6- and 3,5-dihalo systems with $^-CH_2COBu^t$ (equation 31),[65,104] but with the anion of phenylacetonitrile mixtures of mono- and di-substituted products result.[104] It is noteworthy that under different reaction conditions, treatment of 2,6-dibromopyridine with the anion of 2-pyridylacetonitrile gives only the monosubstitution product in a reaction whose mechanism has not been delineated.[105]

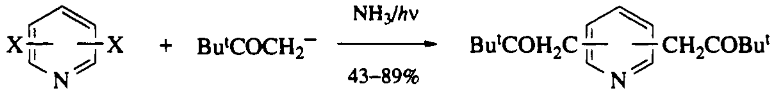

(31)

The relative reactivity of heteroaromatic compounds and their reactivity relative to the benzene system have not been extensively studied, but the reactivity sequences (decreasing) 2-chloroquinoline > 2-bromopyridine > bromobenzene,[65] 2-bromopyridine > 3-bromopyridine > 4-bromopyridine[65] and the reactivity order I > Br > Cl > F[65,106] allow a relative assessment of reactivity to be made. The relative ease of displacement of chlorine in differing environments is clearly shown in the dichloro compounds (**28**) and (**29**), in which the indicated chlorines are cleanly and preferentially replaced.[104]

The trend observed with the polycyclic hydrocarbons (see preceding section), namely that the product radical anions (ArNu$^{-\cdot}$) are more stable than those derived from the simple benzene analogs, is even more evident with the heteroaromatic substrates and, as a consequence, fragmentation processes are minimized.[41] For example, 2-chloroquinoline is the only substrate of many studied to undergo a substitution reaction with $PhCH_2S^-$ ion without fragmentation of the benzyl–S bond,[103] and to react with diphenylarsenide ion without scrambling of the aryl moieties.[25]

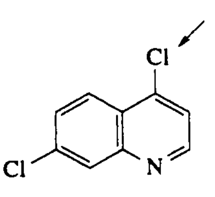

**(28)**

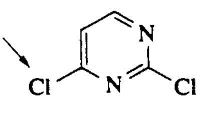

**(29)**

### 2.2.2.4.5 Vinylic compounds

The report by Bunnett and coworkers[107] of substitution of halide by $MeCOCH_2^-$ or $PhS^-$ ions in vinyl bromides or iodides appears to be the only synthetic application of the $S_{RN}1$ reaction at vinylic sites. The reactions, particularly with benzenethiolate ion, are slower than those of aryl halides and the yields are not as good. Tautomers or mixtures of products result in the reactions with $MeCOCH_2^-$ (*e.g.* equation 32).

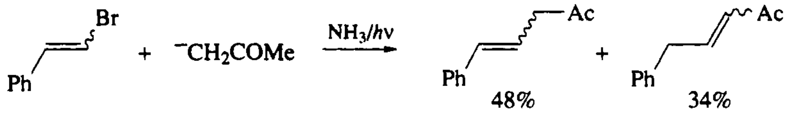

(32)

## 2.2.3 SUBSTITUTIONS BY THE $S_{RN}1$ REACTION

The $S_{RN}1$ reactions are grouped according to the attacking element in the nucleophilic species, *i.e.* according to the new aryl–element bond being formed. These reactions are convenient one-step substitution reactions leading from aryl halides (or arenes with appropriate nucleofuges) to a variety of classes of aromatic compounds.

With the majority of nucleophiles, regiochemical problems resulting from ambident behavior do not present any practical difficulties. Theoretical considerations indicate that in the key bond-forming reaction (equation 3) the aryl radical should attach itself to the site of greatest basicity.[108] This theory is consistent with the observation that enolates (including aryloxides) do not give rise to *O*-arylation products. With aryloxides, arylation *ortho* and *para* to the ionized hydroxy occurs (see Section 2.2.3.1.4). Ambident behavior of anions in aromatic $S_{RN}1$ reactions is very rare, and is observed in the arylation of the delocalized carbanions of conjugated alkenes, arylation of arylamides, where *o*- and *p*-attack usually predominates over *N*-attack,[109] and to a trivial extent in the heteroarylation (in the *o*- and *p*-positions on the benzene ring) of the α-carbanion from phenylacetonitrile. An example of this latter minor irritation is seen in the reaction of 4-bromopyridine with $^-CH(Ph)CN$, which gives 3% of (**30**) and 6% of (**31**).[110] The regiochemistry of the *C*-arylation of ketones, which form different enolate ions is discussed in Section 2.2.3.1.1.

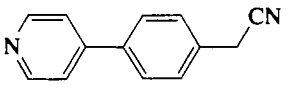

(**30**)

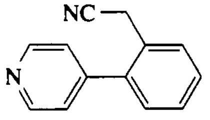

(**31**)

The preparation of cyclic compounds is discussed separately in Section 2.2.4.

### 2.2.3.1 Formation of C—C Bonds, Carbon-based Nucleophiles

### *2.2.3.1.1 Preparation of α-aryl ketones*

The reactions between haloarenes and ketone enolates are by far the most extensively studied among $S_{RN}1$ reactions, and represent one of the few generally applicable methods for preparation of α-aryl ketones. The extensive list of the aromatic substrates and the ketones, from which the enolates are derived, together with the yields of α-arylated or α-heteroarylated ketones are collected in Tables 1 and 2 respectively. Most of these examples are taken from reactions which have been performed under photostimulated conditions, although several take place spontaneously ('in the dark'). Most of the reactions were carried out in liquid ammonia, and the enolate ion was generated from the ketone by treatment with an appropriate base, usually $NH_2^-$ or $Bu^tO^-$. The alternative process, under alkali metal stimulation, is normally best avoided since it leads to formation of products in which either the carbonyl group has been reduced,[56,66,67] the aromatic ring has been reduced (*e.g.* with naphthalene derivatives),[111] or substantial replacement of halogen by hydrogen takes place.[66,67] This change in product distribution is evident when the yield of phenylacetone in the potassium-stimulated reaction (equation 33)[67] is compared with that obtained (60%) in the photostimulated reaction of PhF with $MeCOCH_2^-$.[58]

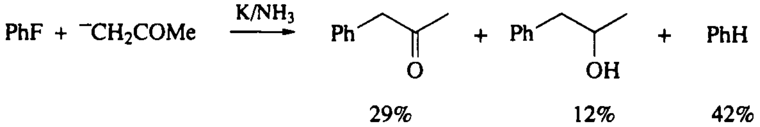

(33)

Even when the reductive processes, so evident in metal-stimulated processes, are avoided, several side reactions can still cause reductions in the yield of the desired α-arylated ketones. The first, abstraction of β-hydrogen atoms from the enolate ion by the aryl radical, has already been mentioned (Section 2.2.2.1) and is sometimes a serious, chain-terminating process.[43–45] This abstraction reaction, however, appears to be quite unpredictable. β-Hydrogen abstraction from the enolate of 2,4-dimethyl-3-pentanone ($Pr^iCOPr^i$; Table 1) which severely disrupts the reaction with iodobenzene, does not prevent high-yielding reactions of the same enolate (and those from other ketones with α-branching) with many other substrates. In in-

**Table 1** Yields of α-Arylated Ketones Formed in Photostimulated Reaction of Ketone Enolates with Aryl Substrates

| *ArX* | *Ketone*[a] | *Yield (%)*[b] | *Ref.* |
|---|---|---|---|
| PhBr | MeCOMe | 93 | 70 |
| PhBr | 3-Pentanone | 80 | 112 |
| PhBr | 4-Heptanone | 80 | 112 |
| PhBr | $\text{Bu}^t\text{COMe}$ | 90 | 112 |
| PhBr | Cyclobutanone | 90 | 112 |
| PhBr | Cyclopentanone | 64 | 112 |
| PhBr | Cyclohexanone | 72 | 112 |
| PhBr | Cycloheptanone | 58 | 112 |
| PhBr | Cyclooctanone | 95 (92) | 112 |
| PhBr | 2-Indanone | 90 | 112 |
| PhI | MeCOMe | 67 | 58 |
| PhI | $\text{Pr}^i\text{COPr}^i$ | 32 | 112 |
| PhI | $\text{Bu}^t\text{COMe}$ | 87[c] | 113 |
| PhI | PhCOMe | 67 | 45 |
| $4\text{-AcC}_6\text{H}_4\text{Br}$ | 2′-Acetonaphthone | 56 | 114 |
| $2\text{-OMeC}_6\text{H}_4\text{I}$ | MeCOMe | 67 | 71 |
| $2\text{-OMeC}_6\text{H}_4\text{I}$ | $\text{Pr}^i\text{COMe}$ | 66 | 71 |
| $2\text{-OMeC}_6\text{H}_4\text{I}$ | $\text{Bu}^t\text{COMe}$ | 100 | 71 |
| $2,4\text{-(MeO)}_2\text{C}_6\text{H}_3\text{Br}$ | MeCOMe | 76 | 70 |
| $3,5\text{-(MeO)}_2\text{C}_6\text{H}_3\text{I}$ | MeCOMe | 68 | 70 |
| $2,4,6\text{-(MeO)}_3\text{C}_6\text{H}_2\text{I}$ | MeCOMe | 92 | 70 |
| $2\text{-(CO}_2^-\text{)C}_6\text{H}_4\text{Br}$ | MeCOMe | 85 | 70 |
| $3\text{-(CO}_2^-\text{)C}_6\text{H}_4\text{Br}$ | MeCOMe | 80 | 70 |
| $4\text{-(CO}_2^-\text{)C}_6\text{H}_4\text{Br}$ | MeCOMe | 70 | 70 |
| $2,5\text{-Pr}^i{}_2\text{C}_6\text{H}_3\text{I}$ | MeCOMe | 78 | 70 |
| $2,5\text{-Bu}^t{}_2\text{C}_6\text{H}_3\text{I}$ | MeCOMe | 26 | 70 |
| $2,4,6\text{-Et}_3\text{C}_6\text{H}_2\text{Br}$ | MeCOMe | 70 | 70 |
| 4-Bromobiphenyl | MeCOMe | 69 | 70 |
| 2-Iodobiphenyl | $\text{Bu}^t\text{COMe}$ | 83 | 69 |
| $3\text{-FC}_6\text{H}_4\text{I}$ | MeCOMe | 56 | 70 |
| $1,2\text{-Br}_2\text{C}_6\text{H}_4$ | $\text{Bu}^t\text{COMe}$ | 62[d] | 94 |
| $1,4\text{-Br}_2\text{C}_6\text{H}_4$ | $\text{Bu}^t\text{COMe}$ | 65[d] | 102 |
| $2\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 12 | 88 |
| $3\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 35 | 70 |
| $3\text{-NH}_2\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 66 | 73 |
| $4\text{-NH}_2\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 33 | 73 |
| $3\text{-NMe}_2\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 82 | 76 |
| $4\text{-NMe}_2\text{C}_6\text{H}_4\text{I}$ | MeCOMe | 90 | 76 |
| $2\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ | $\text{Bu}^t\text{COMe}$ | 12 | 88 |
| $3\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ | $\text{Bu}^t\text{COMe}$ | 40 | 88 |
| $4\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ | $\text{Bu}^t\text{COMe}$ | 21 | 88 |
| 1-Chloronaphthalene | MeCOMe | 88 | 111 |
| 1-Iodonaphthalene | MeCOMe | 76 | 70 |
| 2-Iodonaphthalene | MeCOMe | 75 | 70 |
| 9-Bromoanthracene | MeCOMe | 98 (84) | 70 |
| 9-Bromophenanthrene | MeCOMe | 62 | 70 |

[a] With unsymmetrical methyl ketones arylation occurred at the primary carbon. [b] Where two yields are stated the figure in parentheses is the isolated yield and the other is analytical (*e.g.* determined by GLC or $^1$H NMR). [c] Reaction in the dark, catalyzed by iron(II) sulfate. [d] Both halogens replaced.

termolecular reactions between aryl radicals and enolate ions, which do not have α-branching, β-hydrogen abstraction is usually negligible, except in reactions with *o*-halobenzamides where β-hydrogen abstraction is significant and is even more evident in the *N*-alkylated benzamides.[123]

A second reaction which reduces the yield of α-arylated ketone is α,α-diarylation. This process also appears to be somewhat unpredictable. Although concentrations of the reacting species were a little different, the reaction of iodobenzene with acetone enolate appears to give higher proportions of 1,1-diphenylacetone than bromobenzene.[58] With bromobenzene, reactions with enolates of other ketones generally give diphenylated ketones in 10–20% yields.[112] 3-Bromothiophene with acetone enolate gives a 25:51 ratio of di- to mono-arylated acetones, whereas the 2-bromo isomer appears to give predominant monoarylation.[121] 2-Chlorothiazole, even with a fourfold excess of pinacolone enolate, gave mono- and di-arylation in a 53:25 ratio, but reaction of 2-bromothiazole gave no detectable diarylation.[118] It would appear from inspection of the references cited in Table 1, that yields of monoarylated compounds are good, that monoarylation normally greatly predominates over diarylation and is favored by use of excess of the enolate ion. In a deliberate attempt to improve diarylation, treatment of $\text{MeCOCH}_2^-$ with a three-

**Table 2** Yields of α-Heteroarylated Ketones Formed in Photostimulated Reaction of Ketone Enolates with Heteroaryl Substrates

| *ArX* | *Ketone*[a] | *Yield (%)*[b] | *Ref.* |
|---|---|---|---|
| 2-Chloropyridine | MeCOMe | 85 | 65 |
| 2-Bromopyridine | Pr$^i$COMe | 97 | 65 |
| 2-Bromopyridine | Bu$^t$COMe | 94 | 65 |
| 2-Bromopyridine | Cyclohexanone | 47 | 65 |
| 3-Bromopyridine | MeCOMe | 65 | 65 |
| 4-Bromopyridine | MeCOMe | 28 | 65 |
| 2-Fluoro-3-iodopyridine | Bu$^t$COMe | 92 | 115 |
| 2-Methoxy-3-iodopyridine | Bu$^t$COMe | 84 | 115 |
| 2-Amino-3-iodopyridine | Bu$^t$COMe | 87 | 115 |
| 2,6-Dichloropyridine | Bu$^t$COMe | 86[c] | 65 |
| 2,6-Dibromopyridine | Bu$^t$COMe | 89[c] | 65 |
| 2,3-Dichloropyridine | Bu$^t$COMe | 63[c] | 104 |
| 3,5-Dichloropyridine | Bu$^t$COMe | 43[c] | 104 |
| 3,5-Dibromopyridine | Bu$^t$COMe | 85[c] | 104 |
| 2-Chloropyrimidine | MeCOMe | 61 | 116 |
| 2-Chloropyrimidine | Bu$^t$COMe | 32 | 116 |
| 2-Chloropyrimidine | Pr$^i$COPr$^i$ | 88 | 116 |
| 2,6-(MeO)$_2$-4-Cl-Pyrimidine | Bu$^t$COMe | 98 | 116 |
| 4-Bu$^t$-5-Br-Pyrimidine | MeCOMe | 70–75 | 117 |
| 4-Bu$^t$-5-Br-Pyrimidine | Bu$^t$COMe | 95 | 117 |
| 4-Bu$^t$-5-Br-Pyrimidine | PhCOMe | 85–90 | 117 |
| 4-Ph-5-Br-Pyrimidine | MeCOMe | 25–30 | 117 |
| 4-Ph-5-Br-Pyrimidine | Bu$^t$COMe | 60–65 | 117 |
| 4-Ph-5-Br-Pyrimidine | PhCOMe | 63 | 117 |
| 3-Cl-6-OMe-Pyridazine | MeCOMe | 60[d] | 116 |
| 3-Cl-6-OMe-Pyridazine | Bu$^t$COMe | 72[d] | 116 |
| 2-Chloropyrazine | MeCOMe | 98[d] | 116 |
| 2-Chloropyrazine | Bu$^t$COMe | 95[d] | 116 |
| 2-Chloropyrazine | Pr$^i$COPr$^i$ | 85[d] | 116 |
| 2-Chloropyrazine | PhCOMe | 82[d] | 116 |
| 2-Chlorothiazole | Bu$^t$COMe | 53 | 118 |
| 4-Me-2-Cl-Thiazole | Bu$^t$COMe | 64 | 118 |
| 5-Me-2-Cl-Thiazole | Bu$^t$COMe | 67 | 118 |
| 2-Chloroquinoline | MeCOMe | 90 (55) | 119 |
| 2-Chloroquinoline | 3-Pentanone | 38 (68) | 119 |
| 2-Chloroquinoline | Cyclopentanone | 44 (63) | 119 |
| 2-Chloroquinoline | Pr$^i$COPr$^i$ | 68 (94) | 119 |
| 2-Chloroquinoline | MeCOCH(OMe)$_2$ | 80 | 73 |
| 2-Chloroquinoline | PhCOMe | 14 | 119 |
| 2-Chloroquinoline | PhCOCH$_2$Me | 31 (50) | 119 |
| 5-Cl-7-I-8-Pr$^i$O-Quinoline | MeCOMe | 73[e] | 96 |
| 5-Cl-7-I-8-Pr$^i$O-Quinoline | Bu$^t$COMe | 70[e] | 96 |
| 5-Cl-7-I-8-Pr$^i$O-Quinoline | *p*-MeOC$_6$H$_4$COMe | 70[e] | 96 |
| 5-Cl-7-I-8-Pr$^i$O-Quinoline | 2-Acetylfuran | 80[e] | 96 |
| 2-Chloroquinoxaline | Bu$^t$COMe | 70[d] | 120 |
| 2-Bromothiophene | MeCOMe | 31 | 121 |
| 3-Bromothiophene | MeCOMe | 51 | 121 |
| 6-I-9-Et-Purine | MeCOMe | 87 | 122 |
| 6-I-9-Et-Purine | Cyclopentanone | 65 | 122 |
| 6-I-9-Et-Purine | PhCOMe | 70 | 122 |
| 6-I-9-Et-Purine | 2-Acetylfuran | 67 | 122 |

[a] With unsymmetrical methyl ketones arylation occurred at the primary carbon. [b] Where two yields are stated the figure in parentheses is the isolated yield and the other is analytical (*e.g.* determined by GLC or $^1$H NMR). [c] Both halogens replaced. [d] Photostimulation was not necessary. [e] Only the 7-iodine was replaced.

fold excess of bromobenzene gave a 58:32 ratio of di- to mono-arylation with only trace amounts of triarylation.[70] Other experiments also support the conclusion that triarylation is difficult.[102]

It is noticeable from the data in Table 1, that the number of examples of reactions involving the enolates of aryl alkyl ketones is limited. Bromo- and iodo-benzene were reported not to react with the enolate of acetophenone[112] but the reaction with iodobenzene under 'more intense and longer irradiation' was reported to give a 67% yield of phenacylbenzene.[45] Sufficient examples of the α-arylation of the enolates of aryl (and heteroaryl) alkyl ketones have been cited to indicate that these reactions are worth further investigation.

The regiochemistry of arylation of ketones has not been studied systematically, but there are sufficient data in the literature to allow reasonable predictions to be made. With enolates having one *t*-alkyl group attached to the carbonyl (*e.g.* $^-CH_2COBu^t$) or with those derived from aryl alkyl ketones, clearly no problem arises and attack at the sole available site takes place. Symmetrical ketones such as acetone, 3-pentanone and diisopropyl ketone also present no problems. With unsymmetrical dialkyl ketones, isomeric enolate ions can form and it would appear that the distribution of the two possible products formed by arylation of this mixture of enolate ions is determined principally by the equilibrium concentration of the various possible enolate ions.[124] Although the ratio of attack at the two possible α-positions could vary according to the relative reactivity of the aryl radical toward the various enolate ions, and indeed this is the case, the above generalization explains the observed distribution of products. Reactions with the enolates derived from 2-butanone give predominant formation of products from attack at the secondary α-position; the ratio of products (**32**; Ar = Ph):(**33**; Ar = Ph) in reactions with iodo- or bromo-benzene is in the range 1.3–3.2:1,[124] with *o*-iodoanisole the corresponding ratio (with Ar = *o*-anisyl) is 1.5:1,[71] and with 3-amino-2-chloropyridine the ratio is 2.3:1(Ar = 3-amino-2-pyridyl).[125] In the reaction of several aryl halides with the mixture of enolates from 3-methyl-2-butanone, the predominance of the less-substituted primary enolate is reflected in major formation of isomer (**34**) in all cases. The ratio (**34**):(**35**) varied with the aryl group as follows: 16:1[45] or 9:1[124] (Ar = Ph); 7:1 (Ar = 2-pyridyl);[65] and 5:1 (Ar = 2-quinolinyl).[119] When there is a substituent *ortho* to the halogen being displaced, the attack at the primary α-carbon is enhanced and vanishingly small proportions of products (or intermediates) corresponding to (**35**) were formed.[71,76,123,125,126] In the only reported case of a reaction with an α-substituted cyclohexanone, attack at the tertiary carbon of the thermodynamically more stable enolate occurred.[122,127]

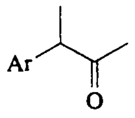

**(32)**

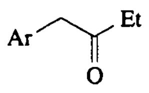

**(33)**

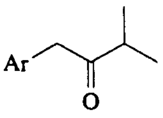

**(34)**

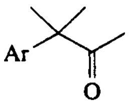

**(35)**

A substantial number of important syntheses that depend on the attack of ketone enolates on *ortho*-functionalized aryl or heteroaryl halides, and that lead to cyclized products are discussed in Section 2.2.4.2.

### *2.2.3.1.2 Preparation of other α-arylated carbonyl compounds*

The arylation of acetaldehyde enolate by iodobenzene[17,128] or *p*-iodoaniline[73] failed, and the reduced products, benzene or aniline were obtained. In the reaction of aldehyde enolates with *o*-substituted derivatives, however, arylation does occur and in these cases subsequent cyclization reactions usually take place (see Section 2.2.4.2). The special effect of the *o*-substituents in facilitating reactions with aldehyde enolates is shown by the rare example of simple substitution (*i.e.* without concomitant cyclization) in equation (34).[71]

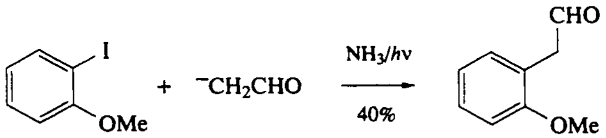

(34)

The α-arylation of the enolates of esters has only been studied superficially, and the results obtained with the *t*-butyl esters of acetic, propionic and isobutyric acids indicate that the method is not very promising in the benzene series. Arylation of the acetic ester with *p*-bromoanisole proceeds in 67%, but is accompanied by 29% α,α-diarylation,[44] and arylation of the isobutyric ester with either bromobenzene or *p*-bromoanisole gave low yields of arylated material (11% and 5%, respectively).[44,45] The principal process occurring with the isobutyric ester was β-hydrogen abstraction from the enolate ion, clearly demonstrated by deuterium-labelling experiments.[44] The reaction of the lithium enolate of the propionic ester with bromobenzene gave an encouraging result, with the α-phenylated ester being formed in 60% yield.[45] The potassium enolates of ethyl phenylacetate and ethyl α-phenylpropionate give 84% and 42% yields, respectively, of the products in which both of the bromines in 2,6-dibromopyridine have been replaced, with no trace of the monosubstituted monobromo compounds being detected.[104]

Most of the information on simple α-arylation reactions on the enolates of amides comes from a single study by Rossi and Alonso.[128] They showed that with acetamide itself no arylation reactions took place, presumably on account of ionization of the N—H rather than the C—H bond and the observation that the

$MeCONH^-$ anion (also $MeCONMe^-$), at least under electrochemically stimulated conditions,[68] does not undergo $S_{RN}1$ reactions. The use of acetamides with the nitrogen protected by *N,N*-disubstitution allowed formation of the enolate ion with sodium amide in liquid ammonia and the resulting enolates gave yields of 50–80% of the α-arylated products (*e.g.* equations 35 and 36).[128] α,α-Diarylation was a minor nuisance (the mono- and di-substituted compounds were separable) and the insolubility of some salts (*e.g.* the potassium enolate of *N*-acetylpiperidine) in liquid ammonia prevented satisfactory reaction. The enolate ion from *N*-(*p*-chlorobenzyl)-*N*-methylacetamide polymerizes on irradiation in liquid ammonia by the $S_{RN}1$ mechanism, but the enolate from *N*-(*p*-bromophenyl)-*N*-methylacetamide does not, a difference explained in terms of an intramolecular interaction in the latter enolate between the nucleophilic and the nucleofugic sites.[102] Examples of intramolecular attacks of amide enolates on *o*-substituted aryl halides are known, and these are discussed in Section 2.2.4.1.

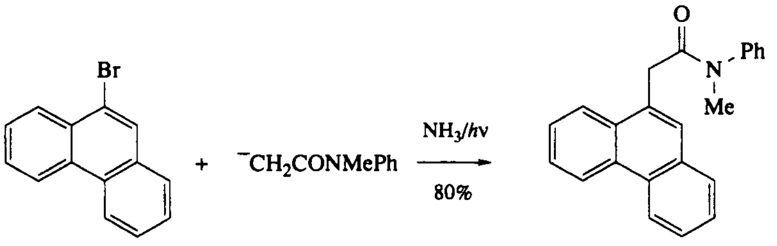

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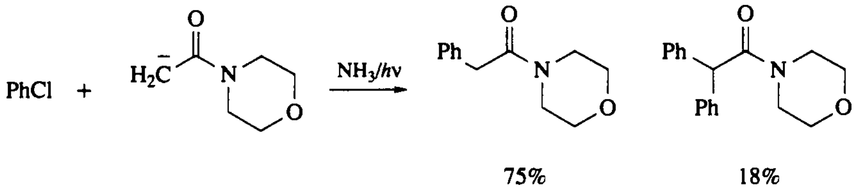

(36)

Initial use of β-dicarbonyl compounds as sources of nucleophiles in aromatic $S_{RN}1$ reactions was disappointing, particularly in view of their successful use in the aliphatic case.[6,10] Monoanions from malonic esters,[45,112,119] acetoacetic esters[112,119] and β-diketones[112,119,129] all failed to react with halobenzenes or 2-chloroquinoline. The dianions could be arylated but these reactions took place at the site α to only one of the carbonyls. Thus the dipotassium salt of 2,4-pentanedione gave an 82% yield of 1-mesityl-2,4-pentanedione on treatment with 2-bromomesitylene[112] and the dialkali metal salts of benzoylacetone reacted readily with 2-chloroquinoline to give a 71% yield of 1-phenyl-4-(2-quinolinyl)-1,3-butanedione.[130] The latter salt was also able to entrain otherwise sluggish $S_{RN}1$ processes.[131] Beugelmans and coworkers found, however, that the presence of a cyano group modifies the reactivity of benzene (and pyridine) rings, facilitating reaction between the monoanions of a wide range of β-dicarbonyl compounds and leads to α-arylated-β-dicarbonyl derivatives in excellent yield, generally in excess of 70% and mostly near 90%.[72] Examples of these reactions are given in equations (37) and (38), and, as shown in equation (38), the reaction can be further modified, for example by basic work-up, to give the product resulting from a retro-Claisen reaction. The difficulty of predicting whether aromatic $S_{RN}1$ reactions will take place with β-dicarbonyl compounds is exemplified by the further observations by Beugelmans' group that although 2-chloro-, 4,7-dichloro-, 5,7-dichloro-8-methoxy-, and 7-iodo-8-methoxy-quinoline are unreactive, 5-chloro-7-iodo-8-methoxyquinoline reacts under photostimulation with the monoanions of diethyl malonate, ethyl acetoacetate and acetylacetone with displacement of only the 7-iodine in yields from 60–100%.[97]

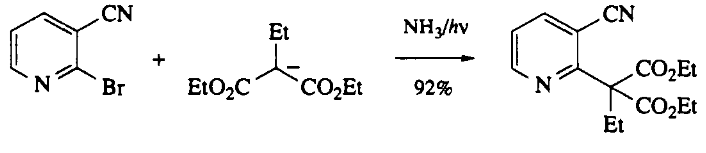

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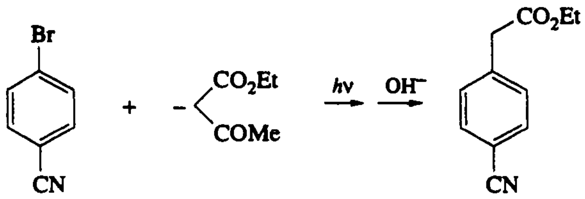

(38)

### 2.2.3.1.3 Preparation of α-arylated nitriles

In general, a number of products can be obtained in the reaction of an aromatic substrate with an α-cyanoalkyl anion as shown in equation (39), and the detailed mechanism of formation of these products is discussed in the early paper by Bunnett and Gloor.[38] The product distribution from the reaction of bromobenzene with $^-CH_2CN$ is typical of that obtained with benzene derivatives, when carried out under metal-stimulated conditions (see equation 9). The reaction with halobenzenes, even under photostimulated (less reducing) conditions, gives less benzene, but still gives low yields of phenylacetonitrile on account of the fragmentation process, discussed earlier in Section 2.2.2.1 (equation 10). It has been suggested[18,38] that the fragmentation could be put to good use in the production of alkylbenzenes (*i.e.* $ArCH_2R$ in equation 39) since in the potassium-stimulated processes with a range of leaving groups and a number of α-cyanoalkyl ions, the principal product other than benzene (in yields up to 56%) is the alkane $PhCH_2R$. This proposal has the added potential that successful nucleofugal groups (X in equation 39) include $Me_3N^+$ and $(EtO)_2P(O)$, readily derived from amino and phenolic functionalities, respectively. This strategy, exemplified by the butylation sequence in Scheme 3,[38] which would allow halogen, amino or hydroxy groups on a benzene ring to be replaced by alkyl groups such as methyl, propyl, isopropyl or benzyl has not, as yet, been further developed.

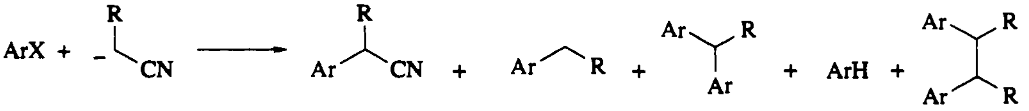

(39)

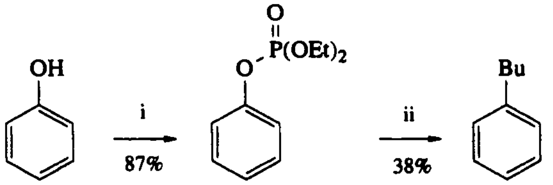

i, $(EtO)_2POCl/NaOH$; ii, $^-CH(CN)(CH_2)_2Me/K/NH_3$

**Scheme 3**

In contrast with the behavior of the benzene derivatives, the reaction of α-cyanoalkyl (principally cyanomethyl) ions with other aromatic substrates, leads mainly to the expected substitution products, $ArCH(R)CN$ (equation 39). This difference in behavior (not as pronounced in the thiophene system)[132] has been rationalized by molecular orbital considerations.[18,41,133] Examples of these successful syntheses are collected in Table 3.

A useful synthesis of heteroaryl ketones uses the photostimulated α-cyanoalkylation reaction followed by oxidation (Scheme 4). The oxidation of products formed from phenylacetonitrile (R = Ph in Scheme 4) proceeded in over 90%.[110]

The reactions of 2,6-dibromopyridine with the carbanions formed from α-phenylbutyronitrile or α-ethyl-α-phenylbutyronitrile give mixtures of products in which one or both of the bromines have been replaced together with products in which one bromine has been replaced by hydrogen and the other by the carbanion.[104]

The reaction of *p*-iodo- or *p*-bromo-anisole or of 1-iodonaphthalene with the anion formed from the α,β-unsaturated nitrile (**36**) gives 60–70% combined yields of the isomeric nitriles (**37**) and (**38**) together with small amounts of the diarylated derivatives (**39**).[135]

**Table 3** Yields of α-Arylated Nitriles Formed in the Photostimulated Reaction of α-Cyanoalkyl Anions with Aryl and Heteroaryl Substrates

| *ArX* | *Nitrile* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| Bromobenzene | MeCN | $8^{a}$ | 38 |
| Bromobenzene | MeCN | 25 | 39 |
| 4-Chlorobiphenyl | MeCN | 94 | 39 |
| 4-Chlorobenzophenone | MeCN | 97 | 39 |
| 1-Chloronaphthalene | MeCN | 89 | 39 |
| 2-Chloronaphthalene | MeCN | 93 | 39 |
| 9-Bromophenanthrene | MeCN | 70 | 39 |
| 2-Chloropyridine | MeCN | 56 | 39 |
| 2-Bromopyridine | $PhCH_2CN$ | 76, 88 | 110, 134 |
| 3-Bromopyridine | $PhCH_2CN$ | 48 | 110 |
| 4-Bromopyridine | $PhCH_2CN$ | 15 | 110 |
| 2-Chloropyrimidine | $PhCH_2CN$ | 31 | 110 |
| 2-Chloropyrazine | $PhCH_2CN$ | $78^{b}$ | 116 |
| 2,4-Dichloropyrimidine | $PhCH_2CN$ | $58^{c}$ | 104 |
| 2-Chloroquinoline | $PhCH_2CN$ | 46, 88 | 110, 134 |
| 3-Bromoquinoline | $PhCH_2CN$ | 45 | 110 |
| 3-Bromothiophene | MeCN | $37^{d}$ | 132 |

[a] Stimulated by potassium metal (see text). [b] In the dark. [c] Only the 4-chlorine is replaced. [d] Also obtained from 2-bromothiophene.

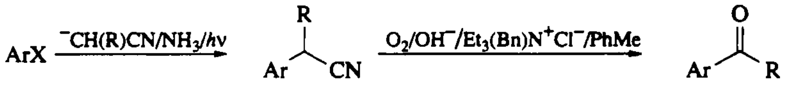

Scheme 4

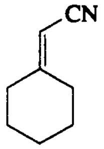

**(36)**

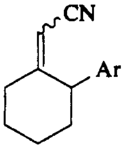

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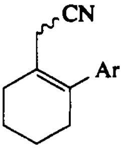

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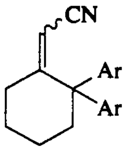

**(39)**

### *2.2.3.1.4 Preparation of hydroxy- and amino-biaryls*

The study of the reactivity of phenoxide ions with aryl halides under $S_{RN}1$ conditions has undergone dramatic changes since the end of 1987, after a negative and confused beginning. In 1973 products were not isolated in the reaction of phenoxide ion with bromobenzene under alkali metal stimulated conditions,[124] but four years later the claim was made that bromobenzene on reaction with phenoxide ion and sodium amalgam in 50% aqueous Bu$^t$OH was converted into diphenyl ether.[51] In 1979, the latter work was shown to be unreproducible,[52] and additionally, phenoxide ion was shown not to react with 2-chloroquinoline under electrochemical stimulus.[68] In 1980, *p*-cresol was recovered in over 90% yield on attempted photostimulated reaction under basic conditions with iodobenzene, although the iodobenzene was consumed.[45] At the end of 1987, it was clearly demonstrated that 2-, 3- and 4-chlorobenzonitrile reacted in electrochemically induced $S_{RN}1$ reaction with 2,6- and 2,4-di-*t*-butylphenoxide ions, as shown in the representative reaction given in equation (40).[86] Since this report the idea that phenoxides were not good substrates in $S_{RN}1$ reactions has been allayed. The electrochemically induced reaction of 4-bromobenzophenone with phenoxide ion was found to give a 40% yield of benzophenone and 60% of a 1:2 mixture of the *para*-coupled compound (**40**) and the *ortho* isomer (**41**), with no trace of any *O*-arylated compounds,[80,81] and the reaction of phenoxide ion with 4-chlorobenzonitrile gave a similar result.[80] The synthetic utility of these coupling reactions (clearly still in their infancy) leading to unsymmetrical hydroxylated biaryls, is seen in the further example in Scheme 5, wherein removable Bu$^t$ groups are used to control the regiochemistry of coupling which takes place under electrochemical or photochemical stimulation in overall yields near 70%.[136] At the same time as the electrochemically induced reactions were being developed, Beugelmans and coworkers carefully reexamined the photostimulated reaction of a variety of phenoxides and 1- and 2-naphthoxides with aryl halides.[75] They confirmed that arylation of *p*-cresol by simple aryl halides was low yielding, with only 3% of *ortho*-phenylated *p*-cresols being detected, but noted that electron-withdrawing substituents *o*- or *p*- to the nucleofuge raised the yield of hydroxylated biaryls, as did electron-donating groups on the phenoxide ion. The presence of an electron-donating group, such as methoxy, *ortho* to the nucleofuge also had the same activating effect. They also recognized the usefulness of Bu$^t$ groups as both blocking and activating groups on the phenoxide moiety (*cf.* Scheme 5). Examples of these processes are given in equations (41) and (42).[75] In the naphthalene series the 1- and 2-naphthoxides also readily undergo arylation in good yields, the former gives mixtures of 2- and 4-arylated products,[75] and the latter give arylation solely in the 2-position.[75,137] The increased activity of the naphthoxides is shown by the fact that substituent effects on the aryl halide are not as critical; 2-naphthoxide ion gives 48% and 85% 1-arylation with *p*-iodoanisole[137] and *p*-bromobenzonitrile[75] respectively, despite the large difference in electronic properties of the methoxy and cyano groups. By a simple extension of this reaction, reasonable yields of unsymmetrical 1,1′-,[137,138] 1,2′-[138] and 2,2′-binaphthyl[138] derivatives are also available in the one-step coupling of naphthoxides and iodonaphthalenes. The anions from *p*-cresol, *p*-methoxyphenol and 2,4-dimethoxyphenol were readily arylated by 5-chloro-7-iodo-8-isopropoxyquinoline in the vacant *o*- or *p*-positions with only the 7-iodine being replaced.[97] It can be seen, that in the elapse of little more than one year, the S$_{\mathrm{RN}}$1 reaction of phenoxides with aryl halides (with judicious choice of substrates) has been developed as an excellent route to hydroxybiaryls.

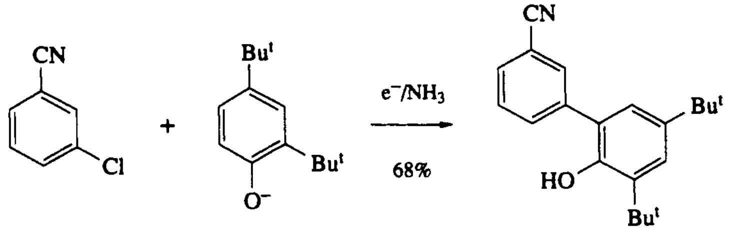

(40)

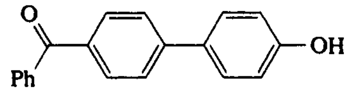

**(40)**

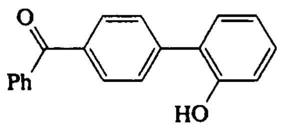

**(41)**

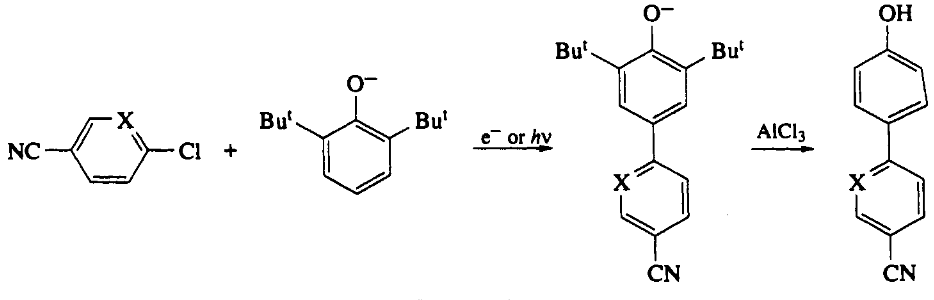

**Scheme 5**

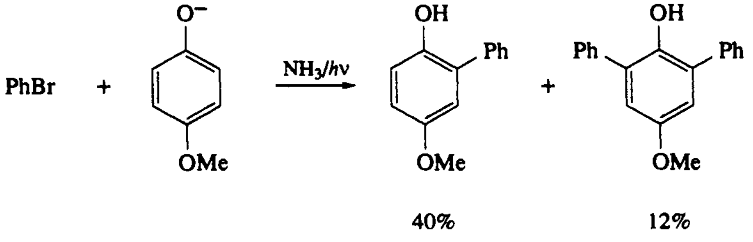

(41)

The study of the arylation of arylamide ions prior to 1987, in similar fashion to that of the analogous reaction with aryloxides discussed above, gave little promise of synthetically useful reactions. In Kim and Bunnett's original papers on the S$_{\mathrm{RN}}$1 reaction,[1] they reported that the anilide ion (PhNH$^-$) behaves

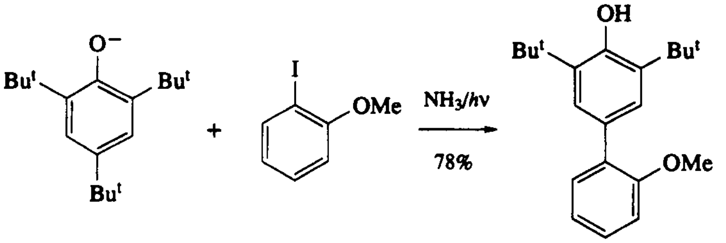

(42)

in ambident fashion and gives poor yields of diphenylamine (19%) and *o*- and *p*-aminobiphenyl (11% each). Rossi and coworkers have opened up another potentially useful biaryl synthesis by examining the reactions of the anion of 2-naphthylamine, which they believed should have a lower ionization potential to initiate the photostimulated reaction than the PhNH$^-$ anion, with aryl iodides and bromides. Indeed, arylation of the arylamide ion, generated from 2-naphthylamine by treatment with NH$_2^-$ or Bu$^t$O$^-$ in liquid ammonia, takes place at the 1-position of the naphthalene ring in 45–63% yields with iodoarenes and to a lower extent with bromoarenes. *N*-Arylation occurs to a maximum extent of only 8% with the substrates studied.[109] An example of this new aminobiaryl synthesis, clearly still in the developmental stage, is shown in equation (43).

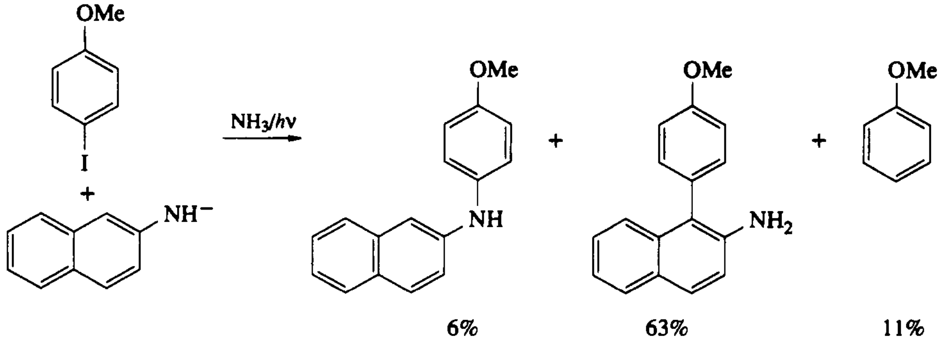

(43)

### 2.2.3.1.5 *Preparation of arenecarbonitriles*

Despite being the nucleophile in the electrochemically induced $S_{RN}1$-like process with *p*-iodonitrobenzene,[27] which predates the discovery of the aromatic $S_{RN}1$ reaction,[1] the use of cyanide ion has been almost totally neglected, except for electrochemical studies, which principally revealed that reactions of haloarenes with cyanide ion either do not take place with, for example, normally reactive substrates such as 2-chloroquinoline,[68] are 'not entirely catalytic'[78,139] or are 'noncatalytic' substitution processes.[140,141] More recent electrochemical studies have shown that coupling between various aryl radicals and cyanide is significantly slower than that with PhS$^-$, $^-$CH$_2$COMe and (EtO)$_2$PO$^-$.[31] This factor, combined with the stability of the product of the association step (equation 3), namely ArCN$^{-\cdot}$, relative to that of the radical anion of the substrate, ArX$^{-\cdot}$, which makes the chain propagation step in equation (4) unfavorable, presumably explains the necessity for more than catalytic amounts of current, even in those reactions which do take place. In what appears to be the only reference to reactions of cyanide with aryl halides under nonelectrochemical conditions (see p. 42 in ref. 18), only failed reactions were reported. The photochemically or electrochemically stimulated reaction of aryldiazo phenyl sulfides, already discussed in Section 2.2.2.3 (see Scheme 2), gives moderate to good yields of arenecarbonitriles, presumably on account of the propagating step (equation 4) becoming thermodynamically favorable.[62]

### 2.2.3.1.6 *Miscellaneous reactions with carbanions*

Very little work has been done on reactions involving nucleophiles formed from hydrocarbons.[124,142] The limitation on basicity of the carbanion, so that it does not react with solvent, has led to use of conjugated hydrocarbons, such as dienes or alkenes conjugated with aromatic rings. When initiated by dissolving alkali metal in liquid ammonia, complex mixtures are often produced on account of reduction processes,[124] and regiochemistry and multiplicity of arylation in conjugated systems also create problems.[142] The photostimulated phenylation of indene anion in DMSO by bromobenzene leads to mixtures of mono-, di- and tri-phenylated indenes[124,142] and similar results are obtained with fluorene and anethole.[124] Phenylation of 1,3-pentadiene, accomplished by potassium-induced reaction with bromobenzene in liquid ammonia, followed by catalytic reduction of all aliphatic double bonds, does give a useful yield of 1-phenylpentane (74%), albeit contaminated with diphenylpentanes (7%) and triphenylpentanes (3%).

The 2- and 4-picolyl anions are phenylated or mesitylated on reaction with chlorobenzene, phenyltrimethylammonium ion and 2-bromomesitylene under stimulation by light or potassium metal. The mechanism of reaction with bromobenzene and iodobenzene is not certain, with the aryne mechanism almost certainly intruding, and with iodobenzene some diarylation of the picolinyl anion results. The reaction of the 2-picolyl anion with 2-bromomesitylene, where an aryne process is impossible, is shown in equation (44).[60] Similar reactions take place between the 4-picolyl anion and 2- or 4-bromopyridine or 2-chloroquinoline.[134]

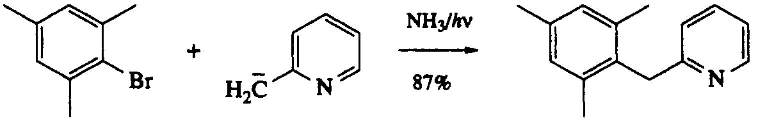

(44)

Although the anions from nitroalkanes have been shown by ESR[36] and electrochemical studies[29] to be very good traps for aryl radicals, the dissociation of the first-formed radical anions, e.g. as shown in equation (45),[29] produces nonchain-propagating radicals, accounting for the lack of photostimulated or metal-promoted examples of this reaction type.[46] The electrochemical reaction (two electrons per molecule) of iodobenzene with the anion from 2-nitropropane gives only 29% of isopropylbenzene and the corresponding reaction with 4-bromobenzophenone gives 4-isopropylbenzophenone in 50% yield.[29]

$$(\mathrm{ArCMe_2NO_2})^{\bullet -} \longrightarrow \mathrm{ArCMe_2}^{\bullet} + \mathrm{NO_2}^- \qquad (45)$$

Dimsyl anion fails to undergo $S_{RN}1$ reactions with aryl halides,[134,143] and the occurrence of fragmentation processes similar to those in equations (11) and (45) have been used to explain this failure,[143] correcting the earlier, falacious claim that dimsyl anion and halobenzenes react to give benzyl methyl sulfoxide in high yield.[144]

Acetylide ions have also been reported as unreactive in $S_{RN}1$ reactions with aryl[45] and heteroaryl[134] halides.

## 2.2.3.2 Formation of Aryl C—N, C—P, C—As and C—Sb Bonds

### *2.2.3.2.1 Preparation of arylamines*

The advantage of the radical process, that substitution of nucleofuges by $NH_2^-$ on an aromatic ring takes place without *cine* substitution (by the aryne mechanism), was clearly seen in the first aromatic $S_{RN}1$ reactions recognized.[1] The same regiochemical advantage is seen in the potassium-stimulated conversion of *o*-haloanisoles predominantly into *o*-anisidine rather than the *m*-isomer (the sole product of the aryne process). Also, unlike substitutions proceeding by the aryne mechanism, reactions readily take place when both *ortho* positions are blocked (equation 46),[1] and 2-bromomesitylene reacted with $NH_2^-$ under photostimulation to give 2,4,6-trimethylaniline in 70% yield.[34]

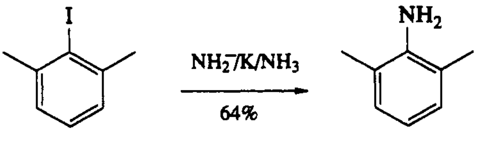

(46)

Despite the abovementioned advantages, the only application of this useful synthetic procedure appears to be the otherwise difficult conversion of phenols into amines *via* the aryl diethyl phosphates in overall yields in excess of 55% (*cf.* Scheme 3).[56] Even this potentially useful reaction does not appear to have been used since the original report. The reaction of amide ion with bromothiophenes is complicated by rearrangement of the 2- to the 3-bromo isomer but 3-thiophenamine is the ultimate product in yields up to 79%.[121]

The reactions of the ambident ArNH⁻ ions, which do not *N*-arylate to a great extent, are discussed in Section 2.2.3.1.4. Based on the negative results obtained with *N*-acyl anions such as AcNH⁻ and AcNMe⁻,[68] and the anion of phthalimide,[134] it would appear that these anions do not undergo *N*-arylation under $S_{RN}1$ conditions.

#### *2.2.3.2.2 Preparation of triarylphosphines*

Triarylphosphines were prepared by the reaction between lithium diphenylphosphide in THF and *m*- and *p*-iodotoluene (or the corresponding bromo compounds), 4-bromobiphenyl and *p*-dibromobenzene in yields of 70–80% (isolated after oxidation, as the phosphine oxides).[145] The absence of *cine* substitution products is a synthetic advantage and would have been taken as a *prima facie* indication that the displacements are examples of the $S_{RN}1$ reaction, had the mechanism been recognized at the time. Operation of the radical ion mechanism in DMSO, or liquid ammonia, in which marginally improved yields are obtained, was confirmed by Swartz and Bunnett,[48] but no extension to the scope of the reaction was made. Rossi and coworkers have developed a procedure for 'one-pot' preparation of triarylphosphines starting from elemental phosphorus (Scheme 6).[146] As an example of the synthesis of a symmetrical triarylphosphine, triphenylphosphine (isolated as its oxide) was obtained in 75% yield, with iodobenzene as the aryl halide (ArX in Scheme 6, steps i–iii only). Unsymmetrical phosphines result from the full sequence of reactions in Scheme 6, and *p*-anisyldiphenylphosphine (isolated as its oxide) was produced in 55% yield, based on the phosphorus used, when chlorobenzene (ArX) and *p*-methoxyanisole (Ar'X) were used.

$$\mathrm{P} \xrightarrow{\text{i, ii}} \mathrm{P^{3-}} \xrightarrow{\text{iii}} \mathrm{Ar_3P} \xrightarrow{\text{i, ii}} \mathrm{Ar_2P^-} \xrightarrow{\text{iv}} \mathrm{Ar_2PAr'}$$

i, $Na/NH_3$; ii, $Bu^tOH$; iii, $ArX/h\nu$; iv, $Ar'X/h\nu$

**Scheme 6**

#### *2.2.3.2.3 Preparation of dialkyl arylphosphonates*

The greatest number of preparative (and mechanistic) studies with phosphorus-based nucleophiles have been carried out with the dialkyl phosphite ions. These reactions generally proceed in good to high yield in either liquid ammonia, THF or DMSO under photostimulation, and representative examples are collected in Table 4. A detailed experimental procedure for the preparation of diethyl phenylphosphonate by this method is available.[147] The reactions generally require photostimulation and the quantum yields have been evaluated.[21,22] In the absence of photostimulation, reactions are slower or do not proceed at all, and in the particular case of *o*-haloiodobenzenes, ionic processes occur to the virtual exclusion of the substitution reaction.[89] With the notable exception of aromatic rings bearing nitro groups, where the $S_{RN}1$ reaction failed, superior results were obtained using the photostimulated reaction in THF, than by using a variety of metal-catalyzed processes.[77] Electrochemically stimulated reactions with $(EtO)_2PO^-$ proceed with remarkably low current input and the reaction with *p*-chlorobenzonitrile proceeds with 100% conversion in 10 min with a current input of only 0.01 electron per molecule of substrate.[139]

#### *2.2.3.2.4 Miscellaneous reactions with phosphanions*

In addition to the dialkyl phosphite ions, discussed in the previous section, a number of other phosphanions readily undergo photostimulated *P*-arylation in liquid ammonia. The yields for these reactions, which have to date only been studied for *P*-phenylations are collected in Table 5.[23] Iodobenzene is more reactive than bromobenzene, which fails to react with the $Ph_2P{-}O^-$ ion.[23]

**Table 4** Yields of Dialkyl Arylphosphonates Formed in the Photostimulated Reaction of Dialkyl Phosphite Ions with Aryl Halides: $ArX + (RO)_2PO^- \rightarrow (RO)_2P(=O)Ar$[a]

| *ArX* | *Yield (%)* | *Ref.* | *ArX* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| Iodobenzene | 93[b] | 90, 147 | *m*-Chloroiodobenzene | 91 | 92 |
| Iodobenzene | 88[c] | 90 | *p*-Chloroiodobenzene | 59[d] | 92 |
| Iodobenzene | 96 | 90 | *m*-Bromoiodobenzene | 87[d] | 90 |
| *p*-Iodotoluene | 95 | 90 | *p*-Bromoiodobenzene | 56[d] | 92 |
| *p*-Iodoanisole | 95 | 90 | *m*-Diiodobenzene | 94[d] | 90 |
| *o*-Iodoaniline | 87 | 77 | *p*-Diiodobenzene | 87[d] | 90 |
| *m*-Iodoaniline | 90 | 77 | 1-Iodonaphthalene | 93 | 90 |
| *p*-Iodoaniline | 90 | 77 | 2-Iodopyridine | 78 | 77 |
| 2-Iodo-*m*-xylene | 87 | 90 | 3-Iodopyridine | 70 | 77 |
| *m*-Iodobenzotrifluoride | 95 | 90 | 2-Methoxy-3-iodopyridine | 78 | 115 |
| *m*-Fluoroiodobenzene | 96 | 90 | 3-Bromoquinoline | 76 | 77 |
| *p*-Fluoroiodobenzene | 91 | 92 | 5-Cl-7-I-8-$Pr^iO$-Quinoline | 70 | 95 |

[a] Unless otherwise stated, the alkyl group is ethyl; *i.e.* R = Et. [b] R = Me. [c] R = Bu. [d] Both halogens are replaced.

**Table 5** Yields of *P*-Phenylated Phosphorus Derivatives Formed in the Photostimulated Reaction of Various Phosphanions with Phenyl Halides in Liquid Ammonia[a]

| *Halobenzene* | *Phosphanion*[b] | *Product* | *Yield (%)* |
|---|---|---|---|
| Iodobenzene | $PhP(OBu)O^-$ | $Ph_2P(=O)OBu$ | 95 |
| Bromobenzene | $PhP(OBu)O^-$ | $Ph_2P(=O)OBu$ | 72 |
| Iodobenzene | $Ph_2P{-}O^-$ | $Ph_3P{=}O$ | 95 |
| Iodobenzene | $(EtO)_2P{-}S^-$ | $PhP(=S)(OEt)_2$ | 95 |
| Iodobenzene | $(Me_2N)_2P{-}O^-$ | $PhP(=O)(NMe_2)_2$ | 64 |
| Bromobenzene | $(Me_2N)_2P{-}O^-$ | $PhP(=O)(NMe_2)_2$ | 65 |

[a] Taken from ref. 23. [b] The counterion in all reactions was $K^+$.

##### 2.2.3.2.5 *Reactions with arsenide and stibide ions*

The earlier literature concerning the reaction of arsenide ions with aryl halides has been summarized by Rossi and coworkers in their paper investigating the $S_{RN}1$ reaction between $Ph_2As^-$ and several haloarenes.[24] In this and subsequent work,[25] it was found that scrambling of aryl groups took place in the reactions of $Ph_2As^-$ with all the substrates examined, except for 4-chlorobenzophenone (quantitative yield of substitution product)[24] and 2-chloroquinoline (60% yield).[25] Consequently, the use of the $Ph_2As^-$ ion and also of the $Ph_2Sb^-$ ion which gives gives scrambling of the aryl groups with all the substrates so far examined,[25] are not generally satisfactory for selective preparation of unsymmetrical triarylarsines or triarylstibines.

The 'one pot' procedure used for conversion of elemental phosphorus into triarylphosphines (see Scheme 6), with appropriate modification (*i.e.* replacement of P by As or Sb), has been used to prepare triphenylarsine (75%), 2-quinolyldiphenylarsine (90%) and triphenylstibine (45%).[146]

### 2.2.3.3 Formation of Aryl C—O, C—S, C—Se and C—Te Bonds

Alkoxide and aryloxide ions are not arylated on oxygen. Tertiary alkoxides do not react, thus making them appropriate bases for generation of nucleophiles, and primary and secondary alkoxides undergo α-hydrogen abstraction with aryl radicals normally making them unsuitable for use as bases; *e.g.* isopropoxide ion reacts with phenyl radicals to give benzene and acetone ketyl.[58] The *C*-arylation of aryloxides is discussed in Section 2.2.3.1.4.

##### 2.2.3.3.1 *Preparation of diaryl and aryl alkyl sulfides*

The photostimulated reaction between aryl halides and arenethiolates gives diaryl sulfides (equation 47) and examples are given in Table 6. The yields obtained from substituted iodobenzenes are generally high but reactions with heteroaryl halides are less prominent and, for example, normally reactive 2-chloroquinoline fails to react with $PhS^-$ under photostimulated conditions.[134] The recently reported reactions of 2- and 3-halothiophenes with benzenethiolate indicate that scrambling of the products, through fragmentation processes, led to complex mixtures.[148] The use of *p*-bifunctionalized thiols/halides in the preparation of poly(1,4-phenylene sulfides) has been mentioned in Section 2.2.2.4.2.[99–102]

$$\mathrm{ArX} + \mathrm{Ar'S^-} \xrightarrow{\mathrm{NH_3}/h\nu} \mathrm{ArSAr'} + \mathrm{X^-} \qquad (47)$$

**Table 6** Yields of Diaryl Sulfides Formed in Photostimulated Reaction of Arenethiolates with Aryl and Heteroaryl Halides

| *ArX* | *Thiol* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| Iodobenzene | PhSH | 94 | 149 |
| Iodobenzene | *p*-$MeOC_6H_4SH$ | 71 | 61 |
| Bromobenzene | PhSH | 23 | 149 |
| *o*-Iodoanisole | PhSH | 91 | 149 |
| *m*-Iodoanisole | PhSH | 88 | 149 |
| *p*-Iodoanisole | PhSH | 76 | 149 |
| *p*-Iodoanisole | *p*-$MeOC_6H_4SH$ | 73 | 61 |
| *o*-Iodotoluene | PhSH | 68 | 149 |
| *m*-Iodotoluene | PhSH | 81 | 149 |
| *p*-Iodotoluene | PhSH | 72 | 149 |
| *m*-Fluoroiodobenzene | PhSH | 96 | 149 |
| *o*-Chloroiodobenzene | PhSH | 77[a] | 91 |
| *m*-Chloroiodobenzene | PhSH | 91[a] | 91 |
| *m*-Chloroiodobenzene | 2-Pyrimidinethiol | 100[b] | 95 |
| *p*-Chloroiodobenzene | PhSH | 89[a] | 91 |
| *m*-Dibromobenzene | PhSH | 92[a] | 91 |
| *m*-Iodobenzotrifluoride | PhSH | 71 | 149 |
| 4-I-$C_6H_4N^+Me_3\ I^-$ | PhSH | 95[a] | 91 |
| 2-Iodo-*m*-xylene | PhSH | 19 | 149 |
| 4-Iododiphenyl ether | PhSH | 92 | 149 |
| 1-Iodonaphthalene | PhSH | 85 | 149 |
| 2-Iodopyridine | PhSH | 58[c] | 106 |
| 2-Bromopyridine | PhSH | 21, 65[d] | 106, 134 |
| 3-Bromopyridine | PhSH | 24[c] | 106 |
| 5-Cl-7-I-8-$Pr^iO$-Quinoline | PhSH | 70[e] | 95 |
| 5-Cl-7-I-8-$Pr^iO$-Quinoline | f | 65–100[e] | 95 |

[a] Both nucleofuges are replaced [b] Only the iodine was replaced. [c] In DMF at 80 °C. [d] In HMPA at 80 °C. [e] Only the 7-iodine was replaced. [f] Various heteroaromatic thiols.

Electrochemical studies indicate that the $PhS^-$ ion is much less reactive (with regard to trapping $Ar\cdot$) than enolate and phosphorus-centered nucleophiles[150] and 2-pyridyl and 2-quinolyl radicals have particularly low reactivity toward thiolate ions.[30] Hydrogen atom abstraction from DMSO (and also from the methyl groups in the $Me_4N^+$ ion of the supporting electrolyte), becomes a significant side reaction in the reaction of bromobenzene with $PhS^-$.[151]

The reaction of aryl halides with alkanethiolate ions is complicated by the problem of fragmentation of the first-formed radical ions (equation 48). The reaction between iodobenzene and ethanethiolate gives only 30% of ethyl phenyl sulfide and 47% of products derived from the benzenethiolate ion.[61] Fragmentation decreases in importance as the stability of the species $ArSR^{-\cdot}$ increases, but is more significant for the more stable aliphatic radicals (*e.g.* when R = $PhCH_2$ or $EtOCOCH_2$ in equation 48).[74,103] As a result, halobenzenes with electron-withdrawing substituents such as cyano or acyl groups,[74,78] or naphthyl halides,[103,111] react to give alkyl aryl sulfides in good yield with simple alkanethiolates or alkanedithiolates[152] with substantially reduced incursion of fragmentation processes (*e.g.* see equation 30). 2-Chloroquinoline and 2-bromopyridine (and its 3-substituted derivatives) behave in similar fashion, thus widening the scope of the reaction significantly.[152] 2-Chloroquinoline, alone among all the aryl halides examined to date, reacts cleanly with $PhCH_2S^-$ to give benzyl 2-quinolyl sulfide,[103] whilst all other substrates give significant, usually major proportions of products resulting from cleavage of the benzyl–S bond. The thiolate, $EtO_2CCH_2S^-$, on reaction with 2-chloroquinoline, however, gives 2-quinolinethiol in 75% yield, with no detectable amount of the expected sulfide.[74] The highly specific fragmentation occurring with this anion could perhaps be used as a method for replacement of halogens on aromatic rings by the thiol group.

$$\mathrm{Ar}\bullet + {}^{-}\mathrm{SR} \longrightarrow \mathrm{ArSR}^{\bullet -} \longrightarrow \mathrm{ArS}^{-} + \mathrm{R}\bullet \qquad (48)$$

### *2.2.3.3.2 Preparation of diaryl selenides and tellurides*

The reactions of aryl halides with $PhSe^-$ and $PhTe^-$ ions are complicated by fragmentation of the intermediate radical anions which leads to scrambling of the aryl groups and production of mixtures (see equations 7 and 8).[35] Diphenyl selenide[54] and telluride[54,55] have been prepared in 73% and 90% respectively from iodobenzene, and *p*-iodobromobenzene gives 70% and 40% isolated yields of *p*-bis(phenylselenyl)- and *p*-bis(phenyltelluryl)-benzene respectively.[54] Unsymmetrical phenyl aryl chalcogenides can be prepared when the aryl moiety sufficiently stabilizes the intermediate radical anions, lowering the occurrence of fragmentation processes. 4-Chlorobiphenyl, 1-halonaphthalenes, 9-bromoanthracene and 2-chloroquinoline give 37–98% yields of the phenyl aryl selenides[54,153,154] and 1-bromonaphthalene and 2-chloroquinoline give 53% and 43% yields of the respective aryl phenyl tellurides.[54,55] In all but the reaction of $PhSe^-$ with 2-chloroquinoline, minor amounts of scrambled products are still formed, and prolonged irradiation or use of an excess of the phenyl chalcogenide further reduce the yield.[35] Several useful methods for *in situ* generation of aryl chalcogenide ions from the respective elements, aryl halides and alkali metals in dipolar aprotic solvents[155] or in liquid ammonia[156] (analogous to that used with phosphorus, see Scheme 6) also have been developed and these lead to diaryl chalcogenides and related derivatives in fair to good yields. Very recently electrochemically stimulated reactions with sonication in acetonitrile, between either $PhSe^-$ or $PhTe^-$ and 4-chlorobenzonitrile have been reported to give yields of 57 and 42% of the respective substitution products, and subsequently it was shown that all three bromobenzonitriles, give 36–70% yields with $PhSe^-$.[83] Similar yields have been obtained from electrochemical reactions of the same chlorobenzonitriles with $PhSe^-$ and $PhTe^-$ ions in the presence of redox catalysts,[82] and the same technique has been successfully applied (in 44–86% yields) in the replacement of either bromine or chlorine by PhTe or PhSe groups in *o*-, *m*- and *p*-halobenzophenones.[79] In reactions involving alkyl chalcogenide ions, fragmentation is expected, and accordingly, photostimulated reactions of adamantyl selenide or telluride ions with iodobenzene give most unpromising mixtures.[157]

## 2.2.4 CYCLIZATIONS UTILIZING THE $S_{RN}1$ REACTION

Cyclization processes taking advantage of the $S_{RN}1$ reaction as one of its steps have been increasingly used in the last decade, and fall into two general categories. The first type have an intramolecular $S_{RN}1$ reaction on an aryl halide by a nucleophile already attached to the aromatic ring, and the second class have an $S_{RN}1$ reaction on *ortho*-functionalized aryl halides followed by cyclization of the initial substitution product. Beugelmans recently summarized the use of both these cyclization sequences for the preparation of heterocyclic systems.[17] The majority of the reactions involve attack on aromatic rings by carbanions, almost exclusively enolate ions. The following sections are divided according to mode of ring closure and the nature of the products.

### 2.2.4.1 Ring Closure by Intramolecular $S_{RN}1$ Reactions

Formation of cyclized products, resulting from intramolecular attack of the intermediate aryl radical in the $S_{RN}1$ reaction on a second aromatic ring (*i.e.* intramolecular homolytic arylation) are rare and not synthetically useful.[64,158–161]

The first reported intramolecular $S_{RN}1$ reaction by Semmelhack and coworkers,[162,163] was the photostimulated ring closure of (**42**) with $Bu^tO^-$ to give a 93% yield of cephalotaxinone (**43**), the immediate precursor of the antileukemia agent, cephalotoxin. As a consequence of this synthesis, Semmelhack and Bargar, studied the viability and the regiochemistry of the photostimulated ring closure of the series of methyl ketones (**44**; X = Br or I; $n$ = 2, 3, 4 or 6) and their α- or α′-permethylated derivatives in the presence of $Bu^tO^-$ in liquid ammonia.[44,45] It was possible to prepare six-, seven-, eight- and ten-membered rings, but competing β-hydrogen abstraction process interfered in some cases. The presence of α-methyl groups enforced regiochemical control on the reaction and prevented internal hydrogen transfer reactions. The regiochemistry of the ring closure for the ketones (**44**; X = Br; $n$ = 3 or 4) appeared to be controlled by the proportion of the respective enolate ions present, and greater proportions of the cyclic ketones resulting from attack through the methyl group occurred to give the seven- and eight-membered cyclic ketones in preference to the products with five- and six-membered rings, respectively. Cyclization of the ketone (**44**; X = I; $n$ = 2) failed completely on account of β-hydrogen abstraction processes.

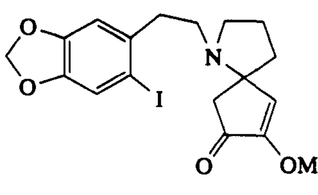

**(42)**

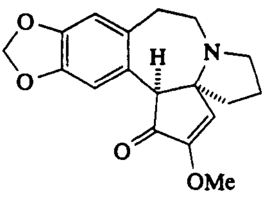

**(43)**

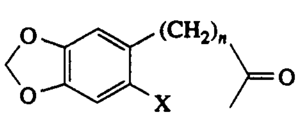

**(44)**

The photoinduced cyclization of mono- and di-anions of *N*-acyl-*o*-chloroanilines and *N*-acyl-*o*-chlorobenzylamines was developed by Wolfe and coworkers as a general method for the preparation of oxindoles[49,50] and 1,4-dihydro-3(2*H*)-isoquinolinones, respectively.[50] The generalized reaction for the oxindole synthesis is shown in equation (49; Z = CH), and the yields range from 32–83%, with most in excess of 60%. The reaction proceeded readily when substituents were *ortho* to the chlorine (*i.e.* not an aryne mechanism) or elsewhere on the ring, except that a $CF_3$ or additional Cl substituents caused the reactions to fail. α,β-Unsaturated-*N*-alkylanilides reacted, but only in liquid ammonia with $KNH_2$ as base, to give 3-alkylideneoxindoles in yields usually over 65%. The method was also extended to the preparation of azaindoles (equation 49; Z = N), but in this case there had to be an alkyl group on the amide nitrogen before successful reactions occurred. The analogous reactions of acylbenzylamines, to give isoquinolone derivatives proceeded in 40–65% yield.

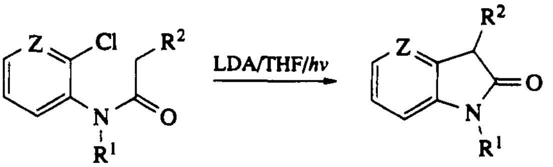

Z = CH, N

(49)

*o*-Iodothiobenzanilide and *o*-iodothioacetanilide undergo ring closure on treatment with $Bu^tO^-$ in DMSO, but only when the reaction is performed with entrainment by $^-CH_2COMe$, to give 2-phenyl- and 2-methyl-1,3-benzothiazoles respectively.[164]

Two further quite different cyclization processes each have an initial intermolecular $S_{RN}1$ reaction followed by a second in which the ring closure is made. The reactions of *o*-dihalobenzenes (**24**) and (**25**) with the dithiolate (**26**) to give (**27**) have already been mentioned (see equation 28), but the yield of analogous product formed between (**26**) and 1-bromo-2-iodonaphthalene is only 24% and use of 1,2-ethanedithiolate with *o*-diiodobenzene gives only 13% of benzo-1,4-dithiane.[98] A rather convenient one-step synthesis of [*m.m*]-*meta*-cyclophanediones (*m* = 3–8) in most acceptable yields is obtained on tandem $S_{RN}1$ reactions of the ketones (**45**; equation 50).[165]

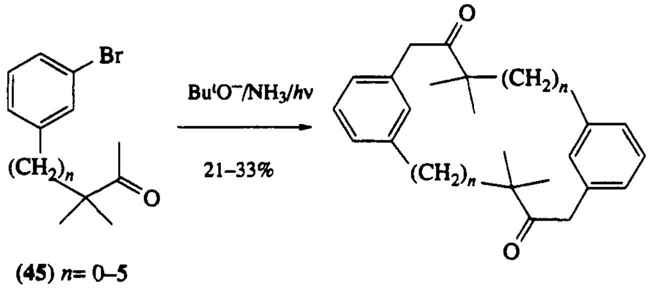

**(45)** *n* = 0–5

(50)

### 2.2.4.2 $S_{RN}1$ Reactions Followed by Cyclization

The only examples of carbocyclic products arising from cyclizations subsequent to $S_{RN}1$ reactions, are the isolated example reported by Bunnett and Singh,[94] which gives products (**18**)–(**20**; Section 2.2.2.4.2) and the recently reported synthesis of unsymmetrically hydroxylated 2,2′-binaphthyls.[114] The final products result from aldol condensation of the primary products under the basic reaction conditions. In the binaphthyl synthesis, an example of which is given in Scheme 7, the sequence of reactions proceeded in 59–83% overall yield.[114]

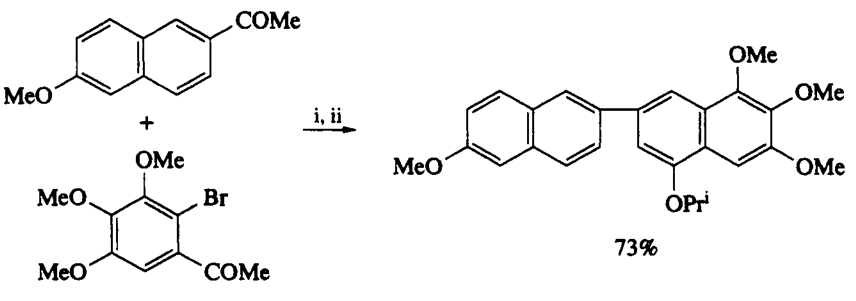

i, Bu$^t$OK/DMSO/$h\nu$ ; ii, 2-bromopropane

Scheme 7

The first of many heterocyclization reactions, depending on an initial $S_{RN}1$ reaction between the enolate of a carbonyl compound and an *o*-substituted haloarene, followed by cyclization, is represented by the formation of indoles from *o*-haloanilines and enolate ions, first reported by Beugelmans and Roussi,[166] and shortly afterwards by Bard and Bunnett.[76] This reaction (Scheme 8; Z = CH; X = Br or I) was used not only with the enolates of a wide range of ketones,[73,76,166,167] but also with enolates derived from aldehydes.[73,166,167] Symmetrical ketone enolates gave single products, and methyl alkyl ketones with branching at the α-carbon gave good yields of the 2-substituted indole. 2-Butanone gave mixtures of 2,3-dimethyl- and 2-ethyl-indole, with the former predominating. Aldehyde enolates ($R^1$ = H) led regiospecifically to 3-alkylindoles but, under these photostimulated reaction conditions, appreciable amounts of dehalogenated products were formed.[73] This competing process was virtually eliminated under electrochemical conditions.[167]

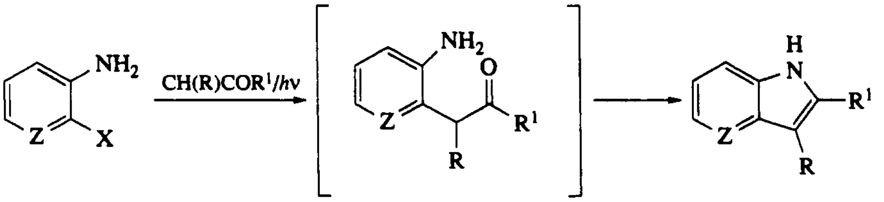

Z = CH, N; R, $R^1$ = H, alkyl; X = I, Br, Cl

Scheme 8

4-Azaindoles (1*H*-pyrrolo[3,2-*b*]pyridines) were prepared by an entirely analogous method with that developed for indoles, starting with 3-amino-2-chloropyridine, and the same diversity of reacting enolates and similar regioselectivity effects were observed (Scheme 8; Z = N; X = Cl).[76,125,168] 1,2-Disubstituted pyrrolo[2,3-*b*]pyridines were also prepared by a related process, in which 2-fluoropyridine was first selectively *o*-lithiated and then iodinated to give 2-fluoro-3-iodopyridine. Preparation of 2-amino derivatives by $S_NAr$ replacement of the 2-fluorine gave the required substrates for the $S_{RN}1$ ring closure sequence. Using similar strategies, 2-alkylpyrrolo[2,3-*b*]-, -[2,3-*c*]- and -[3,2-*c*]-pyridines were also prepared.[115]

The fusion of a furan ring onto isolated benzene rings, the benzene ring of quinolines, or pyridine rings, is readily brought about in good yield by reaction of *o*-halo ethers with ketone enolates followed by ether cleavage and furan ring formation, leading to benzo[*b*]furans,[71] furo[3,2-*h*]quinolines or furo[3,2-*b*]pyridines.[96] Examples of these syntheses are given in Scheme 9.

The isoquinoline system is conveniently prepared from treatment of *o*-iodobenzylamines with the enolate ions derived from symmetrical ketones (or ketones with one α-position blocked), aldehydes, or the dimethyl acetal of pyruvaldehyde, to give aminocarbonyl compounds which condensed *in situ* to give 2- and/or 3-substituted 1,2-dihydroisoquinolines. Catalytic dehydrogenation or borohydride reduction of these products then led to the corresponding isoquinolines or tetrahydroisoquinolines in moderate to high

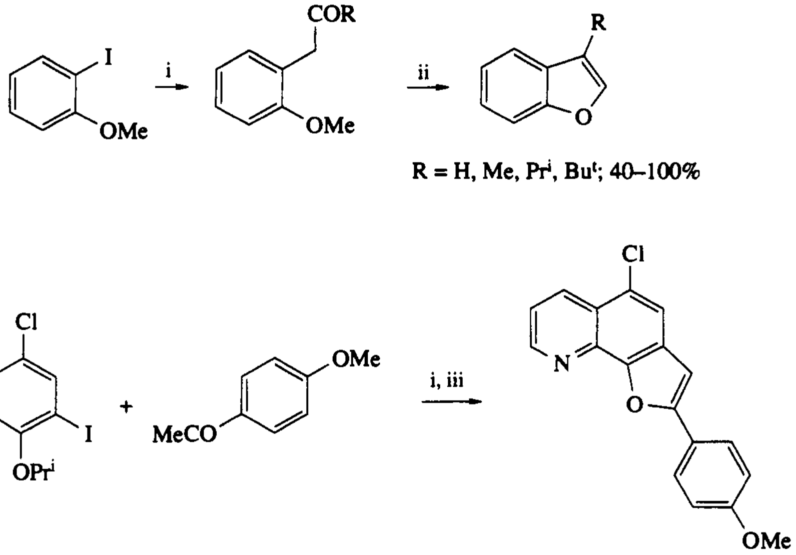

i, MeCOR/KOBu$^t$/NH$_3$/$h\nu$ ; ii, Me$_3$SiCl/NaI; iii, 48% HBr/AcOH/100 °C

Scheme 9

yields.[169,170] Natural products (and analogous compounds) with the benzo[*c*]phenanthridine skeleton, were prepared through this route by using substituted *o*-iodobenzylamines and substituted α-tetralones in the initial $S_{RN}1$ reaction, followed by oxidation and catalytic dehydrogenation of the subsequent condensation product.[171] The isoquinoline system, in the form of 1,2-dihydroisoquinolones is also readily accessible through the $S_{RN}1$ reaction of *o*-halobenzamides (and their *N*-alkyl derivatives) with the enolate ions of ketones, including those from acetophenones, followed by cyclization and dehydration (usually spontaneous) of the primary product, as outlined in Scheme 10.[123,172] An alternate route through isocoumarins is also possible. Treatment of *o*-halobenzoic acids with ketone enolates first gives $S_{RN}1$ products which can be isolated as esters,[70] or can also be cyclized on treatment with acid to give isocoumarins. Subsequent treatment of the isocoumarin with a primary amine leads to dihydroisoquinolones,[172] or when α-tetralones are used as the carbonyl component and catalytic dehydrogenation of the final cyclization product is carried out, the final products are benzo[*c*]phenanthridones.[171]

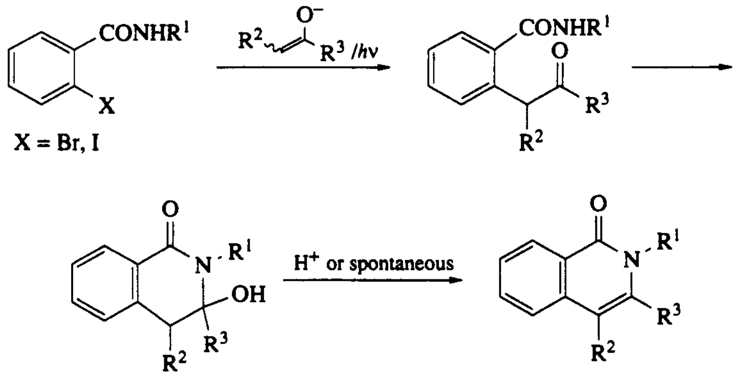

Scheme 10

The halogens in *o*-bromo- or *o*-iodo-veratric acids are replaced by ketone enolates to give primary products which on lactonization or lactamization lead to benzazepines or benzoxepines respectively.[126] There would appear to be no reason why this reaction could not be extended to reactions of *o*-halophenylacetic acids in general.

In one of the few examples not involving enolate ions, the substitution of Br in *o*-bromo-benzaldehyde or -acetophenone by $^-SCH_2CO_2Et$ ion followed by Claisen condensation of the resulting sulfides, (**46**) and (**47**), under the reaction conditions ultimately gave substituted benzo[*b*]thiophenes (**48**) and (**49**) in

55 and 40% yields respectively. The relatively low yields are a result of competing radical anion fragmentation processes which led to the thiols (**50**; 10%) and (**51**; 48%).[74]

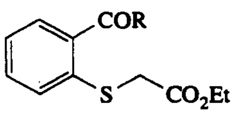

(**46**) R = H
(**47**) R = Me

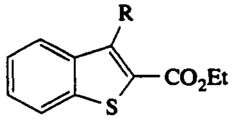

(**48**) R = H
(**49**) R = Me

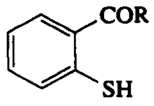

(**50**) R = H
(**51**) R = Me

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# 2.3

# Nucleophilic Coupling with Arynes

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## 2.3.1 INTRODUCTION

Functional group substitution plays a pivotal role in the synthetic chemistry of aromatic compounds, and one important reaction serving this purpose proceeds through arynes. Formally derived from aromatic rings by removal of two *ortho* hydrogen atoms, and kinetically unstable, these intermediates find sporadic reference in the early literature — primarily to explain the strange phenomenon of *cine* substitution. The first decisive evidence came with the observation that equal amounts of anilines (**2**) and (**3**) are formed in the reaction of $^{14}C$-labeled chlorobenzene with $KNH_2$ in liquid ammonia (equation 1).[1] This demonstrated the involvement of a symmetrical intermediate like (**1**). Additional support for aryne intermediacy was found in its reactions with phenyllithium and in Diels–Alder-type trapping.[2] A great deal of work on the generation and reactions of arynes was undertaken in the 1960s, and is covered in a comprehensive monograph by Hoffmann.[3] Much of the subsequent work is dealt with in some more recent reviews.[4,5]

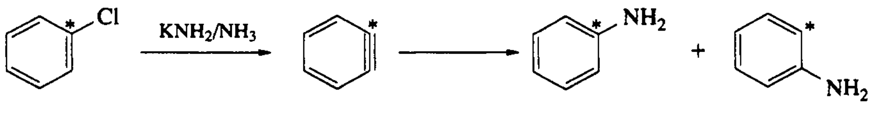

(1)

$* = {}^{14}C$ (**1**) (**2**) (**3**)

The structure of benzyne, the parent member of the aryne group of intermediates, has been the focus of many experimental and theoretical studies. For instance, its IR spectrum has been recorded by low temperature solid matrix photolysis of precursors like benzocyclobutanedione (4) and diazalactone (5).[6–9] Force field calculations based on these observations indicate an extended triple bond in benzyne (**6a**).[10] Semiempirical and *ab initio* calculations also predict the 'arynic bond' to be longer than a normal triple bond and the other C—C bonds to be similar in length to those in benzene.[11,12] The observed microwave spectrum of benzyne is in accord with these conclusions.[13] So are the vertical ionization potentials obtained from its photoelectron spectrum,[14] although some doubts about the assignments have been raised.[15,16] A recent *ab initio* study, in which electron correlation is taken into account, indicates more cumulene (**6b**) like features in benzyne than predicted by earlier calculations at the Hartree–Fock level.[17] Irrespective of the finer details of the geometric dimensions and orbital energy levels of benzyne, it may be considered to have a weak third bond produced by lateral overlap of in-plane orbitals. The symmetric combination (**7**) of these two orbitals is lower in energy than the antisymmetric combination (**8**) and hence the ground state of benzyne should be a singlet. This inference is supported by all recent calculations and there is little evidence for triplet character in any reaction of arynes.

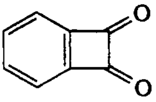

**(4)**

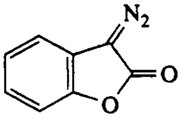

**(5)**

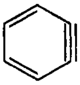
**(6a)**

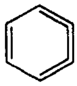
**(6b)**

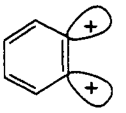

**(7)**

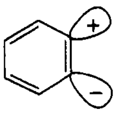

**(8)**

The reactivity of benzyne can be explained in terms of its high enthalpy of formation which has been experimentally determined to be around 120 kcal $mol^{-1}$ (1 cal = 4.18 J).[18–20] The difference between enthalpies of formation of an alkyne and an alkene is usually about 37 kcal $mol^{-1}$; with an enthalpy value of 20 kcal $mol^{-1}$ for benzene, the strain energy in benzyne comes out to be nearly 63 kcal $mol^{-1}$.[4e] Besides general reactivity, benzyne also exhibits marked electrophilicity and from this point of view, its LUMO energy level is of special import. The HOMO of benzyne is calculated to be at –9.58 eV, which is little different in energy from the corresponding bonding orbital of acetylene. However, the LUMO is estimated to be at 1.33 eV, which is much lower in energy than the acetylene LUMO. This has been attributed to 'bending' of the triple bond which results in an efficient mixing of the $\pi^*$ orbital with a $\sigma^*$ orbital lying only slightly higher in energy.[21] The lowering of the benzyne LUMO decreases its energy gap with the HOMO of an attacking nucleophile and makes for an easy reaction between the two. Thus, many nucleophilic reagents which are inert towards alkynes add readily to arynes. If electron-withdrawing substituents such as halogens are present on an aryne, its electrophilicity is further enhanced. Another point of interest in nucleophilic addition to arynes is the high polarizability of the formal triple bond. As a consequence, arynes behave as 'soft' electrophiles and their reactions with polarizable nucleophiles are specially facile. However, sometimes reactions of aryl halides with nucleophiles under seemingly benzyne-generating conditions may not involve these intermediates.[5a,22,23]

Other prominent reactions of arynes include cycloadditions and the ene reaction as shown in equations (2)–(5). The former have been used extensively for the synthesis of a variety of benzo-annulated systems and for the diagnosis of aryne intermediates.[1–5] Normally, these reactions do not fall in the category of nucleophilic coupling. However, in some cases the electrophilic character of the arynic partner is quite manifest and as such a brief discussion is included in Section 2.3.3.

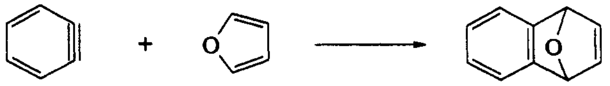

(9)

(2)

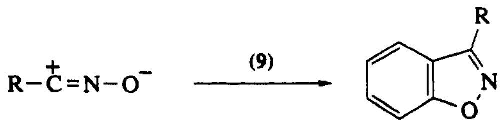

(3)

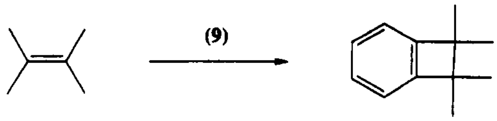

(4)

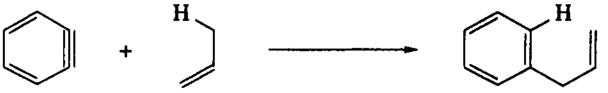

(5)

Dehydroheteroarenes like (**10**) and (**11**) have also been proposed as intermediates in nucleophilic substitution.[23–25] Some of these reactions were evaluated uncritically and operation of other mechanisms like addition–elimination (AE) and ring opening–ring closure (ANRORC) can now be demonstrated in many such cases. Nevertheless, there is conclusive evidence for heteroaryne intermediacy in some reactions of heterocyclic halides. From the preparative point of view, nucleophilic coupling of such intermediates has found only limited applications.[26–28] Reactive intermediates with an additional formal bond between nonadjacent atoms, like (**12**) and (**13**), have also been postulated but again hold little synthetic interest.

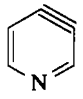

(**10**)

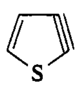

(**11**)

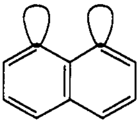

(**12**)

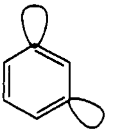

(**13**)

Many stable metal complexes of arynes are known but in most of their reactions of synthetic interest, the yields are poor. For example, thermolysis of titanocene ($Cp_2TiPh_2$) at 80–100 °C gives rise to a titanium–benzyne complex which reacts with molecular nitrogen to afford aniline with low efficiency.[29] However, procedures are available for *in situ* generation of zirconium complexes (**14**) and for their coupling reactions to synthesize functionalized aromatic compounds in preparatively useful yields (Scheme 1).[30] Whether such complexes should be regarded as π-bonded benzynes or σ-bonded *o*-phenylenes, remains a debatable point.[31]

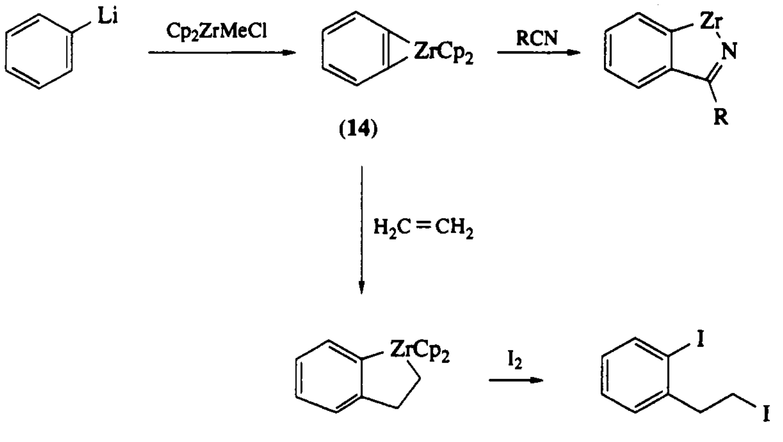

Scheme 1

## 2.3.2 GENERATION OF ARYNES

Much of the early work on arynes was undertaken using the aryl halide–strong base route (equation 6), but a variety of other procedures, discussed below, are also available. In practice, the choice of the method of generation is often governed by the nature of the reaction to be carried out subsequently. Since arynes are transitory intermediates used *in situ*, the conditions employed for their formation have to be compatible with the properties of the other reacting partner. Further, in preparative work, the accessibility of the benzyne precursor and its cost can be important considerations.

### 2.3.2.1 From Aryl Anions

Aryl anions having a good leaving group (X) in the *ortho* position readily afford arynes (equation 6). For this purpose, halides have been used widely but other electrofugic groups, like OPh, OTs, OTf, $N^+_2$, $NR^+_3$, $SR^+_2$, $IR^+$, have also been employed. Since both the deprotonation and the benzyne formation steps can be reversible,[32] many factors such as the nature of the leaving group, the base and the solvent play an important role in the rate and efficiency of aryne generation. The ease of halide expulsion from (**15**) is I > Br > Cl > F but the rates of initial proton removal are in the reverse order. In the case of aryl fluorides, reprotonation can compete effectively with benzyne formation, while with iodides, there is greater ease of reversal in the second step. For these reasons, and because of easier accessibility, chloro- and bromo-benzenes are used most commonly. In general leaving groups other than halogens offer no particular advantage. For example, phenyl benzenesulfonate reacts with lithium 2,2,6,6-tetramethylpiperidide (LTMP) to give benzyne but the yields of adducts are less than those obtained with bromobenzene.[33]

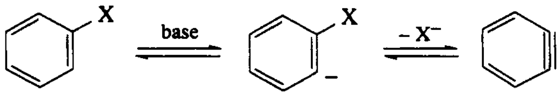

**(15)** **(9)**

(6)

A wide variety of base–solvent combinations can be employed for the deprotonation of aryl halides. However, alkali metal aryls/alkyls in ether solvents or amides in liquid ammonia have been used most extensively. In these systems, reactions of the generated arynes with the solvent or the base can pose a serious problem, especially when coupling with relatively weak nucleophiles is desired. Metal aryls and alkyls can be used in ether solvents which have low reactivity towards arynes but these bases are very powerful nucleophiles. On the other hand, metal amides are somewhat less reactive but ammonia, the commonly employed solvent, has a greater proclivity for aryne capture. Thus, the use of amidic bases in aprotic solvents may be preferable, provided the solubility is acceptable. Sodamide in THF, alone or with HMPA, can function effectively when used in conjunction with a second anionic base such as sodium *t*-butoxide.[34] In reactions carried out with commercial sodamide in THF special precautions to exclude air and moisture are necessary.[35] More recently, LDA in THF is finding extensive use in coupling reactions of arynes.[36–38] For minimizing aryne reaction with the amide base used for its generation, the highly hindered LTMP has also been recommended.[39,40] With this base, another common side reaction, hydride transfer from the α-carbon leading to aryne reduction, is also precluded. It should be noted that whereas

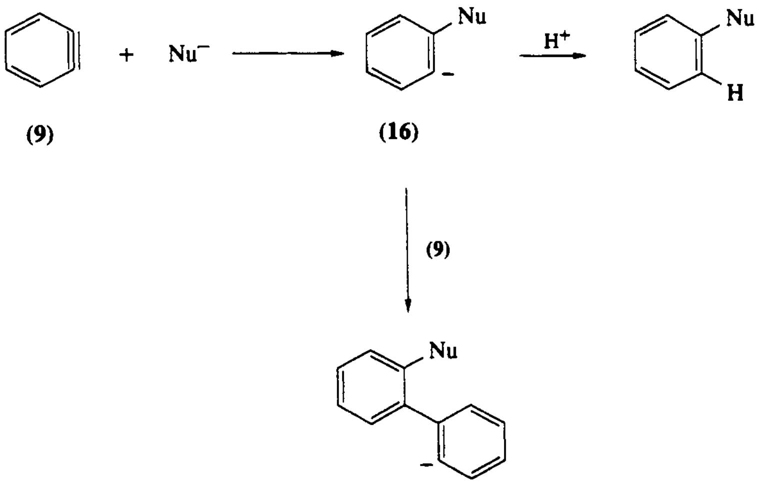

**(9)** **(16)**

**(17)**

(7)

the use of ethers minimizes reaction of the benzyne with the solvent, it also prolongs the life time of the adduct anion (**16**), which in ammonia is protonated promptly. Therefore, undesirable reactions of (**16**) occur to a greater extent under aprotic conditions.

At higher temperatures, weaker bases can be used for the generation of arynes from aryl halides. Sodium methanesulfinyl carbanions in DMSO are effective above room temperature,[41,42] while sodium hydroxide reacts with chlorobenzene at about 250 °C to give phenol, presumably through a benzyne intermediate.[1] With substrates having strongly activating groups, even mild bases lead to deprotonation, *e.g.* betain (**19**) can be generated from (**18**) with potassium acetate (equation 8).[43] Arynes can also be formed from diazonium carboxylates derived by the rearrangement of *N*-nitrosoacylarylamines such as (**20**).[44] However, these methods are more useful for [2 + 4] trapping reactions of arynes than for their coupling with strong nucleophiles.

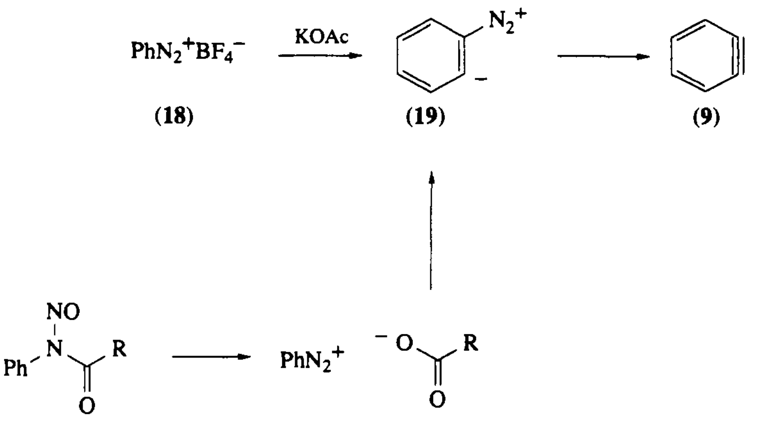

(**18**) (**19**) (**9**)

(**20**)

(8)

A number of procedures for the generation of arynes using disubstituted precursors have also been developed. Metal–halogen exchange in dihalobenzenes with lithium amalgam or magnesium is one such useful method.[1] Electroreduction of dihalobenzenes,[45] reaction of Grignard reagents with aryl sulfoxides[46] or defluorosilylation of arylsilanes[47,48] have also been used for the generation of arynes (equation 9). Decarboxylation of 2-halobenzoates also leads to aryne formation but requires high temperature.[1] However, 1-(*o*-halophenyl)-2-benzenesulfonylhydrazides are decomposed under milder conditions.[49]

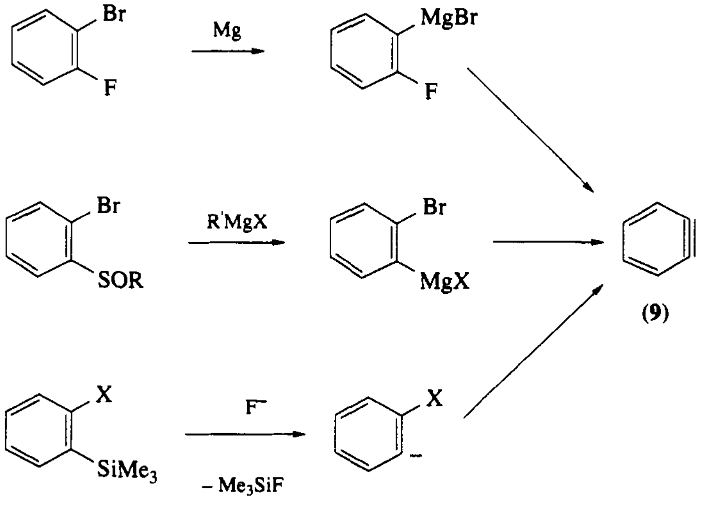

(**9**)

(9)

X = Cl, Br or Tf

A very popular route to arynes involves decomposition of benzenediazonium 2-carboxylates.[50] The explosive nature of diazonium compounds is a major disadvantage of this method, although procedures for safe preparation and handling have been described.[51] An alternative is to carry out the diazotization of anthranilic acid *in situ*, but the yields of benzyne adducts obtained in this manner are usually inferior due to side reactions.[52] In any case, the benzenediazonium carboxylate route is usually not suitable for coupling of arynes with anionic nucleophiles, since in a strongly basic medium dediazotization to benzoic acid eclipses the formation of the reactive intermediate.[53] This method can, however, be used in reactions with uncharged nucleophiles. Diphenyliodonium-2-carboxylate is a safe benzyne precursor but requires decomposition above 150 °C.[54] A new convenient procedure comprising thermolysis of silyl sulfoxides has been developed recently (Scheme 2).[5d]

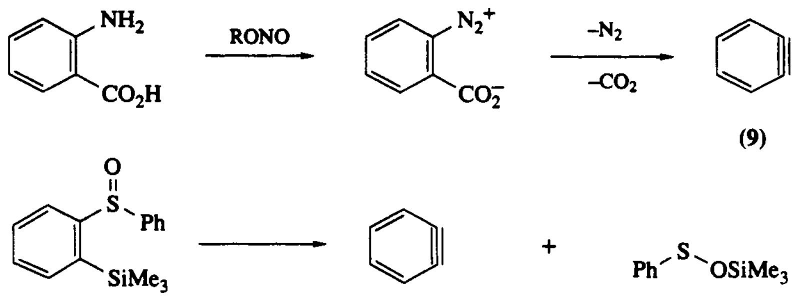

(9)

Scheme 2

### 2.3.2.2 From Fragmentation of Cyclic Systems

Arynes can be readily generated by thermal or photolytic fragmentation of several benzo-fused systems.[1] The conditions required for the cleavage of such precursors vary widely. For instance, azosulfone (**21**), obtained by diazotization of 2-aminobenzenesulfinic acid, decomposes in organic solvents at room temperature to give nitrogen, sulfur dioxide and benzyne.[55] In the case of phthalic anhydride (**22**), gas phase pyrolysis at 700 °C is needed, while phthaloyl peroxide (**23**) affords benzyne on irradiation. Oxidative decomposition of 1-aminobenzotriazole can be effected at temperatures as low as −80 °C (equation 10).[56] Several variations of this method have been explored with a view to avoid oxidizing agents. The salt (**24**) furnishes benzyne on dissolving in polar solvents at room temperature.[57] Of the cyclic benzyne precursors, benzotriazoles have found more preparative use in general but not many examples involving coupling with nucleophiles have been reported.

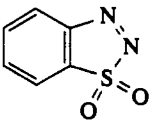

**(21)**

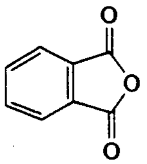

**(22)**

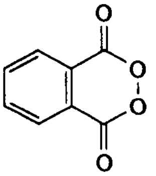

**(23)**

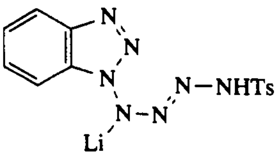

**(24)**

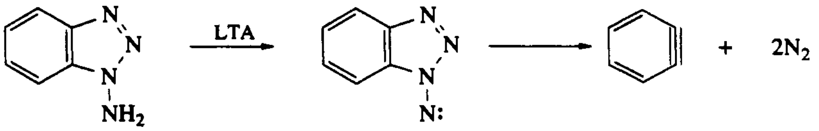

(10)

An important drawback of the aryne routes starting with bidentate or cyclic precursors can be the effort needed to prepare the precursor itself, especially for substituted arynes. However, these have the advantage that the arynic bond can be generated without positional ambiguity as illustrated in the following section.

### 2.3.2.3 Generation of Substituted Arynes

Generation of arynes from *ortho-* and *para*-substituted halides is straightforward. In the *meta* case, aryne formation can take place in two directions (Scheme 3). Regioselectivity in this situation is dependent on the relative rates and reversibility of the deprotonation and the dehalogenation steps. With substituents which exert an electron-withdrawing (–*I*) effect or favor *ortho* metalation by chelation, aryne formation in the adjacent position predominates, if the halide ion loss is fast. In the case of aryl halides with +*I* substituents the regioselectivity can be poor. For example, treatment of 3-bromoanisole (**25a**) with LDA/THF leads to 3-methoxybenzyne (**27a**) primarily.[36] In contrast, the reaction of 3-bromotoluene (**25b**) with $KNH_2/NH_3$ gives (**27b**) and (**29b**) in 40:60 ratio. Interestingly, with the corresponding chloride this ratio is reversed to 79:21. It has been suggested that in both halides, metalation *para* to the methyl group is faster ($k_3 > k_1$).[1] However, in the aryl bromide this step is virtually irreversible due to rapid bromide ion loss. With the chloride, equilibration between the metalated species (**28**) and (**26**) takes place and the chloride ion loss from the latter is faster ($k_2 > k_4$). When there is ambiguity in aryne formation from aryl halides, bidentate precursors can be used to get the arynic bond in a predetermined position. For instance, aryne (**27b**) can be exclusively generated from diazonium carboxylate (**30**). This route has been used for obtaining some other substituted arynes also.[52,58]

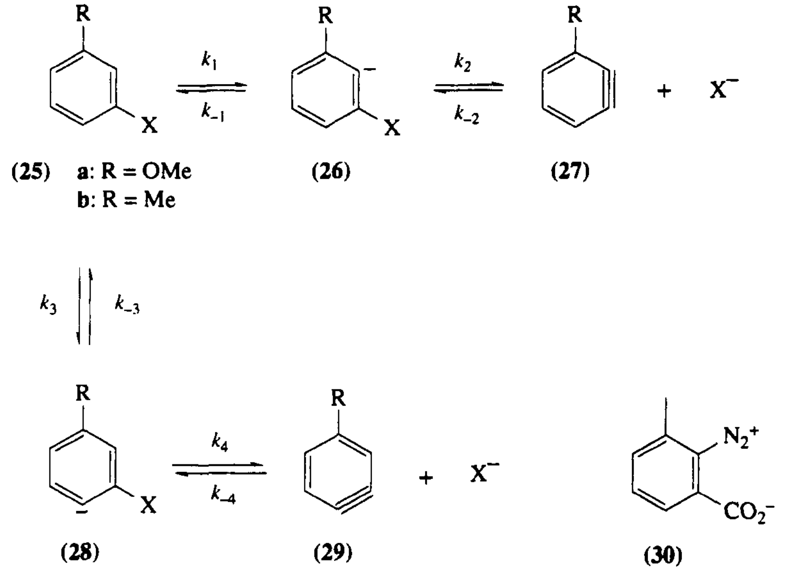

Scheme 3

In polycyclic systems with bond fixation, dehydrohalogenation tends to occur in one direction only, *e.g.* 2-bromonaphthalene gives 1,2-naphthalyne (**31**). The 2,3-isomer (**33**) can be obtained by the oxidation of aminotriazole (**32**).[59,60] Similarly, in some heterocyclic systems marked regioselectivity on dehydrohalogenation is observed. Thus, treatment of 3-bromopyridine with strong base affords (**34**). For the generation of 2,3-dehydropyridine, the dihalogenated substrate (**35**) is required.[24] The question of chemoselectivity comes up with substrates having two potential leaving groups, such as the mixed dihalobenzenes which can afford two different arynes on dehydrohalogenation. In such cases the heavier halogen is often lost preferentially,[61] *e.g.* (**36**) gives 3-chlorobenzyne. The generation of arynes from di- and tri-halogenated arenes can get complicated by prior isomerization, termed 'halogen dance'.[62] However, perchloro- and perfluoro-arynes can be obtained efficiently.[63,64]

Finally, the conditions used for generation of substituted arynes have to be compatible with the nature of the substituent group. In the aryl halide–strong base route, a wide range of substituents can be tolerated; alkyl, aryl, trifluoromethyl, halogen, alkoxy, dialkylamino, methylthio, carboxylic and cyano groups exert no deleterious effect. However, strongly electron-withdrawing substituents can so stabilize the aryl anion that the halide ion loss does not occur under the usual conditions.[1] Thus (**37**) has considerable lifetime at room temperature, while the corresponding bromo compound decomposes somewhat faster. Strongly electron-donating substituents, on the other hand, can retard the deprotonation step and it may be stopped altogether if a negatively charged atom is appended to the aromatic ring. For instance, halophenoxides are not metalated by phenyllithium in ether although *n*-butyllithium is effective.[1] The anions (**38**) and (**39**) are stable towards $KNH_2/NH_3$, whereas in (**40**) and (**41**) aryne formation takes place

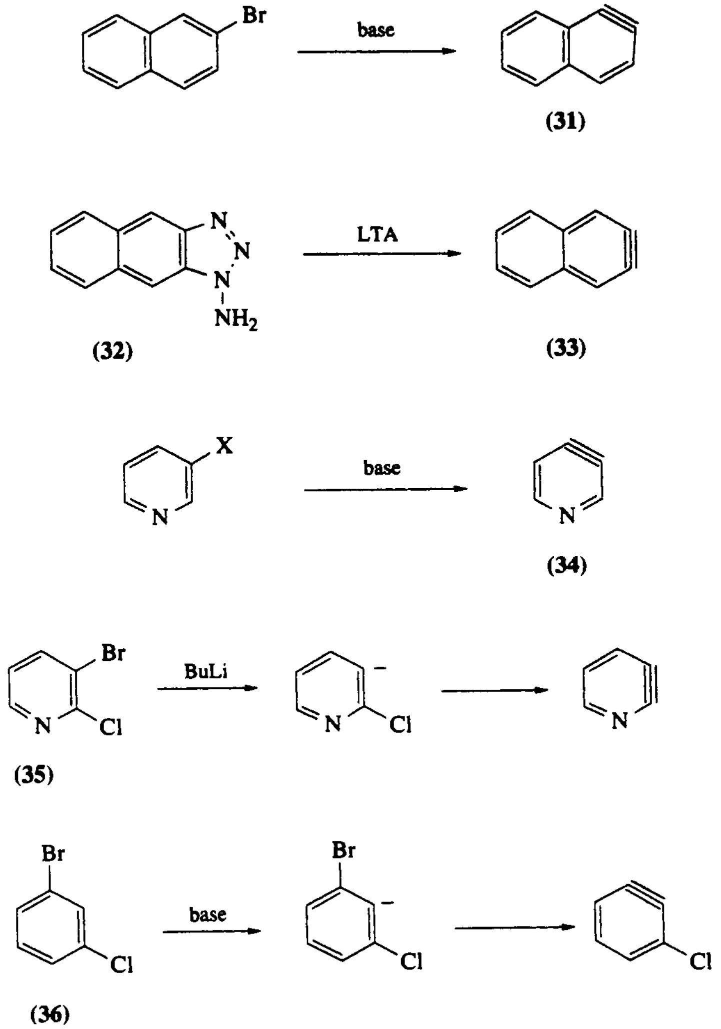
Br
base
(31)
N
N
N
NH2
LTA
(32)
(33)
X
N
base
N
(34)
Br
N
Cl
BuLi
N
Cl
N
(35)
Br
Cl
base
Br
Cl
Cl
(36)

Scheme 4

under similar conditions.[65,66] It is thus clear that the extent of substituent charge delocalization into the aromatic ring imposes a delicate balance on aryne formation. Of course, if the negative charge bearing atom in the side chain is not attached directly to the aromatic ring, benzyne formation proceeds normally.

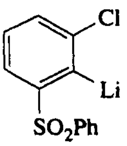

(37)

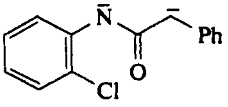

(38)

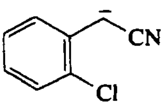

(39)

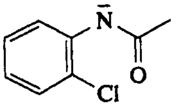

(40)

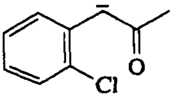

(41)

### 2.3.3 ADDITION OF NUCLEOPHILES TO ARYNES

A wide variety of anionic and uncharged nucleophiles add readily to arynes (Scheme 5). The adduct, anionic or zwitterionic, can abstract a proton from the surroundings or undergo an internal rearrangement. In the absence of such quenching, it can be trapped by addition of electrophiles. However, further aryne addition can also take place to give (17) and polymeric products derived therefrom (equation 7). Another complication in coupling of nucleophiles with arynes arises if the phenylation product is sufficiently acidic to undergo rapid deprotonation; further aryne reaction can then occur. Thus, considerable amounts of di- and tri-phenylation products are formed when α-picoline is reacted with 1 equiv. of an aryl halide in the presence of a strong base.[67]

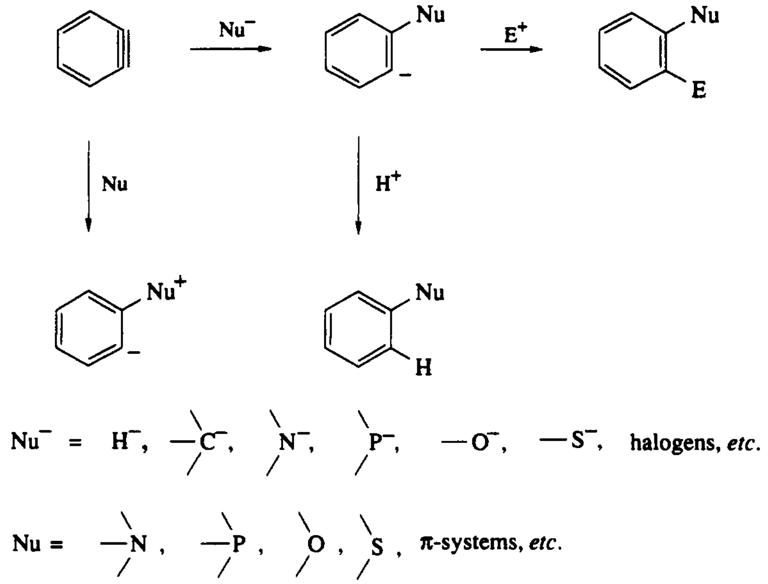
Nu⁻
Nu
E⁺
Nu
E
Nu
H⁺
Nu⁺
Nu
H
Nu⁻ = H⁻, C⁻, N⁻, P⁻, —O⁻, —S⁻, halogens, etc.
Nu = —N , —P , O , S , π-systems, etc.

Scheme 5

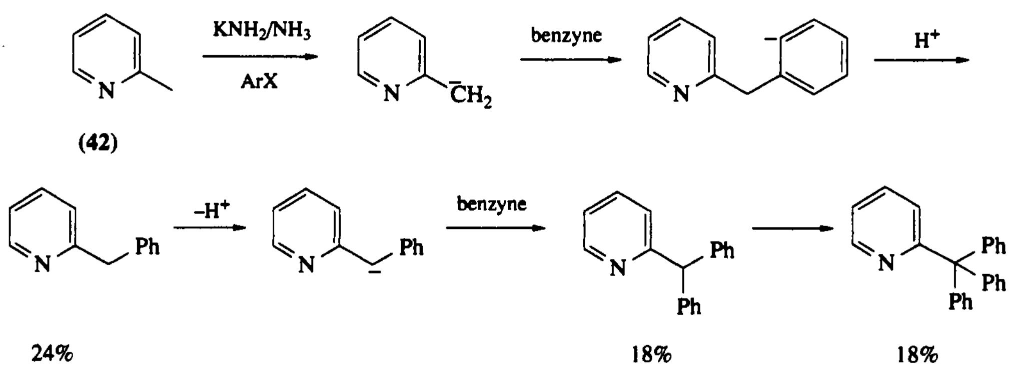

(42)

(11)

#### 2.3.3.1 Relative Reactivity of Nucleophiles

As mentioned in the introductory section, arynes behave as 'soft acids'. Therefore, the relative reactivity of a nucleophile should be governed by basicity as well as polarizability. The following gradations, established through competitive reactions of arynes with different nucleophiles, are more or less in line with this expectation.[1] (i) BuLi > PhSLi > PhNMeLi > $PhC{\equiv}CLi$ > ROLi > ArOLi, for 9,10-phenanthryne in ether; (ii) $PhS^-$ > $Ph_3C^-$ > $PhC{\equiv}C^-$ > enolates > $PhO^-$ > $RO^-$ > $I^-$, $CN^-$, for benzyne in liquid ammonia; (iii) $I^-$ > $Br^-$ > $Cl^-$ > EtOH for benzyne in alcohol.

The above series perhaps do not exactly reflect the order of inherent nucleophilicities towards arynes, because factors like the size of the attacking reagent, its state of association and the nature of the counterion can play an important role. For instance, diethylamine is 18 times more reactive towards benzyne than the bulkier diisopropylamine.[68] Nevertheless, aryne preference for soft nucleophiles is clear in a general way. It is also manifested in reactions with ambident anions derived from phenol, pyrrole and indole as substantial *C*-phenylation is observed in base-promoted reactions with aryl halides.[69]

The fact that the rates for addition of different nucleophiles to arynes vary by a wide margin shows that these intermediates are sufficiently long lived to allow high chemoselectivity. The circumstance that the nucleophilic reactivity is not entirely governed by basicity is useful in reactions where the nucleophile is not strong enough a base to generate the aryne from its precursor. In such an eventuality, another strong base has to be used, and 2 mol equiv. may be needed for the deprotonation of the aryl halide and the conjugate acid of the nucleophile. In some cases, the reaction goes to completion only if a slight further excess of the base is used. This base can compete for the aryne, but good yields of the desired product can still be obtained if the nucleophile has higher reactivity toward the aryne. For example, benzenethiolate ion is not basic enough to generate benzyne from chlorobenzene in liquid ammonia and a metal amide is used for this purpose. Nevertheless, diaryl sulfides are obtained in acceptable yields because the polarizable benzenethiolate ion is a superior aryne nucleophile.[1,70] Under similar conditions, the yield of diaryl ethers is poor and amination predominates over the reaction of benzyne with the weakly nucleophilic phenoxide ions. In the case of addenda which are poor bases and are also weakly nucleophilic, it is customary to use a nonbasic route for aryne generation.

The structure of an aryne can have a marked effect on its selectivity and the efficiency of its coupling reactions.[1,71] In general, any factor which increases the stability and the life time of a reactive intermediate should enhance its discerning power. An example is the superior selectivity of 1,2-naphthalyne, as compared to benzyne, in phenyllithium *vs.* lithium piperidide addition. This was attributed to greater stability of 1,2-naphthalyne arising out of a more effective orbital overlap across the shorter 'dehydro bond'.[1] Detailed analysis revealed that the selectivity of 1,2-naphthalyne is higher at the α-position, which is shielded by the *peri* hydrogen atom.[72] This trend is more pronounced in the case of diethylamine/diisopropylamine pair due to appreciable difference in the size of the two competing nucleophiles (Scheme 6). Thus, steric factors also play an important role in aryne selectivity.

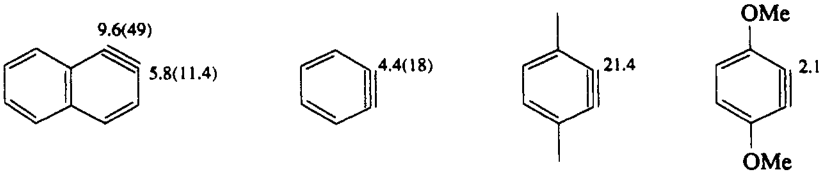

**Scheme 6** Relative aryne selectivity values for phenyllithium/lithium piperidide pair and diethylamine/diisopropylamine pair (in parenthesis)

In connection with the substituent effects, the kinetic stability of benzyne is suggested to be increased by electron withdrawal (–*I*) and decreased by electron release (+*I*).[73] However, the inference cannot be extrapolated to selectivity of substituted arynes in general. For example, in additions involving competition between phenyllithium and lithium piperidide, the methyl substituents (+*I*) on benzyne increase its selectivity, whereas methoxy groups (–*I*) decrease it (Scheme 6). On the other hand, in reactions of carbanions derived from acetonitrile in alkylamine solvents both +*I* and –*I* benzyne substituents lower selectivity and cause predominant amination. Thus, the method was found unsuitable for preparation of many substituted benzyl nitriles.[74] In symmetrically disubstituted arynes there is partial cancellation of polarization, and in fact acceptable yields of acetonitrile adducts could be obtained from 3,6-dimethoxybenzyne.[75] The selectivity of substituted arynes varies with the set of nucleophiles in the competition and no comprehensive theory or simple generalization is available on this point.

### 2.3.3.2 Regioselectivity in Nucleophilic Addition to Unsymmetrical Arynes

A nucleophile can add to either end of the 'triple bond' in an unsymmetrical aryne. Since two products can be formed, the extent and the direction of regioselectivity observed in such a reaction may determine its preparative value. Substituents present on an aryne can orient the incoming nucleophile through electronic and steric effects. As the reacting 'triple bond' is orthogonal to the ring π-system, the inductive effect of the substituents is more important than their mesomeric effect. The inductive effect may be considered to influence the site of the nucleophilic attack by polarization of the 'triple bond' or by stabilization/destabilization of the negative charge in the transition state. Arguments based on either approach lead to similar predictions. The degree of selectivity is also expected to be sensitive to nucleophile reactivity, the stronger nucleophiles being less selective.[76] Significant regioselectivity is usually obtained in additions to arynes having *–I* substituents in position 3 (**43a**), as the developing negative charge can be stabilized to a greater extent in (**44a**) than in (**45a**). The repulsive interactions are also minimal for the *meta* addition. On the other hand, with the *+I* substituents (**43b**) the electronic and the steric effects may operate in opposition to each other. The transition state corresponding to the *ortho* adduct (**45b**) is destabilized to a lesser extent electronically but it is more congested. As a consequence only with powerful electron-releasing groups, like those having a negatively charged atom attached to the aromatic ring,[77] can high *ortho:meta* product ratios be obtained. With weakly electron-releasing alkyl groups, the *ortho:meta* ratio is rarely greater than unity and can be much less if large substituents and nucleophiles are involved. In addition of lithium piperidide to 3-isopropylbenzyne this ratio is 1:24, and it is 1:2 in addition to 3-methylbenzyne. This trend in favor of *meta* addition has been utilized for the synthesis of the *meta*-substituted toluene (**48**).[78] In coupling iodide (**46**) with (**47**), the *ortho* isomer (**49**) was only a minor product. Steric effects arising out of different degrees of association of the nucleophilic anion with its countercation have been invoked to explain the decreasing *ortho:meta* ratio in the reaction of 2-chlorotoluene with $LiNH_2$, $NaNH_2$ and $KNH_2$.[79] Similarly, the preponderance of β-adducts in 1,2-naphthalyne-mediated reactions can be ascribed to *peri* hydrogen shielding of the α-position.[1]

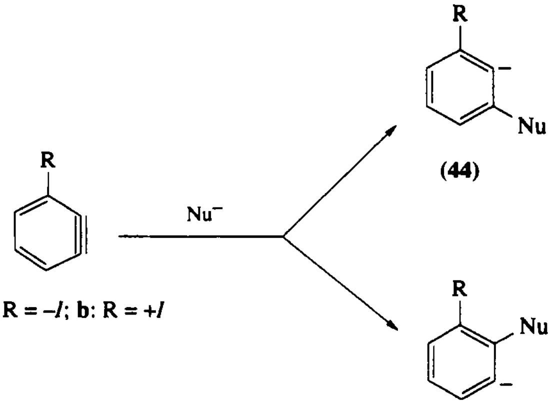

(**43**) a: R = *–I*; b: R = *+I*

(**44**)

(**45**)

Scheme 7

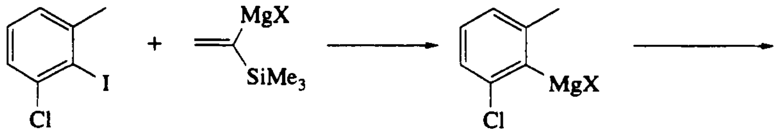

(**46**) (**47**)

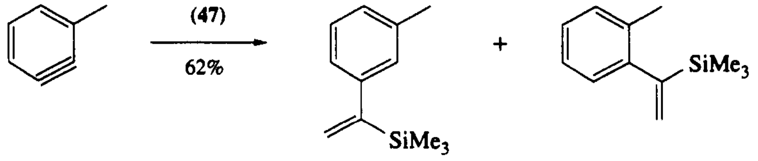

(**48**) 91% (**49**) 9%

(12)

It seems that the repulsive steric interactions play a more dominant role in regioselectivity of aryne reactions than is sometimes realized. In fact, it has been argued that in nucleophilic addition to arynes, the transition state is reached early, while the incipient bond is still very much extended. Consequently, steric effects were considered not to be of great importance.[80,81] It should, however, be noted that the 'dehydro bond' orbitals are so oriented that the optimal approach trajectory for the nucleophile lies in the plane of the *ortho* substituent (**50**). Thus, if the nucleophile is large or is heavily solvated/associated, then considerable steric hindrance to attack at the aryne carbon adjacent to a substituent can be expected.

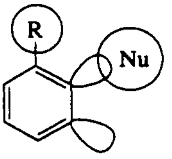

**(50)**

In addition of organometallic reagents to some arynes, prior counterion complexation with the substituent can direct the incoming group to the *ortho* position (kinetic control). Addition of alkyllithiums to oxazolinyl (OXZ) aryne (**51**) to give the *ortho* product (**52**) is explained in this manner. In contrast, lithium dialkylcuprates add to the aryne (**51**) exclusively at the *meta* position. This is ascribed to thermodynamic control of the reaction, which results in the formation of the more ligated and stable adduct (**53**).[82] Control of nucleophilic addition to arynes by complex-induced proximity effects has not been explored with substituents other than OXZ,[83] but has considerable synthetic potential if it can be achieved, say through solvent manipulation.

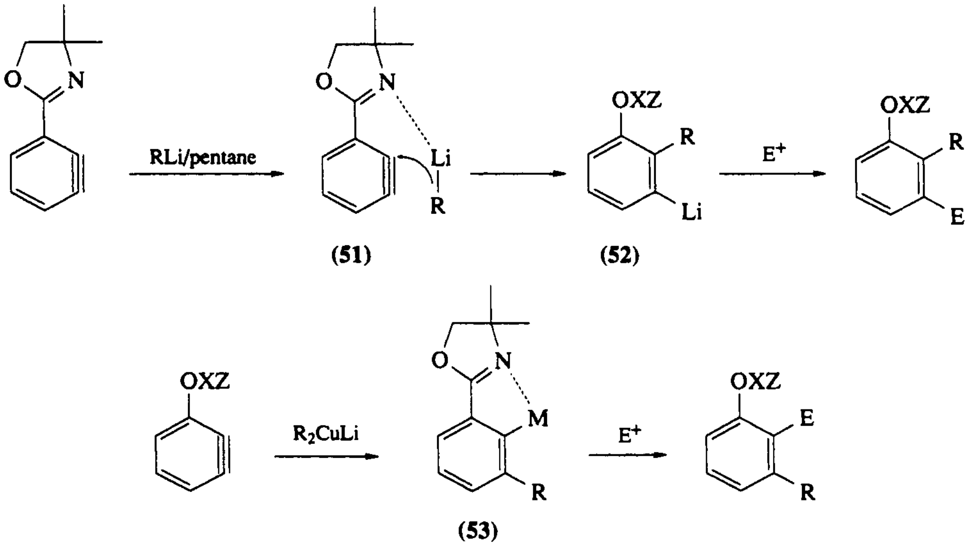

**Scheme 8**

In reactions of 4-substituted benzynes, both the inductive and steric effects are less pronounced and nearly equal addition at the two ends of the 'dehydro bond' occurs with strong nucleophiles. Weak nucleophiles, however, do show some positional selectivity. For example, the *para:meta* ratio in addition of amide ions to 4-chlorobenzyne is near unity but is 4.9 for the addition of ammonia. It was suggested that in the transition state for the addition of weaker nucleophiles, the incipient bond is more developed and there is greater transfer of negative charge. Consequently, sensitivity to the electronic effects of the substituents is heightened.[76] The recent work of Hart provides the only example of high *meta/para* regioselectivity in the addition of a strong nucleophile. Reaction of tetrahalide (**54**) with arylmagnesium bromide gave (**57**) along with a negligible amount of *m*-terphenyl. The pronounced selectivity in the addition of the Grignard reagent to the 'dehydro bond' was traced to the necessity of keeping the two negative charges away from each other in (**55**) and (**56**).[84]

In the case of 3,4-pyridynes there is some preference for nucleophilic attack at the *meta* position, because the 4-pyridyl anion is more stable than its 3-isomer. The selectivity, however, is marginal and disappears altogether when strong nucleophiles are involved. On the other hand, 2,3-pyridynes afford only C-2 adducts. It has been argued that nucleophilic attack at C-3 is highly disfavored because the negative charge developing at C-2 experiences a strong coulombic repulsion from the nitrogen lone pair. How-

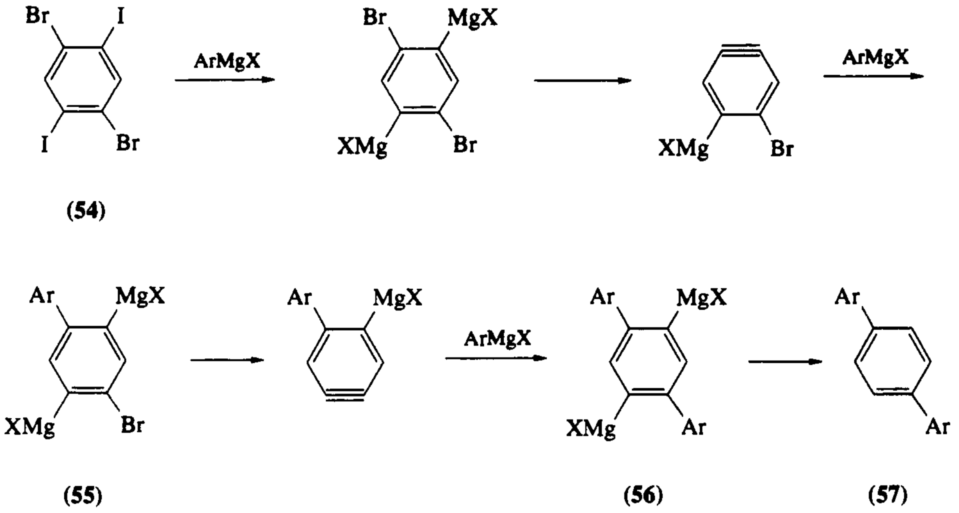

(54) (55) (56) (57)

Scheme 9

ever, pyridyne intermediacy in substitution reactions of 2-halopyridines is not fully established. An addition–elimination mechanism can also explain the exclusive formation of 2-substituted products.[24]

## 2.3.3.3 Use of Arynic Substitution in Synthesis

Arynic substitution is a versatile technique of functional group transformation in aromatic systems and has found varied applications in preparation of simple compounds and in multi-step synthesis.[3,4,5] The present section comprises examples illustrative of its synthetic scope. Attention is also drawn to some allied strategies which, when used in conjunction with the nucleophilic coupling of arynes, have opened convenient routes to complex natural products.

### *2.3.3.3.1 Intermolecular addition of anionic nucleophiles*

A variety of substituted aromatic compounds have been prepared through addition of anionic nucleophiles to arynes generated from readily accessible precursors.[1] Most of the laboratory preparations start with aryl halides. The coupling yields are usually good to modest (equations 13–15) but can be poor (equation 16).[85] Sometimes, a dramatic improvement in reaction efficiency can be achieved by the change of the base/solvent pair or other reaction conditions. For instance, in arylation of phenoxides and benzenethiolates, a switch over to DMSO as the solvent boosted the yield considerably (equation 17).[86] Another example, illustrative of this point, is the reaction of *N*-methylpyrrolidone with aryl halides where an acceptable yield could not be obtained under a variety of conditions except with LICA in THF (equation 18).[71]

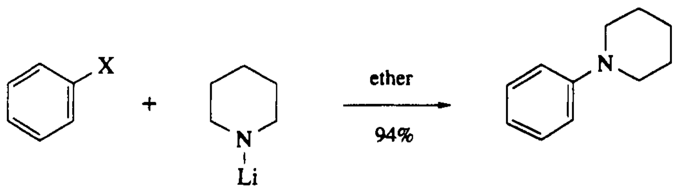

(13)

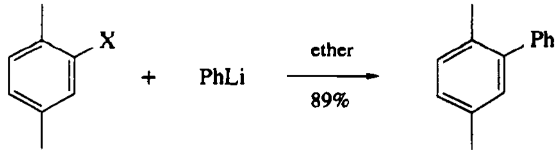

(14)

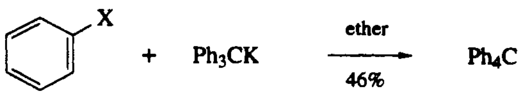
X
+ Ph3CK
ether
46%
Ph4C

(15)

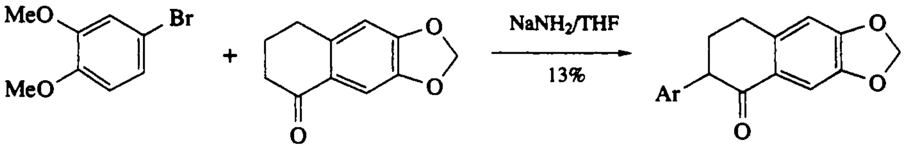
MeO
MeO
Br
+
O
O
O
NaNH2/THF
13%
Ar
O
O
O

(16)

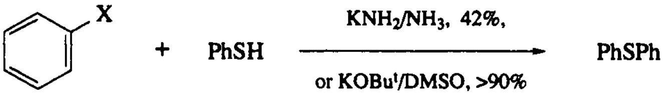
X
+ PhSH
KNH2/NH3, 42%,
or KOBu<sup>t</sup>/DMSO, >90%
PhSPh

(17)

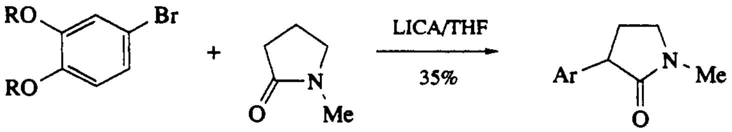
RO
RO
Br
+
O
N
Me
LICA/THF
35%
Ar
N
Me
O

(18)

The synthesis of aromatic compounds through unsymmetrical arynic intermediates entails regioselectivity in the addition step. Possibility of *cine* substitution, however, can be turned into an advantage for getting isomers which are not easily accessible otherwise. Use of oxozolinyl aryl halides for such introduction of substituents was mentioned in Section 2.3.3.2. Some other examples are given in equations (19)–(21).[87–89]

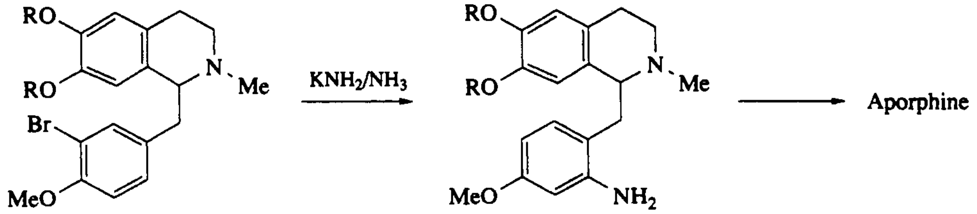
RO
RO
Br
MeO
N
Me
KNH2/NH3
RO
RO
N
Me
MeO
NH2
Aporphine

(19)

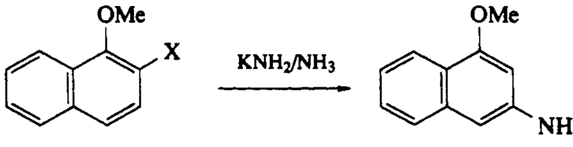
OMe
X
KNH2/NH3
OMe
NH2

(20)

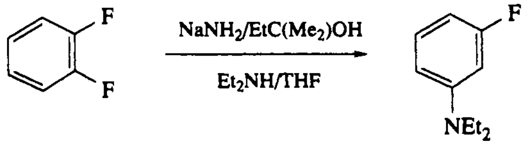
F
F
NaNH2/EtC(Me2)OH
Et2NH/THF
F
NEt2

(21)

Polyhalogenated arenes can function as diaryne equivalents *via* the tandem sequence illustrated in Scheme 10.[90,91] The predominant *meta* addition to aryne (**59**) can be ascribed to steric hindrance, while in addition to (**58**) both steric and electronic effects favor the observed regioselectivity.

If the moeity adding to the aryne carries a suitably placed electrophilic center, cyclization with the initially formed anion can occur as observed in the synthesis of dibenzothiophene (**60**).[92] Of wider synthetic import in this context is enolate addition to arynes. Here, after the initial ring closure many types of products can be formed (Scheme 11).[35] However, with some substrates, a particular reaction course can predominate;[93,94] for example, reaction of cyclodecanone with bromobenzene provides an efficient method for benzo-annulation and ring expansion. Similarly, high yields of benzocyclobutenols can be obtained from the monoketals of α-diketones.[95]

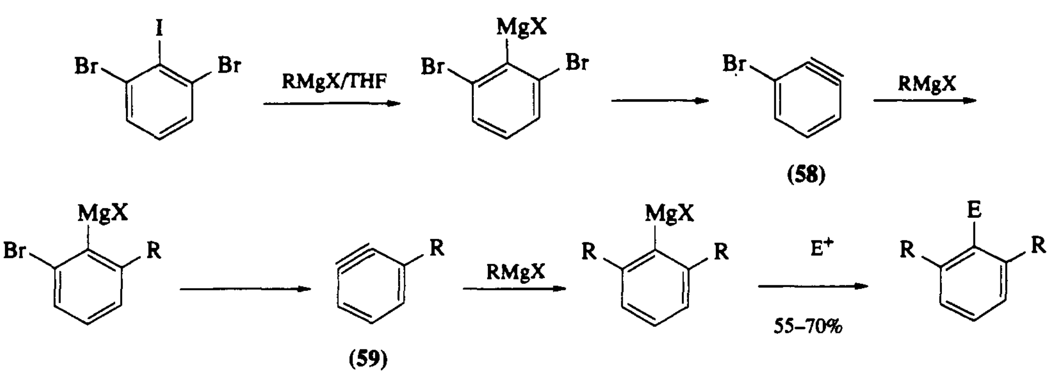

R = cyclopentenyl or neobornyl

**Scheme 10**

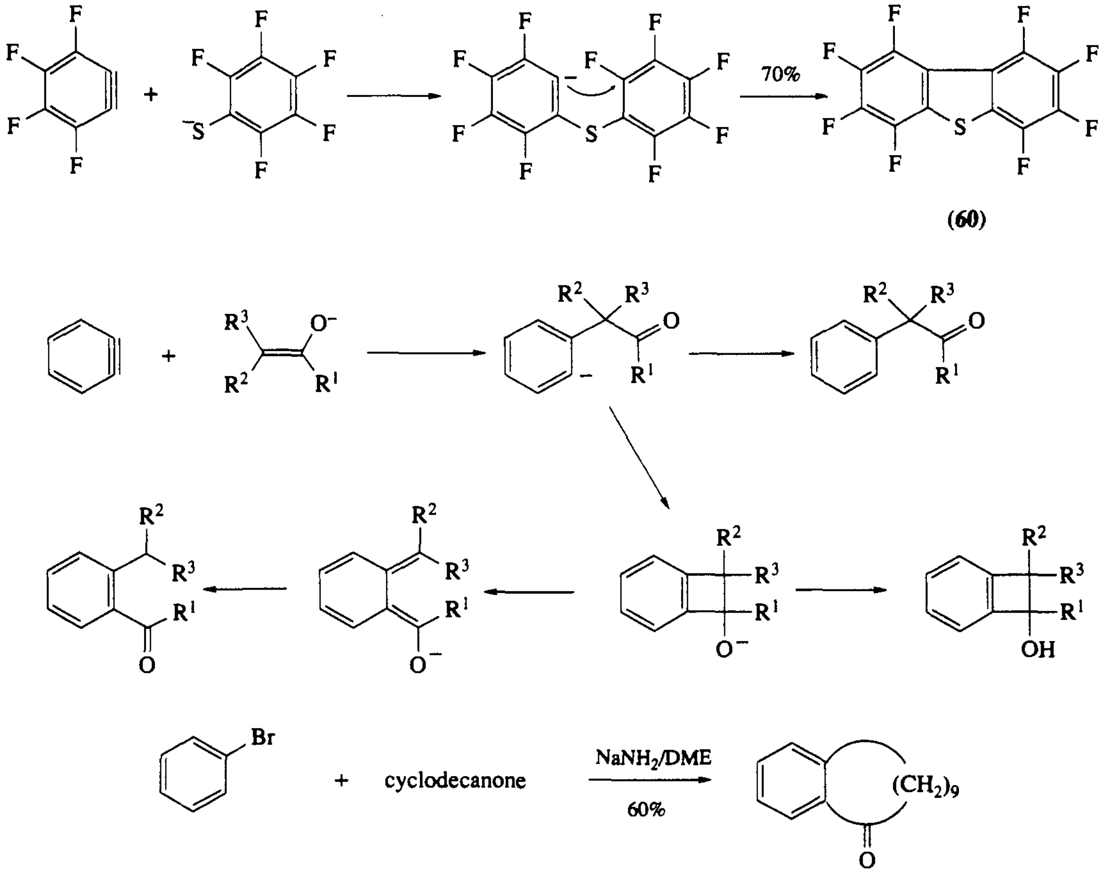

**Scheme 11**

The initial adducts formed from ester dienolates and arynes undergo ring closure to give naphthols in moderate yield (equation 22). Phthalides enter into a similar reaction to furnish 10-hydroxyanthrones which can undergo ready air oxidation to anthraquinones (equation 23).[96,97] The latter can be obtained directly from the phthalides bearing a leaving group at position 3. Thus using cyanophthalides, a number of naturally occurring anthraquinones and a precursor (**61**) of the antineoplastic drug 4-dimethoxyduanomycin have been synthesized (Scheme 12).[5b,98] Aryne reactions of anthranilic acid esters have been used to get acridones like acronycine (**62**).[99]

The nitrile group present on a nucleophile adding to an aryne can also undergo subsequent reactions. Simplest of these is the formation of an imine, which on hydrolytic work-up gives a cyclic ketone.[100] However, further imine rearrangement (**63** → **64**) can occur to give ring-opened products in which two

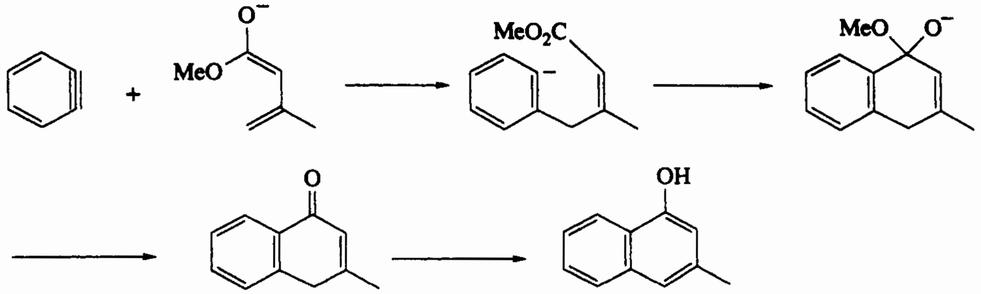

(22)

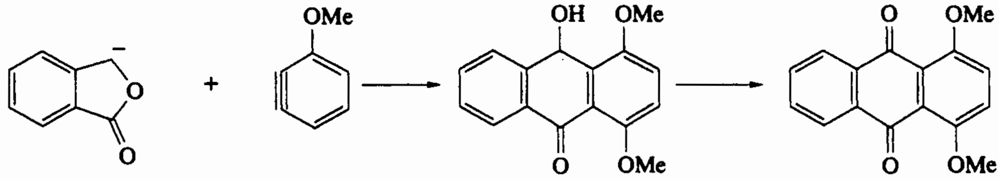

(23)

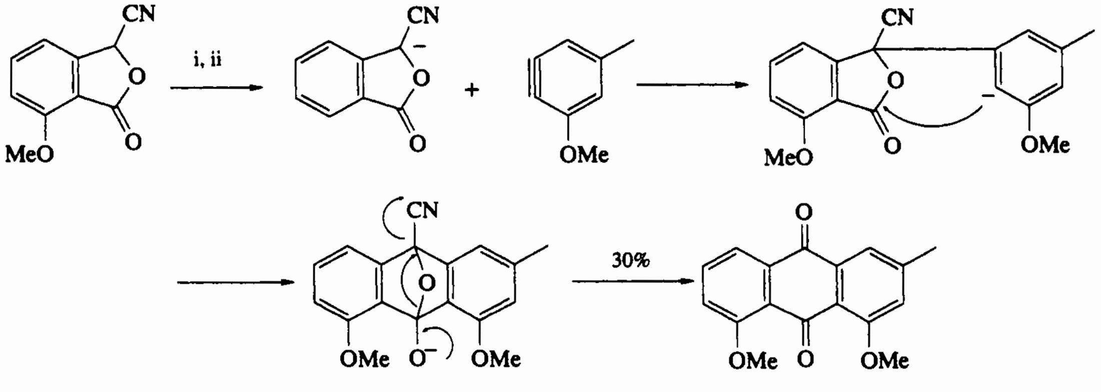

**(61)**

i, LDA (3 moles), THF, –78 to –40 °C; ii, 2-chloro-5-methylanisole

**Scheme 12**

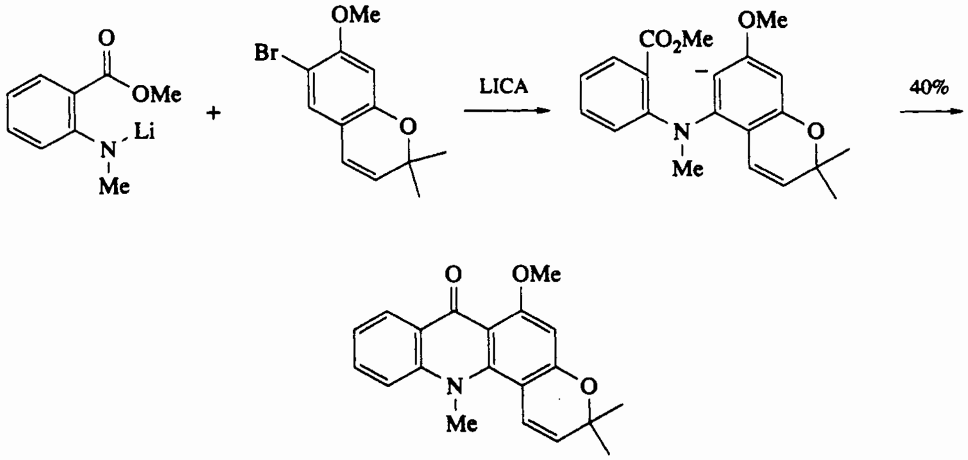

(24)

**(62)**

new groups are attached to the aromatic substrate (equation 25).[101] A number of substituted carboxylic acids and aldehydes have been synthesized in this manner and a new aryne annulation protocol has been developed.[5b,102] This rearrangement needs some driving force which may be provided by the ligation of lithium with the OXZ group. In the case of benzyl nitriles, which also give rearranged products, it may come from the additional stability of (**65**) due to charge delocalization. In the absence of such features, only simple adducts are obtained from the reactions of aryl halides with alkyl nitriles. Also, if ammonia is used as a solvent in these reactions, rapid protonation of the first-formed adduct anion may preclude all subsequent events.

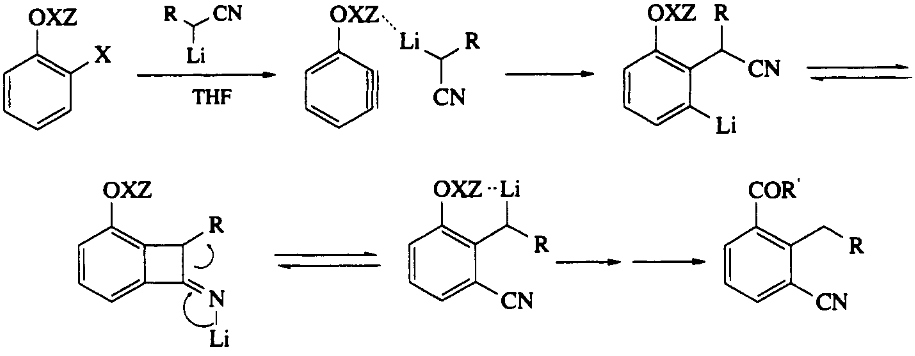

(25)

(**63**) (**64**) R' = H, OH

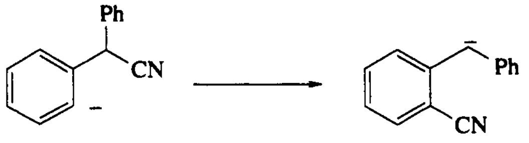

(26)

(**65**)

### 2.3.3.3.2 Intramolecular addition of anionic nucleophiles

One of the most productive applications of nucleophilic aryne coupling is for the construction of benzo-fused polycyclic systems (**66** → **68**).[66] This procedure, often called the benzyne cyclization, has been extensively used for making four-, five- and six-membered rings but larger systems have also been obtained. Its scope is extended because of the fact that some nucleophiles which are sluggish in intermolecular aryne reactions participate readily in ring formation due to favorable entropic factors. A *meta* substituted precursor like (**69**) can also be used, if it is more readily accessible than the *ortho* isomer, although the yield may be inferior due to some benzyne formation on the wrong side. Cyclizatioin of *m*-isomers can sometimes be more efficient, perhaps due to prior complexation of the proton-abstracting base with the side chain nucleophile. In such a case, not only abstraction of the correct proton ($H^1$ in **67**) occurs but also the nucleophile is kept poised for reaction at the time of aryne generation. Usually aryl

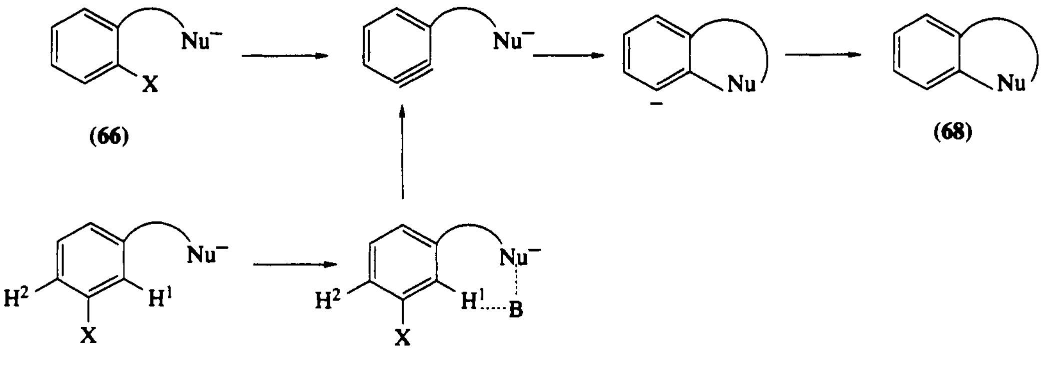

(**66**) (**68**)

(**69**) (**67**)

Scheme 13

bromides afford better yields of cyclic products than the chlorides. These general aspects of the benzyne cyclization are illustrated in equations (27)–(31).[103–107]

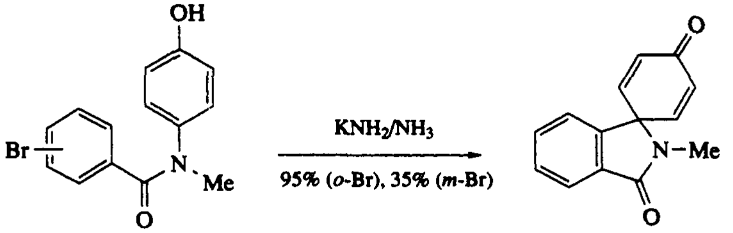
OH
Br
N
Me
O
KNH2/NH3
95% (o-Br), 35% (m-Br)
O
N–Me
O

(27)

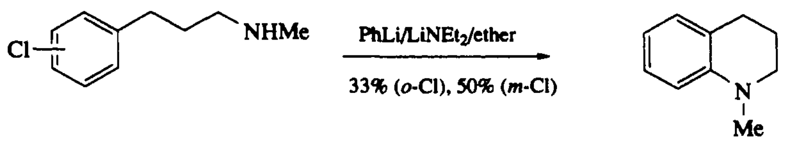
Cl
NHMe
PhLi/LiNEt2/ether
33% (o-Cl), 50% (m-Cl)
N
Me

(28)

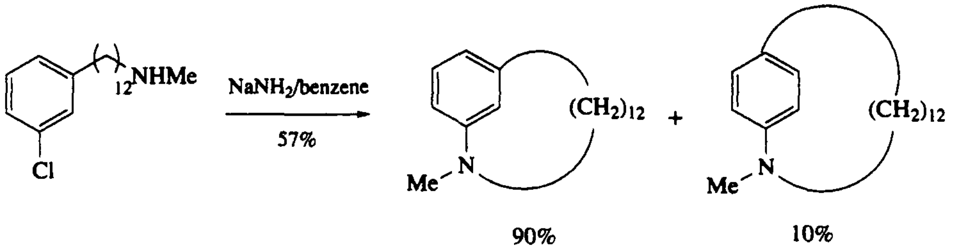
12
NHMe
Cl
NaNH2/benzene
57%
(CH2)12
Me
N
+
(CH2)12
Me
N
90%
10%

(29)

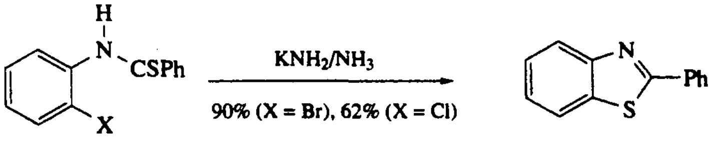
H
N
CSPh
X
KNH2/NH3
90% (X = Br), 62% (X = Cl)
N
S
Ph

(30)

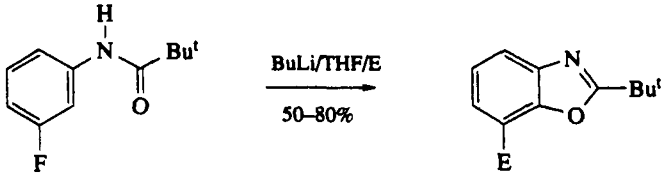
H
N
Bu^t
O
F
BuLi/THF/E
50–80%
N
O
Bu^t
E

(31)

Cyclization of side chain nitriles has found extensive use in the synthesis of benzocyclobutenes (**70**; $n = 2$),[104] the versatile synthons which open on mild thermolysis to give *o*-quinodimethanes for inter- and intra-molecular [4 + 2] trapping.[108] The nitrile group in (**70**) can be manipulated into a variety of functionalities for appending the dienophile portion. For example, in the synthesis of chelidonine, the nitrile (**71**) was converted, by hydrolysis followed by Curtius degradation and reaction of the formed isocyanate with benzyl alcohol, to a urethane (**72**). The latter was then condensed with a benzyl bromide to get the compound (**73**), which was elaborated further as shown in Scheme 14.[109]

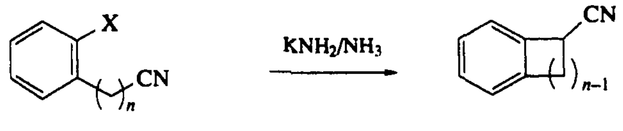
X
CN
n
KNH2/NH3
CN
n–1

(32)

(**70**)

The benzyne route to 1-cyanobenzocyclobutenes has been employed for the synthesis of a myriad of complex natural products. The cyano group in (**74**) was used to attach the dienophile as well as for building the imino bridge of (**75**), an important precursor for some diterpene alkaloids (Scheme 15).[110]

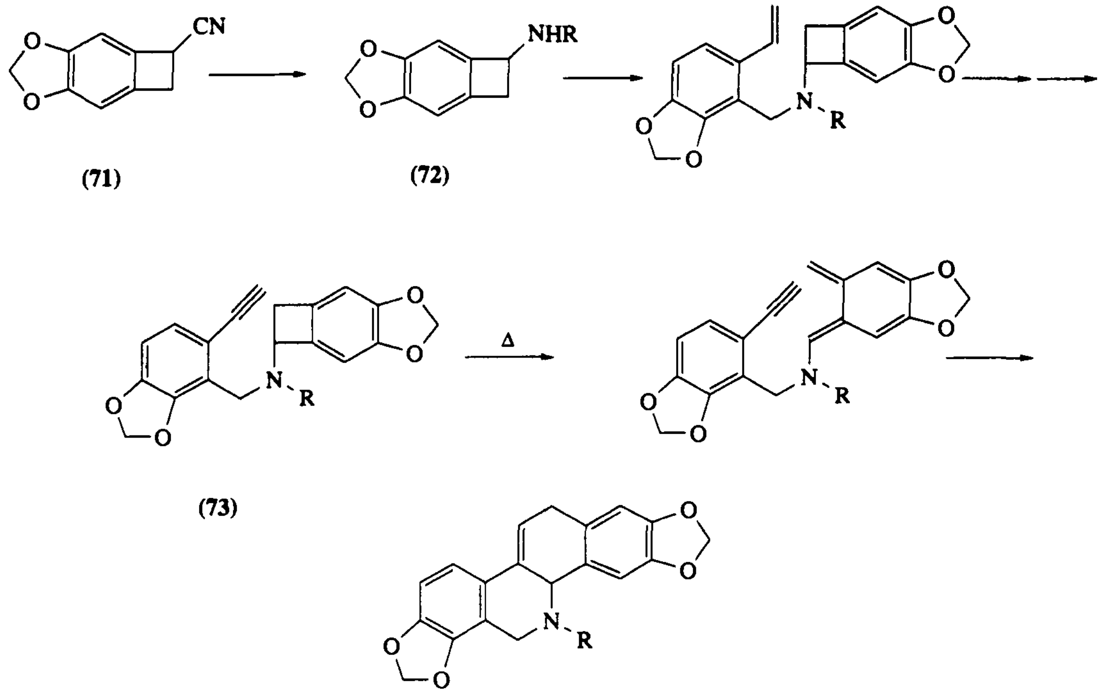

Scheme 14

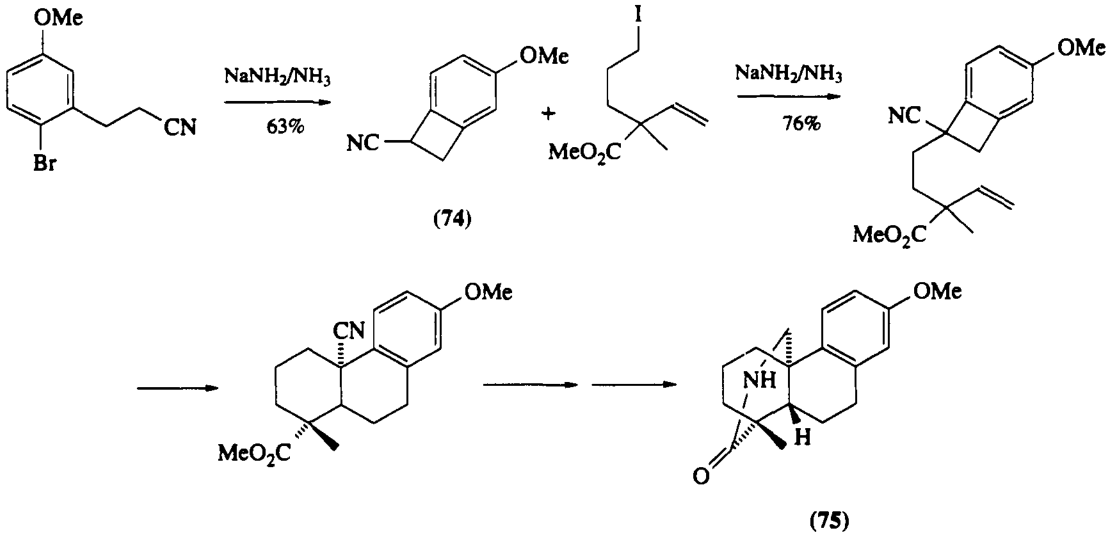

Scheme 15

Attachment of a crotonate chain to the alcohol (78), through a mixed carbonate ester, sets up the intramolecular Diels–Alder reaction in the synthesis of podophylotoxin.[111] The starting benzocyclobutenol (78) was procured by the sequence of steps shown in Scheme 16. A similar route using a carboxylic ester, in place of the nitrile (76), for the benzyne cyclization gave a mixture of *cis*- and *trans*-benzocyclobutenes but ester hydrolysis led to the pure *trans* acid (77).[112]

Among other elaborations of the cyano group of the benzocyclobutenes are Na–$NH_3$ decyanation, DIBAL reduction, and side chain elongation as used in the synthesis of estrogenic steroids.[113–115] Based on this methodology, synthesis of some tetracyclic triterpenes[116] and alkaloids like yohimbine[117] and xylopinine[118] have also been reported.

Benzyne cyclization of the side chain nitriles or carboxylic esters has also been employed for constructing other rings as shown in the synthesis of *N*-methylisoindole (79) and the lysergic acid precursor

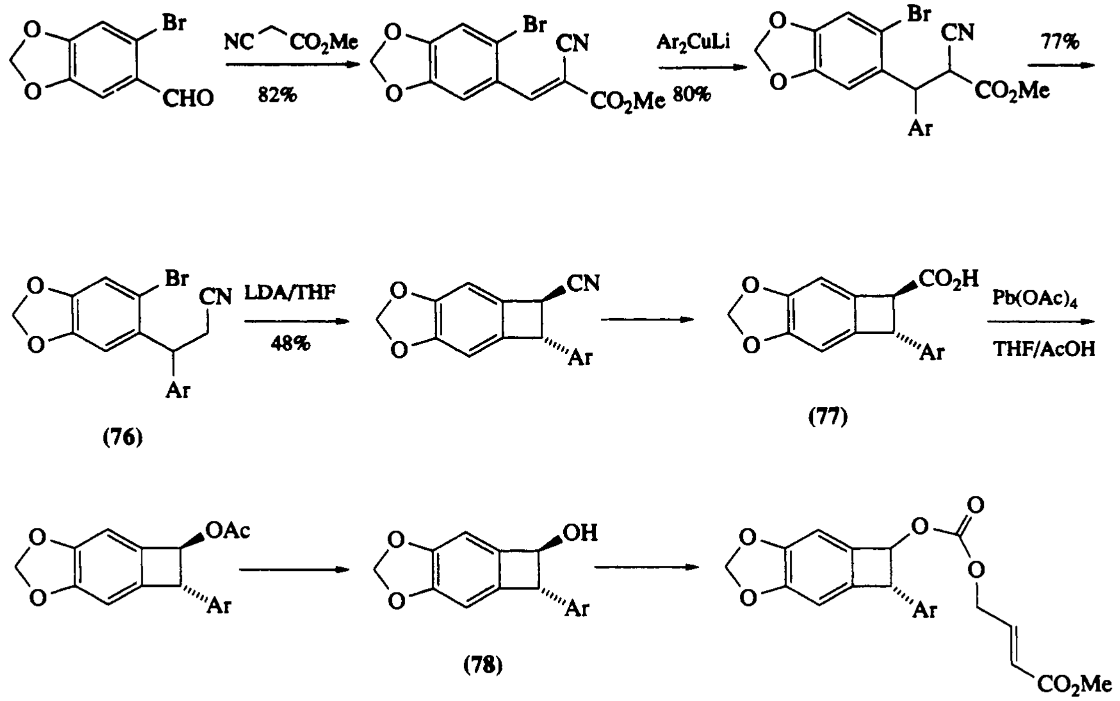

**Scheme 16**

(**80**).[119,120] The low yield in the latter case may be explained in terms of competitive aryne ring closure with the nitrogen atom to give (**81**).

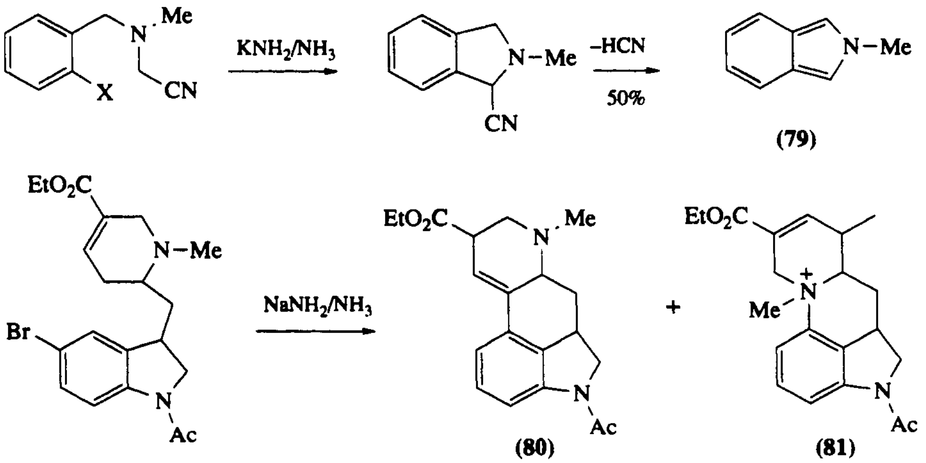

**Scheme 17**

Competition between two nucleophilic sites participating in an arynic cyclization depends upon their relative nucleophilicities as well as on the size of the rings being formed. For example, the bromo compound (**82**) could be cyclized to a lycorane smoothly because coupling with the nitrogen atom would lead to a four-membered ring.[121] In contrast, a similar reaction of enaminones (**83a**) and (**83b**) gave mostly five- or six-membered ring *N*-phenylation products (**84**).[122] Similarly, in cephalotaxine synthesis, closure to a seven-membered ring failed under the usual benzyne-generating conditions. The product (**86**) could be obtained with potassium triphenylmethide as the base, but still the yield was low. A nickel complex mediated cyclization was somewhat more efficient, while irradiation of (**85**) under $S_{RN}1$ reaction conditions[123] afforded (**86**) in 94% yield.[124] This is an example where a nonaryne procedure for ring closure was clearly advantageous.

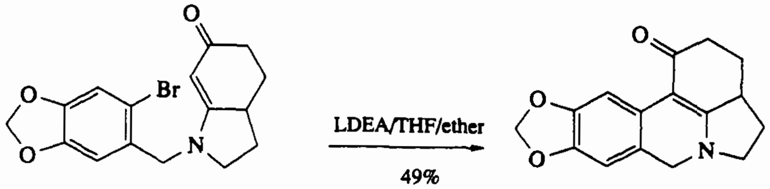

**(82)**

(33)

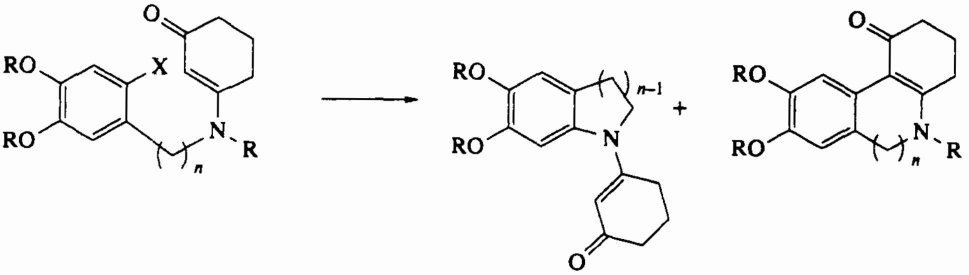

(34)

**(83)** a: $n = 2$; b: $n = 3$; R = H or alkyl **(84)**

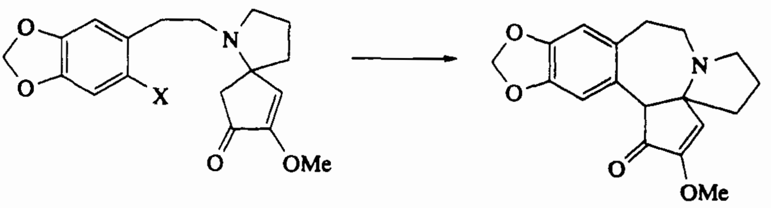

(35)

**(85)** **(86)**

Carbanions derived from side chain tertiary amides have also been cyclized to provide isoquinolones and isoindoles (equation 36).[125,126] While benzyne intermediacy in the formation of the former is likely, the latter seems to arise through a $S_{RN}1$ reaction pathway. Synthesis of indole from the *meta* bromo compound (**87**), on the other hand, clearly involves an aryne cyclization.[127] A more versatile route to indoles is based on intramolecular addition of aminyl anions to arynes (equation 38).[128] A somewhat similar dihydroindole preparation constitutes the first step in a synthesis of lycoranes (equation 39).[129] The synthesis of (**88**) also falls in the same category of reactions, but it is noteworthy because only a few examples of ring closure of heteroarynes are mentioned in literature.[27,28]

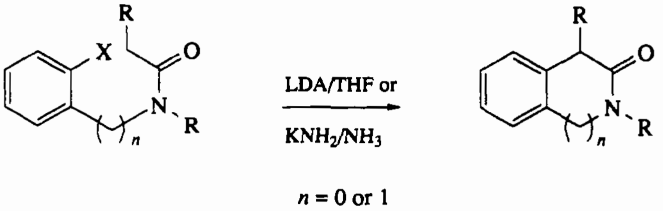

(36)

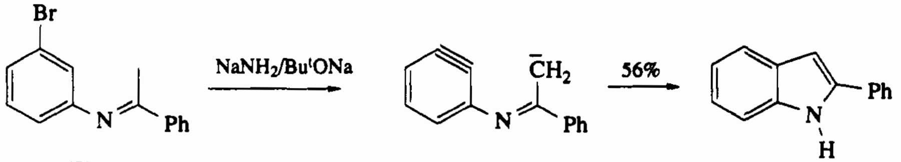

(37)

**(87)**

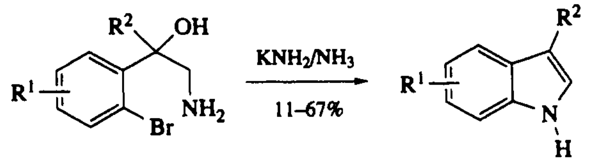
R2
OH
R1
NH2
Br
KNH2/NH3
11–67%
R2
R1
N
H

(38)

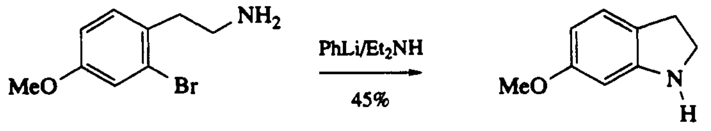
NH2
MeO
Br
PhLi/Et2NH
45%
MeO
N
H

(39)

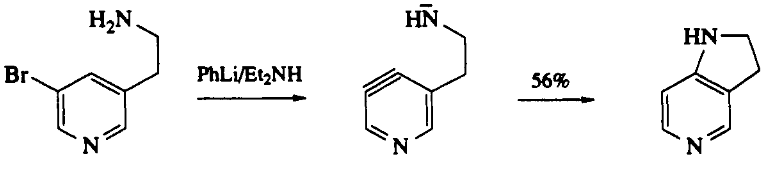
H2N
Br
N
PhLi/Et2NH
HN
N
56%
HN
N

(40)

**(88)**

Normally aromatic systems do not function as effective nucleophiles towards arynes even in intramolecular reactions. For example, the aryne (**89a**), generated from the corresponding halide and $MNH_2$ in liquid ammonia, leads only to amine (**92**) and quaternary compound (**93**). Since (**93**) tends to undergo Hoffmann degradation under the basic reaction conditions, it is preferable to cyclize the *N*-demethyl substrates and carry out the quaternization subsequently to prepare dibenzoindolizidines. The alkaloids cryptausoline (**96a**) and cryptowoline (**96b**) have been synthesized in this manner.[130,131] To forge a biphenyl link by the benzyne route, advantage can be taken of the fact that appendage of a negatively charged atom to an aromatic ring confers strong nucleophilicity at the *ortho* and the *para* positions. Thus, phenolic isoquinolines afford, through the phenoxide (**89b**), aporphines (**90**) in 20–30% yield. In these reactions, dienones (**91**) arising from aryne attack at the *para* position are also formed, albeit in poor

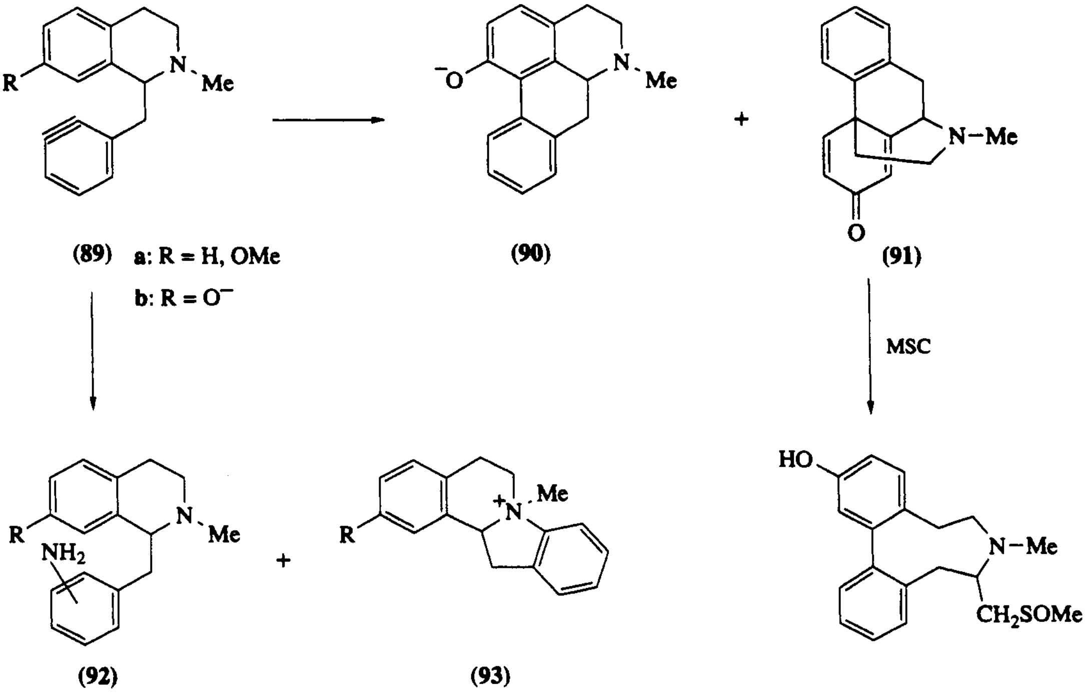
R
N
Me
(89) a: R = H, OMe
b: R = O⁻
⁻O
N
Me
(90)
+
N–Me
O
(91)
MSC
R
NH2
N
Me
(92)
+
R
N
Me
(93)
HO
N–Me
CH2SOMe

Scheme 18

yield.[132–137] If methanesulfinyl carbanion (MSC) in DMSO is employed as the base, ring opening of **(91)** can take place.[138] This base–solvent system affords acceptable yields of aporphinoids from isoquinolinium methiodides even in the absence of anionic activation.[139] Similar conditions have also been used to get cularine alkaloids through a cyclization which involves addition of an oxyanion to the arynic bond (**97** → **98**).[140]

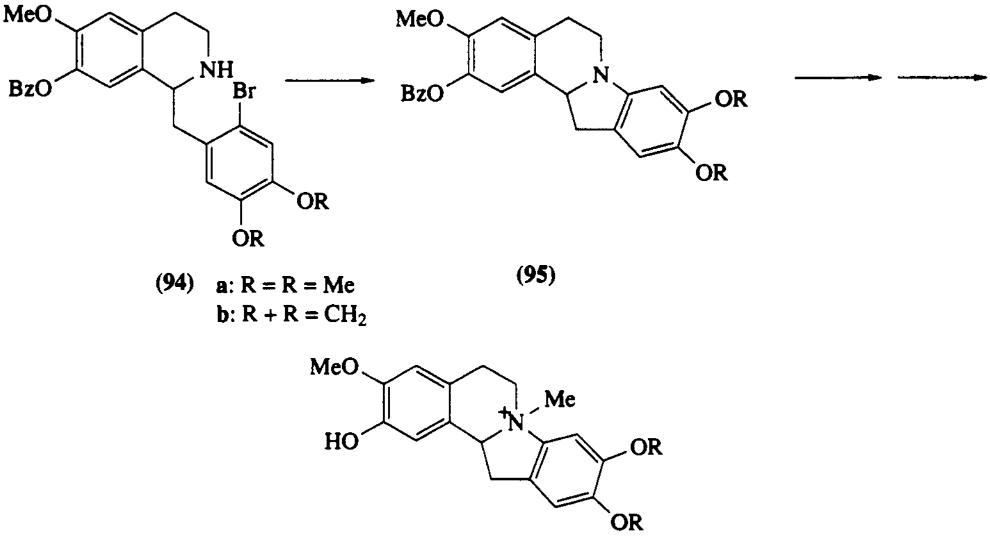

**(94)** a: R = R = Me
b: R + R = $CH_2$

**(95)**

**(96)**

(41)

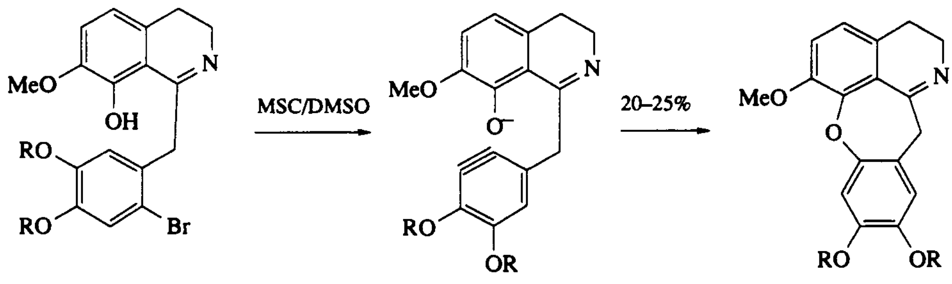

**(97)**

**(98)**

(42)

The above mentioned coupling of arynes with oxyanion-activated aromatic rings proceeds in modest yields. Since nitrogen has a greater proclivity to share negative charge, aminyl anions should serve as more efficient aryl activators. This concept forms the basis of a benzyne route to phenanthridines.[5a,141] Thus, treatment of the chloro compound **(99)** with $KNH_2/NH_3$ affords dihydrophenanthridine **(100)**, almost quantitatively. Under similar conditions, phenanthridine **(103)** can be obtained directly from anil **(101)** even though the rings to be joined are *trans* disposed. Addition–elimination of amide ions across the azomethine bond has been postulated to explain this result.[141] Many substituents and heterocyclic rings are compatible with this cyclization and a variety of systems have been synthesized.[142,143] Pentacyclic compounds, like **(105)**, can be obtained in one step through a double benzyne cyclization.[144] Pyridynes also enter into this reaction as shown in the synthesis of the grass alkaloid perlolidine **(104)**.[145] Further, this route provides a convenient access to the benzo[*c*]phenanthridine nucleus present in some alkaloids and compounds of interest in cancer chemotherapy.[146–149] Low yields in synthesis of the 8,9-oxygenated alkaloids **(106b)** can be much improved by the use of LDA/THF in the benzyne cyclization step.[37]

### *2.3.3.3.3 Addition of uncharged heteroatom nucleophiles*

Molecules having a nucleophilic heteroatom add readily to arynes. In fact, some of these exhibit reactivity comparable to anionic nucleophiles, *e.g.* the reactivity ratio between phenyllithium and triethyl-

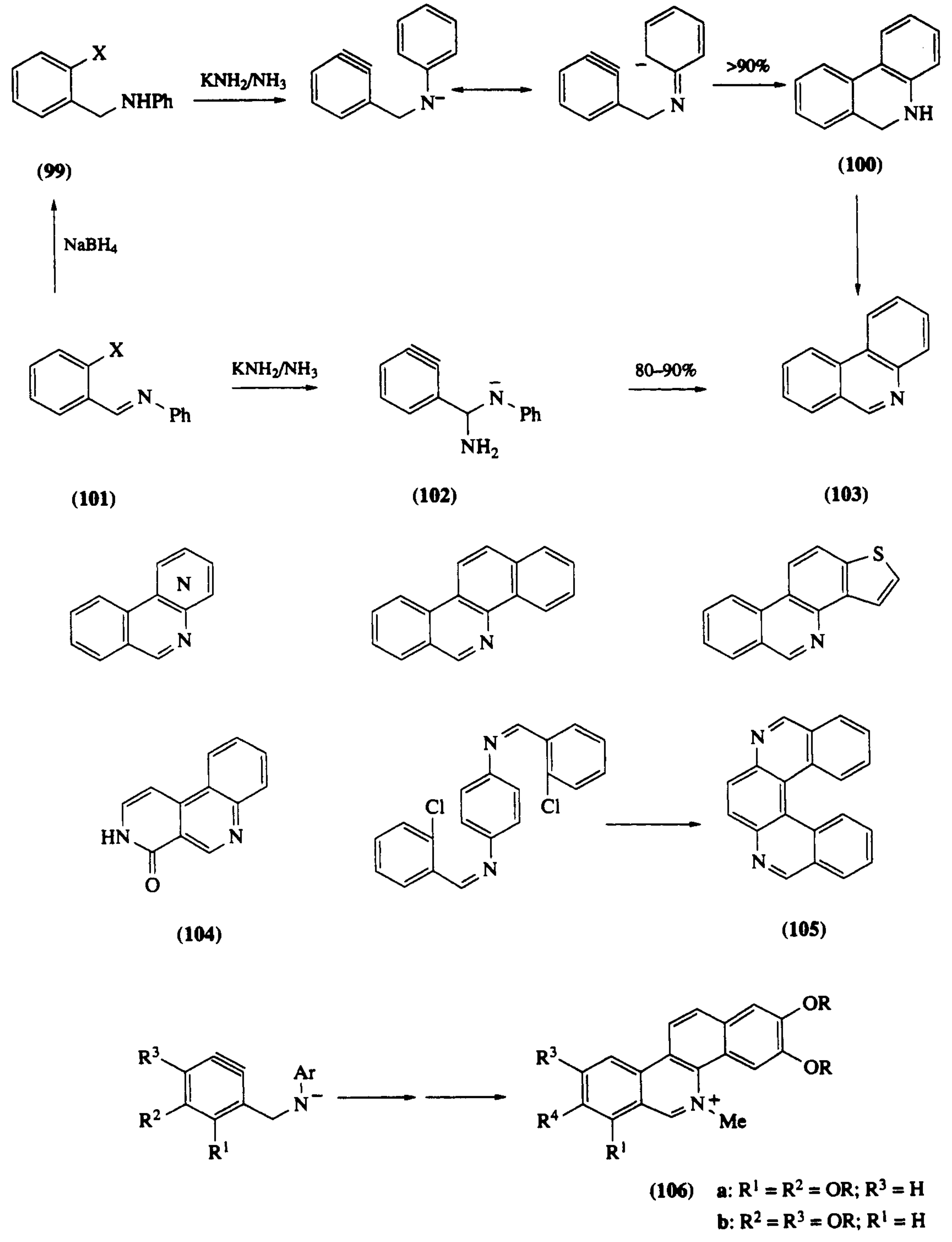
X
NHPh
KNH2/NH3
N⁻
N
>90%
NH
(99)
(100)
NaBH4
X
N
Ph
KNH2/NH3
N
Ph
NH2
80–90%
N
(101)
(102)
(103)
N
N
N
S
N
HN
O
N
N
Cl
Cl
N
N
N
(104)
(105)
R3
R2
R1
Ar
N⁻
OR
OR
R3
R4
R1
N+
Me
(106) a: R1 = R2 = OR; R3 = H
b: R2 = R3 = OR; R1 = H

**Scheme 19**

amine[1] for 2,3-dehydroanisole is only 1.8. Initially a zwitterion (**107**) is formed which may abstract a proton from the surroundings. In an aprotic solvent, it can often be intercepted by addition of electrophiles or may evolve into stable products through a variety of rearrangement and elimination steps. If a hydrogen is available on the heteroatom itself (**108**), migration occurs to give neutral products. Otherwise, a proton can shift from the β- or the α-position, the former process being somewhat more facile (**109** → **110**). The new zwitterion thus formed can undergo further reorganization or fragmentation. Although such reactions normally lead to a mixture of products, structural features of the substrate can

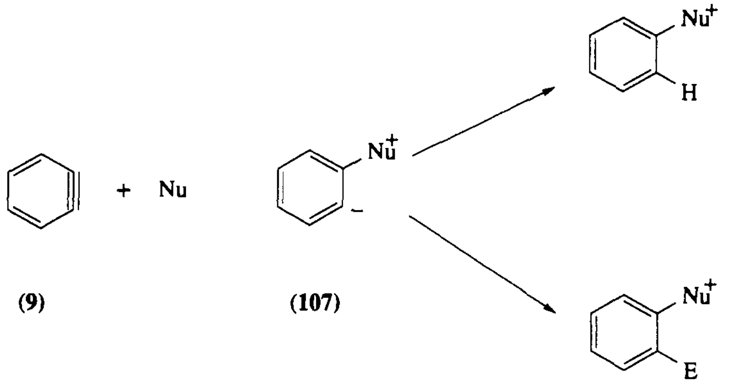

(9) (107)

(43)

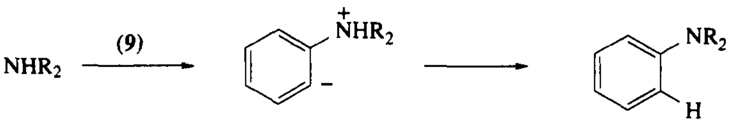

(108)

(44)

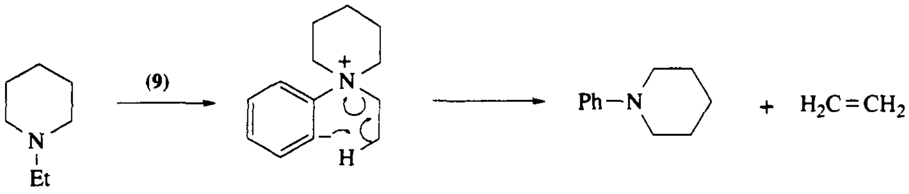

(109) (110)

(45)

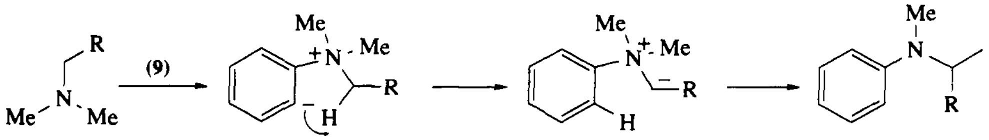

(111) a: R = H
b: R = SiMe 3

(112) (113)

(46)

favor a particular pathway. For instance, in the reaction of trimethylamine (**111a**) with benzyne, very little product (**113a**) corresponding to Stevens rearrangement is obtained. But with silylamine (**111b**), the compound (**113b**) is formed in 60% yield;[150,151] the proton transfer leading to carbanion (**112b**) is obviously promoted by the neighboring silicon atom.

Like tertiary amines, dialkyl sulfides also react with arynes to give betaines prone to rearrangements and some of these have been put to ingenious preparative use.[152] The reaction of thiirane (**114**) with benzenediazonium carboxylate was employed to produce, in a stereospecific manner, unsaturated sulfides (**115**), which serve as valuable synthetic intermediates.[153] Certain betaines, derived from aryne reaction with sulfides, reorganize to give products in which the original sulfur ligands are linked directly. Since dialkyl sulfides are readily accessible and the sulfur pendant on the product can be removed or utilized for further functionalization, this sequence constitutes a powerful method for carbon–carbon bond formation. For example, a 3,2-sigmatropic shift in the ylide (**117**), formed through reaction of farnesyl nerolide sulfide with benzyne, gave (**118a**) which, on treatment with lithium in liquid ammonia, furnished squalene (**118b**) in good yield.[154] An attempt to bring about a similar rearrangement by forming the corresponding methylsulfonium cation, in place of the phenylsulfonium cation (**116**), led to a complex mixture of products. Another useful strategy based on aryne reaction with dialkyl sulfides (**119** → **120**) has been devised to synthesize a number of strained cyclophanedienes.[155,156]

Ethers do not exhibit marked nucleophilicity towards arynes but readily enter into reaction with more electrophilic halogenated analogs like (**121**). In the betaine derived from (**121**) and ethyl ether, a proton

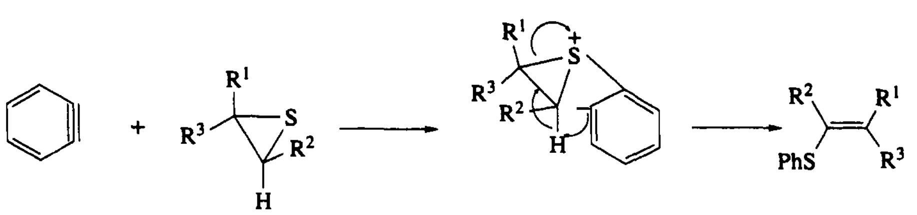

(9) (114) (115)

(47)

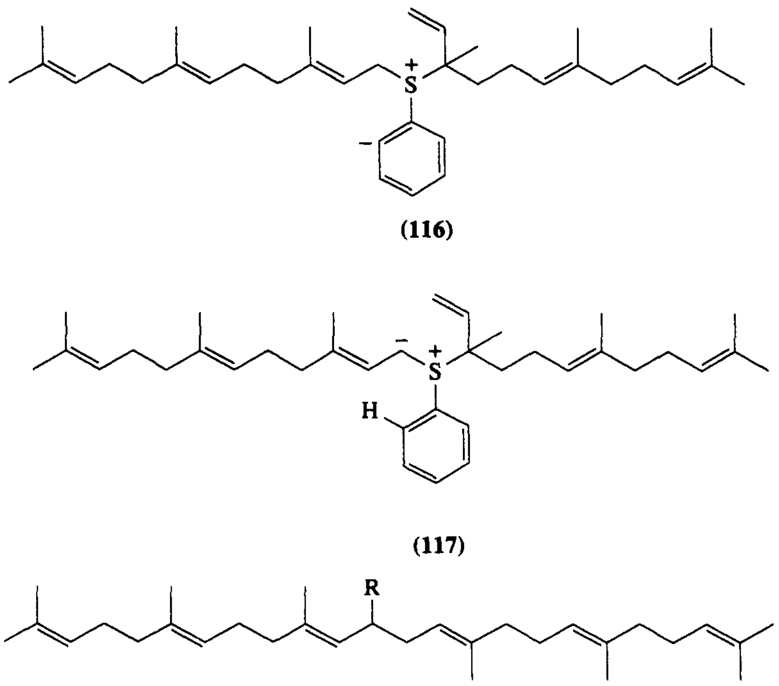

(116)

(117)

(118) a: R = SPh
b: R = H

(48)

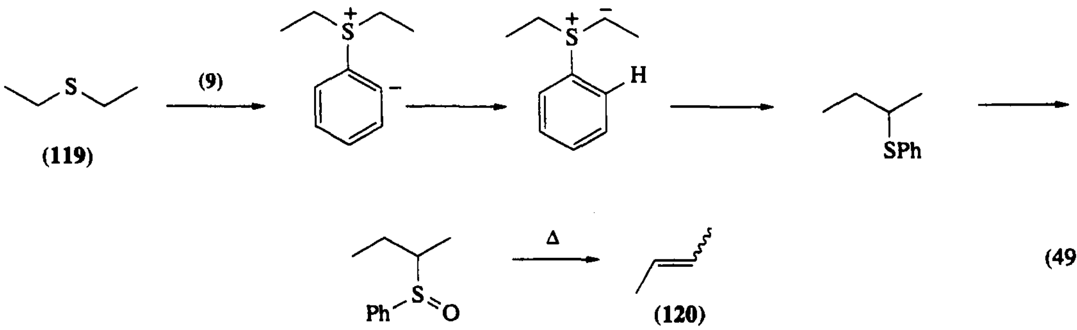

(119) (120)

(49)

shift is followed by alkene elimination.[157] With cyclic ethers such a shift is disfavored and good yields of products arising through ring opening by added nucleophiles can be obtained (**122** → **123**).[158] The oxygen of *N*-oxides is more reactive and even simple arynes are attacked (equation 50).[1]

Reactions of phosphines and phosphites have received some attention but their preparative value is limited. The zwitterion formed from diphenylmethylphosphine and benzyne rearranges to ylide (**124**) which can be captured by Wittig alkenation, with cyclohexanone, in about 20% yield.[159] Some synthetically useful reactions of tellurium and selenium compounds with arynes have been reported. For example, heating diphenyl iodonium carboxylate and bis(*p*-ethoxyphenyl) ditelluride in dichlorobenzene affords the compound (**125**).[160] The corresponding reactions with diphenyl selenide and diphenyl sulfide

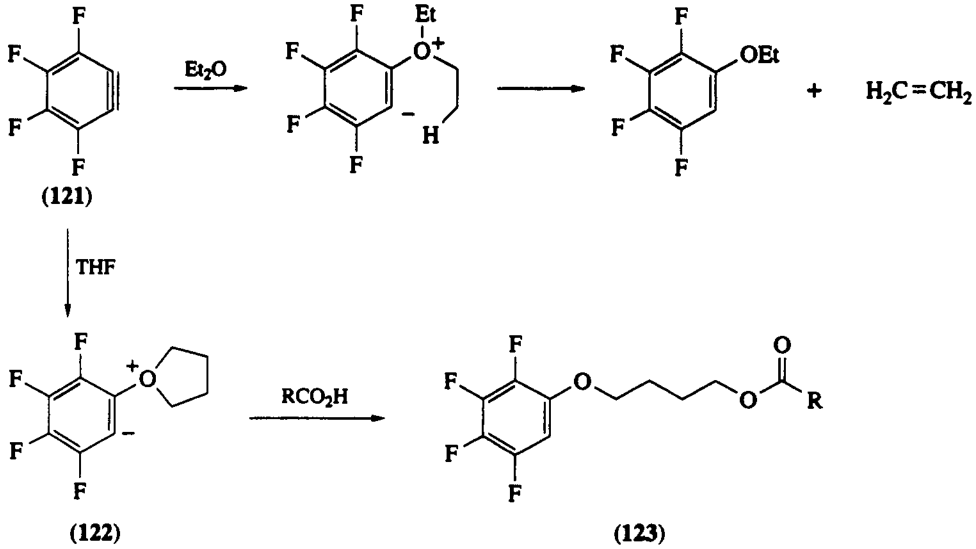
Et2O
THF
RCO2H
(121)
(122)
(123)

**Scheme 20**

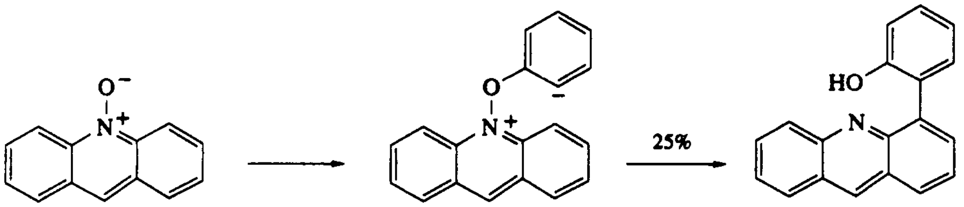

(50)

proceed in slightly lower yield.[161] The selenadiazole (**126**) participates in an interesting aryne reaction to give nitrile (**127**) in excellent yield.[162]

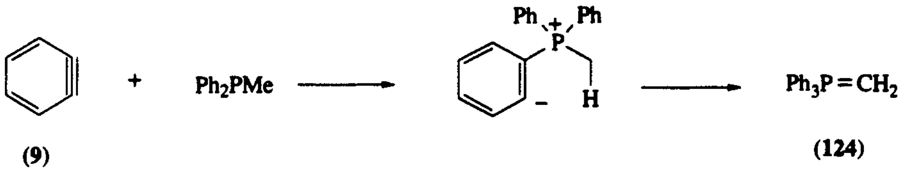
Ph2PMe
Ph3P=CH2
(9)
(124)

(51)

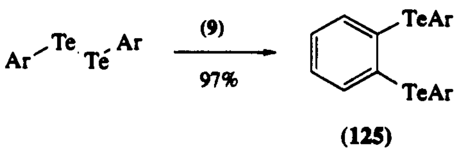

(52)

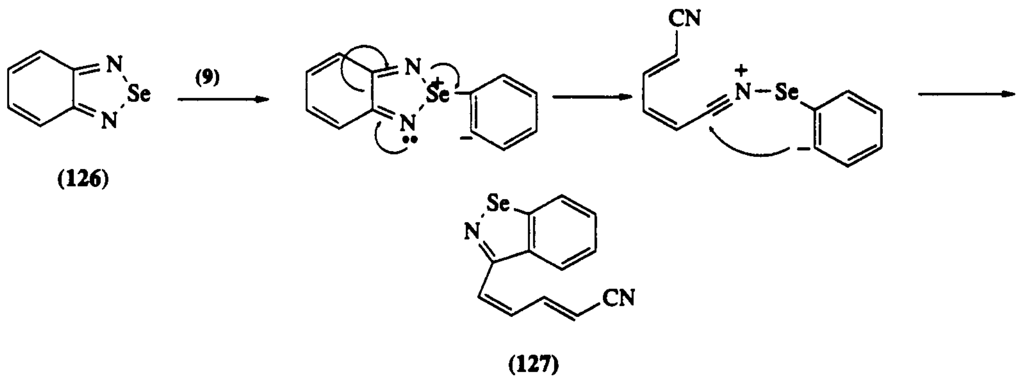

(53)

### *2.3.3.3.4 Additions involving multiple bonds*

Incorporation of a heteroatom into a multiple bond generally lowers its nucleophilicity due to change in hybridization. Still, reaction with arynes can occur to give a zwitterion which may collapse to a four-membered ring or undergo further reactions. For example, interaction of azirine (**128**) with benzyne leads to 2,3-diphenylindole,[163] presumably by the pathway shown in the equation (54). Similarly, anils on reaction with benzyne afford acridines in low yield.[164] Even carbonyl compounds can react, but only with strongly electrophilic arynes. Generation of tetrachlorobenzyne in the presence of aldehydes and ketones was found to give benzodioxan derivatives (**129**).[165]

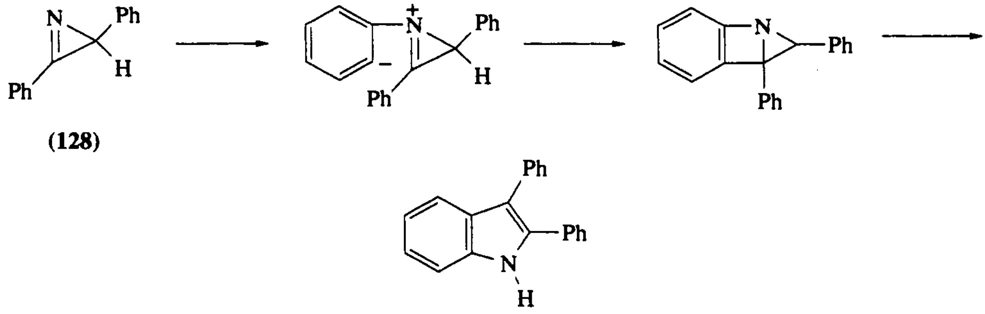

(**128**)

(54)

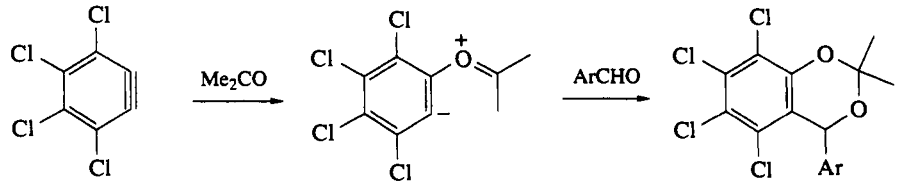

(55)

(**129**)

Alkenes on reaction with arynes afford benzocyclobutenes in low yield. Particularly, if an allylic hydrogen is present the ene reaction tends to predominate. The main interest in this area is perhaps mechanistic, because concerted [2 + 2] addition is forbidden by Woodward–Hoffmann rules. The fact that with 1,2-disubstituted alkenes mixtures of stereoisomers are obtained, although stereoretention predominates, indicates the involvement of an intermediate with a lifetime long enough to allow some bond rotation before ring closure. Extended Hückel calculations also show that the potential energy surface for this reaction has a 'valley' corresponding to an intermediate on the reaction pathway.[166,167] There has been much conjecture on the dipolar/diradical nature of this intermediate. Although calculations indicate a slight charge imbalance in it, the lack of rearrangements and the absence of solvent effects suggest diradical character. In the case of alkenes bearing strong electron donating groups, it is reasonable to consider the first step to be a nucleophilic addition. Good regioselectivity, in accordance with a dipolar intermediate, is observed in reactions of such alkenes with polarized benzynes and, importantly, the yields are high.[168,169] For example, treatment of *o*-bromoanisole with sodamide in the presence of 1,1-dimethoxyethylene gave (**130**) in 70% yield. A similar addition constitutes the key step in an elegant synthesis of taxodione (**131**).[168] In 3-methylbenzyne, inductive polarization of the dehydro bond is weak and the preferred orientation must rely on the steric effect to align the approaching nucleophile. Accordingly, a much lower selectivity is observed in the reaction given in equation (56). Reaction of *O*-silylated enolates of carboxylic esters with benzyne gives *ortho*-alkylbenzoic acids due to ring opening of the initially formed bicyclic product.[170] Monovinyl ethers and acetates also afford [2 + 2] adducts with arynes in acceptable yields (equation 57).[171] Benzocyclobutenes prepared in this manner were used for the synthesis of some protoberberine alkaloids.[172]

The carbon end of enamines should be even more nucleophilic than that of the oxygen analogs. The expected regioselectivity is observed in reactions with arynes (equation 58).[173] However, the yields of benzocyclobutenes are often low because of competitive initial reaction at the nitrogen end.[174] Silylynamines on interaction with benzyne give zwitterionic intermediates (**132**), which can undergo a 1,3-shift leading to stable products (equation 59).[175] In enamides the charge density on the β-carbon must be relatively low, yet intramolecular addition to arynes can take place (equation 60).[176]

Finally, electron rich aromatic rings can also act as nucleophiles towards arynes, *e.g.* 2-phenylanisole is the major product of $Ag^+$-catalyzed decomposition of benzenediazonium carboxylate in anisole (equa-

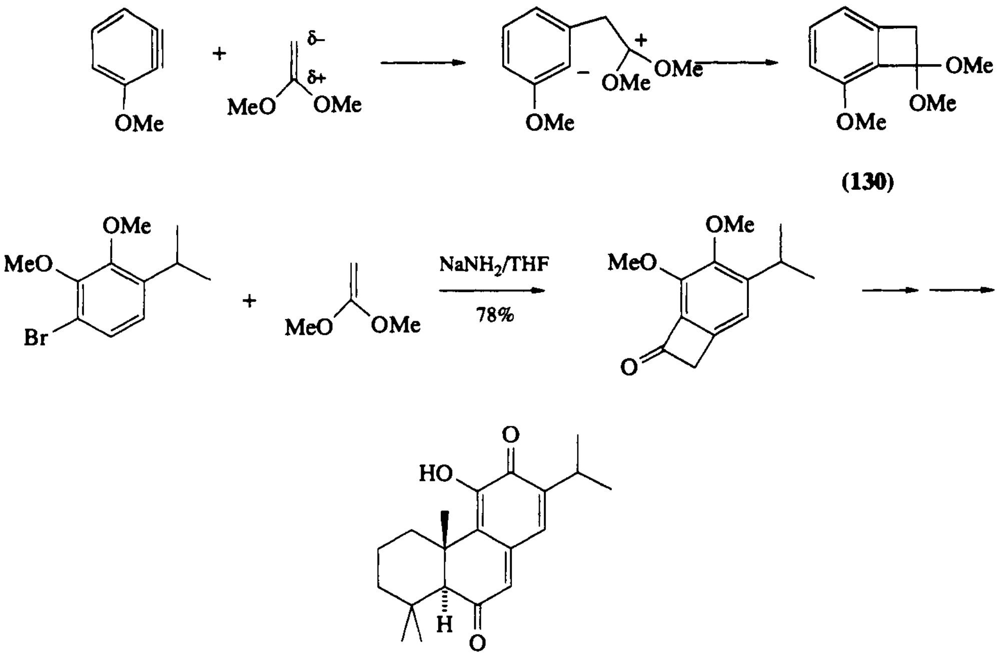
OMe
δ-
δ+
MeO
OMe
OMe
OMe
OMe
NaNH$_2$/THF
78%
MeO
Br
OMe
MeO
O
HO
O
H
O

(130)

(131)

Scheme 21

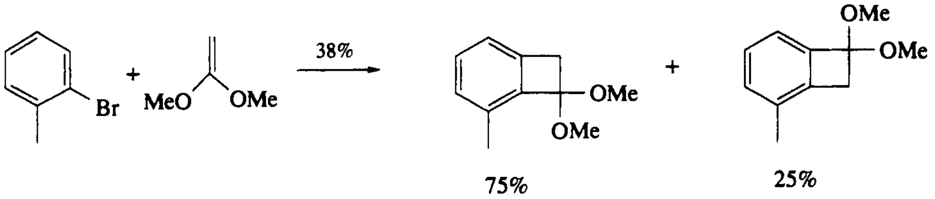
38%
Br
MeO
OMe
OMe
OMe
OMe
OMe
75%
25%

(56)

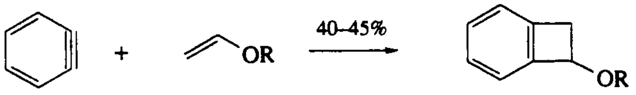

(57)

R = Me or Ac

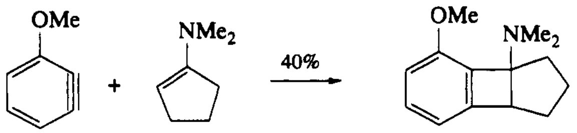
OMe
NMe$_2$
40%
OMe
NMe$_2$

(58)

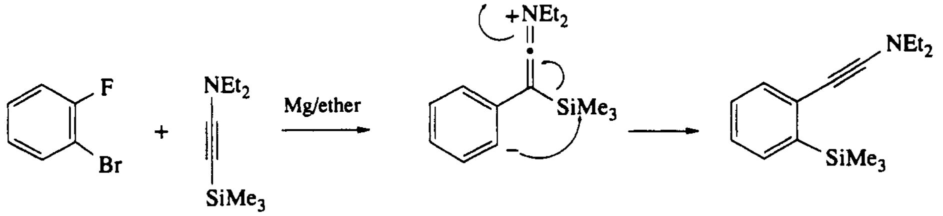
F
Br
NEt$_2$
SiMe$_3$
Mg/ether
+NEt$_2$
SiMe$_3$
NEt$_2$
SiMe$_3$

(59)

(132)

tion 61).[177] In this reaction, benzyne complexation with the silver cation increases its nucleophilicity at the cost of [2 + 4] reactivity. The high regioselectivity obtained under these conditions is indeed remarkable (91.6% *ortho*, 8.4% *para*).[178] However, the yields in nucleophilic coupling of aromatic rings with

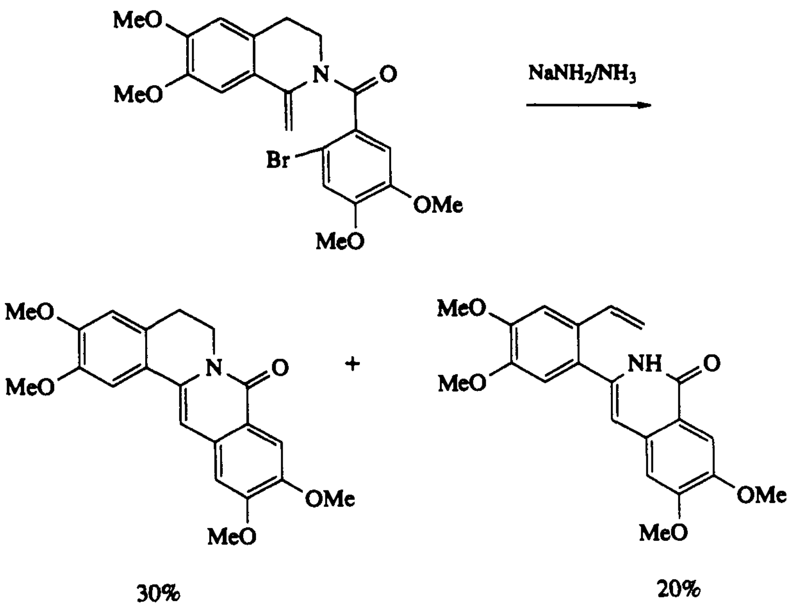
MeO
MeO
N
O
Br
OMe
MeO
NaNH₂/NH₃
MeO
MeO
N
O
+
OMe
MeO
MeO
MeO
NH
O
OMe
MeO
30%
20%

(60)

arynes are poor even under metal ion catalysis, and such reactions have found hardly any synthetic applications.

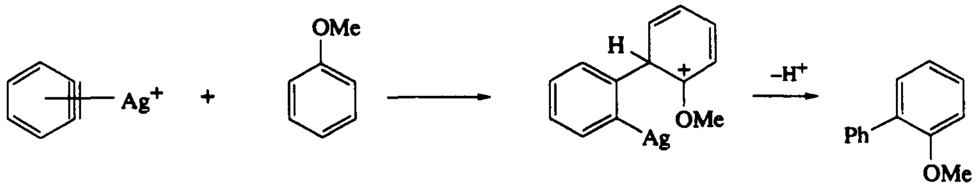
Ag⁺
+
OMe
H
+
OMe
Ag
-H⁺
Ph
OMe

(61)

As mentioned in the introductory section, Diels–Alder and 1,3-dipolar additions of arynes have been used extensively in organic synthesis. In general, electron rich dienes and dipoles are more reactive in these reactions. This fact can be rationalized within the rubric of concerted cycloadditions in terms of a decrease in the HOMO–LUMO energy gap. However, asynchronous reaction, with bond formation at the nucleophilic end of the diene being more advanced and appreciable charge separation in the transition state (**133**), has been invoked to explain the regioselectivity observed in aryne addition to some enamides. For instance, the reaction of amide (**134**) with 3-methoxyarynes was found to give only one

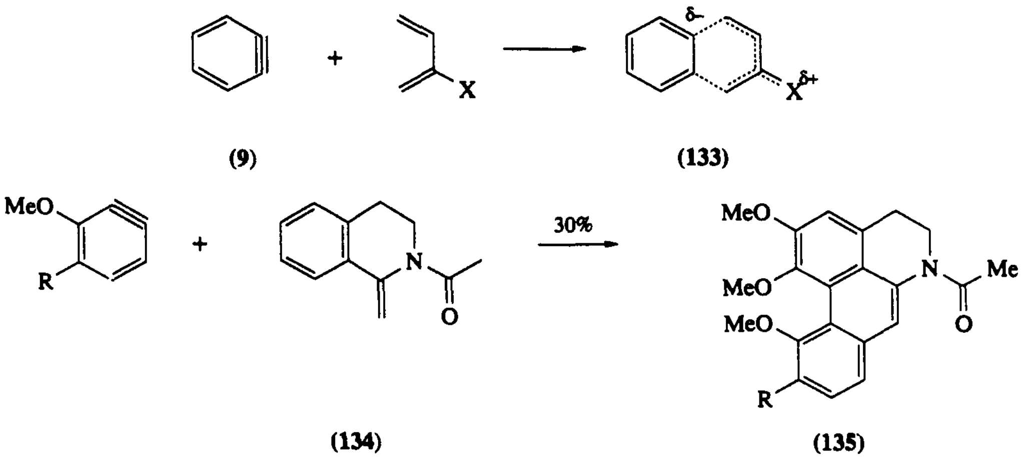
+
X
δ-
δ+
X
MeO
R
+
N
O
30%
MeO
MeO
MeO
R
N
Me
O

(**9**)

(**133**)

(**134**)

(**135**)

**Scheme 22**

isomer, *i.e.* (**135**). The selectivity was attributed to a stabilization of the developing negative charge, in a transition state similar to (**133**), by the adjoining methoxy group although alternate explanations also seem tenable.[179] In any case, this reaction affords a useful access to 11-substituted aporphines which are difficult to synthesize otherwise.[180]

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# 2.4

# Nucleophilic Addition to Arene–Metal Complexes

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## 2.4.1 INTRODUCTION

### 2.4.1.1 Coverage

This chapter covers reactions in which coordination of a transition metal to the $\pi$-system of an arene ring activates the ring toward addition of nucleophiles, to give $\eta^5$-cyclohexadienyl–metal complexes (**1**; Scheme 1). If an electronegative atom is present in the *ipso* position, elimination of that atom (X in **1**) leads to nucleophilic aromatic substitution (path **a**). Reaction of the intermediate with an electrophile (E$^+$) can give disubstituted 1,3-cyclohexadiene derivatives (path **b**). If a hydrogen occupies the *ipso* position, oxidation of the intermediate gives formal nucleophilic substitution for hydrogen (path c). These processes have been uncovered and developed relatively recently and have significant potential in synthesis methodology. General reviews have appeared[1-3] as well as others with an emphasis on [($\eta^6$-arene)Cr(CO)$_3$] complexes,[4-6] on [($\eta^6$-arene)FeCp]$^+$ (Cp = $\eta^5$-cyclopentadienyl) complexes[7,8] and on [($\eta^6$-arene)Mn(CO)$_3$]$^+$ complexes,[9] but none with emphasis on synthesis scope and limitations. The purpose of this chapter is to illustrate the established methodology and to point to future possibilities; mechanistic questions are included when helpful in understanding the scope and limitations. The coverage is representative and not comprehensive.

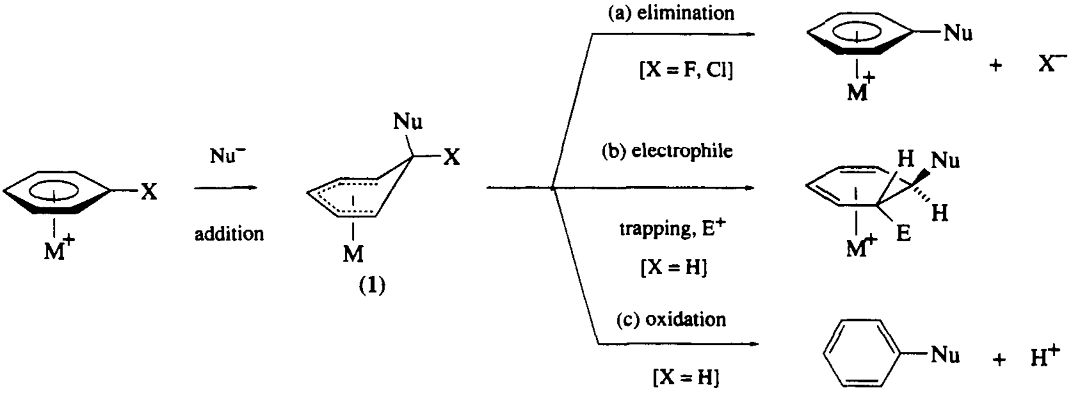

Scheme 1

## 2.4.1.2 Relation to Nucleophilic Aromatic Substitution by the SNAr Mechanism

The reactions are related mechanistically to traditional nucleophilic aromatic substitution (SNAr), but offer several unique features. It may be well to summarize the comparison of general features for traditional arene ring substitution. Arene rings are polarizable and tend to react as electron donors, as in electrophilic aromatic substitution.[10] A cationic intermediate, the phenonium ion, is produced, which spontaneously loses a proton to give overall substitution of an electrophile for a proton. With suitable electron-withdrawing substituents attached to the arene *via* σ-bonds, nucleophiles may add to produce the corresponding anionic intermediate, a cyclohexadienyl anion, stabilized by interaction with the substituents as represented by (2) in Scheme 2.[11] Attack is kinetically favored at a position bearing a hydrogen (path a), but the intermediate thus formed (2) cannot proceed directly to substitution (by loss of a hydride ion). In the general version of the SNAr reaction, an electronegative atom (usually halide) is at-

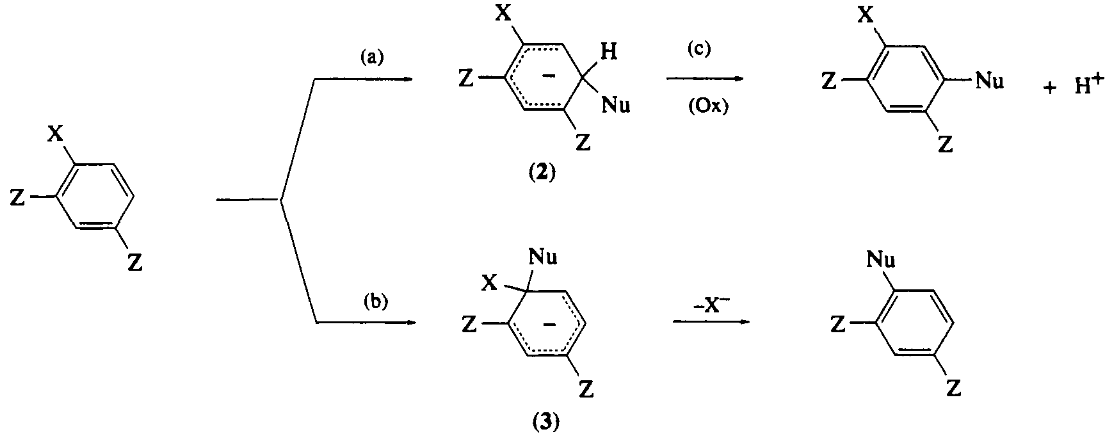

Z = electron-withdrawing group
X = electronegative atom (group)

Scheme 2

tached to the arene *ortho* or *para* to an activating group, and the addition of the nucleophile is reversible. A slower addition occurs at the carbon bearing the electronegative atom to produce an anionic intermediate (**3**), which can lose the electronegative atom in an irreversible step and give the product from nucleophilic substitution for halide (path **b**). In a few cases, loss of hydrogen from intermediates related to (**2**) has been induced by oxidation, which presumably allows departure of a proton, as shown in step **c**, Scheme 2.[11,12] The overall addition–oxidation pathway of nucleophilic aromatic substitution for hydrogen is too limited to be considered synthesis methodology.

### 2.4.1.3 Arene–Metal Complexes, Background

The first arene–transition metal complexes were prepared in the 1950s[13,14] and it was immediately recognized that the added polarizibility or electron deficiency would promote addition of nucleophiles to the arene ligand. A number of cyclohexadienyl complexes were characterized following nucleophilic addition, but the question of inducing the *ipso* hydrogen to depart was not answered (equation 1).

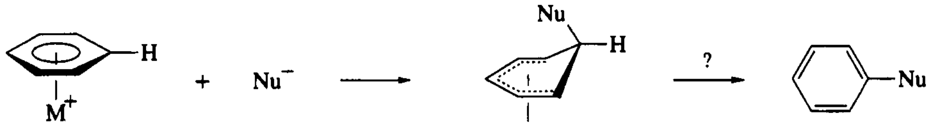

(**4**) (**5**) (1)

The isolation of the first halobenzene complex, ($\eta^6$-chlorobenzene)tricarbonylchromium(0), allowed a test for a direct analog of classical $S_NAr$ reactivity.[15] The activating effect of the $Cr(CO)_3$ unit was found to be comparable to a single *p*-nitro substituent in reaction with methoxide in methanol and the substituted arene ligand was detached with mild oxidation (equation 2).

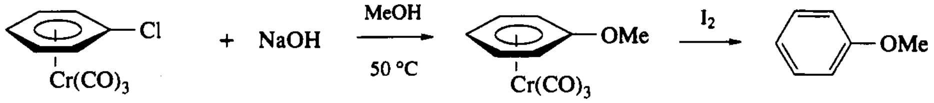

(2)

Three types of arene π-complexes have seen significant development in synthesis methodology: neutral [($\eta^6$-arene)$Cr(CO)_3$] (**6**), the isoelectronic cationic [($\eta^6$-arene)$Mn(CO)_3$] (**7**) and the cationic ($\eta^6$-arene)($\eta^5$-cyclopentadienyl)iron(II) complexes (**8**). The [(arene)$Cr(CO)_3$] species are formed by simple displacement of neutral ligands (L) from [$Cr(CO)_3L_3$] by the arene and a large number of variously substituted [(arene)$Cr(CO)_3$] complexes are available.[14] Gentle and general syntheses of the cationic complexes (**7**) and (**8**) have only recently become available and the development of these complexes as synthesis intermediates is less developed. The focus of this chapter will be on the chromium system, but the iron and manganese analogs will be included for comparison and future potential.

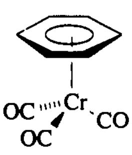

(**6**)

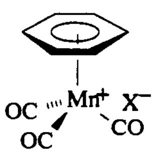

(**7**)

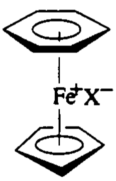

(**8**)

## 2.4.2 PREPARATION OF ARENE–METAL COMPLEXES

### 2.4.2.1 [(Arene)$Cr(CO)_3$]

The general process is shown in equation (3). The L unit in the [$Cr(CO)_3L_3$] can be CO (most common),[15–20] MeCN,[21,22] 2-alkylpyridine,[23] ammonia[24–27] and other donor ligands. The rate (reaction temperature) is related to the nature of L; the most reactive readily available source of $Cr(CO)_3$ is [($\eta^6$-naphthalene)$Cr(CO)_3$], which undergoes favorable arene exchange under mild conditions with many substituted arenes.[28] A technical problem in the use of [$Cr(CO)_6$] is the crystallization of sublimed [$Cr(CO)_6$] in the condenser. The original solution is still used, a fairly complicated heated condenser apparatus known as the Strohmeier apparatus,[16] but a simple air condenser is also effective.[17] The most general and convenient procedure also relies on continuous washing down of the [$Cr(CO)_6$] with a mixture of THF and di-*n*-butyl ether at reflux.[18,19] A variety of polar and nonpolar aprotic solvents have been used, and, for some purposes, such as complexation of α-amino acids with aromatic side chains, water–THF mixtures are effective.[20]

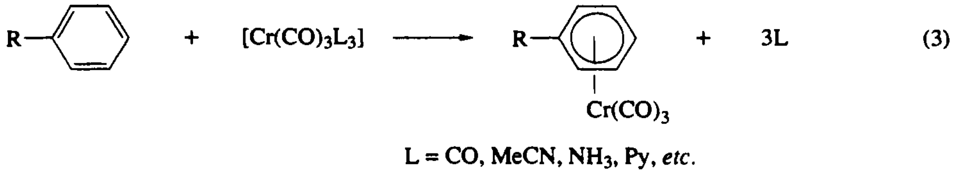

(3)

The primary competing reaction is irreversible oligomerization of the coordinatively unsaturated [$Cr(CO)_n$] species. Addition of small amounts of weak donor ligands, such as α-picoline[29] or THF,[18–20] appear to lower the temperature necessary for the complexation step from 100 °C or more to 60 °C, presumably by assisting in the dissociation of one or more CO ligands and retarding the rate of oligomerization of the reactive source of $Cr(CO)_3$.[18–20] After complexation, the yellow to red [(arene)$Cr(CO)_3$] complex can be purified by crystallization from nonpolar organic solvents or chromatographed on silica gel. The complexes are somewhat sensitive to air while in solution, but the solutions can be handled in air briefly and crystalline solids can be stored without special precautions. Examples are known with a wide variety of arenes, including sensitive species such as [($\eta^6$-indole)$Cr(CO)_3$].[13,14,30] Most common synthesis operations, such as acid and base hydrolysis, hydride reduction and carbanion addition to ketones, can be carried out on side chain functional groups without disturbing the arene–Cr bond.[31] However, even very mild oxidation conditions will detach the arene by oxidizing the metal. An important aspect of the complexation procedure is diastereoselectivity. Complexes of disubstituted (and more highly substituted) arenes can have molecular asymmetry; a stereogenic center in a side chain leads to diastereoisomers. Under favorable conditions, especially with low temperature conditions for complexation, significant diastereoselectivity is observed in the complexation step (equation 4).[32–35]

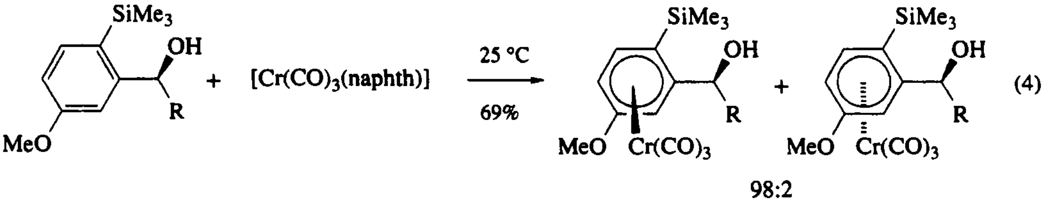

(4)

### 2.4.2.2 [(Arene)$Mn(CO)_3$]$^+$

A gentle procedure has made these complexes available with a variety of substituted arenes.[36] Direct displacement of CO from the perchlorate salts of [$Mn(CO)_5$]$^+$ or [$Mn(CO)_3$(acetone)$_3$]$^+$ with the arene in dichloromethane at reflux leads to precipitation of the [(arene)$Mn(CO)_3$] salt. The conditions are milder than the $AlCl_3$-promoted procedure employed earlier.[37] Only a handful of substituted arenes have been attached to [$Mn(CO)_3$]$^+$, but the general synthesis method suggests few limitations (equation 5).

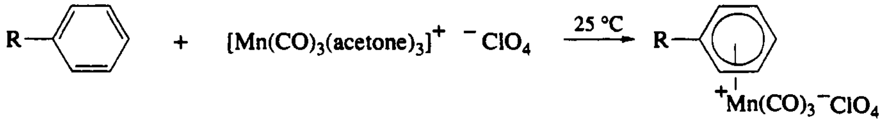

(5)

The complexes are air stable; indeed, a limitation is the need for powerful oxidizing agents, such as Jones reagent $Cr^{VI}$, to detach the arene ligand.[38] They are highly reactive toward nucleophiles. This limits the number of compatible synthesis manipulations that can be carried on in the presence of the [(arene)$Mn(CO)_3$] unit but broadens the scope of effective nucleophiles.

### 2.4.2.3 [(Arene)FeCp]$^+$

One of the few useful reactions of ferrocene is the $AlCl_3$-catalyzed exchange of one Cp group for an arene ligand (equation 6).[39–44]

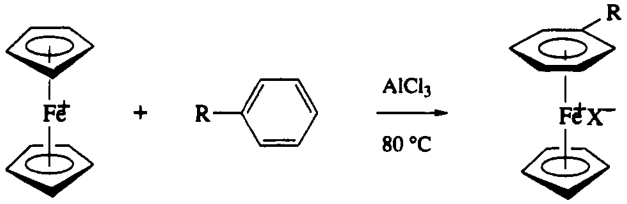

(6)

The requirement for $AlCl_3$ adds some obvious limitations, but a modest number of substituted arenes have been successfully coordinated to the [FeCp]$^+$ unit. Photoinduced arene exchange has been described[45] and is particularly effective with the η$^6$-chlorobenzene-η$^5$-cyclopentadienyliron cation without the need for Lewis acids.[42] More basic (electron rich) arenes readily replace chlorobenzene, leading to FeCp cation complexes of *O*-phenylethyl-*p*-toluenesulfonate and variously substituted thiophenes.[42] The charged complexes are not purified by conventional organic techniques, such as chromatography, but recrystallization is possible. The complexes are very air and heat stable; again, methods of removal of the arene from the Fe are few. The simplest is pyrolysis at >200 °C.[46]

## 2.4.3 NUCLEOPHILIC SUBSTITUTION FOR HETEROATOMS ON ARENE LIGANDS, $S_NAr$ REACTION

The smooth replacement of a heteroatom (usually halide) from arene ligands requires reversible addition of the nucleophile, since the kinetic site of addition is usually at a position bearing a hydrogen substituent (Scheme 3, path $k_1$).

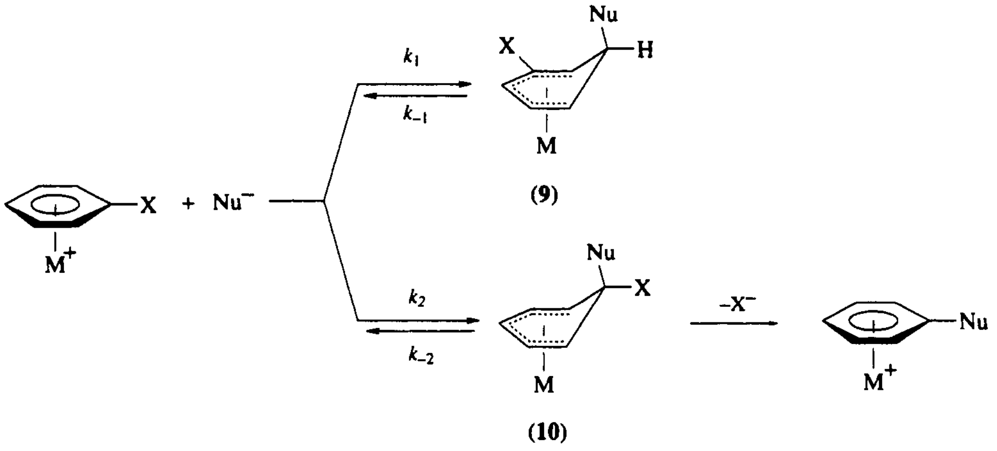

Scheme 3

The relative rates of each step depend critically on the nature of M and of the nucleophile. More reactive nucleophiles and more reactive complexes disfavor equilibration, ($k_1 >> k_{-1}$) and the process can stop with formation of the first cyclohexadienyl intermediate (9). Equilibration leads through (10) to the substitution product. The overall order of reactivity for electron deficient arenes is:[2,47] $[(arene)Mn(CO)_3]^+ > 2,4\text{-}(NO_2)C_6H_3Cl > [(arene)FeCp]^+ >> 4\text{-}(NO_2)C_6H_4Cl > [(arene)Cr(CO)_3]$.

### 2.4.3.1 [(Halobenzene)$Cr(CO)_3$]

#### *2.4.3.1.1 Intermolecular nucleophilic substitution with heteroatom nucleophiles*

A patent issued in 1965 claims substitution for fluoride on [(fluorobenzene)$Cr(CO)_3$] in DMSO by a long list of nucleophiles, including alkoxides (from simple alcohols, cholesterol, ethylene glycol, pinacol, dihydroxyacetone), carboxylates, amines and carbanions (from triphenylmethane, indene, cyclohexanone, acetone, cyclopentadiene, phenylacetylene, acetic acid and propiolic acid).[48] Many of those results have not appeared in the primary literature. In the reaction of methoxide with [(halobenzene)$Cr(CO)_3$], the fluorobenzene complex is *ca.* 2000 times more reactive than the chlorobenzene complex.[47] The difference is taken as evidence for a rate-limiting attack on the arene ligand followed by fast loss of halide; the concentration of the cyclohexadienyl anion complex (*e.g.* **10**) does not build up. In the reaction of [(fluorobenzene)$Cr(CO)_3$] with amine nucleophiles, the coordinated aniline product appears rapidly at 25 °C and a careful mechanistic study suggests that the loss of halide is now rate limiting.[49]

Hydroxide, alkoxide and phenoxide nucleophiles react with [(chlorobenzene)$Cr(CO)_3$] at 25–50 °C in polar aprotic media to give high yields of the phenol or aryl ether chromium complexes; oxidation with excess iodine at 25 °C for a few hours releases the free arene, CO, chromium(III) and iodide anion, as summarized in equation (7).[15,50–52] Only the arene remains in the organic layer after a conventional aqueous extraction. An alternate general procedure for detaching the arene ligand from the $Cr(CO)_3$ unit is to expose a solution of the complex to air in the presence of normal room light or sunlight. The solution soon becomes cloudy with oxidized chromium derivatives and the organic solution can be processed to isolate the free arene.[19]

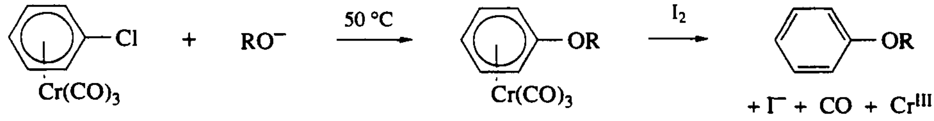

(7)

The reaction proceeds almost exclusively by direct substitution (*ipso*), as shown by reactions of isomeric chlorotoluene complexes (Scheme 4).[50] The relative rates of substitution of the isomeric ligands are similar, in the order 1.0:1.4:2.4 for *o*:*m*:*p*.[50] A version of *cine* substitution is possible under special conditions, as discussed below.

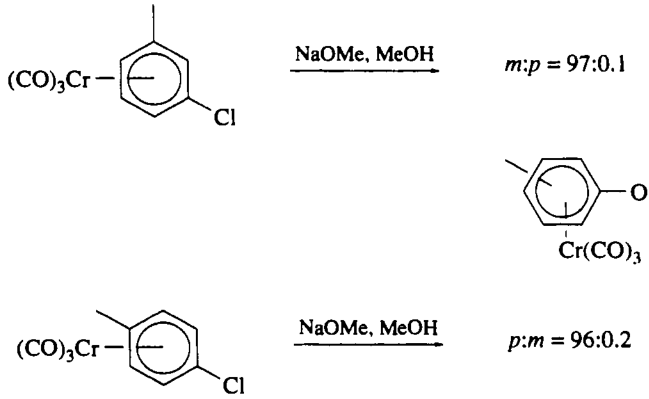

**Scheme 4**

While polar protic solvents, such as MeOH, strongly retard reaction,[53] phase transfer catalysis using benzene[54] or addition of crown ethers to potassium alkoxides in benzene[53] allows reaction at 25 °C. Even with strong electron donors, such as alkyl, methoxy or dialkylamino in the *ortho*, *meta* or *para* positions, substitution for chloride by potassium methoxide proceeds smoothly using the crown ether activation in benzene (equation 8).[53]

In general, replacement of fluoride occurs under milder conditions and in higher yield than chloride; however, compared to chloride, a fluoride substituent slows the complexation of arenes and often leads to lower yields in the formation of the complexes. An excellent procedure for formation of the parent

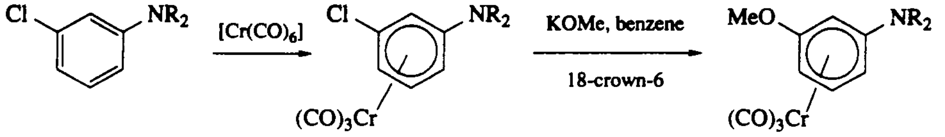

(8)

[(fluorobenzene)Cr(CO)$_3$] complex has been reported.[55] The bromo- and iodo-arene complexes are known, but generally are not effective in the $S_NAr$ reaction.[51]

Direct replacement of oxygen leaving groups, such as *p*-toluenesulfonate, is not effective, perhaps due to steric retardation of the departure of the *endo* leaving group.[49] One intriguing exception which bears further development is the reaction of the diphenyl ether mono-Cr(CO)$_3$ complex (**11**) with reactive anions (Scheme 5).[56] If the intermediate cyclohexadienyl anion complex (**12**) is quenched with an oxidizing agent at low temperature, *meta* substitution for hydrogen and loss of the Cr(CO)$_3$ unit are observed (see below for discussion of this pathway). However, if the same intermediate is allowed to warm to room temperature, anion equilibration can occur even with the very reactive 2-methyl-1,3-dithianyl carbanions and direct (*ipso*) substitution for phenoxide is observed.

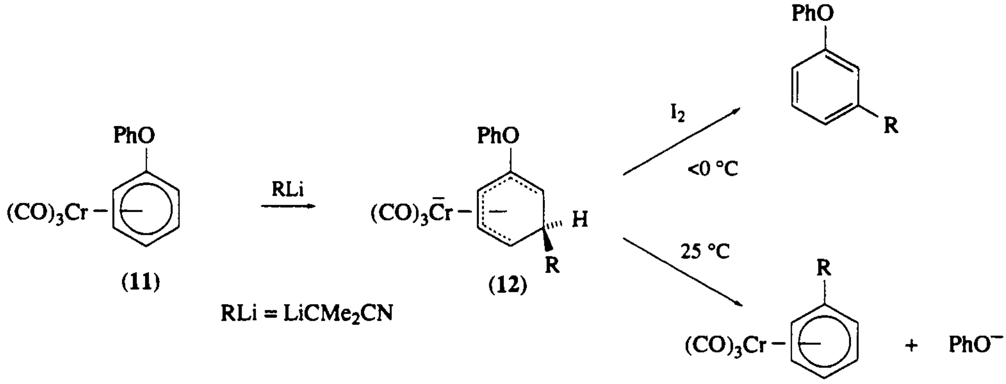

**Scheme 5**

Thiolate anions[57,58] and oxime alkoxides[58] react under phase transfer conditions to give aryl sulfides and *O*-aryl oximes, respectively; the *o*-dichlorobenzene complex can be converted selectively to the monosubstitution product (equation 9). The arylation of oximes leads to a simple process for benzofuran formation (equation 10). Simple primary and secondary amine nucleophiles react smoothly in the absence of added base, in a very general and efficient process for aniline derivatives.[49]

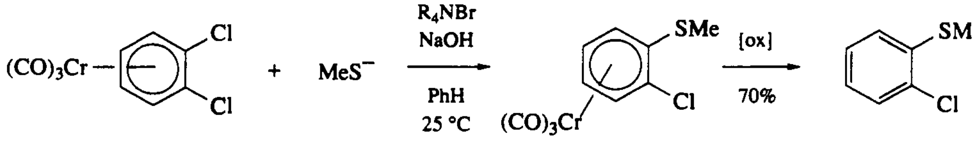

(9)

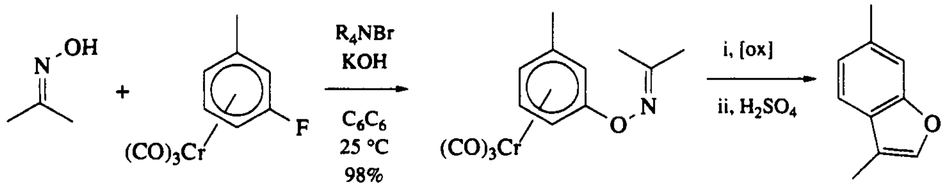

(10)

Chromium activation allows a strategy for aryl ether synthesis in four stages: (i) electrophilic chlorination; (ii) chromium coordination; (iii) alkoxide substitution for chloride; and (iv) oxidative decomplexation.[53] The process is effective for the synthesis of 6-methoxytetrahydroquinolines and 5-methoxydihydroindole derivatives, for example. Chlorination of *N*-acetyltetrahydroquinoline with SO$_2$Cl$_2$ followed by deacetylation provides 6-chlorotetrahydroisoquinoline in 77% yield (equation 11).[53] Complexation with [Cr(CO)$_6$] in diglyme–cyclohexane at 125 °C for 53 h using the Strohmeier apparatus gave the chromium complex (**13**) in 85% yield, based on 40% recovery of starting material. The unreacted tetrahydroisoquinoline can be separated from the complex by simple acid extraction, since the $Cr(CO)_3$ coordination renders the complexed amine relatively nonbasic. Indeed, the complexed amine is moderately acidic and must be protected (*in situ*) as the benzyl ether before methoxide treatment. The overall yield for protection, substitution and oxidative decomplexation is 80%.

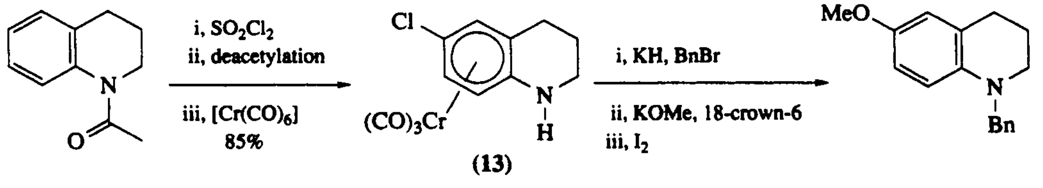

(13)

(11)

### *2.4.3.1.2 Cyclizations* via *heteroatom substitution for halide*

Intramolecular substitution for chloride or fluoride is particularly effective. Oxygen heterocycles with fused benzo rings are obtained from $Cr(CO)_3$ complexes of fluorobenzene with an *o*-(hydroxyalkyl) side chain.[59,60] For example, complexation of 3-(2-fluorophenyl)-1-propanol with $[Cr(CO)_3(pyridine)_3]$ at 25 °C in ether (promoted by $BF_3{\cdot}Et_2O$) followed by reaction in DMSO with excess potassium *t*-butoxide for 3 h at 25 °C gave the chroman complex (**14**).[60] The yield in the cyclization step was 75% and iodine decomplexation was quantitative (equation 12). Efforts to produce the dihydrobenzofuran under the same conditions failed; only intermolecular substitution products were obtained.[60]

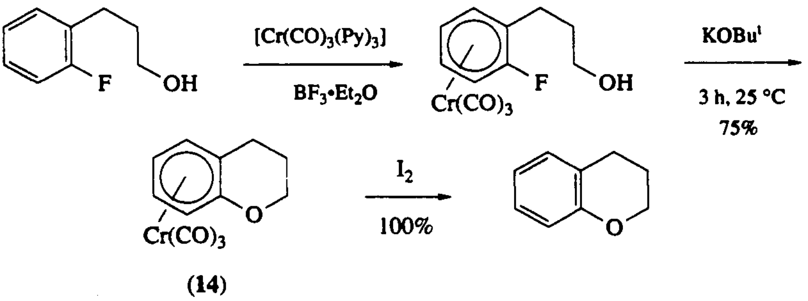

(**14**)

(12)

From the *o*-dichlorobenzene complex, reaction with a dialkoxide can produce a cyclic bisether. This idea has been applied in the preparation of benzo-crown ethers, as outlined in Scheme 6.[61] The first substitution product (**15**) does not undergo cyclization, but a second intermolecular substitution to give (**16**) sets up a final cyclization to the bischromium complex (**17**); the overall yield is 27%. A bisthia analog was also prepared.[61]

Coordination of arenes with $Cr(CO)_3$ also activates the ring hydrogens toward abstraction with strong base (metallation).[59,62] Simple arene ligands can be metallated with alkyllithium reagents; alkoxy, amino and halo substituents on the arene direct the metallation to the *ortho* position with rates and regioselectivity higher than with the corresponding free arene.[55,63–65] This allows a strategy for annulating aromatic rings *via ortho* lithiation, trapping with a bifunctional electrophile, and finally nucleophilic substitution for the electronegative substituent (usually F) (equation 13).

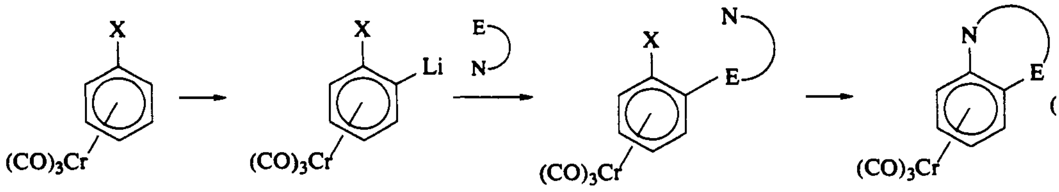

(13)

E = electrophilic unit; N = nucleophile

Following an initial report[59] including carbon nucleophiles for the cyclization (see below), a series of papers have defined useful possibilities with heteroatom nucleophiles.[55,63–65] Although $[(chlorobenzene)Cr(CO)_3]$ undergoes lithiation to give a moderately stable species which can be trapped with elec-

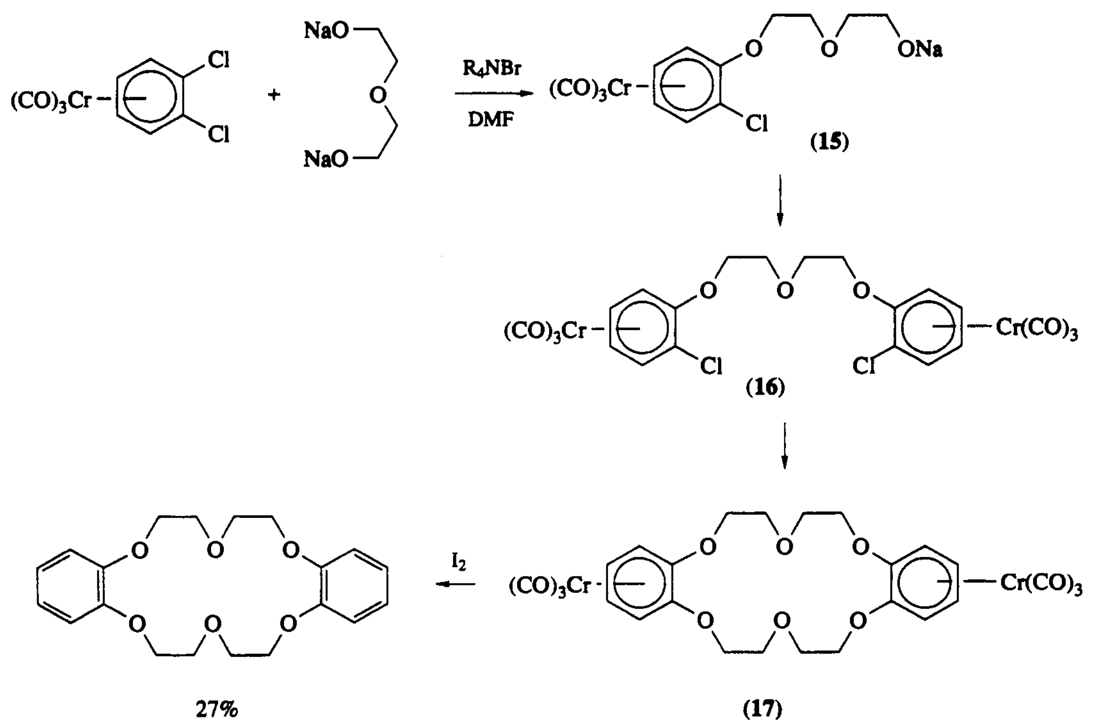

Scheme 6

trophiles to produce the *ortho*-substituted [(chloroarene)Cr(CO)$_3$] complexes,[66] the fluoro analog appears to be more efficient, in the same way. The *ortho* lithio haloarene complexes are highly basic and the electrophilic trapping species is restricted to those with low kinetic acidity and high electrophilicity. Good results are obtained with isocyanates, ketenes and acyl derivatives with α-protons of low acidity.[55,63–65] Examples (Scheme 7) include phenyl isocyanate, which reacts twice to give the the six-membered heterocycle (**18**), while the dimethyl-*N*-carboxy anhydride (**19**) proceeds directly to the five-

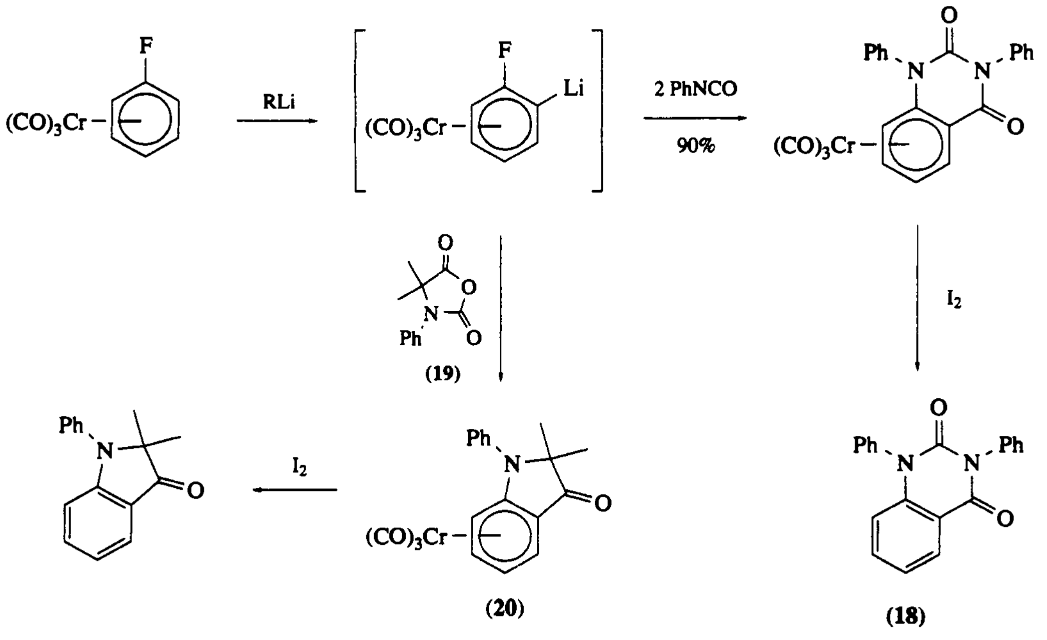

Scheme 7

membered ring (**20**) after spontaneous decarboxylation. It is possible that the *gem*-dimethyl group is important in favoring five-membered ring formation, considering the failure in forming furan rings by direct cyclization with a simple side chain hydroxy group.[55]

A variation is shown in equation (14), in which an arylcuprate is prepared and used to couple with a vinyl halide, leading eventually to the β-methylenedihydrobenzofuran complex (**21**). Cyclization occurs spontaneously upon fluoride-induced removal of the silyl protecting group.[64] The complex (**21**) is much more stable than the free ligand and can be used to advantage as a synthesis equivalent of 3-methylenedihydrobenzofuran.

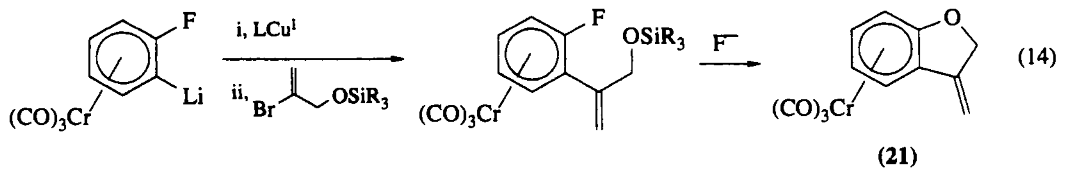

### 2.4.3.1.3 *Nucleophilic substitution with carbon nucleophiles*

#### *(i) Addition–elimination, S$_N$Ar*

While carbon nucleophiles were suggested to be efficient in substitution for fluoride in the early patent,[48] the first examples in the primary literature appeared in 1974.[51,52] It is now clear that there are three reactivity classes of carbon nucleophiles: (i) stabilized carbanions (from carbon acids with $pK_a$ < *ca.* 18); (ii) more reactive carbanions ($pK_a$ > 20), which give complete conversion to cyclohexadienyl addition products prior to slow equilibration *via* reversible anion addition; and (iii) more reactive carbanions ($pK_a$ > 20), which give irreversible addition to the arene ligand (Scheme 8).

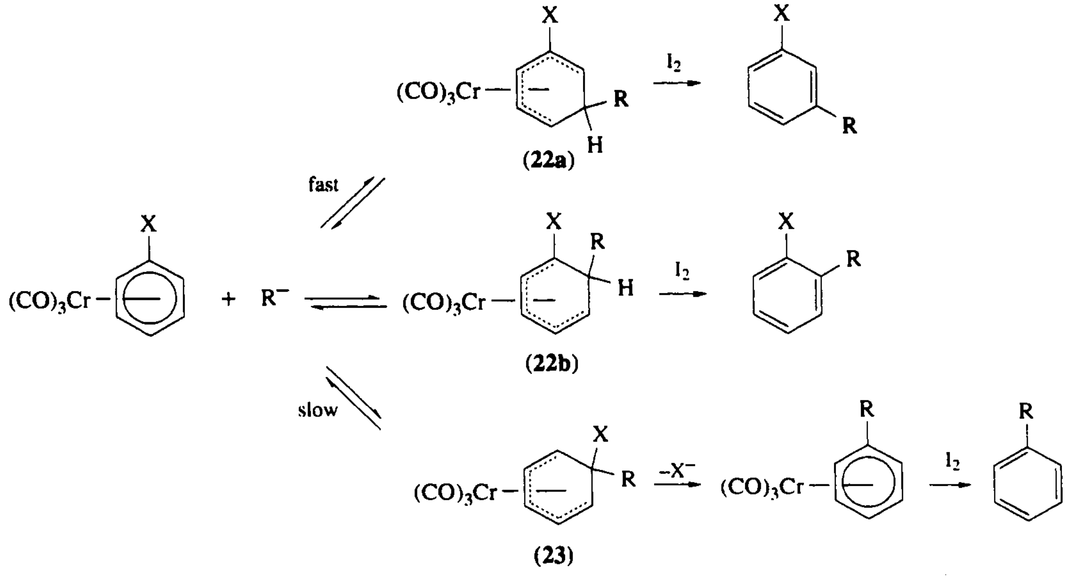

Scheme 8

Diethyl sodiomalonate is an example of type (i). Reaction with [(fluorobenzene)$Cr(CO)_3$] proceeds to completion after 20 h at 50 °C in HMPA to give the diethyl phenylmalonate complex in over 95% yield. Monitoring the reaction by NMR gave no evidence for an intermediate (*e.g.* the cyclohexadienyl anion complex); interruption of the reaction by addition of iodine at less than 20 h gave significant amounts of unreacted fluorobenzene. A satisfactory picture is the simple one, that the anion adds reversibly and unfavorably ($k_1 < k_{-1}$, as in Scheme 3), slowly finding itself at the *ipso* position; then irreversible loss of fluoride gives the substitution product.[51,52]

Lithioisobutyronitrile (from LDA and isobutyronitrile) is an example of anion type (ii). The initial addition to [(chlorobenzene)$Cr(CO)_3$] is over within minutes at −78 °C, but the substitution product does not appear until the mixture is warmed to 25 °C (Scheme 8). Quenching with iodine after short reaction time leads to a mixture of phenylisobutyronitrile and *o*- and *m*-chlorophenylisobutyronitrile. This appears to be a case of fast addition *ortho* and *meta* to the chloride to give cyclohexadienyl anionic complexes (*e.g.* **22**) followed by slow rearrangement to the *ipso* intermediate (**23**). Quenching with iodine before equilibration is complete leads to oxidation of the intermediates (**22**) and formal substitution for hydrogen (see below).

Carbon nucleophiles of type (iii) add to the arene ligand and do not rearrange; examples include the very reactive anions, such as 2-lithio-2-methyl-1,3-dithiane, and the less sterically encumbered anions, such as lithio acetonitrile and *t*-butyl lithioacetate. In these cases, the anion adds to an unsubstituted position (mainly *ortho* or *meta* to Cl, as in **22**) and does not rearrange. Then iodine quenching, even after a long period at 25 °C, gives almost exclusively the products from formal substitution for hydrogen, as from (**22**) in Scheme 8.

Hydrocarbon anions, such as cyclopentadienyl and analogs (fluorenyl, indenyl, pentadienyl), substitute for fluoride, leading, for example, to phenylcyclopentadiene as a Cr(CO)₃ complex on the arene (equation 15).[67]

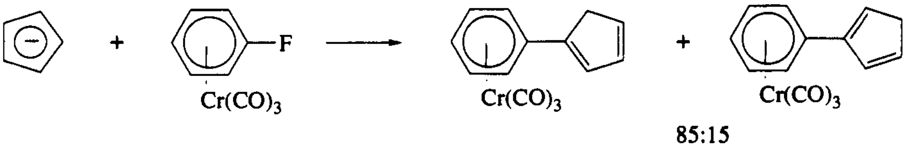

(15)

Scheme 8 summarizes the possibilities. Successful substitution for halogen by carbanions requires reversible addition and that sets upper limits on the reactivity of the anion, although steric effects can also favor equilibration (more-substituted equilibrate faster). As before, fluoride is a better leaving group than chloride. An example is shown in equation (16), producing methyl 2-phenyl-2-(*t*-butylthio)propionate (**24**) in 94% yield after 15 h at 25 °C. There is an important solvent effect on the rate of equilibration of the carbanions[68] and the conditions chosen for these early experiments are not necessarily the best; there may be room to expand the scope of useful anions by careful choice of media (less polar solvents should favor equilibration).

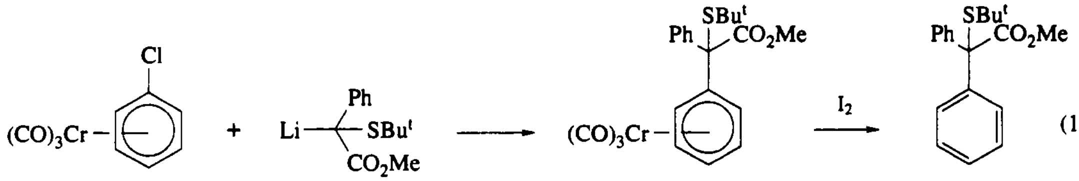

(16)

(**24**) 94% overall

Except in the formation of minor side products, the replacement of halogen by hydride as nucleophile is not observed. Halide exchange is also not a general process with [(haloarene)Cr(CO)₃] species.

### (*ii*) Cine–tele *substitution*

There is an alternate mechanism for halide replacement, following the sequence of nucleophile addition, protonation and elimination of HX (Scheme 9). In this pathway, the addition of the nucleophile need not be at the *ipso* position; it can be *ortho* to halide leading to '*cine*' substitution or it can be at the *meta* or *para* positions, leading to '*tele*' substitution.[69,70] The mechanism is the same for both *cine* and *tele* substitution and the different names reflect a differentiation in the IUPAC naming schemes.

The processes depend on the formation of the cyclohexadienyl anion intermediates in a favorable equilibrium (carbon nucleophiles from carbon acids with $pK_a > 22$ or so), protonation (which can occur at low temperature with even weak acids, such as acetic acid) and hydrogen shifts in the proposed diene–chromium intermediates (**25**) and (**26**). Hydrogen shifts lead to an isomer (**26**), which allows elimination of HX and regeneration of an arene–chromium complex (**27**), now with the carbanion unit indirectly substituted for X (Scheme 9).

An important example of indirect substitution utilizes alkoxy leaving groups; the intermediate (**28**) from the reaction of the [(diphenyl ether)Cr(CO)₃] complex and the 2-methyl-1,3-dithiane anion can be induced to eliminate phenol by protonation at low temperature; the result is *tele* substitution (equation 17).

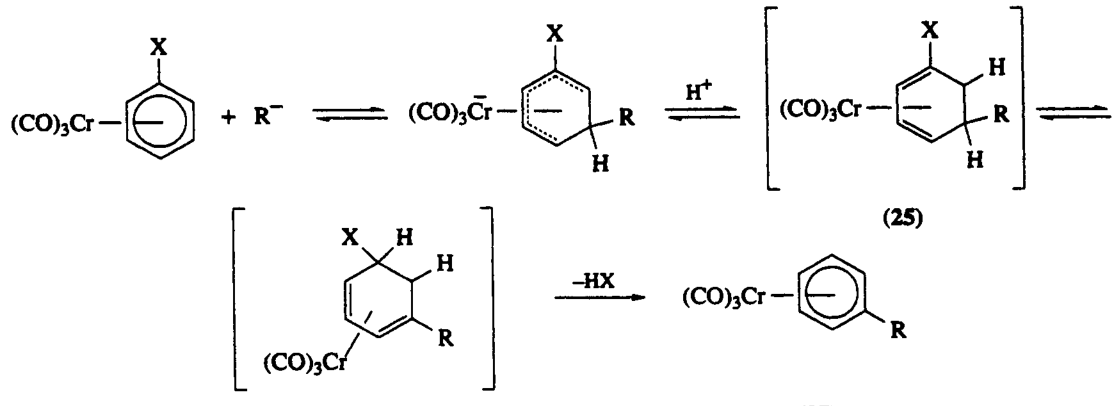

Scheme 9

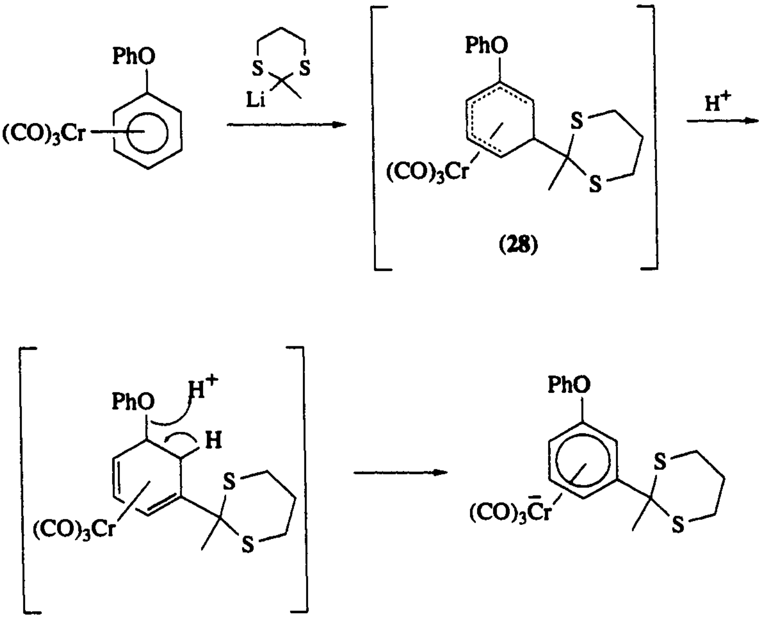

(17)

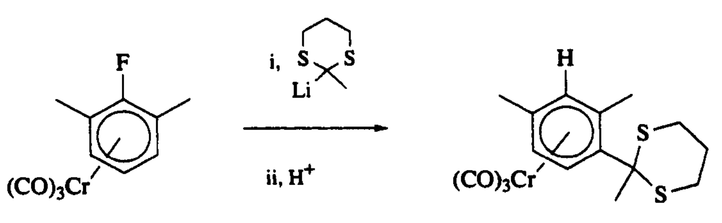

(29)

(18)

An impressive example is the reaction of [(2,6-dimethyl-1-fluorobenzene $Cr(CO)_3$] with 2-lithio-2-methyl-1,3-dithiane at –78 °C followed by treatment with trifluoroacetic acid at –78 °C.[69] Loss of HF leads to the 1,2,4-substitution (*tele*) product (29) in 62% yield (equation 18).[70]

The directing effects of F (strong *meta*) *versus* Cl (weak, *ortho–meta*; discussed below) allow control over the site of *tele* substitution; the chloro analog leads to (30), with the 1,3,5-substitution pattern (equation 19).[71]

Under certain conditions, apparently when the $Cr(CO)_3$ unit is spontaneously displaced from the product by a weak donor ligand (solvent), the simple addition product (1,3-cyclohexadiene derivative 31) can be the major product (equation 20).[71]

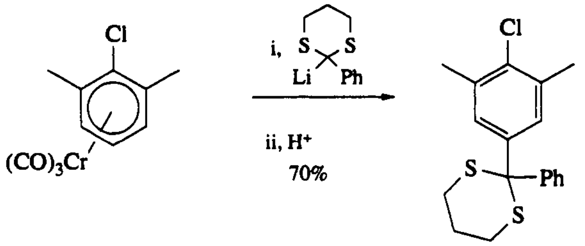

(30)

(19)

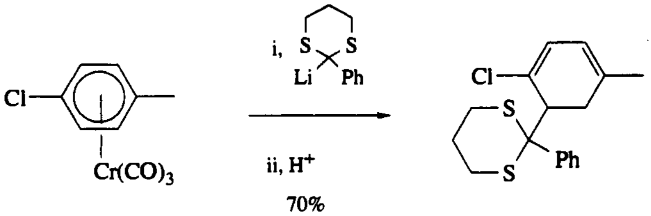

(31)

(20)

### 2.4.3.2 [(Halobenzene)CpFe]$^+$

### *2.4.3.2.1 Nucleophilic substitution with heteroatom nucleophiles*

While the potential for these species in nucleophile substitution for chloride has been demonstrated, the processes have not been fully developed nor applied. The two-stage process of addition–substitution for chloride and arene detachment is exemplified for the iron system in equation (21).

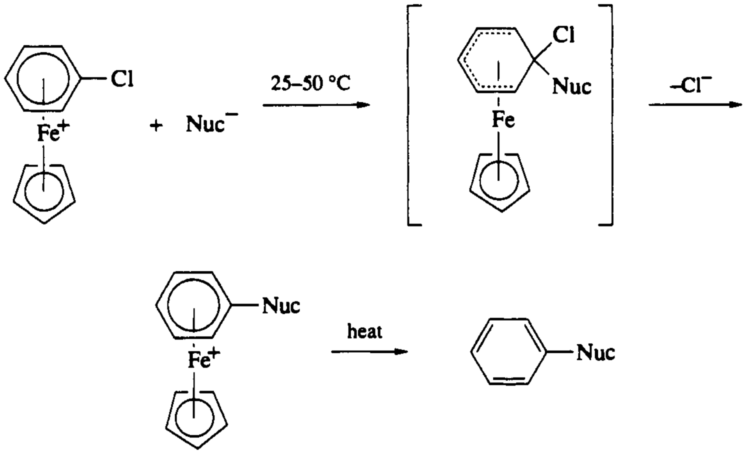

(21)

The first stage (addition–elimination) is well known with CN$^-$ and a variety of N-, O- and S-nucleophiles.[7,72–75] The detachment of the product arene from the Fe is more difficult. The conversions in equation (22) demonstrate the stability of the arene–Fe bond toward oxidation, as a side chain methyl is converted to a carboxylic acid, and suggest the generality of heteroatom substitution under mild conditions.[76]

With [$\eta^6$-(*o*-dichlorobenzene)FeCp]$^+$, selective mono- and di-substitution can be achieved with a variety of N- and O- and stabilized C-nucleophiles.[77] With a bisheteroatom nucleophile, benzo-fused heterocycles are produced (equation 23).[74]

The analogous *p*-dichlorobenzene complex will react rapidly with phenoxide and alkoxide nucleophiles in the first substitution and more slowly in the second; monosubstitution can be readily achieved.[78] Simple amines give only monosubstitution, even in the presence of excess amine (equation 24).

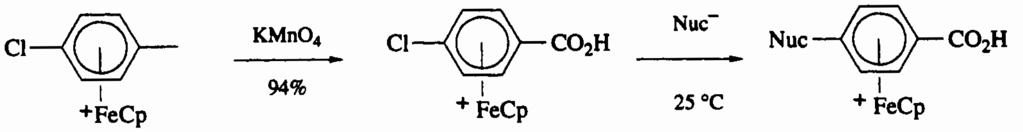
Cl
+FeCp
KMnO4
94%
CO2H
Nuc⁻
25 °C
Nuc

(22)

Nuc = PhS (51%) and EtO (68%)

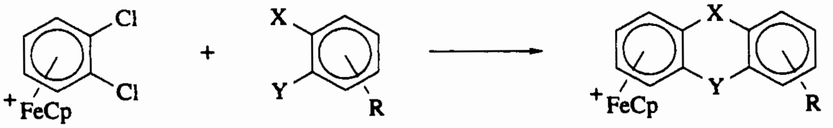

(23)

X, Y = O, S, NH; R = H, Me

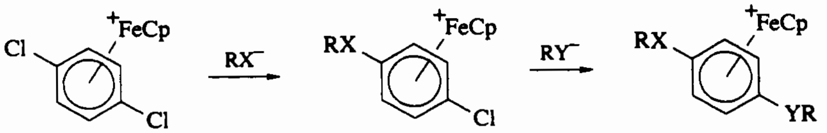
+FeCp
Cl
RX⁻
RX
RY⁻
YR

(24)

Substitution with amine nucleophiles in the series of chlorotoluene complexes showed that the substitution is direct; no *cine* or *tele* substitution was observed.[75] The analogous [(fluoroarene)FeCp]$^+$ complexes are known, but less well developed. Kinetic studies show that the fluoro derivatives are more reactive compared to the chloro analogs.[47]

A special example is the replacement of a nitro group on [($\eta^6$-nitrobenzene)FeCp]$^+$.[78,79] Reaction with O-, S-, N- and stabilized C-nucleophiles gives overall addition–elimination (equation 25). The nitroarene complexes are prepared by oxidation of the corresponding aniline complexes and are readily available.[78,79]

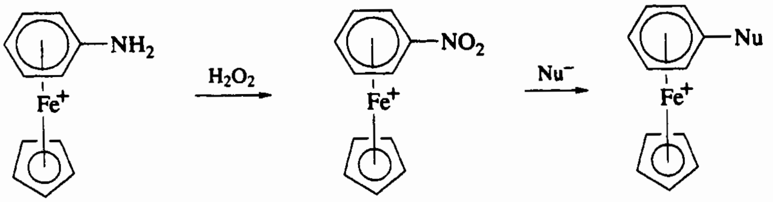
NH2
Fe+
H2O2
NO2
Nu⁻
Nu

(25)

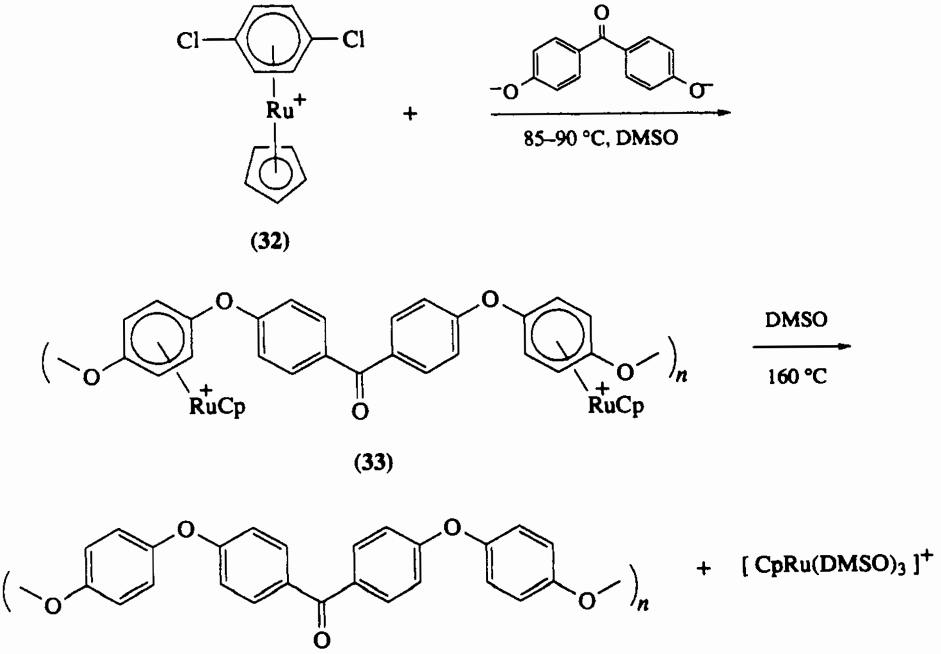
Cl
Cl
Ru+
+
O
⁻O
O⁻
85–90 °C, DMSO
O
RuCp
n
DMSO
160 °C
+ [ CpRu(DMSO)3 ]+

(32)

(33)

(26)

In the isoelectronic ruthenium series, nucleophilic substitution by the disodium salt of 4,4′-dihydroxybenzophenone on the complex (**32**) of *p*-dichlorobenzene with a $[RuCp]^+$ unit produced the aromatic polyether complex represented by (**33**). Displacement by DMSO at 160 °C led to the free polymer and the recoverable complex $[CpRu(DMSO)_3]^+$, which can be recycled directly by complexation with *p*-dichlorobenzene (equation 26). While ruthenium is not attractive to use in stoichiometric processes, this example appears to allow easy recycling.[80]

#### *2.4.3.2.2 Nucleophile addition–substitution with carbon nucleophiles*

Stabilized carbon nucleophiles (*e.g.* from β-diketones, β-keto esters, malonate esters, *etc.*) can be arylated by substitution for chloride on the arene in [Fe(arene)Cp] cation complexes.[72,78,81] A base is necessary and two heterogeneous systems are favored: potassium carbonate in DMF or potassium fluoride prepared on Celite-545. As usual in the $[FeCp]^+$ system, detachment of the substituted arene requires somewhat extreme conditions, usually pyrolytic sublimation at 200 °C.[46] An example is given in equation (27).

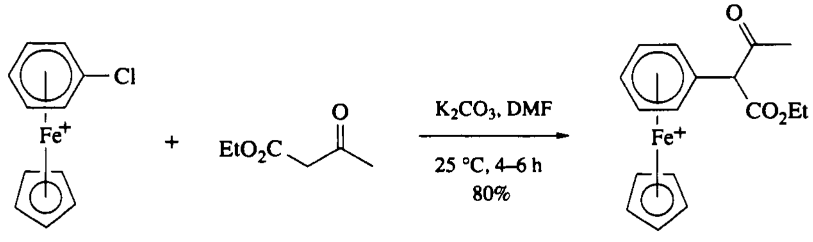

(27)

### 2.4.3.3 $[(Halobenzene)Mn(CO)_3]^+$

The most reactive of the common arene–metal complexes has been the least developed with regard to nucleophilic substitution for halide. It is only an improved, gentler method of complexation that allowed isolation of the fluorobenzene complex.[36] The chlorobenzene analog is easily prepared and undergoes substitution with alkoxy, phenoxy, thiolate, amine and azide nucleophiles (equation 28).[36,82] Reaction is complete with aniline (a weak nucleophile) within 3 min at room temperature. In examples with a methyl substituent on the arene as a label, the substitution is shown to be direct. The detachment of the substituted arene ligand from the $Mn(CO)_3$ unit is still limited by the requirement for strong oxidizing conditions, a serious limitation if this series is to be put forward in synthesis methodology.

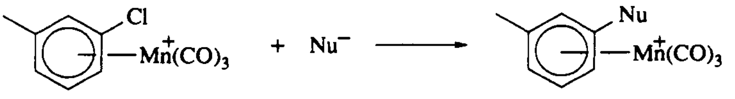

(28)

Nu⁻ = alkoxy, phenoxy, thiolate, amine and azide

## 2.4.4 ADDITION TO ARENE–METAL COMPLEXES TO GIVE $\eta^5$-CYCLOHEXADIENYL INTERMEDIATES

### 2.4.4.1 Addition–Oxidation: Formal Nucleophilic Substitution for Hydrogen

#### *2.4.4.1.1 Addition–oxidation with $[(arene)Cr(CO)_3]$ complexes*

*(i) General features*

Once it is recognized that cyclohexadienyl anionic complexes of chromium (**34**) can be generated by addition of sufficiently reactive nucleophiles and that simple oxidizing techniques convert the anionic intermediates to free substituted arenes, a general substitution process becomes available, which does not depend on a specific leaving group on the arene (equation 29).[52,83] While no heteroatom nucleophile has been successfully utilized, the process is general for carbanions derived from carbon acids with $\mathrm{p}K_a > 22$ or so.[83] Exceptions among the very reactive anions include organolithium reagents (deprotonation of the arene ligand and addition to the CO ligand are favored) and Grignard reagents (addition to the CO ligand is favored). With anions such as ester enolate anions, reaction occurs within minutes at –78 °C and the intermediate cyclohexadienyl complex can be observed spectroscopically.[83] The intermediates are exceedingly air sensitive and are generally quenched directly, without purification. In one case, from the addition of 2-lithio-1,3-dithiane, the adduct has been crystallized and fully characterized by X-ray diffraction analysis.[83] Oxidation with excess iodine (at least 2.5 mol equiv. of $I_2$) also proceeds at –78 °C and is complete within hours below room temperature. The products are the substituted arene, HI, $\mathrm{Cr^{III}}$ and CO. For acid sensitive products, such as trialkylsilyl-substituted arenes, an excess of amine (conveniently, diisopropylamine) can buffer the mixture. Table 1 provides a representative sample of the carbanions, which have been tested with $[(\eta^6\text{-benzene})\mathrm{Cr(CO)_3}]$.

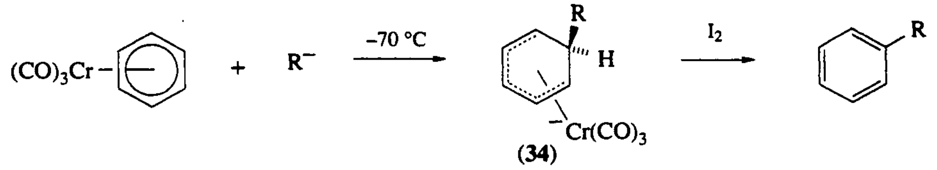

(29)

Table 1 Reactivity of Carbanions (R—Li) Toward [(Benzene)Cr(CO)3]

| *Unreactive* | *Successful* | *Metallation* |
|---|---|---|
| 1. $\mathrm{LiCH(CO_2Me)_2}$ | 7. $\mathrm{LiCH_2CO_2Bu^t}$ | 18. $\mathrm{Bu^nLi}$ |
| 2. $\mathrm{LiCH_2COBu^t}$ | 8. $\mathrm{LiCH_2CN}$ | 19. MeLi |
| 3. MeMgBr | 9. $\mathrm{KCH_2COBu^t}$ | 20. $\mathrm{Bu^sLi}$ |
| 4. $\mathrm{Bu^tMgBr}$ | 10. LiCH(CN)(OR) | |
| 5. $\mathrm{Me_2CuLi}$ | 11. $\mathrm{LiCH_2SPh}$ | |
| 6. LiC(CN)(Ph)(OR) | 12. 2-Li-1,3-dithiane | |
| | 13. $\mathrm{LiCH{=}CH_2}$ | |
| | 14. LiPh | |
| | 15. $\mathrm{LiC{\equiv}CR}$ | |
| | 16. $\mathrm{LiCH_2CH{=}CH_2}$ | |
| | 17. $\mathrm{LiC(Me)_3}$ | |

### *(ii) Regioselectivity*

Regioselectivity has been the subject of numerous studies with a variety of mono- and poly-substituted arene ligands. The addition of synthetically interesting carbanions to the typical arene ligand, especially those bearing electron-donating substitutents, can be reversible at rates comparable to the rate of addition: it is not always obvious whether to assume kinetic or thermodynamic control.[68,84–88] However, correlations have been suggested which allow prediction or rationalization of regioselectivity with a modest degree of confidence. With some significant exceptions as discussed below, the difference between the kinetic and thermodynamic selectivity has not been determined or is small.

With arenes bearing a single resonance donor substituent ($\mathrm{NR_2}$, OMe, F), the addition is strongly preferred at the *meta* position, with small amounts of *ortho* substitution (0–10%).[89,90] Representative examples are shown in Table 2 and equation (30).

The *meta* acylation of anisole, using a carbonyl anion equivalent as the nucleophile, illustrates the unique regioselectivity available with the $\mathrm{Cr(CO)_3}$ activation (equation 31).

However, the selectivity is more complicated with a methyl or chloro substituent. Again, *meta* substitution is always significant, but *ortho* substitution can account for 50–70% of the mixture in some cases.[89–91] More reactive anions (1,3-dithianyl) and less substituted carbanions (*e.g.* *t*-butyl lithioacetate) tend to favor *ortho* substitution. Representative examples are shown in Table 2 and equation (30). Entries 2–4 show that variation of reaction temperatures from –100 to 0 °C has no significant effect in that highly selective system. The added activating effect of the Cl substitutent allows addition of the pinacolone enolate anion (entry 11), whereas no addition to the anisole nor toluene ligand is observed with the same anion. Table 3 and equation (32) also includes results with *para*-directing substituents, $\mathrm{CF_3}$ and $\mathrm{Me_3Si}$ (entries 14 and 15).[90,91] In general, electron-withdrawing substituents such as acyl and cyano are also ac-

**Table 2** Addition–Oxidation with Anisole, *N,N*-Dimethylaniline and [(Fluorobenzene)Cr(CO)$_3$] Complexes

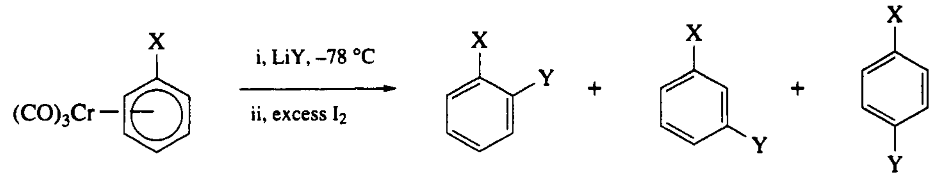

(30)

| *Entry* | *X* | *LiY* | *Ratio (o:m:p)* | *Combined yield (%)* |
|---|---|---|---|---|
| 1 | OMe | $LiCH_2CN$ | 3:97:0 | 38 |
| 2 | OMe | $LiC(Me)_2CN$ | 3:97:0 | 93 |
| 3 | OMe | $LiCH_2CO_2Bu^t$ | 6:94:0 | 86 |
| 4 | OMe | $LiCH(Me)CO_2Bu^t$ | 4:96:0 | 93 |
| 5 | OMe | $LiC(Me)_2CO_2Bu^t$ | 0:100:0 | 76 |
| 6 | OMe | $LiC(CN)(OR)CH_2Ph$[a] | 0:100:0 | 75 |
| 7 | OMe | 2-lithio-1,3-dithiane | 10:90:0 | 35[b] |
| 8 | $N(Me)_2$ | $LiC(Me)_2CN$ | 1:99:0 | 92 |
| 9 | F | $LiC(Me)_2CN$ | 2:98:0 | 84 |

[a] The R group is CH(Me)(OEt). [b] A major side reaction is *ortho* deprotonation of the anisole ligand.

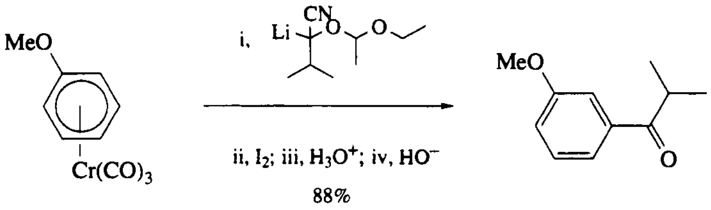

(31)

tivated toward nucleophile addition to the substituent (C=O or CN) and this process competes with addition to the ring itself.

**Table 3** Addition–Oxidation with [(Chlorobenzene)Cr(CO)$_3$] and [(Toluene)Cr(CO)$_3$] Complexes

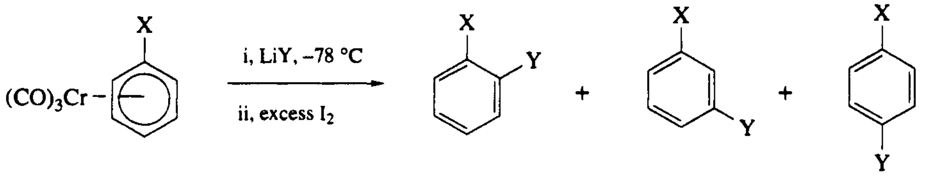

(32)

| *Entry* | *X* | *LiY* | *Ratio (o:m:p)* | *Combined yield (%)* |
|---|---|---|---|---|
| 1 | Me | $LiCH_2CN$ | 35:63:2 | 88 |
| 2 | Me | $LiC(Me)_2CN$ (−100 °C/1.5 min) | 2:96:2 | 52 |
| 3 | Me | $LiC(Me)_2CN$ (−78 °C/1.5 min) | 1:97:2 | 95 |
| 4 | Me | $LiC(Me)_2CN$ (0 °C/20 min) | 1:97:2 | 86 |
| 5 | Me | $LiCH_2CO_2Bu^t$ | 28:72:0 | 89 |
| 6 | Me | $LiC(Me)_2CO_2Bu^t$ | 3:97:0 | 96 |
| 7 | Me | 2-Lithio-1,3-dithiane | 52:46:2 | 94 |
| 8 | Cl | $LiCH_2CO_2Bu^t$ | 54:45:1 | 98 |
| 9 | Cl | $LiCH(Me)CO_2Bu^t$ | 53:46:1 | 88 |
| 10 | Cl | $LiC(Me)_2CO_2Bu^t$ | 5:95:0 | 84 |
| 11 | Cl | $LiCH_2COBu^t$ | 70:24:0 | 87 |
| 12 | Cl | $LiC(Me)_2CN$ | 10:89:1 | 84 |
| 13 | Cl | 2-Lithio-1,3-dithiane | 46:53:1 | 56 |
| 14 | $CF_3$ | $LiC(CN)(Me)(OR)$[a] | 0:30:70 | 33 |
| 15 | $SiMe_3$ | $LiC(Me)_2CN$ | 0:2:98 | 65 |

[a] The R group is —CH(Me)(OEt).

Regioselectivity in *ortho*-disubstituted arenes is often high and useful. A series of examples is summarized in Figure 1. The resonance donor substituent (OMe) appears to dominate the directing influences, favoring addition at the less hindered position *meta* to itself.[91] But with two identical substituents, the addition is preferred in the adjacent position.[88,91,92] For example, with the complex of benzocyclobutene (**35**), six carbon nucleophiles were tested and each gave addition exclusively at C-3.[88,92] With the complex of indane (**36**), selective addition at C-3 was observed with dithianyl anions, but cyano-stabilized anions gave up to 20% of the isomeric product from addition at C-4.[88,92] Substituents at the benzylic carbons in the indane ligand have a strong effect on selectivity and can lead to the 1,2,4-substitution product.[88]

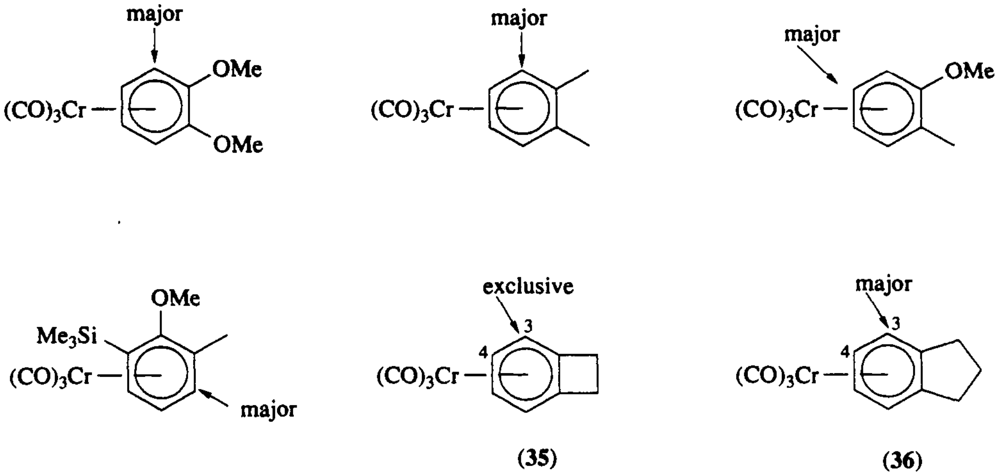

**Figure 1** Summary of regioselectivity of substituted arene ligands

Addition to *o*-alkylaniline complexes has been the subject of a detailed study and presents a clear case of different products from kinetic *versus* thermodynamic control.[87,88] Addition of 2-lithio-2-cyanopropane to [(*N*-methyl(tetrahydroquinoline)$Cr(CO)_3$] (**37**; equation 33) with variation in time, temperature and solvent (THF or THF with 4 mol equiv. of HMPA added) gives product distributions ranging from 2:1 for C-5:C-3 at −78 °C for 1 min to >96% addition at C-5, when the adduct is allowed to equilibrate (8.6 h at −78 °C). The data show that equilibration is occurring within minutes at −78 °C and the product distribution does not change upon warming to 20 °C. The effect of added HMPA is an initial product ratio of 54:44 for C-5:C-3 and strongly inhibited equilibration; the effect of HMPA was also observed in halide substitution (addition–elimination)[90] and clearly established during addition to simple arenes.[68,84] With the less sterically demanding anion, $LiCH_2CN$, addition is incomplete after 22 h at −78 °C and favored at C-3 (82:18 for C-3:C-5).

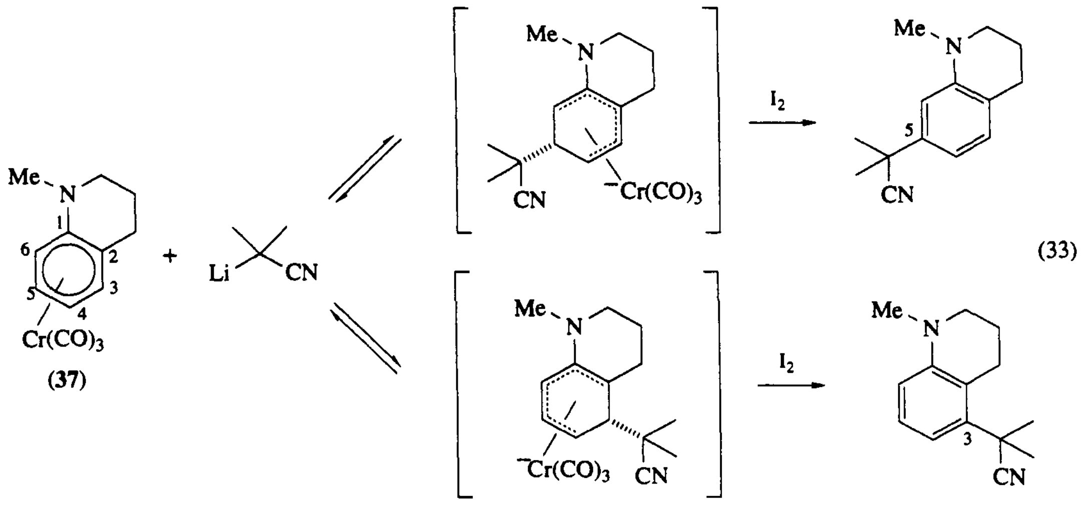

The same study shows that with the complex of *N*,*N*-dimethyl-*o*-toluidine (**38**), the selectivity depends on time, temperature and the nature of the anion (Table 4 and equation 34).[87] Again, equilibration occurs with the tertiary nitrile-stabilized anion, favoring the C-4 substitution product, while lithioacetonitrile favors addition at C-3. The 2-methyl-1,3-dithianyl anion gives precisely the same product mixture at –78 °C and at –30 °C; there is no evidence for equilibration with this anion.

**Table 4** Addition–Oxidation with [(*N*,*N*-Dimethyl-*o*-Toluidine)Cr(CO)$_3$]

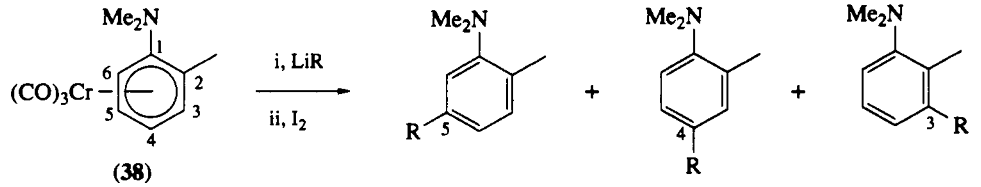

(**38**)

(34)

| *Carbanion* | *Conditions* | *1,2,5 (%)* | *1,2,4 (%)* | *1,2,3 (%)* |
|---|---|---|---|---|
| LiC(Me)$_2$CN | –78 °C/2.5 h | 32 | 32 | 36 |
| LiC(Me)$_2$CN | –50 °C/24 h | 8 | 81 | 11 |
| LiCH$_2$CN | –40 °C/24 h | 3 | 4 | 93 |
| 2-Li-1,3-Thianyl | –78 °C/2.5 h | 25 | 10 | 65 |

The complex of *N*-methylindoline (**39**) gives similar behavior, favoring addition at C-4 (indole numbering), but with significant addition at C-7, depending on the anion and opportunity for equilibration.[87,93] With the 2-methyl-1,3-dithianyl nucleophile, a high selectivity for C-4 is observed (equation 35).

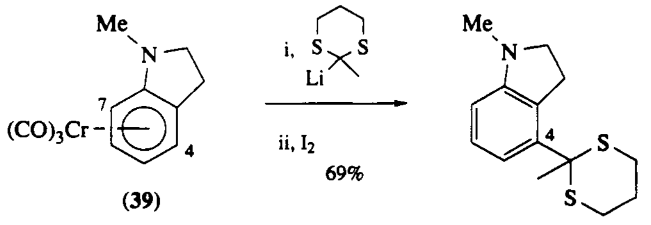

(**39**)

(35)

96% this isomer

Indole is a particularly interesting case, because the Cr(CO)$_3$ unit selectively activates the six-membered ring (**40**),[93,94] while in free indole the five-membered ring dominates the (electrophilic addition) reactivity. The selectivity in addition to the Cr(CO)$_3$ complexes of indole derivatives shows a preference for addition at C-4 (indole numbering) and C-7, with steric effects due to substituents at C-3 and N-1 as well as anion type influencing the selectivity.[93] In Scheme 10, example A, a hydrogen substituent at C-3 and a tertiary carbanion leads to selective C-4 substitution. In example B, the same substrate adds 2-lithio-1,3-dithiane predominantly at C-7. With a trimethylsilylmethyl substituent at C-3, the addition is preferred at C-7 (example C). Finally, even with the silylmethyl substituent at C-3, a sufficiently large *N*-protecting group can disfavor addition at C-7 (example D).

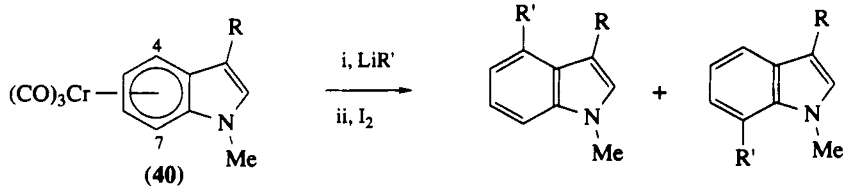

(**40**)

| | | | | | |
|---|---|---|---|---|---|
| A. | R' = CMe$_2$CN; R = H; Y = Me | 99 | : | 1 | (92% yield) |
| B. | R' = (1,3-dithianyl); R = H; Y = Me | 14 | : | 86 | (68%) |
| C. | R' = CMe$_2$CN; R = CH$_2$SiMe$_3$ | 17 | : | 83 | (82%) |
| D. | R' = CMe$_2$CN; R = CH$_2$SiMe$_3$; Y = SiBu$^t$Me$_2$ | 95 | : | 5 | (78%) |

**Scheme 10**

Another example in which the regioselectivity of addition is different under kinetic *versus* thermodynamic control is the naphthalene series. In the addition of $LiCMe_2CN$ to $[(naphthalene)Cr(CO)_3]$ (**41**), a mixture of products is observed from addition at C-α and C-β in the ratio 42:58 under conditions where equilibration is minimized (0.3 h, –65 °C, THF–HMPA). With the same reactants, but in THF and at 0 °C, the product is almost exclusively the α-substituted naphthalene (equation 36).[84,85,92]

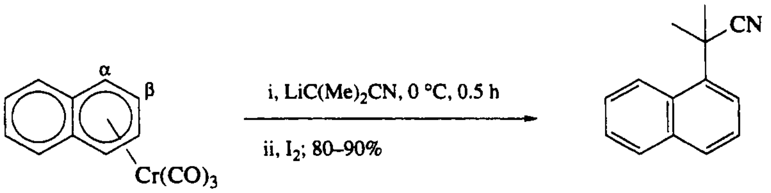

(36)

**(41)** >98% selectivity

Using the standard procedures, 1,4-dimethoxynaphthalene is complexed at the less-substituted ring with high selectivity to give (**42**).[68] Again, under conditions of minimum equilibration of anion addition, $LiCMe_2CN$ gave a mixture (after iodine oxidation) of the 1,4-dimethoxy-β-substituted and 1,4-dimethoxy-α-substituted products in the ratio 78:22. After equilibration, the α-substitution product was essentially the only product found (equation 37).

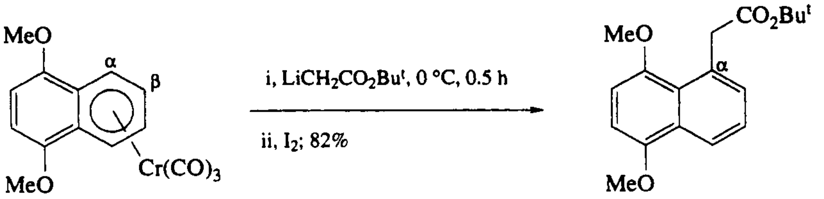

(37)

**(42)**

The 1,4-dimethoxynaphthalene ligand was used to probe for the parameters which influence the rate of equilibration. The change from pure THF to a mixture of 3:1 THF:HMPA slows the rate of equilibration by a factor of 50 000.[68,85] Replacement of Li with K in the carbanion nucleophile also slows equilibration, by a factor of 500. The equilibration is shown to be intermolecular (dissociation of the nucleophile) by elegant 'crossover' experiments with doubly labeled substrates.[68,85] With the 1,4-dimethoxynaphthalene ligand, cyano-stabilized anions (including cyanohydrin acetal anions) and ester enolates equilibrate even at low temperature and strongly favor addition at the α-position (C-5), as in equation (37). The kinetic site of addition is also generally C-α. However, the 2-lithio-1,3-dithiane anion and phenyllithium do not equilibrate over the temperature range –78 to 0 °C, equations (38) and (39). The sulfur-stabilized anions favor addition at C-β, while phenyllithium gives a mixture favoring C-α.

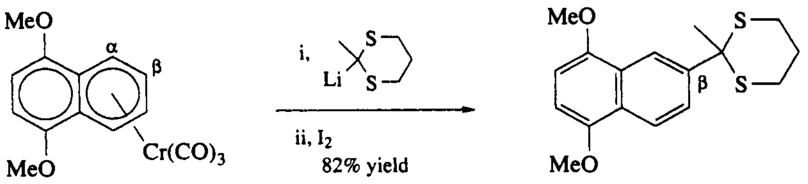

(38)

**(42)**

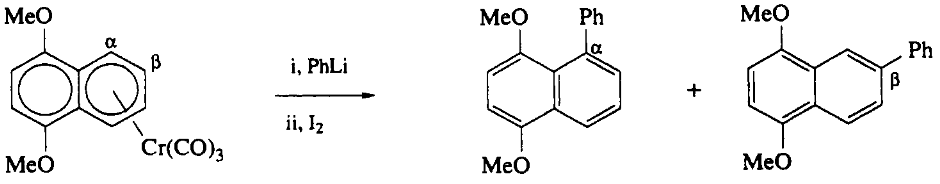

(39)

**(42)** 84:16

The steric effect on regioselectivity shows clearly in the series in Table 5 and equation (40).[95] Comparing similar anion type, except for size, entries 1, 3 and 7 show that *ortho* substitution is very significant with a primary carbanion but essentially absent with a tertiary cyano-stabilized anion. It is striking that as the size of the alkyl substitutent on the arene increases, not only is *ortho* substitution disfavored, but *meta* is as well: compare entries 3–6 and compare 7–9. With the very large $CH(Bu^t)_2$ group (entry 9), only *para* substitution is observed. Regioselectivity is also dependent on the electronic nature of the nucleophile. Most remarkably, addition of the primary sulfur-stabilized anion shows nearly equal amounts of *ortho* and *meta* substitution with the toluene ligand, but, as the size of the arene substituent increases, the *para* substitution product increases at the expense of the *meta* product (entries 10–12).

**Table 5** Steric Effects on Regioselectivity

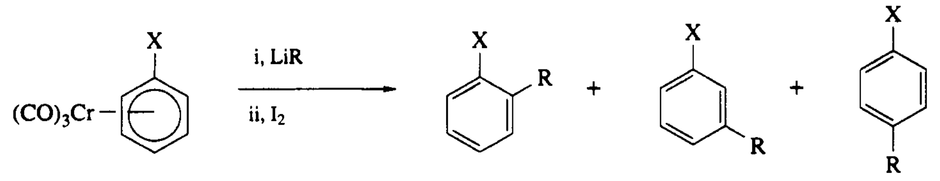

(40)

| *Entry* | *Complex* | *Anion* | *Product Ratio (o:m:p)* | *Combined yield (%)* |
|---|---|---|---|---|
| 1 | X = Me | $LiCH_2CN$ | 35:63:2 | 88 |
| 2 | $X = Bu^t$ | $LiCH_2CN$ | 28:48:24 | 51 |
| 3 | X = Me | LiC(OR)MeCN[a] | 0:96:4 | 75 |
| 4 | X = Et | LiC(OR)MeCN[a] | 0:94:6 | 89 |
| 5 | $X = Pr^i$ | LiC(OR)MeCN[a] | 0:80:20 | 88 |
| 6 | $X = Bu^t$ | LiC(OR)MeCN[a] | 0:35:65 | 86 |
| 7 | X = Me | $LiC(Me)_2CN$ | 1:97:2 | 95 |
| 8 | $X = Bu^t$ | $LiC(Me)_2CN$ | 0:55:45 | 78 |
| 9 | $X = CH(Bu^t)_2$ | $LiC(Me)_2CN$ | 0:0:100 | 63 |
| 10 | X = Me | $LiCH_2SPh$ | 52:46:2 | 96 |
| 11 | $X = Pr^i$ | $LiCH_2SPh$ | 47:46:7 | 86 |
| 12 | $X = Bu^t$ | $LiCH_2SPh$ | 45:32:23 | 88 |

[a] R = C(Me)OEt.

As presented in the next section, the dependence of selectivity on anion type is understood as a change in the balance of charge *versus* orbital control. However, in the anions listed so far there is the possibility that differences in carbanion structure, extent of delocalization *etc.*, might contribute to the changes in regioselectivity. In an effort to compare addition of carbanions, which differ little in structure, a series of 2-(*p*-substituted)aryl-2-lithio-1,3-dithiane nucleophiles was allowed to react with the *t*-butylbenzene ligand.[95] The *para* substitutent in the carbanion was varied in the expectation of varying the reactivity of the anion and thereby varying the addition selectivity. Table 6 and equation (41) presents the results. More reactive anions tend to add to the *meta* position (almost $m{:}p$ = 3:1 in entry 1; to $m{:}p$ = 1:3 in entry 8; *ortho* addition is never significant with this ligand). Obviously, this change in regioselectivity must be due to an electronic factor in the anion; steric effects are constant.

### *(iii) Interpretation of regioselectivity*

Selectivity in polar reactions can be discussed in terms of two features: charge control and orbital control.[96] Analysis of charge control requires a knowledge of charge distribution in the arene ligand. Analysis of orbital control can be approximated by emphasizing interaction of the frontier molecular orbitals, HOMO for the nucleophile and LUMO for the arene complex. It was recognized early that the *ortho–para* selectivity observed with weakly polar substituents, such as Me and Cl, correlated with the LUMO for the free arene and the assumption was made that the LUMO for the arene ligand has a distribution of coefficients similar to the free arene.[91] This has been supported by computation at the level of extended Hückel theory.[88,95,97] LUMOs for (uncoordinated) toluene and chlorobenzene are distributed nearly equally at the *ortho* and *meta* positions and show small density at the *para* position (Figure 2, A).[98–100] Similarly for the case of two donor substituents arranged *ortho*, the LUMO is predicted to be localized at adjacent positions (Figure 2, C), consistent with the observed selectivity. With electron acceptor substituents ($R_3Si$, $CF_3$), LUMO has large coefficients *ipso* and *para* (Figure 2, B), consistent with *para* addition selectivity.

**Table 6** Electronic Effects in Regioselectivity

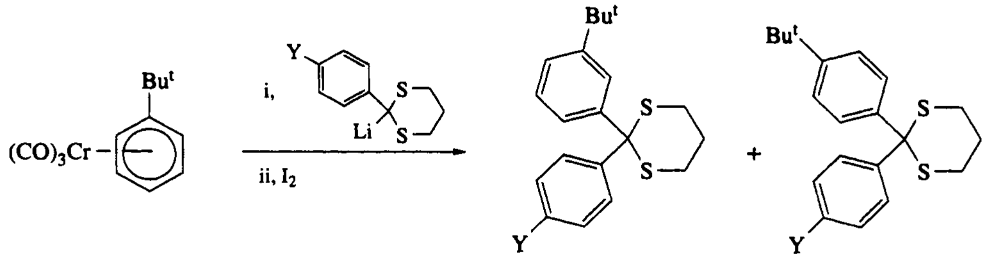

(41)

| *Entry* | *Para Y* | *Ratio (m:p)* | *Combined yield, (%)* | *$\sigma_p$ for Y* |
|---|---|---|---|---|
| 1 | $O^-$ | 73:27 | 84 | — |
| 2 | $NMe_2$ | 63:37 | 80 | −0.83 |
| 3 | $NMe_2$ | 57:43[a] | 78 | −0.83 |
| 4 | OMe | 54:46 | 71 | −0.27 |
| 5 | Me | 43:57 | 75 | −0.17 |
| 6 | H | 28:72 | 75 | 0 |
| 7 | H | 23:77[a] | 85 | 0 |
| 8 | Cl | 21:79 | 80 | +0.23 |

[a] HMPA was added to the medium; in all other cases, THF was the solvent.

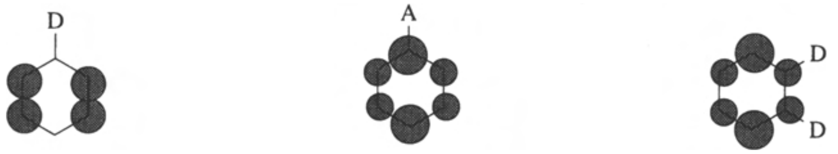

A. LUMO for D = donor (Me, Cl, OMe, $NR_2$)

B. LUMO for A = acceptor (RCO, NC, $Me_3Si$, $F_3C$)

C. LUMO for *ortho*-D (*o*-di-Me, *o*-di-OMe)

**Figure 2** Orbital distributions for substituted benzenes

However, the frontier orbital picture based on the free arene does not account for nearly exclusive *meta* selectivity in addition to [(anisole)Cr(CO)$_3$]; LUMO for anisole shows essentially the same pattern as for toluene.[98–100] With a strong resonance electron donor the traditional electronic picture (deactivation of the *ortho* and *para* positions) is sufficient to account for the observed *meta* selectivity. In this case the balance of charge control and orbital control is pushed toward charge control by strong polarization. The same argument applies to the aniline and fluorobenzene complexes.

A delicate balance of charge and orbital effects can also account for the dependence of selectivity on anion type. The central assumption is that nucleophiles with a higher lying HOMO (softer) should give a better orbital energy match in the HOMO–LUMO interaction and increase the orbital control term. For the toluene ligand, this predicts strong *ortho–meta* selectivity for more reactive anions.

The surprising change in regioselectivity from *meta* to *para* substitution as the size of the alkyl group is increased in [(alkylbenzene Cr(CO)$_3$] complexes (Table 5 and equation 40) is not easily rationalized based on the HOMO–LUMO picture and the direct polarization by arene substituents. A parameter unique to the arene–metal complexes is the conformation of the Cr(CO)$_3$ group, and it has been emphasized that this unit tends to be eclipsed with electron donor substituents and *anti* with electron acceptors, in the absence of overwhelming steric effects (Figure 3).[101] In addition, the arene ligand carbons which are eclipsed with a CO ligand are predicted to be more electrophilic (Figure 3).[102] This factor should favor addition to arene positions eclipsed with a CO ligand, under charge control conditions. In this picture, *meta* selectivity with anisole is consistent with an eclipsed conformation and *meta* activation. In most cases with polar substituents on the arene, the direct polar effect of the substituent and the indirect effect through conformational preferences lead to the same predicted selectivity: donor substitutents favor *meta* substitution and acceptors favor *ortho* and *para*. The emphasis on conformational effects in regioselectivity has been applied in several other systems[87,88,93,103,104] and supported by direct NMR measurements.[104–107]

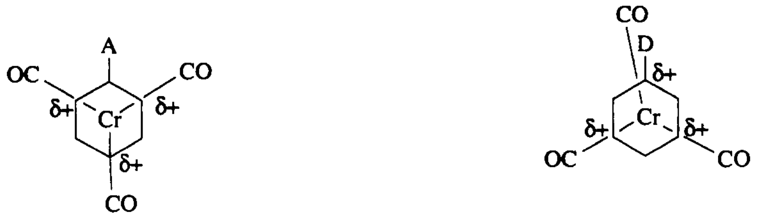

A = electron-withdrawing group

D = electron-donating group

**Figure 3** Conformational preferences in [(arene)Cr(CO)$_3$] complexes

The picture emphasizing conformational effects[102] does not account for significant *ortho–meta* selectivity in some cases, nor preferential addition adjacent to *ortho* donor substituents. However, all of the existing regioselectivity results can be accommodated by analyzing orbital control *versus* charge control, assuming an arene-centered LUMO similar to that for the free arene, and assuming that conformational preferences for the arene ligand have a major influence on the charge distribution of the arene.

The examples in Table 5 and equation (40) were chosen to test exactly these parameters and to separate the direct effect of substituents on charge distribution from the indirect effect of the substituent through its influence on the conformational preferences. With a very large substituent on the arene (*e.g.* $\mathrm{Bu^t}$ and $\mathrm{CH(Bu^t)_2}$), the favored conformation (Figure 4) now positions the CO ligand eclipsed with the *ortho* and *para* positions as steric interactions override electronic preferences.[104] Electron density is predicted to be reduced at these positions and a charge-controlled coupling with a nucleophile would be favored *para* (*ortho* is disfavored by direct steric interactions). The arene-centered LUMO, expected to be relatively independent of the conformation of the Cr(CO)$_3$ unit, has large density at the *ortho* and *meta* positions (Figure 4). Orbital-controlled coupling would be favored *meta*.

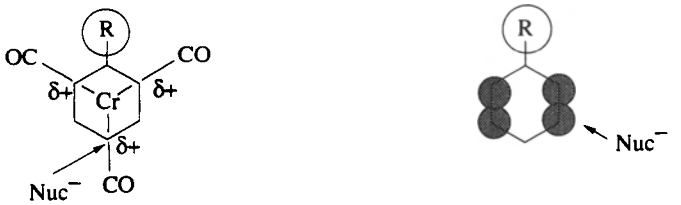

a. Favored conformation and resulting charge distribution

b. LUMO for an alkylbenzene

**Figure 4** Charge distribution and LUMO for [($\mathrm{Bu^t_2CHPh}$)Cr(CO)$_3$]

The series of *para*-substituted 2-aryl-1,3-dithianyl carbanions shown in Table 6 and equation (41) are expected to differ in LUMO energy. The phenoxide-substituted anion (entry 1, Table 6 and equation 41) should have higher LUMO relative to, for example, the simple phenyl-substituted anion (entry 6) and gives a greater preponderance of *meta* substitution due to stronger orbital control. The smooth correlation of selectivity with reactivity for this series of closely related anions is consistent with a simple two-parameter analysis. Other regioselectivity results, such as those with *o*-alkylanilines (Table 2 and equation 30) and [(indole)Cr(CO)$_3$] also have been analyzed in terms of orbital control and conformational effects.[87,88,93]

### *(iv) Application in the synthesis of deoxyfrenolicin.*[108]

The combination of *ortho* metallation and *meta* nucleophilic acylation was used to prepare a key intermediate in a synthesis of deoxyfrenolicin (**42**), as outlined in Scheme 11. The complex of anisole is *ortho*-metallated with *n*-butyllithium and quenched with chlorotrimethylsilane; the resulting [(*o*-(trimethylsilyl)anisole)Cr(CO)$_3$] (**43**) is then metallated again, converted to the arylcuprate, and coupled with (*E*)-2-hexenyl bromide to give the complex of 1-trimethylsilyl-2-methoxy-3-(2-hexenyl)benzene (**44**). Addition of the carbanion from the cyanohydrin acetal of 4-pentenal, followed by the standard iodine oxidation and subsequent hydrolysis of the cyanohydrin acetal to regenerate the carbonyl group gave the trisubstituted arene (**45**). The trimethylsilyl group underwent proto-desilylation during the iodine oxidation step. The yield overall from (**44**) to (**45**) was 61% and the selectivity for addition adjacent to the hexenyl side chain was >95%. The role of the trimethylsilyl group is to disfavor addition at the alternative activated *meta* position (*ortho* to $Me_3Si$). The ketone (**45**) serves as an effective intermediate for the construction of deoxyfrenolicin, using conventional methodology.

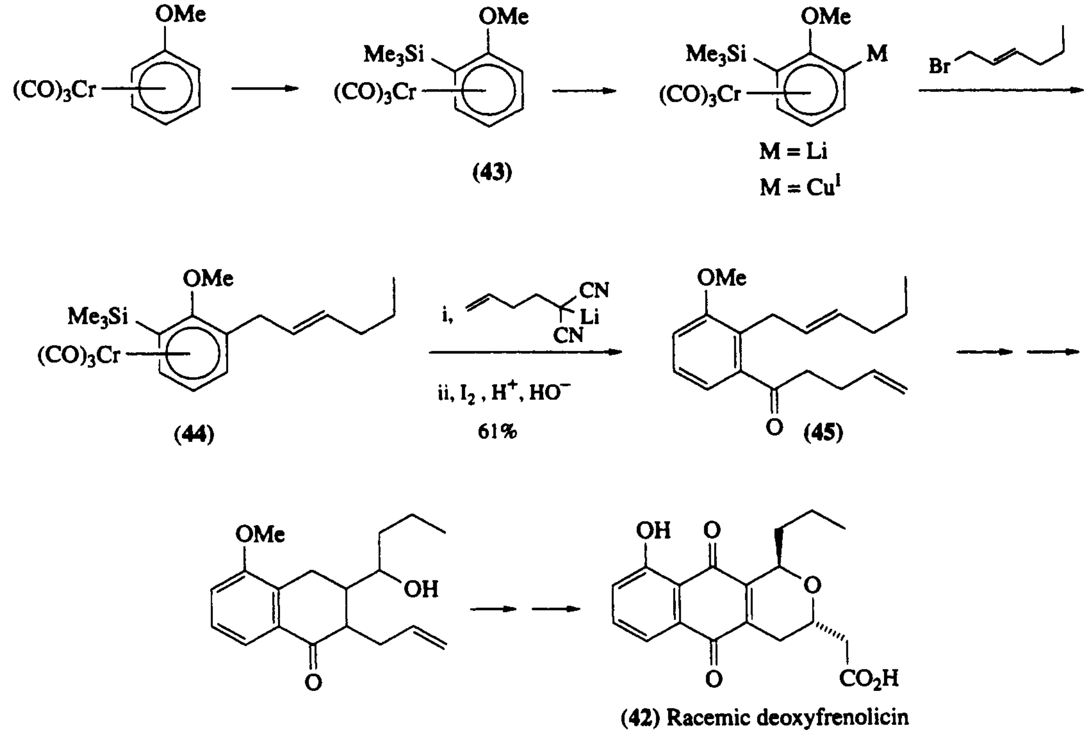
OMe
(CO)3Cr
Me3Si
(43)
M
M = Li
M = CuI
Br
(44)
i, CN Li CN
ii, I2, H+, HO−
61%
(45)
O
OH
OH O
O
CO2H
(42) Racemic deoxyfrenolicin

**Scheme 11**

### (v) *Intramolecular addition–oxidation*

Intramolecular addition–oxidation with reactive carbanions is generally successful; most of the examples involve cyano-stabilized carbanions. Formation of a six-membered fused ring (**46**) is efficient (equation 42), but five-membered fused ring formation is not.[17] The only addition–oxidation product is a cyclic dimer, the [3.3]metacyclophane (**47**).[17]

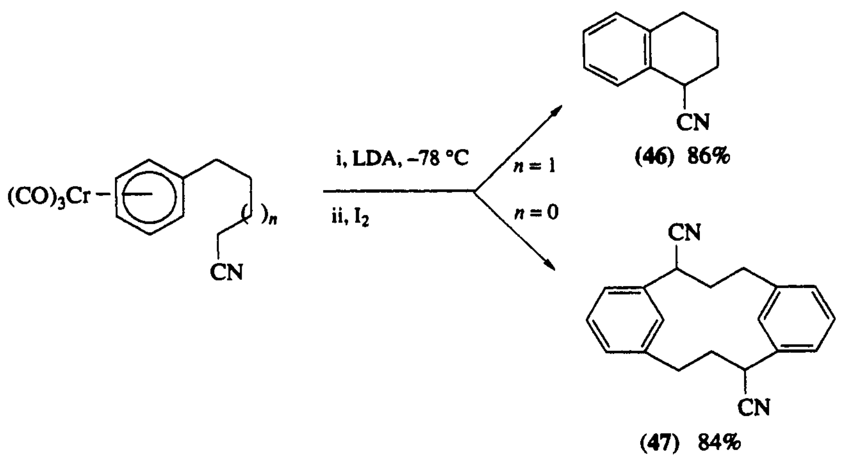
(CO)3Cr
CN
)n
i, LDA, −78 °C
ii, I2
n = 1
n = 0
CN
(46) 86%
CN
CN
(47) 84%

(42)

Reversibility again is apparent with the higher homolog (**48**; Scheme 12). At low temperature (0.5 h, –78 °C), a mixture of cyclohexadienyl anionic intermediates is formed with the spiro ring isomer (**49**) preferred by a factor of almost 3:1. An alternative quenching procedure, using trifluoroacetic acid (see below), retains the spiroring and produces the spiro[5.5]cyclohexadiene product (**51**). If the initial adduct is allowed to warm to 0 °C or above, essentially complete rearrangement to the fused ring adduct (**50**) occurs and oxidative quenching gives the seven-membered ring (**52**) in good yield, Scheme 12.[17]

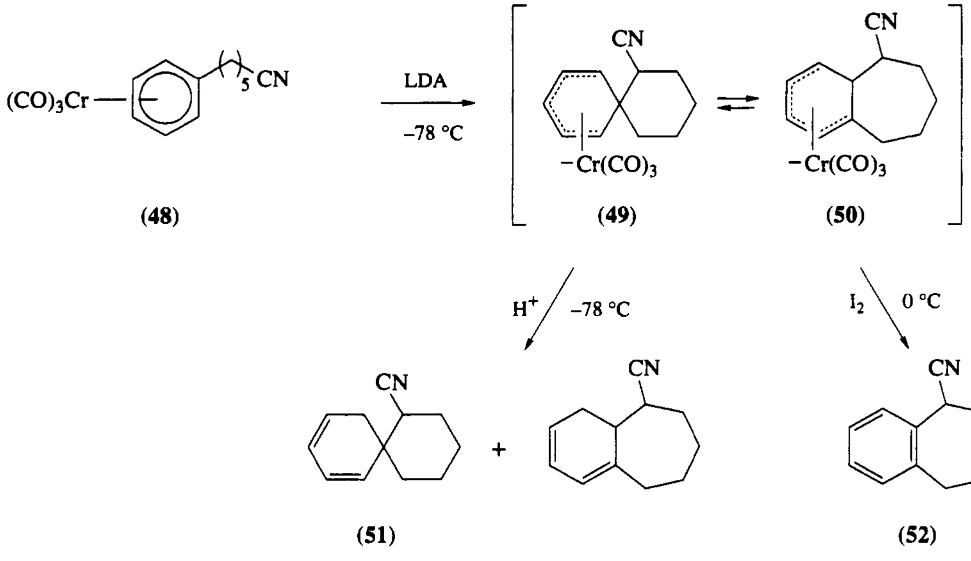

**Scheme 12**

### 2.4.4.1.2 *Addition–oxidation with [(arene)FeCp]$^+$ complexes*

It has been recognized for many years that nucleophiles will add to [($\eta^6$-benzene)FeCp]$^+$ complexes.[109–112] The nucleophiles range from cyanide anion[113] to metal hydrides and methyllithium; the intermediate neutral [($\eta^5$-(6-substituted)cyclohexadienyl)FeCp] complexes can be isolated and characterized. The regioselectivity has been determined for a number of monosubstituted arene ligands. Chloro[110] and methoxycarbonyl[112] substituents are *ortho* directing, while methoxy[111] is a *meta* director, and a methyl group leads to similar amounts of addition at the *ortho*, *meta* and *para* positions.[109] In general, electron-withdrawing groups (nitro, halo, benzoyl, cyano and sulfonyl) favor *ortho* addition, as exemplified for the addition of the acetone enolate in equation (43).[113,114]

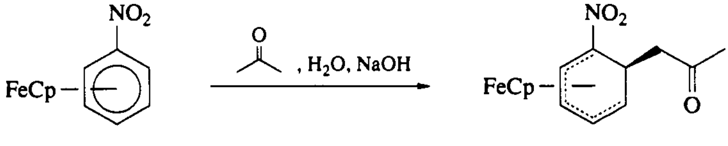

(43)

The primary limitations in applying these complexes are the two-stage detachment of the *endo* C-6 hydrogen (from **53**) and the detachment of the FeCp unit. Direct abstraction with trityl cation has been employed for the first stage,[110] and oxidation with *N*-bromosuccinimide completes both stages, leading to the substituted arene in the few cases tested.[115,116] In the cases with electron-withdrawing substituents on the starting arene, Ce$^{IV}$ has been employed to aromatize and detach the arene unit after addition (equation 44).[113]

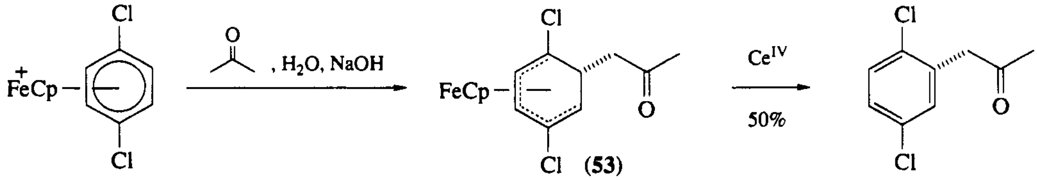

(44)

Because of the high reactivity of the [(arene)FeCp]$^+$ complexes, it can be expected that further developments and definition of selectivity features will be forthcoming.

#### *2.4.4.1.3 Addition–oxidation with [(arene)Mn(CO)$_3$]$^+$ complexes*

The reactivity of the [($\eta^6$-arene)Mn(CO)$_3$]$^+$ complexes toward addition of nucleophiles is high and general, leading to neutral, isolable [($\eta^6$-(6-substituted)cyclohexadienyl)Mn(CO)$_3$] derivatives, *e.g.* (**54**).[9,117] The addition of Grignard reagents to anisole and aniline ligands shows good *meta* selectivity (equation 45).[38,118,119] Addition to the chlorobenzene ligand gives similar amounts of *ortho* and *meta* (orbital control?), while the toluene ligand favors addition at all three positions (*o*, *m*, *p*).[38,119]

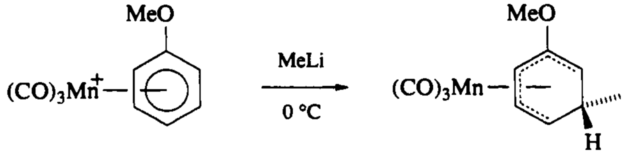

(**54**)

(45)

The completion of the substitution process to produce a substituted arene free of the metal has not been worked out in general. Direct abstraction of the *endo*-hydride of the $\eta^5$-cyclohexadienyl intermediate (**55**) with trityl cation is not effective, but an interesting thermal rearrangement has been observed at 130–150 °C to create an isomeric cyclohexadienyl ligand (in **56**), which bears an *exo* (easily abstracted) hydrogen substituent (equation 46).[119,120]

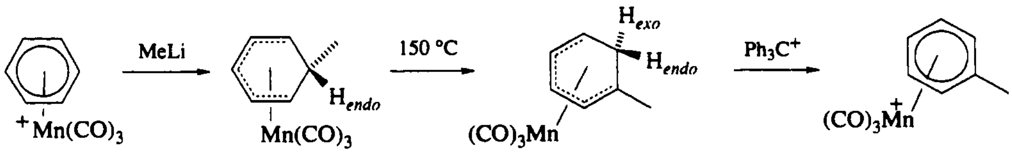

(**55**) (**56**)

(46)

A general process for addition of Grignard reagents and ketone enolates to [(arene)Mn(CO)$_3$]$^+$ complexes includes oxidative decomplexation of the substituted arene with Jones reagent.[38] An alternative is *endo*-hydride abstraction with strong acid, producing hydrogen and, using a coordinating solvent, displacing the arene ligand (equation 47).[38] This latter process allows easy recycling of the MnI reagent.

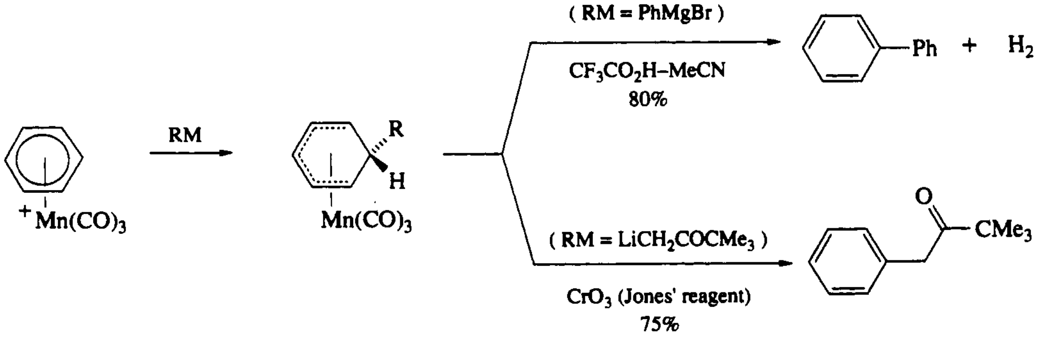

(47)

The [(arene)Mn(CO)$_3$]$^+$ system is very promising, but more development work is necessary in order to assess the full possibilities for overall addition–oxidation, substitution for hydrogen.

### 2.4.4.2 Addition–Protonation: Synthesis of Substituted 1,3-Cyclohexadienes

The intermediate $\eta^5$-cyclohexadienyl anionic species from nucleophilic addition to the [(arene)Cr(CO)$_3$] complexes are obviously highly electron rich and should be susceptible to reactions with electrophiles. Protonation is efficient at low temperature and is suggested to produce a labile $\eta^4$-1,3-cyclohexadiene complex (**57**), which can undergo H-migration to give the more stable 1,3-cyclohexadiene isomer (**58**); in simple systems, the major product is the 1-substituted 1,3-cyclohexadiene, Scheme 13.[83] The products can be aromatized by reaction with 2,3-dichloro-5,6-dicyanobenzoquinone.

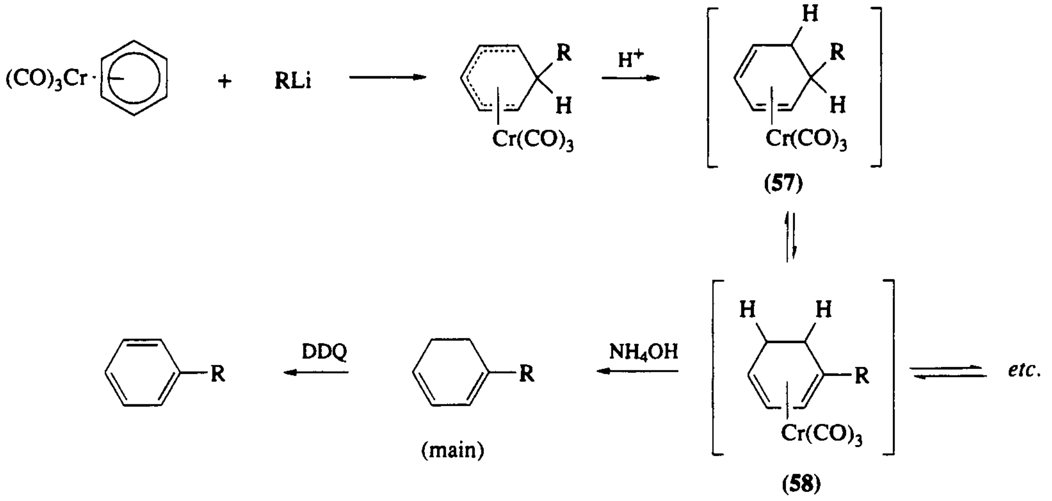

**Scheme 13**

The reaction appears to be general, although a limited number of examples have been reported. A particularly useful process begins with *meta* addition to $[(anisole)Cr(CO)_3]$, followed by protonation and hydrolysis of the enol ether unit (equation 48). The result is a 5-substituted cyclohex-2-en-1-one (**59**).[121] The intermediate dienol ether (**60**) can be isolated in high yield, before the aqueous hydrolysis. Other alkene positional isomers of the product enone can be obtained selectively depending on the conditions of the acid treatment and the acid hydrolysis.[121] The addition–protonation process does not change the oxidation state of the chromium and a procedure has been defined for recovery of the $Cr^0$ in order to allow direct recycling.[122] The addition of CO or other donor ligands during the protonation process does not influence the product distribution; CO insertion to produce formyl derivatives is not observed.

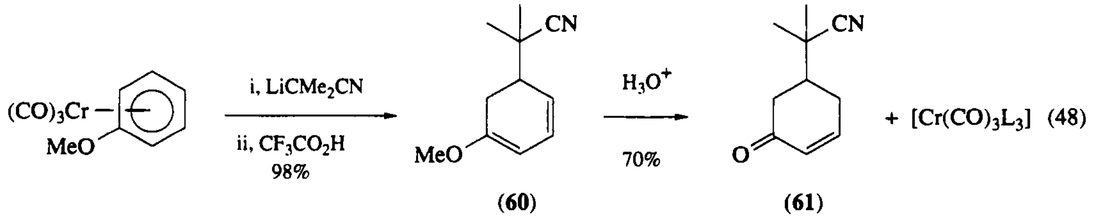

The intramolecular version of addition–protonation with (*m*-cyanoalkyl)anisole ligands produces spirocyclic enones, such as (**62**; equation 49).[121]

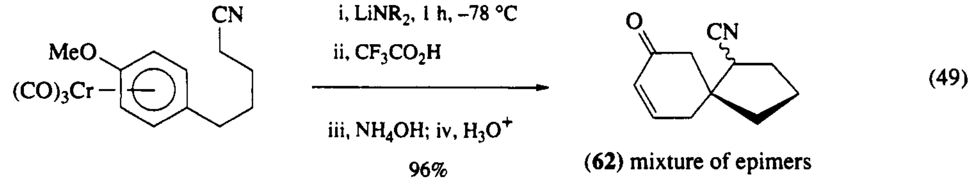

This process has been coupled with *meta* addition of a carbonyl anion equivalent and the controlled *exo* addition of the incoming nucleophile to generate acorenone and acorenone B stereospecifically from $[(o\text{-methylanisole})Cr(CO)_3]$ (**63**; Scheme 14).[123] The first step is addition of a cyanohydrin acetal anion (**64**) to the less-hindered *meta* position in $[(o\text{-methylanisole})Cr(CO)_3]$. Addition of allylMgBr to the resulting ketone, anti-Markovnikov addition of HBr to the alkene, substitution for Br by CN, and coordination of the arene with Cr(CO)3 produces the two diastereoisomeric complexes (**65**) and (**66**); the arene–metal unit is a center of asymmetry. The diastereoisomers were separated by HPLC, and the separate isomers were carried through the sequence of side chain anion generation and acid quenching to lead, separately, to the spirocyclohexenones *e.g.* (**67**). The yields were lower than for the model (equation 49) and the best case (64% for the cyclization in the acorenone B series) is based on recovery of starting material (30%). The isopropyl substituent apparently disfavors the ring closure. Conventional procedures added the appropriate functionality for the natural products. The cyclization process is stereospecific, based on the *exo* addition of the nucleophile. The *meta*-directing effect of the methoxy group favors formation of two new bonds at the quaternary center; spirocyclizations are the only cases of anion addition to a substituted arene carbon in the series with Cr(CO)3 activation.

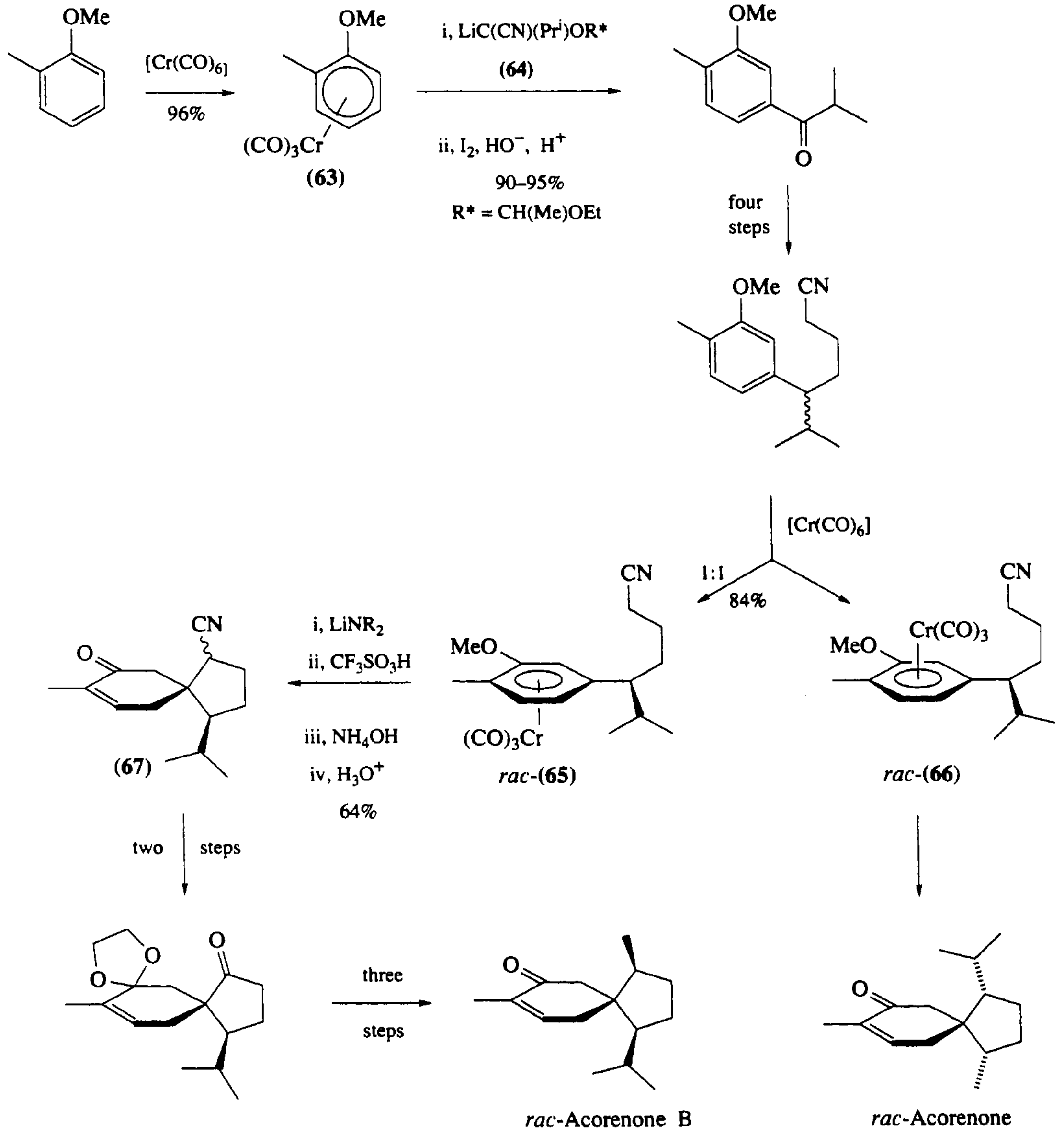
OMe
[Cr(CO)6]
96%
OMe
(CO)3Cr
(63)
i, LiC(CN)(Pri)OR*
(64)
ii, I2, HO⁻, H⁺
90–95%
R* = CH(Me)OEt
OMe
O
four steps
OMe CN
[Cr(CO)6]
1:1
84%
CN
MeO
(CO)3Cr
rac-(65)
CN
MeO
Cr(CO)3
rac-(66)
i, LiNR2
ii, CF3SO3H
iii, NH4OH
iv, H3O⁺
64%
CN
O
(67)
two steps
O
O
O
three steps
O
rac-Acorenone B
O
rac-Acorenone

**Scheme 14**

### 2.4.4.3 Addition–Acylation

The efficient trapping of the cyclohexadienyl anionic intermediates with protons raises the possibility of quenching with carbon electrophiles. The process is not as general as the proton quench; early experiments suggested that reversal of the nucleophile addition and coupling of the electrophile with nucleophile was the preferred pathway.[83] However, when the nucleophile adds essentially irreversibly, quenching with a limited set of carbon electrophiles is successful.[84,124–126] For example, addition of 2-lithio-1,3-dithiane to [(benzene)Cr(CO)$_3$], followed by addition of methyl iodide and then oxidation or addition of a donor ligand (CO, PPh$_3$) produces a cyclohexa-1,3-diene (**68**) substituted by both acetyl (Me + CO) and the nucleophile (Scheme 15). The insertion of CO occurs without exception, with a variety of electrophiles. The insertion is efficient without added CO, but gives somewhat higher yields under a modest pressure (<4 bar) of CO during electrophile coupling. The attachment of the electrophile is from the *endo* direction, consistent with initial addition to the metal following by CO insertion (**70**) and migration up to the arene unit; the products then have the *trans* arrangement of the new substituents.

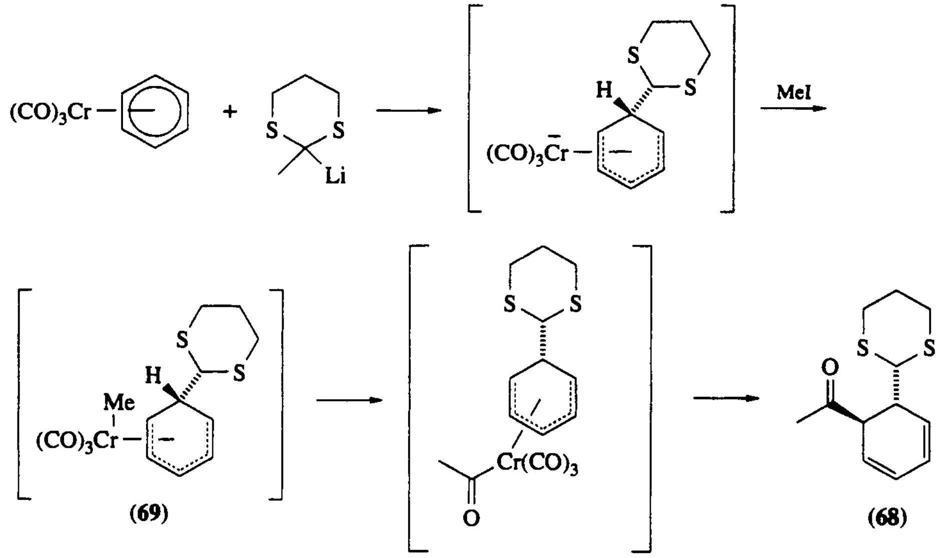

**Scheme 15**

While the addition–oxidation and the addition–protonation procedures are successful with ester enolates as well as more reactive carbon nucleophiles, the addition–acylation procedure requires more reactive anions and the addition of a polar aprotic solvent (HMPA has been used) to disfavor reversal of anion addition. Under these conditions, cyano-stabilized anions and ester enolates fail (simple alkylation of the carbanion) but cyanohydrin acetal anions are successful. The addition of the cyanohydrin acetal anion (**71**) to [(1,4-dimethoxynaphthalene)Cr(CO)$_3$] occurs by kinetic control at C-β in THF–HMPA and leads to the α,β-diacetyl derivative (**72**) after methyl iodide addition, and hydrolysis of the cyanohydrin acetal (equation 50).[84,124–126]

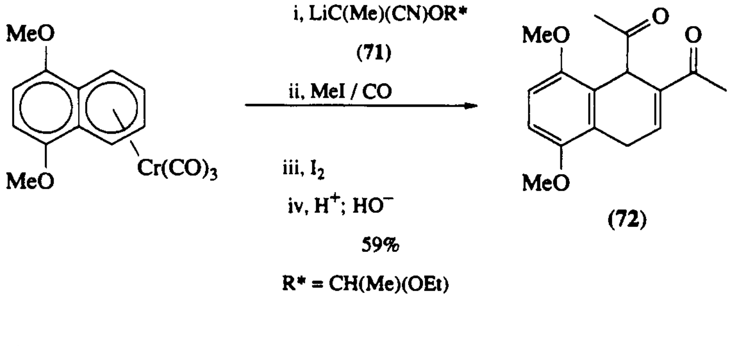

(50)

More reactive anions such as the 2-lithio-1,3-dithiane derivatives, phenyllithium and *t*-butyllithium do not require a special solvent and proceed in high yield in THF. While HMPA is known to suppress the migratory insertion to CO in anionic complexes,[127] it does not deter the CO insertion in these cases; no example of direct alkylation is reported. The only electrophile which adds without CO insertion is the proton, as discussed above. Good alkylating agents (primary iodides and triflates, allyl bromide, benzyl bromide) react below 0 °C, but ethyl bromide requires heating at 50 °C. The reaction is selective for a primary alkyl iodide in the presence of an ester or a ketone unit. Surprisingly, acyl chlorides are unreactive. A simple $S_N2$ process is proposed, based on the reactivity pattern of the electrophiles and the lack of rearrangement during alkylation with cyclopropylcarbinyl iodide (no long-lived radical intermediates).[84,125]

Addition of a cyanohydrin acetal anion to [(benzene)Cr(CO)$_3$] followed by reaction with allyl bromide produces the cyclohexadiene derivative (**73**) in 94% yield, which undergoes a Diels–Alder reaction rapidly to give a tricyclic framework (**74**). After quenching with methyl iodide and disassembling of the cyanohydrin group, the diketone (**75**) is obtained in 50% yield overall (equation 51).[125] These products are obviously interesting as potential intermediates for synthesis.

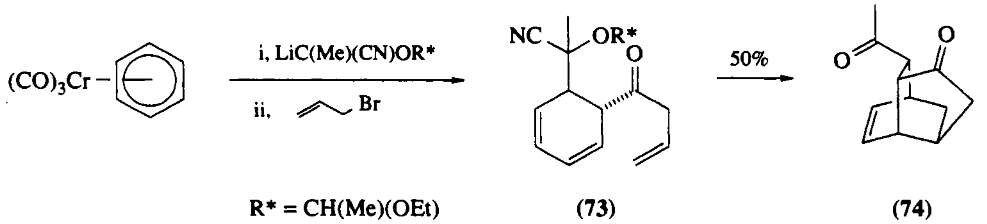

(51)

## 2.4.4.4 Addition to Styrene-type Ligands Activated by Cr(CO)$_3$

Nucleophile addition to styrene derivatives (*e.g.* **75**) coordinated with Cr(CO)$_3$ is another example of addition–electrophile trapping.[23,128] Addition of reactive anions is selective at the β-position of the styrene ligand, leading to the stabilized benzylic anion (**76**). The intermediate reacts with protons and a variety of carbon electrophiles to give substituted alkylbenzene ligands (in **77**) (equation 52).

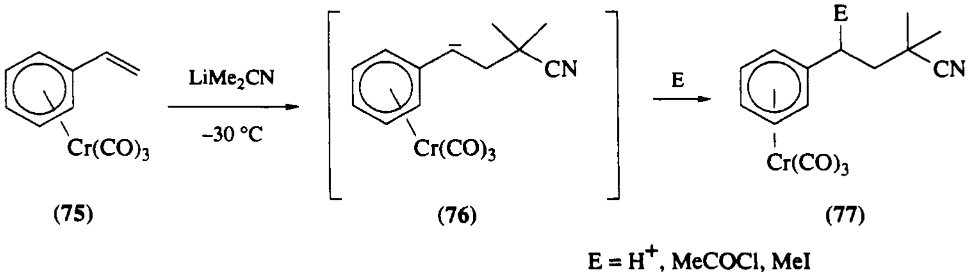

(52)

In the dihydronaphthalene series, the selective *exo* addition of the nucleophile and *exo* addition of the electrophile (steric approach) results in exclusive formation of the *cis*-α,β-disubstituted tetralin (**78**; equation 53).[128]

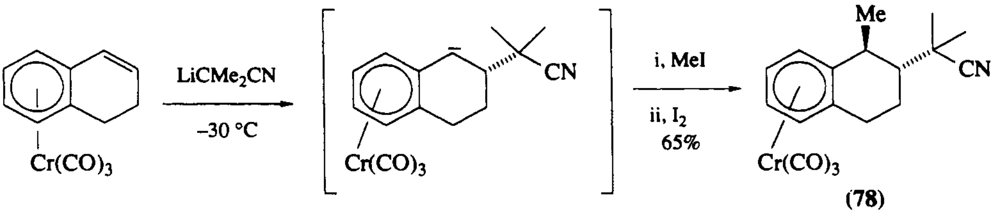

(53)

The addition–protonation procedure maintains the arene–chromium bond and allows further application of the activating effect of the metal. In an approach to the synthesis of anthraquinone antibiotics, the dihydronaphthalene complex (**79**) was allowed to react with a cyanohydrin acetal anion and then quenched with acid.[129] The resulting tetralin complex (**80**) could be metallated effectively and carried on to a key intermediate (**81**) in anthraquinone construction (equation 54)

While it can be expected that the [Mn(CO)$_3$]$^+$ and [FeCp]$^+$ complexes of styrene derivatives would allow addition of a wider variety of nucleophiles, no useful methodology based on this possibility has been put forward.

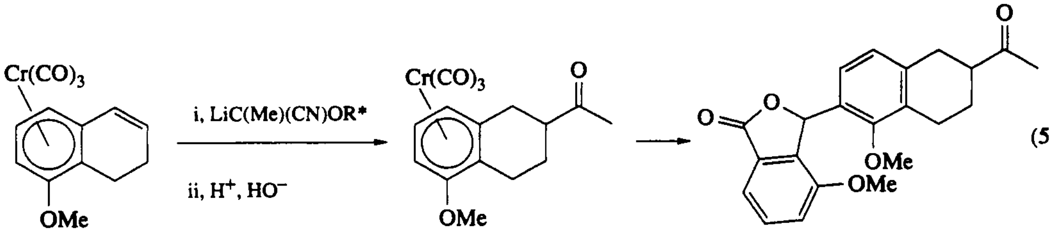

(79) (80) (81) (54)

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# 3.1

# Heteroatom Nucleophiles with Metal-activated Alkenes and Alkynes

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## 3.1.1 INTRODUCTION

Electron-rich, unsaturated hydrocarbons, which are normally resistant to nucleophilic attack, become generally reactive towards nucleophiles upon complexation to an electrophilic transition metal such as palladium(II), platinum(II) or iron(II). Complexation also directs the regio- and stereo-chemistry of the nucleophilic attack, the result of which is a new organometallic complex, which can often be used to promote additional functionalization of the original substrate. Synthetically useful examples of such processes are presented in the following sections.

## 3.1.2 ADDITIONS TO ALKENES

Palladium(II) salts, in the form of organic solvent soluble complexes such as $PdCl_2(RCN)_2$, $Pd(OAc)_2$ or $Li_2PdCl_4$, are by far the most extensively utilized transition metal complexes to activate simple (unactivated) alkenes towards nucleophilic attack (Scheme 1). Alkenes rapidly and reversibly complex to palladium(II) species in solution, readily generating alkenepalladium(II) species (**1**) *in situ*. Terminal monoalkenes are most strongly complexed, followed by internal *cis* and *trans* (respectively) alkenes. Geminally disubstituted, trisubstituted and tetrasubstituted alkenes are only weakly bound, if at all, and intermolecular nucleophilic additions to these alkenes are rare.

Once complexed to palladium(II), the alkene is generally activated towards nucleophilic attack, with nucleophiles ranging from chloride to phenyllithium undergoing reaction. The reaction is, however, quite sensitive to conditions and displacement of the alkene by the nucleophile (path a) or oxidative destruction of the nucleophile can become an important competing reaction. Nucleophilic attack occurs predominately to exclusively at the more-substituted position of the alkene (the position best able to stabilize positive charge) and from the face opposite the metal (*trans* attack, path b) to produce a new carbon–nucleophile bond and a new carbon–metal bond. This newly formed σ-alkylmetal complex (**2**) is

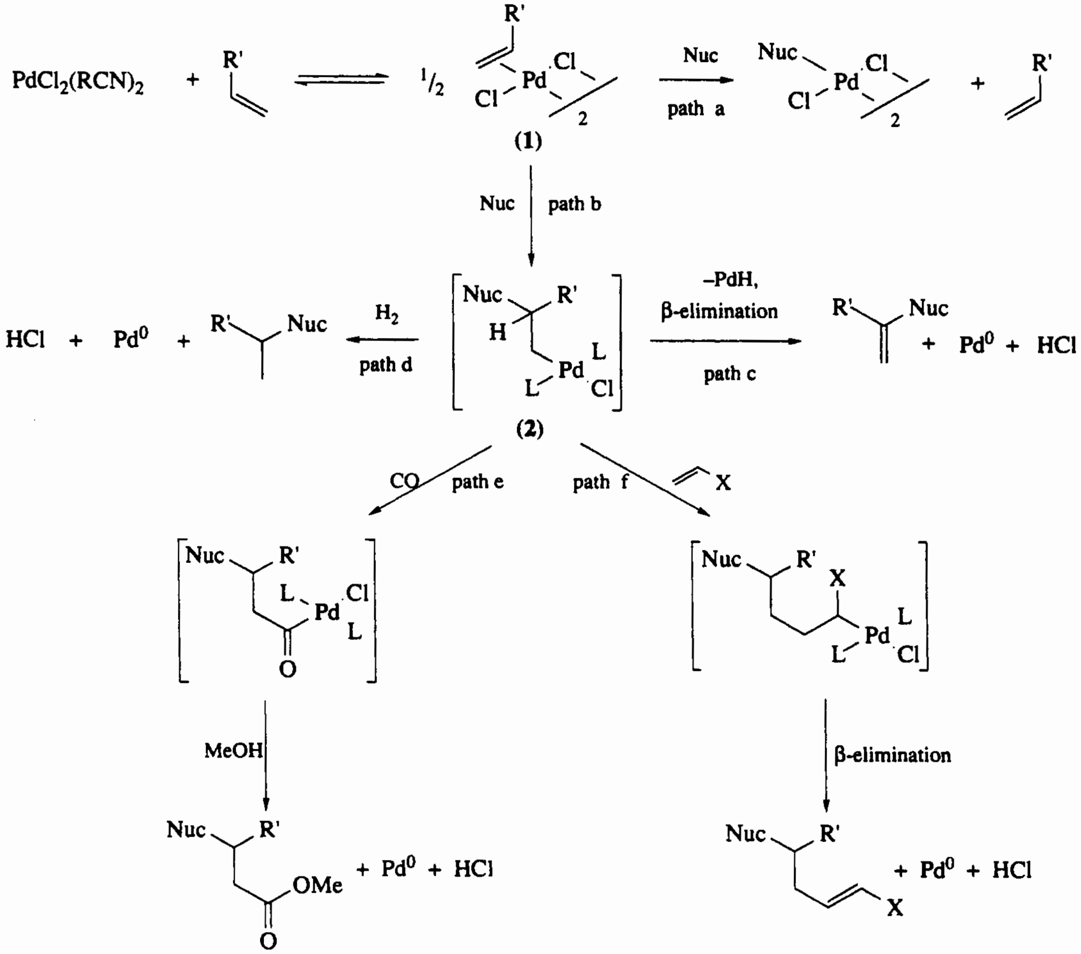

Scheme 1

usually quite reactive and unstable and it can undergo a number of synthetically useful transformations. β-Hydrogen elimination (path c) is facile above *ca.* –20 °C and results in an overall nucleophilic substitution on the alkene. The metal–carbon σ-bond is readily hydrogenolyzed and exposure to 1 atm of hydrogen gas at 25 °C results in an overall nucleophilic addition to the alkene (path d). Small molecules, such as CO or alkenes, readily insert into palladium–carbon σ-bonds permitting further functionalization of the original alkene (paths e and f). All of these transformations ultimately produce palladium(0), while palladium(II) is required to activate alkenes. Thus, for any of these processes to be run in a catalytic fashion, a way to rapidly reoxidize palladium(0) to palladium(II) in the presence of both substrate and product is required. Although many systems have been developed ($CuCl_2/O_2$; $K_2S_2O_8$; benzoquinone), it is often this redox step which is most problematical in palladium(II)-catalyzed nucleophilic additions to alkenes. Notwithstanding these problems, a number of very useful catalytic processes have been developed.

### 3.1.2.1 Addition of Oxygen Nucleophiles to Alkenes

One of the earliest uses of palladium(II) salts to activate alkenes towards additions with oxygen nucleophiles is the industrially important Wacker process, wherein ethylene is oxidized to acetaldehyde using a palladium(II) chloride catalyst system in aqueous solution under an oxygen atmosphere with copper(II) chloride as a co-oxidant.[1,2] The key step in this process is nucleophilic addition of water to the palladium(II)-complexed ethylene. As expected from the regioselectivity of palladium(II)-assisted addition of nucleophiles to alkenes, simple terminal alkenes are efficiently converted to methyl ketones rather than aldehydes under Wacker conditions.

This unique one-step transformation of alkenes — stable to acids, bases and nucleophiles — to methyl ketones has considerable synthetic potential, particularly when applied in a specific manner to more highly functionalized alkenes. Although traditional Wacker conditions are somewhat harsh, modified conditions utilizing DMF–water (7:1) as solvent and benzoquinone or copper(I) chloride–oxygen as reoxidant permit the efficient palladium(II)-catalyzed oxidation of terminal alkenes to ketones in the presence of a wide array of functional groups (Table 1).[3] Under these milder conditions, the reaction is specific for terminal alkenes and will tolerate virtually all common organic functional groups. From a synthetic point of view, this makes terminal alkenes functionally equivalent to methyl ketones. More recently developed variations of this oxidation procedure involving the use of phase transfer catalysis[4] or the use of electrochemical oxidation of palladium(0) back to palladium(II) for catalysis[5] may offer some advantages in specific systems.

Although tolerant of a wide variety of functionality, this process (and most other transition metal catalyzed processes) is sensitive to the presence of adjacent functional groups which can coordinate to the catalyst. This sensitivity often is manifest in a change in the expected regioselectivity or reactivity of a process. For example, catalytic oxidation of the terminal alkene in the β-lactams, shown in equation (1), led exclusively to the aldehyde rather than to the expected methyl ketone.[6] This change in regioselectivity is likely due to coordination of the amide carbonyl group to palladium to generate the more stable (*versus* six-membered) five-membered palladiocycle intermediate (Scheme 2).

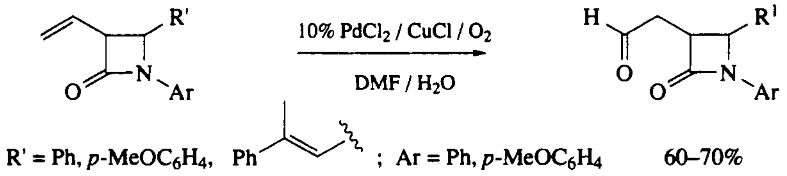

(1)

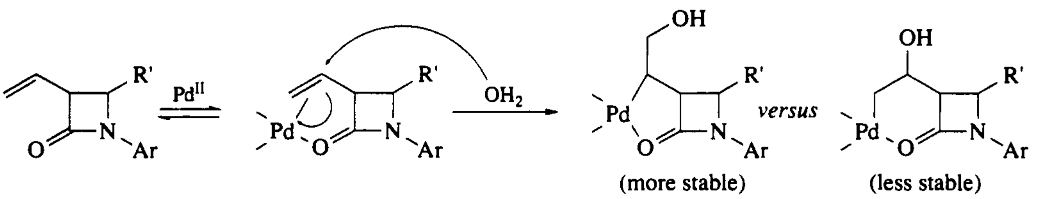

**Scheme 2**

Internal alkenes do not undergo this oxidation under normal circumstances, hence the excellent chemoselectivity observed. However, allyl ethers and acetates with internal double bonds undergo facile oxidation, giving exclusively the β-alkoxy ketone in 60–80% yield (equation 2).[7] In this case additional coordination of the palladium(II) catalyst to the ether oxygen may enhance its activation of the alkene, although the regioselectivity is different from that expected from the arguments advanced for the reaction in equation (1). Simple internal alkenes (*e.g.* 2-decene) were oxidized to mixtures of regioisomeric ketones by a 2% $PdCl_2$/$CuCl_2$/polyethylene glycol 400/$H_2O$ catalyst system.[8]

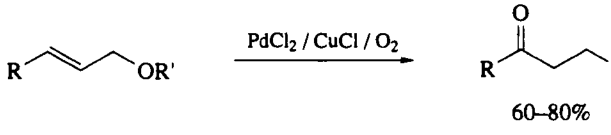

(2)

R = Me, $Pr^n$, $Bu^i$, n-$C_5H_{11}$; R' = Ph, Me, Bn, Ac

Finally, α,β-unsaturated carbonyl compounds are converted to β-keto systems when treated with 20% $Na_2PdCl_4$ catalyst in 50% acetic acid as solvent and *t*-butyl hydroperoxide or hydrogen peroxide as reoxidant (equation 3).[9] It is not clear if the mechanism of this process is related to the other palladium(II)-catalyzed addition of oxygen nucleophiles to alkenes.

Alcohols and carboxylic acids also readily add to metal-activated alkenes[2] and industrial processes for the conversion of ethylene to vinyl acetate, vinyl ethers and acetals are well established. However, very little use of intermolecular versions of this chemistry with more complex alkenes has been developed. In

**Table 1** Palladium(II)-catalyzed Oxidation of Functionalized Terminal Alkenes to Methyl Ketones

| *Entry* | *Alkene* | *Product* | *Yield (%)* |
|---|---|---|---|
| 1 | 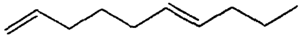 | 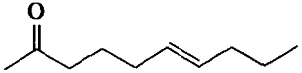 | 78 |
| 2 | 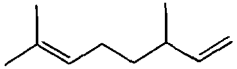 | 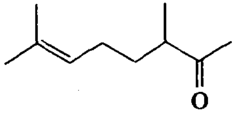 | — |
| 3 | 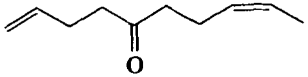 | 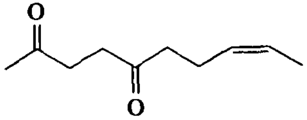 | 70 |
| 4 | 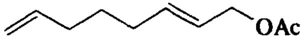 | 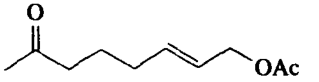 | 83 |
| 5 | 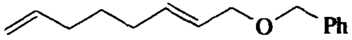 | 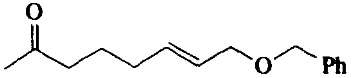 | 76 |
| 6 | 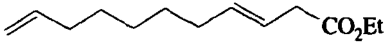 | 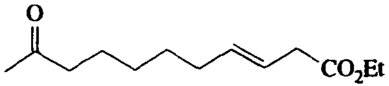 | 86 |
| 7 | 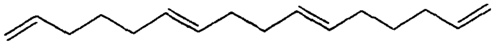 | 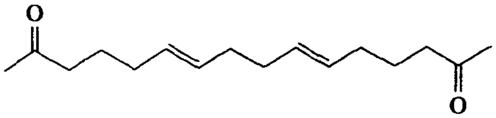 | 62 |
| 8 | 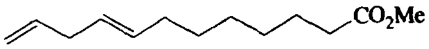 | 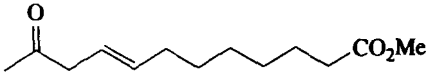 | 67 |

Table 1 *(continued)*

| *Entry* | *Alkene* | *Product* | *Yield (%)* |
|---|---|---|---|
| 9 | 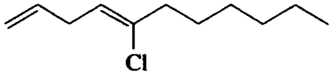 | 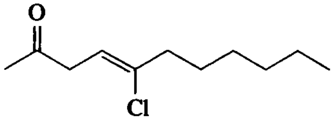 | 62 |
| 10 | 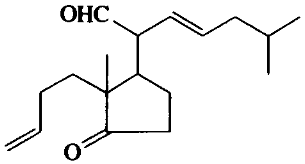 | 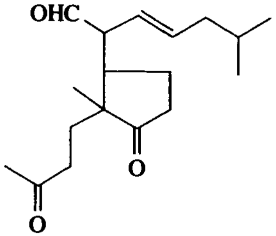 | 59 |
| 11 | 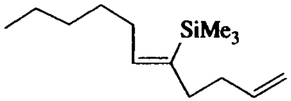 | 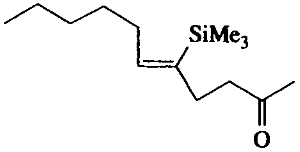 | 74 |
| 12 | 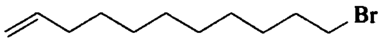 | 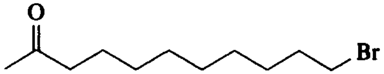 | 74 |
| 13 | 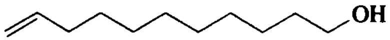 | 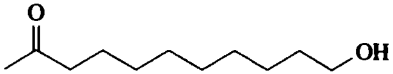 | 79 |
| 14 | 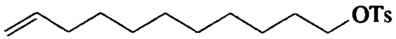 | 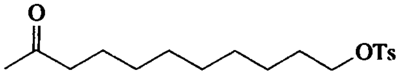 | 82 |
| 15 | 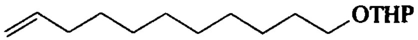 | 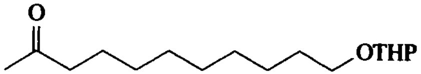 | 81 |

**Table 1** *(continued)*

| *Entry* | *Alkene* | *Product* | *Yield (%)* |
|---|---|---|---|
| 16 | 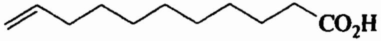 | 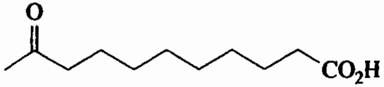 | 83 |
| 17 | 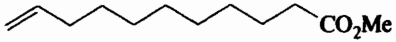 | 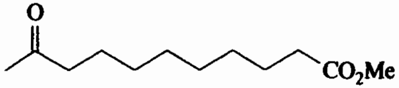 | 86 |
| 18 | 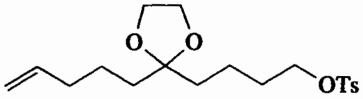 | 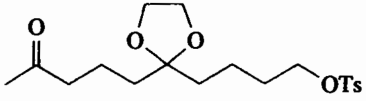 | 70 |
| 19 | 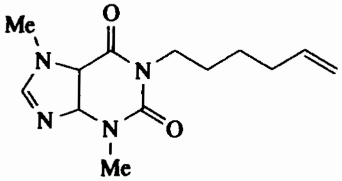 | 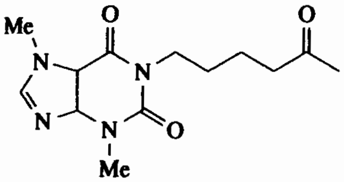 | 85 |

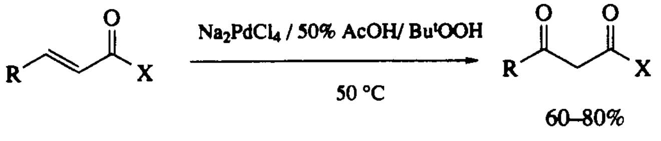

(3)

R = Me, Et, Pr$^i$, n-$C_7H_{15}$, Ph; X = OMe, Me

contrast, intramolecular versions of this process, to form oxygen heterocycles, has been extensively developed.

The earliest studies centered on the cyclization of ω-hydroxyalkenes to furan and pyran ring systems (equations 4 and 5).[10] The regiochemistry (attack at the more substituted position) was that expected and the yields were only modest. However, modern advances in catalysis should permit much more efficient processes and many older systems probably warrant re-examination.

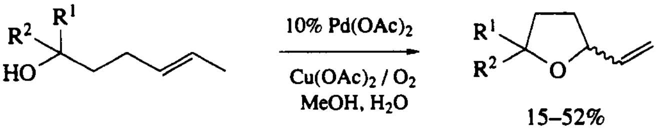

(4)

$R^1$ = Me, Ph; $R^2$ = H, Me, Et, Ph

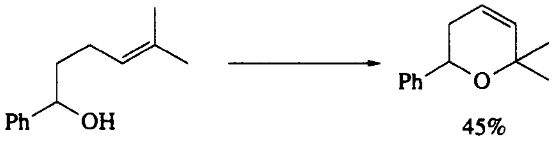

(5)

Palladium-catalyzed cyclization of *o*-allylphenols to benzofurans has been extensively studied.[11] As is usual, early systems were catalytically inefficient but continued studies led to substantial improvement. A wide range of catalyst systems work for this process. One of the most efficient, from a standpoint of catalyst turnover and chemical yield, was based on chiral π-allylpalladium catalysts (equation 6), although the optical yields were low. γ-Pyrones can also be efficiently synthesized by palladium(II)-catalyzed addition of phenolic OH groups to conjugated enones (equation 7).[12]

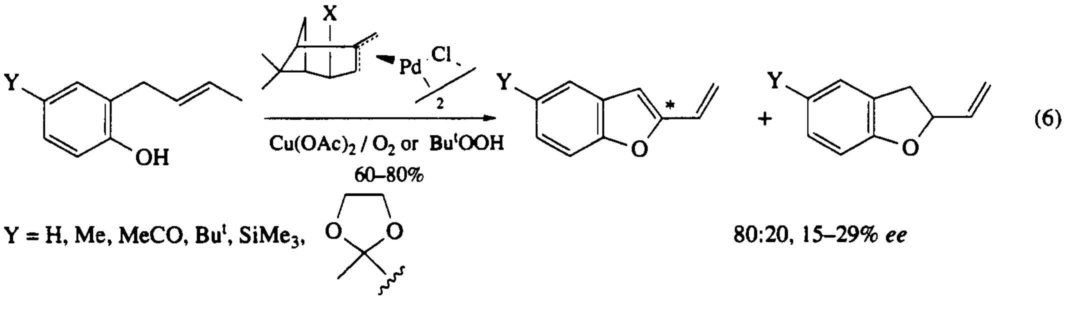

(6)

Y = H, Me, MeCO, Bu$^t$, SiMe$_3$,

80:20, 15–29% *ee*

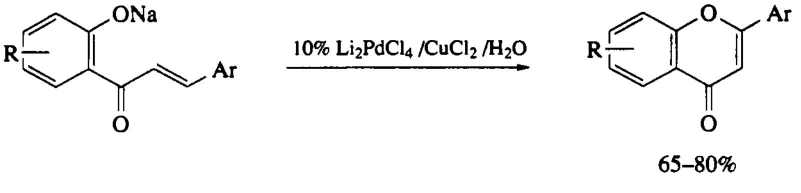

(7)

65–80%

As detailed in Scheme 1, all of these reactions proceed through unstable σ-alkylpalladium(II) complexes (*e.g.* **2**), which have a rich chemistry in their own right. Particularly useful synthetic transformations, which involve trapping of these intermediates with carbon monoxide (path e), have been developed (equations 8 and 9; Scheme 3).[13–15] The yields and catalytic efficiencies in these more recently developed processes are remarkably good and the procedures are simple enough for synthetic chemists with no experience in organometallic chemistry to use. Allenes underwent a similar hydroxylation–carbonylation process to produce functionalized tetrahydrofurans in good yield (equation 10).[16]

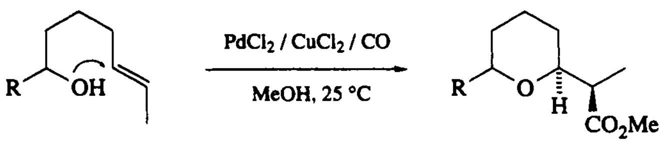
R
OH
PdCl2 / CuCl2 / CO
MeOH, 25 °C
R
O
H
CO2Me

(8)

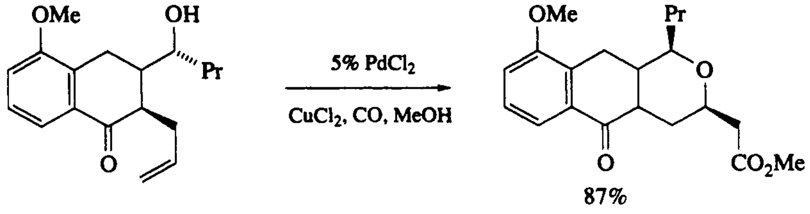
OMe
OH
Pr
O
5% PdCl2
CuCl2, CO, MeOH
OMe
Pr
O
O
CO2Me
87%

(9)

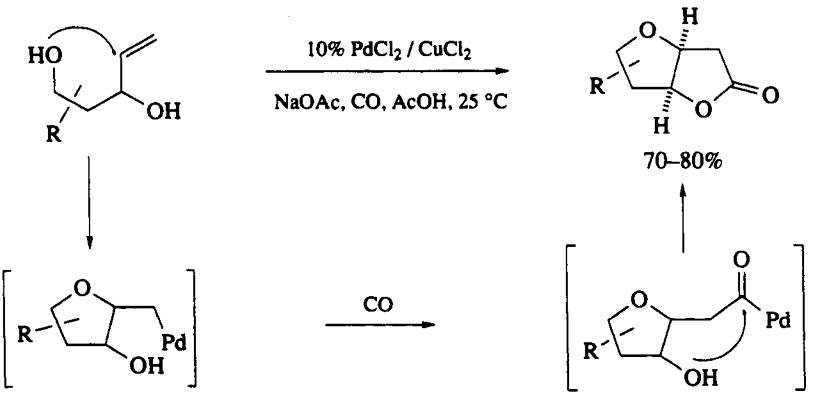
HO
OH
R
10% PdCl2 / CuCl2
NaOAc, CO, AcOH, 25 °C
O
H
R
O
O
H
70–80%
O
R
Pd
OH
CO
O
O
Pd
R
OH

Scheme 3

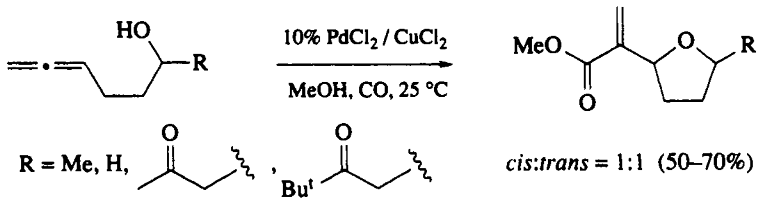
HO
R
10% PdCl2 / CuCl2
MeOH, CO, 25 °C
MeO
O
O
R
R = Me, H,
O
O
Bu^t
cis:trans = 1:1 (50–70%)

(10)

Carboxylate ions are also effective nucleophiles in palladium-catalyzed reactions of alkenes and several classes of lactones including γ-pyrones (equation 11)[17] and isocoumarins (equation 12)[18] have been made in this manner. These early studies used stoichiometric amounts of palladium salts, since efficient redox systems had not yet been developed. However, with more modern techniques catalysis in these systems should be relatively straightforward. The more recent catalytic cyclization–carbonylation process in equation (13) is indicative of this.[19]

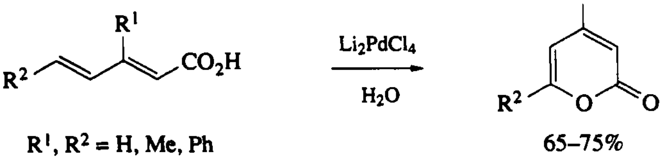
R1
R2
CO2H
R1, R2 = H, Me, Ph
Li2PdCl4
H2O
R1
R2
O
O
65–75%

(11)

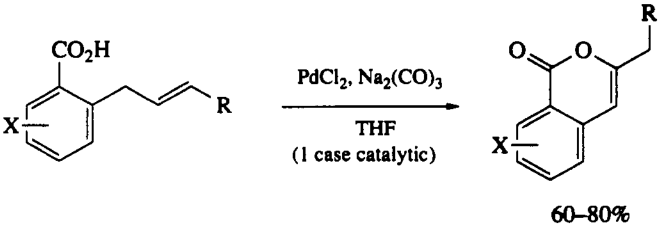
CO2H
X
R
PdCl2, Na2(CO)3
THF
(1 case catalytic)
R
O
O
X
60–80%

(12)

X = 4-Cl, 5-MeO, 6-Cl, 7-MeO

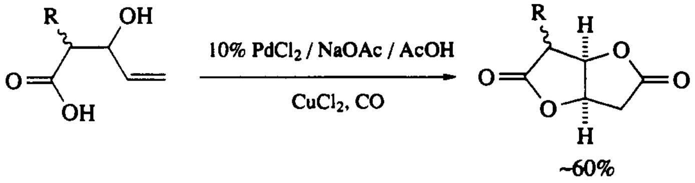
R
OH
O
OH
10% PdCl2 / NaOAc / AcOH
CuCl2, CO
R
H
O
O
O
O
H
~60%

(13)

Chelating dialkenes such as 1,5-cyclooctadiene, norbornadiene and dicyclopentadiene, as well as allylamines, were among the first alkenes whose reactions with oxygen (and other) nucleophiles in the presence of palladium(II) salts were studied. These reactions were quite efficient, but led to stable $\sigma$-alkylpalladium(II) complexes, making the development of catalytic systems difficult. As a consequence, little synthetic use of this chemistry has developed. However, potentially useful synthetic transformations are possible, as evidenced by the reaction described in Scheme 4.[20] This reaction illustrates the importance of reaction conditions to the selectivity of the process, a phenomenon typical of organotransition metal chemistry. Nucleophilic attack of the alcohol on the coordinated dialkene produced stable $\sigma$-alkylpalladium(II) complex (**3**), in which the remote alkene remained coordinated. Carbonylation of this complex proceeded by an initial insertion of the alkene into the palladium–carbon $\sigma$-bond to give (**4**), followed by CO insertion to give (**5**). In contrast, decomplexation of the remote alkene by prior treatment with diisopropylamine, followed by carbonylation, led to the simple alkoxycarbonylation product (**6**). This ability to control selectivity by choice of ligand and conditions is a major feature of organotransition metal chemistry.

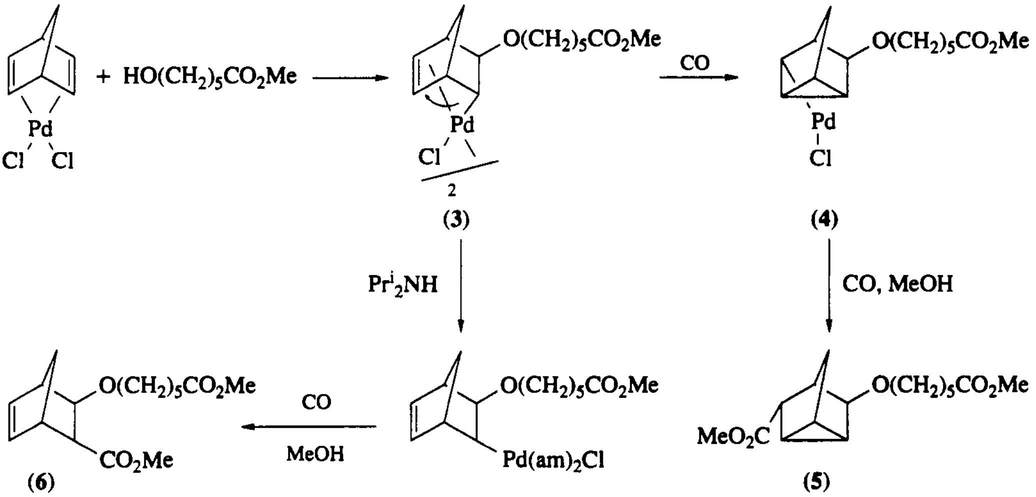
Pd
Cl
Cl
+ HO(CH2)5CO2Me
O(CH2)5CO2Me
Pd
Cl
2
(3)
CO
O(CH2)5CO2Me
Pd
Cl
(4)
Pri2NH
CO, MeOH
O(CH2)5CO2Me
CO2Me
(6)
CO
MeOH
O(CH2)5CO2Me
Pd(am)2Cl
O(CH2)5CO2Me
MeO2C
(5)

**Scheme 4**

### 3.1.2.2 Addition of Nitrogen Nucleophiles to Alkenes

Nitrogen nucleophiles such as amines (and in intramolecular cases, amides and tosamides) readily add to alkenes complexed to palladium(II) and iron(II) with reactivity and regiochemical features parallel to those observed for oxygen nucleophiles. However, these metal-assisted amination reactions are subject to several problems not encountered with oxygen nucleophiles and hence are generally less synthetically useful. Amines are much more potent ligands than are alcohols for the electrophilic metals used to activate alkenes and displacement of the alkene from the metal by the amine resulting in poisoning of the catalyst is a serious problem. Additionally, the product of successful amination is an enamine, which is not only a potent catalyst poison but also prone to Lewis acid catalyzed polymerization. Finally, in contrast to alcohols and ethers, amines and enamines are readily oxidized under conditions normally used to carry the requisite $Pd^0 \rightarrow Pd^{II}$ redox chemistry, making catalysis difficult. For these reasons, efficient catalytic intermolecular amination of alkenes has not yet been achieved. However, the stoichiometric amination of alkenes, followed by further reaction of the resulting σ-alkylpalladium(II) complex has been used to effect unconventional transformations of alkenes (Scheme 5).

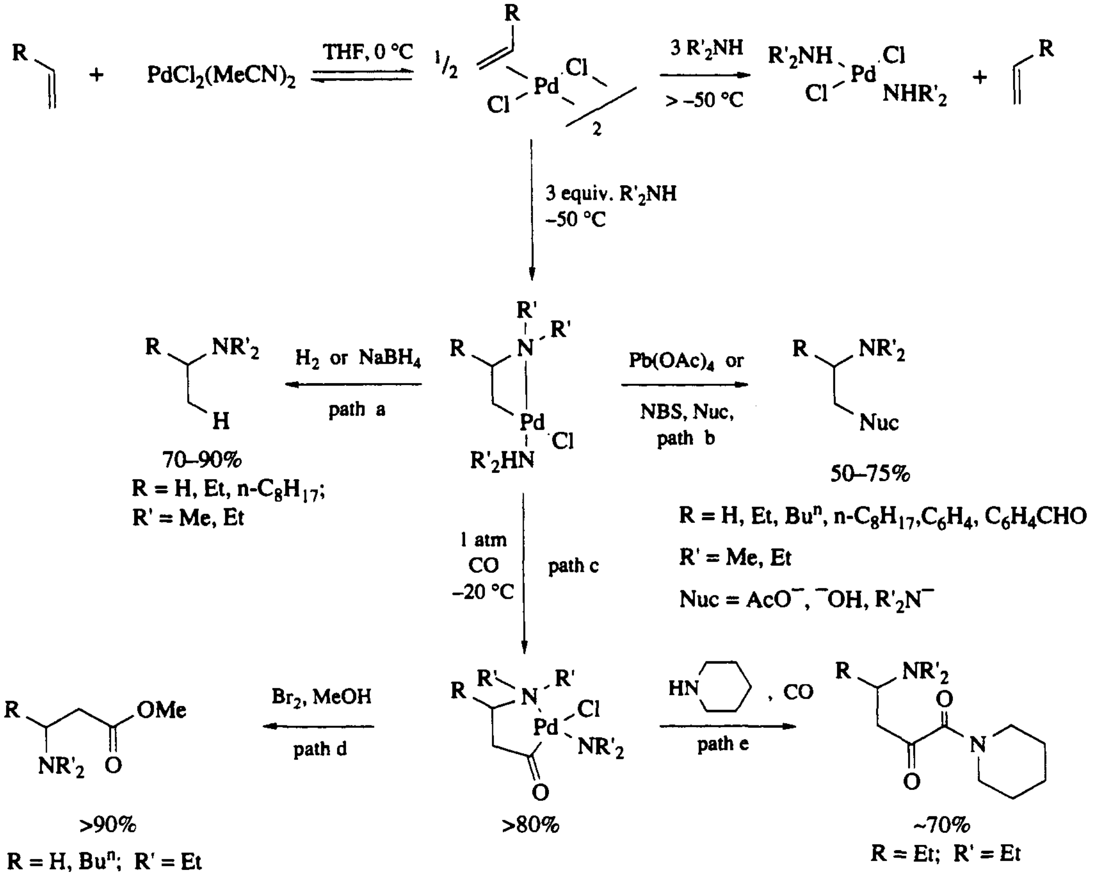

Scheme 5

Terminal alkenes could be efficiently aminated by nonhindered secondary amines in a process requiring 1 equiv. of palladium(II) chloride, 3 equiv. of amine and a reduction at temperatures below –20 °C (path a, Scheme 5);[21,22] however, primary amines and/or internal alkenes were less efficient, producing only 40–50% yields of amination product. Oxidative cleavage of the unstable σ-alkylpalladium(II) in the presence of a nucleophile resulted in vicinal oxamination or diamination of the alkene (path b).[23,24] Carbonylation resulted in the isolation of stable σ-acylpalladium(II) species (path c),[25] which were oxidatively cleaved to give β-amino esters (path d)[26] or further carbonylated to give γ-amino-α-ketoamides (path e).[27]

All of these processes are of limited synthetic utility because of the requirement of the use of stoichiometric amounts of palladium complexes. However, by judicious choice of reactants and conditions the above-mentioned impediments to catalysis can be overcome. For example, an efficient palladium(II) catalyzed cyclization of *o*-allyl- and *o*-vinyl-anilines to indoles has been developed (equation 14).[28] Because arylamines are ~$10^6$ less basic than aliphatic amines, and because the cyclized product in this system gave an enamine (indole) stabilized by aromatization, the problems of catalyst poisoning by substrate or product were circumvented, and catalysis was successfully achieved. The system was quite tolerant of a variety of functional groups and was used to prepare indoloquinones in excellent yield (equation 15).[29] Since this process also proceeded through an unstable σ-alkylpalladium(II) complex both inter- (Scheme 6)[30] and intra-molecular (equation 16)[29,31] insertion processes were possible, resulting in extensive elaboration of the simple starting materials, utilizing two sequential palladium-assisted bond-forming processes.

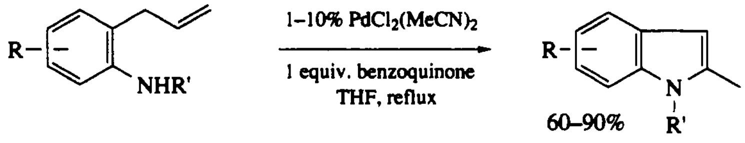
R
NHR'
1–10% $PdCl_2(MeCN)_2$
1 equiv. benzoquinone
THF, reflux
R
N
R'
60–90%

(14)

R = H, 3-Me, 3-$CO_2Et$, 4-MeO, 5-MeO, 4,5-$MeO_2$, 4-Br; R' = H, Me, Ac, Ts

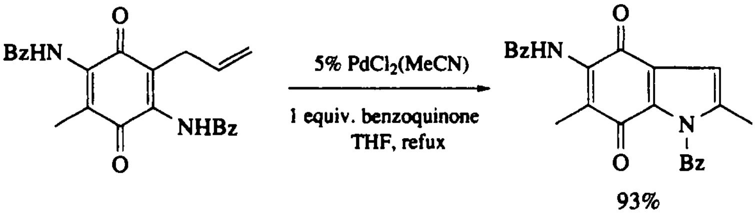
O
BzHN
NHBz
O
5% $PdCl_2(MeCN)$
1 equiv. benzoquinone
THF, refux
BzHN
O
O
N
Bz
93%

(15)

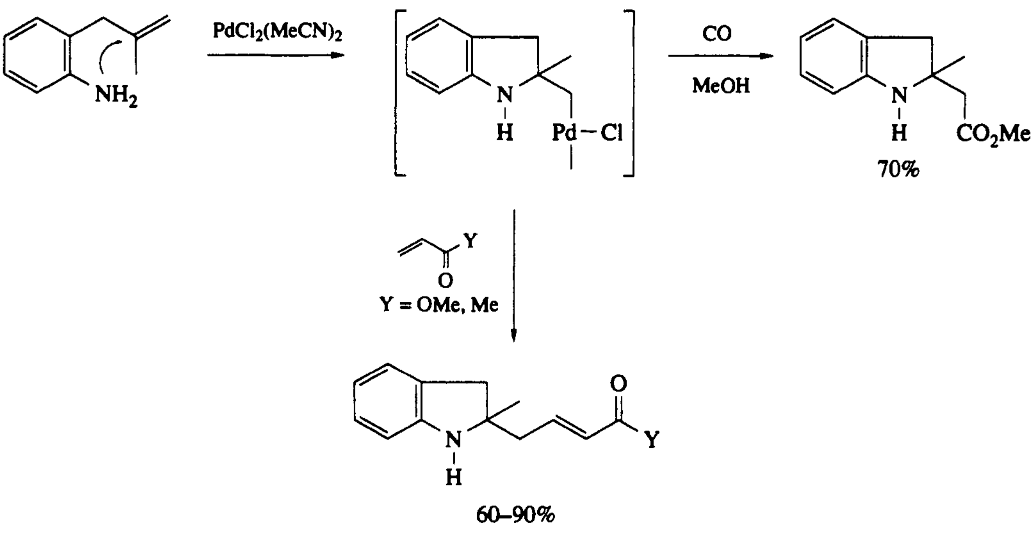
$NH_2$
$PdCl_2(MeCN)_2$
N
H
Pd−Cl
CO
MeOH
N
H
$CO_2Me$
70%
Y
O
Y = OMe, Me
O
Y
N
H
60–90%

**Scheme 6**

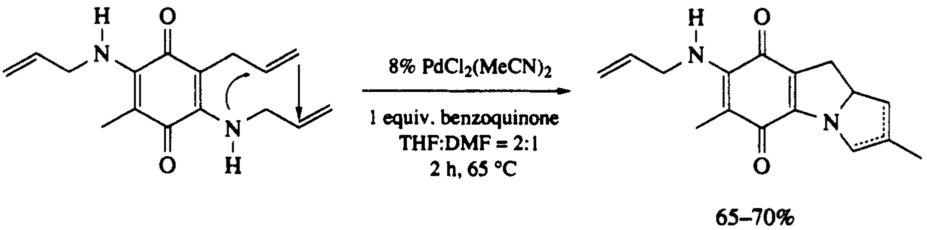
H
N
O
O
N
H
8% $PdCl_2(MeCN)_2$
1 equiv. benzoquinone
THF:DMF = 2:1
2 h, 65 °C
H
N
O
O
N
65–70%

(16)

As stated above, aliphatic amines are potent ligands for electrophilic transition metals and are efficient catalyst poisons in attempted alkene amination reactions. However, tosylation of the basic amino group greatly reduces its complexing ability, yet does not compromise its ability to nucleophilically attack complexed alkenes. Thus, a variety of alkenic tosamides efficiently cyclized under palladium(II) catalysis producing *N*-tosylenamines in excellent yield (equations 17 and 18).[32] Again, this alkene amination proceeded through an unstable σ-alkylpalladium(II) species, which could be intercepted by carbon monoxide, to result in an overall aminocarbonylation of alkenes. With ureas of 3-hydroxy-4-pentenylamines (Scheme 7), this palladium-catalyzed process was quite efficient but it was somewhat less so with

4-hydroxy-5-hexenylamine (equation 19).[33] ω-Aminoallenes underwent a related palladium-catalyzed aminocarbonylation (equation 20).[34]

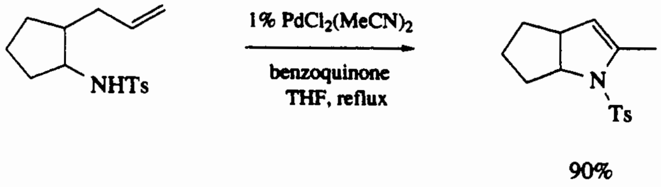
NHTs
1% $PdCl_2(MeCN)_2$
benzoquinone
THF, reflux
N
Ts
90%

(17)

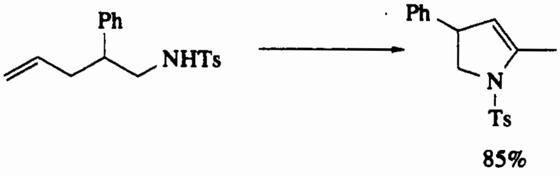
Ph
NHTs
Ph
N
Ts
85%

(18)

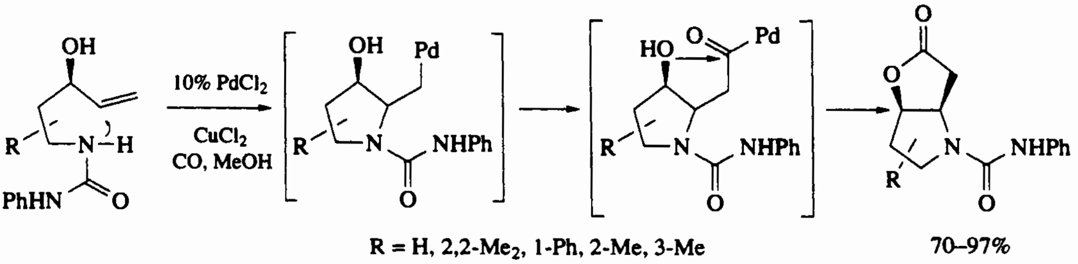
OH
R
N–H
PhHN
O
10% $PdCl_2$
$CuCl_2$
CO, MeOH
OH
Pd
R
N
NHPh
O
HO
O
Pd
R
N
NHPh
O
O
O
R
N
NHPh
O
R = H, 2,2-Me$_2$, 1-Ph, 2-Me, 3-Me
70–97%

**Scheme 7**

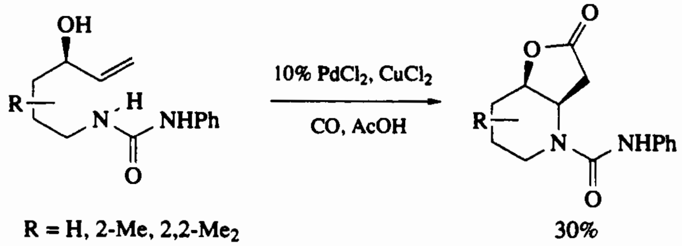
OH
R
N
H
NHPh
O
10% $PdCl_2$, $CuCl_2$
CO, AcOH
O
O
R
N
NHPh
O
R = H, 2-Me, 2,2-Me$_2$
30%

(19)

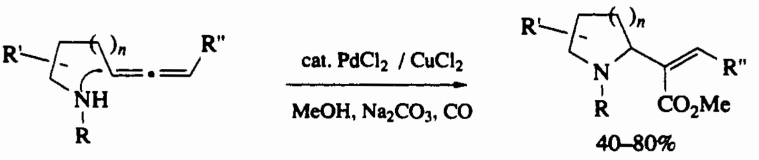
R'
)n
R''
NH
R
cat. $PdCl_2$ / $CuCl_2$
MeOH, $Na_2CO_3$, CO
R'
)n
N
R
R''
$CO_2Me$
40–80%

(20)

R = $C_6H_4Me$, Ts, $CO_2Me$; R' = H, 1-$CO_2Et$; R'' = H, Me, n-$C_5H_{11}$; $n$ = 1, 2

Chelating alkenes, such as 1,5-dienes and allylamines, complexed to palladium(II) undergo facile attack by nitrogen nucleophiles. However, the resulting σ-alkylpalladium(II) complexes are very stable, preventing efficient catalytic processes. These stable complexes undergo all the typical reactions of σ-alkylmetal complexes — hydrogenolysis, carbon monoxide insertion and alkene insertion — so that the organic compound can be freed from the metal and converted into a useful product. An example of this is the stoichiometric addition of phthalimide to tertiary allylic amines (Scheme 8).[35]

Cationic cyclopentadienyliron dicarbonyl ($F_p$) alkene complexes are generally reactive towards a wide variety of nucleophiles, including nitrogen nucleophiles, but they too generate stable σ-alkylmetal complexes from which the metal must be removed in a second chemical step (usually oxidation). This makes catalysis impossible and severely limits application of this methodology to organic synthesis (equation 21).[36] However, in contrast to palladium, iron is relatively inexpensive and stoichiometric procedures

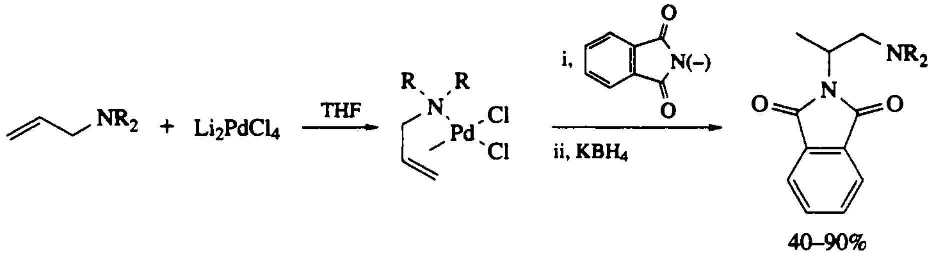
NR2
Li2PdCl4
THF
R
N
Pd
Cl
i,
N(−)
O
ii, KBH4
40–90%

Scheme 8

may be justified when the use of this process greatly simplifies the desired synthesis. The bicyclic β-lactam synthesis in Scheme 9 is such an example.[37]

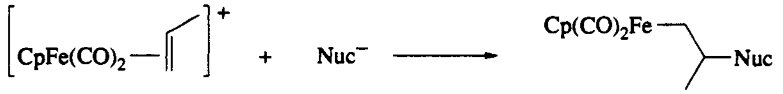
CpFe(CO)2
Nuc−
Cp(CO)2Fe
Nuc

(21)

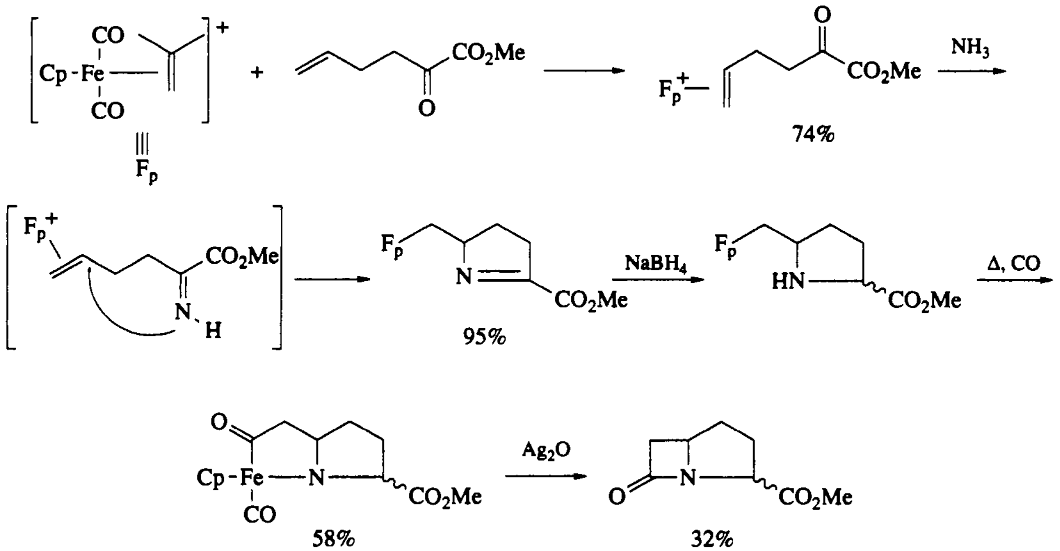
CO
Cp-Fe
Fp
CO2Me
O
NH3
74%
N
H
95%
NaBH4
HN
Δ, CO
Ag2O
58%
32%

Scheme 9

### 3.1.2.3 Metal-catalyzed Allylic Transpositions, Oxy-Cope and Aza-Cope Reactions

Electrophilic transition metals, particularly palladium(II) salts, catalyze a number of heteroatom allylic transposition processes[38] by a mechanism which almost certainly involves nucleophilic attack of a heteroatom on a metal-bound alkene (Scheme 10), often termed 'cyclization-induced rearrangement'.

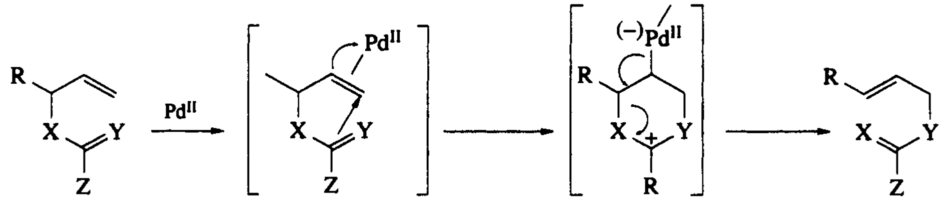
R
X
Y
Z
PdII
(−)PdII
+

Scheme 10

Allylic esters equilibrated under very mild conditions (2 h, 25 °C) in the presence of 2–4% $PdCl_2$ catalyst. These rearrangements were not complicated by skeletal rearrangements, cyclizations or elimination, as is often observed with acid-catalyzed equilibrations. (*Z*)-Alkenes rearranged much more slowly than (*E*)-alkenes and with clean suprafacial stereochemistry. This process was limited to allylic esters unsubstituted at C-2 of the allyl group. Representative synthetically interesting examples are shown in equations (22)[38,39] and (23) to (27).[38]

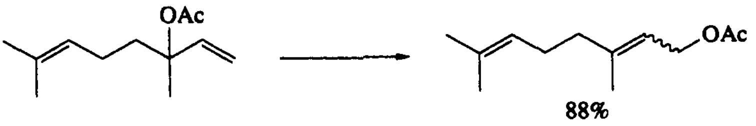

(22)

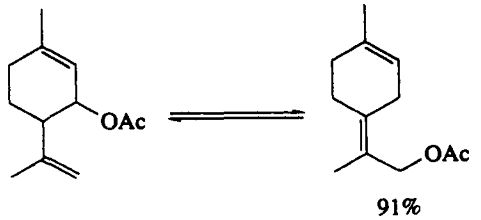

(23)

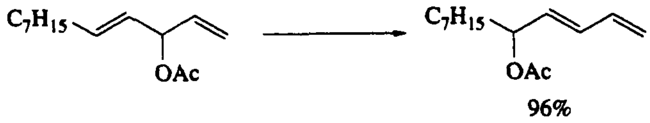
$C_7H_{15}$
OAc
$C_7H_{15}$
OAc
96%

(24)

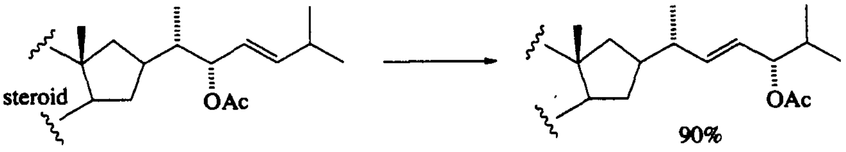
steroid
OAc
OAc
90%

(25)

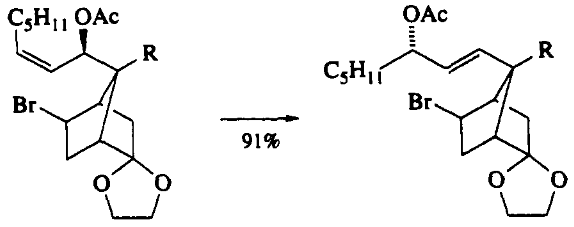
$C_5H_{11}$ OAc
R
Br
O O
91%
OAc
$C_5H_{11}$
R
Br
O O

(100% chirality transfer)

(26)

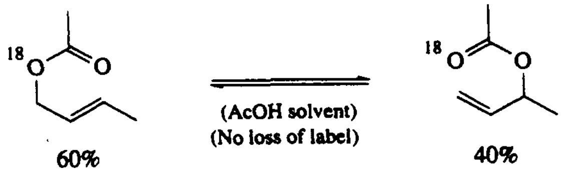
$^{18}O$
O
60%
(AcOH solvent)
(No loss of label)
$^{18}O$
O
40%

(27)

Allylimidates underwent a clean Claisen-type rearrangement in the presence of 5 mol % palladium(II) chloride (equation 28),[40] as did allyl carbamates[39] and *S*-allylthioimidates (equation 29).[41] This S to N rearrangement has found application particularly in the synthesis of pyrimidines, systems for which thermal S to N allylic rearrangements were generally ineffective (equation 30).[42] Finally, *O*-allyl *S*-methyl dithiocarbonates cleanly underwent palladium(II)-catalyzed O to S allylic transposition (equation 31).[43]

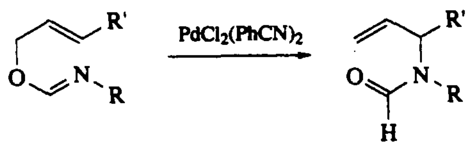
R'
O N R
$PdCl_2(PhCN)_2$
R'
O N R
H

(28)

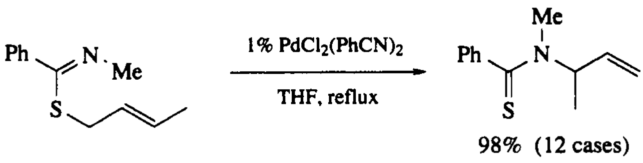

(29)

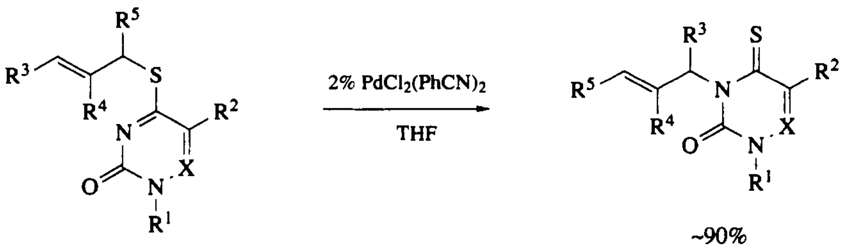

(30)

X = C–R$^6$, N; R$^1$ = Me; R$^2$–R$^6$ = H, *etc.*

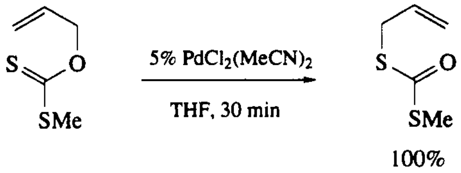

(31)

## 3.1.3 ADDITION OF HETEROATOM NUCLEOPHILES TO METAL-ACTIVATED ALKADIENES

Nonconjugated dienes undergo metal-catalyzed additions of heteroatom nucleophiles as isolated double bonds and most are subject to the general reaction chemistry presented in the previous sections. Conjugated 1,3-dienes are fundamentally different in their reactivity, since addition of a nucleophile to the terminal carbon of a coordinated 1,3-diene produces a $\pi$-allylmetal species (Scheme 11), which itself has a very rich chemistry (Volume 4, Chapter 3.3). Most stable, neutral transition metal $\eta^4$-diene complexes are relatively inert to attack by heteroatom nucleophiles, although a few are attacked by relatively reactive carbanions (Volume 4, Chapter 3.2). However, electrophilic transition metals, particularly palladium(II) salts, which do not form stable complexes with 1,3-dienes, do activate these substrates to undergo a variety of synthetically useful reactions with heteroatom nucleophiles. Most useful of these is the palladium(II)-catalyzed 1,4-additions of nucleophiles to 1,3-dienes. The main features of this process are summarized in Scheme 12, exemplified in the palladium(II) acetate catalyzed 1,4-diacetoxylation, 1,4-acetoxychlorination and 1,4-acetoxy-trifluoroacetoxylation of 1,3-cyclohexadiene.[44] The process involves the regio- and stereo-selective *trans*-acetoxypalladation of a terminus of the diene, producing a *trans*-acetoxy-$\eta^3$-allylpalladium complex. When the reaction is run in the presence of excess chloride ion, external nucleophilic attack of chloride on the $\eta^3$-allylpalladium complex occurs, producing *cis*-1-acetoxy-4-chlorocyclohex-2-ene. In the absence of chloride ion, acetate transferred internally from the same face of the $\eta^3$-allyl complex as the metal, producing *trans*-1,4-diacetoxycyclohex-2-ene. With a catalytic amount of lithium chloride, *cis*-1,4-diacetoxycyclohex-2-ene was the exclusive product. Presumably, chloride displaced acetate from the metal center of the $\eta^3$-allylpalladium intermediate, permitting external nucleophilic attack of the excess acetate present. Finally, in the presence of trifluoroacetic acid, *trans*-1-acetoxy-4-trifluoroacetoxycyclohex-2-ene was formed, presumably by prior coordination of trifluoroacetate to the metal and internal transfer to the $\eta^3$-allyl ligand. The wide range of dienes that underwent this reaction, in good yield and with high regio- and stereo-selectivity are listed in Table 2. The real utility of this chemistry lies in the facile further functionalization of these systems using both conventional and palladium(0)-catalyzed substitution reactions (Volume 4, Chapter 3.3). With a slight change in reaction conditions, this same range of dienes was efficiently dialkoxylated by alcohols (equation 32).[45]

1,2-Dienes underwent facile chloropalladation producing an unstable $\sigma$-vinylpalladium(II) intermediate, which inserted another mole of allene to give an isolable 2-substituted $\eta^3$-allylpalladium complex.

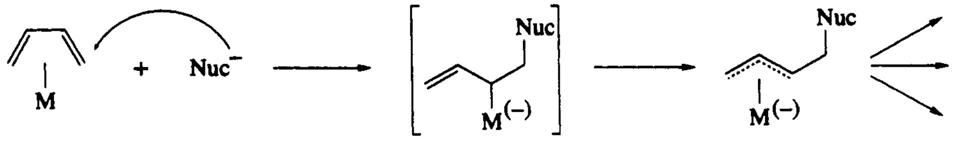
M
+
Nuc⁻
Nuc
M(−)
Nuc
M(−)

**Scheme 11**

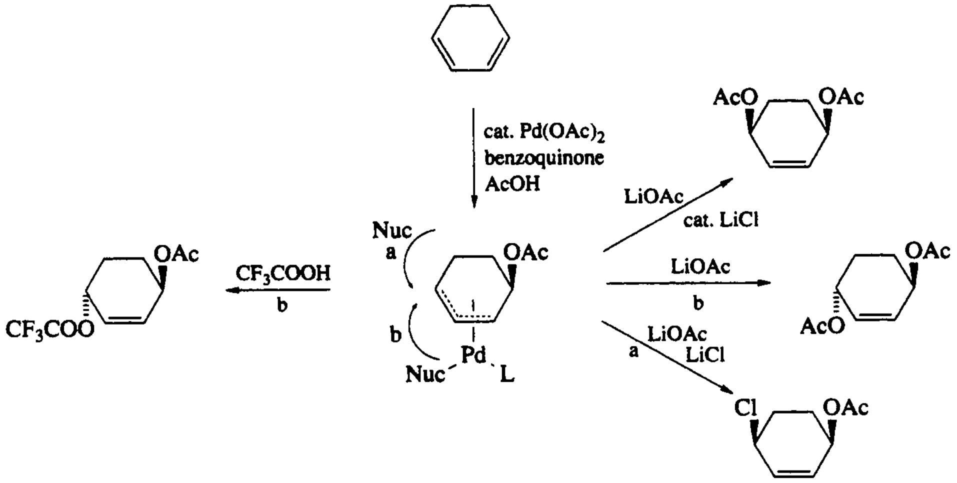
cat. Pd(OAc)₂
benzoquinone
AcOH
Nuc
a
b
OAc
Pd
Nuc
L
CF₃COOH
b
OAc
CF₃COO
AcO
OAc
LiOAc
cat. LiCl
LiOAc
b
OAc
AcO
LiOAc
LiCl
a
Cl
OAc

**Scheme 12**

**Table 2** 1,3-Dienes Catalytically Diacetoxylated

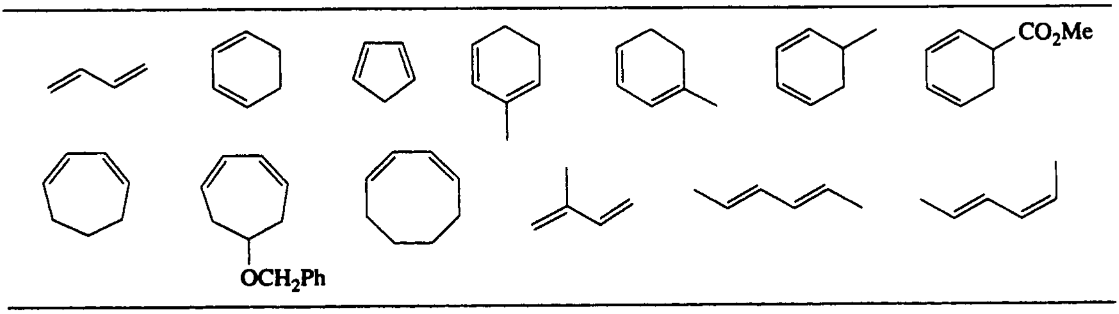
CO₂Me
OCH₂Ph

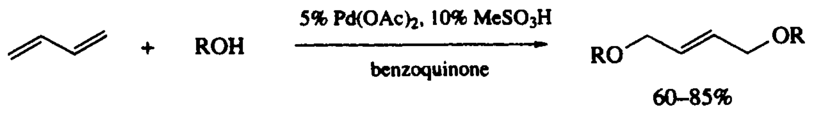
+
ROH
5% Pd(OAc)₂, 10% MeSO₃H
benzoquinone
RO
OR
60–85%

(32)

When this reaction was carried out in the presence of copper(II) chloride as oxidant, efficient catalytic production of bis-2,3-chloromethyl-1,3-butadiene resulted (Scheme 13).[46]

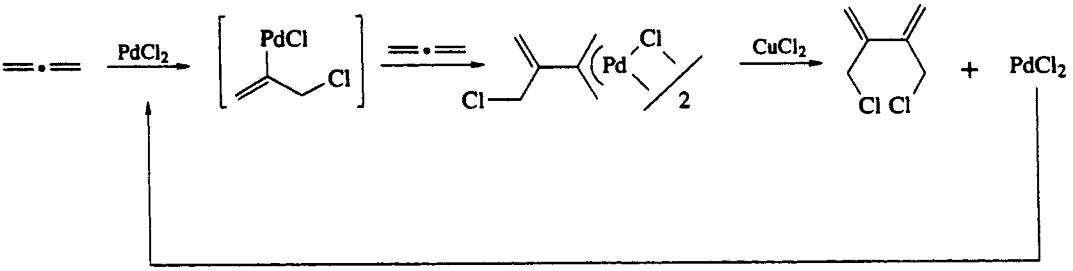
PdCl₂
PdCl
Cl
Cl
Pd
Cl
2
CuCl₂
Cl Cl
+
PdCl₂

**Scheme 13**

## 3.1.4 ADDITION OF HETEROATOM NUCLEOPHILES TO METAL-ACTIVATED ALKYNES

Although alkynes are highly reactive toward a wide range of transition metals, very few instances of metal-catalyzed reactions of nucleophiles with alkynes are known. This is, in part, because most stable alkyne–metal complexes are inert to nucleophilic attack, while most unstable alkyne–metal complexes tend to oligomerize alkynes faster than anything else. Hence synthetic methodology involving this process is quite limited.

There are two notable exceptions to this. Palladium(II) salts catalyzed a number of cyclization reactions of alkynes bearing remote heteroatoms in a process thought to involve nucleophilic attack of the heteroatom on the palladium-complexed alkynes. Thus pyrroles[47] and indoles[48] (Scheme 14), furans and substituted furans (equation 33)[49] and unsaturated lactones (equations 34–36)[40,50] were efficiently produced by treatment of the appropriately disposed alkynic amines, alcohols or carboxylates with 1–5% palladium chloride catalyst. These reactions required a somewhat unusual protolytic cleavage of the $\sigma$-vinylpalladium(II) species to regenerate the palladium(II) chloride catalyst. Evidence for the intermediacy of this species was obtained by intercepting it with allyl chlorides, producing substituted unsaturated lactones (equations 37 and 38).[51]

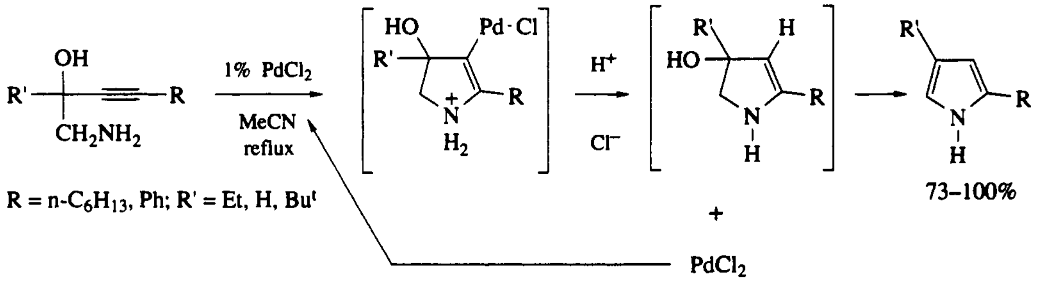

R = n-$C_6H_{13}$, Ph; R' = Et, H, Bu$^t$

73–100%

Scheme 14

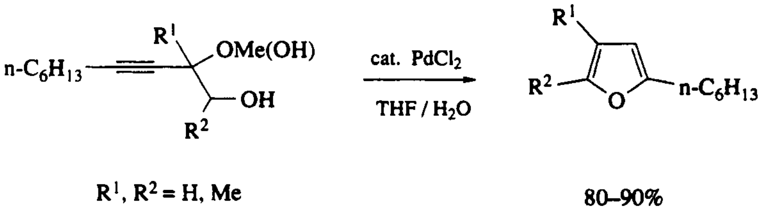

$R^1$, $R^2$ = H, Me

80–90%

(33)

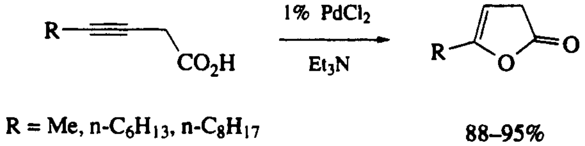

R = Me, n-$C_6H_{13}$, n-$C_8H_{17}$

88–95%

(34)

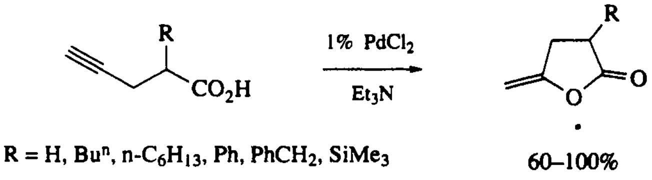

R = H, Bu$^n$, n-$C_6H_{13}$, Ph, $PhCH_2$, $SiMe_3$

60–100%

(35)

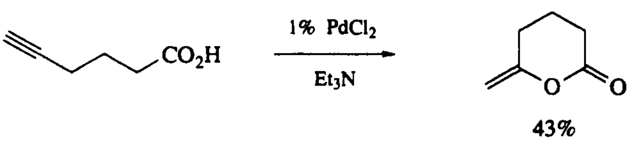

43%

(36)

In contrast to many stable transition metal–alkyne complexes, cationic cyclopentadienyliron–alkyne complexes are reactive toward a range of nucleophiles. However, since most of the nucleophiles studied were carbanions, discussion of this chemistry is deferred to Volume 4, Chapter 3.2, Section 3.2.3.

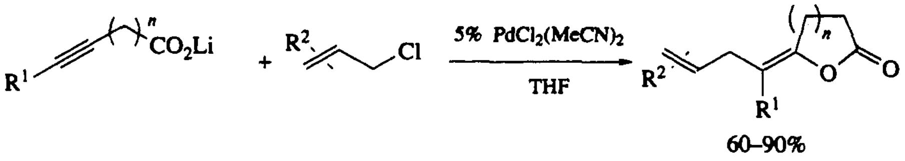

(37)

$R^1$ = H, n-$C_6H_{13}$, Ph, $SiMe_3$; $R^2$ = 1-Me, 2-Me, 3-Me

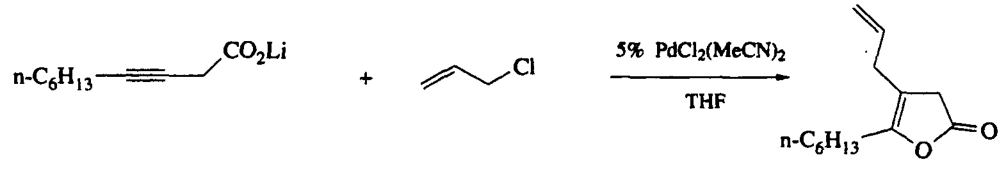

(38)

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# 3.2

# Carbon Nucleophiles with Alkenes and Alkynes

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*Colorado State University, Fort Collins, CO, USA*

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## 3.2.1 INTRODUCTION

The same transition metal systems which activate alkenes, alkadienes and alkynes to undergo nucleophilic attack by heteroatom nucleophiles also promote the reaction of carbon nucleophiles with these unsaturated compounds, and most of the chemistry in Scheme 1 in Section 3.1.2 of this volume is also applicable in these systems. However two additional problems which seriously limit the synthetic utility of these reactions are encountered with carbon nucleophiles. Most carbanions are strong reducing agents, while many electrophilic metals such as palladium(II) are readily reduced. Thus, oxidative coupling of the carbanion, with concomitant reduction of the metal, is often encountered when carbon nucleophiles are studied. In addition, catalytic cycles invariably require reoxidation of the metal used to activate the alkene [usually palladium(II)]. Since carbanions are more readily oxidized than are the metals used, catalysis of alkene, diene and alkyne alkylation has rarely been achieved. Thus, virtually all of the reactions discussed below require stoichiometric quantities of the transition metal, and are practical only when the ease of the transformation or the value of the product overcomes the inherent cost of using large amounts of often expensive transition metals.

## 3.2.2 ALKYLATION OF MONOALKENES

Terminal monoalkenes were alkylated by stabilized carbanions ($pK_a \approx 10–18$) in the presence of 1 equiv. of palladium chloride and 2 equiv. of triethylamine, at low temperatures (Scheme 1).[1] The resulting unstable $\sigma$-alkylpalladium(II) complex was reduced to give the alkane (path a), allowed to $\beta$-hydride eliminate to give the alkene (path b), or treated with carbon monoxide and methanol to produce the ester (path c).[2] As was the case with heteroatom nucleophiles, attack at the more substituted alkene position predominated, and internal alkenes underwent alkylation in much lower (≈30%) yield. In the absence of triethylamine, the yields were very low (1–2%) and reduction of the metal by the carbanion became the major process. Presumably, the tertiary amine ligand prevented attack of the carbanion at the metal, directing it instead to the coordinated alkene. The regiochemistry (predominant attack at the more sub-

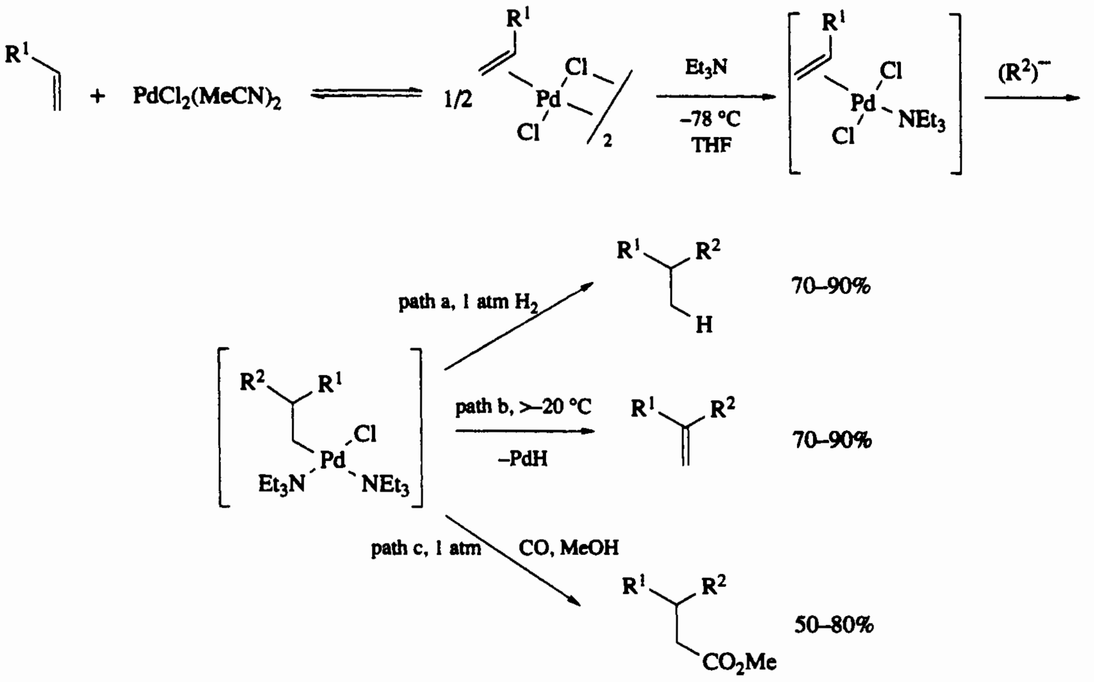

$R^1$ = H, Me, Et, NHAc, Ph, Bu$^n$; $R^2$ = $NaC(Me)(CO_2Et)_2$, $NaCH(CO_2Me)_2$, LiCHPh(OMe), $LiCH(Ph)(CO_2Et)$, $NaC(NHAc)(CO_2Et)_2$

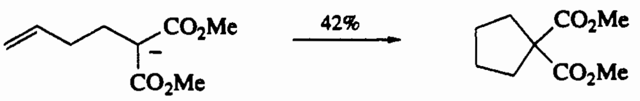

Scheme 1

stituted alkene terminus) is consistent with attack by the nucleophile without prior coordination (see below).

Because it requires stoichiometric amounts of expensive palladium(II) salts, this process has found little use in the synthesis of more complex organic compounds. Two exceptions are seen in equation (1)[3] and Scheme 2.[4]

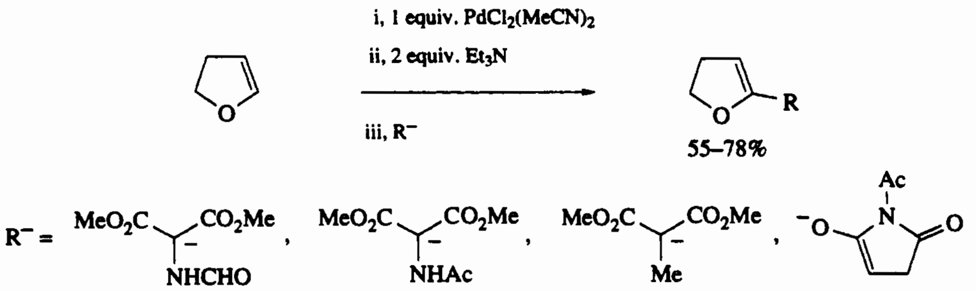

(1)

The above system failed entirely when nonstabilized carbanions such as ketone or ester enolates or Grignard reagents were used as carbon nucleophiles, leading to reductive coupling of the anions rather than alkylation of the alkene. However, the fortuitous observation that the addition of HMPA to the reaction mixture prior to addition of the carbanion prevented this side reaction[1] extended the range of useful carbanions substantially to include ketone and ester enolates, oxazoline anions, protected cyanohydrin anions, nitrile-stabilized anions[5] and even phenyllithium (Scheme 3).[5]

With these nonstabilized carbanions, attack occurred almost exclusively at the less-substituted terminus of the alkene, regioselectivity opposite that observed with stabilized carbanions. This regioselectivity

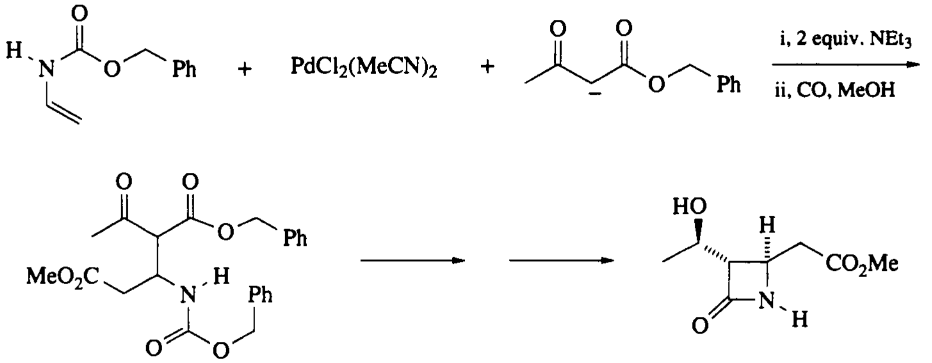

**Scheme 2**

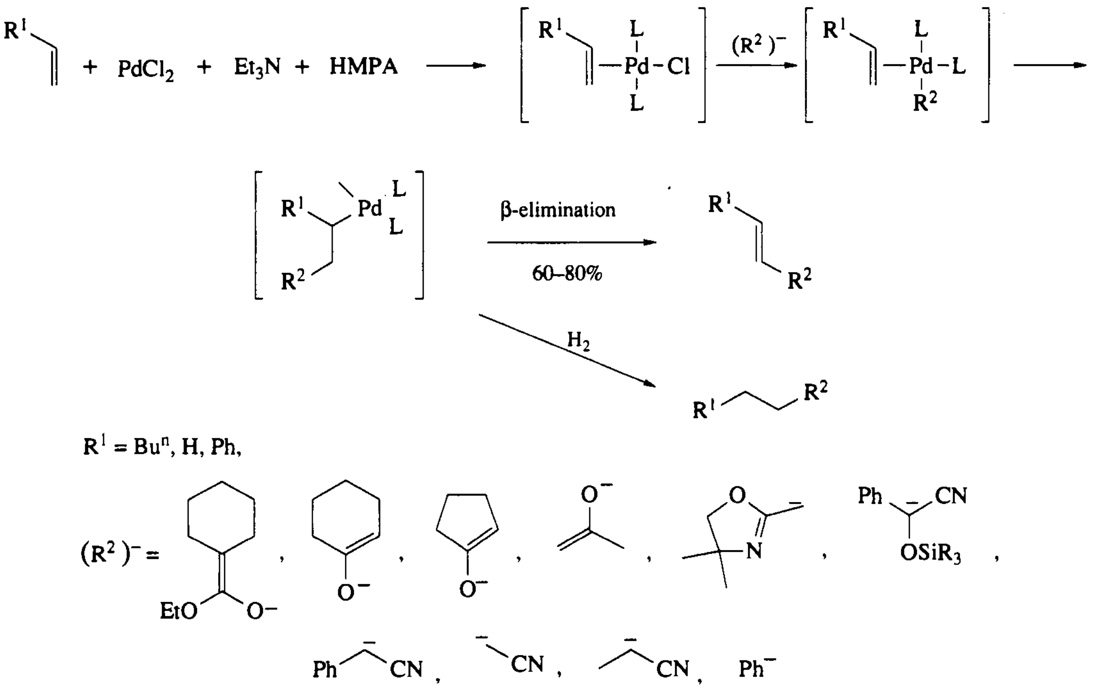

**Scheme 3**

is that commonly observed in the insertion of alkenes into metal–carbon $\sigma$-bonds (Chapter 4.3, Volume 4), and implies a change in mechanism wherein direct alkylation of the metal followed by insertion of the alkene occurred rather than external nucleophilic attack of the carbanion on the metal-bound alkene. Again, the requirement of stoichiometric quantities of palladium salts has limited the synthetic applications of this chemistry.

In contrast, the closely related palladium acetate-promoted intramolecular alkylation of alkenes by trimethylsilyl enol ethers (Scheme 4)[6,7] has been used to synthesize a large number of bridged carbocyclic systems (Table 1). In principle, this process should be capable of being made catalytic in palladium(II), since silyl enol ethers are stable to a range of oxidants used to carry the $Pd^0 \rightarrow Pd^{II}$ redox chemistry required for catalysis. In practice, catalytically efficient conditions have not yet been developed, and the reaction is usually carried out using a full equivalent of palladium(II) acetate. This chemistry has been used in the synthesis of quadrone (equation 2).[8] With the more electrophilic palladium(II) trifluoroacetate, methyl enol ethers underwent this cyclization process (equation 3).[9]

Chelating alkenes such as allylic[10] and homoallylic[11] amines and sulfides underwent alkylation by a range of stabilized carbanions to produce stable $\sigma$-alkylpalladium(II) complexes. In these cases the regioselectivity was strictly governed by the inherent stability of a five (*versus* four or six) membered chelate $\sigma$-alkylpalladium complex, with allylic systems (Scheme 5) being alkylated at the more sub-

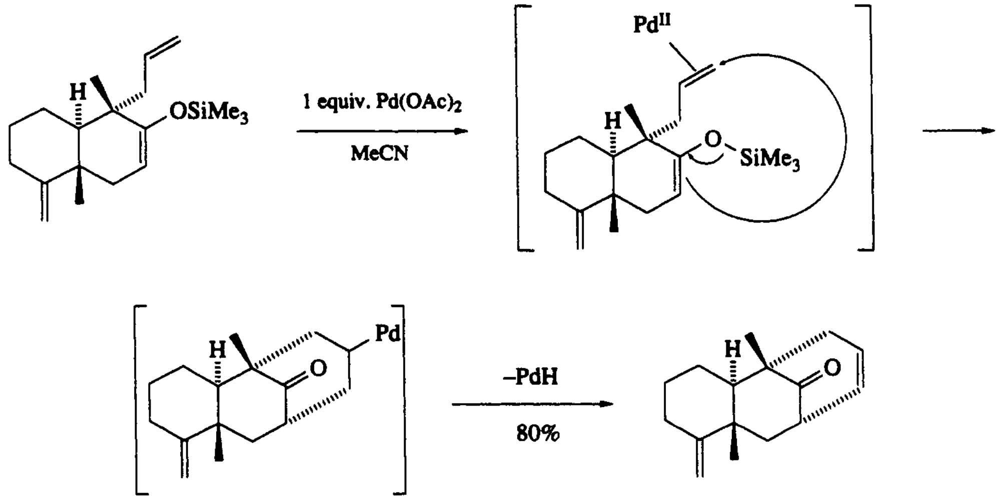
OSiMe3
1 equiv. Pd(OAc)2
MeCN
Pd^II
SiMe3
Pd
–PdH
80%

**Scheme 4**

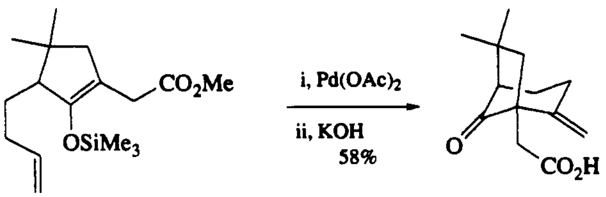
CO2Me
OSiMe3
i, Pd(OAc)2
ii, KOH
58%
CO2H
Quadrone

(2)

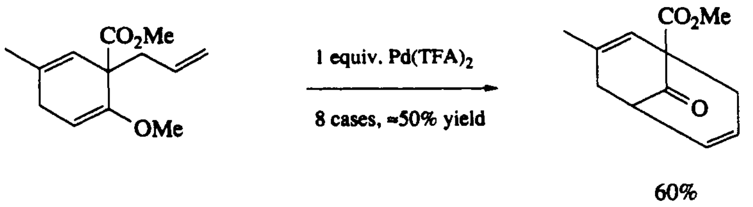
CO2Me
OMe
1 equiv. Pd(TFA)2
8 cases, ≈50% yield
60%

(3)

stituted position and homoallylic systems at the less substituted terminus (Scheme 6). Reduction of these complexes produced the saturated hydrocarbons, while treatment with conjugated enones resulted in insertion of the alkene.

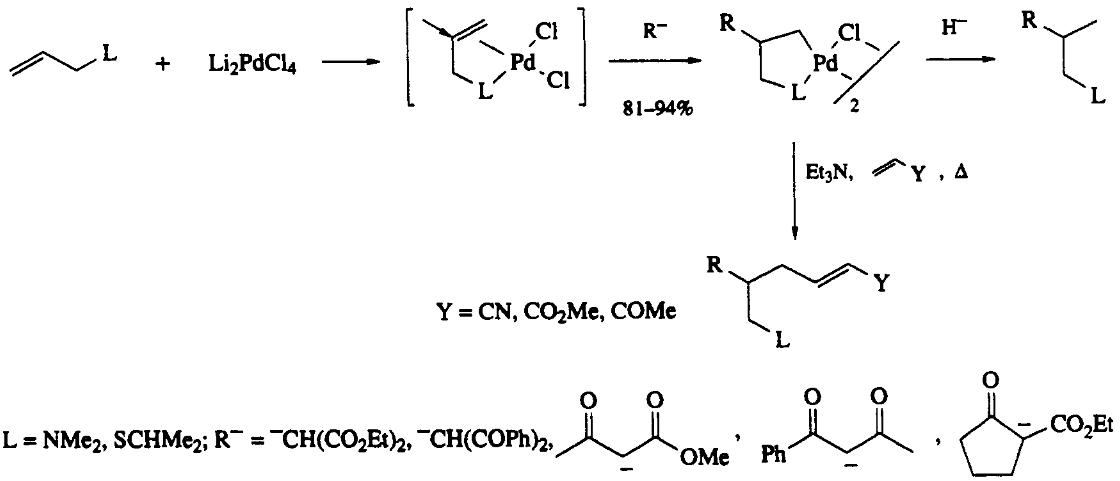
L
Li2PdCl4
Cl
Pd
R⁻
81–94%
H⁻
Et3N, Y, Δ
Y = CN, CO2Me, COMe
L = NMe2, SCHMe2; R⁻ = ⁻CH(CO2Et)2, ⁻CH(COPh)2,
OMe
Ph
CO2Et

**Scheme 5**

**Table 1** Palladium(II) Acetate Assisted Cyclization of Trimethylsilylenol Ethers

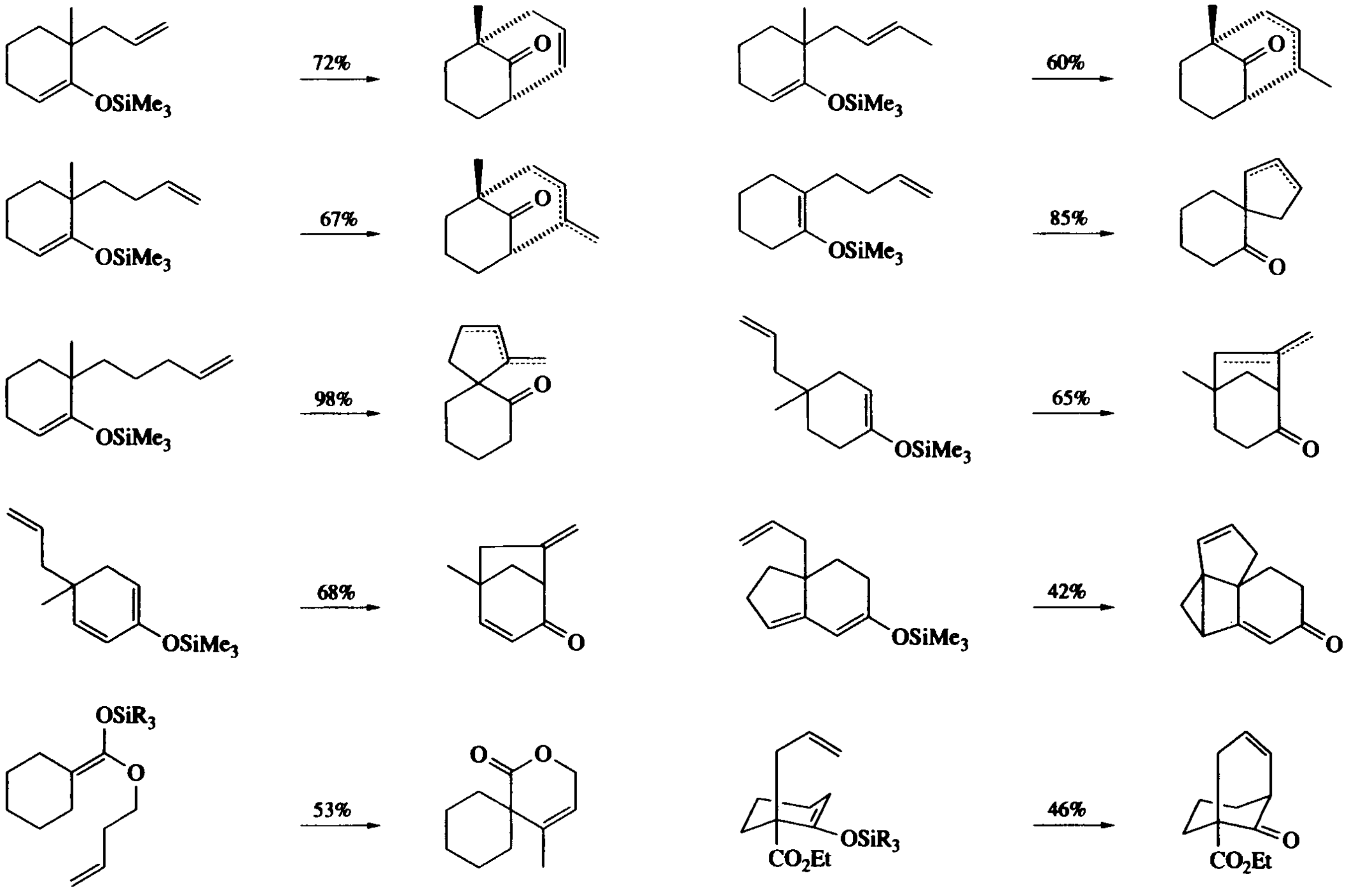
OSiMe3
72%
O
OSiMe3
60%
O
OSiMe3
67%
O
OSiMe3
85%
O
OSiMe3
98%
O
OSiMe3
65%
O
OSiMe3
68%
O
OSiMe3
42%
O
OSiR3
O
53%
O
O
OSiR3
CO2Et
46%
O
CO2Et

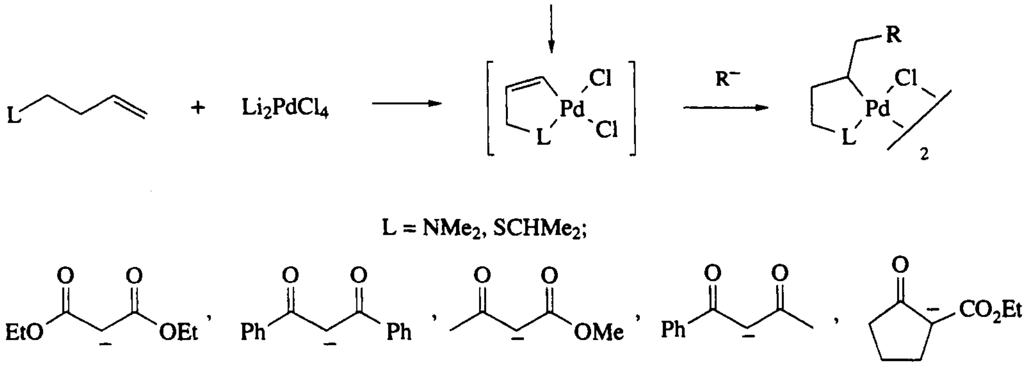

**Scheme 6**

In contrast to the above stoichiometric palladium-assisted reactions, palladium(II) chloride efficiently catalyzed a variety of Cope rearrangements (Scheme 7 and Table 2).[12] The mechanism of this process is not known, but is likely to involve 'cyclization-induced catalysis' as noted in Section 3.1.2.3 of this volume. This rearrangement has several important features. Successful catalysis required that C-2 or C-5 of the diene had an alkyl substituent present, perhaps to stabilize the developing positive charge at these positions during rearrangement. Alkyl substituents at both C-2 and C-5 suppressed the rearrangement, reflecting the steric inhibition of placing the bulky metal at a sterically hindered tertiary position. With chiral, optically active dienes, complete 1,4-transfer of chirality was observed, as was the case in the related palladium-catalyzed allylic transposition of allyl acetates discussed above (Section 3.1.2.3, this volume).

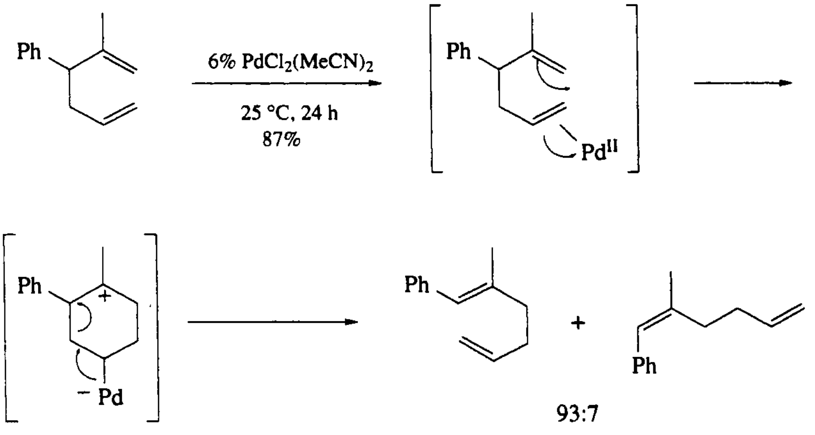

**Scheme 7**

Cationic cyclopentadienyliron dicarbonyl ($F_p$) complexes of alkenes are generally reactive toward a wide range of nucleophiles, including carbanions, producing very stable $\sigma$-alkyliron complexes (Scheme 8).[13,14] Again, attack at the more substituted alkene terminus predominated. These $\sigma$-alkyliron complexes required chemical removal of the iron to free the organic fragment, making catalytic processes impossible. As a consequence little use of these simpler systems in synthesis has resulted. However, a number of synthetically useful transformations involving alkoxyalkenes have been developed.

$\alpha$-Methylene lactones were produced by the reaction of cyclohexanone enolate with the $F_p$–$\alpha$-ethoxyacrylate complex (Scheme 9)[15] while ethoxyethylene was converted to the corresponding $\gamma$-lactones (Scheme 10).[16] Dimethoxyethylene–$F_p$ complexes provided routes to efficiently dialkylate ethylene (Scheme 11).[17] Using this methodology, a variety of furans were synthesized (Scheme 12).[18] This chemistry was noteworthy in two respects. Firstly, all transformations were highly stereoselective, permitting the facile synthesis of complex molecules having multiple stereogenic centers. Secondly, the oxidative cleavage of the $\sigma$-alkyliron complexes led to nucleophilic displacement of the oxidized iron fragment, rather than the normal insertion of CO to form acyl complexes. Thus furans, rather than the expected lactones, were formed.

**Table 2** Palladium(II)-catalyzed Cope Rearrangements

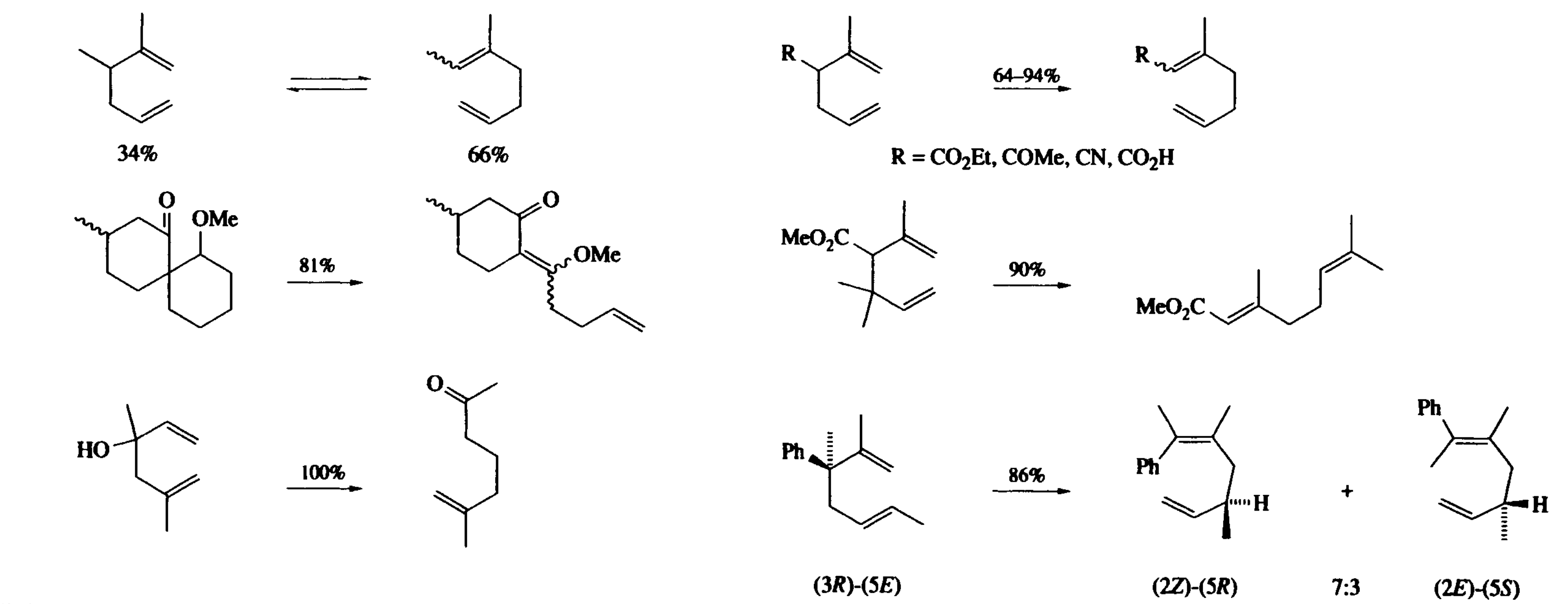
34%
66%
R
64–94%
R
R = CO$_2$Et, COMe, CN, CO$_2$H
O
OMe
81%
O
OMe
MeO$_2$C
90%
MeO$_2$C
HO
100%
O
Ph
86%
Ph
H
+
Ph
H
(3R)-(5E)
(2Z)-(5R)
7:3
(2E)-(5S)

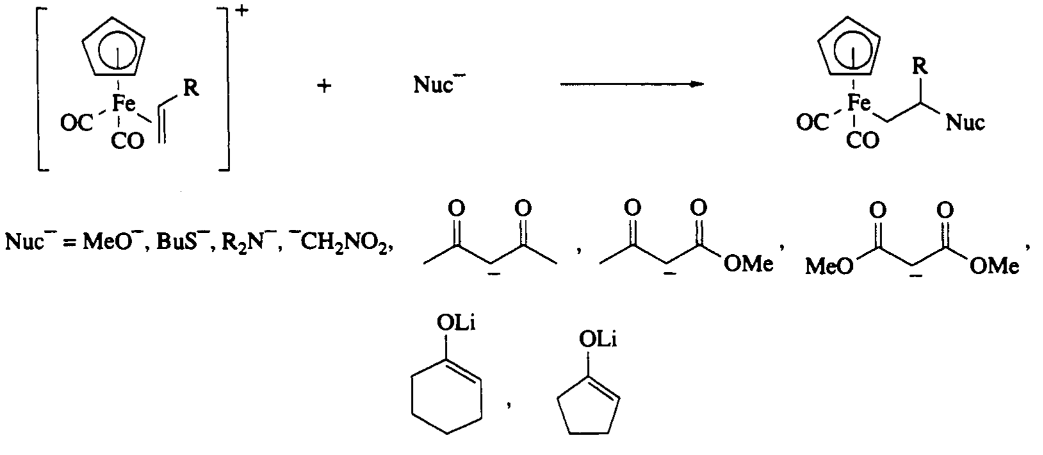
Nuc⁻
Fe
OC
CO
R
Nuc
OLi

$Nuc^- = MeO^-, BuS^-, R_2N^-, {}^-CH_2NO_2,$

R = H, Me, Ph, CHO, $CH_2OMe$

Scheme 8

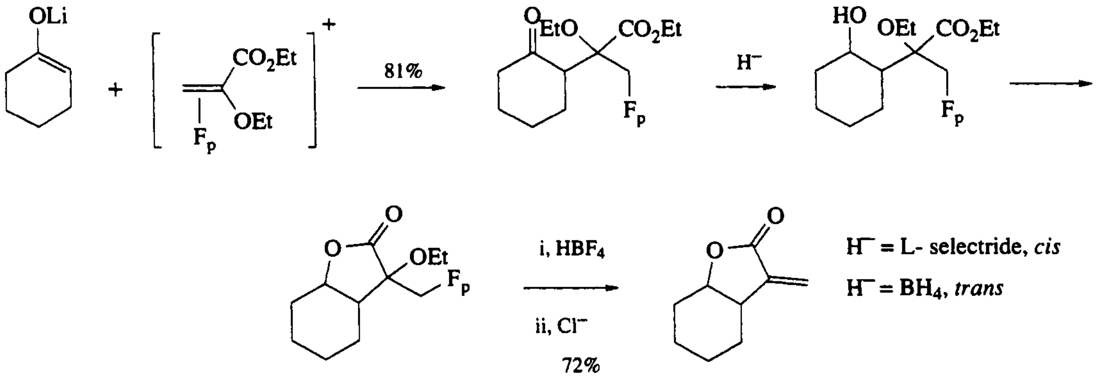
OLi
$CO_2Et$
OEt
$F_p$
81%
EtO
H⁻
HO
i, $HBF_4$
ii, Cl⁻
72%

H⁻ = L- selectride, *cis*
H⁻ = $BH_4$, *trans*

Scheme 9

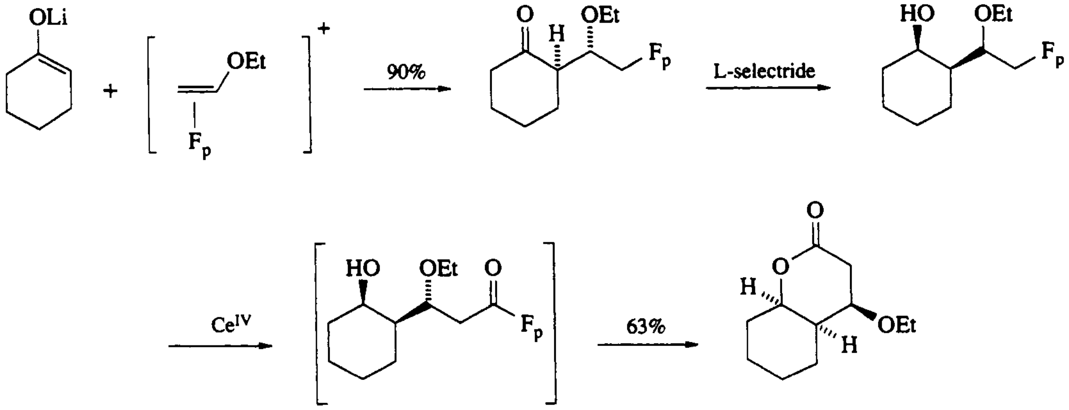
OLi
OEt
$F_p$
90%
O
H
L-selectride
HO
$Ce^{IV}$
63%

Scheme 10

Cationic iron–alkene complexes also participate in an unusual ‘cycloaddition’ process, wherein electron-deficient alkenes are attacked by nucleophilic σ-allylic $F_p$ complexes, generating stabilized carbanions and cationic alkene–iron complexes. Attack of the carbanion on the alkene forming a five-membered ring completes this process (Scheme 13). Oxidative removal of the iron produces useful organic compounds.[19–21]

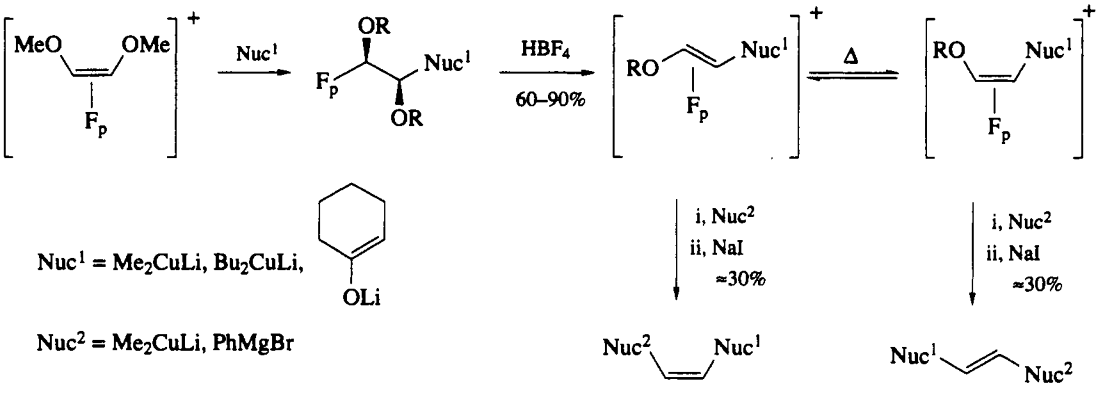
Nuc1
HBF4
60–90%
Δ
i, Nuc2
ii, NaI
≈30%
Nuc1 = Me2CuLi, Bu2CuLi,
Nuc2 = Me2CuLi, PhMgBr

**Scheme 11**

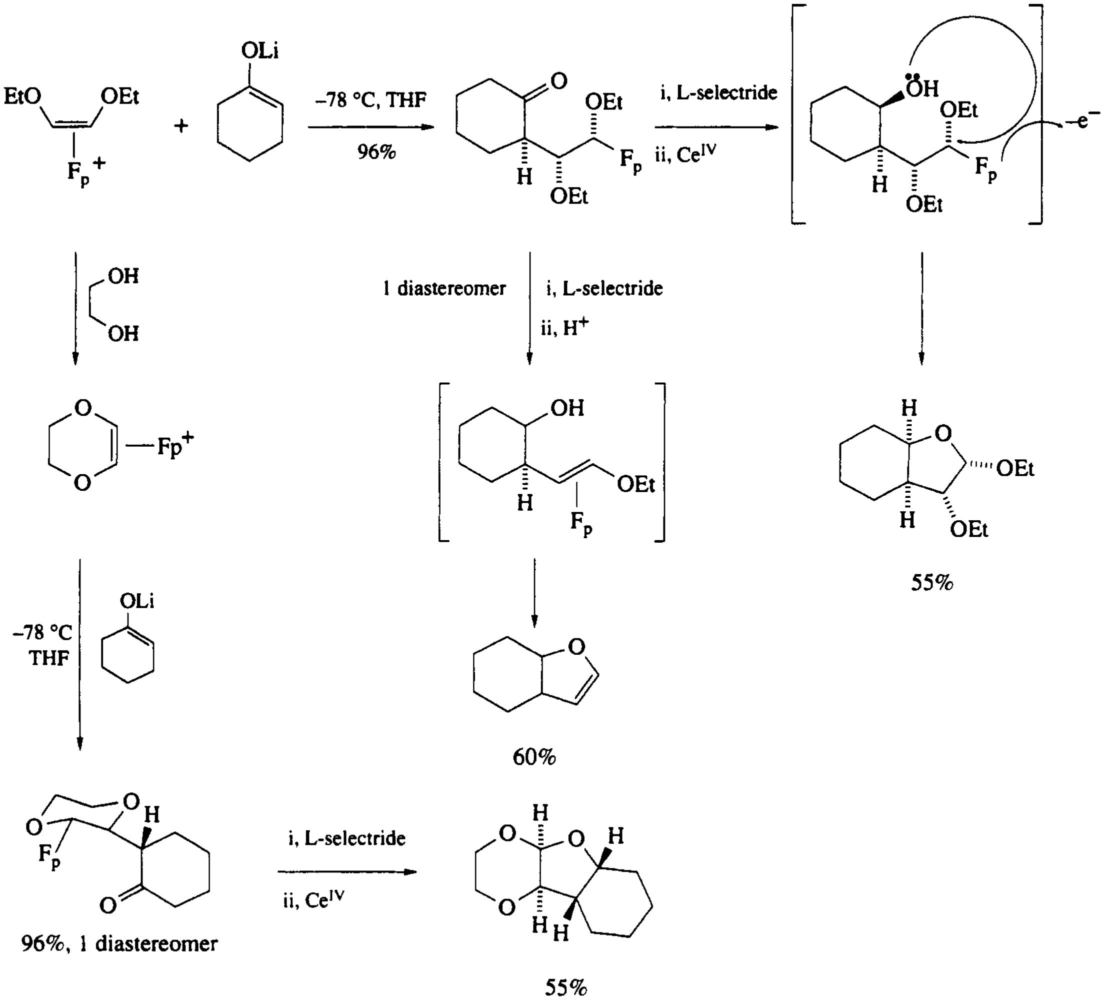
−78 °C, THF
96%
i, L-selectride
ii, CeIV
−e−
1 diastereomer
i, L-selectride
ii, H+
60%
55%
−78 °C
THF
96%, 1 diastereomer
i, L-selectride
ii, CeIV
55%

**Scheme 12**

This chemistry has been used to synthesize cyclopentanoid derivatives used in the synthesis of sarkomycin and brefeldin A.[22] Azulene derivatives were also synthesized using this chemistry (Scheme 14).[23]

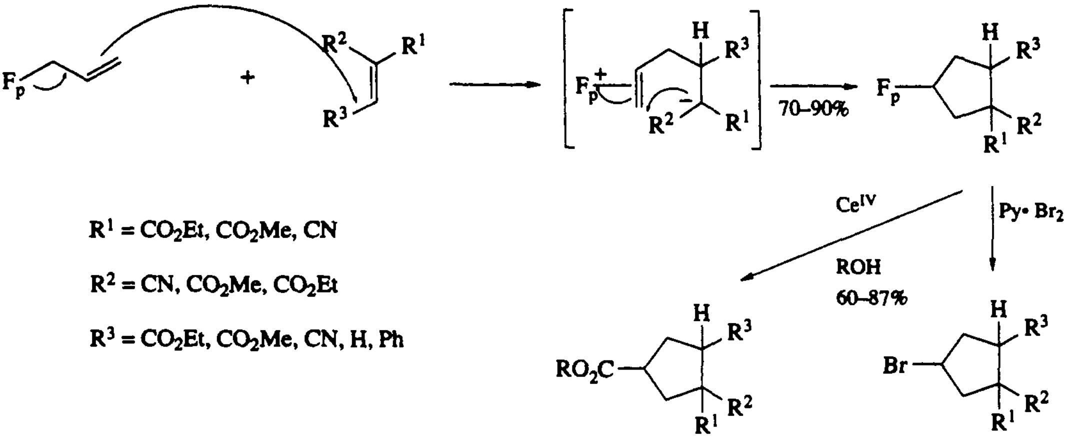
$R^1 = CO_2Et, CO_2Me, CN$

$R^2 = CN, CO_2Me, CO_2Et$

$R^3 = CO_2Et, CO_2Me, CN, H, Ph$

Fp
R2
R1
R3
H
70–90%
Ce^IV
ROH
60–87%
Py• Br2
RO2C
Br

Scheme 13

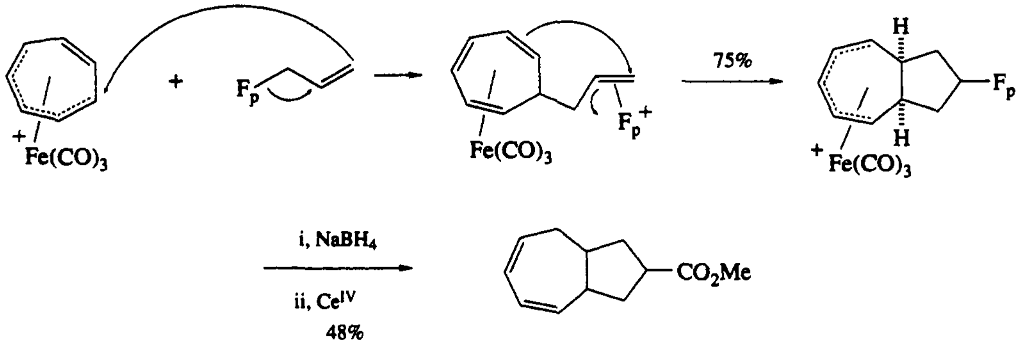

Fe(CO)3
Fp
75%
H
i, NaBH4
ii, Ce^IV
48%
CO2Me

Scheme 14

### 3.2.3 ALKYLATION OF ALKADIENES

1,3-Dienes form very stable complexes with a variety of metal carbonyls, particularly $Fe(CO)_5$, and the neutral $\eta^4$-diene metal carbonyl complexes are quite resistant to normal reactions of dienes (*e.g.* hydrogenation, Diels–Alder). However, they are subject to nucleophilic attack by a variety of nonstabilized carbanions. Treatment of $\eta^4$-cyclohexadiene iron tricarbonyl with nonstabilized carbanions, followed by protonolysis of the resulting complex, produced isomeric mixtures of alkylated cyclohexenes (Scheme 15).[24] With acyclic dienes, this alkylation was shown to be reversible, with kinetic alkylation occurring at an internal position of the complexed dienes but rearranging to the terminal position under thermodynamic conditions (Scheme 16).[25] By trapping the kinetic product with an electrophile, overall 'carbo-

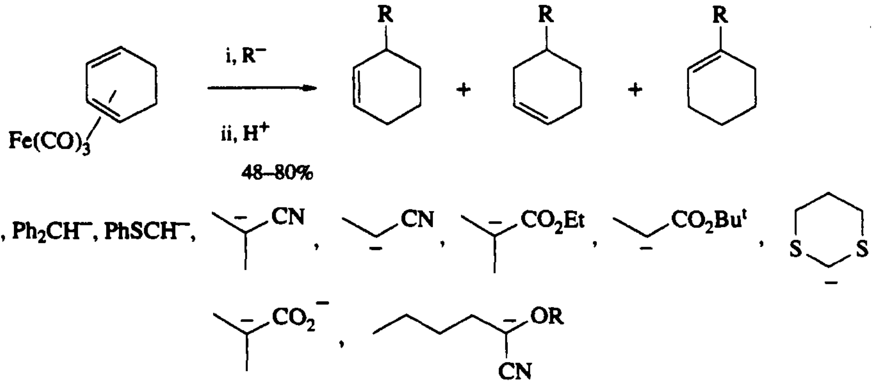

Fe(CO)3
i, R−
ii, H+
48–80%
R
R− = Ph3C−, Ph2CH−, PhSCH−,
CN
CO2Et
CO2But
S
CO2−
OR
CN

Scheme 15

acylation' was achieved (Schemes 17 and 18).[26,27] With cyclic dienes, alkylation occurred from the face opposite the metal, and acylation from the same face as the metal to produce exclusively *trans* product.

As expected, cationic diene complexes (as well as cationic dienyl complexes, see Chapter 3.4, of this volume) are considerably more reactive toward nucleophiles than are the corresponding neutral complexes. Using this feature, very efficient processes for stereocontrolled alkylation of cyclohexadiene (Scheme 19)[28] and cycloheptadiene (Scheme 20)[29] have been developed. They share many common features. A range of carbanions attacked, always from the face opposite the metal, producing a neutral $\eta^3$-allylmolybdenum complex. Further functionalization of the cyclohexadiene system was not studied. However in the cycloheptadiene series the initially formed $\eta^3$-allyl complex was reconverted into a cationic diene complex, which could be alkylated again. Both alkyl groups entered from the face opposite the metal, giving *cis*-1,2- and -1,4-dialkyl systems in high yield and with high diastereoselectivity. The potential for further functionalization of the resulting $\eta^3$-allyl systems is high, but has yet to be extensively explored.

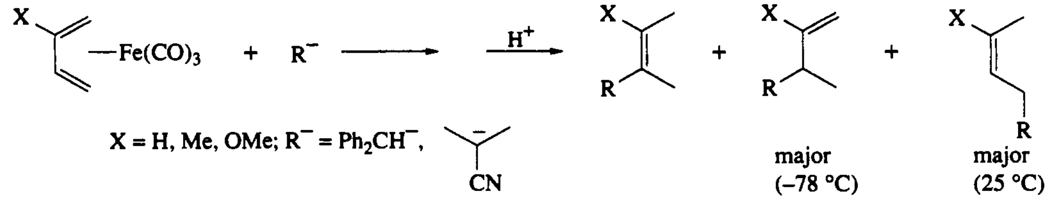
X
—Fe(CO)₃
+ R⁻
H⁺
X
R
+
X
R
+
X
R
X = H, Me, OMe; R⁻ = Ph₂CH⁻,
CN
major
(–78 °C)
major
(25 °C)

**Scheme 16**

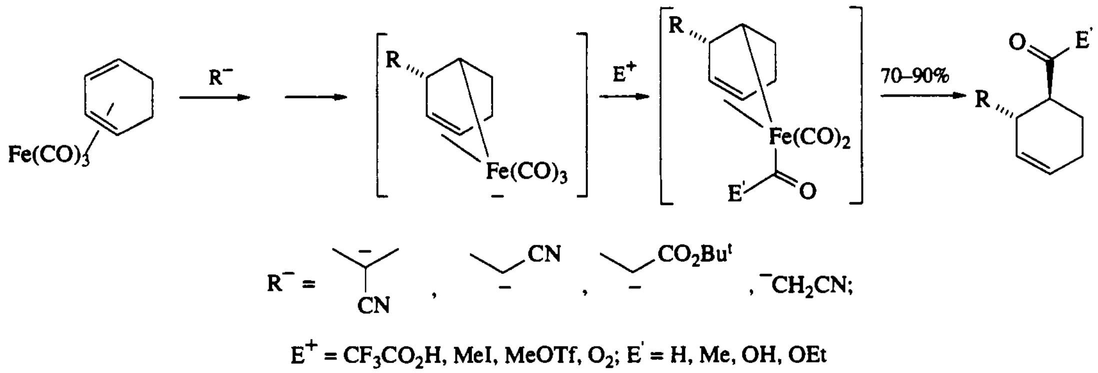
R⁻
Fe(CO)₃
R
Fe(CO)₃
E⁺
R
Fe(CO)₂
E'
O
70–90%
O
E'
R
R⁻ =
CN
CN
CO₂Buᵗ
, ⁻CH₂CN;
E⁺ = CF₃CO₂H, MeI, MeOTf, O₂; E' = H, Me, OH, OEt

**Scheme 17**

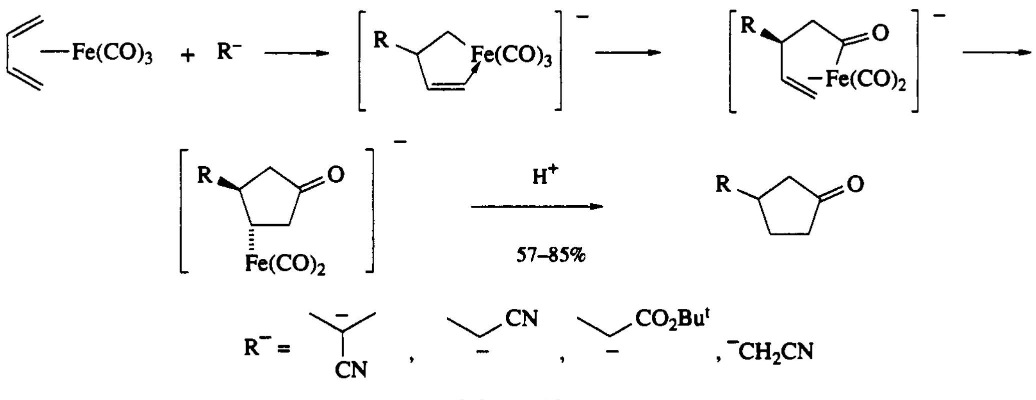
—Fe(CO)₃
+ R⁻
R
Fe(CO)₃
R
O
Fe(CO)₂
R
O
Fe(CO)₂
H⁺
57–85%
R
O
R⁻ =
CN
CN
CO₂Buᵗ
, ⁻CH₂CN

**Scheme 18**

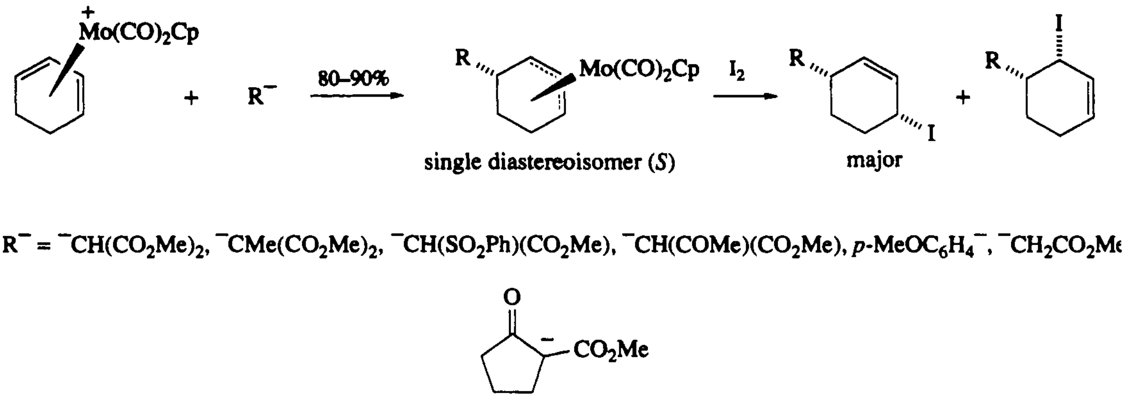

$\overset{+}{Mo}(CO)_2Cp$
$R^-$
80–90%
$Mo(CO)_2Cp$
$I_2$
single diastereoisomer (*S*)
major
$CO_2Me$

$R^- = {}^-CH(CO_2Me)_2$, ${}^-CMe(CO_2Me)_2$, ${}^-CH(SO_2Ph)(CO_2Me)$, ${}^-CH(COMe)(CO_2Me)$, *p*-$MeOC_6H_4^-$, ${}^-CH_2CO_2Me$

Scheme 19

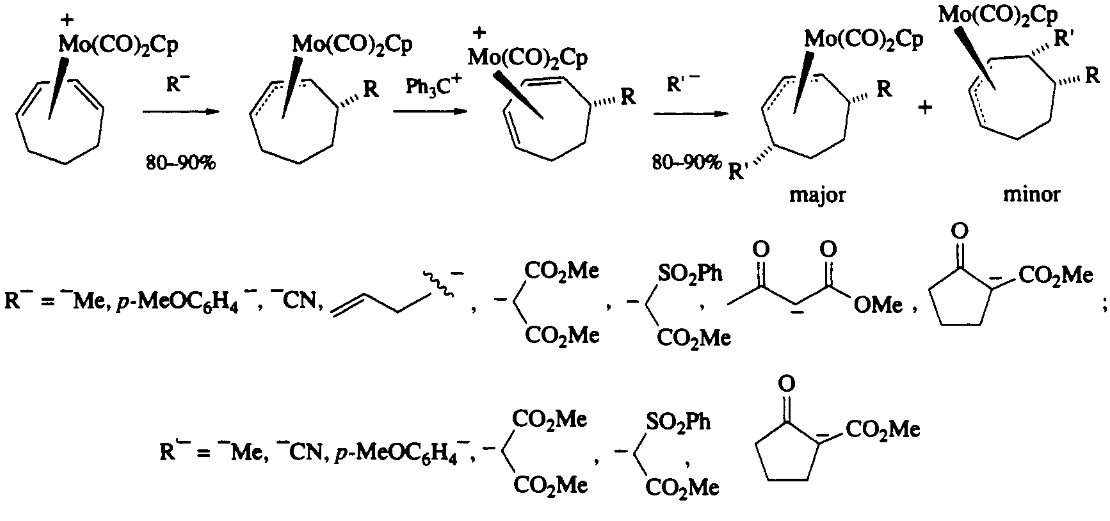

$\overset{+}{Mo}(CO)_2Cp$
$R^-$
80–90%
$Mo(CO)_2Cp$
$Ph_3C^+$
$R'^-$
80–90%
major
minor
$CO_2Me$
$SO_2Ph$
OMe

$R^- = {}^-Me$, *p*-$MeOC_6H_4^-$, ${}^-CN$,

$R'^- = {}^-Me$, ${}^-CN$, *p*-$MeOC_6H_4^-$,

Scheme 20

## 3.2.4 ALKYLATION OF ALKYNES

Although alkynes are highly reactive toward a wide range of transition metals, few instances of metal-catalyzed reactions of carbanions with alkynes are known. The most extensively developed system involves cationic iron complexes of internal alkynes. These complexes underwent alkylation by a range of carbanions to produce stable σ-vinyliron complexes (Scheme 21).[30] The addition was stereoselectively

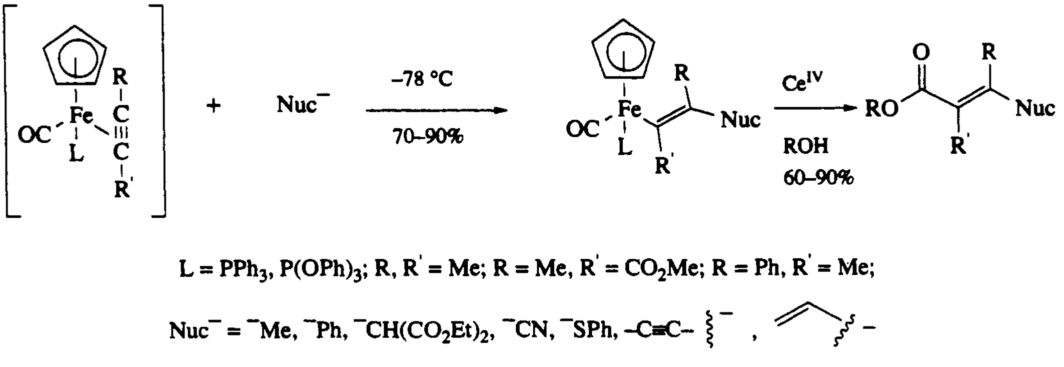

Fe
OC
L
R
R'
Nuc$^-$
−78 °C
70–90%
Nuc
$Ce^{IV}$
ROH
60–90%
RO
O

L = $PPh_3$, $P(OPh)_3$; R, R' = Me; R = Me, R' = $CO_2Me$; R = Ph, R' = Me;

$Nuc^- = {}^-Me$, ${}^-Ph$, ${}^-CH(CO_2Et)_2$, ${}^-CN$, ${}^-SPh$, –C≡C–

Scheme 21

*trans*, and also regioselective, with the nucleophile adding away from ester groups on the alkyne, and on the alkyne carbon bearing a phenyl group. Oxidation promoted CO insertion with retention of alkene geometry (in most cases) producing acyliron complexes which upon further oxidation cleaved to give α,β-unsaturated esters. At present, the process is stepwise, and the metal complex must be destroyed to free the organic ligand. More efficient systems await development.

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# 3.3

# Nucleophiles with Allyl–Metal Complexes

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## 3.3.1 INTRODUCTION

### 3.3.1.1 Scope

Interest in $\pi$-allylpalladium chemistry has undergone incredible growth, particularly over the last decade. This growth is exemplified by the significant number of reviews on this subject that have now appeared, including several within the last few years.[1–16] In light of this substantial coverage, this chapter is not intended to serve as a comprehensive review of this area of chemistry. Rather, the focus of this chapter will be on the selectivities, namely chemo-, diastereo-, regio- and enantio-selectivity, that are exhibited by $\pi$-allylpalladium chemistry. As possible, the mechanistic basis of these selectivities will be elucidated. In addition, the selection of examples provided to illustrate the nature of reactions involving $\pi$-allylpalladium complexes will be largely made from contributions that have appeared in the last decade.

### 3.3.1.2 Nature of $\pi$-Allylpalladium-mediated Functionalization

The essence of $\pi$-allylpalladium-mediated functionalization is the activation of an allylic system to attack by a nucleophilic compound. The regio- and stereo-selectivity associated with this reaction have been found to be functions of the nucleophile, the substitution on the allyl moiety, the nature of the ligands on palladium and the reaction medium.

The means of entry into $\pi$-allyl complexes, the elucidation of the range of nucleophiles that can be employed, a summary of the reaction types available for allylpalladium species and the diastereo-, regio- and enantio-selectivities of this reaction will be discussed in turn.

## 3.3.2 CHEMOSELECTIVITY

### 3.3.2.1 Precursors to π-Allylpalladium Complexes

#### *3.3.2.1.1 Stoichiometric formation from alkenes*

One of the first significant advances in the chemistry of π-allylpalladium complexes was the discovery that alkenes could be directly converted into the corresponding allyl complex by substitution into the allylic C—H bond. A variety of recipes have now been reported that can accomplish this transformation. Initially, palladium chloride[17–23] or its more soluble forms, sodium or lithium tetrachloropalladate[24–27] and bisacetonitrile palladium dichloride,[28–30] in alcohol or aqueous acetic acid solvent were employed. The use of palladium trifluoroacetate, followed by counterion exchange with chloride, represents the mildest and most effective means available to accomplish this reaction.[31]

This C—H substitution process results in a Markovnikov orientation, with the H that is allylic to the more substituted end of the alkene preferentially abstracted. The stereochemistry of the resulting π-allyl complex does not represent the stereochemistry of the starting alkene, as the complexes are capable of isomerization under the conditions in which they are formed. Typically, a thermodynamic mixture is obtained, with the *syn* form of the complex predominating over the *anti* form (equation 1). The *syn* form is more stable due to unfavorable steric interactions that the *anti* form encounters with the coordination sphere of the palladium.

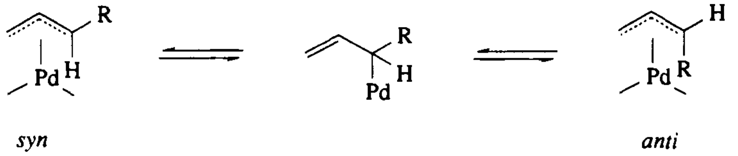

(1)

In addition, the palladium will preferentially position itself on the sterically less demanding face of an allyl system. Both stereoselectivities are neatly demonstrated by reacting either geometric isomer of 2-ethylidenenorpinane (**1**) with $PdCl_2$, where only a single π-allylpalladium complex (**2**) that has a *syn* configuration is observed and has the Pd *trans* to the *gem*-dimethyl bridge (equation 2).[32]

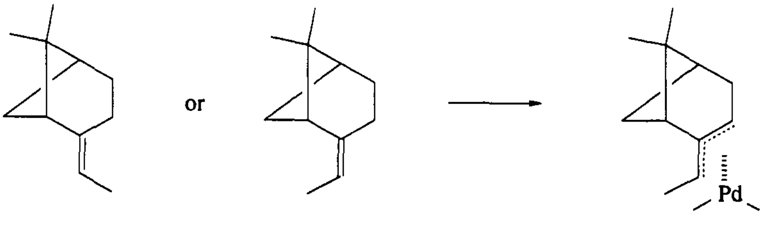

(**1**) (**2**)

(2)

#### *3.3.2.1.2 Stoichiometric formation from other unsaturated precursors*

π-Allylpalladium complexes can also be generated by the addition of $PdCl_2$ to 1,3-dienes,[33–39] allenes,[40,41] vinylcyclopropenes,[42,43] methylenecyclopropanes,[44,45] spirocyclopentanes,[46,47] and cyclopropenes (equations 3–8).[48,49]

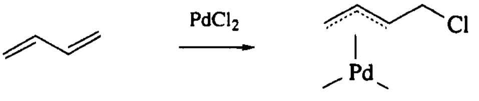

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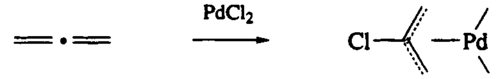

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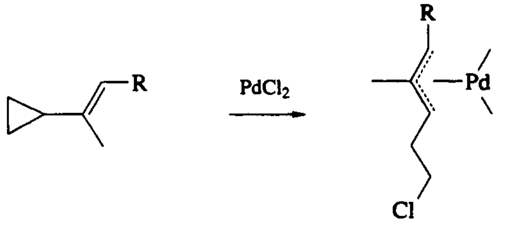

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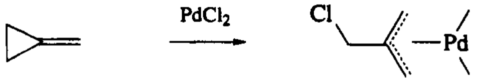

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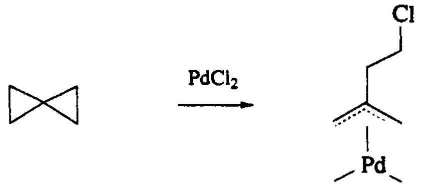

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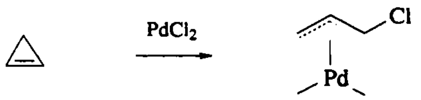

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### 3.3.2.1.3 *Stoichiometric formation* via *addition of alkenyl- and alkynyl-palladium to alkenes*

Alkynyl- or vinyl-palladiums can be generated *in situ* from the corresponding organomercury compounds and added to alkenes to form π-allylpalladium complexes after H-rearrangement (equation 9).[50]

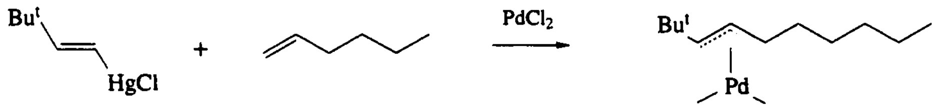

(9)

### 3.3.2.1.4 *Stoichiometric formation* via *addition of palladium complexes to allyl–X substrates*

Allyl halides,[51–63] alcohols,[64] and ethers[65,66] have been converted to their respective π-allyl derivatives by reaction with a $\mathrm{Pd^{II}}$ salt in the presence of a reducing agent. Allyl-silanes[67] and -stannanes[68] have also been found to undergo reaction with lithium palladates in methanol to generate π-allyl chloride dimers.

### 3.3.2.1.5 *Catalytic formation from allyl–X precursors*

The initial investigation of the reactivity of π-allylpalladium complexes generated as their chloride dimers with various nucleophiles indicated that these species were quite limited as electrophiles.[2] In what may be the most significant advance in π-allylpalladium chemistry, it was subsequently noted that the addition of ligands, typically phosphines, dissociated the chloride dimers and greatly enhanced the electrophilicity of the allyl ligand.[2] Importantly, it was further discovered that a ratio of two phosphines per palladium gave optimal performance of the complex as an electrophile.[69–74] This ratio suggested the intermediacy of a bisphosphine cationic complex, with a chloride serving as a counterion (3). The final crucial realization that the same complexes could be generated by reaction of $\mathrm{Pd^0}$ complexes[72] with alkenes allylically substituted with a leaving group, X,[73,74] was the true impetus for the explosive growth in this chemistry as these processes could now be conducted with catalytic, rather than stoichiometric, use of the metal. In this catalytic sequence, the palladium in its zero oxidation state initially acts as a nucleophile, displacing the X leaving group (oxidative addition) with the metal undergoing oxidation to its 2+ state in the process. The cationic metal center activates the allyl ligand to attack by nucleophiles. In the nucleophilic addition, the metal serves as a leaving group (reductive elimination) and returns to its zero oxidation state, thus allowing the process to be catalytic in metal. Catalytic use of Pd in the addition of nucleophiles to allyl intermediates in the dimerization of 1,3-butadiene had previously been observed,[75] but this use did not enjoy the potential generality of that defined by the allyl–X species.

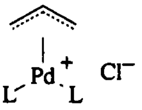

(3)

A wide variety of groups have been found to be capable of serving the role of X in this process, including halogens,[9] esters,[9] alcohols,[9] phosphates,[76] amines,[77] ammonium salts,[78–83] selenides[84] and arsenites.[85] Among this group allyl alcohols and ethers are generally poor actors, and the vast majority of work has been done utilizing allyl esters, principally allyl acetates.

Several new leaving groups have been discovered recently which merit special discussion. Allyl sulfones, surprisingly, function as substrates for palladium catalysis.[86] As the sulfone group had previously been proven to be able to stabilize an adjacent carbanion, this result allowed allyl sulfones now to be considered as synthons for 1,1- and 1,3-dipoles (equation 10). That is, the allyl sulfone can be used alternately as a nucleophile and electrophile, greatly extending its synthetic utility.

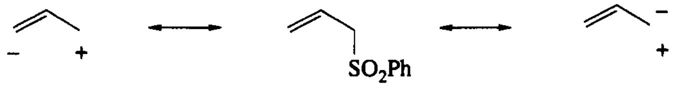

(10)

α-Nitroalkenes have been found to be equivalent to allyl nitro compounds upon treatment with $Et_3N$ and a $Pd^0$ catalyst in DMF.[87,88] The significantly greater availability of the α-nitroalkenes over allyl nitro compounds makes this method of forming π-allyl complexes attractive.

A particularly important advance in the nature of the leaving group, X, used in π-allylpalladium precursors, has been the development of substrates that allow functionalization of the incipient allyl complex under neutral conditions. With these precursors, the leaving group, X, is, or can react further to become, sufficiently basic so as to generate *in situ* $Nu^-$ from Nu—H. In another variation, the X itself is transformed into the nucleophilic partner for the allyl ligand. Examples include vinyl epoxides,[7,9–11] allyl esters of acetoacetate,[7–9,11] allyl carbonates[8,9,11] and carbamates (equation 11).[8,9,11]

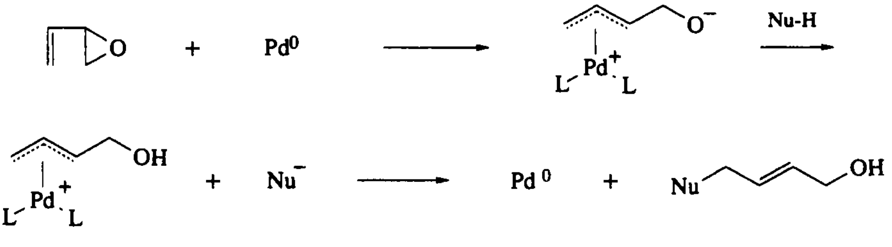

(11)

Although allyl ethers are generally not good actors in the π-allylpalladium reaction, the added relief of ring strain associated with epoxide opening allows vinyl epoxides to become excellent substrates for palladium-mediated processes.[7,9–11] The initially formed alkoxymethylallylbisphosphine cation is capable of deprotonating dimethyl malonate, for example, and then is sufficiently electrophilic to undergo addition by malonate anion on the allyl ligand. The interesting functionality associated with this transformation and the ability to carry it out under neutral conditions has been widely exploited, as reported in the following sections.

Allyl carbonates[8,9,11] serve as excellent substrates with $Pd^0$ catalysts. In this process, the initially formed π-allyl-$PdL_2^+$ RO—$CO_2^-$ undergoes decarboxylation to provide π-allyl-$PdL_2^+$ $RO^-$. The alkoxy group is sufficiently basic to deprotonate *in situ* a number of commonly used Nu—H species. Allyl carbamates react similarly to generate $R_2N^-$ bases *in situ* (equation 12).

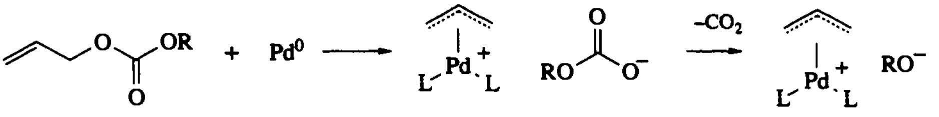 (12)

Allyl esters of acetoacetates[7,8,9,11] react with $Pd^0$ catalysts to generate initially a bisphosphine allylpalladium cation, with the β-ketocarboxylate serving as counterion. Under the reaction conditions the β-ketocarboxylate decarboxylates, yielding a π-allylpalladium ketone enolate complex. The required nucleophile is thus formed *in situ* and is capable of Pd-mediated alkylation. A wide spectrum of reactions have been based on this chemistry which will be discussed in later sections.

Allyl borates,[89] imidates,[90,91] alcohols,[77,92] arsenites[93] and *O*-allylisourea[94,95] have also been found to function as leaving groups that allow neutral functionalization by similar mechanisms, although the chemistry of these compounds has not been widely explored.

A final example of this class of allyl–X compounds is a vinylcyclopropane that is geminally substituted on the three-membered ring with electron withdrawing groups. Upon addition of a $Pd^0$ complex, the allylic C—C bond ruptures, with the stabilized carbanion serving as a leaving group (equation 13).[96] The complex can be independently reacted with electrophiles at the carbanion as well as with nucleophiles on the allyl moiety.

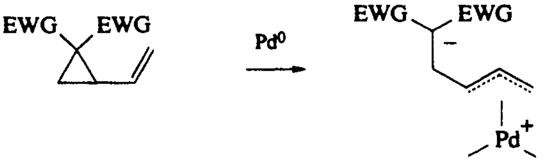 (13)

### 3.3.2.2 Range of Nucleophiles Employed in Palladium-catalyzed Allylic Alkylation

The reactivity of π-allylpalladium–phosphine complexes generated stoichiometrically or from alkenes allylically substituted with a leaving group, is essentially identical and, as a result, allyl species will be generally considered in this section without distinction as to the origin of the palladium complex.

### *3.3.2.2.1 Carbon nucleophiles*

*(i) Soft nucleophiles*

The first examples demonstrating the electrophilicity of π-allyl ligands complexed to Pd involved stabilized 'soft' carbanions, namely the anion of diethyl malonate (equation 14).[97,98] Much of the early work that described the use of carbon nucleophiles in π-allylpalladium chemistry focused on such 'soft' carbanions, which can be generically defined as RCXY, where R = H, alkyl or aryl, and X and Y could be selected from the following list of functionalities known to stabilize adjacent carbanions so as to achieve an acidity of the conjugate acid in the p$K_a$ range of 10–20:[1-16] —$CO_2R^1$, —$C(O)R^1$, —$SR^1$, —$S(O)R^1$, —$SO_2R^1$, —$NO_2$, —CN. Also included in this category are enamines,[1,99,100] the carbanion derived from nitroalkanes[101-104] and the cyclopentadiene anion.[105] Equations (15–18) show examples of their use.

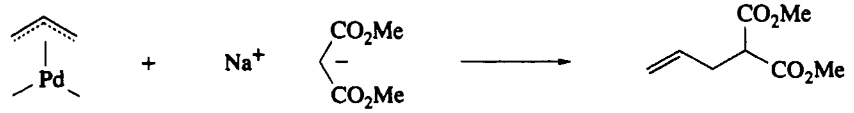 (14)

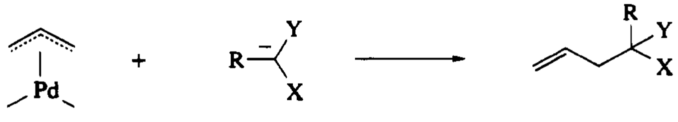 (15)

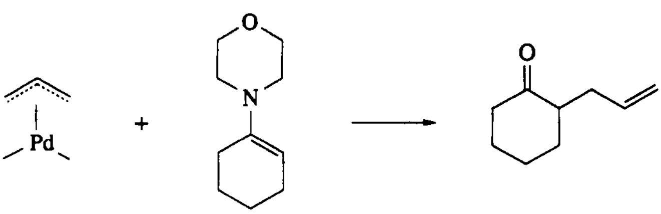

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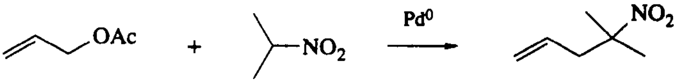

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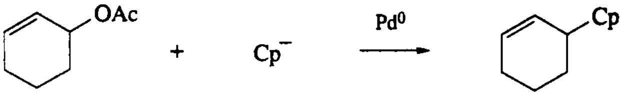

(18)

### *(ii) Enolates*

Initial reports on the use of simple enolates as nucleophiles in π-allylpalladium chemistry met with only limited success.[77,106] The enolate of acetophenone reacted with allyl acetate in the presence of $Pd(PPh_3)_4$, but gave predominantly dialkylated product.[106] The use of the enol silyl ether of acetophenone gave only monoalkylated product with allyl acetate and $Pd^0$ catalysis, but substituted allyl acetates did not function in this reaction.[106] Enol stannanes, however, have been found to give monoalkylated products with a wide variety of allyl acetates (equation 19).[106] *In situ* generation of enol stannanes from lithium enolates and trialkylstannyl trifluoroacetates followed by $Pd^0$-catalyzed allylation has been demonstrated.[107]

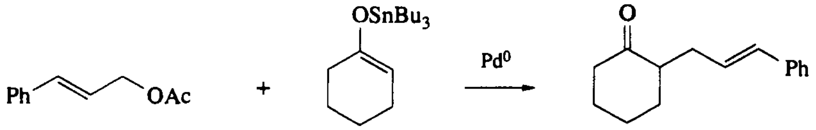

(19)

Similarly, the addition of triethylborane to lithium enolates allowed ready reaction with allyl nitro compounds catalyzed by palladium(0) complexes.[108,109]

The use of bis(dibenzylideneacetonato)palladium and 1,2-bis(diphenylphosphino)ethane as catalyst was reported to allow efficient monoalkylation of lithium enolates of ketones, with allyl acetates.[110] $Pd(PPh_3)_4$ and allylammonium salts have also been reacted successfully with lithium enolates.[80]

The addition of potassium enolates to preformed π-allylpalladium complexes has also been reported.[111]

α-Substituted ketones have also been prepared by the reaction of metallated ketimines with allyl–X compounds catalyzed by $Pd(acac)_2$–$PPh_3$.[79]

The *in situ* generation and alkylation of palladium enolates has gained considerable recent attention. A variety of precursors have been utilized to access the Pd enolate. The first reported use of this intermediate employed an allyl β-ketocarboxylate ester (**4**).[112,113] The suggested mechanism involves oxidative addition into the allylic C—O bond by Pd to yield an allylpalladium β-ketocarboxylate, which subsequently decarboxylates to give an allylpalladium enolate. The enolate then reacts to given an allylated ketone and $Pd^0$ (equation 20). A number of reports on this reaction have appeared,[114–116] including two recent reviews.[8,9,117] Allyl esters substituted in the α-position with esters, nitriles and nitro groups also function in this reaction (equation 21).[118]

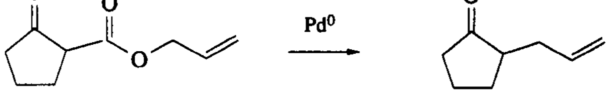

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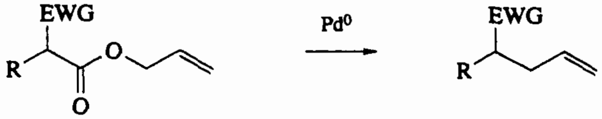

(21)

EWG = $CO_2R'$, CN, $NO_2$

Considerable use has also been made of allyl carbonates as substrates for the allylation of Pd enolates.[9] The reaction of Pd$^0$ complexes with allyl enol carbonates[119,120] proceeds by initial oxidative addition into the allylic C—O bond of the carbonate followed by decarboxylation, yielding an allylpalladium enolate, which subsequently produces Pd$^0$ and the allylated ketone (equation 22). In like fashion, except now in an intermolecular sense, allyl carbonates have been found to allylate enol silyl ethers (equation 23),[121] enol acetates (with $MeOSnBu_3$ as cocatalyst) (equation 24),[122] ketene silyl acetals (equation 25)[123] and anions α to nitro, cyano, sulfonyl and keto groups.[115,124] In these cases, the alkoxy moiety liberated from the carbonate on decarboxylation serves as the key reagent in generating the Pd enolate.

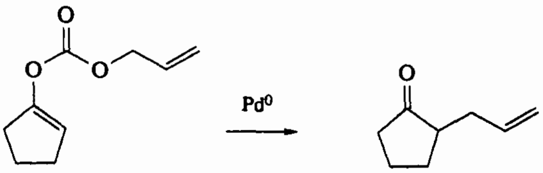

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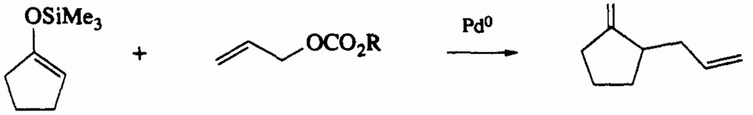

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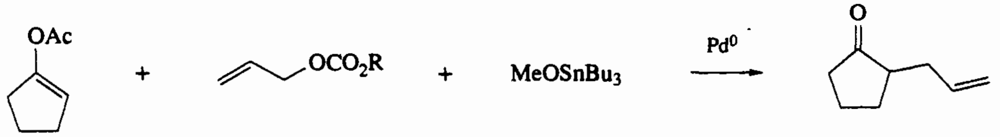

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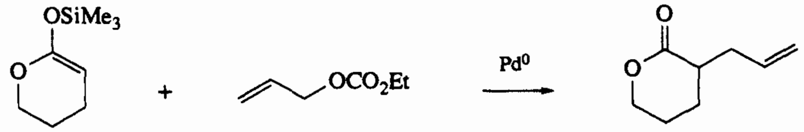

(25)

Allyl carbamates (equation 26)[125] and isoureas (equation 27)[95] generate allylpalladium enolates by virtually identical mechanisms.

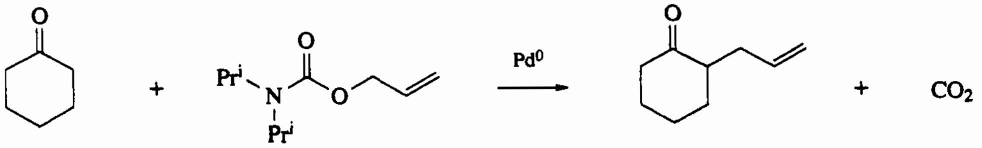

(26)

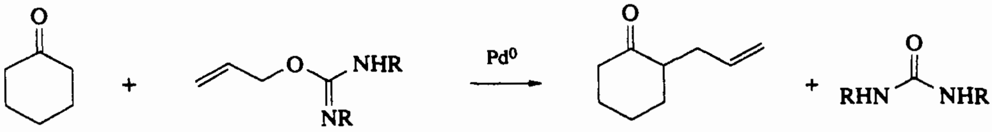

(27)

β-Ketoacids[126,127] form the same intermediates as the allyl β-ketoesters by nucleophilic addition of the carboxylate to a π-allylpalladium complex. Decarboxylation generates the allylpalladium enolate, which again yields Pd$^0$ and allylated ketone. Enol silyl ethers have also been employed with allyl arsenites[93] to provide allylated ketones.

The addition of simple ester or ketoenolates to π-allylpalladium complexes may constitute the second step of an ingenious [3 + 2] cycloaddition reaction. One substrate that undergoes this process is 2-(trimethylsilylmethyl)allyl acetate (**5**). The mechanism proposed involves initial formation of a 2-(trimethylsilylmethyl)allylpalladium cation followed by desilylation by the acetate liberated in the oxidative addition (Scheme 1). The dipolar intermediate can be envisioned as an $\eta^3$-trimethylenemethane–$PdL_2$ species (**6**) or, less likely, an $\eta^4$-complex (**7**).

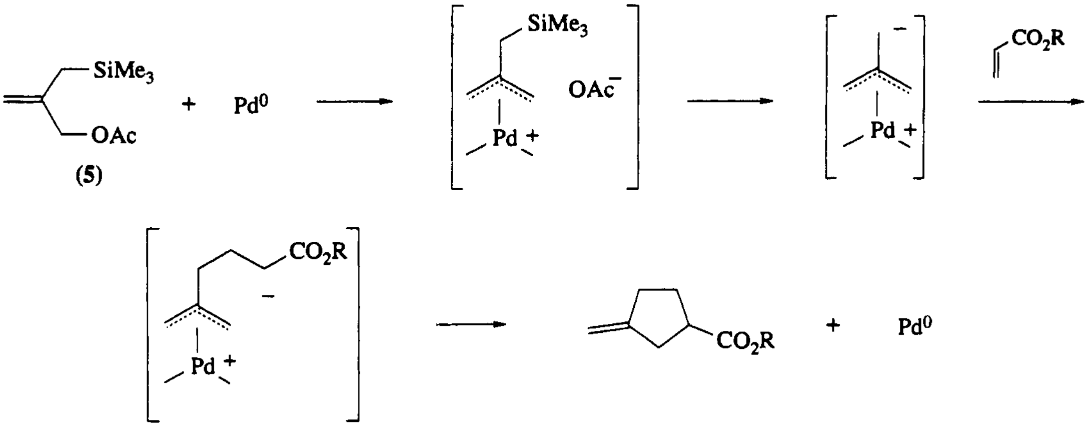

**Scheme 1**

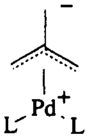

(**6**)

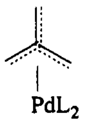

(**7**)

The addition of the trimethylenemethane–palladium complex to alkenes may proceed by a concerted process or *via* a stepwise mechanism in which the anion of the 1,3-dipole attacks Michael-fashion to generate an intermediate anion which collapses to form a five-membered ring by attack on the allylpalladium complex. This [3 + 2] cycloaddition reaction has been reviewed.[128] A number of additional reports of its use have appeared recently.[129–134]

Ethyl-2-(sulfonylmethyl)- and 2-(cyanomethyl)-allyl carbonates[135] as well as (methoxycarbonyl)methylallyl carbonates[136] serve as substrates for the [3 + 2] cycloaddition. Oxidative addition into the allylic C—O bond of the carbonate, followed by decarboxylation, gives a 2-substituted allylpalladium alkoxide. The alkoxide then deprotonates the C—H α to the electron-withdrawing substituent at the 2-position of the allyl. This anion then undergoes a Michael addition to an α,β-unsaturated ketone or ester, followed by intramolecular allylation of the anion of the Michael product (Scheme 2).

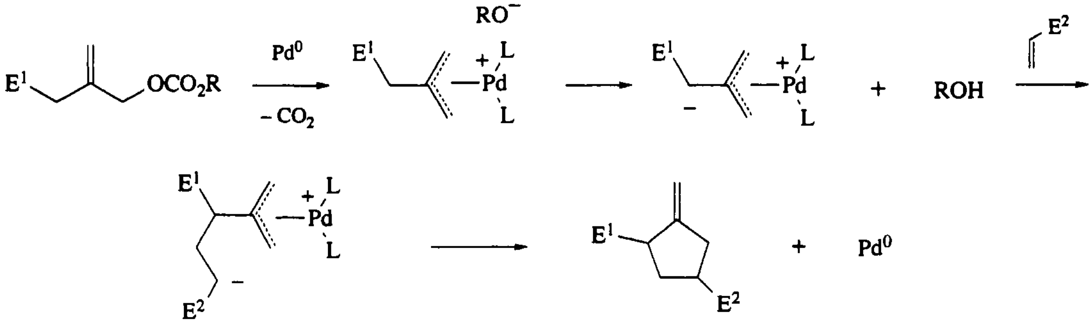

**Scheme 2**

Vinylcyclopropanes having two electron-withdrawing groups geminally substituted on the three-membered ring also have been found to serve as 1,3-dipolar equivalents capable of [3 + 2] cycloadditions.

The enolates of esters or ketones again are envisioned to add to π-allylpalladium intermediates in the second step of the proposed mechanism (Scheme 3).[96]

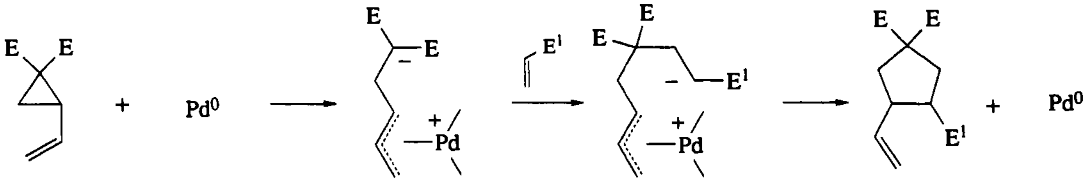

Scheme 3

### (iii) Organotin nucleophiles

The range of nucleophiles that function in π-allylpalladium alkylations encompasses a variety of organotin reagents, including allyl,[137–140] vinyl,[141–143] aryl,[141–144] acetylenyl[144] and heteroaromatic[144–146] stannanes (equations 28–31).

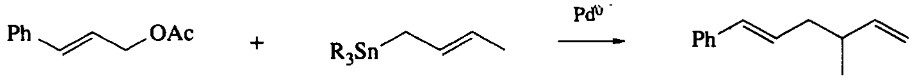

(28)

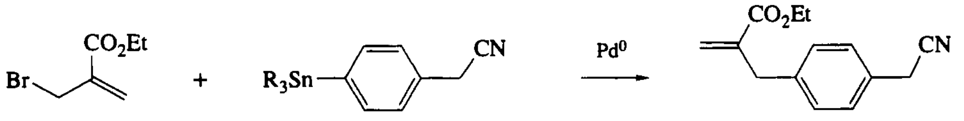

(29)

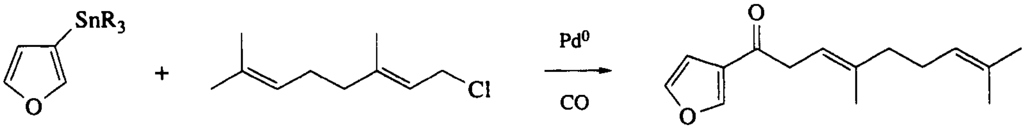

(30)

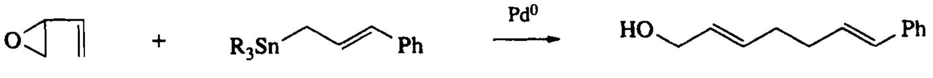

(31)

In the palladium-catalyzed addition of allylstannanes to allyl acetates, complete allyl inversion of the allylstannane is observed.[137] Symmetrical coupling is also possible, for example, by treatment of cinnamyl acetate with hexa-*n*-butyldistannane.[137] In this reaction, cinnamyl tri-*n*-butylstannane is generated *in situ* by Pd catalysis and it then couples with the allyl acetate with allyl inversion (equation 32).

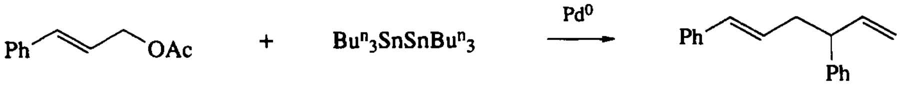

(32)

The mechanism of coupling of allyltin and allylpalladium can be altered by the addition of maleic anhydride to the reaction mixture (*vide infra*).[139] In this modified procedure, reaction of the allylpalladium chloride dimer with allyl-$Bu^n_3Sn$ now gives coupling without allyl inversion of the allyltin reagent.

If the coupling of the allyl halide and tin reagent is run under a CO atmosphere, an allyl R ketone is generated by insertion of CO into the allylpalladium complex, followed by coupling (equation 33).[145–147]

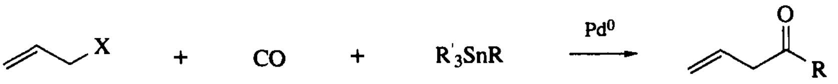

(33)

### (iv) Organo-thallium and -zinc reagents

The π-allyl-σ-arylpalladium–phosphine complexes have been of particular interest in the study of the mechanism of their reductive elimination to yield allylated aromatics.[148,149] Their preparation can be achieved by the addition of a triarylthallium or arylzinc halide to the corresponding allylpalladium phosphino halides (equation 34).

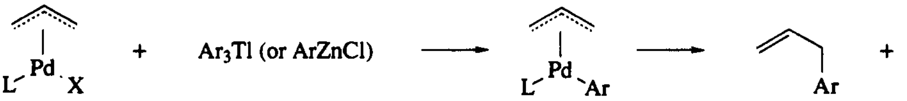

(34)

A variety of additional organozinc-mediated couplings to π-allylpalladium complexes have been reported, including those of perfluoroalkylzinc iodides,[150] vinylzinc bromides,[151] allylzinc acetates[152] and arylzinc bromides (equations 35–37).[153,154]

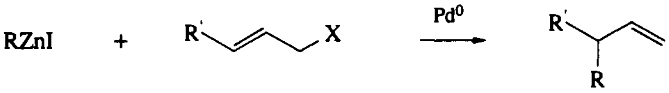

(35)

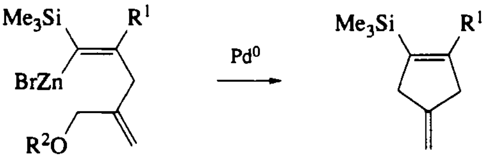

(36)

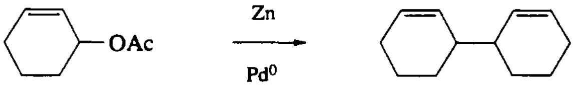

(37)

### (v) Organo-aluminum and -zirconium reagents

Alkenyl-aluminum and -zirconium derivatives have been found to couple with allyl halides in the presence of $Pd^0$ catalysts (equation 38), although simple alkyl-aluminum and -zirconium reagents fail in the reaction.[154] The 1,4-dienes thus generated are important intermediates in organic synthesis.

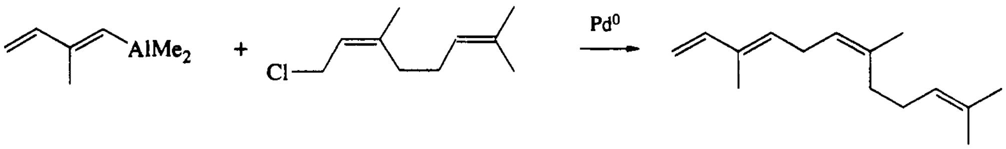

(38)

The coupling of alkenylzirconiums with π-allyl complexes derived from the D-ring of steroids has been demonstrated to be regiospecific and to yield products which possess the natural configuration at C-20 (equation 39).[155]

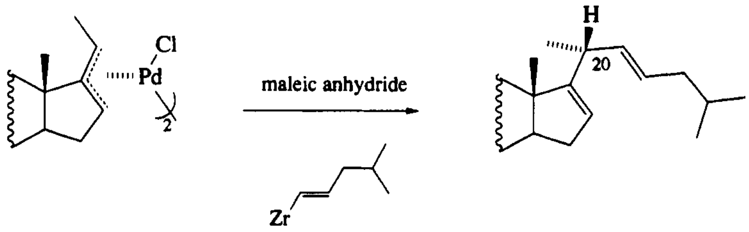

(39)

The effects on coupling efficiency and regiochemical control in nonsymmetrical allyl complexes as a function of added ligand in these reactions has been determined[155,156] (*vide infra*) and applied in the synthesis of flexibilene and humulene.[157]

*(vi) Grignard and organolithium reagents*

Reaction with even harder nucleophiles such as organolithiums and Grignard reagents is substantially limited by virtue of the fact that these carbon nucleophiles add by direct attack at the metal center, as opposed to the softer carbon nucleophiles which add by attack on the allyl ligand. Direct metal addition can lead to the opening of alternative reaction pathways, *e.g.* β-H elimination, in competition with reductive elimination which accomplishes nucleophile allylation (equation 40).

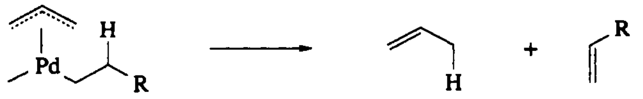

(40)

Successful use of such nucleophiles has been limited to those that are incapable of undergoing these competing reactions, namely, methyl and phenyl organometallics (equations 41–44).[83,158–162]

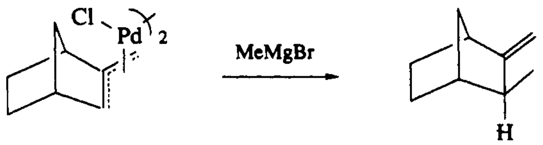

(41)

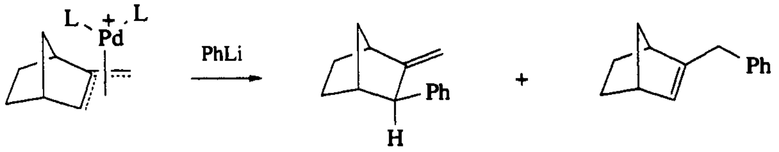

(42)

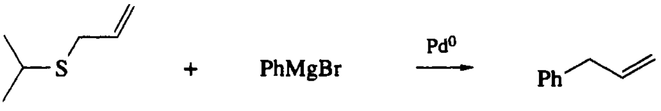

(43)

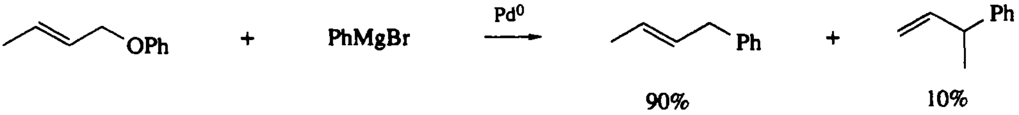

(44)

An interesting reaction in which the initial addition product can be isolated occurs with diallylpalladium and organolithiums (equation 45).[161]

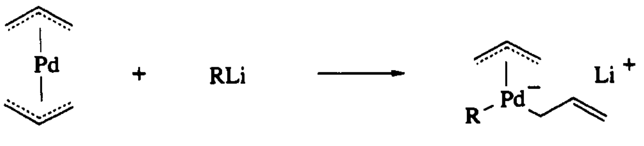

(45)

### *3.3.2.2.2 Heteroatom nucleophiles*

*(i) Oxygen nucleophiles*

Oxygen nucleophiles can be added successfully to π-allylpalladium complexes by various methodologies. Those additions that are fostered by the use of classical oxidizing agents will be treated separately in Section 3.3.2.3.2.

The most intense interest in the addition of oxygen nucleophiles to π-allylpalladium complexes has centered on the delivery of $OAc^-$. For example, in allylpalladium–OAc complexes, acetate can be induced to migrate to the allyl ligand by the addition of CO (equation 46).[162–164] Rearrangements and isomerizations of allyl acetates can also be readily accomplished *via* Pd catalysis (equations 47 and 48).[165–167]

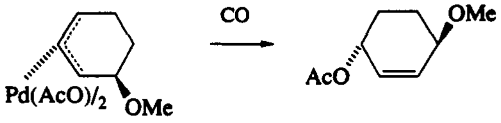
CO
Pd(AcO)/2
OMe
AcO
OMe

(46)

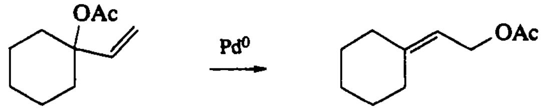

(47)

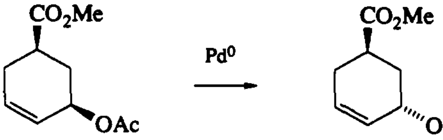
CO2Me
OAc
Pd0
CO2Me
OAc

(48)

Stereocontrol (*vide infra*) can be efficiently engineered in the addition of acetate to π-allylpalladium complexes (equation 49).[168–171] The regioselective addition of acetate of allylpalladium complexes to prepare γ-acetoxy-(*E*)-α,β-unsaturated esters[172] and γ-acetoxy-α,β-unsaturated sulfones has also been achieved (equations 50 and 51).[173,174]

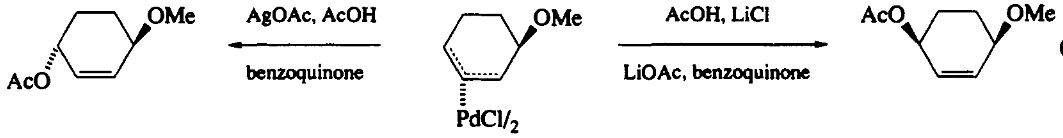
OMe
AcO
AgOAc, AcOH
benzoquinone
OMe
PdCl/2
AcOH, LiCl
LiOAc, benzoquinone
AcO
OMe

(49)

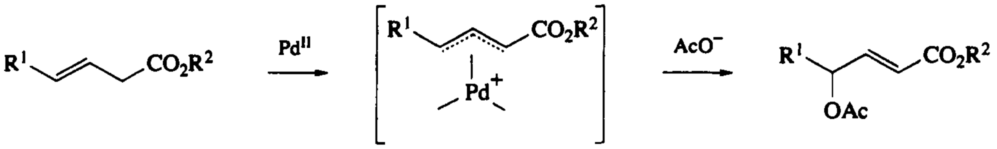
R1
CO2R2
PdII
R1
CO2R2
Pd+
AcO−
R1
CO2R2
OAc

(50)

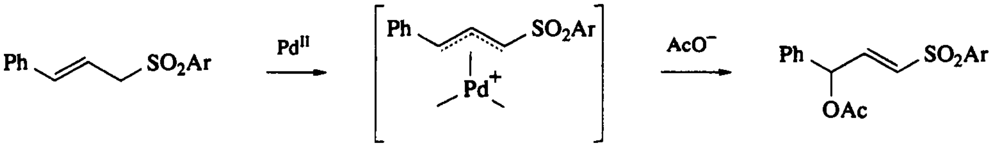
Ph
SO2Ar
PdII
Ph
SO2Ar
Pd+
AcO−
Ph
SO2Ar
OAc

(51)

Other synthetically useful additions of carboxylate anions to π-allylpalladium complexes have been demonstrated, as illustrated in equations (52–54).[175–179] Harder oxygen nucleophiles, such as phenoxides[175,176] and alkoxides,[175–180] can also be added to π-allylpalladium complexes (equation 55). Finally, the addition of $NO_2$ to allylpalladium chloride dimer results in the production of allyl nitrite (equation 56).[181]

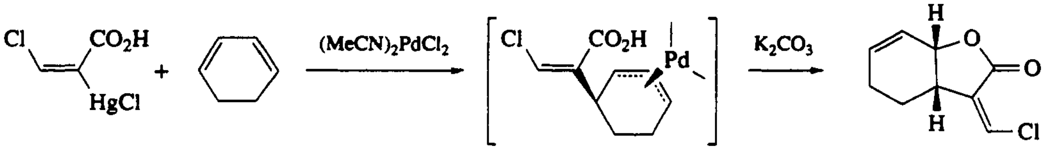
Cl
CO2H
HgCl
+
(MeCN)2PdCl2
Cl
CO2H
Pd
K2CO3
H
O
O
H
Cl

(52)

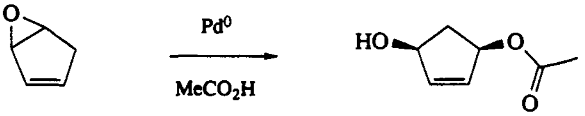
O
Pd0
MeCO2H
HO
O
O

(53)

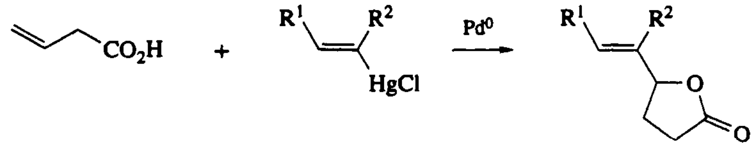
(54)

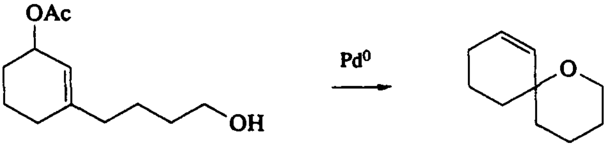
(55)

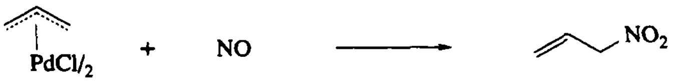
(56)

### (ii) Nitrogen nucleophiles

Ammonia fails to act as an effective nucleophile for π-allylpalladium complexes. Some examples of primary amines[81,181–183] have been reported, although diallylation is often a problem in these reactions. Secondary amines are, however, excellent substrates for palladium-catalyzed allylation.[81,84,181,183–195] Amides,[176,196] sulfonamides,[196,197] azides[198] and magnesium amides[199] have also been shown to be effective nucleophiles.

Due to the failure of ammonia in this reaction, a variety of alternative strategies to prepare primary alkyl amines utilizing Pd catalysis have been investigated.[196–198,200] 4,4′-Dimethoxybenzhydrylamine (DMB; **8**) reacts with allyl acetates under Pd$^0$ catalysis and can be debenzylated with formic acid to yield a primary amine (equation 57).[200] Similarly, *p*-toluenesulfonamides[196,197] and azides can be conveniently converted to amines following their participation in the Pd-catalyzed alkylation.

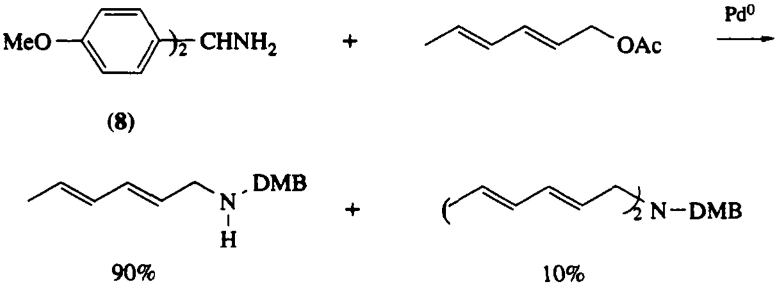
(57)

Some examples of the use of nitrogen nucleophiles as the key step in organic syntheses include the preparation of pyrroles (equation 58),[201,202] a number of alkaloids[203–207] including ibogamine,[204] catharanthine[205,206] and perhydrohistrionicotoxin,[207] amino sugars (equation 59),[208] 5-amino-1,3-pentadienes[209] and 1-azaspirocycles.[210]

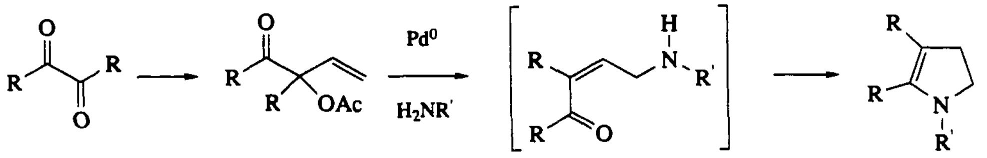
(58)

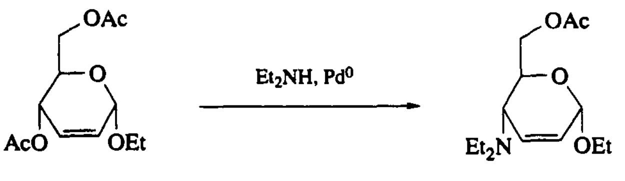
(59)

### *(iii) Other heteroatom nucleophiles*

Sulfur nucleophiles have not been widely used in π-allylpalladium chemistry, principally due to their ability to interfere with the catalyst by coordination. This is a less serious concern for sulfinic acid and sulfinate salts than with sulfides, and as a result, several reports have appeared using $RSO_2H$ and $RSO_2^-$.[211-219] Alkenes allylically functionalized with a leaving group, dienes[214] and vinyl nitro compounds[218,219] have all served as precursors for the required π-allyl species in these reactions (equations 60 and 61).

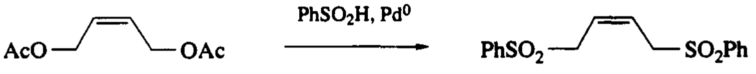

(60)

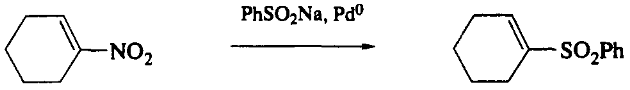

(61)

$Pd^0$ has also been found to catalyze thiono–thiolo allylic rearrangement of *O*-allyl phosphoro- and phosphono-thionates *via* a π-allyl intermediate (equation 62).[220]

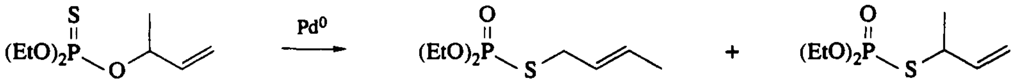

(62)

The use of alkyl sulfides as nucleophiles has been realized by the employment of *O*-allyl *S*-alkylthiocarbonates.[221,222] In this process, oxidative addition by $Pd^0$ is followed by the liberation of COS and generation, *in situ*, of $RS^-$, which subsequently adds to the allylpalladium complex (equation 63).

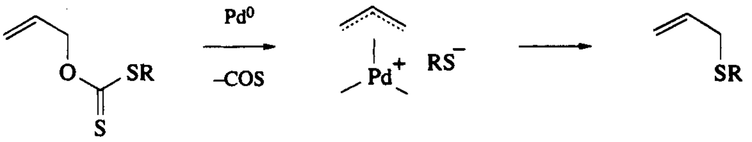

(63)

Trimethylsilyl alkyl and aryl sulfides were found to function as latent sources of a sulfide nucleophile when used in conjunction with allyl carbonates or vinyl epoxides with Pd catalysts (equation 64).[223]

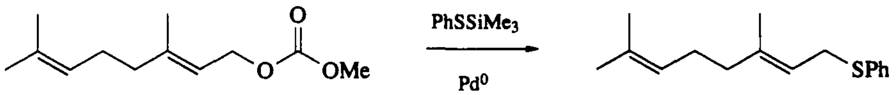

(64)

The addition of phosphites to allyl halides catalyzed by $Pd^0$ has been found to yield alkyl phosphonates (equation 65).[215]

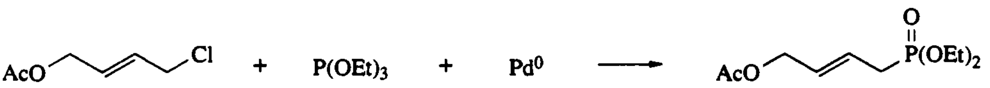

(65)

An additional example utilizing phosphorus nucleophiles employs lithium diphenylthiophosphides and allyl carboxylates and yields allylic diphenylphosphine sulfides (equation 66).[224]

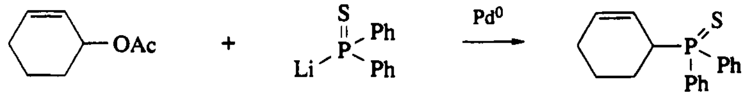

(66)

Palladium(0) catalysts can also function to transfer trimethylsilyl groups from aluminum to carbon *via* π-allyl intermediates (equation 67).[225]

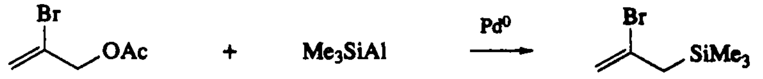
(67)

### (iv) Transition metal nucleophiles

Acyliron anionic complexes, such as, $MeCOFe(CO)_4^- Li^+$, and anionic acylnickel carbonyl complexes, $RCONi(CO)_x^- M^+$, react with allylpalladium complexes to give unsaturated ketones (equations 68 and 69).[226]

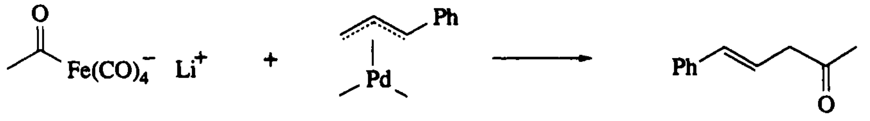
(68)

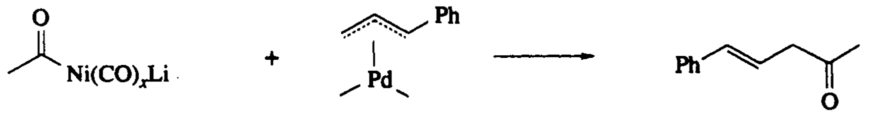
(69)

$NaCo(CO)_4$ was found to carboalkoxylate allylic acetates with $Pd^0$ catalysts under a CO atmosphere (equation 70).[226]

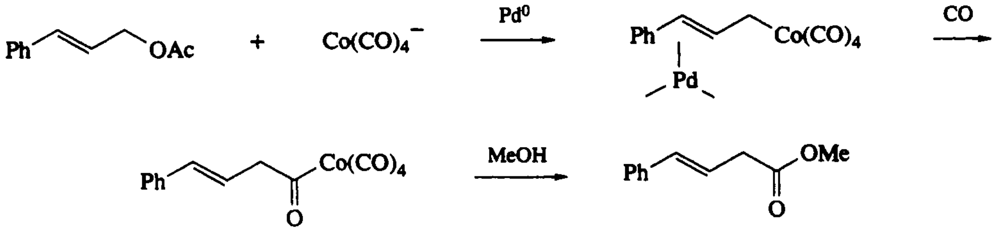
(70)

## 3.3.2.3 Other Reactions of π-Allylpalladium Complexes

### 3.3.2.3.1 Insertion into π-allylpalladium complexes

The insertion of CO into π-allylpalladium complexes has been used to prepare various β,γ-unsaturated carboxylic acid derivatives. The process can be initiated from preformed allyl complexes,[227–235] catalytically from appropriate π-allyl precursors[228,229,236,237] or from diene–Pd complexes.[238,239] Particularly mild conditions, involving low pressures and temperatures, to accomplish this insertion have been discovered.[235] The key reagent in allowing these mild conditions to be employed was found to be carboxylate anions.[235] For unsymmetrical allyl complexes, CO insertion occurs preferentially at the less-substituted allyl terminus (equations 71–73).

Isocyanides react similarly with π-allylpalladium complexes to generate β,γ-unsaturated iminoethers.[240–243] Comparable to the CO reaction, isocyanide insertion occurs preferentially in the less

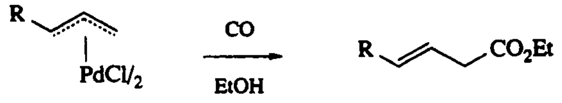
(71)

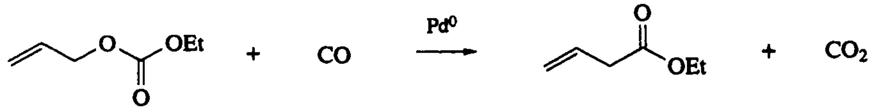
(72)

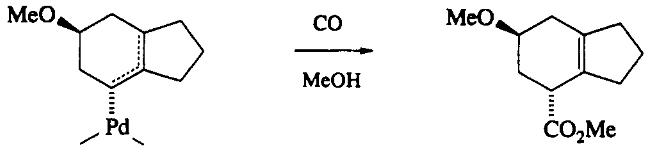
MeO
Pd
CO
MeOH
MeO
CO2Me
(73)

substituted allyl terminus (equation 74). $CO_2$[243–245] and $SO_2$[245] also insert efficiently into π-allylpalladium complexes (equations 75 and 76).

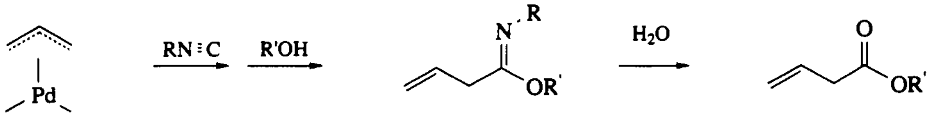
Pd
RN≡C
R'OH
N
R
OR'
H2O
O
OR'
(74)

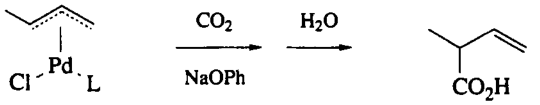
Pd
Cl
L
CO2
NaOPh
H2O
CO2H
(75)

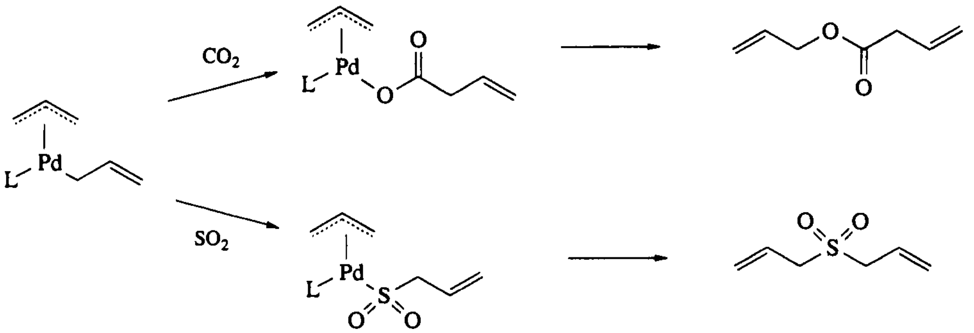
CO2
Pd
L
O
O
O
O
Pd
L
SO2
Pd
L
S
O
O
O
O
S
(76)

The insertion of 1,3-dienes into a π-allylpalladium complex is believed to proceed *via* an intermediate in which the metal is complexed to the less hindered double bond of an unsymmetrical diene, followed by an electrocyclic rearrangement which links the more substituted allyl terminus with the more substituted alkene (equation 77).[246–251] Electron-withdrawing substituents on the π-allyl fragment generally increase the rate of insertion,[248] whereas substituents on the diene generally slow the rate.[268]

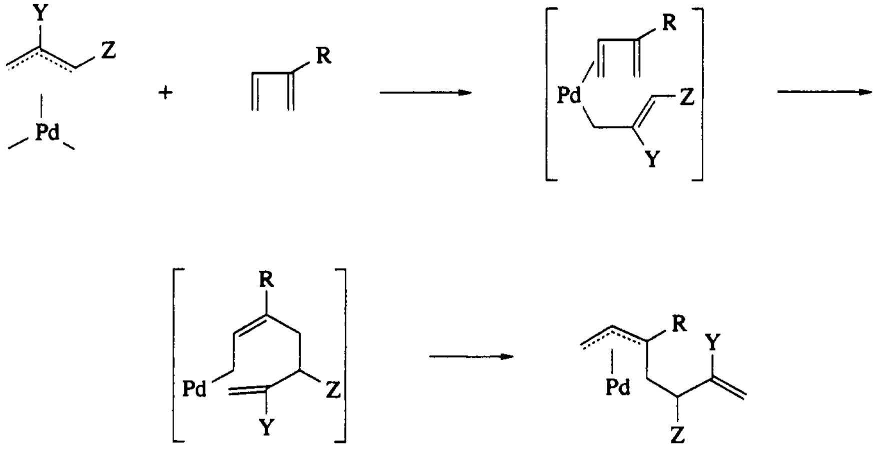
Y
Z
Pd
+
R
R
Pd
Z
Y
R
Pd
Z
Y
R
Y
Pd
Z
(77)

Allenes insert into π-allyl complexes so as to generate new π-allyl species (equation 78).[248]

The insertion of 2-*t*-butyl-1,3-butadiene into π-allylpalladium complexes proceeds normally, but is then followed by an unusual cyclization reaction, presumably due to the disposition of the butenyl frag-

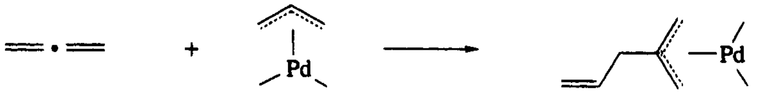

(78)

ment in the *anti* configuration, caused by the preferential positioning of the *t*-butyl in the *syn* site (equation 79).[251]

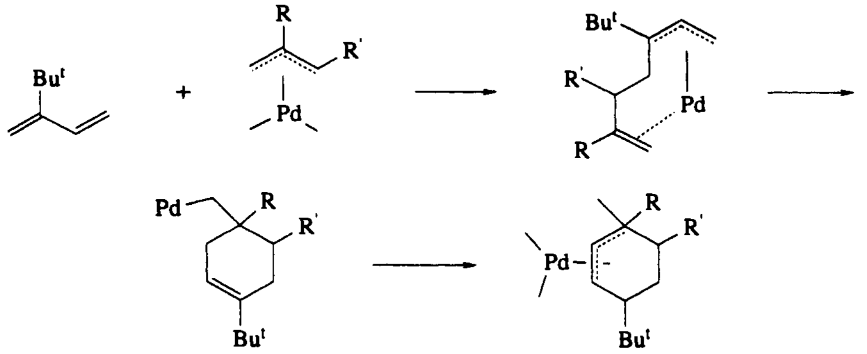

(79)

α-Dienyl-ω-allyl acetates cyclize by isomerization. The key step in this process entails insertion of a 1,3-diene into a π-allyl fragment (equation 80).[252]

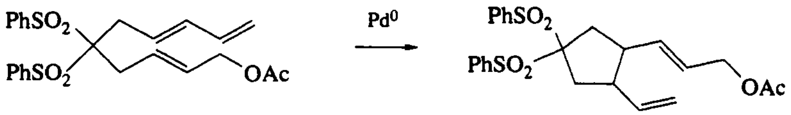

(80)

Strained alkenes such as norbornene, norbornadiene and bicyclo[2.2.2]octenes readily insert into π-allyl complexes with the less substituted allyl terminus linked to the alkene (equation 81).[253–261] This reaction has been utilized to prepare interesting prostaglandin analogs.[253,254]

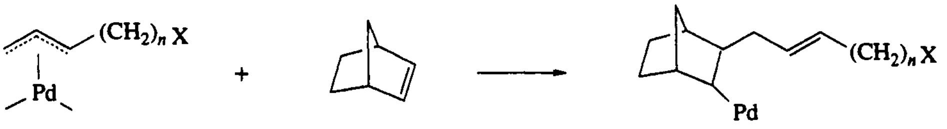

(81)

Intramolecular insertion of a simple alkene into a π-allyl complex has also been demonstrated, resulting in synthetically useful cyclization methodologies (equations 82 and 83).[262,263]

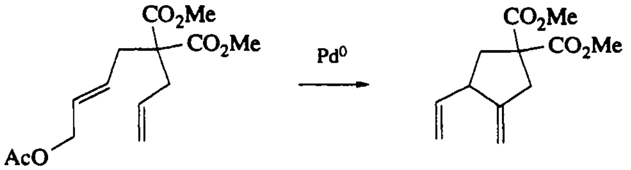

(82)

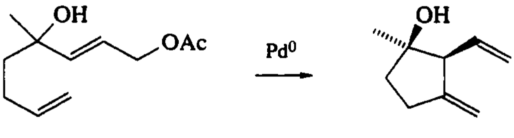

(83)

The course of the insertion of diphenylketene into π-allylpalladium intermediates has been found to depend on the nature of the π-allyl precursor. Allyl acetates give dienes, while allyl carbonates give carboxymethylated products (equations 84 and 85).[264] An intermediate allyl Pd—OR species (**9**) is believed to exist in both cases. When R = Ac, decarbonylation is followed by β-H elimination, whereas if R = Me, alkoxide attacks the acylpalladium intermediate and yields the methoxycarbonyl compound.

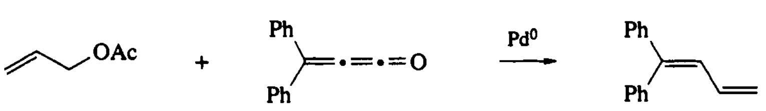
OAc
+
Ph
Ph
O
Pd⁰
Ph
Ph

(84)

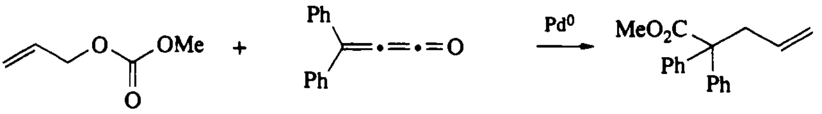
O
OMe
O
+
Ph
Ph
O
Pd⁰
MeO₂C
Ph
Ph

(85)

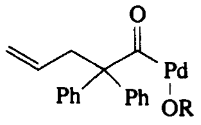

**(9)**

Finally, the reaction of hydrazones with π-allylpalladium complexes may involve insertion of C═N into the allyl ligand.[265,266]

### 3.3.2.3.2 *Oxidation of π-allylpalladium complexes*

Treatment of π-allylpalladium complexes with excess $PdCl_2$,[267–270] or $MnO_2$[267] results in the formation of α,β-unsaturated ketones or aldehydes (equation 86).

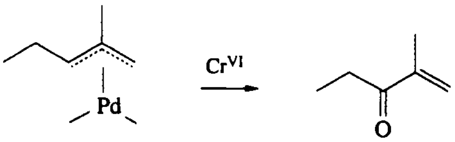

(86)

π-Allyl complexes derived from steroidal substrates have been found to undergo oxidation to allylic alcohols with MCPBA (equation 87).[271,272] Similarly, treatment of preformed allyl complexes with lead tetraacetate[273] or mercury(II) chloride in acetic acid[274] provides the corresponding allyl acetate.

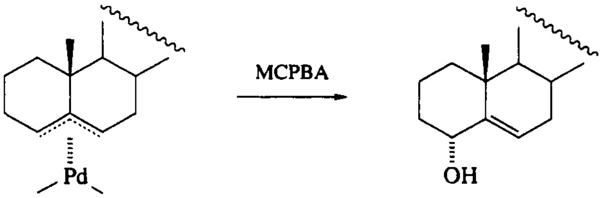

(87)

A $MoO_2(acac)_2$–$Bu^tO_2H$ reagent has been shown to yield mixtures of allyl alcohols and α,β-unsaturated ketones on reaction with π-allyl species (equation 88).[275] Photo-oxidation of preformed allyl complexes has also been reported (equation 89).[276,277]

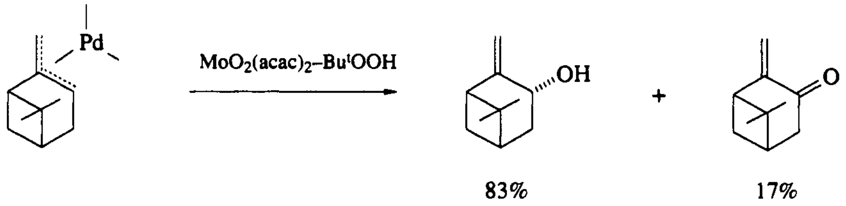
Pd
MoO₂(acac)₂–BuᵗOOH
OH
+
O
83%
17%

(88)

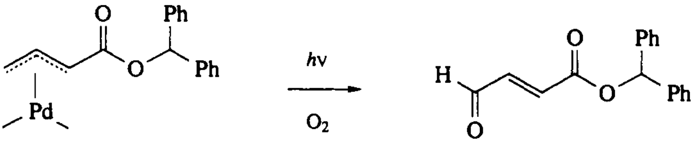
O
Ph
O
Ph
Pd
hv
O₂
H
O
O
Ph
O
Ph

(89)

### *3.3.2.3.3 Reduction of π-allylpalladium complexes*

Basic alcohol solutions have been found to be capable of reducing π-allylpalladium complexes to the corresponding alkene (equations 90 and 91).[278–283] In similar fashion, aqueous NaOH media has been reported to effect a disproportionation of the allylpalladium chloride dimer (equation 92).[284]

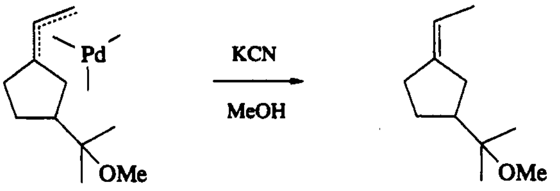
Pd
OMe
KCN
MeOH
OMe

(90)

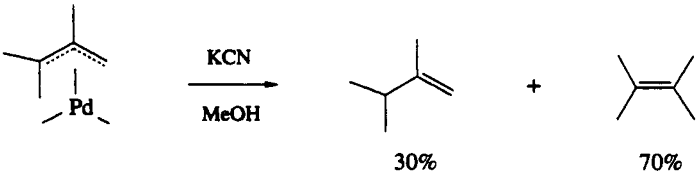
Pd
KCN
MeOH
+
30%
70%

(91)

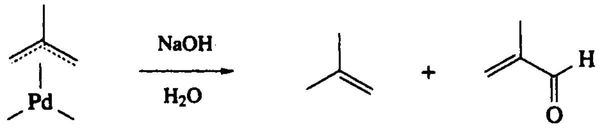
Pd
NaOH
$H_2O$
+
H
O

(92)

A variety of metal hydride reducing agents can also function in this reaction. Sodium borohydride, for example, has demonstrated good regioselectivity, with preferential delivery of the hydride to the less substituted allyl terminus (equation 93).[285–287] Allyl sulfones are substituted by hydride under Pd catalysis and treatment with $NaBH_4$ (equation 94).[288,289] Sodium cyanoborohydride functions in like manner.[290]

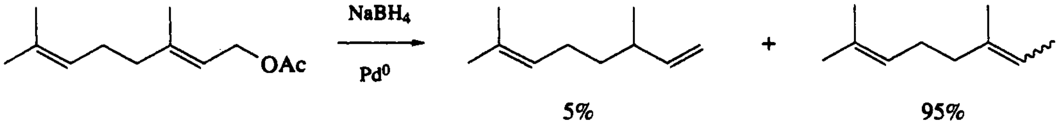
OAc
$NaBH_4$
$Pd^0$
+
5%
95%

(93)

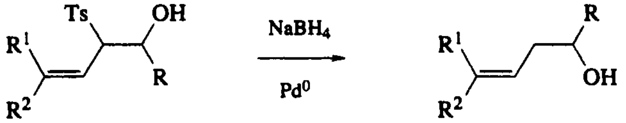
Ts
OH
$R^1$
R
$R^2$
$NaBH_4$
$Pd^0$
R
$R^1$
OH
$R^2$

(94)

$LiBHEt_3$ has been found to reduce allylic ethers, carboxylates, sulfides, sulfones, selenides and silyl ethers (equations 95 and 96).[291]

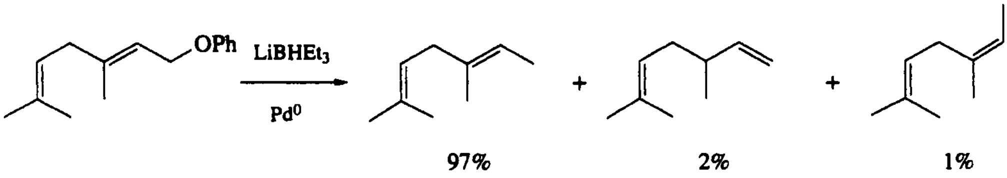
OPh
$LiBHEt_3$
$Pd^0$
+
+
97%
2%
1%

(95)

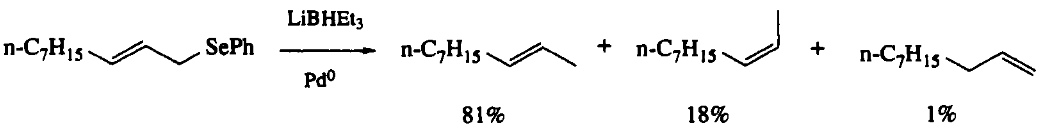
$n\text{-}C_7H_{15}$
SePh
$LiBHEt_3$
$Pd^0$
$n\text{-}C_7H_{15}$
+
$n\text{-}C_7H_{15}$
+
$n\text{-}C_7H_{15}$
81%
18%
1%

(96)

Steroidal π-allylpalladium complexes are reduced by $LiAlH_4$ with high regio- and stereo-selectivity (equation 97).[292] Similar results were found with $LiAlH(OBu^t)_3$.[293]

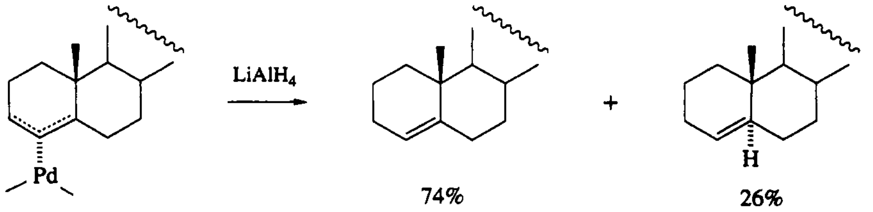

Pd
LiAlH4
+
H
74%
26%

(97)

Considerable work has been done with trialkyltin hydride reducing agents.[287,294–299] These reagents are relatively mild in their reducing properties with respect to typical organic functionalities, yet function well with π-allylpalladium complexes, thereby allowing considerable chemoselectivity to be exercised. For example, allylic acetates and amines are reduced regioselectively with tri-*n*-butyltin hydride under $Pd^0$ catalysis (equation 98).[287] Vinyl chlorides and acetates have been prepared from the corresponding allyl *gem*-dichlorides and diacetates using this methodology (equations 99 and 100).[297,298]

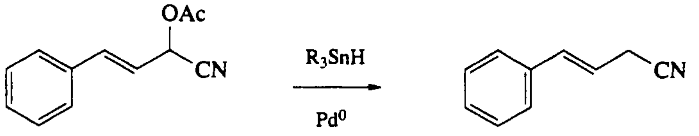

OAc
CN
R3SnH
Pd0
CN

(98)

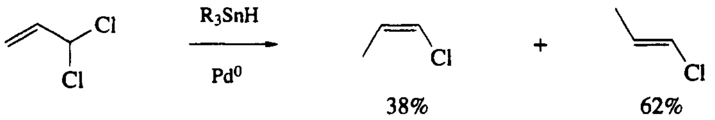

Cl
Cl
R3SnH
Pd0
Cl
+
Cl
38%
62%

(99)

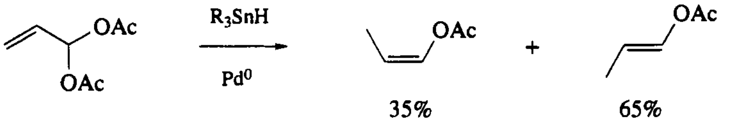

OAc
OAc
R3SnH
Pd0
OAc
+
OAc
35%
65%

(100)

Allyl carbonates can function as protecting groups for alcohols, with removal of the protecting group being effected by $R_3SnH$ and $Pd^0$ (equation 101).[299]

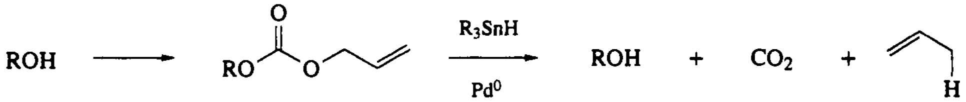

ROH
O
RO
O
R3SnH
Pd0
ROH
+
CO2
+
H

(101)

Tetra-substituted tin enolates of ketones, which are otherwise difficult to prepare, can be formed *via* Pd-catalyzed tin hydride reduction of allyl β-ketocarboxylates (equation 102).[294] Allyl β-ketocarboxylates can also be transformed into α-bromo ketones using this method (equation 103).[296]

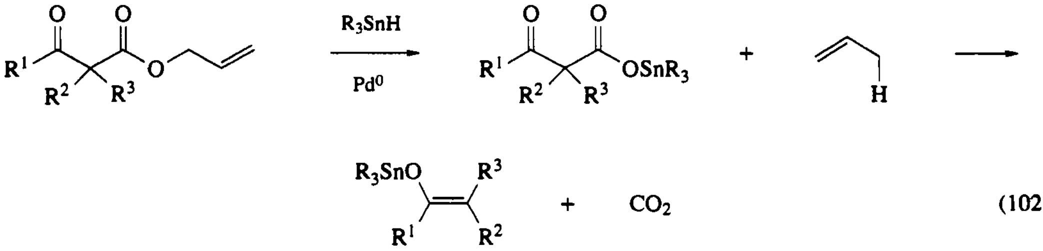

O
O
R1
R2
R3
O
R3SnH
Pd0
O
O
R1
R2
R3
OSnR3
+
H
R3SnO
R3
R1
R2
+
CO2

(102)

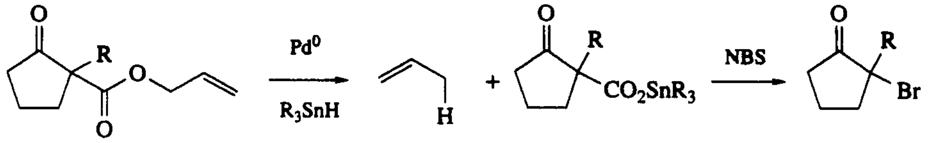
(103)

Polymethylhydrosiloxane (PMHS) has been reported to be a more selective reducing agent when coupled with $Pd^0$ catalysts than $R_3SnH$, permitting, for example, the reduction of allylic acetates in the presence of enones and acyl halides (equation 104).[300]

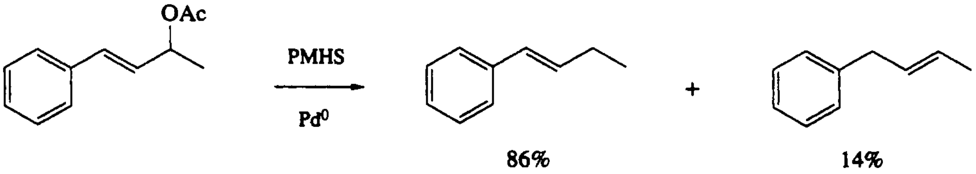
(104)

Formic acid and formate salts are also effective reducing agents for π-allylpalladium complexes (equation 105).[301-303]

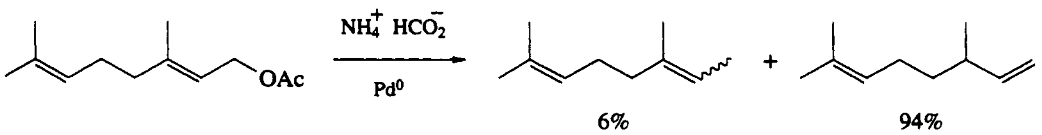
(105)

Two-phase systems utilizing water-soluble palladium phosphine catalysts, formate and allyl chlorides or acetates have also been developed.[303]

Allyl carboxylates can serve as protecting groups for acid functionalities removable by formate and $Pd^0$.[302]

Alkylzinc compounds bearing β-hydrogens reduce allyl acetates on treatment with $Pd^0$ (equation 106).[304]

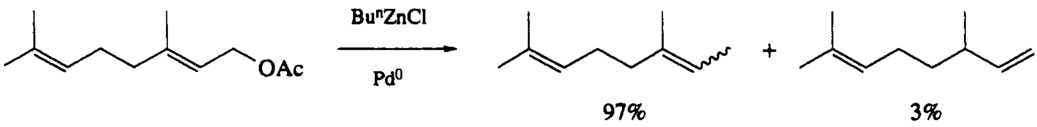
(106)

Allyl acetates can also be reduced by $Pd^0$ catalysts in conjunction with samarium iodide,[305] model NAD(P)H compounds[306] and under electrochemical conditions (equations 107 and 108).[307]

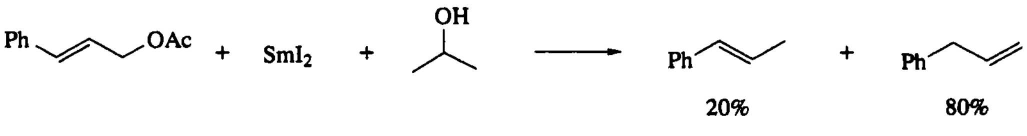
(107)

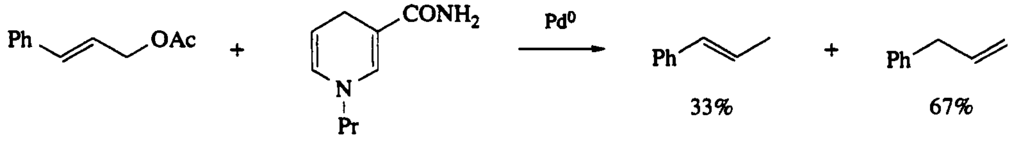
(108)

Finally, dimethylglyoxime has been reported to reduce allylpalladium complexes.[308]

### *3.3.2.3.4 Umpolung of π-allylpalladium complexes*

The reversal in mode of reactivity or umpolung of π-allylpalladium complexes can be accomplished by two strategies. The first involves conversion of the π-allyl species to an allyl–M species, where M is a metal which will impart nucleophilic character to the allyl fragment, in contrast to the normal electrophilicity of the Pd species. Transfer of the allyl moiety from palladium to tin accomplishes such an umpolung, and can be achieved by the reaction of allyl acetates with $Et_2AlSnBu_3$,[309] allyl phosphonates with $Bu_3SnLi$ and $Et_2AlCl$,[310] allyl acetates with $Bu_3SnCl$ and $SmI_2$[311] or allyl acetates with $Sn_2^+$ salts,[312] all catalyzed by $Pd^0$ (equations 109–112). The tin is normally bonded at the less substituted allyl terminus as a result of these reactions.

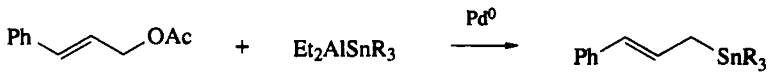
(109)

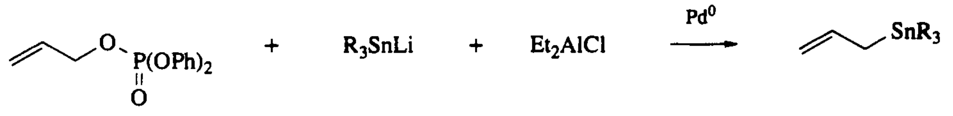
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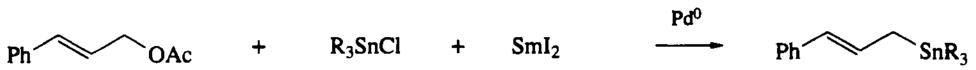
(111)

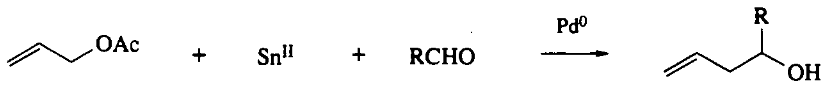
(112)

An analogous process, which provides a nucleophilic allylsilane, has been reported, employing $(Me_3Si)_3Al$ etherate in conjunction with allyl acetates and $Pd^0$ (equation 113).[225]

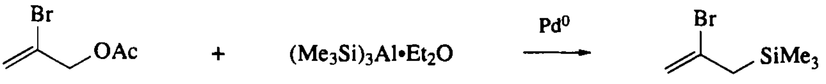
(113)

The conversion of allyl acetates into nucleophiles has also been accomplished by treatment with $Pd^0$ catalysts and $SmI_2$,[305–313] Zn[314] or by electrochemical means (equations 114–116).[307–315]

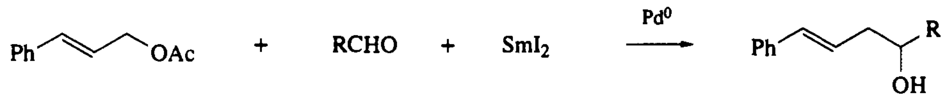
(114)

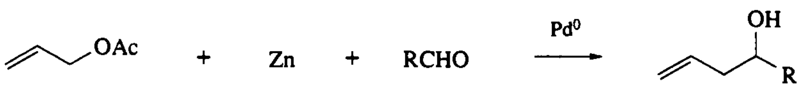
(115)

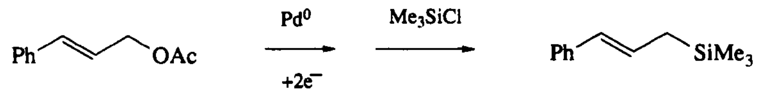
(116)

An alternative strategy for the conversion of allylpalladium species from electrophiles to nucleophiles entails transformation from an $\eta^3$-allyl to an $\eta^1$-allyl. Although often implicated as an intermediate in allylpalladium reactions, there are only a very limited number of characterized, structurally rigid $\eta^1$-allyl complexes available. One such complex is an $\eta^1$-allylarylphosphinepalladium.[316,317] Interestingly, the $\eta^1$-species behaves as a nucleophile and reacts readily with a variety of electrophiles, including electron deficient alkenes (equations 117 and 118).[317]

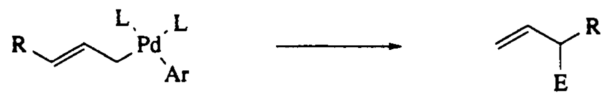
(117)

HCl, E = Cl; $Br_2$, E = Br; NBS, E = Br; $CCl_4$, E = $CCl_3$; $HCCl_3$, E = $HCCl_2$

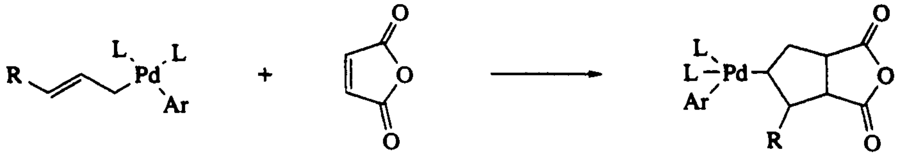

(118)

Diallylpalladium complexes derived from the dimerization of butadienes have been isolated and found to contain both an $\eta^3$- and an $\eta^1$-allyl unit. Although it is difficult to discern which allyl moiety is reacting, treatment of this complex with acetylenedicarboxylate or DOAc yields products consistent with nucleophilic participation by the $\eta^1$-fragment (equations 119 and 120).[318,319]

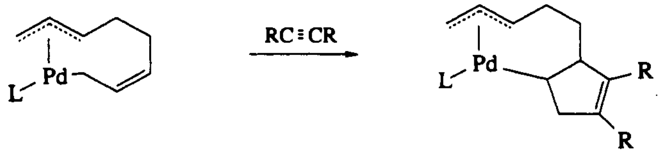

(119)

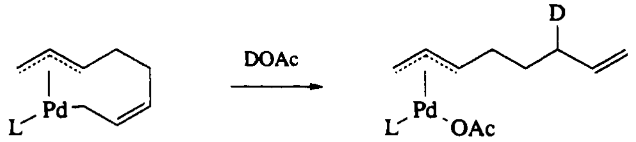

(120)

A likely explanation for the nucleophilicity induced by CN$^-$ in a cyclooctenylallyl complex is its *in situ* conversion to an $\eta^1$-allylpalladium (equation 121).[320]

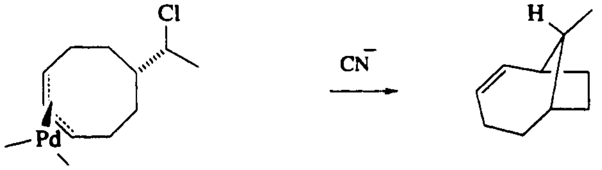

(121)

Dicarbonates of enediols have been converted to conjugated dienes on treatment with Pd$^0$ catalysts. Nucleophilic displacement of the allyl carbonate by an $\eta^1$-allyl complex may be responsible (equation 122).[321]

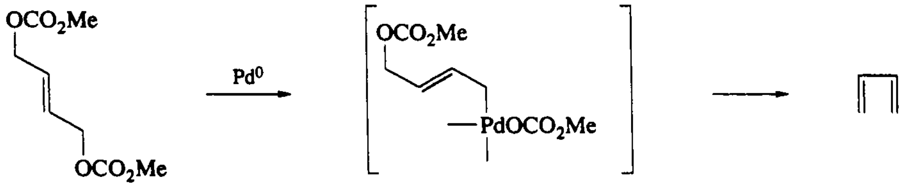

(122)

### 3.3.2.3.5 *Transformation of π-allylpalladium complexes to dienes*

Two methodologies for the conversion of π-allylpalladium complexes to dienes have been elucidated. The first, and most extensively studied, is the induced elimination of a β-hydrogen. Although π-allyl complexes are significantly less susceptible to the loss of a β-H than σ-alkylpalladium complexes, the loss can be accomplished from preformed π-allylpalladium complexes by thermolysis[322,323] or catalytically from allyl–X species by treatment with a weak base. The mild conditions that can be employed in the latter case allow preclusion of isomerization of the alkene into conjugation with a carbonyl[324] or aromatization of a generated cyclohexadiene (equations 123 and 124).[324]

Examples of this process have also been provided with steroidal substrates[325] (equation 125).

An interesting series of transformations have been reported which demonstrate a variety of selectivities of organopalladium chemistry. 1,3-Dienes can be regioselectively functionalized in a 1,4-fashion

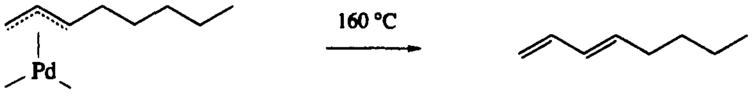
(123)

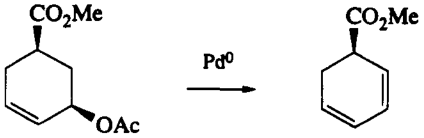
(124)

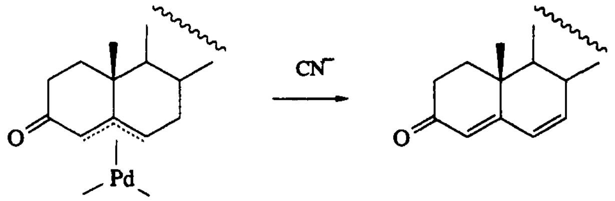
(125)

with $Pd^{II}$ catalysts and $Cl^-$ and $OAc^-$. The resulting alkene can be treated with $Pd^0$, and oxidative addition occurs selectively into the allyl C—Cl bond. The addition of a nucleophile gives exclusive attack remote from the OAc group. Further reaction with $Pd^0$ then ionizes the allyl acetate, and $Et_3N$ induces β-H elimination to provide a nucleophilically substituted 1,4-diene (Scheme 4).[215]

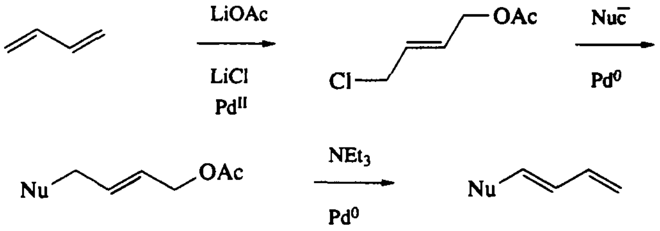

**Scheme 4**

The final step in the Pd-catalyzed reaction of diphenyl ketenes and allyl acetates (Section 3.3.2.3.1) involves β-H elimination to generate a diene (equation 126).[264]

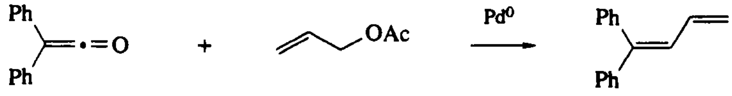
(126)

Vinyl epoxides have been found to eliminate a β-H on treatment with $Pd^0$ in the absence of nucleophiles. Acyclic vinyl epoxides give dienols, whereas cyclic vinyl epoxides yield β,γ-unsaturated ketones (equations 127 and 128).[326] Additional examples of β-H elimination of allylpalladium complexes to generate dienes have been reported.[327–332]

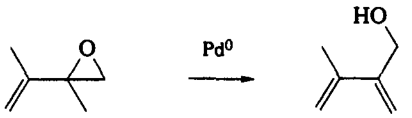
(127)

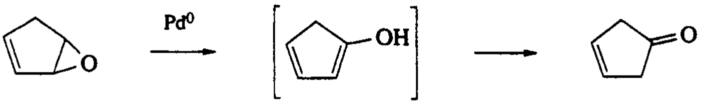
(128)

The second methodology that has been developed features a decarboxylation rather than a β-H elimination. This process gave exclusive formation of (*E*)-isomers from mixtures of diastereomeric starting materials (equation 129).[333]

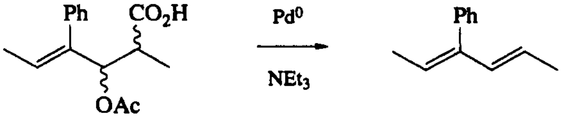

(129)

### 3.3.2.3.6 Photochemistry of π-allylpalladium complexes

The photochemistry of π-allylpalladium complexes has been studied to a limited extent. Two basic reactions have been observed. Irradiation at 366 nm of π-allylpalladium complexes produced 1,5-diene dimers, reportedly *via* a radical coupling mechanism.[334,335] Similar irradiations in the presence of species capable of trapping the presumed allyl radical intermediate, such as $BrCCl_3$, $BrCH_2Ph$ or allyl bromide, now yield alkylated and halogenated allyls, in addition to 1,5-diene dimer. This reaction fails for simple alkyl or aryl halides due to the instability of the associated radical (equations 130 and 131).[336]

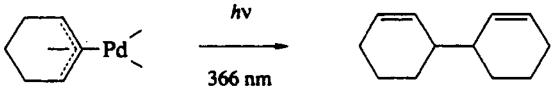

(130)

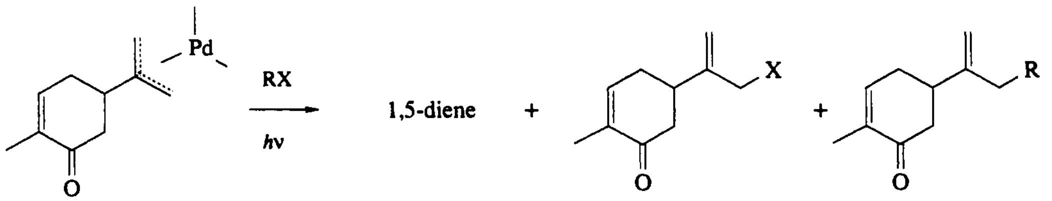

(131)

### 3.3.2.3.7 Addition reactions to π-allylpalladium complexes

π-Allylpalladium complexes can undergo reactions with weak σ-bonds which formally appear to result from addition to the metal, followed by coupling to the allyl fragment. The reaction of methyl- and chloromethyl-disilanes, $Me_nSi_2Cl_{6-n}$, $n = 2–6$, exemplifies the process. Treatment of, for example, hexamethyldisilane, allyl chloride and a $Pd^0$ catalyst produces allyltrimethylsilane and chlorotrimethylsilane as products. When unsymmetrical chloroalkyldisilanes were employed, the predominant product originated from the more highly chlorinated silicon moiety transferring to the allyl group. Unsymmetrical allyls position the silyl group at the less substituted terminus (equation 132).[337–339]

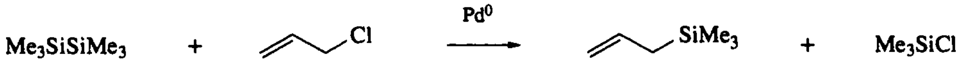

(132)

Hexamethyldistannane reacts with allyl acetates or halides in a similar fashion.[340,341] Again, the trialkylstannane will preferentially couple to the less substituted allyl terminus (equation 133).

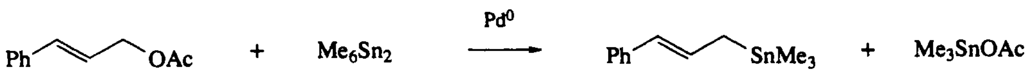

(133)

Both of these methods could be included as examples of umpolung of π-allyl species, as the electrophilic allylpalladium has now been transformed into a nucleophilic allyl moiety. Finally, $Br_2$ can also be added to π-allylpalladium complexes (equation 134).[342]

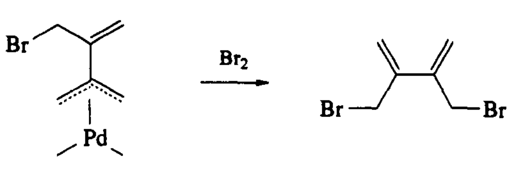

(134)

### *3.3.2.3.8 Oxa-π-allylpalladium complexes*

Oxa-π-allylpalladium complexes (**10**), which can also be envisioned as palladium enolates (**11**), are susceptible to β-hydride elimination, and as such have been principally used in methodologies for the preparation of β,β-unsaturated carbonyl compounds.

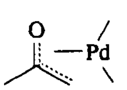

**(10)**

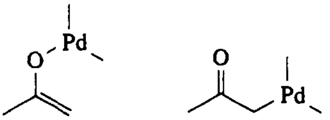

**(11)**

The direct reaction of ketones with $Pd^{II}$ salts does effect the transformation, but the conversions are typically low and the process is largely nonregiospecific (equation 135).[343–345]

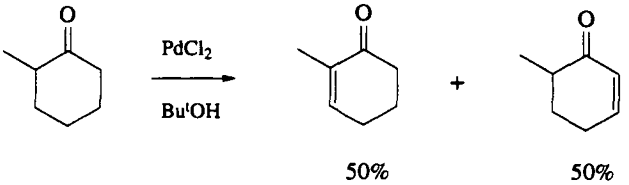

(135)

Enediones can successfully be generated from diones,[346,347] except for cyclohexandiones where aromatization can be a competitive process.[348,349] This reaction has been specifically used as an aromatization procedure with various heterocycles.[350–353]

A significant advance in this methodology was based on the realization that enol silyl ethers could be employed with $Pd^{II}$ complexes to allow selective generation of oxa-π-allylpalladium complexes and, thereby, regiospecific dehydrogenation.[354] Considerable use of this process has been made in the synthesis of natural products (equation 136).[355–358] Decarboxylation of β-ketocarboxylates in the presence of $Pd^{II}$ salts also specifically generates oxa-π-allyls, which subsequently dehydrogenate (equation 137).[359]

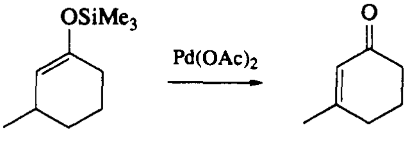

(136)

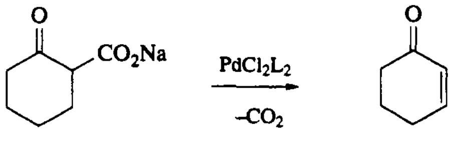

(137)

An extremely useful alternative method, employing catalytic amounts of $Pd^0$ complexes, rather than stoichiometric (or near stoichiometric) quantities of $Pd^{II}$ salts has been developed. The oxa-π-allyl complex is accessed *via* allyl β-ketocarboxylates[360–363] or allyl alkenylcarbonates[360,361,363,364] in the 'intramolecular' cases and *via* enol acetates,[361,363,365] enol silyl ethers[361,366] or ketene silyl acetals[367] with allyl carbonates in the 'intermolecular' cases. The products of these reactions are the corresponding α,β-unsaturated ketones, aldehydes and esters (equations 138–142).

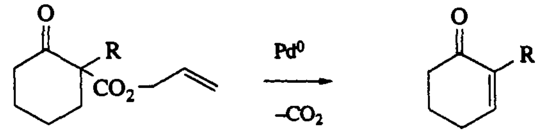
O
R
$CO_2$
$Pd^0$
$-CO_2$
O
R

(138)

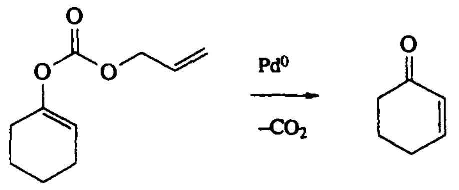
O
O
O
$Pd^0$
$-CO_2$
O

(139)

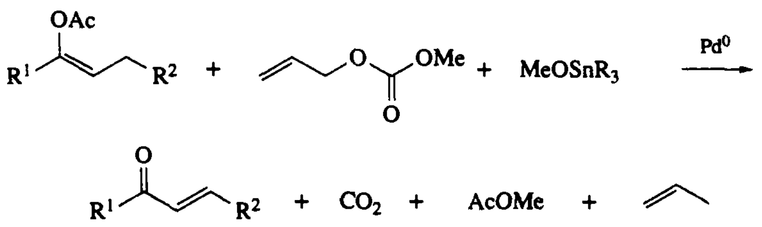
OAc
$R^1$
$R^2$
+
O
OMe
O
+ $MeOSnR_3$
$Pd^0$
O
$R^1$
$R^2$
+ $CO_2$ + AcOMe +

(140)

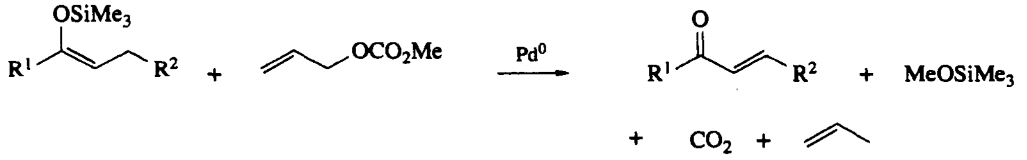
$OSiMe_3$
$R^1$
$R^2$
+
$OCO_2Me$
$Pd^0$
O
$R^1$
$R^2$
+ $MeOSiMe_3$
+ $CO_2$ +

(141)

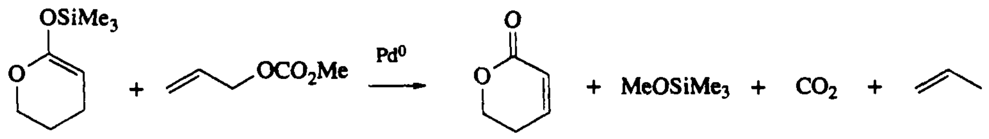
$OSiMe_3$
O
+
$OCO_2Me$
$Pd^0$
O
O
+ $MeOSiMe_3$ + $CO_2$ +

(142)

The mechanisms proposed for these reactions are all quite analogous, and only the intramolecular cases will be considered in detail (Scheme 5). Oxidative addition by $Pd^0$ into the allylic C—O bond of the allyl β-ketocarboxylate produces an allylpalladium carboxylate. This species then undergoes decarboxylation to yield an allylpalladium enolate (oxa-π-allyl), which subsequently eliminates a β-H to form the enone and provide an allyl-Pd-H. Reductive elimination from the allyl-Pd-H yields propene and returns Pd to its zero oxidation state. A similar mechanism can be imagined for the alkenyl allylcarbonate. Oxidative addition by the $Pd^0$ forms an allylpalladium carbonate, which decarboxylates again to give an allylpalladium enolate (oxa-π-allyl). β-Hydride elimination and reductive elimination complete the process. The intermolecular cases derive the same allylpalladium enolate intermediates, only now as the result of bimolecular processes.

Dehydrogenation of an allyl β-ketocarboxylate is a key step in a synthesis of methyl jasmonate that has been reported.[362]

The biologically significant α-methylene ketones have been prepared by a similar strategy, entailing a $Pd^0$-catalyzed decarboxylation–deacetoxylation of allyl-α-acetoxymethyl β-ketocarboxylates. The crucial allylpalladium enolate now β-eliminates OAc rather than H (equation 143).[368]

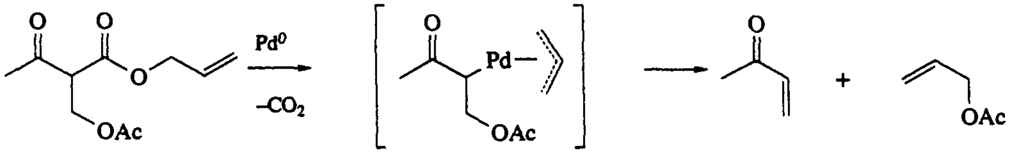
O
O
O
OAc
$Pd^0$
$-CO_2$
O
Pd
OAc
O
+
OAc

(143)

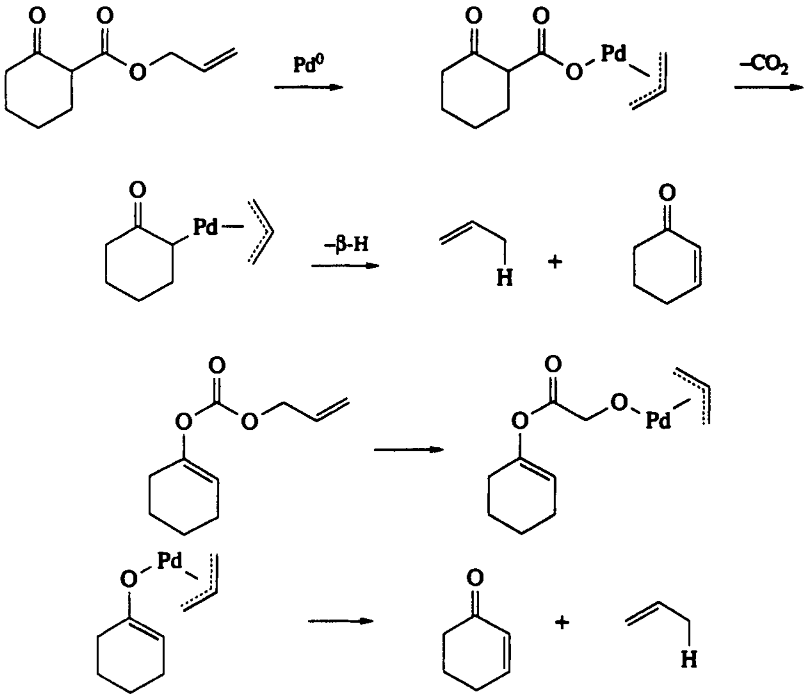

Scheme 5

What may be characterized as an aza-π-allylpalladium complex has been proposed as an intermediate in the preparation of α,β-unsaturated nitriles by decarboxylation–dehydration of allyl α-cyanocarboxylates (equation 144).[369] These reactions have been summarized in the context of several reviews.[89,117] If the oxa-π-allyl species is blocked from the elimination of a β-H, then it can undergo typical π-allylpalladium chemistry, such as insertion by alkenes, dienes and CO (equation 145).[370,371]

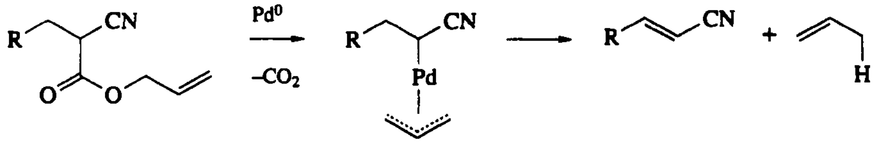

(144)

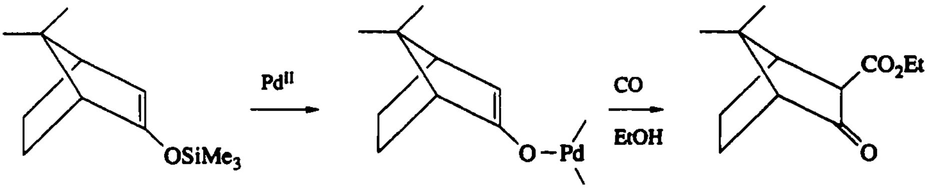

(145)

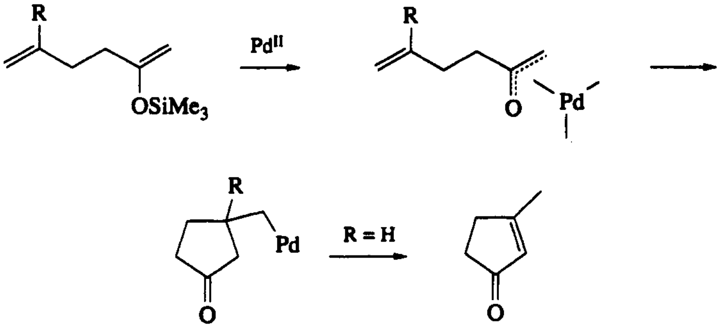

(146)

An intramolecular variation, which may involve insertion into an oxa-π-allyl, has proven to be a valuable new cyclization methodology (equation 146).[372-374]

A similar palladium-catalyzed cyclization procedure has recently been developed which involves enol ethers capable of β-H elimination.[375] Significant evidence has been accumulated suggesting that an oxa-π-allyl complex is not an intermediate in these reactions, but that it is better characterized as an enolate addition to a $\mathrm{Pd^{II}}$–alkene complex.[376,377] Synthetic applications of this reaction have also appeared.[376-379]

## 3.3.3 DIASTEREOSELECTIVITY

### 3.3.3.1 Diastereoselectivity and Mechanism

In considering the diastereoselectivity associated with reactions of π-allylpalladium complexes, the stereochemical nature of two processes must be evaluated. The first is the formation of the π-allylpalladium complex, and the second is the allylic functionalization of a nucleophile reacting with the allyl complex. As previously described (Section 3.3.2.1.1) the generation of π-allyl complexes from alkenes by their reaction with stoichiometric amounts of palladium proceeds so as to leave the substituents on the allyl termini preferentially in the *syn* rather than the *anti* position and the palladium situated on the sterically less congested face of the allyl ligand, regardless of the stereochemistry of the starting alkene (**12**).

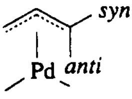

**(12)**

The *syn–anti* interconversions and facial rearrangements necessary to achieve this preferred configuration are generally believed to be accomplished *via* $\eta^1$-intermediates (equation 147).

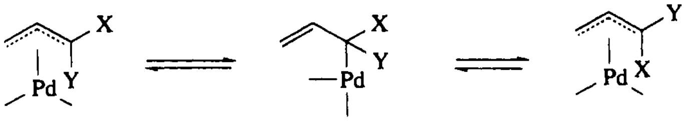

(147)

In the catalytic process, $\mathrm{Pd^0}$ complexes react with alkenes possessing an allylic C—X bond, displacing X and forming a π-allyl species. The stereochemistry of this oxidative addition reaction was initially determined indirectly by ascertaining the overall stereochemistry of the two-step process (formation of π-allyl; reaction with nucleophile) and by having previously established the stereochemical course of the attack of a given nucleophile on a stoichiometrically generated allyl complex. By this difference method, the oxidative addition was found to proceed with inversion of configuration of the initial C—X bond.[32,327,380] This determination was strongly supported by the analogous oxidative addition of $\mathrm{Pd^0}$ into the C—X bond of benzyl halides, which was previously known to proceed with inversion of configuration.[381] Recently, the stereochemistry of the oxidative addition of $\mathrm{Pd^0}$ into an allyl acetate was directly verified as proceeding with inversion of configuration.[382]

It is reasonable to assume that the identical complex will be generated whether it be done stoichiometrically from an alkene, to give a chloride or carboxylate dimer followed by the addition of 2 equiv. of a phosphine per Pd, or by the addition of an allyl–X compound to give a phosphine–$\mathrm{Pd^0}$ complex. This assumption is supported by the fact that complexes generated in either manner have been found to exhibit identical reaction profiles.[380] Furthermore, for the vast majority of allylpalladium reactions studied, it is most likely that the reactive species is a cationic bisphosphine–palladium complex (**13**).[13] Calculations

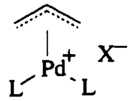

**(13)**

also support that the cationic bisphosphine complex is the most reactive species of the various allylpalladium species that can be reasonably considered.[383] As a result, all mechanistic rationales will be made assuming this to be the active catalyst.

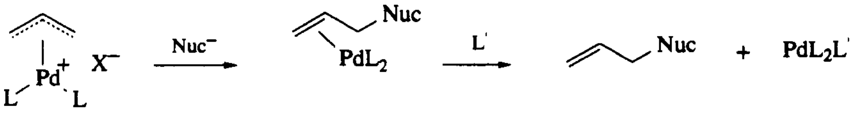

(148)

Attack by nucleophiles on the electrophilic π-allylpalladium complex can take place by two distinct mechanisms, which have opposite stereochemical consequences. Stereochemical inversion is achieved by attack of the nucleophile directly on the allyl ligand on the face opposite the palladium (equation 148). Retention is achieved by attack of the nucleophile at the metal center, followed by reductive elimination (equation 149). The reductive elimination step could proceed through an $\eta^1$-allylpalladium–Nuc species or directly from an $\eta^3$-allylpalladium–Nuc complex. Recent evidence strongly suggests the latter pathway.[384]

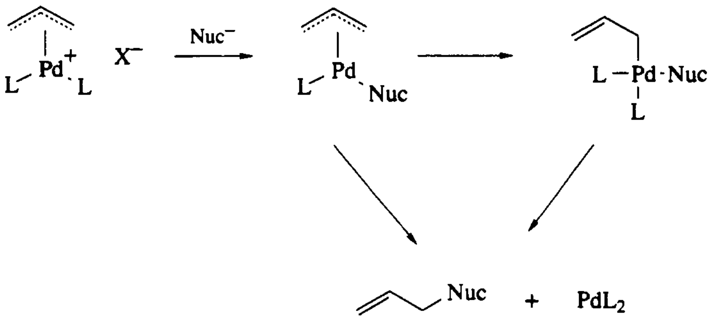

(149)

Nucleophiles partition between the two mechanisms based on their 'hard–soft' characteristics, with soft nucleophiles undergoing ligand attack and hard nucleophiles attacking at the metal. A limited class of nucleophiles appear capable of adding by either mechanism, with secondary factors controlling their choice of mode of addition.

The various nucleophiles enumerated in the chemoselectivity section (Section 3.3.2.2) will be considered in turn and classified as to the stereochemistry of addition and, thereby, the mechanism they follow.

In addition to direct determination of the stereochemistry of the allylation process, alternative means of classification of nucleophiles as to those that proceed by ligand or metal addition have been advanced. In one case the classification is made based on the regiochemistry of addition to a specific unsymmetrical allyl complex,[385] and in a second by the ability of a particular allyl complex to react only by ligand addition,[386] and therefore to be inert to nucleophiles that add *via* attack at the metal.

It must also be noted that despite the ability of stereochemical interconversions to take place in many π-allyl complexes *via* a variety of mechanisms, the addition of nucleophiles has been found to be sufficiently fast such that the allylation process is generally stereospecific.

## 3.3.3.2 Stereochemistry of Addition of Carbon Nucleophiles

### 3.3.3.2.1 *Soft carbanions*

Soft carbanions, $R\bar{C}XY$, as defined in Section 3.3.2.2.1, have been shown to add to π-allylpalladium complexes directly on the allyl ligand, on the face opposite the Pd (inversion) (equations 150 and 151).[32,72,153,327,380,387-392]

In combination with the inversion step in the oxidative addition, allyl–X π-allyl precursors show overall retention of configuration relative to the C—X bond *via* a double inversion process (equation 152).

The anion of cyclopentadiene has also been demonstrated to add *via* ligand addition (inversion).[105,385,386] Indenyl nucleophiles derived from the corresponding allylsilane have been classified as adding *via* ligand addition,[385] but the sodium salt of the indenyl anion has curiously been suggested to add *via* addition directly to the metal.[386]

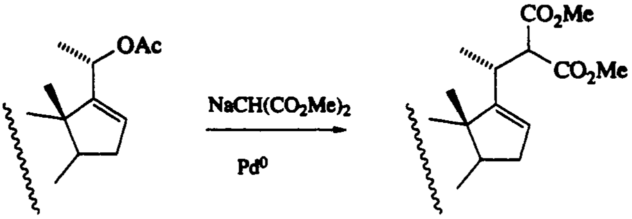
OAc
NaCH(CO2Me)2
Pd0
CO2Me
CO2Me

(150)

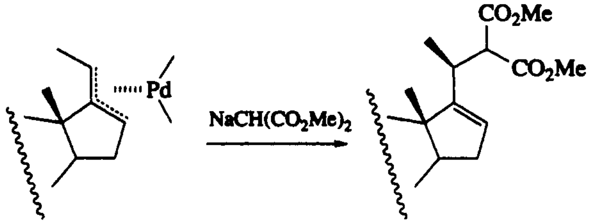
Pd
NaCH(CO2Me)2
CO2Me
CO2Me

(151)

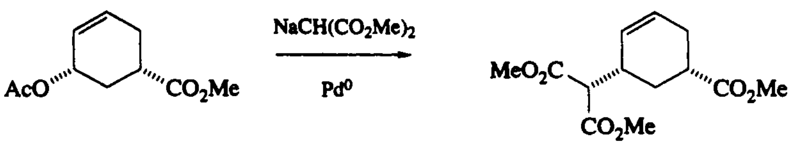
AcO
CO2Me
NaCH(CO2Me)2
Pd0
MeO2C
CO2Me
CO2Me

(152)

Highly acidic carbon nucleophiles, p$K_a$ < 10, have also been investigated and found to add *via* ligand addition (equation 153).[393]

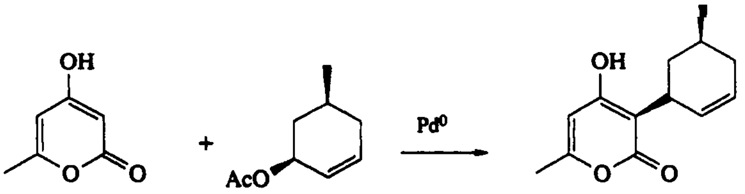
OH
O
O
+
AcO
Pd0
OH
O
O

(153)

Loss of stereospecificity in the addition of soft carbon nucleophiles can occur if the rate of nucleophilic attack is slow, due, for example, to extreme steric bulk, *e.g.* NaCH($SO_2Ph)_2$,[167] of the nucleophile (equation 154). In this case, the initially displaced $OAc^-$ has sufficient time to return and attack the π-allyl complex. Acetate anions (*vide infra*) are capable of either ligand or metal addition, thus scrambling the stereochemistry of the starting allyl acetate.

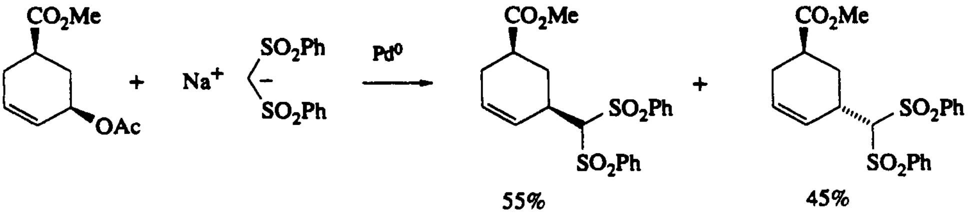
CO2Me
OAc
+
Na+
SO2Ph
SO2Ph
Pd0
CO2Me
SO2Ph
SO2Ph
55%
+
CO2Me
SO2Ph
SO2Ph
45%

(154)

### 3.3.3.2.2 Enolates

Tin enolates add to π-allylpalladium complexes directly on the allyl ligand (inversion).[106,385] Therefore, in tandem with the inversion of configuration incurred in the oxidative addition of a $Pd^0$ catalyst into an allyl acetate, a net overall retention is observed (equation 155).

Similarly, lithium enolates of ketones add to allyl acetates *via* $Pd^0$ catalysis by a double inversion process,[110] and potassium ketone enolates have been shown to add to preformed π-allyl complexes with inversion (equations 156 and 157).[111]

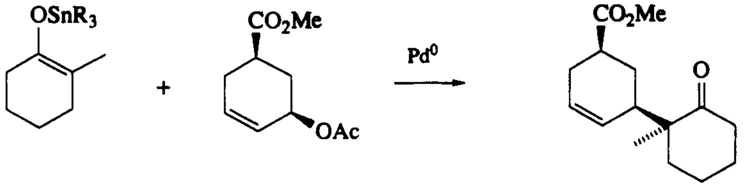
OSnR3
CO2Me
OAc
Pd0
CO2Me
O

(155)

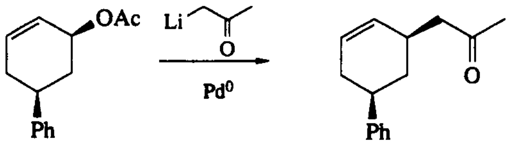
OAc
Li
O
Pd0
Ph
O
Ph

(156)

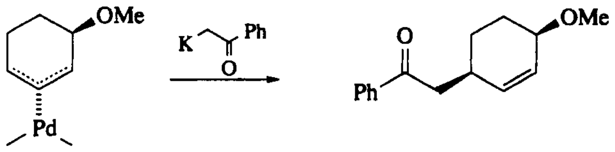
OMe
Pd
K
Ph
O
O
Ph
OMe

(157)

The predominant stereochemical course of the allylation of Pd enolates follows that previously shown by the other enolates, but also consistently exhibits some loss of stereointegrity (equations 158–160).[114,115,126] This lessening of stereospecificity can be attributed either to scrambling of the stereochemistry of the starting material by attack of the initially ionized carboxylate at the metal (equation 161)

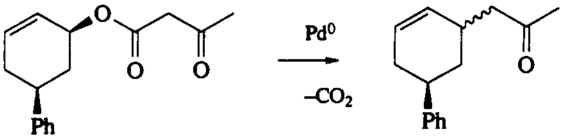
O
O
O
Ph
Pd0
−CO2
O
Ph

95:5 *cis*:*trans* 80:20 *cis*:*trans*

(158)

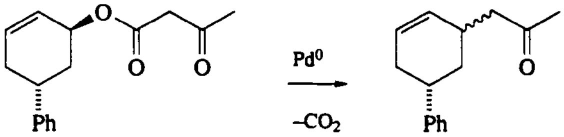
O
O
O
Ph
Pd0
−CO2
O
Ph

24:76 *cis*:*trans* 34:66 *cis*:*trans*

(159)

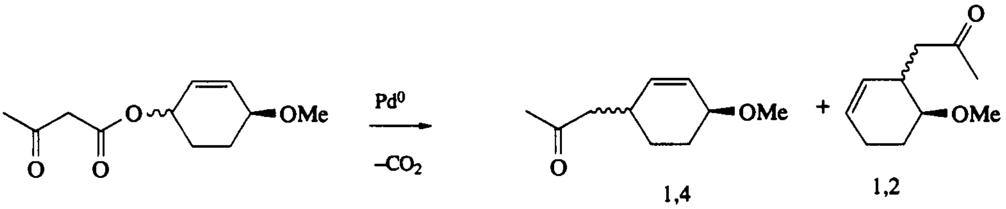
O
O
O
OMe
Pd0
−CO2
O
OMe
O
OMe
1,4
1,2

*cis* ⟶ 61% *cis*-1,4<br>14% *trans*-1,4<br>23% 1,2

(160)

*trans* ⟶ 51% *cis*-1,4<br>26% *trans*-1,4<br>23% 1,2 or by direct reductive elimination of an allylpalladium enolate intermediate (equation 162). Epimerization of the starting material has been noted in this reaction.[115]

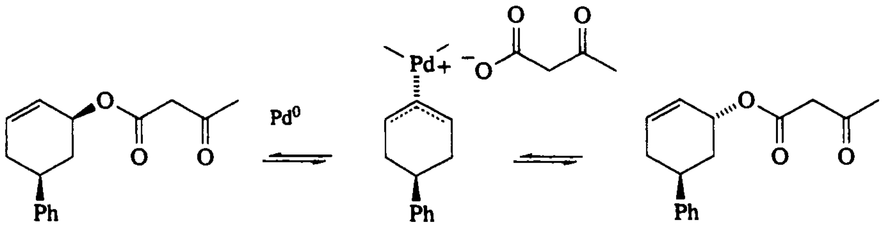

(161)

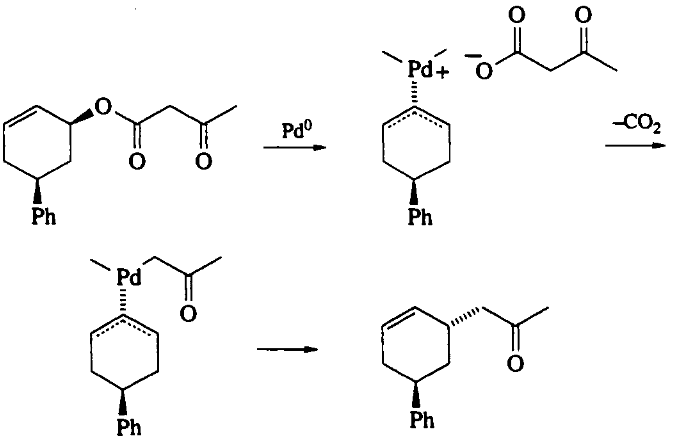

(162)

The reaction of β-ketoacids with allyl carboxylates is also believed to proceed *via* a palladium enolate intermediate.[126] Less than complete stereospecificity is also observed in these reactions (equation 163). Interestingly, the bicyclic lactone substrate employed to ascertain the stereointegrity of this reaction, in addition to being incapable of any *syn–anti* isomerization, cannot epimerize the starting material by carboxylate attack at the metal. The observed stereochemical leakage could be due to epimerization of the intermediate allyl complex (equation 164) or reductive elimination of an allylpalladium enolate (retention) (equation 165).

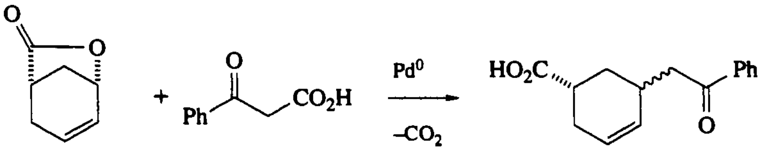

68:32 *trans:cis*

(163)

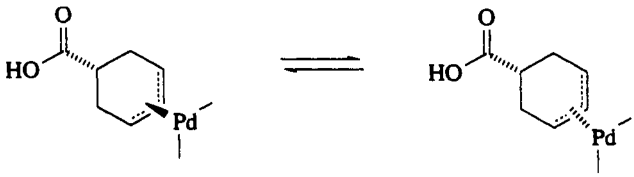

(164)

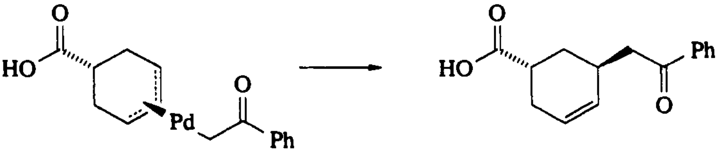

(165)

### *3.3.3.2.3 Organotins*

The palladium-catalyzed reaction of aryl- and vinyl-tin reagents with stereochemically defined allyl chlorides proceeds with overall retention of configuration, indicating that the second step, entailing interaction of the π-allylpalladium complex and the organotin, proceeds by transmetallation and reductive elimination (attack at Pd, retention) (equations 166 and 167).[142,145] Comparable results were obtained with cyclic vinyl epoxides and aryltins.[143]

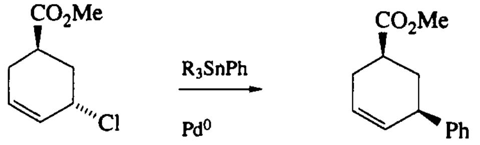

(166)

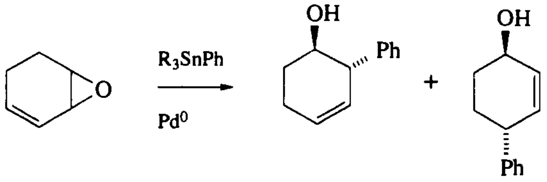

(167)

Allyltin reagents were suggested to add to π-allylpalladium complexes directly on the allyl ligand,[137,138] although a definitive stereochemical experiment could not be successfully carried out. The fact that these reactions proceed with allyl inversion of the stannane (equation 168) would require an unlikely, sterically unfavorable allylpalladium–R intermediate if metal attack was followed.

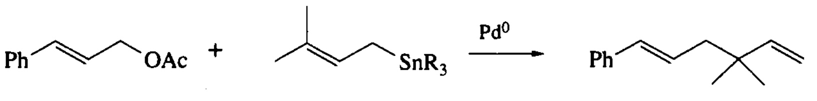

(168)

However, the reaction of preformed allylpalladium complexes with allyltin reagents with coadded maleic anhydride does proceed *via* metal addition (equation 169).[139]

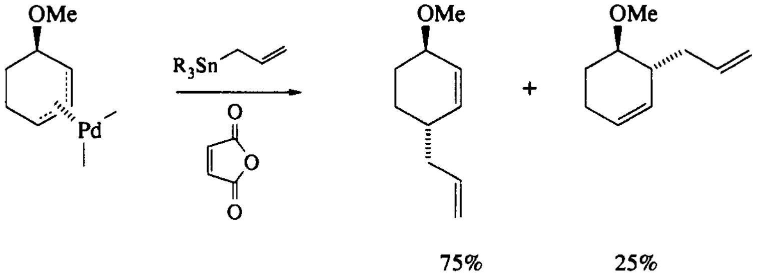

(169)

It is clear that allyltin compounds do add to allylpalladium complexes at the metal center and that these intermediates can be induced to undergo reductive elimination with maleic anhydride. In view of the phenyl- and vinyl-tin results (metal attack), it is tempting to assume all organotin reagents proceed by metal addition, but this remains to be verified.

### *3.3.3.2.4 Organozincs*

Direct assays of the stereochemistry of the addition of phenylzinc halides to allylic esters catalyzed by palladium uniformly agree that this process takes place with overall inversion of configuration, indicating direct addition to the metal by the zinc reagent (equations 170–172).[153,154,386] Methods of classification of the mode of nucleophilic addition based on regiochemical considerations also support this result.[385] A large number of studies have been conducted on the allylpalladium–Ar intermediate in this reaction. Two interesting aspects emerge from these studies. First, these species appear to be capable of reductive elimination directly from an $\eta^3$-allyl form without collapse to an $\eta^1$-allyl, and second, that the reductive elimination process is greatly accelerated by the addition of coordinating electron deficient alkenes, *e.g.* acrylates.[394]

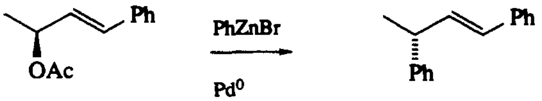

(170)

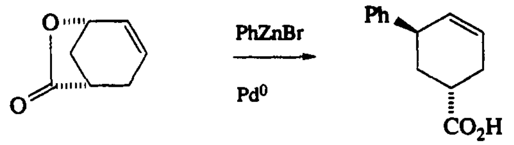

(171)

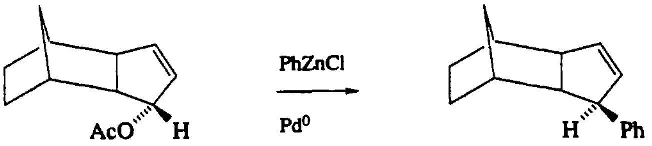

(172)

### 3.3.3.2.5 Organo-aluminum, -zirconium and -mercury compounds

Dialkylvinylaluminums transfer their vinyl substituent to stereodefined allylic acetates with $Pd^0$ catalysis with overall inversion of configuration. Metal attack of the organoaluminum is thereby indicated (equation 173).[154]

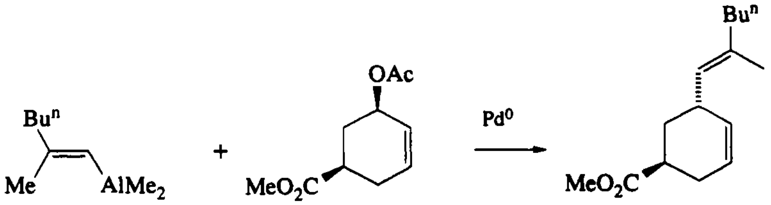

(173)

Alkenylzirconiums react with either preformed allylpalladium complexes[155] or allyl acetates and $Pd^0$ catalysts[156,395] *via* addition directly to the palladium, followed by reductive elimination. In the reaction with steroidal π-allylpalladium complexes (equation 174) the natural configuration at C-20 is now obtained, in contrast with the addition of malonates (ligand attack) which yielded the unnatural configuration.[74]

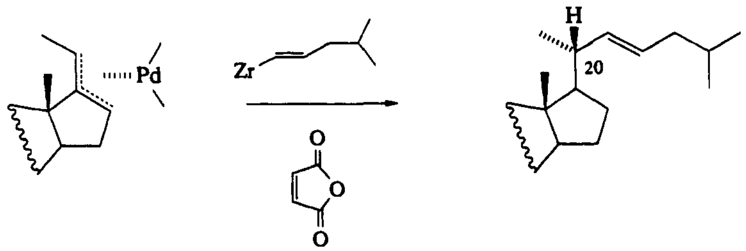

(174)

Similar to the tin- and zinc-based methodologies, electron deficient alkenes were found to strongly catalyze the reductive elimination step.[155,156,395]

Organomercury reagents are also believed to add *via* metal addition.[385]

### 3.3.3.2.6 Grignards and organolithiums

Grignard reagents have been shown to add to preformed π-allylpalladium complexes directly at the metal center.[158,387,396,397] Reductive elimination completes the allylation process with retention of configuration with respect to the metal. Again, electron deficient alkenes (maleic anhydride) were found to accelerate the reductive elimination (equations 175 and 176).

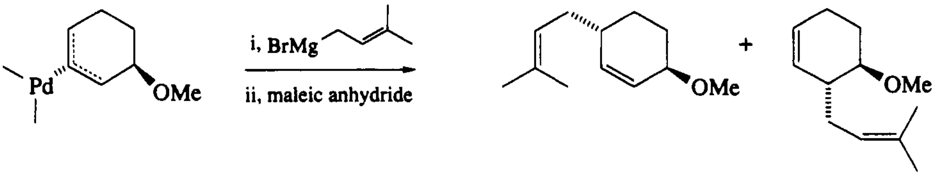

(175)

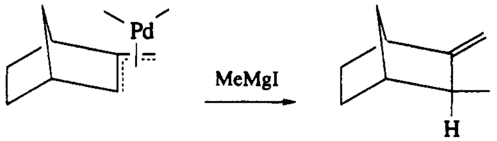

(176)

Organolithiums[158,160,385] behave in identical fashion to the Grignard reagents, adding with retention of configuration with respect to the Pd.

### 3.3.3.3 Stereochemistry of Addition of Oxygen Nucleophiles

In choosing between the two possible modes of addition to a π-allylpalladium complex, namely ligand or metal attack, the overwhelming majority of nucleophiles opt for one mode to the total exclusion of the other. Oxygen nucleophiles, specifically carboxylates, however, appear to enjoy a relatively unique position in being able to add by both mechanisms.

The initial suggestion that acetates might be capable of migration directly from the metal to the allyl ligand came from the report that π-allylpalladium acetate dimers could be induced by treatment with CO to undergo acetoxylation of the allyl ligand.[163] Although the required stereochemical evidence was not determined in this early report, the use of CO to effect this reaction was highly reminiscent of other processes which occur by a *cis* reductive elimination mechanism.

The loss of stereospecificity in the addition of bis(sulfone) anions to cyclohexenyl allylic acetates was attributed to a scrambling of the stereochemistry of the starting acetate. The ability of $Pd^0$ catalyst to effect this epimerization was confirmed in the absence of added nucleophile. This epimerization was attributed to the ability of the acetate to return to add to the π-allyl complex *via* attack at the metal center (equation 177).[167] This suggestion was confirmed by treatment of a preformed allylpalladium acetate dimer with CO, which resulted in *cis* migration of the acetate from Pd to the allyl ligand (equation 178).[164]

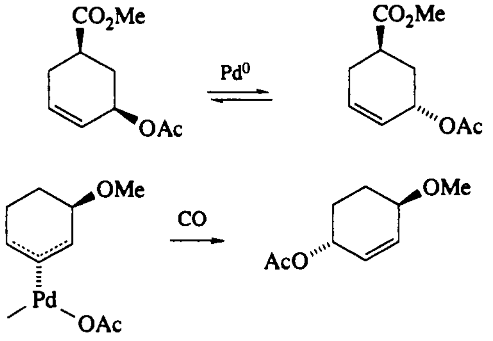

(177)

(178)

That acetate could add *via* either ligand or metal addition was subsequently verified.[168–170,175] Of crucial importance to the synthetic utility of this addition, conditions have been determined which allow virtually complete control of the mode of attack of acetate by manipulation of the ligands present in the reaction mixture (equation 179). Addition of acetate to a preformed allyl complex was shown to result in metal addition, followed by *cis* migration (reductive elimination) to the allyl ligand. When chloride ion was added, addition now proceeded *via* attack on the ligand on the face opposite the palladium. The chloride ion appears to block addition to the Pd by occupying its available coordination sites and forcing ligand addition as an alternative.[168]

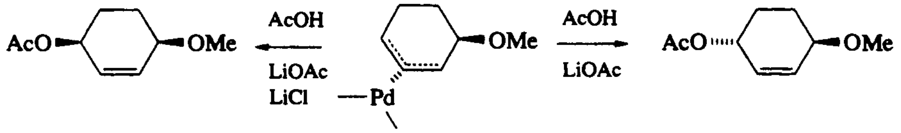
AcO
OMe
AcOH
LiOAc
LiCl
OMe
Pd
AcOH
LiOAc
AcO
OMe

(179)

Carboxylates may enjoy their ability to undergo metal addition and *cis* migration because of their bidentate nature and could effect this migration *via* an oxygen isomerization process (equation 180). Carboxylate and phenolate nucleophiles can also add *via* ligand addition without $Cl^-$ blocking of the metal (equation 181).[176] The reported loss of stereochemical integrity in the intramolecular addition of alkoxides to a π-allylpalladium complex could also be rationalized by competing metal–ligand addition processes (equation 182).[180]

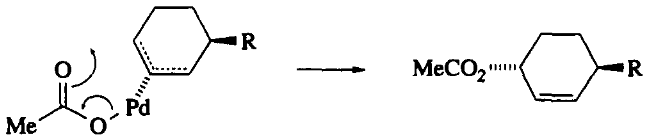
R
O
Me
O
Pd
$MeCO_2$
R

(180)

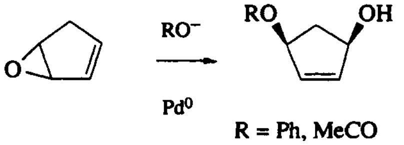
O
$RO^-$
$Pd^0$
RO
OH
R = Ph, MeCO

(181)

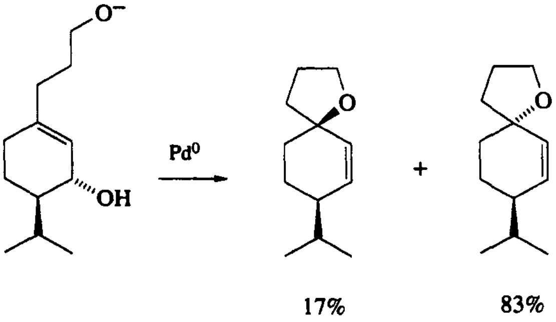
$O^-$
OH
$Pd^0$
O
+
O
17%
83%

(182)

## 3.3.3.4 Stereochemistry of Addition of Amine Nucleophiles

Amine nucleophiles appear, in general, to prefer addition to the allyl ligand on the face opposite the palladium.[185,195,208,386]

Addition of dimethylamine to 1,3-cyclohexadiene catalyzed by $Pd^{II}$ complexes proceeds *via* an amino-π-allyl complex of known configuration, to which a second equivalent of $HNMe_2$ adds on the face opposite Pd to yield a *cis*-1,4-diaminocyclohexene (equation 183).[185] Similar results were obtained from an acetoxychlorocyclohexene (equation 184)[195] and in the preparation of amino sugars (equation 185).[208]

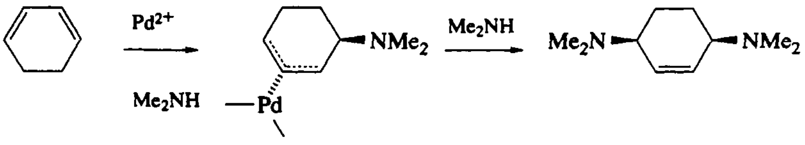
$Pd^{2+}$
$Me_2NH$
$NMe_2$
Pd
$Me_2NH$
$Me_2N$
$NMe_2$

(183)

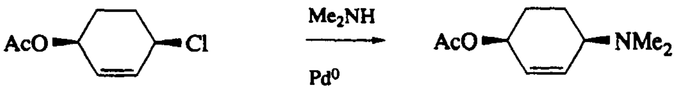
AcO
Cl
$Me_2NH$
$Pd^0$
AcO
$NMe_2$

(184)

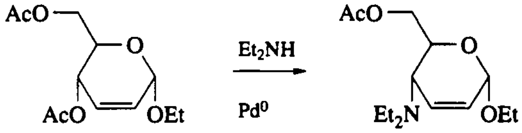

(185)

Loss of stereospecificity, however, has also been reported in the addition of amines. The use of homogeneous Pd$^0$ catalysts in the addition of dimethylamine to a cyclohexenyl acetate led to substantial stereochemical scrambling (equation 186). Employment of polymer-bound Pd$^0$ catalysts, however, gave complete stereospecificity *via* ligand addition.[398] The epimerization noted in this reaction is apparently due to acetate attack at the metal center, which is prohibited by steric congestion of the metal in the polymer matrix (equation 187).[398]

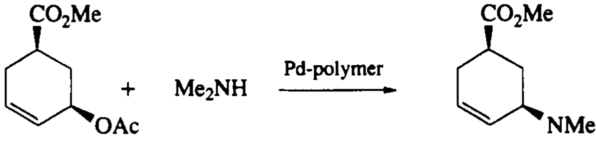

(186)

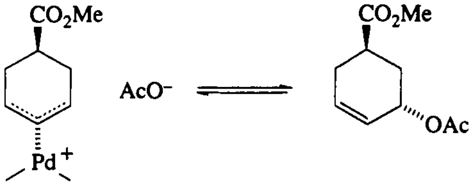

(187)

The reaction of dimethylamine with a preformed allylpalladium complex was found to yield products resulting from, on one extreme, complete ligand addition, on the other extreme, to up to 14% loss of stereospecificity, depending on the reaction conditions (equation 188).[190]

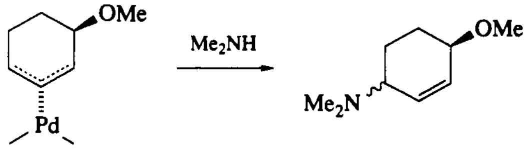

(188)

Dimethoxybenzhydrylamine (DMB) exhibited loss of stereospecificity in its Pd-catalyzed addition to acyclic allylic acetates. Pure (*Z*)-allylic acetates yielded only (*E*)-products in contrast to the complete stereospecificity in the addition of malonate anions to the same substrates, presumably due to the enhanced rate of *syn–anti* interconversion caused by the ability of the amine to coordinate to Pd (equation 189).[200]

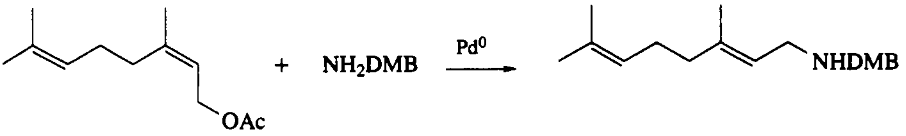

(189)

DMB-NH$_2$ also showed significant stereoscrambling in its addition to cyclohexenyl allylic acetates[200] (equation 190). This loss of stereointegrity could be due to either: (i) epimerization of the methoxycarbonyl group, although this seems unlikely under the reported reaction conditions; (ii) epimerization of the allylic acetate *via* metal addition, although no epimerized unreacted starting material could be detected; (iii) epimerization of the intermediate π-allyl complex by attack of uncomplexed PdL$_2$; or (iv) attack of the amine at both the ligand and metal center.[200]

Amides have been shown to add by both ligand (equation 191)[197] and metal attack (equation 192).[175]

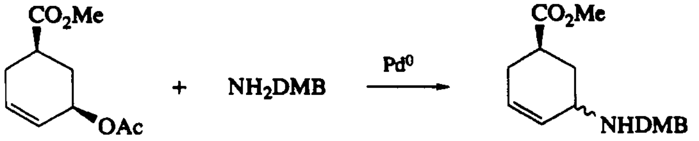

(190)

60% *cis*
40% *trans*

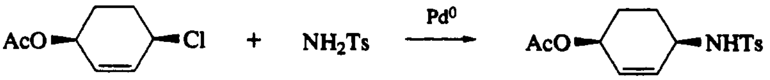

(191)

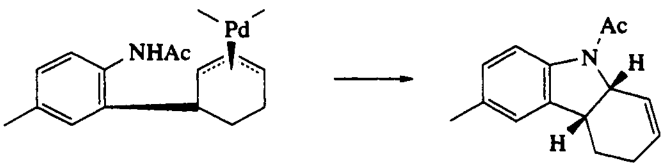

(192)

### 3.3.3.5 Stereochemistry of Addition of Sulfur Nucleophiles

The addition of sodium phenylsulfinate nucleophiles to stereodefined acyclic allylic chlorides was reported to proceed with complete overall retention of configuration, indicating that this nucleophile adds with inversion of configuration, *i.e. via* attack at the allyl ligand (equation 193).[215] A cyclohexenyl acetate substrate also showed predominant ligand addition, but some isomeric product was also produced (equation 194).[216] This loss could be due to acetate epimerization of starting material, π-allyl epimerization by $PdL_2$, or by attack of the sulfur at the metal, followed by reductive elimination.

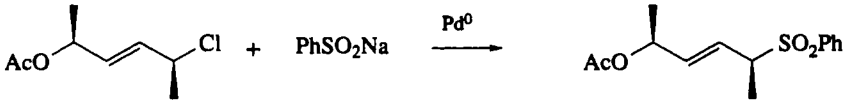

(193)

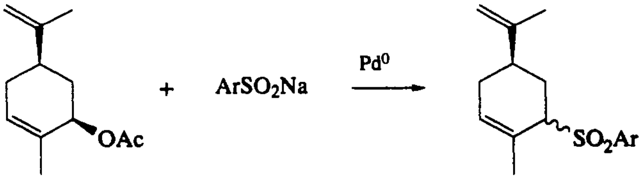

(194)

75:25 *cis:trans*

*O*-Allyl-*S*-alkyl dithiocarbonates react with $Pd^0$ catalysts to provide a π-allyl complex with a thiocarbonate serving as counterion. Under the reaction conditions the carbonate expels free methyl mercaptide, generating COS. Attack of the mercaptide was shown to occur exclusively *via* ligand addition (equation 195).[221]

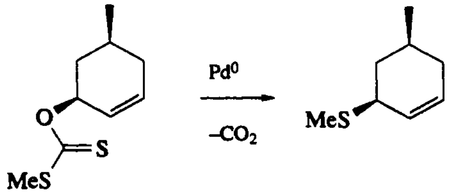

(195)

A similar *in situ* generation of a sulfide nucleophile can be accomplished by the reaction of an allylic carbonate with a $Pd^0$ catalyst and $PhSSiMe_3$. Following oxidative addition by the $Pd^0$ into the allylic C—O bond to form the π-allyl complex, $CO_2$ is lost from the carbonate counterion, generating methoxide ion. The methoxide attacks the thiosilane, liberating thiophenoxide which subsequently adds *via* ligand addition to the Pd complex (equation 196).[223]

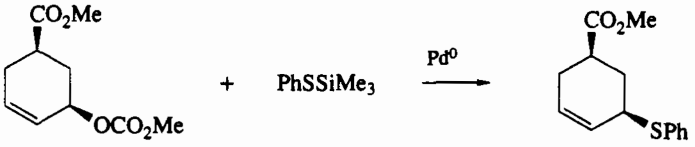

(196)

### 3.3.3.6 Stereochemistry of Addition of Other Heteroatom Nucleophiles

The stereochemistry of the Pd-catalyzed reaction of lithium diphenylthiophosphides with allyl acetates was determined using a 5-phenylcyclohex-2-enyl system. This phosphorus nucleophile was found to add exclusively *via* ligand addition (equation 197).[224,386]

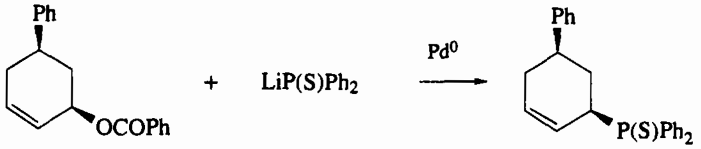

(197)

The silylation of allylic acetates has been accomplished utilizing tris(trimethylsilyl)aluminum and $Pd^0$ catalysts. The stereochemistry of this reaction has been determined and is consistent with exclusive ligand addition (equation 198).[225]

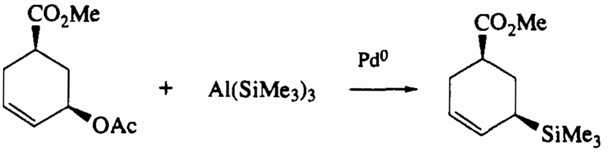

(198)

### 3.3.3.7 Diastereoselectivity of other Reactions of π-Allylpalladium Complexes

#### *3.3.3.7.1 Insertion into π-allylpalladium complexes*

The insertion of CO[239] or alkenes[253] into π-allylpalladium complexes proceeds with complete retention of configuration with respect to the metal (equations 199 and 200).

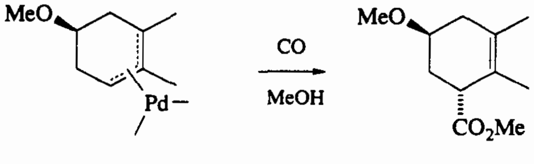

(199)

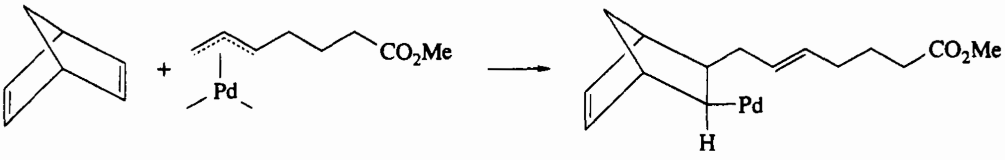

(200)

#### *3.3.3.7.2 Oxidation of π-allylpalladium complexes*

Treatment of preformed, stereodefined π-allylpalladium complexes derived from steroids with MCPBA gave an allylic alcohol product with retention of configuration with respect to the metal (metal attack) (equation 201).[272] In like fashion, $MoO_2(acac)_2$–$Bu^tO_2H$ oxidation of preformed π-allylpalladium complexes provided allylic hydroxy compounds with retention of configuration with respect to the Pd (equation 202).[275]

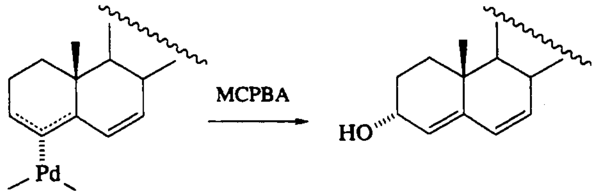

(201)

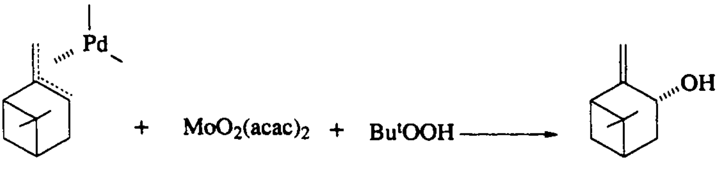

(202)

### 3.3.3.7.3 Reduction of π-allylpalladium complexes

Addition of hydride to π-allylpalladium complexes uniformly proceeds by attack at the metal, followed by reductive elimination, irrespective of the source of the hydride, *e.g.* $NaBH_4$,[286,287] $LiAlH_4$,[292] $R_3SnH$[385] or $NH_4^+$ $HCO_2^-$ (equation 203).[385]

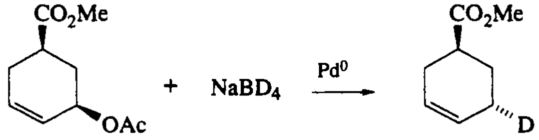

(203)

### 3.3.3.7.4 Umpolung

Conversion of allylic acetates of allylstannanes by treatment with $Et_2AlSnBu_3$ and $Pd^0$ catalysts proceeds by addition of the tin to the metal, followed by reductive elimination (equation 204).[309] The corresponding allyl phosphonate, however, showed some loss of stereochemical integrity (equation 205).[310] The $Pd^0$-catalyzed reaction of allylic acetates, trialkyltin chlorides and $SmI_2$ produced allylstannanes with no stereospecificity.[311]

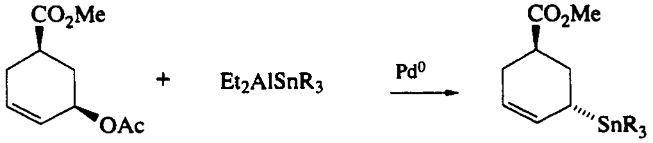

(204)

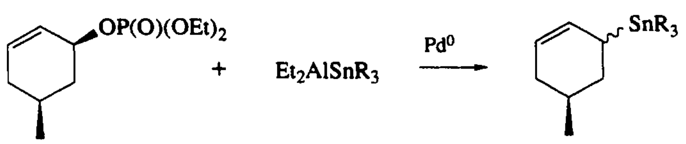

(205)

78:22 *cis*:*trans*

### 3.3.3.7.5 Addition reactions

The addition of 1,1,1-trichloro-2,2,2-trimethyldisilane to preformed allyl complexes proceeded *via* retention of configuration with respect to the metal (equation 206).[339]

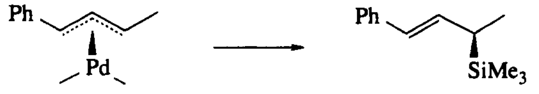

(206)

## 3.3.4 REGIOSELECTIVITY

### 3.3.4.1 Regioselectivity in the Addition of Nucleophiles to π-Allylpalladium Complexes

#### *3.3.4.1.1 Nucleophiles that add* via *attack at the π-allyl ligand*

The factors that determine the regiochemistry of addition of nucleophiles that attack directly on the allyl ligand can be partitioned between those based on steric and those based on electronic influences. The most important factor overall in determining regioselectivity is the steric interaction between the incoming nucleophile and the allyl terminus to which it is bonding. The relative steric environments of the allyl termini, as well as the size of the nucleophile, are key in determining regiochemistry. A secondary steric factor that can be significant is based on consideration of the alkene–palladium complex that is formed as the reaction proceeds. In general, Pd complexes to less substituted alkenes are favored. The size of the ligands on the palladium will also affect the ability of the metal to interact with an alkene, with less sterically demanding ligands being favored.

The electronic factors in determining regiochemistry are based on the ability of substituents on the allyl moiety or ligands on the palladium to induce an asymmetric distribution of the electron deficiency present in the allyl ligand, thereby making one terminus more reactive with an electron-rich nucleophile.

Asymmetric bonding of the π-allyl ligand to the palladium, which is not a distinct consideration from these steric and electronic factors but rather a manifestation of them, must also be assimilated into an understanding of the regiochemistry of π-allyl alkylations.

#### *3.3.4.1.2 Nucleophiles that add* via *attack at the metal*

Since the coupling of the nucleophile and the allyl ligand constitutes a reductive elimination from the metal, it is believed to proceed with a *cis* geometry of these groups about the metal. The geometric distribution of ligands in the allylpalladium complex that would foster the formation of a *cis* orientation between the palladium–Nuc bond and a specific allyl terminus must then be considered in understanding the regiospecificity of this reaction.

### 3.3.4.2 Regioselectivity in the Addition of Soft Carbon Nucleophiles to π-Allylpalladium Complexes

Soft carbon nucleophiles (p$K_a$ 10–20) have been shown to add to π-allylpalladium complexes by direct attack at the allyl ligand and to add preferentially to the sterically less congested allyl terminus. Although all the effects responsible for the regioselectivity demonstrated in a particular case cannot easily be accounted for, the discussion will be organized by the apparent dominant controlling factor being exhibited.

#### *3.3.4.2.1 Effect of substituents on the allyl ligand*

##### *(i) Alkyl- and aryl-substituted π-allyl complexes*

Asymmetry on the allyl ligand caused by the substitution of alkyl or aryl groups on the terminus results in preferential addition by the nucleophile at the less substituted end of the allyl group. As is often observed in these reactions, the relative steric interactions between the allyl termini and the nucleophile must be the dominating factor in determining regioselectivity. Arguments based on electronic factors would predict greater stabilization of cationic character in the allyl ligand at the more substituted terminus and preferential addition there. Similarly, if the relative stability of the incipient palladium–alkene complex dominated, then attack at the more substituted end should be observed, as this leads to a less substituted and more stable alkene complex.

Relatively subtle changes in the steric environment of the allyl termini result in substantial variations in regioselectivity, as shown in a series of π-allyl ligands having a methyl at one terminus and either Pr$^n$, Bu$^i$ or Pr$^i$ at the other terminus. This series varies from a 77:23 ratio favoring the less substituted terminus to >99:1 as the difference in group size increases, with dimethyl malonate as nucleophile (equation 207).[399]

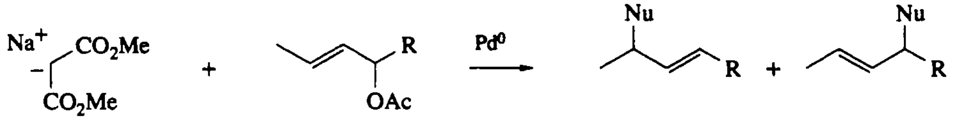

(207)

| | | |
|---|---|---|
| R = Pr$^n$ | 77 | 23 |
| R = Bu$^i$ | 93 | 7 |
| R = Pr$^i$ | >99 | 1 |

The size of the nucleophile can also exert effects on the regiochemical outcome of the reaction. On switching from a dimethyl malonate to a more bulky methyl(methylsulfonyl) acetate, the preference for attack at the less substituted terminus increases, as seen by comparing equations (208) and (209).[380]

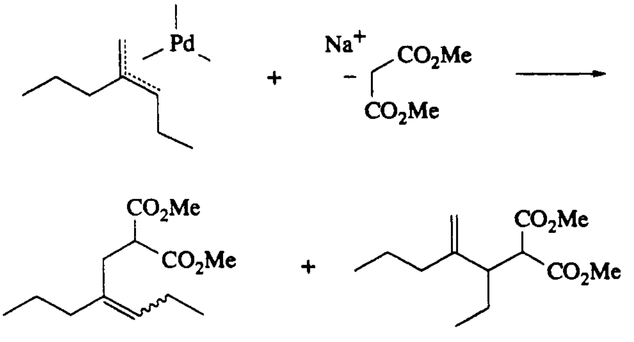

(208)

89% 11%

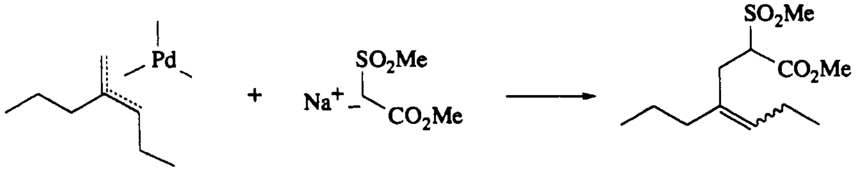

(209)

A fascinating control of regiochemistry has been discovered in the preparation of medium size rings. Intramolecular cyclization of phenylsulfonyl acetates, when confronted by a choice of attack at the allyl termini to create an *n* or *n* + 2 ring, *n* = 6–14, invariably opts for the larger ring.[400–402] Although this reflects the usual propensity for attack at the less substituted allyl terminus, other factors including the nature of the nucleophile, the ligands on the Pd and the chain configuration have also been cited as contributing to the observed selectivity (equation 210).

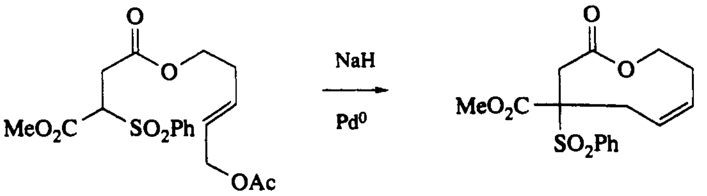

(210)

mixture of alkene isomers

Soft carbon nucleophiles other than malonate derivatives follow similar patterns of regioselectivity, as shown by the addition of cyclopentadiene anion (equation 211)[105] and the highly acidic 4-hydroxy-6-methyl-2-pyrone (equation 212).[393]

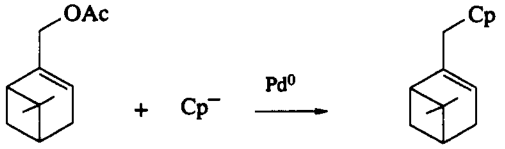

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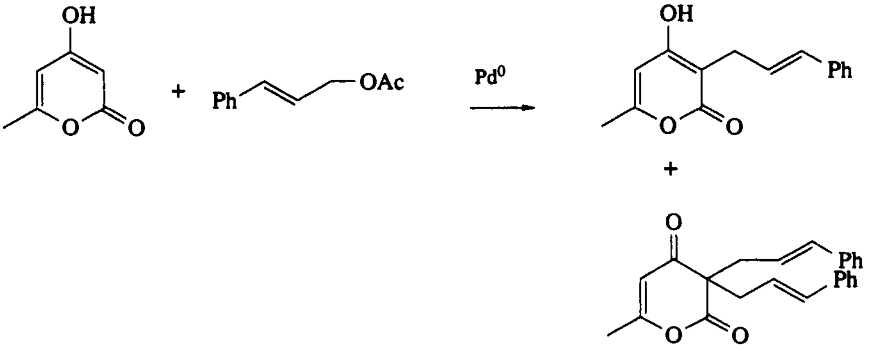

(212)

*(ii) Functional group effects*

The substitution of various functional groups on the terminus of a π-allyl ligand, including carbonyls (equation 213)[327,391,392,403,404] and nitriles (equation 214),[405] as well as heteroatoms such as —SR (equation 215)[406,407] and —P(O)$R_2$ (equation 216),[408] induces a strong tendency for addition of soft carbon nucleophiles to the remote terminus. This tendency is difficult to rationalize on steric grounds as isosteric alkyl groups do not exert nearly as effective regiocontrol. Analysis of electronic factors also does not offer an obvious explanation. Extrapolating the electrophilicity imparted to the allyl ligand by the $Pd^{II}$ to the extreme limit of an allyl cation simplifies the analysis. The charge distribution created by a carbonyl group, *versus* an oxygen or sulfur group, must be vastly different, as judged by the relative contributions of the resonance forms pictured in equations (217)–(219). The only common electronic property enjoyed by these functionalities is their ability to withdraw electrons in the σ-sense. The relevance of this feature, and the irrelevance of their widely differing π-electron effects, remains unclear. The ability of these groups to promote asymmetry in the bonding of the allyl ligand,[409] either through electronic interactions or by internal coordination, remains largely unstudied by X-ray structure determination.

The effects created by these functionalities are, surprisingly, capable of being transmitted from positions even more remote to the allyl ligand. 1,3-Diene monoepoxides, for example, selectively undergo the addition of nucleophiles remote from the incipient hydroxymethyl group (equation 220).[410–413] Nitro,[414] malonate[415] and acetoxy[416,417] functionalities show similar tendencies (equations 221–223). Tri-

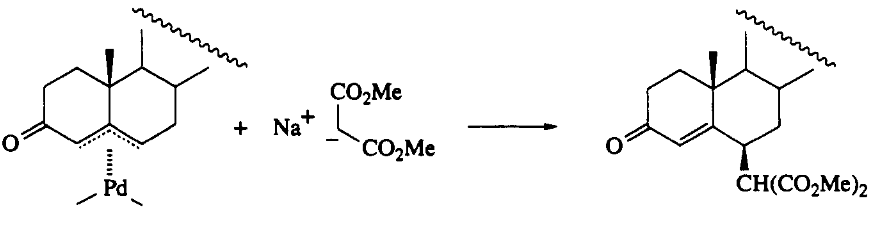

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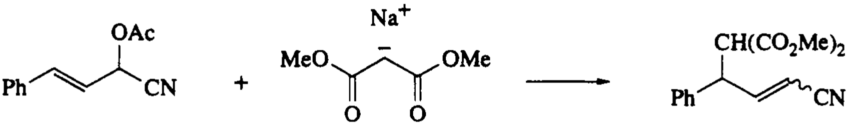

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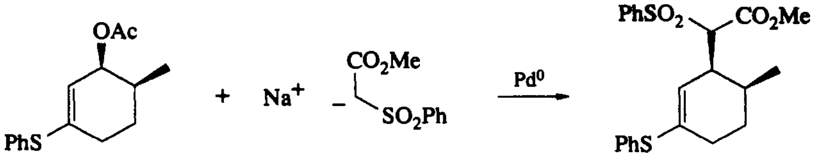

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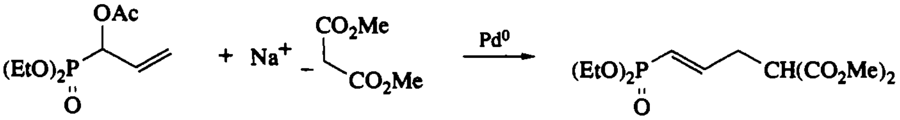

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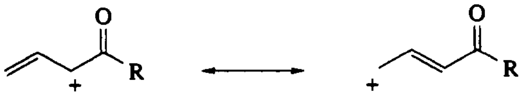

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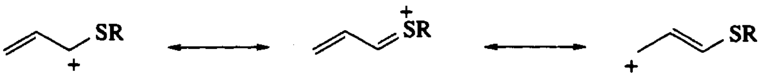

(218)

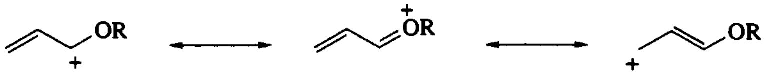

(219)

methylsilyl-substituted allyl ligands also direct carbon nucleophiles to the remote terminus, presumably based on simple steric considerations (equation 224).[418,419]

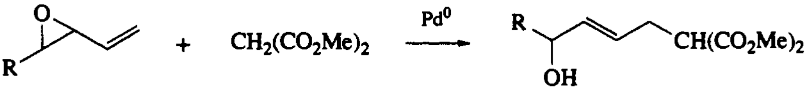

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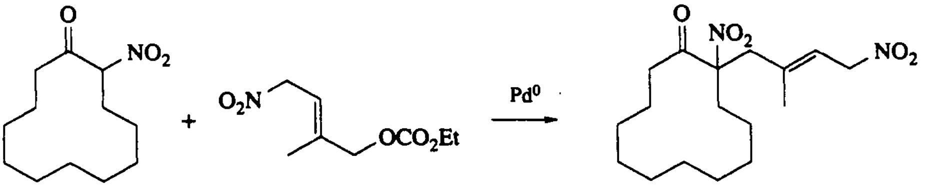

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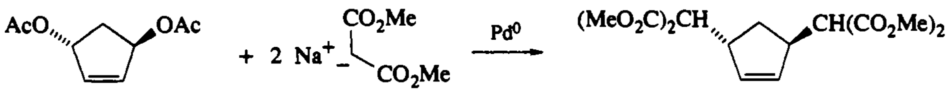

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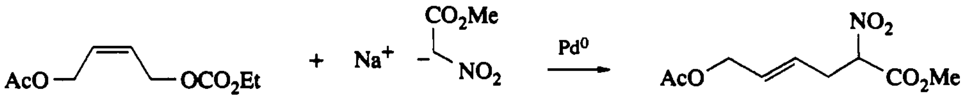

(223)

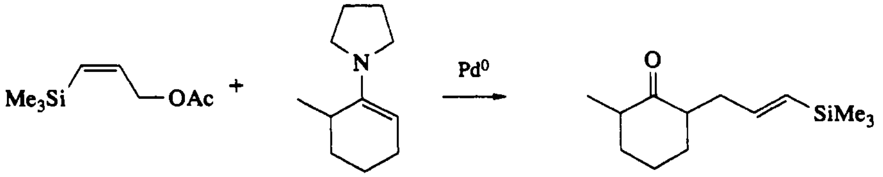

(224)

### *(iii) Ligand effects*

The nature of the ligands on the palladium in π-allyl complexes can influence the regioselectivity exhibited by soft carbon nucleophiles. π-Allylpalladium complexes generated from methylenecycloalkanes provide an example of the effect of ligands on regiochemistry. The complexes derived from methylenecyclopentane and methylenecycloheptane both exhibit exclusive exocyclic addition by the anion of methyl(methylsulfonyl) acetate with triphenylphosphine ligands on the Pd (equation 225). In contrast, the complex derived from methylenecyclohexane yields a 62:38 ratio of exocyclic:endocyclic addition (equation 226).

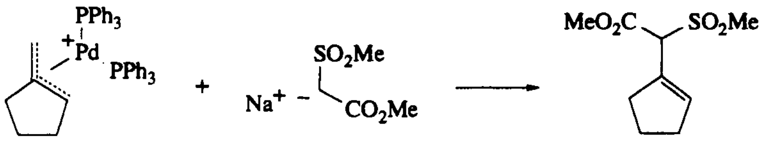

(225)

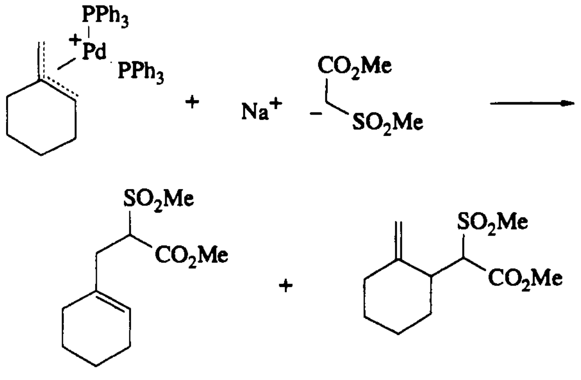

(226)

62% 38%

This result has been explained[72,390] by the particular instability of the alkene complex resulting from exocyclic addition (**14**) relative to endocyclic addition (**15**) in the cyclohexyl system. This rationale is supported by the results obtained by the use of the considerably more sterically bulky tri-*o*-tolylphosphine instead of triphenylphosphine. A 15:85 exocyclic:endocyclic ratio is obtained with the bulky phosphine. This result is nicely explained by the ability of the bulky phosphine to magnify the instability of the endocyclic alkene–palladium complex (**14**) relative to the exocyclic alkene complex (**15**) and favor endocyclic addition.

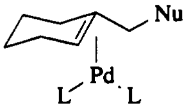

**(14)**

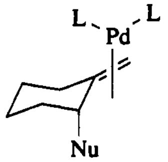

**(15)**

An elegant study on the influence of ligands on the regiochemistry of π-allylpalladium alkylations has recently appeared.[420] This study is based on the premise that acceptor ligands should induce greater positive charge at the more substituted terminus of the $\eta^3$-allyl ligand, leading to a greater preference for reaction at this terminus, and thereby modifying the usual steric preference for attack at the less substituted terminus.

The model reaction employed the allyl complex derived from 3-methylbutene and sodiodiethyl malonate as nucleophile (equation 227). The ratio of products observed was consistent with the relative induced charge as indicated by the $^{13}C$ NMR shift of C-3 and by the difference between the shifts at C-1 and C-3.[421] Thus, the ratio of product from attack at the less substituted terminus to attack at the more substituted terminus was small for the best acceptor ligands, 1.3:1 for L = $P(OPh)_3$ and 2.7:1 for L = $PPh_3$, and increases for less potent acceptors, *e.g.* 10:1 for L = $As(PPh_3)_3$. For donor ligands such as L = pyridine, only attack at the less substituted terminus was observed.

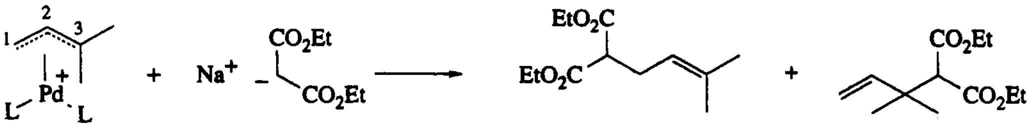
1
2
3
Pd
L
L
+
Na+
CO2Et
CO2Et
EtO2C
EtO2C
CO2Et
CO2Et

(227)

### 3.3.4.3 Regioselectivity in the Addition of Enolates to π-Allylpalladium Complexes

Since enolates also add *via* a ligand attack process, the regioselectivity that they exhibit is quite comparable to soft carbon nucleophiles. Alkyl or aryl substituents at the allyl termini direct attack to the less substituted terminus (equations 228–232); functional groups such as $CO_2Me$ and halogen at one allyl terminus direct attack to the remote terminus (equations 233 and 234). Remote functionalities such as —OR also direct addition to the allyl terminus more removed from the substituent (equations 235 and 236).

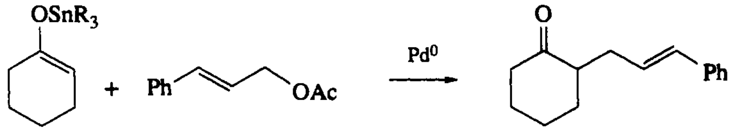
OSnR3
Ph
OAc
Pd0
O
Ph

(228)

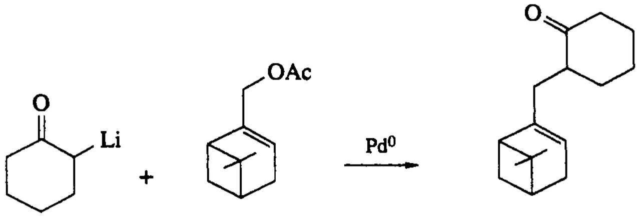
O
Li
OAc
Pd0
O

(229)

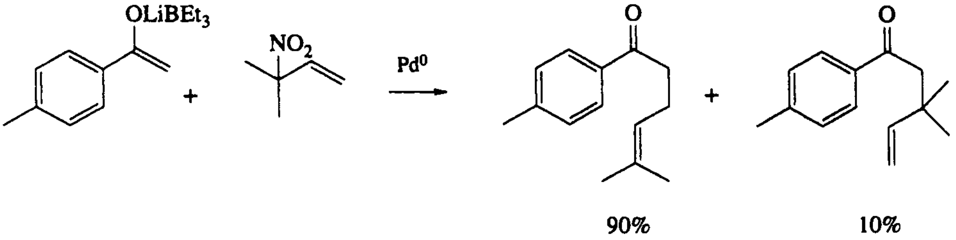
OLiBEt3
NO2
Pd0
O
O
90%
10%

(230)

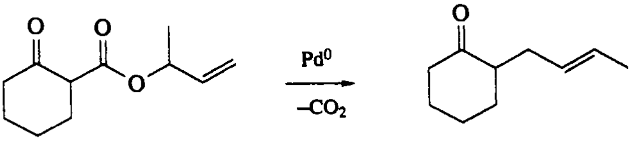
O
O
O
Pd0
-CO2
O

(231)

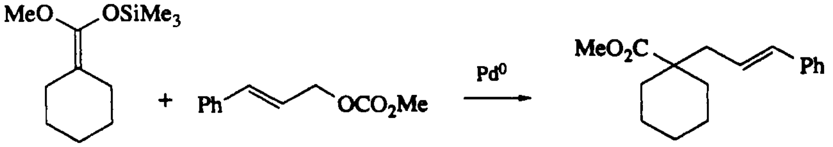
MeO
OSiMe3
Ph
OCO2Me
Pd0
MeO2C
Ph

(232)

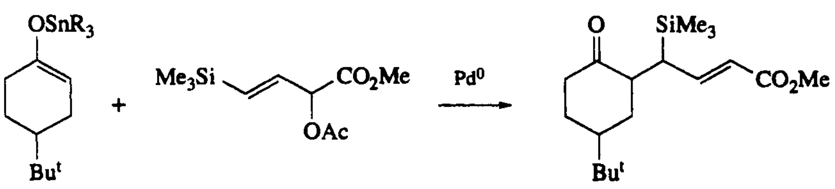
OSnR3
But
Me3Si
CO2Me
OAc
Pd0
O
SiMe3
CO2Me
But

(233)

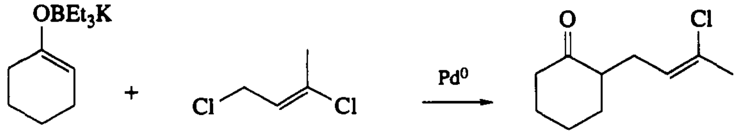

(234)

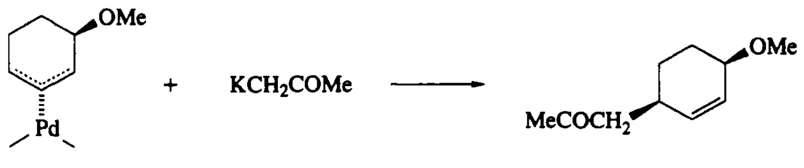

(235)

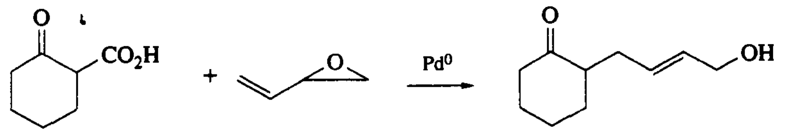

(236)

These regioselectivity patterns are observed for tin enol ethers (equations 228 and 233),[106,107,399] alkali metal enolates (equations 229 and 235),[111] lithium trialkylborate enolates (equations 230 and 234)[108,109] and palladium enolates (equations 231, 232 and 236).[95,111,112,115,126,127]

Two cases merit brief further discussion. In a competition between the regiochemical directing effects of a TMS and a $CO_2Me$ group positioned on opposite termini of an allyl ligand, the $CO_2Me$ group dominates and directs the enolate nucleophile to the TMS end (equation 233).[107] The palladium ester enolate derived from oxidative addition into a vinylcyclopropane, followed by Michael addition, closes to give only a five-membered ring product in preference to the alternative seven-membered ring (equation 237).[96]

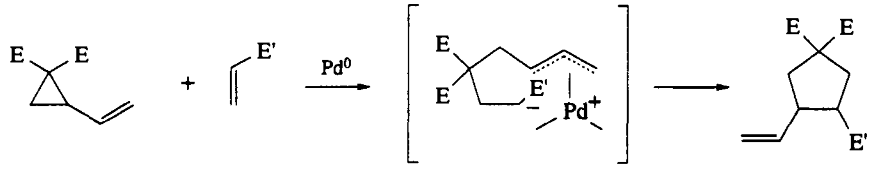

(237)

### 3.3.4.4 Regioselectivity of Organotins

Aryl- and vinyl-tins have been shown to add *via* attack at the metal, in contrast to the soft carbon nucleophiles and enolates. Although this change in mechanism is accompanied by a change in the factors controlling regiochemistry, these tin reagents behave comparably to the carbon nucleophiles that act *via* ligand addition. Alkyl- (equation 238),[145] alkoxycarbonyl- (equation 239),[142] and epoxy-substituted (equation 240)[143] allyls all efficiently direct the organotin to the remote terminus. Allyltins have been reported to add with inversion of the allyl moiety and suggested to attack directly the allyl ligand, except if maleic anhydride is added to the reaction mixture, when metal addition is observed.

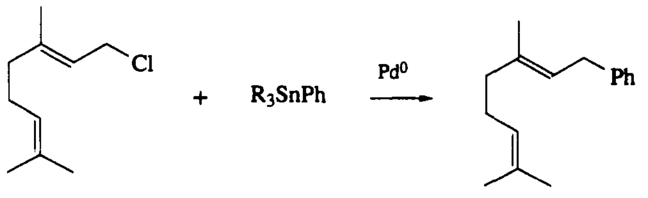

(238)

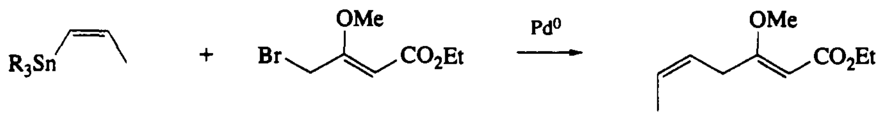

(239)

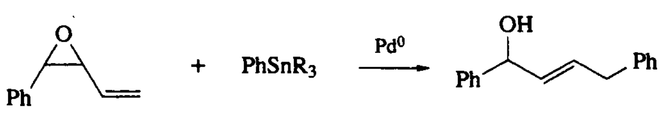

(240)

The opposite regioselectivity observed for the addition of methylbutenyltin to similar allyl substrates (equations 241 and 242),[137,139] caused by the presence of maleic anhydride in the latter case (equation 242), may be viewed as support for a change in mechanism when the electron deficient alkene ligand is present. Conversely, both reactions could proceed by metal addition, with the regiocontrol exercised by the maleic anhydride acting in the addition–reductive elimination sequence.

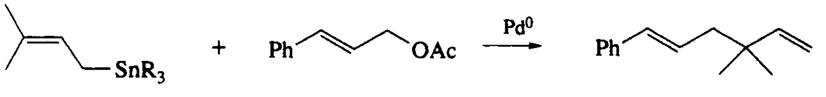

(241)

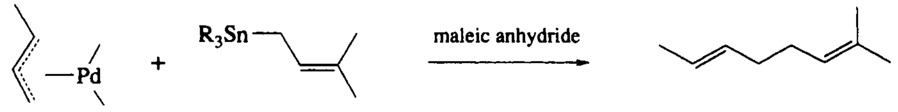

(242)

*In situ* generation of an allylstannane from an allylic acetate and hexamethyldistannane results in five-membered ring formation in preference to the allyl alternative seven-membered ring (equation 243).[140]

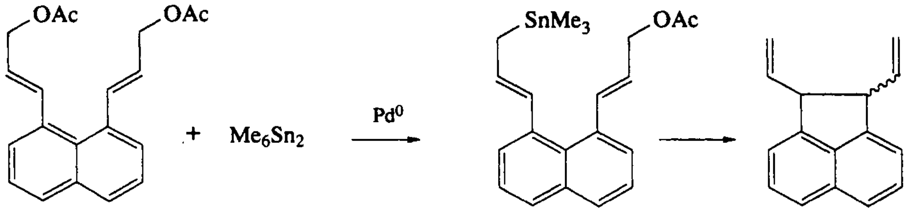

(243)

A remote methoxy substituent directs maleic anhydride-mediated allylation predominantly in the 1,4-sense, comparable to the phenyltin–vinyl epoxide example (equation 244).[139]

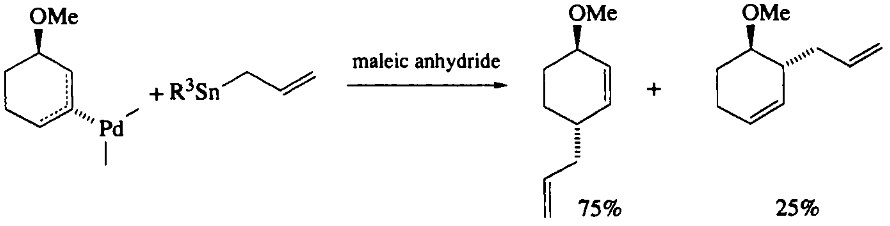

(244)

### 3.3.4.5 Regioselectivity of Organozincs

In contrast to the organotin derivatives which proceed by metal addition but apparently respond to asymmetry in the allyl ligand with regiochemical outcomes similar to those displayed by soft carbon nucleophiles (ligand attack), organozinc derivatives add by metal addition and show the complementary regiochemistry.[155,399] For example, perfluoroalkylzinc halides and phenylzinc chloride preferentially add to the more substituted allyl terminus (equations 245 and 246). In addition to exhibiting complementary regiochemical selectivity to the soft carbon nucleophiles, PhZnCl is also pronouncedly more discriminating, showing a 99:1 selectivity in an allyl system possessing a methyl at one terminus and a $Pr^n$ at the other (equation 246) (*cf.* diethyl malonate, 22:73). Explanations based on differential donor–acceptor properties of the allyl termini that have been advanced to explain regioselectivity in metal addition processes appear difficult to apply here, as the termini would appear to be electronically equivalent.

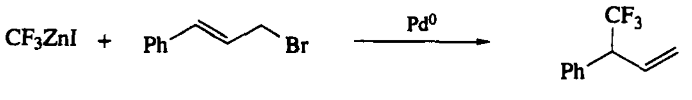

(245)

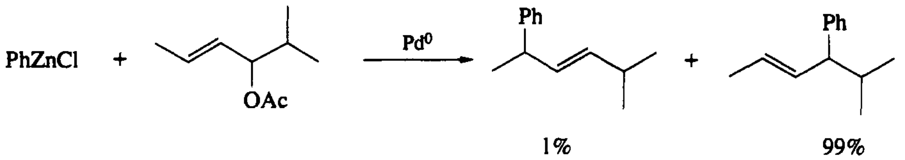

(246)

### 3.3.4.6 Regioselectivity of Organoaluminums and Organozirconiums

Alkenylaluminums add *via* metal addition and prefer coupling to the less substituted allyl terminus (equation 247).[154]

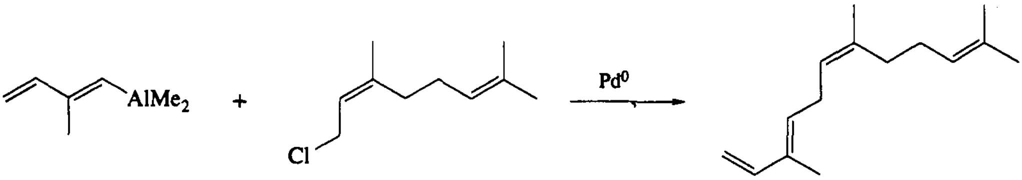

(247)

The most elegant and comprehensive mechanistic work associated with controlling the regiochemistry of additions to π-allylpalladium complexes that occur *via* metal attack–reductive elimination has been done in the area of organozirconiums.[155,156,395] The coupling of the ligands of the palladium allyl–alkenyl complex, formed on addition of an alkenylzirconium to a π-allylpalladium, was assumed to be an intramolecular process which requires a *cis* orientation of the groups that bond. As a result, the geometric distribution of ligands in the allylpalladium–alkenyl complexes immediately preceding formation of the carbon–carbon bond should determine the regioselectivity.

The model systems employed in these studies were derived from steroids. In these systems, it was reasoned that an asymmetrical allyl ligand should exert unequal *trans* influences upon the ligands on the palladium. The favored situation would have the stronger acceptor ligand *trans* to the more strongly donating (closer) terminus of the allyl ligand. In the allyl ligands studied, it was suggested that the distance Pd–C(20) would be less than the distance Pd–C(16), based on relative steric environments. As a result, the exocyclic C-20 allyl terminus would exert a stronger electron donating interaction towards the Pd and prefer to have an acceptor ligand *trans*. That is, complex (**16**) would be favored over (**17**). A donor ligand L should alternatively favor (**17**). In agreement with this rationale, coupling in the absence of maleic anhydride (L = Cl) gave a predominance of C-16 addition and in the presence of the acceptor ligand (L = maleic anhydride) gave a >95:5 ratio favoring alkenylation at C-20.

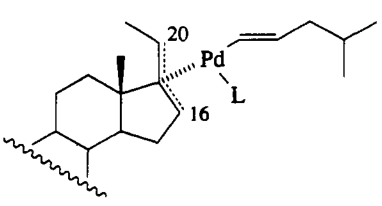

(**16**)

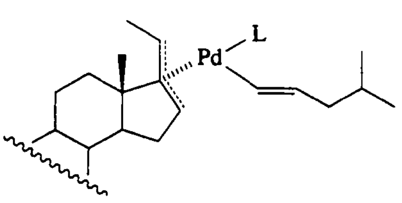

(**17**)

### 3.3.4.7 Regioselectivity of Grignards and Organolithiums

The addition of Grignards and organolithium reagents proceeds by attack at the metal center in π-allylpalladium complexes. The regiochemical selectivity exhibited by these hard carbon nucleophiles with π-allyl complexes substituted at the termini with alkyl or aryl groups is comparable to the soft carbon nucleophiles (ligand attack) in most cases, with addition occurring predominantly at the less substituted terminus (equations 248 and 249).[159,387]

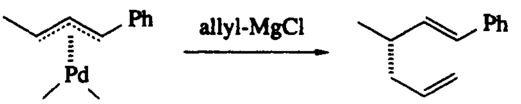

(248)

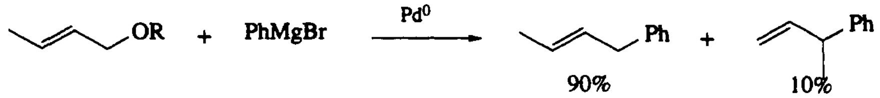

(249)

An elegant procedure has been elucidated for allyl–allyl′ coupling which demonstrates the crucial need for a π-acceptor ligand, such as maleic anhydride, to promote the reductive elimination (C—C bond-forming step).[366,367] These allyl–allyl′ couplings proceed with predominant 'head to head' regiochemistry, that is, with C—C bond formation between the less substituted allyl termini (equation 250). This is in contrast to the addition of allyltin reagents which are suggested to proceed by ligand addition in the absence of maleic anhydride and give 'head to tail' allyl–allyl′ couplings.

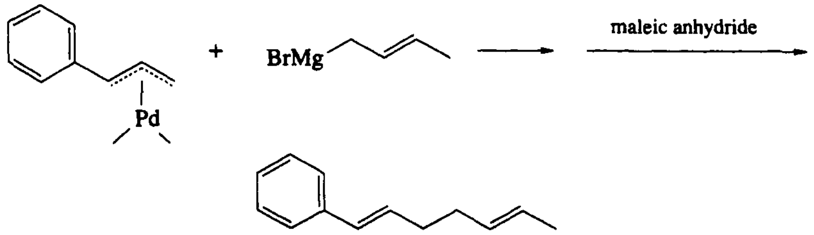

(250)

Some additional examples of regioselectivity of Grignard reagents have been reported. In contrast to the addition of alkenylzirconiums to the identical steroidal π-allyl complexes which selectively coupled to C-20, the Grignard reagent in the presence of maleic anhydride shows complete selectivity for addition to C-16 (equation 251).[396,397]

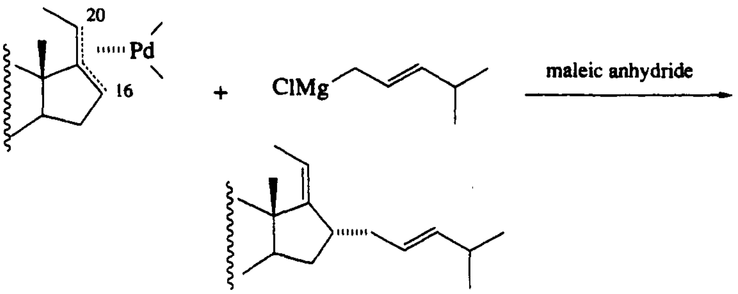

(251)

Addition of MeMgI[158] or PhLi[160] to π-allylpalladium complexes derived from methylenenorbornane exhibits selective C—C bond formation at the more hindered allyl terminus. Soft carbon nucleophiles with the same allyl species show the opposite regioselectivity (equation 252).[158,160]

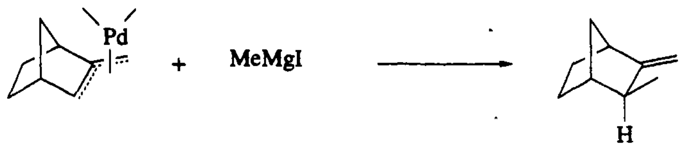

(252)

Regiodirection by remote oxygen functionality in the addition of Grignards parallels that observed by soft carbon nucleophiles, showing predominant attack at the more remote allyl terminus (equation 253).[397]

It is clear that although substantial progress has been made in the understanding and control of regioselectivity in the addition of nucleophiles to π-allylpalladium complexes *via* attack at the metal, considerable variability still exists in these reactions that is not readily mechanistically rationalized.

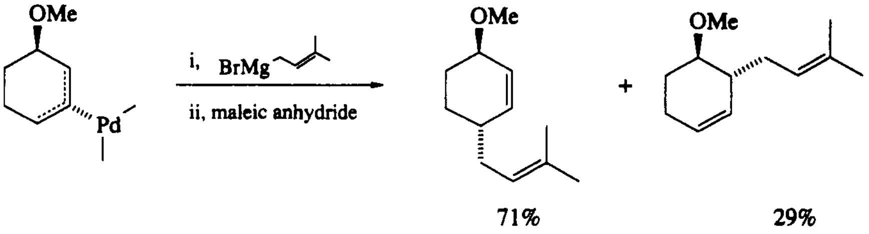
OMe
Pd
i, BrMg
ii, maleic anhydride
OMe
OMe
71%
29%

(253)

### 3.3.4.8 Regioselectivity of Oxygen Nucleophiles

Understanding the factors that control the addition of oxygen nucleophiles to π-allylpalladium complexes is complicated by the fact that: (i) oxygen nucleophiles, especially carboxylates, can add *via* ligand or metal addition; and (ii) the oxygen nucleophile can also serve as a leaving group, allowing equilibration of the products, thus superimposing thermodynamic over kinetic control of the addition.

Under conditions where metal attack is known to occur, an acetate nucleophile will preferentially add to the more substituted allyl terminus when directed by alkyl substitution (equation 254).[163] Remote oxygen-containing functionality directs acetate addition to the more distant terminus when metal attack is fostered (equations 255 and 256). Identical directing effects are observed from remote oxygen groups under conditions known to favor ligand addition (equations 257 and 258).[68,169,176] Reports on the addition of acetate where stereochemical information is not available and therefore the mechanism of attack is unknown indicate that $CO_2R$,[172] $SO_2R$[173,174] and CN[385] groups substituted directly on the allyl ligand all direct attack at the remote allyl terminus (equations 259–261).

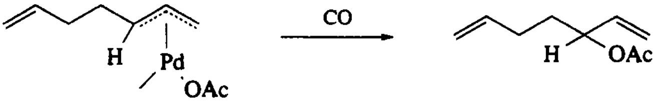
H
Pd
OAc
CO
H
OAc

(254)

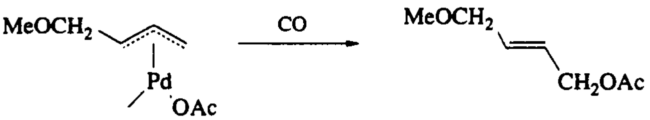
MeOCH2
Pd
OAc
CO
MeOCH2
CH2OAc

(255)

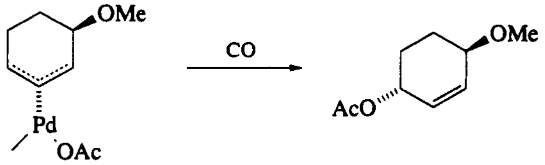
OMe
Pd
OAc
CO
OMe
AcO

(256)

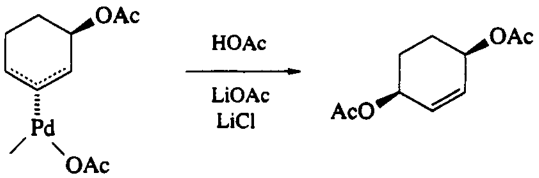
OAc
Pd
OAc
HOAc
LiOAc
LiCl
OAc
AcO

(257)

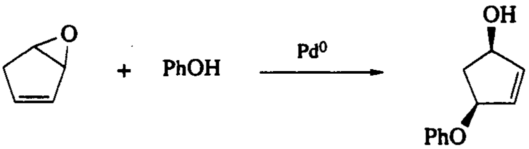
O
+ PhOH
Pd0
OH
PhO

(258)

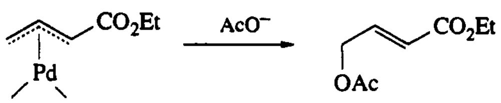
CO2Et
Pd
AcO−
CO2Et
OAc

(259)

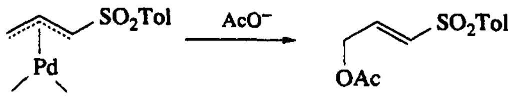
SO2Tol
Pd
AcO−
SO2Tol
OAc

(260)

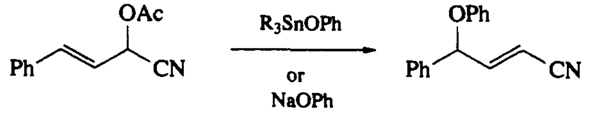
OAc
Ph
CN
R3SnOPh
or
NaOPh
OPh
Ph
CN

(261)

### 3.3.4.9 Regioselectivity of Amine Nucleophiles

Amine nucleophiles appear generally to add by attack at the allyl ligand. Similar to oxygen nucleophiles, however, a caveat must be noted in evaluating the observed regioselectivities in that the allyl amine products are capable of rearrangement by reentry into the π-allyl manifold.

Substitution on the terminus of the allyl ligand by alkyl[81,183,186,191,199,200] or aryl groups generally directs the addition of the amine to the less substituted allyl terminus (equations 262 and 263). The preference for reaction at the less substituted terminus of the allyl group increases as the amine nucleophile becomes more bulky (equations 264 and 265).[422]

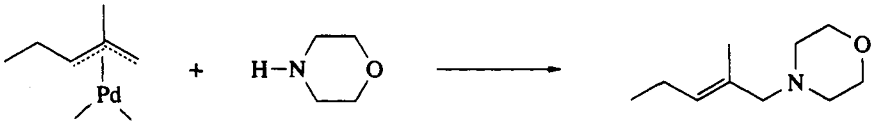

(262)

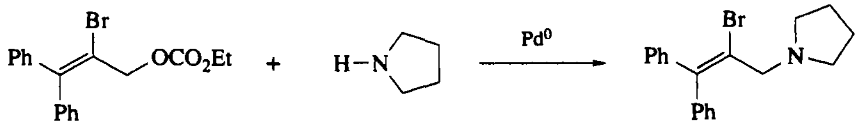
Br
Ph
OCO2Et
Ph
+
H−N
Pd0
Br
Ph
N
Ph

(263)

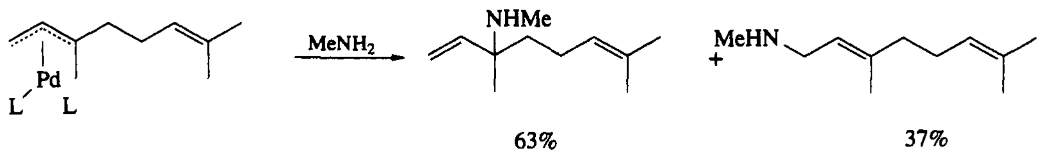
Pd
L
L
MeNH2
NHMe
63%
MeHN
+
37%

(264)

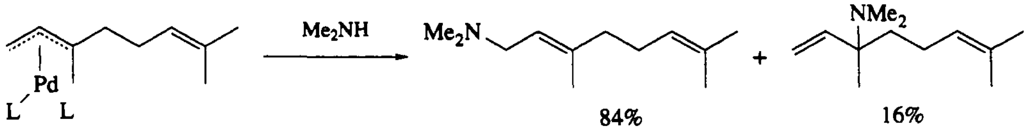
Pd
L
L
Me2NH
Me2N
84%
+
NMe2
16%

(265)

Carbonyl substitution on the allyl ligand leads to amine addition to the allyl terminus remote from the carbonyl moiety (equation 266).[202]

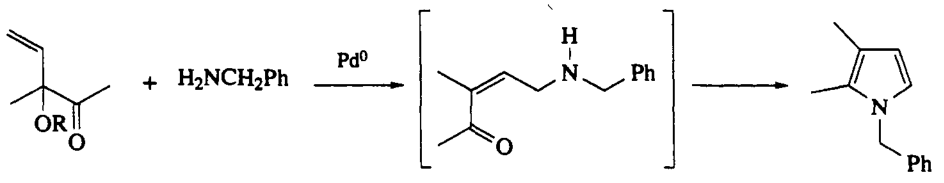
OR
O
+ H2NCH2Ph
Pd0
H
N
Ph
O
N
Ph

(266)

When presented with the choice between cyclization to give a five- or seven-membered ring, an amine nucleophile yields the five-membered ring.[203] However, reaction of an amine with the option to give either a bicyclo[4.2.0] or bicyclo[2.2.2] system produced the latter exclusively (equations 267 and 268).[204,205]

Functionality remote to the allyl ligand, whether it be oxygen,[181,183,190,193,195,201,410] nitrogen,[185] or phosphorus,[209] directs selective attack of an amine remote to the electronegative substituent (equations

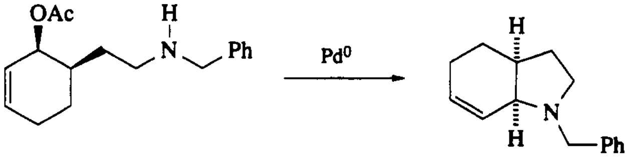

(267)

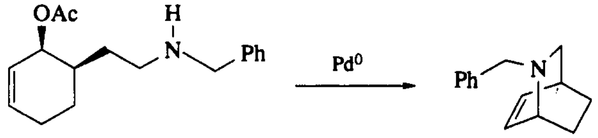

(268)

269 and 270). Ligand effects can also be significant in directing the regioselectivity of the addition of amines to π-allylpalladium complexes. In a study of the reactivity of geranyl- **18**) and neryl-palladium (**19**) complexes, it was noted that donor ligands on the palladium, *e.g.* pyridine or simple amines, direct the addition to the less substituted terminus. Triphenylphosphine complexed to the palladium, however, gave preferential addition to the more substituted terminus.

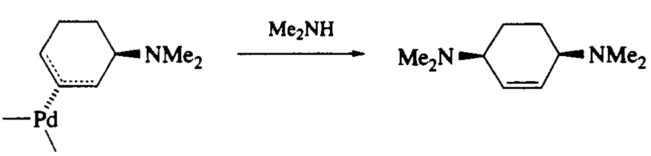

(269)

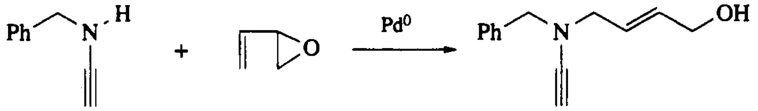

(270)

The regioselectivity of addition in these complexes also seems to depend on whether the side chain occupies a *syn* (geranyl; **18**) or *anti* (neryl; **19**) position. The bisphosphine neryl complex gives exclusive attack at the more substituted terminus with $MeNH_2$, while the geranyl complex gives 70% attack at the more substituted end but also 30% addition to the less substituted allyl terminus. The difference is greater in the reactions with dimethylamine where the geranyl complex mainly gives attack at the less substituted end, while the neryl complex preferentially gives addition to the more substituted allyl terminus.

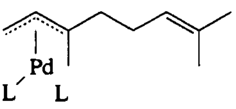

(**18**) Geranyl

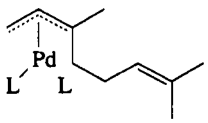

(**19**) Neryl

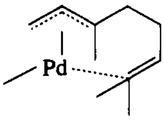

(**20**)

The possibility for internal coordination by the remote double bond exists for the geranyl complex (**20**). The alkene can act as an acceptor ligand and intensify the positive charge at the allyl terminus *trans* to it. This can account for the greater propensity of the geranyl system to add an amine to the less substituted terminus.

Amide nucleophiles can add to π-allylpalladium complexes by either ligand or metal addition. Only a limited number of examples have been examined, but these nucleophiles show a surprising tendency to add to the more substituted allyl terminus (equation 271).[197] However, in common with amine nucleophiles, they do add to the more distant terminus from remotely substituted polar functionalities (equation 272).[197]

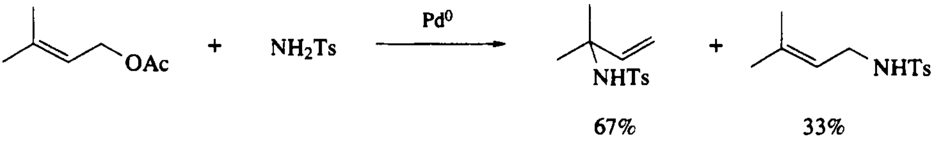

(271)

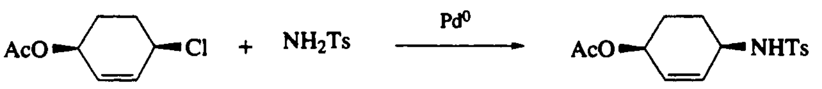
AcO
Cl
+
NH2Ts
Pd0
AcO
NHTs

(272)

Azides have been found to add to π-allylpalladium complexes on the less alkyl- or aryl-substituted terminus (equations 273 and 274).[423]

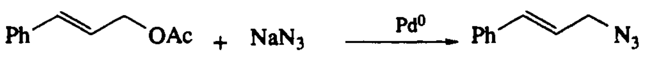
Ph
OAc
+
NaN3
Pd0
Ph
N3

(273)

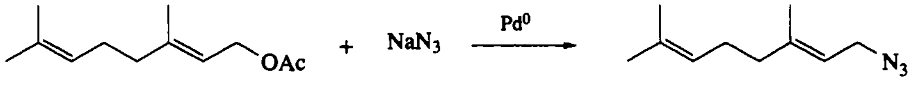
OAc
+
NaN3
Pd0
N3

(274)

Magnesium amides also add to unsymmetrical π-allylpalladium complexes on the less substituted terminus (equation 275).[199]

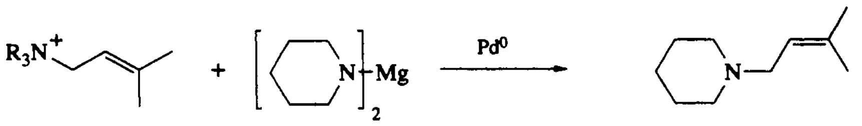
R3N+
+
N-Mg
2
Pd0
N

(275)

### 3.3.4.10 Regioselectivity of Sulfur Nucleophiles

All of the various sulfur nucleophiles that have been studied, including $PhSO_2$—, RS— and $(EtO)_2P(O)S$—, have been demonstrated to add to π-allylpalladium complexes by ligand addition. Interpretation of the regioselectivities of these nucleophiles must be tempered by the realization that the allyl–$SO_2Ph$, –SR and –$SP(O)(OEt)_2$ products are capable of isomerization by means of reentering the π-allylpalladium manifold.

The regioselectivity of *p*-toluenesulfonate nucleophiles as directed by alkyl groups asymmetrically substituted on the allyl ligand is very difficult to characterize, with preferential attack at both the more[211-213] and less[213,218] substituted allyl terminus alternately observed (equations 276–278).

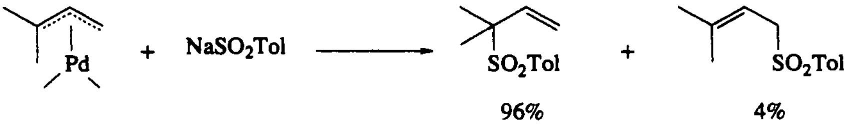
Pd
+
NaSO2Tol
SO2Tol
+
SO2Tol
96%
4%

(276)

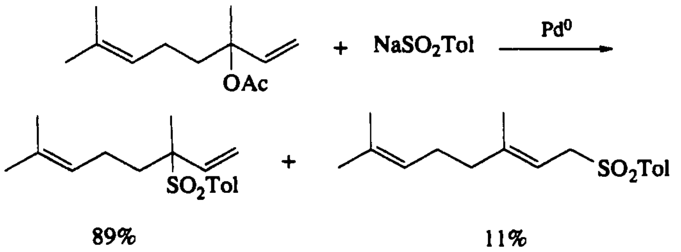
OAc
+
NaSO2Tol
Pd0
SO2Tol
+
SO2Tol
89%
11%

(277)

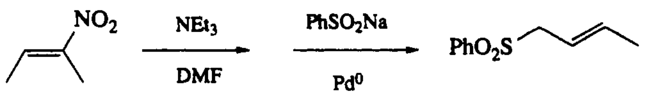
NO2
NEt3
DMF
PhSO2Na
Pd0
PhO2S

(278)

Particularly perplexing is a result obtained with the two possible crotyl precursors which should give the same π-allylpalladium complex, yet gave opposite regiochemical results (equations 279 and 280).[213]

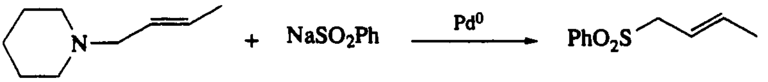
N
+
NaSO2Ph
Pd0
PhO2S

(279)

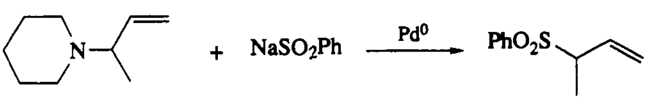

N
+ NaSO2Ph
Pd0
PhO2S

(280)

Aryl-substituted allyls give the addition of sulfonate at the remote allyl terminus (equation 281).[212]

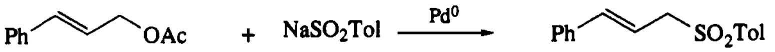

Ph
OAc
+ NaSO2Tol
Pd0
Ph
SO2Tol

(281)

In contrast to the malonate additions to methylenecycloalkane-derived π-allyl complexes, where substantial endocyclic addition has been observed with the cyclohexyl analog, essentially exclusive exocyclic addition occurs for both the five- and six-membered ring cases with $PhSO_2Na$ (equations 282 and 283).[219]

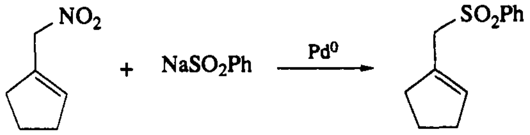

NO2
+ NaSO2Ph
Pd0
SO2Ph

(282)

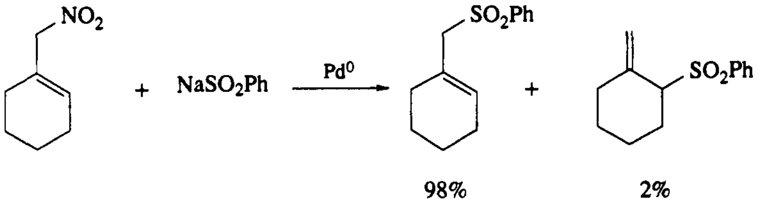

NO2
+ NaSO2Ph
Pd0
SO2Ph
+
SO2Ph
98%
2%

(283)

Ethoxycarbonyl groups show efficient regiodirecting powers in sulfonate additions, giving exclusive C—S bond formation at the allyl terminus remote to the carbonyl functionality (equation 284).[219] Remote oxygen functionality also directs incoming sulfonate nucleophiles to the distal allyl terminus (equation 285).[215]

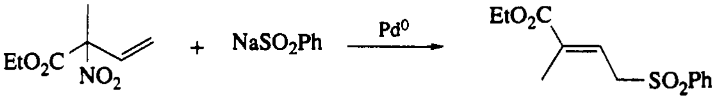

EtO2C
NO2
+ NaSO2Ph
Pd0
EtO2C
SO2Ph

(284)

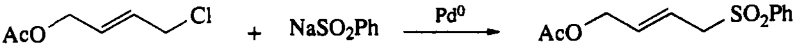

AcO
Cl
+ NaSO2Ph
Pd0
AcO
SO2Ph

(285)

*S*-Allyl dithiocarbonates on treatment with Pd$^0$ catalyst expel COS and serve as precursors to RS$^-$ nucleophiles. Alkyl-substituted precursors show preferential attack at the more substituted allyl terminus, while aryl-substituted precursors give exclusive attack at the less substituted allyl terminus (equation 286).[222]

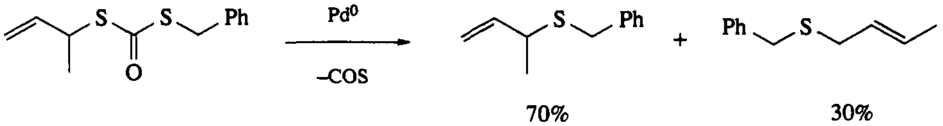

S
S
Ph
O
Pd0
–COS
S
Ph
+
Ph
S
70%
30%

(286)

*O*-Allyl-*S*-alkyl dithiocarbonates show attack at the less substituted allyl end when directed by alkyl or aryl groups appended to the allyl ligand (equations 287 and 288).[221]

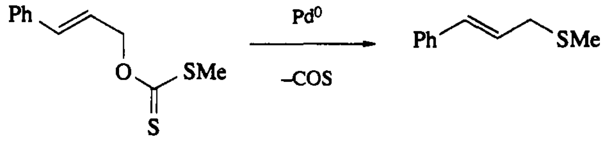

Ph
O
SMe
S
Pd0
–COS
Ph
SMe

(287)

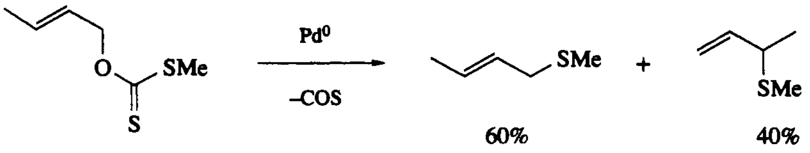
SMe
Pd0
-COS
60%
40%

(288)

*O*-Allyl phosphonothionates rearrange on treatment with Pd$^0$ catalysts to the *S*-allyl derivatives.[220] Alkyl substituents on the allyl group direct attack to the less substituted allyl terminus (equation 289).

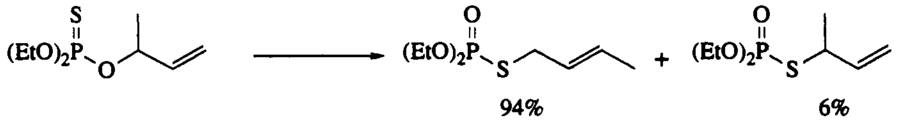

(289)

Trimethylsilyl alkyl and aryl sulfides react with allyl carbonates and vinyl epoxides to deliver the alkyl or aryl sulfide to the allyl unit. These species show typical regioselectivities by: (i) adding to the less substituted end of alkyl substituted allyls (equation 290); (ii) adding to the allyl terminus more distant from remote oxygen functionality (equation 291); and (iii) showing substantial endocyclic addition to methylenecyclohexane-derived allyls (equation 292).[223]

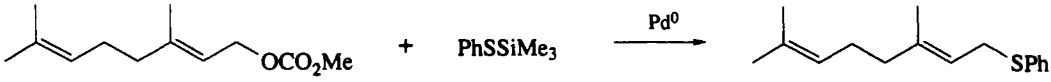
OCO2Me
+ PhSSiMe3
Pd0
SPh

(290)

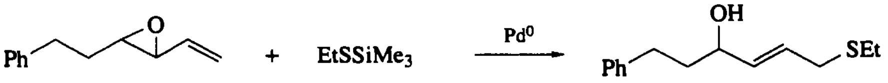
Ph
O
+ EtSSiMe3
Pd0
OH
Ph
SEt

(291)

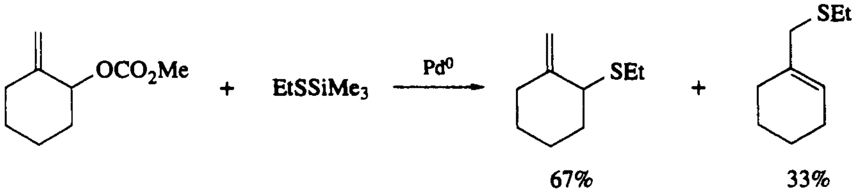
OCO2Me
+ EtSSiMe3
Pd0
SEt
+
SEt
67%
33%

(292)

### 3.3.4.11 Regioselectivity in Other Heteroatom Nucleophiles

Lithium diphenylthiophosphides add *via* ligand addition and, in the single case studied, couple preferentially to the more substituted allyl terminus (equation 293).[224]

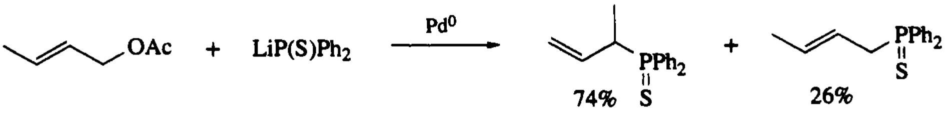
OAc + LiP(S)Ph2
Pd0
PPh2
S
74%
+
PPh2
S
26%

(293)

Tris(trimethylsilyl)aluminum reacts with π-allylpalladium complexes to yield allylsilanes. The regiochemistry of this addition is highly dependent on reaction conditions, and no trends can be readily discerned.[225]

Acyliron and acylnickel anions, as well as NaCo(CO)$_4$, acylate π-allylpalladium complexes selectively at the less substituted allyl terminus (equation 294).[225]

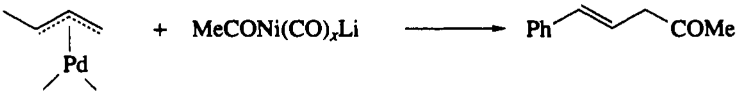
Pd
+ MeCONi(CO)xLi
Ph
COMe

(294)

### 3.3.4.12 Regioselectivity in Other π-Allylpalladium Reactions

#### *3.3.4.12.1 Insertion of CO, CO₂, C≡N*

The reaction of CO with π-allylpalladium complexes shows highly regioselective insertion into the less substituted allyl terminus[235,237–239] as illustrated in equations (295)–(297). One interesting exception is shown in an allyl complex possessing a Cl group on its terminus, where insertion takes place into the more substituted allyl end (equation 298).[234]

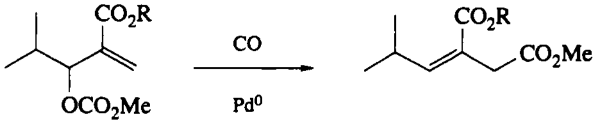

(295)

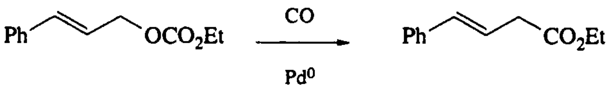

(296)

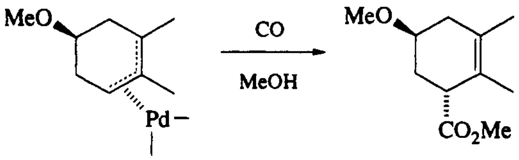

(297)

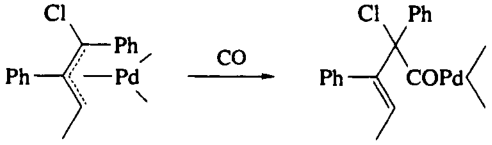

(298)

$CO_2$ insertion into π-allylpalladium complexes exhibits the opposite regioselectivity, with, for example, exclusive reaction at the more substituted terminus of a butenylpalladium complex (equation 299).[244]

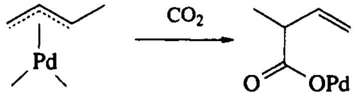

(299)

Isocyanide insertion into π-allylpalladium complexes generally occurs regioselectivity into the less substituted allyl terminus (equation 300).[240]

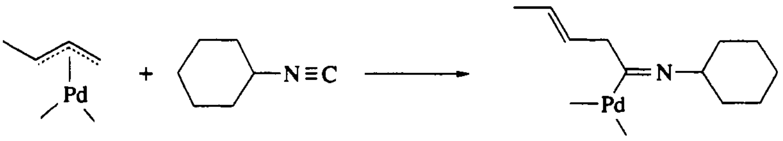

(300)

#### *3.3.4.12.2 Insertion of dienes*

The regioselectivity of the insertion of 1,3-dienes into π-allylpalladium complexes possesses two components. First, with respect to the allyl unit, the insertion takes place at the more substituted terminus.[248,249,251,252] Second, with regard to the diene it has been shown that 2-substituted-1,3-dienes insert at the more substituted alkene.[248,249] These interesting features have been explained by the intermediacy of an $\eta^1$-allyl species which is bound to the palladium at the less substituted terminus and with the Pd complexed to the less substituted alkene of the diene. The insertion process proceeds from this intermediate by an electrocyclic reaction which occurs outside the coordination sphere of the Pd (equation 301). This diene insertion has been recently employed as the key step in a potentially highly useful cyclization process (equation 302).[252]

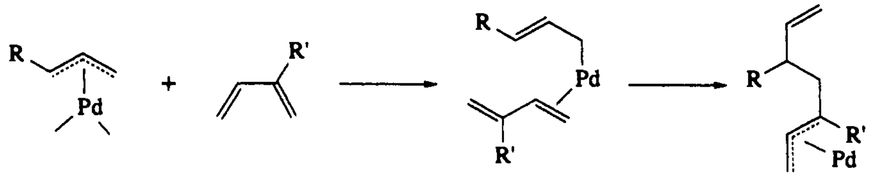

(301)

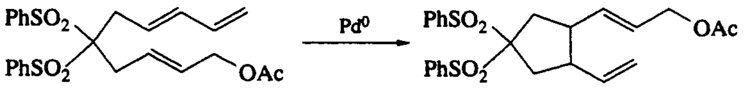

(302)

### 3.3.4.12.3 Insertion of alkenes into π-allylpalladium complexes

Intramolecular insertion of alkenes into π-allylpalladium complexes has been shown to proceed regioselectively to yield five-membered rings.[262,263] This transformation is equivalent to a palladium ene reaction and is completed by a β-hydride elimination. The C═C bond of ketenes is also capable of undergoing insertion into π-allylpalladium intermediates.[264] The final course of this reaction is dependent on the leaving group in the initial allyl–X precursor. For X = OAc, dienes are observed; for X = $MeOCO_2$, a methoxycarbonyl adduct is obtained (equation 303).[264]

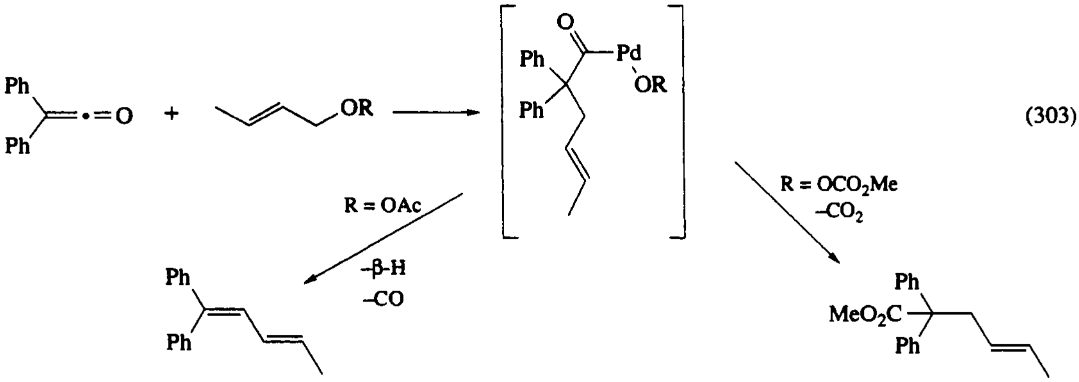

(303)

### 3.3.4.12.4 Insertion of C═N into π-allylpalladium complexes

The bis(π-allyl) complex derived from the linear dimerization of butadiene can be trapped with phenylhydrazones in a process involving C═N insertion into a π-allyl intermediate.[265] Predominant insertion into the more substituted terminus is observed (equation 304).

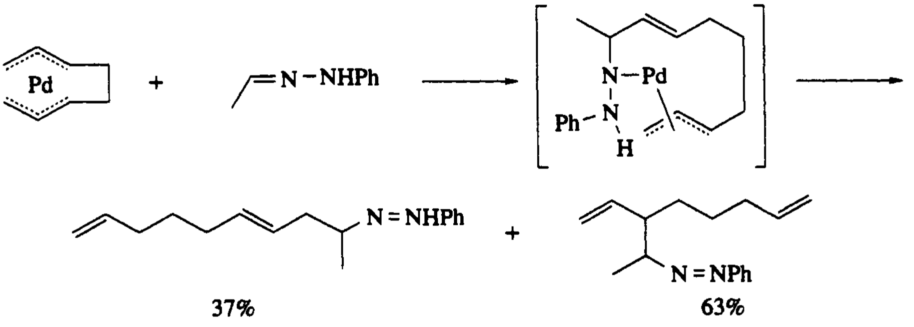

(304)

### 3.3.4.12.5 *Oxidation of π-allylpalladium complexes*

The oxidation of preformed π-allylpalladium complexes with MCPBA proceeds by attack at the metal to give oxidation at the less substituted allyl terminus (equation 305).[272] $MoO_2(acac)_2$–$Bu^tO_2H$ oxidations also involve attack at palladium, but, in contrast to MCPBA, give oxidation preferentially at the more substituted allyl end (equations 306–308).[275]

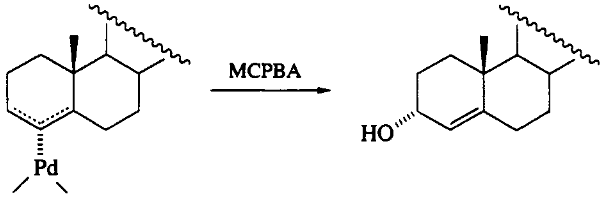

(305)

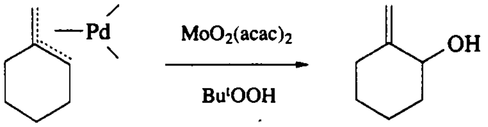

(306)

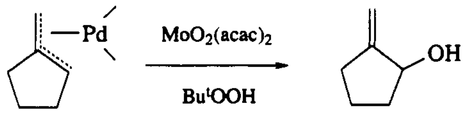

(307)

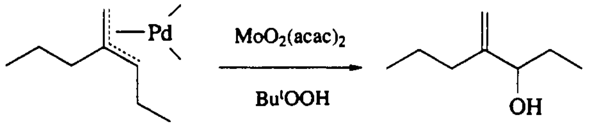

(308)

Oxidation of preformed π-allylpalladium complexes with $Cr^{VI}$ salts appears particularly capricious. $Na_2Cr_2O_7$ gave exclusive attack at the more substituted terminus (equation 309),[267] while a similar allyl substrate gave oxidation at the less substituted terminus with Collins reagent ($Cr^{VI}$ oxide, pyridine; equation 310).[269] Photo-oxidation of π-allylpalladium complexes also shows inconsistent regioselectivity when directed by alkyl substituents on the terminus of an allyl ligand (equations 311 and 312).[276] A carbonyl or sulfonyl group appended on the allyl unit, however, gave exclusive oxidation at the allyl end remote to the functionality (equations 313 and 314).[277]

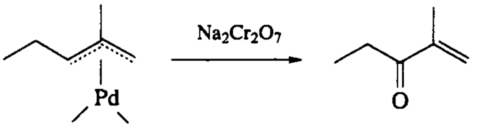

(309)

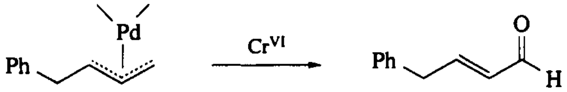

(310)

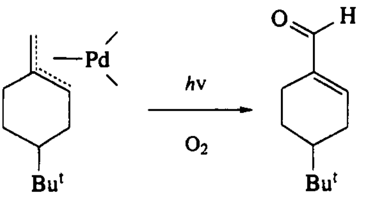

(311)

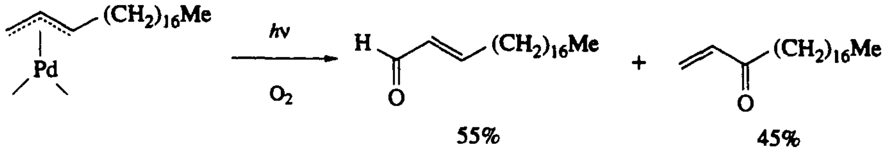
(CH2)16Me
Pd
hν
O2
H
(CH2)16Me
O
+
(CH2)16Me
O
55%
45%

(312)

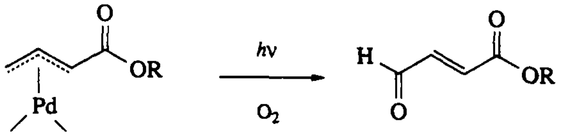
O
OR
Pd
hν
O2
H
O
O
OR

(313)

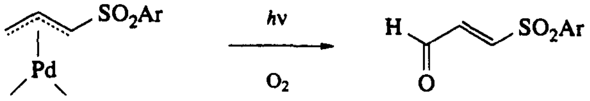
SO2Ar
Pd
hν
O2
H
SO2Ar
O

(314)

### *3.3.4.12.6 Reduction of π-allylpalladium complexes*

A wide variety of methodologies have been developed for the reduction of a π-allylpalladium complex. Although these processes appear to uniformly involve attack at the metal center, the regiochemistry of the reduction is highly dependent on the reagent selected. For example, the regiodirection exerted by alkyl or aryl groups at the allyl terminus is clearly reagent dependent. KOH–MeOH can accomplish reduction of π-allyl complexes, and does so with hydride addition to the less substituted allyl terminus (equations 315 and 316).[281]

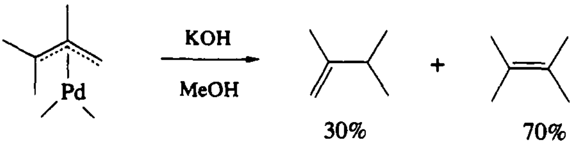
Pd
KOH
MeOH
+
30%
70%

(315)

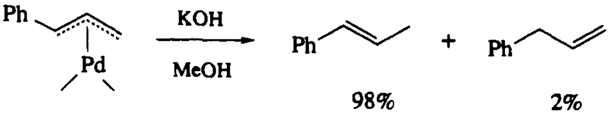
Ph
Pd
KOH
MeOH
Ph
+
Ph
98%
2%

(316)

Reduction with $LiAlH(OBu^t)_3$[293] or LAH[292] also gives selective hydride addition to the less substituted allyl end (equations 317 and 318). In contrast, formate reductions selectively deliver hydride to the more substituted allyl terminus (equations 319 and 320).[302,303]

Si—H-mediated reduction, conveniently performed with polymethylhydrosiloxane (PMHS), demonstrates no clear pattern of regioselectivity (equation 321).[320]

$LiHBEt_3$ delivers hydride regioselectivity to the less substituted allyl terminus (equation 322).[289–291]

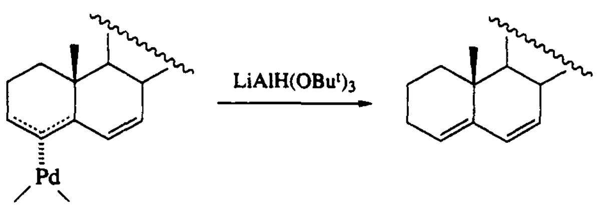
Pd
LiAlH(OBu^t)3

(317)

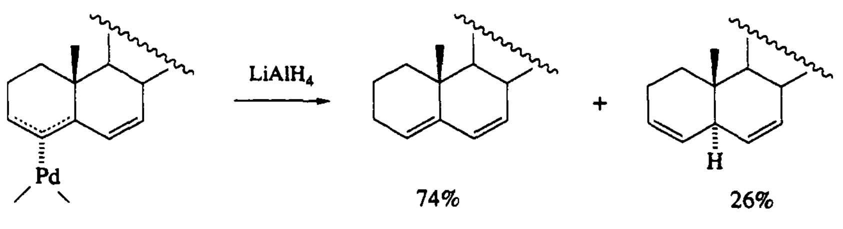
Pd
LiAlH4
+
H
74%
26%

(318)

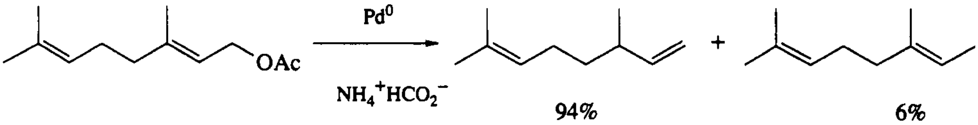
Pd$^0$
NH$_4^+$HCO$_2^-$
OAc
94%
6%

(319)

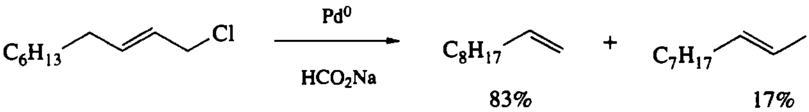
C$_6$H$_{13}$
Cl
Pd$^0$
HCO$_2$Na
C$_8$H$_{17}$
83%
C$_7$H$_{17}$
17%

(320)

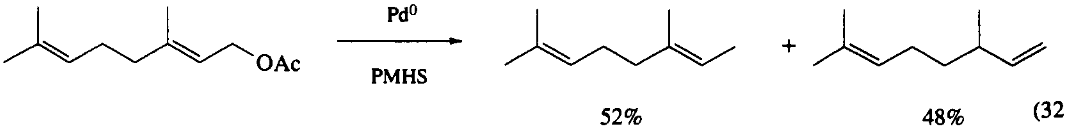
OAc
Pd$^0$
PMHS
52%
48%

(321)

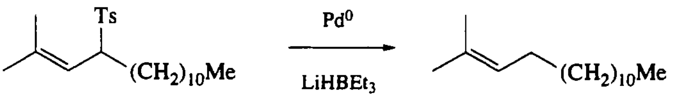
Ts
(CH$_2$)$_{10}$Me
Pd$^0$
LiHBEt$_3$
(CH$_2$)$_{10}$Me

(322)

Electrochemical reduction of a π-allylpalladium complex results in preferred formation of the more substituted alkene (equation 323).[307] Conversely, reduction by $SmI_2$, followed by protonation, provides the less substituted alkene predominantly (equation 324).[305]

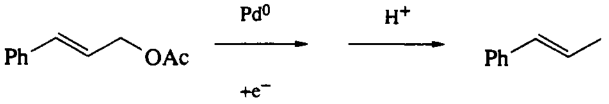
Ph
OAc
Pd$^0$
+e$^-$
H$^+$
Ph

(323)

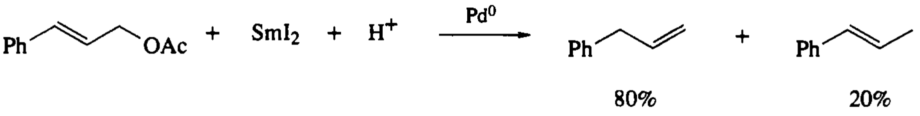
Ph
OAc
+ SmI$_2$ + H$^+$
Pd$^0$
Ph
80%
Ph
20%

(324)

Delivery of hydride from a NAD(P)H model, *i.e.* *N*-Pr-1,4-dihydronictotinamide, occurs prefentially at the more substituted allyl end (equation 325).[306]

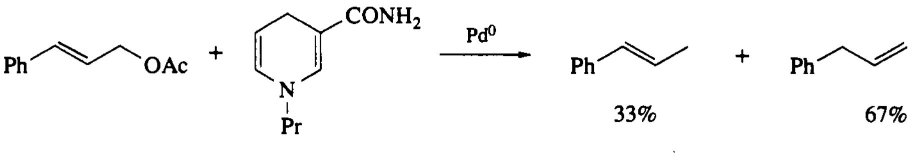
Ph
OAc
CONH$_2$
N
Pr
Pd$^0$
Ph
33%
Ph
67%

(325)

An informative comparison of a number of these reducing agents reacting with a single π-allyl substrate has been reported (Scheme 6).[291]

Some special directing effects have been observed in these reductions. For example, $R_3SnH$ is directed by an OAc or Cl substituent on the allyl terminus to deliver hydride to the remote terminus,[297] but a CN directs delivery to the proximal terminus (equations 326–328).[287] Electrochemical reduction[307] also results in formation of an α,β-unsaturated organo product (equation 329). A remote OH functionality appears to direct $NaBH_4$ reduction to the proximal allyl terminus (equation 330).[288]

### *3.3.4.12.7 Umpolung*

π-Allylpalladium complexes, which act as electrophiles, can be transformed into allyl-silanes and -stannanes, which typically act as nucleophiles. The allylsilanes, generated by electrochemical reduction and trapping with $R_3SiCl$,[307] and allylstannanes, formed by treatment with $Et_2AlSnBu_3$[309,310] or $SmI_2$ and

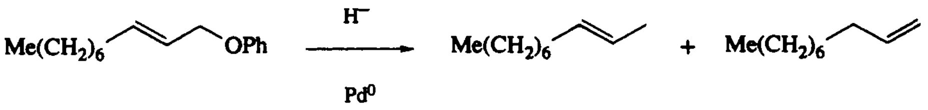
Me(CH2)6
OPh
H−
Pd0
Me(CH2)6
+
Me(CH2)6

| *Reducing agent* | *2-Alkene* | *1-Alkene* |
|---|---|---|
| $LiBHEt_3$ | 100 | 0 |
| $LiAlH_4$ | 97 | 3 |
| $Bu^t_2AlH$ | 100 | 0 |
| $NaBH_4$ | 45 | 55 |
| $NaBH_3CN$ | 71 | 29 |
| $Ph_2SiH_2$ | 55 | 45 |
| $NH_4^+HCO_2^-$ | 12 | 88 |

**Scheme 6**

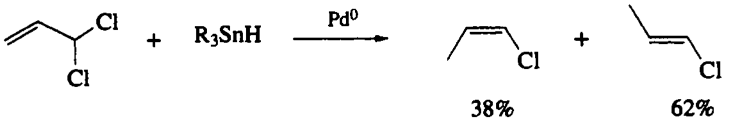
Cl
Cl
+
R3SnH
Pd0
Cl
+
Cl
38%
62%

(326)

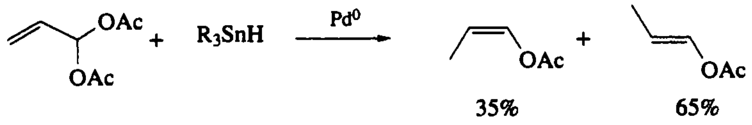
OAc
OAc
+
R3SnH
Pd0
OAc
+
OAc
35%
65%

(327)

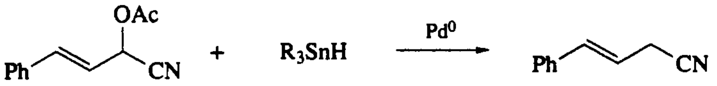
OAc
Ph
CN
+
R3SnH
Pd0
Ph
CN

(328)

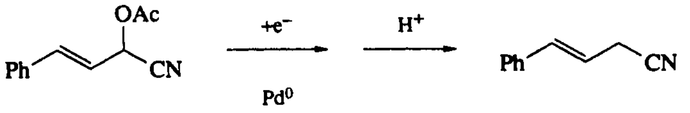
OAc
Ph
CN
+e−
Pd0
H+
Ph
CN

(329)

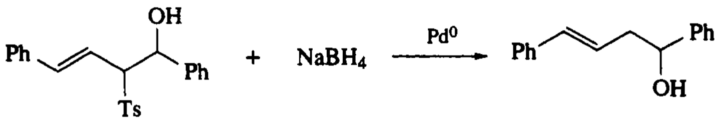
OH
Ph
Ph
Ts
+
NaBH4
Pd0
Ph
Ph
OH

(330)

$R_3SnCl$,[311] have the heteroatom selectivity positioned at the less substituted allyl terminus (equations 331–334).

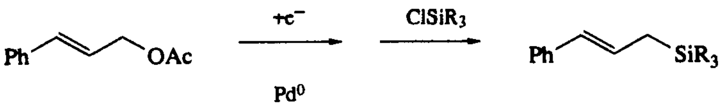
Ph
OAc
+e−
Pd0
ClSiR3
Ph
SiR3

(331)

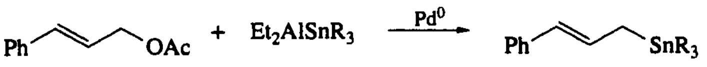
Ph
OAc
+
Et2AlSnR3
Pd0
Ph
SnR3

(332)

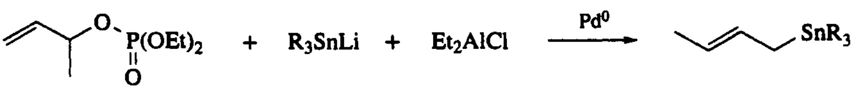
O
P(OEt)2
O
+
R3SnLi
+
Et2AlCl
Pd0
SnR3

(333)

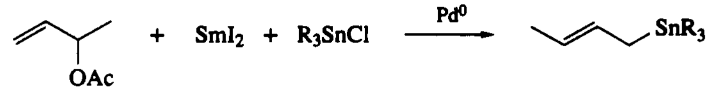

(334)

### *3.3.4.12.8 Regioselectivity of addition reactions*

Addition of disilanes to π-allylpalladium complexes proceeds selectively to yield the silyl group appended to the less substituted allyl terminus (equations 335 and 336).[338,339]

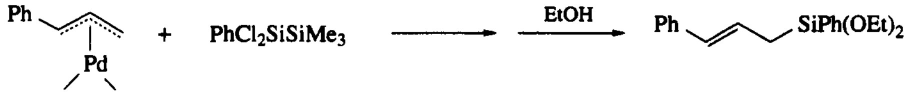

(335)

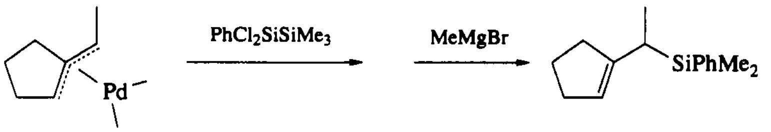

(336)

## 3.3.5 ENANTIOSELECTIVITY

### 3.3.5.1 Introduction

Three basic types of enantioselectivity have been investigated in conjunction with the reaction of π-allylpalladium complexes with nucleophiles. In the first type, the chirality exists in the allyl–X precursor. The stereospecificities associated with the oxidative addition to convert it to a π-allyl complex and the subsequent attack by the nucleophile are key in the chirality transfer (equation 337).

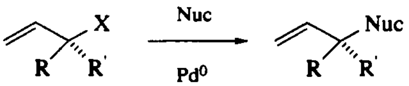

(337)

In the second type, the source of the chirality is the phosphine ligand on the palladium. Two scenarios have been evaluated. In the first, an achiral *meso* allyl ligand is employed. This ligand when complexed to an optically active $PdL_2^*$ creates a chiral π-allyl complex. The transition states leading to attack at one terminus or the other are then diastereomeric and can lead to optically active products. The second scenario employs a prochiral allyl ligand. The resulting π-allyl complexes with $PdL_2^*$ are now diastereomeric and the relative reactivity of these diastereomeric complexes with the nucleophile is the source of formation of optically active products. The third and last type involves the use of a chiral leaving group or chirality in the nucleophile in the allyl alkylation (equations 338 and 339).

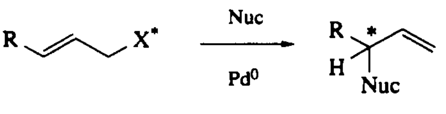

(338)

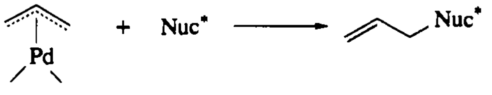

(339)

### 3.3.5.2 Chirality Transfer

Optically active methyl (*R*)-3-oxo-7-(methoxycarbonyloxy)-8-nonenoate, when converted to its sodium salt and treated with a $Pd^0$ catalyst, proceeds to form an optically active allylcyclohexanone with complete retention at the original chiral center.[424] For this chirality transfer from a C—O to a C—C bond to be successful, both the formation of the π-allyl complex and the attack of the nucleophile must be completely stereospecific. In addition, the attack by the nucleophile must be fast relative to a *syn–anti* type interconversion of the π-allyl intermediate (*via* an $\eta^1$-allyl, with the Pd attached to the less substituted terminus) which would result in racemization (Scheme 7).

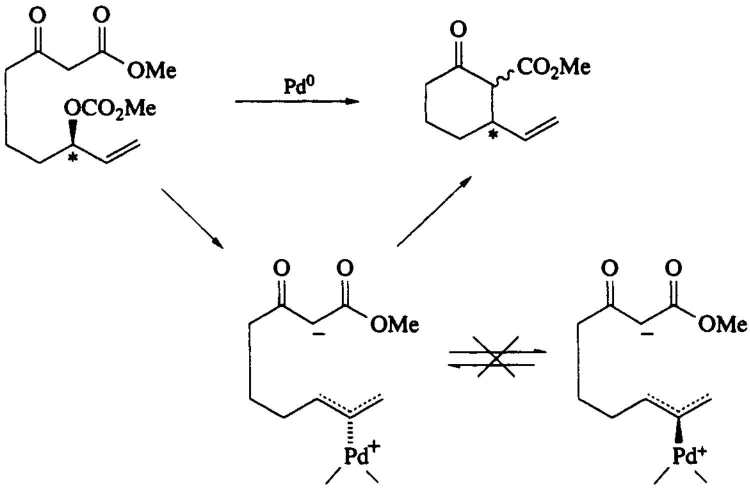
O
O
OMe
$OCO_2Me$
*
$Pd^0$
O
$CO_2Me$
*
O
O
OMe
$Pd^+$
O
O
OMe
$Pd^+$

**Scheme 7**

An efficient cyclization is also observed with methyl (5*R*)-methoxycarbonyl-(3*E*)-decenyl malonate to yield an optically active product (equation 340).[425]

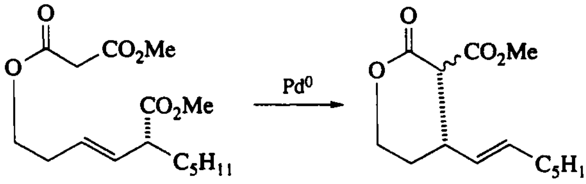
O
O
$CO_2Me$
$CO_2Me$
$C_5H_{11}$
$Pd^0$
O
O
$CO_2Me$
$C_5H_{11}$

(340)

An intermolecular example of this process was also shown to proceed with a high degree of chirality transfer (equation 341).[426] The chirality transfer process can also function with oxygen nucleophiles as shown in equations (342) and (343).[427]

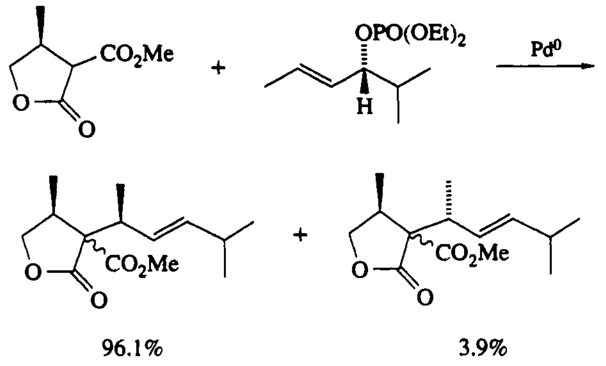
$CO_2Me$
O
O
+
$OPO(OEt)_2$
H
$Pd^0$
$CO_2Me$
O
O
+
$CO_2Me$
O
O
96.1%
3.9%

(341)

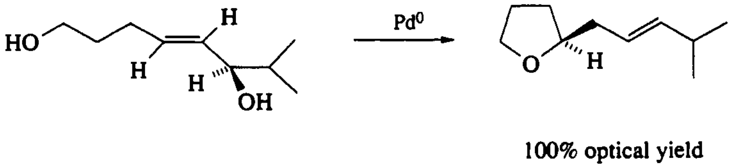
HO
H
H
H
OH
$Pd^0$
O
H
100% optical yield

(342)

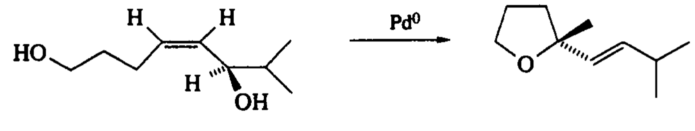

(343)

90% optical yield

A net C—O to C—C bond chirality transfer has been demonstrated in the preparation of a cyclopropane (equation 344).[428] Another C—O to C—C chirality transfer was accomplished starting with an optically active alkylidenetetrahydrofuran.[429] Not only was complete stereospecificity *via* a double inversion mechanism observed, but, in addition, regioselectivity had to be exercised to avoid the alternate cyclization to give a seven-membered ring product (equation 345).

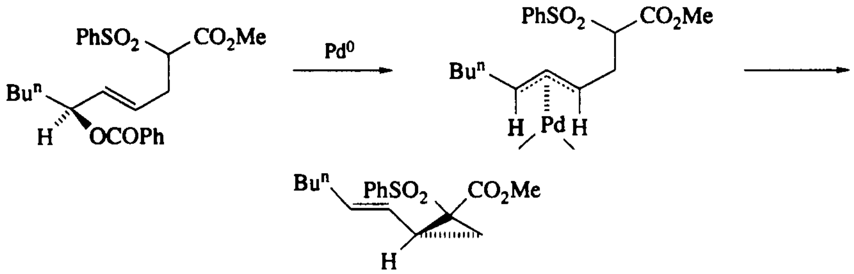

(344)

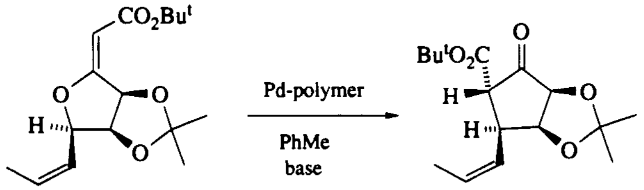

(345)

An elegant example of a stereo relay in a nonrigid system employed a chiral vinyl lactone.[430] For the relay to be completely successful (i) the ionization of the vinyl lactone must occur from one conformation, (ii) the intermediate π-allylpalladium complex must retain its stereochemistry, and (iii) the nucleophile must attack regioselectively at the carbon of the allyl system distal to the incipient carboxylate. This distal transfer of chirality was achieved as shown in equation (346). This same process has been utilized in a synthesis of an optically active vitamin E side chain from D-glucose.[431]

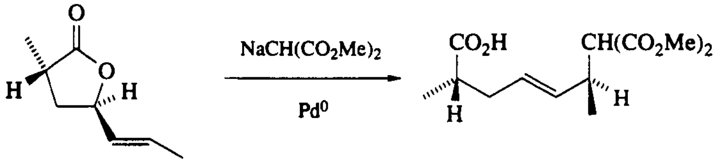

(346)

### 3.3.5.3 Enantioselectivity with Optically Active Phosphines

Significant progress has been made in enantioselective C—C bond formation in π-allylpalladium chemistry, where the source of the chirality is the phosphine ligand on the palladium. A number of potential difficulties must be addressed in order for this approach to result in synthetically useful optical yields. Racemization can occur by a variety of mechanisms. Intermediates not bearing substituents at both allyl termini can undergo *syn–anti* isomerization, which accomplishes racemization (equation 347).

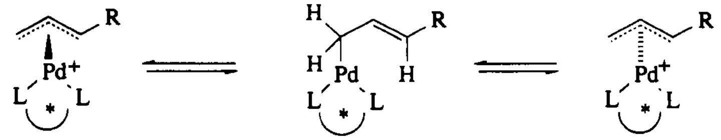

(347)

Allyl acetates are the preferred precursors for π-allyl complexes. The acetate liberated on oxidative addition (stereochemical inversion step) to form the π-allyl complex can add again to the allyl ligand, displacing the palladium. It has been demonstrated[167] that this addition can take place either *via* direct attack on the allyl ligand on the face opposite the palladium or at the palladium, followed by reductive elimination (equation 348). These processes have opposite stereochemical results, and with respect to enantioselectivity, attack at the metal will result in racemization of the starting allyl acetate (equation 349). It has been shown that this process can become competitive if the incoming nucleophile is particularly sterically bulky and slow to add to the allyl ligand.[167]

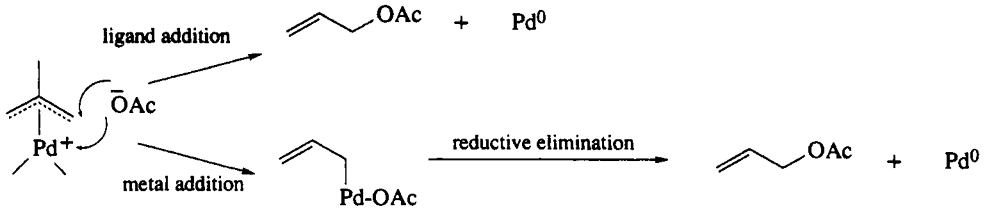

(348)

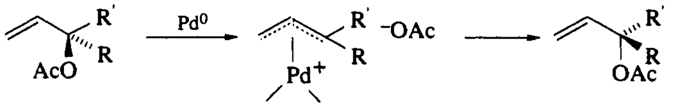

(349)

A recently uncovered mode of racemization involves attack of the π-allylpalladium complex by an uncomplexed $PdL_2$ species present in the solution. This mode of racemization can be significant if high concentrations of $PdL_4$ catalyst are employed in the reaction (equation 350).

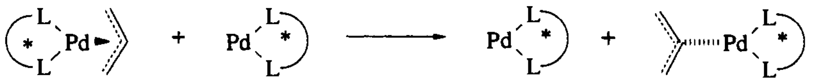

(350)

An inherent difficulty in achieving high optical yields in π-allylpalladium reactions is that with the soft carbon nucleophiles employed, attack occurs on the allyl ligand on the face opposite the palladium. This places the source of the chirality (the phosphine ligand) remote from where C—C bond formation is taking place. Despite these limitations, considerable success has been achieved in these reactions.

The initial study in this area employed the *meso*-1,3-dimethylallyl ligand.[432] The chloride dimer was generated from 2-pentene, and a variety of optically active phosphine ligands were added to form the chiral bisphosphine complexes. Reaction of these allyl complexes with sodiodiethyl malonate resulted in optical yields in the range of 2–29% (equation 351).

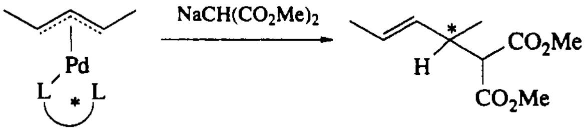

(351)

Asymmetric induction in catalytic allylic alkylation was next evaluated.[433] Alkylation of a racemic ethylcyclopentenyl acetate with the sodium salt of methyl phenylsulfonylacetate with (+)-DIOP gave the best result (optical yield 46%; equation 352). The asymmetry of the allyl ligand in this case results in diastereomeric π-allyl complexes with the $PdL_2$* moieties. The optical yields observed demand a racemization of the starting allyl acetate or interconversion of the diastereomeric complexes. If the re-

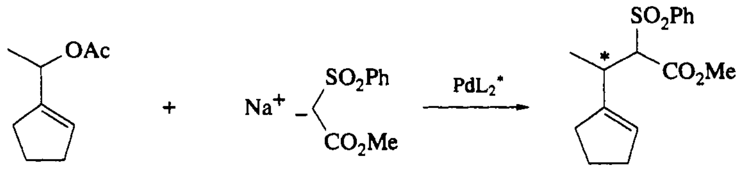

(352)

action proceeded without racemization or interconversion and strictly by a double inversion process from the racemic allyl acetate, then the product would of necessity be racemic (equation 352).

A variation on this asymmetric catalytic allylation scheme employed β-diketones or β-keto ester nucleophiles with allyl ethers and a palladium–DIOP catalyst.[434] The chiral center generated is now one carbon removed from the allyl ligand. As a result, somewhat lower optical yields were observed (≈10%; equation 353). A variety of chiral phosphines were evaluated in the cyclization of β-keto esters. Optical yields up to 48% were measured in these reactions.[435]

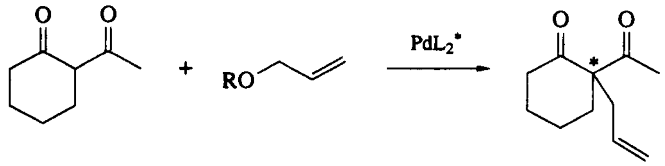

(353)

Allylic alkylations using a benzophenone imine of glycine methyl ester as a prochiral nucleophile and chiral phosphine ligands on palladium produced optical yields up to 57% (equation 354).[436]

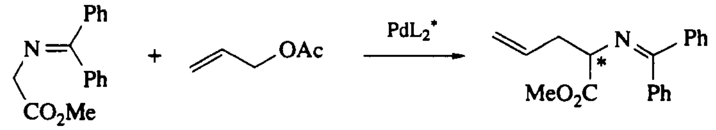

(354)

Attempts to address the difficulty associated with the distance of the chirality in the Pd ligand to the site of C—C bond formation have been most fruitful. New chiral phosphine ligands containing an optically active functional group remote from the phosphines have been very effective, providing optical yields up to 52% in the case where the new chiral center is one carbon removed from the allyl ligand[437] (*cf.* 10% optical parity obtained previously;[434] equation 355).

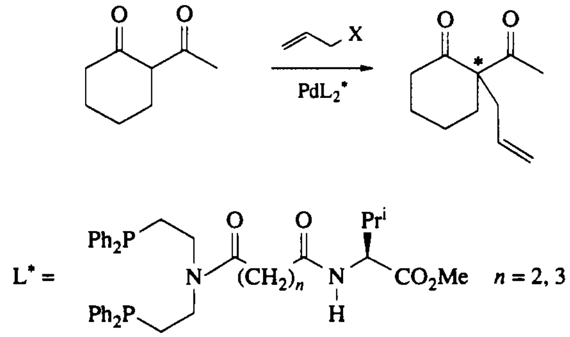

(355)

'Chiral pockets' have been created, employing optically active ligands derived from 1,2′-binaphthol. Asymmetric alkylations with nearly 70% optical yield have been realized using this method.[438]

Optically active ferrocenylphosphines containing a functional group on the side chain, which may complex to the incoming nucleophile and induce asymmetric attack, have proven to be most effective in π-allyl allylations, with optical yields up to 92% being observed (equations 356 and 357).[439–442]

The most detailed and thorough studies on asymmetric catalytic allylation using palladium chiral phosphine complexes have come from the work of Bosnich *et al.*[443–445] Employing a combination of NMR, chemical and labelling studies on this process, this group was able to determine that with 1,1-diphenyl-3-

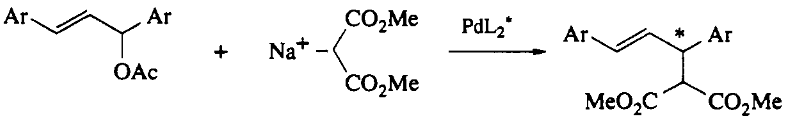

(356)

92% optical yield

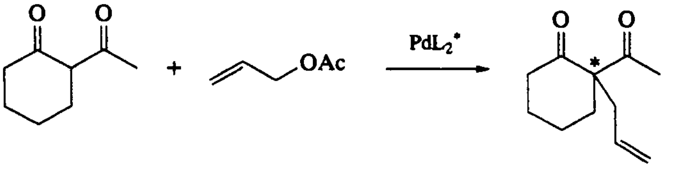

(357)

73% optical yield

alkyl- or aryl-substituted allyls: (i) nucleophilic attack is the turnover limiting step and is also the enantioselective step; (ii) the major product enantiomer originates from the major four-coordinate π-allyl diastereomeric intermediate and that the diastereomeric complexes rapidly interconvert; (iii) the enantioselectivity is relatively insensitive to the nucleophile employed; (iv) a *syn* substituent at C-2 or C-3 in these allyl units is not significant in determining optical yields; and (v) a viable mechanism for racemization is attack by an uncomplexed $PdL_2$ on a π-allyl complex with inversion of configuration.

An X-ray structure of the major diastereomeric complex was also obtained to give further insight into the origin of asymmetry in the attack by nucleophiles.[446]

### 3.3.5.4 Chiral Nucleophiles and Leaving Groups

The final modes of enantioselective allyl alkylations catalyzed by palladium involve the use of chiral nucleophiles[447] and chiral leaving groups.[448,449] Chiral enamines were found to undergo allylation in 100% optical yield in an intramolecular case and in up to 50% optical yield in intermolecular reactions (equation 358).

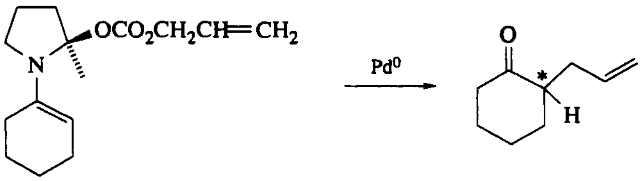

(358)

A palladium-catalyzed allylic sulfonate–sulfone rearrangement with chiral sulfonates produced 92% optical yields (equation 359).[448,449] Presumably, the optically active sulfonate induces chirality in the oxidative addition by $Pd^0$ in these reactions.

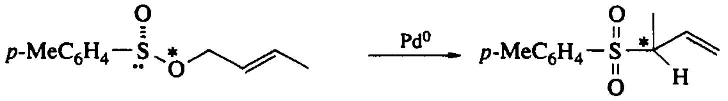

(359)

92% optical yield

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# 3.4

# Nucleophiles with Cationic Pentadienyl–Metal Complexes

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## 3.4.1 INTRODUCTION

This chapter includes those transition metal–pentadienyl cationic complexes that are quite stable, can be stored and handled easily, and are therefore useful as stoichiometric intermediates for organic synthesis. The dienyliron systems, which are readily available and inexpensive, have dominated this area of chemistry, and will occupy the larger part of the discussion. The chemistry of more expensive and less easily prepared dienylmetal complexes, such as those of manganese and cobalt, will be dealt with at the end of the chapter.

Although tricarbonylbutadieneiron (**1**) was prepared by Reihlen *et al.*[1] in 1930, some considerable time passed before the corresponding cyclohexadiene complex (**2**; equation 1) was reported.[2] Fischer and Fischer described the conversion of (**2**) to the cationic cyclohexadienyliron complex (**3**; equation 1) by reaction with triphenylmethyl tetrafluoroborate in dichloromethane.[3] This particular complex is extremely easy to prepare and isolate; as the hydride abstraction reaction proceeds the product (**3**) crystallizes out. Precipitation is completed by pouring the reaction mixture into 'wet' diethyl ether, the small amount of water present serving to destroy any excess triphenylmethyl tetrafluoroborate by conversion to triphenylmethanol. Filtration, followed by washing the residue with ether, gives pure dienyl complex.

The analogous cycloheptadienyl complex (**5**; equation 1) was similarly prepared by Dauben and Bertelli,[4] but the acyclic pentadienyl systems were a little more difficult to obtain. The triphenylmethyl cation does not remove hydride from tricarbonyl(*trans*-pentadiene)iron (**6**; equation 2). The corresponding *cis*-pentadiene complex (**7**; equation 3) cannot be prepared directly from the diene and an iron carbonyl,

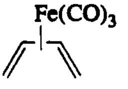

**(1)**

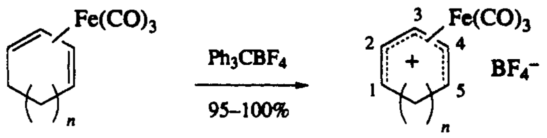

**(2)** *n* = 1
**(4)** *n* = 2

**(3)** *n* = 1
**(5)** *n* = 2

(1)

since this reaction always leads to (6), although it is now known that (7) can be converted to (8; equation 3) by treatment with triphenylmethyl tetrafluoroborate.

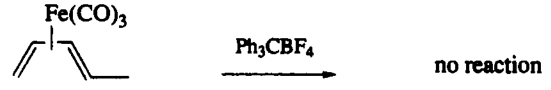

**(6)**

(2)

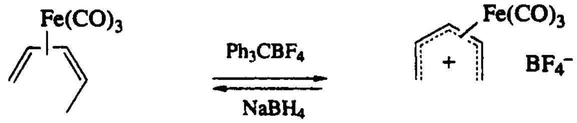

**(7)** **(8)**

(3)

An elegant solution to this problem was devised by Mahler and Pettit,[5] who showed that treatment of the (pentadienol)Fe(CO)$_3$ complex (9; equation 4) with acid gave (8), which was isolated as the perchlorate in 50% yield. These two methods (hydride abstraction and dehydroxylation) form the basis for the majority of preparations of dienyliron complexes.

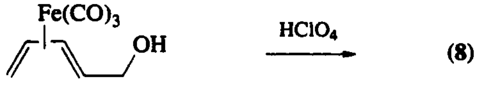

**(9)**

(4)

In these dienylmetal complexes, the metal is bound to all five carbon atoms, and these are almost coplanar. The methylene carbon of (3) is bent out of the dienyl plane, pointing away from the metal. The angle between the dienyl plane and the C(1)–C(6)–C(5) plane is approximately 39°, as measured by X-ray crystallography.[6] The complexes such as (3) can be drawn as shown in Figure 1, but are more conveniently depicted as in the above structures.

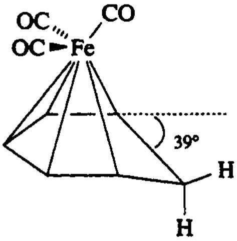

**Figure 1** Structure of the tricarbonylcyclohexadienyliron cation

Generally, the dienyliron complexes discussed here are stable towards air and moisture (indeed, some of them can be recrystallized from hot water), and most can be stored for extended periods of time at room temperature. In spite of their stability, they are extremely reactive towards nucleophiles. The result of nucleophile addition to complex (3) is shown in equation (5), giving substituted cyclohexadieneiron complexes (10) resulting from *exo* attack. On the other hand, complexes (5) and (8) are more problematic; mixtures of regioisomers (11) and (12; equation 6) result from (5), while the initial products from (8) are prone to isomerization to the more stable systems (14; Scheme 1).

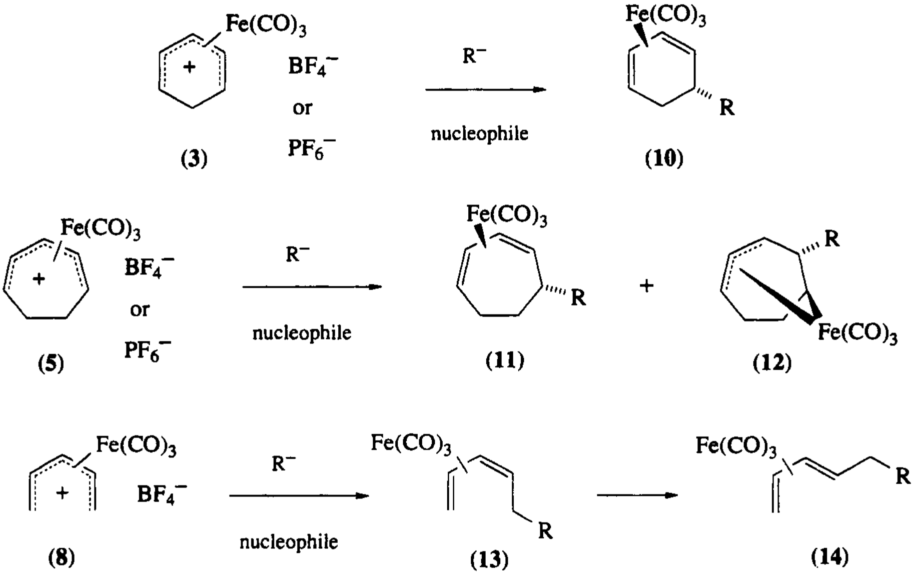

(5)

(6)

**Scheme 1**

Because of the highly efficient nucleophile additions to (3), substituted cyclohexadienyliron complexes have been exploited for natural products synthesis. The problems associated with (5) have been largely overcome and the seven-membered ring systems now show promise as synthetic building blocks. On the other hand, very little attention has been given to the acyclic systems, and this remains a virgin area. Finally, in order to be useful in organic synthesis, it is essential that the metal can be removed from the product dienes selectively and without detriment to any functional groups in the molecule.

## 3.4.2 DIENYL COMPLEXES OF IRON

### 3.4.2.1 Preparation of Substituted Tricarbonylcyclohexadienyliron Complexes

Since these complexes are all prepared from appropriate (cyclohexadiene)tricarbonyliron derivatives, we shall first briefly review the preparation of the diene complexes. As mentioned earlier, complex (2) was initially prepared by reaction of cyclohexa-1,3-diene with pentacarbonyliron (autoclave; 135–140 °C). Amet and Pettit observed[7] that cyclohexa-1,4-diene also gave (2; equation 7) on reaction with pentacarbonyliron at elevated temperature, *via* a rearrangement of the diene which is promoted by the iron carbonyl. Birch and coworkers[8] applied this observation to the reaction of iron carbonyls with various dihydrobenzene derivatives that are readily prepared by metal–ammonia (Birch) reduction of the aromatic compound. Various iron carbonyls have been investigated as starting materials. Pentacarbonyliron in refluxing di-*n*-butyl ether, and dodecacarbonyltriiron [$Fe_3(CO)_{12}$] in hot benzene are reported[8] to convert cyclohexa-1,4-dienes to their (1,3-diene)$Fe(CO)_3$ complexes; since pentacarbonyliron is inexpensive and usually gives better yields, this is the reagent of choice. Nonacarbonyldiiron [$Fe_2(CO)_9$] may also be used, usually in an inert solvent at *ca.* 60 °C, but invariably is successful only with 1,3-dienes. For sensitive 1,3-dienes the heterodiene complex (benzylideneacetone)tricarbonyliron is a useful tricarbonyliron transfer reagent,[9] which can be employed under mild conditions.

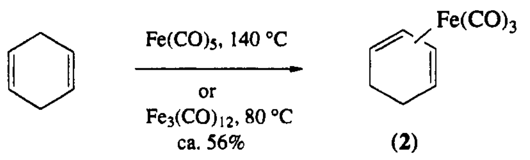

(7)

The earlier work of Birch *et al.*[8,10,11] laid the foundations for much of the synthetic application of cyclohexadienyliron complexes. Of particular interest are the reactions of dihydroanisole derivatives[8,10] and dihydrobenzoic esters[11] with iron carbonyls, which are summarized in Schemes 2 and 3 and equations (8)–(10).

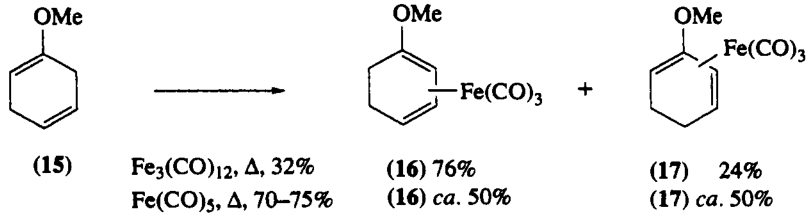
OMe
Fe(CO)3
(15)
Fe3(CO)12, Δ, 32%
Fe(CO)5, Δ, 70–75%
(16) 76%
(16) ca. 50%
(17) 24%
(17) ca. 50%

**Scheme 2**

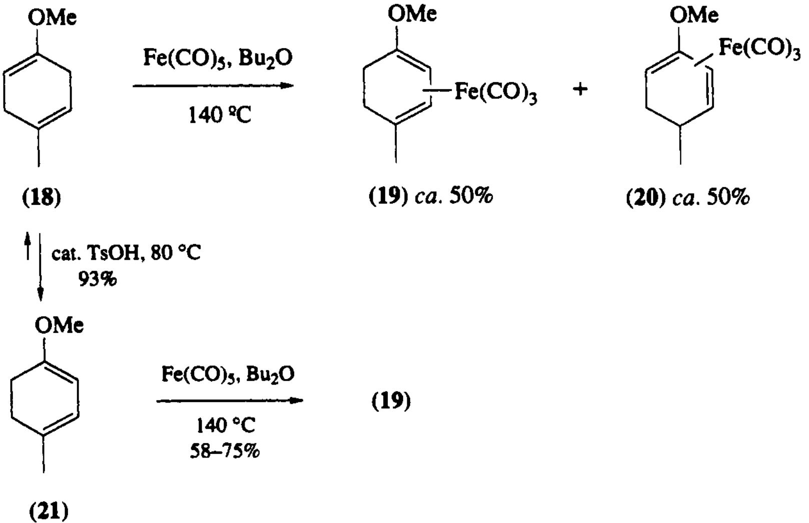
OMe
Fe(CO)5, Bu2O
140 °C
Fe(CO)3
(18)
(19) ca. 50%
(20) ca. 50%
cat. TsOH, 80 °C
93%
Fe(CO)5, Bu2O
140 °C
58–75%
(19)
(21)

**Scheme 3**

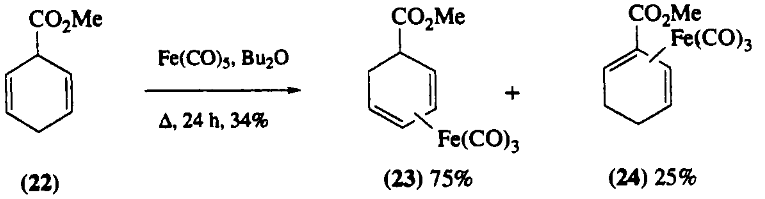
CO2Me
Fe(CO)5, Bu2O
Δ, 24 h, 34%
Fe(CO)3
(22)
(23) 75%
(24) 25%

(8)

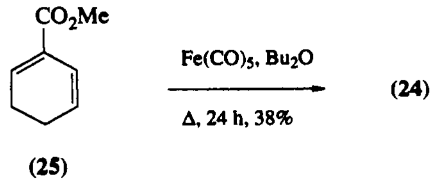
CO2Me
Fe(CO)5, Bu2O
Δ, 24 h, 38%
(24)
(25)

(9)

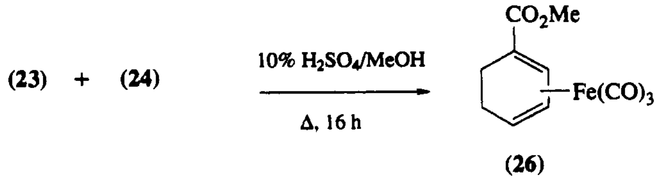
(23) + (24)
10% H2SO4/MeOH
Δ, 16 h
CO2Me
Fe(CO)3
(26)

(10)

With substituted 1,4-dienes, such as (**15**), (**18**) and (**22**), the isomerization/complexation reaction invariably produces mixtures of complexes. Although these can often be separated chromatographically, it is better to preconjugate the diene for synthetic applications. A useful example is the conversion of diene (**18**) to an equilibrium mixture (*ca.* 1:4) of (**18**) and (**21**), followed by reaction with $Fe(CO)_5$ to give complex (**19**; Scheme 3) in 58% yield.[12]

The methoxy- and methoxycarbonyl-substituted complexes show pronounced electronic effects during the hydride abstraction process, leading to good regiocontrol in most cases. Examples are shown in equations (11)–(15).[10–13]

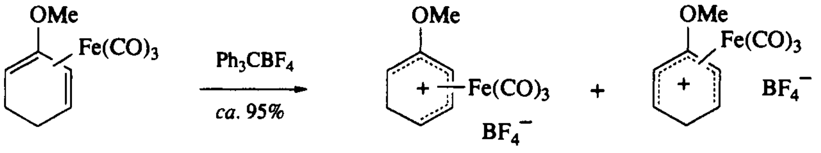

(**17**) (**27**) 94% (**28**) 6% (11)

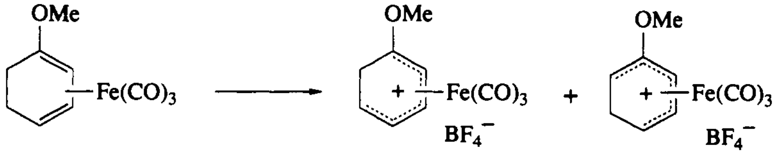

(**16**) (**29**) 80% (**27**) 20% (12)

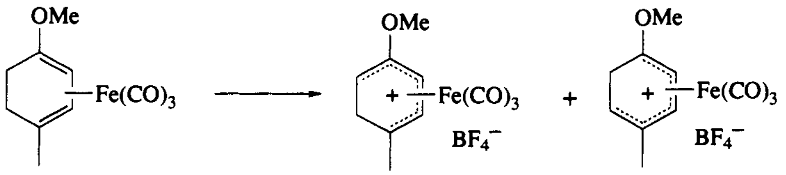

(**19**) (**30**) 95% (**31**) 5% (13)

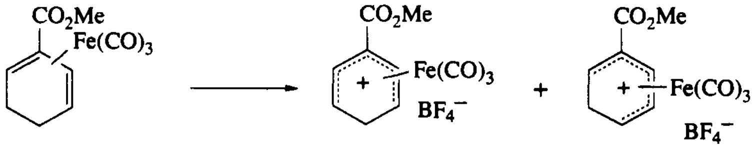

(**24**) (**32**) 80% (**33**) 20% (14)

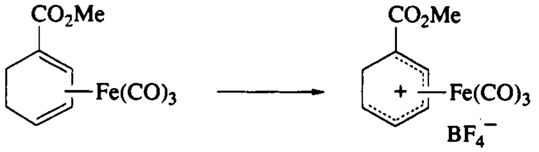

(**26**) (**34**) (15)

With complexes such as (**17**), (**24**) and (**35**) that do not have sterically demanding substituents adjacent to the point of hydride abstraction, the reaction is controlled by electronic effects from the substituent. The results of these particular reactions are somewhat unexpected by comparison with the anticipated stabilities of the corresponding noncomplexed dienyl cations. For example, (**27**; equation 11) corresponds to a less stable dienyl ligand than (**28**), and (**32**; equation 14) is expected to be less stable than (**33**). In the conversion of (**35**) to (**36**; equation 16) reported by Paquette *et al.*,[13] the trimethylsilyl group appears to act as an electron acceptor, and is therefore analogous to the methoxycarbonyl group. These results of hydride abstraction have been rationalized using molecular orbital calculations,[6b] the synergistic interaction between metal *d*-orbitals and dienyl HOMO and LUMO being the most important consideration. A detailed discussion will not be presented here. Suffice it to say that the dienyl with highest energy HOMO and lowest energy LUMO gives the strongest net bonding interaction with the $Fe(CO)_3$ fragment, and the hydride abstraction is thermodynamically driven.

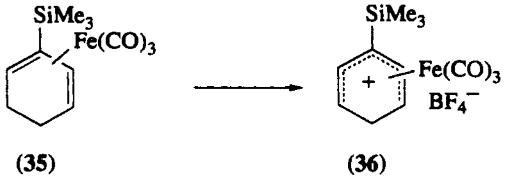

(16)

In complexes (**16**) and (**26**), the situation is rather different, because there is now steric hindrance from the diene terminal substituent. As a result, the electronically less favorable products are predominant. However, when steric effects at both methylene groups are balanced, as in complex (**19**), the hydride abstraction proceeds with 'electronic' control to give (**30**; equation 13).

With methyl-substituted cyclohexadienes, very little selectivity is observed during the preparation of the complexes and the hydride abstraction reaction. Dihydrotoluene, on heating with pentacarbonyliron, gives a mixture of complexes (**37**) and (**38**; Scheme 4). These cannot be easily separated using standard chromatographic procedures, and little is known about hydride abstraction from the individual complexes. Treatment of the equimolar mixture with trityl tetrafluoroborate gives a mixture of all three possible products (**39**–**41**; Scheme 4).

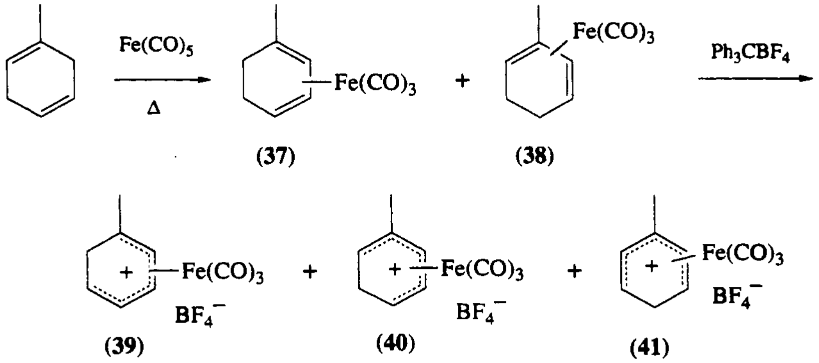

**Scheme 4**

A method for preparing specific alkyl-substituted dienyl complexes takes advantage of the propensity of (diene)Fe(CO)$_3$ complexes to rearrange under acidic conditions, coupled with the acid-promoted dehydration illustrated earlier for the conversion of (**9**) to (**8**). Birch and Haas[14] discovered that complexes derived from methylanisoles could be converted to methyl-substituted cyclohexadienyliron complexes, whose substitution pattern is defined by the relative positions of the methoxy and methyl substituents in the precursor. Several examples are given in Schemes 5 and 6 and equation (17).

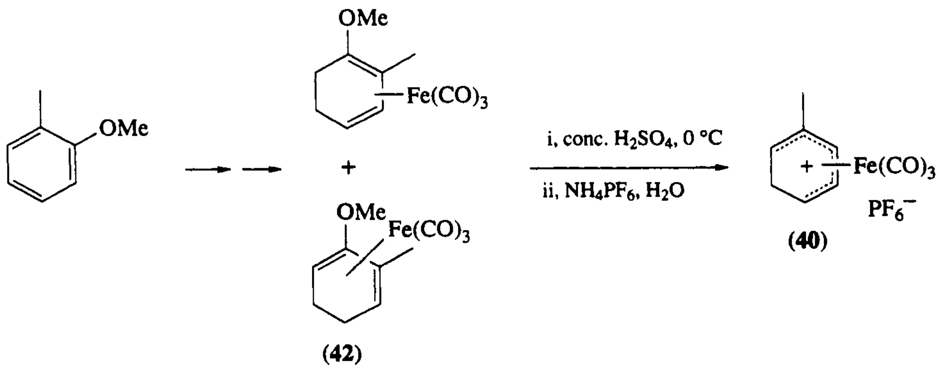

**Scheme 5**

$$(\mathbf{19}) + (\mathbf{20}) \xrightarrow[\text{ii, NH}_4\text{PF}_6\text{, H}_2\text{O}]{\text{i, conc. H}_2\text{SO}_4\text{, 0 °C}} (\mathbf{40}) \qquad (17)$$

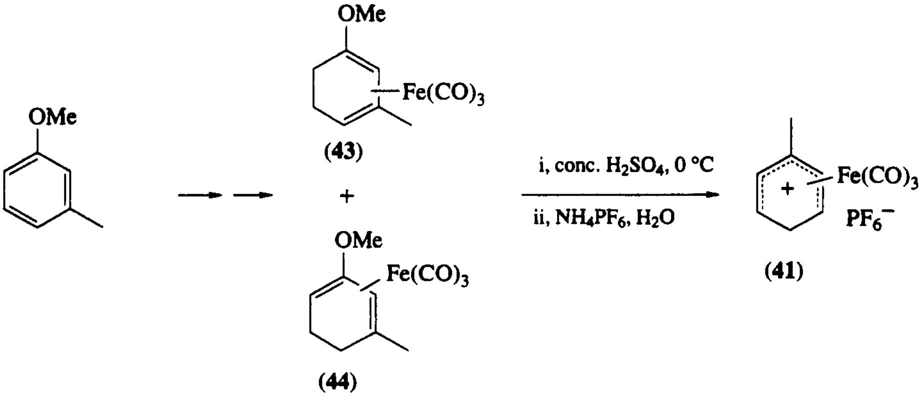
OMe
OMe
Fe(CO)3
(43)
+
OMe
Fe(CO)3
(44)
i, conc. H2SO4, 0 °C
ii, NH4PF6, H2O
+
Fe(CO)3
PF6⁻
(41)

**Scheme 6**

Related to this reaction is the acid treatment of the (1-hydroxymethylcyclohexadiene)tricarbonyliron (**45**), prepared *via* DIBAL-H reduction of ester (**26**) or borane reduction of the corresponding carboxylic acid, which leads to the 1-methylcyclohexadienyliron complex (**46**; equation 18).[11] Using these methods, it is therefore possible to prepare a range of alkyl-substituted dienyl complexes having a defined substitution pattern.

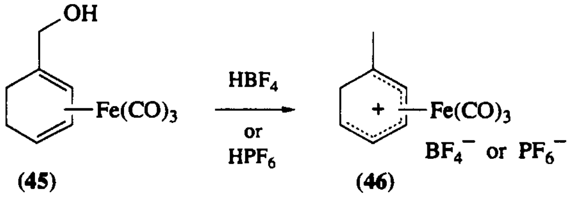
OH
Fe(CO)3
(45)
HBF4
or
HPF6
+
Fe(CO)3
BF4⁻ or PF6⁻
(46)

(18)

As mentioned earlier, steric effects can be important in determining the outcome of the hydride abstraction reaction. This is particularly vexing in cases where an alkyl substituent is present at the $sp^3$ carbon of the cyclohexadiene complex. For example, complexes such as (**47**; equation 19) are untouched by trityl cation, provided traces of acid are not present (these are formed by hydrolysis of the trityl tetrafluoroborate due to atmospheric moisture, and will cause rearrangement of the diene complex). This is due to the fact that only the hydride *trans* to the Fe(CO)3 group can be removed, and the methyl substituent prevents close approach to this hydrogen.

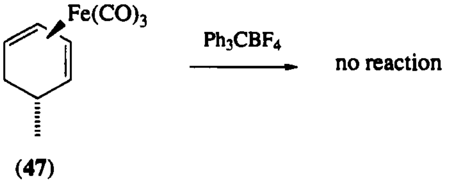
Fe(CO)3
(47)
Ph3CBF4
no reaction

(19)

The trimethylsilyl substituent proves to be of considerable value in this respect. It appears to activate the diene towards hydride abstraction to such an extent that conversion of complexes such as (**48**) and (**50**) to the dienyl derivatives (**49**; equation 20) and (**51**; equation 21) proceeds quite readily.[13]

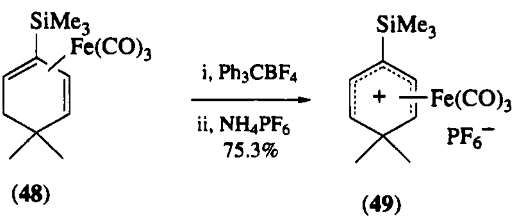
SiMe3
Fe(CO)3
(48)
i, Ph3CBF4
ii, NH4PF6
75.3%
SiMe3
+
Fe(CO)3
PF6⁻
(49)

(20)

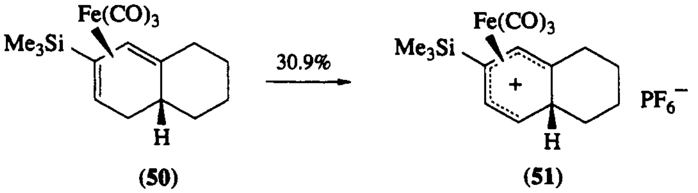

(21)

In those cases where a hydroxyethyl substituent is attached to the cyclohexadiene ring, an oxidative cyclization procedure has been developed to effect conversion to cyclohexadienyliron complexes.[14] Thus, treatment of complex (**52**) with manganese dioxide gives the cyclic ether (**53**) which can be converted to the dienyl complex (**54**; Scheme 7) by treatment with tetrafluoroboric acid in acetic anhydride.

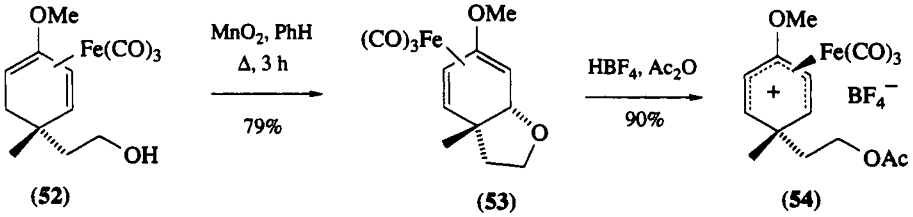

**Scheme 7**

### 3.4.2.2 Nucleophile Additions to Dienyliron Complexes; General Comments

Imagining tricarbonyldienyliron complexes to consist of a positively charged iron surrounded by dienyl and carbon monoxide ligands, there are clearly two types of ligand site at which nucleophile addition might take place. However, only in rare instances does attack occur at a carbonyl ligand, and so this leads to an extremely powerful method for preparing substituted dienes. A wide range of nucleophiles are available for this method, including alkoxides, hydroxide, amines, borohydride (as a source of hydride), enols of simple ketones and β-dicarbonyl compounds,[8,10] enamines,[10] aromatic amines and ethers,[15] silyl enol ethers,[16] allylsilanes,[17] organocuprates,[18] organo-zinc and -cadmium reagents[19] (but not dimethylzinc), phosphines,[20] phosphites and sulfites,[21] alkynylborates,[22] lithium[23] and tin[24] enolates, silylketene acetals,[25] as well as the enolates from arylsulfonyl esters,[26] malonates,[27] and β-keto esters.[27] Typical reactions of representative nucleophiles with the parent cyclohexadienyliron complex (**3**) are summarized in equations (22)–(37).

All of these reactions are chemospecific (only the dienyl ligand undergoes nucleophile addition), regiospecific (only the terminal dienyl carbon is attacked), and stereospecific (the nucleophile always adds *anti* to the metal). However, the addition of organolithium and Grignard reagents in ether solvents to (**3**) gives very low yields of alkylation products, the major product being the dimer (**71**; Scheme 8). This is presumed to arise by electron transfer from the RLi or RMgX to the dienyl complex, giving the free radical (**70**) which then dimerizes.

Use of less reactive alkylating agents such as dialkylcuprates, $R_2Zn$ or $R_2Cd$, as described above, is one way to overcome this problem, but the yields are variable. The use of dichloromethane as solvent at –78 °C resulted in good yields of alkylation product (84–94%),[28] and a more general solution is achieved

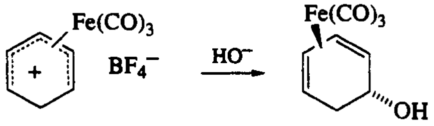

(**3**) (**55**)

(22)

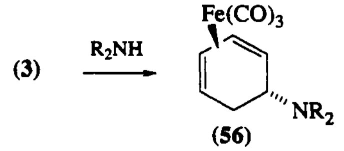

(**56**)

(23)

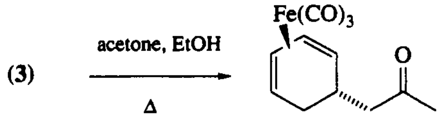
(3)
acetone, EtOH
Δ
Fe(CO)$_3$
O

(57)

(24)

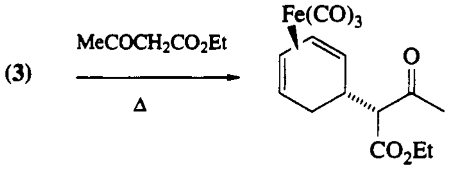
(3)
MeCOCH$_2$CO$_2$Et
Δ
Fe(CO)$_3$
O
CO$_2$Et

(58)

(25)

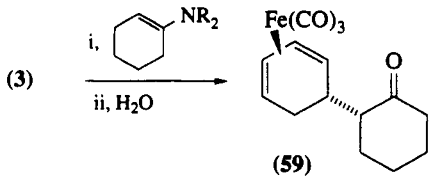
(3)
i, NR$_2$
ii, H$_2$O
Fe(CO)$_3$
O

(59)

(26)

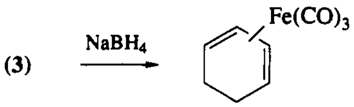
(3)
NaBH$_4$
Fe(CO)$_3$

(2)

(27)

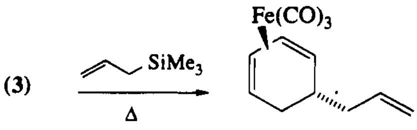
(3)
SiMe$_3$
Δ
Fe(CO)$_3$

(60)

(28)

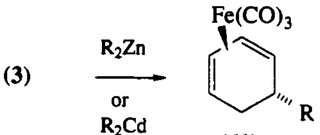
(3)
R$_2$Zn
or
R$_2$Cd
Fe(CO)$_3$
R

(61)

(29)

R = Ph, PhCH$_2$, Me$_2$CH; CH=CHMe, CH$_2$CH=CH$_2$

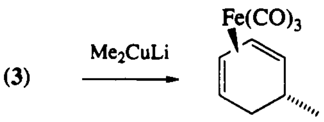
(3)
Me$_2$CuLi
Fe(CO)$_3$

(62)

(30)

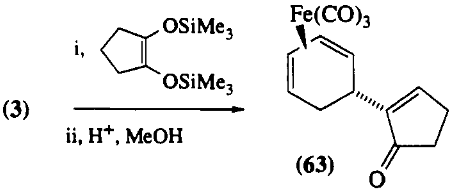
(3)
i, OSiMe$_3$
OSiMe$_3$
ii, H$^+$, MeOH
Fe(CO)$_3$
O

(63)

(31)

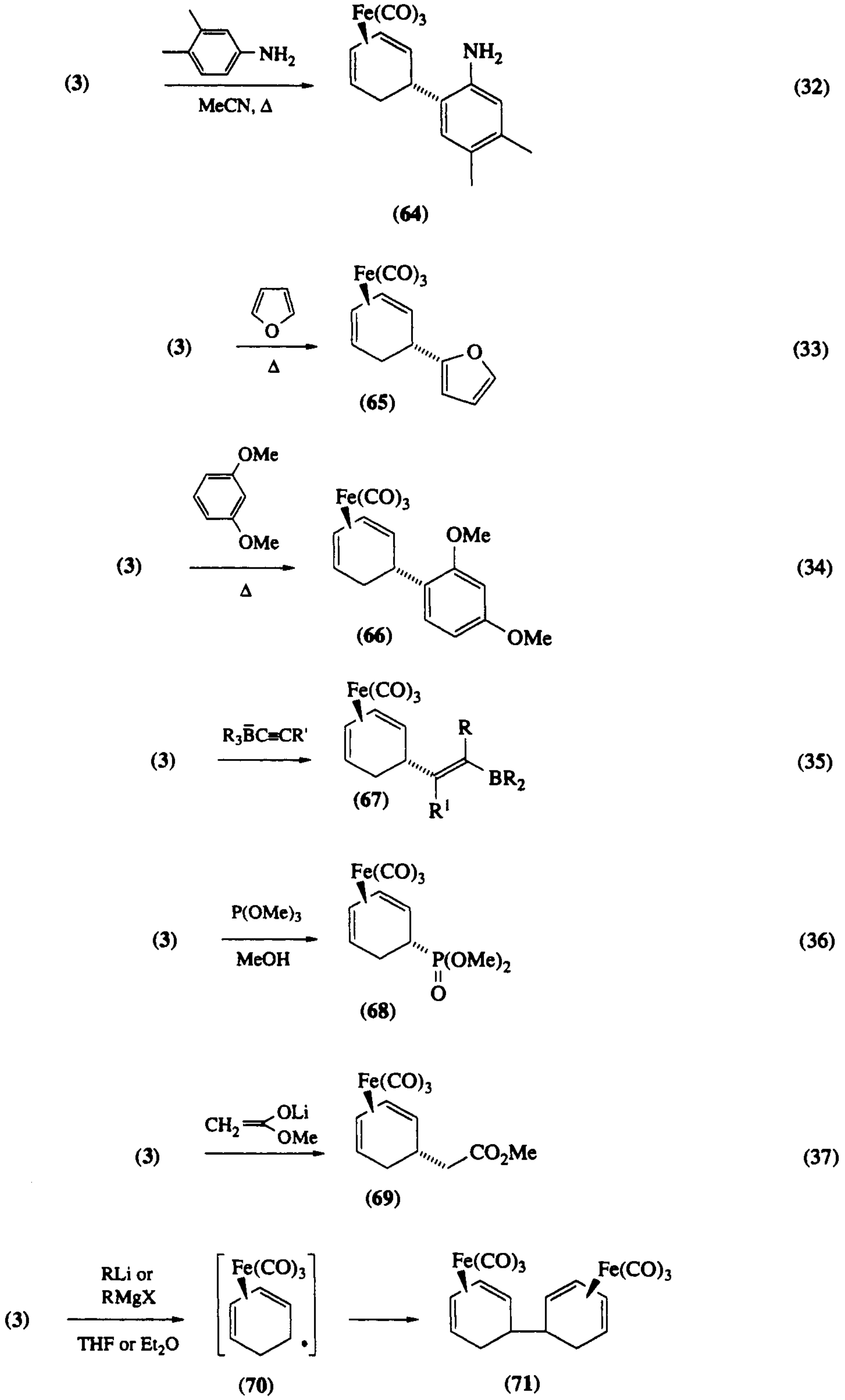
(3)
NH2
MeCN, Δ
Fe(CO)3
NH2
(64)
(32)
(3)
Δ
Fe(CO)3
(65)
(33)
OMe
OMe
(3)
Δ
Fe(CO)3
OMe
(66)
OMe
(34)
(3)
R3B̄C≡CR'
Fe(CO)3
R
BR2
(67)
R1
(35)
(3)
P(OMe)3
MeOH
Fe(CO)3
P(OMe)2
O
(68)
(36)
(3)
CH2=C(OLi)(OMe)
Fe(CO)3
CO2Me
(69)
(37)
(3)
RLi or
RMgX
THF or Et2O
Fe(CO)3
(70)
Fe(CO)3
Fe(CO)3
(71)

**Scheme 8**

by replacing a carbonyl ligand by, *e.g.* triphenylphosphine, a poorer π-acceptor. Very good yields of alkylation can be obtained using Grignard reagents under standard conditions.[29] This was especially noticeable with vinylmagnesium bromide, which converts complex (**3**) almost exclusively to the dimer

(**71**), even in dichloromethane at low temperature, but which gives exclusively the addition product (**73**) on reaction with complex (**72**; equation 38).

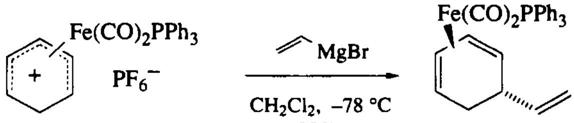

(**72**) (**73**) (38)

This observation has been used in a key step during a total synthesis of the alkaloid (±)-dihydrocannivonine (**77**) outlined in Scheme 9.[30] The final product is formed by intramolecular hetero-Diels–Alder reaction of the intermediate (**76**), which is not isolated.

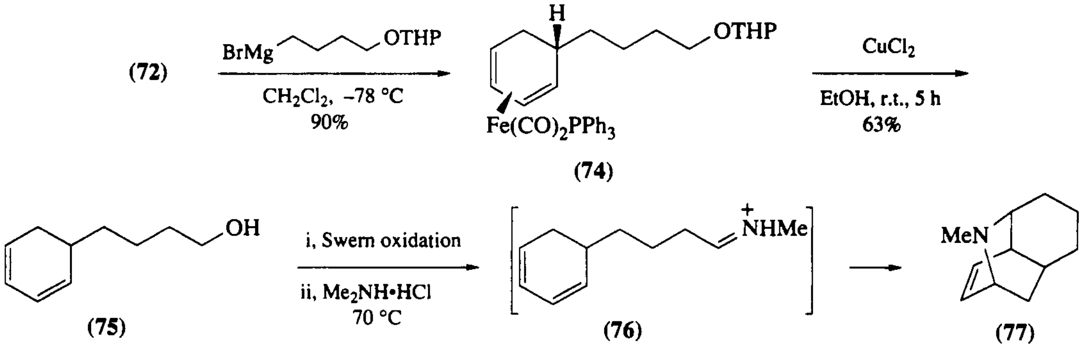

**Scheme 9** Grieco's synthesis of (±)-dihydrocannivonine (**77**)

Substitution of a CO ligand by a phosphine or phosphite derivative similarly leads to reactivity control in the cycloheptadienyliron system. The tricarbonyliron complex (**5**) invariably gives mixtures of products from nucleophile addition.[31] For example, treatment of (**5**) with sodium borohydride or sodium cyanide gives mixtures of products of general structure (**11**) and (**12**; equation 39), resulting from addition of nucleophile at C-1 and C-2, respectively, while addition of cyanide to the triphenylphosphine complex (**78**) gives exclusively (**80**; R = CN; equation 39).

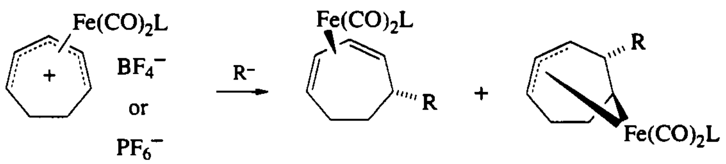

(**5**) L = CO (**11**) L = CO (**12**) L = CO
(**78**) L = PPh3 (**79**) L = PPh3 (**80**) L = PPh3 (39)

Similarly, reaction of lithium dimethylcuprate with (**5**) gave (**11**; R = Me) in low yield, together with significant amounts of the dimeric complex (**81**; equation 40) and substantial decomposition, but the phosphine analog (**78**) was more useful. Reaction of cuprate reagents with (**78**) gives (**79**; R = Me) in yields greater than 95%. The ligand exchange reaction on complex (**4**) does not proceed in good yield on a large scale using triphenylphosphine under thermal conditions ($Bu_2O$, reflux, 24 h). However, this same reaction using triphenyl phosphite proceeds well, giving complex (**82**) in *ca.* 95% yield.[32] Conversion to the dienyl complex (**83**) is essentially quantitative. Complex (**83**) behaves similarly to (**79**), and some of its reactions with nucleophiles are summarized in Scheme 10. Interestingly, dimethylcuprate reacts exclusively at C-1, while methyllithium adds exclusively to C-2. In general it appears that 'soft' nucleophiles add to the dienyl terminus, while harder nucleophiles attack C-2. (This contrasts with the reactions of cyclohexadienyliron complexes which always give C-1 addition products.) The high yields from these reactions, coupled with the ease of preparation of (**83**) on a large scale (>200 g batches), augurs well for this methodology as a means of stereoselectively functionalizing the seven-membered ring. We shall return to this in Section 3.4.2.4.

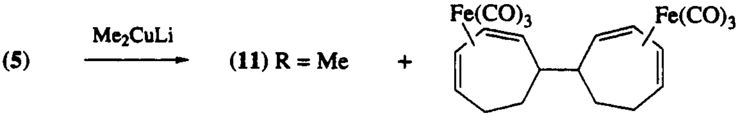
(5)
Me2CuLi
(11) R = Me
+
Fe(CO)3
Fe(CO)3

(81)

(40)

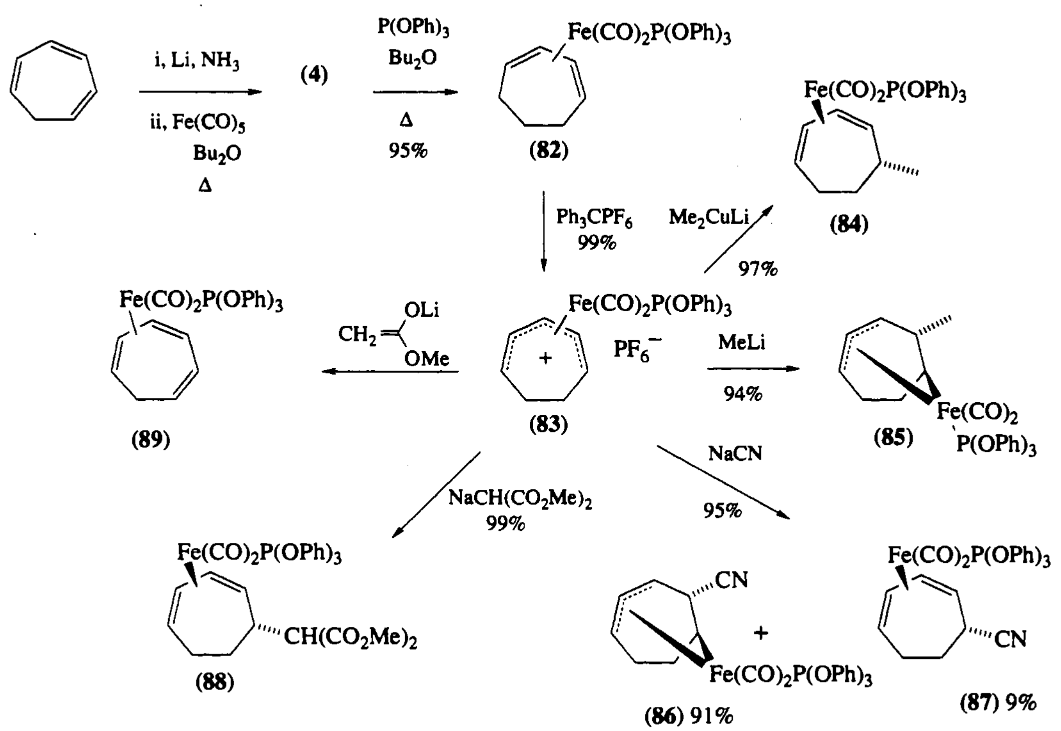
i, Li, NH3
ii, Fe(CO)5
Bu2O
Δ
(4)
P(OPh)3
Bu2O
Δ
95%
Fe(CO)2P(OPh)3
(82)
Ph3CPF6
99%
Me2CuLi
97%
Fe(CO)2P(OPh)3
(84)
Fe(CO)2P(OPh)3
(89)
OLi
CH2=
OMe
Fe(CO)2P(OPh)3
+
PF6−
(83)
MeLi
94%
Fe(CO)2
P(OPh)3
(85)
NaCN
95%
NaCH(CO2Me)2
99%
Fe(CO)2P(OPh)3
CH(CO2Me)2
(88)
CN
+
Fe(CO)2P(OPh)3
(86) 91%
Fe(CO)2P(OPh)3
CN
(87) 9%

**Scheme 10** Preparation of dicarbonyl(triphenyl phosphite)(cycloheptadienyl)iron hexafluorophosphate and its reactions with simple nucleophiles

The major limitation on the reactivity of cycloheptadienyliron complexes is the fact that treatment with hard enolates, such as methyl lithioacetate results in deprotonation to give, *e.g.* the $\eta^4$-triene complex (**89**). This appears to be less of a problem in the corresponding cyclohexadienyl systems.

### 3.4.2.3 Regiocontrol During Nucleophile Addition to Cyclohexadienyliron Complexes: Applications of Alkoxy- and Methoxycarbonyl-substituted Complexes in Organic Synthesis

A methoxy substituent at C-2 of the cyclohexadienyl ligand, as in complex (**27**), exerts a very powerful directing effect. The C-1 terminus appears to be electronically deactivated, so that nucleophiles add exclusively to C-5, giving products of general structure (**90**; Scheme 11).[8,10] The tricarbonyliron group can be removed quite easily using trimethylamine *N*-oxide[33] to give the dienes (**91**), which are readily hydrolyzed under mild acid conditions to give substituted cyclohexenones (**92**). Alternatively, direct conversion of (**90**) to (**92**) can be accomplished by treatment of the complex with ethanolic copper(II) chloride.[34]

Various other oxidizing agents have been used successfully for the conversion of iron complexes to the dienes or enones, including iron(III) chloride in ethanol,[8,35] Jones' reagent,[17] and cerium(IV) ammonium nitrate.[8] Overoxidation to give the aromatic compound is noted with methoxy-substituted complexes, and can be minimized by using trimethylamine *N*-oxide or copper(II) chloride. Sometimes, further oxidation of dienes such as (**91**) to aromatic compounds is a desirable transformation. This can be accomplished in good yield using either DDQ or palladium on charcoal, and this has been utilized in a formal synthesis of the natural product *O*-methyljoubertiamine (**93**; Scheme 12).[36]

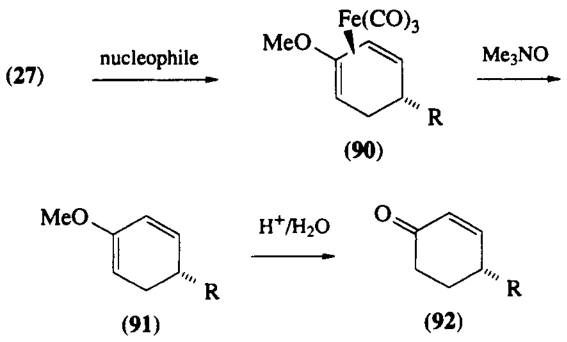

**Scheme 11**

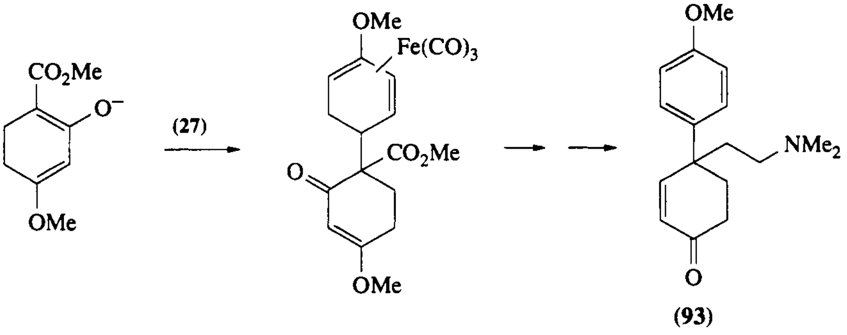

**Scheme 12**

The addition of carbon nucleophiles to complex (**27**), followed by demetallation, is equivalent to the $\gamma$-alkylation of cyclohexenone. This overall transformation can also be accomplished directly *via* addition of electrophiles to dienolsilanes, but it becomes nontrivial for cases where the cyclohexenone C-4 position is already substituted.[37] On the other hand, 1-substituted cyclohexadienyliron complexes, such as (**30**), react very cleanly with certain carbon nucleophiles, at the substituted dienyl terminus. This provides useful methodology for the construction of 4,4-disubstituted cyclohexenones, and has been employed in a variety of natural product syntheses.

Reaction of (**30**) with diethyl sodiomalonate gives exclusively complex (**94**), which can be demetallated to give the cyclohexenone derivative (**95**; Scheme 13) in good overall yield.[27] A range of nucleophiles can be used, including cyanide, and keto ester enolates, giving, *e.g.* (**96**) or (**97**; Scheme 13), respectively.

The steric bulk of the nucleophile does not seem to affect the regioselectivity during reaction with complex (**30**), but mixtures are obtained when the complex carries bulky substituents at the dienyl terminus. This is illustrated in equations (41)–(46), where some of the potential problems are highlighted.[27,38]

The regioselectivity during these reactions can be improved by using isopropoxy instead of methoxy as the directing group. In this case the electronic deactivation of the neighboring dienyl terminus is reinforced by the steric demand of the more bulky isopropyl group. For example, (**114**; Scheme 14) and (**117**; Scheme 15) give dienyl complexes (**115**) and (**118**) in high yield on treatment with triphenylmethyl hexafluorophosphate[39] and these add to dimethyl malonate anion with much better regiocontrol than the corresponding methoxy derivatives. Cleaner reaction occurs if potassium enolates are used in place of the sodium derivatives,[39] as summarized in Schemes 14 and 15.

Multiple substitution on the dienyl ligand has not been extensively investigated. The dimethyl-substituted complexes (**121** and **122**; equation 47) and (**123**; Scheme 16)[40,41] all react with malonate anion to give good yields of the desired products, although the isopropoxy derivative (**122**) gives better regioselectivity than the methoxy compound (**121**). A sterically more demanding substituent *para* to the alkoxy directing group has adverse effects though, and complexes (**124**) and (**125**; equation 48) react with nucleophiles exclusively or predominantly at the unsubstituted dienyl terminus.[40]

Steric hindrance to nucleophile addition becomes a major problem with 6-*exo*-substituted cyclohexadienyliron complexes, and the outcome of these reactions is highly dependent on the size of the substi-

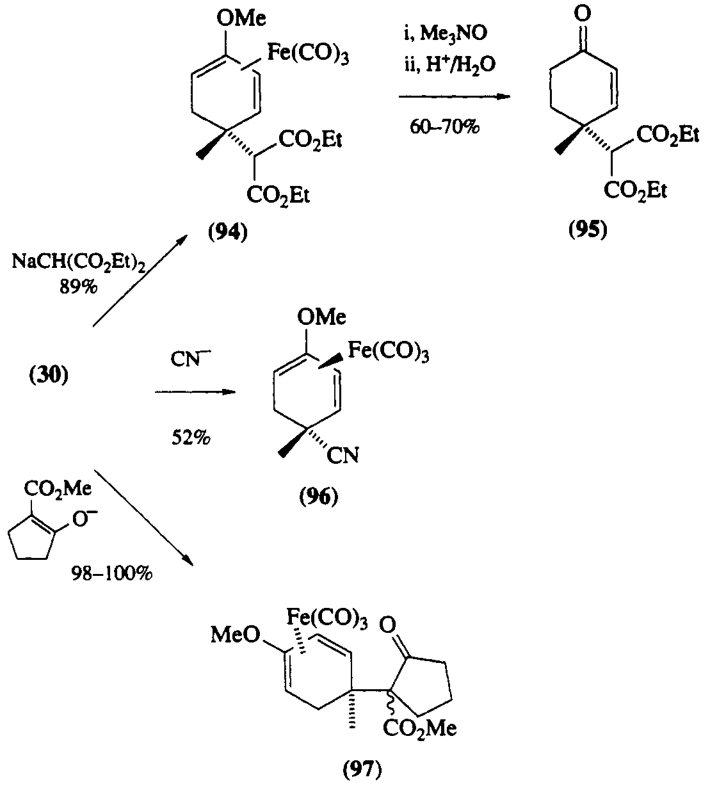
OMe
Fe(CO)3
CO2Et
CO2Et
(94)
i, Me3NO
ii, H+/H2O
60–70%
O
CO2Et
CO2Et
(95)
NaCH(CO2Et)2
89%
(30)
CN−
52%
OMe
Fe(CO)3
CN
(96)
CO2Me
O−
98–100%
Fe(CO)3
MeO
O
CO2Me
(97)

Scheme 13

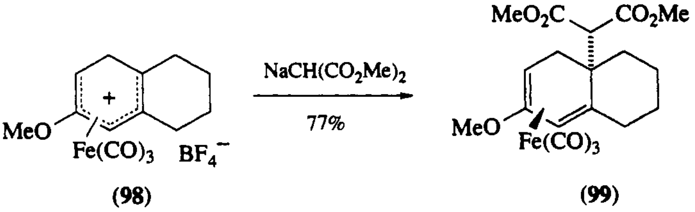
MeO
+
Fe(CO)3
BF4−
(98)
NaCH(CO2Me)2
77%
MeO2C
CO2Me
MeO
Fe(CO)3
(99)

(41)

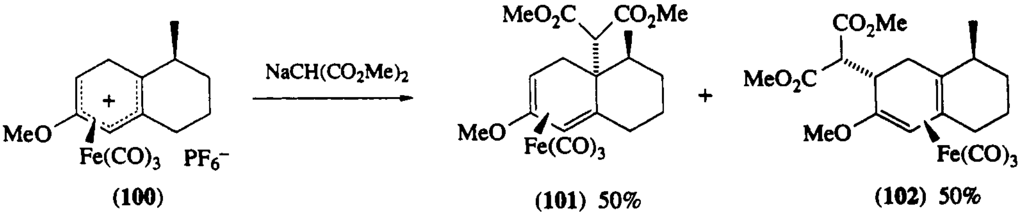
MeO
+
Fe(CO)3
PF6−
(100)
NaCH(CO2Me)2
MeO2C
CO2Me
MeO
Fe(CO)3
(101) 50%
+
CO2Me
MeO2C
MeO
Fe(CO)3
(102) 50%

(42)

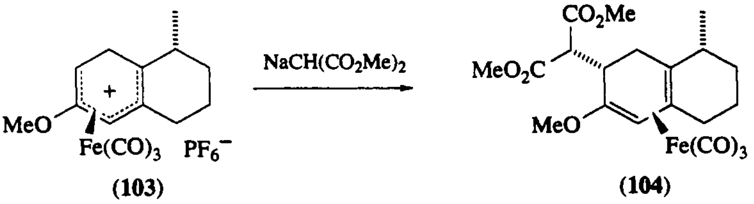
MeO
+
Fe(CO)3
PF6−
(103)
NaCH(CO2Me)2
CO2Me
MeO2C
MeO
Fe(CO)3
(104)

(43)

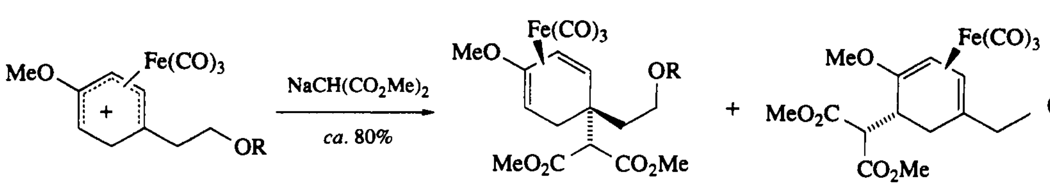

MeO
Fe(CO)3
+
OR
NaCH(CO2Me)2
ca. 80%
MeO
Fe(CO)3
OR
MeO2C
CO2Me
+
MeO
Fe(CO)3
MeO2C
CO2Me

(44)

**(105)** R = Me
**(108)** R = Ac

**(106)** R = Me, 72%
**(109)** R = Ac, 50%

**(107)** R = Me, 28%
**(110)** R = Ac, 50%

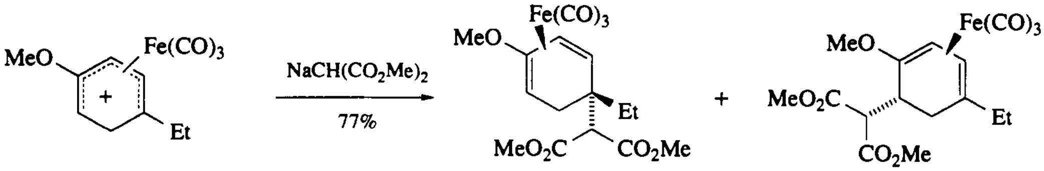

MeO
Fe(CO)3
+
Et
NaCH(CO2Me)2
77%
MeO
Fe(CO)3
Et
MeO2C
CO2Me
+
MeO
Fe(CO)3
MeO2C
Et
CO2Me

(45)

**(111)** **(112)** 82% **(113)** 18%

$$\textbf{(111)} \xrightarrow[96\%]{\text{KCH(CO}_2\text{Me)}_2} \underset{85\%}{\textbf{(112)}} + \underset{15\%}{\textbf{(113)}} \qquad (46)$$

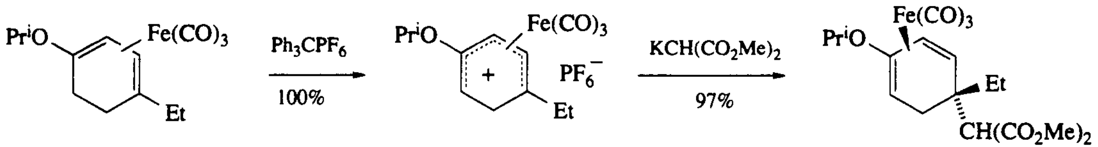

PriO
Fe(CO)3
Et
Ph3CPF6
100%
PriO
Fe(CO)3
+
PF6−
Et
KCH(CO2Me)2
97%
PriO
Fe(CO)3
Et
CH(CO2Me)2

**(114)** **(115)** **(116)**

Scheme 14

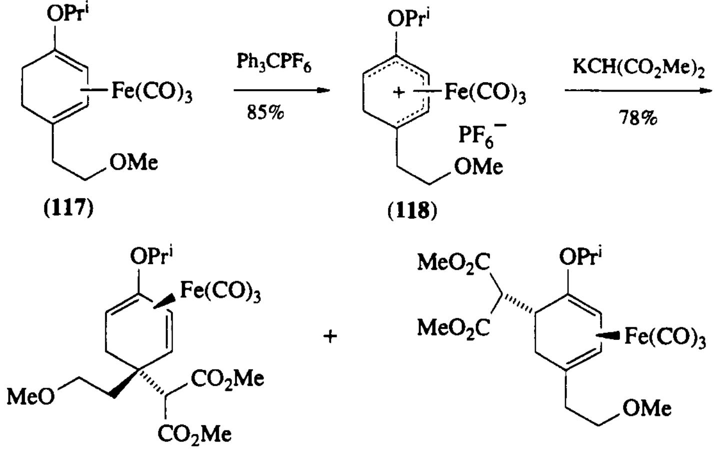

OPri
Fe(CO)3
OMe
(117)
Ph3CPF6
85%
OPri
+
Fe(CO)3
PF6−
OMe
(118)
KCH(CO2Me)2
78%
OPri
Fe(CO)3
MeO
CO2Me
CO2Me
+
MeO2C
MeO2C
OPri
Fe(CO)3
OMe

**(119)** 90% **(120)** 10%

Scheme 15

tuent. For example, complex (**54**; Scheme 17), which has a linear, sterically undemanding 6-*exo* substituent, reacts with malonate and cuprate nucleophiles with excellent stereocontrol to give complexes (**126**) or (**127**), and (**126**) is readily converted to the cyclohexenone (**128**).[14]

A range of enolate nucleophiles have been added to trimethylsilyl-substituted cyclohexadienyl complexes (**49**; Scheme 18) and (**51**; equation 49) and related compounds. Again, high yields are obtained and stereodirection by the $Fe(CO)_3$ group is very powerful.[13]

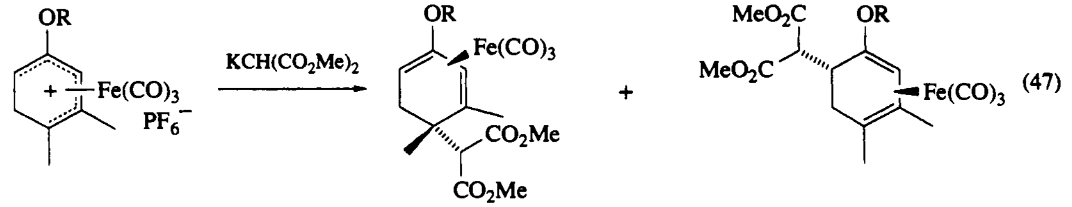
OR
Fe(CO)3
$PF_6^-$
$KCH(CO_2Me)_2$
OR
Fe(CO)3
CO2Me
CO2Me
+
MeO2C
OR
MeO2C
Fe(CO)3

(47)

| | | | |
|---|---|---|---|
| (**121**) R = Me | 76% | 78% | 22% |
| (**122**) R = Pr$^i$ | 86% | 90% | 10% |

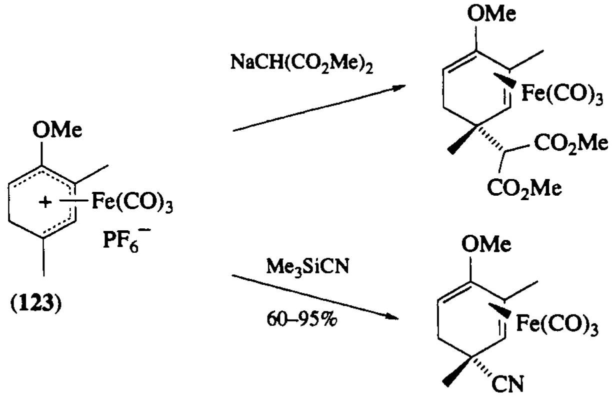
OMe
Fe(CO)3
$PF_6^-$
$NaCH(CO_2Me)_2$
OMe
Fe(CO)3
CO2Me
CO2Me
Me3SiCN
60–95%
OMe
Fe(CO)3
CN

(**123**)

Scheme 16

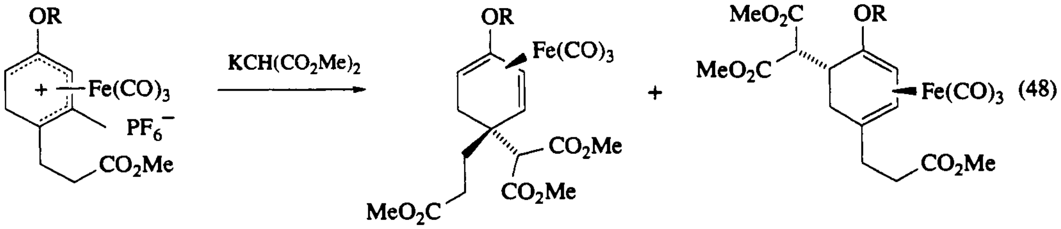
OR
Fe(CO)3
$PF_6^-$
CO2Me
$KCH(CO_2Me)_2$
OR
Fe(CO)3
CO2Me
CO2Me
MeO2C
+
MeO2C
OR
MeO2C
Fe(CO)3
CO2Me

(48)

| | | | |
|---|---|---|---|
| (**124**) R = Me | 89% | 0% | 100% |
| (**125**) R = Pr$^i$ | 97% | 22% | 78% |

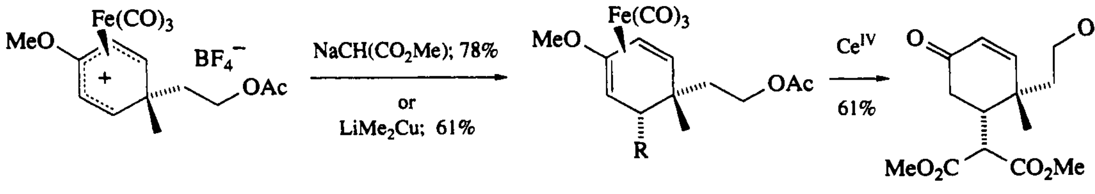
Fe(CO)3
MeO
$BF_4^-$
OAc
$NaCH(CO_2Me)$; 78%
or
$LiMe_2Cu$; 61%
Fe(CO)3
MeO
OAc
R
$Ce^{IV}$
61%
O
OAc
MeO2C
CO2Me

(**54**)

(**126**) R = $CH(CO_2Me)_2$

(**127**) R = Me

(**128**)

Scheme 17

*Exo* addition is always observed. When the 6-*exo* substituent is very bulky, as in complex (**132**; equation 50), nucleophile addition to the dienyl ligand is completely suppressed. Instead, decomplexation is observed giving the dienone (**133**), possibly *via* attack of nucleophile at the metal (*i.e.* ligand exchange).[42] *Endo* addition is not observed.

Regioselectivity problems, such as those encountered with complexes (**124**) or (**125**), may be overcome by using an intramolecular addition of the nucleophile. Spirocyclization of keto ester groups onto the dienyliron system proceeds in good yield to form a six-membered ring, *e.g.* (**134**) gives (**135**; equation 51), but *O*-alkylation occurs when five-membered ring formation is attempted, *e.g.* (**136**) gives (**137**;

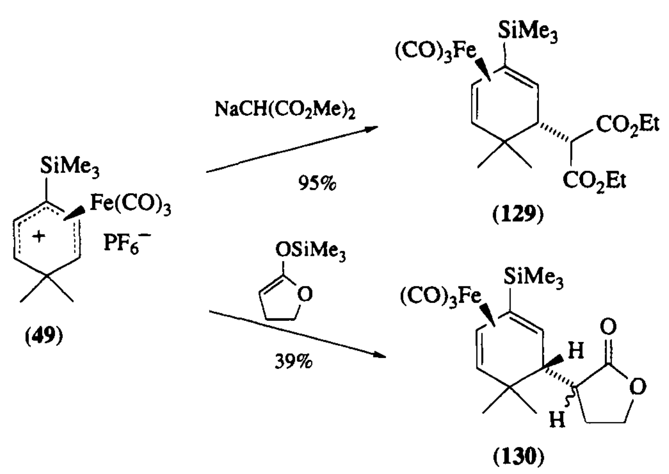

Scheme 18

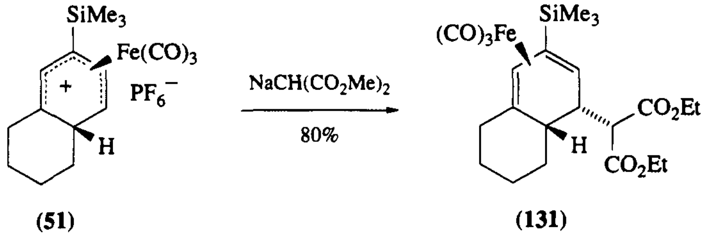

(49)

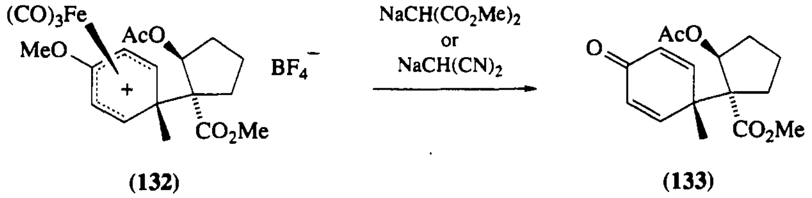

(50)

equation 52).[43] A malonate group is insufficiently acidic for selective anion generation, and treatment of (**138**) with base results in deprotonation of the side chain to give (**139**; equation 53). On the other hand, the more acidic malononitrile or cyano ester groups can be deprotonated and cyclized to give spiro[4.5]decane derivatives such as (**141**; equation 54) and (**143**; equation 55).[40,44,45]

Regioselectivity during the addition of heteroatom nucleophiles to these complexes can be influenced in special cases by taking advantage of the reversibility of the reaction. For example, primary amine nucleophiles add reversibly to dienyliron complexes. When they are allowed to react with complexes such as (**144**) and (**149**), containing a leaving group in the side chain, the adducts (**146**) and (**151**) can undergo further reaction to generate azaspirocyclic systems (**147**) and (**152**), while the regioisomers (**145**) and (**150**) cannot (Scheme 19).[45] Since the formation of the amine adducts is reversible, the net result is that the azaspirocycles can be produced in high yield. These are readily converted to enones (**148**) and (**153**), and (**153**) has been used in a formal total synthesis of (±)-perhydrohistrionicotoxin (**154**; Scheme 20).[46]

The regiocontrol displayed by an alkoxy substituent at C-2 of the dienyl system has been exploited for the total synthesis of a number of relatively complex natural products. For example, the malonate ad-

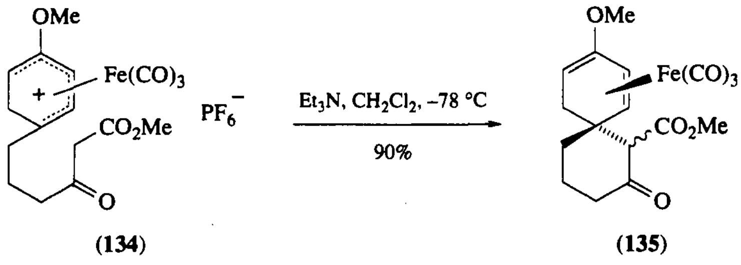

(51)

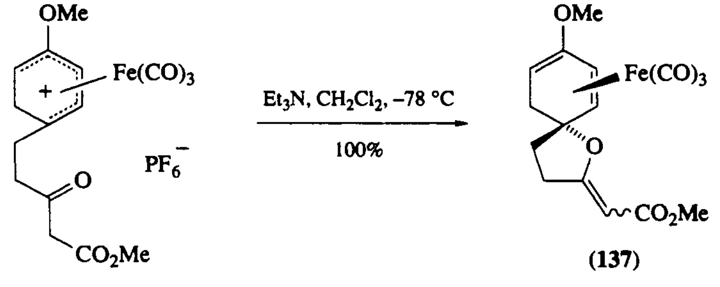
OMe
Fe(CO)3
PF6⁻
O
CO2Me
Et3N, CH2Cl2, -78 °C
100%
OMe
Fe(CO)3
O
CO2Me

**(136)** **(137)** (52)

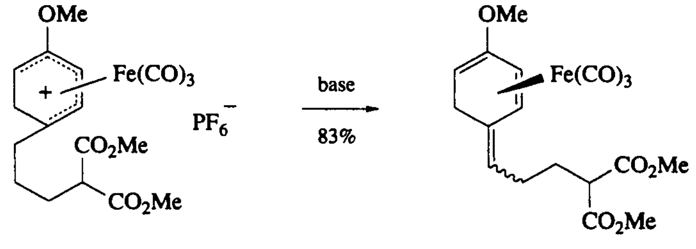
OMe
Fe(CO)3
PF6⁻
CO2Me
CO2Me
base
83%
OMe
Fe(CO)3
CO2Me
CO2Me

**(138)** **(139)** (53)

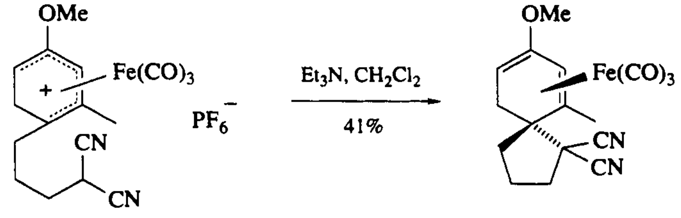
OMe
Fe(CO)3
PF6⁻
CN
CN
Et3N, CH2Cl2
41%
OMe
Fe(CO)3
CN
CN

**(140)** **(141)** (54)

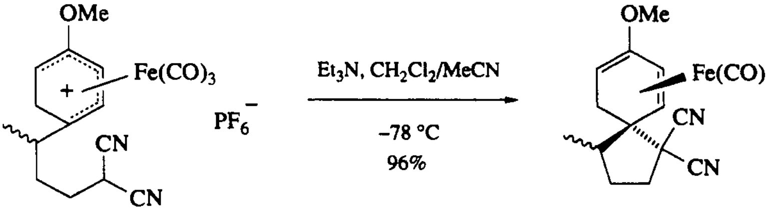
OMe
Fe(CO)3
PF6⁻
CN
CN
Et3N, CH2Cl2/MeCN
-78 °C
96%
OMe
Fe(CO)3
CN
CN

**(142)** **(143)** (55)

ducts (**112**) or (**116**) can be employed in a formal synthesis of the alkaloid aspidospermine (**158**; Scheme 21).[47,48] A diverse range of organic transformations can be accomplished in the presence of the (diene)Fe(CO)3 unit; the tricarbonyliron group may be regarded as an enone protecting group in complexes such as (**155**) and (**156**).

Since the perhydroquinoline derivative (**157**) had previously been converted to (**158**) by Stork and Dolfini,[49] the conversion of (**112**) to (**157**; Scheme 21) constitutes a formal total synthesis of the natural product. However, this route to (**157**) is a longer sequence of reactions than that employed by Stork so that, while demonstrating the applications of dienyliron complexes in natural products synthesis, there is a need for considerable improvement in efficiency. Aspidosperma alkaloids bearing oxygen functionality at C-18 are less readily accessible *via* standard organic methodology,[50] and the application[48,51] of dienyl complex (**118**) in the total synthesis of limaspermine (**163**; Scheme 22) is of greater significance. This route parallels that described above for the construction of intermediate (**157**), and gives the analogous perhydroquinoline (**161**) in eight steps from (**118**). Conversion of (**161**) to (**163**) proceeds according to standard methods, resulting in a total synthesis of (±)-limaspermine in 16 steps from complex (**118**).

The trichothecenes, a group of sesquiterpenes having a reasonably complex tricyclic structure, represent useful targets for the synthetic application of cyclohexadienyliron complexes. Several members of

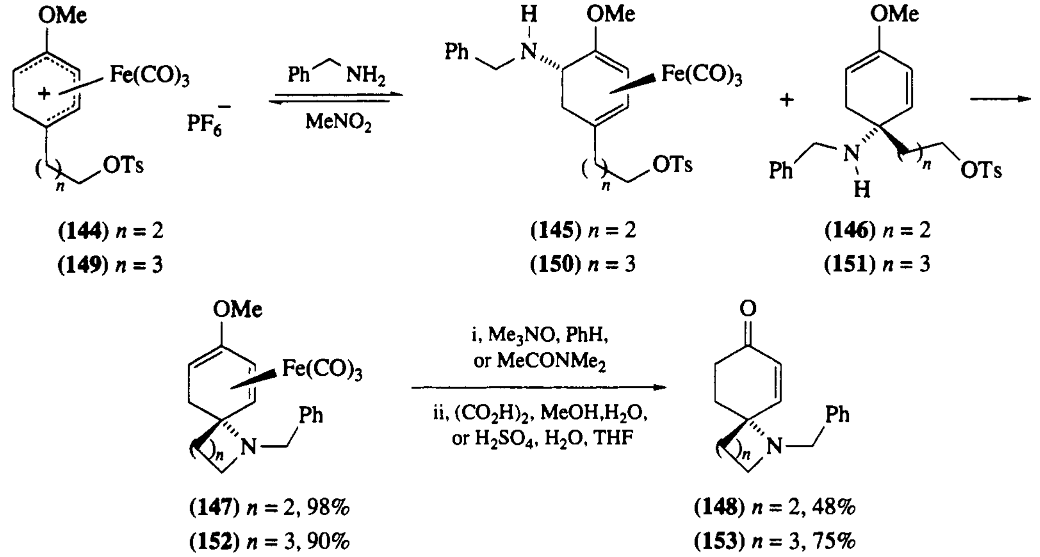
OMe
Fe(CO)3
PF6−
OTs
Ph NH2
MeNO2
H OMe
Ph N
Fe(CO)3
OTs
+
OMe
Ph N H
OTs
(144) n = 2
(149) n = 3
(145) n = 2
(150) n = 3
(146) n = 2
(151) n = 3
OMe
Fe(CO)3
Ph
N
i, Me3NO, PhH, or MeCONMe2
ii, (CO2H)2, MeOH,H2O, or H2SO4, H2O, THF
O
Ph
N
(147) n = 2, 98%
(152) n = 3, 90%
(148) n = 2, 48%
(153) n = 3, 75%

Scheme 19

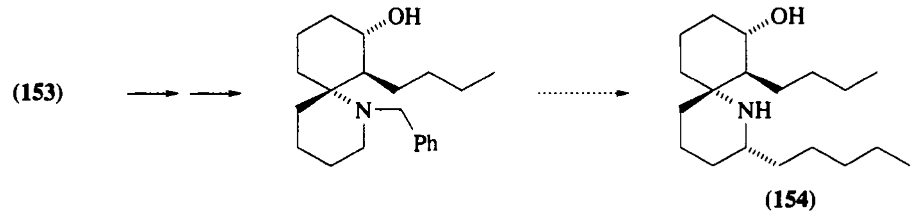
(153)
OH
N
Ph
OH
NH
(154)

Scheme 20

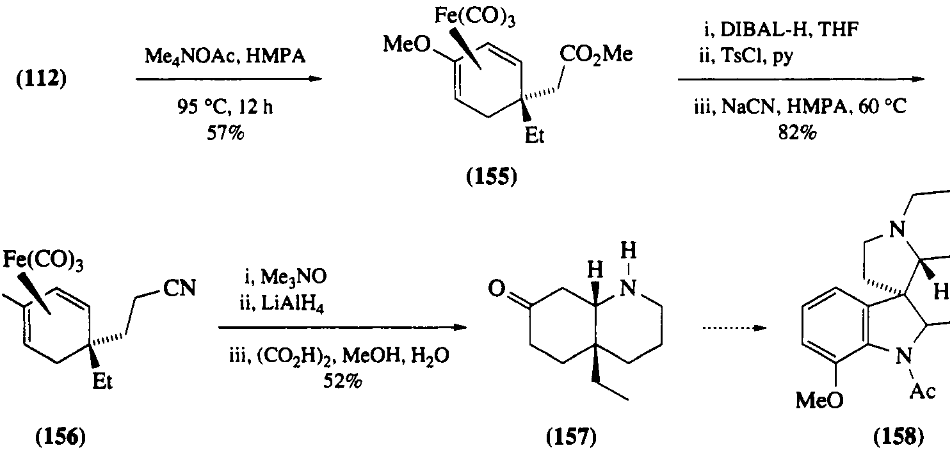
(112)
Me4NOAc, HMPA
95 °C, 12 h
57%
Fe(CO)3
MeO
CO2Me
Et
(155)
i, DIBAL-H, THF
ii, TsCl, py
iii, NaCN, HMPA, 60 °C
82%
Fe(CO)3
MeO
CN
Et
i, Me3NO
ii, LiAlH4
iii, (CO2H)2, MeOH, H2O
52%
O
H
H
N
N
H
N
Ac
MeO
(156)
(157)
(158)

Scheme 21

this class, exemplified by trichodermol (**164**), verrucarol (**165**), and calonectrin (**166**), as well as their biogenetic precursor trichodiene (**167**), show interesting biological activity and have been the objects of a number of total syntheses.[52–54]

The reaction of complex (**30**) with the enolate from methyl 2-oxocyclopentanecarboxylate to give complex (**97**), provides a method of joining five- and six-membered rings at highly substituted positions, generating contiguous quaternary centers appropriate for trichothecene synthesis. An equimolar mixture of diastereomers is generated in almost quantitative yield, and these are readily separated by crystallization to give (**168**; Scheme 23), which has relative configurations about the two quaternary centers appropriate for trichothecene synthesis. This intermediate has been converted to the trichothecene analogs

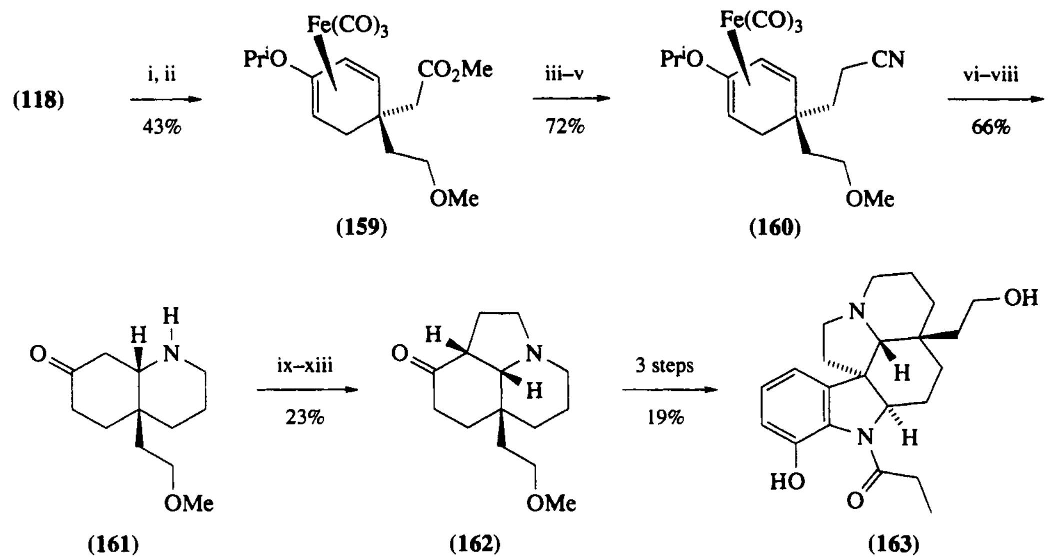

i, $KCH(CO_2Me)_2$; ii, KCN, DMSO, $H_2O$, 100–120 °C, 22 h; iii, DIBAL-H; iv, TsCl, py; v, NaCN, HMPA, 60 °C; vi, $Me_3NO$; vii, $LiAlH_4$; viii, $H^+$, $H_2O$; ix, $ClCH_2COCl$, py, PhH; x, $KOBu^t$; xi, $H^+$, $(CH_2OH)_2$; xii, $LiAlH_4$; xiii, $H^+$, $H_2O$

Scheme 22

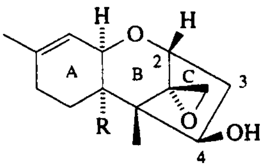

**(164)** R = Me
**(165)** R = $CH_2OH$

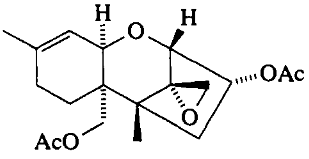

**(166)**

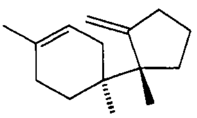

**(167)**

(**171**; Scheme 23) and (**172**; Scheme 24), and the two sequences of reactions illustrate the wide range of organic manipulations that can be performed without detriment to the (diene)$Fe(CO)_3$ unit.[12,55]

For an effective synthesis of trichodermol, there remain three points of concern. First, the formation of an equimolar mixture of diastereomers (**97**) leads to inefficiency, since realistically only half of the material can be used. Second, the ester group of complex (**168**) has to be reduced to methyl, a multistep operation which again is unattractive; it would be better to attach to complex (**30**) an enolate having methyl in place of the ester. Third, the introduction of the trichodermol 4-hydroxy group must be accomplished in some manner.

The direct coupling of the tin enolate (**175**; Scheme 25) with (**30**) gives complex (**176**) in good yield (87%). Fortuitously, the bond formation gives approximately a 5:1 mixture in favor of the diastereomer required for trichothecene synthesis. Further elaboration of the major isomer leads to (±)-trichodiene (**167**), representing an eight step diastereoselective total synthesis of the natural product from *p*-methylanisole, which compares very favorably with previous methods.[52,56]

In order to address the problem of 4-hydroxy group introduction, a tin enolate bearing a substituent that can be later converted to hydroxy must be employed. A suitable OH surrogate is the phenyldimethylsilyl group.[57] The readily prepared silyl-substituted tin enolate (**177**) reacts with complex (**30**) with a high degree of diastereoselectivity (*ca.* 6:1) to give complex (**178**) as the major product (72%).[58] Subsequent manipulation of (**178**) leads to a stereoselective total synthesis of (±)-trichodermol (**164**; Scheme 26) in 13 steps from complex (**30**), which is itself easily prepared from *p*-methylanisole on a large scale (>200 g batches).

The regioselectivity during hydride abstraction afforded by an ester substituent attached to cyclohexadiene has also been exploited for total synthesis. The synthesis of (+)- and (–)-gabaculine in homochiral

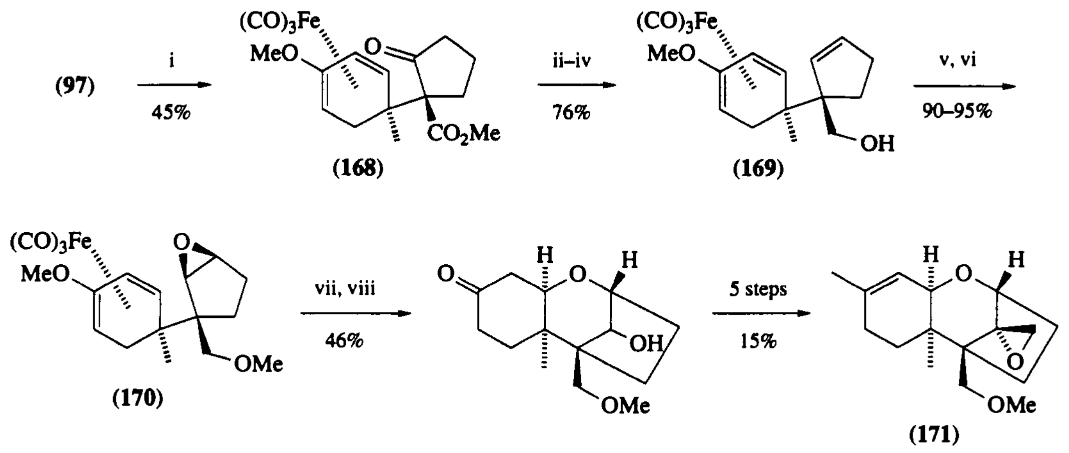
(97)
i
45%
(CO)3Fe
MeO
O
CO2Me
(168)
ii–iv
76%
(CO)3Fe
MeO
OH
(169)
v, vi
90–95%
(CO)3Fe
MeO
O
OMe
(170)
vii, viii
46%
O
H
O
H
OH
OMe
5 steps
15%
H
O
H
O
OMe
(171)

i, recryst.; ii, $NaBH_4$; iii, $SOCl_2$, py; iv, DIBAL-H; v, $Bu^tOOH$, $VO(acac)_2$, PhH; vi, MeI, NaH, THF; vii, $Me_3NO$; viii, $H^+$, $H_2O$

Scheme 23

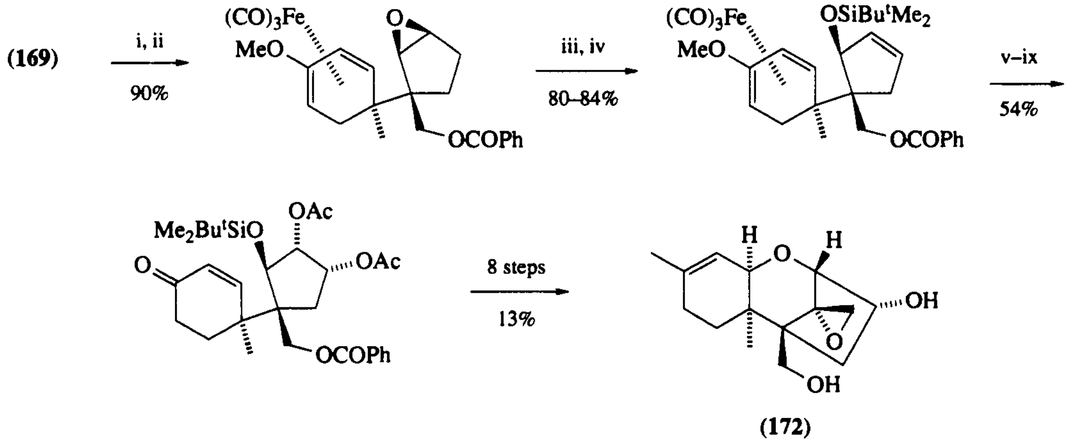
(169)
i, ii
90%
(CO)3Fe
MeO
O
OCOPh
iii, iv
80–84%
(CO)3Fe
MeO
OSiBu^tMe2
OCOPh
v–ix
54%
Me2Bu^tSiO
OAc
OAc
O
OCOPh
8 steps
13%
H
O
H
OH
O
OH
(172)

i, $Bu^tOOH$, $VO(acac)_2$, PhH; ii, PhCOCl, py; iii, $Bu^tMe_2SiI$, MeCN, 0 °C, 20 min; iv, DBU, THF, Δ, 48 h; v, $OsO_4$, py, 20 °C, 24 h; vi, $Na_2S_2O_5$, $H_2O$; vii, $Ac_2O$, py; viii, $Me_3NO$; ix, $H^+$, $H_2O$

Scheme 24

form takes advantage of the efficient resolution of the carboxylic acid derived from complex (**26**), which in turn allows the preparation of homochiral dienyl complex (**34**), as either enantiomer.[59] Gabaculine (**181**) is a naturally occurring unsaturated amino acid, which has been found to act as a potent inhibitor of 4-aminobutyrate:2-oxoglutarate aminotransferase, and which is therefore of interest in the treatment of certain neurochemical disorders, *e.g.* Parkinsonism, epilepsy and schizophrenia. The elegant synthesis described here illustrates two important features of dienyliron chemistry: (i) the stereospecific addition of nucleophiles, and (ii) the ability to remove the $Fe(CO)_3$ group from a delicate ligand. Reaction of optically pure (–)-(**34**) with *t*-butyl carbamate in the presence of Hunig's base leads to the formation of (–)-(**179**), which is decomplexed under mild conditions using trimethylamine *N*-oxide in dimethylacetamide. The resulting diene (**180**) is converted to (–)-gabaculine (**181**) in two steps (Scheme 27).

The ester-substituted complex (**34**) has been used in synthesis of (+)- and (–)-shikimic acid, an important intermediate in the biosynthesis of aromatic compounds, as well as stereospecifically deuterium labeled shikimic acid.[60] Addition of hydroxide anion to (+)-(**34**) gives the diene complex (+)-(**182**),

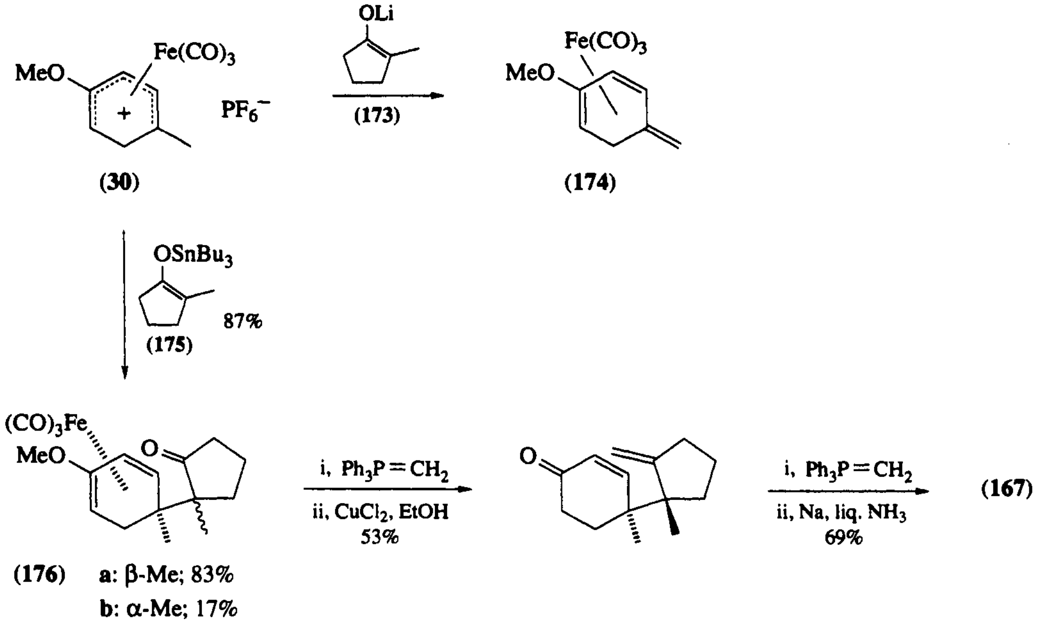
MeO
Fe(CO)3
+
PF6⁻
(30)
OLi
(173)
Fe(CO)3
MeO
(174)
OSnBu3
(175)
87%
(CO)3Fe
MeO
O
i, Ph3P=CH2
ii, CuCl2, EtOH
53%
O
i, Ph3P=CH2
ii, Na, liq. NH3
69%
(167)
(176) a: β-Me; 83%
b: α-Me; 17%

**Scheme 25**

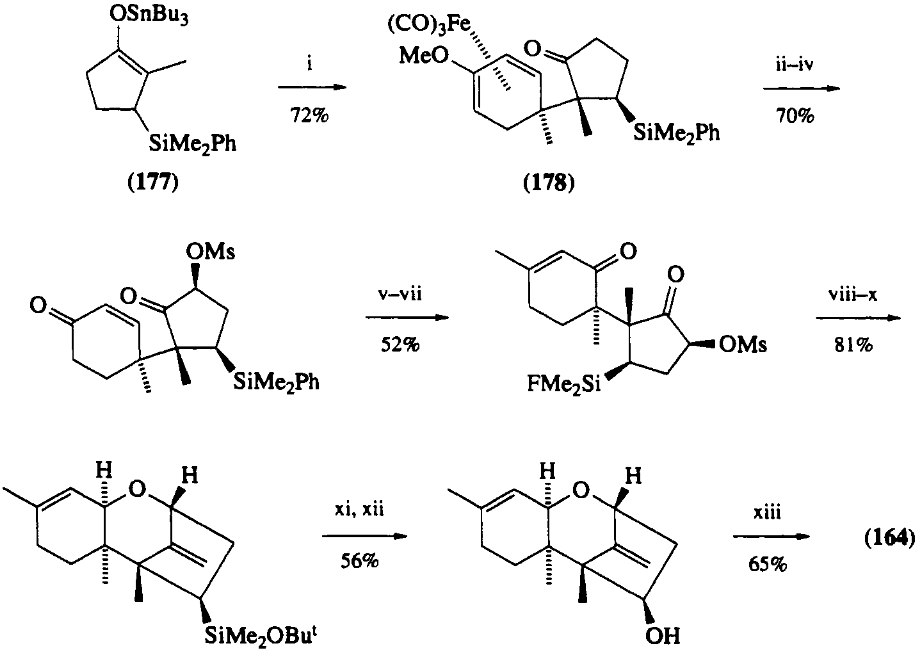
OSnBu3
SiMe2Ph
(177)
i
72%
(CO)3Fe
MeO
O
SiMe2Ph
(178)
ii–iv
70%
OMs
O
O
SiMe2Ph
v–vii
52%
O
O
OMs
FMe2Si
viii–x
81%
H
O
H
SiMe2OBu^t
xi, xii
56%
H
O
H
OH
xiii
65%
(164)

i, (**30**); ii, LDA, THF, MoOPH; iii, MsCl, py, r.t.; iv, $CuCl_2$, EtOH; v, MeMgBr; vi, PCC; vii, $HBF_4{\bullet}Et_2O$, $CH_2Cl_2$; viii, DIBAL-H; ix, PCC; x, $[Ph_3PMe]Br$, $KOBu^t$, $Et_2O$, $Bu^tOH$; xi, excess $Bu_4NF$, THF, $H_2O$; xii, $H_2O_2$, KF, $NaHCO_3$, THF, MeOH, 60 °C; xiii, MCPBA

**Scheme 26**

which is protected and decomplexed to give the diene (**183**). This is converted to (–)-methyl shikimate (**184**) using standard procedures (Scheme 28).

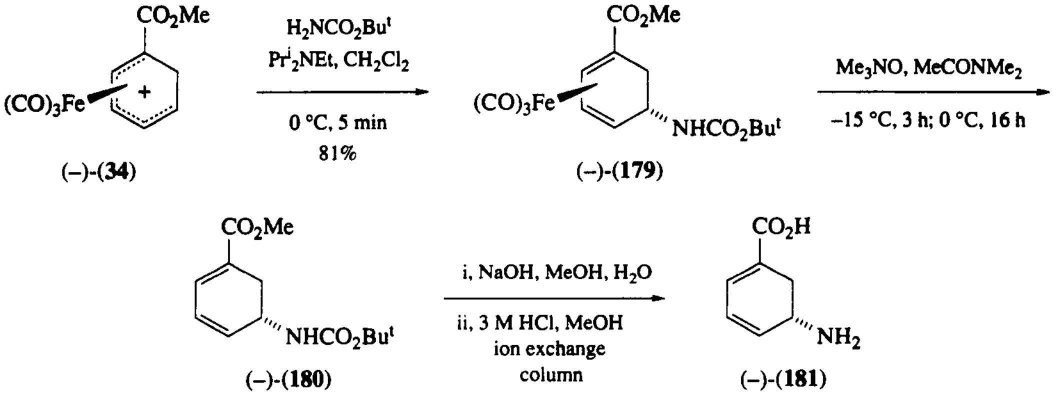
$CO_2Me$
$(CO)_3Fe$
(–)-(34)
$H_2NCO_2Bu^t$
$Pr^i{}_2NEt$, $CH_2Cl_2$
0 °C, 5 min
81%
$CO_2Me$
$(CO)_3Fe$
$NHCO_2Bu^t$
(–)-(179)
$Me_3NO$, $MeCONMe_2$
–15 °C, 3 h; 0 °C, 16 h
$CO_2Me$
$NHCO_2Bu^t$
(–)-(180)
i, NaOH, MeOH, $H_2O$
ii, 3 M HCl, MeOH
ion exchange
column
$CO_2H$
$NH_2$
(–)-(181)

Scheme 27

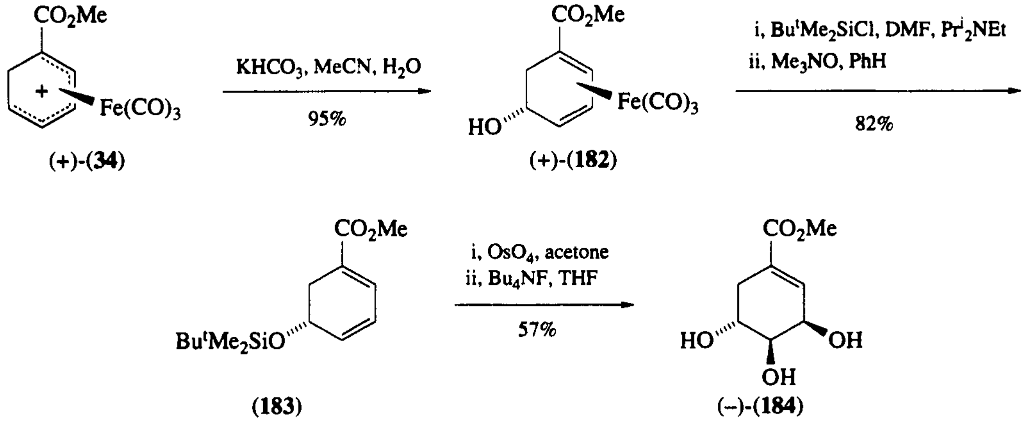
$CO_2Me$
$Fe(CO)_3$
(+)-(34)
$KHCO_3$, MeCN, $H_2O$
95%
$CO_2Me$
HO
$Fe(CO)_3$
(+)-(182)
i, $Bu^tMe_2SiCl$, DMF, $Pr^i{}_2NEt$
ii, $Me_3NO$, PhH
82%
$CO_2Me$
$Bu^tMe_2SiO$
(183)
i, $OsO_4$, acetone
ii, $Bu_4NF$, THF
57%
$CO_2Me$
HO
OH
OH
(–)-(184)

Scheme 28

### 3.4.2.4 Stereocontrol During Nucleophile Addition: Applications in Relative Stereocontrol During Multiple Functionalization of Six- and Seven-membered Rings

Given that nucleophile addition to (dienyl)Fe(CO)3 complexes proceeds stereospecifically *trans* to the metal, the question arises as to whether this can be used to control relative stereochemistry during multiple functionalization of cyclohexadienes and cycloheptadienes. A hypothetical example is shown in Scheme 29, where nucleophile addition is followed by a second hydride abstraction, or its equivalent, to generate a substituted dienyl complex. Addition of a second nucleophile, assuming stereocontrol from the metal, would generate a disubstituted derivative with defined relative stereochemistry.

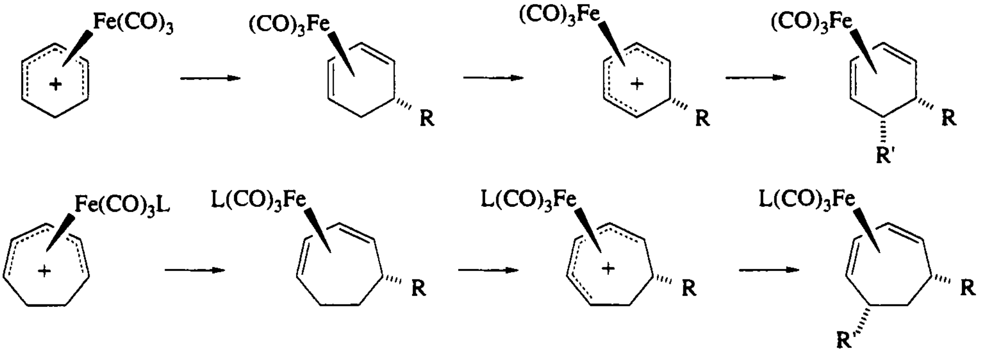
$Fe(CO)_3$
$(CO)_3Fe$
R
$(CO)_3Fe$
R
$(CO)_3Fe$
R
R'
$Fe(CO)_3L$
$L(CO)_3Fe$
R
$L(CO)_3Fe$
R
$L(CO)_3Fe$
R
R'

Scheme 29 Stereocontrolled multiple functionalization of dienyliron complexes

As mentioned earlier, direct hydride abstraction from 5-*exo*-substituted cyclohexadiene complexes is in general difficult, except for the 2-trimethylsilyl-substituted derivatives such as (**48**) and (**50**). Oxidative cyclization techniques have been developed to overcome this problem, exemplified by the conversion of (**52**) to (**53**) and thence to (**54**; Scheme 7). Stereocontrolled addition of a second nucleophile has already been illustrated by the conversion of (**54**) to (**126**) or (**127**), and the limitations imposed by a sterically demanding 6-*exo* substituent have been mentioned.

Hydride abstraction from cycloheptadienyl complex (**84**), having a sterically less encumbered allylic $CH_2$ group, occurs in excellent yield to generate complex (**185**; Scheme 30). Addition of nucleophiles to (**185**) provides complexes of general structure (**186**; Scheme 30) in high selectivity. The regioselectivity of this reaction is controlled only by steric hindrance from the methyl group in (**185**), but this is sufficient to give high selectivity.

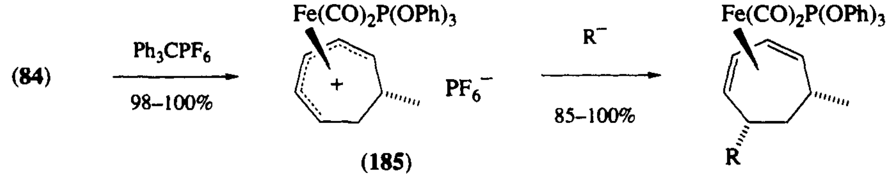
(84)
Ph3CPF6
98–100%
Fe(CO)2P(OPh)3
+
PF6−
R−
85–100%
Fe(CO)2P(OPh)3
R

**(185)**

**(186)**
**a**: R = Me
**b**: R = $CH_2CH{=}CH_2$
**c**: R = $CH(CO_2Me)_2$
**d**: R = $CH(SO_2Ph)CO_2Me$

**Scheme 30**

The symmetrical dimethyl-substituted complex (**186a**) has been employed in an asymmetric synthesis of the Prelog–Djerassi lactone (Scheme 31).[61] Decomplexation of (**186a**) affords the diene (**187**), which undergoes stereospecific palladium-catalyzed 1,4-diacetoxylation to give (**188**). Enzymatic hydrolysis of this compound allows the preparation of optically pure hydroxy acetate (**189**) which is readily converted to the (+)-Prelog–Djerassi lactone (**190**), an important degradation product of several macrolide antibiotics and a building block for their chemical synthesis.

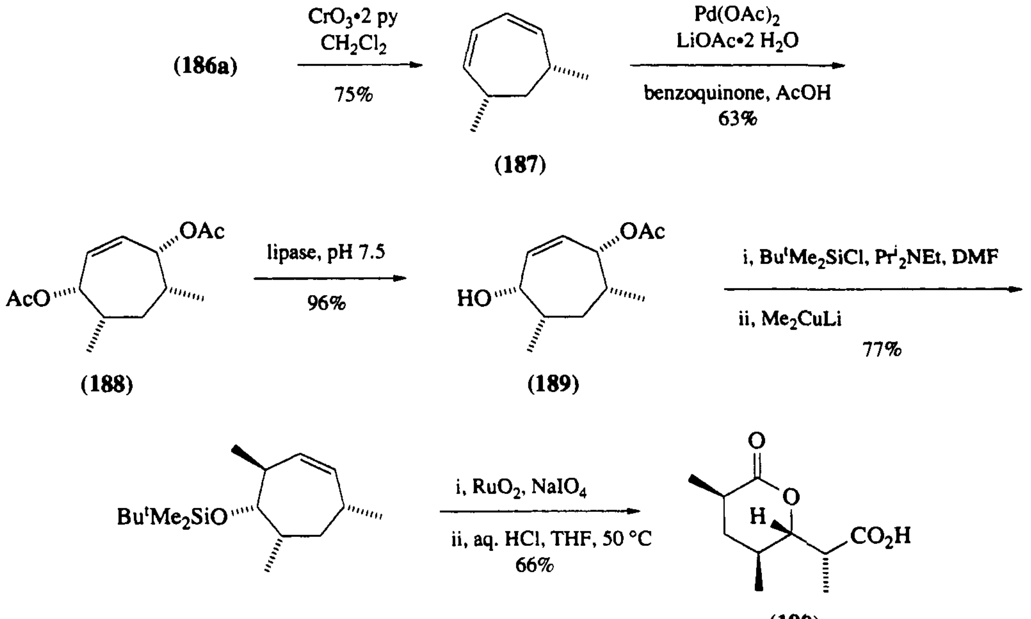
(186a)
CrO3•2 py
CH2Cl2
75%
Pd(OAc)2
LiOAc•2 H2O
benzoquinone, AcOH
63%
OAc
AcO
lipase, pH 7.5
96%
OAc
HO
i, ButMe2SiCl, Pri2NEt, DMF
ii, Me2CuLi
77%
ButMe2SiO
i, RuO2, NaIO4
ii, aq. HCl, THF, 50 °C
66%
O
O
H
CO2H

**(187)**

**(188)**

**(189)**

**(190)**

**Scheme 31**

The malonate adduct (**186c**) has been used[62] as an intermediate for the preparation of molecules corresponding to substructures of the macrolide antibiotics tylosin (**193**) and carbomycin B (**194**; Scheme 32). Decomplexation of (**186c**), followed by decarboxylation and ester hydrolysis, gives the carboxylic acid

(**191**), which undergoes conjugate bromolactonization to generate (**192**), and this can serve as an intermediate for approaches to the right-hand section of either (**193**) or (**194**), as shown in Scheme 32.

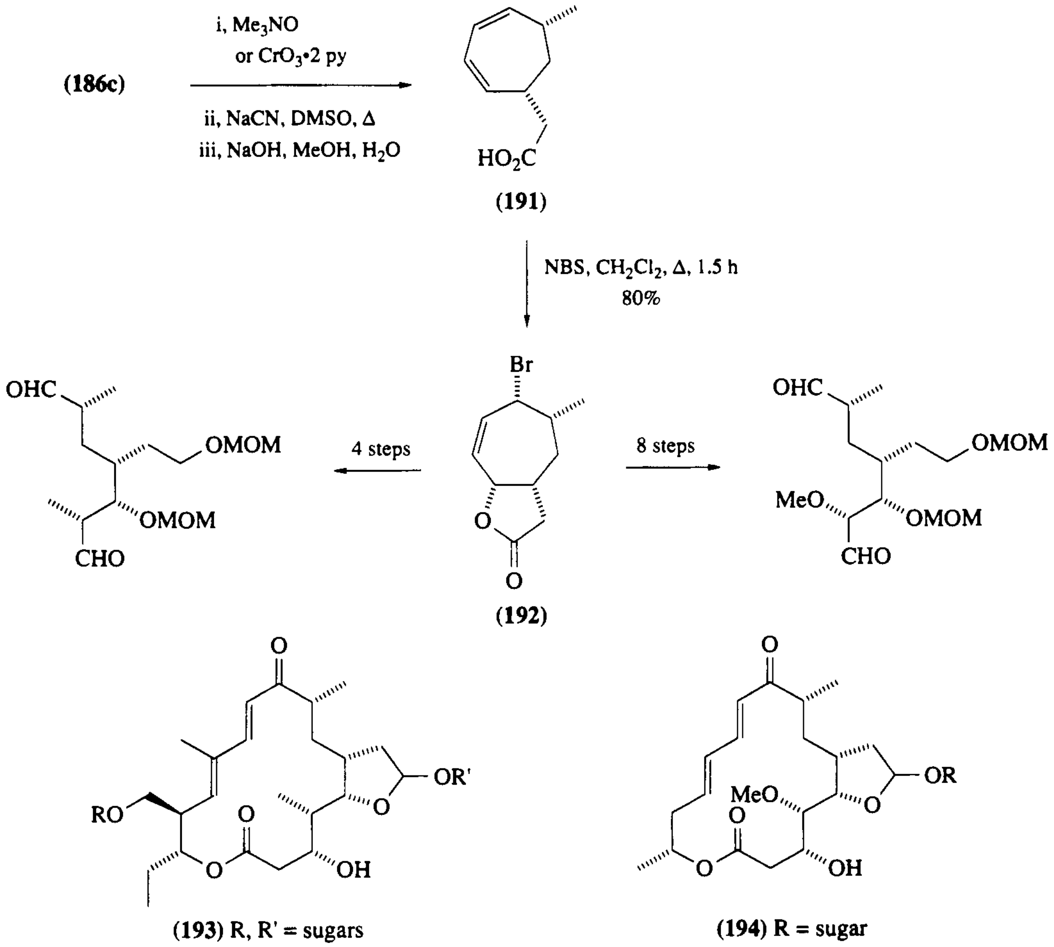

Scheme 32

Double functionalization appears to be quite general, since a variety of 5-substituted cycloheptadiene-iron complexes are readily converted to 6-substituted cycloheptadienyliron systems, which in turn undergo regio- and stereo-controlled nucleophile addition.[23]

## 3.4.2.5 Control of Absolute Stereochemistry During Carbon–Carbon Bond Formation Using Dienyliron Complexes

### *3.4.2.5.1 Preparation of enantiomerically enriched complexes*

There are two approaches for obtaining enantiomerically pure, unsymmetrically substituted, dienyliron complexes: (i) Resolution of either the dienyl complex itself or its dieneiron complex precursor; and (ii) asymmetric synthesis of the diene or dienyl complex.

The first method, resolution, is unattractive unless both enantiomers are useful in synthesis. In some cases, such as the resolution of dienecarboxylic acid derivatives mentioned earlier (*via* the phenylethylammonium salt), the resolution is efficient and provides optically pure materials in good yield.[59,60,63] In certain cases, the dienyliron complex can be treated with a chiral nucleophile to give a mixture of diastereomers which are separated and then reconverted to enantiomerically pure dienyl complex.[64] An example of this method is the resolution of complex (**27**; Scheme 33), *via* the menthyl ethers (**195**) and

(**196**), which can be separated chromatographically. Treatment of the separated ethers with acid leads to regeneration of optically pure complexes (+)- and (−)-(**27**).

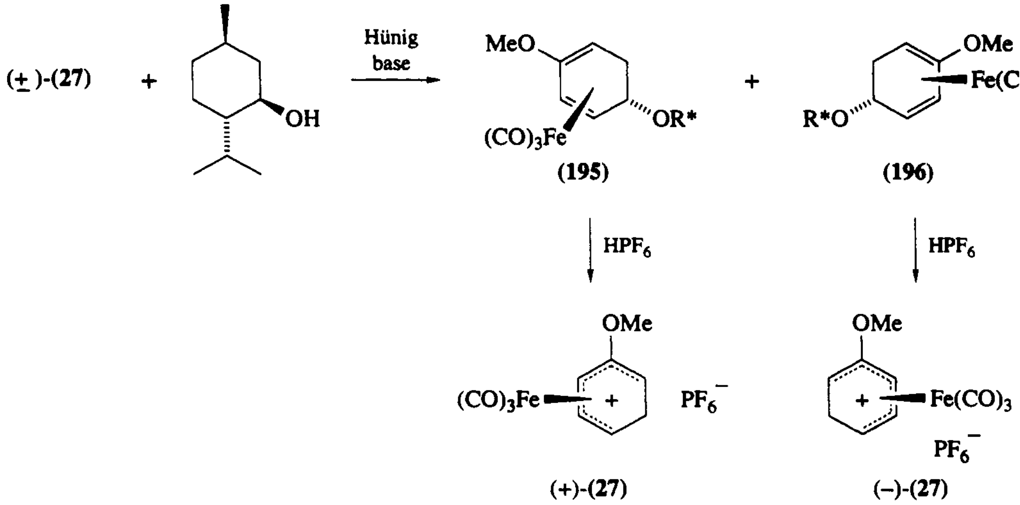
(±)-(27)
+
OH
Hünig base
MeO
(CO)3Fe
OR*
(195)
+
OMe
Fe(CO)3
R*O
(196)
HPF6
HPF6
OMe
(CO)3Fe
+
PF6−
(+)-(27)
OMe
+
Fe(CO)3
PF6−
(−)-(27)

Scheme 33

A modest degree of kinetic and/or thermodynamic discrimination has been observed during reactions of unsymmetrically substituted cyclohexadienyliron complexes with a deficiency of chiral nucleophile,[65] but this does not generate synthetically useful amounts of optically pure complexes and also involves loss of at least 50% of the complex (as does any classical resolution). A more promising approach,[66] which has not been fully refined to give high optical yields, is based on the knowledge that iron carbonyl complexes of α,β-unsaturated ketones, such as benzylideneacetone, readily transfer the $Fe(CO)_3$ group to 1,3-dienes.[9,35,67] The use of $Fe(CO)_3L_2$ complexes derived from chiral enones as asymmetric transfer reagents allows preparation of both enantiomers of complexes (**16**) and (**19**) with enantiomeric excesses of up to 43%. Assignments of absolute stereochemistry have been made, and it is noteworthy that the enantiomer which predominates is dependent on the chiral enone used to generate (*in situ*) the (enone)$Fe(CO)_3$ complex. For example, the use of (+)-pulegone (**197**; equation 56) gives (+)-(**19**), while the use of (−)-3β-(acetyloxy)pregna-5,16-dien-20-one (**198**; equation 57) gives (−)-(**19**).

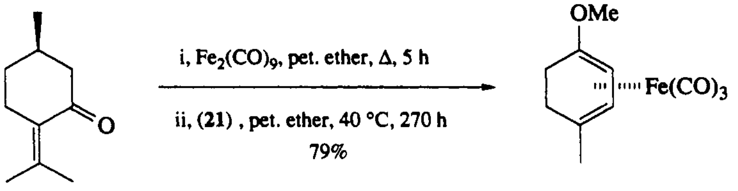
O
i, Fe2(CO)9, pet. ether, Δ, 5 h
ii, (21), pet. ether, 40 °C, 270 h
79%
OMe
Fe(CO)3

(56)

(**197**) (+)-(**19**) 10% *ee*

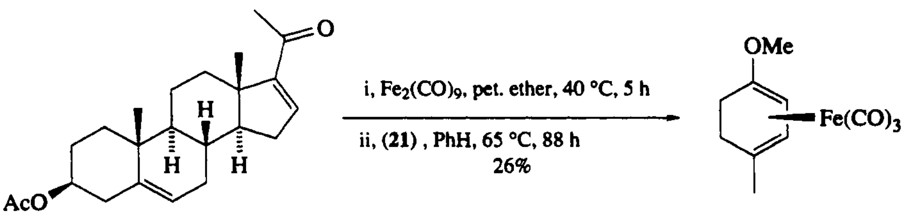
O
H
H
H
AcO
i, Fe2(CO)9, pet. ether, 40 °C, 5 h
ii, (21), PhH, 65 °C, 88 h
26%
OMe
Fe(CO)3

(57)

(**198**) (−)-(**19**) 43% *ee*

While the optical yields are rather low for useful synthetic application, this represents a promising lead for future work in the area of asymmetric complexation reactions.

#### *3.4.2.5.2 Reactions of symmetrical dienyliron complexes with chiral nucleophiles*

An alternative approach to asymmetric synthesis using dienyliron complexes involves addition of an enolate nucleophile bearing a chiral auxiliary to the complex.[68] Reaction of complex (**83**) with the enolate from optically pure sulfoximine-stabilized ester (**199**) gives the adduct (**200**), desulfonylation of which leads to the monoester derivative (**201**; Scheme 34), obtained in 50% enantiomeric excess. Since this complex undergoes hydride abstraction to give (**202**), which in turn reacts with a variety of carbon nucleophiles to generate complexes (**203**; Scheme 35), this represents a potentially useful approach to asymmetric multiple functionalization of the seven-membered ring. However, an enantiomeric excess of 50% is disappointing and there is much work to be done in seeking chiral auxiliaries that give higher asymmetric induction.

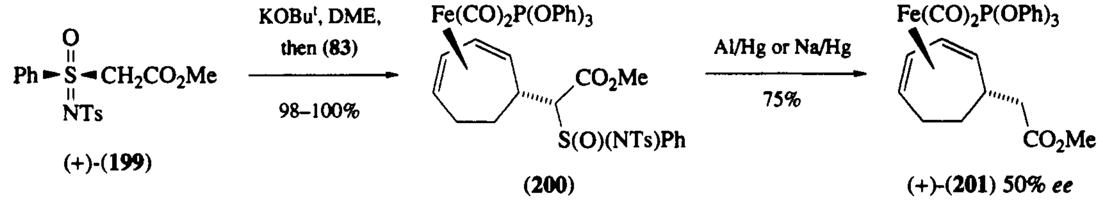

**Scheme 34**

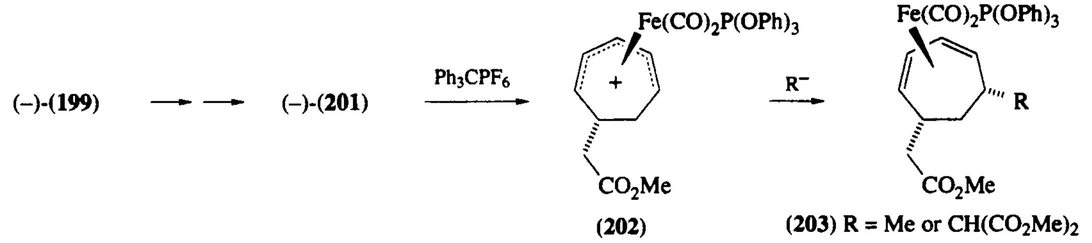

**Scheme 35**

### 3.4.3 CATIONIC DIENYL COMPLEXES OF OTHER METALS

The chemistry of pentadienyl complexes of metals other than iron has not been explored in depth, and consequently few applications in synthesis have emerged. The most noteworthy systems are the complexes of manganese and cobalt, and these will be described briefly in this section. One of the major problems with the use of these metals stoichiometrically is the high cost of their carbonyl complexes compared to iron [at the time of writing $Fe(CO)_5$ was cataloged at *ca.* $75.00 kg$^{-1}$, $Mn_2(CO)_{10}$ at $79.60 for 10 g, and $CpCo(CO)_2$ $142.75 for 25 g (Aldrich Catalog 1988/89)]. While this may reflect the rather low demand for these reagents, the high price is certainly a disincentive for extensive research that requires large amounts.

#### 3.4.3.1 Dienylmanganese Complexes

Treatment of 1,3-cycloheptadiene with $Mn_2(CO)_{10}$ at high temperature (refluxing mesitylene) gives the (cycloheptadienyl)$Mn(CO)_3$ derivative (**204**) in high yield.[69] This complex bears no charge and is unreactive towards most nucleophiles. However, substitution of CO ligand by $NO^+$ gives complex (**205**), which reacts with nucleophiles to give substituted diene complexes (**206**; Scheme 36).[70] Stereocontrolled double functionalization of the cycloheptadiene ring is possible since (**204**) can be converted to the (triene)$Mn(CO)_3$ complex (**207**), which also undergoes nucleophile addition. Using these tactics, substituted (dienyl)$Mn(CO)_2NO$ cation complexes (**208**; Scheme 37) can be prepared and converted to diene complexes (**209**). In several cases, the addition of nucleophiles is improved by using the trialkylphosphine or trialkyl phosphite derivatives (**210**) or (**211**; Scheme 37).[70]

(Arene)tricarbonylmanganese complexes react with nucleophiles to give substituted (cyclohexadienyl)$Mn(CO)_3$ complexes[71] which can be activated towards nucleophile addition by $CO/NO^+$ exchange giving, *e.g.* (**214**).[72] Kinetic studies[73] indicate that the $[Mn(CO)_2NO]^+$ and $[Fe(CO)_3]^+$ groups are vir-

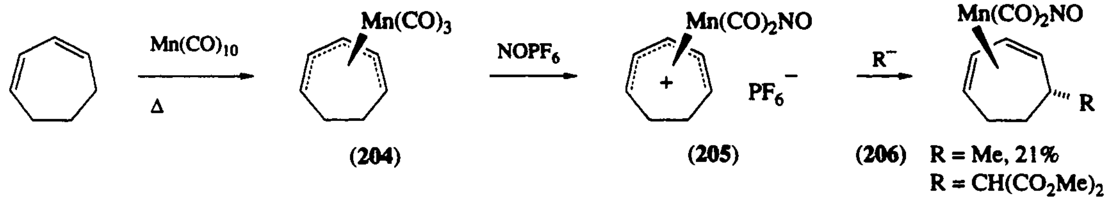
Mn(CO)10
Δ
Mn(CO)3
(204)
NOPF6
Mn(CO)2NO
+
PF6−
(205)
R−
Mn(CO)2NO
R
(206) R = Me, 21%
R = CH(CO2Me)2

Scheme 36

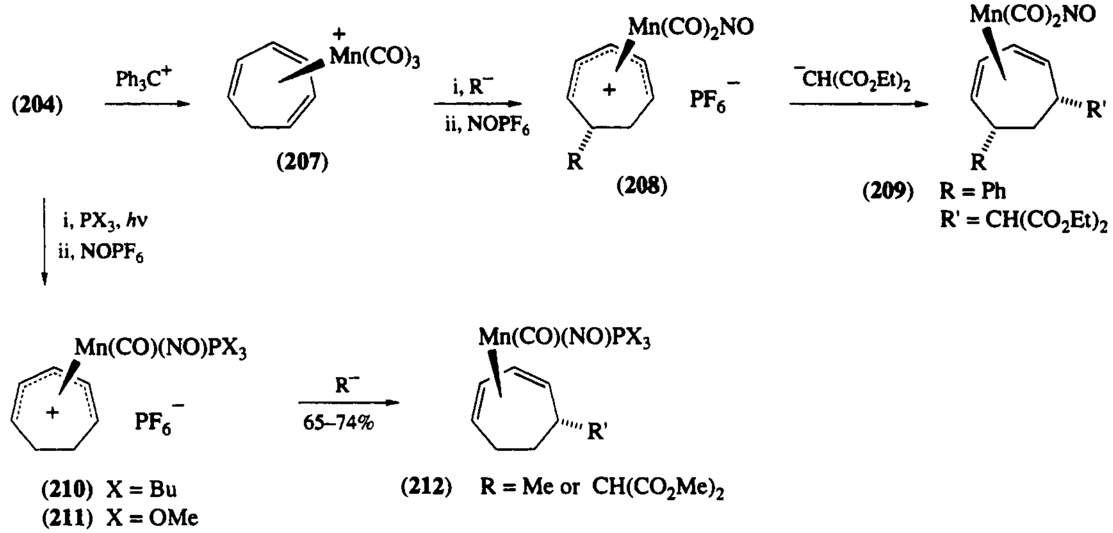
(204)
Ph3C+
+
Mn(CO)3
(207)
i, R−
ii, NOPF6
Mn(CO)2NO
+
PF6−
R
(208)
−CH(CO2Et)2
Mn(CO)2NO
R'
R
(209) R = Ph
R' = CH(CO2Et)2
i, PX3, hν
ii, NOPF6
Mn(CO)(NO)PX3
+
PF6−
(210) X = Bu
(211) X = OMe
R−
65–74%
Mn(CO)(NO)PX3
R'
(212) R = Me or CH(CO2Me)2

Scheme 37

tually identical in their activating power, so that they can be expected to react with similar nucleophiles. From the reactions of (**214**; Scheme 38), it can be seen that all nucleophiles add *exo*, except borohydride (borodeuteride) which adds *endo*, possibly *via* initial attack on a CO or NO ligand. (It may be noted that hydride adds only *exo* to dienyliron complexes.)

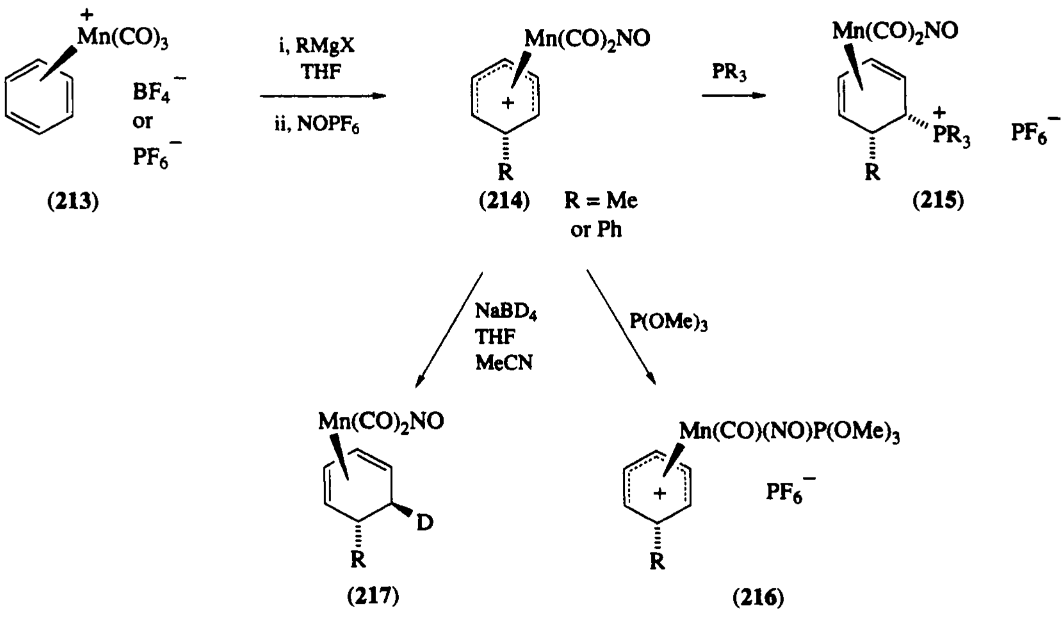
+
Mn(CO)3
BF4−
or
PF6−
(213)
i, RMgX
THF
ii, NOPF6
Mn(CO)2NO
+
R
(214) R = Me
or Ph
PR3
Mn(CO)2NO
+
PR3
PF6−
R
(215)
NaBD4
THF
MeCN
P(OMe)3
Mn(CO)2NO
D
R
(217)
Mn(CO)(NO)P(OMe)3
+
PF6−
R
(216)

Scheme 38

Of potentially greater interest are the preparation and reactions[74] of (dienyl)Mn(CO)$_2$NO complexes such as (**219**; Scheme 39), which take advantage of the *meta*-directing effect of a methoxy substituent during nucleophile addition to the (arene)Mn(CO)$_3$ complex (**218**). The dienyl system of (**219**) is very similar to the organoiron derivatives such as (**30**), and so it is interesting to note that sodium borohydride reduction of this complex gives a 1.5:1 mixture of regioisomers (**220**) and (**221**; Scheme 39) (hydride again adds *endo*). While there is some regioselectivity, it is unlikely to be of sufficient interest to prompt synthetic applications of this complex. Perhaps the use of isopropoxy in place of the methoxy group will allow greater regiocontrol, as seen with the iron analogs, but no study has been reported. Similarly, the arenemanganese complex (**222**; equation 58) has been converted to (**223**; 9:1 regioselectivity is observed).[75] No reports of nucleophile addition to this complex have appeared.

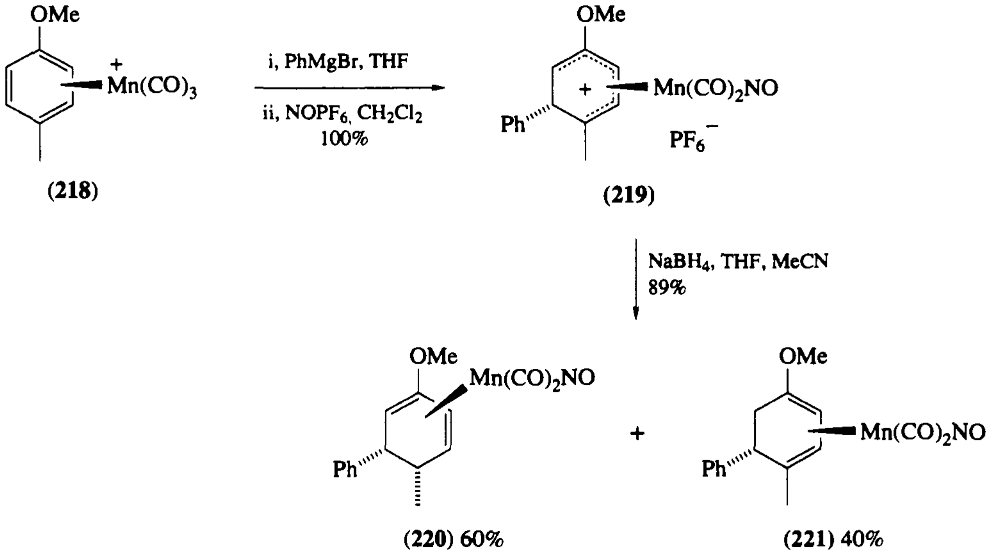

(**218**) (**219**)

(**220**) 60% (**221**) 40%

**Scheme 39**

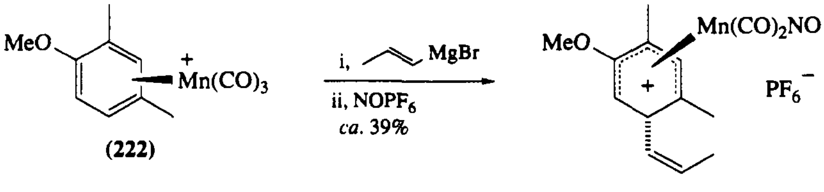

(**222**) (**223**) (58)

The range of nucleophiles that will react with complexes such as (**219**) and (**223**) has not been extensively investigated. The regiocontrolled addition of carbon nucleophiles, if successful, might provide new methodology for construction of highly functionalized cyclohexenones.

### 3.4.3.2 Dienylcobalt Complexes

The reactivity of the cobalt complexes has not been extensively investigated. The methods of preparation[76] of (dienyl)CoCp complexes are very similar to those for (dienyl)Fe(CO)$_3$ systems, including acid-promoted dehydroxylation, hydride abstraction, *etc.* and are illustrated here for complex (**224**; Scheme 40) and the analogous rhodium complex (**225**; Scheme 41). Somewhat surprisingly, the sterically congested (diene)CoCp complex (**226**) undergoes hydride abstraction, on treatment with trityl hexafluorophosphate under mild conditions, to give (**228**; Scheme 42).[77]

Nucleophilic addition to these complexes is a little less predictable than for the dienyliron systems. For example, the nucleophiles studied add to C-3 of the acyclic dienyl ligand in (**224**), but to C-1 of the cyclic system (**225**). Alkyllithiums add both to the cyclohexadienyl ligand, *e.g.* (**227**) gives (**229**), and to the cyclopentadienyl ligand, followed by interligand hydrogen transfer to give, *e.g.* (**228**). However, the fact that a hindered, very basic alkyllithium adds to a sterically hindered dienyl terminal carbon and does

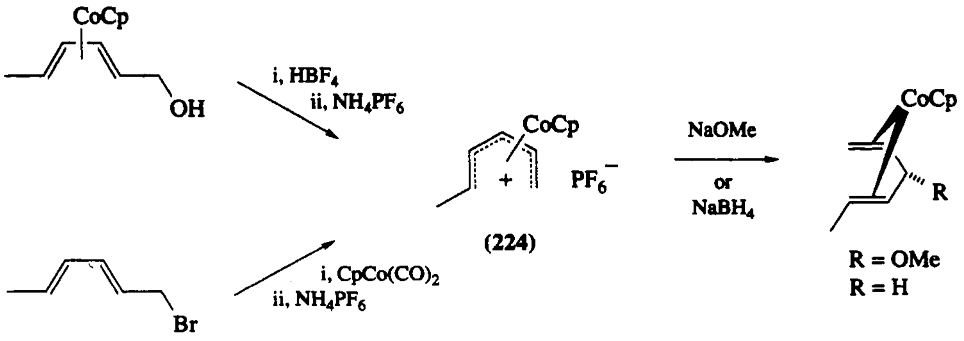
CoCp
OH
i, HBF4
ii, NH4PF6
Br
i, CpCo(CO)2
ii, NH4PF6
CoCp
+
PF6−
(224)
NaOMe
or
NaBH4
CoCp
R
R = OMe
R = H

Scheme 40

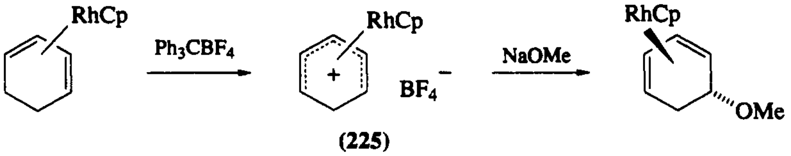
RhCp
Ph3CBF4
RhCp
+
BF4−
(225)
NaOMe
RhCp
OMe

Scheme 41

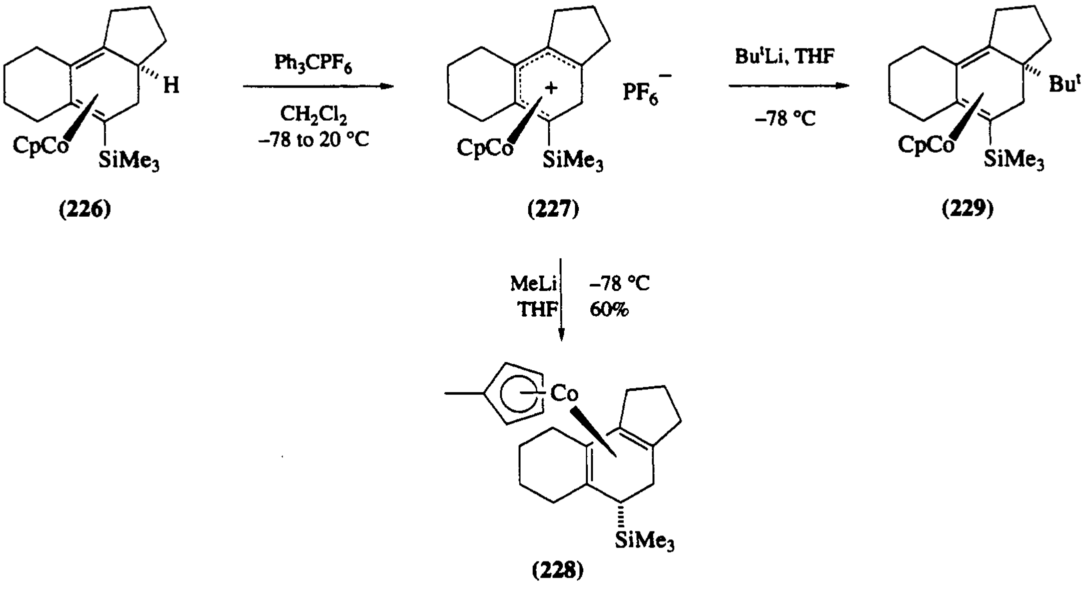
H
CpCo
SiMe3
(226)
Ph3CPF6
CH2Cl2
−78 to 20 °C
+
PF6−
CpCo
SiMe3
(227)
BuᵗLi, THF
−78 °C
Buᵗ
CpCo
SiMe3
(229)
MeLi
THF
−78 °C
60%
Co
SiMe3
(228)

Scheme 42

not deprotonate the complex is very encouraging and indicates that a set of reactions might be developed that are complementary to those already known for the organoiron derivatives.

## 3.4.4 REFERENCES

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# 3.5

# Carbon Electrophiles with Dienes and Polyenes Promoted by Transition Metals

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## 3.5.1 INTRODUCTION

Numerous synthetically useful carbon–carbon bond-forming reactions are based on the fact that unsaturated hydrocarbon ligands bound to electrophilic transition metal moieties are activated toward addition of nucleophiles. Normally the metal moiety in such complexes is a neutral or cationic metal carbonyl group. Prominent and well-studied examples include $[Cr(arene)(CO)_3]$ complexes (covered in Chapter 2.4, this volume),[1] $[Fe(dienyl)(CO)_3]^+$ complexes (covered in Chapter 3.4, this volume),[2] $[FeCp(CO)_2(alkene)]^+$ complexes[3] and $[M(CO)_n(diene)]$ complexes.[4]

The complementary approach, activation of unsaturated hydrocarbons toward electrophilic attack by complexation with electron-rich metal fragments, has seen limited investigation. Although there are certainly opportunities in this area which have not been exploited, the electrophilic reactions present a more complex problem relative to nucleophilic addition. For example, consider the nucleophilic *versus* electrophilic addition to a terminal carbon of a saturated 18-electron metal–diene complex. Nucleophilic addition generates a stable 18-electron saturated π-allyl complex. In contrast, electrophilic addition at carbon results in removal of two valence electrons from the metal and formation of an unstable π-allyl unsaturated 16-electron complex (Scheme 1).

The 16-electron species invariably must be stabilized by addition of an external ligand or by internal coordination. For example, as will be discussed later, acylation of a $[Fe(diene)(CO)_3]$ complex yields a

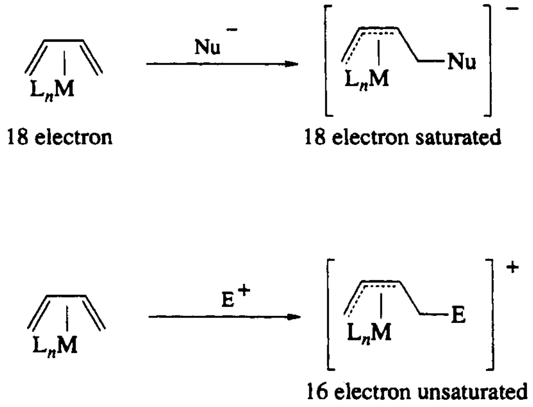
L$_n$M
Nu$^-$
L$_n$M
Nu
18 electron
18 electron saturated
L$_n$M
E$^+$
L$_n$M
E
+
16 electron unsaturated

**Scheme 1**

carbonyl-coordinated complex, while alkylation of a $[Mn(diene)(CO)_3]^-$ complex gives an 18-electron agostic species (Scheme 2).

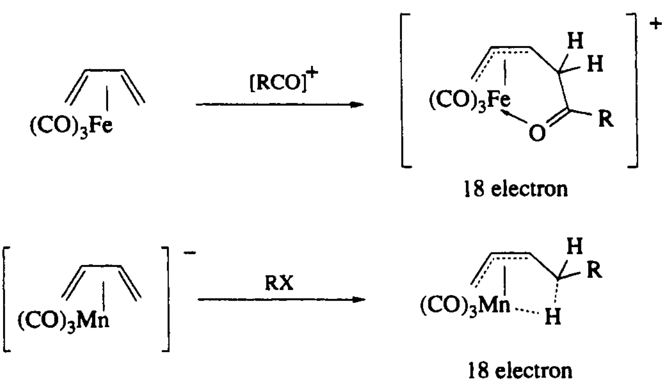
$(CO)_3Fe$
$[RCO]^+$
H
H
$(CO)_3Fe$
O
R
+
18 electron
$(CO)_3Mn$
RX
H
R
$(CO)_3Mn$
H
18 electron

**Scheme 2**

A common observation is that electrophiles add readily to complexes containing uncomplexed double bonds (normally at the uncomplexed double bond) to give 18-electron species as the initially generated complex. For example, acylation of $[Fe(cycloheptatriene)(CO)_3]$ yields an 18-electron dienyl complex, as shown in equation (1).

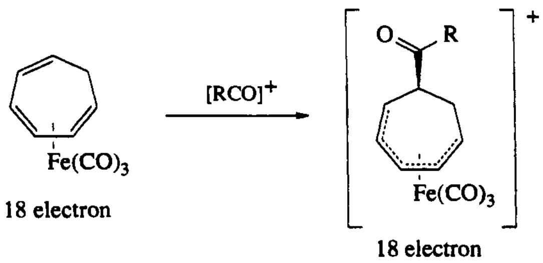 (1)
$Fe(CO)_3$
18 electron
$[RCO]^+$
O
R
$Fe(CO)_3$
+
18 electron

There are a few examples of additions of carbon electrophiles to metal complexes of allyl[5] and dienyl[6] moieties and arenes[7] which suggest many possible future extensions. However, the vast majority of systems examined involve additions of carbon electrophiles to electron-rich metal–diene complexes. This chapter will present a general discussion and several examples of such additions. Section 3.5.2 will examine simple $\eta^4$-diene complexes, while Section 3.5.3 will treat polyalkene complexes containing an $\eta^4$-diene unit and one or more uncomplexed double bonds.

## 3.5.2 REACTIONS OF $\eta^4$-DIENE TRANSITION METAL COMPLEXES WITH ELECTROPHILES

### 3.5.2.1 $\eta^4$-Diene Iron Tricarbonyl Complexes

Electrophilic substitution of $[Fe(diene)(CO)_3]$ complexes was first described by Ecke who reported that acetylation of $[Fe(butadiene)(CO)_3]$, **(1)**, gives 1- and 2-acetyl derivatives.[8] Subsequent studies showed that acylation occurred only at the terminal carbons,[9-12] to give the *trans* and *cis* isomers **(2)** and **(3)**, respectively (equation 2).

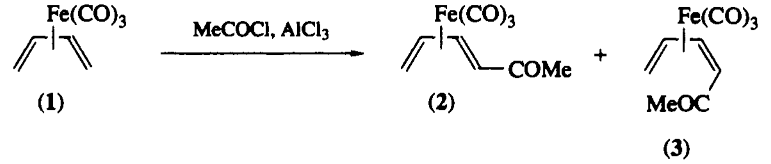
Fe(CO)3
MeCOCl, AlCl3
Fe(CO)3
COMe
Fe(CO)3
MeOC
(1)
(2)
(3)

(2)

The acylation is thought to occur as shown in Scheme 3. The π-allyl intermediate **(5)** was isolated in 86% yield and characterized by X-ray analysis.[13] The NMR spectrum and crystal structure of **(5)** indicate that only the *anti*-allyl structure is formed; no other positional isomers were detected. The iron atom in **(5)** obtains a closed-shell electron configuration by intramolecular σ-donation of a lone pair of electrons from the acyl oxygen atom, which is confirmed by a lowering the acyl CO bond order ($\nu_{CO}$ 1637 $cm^{-1}$).[12] There is no direct evidence for formation of **(4)**; its intermediacy has been suggested primarily based on the *endo* stereochemistry of the acylation reaction (see below).

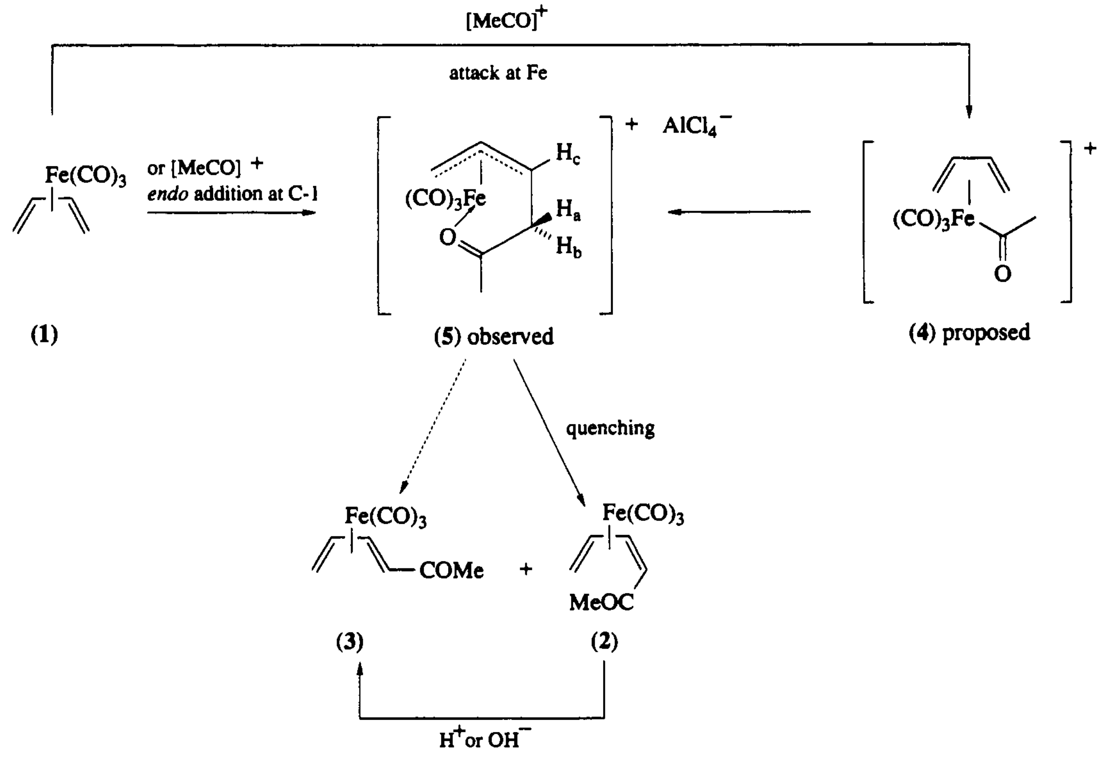
[MeCO]+
attack at Fe
Fe(CO)3
or [MeCO] +
endo addition at C-1
(1)
(CO)3Fe
Hc
Ha
Hb
O
+ AlCl4−
(5) observed
(CO)3Fe
O
+
(4) proposed
quenching
Fe(CO)3
COMe
+
Fe(CO)3
MeOC
(3)
(2)
H+or OH−

**Scheme 3**

The kinetic product of deprotonation of **(5)** is the *cis* isomer **(2)**; however, **(2)** is readily isomerized to the thermodynamically more stable *trans* isomer **(3)** under both acidic and basic conditions. Thus acylation reactions can often lead to a mixture of isomers and product ratios are dependent on the precise quenching conditions. Convincing evidence for *endo* addition of $[RCO]^+$ to iron–diene complexes first came from the X-ray crystal structure determination of the cationic intermediate (**7**) formed from acylation of the 1,4-dimethylbutadiene complex (**6**; equation 3).[14]

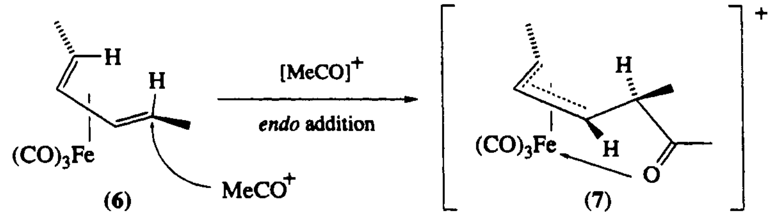

(3)

Using a competition method, Lillya *et al.*[15,16] obtained relative reactivities for a series of substituted diene–tricarbonyliron compounds toward the methyloxocarbonium tetrachloroaluminate ion pair in dichloromethane. The results are qualitatively summarized in Scheme 4.

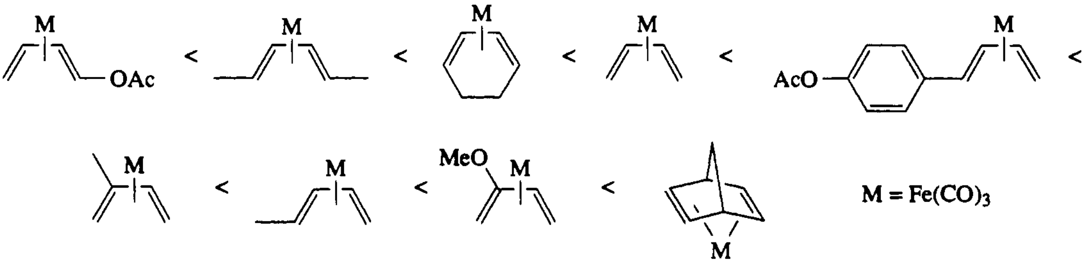

**Scheme 4**

Quantitative relative partial rate factors for acetylation of several of these iron–diene complexes were also obtained and are summarized in Scheme 5.[15,16]

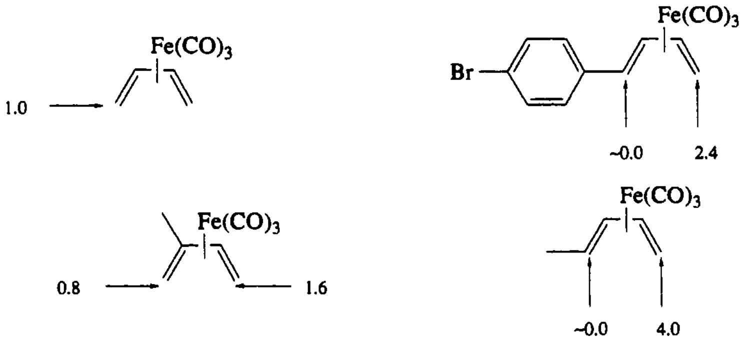

**Scheme 5** Relative partial rate factors for acylation with acetyl chloride/$AlCl_3$ in dichloromethane at 25 °C

These results show that substitution of a terminal carbon decreases its reactivity dramatically presumably due to a steric effect. Substituent effects are moderate; for example, a 1-methyl group increases the rate of substitution at C-4 by a factor of 4. A 2-methyl group exerts a small directing effect to C-4;[16] however, substitution of more strongly electron-donating groups at C-2 (*e.g.* $SiEt_3$, $SiPr^i_3$) results in higher regioselectivity for substitution at C-4 (see below).[17]

As mentioned earlier, the *cis*:*trans* ratios of acylation products are highly dependent on the method of quenching.[18] Quenching with cold 28% aqueous ammonia gives high yields of *cis*-dienone complex. In contrast, quenching with potassium *t*-butoxide in *t*-butanol gives high yields of *trans*-dienone (equation 4 and Table 1).

*Cis* isomers can be isomerized to *trans* isomers by various methods. Illustrative examples are shown in equations (5) and (6), Tables 2 and 3.

Birch and Pearson[22] have studied electrophilic substitution of a triphenylphosphine-substituted system, $[Fe(cyclohexadiene)(CO)_2PPh_3]$, (**8**; equation 7). Several features of their results are instructive. First, substitution of CO by the better $\sigma$-donor, poorer $\pi$-acceptor $PPh_3$ ligand renders the complex more reac-

**Table 1** Variation of *cis:trans* Isomer Ratios with Quenching Method

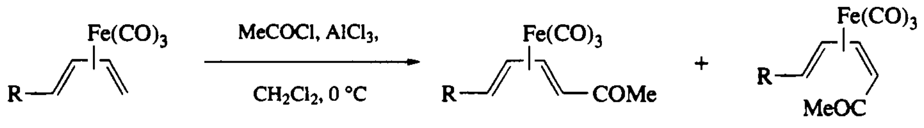
Fe(CO)3
R
MeCOCl, AlCl3,
CH2Cl2, 0 °C
Fe(CO)3
R
COMe
+
Fe(CO)3
R
MeOC

A B

(4)

| *R* | *Quenching method* | *A:B* | *Yield (%)* |
|---|---|---|---|
| H | Aq. ammonia (28%) | 1:0 | 86 |
| Me | Aq. ammonia (28%) | 1:0 | 84 |
| *p*-BrC$_6$H$_4$ | Aq. ammonia (28%) | 1:0 | 90 |
| *p*-MeCOC$_6$H$_4$ | K$_2$CO$_3$ (5%) | 0:1 | 90 |

**Table 2** Isomerization of *cis* Isomers to *trans* Isomers Under Basic Conditions

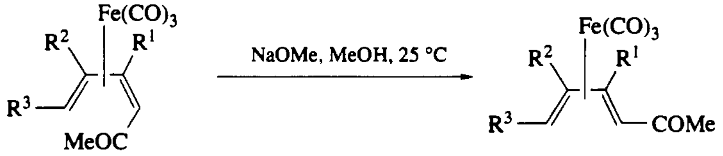
Fe(CO)3
R2
R1
R3
MeOC
NaOMe, MeOH, 25 °C
Fe(CO)3
R2
R1
R3
COMe

(5)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| H | H | H | 69 | 18 |
| H | H | Me | 71 | 18 |
| H | H | *p*-BrC$_6$H$_4$ | 79 | 18 |
| H | OMe | H | 60 | 18 |
| Me | H | Me | 75 | 18 |
| H | H | SiMe$_3$ | 85 | 19 |
| Me | H | SiMe$_3$ | 95 | 19 |
| MeCO | SiEt$_3$ | H | 92 | 20 |

**Table 3** Isomerization of *cis* Isomers to *trans* Isomers in the Presence of Acetyl Chloride

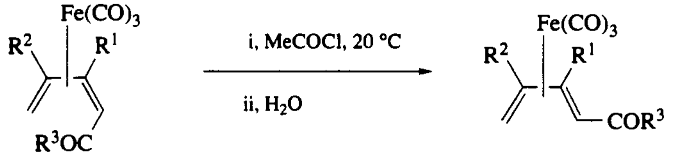
Fe(CO)3
R2
R1
R3OC
i, MeCOCl, 20 °C
ii, H2O
Fe(CO)3
R2
R1
COR3

(6)

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| H | Me | Me | 89 | 21 |
| Me | Me | Me | 99 | 21 |
| Me | H | Me | 89 | 21 |
| H | SiEt$_3$ | Me | 95 | 20 |
| H | SiPr$^i_3$ | Me | 95 | 20 |
| SiEt$_3$ | H | Ph | 68 | 17 |
| H | SiEt$_3$ | Ph | 68 | 17 |
| SiEt$_3$ | H | Bu$^t$ | 73 | 17 |
| H | SiEt$_3$ | Bu$^t$ | 73 | 17 |
| SiEt$_3$ | H | Pr$^i$ | 96 | 17 |
| H | SiEt$_3$ | Pr$^i$ | 96 | 17 |

tive toward electrophiles. Thus, substitutions can be carried out under milder conditions and in better yields.

Second, acylation reactions of (**8**) yield only isomer (**10**); (**11**) is not formed. This observation can be explained by considering intermediate (**9**; Scheme 6). The coordination between the acyl oxygen and the

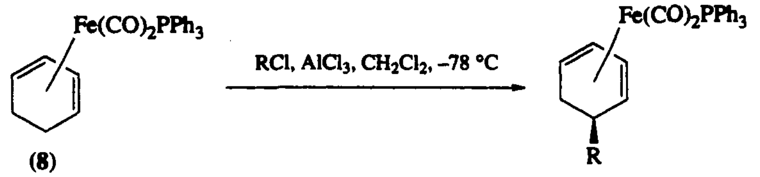
Fe(CO)2PPh3
RCl, AlCl3, CH2Cl2, –78 °C
Fe(CO)2PPh3
(8)
R

(7)

R = COMe, 96%; R = COPh, 50%; R = $CH_2OMe$, 65%

iron atom in cationic intermediate (**10**) would result in the carbonyl π-orbital being orthogonal to a developing carbanion lone pair orbital at the α-position, thereby making the α-hydrogen, $H_{1X}$, less acidic than the alternative methylene hydrogen, $H_{5N}$.

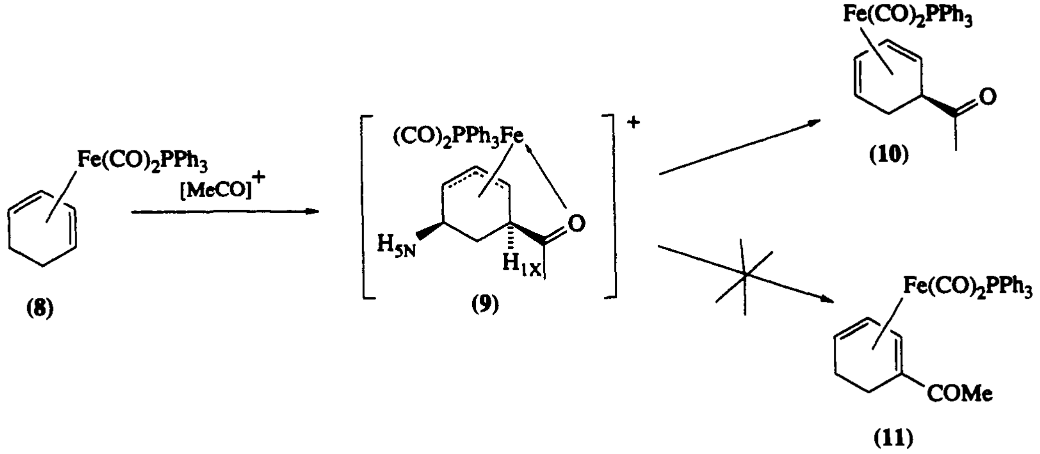
Fe(CO)2PPh3
[MeCO]+
(8)
(CO)2PPh3Fe
H5N
H1X
O
(9)
+
Fe(CO)2PPh3
O
(10)
Fe(CO)2PPh3
COMe
(11)

**Scheme 6**

All of the examples cited above involve monoacylation of iron–diene complexes. Frank-Neumann has recently demonstrated that monoacylated derivatives are subject to a second acylation and that bis-1,4-diacylated complexes could be obtained in moderate to good yields. Examples are given in equations (8) and (9) and Table 4.[20,23]

**Table 4** Diacylation Reactions of [Fe(2-Triethylsilylbutadiene)$(CO)_3$]

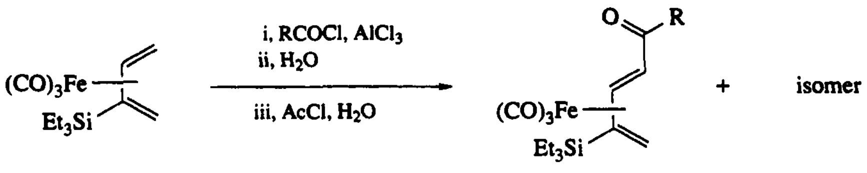
(CO)3Fe
Et3Si
i, RCOCl, AlCl3
ii, H2O
iii, AcCl, H2O
O
R
(CO)3Fe
Et3Si
+
isomer

(8)

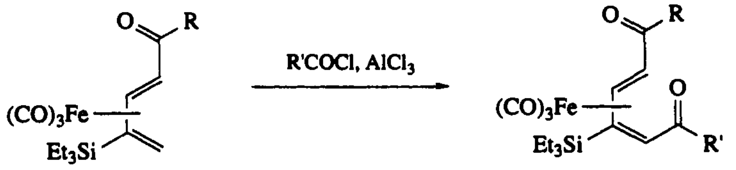
O
R
(CO)3Fe
Et3Si
R'COCl, AlCl3
O
R
O
(CO)3Fe
Et3Si
R'

(9)

| *R* | *R'* | *Yield (%)* |
|---|---|---|
| Me | Pr$^i$ | 50 |
| Me | $(CH_2)_4CO_2Me$ | 76 |
| Pr$^i$ | Me | 40 |
| Bu$^t$ | Me | 32 |
| Ph | Me | 55 |
| $(CH_2)_7COMe$ | Et | 90 |

Formylation of diene–tricarbonyliron complexes has also been reported by Lillya *et al.*[18,24] Examples are given in Scheme 7.

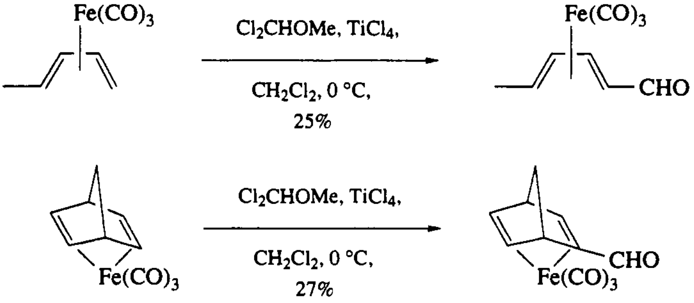
Fe(CO)3
Cl2CHOMe, TiCl4,
CH2Cl2, 0 °C,
25%
Fe(CO)3
CHO
Fe(CO)3
Cl2CHOMe, TiCl4,
CH2Cl2, 0 °C,
27%
CHO
Fe(CO)3

**Scheme 7**

In a series of classic studies, Pettit *et al.* reported the synthesis of (cyclobutadiene)iron tricarbonyl together with a variety of electrophilic substitution reactions of this 'aromatic' system (Scheme 8).[25–27]

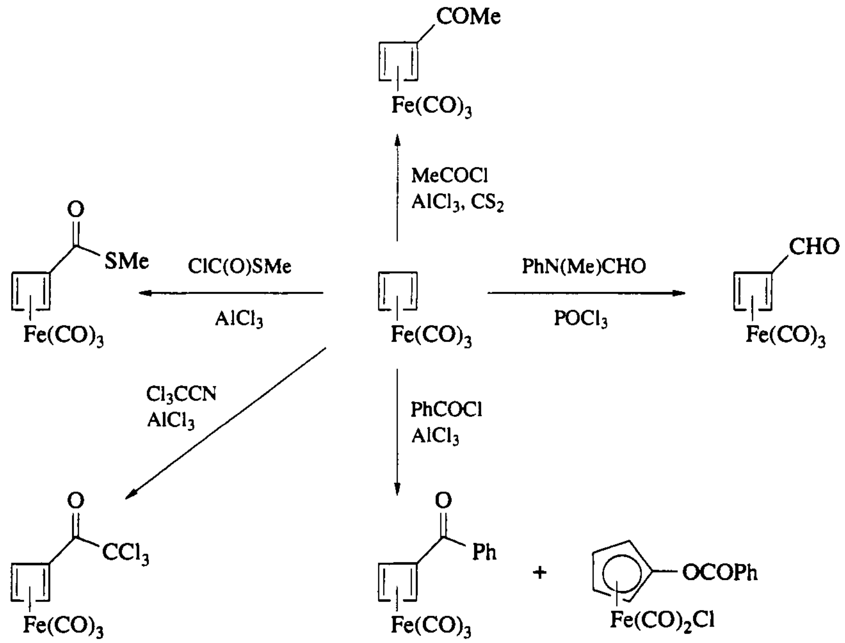
COMe
Fe(CO)3
MeCOCl
AlCl3, CS2
O
SMe
Fe(CO)3
ClC(O)SMe
AlCl3
Fe(CO)3
PhN(Me)CHO
POCl3
CHO
Fe(CO)3
Cl3CCN
AlCl3
PhCOCl
AlCl3
O
CCl3
Fe(CO)3
O
Ph
Fe(CO)3
+
OCOPh
Fe(CO)2Cl

**Scheme 8**

There are numerous methods available for the cleavage of the iron tricarbonyl group from the diene moiety and recovery of the organic ligand in good yields. The most frequently used methods involve oxidative procedures including reaction of the diene complexes with $Me_3NO$, $H_2O_2/OH^-$ and $Fe^{III}$ and $Ce^{IV}$ salts. Reactions of iron–diene complexes with $LiAlH_4$ normally leads to cleavage and complete reduction of the diene unit.[28,29]

The availability of such procedures coupled with several straightforward methods for synthesis of the diene complexes make these species attractive for use in organic synthesis. Several illustrative examples follow, which include acylation (or diacylation) of iron–diene complexes followed by cleavage and recovery of the free organic ligand.

Frank-Neumann has described a series of double acylations followed by oxidative cleavage reactions to yield 1,6-dione-2,4-dienes (Schemes 9 and 10).[21]

In an elegant synthetic application of iron–diene complexes, Knox[30] has reported acylation of a series of 1-alkyl-substituted diene complexes which after cleavage, reduction and esterification give a series of moth pheromones (Scheme 11).

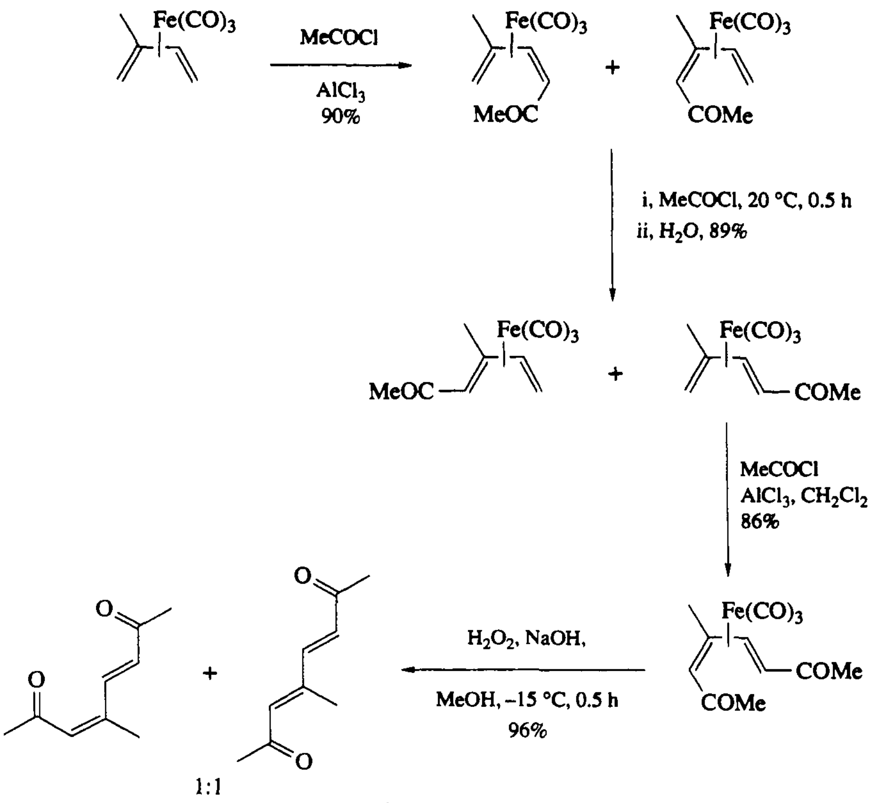
Fe(CO)3
MeCOCl
AlCl3
90%
MeOC
COMe
+
i, MeCOCl, 20 °C, 0.5 h
ii, H2O, 89%
MeCOCl
AlCl3, CH2Cl2
86%
H2O2, NaOH,
MeOH, -15 °C, 0.5 h
96%
O
1:1

Scheme 9

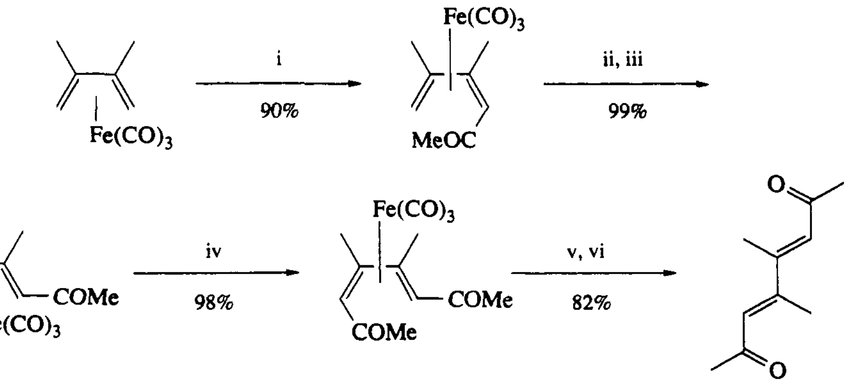
Fe(CO)3
i
90%
MeOC
ii, iii
99%
iv
98%
COMe
v, vi
82%
O

i, MeCOCl, $AlCl_3$; ii, MeCOCl, 20 °C, 5 h; iii, $H_2O$; iv, MeCOCl, $AlCl_3$;
v, NaOMe, MeOH, 20 °C, 15 h; vi, $H_2O_2$, NaOH, MeOH, -15 °C, 0.5 h

Scheme 10

Cleavage of acylated diene–iron complexes with $LiAlH_4$ is illustrated by the following reports of Nesmeyanov and Anisimov (Scheme 12).[28,29]

Pearson[31] has reported an example of intramolecular alkylation under CO to yield an allyliron tetracarbonyl cation. Hydride reduction yields the alkene (Scheme 13).

### 3.5.2.2 $\eta^4$-Diene Manganese Tricarbonyl Anions

$[Mn(diene)(CO)_3]^-$ complexes are isoelectronic with $[Fe(diene)(CO)_3]$ complexes but owing to their anionic character are much more reactive toward electrophiles than the neutral iron analogs. The first examples of these species to be reported were $[Mn(cyclohexadiene)(CO)_3]^-$ complexes prepared *via*

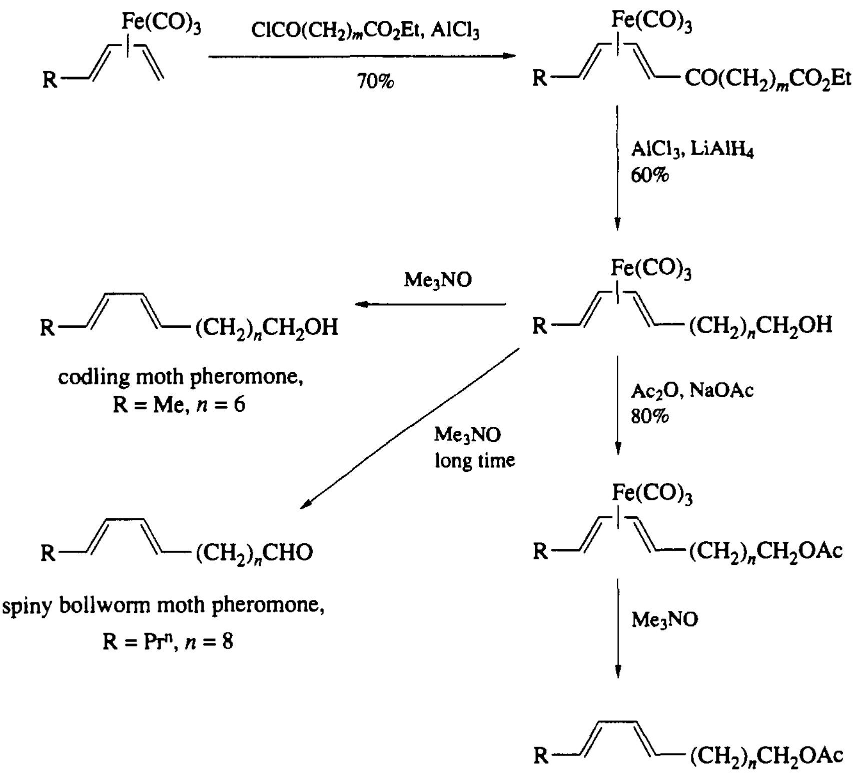
Fe(CO)3
R
ClCO(CH2)mCO2Et, AlCl3
70%
CO(CH2)mCO2Et
AlCl3, LiAlH4
60%
Me3NO
(CH2)nCH2OH
codling moth pheromone,
R = Me, n = 6
Me3NO
long time
Ac2O, NaOAc
80%
(CH2)nCHO
spiny bollworm moth pheromone,
R = Prn, n = 8
(CH2)nCH2OAc
Me3NO

| *R* | *m* | *n* | *Moth species* |
|---|---|---|---|
| H | 6 | 7 | red bollworm moth |
| Me | 5 | 6 | pea moth; pitch pine tip moth |
| Et | 6 | 7 | light-brown apple moth |

**Scheme 11**

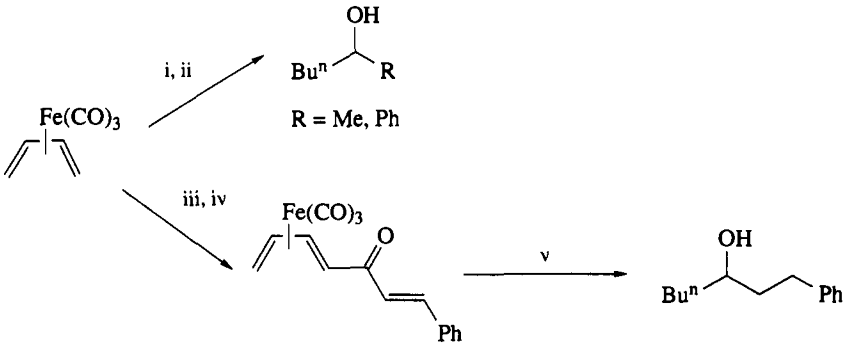
i, ii
OH
Bun
R
R = Me, Ph
Fe(CO)3
iii, iv
Fe(CO)3
O
Ph
v
OH
Bun
Ph

i, RCOCl, $AlCl_3$; ii, $LiAlH_4$, THF, reflux; iii, MeCOCl, $AlCl_3$; iv, PhCHO, NaOH; v, $LiAlH_4$, THF, reflux

**Scheme 12**

double hydride reduction of $[Mn(arene)(CO)_3]^+$ complexes (Scheme 14).[32] An acyclic example (**12**) was prepared by thermolysis of $[1,1\text{-dimethylallylMn(CO)}_4]$, (**13**), to give agostic complex (**14**) followed by deprotonation with KH (Scheme 14).[33]

A more general route to these anionic manganese complexes has recently been described[34,35] and involves Red-Al reduction of $[Mn(2\text{-methylallyl})(CO)_4]$ to yield $[Mn(butene)(CO)_4]$,$^-$ which reacts with a variety of both cyclic and acyclic dienes or polyenes to give $[Mn(\eta^4\text{-diene})(CO)_3]^-$ or $[Mn(\eta^4\text{-polyene})(CO)_3]^-$ complexes in moderate to good isolated yields (equation 10).

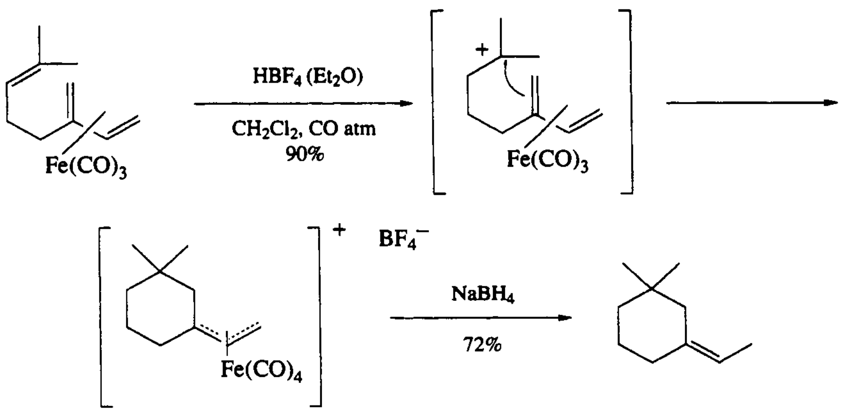

Scheme 13

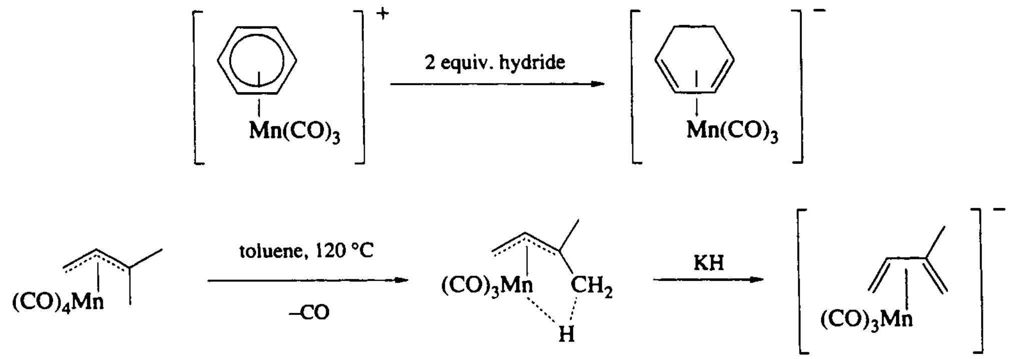

(13) (14) (+ isomer) (12)

Scheme 14

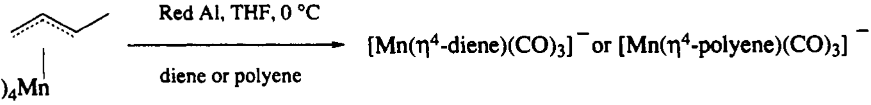
(CO)$_4$Mn
Red Al, THF, 0 °C
diene or polyene
[Mn(η$^4$-diene)(CO)$_3$]$^-$ or [Mn(η$^4$-polyene)(CO)$_3$]$^-$

(10)

As indicated above, the anionic manganese species are quite nucleophilic and much more reactive toward electrophiles than are the neutral iron analogs. Although little has been done with regard to applying these reactions in synthesis, their potential is illustrated by the reactions of these complexes with methylating reagents. [Mn(cyclohexadiene)(CO)$_3$]$^-$ reacts with methyl iodide to give the equilibrating mixture of agostic isomers (**15a** and **15b**) possessing an *endo* methyl group (Scheme 15). Based on *endo* addition of the electrophile, the reaction likely proceeds *via* a methylmanganese intermediate (**16**). Following methyl migration, the 16-electron allyl intermediate aquires an 18-electron configuration *via* bridging to an *endo* C—H bond to give initially agostic isomer (**15a**) which can reversibly rearrange to isomer (**15b**). The isomers (**15a** and **15b**) can be deprotonated with KH to yield the anionic *endo*-methylcyclohexadiene complex (**17**). This anion can be methylated a second time or can be readily oxidatively cleaved with $O_2$ to give 5-methyl-1,3-cyclohexadiene.[32] The conversion of 1,3-cyclohexadiene to 5-methyl-1,3-cyclohexadiene thus represents a stepwise procedure for electrophilic substitution of cyclohexadiene *via* nucleophilic anionic diene complex (**18**; Scheme 15).

Reactions of acyclic derivatives with carbon electrophiles have also been examined.[33,34] An illustrative reaction involving methylation of the unsubstituted complex [Mn(η$^4$-butadiene)(CO)$_3$]$^-$, (**19**), is shown in Scheme 16. Again, the reaction is presumed to occur *via* a methylmanganese species (**20**) and after methyl migration the unsaturated metal center is stabilized by formation of a Mn---H---C bridge (isomers **21a** and **21b**). Deprotonation of equilibrating (**21a** and **21b**) yields the [Mn(1-methylbutadiene)(CO)$_3$]$^-$ complex (**22**), which has exclusively *trans* stereochemistry.[34] This sequence represents alkylation of the terminal carbon of butadiene and complements the iron carbonyl chemistry, where terminal acylation has been achieved as described above. Unpublished results indicate that a second methylation of (**22**) occurs

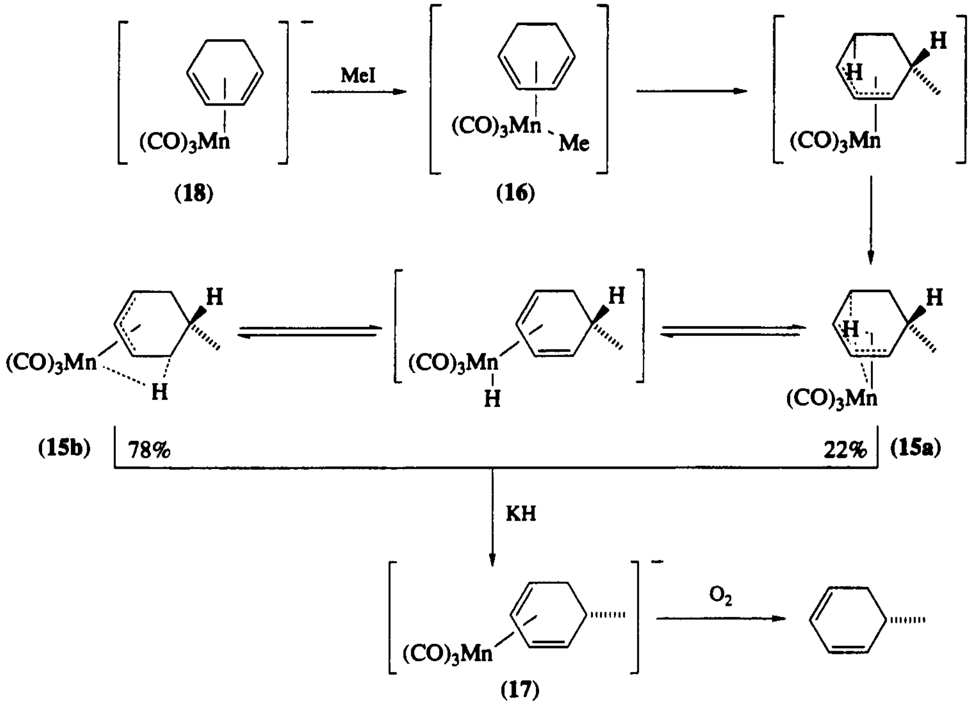
(CO)$_3$Mn
(18)
MeI
(CO)$_3$Mn Me
(16)
H
(CO)$_3$Mn
(15b)
78%
22%
(15a)
KH
(17)
O$_2$

**Scheme 15**

exclusively at C-4.[34b] The basic reactivity patterns described here suggests that, using these manganese reagents, procedures may be available for multiple alkylation of butadiene with control of regio- and stereo-chemistry.

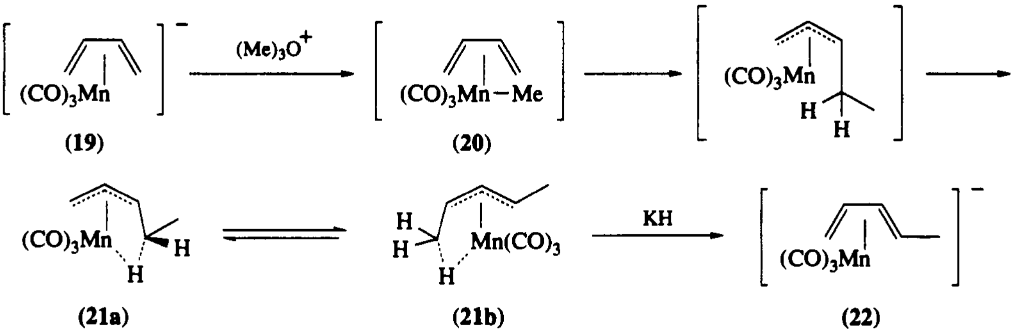
(CO)$_3$Mn
(19)
(Me)$_3$O$^+$
(CO)$_3$Mn−Me
(20)
H
(21a)
Mn(CO)$_3$
(21b)
KH
(22)

**Scheme 16**

## 3.5.3 REACTIONS OF $\eta^4$-TRIENE AND $\eta^4$-TETRAENE TRANSITION METAL COMPLEXES WITH ELECTROPHILES

### 3.5.3.1 $\eta^4$-Triene and $\eta^4$-Tetraene Iron Tricarbonyl Complexes

#### *3.5.3.1.1 Acylation and alkylation reactions*

[Fe($\eta^4$-cyclooctatetraene)(CO)$_3$] can be formylated by treatment with $POCl_3$ in DMF.[36,37] The resulting aldehyde can then be cleaved from the metal with Ce$^{IV}$ ion or further elaborated using standard procedures (Scheme 17).

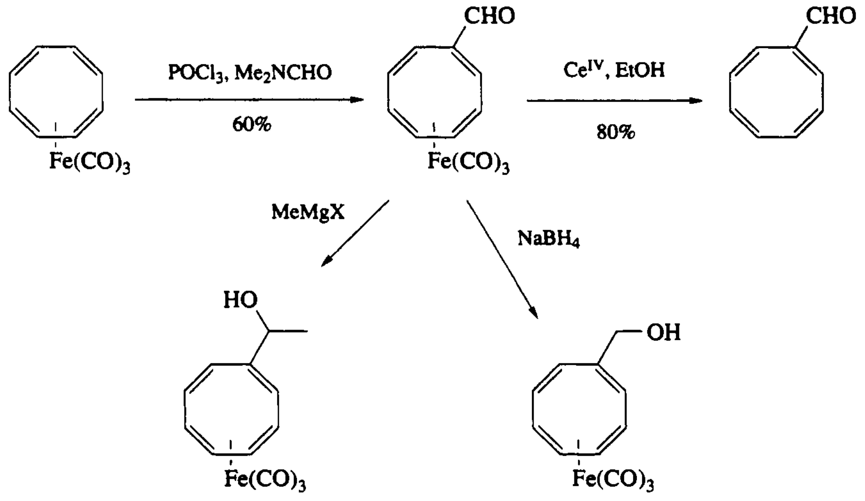

**Scheme 17**

A general mechanism for the formylation of [Fe(cyclooctatetraene)(CO)$_3$] is depicted in equation (11). The first step is electrophilic attack on the ring to form a cationic $\eta^5$-dienyl intermediate (**23**). Subsequent proton loss yields the substituted product.

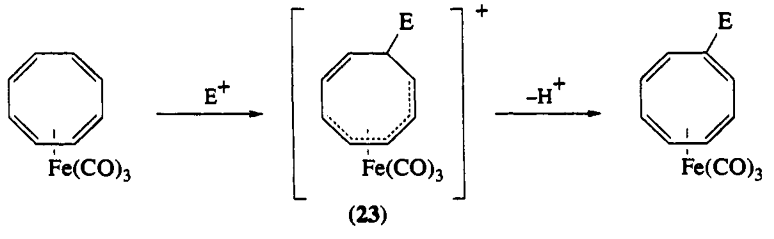

(11)

[Fe(cyclooctatetraene)(CO)$_3$] reacts under Friedel–Crafts acetylation conditions (acetyl chloride/$AlCl_3$), but only low yields of the substituted product (**24**) are formed; the major product being the bicyclic cation (**25**) (equation 12).[36–38]

Bicyclic cation (**25**) is likely formed by the route shown in Scheme 18. The [5.1.0] cation (**26**) has been intercepted with methoxide to give (**27**), which can be oxidatively cleaved to give the free bicyclic diene (**28**).[37] The bicyclo[3.2.1] complex (**25**) reacts with a variety of anionic nucleophiles to give neutral [3.2.1] derivatives.[38]

[Fe(cycloheptatriene)(CO)$_3$] can be formylated in the same manner as [Fe(cyclooctatetraene)(CO)$_3$] and likely proceeds through the same mechanism. Reaction of [Fe(cycloheptatriene)(CO)$_3$] with $POCl_3$ in DMF gives the corresponding aldehyde (70% yield), which can be converted to the primary alcohol with $NaBH_4$ or secondary alcohols using Grignard reagents (Scheme 19).[39,40]

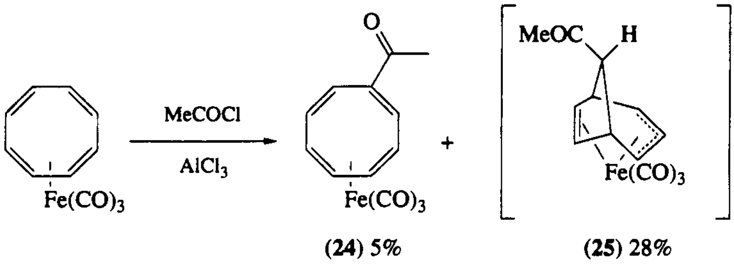

(12)

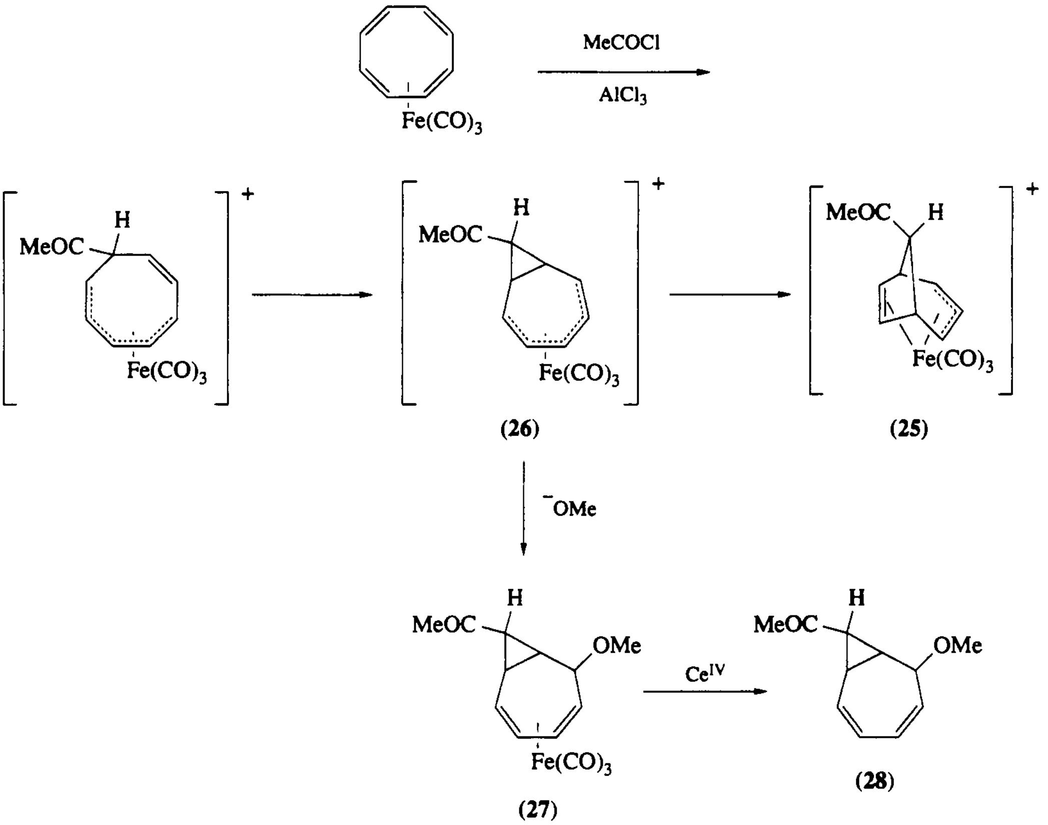

**Scheme 18**

The reaction of [Fe(cycloheptatriene)(CO)$_3$] with acyl tetrafluoroborates yields only cationic complex (**29**), which can then be converted to the acylated product (**30**) in high yield *via* the methoxide adduct (**31**; Scheme 20).[40]

Complex (**29**) results from *exo* addition of [RCO]$^+$, and when treated with Et$_3$N does not yield the neutral acyl derivatives. In contrast the *endo* salt, (**32**) does deprotonate readily to give the acyl derivative (**30**; Scheme 21). These observations suggest *endo* (**32**) may be the intermediate responsible for formation of (**30**) under Friedel–Crafts conditions.

When various [Fe(heptafulvene)(CO)$_3$] complexes are treated with POCl$_3$ in DMF formylated products are produced.[41] The reactivity of the iron carbonyl complex is markedly different than the reactivity of uncoordinated heptafulvenes which react with electrophiles to form the tropylium ion.

Azepines do not undergo electrophilic substitution reactions and introduction of substituents at the 3- or 4-position is a difficult problem. Acylation at C-3 can be achieved *via* the iron tricarbonyl complex as shown in Scheme 22.[42] The *N*-ethoxycarbonyl group of the acylated product can be removed with methoxide methanol and the resulting 1*H* compound can then be methylated.

Franck-Neumann has reported the synthesis of naturally occurring tropolones β-thujaplicin and β-dolabrin *via* the readily available [Fe(tropone)(CO)$_3$] as shown in Scheme 23.[43] A key step in the sequence is regiospecific acetylation of the [Fe(tropone)(CO)$_3$] complex, a reaction which cannot be carried out on

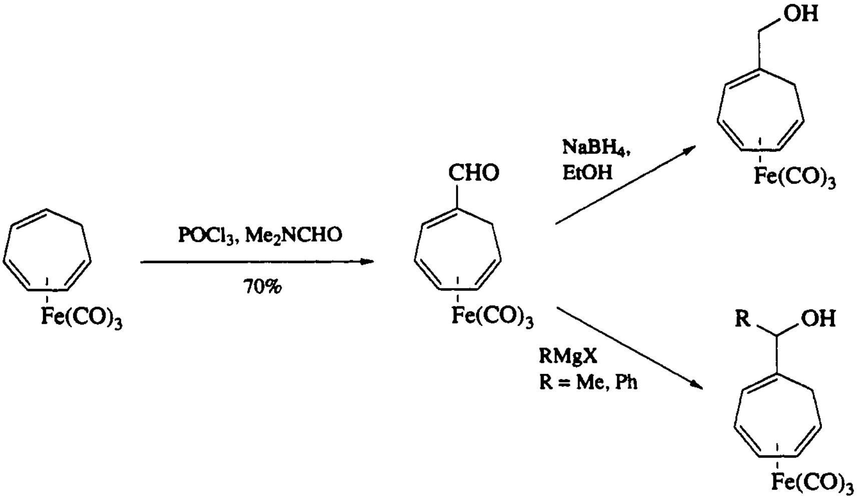

Fe(CO)3
POCl3, Me2NCHO
70%
CHO
Fe(CO)3
NaBH4, EtOH
OH
Fe(CO)3
RMgX
R = Me, Ph
R
OH
Fe(CO)3

Scheme 19

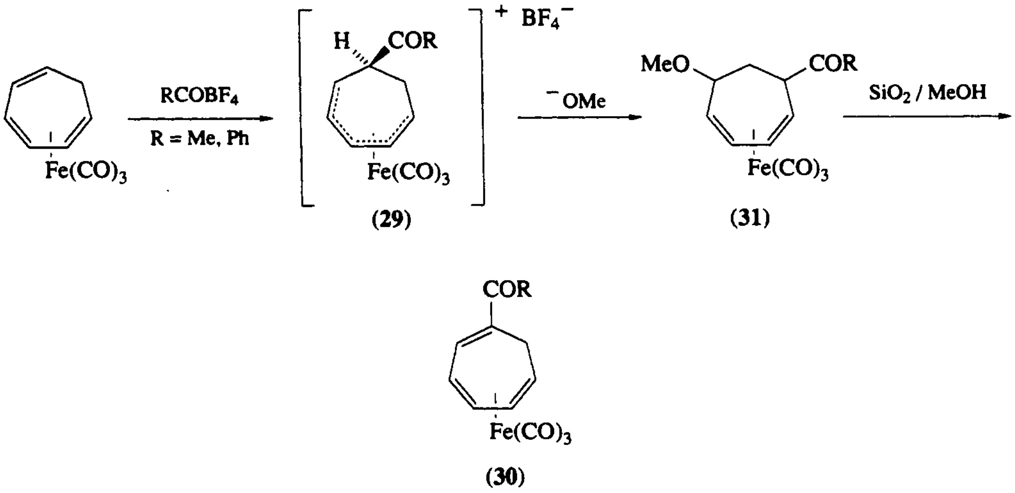

Fe(CO)3
RCOBF4
R = Me, Ph
H
COR
Fe(CO)3
(29)
+ BF4−
−OMe
MeO
COR
Fe(CO)3
(31)
SiO2 / MeOH
COR
Fe(CO)3
(30)

Scheme 20

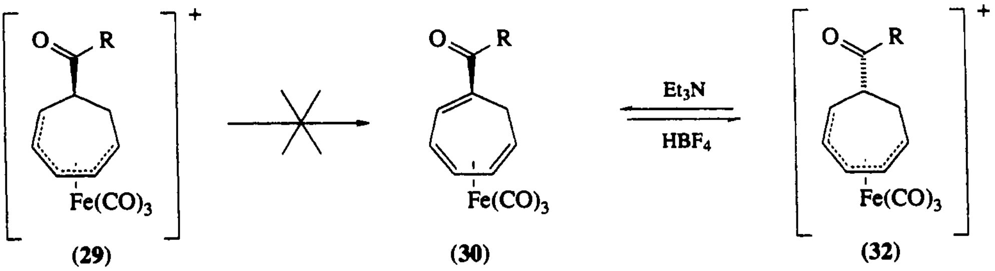

O
R
Fe(CO)3
(29)
+
O
R
Fe(CO)3
(30)
Et3N
HBF4
O
R
Fe(CO)3
(32)
+

Scheme 21

tropone itself. Acetylation was necessary in order to induce the proper orientation of addition of the 1,3-dipolar dimethyldiazomethane.

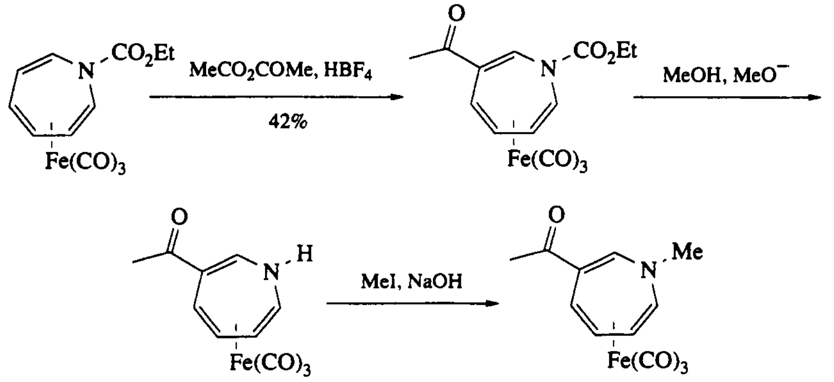

CO2Et
Fe(CO)3
MeCO2COMe, HBF4
42%
MeOH, MeO−
MeI, NaOH
H
Me

**Scheme 22**

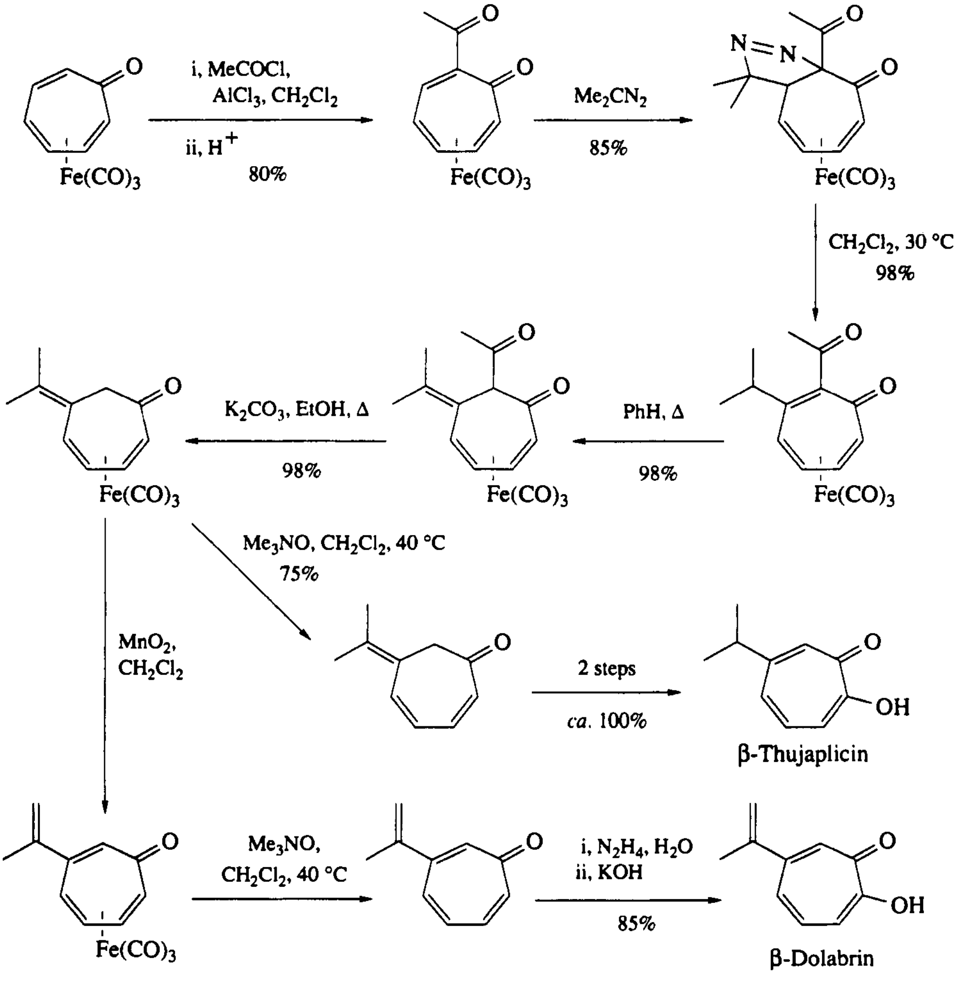

i, MeCOCl, AlCl3, CH2Cl2
ii, H+
80%
Me2CN2
85%
CH2Cl2, 30 °C
98%
PhH, Δ
98%
K2CO3, EtOH, Δ
98%
Me3NO, CH2Cl2, 40 °C
75%
2 steps
ca. 100%
β-Thujaplicin
MnO2, CH2Cl2
Me3NO, CH2Cl2, 40 °C
i, N2H4, H2O
ii, KOH
85%
β-Dolabrin
Fe(CO)3

**Scheme 23**

### *3.5.3.1.2 Reactions with electrophilic alkenes, ketones and ketenes*

[Fe(cyclooctatetraene)(CO)3] reacts with TCNE to form a cycloadduct having the bicyclic structure (**33**) shown in equation (13).[44–47] Addition is *exo* to the metal. Similar reactions with other electrophilic alkenes such as 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene have also been observed.[46]

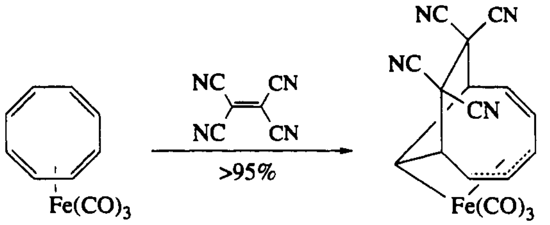

**(33)**

(13)

Initially, the mechanism for these types of reactions was thought to involve the formation of a Zwitterionic intermediate which would then collapse to form the product.[44,46–48] However, recent evidence suggests that such reactions proceed *via* concerted addition (equation 14).[49,50]

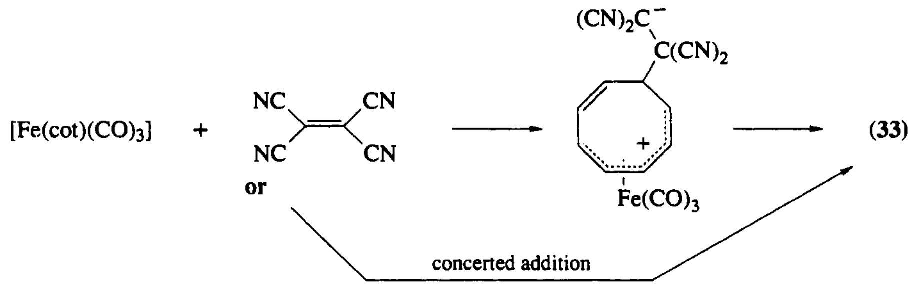

(14)

Oxidative cleavage of the organic fragment from the metal is possible using $\mathrm{Ce^{IV}}$ and gives the tricyclic rearrangement product (**34**) in very high yields (equation 15).[45,46] The tetranitrile, (**34**), prepared in this manner has been used as a key intermediate in the synthesis of chiral 2-substituted triquinacene derivatives.[51]

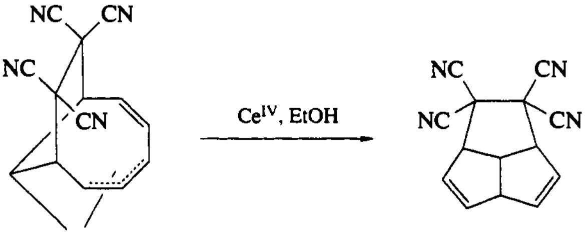

**(34)**

(15)

TCNE addition to substituted derivatives of $[\mathrm{Fe(cyclooctatetraene)(CO)_3}]$ including benzocyclooctatetraene have been examined to gain information on regioselectivity.[47,52]

$[\mathrm{Fe(cycloheptatriene)(CO)_3}]$ and its ring-substituted derivatives react with a variety of strong dienophiles including TCNE,[46,53–56] 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene,[47] 1,2-dicyano-1,2-bis(trifluoromethyl)ethylene,[47] carbomethoxymaleic anhydride,[57] hexafluoroacetone[47,49] and arylketenes.[58–60] For example, reaction with TCNE produces compound (**35**) as the major product (Scheme 24).[46,53,54] Treatment of (**35**) with $\mathrm{Ce^{IV}}$ or $\mathrm{FeCl_3}$ cleaves the organic fragment from the metal to yield rearranged diene (**36**) in good yields.[46,54] Complex (**35**) can be converted to (**37**) by heating.[54,53] Cleavage of (**37**) with $\mathrm{Ce^{IV}}$ yields (**38**).

Reaction of $\mathrm{(CN)_2C{=}C(CF_3)_2}$ with $[\mathrm{Fe(cycloheptatriene)(CO)_3}]$ yields adduct (**39**), which under CO pressure gives tricyclic ketone (**40**) presumably *via* iron–acyl complex (**41**; equation 16).[47]

Treatment of $[\mathrm{Fe(cycloheptatriene)(CO)_3}]$ with diphenylketene at room temperature yields the [2 + 2] product (**42**; Scheme 25).[58] Heating (**42**) leads to the rearrangement product, (**43**),[58,60] which can be cleaved from the metal with $\mathrm{Ce^{IV}}$ to yield the tricyclic ketone (**44**).[58]

The TCNE adducts of a variety of other $[\eta^4\text{-}\mathrm{Fe(CO)_3}]^-$ complexed trienes and tetraenes have been investigated. In most cases the adducts have been oxidatively cleaved from the metal with $\mathrm{Ce^{IV}}$ and the free ligands recovered in good yields. Reactivity patterns generally follow those described above for cycloheptatriene and cyclooctatetraene complexes. Specific complexes investigated include $[\mathrm{Fe(2,4,6\text{-}cyclooctatrieneone)(CO)_3}]$,[61] $[\mathrm{Fe(tropone)(CO)_3}]$,[62,63] $[\mathrm{Fe(heptafulvalene)(CO)_3}]$ and various 8-substituted

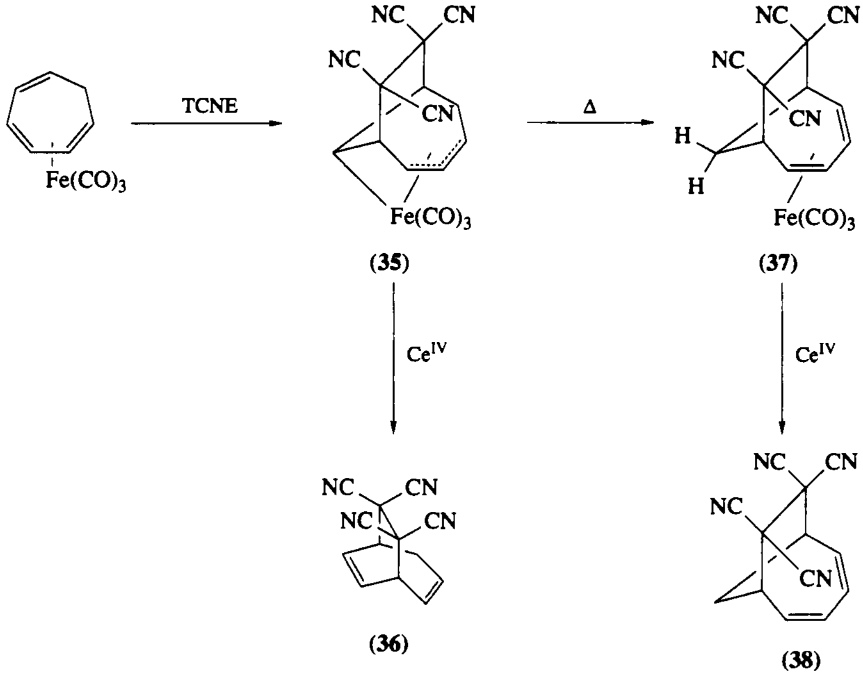
Fe(CO)3
TCNE
NC
CN
Fe(CO)3
(35)
Δ
H
(37)
Ce^IV
(36)
(38)

Scheme 24

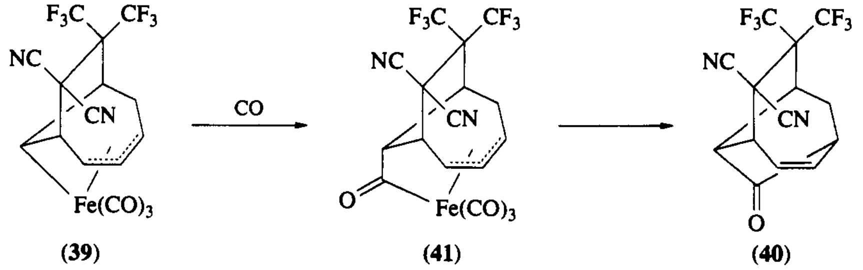
F3C
CF3
NC
CN
Fe(CO)3
(39)
CO
O
(41)
(40)

(16)

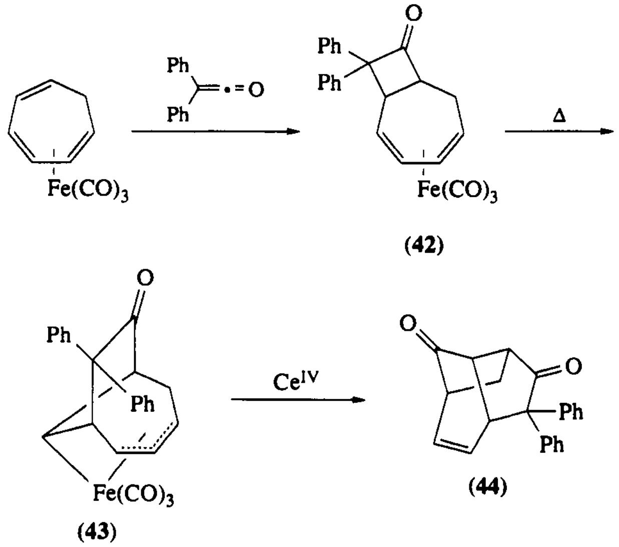
Fe(CO)3
Ph
O
Δ
(42)
Ce^IV
(43)
(44)

Scheme 25

derivatives,[64–67] derivatives of [Fe(1,3,5-heptatriene)$(CO)_3$][68] and [Fe(vinylcyclobutadiene)$(CO)_3$].[69] A comprehensive investigation of the reactions of [M(*N*-methoxycarbonylazepine)$(CO)_3$] (M = Fe, Ru) with TCNE, $(CN)_2C{=}C(CF_3)_2$ and $(CF_3)_2C{=}O$ has been reported.[49,70]

### 3.5.3.2 $\eta^4$-Triene and $\eta^4$-Tetraene Manganese Tricarbonyl Anions

As noted in Section 3.5.2.2, a general method has been recently reported for the synthesis of anionic [Mn($\eta^4$-polyene)$(CO)_3$]$^-$ complexes. While reactions with carbon electrophiles have not been extensively examined, it is clear these species are much more reactive than their neutral iron analogs. For example, whereas [Fe(cycloheptatriene)$(CO)_3$] and [Fe(cyclooctatetraene)$(CO)_3$] are inert toward alkyl halides, the corresponding anionic manganese derivatives (**45**) and (**46**) can be methylated under mild conditions[34,35] with methyl iodide or methyl triflate as shown in Scheme 26. X-Ray analysis of (**47**) establishes the *exo* stereochemistry of the methyl group and suggests attack of the methylating reagent at the uncoordinated double bond.[35] Similar to these reports is the reaction of $PhCH_2Br$ with [Cr($\eta^4$-$C_6H_6$)$(CO)_3$]$^{2-}$ to give [Cr(*S*-*exo*-benzylcyclohexadienyl)$(CO)_3$]$^-$ reported by Cooper.[7(b)]

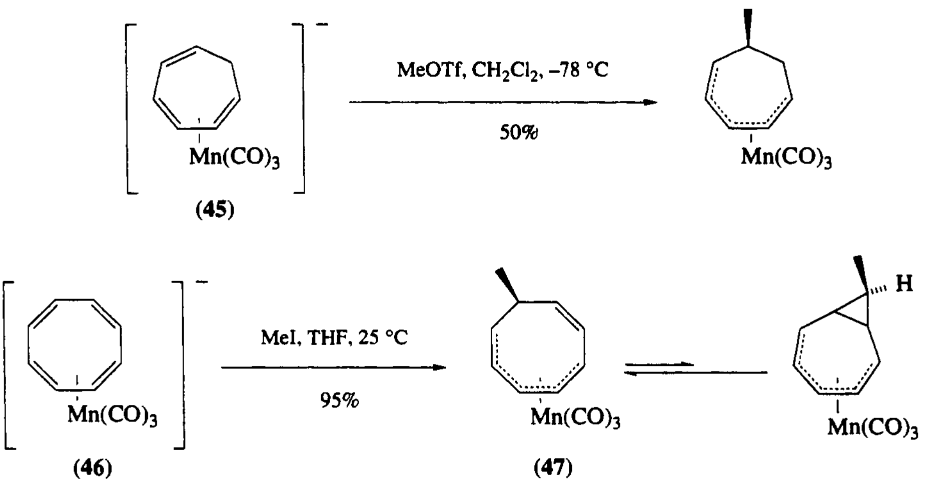

Scheme 26

## 3.5.4 SUMMARY

This chapter illustrates that electron-rich transition metal–diene complexes can couple with carbon electrophiles and, thereby, provide unusual methods for carbon–carbon bond formation. These procedures are of interest from a synthetic viewpoint since normally uncomplexed dienes or polyenes are not reactive toward weak carbon electrophiles or, with strong electrophiles, undesirable reactions such as polymerization occur. Furthermore, the metal-mediated route often results in desirable regio- and/or stereo-selectivity. Important to the utility of these methods is the ability to free the organic ligand from the metal. In most instances efficient oxidative procedures have been developed for such cleavage reactions.

As noted in the introduction, in contrast to attack by nucleophiles, attack of electrophiles on saturated alkene–, polyene– or polyenyl–metal complexes creates special problems in that normally unstable 16-electron, unsaturated species are formed. To be isolated, these species must be stabilized by intramolecular coordination or *via* intermolecular addition of a ligand. Nevertheless, as illustrated in this chapter, reactions of significant synthetic utility can be developed with attention to these points. It is likely that this area will see considerable development in the future. In addition to refinement of electrophilic reactions of metal–diene complexes, synthetic applications may evolve from the coupling of carbon electrophiles with electron-rich transition metal complexes of alkenes, alkynes and polyenes, as well as allyl– and dienyl–metal complexes. Sequential addition of electrophiles followed by nucleophiles is also viable to rapidly assemble complex structures.

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# 4.1

# Radical Addition Reactions

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## 4.1.1 INTRODUCTION

The formation of a new σ-bond at the expense of an existing π-bond is a transformation that rests at the heart of modern organic synthesis. It underlies such diverse reactions as nucleophilic additions to carbonyls and activated alkenes, transition metal catalyzed additions, and pericyclic reactions. The addition of a radical to a π-bond, to form a σ-bond and a new radical, is a fundamental reaction of organic radicals that organic polymer chemists have continuously applied to the synthesis of new materials. Applications in small molecule synthesis evolved more slowly for a time.[1,2] However, over the last decade, the application of radical addition reactions to problems in fine synthesis has grown from the level of a curiosity to that of a major reaction class. For recent reviews see refs. 3–5. This rapid growth can be attributed, in part, to the high level of understanding of organic radicals that has been provided by fundamental research on structure and reactivity and, in part, to the fact that the transformations that can be accomplished by radical additions are often those that are difficult to accomplish by more traditional means.

This chapter begins with an introduction to the basic principles that are required to apply radical reactions in synthesis, with references to more detailed treatments. After a discussion of the effect of substituents on the rates of radical addition reactions, a new method to notate radical reactions in retrosynthetic analysis will be introduced. A summary of synthetically useful radical addition reactions will then follow. Emphasis will be placed on how the selection of an available method, either chain or non-chain, may affect the outcome of an addition reaction. The addition reactions of carbon radicals to multiple bonds and aromatic rings will be the major focus of the presentation, with a shorter section on the addition reactions of heteroatom-centered radicals. Intramolecular addition reactions, that is radical cyclizations, will be covered in the following chapter with a similar organizational pattern. This second chapter will also cover the use of sequential radical reactions. Reactions of diradicals (and related reactive intermediates) will not be discussed in either chapter. Photochemical [2 + 2] cycloadditions are covered in Volume 5, Chapter 3.1 and diyl cycloadditions are covered in Volume 5, Chapter 3.1. Related functional group transformations of radicals (that do not involve π-bond additions) are treated in Volume 8, Chapter 4.2.

## 4.1.2 BASIC PRINCIPLES

### 4.1.2.1 Introduction

New organic compounds are synthesized by the chemical reactions of diverse molecules that range from stable reagents to highly reactive intermediates. These molecules usually have one common feature: their electrons are paired. In the accounting system that is used to follow electrons from reactants to products, 'double-headed' arrows symbolize two electrons (Scheme 1). Radicals are species that contain at least one unpaired electron.[6] This feature gives radicals a unique reactivity profile relative to closed shell species. And with an understanding of the basic principles of radicals, this reactivity profile can be exploited in synthesis. To account for electrons in radical reactions, 'single-headed' arrows symbolizing one electron are used by convention. Bear in mind that, as with double-headed arrows, the use of single-headed arrows helps one to quickly grasp the changes in electron distribution in a step or transformation but does not necessarily indicate the mechanism.

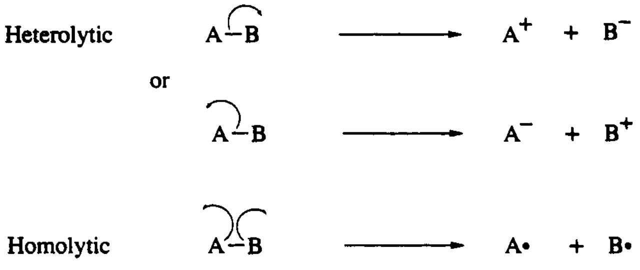

Scheme 1 Bond cleavage formalisms

This section will provide an introduction to the basic principles of organic radicals that are needed for synthetic application. Many of these principles have been understood and applied for more than 30 years[7] and a variety of good treatments are available.[8] The book of Prior still provides a thorough, readable introduction for newcomers to the field.[9] The first chapter of Giese's excellent book[3] and an article by Walling[10] are especially good introductions for the synthetic chemist. Although it was published in 1973, the two volume set edited by Kochi[11] still provides a wealth of information on many fundamental aspects of radical chemistry.

### 4.1.2.2 Transiency of Radicals

A major difference between radicals and other reactive species that are employed in synthesis is that virtually all radicals react rapidly with themselves. Compare *t*-butyllithium and *t*-butyl radical, for example. *t*-Butyllithium is one of the most reactive organometallic species that synthetic chemists employ. It reacts in some fashion with virtually all types of organic molecules, even most solvents, given long enough time and high enough temperature. However, *t*-butyllithium does not react readily with itself! As a result, one can purchase a bottle of *t*-butyllithium and admix it with a desired reactant. In many cases, a new reactive intermediate is formed (by deprotonation, for example) and another reagent is then added.

In contrast, one need not consult an Aldrich catalog to see if *t*-butyl radical is commercially available. Nor can one generate a significant quantity of *t*-butyl radical in solution prior to the addition of a reagent with which it is destined to react. This is because *t*-butyl radical, like nearly every other radical that is employed in synthesis, is transient. The lifetime of a transient radical rarely exceeds 1 μs and is limited by the rate of self reaction. This self reaction, which can be either a disproportionation or a recombination (Scheme 2), typically occurs at the diffusion-controlled limit; the enthalpy of activation of most radical–radical reactions ≈ 0 kcal $mol^{-1}$.

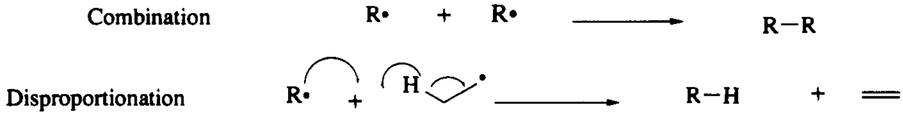

**Scheme 2** Termination

Radicals can be stabilized by substituents and a simple and useful measure of radical stabilization is C—H bond dissociation energy [*D*(C—H)].[12] The approximate bond dissociation energies of some representative C—H bonds are given in Scheme 3.[13] However, these can be misleading: tertiary C—H bonds are weaker than primary C—H bonds, not so much because the alkyl groups stabilize the radical (although they do), but more because repulsion between these alkyl groups in the tetrahedral precursor is diminished in the radical. Conjugating groups and heteroatoms stabilize radicals and such electronically stabilized radicals sometimes react more slowly with neutral molecules than their non-stabilized counterparts. However, radical–radical reactions are so exothermic that the rates of the self reactions of stabilized radicals are not retarded. Thus, the benzyl radical is much less reactive than the methyl radical in common reactions such as C—H abstraction, yet it still reacts with itself or with another radical at the diffusion-controlled rate.

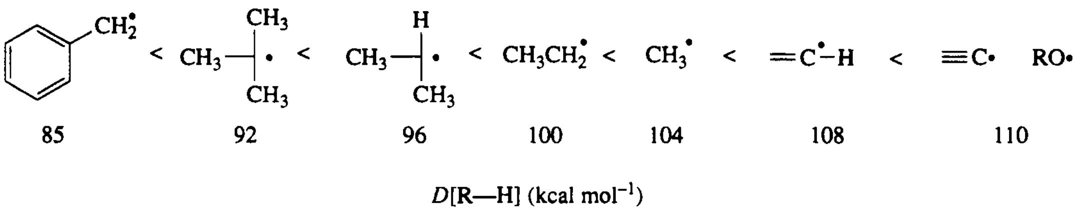

**Scheme 3** Bond dissociation energies

In radical terminology, the opposite of transience is not stability but persistence.[14] Persistent radicals do not react with themselves at diffusion-controlled rates; however, they may still react readily with other radicals or with triplet oxygen. Thus, persistence is a kinetic property that is more often related to sterically hindered recombination than to electronic stabilization. Persistent radicals typically also lack β-C—H bonds and they cannot disproportionate. Several persistent radicals are illustrated in Scheme 4. Persistent radicals are rarely present in synthetic applications, but when they are, there will be important consequences.

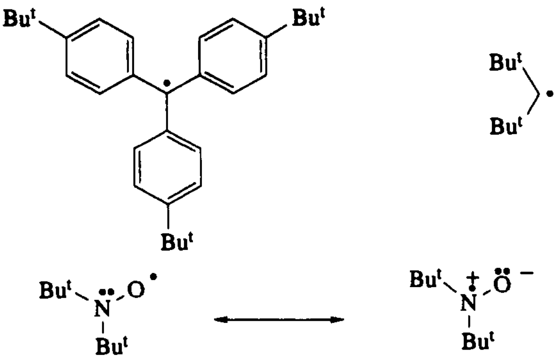

Scheme 4 Persistent radicals

The thermodynamic driving force notwithstanding, the coupling of two different radicals is not an especially practical preparative method to form a new bond. This is because the preparation of precursors that directly decompose to radicals is rarely convenient, because disproportionation can often compete effectively with recombination, and especially because chemoselectivity (that is, the selective-coupling of two different radicals to the exclusion of self-coupling) is difficult to achieve if all coupling reactions occur at the same rate (the diffusion-controlled limit).

The reactions of radicals with nonradicals (typically, neutral organic molecules[15]) have much greater use in synthesis. These reactions occur with a wide and predictable range of rate constants, and the concentration of a nonradical component is a readily controlled experimental variable that can greatly affect the chemoselectivity of a reaction. For radical–reagent reactions to be synthetically useful, they must be faster than radical–radical reactions and radical–solvent reactions. By estimating the rates of these destructive reactions, one can determine lower rate limits for synthetic procedures. The rate expression for the self reaction of two radicals (R·)[16] is shown in equation (1), while the rate expression for the addition of the same radical to an alkene (A═B) is shown in equation (2). For a useful addition reaction to occur, the rate of disappearance of R· by equation (2) must be significantly greater than that by equation (1). This comparison is stated in equation (3).[17] By substituting $k_t \approx 10^{10}\ \mathrm{M^{-1}\ s^{-1}}$ (the approximate diffusion-controlled limit) and by assuming that $10^{-8}$ M is a typical radical concentration in a chain reaction, we find that the rate of formation of the adduct radical R—A—B· must be $>10^2\ \mathrm{s^{-1}}$ (equation 3). Equation (4) shows the requirement for a first order reaction such as a cyclization.

$$\mathrm{R{\bullet}} + \mathrm{R{\bullet}} \xrightarrow{k_t} \mathrm{R{-}R} \tag{1}$$

$$\frac{d[\mathrm{R{-}R}]}{dt} = k_t[\mathrm{R{\bullet}}][\mathrm{R{\bullet}}]$$

$$\mathrm{R{\bullet}} + \mathrm{A{=}B} \longrightarrow \mathrm{R{-}A{-}B{\bullet}} \tag{2}$$

$$\frac{d[\mathrm{R{-}A{-}B{\bullet}}]}{dt} = k_a[\mathrm{R{\bullet}}][\mathrm{A{=}B}]$$

$$k_a[\mathrm{A{=}B}] > k_t[\mathrm{R{\bullet}}] \tag{3}$$

$$k_a[\mathrm{A{=}B}] > 10^2\ \mathrm{s^{-1}}$$

$$\mathrm{R{\bullet}} \xrightarrow{k_c} \mathrm{R'{\bullet}} \tag{4}$$

$$k_c > 10^2\ \mathrm{s^{-1}}$$

This simple example illustrates how the rates of two reactions competing for the same radical (R·) are compared. Provided they are not too rapid, the rates of termination steps are not of concern, but comparison of the rates of competing propagation steps is very informative. Fortunately, all propagation steps are first order in [R·] and this term (which is difficult to know accurately) cancels when two propagation steps are compared.

Concerns about nonproductive reactions of radicals apply not only to carbon–carbon bond forming steps, such as additions and cyclizations, but to every step in a sequence of radical reactions. For example, to obtain a good yield of product from the reaction in equation (2), not only must the addition of R· to A═B occur but the conversion of R—A—B· to a nonradical product must also be efficient. In a chain reaction, the slowest propagation step must still be rapid relative to loss of the radicals by radical–radical or radical–solvent reactions. In practice, reactions with rates of product formation of $10^2$–$10^3$ $s^{-1}$ are experimentally difficult to conduct. Reactions with rates of $10^4$–$10^5$ $s^{-1}$ are manageable and those with rates $>10^6$ $s^{-1}$ are usually conducted with ease.

The reactions of radicals with solvents may also limit the types of radical–nonradical reactions that can be conducted. The two types of reactions encountered are addition and hydrogen atom abstraction. Alkyl radicals add to benzene, a popular solvent for radical reactions, with pseudo first order rate constants $\approx 10^2$ $s^{-1}$.[18] This is roughly competitive with radical–radical reactions. Ethereal solvents provide a different limitation: alkyl radicals abstract an α-hydrogen atom from ether with a pseudo first order rate constant $k_H \approx 10^3$ $s^{-1}$. THF is a better H-donor than ether ($k_H \approx 10^4$ $s^{-1}$).[19]

### 4.1.2.3 Structure and Stereochemistry of Radicals

It is generally safe to assume that the complex radicals formed in synthesis will have predictable structural and stereochemical features that can be extrapolated from simple radicals.[20] The methyl radical is known to be planar (or perhaps very slightly pyramidalized with a low barrier to inversion). The replacement of hydrogen atoms by alkyl groups or heteroatoms causes pyramidalization but the inversion barrier remains very low. Conjugating substituents favor planar structures. In practice, this means that the stereochemistry of a reaction that occurs at an alkyl radical center cannot be dictated by the stereogenicity of the pro-radical center because stereoisomeric precursors generate the same radical. Instead, the stereochemistry of reaction at a radical center is controlled by the relative rates of the competing reactions. Scheme 5 provides examples where the competing reactions are axial and equatorial hydrogen atom transfer.[21]

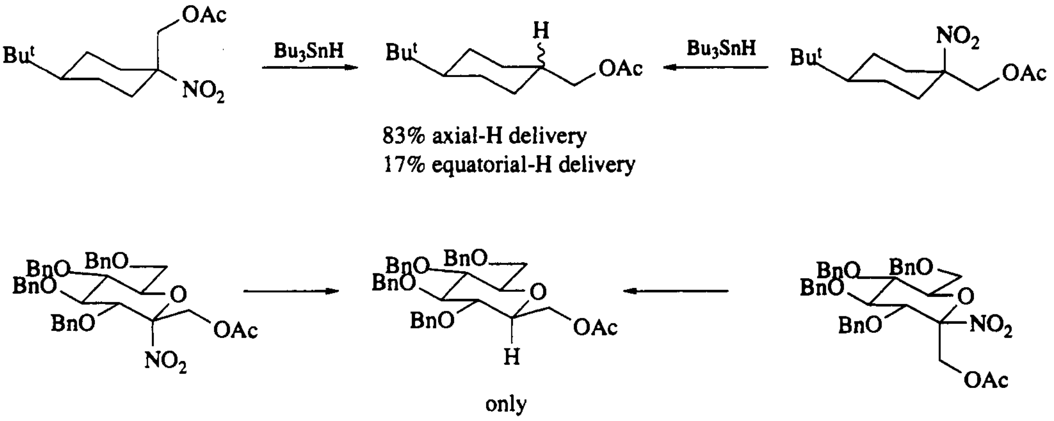

**Scheme 5** Stereochemistry of alkyl radicals

Somewhat less is known about the structures of vinyl radicals. Two limiting structures, bent and linear, are possible (Scheme 6). The vinyl radical itself exists in a bent form ($sp^2$-hybridized) but with a very low barrier to inversion.[22] It is generally assumed that alkyl-substituted vinyl radicals behave similarly. Thus, as with alkyl radicals, the stereochemical outcome of a reaction of a vinyl radical does not generally depend on the stereochemistry of the precursor (Scheme 6).[23] However, there are several examples in which a subsequent reaction of a vinyl radical has been proposed to be more rapid than its inversion.[24] Heteroatom substituents (notably ethers[25]) substantially raise the barrier for inversion of vinyl radicals and it seems likely that stereoselective methods that capitalize on this barrier might be developed.[26] In contrast, π-conjugating substituents are usually thought to favor the linear ($sp$-hybridized) form to promote resonance overlap.[27] With a linear vinyl radical, there is again no correlation between precursor and product stereochemistry. However, to understand the stereochemical outcome of a reaction of a vinyl radical, it may be important to know whether it is bent and rapidly inverting or linear.

In return for the possible disadvantage that existing stereochemistry at the radical site is lost, radicals provide several advantages (see below). Not the least of these is that the synthesis of the radical precursor is often facilitated because stereochemistry at the pro-radical center is not a concern.

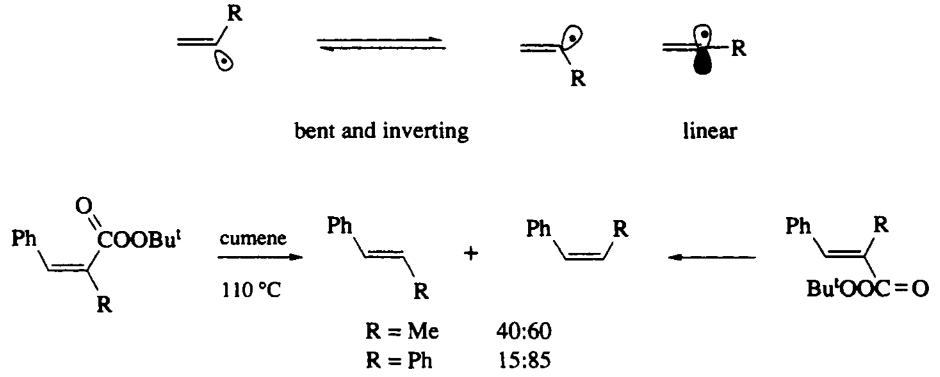

Scheme 6 Stereochemistry of vinyl radicals

### 4.1.2.4 General Considerations for the Use of Radical Reactions in Synthesis

This section presents some general chemoselectivity considerations for designing substrates and planning experimental conditions for radical reactions. More detailed concerns of chemo-, regio- and stereoselectivity are addressed for each specific technique in the individual sections below.

Synthetic chemists are well-accustomed to designing experimental conditions for reactions that are ionic.[28] The alkylation, hydroxyalkylation and acylation reactions of metal enolates provide typical examples. Such reactions generate intermediates that may be sensitive to oxygen, water or heat. The relative rates of competing reactions (and, hence, chemo-, regio- and stereo-selectivities) of such intermediates are sometimes strongly influenced by solvent (and cosolvent additives), metal counterions and additives, and temperature. Depending on the reaction, such characteristics can either be significant advantages or severe limitations. Many radical reactions have a very different profile.

Nearly all radicals add to triplet oxygen at rates approaching the diffusion-controlled limit. Unless this is a desired reaction, it is advisable to take some precautions to exclude atmospheric oxygen. However, rigorous measures, such as freeze–thaw degassing, are not usually required in either exploratory or preparative experiments. The evacuation of a reaction vessel by using a water aspirator or a house vacuum apparatus, followed by repressurization with nitrogen or argon, suffices for most purposes. Sometimes the solvent is purged by bubbling inert gas for several minutes. After such standard measures, the concentration of oxygen is too low to interfere with most radical chains.

Most researchers distil solvents for radical reactions in the same manner as they might for use with a reactive organometallic. This practice is recommended to ensure that solvents are sufficiently pure. That the solvents are simultaneously dried during purification is of little consequence. Water is a much poorer hydrogen atom donor than any common solvent (conversely, the hydroxyl radical is a powerful hydrogen atom abstractor). Thus, the presence of trace quantities of water will have no adverse effect on most radical reactions. As a corollary, water can be a useful solvent or cosolvent provided that the reagents or substrates are not susceptible to hydrolysis or protonolysis.

Few radicals live long enough to decompose the way ionic intermediates might. The lifetimes of radicals are strictly limited by radical–radical and radical–solvent reactions. Since such reactions are temperature dependent, changing the reaction temperature can be a productive technique. Temperature changes are commonly used to effect the partitioning between competing unimolecular and bimolecular processes. For entropic reasons, bimolecular processes usually exhibit a much greater temperature dependence.

Effects analogous to ion-pairing and aggregation are nonexistent for radicals; their structures are not especially solvent dependent. Solvent effects on the rates of radical–neutral reactions are often small and are frequently neglected (although the transition states of many radical reactions have some polar character that might be influenced by solvent). The solvent for a radical reaction is often chosen based on concerns about solubility of reagents and reactants, solvent boiling point, and rate of radical–solvent reactions. Restrictions in solvent selection apply mainly to radical reactions of slow or intermediate rates. Certain chains (such as tin hydride mediated cyclizations of some hexenyl radicals) comprise only rapid propagation steps and they could be conducted in a wide variety of common solvents.

Aromatic hydrocarbons that lack benzylic hydrogen atoms react especially slowly with radicals. Thus benzene is a popular solvent. One can conveniently conduct exploratory reactions in $d_6$-benzene in an NMR tube and monitor progress by periodically recording an NMR spectrum of the reaction mixture. Higher boiling alternatives to benzene include dichlorobenzene and *t*-butylbenzene. While benzene is an acceptable solvent for small scale reactions, its toxicity can be a concern for industrial applications. *t*-Butyl alcohol[29] is an inexpensive, general purpose solvent that is an excellent substitute for benzene in many radical reactions. Its boiling point (83 °C) is similar to that of benzene (80 °C) and is convenient for the decomposition of some common radical initiators. Because *t*-butyl alcohol contains strongly bonded hydrogen atoms (methyl and hydroxy), rates of H-atom transfer are lower than those for other alcohols (such as methanol and ethanol) and for ethers. Scrupulous drying of *t*-butyl alcohol is not critical.

Alcohols, water and even acetic acid are useful solvents for some radical reactions. However, they cannot be employed with organometallics that are basic. Conversely, halocarbon solvents are popular for many types of ionic reactions but they are not generally useful for radical reactions. Chloroform and carbon tetrachloride (and to a lesser extent, dichloromethane) can interfere by donating either hydrogen or halogen atoms to intermediate radicals and they are used only in atom transfer reactions where the solvent is also a reagent.

Radicals are highly reactive intermediates, but they are often very chemoselective. This is because the rates of reactions of radicals with nonradicals are a function of the structure of both components and vary over a wide range. The planned execution of chemoselective radical reactions will be a major theme of the remainder of this chapter. For the moment, recall that reactions proceeding at rates below the the solution limit cannot be conducted. This negative statement has a very positive side: functional groups that react at rates below the critical limit can be deemed stable to free radical reaction conditions. The homolytic strength of O—H bonds makes them inert to hydrogen transfer reactions. Hence, free acids and alcohols do not interfere with radical reactions. Amide N—H bonds are also relatively strong. Even most bimolecular abstractions of hydrogen atoms from C—H bonds are relatively slow, competing only with other slow reactions. Even though acidic O—H and N—H groups do not require protection in most radical reactions, they are often present in protected form to be compatible with other reactions in a multistep sequence. Virtually all common protecting groups are stable to typical radical reactions. Potential problems can usually be anticipated based on standard radical reactions: protecting groups should not have weak C—H bonds six atoms from any pro-radical site (problems with 1,5-H transfer may arise) nor should they have reactive π-bonds five or six atoms away from a pro-radical site (cyclization to the protecting group may occur).

Unless a substrate or reagent contains an acidic or basic site, the conditions for most radical reactions are neutral. Thus, ionic side reactions such as base-catalyzed epimerization are rarely a problem. While radical reactions are typically conducted at temperatures above ambient, this is often solely for experimental convenience: most commercially available initiators require heating to generate radicals. Many radical reactions should succeed at lower temperatures provided that the chain is maintained (in chain methods) or that the rate of generation of radicals is sufficiently rapid (in nonchain methods). Low temperature initiators are available.[30,31]

In contrast to ionic or organometallic intermediates, most radicals are inert to reactions that involve fragmentation of a β-bond. Elimination of β-oxygen and β-nitrogen groups is frequently a rapid reaction

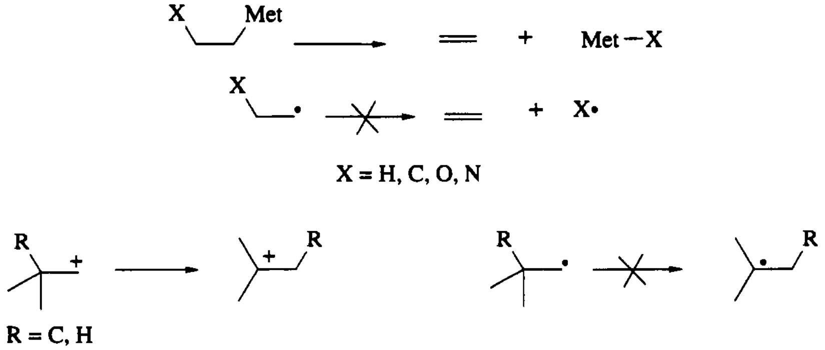

Scheme 7 β-Bond cleavage

that limits the use of many metals (Scheme 7). Transition metal alkyls are often prone to β-hydride eliminations. In contrast, the related elimination reactions of radicals are usually so slow in the normal reaction temperature range[32] that their occurrence can be discounted (for some useful exceptions, see Chapter 4.2, this volume). However, β-elimination reactions can be rapid and useful with halogens, sulfides and stannanes.

In carbocation chemistry, 1,2-alkyl and -hydride migrations are very common. In contrast, the direct 1,2-migration of hydrogen atoms to radicals is virtually unknown. While useful migrations of carbon substituents to radicals are known, they frequently proceed by a sequence of addition to a π-bond followed by elimination. The 1,2-migration of saturated alkyl groups to radicals is also virtually unknown.

### 4.1.2.5 Rate Constants and Synthetic Planning

Despite our increasing knowledge of the structures and reactions of organometallic intermediates, it is virtually impossible to plan complex ionic reactions by using known rate constants from simple model systems. Rate constants are potentially more useful when planning pericyclic reactions because they are easier to measure and because pericyclic reactions are much less susceptible to medium effects than ionic reactions. However, the need to evaluate the rates of competing pericyclic reactions is relatively rare (often there is only one reasonable possibility).

In contrast, the need to evaluate the relative rates of competing radical reactions pervades synthetic planning of radical additions and cyclizations. Further, absolute rate constants are now accurately known for many prototypical radical reactions over wide temperature ranges.[19,33–35] These absolute rate constants serve to calibrate a much larger body of known relative rates of radical reactions.[33] Because rates of radical reactions show small solvent dependence, rate constants that are measured in one solvent can often be applied to reactions in another, especially if the two solvents are similar in polarity. Finally, because the effects of substituents near a radical center are often predictable, and because the effects of substituents at remote centers are often negligible, rate constants measured on simple compounds can often provide useful models for the reactions of complex substrates with similar substitution patterns.

One of the goals of this and the following chapter is to show how a knowledge of a few of the most important rate constants of radical reactions and some substituent effect trends can be used to design successful experimental conditions for applications of known radical-based synthetic methods. The design of new synthetic methods is only a small step beyond this.

Table 1 contains representative absolute rate constants for prototypes of the most important radical reactions.[36] While some known rate constants (like those in Table 1) are very precise (<25% error), others are only rough estimates because they have not been measured directly but by competition against a reaction of known absolute rate. In such competition studies, any error in the original direct measurement is compounded by errors in the competition reaction. It is often difficult to estimate the error limits precisely (errors could exceed a factor of two). In some cases, rates measured by indirect methods become two (or even three) reactions removed from known absolute rate constants. These errors should not be ignored during synthetic planning. When estimating the rates of two competing radical reactions by using approximate rate constants, an order of magnitude is probably about the highest level of precision that is meaningful.

Rate constants are a function of temperature and should be compared at the same temperature whenever possible. Arrhenius equations for the reactions in Table 1 are provided and these equations can often be used as substitutes to calculate the temperature dependence for similar reactions. In practice, the error introduced by temperature uncertainties in the normal range of 25–80 °C is not particularly important in the comparison of two indirectly measured rate constants. Because competitive rate studies are so simple to conduct, synthetic chemists can (and sometimes do!) measure the rates of reactions that are required to plan a new synthetic method or total synthesis. Such 'quick and dirty' experiments are often conducted at only one temperature. A temperature in the middle of the normal range (~50 °C) is particularly useful because the rate constants that are obtained can be directly compared (with the above provisos) to rate constants in the normal range.

### 4.1.2.6 A Word about Concentrations

Include them! Synthetic chemists are accustomed to publishing communications or letters in which the conditions of relatively standard procedures are summarized in a scheme. Except for special reactions such as macrocyclizations, reaction concentrations are rarely included in these schemes. However, the

**Table 1** Representative Rate Constants of Radical Reactions

| *Reaction* | *Log A* ($M^{-1}$ $s^{-1}$) | $E_a$ (kcal $mol^{-1}$) | *k at* 25 °C | 50 °C | 80 °C | *Ref.* |
|---|---|---|---|---|---|---|
| *Fragmentation* | | | | | | |
| 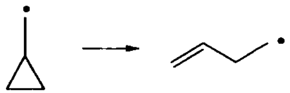 | 13.15 | 7.05 | 0.91 | 2.3 | 5.9 x $10^8$ $s^{-1}$ | 37 |
| *Cyclization* | | | | | | |
| 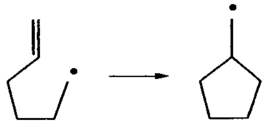 | 10.42 | 6.85 | 0.24 | 0.58 | 1.5 x $10^6$ $s^{-1}$ | 38 |
| *Hydrogen transfer* | | | | | | |
| $Bu^n$• + $HSnBu_3$ | 9.06 | 3.65 | 2.3 | 3.8 | 6.2 x $10^6$ $M^{-1}$ $s^{-1}$ | 39 |
| *Iodine transfer* | | | | | | |
| n-$C_8H_{17}$• + 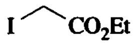 | 10.4 | 4.4 | 1.4 | 2.6 | 4.7 x $10^7$ $M^{-1}$ $s^{-1}$ | 40 |
| *Thiohydroxamate transfer* | | | | | | |
| n-$C_8H_{17}$• + 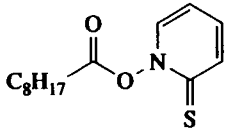 | 9.04 | 3.95 | 1.3 | 2.3 | 3.2 x $10^6$ $M^{-1}$ $s^{-1}$ | 41 |
| *Alkene addition* | | | | | | |
| $Bu^t$• + PhCH=$CH_2$ | 7.60 | 3.42 | 1.2 | 1.9 | 3.0 x $10^5$ $M^{-1}$ $s^{-1}$ | 42 |
| *Pyridinium addition* | | | | | | |
| n-$C_7H_{15}$• + 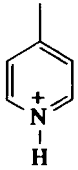 | 9.2 | 6.9 | 1.3 | 3.0 | 8.1 x $10^4$ $M^{-1}$ $s^{-1}$ | 18 |

relative rates of competing radical processes and the general efficiency of radical chain reactions are highly dependent on the concentration of the reagents. Omit the yield, the product ratio, the solvent, the temperature, the work-up procedure or the method of initiation, but never omit the concentration! For reactions (such as syringe pump additions) that are not conducted at a fixed concentration, a brief comment on the initial concentrations and the rate of addition is helpful.

### 4.1.3 METHODS TO CONDUCT RADICAL REACTIONS

Although the synthetic transformations that can be accomplished by radical reactions are virtually limitless, precious few general methods exist by which radical reactions can be conducted. These methods can be classified in two main groups: chain and nonchain.

As illustrated in Scheme 8, useful methods to conduct radical addition (and cyclization) reactions must: (i) generate an initial radical; (ii) provide this radical some lifetime in which to undergo the desired reaction(s); and (iii) productively remove the final radical before radical–radical, radical–solvent or undesired radical–reagent reactions intervene. High chemoselectivity is required at all stages. Radical generation must occur at a single site in the molecule to the exclusion of all other sites. The initially formed radical is usually a precursor for one or more subsequent radicals, hence, several intermediate radicals will be simultaneously present in a reaction. Ideally, each intermediate radical must suffer a single fate. This selectivity is imparted by the radicals themselves (structural variations in radicals can dramatically affect the rates of reactions with other molecules) and by the experimental conditions (especially concentration and temperature). Finally, the method employed must selectively remove the final radical in a sequence before it is destroyed, but it must not prematurely remove any prior radicals.

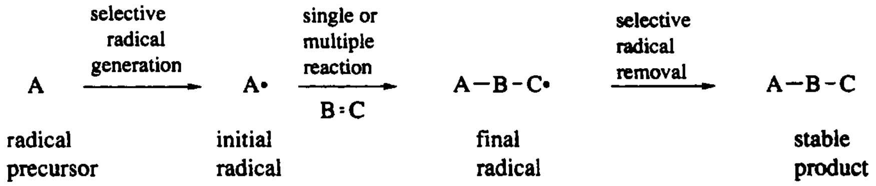
A
selective radical generation
A•
single or multiple reaction
B=C
A–B–C•
selective radical removal
A–B–C
radical precursor
initial radical
final radical
stable product

Potential problems: (1) radical–molecule or radical–solvent reactions of A• or A–B–C•; (2) removal of A• prior to reaction with B=C; (3) reaction of A–B–C with B=C prior to removal.

**Scheme 8** Selectivity requirements

#### 4.1.3.1 Chain Reactions

Chain reactions offer an ideal vehicle to conduct radical additions because the concentration of radicals is maintained at a low, steady level by nature (it is limited by the rates of initiation and termination) and because the first and last stages of the reaction sequence are directly linked. That is, the process of productively removing the final radical either directly or indirectly (*via* the intermediacy of a chain transfer agent such as $Bu_3Sn\cdot$) regenerates the initial radical.

Chain reactions comprise initiation, propagation and termination steps. Initiation steps generate radicals from nonradicals, while termination steps generate nonradicals by removing radicals. All of the desired transformations in a chain occur in propagation steps, which involve the inter- or intra-molecular reactions of radicals with nonradicals. Propagation steps effect no net gain or loss of radicals. In an ideal chain, initiation and termination steps are rare and propagation steps are common.

Initiation can be accomplished by photochemical or redox reactions, but it is most often accomplished by homolytic bond cleavage of a chemical initiator (promoted by heat or light) to give two radicals. A steady source of initiation is critical because, even under ideal conditions, the life of a single chain (from initiation to termination) rarely exceeds 1 s and can be much shorter if slow propagation steps are involved. The amount of initiator that is required depends on the efficiency of the chain (chain length) and on the temperature. Efficient chains (such as tin hydride reductions conducted at relatively high concentrations) require only trace amounts of initiator: 0.1–1% is more than sufficient. Low reagent concentrations or inherently slow reactions allow terminations to compete more effectively. To maintain the chain, additional initiator is required.

Most initiators are either peroxides (or peresters)[43] or azo compounds.[44] Several common initiators are listed in Scheme 9 along with their half-lives for unimolecular scission (first order decomposition to two radicals).[10] Although the peroxides shown are regarded as relatively stable, it is advisable to take appropriate safety precautions during their handling and use.[43] 2,2′-Azobisisobutyronitrile (AIBN) is probably the most generally useful and commonly employed initiator. It is a stable, free-flowing solid that decomposes in a useful temperature range for preparative experiments. This decomposition is well understood if not widely appreciated in the synthetic arena: AIBN decomposes to two free isobutyronitrile radicals[45] with only about 60% efficiency.[46] The remainder of the radicals undergo cage recombination.[47] The useful temperature range for AIBN is about 60–120 °C. At lower temperatures, too few radicals are produced. At higher temperatures, the decomposition of AIBN may be too rapid and the chain may break after the AIBN is consumed (if another initiation step is not available). To counter this rapid decomposition, AIBN can be added slowly to the reaction mixture.[48] Photolysis of initiators such as AIBN and benzoyl peroxide can generate radicals at room temperature or below and special low temperature initiators are not difficult to use.[30,31]

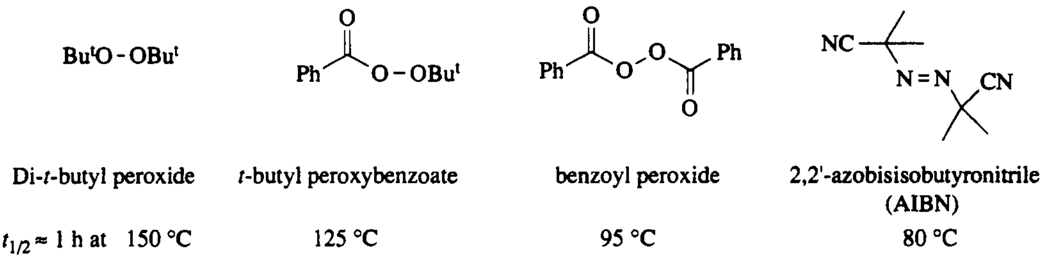

**Scheme 9** Useful initiators

Propagation steps are the heart of any chain and generally fall into two classes: atom or group transfer reactions and addition reactions to $\pi$-bonds (or the reverse: elimination). The rate of the chain transfer step is especially important in synthetic planning because, by fixing the maximum lifetime that radicals can exist, it determines what reactions will (or will not) be permitted. Termination steps are generally undesirable but are naturally minimized during chain reactions because initiation events are relatively uncommon.

The overall kinetics of a radical chain (that is, the rate at which a nonradical starting material is converted to a nonradical product) are well-modeled by the steady state approximation.[49] According to this treatment, the overall rate of a radical chain depends to the first order on the rate of the slowest propagation step and to the half order on the ratio of initiation to termination rates. Thus, the overall rate is not extremely sensitive to the initiator concentration. For synthetic purposes, a knowledge of the overall rate is not often especially useful; even slow propagation steps provide reasonable conversion rates. It is the knowledge of the kinetics of the individual, competing propagation steps that is useful.

### 4.1.3.2 Nonchain reactions

Nonchain processes differ significantly from chain processes in their methods of generating and removing radicals from a reaction. Nonetheless, useful reactions can be conducted between the generation and removal of a radical provided that the selectivity requirements are met (Scheme 8). In nonchain processes, radicals can be generated by stoichiometric bond homolysis and removed by selective radical–radical couplings. In effect, such reactions consist of only initiation and termination steps. Radicals can also be both generated and removed by redox methods (oxidative or reductive). Some fundamental redox reactions that can be used to generate both neutral and charged radicals are outlined in Scheme 10.

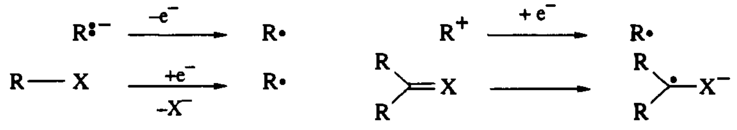

**Scheme 10** Redox generation of radicals

### 4.1.4 ELEMENTARY RADICAL REACTIONS

Almost all of the reactions of radicals can be grouped into three classes: redox reactions, atom (or group) transfer reactions and addition reactions. A detailed discussion of these reactions is beyond the scope of this chapter, but a summary of some important features (with references to more in-depth discussions) is essential. Although addition reactions will receive the most attention, redox and atom transfer reactions are important because nearly all radicals formed by addition reactions will be removed from the radical pool to give nonradical products by one of these methods.

#### 4.1.4.1 Redox (Electron Transfer) Reactions

Radicals can be either reduced (to anions or organometallics) or oxidized to cations by formal single electron transfer (Scheme 11).[50] Such redox reactions can be conducted either chemically or electrochemically[51] and the rates of electron transfer are usually analyzed by the Marcus theory and related treatments.[50] These rates depend (in part) on the difference in reduction potential between the radical and the reductant (or oxidant). Thus a species such as an α-amino radical with high-lying singly occupied molecular orbital (SOMO) is more readily oxidized, while a species such as the malonyl radical with a low-lying SOMO is more readily reduced. The inherent difference in reduction potential of substituted radicals is an important control element in several kinds of reactions.

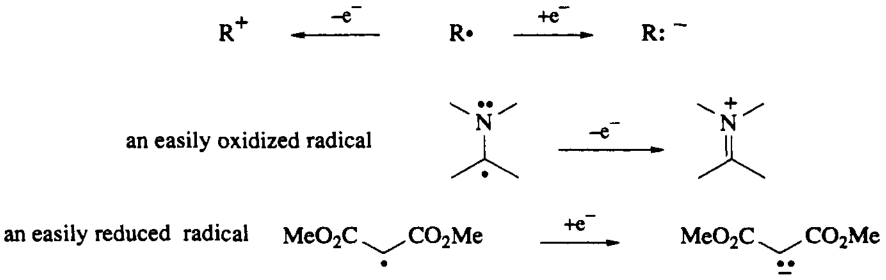

**Scheme 11** Redox reactions of radicals

#### 4.1.4.2 Atom and Group Transfer Reactions

In this very broad class of reactions, also called atom abstractions or homolytic substitutions, a univalent atom (hydrogen[52] or a halogen[53]) or a group (such as SPh, SePh) is transferred from a neutral molecule to a radical to form a new σ-bond and a new radical (Scheme 12). As with nucleophilic substitution reactions, the energy gained by the forming A—X bond helps to lower the transition state energy below that required for complete cleavage of the R—X bond. The site of the new radical is determined by the location of the abstracted atom or group X. The direction of the reaction is determined by the strength of the forming and breaking bonds and the rate of the reaction often roughly parallels its exothermicity. Endothermic atom or group transfers are rarely rapid enough to proceed at a useful rate so most transfers are irreversible under normal solution conditions. The reactions of alkyl radicals with alkyl iodides are an important exception to this generalization.

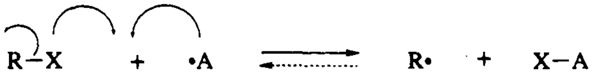

**Scheme 12** Atom or group abstraction

Factors besides those associated with thermodynamics can also greatly effect the rates. For example, in the reaction of a carbon-centered radical with a univalent atom donor (alkyl halide or alkane, R—X), the following decreasing order of reactivity is observed: R—I > R—Br > R—H > R—Cl >> R—F.[53] The range of reactivity is impressive; alkyl iodides are outstanding iodine atom donors that can suffer even slightly endothermic atom transfers, while alkyl fluorides are virtually inert to even the most exothermic of reactions. In general, atoms connected by weaker bonds are transferred more rapidly, even though the forming bonds are also weaker. The unusual placement of hydrogen is thought to be due at least in part to repulsive interactions of the incoming radical with the lone pairs of chlorine and fluorine.

Polar effects can also be important in atom transfer reactions.[54] In an oft-cited example (Scheme 13), the methyl radical attacks the weaker of the C—H bonds of propionic acid, probably more for reasons of bond strength than polar effects. However, the highly electrophilic chlorine radical attacks the stronger of the C—H bonds to avoid unfavorable polar interactions. As expected, the hydroxy hydrogen remains intact in both reactions.

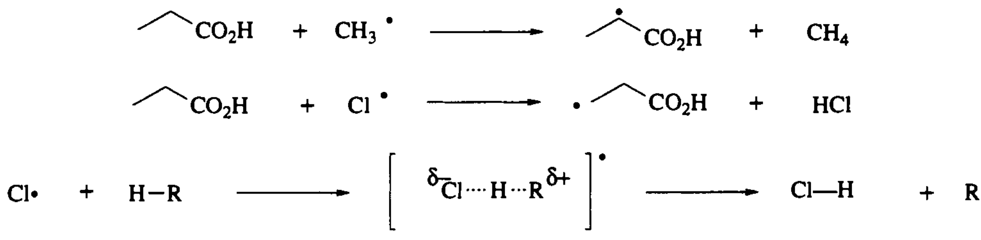

**Scheme 13** Polar effects

### 4.1.4.3 Addition Reactions

Redox and homolytic substitution reactions almost never directly form C—C, C—N and C—O bonds. Such bonds are generated in radical addition reactions (Scheme 14). Intermolecular addition reactions are presented in this chapter. Cyclization reactions have important similarities with, and differences from, bimolecular additions, and they are presented in Chapter 4.2 of this volume. Falling under the umbrella of addition reactions are radical eliminations (the reverse of addition) and radical migrations (which are usually, but not always, comprised of an addition and an elimination).

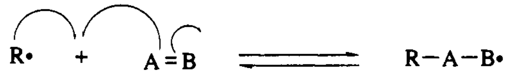

**Scheme 14** Addition–elimination

Radical addition reactions are reversible in principle and sometimes in practice. The addition of a carbon-centered radical to a carbon–carbon double bond is not reversible at normal reaction temperatures because of its exothermicity; the conversion of a C—C π-bond to a C—C σ-bond is highly favorable. Additions can become reversible if the π-bond is strong or if the σ-bond is weak or if the starting radical is significantly more stable than the adduct radical. For example, additions of carbon-centered radicals to carbonyl groups are often reversible; fragmentation reactions of oxy radicals are more common than additions to carbonyls. Whether an addition or a fragmentation reaction occurs depends not only on the position of the equilibrium but also on the rates of subsequent reactions of the starting and product radicals with reactants. Thus, the choice of reaction method can greatly affect the product distribution when reversible reactions are involved. The additions of heteroatom-centered radicals to multiple bonds are frequently reversible (and the equilibrium may lie to the left) for elements (R) that are not in the first row. The fragmentation reactions of these radicals can be very useful, especially when R = $SnR_3$ or SPh.

The additions of carbon-centered radicals to C—C double and triple bonds are the most important reactions for preparative purposes and are also the most well understood. Because of the exothermicity of these additions, they are generally regarded as having early transition states. As such, thermodynamic considerations, such as stability of the adduct radical with respect to the starting radical, are not especially useful in predicting the rates of radical additions. However, Frontier Molecular Orbital (FMO) Theory[55] has provided an excellent framework to interpret and predict the rates of addition reactions of carbon-centered radicals.[3,56] The summary that follows is intended as an introduction of the most important concepts and conclusions. The authoritative review by Giese[56] is highly recommended as an in-depth treatment with references to the primary literature.

Radicals are often classified according to their rates of reactions with alkenes. Those radicals that react more rapidly with electron poor alkenes than with electron rich are termed nucleophilic radicals. Conversely, those that react more rapidly with electron rich alkenes than electron poor are termed electrophilic radicals. Recently, it has been found that this simple division does not suffice because certain radicals react more rapidly with both electron rich and electron poor alkenes than they do with alkenes of intermediate electron density. These radicals are termed ambiphilic. The appropriate pairing of a radical and an acceptor is important for the success of an addition reaction.

### *4.1.4.3.1 Nucleophilic radicals*

Most synthetically useful radical addition reactions pair nucleophilic radicals with electron poor alkenes. In this pairing, the most important FMO interaction is that of the SOMO of the radical with the LUMO of the alkene.[56] Thus, many radicals are nucleophilic (despite being electron deficient) because they have relatively high-lying SOMOs. Several important classes of nucleophilic radicals are shown in Scheme 15. These include: heteroatom-substituted radicals, vinyl, aryl and acyl radicals, and most importantly, alkyl radicals.

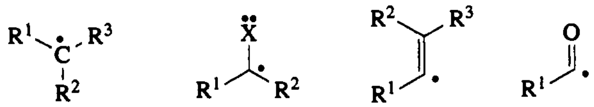

$R^1, R^2, R^3$, = H, alkyl, vinyl, aryl

**Scheme 15** Nucleophilic radicals

A large number of accurate rate constants are known for addition of simple alkyl radicals to alkenes.[33–35] Table 2 summarizes some substituent effects in the addition of the cyclohexyl radical to a series of monosubstituted alkenes.[56] The resonance stabilization of the adduct radical is relatively unimportant (because of the early transition state) and the rate constants for additions roughly parallel the LUMO energy of the alkene. Styrene is selected as a convenient reference because it is experimentally difficult to conduct additions of nucleophilic radicals to alkenes that are much poorer acceptors than styrene. Thus, high yield additions of alkyl radicals to acceptors, such as vinyl chloride and vinyl acetate, are difficult to accomplish and it is not possible to add alkyl radicals to simple alkyl-substituted alkenes. Alkynes are slightly poorer acceptors than similarly activated alkenes but are still useful.[57]

**Table 2** Substituent Effects — Alkene

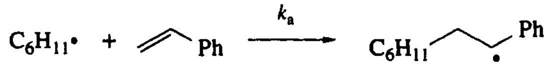

$k_{relative} = 1$ ($k_a \cong 4 \times 10^4$ $M^{-1}s^{-1}$)

| *Alkene* | $k_{rel}$ | *Alkene* | $k_{rel}$ | *Alkene* | $k_{rel}$ |
|---|---|---|---|---|---|
| 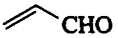 CHO | 34 | 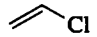 Cl | 0.1 | 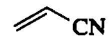 CN | 24 |
| 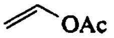 OAc | 0.02 | 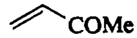 COMe | 13 | 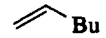 Bu | <0.005 |

Other alkene substituent effects are summarized in Table 3 with reference to the addition of cyclohexyl radical to methyl acrylate, a good acceptor. β-Alkyl substituents have a powerful decelerating effect which is usually attributed to unfavorable steric interactions with the incoming radical. Indeed, this effect is very general; virtually any radical will add more rapidly to the less-substituted end of any multiple bond in any bimolecular reaction. Most preparatively useful addition reactions have been conducted with terminal alkene acceptors (methyl crotonate is less reactive than styrene). Also useful are alkenes with β-electron-withdrawing groups. These groups provide a very modest acceleration (compare methyl acrylate to dimethyl fumarate); apparently the electronic activation provided by the lowering of the LUMO slightly outweighs unfavorable steric interactions.

**Table 3** Relative Rates of Addition of $C_6H_{11}•$ to Acrylates

| *Compound* | *Rate* | *Compound* | *Rate* |
|---|---|---|---|
| 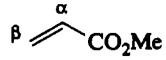 α β $CO_2Me$ | 1 | 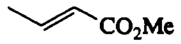 $CO_2Me$ | 0.01 |
| 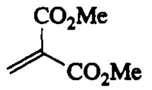 $CO_2Me$ $CO_2Me$ | 150 | 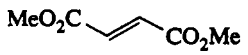 $MeO_2C$ $CO_2Me$ | 5 |

Substituent effects on the radical-bearing carbon are summarized by the examples in Table 4.[58] Although they must increase steric interactions between the radical and the alkene, alkyl substituents on the radical serve to raise the SOMO and a small acceleration of addition occurs with increasing substitution. This ability to tolerate a high degree of substitution at the radical-bearing carbon is an important asset for synthesis. The introduction of a powerful electron-withdrawing group on the radical generates an electronic mismatch and deceleration results. However, this 'mismatching' of electron-withdrawing substituents may not be as general as was once thought (see Ambiphilic Radicals, below). Conjugated substituents like aryl and vinyl thermodynamically stabilize the radical (by lowering the HOMO) without greatly affecting the position of the SOMO. Thus, most benzylic and allylic radicals will probably be nucleophilic but will exhibit reduced rates relative to simple alkyl radicals due to the reduced exothermicity of the addition.

**Table 4** Substituent Effects — Radical

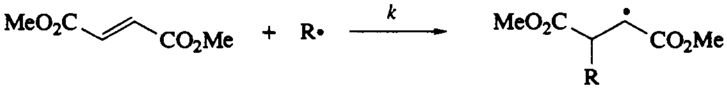

| *Radical* | $k_{rel}$ | *Radical* | $k_{rel}$ |
|---|---|---|---|
| n-$C_7H_{15}\bullet$ | 1 | $Bu^t\bullet$ | 1.6 |
| c-$C_6H_{11}\bullet$ | 1.1 | Alkyl-$OCH_2\bullet$ | 2.2 |

The transition states for additions of simple alkyl radicals to alkenes have been studied at high levels of theory[59] and the model that emerges (Figure 1) fits well with intuitive expectations based on an early transition state dominated by the SOMO(radical)–LUMO(alkene) interaction.[56] The forming C—C bond is very long yet still perfectly staggered, all the carbons involved are only slightly pyramidalized and the angle of attack of the radical is close to the ideal tetrahedral angle of 109°. There is little charge separation in the transition state, consistent with the small solvent effects that are usually observed. In summary, the reactions of nucleophilic radicals are favored by high radical SOMOs and low alkene LUMOs. Substituents are well tolerated at the radical-bearing carbon and the remote alkene carbon but strongly retard the addition when directly attached to the alkene carbon that is being attacked.

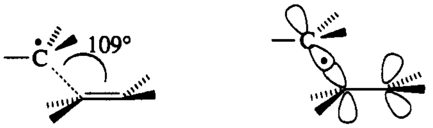

Exothermic reaction, early transition state (TS)
Forming C—C bond staggered and >2.0 Å
All carbons only slightly pyramidalized

**Figure 1** Transition state for addition of radicals to alkenes

#### *4.1.4.3.2 Electrophilic radicals*

Radicals that add more rapidly to electron rich alkenes and more slowly to electron poor alkenes are classified as electrophilic. Although the use of electrophilic radicals in synthesis is increasing, the body of rate data for electrophilic radical additions is presently much smaller than that for the nucleophilic counterparts.[60–62] Until very recently, virtually all radicals that possessed conjugative electron-withdrawing substituents were classed as electrophilic. The notion that ambiphilic radicals exist has only recently been introduced and the transition between nucleophilic, ambiphilic and electrophilic radicals is a continuum with rather ill-defined borders at present. The distinction between electrophilic radicals and ambiphilic radicals is especially gray. For the purposes of simplicity, radicals with two or more strong electron-withdrawing groups will be classed as electrophilic (perhalo-substituted radicals are also electrophilic),[63] while radicals with a single electron-withdrawing group will be classed as ambiphilic. However, certain radicals with one powerful electron-withdrawing group (like cyano) might best be thought of as electrophilic radicals. Future rate studies will no doubt define these borders more accurately.

Most of the information on substituent effects on the addition of electrophilic radicals to alkenes comes from several relative rate studies with substituted malonyl and malononitrile radicals. FMO theory predicts that such reactions will be accelerated by substituents that lower the SOMO of the radical or that raise the HOMO of the alkene. Experiments indicate that electron-donating alkene substituents modestly accelerate the additions of electrophilic radicals[60] and electron-withdrawing groups dramatically decelerate such additions. The relative rates of addition of the malononitrile radical to several monosubstituted alkenes are listed in Table 5.[61] The interplay between steric deactivation and electronic activation for substituents at the attacking carbon is less well defined. There are indications that electronic activating effects may outweigh steric effects for small, highly electrophilic radicals.[61,64]

**Table 5** Substituent Effects — Electrophilic Radicals

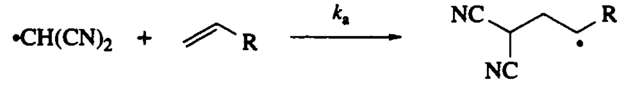

| *Alkene* | $k_{rel}$ | *Alkene* | $k_{rel}$ |
|---|---|---|---|
| 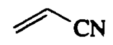 | $<10^{-3}$ | 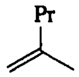 | 16 |
| 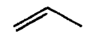 | 1 | | |

### 4.1.4.3.3 Ambiphilic radicals

One of the triumphs of FMO theory is the ability to rationalize the reactivity profile of 1,3-dipoles.[65] Certain classes of dipoles prefer electron rich cycloaddition partners, while others prefer electron poor partners. There is a relatively large group of 1,3-dipoles that have a U-shaped reactivity curve; that is, their cycloaddition reactions are accelerated by both electron-donating and electron-withdrawing substituents on the alkene. Extending this cycloaddition analogy, there must be a certain number of radicals whose SOMOs lie in an intermediate range. The addition reactions of such ambiphilic radicals would be accelerated by either electron-withdrawing or electron-donating alkene substituents. Recent rate studies from the laboratories of Fischer[66] and of Giese[67] indicate that this is indeed the case. Fischer[66] has determined accurate rate constants for the addition of $\cdot CH_2CO_2Bu^t$ to 19 terminal alkenes. A classic U-shaped

**Table 6** $\cdot CH_2CO_2Bu^t$ – An Ambiphilic Radical

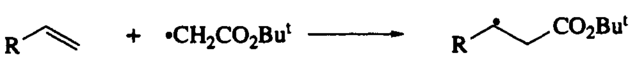

| *R* | $k_{rel}$ | *R* | $k_{rel}$ |
|---|---|---|---|
| $CO_2Me$ | 12 | OEt | 3 |
| Et | 1 ($5 \times 10^4\ M^{-1}s^{-1}$) | Ph | 40 |

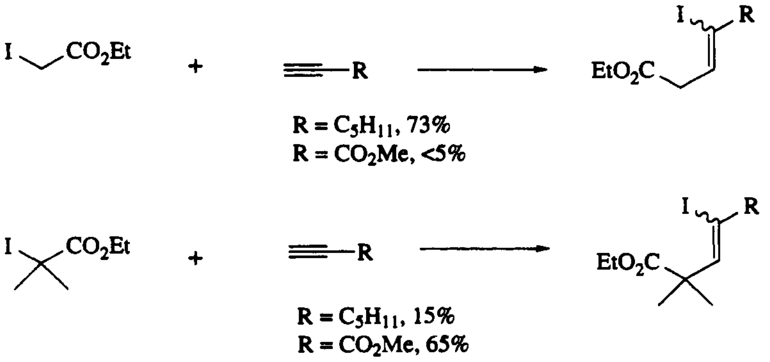

**Scheme 16** Atom transfer addition to alkynes

reactivity curve is obtained (when log *k* is plotted against ionization potential) and this series of experiments is the most clear-cut evidence to date for the existence of ambiphilic radicals. Selected examples from this study are summarized in Table 6.

From the Fischer rate study, it appears that primary ester-substituted radicals are not electrophilic but ambiphilic and the borderline between ambiphilic and electrophilic radicals is not at all clear. Consider our results[68] (Scheme 16) on the atom transfer additions of ester-substituted radicals to alkynes (with the caution that it may be dangerous to compare yields in place of rate constants). The primary ester-substituted radical adds more efficiently to 1-heptyne but the tertiary ester-substituted radical prefers ethyl propiolate.

Because of the centrality of the carbonyl group in synthesis, carbonyl-substituted radicals are especially useful. The above results indicate that, if planned addition or cyclization reaction of a carbonyl-substituted radical fails due to lack of reactivity of the acceptor, one should consider activation of the alkene not only with electron donors but also with electron acceptors.

### *4.1.4.3.4 Heteroatom-centered radicals*

The reactivity of heteroatom-centered radicals depends on both thermodynamic factors (stabilities of starting and product radicals and strengths of forming and breaking bonds) and kinetic factors. The electronegativity of the radical-bearing element is an important consideration. For example, radicals such as $Cl\cdot$, $RO\cdot$ and $R_3N^{+\cdot}$ are strongly electrophilic, while $R_3Sn\cdot$ is more nucleophilic.

## 4.1.5 RADICALS AND SYNTHETIC PLANNING

The notion of retrosynthetic analysis, first introduced by Corey,[69] is an excellent heuristic device that has become standard practice in synthetic planning.[70] Dissection of a molecule leads to imaginary synthons from which real reagents with the desired reactivity profiles are selected or designed. The notation of this thought process (and as a result, the process itself) has focused on the natural alternating polarity imposed on a carbon chain by a heteroatom. Bonds are dissected in a polar sense to give either normal or polarity-inverted (umpoled[71]) synthons.[72] The polarity of these synthons (nucleophilic or electrophilic) is often represented simply by plus (+) and minus (–) signs (Scheme 17). A more rigorous notation introduced by Seebach is also popular.[73] Here, nucleophilic sites are classed as donors (**d**) and electrophilic site are classed as acceptors (**a**). Such notations are useful not only in the planning of complex synthetic paths but also in the conceptualization of such paths (many steps can often be summarized with one picture) and in the conceptualization and design of multifunctional reagents.

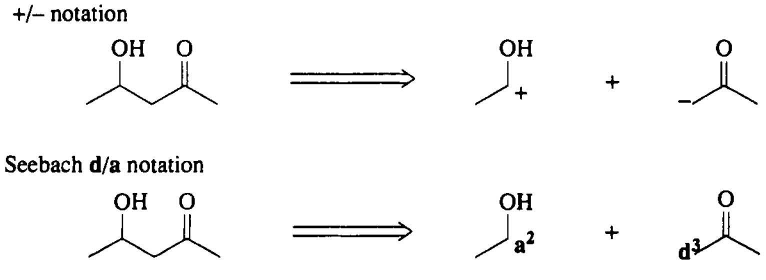

**Scheme 17** Notations for retrosynthetic planning

As radical reactions are increasingly applied in synthesis, a convenient and informative method to notate these reactions in retrosynthetic analysis becomes desirable. Currently, two fragments united by a radical reaction are sometimes represented simply by dots '·'. Seebach has introduced the radical synthon, notated as '**r**' (Scheme 18).[74] Both of these notations have two related limitations: first, they imply that C—C bonds are formed by radical–radical coupling, and second, they do not indicate which site provided the radical and which site accepted it. I introduce here a notation for radicals in retrosynthetic analysis that strives to be in harmony with current ionic notations without artificially imposing[75] on radical reactions the features needed for the planning of ionic reactions.

In this notation, there are two kinds of sites that a synthon may possess: radical sites themselves and sites that react with radicals. In synthons, radical sites are designed simply by '·' to integrate with the

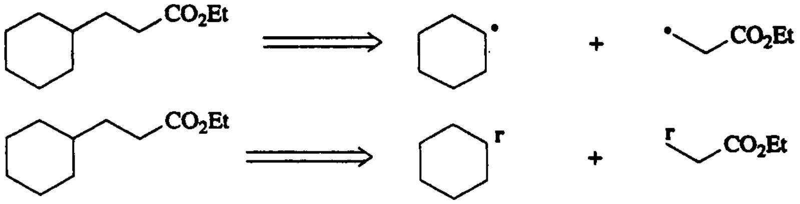

Scheme 18 Current notations for radical reactions

plus–minus convention and more precisely by '·r' to integrate with Seebach's donor–acceptor notation. Sites that react with radicals may be either atom (or group) donors or multiple bonds. Such sites are designated by '∘' in the plus–minus convention and by '∘' in the Seebach convention. This modification clearly shows the direction in which radical reactions are occurring and it is especially illustrative when sequences of reactions (either all radical or combined radical and ionic) are notated.

The simple addition reaction in Scheme 19 illustrates how the notation is used. Ester (**1**) can be dissected into synthons (**2**), (**3**) and (**4**). Synthons for radical precursors (pro-radicals) possess radical sites (·). A reagent that is an appropriate radical precursor for the cyclohexyl radical, such as cyclohexyl iodide, is the actual equivalent of synthon (**2**). By nature, alkene acceptors have one site that reacts with a radical (∘) and one adjacent radical site (·) that is created upon addition of a radical. Ethyl acrylate is a reagent that is equivalent to synthon (**3**). Atom or group donors are represented as sites that react with radicals (∘). Tributyltin hydride is a reagent equivalent of (**4**). In practice, such analysis will usually focus on carbon–carbon bond forming reactions and the atom transfer step may be omitted in the notation for simplicity.

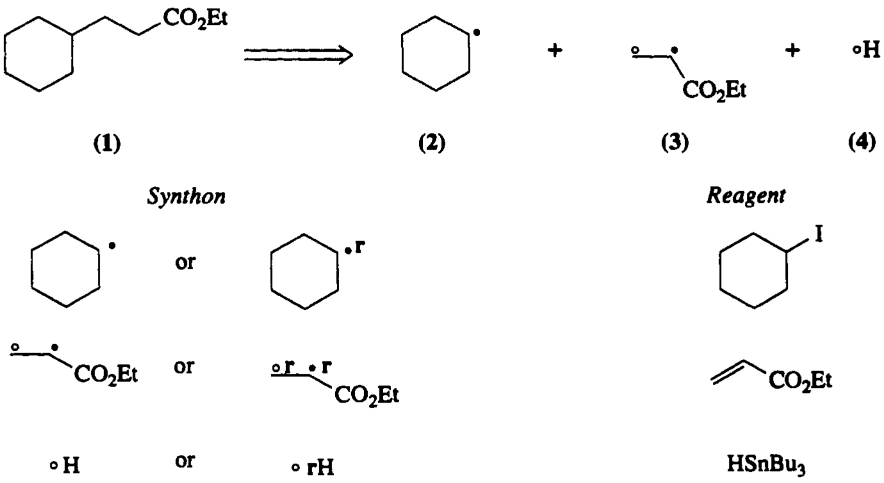

Scheme 19 Retrosynthetic notation of radical reactions

This notation blends smoothly with the plus–minus notation to indicate sequences of reactions or multifunctional reagents. In the simple, hypothetical transformation in Scheme 20, dibromomethane might serve as a reagent for the synthon (**5**). A slash (/) separates the two symbols (–/·) to indicate that (**5**) will behave separately as a nucleophilic site and a radical site, rather than as a radical anion. The more rigorous notation of Seebach avoids this confusion. Related transformations have actually been executed by Wilcox and Gaudino.[76]

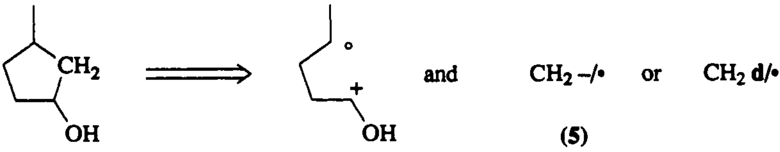

Scheme 20 A simple synthon

The notation becomes useful in the planning and conceptualization of a complex synthesis. A propellane triquinane such as modhephene presents almost limitless opportunities for the design of strategies based on radical cyclizations. Scheme 21 illustrates four of the 24 possible[77] strategies for the synthesis of modhephene that would conduct two radical cyclizations of a precursor that contains a pre-existing ring and two geminal side chains. In strategy A, both radical sites are generated in the side chains and both acceptor sites are on the ring. In strategy B, the roles are reversed; both radical sites are generated on the ring and cyclize to the chains. Strategies C and D have one site each on the ring and the chain. The notation systems used in Scheme 18 would have represented all four different strategies in Scheme 21 in the same way. In contrast, the new notation method clearly differentiates the four strategies.

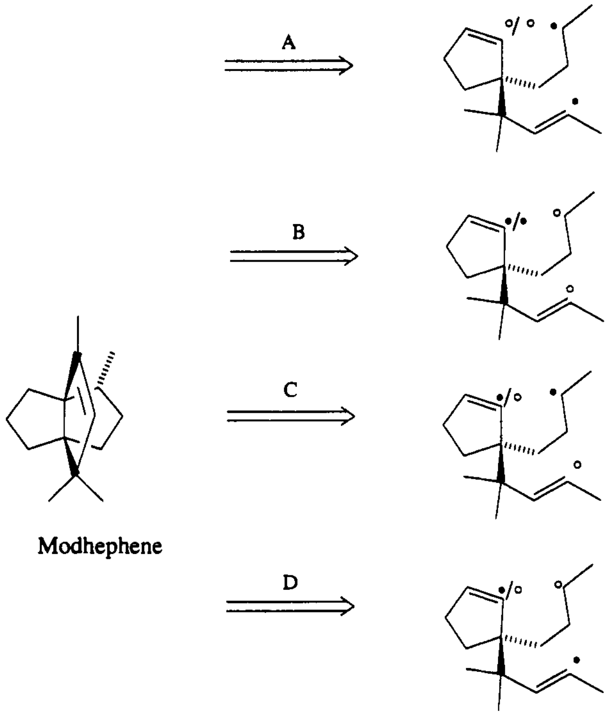

**Scheme 21** Four strategies for modhephene

As with any retrosynthetic analysis, once potential strategies are identified, one must address the problems posed by each route. In the present synthesis, such questions arise as: Are the planned cyclizations likely to succeed? Will the two cyclizations be conducted together or separately? In what order will they occur? How will the stereochemistry of the methyl group be controlled? By what method will the cyclizations be conducted and what will the actual cyclization precursor(s) be? How will the precursors be prepared? The answers to these questions will help determine the selection of a practical synthetic pathway.

In practice, Jasperse has developed a synthesis of modhephene that is a variant of strategy A (Scheme 22).[78] Modhephene can be prepared from the enone (**6**). In turn, enone (**6**) is prepared by two separate radical cyclizations with complete control of regio- and stereo-chemistry. The vinylstannane serves as the synthetic equivalent of a double radical acceptor site (∘/∘). The whole synthetic route can be conceptualized in one simple diagram as shown in Scheme 23. Below the diagram, each synthon is associated with the actual starting material that was used to accomplish the required transformation in the synthesis.

Scheme 24 illustrates how this notation can be combined with that of Seebach.[73] Clive has formed a new ring by sequencing a Michael reaction, a carbonyl addition, and a radical cyclization.[79] Phenylselenoacrylonitrile is the actual reagent that accomplishes the transformation implied by synthon (**7**).

No heuristic device for retrosynthesis can replace a knowledge of the synthetic literature. This device aids the synthetic chemist in planning possible strategic routes to a target, but it remains to the chemist to evaluate the viability of these routes and to make an informed selection. A knowledge of the principles of radical addition and cyclization reactions and the methods to conduct these reactions is essential for the evaluation of synthetic strategies, however they are devised. To provide a foundation of this knowledge is the principle goal of this and the following chapter.

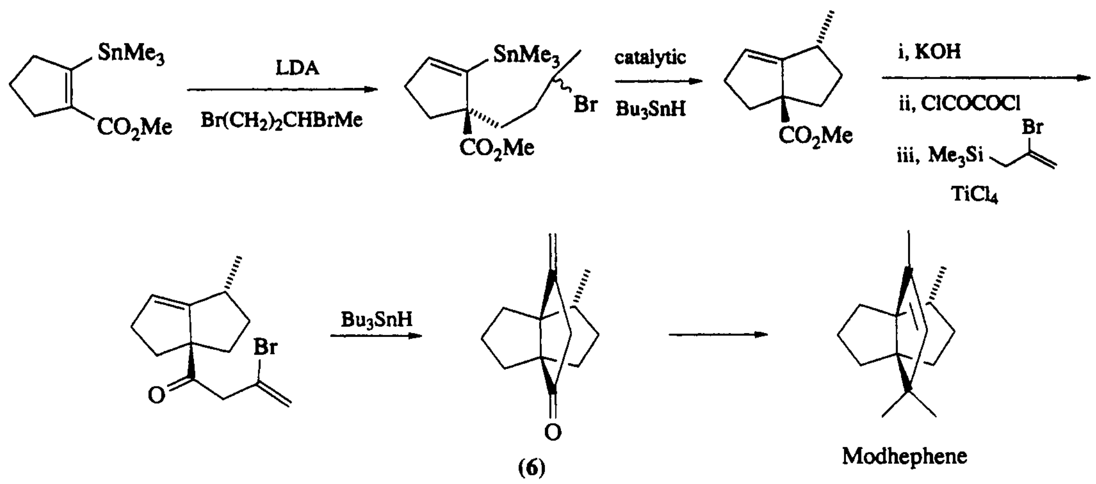
SnMe3
CO2Me
LDA
Br(CH2)2CHBrMe
SnMe3
Br
CO2Me
catalytic
Bu3SnH
CO2Me
i, KOH
ii, ClCOCOCl
iii, Me3Si
Br
TiCl4
Br
O
Bu3SnH
O
(6)
Modhephene

**Scheme 22**

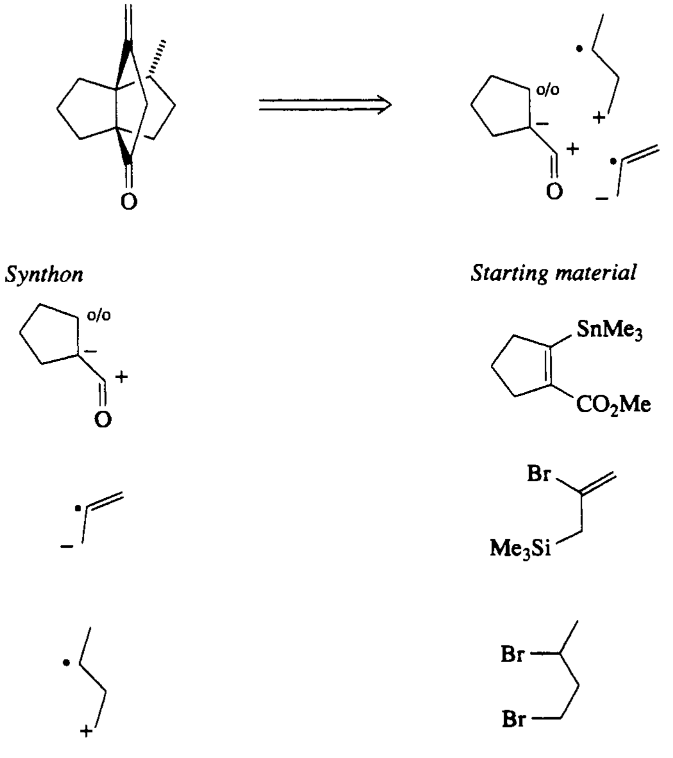
O
o/o
O
Synthon
Starting material
o/o
O
SnMe3
CO2Me
Br
Me3Si
Br
Br

**Scheme 23** An analysis of the modhephene synthesis

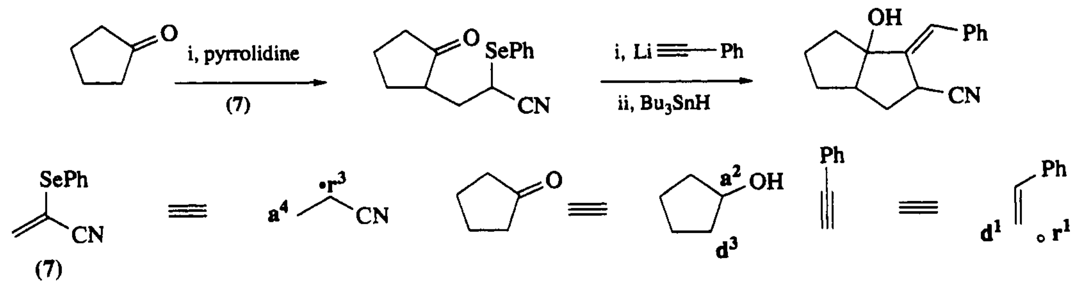
O
i, pyrrolidine
(7)
O
SePh
CN
i, Li≡—Ph
ii, Bu3SnH
OH
Ph
CN
SePh
CN
(7)
≡
a4
•r3
CN
O
≡
a2
OH
d3
Ph
≡
Ph
d1
r1

**Scheme 24** Seebach notation

## 4.1.6 ADDITIONS OF CARBON-CENTERED RADICALS TO ALKENES AND ALKYNES

One of the mildest general techniques to extend a carbon chain entails the addition of a carbon-centered radical to an alkene or alkyne. The method for conducting these addition reactions often determines the types of precursors and acceptors that can be used and the types of products that are formed. In the following section, synthetically useful radical additions are grouped into chain and non-chain reactions and then further subdivided by the method of reaction. Short, independent sections that follow treat the addition of carbon-centered radicals to other multiple bonds and aromatic rings and the additions of heteroatom-centered radicals.

### 4.1.6.1 Chain Methods

#### *4.1.6.1.1 Metal hydrides (the Giese method)*

Developed in large measure by Giese and coworkers, metal hydride mediated addition reactions are among the most useful and commonly employed synthetic reactions that involve radical intermediates. Two classes of metal hydrides have emerged as superior reagents to conduct addition reactions by radical chains: tin hydrides (and closely related germanium and silicon hydrides) and mercury(II) hydrides. This subject has been recently covered in detail in a number of specific[80–82] and general reviews[3–5,83,84] and the following treatment is intended only as an introduction.

*(i) Tin hydride*

The tin hydride method[85] generates radicals by abstraction of an atom or group from a pro-radical by $Bu_3Sn\cdot$ and removes radicals by hydrogen transfer from $Bu_3SnH$. Selectivity is often imparted by controlling reagent concentrations. Most of the applications of the tin hydride method pair nucleophilic radicals, generated from alkyl iodides, bromides or related precursors, with electron deficient alkenes (Scheme 25). This reaction is complementary to the more common tactic of conjugate addition of an organometallic reagent (such as a cuprate) to an electron deficient alkene. For many applications, the standard organometallic route will remain the method of choice because yields are consistently high and the conjugate addition reaction is more tolerant to the presence of β-substituents on the acceptor. However, there are situations in which the radical method may be advantageous. These include additions of secondary, tertiary and heteroatom-substituted radicals (where organometallic derivatives are often difficult to prepare or are unstable) and additions in which either the halide or the alkene contains functionality sensitive to organometallic methods. Scheme 26 provides some representative examples in which readily available, optically active precursors have been chain extended.[85c–87] Although very high yields have been obtained in favorable cases, isolated yields typically fall in the range of 40–75%. Reduction products or short telomers often account for the remainder of the mass balance (see below).

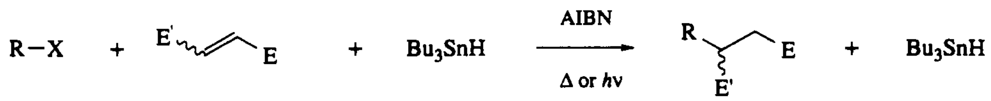

R = primary, secondary, tertiary or heteroatom-substituted alkyl, phenyl

X = I or Br, SePh, xanthate, $NO_2$

E = COR, $CO_2R$, CN, Ph, $SO_2Ph$

E' = H, activating group

Scheme 25

A detailed mechanistic analysis of the factors affecting the success of these tin hydride mediated addition reactions has been provided by Giese.[3] This analysis, which is especially illustrative of how experimental conditions for free radical reactions are planned, is summarized in Scheme 27. Three intermediate radicals, (**8**), (**9**) and (**10**), are involved. As is characteristic of all radical reactions, these radicals are simultaneously exposed to the same reagent pool and each can potentially undergo an addition reaction or an atom transfer reaction. The required reaction of the tributyltin radical (**8**) is atom ab-

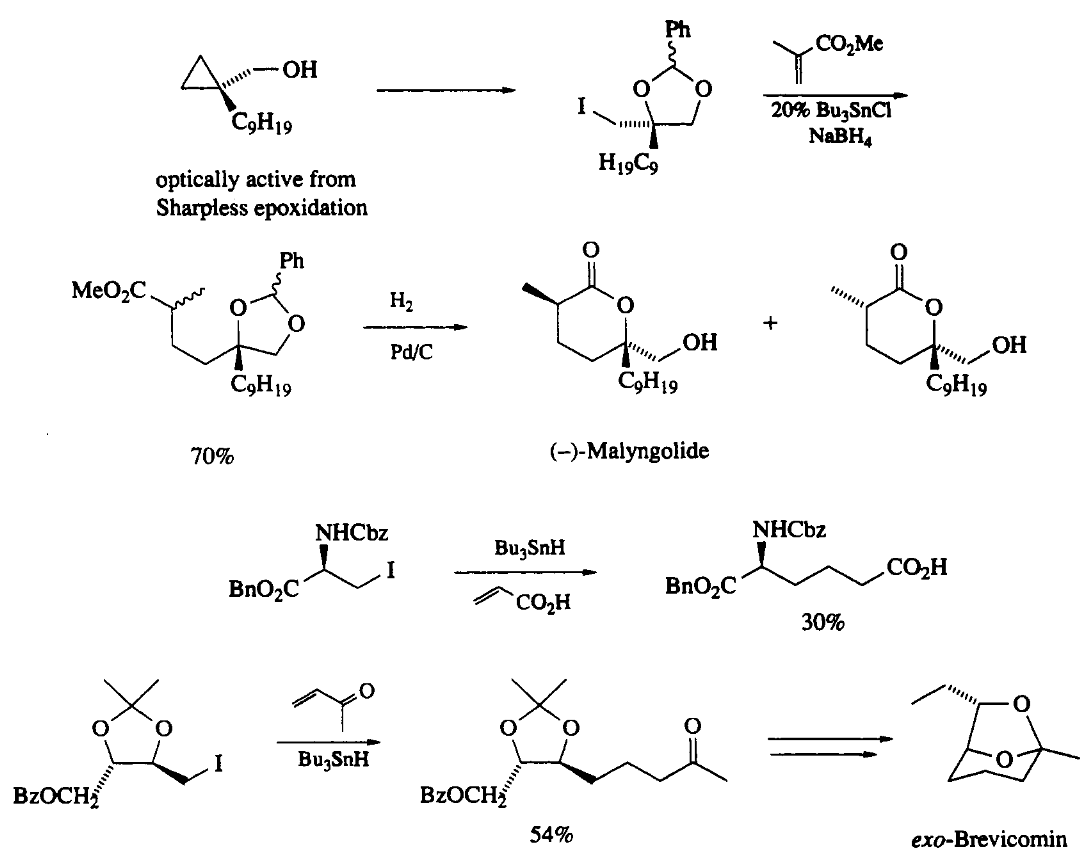

**Scheme 26**

straction to generate the initial carbon-centered radical (9); a possible competing reaction is the well-known hydrostannylation reaction of electron deficient alkenes. Because it is not possible to use low alkene concentrations to retard hydrostannylation (this also retards the desired addition), the selectivity problem in step 1 is solved by using a highly reactive atom donor. Iodides are often the precursors of choice because trialkyltin radicals abstract iodine from alkyl iodides at rates approaching the diffusion-controlled limit.[88] Iodide precursors of more stable radicals (tertiary alkyl, α-oxy, acyl) are often difficult to prepare but are not usually required. Substituents that stabilize radicals also facilitate atom transfer and less reactive bromides, phenyl selenides, nitro groups and xanthates often become acceptable precursors.

In steps 2 and 3, addition to the electron deficient alkene and hydrogen abstraction from tin hydride compete. Step 2 requires addition of R· to be faster than hydrogen atom transfer and step 3 requires precisely the reverse. That this reaction can be conducted at all is a result of the electronic properties of the intermediate radicals: alkyl radical (9) is a nucleophilic radical that pairs well in the addition to the electrophilic alkene, but the resulting adduct radical (10) does not add as rapidly in the corresponding reaction to give (11). Better yields are obtained as the alkene becomes more electron deficient because electron-withdrawing substituents increase $k_{a1}$ and, at the same time, may decrease $k_{a2}$. The ratio of the two rate constants ($k_{a1}$:$k_{a2}$) may range anywhere from 10 in borderline cases up to 1000 in ideal cases, depending on radical and alkene substituents. The rate constants $k_{H1}$ and $k_{H2}$ are also important and it is often assumed that they are approximately equal.[89]

To successfully conduct the desired addition reaction, one must adopt conditions so that the partitioning in step 2 between reduction and addition of (9) favors addition, without going so far as to disrupt the natural rate constant bias in favor of reduction over addition in step 3. A specific example, the addition of cyclohexyl radical to methyl acrylate, best illustrates this point. Equation (5) states the requirement that addition of the cyclohexyl radical be more rapid than reduction with tin hydride. The rate constant for the addition of the cyclohexyl radical is about $3 \times 10^5$ $M^{-1}$ $s^{-1}$ while the rate constant for abstraction of hydrogen is about $2 \times 10^6$ $M^{-1}$ $s^{-1}$. This slight bias in rate constant ratio in favor of hydrogen transfer must be offset by altering the concentrations of the reagents as indicated in Equation (6); the concentration of methyl acrylate must be greater than that of tin hydride. This alteration of reagent concentrations is ac-

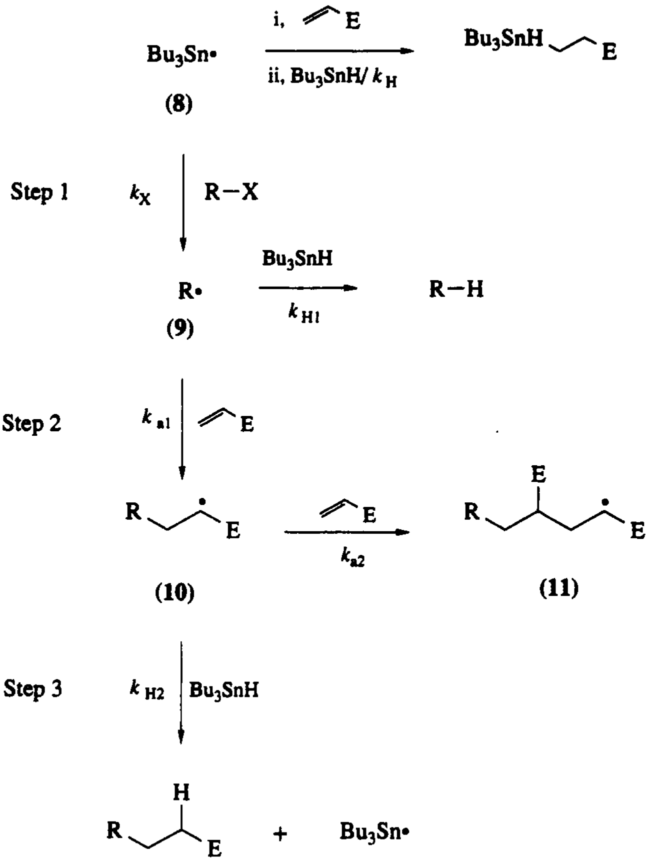
Bu3Sn•
(8)
i, E
ii, Bu3SnH/ kH
Bu3SnH E
Step 1
kX
R−X
R•
(9)
Bu3SnH
kH1
R−H
Step 2
ka1
E
R E
(10)
E
ka2
R E E
(11)
Step 3
kH2
Bu3SnH
H
R E
+ Bu3Sn•

Scheme 27

ceptable provided that it is not sufficiently great to offset the inherent rate constant bias in favor of hydrogen transfer in step 3, as illustrated in equations (7) and (8).

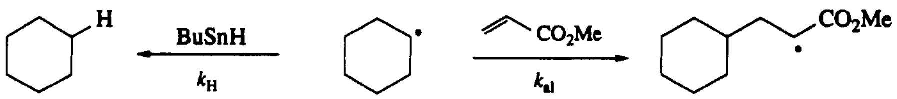
H
BuSnH
kH
CO2Me
ka1
CO2Me

$$k_{a1}[\text{CH}_2{=}\text{CHCO}_2\text{Me}] > k_H[\text{Bu}_3\text{SnH}] \qquad (5)$$

$$k_{a1} \approx 3 \times 10^5\ \text{M}^{-1}\,\text{s}^{-1}$$

$$k_H \approx 2 \times 10^6\ \text{M}^{-1}\,\text{s}^{-1}$$

$$\frac{[\text{CH}_2{=}\text{CHCO}_2\text{Me}]}{[\text{Bu}_3\text{SnH}]} > 7 \qquad (6)$$

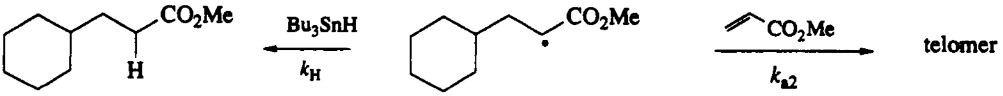
CO2Me
H
Bu3SnH
kH
CO2Me
CO2Me
ka2
telomer

$$k_{a2}[\text{CH}_2{=}\text{CHCO}_2\text{Me}] < k_H[\text{Bu}_3\text{SnH}] \qquad (7)$$

$$7k_{a2} < k_H \qquad (8)$$

A quantitative analysis of all the competing reactions is possible in some simple systems. Rate constants to permit analysis of the partitioning at step 2 are well established; however, specific rate constants to model the partitioning at step 3 are often lacking.[89] Nonetheless, general guidelines are forthcoming from the mechanistic analysis. First and foremost, use the most reactive acceptor possible in order to favor addition in step 2 (by increasing $k_{a1}$) and reduction in step 3 (by decreasing $k_{a2}$). This simplifies the design of reaction conditions. Next, once an acceptor is selected, choose reaction conditions carefully to maximize the yield of addition. For reactive, inexpensive acceptors like acrylonitrile, the components can simply be mixed in an appropriate ratio and the reaction initiated.[90] However, because alkyl radicals react with most acceptors with rate constants equal to or slightly lower than with tin hydride, it is desirable to maintain a situation where the concentration of the alkene exceeds that of the tin hydride. This is best accomplished by using reaction conditions that minimize the tin hydride concentration and by employing a modest excess of an alkene acceptor. The two most popular ways to mininize the tin hydride concentration are by using syringe pump addition techniques or by using a limited quantity of a catalytic precursor of tin hydride.

In the syringe pump method, the halide and the alkene acceptor are typically refluxed in benzene and a solution of tributyltin hydride and AIBN in benzene is added slowly over a period of hours by syringe drive. The exact concentration of tin hydride is not known but it remains low, provided that the chain continues at a rate more rapid than syringe pump addition. Telomerization may intervene if the tin hydride concentration falls too low. To insure that the chain continues, it is important to use a reactive atom donor (to maximize the rate of step 1) and to insure that a constant source of initiator is present.[91]

Catalytic procedures (introduced by Kuivila and Menapace[92]) are easier to conduct and the tin hydride concentration is more easily controlled. A catalytic amount of tributyltin hydride or tributyltin chloride is mixed with the radical precursor, the alkene acceptor and a stoichiometric quantity of a coreductant such as sodium borohydride[93] or sodium cyanoborohydride.[29] Over the course of the reaction, the borohydride continuously converts the tin halide to tin hydride. The use of the catalytic procedure is probably restricted to halide precursors (tin products derived from other precursors may not be reduced to tin hydrides). This method has several advantages over the standard procedures: (i) it is simple to conduct; (ii) most functional groups are stable to the coreductants (especially sodium cyanoborohydride); (iii) the tin hydride concentration is known, is stationary (assuming that the tin halide is rapidly reduced to tin hydride), and can be varied by either changing the concentration of the reaction or the quantity of the tin reagent (10% is a typical value, but lower quantities can be used); and finally, (iv) the amount of tin hydride precursor that is added limits the amount of tin by-product that must be removed at the end of the reaction.

This last advantage should not be underestimated because the removal of large amounts of tin products on a preparative scale can be inconvenient. With relatively polar organic products, the non-polar tin products are often removed by chromatographic purification.[80] Partitioning between acetonitrile and hexane has also been used.[94] Nonpolar reaction products sometimes present more problems. Pretreatment of reaction mixtures with fluoride anion to convert tin halides to insoluble tin fluorides in a popular work-up technique.[95] Chang has recently introduced a work-up procedure with DBU that serves to remove much of the tin halide by-product from a crude product prior to chromatography.[96] These work-up procedures are designed to remove tin halides and it is recommended that any work-up procedure be prefaced by treatment of the crude reaction mixture with iodine to destroy any residual tin hydride.[97] Methods based on polymer-bound tin hydrides have not become popular, but offer the potential advantages of low concentration of tin hydride and easy removal of the tin products.[98]

Another strategy to improve the partitioning of the initial radical between direct reduction and desired addition is to design a reagent that is a poorer hydrogen donor than tributyltin hydride.[99] Bulky substituents on the tin atom do not significantly decrease the rate of hydrogen transfer and substituents like aryl groups and heteroatoms actually accelerate hydrogen transfer.[100] Germanium is above tin in the periodic table and forms stronger bonds to most elements, making it a poorer atom donor and a better atom abstractor. Indeed, tributylgermanium hydride is known to be about 10–20 times poorer as a donor of a hydrogen atom towards alkyl radicals than tin hydride[38,101] and it is also a powerful halogen atom abstractor.[38] Thus it would appear to offer significant advantages over tributyltin hydride in slow addition reactions by giving better partitioning in favor of addition over reduction.[99] However, there are two problems. First, hydrogermylation is more rapid than hydrostannylation and it can be a serious competing side reaction,[102] and second, there is evidence that reactions of germanium hydride with stabilized radicals (such as tertiary alkyl) may be too slow to propagate chains at low concentrations[101] (that is, what is gained by decreasing $k_H$ might be lost by increasing the germanium hydride concentration in order to maintain the chain).[103]

A detailed study by Hershberger has evaluated the efficacy of germanium hydride compared to tin hydride under a standard set of conditions.[104] In general, tin hydride propagates chains more efficiently[105] and gives superior yields in additions to acrylonitrile. However, in the addition of a primary radical to acrylonitrile (Scheme 28), the germanium hydride was found to be superior provided that acetonitrile was used as a solvent rather than benzene[105] and that an iodide was used as the radical precursor.[102]

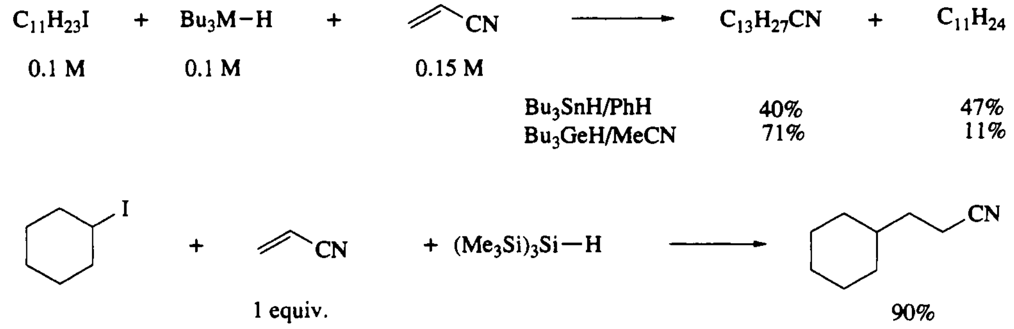

Scheme 28

Silicon–hydrogen bonds in most trialkylsilanes are too strong to donate hydrogen atoms to alkyl radicals. However, Griller and Chatgilialoglu have recently shown that tris(trimethylsilyl)silane has a significantly weaker Si—H bond than normal silicon hydrides (but still stronger than tin hydrides) and that it can be used as a reagent to propagate chain reductions of halides.[106] Very recently, Giese and Chatgilialoglu have shown that this new reagent is a useful substitute for tin hydride in simple addition and cyclization reactions (Scheme 28).[107] Future work will be required to determine the general suitability of this promising reagent as a substitute for tin hydride.

The level of stereoselectivity in tin hydride mediated addition reactions often depends on whether cyclic or acyclic systems are involved. Two recent, representative examples are shown in Scheme 29.[108,109] Good selectivity is often observed with cyclic radicals in both the addition and hydrogen transfer steps. The reagent attacks the less-hindered face of the radical. Acyclic systems have been less frequently studied and typically show low asymmetric induction in either addition or hydrogen transfer reactions.[110] There is at least one example where reasonable stereoselectivity has been observed (albeit in only 13% yield) in the addition of an alkyl radical to an acceptor bearing a stereogenic center (Scheme 30).[111] There are currently no generally useful methods for absolute asymmetric induction although this is an ongoing area of research in several laboratories.

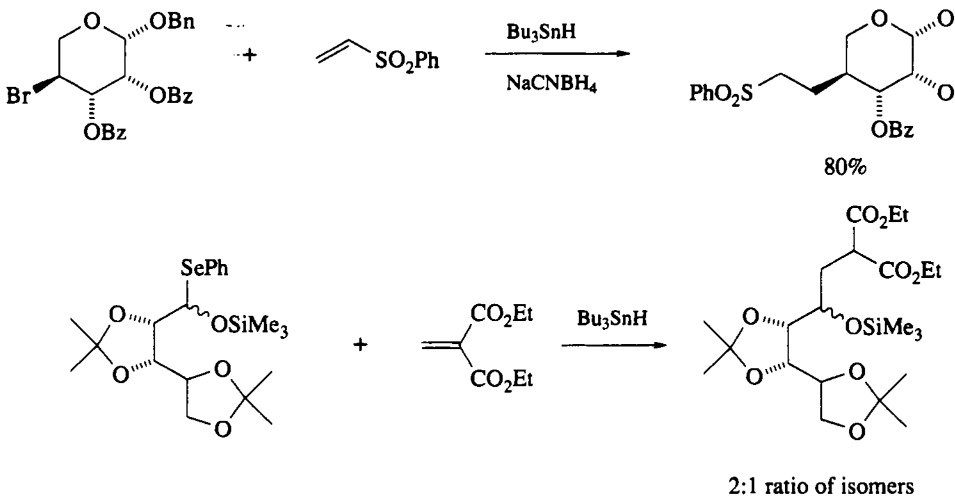

Scheme 29

In addition to alkyl radicals, other nucleophilic radicals can participate in tin hydride mediated addition reactions (Scheme 31). Phenyl radicals are highly reactive[112] but give only modest yields of addition products[113] and one suspects that vinyl radicals should behave similarly.[114] α-Oxy radicals have been

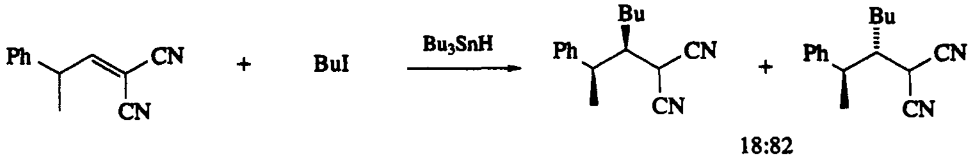
Ph
CN
CN
+
BuI
Bu3SnH
Bu
Ph
CN
CN
+
Bu
Ph
CN
CN
18:82

**Scheme 30**

used frequently and with good success, especially at the anomeric center in carbohydrates. In such anomeric radicals, stereoelectronic effects can cause very high levels of asymmetric induction.[115,116] Very recently, acyl selenides have been demonstrated to be useful precursors for the addition of acyl radicals to alkenes.[117]

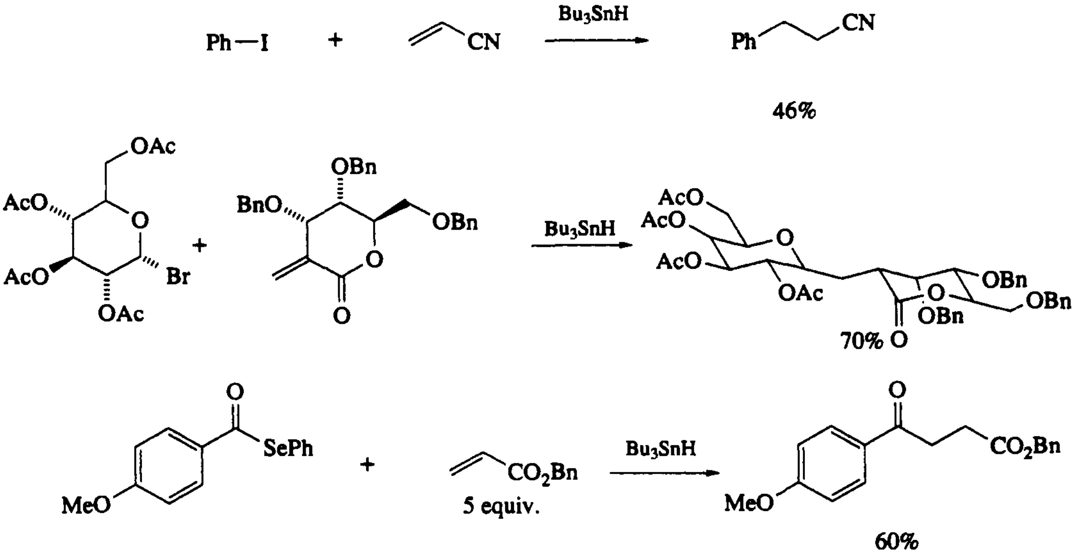
Ph—I
+
CN
Bu3SnH
Ph
CN
46%
OAc
AcO
O
AcO
OAc
Br
+
OBn
BnO
OBn
O
O
Bu3SnH
AcO
AcO
O
AcO
OAc
O
OBn
OBn
OBn
70% O
O
SePh
MeO
+
CO2Bn
5 equiv.
Bu3SnH
O
CO2Bn
MeO
60%

**Scheme 31**

There are several examples of the addition reactions of carbonyl-substituted radicals to alkenes by the tin hydride method. The first reaction cited in Scheme 32 is a clear-cut example of reversed electronic requirement: an electrophilic radical pairing with a nucleophilic alkene.[60] Because enol ethers are not easily hydrostannylated, the use of a chloride precursor (which is activated by the esters) is possible. Indeed, the use of a bromomalonate results in a completely different product (Section 4.1.6.1.4). The second example is more intriguing (especially in light of the recent proposals on the existence of ambiphilic radicals) because it appears to go against conventional wisdom in the pairing of radicals and acceptors.[118,119]

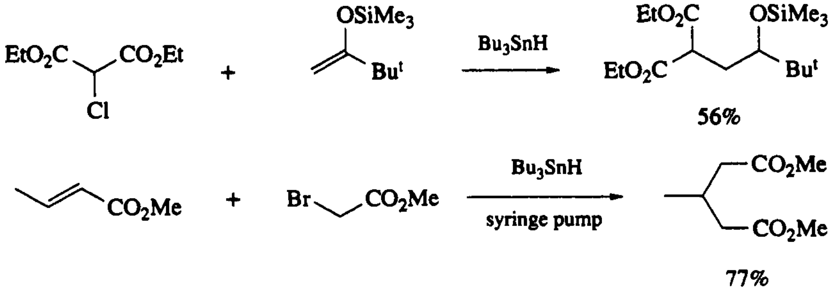
EtO2C
CO2Et
Cl
+
OSiMe3
Bu^t
Bu3SnH
EtO2C
OSiMe3
EtO2C
Bu^t
56%
CO2Me
+
Br
CO2Me
Bu3SnH
syringe pump
CO2Me
CO2Me
77%

**Scheme 32**

### *(ii) Mercury(II) hydrides*

Radical addition reactions conducted by the mercury(II) hydride method were also pioneered by Giese and are very similar in principle to the tin hydride method. The radical is generated from an organomercurial (rather than a halide) and removed by hydrogen transfer from a mercury(II) hydride (rather than a tin hydride). Mercury(II) hydride reductions have been covered in several recent reviews.[3,5,81,82]

The basic transformation and mechanism are outlined in Scheme 133. Addition of a reducing agent ($NaBH_4$, $NaCNBH_3$, $Bu_3SnH$) to a solution (methanol, THF, dichloromethane) of an organomercury(II) halide or acetate in the presence of an excess of a reactive acceptor provides addition products in modest to good yield. The directly reduced hydrocarbon is a common by-product. It is believed that the organomercurial is rapidly reduced to an alkylmercury(II) hydride and the accepted mechanism for addition is a mercury(II) hydride chain.[120] This chain is probably initiated by spontaneous decomposition of the alkylmercury(II) hydride. Alkyl radicals can compete for addition of the alkene (step 1) or hydrogen atom abstraction from the alkylmercury(II) hydride. Adduct radicals transfer the chain by abstracting hydrogen from the mercury(II) hydride (step 2).

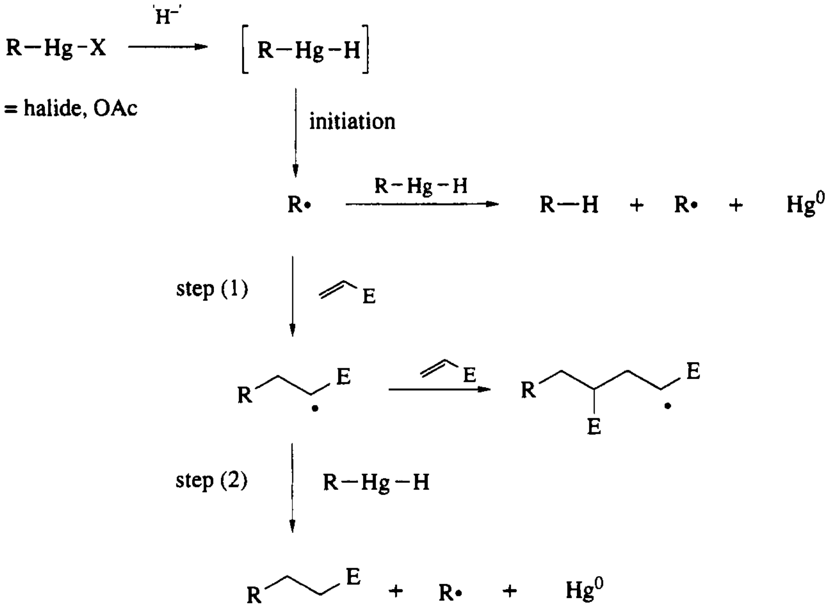

Scheme 33

It is known that mercury(II) hydrides are better hydrogen donors towards alkyl radicals than tin hydride by about one order of magnitude.[121] This means that very reactive acceptors are required to attain useful yields in the mercury(II) hydride method. For many applications, tin hydride will be the reagent of choice. However, the mercury(II) hydride method does have advantages: (i) the mercury(II) hydride is both the radical trap and the radical precursor and thus there are only two radicals involved in the reaction (rather than three as in the tin hydride method);[122] (ii) the reaction is very easy to conduct and proceeds rapidly at room temperature; (iii) the organomercurials are often formed *in situ*; and (iv) the separation of products from reagents is very straightforward (metallic mercury is removed by filtration and the inorganic products are removed by water extraction).

A useful aspect of the mercury(II) hydride method is that it can be directly coupled with the many standard techniques for heteromercuration of alkenes and cyclopropanes. The resulting overall transformation adds a heteroatom and a carbon atom across the carbon–carbon double bond of an alkene or the carbon–carbon single bond of a cyclopropane. This is a difficult transformation to conduct by standard ionic techniques. An alkene thus becomes an equivalent of synthon (**12**) and a cyclopropane of synthon (**13**; Scheme 34). Many equivalent transformations (like haloetherification and phenylselenolactonization) are available to make precursors for tin hydride mediated additions.

The selection of examples collected in Scheme 35 illustrates just a few of the many transformations that are possible with mercurials.[123–126] (The comprehensive review of Barluenga is recommended as a complete source of references.)[82] The oxy- or amido-mercuration can be inter- or intra-molecular and the addition products are often converted to lactones or lactams. The last example illustrates a simple prep-

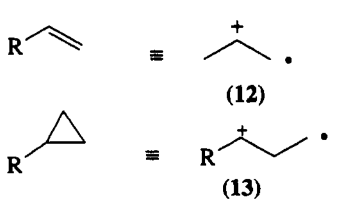

**Scheme 34** Synthons in the mercury(II) hydride method

aration of a 1,6-dicarbonyl compound. The standard ionic approach to such molecules calls for umpolung; a reagent equivalent to homoenolate synthon (**14**) would need to be prepared. The preparation of a reagent for the radical synthon (**15**) and the execution of the coupling are very simple compared to many ionic methods for the equivalent transformation.

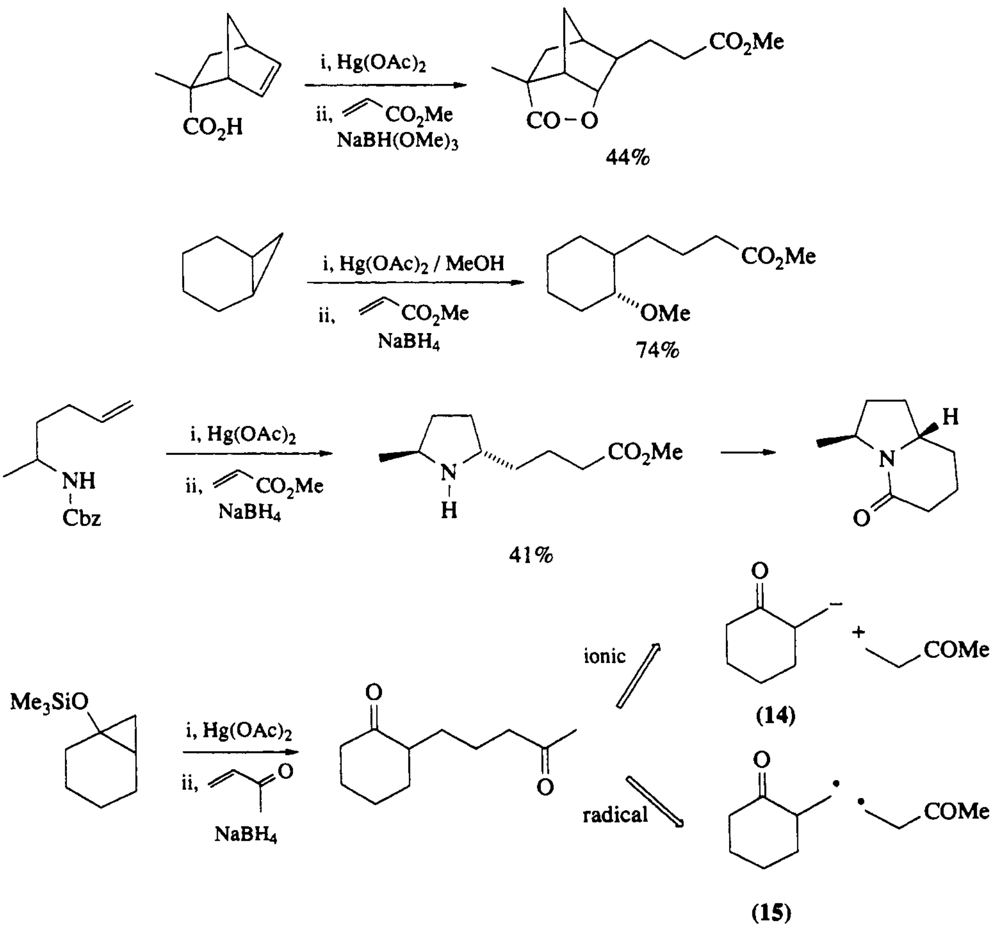
CO2H
i, Hg(OAc)2
ii, CO2Me
NaBH(OMe)3
CO2Me
CO-O
44%
i, Hg(OAc)2 / MeOH
ii, CO2Me
NaBH4
CO2Me
OMe
74%
NH
Cbz
i, Hg(OAc)2
ii, CO2Me
NaBH4
N
H
CO2Me
41%
H
N
O
Me3SiO
i, Hg(OAc)2
ii, O
NaBH4
O
O
ionic
radical
O
COMe
(14)
O
COMe
(15)

**Scheme 35**

### 4.1.6.1.2 The fragmentation method

While carbon and oxygen radicals add irreversibly to carbon–carbon double bonds, the fragmentation reaction is rapid (and often reversible) for elements like tin, sulfur, selenium and the halogens (Scheme 36). This elimination reaction can be very useful in synthesis if the eliminated radical Y· can either directly or indirectly react with a radical precursor to propagate a chain. Given this prerequisite, an addition chain can be devised with either an allylic or a vinylic precursor, as illustrated in Scheme 37. Carbon radicals are generated by the direct or indirect reaction with Y· and are removed by the β-elimination of Y·. Selectivity is determined by the concentration of the alkene acceptor and the rate of β-elimination (which is usually very fast).[127] The allylic variant (**16**) is more straightforward because the alkene substituent ($CH_2Y$) sterically (and perhaps also electronically) biases addition in the desired sense to form (**17**). For selectivity, the addition of R· to the allylic precursor (**16**) must of course be more rapid than radical–radical or radical–solvent reactions, but it must also be more rapid than addition of R· to the final product. In the vinylic variant, an activating group A must be introduced as in (**18**) to prevent the direct addition of R· to the carbon remote from Y.

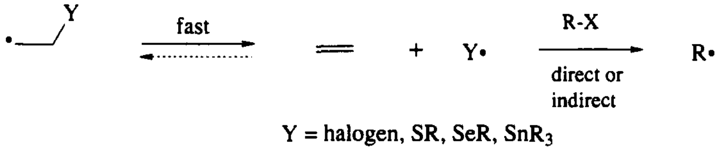

**Scheme 36** Fragmentation reactions

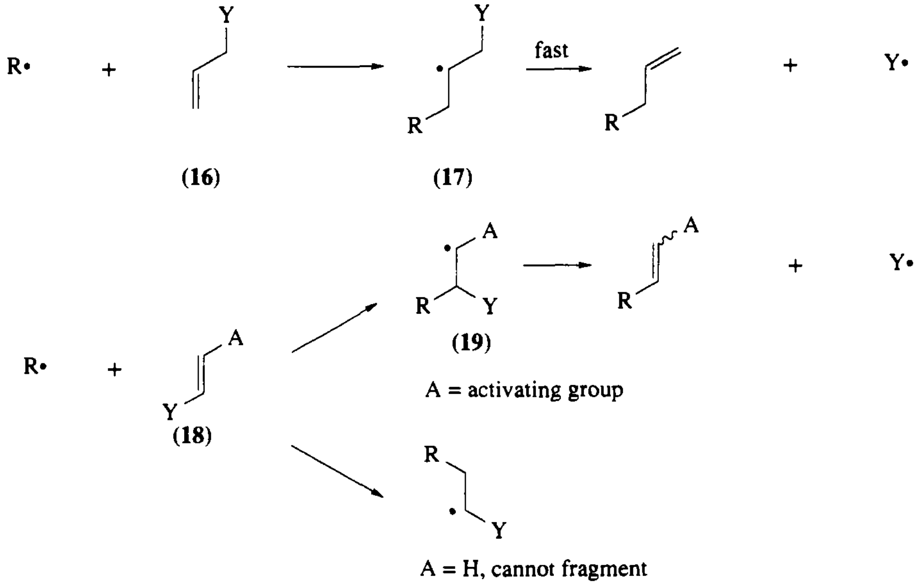

**Scheme 37** Allyl and vinyl fragmentation chains

A strategy that propagates the chain by β-elimination has important advantages over metal hydride methods that propagate chains by hydrogen transfer. Because the overall transformation is a substitution and not a reduction, there is no metal hydride reagent present in a fragmentation chain. The problem of reduction of an initial radical by the reagent prior to addition does not exist. Relatively unreactive acceptors can be used and the reactions can (and generally should) be conducted at high concentrations. The differentiation of the initial radical from the final radical is also not difficult because most fragmentation reactions are very fast unimolecular processes with which few bimolecular processes can compete;[127] that is, radicals (**17**) and (**19**) fragment much more rapidly than they add to the starting alkenes (**16**) and (**18**), even if these alkenes are present in high concentration. The trade-off in using the fragmentation strategy is that it is presently more limited in the type and location of substituents that can be introduced compared to the metal hydride method (see below).

### *(i) Allyl- and vinyl-stannanes*

The most popular fragmentation methods use allyl- or vinyl-stannane reagents. These reagents have all the advantages associated with using the trialkyltin radical (a reactive atom and group abstractor) as a chain transfer agent without the disadvantages of tin hydride (a reactive hydrogen donor). Several recent reviews provide sources of references in this field.[3-5]

Allylation reactions with allyltributylstannane[128] are now routine (Scheme 38) and have been used to advantage in complex synthetic endeavors. The experimental procedures developed by Keck are popular.[129] Thermal methods involve heating of allyltributylstannane (or allyltrimethylstannane), the radical precursor, and AIBN in degassed benzene for several hours. If lower temperatures are desired, AIBN can be omitted and the reaction can be irradiated through a Pyrex filter with a standard Hanovia lamp. Two equiv. of the stannane are typically employed and the initial concentration is about 0.5 M in radical precursor. The products are isolated simply by evaporation of the solvent and chromatography of the residue. Alternatively, methods to remove tin halides can be applied prior to work-up and chromatography. Keck has shown that this allylation is very powerful because it succeeds in complex synthetic settings, where more traditional synthetic methods would be inappropriate.[130]

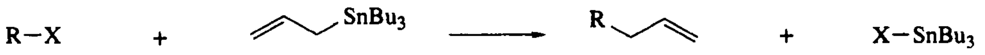

X = I, Br, SeR, $NO_2$, xanthate, activated SPh, Cl

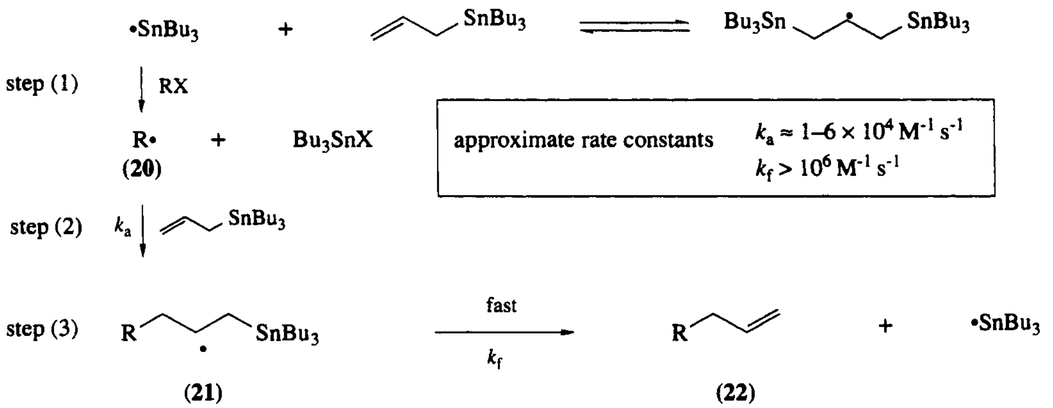
•SnBu3
+
SnBu3
Bu3Sn
SnBu3
step (1)
RX
R•
+
Bu3SnX
(20)
approximate rate constants
$k_a \approx 1\text{–}6 \times 10^4\ M^{-1}\ s^{-1}$
$k_f > 10^6\ M^{-1}\ s^{-1}$
step (2)
$k_a$
SnBu3
step (3)
R
SnBu3
fast
$k_f$
R
+
•SnBu3
(21)
(22)

Scheme 38

The mechanism of this transformation is outlined in Scheme 38 and each step has important features. In step 1, the tributyltin radical abstracts the radical precursor X. A possible side reaction, the addition of the tributyltin radical to the allylstannane, is much slower than comparable additions to activated alkenes. Even if this addition occurs, the stannyl radical is simply eliminated to regenerate the starting materials. Thus, for symmetric allylstannanes, this reaction is of no consequence. As a result, the range of precursors X that can be used in allylation is more extensive than in the tin hydride method. Even relatively unreactive precursors like chlorides and phenyl sulfides can be used if they are activated by adjacent radical-stabilizing groups.

That step 2 succeeds implies that there must be some activating effect of the tin on the rate of radical addition to the allylstannane.[131,132] Otherwise the product (**22**) would be of equal reactivity to the allylstannane reagent. However, this activation may only be modest enough so that addition of radical (**20**) to allylstannane is more rapid than its addition to benzene or its reaction with another radical; there are no rapid alternative reactions for (**20**) to undergo. Although there are no accurate rate constants yet available for $k_a$ in step 2, we have recently estimated the rate constant for addition of octyl radical to allyltributylstannane at 50 °C: $k_a \approx 1\text{–}6 \times 10^4\ M^{-1}\ s^{-1}$.[133] Likewise, there are no accurate rate constants known for the fragmentation reaction in step 3; however, this must be a very fast reaction.[127] In some cases (see below) fragmentation of a β-stannyl radical is even competitive with σ-bond rotation. It is very likely that $k_f > 10^6\ M^{-1}\ s^{-1}$. Addition of (**21**) to the starting allylstannane cannot possibly compete with fragmentation.

Illustrative examples of the kinds of transformations that can be conducted with allylstannane reagents are presented in Scheme 39. Example 1 emphasizes that activating groups on the alkene provide especially reactive partners for radicals.[134] Example 2 illustrates in the context of a prostaglandin synthesis that allylstannanes need not be paired with nucleophilic radicals.[135] Ambiphilic and electrophilic radicals should be equally useful, if not more. Example 3 illustrates that allenylations can be accomplished with the appropriate propargylstannane.[136] Finally, example 4 illustrates the kinds of new synthons and reagents that can be developed by combining this type of allylation with known transformations.[137] Silylstannane (**23**) becomes a useful reagent for the synthon (**24**).

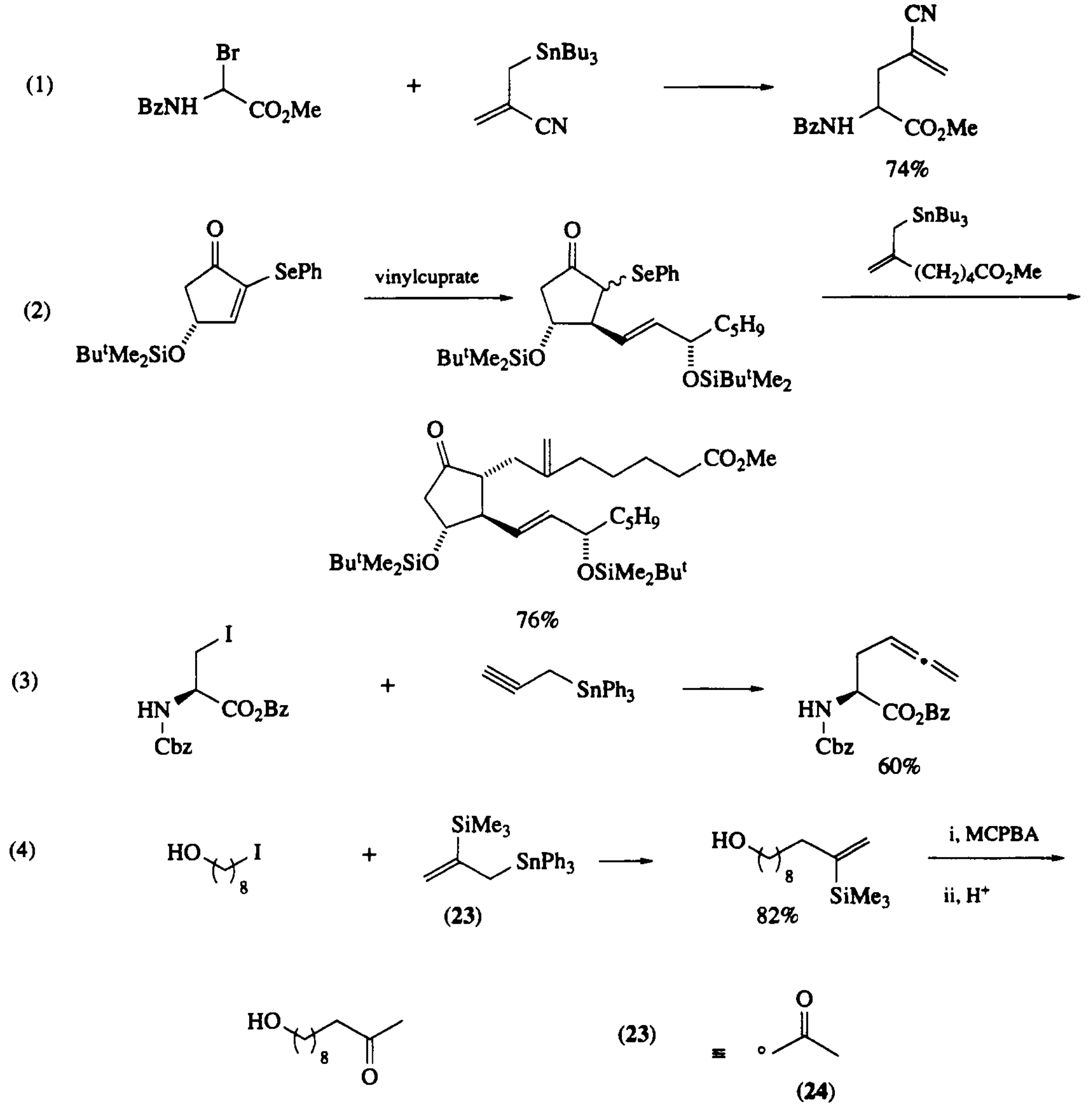

Scheme 39

A sequence of reactions that was recently reported by Hanessian and Alpegiani nicely illustrates how the allylstannane method is useful for functionalization of complex, sensitive substrates and, more generally, how stereochemistry can be controlled in radical addition reactions (Scheme 40).[138] Dibromo-β-lactam (**25**) can be monoallylated with a slight excess of allyltributylstannane and then reduced with tributyltin hydride to provide β-allylated β-lactam (**26**) (the acid salt of which shows some activity as a β-lactamase inhibitor). Stereochemistry is fixed in the reduction step: hydrogen is delivered to the less-hindered face of the radical. Alternatively, monodebromination, followed by allylation, now delivers the allyl group from the less-hindered face to provide stereoisomer (**27**). Finally, allylation of (**25**) with excess allylstannane produces the diallylated product (not shown).

At present, bimolecular allylation is limited to unsubstituted and 2-substituted allylstannanes (which are symmetrical so that addition and elimination of a tin radical are degenerate). 1-Substituted allylstannanes (for example, crotylstannane) are not useful reagents because the substituent decelerates the rate of the radical addition step below the useful limit.[139] The usefulness of 3-substituted allylstannanes has been limited by their relatively facile isomerization to the inert 1-substituted isomers under typical reaction conditions.[140]

A useful solution to the latter problem, introduced by Keck and Byers,[141] makes possible crotylation and isoprenylation. Irradiation of an allyl sulfide (**28**; 3 equiv.), a reactive radical precursor (**29**; 1 equiv.) and hexabutylditin (1.5 equiv.) produces substitution products (**30**) in good yields (Scheme 41). The

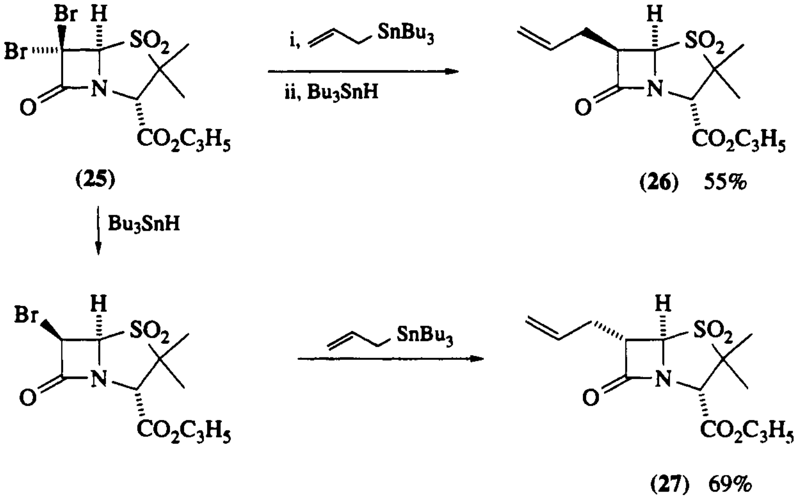

Scheme 40

mechanism is similar to that with an allylstannane except that the thiophenyl radical is ejected in the fragmentation step. This thiophenyl radical cleaves hexabutylditin to give $Bu_3SnSPh$ and the chain-carrying tributyltin radical. Reactive radical precursors must be used because addition of the tributyltin radical to (**28**) is a reasonably rapid competing reaction.

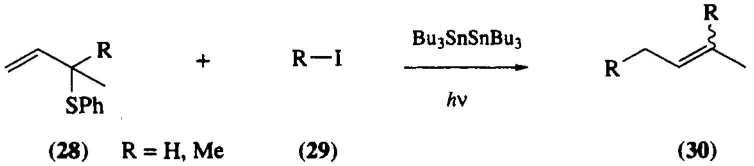

Scheme 41

Vinylstannanes can also be used in the fragmentation method provided that an activating group is introduced to accelerate and direct the addition of the radical to the carbon bearing the tin (Scheme 42). Useful activating groups include carbonyls,[142] phenyl,[143] phenylsulfonyl and diphenylphosphinyl.[144] Most preparative studies have reported the predominant or exclusive formation of the (*E*)-isomer of the product regardless of whether the starting stannane was (*E*) or (*Z*). However, careful studies by Russell[143] on the addition of alkyl radicals (generated from alkylmercury(II) chlorides) to the individual stereoisomers of β-stannylstyrene have shown that the stereochemistry of the vinylstannane precursor is retained to a significant extent in the product.[145] These studies demonstrate that fragmentations of β-stannyl radicals are very rapid. The success of these procedures again implies that there is at least a modest activating effect of the β-stannyl group on the rate of addition, otherwise the product would be equally reactive with the starting vinylstannane. Even so, β-stannyl groups must be decelerating relative to hydrogen and an excess of the acceptor is usually employed.

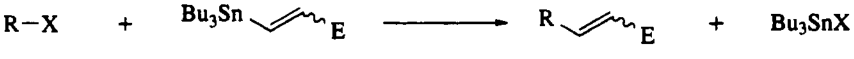

E = COR, Ph, $SO_2Ph$, $P(O)Ph_2$

Scheme 42

### *(ii) Other reagents*

A variety of other fragmentation reactions are potentially useful in the formation of carbon–carbon bonds, although none has yet shown the generality of the allyl- and vinyl-stannanes.[146] In addition to the use of allyl sulfides discussed above (Scheme 41), allylcobalts have also been employed.[147] Extensive studies by Russell have shown that a variety of activated vinyl (and propargyl) acceptors will propagate chains when alkylmercury(II) halides are used as radical precursors (Scheme 43).[148]

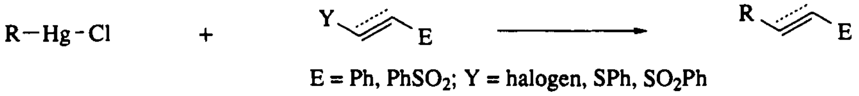

Scheme 43

#### 4.1.6.1.3 Thiohydroxamate esters (the Barton method)

One of the most important chain methods to conduct radical addition reactions that does not revolve around the chemistry of the trialkyltin radical is Barton's thiohydroxamate method.[149] This is presently the most generally useful method to conduct addition reactions of nucleophilic radicals to electrophilic acceptors that are not terminated by hydrogen atom transfer. In the thiohydroxamate method, radicals are generated and removed in the same process: the addition of a radical to a thiohydroxamate ester and the fragmentation of the ensuing intermediate. Thus, the lifetimes of radicals are limited by their rate constants for addition to the radical precursor and by the concentration of this precursor. Several pertinent reviews of the chemistry of thiohydroxamate esters are available;[3–5] a thorough, succinct review by Crich is an excellent starting point for citations to the original literature.[150] In addition to serving as radical precursors for C—C bond-forming reactions, these esters are excellent precursors for the decarboxylative functionalization of carboxylic acids with a variety of heteroatomic groups. This aspect of thiohydroxamate chemistry is described in Volume 7, Chapter 5.4.

Scheme 44 summarizes an addition reaction by the Barton method. Thiohydroxamate esters (**32**) are readily prepared and isolated, but, more typically, they are generated *in situ*. Experimental procedures have been described in detail[148,151] and often entail the slow addition of an acid chloride to a refluxing chlorobenzene solution of the readily available sodium salt (**31**), dimethylaminopyridine (DMAP, to catalyze the esterification), and excess alkene. The products are usually isolated by standard aqueous work-up and chromatographic purification.

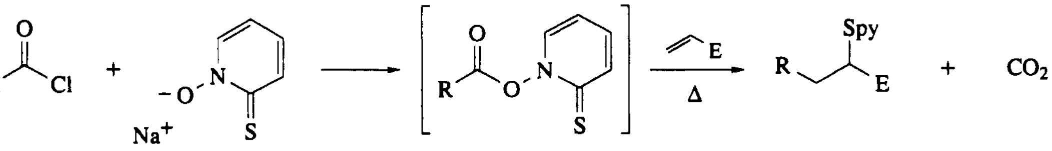

Scheme 44 The Barton method

The basic transformation that underlies the Barton method is outlined in Scheme 45, steps 1 and 2.[152] Thermolysis in refluxing toluene or photolysis with a sunlamp rapidly converts a thiohydroxamate ester (**32**) to the decarboxylated pyridyl sulfide (**33**). This pyridyl sulfide is formed by addition of an alkyl radical R· to the thiohydroxamate (**32**) followed by fragmentation of (**34**) as indicated. In the planning of addition reactions by the Barton method, it is usually assumed that the addition step 1 is rate limiting. However, there is now evidence that step 1 may sometimes be reversible and step 2 may be rate limiting.[153]

In the presence of a reactive alkene acceptor, the intermediate radical R· can be intercepted by addition to a reactive alkene (step 3) prior to reaction with the starting thiohydroxamate (step 2). If the adduct radical (**35**) then adds to the thiohydroxamate (step 4) more rapidly than it adds to another molecule of alkene, a successful chain addition reaction results. In practice, a wide variety of addition reactions can be conducted by this method in yields that range from 30–90%.

Considerations for synthetic planning are remarkably similar to the tin hydride method. The initial radical can either add to the alkene or add to its own precursor (**32**). To maximize the addition, it is advisable to use a reactive alkene (typically in excess) and to keep a relatively low concentration of the thiohydroxamate (**32**); hence the slow addition of the acid chloride. At present, rate constants for the addition of a primary and a tertiary alkyl radical to a thiohydroxamate are known (Scheme 46)[38,40] and these are useful in selecting alkene acceptors and in planning reaction conditions.

Like the tin hydride method, this addition succeeds because of differences in reactivity of the starting and the adduct radicals towards the alkene acceptor.[154] Unlike the tin hydride method, there is a loss of

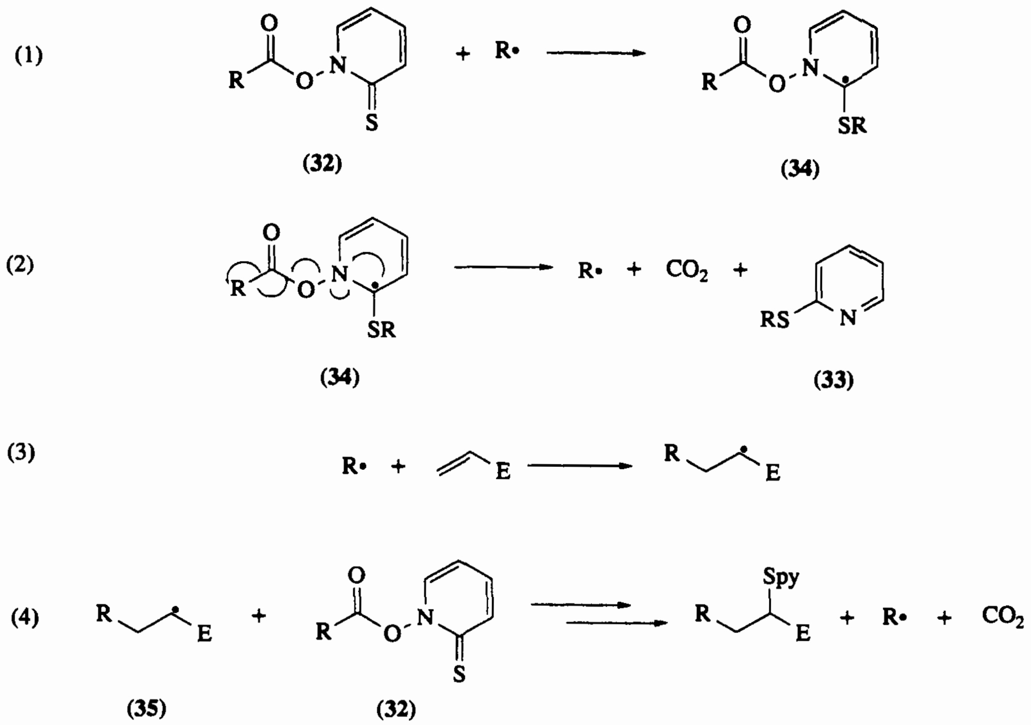

Scheme 45

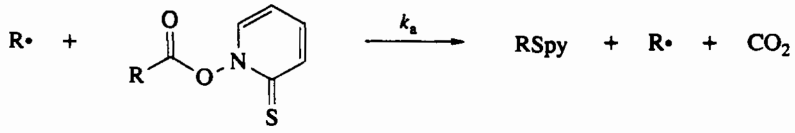

R = primary alkyl $k_a \approx 1\times10^6\ M^{-1}\ s^{-1}$
R = tertiary alkyl $k_a \approx 5\times10^5\ M^{-1}\ s^{-1}$

Scheme 46 Rates of addition to thiohydroxamates

one carbon in the radical precursor (as carbon dioxide). Also unlike the tin hydride method, the addition reaction is not terminated by hydrogen atom transfer. Instead, the thiopyridyl group, a useful precursor for several other functionalities, is introduced. Several addition reactions, along with subsequent transformations of the adducts, are compiled in Scheme 47.[155–158]

Fragmentation reactions can also be executed within the framework of the thiohydroxamate method, as illustrated in Scheme 48. Addition of acid chloride (**36**) to a mixture of activated allyl sulfide (**37**) and sodium salt (**31**) provides allylated product (**38**) in 75% yield. The activating group insures that the initial radical adds to the acceptor more rapidly than to the thiohydroxamate. Rapid fragmentation of the resulting intermediate provides the product (**38**) and the thiobutyl radical. This last radical propagates the chain by addition to the starting thiohydroxamate.

Loss of a carbon atom from the precursor need not always result. Barton and Crich have introduced a related procedure based on the chemistry of mixed oxalates, an example of which is provided in Scheme 49.[159] Double decarboxylation is involved in the decomposition of oxalate precursors, such as (**39**). Unfortunately, there are indications that this method may to be limited to tertiary alcohols; one secondary alcohol derived mixed oxylate did not fragment completely to the alkyl radical.

In the thiohydroxamate method, activated acceptors are required for successful addition reactions because the thiohydroxamate is relatively reactive towards alkyl radicals. An ingenious method to circumvent this problem has recently been communicated by Zard.[160] Photolysis of benzyl xanthate (**40**) with a UV lamp in the presence of *N*-methylmaleimide (NMM) provided the adduct (**41**) in 40% yield, as illustrated in Scheme 50. In this reaction, the competition reaction between the desired addition to the acceptor and the addition to the precursor still exists. However, addition to the precursor is reversible and,

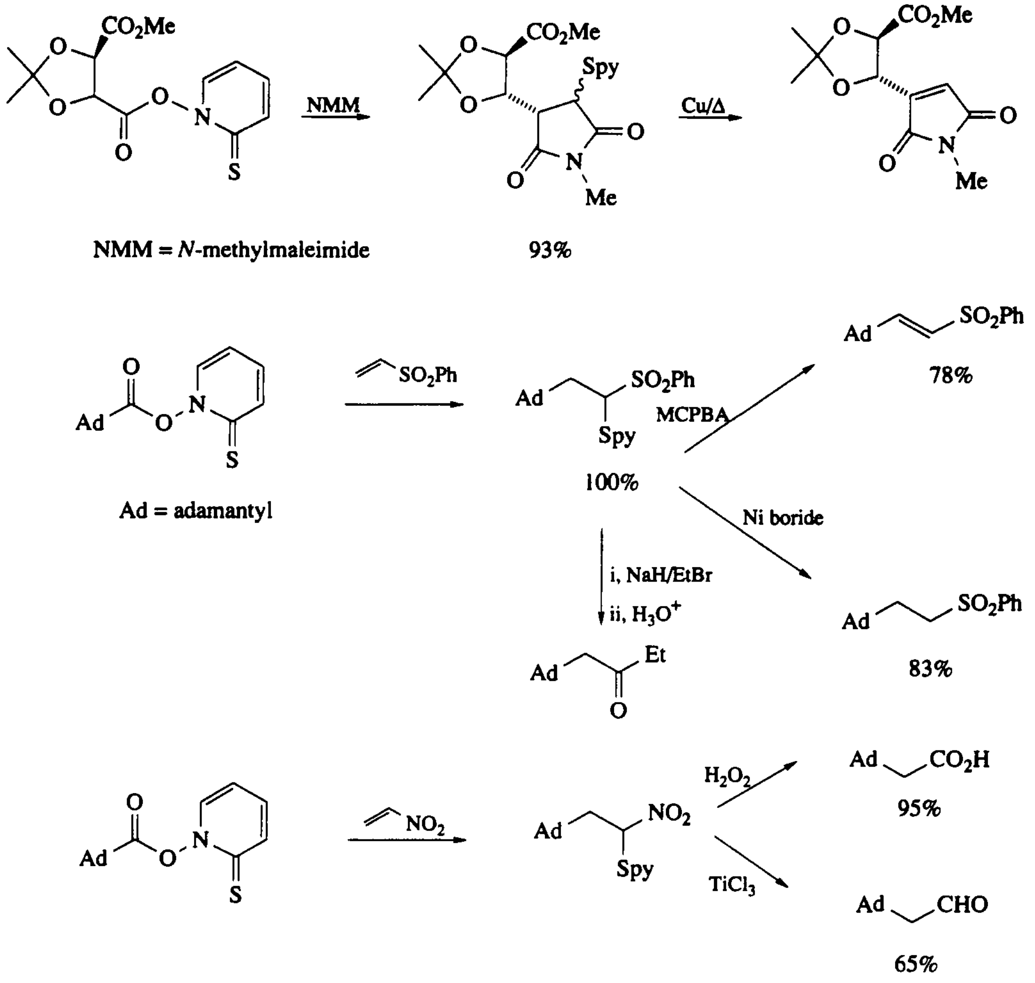
CO2Me
NMM
Spy
Cu/Δ
Me
NMM = N-methylmaleimide
93%
SO2Ph
Ad
MCPBA
Spy
100%
78%
Ad = adamantyl
Ni boride
i, NaH/EtBr
ii, H3O+
Et
83%
NO2
H2O2
CO2H
95%
TiCl3
CHO
65%

Scheme 47

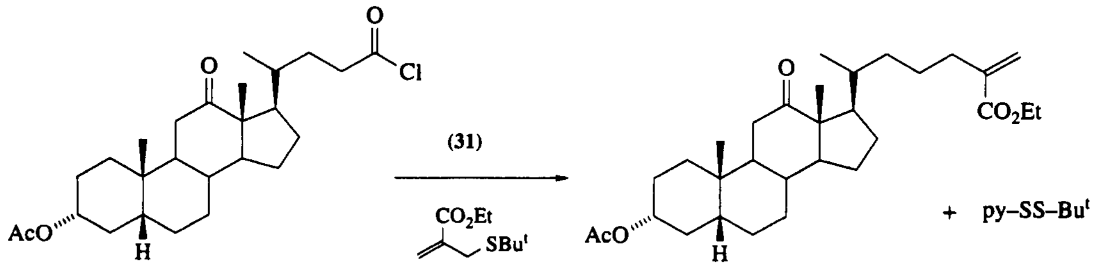
(31)
CO2Et
SBu'
AcO
H
CO2Et
+ py-SS-Bu'

(36) (37) (38) 75%

Scheme 48

by the design of the method, it can only regenerate the starting radical (fragmentation to generate the unstable methyl radical is not rapid). One potential problem is that the product (**41**) contains the same reactive functional group as the starting material (**40**) and it is continuously recycled to the radical pool. This recycling may result in a reduced yield.

This problem is not so severe when acyl xanthates are used as precursors because these substrates absorb in the visible region, while the products do not (however, the products might still be recycled to the radical pool by radical addition–elimination). Visible light photolysis of benzoyl xanthane (**42**) and allyl acetate provides (**43**) in 60% yield. Standard (ionic) β-elimination of the xanthane is a facile reaction that gives (**44**). When the tertiary acyl xanthane (**45**) is irradiated in the presence of *N*-benzylmaleimide

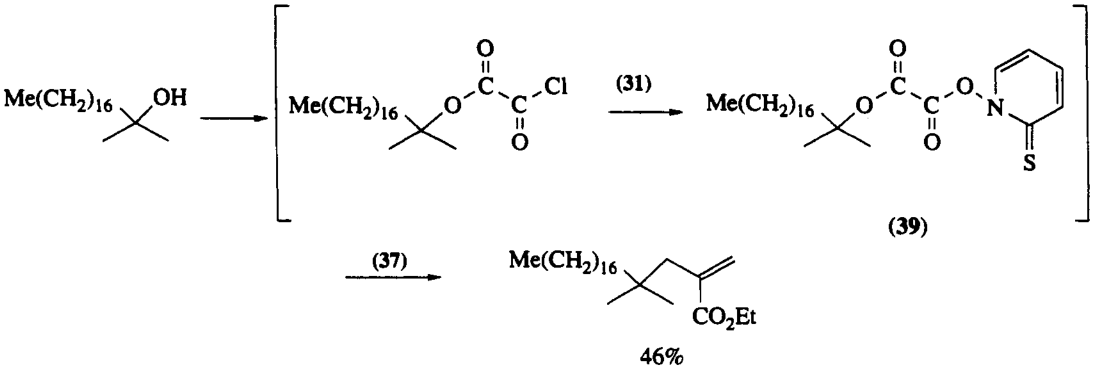
Me(CH2)16
OH
Me(CH2)16
Cl
(31)
(39)
(37)
CO2Et
46%

Scheme 49

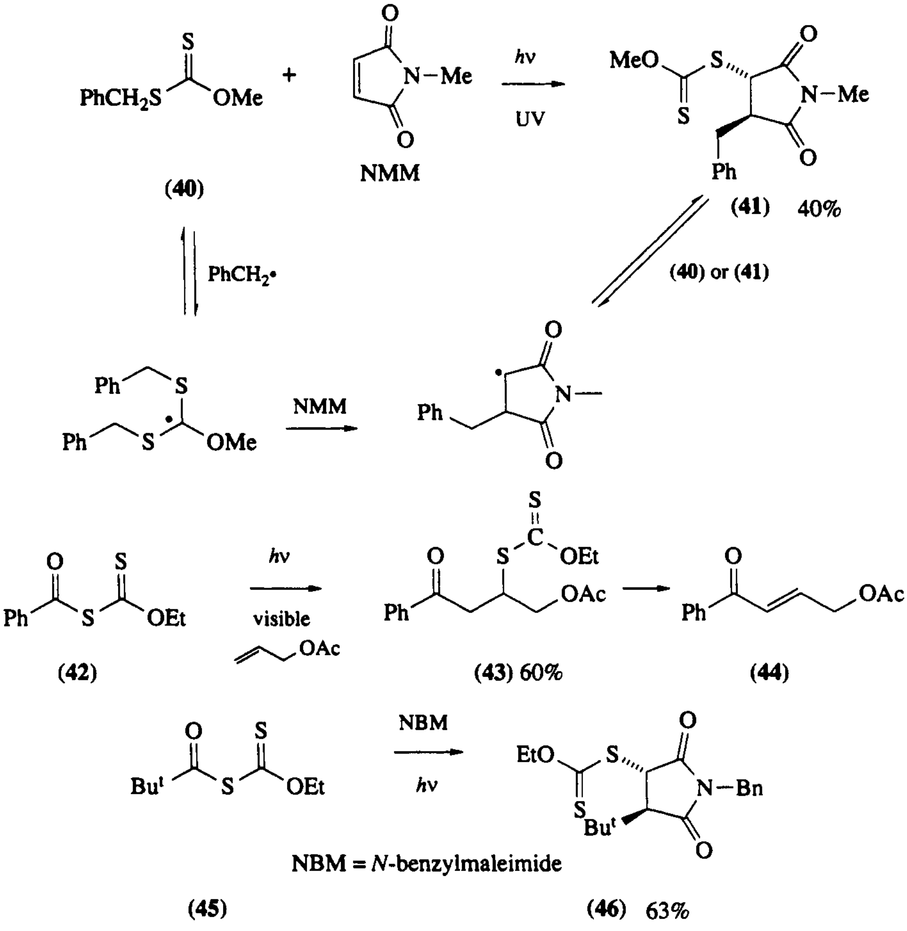
PhCH2S
OMe
(40)
NMM
hv
UV
MeO
N−Me
Ph
(41) 40%
PhCH2•
(40) or (41)
NMM
OEt
(42)
hv
visible
OAc
(43) 60%
(44)
Bu'
NBM
hv
EtO
N−Bn
NBM = N-benzylmaleimide
(45)
(46) 63%

Scheme 50

(NBM), decarbonylated adduct (**46**) is isolated in 63% yield. The initially formed acyl radical decarbonylates to give the *t*-butyl radical (in contrast, aroyl radicals are much more reluctant to decarbonylate). Now a true competition again exists because addition of the *t*-butyl radical to the precursor is not necessarily degenerate. Nonetheless, addition to the acceptor is more favorable and a useful yield is obtained. Although the scope and limitations remain to be determined, this new method shows the promise of being especially useful for conducting reactions of stabilized radicals and aroyl radicals.

#### *4.1.6.1.4 Atom transfer reactions (the Kharasch method)*

The addition of a single-bonded reagent across a multiple bond is one of the fundamental reactions of organic radicals. The basic principles of this reaction were first advanced by Kharasch in pioneering studies on the mechanism of the peroxide-initiated anti-Markovnikov addition of hydrogen bromide to alkenes.[1] In the atom transfer method, the generation and removal of radicals are coupled and occur in the key atom transfer step. Compared to other methods, the atom transfer method provides unique options for synthetic reactions. But there are also important limitations. Recently, there has been a renewed interest in the application of the characteristics of atom transfer reactions in synthesis and new developments have been reviewed.[5,161]

The basic mechanism for the addition of a reagent containing a C—X bond across an alkene acceptor is outlined in Scheme 51. In the formation of C—C bonds, the group X is usually limited to one of the univalent atoms (listed in increasing order of reactivity): Cl, H, Br, I. Many more groups X can be used in forming C–heteroatom bonds because of the weak nature of most interheteroatom bonds (Section 4.1.8). The first propagation step is the addition of the carbon radical (**47**) to an alkene. The adduct radical (**48**) then abstracts the univalent atom X from the starting reagent to transfer the chain. That the atom donor and the radical precursor are the same molecule (**49**) is a great advantage because the reaction of the initial radical (**47**) with the atom donor is degenerate (and often slow anyway because it is thermoneutral). Compare this to the tin hydride or thiohydroxamate methods, where reactions of the starting radical with the radical precursor can efficiently compete with the desired addition reaction. Thus, the atom transfer method should be ideal to conduct relatively slow addition reactions because there is no competing trap for the starting radical (of course it must still be trapped by the alkene faster than radical–radical or radical–solvent reactions). The limitations in the atom transfer method are imposed by step 2. This step must be sufficiently rapid, otherwise the adduct radical (**48**) can add to another molecule of acceptor as shown in step 3. For an atom transfer reaction to be rapid, it is usually important that it be exothermic: the more exothermic the better. Thus, the adduct radical (**48**) must be a more reactive (that is, less resonance stabilized) radical than the starting radical (**47**). This increase in radical reactivity is made possible because the gain in energy associated with conversion of a π-bond to a σ-bond in the addition step often offsets any loss in energy associated with decreased resonance stabilization of the product radical.

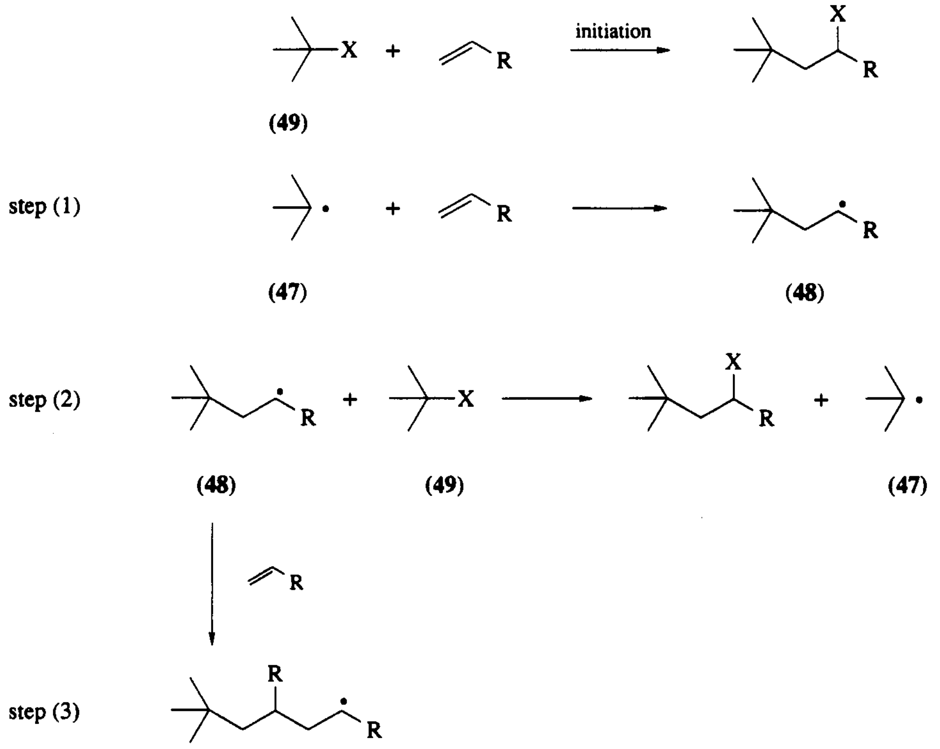

**Scheme 51**

To summarize, an atom transfer sequence has two basic requirements: (i) a rapid, exothermic addition, cyclization or fragmentation reaction must convert a starting radical into a more reactive (less resonance stabilized) counterpart; and (ii) atom transfer from the radical precursor to the adduct must occur more rapidly than any other competing reaction. Considering these requirements, one can conclude that the atom transfer method will not be particularly useful for conducting addition reactions of nucleophilic radicals to electron deficient alkenes because most electron-attracting groups that are used to activate alkenes also stabilize radicals. Thus, although addition might succeed, atom transfer will fail because the adduct radical is more stable than the starting radical. In contrast, the atom transfer method should be very useful for the additions of ambiphilic and electrophilic radicals (which are usually resonance-stabilized) to alkyl-substituted alkenes. Thus, the tin hydride and the thiohydroxamate methods are nicely complemented by the atom transfer method. In the former methods, it is the rate of the addition step that is important for success and not the relative stabilities of the starting and adduct radicals; in the atom transfer method, it is precisely the reverse.

### *(i) Hydrogen atom transfer additions*

The addition of a C—H bond across a C—C multiple bond has often been applied to the synthesis of simple organic molecules, but has rarely been used in complex synthetic settings.[3,5,162] This is because the abstraction of hydrogen atoms from C—H bonds by carbon-centered radicals is a relatively slow process and reaction conditions must be designed around this serious limitation (Scheme 52). To serve as a hydrogen donor, a molecule should have one C—H bond that is significantly weaker than the rest. Almost any resonance-stabilizing group can serve as an activator for an adjacent C—H bond. In classical reaction conditions, a peroxide initiator is added slowly to an excess of the radical precursor and the acceptor (sometimes the acceptor is also added slowly with the initiator). There is usually no solvent other than the excess of the precursor and reaction temperatures over 100 °C often give the best results. Such conditions favor hydrogen transfer over telomerization of the initial adduct. Even so, the chains are very short in such processes because of the inherent inefficiency of hydrogen transfer between carbon radicals. Large amounts of initiator are required and the formation of short telomers as by-products is very common. The products are often isolated by fractional distillation or chromatography.

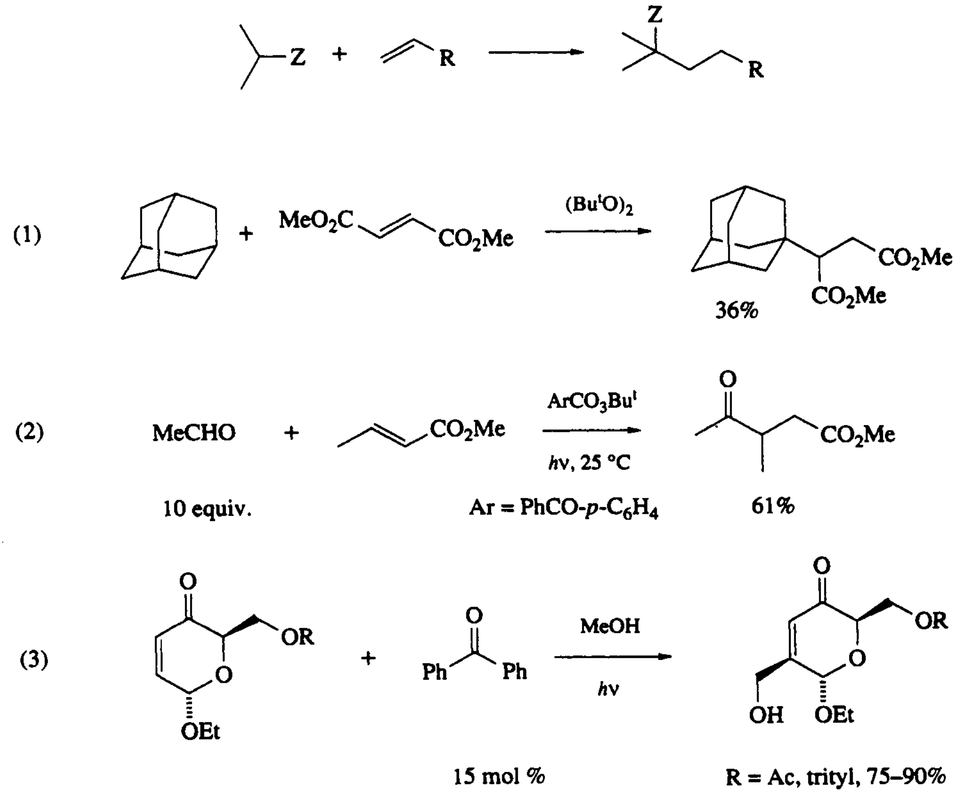

Scheme 52

Scheme 52 provides a sample of the types of reactions that have recently been conducted under a variety of different conditions. Example (1) illustrates the classical conditions,[163] while example (2) shows that modified initiators that permit low temperature reactions may prove beneficial.[29] Finally, example (3) illustrates that the photochemical addition of alcohols (and also acetals) to enones in the presence of benzophenone is a very useful preparative procedure.[164] Here, the carbinyl hydrogen is abstracted by an excited state benzophenone molecule rather than a peroxy radical.[165]

The problem of inefficient hydrogen atom transfer to carbon-centered radicals has been circumvented by Maillard as outlined in Scheme 53.[166] Heating of excess methyl propionate with allyl *t*-butyl peroxide provides a mixture of adducts in which (**49**) is the major component. In this reaction, the carbon-centered adduct radical (**50**) reacts in an intramolecular homolytic substitution (group transfer) reaction with a neighboring O—O bond. The highly reactive (but relatively unselective) alkoxy radical that is generated in this step then serves as the hydrogen abstractor. A net addition of a carbon and an oxygen across a C—C double bond is accomplished in modest yield. The synthetic price to pay is that the peroxide or perester must be built into one of the reagents.

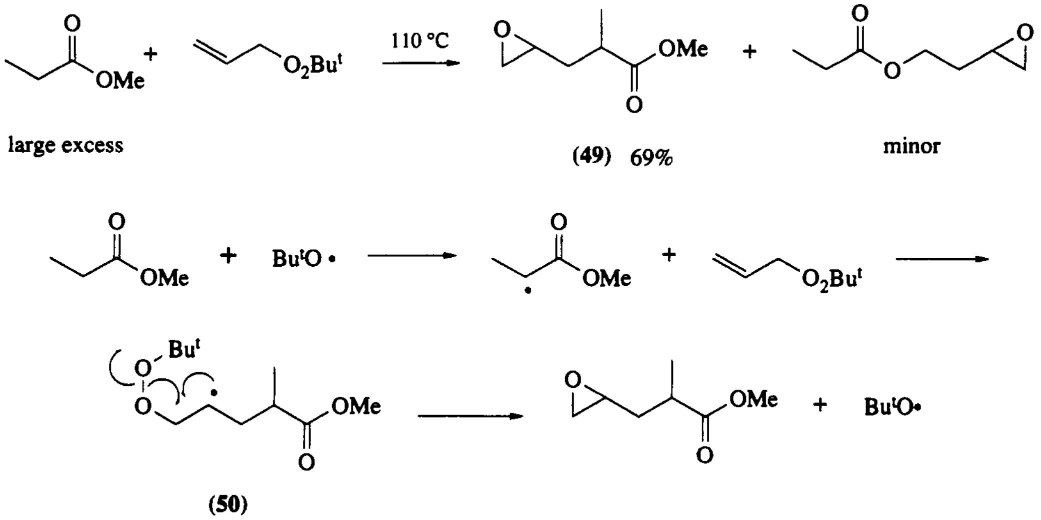

(**49**)

(**50**)

Scheme 53

Because it is inexpensive and very simple, the hydrogen atom transfer method is useful for the preparation of many kinds of simple molecules. Its use in complex synthetic tasks is limited because the yields are often modest, a large excess of the H-donor is required, and chemoselectivity is certain to be poor in polyfunctional molecules with several relatively weak C—H bonds. It can be best employed to advantage when the addition of a relatively small molecule to a complex acceptor is required.

### *(ii) Halogen atom transfer additions*

Replacement of a C—H bond by a C—halogen bond may have relatively little effect on the overall thermodynamics of an atom transfer reaction, but it can dramatically influence the kinetics. While C—Cl bonds are often poorer atom donors than corresponding C—H bonds, C—Br and C—I bonds are dramatically better. Thus the introduction of a halogen can improve an atom transfer reaction by: (i) ensuring that the generation of the radical is site selective; (ii) allowing more practical reaction conditions by accelerating the atom transfer step; and (iii) providing a functional group handle (the C–halogen bond in the product) for subsequent synthetic transformations.

The addition of a polyhaloalkane across an alkene is a mild and practical way to form a carbon–carbon bond and some representative examples are shown in Scheme 54.[159,167–169] Polyhaloalkyl radicals are regarded as electrophilic and are usually paired with electron rich alkenes. The halogen substituents also accelerate atom transfer by stabilizing the starting radical relative to the adduct radical. The addition reactions of polyhaloalkanes are often dramatically facilitated and become very practical in the presence of certain metal additives[170] including complexes of palladium,[171] aluminum,[167] ruthenium,[172,173] samarium[168] and others. However, the function of the metal is not always clear. It may simply initiate an atom transfer chain or provide a reactive halogen source (through a metal–halogen intermediate) or provide a source of metal-complexed radicals or even initiate a catalytic cycle that does not involve radical intermediates.

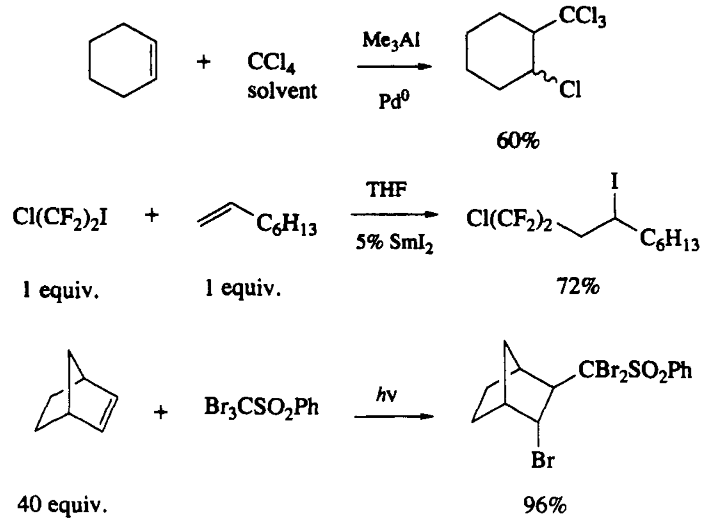

Scheme 54

The most common and useful additives are copper(I) salts (such as CuCl), which produce high yields of 1:1 adducts in many cases.[174] Several examples from the extensive work of the Ciba-Geigy group in Basel are compiled in Scheme 54, with an emphasis on subsequent conversions of the highly functionalized products into important heterocycles.[175] These procedures are very simple and have been conducted on a multigram scale. Typically, the halogen component and the acceptor are heated without solvent at 110 °C in the presence of 1–10% CuCl. After several hours, the copper salts are removed by filtration and the product is isolated by distillation. It is clear that the copper additive behaves as more than just an initiator; the additions of electrophilic radicals to electron deficient alkenes like those shown in Scheme 54 would not be likely to succeed otherwise.

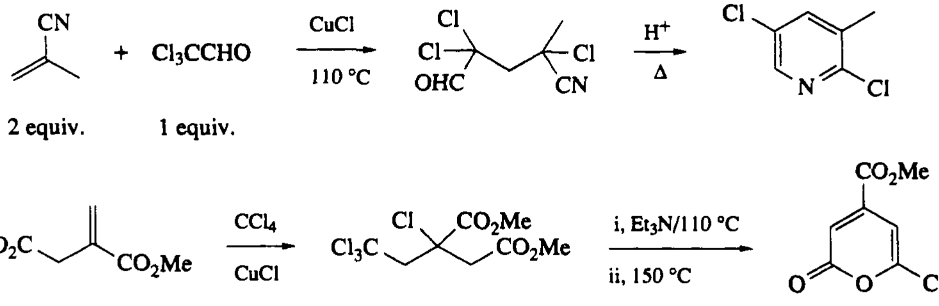

Scheme 55

The move away from polyhalogenated precursors to simple monohalogenated compounds has recently accelerated. One need only retain a radical-stabilizing group to promote atom transfer and to substitute a reactive iodine atom as the donor halogen (with radicals possessing two stabilizing groups, bromine can often be used). From the examples shown in Scheme 56, it is beginning to appear as if the additions of iodocarbonyls across multiple bonds will be a very general reaction.[58,176–178] The γ-iodocarbonyl adducts are versatile precursors of several different functional groups and the subsequent transformations outlined in Scheme 56 are often conducted *in situ*.

These reactions are often initiated by sunlamp photolysis of the iodide and the acceptor in benzene containing 10% hexabutylditin.[175,179] Because the iodine donor is the radical precursor, high reaction concentrations are beneficial rather than detrimental: 0.3 M is a typical value. Initiation can occur either directly by photolytic cleavage of the C—I bond or indirectly by cleavage of the Sn—Sn bond (the resulting tin radicals will abstract iodine from the precursor). An important function of the ditin is as a trap for iodine (either atomic or molecular), which is invariably produced when iodides are photolyzed but which strongly suppresses radical chains. Isolated yields for these bimolecular reactions are rarely higher than 80% but often exceed 50%. By using a slight excess of either the iodide or the alkene (1.5 to 2 equiv.), a significant increase in yield is often observed.

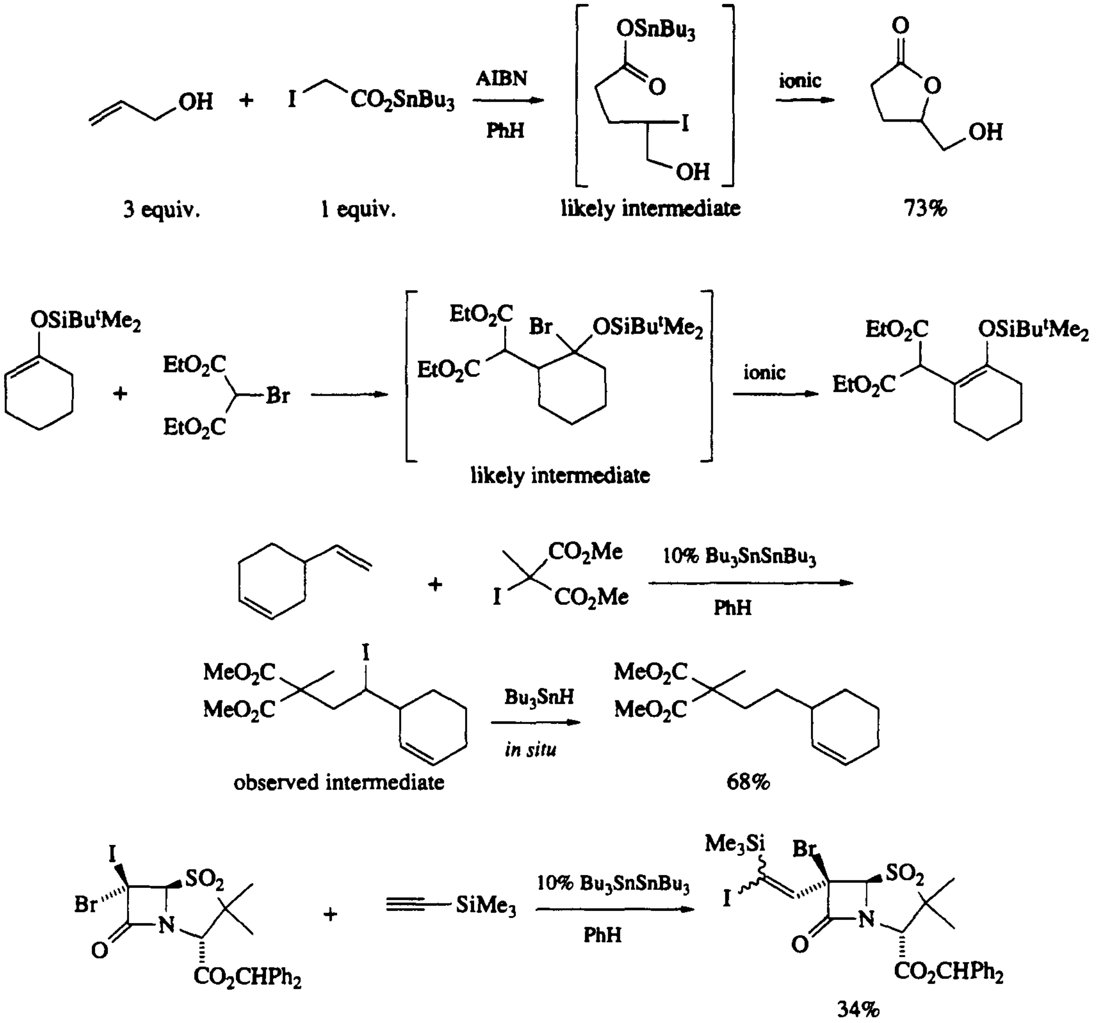
AIBN
PhH
ionic
3 equiv.
1 equiv.
likely intermediate
73%
likely intermediate
10% Bu₃SnSnBu₃
PhH
Bu₃SnH
*in situ*
observed intermediate
68%
10% Bu₃SnSnBu₃
PhH
34%

**Scheme 56**

Rate constants for the abstraction of halogens by primary alkyl radical from representative halocarbonyls have recently been measured and they are very high (considerably higher than the rate constant for the transfer of hydrogen from tin hydride, for example).[180] It is no wonder that telomerization is not as big a problem as in hydrogen transfer reactions. Of greater concern is the rate of the initial addition step; yields decrease as this step slows. A common by-product is the reduced iodide resulting from hydrogen transfer from the medium, and the yield of this reduction product increases as the efficiency of the addition step decreases.

It is more difficult to conduct the addition reactions of nucleophilic radicals to electron poor alkenes because the resulting atom transfer steps are often endothermic and are too slow to propagate chains, even with iodides. An exception is illustrated in Scheme 57: resonance-stabilized vinyl radicals (especially if they are secondary or tertiary) are reactive enough to abstract iodine from alkyl iodides.[178]

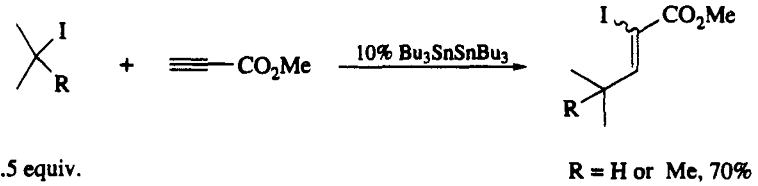
10% Bu₃SnSnBu₃
2.5 equiv.
R = H or Me, 70%

**Scheme 57**

### *(iii) Group transfer of organoboranes*

There is at least one preparatively useful method for conducting addition reactions by using group transfer (rather than atom transfer). The transfer of alkyl substituents from organoboranes to enones is a chain reaction that was discovered by Brown in the late 1960s.[181] Since that time, the reaction has been neglected by synthetic practitioners; however, it has good synthetic potential and a recent development promises to significantly expand its current scope.

In the basic reaction, outlined in Scheme 58, an organoborane (**51**; usually formed by hydroboration of an alkene with diborane) is admixed with an enone or enal and the solution is exposed to atmospheric oxygen to initiate the reaction. After aqueous work-up, adducts (**52**) are isolated in good to excellent yield, even with some β-substituted acceptors. The proposed chain mechanism involves addition of an alkyl radical to the enone followed by (stepwise or concerted) group transfer of the organoborane to give a stable enol borane (**53**).[182] This product is hydrolyzed on work up. There are two main limitations to this method: (i) it fails with certain good radical traps like unsaturated esters (presumably because the adduct radicals bearing these substituents telomerize more rapidly than they add to the borane); and (ii) only one of the three initial borane substituents is transferred. The latter limitation can be circumvented for secondary- and tertiary-radicals by adjusting the substituents on boron as outlined in Scheme 59.[183] This transformation provides an alternative to the usual tactic of conversion of the borane to a halide or mercury(II) halide for use in a metal hydride mediated addition.

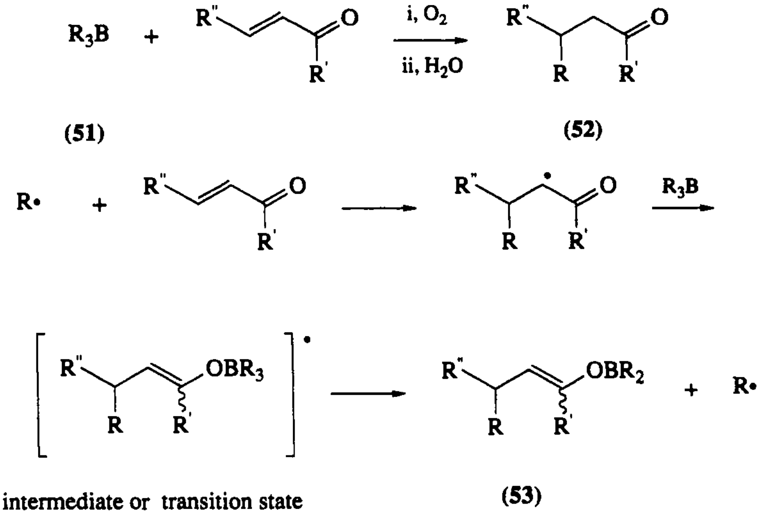

Scheme 58

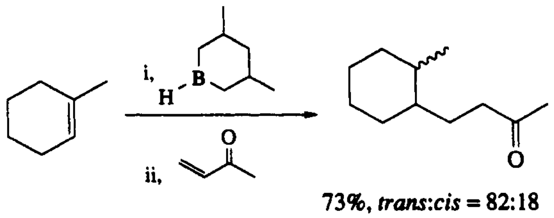

Scheme 59

A beautiful extension of this reaction has recently been communicated by Nozaki, Oshima, and Utimoto.[184] These workers simply admixed *t*-butyl iodide (3 equiv.), benzaldehyde (1 equiv.), methyl vinyl ketone (1 equiv.) and triethylborane (1 equiv.) in benzene (Scheme 60). After 5 min at 25 °C, the reaction was subjected to standard extractive work-up and the crude product was purified by chromatography to give (**54**) in 63% yield. If methanol is substituted for benzaldehyde, the protonated product (**55**) is isolated in 79% yield. Although enones are equivalents of synthon (**56**), such a direct coupling of radical and ionic reactions had not been achieved previously.

The mechanism outlined in Scheme 61 is probably responsible for the observed transformation. Adduct radicals (**57**) react with the triethylborane to form the enol boronate (**58**) and release an ethyl radical. The enol borate is then trapped in a standard aldol reaction. The ethyl radical partitions between

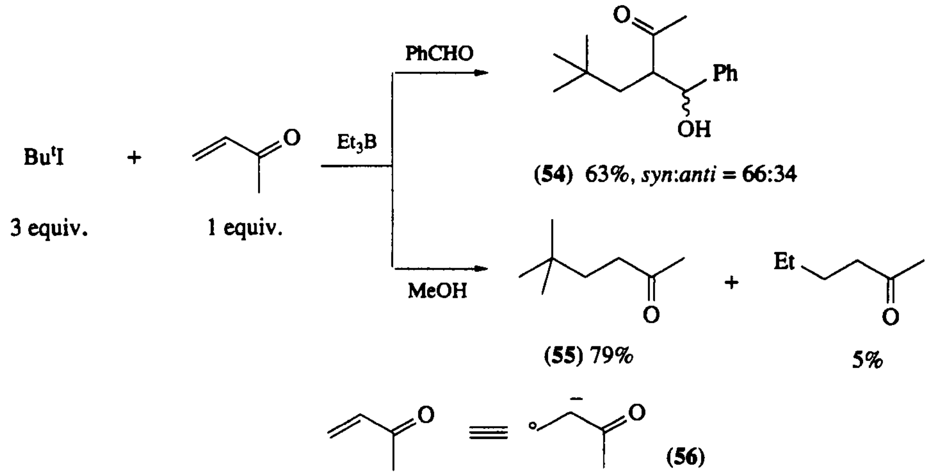

**Scheme 60**

addition to the acceptor (a minor pathway) and abstraction of iodine from *t*-butyl iodide (the major pathway). This so-generated *t*-butyl radical (which is more reactive than the ethyl radical) adds to the enone to continue the chain. Accurate rate constants for the reaction of octyl radical (a good model for ethyl radical) with alkyl iodides are now available.[185] By comparing the estimated rate of iodine transfer (step 2) to that of addition to methyl vinyl ketone, one can plan successful reaction conditions to ensure a favorable partitioning in step 2.[186] This use of a reactive, easily generated alkyl radical (Et·) as a 'relay' in a reaction with an iodide to translocate a radical site has many potential applications, and it was first applied to synthesis by Minisci in addition reactions to protonated aromatics (Section 4.1.7.2).

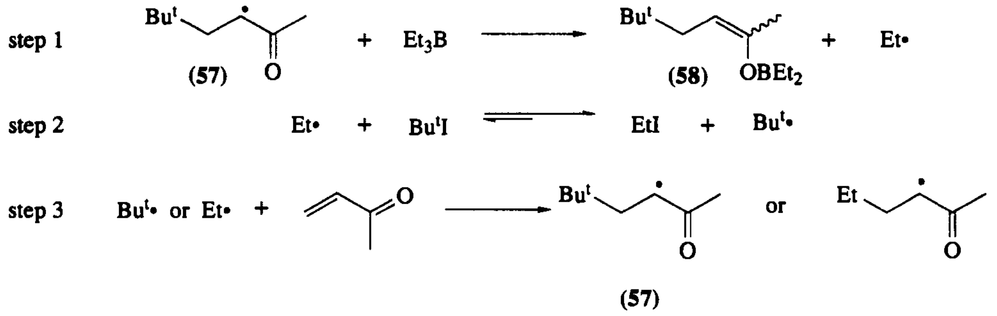

**Scheme 61**

*(iv) Meerwein arylation*

The Meerwein arylation is at least formally related to the atom transfer method because a net introduction of an aromatic ring and a chlorine across a double bond is accomplished (Scheme 62). Facile elimination of HCl provides an efficient route to the kinds of substituted styrenes that are frequently prepared by Heck arylations. Standard protocol calls for the generation of an arene diazonium chloride *in situ*, followed by addition of an alkene (often electron deficient because aryl radicals are nucleophilic) and a catalytic quantity of copper(II) chloride. It is usually suggested that the copper salt operates in a catalytic redox cycle, reducing the diazonium salt to the aryl radical as $Cu^I$ and trapping the adduct radical as $Cu^{II}$.

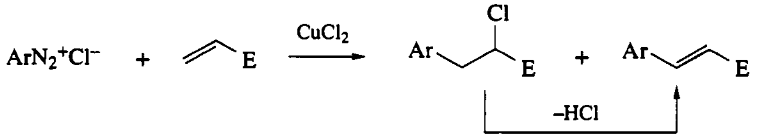

**Scheme 62**

Preparatively useful yields are frequently obtained and a wide variety of alkene activators have been used. Authoritative reviews provide more details for this reaction, which is probably the most general method available for the addition of aryl radicals across carbon–carbon double bonds.[187,188]

### 4.1.6.2 Nonchain Methods

Although chain methods have been the foundation of the recent resurgence of radical reactions in synthesis, many of the earliest preparatively useful radical addition reactions were based on nonchain processes. Of late, such nonchain processes have regained importance.

Nonchain reactions do not couple the formation and removal of carbon-centered radicals the way chain processes do. Instead of needing only a small quantity of initiator, nonchain additions need a method to generate and remove stoichiometric quantities of radicals. Generation of radicals poses special problems due to the transiency of radicals: if high concentrations of radicals are generated, the rates of radical–radical reactions will surpass those of radical–molecule reactions and addition reactions will not be possible. Removal of radicals poses the usual selectivity problem: how is an adduct radical removed without intercepting an initial radical prior to addition? Nonchain methods can be classified into two groups by the method in which the radicals are removed from the reaction: radical–radical coupling and redox.

#### *4.1.6.2.1 Radical–radical coupling*

In chain methods, it is important to avoid radical–radical reactions. However, radicals that are generated in a stoichiometric quantity by bond homolysis can be productively removed by radical–radical coupling. Despite the inherent problems in controlling reactions that occur at rates near the diffusion-controlled limit, radical–radical coupling reactions can be selective and preparatively useful.

The addition reactions to capto-dative alkenes developed by Viehe[189] illustrate one way to employ selective radical–radical coupling in product formation (Scheme 63).[190] Heating of cyclopentanone, capto-dative alkene (**59**) and a stoichiometric amount of di-*t*-butyl peroxide gives dimer (**60**) in 46% yield. Initial radicals are generated by slow cleavage of the peroxide O—O bond and subsequent hydrogen abstraction from cyclopentanone. Under the conditions of the reaction, these radicals (**61**) add to the reactive alkene (**59**) more rapidly than they undergo radical–radical reaction. However, the intermediate capto-dative radical (**62**) does not add rapidly to another molecule of (**59**). Instead, it suffers radical recombination to give (**60**). The reaction succeeds because capto-dative radicals are especially unreactive in radical–molecule reactions[191] (preventing telomerization) but they still react with each other (mainly by recombination rather than disproportionation) at diffusion-controlled rates.

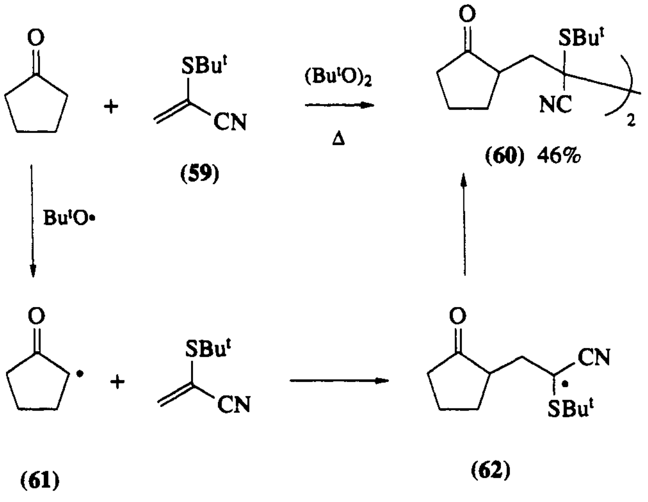

Scheme 63

Such recombinations produce self-coupled dimers. In general, selective cross-coupling of two radicals (A· + B· → A—B) cannot be conducted because: (i) the two radicals are generated at the same rate; and

(ii) both possible self-coupling reactions (2A· → A—A; 2B· → B—B) and the cross reaction all proceed at the diffusion-controlled rate. Given these two conditions, cross-coupling and self-coupling must proceed at the same rate and no selectivity is possible. However, if either condition is violated, selective radical–radical couplings are possible.

Some selectivity can be enforced in cross-coupling by generating radicals at different rates. Schäfer has shown that Kolbe electrolysis of two acid salts, one major component (A) and one minor component (B), produces a near-statistical mixture of the self-coupled product of the major component (A—A) and the cross-coupled product of the major and minor components (A—B) (Scheme 64).[192] Provided that recombination is preferred over disproportionation and that the self-coupled product is easily removed, this is a useful method for coupling a precious component (B) with an inexpensive component (A); however, it is relatively energy inefficient since the self-coupled dimer is the major product. Scheme 65 illustrates how this principle has been applied to a simple addition reaction.[193] Presumably, methyl radicals generated in electrolysis add rapidly to the alkene and the resulting adduct radicals couple preferentially with methyl radicals (which are present in much higher concentration). Ethane is probably formed in large amounts by the self-coupling of methyl radicals, but it just evaporates.

$$\underset{\text{5–10 equiv.}}{A{-}CO_2^-} \quad + \quad B{-}CO_2^- \xrightarrow{-e^-} \underset{\text{major product}}{A{-}A} \quad + \quad B{-}B$$

minor product
but useful yield
based on B-CO$_2^-$

**Scheme 64** Kolbe cross-coupling

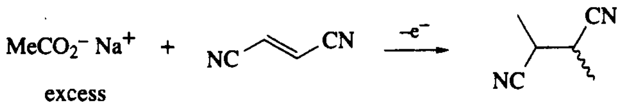

55% based on alkene

**Scheme 65**

A potentially more useful way to control cross-coupling is to mediate radical–radical reactions with a persistent radical (that is, one that does not react with itself at a diffusion-controlled rate). This strategy has not been widely recognized, but an excellent paper by Fischer has recently provided a quantitative theoretical framework for such reactions.[194] The basic strategy is qualitatively summarized in Scheme 66. Assume that a molecule A—P homolyzes to give two radicals A· and P·. Assume also that A· reacts with both itself and P· at diffusion-controlled rates but that P· is a persistent radical that couples with itself at a significantly lower rate. Throughout the reaction, A· and P· are produced at the same rate. However, transient radical A· is removed by self- and cross-couplings but P· is removed only by cross-coupling. Because P· is not removed by self-coupling, the concentration of P· soon exceeds that of A· and selective cross-coupling reactions become possible. For example, if A· is converted to B·, and if this new radical B· lives long enough to suffer radical–radical reactions, it may react exclusively with P·. The extent of the concentration gradient in favor of P· depends of its rate of self reaction (the more slowly it dimerizes, the higher the gradient).[192] More importantly, this concentration gradient can be estab-

$$A{-}P \longrightarrow A\bullet + P\bullet \quad \text{(a persistent radical)}$$

$$A\bullet + A\bullet \longrightarrow A{-}A$$

depletes concentration of A• at early reaction time

$$\left[P\bullet\right] \gg \left[A\bullet\right] \text{ at steady state}$$

$$A\bullet \longrightarrow B\bullet \xrightarrow{+P\bullet} B{-}P$$

**Scheme 66** Transient radical–persistent radical coupling lished very early in the reaction and it is maintained at a steady state throughout the course of the reaction. From the preparative standpoint, this means that very high yields of radical–radical coupling product are theoretically possible because practically all radical–radical encounters involve P·.

Hart has recently developed an exciting new method to conduct radical addition reactions that probably operates by selective transient radical–persistent radical coupling.[195] When tin pinacolate[196] (TINPIN; **63**), methyl crotonate and cyclohexyl iodide are simply heated in benzene, adduct (**64**) is isolated in 60% yield after chromatography (Scheme 67).[197] This is a very respectable yield considering that: (i) the acceptor is not used in large excess (1–3 equiv.); (ii) it possesses a β-substituent; and (iii) the reaction is conducted at high concentration (0.3 M). Indeed, this reaction promises to be a first step towards the development of a second generation of addition reactions based on the trialkyltin radical that permit the addition of nucleophilic radicals to electron deficient alkenes at a high reaction concentration without special experimental techniques. One potential disadvantage of this method is that stoichiometric quantities of tin by-products and benzophenone must be separated from the desired product.

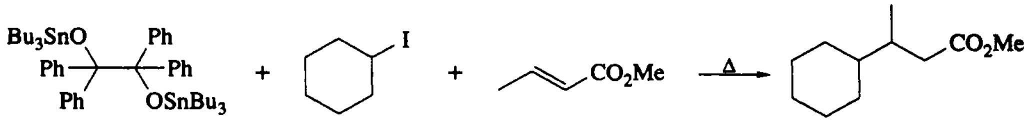

(**63**) = TINPIN

(**64**)

Scheme 67

Although uncertainties remain, the mechanism outlined in Scheme 68 is supported by observations of both Hart[197] and Neumann.[196] Neumann has shown that thermolysis of (**63**) causes homolytic cleavage to give the suspected persistent radical (**65**), which is in equilibrium with benzophenone and the trialkyltin radical. This radical (**65**) resembles a ketyl and it is stabilized both sterically and electronically. The trialkyltin radical abstracts iodine from the radical precursor to give a new radical, which in turn adds to the alkene to give (**66**). At very early reaction time, a concentration gradient in favor of (**65**) over all transient radicals develops because it is the only persistent radical. The most rapid reaction of (**66**) is radical–radical coupling, and this occurs selectively with (**65**) because it is present in the highest concentration. The coupled product (**67**) is then converted to (**64**) by thermal retroaldol reaction and hydrolysis. The use of a persistent radical does not eliminate the usual selectivity concerns. If the concentration of the persistent radical is too high, initial radicals may be trapped by coupling prior to addition, but if it is too low, the adduct radical may begin to telomerize. Thus, the concentration of the persistent radical is an important, yet ill-defined, variable in these reactions.

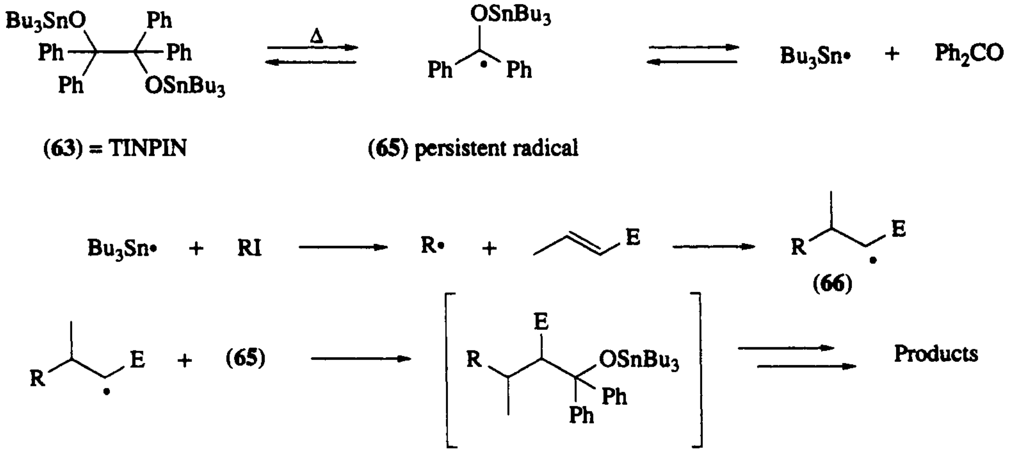

(**63**) = TINPIN

(**65**) persistent radical

(**66**)

(**67**) suspected intermediate

Scheme 68

In contrast to the relatively small number of persistent carbon-centered radicals, there are many persistent metal-centered radicals, some of which are very stable. Indeed, it now appears that the emerging synthetic methods based on the chemistry of alkylcobalt compounds should be classed as reactions controlled by selective transient radical–persistent radical coupling.[198] In this case, the persistent radical is a cobalt(II) entity.

Alkyl- or acyl-cobalt(III) salen, salophen or dimethylglyoximato complexes are readily prepared by the displacement of a wide variety of halides and related leaving groups with highly nucleophilic cobalt(I) anions.[199,200] Because such alkylations may sometimes proceed *via* $S_{RN}1$ mechanisms, even cobalt complexes derived from unreactive (in an $S_N2$ sense) halides can be formed. The resulting carbon–cobalt bonds are very weak and Pattenden[201] and Branchaud[202] have shown that simple irradiation of these complexes in the presence of excess alkene produces adducts by the mechanism outlined in Scheme 69. This mechanism has been discussed in detail by Branchaud[202] and Giese,[203] and a key feature is that high concentrations of cobalt(II) are present in the reaction[204] because it does not readily dimerize or disproportionate (by electron transfer to give cobalt(III) and cobalt(I)). This permits the selective formation of products by radical–$Co^{II}$ coupling. A high concentration of cobalt(II) can be both a blessing and a curse: a blessing because the adduct radicals are efficiently trapped and a curse because initial radicals can also be trapped. While this latter trapping only regenerates the starting complex, if it becomes too efficient, few of the radicals will live long enough to undergo addition.[204] A key feature of the reaction is that substituents that facilitate radical addition apparently also accelerate cobalt hydride elimination. Thus, the adducts are more prone to elimination of cobalt hydride than the starting complexes.

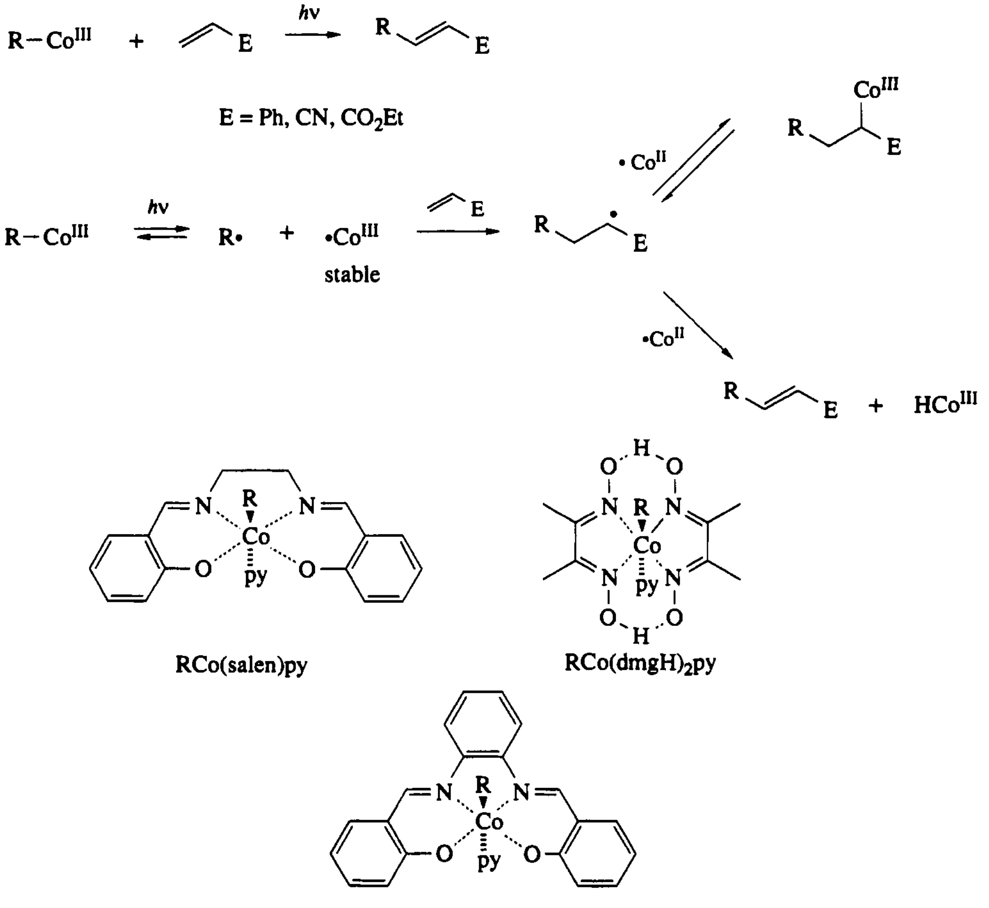

RCo(salen)py

RCo(dmgH)₂py

RCo(salophen)py

**Scheme 69** Common cobalt complexes

Several recent examples of this technique are outlined in Scheme 70.[199,201,205,206] The starting cobalt complexes are highly colored, air stable compounds that require no special precautions in handling. The process is relatively cost effective: most cobalt precursors are less expensive per mole than tributyltin hydride. The reactions are conducted by visible light irradiation in a variety of solvents and can often be followed by color changes characteristic of the different oxidation states of cobalt. A disadvantage is that large excesses of alkene are often required for maximum yields. The products of the reaction are usually derived from apparent β-hydride elimination although sometimes protonated products are isolated.

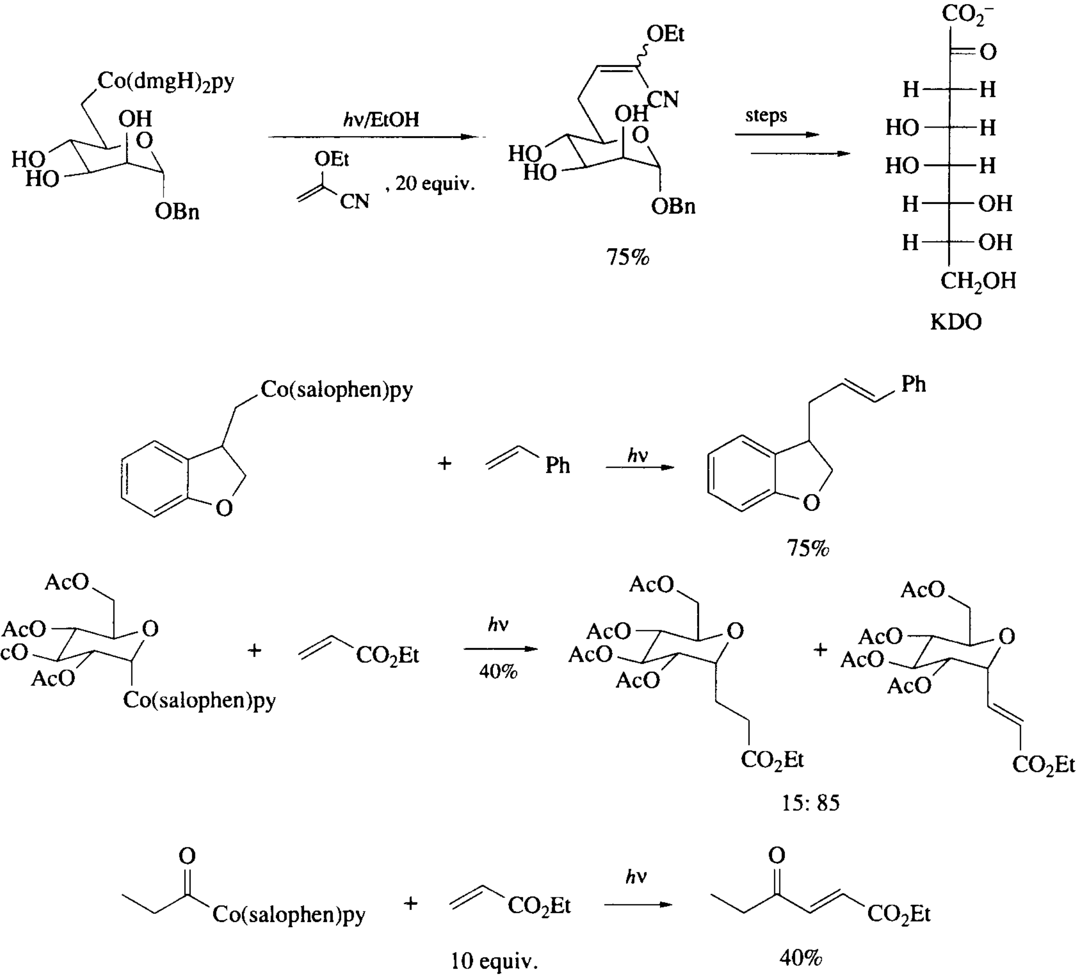
Co(dmgH)2py
OH
O
HO
HO
OBn
hv/EtOH
OEt
CN
, 20 equiv.
OEt
CN
OH
O
HO
HO
OBn
75%
steps
CO2−
O
H
H
HO
H
HO
H
H
OH
H
OH
CH2OH
KDO
Co(salophen)py
O
+
Ph
hv
Ph
O
75%
AcO
AcO
AcO
O
AcO
Co(salophen)py
+
CO2Et
hv
40%
AcO
AcO
AcO
O
AcO
CO2Et
+
AcO
AcO
AcO
O
AcO
CO2Et
15: 85
O
Co(salophen)py
+
CO2Et
10 equiv.
hv
O
CO2Et
40%

**Scheme 70**

The preliminary developments with TINPIN and organocobalt species are very encouraging and bode well for the future development of synthetic procedures that use radical–radical coupling methods controlled either by organic or organometallic persistent radicals.

### *4.1.6.2.2 Redox methods*

In redox methods, radicals are generated and removed either by chemical or electrochemical oxidation or reduction. Initial and final radicals are often differentiated by their ability to be oxidized or reduced, as determined by substituents. In oxidative methods, radicals are removed by conversion to cations. Such oxidations are naturally suited for the additions of electrophilic radicals to alkenes (to give adduct radicals that are more susceptible to oxidation than initial radicals). Reductive methods are suited for the reverse: addition of alkyl radicals to electron poor alkenes to give adducts that are more easily reduced to anions (or organometallics).

The oxidative method is often conducted on enol (or enolate) derivatives and a simplified mechanism is shown in Scheme 71. Initial chemical or electrochemical oxidation gives an electrophilic radical (**68**; that may be free or metal-complexed) that is relatively resistant to further oxidation. Addition to an alkene now gives an adduct radical (**69**) that is more susceptible to oxidation. Products are often derived from the resulting intermediate cation (**70**) by inter- or intra-molecular nucleophilic capture or by loss of a proton to form an alkene. The concentration and oxidizing potential of the reagent help to determine the selectivity in such reactions.

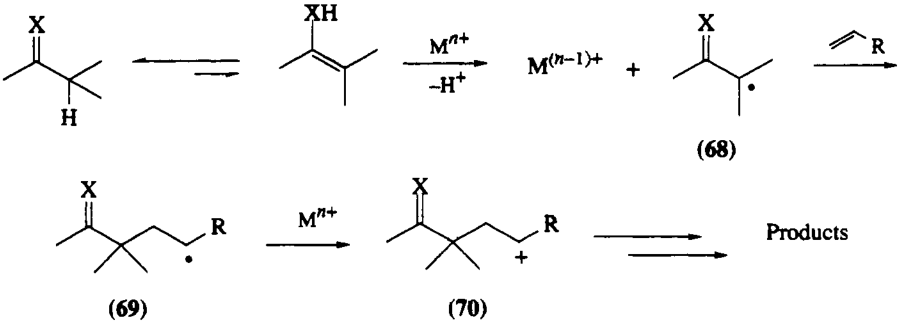
X
H
XH
$M^{n+}$
$-H^+$
$M^{(n-1)+}$
+
X
R
(68)
X
R
(69)
$M^{n+}$
X
R
+
(70)
Products

**Scheme 71** Oxidative addition reactions

In addition to electrochemical methods,[192] copper(II),[207] iron(III)[208] and cerium(IV)[209] oxidants are useful for mediating addition reactions. During the last decade, manganese(III) acetate has emerged as the the most popular reagent for conducting such transformations.[210] The basic reaction, first studied by Heiba and Dessau,[211] is the oxidation of acetic acid in the presence of alkenes and 2 equiv. of $Mn^{III}$ triacetate dihydrate (which is actually an oxo-centered manganese(III) trimer). Lactones are formed in good yields as shown in Scheme 72.

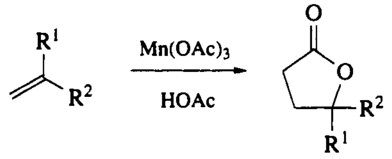
$R^1$
$R^2$
$Mn(OAc)_3$
HOAc
O
O
$R^2$
$R^1$

**Scheme 72**

Variants on this theme have provided many useful preparative procedures and a few representative examples are provided in Scheme 73.[212-214] Acetic acid is a relatively unreactive substrate and is often used as a solvent. However, more enolizable substrates, especially those possessing two activating groups, are readily oxidized on a stoichiometric basis at 25–50 °C in acetic acid. If the products contain enolizable hydrogens, over oxidation is a potential problem (see the first example). The reactions can often be monitored by the disappearance of the characteristic brown color of the oxidant. While it is clear

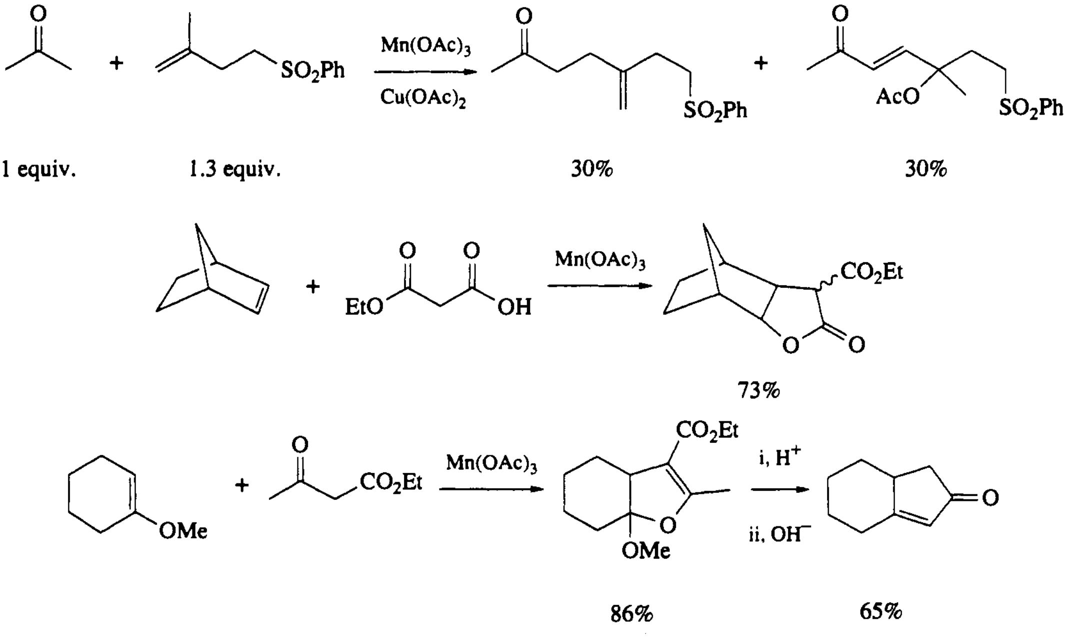
O
+
$SO_2Ph$
$Mn(OAc)_3$
$Cu(OAc)_2$
O
$SO_2Ph$
+
O
AcO
$SO_2Ph$
1 equiv.
1.3 equiv.
30%
30%
+
O
O
EtO
OH
$Mn(OAc)_3$
$CO_2Et$
O
O
73%
OMe
+
O
$CO_2Et$
$Mn(OAc)_3$
$CO_2Et$
O
OMe
i, $H^+$
ii, $OH^-$
O
86%
65%

**Scheme 73**

that these $\mathrm{Mn^{III}}$ oxidations follow the general mechanism outlined in Scheme 71, the exact details can vary as a function of substrate. $\mathrm{Mn^{III}}$ enols are often postulated as intermediates and it appears that Mn-complexed radicals may actually be responsible for addition reactions in some cases,[215] but in others (particularly where more stable radicals are involved), true free radical intermediates are strongly implicated. A recent paper by Snider provides a detailed mechanistic discussion with complete references to previous synthetic and mechanistic studies.[216]

In contrast to oxidative methods, reductive methods are more suited to conduct additions of nucleophilic radicals to electron deficient alkenes as shown in Scheme 74. A useful reagent should reduce a radical precursor but give the resulting radical sufficient lifetime to add to an alkene prior to reduction. The adduct radical should then be readily reduced to remove it from the radical pool. This reaction is formally equivalent to the much more common conjugate addition of an organometallic reagent. In principle, the organometallic intermediate that is formed can be trapped by electrophiles, but in practice most reductions have been conducted in protic solvents and have formed only protonated products. Several examples of addition reactions in which the products are trapped by reduction are contained in Scheme 75. The first example illustrates a convenient reductive equivalent of the Meerwein arylation,[112,217] while the second example shows the reductive generation of alkoxy radicals for use in C—H abstraction.[218,219] The last example is particularly interesting because it appears on the surface to be a standard organometallic conjugate addition but experimental evidence gathered by Luche indicates that the reductive radical mechanism is operating.[220]

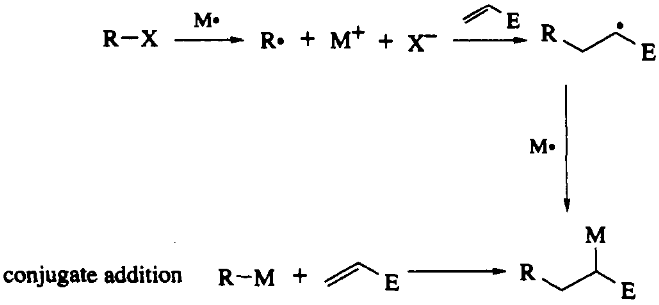

Scheme 74 Reductive addition reaction

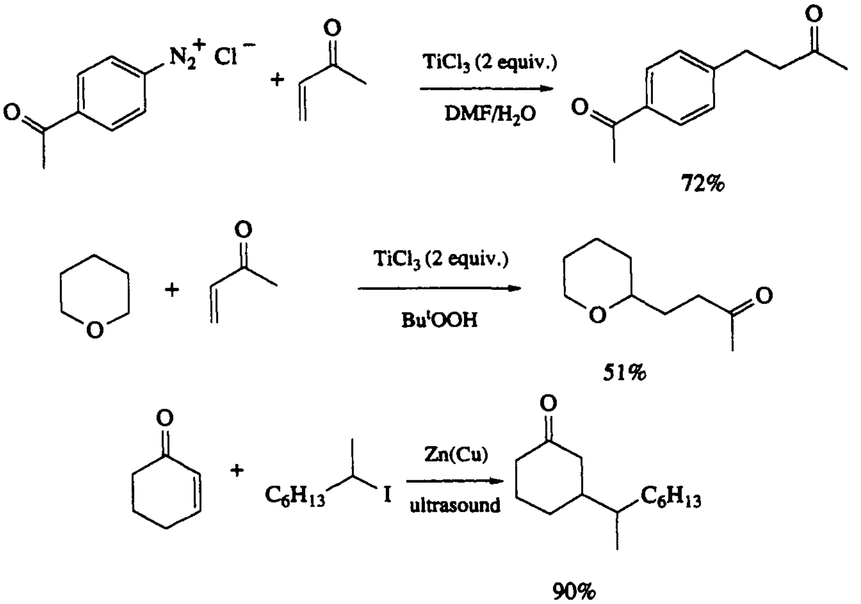

Scheme 75

Perhaps the most generally useful reaction of this type is the vitamin $B_{12}$ catalyzed reductive addition shown in Scheme 76.[221] This reaction, pioneered by Scheffold,[222] is related to the organocobalt additions in Section 4.1.6.1, but only a catalytic quantity of vitamin $B_{12}$ is required along with a chemical or electrochemical coreductant. This procedure is a very practical alternative to the metal hydride method for conducting addition reactions of nucleophilic radicals. The catalytic cycle outlined in Scheme 76 is a reasonable mechanism but variants are possible.[222] The coreductant recycles cobalt(II) products to the nucleophilic cobalt(I) complexes required for radical generation.

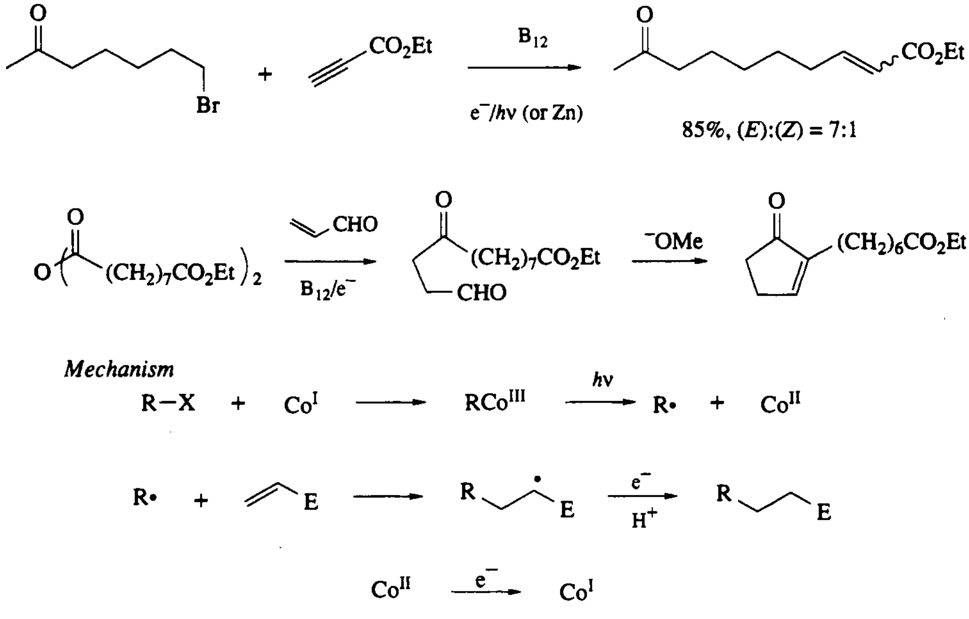

Scheme 76

## 4.1.7 ADDITIONS OF CARBON-CENTERED RADICALS TO OTHER MULTIPLE BONDS AND AROMATIC RINGS

### 4.1.7.1 Additions to Other Multiple Bonds

Besides alkenes and alkynes, other multiple bonds can be used as acceptors in addition reactions of carbon radicals provided the usual requirements of reactivity and selectivity are met. Other types of carbon–carbon multiple bonds that have been used as acceptors include dienes,[162] allenes,[61] enolates (and nitronates, see below) and quinones.[223] Even highly strained $\sigma$-bonds have served as acceptors on occasion.[224]

Addition reactions of carbon radicals to C—O and C—N multiple bonds are much less-favored than additions to C—C bonds because of the higher $\pi$-bond strengths of the carbon–heteroatom multiple bonds. This reduction in exothermicity (additions to carbonyls can even be endothermic) often reduces the rate below the useful level for bimolecular additions. Thus, acetonitrile and acetone are useful solvents because they are not subject to rapid radical additions. However, entropically favored cyclizations to C—N and C—O bonds are very useful, as are fragmentations (see Chapter 4.2, this volume).

Only a few additions to highly activated (electron deficient) carbonyls are known[222,225] and at present they provide little competition for standard ionic carbonyl addition reactions. But additions to C–N multiple bonds show more preparative potential. Both Stork and Sher,[29] and Barton[226] have developed useful additions to isonitriles; additions to oximes are also known.[227] The TINPIN method (Scheme 67) of adding nucleophilic radicals to oxime ethers recently reported by Hart and Seely appears to be one of the most useful reactions in this class.[197] This reaction oxaminomethylates radical precursors under very mild conditions in good yields and it might often be advantageous compared to the standard tactic of addition of an organometallic reagent to an oxime ether (Scheme 77).

Even though they are electron deficient, radicals do not react rapidly with simple anions and organometallic species because the resulting radical anions would place an electron in a very high energy orbital. However, conjugated anions with low lying LUMOs can react readily with radicals. Indeed, nitronates and certain enolates are good radical acceptors and a large class of chain reactions, termed $S_{RN}1$ substitutions, rely on this capability.[228] Several examples of $S_{RN}1$ reactions and a generic mechan-

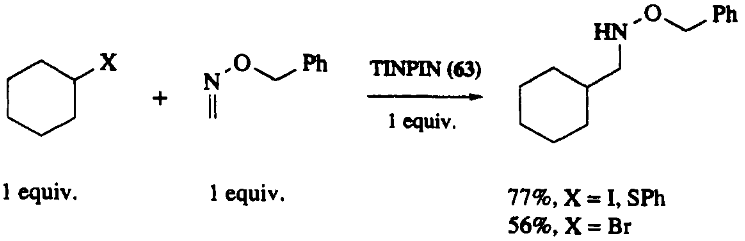

Scheme 77

ism are collected in Scheme 78.[229,230] These chain reactions often require chemical or photochemical initiation. While the overall transformation is the same as that of an alkylation, $S_{RN}1$ reactions nicely complement standard enolate alkylations, working best with tertiary alkyl and aryl halides (and related precursors). The key step in Semmelhack's classic cephalotaxine synthesis is an $S_{RN}1$ reaction that illustrates this point very well (Scheme 78).[229]

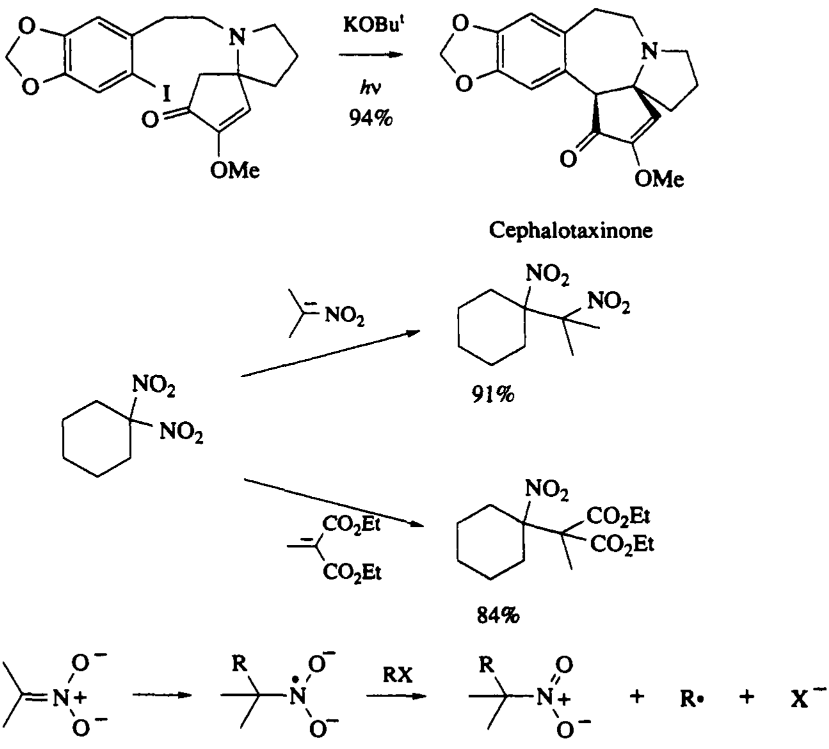

Scheme 78

## 4.1.7.2 Additions to Aromatic Rings

Most known addition reactions of radicals to aromatic rings involve net substitution for a hydrogen atom by the general mechanism outlined in Scheme 79. The cyclohexadienyl radical (**71**) that is produced on addition is a powerful reductant compared to most other radicals. It is important to have a mild oxidant present to trap this radical to prevent it from undergoing standard radical–radical reactions. Thus, the overall driving force for these substitutions is usually provided by the oxidant. Unlike additions to C—C multiple bonds, fragmentation can sometimes be important in these less exothermic additions to aromatic rings (because aromaticity is sacrificed on addition). The oxidant may play an important role in reversible additions by oxidizing the cyclohexadienyl radical more readily than the starting radical.

The addition reactions of alkyl and substituted alkyl radicals to simple aromatic rings are very slow (see Section 4.1.2.2). Hence, benzene is a good solvent. The additions of aryl radicals to aromatic rings are considerably faster and, while such reactions have been studied intensely,[231] their preparative utility

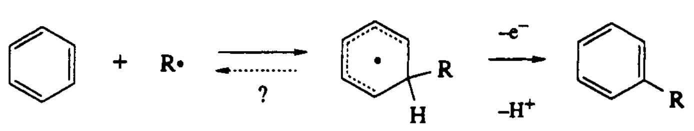

**(71)**

**Scheme 79** Additions to aromatic rings

is not high because of low regio- and chemo-selectivity. However, the addition of an aryl radical to benzene can become a limiting side reaction when techniques like slow syringe pump addition of tin hydride are used and there is no good trap for the aryl radical. An example is provided in Scheme 80.

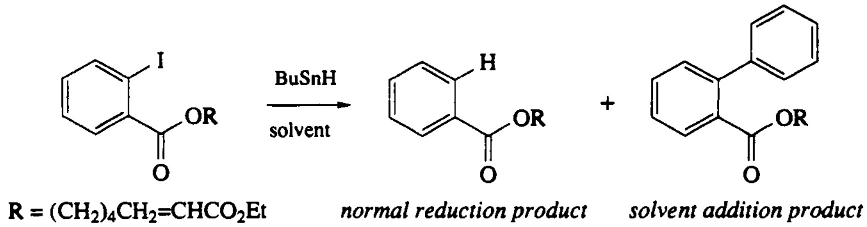
I
OR
O
BuSnH
solvent
H
OR
O
+
OR
O
R = (CH2)4CH2=CHCO2Et
*normal reduction product*
*solvent addition product*

| | | |
|---|---|---|
| <0.02M $Bu_3SnH$, t-butyl alcohol | only product | not formed |
| syringe pump, benzene | 47% | 26% |

**Scheme 80**

Additions to aromatic rings can become useful when radicals and acceptors are electronically paired. The additions of electrophilic radicals to electron rich aromatic rings are growing in importance and the additions of nucleophilic radicals to electron poor alkenes have long been of preparative value. This chapter can provide only a few representative examples of each class. Giese's book is recommended as a more thorough overview of additions to aromatic rings.[232]

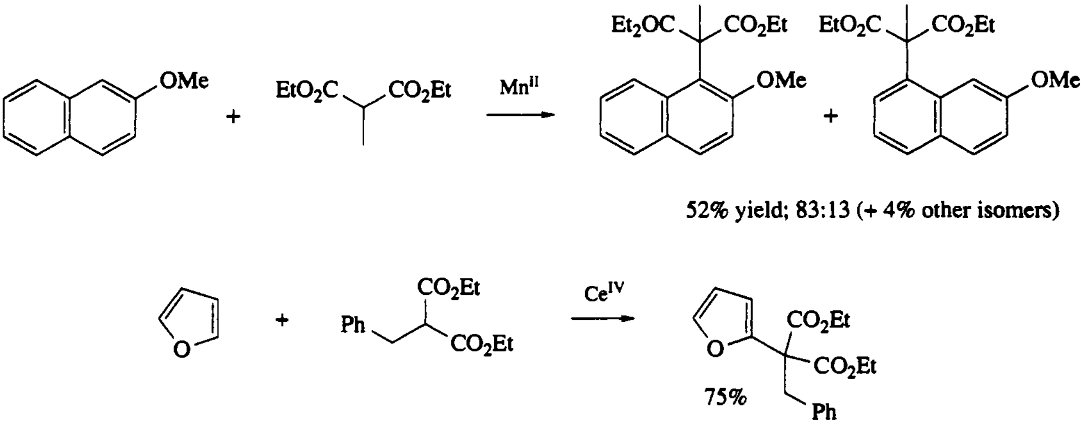
OMe
+
EtO2C
CO2Et
Mn^II
Et2OC
CO2Et
OMe
+
EtO2C
CO2Et
OMe
52% yield; 83:13 (+ 4% other isomers)
O
+
Ph
CO2Et
CO2Et
Ce^IV
O
CO2Et
CO2Et
Ph
75%

**Scheme 81**

### *4.1.7.2.1 Additions of electrophilic radicals to electron rich aromatic rings*

Oxidation of enolizable nitro, carbonyl and dicarbonyl compounds with $Fe^{III}$ $Mn^{III}$ and $Ce^{IV}$ reagents in the presence of electron rich aromatic (or heteroaromatic) rings often provides modest to good yields of substituted products. Typical examples are shown in Scheme 81.[233,234] The oxidant functions both to generate the initial radical (Scheme 71) and to trap the adduct radical. Products of *ortho* substitution usually predominate but significant amounts of *para* and *meta* products are often formed, and in some cases, reversibility in the addition step may influence the product distribution. A recent paper by Citterio and Santi provides a nice introduction to these types of reactions.[219]

### 4.1.7.2.2 Addition of nucleophilic radicals to protonated heteroaromatics (the Minisci reaction)

The functionalization of electron rich aromatics rings is often accomplished by electrophilic aromatic substitution. However, electrophilic substitutions require stringent conditions or fail entirely with electron deficient aromatic rings. Nucleophilic aromatic substitutions are commonly used but must usually be conducted under aprotic conditions. In contrast, nucleophilic radicals can add to electron deficient aromatic rings under very mild conditions.

The addition of radicals to protonated nitrogen heterocycles is by far the most important reaction in this class. Pioneered by the group of Minisci, this reaction was recognized as being preparatively useful well before the recent resurgence of radical reactions in synthesis. In addition, associated mechanistic studies contributed significantly to our present understanding of polar effects in free radical reactions. The general reaction is outlined in Scheme 82 and, because there are many important variants, several reviews are recommended for more comprehensive coverage.[235]

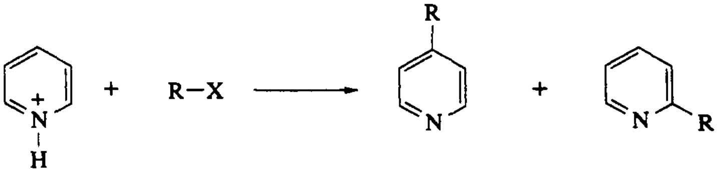

X = H, I, Co, Hg, $CO_2H$; R = alkyl, hydroxyalkyl, aminoalkyl, acyl

**Scheme 82** Additions to protonated pyridines

Alkyl radicals add to pyridine relatively slowly; however, the rate of addition is dramatically accelerated by simple protonation, and alkyl radicals add to pyridinium salts at about the same rate as they add to styrene ($k \approx 5 \times 10^4$ $M^{-1}$ $s^{-1}$).[236] While pyridine itself gives mixture of 2- and 4-substituted products, substituted pyridines and polycyclic *N*-heterocycles often exhibit good regioselectivity. Electronegative substituents on the ring accelerate additions of nucleophilic radicals and rates comparable to those with reactive alkenes like acrylonitrile are not uncommon.[236] Radicals can be generated by a variety of methods from C—H and C—I bonds (by abstraction), from C—Co[237] and C—Hg[238] bonds, and from carboxylic acids (by oxidative decarboxylation or from thiohydroxamates[239]). Representative examples are provided in Scheme 83.[240–242] The Minisci reaction has two potential advantages over nucleophilic aromatic substitution: (i) it readily introduces acyl and related functional groups that are not usually directly available by nucleophilic substitutions; and (ii) it proceeds under mild, protic conditions and does not require organometallic intermediates. Activation of *N*-heterocycles for organometallic additions is often beneficial but simple protonation does not suffice because addition reactions are usually precluded by simple acid–base reactions with the nucleophile.

A representative example from the recent literature illustrates that a redox chain substitution is one of the most practical means to conduct these reactions.[243] Simple heating of lepidine (**72**) and *t*-butyl hydroperoxide in aqueous acidic methanol with 5% iron sulfate provides hydroxymethyllepidine (**73**) in 93% yield. The accepted mechanism is a redox chain outlined in Scheme 84. Iron(II) reduces the *t*-butyl hydroperoxide to generate the *t*-butoxyl radical (**74**) in the classical Fenton reaction. This radical (**74**) abstracts a hydrogen from the solvent to give the hydroxymethyl radical (**75**), which in turn adds to the lepidinium salt to form (**76**). Such addition reactions may sometimes be reversible but subsequent loss of a proton (from carbon) is not. The resulting radical (**77**) is a very weak base compared to lepidine. But it is a potent reductant because of its high-lying HOMO and it reduces iron(III) to iron(II).

These redox chain reactions, which cycle iron(II) and iron(III), have advantages over methods that use stoichiometric quantities of oxidants because the hydroxymethyl radical is also a good reductant and, at high oxidant concentrations, it may be oxidized more rapidly than it adds to (**72**). The disadvantage of this type of reaction is that the initial radical is generated by a relatively non-selective hydrogen atom abstraction reaction. To be efficient, the H-donor must be used in large excess; it is often a cosolvent. Nonetheless, this is a very practical method to prepare hydroxyalkylated and acylated heteroaromatic and related derivatives.

The addition of functionalized alkyl radicals to protonated heteroaromatics was more difficult (because the radicals could not be generated by H-atom abstraction), but a recent development holds promise to resolve this problem. Generation of a methyl radical in the presence of an alkyl iodide sets up a relatively rapid equilibrium as indicated in Scheme 85. This equilibrium will favor any more highly substituted alkyl radical over methyl, and further, this latter radical will be significantly more nucleophilic. Thus when methyl radicals are generated in the presence of cyclohexyl iodide and a protonated quinaldine, the

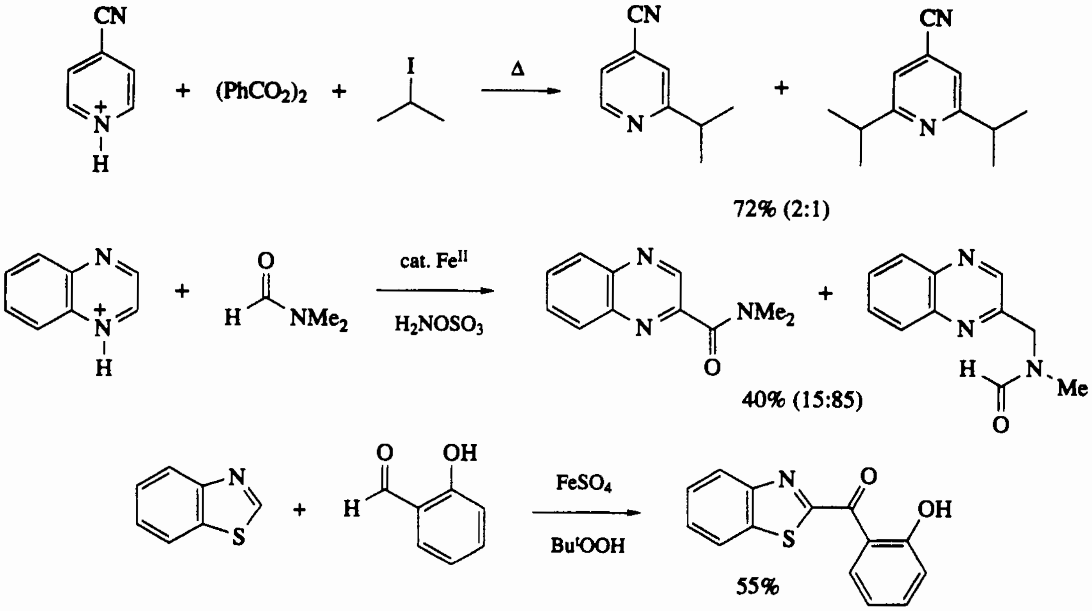
(PhCO2)2
Δ
72% (2:1)
cat. FeII
H2NOSO3
40% (15:85)
FeSO4
ButOOH
55%

**Scheme 83**

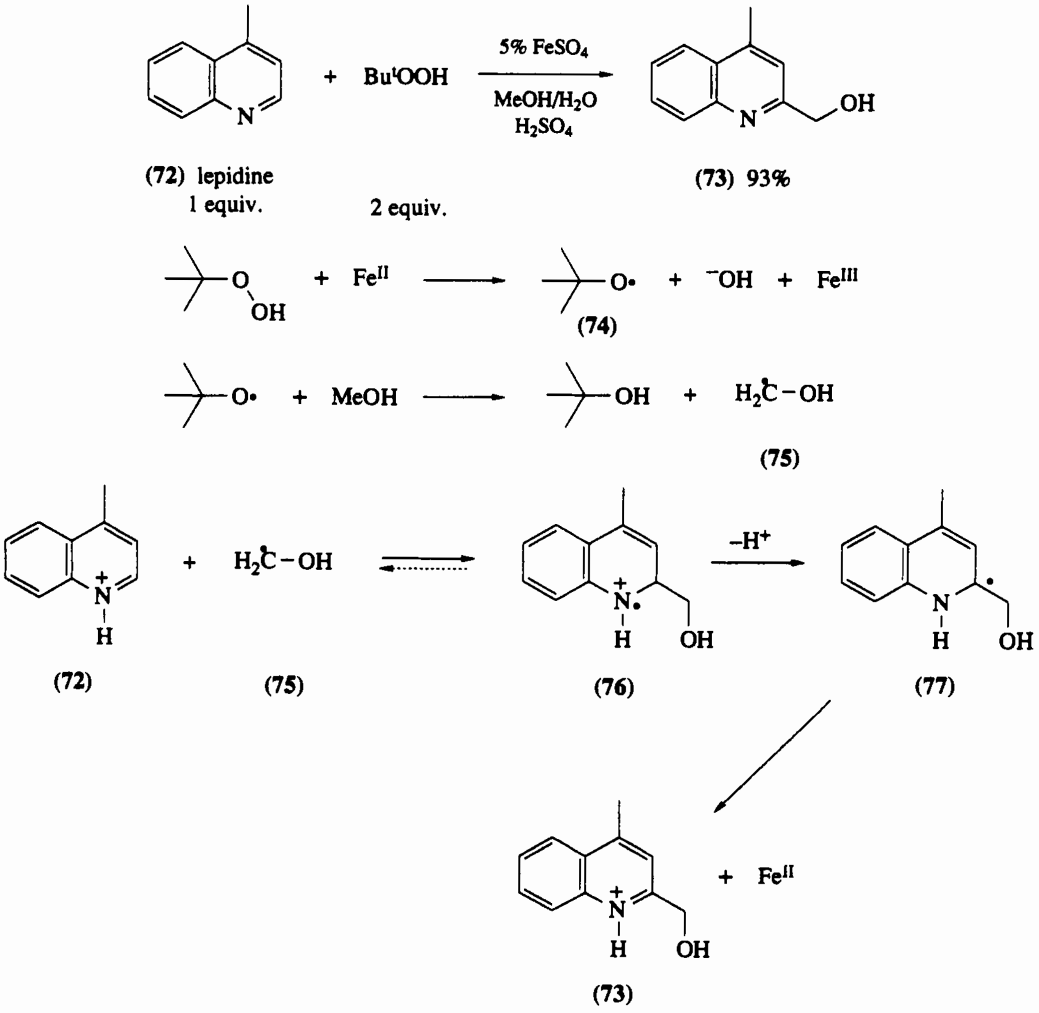
ButOOH
5% FeSO4
MeOH/H2O
H2SO4
(72) lepidine
1 equiv.
2 equiv.
(73) 93%
FeII
(74)
⁻OH
FeIII
MeOH
(75)
(72)
(75)
(76)
-H+
(77)
FeII
(73)

**Scheme 84**

product results not from methyl addition but from cyclohexyl addition.[244] Scheme 85 illustrates one of several methods that Minisci has used to generated the methyl radicals for such a procedure: the oxidative cleavage of DMSO. As above, the iron catalyst mediates a redox chain and the ultimate oxidant is hydrogen peroxide. In principle then, any alkyl radical that is more stable than methyl might be generated by this elegant method and added not only to protonated heteroaromatics but to other acceptors as well.

$$CH_3\bullet + R{-}I \rightleftharpoons MeI + R\bullet$$

R = substituted alkyl

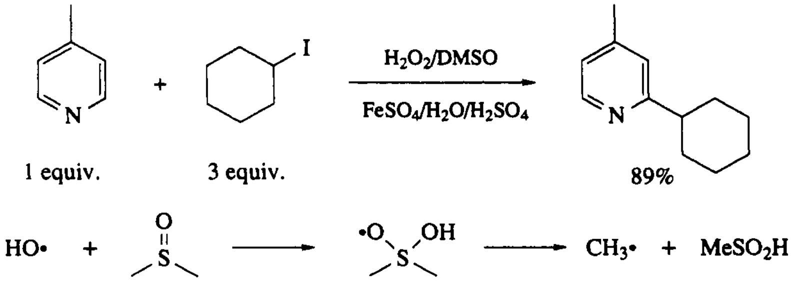

Scheme 85

## 4.1.8 ADDITIONS OF HETEROATOM-CENTERED RADICALS

Addition and substitution reactions of heteroatom-centered radicals with multiple bonds have been extensively studied and are sometimes preparatively useful.[11] This section will briefly consider the addition reactions of H—Y and X—Y reagents (Kharasch reactions) and substitution reactions (Scheme 86).[245]

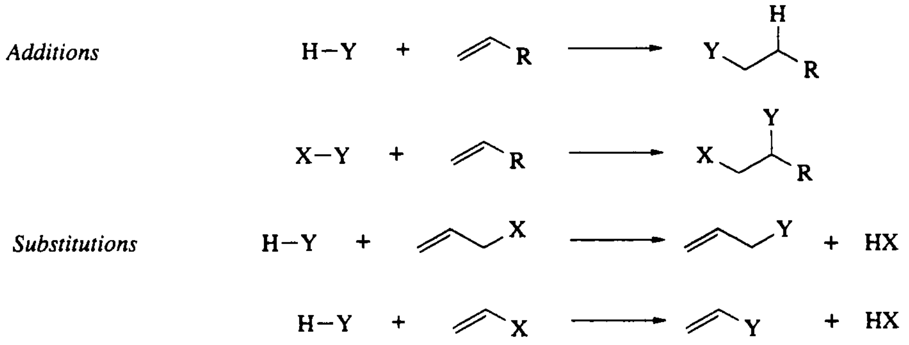

Scheme 86 Reactions of heteroatom radicals with alkenes

The anti-Markovnikov addition of HBr to alkenes is an historically important reaction in the development of organic chemistry, but its synthetic value for alkene functionalization has waned with the advent of reactions such as hydroboration. Radical additions of thiols and selenols to alkenes and alkynes are important preparative reactions for the synthesis of sulfides and selenides.[246] Acid- and base-catalyzed additions of thiols and selenols are also popular. Hydrostannylation and hydrogermylation (but not hydrosilylation) can also be accomplished by radical chain addition.[80,83,84] Metal-catalyzed additions and ionic conjugate additions of stannyl metals are also popular. Like most radical additions, radical hydrostannylation is not stereospecific (that is, alkene geometry is not conserved in the product) but it can be highly stereoselective in cyclic systems. Hydrostannylations are usually conducted at high concentrations because the addition of a tin radical is reversible and a high tin hydride concentration favors trapping of the adduct. Scheme 87 provides several recent examples.[247–249]

Many variants on the addition of two heteroatoms (X—Y) across an alkene or alkyne have been developed.[245] These reactions always proceed by the atom transfer method and require a reactive atom or group donor (X = halogen, SPh, SePh). Many atoms and groups Y can be introduced including oxygen and nitrogen. However, such additions are only occasionally advantageous when compared to ionic

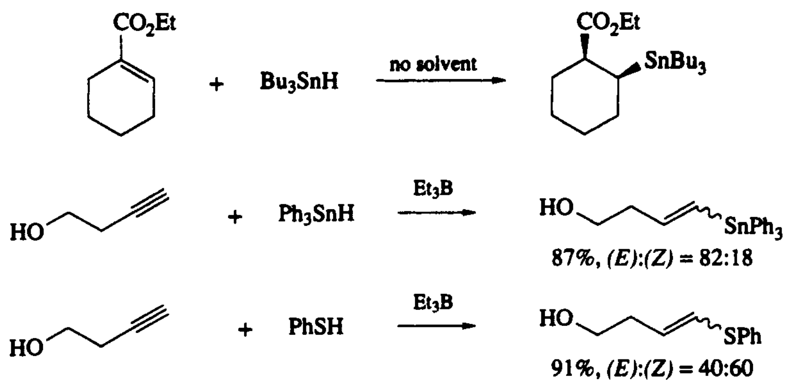
CO2Et
Bu3SnH
no solvent
CO2Et
SnBu3
HO
Ph3SnH
Et3B
HO
SnPh3
87%, (E):(Z) = 82:18
HO
PhSH
Et3B
HO
SPh
91%, (E):(Z) = 40:60

Scheme 87

equivalents like oxy- and amido-mercuration, sulfenylation, iodination and the like. These ionic additions are often stereospecific, high yielding and very general.

Among the many variants that add two heteroatoms, those that add phenylsulfonyl groups are particularly useful because they proceed in high yield under mild conditions and provide functionality for subsequent synthetic transformations. The examples contained in Scheme 88 illustrate some recent applications.[250–252] In contrast to most radical additions to alkynes, the additions of $ArSO_2X$ are often highly stereoselective.

The interchange of heteroatom groups by free radical substitution of allyl or vinyl groups (see Section 4.1.6.2) is also a common and preparatively useful reaction that occurs by an addition–elimination mechanism. Those groups that participate in fragmentation reactions (halogen, tin, sulfur, selenium) are susceptible to interchange. Depending on reaction conditions, such substitutions can sometimes be conducted in either direction. Representative examples are provide in Scheme 89.[253,254]

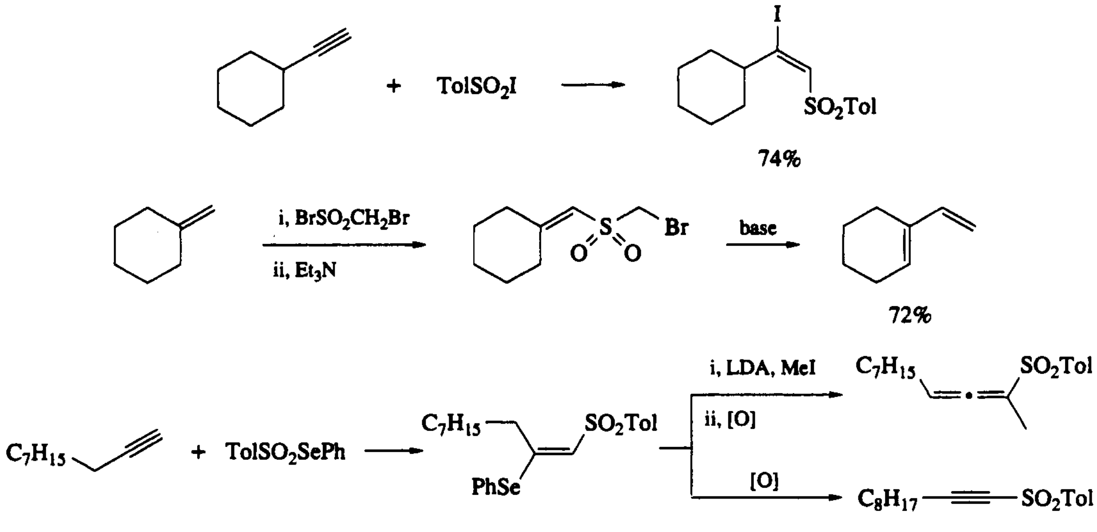
TolSO2I
I
SO2Tol
74%
i, BrSO2CH2Br
ii, Et3N
S
O
O
Br
base
72%
C7H15
TolSO2SePh
C7H15
SO2Tol
PhSe
i, LDA, MeI
ii, [O]
C7H15
SO2Tol
[O]
C8H17
SO2Tol

Scheme 88

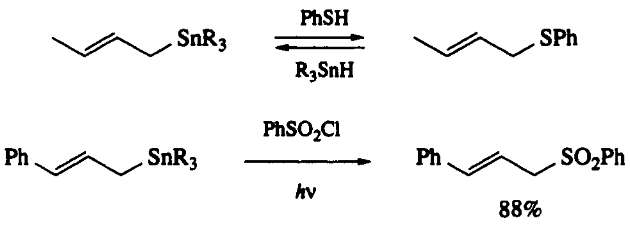
SnR3
PhSH
R3SnH
SPh
Ph
SnR3
PhSO2Cl
hv
Ph
SO2Ph
88%

Scheme 89

## 4.1.9 CONCLUSIONS

Radical addition reactions are useful in the formation of a diverse collection of structural motifs and they often offer advantages over standard transformations. This chapter has attempted to show that the barrier to becoming familiar with the principles and techniques of radical reactions is small compared to the rewards, both practical and intellectual, that derive from this familiarity. The following chapter (Chapter 4.2) assumes that the reader has now acquired this familiarity and it presents radical cyclization reactions and sequences of radical reactions.

## ACKNOWLEDGMENTS

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# 4.2

# Radical Cyclizations and Sequential Radical Reactions

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## 4.2.1 INTRODUCTION

Reactions that form rings are the central steps in the synthesis of cyclic organic compounds, and the development of cyclization reactions that are mild and general has been a recurring theme since the emergence of organic synthesis as a discipline. Although they have been recognized only recently, intramolecular addition reactions of radicals (hereafter called cyclizations) are among the most powerful tools at the disposal of the synthetic chemist. These radical cyclization reactions have all the advantages of their bimolecular counterparts, such as predictability and functional group tolerance; furthermore, because of the entropic advantages, cyclization reactions are of much broader scope.

The purpose of this chapter is to provide an introduction to the scope and limitations of radical cyclization reactions. Emphasis will be placed on the reactivity profile of radicals with respect to chemo-, regio- and stereo-selectivity. Because most sequential radical reactions include at least one cyclization, they are also presented in this chapter. The organization of this chapter is similar to the previous chapter on radical additions. However, the basic principles of radical reactions, selectivity requirements, methods to conduct radical reactions (including experimental techniques), and mechanisms are extensively discussed in the previous chapter, and these aspects will be reiterated rather sparingly. A reader who is not familiar with the principles of radical reactions as applied to synthesis should read the addition chapter (Chapter 4.1, this volume) first.

The general requirements to conduct a selective radical cyclization are summarized in Scheme 1. Like an addition reaction, one must have selective radical generation, cyclization and selective radical removal. Each step must be more rapid than the loss of radicals by (nonselective) radical/radical or radical/solvent reactions, and the method which is chosen must convert the cyclic radical, but not the initial radical, to a stable product. Cyclization reactions are often easier to conduct than additions. Indeed, some cyclizations are so rapid that it is difficult to trap initial radicals with standard reagents (like tin hydride) prior to closure. If bimolecular trapping is a problem, the standard experimental approach is to reduce the concentration of the trapping reagent, thus slowing bimolecular reactions relative to unimolecular competitors. In intermolecular additions, reaction of the product radical with the starting alkene is an important competing reaction, and the electronic differences between the initial and the product radicals are of great concern. However, in cyclizations this bimolecular reaction is rarely a problem because (for certain ring sizes) entropy greatly favors cyclization relative to addition. Indeed, many potential competing bimolecular addition reactions are so slow that they do not occur at all. Thus, the selectivity concerns arise mainly at the stage of the initial radical. The cyclic radical need only be converted to a stable product more rapidly than it is lost by radical/radical or radical/solvent reactions. In practice, this means that cyclizations can often be conducted down to the lower solution rate limit ($10^2$–$10^3$ $s^{-1}$), provided that the chains are maintained.

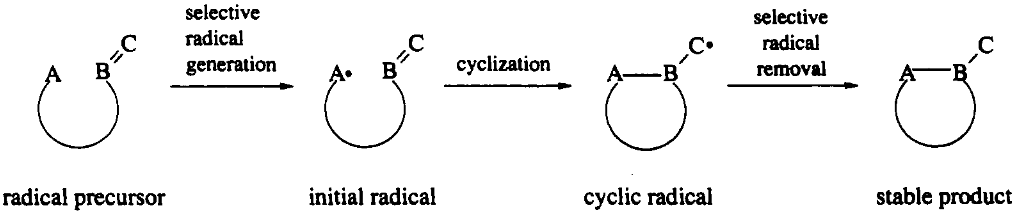

Potential problems: i, reactions of radicals with other radicals or solvent;
ii, removal of initial radical before cyclization

Scheme 1 Selectivity requirements for cyclization

The following introduction will briefly recount some of the key features of radical cyclizations with an emphasis on basic concepts that control regio- and stereo-selectivity. More details will be provided in the following sections, which describe specific types of reactions. The factors affecting the cyclization reactions to carbon–heteroatom multiple bonds are treated separately in Section 4.2.5, and the cyclizations of heteroatom-centered radicals are contained in Section 4.2.4.

Several excellent reviews[1–4] on the subject of radical cyclizations have stimulated synthetic advances in the past and will continue to do so in the future; they are highly recommended reading. As with radical additions, the book by Giese[5] provides a very good overview of the whole field (and it also includes cyclizations that do not occur by additions to $\pi$-bonds).

### 4.2.1.1 Hexenyl Radical Cyclizations

Hexenyl radical cyclizations are typically more rapid than higher homologs, and, unlike lower homologs, they are irreversible. Therefore, they are the most generally useful class of radical cyclizations. Thanks to intensive mechanistic study, they are also the most well understood.

#### *4.2.1.1.1 The 5-hexenyl radical*

The behavior of the 5-hexenyl radical merits special attention not only because it is one of the best understood reactive intermediates in organic chemistry, but also because it is a representative parent of a larger class of cyclizations. Because it is a cyclization of intermediate rate, it provides a convenient (if arbitrary) dividing point for synthetic planning: cyclizations that are more rapid than that of the hexenyl radical are easily conducted, but those that are significantly slower may present experimental difficulties.

As shown in Scheme 2, the hexenyl radical partitions between 5-exo cyclization (to give the cyclopentylmethyl radical) and 6-endo cyclization (to give the cyclohexyl radical) with the indicated rate constants (the terms 'exo' and 'endo' derive from the orientation of the reacting alkene with respect to the forming rings). At standard operating temperatures (25–80 °C), this partitioning translates to a ratio of about 98:2 in favor of 5-exo over 6-endo closure. This cyclization is highly exothermic, and strictly kinetically controlled (in this example, the less stable product is preferred). The contrast between this cyclization and an electronically equivalent bimolecular addition is dramatic. The addition of an alkyl radical to an unactivated alkene is not sufficiently rapid to be a preparatively useful reaction; its bimolecular rate constant is about three orders of magnitude below that of cyclization. However, when such an addition occurs, the alkyl radical adds exclusively to the terminus of the alkene. The bimolecular addition of an alkyl radical to the internal carbon of a simple alkene is virtually an unknown reaction. The hexenyl radical cyclization, a rapid addition to the more substituted end of an alkene, is indeed a special transformation.

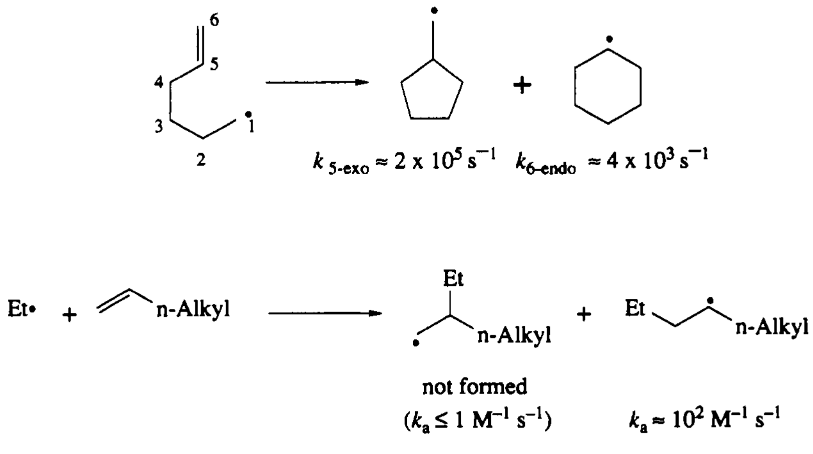
6
5
4
3
2
1
$k_{5\text{-exo}} \approx 2 \times 10^5\ s^{-1}$
$k_{6\text{-endo}} \approx 4 \times 10^3\ s^{-1}$
Et•
n-Alkyl
Et
n-Alkyl
Et
n-Alkyl
not formed
$(k_a \leq 1\ M^{-1}\ s^{-1})$
$k_a \approx 10^2\ M^{-1}\ s^{-1}$

**Scheme 2** The hexenyl radical cyclization

Determining the underlying factors that control the cyclization reactions of hexenyl and related radicals has been the object of much study. The recent theoretical treatments of Beckwith and Schiesser,[6] and Houk and Spellmeyer,[7] relate the current state of understanding with many important references to the extensive body of prior work.

Not surprisingly, the hexenyl radical cyclization is entropically favored over its bimolecular counterpart (enthalpies of activation are similar). However, entropy is not the whole story in the preferential formation of the less stable 5-exo product by attack at the more substituted carbon. To understand this key feature, we must turn to the transition state model outlined in Figure 1. At least three low energy transition states are important to consider: the 5-exo chair (**1**), the 5-exo boat (**2**), and the 6-endo chair (**3**).[8] This model, which will be used to interpret both regio- and stereo-chemical features, was proposed and developed by Beckwith in pioneering work that spans more than a decade.[6] The recognition by Houk and Spellmeyer[7] that the 5-exo boat transition state is relatively low in energy and cannot be neglected is a very significant advance that aids in the understanding of stereoselectivity.

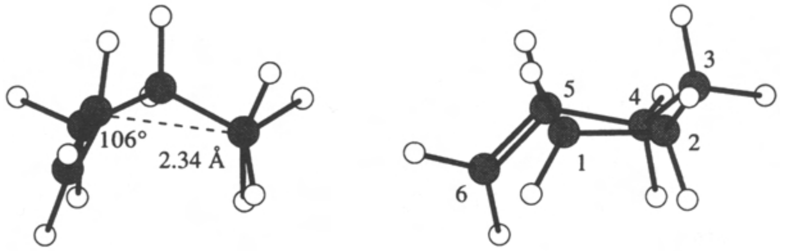

5-exo chair (**1**), 0 kcal mol$^{-1}$

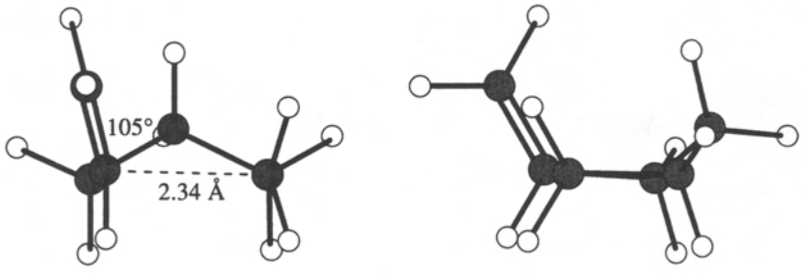

5-exo boat (**2**), +1 kcal mol$^{-1}$

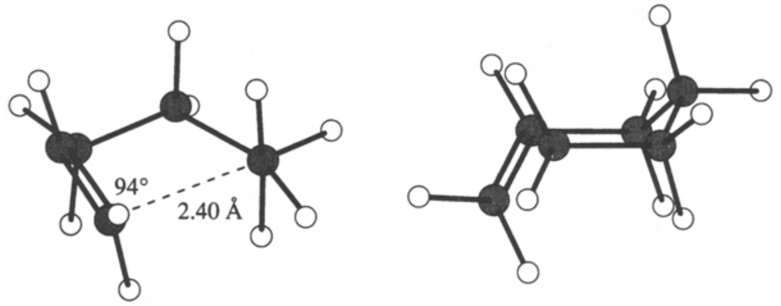

6-endo chair (**3**), +3 kcal mol$^{-1}$

**Figure 1** Transition states for hexenyl radical cyclization

The energetic differences between these three transition states are mainly enthalpic in origin, and the relative energy values calculated by Houk/Spellmeyer (STO-3G level) are included in Figure 1.[9] Provided that the 5-exo boat transition state (**2**) is not neglected, the Houk computational model closely reproduces the experimentally observed regioselectivity. The 5-exo chair transition state (TS) bears a striking resemblance to a cyclohexane chair, as originally proposed by Beckwith. Reflective of the early TS, the forming C—C bond is very long (its length is similar to the distance between C-1 and C-3 in cyclohexane), and the radical and alkene carbons have deviated little from their $sp^2$ geometries. The angle of attack (106°) is near to the preferred angle for unconstrained bimolecular additions (109°) and, because the forming bond is long, the angle and torsional strain of the connecting chain resemble more a cyclohexane ring than the product cyclopentane ring. The forming bond is nearly eclipsed, but it is so long that the energetic penalty is minimal. The length of the forming bond in the 6-endo TS (**3**) is similar to that of the 5-exo TS (**1**), but the angle of attack is constrained to be much smaller (94°) because of the endo orientation of the alkene. Thus, the overlap between the SOMO of the radical and the LUMO of the alkene is poorer, and energy is sacrificed. This stereoelectronic rationale, first proposed by Beckwith, is generally regarded as the single most important factor that favors 5-exo over 6-endo cyclization. Baldwin's guidelines for ring closure integrated these stereoelectronic preferences for radicals with those for other types of cyclizations.[10] Because of the importance of SOMO–LUMO overlap, cyclizations of radicals are more closely related to those of anions than of cations.

In addition to this important stereoelectronic effect, it is less widely recognized that the 6-endo transition state (**3**) is believed to have a higher degree of torsional and/or bending strain that its 5-exo counterpart (**1**).[11] This added strain may be due to deformations in the chain, which are necessary to accommodate the best possible angle of attack, or to the elongated forming bond, which stretches the 'cyclohexane ring' away from its ideal geometry.

The comparison of exo and endo transition states has emphasized the similarity of the 5-exo transition state (**1**) with a cyclohexane chair. The comparison of the two 5-exo transition states, (**1**) and (**2**), illustrates the all-important differences. The two transition states are very similar, but only five of the six atoms have analogies in chair or boat cyclohexane. The terminal alkene carbon (C-6) is well out of place compared to its partner in cyclohexane. Thus, the transition states really resemble stretched cyclopentane rings more than cyclohexanes. A boat cyclohexane is disfavored relative to a chair by two eclipsed carbon–carbon bonds and by the 'flagpole' interaction. In the 5-exo boat transition state, all of these interactions are greatly reduced: the flagpole interaction because the terminal alkene carbon is not appropriately placed, and the eclipsing interactions because of the presence of the $sp^2$ atoms that have yet to rehybridize. The small energy difference disfavoring the boat (**2**) relative to the chair (**1**) probably results from the remnants of the flagpole interaction (if any), and from the presence of a *gauche* butene arrangement (allylic C—H eclipsing vinylic C—H) rather than the more favored skew butene (allylic C—H eclipsing C=C). That (**1**) and (**2**) are comparable in energy is important for understanding stereoselectivity (see below).

The analogy between 5-exo transition states and the chair/boat cyclohexane is simple to apply and has useful predictive and interpretive value, provided that one recalls the differences as well as the similarities.

Substituent effects on cyclizations of simple nucleophilic hexenyl radicals have been well studied, and much quantitative rate data is available.[12] The trends that emerge from this data can often be translated to qualitative predictions in more complex settings. Once the large preference for 5-exo cyclization is understood, other substituent effects can often be interpreted in the same terms as for addition reactions. For example, electronegative substituents activate the alkene towards attack, and alkyl substituents retard attack at the carbon that bears them. The simple hexenyl radical provides a useful dividing point: $k_c \approx 2 \times 10^5\ s^{-1}$. More rapid cyclizations are easily conducted by many methods, but slower cyclizations may cause difficulties. Like the hexenyl radical, most substituted analogs undergo irreversible 5-exo closure as the predominate path. However, important examples of kinetic 6-endo closure and reversible cyclization will be presented.

### *4.2.1.1.2 Accelerating substituents*

Fortunately for the synthetic chemist, most substituents accelerate 5-exo cyclizations, and the complete absence of 6-endo products is not uncommon. Several important types of accelerating groups are summarized in Scheme 3. Like addition reactions, activating groups on the alkene (C-6) provide a large rate enhancement due to favorable FMO interactions. Unlike additions, such activating substituents are not required for successful cyclizations; however, they can prove beneficial to offset deactivating substituents in hexenyl radical cyclizations, and they are often essential when forming larger rings. Most substituents on the chain also accelerate the hexenyl radical cyclization, probably by raising the energy of the ground state relative to the transition state (as in the *gem* dimethyl effect). The presence of additional rings in the cyclization substrate is usually beneficial, provided that a relatively unstrained ring is forming. In general, fused rings are preferred over bridged; however, bridged rings have been formed on many occasions. Substitutions of oxygen or nitrogen for C-3 are powerfully accelerating because they provide better overlap in the 5-exo transition state. Most alkyl substituents on the radical carbon (C-1) have relatively little effect on the rate: simple primary, secondary and tertiary alkyl radicals all cyclize at about the same rate. Vinyl and phenyl radicals are much more reactive in cyclizations than alkyl radicals. Acyl radicals are also excellent substrates.

### *4.2.1.1.3 Decelerating substituents*

The most common reason that 6-endo products are observed in radical cyclizations is because 5-exo cyclizations are decelerated by substituent effects (see Scheme 4). Just as in addition reactions, the substitution of any group for hydrogen at the β-alkene carbon (C-5) slows 5-exo cyclization significantly, and 6-endo products are formed, sometimes predominantly. This effect also appears to be sensitive to radical substitution: 5-alkyl-substituted tertiary radicals give increased amounts of 6-endo products compared to primary radicals. The introduction of a radical-stabilizing heteroatom endocyclic to the forming ring (substitution of X for C-2) also retards 5-exo closure due either to its stabilizing effect, or (more

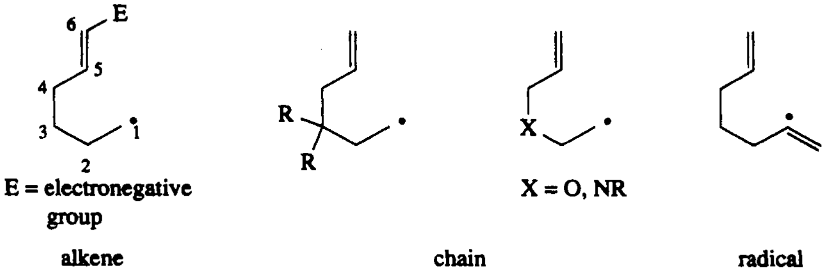
6
E
5
4
3
2
1
E = electronegative group
alkene
R
R
X
X = O, NR
chain
radical

**Scheme 3** Accelerating substituents

likely) to geometric constraints imposed on the radical by resonance.[13] Relatively little is known about the effect of heteroatom substituents attached to the radical (C-1) exocyclic to the forming ring. One suspects that they will be at least modest rate depressors because they stabilize the radical.

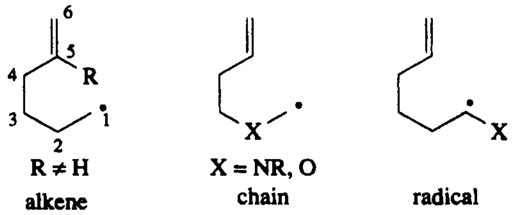
6
5
4
R
3
1
2
R ≠ H
alkene
X
X = NR, O
chain
X
radical

**Scheme 4** Decelerating substituents

All of these decelerating effects are easily overridden by appropriate alkene substitution. Indeed, any terminal alkene substituent will decelerate 6-endo cyclization. To accelerate 5-exo cyclization, one requires only an electronegative alkene substituent at C-6.

The appropriate placement of activating groups can also be used to accelerate 6-endo cyclizations, as illustrated by the examples in Scheme 5.[14–16] However this prescription is not a guaranteed cure to overcome 5-exo cyclizations when 6-endo products are desired. As illustrated by the last example in Figure 6,[17] the preference for 5-exo cyclization can often be so high that it cannot be overridden by an activating group.

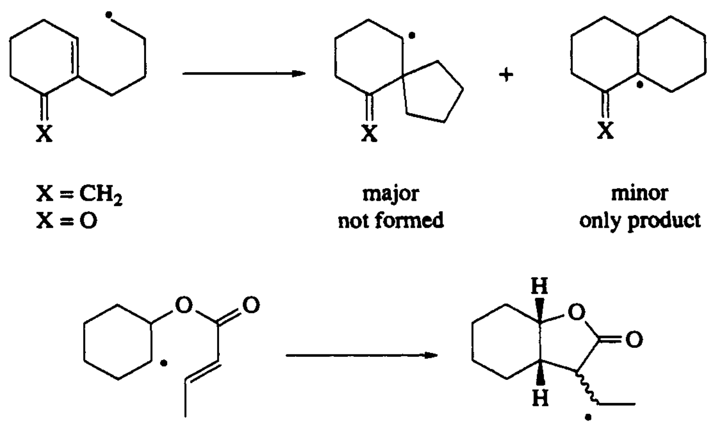
X
X
X
X = CH2
X = O
major
not formed
+
minor
only product
O
O
H
O
O
H

**Scheme 5** Activation of 6-*endo* cyclizations

#### *4.2.1.1.4 Carbonyl-substituted radicals*

Because of the centrality of the carbonyl group in synthesis, the cyclizations of carbonyl-substituted radicals are of special importance. At present, there are no accurately known rate constants for the cyclizations of any carbonyl-substituted radicals, and quantitative statements are risky. Because carbonyl-substituted radicals add more rapidly to simple alkenes than alkyl radicals add, it might be suspected that they cyclize more rapidly as well. However, qualitative evidence does not support this analogy.

Cyclizations of carbonyl-substituted radicals can sometimes provide very high levels of 6-endo products by either kinetic or thermodynamic methods. Reversible hexenyl radical cyclizations are presently restricted to radicals with two carbonyl or cyano groups.[18] The discussion of reversible cyclizations is reserved for the hydrogen atom transfer section (Section 4.2.2.1.4) because this is the only method by which they have been conducted. Some kinetic substituent effects are summarized in Scheme 6.[19] If the carbonyl group is outside the forming ring, there is a slight increase in the amount of 6-endo product with monosubstituted alkenes (R = H); however, when R is an alkyl group, the 6-endo cyclization is often the only pathway. The placement of a ketone (but not an ester or an amide) inside the forming ring also greatly favors 6-endo closure.[19–21] It has been proposed that 5-exo cyclizations of the ketone-substituted radicals are retarded because overlap between the radical and the carbonyl group must be sacrificed to attain the transition state geometry.[19] Even without knowing rate constants, it is clear from experiment that the cyclizations of these latter types of radicals are very slow (although still useful).

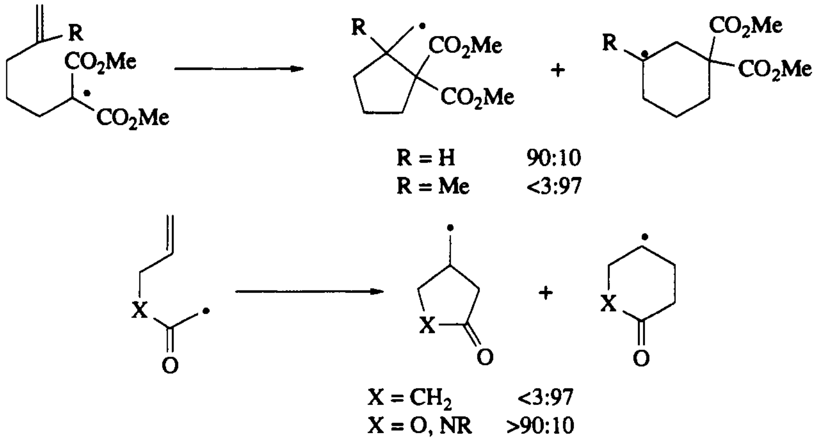

**Scheme 6** Carbonyl-substituted radicals

### 4.2.1.2 Butenyl, Pentenyl, Heptenyl and Other Radical Cyclizations

Although cyclizations of hexenyl radicals are the best understood and most common, other cyclizations have unique features that can be exploited in synthesis. The basics for cyclization of butenyl and pentenyl radicals are summarized in Scheme 7. In accord with the stereoelectronic rationale, these radicals are very reluctant to cyclize in an endo mode due to the very small angle of attack that is required. The butenyl radical undergoes 3-exo cyclization with a rate that is near the lower limit of synthetic utility.[22] Like the hexenyl radical, this rate may be dramatically increased by substituents (for example, *gem* dimethyl substituents on the chain dramatically accelerate the closure).[23] Unlike the hexenyl radical, the cyclization is reversible and, due to ring strain, the equilibrium usually lies far to the side of the open radical. Accordingly, 3-exo cyclizations that synthesize cyclopropanes are only useful if there is a means to rapidly trap the cyclic radical (but not the initial radical) or if substituents dramatically shift the unfavorable equilibrium. Selective trapping of equilibrating radicals can be planned within the framework of the Curtin–Hammett principle, as described for cyclizations to carbonyls (see Section 4.2.5). 3-Exo fragmentations are very useful reactions, either alone, or in combination with 3-exo cyclizations (this combination results in rearrangement if the forming and fragmenting bond are not the same; see Section 4.2.6.2.1).

Like many ionic cyclizations, the formation of cyclobutane rings by radical cyclizations is very slow, and powerful accelerating effects will be required for any synthetic applications (see Scheme 7).[2] These cyclizations are again reversible, and, in the absence of any other effects, the equilibrium lies to the side of the open radical due to ring strain. The fragmentations of simple cyclobutyl carbinyl radicals are slow,

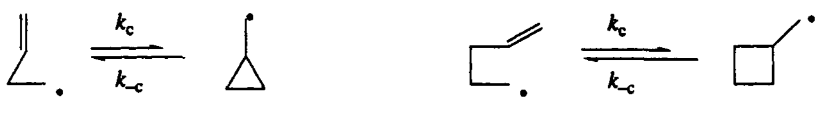

$k_c \approx 2 \times 10^3\ s^{-1}$
$k_{-c} \approx 1 \times 10^8\ s^{-1}$

$k_c \leq 1\ s^{-1}$
$k_{-c} \approx 5 \times 10^3\ s^{-1}$

**Scheme 7** Butenyl and pentenyl radical cyclizations

but still potentially useful. Any stabilization of the open radical relative to the cyclic radical should accelerate such fragmentations.

Cyclizations of higher homologs of the hexenyl radical are useful, and they are generally irreversible. As the size of the forming ring increases, the rate of ring closure begins to decrease for entropic reasons. In addition, larger rings can better accommodate the favored trajectory angle for an endo transition state, and the large preference for exo cyclization that is seen in smaller rings begins to erode.

Heptenyl radical cyclizations are very useful in synthesis, and the behavior of the parent radical is summarized in Scheme 8.[24] Rate constants of 6-exo and 7-endo closure are near the lower limit of synthetic utility, and the ratio of cyclohexylcarbinyl radical to cycloheptyl radical is about 85:15 at normal operating temperatures. Besides cyclization, there is another competing unimolecular reaction that is unique to heptenyl radicals: 1,5-allylic hydrogen transfer. This intramolecular H-transfer is always thermodynamically favorable, but is strongly disfavored kinetically in both smaller rings (for stereoelectronic reasons) and larger rings (for entropic reasons). In the parent heptenyl radical, the rate of 1,5-hydrogen transfer is comparable to that of 7-endo cyclization, but there are examples where it can even exceed the rate of 6-exo cyclization. Thus, there are at least three problems to consider when planning a heptenyl radical cyclization; (i) the rates of cyclization are relatively slow, (ii) an overriding bias for exo cyclization does not exist, and (iii) competitive 1,5-hydrogen transfer may occur if there are accessible allylic hydrogens. Fortunately, these problems can often be solved by placement of appropriate substituents. For example, the introduction of an activating group on the alkene terminus often accelerates 6-exo cyclization sufficiently so that all three problems are simultaneously solved. It is also possible to effect selective 7-endo cyclizations in some cases.

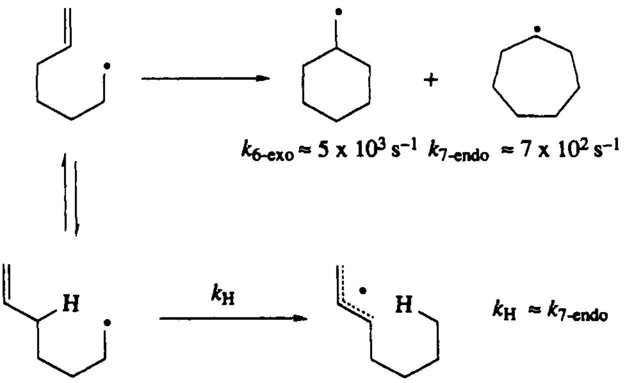

$k_{6\text{-exo}} \approx 5 \times 10^3\ s^{-1}$ $k_{7\text{-endo}} \approx 7 \times 10^2\ s^{-1}$

$k_H \approx k_{7\text{-endo}}$

**Scheme 8** The heptenyl radical cyclization

The formation of medium and large rings by radical cyclizations is no different from most other standard methods. The formation of medium-sized rings by radical cyclizations is difficult. For example, the octenyl radical undergoes selective 8-endo closure rather than 7-exo closure[6] but the rate constant for cyclization is very low ($k \approx 1 \times 10^2\ s^{-1}$). However, one suspects that the kinds of substituent effects that favor medium ring formation in standard ionic reactions (like the introduction of (*Z*)-double bonds in the connecting chain)[25] should also accelerate radical cyclizations. As the ring size becomes larger and transannular interactions decrease, unimolecular rate constants for cyclization recover and begin to approach those of bimolecular addition. Pioneering work of Porter[26] has shown that, with appropriate electronic pairing and reaction concentration, large rings can be formed with a facility comparable to typical ionic processes (see Section 4.2.2.1.1).

### 4.2.1.3 Stereoselectivity

Although radical cyclizations have a reputation of exhibiting poor stereoselectivity, there are now many examples where highly stereoselective transformations have occurred, and both empirical and theoretical guidelines are beginning to emerge. As with regiochemistry, the papers of Beckwith[6] and Houk[7] are highly recommended starting points for stereochemical information. When predicting stereochemistry, it is important to keep in mind that transition states for radical cyclizations are early, and steric interactions in the final product may not be important in the transition state. More important are local conformation effects about the alkene, and allylic substituents and *cis*-substituted alkenes have large effects on stereoselectivity.

#### *4.2.1.3.1 Hexenyl radical cyclizations*

Stereoselectivity in the cyclization of substituted hexenyl radicals often follows the guidelines originally proposed by Beckwith.[27] The Beckwith model, shown in Figure 2, is probably a good representation of the lowest energy transition state, and it predicts the major product by placing a chain substituent in an equatorial-like orientation. Thus, 3-substituted hexenyl radicals give *cis* products, and 2- and 4-substituted radicals give *trans* products. The stereoselectivity of C-1-substituted radicals requires special comment because this center is $sp^2$ hybridized, and thus the substituent ($R^1$) is not in an equatorial-like orientation but actually eclipses the alkene $CH_2$ about the forming bond. (However, this eclipsing interaction is relatively small because of the long forming bond and the obtuse angle of attack.) The Beckwith model correctly predicts that C-1 alkyl substituents will give mainly *cis* products, although the underlying cause for the *cis* selectivity has been the source of considerable speculation. Houk and Spellmeyer[7] have suggested that van der Waals attraction is a likely cause. Although simple alkene substituents give 1,2-*cis* products, larger $R^1$ groups are *trans* selective, as are most ethers ($R^1$ = *O*-alkyl or *O*-silyl). Esters and ketones show virtually no selectivity in simple examples.[19]

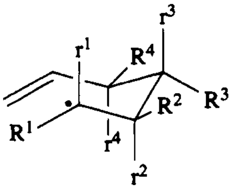

R = location of substituent in major diastereomer
r = location of substituent in minor diastereomer

**Figure 2** Beckwith model for stereoselectivity

The understanding of the stereoselectivity in these cyclizations (and hence the prediction of which cyclizations will be highly selective) was significantly advanced by Houk and Spellmeyer.[7] They proposed that the minor diastereomeric product may arise not only from the 5-exo chair transition state with an axial-like substituent, but also from the 5-exo boat TS. Scheme 9 gives a specific example: the cyclization of the 3-methylhexenyl radical. The relative energies (rounded to the nearest 0.5 kcal $mol^{-1}$ (1 kcal = 4.18 kJ)) are derived from force field calculations. The Beckwith model correctly predicts the formation of the major *cis* product, which arises *via* transition state A (chair, methyl equatorial). However, the calculations indicate that the minor product arises not only from the chair transition state C with the methyl group axial-like, but also from the boat transition state D with the methyl group equatorial-like. According to the force field model, this is a general phenomenon for simple systems: a single low energy transition state accounts for the major product but two transition states of intermediate level combine to produce the minor product.

The important studies of RajanBabu provide solid experimental support for the postulated energetic importance of boat transition states (Scheme 10).[28,29] Cyclization of (4α,β) gives a stereochemical outcome that is at first glance surprising: the stereochemistry of the methyl group is apparently controlled by the remote *t*-butyl group, and not by the neighboring residues on C-1 and C-2. The *t*-butyl group not only locks the conformation of the cyclohexane ring, but it also locks the conformation of the forming ring because the forming ring must be *cis* fused (the orbital overlap to form a *trans* ring is extremely poor). This is akin to locking a *cis* decalin with a *t*-butyl group (see the triple Neumann projections in Scheme 10), and instead of four transition states, only two (one chair and one boat) are now accessible. In each case, the major diastereoisomer (5α) or (6β) results from the chair-like transition state of the forming ring. Be-

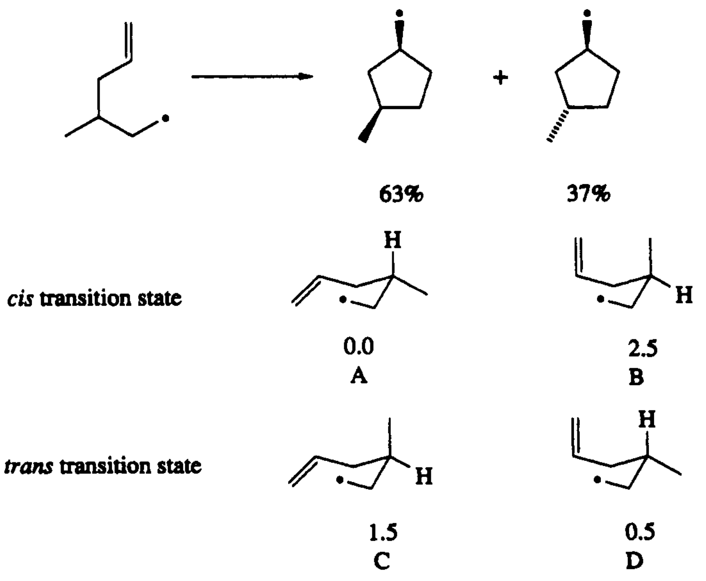
63%
37%
*cis* transition state
*trans* transition state
H
H
H
H
0.0
A
2.5
B
1.5
C
0.5
D

**Scheme 9** Houk/Spellmeyer model for cyclization of a 3-substituted hexenyl radical

cause the other chair is prohibitively high in energy, it is very likely that the minor products (**5β**) and (**6α**) result from boat-like transition states.

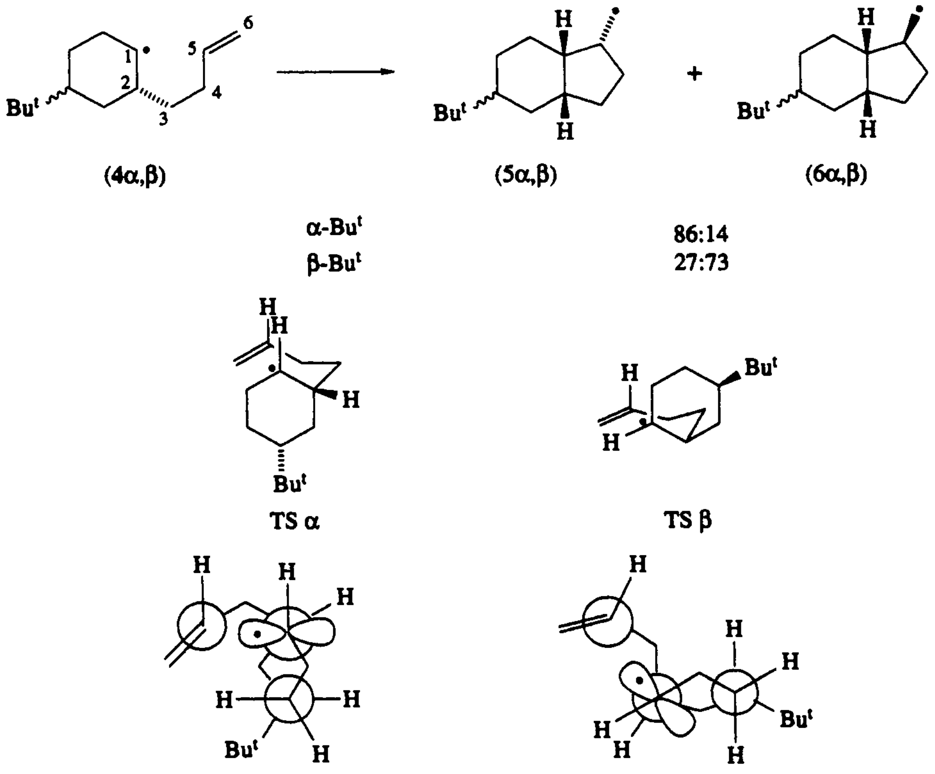
1
2
3
4
5
6
Bu$^t$
H
H
(4α,β)
(5α,β)
(6α,β)
α-Bu$^t$ 86:14
β-Bu$^t$ 27:73
TS α
TS β
H
Bu$^t$

**Scheme 10** Evidence for boat transition states

Indeed, RajanBabu has shown that the introduction of allylic substituents at C-4 can either reinforce or completely override the preference for a chair transition state, depending on the configuration. Two examples are provided in Scheme 11. In the framework of the stereochemical model, high selectivity results in these examples because three of the four normally accessible transition states have been eliminated by unfavorable interactions (the locked dioxolane ring eliminates one chair and one boat, and A-strain caused by the allylic substituent selects between the remaining chair and boat). The recognition that boat transition states are important, and can even dominate, should greatly facilitate the design of stereoselective hexenyl radical cyclizations.

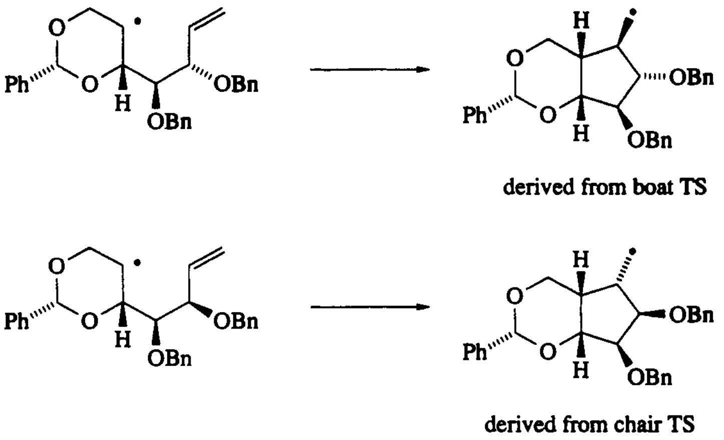

derived from boat TS

derived from chair TS

**Scheme 11** Highly stereoselective cyclizations

### *4.2.1.3.2 Heptenyl radical cyclizations*

Stereoselectivity in the cyclization of heptenyl radicals has recently been studied and the analogy to chair cyclohexane has again been drawn.[30] Figure 3 illustrates the two chair-like transition states that have been considered (in most cases, an activating group is present to facilitate the cyclization). The assumptions that model A is of lower energy than B, and that equatorial-like substituents are preferred, suffice to rationalize some of the literature examples; however, the situation is less straightforward than with hexenyl radical cyclizations. For example, this model predicts that 2- and 4-substituted precursors will give *cis* products, and that 3- and 5-substituted precursors will give *trans*. However, Hanessian has shown that 2-, 3- and 4-methyl-substituted heptenyl radicals (*E* = *trans* $CO_2Me$) all show a very slight preference for formation of the *trans* product.[30] This serves as a reminder that the forming bond in the transition state for the heptenyl radical cyclization is so long that distortions are inevitable, and the connecting chain cannot closely resemble a cyclohexane chair. Indeed, if the connecting chain in a hexenyl radical reaction resembles a cyclohexane ring, then cycloheptane-like conformers might be of considerable importance in the cyclizations of heptenyl radicals.

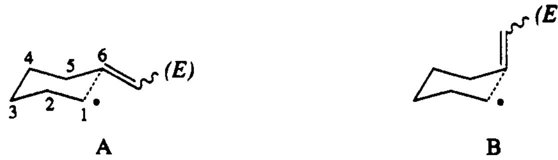

**Figure 3** Stereoselectivity in heptenyl radical cyclizations

## 4.2.2 CYCLIZATIONS OF CARBON-CENTERED RADICALS TO CARBON–CARBON MULTIPLE BONDS

Most of the recent synthetic developments in the field of radical cyclization have involved the reactions of carbon-centered radicals with alkenes and alkynes. Other useful acceptors include allenes,[31] dienes[30] and vinyl epoxides.[32] The same methods are used for cyclizations to these acceptors as for radical additions, and the preceding chapter should be consulted for specific details on an individual method (the organization of this section parallels that of Section 4.1.6). Selection of a particular method to conduct a proposed cyclization is based on a variety of criteria, including the availability of the requisite precursor, the electronic properties of the radical, the expected rate of the cyclization, the type of functionality that is desired in the product, and the ease of purification of the products. These aspects will be briefly featured with each cyclization method.

The literature on radical cyclizations has grown so rapidly over the last decade that an introductory review cannot even sample all of the important types of reactions. In broad areas such as tin hydride cyclizations, this chapter will try to focus on the most commonly used types of cyclizations. With lesser used techniques, the selected examples will attempt to illustrate the synthetic possibilities and limitations. Several recent reviews that cover major parts of the radical cyclization field can be consulted for more detailed coverage.[3–5,33,34]

## 4.2.2.1 Chain Methods

Most radical cyclizations are conducted by one of the common chain methods. Kinetic analysis and synthetic planning are usually more straightforward than in addition reactions because the cyclizations are intramolecular.

### *4.2.2.1.1 Metal hydrides*

#### *(i) Tin hydride, general considerations*

The use of tin hydride is by far the most popular and generally applicable method to conduct radical cyclizations. Because the tin radical is such a powerful atom and group abstractor, a wide variety of radical precursors can be used. A partial list of precursors (in rough order of decreasing reactivity) includes iodides, bromides, phenyl selenides, xanthates (and related derivatives),[35] nitro groups,[36] thio acetals,[37] phenyl sulfides and chlorides. The less reactive precursors are more useful for the production of more stable radicals. Although the tin hydride method is most commonly used for the cyclizations of nucleophilic radicals, it is appropriate for electrophilic (and ambiphilic) radicals as well. The kinds of radicals that can be generated for cyclization range from the most reactive aryl and vinyl radicals, through alkyl radicals, to stable radicals such as allyl[38] and benzyl.[39]

The tin hydride method is reductive, and the cyclic radical is almost always trapped by a hydrogen atom. In simple cyclizations, both the radical precursor and the alkene are lost during tin hydride reduction, and this sometimes results in underfunctionalized products, necessitating the introduction of extra functional groups for subsequent transformations. However, in the synthesis of simple molecules, this is often an advantage as steps to remove residual alkenes, carbonyl groups and the like, left by ionic methods of C—C bond formation, are not required. Work-up requires separation of the desired products from the tin by-products (see Section 4.1.6.2.1).

The most important consideration in conducting a tin hydride cyclization is not the electronic nature of the radical but the rate of cyclization. Equation 1 expresses the requirement for the successful cyclization of the initial radical prior to trapping with tin hydride. Cyclizations more rapid than that of the hexenyl radical are easily conducted by mixing the precursors with a slight excess of tin hydride (1.1 equiv. is common) at 0.01–1.0 M, and then initiating the chain. Slow cyclizations require high dilution conditions: syringe pump addition or catalytic tin hydride techniques are the most popular. With reactive radical precursors and proper conditions, cyclizations approaching the lower rate limit in solution can be conducted with the tin hydride method.[40] To maintain the chains, excess initiator and a greater excess of reducing agent (either tin hydride in the syringe pump method or the coreductant in the catalytic method) are often required.

$$k_c > k_H\,[\mathrm{Bu_3SnH}] \qquad (1)$$

As the rate of cyclization becomes slower, the reactivity of the precursor becomes more important. To ensure that the radical generation step does not break the chain, it is important to use the most reactive precursor available. For very slow cyclizations, the advice is simple: use iodides whenever possible. The purity of the precursor is also critical for slow cyclizations because tin hydride can sometimes react with impurities to generate hydrogen atom sources that are much more reactive than itself. Any impurities that might generate thiols or selenols may cause undue amounts of reduction (thus, the purity of phenyl sulfides and selenides is especially important). Metal impurities, which may form transition metal hydrides, can be devastating, even for fast cyclizations.[41] Empirically, it seems that breaking of the chain is less of a concern in the hydrogen transfer step, probably because radicals often react with each other or with the medium by hydrogen transfer. Thus, even if hydrogen transfer from tin hydride fails at low concentration, many of the product radicals will nevertheless end up with a hydrogen. Finally, high temperatures usually favor cyclization over atom transfer, and the use of a higher boiling solvent can be a productive means to favor the formation of cyclic products. Rapid cyclizations can be conducted at temperatures as low as –78 °C by using triethylborane initiation as prescribed by Oshima and Utimoto.[42]

The following sections provide selected examples of tin hydride cyclizations that are organized by the nature of the radical. More detailed coverage is provided in several general reviews,[5,33,34] and in the excellent specialized review of Neumann.[43]

### *(ii) Substituted alkyl radicals (carbocycles)*

Many synthetic methods are currently available to form simple, isolated rings, and radical cyclizations, although certainly applicable, are not often used. However, as the complexity of the molecules is increased, radical cyclizations begin to offer advantages even in the preparation of isolated rings; preparations of highly oxygenated carbocycles from sugars are prime examples.[44–46] For the synthesis of polycyclic molecules, radical cyclizations offer a powerful alternative to traditional means for ring closure, and tin hydride cyclizations are useful for the preparation of fused, bridged and spiro rings.

Recent representative examples in which fused rings have been formed are shown in Scheme 12. As illustrated by the conversion of (7) to (**8**),[47] the forming of bonds to preexisting small rings results in *cis* ring fusion (5,5-, 5,6- and 6,6-bicycles). However, in extensive studies that provide insight into both stereo- and regio-selectivity in complex cyclizations,[41] Hart has shown that smaller rings take precedence over larger in formation of *cis*-fused rings. For example, cyclization of (**9**) provides (**10α**) and (**10β**), both of which contain a *trans* 6,5-ring fusion and a *cis* 5,5-fusion.[48] Likewise, when the activating group is relocated, a *trans* 6,6/*cis* 6,5 fusion is preferred [see (**11**) → (**12**)].[41] The stereoselectivity in the first two examples is noteworthy; in each case the C-1 alkyl group is *cis* to the alkene acceptor in the transition state leading to the major product. As larger rings are involved, overlap to form *trans*-fused rings can improve.[49] Winkler and Sridar have shown that high selectivity in the formation of *trans*-fused 5,8-rings can be obtained by using ring allylic substituents to dictate the local conformation of the alkene acceptor.[50] For example, cyclization of (**13**) provides exclusively (**14**), but the hydroxy epimer of (**13**) gives about a 1:1 mixture of products derived from *cis* and *trans* cyclization.

Examples of bridged and spiro ring formation are provided in Scheme 13. In the formation of bridged rings[51] the conformation of the radical is important, as illustrated by two examples from Giese.[52] Cyclization of (**15**) gives (**16**) in excellent yield but the related compound (**17**) is reduced to (**18**) under the same conditions (however, this unsuccessful cyclization is 6-exo, not 5-exo). These results are taken as evidence that the intermediate radicals adopt conformations like (**19**), in which a group at C-3 is appropriately oriented for cyclization, but one at C-5 is not. The formation of spiro rings has been extensively investigated by Clive,[53] and the conversion of (**20**) to (**21**) provides an example that also illustrates that alkynes are very useful acceptors for cyclization. The resulting alkene then provides a handle for subsequent transformations.

The combination of standard synthetic transformations with radical cyclizations can often result in efficient, stereocontrolled methods to build rings. For example, protocols that form cyclization precursors by Michael additions[54] and aldol reactions[55] have been developed. Scheme 14 illustrates a stereocontrolled method of ring formation developed by Clive that relies on the Ireland–Claisen rearrangement.[56] One of the most elegant examples of this approach to ring construction is the combination of Diels–Alder reactions with radical cyclizations, as recently described by Ghosh and Hart.[57] In the example provided in Scheme 14, an aryl radical cyclization is conducted (see below for aryl radical cyclizations).

Cyclizations to form larger rings are also possible as the two examples contained in Scheme 15 illustrate. 6-Exo cyclizations usually require activating groups unless other substituents accelerate the cyclization.[30,58] A few 7-endo cyclizations are known, but intermediate size rings (8–10) will be difficult to form unless special conformational advantages are built into the precursors. The formation of larger rings has been accomplished with great success by Porter.[21,40] Substituent effects in these cyclizations parallel those in bimolecular additions, and electronic pairing of the radical and the acceptor is essential. Because the effective molarities of macrocyclization are favorable, low concentrations (0.01–0.001 M) promote cyclization over addition. Scheme 15 features a recent application of this macrocyclization by Pattenden with several interesting features.[59] An allylic radical undergoes cyclization, but, due to rotation, some alkene stereochemistry is lost. The product is converted to the cembranolide mukulol by reduction of the carbonyl.

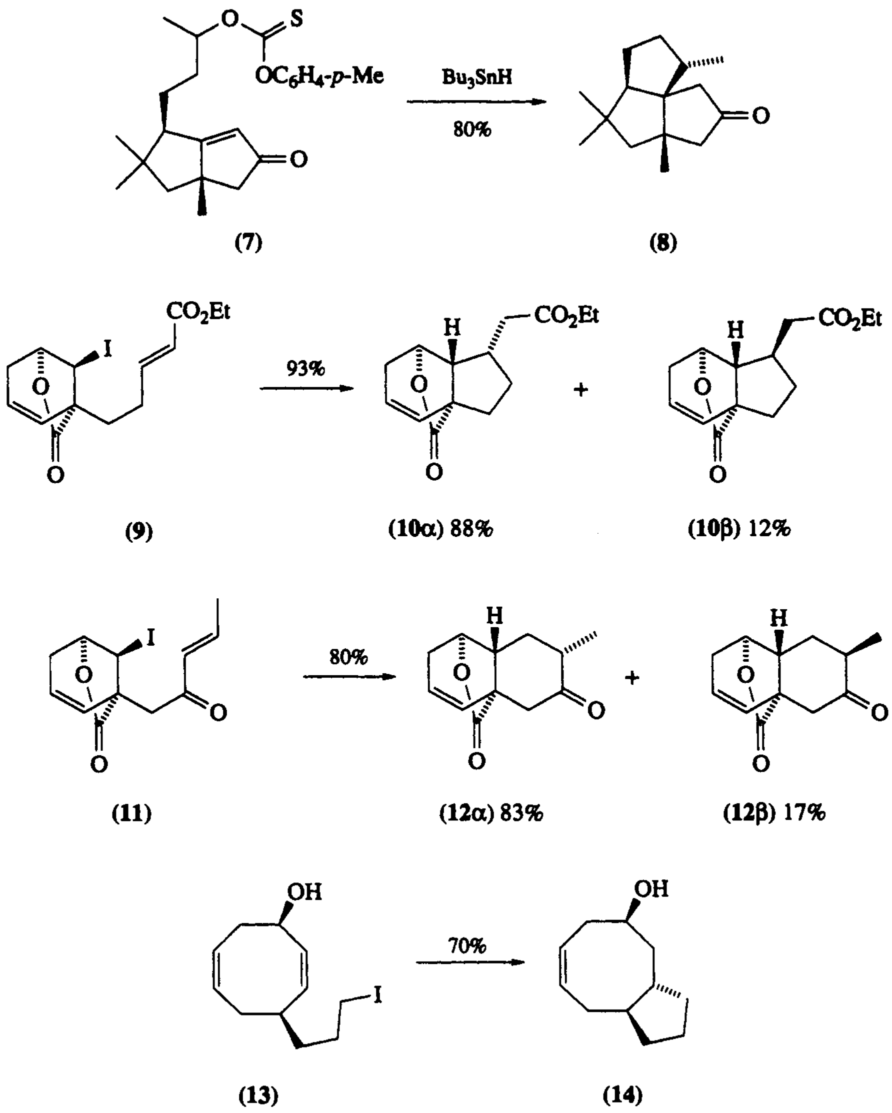

Scheme 12

*(iii) Substituted alkyl radicals (heterocycles)*

As indicated above, nuclear substitution of C-3 by oxygen or nitrogen accelerates 5-exo cyclizations, and some of the best radical cyclizations form heterocycles. Several examples are provided in Scheme 16. As indicated by the conversion of (**22**) to (**23**), the directing effect of the heteroatom is often powerful enough to overcome an otherwise detrimental C-5 methyl substituent.[60] Several research groups[61,62] have developed mild methods to form fused carbohydrates, and the conversion of (**24**) to (**25**) is a representative example.[63] Although the stereochemistry of most such cyclizations follows the Beckwith guidelines, Watanabe and Endo have recently shown that dichloroalkyl radicals give the opposite stereoselectivity when compared to simple alkyl radicals.[64] This observation appears to have some generality,[65] and it is synthetically significant because the perchlorinated products can be reductively dechlorinated.

The cyclizations of halo acetals, introduced by Stork[66] and Ueno,[67] are among the most popular of all radical methods because the precursors are easy to prepare, the cyclizations are very rapid, and the products can be converted to a variety of different heterocycles. The conversion of (**26**) to (**28**; Scheme 17) illustrates the basic procedure.[68] Standard bromoacetalization of an alcohol provides the precursor (**27**). After tin hydride cyclization and acidic oxidation, lactone (**28**) is formed in excellent yield with 97%

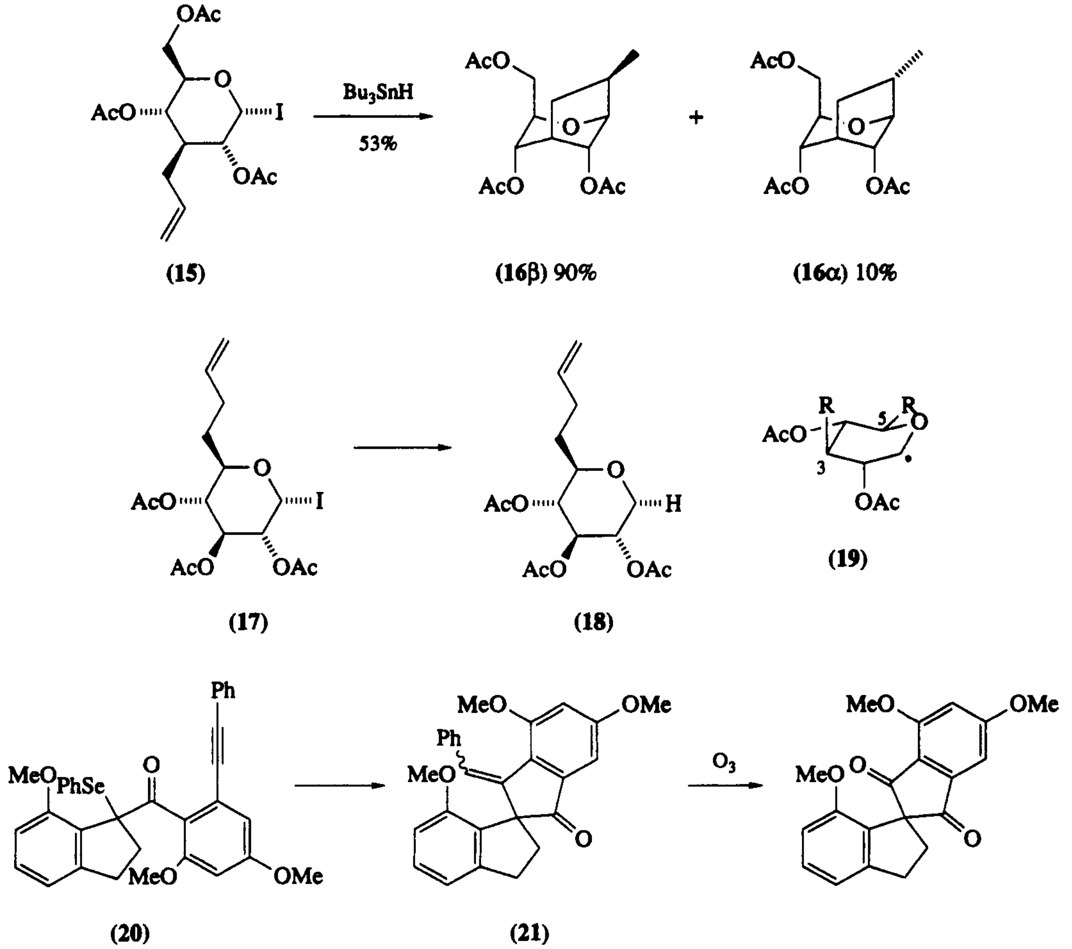
Bu3SnH
53%
(15)
(16β) 90%
(16α) 10%
(17)
(18)
(19)
(20)
(21)
O3

Scheme 13

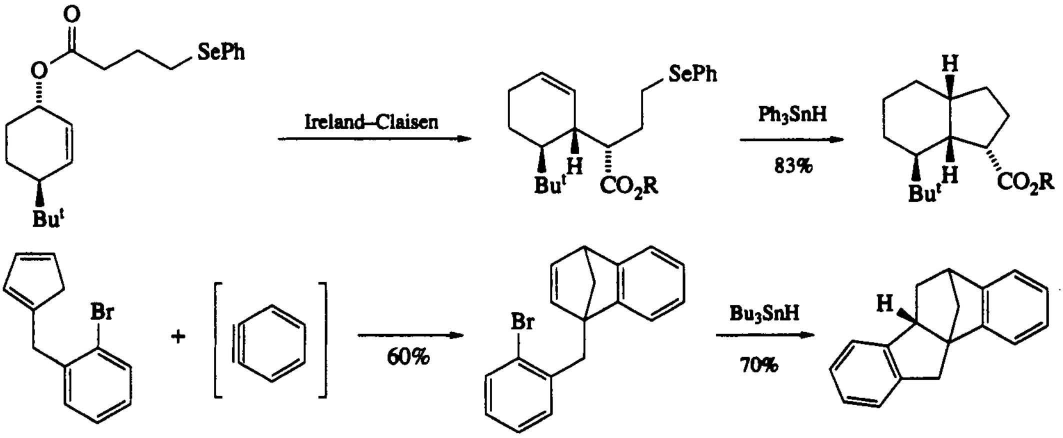
Ireland–Claisen
Ph3SnH
83%
60%
Bu3SnH
70%

Scheme 14

*trans* selectivity. The cyclizations of halo esters provide a potentially more direct route from alcohols to lactones; however, these cyclizations are much slower than the hexenyl radical benchmark, while the acetal cyclizations are much more rapid. Recent variants on this theme include the formation of 6-exo products,[69] furans[70] and unsaturated lactones,[71,72] as illustrated in Scheme 17.

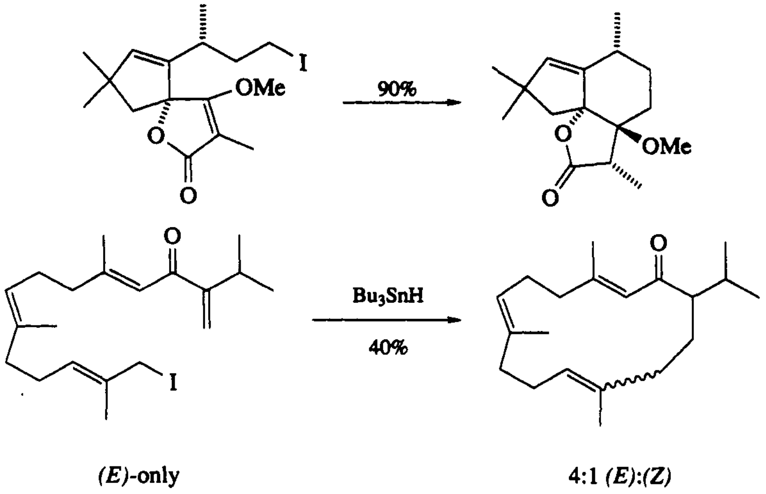
I
OMe
O
O
90%
O
OMe
O
O
O
I
Bu$_3$SnH
40%
(E)-only
4:1 (E):(Z)

**Scheme 15**

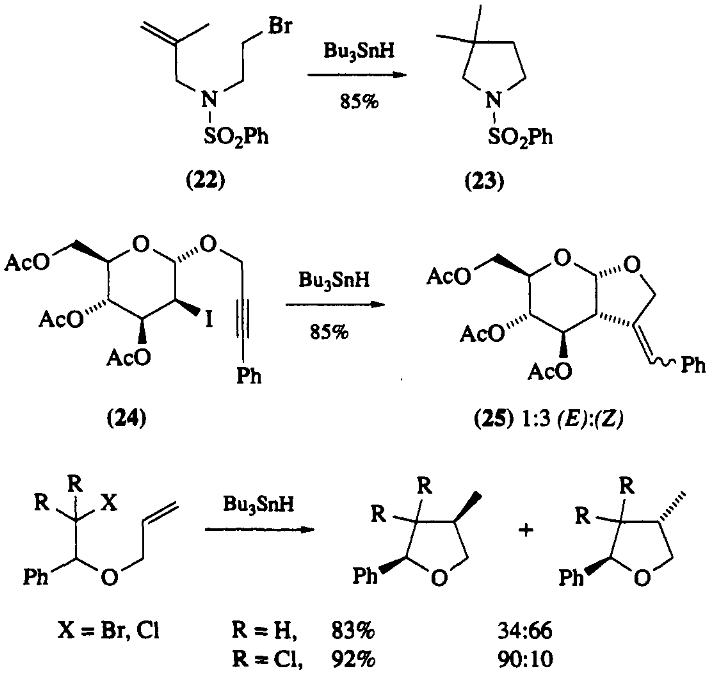
Br
N
SO$_2$Ph
Bu$_3$SnH
85%
N
SO$_2$Ph
(22)
(23)
AcO
O
O
AcO
I
AcO
Ph
Bu$_3$SnH
85%
AcO
O
O
AcO
AcO
Ph
(24)
(25) 1:3 (E):(Z)
R
R
X
Ph
O
Bu$_3$SnH
R
R
Ph
O
+
R
R
Ph
O
X = Br, Cl
R = H, 83% 34:66
R = Cl, 92% 90:10

**Scheme 16**

Silylmethyl radical cyclizations are a related class of reactions in which the heterocycle serves a temporary purpose to direct the introduction of an alkyl or hydroxyalkyl group adjacent to an alcohol. These reactions were introduced by Stork[73] and Nishiyama,[74] and a recent example from Crimmins[75] nicely shows the usefulness of the method (Scheme 18). Talaromycin A (**31**) is a challenging target because it is the less stable of the two possible spiroacetal diastereomers. The problem is to introduce the axial hydroxymethyl group after the formation of the spiroacetal (if it is introduced before, the diastereomeric spiroacetal will form). Cyclization of (**29**) produces (**30**) which, upon direct oxidation, gives talaromycin A (**31**) in 78% yield. Silylmethyl radical cyclizations can provide stereocontrol in acyclic systems,[74,76] and 6-endo examples are also known.[77] Finally, in addition to oxidative cleavage, protiodesilylation is also possible.[73]

The placement of heteroatoms adjacent to the radical center often slows the rate of cyclization and, although low concentration techniques are required, good yields of cyclic products can still be obtained. Hart's systematic studies on the cyclizations of acylamino radicals were among the first to demonstrate the preparative utility of radical cyclizations.[78] Scheme 19 provides some recent examples. In general,

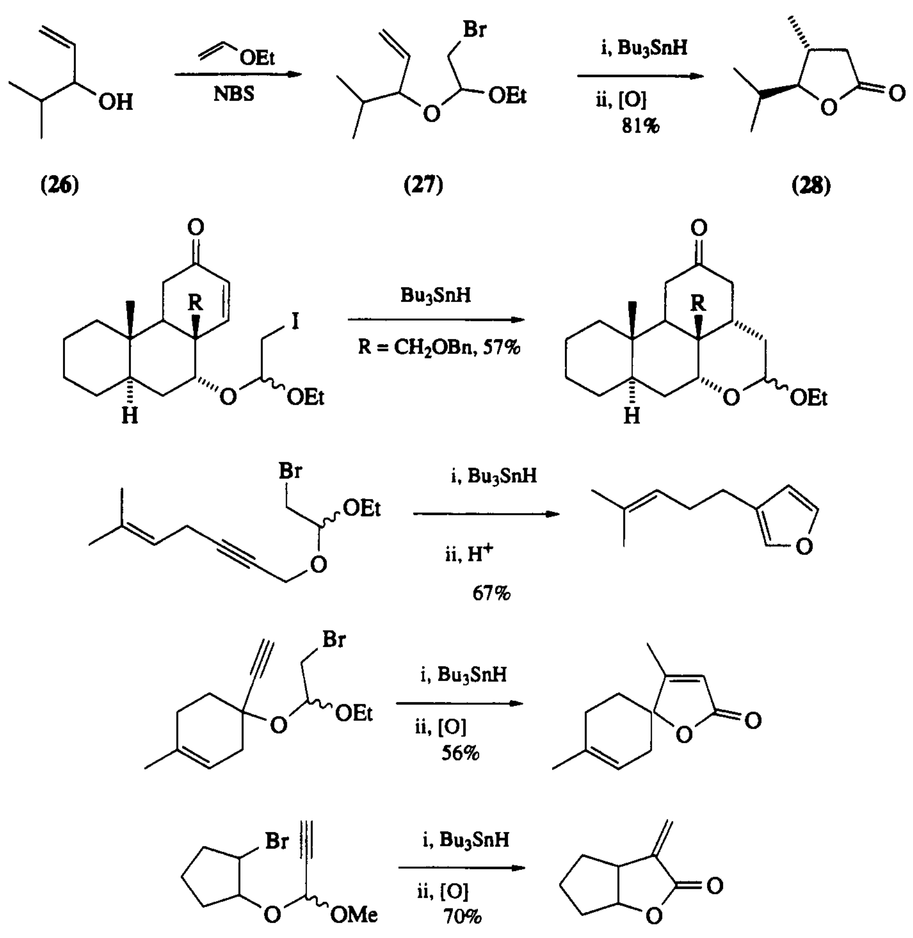
OH
OEt
NBS
Br
OEt
O
i, Bu3SnH
ii, [O]
81%
O
O
(26)
(27)
(28)
O
R
I
O
OEt
H
Bu3SnH
R = CH2OBn, 57%
O
R
O
OEt
H
Br
OEt
O
i, Bu3SnH
ii, H+
67%
O
Br
O
OEt
i, Bu3SnH
ii, [O]
56%
O
O
Br
O
OMe
i, Bu3SnH
ii, [O]
70%
O
O

Scheme 17

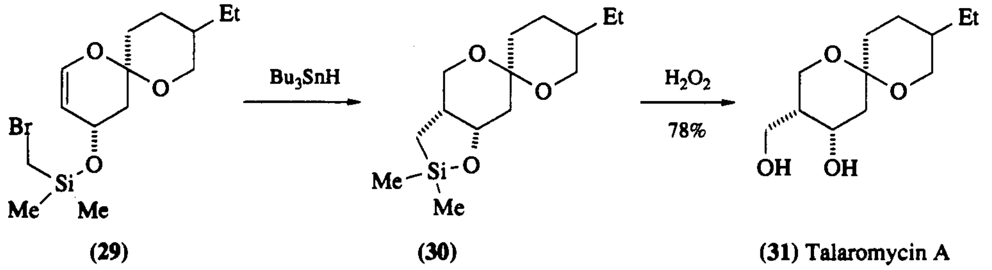
Et
O
O
Br
O
Si
Me
Me
Bu3SnH
Et
O
O
Me
Si
O
Me
H2O2
78%
Et
O
O
OH
OH
(29)
(30)
(31) Talaromycin A

Scheme 18

phenylthio precursors are preferred because acylamino halides are prone to solvolysis.[79] The first example in Scheme 19 shows that these cyclizations are dramatically improved by an accelerating substituent.[80] The cyclization of (32) to (33) succeeds even though a relatively high energy conformer is required. The cyclization of the unactivated alkene acceptor fails. The second example illustrates that even 6-exo cyclizations are possible with activated acceptors.[81] In the absence of directing alkene substituents, acylamino radicals often give significant amounts of endo products. This is especially true in the β-lactam series,[82,83] as shown by the third example in Scheme 19.[84] There are even examples of 7-endo cyclizations to fused β-lactams.[85] Although Scheme 19 shows only acylamino radicals, amino radicals[86] and ether-substituted radicals have also been studied.[37,87–89]

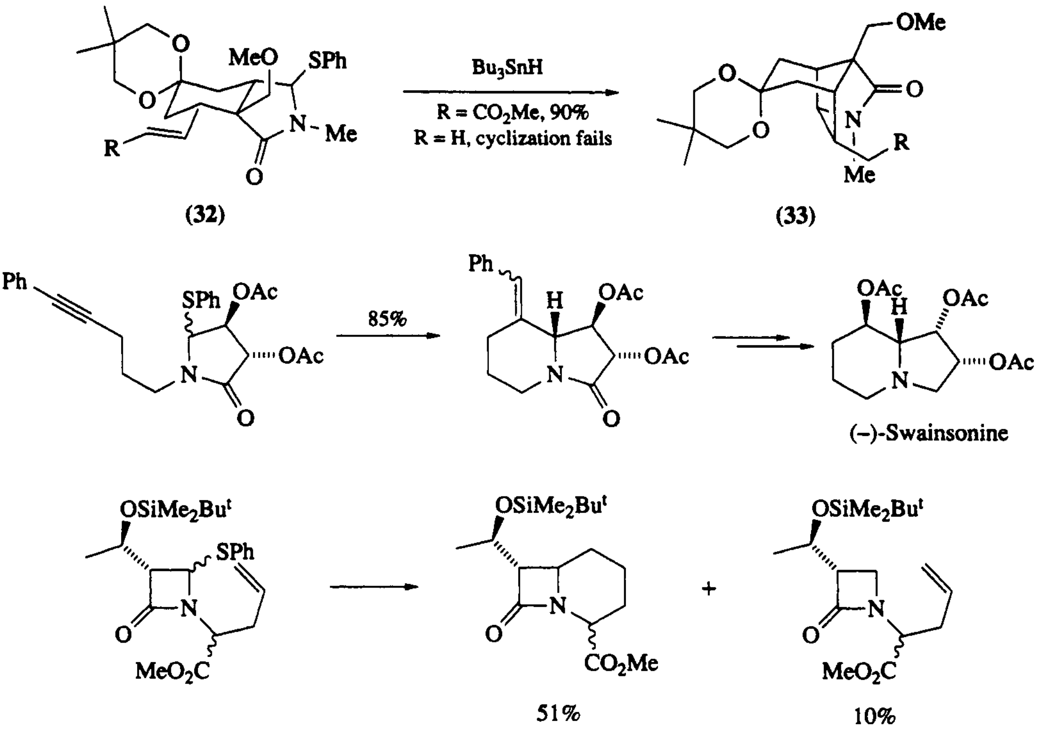

Scheme 19

*(iv) Vinyl and aryl radicals*

The use of vinyl radicals (pioneered by Stork)[90] and aryl radicals (introduced by Beckwith)[91] in the tin hydride method is attractive because these radicals are extremely reactive,[92] and often provide excellent yields of cyclic products that contain useful functionality for subsequent transformations.

Each of the syntheses of seychellene summarized in Scheme 20 illustrates one of the two important methods for generating vinyl radicals. In the more common method, the cyclization of vinyl bromide (**34**) provides tricycle (**35**).[93] Because of the strength of *sp*$^2$ bonds to carbon, the only generally useful precursors of vinyl radicals in this standard tin hydride approach are bromides and iodides. Most vinyl radicals invert rapidly, and therefore the stereochemistry of the radical precursor is not important. The second method, illustrated by the conversion of (**36**) to (**37**),[94] generates vinyl radicals by the addition of the tin radical to an alkyne.[95–98] The overall transformation is a hydrostannylation, but a radical cyclization occurs between the addition of the stannyl radical and the hydrogen transfer. Concentration may be important in these reactions because direct hydrostannylation of the alkyne can compete with cyclization. Stork has demonstrated that the reversibility of the stannyl radical addition step confers great power on this method.[95] For example, in the conversion of (**38**) to (**39**), the stannyl radical probably adds reversibly to all of the multiple bond sites. However, the radicals that are produced by additions to the alkene, or to the internal carbon of the alkyne, have no favorable cyclization pathways. Thus, all the product (**39**) derives from addition to the terminal alkyne carbon. Even when cyclic products might be derived from addition to the alkene, followed by cyclization to the alkyne, they often are not found because β-stannyl alkyl radicals revert to alkenes so rapidly that they do not close.

The cyclizations of vinyl, aryl, and acyl radicals differ from those of alkyl radicals because there is a mechanism by which cyclic radicals can interconvert that does not entail reversal of the original cyclization. This mechanism is shown in Scheme 21. Reduction of (**40**) with tin hydride at low concentration gives a mixture of 5-exo and 6-endo products (**41**) and (**42**).[99] However, only the 5-exo product (**41**) is obtained at high concentration, indicating that the 6-endo product is not kinetic. (Direct reduction of the vinyl radical cannot compete with cyclization even at 1.7 M!) Beckwith[100] and Stork[99] have convincingly demonstrated that the cyclic radicals (**43**) and (**45**) equilibrate, not through reversible 5-exo cyclization, but through (**44**), which arises from reversible 3-exo cyclization. At high tin hydride concentrations, (**43**) is trapped, but at lower concentrations, equilibration can compete. This isomerization, which is a

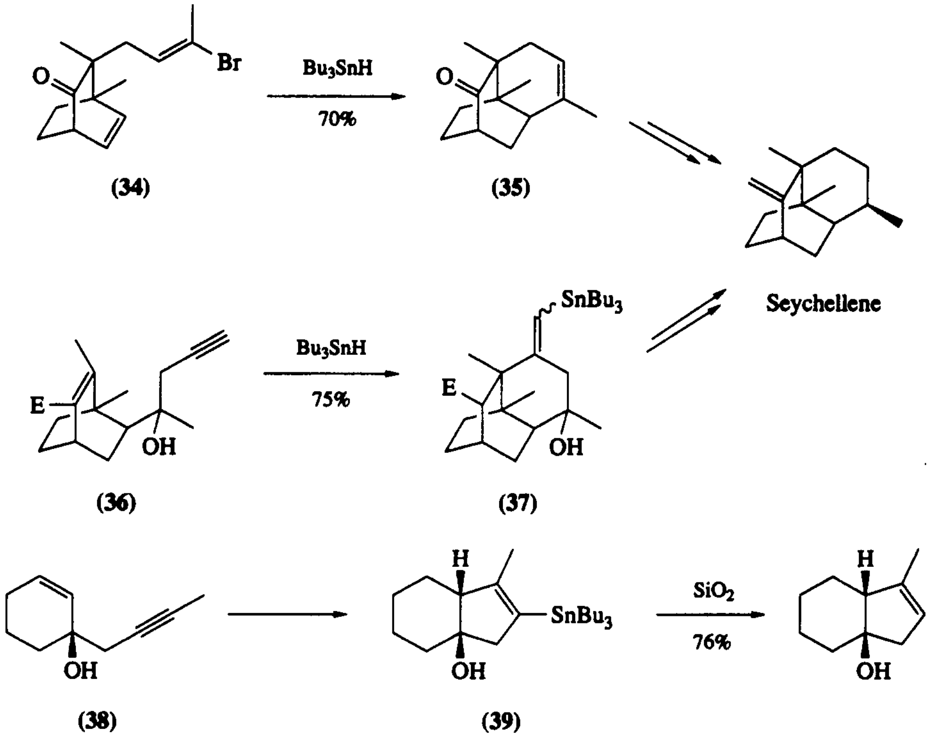

Br
O
Bu$_3$SnH
70%
(34)
(35)
Seychellene
E
OH
Bu$_3$SnH
75%
SnBu$_3$
(36)
(37)
OH
SnBu$_3$
H
SiO$_2$
76%
(38)
(39)

Scheme 20

general phenomenon for radicals oriented β to unsaturated groups, was not widely recognized by practitioners of vinyl radical cyclizations prior to the work of Stork and Beckwith. To date, conditions have usually been designed to trap kinetic 5-exo products, but equilibration to 6-endo products has potential utility. Such isomerizations are well developed in cases where the acceptor for the cyclization is a carbonyl group (see Section 4.2.6).

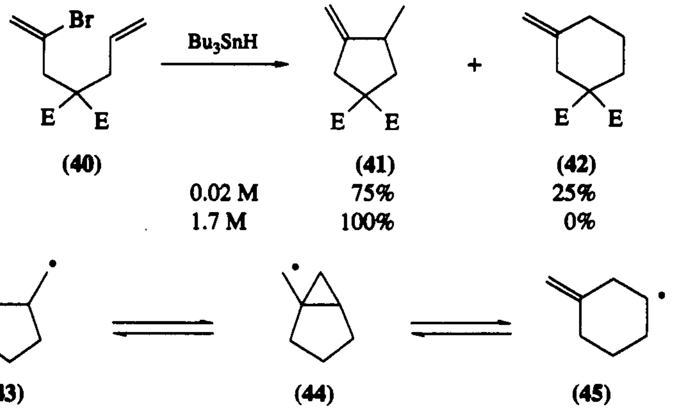

Br
Bu$_3$SnH
E E
(40)
(41)
(42)
0.02 M 75% 25%
1.7 M 100% 0%
(43)
(44)
(45)

Scheme 21

Scheme 22 presents some selected aryl radical cyclizations. The first example shows that isomerization of the intermediate radicals is again a concern. This isomerization, which is usually called the neophyl rearrangement,[101] is promoted by the activating aldehyde group in the case at hand.[102,103] The other examples illustrate that aryl radical cyclizations provide practical routes to benzo-fused heterocycles.[104,105]

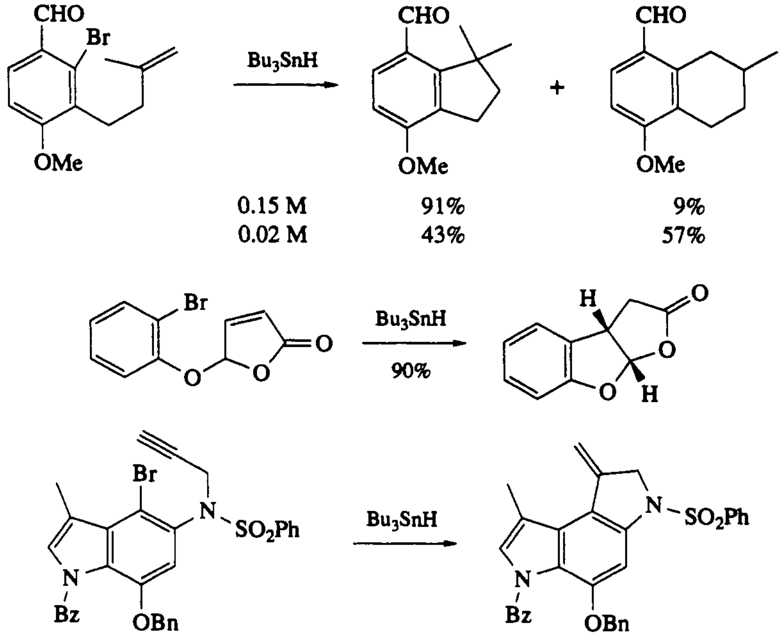
CHO
Br
OMe
Bu3SnH
CHO
OMe
+
CHO
OMe
0.15 M 91% 9%
0.02 M 43% 57%
Br
O
O
O
Bu3SnH
90%
H
O
O
O
H
Br
N
SO2Ph
N
Bz
OBn
Bu3SnH
N-SO2Ph
N
Bz
OBn

**Scheme 22**

*(v) Acyl radicals*

Acyl, carbonyloxy and related radical cyclizations are rapidly gaining prominence and appear to have excellent scope. Examples of 5-exo (bridged and fused), 6-endo (possibly through equilibration as in Scheme 21) and 6-exo cyclization[106] have appeared. It is not presently clear whether the favorable ratios of cyclic to reduced products obtained with acyl radicals are due to inherently high reactivity of acyl radicals towards cyclization or to low reactivity towards tin hydride (due to the relative weakness of the forming C—H bond).

Two recent examples are contained in Scheme 23. The acyl radical cyclization, selected from the work of Boger and Mathvink,[107] illustrates that bridged rings can be formed in good yields (the corresponding alkyl radical cyclizes very slowly). Cyclizations of carbonyloxy[108] and related[109] radicals have been pioneered by Bachi, and the example in Scheme 23, from the work of Corey,[110] is a key step in the synthesis of atractyligenin. The precursor of choice for such radicals is often the phenyl selenide; halides are susceptible to ionic reactions. If a stable radical will be generated, decarboxylation or decarbonylation can sometimes compete with cyclization.

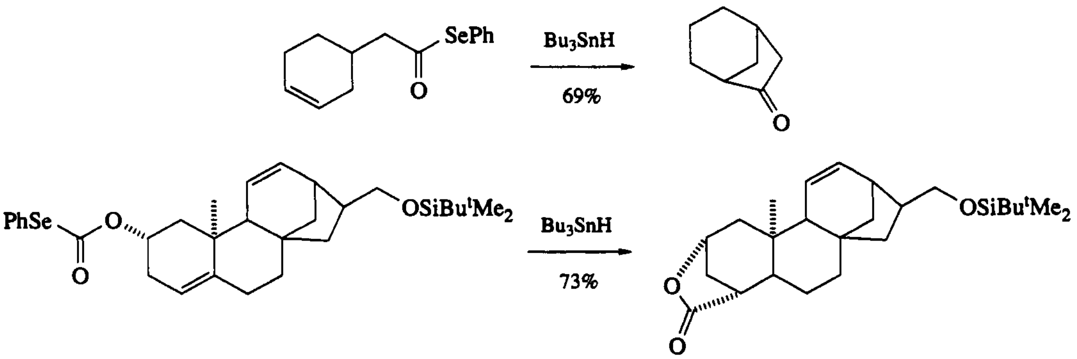
SePh
O
Bu3SnH
69%
O
PhSe
O
O
OSiBu$^t$Me$_2$
Bu3SnH
73%
OSiBu$^t$Me$_2$
O
O

**Scheme 23**

### *(vi) Mercuric hydride*

Although most reductive cyclizations have been conducted by the tin hydride method, cyclizations of mercuric hydrides are also straightforward to conduct. Precursors are usually prepared by heteromercuration of an alkene, and substituted alkyl radicals (nucleophilic) often result. Cyclizations are conducted like addition reactions: oxymercuration is followed by the direct addition of a hydride source to convert the intermediate mercuric halide or acetate to a mercuric hydride. It may be difficult to conduct slow cyclizations because mercuric hydrides are very good hydrogen atom donors. In principle, the concentration of the mercuric hydride can be controlled, but mercuric hydrides are unstable and their exact concentrations are not usually known. Purification of the products is straightforward (there are no by-products that require chromatographic separation), but the toxicity of metallic mercury may cause problems on a larger scale. The recent review of Barluenga and Yus provides comprehensive coverage of the radical cyclization reactions of mercurials,[111] and two representative transformations are contained in Scheme 24.[112,113]

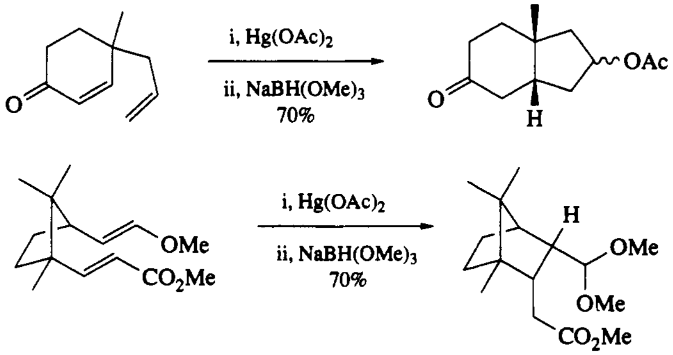

Scheme 24

#### *4.2.2.1.2 The fragmentation method*

Conducting radical cyclizations by fragmentation reactions offers a powerful alternative to the tin hydride method. Instead of obtaining reduced products, one obtains products of substitution; an alkene is regenerated in the fragmentation step.

Even though there are relatively few examples, the use of allyl- and vinyl-stannanes in radical cyclizations is probably very general.[114] This should be a very good method to conduct relatively slow cyclizations. Since high dilution is not necessary, a wide range of radical precursors (including the less reactive types) can be used. Although most of the examples in the literature use nucleophilic radicals, all classes of radicals (nucleophilic, electrophilic, ambiphilic) should be amenable to cyclization by this method. Scheme 25 provides examples of addition reactions to both allyl- and vinyl-stannanes. The first example is a convenient route to enol acetates.[115] The second example is particularly interesting because it illustrates that control over the stereochemistry of exocyclic alkenes is possible because fragmentation of the intermediate β-stannyl radical is more rapid than σ-bond rotation[116] (however, there are also examples where rotation is faster than elimination, see Section 4.2.6). The complete control of relative stereochemistry in the third example is noteworthy.[117]

Allyl sulfones offer the possibility to conduct cyclization reactions that are isomerizations, and investigations by Smith and Whitham indicate that this is a very promising technique for the preparation of functionalized products.[118] The mechanism consists of reversible addition of a sulfonyl radical to a terminal alkene or alkyne, cyclization, and fragmentation of the resulting β-sulfonyl radical. Two examples of these isomerizations are provided in Scheme 26.

#### *4.2.2.1.3 The Barton thiohydroxamate method*

Cyclizations conducted by the thiohydroxamate method are even less common than those conducted by the fragmentation method, but there is every reason to believe that thiohydroxamate cyclizations should be generally applicable.[119] Precursors are formed from carboxylic acids, and require the inclusion of an extra carbon since decarboxylation occurs. This feature may be very useful when normal precursors containing carbon–heteroatom bonds are unstable or difficult to prepare. The thiohydroxamate

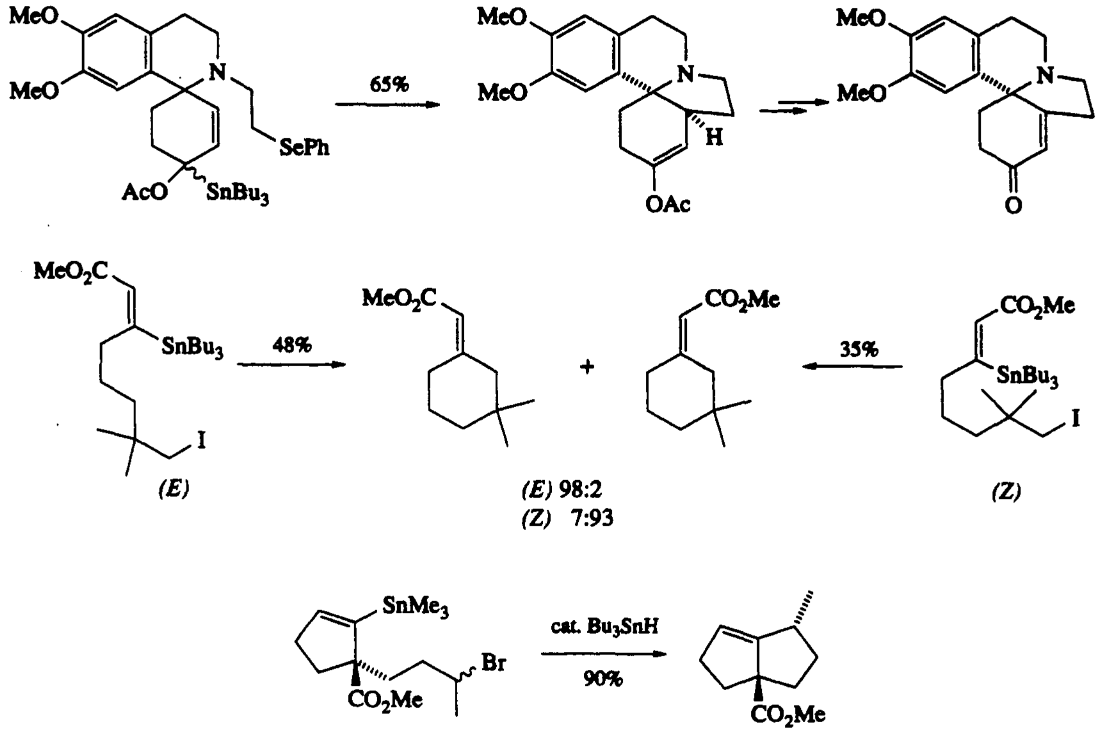
MeO
MeO
N
SePh
AcO
SnBu3
65%
MeO
MeO
N
H
OAc
MeO
MeO
N
O
MeO2C
SnBu3
I
(E)
48%
MeO2C
+
CO2Me
35%
CO2Me
SnBu3
I
(Z)
(E) 98:2
(Z) 7:93
SnMe3
Br
CO2Me
cat. Bu3SnH
90%
CO2Me

Scheme 25

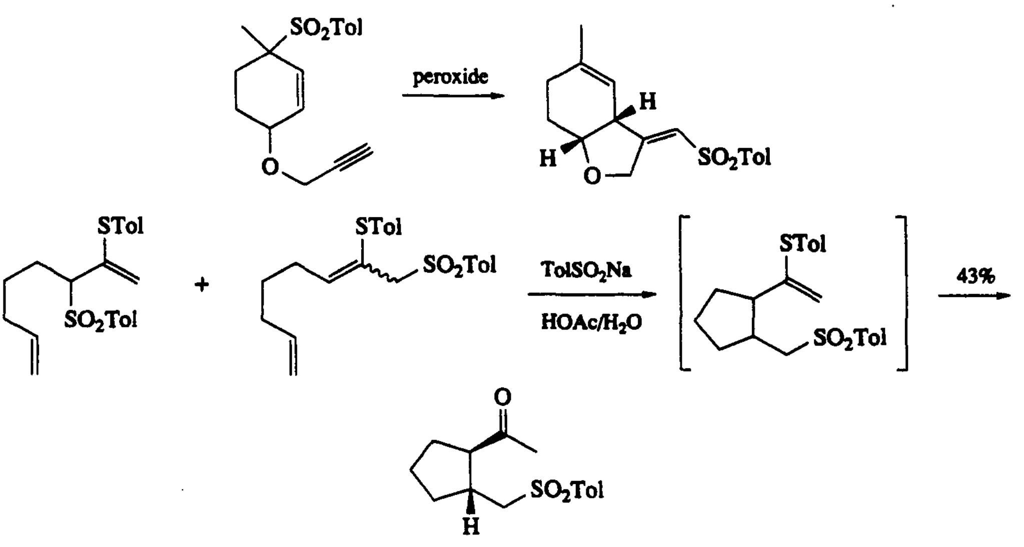
SO2Tol
O
peroxide
H
H
O
SO2Tol
STol
SO2Tol
+
STol
SO2Tol
TolSO2Na
HOAc/H2O
STol
SO2Tol
43%
O
SO2Tol
H

Scheme 26

method is usually used to generate nucleophilic radicals, and, if the standard techniques are used to minimize the thiohydroxamate concentration, it should be possible to conduct relatively slow cyclizations. The most important feature of the thiohydroxamate method is that it is not reductive (although reduction products are readily obtained if desired). In the standard procedure, cyclic radicals are trapped by addition to the thiohydroxamate, and a thiopyridyl group results. Equation 2 presents an example from the work of Barton in which optically active indolizidines are prepared from glutamic acid.[120,121]

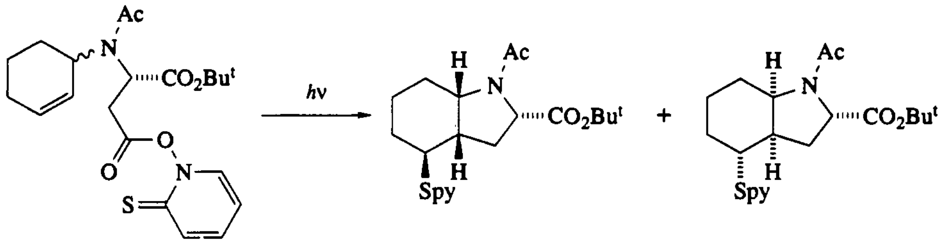

(2)

#### 4.2.2.1.4 The atom transfer method

Cyclizations conducted by the atom transfer method offer a powerful alternative to tin hydride chemistry. Both hydrogen and halogen atom transfer cyclizations are possible; however, the scope of halogen atom transfer cyclizations is far greater. Although the mechanisms of hydrogen and halogen atom transfer cyclizations are similar, the same types of products are not always obtained. Halogen atom transfer cyclizations virtually always provide kinetically controlled products, but thermodynamic control can operate in hydrogen atom transfer cyclizations.

##### (i) Hydrogen atom transfer cyclizations

Preparative and mechanistic aspects of hydrogen atom transfer cyclizations were studied extensively by the group of Julia,[122] and the review of Surzur[4] provides an excellent overview of these pioneering contributions. Although most hexenyl radical cyclizations are not reversible, Julia demonstrated that the rate of reverse cyclization can be rapid enough to be preparatively useful if multiple radical-stabilizing groups are present on the initial radical center. These radical-stabilizing groups also facilitate hydrogen transfer, and the most important preparative use of the hydrogen atom transfer method is to obtain thermodynamically controlled products in reversible cyclizations. If kinetically controlled products are desired, it is usually better to prepare a halide (or related precursor) and to conduct the cyclization by either the tin hydride method or by halogen atom transfer.

The hydrogen atom transfer method is most useful for electrophilic radicals (for example, malonate, acetoacetate, *etc*.). Because radicals are generated from C—H bonds, the preparation of cyclization precursors by alkylation is routine. The hydrogen atom transfer method is very good for conducting slow cyclizations. In addition reactions, the hydrogen donor is typically used in large excess relative to the acceptor to facilitate H-transfer; however, cyclizations must use different conditions because the H-donor and the alkene acceptor are in the same molecule.

An example from the work of Julia,[123] which illustrates how reversible cyclizations can be conducted, is presented in Scheme 27. A solution of 2 equiv. of benzoyl peroxide in cyclohexane is added in portions over 2 d to a refluxing solution of cyanomalonate (**46**) in cyclohexane. After an additional 3 d at reflux, the solvent is removed and the 6-exo product (**47**) is isolated in 75% yield. Because a benzoyloxy radical produced by cleavage of the peroxide is highly reactive (and very nonselective), it probably abstracts a hydrogen from the solvent cyclohexane. The cyclohexyl radical is less reactive (and more selective), and it may abstract a hydrogen from (**46**) to form the initial radical (**48**). Thus, the selectivity of the cyclohexyl radical helps to offset the usual requirement for a large excess of hydrogen atom donor; however, the inefficiency of such C–H transfers necessitates the use of a very large amount of peroxide. It has recently been shown that (**48**) closes almost exclusively by 5-exo cyclization to (**49**),[19] but, because the ensuing hydrogen transfer is very slow, equilibration occurs to produce (**50**).[124] The source of the hydrogen atom in the final product is not certain. It may derive from the cyclohexane, or from (**46**), or from disproportionation. If chains are involved, they must be very short.

Substrates for hydrogen atom transfer cyclization are limited in the functional groups that they can bear because of the hydrogen atom transfer step. Even the allylic hydrogens in the acceptor are at risk of being abstracted. Further, such cyclizations are only useful when the kinetic cyclization product is different for the thermodynamic product (sometimes they are the same), and when the reverse cyclization is sufficiently rapid so that equilibrium is possible. Many reverse cyclizations are just too slow to be useful. Cyano groups appear to be good at increasing the rate of reverse cyclization, but even so, the conversion of (**49**) to (**48**) is very slow (see $k_{-c}$ in Scheme 27). All the limitations not withstanding, hydrogen transfer cyclization can sometimes be the best method to obtain product ratios that are not kinetically controlled.[125]

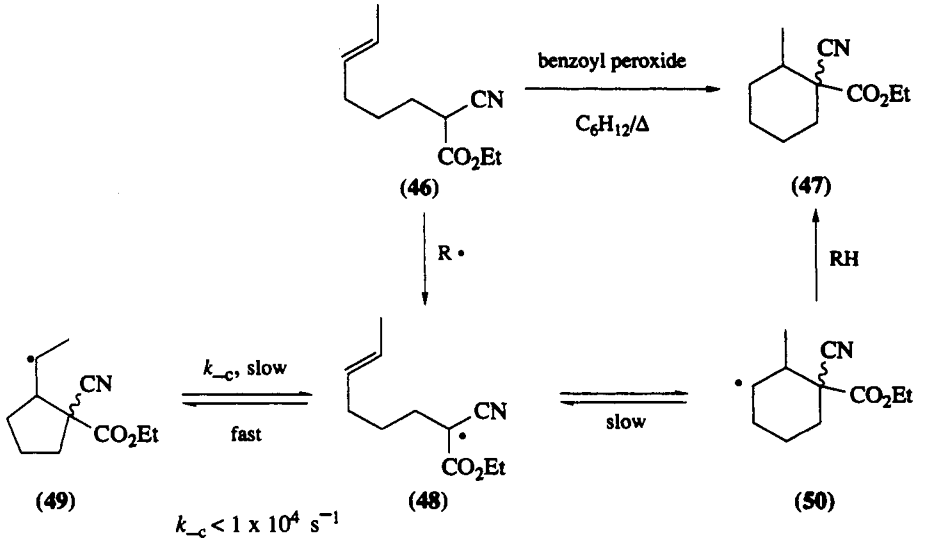

Scheme 27

*(ii) Halogen atom transfer cyclizations*

Halogen atom transfer cyclizations are conceptually similar to their hydrogen atom transfer counterparts, but, because halogen transfers are much more rapid, these cyclizations have a much broader scope and usually trap kinetic products efficiently.[34] Early examples of halogen transfer cyclization used perhalo-substituted radicals. In such cases, any halogen can serve as the radical precursor, and, while certain functional groups (like trichloroacetates) are very readily prepared, the incorporation of a polyhalogenated radical precursor in a complex molecule can sometimes be difficult. Polyhalogenated radicals are electrophilic and their cyclizations are usually promoted by metal additives. Any exothermic iodine atom transfer reaction will be very fast, and the recent development of methods based on iodine atom transfer has considerably expanded the types of atom transfer cyclizations that can be conducted.[126] The iodine atom transfer method is excellent for iodocarbonyl and related derivatives, but it can also be used for some nucleophilic radical cyclizations. The halogen atom transfer method is excellent for conducting slow cyclizations at high concentrations because there is nothing present to intercept the initial radical. However, for the reaction to succeed, it is critical that the halogen atom transfer step be sufficiently rapid to propagate the chain. Final products either retain the original halogen atom (in a new location) or are derived from subsequent ionic reactions of the initial products.

Several recent examples of metal-promoted cyclizations of perchlorocarbonyl compounds are presented in Scheme 28, and a full paper by Weinreb is recommended as an excellent source of references to prior work in this area (including mechanistic studies on the role of the metal).[127] The first two examples illustrate that the choice of substrates can dictate the types of products that are formed: the initially formed $\gamma$-chloro esters are stable to subsequent ionic reactions, but the *cis*-$\gamma$-chloro acids form lactones. Interestingly, Weinreb has shown that the metal can equilibrate the *cis*- and *trans*-$\gamma$-chloro esters by reversible chlorine atom transfer. The third example[128] illustrates a general feature of the atom transfer method: yields at high concentration are comparable to (and sometimes better than) those provided by using tin hydride at low concentrations. Indeed, in the third example, the three chlorines on the ester provided three opportunities for cyclization during the tin hydride reduction, but 40% of the product still failed to cyclize. (Unfortunately, the tin hydride concentration was not specified.)

Iodocarbonyls are excellent substrates for atom transfer cyclization, as shown by examples from our recent work in Scheme 29.[19,129] When two carbonyl (or cyano) groups are present, bromides can also serve as radical precursors. Photolysis with 10% ditin usually provides excellent yields of kinetic products at high concentration, and alkene substituents often dictate the regioselectivity. The $\gamma$-iodo ester products are particularly versatile for subsequent transformations, which can often be conducted *in situ*. Although tertiary iodine products sometimes go on to give lactones or alkenes, primary and secondary iodides can often be isolated if desired. The last example is particularly noteworthy: the kinetic product from the cyclization presented in Scheme 27 is trapped, because bromine atom transfer is much more rapid that reverse cyclization.

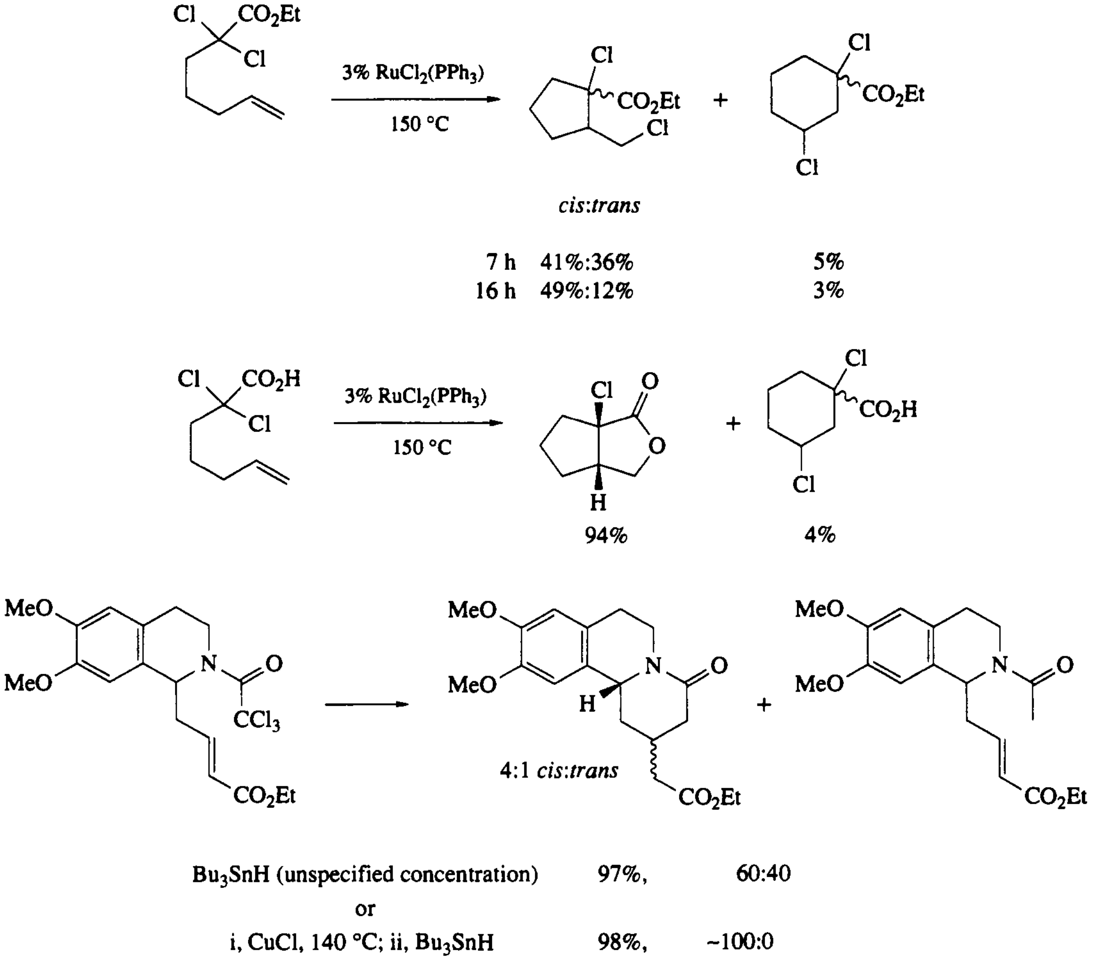

Scheme 28

Iodine atom transfer reactions between alkyl radicals and iodocarbonyls are very rapid ($10^7$ $M^{-1}$ $s^{-1}$ to $10^9$ $M^{-1}$ $s^{-1}$).[130] This means that, even when these iodides are cyclized by the tin hydride method, iodine atom transfer may supersede hydrogen transfer, and the reductively cyclized product will ultimately be derived from the reduction of a cyclic iodide. Tin hydride cyclizations of halocarbonyls also often require very low concentration to avoid reduction of the initial radical prior to cyclization. For these reasons, reductively cyclized products are best formed by atom transfer cyclization at high concentration, followed by reduction of the product *in situ*. In a recent full paper, we have described in detail the preparative and mechanistic features of these cyclizations,[19] and Jolly and Livinghouse have reported a modification of our reaction conditions that appears to be especially useful for substrates that cyclize very slowly.[131] Cyclizations of α-iodocarbonyls can also be promoted by palladium.[132]

Cyclizations of nucleophilic radicals by the atom transfer method are more restricted in scope. Iodine transfer usually is too slow to be useful when the cyclic radicals are more stable than the initial radicals (as is often the case with alkyl radical cyclizations), and iodide precursors of stabilized nucleophilic radicals (α-iodo ethers, for example) are often too unstable to use. However, Scheme 30 illustrates that there are at least two types of atom transfer cyclizations that are preparatively useful. In the first type, we have found that the isomerization of hex-5-ynyl iodides to iodomethylenecyclopentanes is a very general reaction, which is made possible by the rapid, exothermic abstraction of iodine atoms from alkyl iodides by vinyl radicals.[133,134] Indeed, this transfer is so rapid that normal tin hydride reductive cyclizations of hexenyl iodides can proceed through iodomethylenecyclopentane intermediates. In the second type, the exchange of iodine atoms among alkyl radicals[135] is sufficiently rapid that isomerizations based on slightly exothermic (or even thermoneutral) iodine atom transfers are possible. The second example in Scheme 30 is representative of this type of reaction.[136] Even though the iodine transfer is reversible, the cyclization is not, and so the acyclic iodide is eventually isomerized to the cyclic iodide. Modest yields

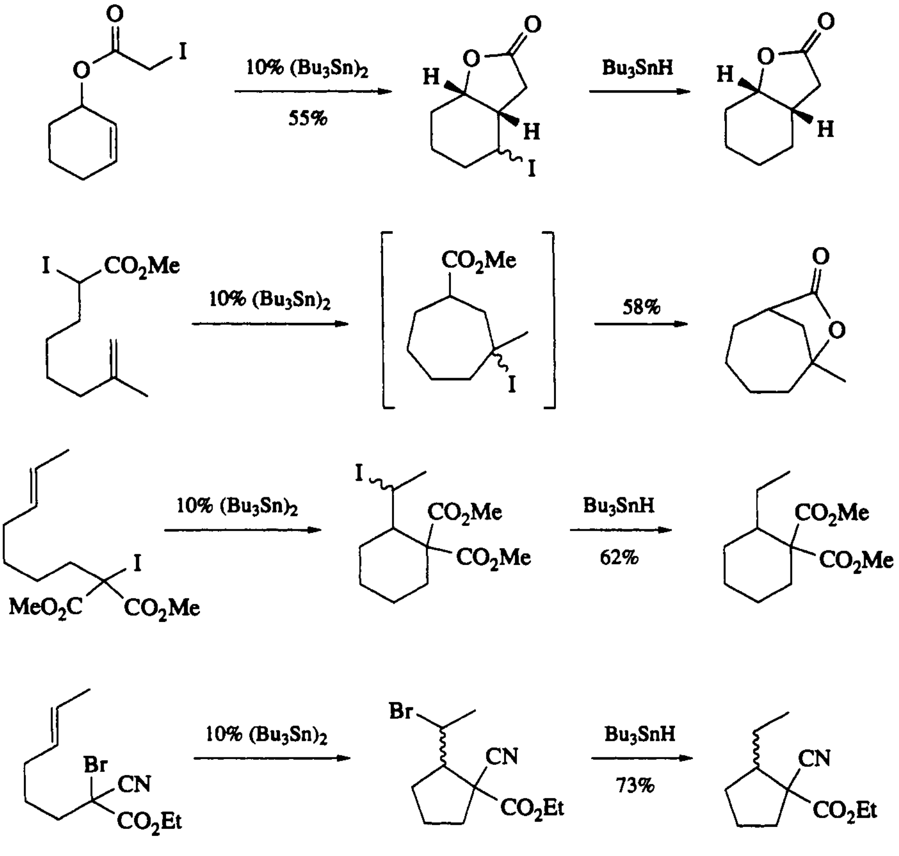

Scheme 29

are the rule because the product is continuously recycled to the radical pool, subjecting it to radical/radical and radical/solvent reactions. In such cases, higher yields of reduced products can probably be obtained by the tin hydride method (by using low concentration, if necessary).[137] But the atom transfer method may still be useful because the iodide in the product is suitable for further functionalization. Cyclizations like those outlined in Scheme 30 must be conducted with iodides because alkyl bromides are not sufficiently good bromine atom donors.

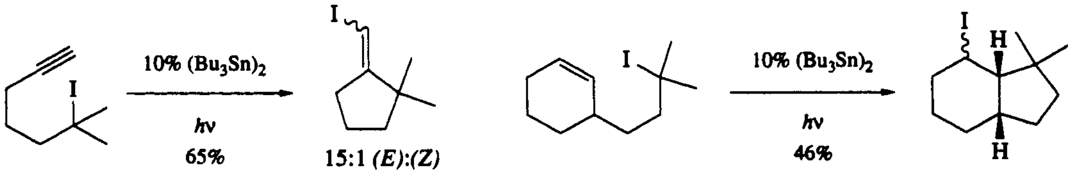

Scheme 30

### (iii) Aromatic diazonium salts

Cyclizations of aromatic diazonium salts[138] (intramolecular Meerwein arylations) are preparatively related to atom transfer reactions because a radical cyclization is terminated by the transfer of an atom or group other than hydrogen. However, the two methods are not mechanistically related. In the atom transfer method, the atom that is transferred to the cyclic product always derives from the radical precursor, but in the cyclizations of aryldiazonium salts, the atom or group transferred derives from an added reagent. This means that many different products can be prepared from a single diazonium precursor, but it also means that the standard competition is operative, and initial radicals are at risk of being intercepted by reagents prior to cyclization. Illustrative examples of cyclizations of aromatic diazonium salts taken from the recent work of Beckwith are presented in equation (3).[139–141]

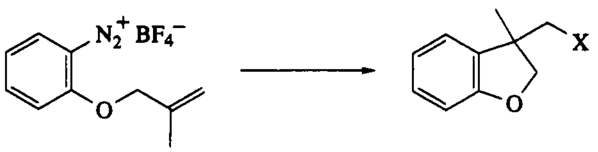

(3)

| | NaI | CuCl | CuBr | CuCN | NaSPh |
|---|---|---|---|---|---|
| X | I | Cl | Br | CN | SPh |
| % | 89 | 63 | 60 | 40 | 60 |

### 4.2.2.2 Nonchain Methods

Cyclization reactions can be conducted by methods that remove cyclic radicals by selective radical/radical coupling, oxidation, or reduction. The usual selectivity concerns are operative: initial radicals must cyclize, and cyclic radicals must be productively removed.

#### *4.2.2.2.1 Selective radical/radical coupling*

Becking and Schäfer have shown that mixed Kolbe coupling reactions can provide useful yields (40–60%) of cyclic products.[142] In the example provided in equation (4), 1 equiv. of acid (**51**) and 4 equiv. of acid (**52**) are electrochemically cooxidized, and the cyclic cross adduct (**53**) is formed in 53% yield. Because the rates of oxidation of (**51**) and (**52**) are similar, the concentration of radicals derived from (**52**) is higher. Thus, radicals derived from (**51**) are more likely to cross couple than to self couple. The strength of the mixed Kolbe method is that two carbon–carbon bonds are formed rather than one because the cyclic radical is removed by radical/radical coupling.

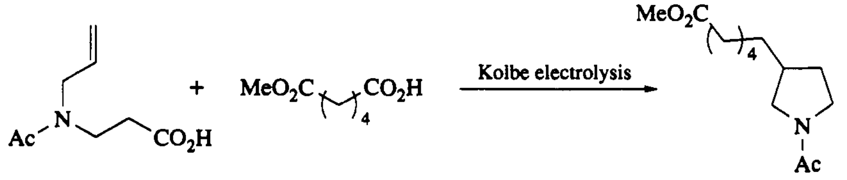

(4)

(**51**) 1 equiv. (**52**) 4 equiv. (**53**) 53% based on (**51**)

The cyclization reactions of organocobalt complexes are very useful, and they offer an excellent alternative to the tin hydride method when reduced products are not desired. Most cobalt cyclizations have been conducted with nucleophilic radicals. Precursors are prepared by alkylation of cobalt(I) anions, and are usually (but not always) isolated. One suspects that alkylcobalt precursors should be useful for slow cyclizations because there are no rapid competing reactions that would consume the initial radical (coupling of the initial radical with cobalt(II) regenerates the starting complex).

The most important feature of organocobalt cyclizations is that a variety of functionalized products can be obtained, depending on the nature of the substrate and the reaction conditions. The most common transformation has been formation of an alkene by cobalt hydride elimination. Alkenes are often formed *in situ* during the photolysis, and with activated alkene acceptors the formation of these products by cobalt hydride elimination is very facile. Scheme 31 provides a representative example from the work of Baldwin and Li.[143] The alkene that is formed by cobalt hydride elimination maintains the correct oxidation state in the product (**54**) for formation of the pyrimidone ring of acromelic acid. Under acidic conditions, protonation of the cyclic organocobalt compound may compete;[144] however, if protonated products are desired, the cyclization can probably be conducted by the reductive method with only catalytic quantities of cobalt (see Section 4.2.2.2.2).

When simple terminal alkenes are used as acceptors, the cyclic primary alkyl cobalt species are stable, and can often be isolated and purified by standard techniques.[145] Scheme 32 shows some of the transformations that Pattenden has accomplished with the cyclic alkylcobalt complex (**55**).[146] In addition to standard elimination to an alkene, the complexes can be converted to alcohols, halides, oximes, and phe-

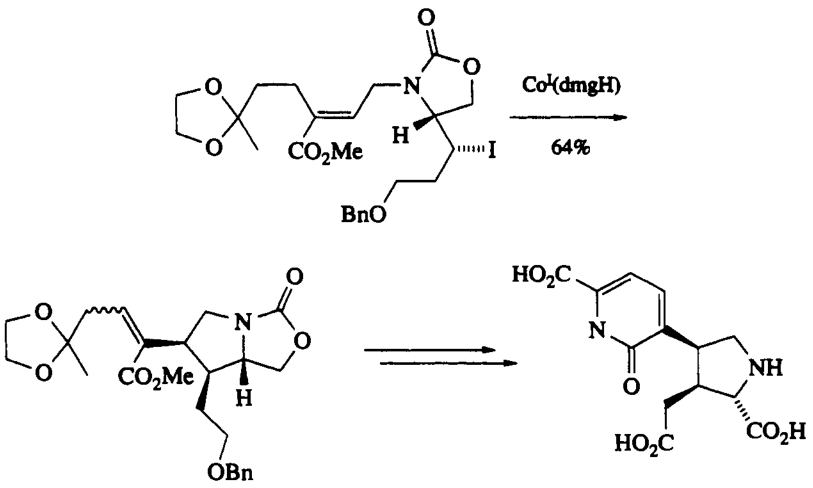
Co^I(dmgH)
64%
CO2Me
BnO
OBn
H
HO2C
NH
CO2H

(54)

Acromelic acid

Scheme 31

nyl sulfides and selenides. Of course, complexes like (55) are also precursors for subsequent radical reactions.

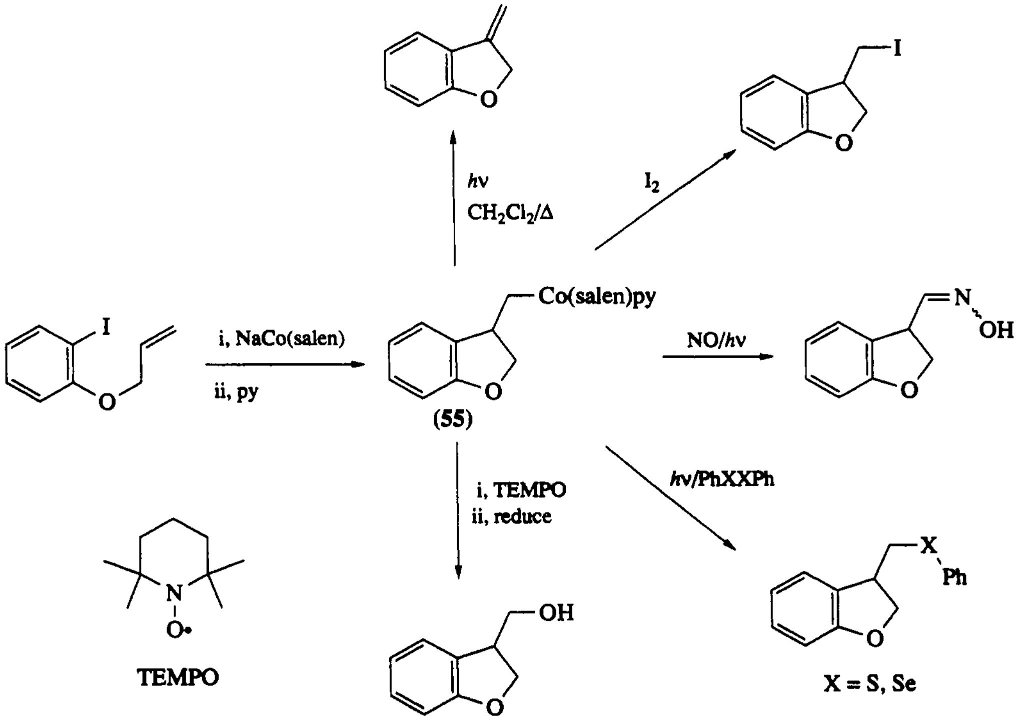
hν
CH2Cl2/Δ
I2
i, NaCo(salen)
ii, py
Co(salen)py
NO/hν
hν/PhXXPh
i, TEMPO
ii, reduce
OH
X
Ph

(55)

TEMPO

X = S, Se

Scheme 32

### 4.2.2.2.2 Redox methods

Among the oxidants that have been used to generate radicals, manganese(III) acetate has emerged as a powerful reagent to mediate radical cyclizations.[147] The manganese(III) acetate-mediated oxidation of enolizable carbonyl compounds is one of the best methods available for the cyclization of electrophilic radicals. The substrates are very easily prepared by standard alkylation and acylation reactions. Radicals are formed with high selectivity by oxidation of acidic C—H bonds, and, because the reaction is an oxidation, the product actually has a higher level of functionality than the starting material. While cyclic radicals are readily oxidized by manganese(III) if they are tertiary or heteroatom-substituted, the initial electrophilic radicals are inert to oxidation. Therefore, the manganese(III) method is excellent for slow cyclizations. In addition to the usual 5-exo cyclizations, 6-endo, 6-exo, 7-endo, and even 8-endo[148] cyclizations can be conducted depending on substituents. Substrates should be somewhat resistant to acid because the usual solvent is acetic acid. Standard extractive work-up procedures are the norm.

When one of the activating groups is an ester or acid, the cyclic cation is often trapped as a lactone.[149,150] As illustrated by the first two examples in Scheme 33,[151,152] this results in the simultaneous formation of two rings. The oxidation of secondary radicals to cations by $Mn^{III}$ is much slower than that of tertiary radicals. However, addition of $Cu^{II}$ salts smoothly (and often regioselectively) promotes the formation of alkenes, probably through copper hydride elimination from an intermediate alkylcopper species. The last two examples in Scheme 33, from the extensive studies of Snider,[148,153] show that this is an excellent technique for conducting other cyclizations besides the most common 5-exo variety. It appears that the regiochemistry of these cyclizations is controlled mainly by the alkene substitution pattern. As would be expected for free acetoacetate radicals, terminal alkenes provide significant amounts of endo-cyclized products, and Snider has provided evidence that tertiary radicals (but not secondary) formed by $Mn^{III}$ oxidation are indeed free, rather than metal complexed.[153] The ratios of cyclic products are in line with expectations for irreversible cyclizations.

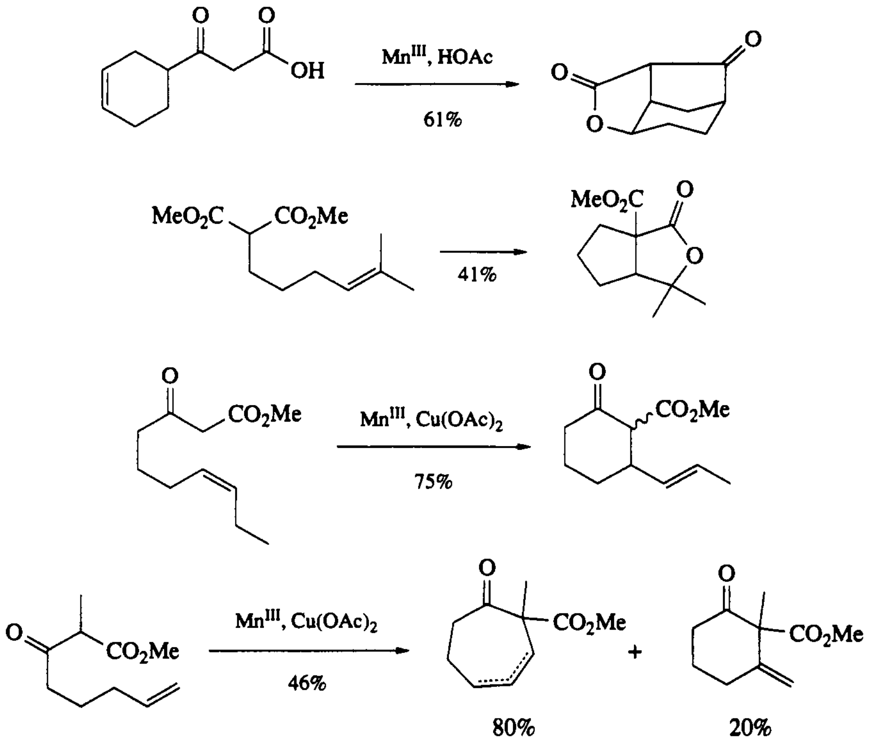

Scheme 33

If the products contain an enolizable hydrogen, overoxidation is a concern. When cyclopentanones are involved, the cyclic products are often more rapidly oxidized than the starting materials. However, further oxidation of the cyclic products is not necessarily undesirable. For example, Snider has developed a simple synthesis of phenols in which a manganese(III)-mediated 6-endo radical cyclization is followed by oxidative aromatization.[154] An example of this process is provided in Scheme 34. Snider has also shown that the overoxidation can be blocked with a chlorine atom, as shown by the second example in Scheme 34.[153]

Even though radical intermediates are involved in many reductive metallations, cyclizations of alkyl radicals by reductive trapping methods are relatively uncommon. When protonated products are formed, the overall transformations are similar to a tin hydride reductions; however, reductive methods may facilitate purification of the cyclic product because tin by-products are absent. Two examples of simple reductive cyclizations are shown in Scheme 35. The first example illustrates that Sheffold's procedure, which uses catalytic quantities of vitamin $B_{12}$ with a chemical or electrochemical coreductant, is attrac-

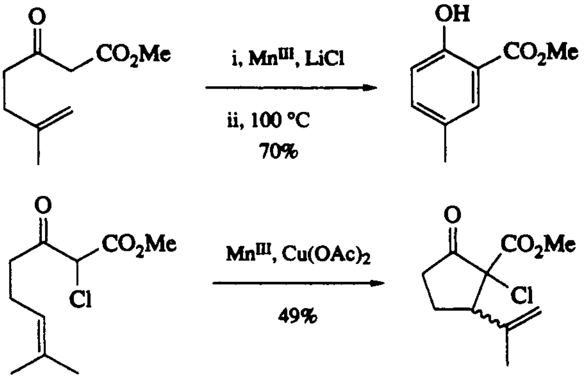

CO2Me
i, MnIII, LiCl
ii, 100 °C
70%
OH
CO2Me
CO2Me
Cl
MnIII, Cu(OAc)2
49%
CO2Me
Cl

Scheme 34

tive for preparative cyclizations.[155] The second example illustrates that $Cr^{II}$ salts are excellent reductants.[156] In this case, the $Cr(ClO_4)_2$ must be added slowly to the substrate so that the initial radical is not reduced to an alkylchromium(III) complex prior to cyclization (this is a general problem when powerful reductants are employed). Although alkyl radicals derived from such cyclizations can be reduced to alkylmetal complexes,[157] vinyl (and phenyl) radicals (such as those produced in the second example) often abstract a hydrogen atom from the solvent more rapidly than they are reduced.

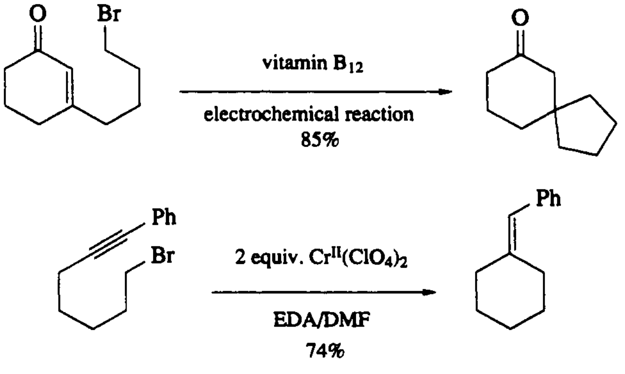

O
Br
vitamin B12
electrochemical reaction
85%
O
Ph
Br
2 equiv. CrII(ClO4)2
EDA/DMF
74%
Ph

EDA = ethylenediamine

Scheme 35

If reduction of the cyclic radical is more rapid than hydrogen abstraction from the solvent, then organometallic intermediates are produced. That these can be trapped by electrophiles other than protons significantly extends the power of the reductive method. Two examples of sequences of (i) radical cyclization, (ii) reduction of the cyclic radical to an organometallic, and (iii) electrophilic trapping are provided in Scheme 36.[158,159]

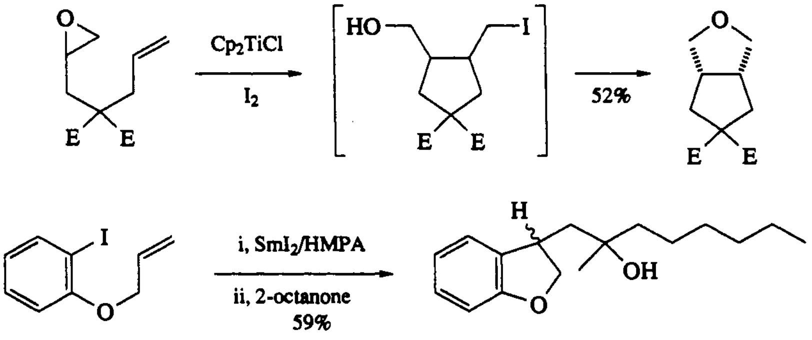

O
E
E
Cp2TiCl
I2
HO
I
E
E
52%
O
E
E
I
O
i, SmI2/HMPA
ii, 2-octanone
59%
H
O
OH

Scheme 36

The most common type of reductive cyclization involves the conversion of an aldehyde or a ketone to a ketyl. Ketyls are radical anions, and, while dimerization to form pinacols is a common reaction, it does not occur at the diffusion-controlled rate because of charge repulsion. Nonetheless, pinacol coupling can sometimes compete with cyclization, as can reduction to give an alcohol. As illustrated by the examples in Scheme 37, ketyl cyclizations can be conducted in several ways. Chemical reductions are the most common techniques, and these are conducted like standard metal reductions.[160] Samarium(II) iodide is a particularly useful reagent due to its high reducing power and its solubility in common solvents. Molander has shown that the degree of asymmetric induction in samarium-mediated ketyl cyclizations is often very high.[161] Electrochemical reductions are also useful, and can be further facilitated by the presence of soluble catalysts that aid in electron transfer.[162] Cossy has shown that photolysis of carbonyls in the presence of HMPA or triethylamine is an especially simple preparative method to conduct ketyl cyclizations.[163] Levels of stereocontrol in ketyl cyclizations are usually much higher than in the corresponding cyclizations of α-oxy radicals; the alkene-derived substituent is oriented *trans* to the ketyl oxygen in the final product.

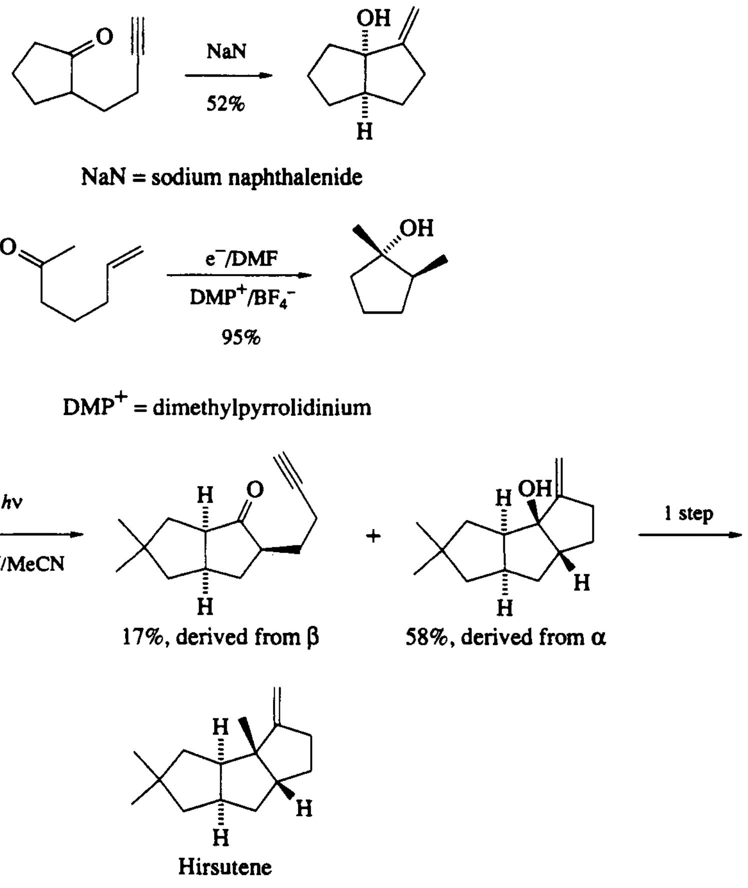

**Scheme 37**

Cyclizations of carbonyl-containing α,β-unsaturated esters like those illustrated in Scheme 38[164,165] are conceptually very similar to ketyl cyclizations, but they may be very different mechanistically. At least for electrochemical cyclizations, Little has proposed, based on reduction potentials, that the unsaturated ester is reduced first.[164] Even though questions remain about the timing of electron transfer and proton transfer steps, such cyclizations often provide good yields of products.

## 4.2.3 CYCLIZATIONS OF CARBON-CENTERED RADICALS TO AROMATIC RINGS

The recent resurgence in the application of radical reactions to organic synthesis has provided only a few examples of additions to aromatic rings; however, radical cyclizations should be applicable for con-

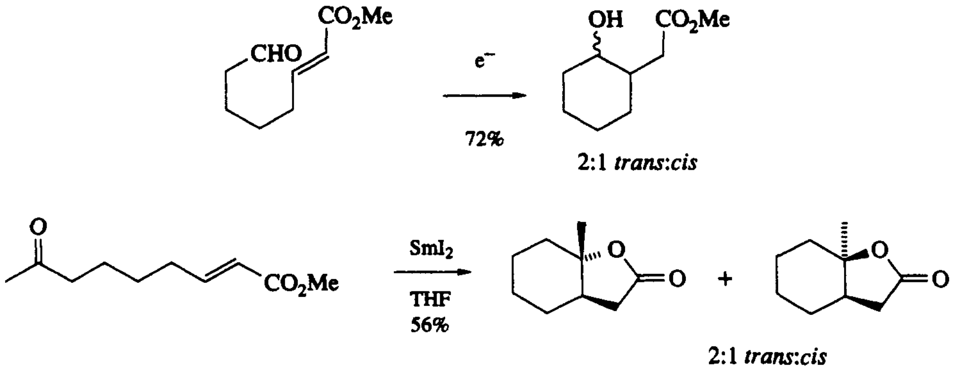

Scheme 38

structing many types of fused aromatic rings. Most such cyclizations occur under oxidative conditions that effect the rearomatization of intermediate cyclohexadienyl radicals. Several recent examples of additions to aromatic rings are provided in Scheme 39.[166,167] Unlike cyclizations with alkenes, cyclizations to aromatic nuclei that form six-membered rings are very good. Indeed, Citterio has shown that malonyl radicals add more rapidly to aromatic rings if six-membered rings are formed than if five-membered rings are formed.[168] As with addition reactions, one must be concerned that cyclizations to aromatic rings could be reversible, especially when stabilized initial radicals are involved.

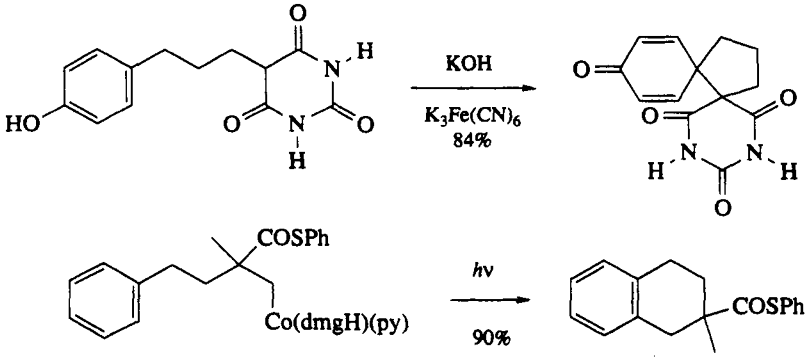

Scheme 39

Reductive cyclizations to aromatic rings are less common. The first example in Scheme 40 illustrates that cyclizations of ketyls to aromatic rings can be performed in good yields with high levels of stereocontrol.[169] The intermediate cyclohexadienyl radical is reduced and protonated to form a 1,4-cyclohexadiene. Tin hydride can also be used to conduct cyclizations to aromatic rings. And even though tin hydride is a reducing agent, rearomatized products are usually isolated, as indicated by the other example in Scheme 40.[170,171] The mechanism that converts the presumed intermediate cyclohexadienyl radical to the aromatized product is not clear.

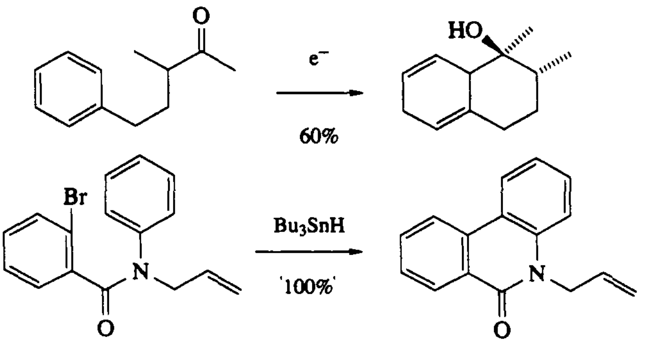

Scheme 40

Although the bimolecular additions of aryl radicals to aromatic rings are not useful due to a lack of selectivity, the corresponding cyclizations are useful for constructing biaryl bonds. Equation (5) provides a generalized example of the Pschorr reaction.[172] This cyclization of a diazonium salt is one of the classical methods for biaryl bond formation, and there are a variety of related reactions.[138]

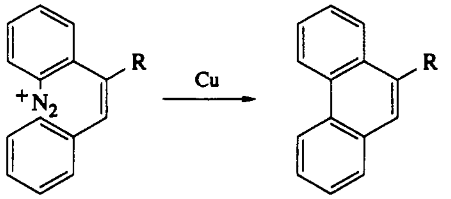

(5)

## 4.2.4 CYCLIZATIONS OF OXYGEN- AND NITROGEN-CENTERED RADICALS

Cyclizations of heteroatom-centered radicals offer alternatives to standard ionic methods for forming heterocyclic rings. Among the many heteroatom-centered radicals, those centered on nitrogen and oxygen are the most important for synthetic applications. There are significant differences between carbon-centered radicals and their nitrogen- and oxygen-centered counterparts, and these differences must be considered in synthetic planning. In general, oxy radicals are much more reactive than carbon radicals. In contrast, aminyl radicals are less reactive than carbon radicals, but their reactivity can be increased by protonation or by metal complexation. As always, consideration of the factors that will permit selective trapping of the cyclic radical without premature trapping of the initial radical is essential.

An important factor that provides insight into the reactivity of oxy and aminyl radicals is reactivity towards tin hydride. Figure 4 lists approximate rate constants for abstraction of a hydrogen atom from tributylin hydride by alkyl, aminyl,[173] and alkoxyl radicals.[174] The differences in reactivity are striking, and they do not parallel the order of elements in the periodic table: aminyl radicals are much less reactive than alkyl radicals, but alkoxyl radicals are much more reactive. This reactivity pattern follows the X—H bond strengths. Due to the high electronegativity of oxygen, alkoxyl radicals are very reactive in hydrogen abstraction, and the resulting OH bonds are very strong. Even though nitrogen is more electronegative than carbon, it forms weaker bonds to hydrogen. This is because electron–electron repulsions between bonded electron pairs and lone pairs are greater than repulsions between bonded electron pairs and other bonded electron pairs. This effect, which raises the ground state energy of an amine (as opposed to lowering the energy of an aminyl radical), is apparently more important than electronegativity in determining reactivity of aminyl radicals. Such large differences in reactivity can be very important for preparative applications. It is not uncommon (see below) to have alkyl radicals present in equilibrium with aminyl or alkoxyl radicals. If tin hydride is present, it provides a factor of 50–100 bias in rate that favors the trapping of alkoxyl radicals over carbon radicals, or the trapping of carbon radicals over aminyl radicals.

| | | | |
|---|---|---|---|
| $R_3C\cdot$ | $R_2\ddot{N}\cdot$ | $R\underset{\cdot\cdot}{\ddot{O}}\cdot$ | |
| $k_H \approx 3 \times 10^6\ M^{-1}\ s^{-1}$ | $8 \times 10^4\ M^{-1}s^{-1}$ | $2 \times 10^8\ M^{-1}\ s^{-1}$ | at 50 °C |

**Figure 4** Rates of hydrogen abstraction from $Bu_3SnH$

### 4.2.4.1 Nitrogen-centered Radicals

In contrast to the large body of kinetic data that is available on hexenyl radical cyclizations, relatively little is known about the cyclizations of 'azahexenyl' analogs. Only very recently have the detailed studies of Newcomb permitted a complete analysis of a useful parent cyclization.[175] As illustrated in equation (6), aminyl radical (**55**) cyclizes to (**56**) with a rate constant of about $3 \times 10^3\ s^{-1}$, but (**56**) reverts to (**55**) with a slightly greater rate constant of $7 \times 10^3\ s^{-1}$. That the cyclization of (**55**) is very slow, and that (**55**) is actually slightly preferred at equilibrium over (**56**), can be understood in terms of the above explanations for N—H bond strengths.

The slow rate of cyclization and the unfavorable equilibrium may cause problems for aminyl radical cyclizations. However, most chain substituents should accelerate such cyclizations, and in so doing, shift

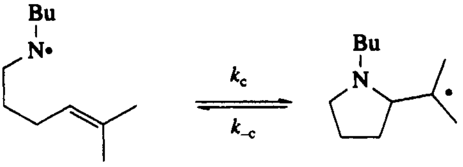

(55) (56)

(6)

$$k_c \approx 3 \times 10^3\ s^{-1};\ k_{-c} \approx 7 \times 10^3\ s^{-1}$$

the equilibrium to the cyclic product. Further, cyclic carbon-centered radicals can be trapped either kinetically (if the trapping reaction is faster than reverse cyclization), or at equilibrium. In either case, a reaction that traps alkyl radicals more rapidly than aminyl radicals is required. Aminyl radicals can be generated and cyclized by the halogen atom transfer method (N–halogen bonds are very weak), by the Barton method,[176] or by oxidation of metal amides.[177]

To facilitate the cyclizations of nitrogen-centered radicals, one need only increase the electronegativity at nitrogen. This makes the radical more electrophilic (which accelerates the cyclization), and strengthens the forming bonds (which shifts the equilibrium to the cyclic product). Amminium radical cations are more well-behaved in cyclizations than aminyl radicals, and these radical cations can either be formed directly from ammonium salts, or by protonation of aminyl radicals (which are relatively weak bases and require strong acids for protonation). Metal-complexed aminyl radicals are highly reactive, and amidyl radicals are also useful.[178]

The atom transfer method is most commonly employed for the cyclizations of *N*-haloamines, and pioneering work by the groups of Minisci[179] (in arylations), and Surzur and Stella[180] (in cyclizations) has shown that this is a powerful method for construction of N-heterocycles. These reactions are usually promoted by metals: popular procedures use $TiCl_3$, $FeSO_4$, or CuCl and $CuCl_2$. It is proposed that the aminyl radicals formed in some of these reactions are complexed rather than free.[180] The atom transfer mechanism operates, but it is not always clear whether the donor is the starting *N*-halide or a metal halide additive (for example, $CuCl_2$ is an excellent chlorine donor). Because *N*-haloamines are reactive sources of positive halogen, ionic products are also sometimes formed. The first example in Scheme 41 illustrates a typical radical reaction and the basic mechanism. The products of such reactions are nitrogen mustards that can be used to form additional bonds through the intermediacy of aziridinium ions (sometimes *in situ*). Recent work of Broka also shown in Scheme 41 illustrates how such combinations can lead to rapid construction of complex heterocyclic skeletons like the morphans.[181]

Recent work by Newcomb has resulted in the emergence of a second method for the cyclizations of amminium radical cations that shows good synthetic potential.[175,176] As illustrated in Scheme 42, *N*-hydroxypyridine-2-thione carbamates can be generated and cyclized by analogy to the Barton method (which uses thione esters). In Scheme 42, the preparation of the precursors and two variants on the cyclization, reductive trapping and thiopyridyl trapping are illustrated.

### 4.2.4.2 Oxygen-centered Radicals

In contrast to aminyl radicals, alkoxyl (and acyloxy) radicals are highly reactive. As illustrated in equation (7), their cyclization reactions are extremely rapid and irreversible. However, the rapidity of such cyclizations does not guarantee success because alkoxyl radicals are also reactive in inter- and intramolecular hydrogen abstractions, and β-fragmentations (see Section 4.2.5.2). This lack of selectivity may limit the use of alkoxyl radicals in cyclizations, but 5-exo cyclizations are so rapid that they should succeed in many cases, and other types of cyclizations may also be possible.

Alkoxyl radicals can be generated by a variety of methods including peroxide reduction, nitrite ester photolysis, hypohalite thermolysis, and fragmentation of epoxyalkyl radicals (for additional examples of alkoxyl radical generation, see Section 4.2.5.2). Hypohalites are excellent halogen atom donors to carbon-centered radicals, and a recent example of this type of cyclization from the work of Kraus is illustrated in Scheme 43.[182] Oxidation of the hemiketal (**57**) presumably forms an intermediate hypoiodite, which spontaneously cyclizes to (**58**) by an atom transfer mechanism. Unfortunately, the direct application of the Barton method for the generation of alkoxyl radicals fails because the intermediate pyridinethione carbonates are sensitive to hydrolytic reactions. However, in a very important recent development, Beckwith and Hay have shown that alkoxyl radicals are formed from *N*-alkoxypyridinethiones.[183] Al-

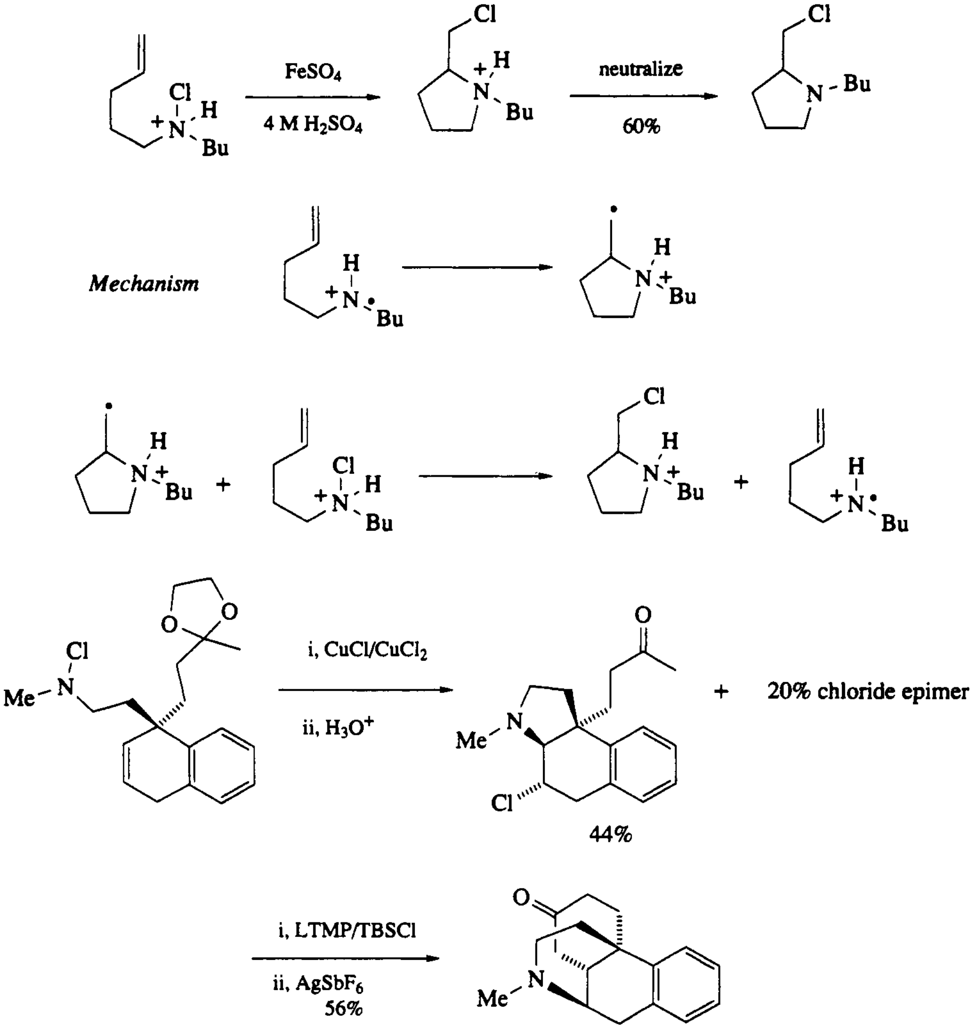
FeSO$_4$
4 M H$_2$SO$_4$
neutralize
60%
Mechanism
i, CuCl/CuCl$_2$
ii, H$_3$O$^+$
+ 20% chloride epimer
44%
i, LTMP/TBSCl
ii, AgSbF$_6$
56%

**Scheme 41**

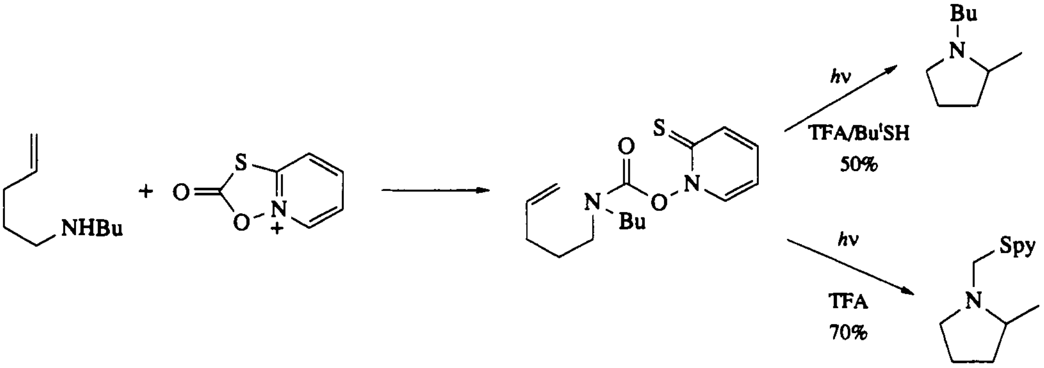
hν
TFA/Bu$^t$SH
50%
hν
TFA
70%

**Scheme 42**

though the only current example of a cyclization is the closure of the simplest precursor (**59**) to give methyl tetrahydrofuran (**60**), this method should allow access to Barton-like products in alkoxyl radical cyclizations. Precursors are formed by *O*-alkylation of *N*-hydoxypyridinethione salts, and a potential problem with such amibident nucleophiles is *S*-alkylation. In a related method, Fraser-Reid has recently shown that reductions of nitrate esters with tin hydride give products derived from alkoxyl radicals.[184,185]

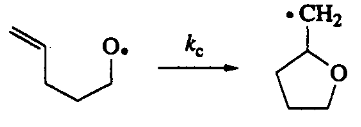

(7)

$k_c > 6 \times 10^8\ s^{-1}$

This is rather surprising because primary nitroalkanes (which would give more stable alkyl radicals) are not readily reduced by tin hydride. The third example in Scheme 43 illustrates a cyclization of an alkoxyl radical derived from a nitrate ester.

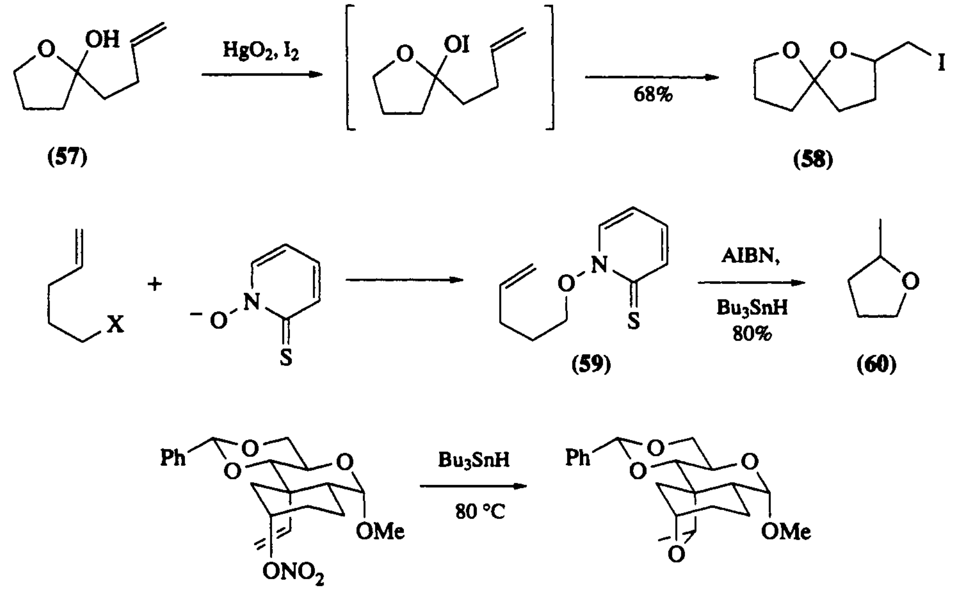
O
OH
HgO₂, I₂
O
OI
68%
O
O
I
(57)
(58)
X
+
⁻O
N
S
O
N
S
AIBN,
Bu₃SnH
80%
O
(59)
(60)
Ph
O
O
O
OMe
ONO₂
Bu₃SnH
80 °C
Ph
O
O
O
OMe
O

Scheme 43

There is another standard method for formation of heterocyclic rings from nitrogen- and oxygen-centered radicals that does not involve cyclization of a radical to a π-bond. Instead, δ-halo ethers or amines are formed by a chain reaction comprised of hydrogen and halogen atom transfer steps, and the ring closure occurs by ionic ($S_N1$ or $S_N2$) substitution. Two recent examples of this broad class of reactions are provided in Scheme 44.[186,187] When nitrogen-centered radicals are involved, this transformation is usually called the Hofmann–Löffler–Freytag reaction.[188]

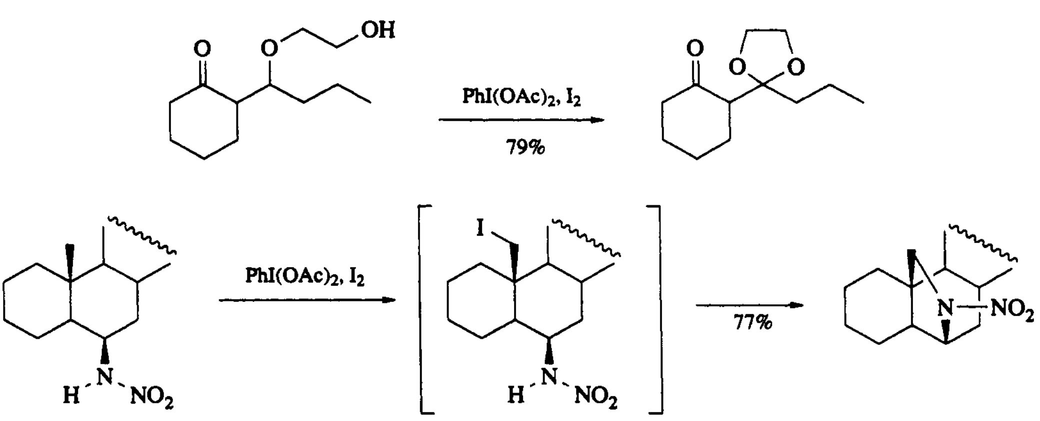
O
O
OH
PhI(OAc)₂, I₂
79%
O
O
O
H
N
NO₂
PhI(OAc)₂, I₂
I
H
N
NO₂
77%
N
NO₂

Scheme 44

## 4.2.5 ADDITIONS TO CARBON–NITROGEN AND CARBON–OXYGEN MULTIPLE BONDS, AND β-FRAGMENTATIONS

When constructing five-membered rings by radical cyclizations, it is required that the multiple bond acceptor be exocyclic to the forming ring. Thus, with C—C multiple bond acceptors, an exocyclic ring residue of at least one carbon atom is always produced. When this residue is not required, an alkyne acceptor is often used, and the resulting alkylidene chain is excised by ozonolysis (see Scheme 13). A more direct route to rings that do not possess carbon substituents at the site of cyclization uses a carbon–nitrogen or carbon–oxygen multiple bond as the acceptor.

### 4.2.5.1 Carbon–Nitrogen Multiple Bonds

Radical cyclizations to carbon–nitrogen multiple bonds resemble additions to carbon–carbon multiple bonds in that they usually give products of irreversible exo cyclization. To date, the most useful acceptors have been oximes[189] and nitriles,[190] and one example of each type of cyclization is given in Scheme 45.[191] Nitriles are useful because the intermediate imines are readily hydrolyzed by mild acid to ketones. Although this route to ketones is shorter than the two-step sequence of alkyne cyclization/ozonolysis, nitriles are slightly poorer acceptors than terminal alkynes, and much poorer acceptors than activated alkynes. Thus, when slow cyclizations are involved, the two-step protocol is preferable.

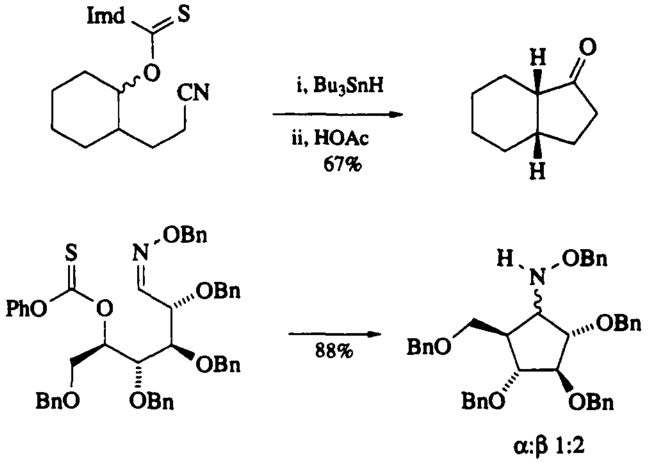

Scheme 45

### 4.2.5.2 Carbon–Oxygen Multiple Bonds

Radical cyclizations to carbon–oxygen multiple bonds are considerably different from cyclizations to C—C and C—N double bonds. Indeed, before the recent discoveries of Fraser-Reid and Tsang,[185,192–194] cyclizations to C–O multiple bonds were not considered generally useful, and only the reverse reaction (β-fragmentation of an alkoxyl radical) was common. However, a much better understanding of these reactions is beginning to emerge. As illustrated in Scheme 46, the cyclizations of radicals to carbonyl groups are best interpreted in the framework of the Curtin–Hammett principle.[195] A semiquantitative analysis of these reactions (introduced in a recent review)[196] has been greatly facilitated by the recent rate studies of Beckwith and Hay.[197]

Analysis of the behavior of the parent substrates for 5-exo cyclization (**61a**) and 6-exo cyclization (**61b**) is an instructive point of departure. As indicated in Scheme 46, these cyclizations are approximately equal in rate,[198] and both are more rapid than the cyclization of the hexenyl radical (see Scheme 2). The high rate of cyclization and the complete absence of *endo* products (which would be much more stable radicals) indicate the importance of FMO effects on rates: the carbonyl group has a low-lying LUMO with the large orbital coefficient on carbon. Unlike the hexenyl radical, the products of cyclization (**62a**) and (**62b**) can revert to the starting radicals. Indeed, both reverse cyclizations are faster than the forward cyclizations; that is, the starting radicals (**61a**) and (**61b**) are favored at equilibrium. That (**61a,b**) are more stable than (**62a,b**) is not surprising: the cyclization sacrifices a C=O bond (which is much stronger than a C=C bond that is lost in a hexenyl radical cyclization) and generates an alkoxyl radical (which is much less stable than the starting carbon radical). Because of the increased strain in the cyclopentane ring relative to cyclohexane, alkoxyl radical (**62a**) fragments much more rapidly than (**62b**).

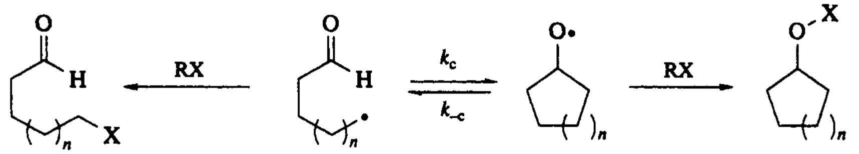

(**63a,b**) (**61a**) $n = 1$ (**61b**) $n = 2$ (**62a**) (**62b**) (**64a,b**)

at 80 °C, $n = 1$, $k_c = 9 \times 10^5\ \mathrm{s}^{-1}$; $k_{-c} = 5 \times 10^8\ \mathrm{s}^{-1}$; $K_{eq} \approx 0.002$

$n = 2$, $k_c = 1 \times 10^6\ \mathrm{s}^{-1}$; $k_{-c} = 1 \times 10^7\ \mathrm{s}^{-1}$; $K_{eq} \approx 0.1$

**Scheme 46** Cyclization to carbonyls

Whether products derived from cyclization or fragmentation are isolated depends not only on the rates of forward and reverse cyclization, but also on the rates of trapping of the intermediate radicals to give (**63a,b**) or (**64a,b**). Several different scenarios are possible (the reader is referred to more quantitative discussions).[196,197] If cyclization is the desired pathway, a reagent (RX) that reacts much more rapidly with alkoxyl radicals than with carbon radicals is required. As mentioned in Figure 4, tin hydride is just such a reagent (RX = $Bu_3SnH$).[199] When forming six-membered rings, it is often possible to trap cyclic radicals (**62b**) with tin hydride more rapidly than they revert to (**61b**). Even if partial equilibrium occurs, an excellent yield of cyclic product is still possible because tin hydride reacts about 100 times more rapidly with (**62b**) than with (**61b**). Therefore, (**62b**) will be selectively trapped at equilibrium provided that the equilibrium constant is not too low (that is $k_c$ is not too much smaller than $k_{-c}$). The formation of five-membered ring products is more difficult because the reverse cyclization of (**62a**) is so rapid. When tin hydride is used, its concentration must be sufficiently low to allow most of (**61a**) to close before it is directly reduced to (**63a**). At such concentrations (<0.1M), most of (**62a**) will revert to (**61a**) before it is trapped to give (**64a**). The increased reactivity of tin hydride toward (**62a**) over (**61a**) will not be sufficient to offset the equilibrium constant, which strongly favors (**61a**) because of the magnitude of $k_{-c}$. Thus, both (**63a**) and (**64a**) will be produced.

Even though there are no reaction conditions that can promote the high yield formation of (**64a**) in this simple example, the prospects for forming five-membered rings are far from hopeless. Most substituents along the forming ring should increase the equilibrium constant either by increasing $k_c$ or decreasing $k_{-c}$, thus facilitating the trapping of cyclic products. The important experimental lesson from Scheme 46 is that cyclizations to aldehydes are fast, and low tin hydride concentrations are not necessarily required to obtain good yields of cyclic products.

Because equilibrium constants often favor open products, fragmentation reactions of alkoxyl radicals are easy to conduct and are generally useful. The atom transfer method is excellent for fragmentations. Alkoxyl radicals are formed from *in situ* generated hypohalites (RX = O—halogen). Hypohalite bonds are very weak, and thus oxygen-centered radicals (**62**) are not efficiently trapped, but carbon-centered radicals (**61**) abstract halogen very rapidly to give (**63**) (X = halogen). Peroxides are also good precursors for alkoxyl radical fragmentations. When radical-stabilizing groups are present, or when strained rings are involved, the fragmentation reactions are often so rapid that no reagent can trap the alkoxyl radical prior to its scission. Indeed, fragmentation reactions are especially valuable when conducted in sequence with other radical reactions because group transfers or ring expansions can result (see Section 4.2.6.2.1).

In cases where the fragmentation reactions are not prohibitively rapid, it may be possible to conduct either cyclization or fragmentation by selection of appropriate reagents and conditions. Scheme 47 provides an example where the same two intermediate radicals are involved.[200,201] The cyclized product is formed in the presence of tin hydride, but the fragmented product is produced under the atom transfer conditions.

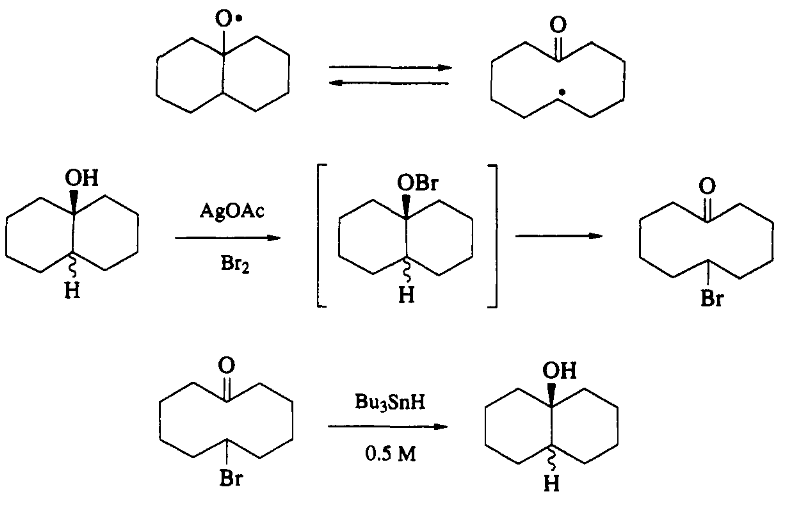

**Scheme 47**

### *4.2.5.2.1 Cyclizations to aldehydes and ketones*

Additions to carbonyls are probably restricted to aldehydes and ketones, and ketones will be less reactive than aldehydes because the extra alkyl group on a ketone is at the carbon that the radical is attacking. Carbonyl groups (like esters and amides) with resonance-stabilizing substituents are usually too unreactive to serve as acceptors. In contrast, fragmentations to give resonance-stabilized carbonyls will be very rapid. Two examples of cyclization to aldehydes from the work of Frasier-Reid and Tsang are presented in Scheme 48.[193,194] There is good evidence to indicate that the first cyclization is not reversible; tin hydride traps the cyclic radical before it can revert.[185]

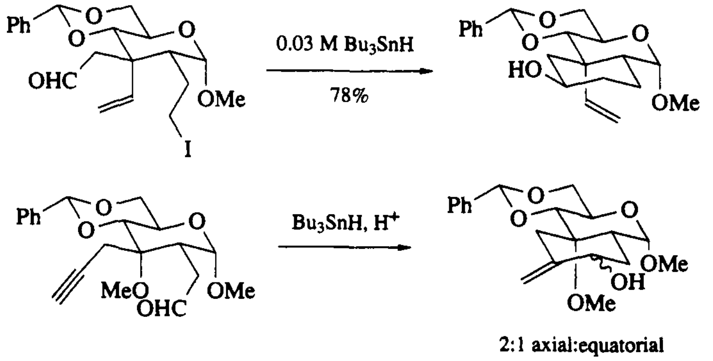

**Scheme 48**

### *4.2.5.2.2 Fragmentations of alkoxyl radicals*

Fragmentation reactions of alkoxyl radicals have been extensively studied by the groups of Suginome,[202] Suarez[203] and others. As shown in Scheme 49, they provide an excellent means for the preparation of medium ring ketones (first example)[204] and lactones (second example)[205] by scission of a ring fusion bond. Schreiber has shown that alkoxyl radicals generated from peroxides can fragment, and the resulting radicals can be trapped by $Cu^{II}$. The ensuing copper hydride elimination often proceeds with very high regio- and stereo-selectivity (third example).[206] The last example in Scheme 49 illustrates an important variant: when readily eliminated groups are present β to the cleaving bond, an additional fragmentation occurs to introduce an alkene whose stereochemistry is dictated by the configuration of the precursor.[207,208]

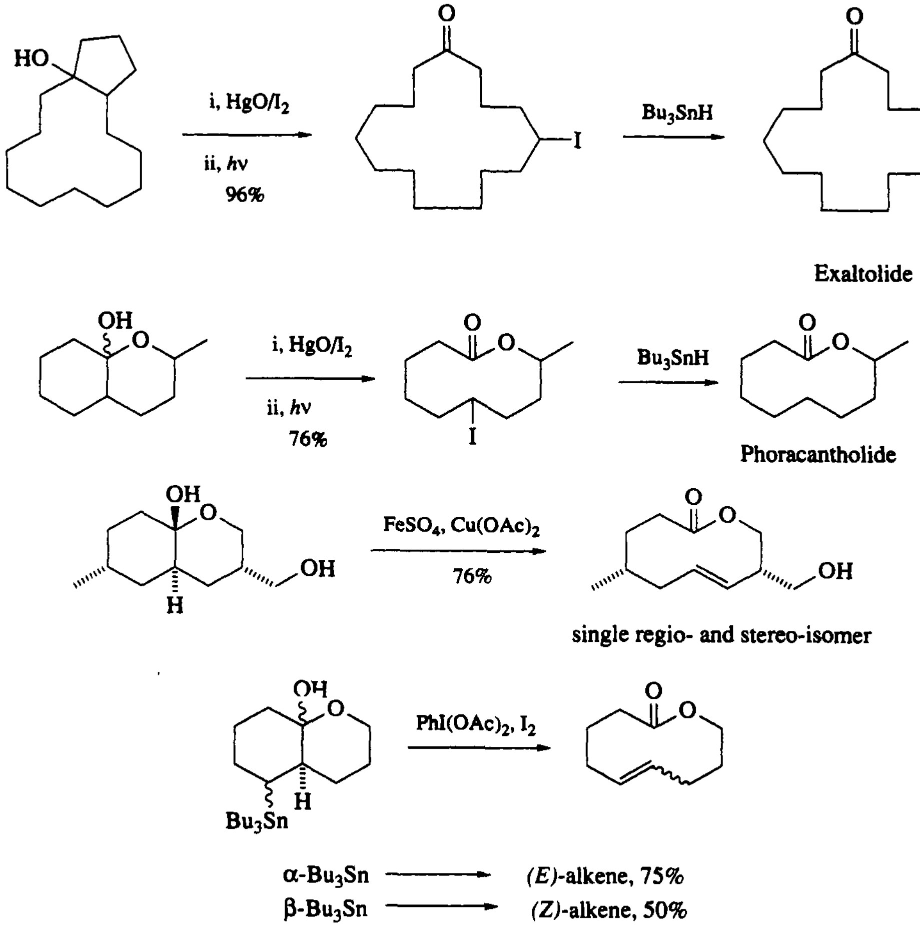

Scheme 49

## 4.2.6 SEQUENTIAL RADICAL REACTIONS

Radical reactions are naturally suited to sequencing, because a new radical results from every radical addition, cyclization, or fragmentation. In a real sense, virtually every radical chain reaction (and many nonchain reactions as well) is a sequence of reactions in which several intermediate radicals are involved. However, for synthetic purposes, we define a radical sequence more narrowly as any reaction in which *more than one radical transformation occurs in the substrate, excluding steps that involve radical generation and radical removal.* By this definition, simple addition or cyclization reactions are not sequences because only one reaction (the addition or cyclization) occurs between radical generation in the substrate and radical removal. Within this definition, we classify two groups of radical sequences: simple sequences and tandem (and higher) sequences. In simple sequences, there are two or more radical precursors present in the radical substrate(s), and the two radical reactions occur separately. In tandem (and higher) sequences, the radical reactions are intimately linked because the precursor for the second radical reaction is generated by the first reaction. Aspects of sequential radical chain reactions have been discussed in a recent review.[34]

### 4.2.6.1 Simple Sequences

In simple sequences, reactions are conducted by repeating at least once the three stages of a radical reaction: (i) radical generation, (ii) addition, cyclization, or fragmentation, and (iii) radical removal. This means that two (or more) radical precursors will be required, and the only difference between a simple sequence and a standard cyclization or addition is that one must control the timing and location of the first set of radical reactions relative to the second. Because the transformations occur individually, there is no requirement that the two reactions of a simple sequence be conducted in the same step rather than in separate steps; however, the potential to conduct two important synthetic transformations together is attractive.

There are only a few examples of simple sequences in the literature, and the two provided in Scheme 50 illustrate different ways in which the timing of the individual steps in the sequence can be controlled. The first example from Bellus sequences an addition reaction prior to a cyclization by using the atom transfer method.[209] Because the initial radicals for both the addition and the cyclization are generated on the same carbon atom, there is no problem with selective radical generation. Selection between the two alkenes for the initial addition step is interesting: the dichloroacetate radical adds to the terminal alkene (even though this alkene is electron deficient) rather than the disubstituted alkene. The second example from our laboratory[210] illustrates the sequencing of an addition reaction, conducted by the Keck/Byers fragmentation method,[211] with a cyclization reaction, conducted by the tin hydride method. To ensure that the radicals are generated in the correct order, a highly reactive alkyl iodide is used as the radical precursor for the first step while a less reactive vinyl bromide serves as the precursor for the second step. The two reactions of this sequence can be conducted either together in one pot, or individually.

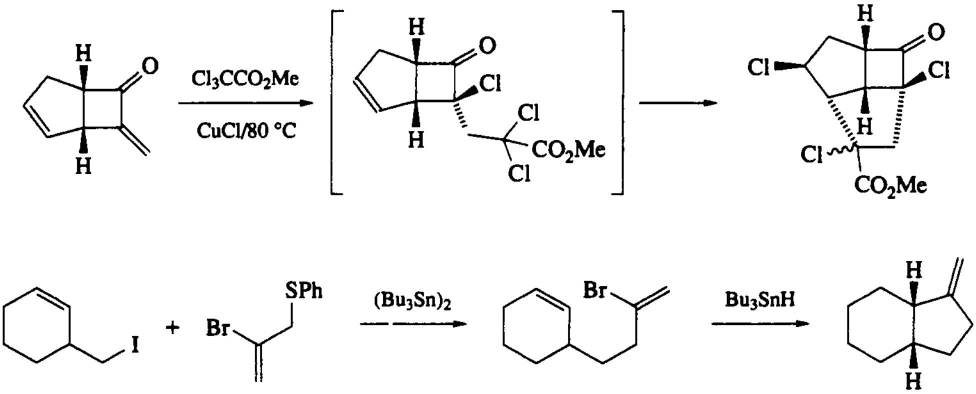

Scheme 50

### 4.2.6.2 Tandem (and Higher) Sequences

Tandem sequences are far more common than simple sequences, and they are far more powerful. In a tandem sequence, the radical precursor for the second transformation is generated not from a standard precursor (like a halide), but from the preceding transformation in the sequence. There is only one step that generates an initial radical and one step that removes a final radical. In effect, all of the transformations that are conducted must occur during the solution lifetime of a single radical. General considerations for tandem sequences are shown schematically in Scheme 51. The radical generation step provides the initial radical A·. This undergoes an inter- or intra-molecular reaction to form B·, the precursor for the second step in the sequence. The final radical in the sequence, C·, must be converted to a stable product. In many respects, designing tandem sequences is no different from simple additions and cyclizations. All the reactions must be faster than radical/radical reactions or radical/solvent reactions, and the final radical must be selectively removed from the radical pool (but now in the presence of two other substrate radicals rather than one). In principle, many reactions can be conducted between radical generation and radical removal. The radical polymerization of alkenes is a prime example: thousands of addition steps take place between radical generation and radical removal. The problem in synthesis is how to have several different intermediate radicals (A·, B·, C·), which are simultaneously present, avoid suffering the same fate.

The types of reactions that are sequenced and the order in which they occur often dictate the choice of an appropriate method. Thus, sequential radical reactions are classified by transformation, and they are presented below in roughly increasing order of difficulty. With careful substrate design and selection of an appropriate method and reaction conditions, a diverse collection of tandem radical reactions has been executed. Yet the known reactions only begin to show the potential of such radical sequences for the rapid assemblage of complex molecules.

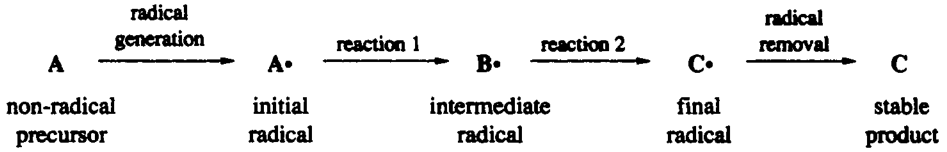

Potential problems: all reactions must be faster than radical–radical or radical–solvent reactions
radicals A•, B• and C• must be differentiated
radical C• must be selectively removed in the presence of A• and B•

**Scheme 51** Sequential radical reactions

### *4.2.6.2.1 Sequences involving only intramolecular transformations*

Sequences that involve all intramolecular transformations are by far the easiest to conduct, yet they are among the most powerful. The requirements for success are similar to those for standard radical cyclizations. In general, the slowest intramolecular reaction must still be more rapid than the reaction that converts that radical to a nonradical product (this ensures that the initial and intermediate radicals are not intercepted prior to intramolecular reaction). The differentiation of the intermediate radicals is provided by the structure of the substrate itself: radicals A· and B· should have only one reasonably rapid intramolecular option, and radical C· should have none.

*(i) Cyclization/cyclization*

The sequencing of two cyclizations is a simple but very powerful strategy to construct polycyclic rings. Any method that is useful for a single cyclization can be used for a tandem cyclization as well, and standard techniques are used to allow intermediate radicals to live long enough to cyclize (for example, in the tin hydride method, syringe pump additions or catalytic methods are common). Scheme 52 provides just a sampling of the types of tandem cyclizations that have recently been conducted by the tin hydride method,[192,212–216] hydrogen[50] and halogen[133] atom transfer methods, oxidation by Mn$^{III}$,[217] and reduction by SmI$_2$.[218] Provided that the cyclizations are rapid, it should be possible to sequence more than two reactions, and there are already several examples of triple radical cyclizations.[219,220]

*(ii) Intramolecular 1,5-hydrogen atom transfer/cyclization (radical translocation)*

Intramolecular 1,5-hydrogen atom transfer reactions of radicals are well known and have often been used to introduce functional groups at unactivated centers. For example, the Barton photolysis of nitrite esters is a preparatively useful method to make oximes,[221] and the Hoffman–Löffler–Freytag and related reactions are also important methods to construct heterocycles (see Scheme 44). These reactions use highly reactive alkoxyl or amminium radicals. 1,5-Hydrogen transfer reactions of alkoxyl radicals have also been used to generate radicals for subsequent cyclizations[222] and additions.[168]

We have recently introduced a variant of this class of reaction, termed radical translocation, that will be especially useful because it operates within the confines of the commonly used tin hydride method.[223] In this variant, the initial radical is generated at a remote location by standard halogen atom abstraction, and then translocated by a 1,5-hydrogen atom shift. The intermediate radical that results then undergoes standard cyclization. The two approaches illustrated in Scheme 53 have a common theme: the radical is translocated from a site where it is easily generated to another site where a standard radical precursor might be difficult either to prepare or to carry through a multistep synthetic sequence. In the first example, the initial radical center is in a 'protecting group', and in the second, it is on the alkene that is destined to become the acceptor. In an indirect way, this allows a simple C—H bond to be a radical precursor in the tin hydride method. It is important that the 1,5-hydrogen transfer be as exothermic as possible so that it is sufficiently rapid to compete with direct tin hydride reduction.

*(iii) Cyclization/fragmentation*

When a cyclization reaction precedes a fragmentation, carbon–carbon bonds are exchanged rather than created. Nonetheless, such sequences are very useful for reorganizing the carbon skeleton of a molecule, especially when easily fragmentable alkoxyl radicals are formed in the cyclization step. Depending on

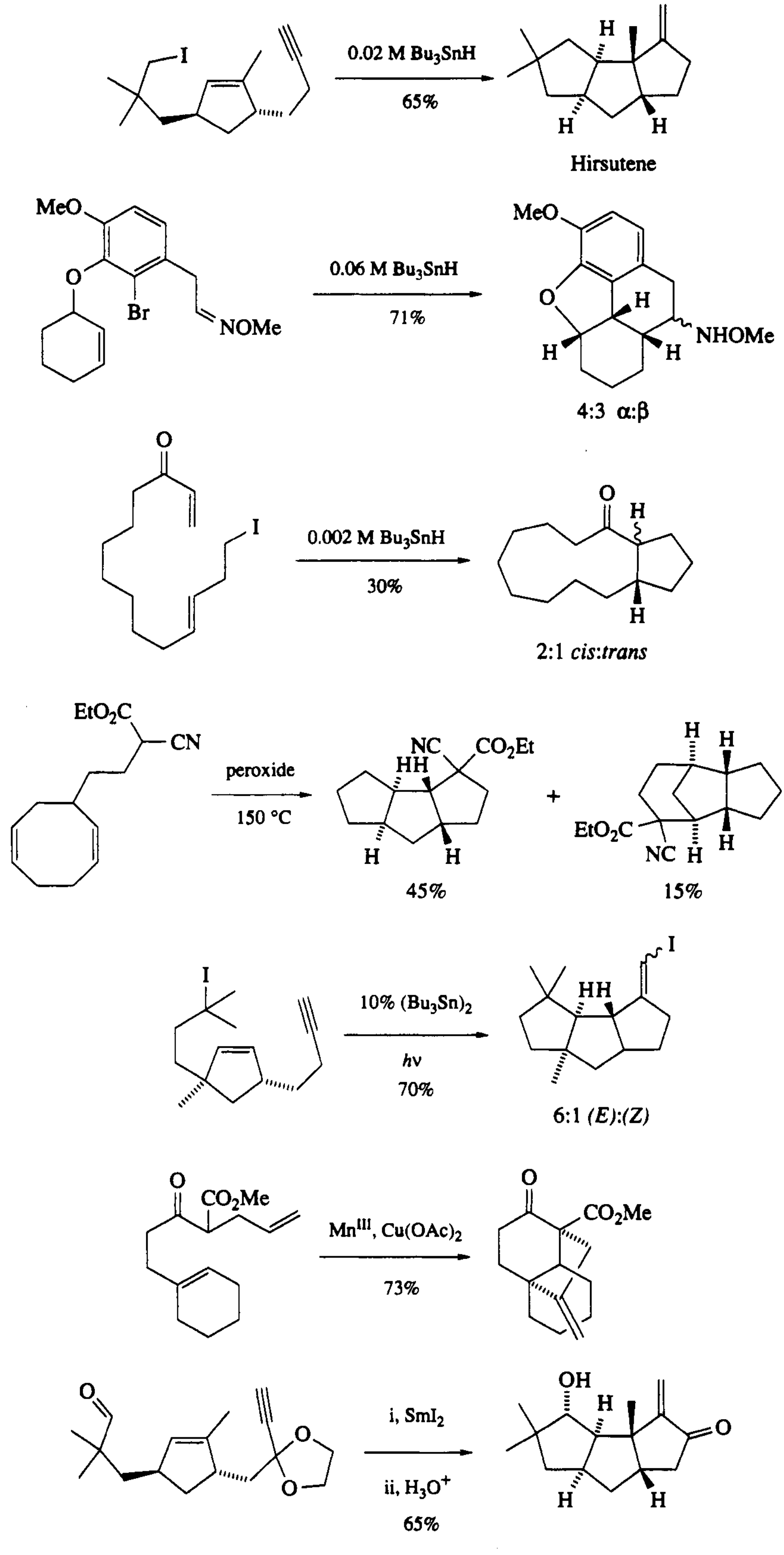
0.02 M $Bu_3SnH$
65%
Hirsutene
MeO
Br
NOMe
0.06 M $Bu_3SnH$
71%
NHOMe
4:3 α:β
I
0.002 M $Bu_3SnH$
30%
2:1 *cis*:*trans*
$EtO_2C$
CN
peroxide
150 °C
NC
$CO_2Et$
45%
+
15%
10% $(Bu_3Sn)_2$
hν
70%
6:1 *(E)*:*(Z)*
$CO_2Me$
$Mn^{III}$, $Cu(OAc)_2$
73%
i, $SmI_2$
ii, $H_3O^+$
65%
OH

Scheme 52

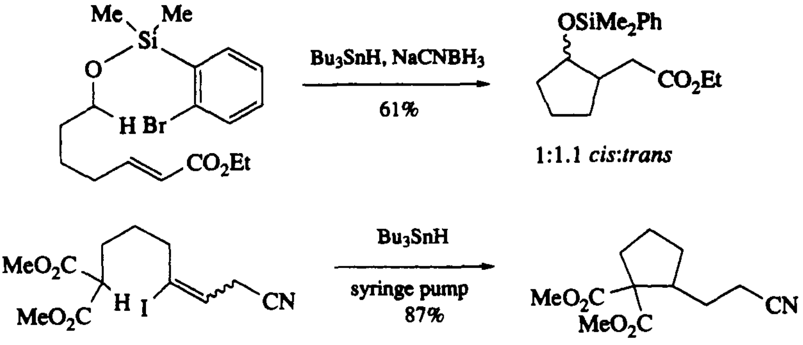
Me
Me
Si
O
H Br
CO2Et
Bu3SnH, NaCNBH3
61%
OSiMe2Ph
CO2Et
1:1.1 cis:trans
MeO2C
MeO2C
H
I
CN
Bu3SnH
syringe pump
87%
MeO2C
MeO2C
CN

Scheme 53

the structure of the substrate, group migration or ring expansion can occur. Scheme 54 provides examples from the work of Beckwith,[224] Dowd and Choi[225] and Baldwin.[226] In these sequences, a radical-stabilizing group often controls the direction of fragmentation, and thus the final radical is usually more stable than the starting radical. Methods like atom transfer will not be useful for such sequences, but the tin hydride method and the tin/sulfur fragmentation method are appropriate.

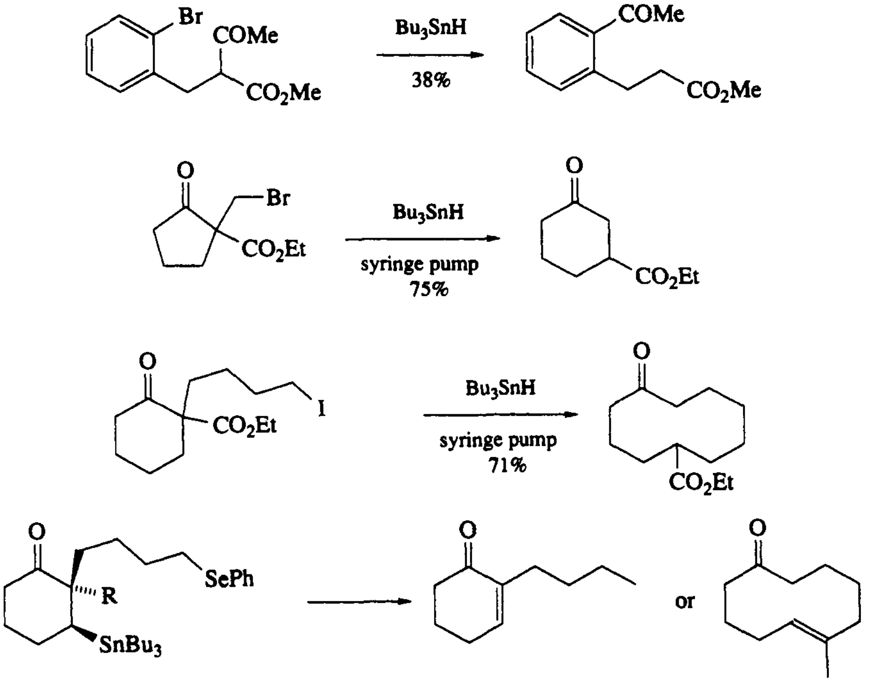
Br
COMe
CO2Me
Bu3SnH
38%
COMe
CO2Me
O
Br
CO2Et
Bu3SnH
syringe pump
75%
O
CO2Et
O
CO2Et
I
Bu3SnH
syringe pump
71%
O
CO2Et
O
R
SePh
SnBu3
O
or
O

(65) R = H
(66) R = Me

(67) R = H, 86% or (68) R = Me, 89%

Scheme 54

The first example in Scheme 54 illustrates the migration of an acetyl group while the second example illustrates the expansion of a ring by one carbon atom (see also Scheme 21). As shown in the third example, rings can also be expanded by three and four atoms (but not two atoms because the 4-exo closure is too slow). Thus, although medium size rings are not directly available by radical cyclization of an acyclic precursor, they are readily prepared by ring expansion of a standard small ring. In the second and third examples, the ester group not only controls the direction of fragmentation, but it also accelerates the initial cyclization to the carbonyl. Even so, syringe pump methods must be used to minimize direct reduction of the starting halide. As usual, this difficulty can be overcome by building the tin group into the precursor and conducting the cyclization by the fragmentation method, as shown in the last example of Scheme 54. One of the pitfalls of this approach is 1,5-hydrogen transfer. When (65) is heated with

AIBN, (67) forms in high yield because the initial radical abstracts the hydrogen α to the carbonyl (with concomitant elimination of $Bu_3Sn\cdot$) more rapidly than it cyclizes. However, blocking this pathway results in smooth ring expansion, as illustrated by the conversion of (66) to (68). The alkene stereochemistry is dictated by the configuration of the precursor (see Scheme 49).

### *(iv) Fragmentation/cyclization*

Very useful transformations can also be designed when the fragmentation precedes the cyclization, as shown in Scheme 55. Motherwell and Harling have demonstrated that the stereochemistry of a spirocyclic ring can be controlled by a fragmentation of a cyclopropyl carbinyl radical, followed by cyclization, as illustrated by the first two examples.[227] The hydroxy group ultimately dictates the stereochemistry of the spirocycle by directing the Simmons–Smith cyclopropanation. Such fragmentations of cyclopropyl carbinyl radicals are useful even when they are not conducted in a sequence,[228] and the kinetic cleavage of a lateral bond of a fused cyclopropane is usually observed unless radical-stabilizing groups accelerate cleavage of the ring fusion bond. The third example, taken from the studies of Citerrio, illustrates how a fragmentation/cyclization sequence conducted by a reductive method can result in ring contraction.

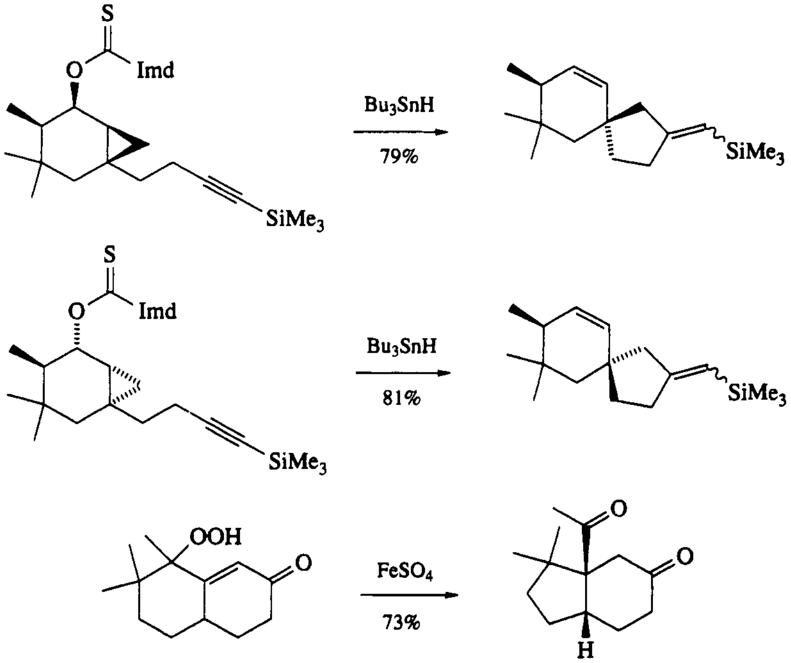

Scheme 55

### *4.2.6.2.2 Sequences combining inter- and intra-molecular reactions*

Sequences that combine inter- and intra-molecular reactions are very powerful, but they require more careful planning to ensure selectivity. The order in which such reactions are conducted has a significant impact on the design of substrates and the selection of a method.

### *(i) Cyclization/addition*

When combining cyclizations and additions, design is simpler if the cyclization precedes the addition. The usual considerations apply for the success of the addition step (see the preceding chapter). Any cyclization that is more rapid than a given addition can be sequenced before that addition. Thus, rapid cyclizations are easily conducted prior to additions, but slow cyclizations may be problematic since the initial radical might competitively add to the acceptor. However, even slow cyclizations can probably be conducted by electronically mismatching the initial radical and the acceptor, or by using relatively unreactive acceptors like allylstannanes. Examples of cyclization/addition sequences conducted by the tin hydride method,[229,230] the fragmentation method,[231,232] and the reductive method[168] are presented in Scheme 56.

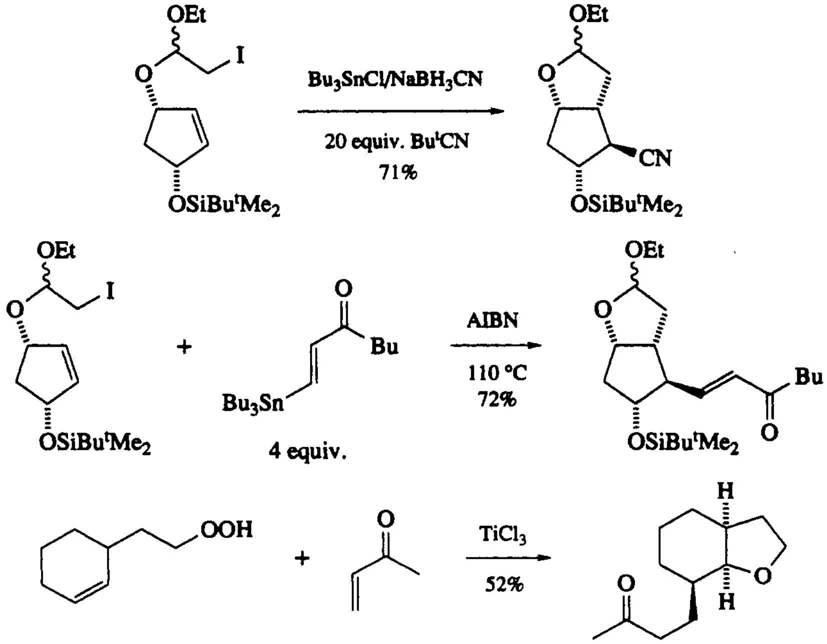

Scheme 56

*(ii) Addition/cyclization*

Sequences in which addition precedes cyclization are not as straightforward to conduct as the reverse; however, they are very important because a net annulation results (that is, a new ring is formed by the union of two acyclic precursors in one experimental step). The intermediate radical is differentiated from the other radicals provided that the cyclization reaction is rapid, but it can be difficult to differentiate the initial radical from the final radical. As illustrated in Scheme 57, this is particularly true in the tin hydride method because many different types of radicals react with tin hydride at similar rates. Reaction of (**69**) under standard radical addition conditions produces (**70**), which results from a sequence of addition/cyclization/addition.[233] That the last C—C bond is formed actually results from a lack of selectivity: the initial and final radicals are not differentiated and they must undergo the same reaction. Of course, this 'lack of selectivity' is of no consequence if the product contains the desired skeleton and the needed functionality for subsequent transformations. Such sequences are very useful for forming three carbon–carbon bonds, and they can also be conducted by Barton's thiohydroxamate method.[234] Structural modifications are required to differentiate the initial and final radicals, and, as illustrated by the conversion of (**71**) to (**72**), phenyl groups can provide the needed differentiation (probably by retarding the rate of addition more than they retard the rate of hydrogen abstraction). Clive has demonstrated that phenyl-substituted vinyl radicals also provide the needed selectivity, as illustrated by the second example in Scheme 57.[235]

Work from our group has shown that the atom transfer method[236,237] and the fragmentation method[238] are especially useful for conducting these radical annulations. As illustrated by the first two examples in Scheme 58, atom transfer annulations can be designed by pairing nucleophilic radicals with electrophilic acceptors, or by the reverse. In either case, the substrates are designed such that the least resonance stabilized radical appears last in the sequence. This radical rapidly abstracts iodide from either the starting iodide or from an intermediate iodide, thereby terminating the sequence before the final radical can undergo a second addition reaction. The last example in Scheme 58 illustrates that fragmentation reactions should be especially powerful in controlling such annulations: whenever a β-stannyl radical arises, its rapid fragmentation will terminate the sequence and transfer the chain. In contrast to other cyclization and addition reactions of vinylstannanes (see Scheme 25), the example in Scheme 58 provides a high level of inversion of alkene stereochemistry, and an explanation for this phenomenon has been proposed.[238]

Feldman[239,240] and Oshima and Utimoto[241] have introduced a very sophisticated sequence of reactions that effects a radical annulation starting from a vinylcyclopropane. Scheme 59 provides two examples and a likely mechanism for this sequence, which involves fragmentation, addition and cyclization. The

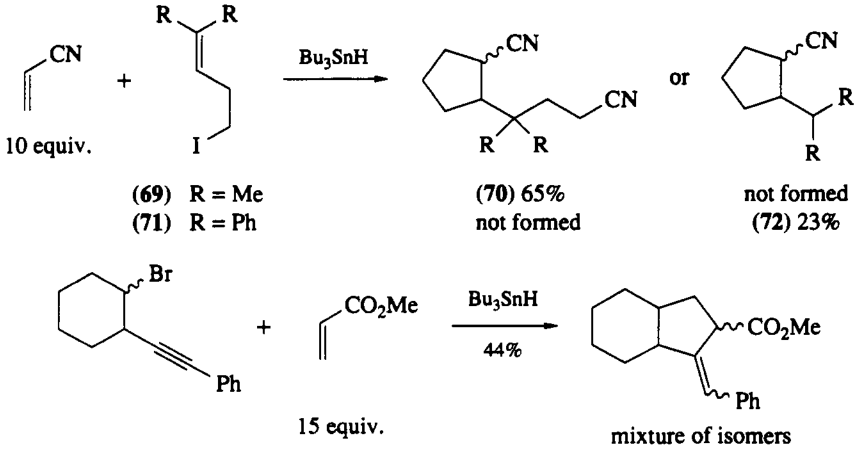
10 equiv.
Bu$_3$SnH
(69) R = Me
(71) R = Ph
(70) 65%
not formed
or
not formed
(72) 23%
Bu$_3$SnH
44%
15 equiv.
mixture of isomers

Scheme 57

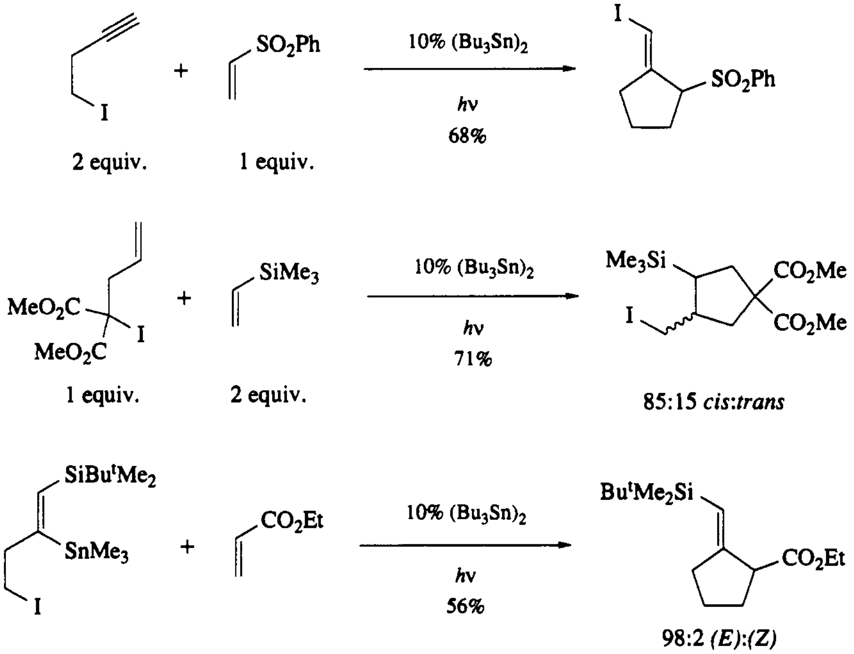
2 equiv.
1 equiv.
10% (Bu$_3$Sn)$_2$
hv
68%
1 equiv.
2 equiv.
10% (Bu$_3$Sn)$_2$
hv
71%
85:15 cis:trans
10% (Bu$_3$Sn)$_2$
hv
56%
98:2 (E):(Z)

Scheme 58

irreversibility of the addition and 5-exo cyclization steps drives the sequence forward, and a rapid fragmentation reaction (of a β-phenylthio radical) plays a key role in terminating the sequence before the final radical can undergo another addition.

With the goal of sequencing several addition reactions, Feldman and Lee have recently introduced a beautiful protocol, termed template-controlled oligomerization, that allows a controlled number of addition reactions to take place prior to a radical macrocyclization.[242] As illustrated in equation (8), the number of additions is dictated by the distance of the gap between the 'initiator' and the 'terminator' in this strictly controlled oligomerization. The requirement here is that the macrocyclization be more rapid than the bimolecular addition. A rapid fragmentation of a phenylthio radical is again used to terminate the sequence, and this prevents the final radical from continuing to polymerize. When the oligomer is detached from the template, it appears as if four sequential additions (three to the external acceptor and one to the acceptor on the template) have occurred. This type of reaction is virtually impossible to conduct in a controlled fashion by sequencing addition reactions (see below).

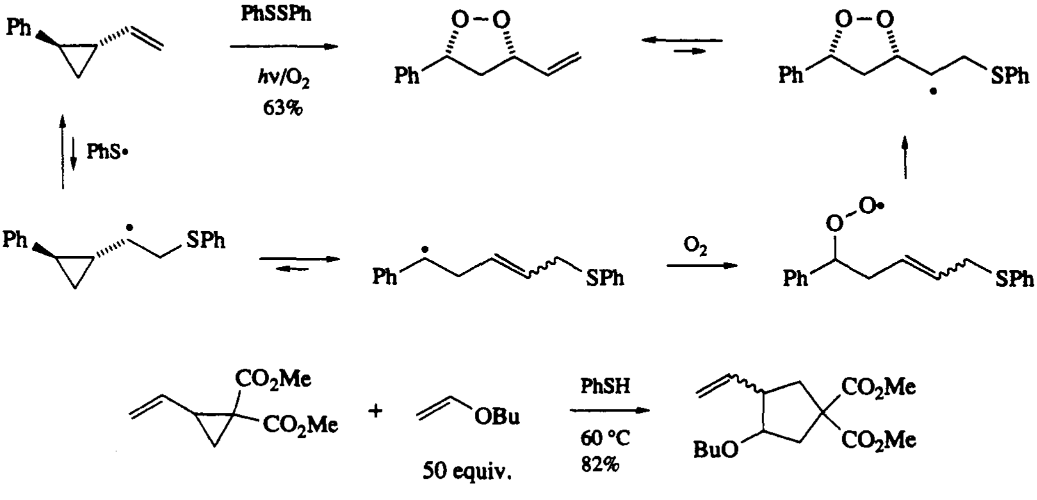
Ph
PhSSPh
hv/O2
63%
O–O
Ph
O–O
Ph
SPh
PhS•
Ph
SPh
Ph
SPh
O2
O•
O
Ph
SPh
CO2Me
CO2Me
+
OBu
50 equiv.
PhSH
60 °C
82%
CO2Me
BuO
CO2Me

Scheme 59

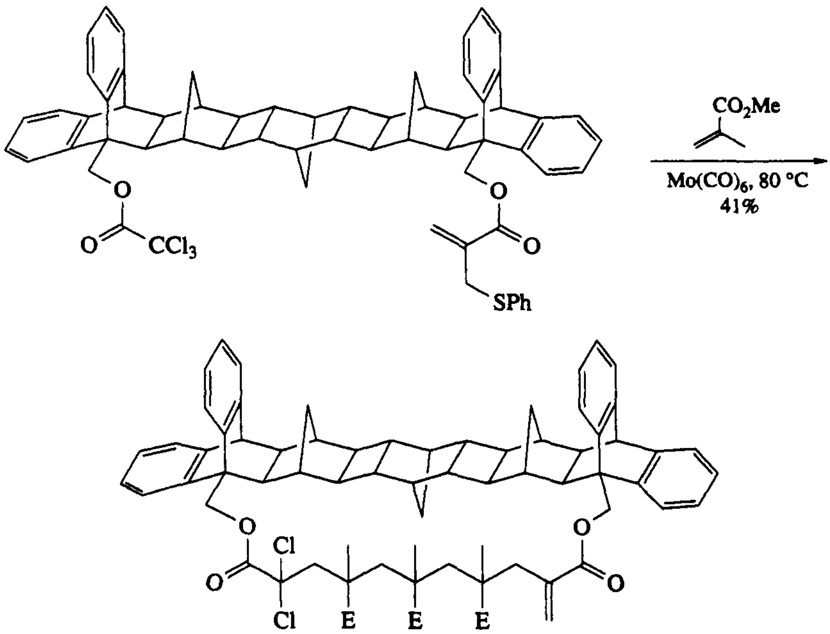
O
O
CCl3
O
O
SPh
CO2Me
Mo(CO)6, 80 °C
41%
O
O
Cl
Cl
E
E
E
O
O

(8)

#### 4.2.6.2.3 Sequences involving only intermolecular reactions

The sequencing of addition reactions is more difficult to design because polymerization is a natural outcome. Two addition reactions can be sequenced by alternating the reactivity of the radicals: one nucleophilic, the other electrophilic, or the reverse. This approach is reminiscent of radical copolymerization, except that reaction conditions are designed to intercept the radical after only one pair of additions. The first example in Scheme 60 provides a very slick example from the pioneering work of Minisci[243] in which two electronically reversed additions occur in sequence. Although the prior radicals are not susceptible to oxidation, the final allylic radical is removed by oxidation (and the allylic cation lactonizes), thus preventing polymerization. The second example again shows the power of the fragmentation method for conducting difficult sequences; when the β-stannyl radical arises, its rapid elimination shuts down the sequence.[244]

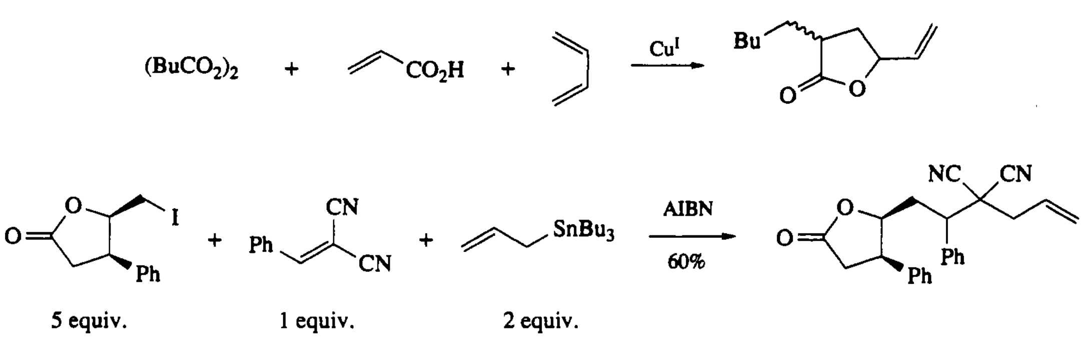

Scheme 60

## 4.2.7 CONCLUSIONS

Radical cyclization reactions offer a valuable synthetic tool with which to construct both carbocyclic and heterocyclic rings. The success and the diversity of recent advances have dispelled the old notion that radical cyclizations are only useful for making five-membered rings, and with poor stereoselectivity at that. With the exception of three- and four-membered rings, almost any ring size can be built either by direct radical cyclization or by ring expansion, and the design of highly stereoselective radical cyclizations is now possible. The general principles that have emerged from this work facilitate the planning of new radical reactions, whether individual or sequenced. Radical additions and cyclizations that are chemo- and regio-selective, and exhibit control of relative stereochemistry are now appearing regularly in synthetic journals; can the development of new radical reactions that control absolute stereochemistry be far behind?

## ACKNOWLEDGEMENTS

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8. In some cases, other conformations of the 6-endo transition state may be important, see ref. 7.
9. The diagrams in Figure 1 were produced from the coordinates of the transition states in the Houk/Spellmeyer force field model. I am grateful to Professor K. N. Houk for providing these coordinates.
10. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
11. The two computational models differ on this point. The Beckwith model (ref. 6) indicates increased bending and torsional strain in the 6-endo TS. The Houk model (ref. 7) indicates increased bending strain only, and states this strain is due in part to the bending of the allylic carbon out of the alkene plane to accommodate a better angle of attack.
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# 4.3
# Vinyl Substitutions with Organopalladium Intermediates

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## 4.3.1 INTRODUCTION

### 4.3.1.1 Basic Reaction

Organopalladium halides, acetates, triflates and similar derivatives lacking β $sp^3$-bonded hydrogens generally react easily with unhindered alkenes to form new alkenes in which an original, vinyl hydrogen is replaced by the organic group of the palladium reactant. The reactions occur in solution. Other Group VIII metals are ineffective in bringing about this transformation in acceptable yields. In the palladium reaction the organopalladium(II) reactant is reduced to the zero valent state while the halide, acetate, triflate or other, initial anionic ligand is converted into the corresponding acid (equation 1). If alkyl groups are attached directly to the double-bond carbons, double-bond rearrangement may occur and allylically substituted products can be produced. Normally, substitution occurs before any double-bond rearrangement occurs in the reactant alkene and the substituent is placed on one of the initial double-bond carbons (equation 2). Rearrangement of the double bond along a hydrocarbon chain to positions more distant from the substituent than the allylic position is occasionally observed, most often when X is a halogen and the halogen acid produced by the reaction is not neutralized as it is formed by inclusion of a base.

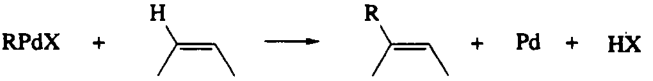

(1)

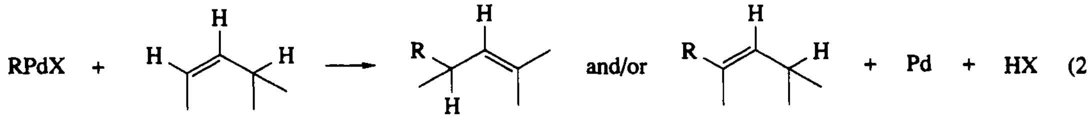

(2)

If two hydrogen atoms on a β-carbon atom are available for elimination, (*E*)-alkenes are strongly preferred. If only one hydrogen atom is present the product stereochemistry will be predictable on the basis of a *syn* addition of the organopalladium group to the double bond followed by a *syn* elimination of a palladium hydride group, provided the reaction is conducted under the proper conditions as described in Section 4.3.5.1.2.i. Yields of substituted alkenes from these reactions generally decline as the number and size of the substituents on the vinyl carbons increase.

Other atoms or groups than hydrogen may be lost in the final elimination step. Chlorine (or bromine or iodine) especially is lost easily, in fact in preference to hydrogen when it occurs in positions β to the palladium group.

Some isolated organopalladium compounds, particularly cyclopalladated complexes, have been employed in the vinyl substitution, but most often simple organopalladium compounds are unstable and must be formed *in situ*. Even then, alkylpalladium derivatives with β-hydrogens (on saturated carbon) generally decompose by elimination of Pd—H too rapidly to be useful except in some favorable intramolecular examples. The situation is somewhat complicated by the fact that palladium(II) compounds are usually four coordinate and the organopalladium derivatives will normally have two, two-electron donor ligands associated with them in addition to the organic group and the anionic ligand. These ligands may be various species such as solvent, halide ions, organophosphines or amines. The basic chemistry of the organopalladium derivatives is not usually greatly altered by the ligands but they can and do affect the stability of intermediates, reaction rates and selectivity. Under the proper conditions vinyl substitution can be carried out with aryl, heterocyclic, vinyl and occasionally alkyl derivatives lacking β-hydrogens. A very few examples of vinyl substitution with acyl groups are known, also.

Three methods are commonly employed for the *in situ* preparation of organopalladium derivatives: (i) direct metallation of an arene or heterocyclic compound with a palladium(II) salt; (ii) exchange of the organic group from a main group organometallic to a palladium(II) compound; and (iii) oxidative addition of an organic halide, triflate or aryldiazonium salt to palladium(0) or a palladium(0) complex.

The vinyl substitution reaction often may be achieved with catalytic amounts of palladium. Catalytic reactions are carried out in different ways depending on how the organopalladium compound is generated. Usually copper(II) chloride or *p*-benzoquinone is employed to reoxidize palladium(0) to palladium(II) in catalytic reactions when methods (i) or (ii) are used for making the organopalladium derivative. The procedures developed for making these reactions catalytic are not completely satisfactory, however. The best catalytic reactions are achieved when the organopalladium intermediates are obtained by the oxidative addition procedures (method iii), where the halide is both the reoxidant and a reactant. Reviews of some aspects of these reactions have been published.[1a–1c]

Methods (i) and (ii) require palladium(II) salts as reactants. Either palladium acetate, palladium chloride or lithium tetrachloropalladate(II) usually are used. These salts may also be used as catalysts in method (iii) but need to be reduced *in situ* to become active. The reduction usually occurs spontaneously in reactions carried out at 100 °C but may be slow or inefficient at lower temperatures. In these cases, zero valent complexes such as bis(dibenzylideneacetone)palladium(0) or tetrakis(triphenylphosphine)palladium(0) may be used, or a reducing agent such as sodium borohydride, formic acid or hydrazine may be added to reaction mixtures containing palladium(II) salts to initiate the reactions. Triarylphosphines are usually added to the palladium catalysts in method (iii), but not in methods (i) or (ii). Normally, 2 equiv. of triphenylphosphine, or better, tri-*o*-tolylphosphine, are added per mol of the palladium compound. Larger amounts may be necessary in reactions where palladium metal tends to precipitate prematurely from the reaction mixtures. Large concentrations of phosphines are to be avoided, however, since they usually inhibit the reactions.

### 4.3.1.2 Chapter Coverage

This chapter will be concerned only with substitutions of vinyl hydrogens with groups forming carbon–carbon bonds to one of the vinyl carbons. Replacements of halogens or other heteroatom-bound groups at vinylic positions will not be included. Likewise, replacements of vinyl hydrogens by groups forming heteroatom bonds to vinyl carbons will not be covered. Substitutions at alkynyl carbons by any substituents and additions to alkynes also will not be discussed.

### 4.3.1.3 Advantages and Disadvantages of the Various Procedures

Normally, the most practical vinyl substitutions are achieved by use of the oxidative additions of organic bromides, iodides, diazonium salts or triflates to palladium(0)–phosphine complexes *in situ*. The organic halide, diazonium salt or triflate, an alkene, a base to neutralize the acid formed and a catalytic amount of a palladium(II) salt, usually in conjunction with a triarylphosphine, are the usual reactants at about 25–100 °C. This method is useful for reactions of aryl, heterocyclic and vinyl derviatives. Acid chlorides also react, usually yielding decarbonylated products, although there are a few exceptions. Likewise, arylsulfonyl chlorides lose sulfur dioxide and form arylated alkenes. Aryl chlorides have been reacted successfully in a few instances but only with the most reactive alkenes and usually under more vigorous conditions. Benzyl iodide, bromide and chloride will benzylate alkenes but other alkyl halides generally do not alkylate alkenes by this procedure.

The main group organometallic exchange with palladium salts is useful for vinylic substitution with all types of groups: aryl, heterocyclic, vinyl and alkyl groups, but the only effective way to make the reaction catalytic is to use a stoichiometric amount of copper(II) chloride with a catalytic quantity of palladium. This procedure is acceptable on a small scale but is a problem on a large scale because of the large quantities and thick slurry of copper(II) salts involved. Other reoxidants, such as *p*-benzoquinone, silver salts, peracids or oxygen, are often not effective or give only low turnovers of the palladium.

The direct palladation procedure is limited to substitution with aryl and heterocyclic groups. The metallation is an electrophilic process and therefore does not work well with deactivated aromatics. When possible, mixtures of isomers may be obtained. Since the palladium salts employed for the metallation are moderately strong oxidizing agents, the reaction cannot be used with easily oxidizable alkenes or aromatics. The only effective method for making this procedure catalytic is to reoxidize the palladium *in situ* with oxygen under pressure; an inconvenient and potentially dangerous procedure.

Stable, cyclopalladated complexes sometimes may be used in vinyl substitution but these reactions cannot be carried out catalytically. A major limitation is that few cyclopalladated structures are available and only a few types of vinyl substitution products can be made by this procedure.

## 4.3.2 VINYL SUBSTITUTION WITH ARENES AND HETEROCYCLES

A variety of arenes and heterocyclic compounds will react with alkenes in the presence of palladium(II) salts to produce vinyl substitution products (equation 3).

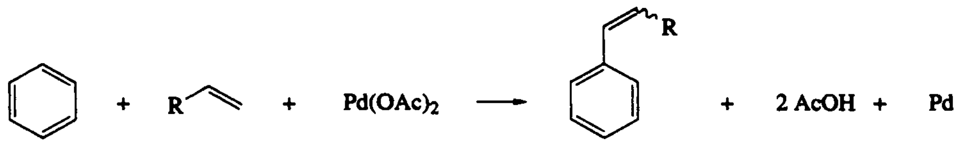
(3)

### 4.3.2.1 Mechanism

Two mechanisms of reaction appear possible depending upon the reactants. Initial palladation of either the alkene or the arene may occur: alkene palladation is proposed to occur initially in reactions of chlorinated alkenes.[2,3] Alkenes without strongly electron-withdrawing chloride substituents and moderately reactive arenes generally react *via* an initial arene palladation, and the reaction takes the route shown in Scheme 1.[4]

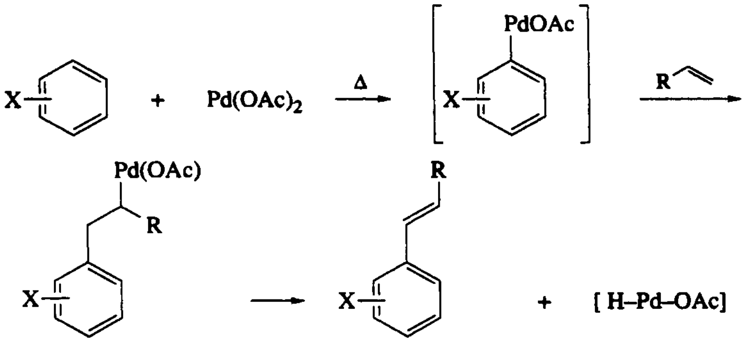
Scheme 1

### 4.3.2.2 Limitations

The mechanism shown in Scheme 1 seems to be the one operating in most of the known examples of the reaction. The initial aromatic palladation is an electrophilic substitution, but unfortunately it is not a very selective one.[4] Therefore, isomeric mixtures of products may be expected in cases where palladation can occur at different aromatic positions.

### 4.3.2.3 Reaction Scope and Conditions

#### *4.3.2.3.1 Stoichiometric reactions*

The majority of examples reported have been carried out in refluxing acetic acid with stoichiometric amounts of palladium acetate.[5] Occasionally lower temperatures give higher yields, however.

Several examples of the cyclization of indole derivatives with alkenic side chains in the 3-position have been reported.[6] In these examples, palladium chloride in combination with silver tetrafluoroborate is the cyclizing agent. The palladium tetrafluoroborate, presumably formed, should be a very reactive palladating species and probably is the reason why these reactions proceed at room temperature, although the mechanism is not yet completely clear. These reactions were worked up reductively (by addition of sodium borohydride) in order to reduce the expected alkenic product or any relatively stable organopalladium complexes that may have been formed (equation 4).[6]

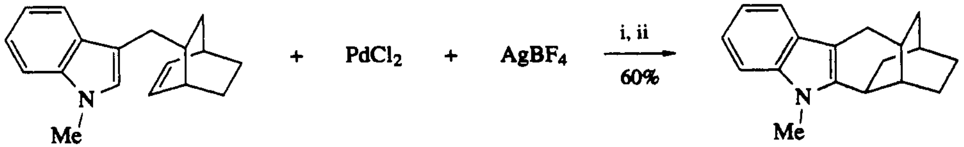
(4)

i, $Et_3N$, MeCN, 25 °C; ii, $NaBH_4$

Several other heterocyclic compounds have been used in the vinyl substitution. Quinones, for example, are readily substituted with a variety of heterocycles as well as with benzene.[7] Heterocycles which react include 2-acetylfuran (5-position), furfural (5-position) (equation 5) methyl furoate (5-position), 2-acetylthiophene (5-position), *N*-benzenesulfonylpyrrole (2-position), *N*-benzenesulfonylindole (3-position), 4-pyrone (3-position) and *N*-methyl-2-pyridone (3- and 5-positions).

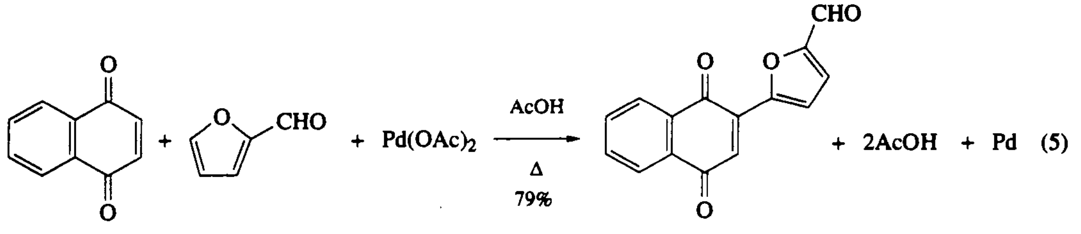

Acrylate esters have been substituted with *N*-methyl-2-pyridone (5-position), furfural (5-position) and 2-thiophenecarbaldehyde (5-position).[8] Benzo[*b*]furan reacts similarly with alkenes (2-position).[9] Alkene substitutions with furan,[10] thiophene,[10] benzothiophene[10] and *N*-acetylindoles,[10,11] also, have been reported. Furan and thiophene yield mainly 2,5-dialkenylated products.[9] α-Substituted chalcones with strongly electron-withdrawing substituents substitute with benzene.[12] Ferrocene[13] and $\eta^4$-cyclobutadienetricarbonyliron[14] will substitute alkenes as well.

### *4.3.2.3.2 Catalytic methods*

Silver acetate has a small catalytic effect on the alkene substitution reaction but 5 equiv. of the salt only give 140% of stilbene in the styrene phenylation, based upon palladium.[15] The same reaction carried out at 80 °C under 300 lbf $in^{-2}$ (1 lbf $in^{-2}$ = 6.89 kPa) of oxygen gives stilbene in 248% yield, based upon palladium.[16] The best reoxidation reagent is *t*-butyl perbenzoate, which yields 10–14 turnovers of the palladium in the vinyl substitution of cinnamaldehyde and similar alkenes with benzene.[17]

Methyl acrylate and benzene under the above conditions give a mixture of methyl cinnamate and methyl 3,3-diphenylacrylate.[17]

## 4.3.3 VINYL SUBSTITUTION WITH CYCLOPALLADATED COMPLEXES

A variety of isolable cyclopalladated complexes are readily available by direct reaction of palladium(II) salts, usually the chloride or acetate, with aromatic derivatives. The aromatic compound needs only to have a side chain with a good coordinating atom, usually nitrogen (although sulfur, oxygen, arsenic and phosphorus atoms also will work), in a position such that a five- or rarely a four- or six-membered chelate ring can form when orthopalladation occurs.[18] Reactions are slowed or even totally inhibited by strongly electron-withdrawing substituents in the ring being palladated.

The cyclopalladated complexes have limited practical value in organic synthesis because of the high cost of the stoichiometric amount of palladium required. Some compensation for their expense may be obtained, however, if several steps can be saved compared with an alternate method and, of course, the palladium may be recovered relatively easily.[1a]

Vinyl substitutions with *N,N*-dialkylbenzylamine-cyclopalladated complexes have been studied most thoroughly. In the presence of triethylamine the substitution occurs quite selectively with styrene derivatives[19] and α,β-unsaturated carbonyl compounds.[20] For example, chloride-bridged cyclopalladated *N,N*-dimethylbenzylamine dimer and methyl vinyl ketone give 92% of *o*-dimethylaminomethylbenzalacetone in 1 h at 110 °C (equation 6).

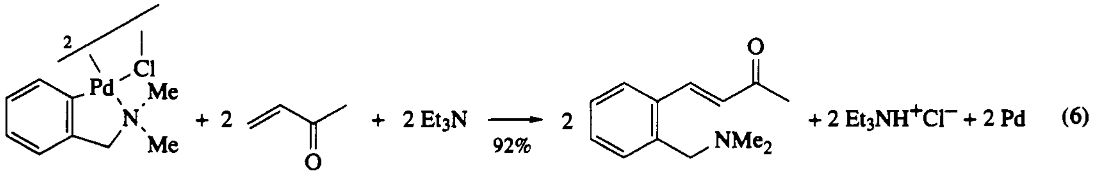

## 4.3.4 VINYL SUBSTITUTION WITH MAIN GROUP ORGANOMETALLICS

A variety of main group organometallics and some nonmetal organic derivatives have served as the source of organic groups, transferred *via* palladium to the vinyl carbons of alkenes.

### 4.3.4.1 Organomercury Compounds

Organomercury compounds are often obtainable from the reaction of Grignard reagents with mercury(II) chloride or in the aromatic series by direct mercuration of the aromatic compound. They are air and water stable but have the disadvantages of being highly toxic, having high molecular weights and being relatively expensive. Some arylmercury(II) chlorides also have quite low solubility in organic solvents, which may limit their reactivity. Exchange of the organic group from an organomercury species to a palladium salt (usually chloride or acetate) frequently occurs at or below room temperature, allowing vinyl substitutions to be carried out at or below 25 °C.

#### *4.3.4.1.1 Alkylation*

Vinyl substitution with aliphatic groups has been achieved with several mercurials in which the organic substituents are lacking *sp*$^3$-bound hydrogens on a carbon one-removed from the mercury. Other aliphatic organomercury reagents generally yield intermediate palladium derivatives which eliminate palladium hydride faster than vinyl substitution takes place, except where favorable intramolecular reactions can occur. Methyl,[21] alkoxycarbonyl,[21] neopentyl[22] and neophyl[22] groups have been substituted for vinyl hydrogens by this reaction (equation 7).

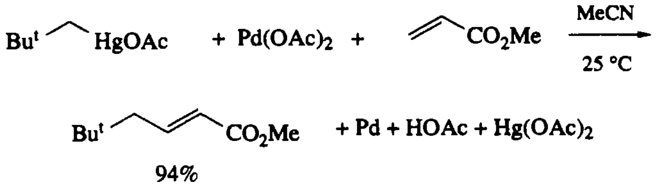

(7)

Usually, lithium tetrachloropalladate(II) or palladium acetate have served as the palladium reagents because of their solubilities in organic solvents such as acetonitrile and methanol. This reaction has only been carried out with stoichiometric quantities of the palladium salt. The neophyl group has been observed to rearrange or partially rearrange in its reactions with methyl acrylate or styrene.[22] The regiochemistry of the addition of aliphatic groups to unsymmetrical alkenes is known in only a few cases where reactions are quite selective. The results are consistent with the general rule that vinyl substitution takes place (predominantly or exclusively) at the least-substituted vinyl carbon and/or at the vinyl carbon having the smallest substituents. Substitution, also, usually occurs β in α,β-unsaturated esters and other α,β-unsaturated carbonyl compounds. It is to be expected that vinyl substitution with electron-donating aliphatic groups on alkenes with electron-donating substituents will give mixtures of regioisomeric products in the absence of significant steric effects.

#### *4.3.4.1.2 Arylation*

Vinyl substitution with arylmercury reagents is a very general reaction.[21] Arylmercury(II) chlorides and acetates as well as diarylmercury compounds with various substituents — diethylamino, nitro, carboxy, chloro, amide, hydroxy, and aldehyde groups — have been employed in the reaction. Naphthylmercury reagents and very hindered compounds such as mesitylmercury(II) chloride react normally. The regiochemistry of the arylation with arylmercury(II) acetates follows the usual rules as stated in Section 4.3.4.1.1. (*E*)-Alkene products are strongly favored if two β-hydrogens on one carbon are available for elimination, while if only one is present the product sterochemistry is predictable on the basis of a *syn* addition of the organopalladium species followed by a *syn* elimination of the palladium hydride. Arylmercury(II) chlorides, however, do not give very selective reactions. Both *cis–trans* isomerization and double-bond migration are seen in the chloride reactions.[23] Quantitative data on regiochemistry for the *p*-methoxyphenylation of propene indicates solvent also can play a significant role.[23]

All of the organomercury reactions may be carried out catalytically in palladium by use of copper(II) chloride as a reoxidant for the palladium. This modification, however, often reduces the yield of product and lowers the stereospecificity of the arylation.[21,23]

### *4.3.4.1.3 Vinyl substitution of dienes*

Vinyl substitution occurs with conjugated dienes as well as with alkenes, employing aryl-, vinyl-, methyl-, alkoxycarbonyl- or benzyl-mercury reagents and lithium tetrachloropalladate(II), but the products are usually π-allylpalladium complexes if the reactions are carried out under mild conditions (equation 8).[24,25] The π-allylic complexes may be decomposed thermally to substituted dienes[26] or reacted with nucleophiles to form allylic derivatives of the nucleophile. Secondary amines, for example, react to give tertiary allylic amines in modest yields, along with dienes and reduced dienes (equation 9).[25]

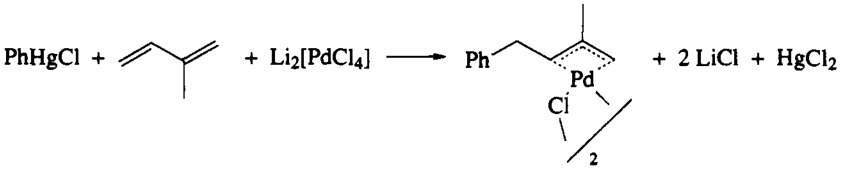

(8)

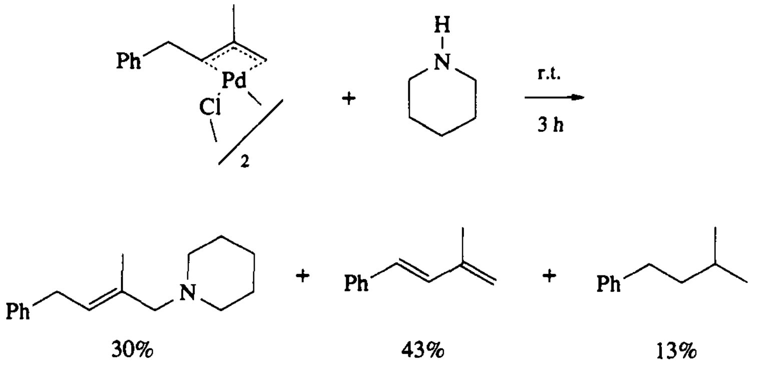

(9)

### *4.3.4.1.4 Formation of heterocyclic derivatives*

It is to be expected that organomercury reagents of all of the heterocycles that are employed in the palladation–vinyl substitution reaction (Section 4.3.2.3.1) could be used in the exchange palladation–substitution, also. Few of these organomercury reagents have been tried in the reaction, however. 2-Chloromercuriothiophene[21] and both chloromercurio- and 1,1-bischloromercurio-ferrocene[27] react as expected with styrene and with α,β-unsaturated carbonyl compounds. 4-Acetoxymercurio-*N*-methylisocarbostyril also yields the expected products with styrene and methyl acrylate.[28] Pyrimidinylmercury(II) acetates have found application in the synthesis of *C*-nucleosides in their reactions with chiral furanoid glycals[29] and other unsaturated cyclic ethers.[30]

### *4.3.4.1.5 Vinylation*

In the absence of base, vinylmercury reagents and lithium tetrachloropalladate(II) react with alkenes to form π-allylpalladium complexes arising from addition of the 'vinylpalladium chloride' to the alkene followed by palladium hydride elimination, a reverse readdition and π-allyl formation (equation 10).[31]

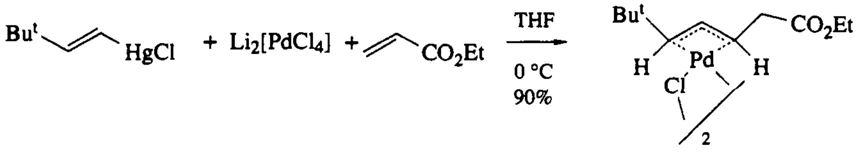

(10)

In the presence of triethylamine, decomposition of the π-allylic complexes to conjugated dienes may occur, particularly when electron-withdrawing substituents are present on a methyl group in the 1- or 3-position of the π-allyl system.[31] Cyclic alkenes and vinylpalladium chlorides also yield π-allylic complexes in the absence of an amine. If a tertiary amine is present, however, 1,4-dienes are obtained (equation 11).[32]

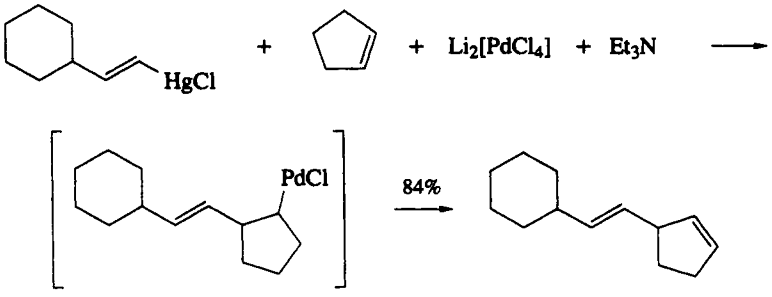

(11)

### 4.3.4.2 Silanes and Silyl Enol Ethers

#### *4.3.4.2.1 Vinyl substitution with silanes*

One organic group is readily transferred from tetraorganosilanes (and some other silanes) to palladium(II). Tetramethylsilane, lithium tetrachloropalladate(II) and styrene at 120 °C in acetonitrile solution form 1-phenyl-1-propene in 65% yield along with *ca.* 1.5% 2-phenyl-1-propene.[33] Trimethylphenylsilane transfers phenyl and with styrene under the above conditions gives *trans*-stilbene in 94% yield.[33] Similar vinyl substitution reactions have been achieved with potassium (*E*)-alkenyl pentafluorosilicates.[34]

#### *4.3.4.2.2 Vinyl substitution with silyl enol ethers*

Palladium(II) enolates are produced by the exchange reaction of trimethylsilyl enol ethers with palladium chloride or acetate. If β-hydrogens are present the enolates usually decompose by eliminating palladium hydride, forming α,β-unsaturated ketones (equation 12).[35] *p*-Benzoquinone (50%) was added in this example as a reoxidant for the palladium. Palladium enolates have been isolated in cases where β-hydrogens are absent.[36] The isolated complexes react with ethylene to yield the α-vinylated ketones.[36] It may be presumed that palladium enolates possessing β-hydrogens do not successfully substitute alkenes intermolecularly, since no examples have been reported. Intramolecular examples are well known, however, and these reactions provide a useful method for preparing five- and six-membered ring ketones (equation 13).[37]

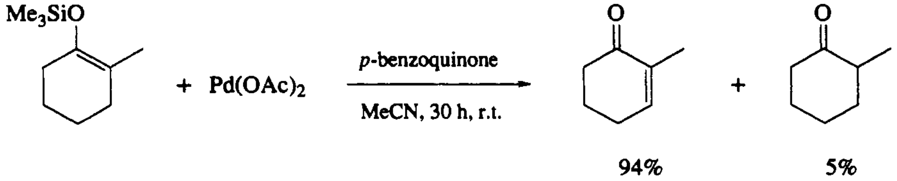

(12)

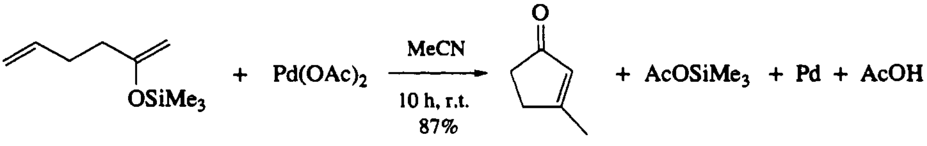

(13)

Bicyclic ketones, also, have been prepared intramolecularly from silyl enol ethers. Six-membered rings are formed more easily in these reactions than in the reactions forming monocyclic products, described earlier.[38]

The mechanism of the trimethylsilyl enol ether cyclization may involve formation of a palladium enolate which adds to the double bond. However, another mechanism is also possible involving attack of a palladium(II)–alkene complex upon the silyl enol ether double bond.

### 4.3.4.3 Organothallium Reagents

Thallation of aromatic compounds with thallium tris(trifluoroacetate) proceeds more readily than mercuration and in many instances more selectively. *Ortho* derivatives are obtained frequently when functional groups with unshared electron pairs are present to direct the metallation.[39]

Several examples of the arylation of vinyl ketones with arylthallium bis(trifluoroacetate) and lithium tetrachloropalladate(II) have been reported (equation 14).[40]

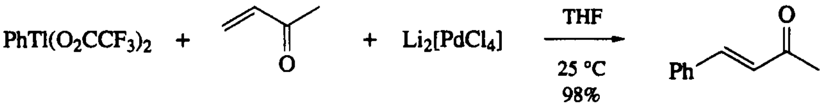

(14)

Benzoic acid and its derivatives orthothallate. Reaction of *o*-carboxyphenylthallium bis(trifluoroacetate) with palladium chloride and alkenes followed by base treatment yields isocoumarin derivatives (equation 15).[41] Cyclization does not occur until base is added in the second step.

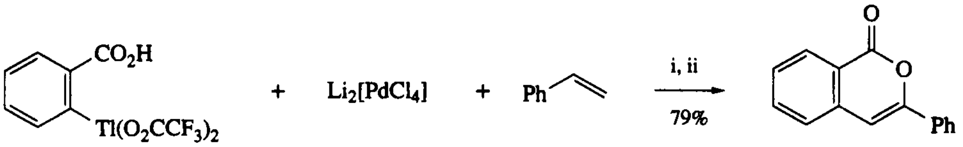

(15)

i, $PdCl_2$, MeCN, 25 °C; ii, $Et_3N$, $Na_2CO_3$

Several similar reactions have been carried out with other orthothallated derivatives to produce various oxygen and nitrogen heterocycles.[42]

### 4.3.4.4 Vinyl Substitution with Other Organometal and Nonmetal Derivatives

A very few examples of the use of aryl-tin,[21] -lead,[21] -lithium[43] and -magnesium[21,43,44] derivatives as the source of the aryl group in vinyl substitutions have been reported. Tin derivatives have been used with palladium dichloride bis(benzonitrile) and a copper(II) chloride reoxidant in a regioselective synthesis of oxygen heterocycles from unsaturated alcohols.[45]

Organo-iron and -cobalt phthalocyanines are reported to transfer the organic groups to palladium salts, and they have been used to substitute alkenes.[46]

There is one report of vinyl substitution with an organosodium derivative.[47] Organoboronic acids, also, have been used.[48]

Triarylphosphines, which are often employed with palladium in catalysts, also can transfer aryl groups to the palladium and cause vinyl substitution reactions with alkenes.[49,50] Fortunately, this reaction is usually slower than other methods for generating arylpalladium derivatives so that it usually is not a problem, but there are exceptions (equation 16).

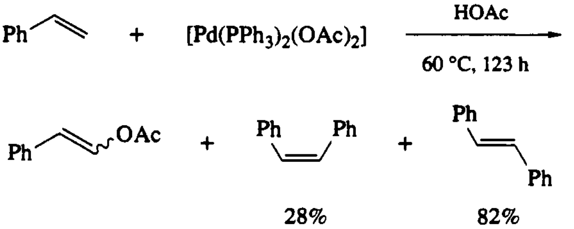

(16)

## 4.3.5 VINYL SUBSTITUTION WITH ORGANIC HALIDES, DIAZONIUM SALTS, ACID CHLORIDES, SULFINATE SALTS AND TRIFLATES

These reactions are grouped together because they all involve replacement of a leaving group by palladium(0) to form the organopalladium reactant. The ease of replacement varies significantly with the leaving group. The diazonium group is most easily replaced and reactions of these salts may be carried out at room temperatures. Triflate esters are less reactive and generally require temperatures of 50 °C or more to form the palladium derivatives. Under some conditions some vinyl iodides will react at room temperature, but generally higher temperatures (*ca.* 100 °C) are employed. Vinyl bromides and aryl iodides and bromides also are usually reacted at 100 °C. Carboxylic acid chlorides, sulfonyl chlorides and sulfinate salts also generally need a higher temperature.

These reactions do not require reoxidants since the organic compounds reoxidize the palladium(0) in the initial replacement step. Most results have been obtained with vinyl, aryl and heterocyclic iodides and bromides because of the easy and convenient availability of the required halides, and because this reaction was discovered for these reactants first.

It is necessary to have a base present in all of these reactions since strong acids are formed in every case. Secondary or tertiary amines, bicarbonates, carbonates and acetates have been the usual bases employed.

### 4.3.5.1 Vinyl Substitution with Alkyl, Aryl and Vinyl Halides

#### *4.3.5.1.1 Alkylation and benzylation of alkenes*

Alkyl halides with β-hydrogens generally undergo only elimination reactions under the conditions of the vinyl substitution (100 °C in the presence of an amine or other base). Exceptions are known only in cases where intramolecular reactions are favorable. Even alkyl halides without β-hydrogens appear not to participate in the intermolecular alkene substitution since no examples have been reported, with the exception of reactions with benzyl chloride and perfluoroalkyl iodides.

Benzyl chloride reacts easily with methyl acrylate in the presence of tri-*n*-butylamine and palladium acetate (1 mol %) as catalyst.[51] The product is a mixture of (*E*)-methyl 4-phenyl-3-butenoate (67%) and (*E*)-methyl 4-phenyl-2-butenoate (9%), arising from elimination–addition reactions of the palladium hydride group which largely isomerize the initial elimination product.

Several perfluoroalkyl iodides add to alkenes in the presence of 1 mol % of tetrakis(triphenylphosphine)palladium(0) at room temperature in fair to good yields forming fluoroalkyl iodides.[52] Palladium hydride elimination is less favorable than substitution of the palladium by iodide in these examples. This is due to the reaction proceeding by an unusual radical chain mechanism (equation 17).

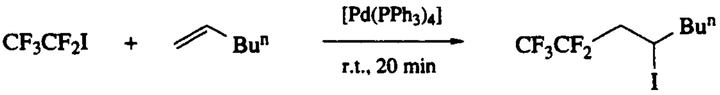

(17)

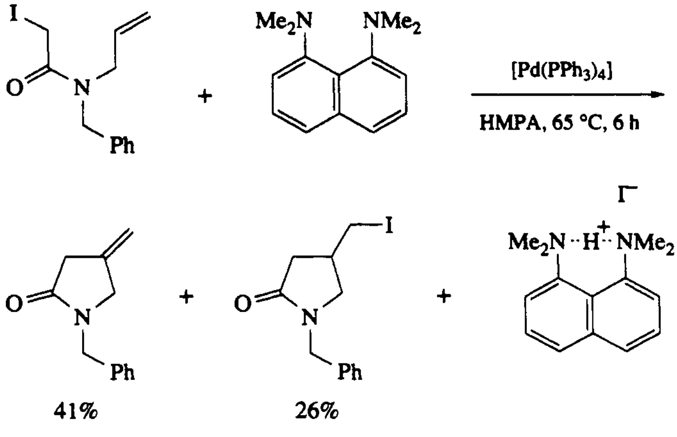

(18)

Several (*N*-alkenyl)iodoacetamides undergo cyclization when they are reacted with tetrakis(triphenylphosphine)palladium(0). The highest yields (which are generally only moderate) are obtained in DMF solution with 1,8-dimethylaminonaphthalene (Proton Sponge) to take up the hydrogen iodide formed. This reaction has been used to prepare piperidones, oxindoles, indolizidines, quinolizidines, pyrrolidines, indoles, quinolines[53] and pyrrolizidines (equation 18).[54]

Similar reactions in which β-hydrogens are available in the presumed intermediate palladium complex also give cyclized products.[55] Quite possibly these are radical chain reactions also, and that is why the hydride elimination is not observed (equation 19).

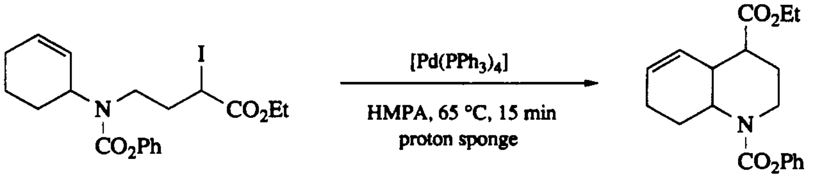

(19)

### 4.3.5.1.2 *Vinyl substitution with aryl halides*

*(i) Arylation of alkenes*

Alkene arylation has been the most-studied of the several vinyl substitution reactions. Not only is the reaction convenient to carry out but it is easily made catalytic in palladium, it is often quite regio- and stereo-specific and yields generally are good.

*(a) Mechanism and catalyst formation.*

The many known examples of this reaction support a mechanism involving an oxidative addition of the aryl halide to the palladium(0) catalyst as the initial step. The catalyst actually added to the reaction mixtures is often a palladium(II) salt or complex. This must be reduced before the catalytic cycle can begin. Reduction usually occurs simply by heating the palladium salts with the alkene in the reaction mixture at about 80–100 °C. The alkene is oxidized to a vinyl or allyl derivative of the anion of the salt and in the process the palladium is reduced. Alternatively, the catalyst may be reduced with reagents such as sodium borohydride, formic acid or hydrazine. The use of an added reducing reagent sometimes allows the reaction to be carried out at lower temperatures than when reduction is achieved by reaction with an alkene. Some aryl iodides add easily to unhindered alkenes even at room temperature when silver salts are added to remove the apparently inhibiting halide ion from the reaction mixture or when quaternary ammonium chlorides are introduced, especially if potassium carbonate is the base. In the second step of the reaction, the arylpalladium halide adds *syn* to the alkenic double bond. A final *syn* elimination of a hydridopalladium halide yields the arylated alkene, probably by way of an alkene π-complex. A base must be added to neutralize the hydrogen halide produced by the reaction, if it is to be catalytic. The free hydrogen halide appears to inactivate the palladium by keeping it in the hydridopalladium halide form. Palladium(0) or (II) are normally tetracoordinated, but tri- and even di-coordinated complexes are known. Scheme 2 summarizes the proposed mechanism, presuming a dicoordinated palladium(0) complex to be involved in the catalytic cycle.

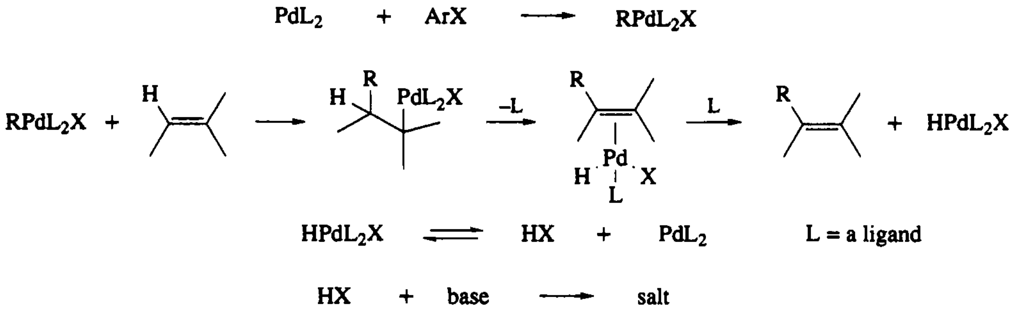

Scheme 2

*Ligands*: The ligands associated with the catalyst are a halogen anion, often added triphenyl-, or tri-*o*-tolyl-phosphine, possibly an amine, solvent, reactants or products. Arylphosphine ligands (two or more equivalents) are generally required when aryl bromides are to be reacted, in order to keep the palladium metal from precipitating, while with iodides no special ligand needs to be added. In the latter case, reactants, solvent or product(s), no doubt, function as ligands. The situation with aryl bromides is not clearly defined, however. In some examples at least, aryl bromide reactions proceed homogeneously without phosphines and with only sodium carbonate or bicarbonate as base. In these reactions, tetra-*n*-butylammonium chloride is frequently added as a solid–liquid phase transfer agent. There is evidence that tetraalkylammonium chlorides may have other beneficial effects upon palladium-catalyzed reactions than simply acting as phase transfer agents.[56] The effect may be due to coordination of chloride ions with palladium(0) keeping it in solution in catalytic reactions. The secondary amine, piperidine, is also capable of keeping palladium metal in solution in the absence of phosphines.[57]

*Aryl chlorides*: Aryl chlorides will substitute alkenes only under very special conditions, and then catalyst turnover numbers are generally not very high. Palladium on charcoal in the presence of triethylphosphine catalyzes the reaction of chlorobenzene with styrene,[58] but the catalyst becomes inactive after one use.[59] Examples employing an activated aryl chloride and highly reactive alkenes, such as acrylonitrile, with a palladium acetate–triphenylphosphine catalyst in DMF solution at 150 °C with sodium acetate as base react to the extent of only 51% or less.[60] Similar results have been reported for the combination of chlorobenzene with styrene in DMF–water at 130 °C, using sodium acetate as the base and palladium acetate–diphos as a catalyst.[61] Most recently, a method for reacting chlorobenzene with activated alkenes has been claimed where, in addition to the usual palladium dibenzilideneacetone–tri-*o*-tolylphosphine catalyst, nickel bromide and sodium iodide are added. It is proposed that an equilibrium concentration of iodobenzene is formed from the chlorobenzene–sodium iodide–nickel bromide catalyst and the iodobenzene then reacts in the palladium-catalyzed alkene substitution. Moderate to good yields were reported from reactions carried out in DMF solution at 140 °C.[62]

The problem with aryl chlorides seems to be that they do not compete effectively with reactant alkenes or even many solvents as ligands or reactants at palladium(0). Even if the arylpalladium chloride is formed its equilibrium concentration under the usual reaction conditions is probably very low.

*The catalyst*: The amount of catalyst required in an aryl bromide or iodide alkene substitution varies widely with the reactants and the reaction conditions. Most examples reported have used 1–2 mol % of palladium salt relative to the aryl halide, but much lower amounts are sufficient in some instances. In an extreme case, where very reactive *p*-nitrobromobenzene was added to the very active alkene, ethyl acrylate and sodium acetate was the base in DMF solution at 130 °C with a palladium acetate–tri-*o*-tolylphosphine catalyst; in 6 h the palladium turned over 134 000 times and ethyl *p*-nitrocinnamate was obtained in 67% yield.[63]

The phosphorus ligand most often used with the palladium catalyst has been triphenyl- or tri-*o*-tolylphosphine. The second phosphine is more stable under the reaction conditions because it does not undergo the palladium-catalyzed arylation of the phosphorus as triphenylphosphine does.[64] Reactions employing tri-*o*-tolyphosphine are often faster than the triphenylphosphine reactions, also. Other triarylphosphines, phosphites, trialkylphosphines and chelating diphosphines do not usually give as good catalysts. The molar ratio of the phosphine to the palladium is usually 2:1; however, larger amounts of phosphines are sometimes advantageous because this often prevents premature precipitation of the metal from the reaction mixtures. High concentrations of triarylphosphines are usually to be avoided, however, because they inhibit the reaction.

*The base*: One equivalent, at least, of a base relative to the aryl halide must be present to achieve the alkene substitution catalytically. Most often a tertiary amine is employed. Secondary amines also appear to be suitable but primary amines usually are not. The base strength of the amine is important since only quite basic amines such as triethylamine work well. Acetate salts, carbonates and bicarbonates also are suitable bases but solubility may cause difficulties in some instances. The addition of a phase transfer agent such as a quaternary ammonium salt has often solved this problem. The inorganic bases, of course, may cause other problems such as ester hydrolysis, aldol condensations and other undesired side reactions.

*Solvent and temperature*: The alkene substitution may be carried out in a variety of solvents or without an added solvent if the reactants form a homogeneous solution. DMF and acetonitrile are the most popular solvents but DMSO, HMPA, THF and methanol have also been used.

Reaction temperatures range from room temperature to about 140 °C. Higher temperatures generally cause premature precipitation of the palladium and at lower temperatures than about 20 °C reactions are usually very slow.

### *(b) Regio- and stereo-chemistry.*

The regiochemistry of the alkene substitution reaction is primarily controlled by steric factors in noncyclic cases. The aryl group of the organopalladium halide adds preferentially to the least-substituted alkenic carbon. There is a secondary electronic influence which directs the aryl group to the most electron deficient vinyl carbon. Thus, α,β-unsaturated carbonyl compounds usually react quite selectively at the β-carbon, while terminal alkenes yield about 80:20 mixtures of 1- and 2-arylated alkenes in the absence of major steric influences. The regiochemistry is only slightly influenced by the substituents on the aryl halide. Aryl bromides and iodides give similar reaction mixtures and the substituents in any phosphines used with the catalyst have little influence on the regiochemistry of the reaction. Iodides are much more reactive than bromides in the substitution in the absence of phosphines, but the factor is usually less than about 10 when phosphines are present.

Isomeric alkene mixtures are often obtained in the alkene substitution reaction when different hydrogen atoms are available for the final elimination step. The factors controlling the direction of elimination are obscure. It is clear that a *syn* palladium hydride elimination is much preferred over an *anti* elimination. In the arylation of cyclic alkenes, therefore, allylically arylated compounds are major products. Rearrangements of the allylic isomers to 4-aryl-1-cycloalkenes also occur often, presumably because the neighboring hydrogen atoms are relatively favorably placed for multiple palladium hydride elimination–readdition sequences. This isomerization may be prevented by performing the reactions at the lowest possible temperatures and by employing either potassium acetate[65] or silver carbonate[66] as the base. The acetate anion or silver cation presumably decompose the intermediate product/hydridopalladium iodide complex before it has time to readd to the double bond and cause isomerization. Reactions of noncyclic alkenes generally do not yield rearranged arylated alkenes. In general, the conjugated alkenes are favored in these cases with the (*E*)-isomer as the main or sole product, if there is a choice. The stereochemistry of the products is determined by the *syn* addition–*syn* elimination mechanism. However, more or less equilibration may occur by multiple hydride addition–elimination steps if the reaction conditions cannot be kept mild enough (equation 20).[67]

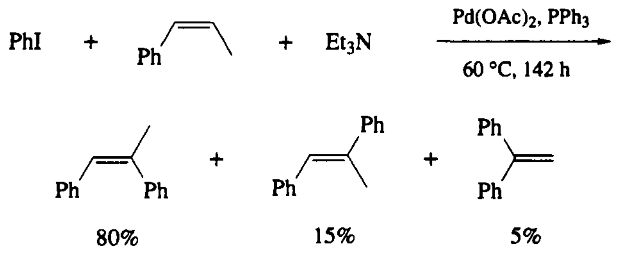

(20)

### *(c) Intermolecular reactions.*

The alkene arylation reaction is tolerant of a wide variety of substituents.[1b] A partial listing of substituents which may be on the aromatic halide includes: carboxy, alkoxycarbonyl, formyl, nitrile, methylthio, alkyl, nitro, hydroxy, alkoxy, acetoxy, amino, dimethylamino, acetamido, aminocarbonyl, chloro, trifluoromethyl, acyl and methylenedioxy. These substituents may be in the *o*-, *m*- or *p*-position and more than one or a combination may be present. A strong chelating effect of an *o*-carboxy group inhibits reactions of *o*-bromobenzoic acid but the methyl ester reacts normally.[68] It should be noted that free carboxy groups are not actually tolerated by the reaction since they are acidic, but an extra equivalent of base should be present to neutralize the acid and achieve catalytic reaction. Of course, if the reacting halogen group is hindered the reaction rate will decrease, but even 2,5-diisopropylbromobenzene reacts normally at 125 °C.[68] As noted above, aryl halides with strongly electron-supplying substituents often do not undergo the substitution reaction in high yield. The use of tri-*o*-tolylphosphine with these halides eliminates the phosphine quaternization problem[64] but product palladation and oxidation, as well as dehalogenation of the aromatic reactant, are other problems that may be encountered.

Very few examples of vinyl substitution with polynuclear aromatic halides have been reported but indications are that they generally react like the halobenzenes.

Essentially the same substituents as listed above may be present in the alkene being substituted, with the possible exception of chloro, alkoxy and acetoxy groups on vinyl or allyl carbons. These groups, especially chloro, may be lost or partially lost with palladium when the final elimination step occurs. For example, vinyl acetate, iodobenzene and triethylamine with a palladium acetate–triphenylphosphine catalyst at 100 °C form mainly (*E*)-stilbene, presumably *via* phenylation of styrene formed in the first arylation step (equation 21).[69]

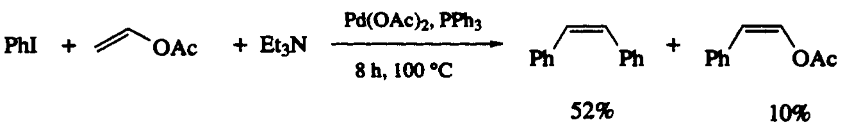

(21)

Trimethylsilyl groups also may be lost from vinylic or allylic positions in the arylation reaction.[70] Halide ion facilitates the desilylation as well as the loss of alkoxy and acetoxy groups. Inclusion of soluble silver salts in reactions where trimethylsilyl groups are lost prevents this reaction.[70] The reaction in the absence of silver ion is useful for preparing styrene derivatives. However, they also may be prepared directly from aryl halides and ethylene in fair to good yields.[71]

The large difference in reactivity between aryl iodides and bromides in the absence of phosphines allows the iodo group to be reacted in the presence of a bromo group in the same molecule. Subsequently the bromide may be reacted with another alkene if a phosphine is added.[72] Aryl chloride groups are usually inert in the presence of bromo or iodo substituents.

Numerous methods for forming heterocycles and carbocycles by means of the alkene substitution reaction have been published. There are a few examples of direct intermolecular ring-forming reactions. *o*-Iodoaniline and dimethyl maleate, for example, form 4-methoxycarbonyl-2-quinolone in 71% yield (equation 22).[73] As a result of the *syn* addition of the organopalladium complex and the *syn* hydride elimination, the *cis* ester (maleate) yields the correct stereoisomer for cyclization. However, the *trans* ester, dimethyl fumarate, also gives the quinolone but only in 47% yield. Isomerization must be occurring at some stage of the reaction.

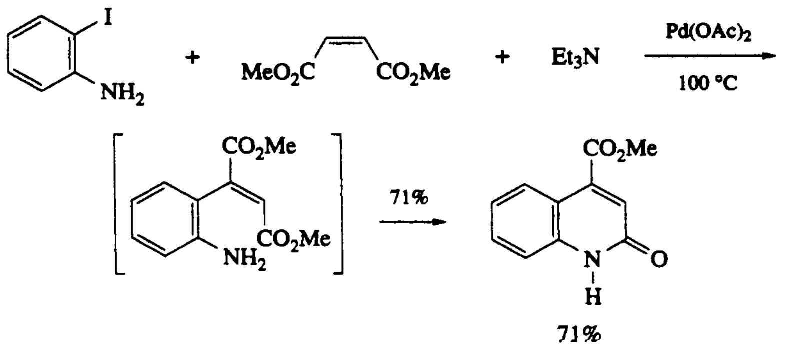

(22)

Further examples of the vinyl substitution reaction with aryl halides are given in Table 1.

### (d) Intramolecular reactions.

Intramolecular vinyl substitutions are commonly used to form cyclic products. In a typical reaction, β-indoleacetic acid has been prepared in up to 43% yield from an *o*-bromoaniline derivative, as shown in equation (23).[74]

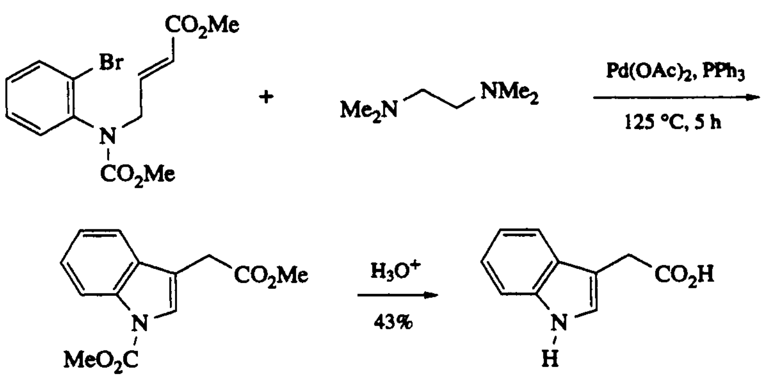

(23)

Cyclizations occur with secondary amine derivatives, also. *N*-Allyl-*o*-iodoaniline produces 3-methylindole, for example, in high yield at 25 °C using sodium carbonate as the base with tetrabutylammonium chloride in DMF solution (equation 24).[75] Similar procedures have been applied to the synthesis of indolines, oxindoles, quinolines, isoquinolines and isoquinolones.[75] Some *N*-vinyl-*o*-bromoaniline derivatives cyclize to substituted indoles, also.[76]

Similar reactions with 3-(*o*-bromoarylamino)cyclohexenones yield carbazole derivatives.[77] Spiropyrrolidinones are obtained from *N*-(cyclohexylcarbonyl)-*o*-iodoaniline derivatives.[66] The use of silver nitrate in reactions significantly reduces the amount of double-bond isomerization observed. This system is useful for preparing six- and seven-membered ring analogs, also. Even quaternary centers can be

**Table 1** Palladium-catalysed Arylations with Aryl Halides

| *Aryl halide* | *Alkene* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 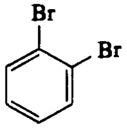 | $H_2C=CH_2$ | 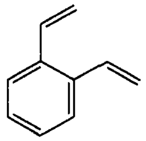 | 78 | |
| | | 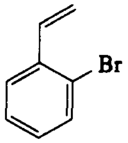 | 12 | 71 |
| 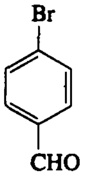 | 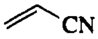 | 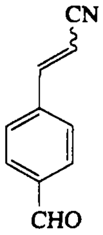 | 79 | 63 |
| PhI | 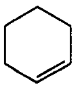 | 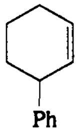 | 72 | 73 |
| 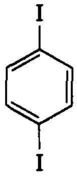 | 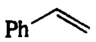 | 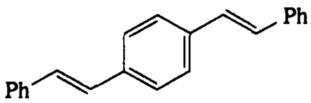 | 67 | 51 |
| PhBr | 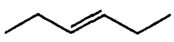 | 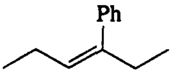 | 23 | |
| | | 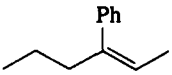 | 23 | 73 |
| 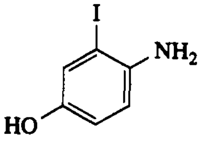 | 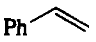 | 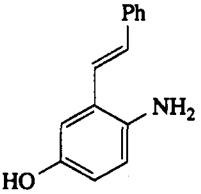 | 50 | 68 |

**Table 1** *(continued)*

| *Aryl halide* | *Alkene* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 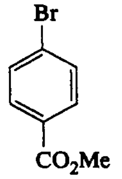 | 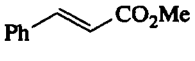 | 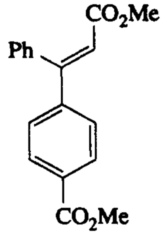 CO₂Me<br>Ph<br>CO₂Me | 52 | 73 |

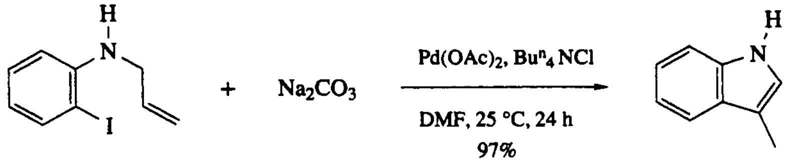

H
N
I
+
Na2CO3
Pd(OAc)2, Bun4NCl
DMF, 25 °C, 24 h
97%
H
N

(24)

formed from tetrasubstituted double bonds. Carbocycles are formed by an analogous procedure (equation 25).[66,78] In this example, silver carbonate functions as both a base and a precipitant for the halogen to minimize double-bond isomerization. Another variation of this reaction permits the synthesis of bridged ring systems (equation 26).[66] Other polynuclear systems have been prepared with the potassium carbonate–tetra-*n*-butylammonium chloride phase transfer system.[79]

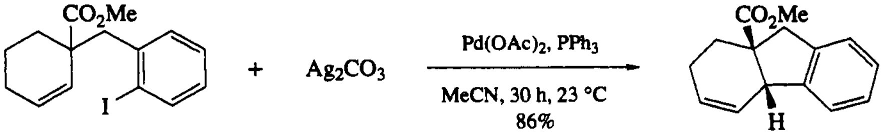

CO2Me
I
+
Ag2CO3
Pd(OAc)2, PPh3
MeCN, 30 h, 23 °C
86%
CO2Me
H

(25)

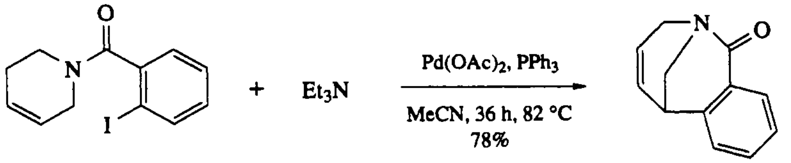

O
N
I
+
Et3N
Pd(OAc)2, PPh3
MeCN, 36 h, 82 °C
78%
N
O

(26)

Some success has been achieved in the tandem formation of two rings when two double bonds are appropriately situated on an *ortho* side chain of iodobenzene (equation 27).[80]

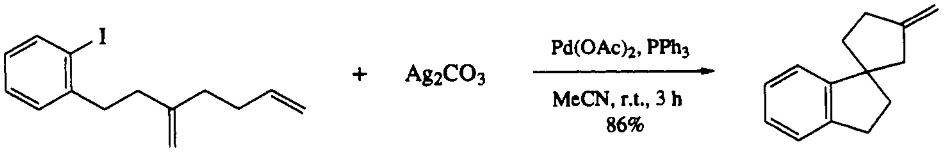

I
+
Ag2CO3
Pd(OAc)2, PPh3
MeCN, r.t., 3 h
86%

(27)

*(ii) Arylation of allylic and other unsaturated alcohols*

Vinyl substitution of primary or secondary allylic alcohols with aryl halides usually produces 3-aryl aldehydes or ketones, respectively. The reaction is believed to involve an addition of the intermediate arylpalladium halide to the double bond, placing the aryl group mainly on the more distant carbon from the hydroxy group, followed by palladium hydride elimination, a reverse readdition and another elimination with a hydrogen atom on the carbon bearing the hydroxy group. The product is probably a π-complex of the enol which ultimately either dissociates or collapses to a σ-complex with palladium on the carbon bearing the hydroxy group. In the latter case, palladium hydride elimination with the hydroxy hydrogen will yield the carbonyl product (Scheme 3). The procedure for this reaction is the same as that for the vinyl substitution of simple alkenes. Triethylamine, sodium bicarbonate or potassium carbonate are the usual bases employed. When the products are aldehydes with two α-hydrogens potassium carbonate may cause aldol condensations, so it probably should be avoided in these cases.

Mixtures of regioisomers are frequently obtained in these reactions.[80] The problem is most serious with primary allylic alcohols without α- or β-substituents. Even the 2-arylated products generally rearrange to saturated aldehydes. Allyl alcohol itself, when reacted with iodobenzene and triethylamine, with palladium acetate as catalyst, for example, produces a 71% yield of an 84:16 mixture of 3-phenyl- and 2-phenyl-propanal (equation 28).

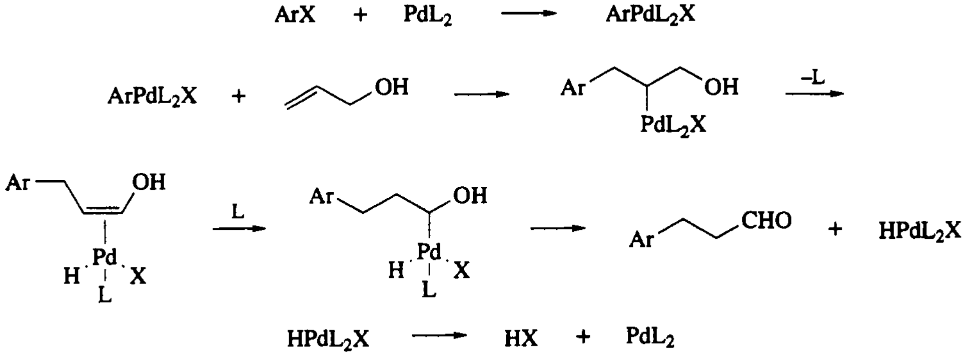

Scheme 3

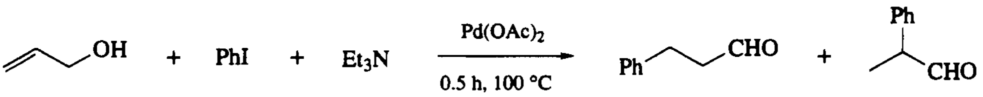

(28)

Allylic alcohols also may be arylated in *N*-methylpyrrolidinone or DMF solution with sodium bicarbonate as the base.[81] The use of this base improves the yields of aldehydes obtained compared with tertiary amine bases in the case of aryl bromides with electron-withdrawing substituents, where reduction to an arene is sometimes a problem.

### *(iii) Arylation of dienes and trienes*

#### *(a) Arylation with elimination.*

As noted in Section 4.3.4.1.3, organopalladium halides add to conjugated (and some nonconjugated) dienes to give isolable π-allylpalladium halide dimers at room temperature. At higher temperatures (100 °C) some of these complexes are stable and some eliminate palladium hydride to form dienes. The elimination does not appear to be base catalyzed since the presence of tertiary amines has little effect upon the reaction. The elimination is most facile in cases where three or more conjugated double bonds are formed in the reaction. Thus, arylated dienes may be prepared catalytically by the reaction of aryl halides with conjugated dienes, a tertiary amine and a palladium catalyst at about 100 °C (equation 29).[82] The reaction proceeds in better yield if an additional conjugating group such as a carboxy group is in the diene. Vinyl substitution generally takes place at the least-substituted end of the diene system. 1,3-Butadiene may be diarylated easily. In fact, 1-phenyl-1,3-butadiene is more reactive than butadiene itself in the reaction. With a 1:2 ratio of butadiene to iodobenzene only 2% 1-phenyl-1,3-butadiene is formed along with 43% 1,4-diphenyl-1,3-butadiene, while if the ratio is 2.5:1 only 1-phenyl- and 1,4-diphenyl-1,3-butadiene are obtained in 24% and 34% yields, respectively.[83] In this reaction it is necessary to use 10 mol % palladium acetate and 20 mol % of tri-*o*-tolylphosphine as catalyst, since the reaction is very slow with the usual 1–2 mol %. Aryl halides with strongly electron-withdrawing substituents react with dienes much more readily and require only 1–2 mol % catalyst. They yield only 1,4-diarylated products even with a diene to aryl halide ratio of only 2:1. Butadiene yields products with *trans* double bonds while mixtures of isomers may be obtained from substituted butadienes. The phenylation of (*E*)-3-methyl-1-phenyl-1,3-butadiene, for example, yields 37% (*E,E*)- and 9% (*E,Z*)-1,4-diphenylisoprene.

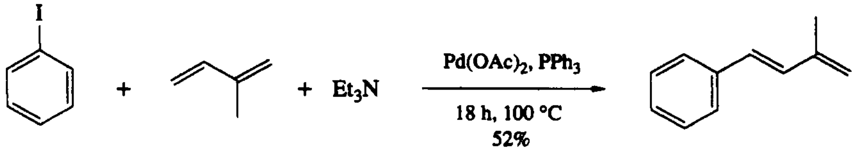

(29)

1,3,5-Hexatriene may be arylated similarly to 1,3-butadiene. Iodobenzene and aryl halides with electron-donating substituents require more catalyst (as in the butadiene reactions) than aryl halides with electron-withdrawing substituents to give 1,6-diarylated hexatrienes in a reasonable time.

*(b) Arylation with substitution.*

π-Allylpalladium complexes are well known to undergo nucleophilic attack at the terminal π-allylic carbons. This reaction sometimes can be coupled with the catalytic vinyl substitution reaction of conjugated dienes. In these cases the nucleophile attacks the intermediate π-allylic complex forming the allylated nucleophile, and the catalyst is recycled. This variation is successful even with simple dienes not possessing conjugating substituents which sometimes fail to react in good yield in the usual diene substitution reaction.

The reaction proceeds well with unhindered secondary amines as both nucleophiles and bases. The yield of allylic amine formed depends upon how easily palladium hydride elimination occurs from the intermediate. In cases such as the phenylation of 2,4-pentadienoic acid, elimination is very facile and no allylic amines are formed with secondary amine nucleophiles, while phenylation of isoprene in the presence of piperidine gives 29% phenylated diene and 69% phenylated allylic amine (equation 30).[84] Arylation occurs at the least-substituted and least-hindered terminal diene carbon and the amine attacks the least-hindered terminal π-allyl carbon. If one of the terminal π-allyl carbons is substituted with two methyl groups, however, then amine substitution takes place at this carbon. The reasons for this unexpected result are not clear but perhaps the intermediate reacts in a σ- rather than a π-form and the tertiary center is more accessible to the nucleophile. Primary amines have been used in this reaction also, but yields are only low to moderate.[85] A cyclic version occurs with *o*-iodoaniline and isoprene.[85]

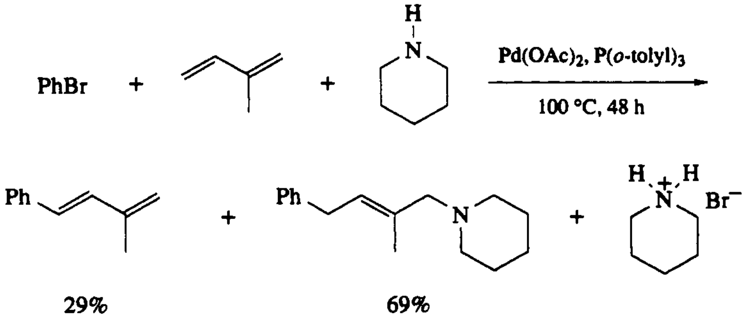

(30)

Other nucleophiles than amines which have been employed in the reaction are malononitrile and cyanoacetic ester anions. Both of these anions undergo a preliminary reaction with the aryl halide to form the *C*-aryl derivatives before they attack the π-allylpalladium intermediate, so that diarylated products are formed (equation 31).[86] Phenylmalononitrile anion reacts with iodobenzene and butadiene to give the same product in 70% yield.

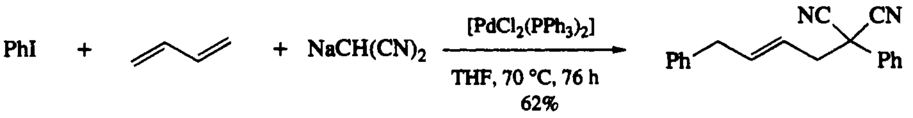

(31)

### 4.3.5.1.3 Vinyl substitution with heterocyclic halides

A variety of *N*-, *O*- and *S*-heterocyclic halides have been found to undergo the palladium-catalyzed alkene substitution reaction. Halogen derivatives of furan, thiophene, pyridine, pyrazine, uracil, indole, quinoline and isoquinoline, for example, undergo the reaction. Iodoferrocene also reacts normally.

### 4.3.5.1.4 Vinyl substitution with vinyl halides

#### (i) Alkene reactions

*(a) Variations and mechanism.*
Alkenes generally are believed to react with vinylpalladium halides to form π-allylpalladium halide dimers.[87] This reaction also is proposed to occur in the vinylation of alkenes with vinyl halides and a palladium catalyst. The stability of the π-allylic complexes varies greatly with structure. In the vinylation reaction, if the thermal decomposition of the π-allylic intermediate to diene takes place easily, a useful catalytic diene synthesis occurs. In other cases the reaction may occur only very slowly or not at all. As described in Section 4.3.5.1.2.iii, the decomposition (elimination of palladium hydride) takes place easily when the diene formed in the reaction will have one or more additional groups conjugated with it, such as an aromatic ring or a carbonyl group. In other cases, the π-allylic complex may be decomposed by nucleophilic substitution analogously to the diene arylation reactions (Section 4.3.5.1.2.iii) and catalytic reactions are produced. Unhindered secondary amines have usually been employed as the nucleophile and the base in these reactions, in which case allylic amines are the products. Even in reactions where decomposition of the π-allylic complex occurs thermally, inclusion of a secondary amine in the reaction mixture often leads to the formation of allylic amines as major products. The π-allylpalladium complexes formed under conditions giving catalytic reactions usually undergo equilibration of *syn* and *anti* isomers through σ-allylpalladium derviatives and the stereochemistry of the starting vinyl halide or alkene is not retained in the products. Generally, (*E*,*E*)-dienes or (*E*)-allylic amines are the products of this reaction. However, it is sometimes possible to intercept the initial palladium hydride–diene complex before it forms a π-allylic complex. Conducting the reactions at as low a temperature as possible increases the stereoselectivity, as does addition of triarylphosphines even at higher temperatures. Under favorable conditions the stereochemistry of the diene should be the same as that of the vinyl halide at one double bond and reflect the *syn* addition–*syn* elimination mechanism at the other. The reactions believed to be involved in the vinyl substitution with vinyl halides are summarized in Scheme 4. The scheme is shown with several substituents present but it should be remembered that, like other vinyl substitution reactions, steric effects are quite important and too many or too large substituents can inhibit the reaction or even prevent it entirely.

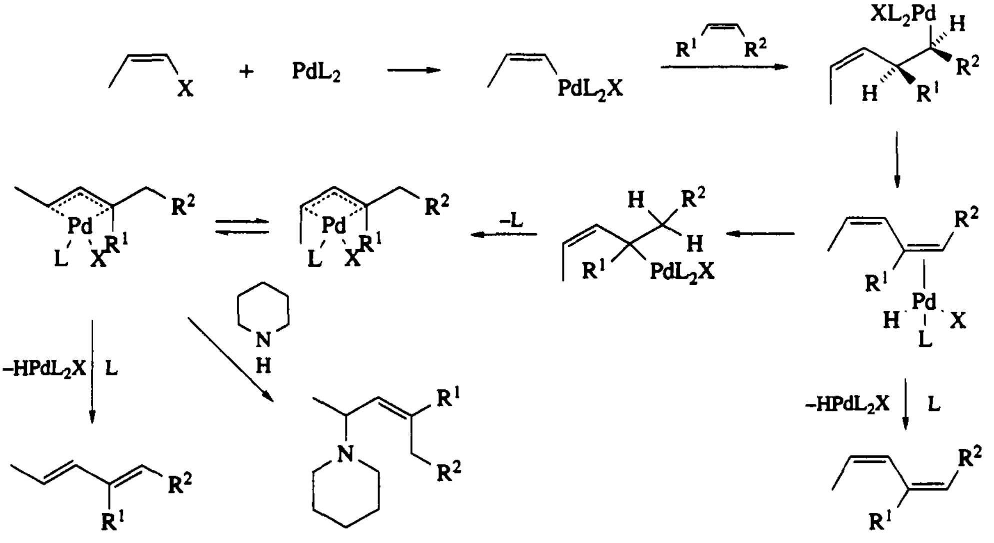

Scheme 4

### *(b) Intermolecular reactions.*

Vinyl iodides are considerably more reactive than bromides in the vinylations. It may be presumed that chlorides are not generally useful, with one exception noted below, since they have not been employed in the reaction. The bromides are usually reacted with a palladium acetate–triphenyl- or tri-*o*-tolyl-phosphine catalyst at about 100 °C. The reaction will occur without the phosphine if a secondary amine is present. Vinyl iodides will react in the absence of a phosphine even with only a tertiary amine present.[48,57] The iodides are so reactive, in fact, that reactions occur even at room temperature if potassium carbonate is the base and tetra-*n*-butylammonium chloride is used as phase transfer agent in DMF solution when palladium acetate is the catalyst.[88]

The regiochemistry of the vinylation is quite structure dependent. Additions to alkenes with strongly electron-withdrawing substituents on one of the double-bond carbons causes addition of the vinyl group, regardless of structure, to the other double-bond carbon, in the absence of large steric effects. Additions to 1-alkenes and other alkenes with electron-donating substituents at the double bond may give mixtures of regioisomers. Vinyl bromide itself and 2-bromo-1-propene (and very probably other 2-bromo-1-alkenes) add quite selectively to the terminal carbon of 1-hexene. 2-Alkyl-1-bromo-1-alkenes usually yield mixtures. Stereospecific vinylations of alkenes only have been reported for α,β-unsaturated carbonyl compounds. If vinyl bromides are used, elevated temperatures are needed and the bromide or the diene product may isomerize under the reaction conditions. Stereospecific reactions have been obtained with the 1-iodo-1-hexenes at low temperatures (18–27 °C) using the phase transfer DMF procedure mentioned above. Under these conditions even acrolein and methyl vinyl ketone, as well as methyl acrylate, give better than 95% stereospecific reactions with the 1-iodo-1-hexenes (equation 32).[88]

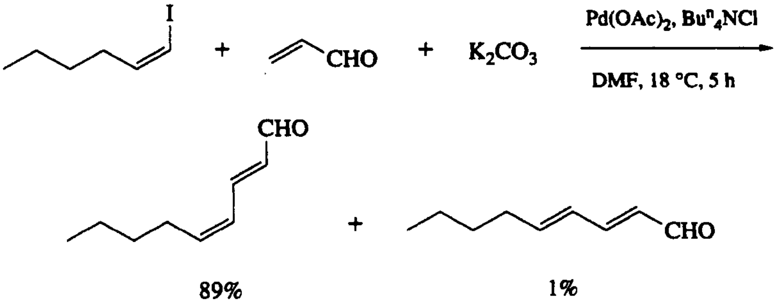

(32)

2-Chlorotropone, apparently, is the only example of a vinyl-type chloride which is known to undergo the substitution reaction. This chloride and styrene with triethylamine gives a 25% yield of 2-styryltropone (equation 33).[89]

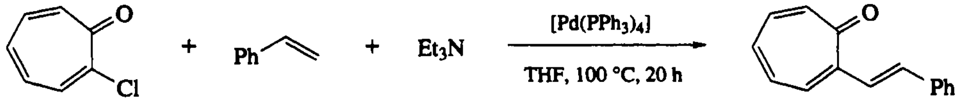

(33)

Vinyl substitutions on alkenes not having their double bonds conjugated with carbonyl groups often proceed more rapidly and give better product yields when the reactions are conducted in the presence of an unhindered secondary amine. Conjugated and nonconjugated dienes are usually only minor products in these cases. The major products normally are allylic amines obtained by nucleophilic attack of the secondary amine upon the π-allylpalladium intermediates. Since allylic amines may be quaternized and subjected to the Hoffmann elimination, this is a two-step alternative to the direct vinyl substitution reaction.[90]

As expected from the results obtained in the arylation of dienes with secondary amines (Section 4.4.5.1.2.iii), the amine attacks the least-substituted (hindered) end of the π-allylic group. An exception to this behavior occurs in these reactions as it did in the diene arylation case where there are two methyl substituents on one terminal allylic carbon, in which case the amine attacks this tertiary carbon (equation 34).[57] If groups larger than methyls are present on one terminal allylic carbon, steric hindrance to attack at that carbon causes reaction at the other end of the allyl system.

Reactions of vinyl halides with acrolein acetals and secondary amines lead to the formation of minor amounts of dienal acetals and major amounts of aminoenal acetals (equation 35).[53] The diene product retains the sterochemistry in the vinyl halide while the aminoenal acetal loses it through equilibration of the π-allylpalladium intermediate.

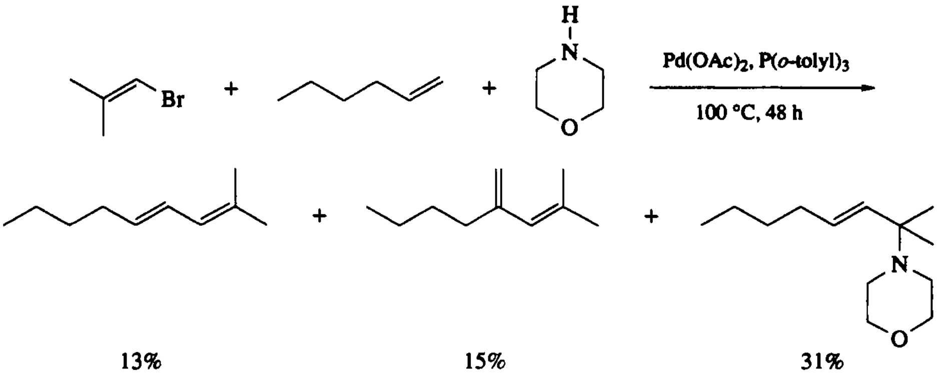

(34)

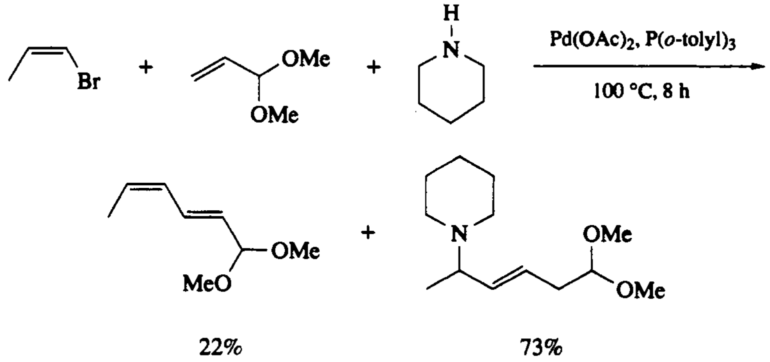

(35)

*(c) Intramolecular reactions.*

Several bromodienes have been cyclized by use of the palladium–tri-*o*-tolylphosphine catalyst with a secondary amine as nucleophile and base. The regiochemistry of the substitution may be different from the intermolecular cases. For example, (*Z*)-1-bromo-1,5-hexadiene and piperidine form exclusively five-membered rather than six-membered ring products as might have been expected since they would arise from vinylation at the least-substituted double-bond carbon (equation 36).[91] It is surprising that even 9% of the very hindered *N*-tertiary alkylamine is formed in this example. The ratio of products obtained varies significantly with solvent. In benzene solution, for example, the yield of the tertiary alkylamine is 29% and the allylic isomer is 50%. Ring closure is not observed with 2-bromo-1,5-hexadiene and only polymers are formed. Six-membered ring products are obtained from 2-bromo-1,7-octadiene, along with a minor amount of a five-membered ring product (equation 37). In the absence of acetonitrile, the reaction in equation (37) gives a much lower yield (28%) of the six-membered ring amine. The origin of the five-membered ring product is not clear but it is proposed to be formed by a double-bond shift in the intermediate palladium complex followed by ring closure. An attempt to form a seven- or eight-membered ring from 2-bromo-1,8-nonadiene and piperdine gave only 8% of the seven-membered ring amine

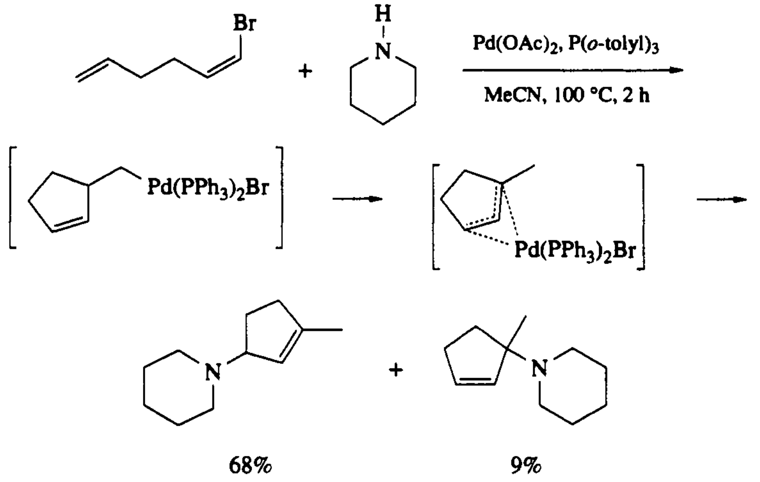

(36)

and 4% of the rearranged six-membered ring amine. The reaction, therefore, in the carbocyclic series appears to be useful for forming only five- and possibly six-membered rings.

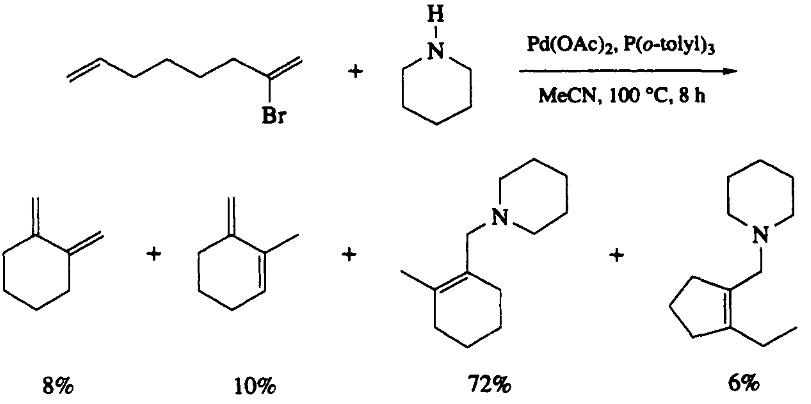

(37)

Further examples of the formation of carbocyclic and carbopolycyclic compounds from (*Z*)-vinyl iodides with triethylamine as base have been reported and as noted in the related bromide reactions, double-bond isomerization is commonly observed.[92]

The same reactions, carried out with potassium carbonate as base in place of a secondary amine, yield exocyclic dienes in good yield, although double-bond isomerization sometimes occurs (equation 38).[93] Inclusion of tetra-*n*-butylammonium chloride in the reaction mixture stops the double-bond isomerization. Thus, the reaction in equation (38) with the chloride yields only the bis(exomethylene) product in 45% yield in a slow reaction. Some *N*- and *O*-heterocyclic products, also, have been prepared by the intramolecular vinyl substitution reaction.[94] A 16-membered ring lactone was made by the ring closure of a vinylic iodide group with a vinyl ketone group. The yield, based upon the reactant, was 55% but a stoichiometric amount of bis(acetonitrile)palladium dichloride was employed. The 'catalyst' was prereduced with formic acid so that the reaction proceeded at 25 °C (equation 39).[95]

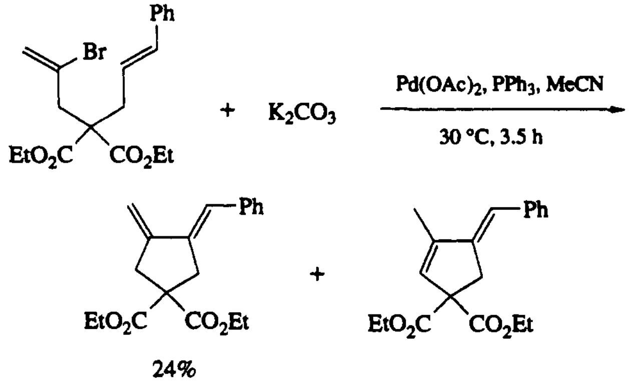

(38)

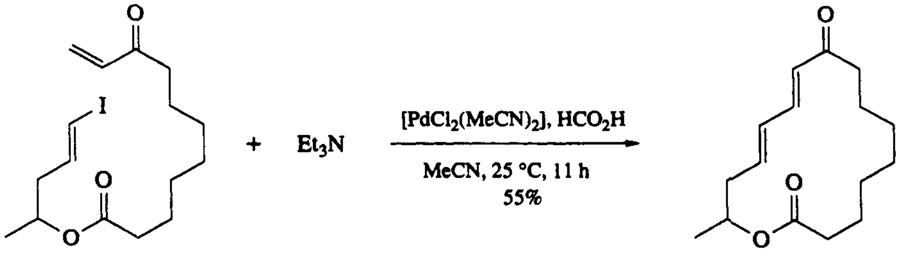

(39)

### (*ii*) *Allylic alcohols and allylic amines*

Vinylation of allylic alcohols with only a tertiary amine as base is often a very slow reaction in which product (if any) decomposition may be a serious side reaction. Exceptions to this behavior occur when β-halo-α,β-unsaturated esters (and other β-halo-α,β-unsaturated carbonyl compounds and nitriles if they are stable under the reaction conditions) are reacted with allylic alcohols. The presence of the conjugating substituent in the adduct is usually necessary to facilitate the hydridopalladium halide elimination. In most other cases, at least part of the reaction proceeds by way of a π-allylpalladium complex and these complexes with the β-hydroxy substituents are often unusually stable, probably as a result of coordination of the hydroxy group with the palladium. In these cases, the reactions proceed easily if a nucleophilic secondary amine is added to decompose the intermediate π-allylic complexes to amino enols. Usually, hydridopalladium halide elimination from the initial vinylpalladium adduct with the allylic alcohol takes place in both possible directions and two products are formed. Elimination of the hydrogen atom on the carbon bearing the hydroxy group leads to formation of an enone, while elimination in the other direction gives a conjugated diene π-complex which usually goes on to a π-allylpalladium complex and finally reacts with the amine to yield an amino enol. The mechanism proposed is illustrated in Scheme 5 with the reaction between 2-bromopropene and 3-buten-2-ol, where only one regioisomer is formed.[96]

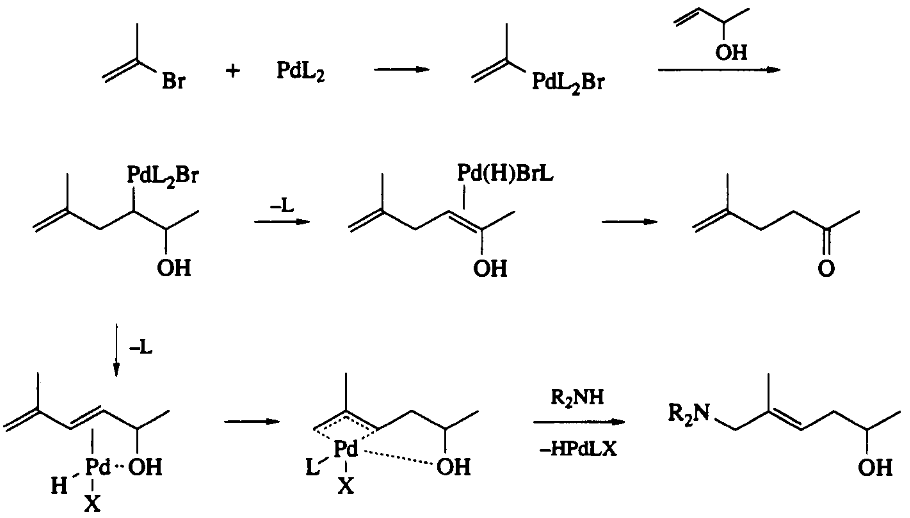

Scheme 5

### (iii) Dienes and trienes

Vinylation of dienes in the presence of piperidine or morpholine yields aminodienes as major products. Sometimes trienes are minor products. The reaction is believed to proceed by way of a π-allylpalladium complex formed by addition of the vinylpalladium halide to the least-substituted diene double bond. Nucleophilic attack of the amine upon the π-allylic complex gives the aminodienes, while hydridopalladium halide elimination yields trienes (Scheme 6).[97]

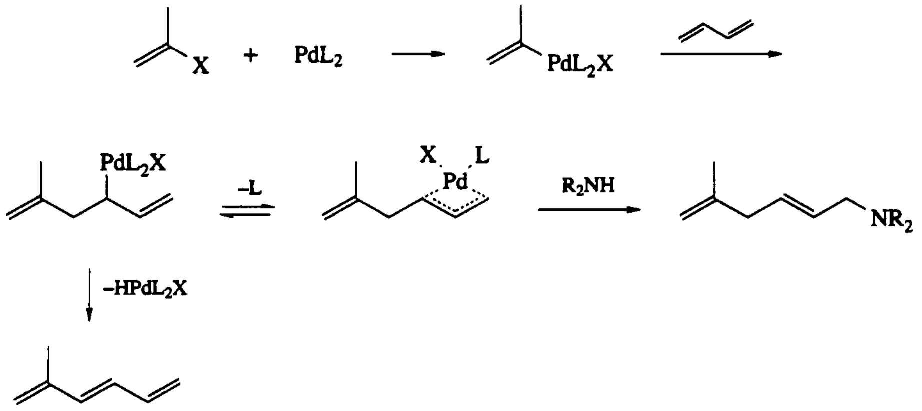

Scheme 6

Stereochemistry is largely lost in the diene vinylation, at least at 100 °C, as evidenced by the reaction of (*Z,E*)-3-methyl-2,4-pentadienoic acid shown in equation (40).

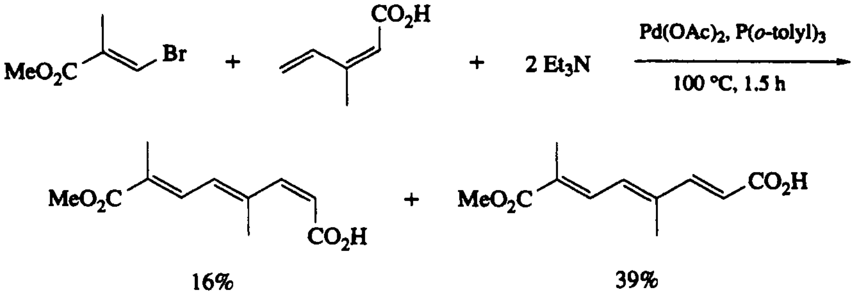

(40)

Many conjugated dienes react twice with methyl 3-bromo-2-propenoate and triethylamine, making this procedure convenient for preparing a variety of dimethyl 2,4,6,8-decatetraenedioates.[98] 1,3,5-Hexatriene and its substituted derivatives undergo vinylation also, to form tetraenes and pentaenes in low yields.[83]

### 4.3.5.2 Vinyl Substitutions with Aryldiazonium Salts and Arylamines

Aryldiazonium salts react with bis(dibenzylideneacetone)palladium to form arylpalladium salts and nitrogen. Therefore, diazonium salts may be employed to catalytically arylate alkenes under mild conditions. Since many aryl halides are made from diazonium salts this variation could even be more convenient than using aryl halides. The reaction proceeds in good to excellent yields in nonaqueous solvents, using sodium acetate as the base at room temperature with terminal alkenes and cyclopentene.[99] Internal alkenes usually give poor yields, however.

Palladium(II) salts apparently oxidize arylamines to arylpalladium salts since alkenes are arylated by reaction with only an aromatic amine and a palladium salt. However, yields are generally low.[100] Much better yields are obtained if *t*-butyl nitrite is added and, of course, this forms the diazonium salt *in situ*. This not only saves a step but some diazonium salts which are too unstable to be isolated may be used as well. The reactions are carried out in the presence of acetic or chloroacetic acid with 5–10% bis(dibenzylideneacetone)palladium as catalyst (equation 41).[101]

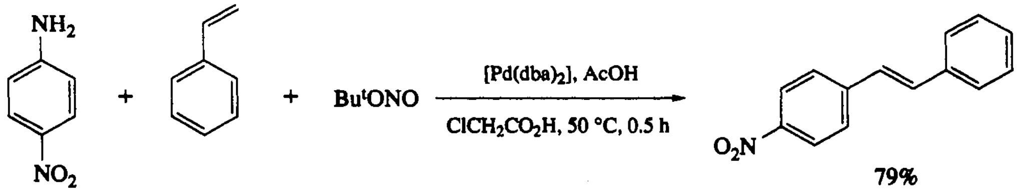

(41)

### 4.3.5.3 Vinyl Substitutions with Carboxylic Acid Halides, Aryl Sulfinates and Arylsulfonyl Chlorides

#### *4.3.5.3.1 Vinyl acylation*

Carboxylic acid chlorides and chloroformate esters add to tetrakis(triphenylphosphine)palladium(0) to form acylpalladium derivatives (equation 42).[102] On heating, the acylpalladium complexes can lose carbon monoxide (reversibly). Attempts to employ acid halides in vinylic acylations, therefore, often result in obtaining decarbonylated products (see below). However, there are some exceptions. Acylation may occur when the alkenes are highly reactive and/or in cases where the acylpalladium complexes are resistant to decarbonylation and in situations where intramolecular reactions can form five-membered rings.

$$\mathrm{MeCOCl} \quad + \quad [\mathrm{Pd(PPh_3)_4}] \quad \xrightarrow[\mathrm{PhH}]{25\ ^\circ\mathrm{C}} \quad [\mathrm{MeCOPd(PPh_3)_2Cl}] \quad + \quad 2\mathrm{PPh_3} \qquad (42)$$

Vinyl ethers yield acylated vinyl ethers when they are reacted with aroyl chlorides or 3-thienylcarbonyl chloride, triethylamine and a palladium acetate catalyst at 60–70 °C (equation 43).[103] The products of this reaction are useful 1,3-dicarbonyl equivalents. At higher temperatures the reaction yields arylated vinyl ethers. It is interesting that the acylations of vinyl ethers are regioselective while the direct arylations are usually not.[104]

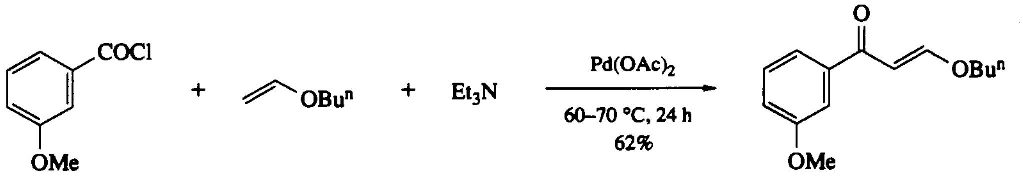
COCl
OMe
+
OBu$^n$
+
Et$_3$N
Pd(OAc)$_2$
60–70 °C, 24 h
62%
O
OBu$^n$
OMe

(43)

Homoallyl chloroformates cyclize catalytically to α-methylene-γ-butyrolactones in moderate yields at 130 °C with tetrakis(triphenylphosphine)palladium(0) (equation 44).[105] This reaction only gives 1–2% of product when it is carried out intermolecularly. The presumed intermediate in the homoallyl chloroformate cyclization has been isolated and kinetic measurements show that that cyclization is inhibited by an excess of triphenylphosphine. A chelated π-alkene intermediate is proposed.[106]

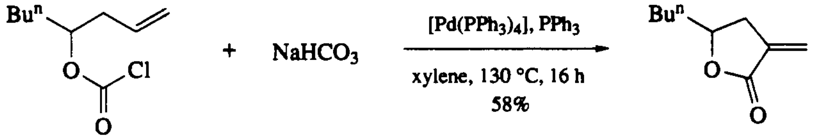
Bu$^n$
O
Cl
O
+
NaHCO$_3$
[Pd(PPh$_3$)$_4$], PPh$_3$
xylene, 130 °C, 16 h
58%
Bu$^n$
O
O

(44)

Since vinylic iodides (and bromides) can be catalytically carbonylated with a palladium catalyst, intermolecular acylations sometimes can be carried out with appropriate halodienes and carbon monoxide as, for example, is shown in equation (45).[107]

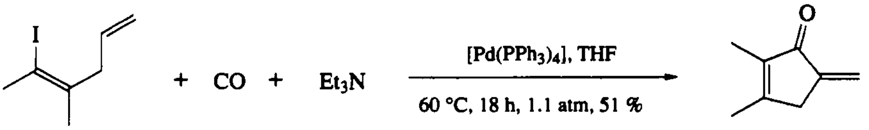
I
+
CO
+
Et$_3$N
[Pd(PPh$_3$)$_4$], THF
60 °C, 18 h, 1.1 atm, 51 %
O

(45)

### 4.3.5.3.2 *Arylation with carboxylic acid chlorides*

Aromatic acid chlorides are decarbonylated to aryl chlorides when they are heated to 300–360 °C with palladium on carbon. The reaction proceeds by way of an aroylpalladium chloride, then to an arylpalladium chloride and finally through a reductive elimination to the aryl chloride. If the reaction is conducted in the presence of a reactive alkene under mild conditions the aroylpalladium chloride intermediate will sometimes acylate the alkene, as noted in Section 4.3.5.3.1. More usually, however, decarboxylation is more rapid than acylation, especially at higher temperatures (>100 °C), and decarbonylation occurs. The

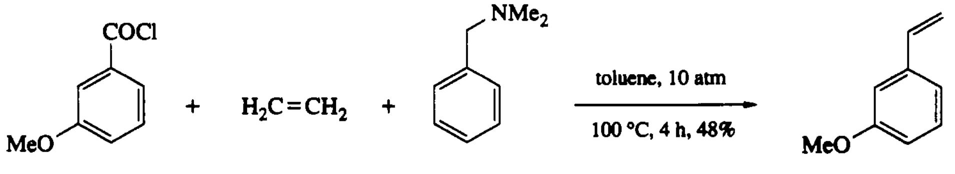
COCl
MeO
+
H$_2$C=CH$_2$
+
NMe$_2$
toluene, 10 atm
100 °C, 4 h, 48%
MeO

(46)

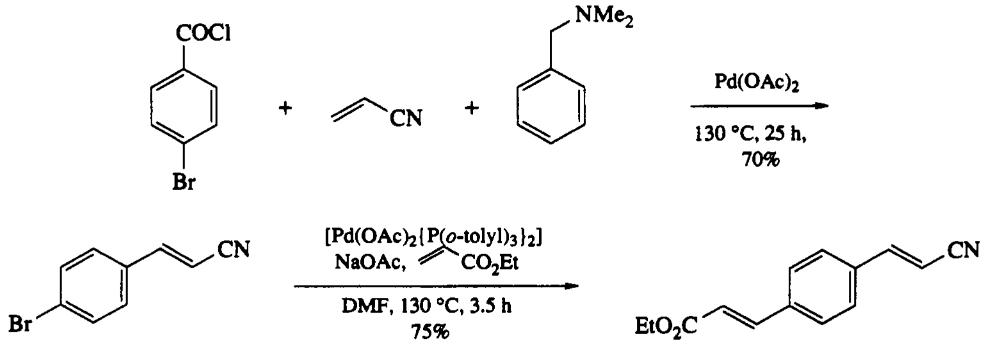
COCl
Br
+
CN
+
NMe$_2$
Pd(OAc)$_2$
130 °C, 25 h,
70%
Br
CN
[Pd(OAc)$_2${P(o-tolyl)$_3$}$_2$]
NaOAc, CO$_2$Et
DMF, 130 °C, 3.5 h
75%
CN
EtO$_2$C

(47)

arylpalladium chloride formed is relatively stable and usually will arylate the alkene. Many examples of this reaction are known (equation 46). The reaction only appears to go well with ethylene, styrene, vinyl ethers and α,β-unsaturated carbonyl compounds and nitriles. Since aromatic carboxylic acid chlorides are often more readily available than the corresponding aryl bromides or iodides this variation will be useful for some syntheses. Bromobenzoyl chlorides give aryl bromides as products which can be used in a subsequent vinyl substitution (equation 47).[108]

### *4.3.5.3.3 Arylation with sulfinate salts and sulfonyl chlorides*

Sodium arylsulfinates and palladium salts react to form arylpalladium salts and sulfur dioxide. When carried out in the presence of some dienes, stable organopalladium complexes have been obtained. For example, 1,5-cyclooctadiene and sodium *p*-toluenesulfinate with palladium chloride yields the σ,π-complex shown in equation (48).[109]

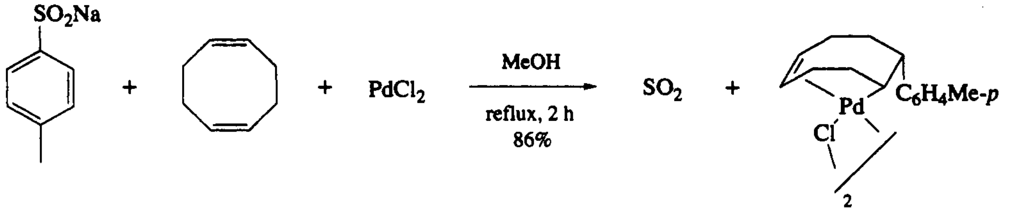

(48)

Arylsulfonyl chlorides react similarly with palladium(0) catalysts, producing sulfur dioxide and arylpalladium chlorides. In the presence of activated alkenes, the combination forms arylated alkenes in modest yields (equation 49).[110]

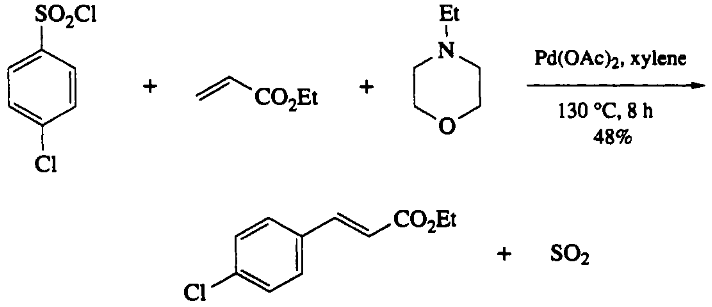

(49)

## 4.3.5.4 Vinyl Substitution with Triflate Esters and Related Esters

### *4.3.5.4.1 Arylation with aryl triflates*

Only a few examples of vinyl substitution with aryl fluorosulfonate esters have been reported but the reaction will surely turn out to be general.[111] A tetrafluoroethoxytetrafluoroethanesulfonate ester was used in the example shown in equation (50)

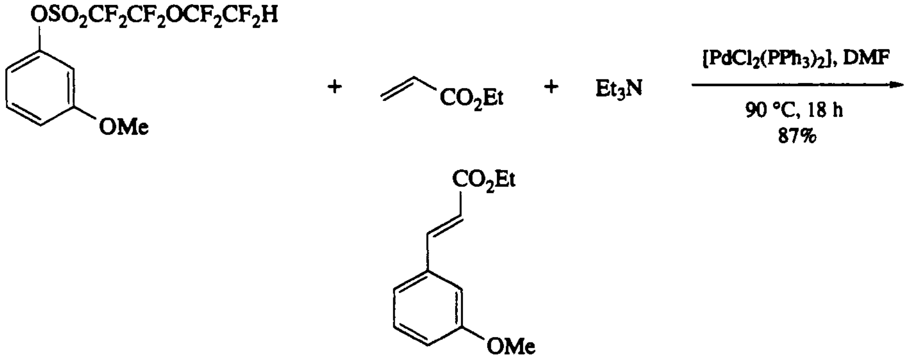

(50)

#### *4.3.5.4.2 Vinylation with enol triflates*

Many examples of the vinylation of alkenes with enol triflates have been reported. In general, the reactions proceed in good yields under similar conditions to the vinyl iodide vinylations. Most examples have been carried out in DMF solution with triethylamine as base at 60–75 °C. At these temperatures reduction of the palladium(II)–triphenylphosphine catalyst is sometimes slow and the use of tetrakis(triphenylphosphine)palladium(0) is preferred. The reaction appears to be relatively tolerant of steric congestion around the triflate group since 2,5,5-trimethyl-1-cyclopentenyl triflate reacts easily in good yields. The stereochemistry of the vinyl triflate is largely retained in the reaction while the second double bond of the product should have sterochemistry resulting from a *syn* addition of the vinylpalladium derivative followed by *syn* elimination of the palladium hydride group, although no reactions with 1,2-disubstituted alkenes have been reported to confirm this prediction. This reaction appears to be a very useful variation of the vinyl substitution since yields are generally good and the vinyl triflates are easily available from ketones and trifluoromethanesulfonic anhydride. Examples of the reaction are shown in equation (51) and Table 2.

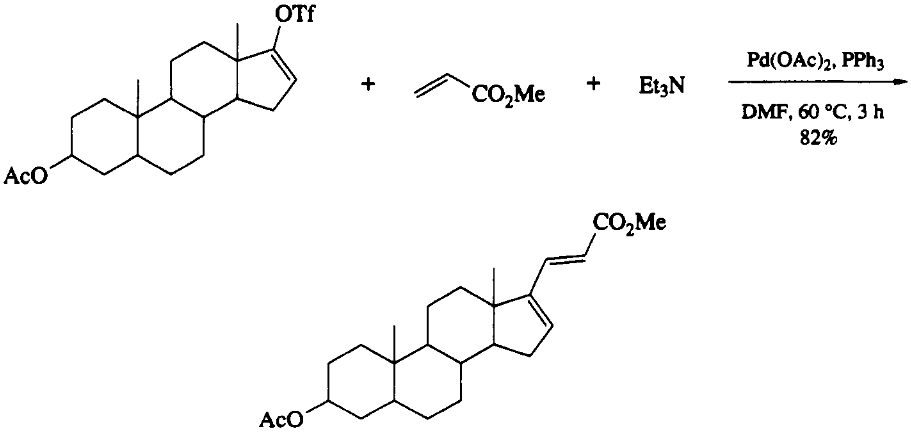

(51)

**Table 2** Vinyl Substitution with Vinyl Triflates

| *Triflate* | *Alkene* | *Catalyst* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 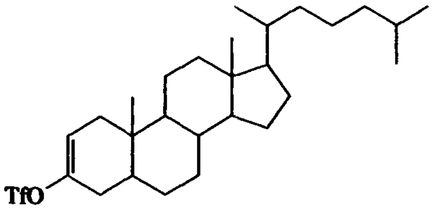 | 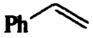 | $[Pd(OAc)_2(PPh_3)_2]$ | 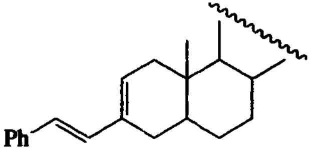 | 77 | 112 |
| 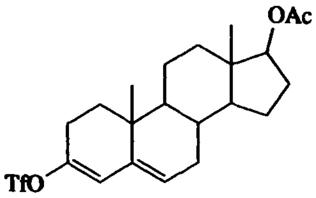 | 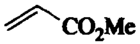 | $[Pd(OAc)_2(PPh_3)_2]$ | 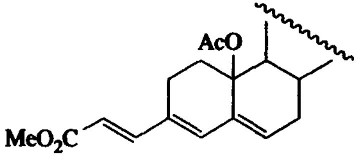 | 82 | 112 |
| 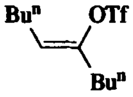 | 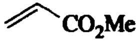 | $[Pd(OAc)_2(PPh_3)_2]$ | 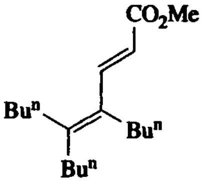 | 20 | |
| | | | 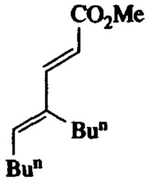 | 5 | 112 |

**Table 2** *(continued)*

| *Triflate* | *Alkene* | *Catalyst* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 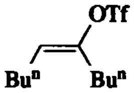 | 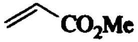 | $[Pd(OAc)_2(PPh_3)_2]$ | 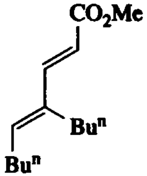 CO2Me<br>Bu^n<br>Bu^n | 24 | 112 |
| 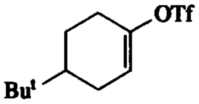 | 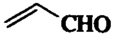 | $[PdCl_2(PPh_3)_2]$ | 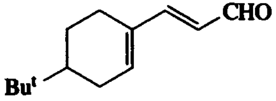 | 86 | 113 |
| 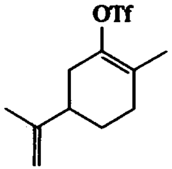 | 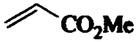 | $[PdCl_2(PPh_3)_2]$ | 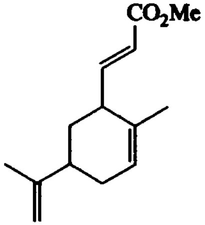 | 88 | 113 |
| 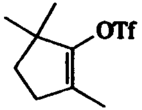 | 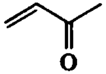 | $[PdCl_2(PPh_3)_2]$ | 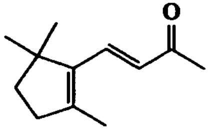 | 83 | 113 |
| 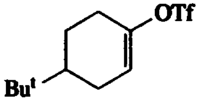 | 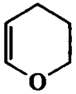 | $[Pd(PPh_3)_4]$ | 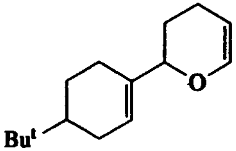 | 53 | 113 |

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# 4.4

# Carbometallation of Alkenes and Alkynes

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## 4.4.1 INTRODUCTION

Reactions which result in the addition of the carbon–metal bond of an organometallic (**1**) across a carbon–carbon multiple bond (**2**) leading to a new organometallic (**3**) are called carbometallation reactions (equation 1).[1–3] Only those reactions in which the newly formed carbon–metal bond of (**3**) can be used for further synthetic transformations will be considered here. Since the first carbometallation discovered by Ziegler and Bähr[4] in 1927 (equation 2), an ever-increasing number of additions of organometallics to carbon–carbon multiple bonds have been reported.[3] To be synthetically useful, a carbometallation reaction must show good chemo-, regio- and stereo-selectivity.

$$\underset{(\mathbf{1})}{\text{R}-\text{M}} \quad + \quad \underset{(\mathbf{2})}{\text{C}\equiv\text{C}} \quad \longrightarrow \quad \underset{(\mathbf{3})}{\text{R}-\text{C}=\text{C}-\text{M}} \qquad (1)$$

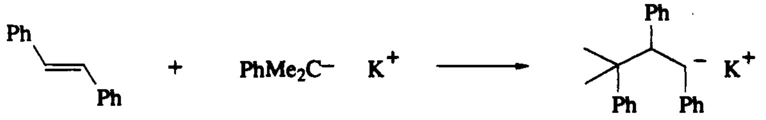

(2)

Most organometallics which undergo additions to carbon–carbon bonds are polar reagents and they may react with several functional groups before they add to a relatively nonpolar carbon–carbon multiple bond. In practice, only a limited number of functional groups of low reactivity (such as ethers, sulfides, acetals, hydroxy and amino groups) can be present in the unsaturated organic substrate submitted to a carbometallation. Organometallics can also act as bases, especially organolithium and organomagnesium derivatives, abstracting acidic allylic, propargylic or alkynic protons. The deprotonation of terminal alkynes, instead of their carbometallation, is a common side reaction.[3] Furthermore, the addition of an organometallic (**1**) to a multiple bond (**2**) affords a new organometallic compound (**3**; Scheme 1), which can participate in a subsequent carbometallation if its reactivity is too similar to that of (**1**). In this case, a polymerization of the unsaturated substrate will result. In order to realize a controlled monoaddition, the carbometallation ability of (**1**) must be higher than that of (**3**). In the case of an intramolecular carbometallation, this does not necessarily have to be true because the entropy effect will favor the monoaddition even if the starting organometallic and the product have similar reactivities.

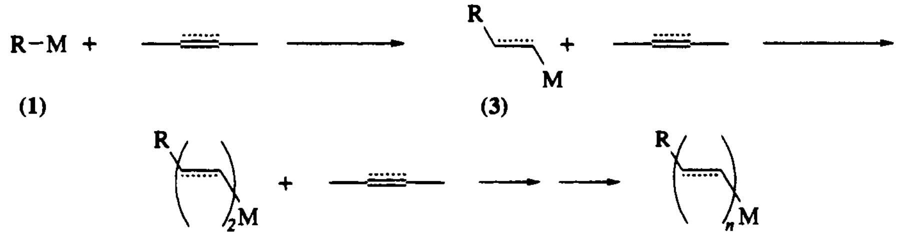

**Scheme 1**

The carbometallation of an unsymmetrical alkyne or alkene can lead to two regioisomers (**4**) and (**5**) (equation 3). The ratio of (**4**) to (**5**) depends on the nature of the organometallic, the organic substrate and the reaction conditions used (presence of a catalyst, solvent, cosolvent, *etc.*).

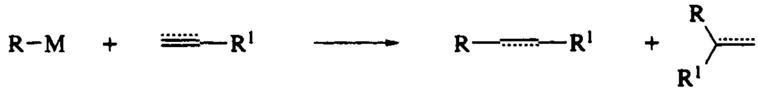

(3)

(**4**) (**5**)

The addition to an alkyne can either be *syn* or *anti*, leading respectively to the two stereoisomers (**6**) and (**7**) (Scheme 2). Most carbometallations of alkynes are *syn* additions and certain organometallics such as organocopper reagents show an almost perfect *syn* selectivity.[3] With others, such as organomagnesium derivatives, an *anti* addition is preferred in the case of some functionalized alkenes and alkynes. Since most C($sp^3$)—M bonds of polar organometallics are not configurationally stable, the *syn* or the *anti* character of the addition to alkenes often cannot be established. However, in the case of cyclopropenes, which leads, after carbometallation, to configurationally stable cyclopropyl organometallics, a *syn* addition is always observed.

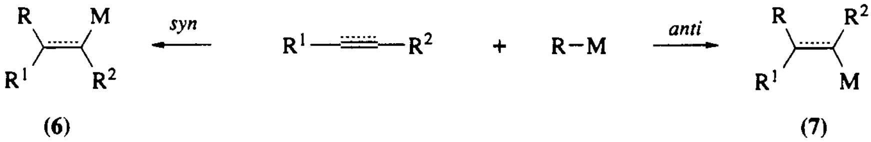

(**6**) (**7**)

**Scheme 2**

More severe reaction conditions are required for the carbometallation of alkenes and dienes than for alkynes. Most carbometallations of alkenes strongly depend on the structure of the organic substrate, and generally show a narrow synthetic scope. More successful are additions to functionalized alkenes in which the heteroatom, by precoordination of the organometallic, directs the carbometallation reaction. Also, intramolecular carbometallation reactions proceed more readily and may show very high regio- and diastereo-selectivities. Alkynes, which are more reactive, are carbometallated with several organometallics under mild conditions. The carbocupration discovered by Normant[3] has the largest synthetic possibilities. It shows an excellent chemo-, regio- and stereo-selectivity with nonfunctionalized alkynes. A very high regioselectivity and almost perfect stereoselectivity can be reached with functionalized alkynes by the fine tuning of the reaction conditions (solvent, ligand, cosolvent, *etc.*). Of special interest is also the zirconium-catalyzed carboalumination discovered by Negishi,[1,2,5] which complements the carbocupration reaction and allows the performance of methylaluminations with excellent regio- and stereoselectivity. These carbometallations give an easy access to a wide range of stereo-defined alkenyl-copper and -aluminum reagents, of great synthetic interest. Both alkenyl organometallics are able to form new carbon–carbon bonds with a variety of electrophiles and have found numerous synthetic applications.[1-3,5]

## 4.4.2 THE CARBOLITHIATION REACTION

### 4.4.2.1 General Considerations[6,7]

Due to its high ionic character, the carbon–lithium bond is very reactive and adds under mild conditions to ethylene or dienes and under more severe conditions to other alkenes. Some functionalized alkenes can be used, and high regio- and stereo-selectivity is usually observed in these carbolithiation reactions, especially if a precoordination of the lithium organometallic with the alkene is possible. Intramolecular carbolithiations of alkenes proceed under mild conditions and allow the preparation of several stereochemically well defined mono- and bi-cyclic compounds. Alkynes are too reactive, and can lead, with organolithium derivatives, to several side reactions, and seldom afford the desired carbolithiated product in good yield.

### 4.4.2.2 The Carbolithiation of Alkenes and Dienes

#### *4.4.2.2.1 Intermolecular reactions*

The controlled addition of organolithium reagents to isolated double bonds is of limited preparative interest. The carbolithiation of ethylene under pressure by primary lithium organometallics (*e.g.* BuLi, EtLi) leads to new lithium derivatives, $RCH_2CH_2Li$, which have a similar reactivity toward ethylene as their precursor, RLi, and thus low molecular weight polymers are formed.[8] In the presence of ligands like DABCO or TMEDA, which enhance the reactivity of organolithium derivatives by reducing their aggregation,[9] extensive polymerization is observed, and alkyllithium reagents are in fact excellent initiators for anionic polymerization, especially of styrene and conjugated dienes.[10] Secondary and tertiary alkyllithium reagents are far more reactive toward addition to ethylene ($Bu^{s}Li$ is at least $10^6$ times more reactive than $Bu^{n}Li$), and afford primary alkyllithium compounds in good yields under mild conditions. These organometallics are inert toward further addition of ethylene (equation 4).[11] Other isolated alkenes[12] like 1-octene are far less reactive and the addition will occur in moderate yield only at a higher temperature (80 °C). At higher temperatures, allylic proton abstraction and decomposition of the lithium reagent (β-hydride elimination) become important side reactions. Noteworthy is the high regioselectivity of the carbolithiation. In the case of 1-octene, only the primary alkyllithium (**8**) is formed, in strong contrast to the corresponding aluminum and magnesium organometallics, which afford the opposite regioisomer (equation 5).[12]

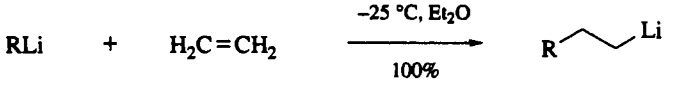

(4)

R = $Bu^t$, $Bu^s$, $Pr^i$, cyclohexyl

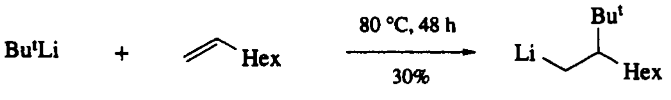

(5)

(**8**)

The addition to aryl-substituted alkenes and to dienes occurs readily in $Et_2O$ or THF, but controlled reaction conditions have to be used in order to avoid polymerization.[13] Alkyllithium reagents are more reactive than allyllithiums,[14] and the fast addition of $Bu^tLi$ to butadiene[16] provides a quantitative formation of 5,5-dimethyl-2-hexenyllithium (**9**). The subsequent addition of (**9**) to butadiene is more sluggish and occurs with low regioselectivity (Scheme 3). The addition of lithium organometallics to enynes[15] is a useful reaction for the preparation of allenes. Strained alkenes such as norbornene,[17] methylcyclopropene[18] or *trans*-cyclooctene[19] react under moderate reaction conditions (Scheme 4). In the case of

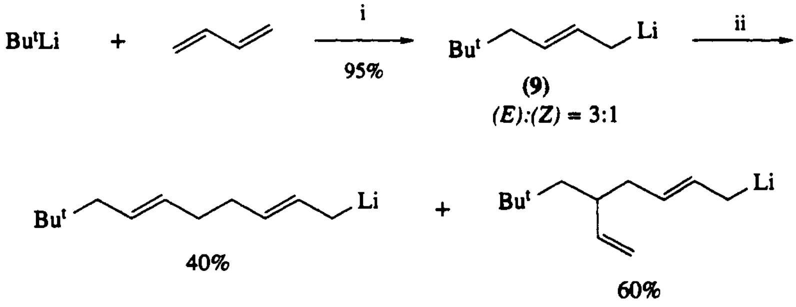

i, pentane, –78 °C to 20 °C, 0.5 h; ii, butadiene, 25 °C, 8 h

**Scheme 3**

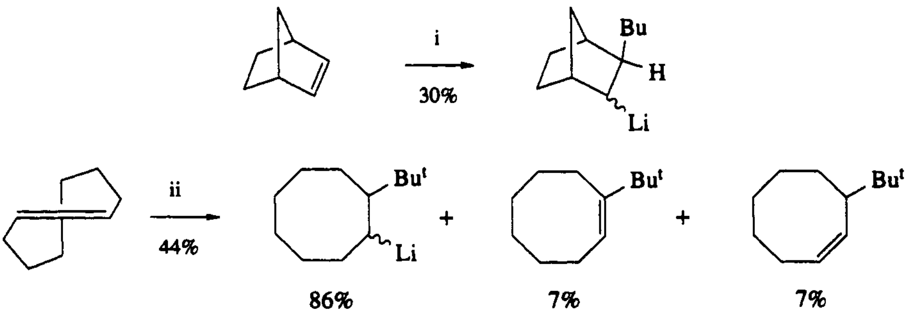

i, BuLi, TMEDA, hexane, 25 °C, 36 h; ii, $Bu^tLi$, $Et_2O$, 25 °C, 18 h

**Scheme 4**

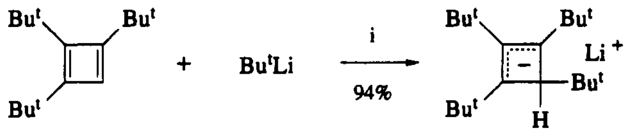

(6)

**(10)**

i, TMEDA, Et$_2$O, −78 °C

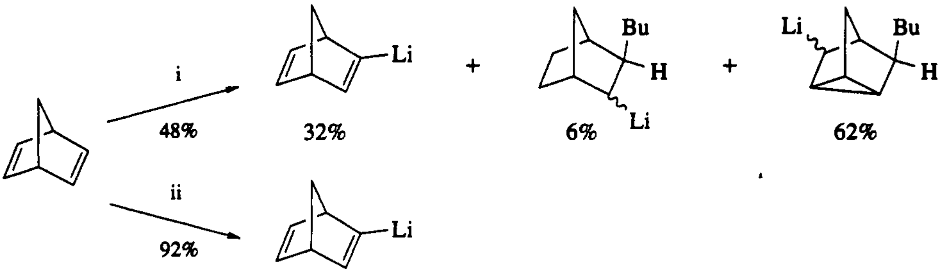

i, BuLi, Et$_2$O; ii, BuLi, Bu$^t$OK, THF, −80 °C to −60 °C, then LiBr

**Scheme 5**

norbornene, only the product of *exo* attack is observed.[17] The addition of Bu$^t$Li to a cyclobutadiene derivative[20] occurs readily and affords the addition product (**10**) in a very high yield (equation 6). In some cases, such as that of norbornadiene,[21] a proton abstraction can compete with the carbolithiation reaction and, depending on the reaction conditions, can become the predominant reaction pathway (Scheme 5).[22]

The presence of a donor group at the proximity of the double bond of the alkene promotes the carbolithiation reaction, as has been shown by Wittig,[21] Bickelhaupt,[23] Klumpp[23] and their respective coworkers (equation 7). The precoordination of the lithium reagent with the heteroatom explains both the high rate of the carbometallation and the high regio- and stereo-selectivity (*syn* addition) observed in these reactions. The addition proceeds well with several acyclic alkenyl ethers and amines,[24,25] regiospecifically affording the stabilized lithium derivatives of type (**11**) and (**12**) (Scheme 6). Similarly, the addition of organolithium compounds to β-substituted homoallylic sulfides provides an approach to γ-lithiated sulfides (**13**; equation 8).[26]

The addition of organolithium compounds[27] to allylic alcohols in the presence of TMEDA is a preparatively useful method which allows a high regio- and stereo-selective synthesis of alcohols. Several side reactions can be observed depending on the structure of the allylic alcohol (**14**; Scheme 7). If the

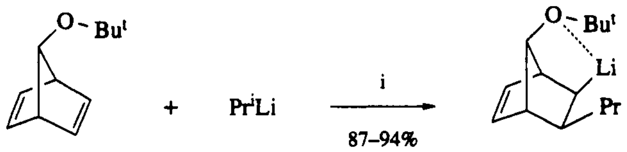

(7)

i, petroleum ether, −20 °C

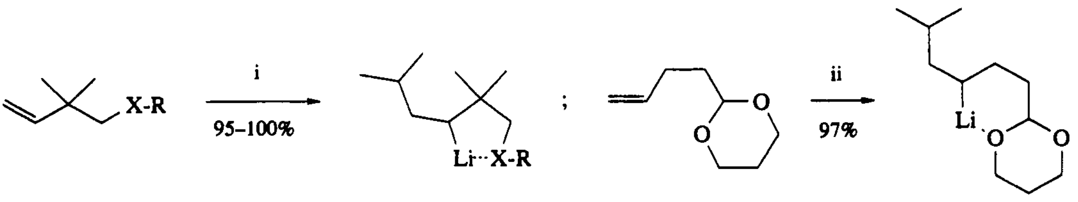

X = OMe or NMe$_2$ **(11)** **(12)**

i, Pr$^i$Li (1.5 equiv.), pentane/Et$_2$O, 25 °C, 0.3 h; ii, Pr$^i$Li (3 equiv.), no solvent, 0 °C, 2 h

**Scheme 6**

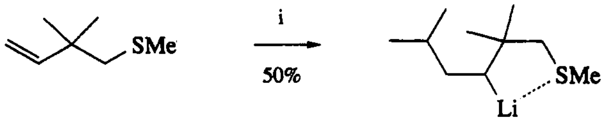

SMe
i
50%
SMe
Li

**(13)**

(8)

i, Pr$^i$Li, Et$_2$O/pentane, 25 °C, 2 h

substituent R$^2$ of (**14**) is a methyl group, then the carbolithiation is disfavored and an allylic deprotonation occurs, leading to the allylic lithium derivative (**15**).[28] If R$^1$ or R$^3$ is a phenyl group, another allylic deprotonation can occur, furnishing the dilithiated compound (**16**). Finally, if the carbolithiation leads to a β-lithioalcoholate of type (**17**), a fast elimination of lithium oxide will occur, affording the alkene (**18**; Scheme 7). This reaction pathway is the most important if R$^1$ and R$^3$ are part of a five- or six-membered ring, or if a bulky organolithium reagent is used.[27] Representative synthetic applications, as developed by Crandall and coworkers, are shown in Scheme 8. Felkin and coworkers[27] demonstrated that these car-

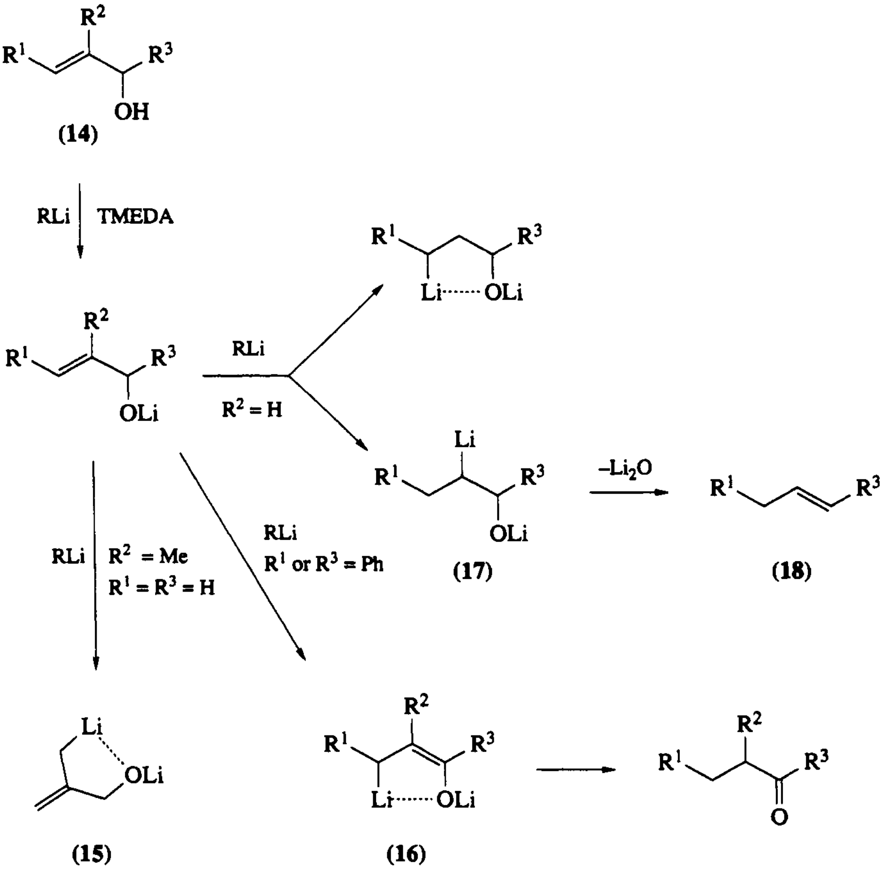

R2
R1
R3
OH
(14)
RLi
TMEDA
R1
R3
Li
OLi
R2
R1
R3
OLi
RLi
R2 = H
Li
R1
R3
OLi
(17)
-Li2O
R1
R3
(18)
RLi
R2 = Me
R1 = R3 = H
RLi
R1 or R3 = Ph
Li
OLi
(15)
R2
R1
R3
Li
OLi
(16)
R2
R1
R3
O

**Scheme 7**

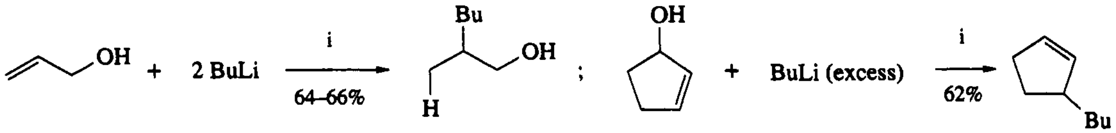

OH
+
2 BuLi
i
64–66%
Bu
OH
H
;
OH
+
BuLi (excess)
i
62%
Bu

i, TMEDA, pentane, 25 °C, then H$_3$O$^+$

**Scheme 8**

bolithiations can be highly diastereoselective, and a chelate-type transition state (**19**) has been proposed to account for the observed stereochemistry (Scheme 9).[27] Other related compounds like allylic amines[29] and α-amino- or α-hydroxy-enynes[30] are also able to add various lithium organometallics across the double bond, but in moderate yields (30–60%). The direct addition of organolithium reagents to aromatic compounds such as naphthalene or phenanthrene occurs only under severe reaction conditions (decalin, 165 °C).[31]

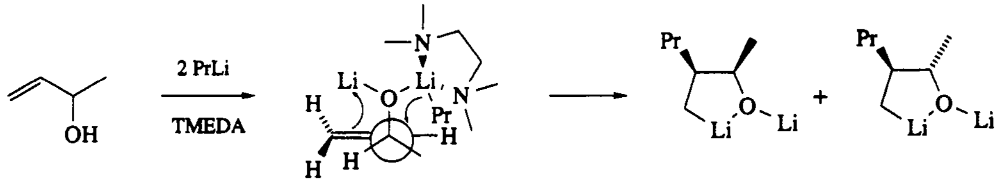

**(19)** >98% <2%

**Scheme 9**

### *4.4.2.2.2 Intramolecular reactions*

Intramolecular carbolithiations proceed more readily than intermolecular carbolithiations.[32] Thus, 5-hexen-1-yllithium (**20**) is indefinitely stable at –78 °C, but undergoes a rapid cyclization upon warming to higher temperatures (at 23 °C, $t_{1/2}$ = 5.5 min; see Scheme 10). However, it has been estimated that the rate of cyclization of (**20**) is $10^8$ times slower than that of the corresponding radical.[33] Bailey and coworkers showed that several intramolecular organolithium cyclizations occur in good yields and with very high diastereoselectivities, as indicated in Scheme 11.[34]

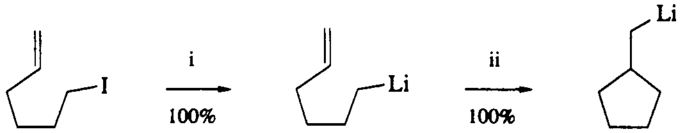

**(20)**

i, Bu$^t$Li (2 equiv.), pentane/Et$_2$O, –78 °C, 5 min; ii, –78 °C to 25 °C

**Scheme 10**

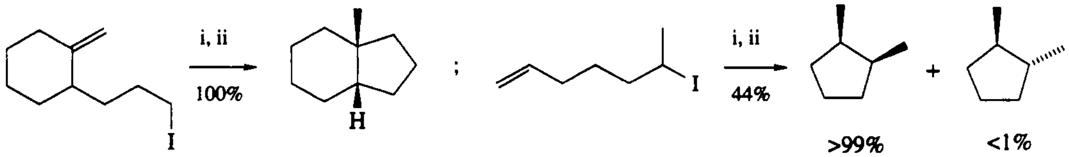

i, Bu$^t$Li (2.2 equiv.), pentane/Et$_2$O, 5 min; ii, 5 h at –20 °C, then $H_3O^+$

**Scheme 11**

The ring closures can be reversible, as in the case of the diphenylcyclopropylcarbinyllithium species (**21**), which is stable in THF but completely undergoes opening to 4,4-diphenylbuten-3-yllithium (**22**) in ether (equation 9).[35] The equilibrium between unsaturated primary and secondary organolithium organometallics such as (**23**) and (**24**) proceeds *via* a reversible intramolecular carbolithiation reaction[36] which favors the more stable primary organolithium (**23**) in over 99% (equation 10). Even the relatively unreactive aryllithium reagent (**25**) cyclizes to the corresponding indanyllithium (**26**) in good yield (Scheme

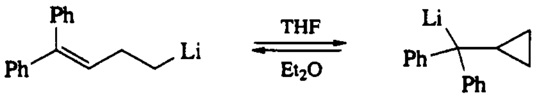

**(22)** **(21)** (9)

12).[37] Chamberlin and coworkers[38] showed that vinyllithium reagents derived from ketone (2,4,6-triisopropylphenyl)sulfonylhydrazones undergo intramolecular carbolithiation reactions with high diastereoselectivity (Scheme 13).

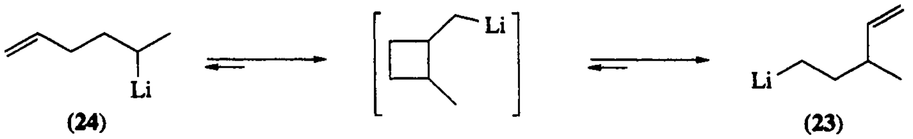

**(24)** **(23)** (10)

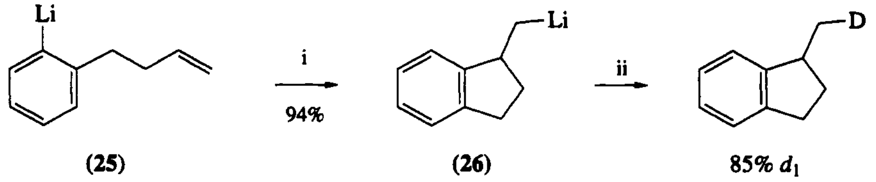

i, $Et_2O$/TMEDA, 23 °C, 0.5 h, ii, $D_2O$

**Scheme 12**

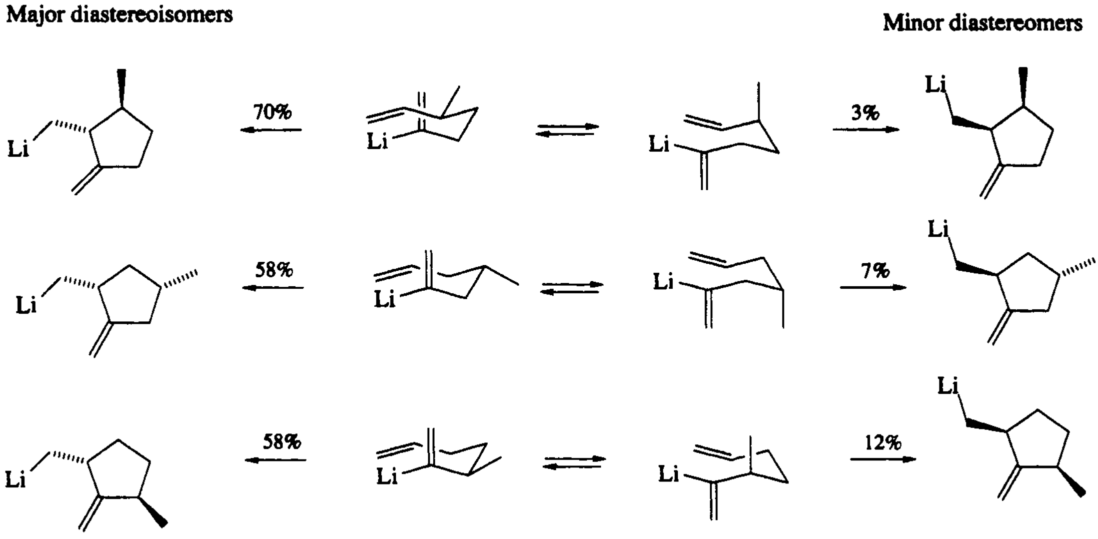

**Scheme 13**

### 4.4.2.3 The Carbolithiation of Alkynes

The carbolithiation of alkynes is of limited preparative value. Terminal alkynes are always deprotonated by organolithium reagents and disubstituted alkynes are not readily carbolithiated since other reaction pathways, such as deprotonations at propargylic positions, occur more readily. The addition to 1,2-diphenylacetylene, however, has been studied in some detail[39] and the structures of the mono- and di-lithiated products (**27**) and (**28**) (Scheme 14) have been elucidated.[40] The carbolithiation proceeds in various solvents and is accelerated by the presence of TMEDA. An initial *syn* addition product (**29**) has been postulated, since it has been found that $Bu^tLi$ reacts with 1,2-diphenylacetylene to afford mainly the *syn* addition product. A rapid isomerization of (**29**) leads to the only detectable *trans* isomer (**27**), which is again lithiated to afford (**28**). *Ab initio* calculations[41] on the addition of lithium hydride to acetylene also predict a *syn* addition and support the postulated mechanism of Mulvaney (Scheme 14).[39b] Functionalized alkynes, such as 3-phenylpropargyl alcohol, readily add BuLi to provide, after hydrolysis, the stereoisomerically pure alcohol (**30**; Scheme 15).[42] The addition of organolithium reagents to benzyne and benzyne derivatives is of preparative interest.[43] Meyers and coworkers[44] showed that the reaction of the functionalized aryl chloride (**31**) with BuLi allows the *in situ* generation of the benzyneoxazoline (**32**), which undergoes a regioselective carbolithiation with lithium organometallics to afford mainly the aryllithium derivatives (**33**). The carbocupration of the benzyne (**32**) furnishes the opposite regioisomer

(**34**; Scheme 16). This regioisomer is also obtained in appreciable amounts if bulky lithium organometallics are used. Intramolecular carbolithiations have been reported, such as the cyclization of 5-alkynyllithium compounds to furnish the cyclized products in low yields.[3]

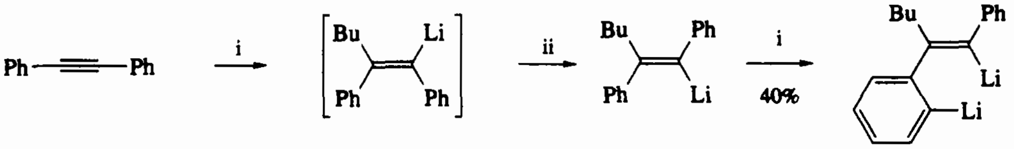
Ph
Ph
i
Bu
Li
Ph
Ph
ii
Bu
Ph
Ph
Li
i
40%
Bu
Ph
Li
Li

(**29**) (**27**) (**28**)

i, BuLi, hexane/TMEDA or $Et_2O$; ii, fast isomerization

Scheme 14

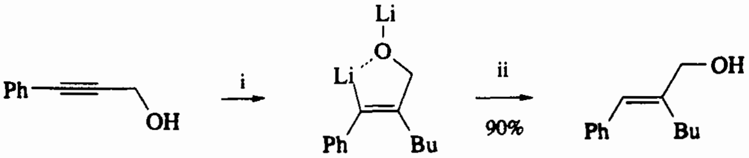
Ph
OH
i
Li
O
Li
Ph
Bu
ii
90%
OH
Ph
Bu

(**30**)

i, BuLi (2.5 equiv.), $Et_2O$, TMEDA (0.2 equiv.), −30 °C to 20 °C, 3 h, ii, $H_2O$

Scheme 15

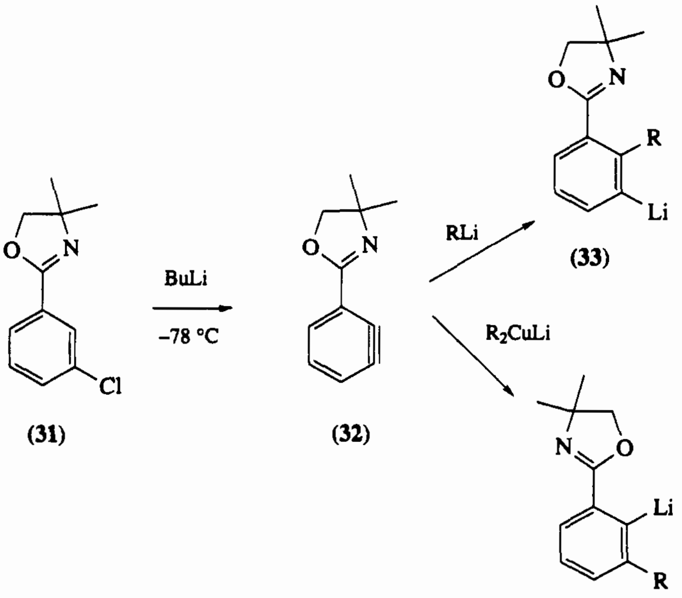
O
N
Cl
BuLi
−78 °C
O
N
RLi
R
Li
R₂CuLi
N
O
Li
R

(**31**) (**32**) (**33**) (**34**)

Scheme 16

## 4.4.3 THE CARBOMAGNESIATION REACTION

### 4.4.3.1 General Considerations[45]

The carbomagnesiation of alkenes has been extensively investigated in the last 40 years and several reactions with high synthetic potential have been discovered. The addition of Grignard reagents to nonfunctionalized alkenes usually requires severe reaction conditions and only the zirconium-catalyzed addition proceeds under mild conditions, but its scope seems limited. The introduction of a heteroatom in the proximity of the double bond considerably facilitates the addition by a precoordination of the Grignard reagent to the heteroatom. In these cases, high regio- and stereo-selectivity of the addition usually results. The intramolecular carbomagnesiation requires more severe conditions than the corresponding carbolithiation, but if the Grignard reagent is allylic the reaction proceeds well and is of high synthetic utility (see Volume 5, Chapter 1.2). In contrast to many carbometallations, the addition of Grignard reagents to functionalized alkynes shows an *anti* selectivity. It is highly regioselective and leads to useful functionalized alkenyl organomagnesium derivatives. The addition of magnesium derivatives to alkynes can, in several cases, be catalyzed by salts of transition metals such as copper or nickel.

## 4.4.3.2 The Carbomagnesiation of Alkenes

### *4.4.3.2.1 Addition to nonfunctionalized alkenes*

*(i) Intermolecular reactions*

Intermolecular and uncatalyzed additions of Grignard reagents to nonfunctionalized alkenes proceed only under very severe conditions and are of limited synthetic interest. In order to avoid polymerization reactions, the reactivity of the starting magnesium organometallic has to be higher than that of the carbomagnesiated product. Lehmkuhl[46] and coworkers have shown that secondary and tertiary alkyl,[47] benzylic,[48] and allylic[49] magnesium derivatives add to alkenes, whereas the less reactive primary alkylmagnesium compounds do not. In most cases, forcing reaction conditions have to be used. Ethylene reacts under pressure with allylic magnesium halides[49,50] in ether (40–70 atm, 20–80 °C, 2–100 h) to afford unsaturated Grignard derivatives of type (**35**; equation 11). Ether is the best solvent for these reactions; stronger Lewis bases like THF or dioxane diminish the reaction rate. Lehmkuhl and coworkers have shown that the reaction is first order both for the alkene and the allylic Grignard reagent. A cyclic six-membered transition state of type (**36**) has been proposed since relatively high activation entropies have been observed (between −17 and −24 cal °C$^{-1}$ mol$^{-1}$; 1 cal = 4.2 J). The activation parameters ($\Delta H^\ddagger$ = 20 kcal mol$^{-1}$ and $\Delta G^\ddagger$ = 26–30 kcal mol$^{-1}$) are very similar to those of Diels–Alder or ene reactions.[46] The reaction usually proceeds with almost complete allylic rearrangement (Scheme 17).[51] The reactivity of alkenes increases in the order: 1-alkene < styrene < butadiene < ethylene. Alkenes with an internal double bond do not react. Strained alkenes such as cyclopropenes[50,52] or norbornene[50–52] are exceptions and add readily to a variety of Grignard reagents under mild conditions and in good yields. The stereospecific *syn* addition of 2-methylpropenylmagnesium chloride to 3,3-dimethylcyclopropene has been used by Lehmkuhl[50,52,53] for a short and efficient approach to (*Z*)-chrysanthemic acid (Scheme 18).

The regioselectivity of the carbomagnesiation of 1-alkenes depends strongly on the structure of the Grignard reagent.[54] Primary organomagnesium halides attack the alkene preferentially at C-2, leading to a new primary organometallic, whereas secondary and tertiary magnesium derivatives give more C-1 attack (formation of a secondary Grignard reagent; see Table 1). These reactions require temperatures between 70 and 120 °C and afford only moderate yields of the addition products.[50] Allylic magnesium halides[53,55] react with more than 90% regioselectivity with butadiene (Mg at C-2) to afford the 2,6-heptadienylmagnesium derivatives (**37**) as the major products (Scheme 19). In the presence of an excess of bu-

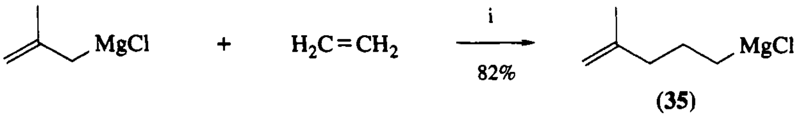

(11)

i, Et$_2$O, 40–70 atm, 20–62 °C

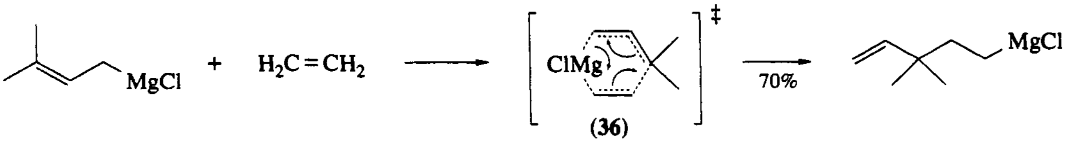

**Scheme 17**

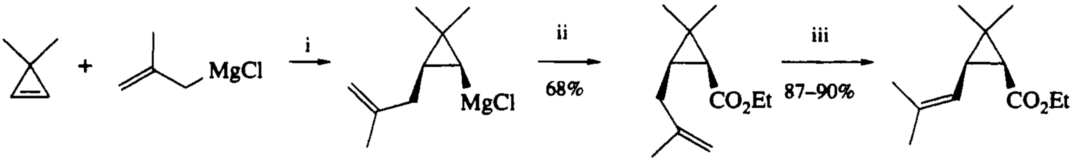

i, $Et_2O$, 0–20 °C; ii, $ClCO_2Et$, $Et_2O$; iii, $H^+$ (cat.), dioxane

**Scheme 18**

tadiene, a second carbomagnesiation takes place leading to the 1:2 adduct (**38**), which undergoes a fast intramolecular ring closure to give the cyclic Grignard reagent (**39**). Isoprene shows a similar reactivity pattern, and the initial carbomagnesiation occurs predominantly at C-4 (Mg at C-3). Allene also reacts with 2-methylallylmagnesium chloride[47] (10 atm, $Et_2O$) to provide a cyclic 1:2 adduct in 44% yield (equation 12). Allylic magnesium compounds add across the double bond of enynes to afford mixtures of alkynes and the corresponding isomeric allenes.[30b]

**Table 1** Proportion of Mg at C-2 (Formation of a Secondary Carbomagnesiation Adduct) in the Reaction of Organomagnesium Chloride with 1-Octene

| *Organo group* | *Mg at C-2 (%)* |
|---|---|
| $—CH_2CH{=}CH_2$ | 0 |
| $—CH_2CMe{=}CH_2$ | 0.6 |
| $—CH_2Ph$ | 0 |
| $—CHMeCH{=}CH_2$ | 31 |
| $Pr^i$ | 81–88 |
| $Bu^t$ | 98–99 |

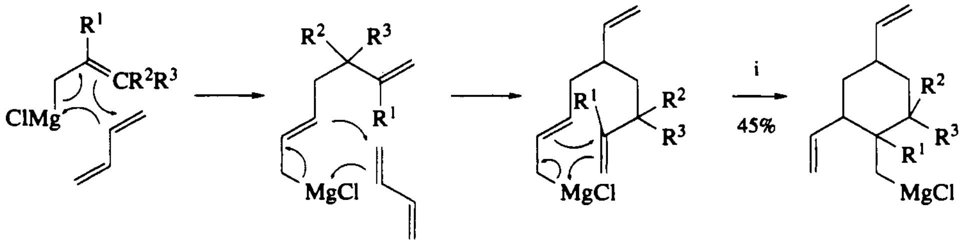

(**37**) (**38**) (**39**)

i, $R^1 = R^2 = R^3 = H$, $Et_2O$, 85 °C, 24 h

**Scheme 19**

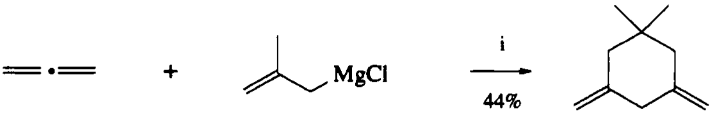

(12)

i, 10 atm, $Et_2O$, 80–88 °C

In strong contrast, the transition metal catalyzed carbomagnesiation occurs under much milder conditions. Dzhemilev and coworkers[56] have shown that $Et_2Mg$ adds regiospecifically to terminal alkenes in the presence of a catalytic amount of $Cp_2ZrCl_2$ (equation 13). Several functional groups, such as a double bond, a dialkylamino, a ketal, a trimethylsilyl, an alkoxy or a hydroxy group, are tolerated under these mild reaction conditions (equation 14). The use of higher homologs of $Et_2Mg$, such as $Pr_2Mg$ or $Bu_2Mg$, is complicated by the formation of appreciable amounts of elimination and dimerization products. Several other ethylmagnesium derivatives (EtMgX; X = alkyl, halide, $NR_2$, $SiMe_3$ or Cp) can also be used, but slower addition rates are observed.

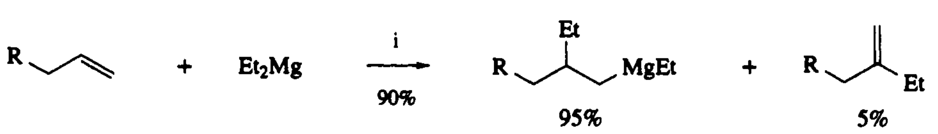

(13)

i, $Cp_2ZrCl_2$ (1 mol %), $Et_2O$, 2–4 h

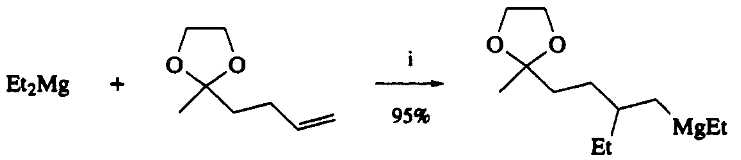

(14)

i, $Cp_2ZrCl_2$ (1 mol %), $Et_2O$, 4 h

### *(ii) Intramolecular reactions*

The intramolecular carbomagnesiation[57] of alkenes has been extensively studied in the past 40 years and reversible intramolecular carbomagnesiation reactions have been postulated in isomerizations (Scheme 20).[58] All cyclizations proceed by an exo-trig (or dig) mode[59] leading to the smaller ring (Scheme 21).[60,61] A similar preference has been observed in radical cyclizations.[62] The ring closure rates can be modified by several factors.[57] For example, the use of the more basic solvent THF in place of ether leads to slower cyclization rates by factors ranging from 2 to over 100. Hydrocarbon cosolvents, as well as aprotic solvents like HMPA, generally increase the reaction rate. Higher Grignard concentrations usually lead to a rate increase, possibly by formation of more reactive ate complexes.[35b] In several rearrangement studies, an increased rate has been observed with dialkylmagnesium derivatives (prepared by precipitation in dioxane).[57] The relative rates for the formation of various ring sizes follows the order $C_3 > C_5 > C_4 > C_6$. The effects of substituents have been well studied[57] and substituents at the double bond lead to a rate decrease. Allylic and secondary Grignard compounds are more reactive than primary alkyl Grignard compounds, as shown in Scheme 22.[57,60,63] Interestingly, the cyclized product (**40**) has a *cis*-configuration, whereas the cyclizations of secondary alkylmagnesium compounds mainly afford the *trans* product (*trans*:*cis* > 10:1).[57] The high stereoselectivity in the ring closure of allylic Grignard reagents has been used by Oppolzer and coworkers[64] for the formation of five-, six-, and seven-membered rings (Volume 5, Chapter 1.2).

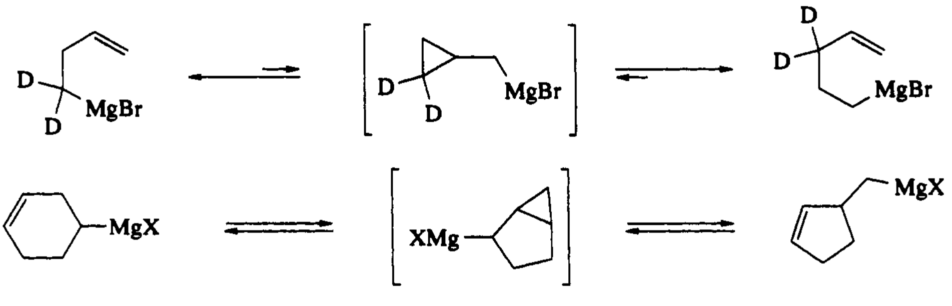

**Scheme 20**

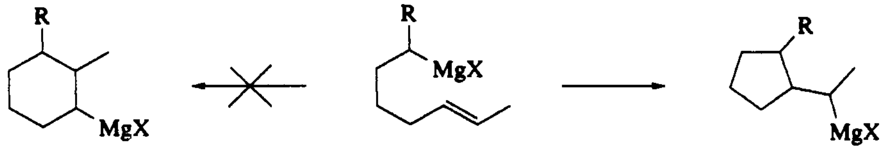

**Scheme 21**

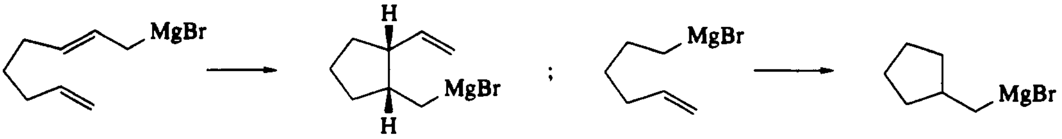

$k \approx 10^{-4}\ \mathrm{s}^{-1}$ (refluxing ether) (40) $k \approx 10^{-5}\ \mathrm{s}^{-1}$ (THF, 100 °C)

Scheme 22

#### *4.4.3.2.2 Addition to functionalized alkenes and dienes*

The presence of a neighboring hydroxy, alkoxy or amino group facilitates the addition of reactive Grignard reagents (allylic and benzylic) to alkenes. Eisch,[65] Felkin,[27d,66] Richey[67] and coworkers found that allylic magnesium organometallics add in a *syn* fashion to alkenols and some unsaturated amines under mild conditions. The reaction proceeds by a precoordination of the organomagnesium derivative[68] to the heteroatom followed by a *syn* addition (Scheme 23).[65,67] The addition of diallylmagnesium to 3-cyclopentenol provides only *cis*-3-allylcyclopentanol.[65] Felkin and coworkers[27d,66] showed that a high diastereoselectivity can also be observed for open chain systems. The addition of allylmagnesium bromide to 3-buten-2-ol affords mainly (*R**,*R**)-3-methyl-5-hexen-2-ol. In this case, a different mechanism has been proposed. The allylic magnesium reagent adds in an *anti* fashion to the double bond (Scheme 24). Functionalized enynes also react under mild conditions with allylic and vinylic magnesium bromides in ether to afford mixtures of isomeric allenes and alkynes in good yields.[30] Oxygen and nitrogen heterocycles have been prepared by Klumpp and coworkers *via* an intramolecular carbomagnesiation reaction (Scheme 25).[69]

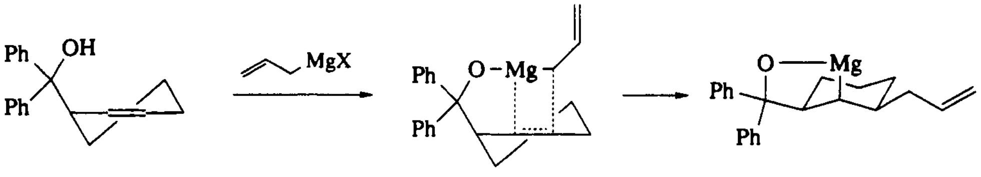

Scheme 23

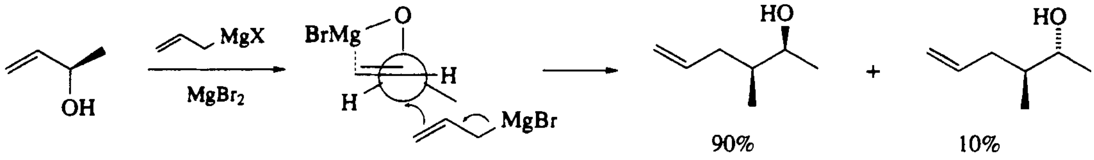

Scheme 24

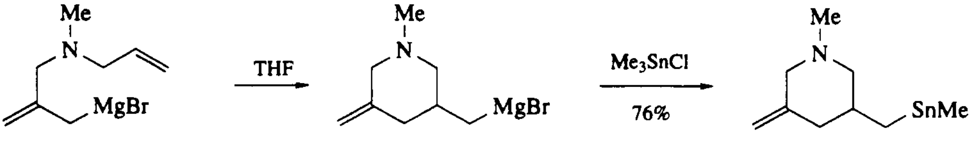

Scheme 25

### 4.4.3.3 The Carbomagnesiation of Alkynes

#### *4.4.3.3.1 Addition to nonfunctionalized alkynes*

Terminal alkynes are readily deprotonated by Grignard reagents, and no further addition occurs to alkynylmagnesium halides. In the presence of transition metal complexes of titanium,[70] iron,[70] rhodium,[71] nickel,[70,72] palladium[70] or copper,[73] the carbomagnesiation takes place in moderate yields. The regio- and stereo-selectivity of the additions are variable. In the presence of a copper(I) salt, however, only the *syn* addition product is obtained (equation 15). As shown by Richey,[74] and Crandall and coworkers,[75] the intramolecular carbomagnesiation[57] of alkynes proceeds more readily. Here also, the addition of a catalytic amount of a copper salt facilitates the reaction. *In situ* generated benzynes add to various organomagnesium derivatives,[76] representing a useful method for the generation of a wide range of arylmagnesium organometallics (Scheme 26).

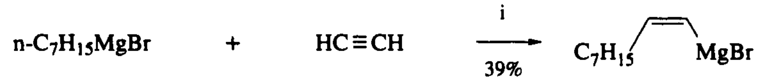

(15)

i, CuBr (5 mol %), $Et_2O$, −10 °C, 1 h

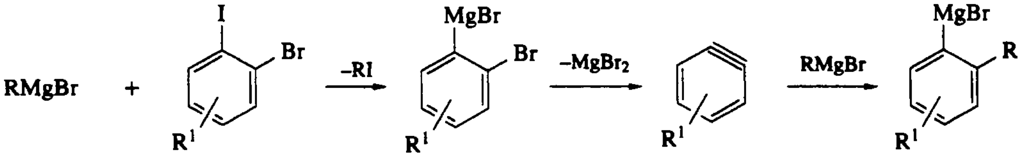

R = alkenyl, aryl, alkynyl

Scheme 26

### *4.4.3.3.2 Addition to functionalized alkynes*

Propargylic alcohols react regiospecifically with allylic magnesium halides by an *anti* addition to furnish relatively unreactive cyclic magnesium compounds of type (**41**; $R^1$ = allyl, $R^2$ = alkyl) in good yields (equation 16).[77] Other Grignard reagents add efficiently to propargyl alcohol and higher alkynols in the presence of a catalytic amount of copper(I) iodide. Only the *anti* addition product is obtained in ether.[78] Metallated propargylic alcohol[59,79] is also able to add allylmagnesium bromide in the presence of a copper(I) salt, and leads to the 1,1-dimetallic alkenyl derivative (**42**) which undergoes a further carbomagnesiation reaction leading to (**43**) in 50% yield (Scheme 27). The carbomagnesiation of propargylic amines proceeds less effectively.[80] Functionalized propargylic derivatives[81] add a wide range of Grignard reagents in an *anti* fashion (equation 17). The addition of the dimagnesium alcoholate of 2-butyne-1,4-diol and related derivatives has found several synthetic applications (equation 18).[82,83]

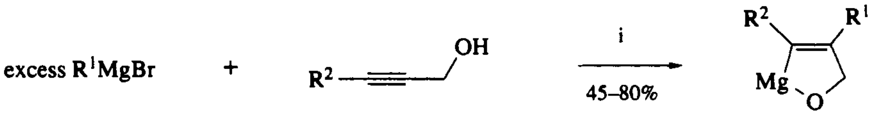

(16)

(**41**)

$R^1$ = alkyl, aryl, allyl, benzyl

$R^2$ = H, alkyl, aryl, alkenyl, trimethylsilyl

i, 10% CuI, $Et_2O$, 0 °C, 1 h

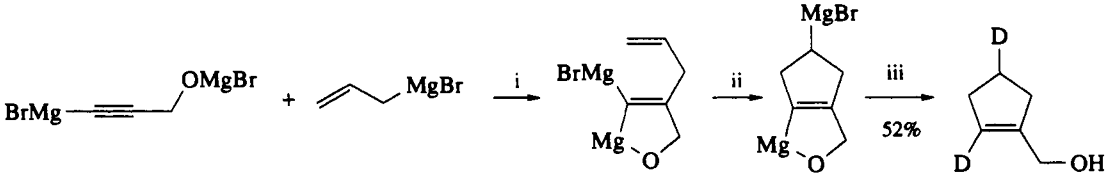

(**42**) (**43**)

i, 10 mol % CuI, $Et_2O$, 25 °C, 3h, ii, 5 h reflux; iii, $D_2O$

Scheme 27

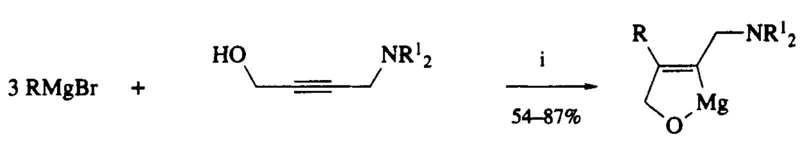

(17)

i, $Et_2O$, reflux 4–30 h

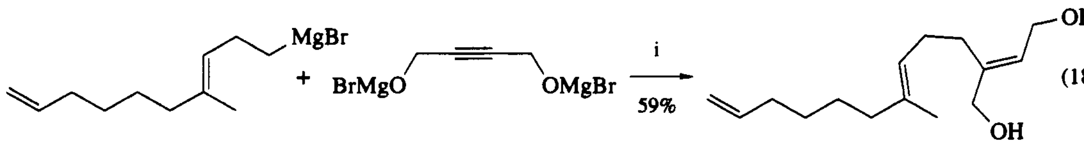

(18)

i, THF, $Et_2O$, reflux, 5 h, then aq. $NH_4Cl$

In contrast, the addition of allylmagnesium bromides to homopropargylic alcohols proceeds with low regioselectivity.[65,77] Snider and coworkers found that methylmagnesium bromide adds to silylalkynes in the presence of a 1:1 mixture of nickel acetylacetonate and trimethylaluminum (10 mol %) to afford mainly the *syn* addition product. The use of ethylmagnesium bromide leads only to hydromagnesiation and coupling products.[84] Utimoto and coworkers[85] have described an intramolecular version of this reaction and have formed cyclic tetrasubstituted vinylsilanes in high yields (Scheme 28). The intramolecular carbomagnesiation of an alkenylsilane is also possible.[85] The reaction proceeds specifically in a suprafacial and 5-exo-trig manner and produces, after allylation, the silane (**44**) with complete control of the stereochemistry of the three adjacent chiral centers (equation 19).

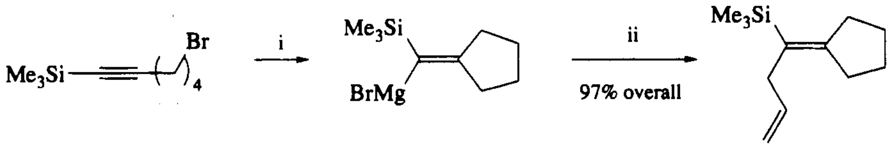

i, Mg, $Et_2O$, reflux, 5 h; ii, allyl bromide

**Scheme 28**

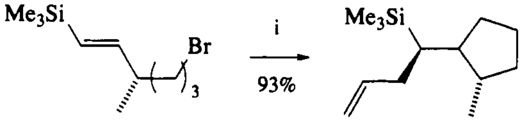

(**44**)

(19)

i, Mg, THF, 67 °C, 6 h, then allyl bromide

## 4.4.4 THE CARBOZINCATION REACTION

### 4.4.4.1 General Considerations[86]

Di-*t*-butyl- and diallyl-zinc compounds are able to add to alkenes, whilst other types of organozinc derivatives are usually inert toward nonfunctionalized alkene addition. In strong contrast, allylic zinc halides add readily to alkenyl organometallics under mild conditions to give mixed 1,1-diorganometallics. Alkynes are more reactive toward carbozincation than alkenes, and dialkylzinc and allylic zinc halides add to alkynes in the presence of transition metal salts. The addition of allylic zinc halides to alkynyl organometallics allows a unique approach to 1,1,1-triorganometallics. Allylic zinc halides show a higher reactivity toward the addition to alkynes than any other main group allylic organometallic.

### 4.4.4.2 The Carbozincation of Alkenes

#### *4.4.4.2.1 Addition to nonfunctionalized alkenes*

As shown by Lehmkuhl,[87] the addition of di-*t*-butylzinc to alkenes and 1,3-dienes proceeds between −20 and 75 °C and affords the addition products in good yields (Scheme 29), the reaction showing a good regioselectivity. The addition to octene or propene furnishes a secondary dialkylzinc with over 90% selectivity.[87] Several diallylic zinc derivatives[88] add to ethylene, giving the corresponding dialk-4-enylzinc compounds in high yields (>90%) and under mild conditions (20 °C, toluene, 36–96 h). The addition to octene is again highly regioselective (opposite regioselectivity than that with di-*t*-butylzinc) and furnishes primary dialk-4-enylzinc derivatives of type (**45**; equation 20). Diallylic zinc compounds add in a *syn* fashion to cyclopropenes in almost quantitative yields and under very mild conditions.[88] In all these cases, the new carbon–carbon bond is formed from the most-substituted end of the allylic organometallic. The addition to various substituted styrenes proceeds with moderate regioselectivity. A Hammett correlation between the observed regioselectivity and substituent constant $\sigma^*$ has been found.[89] Diallylzinc and allylzinc bromide have only a moderate stability[90] and undergo a carbozincation reaction leading to 1,3-diorganometallic compounds of type (**46**). The reaction of (**46**) with acetaldehyde furnishes, after β-hydride elimination, the corresponding addition product (Scheme 30).

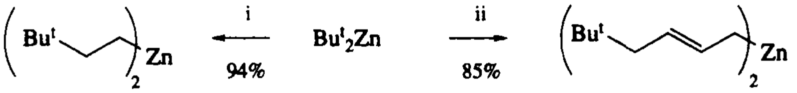

i, ethylene, 60 atm, 50–70 °C, 48 h; ii, butadiene, pentane, −20 to 10 °C, 21 h

Scheme 29

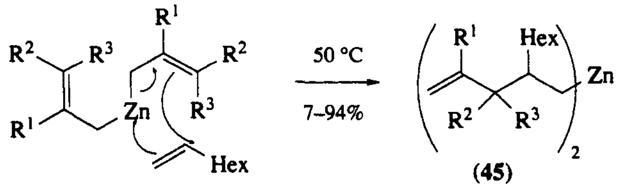

(20)

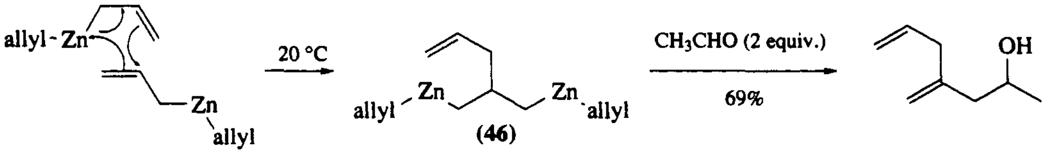

Scheme 30

#### *4.4.4.2.2 Addition to functionalized alkenes*

In 1971, Gaudemar[91] discovered that allylzinc bromide was able to add to alkenylmagnesium bromides to furnish the mixed 1,1-diorganometallics of zinc and magnesium of type (**47**). Knochel and coworkers[92] showed that this reaction was quite general and that various alkenyl organometallics of magnesium, lithium and aluminum showed similar reactivity. The reaction is believed to proceed through the formation of a mixed allylic, vinylic zinc compound of type (**48**) which then undergoes a 3,3-sigmatropic shift (metallo-Claisen reaction; compare with Volume 5, Chapter 1.2) to give the corresponding 1,1-diorganometallic (**47**) in fair to good (60–95%) yields (Scheme 31). The substitution pattern of both allylic and alkenylorganometallics (**49** and **50**, respectively) can be quite varied and many new and, in some cases, highly functionalized mixed 1,1-diorganometallics of zinc, lithium, magnesium and aluminum can be obtained. The compounds (**51**) to (**56**), which were all prepared in good yields, illustrate the synthetic potential of the method. The cyclic transition state leading to compounds of type (**47**; Scheme 31) confers a complete regioselectivity and a high stereoselectivity to this carbozincation reaction.[92,93] Thus, the alkoxy-substituted allylic zinc compound (**57**) reacts with alkenylmagnesium bromides stereospecifically through chair transition state intermediates of types (**58a**) and (**58b**), in which the configuration of both starting organometallics is retained. The diastereomeric diorganometallics (**59a**) and (**59b**) formed in this reaction can then be converted stereospecifically by a mild oxidation[93,94] reaction into the aldol products (**60a**) and (**60b**), the ratio of (**60a**) to (**60b**) being the same as the ratio between the starting (*E*)- and (*Z*)-octenylmagnesium bromides (Scheme 32).

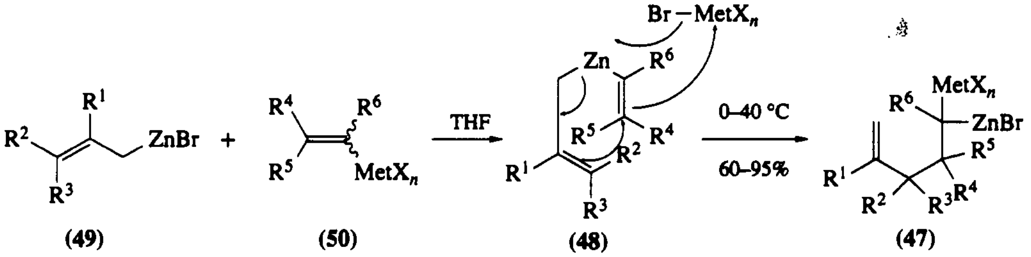
R¹
R²
ZnBr
R³
+
R⁴
R⁶
R⁵
MetXn
THF
Br—MetXn
Zn
R⁶
R⁵
R⁴
R²
R¹
R³
0–40 °C
60–95%
MetXn
R⁶
ZnBr
R⁵
R¹
R²
R³R⁴
(49)
(50)
(48)
(47)

MetX$_n$ = Li, MgBr, AlR$_2$

**Scheme 31**

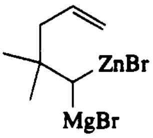

**(51)**

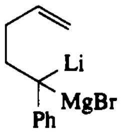

**(52)**

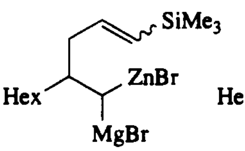
SiMe₃
Hex
ZnBr
MgBr

**(53)**

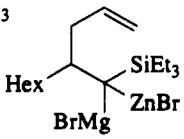
Hex
SiEt₃
ZnBr
BrMg

**(54)**

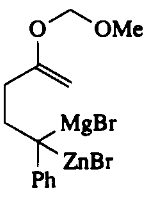
O
OMe
MgBr
ZnBr
Ph

**(55)**

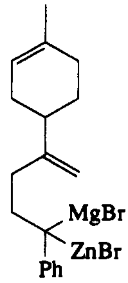
MgBr
ZnBr
Ph

**(56)**

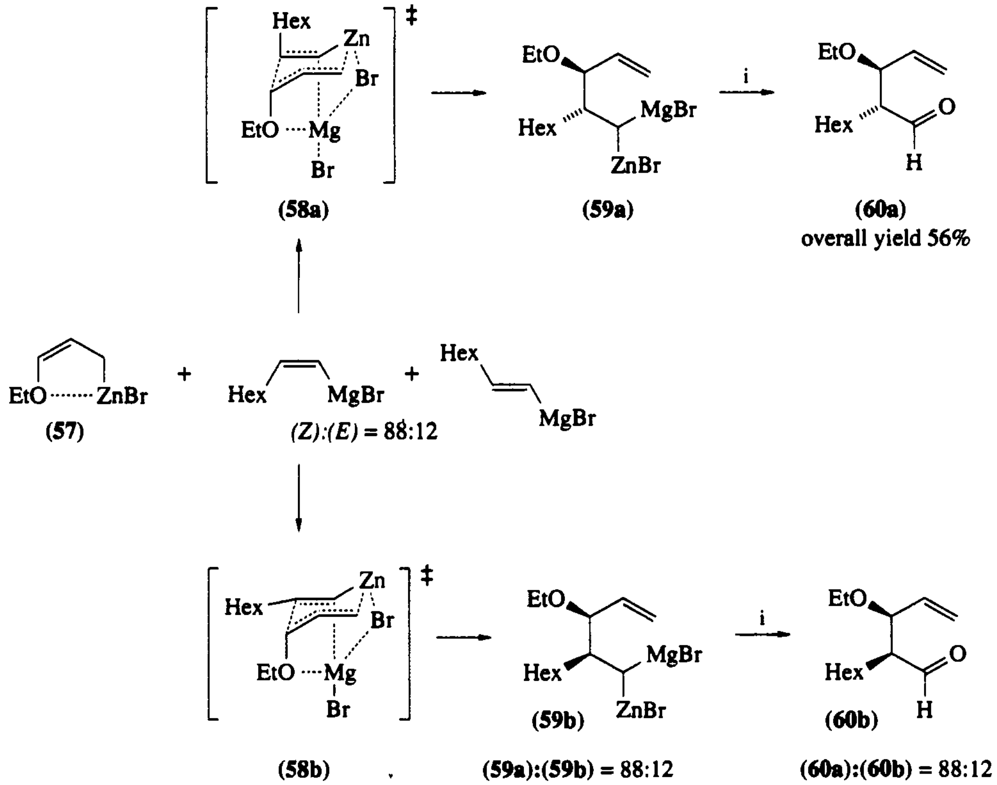
Hex
Zn
Br
EtO
Mg
Br
‡
(58a)
EtO
Hex
MgBr
ZnBr
(59a)
i
EtO
Hex
O
H
(60a)
overall yield 56%
EtO
ZnBr
(57)
+
Hex
MgBr
(Z):(E) = 88:12
+
Hex
MgBr
Hex
Zn
Br
EtO
Mg
Br
‡
(58b)
EtO
Hex
MgBr
ZnBr
(59b)
i
EtO
Hex
O
H
(60b)
(59a):(59b) = 88:12
(60a):(60b) = 88:12

i, Me$_3$SnCl (1 equiv.), –40 to 0 °C, air (–15 °C, 6 h)

**Scheme 32**

The reactivity of the 1,1-diorganometallics (**61**) has been extensively investigated by Knochel and coworkers.[92,93] Since the reactivity of a carbon–lithium or a carbon–magnesium bond is considerably different from that of a carbon–zinc bond, a selective reaction of (**61**) with two different electrophiles is often possible. The general reaction pathways are summarized in Scheme 33. The addition of allylic zinc

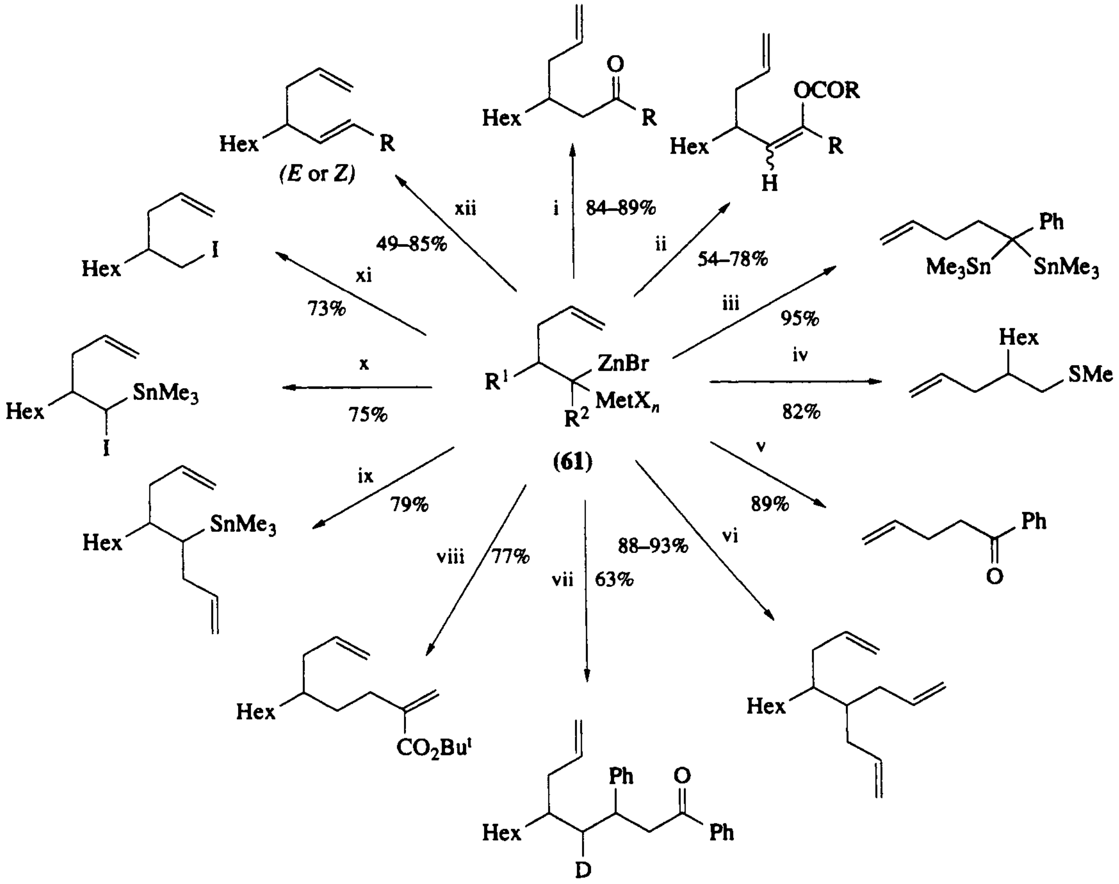

i, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = Li, Pr$^i$OH (1.01 equiv.), –70 to –30 °C, RCOCl (2.5 equiv.), $[Pd(PPh_3)_4]$ (0.05 equiv.), 0 °C, 0.5–2 h; ii, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = MgBr; CuCN (1 equiv.), –35 °C, 0.25 h, RCOCl (3 equiv.), –10 °C, 2 h; iii, $R^1$ = H, $R^2$ = Ph, $MetX_n$ = MgBr; CuCN (1 equiv.), –20 °C, 0.5 h, then $Me_3SnCl$ (2 equiv.), –40 to 0 °C; iv, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = MgBr; MeSSMe, –40 to 25 °C, then AcOH; v, $R^1$ = H, $R^2$ = Ph, $MetX_n$ = MgBr; $Me_3SnCl$ (1 equiv.), –40 to 0 °C, 0.3 h, then dry air, –10 to 0 °C, 0.5 h; vi, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = MgBr or Li; CuCN (1 equiv.), –35 °C, 0.25 h, then allyl bromide (excess), –40 to 0 °C, 0.5 h; vii, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = Li; benzylideneacetophenone (1.0 equiv.), –78 to 0 °C, 1 h, $D_3O^+$; viii, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = Li; MeOH (1 equiv.), –78 to 30 °C, then CuCN (1 equiv.), –40 °C, 0.5 h, *t*-butyl bromomethylacrylate, –78 to 0 °C, 0.5 h; ix, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = Li; $Me_3SnCl$ (1 equiv.), –40 to 0 °C, 0.5 h, CuCN (1 equiv.), –30 °C, 0.5 h, allyl bromide (3.0 equiv.), –30 to –10 °C, 0.5 h; x, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = MgBr; $Me_3SnCl$ (1 equiv.), –25 to 0 °C, 0.5 h, $I_2$ (1 equiv.), –78 °C, 0.5 h; xi, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = Li, MeOH (1.05 equiv.), –70 to –30 °C, then $I_2$ (1 equiv.), –78 to –40 °C, 0.1 h; xii, $R^1$ = Hex, $R^2$ = H, $MetX_n$ = MgBr, $BF_3{\bullet}OEt_2$ (1 equiv.), –90 °C, RCHO, –90 to –50 °C, 0.25 h (formation of the *E*-isomer in over 90% selectivity), or $RCH{=}C(CO_2Et)_2$, –78 °C, 0.5 h (formation of the *Z*-isomer in over 84% selectivity; R = alkyl)

**Scheme 33**

bromides to α,β-unsaturated esters proceeds, in the presence of $[NiBr_2(PPh_3)_2]$, with moderate regioselectivity.[95]

### 4.4.4.3 The Carbozincation of Alkynes

#### *4.4.4.3.1 Addition to nonfunctionalized alkynes*

Gaudemar[86,90,91,96] found that allylic zinc bromides readily add to terminal alkynes. The first step in these reactions is always the deprotonation of the alkyne, leading to an alkynylzinc bromide (**62**), which subsequently adds the allylic zinc bromide, leading to vinylic 1,1-diorganometallics of type (**63**). Depending on the reaction conditions and on the substitution pattern of the allylic zinc reagent, a further carbozincation can occur, leading to 1,1,1-triorganometallics of type (**64**). The deuterolysis of (**64**) affords trideuterated dienes of type (**65**; Scheme 34). Miginiac and coworkers[86,97] showed that these additions are reversible, so that the amount of the thermodynamically more stable adduct (**66**) can be increased by longer reaction times (equation 21). Whereas disubstituted nonfunctionalized alkynes do not react, an intramolecular allylzincation reaction[98] is possible and affords, after hydrolysis, the *syn* addition product (**67**) stereospecifically (Scheme 35).

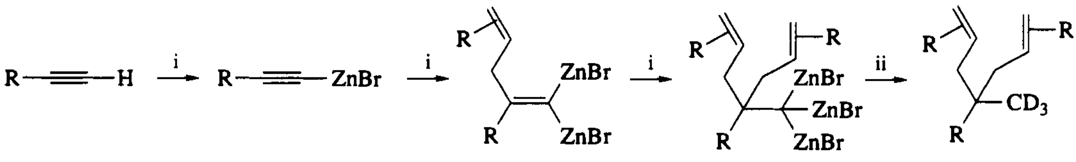

**(62)** **(63)** **(64)** **(65)**

i, allyl zinc bromide, THF; ii, $D_2O$

**Scheme 34**

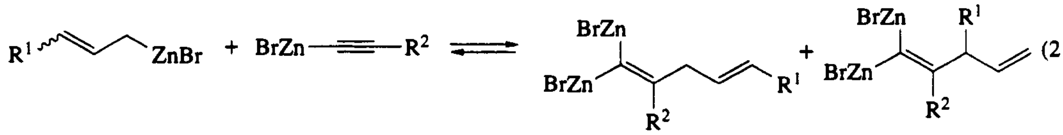

(21)

**(66)**

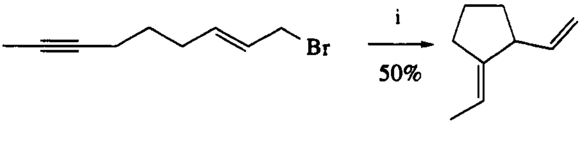

**(67)**

i, Zn, THF, 24 h, 65 °C, then $H_3O^+$

**Scheme 35**

Although several less reactive organozinc derivatives add to alkynes, the scope of these reactions is more limited. Di-*t*-butylzinc, for example, adds only to phenylacetylene, affording the *anti* addition product, (*Z*)-3,3-dimethyl-1-phenylbutene.[99] More interestingly, zinc malonates of type (**68**) add to various alkynes[100] in fair yields to give derivatives of type (**69**; Scheme 36). Propargylic zinc bromides[101] add to terminal alkynes and afford 1,4-enynes in good yields (equation 22). Negishi and coworkers[5,102] showed that dialkylzinc reagents, in the presence of $I_2ZrCp_2$, add to terminal and internal alkynes in good yields to furnish the *syn* adducts with good regioselectivity (70–90%) and very high stereoselectivity (>98%). The reaction seems to involve a direct addition of the carbon–zinc bond across the alkyne (equation 23).

The zirconium-promoted addition of diethylzinc to an alkynylzinc derivative is also possible,[102,103] and allows for several interesting synthetic applications (Scheme 37).[104]

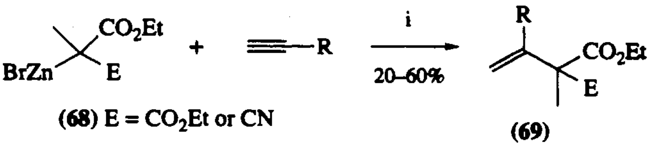

(68) E = CO$_2$Et or CN

(69)

i, THF, 4–24 h, 42 °C, then H$_2$O

Scheme 36

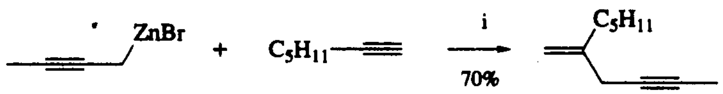

(22)

i, THF, 24 h, 30 °C, then H$_3$O$^+$

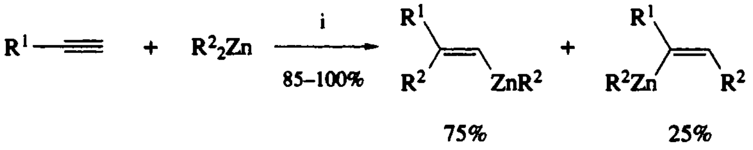

(23)

i, I$_2$ZrCp$_2$ (0.1 to 1 equiv.), ClCH$_2$CH$_2$Cl, 20 °C, 3–48 h

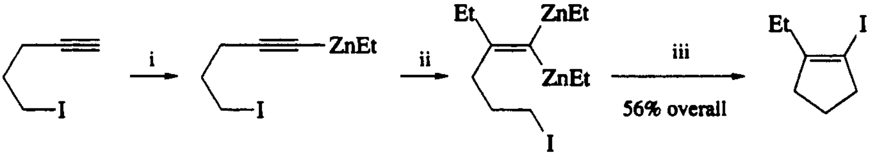

i, BuLi, then EtZnCl, CH$_2$Cl$_2$; ii, Et$_2$Zn, I$_2$ZrCp$_2$; iii, evaporation, then THF and I$_2$

Scheme 37

#### *4.4.4.3.2 Addition to functionalized alkynes*

A number of functionalized alkynes containing halides or hydroxy, alkoxy and amino groups react with allylic[80,90,96,97,105] and propargylic zinc halides,[101,106] zinc malonates,[100] and di-*t*-butylzinc.[99] The presence of a functional group in the alkyne allows new synthetic possibilities, such as cyclization reactions leading to the highly functionalized cyclopropanes (**70**)[101,106] and (**71**)[101,106] or to the unsaturated lactone (**72**; Scheme 38).[100] The addition of zinc organometallics to enynes has also been extensively studied by Miginiac and coworkers.[15] The *syn* addition of allylic zinc bromides to 1-trimethylsilylalkynes has been reported by Molander,[107] Negishi,[107] Klumpp[108] and coworkers and has led to several new cyclization reactions (Scheme 39).[103,104,107b,108]

## 4.4.5 THE CARBOBORATION REACTION

### 4.4.5.1 General Considerations

Trialkylboranes generally show a low reactivity toward addition to alkenes and alkynes. Only triallylboranes react with alkynes under mild conditions. This reaction is often complicated by further intramolecular carboboration reactions and has found only limited synthetic application.

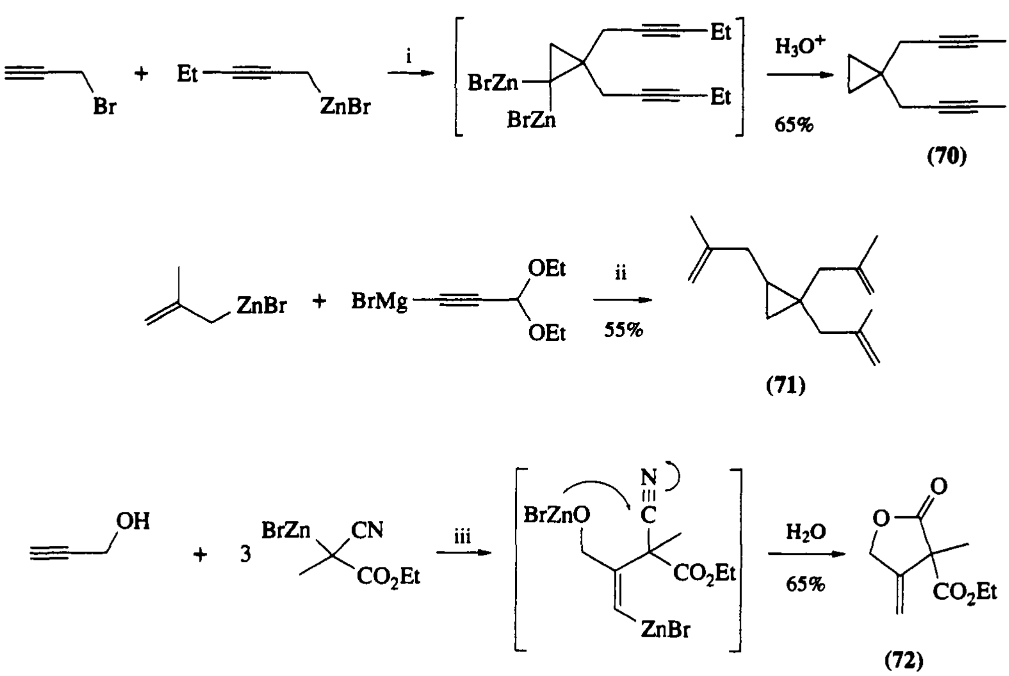
Br
Et
ZnBr
i
BrZn
BrZn
Et
Et
H3O+
65%
Et
Et
ZnBr
BrMg
OEt
OEt
ii
55%
OH
3
BrZn
CN
CO2Et
iii
BrZnO
N
C
CO2Et
ZnBr
H2O
65%
O
O
CO2Et

(70)

(71)

(72)

i, 40 °C, 24 h, THF; ii, 65 °C, 1.5 h, THF; iii, 42 °C, 23 h, THF

Scheme 38

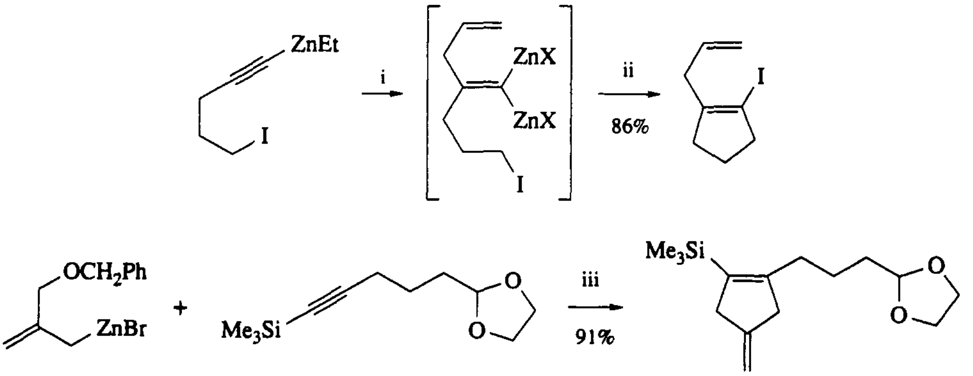
ZnEt
I
i
ZnX
ZnX
I
ii
86%
I
OCH2Ph
ZnBr
Me3Si
O
O
iii
91%
Me3Si
O
O

i, allylzinc bromide, THF; ii, cyclization, then $I_2$; iii, 100 °C, 30 h, then $[Pd(PPh_3)_4]$ (10 mol %), 24 h, 65 °C

Scheme 39

### 4.4.5.2 The Carboboration of Alkenes

As has been shown by Köster,[109] trialkylboranes react with alkenes and dienes at high temperatures (>140 °C) to give hydroboration adducts by a dehydroboration/hydroboration mechanism. It is only under special reaction conditions that carboboration reactions can be observed. Triethylborane adds slowly to 1-decene at 160–170 °C to give diethyl(2-ethyldecyl)borane.[109] In the presence of trialkylaluminum, trialkylboranes react with ethylene at 150–170 °C.[110] Under irradiation, trialkylboranes give a formal *syn* addition to cycloalkenes.[111] The highly strained *trans*-cyclohexenes (**73**) have been assumed to be the reactive intermediates in this reaction (Scheme 40). The more reactive triallylboranes add at 120–140 °C to alkyl enol ethers.[113] The reaction with 2-methyl-4,5-dihydrotetrahydrofuran (**74**) proceeds readily at 80 °C and affords, after hydrolysis, (*E*)-4-methylhepta-1,4-dien-1-ol (**75**) stereospecifically (Scheme 41). Strained alkenes like 1-methylcyclopropene react readily with trialkylboranes in two ways:[114] *syn* addition of the organoborane leading to the cyclopropylborane (**76**; the predominant mode of reaction), and cleavage of the C(2)—C(3) bond of the cyclopropene ring leading to the allylic borane (**77**; equation 24). Triallylboranes also react with allenes at high temperatures.[115]

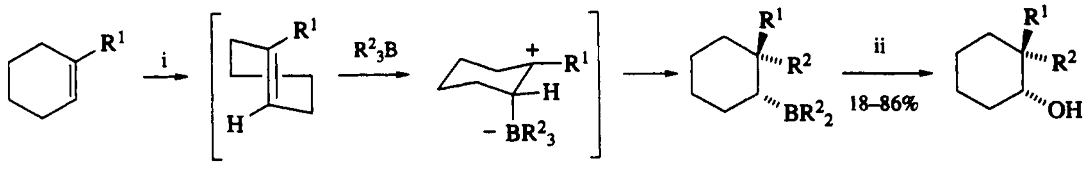

(73)

$R^1$ = H, Et; $R^2$ = alkyl
i, *h*ν, xylene, benzene; ii, $H_2O_2$

Scheme 40

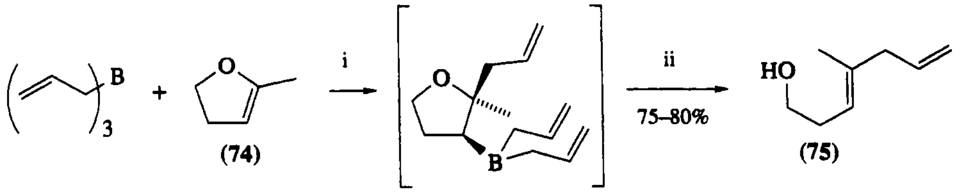

(74) (75)

i, 80–100 °C, 5–10 min; ii, $OH^-$

Scheme 41

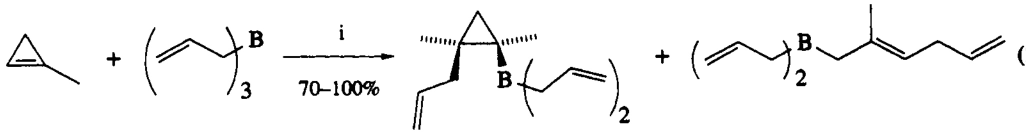

(24)

(76) 50–60% (77) 20–40%

i, –70 to 0 °C, heat

### 4.4.5.3 The Carboboration of Alkynes

Like alkenes, alkynes do not react readily with trialkylboranes. Under severe reaction conditions, only hydroboration products are obtained.[116] Mikhailov[115] showed that triallylboranes react with various alkynes (20 °C) to afford *syn* addition products of type (**78**) which rapidly cyclize (40–60 °C) to give the cyclic boranes of type (**79**; Scheme 42). In the case of trimethylsilylacetylene and ethoxyacetylene, the reaction affords compounds of type (**78**; R = $Me_3Si$ or OEt) which do not cyclize further.[115] Recently, a transition metal silylboration reaction has been described by Oshima and coworkers.[117] A formal *syn* carboboration reaction leading to a variety of alkenylboranes has been reported by Suzuki and coworkers[118] (Scheme 43). Hexamethyldistannylacetylene (**80**) reacts readily with various trialkylboranes[119] to afford *syn* addition products of type (**81**; equation 25).

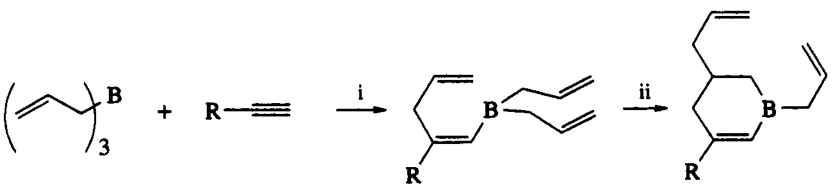

(78) (79)

i, 20 °C; ii, 40–60 °C

Scheme 42

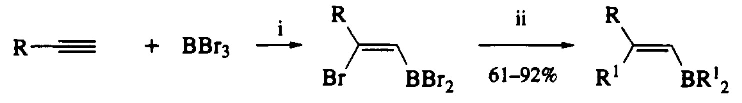

i, CH$_2$Cl$_2$, –78 to 25 °C, 30 min; ii, [PdCl$_2$(PPh$_3$)$_2$] ( 5 mol %), 3 equiv. R$^1$ZnCl

**Scheme 43**

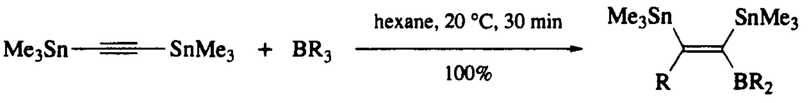

(25)

**(80)** **(81)**

## 4.4.6 THE CARBOALUMINATION REACTION

### 4.4.6.1 General Considerations

The uncatalyzed carboalumination[120] of nonfunctionalized alkenes and alkynes occurs generally under quite severe conditions. The reaction is of limited synthetic interest because of the low regioselectivity observed and the numerous side reactions, such as polymerization, oligomerization and dehydroalumination, which can occur. The intramolecular carboalumination of alkenes is easier and good stereoselectivities may be observed. Transition metal catalyzed carboalumination of alkynes is far more useful. These reactions occur under mild conditions, are highly regioselective and stereoselective (*syn* addition), and represent a powerful synthetic tool, especially the zirconium-catalyzed methylalumination reaction.

### 4.4.6.2 The Carboalumination of Alkenes

The reaction of organoaluminum compounds with alkenes was discovered and studied in great detail by Ziegler and coworkers.[121,122] Triethylaluminum adds to ethylene to give a Poisson distribution[122] of oligomeric trialkylaluminum organometallics (equation 26). A stepwise carboalumination reaction is not possible, and a clean synthesis of defined oligomers cannot be achieved by this method. However, with substituted alkenes, only monoaddition occurs. Carboaluminations of 1-alkenes are regioselective, and the new carbon–carbon bond is formed in 90–95% at the 2-position.[123] Secondary trialkylaluminum derivatives are very reactive toward addition to double bonds, but show a low regioselectivity.[12] Tertiary aluminum organometallics are even more reactive, and, in this case, a selective monoaddition is observed (equation 27).[124] The addition of triphenylaluminum to conjugated dienes, styrenes and strained alkenes occurs more readily.[125] More synthetically useful is the intramolecular carboalumination of 1,5-dienes, which allows a high yield preparation of bicyclic systems[126,127] of type (**82**) or (**83**) under mild conditions. The dehydroalumination of (**83**) in the presence of ethylene affords the diene (**84**) in 90% overall yield (Scheme 44).[126] Since the elimination of Et$_2$AlH occurs at similar temperatures as the carboalumination step, a catalytic amount of this hydride can be used to promote cyclization reactions (equation 28).[128] Donor solvents like ether can prevent intramolecular carboaluminations,[129] although exceptions[130] are known. The presence of ether also may prevent the formation of dehydroalumination products.[130b] If substituted 1,5-dienes are used, a very high diastereoselectivity is observed in the ring closure (Scheme 45).[131]

$$\mathrm{Et_3Al} + 3n\,\mathrm{H_2C{=}CH_2} \longrightarrow [\mathrm{Et(CH_2CH_2)}_n]_3\mathrm{Al} \qquad (26)$$

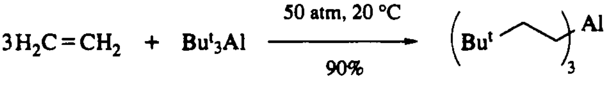

(27)

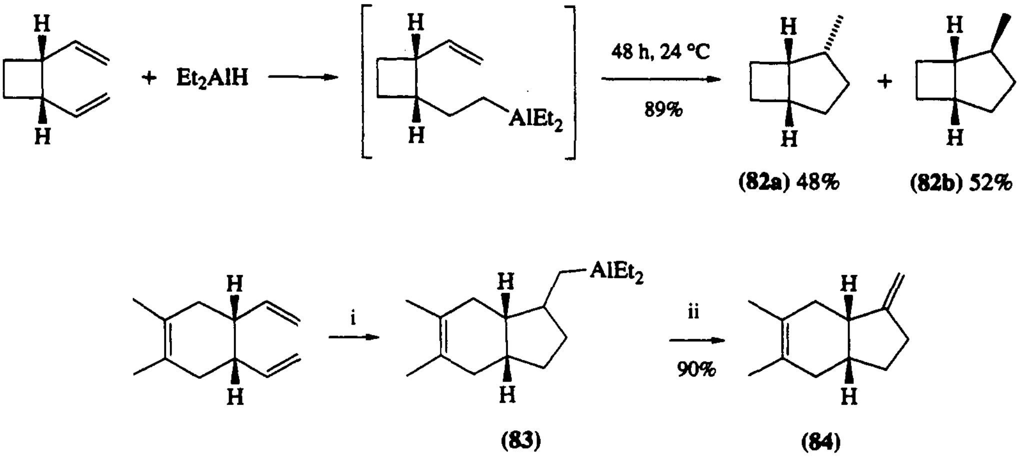

(82a) 48% (82b) 52%

(83) (84)

i, $Et_2AlH$, benzene, 24 h, heat; ii, ethylene, 70 atm, 18 h, 50 °C

Scheme 44

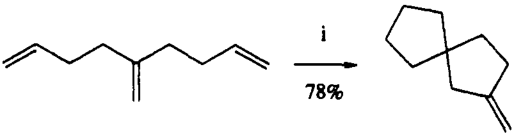

(28)

i, $Bu^i{}_2AlH$, mineral oil, 110 °C, 48 h

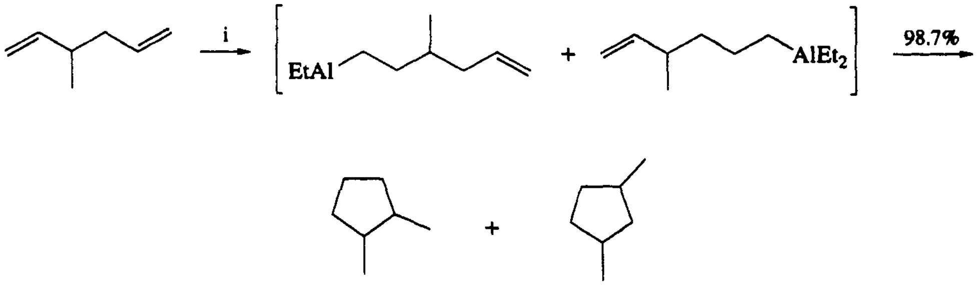

53.1% 45.6%
*cis:trans* = 2.3:97.7 *cis:trans* = 91.1:8.9

i, $Et_2AlH$, toluene, 24 h, 25 °C

Scheme 45

### 4.4.6.3 The Carboalumination of Alkynes

#### *4.4.6.3.1 Addition to nonfunctionalized alkynes*

Acetylene[132] itself reacts readily with trialkylaluminum compounds and affords the *syn* addition products in good yields and under mild conditions (20 to 60 °C compared to 150 °C if ethylene is the substrate; see equation 29). The reaction with higher alkynes[133] is more complex. The metallation of the alkyne leading to an alkynylaluminum organometallic of type (**85**) is the major pathway. The reaction shows a low regioselectivity, and a mixture of the two regioisomers (**86**) and (**87**) is generally obtained (equation 30). Thus, the addition of triethylaluminum to phenylacetylene affords a 1:1 mixture of the two possible regioisomers.[133] If an excess of alkyne is used, then the corresponding alkynylaluminum derivative (**85**) can be obtained in excellent yields.[123] Interestingly, the carboalumination reaction proceeds with retention of the configuration of the alkyl group (equation 31).[134] Disubstituted alkynes react only at temperatures higher than 80 °C, where the adducts of type (**86**) and (**87**) are no longer stable and give further reactions.[132,134] Only diphenylacetylene gives a clean *syn* addition (equation 32). The reaction conditions required for the addition to disubstituted alkynes are sufficiently severe for the alkenylaluminum reagent (**88**) to add again to the starting alkyne, leading to the dienylalane (**89**). The organometallics of type (**89**) can be further elaborated into stereodefined 1,3-dienes (Scheme 46).[137]

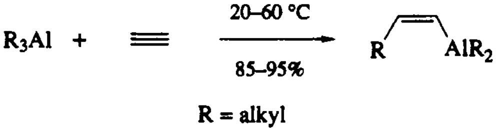
R3Al +
20–60 °C
85–95%
R
AlR2
R = alkyl

(29)

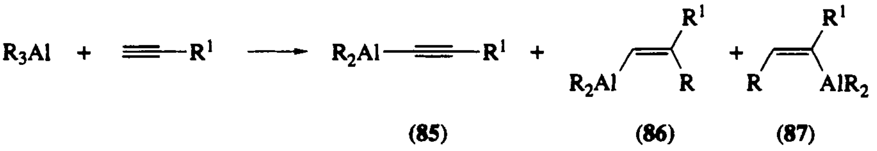
R3Al +
R1
R2Al
R1 +
R1
R2Al
R
+
R1
R
AlR2
(85)
(86)
(87)

(30)

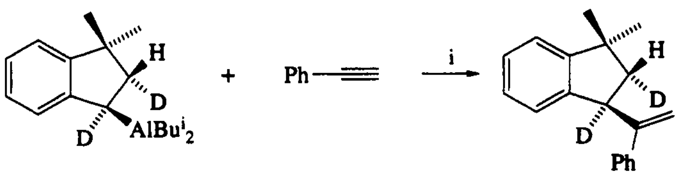
H
D
D
AlBui2
+ Ph
i
H
D
D
Ph

(31)

i, $Et_2O$, 110 °C, several days, then $H_3O^+$

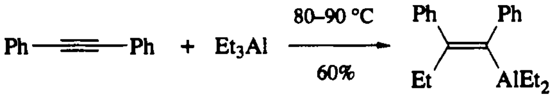
Ph
Ph + Et3Al
80–90 °C
60%
Ph
Ph
Et
AlEt2

(32)

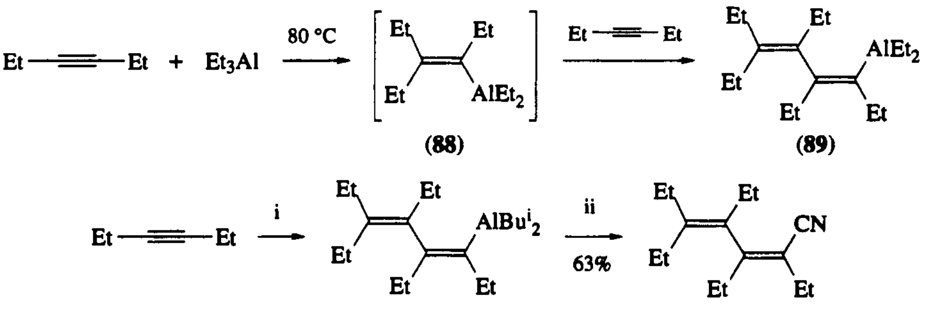
Et
Et + Et3Al
80 °C
Et
Et
Et
AlEt2
(88)
Et
Et
Et
Et
AlEt2
Et
Et
Et
(89)
Et
Et
i
Et
Et
AlBui2
Et
Et
Et
ii
63%
Et
Et
CN
Et
Et
Et

i, $Bu^i{}_2AlH$, 3-hexyne, 70 °C; ii, MeLi, –78 °C, then $(CN)_2$, then $H_3O^+$

**Scheme 46**

The low chemo- and regio-selectivity of the carboalumination reaction can be dramatically improved by the use of transition metal catalysts. Negishi and coworkers[135] showed that $Me_3Al—Cl_2TiCp_2$ reacts with diphenylacetylene to give a single organometallic species (**90**) which, after hydrolysis or iodolysis, affords, respectively, (*Z*)-1,2-diphenylpropene and (*E*)-1-iodo-1,2-diphenylpropene (Scheme 47). The scope of this reaction is limited, and the use of other alkynes leads to the formation of side products[135,136] due to the high reactivity of the Al–Ti reagent. The corresponding Al–Zr reagent ($Me_3Al—Cl_2ZrCp_2$) has been shown by Negishi to have much better synthetic utility. The reaction of phenylacetylene with $Me_3Al—Cl_2ZrCp_2$ gives 2-phenylpropene (**91**) and (*E*)-1-phenylpropene (**92**) in a 96:4 ratio and a 98% overall yield (Scheme 48). The reaction can be performed in the presence of only a catalytic amount of $Cl_2ZrCp_2$ (10 mol %), but the reaction then proceeds at a slower rate and a slight yield decrease is observed.[136] A wide range of alkynes containing alkyl, aryl, conjugated alkenyl or isolated alkenyl groups give the methylalumination products in excellent yields. The regioselectivity observed with terminal alkynes is always better than 96% and the *syn* stereoselectivity is always higher than 98%.[136] Internal alkynes such as 5-decyne give a relatively smooth carboalumination with $Me_3Al$—$Cl_2ZrCp_2$ and furnish *syn* addition products in good yields (equation 33).[136]

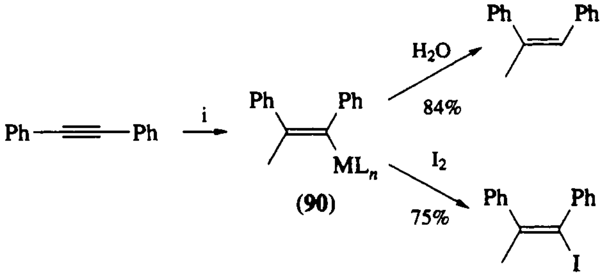

i, $Me_3Al$–$Cl_2TiCp_2$, $ClCH_2CH_2Cl$, 20 to 25 °C
$ML_n$ = $-Ti(Cp)_2Cl$ or $-AlMe_2$

Scheme 47

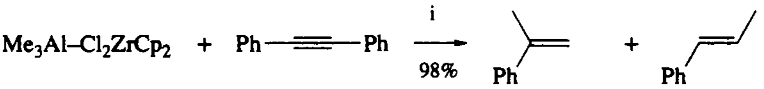

(91) (92)

i, $Me_3Al$ (2 equiv.), $Cl_2ZrCp_2$ (1 equiv.), 20–25 °C, 24 h, then $H_3O^+$

Scheme 48

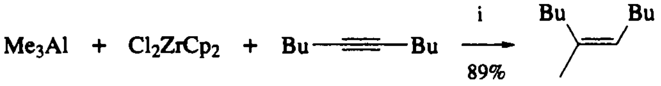 (33)

i, $ClCH_2CH_2Cl$, 60 °C, 6 h, then $H_3O^+$

Higher homolog organoaluminum reagents can also carboaluminate alkynes, but the reaction is less regioselective, and the reagent $R_2AlCl$ has to be used instead of $R_3Al$ in order to avoid competitive hydrometallations (equation 34). The mechanism of the reaction has been carefully studied by Negishi and coworkers.[136] All data are consistent with a zirconium-assisted carboalumination reaction in which an intermediate of type (93) is involved (Scheme 49). The Lewis acid–base interactions between the aluminum and the zirconium reagent enhance the carbometallation ability of (93) and favor the addition to the alkyne. The following facts support this mechanism: the reaction of a 1:1 mixture of $Et_3Al$ and $Cl(Me)ZrCp_2$ with 1-heptyne affords, after hydrolysis, only ethylalumination products. No methylalumination products were detected. Also, the reaction of 1-heptyne with $CD_3(Cl)ZrCp_2$ and $Me_3Al$ affords, after iodolysis, only nondeuterated products (less than 4% of deuterium incorporation; see equation 35). An aluminum-assisted carbozirconation has also been observed by Negishi and coworkers.[138] The reaction of $Cl(Me)ZrCp_2$ with 1-pentynyldimethylalane (94) gives the mixed vinylic 1,1-diorganometallic of zirconium and aluminum (95) which, after iodolysis, affords a 1,1-diiodoalkene in good yield (Scheme 50).

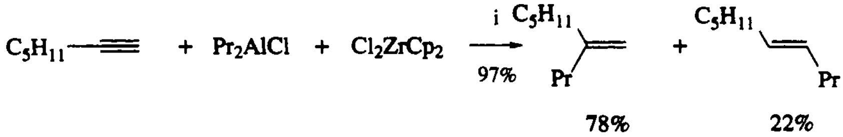 (34)

i, $ClCH_2CH_2Cl$, r.t., 20 h, then $H_3O^+$

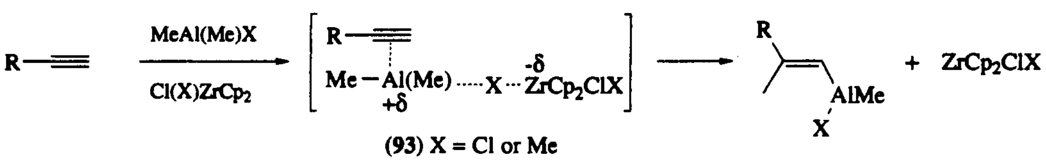
MeAl(Me)X
Cl(X)ZrCp2
R
Me – Al(Me) ..... X ··· ZrCp2ClX
+δ
-δ
AlMe
X
+ ZrCp2ClX

(**93**) X = Cl or Me

**Scheme 49**

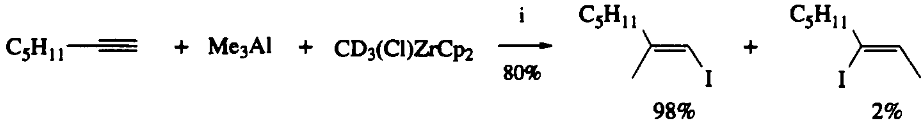
C5H11
+ Me3Al + CD3(Cl)ZrCp2
i
80%
I
98%
2%

(35)

i, $ClCH_2CH_2Cl$, 25 °C, 6 h, then –10 °C, $I_2$

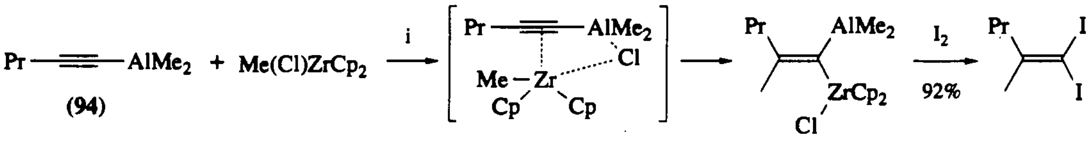
Pr
AlMe2
+ Me(Cl)ZrCp2
i
Me – Zr
Cl
Cp
Cp
ZrCp2
Cl
I2
92%
I

(**94**)

i, $CH_2Cl_2$, 25 °C, 3 h

**Scheme 50**

Allylalanes and benzylalanes[139] also react with terminal and internal alkynes in the presence of $Cl_2ZrCp_2$ to produce *syn* allylation products (>98% *syn* addition) with a moderate regioselectivity (equation 36). Interestingly, in the case of substituted allylic alanes, the addition product (**96**), formed without allylic rearrangement *via* a four-membered transition state, is obtained as the major isomer. This is in contrast with most allylmetallations, which afford the allylic rearrangement regioisomer of type (**97**)[107b] *via* a six-membered transition state (Scheme 51).

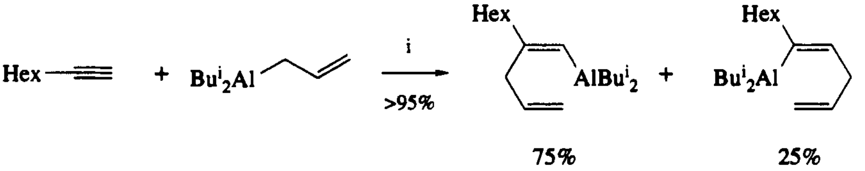
Hex
+ Bu^i2Al
i
>95%
AlBu^i2
Bu^i2Al
75%
25%

(36)

i, $Cl_2ZrCp_2$ (1 equiv.), $ClCH_2CH_2Cl$, 25 °C, 1–2 h

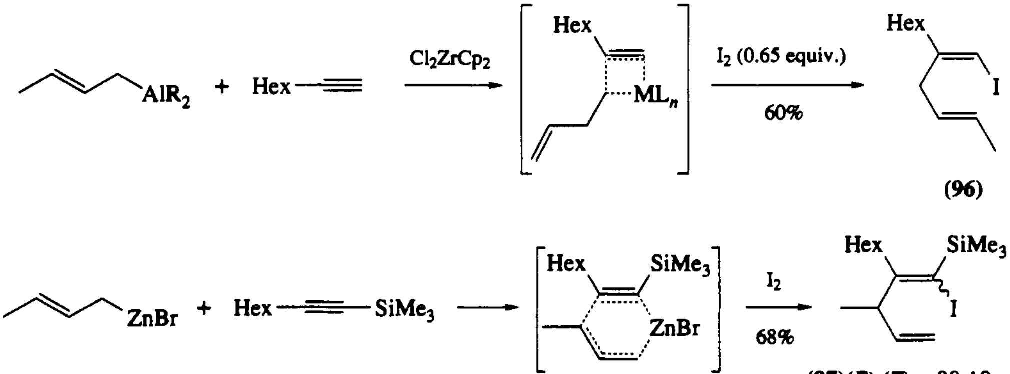
AlR2
+ Hex
Cl2ZrCp2
Hex
MLn
I2 (0.65 equiv.)
60%
I
ZnBr
+ Hex
SiMe3
SiMe3
ZnBr
I2
68%
I

(**96**)

(**97**)(*E*):(*Z*) = 90:10

**Scheme 51**

### *4.4.6.3.2 Addition to functionalized alkynes*

The zirconium-catalyzed carboalumination[140] reaction can tolerate various functional groups such as hydroxy, OTBDMS, SPh, halogens, alkenes and arenes. The addition of $Me_3Al$ to phenyl propynyl sulfide[141] affords the *syn* addition product with excellent regio- and stereo-selectivity (equation 37). The addition to alkynols in the presence of $Cl_2TiCp_2$ proceeds in good yields with moderate regioselectivity. However, the dimethylaluminum alkoxide of 3-hexyn-1-ol undergoes a regio- and stereo-specific carbotitanation reaction and leads to the *syn* adduct (**98** Scheme 52). The addition of various organoaluminum compounds to alkynylsilanes in the presence of titanium or zirconium complexes gives mainly the *syn* carboalumination products (equation 38).[136,144] A high yield regiospecific dialkylmagnesium-promoted carboalumination of alkynylsilanes has been reported by Oshima and coworkers.[143] It was found that alkynylsilanes furnish mainly the *syn* addition product. Negishi and coworkers demonstrated that the vinylic 1,1-diorganometallics obtained by carbometallation can participate in various cyclization reactions.[104] The zirconium-catalyzed methylalumination of 4-haloalkynylsilanes gives cyclobutene derivatives in excellent yields (Scheme 53). Although three- and six-membered rings are formed by the same method, five-membered rings cannot be prepared directly.[104,145] An intramolecular carboalumination reaction of alkynylsilanes can also be used to produce five- and six-membered rings.[104,146] Although the

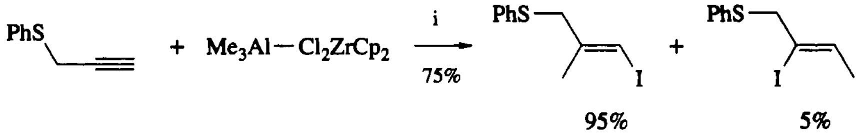
PhS
+ Me3Al—Cl2ZrCp2
i
75%
PhS
I
+
PhS
I
95%
5%

(37)

i, $ClCH_2CH_2Cl$, 25 °C, 3 h

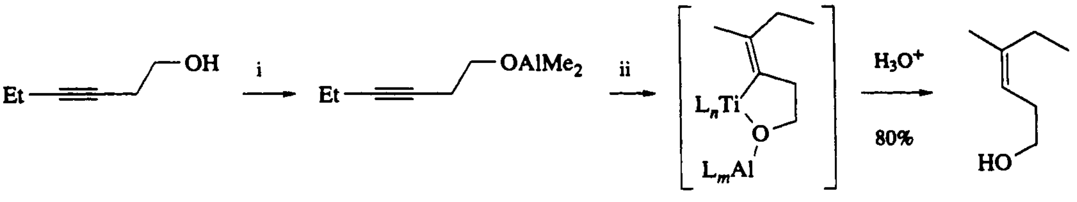
Et
OH
i
Et
OAlMe2
ii
LnTi
O
LmAl
H3O+
80%
HO

**(98)**

i, $Me_3Al$, $CH_2Cl_2$, 0 to 25 °C; ii, $TiCl_4$, –78 °C, 6 h

Scheme 52

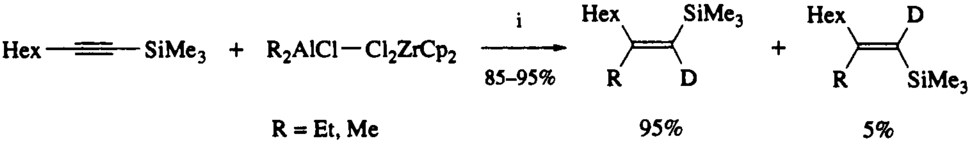
Hex
SiMe3
+ R2AlCl—Cl2ZrCp2
i
85–95%
Hex
SiMe3
R
D
+
Hex
D
R
SiMe3
R = Et, Me
95%
5%

(38)

i, $CH_2Cl_2$, 25 °C, 2 h, then $D_2O$/NaOD

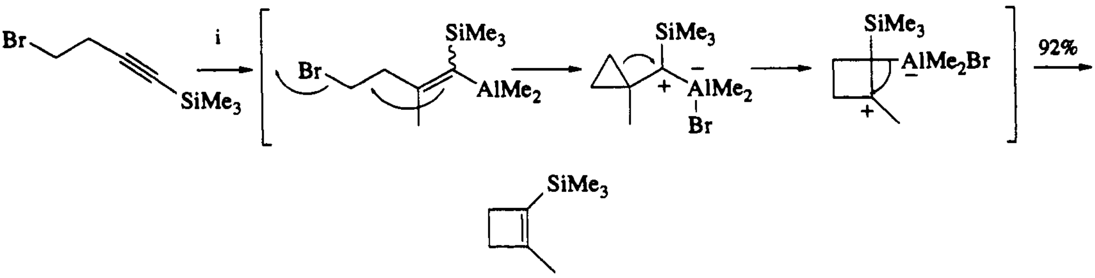
Br
SiMe3
i
SiMe3
Br
AlMe2
SiMe3
AlMe2
Br
SiMe3
AlMe2Br
92%
SiMe3

i, $Me_3Al$, $Cl_2ZrCp_2$, $ClCH_2CH_2Cl$, 25 °C, 6 h

Scheme 53

carboalumination of nonfunctionalized alkynylsilanes does not produce stereoisomerically pure α-silylalkenylalanes of type (**99**; Scheme 54), since these are configurationally unstable,[147] it is possible to achieve a highly stereoselective chelation-controlled cyclization by using the α-hydroxyalkynylsilane (**100**) as a substrate.

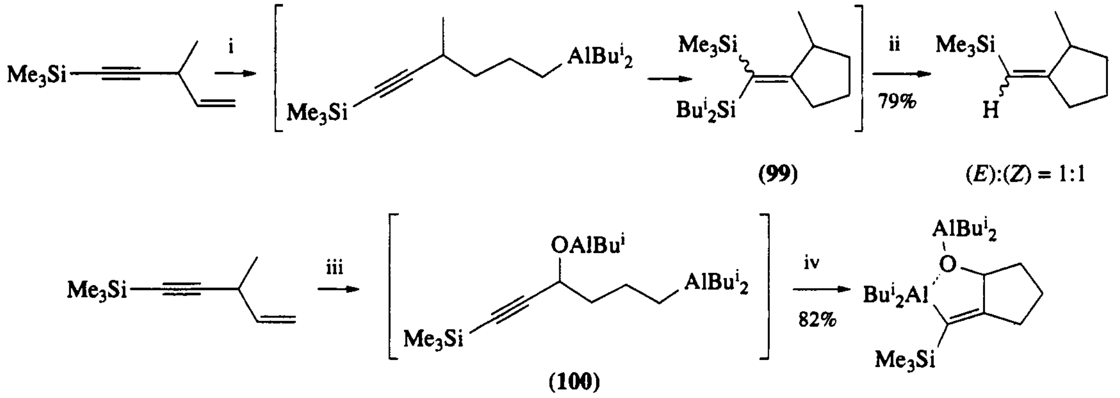

i, $Bu^i_3Al$, $Cl_2ZrCp_2$ (10 mol %), $CH_2Cl_2$, 0 °C, 2 h, then 25 °C, 18 h; ii, $H_3O^+$; iii, $Bu^i_3Al$, $ClCH_2CH_2Cl$, 0 to 25 °C; iv, $Cl_2ZrCp_2$ (5 mol %), 0 °C, 2 h, then 25 °C, 4 h

**Scheme 54**

### 4.4.6.4 Synthetic Applications of Alkenylaluminum Organometallics

As mentioned in the previous section, alkenylaluminum reagents of type (**101**) obtained by methylalumination are synthetically very useful reagents which react with a variety of electrophiles. The carbon–aluminum bond can be readily converted in good yields into carbon–hydrogen, –deuterium, –iodine, –mercury, –boron, –zirconium and –carbon bonds[107b,136,148] (Scheme 55). The initial reactivity pattern of organometallics (**101**) can be considerably increased by the transmetallation to more reactive derivatives, such as organozinc halides, which undergo a variety of cross-coupling reactions[136] in the presence of palladium(0) complexes. With other types of less reactive electrophiles the use of the corresponding alanates (**102**), prepared by the addition of one equivalent of an organolithium reagent to (**101**), is required and further expands their synthetic application (Scheme 56). Applications to the synthesis of a number of natural products such as geraniol,[149] farnesol,[150] monocyclofarnesol,[151] ocimene,[152] α-farnesene,[152] dendrolasin (**103**),[150] mokupalide (**104**),[150] vitamin A (**105**),[153] brassinolide,[154] milbemycin,[155] verrucarin[156] and zoapatanol[157] have been reported.

## 4.4.7 THE CARBOCUPRATION REACTION

### 4.4.7.1 General Considerations

The carbocupration[3,158,159] of isolated double bonds is generally not possible, but some strained alkenes, as well as conjugated 1,2- and 1,3-dienes, react with several organocopper reagents. The carbocupration of alkynes is certainly the most versatile carbometallation reaction. It proceeds with very high stereoselectivity and affords the *syn* addition product (>99.5% *syn*) regardless of the substrate used. The regioselectivity of the addition is usually very good, but may be complicated by the presence of heteroatoms at α- or β-positions to the triple bond. The scope of the reaction is very broad. Besides alkynyl- and, surprisingly, allyl-copper reagents, most organic groups can be added across alkynes by a carbocupration reaction. The best substrates are certainly primary alkylcopper derivatives; however, secondary, tertiary, alkenyl and even the less reactive methylcopper can undergo carbocuprations. The alkenylcopper reagents formed after carbocupration have found a wide range of applications. They have proven to be very useful intermediates for the synthesis of a variety of natural products.[3,158,159]

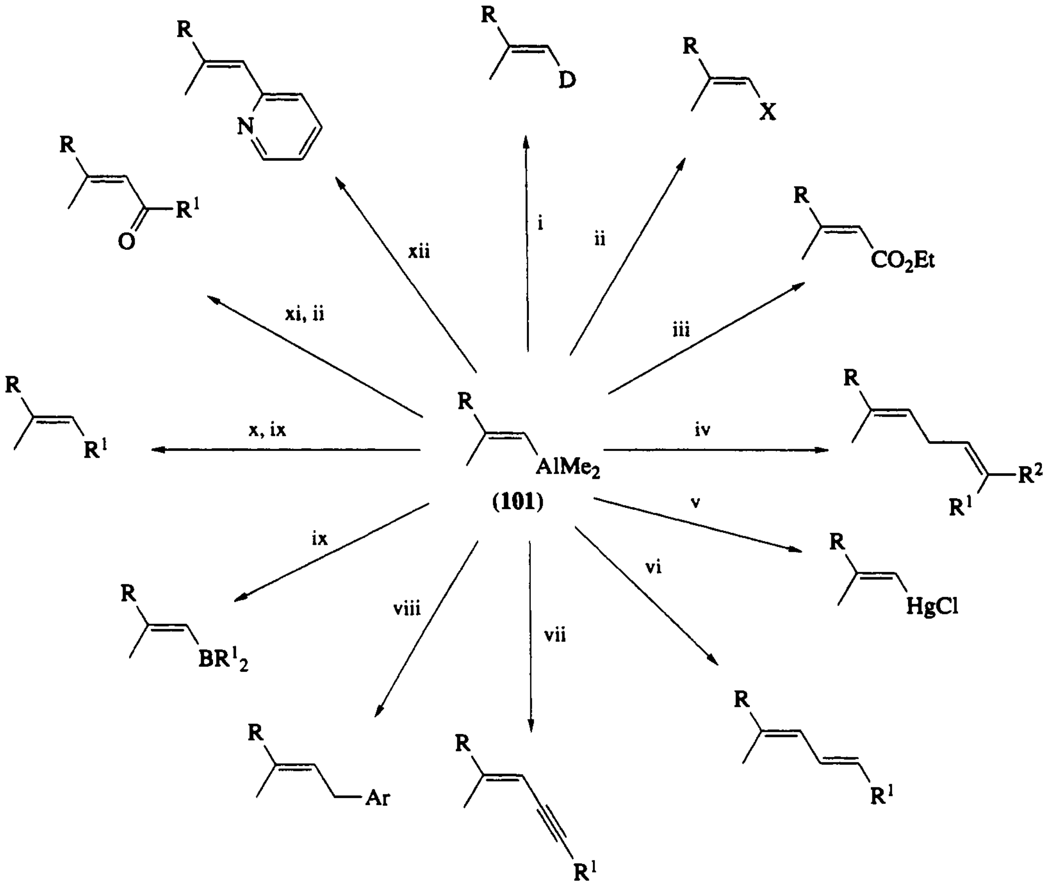
R
D
X
N
O
R1
CO2Et
xii
i
ii
xi, ii
iii
x, ix
iv
AlMe2
(101)
R2
v
HgCl
ix
vi
viii
vii
BR12
Ar

i, $D_3O^+$; ii, X = I, $I_2$; X = Br, NBS or $Br_2$; iii, $ClCO_2Et$; iv, allyl chloride or bromide, $[Pd(PPh_3)_4]$ (5 mol %), 0 to 25 °C, 3 h; v, $HgCl_2$ (1.5 equiv.), THF, 0 °C; vi, $[Pd(PPh_3)_4]$ (5 mol %), $ZnCl_2$, (I)BrCH=CHR$^1$, 20–25 °C; vii, $[Pd(PPh_3)_4]$ (5 mol %), $ZnCl_2$, $R^1{-}{\equiv}{-}I$, 20–25 °C; viii, $ArCH_2Cl$, $[Pd(PPh_3)_4]$ (3 mol %), THF, 25 °C, 3 h; ix, *B*-methoxy-9-borabicyclo[3.3.1]nonane, hexane, 25 °C, 1 h; x, $R^1Li$, THF, –78 °C, then $I_2$, –78 to 25 °C; xi, BuLi, –78 °C, then $ZnCl_2$, evaporation, THF, $Pd^0L_n$ (1 mol %), RCOCl (1.2 equiv.); xii, ArI, $[Pd(PPh_3)_4]$ (5 mol %), THF, 25 °C, 5 h

**Scheme 55**

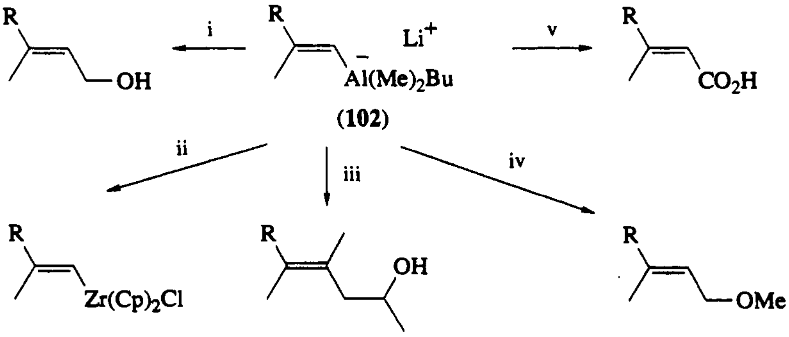
R
OH
i
Li+
Al(Me)2Bu
(102)
v
CO2H
ii
iii
iv
Zr(Cp)2Cl
OMe

i, $(CH_2O)_n$, THF, 25 °C, 3 h; ii, $Cl_2ZrCp_2$, –78 to 25 °C; iii, 1,2-epoxypropane, –30 °C; iv, $MeOCH_2Cl$, 0 °C, 2 h; v, $CO_2$, –30 to –10 °C

**Scheme 56**

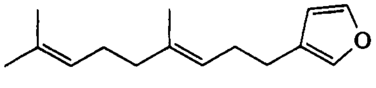

**(103)**

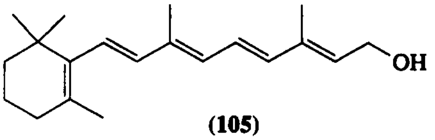

**(105)**

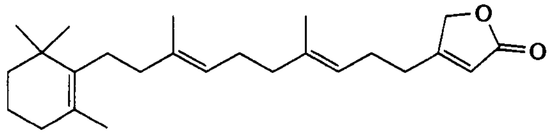

**(104)**

### 4.4.7.2 The Carbocupration of Alkenes, 1,2- and 1,3-Dienes

The addition of organocopper reagents to isolated double bonds does not occur readily and only some classes of transition metal–alkene complexes add copper organometallics in good yields (see Volume 4, Chapter 3.2).[160] Strained alkenes such as cyclopropenes are more prone to undergo addition reactions. The *in situ* generated cyclopropene derivative (**106**) adds PrCu·MgBr$_2$ at –25 °C and affords, after hydrolysis, the *syn* adduct (**107**) stereospecifically.[161] Functionalized cyclopropenes can also be used and the cyclopropene ketal (**108**) adds a wide range of organocopper reagents[162] in a *syn* fashion to afford stereodefined cyclopropylcopper derivatives of type (**109**), which can be trapped by various electrophiles with retention of configuration (Scheme 57).

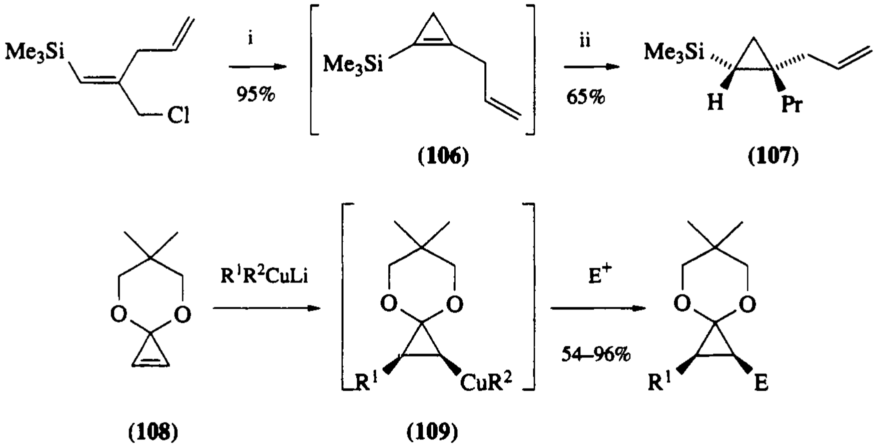

i, BuLi, Et$_2$O, –78 °C; ii, PrCuMgBr$_2$, Et$_2$O, –25 °C, 1–2 h, then H$_2$O

Scheme 57

It has been shown that magnesium organocopper and cuprate reagents[163] add to 1-methoxy-1,2-propadiene with low stereoselectivity. In strong contrast, Alexakis and Normant[164] showed that lithium organocopper and cuprate reagents allow a very high control of the newly formed double-bond stereochemistry. Thus, lithium diorganocuprates in ether furnish mostly the (*E*)-substituted enol ethers (**110**), whereas lithium organocopper reagents in THF afford the corresponding (*Z*)-substituted enol ethers (**111**; Scheme 58). The observed stereoselectivity has been explained by a delicate balance between chelate and steric effects. In a solvent of low basicity like ether, the organometallic reagent will complex with the methoxy group of 1-methoxy-1,2-propadiene and will lead to a transition state like (**112**). In the more basic solvent THF, only steric effects are important and the attack of the organocopper will come from the less-hindered side (*anti* to the methoxy group), leading to a transition state like (**113**).

Pulido and coworkers[165] showed that lithium bis(phenyldimethylsilyl)cuprate adds readily to 1,2-propadiene to afford allylic copper reagents, which react with various electrophiles, leading to functionalized alkenylsilanes (Scheme 59). Normant and coworkers[166] have shown that secondary and tertiary organocopper reagents (R$_2$CuMgBr) readily add to butadiene in HMPA/THF to afford regiospecifically the C-1 addition product (**114**). This allylic organometallic can be trapped in good yields with several

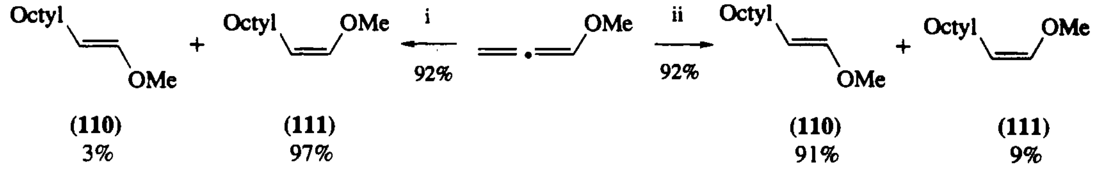

i, heptylCu, LiX, THF, –30 °C, then $H_2O$; ii, $heptyl_2CuLi$, $Et_2O$, –40 °C, 0.5 h, then $H_2O$

Scheme 58

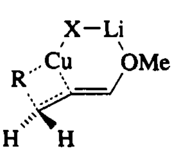

**(112)**

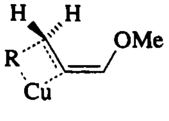

**(113)**

electrophiles (Scheme 60). The scope of the reaction seems to be limited, as primary copper reagents do not give an addition and 1-substituted dienes such as 1,3-pentadiene are inert.

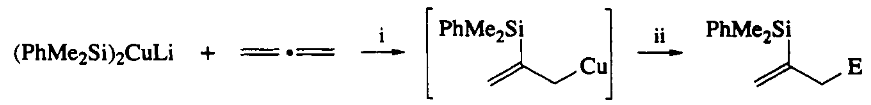

i, THF, –78 °C, 1 h; ii, $E^+$, –78 to 0 °C, 1 h

Scheme 59

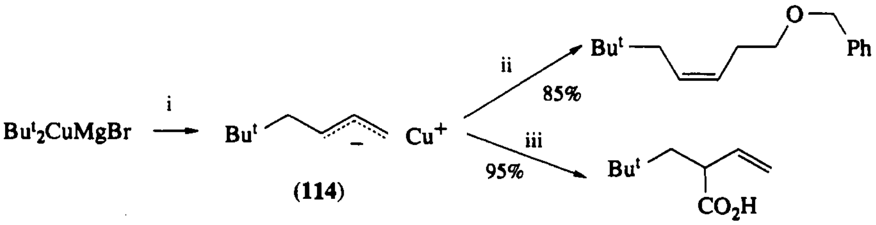

i, butadiene (excess), HMPA, THF, –15 °C; ii, $PhCH_2OCH_2Cl$; iii, $CO_2$

Scheme 60

### 4.4.7.3 The Carbocupration of Alkynes

#### *4.4.7.3.1 Addition to nonfunctionalized alkynes*

In 1971, Normant and Bourgain[167] discovered that organocopper reagents were able to add in a *syn* fashion, with almost complete stereoselectivity (>99.5%) and very high regioselectivity, to terminal alkynes and acetylene itself, leading to vinylcopper reagents of type (**115**; equation 39). The reaction was found to be quite general,[3] and of very high synthetic utility. Several organocopper or organocuprate reagents can be used, such as $RCu{\cdot}MgX_2$, $R_2CuMgX$, $R_2CuLi$ or $RCu{\cdot}(X)Li$ ($X = OBu^t$, SPh, CN), but for each reagent the choice of the reaction conditions (solvent, cosolvents, ligands) is critical for the success of the reaction. Acetylene is the most reactive nonfunctionalized alkyne[168] and adds all types of copper reagents. Lithium cuprates react particularly well and insert two acetylene units to afford vinylcuprates of type (**116**; equation 40).

A controlled oligomerization[3,169,170] of acetylene is possible by carefully controlling the reaction temperature and adding the two first equivalents of acetylene at –50 °C and the remaining acetylene at 0 °C.

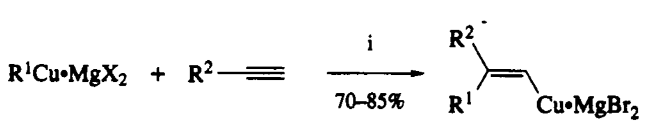
$R^1Cu{\bullet}MgX_2$ + $R^2$—≡
i
70–85%
$R^2$
$R^1$
$Cu{\bullet}MgBr_2$

**(115)**

(39)

i, addition at −35 °C, then warm to −15 °C

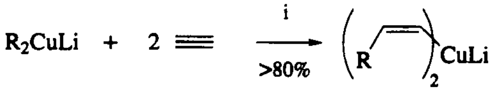
$R_2CuLi$ + 2 ≡
i
>80%
R
CuLi
2

**(116)**

(40)

i, $Et_2O$, −50 °C to −20 °C, 15 min

Under these conditions, the (*Z,Z*)-dienylcuprates (**117**) are formed in fair yields and can be trapped by various electrophiles (Scheme 61). α-Substituted alkenylcuprates react even more readily with acetylene and dienylcuprates are obtained in high yields (Scheme 62).[170]

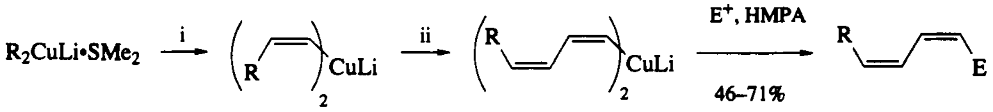
$R_2CuLi{\bullet}SMe_2$
i
R
CuLi
2
ii
R
CuLi
2
$E^+$, HMPA
46–71%
R
E

**(117)**

i, acetylene (2 equiv.), −50 °C, then 30 min at −25 °C; ii, acetylene (4 equiv.), 0 °C

**Scheme 61**

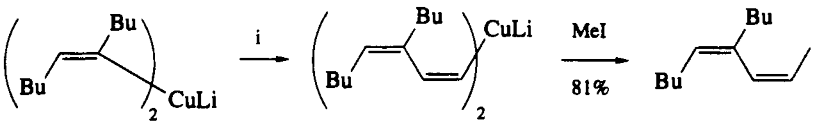
Bu
Bu
CuLi
2
i
Bu
CuLi
Bu
2
MeI
81%
Bu
Bu

i,acetylene (2 equiv.), $Et_2O$, 20 °C, 15 min

**Scheme 62**

Organocuprates in which the R group is phenyl, allyl, alkynyl or vinyl do not add to acetylene or to other alkynes. Phenylacetylene and propyne, although less reactive than acetylene, show a higher reactivity toward carbocupration than most higher alkynes and Vermeer[171] showed that secondary and tertiary magnesium alkylcopper reagents and dialkylcuprates add in THF to phenylacetylene under very mild conditions, albeit with a low regioselectivity (equation 41).

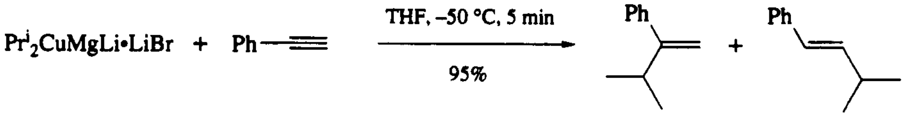
$Pr^i_2CuMgLi{\bullet}LiBr$ + Ph—≡
THF, −50 °C, 5 min
95%
Ph
+
Ph

(41)

68% 32%

As indicated previously, higher terminal alkynes react with copper reagents derived from magnesium organometallics in ether and afford the *syn* addition products with high regio- and stereo-selectivity (equation 39). The first step in these carbocuprations seems to be the formation of a π-complex between the alkyne and the copper reagent, since it has been found by Normant and coworkers[172] that the stability of an alkylcopper in ether can be increased substantially by the presence of an alkyne. The presence of magnesium salts is also essential and no carbocupration takes place in their absence, indicating that mixed magnesium–copper clusters are certainly the reactive species. Similarly, the addition of RMgX/CuCl to terminal alkynes can only be achieved in the presence of an excess of $MgBr_2$.[173] The carbocupration of terminal alkynes has also been improved and made more reproducible by the use of dimethyl sulfide–copper halide complexes instead of crude copper salts, which did not always have the required purity. Helquist and coworkers have used dimethyl sulfide as a cosolvent to achieve higher yields and a broader range of applicability (Scheme 63).[174] Of special interest is that this procedure allows one to perform methylcupration reactions, which are usually difficult due to the low reactivity of methylcopper derivatives.[3,171] This gives access to trisubstituted alkenes which are of widespread occurrence among natural products (Scheme 64).[174]

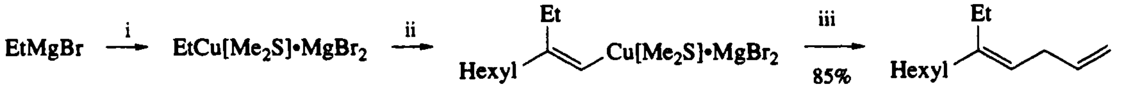

i, $CuBr{\bullet}Me_2S$ (1 equiv.), $Et_2O$:dimethyl sulfide (1:1), –45 °C, 2 h; ii, 1-octyne (0.9 equiv.), –45 °C, 2 h; iii, HMPA, allyl bromide (1 equiv.), –78 °C to –30 °C, 12 h, then aq. $NH_4Cl$

**Scheme 63**

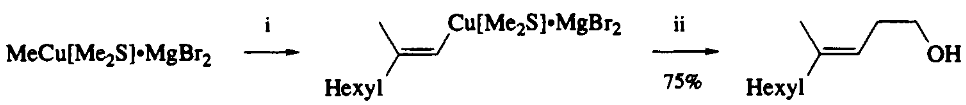

i, octyne (0.9 equiv.), $Et_2O$, dimethyl sulfide,–25 °C, 120 h; ii, 1-lithiopentyne (1 equiv.), HMPA (2 equiv.), $Et_2O$, ethylene oxide (1 equiv.), –78 °C, 2 h, then –25 °C, 24 h, then aq. $NH_4Cl$

**Scheme 64**

The addition of secondary alkylcopper derivatives often proceeds with low stereoselectivity. Only the magnesium diisopropylcuprate adds regioselectively to 1-octyne.[171] A procedure developed recently by Periasamy, using RMgX/CuCl in the presence of an excess of $MgBr_2$ in THF, seems to allow a regiospecific addition of secondary and tertiary alkylcopper reagents.[173] While nonfunctionalized disubstituted alkynes usually do not undergo carbocuprations,[175] the intermolecular reaction, as shown by Crandall and coworkers,[75,176] proceeds under mild conditions and with high yields (equation 42). Some functionalized organocopper reagents bearing various protected hydroxy and thiol functions have been added to acetylene and propyne. The optimum conditions for these reactions have been determined (equations 43 and 44).[177] Normant and coworkers[178] also showed that trimethylsilylmethylcopper adds, under forcing

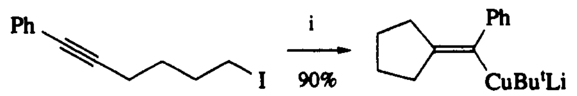

(42)

i, $Bu^t_2CuLi$, $PBu_3$, pentane:ether (7:1)

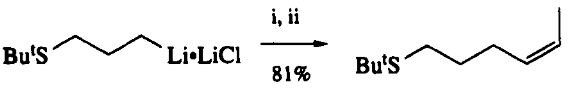

(43)

i, CuI, then acetylene, –50 °C, warm to –30 °C, 0.5 h; ii, MeI, HMPA, –40 °C to 25 °C, then $H_3O^+$

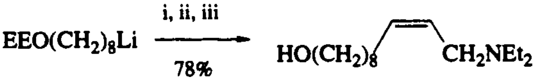

(44)

i, $CuBr{\bullet}Me_2S$, $Et_2O$, –35 °C, 0.5 to 1 h; ii, acetylene, –50 °C, then warm to –30 °C, 0.5 h; iii, $PhSCH_2NEt_2$, THF, 20 °C, 2 h, then $H_3O^+$

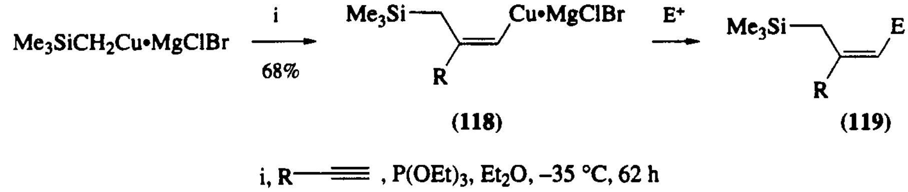

**Scheme 65**

conditions, to alkynes to afford functionalized copper derivatives of type (**118**) which react with a wide range of electrophiles to afford stereoisomerically pure allylsilanes (**119**; Scheme 65).

In summary, lithium diorganocuprates[3] are the reagents of choice for the carbocupration of acetylene itself. For higher alkynes, the use of copper organometallics made from Grignard reagents[3] ($RCu{\cdot}MgX_2$ in ether and $R_2CuMgX$ in THF[171]) is recommended. The use of dimethyl sulfide[174] as a cosolvent significantly improves the yields.

### *4.4.7.3.2 Addition to functionalized alkynes*

Whereas nonfunctionalized alkynes undergo carbocupration with high, predictable regioselectivity, the introduction of a heteroatom at the propargylic position, the homopropargylic position or directly at the triple bond has a strong influence on the regioselectivity of the carbocupration. It has been shown by Alexakis and Normant[3] that the observed regioselectivity is determined by complexation and steric effects. The use of a solvent of low basicity usually favors the complexation between the organocopper derivative and the heteroatoms present in the alkyne, whereas in a more basic solvent like THF steric interactions are more important. These points are illustrated in equations (45) and (46). The addition of $BuCu{\cdot}MgBr_2$ to the homopropargylic acetal (**120**) in ether is nonregioselective due to a partial complexation of the copper reagent to the acetal, and affords equal amounts of (**121**) and (**122**) (equation 45). In THF, the copper reagent, already strongly complexed by the solvent, does not coordinate to the acetal function of (**120**) and steric effects lead to the formation of (**121**; equation 45). With the cyclic acetal (**123**), a better chelation of the copper reagent is possible, leading mostly to the regioisomer (**125**; equation 46).

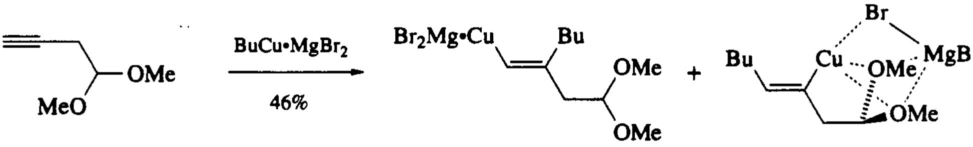

(45)

| (**120**) | | (**121**) | (**122**) |
|---|---|---|---|
| | in Et2O | 49% | 51% |
| | in THF | 98% | 2% |

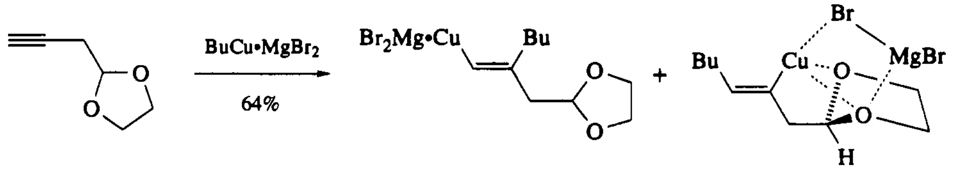

(46)

| (**123**) | | (**124**) | (**125**) |
|---|---|---|---|
| | in Et2O | 13% | 87% |

For propargylic substrates, a similar rationale is possible to explain the regiochemistry of the carbocupration. A propargylic trimethylsilyloxy group does not seem to undergo any complexation with copper reagents, and steric interactions are dominant, leading to the formation of only one regioisomer (equation 47). Propargylic ethers show a higher reactivity compared to nonfunctionalized alkynes and the addition of methylcopper[3] proceeds smoothly leading to the interesting reagent (**126**). In contrast, propargylic acetals give low regioselectivities with lithium- or magnesium-derived organocopper reagents, RCu·MX$_n$, but Alexakis and coworkers[165,179] showed that the chelate-controlled product (**127**) was obtained regiospecifically with lithium organocuprates, $R_2CuLi$ (equation 48).

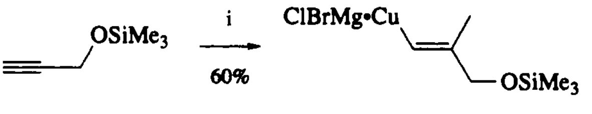

(47)

**(126)**

i, MeCu•MgClBr, THF, –25 °C, 24 h

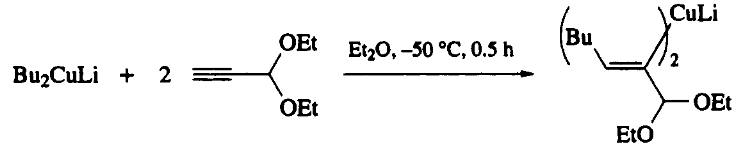

(48)

**(127)**

Secondary and tertiary dialkylcuprates, lithium dialkenyl-, and even diphenyl-cuprates, add in very good yields to the reactive propionaldehyde diethyl acetal. The *syn* addition products may be trapped with a variety of electrophiles such as alkyl, alkenyl, alkynyl and aryl halides. The method has been used for the synthesis of several natural products. Substituted alkynic acetals also react with lithium dialkylcuprates in ether to furnish stable dialkenylcuprates of type (**128**) which do not eliminate to the corresponding alkoxy allenes (**129**) if the temperature is maintained below –20 °C.[164,179]

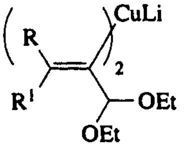

**(128)**

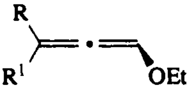

**(129)**

Heteroatom-substituted alkynes of type (**130**) react regio- and stereo-specifically with various organocopper reagents[3,180,181] to afford the regioisomer (**131**) if X = OR, $NR_2$ or $SiMe_3$, and the regioisomer (**132**) if X = SR or $PR_2$ (Scheme 66). Some adducts, (**131**) and (**132**), have limited thermal stability. Thus, the organocopper derivatives (**131**), where X = OR and $NR_2$, undergo an elimination reaction at temperatures higher than –20 °C and +20 °C, respectively. However, the vinylic carbenoid (**132**), where X = SR, is stable up to 60 °C. Vermeer[181] and coworkers showed that the alkenylcopper reagents derived from the addition to ethoxyacetylene are useful intermediates for the preparation of 1,4-diketones (Scheme 67). The addition of RCu·$MgBr_2$ to alkynylsilanes[182] allows an easy access to various regio- and stereo-isomerically pure alkenylsilanes (Scheme 68).

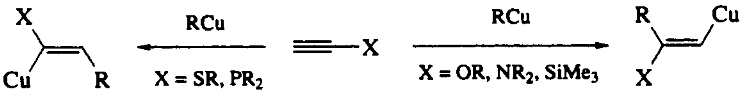

**(132)** **(130)** **(131)**

**Scheme 66**

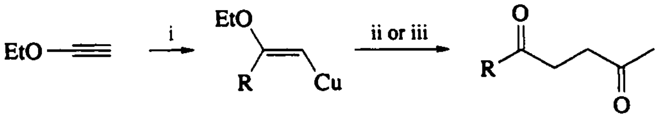

i, RCu•$MgX_2$ (1.0 equiv.), THF, –50 °C, 1 h, several hours at –25 °C; ii, allyl bromide (1.0 equiv.), HMPA, –20 °C, 3 h, then 3 M HCl followed by Wacker oxidation ($PdCl_2$, CuCl, $O_2$ in DMF, $H_2O$);
iii, 2,3-dibromopropene (1.0 equiv.), HMPA, –20 °C, 4 h, then $Hg(OAc)_2$, $HCO_2H$

**Scheme 67**

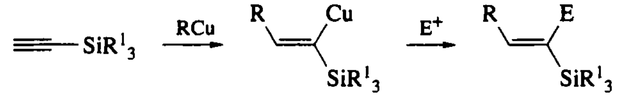

E = Cl, Br, I, CN, SMe, Me, alkyl, allyl

**Scheme 68**

Finally, silyl,[183,184] germyl,[185] and stannyl[184,186] cuprations of alkynes have also been described. Fleming[183,184] and coworkers showed that silylcuprate reagents of type (**133**; $R^1 = R^2$ = Me or $R^1$ = Me, $R^2$ = Ph) add readily to various alkynes with high regioselectivity, affording the *syn* addition products. After reaction with electrophiles, such as the proton, iodine, acyl and alkyl halides, enones and epoxides, highly functionalized vinylsilanes of defined stereochemistry are formed in good yields. It is noteworthy that the regiochemistry of the silylcupration is opposite to that observed with other organocopper reagents (see Section 4.4.7.3.1 and Scheme 69). Oshima and coworkers[185] showed that germylcopper reagents add to alkynes, but that the regiochemistry of the addition depends on the nature of the copper reagent and of the alkynic compound (equation 49). Due to their reversibility,[185,186] some germylcuprations and stannylcuprations need to be performed in the presence of a proton source, such as an alcohol, in order to drive the addition to completion, as has been shown by Piers and coworkers.[186a] With some reactive alkynes, the *syn* addition proceeds even in the absence of a proton source, but shows only a moderate regioselectivity (equation 50). Related reactions have been developed by Fleming, Oshima and Oehlschlager and coworkers.[186]

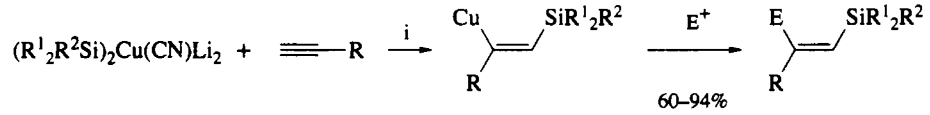

$R^1$ = Me; $R^2$ = Me or Ph

i, THF, –50 °C to 0 °C, 15 min

**Scheme 69**

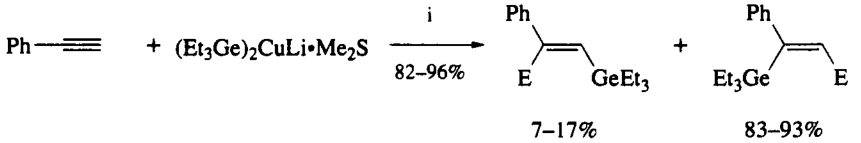

(49)

i, E⁺ = D₂O, MeI, or allyl bromide

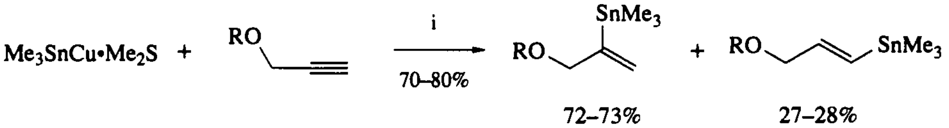

(50)

R = THP, TBDMS

i, THF, –78 °C, 6 h, then MeOH, aq.$NH_4Cl$

### 4.4.7.4 Synthetic Applications of Alkenylcopper Organometallics

The synthetic applications of alkenylcopper reagents have been reviewed in detail by Normant and Alexakis.[3] The high synthetic potential of these reagents has been summarized in Scheme 70. It is important to notice that the reactivity of alkenylcoppers and dialkenylcuprates is not the same, the latter being more reactive. Thus, some electrophiles[3] do not react readily with alkenylcoppers, but only with

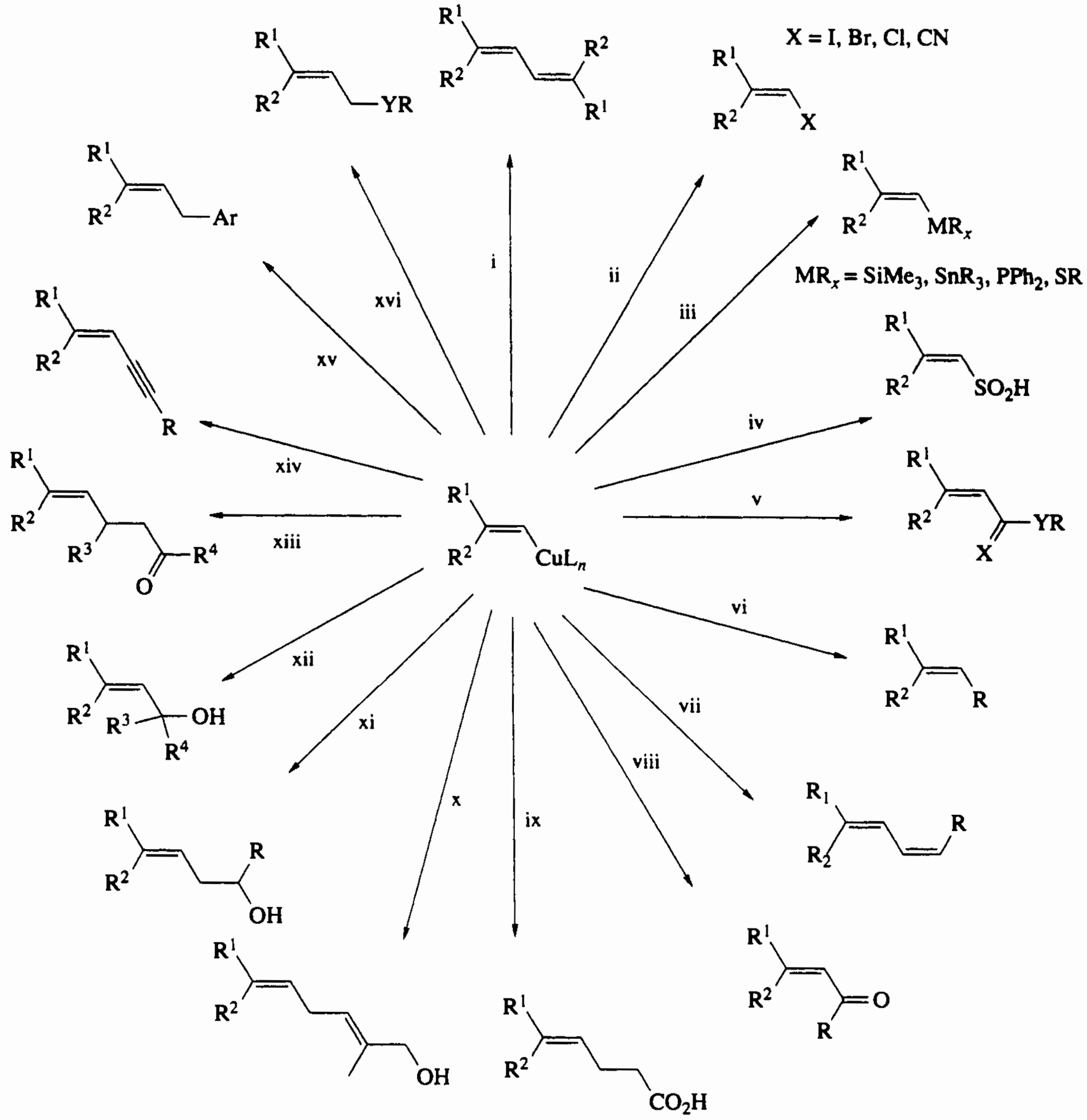
X = I, Br, Cl, CN
MR_x = SiMe_3, SnR_3, PPh_2, SR
CuL_n
i
ii
iii
iv
v
vi
vii
viii
ix
x
xi
xii
xiii
xiv
xv
xvi

i, thermal decomposition (10–20 °C) or $O_2$, –20 °C (60–80%); ii, X = I: $I_2$, –78 °C, 0.5 h (90–100%); X = Br: $HgX_2$, HMPA, $Br_2$, pyridine or NBS (50–90%); X = Cl: NCS, –45 °C (50–79%); X = CN: NCCl, $NCSO_2Ph$ or $NCSO_2Tol$, –50 °C to –20 °C (90–97%); iii, $Me_3SiCl$ (80%); $ClSnR_3$ or $ClPPh_2$, –40 °C, 1.5 h (80–90%); RSSR, HMPA, –50 °C to 25 °C, 3–4 h (58–84%); iv, $SO_2$, –40 °C to 10 °C (70%); v, X=C=Y: X = O, Y = NPh (50%); X = Y = S, then MeI (R = Me) (98%); X = Y = O (R = H) (80–100%); vi, allylic and benzylic halides, HMPA (80–98%); primary iodides and bromides, HMPA, $P(OEt)_3$, –20 °C (77–85%); vii, for magnesium copper reagents: $[Pd(PPh_3)_4]$ (5 mol %) (50–78%); for cuprates ($R_2CuM$): $ZnCl_2$ (1 equiv.), THF, $[Pd(PPh_3)_4]$ (5 mol %), –10 °C to 20 °C, 30 min (80–94%);[188] viii, $ZnCl_2$, RCOCl, $[Pd(PPh_3)_4]$ (5 mol %), 25 °C, 1 h (70–100%);[188,189] ix, propiolactone,[190] –70 °C to –10 °C, then 5 M HCl (40–95%);

**Scheme 70**

x, 1,2-epoxyisoprene,[191] –20 °C, 1 h (70–90%), *(E)*:*(Z)* = 95:5; xi, epoxide,[191] HMPA, –78 °C, 3 h, –33 °C, 24 h (60–90%);[3,174,192] xii, lithium cuprate, $BF_3 \cdot OEt_2$ (1 equiv.), aldehyde or ketone (0.7 equiv.) (60–70%);[3,193] xiii, enone or α,β-unsaturated aldehyde (65–95%);[3,174,194] xiv, R–≡–X (X = Br or I), TMEDA (1.2 to 2 equiv.), –15 °C, 1–2 h, then $H_3O^+$;[3,195] xv, aryl iodide, $ZnBr_2$, THF, $[Pd(PPh_3)_4]$ (5 mol %), –15 °C to 20 °C, 0.5 h (65–85%);[188] xvi, $RYCH_2X$: (a) $MeOCH_2Cl$[3] or $ClCH_2SR$[196] (1 equiv.), HMPA or $P(OEt)_3$, 25 °C, 4 h, $H_3O^+$ (60–99%); (b) $ClCH_2N(Me)CHO$ or *N*-chloromethylphthalimide,[197] THF, 25 °C, 4 h, $H_3O^+$ (50–89%)

**Scheme 70** *(continued)*

dialkenylcuprates. The addition of polar cosolvents, such as HMPA, or of ligands, such as 1-pentynyllithium or magnesium salts, can often enhance the reactivity of an alkenylcopper. Of special interest is the transmetallation, described by Alexakis and coworkers,[188,189] from dialkenylcuprates to the corresponding zinc derivatives, since it is known that these alkenylzinc reagents react efficiently with alkenyl and aryl halides, as well as acid chlorides,[198] under palladium(0) catalysis (equation 51). This method allows an easy access to a variety of dienes with defined stereochemistry, and has been used extensively by Alexakis and coworkers for the synthesis of insect sex pheromones.[199]

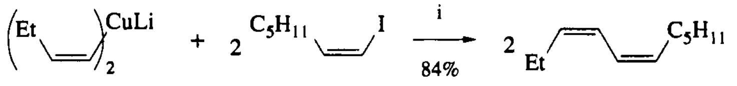

(51)

i, $MgCl_2$ (1 equiv.), $ZnBr_2$ (1 equiv.), $[Pd(PPh_3)_4]$ (5 mol %), –20 °C to 15 °C, 1 h

## 4.4.8 OTHER CARBOMETALLATION REACTIONS

### 4.4.8.1 General Considerations

A number of transition metal complexes react with alkenes, alkynes and dienes to afford insertion products (see Volume 4, Part 3). A general problem is that the newly formed carbon–metal bond is usually quite reactive and can undergo a variety of transformations, such as β-hydride elimination or another insertion reaction, before being trapped by an electrophile.[200] Usually, a better stability and lower reactivity is observed if the first carbometallation step leads to a metallacycle. It is worthy to note that the carbometallation of perfluorinated alkenes and alkynes constitutes a large fraction of the substrates investigated with transition metal complexes.[200b]

### 4.4.8.2 Addition to Alkenes and Dienes

The organomercurial-mediated[201] addition of organopalladium derivatives across alkenes is a common reaction (Heck reaction[201b]). The new carbon–carbon bond is formed mainly from the less-hindered end of the double bond (Scheme 71).[201] The initial carbopalladation product (**134**) is usually not stable and undergoes a β-hydride elimination, leading to the alkene (**135**). However, the *syn* adducts (**134**) can be isolated in certain systems where there are no β-hydrogens available for elimination, or where the palladium complex is stabilized by coordination with a neighboring π-system or a heteroatom, as shown in Scheme 72.[201,202] Besides arylpalladium compounds, the addition of π-allyl, heterocyclic, alkenyl and

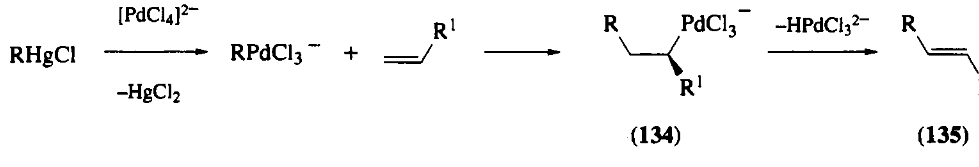

**Scheme 71**

benzylic organopalladium compounds to bicyclic alkenes is well known.[202,203] These *syn* palladium adducts can undergo a variety of synthetically useful transformations which all occur with retention of the *exo* stereochemistry and complement the Diels–Alder approach to bicyclic systems (Scheme 73).

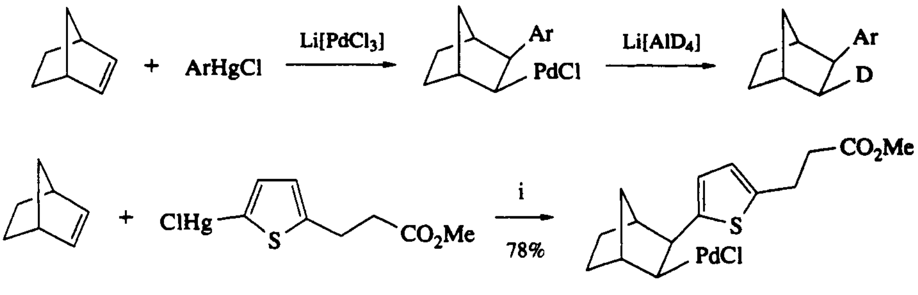
+ ArHgCl
Li[PdCl3]
Ar
PdCl
Li[AlD4]
Ar
D
+ ClHg
S
CO2Me
i
78%
CO2Me
S
PdCl

i, Li[PdCl$_4$], MeCN, 0 to 25 °C

**Scheme 72**

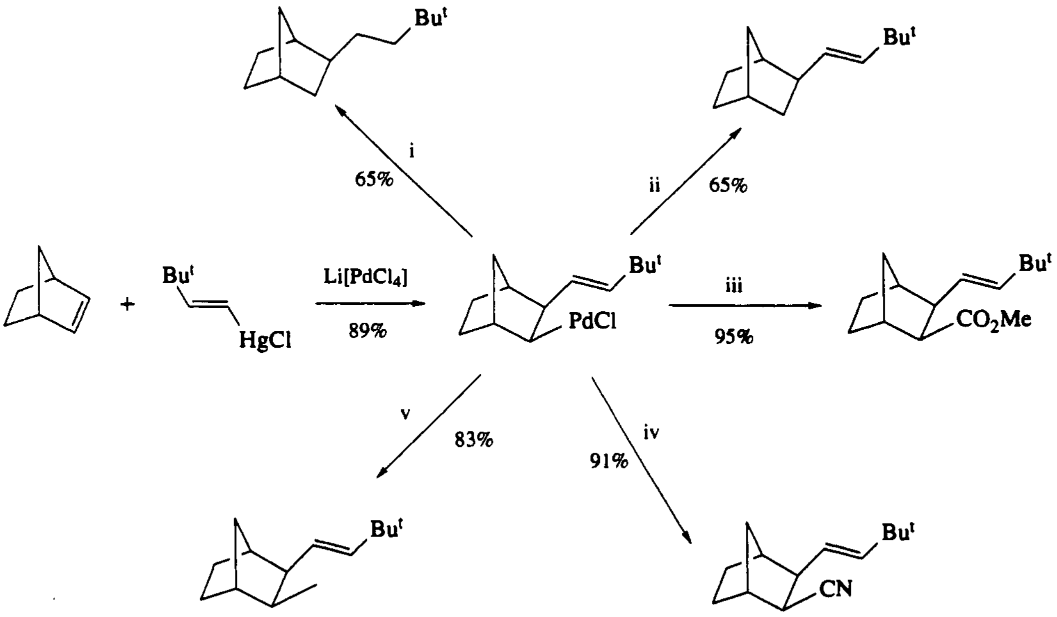
Bu^t
i
65%
Bu^t
ii
65%
+
Bu^t
HgCl
Li[PdCl4]
89%
Bu^t
PdCl
iii
95%
Bu^t
CO2Me
v
83%
iv
91%
Bu^t
Bu^t
CN

i, H$_2$; ii, NaOMe/MeOH; iii, CO/MeOH/Et$_3$N; iv, CuCN; v, MeLi, 2PPh$_3$

**Scheme 73**

A functionalized mercury(II) compound like ethyl (acetoxymercurio)acetate (**136**) allows an easy approach to prostaglandin endoperoxide analogs (equation 52).[204] Several organomercury(II) compounds, RHgCl (R = Me, aryl, benzylic), are able to add to 1,3-dienes in the presence of a stoichiometric amount of a palladium(II) salt and afford π-allylpalladium compounds of type (**137**) in variable yields (equation 53).[205] A related intramolecular carbomercuration has been reported by Snider.[206] It allows a stereospecific approach to the chloromercury compound (**138**; equation 54). Similar palladium-mediated reactions

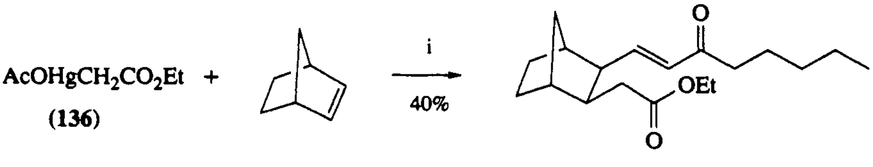
AcOHgCH2CO2Et +
(136)
i
40%
O
OEt
O

(52)

i, Li$_2$[PdCl$_4$] (1 equiv.), H$_2$C=CHCOC$_5$H$_{11}$ (10 equiv.), THF, 0 °C, 1 h, then 25 °C, 4 d have been studied by Saegusa,[207] Kende[208] and coworkers. Of interest is also the carbometallation of enynes with stabilized organosilver[209] compounds RAg·2LiBr. These organometallics show a high tendency to add to the double bond of enynes (**139**) to afford, after hydrolysis, the allene (**140**), whereas the corresponding copper reagent mainly adds to the triple bond to give the 1,3-diene (**141**; Scheme 74).

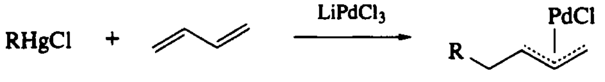

(53)

**(137)**

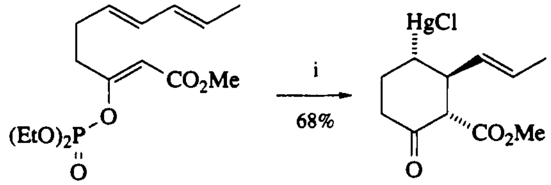

(54)

**(138)**

i, Hg(OCOCF$_3$)$_2$, MeNO$_2$, –20 °C, NaCl

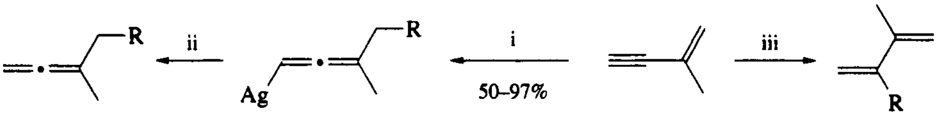

**(140)** **(139)** **(141)**

i, RAg•2LiBr, THF/HMPA, –40 to –10 °C, 3–6 h; ii, $H_3O^+$; iii, $R_2CuMgCl$, THF, then $H_3O^+$

Scheme 74

### 4.4.8.3 Addition to Alkynes

Drouin and Conia[210] have shown that alkynic silyl enol ethers undergo a highly stereoselective (>95% *syn* addition) carbomercuration, leading to five- or six-membered rings in high yields (72–90%). The intermediate alkenylmercury derivative can be trapped by various electrophiles (Scheme 75). Several transition metal complexes[200b,211] can effect the methylmetallation of alkynes in moderate yields, low selectivity and no special advantage compared with main group organometallics. Acylmetallation reactions, however, which are very difficult with main group organometallics, proceed far more readily with transition metal complexes and are of some synthetic utility. Hoberg and coworkers[212] showed that several symmetrical alkynes react with $CO_2$ in the presence of nickel(0) complexes to give five-membered cyclic nickel complexes of type (**142**) in fair to good yields, which can be further converted into a variety of organic products (Scheme 76). DeShong and coworkers[213] showed that the sequential insertion of carbon monoxide and alkynes into various alkylmanganese pentacarbonyl complexes of type (**143**)

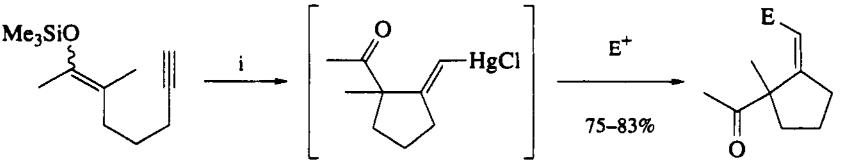

E = COMe, CO$_2$Me, Br

i, HgCl$_2$, CH$_2$Cl$_2$, hexamethyldisilazane, 30 °C, 0.5 h

Scheme 75

proceeds readily at high pressures (2–10 kbar), and provides the manganacycles (**144**) in good yields. These manganese complexes are valuable intermediates for the preparation of organic compounds. By demetallation under acidic conditions, (*E*)-enones are obtained. Alternatively, hydride reduction of complexes (**144**) affords the butenolides (**145**) by an intramolecular Reppe reaction (Scheme 77). The presence of an electron-withdrawing group in the alkyne makes the addition easier, but nonfunctionalized alkynes can also add with excellent regioselectivity.

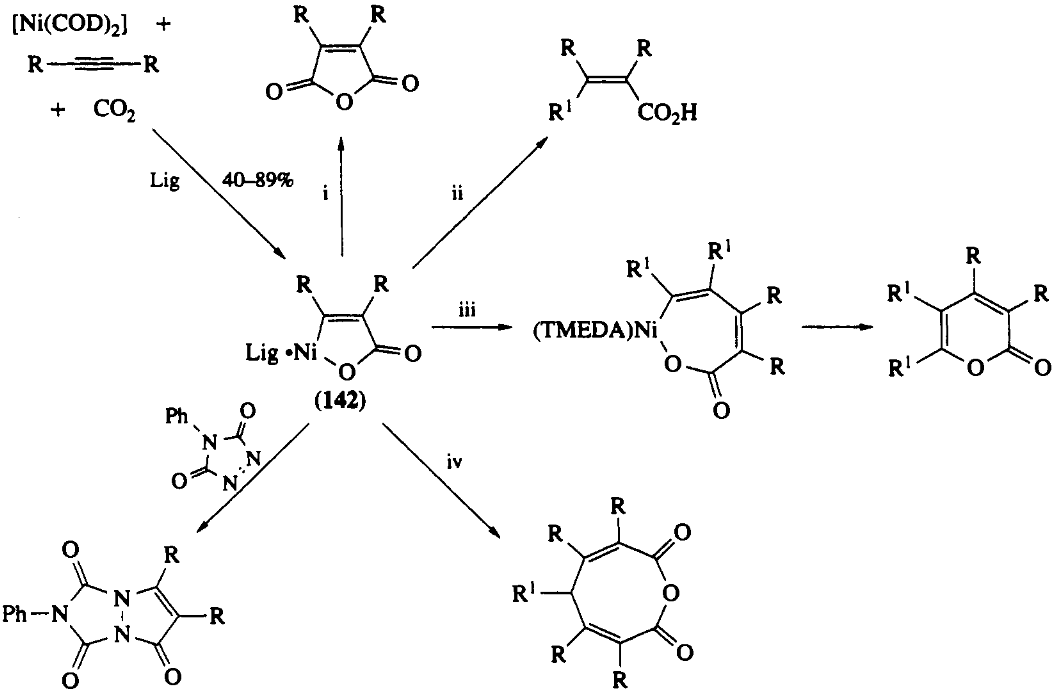
[Ni(COD)2] +
R—≡—R
+ CO2
Lig
40–89%
i
ii
iii
iv
R
R1
CO2H
Lig •Ni
(TMEDA)Ni
(142)
Ph
Ph—N
O
N

R = Me (H, Ph); Lig = TMEDA, 1,2-bis(dicyclohexylphosphino)ethane or 2,2'-bipyridine

i, CO; ii, $R^1X$, then $H_3O^+$; iii, TMEDA, $R^1CCR^1$; iv, $R^1CHX_2$

**Scheme 76**

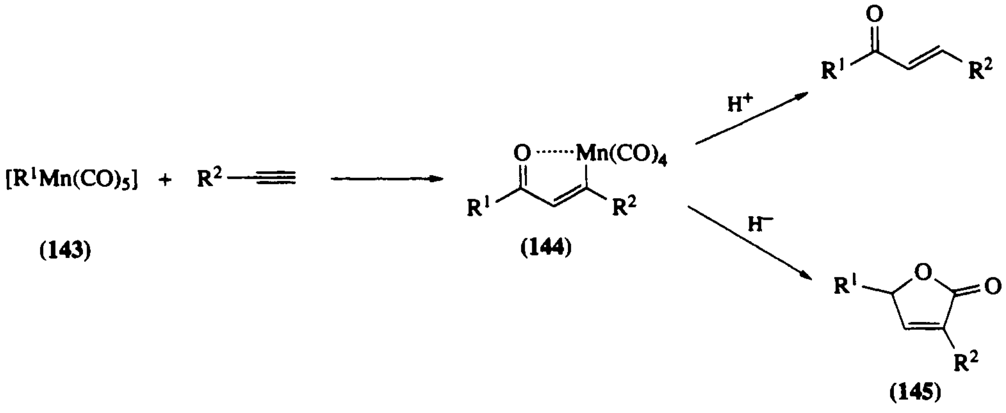
[R1Mn(CO)5] + R2—≡
(143)
O·······Mn(CO)4
R1
R2
(144)
H+
H−
O
(145)

**Scheme 77**

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# 4.5

# Hydroformylation and Related Additions of Carbon Monoxide to Alkenes and Alkynes

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## 4.5.1 INTRODUCTION

The hydroformylation reaction — the addition of dihydrogen and carbon monoxide to an alkene or alkyne to produce an aldehyde — is one of the most important industrial chemical reactions. It is remarkable in that it converts simple, inexpensive starting materials into useful products. A new carbon–carbon bond is formed along with a very useful and reactive functionality.

The following discussion deals not only with this reaction, but related reactions in which a transition metal complex achieves the addition of carbon monoxide to an alkene or alkyne to yield carboxylic acids and their derivatives. These reactions take place either by the insertion of an alkene (or alkyne) into a metal–hydride bond (equation 1) or into a metal–carboxylate bond (equation 2) as the initial key step. Subsequent steps include carbonyl insertion reactions, metal–acyl hydrogenolysis or solvolysis and metal–carbon bond protonolysis.

Reactions of alkenes and alkynes that generate a carbon–metal bond by nucleophilic addition to a metal $\pi$-complex and subsequently undergo carbon monoxide insertion to yield a carbonyl product are

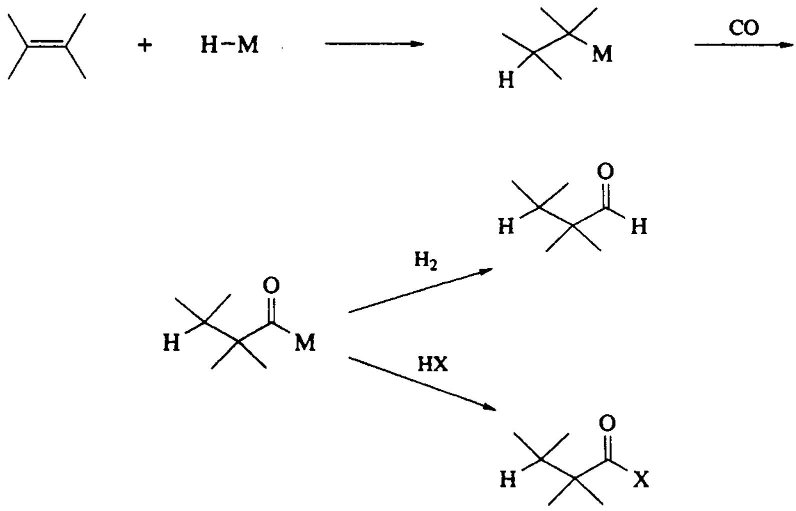

(1)

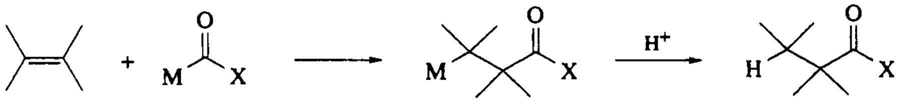

(2)

covered in Volume 4, Chapter 3.1. Reactions of carbon monoxide with alkenes and alkynes generating quinones, cyclopentanones and their derivatives that proceed *via* a metal-assisted cycloassembly (Pauson–Khand reaction) are discussed in Volume 5, Chapter 9.1.

The hydroformylation of alkenes generally has been considered to be an industrial reaction unavailable to a laboratory scale process. Usually bench chemists are neither willing nor able to carry out such a reaction, particularly at the high pressures (200 bar) necessary for the hydrocarbonylation reactions utilizing a cobalt catalyst. (Most of the previous literature reports pressures in atmospheres or pounds per square inch. All pressures in this chapter are reported in bars (SI); the relationship is 14.696 p.s.i. = 1 atm = 101 325 Pa = 1.013 25 bar.) However, hydroformylation reactions with rhodium require much lower pressures and related carbonylation reactions can be carried out at 1–10 bar. Furthermore, pressure equipment is available from a variety of suppliers and costs less than a routine IR instrument. Provided a suitable pressure room is available, even the high pressure reactions can be carried out safely and easily. The hydroformylation of cyclohexene to cyclohexanecarbaldehyde using a rhodium catalyst is an *Organic Syntheses* preparation (see Section 4.5.2.5).

Several excellent comprehensive reviews that include the hydroformylation reaction and related reactions of carbon monoxide have appeared in the past decade.[1,2] Because of the industrial importance of these reactions, much of the literature is process oriented and has focused on the carbonylation of simple alkenes derived from petroleum feedstock.

## 4.5.2 HYDROFORMYLATION[1-5]

The reaction of alkenes (and alkynes) with synthesis gas (CO + $H_2$) to produce aldehydes, catalyzed by a number of transition metal complexes, is most often referred to as a hydroformylation reaction or the oxo process. The discovery was made using a cobalt catalyst, and although rhodium-based catalysts have received increased attention because of their increased selectivity under mild reaction conditions, cobalt is still the most used catalyst on an industrial basis. The most industrially important hydrocarbonylation reaction is the synthesis of *n*-butanal from propene (equation 3). Some of the butanal is hydrogenated to butanol, but most is converted to 2-ethylhexanol *via* aldol and hydrogenation sequences.

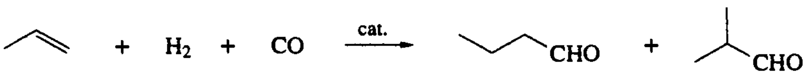

(3)

### 4.5.2.1 The Catalysts

All Group VIII, IX and X transition metals show some catalytic activity for hydroformylation, although cobalt and rhodium are the most active, rhodium catalysts being $10^4$ times more reactive. More recently, platinum catalysts containing the trichlorostannate ligand have been shown to be selective catalysts that effect hydroformylation under mild conditions.[6]

The treatment of a cobalt(II) salt with synthesis gas generates sequentially $Co_2(CO)_8$ then $HCo(CO)_4$. This catalyst is generated only at 120–140 °C; for the carbonylation to proceed smoothly 200–300 bar is required to stabilize the catalyst. If the hydridocobalt catalyst is prepared separately and then introduced into the reaction, temperatures as low as 90 °C can be used for the hydrocarbonylation. An important consideration in industrial reactions is the normal to branched *n*/*b* ratio to give the desired straight chain aldehyde, the hydridocobalt catalyst providing an *n*/*b* ratio of ~4 in the hydroformylation of propene under the lower temperature conditions. This catalyst will stoichiometrically hydroformylate 1-alkenes under ambient conditions.

Rhodium carbonyl catalysts effect hydrocarbonylation under very mild reaction conditions at higher rates and selectivity. Rhodium introduced as $Rh_4(CO)_{12}$, for example, probably is converted to $RhH(CO)_n$, but there is no direct evidence for such species. These rhodium carbonyls are not particularly attractive since they produce mostly branched aldehydes.

Both cobalt and rhodium catalysts containing phosphine ligands have the advantages that they operate at lower pressures and are more selective. The cobalt catalyst is stabilized by phosphines, *e.g.* $HCo(CO)_3(PBu_3)$, and therefore lower CO pressures (100 bar) can be utilized. The catalyst is less active for hydroformylation than $HCo(CO)_4$ but gives an *n*/*b* ratio of 7 instead of 4 for $HCo(CO)_4$. This phosphine-stabilized catalyst is active for the hydrogenation of butanal, so instead of aldehydes, alcohols are generated under the reaction conditions. Propene can be hydroformylated under 10–20 bar at 100 °C with a rhodium catalyst, $HRh(CO)(PPh_3)$, to give predominately *n*-butanal (*n*/*b* = 9). In this case, little or no hydrogenation to butanol takes place.

Until recently, the use of platinum complexes for hydroformylation reactions was less encouraging because of the lower reaction rates and the tendency for the substrate to undergo competitive hydrogenation. However, the complex $HPt(CO)(PPh_3)_2SnCl_3$ hydroformylates alkenes under mild reaction conditions selectively without hydrogenating the alkene directly.[6,7] The function of the $SnCl_3^-$ is apparently to stabilize the ligand *trans* to it and to provide an easily dissociating ligand for coordination of an alkene.[8,9] Indeed, the use of certain phosphine ligands in place of triphenylphosphine yields catalysts that give even higher reaction rates than $HRh(CO)(PPh_3)$ and provide *n*/*b* ratios of 99.[10] Hydroformylations using $HPt(CO)(PPh_3)_2SnCl_3$ generally give high yields of aldehyde (90%) at 60–80 °C and 65–100 bar.[7]

### 4.5.2.2 Mechanisms

Although the overall reaction mechanisms (catalytic cycles) written for hydroformylation reactions with an unmodified cobalt catalyst (Scheme 1) and the rhodium catalyst (Scheme 2) serve as working models for the reaction, the details of many of the steps are missing and there are many aspects of the reaction that are not well understood.

The key features of both catalytic cycles are similar. Alkene coordination to the metal followed by insertion to yield an alkyl–metal complex and CO 'insertion' to yield an acyl–metal complex are common to both catalytic cycles. The oxidative addition of hydrogen followed by reductive elimination of the aldehyde regenerates the catalyst (Scheme 2 and middle section of Scheme 1). The most distinct departure in the catalytic cycle for cobalt is the alternate possibility of a dinuclear elimination occurring by the intermolecular reaction of the acylcobalt intermediate with hydridotetracarbonylcobalt to generate the aldehyde and the cobalt(0) dimer.[11,12] In the cobalt catalytic cycle, therefore, the valence charges can be from +1 to 0 or +1 to +3, while the valence charges in the rhodium cycles are from +1 to +3.

In both catalytic cycles none of the complexes exceed 18 electrons. In order to account for the effect of phosphine on the *n*/*b* ratio in rhodium catalysis (*vide infra*), an associative mechanism has been proposed in which alkene coordinates directly to the 18-electron $HRh(CO)_2L_2$ complex. Since this gives a 20-electron complex, this mechanism is not particularly attractive. A number of the intermediates in the rhodium catalytic cycle have been verified by various spectroscopic techniques.[13,14]

Much less is known concerning the platinum-catalyzed hydroformylations. However, a reasonable catalytic cycle can be constructed (Scheme 3) from the available information on the generation and reactions of many of the intermediate complexes shown.[6,8,9,15] The ability of platinum to catalyze hydroformylation reactions while palladium is not a good catalyst could be due to the ability of platinum to achieve the +4 oxidation state more readily.

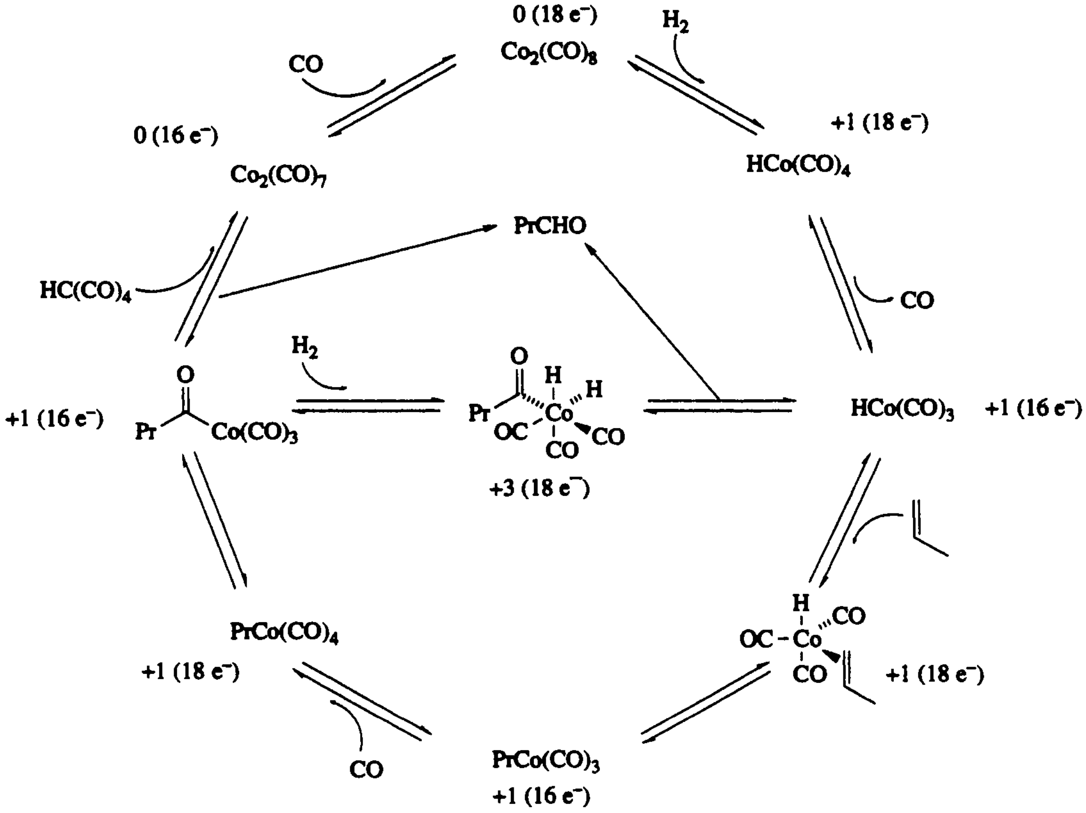

**Scheme 1**

In the unmodified catalyst system (Scheme 1), the rate shows a first-order dependence on hydrogen pressure and an inverse first-order dependence on carbon monoxide pressure, so that the rate is nearly independent of total pressure. The reaction is first order in alkene and first order in cobalt at higher CO pressures. With phosphine-modified cobalt catalysts, the rate-determining step depends on the ligand and the alkene.

Catalysis by phosphine-modified rhodium is even more complex and the rate-limiting steps under different conditions are uncertain. Addition of excess phosphine to the system or a high CO pressure slows the rate, a result consistent either with the rate-determining step being dihydrogen oxidative addition (6) → (7) or alkene complexation (2) → (3), both steps requiring coordinatively unsaturated species. At high alkene concentration the reaction is insensitive to alkene concentration, the reaction being saturated with acyl complex (6), but at low alkene concentration or with highly substituted (unreactive) alkene, the rate is first order in alkene concentration, the rate-limiting step changing to the complexation of alkene (2) → (3).

### 4.5.2.3 Regio- and Stereo-chemistry

The direction of insertion of the alkene into the metal–hydride bond can take place to yield the normal or branched metal alkyl, which ultimately determines the *n*/*b* ratio of aldehydes (equation 4).

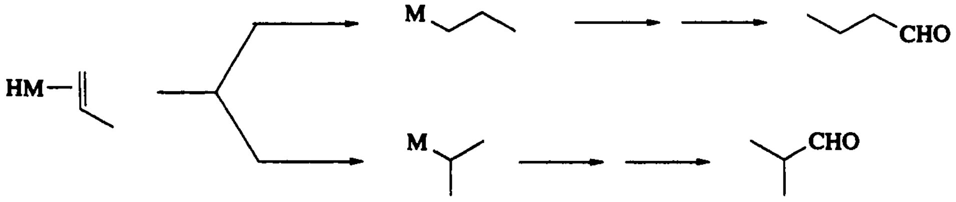

(4)

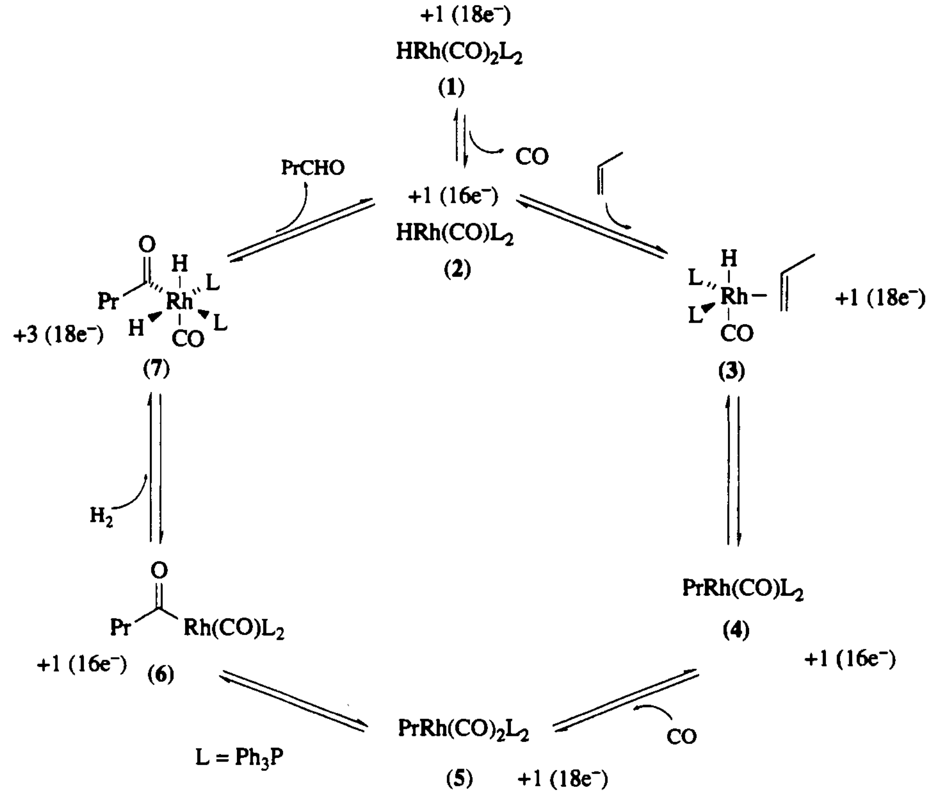
+1 (18e⁻)
HRh(CO)₂L₂
(1)
CO
PrCHO
+1 (16e⁻)
HRh(CO)L₂
(2)
O
H
L
Pr
Rh
+3 (18e⁻)
H
CO
L
(7)
H
L
Rh
L
CO
+1 (18e⁻)
(3)
H₂
O
Pr
Rh(CO)L₂
+1 (16e⁻)
(6)
PrRh(CO)L₂
(4)
+1 (16e⁻)
PrRh(CO)₂L₂
CO
L = Ph₃P
(5)
+1 (18e⁻)

Scheme 2

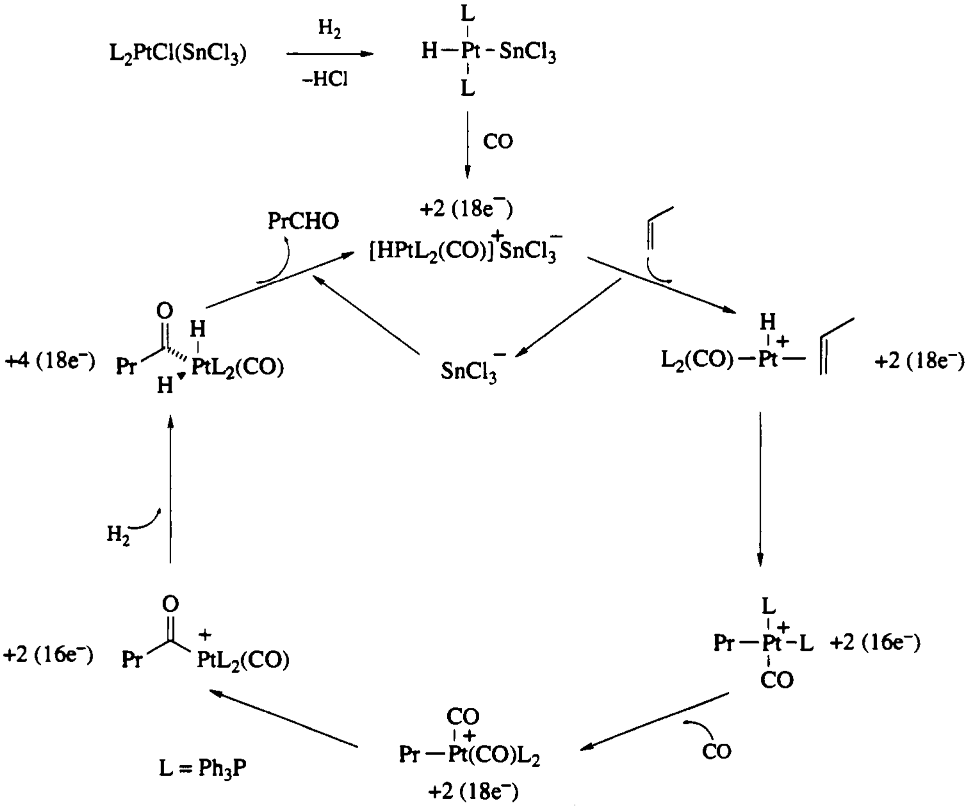
L₂PtCl(SnCl₃)
H₂
-HCl
L
H−Pt-SnCl₃
L
CO
+2 (18e⁻)
PrCHO
[HPtL₂(CO)]⁺SnCl₃⁻
O
H
+4 (18e⁻)
Pr
PtL₂(CO)
H
SnCl₃⁻
H
L₂(CO)−Pt⁺−
+2 (18e⁻)
H₂
O
+
+2 (16e⁻)
Pr
PtL₂(CO)
L
Pr−Pt⁺-L
+2 (16e⁻)
CO
CO
Pr−Pt⁺(CO)L₂
CO
L = Ph₃P
+2 (18e⁻)

Scheme 3

Higher *n*/*b* ratios in cobalt-modified catalysts are apparently achieved as a result of the phosphine presenting more steric bulk to the insertion reaction of the alkene. The effect is predominately steric, since there is little correlation with regiochemistry and phosphine bacisity. A combination of electronic ($\chi_i$) and steric (cone angle $\theta$) effects provide a more rational explanation of the increase in *n*/*b* ratio with added phosphines.[16,17]

The addition of excess triphenylphosphine to rhodium catalysts can improve the *n*/*b* ratio to 9. The concentration of added phosphine and the partial pressure of CO may determine whether the species undergoing a reaction with the alkene is (**2**) (Scheme 2), containing two phosphine ligands and one carbonyl, or $HRh(CO)_2L$. Certainly with a more sterically hindered complex containing two phosphine ligands (**3**), insertion could be expected to take place to provide the linear metal alkyl. At lower phosphine concentrations the alkene complex derived from $HRh(CO)_2L$, containing only one phosphine ligand, should lead to more branched aldehyde. There are major uncertainties as to the numbers of phosphine and carbonyl ligands on rhodium and certainly mixtures of these complexes are present in the catalytic reaction leading to *n*/*b* mixtures of products.

High *n*/*b* ratios (5.7–13) are obtained in the platinum-catalyzed hydroformylation reaction; *n*/*b* ratios as high as 99 have been obtained utilizing a chelating phosphine, *trans*-1,2-diphenylphosphinocyclobutane.[10]

The *n*/*b* ratios are also affected by the alkene structure and are sensitive to steric hindrance. For example, dicobaltoctacarbonyl hydroformylates longer chain 1-alkenes more slowly than the shorter alkenes. Methyl substitution on the alkene chain not only slows the reaction as the methyl group is moved closer to the double bond, but the *n*/*b* ratio increases (Table 1). A quaternary carbon does not undergo CO insertion and, as a result, the aldehyde is almost never attached at a fully substituted $sp^2$ carbon of an alkene.

**Table 1** Hydroformylation of Alkenes: Relative Rate and Isomer Ratios

| | | *Substitution (%)* | |
|---|---|---|---|
| *Alkene* | *Relative rate constant* | *Carbon 1* | *Carbon 2* |
| 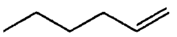 | 1 | 82 | 18 |
| 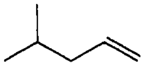 | 0.97 | 86 | 14 |
| 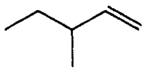 | — | 96 | 4 |
| 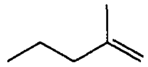 | 0.11 | 100 | 0 |
| 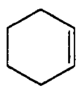 | 0.088 | — | — |

Once metal hydride addition (alkene insertion) has taken place, for example (**3**) → (**4**), β-elimination (**4**) → (**3**) and readdition can occur (Scheme 2). Accordingly, alkene isomerization can take place in the hydroformylation process (equation 5).

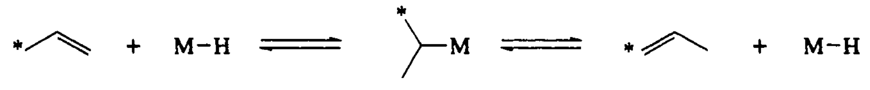

(5)

This becomes especially apparent in hydroformylation reactions of internal alkenes, since not only does (*E*)/(*Z*)-isomerization take place, but *n*-aldehydes are obtained. Thus, in the hydroformylation of (*E*)-4-octene by $Co_2(CO)_8$, *n*-nonanal (78%), 2-methyloctanal (10%), 2-ethylheptanal (6%) and 2-propylhexanal (6%) are obtained. This isomerization is supressed with the phosphine-modified catalysts, in the presence of excess phosphine and at high CO pressures. Both carbon monoxide and phosphine can react with a 16-electron complex to provide an 18-electron complex (*e.g.* **4** → **5**; Scheme 2), the reverse β-hydride elimination is prevented, a requirement for this elimination being the presence of a vacant coordination site (16-electron complex). Hydroformylation of 2,3-dimethyl-2-butene yields only 3,4-dimethylpentanal (equation 6).

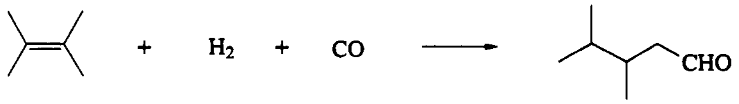

(6)

The overall stereochemistry of the hydroformylation reaction exhibits *syn* addition of the hydride and the formyl groups, both with cobalt and rhodium catalysts. Thus in the hydroformylation of 1-methylcyclohexene, where (*E*)/(*Z*)-isomerization cannot occur, the predominate product is *trans*-2-methylcyclohexanecarbaldehyde (equation 7) resulting from the delivery of the aldehyde and the formyl groups from the same face of the alkene.[18] Similarly the hydroformylation of (*Z*)-3-methyl-2-pentene gives mainly the *erythro*-aldehyde (equation 8).[19]

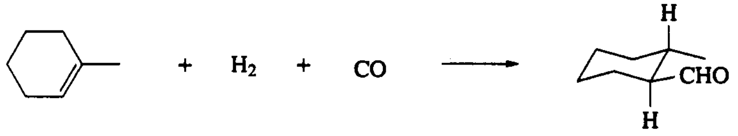

(7)

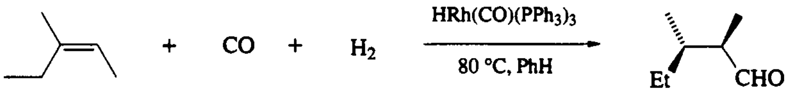

(8)

This stereochemistry is a result of *syn* metal hydride addition across the alkene followed by CO 'insertion' with retention of configuration at the carbon bound to the metal (*e.g.* steps **3** → **4** and **5** → **6**; Scheme 2).

### 4.5.2.4 Hydroformylation of Unfunctionalized Alkenes

The hydroformylation of 1-alkenes and some of the simpler alkenes has been discussed (*vide supra*). In many cases these aldehydes are commercially available or are not of particular interest as fine chemicals for organic syntheses. The hydroformylation of alkenes is especially useful when isomerization is difficult or only one regioisomer can be obtained.

The hydroformylation of cyclohexene, as mentioned earlier, provides good yields of cyclohexanecarbaldehyde (entry 1, Table 2). The regiochemistry of the hydroformylation of vinyl aromatics is strongly influenced by electronic effects, the formyl group being incorporated at the most electron-deficient carbon. Consequently the hydroformylation of indene places the formyl group predominately at the carbon adjacent to the aromatic ring (entry 2). The indanealdehyde and aldehyde derived from acenaphthalene (entry 3) can be converted to β-phenylethylamines (**8**) and (**9**), respectively, that have interesting hypotensive properties.

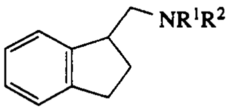

(**8**)

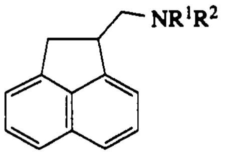

(**9**)

Similarly, hydroformylation of substituted styrenes yields the corresponding aldehydes, the β-substituted styrene providing the α-phenyl aldehyde (entry 4). This aldehyde can be converted to the pharmacologically active amine.

(–)-α-Pinene (entry 5) from the cluster pine (*Pinus pinaster* Sol.) is diastereoselectively hydroformylated to (–)-3-pinanecarbaldehyde. Hydroformylation of (+)-α-pinene from Aleppo pine (*Pinus pinaster* Mill.) yields the diastereomer. This selective hydroformylation takes place from the least-hindered alkene face. Depending on the reaction conditions, selectivities as high as 85% can be achieved.

**Table 2** Hydroformylation of Alkenes

| *Entry* | *Alkene* | *Catalyst* | *Temperature* (°C) | *Pressure* (bar) | *Aldehyde* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | 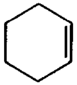 | $Rh_2O_3$ | 100 | 150 | 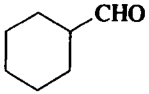 | 82–84 | 20 |
| 2 | 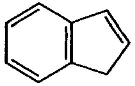 | $[RhCl(COD)]_2$ | 100 | 700 | 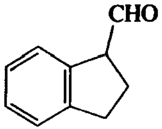 | a | 22 |
| 3 | 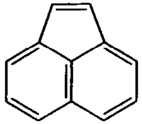 | $[RhCl(COD)]_2$ | 100 | 700 | 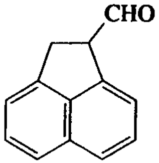 | 54 | 22 |
| 4 | 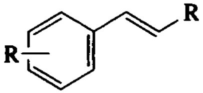 | $[RhCl(COD)]_2$ | 100 | 160 | 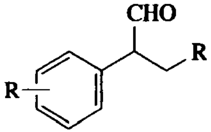 | 83 | 22 |
| 5 | 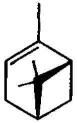 | $[RhCl(COD)]_2$ | 70 | 600 | 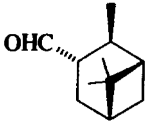 | a | 22–24 |
| 6 | 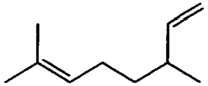 | $[RhCl(COD)]_2$ | 70 | 600 | 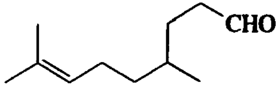 | a | 22 |

Table 2 *(continued)*

| *Entry* | *Alkene* | *Catalyst* | *Temperature* (°C) | *Pressure* (bar) | *Aldehyde* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 7 | 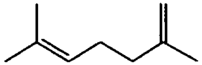 | $[RhCl(COD)]_2$ | 70 | 600 | 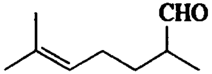 | 37 | 22 |
| 8 | 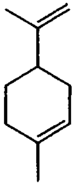 | [Rh(OAc)COD]<br>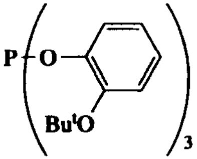 | 90 | 14 | 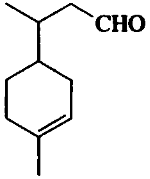 | b | 21 |
| 9 | 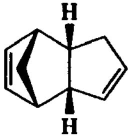 | $RhH(CO)(PPh_3)_3$<br>$Et_3N$ | 70 | 100 | 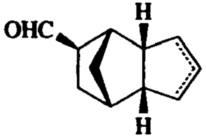 | 82 | 26 |
|  |  |  | 130 | 82 | 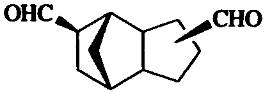 | 75 | 27 |
|  |  |  | 180 | 150 | 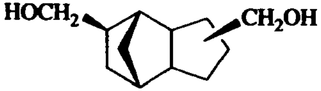 | 67 | 28 |

CHO
CHO
P
O
Bu$^t$O
3
H
H
OHC
H
H
OHC
CHO
HOCH$_2$
CH$_2$OH

---

[a] Yields not provided; conversions varied, depending on reaction time. [b] Conversion run to 50% to determine rates.

The enantiomeric purity of the 3-pinanecarbaldehyde corresponds to the α-pinane utilized (70–85%). Enantiomerically pure aldehyde can be obtained by the acid-catalyzed trimerization of the aldehyde, with only one enantiomer being preferentially cyclotrimerized to a crystalline compound.[23b] Cleavage of the trimer results in enantiomerically pure aldehyde. If cobalt catalysts are employed in the cyclization, rearrangement to the bornane structure takes place (equation 9).[25]

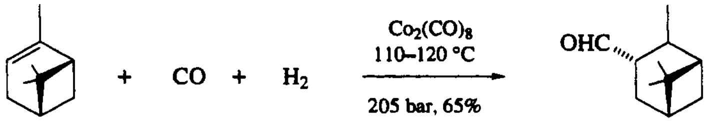

(9)

Selective hydroformylation of nonconjugated dienes can be carried out such that the least-hindered double bond reacts. Thus citronellene (entry 6) and 2,6-dimethyl-1,5-heptadiene both undergo preferential reaction at the least-substituted double bond, the hydroformylation of citronellene patterned after that of 3-methyl-1-pentene (Table 1) and the hydroformylation of 2,6-dimethyl-1,5-heptadiene to citronellal following that of 2-methyl-1-pentene, avoiding placing the formyl group at the quaternary carbon. The reaction of limonene (entry 8) shows similar behavior.

Because the norbornene double bond of dicyclopentadiene is more strained, its selective hydroformylation can be achieved under mild reaction conditions (entry 9). Under more vigorous reaction conditions both double bonds are hydroformylated. The *exo* faces of both rings are the least hindered, accounting for the selectivity.

The hydroformylation of conjugated dienes with unmodified cobalt catalysts is slow, since the insertion reaction of the diene generates an $\eta^3$-cobalt complex by hydride addition at a terminal carbon (equation 10).[5] The stable $\eta^3$-cobalt complex does not undergo facile CO insertion. Low yields of a mixture of *n*- and iso-valeraldehyde are obtained. The use of phosphine-modified rhodium catalysts gives a complex mixture of $C_5$ monoaldehydes (58%) and $C_6$ dialdehydes (42%). A mixture of mono- and di-aldehydes are also obtained from 1,3- and 1,4-cyclohexadienes with a modified rhodium catalyst (equation 11).[29] The 3-cyclohexenecarbaldehyde, an intermediate in the hydrocarbonylation of both 1,3- and 1,4-cyclohexadiene, is converted in 73% yield, to the same mixture of dialdehydes (*cis*:*trans* = 35:65) as is produced from either diene.

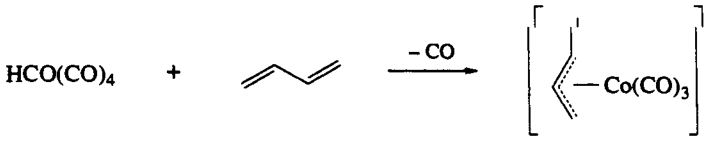

(10)

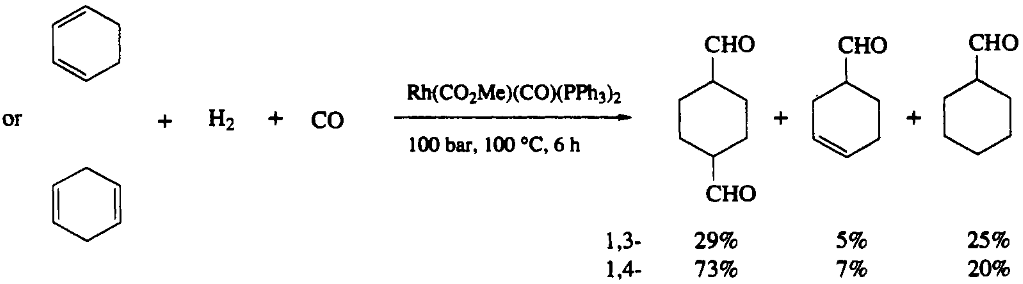

(11)

Phosphine-modified rhodium catalysts hydroformylate alkynes to saturated aldehydes.[1] The reaction most likely proceeds by a rapid hydrogenation to yield the alkene, followed by hydroformylation.

### 4.5.2.5 Hydroformylation of Functionalized Alkenes

The hydroformylation of alkenes containing a variety of functional groups can be carried out without poisoning the catalyst and without reaction of the functionality taking place. Exceptions are those in which the functional group reacts with the newly formed aldehyde. Alcohols, ethers, acetals and ketals are tolerated in hydroformylations. If the double bond is remote enough from the functional group, then the hydroformylation regiochemistry and rate are similar to the analogous alkene. If the double bond is closer to the functionality, then alkene isomerization may be favored and the regiochemistry may be altered or even reversed.

Hydroformylation of 2,6-dimethyl-6-hepten-2-ol produces hydroxycitronellal (equation 12).[22] Subjecting allyl alcohol to hydroformylation reaction conditions with $HCo(CO)_4$ yields only propanal, isomerization taking place more rapidly than hydroformylation.[2] Phosphine-modified rhodium catalysts will convert allyl alcohol to butane-1,4-diol under mild conditions in the presence of excess phosphine, however (equation 13).[5,30,31] When isomerization is blocked, hydroformylation proceeds normally (equation 14). An elegant synthesis of the Prelog–Djerassi lactone has been accomplished starting with the hydroformylation of an allylic alcohol (equation 15).[32]

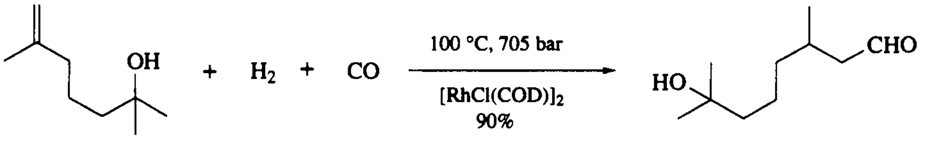
OH
+ H2 + CO
100 °C, 705 bar
[RhCl(COD)]2
90%
HO
CHO

(12)

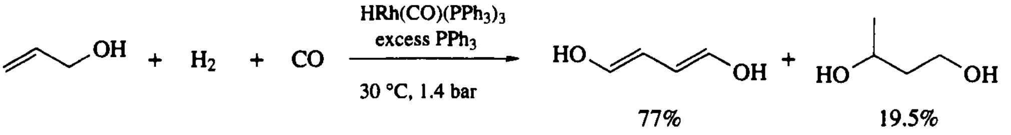
OH
+ H2 + CO
HRh(CO)(PPh3)3
excess PPh3
30 °C, 1.4 bar
HO
OH
+
HO
OH
77%
19.5%

(13)

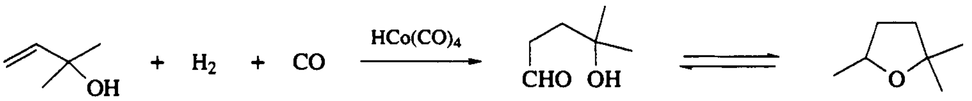
OH
+ H2 + CO
HCo(CO)4
CHO OH
O

(14)

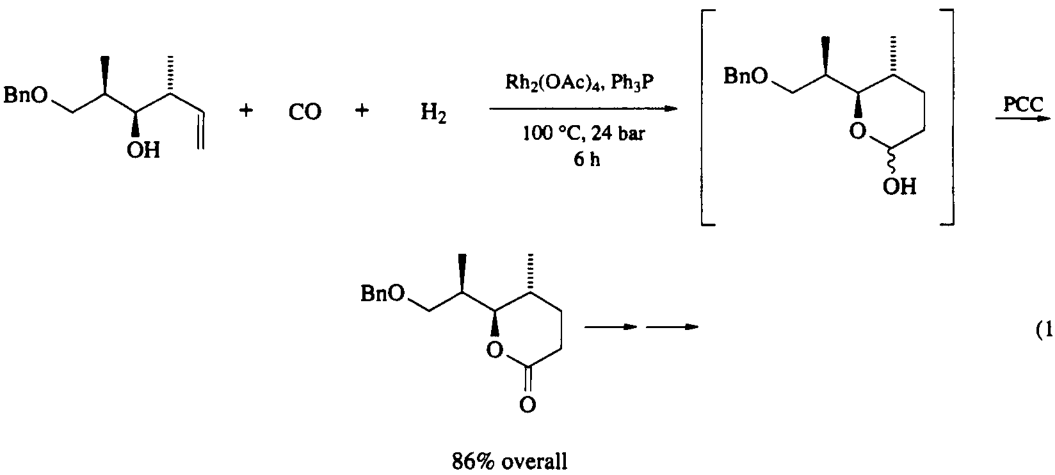
BnO
OH
+ CO + H2
Rh2(OAc)4, Ph3P
100 °C, 24 bar
6 h
BnO
O
OH
PCC
BnO
O
O
86% overall

(15)

The electron-withdrawing ability of an ether oxygen alters the regiochemistry of hydroformylation. This effect is present even in allyl ethers such as ethyl allyl ether, which gives predominately 2-methyl-3-ethoxypropanol.[2] The reaction with vinyl ethers is regioselective (equation 16)[5] or in some examples regiospecific (equation 17).[22] The products of hydroformylation of phenyl vinyl ethers can be converted into pharmacologically active aryloxypropylamines by reductive amination.

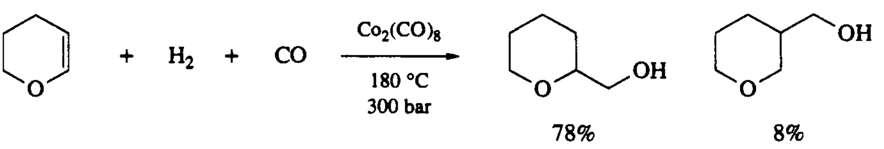
O
+ H2 + CO
Co2(CO)8
180 °C
300 bar
O
OH
O
OH
78%
8%

(16)

The regiochemistry of hydroformylation of acrolein cyclic acetals can be controlled to some extent by the presence or absence of phosphine. Excess phosphine provides predominately the straight chain alde-

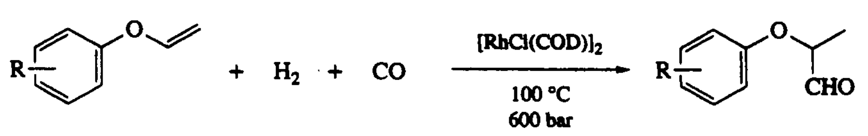

(17)

hyde with a number of catalysts (equation 18).[5] In the absence of phosphine, the major product is the branched aldehyde (equation 19).[22]

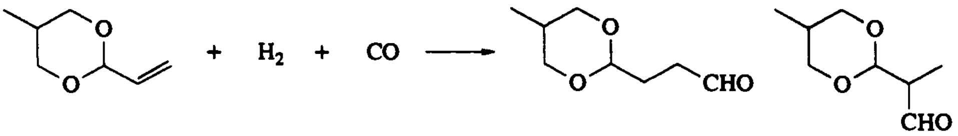

(18)

| | | |
|---|---|---|
| $Co_2(CO)_8$, $(C_8H_{17})_3P$<br>150 °C, 68–82 bar, 86% | 81% | 19% |
| $Rh_6(CO)_{11}$, $(MeO)_3P$<br>110 °C, 7.2 bar, 97% | 80% | 12% |
| $HRh(CO)(PPh_3)_3$<br>140 °C, 21–41 bar, 89% | 81% | 19% |

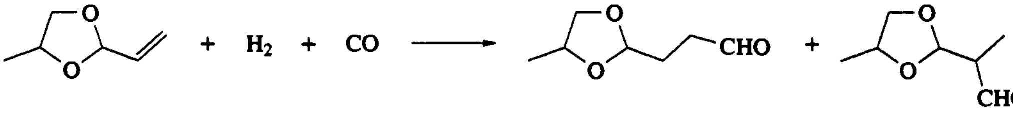

(19)

| | | |
|---|---|---|
| $[RhCl(COD)]_2$<br>100 °C, 600 bar | 33% | 57% |
| $[RhCl(COD)]_2$, 50 equiv. $PPh_3$<br>140 °C, 20 bar | 70% | 30% |

The hydroformylation of allyl and vinyl acetals yields some useful intermediates. Allyl acetate undergoes partial double bond migration prior to hydroformylation with a cobalt catalyst in the absence of phosphine (equation 20).[2,5] Rhodium catalysts containing chelating phosphines are more selective to the linear aldehyde.[31]

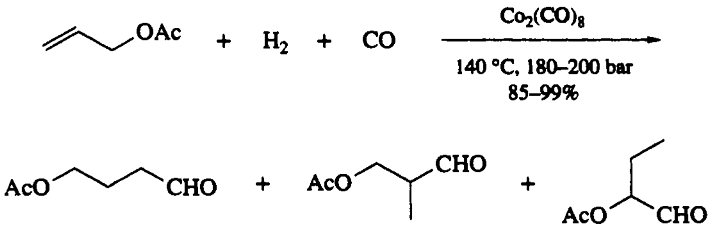

60–70% 15–20% 15–20%

(20)

Industrial (BASF) syntheses of vitamin A and vitamin A aldehyde have been accomplished utilizing the aldehydes obtained from allyl acetate hydroformylation.[22] Either aldehyde (**10**) or (**11**) reacts with the same phosphorus ylide to give vitamin A or retinal (Scheme 4). Hydroformylation of 3-methyl-2-butenyl acetate gives a high yield of 2-formyl-3-methylbutyl acetate. Elimination of acetic acid followed by isomerization provides trimethylacrylaldehyde, which is an intermediate in the synthesis of irones (Scheme 5).

The hydroformylation of vinyl acetate has been accomplished by a number of different catalysts.[30,31,33,34] The branched isomer is the major product, the regioselectivity being attributed both to the electron-withdrawing effect of oxygen and the chelating effect of the ester carbonyl.[4] High regioselectivity can be achieved in a polar solvent with a rhodium catalyst (equation 21).[33,34] Vinyl pivalate shows nearly a five times greater selectivity for the branched aldehyde.[34]

Unsaturated aldehydes, ketones and esters undergo hydroformylation of the double bond without reaction at the carbonyl group. For example, dienes yield aldehydes in a stepwise fashion (*vide supra*); however, α,β-unsaturated aldehydes and ketones undergo rapid hydrogenation to the saturated aldehyde

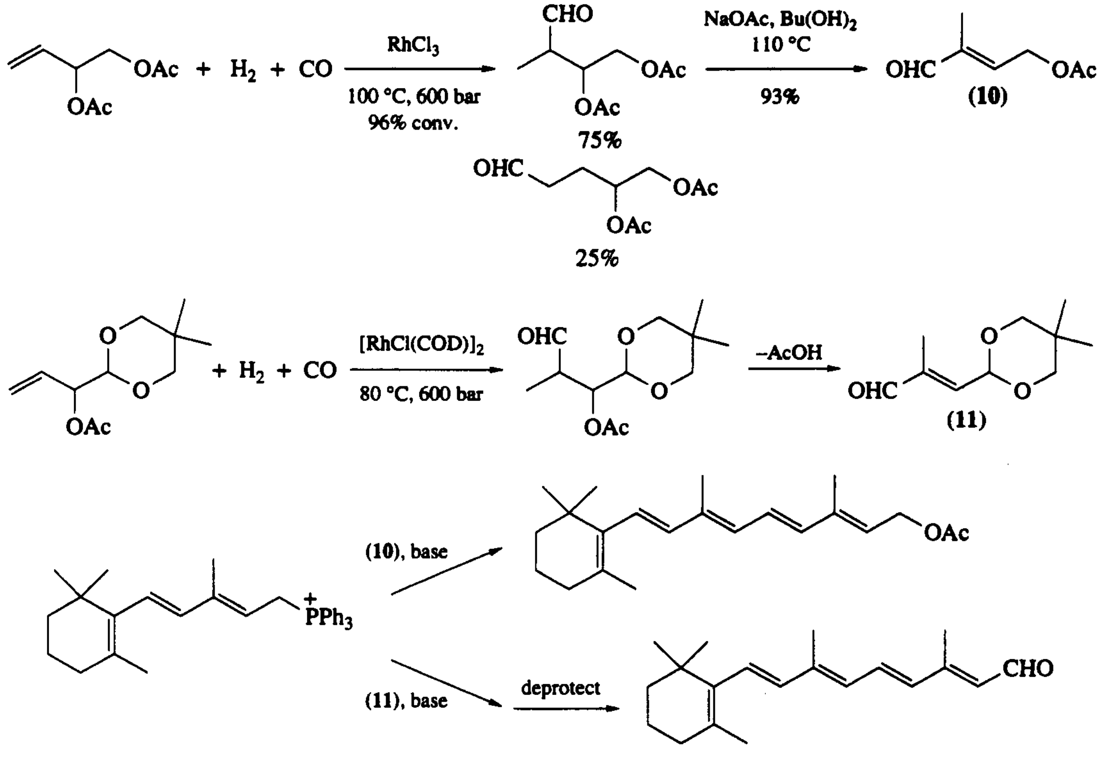
OAc
OAc
+ H2 + CO
RhCl3
100 °C, 600 bar
96% conv.
CHO
OAc
OAc
75%
OHC
OAc
OAc
25%
NaOAc, Bu(OH)2
110 °C
93%
OHC
OAc
(10)
O
O
OAc
+ H2 + CO
[RhCl(COD)]2
80 °C, 600 bar
OHC
O
O
OAc
-AcOH
OHC
O
O
(11)
PPh3
(10), base
OAc
(11), base
deprotect
CHO

**Scheme 4**

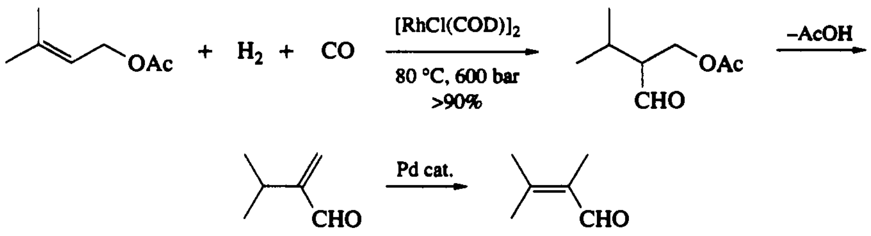
OAc
+ H2 + CO
[RhCl(COD)]2
80 °C, 600 bar
>90%
OAc
CHO
-AcOH
CHO
Pd cat.
CHO

**Scheme 5**

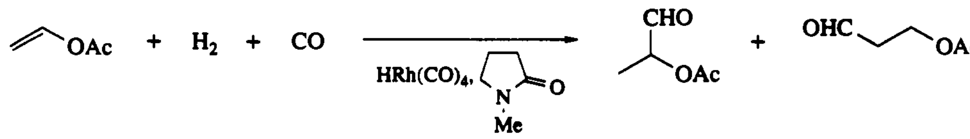
OAc
+ H2 + CO
HRh(CO)4,
N
Me
O
CHO
OAc
+
OHC
OAc

(21)

| | | |
|---|---|---|
| 60 °C, 200 bar, 83% | 95% | 5% |
| Rh(CO)$_2$(acac), 15 equiv. Ph$_3$P<br>DMSO or DMF, 8 bar, 86% | 86% | 14% |

or ketone instead of undergoing hydroformylation.[1,2,5] Hydroformylation of an unsaturated ketone (in which the carbonyl is not conjugated) takes place selectively at the more reactive double bond to give an aldehyde that can be converted to guaiazulene (equation 22).[22]

α,β-Unsaturated esters are not hydrogenated as readily with hydroformylation catalysts, so aldehydes can be obtained (equation 23).[5,30,31,35,36] The regioselectivity is sensitive to substitution and reaction conditions. Formylation at the β-position is driven by conjugation of the double bond with the carbonyl, substitution at the α-position, and excess phosphine (equations 24 and 25). Similarly, the selectivity in the hydroformylation of dimethyl itaconate can be reversed by phosphine-modified catalysts (equation 26).

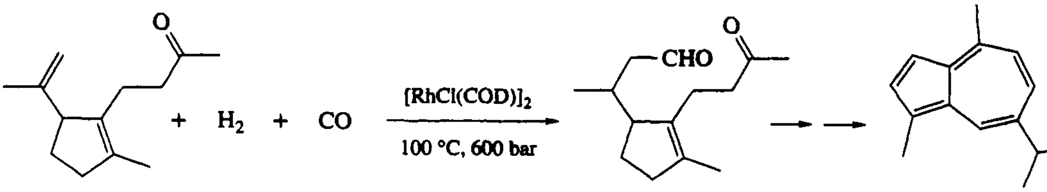
+ H2 + CO
[RhCl(COD)]2
100 °C, 600 bar
CHO

(22)

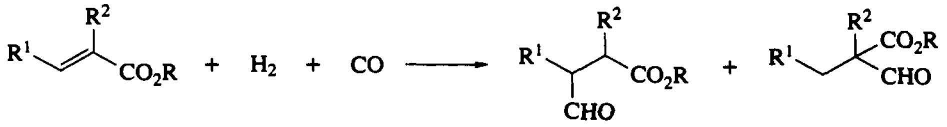
R2
R1
CO2R
+ H2 + CO
CHO

(23)

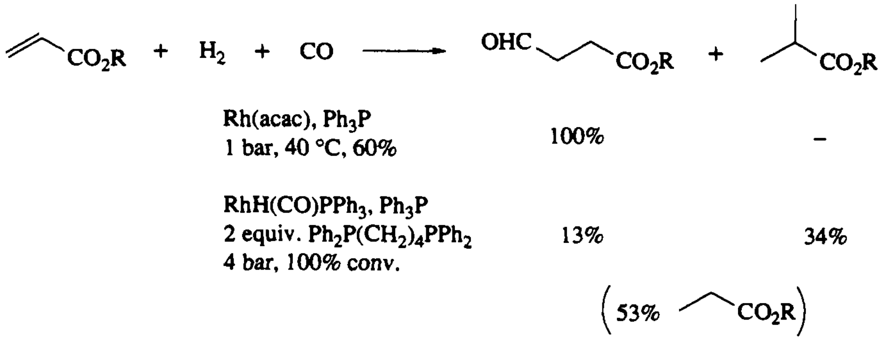
CO2R
+ H2 + CO
OHC
53%

(24)

| | | |
|---|---|---|
| Rh(acac), $Ph_3P$<br>1 bar, 40 °C, 60% | 100% | - |
| $RhH(CO)PPh_3$, $Ph_3P$<br>2 equiv. $Ph_2P(CH_2)_4PPh_2$<br>4 bar, 100% conv. | 13% | 34% |

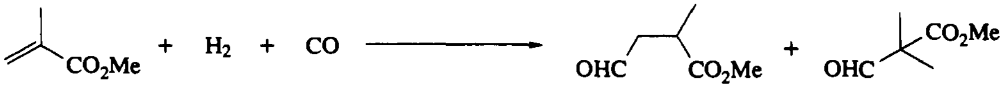
CO2Me
+ H2 + CO
OHC
CO2Me
+
OHC
CO2Me

(25)

| | | |
|---|---|---|
| $Rh_4(CO)_{12}$, 100 °C, 15 bar, 98% | 6% | 94% |
| $[Rh(nbd)Cl]_2$, 150 °C, 80 bar, 100% | 53% | 47% |
| $[Rh(nbd)Cl]_2$, $Bu_3P$, 100 °C, 15 bar, 58% | 82% | 18% |

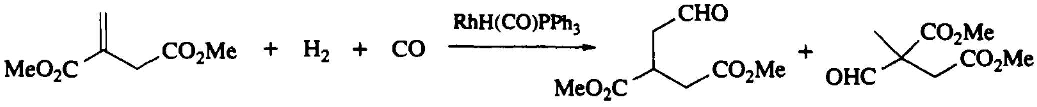
MeO2C
CO2Me
+ H2 + CO
RhH(CO)PPh3
CHO
CO2Me
MeO2C
+
OHC
CO2Me
CO2Me

(26)

Acrylonitrile yields predominately the linear cyano aldehyde, although considerable double bond reduction takes place (equation 27).[37] The reaction has received considerable attention since it is a precursor to glutamic acid *via* a Strecker reaction.[1,2]

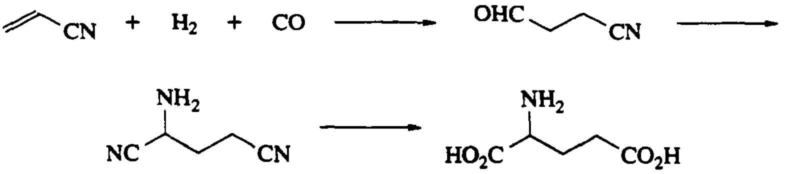
CN
+ H2 + CO
OHC
CN
NH2
NC
CN
NH2
HO2C
CO2H

(27)

Nitro groups are tolerated in hydroformylation as are amines, provided they are protected. The reaction of *o*-nitrostyrene gives an intermediate for the synthesis of 3-methylindole (equation 28).[38] With a phosphine-modified rhodium catalyst, the reaction is regioselective, placing the formyl group in the α-position.

Vinylamides are not regioselectively hydroformylated but rhodium catalysts tend to cause formylation at the carbon adjacent to the nitrogen (Table 3).[2] *N*-Allylamides exhibit a regiochemistry that indicates some electronic influence of nitrogen even though it is one methylene removed from the double bond. The aldehydes obtained from the regioselective hydroformylation of *N*-vinylamides are of interest because they represent intermediates for amino acid synthesis.[40]

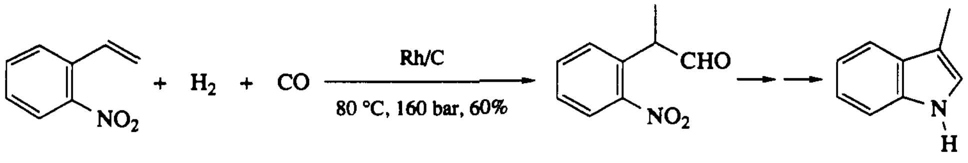
NO2
+ H2 + CO
Rh/C
80 °C, 160 bar, 60%
CHO
NO2
N
H

(28)

Although *N*-methyltetrahydropyridines are not selectively hydroformylated, an equal mixture of the two aldehydes being obtained from *N*-methyl-1,2,3,6-tetrahydropyridine, *N*-methyltropidenes are selectively formylated at the 3-position (equation 29). The difference in the selectivity can be attributed to the substitution in tropidine (bridge head carbon).

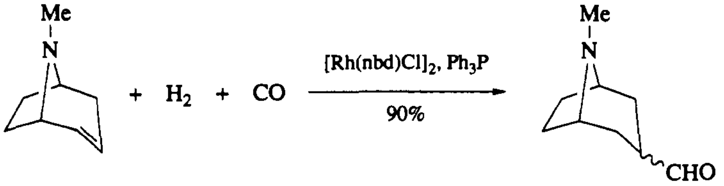
Me
N
+ H2 + CO
[Rh(nbd)Cl]2, Ph3P
90%
Me
N
CHO

(29)

Fluoroalkenes such as trifluoropropene and pentafluorostyrene show unique regioselectivities in hydroformylation reactions.[41] While cobaltoctacarbonyl catalysts give *n*/*b* ratios of about 93/7 and 90/10 for trifluoropropene and pentafluorostyrene, respectively, ruthenium and rhodium catalysts show selectivities of about 3/97, regardless of the ligands (the exception being that a ruthenium carbonyl catalyst gave a *n*/*b* ratio of 26/74 for pentafluorostyrene). These selectivities are in marked contrast to those obtained for the unfluorinated alkenes: propene, $Co_2(CO)_8$, 80/20; $Ru_3(CO)_{12}$, 74/26; styrene, $Co_2(CO)_8$, 41/59; $Rh_2Cl_2(CO)_4/PPh_3$, 57/43. The hydroformylation of these fluorinated alkenes has been utilized in the synthesis of fluorinated amino acids (Scheme 6).

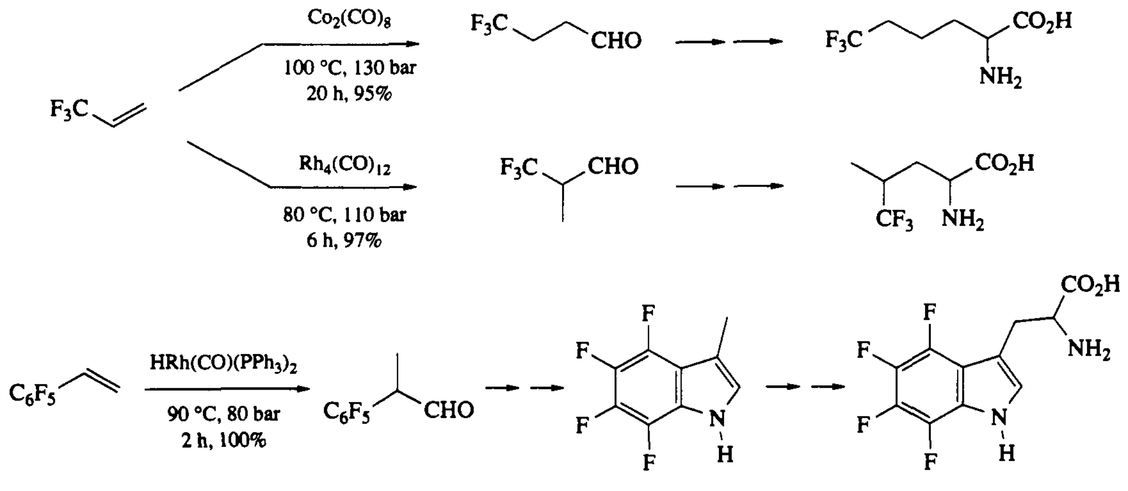
F3C
Co2(CO)8
100 °C, 130 bar
20 h, 95%
F3C
CHO
F3C
CO2H
NH2
Rh4(CO)12
80 °C, 110 bar
6 h, 97%
F3C
CHO
CO2H
CF3
NH2
C6F5
HRh(CO)(PPh3)2
90 °C, 80 bar
2 h, 100%
C6F5
CHO
F
F
F
F
N
H
CO2H
NH2
F
F
F
F
N
H

Scheme 6

### 4.5.2.6 Asymmetric Hydroformylation[42–44]

The generation of a chiral center as a result of alkene hydroformylation can take place either by formylation or hydride addition at the prochiral carbon (equations 30 and 31). Kinetic resolution in the hydroformylation reaction of a racemic alkene containing a chiral center could also occur, but in this example the chiral center is not generated as a result of the hydroformylation reaction.

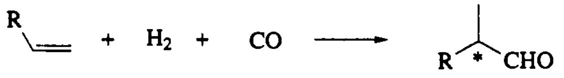

(30)

**Table 3** Hydroformylation of Unsaturated Amides

| *Vinylimide* | *Catalyst* | *Temperature* (°C) | *Pressure* (bar) | *Products* | | | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 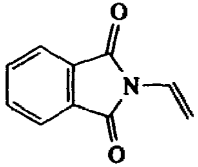 | $Co_2(CO)_8$ | 120 | 170 | 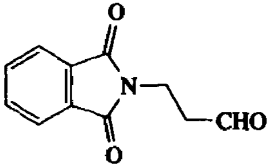 | | 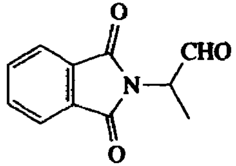 | 78 | 38 |
| | | | | 15 | : | 1 | | |
| | $HRh(CO)(PPh_3)_3$ | 65 | 34 | None | | Only | 100 | 39 |
| 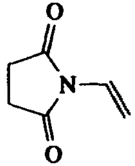 | $HRh(CO)(PPh_3)_3$ | 65 | 34 | | | 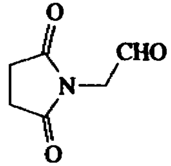 | 100 | 39 |
| | $[RhCl(COD)]_2$ | 90 | 700 | | | Only | 90 | 2 |
| 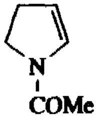 | $HRh(CO)(PPh_3)_3$,<br>DIPHOL[a] | 60 | 34 | | | 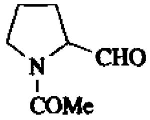 | 100 | 39 |
| 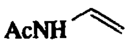 | $HRh(CO)(PPh_3)_3$ | 40–45 | 34 | 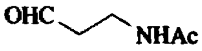 | | 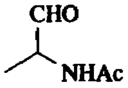 | 70 | 39 |
| | | | | 46 | : | 54 | | |
| 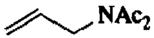 | $Co_2(CO)_8$ | 120 | 170 | 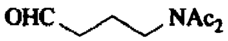 | | 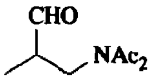 | 90 | 38 |
| | | | | 6.7 | : | 1 | | |

**Table 3** *(continued)*

| *Vinylimide* | *Catalyst* | *Temperature* (°C) | *Pressure* (bar) | *Products* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 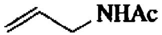 | $HRh(CO)(PPh_3)_3$ | 40 | 34 | 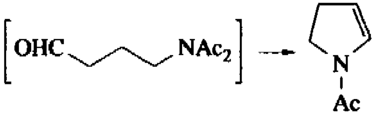 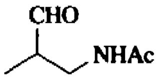<br>46 : 54 | 100 | 39 |

[a] See structure (**13**).

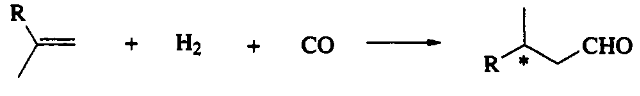

(31)

The enantioselective step in rhodium-catalyzed hydroformylation reactions (refer to Scheme 2) can take place either in the formation of the alkene complex (**3**), at the insertion of the alkene to yield (**4**), or in the CO insertion step (**5**), since these steps are all reversible. For example, if the diastereomers (**3**), obtained from the complexation of the alkene *re* and *si* faces, are converted in a fast step to (**4**), then the ratios of the diastereomeric complexes (**3**) will determine the enantiomeric excess. If, however, one diastereomer (for example, the highest energy complex, present in a minor amount) undergoes the insertion reaction several orders of magnitude more rapidly than the other diastereomer, then it is possible, depending on the subsequent step, that the diastereomeric ratios of (**4**) are representative of the enantiomeric excess. This question has been addressed by carrying out the asymmetric hydroformylation of 1-butene, (*Z*)-2-butene and (*E*)-2-butene, which yield the same product, 2-methylbutanol. This means that all three substrates must pass through a common alkylmetal intermediate (Scheme 7).[45] Since with both rhodium and platinum catalysts, the prevailing chirality of the product and the enantiomeric excesses depend on substrate structure, this suggests that the enantioselection occurs before or during the formation of the alkyl metal intermediate.

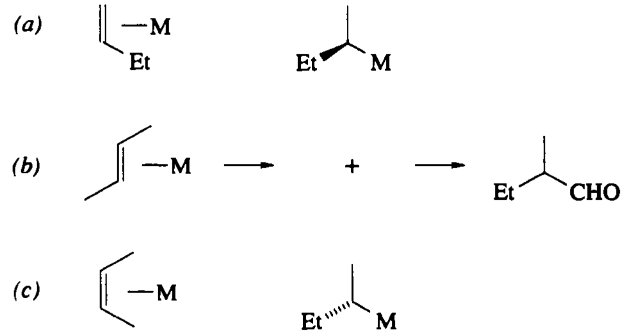

| *S.M.* | *M* | *Absolute configuration* | *% ee* |
|---|---|---|---|
| *a* | Rh | *(R)* | 18.8 |
|  | Pt | *(R)* | 46.7 |
| *b* | Rh | *(S)* | 32.0 |
|  | Pt | *(S)* | 24.2 |
| *c* | Rh | *(S)* | 27.0 |
|  | Pt | *(S)* | 14.5 |

**Scheme 7**

By using a stereochemical model for the transition state of the insertion reaction with nonbonded interactions between a complex of given chirality and the alkene the enantiomeric excesses as well as the regioisomeric excesses of aldehydes from monosubstituted, and 1,1- and 1,2-disubstituted ethylenes can be predicted. The prediction is correct in more than 80% of the cases studied.[46,47]

Until recently, only moderate enantiomeric excesses of branched aldehydes had been realized in hydroformylation reactions with rhodium and platinum catalysts. Utilizing the chelating ligand (4*R*,5*R*)-2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane (**12**; (–)-DIOP) in the presence of the appropriate rhodium complex generates HRh(CO)[(–)-DIOP], which catalyzes the hydroformylation of styrene to hydrotropaldehyde in 25% *ee*.[42,43] Replacing the diphenylphosphino groups with dibenzophosphole gives the (–)-DBP-DIOP ligand (**13**), which yields a rhodium catalyst that hydroformylates styrene in 33% *ee*.[45] Other chelating ligands such as phosphinites, phosphines and phospholes of 1,2-dimethylene-cyclohexane and -cyclobutane gave lower enantiomeric excesses (2–30%).[41] Low enantiomeric excesses (~25%) have also been obtained with the use of CHIRAPHOS (**14**)[48] and EPHOS (**15**).[49] A variety of other alkene substrates have been hydroformylated but enantiomeric excesses have never been higher than about 50% with rhodium as a catalyst,[42,50,51] the highest enantiomeric excess being achieved in the hydroformylation of vinyl acetate with Rh/(–)-DBP-DIOP (equation 32).[50] In a number of reactions, the optical yields were observed to be dependent on the temperature, as expected, and on the partial pressures of carbon monoxide and hydrogen.[42,52] This reaction is particularly attractive since 2-acetoxypropanol is a precursor for the Strecker synthesis of threonine.

Until recently, the use of platinum complexes in asymmetric hydroformylation had been less encouraging because of the lower reaction rates and the tendency for the substrate to undergo competitive hydrogenation. In addition, relatively high normal to branched (*n*/*b*) ratios have been observed in the hydroformylation of monosubstituted alkenes. Hydroformylation of 1- and 2-butenes in the presence of [(–)-DIOP]$PtCl_2/SnCl_2$ was reported by two groups to give nonreproducible (and sometimes contradictory) results.[53] In contrast, the use of the preformed [(–)-DIOP]$Pt(SnCl_3)Cl$ complex as a catalyst precursor did give reproducible results.[54]

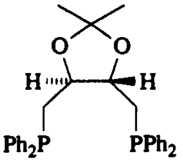

**(12)**

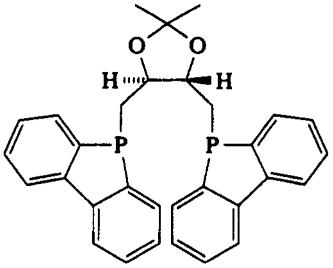

**(13)**

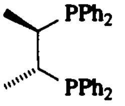

**(14)**

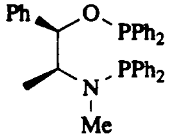

**(15)**

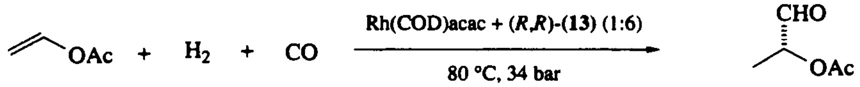

(32)

51% *ee*
75–95% selectivity

Although the enantiomeric excesses, selectivity and *n*/*b* ratios are dependent on such variables as the $H_2$/CO ratio, the total pressure, the substrate concentration and the ratio of phosphorus to platinum, no consistent pattern emerges to reveal much information as to the reaction mechanism.[55] The hydroformylation of a variety of substrates has been carried out, with enantiomeric excesses ranging from 20 to 44%,[56] usually with DIOP (**12**) or CHIRAPHOS (**14**) as ligands.[48,56] The highest enantiomeric excesses (73% and 85%, respectively) obtained from the hydroformylation of styrene were with [(–)-DBP-DIOP]$PtCl_2$/$SnCl_2$ at 40–60 °C, 220 bar, $H_2$/CO = 2.4[57] and (*R*,*R*)-2,3-bicyclo[2.2.2]octanediylbis(methylene)bis(diphenylphosphine)$PtCl_2$/$SnCl_2$ (equation 33).[58]

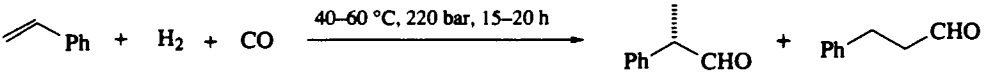

(33)

5:1

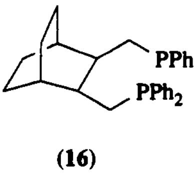

**(16)**

| | |
|---|---|
| $PtCl_2$•$SnCl_2$ (**13**) | 73% *ee* |
| (**16**)•$PtCl_2$•$SnCl_2$ | 85% *ee* |

Thus the enantiomeric excesses obtained in the platinum-catalyzed hydroformylation reactions of certain alkenes were achieved at a level (75–85% *ee*) necessary for facile enrichment to optically pure compounds, presenting an opportunity to establish this reaction as a viable asymmetric synthesis of aldehydes.

Some of the highest enantiomeric excesses in hydroformylation reactions of styrene (~70–80% *ee*) have been obtained with a platinum catalyst containing the chiral ligand (2*S*,4*S*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (**17**; (–)-BPPM).[59]

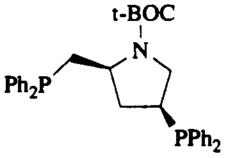

**(17)**

Styrene hydroformylation with [(–)-BPPM]$PtCl_2$ and added $SnCl_2$ to yield a mixture of 2- and 3-phenylpropanal has been carried out in benzene at different reaction pressures (100–180 bar), temperatures (50–95 °C) and reaction times (2–15 h; equation 34).[59] The normal to branched ratio was relatively high (*n*/*b* = 2), but the selectivity to aldehyde was high, less than 2% of ethylbenzene being obtained in each case. Branched aldehyde, 2-phenylpropanal, was obtained in relatively high enantiomeric excess, particularly when the reaction times were short and the temperature was low, 78–80% *ee* being obtained at 56–57 °C after 2–4 h, and low conversion. The lower enantiomeric excesses obtained at longer reaction times are a result of product racemization under the reaction conditions.

The hydroformylation reaction of vinyl aromatics (Table 4)[60] lends itself to the synthesis of a number of 2-arylpropionic acids in high enantiomeric excess that are nonsteroidal antiinflammatory agents.[61] Previous asymmetric syntheses of these acids required the use of stoichiometric amounts of chiral auxiliaries, which in most cases are not easily recovered. The branched aldehyde was oxidized to (*S*)-(+)-naproxen,[62] in 84% yield.

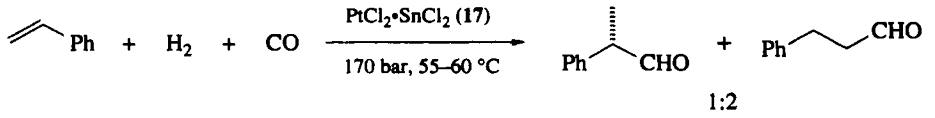

(34)

An analgesic with greater antiinflammatory and antipyretic activity than Naproxen is α-methyl-4-(2-thienylcarbonyl)benzeneacetic acid, Suprofen.[63] This compound has been tested only as a racemic mixture, and any difference in the activity of the enantiomers is not known. Hydroformylation of 4-(2-thienylcarbonyl)styrene (entry 5, Table 4) to the 2-arylpropanal was achieved in 78% *ee* for the branched aldehyde [(+)-enantiomer in excess], which can be converted to Suprofen by oxidation.

Hydroformylations of several other vinyl substrates were carried out (Table 4). Vinyl acetate is a particularly interesting substrate, since, as mentioned earlier, it gives 2-acetoxypropanal, a precursor in the Strecker synthesis of threonine. The product can be converted to 2-hydroxypropanal, a useful intermediate in the synthesis of steroids, pheromones, antibiotics and peptides.

Hydroformylation of norbornene proceeds slowly in spite of the expected reactivity of the strained double bond. Racemization of the product aldehyde does not occur under the reaction conditions. The hydroformylation of methyl methacrylate gives only one isomer, which is a useful chiral synthon. Dimethyl itaconate also can be hydroformylated using (**12**) as the chiral ligand to give aldehyde product in 82% *ee* accompanied by hydrogenated ester.[64]

In the hydroformylation reactions of vinyl aromatics, racemization of the products takes place under the reaction conditions. Presumably racemization of the aldehydes also can take place in hydroformylations carried out with substrates other than vinyl aromatics, although this was not verified in all examples.

The hydroformylation of styrene in triethyl orthoformate is slower than that observed in benzene, but a 98% *ee* is obtained, since racemization of the product acetal does not occur. Hydrolysis of the acetal to the aldehyde can be accomplished without racemization. A number of other substrates are hydroformylated in the presence of triethyl orthoformate. The reactions are slower, but with all substrates tried except norbornene, enantiomerically pure products can be obtained.

## 4.5.3 CARBOXYLATION[1,2,65]

The hydrocarboxylation reaction of alkenes and alkynes is one which utilizes carbon monoxide to produce carboxylic acid derivatives. The source of hydrogen is a protic solvent (equation 35); dihydrogen is not usually added to the reaction. There are a number of variations to this reaction, since the solvent can be water, alcohols, amines, acids, *etc*. The catalysts can be Group VIII–X transition metals, but cobalt, rhodium, nickel, palladium and platinum have found the most use.

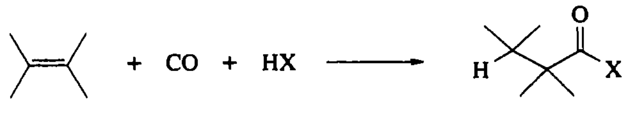

(35)

X = OH, OR, SR, $NR_2$, OCOR, Cl

Industrially, low molecular weight acids can be made from water, carbon monoxide and an alkene, but higher molecular weight acids are produced as esters. In water a phase-transfer agent is required for the

**Table 4**[60] Hydroformylation of Alkenes[a]

| *Entry* | *Alkene* | *Reaction time* (h) | *Solvent* | *Product* | *Conversion* (%) | *n/b* | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 1 | 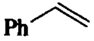 | 4 | PhH | 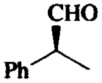 | 50–90 | 2 | 80 |
| 2 |  | 150 | $HC(OEt)_3$ | 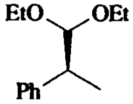 | 100 | 2 | >96 |
| 3 | 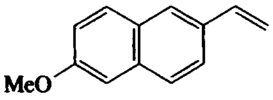 | 9 | PhH | 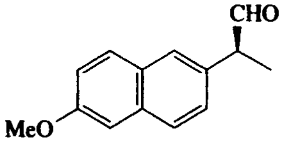 | 90 | 1.4 | 81 |
| 4 |  | 200 | $HC(OEt)_3$ | 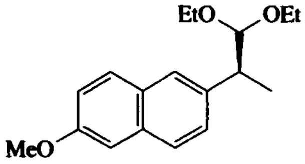 | 55 | 1.4 | >96 |
| 5 | 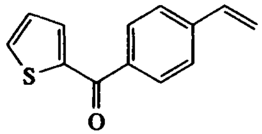 | 9 | PhH | 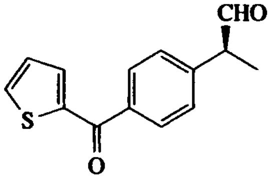 | 73 | 2 | 78 |
| 6 | 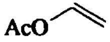 | 40 | PhH | 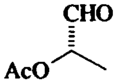 | 50 | 2.3[b] | 82 |

**Table 4** *(continued)*

| *Entry* | *Alkene* | *Reaction time* (h) | *Solvent* | *Product* | *Conversion* (%) | *n/b* | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 7 | 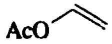 | 240 | $HC(OEt)_3$ | 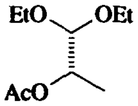 | 25 | 0.67[b] | >98 |
| 8 | 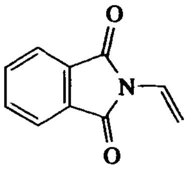 | 46 | PhH | 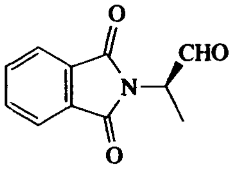 | 52 | 2 | 73 |
| 9 | | 240 | $HC(OEt)_3$ | 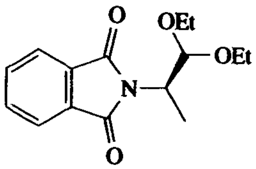 | 46 | 2 | >96 |
| 10 | 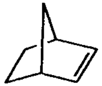 | 20 | PhH | 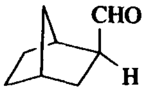 | 84 | c | 60 |
| 11 | | 140 | $HC(OEt)_3$ | 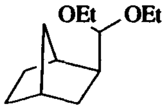 | 100 | c | 60 |
| 12 | 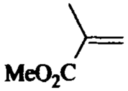 | 50 | PhH | 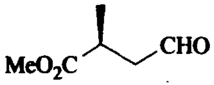 | 36 | c | 60 |

**Table 4** *(continued)*

| *Entry* | *Alkene* | *Reaction time* (h) | *Solvent* | *Product* | *Conversion* (%) | *n/b* | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 13 | 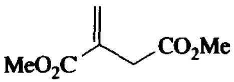 | 45 | PhMe[d,e] | 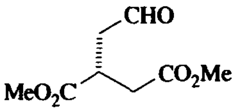 | 28 | f | 82 |

[a] Entries 1–12: (17)•$PtCl_2$•$SnCl_2$; $H_2/CO = 1$; temperature = 60 °C (except entry 1, 55 °C and entries 10 and 11, 30 °C); pressure = 165–185 bar; selectivities > 98% except entry 8, 85%. [b] Linear aldehyde and acetal partially decomposed. [c] Only one aldehyde (or acetal) obtained. [d] $H_2/CO = 3$. [e] From ref. 64: (12)•$PtCl_2$•$SnCl_2$; $H_2/CO = 1$; temperature = 50 °C; pressure = 40 bar. [f] 45% of product was $MeCH(CO_2Me)CH_2CO_2Me$, 35% *ee*.

higher molecular weight alkenes. A problem with aqueous hydrocarboxylation is that most of the catalysts also effect the water gas shift reaction.

### 4.5.3.1 Mechanisms[66]

There are two different reaction mechanisms that are possible for the overall transformation shown in equation (35). It is not always apparent which of the two mechanisms may be operative, the mechanistic pathway apparently depending on the reaction conditions (particularly added acids or bases), the transition metal and the substrate.

The hydrocarboxylation can take place by insertion of the alkene into a metal–hydride bond followed by CO insertion and finally reaction of the acyl complex with solvent as illustrated in equation (36). Alternatively, a transition metal–carboxylate complex can be generated initially. Insertion of the alkene into the metal–carbon bond of this carboxylate complex followed by cleavage of the metal–carbon bond by solvent completes the addition, as shown in equation (37). Both sequences provide the same product.

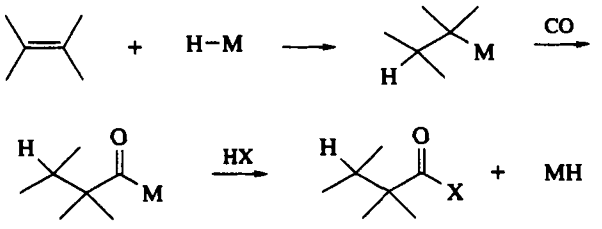

(36)

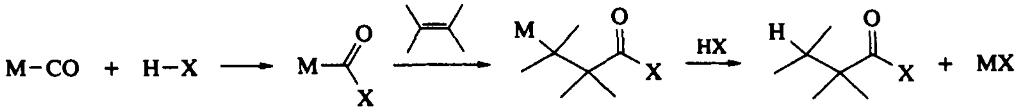

(37)

The metal hydride mechanism has been written particularly for hydrocarboxylation reactions with a palladium catalyst.[67,68] In the reactions of propene in the presence of $(Ph_3P)_2PdCl_2$, the acyl complex (**18**) was isolated from the reaction mixture, and also shown to be a catalyst for the reaction.

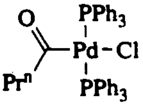

(**18**)

Both mechanisms are predicted to show *syn* addition of hydride and carboxylate to the alkene. In the metal hydride mechanism (equation 36) alkene insertion is *syn* and CO insertion proceeds with retention of configuration at carbon. In the metal carboxylate mechanisms (equation 37) alkene insertion is *syn* and cleavage of the metal–carbon bond can take place with retention at carbon. The palladium-catalyzed hydroesterification reaction produces the *erythro* ester from (*Z*)-3-methyl-2-pentene (equation 38) and the *threo* ester from (*E*)-3-methyl-2-pentene (equation 39).[69]

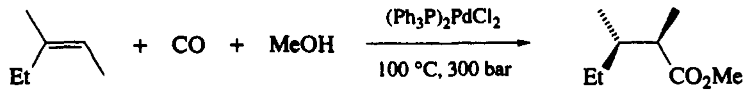

(38)

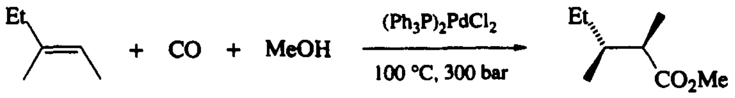

(39)

In certain other systems, there is compelling evidence for the insertion into a metal–carboxylate complex (equation 37). For example, in the synthesis of α-methylene-γ-lactones from alkynic alcohols,[70,71] no double bond rearrangement to a butenolide occurs, a reaction shown to take place in the presence of transition metal hydrides. The source of the vinyl proton (deuterium) on the α-methylene group is indeed the alcohol function. Finally, palladium carboxylate complexes containing alkynic (equation 40) or vinyl tails (equation 41) can be isolated and the corresponding insertion reaction can be observed.

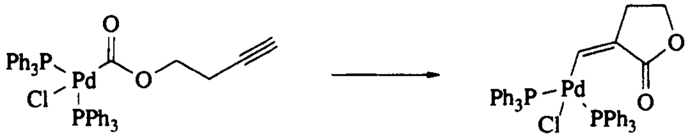

(40)

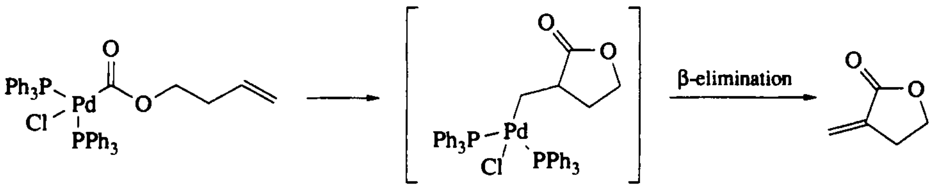

(41)

The metal carboxylate insertion mechanism has also been demonstrated in the dicobaltoctacarbonyl-catalyzed carbomethoxylation of butadiene to methyl 3-pentenoate.[66,72] The reaction of independently synthesized cobalt–carboxylate complex (**19**) with butadiene (Scheme 8) produced $\eta^3$-cobalt complex (**20**) *via* the insertion reaction. Reaction of (**20**) with cobalt hydride gives the product. The pyridine–CO catalyst promotes the reaction of methanol with dicobalt octacarbonyl to give (**19**) and $HCo(CO)_4$.

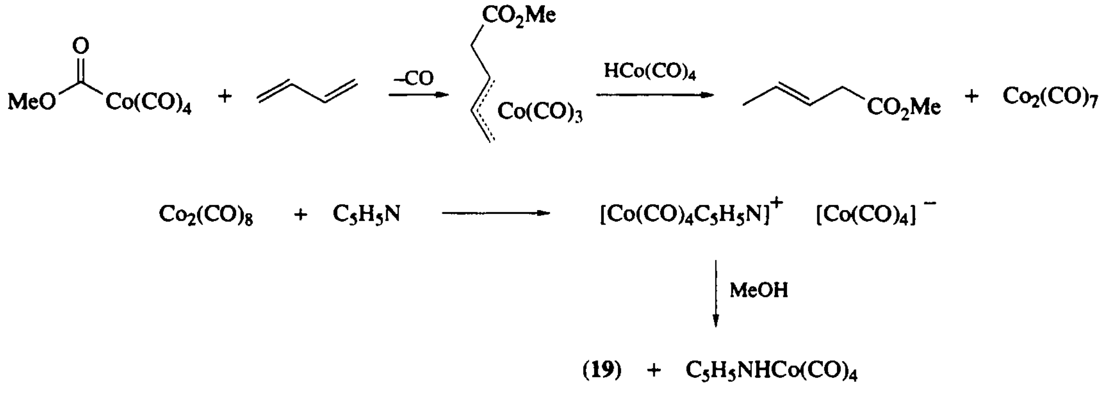

**Scheme 8**

Thus the catalytic cycles that have been written reflect these mechanistic findings. In the hydride mechanism, illustrated with cobalt (Scheme 9), the hydride is generated either by the alcohol *vide supra* or by adventitious hydrogen (*e.g.* from a water gas shift reaction). In the case of a palladium catalyst introduced as $(Ph_3P)_2PdCl_2$, the palladium is first reduced to palladium(0), which then undergoes the rapid oxidative addition of HCl to yield $(Ph_3P)_2Pd(Cl)H$. Alkene insertion and carbon monoxide insertion steps are the characteristic sequence of events in such catalysis. The hydride $HCo(CO)_4$ is acidic and readily decomposes as cobalt metal in the absence of carbon monoxide; high CO pressures are necessary to stabilize $HCo(CO)_4$ and the intermediates in the catalytic cycle.

The mechanism of the reaction of the alcohol (or water) with the acyl complex to produce ester (or acid) and regenerate the cobalt hydride complex is not known. Because the reaction of the analogous manganese complex with alcohols is known to proceed through a hemiacetal-like complex, this mechanism has been written for the carboxylation reaction (equation 42).

The transition metal carboxylate mechanism (Scheme 10), illustrated with palladium, requires the generation of this type of complex in the initial steps. This can occur by the alcoholysis of dicobalt octacarbonyl (Scheme 6) or by, for example, the reaction of methanol with a palladium(II) carbonyl (equa-

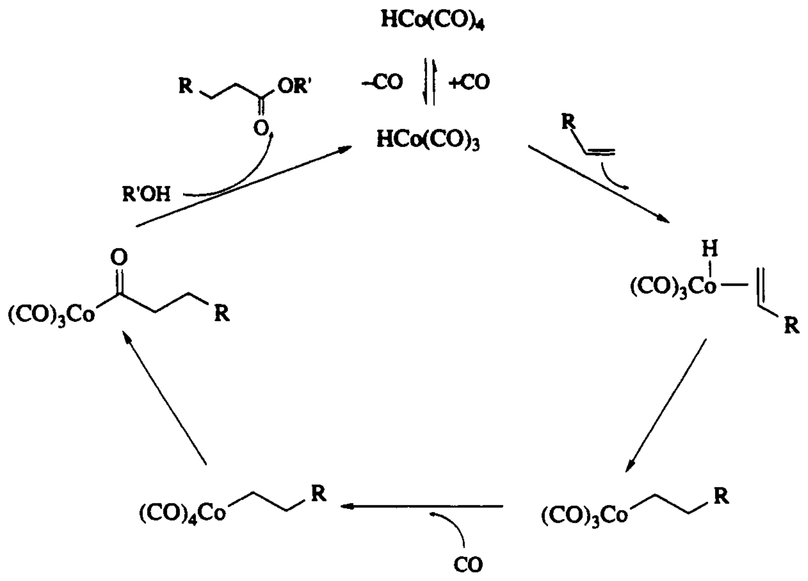
HCo(CO)4
-CO
+CO
HCo(CO)3
R'OH
(CO)3Co
(CO)4Co
CO
R
OR'
H

**Scheme 9**

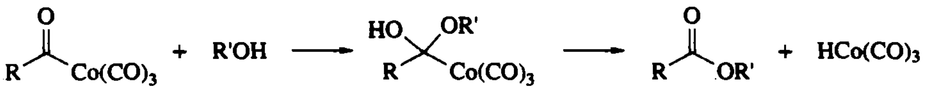
+ R'OH
HO
OR'
Co(CO)3
+ HCo(CO)3
(42)

tion 43). The palladium catalyst containing a trichlorostannate ligand, an excellent catalyst for the hydrocarboxylation, has been shown to proceed by the palladium carboxylate insertion mechanism.[70,71]

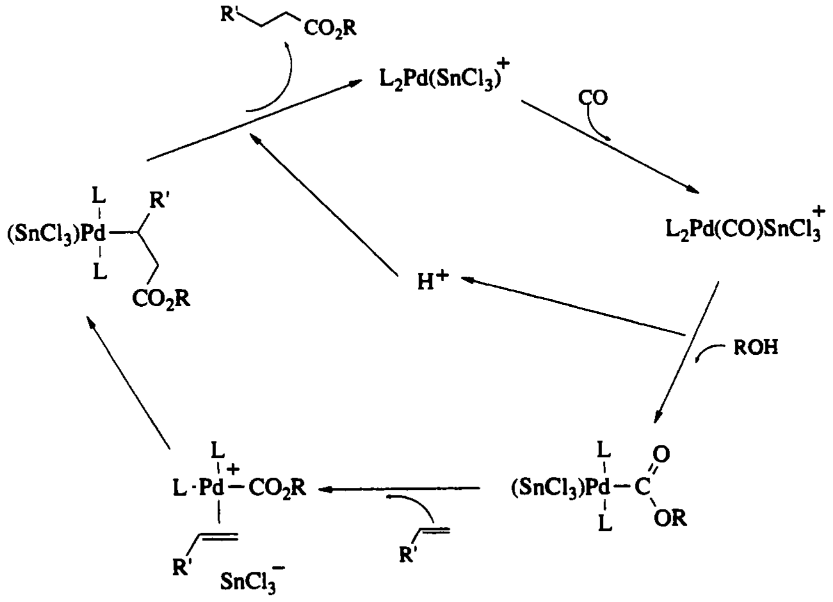
$L_2Pd(SnCl_3)^+$
CO
$L_2Pd(CO)SnCl_3^+$
ROH
$H^+$
$(SnCl_3)Pd$
$CO_2R$
L
R'
OR
$SnCl_3^-$

**Scheme 10**

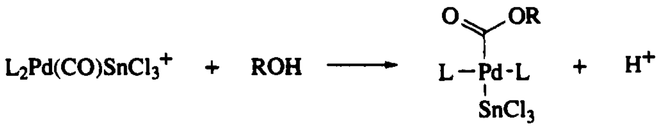

$$L_2Pd(CO)SnCl_3^+ + ROH \longrightarrow L-\overset{\overset{O\!=\!C-OR}{|}}{\underset{\underset{SnCl_3}{|}}{Pd}}-L + H^+$$
(43)

The final step in the catalytic cycle is the cleavage of the metal–alkyl bond with acid, which must take place faster in the hydrocarboxylation of alkenes than β-elimination.

### 4.5.3.2 Catalysts and Products

Nickel catalysts are utilized for the industrial synthesis of acrylic acid or esters either in a semicatalytic process with $Ni(CO)_4$ or a catalytic process with $NiBr_2$ (equation 44).[73] The reaction is carried out in THF containing water or alcohol (to avoid acetylene detonation at 60 bar).

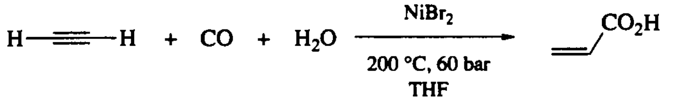

(44)

Most industrial carboxylation reactions utilize cobalt catalysts, which produce predominately linear acids or esters from 1-alkenes. The hydroesterification of 1-pentene produces 70% methyl hexanoate and 30% branched esters (entry 1, Table 5). Hydroesterification reactions utilizing the palladium catalyst $(Ph_3P)_3PdCl_2$[74] take place under milder conditions than required for a cobalt catalyst. However, the branched isomer is produced in larger amounts (entry 2, Table 5). As in the hydroformylation reaction, the addition of excess phosphine improves the *n*/*b* ratio.[75] The hydrocarboxylation reaction of styrene under these conditions yields the branched ester almost exclusively. Chelating phosphines such as 1,4-bis(diphenylphosphino)butane shift the *n*/*b* ratio for styrene to 1/1.[76] The addition of tin(II) chloride to the palladium catalyst shifts the isomer ratio dramatically.[77] Thus 87% selectivity to the straight chain product is achieved. This combined with the relatively mild conditions makes the palladium-catalyzed hydroesterification particularly attractive for the production of straight chain acids (entry 3, Table 5). It is likely that under these latter conditions a metal carboxylate mechanism is taking place, while without added tin(II) chloride, the metal hydride mechanism is operative. Hydroesterification reactions of $C_6F_5CH{=}CH_2$ and $CF_3CH{=}CH_2$ show approximately the same regioselectivities with these palladium catalysts.[41]

Platinum also catalyzes hydrocarboxylation, under comparable reaction conditions (240 bar, 80 °C). The best ligand in this case is triphenylarsine and a 10-fold excess of tin(II) chloride provides even higher selectivity to the linear ester (entry 4, Table 5).[78]

Branched acids and esters are obtained from the palladium-catalyzed reaction in the absence of phosphines, and in the presence of copper chloride and HCl.[79] The mild reaction conditions and the regiospecificity make this a very attractive carboxylation procedure (entry 5, Table 5). Internal straight chain alkenes can be hydrocarboxylated, but the rates are slower and the reaction is not regiospecific.

### 4.5.3.3 Hydrocarboxylation of Alkenes

Although the hydrocarboxylation of 1-alkenes is not of interest for the synthesis of more complex organic molecules, the information obtained from the hydrocarboxylation reactions with various catalysts can be applied to the synthesis and reactions of other alkene substrates.

The reaction with norbornene gives the *exo* acid (equation 45).[2] Under mild conditions, vinylcyclohexene is carbonylated at the least-substituted double bond; higher temperatures (120 °C) are necessary to attain the diester (equation 46).[74,80]

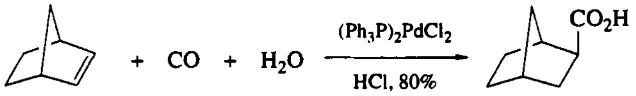

(45)

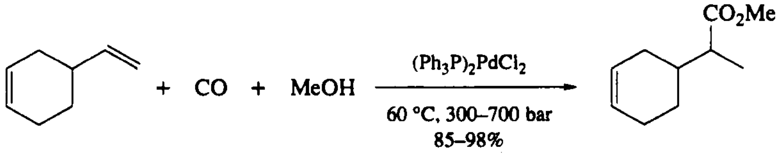

(46)

**Table 5** Hydroesterification Reaction of 1-Alkenes with Methanol

| *Entry* | *Alkene* | *CO/pressure* (bar) | *Temperature* (°C) | *Catalyst* | *Yield* (%) | *Products* | *Relative yield* (%) |
|---|---|---|---|---|---|---|---|
| 1 | 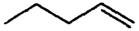 | 100–200 | 140–170 | $Co_2(CO)_8$ | 80–90 | 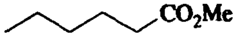 | 70 |
| | | | | | | 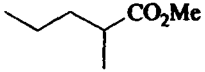 | 30 |
| 2 | 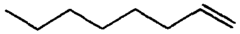 | 35 | 80–110 | $(Ph_3P)_2PdCl_2$ | 80 (conv.) | 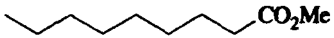 | 60 |
| | | | | | | 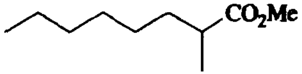 | 40 |
| 3 | 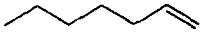 | 138 | 80 | $(Ph_3P)_2PdCl_2$,<br>$10SnCl_2$ | 96 (conv.) | 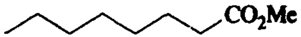 | 87 |
| | | | | | | 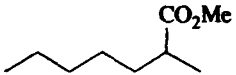 | 14 |
| 4 | 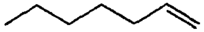 | 240 | 80 | $(Ph_3As)_2PtCl_2$,<br>$10SnCl_2$ | 95 (conv.) | 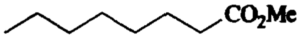 | 98 |
| 5 | 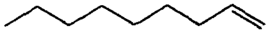 | 1 | 25 | $PdCl_2$, $10CuCl_2$<br>$O_2$, HCl | 100 | 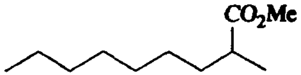 | 100 |

The reaction of nonconjugated dienes such as 1,4-pentadiene and 1,5-hexadiene yields cyclopentanone derivatives, while 1,6-heptadiene gives only traces of ketone (equation 47).[1,2,80] The yields in these reactions are low, 1,4-pentadiene giving only 10% of cyclic ketone product.

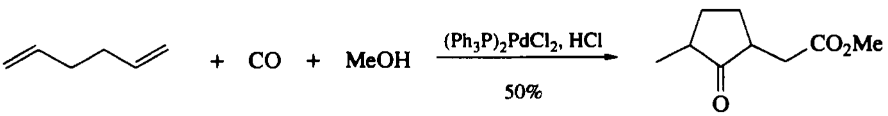

(47)

The hydrocarboxylation reaction of simple alkenes and alkynes in the presence of primary or secondary amines or ammonia yields amides (equations 48 and 49). The fact that formamides can be used in place of amines suggests that a key intermediate in the reaction is the hydride metal carboxamide (**20**).

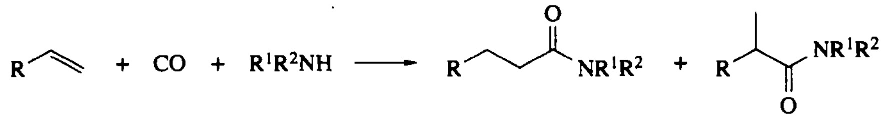

(48)

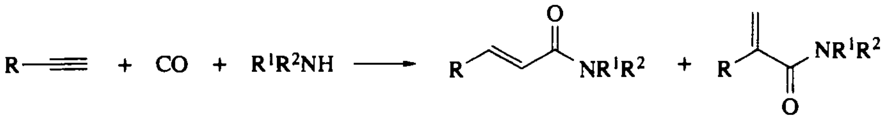

(49)

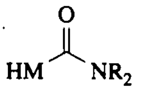

**(20)**

### 4.5.3.4 Alkenes and Alkynes Containing Functional Groups

The hydrocarboxylation of *N*-vinylphthalimide catalyzed by palladium takes place regioselectively, under mild conditions, to give the α-amino acid derivative (equation 50).[39]

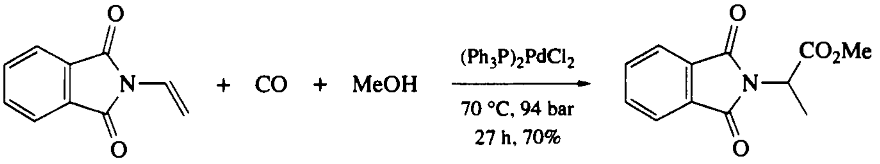

(50)

When either an alcohol or an amine function is present in the alkene, the possibility for lactone or lactam formation exists. Cobalt or rhodium catalysts convert 2,2-dimethyl-3-buten-1-ol to 2,3,3-trimethyl-γ-butyrolactone, with minor amounts of the δ-lactone being formed (equation 51).[2] In this case, isomerization of the double bond is not possible. The reaction of allyl alcohols catalyzed by cobalt or rhodium is carried out under reaction conditions that are severe, so isomerization to propanal occurs rapidly. Running the reaction in acetonitrile provides a 60% yield of lactone, while a rhodium carbonyl catalyst in the presence of an amine gives butane-1,4-diol in 60–70% (equation 52).[81] A mild method of converting allyl and homoallyl alcohols to lactones utilizes the palladium chloride/copper chloride catalyst system (Table 6).[79,82,83]

The synthesis of α-methylenelactones from alkynic alcohols can be effected in 84% yield utilizing $HPt(SnCl_3)(PPh_3)_2$ (equation 53).[84] This is essentially the same α-methylenelactone synthesis elegantly developed earlier utilizing a palladium catalyst (Table 7).[85] The starting *trans* alkynic alcohols are ob-

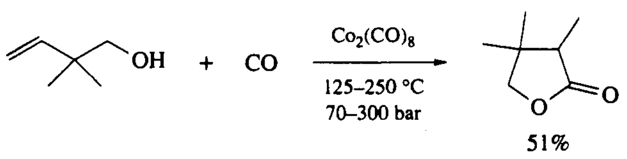

(51)

**Table 6** Hydrocarboxylation of Alkenols[a]

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *cis:trans* |
|---|---|---|---|---|
| 1 | 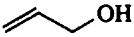 | 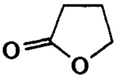 | 35 | |
| 2 | 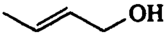 | 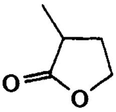 | 50 | |
| 3 | 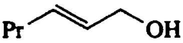 | 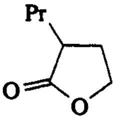 | 35 | |
| 4 | 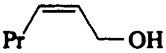 | 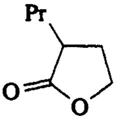 | 60 | |
| 5 | 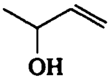 | 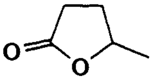 | 70 | |
| 6 | 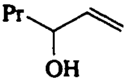 | 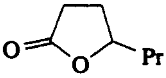 | 40 | |
| 7 | 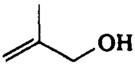 | 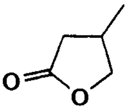 | 15 | |
| 8 | 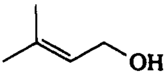 | 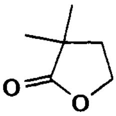 | 45 | |
| 9 | 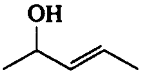 | 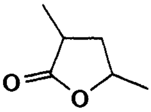 | 65 | 1:1 |
| 10 | 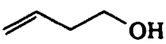 | 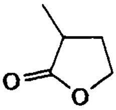 | 60 | |
| 11 | 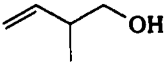 | 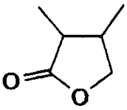 | 42 | 1:2 |
| 12 | 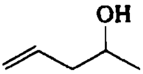 | 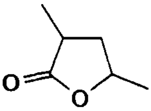 | 80 | 1:1 |

**Table 6** *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *cis:trans* |
|---|---|---|---|---|
| 13 | 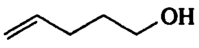 | 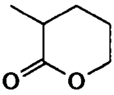 | 75 | |
| 14 | 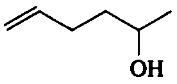 | 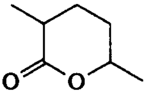 | 50 | 2:3 |

[a] $PdCl_2$:$CuCl_2$ (<1:5 or 1:10), HCl, $O_2$, 25 °C, 1 bar.

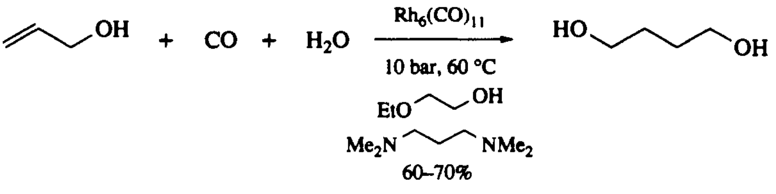
OH
+ CO + $H_2O$
$Rh_6(CO)_{11}$
10 bar, 60 °C
HO
OH
EtO
OH
$Me_2N$
$NMe_2$
60–70%

(52)

tained by the reaction of the corresponding epoxides with aluminum acetylides, the *cis* alcohols are obtained from the *trans* by an oxidation–reduction sequence (equation 54). The reaction does not work well for 3-butenol, only a 26% yield being obtained.

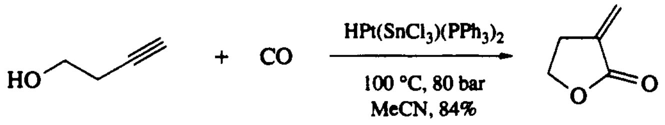
HO
+ CO
$HPt(SnCl_3)(PPh_3)_2$
100 °C, 80 bar
MeCN, 84%
O
O

(53)

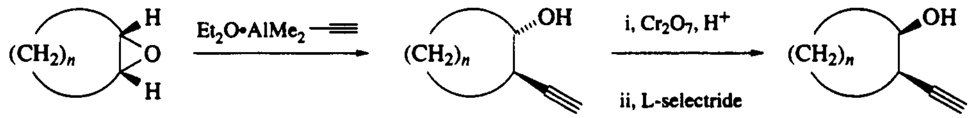
$(CH_2)_n$
H
O
H
$Et_2O{\bullet}AlMe_2$—≡
$(CH_2)_n$
OH
i, $Cr_2O_7$, $H^+$
ii, L-selectride
$(CH_2)_n$
OH

(54)

Allylamines cyclize readily with a dicobalt octacarbonyl catalyst (equation 55).[1,2] Rhodium catalysis generally allows the carbonylative cyclization to be carried out under milder conditions.[86] Application of this reaction to unsaturated amides yields the corresponding imides, the best yields arising when $R^1$ = H and $R^2$ = allyl (equation 56).[1,2]

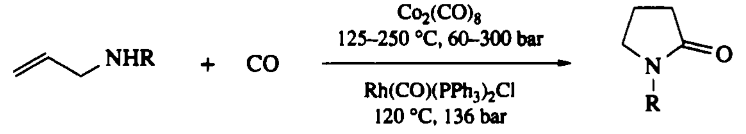
NHR
+ CO
$Co_2(CO)_8$
125–250 °C, 60–300 bar
$Rh(CO)(PPh_3)_2Cl$
120 °C, 136 bar
N
O
R

(55)

R = H, alkyl, aryl

R = Me, 78%; R = H, 68%

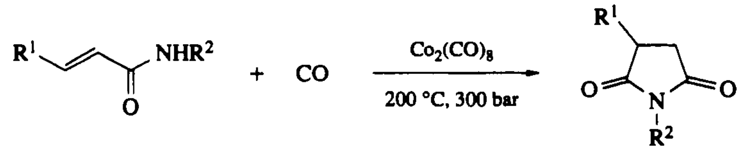
$R^1$
$NHR^2$
O
+ CO
$Co_2(CO)_8$
200 °C, 300 bar
$R^1$
O
N
O
$R^2$

(56)

**Table 7** Synthesis of α-Methylenelactones[a]

| *Entry* | *Substrate* | *Phosphine* | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 1 | 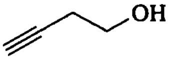 | $PPh_3$ | 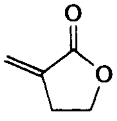 | 100 |
| 2 | 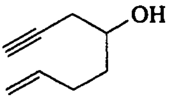 | $PPh_3$ | 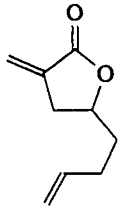 | 43 |
| 3 | 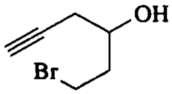 | $PBu_3$ | 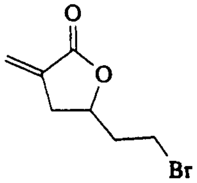 | 77 |
| 4 | 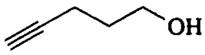 | $PPh_3$[b] | 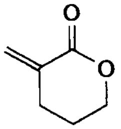 | 52 |
| 5 | 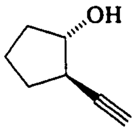 | $PPh_3$[c] | 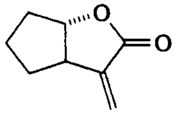 | 27 |
| 6 | 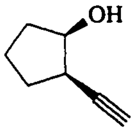 | $PPh_3$[c] | 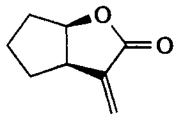 | 93 |
| 7 | 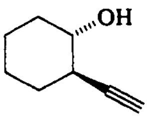 | $PBu_3$ | 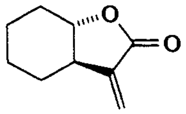 | 85 |
| 8 | 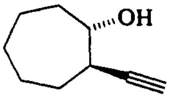 | $PBu_3$ | 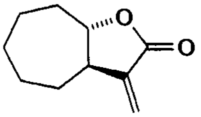 | 71 |
| 9 | 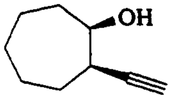 | $PBu_3$ | 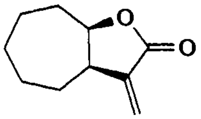 | 83 |

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[a] $PdCl_2$:$PR_3$:$SnCl_2$ 1:1:2 in MeCN, 7.8 bar CO, 75 °C. [b] 5.1 bar CO. [c] 5.7 bar CO, 65 °C.

### 4.5.3.5 Conjugated Diene Hydrocarboxylation

The hydrocarboxylation of conjugated dienes such as butadiene can yield monocarboxylate, dicarboxylate or diene dimerized carboxylated products. The carboxylation reaction is important because it is a potential route to adipic acid.

Palladium catalysts that are free of halide ions effect the dimerization and carboxylation of butadiene to yield 3,8-nonadienoate esters. Palladium acetate, solubilized by a tertiary amine or an aromatic amine, gives the best yields and selectivities (equation 57).[87] Palladium chloride catalyzes the hydrocarboxylation to yield primarily 3-pentenoates.[88] The hydrocarboxylation of isoprene and chloroprene is regioselective, placing the carboxy function at the least-hindered carbon (82% and 71% selectively); minor amounts of other products are obtained (equation 58). Cyclic dienes such as 1,3-cyclohexadiene and 1,3-cyclooctadiene are similarly hydrocarboxylated.

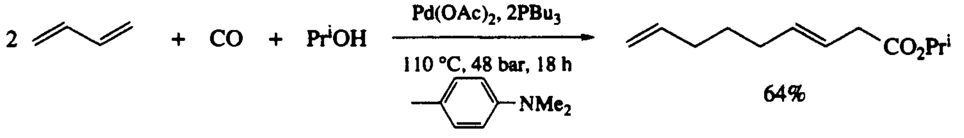
2
+ CO + Pr$^i$OH
Pd(OAc)$_2$, 2PBu$_3$
110 °C, 48 bar, 18 h
NMe$_2$
CO$_2$Pr$^i$
64%

(57)

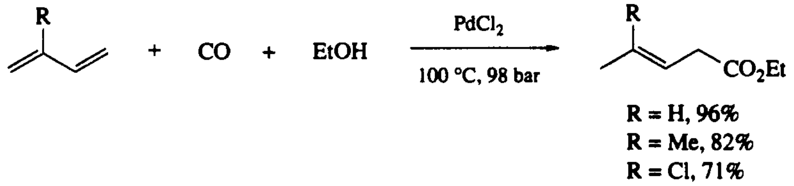
R
+ CO + EtOH
PdCl$_2$
100 °C, 98 bar
R
CO$_2$Et
R = H, 96%
R = Me, 82%
R = Cl, 71%

(58)

Cobalt is the catalyst of choice for the hydrocarboxylation of butadiene to adipic esters.[89] The reaction is carried out in two steps, the first of which yields methyl-3-butenoate. This product can either be isolated or carried on to dimethyl adipate at high temperatures (Scheme 11). The first hydrocarboxylation occurs by the metal carboxylate insertion mechanism (*vide supra*).

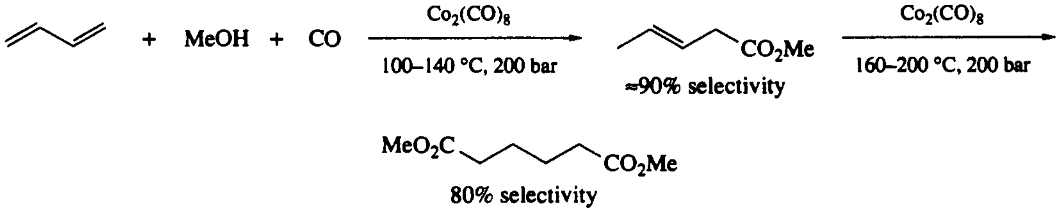
+ MeOH + CO
Co$_2$(CO)$_8$
100–140 °C, 200 bar
CO$_2$Me
≈90% selectivity
Co$_2$(CO)$_8$
160–200 °C, 200 bar
MeO$_2$C
CO$_2$Me
80% selectivity

**Scheme 11**

### 4.5.3.6 Asymmetric Hydrocarboxylation[42–44]

High enantiomeric excesses in the hydroesterification of alkenes have not been achieved. The reaction carried out with unbranched 1-alkenes or internal alkenes gives products in less than 20% enantiomeric excess (equation 59). The low enantiomeric excesses are due, in part, to the relatively high temperatures necessary to effect the reaction.

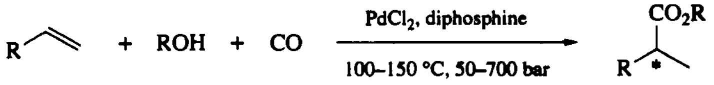
R
+ ROH + CO
PdCl$_2$, diphosphine
100–150 °C, 50–700 bar
CO$_2$R
R
*

(59)

Much higher enantiomeric excesses have been achieved in the hydroesterification of α-methylstyrene.[90,91] In this case, the asymmetric center is generated by hydrogen addition at the tertiary site. The reaction is sensitive to the alcohol, the highest enantiomeric excesses being obtained with isopropanol or *t*-butanol (equation 60).

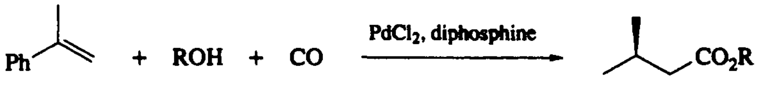

(60)

| *R* | *Solvent* | *Diphosphine* | *Temperature* (°C) | *Pressure* (bar) | *ee* (%) |
|---|---|---|---|---|---|
| Bu$^t$ | PhH | DIOP (**12**) | 100 | 45–400 | 58 |
| Pr$^i$ | 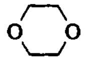 | 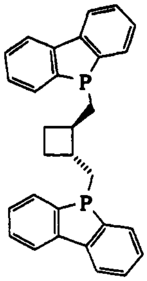 **(21)** | 100 | 220 | 52 |

## 4.5.4 DICARBOXYLATION[92]

Dicarboxylation reactions of alkenes can be carried out such that predominately 1,2-addition of the two ester functions occurs (equation 61). The reaction takes place under mild conditions (1–3 bar, 25 °C) in alcohol. It is stoichiometric in palladium, since the palladium(II) catalyst is reduced to palladium(0) in the process, but by use of an oxidant (stoichiometric copper chloride or catalytic copper chloride plus oxygen; equation 62 and 63) the reaction becomes catalytic in palladium. In the reoxidation process, water is generated and the build-up of water increases the water gas shift reaction at the expense of the carboxylation. Thus a water scavenger such as triethyl orthoformate is necessary for a smooth reaction.

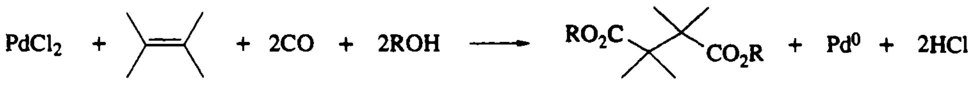

(61)

$$2CuCl_2 + Pd^0 \longrightarrow CuCl_2 + PdCl_2 \qquad (62)$$

$$CuCl_2 + 2HCl + 1/2O_2 \longrightarrow 2CuCl_2 + H_2O \qquad (63)$$

### 4.5.4.1 Mechanisms

The key palladium intermediate is a carboalkoxypalladium complex formed through the nucleophilic attack by alcohol on carbonyl coordinated to palladium. The addition of a base with the appropriate p$K_a$ [sodium butyrate; p$K_a$ = 4.82 ($H_2O$)] promotes the formation of the palladium carboxylate (**22**).[93] The reaction is a general method for formation of inorganic alkoxycarbonyl derivatives.

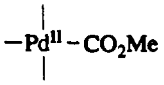

$$-Pd^{II}-CO_2Me$$

**(22)**

The sequence of events is: (i) the insertion of the alkene into the palladium–carboxylate bond; followed by (ii) CO insertion into the newly generated palladium–carbon bond; followed by (iii) the reaction with solvent to give a palladium hydride that undergoes reductive elimination to palladium(0) (Scheme 12).

The formation of dimethyl succinates is stereospecific, *syn* addition of the two carbomethoxy functions taking place, as illustrated by the dicarboxylation of (*Z*)-2-butene to the *meso* diester and (*E*)-2-butene to the (±)-diester (equations 64 and 65). This occurs since the alkene insertion to yield intermediate (**23**) is *syn* and the CO insertion (**23**) → (**24**) takes place with retention of configuration at carbon.

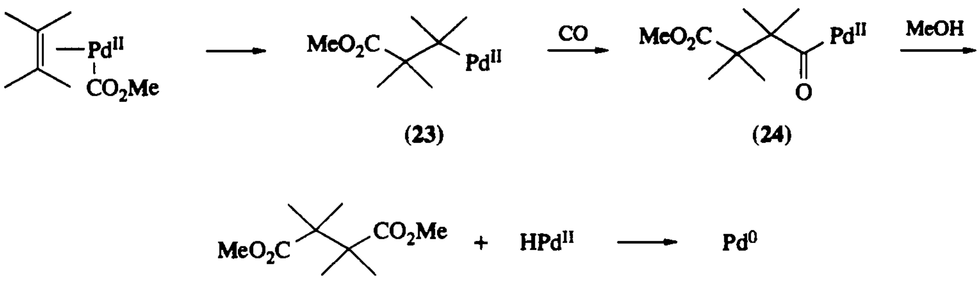
Pd^II
CO2Me
MeO2C
Pd^II
(23)
CO
MeO2C
Pd^II
O
(24)
MeOH
MeO2C
CO2Me
+ HPd^II
Pd^0

Scheme 12

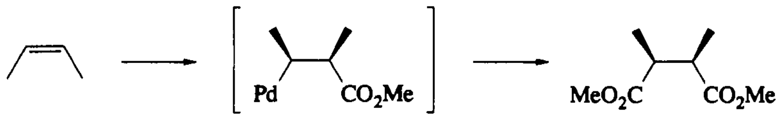
Pd
CO2Me
MeO2C
CO2Me

(64)

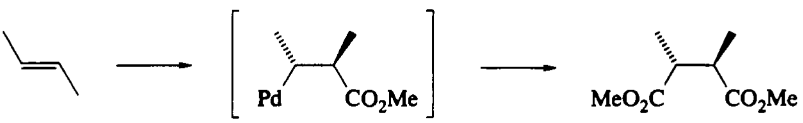
Pd
CO2Me
MeO2C
CO2Me

(65)

### 4.5.4.2 Dicarboxylation of Alkenes

The catalytic dicarbonylation of ethylene to dimethyl succinate can be carried out in 90% conversion.[94] High reaction temperatures and low carbon monoxide pressures can lead to unsaturated esters as a result of a faster β-hydride elimination from the intermediate (**23**) than carbon monoxide insertion. This later reaction path has been termed oxidative carboxylation.

The reaction of norbornene yields the *cis exo* diester (equation 66).[93] This *exo* isomer is not obtained directly by Diels–Alder chemistry. Other cyclic alkenes such as cyclopentene yield *cis* diesters, but isomers are obtained as a result of β-hydride elimination–readdition from intermediates such as (**23**) prior to CO insertion (equation 67). Thus the palladium walks around the ring to some extent, but always stays on the same face. The extent of rearrangement can be minimized by higher CO pressures since CO insertion becomes more competitive with β-elimination. This rearrangement becomes a critical problem in the dicarboxylation of 1-alkenes, since a variety of diesters are formed and the reaction is not particularly useful. These reactions were carried out with catalytic amounts of palladium and stoichiometric amounts of copper chloride.

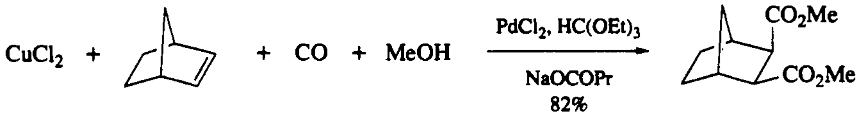
CuCl2 +
+ CO + MeOH
PdCl2, HC(OEt)3
NaOCOPr
82%
CO2Me
CO2Me

(66)

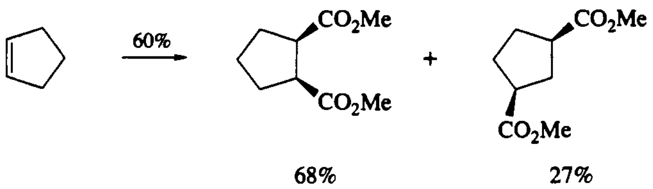
60%
CO2Me
CO2Me
+
CO2Me
CO2Me
68%
27%

(67)

Tertiary carbons are not carboxylated, however, so the rearrangement reaction can be of advantage for the synthesis of certain symmetrical glutaric esters (equation 68).

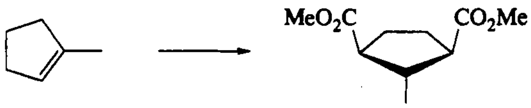
MeO2C
CO2Me

(68)

The dicarboxylation of 2-methyl-4-penten-2-ol provides an interesting example in that palladium carboxylate is generated from the pentenol alcohol function producing a γ-lactone (Scheme 13).[95]

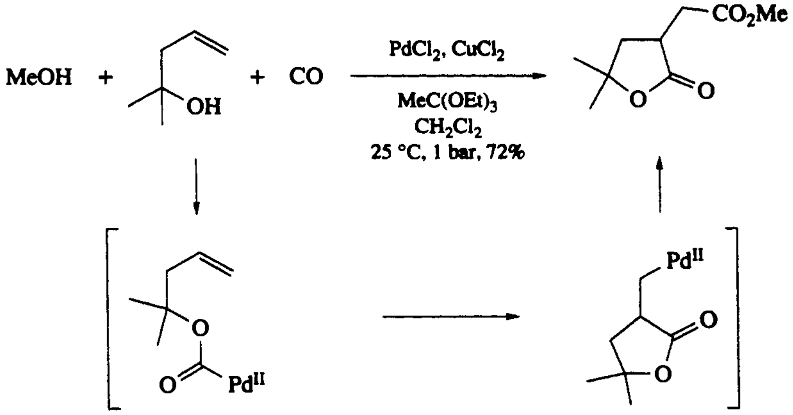
MeOH
+
OH
+ CO
PdCl$_2$, CuCl$_2$
MeC(OEt)$_3$
CH$_2$Cl$_2$
25 °C, 1 bar, 72%
CO$_2$Me
O
O
O
O
Pd$^{II}$
Pd$^{II}$
O
O

**Scheme 13**

Under these reaction conditions, cyclopentenone, allyl acetate, and butenyl acetate are dicarboxylated in high yields (equations 69–71).[96]

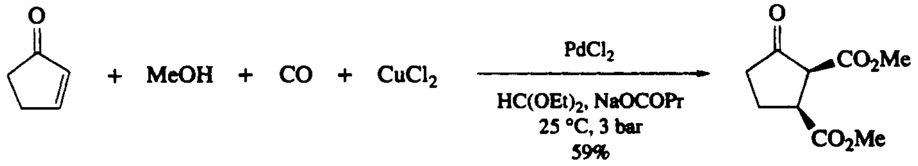
O
+ MeOH + CO + CuCl$_2$
PdCl$_2$
HC(OEt)$_2$, NaOCOPr
25 °C, 3 bar
59%
O
CO$_2$Me
CO$_2$Me

(69)

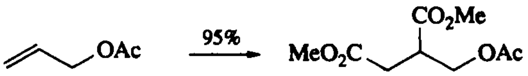
OAc
95%
CO$_2$Me
MeO$_2$C
OAc

(70)

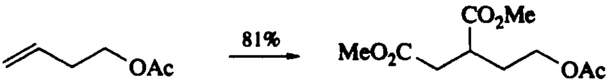
OAc
81%
CO$_2$Me
MeO$_2$C
OAc

(71)

When the substrate contains two double bonds, either di- or tetra-carboxylation can be achieved.[96] The reaction of 1,5-hexadiene at 5 bar CO gives the diester, while at 1–3 bar the tetraester is obtained (equation 72). These somewhat surprising results are consistent with a pressure-dependent competition of the alkene and carbon monoxide for coordination sites on palladium. Since 1,5-hexadiene is not easily displaced by CO, even at higher pressures, the carboxylation of one double bond is ensured. Competition of the resulting monoalkenic diester with carbon monoxide is dependent on the CO pressure, lower pressures allowing monoalkene coordination and thus dicarboxylation.

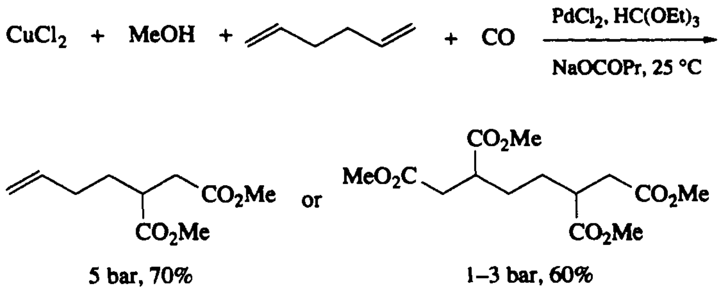
CuCl$_2$ + MeOH +
+ CO
PdCl$_2$, HC(OEt)$_3$
NaOCOPr, 25 °C
CO$_2$Me
CO$_2$Me
or
CO$_2$Me
MeO$_2$C
CO$_2$Me
CO$_2$Me
5 bar, 70%
1–3 bar, 60%

(72)

Vinylcyclohexene can be dicarboxylated under these conditions at the more reactive vinyl double bond, which is 100 times more reactive than the internal one (equation 73).

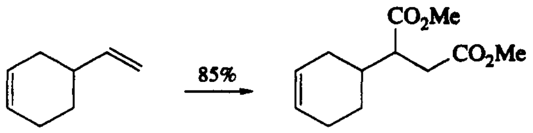

(73)

Butadiene carboxylation requires somewhat higher reaction temperatures, producing (*Z*)- and (*E*)-dimethylhex-3-ene-1,6-dioate (equation 74).

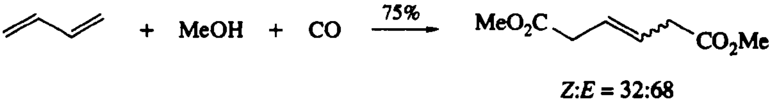

(74)

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# 4.6

# Methylene and Nonfunctionalized Alkylidene Transfer to Form Cyclopropanes

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## 4.6.1 INTRODUCTION

### 4.6.1.1 Scope of Chapter

Cyclopropanes occur among several classes of natural products, they have a number of commercial applications, and they serve as useful synthetic intermediates leading to other classes of cyclic and acyclic compounds. Methods for the synthesis of cyclopropanes have been the subject of several earlier reviews.[1] The principal methods may be divided into two broad categories: (i) addition of a one-carbon unit (*e.g.* a carbene) to a two-carbon unit, most commonly an alkene; and (ii) 1,3-coupling of difunctional compounds. Much rarer are examples of direct joining of three one-carbon units.

The coverage of this chapter emphasizes category (i) reactions in which a simple methylene group is transferred, or added, to an alkene substrate. Also covered is transfer of nonfunctionalized alkylidene groups when these reactions may be regarded as simple extensions of the methylene transfer reactions. Whenever appropriate, aspects of the stereoselectivity, enantioselectivity, regioselectivity and chemoselectivity of these reactions will be emphasized by means of specific examples.

Methods for cyclopropane formation which fall outside of the defined scope of this chapter and which are not specifically covered herein are the following: (i) transfer of 1,1-dihalo-carbenes or -carbenoids (see Volume 4, Chapter 4.7); (ii) transfer of other heterosubstituted alkylidene groups;[2] (iii) cyclopropanations using diazocarbonyl compounds (see Volume 4, Chapter 4.8);[3] (iv) transfer of other functionalized alkylidene groups when these reactions are dependent upon this functionalization (although reactions are included when the presence of a functional group in the alkylidene unit instead emphasizes aspects of chemoselectivity); (v) direct 1,3-coupling reactions;[4] (vi) intramolecular C—H insertions of carbenes (see Volume 3, Chapter 4.2);[5] (vii) ring contraction and other rearrangements; (viii) generation of vinyl- or divinyl-cyclopropanes as intermediates directed specifically toward the synthesis of cyclopentenes or cycloheptadienes (see Volume 5, Chapters 8.1 and 8.3);[6] (ix) synthesis of alkylidenecyclopropanes; (x) synthesis of cyclopropenes; and (xi) intramolecular alkylidene transfer, since most examples involve the use of diazocarbonyl compounds (see Volume 4, Chapter 4.8).[7]

## 4.6.1.2 Stereochemical Definitions

There are several aspects of stereochemistry that must be considered when cyclopropanes are produced by the usual methods of alkylidene group addition to alkenic substrates. In turn, several terms have been devised to express the extent to which different types of stereoisomers are formed selectively, but unfortunately, the meanings of these terms have become confused because of their inconsistent usage in the literature. In the context of this chapter, the term stereoselectivity refers to the degree of selectivity for formation of cyclopropane products having *endo versus exo* or, alternatively, *syn versus anti* stereochemistry of the substituents originating in the alkylidene group relative to substituents originating in the alkene substrate. The term stereospecificity refers to the stereochemistry of vicinal cyclopropane substituents originating as double-bond substituents in the starting alkene, *i.e.* a cyclopropane-forming reaction is stereospecific if the *cis/trans* relationship of the double-bond substituents is retained in the cyclopropane product. Diastereofacial selectivity refers to the face of the alkene to which addition occurs relative to other substituents in the alkene substrate. Finally, enantioselectivity refers to the formation of a specific enantiomer of the cyclopropane product. These stereochemical principles are illustrated by general examples in equations (1) to (4).

Stereoselectivity:

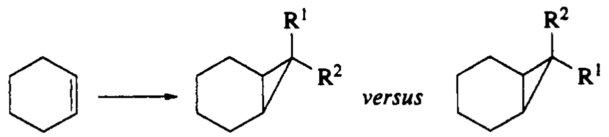

(1)

Stereospecificity:

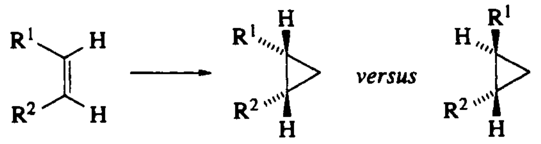

(2)

Diastereofacial selectivity:

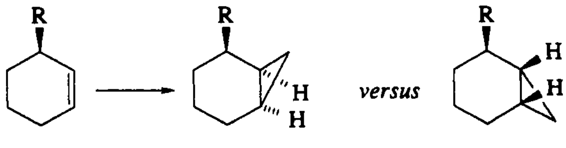

(3)

Enantioselectivity:

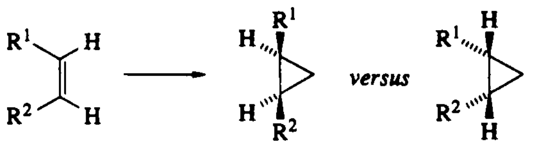

(4)

## 4.6.2 USE OF SIMPLE DIAZOALKANES

The most generally employed approach for the formation of cyclopropanes is the addition of a carbene or carbenoid to an alkene. In many cases, a free carbene is not involved as an actual intermediate, but instead the net, overall transformation of an alkene to a cyclopropane corresponds, in at least a formal sense, to carbene addition. In turn, the most traditional method for effecting these reactions is to employ diazo compounds, $R^1R^2C{=}N_2$, as precursors. Thermal, photochemical and metal-catalyzed reactions of these diazo compounds have been studied thoroughly and are treated separately in the discussion below. These reactions have been subjects of several comprehensive reviews,[8] to which the reader is referred for further details and literature citations. Emphasis in the present chapter is placed on recent examples.

In considering the possible use of diazoalkanes in synthetic applications, the prospective user must bear in mind that the handling of these compounds is very hazardous. They are highly toxic, and they are susceptible to undergoing violent explosions. Therefore, they must be handled with proper precautions and by properly informed laboratory personnel.

### 4.6.2.1 Thermal Reactions

The thermal reactions of diazo compounds with alkenes generally do not proceed *via* direct formation of cyclopropanes. Rather, the diazo compounds serve as 1,3-dipoles that first undergo [3 + 2] cycloaddition to form 1-pyrazolines (1) that in a separate step undergo extrusion of nitrogen to give the cyclopropane products (Scheme 1).[1h,8a–8g,8i] The extrusion may occur under thermal or under either direct or triplet-sensitized photochemical conditions. The initially formed 1-pyrazolines may first undergo double-bond positional isomerization to give 2-pyrazolines (2), especially when a hydrogen substituent next to nitrogen is reasonably acidic due to the presence of electron-withdrawing substituents. In many cases, the pyrazolines are unstable under the conditions of their formation and are consequently not observed, but instead, the cyclopropanes are isolated directly from the two-step reaction sequence.

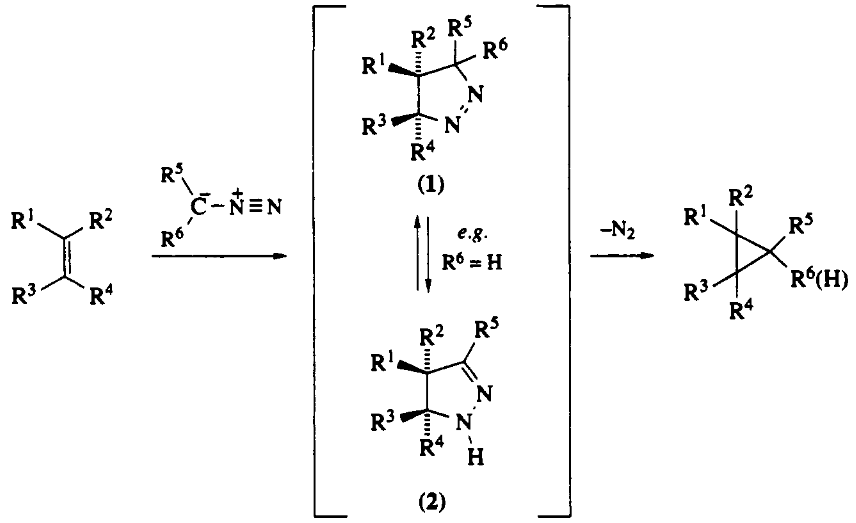

Scheme 1

Addition to simple, unstrained alkenes is usually quite slow, but these reactions become more useful when electron-withdrawing and electron-donating substituents are present on the double bond. On the other hand, the reactivity of diazo compounds is reduced when they bear conjugating substituents (*e.g.* aryl or carbonyl groups). Acceleration of these reactions by high pressure has been reported.[9] The initial cycloaddition is generally stereospecific and is considered to be concerted. The regioselectivity of these dipolar additions is not as consistently predictable, based upon substitution patterns, as other cycloadditions such as the Diels–Alder reaction. However, this point is usually of little consequence in the overall transformation leading to cyclopropanes since the two possible regioisomers are converted into the same final product upon loss of nitrogen. Several types of side reactions of diazo compounds frequently compete with the cycloadditions. Insertions into various C—H and heteroatom X—H bonds are well known, but especially commonly encountered are insertions into O—H bonds of alcohols and carboxylic acids, leading to ether and ester derivatives, respectively.

The subsequent extrusion of nitrogen from pyrazolines to produce cyclopropanes is also subject to complications. The cyclopropanes may be formed along with alkenes, resulting from rearrangements and eliminations, especially under thermal and direct photolysis conditions, whereas triplet-sensitized photochemical conditions often lead to much smaller amounts of alkenes. Nitrogen extrusion and carbon–carbon bond formation proceed largely with retention of configuration of the pyrazoline under direct photochemical conditions, but scrambling of stereochemistry occurs to a large extent in many cases of triplet-sensitized photochemical reactions and thermal reactions. Many examples of these reactions have shown evidence for the formation of singlet or triplet diradical intermediates upon extrusion of nitrogen, although zwitterionic intermediates have also been proposed. The formation of triplet diradicals, having longer lifetimes than their singlet counterparts, would explain the greater extent of stereochemical scrambling in the triplet-sensitized photochemical reactions.

A variation on the thermal reactions of diazo compounds with alkenes is the decomposition of salts of sulfonylhydrazones. This procedure, known as the Bamford–Stevens reaction, is believed to occur *via* the formation of diazo compounds. Subsequent 1,2-hydrogen shifts generally lead to the formation of alkenes as the final products. Cyclopropanes may also be formed as the result of intramolecular 1,3-C—H insertion reactions or when the original hydrazone substrate contains a remote alkenic group as a site for intramolecular cyclopropanation.[10]

Examples of the overall conversion of alkenes to cyclopropanes under the above sets of conditions are summarized in Table 1.

### 4.6.2.2 Photochemical Reactions

The reaction of diazoalkanes with alkenes under either direct or sensitized photochemical conditions has been investigated extensively.[1h,8a,8b,8d–8f,8i,8l,8m,8p] These reactions proceed *via* formation of carbenes as reactive intermediates. Side reactions, such as C—H insertions, compete with the cyclopropanations. The relative reactivities of singlet and triplet carbenes have been studied. Direct photolysis generally produces singlet carbenes, but these may in turn undergo intersystem crossing to produce lower energy triplet carbenes. Alternatively, triplet carbenes may be produced through use of sensitizers. Singlet carbenes add stereospecifically (equation 2) to alkenes, whereas triplet carbenes generally undergo nonstereospecific addition. Interesting stereoselectivity (equation 1) is seen in several cases in which there is at least a small predominance of the thermodynamically less stable *syn* (or *cis* or *endo*) product. Even though singlet carbenes are generally of higher reactivity than the triplets, there is evidence that, unlike the usual intermolecular reactions, certain intramolecular additions of arylcarbenes to alkenes occur more readily *via* triplets than singlets.[29] As is also true of thermal reactions (see previous section), hydrazones may be used as substrates in photochemical reactions. A brief compilation of examples, with emphasis on more recent work, is found in Table 2.

### 4.6.2.3 Metal-catalyzed Reactions

The use of metal catalysts for the addition of diazoalkanes to alkenes has become increasingly common,[1h,8a–8e,8i,8k,8m–8o] while the use of thermal and photochemical reactions has waned. Many generalizations have been made to describe several different aspects of the metal-catalyzed reactions, but one must bear in mind that many of the detailed studies of these reactions have involved primarily diazocarbonyl compounds and not necessarily the simpler diazoalkanes that pertain to the general topic of the present chapter.

Both heterogeneous and homogeneous catalysts have been used in these reactions. These catalysts have consisted of compounds or complexes of many different metals, but the most common have been copper derivatives or metallic copper itself. In recent years, palladium and rhodium compounds have been shown to be particularly effective catalysts and have increased in popularity relative to many other

**Table 1** Thermal Reactions of Diazoalkanes with Alkenes

| *Alkene* | *Diazoalkane* | *Method of pyrazoline decomposition* | *Products*[a] *and yields* | | *Ref.* |
|---|---|---|---|---|---|
| 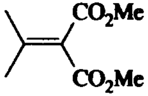  CO2Me<br>CO2Me | $CH_2N_2$ | Xylene at reflux | 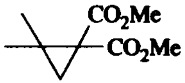  CO2Me<br>CO2Me 67% | | 11 |
| 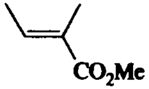 | $MeCHN_2$ | 120 °C | 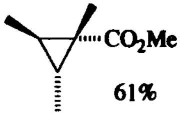 61% | 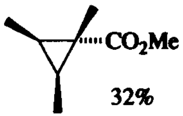 32% | 12 |
| | | Photolysis | 88% | 10% | |
| 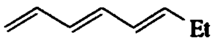 | $CH_2N_2$ | 140 °C or photolysis | 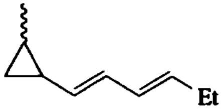 | *ca.* 60% | 13 |
| | $MeCHN_2$ | 140 °C | 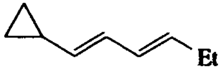 <br>(*cis*:*trans* = 0.5:1.0) | *ca.* 82% | 13 |
| | $MeCHN_2$ | Photolysis | (*cis*:*trans* = 0.5:1.0) | | 13 |
| LiTsNN 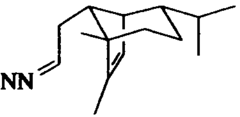 | | Photolysis | 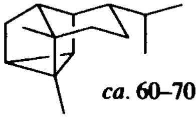 *ca.* 60–70% | | 14 |
| NNTsNa 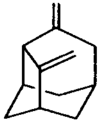 | | 200 °C | 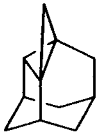 75% | | 15 |

**Table 1** *(continued)*

| *Alkene* | *Diazoalkane* | *Method of pyrazoline decomposition* | *Products*[a] *and yields* | *Ref.* |
|---|---|---|---|---|
| 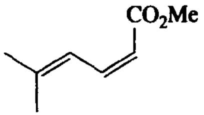 | $Me_2CN_2$ | 110 °C | 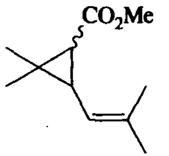 *ca.* 44%<br>(*cis*:*trans* = 2:1) | 16 |
| | $Me_2CN_2$ | Photolysis (direct) | (*cis*:*trans* = 4:1) *ca.* 44% | 16 |
| | $Me_2CN_2$ | Photolysis (sensitized) | (*cis*:*trans* = 0.25:1) *ca.* 44% | 16 |
| 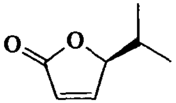 | $Me_2CN_2$ | Photolysis (sensitized) | 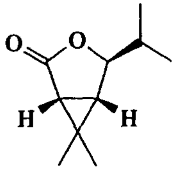 81% | 17 |
| 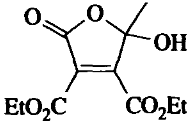 | $CH_2N_2$ | ? | 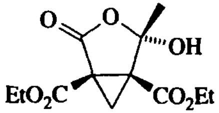 70% | 18 |
| 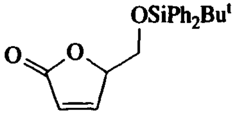 | $Me_2CN_2$ | Photolysis (sensitized) | 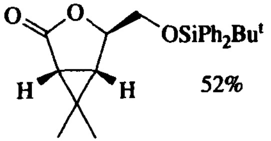 52% | 19 |
| 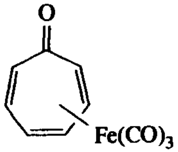 | $Me_2CN_2$ | 80 °C | 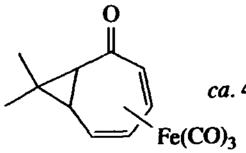 *ca.* 45% | 20 |

**Table 1** *(continued)*

| *Alkene* | *Diazoalkane* | *Method of pyrazoline decomposition* | *Products*[a] *and yields* | *Ref.* |
|---|---|---|---|---|
| 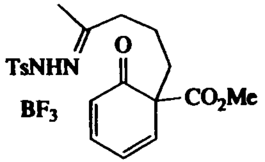 O<br>TsNHN<br>BF$_3$<br>CO$_2$Me |  | 110 °C | 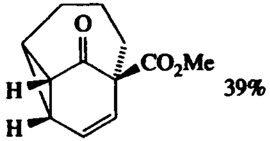 39% | 21 |
| 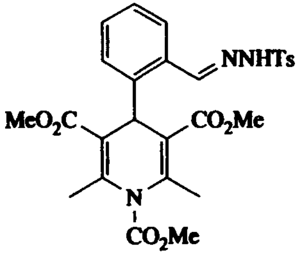 NNHTs<br>MeO$_2$C<br>CO$_2$Me<br>N<br>CO$_2$Me |  | Benzene at reflux | 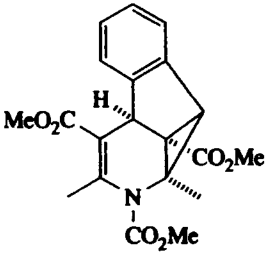 H<br>MeO$_2$C<br>CO$_2$Me<br>N<br>CO$_2$Me 32% | 22 |
| 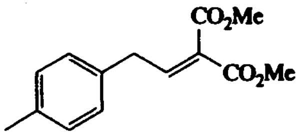 CO$_2$Me<br>CO$_2$Me | $CH_2CN_2$ | $Ce(NH_4)_2(NO_3)_6$ | 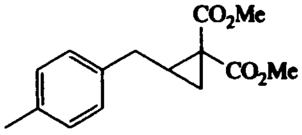 CO$_2$Me<br>CO$_2$Me (yield not reported) | 23 |
| 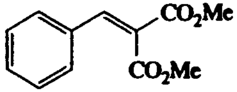 CO$_2$Me<br>CO$_2$Me | $(MeO)_2CHCHN_2$ | Photolysis | 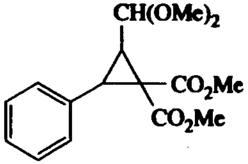 CH(OMe)$_2$<br>CO$_2$Me<br>CO$_2$Me *ca.* 80% | 24 |

**Table 1** *(continued)*

| *Alkene* | *Diazoalkane* | *Method of pyrazoline decomposition* | *Products*[a] *and yields* | | *Ref.* |
|---|---|---|---|---|---|
| 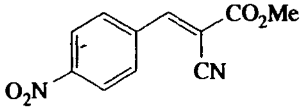 | $PhCMeN_2$ | 25 °C | 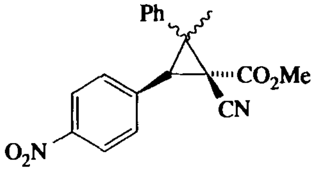<br>(*cis*:*trans*-diaryl = 9:29) | 38% | 25 |
| 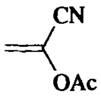 | $PhCMeN_2$ | 25 °C | 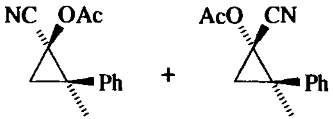 | 81% (1.6:1) | 26 |
| 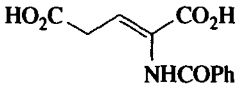 | $CH_2N_2$ | Photolysis | 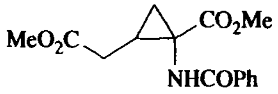 | 78% | 27 |
| 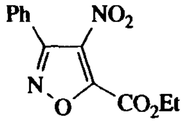 | $Me_2CN_2$ | 25 °C | 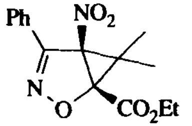 | 73% | 28 |

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[a] Only the cyclopropane products are shown, although alkenes and other side products may also have been produced.

**Table 2** Photochemical Reactions of Diazoalkanes with Alkenes

| *Alkene* | *Diazoalkane* | *Method of photolysis* | *Products*$^a$ | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 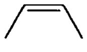 | $CH_2N_2$ | Direct | 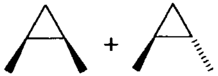<br>46:1 | Not reported | 30 |
| | | Sensitized ($Ph_2CO$) | 1.9:1 | | 31 |
| 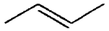 | $CH_2N_2$ | Direct | 0:1 | | 30 |
| | | Sensitized ($Ph_2CO$) | Trace Major isomer | | 31 |
| 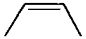 | *p*-$MeOC_6H_4CHN_2$ | Direct | 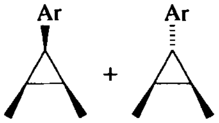<br>2.8:1<br>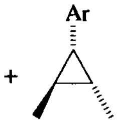<br>(trace) | 21 | 32 |
| 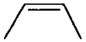 | 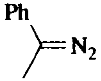 | Direct | 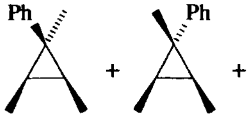<br>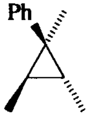<br>44:52:4 | | 33 |
| | | Sensitized ($Ph_2CO$) | 47:38:15 | | |
| 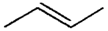 | | Direct | 6:3:91 | | |

**Table 2** *(continued)*

| *Alkene* | *Diazoalkane* | *Method of photolysis* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 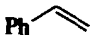 | PhCHN$_2$ | Direct | 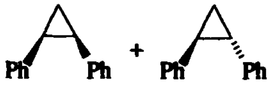 <br>1.0:1.4 | 73 | 34 |
| | | Direct (but in crystalline state) | 1.0:5.0 | 54 | |
| 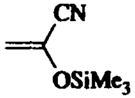 | 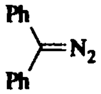 | Direct | 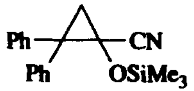  Ph CN Ph OSiMe$_3$ | 63 | 26 |
| 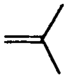 | 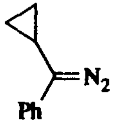 | Direct (128 °C) | 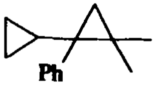 | 42 | 35 |
| 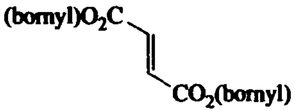  (bornyl)O$_2$C CO$_2$(bornyl) | 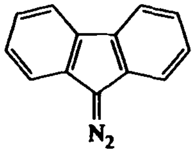 | Direct | 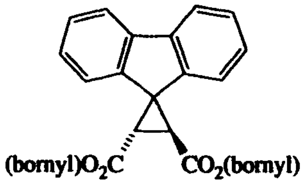  (bornyl)O$_2$C CO$_2$(bornyl)<br>+ diastereomer (ratio = 1.3) | | 36 |
| 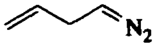 | | Direct | 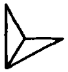 | 16 | 37 |

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[a] Only the cyclopropane products are shown, although alkenes and other side products may also have been produced.

metals. Evidence has been reported for the intermediacy of metal carbene complexes in these reactions. (The discussion of well-defined examples of metal carbene complexes is reserved for Section 4.6.5.)

The range of alkenes that may be used as substrates in these reactions is vast. Suitable catalysts may be chosen to permit use of ordinary alkenes, electron deficient alkenes such as α,β-unsaturated carbonyl compounds, and very electron rich alkenes such as enol ethers. These reactions are generally stereospecific, and they often exhibit *syn* stereoselectivity, as was also mentioned for the photochemical reactions earlier. Several optically active catalysts and several types of chiral auxiliaries contained in either the alkene substrates or the diazo compounds have been studied in asymmetric cyclopropanation reactions, but diazocarbonyl compounds, rather than simple diazoalkanes, have been used in most of these studies. When more than one possible site of cyclopropanation exists, reactions of less highly substituted alkenes are often seen, whereas the photochemical reactions often occur predominantly at more highly substituted double bonds. However, the regioselectivity of the metal-catalyzed reactions can be very dependent upon the particular catalyst chosen for the reaction.

The occurrence of competing side reactions is generally reduced when metal catalysts are employed instead of photochemical conditions. For example, insertions into C—H bonds are of diminished importance, although insertions into O—H and other X—H bonds are still commonplace. The extent to which any of these other reactions compete with cyclopropanation is, however, again dependent upon the choice of catalyst.

Examples of metal-catalyzed reactions are compiled in Table 3.

## 4.6.3 USE OF CARBENES FROM OTHER PRECURSORS

Carbenes may be generated by many other methods for use in cyclopropanation reactions. However, relatively few of these methods are used very commonly in actual applications in synthetic organic chemistry and, therefore, the discussion that follows is limited to just these few methods.

### 4.6.3.1 α-Elimination Reactions

Treatment of an appropriate substrate with a base can lead to a carbanionic intermediate that bears a leaving group on the carbanionic center. Upon loss of this group, a carbene may be formed, the net overall process being called an α-elimination since both the hydrogen substituent and the leaving group are lost from the same carbon center (equation 5). The resulting carbene may then participate in cyclopropanation reactions.

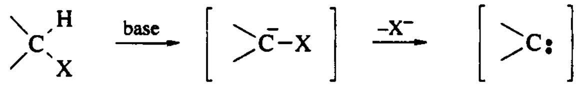

(5)

Most often, the starting materials bear additional substituents, especially electronegative groups, on the prospective carbene centers. Consequently, there are only a small number of examples in which this approach has been used to add a simple alkylidene group to an alkene (Table 4).

A related approach is the treatment of geminal dihalides with metal reagents to give an intermediate α-haloalkylmetal species, from which halide may in principle be lost in a net overall α-elimination of the two halide substituents (see Section 4.6.4.2).

### 4.6.3.2 Carbenes from Other Sources

Other methods for the formation of carbenes that have seen at least limited application in cyclopropanation reactions include the use of diazirines, epoxides, ketenes and *N*-nitrosoureas.[1h,8e,8f,8l,8m,8p]

## 4.6.4 USE OF GEMINAL DIHALOALKANES AND RELATED COMPOUNDS

Geminal dihaloalkanes are very commonly used reagents for the addition of alkylidene groups to alkenes. The simpler dihalides, especially the dihalomethanes, are readily available and are certainly much less hazardous to use than the corresponding diazoalkanes. Nevertheless, any reactive alkylating agent should be regarded as a toxic substance.

**Table 3** Metal-catalyzed Reactions of Diazoalkanes with Alkenes

| *Alkene* | *Diazoalkane* | *Catalyst* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 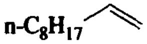 | $CH_2N_2$ | $Pb(OAc)_2$ | 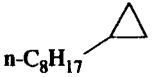 | 89 | 37 |
| 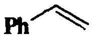 | $CH_2N_2$ | $ZnI_2$[b] | 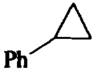 | 85 | 38 |
| 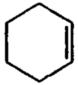 | $CH_2N_2$ | $Et_2AlCl$[b] | 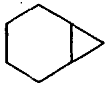 | 83 | 39 |
| 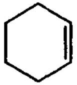 | $PhCHN_2$ | $ZnCl_2$[b] | 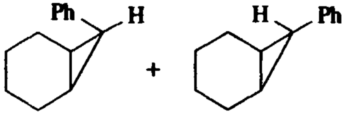<br>3:1 | 90 | 40 |
| 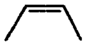 | 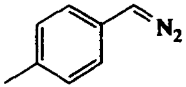 | $ZnI_2$[b] | 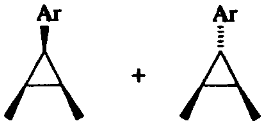<br>21:1 | 60 | 40 |
| 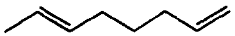 | $CH_2N_2$ | $Cu(acac)_2$ | 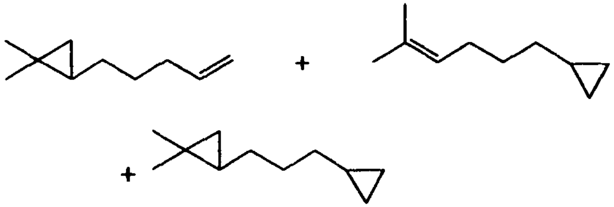<br>1.0:0.1:0.6 | 90 | 41 |
|  |  | $Cu(OTf)_2$ | 1.0:2.5:0.4 | 50 | 41 |

**Table 3** *(continued)*

| *Alkene* | *Diazoalkane* | *Catalyst* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 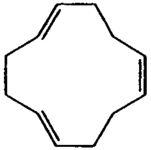 | $CH_2N_2$ | 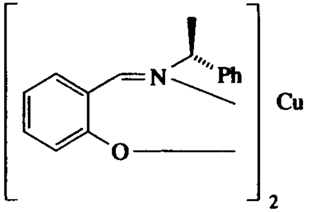 <br>(optically active) | 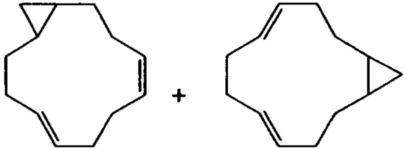 <br>9:1 (low *ee*) | 40 | 42 |
| 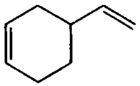 | $CH_2N_2$ | $Pd(OAc)_2$ | 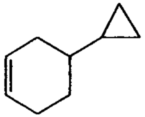 | 77 | 37 |
| 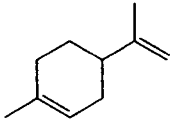 | $CH_2N_2$ | $Pd(OAc)_2$ | 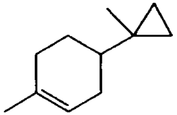 | 82 | 37 |
| 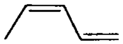 | $CH_2N_2$ | $[(PhCN)_2PdCl_2]$ | 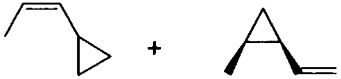 <br>>30:1 | 90 | 43 |
| 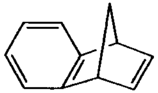 | $CH_2N_2$ | 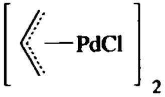 | 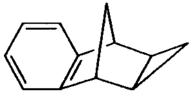 | 100 | 44 |

**Table 3** *(continued)*

| *Alkene* | *Diazoalkane* | *Catalyst* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 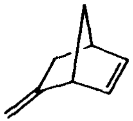 | $Ph_2CN_2$ | $Rh_2(OAc)_4$ | 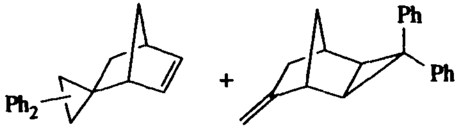 >100:1 |  | 45 |
|  | $Ph_2CN_2$ | $[(PhCN)_2PdCl_2]$ | <1:50 |  | 45 |
| 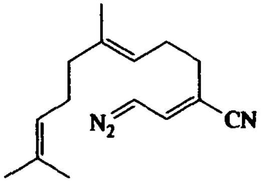 |  | CuI | 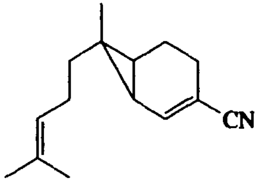 | >45 | 46 |
| 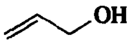 | $CH_2N_2$ | $[(PhCN)_2PdCl_2]$ | 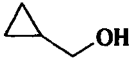 | *ca.* 70 | 47 |
| 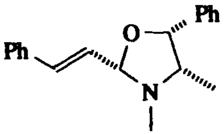 | $CH_2N_2$ | $Pd(OAc)_2$ | 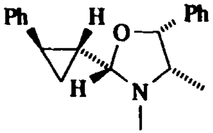 (>90% *de*) | *ca.* 100 | 48 |
| 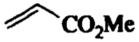 | $CH_2N_2$ | $Ni(Bu^tNC)_2$ | 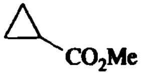 | 66 | 49 |
| 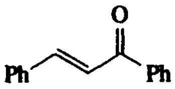 | $CH_2N_2$ | $Pd(OAc)_2$ | 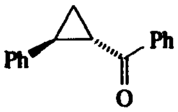 | 98 | 50 |

**Table 3** *(continued)*

| *Alkene* | *Diazoalkane* | *Catalyst* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 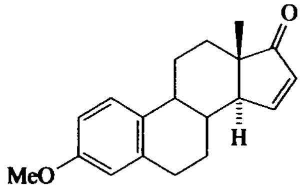 | $CH_2N_2$ | $Pd(OAc)_2$ | 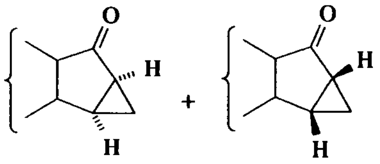<br>7:3 | 100 | 50 |
| 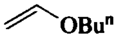 | $PhCHN_2$ | $Rh_2(OAc)_4$ | 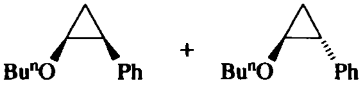<br>2.5:1 | 92 | 51 |

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[a] Only the cyclopropane products are shown, although alkenes and other side products may also have been produced. [b] Stoichiometric or near stoichiometric rather than catalytic quantities of metal species employed.

**Table 4** Cyclopropanations *via* α-Eliminations

| *Alkene* | *Substrate* | *Base* | *Products*[a] | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 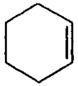 | $PhCH_2Cl$ | $Bu^nLi$ | 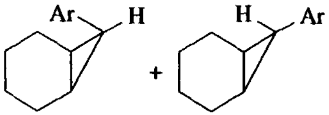 | 14[b] | 52 |
| 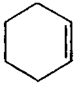 | $PhCH_2Cl$ | 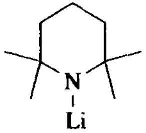 | 2.2:1 | 53 | 53 |
| 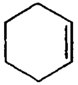 | 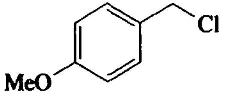 | 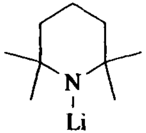 | 10:1 | 82 | 53 |
| 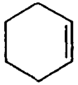 | $PhCH_2OPh$ | $Bu^nLi$ | | 2[c] | 54 |
| 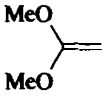 | 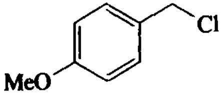 | 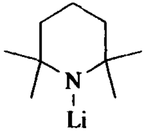 | 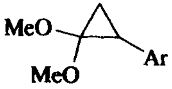 | 87 | 53 |
| 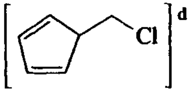 | | MeLi | 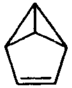 | 29 | 55 |

**Table 4** *(continued)*

| *Alkene* | *Substrate* | *Base* | *Products*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 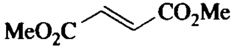 | 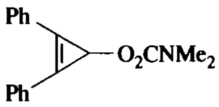 | KOBu$^t$ | 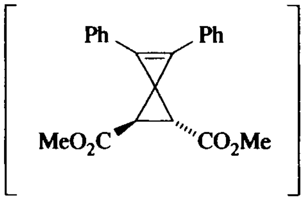 [e] | >70 | 56 |

[a] Only the cyclopropane products are shown, although alkenes and other side products may also have been produced. [b] Ratio of isomers not reported. [c] A 3:1 mixture was obtained, but the isomers were not assigned. [d] Generated as an intermediate from cyclopentadiene + $CH_2Cl_2$ + MeLi. [e] Unstable — rearranges to an alkylidene cyclopropene.

### 4.6.4.1 Simmons–Smith Reaction

The Simmons–Smith reaction has become a very popular method for the addition of a methylene or certain other simple alkylidene groups to alkenes in the course of normal synthetic organic research applications.[1,8e,57] The originally developed procedure employed the reaction of diiodomethane with a zinc–copper couple in the presence of an alkene to give a cyclopropane as a methylene transfer product (equation 6). The mechanism of this reaction is not well understood, but an α-iodomethylmetal species, such as $ICH_2ZnI$, is generally regarded as being a key intermediate. Similar species may be involved in reactions of diazoalkanes promoted by zinc halides and related salts (see Section 4.6.2.3).

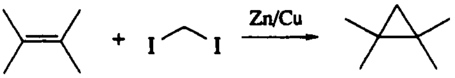

(6)

Many modifications have been made in the Simmons–Smith reaction over the years. A disadvantage of the original procedure was that the preparation of the required zinc–copper couple was a rather messy operation. Therefore, some of the modifications have been directed at developing other metal reagents. Among the several that have been reported, diethylzinc[58] and trialkylaluminums[59] are quite useful, but these reagents are, of course, quite air and moisture sensitive. A disadvantage of using diiodomethane is its expense, but the much less expensive dibromomethane has been found to be a useful substitute under various conditions, including sonication with zinc–copper couple.[60] A photochemical variant of the reaction using diiodomethane has also been reported which avoids the use of metal reagents altogether and which is less sensitive to steric hindrance.[61] The extension of the Simmons–Smith reaction to transfer of alkylidene groups other than just the simple methylene group has been limited. Ethylidene and benzylidene transfers have been the most thoroughly studied extensions of the method.

The Simmons–Smith reaction is stereospecific. Also, when other than just the simple methylene group is transferred, a low to modest level of *syn* stereoselectivity is typically seen. One of the most useful stereochemical features of the reaction is the directing effect of various heteroatomic functional groups. Experimental studies of this effect have been followed by theoretical studies.[62] The effect has been studied most commonly for allylic hydroxy groups. In these cases, the general outcome is diastereoselective delivery of the incoming methylene or alkylidene group to the face of the double bond having the closer proximity to the hydroxy group. The diastereoselectivity can be reversed by introducing an appropriate blocking or protecting group on the free hydroxy function. Also, the effect of the hydroxy group can be exploited in cases of substrates containing more than one alkene unit; regioselective delivery of the incoming group to a double bond having an associated allylic hydroxy function occurs in preference to double bonds not in close proximity to the directing group. Asymmetric versions of the Simmons–Smith reaction have also been studied, with the most common involving the use of alkene substrates containing chiral auxiliaries.

The intermediates in the Simmons–Smith reaction show much more controlled reactivity than, for example, diazoalkanes. Competing side reactions are greatly reduced, and insertion reactions are generally not seen. For example, the free hydroxy group is tolerated as indicated by the above discussion of directing effects. The reaction is also compatible with many other functional groups.

A wide range of alkenes may be used as substrates. The reaction is most commonly performed with alkenes of normal electronic nature, but electron deficient alkenes, such as α,β-unsaturated carbonyl compounds, and very electron rich alkenes, such as enol ethers and enamines, have also been used successfully. Not surprisingly, the cyclopropylcarbinyl ethers and amines that are formed in the latter reactions (see Table 5) are subject to facile rearrangements.

Examples of the Simmons–Smith reaction are presented in Table 5, with emphasis on more recent work. For additional examples, the reader is referred to extensive tabulations in earlier, comprehensive reviews.[1,8e,57]

### 4.6.4.2 Related Procedures

Organomercury compounds such as $ICH_2HgI$ and $Hg(CH_2Br)_2$ may be prepared by the reaction of metallic mercury with diiodomethane or by reaction of mercury(II) salts with diazoalkanes. These mercury derivatives are related to the intermediate that has been proposed in the Simmons–Smith reaction, and likewise, they have been found to convert alkenes into cyclopropanes.[92]

A procedure which combines characteristics of the Simmons–Smith reaction with the previously discussed α-eliminations (see Section 4.6.3.1) is the reaction of a geminal dihalide with an alkyllithium re-

Table 5 Simmons–Smith Reactions and Modifications

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 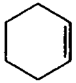 | $CH_2I_2$ | Zn(Cu) (or Zn/CuCl) | 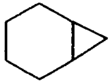 | 86–92 | 63 |
|  | $CH_2Br_2$ | Zn powder |  | 94 | 64 |
|  | CHBrI | Cu powder |  | 69 | 65 |
| 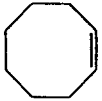 | $CH_2Br_2$ | Zn/CuCl, sonication | 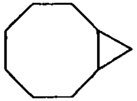 | 72 | 60 |
| 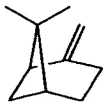 | $CH_2I_2$ | $Me_3Al$ | 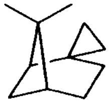 | 96 | 59 |
| 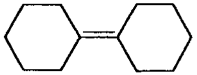 | $CH_2I_2$ | *hν* | 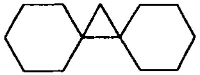 | 86 | 61 |
| 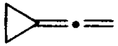 | $CH_2I_2$ | Zn/CuCl, sonication | 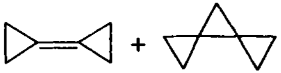<br>30–40% 10–15% |  | 66 |
| 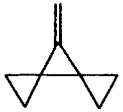 | $CH_2I_2$ | Zn(Ag) | 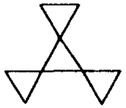 | 100 | 67 |
| 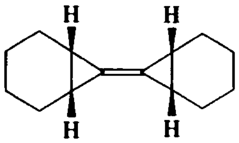 | $CH_2I_2$ | $Et_2Zn$ | 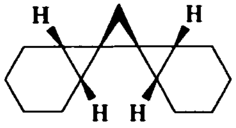 | 92 | 68 |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 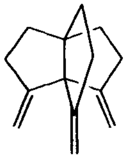 | $CH_2I_2$ | $Et_2Zn$ | 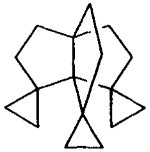 | Not reported | 69 |
| 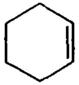 | $MeCHI_2$ | $Et_2Zn$ | 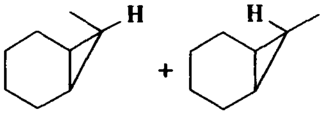<br>1.5:1 | 66 | 58b |
| 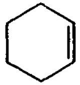 | $PhCHI_2$ | $Et_2Zn$ | 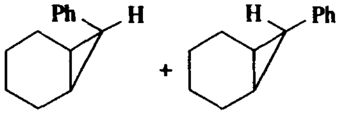<br>17:1 | 69 | 70 |
| 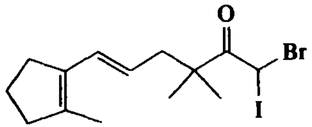 |  | $Bu_3SnH$, AIBN | 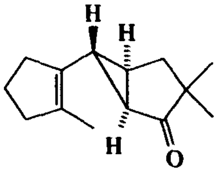 | 45 | 71 |
| 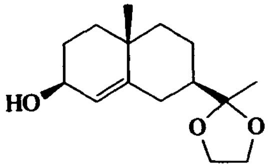 | $CH_2I_2$ | Zn(Cu) | 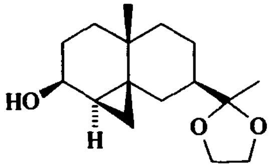 | 78 | 72 |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 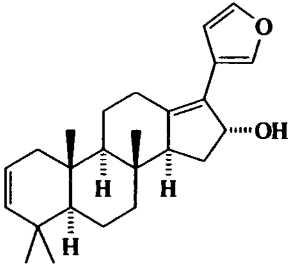 | $CH_2I_2$ | Zn(Ag) | 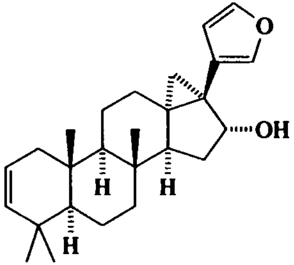 | 89 | 73 |
| 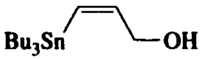 | $CH_2I_2$ | Zn(Cu) | 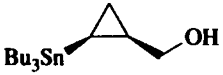 | 70 | 74 |
| 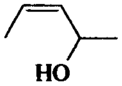 | $CH_2I_2$ | Zn(Cu) | 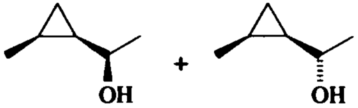<br>>99:1 |  | 75 |
| 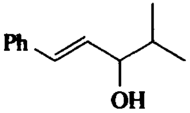 | $CH_2I_2$ | Sm(Hg) | 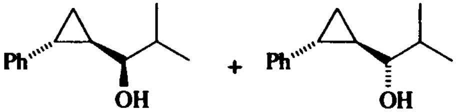<br>>200:1 | 88 | 76 |
| 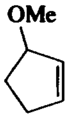 | $CH_2I_2$ | Cu | 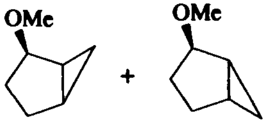<br>88:12 | 75 | 77 |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 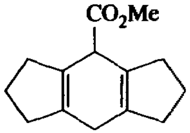 | $CH_2I_2$ | Zn(Cu) | 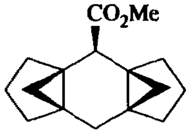 | >45 | 78 |
| 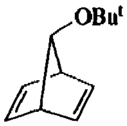 | $Zn(CH_2I)_2$ | | 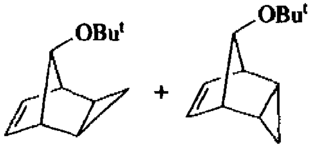<br>1.8:1 | Not reported | 79 |
| 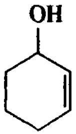 | $MeCHI_2$ | $Et_2Zn$ | 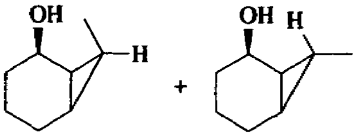<br>1:1.6 | 79 | 80 |
| | | Sm(Hg) | 1:5 | 100 | 76 |
| 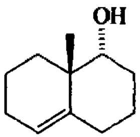 | $CH_2I_2$ | Zn(Cu) | 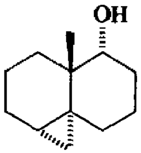 | 63 | 81 |
| 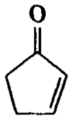 | $CH_2I_2$ | Zn(Cu) | 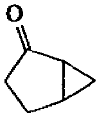 | 80 | 82 |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 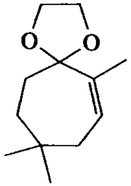 | $CH_2I_2$ | EtZnI | 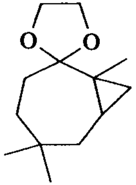 | 92 | 83 |
| 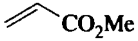 | $CH_2Br_2$ | $[Ni(PPh_3)_4]/ZnBr_2$ | 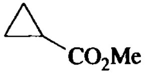 | 75 | 84 |
| 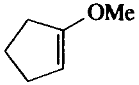 | $CH_2I_2$ | Zn(Cu) | 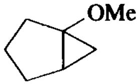 | 72 | 85 |
| 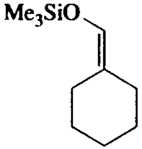 | $CH_2I_2$ | Zn(Cu) | 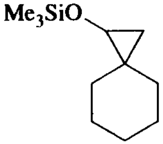 | 86 | 85 |
| 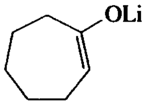 | $CH_2I_2$ | $SmI_2$ (then HCl) | 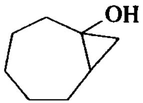 | 58 | 86 |
| 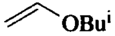 | $MeCHI_2$ | $Et_2Zn$ | 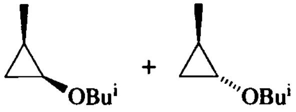 <br>2.3:1 | 96 | 58b |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 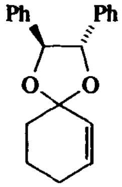<br>(optically active) | $CH_2I_2$ | Zn(Cu) | 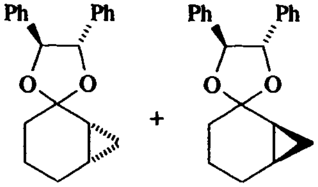<br>19:1 | 90 | 87 |
| 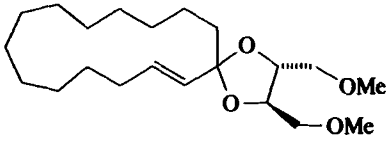<br>(optically active) | $CH_2I_2$ | Zn(Cu) | 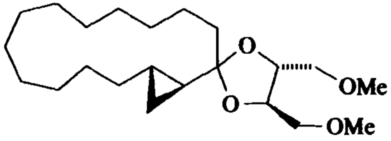<br>+ diastereomer (>20:1) | 95 | 88 |
| 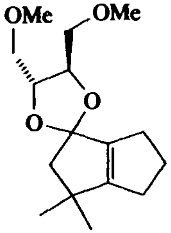<br>(optically active) | $CH_2I_2$ | Zn(Cu) | 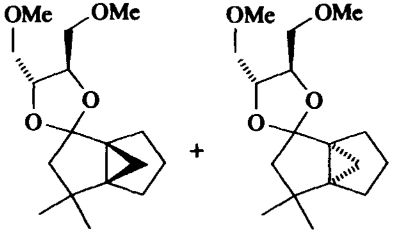<br>8:1 | 84 | 89 |
| 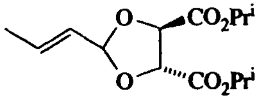 | $CH_2I_2$ | $Et_2Zn$ | 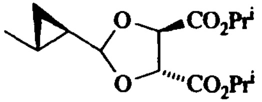<br>+ diastereomer (97:3) | 90 | 90 |

**Table 5** *(continued)*

| *Alkene* | *Dihalide* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 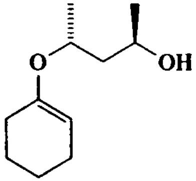 | $CH_2I_2$ | $Et_2Zn$ | 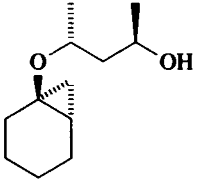 + 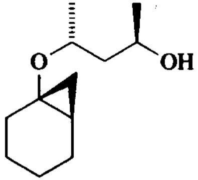<br>97:3 | 65 | 91 |

agent in the presence of an alkene. Halogen–lithium exchange occurs to give again an α-haloalkylmetal species as an apparent intermediate which then leads to alkylidene transfer to the alkene (equation 7).

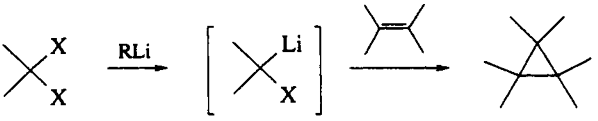

(7)

Finally, aldehydes have also been reported to serve as alkylidene transfer reagents.[93] Examples of these further cyclopropanation procedures are summarized in Table 6.

#### 4.6.4.3 Dialkylation of 1,2-Dicarbanionic Species by Geminal Dihaloalkanes

In principle, a vicinal or 1,2-dicarbanion, as at least a formal intermediate, should be capable of undergoing a double alkylation by an appropriate 1,1-difunctionalized electrophile to give a cyclopropane. Indeed, examples of this general strategy have been reported. In one case, a 1,2-bis(oxazolinyl)ethane derivative undergoes dilithiation followed by reaction with bromochloromethane to give the corresponding disubstituted cyclopropane (equation 8), although the stereochemistry was not explicitly reported.[96] A related asymmetric cyclopropanation occurs with optically active (–)-dimenthyl succinate (equation 9).[97] Finally, a β-tosyloxy-α,β-unsaturated ketone undergoes a related cyclopropanation *via* an apparent double Michael addition pathway (equation 10).[98] This last reaction was said to produce only one stereoisomer, but the *endo*/*exo* stereochemistry was not stated explicitly.

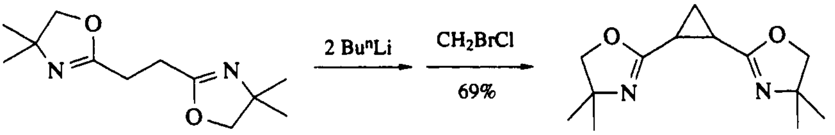

(8)

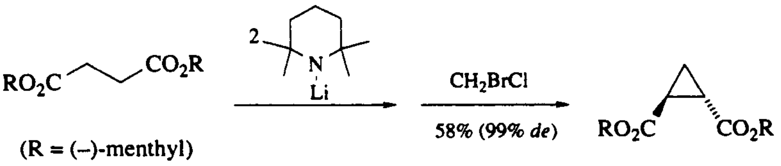

(9)

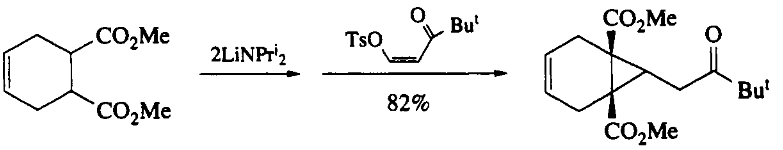

(10)

### 4.6.5 USE OF TRANSITION METAL CARBENE COMPLEXES

Complexes containing carbenes formally coordinated to transition metals were first reported by E. O. Fischer and his coworkers in the early 1960s.[99] The particular compounds that they studied were of the general structure $[(OC)_5M{=}C(OR^1)R]$ (M = Cr, Mo, W), having alkoxycarbenes coordinated to the Group VI metals. Note that the structures of these complexes are written with a double bond between the carbene center and the metal. This notation signifies the combination of donation of electron density from carbon to the metal to form a normal coordinative, or dative, σ-bond and donation from a *d*-like orbital of the metal to the empty *p*-orbital of the carbene, resulting in back-bonding to form a retrodative π-bond.

Since the pioneering studies of Fischer, carbene complexes have become the subjects of very extensive investigations in several laboratories, and they have become known for a large number of the transition metals.[100] A fairly general statement about their chemistry is that these compounds usually are neither prepared directly from free carbenes nor are they to be considered as sources of free carbenes, *i.e.* free carbenes are generally not in equilibrium with the carbene complexes. Instead, they are prepared by indi-

**Table 6** Further Cyclopropanation Procedures Related to the Simmons–Smith Reaction

| *Alkene* | *Reagents* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 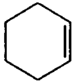 | $ICH_2HgI/Ph_2Hg$ | 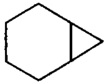 | 64 | 92 |
| 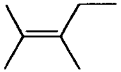 | $Hg(CH_2Br)_2$ | 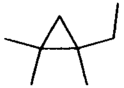 | 72 | 92 |
| 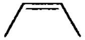 | 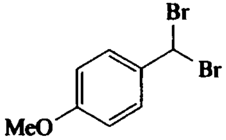 / MeLi | 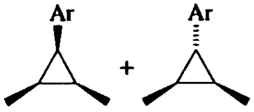 8.1:1 | 55 | 32 |
| 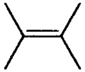 | $Me_2CBr_2/Bu^nLi$ | 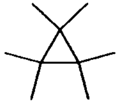 | 46[a] | 94 |
| 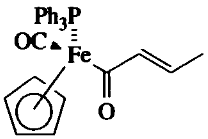 | $CH_2ClI/MeLi$ | 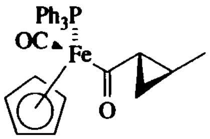 + diastereomer (>50:1) | 85 | 95 |
| 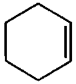 | 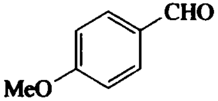 $Zn(Hg)/BF_3•OEt_2$ | 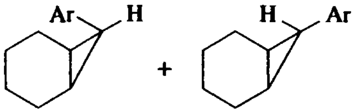 95:5 | 60 | 93 |
| 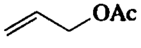 | $PhCHO/Zn(Hg)/BF_3•OEt_2$ | 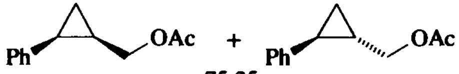  Ph<br>OAc<br>+<br>Ph<br>OAc 75:25 | 50 | 93 |

Table 6 *(continued)*

| *Alkene* | *Reagents* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 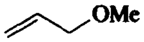 | PhCHO/Zn(Hg)/$BF_3$•$OEt_2$ | 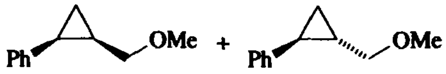<br>33:67 | 56 | 93 |

---

[a] Product yield corrected for unreacted starting material.

rect routes not proceeding *via* free carbenes. Furthermore, the vast majority of these complexes do not exhibit typical carbene-like reactivity. For example, relatively few of them to date have shown reactivity toward alkenes to give cyclopropanes. Rather, for the most part, these complexes behave as a distinctly new class of chemical species showing their own unique types of reactivity.

Another broad class of compounds are the bridged carbene complexes. These compounds contain two identical or two different metal centers with the carbene centers bonded to both of the metal atoms in a bridging relationship. However, these binuclear complexes generally do not show classical carbene reactivity and will therefore not be discussed further, except to mention briefly the special case of the titanium–aluminum complex (**3**) developed by Tebbe and Grubbs and their coworkers.[101] This, and related complexes, has proven to be particularly useful in organic synthesis, although its principal importance is in reactions other than cyclopropanations.

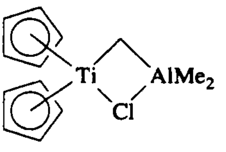

(**3**)

A special note about nomenclature is in order. Both the terms 'carbene' and 'alkylidene' complex have come into use, and attempts have been made to use these terms to differentiate various types of reactivity of these species. However, the term 'carbene' complex is used throughout this chapter, primarily because of the emphasis on cyclopropanation reactivity.

Several methods have been reported for the formation of carbene complexes, but three of these methods have been used especially commonly. The first method, as used by Fischer in his original studies, involves the addition of an organolithium reagent to a transition metal carbonyl complex to give an anionic intermediate which upon *O*-alkylation produces an alkoxycarbene complex (equation 11). In turn, the alkoxy group may undergo substitution by other heteroatomic groups. The second method involves the use of transition metal alkyls which bear a prospective leaving group on the carbon atom bonded to the metal. Upon either direct loss of this group or upon its prior activation, a carbocationic species is formed for which a resonance structure can be written based upon retrodative π-bonding from the metal to the carbon (equation 12). The resulting species may be regarded as a metal-stabilized carbocation or, in the context of this chapter, as a cationic metal–carbene complex. The third method to be discussed here involves addition of an electrophilic reagent, most commonly just a proton source ($E^+ = H^+$), to an alkenylmetal complex. The resulting adduct may again be regarded as a cationic carbene complex (equation 13).

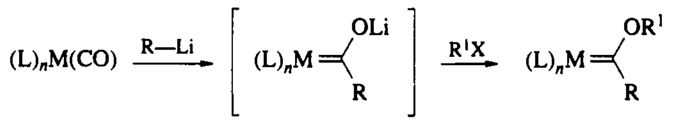

(11)

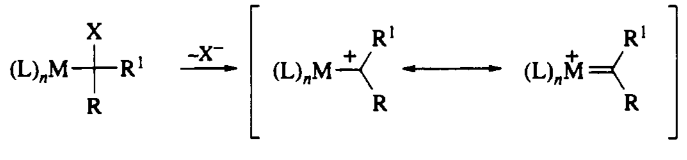

(12)

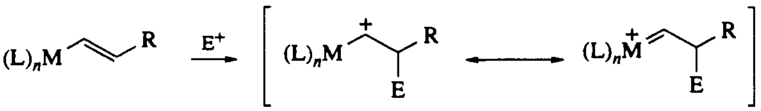

(13)

Several carbene complexes prepared by the first route are sufficiently stable to be isolated and characterized. However, the cationic complexes prepared by the second and third methods are quite reactive species that usually cannot be isolated and for which only partial characterization has been possible through special spectroscopic techniques. Exceptions are those complexes bearing substituents R or $R^1$ that are good cation-stabilizing groups. Consequently, these cationic carbene complexes are most commonly generated *in situ* from their precursors in the presence of the substrates desired for further reactions.

Of the several carbene complexes that are presently known, only a relatively small fraction of them have shown synthetically useful reactivity in cyclopropanations of alkenes. Comprehensive reviews of this aspect of their chemistry appeared in 1987 and 1989,[100j,100k] and the reader is referred to these articles for more detailed treatment of the topic than is given in the present chapter.

The original Fischer-type carbene complexes react with electron deficient alkenes such as α,β-unsaturated esters[102] and especially electron rich alkenes such as enol ethers[103] and enamines,[104] but reactions with simple alkenes have been limited in their usefulness. Furthermore, because these particular carbene complexes most commonly contain heterosubstituted carbene units, they formally fall outside the scope of this chapter. A few nonheterosubstituted examples that have proven to be useful are benzylidene[105] and diphenylcarbene[106] complexes of tungsten.

The most generally useful carbene complexes for transfer of methylene and other simple alkylidene groups are the cationic complexes of the general types shown in equations (12) and (13). In particular, the complexes containing the cyclopentadienyldicarbonyliron group, commonly written as $Cp(CO)_2Fe$ or simply Fp, have been the most useful to date. Also, derivatives of this system have been studied in which at least one of the carbonyl ligands has been replaced by another ligand such as a phosphine or a phosphite.

The first examples of these iron complexes arose from early work of Pettit[107] and Green[108] and their coworkers in the middle 1960s. A key finding was that the reaction of the methoxymethyliron complex (4) with acid in the presence of cyclohexene produced a modest yield of the cyclopropane norcarane (equation 14). The cationic methylene complex (5) was proposed as an intermediate. This species is very reactive and has not been studied by direct means in solution, although it has been detected in gas phase studies.[109]

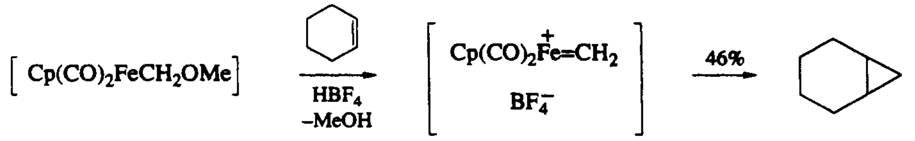

(4) (5) (14)

Since the time of this early work, many other investigators have studied the parent methylene complex (5), several substituted derivatives, and various precursors of these species.[100j,100k] The sulfonium salt (6) has proven to be particularly useful (equation 15) because of its unusually high stability. It is a highly crystalline solid that is stable in air and even in hot water.[110] Substituted derivatives have also been developed. In addition, several α-alkoxyalkyliron derivatives related to the parent compound (4) have been studied extensively.

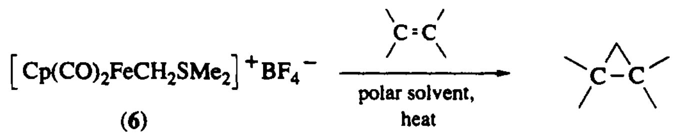

(15)

The reactions of these iron carbene reagents with alkenes to give cyclopropanes are stereospecific. They also exhibit high *syn* stereoselectivity in many cases. Optically active derivatives have been reported that have chiral ligands on iron or chiral alkoxy groups on the prospective carbene center and which have been resolved with the iron itself as a chiral center. Resulting from this work have been some highly enantioselective cyclopropanations.

The cyclopropanation reactions of the cationic iron carbene complexes occur most efficiently with alkenes of normal electronic characteristics. Very electron deficient alkenes such as α,β-unsaturated carbonyl compounds are very poor substrates. Very electron rich alkenes such as enol ethers react rapidly, but the expected cyclopropanes generally cannot be isolated; if they are indeed formed, they apparently undergo further reactions, perhaps promoted by the metallic species present in the reaction mixtures.

Specific examples of cyclopropanations using carbene complexes in general are summarized in Table 7, but the reader is referred to other recent reviews for much more extensive compilations.[100j,100k]

A recent modification of these reactions that appears to have significant potential in organic synthesis is a tandem sequence of alkyne insertion and cyclopropanation (Scheme 2).[115] One particularly impressive, fully intramolecular case is shown in Table 7 (ref. 115).

**Table 7** Cyclopropanations Using Transition Metal–Carbene Complexes

| *Alkene* | *Carbene complex or precursor* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 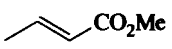 | 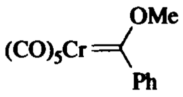 | 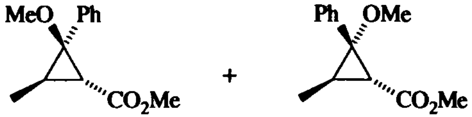<br>2.5:1 | 60 | 102a |
| 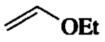 | | 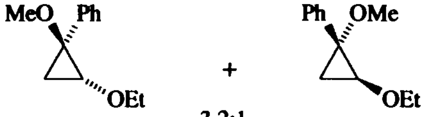<br>3.2:1 | 61 | 103 |
| 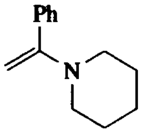 | | 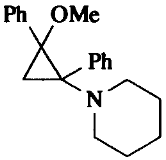 | 16 | 104 |
| 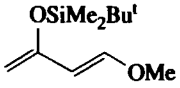 | 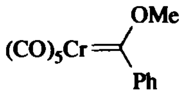 | 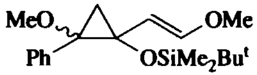 2:1 | 67 | 111 |
| 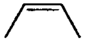 | $(CO)_5W{=}CHPh$ | 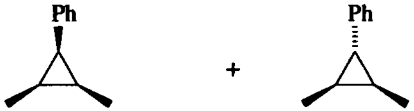<br>41:1 | 60 | 105 |
| 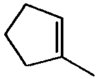 | | 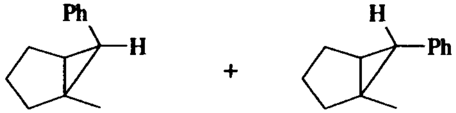<br>8:1 | 50 | 105 |
| 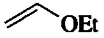 | $(CO)_5W{=}CPh_2$ | 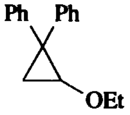 | 65 | 106 |

**Table 7** *(continued)*

| *Alkene* | *Carbene complex or precursor* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 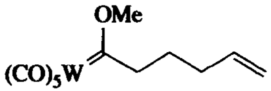 | | 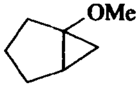 | *ca.* 100 | 112 |
| 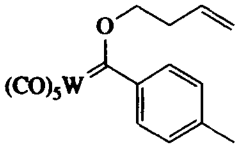 | | 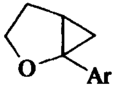 | *ca.* 95 | 113 |
| 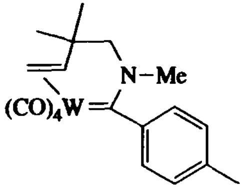 | | 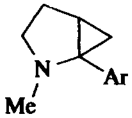 | *ca.* 90 | 114 |
| 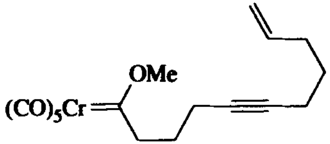 | | 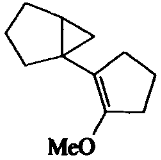 | 97 | 115 |
| 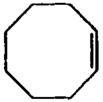 | $[Cp(CO)_2FeCH_2SMe_2]^+ BF_4^-$ | 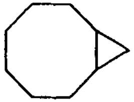 | 92 | 110 |
| 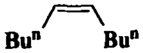 | | 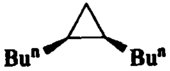 | 87[a] | 110 |

Table 7 *(continued)*

| *Alkene* | *Carbene complex or precursor* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 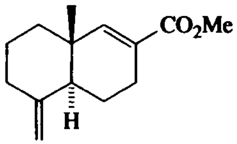 | $[Cp(CO)_2FeCH_2SMe_2]^+ BF_4^-$ | 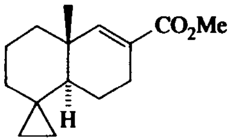 | 86 | 116 |
| 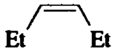 | $[Cp(CO)_2FeCH(OMe)Me]$,<br>$CF_3SO_3SiMe_3$ | 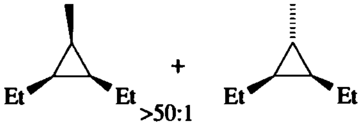<br>>50:1 | 58 | 117 |
| 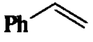 | | 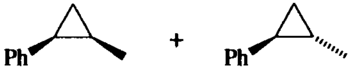<br>4.7:1 | 75 | 117 |
| 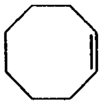 | $[Cp(CO)_2FeCH(SPh)Me]$,<br>$Me_3O^+ BF_4^-$ | 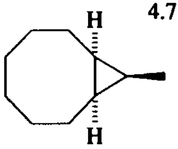 | 73 | 118 |
| 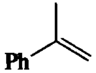 | | 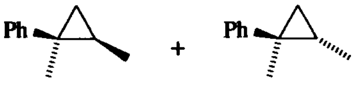<br>2.4:1 | 58 | 118 |
| 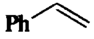 | 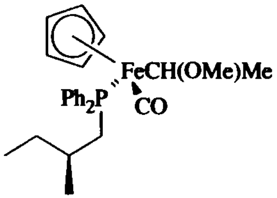<br>(optically active) | 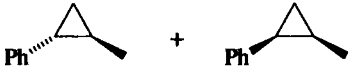<br>3.5:1 | 75 (*ca.* 90% *ee*) | 119 |

Table 7 *(continued)*

| *Alkene* | *Carbene complex or precursor* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 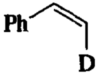 | [Cp(CO)$_2$FeCH(OMe)Me],<br>CF$_3$SO$_3$SiMe$_3$ | 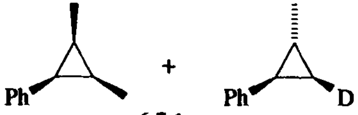<br>6.7:1 | Not reported | 120 |
| 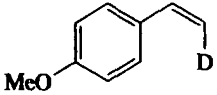 |  | 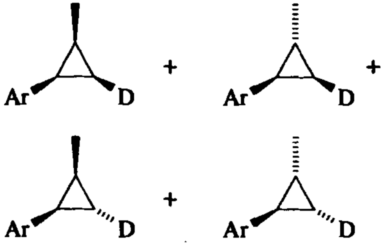<br>6.8:2.2:6.7:1 | Not reported | 120 |
| 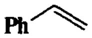 | 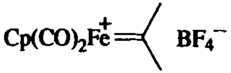 | 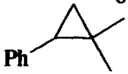 | 45 | 121 |
| 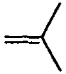 | 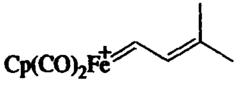<br>BF$_4^-$ | 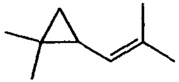 | 56 | 121, 122 |
| 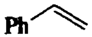 | 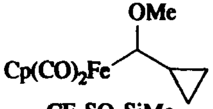<br>CF$_3$SO$_3$SiMe$_3$ | 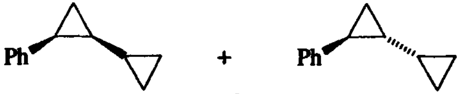<br>1:3.4 | 66 | 123 |
| 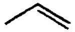 | 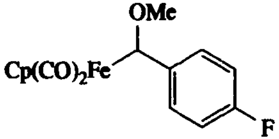<br>CF$_3$SO$_3$SiMe$_3$ | 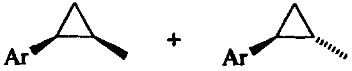<br>9.4:1 | 80 | 124 |

**Table 7** *(continued)*

| *Alkene* | *Carbene complex or precursor* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 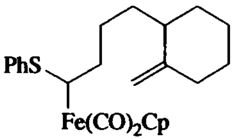<br>$Me_3O^+BF_4^-$ | | 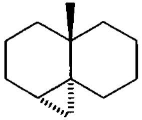 | 50 | 125 |
| 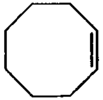 | $[Cp(CO)_2FeCH_2SPh_2]^+ BF_4^-$ | 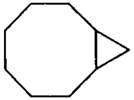 | 85 | 126 |
| 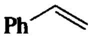 | $[(C_5Me_5)(CO)_2MCH_2OMe]$<br>(M = Fe, Ru)<br>$CF_3SO_3SiMe_3$ | 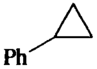 | 100 | 127 |
| 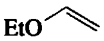 | $(CO)_5WCH(Ph)SEt_2$ | 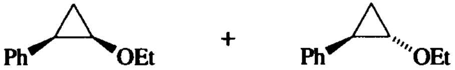 | Not reported | 128 |
| $(H_2C{=}CH_2)_2NiCH_2S(O)Me_2$ | | | 16 | 129 |
| 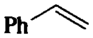 | $[Cp(CO)_2(PPh_3)WCH_2OC(O)Bu^t]$<br>$CF_3SO_3SiMe_3$ | 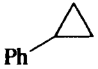 | 50 | 130 |
| 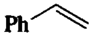 | $[Cp(CO)_2(PPh_3)WMe]$,<br>$Ph_3C^+ BF_4^-$ | 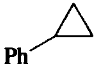 | 52 | 130 |
| 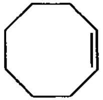 | $[Cp(PPh_3)NiCH_2SMe_2]^+ BF_4^-$ | 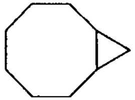 | 49 | 131 |

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[a] Product yield corrected for unreacted starting material.

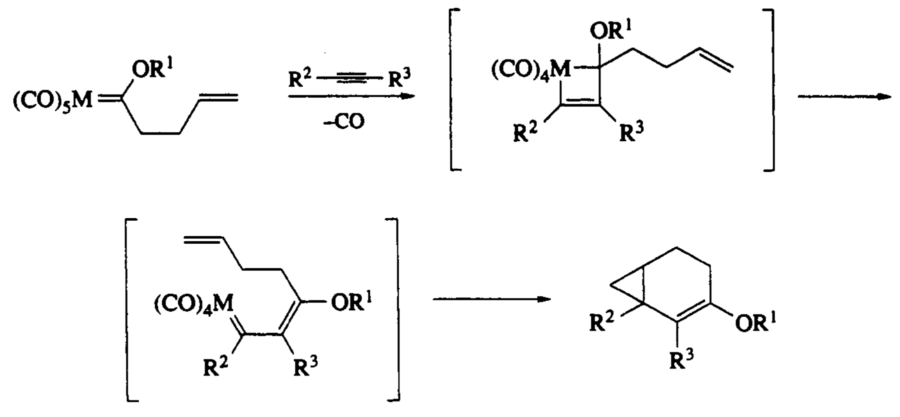

Scheme 2

## 4.6.6 TANDEM CARBANIONIC ADDITION/INTRAMOLECULAR ALKYLATIONS

A number of methods for forming cyclopropanes are based upon the general reaction sequence shown in Scheme 3. In the first step, a carbanionic intermediate (7) is formed which bears a substituent G. This substituent generally serves as both a carbanion-stabilizing group and, eventually, as a leaving group. The intermediate (7) then undergoes addition to an alkene double bond bearing an electron-withdrawing group (EWG). The resulting adduct (8) is another carbanionic species which undergoes intramolecular alkylation, with displacement of the group G, to produce a cyclopropane.

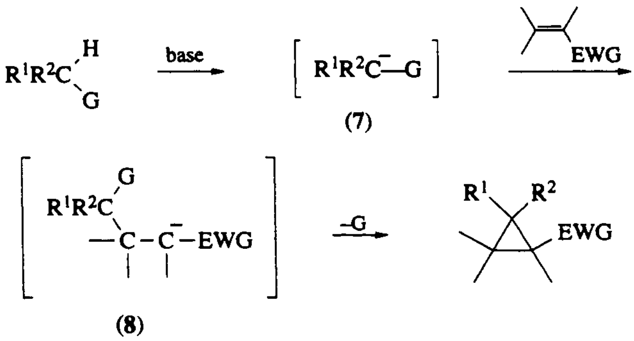

Scheme 3

This set of methods is inherently related to some of the carbene-based approaches to cyclopropanes. The relationship is especially close to the α-elimination pathways (Section 4.6.3.1) with a principal difference being the ordering of steps with respect to loss of the leaving group.

Because of the stepwise formation of the two new carbon–carbon bonds of the cyclopropane product, and because of the intermediacy of the carbanionic adduct (8), the double-bond configuration of the alkene substrate may be lost, depending upon the lifetime of the intermediate relative to carbon–carbon single-bond rotations. Consequently, the stereospecificity of these cyclopropanations varies from one case to another.[132]

### 4.6.6.1 Use of Ylides

With reference back to Scheme 3, the substituent G in these reactions is most commonly an onium group bearing a positive charge. Examples are sulfonium and phosphonium groups. The intermediates (7) are thus various types of ylides, and the adducts (8) are defined as being betaines.

### *4.6.6.1.1 Sulfur ylides*

Ylides based upon sulfur are the most generally useful in these cyclopropane-forming reactions.[133] Early work in this area was done with the simple dimethyloxysulfonium methylide (**9**) derived from dimethyl sulfoxide. The even simpler dimethylsulfonium methylide (**10**) was studied at the same time as a reagent primarily for the conversion of carbonyl compounds into epoxides.[134] Somewhat later, other types of sulfur ylides were developed, among which the nitrogen-substituted derivatives such as (**11**) are particularly important.[135]

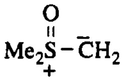

$\mathrm{Me_2}\overset{\mathrm{O}}{\underset{+}{\mathrm{S}}}-\bar{\mathrm{C}}\mathrm{H_2}$

**(9)**

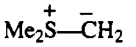

$\mathrm{Me_2}\overset{+}{\mathrm{S}}-\overset{-}{\mathrm{C}}\mathrm{H_2}$

**(10)**

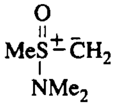

$\mathrm{Me}\overset{\mathrm{O}}{\underset{\mathrm{NMe_2}}{\mathrm{S}}}\overset{+}{-}\bar{\mathrm{C}}\mathrm{H_2}$

**(11)**

Despite the stepwise pathway for these reactions, some cyclopropanations using ylides may be stereospecific.[132] Successful efforts have also been reported for the development of enantioselective cyclopropanations through use of, for example, optically active ylides related to (**11**)[136] and of alkene substrates bearing chiral auxiliaries.

The use of sulfur ylides has been covered by thorough reviews[133] to which the reader is referred for extensive listings of examples. A few representative cases are given in Table 8.

The reactions are normally limited to the use of electron deficient alkenes as substrates. However, there have been some reports of copper-catalyzed reactions of sulfur ylides with simple alkenes, as exemplified in equation (16).[147]

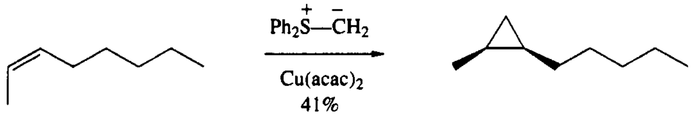
$\mathrm{Ph_2}\overset{+}{\mathrm{S}}-\overset{-}{\mathrm{C}}\mathrm{H_2}$
Cu(acac)$_2$
41%

(16)

### *4.6.6.1.2 Other ylides*

Ylides of other elements have been used much less commonly than sulfur ylides in cyclopropanations. Rather, other ylides are better known for their uses in other types of reactions, the best example being the use of phosphonium ylides in the Wittig reaction with carbonyl compounds to give alkenes. Nonetheless, some cases of cyclopropanations have been reported with phosphonium ylides and the related arsenic derivatives. Examples are given in Table 9.

### 4.6.6.2 Addition of Other Carbanionic Species Bearing Leaving Groups

Cyclopropanations are known for several other carbanionic intermediates of the general type (**7**), in which the substituent G is ultimately lost as an anionic leaving group in the last step of the ring-forming pathway (see Scheme 3 above). The substituent G is most often a functional group based upon sulfur, selenium or nitrogen. Halide-substituted derivatives probably react *via* the α-elimination pathway in most cases (see Section 4.6.3.1), but in some reactions with electron deficient alkenes as substrates, the normal order of steps may be altered (*e.g.* Table 10, ref. 162).

Representative examples of these further carbanionic cyclopropanations are compiled in Table 10.

## 4.6.7 CONCLUSION

A large number of useful synthetic methods are available for the addition of methylene and other simple alkylidene groups to alkenes to give cyclopropanes. The methods that are most commonly used with alkenes of normal electronic characteristics are based upon the intermediacy of carbenes and related species. Very electron rich alkenes bearing electron-donating substituents are also good substrates for many of these carbene-based methods. Some of these same methods may be used with electron deficient alkenes, but the carbanion-based methods have been developed more specifically for these latter substrates.

**Table 8** Cyclopropanations Using Sulfur Ylides

| *Alkene* | *Ylide* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 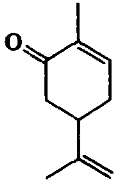 | 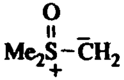 $Me_2\overset{O}{\overset{\parallel}{\underset{+}{S}}}-\bar{C}H_2$ | 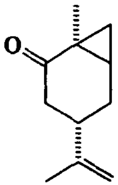 | 81 | 134 |
| 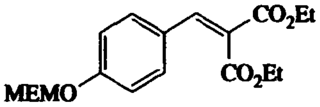 |  | 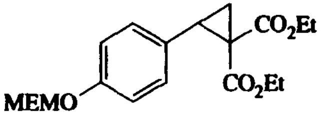 | 76 | 137 |
| 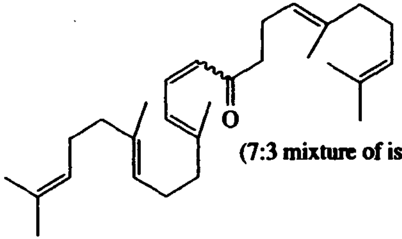 (7:3 mixture of isomers) |  | 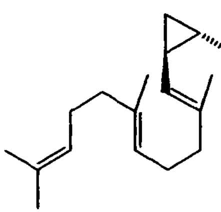 + *cis* isomer (19:1) | Not reported | 138 |
| 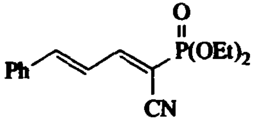 |  | 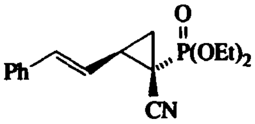 + 9:1 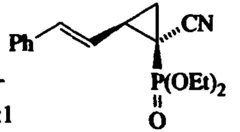 | 87 | 139 |
| 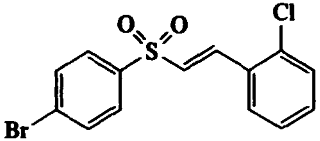 | 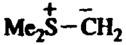 $Me_2\overset{+}{S}-\bar{C}H_2$ | 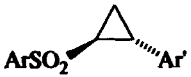 | 80 | 140 |

Table 8 *(continued)*

| *Alkene* | *Ylide* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 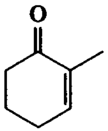 | $Ph_2\overset{+}{S}-\overset{-}{C}Me_2$ | 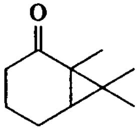 | 86 | 141 |
| 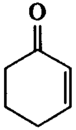 | $Me_2\overset{+}{S}-\overset{-}{C}HSiMe_3$ | 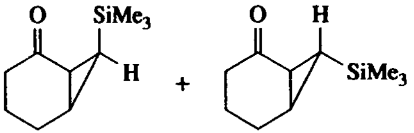<br>1:7 | 55 | 142 |
| 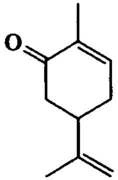 | 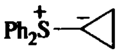 | 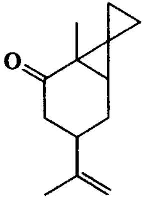<br>(stereochemistry not reported) | 75 | 143 |
| 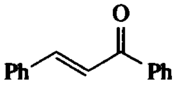 | 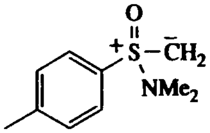<br>(optically active) | 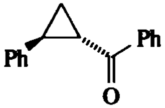 | 94 (35% optical yield) | 136 |
| 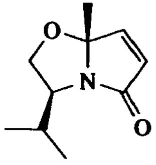<br>(optically active) | 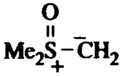<br>$Me_2\underset{+}{\overset{O}{\overset{\Vert}{S}}}-\overset{-}{C}H_2$ | 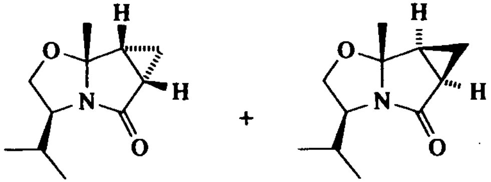<br>39:1 | 64 | 144 |

Table 8 *(continued)*

| *Alkene* | *Ylide* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 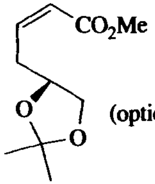 (optically active) | $Ph_2\overset{+}{S}-\overset{-}{C}Me_2$ | 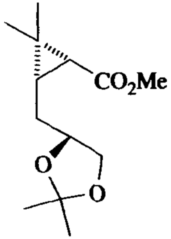 | 84 (>96% *de*) | 145 |
| 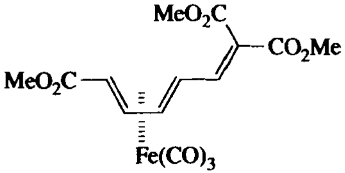 (optically active) | $Me_2\overset{+}{S}-\overset{-}{C}HCO_2Me$ | 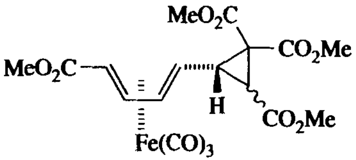 | Not reported<br>(≥90% *de*) | 146 |

**Table 9** Cyclopropanations Using Other Ylides

| *Alkene* | *Ylide* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 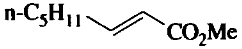 | $Ph_3\overset{+}{P}-\overset{-}{C}Me_2$ | 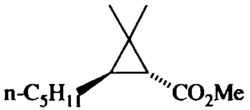 | 75 | 148 |
| 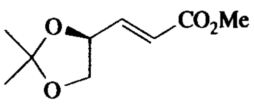<br>(optically active) | | 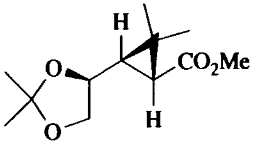 | 60 (>96% *de*) | 149 |
| 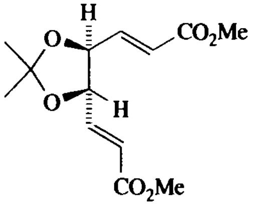 | | 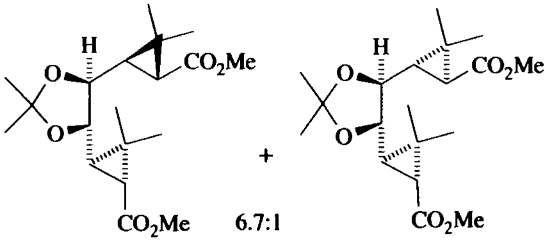 | 75 | 150 |
| 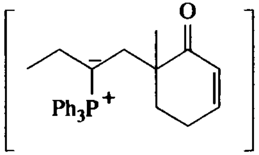 | | 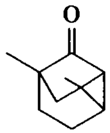 | 44 | 151 |
| 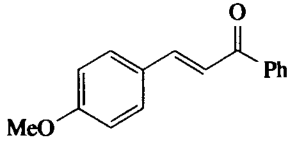 | $Ph_3\overset{+}{As}-\overset{-}{C}HSiMe_3$ | 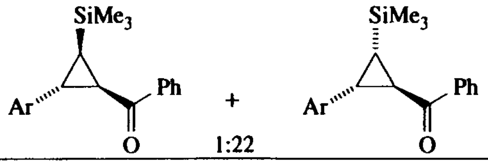 | 47 | 152 |

Table 10 Other Carbanionic Cyclopropanations

| *Alkene* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 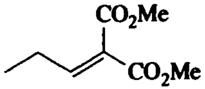 | 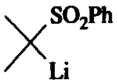 | 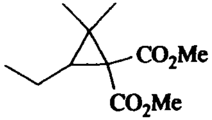 | 63 | 153 |
| 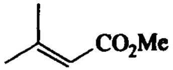 | 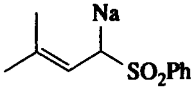 | 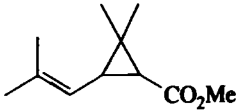<br>(stereochemistry not reported) | Not reported | 154 |
| 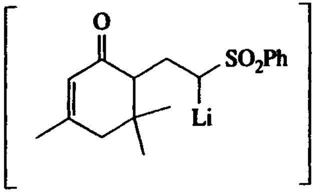 |  | 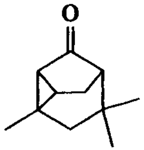 | 38 | 155 |
| 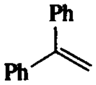 | 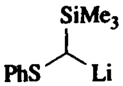 | 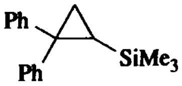 | 75 | 156 |
| 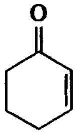 | 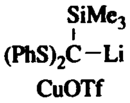 $(PhS)_2\overset{SiMe_3}{\overset{\mid}{C}}-Li$<br>CuOTf | 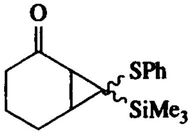 | 76 | 157 |
| 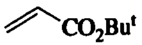 | 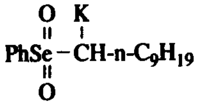 $PhS\underset{O}{\overset{O}{e}}-\overset{K}{C}H\text{-n-}C_9H_{19}$ | 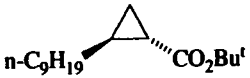 | 76 | 158 |

Table 10 *(continued)*

| *Alkene* | *Reagent* | *Products* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 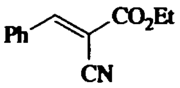 | 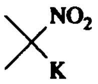 | 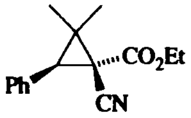 | 81 | 159a |
| 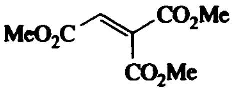 | 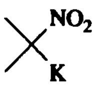 | 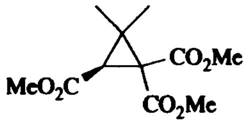 | 72 | 160 |
| 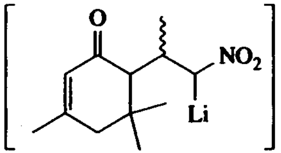 |  | 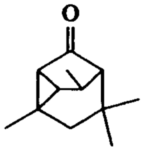 + 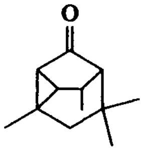<br>12:1 | 63 | 161 |
| 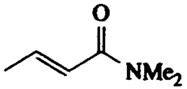 | 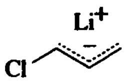 | 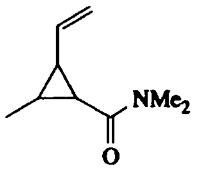<br>(mixture of stereoisomers) | 80 | 162 |

With the wide choice of methods now available, typical cyclopropanations may be performed with excellent stereospecificity, stereoselectivity, diastereofacial selectivity, regioselectivity and chemoselectivity. Good progress has also been made with respect to enantioselective cyclopropanations, but much further work in this area during the coming years would be appropriate. Ideal methods would not only exhibit high enantioselectivity with a wide range of alkenes, but they would also use very readily available and inexpensive starting materials as the sources of the methylene or alkylidene groups that undergo the alkene additions, and if catalysts are needed, they should be reasonably inexpensive, exhibit high catalytic turnovers and be readily recyclable. In terms of availability, aldehydes and ketones would appear to be particularly ideal starting materials, but methods for their use in direct, deoxygenative alkylidene transfer reactions as suggested in equation (17) are still relatively rare.[93] Further studies of reactions of this type are surely justified, especially with recyclable, oxygenophilic metal species that are also chiral.

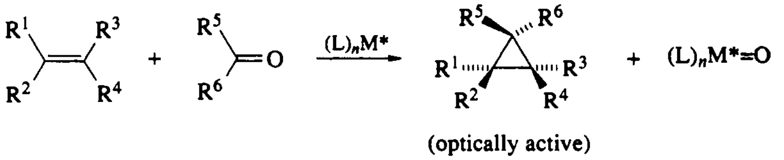

(17)

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# 4.7

# Formation and Further Transformations of 1,1-Dihalocyclopropanes

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## 4.7.1 INTRODUCTION

In this chapter we will be concerned with only 1,1-dihalocyclopropanes and these will be referred to as dihalocyclopropanes throughout the text.

The first description of a dihalocyclopropane[1] was made nearly a century ago and the idea that dichlorocarbene is an intermediate in the basic hydrolysis of chloroform dates back to 1862.[2] The pioneering work of Hine confirmed the existence of dichlorocarbene[3,4] and Doering then demonstrated its generation and its addition to alkenes leading to the formation of dichlorocyclopropanes (Doering reaction).[5] Undoubtedly, this work laid the foundation for dihalocyclopropane chemistry and has opened a new vista in organic chemistry. The formation and transformations of dihalocyclopropanes including synthetic applications have received considerable attention during the last three decades. Excellent reviews on aspects of dihalocyclopropanes also have been published.[6–10] Effort has been made to expose all the original work with special attention being paid to publications that have appeared during the last ten years.

Dihalocyclopropanes containing all possible combinations of halogens have been synthesized. From the vantage point of the synthetic chemist, dibromo- and dichloro-cyclopropanes elicit the most useful and fascinating chemistry, and therefore this discussion will be centered around the formation and transformations of these two groups of compounds. For the sake of completeness, dihalocyclopropenes have been discussed where appropriate. To emphasize the synthetic potential, separate subsections are devoted to certain topics, *e.g.* formation of heterocycles.

## 4.7.2 SYNTHESIS OF DIHALOCYCLOPROPANES

Dihalocyclopropanes are generally prepared by the addition of dihalocarbenes to alkenic substrates. As indicated in the introduction, the first synthesis of a dihalocyclopropane was accomplished by Doering and Hoffmann by the addition of dichlorocarbene, generated from chloroform and potassium *t*-butoxide ($Bu^tOK$), to cyclohexene giving dichloronorcarane (**1**), as shown in equation (1).[5]

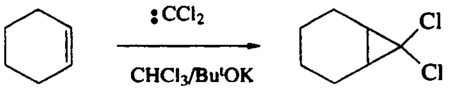

(1)

(**1**)

Subsequently, other dihalocarbenes (**2**) have been generated and their addition to alkenes investigated in varying detail.

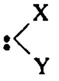

(**2**)

X = Y = F, Cl, Br, I
X = F, Y = Cl
X = Cl, Y = Br
X = F, Y = Br
X = F, Y = I

### 4.7.2.1 Methods for the Generation of Dihalocarbenes

The original procedure for the generation of dichlorocarbene from chloroform by $Bu^tOK$ (equation 2) still finds limited use.[5] In one variation[11] dichlorocarbene is generated by the reaction of an alkyllithium with bromotrichloromethane (equation 3). However, these procedures have largely been replaced by milder and synthetically more useful methods. Thermal decomposition of sodium trichloroacetate in dimethoxyethane has found extensive use in the generation of dichlorocarbene (equation 4).[12] Similarly, difluorochloroacetate has been used as a convenient source of difluorocarbene (equation 5).[13] Trichloroacetic acid itself undergoes thermal decomposition to give dichlorocarbene (equation 6).[14]

$$CHCl_3 \xrightarrow{Bu^tOK} :CCl_2 + KCl + Bu^tOH \qquad (2)$$

$$BrCCl_3 \xrightarrow{Bu^nLi} :CCl_2 + LiCl + Bu^nBr \qquad (3)$$

$$Cl_3CCO_2Na \xrightarrow{\Delta} :CCl_2 + NaCl + CO_2 \qquad (4)$$

$$ClF_2CCO_2Na \xrightarrow{\Delta} :CF_2 + NaCl + CO_2 \qquad (5)$$

$$Cl_3CCO_2H \xrightarrow{\Delta} :CCl_2 + HCl + CO_2 \qquad (6)$$

The observation that phenyl(trichloromethyl)mercury undergoes dissociation at 150 °C to give phenylmercury(II) chloride and dichlorocarbene has led to a wide range of organomercury compounds ($PhHgCX_3$ — Seyferth reagents)[15–18] which serve as efficient dihalocarbene transfer reagents (equation

7). Seyferth reagents are ideal for the dihalocyclopropanation of deactivated or base sensitive substrates such as allyl halides, allyl isocyanates, polychloroalkenes, α,β-unsaturated ketones, esters, nitriles and sulfones.[19]

$$\mathrm{PhHgCX_2Y} \xrightarrow{\Delta} \mathrm{{:}CX_2} + \mathrm{PhHgY} \qquad (7)$$

X = Cl, Br or F, Y = Cl or Br

Undoubtedly the most important and widely used procedure for the generation of dichlorocarbene involves the reaction of chloroform with aqueous sodium hydroxide under the conditions of phase transfer catalysis (PTC), introduced by Makosza.[20–22] Under these conditions chloroform reacts with sodium hydroxide to form sodium trichloromethylide which on exchange with a quaternary ammonium salt, usually benzyltriethylammonium chloride, is converted to the unstable quaternary ammonium methylide which dissociates in the organic phase to give dichlorocarbene. The dichlorocarbene irreversibly adds to the alkene (Scheme 1).

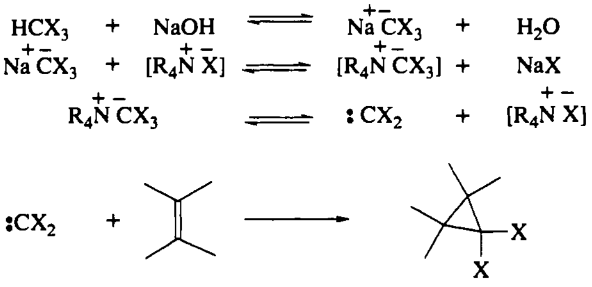

$$\mathrm{HCX_3} + \mathrm{NaOH} \rightleftharpoons \overset{+}{\mathrm{Na}}\overset{-}{\mathrm{C}}\mathrm{X_3} + \mathrm{H_2O}$$

$$\overset{+}{\mathrm{Na}}\overset{-}{\mathrm{C}}\mathrm{X_3} + [\mathrm{R_4}\overset{+}{\mathrm{N}}\overset{-}{\mathrm{X}}] \rightleftharpoons [\mathrm{R_4}\overset{+}{\mathrm{N}}\overset{-}{\mathrm{C}}\mathrm{X_3}] + \mathrm{NaX}$$

$$\mathrm{R_4}\overset{+}{\mathrm{N}}\overset{-}{\mathrm{C}}\mathrm{X_3} \rightleftharpoons \mathrm{{:}CX_2} + [\mathrm{R_4}\overset{+}{\mathrm{N}}\overset{-}{\mathrm{X}}]$$

X = Cl or Br

**Scheme 1**

Although illustrated for the generation of dibromo- and dichloro-carbenes, the PTC method has found application in the generation of other dihalocarbenes. Indeed the PTC method has assumed great importance in recent years in the synthesis of a variety of organic compounds and the procedure is well documented in excellent reviews[21–25] and books.[26–28] The procedure has been used extensively[21–28] for the addition of dihalocarbenes to a variety of substrates such as alkenes, alkynes, conjugated polyalkenes, allenes, α,β- and γ,δ-unsaturated esters, imines, enamines, enol acetates, enol ethers, electron rich aromatic compounds, sterically hindered arylated alkenes, ferrocene-substituted alkenes, methylfurans, thiophenes, indenes, strained alkenes such as bicyclo[2.2.1]heptenes and a number of other π-systems. Dehmlow has investigated[24,25,28] the PTC method for the generation of dichlorocarbene in great detail and his prescription calls for the use of a 4 mol excess of $CHCl_3$, 50% aqueous sodium hydroxide and 1 mol % of the catalyst in proportion to the alkenic substrate. Quaternary ammonium salts such as benzyl triethylammonium chloride and tetra-*n*-butylammonium chloride are the most efficient catalysts.

Improvements in the generation of dibromocarbene have also been reported.[29,30] Although diiodocarbene has been generated and added to alkenes under PTC conditions,[31] the $CHI_3$/Bu$^t$OK procedure seems to be superior.[32,33] Dihalocarbenes carrying two different halogens, *viz.* :CBrCl,[34,36] :CBrF,[37,38] :CClF,[37] :CClI[36] and :CFI[39] have been generated under PTC conditions. A number of modifications, such as solid/liquid PTC involving $Cl_3CCO_2Na$/$CHCl_3$/catalyst,[40] powdered NaOH/$CHCl_3$/catalyst[41] with ultrasonic irradiation,[42] have enhanced the usefulness of the PTC procedure. Tertiary amines have also been used as catalysts for the generation of dichlorocarbene from chloroform in two-phase systems consisting of aqueous organic solvents.[43,44]

Dihalocarbenes generated by PTC exhibit enhanced reactivity which may be attributed to the fact that the carbene is formed in the proximity of the substrate and a large excess of it is generated, albeit in small quantities at a time. In addition, the dihalocarbene generated in this fashion is completely 'free' and not associated with any metallic species, thereby attenuating the reactivity. The use of crown ethers and $CH_2Cl_2$ has been shown to suppress halogen exchange during the generation of mixed dihalocarbenes.[34–36]

In comparison to other dihalocarbenes, difluorocarbene reactions are less well investigated. Invariably, difluorocarbene is generated thermally and a number of reagents have been investigated.[19,45] The method of choice appears to be the reaction of $PhHgCF_3$ with NaI, which gives excellent results with a variety of alkenes[45]

The low valent titanium species obtained from $TiCl_4$ and LAH has been used[46] to generate dichlorocarbene from $CCl_4$. Finally, it has been shown that certain dihalocyclopropanes dissociate thermally[47] or photochemically[48] to generate the carbene. Such procedures may be useful under special circumstances.

### 4.7.2.2 Addition of Dihalocarbenes to π-Bonds

The electronic description and hybridization of dihalocarbenes (3) are similar to those of carbocations. Not surprisingly, therefore, dihalocarbenes behave as electrophiles in their reactivity towards alkenic substrates and this is discussed in the following sections.

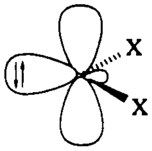

(3)

#### *4.7.2.2.1 Alkenes*

By virtue of their electrophilic nature, dihalocarbenes add to alkenes smoothly. Predictably, the following order of reactivity is observed: tetraalkyl- > trialkyl- > unsymmetrical dialkyl- > symmetrical dialkyl- > monoalkyl-substituted alkenes. It has long been known that dihalocarbene addition to alkenes is stereospecific (equations 8 and 9).[49,50] The stereospecificity has its origin in the spin state of the carbene, a ground state singlet,[51] which allows concerted reaction. The ground state singlet is stabilized by the interaction of one of the nonbonding orbitals of the carbene with orbitals on the halogen.

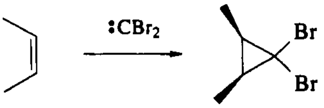

(8)

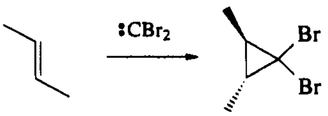

(9)

The general methods outlined (Section 4.7.2.1) are suitable for the dihalocyclopropanation of simple alkenes, although the PTC procedure is preferable in the vast majority of cases, with the exception of alkenes carrying electron-withdrawing groups. Seyferth reagents are ideal in such cases, as illustrated by the conversion of acrylonitrile to 1-cyano-2,2-dihalocyclopropane (equation 10).[52] Dihalocyclopropanes are generally stable compounds and are readily isolable. However, those resulting from the addition of dihalocarbenes to strained alkenes are unstable and often undergo rearrangements (equation 11).[10,53,54] Selected examples of the addition of dihalocarbenes to alkenes are given in equations (12) to (16). The addition of dichlorocarbene to methylenecyclopropane, giving a spiro compound (equation 12),[55] is similar to the earlier work on the addition of dibromo- and dichloro-carbenes to cyclopropylidenecycloalkenes.[56] A monoadduct can be conveniently prepared from isotetralin by reaction with dihalocarbenes (equation 13).[57] However, with a large excess of $:CCl_2$, the reaction gives a mixture of di- and tri-adducts.[58] Normally 1,3-dienes add dichlorocarbene to give the 1,2-adduct (equation 14),[59] but there are instances where both the 1,2- and the 1,4-adducts are obtained.[60] Certain metal complexes of alkenes have been shown to add dichlorocarbene (equation 15).[61] Dichlorocarbene generated from sodium trichloroacetate adds to 2-bromovinyltrimethylsilane (equation 16).[62]

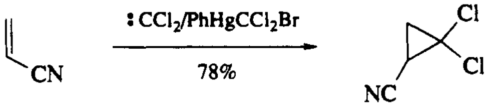

(10)

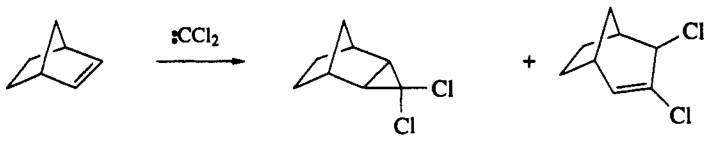
:CCl2
Cl
Cl
+
Cl
Cl

(11)

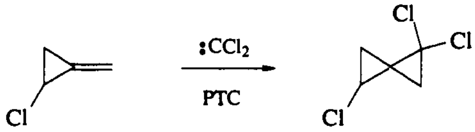
Cl
:CCl2
PTC
Cl
Cl
Cl

(12)

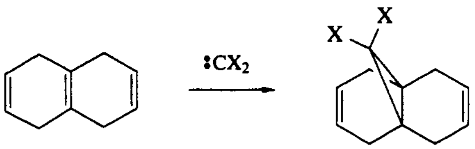

(13)

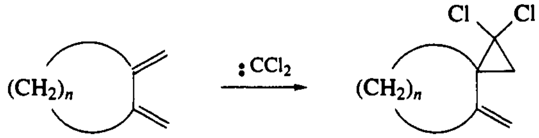
(CH2)n
:CCl2
(CH2)n
Cl
Cl

(14)

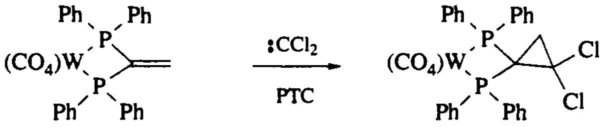
Ph
Ph
P
(CO4)W
P
Ph
Ph
:CCl2
PTC
Ph
Ph
P
(CO4)W
P
Ph
Ph
Cl
Cl

(15)

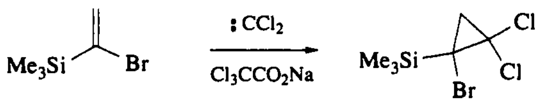
Me3Si
Br
:CCl2
Cl3CCO2Na
Me3Si
Br
Cl
Cl

(16)

Predictably, with enynes dihalocarbene addition occurs preferentially with the double bond (equation 17).[63,64] The reaction of dichlorocarbene with allenes usually gives rise to spiro-linked dichlorocyclopropanes (equation 18),[65] but rearranged products are obtained in some cases (equation 19).[65,66] Somewhat surprisingly, a measure of stereoselectivity has been observed in the formation of dichlorocyclopropylcarbinols from secondary allylic alcohols and dichlorocarbene (equation 20).[67]

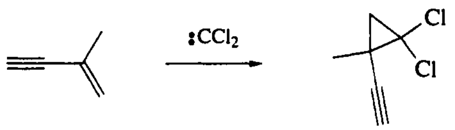

(17)

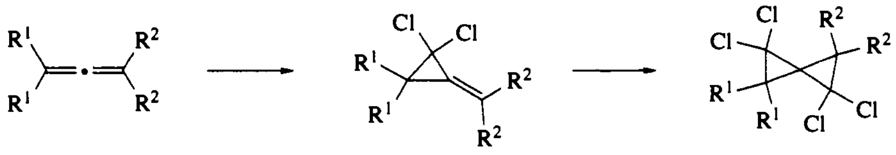
R1
R1
R2
R2
Cl
Cl
R1
R1
R2
R2
Cl
R2
R2
Cl
R1
R1
Cl
Cl

(18)

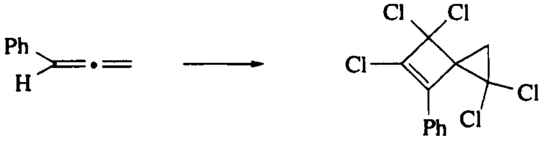
Ph
H
Cl
Cl
Cl
Ph
Cl
Cl

(19)

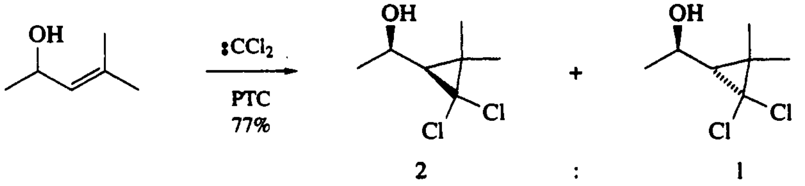

(20)

#### *4.7.2.2.2 Electron rich π-systems*

The electrophilic nature of dihalocarbenes makes them highly reactive towards enamines, enamides, enol ethers, vinyl sulfides, vinyl selenides and electron rich aromatic and heteroaromatic systems. Unlike in the case of simple alkenes, the products are often unstable and readily undergo rearrangement. The reaction of dichlorocarbene with the enamine of cyclohexanone (**4a**) affords an adduct (**5a**) which on hydrolysis gives 2-chloromethylenecyclohexanone (Scheme 2).[68] Subsequently, the reactions of dihalocarbenes with a variety of enamines have been studied.[69–74] The dichlorocarbene adduct of cyclohexanone enamine is stable, whereas the one resulting from cyclopentanone enamine (**5b**) undergoes ring expansion (Scheme 2).[69] Such ring expansions are discussed in a later section (4.7.3.7.1). As with other substrates, the dihalocarbene is generated by PTC, by the thermal decomposition of sodium trihaloacetate or from a Seyferth reagent.

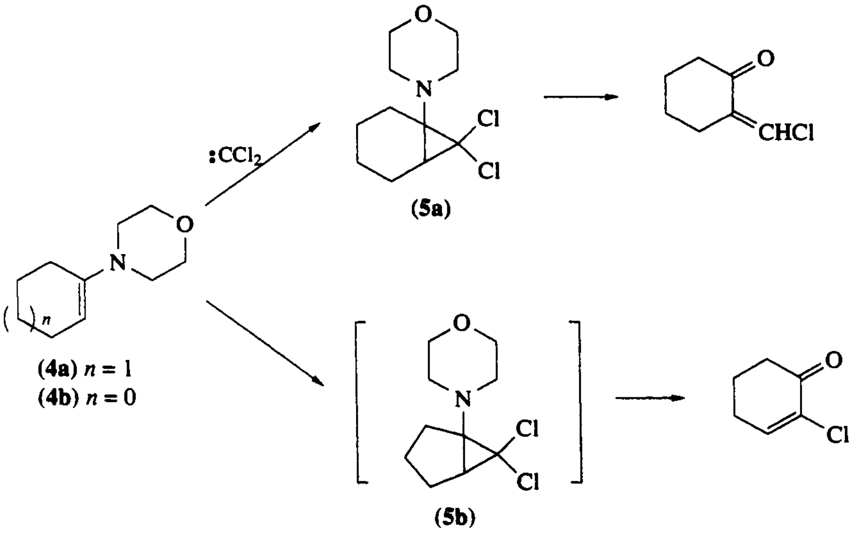

Scheme 2

In addition to acyclic and monocyclic enamines, bicyclic and tricyclic enamines also undergo cycloaddition with dihalocarbenes. 'Endocyclic enamines', such as pyrrole and indole, add dichlorocarbene and the adducts rapidly undergo ring cleavage to afford 3-chloropyridine and 3-chloroquinoline, respectively, in moderate yields (*cf.* Section 4.7.3.9).[75–77]

Although less reactive than enamines, enamides also undergo cycloaddition with dihalocarbenes and the adducts are usually stable.[73,74] A variety of other nitrogen heterocycles, in which the nitrogen lone pair is in conjugation with a π-system, have been shown to undergo dihalocyclopropanation leading to synthetically useful intermediates.[74] An example from isoquinoline alkaloid synthesis[78] is shown in equation (21).

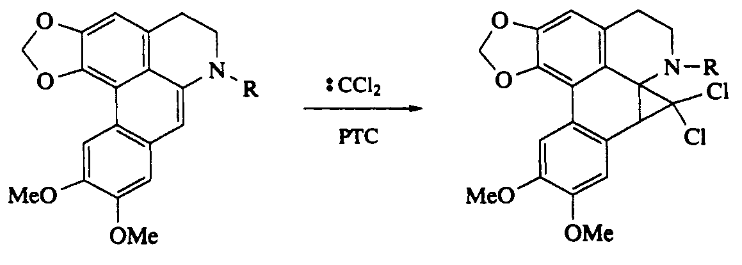

(21)

Like enamines, dihalocarbenes add smoothly to enol ethers and in many cases it is possible to isolate the dihalocyclopropyl intermediates which are valuable synthons for chloroenones (*cf.* Section 4.7.3.7.1). The earliest example of the addition of a dihalocarbene to an enol ether was provided by Parham,[6,79] who studied the addition of dichlorocarbene to dihydropyran (equation 22). An example which illustrates the synthetic potential of the process is the conversion of the cyclohexanone enol ether (**6**) to the dichlorocyclopropane (**7**; equation 23).[80] The latter served as a useful intermediate in a stereospecific synthesis of Prelog–Djerassi lactonic acid.

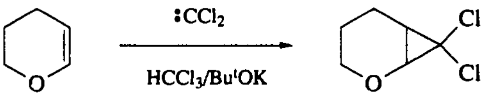

(22)

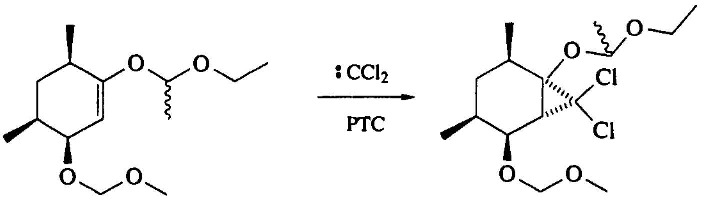

(**6**) (**7**)

(23)

Enol silyl ethers,[81–83] enol acetates,[84,85] and enol lactones[86] also undergo facile dihalocyclopropanation with dihalocarbenes generated by the thermal decomposition of Seyferth reagents or sodium trihaloacetates. Ketene acetals give unstable dihalocarbene adducts which are synthons for α-haloacrolein and other valuable intermediates.[87,88] Vinyl sulfides[89] and selenides[90] have been reported to undergo addition with dichlorocarbene.

### 4.7.2.2.3 Alkynes

Interest in the reaction of dihalocarbenes with alkynes has been limited. In comparison with alkenes, dihalocarbenes react sluggishly with alkynes (*cf.* equation 17) and the resulting dihalocyclopropenes are unstable (Scheme 3). These are, however, valuable precursors for cyclopropenones (equations 24 and 25).[91–95]

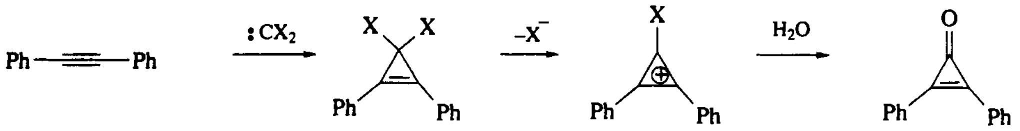

**Scheme 3**

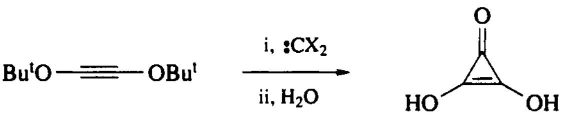

(24)

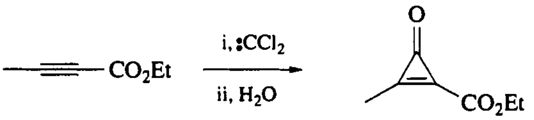

(25)

### 4.7.2.3 Other Methods for the Formation of Dihalocyclopropanes

Indirect methods, which are primarily essentially of academic interest, nevertheless may find use under special circumstances. One of these, involving the brominative decarboxylation (Borodin–Hunsdiecker reaction) of silver α-fluorocyclopropanecarboxylate, provides a convenient and stereospecific route to the synthesis of fluorobromocyclopropyl compounds (equation 26).[96] Another approach makes use of the Diels–Alder reaction between tetrachlorocyclopropene and dienes (equation 27).[97,98] The adducts can undergo facile dehydrohalogenation or ring opening.

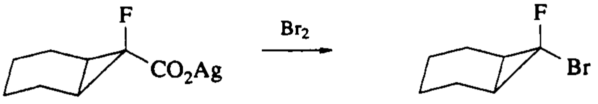

(26)

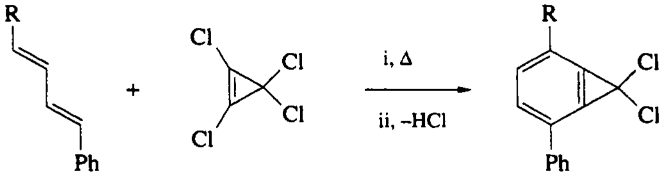

(27)

## 4.7.3 TRANSFORMATIONS OF 1,1-DIHALOCYCLOPROPANES

The electronic and geometric features of dihalocyclopropanes make them susceptible to a variety of chemical transformations. Some of these are manifested in simple peripheral changes involving only the halogen atoms while others involve complex transformations resulting from highly reactive species — carbenes and carbenoids — unleashed by the removal of the halogens. Yet another set of reactions emerge from the electrocyclic opening of the cyclopropane ring attended by the departure of a halide ion. These transformations are described in the following sections with emphasis on synthetic utility.

### 4.7.3.1 Reductive Dehalogenation

Dihalocyclopropanes readily undergo reductive dehalogenation under a variety of conditions. Suitable choice of reagents and reaction conditions will allow the synthesis of monohalocyclopropanes or the parent cyclopropanes.[19,99] The ease of reduction follows the expected order: I > Br > Cl > F. In general, complete reduction of dibromo and dichloro compounds is accomplished by alkali metal in alcohol,[99–102] liquid ammonia[103] or tetrahydrofuran (equations 28 and 29).[104] The dihalocyclopropanes can be reduced conveniently with LAH (equation 30).[105] LAH reduction is particularly suited for difluoro compounds which are resistant to dissolving metal reductions.[19,106] It is noteworthy that the sequence of dihalocarbene addition to an alkene followed by the reduction of the dihalocyclopropyl compounds (equation 31) provides a convenient and powerful alternative to Simmons–Smith cyclopropanation, which is not always reliable.

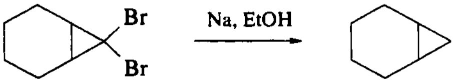

(28)

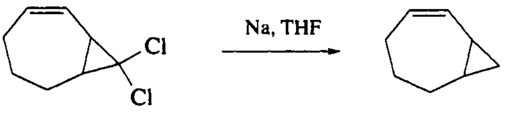

(29)

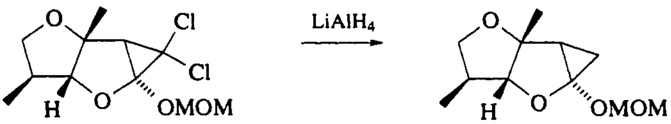

(30)

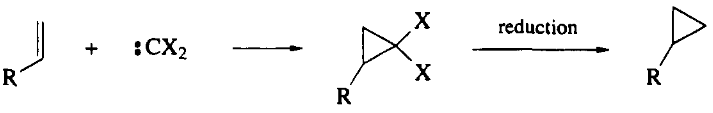

(31)

The selective or partial reduction of dihalocyclopropanes to monohalocyclopropanes[107] can be achieved with LAH[108] or $Bu_3SnH$ (equations 32 to 34).[109,110] A number of other reducing agents also lead to partial reduction.[19] Reduction of dihalocyclopropanes proceeds *via* radical intermediates and the cyclopropyl radical thus generated can be trapped by an adjacent homoallylic double bond leading to a bicyclo[3.1.0]hexane system (equation 35).[111,112]

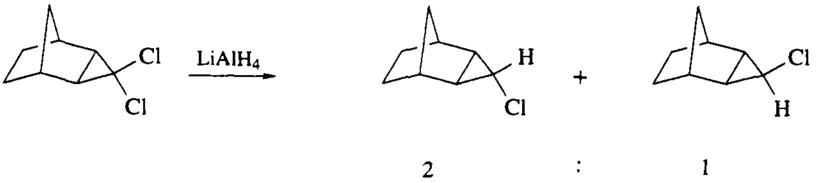

(32)

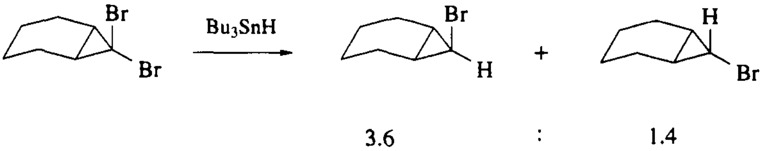

(33)

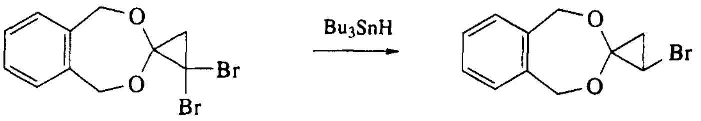

(34)

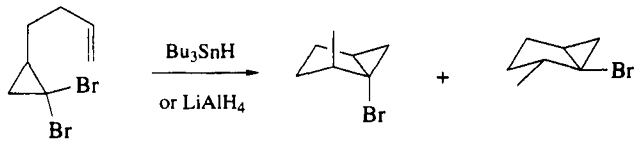

(35)

Halogen–lithium exchange (*cf.* Section 4.7.3.2) at low temperatures with an alkyllithium followed by quenching with methanol or water results in stereospecific reduction of dihalocyclopropyl compounds.[113] Stereospecific reduction has also been achieved by reaction with potassium diphenylphosphide (equation 36).[114]

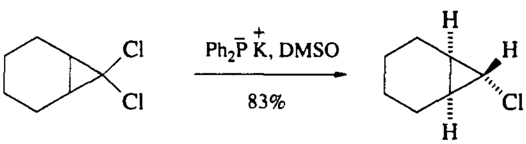

(36)

### 4.7.3.2 Lithium–Halogen Exchange and the Chemistry of 1-Lithio-1-halocyclopropanes

Dihalocyclopropanes undergo rapid metal–halogen exchange with alkyllithiums at low temperature.[19,115] The exchange is most convenient with dibromocyclopropanes and the resulting lithium carbenoids[116,117] are versatile intermediates which can be trapped by electrophiles (equation 37). Alkyl halides,[118–120] aldehydes,[121,122] ketones,[121,122] disulfides,[123] iminium salts,[124] trimethylsilyl chloride,[125,126] trimethylstannyl chloride,[127] carbon dioxide[115,128] and sulfur dioxide[129] react smoothly giving the corresponding 1-bromocyclopropyl derivatives (Scheme 4). In many cases the products themselves serve as valuable intermediates in synthesis by virtue of their ability to undergo a variety of substitution reactions.[19,130] For example, methanol reacts with 1-bromo-1-methylthiocyclopropane (**8**) to give (**9**) and subsequently (**10**) with methanethiol (equation 38).[131] Other nucleophiles react in an analogous manner (equation 39) to provide useful synthetic intermediates. The lithio compound resulting from (**8**) on reaction with an aldehyde gives a carbinol which is a cyclobutanone synthon.[123] 1-Bromo-1-trimethylsilylcyclopropanes have been used in the synthesis of alkylidenecyclopropanes by Peterson alkenation (equation 40).[126,132] A stereoselective cyclopropanol synthesis is based on the sequential reaction of lithiobromocyclopropane with catechol borane followed by alkaline hydrogen peroxide oxidation (equation 41).[133] With cyclopentenone, 1,2-addition occurs predominantly (equation 42) and the product is a precursor for fulvene derivatives.[134]

It was noted earlier that the lithium carbenoids on reaction with alkyl halides afford 1-alkyl-1-halocyclopropanes. It is possible to effect *endo* selective monoalkylation, as illustrated with a benzobarrelene

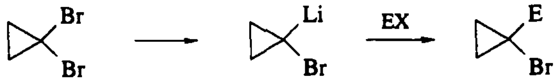

Br
Br
Li
Br
EX
E
Br

(37)

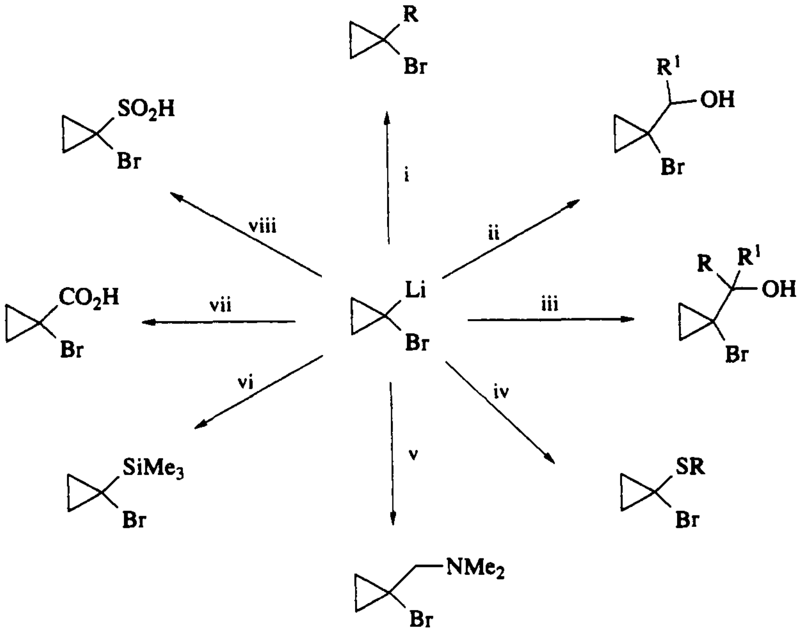

R
Br
SO₂H
Br
R¹
OH
Br
i
viii
ii
CO₂H
Br
vii
Li
Br
iii
R R¹
OH
Br
vi
iv
v
SiMe₃
Br
SR
Br
NMe₂
Br

i, RX; ii, $R^1CHO$; iii, $RR^1CO$; iv, RSSR; v, $H_2C{=}\overset{+}{N}Me_2\,X^-$, vi, $Me_3SiCl$; vii, $CO_2$; viii, $SO_2$

**Scheme 4**

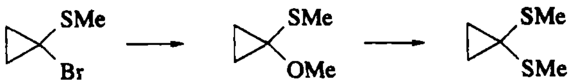

SMe
Br
SMe
OMe
SMe
SMe

(38)

(**8**) (**9**) (**10**)

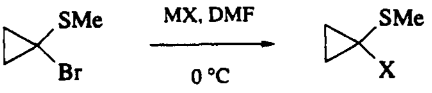

SMe
Br
MX, DMF
0 °C
SMe
X

(39)

$X = O_2CH, I, N_3, SH$

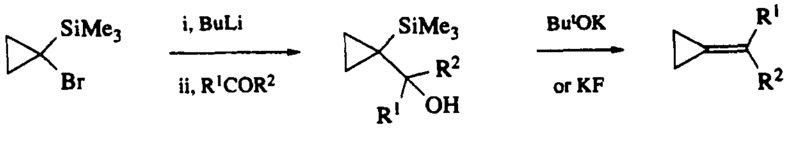

SiMe₃
Br
i, BuLi
ii, R¹COR²
SiMe₃
R²
R¹
OH
BuᵗOK
or KF
R¹
R²

(40)

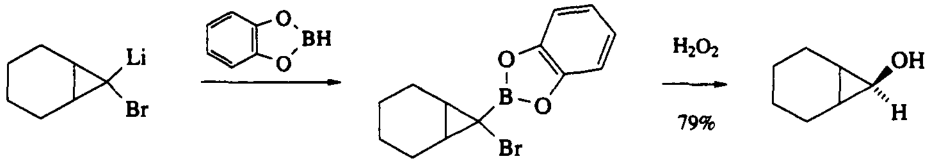

Li
Br
O
BH
O
O
B
O
Br
$H_2O_2$
79%
OH
H

(41)

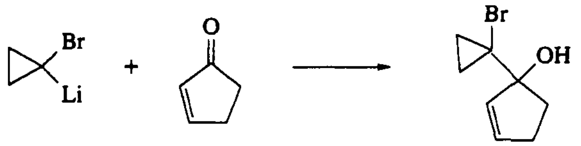

(42)

derivative in equation (43).[135] Stereoselective dialkylation is also possible.[136,137] Dialkylation with lithium dialkylcuprate, involving copper carbenoids, is a synthetically useful reaction (Scheme 5),[138,139] and has been employed in the synthesis of sesquicarene and (±)-sirenin.[118,136] An efficient conversion of dihalocyclopropanes to *gem* dialkyl compounds utilizes higher order organocuprates (equation 44).[140–142] This procedure has been used for the introduction of *gem* dimethyl groups in the phorbol skeleton.[142]

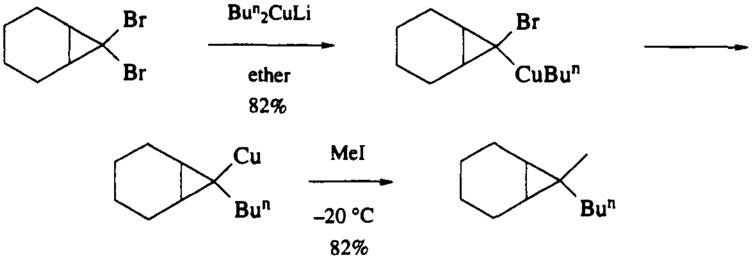

Br
Br
$Bu^n_2CuLi$
ether
82%
Br
$CuBu^n$
Cu
$Bu^n$
MeI
-20 °C
82%
$Bu^n$

**Scheme 5**

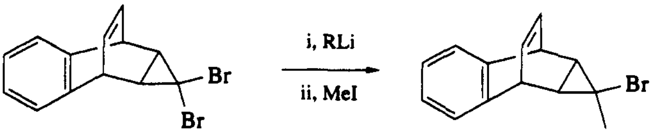

Br
Br
i, RLi
ii, MeI
Br

(43)

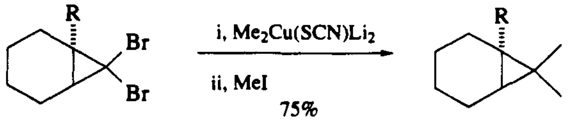

R
Br
Br
i, $Me_2Cu(SCN)Li_2$
ii, MeI
75%
R

(44)

Intramolecular alkylation of a lithiated species has been exploited in the synthesis of [1.1.0]- and [1.1.1]-propellanes (equation 45).[143–145] In what appears to be a related reaction, the bis(dibromocarbene) adduct (**11**) on treatment with methyllithium undergoes a ring closure by 1,6-elimination, presumably *via* a four-center transition state, to give (**12**; equation 46), which was subsequently converted to a bis(homobenzene).[146]

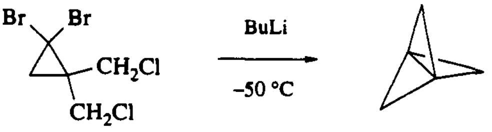

Br
Br
$CH_2Cl$
$CH_2Cl$
BuLi
-50 °C

(45)

### 4.7.3.3 Doering–Moore–Skattebøl Allene Synthesis

Dehalogenation of dihalocyclopropanes with sodium or magnesium gives allenes (equation 47).[147] Since the original observation, a number of reagents have been introduced for the allene synthesis *via* de-

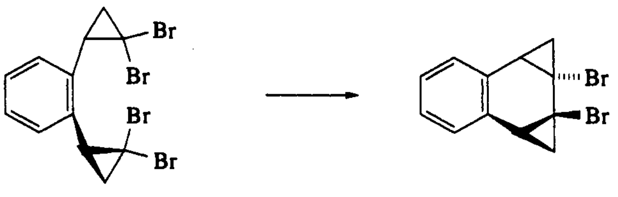

**(11)** **(12)**

(46)

halogenation of dihalocyclopropanes, but the greatest improvement has resulted from the use of alkyllithiums.[148,149] In general, methyllithium is the reagent of choice and the reaction is usually carried out in ether at low temperature. Dibromocyclopropanes are preferred over the dichloro analogs. The reaction can be viewed as a multistep process initiated by metal–halogen exchange to produce an α-haloalkyllithium intermediate. The latter then eliminates lithium halide to generate a carbene which rearranges to allene by cyclopropane ring scission (Scheme 6). The overall process represents the most versatile and practical synthesis of acyclic mono-, di-, and tri-substituted allenes, cyclic allenes, allenes containing functional groups, and acyclic and cyclic cumulenes. An important feature of the reaction is the absence of alkynic side products, which beset other procedures for the synthesis of terminal allenes.

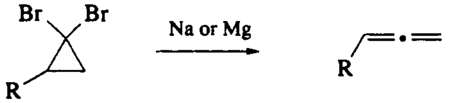

(47)

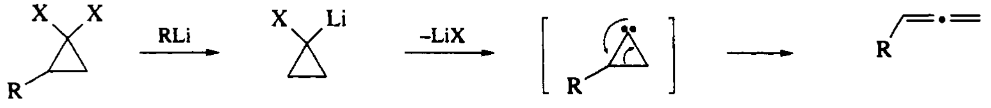

**Scheme 6**

Since the synthesis of allenes from dihalocyclopropanes has been reviewed,[150–152] only representative examples highlighting the process, along with the more recent results, are presented in this section. The formation of diallenes (equation 48) illustrates the usefulness of this process.[153,154] Two other interesting examples are given in equations (49) and (50).[155–157]

Cyclic allenes have been obtained in high yields, as illustrated by the synthesis of 1,2-cyclononadiene from the dibromocarbene adduct of the readily available cyclooctene (equation 51).[158] The smallest stable cyclic allene known to date is (**14**): it was prepared from the dibromocyclopropane (**13**) in high yield.[159] A small amount of the tricyclic compound (**15**) was also obtained (equation 52). The cyclic allene (**14**) did not undergo dimerization even on prolonged standing at ambient temperatures. In contrast, the unsubstituted analog was detected only at –60 °C by $^1$H NMR. It should also be noted that cyclohexa-1,2-diene was generated by the reaction of methyllithium on dibromobicyclo[3.1.0]hexane and trapped as the Diels–Alder adduct.[160]

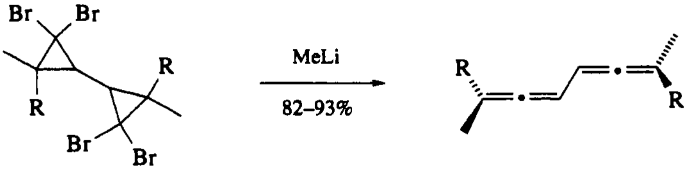

(48)

R = Me, Et, Ph, Bu$^t$

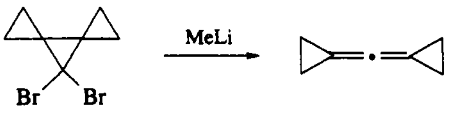

(49)

The conversion of dihalocyclopropane to allene can be extended to the synthesis of cumulenes by repeating the sequence, as illustrated by the synthesis of 1,2,3-cyclononatriene (Scheme 7).[161]

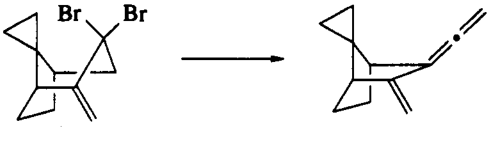

(50)

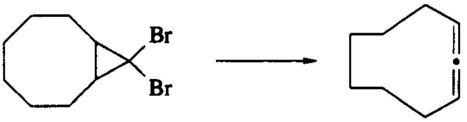

(51)

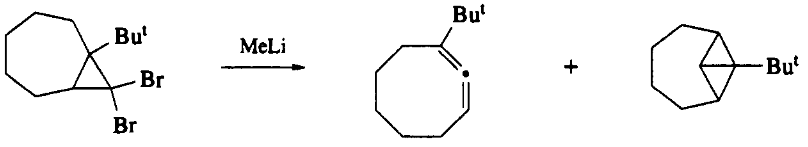

(52)

**(13)** **(14)** **(15)**

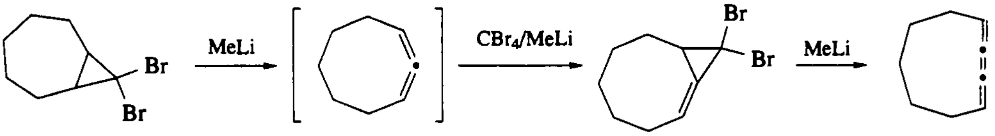

Scheme 7

The rigidity of the allene and its facile formation were imaginatively exploited in a synthesis of the vitamin E side chain alcohol, in which an overall transfer of 1,4 to 1,5 'acyclic stereoselection process' was achieved (Scheme 8).[162]

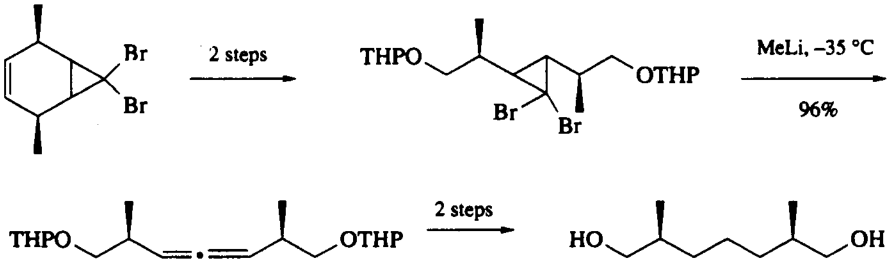

Scheme 8

Interestingly, the alkene to allene conversion can be carried out directly without isolation of the intermediate dihalocyclopropane. This process involves the treatment of the alkene with 1 equiv. of carbon tetrabromide and 2 equiv. of methyllithium in ether at –65 °C.[163] Ultrasonic irradiation facilitates the formation of cyclopropylidenes, and therefore the allenes, from dihalocyclopropanes under the influence of Li, Na or Mg.[164] The reactions are usually complete in 5–15 min. A report[165] on the use of *n*-butyllithium complexed with the chiral tertiary amine (–)-sparteine, leading to optically active allenes, seems to be of questionable value.

It should be pointed out that while the dihalocyclopropane–allene conversion discussed here represents the best general synthesis of allenes, occasional problems due to the formation of side products have been reported. An example is the formation of the bicyclobutane (**16**) along with the expected allene (equation 53).[166] The method is especially unsuitable for the synthesis of tetrasubstituted allenes. Sterically demanding substituents on the dihalocyclopropanes are believed to be responsible for the change of course of the reaction.

Endocyclic allenes which contain other double bonds lead to rearranged products. An example is the reaction of dibromobicyclononatriene (**17**) with methyllithium to form initially a carbenoid (**18**) which

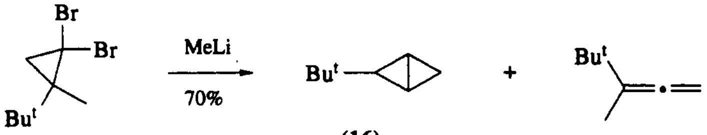

(16)

(53)

rearranges to the nine-membered allenic triene (**19**). The latter rearranges to the bicyclic compound (**20**) and finally a [1,5] sigmatropic rearrangement of (**20**) yields indene (Scheme 9).[167]

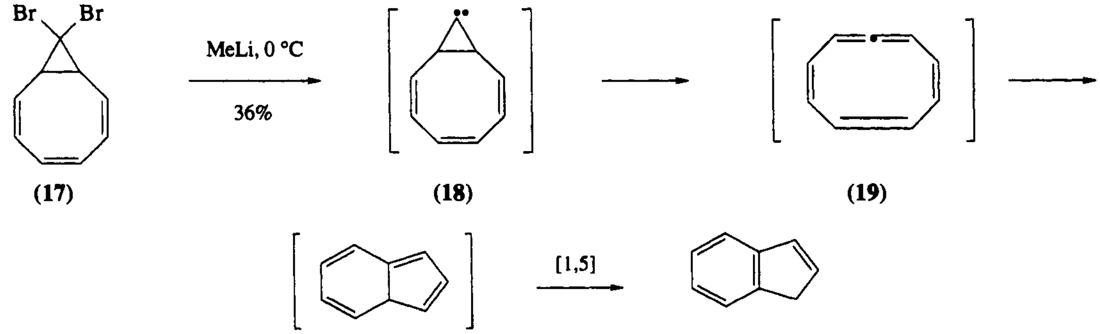

(17) (18) (19) (20)

**Scheme 9**

### 4.7.3.4 Skattebøl Rearrangement

Vinyldihalocyclopropanes on treatment with methyllithium give rise to cyclopentadienes, formally resulting from a vinylcyclopropylidene–cyclopentylidene rearrangement followed by a rapid 1,2-hydrogen shift (Scheme 10). This unique carbene–carbene rearrangement is known as the Skattebøl rearrangement.[168] It occurs in competition with the cyclopropylidene–allene rearrangement. The Skattebøl rearrangement has been investigated thoroughly[169–172] and the earlier results as well as the mechanistic interpretations have been the subject of critical discussions.[173,174] It is now recognized that carbenoid species rather than free carbenes are intermediates in the rearrangement.[117,175] The conversion of the dibromobicyclo[4.1.0]heptene (**21**) to the norbornene derivative (**22**) is a good illustration of the Skattebøl rearrangement (equation 54).[169] Mechanistically the reaction is formulated as proceeding *via* the ionic rearrangement of the carbenoid (**23**) to the ion pair (**24**), and the conversion of the latter by sequential reaction with methyllithium and methyl bromide (Scheme 11).[175] The stereospecificity in the product formation is consistent with this interpretation and argues strongly against the involvement of free carbene. Two other representative examples of the Skattebøl rearrangement are given in equations (55)[176] and (56).[177]

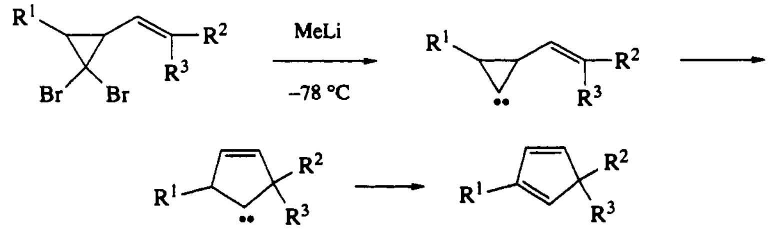

**Scheme 10**

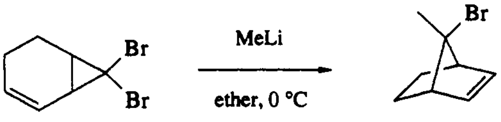

(21) (22)

(54)

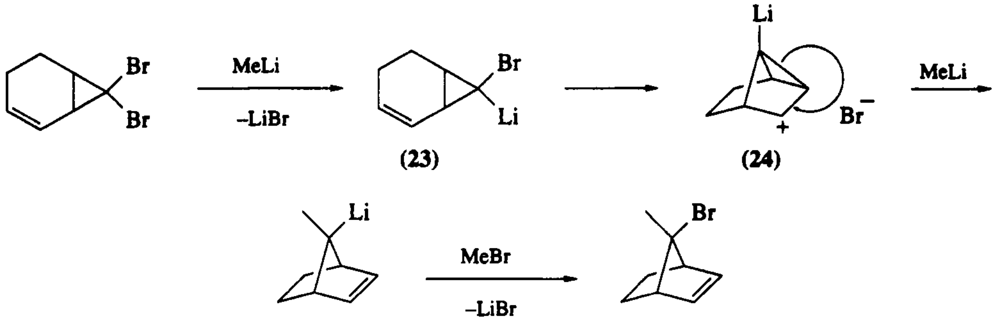
Br
Br
MeLi
-LiBr
Br
Li
Li
+
Br⁻
MeLi
Li
MeBr
-LiBr
Br

(23) (24)

Scheme 11

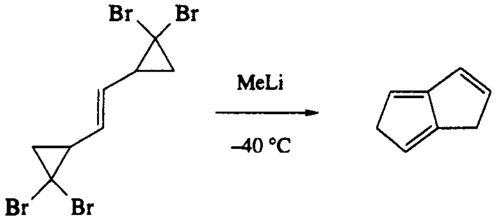
Br
Br
Br
Br
MeLi
-40 °C

(55)

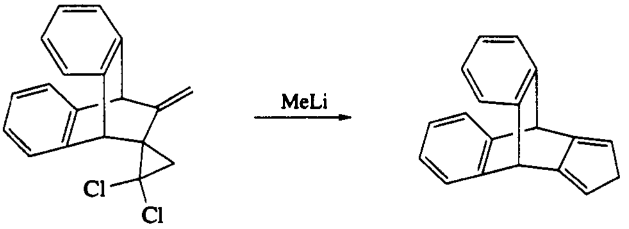

(56)

### 4.7.3.5 Other Carbenoid Reactions

When the carbene or carbenoid resulting from a dihalocyclopropane is unable to rearrange to the allene due to steric or other factors, insertion or addition reactions characteristic of carbenes take place. Thus dibromonorcarane on reaction with methyllithium gives a bicyclobutane derivative by insertion of the carbene into a β-C—H bond (equation 57).[178] Allene formation is sterically unfavorable in this case. Similarly, dibromotetramethylcyclopropane gives 1,2,2-trimethylbicyclo[1.1.0]butane instead of tetramethylallene (equation 58).[179–181] An example involving a tricyclic dibromocyclopropane is given in equation (59).[182]

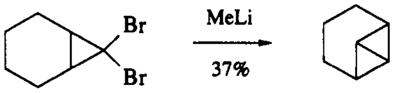
Br
Br
MeLi
37%

(57)

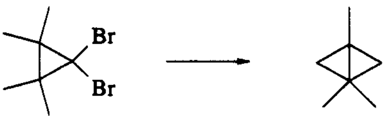

(58)

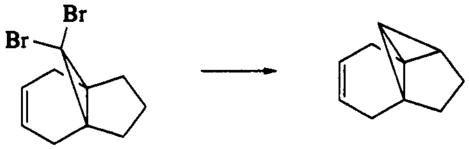

(59)

In general, tetrasubstituted dibromocyclopropanes lead to bicyclobutanes predominantly, whereas mixtures of bicyclobutanes and allenes result from trisubstituted dihalocyclopropanes and those bearing bulky substituents (see also Section 4.7.3.3).

In addition to insertion into β-C—H bonds, cyclopropylidenes can undergo other reactions such as alkylation (*cf.* Section 4.7.3.2), dimerization, insertion into C—H bonds of the ether solvent (equation 60)[183] or reaction with alkenes to afford spirocyclopropanes (equation 61).[184] Addition of stoichiometric amounts of $Bu^tOK$ has been shown to promote the reactions of lithium carbenoids, even at −85 °C, with THF to give the insertion product (equation 62).[185] Addition to alkenes is also promoted under these conditions. Intramolecular addition of the carbenoid to double bonds has been exploited in the synthesis of spirotricyclic compounds (equation 63).[186]

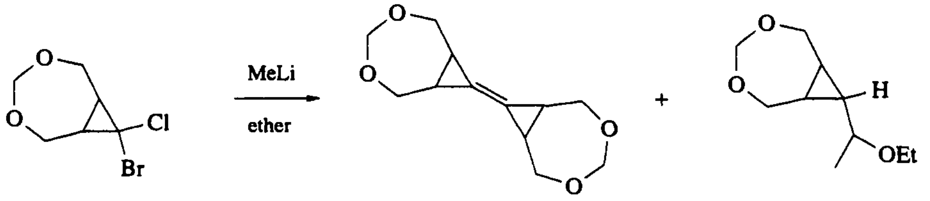

(60)

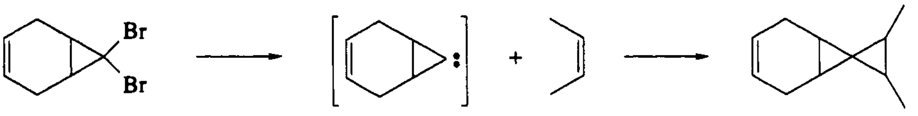

(61)

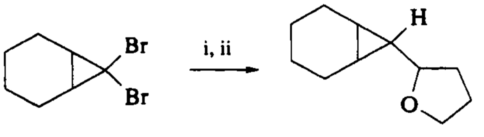

(62)

i, BuLi, THF, −85 °C; ii, $Bu^tOK$

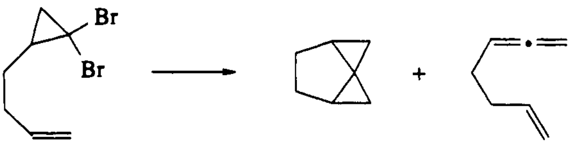

(63)

Insertions into O—H bonds, N—H bonds and C—H bonds adjacent to oxygen and nitrogen have found use in the synthesis of a number of heterocycles (see Section 4.7.3.9).[187–189] The reaction of alcohol (**25**) with methyllithium in ether, leading to the ketone (**26**), has been interpreted[190] as involving the insertion of an intermediate carbenoid into a β-C—H bond followed by ring opening (equation 64).

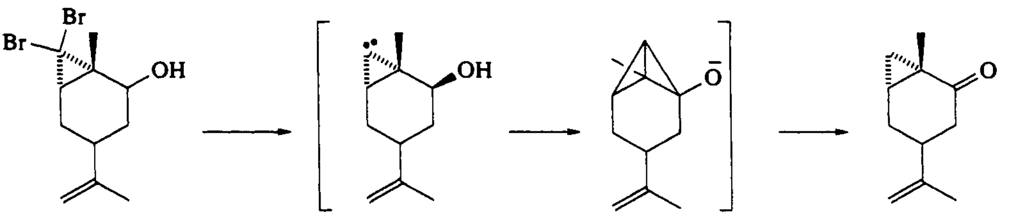

(**25**) (**26**) (64)

#### 4.7.3.6 Elimination and Elimination–Addition

Elimination of hydrogen halide from dihalocyclopropanes occurs under the influence of strong bases, leading to halocyclopropenes. Simple halocyclopropenes are unstable but can be trapped by nucleophiles (Scheme 12).[191,192] In situations where hydrogen migration is possible, isomerization of the chlorocyclopropene to alkylidenecyclopropane takes place readily. Thus (**27**; equation 65) is an excellent precursor for vinylmethylenecyclopropane.[193–195] The latter is a valuable synthon for methylenecyclopentene. The double-bond migration attending dehydrohalogenation by Bu$^t$OK has been utilized in the synthesis of benzocyclopropene,[196] a remarkably stable compound, and its analogs (equation 66). The dehydrohalogenation of (**28**) gives a mixture of (**29**) and (**30**) in a ratio of 3:2, presumably *via* a carbene intermediate (equation 67).[197] A related reaction occurs with (**31**), as shown in equation (68) (*cf.* Section 4.7.3.9).[198]

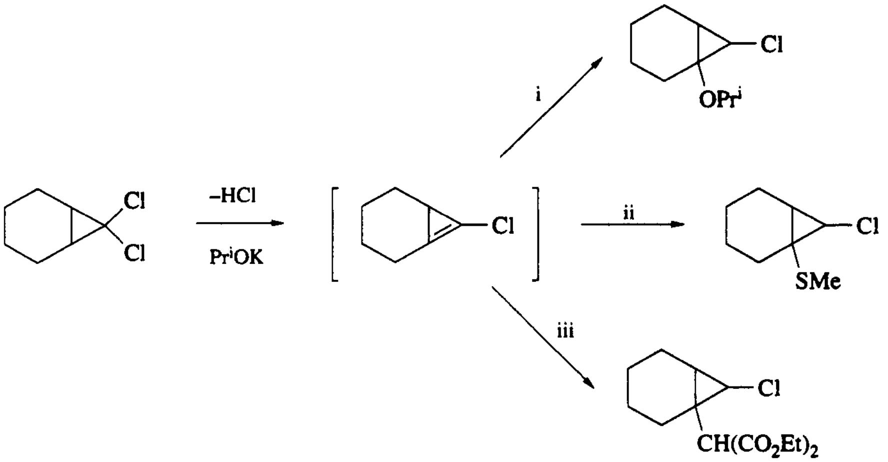

i, Pr$^i$OH; ii, MeSH; iii, $^-$CH(CO$_2$Et)$_2$

**Scheme 12**

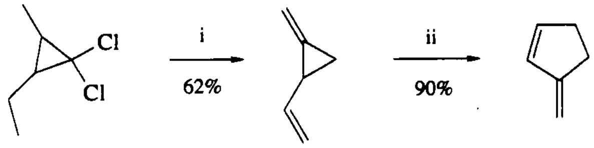

(65)

(**27**)

i, Bu$^t$OK, DMSO; ii, 80 °C, 13 h

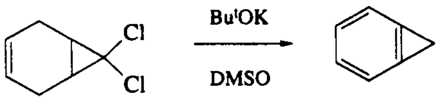

(66)

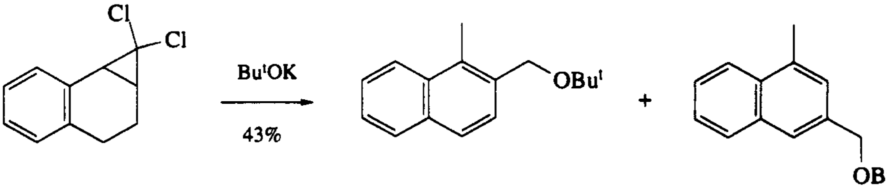

(67)

(**28**) (**29**) (**30**)

In cases such as the one shown in equation (69), what appears to be displacement is more likely a multistep elimination–addition process.[37] Carbonyl or sulfonyl groups in the 2-position greatly facilitate each of these two steps. Thus (**32**) on treatment with alkoxide or thiolate gave the cyclopropane acetal or thioacetal, respectively (equation 70).[199] In related work, tetrachlorocyclopropene, which has interesting synthetic potential, is formed from pentachlorocyclopropane by treatment with potassium hydroxide (equation 71).[200] Certain 1,1,2-trihalocyclopropanes on reaction with methyllithium in ether at low temperature afford the corresponding halocyclopropenes by 1,2-dehalogenation (equation 72).[201] Similarly,

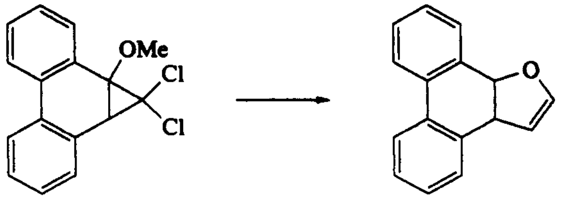

(31)

(68)

2-bromo-2-trimethylsilyldibromocyclopropane on reaction with tetra-*n*-butylammonium fluoride undergoes elimination to give 1,2-dibromocyclopropene (equation 73).[202]

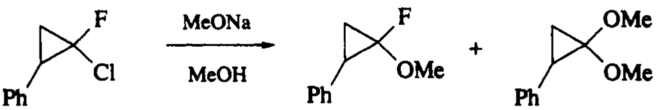

(69)

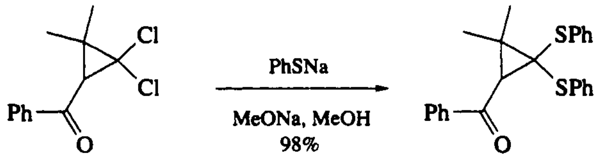

(32)

(70)

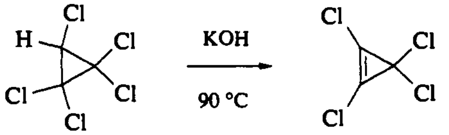

(71)

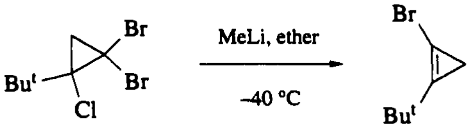

(72)

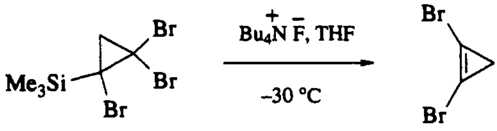

(73)

### 4.7.3.7 Electrocyclic Ring Opening

Shortly after the advent of the Doering reaction, it was recognized that dihalocyclopropanes derived from certain cyclic alkenes can undergo facile thermal rearrangement to ring-opened products.[6,9,10] The first example of this rearrangement was the rapid conversion of the dichlorocarbene adduct of indene to 2-chloronaphthalene, observed by Parham (equation 74).[6,203] A number of dihalocyclopropanes, however, are thermally stable and the facility of the rearrangement depends on factors such as ring size, stereochemical disposition and the nature of the halogens. In addition to the thermal rearrangement, the cyclopropyl–allyl conversion can be facilitated by electrophiles such as silver ion, protic and Lewis acids, and by nucleophiles. On the basis of theoretical considerations, the rearrangement has been characterized as a concerted process proceeding *via* stereospecific disrotatory opening.[204–209] The ring opening is concomitant with the departure of the leaving group, leading to a transition state where the positive charge is delocalized (equation 75). Important sterochemical consequences of the concerted nature of the rearrangement include the formation of the *cis* and *trans* allyl cations from the *endo* and *exo* derivatives (**33**; equation 76) and (**34**; equation 77), respectively. The electrocyclic ring opening of dihalocyclopropanes has been exploited in the synthesis of one-carbon ring-expanded carbocycles and heterocycles and chain-extended compounds.

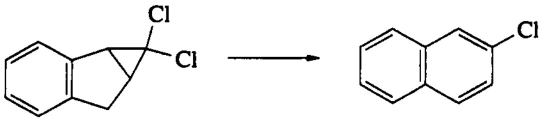

(74)

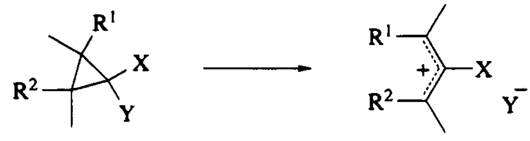

(75)

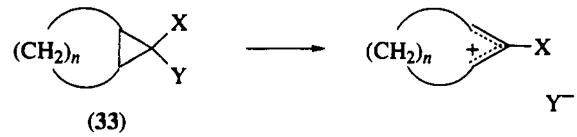

(33)

(76)

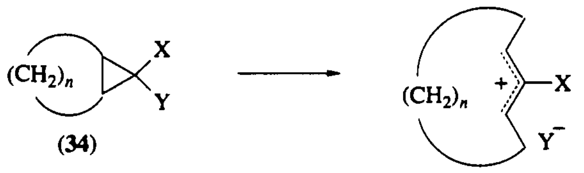

(34)

(77)

### 4.7.3.7.1 Ring expansion/chain extension

It has been already noted (Section 4.7.3.7) that the facility of the dihalocyclopropane–allyl cation rearrangement depends on a number of factors, including the stability of the allyl cation, which in turn is influenced by electronic factors. The addition of dichlorocarbene to cyclopentadiene to afford chlorobenzene *via* the unstable adduct (**35**) and the relatively stable cation (**36**) is illustrative (equation 78).[210] In the absence of external nucleophiles, the departing halide ion is usually captured by the allyl cation to form a haloene. Alternatively, the cation loses a proton to form a halodiene. Even the substitution product itself is thermally unstable and can lose hydrogen halide at higher temperatures to give the halodiene. For instance, when *endo*-6-chloro-*exo*-6-fluorobicyclo[3.1.0]hexane is heated in quinoline at 110 °C 3-chloro-2-fluorocyclohexene is obtained which at higher temperatures loses HCl to give 2-fluoro-1,3-cyclohexadiene (equation 79).[211] This example also illustrates the effect of stereochemistry and the nature of the halogens on the rearrangement. Not surprisingly, the cyclopropyl–allyl rearrangement of dihalocyclopropanes has found a number of synthetic applications. Selected examples are given in equations (80) to (92). The adducts resulting from the addition of a dihalocarbene to the internal double bond of bicyclic systems lead to rearrangement products *via* bridgehead alkenes. This process has been exploited in the synthesis of [6]- and even [5]-metacyclophanes (equation 80).[212,213] The dibromocarbene adduct (**37**) on heating in acetonitrile gives (**38**), which has found use in the synthesis of 3-phenyl-5-bromooctavalene (equation 81).[214] The diadduct (**39**) on thermal rearrangement affords a mixture of dichloroazulenes (equation 82).[215] Such rearrangements have been employed in a number of similar systems.[216]

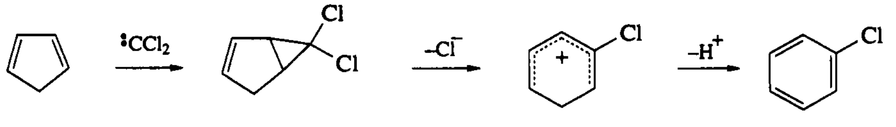

(35) (36)

(78)

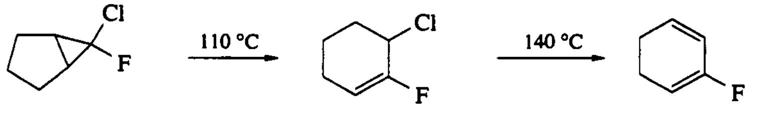

(79)

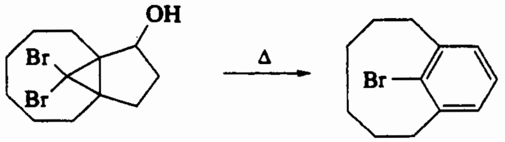

(80)

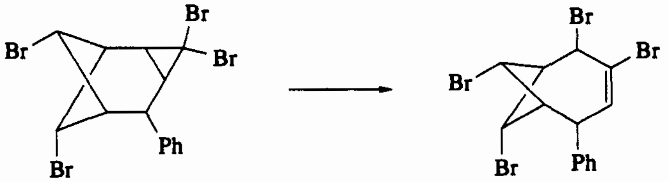

(37) (38)

(81)

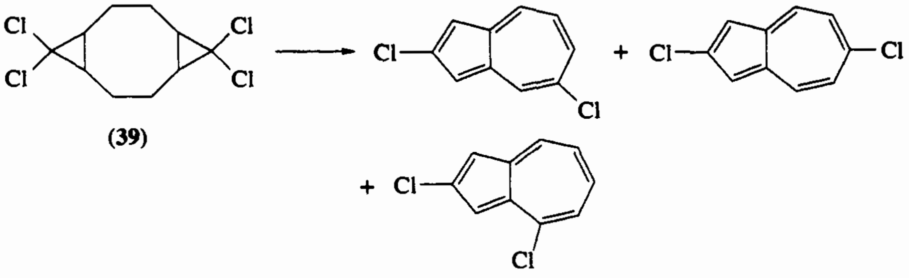

(39)

(82)

Acid-catalyzed hydrolysis followed by ring opening of the dichlorocyclopropane adduct (**7**) proceeded smoothly on treatment with aqueous acetic acid buffered with sodium acetate to afford the chlorocycloheptenone (**40**), an intermediate in the stereoselective synthesis of Prelog–Djerassi lactonic acid (equation 83).[80] Similar ring expansion has been used in the synthesis of muscone and tropolones such as thujaplicins.[81–83] A recent synthesis of α-tropolone[217,218] involves the ring expansion attended by the loss of hydrogen halide when a dihalocarbene adduct, such as (**41**), is subjected to Albright–Swern oxidation conditions (equation 84). The method is also quite suitable for the synthesis of open chain α-chloroenones. An efficient and somewhat related cyclopentenone synthesis[219] involves the acid-catalyzed rearrangement of the dichlorocarbene adduct (**42**), as shown in equation (85).

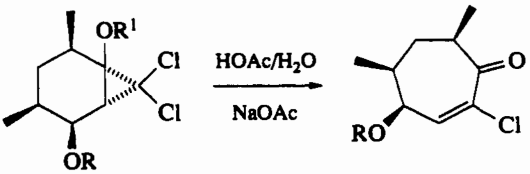

(7) (40)

(83)

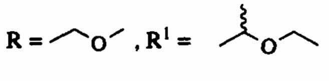

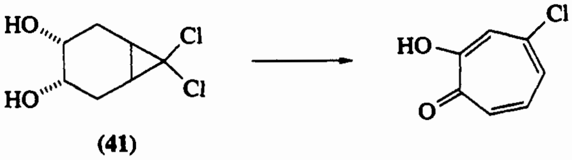

(41)

(84)

The silver ion assisted carbon–halogen bond cleavage and the unraveling of the cyclopropane ring by the cyclopropyl–allyl rearrangement was first noted in the formation of 2-bromocyclohexen-1-ol from dibromobicyclo[3.1.0]hexane under solvolytic conditions (equation 86).[220] The silver ion assisted solvolysis of the dihalocyclopropane adduct (**43**), derived from a Birch reduction product, smoothly rearranges to the tropone (equation 87).[221] A number of other synthetic applications[222–226] have been reported

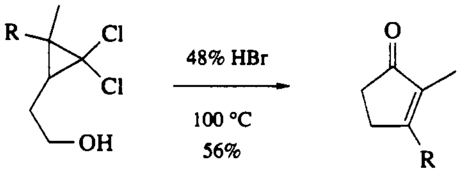
R
Cl
Cl
OH
48% HBr
100 °C
56%
O
R

**(42)**

(85)

recently. Analogous to the formation of a [5]metacyclophane,[213,223] the dibromocarbene adduct (**44**) undergoes silver ion assisted solvolysis to give (**45**) in high yield (equation 88).[224] Similarly, (**46**) has been reported[225] to give (**47**), albeit in low yield (equation 89). It should be noted that (**46**) is thermally stable.

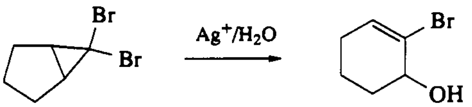
Br
Br
Ag⁺/H₂O
Br
OH

(86)

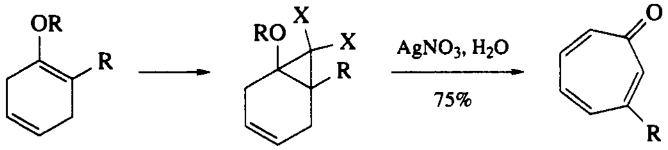
OR
R
RO
X
X
R
AgNO₃, H₂O
75%
O
R

**(43)**

(87)

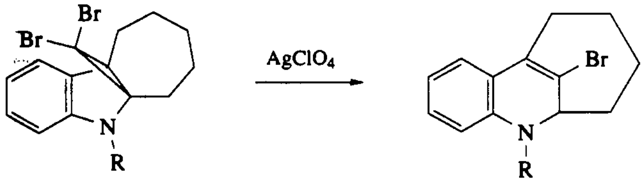
Br
Br
N
R
AgClO₄
Br
N
R

**(44)** R = t-BOC **(45)**

(88)

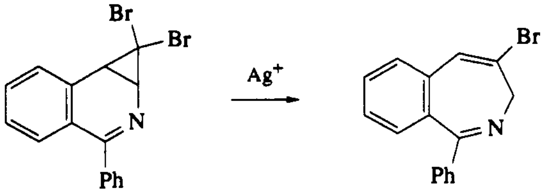
Br
Br
N
Ph
Ag⁺
Br
N
Ph

**(46)** **(47)**

(89)

In certain cases, the silver ion assisted solvolysis fails to initiate electrocyclic reaction to give ring-expanded compounds, leading instead to a cleavage product (equation 90).[227] The dichlorocarbene adduct (**48**) on $FeCl_3$-promoted cleavage in ether affords exclusively α-trichloromethylcyclohexanone, whereas in DMF a small amount of chlorocycloheptenone also was obtained (equation 91).[228]

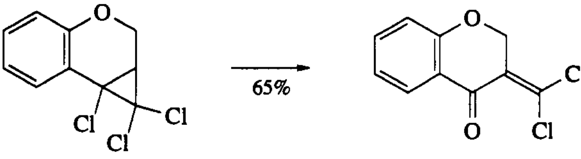
O
Cl
Cl
Cl
65%
O
Cl
O
Cl

(90)

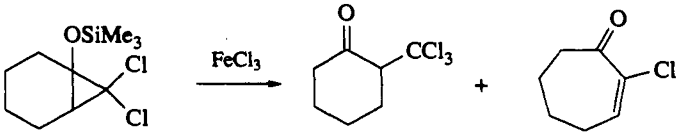
OSiMe3
Cl
Cl
FeCl3
O
CCl3
+
O
Cl

(48)

(91)

Not much is known about the opening of dihalocyclopropanes by Lewis acids beyond reports on the reaction of dibromo- and dichloro-cyclopropanes with aromatic hydrocarbons under the influence of $AlCl_3$ or $FeCl_3$ leading to indenes.[229–231]

The cyclopropyl–allyl rearrangement has been shown to proceed with nucleophilic assistance,[87,232,233] and the intermediate allyl cation can be trapped by nucleophiles leading to synthetically useful derivatives. An example is the formation of an unsaturated acetal and the propiolic acid ortho ester (equations 92 and 93).[232]

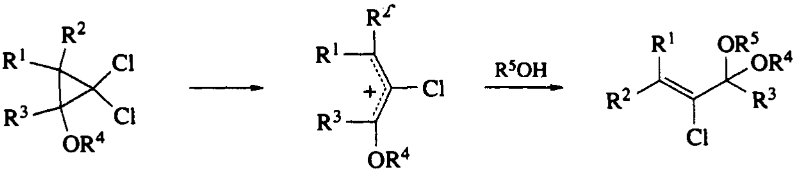
R2
R1
Cl
R3
Cl
OR4
R2
R1
+
Cl
R3
OR4
R5OH
R1
OR5
OR4
R2
R3
Cl

(92)

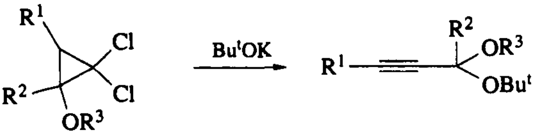
R1
Cl
R2
Cl
OR3
BuᵗOK
R2
OR3
R1
OBuᵗ

(93)

A stereospecific synthesis of conjugated dienes involving the ring opening of difluorocyclopropanes has been reported.[234] In an extension of this work, 1-acetoxy-3-alkyldifluorocyclopropanes undergo ring opening with LAH to give β-fluoroallylic alcohols with high stereospecificity and in good yields (equation 94).[235] Similarly, chlorofluorocyclopropyl ethers undergo rearrangement to give α-fluoroacrolein[236] *via* its acetal and chlorofluoro-2-(trimethylsilyl)methylcyclopropane gives 2-fluoro-1,3-butadiene in high yield.[237]

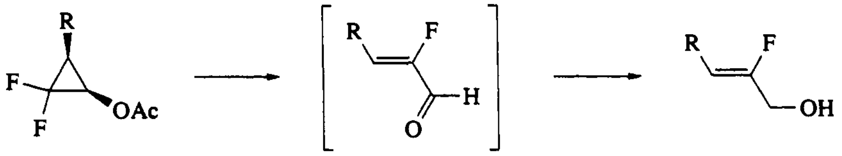
R
F
F
OAc
R
F
H
O
R
F
OH

(94)

The c-ring expansion of aporphines *via* the dichlorocyclopropane ring opening[238] induced by LAH has been utilized in a synthesis of homoaporphine alkaloids (equation 95). Reductive cleavage of 2-silyloxy-dibromocyclopropanes gives α,β-unsaturated ketones directly (equation 96).[239]

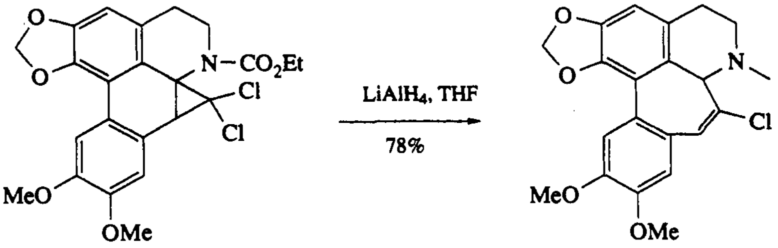
O
O
N–CO2Et
Cl
Cl
MeO
OMe
LiAlH4, THF
78%
O
O
N
Cl
MeO
OMe

(95)

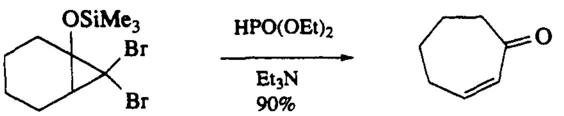
OSiMe3
Br
Br
HPO(OEt)2
Et3N
90%
O

(96)

### 4.7.3.8 Solvolysis without Ring Opening

It is clear from the discussion in the previous section that generally dihalocyclopropanes undergo solvolysis with concomitant electrocyclic ring opening. However, dihalocyclopropanes with a barrier to ring opening have been shown to undergo silver ion assisted solvolysis to give both substituted cyclopropanes and ring-opened products (equation 97).[211,212,240] The [4.4.1]propellane undergoes solvolysis without ring opening (equation 98). Similar results were obtained with [3.3.1]propellanes.[241] Dihalocyclopropanes that carry a β-TMS group undergo a unique solvolytic displacement of the halogens without rupture of the cyclopropane ring when treated with silver trifluoroacetate and alcohol (equation 99).[242] Finally, it has been shown that halogens can be displaced by nucleophiles under photolytic conditions.[243] A mixture of mono- and di-substitution products are obtained (equation 100).

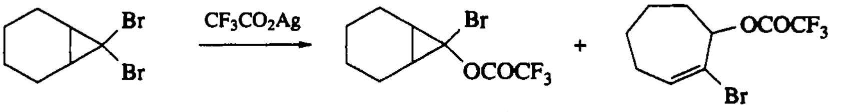

(97)

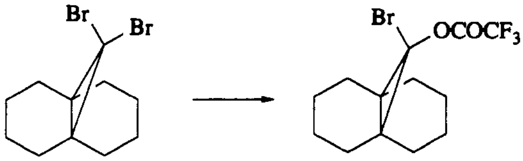

(98)

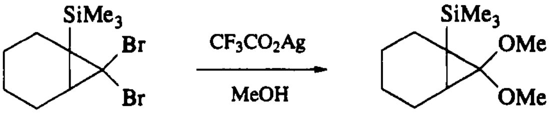

(99)

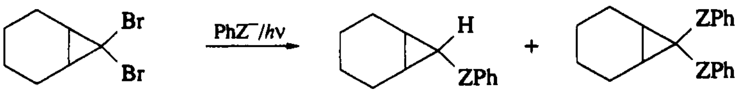

(100)

Z = S or Se

### 4.7.3.9 Formation of Heterocycles

Although the use of dihalocyclopropanes in the synthesis of heterocycles has not been investigated in great detail, there are a number of examples which illustrate the usefulness in heterocyclic synthesis. The earliest example is the conversion of pyrrole to 3-chloropyridine with chloroform and strong base (*cf.* Section 4.7.2.2.2), a reaction now recognized as involving the formation and electrocyclic rearrangement of a dihalocyclopropane (equation 101).[75,76,244,245] The yield of 3-chloropyridine is influenced by the source of dichlorocarbene and the formation of significant amounts of side products limits the usefulness of the reaction. The formation of 3-chloroquinolines from indoles by the reaction of chloroform and sodium ethoxide can be considered to proceed in an analogous manner.[75,77,246-248] This reaction is also complicated by side products resulting from the Reimer–Tiemann reaction (equation 102).[246] Pyrrole reacts with dichlorocarbene in the gas phase to give a mixture of 2-chloro- and 3-chloro-pyridines.[249] Imidazole under similar conditions affords a mixture of chloropyrazine and 5-chloropyrimidine (equation 103).[250]

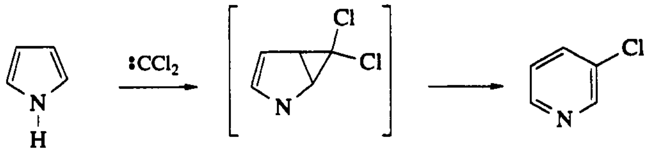

(101)

In what can be viewed as a heterocyclic version of the Skattebøl rearrangement (*cf.* Section 4.7.3.4), the dibromocarbene adduct (**49**) on treatment with methyllithium affords the pyrrole (**50**), albeit in low yield (equation 104).[251] The propensity of the carbenoid species resulting from dihalocyclopropanes to insert into C—H bonds adjacent to oxygen and nitrogen was mentioned previously (Section 4.7.3.5).

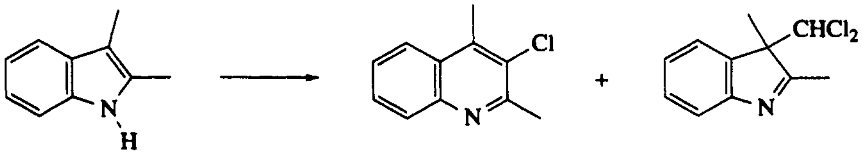

(102)

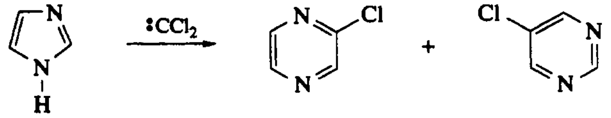

(103)

This process has found occasional use in the synthesis of heterocycles. The major product resulting from the reaction of MeLi on the dibromocarbene adduct (**51**) is the tetrahydrofuran (**52**), as shown in equation (105).[189] In a novel approach to the synthesis of spiroacetal pheromones, carbene insertion into an acetal C—H bond was studied (equation 106).[252] Unfortunately, the reaction proceeds in low yield and the approach is further hampered by the lack of stereocontrol in the ring opening of the cyclopropane. Carbene insertions into N—H and C—H bonds adjacent to nitrogen have been shown to give azabicyclo systems, as shown in equations (107) and (108).[188]

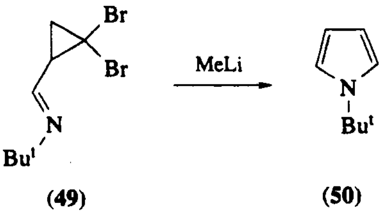

(104)

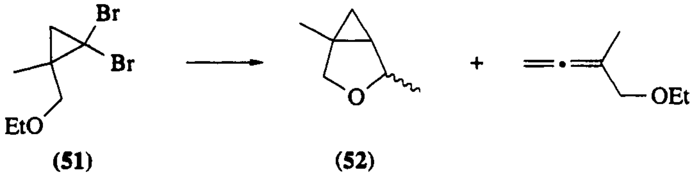

(105)

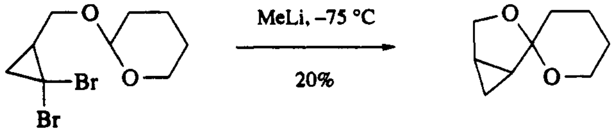

(106)

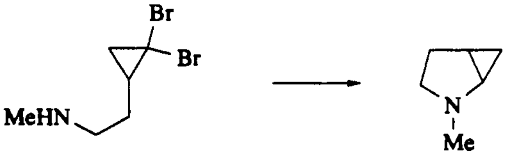

(107)

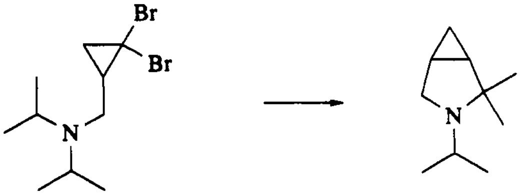

(108)

A crucial step in the synthesis of a methyleneaziridine involves the nucleophile-induced ring opening of a dibromocyclopropane (equation 109).[253] Nucleophile-assisted opening of a dichlorocyclopropyl ketone leads to 2,2-dimethoxy-2,3-dihydrofurans which are useful γ-keto aldehyde synthons (equation

110).[254] The reaction of acyloxydihalocyclopropanes with hydrazine has been reported to yield pyrazoles.[255]

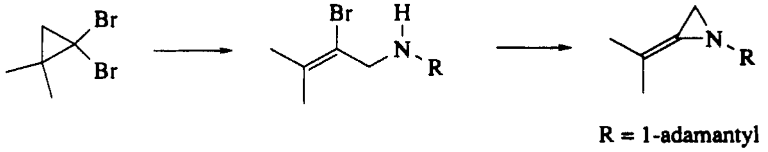

(109)

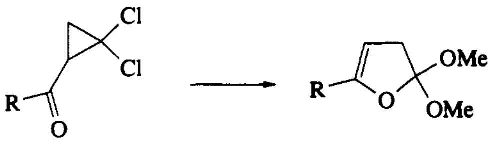

(110)

The allyl cation generated by the electrocyclic cleavage of dibromocyclopropanes (*cf.* Section 4.7.3.7.1) has been trapped by a carboxyl group in a highly efficient synthesis of furanones (equation 111) and pyranones.[256] Acid-catalyzed openings of dihalocyclopropanes also give similar results.[257]

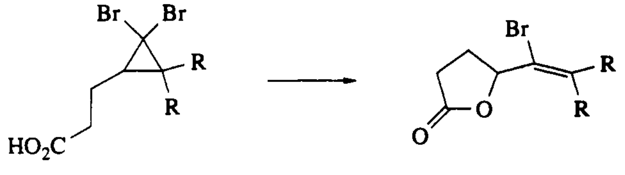

(111)

An elegant synthesis of the neurotoxic alkaloid anatoxin has exploited the electrocyclic opening of the dibromobicyclo[5.1.0]octane followed by transannular cyclization (Scheme 13).[258] Similarly, the thermal electrocyclic opening of the dichlorocyclopropane followed by intramolecular trapping of the developing allylic cation by a suitably positioned amine has been used in a homoaporphine synthesis.[238]

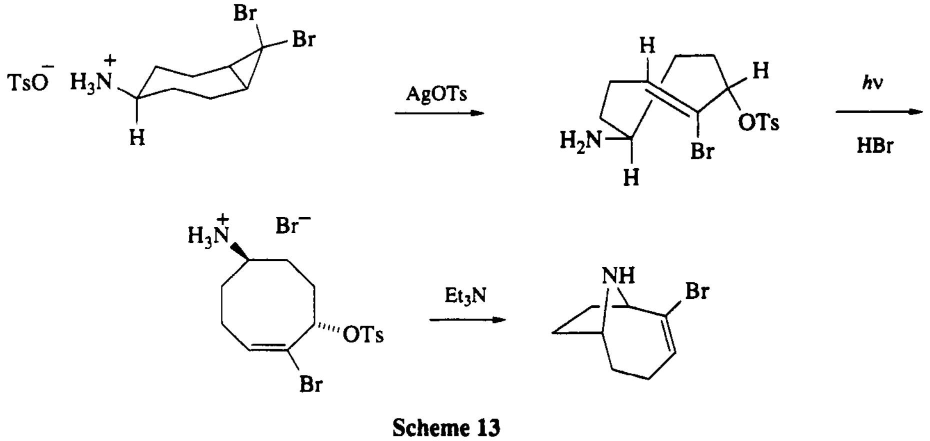

**Scheme 13**

### 4.7.3.10 Miscellaneous Reactions

Dihalocyclopropanes elicit a number of reactions which cannot be conveniently accommodated in the above categories and these are outlined in this section. Photolysis of the bis(dichlorocarbene) adduct (**53**) gave only the ring cleavage products (equation 112).[259] The vinyldichlorocyclopropane (**54**) has been shown to undergo thermal rearrangement to give the dichlorocyclopentene (**55**; equation 113).[260] Electrolysis of dihalocyclopropanes has been reported to give ring-opened products (equation 114).[261]

Dibromocyclopropanes with vicinal chloromethoxy or mesyloxymethyl substituents undergo [$Ni(CO)_4$]-induced ring opening–carbonylation in the presence of alcohol or amine, leading to $\gamma,\delta$-unsaturated carboxylic acid derivatives selectively *via* intermediate nickel enolates (equation 115).[262] Di-

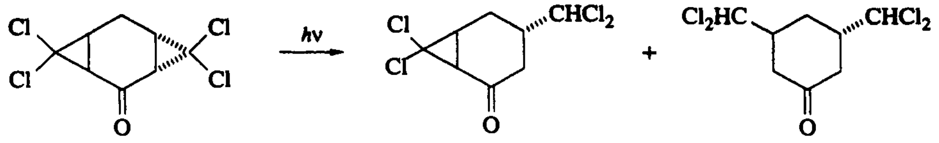
Cl
Cl
Cl
Cl
O
hν
Cl
Cl
CHCl₂
O
Cl₂HC
CHCl₂
O

**(53)**

(112)

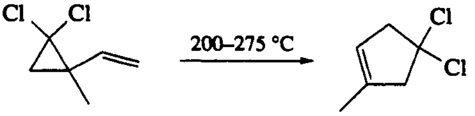
Cl
Cl
200–275 °C
Cl
Cl

**(54)** **(55)**

(113)

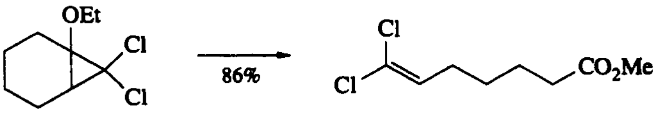
OEt
Cl
Cl
86%
Cl
Cl
CO₂Me

(114)

bromo-2-chlorocyclopropanes also undergo a similar ring-opening carbonylation with $[Ni(CO)_4]$ to give a mixture of β,γ-unsaturated esters, along with a small amount of the reduced cyclopropane derivative (equation 116).[263] The same authors have shown that $[Ni(CO)_4]$-induced reductive carbonylation of dibromocyclopropanes is a versatile method for the synthesis of cyclopropanecarboxylic acid derivatives (equation 117).[264]

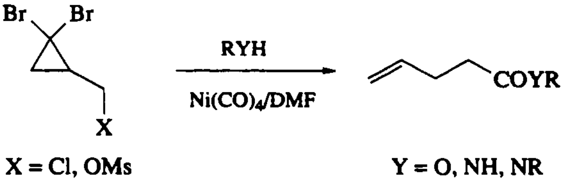
Br
Br
X
RYH
Ni(CO)₄/DMF
COYR
X = Cl, OMs
Y = O, NH, NR

(115)

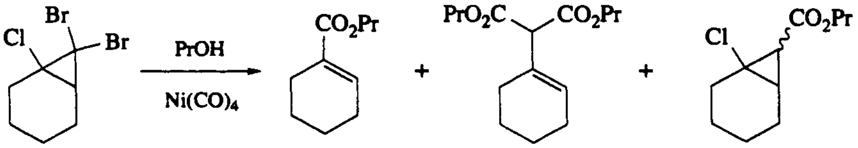
Br
Cl
Br
PrOH
Ni(CO)₄
CO₂Pr
PrO₂C
CO₂Pr
Cl
CO₂Pr

(116)

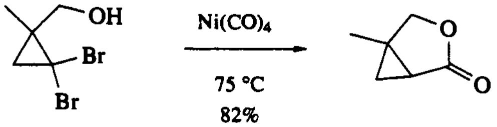
OH
Br
Br
Ni(CO)₄
75 °C
82%
O
O

(117)

In a somewhat intriguing sequence of reactions, the organometallic compound (**56**) on treatment with methyllithium afforded the rearranged product (**57**), as shown in equation (118).[265] While the mechanism of this transformation is not known, it has been speculated that the initially formed carbene rearranges to a spirocyclopropene intermediate *via* a novel ring contraction.

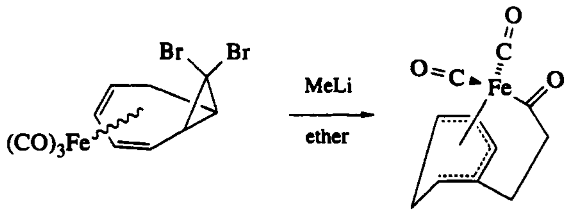
Br
Br
(CO)₃Fe
MeLi
ether
O
C
O=C
Fe
O

**(56)** **(57)**

(118)

## 4.7.4 CONCLUSION

It is abundantly clear from the preceding discussion that dihalocyclopropanes are versatile intermediates in organic synthesis. Although a wealth of chemistry has already been uncovered, prospects remain bright for interesting developments in the future. Areas such as the application of dihalocyclopropanes in heterocyclic synthesis *via* carbene insertion into C—H bonds adjacent to heteroatoms, reactions of dihalocyclopropanes with organometallics and the synthetic applications of metallated derivatives deserve further exploration. The chemistry of difluoro-, diiodo- and mixed dihalo-cyclopropanes can be expected to attract some attention. Finally, other heteroatom-substituted cyclopropanes derived from dihalocyclopropanes will also invoke further investigation.

## 4.7.5 REFERENCES

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# 4.8

# Addition of Ketocarbenes to Alkenes, Alkynes and Aromatic Systems

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## 4.8.1 INTRODUCTION

The reactions of keto-carbenes (**1**) or -carbenoids with C═C π-bonds[1–7] offer a direct entry to highly functionalized cyclopropanes (**2**),[8] which, due to their lability, are readily transformed to a range of products (Scheme 1). The cyclopropanation is often highly stereoselective and further reaction can lead to products of defined stereochemistry, controlled by the compact arrangement of functionality within the cyclopropane ring. Although free carbenes undergo additions to alkenes, these reactions are unselective and competing carbene rearrangements tend to occur. Consequently, metal-stabilized ketocarbenoids, generally formed by catalyzed decomposition of diazo compounds, are of much greater synthetic utility and will be the emphasis of this chapter.

Extensive synthetic developments have occurred recently in this field, primarily because of improvements in the catalysts used and the procedures for preparation of the carbenoid precursors. Consequently,

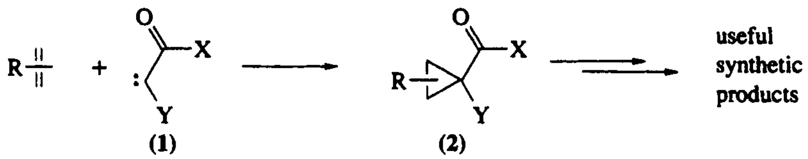

**Scheme 1**

previously inefficient yet intriguing carbenoid reactions can often now be carried out in synthetically viable yields.

In order to outline the scope of this chemistry, Sections 4.8.2 and 4.8.3 will discuss the catalysts and carbenoid precursors used. This will be followed by reactions of carbenoids with π-systems, organized according to the π-system involved, alkenes (Section 4.8.4), alkynes (Section 4.8.5), benzenes and electron-rich heterocycles (Section 4.8.6). Particular emphasis will be placed on the stereochemical outcome of these reactions with reference to applications in organic synthesis.

## 4.8.2 GENERATION OF KETOCARBENOIDS

Ketocarbenes (1) are usually generated from the corresponding diazo compounds (3).[5] Other sources which are occasionally used are α,α-dibromo compounds (4),[9] sulfur ylides (5)[10] and iodonium ylides (6; Scheme 2).[11] The thermal or photochemical decomposition of diazo compounds in the presence of π-systems is often complicated by indiscriminate side reactions, such as Wolff rearrangements,[12] C—H insertions and hydride migrations. To avoid such problems, the use of metal-catalyzed decomposition of diazo compounds is generally preferred.[1,2]

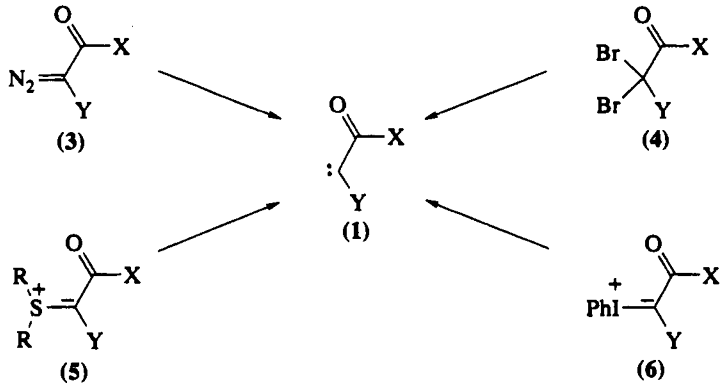

**Scheme 2**

Up until quite recently, the most commonly used catalysts for decomposition of diazo compounds were copper based. Heterogeneous catalysts such as copper bronze, copper powder, copper halide and copper sulfate have been largely superseded by soluble copper complexes.[1] The most extensively used are based on the 1,3-diketone (7), salicylaldehyde (8) and iminosalicylaldehyde (9) ligands, and a wide range of complexes have been employed,[13] including chiral systems. Other catalysts which are occasionally used are copper tetrafluoroborate, copper(I) and copper(II) triflate,[14] and (trialkyl phosphite)copper(I) iodide.[15] Even though copper sources ranging in oxidation state from zero to two have been used, it has often been found[14] that the active catalytic species is copper(I), which is generated under the reaction conditions.

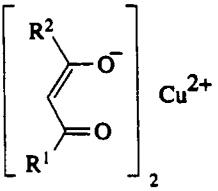

(7)

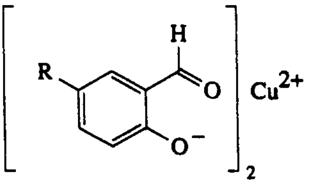

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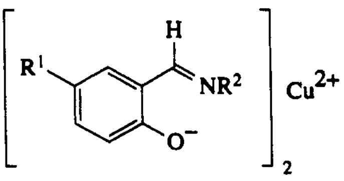

(9)

The development of the dimeric rhodium(II) carboxylates (**10**)[16] as extremely mild catalysts for decomposition of diazo compounds has greatly enhanced the whole field of carbenoid chemistry, and these have quickly become the preferred catalysts in most instances. Commercially available rhodium(II) acetate (**10a**) has been most extensively used, but rhodium(II) pivalate (**10b**) and rhodium(II) hexanoate (**10c**) often offer advantages due to their greater solubility. The ligands can also be varied to fine tune the catalyst. Complexes with electron-withdrawing ligands such as trifluoroacetate (**10d**) result in less back-bonding to the carbenoid, producing a more reactive electrophilic carbenoid.[16d] Alternatively, the use of rhodium(II) acetamide, $Rh_2(NHCOMe)_4$, generates a carbenoid with greater back-bonding to the metal than in the case of rhodium(II) acetate, resulting in a system with greater selectivity.[17] Sterically hindered ligands do not have a great effect on reactivity except in extreme cases, such as (**10e**)[18] and the porphyrin complex (**11**).[19] Rhodium–carbonyl complexes such as $Rh_6(CO)_{16}$ and $[Rh(CO)_2Cl]_2$ are also effective catalysts.[20]

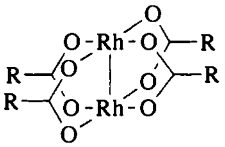

(**10**) **a**: R = Me
**b**: R = Bu$^t$
**c**: R = $(CH_2)_4Me$
**d**: R = $CF_3$
**e**: R = 2,4,6-triarylphenyl

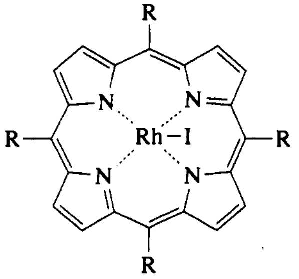

(**11**) R = 2,4,6-trimethylphenyl

The rhodium(II) catalysts and the chelated copper catalysts are considered to coordinate only to the carbenoid, while copper triflate and tetrafluoroborate coordinate to both the carbenoid and alkene and thus enhance cyclopropanation reactions through a template effect.[14] Palladium-based catalysts, such as palladium(II) acetate and bis(benzonitrile)palladium(II) chloride,[16e] are also believed to be able to coordinate with the alkene. Some chiral complexes based on cobalt have also been developed,[21] but these have not been extensively used.

## 4.8.3 CLASSES OF KETOCARBENOIDS

One of the most attractive features about the application of carbenoid chemistry in organic synthesis is that their diazo precursors are readily prepared. Diazoacetates (**12a**) have been most extensively used, but a variety of other systems including diazoacetamides (**12b**),[17,22,23] diazo ketones (**12c**),[24] diazomalonates (**12d**),[25] diazoacetoacetates (**12e**) and others with two electron-withdrawing groups, diazopyruvates (**12f**)[26] and vinyldiazomethanes (**12g**),[27] have also been exploited in useful synthetic processes. A particular advantage of the diazocarbonyl compounds is that the presence of an electron-withdrawing group causes the system to be more stable than simple diazoalkanes.

The diazo transfer reaction with sulfonyl azides has been extensively used for the preparation of diazo compounds with two electron-withdrawing groups (equation 1).[28] Toluenesulfonyl azide (**13a**)[29] is the standard reagent used, but due to problems of safety and ease of product separation, several alternative reagents have been developed recently. *n*-Dodecylbenzenesulfonyl azide (**13b**)[30] is very effective for the preparation of crystalline diazo compounds, while *p*-acetamidobenzenesulfonyl azide (**13c**)[31] or naphthalenesulfonyl azide (**13d**)[30] are particularly useful with fairly nonpolar compounds. Other useful reagents are methanesulfonyl azide (**13e**)[32] and *p*-carboxybenzenesulfonyl azide (**13f**).[33]

The diazo transfer reaction can be used to prepare, indirectly, compounds with only one electron-withdrawing group because base-induced deacylation is very favorable (equation 2;[28] Scheme 3[22a]). Diazo ketones are also conveniently prepared by reaction of acid chlorides with diazoalkanes (equation 3),[34] while diazoacetates are readily formed through reaction of the toluenesulfonylhydrazone (**14**)[35] or the corresponding triisopropylphenylhydrazone[36] with alcohols (equation 4). Other classical methods for preparation of diazocarbonyl compounds include the nitrosation of amines and dehydrogenation of hydrazones.[28]

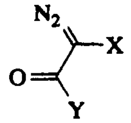

$RSO_2N_3$

**(12)**
a : Y = OEt, X = H
b : Y = $NR_2$, X = H
c : Y = alkyl, X = H, Me
d : Y = OEt, X = $CO_2Et$
e : Y = OEt, X = COMe
f : Y = $CO_2Et$, X = H
g : Y = OEt, X = CH=CHR

**(13)**
a: R = 4-$MeC_6H_4$–
b: R = 4-($C_{12}H_{25}$)$C_6H_4$–
c: R = 4-(MeCONH)$C_6H_4$–
d: R = 1-naphthyl–
e: R = Me–
f: R = 4-($HO_2C$)$C_6H_4$–

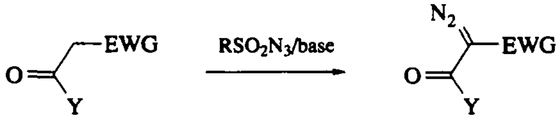
EWG
O
Y
$RSO_2N_3$/base
$N_2$
EWG
O
Y
(1)

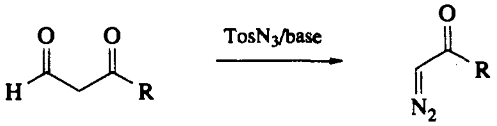
O
O
H
R
$TosN_3$/base
O
R
$N_2$
(2)

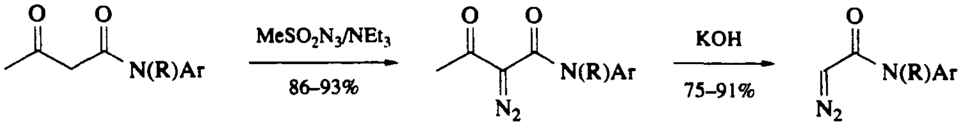
O
O
N(R)Ar
$MeSO_2N_3$/$NEt_3$
86–93%
O
O
N(R)Ar
$N_2$
KOH
75–91%
O
N(R)Ar
$N_2$

Scheme 3

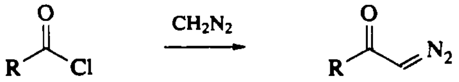
O
R
Cl
$CH_2N_2$
O
R
$N_2$
(3)

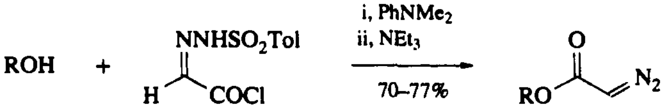
ROH
+
$NNHSO_2Tol$
H
COCl
i, $PhNMe_2$
ii, $NEt_3$
70–77%
O
RO
$N_2$
(4)

**(14)**

## 4.8.4 ADDITION OF KETOCARBENOIDS TO ALKENES

### 4.8.4.1 Intermolecular Reactions

The addition of carbenoids derived from alkyl diazoacetates to alkenes has been extensively studied. As two thorough reviews on the subject,[1,2] dealing with a detailed comparison of the various catalysts, have recently appeared, only a general summary concerning regioselectivity, competing reactions, diastereoselectivity and enantioselectivity will be presented here.

### *4.8.4.1.1 Regioselectivity*

Rhodium(II) acetate appears to be the most generally effective catalyst, and most of this discussion will center around the use of this catalyst with occasional reference to other catalysts when significant synthetic advantages can be gained. Cyclopropanation of a wide range of alkenes is possible with alkyl diazoacetate, as is indicated with the examples shown in Table 1.[16e,37] The main limitations are that the alkene must be electron rich and not too sterically crowded. Poor results were obtained with *trans*-alkenes. Comparison studies have been carried out with copper and palladium catalysts and commonly the yields were lower than with rhodium catalysts. Cyclopropanation of styrenes and strained alkenes, however, proceeded extremely well with palladium(II) acetate, while copper catalysts are still often used for cyclopropanation of vinyl ethers.[38–40]

**Table 1** Yield of Cyclopropanation with Ethyl Diazoacetate

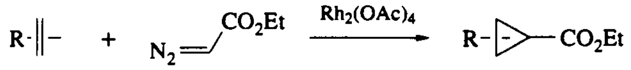

| *Alkene* | *Yield (%)* |
|---|---|
| $\mathrm{PhCH{=}CH_2}$ | 93 |
| $\mathrm{EtOCH{=}CH_2}$ | 88 |
| $\mathrm{AcOCH{=}CH_2}$ | 77 |
| $\mathrm{Bu^tCH{=}CH_2}$ | 87 |
| $\mathrm{ClCH_2CH{=}CH_2}$ | 90 |
| $\mathrm{Me_2C{=}CMe_2}$ | 70 |
| *cis*-$\mathrm{MeCH{=}CH(CH_2)_4Me}$ | 65 |
| *trans*-$\mathrm{MeCH{=}CH(CH_2)_4Me}$ | 24 |
| *trans*-$\mathrm{Me(CH_2)_2CH{=}CH(CH_2)_2Me}$ | 7 |
| $\mathrm{Me_2C{=}CHCH{=}CMe_2}$ | 81 |
| Cyclohexene | 90 |
| Cyclohexadiene | 90 |
| 2,3-Dihydropyran | 91 |

Another series of experiments which nicely demonstrates the regioselectivity of cyclopropanation reactions has been carried out with substituted dienes.[41] In general, cyclopropanation occurs at the least-substituted double bond with terminal dienes (equation 5), but electronic factors control the position of cyclopropanation with 2-substituted dienes (equation 6). With the fluorodiene (**15**) the predominant product was (**16a**; equation 7), which arose through cyclopropanation at the fluorine-bound double bond.[42] This result and related observations have been rationalized by assuming a nonsynchronous cyclopropanation mechanism in which the adverse electron-withdrawing effect of the fluoride in the somewhat zwitterionic transition state is compensated by a mesomeric electron-releasing effect. Even though extensive studies of the rhodium-catalyzed cyclopropanation with diazoacetates have been reported,[1,2] similar studies with other carbenoids are less common[26a,43] and most of the available information on regioselectivity is based on earlier work using less efficient copper catalysts.[5]

The structure of the carbenoid has considerable effect on the outcome of the reaction with vinyl ethers. Unlike the case with diazoacetate, reaction with diazopyruvate resulted in the formation of a dihydrofuran (**17**) rather than a cyclopropane (equation 8).[26d] The reaction is a formal [2 + 3] cycloaddition but it

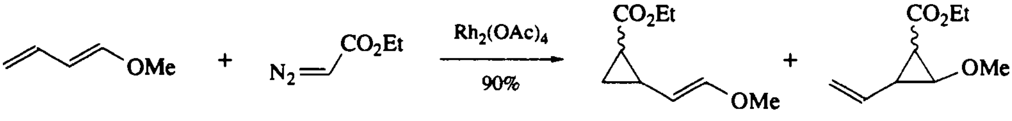

89% 11%

(5)

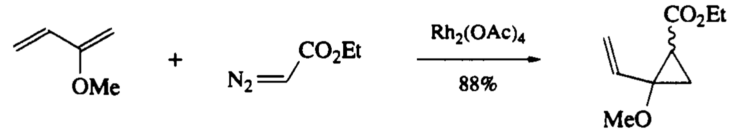

(6)

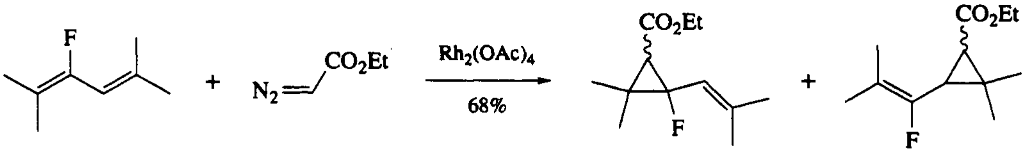

**(15)** **(16a)** 56% **(16b)** 44% (7)

has been proposed[26c] that the mechanism involves a dipolar intermediate. Similar reactions were observed with diazoacetoacetates[44] and also with diazo ketones reacting with ketene acetals.[45]

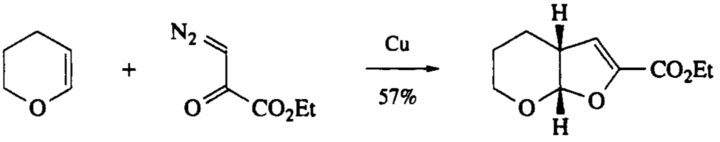

**(17)** (8)

### *4.8.4.1.2 Competing reactions*

One of the main side reactions that can occur in cyclopropanation reactions is a competitive capture of the carbenoid with unreacted diazo compound rather than with the alkene, which results in the formation of dimeric products such as (**18**) and (**19**) (equation 9).[1,46] This reaction is usually avoided by using a five- to ten-fold excess of alkene and ensuring that a low concentration of the diazo compound is maintained. Indeed, Doyle has shown that by very slow addition of the diazo compound it is possible to obtain reasonable yields of cyclopropane even when stoichiometric quantities of the carbenoid precursor and alkene were used.[47]

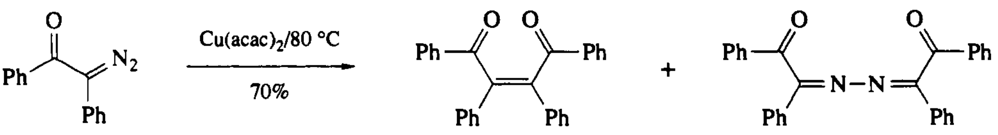

**(18)** 86% **(19)** 14% (9)

Insertion into an O—H bond is generally favored over cyclopropanation, and consequently protection of hydroxy functionality is normally required. The ease of O—H insertion is nicely illustrated in a recent synthesis of chorismic acid derivatives, where the alkene functionality in (**20**) was totally unaffected by the carbenoid (Scheme 4).[48]

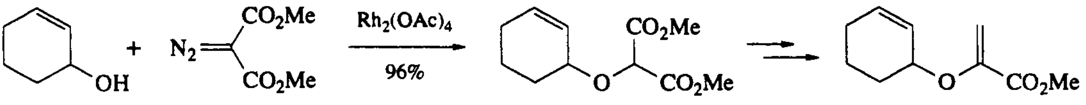

**(20)**

**Scheme 4**

The carbenoid can also be competitively captured by halogens, as demonstrated in a series of experiments on allyl halides (Scheme 5).[49] Capture of the carbenoid with the halide generated an ylide capable of a 2,3-sigmatropic rearrangement, forming (**21**). As would be expected, the order of reactivity was iodide > bromide > chloride, but the carbenoid structure was also crucial because halogen insertion was much more favorable with diazomalonate than diazoacetate. Other nucleophilic sites such as oxygen,[50] nitrogen and sulfur can also effectively compete for the carbenoid.

Although C—H insertion reactions rarely occur in intermolecular reactions with diazoacetates, these are common side reactions with diazomalonates[51,52] (equation 10) and diazo ketones (with α-allyl vinyl ethers).[53] Several mechanistic pathways are available to generate the products of an apparent direct C—H insertion reaction and these include dipolar intermediates, π-allyl complexes and ring opening of cyclopropanes.[1] Oxidative problems due to the presence of oxygen are common with copper catalysts, but these are rarely encountered with rhodium catalysts except in systems where the carbenoid is ineffectively captured.[54]

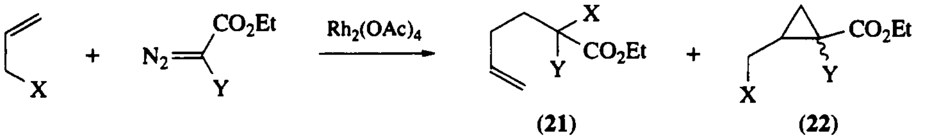

| *X* | *Y* | *Yield (%)* | *Ratio (21):(22)* |
|---|---|---|---|
| I | H | 98 | 100:0 |
| Br | H | 76 | 28:72 |
| Cl | H | 95 | 5:95 |
| Br | $CO_2Et$ | 92 | 93:7 |

**Scheme 5**

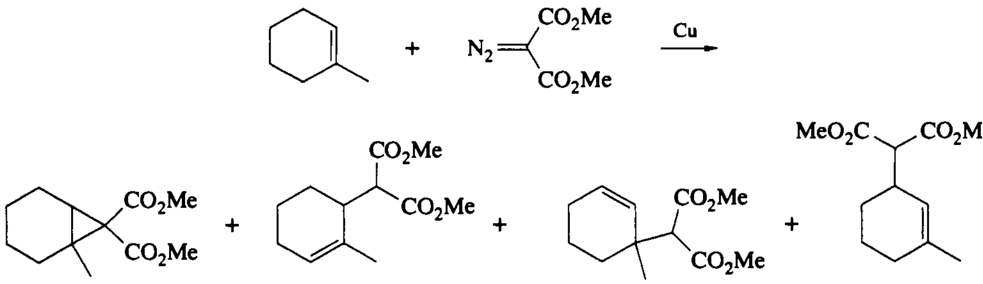

(10)

### 4.8.4.1.3 Diastereoselectivity

Considering that the ring opening of cyclopropanes can proceed in a stereodefined manner, very valuable synthetic sequences would be possible if the original cyclopropanation was also stereoselective. Cyclopropanation of alkenes generally proceeds stereospecifically from the point of view of alkene geometry, although this is not the case with cobalt catalysis.[21] The stereoselectivity with respect to the arrangement of the alkene and carbenoid, however, is not usually particularly impressive with ethyl diazoacetate, as can be seen in some representative examples shown in Table 2.[37] A slight preference for the thermodynamically more stable *trans* isomer (**23a**) was observed. Further enhancement occurred when *cis*-disubstituted alkenes were used as substrates. This tendency was greater for copper catalysts than the rhodium(II) salts, while palladium catalysts were less selective. Ligands on the catalyst do not exert a great effect but with extremely hindered systems such as (**11**)[18] it was possible to change the distribution to slightly favor the *cis* isomer.

**Table 2** Stereoselectivity of Cyclopropanation Reactions with Ethyl Diazoacetates

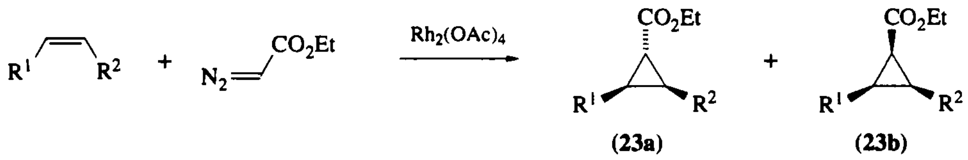

| $R^1$ | $R^2$ | *Ratio* (**23a**)*:*(**23b**) |
|---|---|---|
| $Me(CH_2)_3O$ | H | 1.7 |
| Ph | H | 1.4 |
| $Me(CH_2)_3$ | H | 1.5 |
| $Me_2CH$ | H | 2.0 |
| $Bu^t$ | H | 4.2 |
| —c-$(CH_2)_4$— | | 3.8 |
| —c-$(CH_2)_3$— | | 2.1 |
| —c-$(CH_2)_3O$— | | 6.5 |

Some recent studies suggest that considerable improvement in the stereoselectivity of the cyclopropanation reaction may be possible by altering the carbenoid structure. For example, Doyle[17] has shown that the use of sterically bulky diazoacetates, such as (**24a**) and (**24b**) resulted in a much more selective cyclopropanation, favoring the *trans* isomer (**25a**), particularly when rhodium(II) acetamide was used as catalyst (Scheme 6). Unfortunately, (**24b**) may be of limited utility because cyclopropanation proceeded in low yield due to competing intramolecular C—H insertion. Entirely different carbenoid structures may be much more selective, as can be seen with the vinyldiazomethane (**26**), whose reaction with styrene under standard conditions produced an isomer ratio of 13:1 (equation 11).[55]

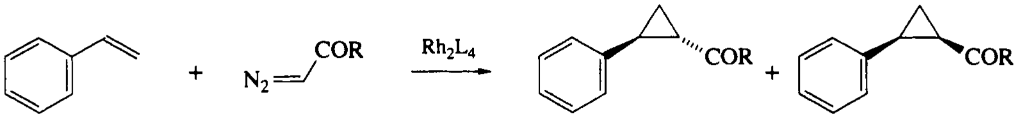

(**24**) (**25a**) (**25b**)

| *Substrate* | *R* | *L* | *Yield* (%) | *Ratio* (*25a*):(*25b*) |
|---|---|---|---|---|
| (**24a**) | $OCMePr^i_2$ | OAc | 95 | 2.4:1 |
| (**24a**) | $OCMePr^i_2$ | NHCOMe | 87 | 4.4:1 |
| (**24b**) | $NPr^i_2$ | OAc | 53 | 64:1 |
| (**24b**) | $NPr^i_2$ | NHCOMe | 47 | 114:1 |

**Scheme 6**

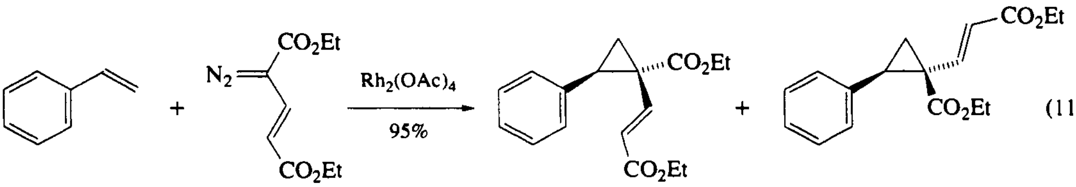

(11)

(**26**) 92% 8%

The effect of the alkene is rather subtle and is not simply caused by steric factors. This is clearly demonstrated in the cyclopropanation of alkenes substituted with halide in the side chain, *e.g.* with (**27**) the predominant product was the thermodynamically unfavored *cis* isomer (**28a**; equation 12).[56]

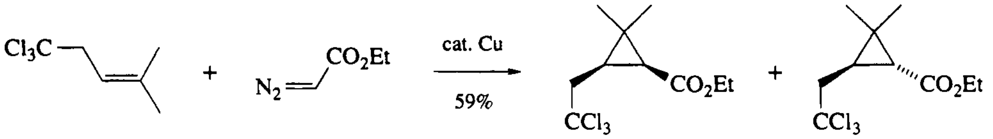

(12)

(**27**) (**28a**) 85% (**28b**) 15%

#### 4.8.4.1.4 *Enantioselectivity*

The development of asymmetric cyclopropanation protocols has been actively studied and in recent years remarkable progress has been made. The extent of chiral induction that can now be obtained in these reactions approaches the level of other classic catalytic asymmetric reactions on alkenes, such as catalytic hydrogenation and the Sharpless' epoxidation.[57]

The use of ketocarbenoids with chiral auxiliaries has not been terribly effective at chiral induction. Menthol and borneol esters of diazoacetates resulted in very low enantioselectivity.[58] Some improvements were obtained by using the chiral amide (**29**; equation 13), but low overall yields were obtained due to competing intramolecular side reactions.[59] Related studies with other types of carbenoids, however, have resulted in high enantioselectivity.[60]

In contrast, much more effective asymmetric reactions have been obtained by using chiral copper catalysts. Since the pioneering work of Nozaki and coworkers[61] with a chiral salicylamide catalyst (**30**), a wide variety of other chiral complexes has been developed, the most significant of which are (**31**)–(**34**). Another useful catalyst is the cobalt complex (**35**).

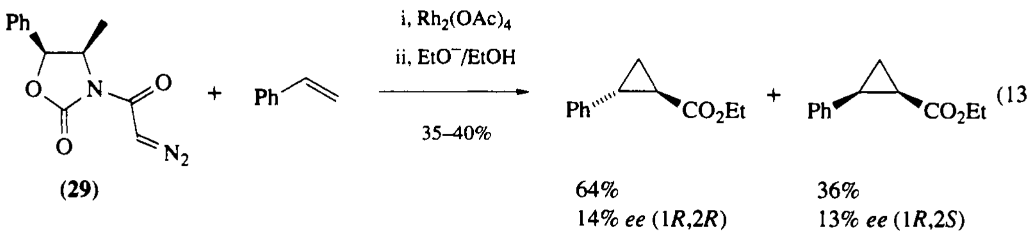

**(29)** (13)

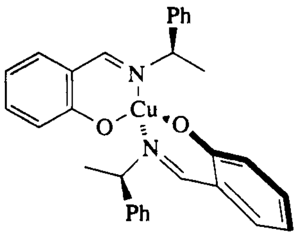

**(30)**

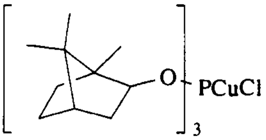

**(31)**

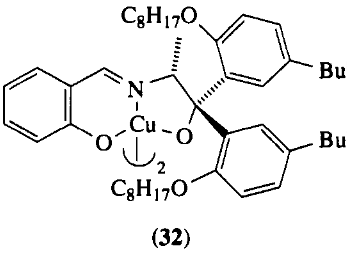

**(32)**

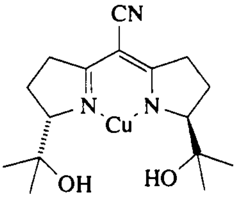

**(33)**

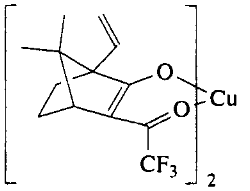

**(34)**

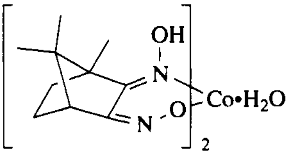

**(35)**

The initial studies in the 1960s with (**30**) and Moser's catalyst (**31**)[15] resulted in rather low levels of enantioselectivity. Great enhancements were obtained by Aratani and coworkers[56,58] using complex (**32**), which is closely related to Nozaki's catalyst except that the chiral ligand is tridentate. Much of Aratani's work was directed towards the enantioselective synthesis of pyrethroid derivatives and a representative example is shown in equation (14). The extent of enantioselectivity was dependent on the nature of the ester functionality and the highest value (90% *ee*) was obtained using the (1*S*,3*S*,4*R*)-menthyl group. Even though (1*R*,3*R*,4*S*)-menthyl diazoacetate produced minimal chiral induction with achiral catalysts, the interaction between (**36**) and (**32**) significantly enhanced the selectivity. Further applications of (**32**) to the synthesis of pyrethroid derivatives[62] and deuterated cyclopropanes[63] have been reported.

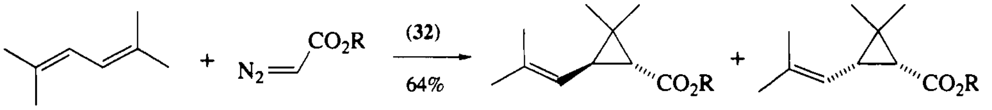

(14)

(**36**) R = (1*S*,3*S*,4*R*)-menthyl

81% 90% *ee* (1*R*,3*R*)

19% 59% *ee* (1*R*,3*S*)

A remarkable complex (**33**) with a $C_2$-symmetric semicorrin ligand has been recently developed by Pfaltz and coworkers.[64] A copper(II) complex was used as a procatalyst, but (**33**) was shown to be the active cyclopropanation catalyst. As shown in Table 3, this complex resulted in spectacular enantioselectivities in the range of 92–97% *ee*. Once again, the (1*S*,3*S*,4*R*)-menthyl group attenuated the selectivity. Unfortunately, even though respectable yields were obtained with dienes and styrenes, the reaction with 1-heptene was rather inefficient.

Another efficient chiral catalyst (**34**) has been developed by Matlin.[65] The only reaction of (**34**) reported so far has been between 2-diazodimedone (**38**) and styrene, which resulted in the exclusive production of only one enantiomer of (**39**) as determined by NMR (equation 15). An immobilized derivative of (**34**) was also found to be an effective catalyst, generating (**39**) in 98% enantiomeric excess (43% yield). These results are remarkable because they represent efficient chiral induction at the prochiral al-

**Table 3** Asymmetric Induction with (33)

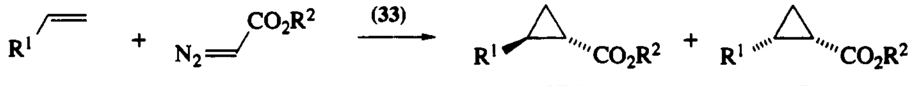

**(37a)** **(37b)**

| $R^1$ | $R^2$ | Yield (%) | (37a):(37b) | ee (%) | (37a) | ee (%) | (37b) |
|---|---|---|---|---|---|---|---|
| Ph | (1*R*,3*R*,4*S*)-Menthyl | 65–75 | 85:15 | 91 | (1*S*,2*S*) | 90 | (1*S*,2*R*) |
| Ph | (1*S*,3*S*,4*R*)-Menthyl | 60–70 | 82:18 | 97 | (1*S*,2*S*) | 95 | (1*S*,2*R*) |
| $CH_2{=}CH$ | (1*S*,3*S*,4*R*)-Menthyl | 60 | 63:37 | 97 | (1*S*,2*R*) | 97 | (1*S*,2*S*) |
| $Me_2C{=}CH$ | (1*S*,3*S*,4*R*)-Menthyl | 77 | 63:37 | 97 | (1*S*,2*R*) | 97 | (1*R*,2*S*) |
| $C_5H_{11}$ | (1*S*,3*S*,4*R*)-Menthyl | 30 | 82:18 | 92 | (1*S*,2*S*) | 92 | (1*S*,2*R*) |

kene, rather than induction at the prochiral carbenoid, which occurs with all the other asymmetric cyclopropanation systems. Further examination of the scope of this type of induction would be very valuable.

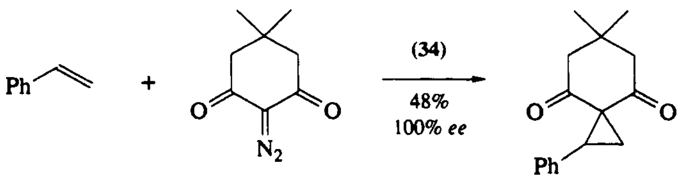

**(38)** **(39)** (15)

Although cobalt catalysts have been rarely used in cyclopropanation reactions, Nakamura and coworkers[21] have developed the camphor-based complex (**35**) as a useful asymmetric catalyst, as shown in a typical example in equation (16). High yields were obtained with dienes and styrenes but cyclopropanation did not occur with simple alkenes. Studies with *cis*-$d_2$-styrene showed that, unlike other catalytic systems, the reaction was not stereospecific with respect to alkene geometry.

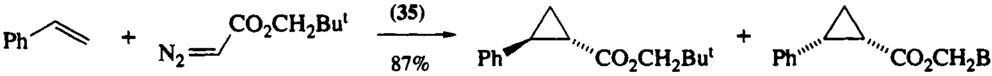

(16)

70% 30%

88% *ee* (1*S*,2*S*) 81% *ee* (1*S*,2*R*)

### 4.8.4.2 Intramolecular Reactions

The intramolecular cyclopropanation of alkenes has been extensively employed in the synthesis of natural products and molecules of theoretical interest. Reactions which generate [3.1.0]-[1,7,66–94] and [4.1.0]-bicyclic[1,7,95–98] systems are the most common, while longer tethers tend to result in inefficient capture of the carbenoid (equation 17).[99] The main side reactions are due to C—H insertions,[100] but even these can be minimized by appropriate substitution, as shown in equation (18).[101]

With β,γ-unsaturated α′-diazo ketones, the resulting [2.1.0]-bicyclic systems (**40**) were quite unstable and underwent a [2 + 2] cycloreversion to generate ketenes (**41**), which were then trapped by nucleophiles (Scheme 7). The overall scheme has been named a vinylogous Wolff rearrangement and offers a novel entry to products usually derived from a Claisen rearrangement.[102] A recent report describes its application for functionalized angular alkylation in fused ring systems.[103] In contrast, the intramolecular re-

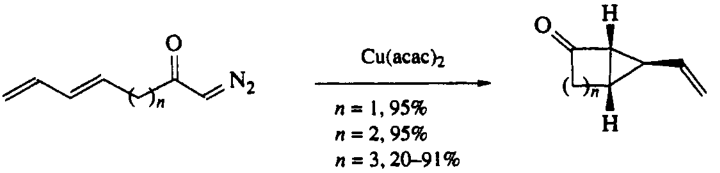

(17)

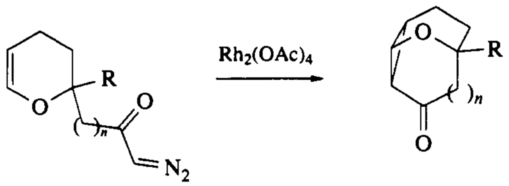

$n = 0$, R = H; 58%
$n = 1$, R = H; 61%
$n = 2$, R = H; 0%
$n = 2$, R = Me; 95%
$n = 3$, R = Me; 95%
$n = 4$, R = H; 0%

(18)

action to cyclopropenes such as (**42**) leads to the highly strained but isolable tricyclic ketone (**43**; equation 19).[104] Other novel structures that have been derived through intramolecular cyclopropanations include barbaralone and 4,4,4-propellane.[7] A recent example includes the rhodium(II) acetate catalyzed decomposition of (**44**), which generated the novel structure (**45**; equation 20).[105] The reaction was considered to proceed through an unusual 1,6-addition, although cyclopropanation followed by a 1,5-sigmatropic rearrangement would be a reasonable alternative mechanism.

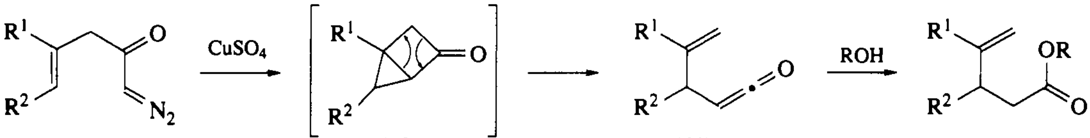

(**40**) (**41**)

Scheme 7

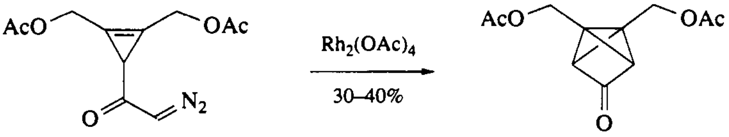

(19)

(**42**) (**43**)

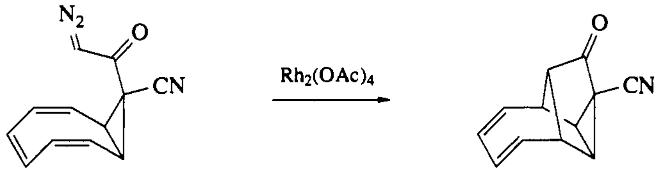

(20)

(**44**) (**45**)

Unlike their intermolecular counterparts, intramolecular cyclopropanations are stereospecific with respect to both alkene and carbenoid structure, as can be seen in equations (21) and (22).[87] The influence of other stereogenic centers can also be significant. Numerous examples are known where excellent stereocontrol is obtained when the stereogenic center is part of a tether constrained within a ring, as illustrated in equation (23).[96] Stereocontrol is less certain in acyclic systems. With the extremely bulky grouping in (**46**) excellent stereocontrol was observed to generate only (**47**; equation 24).[95a] In the case of (**48**), which has a longer and more flexible tether, only moderate stereoselectivity was observed (equation 25),[95b] while with (**49**) the methyl group has no influence on the product distribution (equation 26).[66] Only moderate asymmetric inductions by chiral catalysts[93] or chiral auxiliaries[94] have been reported so far for intramolecular cyclopropanations. More effective chiral catalysts such as (**33**) and (**34**) are now available and it is reasonable to predict that high asymmetric inductions should be feasible in the near future.

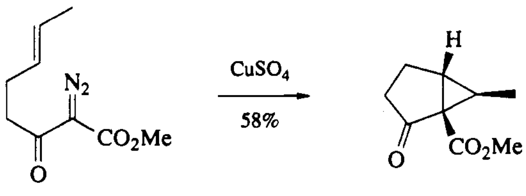

(21)

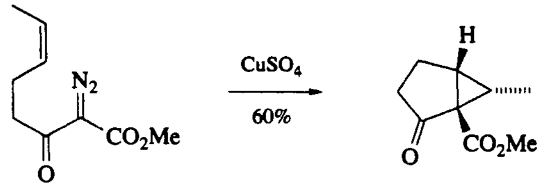

N2
CO2Me
O
CuSO4
60%
H
O
CO2Me

(22)

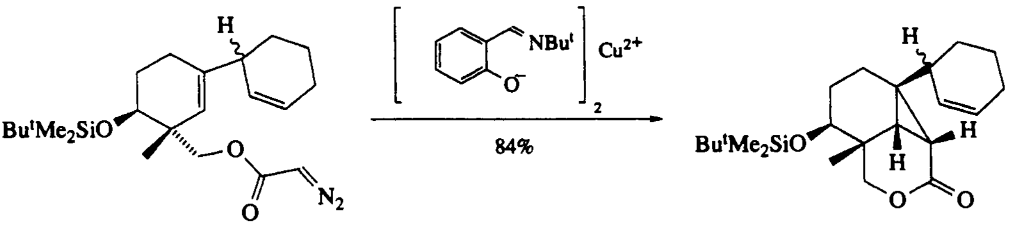

H
Bu'Me2SiO
O
O
N2
NBu'
O⁻
Cu2+
2
84%
H
Bu'Me2SiO
H
H
O
O

(23)

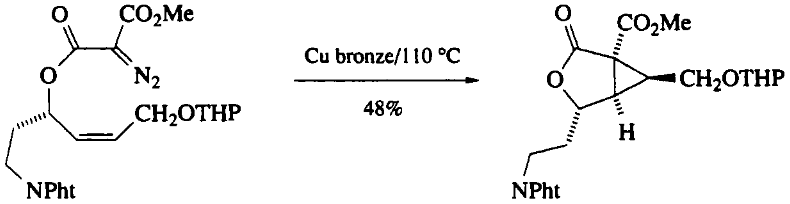

O
CO2Me
O
N2
CH2OTHP
NPht
Cu bronze/110 °C
48%
O
CO2Me
O
CH2OTHP
H
NPht

(46) (47)

(24)

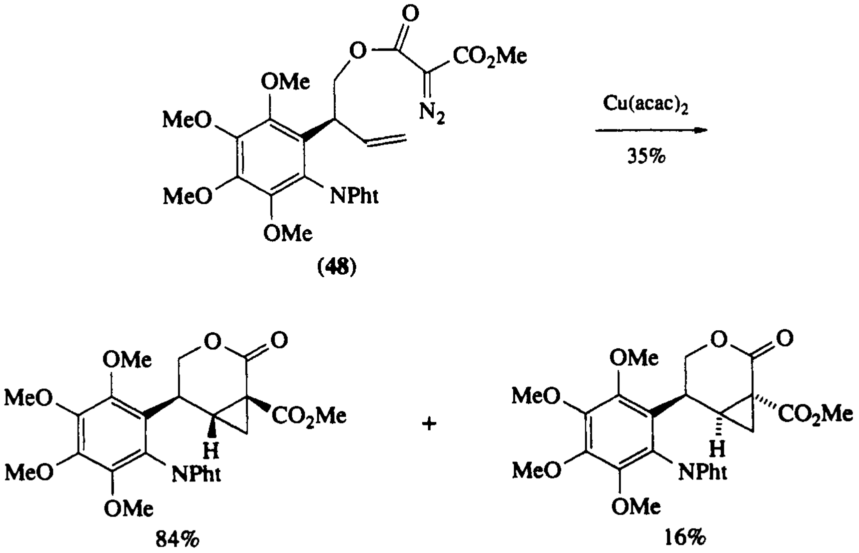

O
O
CO2Me
OMe
MeO
N2
MeO
NPht
OMe
Cu(acac)2
35%
OMe
O
O
MeO
CO2Me
MeO
H
NPht
OMe
84%
+
OMe
O
O
MeO
CO2Me
MeO
H
NPht
OMe
16%

(48)

(25)

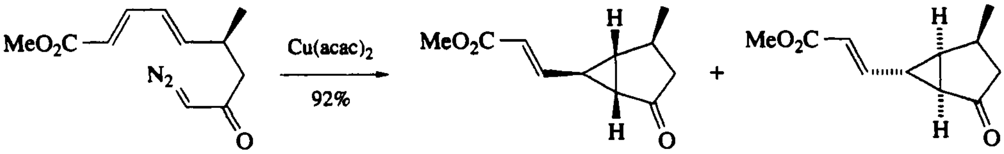

MeO2C
N2
O
Cu(acac)2
92%
MeO2C
H
H
O
+
MeO2C
H
H
O

(49) 50% 50%

(26)

A spectacular example showing the effect of catalyst on product distribution is shown in Scheme 8.[92] Palladium(II) acetate catalyzed decomposition of (**50**) resulted in cyclopropanation to form (**51**). When rhodium(II) acetate was used as catalyst, however, a different reaction occurred, whereby the carbenoid was predominantly captured by the carbonyl to generate ultimately (**52**).

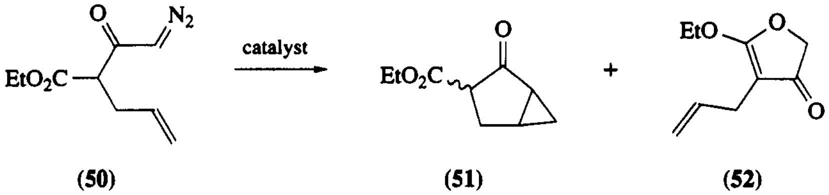

| | (51) | (52) |
|---|---|---|
| $Pd(OAc)_2$ | 53% | - |
| $Rh_2(OAc)_4$ | 1% | 58% |

**Scheme 8**

Cyclopropanes are present in a variety of natural products and the intramolecular cyclopropanation sequence allows ready access to such compounds. The sesquiterpenoid antibiotic (±)-cycloeudesmol (**53**) was readily prepared from the monocyclic system (**54**; Scheme 9).[91] Copper sulfate catalyzed decomposition of (**54**) generated the tricyclic system (**55**) with full control of stereochemistry. Further conversion of (**55**) to (±)-cycloeudesmol was achieved in four steps in 81% overall yield. A second example shown in equation (27)[73] allowed access to (**56**), an important substructure of the antibiotic CC-1066.

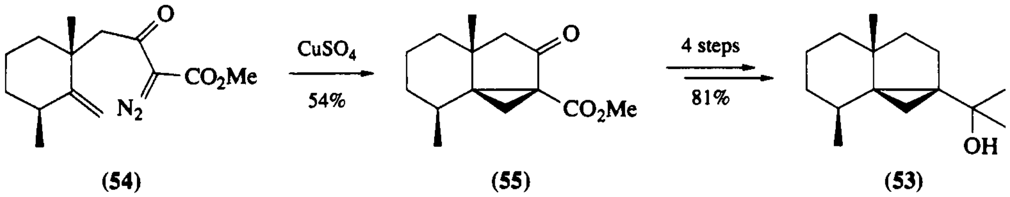

**Scheme 9**

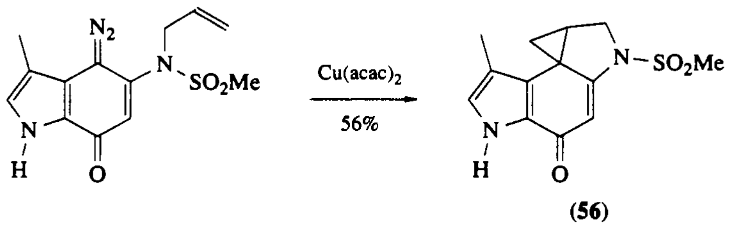

(27)

### 4.8.4.3 Further Transformations of Cyclopropanes

Due to the strain associated with the cyclopropane system, a variety of ring-opening transformations can occur. As this material has been extensively reviewed in recent years,[6–8,106–108] this section will concentrate only on the most useful synthetic processes by means of some illustrative examples.

Cyclopropanes in rigid systems have been selectively cleaved by catalytic hydrogenation[80] or lithium/liquid ammonia reduction.[81,97,98] Only the bond with greater overlap to the carbonyl was ruptured. A particularly attractive application of this transformation is the synthesis of spiro compounds such as (**57**) by cleavage of the tricyclic system (**58**; Scheme 10).[97] Alternatively, under acidic conditions, ring opening to the bicyclic system (**59**) was observed. The flexibility of this approach to spiro compounds has been nicely demonstrated through the synthesis of (±)-α-chamigrene (**60**) and (±)-acorenone (**61**).[98]

The cyclopropane ring can also be cleaved by a retro-Michael reaction. By appropriate positioning of the carbonyl groups by means of an intramolecular cyclopropanation, controlled ring opening to spiro systems (**62**),[84] bicyclo[3.2.1]octanes (**63**)[82] or bicyclo[2.2.2]octanes (**64**),[82] has been achieved (equations 28–30).

α-Hydroxyalkylcyclopropanes readily ring open under elimination conditions. An example of this sequence is the synthesis of (±)-hinesol (**65**), as shown in Scheme 11.[83,84] Corey and coworkers have reported several elegant applications of this ring-opening sequence, as shown in the synthesis of (±)-cafestol (**66**; Scheme 12).[71] An intramolecular cyclopropanation generated (**67**) stereoselectively. On conversion of (**67**) to the triflate (**68**) a remarkable transformation occurred to generate the polycyclic

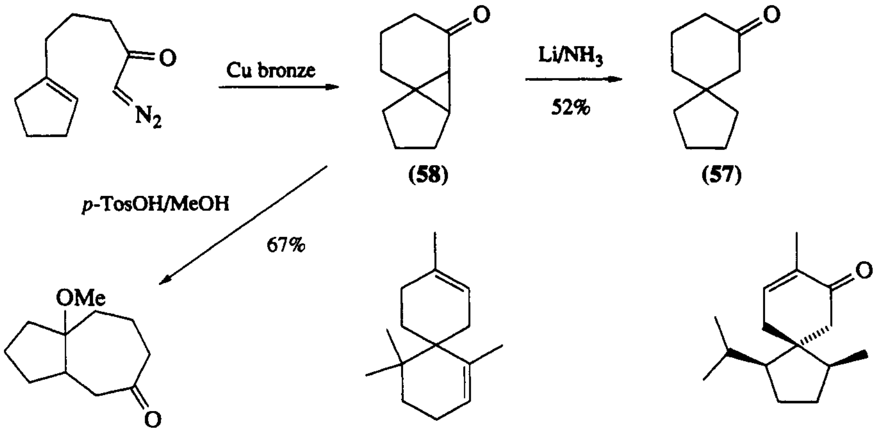
O
N₂
Cu bronze
O
(58)
Li/NH₃
52%
O
(57)
p-TosOH/MeOH
67%
OMe
O
(59)
(60)
O
(61)

**Scheme 10**

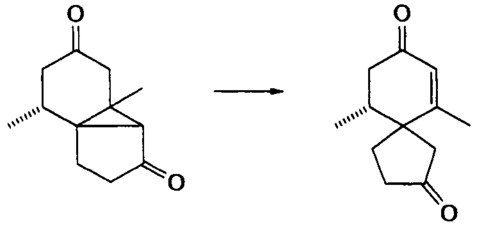

(28)

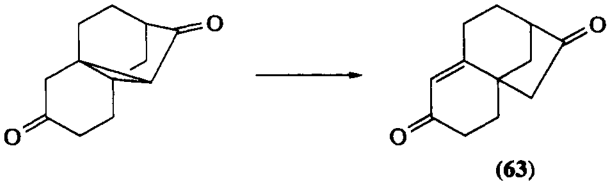

(29)

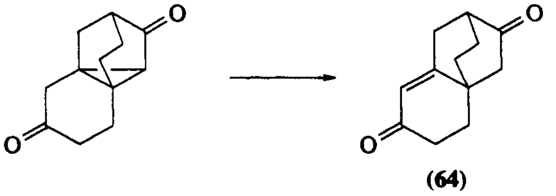

(30)

system (**69**) which was then modified to cafestol (**66**). Variations of this strategy have been used for the synthesis of (±)-atractyligenin[72] and (±)-kahweol.[70]

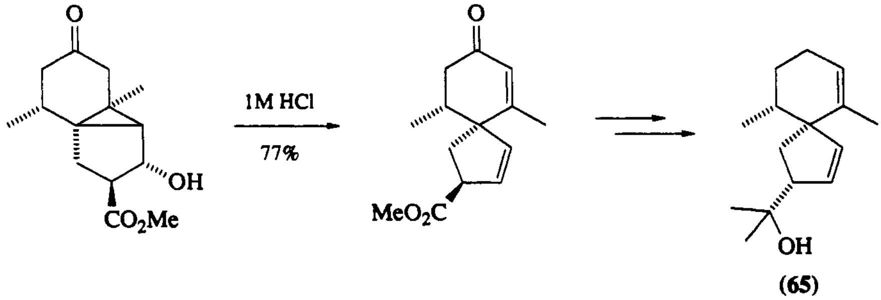
O
OH
CO₂Me
1M HCl
77%
O
MeO₂C
OH
(65)

**Scheme 11**

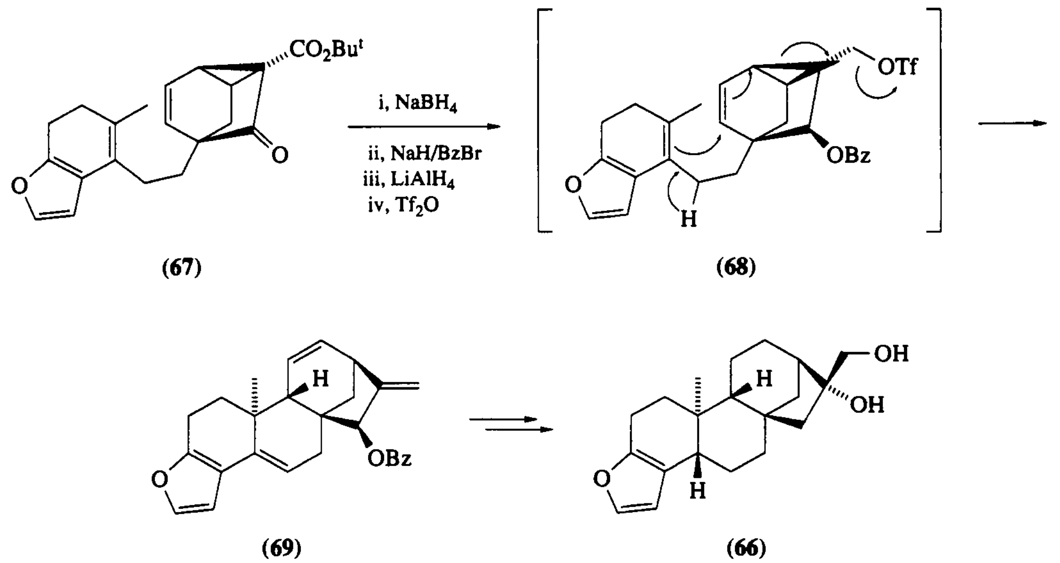

Scheme 12

Nucleophile-induced ring opening of cyclopropanes generally proceeds with inversion of configuration.[8a] Only very powerful soft nucleophiles will react with monoactivated cyclopropanes, but a much wider range of nucleophiles is possible if two electron-withdrawing groups are present. An early example of the use of this chemistry was reported by Corey and Fuchs (Scheme 13).[85] Copper powder induced decomposition of the diazo compound (**70**) generated the tricyclic system (**71**). Nucleophilic ring opening of the doubly activated cyclopropane with divinylcuprate followed by decarboxylation generated the advanced prostanoid precursor (**72**). Another study in the prostaglandin field was carried out by Kondo and coworkers (Scheme 14).[86] Copper(acetylacetonate)-catalyzed decomposition of (**73**) generated an inseparable mixture (2:1) of (**74a**) and (**74b**). Fortunately, (**74a**) and (**74b**) were distinguishable in their reaction with benzenethiol, because under controlled conditions only the desired isomer (**74a**) underwent ring opening with backside displacement to form (**75**; 85% yield based on **74a** in the mixture). In a series of further transformations (**75**) was converted to (±)-prostaglandin $F_{2\alpha}$ (**76**). A key step in a recent synthesis of (±)-quadrone also involved a nucleophilic ring opening of a cyclopropane.[89,90]

Stereoselective synthesis of medium-sized rings was possible from compounds such as (**77**; Scheme 15),[101a] which were readily derived from intramolecular cyclopropanations (see equation 18). Treatment of (**77**) with 1 equiv. of ethanethiol in the presence of a catalytic amount of zinc chloride generated the hemithioacetal (**78**), which in the presence of boron trifluoride etherate formed the cycloheptane system (**79**), in which the two carbonyls are differentiated.

Ring opening of cyclopropanes by nitrogen nucleophiles has been extensively used by Danishefsky and coworkers for the synthesis of alkaloids.[109] The synthesis of (±)-hastanicine (**80**; Scheme 16)[95a] is described to illustrate the strategy. The stereodefined system (**47**) was obtained through an intramolecular cyclopropanation (equation 24). Deprotection of the amine in (**47**) was achieved by treatment with hydrazine, which then opened the cyclopropane to form (**81**), in which the correct stereochemistry was obtained for further conversion to (**80**). A more ambitious target, based on the same overall strategy, was the synthesis of a potential mytomycine precursor.[95b]

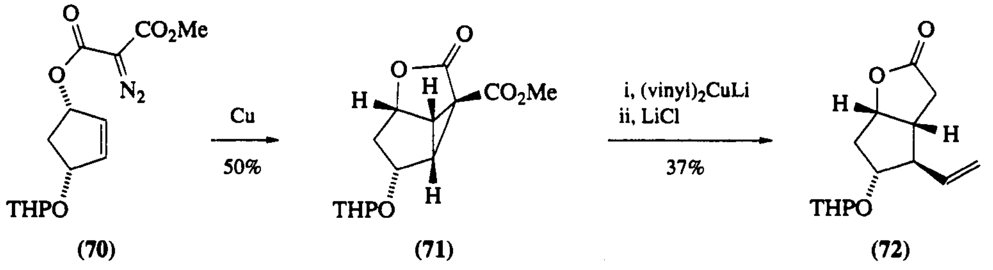

Scheme 13

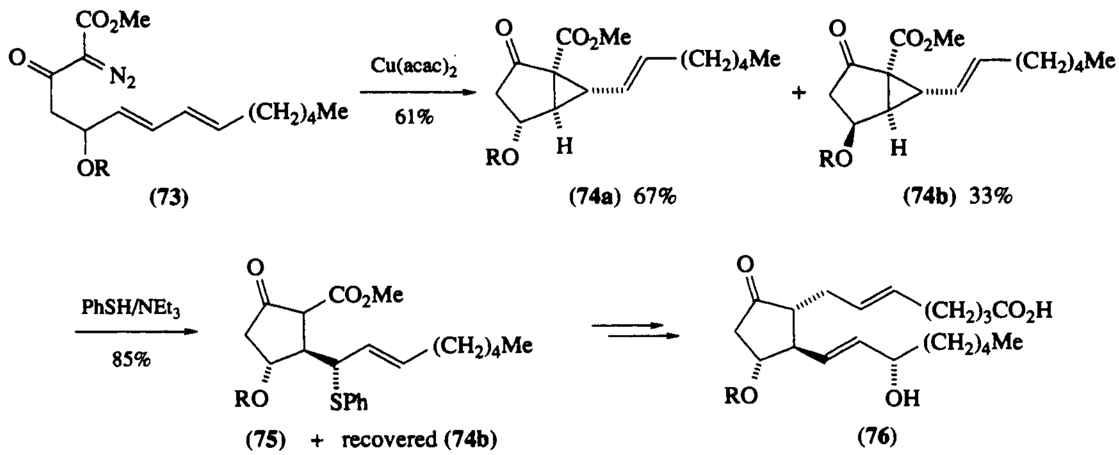

Scheme 14

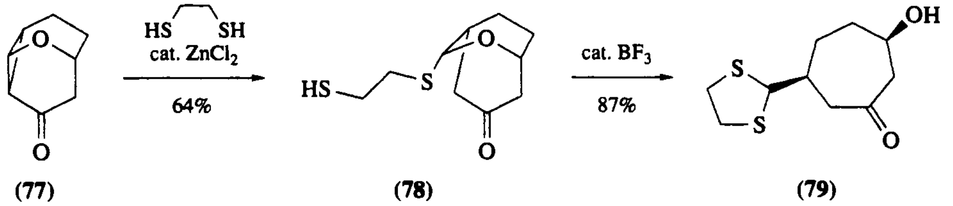

Scheme 15

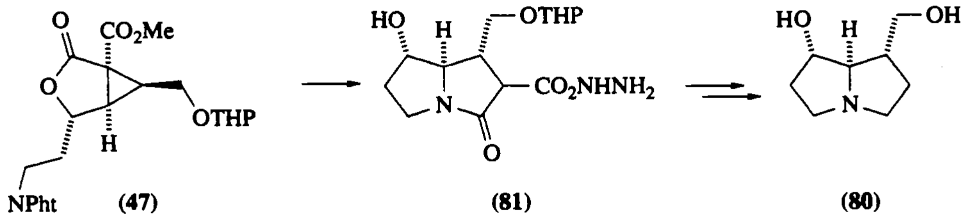

Scheme 16

Vinyl ethers are very efficiently cyclopropanated and the resulting donor–acceptor-substituted cyclopropanes (**82**) have been widely used in organic synthesis.[8a,106] Ring opening can be achieved under very mild conditions resulting in a versatile approach to 1,4-difunctionalized compounds. On treatment with mild acid ring opening of (**82**) occurred to form 1,4-dicarbonyl compounds (**83**),[110] which are useful precursors for cyclopentenones (**84**)[110] or furans (**85**).[26a,b,110,111] Alternatively, treatment of (**82**) with phenylselenyl chloride,[112] or bromine,[113] generated the substituted systems (**86**) and (**87**), respectively. Another mild procedure involved treatment of (**82**) with a catalytic amount of trimethylsilyl chloride and bis(trimethylsilyl)amine, which resulted in the formation of the silylated product (**88**).[114] If (**82**) was first reduced to the corresponding alcohol (**89**), the resulting mild acid hydrolysis generated β,γ-unsaturated ketones (**90**; Scheme 17).[115]

Some recent studies have shown that the enolate of the cyclopropane (**91**) was readily formed, and the resulting aldol product (**92**) underwent a remarkable diversity of ring-opening reactions, as shown in Scheme 18.[39] Treatment with acid generated the β,γ-unsaturated ketone (**93**), which under more vigorous conditions cyclized to the furanone (**94**). On treatment of (**92**) with acidic methanol the tetrahydrofuran (**95**) was formed, which on thermolysis was converted to the dihydrofuran (**96**).

Wenkert and coworkers have reported several applications of this chemistry to the synthesis of alkaloids and terpenes.[110] A recent example, leading to the methyl ether of tetrahydropyrethrolone (**97**), is illustrated in Scheme 19.[116] Reaction of 1,2-dimethoxypropene with 1-diazo-2-heptanone (**98**) resulted in the formation of the labile cyclopropane (**99**), which was directly converted to the 1,4-diketone (**100**). Base-induced aldol condensation of (**100**) readily formed (**97**). Stereoselective syntheses of prostaglandins[117] and dicranenone A[118] have also been developed using acid-induced ring-opening reactions.

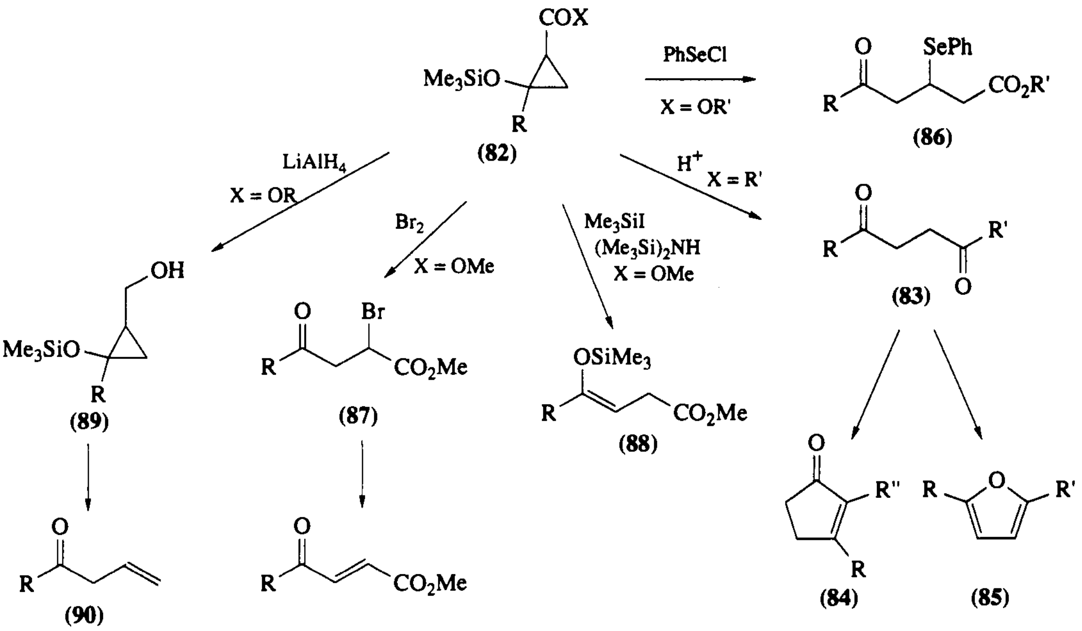
COX
Me3SiO
R
(82)
PhSeCl
X = OR'
SePh
CO2R'
(86)
H+
X = R'
R'
(83)
LiAlH4
X = OR
OH
(89)
Br2
X = OMe
Br
CO2Me
(87)
Me3SiI
(Me3Si)2NH
X = OMe
OSiMe3
(88)
R''
(84)
(85)
(90)

Scheme 17

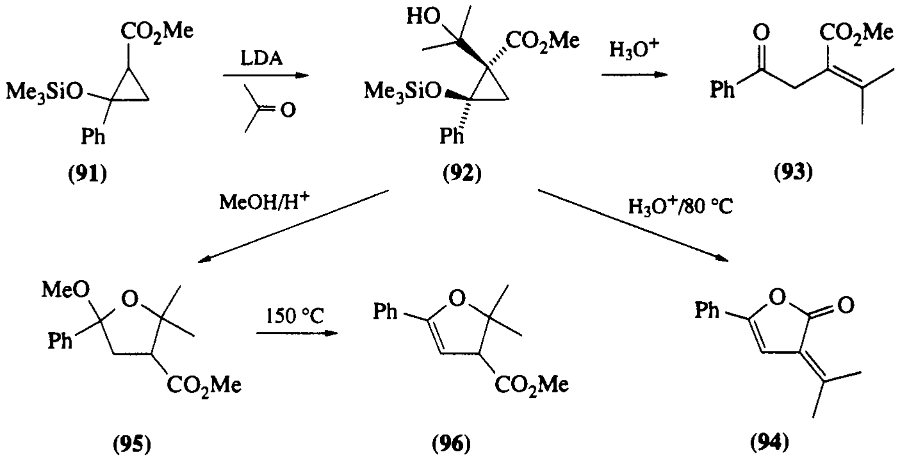
CO2Me
Me3SiO
Ph
(91)
LDA
HO
(92)
H3O+
(93)
MeOH/H+
H3O+/80 °C
MeO
150 °C
(95)
(96)
(94)

Scheme 18

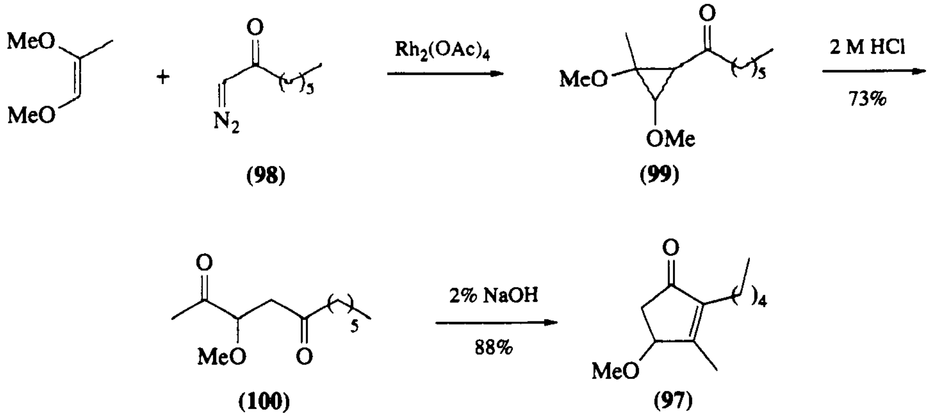
MeO
MeO
+
N2
)5
(98)
Rh2(OAc)4
(99)
OMe
2 M HCl
73%
(100)
2% NaOH
88%
)4
(97)

Scheme 19

Reissig and coworkers recently reported a rather direct route to the intramolecular Diels–Alder precursor (**101**).[119] Alkylation of the enolate from (**102**) followed by fluoride-induced ring opening generated (**101**), which on standing underwent a smooth transformation to the cycloadducts (**103a**) and (**103b**) (Scheme 20).

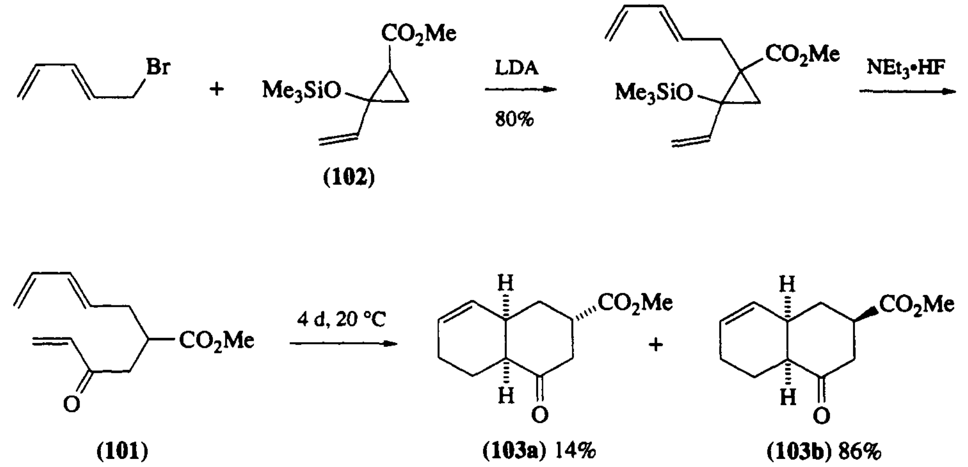
Br
+
$CO_2Me$
$Me_3SiO$
LDA
80%
$CO_2Me$
$Me_3SiO$
$NEt_3{\cdot}HF$
(102)
$CO_2Me$
O
4 d, 20 °C
H
$CO_2Me$
H
O
+
H
$CO_2Me$
H
O
(101)
(103a) 14%
(103b) 86%

**Scheme 20**

An elegant strategy for the synthesis of fused cyclopentanoids has been reported by Marino and coworkers (Scheme 21).[38] Reaction of (**104**) with the phosphonium salt (**105**) generated the bicyclic system (**106**). Further conversion of (**106**) to (**107**) enabled the annulation sequence to be repeated to form triquinane derivatives such as (**108**).

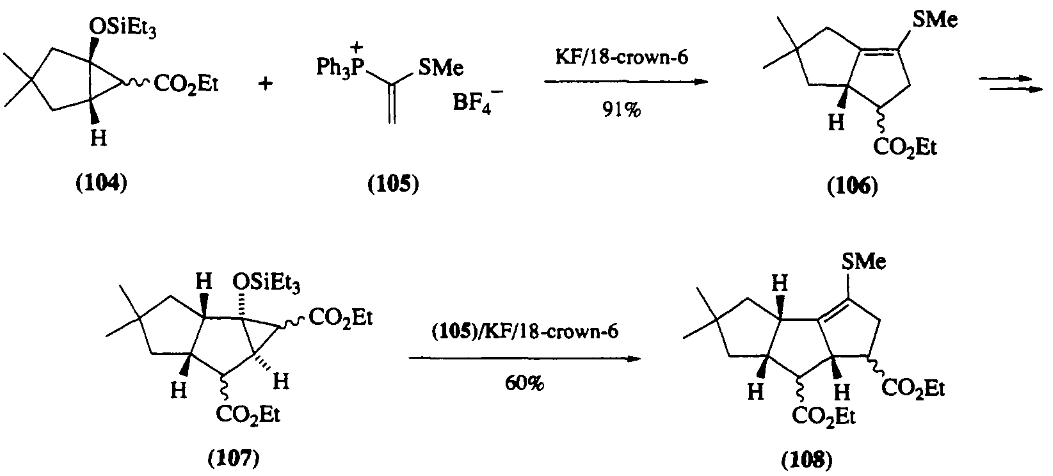
$OSiEt_3$
$CO_2Et$
H
+
$Ph_3\overset{+}{P}$
SMe
$BF_4^-$
KF/18-crown-6
91%
SMe
H
$CO_2Et$
(104)
(105)
(106)
H $OSiEt_3$
$CO_2Et$
H
H
$CO_2Et$
(105)/KF/18-crown-6
60%
SMe
H
H
H
$CO_2Et$
$CO_2Et$
(107)
(108)

**Scheme 21**

Thermolysis of vinylcyclopropanes offers a direct approach to the synthesis of cyclopentenes and several imaginative applications have been developed.[107,108] Hudlicky and coworkers[88] have used this chemistry to synthesize a range of compounds, as demonstrated in Scheme 22.[88a] Decomposition of (**109**) by a mixture of copper salts generated (**110**) in 75% yield. This particular example of cyclopropanation is quite significant because it showed that dienes with electron-withdrawing groups were tolerated and also that two contiguous quaternary carbons were readily formed. Flash vacuum pyrolysis of (**110**) generated the tricyclic system (**111**), which was further transformed to the triquinane derivative (**112**). This strategy has been applied to the synthesis of (±)-pentalene,[88c] (±)-sakromycin,[88g] a guaiane ring system[88b] and the plant hormone antheridiogen-An.[96]

The Cope rearrangement of *cis*-divinylcyclopropanes is thermally allowed and offers an attractive stereoselective approach to cycloheptadienes. Cyclopropanation reactions can be used to prepare divinylcyclopropanes, as shown in Scheme 23.[120] Reaction of ethyl diazopyruvate with butadiene generated

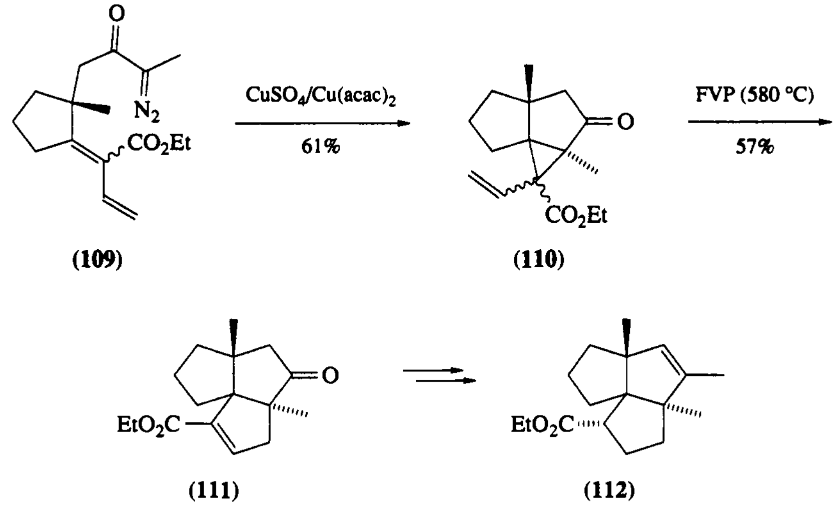

Scheme 22

the *trans*-cyclopropane (**113**), the dihydrooxepine (**114**; presumably derived from the corresponding *cis*-cyclopropane) and the dihydrofuran (**115**). The *trans*-cyclopropane (**113**) was readily converted to the *trans*-divinylcyclopropane (**116**) by a Wittig reaction. Pyrolysis of (**116**) led to the cycloheptadiene (**117**), presumably *via* initial isomerization of (**116**) to the *cis*-divinylcyclopropane. Further transformations on (**117**) generated the tropone natural product, nezukone (**118**).

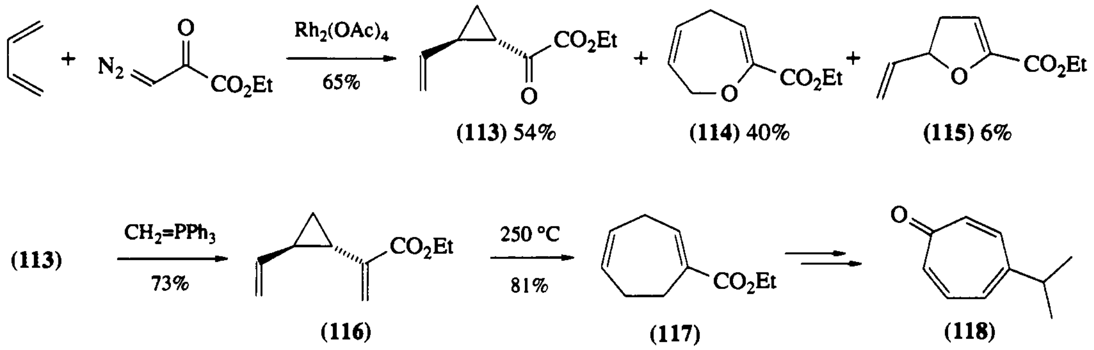

Scheme 23

An elegant application of this chemistry to the formal synthesis of (±)-quadrone has been reported by Piers and coworkers.[78a,121a] Decomposition of ethyl diazoacetate in the presence of the bicyclic structure (**119**) resulted in selective cyclopropanation to form (**120**). Further modification of (**120**) generated the *trans*-divinylcyclopropane (**121**), which on thermolysis followed by desilylation produced the tricyclic system (**122**). Conversion of (**122**) to the ketone (**123**) completed the formal synthesis because (**123**; Scheme 24) had been previously converted to (±)-quadrone.[121b]

Recently, Davies and coworkers have shown that direct formation of *cis*-divinylcyclopropanes is possible by reaction of dienes with vinylcarbenoids, as illustrated in Scheme 25.[27] The reaction of (**26**) with cyclopentadiene gave exclusively the *cis* isomer (**124**) which rearranged to the bicyclo[3.2.1]octadiene system (**125**) under the reaction conditions. The involvement of a divinylcyclopropane intermediate in this reaction was confirmed by using more sterically congested vinylcarbenoids, as this enabled the presumed intermediate to be isolated. The remarkable *cis* selectivity for the cyclopropanation of vinylcarbenoids is in stark contrast to the poor selectivity that is generally observed in cyclopropanations with ethyl diazoacetate.[1,2] The reaction has been applied to intramolecular examples and the results were dependent on diene geometry.[79] A system with a *trans* double bond nearest the tether (**126**) gave rise to a fused cycloheptadiene (**127**) *via* rearrangement of the *cis*-divinylcyclopropane intermediate (**128**), while the system with a *cis* geometry (**129**) gave exclusively the *trans*-divinylcyclopropane (**131**; Scheme 26).

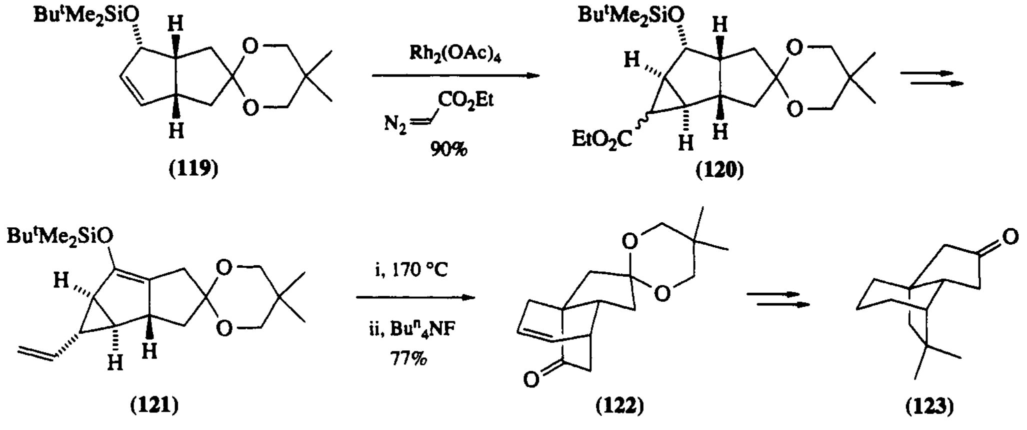
Bu$^t$Me$_2$SiO
H
(119)
Rh$_2$(OAc)$_4$
N$_2$=CHCO$_2$Et
90%
(120)
EtO$_2$C
(121)
i, 170 °C
ii, Bu$^n_4$NF
77%
(122)
(123)

Scheme 24

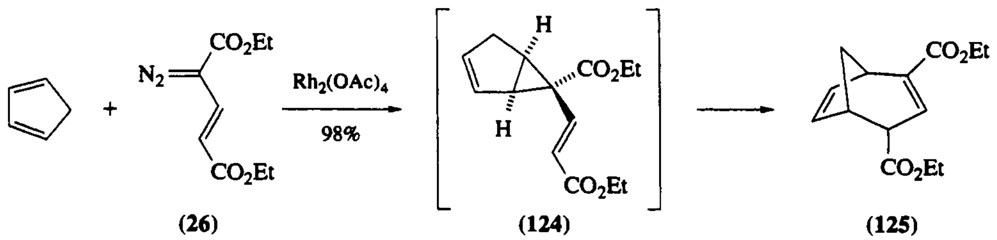
CO$_2$Et
N$_2$
(26)
Rh$_2$(OAc)$_4$
98%
H
(124)
(125)

Scheme 25

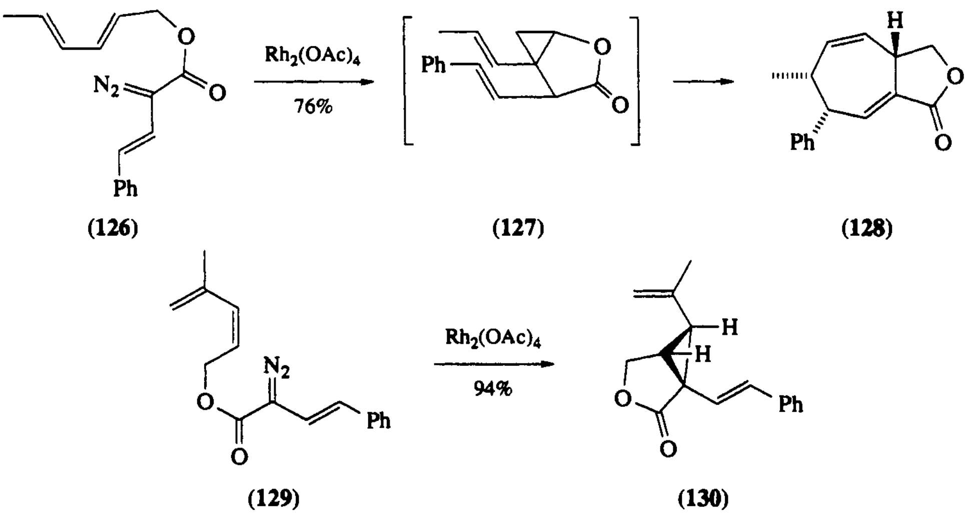
N$_2$
Ph
(126)
Rh$_2$(OAc)$_4$
76%
(127)
(128)
(129)
Rh$_2$(OAc)$_4$
94%
H
(130)

Scheme 26

## 4.8.5 ADDITION OF KETOCARBENOIDS TO ALKYNES

The reaction of ketocarbenoids with alkynes is a direct method for the synthesis of functionalized cyclopropenes.[1,122,123] Until quite recently copper catalysis was generally used and the reactions proceeded in fairly moderate yields, except with terminal alkynes, which failed to generate cyclopropenes due to competing C—H insertions.[1] This limitation could be circumvented, however, by using trimethylsilyl derivatives. This approach is illustrated in the synthesis of (**131**), the unsaturated analog of 1-aminocyclopropanecarboxylic acid, the biosynthetic precursor to ethylene in plants (Scheme 27).[124] The initial cyclopropene (**132**) could be readily desilylated by stirring in aqueous potassium carbonate solution at room temperature.

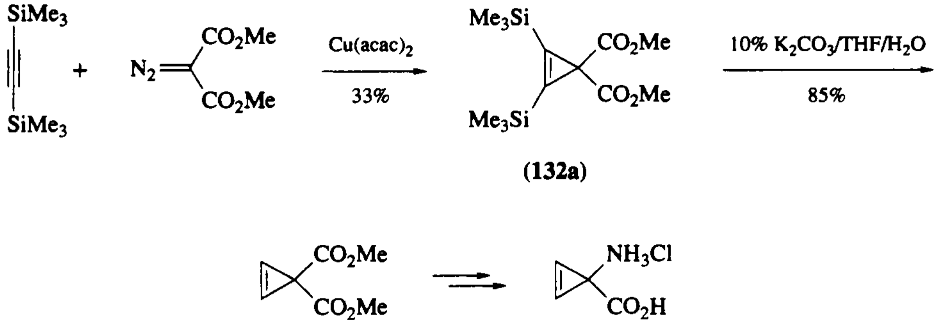

**(132a)**

**(131)**

**Scheme 27**

Over the last few years it has become clear that rhodium(II) acetate is more effective than the copper catalysts in generating cyclopropenes.[125,126] As shown in Scheme 28,[125] a range of functionality, including terminal alkynes, can be tolerated in the reaction with methyl diazoacetate. Reactions with phenylacetylene and ethoxyacetylene were unsuccessful, however, because the alkyne polymerized under the reaction conditions.

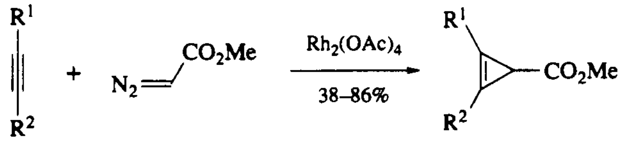

$R^1 = Bu^n, Bu^t, c\text{-}C_6H_{11}, MeCO_2CH_2, MeOCH_2, Et; R^2 = H, Et, MeOCH_2$

**Scheme 28**

Depending on the carbenoid and alkyne used, furans rather than cyclopropenes may become the predominant products. Indeed, copper salts are known to catalyze the thermal rearrangement of cyclopropenyl esters to furans (equation 31).[127] In systems where a dipolar intermediate is stabilized, furan formation is prevalent. Copper-catalyzed decomposition of ethyl diazopyruvate in the presence of 3-hexyne generated the furan (**133**) in moderate yield (equation 32).[26a] With an unsymmetrical alkyne, a mixture of furans was formed. In contrast, carbenoids with two electron-withdrawing groups are more regioselective in their reaction with unsymmetrical alkynes. Reaction of ethyl diazoacetoacetate with phenylacetylene produced the furan (**134**), in which the keto carbonyl has been incorporated into the ring (equation 33).[128] Alternatively, fused furans (**135**) could be prepared from the copper-catalyzed decomposition of the dibromo compound (**136**) in the presence of alkynes (equation 34).[9] The formation of furans could conceivably be derived directly or *via* an unstable cyclopropene precursor and unless the cyclopropene has been observed or its stability under the reaction conditions determined, definitive conclusions about the actual reaction pathway cannot be made.

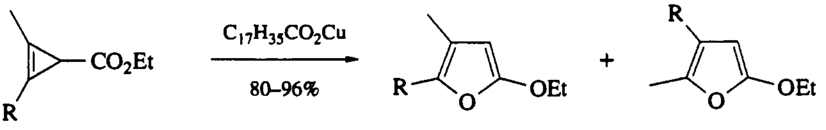

$R = Ph, Bu^n, Bu^t$

(31)

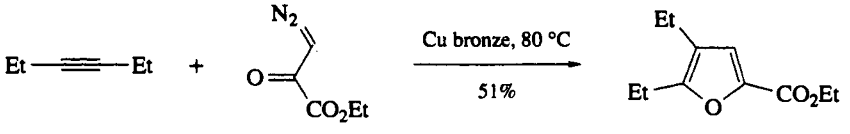

**(133)** (32)

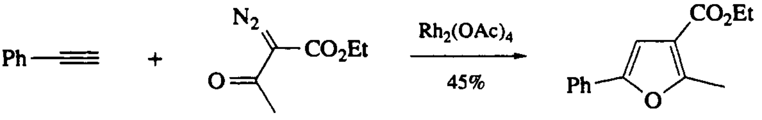

**(134)** (33)

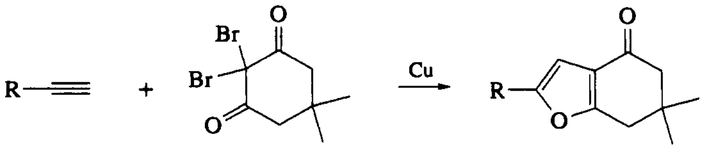

**(136)** **(135)** (34)

## 4.8.6 ADDITION OF KETOCARBENOIDS TO AROMATIC SYSTEMS

### 4.8.6.1 Benzenes

The reaction of carbenoids with aromatic systems was first reported by Buchner and coworkers in the 1890s.[6] The reaction offers a direct entry to cycloheptatrienes and has been used to synthesize tropones, tropolones and azulenes.[6] Neither the thermal nor copper-catalyzed reactions, however, proceed in good yield. The problems associated with these transformations were clearly demonstrated in a recent reexamination of the thermal decomposition of ethyl diazoacetate in excess anisole (**137**).[129] A careful analysis of the reaction mixture revealed the presence of seven components (**138**–**144**) in 34% overall yield (Scheme 29). The cycloheptatrienes (**138**)–(**142**) were considered to be formed by cyclopropanation followed by electrocyclic ring opening of the resulting norcaradienes. A mixture of products arose because the cyclopropanation was not regioselective and, also, the initially formed cycloheptatrienes were labile under the reaction conditions.

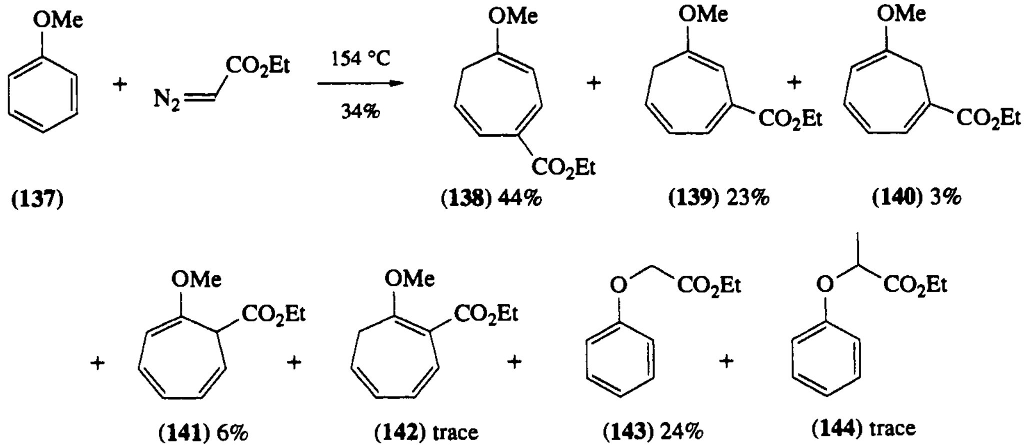

**(137)** **(138)** 44% **(139)** 23% **(140)** 3%

**(141)** 6% **(142)** trace **(143)** 24% **(144)** trace

Scheme 29

A considerable improvement in the efficiency of the reaction of alkyl diazoacetates with benzenoid systems occurred with the development of rhodium(II) carboxylates as catalysts.[16d] As can be seen in the reaction with benzene, rhodium(II) salts with electron-withdrawing ligands were far superior (Scheme

30), which is presumably because a highly electrophilic carbenoid is required for good interaction with the aromatic system. A particular advantage of rhodium catalysis is that the reaction conditions are quite mild and sigmatropic rearrangement of the rather labile cycloheptatrienes (**145**) usually can be avoided. The carbenoid in these reactions was not particularly selective. With substituted benzenes mixtures were invariably formed (Scheme 31) and selectivity between electronically different aromatic systems was minimal. Alkyl, methoxy and halo substituents could be tolerated on the aromatic ring. Another interesting feature of this system is that steric effects on the carbenoid are significant because as the ester increases in size, from methyl to ethyl to *t*-butyl, a steady decrease in yield was observed.

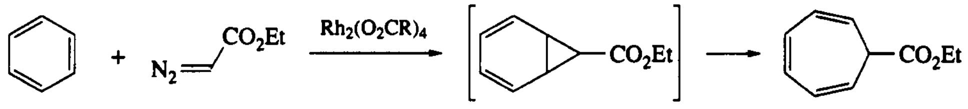

(**145**)

| *R* | *Yield* (%) |
|---|---|
| $CF_3$ | 100 |
| Ph | 87 |
| $MeOCH_2$ | 30 |
| Me | 7 |
| $Bu^t$ | 5 |

Scheme 30

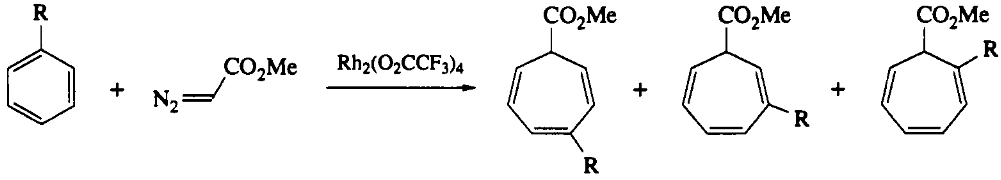

(**146a**) (**146b**) (**146c**)

| *R* | *Yield* (%) | (**146a**):(**146b**):(**146c**) |
|---|---|---|
| Me | 95 | 58:24:18 |
| OMe | 73 | 60:9:31 |
| Cl | 72 | 80:15:5 |
| F | 46 | 80:12:8 |

Scheme 31

A similar transformation was observed with the rhodium trifluoroacetate catalyzed decomposition of diazo ketones in the presence of benzene (Scheme 32).[130] The cycloheptatrienes (**147**) formed in this case were acid labile and could be readily rearranged to benzyl ketones (**148**) on treatment with TFA. The reaction was effective even when the side chain contained reactive halogen and cyclopropyl functionality, but competing intramolecular reactions occurred with benzyl diazomethyl ketone. A more exotic example of this reaction is the rhodium(II) trifluoroacetate catalyzed decomposition of the diazopenicillinate (**149**) in the presence of anisole, which resulted in the formation of two cycloheptatriene derivatives (**150**) and (**151**) (equation 35).[131]

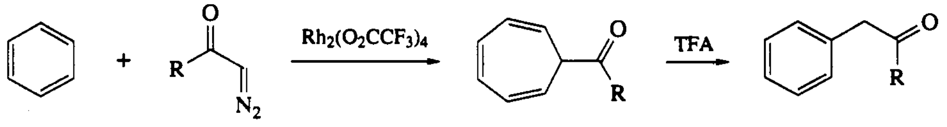

(**147**) (**148**)

Scheme 32

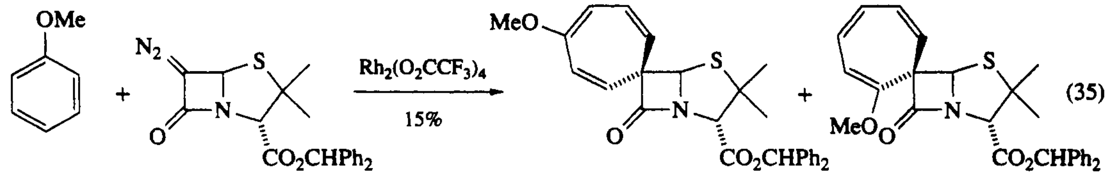
OMe
$N_2$
S
N
O
$CO_2CHPh_2$
$Rh_2(O_2CCF_3)_4$
15%
MeO
S
N
O
$CO_2CHPh_2$
MeO
S
N
O
$CO_2CHPh_2$

(35)

**(149)** **(150)** 87% **(151)** 13%

The products formed in these reactions are very sensitive to the functionality on the carbenoid. A study of Schechter and coworkers[132] using 2-diazo-1,3-indandione (**152**) nicely illustrates this point. The resulting carbenoid would be expected to be more electrophilic than the one generated from alkyl diazoacetate and consequently rhodium(II) acetate could be used as catalyst. The alkylation products (**153**) were formed in high yields without any evidence of cycloheptatrienes (Scheme 33). As can be seen in the case for anisole, the reaction was much more selective than the rhodium(II)-catalyzed decomposition of ethyl diazoacetate (Scheme 31), resulting in the exclusive formation of the *para* product. Application of this alkylation process to the synthesis of a novel *p*-quinodimethane has been reported.[133] Similar alkylation products were formed when dimethyl diazomalonate was decomposed in the presence of aromatic systems, but as these earlier studies[134] were carried out either photochemically or by copper catalysis, side reactions also occurred, as can be seen in the reaction with toluene (equation 36).

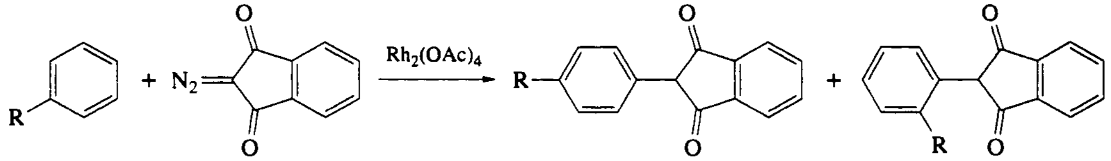
R
$N_2$
O
O
$Rh_2(OAc)_4$
R
O
O
R
O
O

**(152)** **(153a)** **(153b)**

| *R* | *Yield* (%) | **(153a)**:**(153b)** |
|---|---|---|
| H | 95 | – |
| OMe | 73 | 100:0 |
| Me | 86 | 75:25 |
| Cl | 62 | 75:25 |
| Br | 21 | – |
| $NO_2$ | 0 | – |

**Scheme 33**

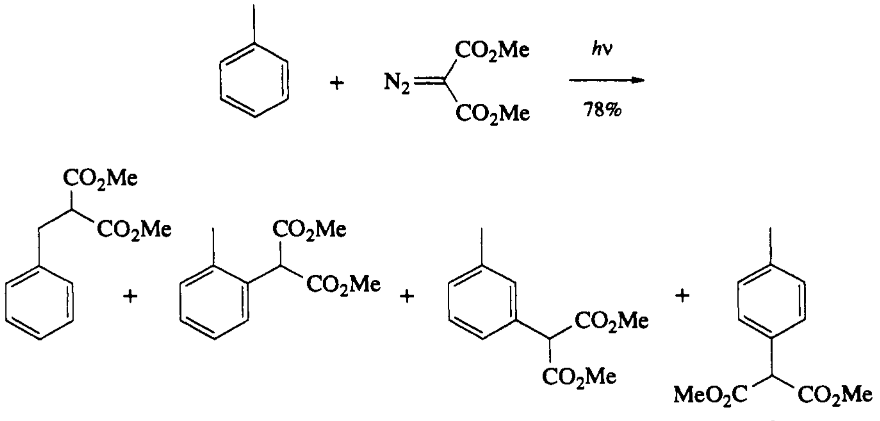
$N_2$
$CO_2Me$
$CO_2Me$
*hv*
78%
$CO_2Me$
$CO_2Me$
$CO_2Me$
$CO_2Me$
$CO_2Me$
$CO_2Me$
$MeO_2C$
$CO_2Me$

(36)

33% 40% 4% 23%

The intramolecular reaction between diazo ketones and benzenes is an effective way to generate a range of bicyclic systems.[7] The earlier copper-based catalysts have largely been superseded by rhodium(II) salts. Unlike the case in the intermolecular reactions, rhodium(II) acetate is the catalyst that has been most commonly used. Studies by McKervey,[135,136] however, indicated that rhodium(II) mandelate, which would be expected to generate a slightly more electrophilic carbenoid than rhodium(II) acetate, often gave improved yields.

Decomposition of 1-diazo-4-arylbutan-2-ones offers a direct entry to bicyclo[5.3.0]decatrienones and the approach has been extensively used by Scott and coworkers to synthesize substituted azulenes.[137] Respectable yields were obtained with copper catalysis,[137] but a more recent study[24] showed that rhodium(II) acetate was much more effective, generating bicyclo[5.3.0]decatrienones (**154**) under mild conditions in excess of 90% yield (Scheme 34). The cycloheptatrienes (**154**) were acid labile and on treatment with TFA rearranged cleanly to 2-tetralones (**155**), presumably *via* norcaradiene intermediates (**156**). Substituents on the aromatic ring exerted considerable effect on the course of the reaction. With *m*-methoxy-substituted systems the 2-tetralone was directly formed. Thus, it appeared that rearrangement of (**156**) to (**154**) was kinetically favored, but under acidic conditions or with appropriate functionality, equilibration to the 2-tetralone (**155**) occurred.

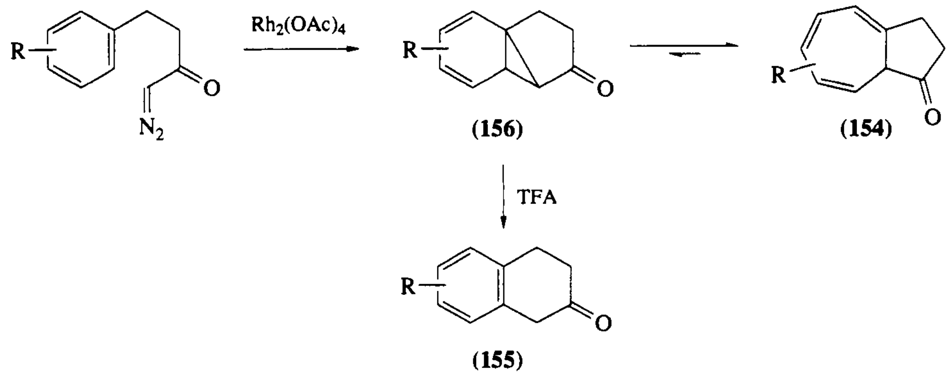

(**156**) (**154**) (**155**)

R = H, 4-Me, 4-OMe, 4-OAc, 2-Me, 2-OMe, 3-OAc, 2,3-$(OMe)_2$, 3,4,5,-$(OMe)_3$

Scheme 34

This methodology has been applied to the synthesis of the bicyclic system (**157**),[135] an advanced intermediate previously used in the synthesis of confertin.[138] Reaction of the diazo compound (**158**) with rhodium(II) mandelate gave an equilibrating mixture of the norcaradiene (**159**) and the fused cycloheptatriene (**160**) in essentially quantitative yield (Scheme 35). The mixture of (**159**) and (**160**) was converted to (**157**) in six steps in 20% overall yield.

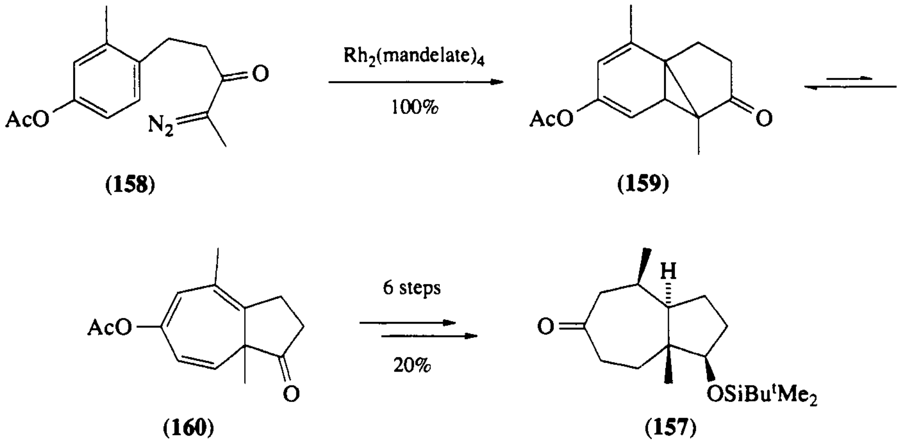

(**158**) (**159**) (**160**) (**157**)

Scheme 35

Further extensions of this chemistry have been reported, leading to more complex aromatic systems. Decomposition of the biphenyl (**161**) led to the trienone (**162**; Scheme 36).[136] Treatment of (**162**) with acid generated the fused cycloheptanone (**163**), but an alternative aromatization to (**164**) occurred on exposure of (**162**) to triethylamine. A similar reaction with the lower homolog efficiently generated a phenanthrol, but the higher homolog failed to produce a colchicine framework. Naphthalene derivatives have also been generated through intramolecular reactions.[139]

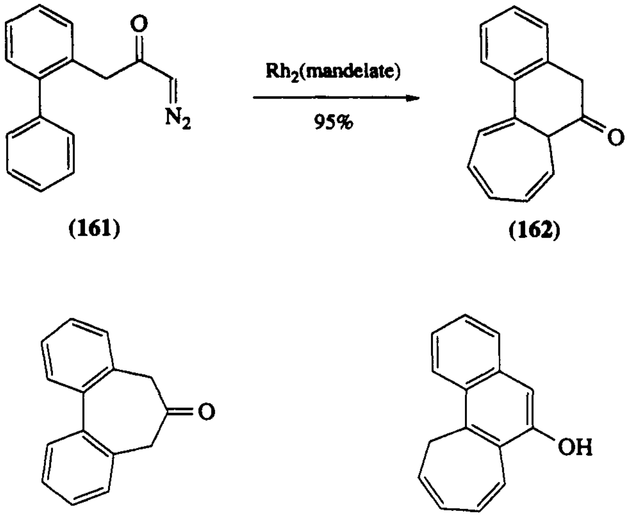

**(161)** **(162)**

**(163)** **(164)**

**Scheme 36**

Intramolecular reactions using lower homologs invariably result in substitution products because competitive formation of bicyclo[5.2.0]nonatrienones is unfavorable due to the strained ring. Consequently, reaction of (**165**) with rhodium(II) acetate cleanly generated (**166**) in 98% yield (equation 37).[140] Aliphatic C—H insertion can be a competing reaction with aromatic substitution, and which reaction occurs appears to be very sensitive to steric and electronic effects.[100] Alkylation also occurred with phenolic diazo ketones (**167**), leading to the formation of spirodienones (**168**; Scheme 37).[141] Further reactions on (**170**) allowed ready access to (±)-solavetivone (**169**).[141b]

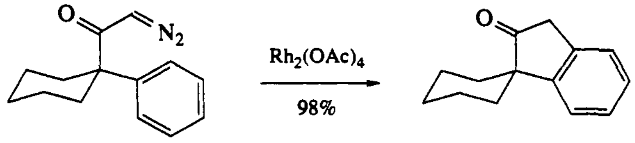

**(165)** **(166)** (37)

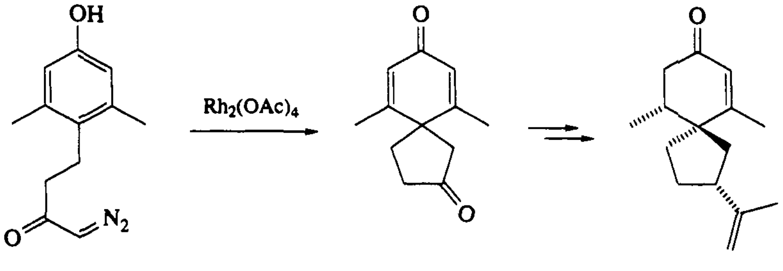

**(167)** **(168)** **(169)**

**Scheme 37**

The role of the catalyst is often crucial in determining the outcome of this chemistry and this is nicely illustrated in Scheme 38. Decomposition of (**170**) with rhodium(II) acetate resulted in insertion into the benzene ring, forming (**171**), but with palladium(II) acetate a different insertion occurred to give (**172**).[142]

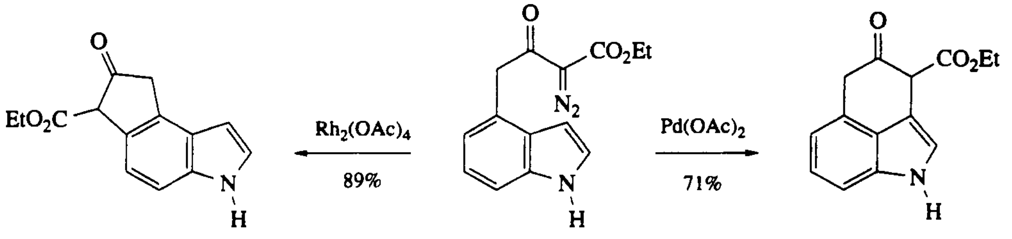

(**171**) (**170**) (**172**)

Scheme 38

Cyclizations can occur with heteroatoms present in the tether as long as the groups are not strongly nucleophilic. Decomposition of α-diazo-β-arylmethanesulfonyl esters (**173**) resulted in the formation of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides (**174**; equation 38),[143] which are valuable precursors to *o*-quinodimethanes. Reaction with *N*-aryldiazoamides (**175**) has been shown to be a useful method for preparing 2(3*H*)-indolinones (**176**; equation 39),[22a] while reaction of α-diazo-β-keto esters (**177**) has been developed as a process to synthesize 3-acetylbenzofuran-2(3*H*)-ones (**178**; equation 40).[144]

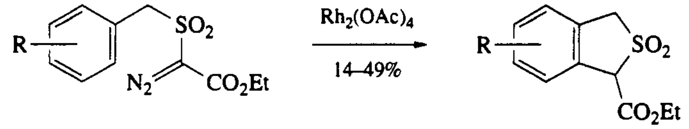

(**173**) (**174**) (38)

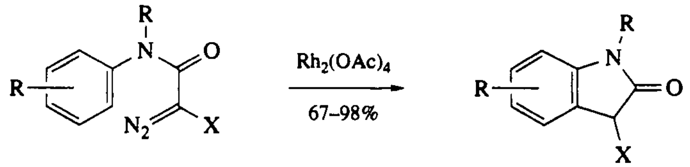

(**175**) (**176**) (39)

X = H, MeCO

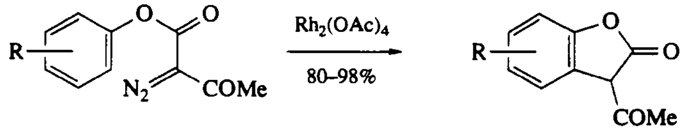

(**177**) (**178**) (40)

When the heteroatom is contained within a longer tether, fused cycloheptatrienes once again become viable products. Rhodium(II) acetate catalyzed decomposition of *N*-benzyldiazoamides (**179**; X = H)[22b] formed cycloheptatrienes (**180**) in excellent yield as long as the R group was bulky such as *t*-butyl (Scheme 39). The carbenoid structure played an important role as reaction with *N*-benzyldiazoacetoacetamides (**179**; X = COMe)[22c] resulted in an entirely different reaction pathway, generating β-lactams (**181**) by aliphatic C—H insertion. Subtle conformational effects were also shown to be significant in this reaction because with (**182**) the predominant product (**183a**) arose from capture of the carbenoid by the inherently less reactive benzene ring (equation 41).[22b] Similar reactions have been carried out on systems with an oxygen tether[145,146] and these generated a mixture of fused cycloheptatrienes and chromanones, formal C—H insertion products.

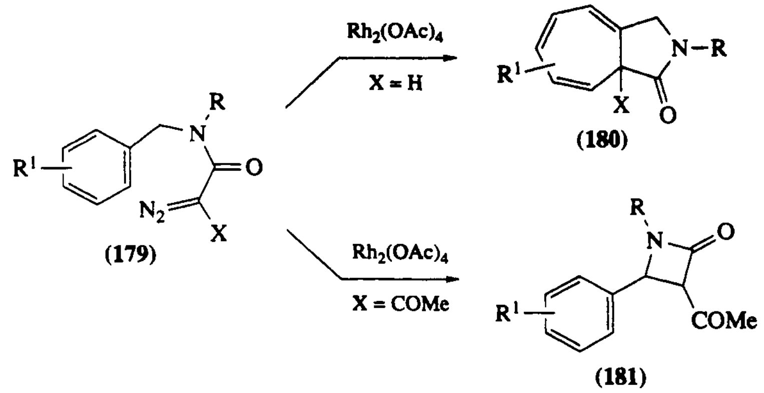

Scheme 39

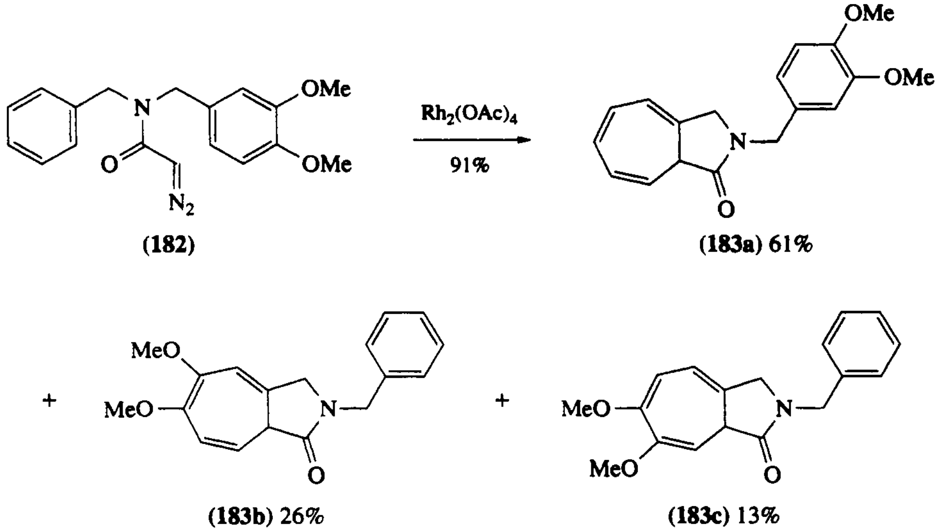

(41)

The overall mechanistic picture of these reactions is poorly understood, and it is conceivable that more than one pathway may be involved. It is generally considered that cycloheptatrienes are generated from an initially formed norcaradiene, as shown in Scheme 30. Equilibration between the cycloheptatriene and norcaradiene is quite facile and under acidic conditions the cycloheptatriene may readily rearrange to give a substitution product, presumably *via* a norcaradiene intermediate (Schemes 32 and 34). When alkylated products are directly formed from the intermolecular reaction of carbenoids with benzenes (Scheme 33 and equation 36) a norcaradiene considered as an intermediate; alternatively, a mechanism may be related to an electrophilic substitution may be involved leading to a zwitterionic intermediate. A similar intermediate has been proposed[143] in the intramolecular reactions of carbenoids with benzenes, which result in substitution products (equations 37–40). It has been reported,[144] however, that a considerable kinetic deuterium isotope effect was observed in some of these systems. Unless the electrophilic attack is reversible, this would indicate that a C—H insertion mechanism is involved in the rate-determining step.

### 4.8.6.2 Furans

The reaction of carbenoids with furans usually leads to the unravelling of the heterocycle, resulting in the formation of differentially functionalized dienes in good yield.[147–151] A recent reexamination of the reaction between ethyl diazoacetate with furan revealed the formation of four products, a furanocyclopropane (**184**), two isomeric dienes (**185** and **186**) and a trace of an alkylated product (**187**), in 65% overall yield (Scheme 40).[152] The furanocyclopropane (**184**) was unstable, however, and on prolonged standing rearranged cleanly to the (*Z,E*)-diene (**185**). Also, both the (*Z,E*)- and (*Z,Z*)-dienes (**185** and **186**) cleanly rearranged to the (*E,E*)-isomer (**188**) on treatment with iodine. Thus, the reaction could be used to prepare predominantly the (*Z*,*E*)- or (*E*,*E*)-products (**185** or **188**) by appropriate choice of work-up conditions. Furans with electron-withdrawing groups such as esters and unsaturated esters could be tolerated, but with vinylfurans competing cyclopropanation of the vinyl group occurred.[153]

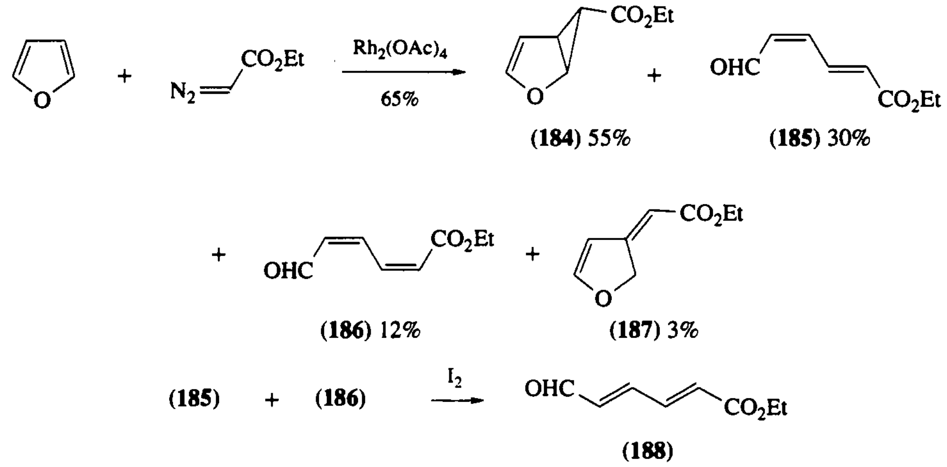
O
+
N$_2$
CO$_2$Et
Rh$_2$(OAc)$_4$
65%
CO$_2$Et
O
+
OHC
CO$_2$Et
(184) 55%
(185) 30%
+
OHC
CO$_2$Et
+
CO$_2$Et
O
(186) 12%
(187) 3%
(185)
+
(186)
I$_2$
OHC
CO$_2$Et
(188)

Scheme 40

Numerous applications of this chemistry to the synthesis of leukotrienes have been reported, as illustrated for the preparation of 12-hydroxyeicosatetraenoic acid (**189**; Scheme 41).[154] Reaction of the carbenoid precursor (**190**) with furan in the presence of rhodium(II) acetate generated a furanocyclopropane, which on standing reverted to predominantly the (*Z*,*E*)-isomer (**191**). Reduction of the dicarbonyl compound (**191**) gave the diol (**192**), which was then selectively converted to the bromide (**193**). Subsequently, (**193**) was coupled with the alkynide (**194**), followed by Lindlar reduction and deprotection to produce (**189**). The overall procedure is quite general and has been applied to a range of related compounds (**195–199**)[155–158] and useful synthetic fragments (**200** and **201**).[152]

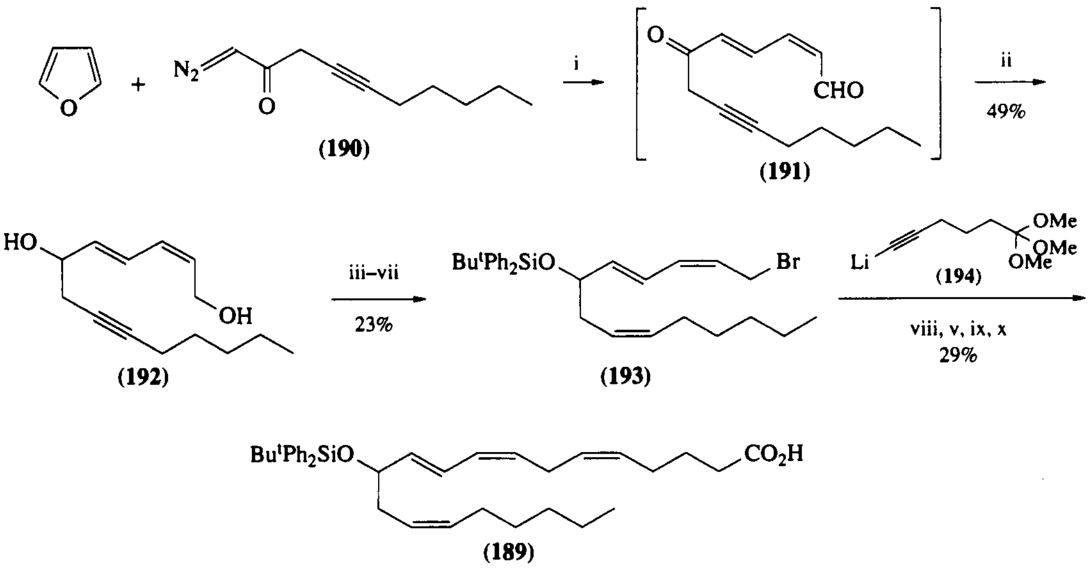
O
+
N$_2$
O
(190)
i
O
CHO
(191)
ii
49%
HO
OH
(192)
iii–vii
23%
Bu$^t$Ph$_2$SiO
Br
(193)
Li
OMe
OMe
OMe
(194)
viii, v, ix, x
29%
Bu$^t$Ph$_2$SiO
CO$_2$H
(189)

i, Rh$_2$(OAc)$_4$; ii, NaBH$_4$, CeCl$_3$; iii, ($p$-(MeO)C$_6$H$_4$)Ph$_2$Cl, pyridine; iv, Bu$^t$Ph$_2$SiCl, imidazole, DMF; v, Lindlar H$_2$; vi, 80% AcOH; vii, DIPHOS, CBr$_4$; viii, (**194**), CuI, THF, HMPA; ix, Bu$^n_4$NF, THF; x, HO$^-$

Scheme 41

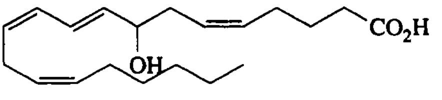

**(195)**

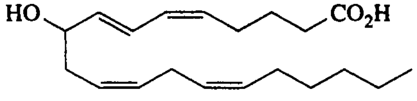

**(196)**

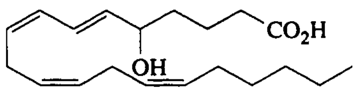

**(197)**

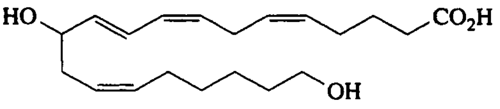

**(198)**

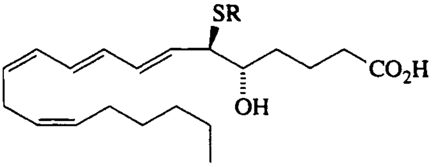

**(199)**

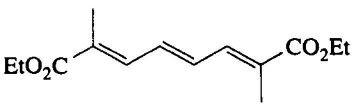
EtO2C
CO2Et

**(200)**

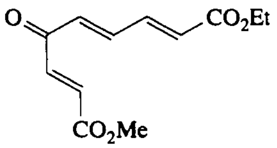
O
CO2Et
CO2Me

**(201)**

Reaction of vinylcarbenoids with furans offers another level of complexity because the furanocyclopropanes in this case would be divinylcyclopropanes capable of a Cope rearrangement as well as electrocyclic ring opening to trienes.[27b,c] As illustrated in Scheme 42, the product distribution was dependent on the furan structure. With 2,5-disubstituted furans [3.2.1]-bicyclic systems (**202**) were exclusively formed, but with furan or 2-substituted furans, trienes (**203**) were also produced.

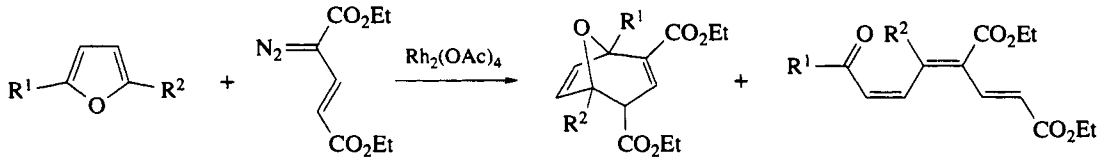
R1
O
R2
+
N2
CO2Et
CO2Et
Rh2(OAc)4
O
R1
CO2Et
R2
CO2Et
+
O
R2
R1
CO2Et
CO2Et

**(202)** **(203)**

| *R¹* | *R²* | **(202)** (%) | **(203)** (%) |
|---|---|---|---|
| Me | Me | 70 | 0 |
| H | H | 62 | 26 |
| Me | H | 8 | 74 |
| MeO | H | 0 | 92 |

**Scheme 42**

A similar unravelling of the heterocyclic ring occurred in intramolecular reactions with furans,[79b,159–161] leading to cyclic 1,4-diacyl-1,3-butadienes (**204**; equation 42)[159] and (**205**; equation 43).[79b] The ideal size for the tether was five, but less efficient capture of the carbenoid was also possible with six- and seven-membered rings. With the 3-furanyl derivative (**206**), the acid labile structure (**207**) was formed, which readily rearranged to *p*-hydroxyphenylacetaldehyde (**208**; Scheme 43).[161]

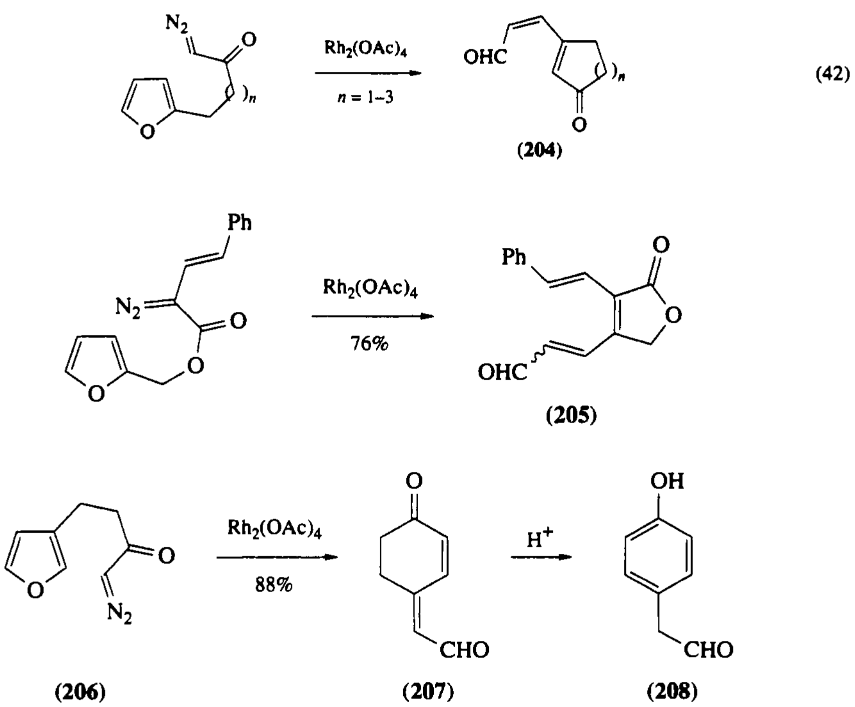

Scheme 43

### 4.8.6.3 Pyrroles

The reaction of ketocarbenoids with pyrroles leads to either substitution or cyclopropanation products, depending on the functionality on nitrogen. With *N*-acylated pyrrole (**209**) reaction of ethyl diazoacetate in the presence of copper(I) bromide generated the 2-azabicyclo[3.1.0]hex-3-ene system (**210**) and some of the diadduct (**211**; Scheme 44).[162,163] On attempted distillation of (**210**) in the presence of copper(I) bromide rearrangement to the 2-pyrrolylacetate (**212**) occurred, which was considered to proceed through the dipolar intermediate (**213**). In contrast, on flash vacuum pyrolysis (**210**) was transformed to the dihydropyridine (**214**). A plausible mechanism for the formation of (**214**) involved rearrangement of (**210**) to the acyclic imine (**215**), which then underwent a 6π-electrocyclization.

The reaction of *N*-alkylated pyrroles with carbenoids leads exclusively to substitution products. Due to the pharmaceutical importance of certain pyrrolylacetates, the reaction with alkyl diazoacetates (Scheme 45) has been systematically studied using about 50 different catalysts.[13] Both the 2- and 3-alkylated products (**216**) and (**217**) could be formed and the ratio was dependent on the size of the *N*-alkyl group and ester and also on the type of catalyst used. This has been interpreted as evidence that transient cyclopropane intermediates were not involved because if this were the case, the catalyst should not have influenced the isomer distribution. Instead, the reaction was believed to proceed by dipolar intermediates, whereby product control is determined by the position of electrophilic attack by the carbenoid. Similar alkylations with dimethyl diazomalonate gave greater selectivity and yields.[164]

The intramolecular reaction of carbenoids with pyrroles is extremely effective and leads to the formation of heterobicyclic systems in high yield, as can be seen in the simple systems shown in equation (44).[165] The reaction is so favorable that even an alkylcarbenoid capable of hydride migration could be utilized to generate a bicyclic system (**218**), but formation of (**219**) was a competing reaction in this case (equation 45).[166]

Intramolecular carbenoid reactions of pyrrole derivatives have recently been applied in a total synthesis of ipalbidine (**220**; Scheme 46).[167] The carbenoid generated from (**221**) was preferentially captured by the pyrrole ring, producing the indolizidinone (**222**) in 82% isolated yield, with only a trace of the indanone side product (**223**) formed. In four steps (**222**) was readily converted to (**220**) in 13% overall yield.

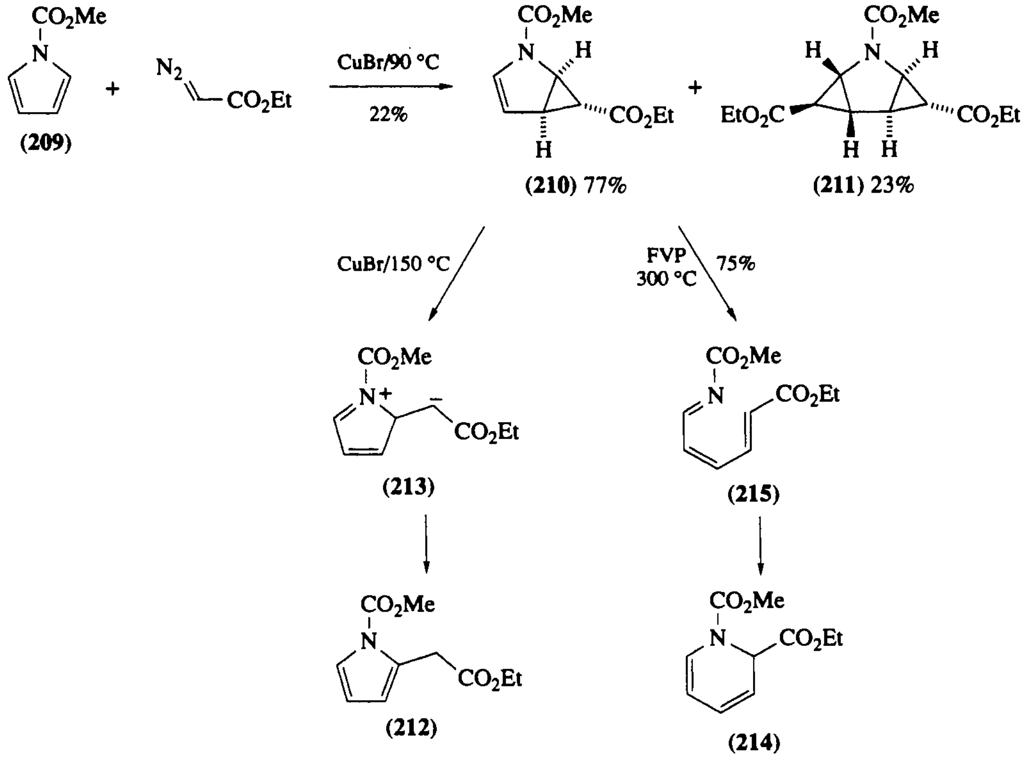
CO2Me
N2
CO2Et
CuBr/90 °C
22%
(209)
(210) 77%
(211) 23%
H
EtO2C
CuBr/150 °C
FVP
300 °C
75%
(213)
(215)
(212)
(214)

**Scheme 44**

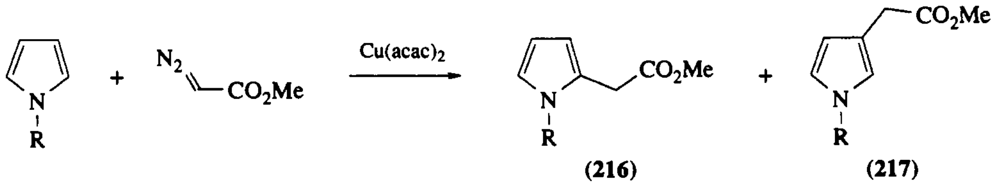
N2
CO2Me
Cu(acac)2
R
(216)
(217)

| *R* | *Yield* (%) | **(216)**:**(217)** |
|---|---|---|
| H | 53 | 94:6 |
| Me | 42 | 92:8 |
| Bu$^t$ | 34 | 0:100 |

**Scheme 45**

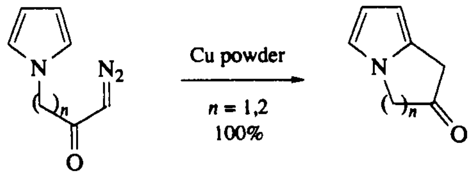
N2
Cu powder
n = 1,2
100%
( )n
O

(44)

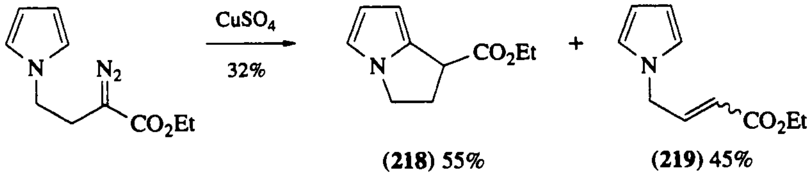
N2
CO2Et
CuSO4
32%
(218) 55%
(219) 45%

(45)

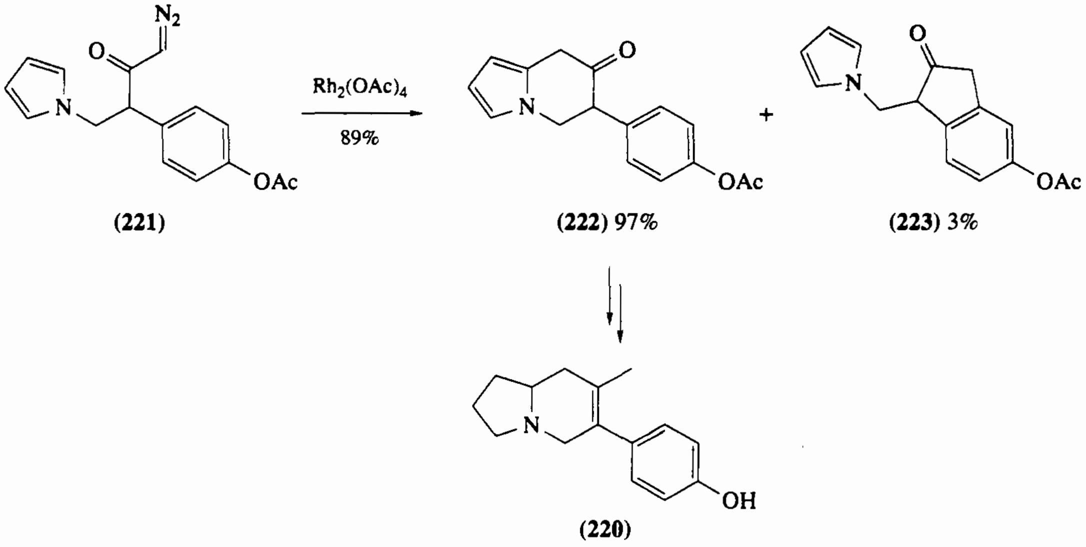

Scheme 46

### 4.8.6.4 Thiophenes

Usually, the initial reaction between ketocarbenoids and thiophenes is formation of a sulfur ylide (**224**).[1,6,7,168–170] Further rearrangement of (**224**) may then lead to products which formally could have been considered to have been derived from direct interaction of the carbenoid with the π-system. Depending on the functionality, rearrangement of (**224**) to the thiophenocyclopropane (**225**),[170] the dihydrothiopyran (**226**)[168,171] or the substitution product (**227**; Scheme 47)[10a] has been reported. Cross-over experiments have shown[168] that the formation of (**227**) was by an intramolecular process and theoretical calculations have indicated[169] that all three products were probably formed from the common intermediate (**228**). 2-Alkenylthiophenes undergo competing cyclopropanation at the vinyl group.[172] The ylide from 2,5-dichlorothiophene has been used as a carbenoid precursor,[10] but depending on the carbenoid, a 2,3-sigmatropic rearrangement to a 1,4-oxathiocine has been shown to be an alternative reaction pathway.[173] A variety of carbenoid systems have been examined including a penicillin derivative.[131]

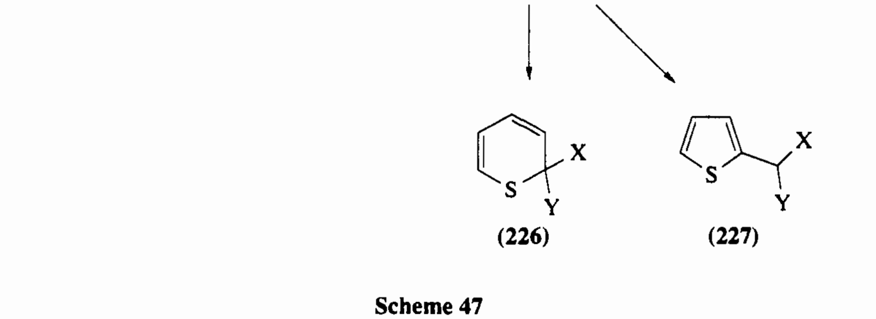

Scheme 47

In intramolecular reactions, direct interaction with the thiophene ring is possible by appropriate positioning of the tether as shown for the 3-substituted thiophene (**229**), which resulted in alkylation to form (**230**) and (**231**) (equation 46).[161a] In contrast, the rhodium(II) acetate catalyzed decomposition of the 2-

substituted thiophene (**232**) resulted in the formation of a mixture of the fused dihydrothiopyran (**233**), presumably generated from an initially formed ylide, and the alkylated product (**234**; equation 47).[174]

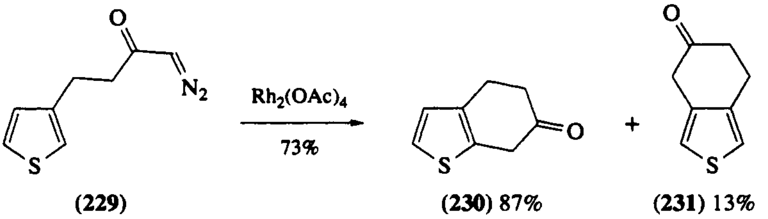

(46)

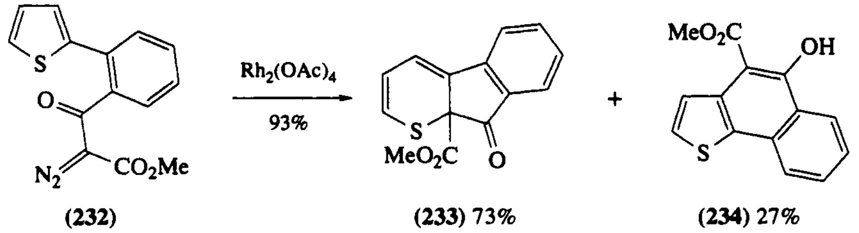

(47)

## 4.8.7 SUMMARY

The novel and varied chemistry of carbenoids has intrigued the practicing synthetic chemist for several decades. The development of rhodium(II) salts as extremely mild catalysts for the generation of metal-stabilized carbenoids has made a remarkable impact on this area of research because much more efficient synthetic pathways based on carbenoids have now become available. With the diverse range of rearrangements possible for cyclopropanes whose generation can now be achieved with high enantioselectivity, the future application of carbenoids to organic synthesis is assured to be an active field.

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# 4.9

# Intermolecular 1,3-Dipolar Cycloadditions

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## 4.9.1 INTRODUCTION

Cycloaddition reactions have figured prominently in both synthetic and mechanistic organic chemistry.[1,2] Current understanding of the underlying principles in this area has grown from a fruitful interplay between theory and experiment.[3] The monumental work of Huisgen and coworkers in the early 1960s led to the general concept of 1,3-dipolar cycloaddition.[4–7] Few reactions rival this process in the number of bonds that undergo transformation during the reaction, producing products considerably more complex than the reactants. Over the years this reaction has developed into a generally useful method of five-membered heterocyclic ring synthesis, since many 1,3-dipolar species are readily available and react with a wide variety of dipolarophiles. 1,3-Dipolar cycloadditions are bimolecular in nature and involve the addition of a 1,3-dipole (**1**) to a multiple π-bond system (**2**) leading to five-membered heterocycles (**3**; equation 1).

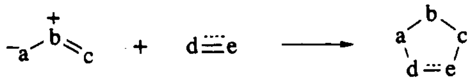

(1) (2) (3)

(1)

## 4.9.2 NATURE OF THE DIPOLE

A 1,3-dipole is basically a system of three atoms over which are distributed four $\pi$-electrons, as in the allyl anion system. The three atoms can be a wide variety of combinations of C, O and N. Table 1 provides a list of the more common 1,3-dipoles possessing carbon, nitrogen and oxygen centers which are known to undergo the dipolar cycloaddition reaction. The dipolarophiles can be virtually any double or triple bond. The term 1,3-dipole arose because in valence bond theory such compounds can only be described in terms of dipolar resonance contributors, as shown for diazomethane (Scheme 1). The extreme 1,3-dipolar forms with their complementary nucleophilic and electrophilic centers readily explain the tendency to undergo addition to $\pi$-bonds. Indeed, it must be possible to write 1,3-dipolar forms for all such species that undergo this type of addition. Significant computational efforts have been directed toward characterization of 1,3-dipoles and the literature in this area has recently been reviewed by Houk and Yamaguchi.[8]

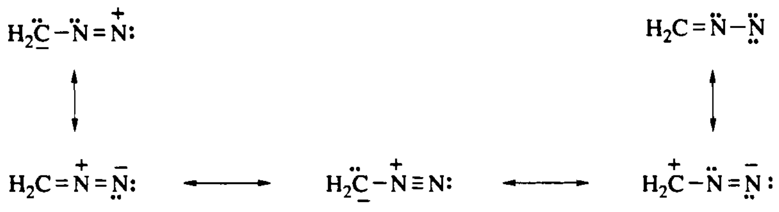

Scheme 1

## 4.9.3 MECHANISTIC CONSIDERATIONS

Huisgen and coworkers have systematically studied the mechanism of 1,3-dipolar cycloadditions.[4–7] In the majority of 1,3-cycloadditions, the reaction rate is not markedly influenced by the dielectric constant of the solvent medium in which the reaction is conducted. The independence of solvent polarity, the very negative entropies of activation and the stereospecificity and regiospecificity point to a highly ordered transition state.[7] In most 1,3-dipolar cycloaddition reactions, when two isomers are possible as a result of the use of unsymmetrical reagents, one isomer usually predominates, often to the exclusion of the other. The principal question that arises when considering the regiospecificity of the 1,3-dipolar additions is whether the two new $\sigma$-bonds formed on addition of the 1,3-dipole to the dipolarophile are formed simultaneously, or one after the other. The mechanism that has emerged from Huisgen's group is that of a single-step, four-center, 'no mechanism' cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent.[9] A symmetry–energy correlation diagram reveals that such a thermal cycloaddition reaction is an allowed process.[10] A proposed alternative mechanism is a two-step process involving a spin-paired diradical intermediate.[11]

The controversy between Huisgen and Firestone concerning the mechanism for 1,3-dipolar cycloaddition is longstanding.[9,11] For nitrile oxide cycloadditions, experimental data have been interpreted either as supportive of a concerted mechanism[9] or in favor of a stepwise mechanism with diradical intermediates.[11] Theory has compounded, rather than resolved, this problem. *Ab initio* calculations on the reaction of fulmonitrile oxide with acetylene predict a concerted mechanism at the molecular orbital level,[12,13] but a stepwise mechanism after inclusion of extensive electron correlation.[14] MNDO predicts a stepwise mechanism with a diradical intermediate.[15] The existence of an extended diradical intermediate such as (**4**; Scheme 2) has been postulated by Firestone in order to account for the occasional formation of 1,4-addition products such as the oxime (**5**).[11] Of course, the intermediates (**4**) and (**5**) for the Firestone mechanism do not correspond to the initial transition states in Firestone's theory. These are attained prior to the formation of, and at higher energy than, the intermediates.

**Table 1** Classification of 1,3-Dipoles Consisting of Carbon, Nitrogen and Oxygen Centers

| | | |
|---|---|---|
| | *Propargyl–Allenyl Type* | |
| *Nitrilium betaines* | 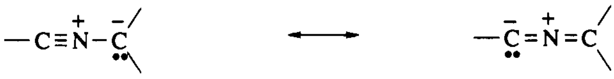 | Nitrile ylides |
| | 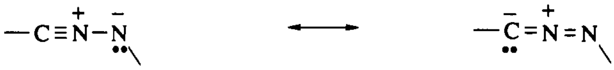 | Nitrile imines |
| | 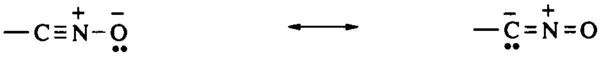 | Nitrile oxides |
| *Diazonium betaines* | 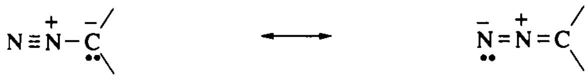 | Diazoalkanes |
| | 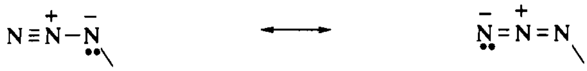 | Azides |
| | 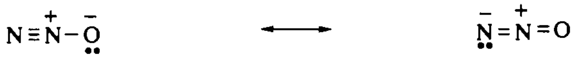 | Nitrous oxide |
| | *Allyl Type* | |
| *Nitrogen function as middle center* | 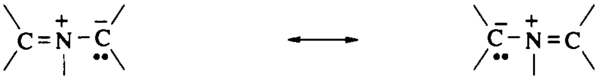 | Azomethine ylides |
| | 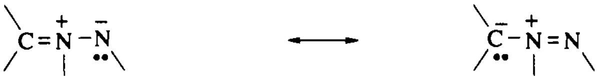 | Azomethine imines |
| | 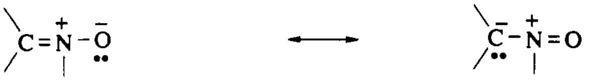 | Nitrones |
| | 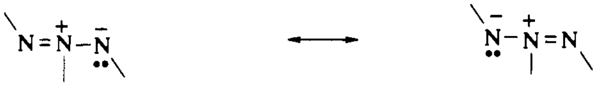 | Azimines |
| | 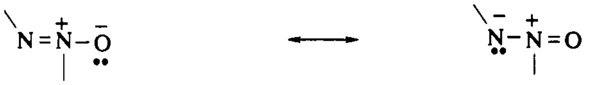 | Azoxy compounds |
| | 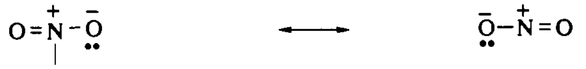 | Nitro compounds |
| *Oxygen atom as middle center* | 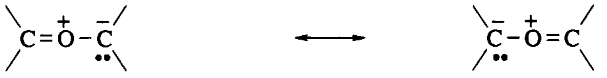 | Carbonyl ylides |
| | 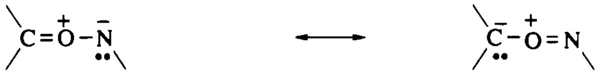 | Carbonyl imines |
| | 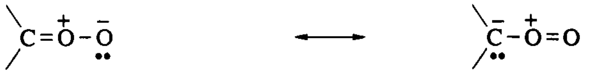 | Carbonyl oxides |
| | 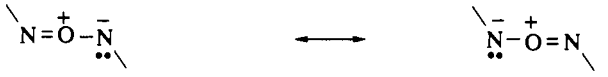 | Nitrosimines |
| | 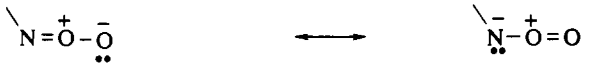 | Nitrosoxides |
| | 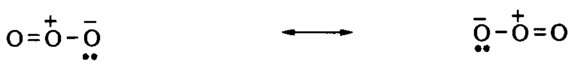 | Ozone |

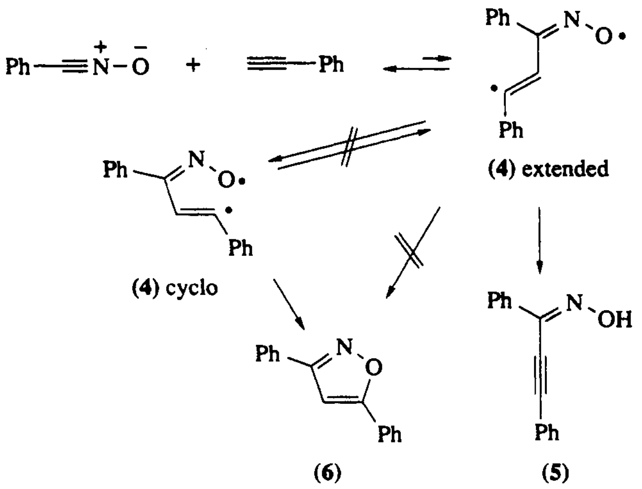

Scheme 2

### 4.9.3.1 Stepwise Mechanism

The stereospecificity observed in many 1,3-dipolar cycloadditions is often considered to be compelling, if not conclusive, evidence for concert in these reactions.[9] However, if the rate constant for rotation ($k_r$) about bond 'a' in diradical intermediate, (**7a**) or (**7b**), was much smaller than the rate constant for cyclization ($k_c$), high stereospecificity would still be observed (Scheme 3).[11] The reported examples of stereospecific 1,3-dipolar cycloadditions involve di-, tri- or tetra-substituted alkenes. Barriers to rotation of simple primary, secondary and tertiary alkyl radicals are only 0–1.2 kcal mol$^{-1}$ (1 kcal = 4.18 kJ),[16] but more highly substituted radicals have barriers to rotation estimated to be as high as 4 kcal mol$^{-1}$.[17] The rate ratio of rotation to ring closure is highly dependent on the degree of substitution at the termini. A deuterium-labeled methylene rotor offers the highest chance to bring about an intermediate in the cycloaddition reaction. This was the reason why Houk and Firestone studied the 1,3-dipolar cycloadditions of 4-nitrobenzonitrile oxide to *cis*- and *trans*-dideuterioethylene (Scheme 3; R = D).[18] These experiments establish that the reaction is ≥98% stereospecific. If a diradical intermediate were formed, the barrier to rotation about bond a would have to be at least 2.3 kcal mol$^{-1}$ higher than the barrier to cyclization. Since the rotational barrier of bond a is that expected for a normal primary radical (*i.e.* ≤0.4 kcal mol$^{-1}$), there can be no barrier to cyclization for the predominant cycloaddition pathway. Thus, the most reasonable mechanism for 1,3-dipolar cycloadditions appears to be a concerted one.

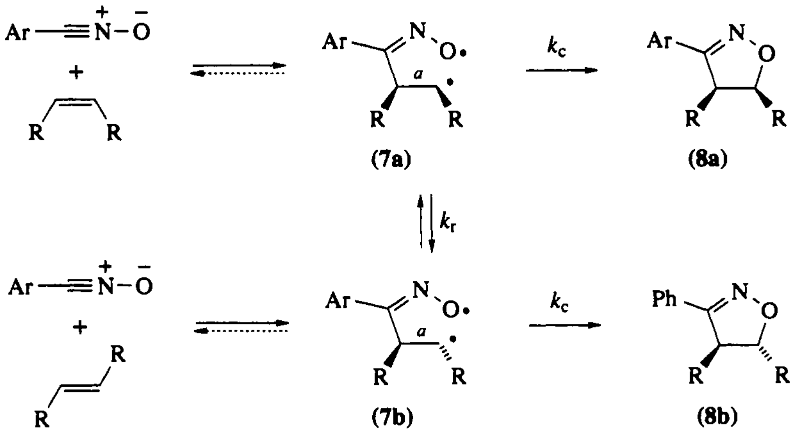

Scheme 3

## 4.9.4 FRONTIER MOLECULAR ORBITAL THEORY

It was only through the application of frontier molecular orbital (FMO) theory that a coherent picture of a mechanism based on a concerted nonsynchronous process emerged.[19,20] This theoretical solution to the mechanistic dilemma went far beyond the usual rationalization of steric and electronic effects in the transition state of a concerted process. The reactivity and regiochemical control in the [3 + 2] dipolar cycloaddition of 1,3-dipole to a substituted alkene can now be understood by consideration of the interactions of the corresponding molecular orbitals. Sustmann has categorized cycloaddition processes into three types.[21] The first (Type 1, Figure 1) involves a dominant interaction between the highest occupied molecular orbital of the dipole [HOMO (dipole)] and the lowest unoccupied molecular orbital of the dipolarophile [LUMO (dipolarophile)]. The majority of Diels–Alder reactions are accommodated by this classification. A second possibility (Type 3) is dominated by the interaction between the LUMO (dipole) and the HOMO (dipolarophile). The ozonization of alkenes may be a reaction that fits this description.[22] In the case of a Type 2 cycloaddition reaction, the similarity of LUMO and HOMO energies in dipole and dipolarophile implies that both HOMO (dipole)–LUMO (dipolarophile) and LUMO (dipole)–HOMO (dipolarophile) interactions may be important in determining reactivity and regiochemistry.

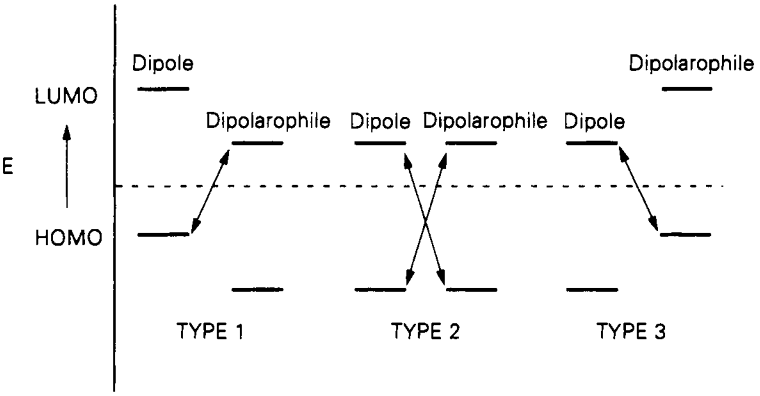

**Figure 1** Frontier molecular orbital classification of cycloaddition reactions

The frontier orbital energies may be obtained from empirical ionization potential (IP) data to give the HOMO energies. The LUMO energies are derived from electron affinity (EA) data. The electron affinities may be estimated by $EA = IP - \Delta E\ (\pi\pi^*) - 4.5$ eV.[23] As the two addends in a cycloaddition reaction approach each other in proper orientation for reaction, an interaction occurs between the reactant frontier molecular orbitals. According to second-order perturbation theory, this interaction leads to a stabilization of the occupied molecular orbital that is inversely proportional to the energy separation between the orbitals involved.[24] The more proximate the orbitals are in energy, the more extensive the interaction. Additionally, the magnitude of interaction depends on the degree of overlap involved, the larger the overlap, the greater the interaction. When reactant HOMO–LUMO interactions occur, the result of the process will be to stabilize the bonding orbital (HOMO) and to destabilize the antibonding orbital (LUMO). When the interaction involves one filled HOMO and one vacant LUMO orbital, the result of the interaction will be to stabilize the system as a whole, since both electrons will enter the orbital of lower energy. Sustmann first applied FMO theory to the 1,3-dipolar cycloadditions,[25] while Houk[19] and Bastide and Henri-Rousseau[26] used it to explain reactivity and regioselectivity of the reaction. In order to predict regioselectivity, it becomes necessary to determine the relative magnitudes of the coefficients in the HOMO and LUMO of the 1,3-dipole and dipolarophile. The favored cycloadduct will be that formed by union of the atoms with the largest coefficients.

## 4.9.5 NONCONCERTED CYCLOADDITIONS

Recently, Huisgen and coworkers have reported on the first unequivocal example of a nonconcerted 1,3-dipolar cycloaddition.[27] Sustmann's FMO model of concerted cycloadditions envisions two cases in which the stepwise mechanism might compete with the concerted one.[21] Two similar HOMO–LUMO interaction energies correspond to a minimum of rate and a diradical mechanism is possible, especially if stabilizing substituents are present. A second case is when the HOMO (1,3-dipole)–LUMO (dipolarophile) is strongly dominant in the transition state. The higher the difference in π-MO energies of reactant, the lower would be the energy contribution by the second HOMO–LUMO interaction. In the extreme case, the interaction of the LUMO of the dipole with the HOMO of the dipolarophile would no longer contribute to the attractive forces in the transition state. The unidirectional electron flow from HOMO (1,3-dipole) to LUMO (dipolarophile) would establish one bond between the reactants and a zwitterionic intermediate would result.

Thiocarbonyl ylides are the 1,3-dipoles with the highest π-MO energies.[28,29] Huisgen described the cycloadditions of 2,2,4,4-tetramethyl-1-oxocyclobutane-3-thione *S*-methylide (**10**) and of adamantanethione *S*-methylide (**11**) to dimethyl 2,3-dicyanofumarate which proceed in a nonstereospecific manner (Scheme 4).[27] The presence of four electron-attracting substituents in the dipolarophile significantly lowers the MO energy of the ethylenic dipolarophile. Thus, in this particular case, the pair of reactants ful-

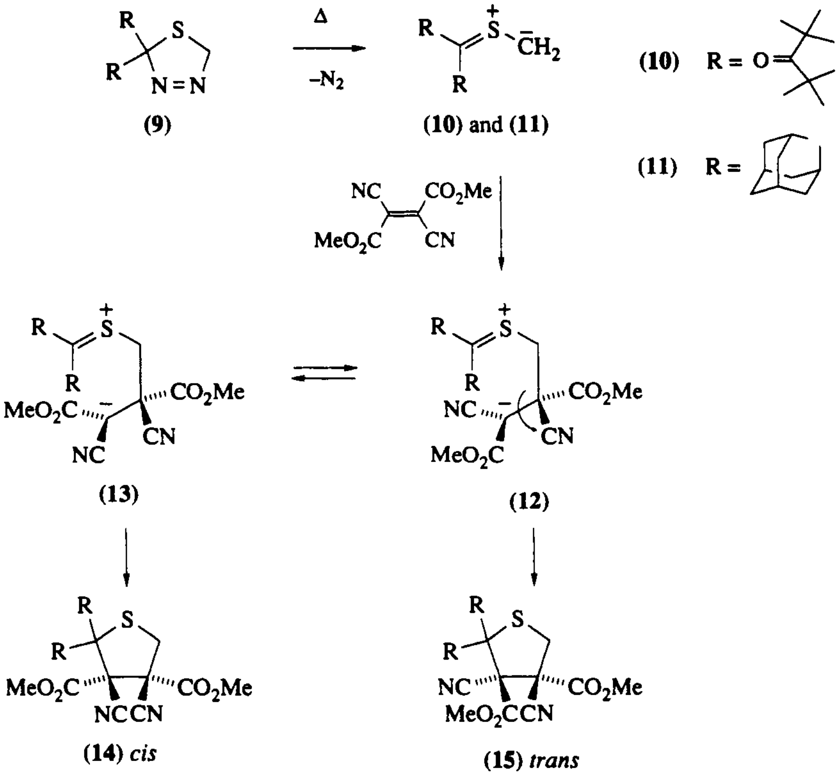

**Scheme 4**

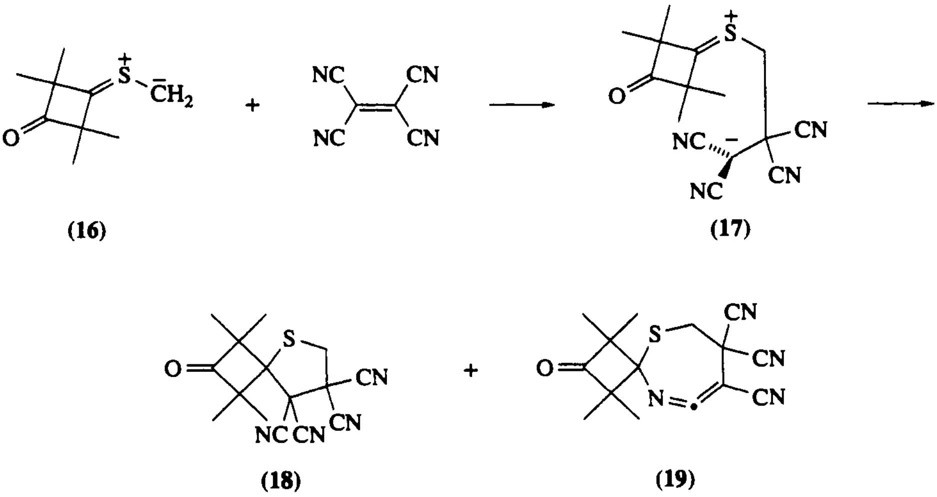

fills the prerequisite of zwitterion formation with its extremely different π-MO energies. Huisgen has also reported that the zwitterionic intermediate (**17**) derived from thiocarbonyl ylide (**10**) and tetracyanoethylene can also undergo competing cyclizations to give the normal cycloadduct (**18**) as well as a seven-membered ketenimine (**19**; Scheme 5). The existence of a discrete intermediate with these thiocarbonyl ylide cycloadditions also testifies to the fact that normal stereospecific 1,3-dipolar cycloadditions follow a fundamentally different mechanism that does not involve any intermediates.

### 4.9.5.1 [4 + 3] Cycloaddition

The principles of orbital symmetry conservation provide a permissive, although not obligatory, theoretical basis for the [3 + 2] concerted mechanism,[10] as do the observations of $[\pi^4 s + \pi^6 s]$ to the exclusion of $[\pi^4 s + \pi^4 s]$ dipolar cycloadditions in the reactions of 1,3-dipoles with trienes.[30] In accordance with the orbital symmetry rules,[10] 1,3-dipoles have been found to react with 1,3-dienes to give vinyl-substituted five-membered rings exclusively.[31] Corresponding [4 + 3] cycloadditions have only been observed in the ozonization of anthracenes,[32] and in one case as an intramolecular variant.[33] Recent work by Mayr has uncovered the first example of a [4 + 3] cycloaddition of a 1,3-dipole with a diene (Scheme 6).[34] The reaction of hexamethylcyclopentadiene (**20**) with *C*,*N*-diphenylnitrone (**21**) afforded a mixture of diastereomeric [3 + 2] cycloadducts (**22**; 32%) as well as a [4 + 3] cycloadduct (**23**; 18%). If the applicability of orbital symmetry is taken for granted, then a concerted $[\pi^4 s + \pi^4 s]$ process cannot account for the formation of (**23**). Mayr has suggested that the isolation of (**23**) requires the intervention of a diradical intermediate (*i.e.* **24**). He also claims that the activation energy for the stepwise mechanism is only 2–3 kcal mol$^{-1}$ greater than that of the concerted process. It remains to be seen whether other examples of nonconcerted dipolar cycloadditions will be discovered in the future.

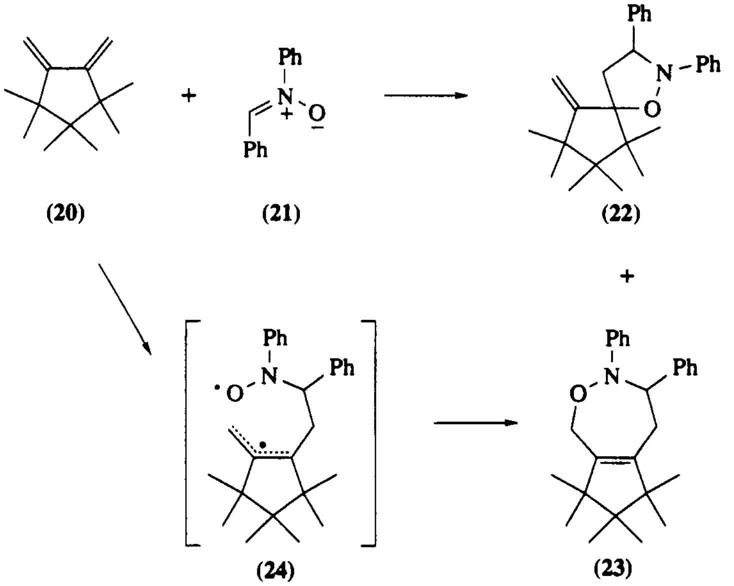

Scheme 6

The aim of the present chapter is to review the characteristics of the dipolar cycloaddition reaction of the most common 1,3-dipoles. The scope, generality and limitations of the cycloaddition reaction will be summarized and the general outline and potential synthetic use for the cycloadditions noted. It is hoped that general and specific points in need of study will be revealed, stimulating further work in this field.

## 4.9.6 1,3-DIPOLAR CYCLOADDITIONS

### 4.9.6.1 Nitrones

Nitrones represent a long-known and thoroughly investigated class of 1,3-dipoles.[35] Through the use of nitrone cycloaddition chemistry, numerous isoxazolidines have been prepared with excellent stereochemical control.[36,37] The 1,3-dipolar cycloaddition reaction of nitrones has attracted considerable attention as a convenient tool for the rapid construction of widely varied classes of natural products (Scheme 7).[38–43] The presence of a nitrogen atom within the isoxazolidine ring has made this heterocycle moiety especially attractive for the synthesis of the β-lactam ring (Scheme 8).[42,43] The key feature of this approach involves a reductive cleavage of the isoxazolidine ring to give a γ-amino alcohol, which undergoes subsequent cyclization with a neighboring methoxycarbonyl group.[44–46]

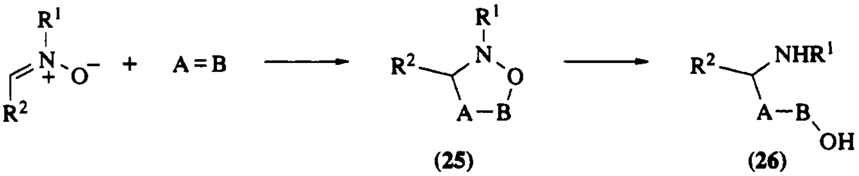

Scheme 7

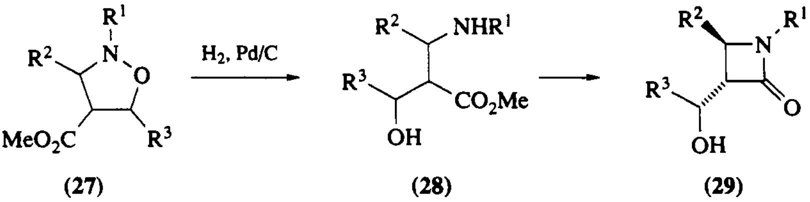

Scheme 8

1,3-Dipolar cycloadditions of nitrones have been reported with a variety of alkenes, alkynes, isocyanates, isothiocyanates, thiocarbonyl compounds, phosphoranes, sulfenes and sulfinyl groups.[35] All these reactions are usually carried out by heating the two reagents together in an inert solvent, and the products are often easily isolated in high yield. It should be pointed out that the cycloadducts are not stable in all cases and sometimes undergo interesting transformations. The regiochemical control exhibited by nitrone–alkene cycloadditions has been accommodated by the development of a FMO treatment.[19–21] Nitrone cycloadditions are believed to be Type 2 processes (Scheme 9). As such, both possible FMO interactions may be significant. The interaction that dominates in a particular case will depend on the nature of both the dipole and the dipolarophile. Most dipolarophiles undergo cycloaddition to give 5-substituted isoxazolidines with high regioselectivity. As the ionization potential of the nitrone decreases or the electron affinity of the dipolarophile increases, an increasing tendency toward production of the 4-substituted isoxazolidines is found.[47] At some point, there must be a switch over from LUMO to HOMO control as one increases the electron-withdrawing power of the substituents on the alkene. That point is apparently approached with methyl acrylate, since regioisomeric mixtures of adducts are encountered with this dipolarophile.[48,49]

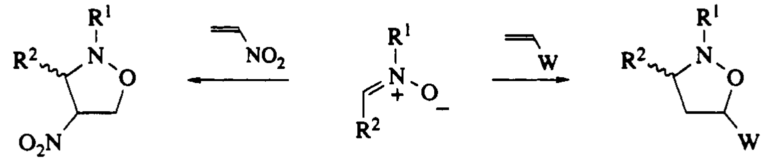

(31) 4-regioisomer

(30) 5-regioisomer

Scheme 9

Monosubstituted alkenes react with nitrones to give rise to a diastereomeric ratio of *cis*- and *trans*-disubstituted isoxazolidines (**32**) and (**33**). The *exo* approach gives the *cis* product, provided that the $NR^1$ and $CR^2$ substituents are in a *trans* relationship; the *endo* approach gives the *trans* product (Scheme 10). Inspection of the available data tends to show that the *exo* approach is favored in most cases when secondary orbital interactions are negligible. When X = $CO_2Me$, CN or Ph such secondary interactions could stabilize the transition state and give predominantly the *trans* adduct. These secondary interactions are analogous to those directing the *endo*/*exo* approach in the Diels–Alder reaction. However, there are data available that are inconsistent with this interpretation.[48] Predictions are therefore unreliable, and it is advisable to determine structures thoroughly for every reaction. The unpredictable behavior of nitrones is demonstrated by the reactions of *N*,*C*-diphenylnitrone and *N*-methylnitrone with diethyl methylenemalonate; which in the former case gives only the 4,4-disubstituted regioisomer (**34**), and in the latter case the 5,5-disubstituted regioisomer (**35**).

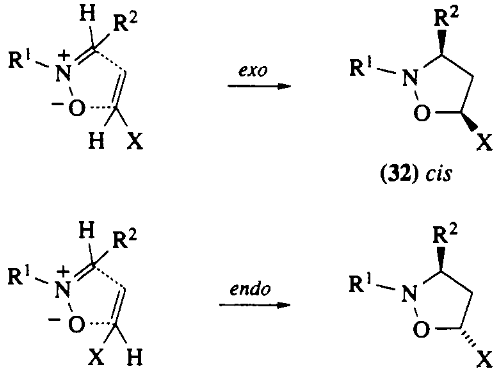

(**32**) *cis*

(**33**) *trans*

Scheme 10

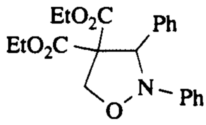

(**34**)

*versus*

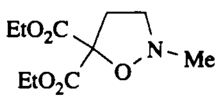

(**35**)

Entropic factors allow the intramolecular version of the nitrone–alkene cycloaddition reaction to proceed under milder conditions than the corresponding bimolecular equivalent.[51,52] The regiochemistry of the internal reaction is complicated by a complex interplay of such factors as alkene polarity, ring strain and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between the bridged and fused modes of cycloaddition. Since LeBel first reported the facile intramolecular cycloaddition of unsaturated nitrones to form bicyclic isoxazolidines,[53] there has been considerable interest in this reaction (Scheme 11). When the dipolarophile is substituted at the 2-position with an alkyl group and the nitrone is substituted at the α-position, there is a tendency for the predominant formation of a fused bicyclic system (**38**) as opposed to the bridged system.[51,52] The intramolecular cycloaddition of *C*-alkenyl-substituted nitrones represents an efficient and general route to five-, six- and higher-membered carbocyclic and heterocyclic rings. This methodology has been used to synthesize prostanoids, terpenoids, various bridged and condensed cycloalkanes, alkaloids, carbohydrates and miscellaneous natural products.[51] Some typical examples are outlined in Scheme 12.

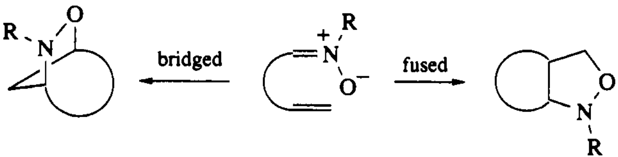

(**37**) (**36**) (**38**)

Scheme 11

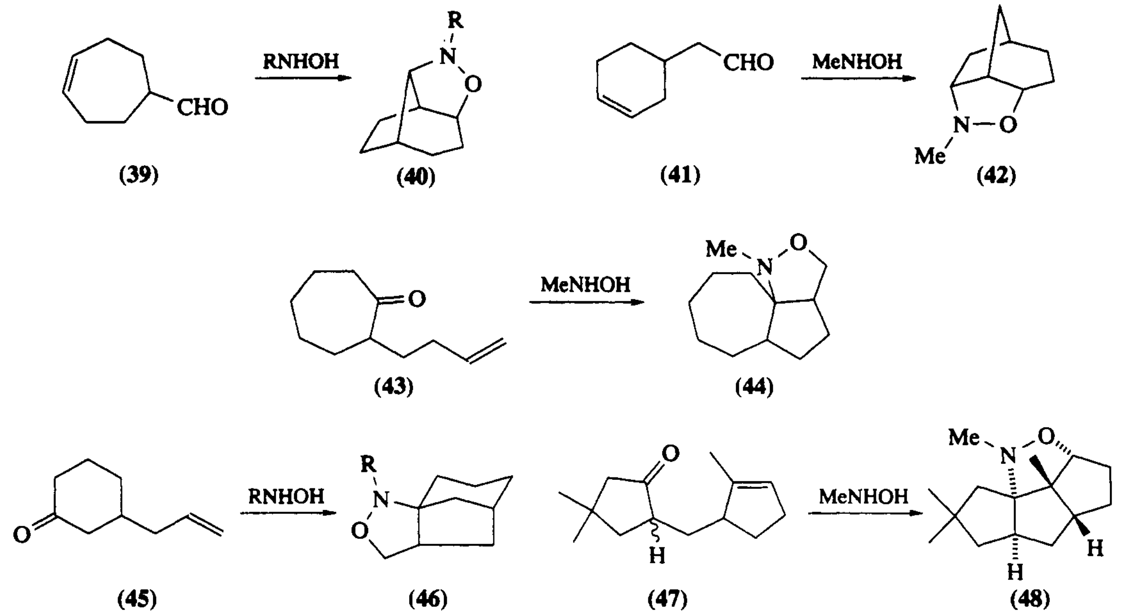

**Scheme 12**

The utility of nitrone–alkene [3 + 2] cycloadditions in the total synthesis of natural products arises not from the presence of the isoxazolidine moiety in naturally occurring substances but from the various transformation products of this saturated heterocycle. The most important of these is the conversion of the isoxazolidine ring system to an *N*-substituted 1,3-amino alcohol by a reduction step (equation 2). The formation of these 1,3-amino alcohols from readily available aldehydes and alkenes represents a very powerful synthetic method. Since this transformation not only yields new carbon–carbon and carbon–oxygen bonds but also incorporates a nitrogen atom in the molecule, the obvious synthetic targets have been nitrogenous substances, particularly alkaloids. Applications of this method to nonnitrogenous targets have also been reported.[48–52]

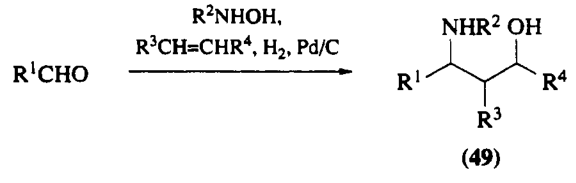

(2)

## 4.9.6.2 Nitrile Oxides

1,3-Dipoles can be classified into two major types: (i) those with internal octet stabilization, where a mesomeric formula can be drawn such that the central atom of the dipole has a positive charge and all centers have completely filled valences; and (ii) those without internal octet stabilization, where each mesomeric form has an electron sextet.[4] By far the more common group of dipoles is the former, mainly because the dipoles in the second group are all unstable and must be prepared *in situ*. In recent years a good deal of attention has focused on the chemistry of the octet-stabilized class of dipoles known as the nitrile oxides.[54,55] Nitrile oxides readily cycloadd to a wide variety of alkenes to generate isoxazolines which represent an extremely useful class of heterocycles (Scheme 13). The presence of a nitrogen atom within the isoxazoline ring has made this heterocycle moiety especially attractive for the synthesis of a wide assortment of natural products. The key feature of this approach generally involves a reductive cleavage of the isoxazoline ring to give either a γ-amino alcohol (**52**) or a β-hydroxy ketone (**53**) which can be further manipulated.[56] Nitrile oxides are conveniently generated by the base treatment of hydroxamic acid chlorides,[54] by the oxidation of aldoximes[55] or by the dehydrogenation of primary nitroalkanes.[57] Most nitrile oxides (**50**) are highly reactive and, in the absence of added trapping agents, undergo rapid dipolar cycloaddition with themselves to give furoxans (**54**; equation 3) Steric bulk increases the stability of the nitrile oxide. For example, *t*-butyl nitrile oxide is readily generated and handled in solution, whereas mesityl nitrile oxide is a normal crystalline organic compound that is indefinitely stable in the pure form. The cycloadditions of nitrile oxides with electron-rich and conjugated alkenes are LUMO controlled.[58] Union of the larger coefficients leads to 5-substituted isoxazolines. Electron-deficient dipolarophiles also react rapidly due to the influence of both dipole HOMO and LUMO interactions. With this class of dipolarophiles, regioselectivity is decreased, since the dipole LUMO tends to produce 5-substituted isoxazolines, whereas the dipole HOMO produces 4-substituted isoxazolines.[59]

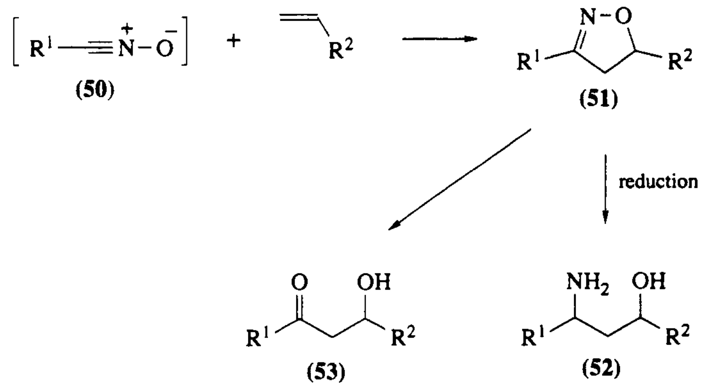

**Scheme 13**

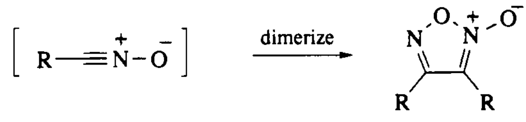

(50) (54) (3)

Asymmetric induction has become one of the cornerstones in modern synthetic methodology, leading to a host of enantiomerically enriched compounds.[60] The use of chiral auxiliaries to induce biased stereochemical changes has allowed investigators to form a variety of C—X bonds with high enantioselectivity. Recently, the asymmetric Diels–Alder reaction has received a great deal of attention.[61] Some of these [4 + 2] cycloadditions proceed with very high, and sometimes near perfect, diastereoselection.[62] In contrast to the well-documented asymmetric Diels–Alder reactions, asymmetric 1,3-dipolar cycloadditions have not been extensively explored. There are, however, several reports of stereoselective cycloadditions involving nitrile oxides and nitrones. Nitrones which carry a chiral substituent on nitrogen often display high diastereoselectivity in dipolar cycloadditions with a variety of achiral dipolarophiles.[63–66] In certain cases, the reaction of chiral dipolarophiles with nitrile oxides leads to reasonably high diastereoselectivity in the formation of the cycloadducts. Since the N—O bonds of the cycloadducts are readily cleaved to produce acyclic molecules, the diastereoselectivity displayed in the cycloadditions serves as a means of controlling acyclic stereochemistry (equation 4).[56]

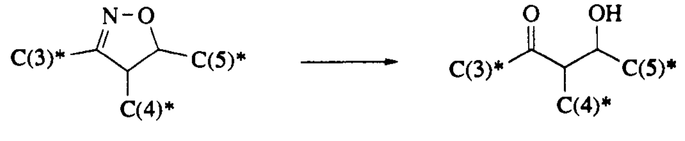

(4)

C* = stereogenic center

Curran and coworkers[67] have reported high diastereoselectivity (9:1) in the cycloaddition reactions of Oppolzer's chiral sultam[68] (**55**) with nitrile oxides (equation 5). The major diastereomer (**56**) results from 'top-side' attack of the incoming nitrile oxide and it has been suggested that the α-oxygen atom of the sultam provides a steric or electronic encumbrance to 'bottom-side' attack. These results point the way to the design of new chiral auxiliaries in which both the facial selectivity and the acrylate conformer are controlled in the transition state for cycloaddition.

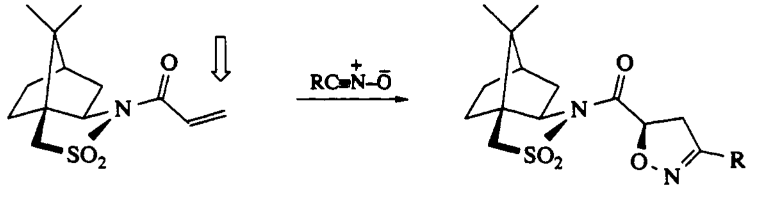

(5)

The application of intramolecular dipolar cycloaddition reactions to the synthesis of complex natural products has recently come to be recognized as a very powerful synthetic tool, one equally akin to the intramolecular Diels–Alder reaction in its potential scope of application.[69] This is particularly the case with nitrile oxides and the INOC reaction has been extensively utilized in total synthesis.[70] The intramolecular nitrile oxide cycloaddition (INOC) generally displays exceptional regio- and stereo-chemical control which undoubtedly accounts for the popularity of this reaction. Internal cycloadditions of nitrile oxides have been found to offer a powerful solution to many problems in complex natural product synthesis.[48] For example, Confalone and coworkers have utilized the INOC reaction for the stereospecific synthesis of the key amino alcohol (**60**), which was converted in five subsequent steps to (±)-biotin (**61**; Scheme 14).[71]

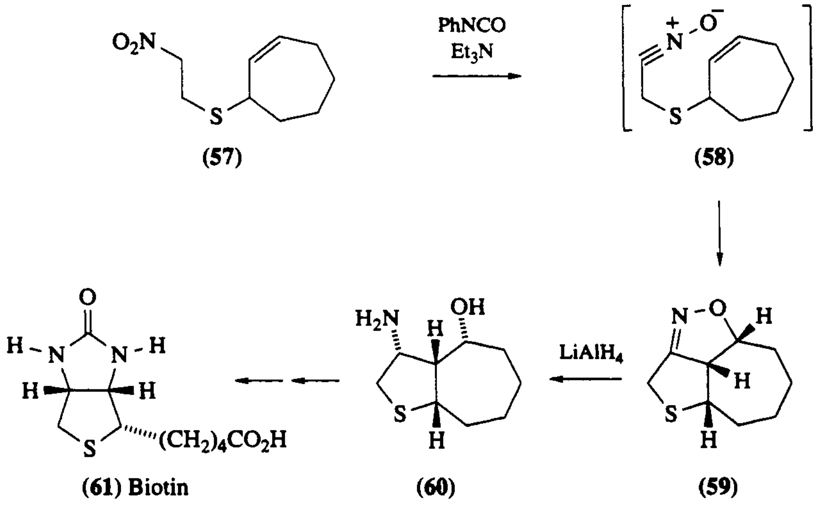

Scheme 14

Kozikowski's group has been particularly active in the application of the INOC reaction toward the construction of a variety of natural products. One of the many examples from his laboratory involves the synthesis of tetracyclic compounds possessing suitably functionalized C rings for elaboration to a diverse number of ergot alkaloids *via* the INOC reaction. A total synthesis of chanoclavine I (**65**) was accomplished by this chemistry (Scheme 15). The key step in the synthesis involved the conversion of the nitro group of indole (**62**) into the corresponding nitrile oxide using the phenyl isocyanate procedure developed by Mukaiyama.[57] The major product corresponded to isoxazoline (**64**). The isoxazoline nucleus was converted into chanoclavine I (**65**) in a series of subsequent steps. The application of nitrile oxide cycloaddition chemistry to the construction of other natural products can be expected to be an active area in future years.

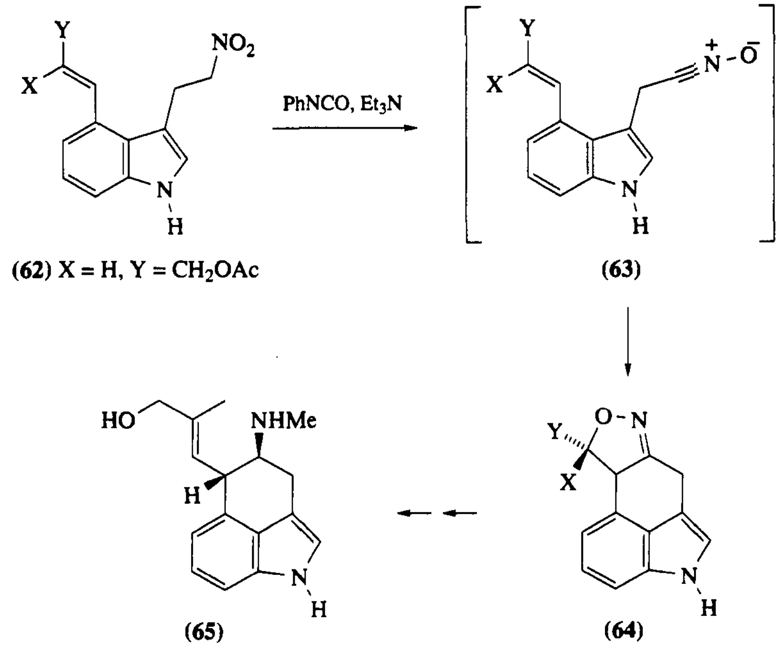

**(62)** X = H, Y = CH₂OAc

**(63)**

**(64)**

**(65)**

**Scheme 15**

### 4.9.6.3 Nitrile Ylides

One of the more interesting members of the nitrilium betaine family is the nitrile ylides.[72-74] This class of dipoles has traditionally been prepared by: (i) treatment of imidoyl halides with base,[75] (ii) thermal or photochemical elimination of phosphoric acid esters from 4,5-dihydro-1,3,5-oxazaphospholes,[76] and (iii) photolysis of aryl-substituted azirines.[77,78] Nitrile ylides have also been observed to be formed upon photolysis of carbene precursors in nitrile solvents.[79,80] FMO theory correctly rationalizes the regioselectivity of nitrile ylide cycloadditions (equation 6).[3] When nitrile ylides are used as 1,3-dipoles, the dipole highest occupied and dipolarophile lowest unoccupied orbital interaction stabilizes the transition state. MNDO calculations of simple nitrile ylides indicate that the coefficient size in both the HOMO and LUMO is slightly greater at the unsubstituted carbon atom.[81] The photoconversion of arylazirines to alkoxyimines in alcoholic solvents (Scheme 16) indicates that in the highest occupied orbital of the nitrile ylide, the electron density at the disubstituted carbon is greater than at the trisubstituted carbon atom.[82] The preferred regioisomeric transition state will be that in which the larger terminal coefficients of the interacting orbitals are united. With this conclusion, all of the regiochemical data found in the literature can be rationalized (Scheme 17).[72-74]

Inductive effects exerted by substituents on the nitrile ylide also have an important effect on the regioselectivity of the cycloaddition. Benzonitriliohexafluoro-2-propanide (73) and methyl acrylate yield products with inverse regioselectivity, as compared with the reactions of the related benzonitrilio-2-propanide (76; Scheme 18).[83] The difference in regioselectivity has been attributed to the larger coefficient

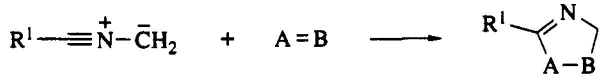

(6)

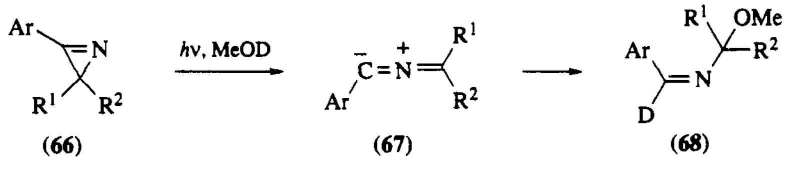

**(66)**

**(67)**

**(68)**

**Scheme 16**

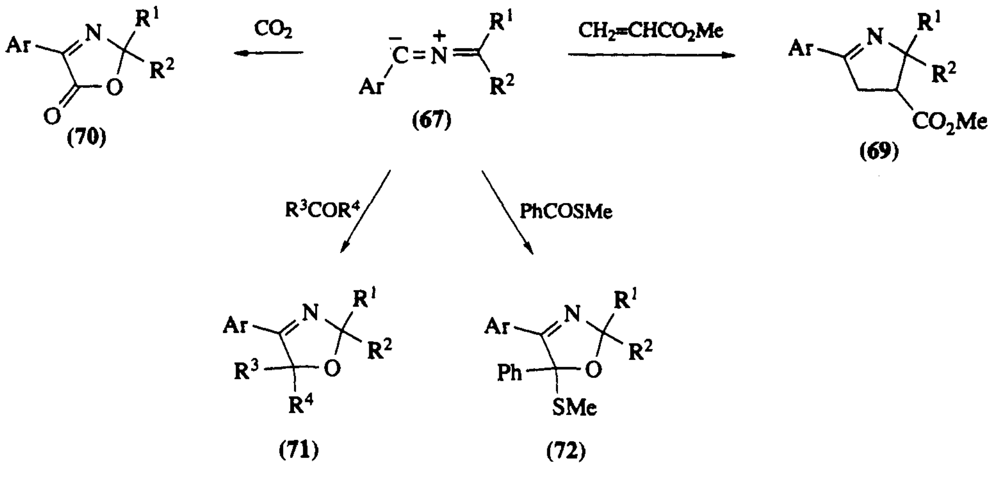

Scheme 17

at the trisubstituted carbon atom of the gem-trifluoromethyl-substituted nitrile ylide (73). This result also parallels the different mode of addition of alcohols to nitrile ylides (73) and (76).

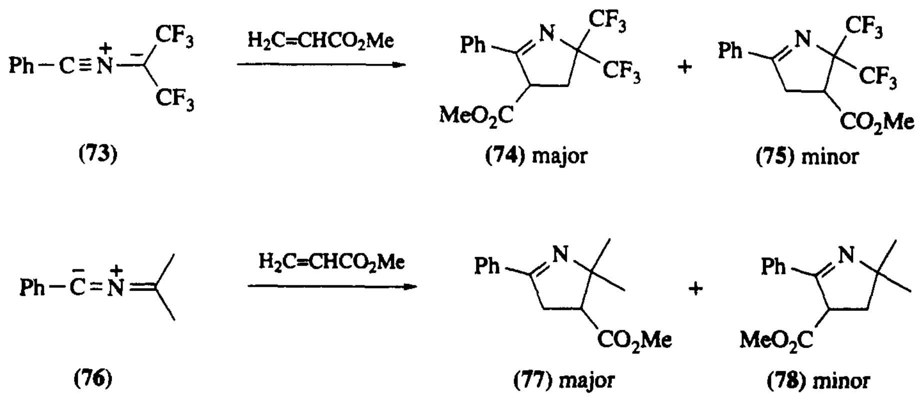

Scheme 18

Among the possible geometric forms of a nitrile ylide, a carbene structure (79) can be envisaged,[4] which makes conceivable a 1,1-cycloaddition of this 1,3-dipole (Scheme 19). Molecular orbital calculations have shown that nitrile ylides exist preferentially in the bent form with an HCN angle of 114–116°.[84–86] The nitrile ylide HOMO is heavily concentrated at C-1, but still resembles the normal three-orbital, four-electron system present in other 1,3-dipoles, so that concerted cycloaddition can still occur. In a series of papers, Padwa and coworkers have shown that there are two pathways by which nitrile ylides react with multiple π-bonds.[87] The most frequently encountered path involves a 'parallel-plane' approach of addends and can be considered to be an orbital symmetry allowed [4 + 2] concerted process.[88] With this path, the relative reactivity of the nitrile ylide toward a series of dipolarophiles will be determined primarily by the extent of stabilization afforded the transition state by interaction of the dipole HOMO and dipolarophile LUMO orbitals. Substituents which lower the dipolarophile LUMO energy will accelerate the 1,3-dipolar cycloaddition reaction. Bimolecular reactions of nitrile ylides with electron-rich alkenes have never been observed, thereby indicating that the dipole LUMO–dipolarophile HOMO interaction is never large. Because of their high nucleophilicities, nitrile ylides generally undergo reactions with their precursors, dimerize or isomerize faster than they undergo reactions with electron-rich alkenes.[89–91]

The other path by which nitrile ylides react with π-bonds occurs only in certain intramolecular cases and has been designated as a 1,1-cycloaddition reaction.[87] It occurs when the *p*-orbitals of the alkenic group have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Houk and Caramella have suggested that the 1,1-cycloaddition reaction is initiated by interaction of the terminal carb-

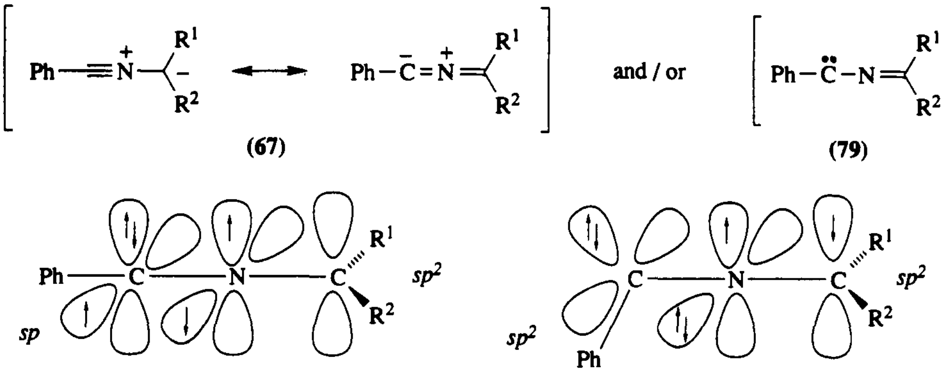

Scheme 19

on of the alkene with the second LUMO of the nitrile ylide.[81] The second LUMO of the dipole is perpendicular to the ylide plane and presents a large vacancy at C-1 of the dipole for attack by the terminus of the neighboring double bond, without the possibility of simultaneous bonding at the C-3 carbon. In fact, the HOMO and second LUMO of the bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. Placement of electron-releasing substituents on the $\pi$-bond will raise both the HOMO and LUMO orbital energies of the alkene, and consequently facilitate the rate of the 1,1-cycloaddition reaction.[87]

As was clearly pointed out by Huisgen,[4,7] 1,3-dipolar additions generally proceed *via* a two-plane orientation complex, in which the dipole and dipolarophile approach each other in parallel planes. Inspection of molecular models of the nitrile ylides (**81**) and (**85**) derived from azirines (**80**) and (**84**), indicates that the normal two-plane orientation approach of the nitrile ylide and the allyl $\pi$-system is impossible as a result of the geometric restrictions imposed on the system. Consequently, the normal mode of 1,3-dipolar cycloaddition cannot occur here. Instead, attack of the carbene carbon on the neighboring double bond generates a six-membered ring trimethylene intermediate (Scheme 20). Collapse of this species results in the formation of the observed azabicyclohexene system (**83**) and (**87**). This sequence proceeds in a nonconcerted manner and bears a strong resemblance to the stepwise diradical mechanism suggested by Firestone to account for bimolecular 1,3-dipolar cycloadditions.[11] It is evident from the available data that, unless the dipole and dipolarophile approach each other in parallel planes, an alternative nonconcerted mechanism for dipolar cycloaddition can occur.

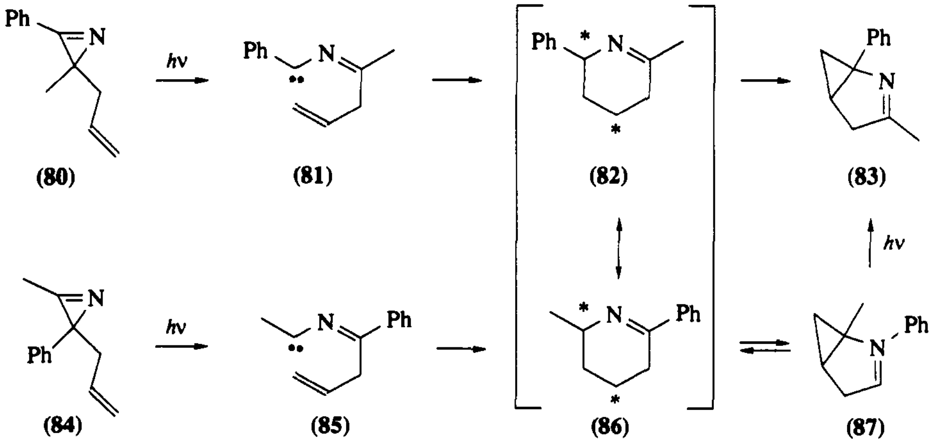

Scheme 20

### 4.9.6.4 Nitrilimines

Nitrilimines represent a well investigated class of 1,3-dipoles.[55] Access to this group of dipoles can be realized by: (i) treatment of hydrazonyl halides with base,[92] (ii) thermal or photochemical decomposition of tetrazoles,[93,94] (iii) photolysis of sydnones,[95] and (iv) thermal elimination of carbon dioxide from oxadiazolin-5-ones.[96,97] 1,3-Dipolar cycloaddition of this class of 1,3-dipoles has been widely investigated, and in many cases has led to the synthesis of a variety of interesting heterocyclic compounds (Scheme 21). The cycloadditions of simple nitrilimines with electron-rich dipolarophiles are LUMO (dipole)–HOMO (dipolarophile) controlled.[55] For conjugate dipolarophiles, both HOMO and LUMO interactions are important, but the greater difference in LUMO coefficients leads to a preference for 5-substituted $\Delta^2$-pyrazolines. With electron-deficient dipolarophiles, the regioselectivity is reversed since the cycloaddition becomes HOMO (1,3-dipole)–LUMO (dipolarophile) controlled.

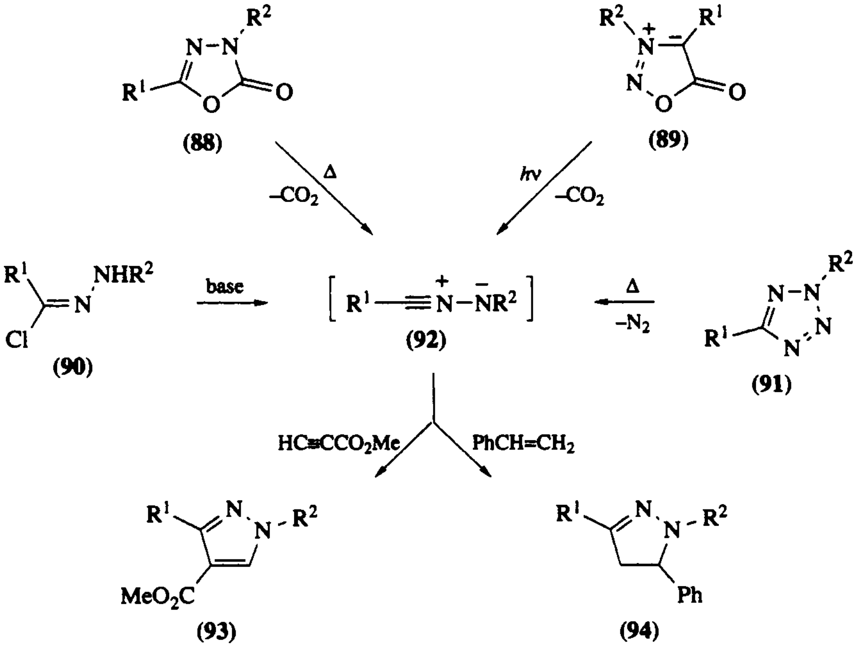

Scheme 21

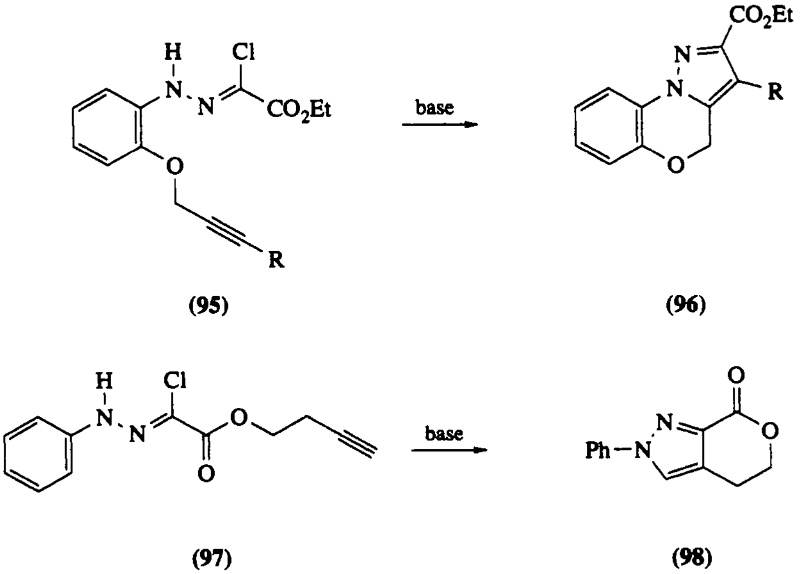

Scheme 22

During the past few years a large number of studies dealing with the intramolecular 1,3-dipolar cycloaddition reactions of nitrilimines have been reported.[51] The reaction products are generally complex polycyclic, annelated and fused-ring molecules that are very difficult to prepare by other methods. A typical example involves the treatment of hydrazidryl chloride (**95**) with base to give a nitrilimine that can be readily intercepted by the adjacent alkynic functionality present in the molecule to give pyrazole (**96**).[98] Similarly, treatment of (**97**) with base affords cycloadduct (**98**) in high yield.[99] These ring closures are particularly interesting in that they involve cycloadditions with unconjugated alkynes, substrates that are generally unreactive toward nitrilimines.[100] Furthermore, although the usual orientation of monosubstituted alkynes in the bimolecular cycloadducts with nitrilimines is such as to afford 5-substituted pyrazoles,[100-102] obtainment of the 4-substituted pyrazole (**98**) reveals that in a properly chosen substrate the regiospecificity of monosubstituted alkynes can be inverted (Scheme 22).

MO calculations by Houk and Caramella suggest that nitrilimine is a flexible 1,3-dipole able to adapt its geometry according to the nature of the reaction.[85] Electrophilic reagents tend to favor a planar nitrilimine structure possessing a relatively high-lying HOMO, whereas nucleophilic reagents promote the bent azo carbene-like form, which possesses a low-lying LUMO. Independent results by Garanti[103] and Padwa[104] have shown that the 1,1-cycloaddition of nitrilimines to π-bonds can occur when the *p*-orbitals of the dipolarophile have been deliberately constrained to attack perpendicular to the nitrilimine plane. Thus, treatment of *o*-vinylphenyl-substituted chloroglyoxylate phenylhydrazones with base leads to nitrilimines that undergo intramolecular 1,1-cycloaddition to give cyclopropa[*c*]cinnolines (Scheme 23). The results with a set of *cis* and *trans* methyl-substituted chlorohydrazones indicate that complete retention of stereochemistry about the π-bond has occurred in the cycloaddition reaction.

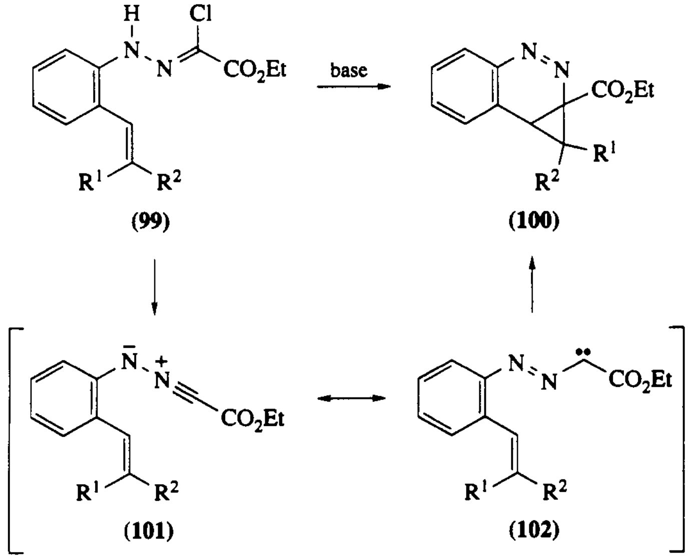

Scheme 23

### 4.9.6.5 Azomethine Ylides

Azomethine ylides have represented attractive synthetic building blocks for pyrrolidine synthesis since the discovery that they can be generated by pyrolysis of aziridines.[105] The reaction of 1,2,3-triphenylaziridine with electron-deficient alkenes or alkynes to yield five-membered nitrogen rings was initially reported by Heine[106] and similar findings were described by Padwa[107] and by Huisgen[108] shortly thereafter. Due to the systematic investigations by Huisgen,[109] it is well known that the thermolysis of 1-phenyl-2,3-bis(methoxycarbonyl)aziridine involves conrotatory ring opening to the carbonyl-stabilized ylides (**104**) or (**105**; Scheme 24). Trapping products of the S-dipole (**104**) are obtained from the *cis*-aziridine (**103**), while adducts of the isomeric W-dipole (**105**) result from the *trans*-aziridine (**106**). The S-dipole (**104**) is trapped by several dipolarophiles without loss of dipole geometry. In contrast, the W-dipole (**105**) reacts cleanly only with the most reactive of trapping agents such as dimethyl acetylenedicarboxylate (DMAD). With less reactive dipolarophiles, products derived from the S-dipole (**104**) are also observed due to dipole interconversion. These topics have been extensively reviewed, and the concepts have also been extended to nonstabilized azomethine ylides.[110–113] Many other examples of aziridine thermolysis have been reported in the literature.[105] Although *N*-arylaziridines have been investigated most intensively, cycloadditions using *N*-alkyl, *N*-H and *N*-acyl derivatives have also been encountered. Other routes to stabilized azomethine ylides include the thermolysis of benzaldimines,[114] the related method of thermal *N*-alkylamino ester/aldehyde condensation[115,116] and carbene insertion into an imine nitrogen lone pair.[117]

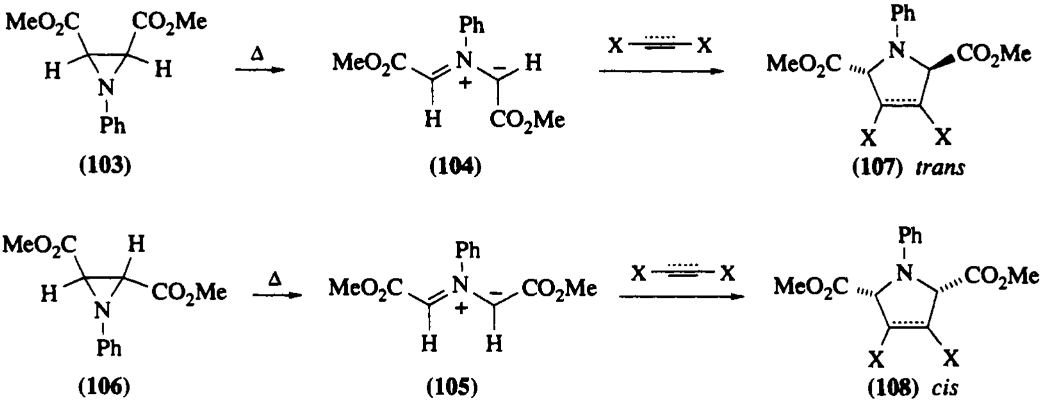

Scheme 24

In frontier molecular orbital terms, the reaction of an azomethine ylide with an electron-deficient dipolarophile is suggested to be a dipole HOMO controlled reaction.[118] Thus, the dominant FMO involves the HOMO of the dipole and the LUMO of the dipolarophile, and factors that decrease the HOMO–LUMO gap increase the efficiency of the reaction. Generally, donor and/or conjugative groups (alkyl, alkoxy, aryl) on the dipole raise the HOMO energy, while acceptor groups on the dipolarophile lower the LUMO energy. This combination of effects facilitates the reaction. In the case of stabilized azomethine ylides, the dipole contains electron-deficient groups which tend to lower the HOMO and moderate the dipole reactivity. These stabilized dipoles are still reactive enough to participate in cycloadditions with highly electron-deficient dipolarophiles such as acrylate, DMAD and maleimide.

Although ring openings of aziridines to azomethine ylides work well when the substituent groups are capable of stabilizing the dipole centers,[105] the ring cleavage generally fails when simple alkyl substituents are used. Recent studies by Vedejs and coworkers have shown that the desilylation of α-trimethylsilylonium salts represents a convenient method for azomethine ylide generation.[119] Cycloaddition of these transient species with various dipolarophiles gives rise to dipolar cycloadducts in high yield (Scheme 25). The advantage of using cesium fluoride for these desilylations is related to its reasonable

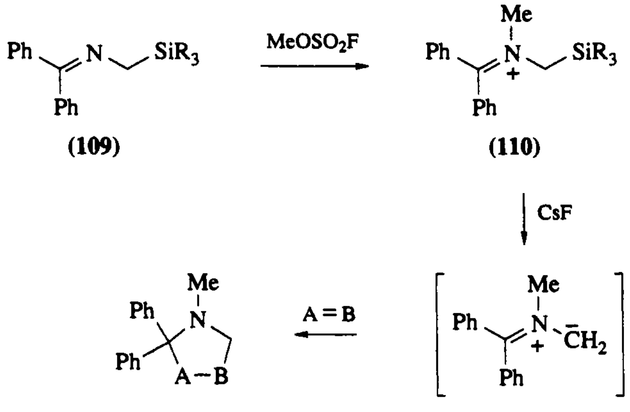

Scheme 25

thermal stability, which allows thorough drying under vacuum to remove water of hydration. Similar results can be achieved more tediously with scrupulously dried KF/18-crown-6, but organic fluoride donors are less effective because they are contaminated with water. The presence of water results in the ready protonation of the nonstabilized ylides and the net result is protodesilylation.

Generation of intermediates having azomethine ylide reactivity has also been achieved by the cesium fluoride-induced desilylation reaction of several immonium salts derived from amides, thioamides and vinylogous amides. A variety of dipolarophiles have been used to trap the azomethine ylide (Scheme 26). Methyl acrylate or α-chloroacrylonitrile are especially efficient trapping agents, and in both cases the more hindered product is formed.[110] The same regiochemical preference is seen in virtually all of the trapping experiments as long as unsymmetrical dipolarophiles derived from acrylic acid are used.

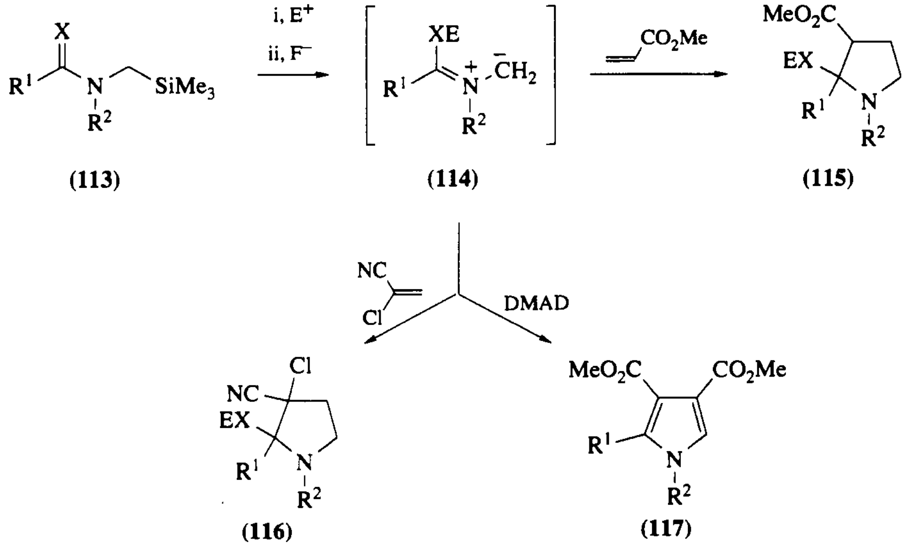
X
R¹
N
SiMe₃
R²
(113)
i, E⁺
ii, F⁻
XE
R¹
N
CH₂
R²
(114)
CO₂Me
MeO₂C
EX
R¹
N
R²
(115)
NC
Cl
DMAD
Cl
NC
EX
R¹
N
R²
(116)
MeO₂C
CO₂Me
R¹
N
R²
(117)

Scheme 26

Imidate-derived dipoles have played a prominent role in the synthesis of the pyrrolizidine alkaloid retronecine (**121**).[119] The imidate salt derived from lactam (**118**) was found to undergo a smooth desilylation reaction to produce azomethine ylide (**119**). Trapping of this dipole with methyl acrylate affords

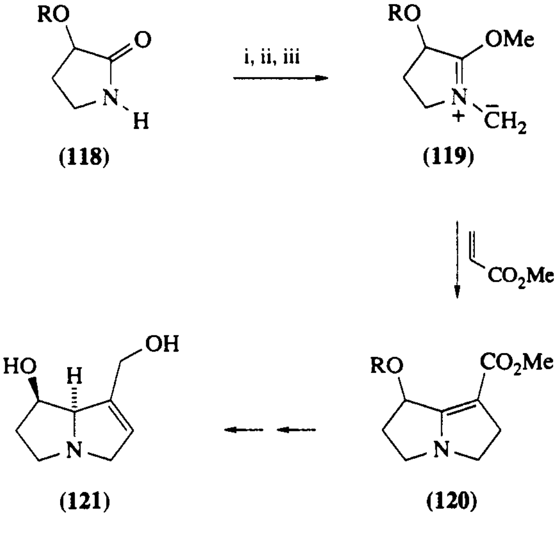
RO
O
N
H
(118)
i, ii, iii
RO
OMe
N
CH₂
(119)
CO₂Me
HO
H
OH
N
(121)
RO
CO₂Me
N
(120)

i, $Me_3SiCH_2I$; ii, MeOTf; iii, $F^-$

Scheme 27

the conjugate enamine ester (**120**). This material was converted to retronecine in several additional steps (Scheme 27).

Amidine-derived azomethine ylides can also be used in dipolar cycloaddition reactions. Livinghouse has applied the cycloaddition of this class of dipoles to the synthesis of eserethiole (**125**).[120] The starting amidine (**123**) is made by coupling the imidate salt (**122**) with trimethylsilylmethylamine. *N*-Alkylation followed by desilylation affords the azomethine ylide which readily undergoes intramolecular dipolar cycloaddition to give the natural product (Scheme 28). Other attempts to trap nonstabilized azomethine ylides by intramolecular cycloaddition across unactivated π-bonds using the desilylation technique have so far been unsuccessful.

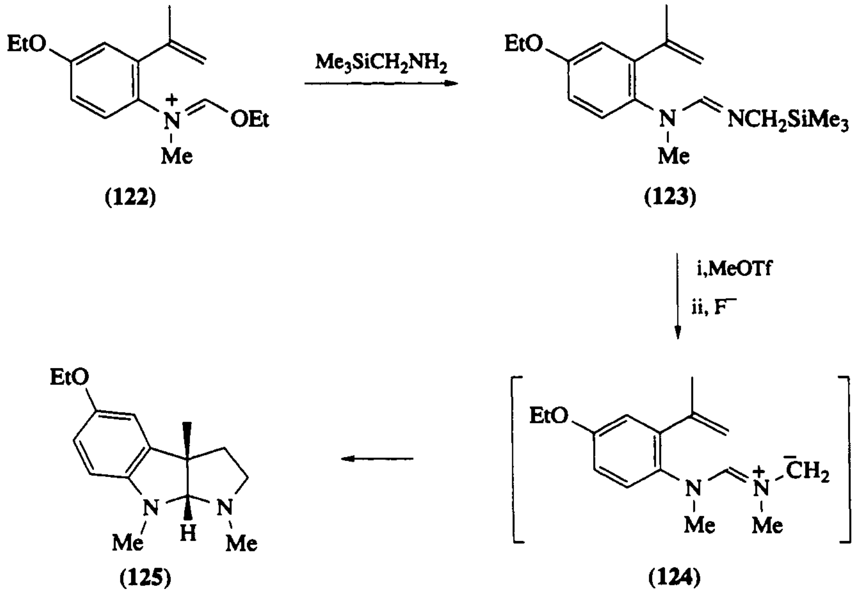

Scheme 28

There have been a number of additional approaches used for the synthesis of nonstabilized azomethine ylides. Padwa and Chen have reported that α-cyanosilylamines (**126**) are useful and convenient synthons for azomethine ylides.[121] The development of this strategy was based on literature reports that cyanomethylamines can function as convenient iminium ion precursors.[122] The propensity of silicon to transfer to a silylophile[123] when bound to an electronegative carbon strongly inferred that the treatment of α-cyanosilylamines with silver fluoride will generate azomethine ylides. Further reports by Padwa[118] and Sakurai[124] have described a mechanistically related method using the aminal (**127**) as starting material for TMSI-induced dipole generation (Scheme 29).

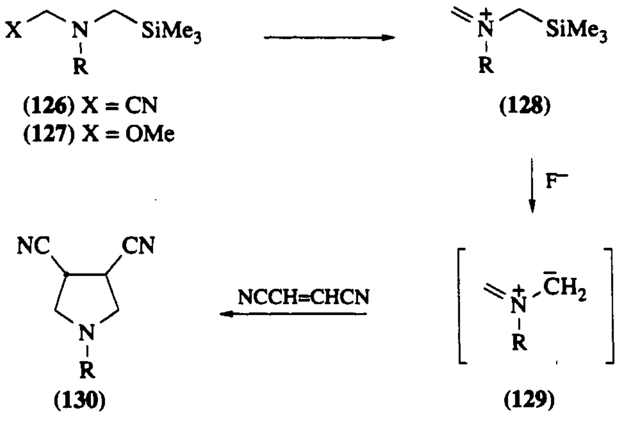

Scheme 29

The examples of desilylation discussed so far all assume that the reactive intermediates are silicon-free azomethine ylides. It is conceivable, however, that pentacoordinated silicon-containing intermediates may be able to mimic the reactivity of nucleophilic azomethine ylides. Two groups have probed this question and have reported evidence in favor of the dipole pathway. If silicon is still present as bond formation occurs, then it should matter which of the isomeric starting materials (**131**) or (**132**) is used in the desilylation experiment (Scheme 30). Work by Padwa and Dent has shown that treatment of either isomeric aminonitrile with AgF affords the same mixture of product regioisomers using methyl propiolate as the trapping agent.[118] Achiwa has observed that the deuterated ylide precursor (**133**) affords cycloadducts with complete scrambling of the label as expected in a silicon-free azomethine ylide.[125]

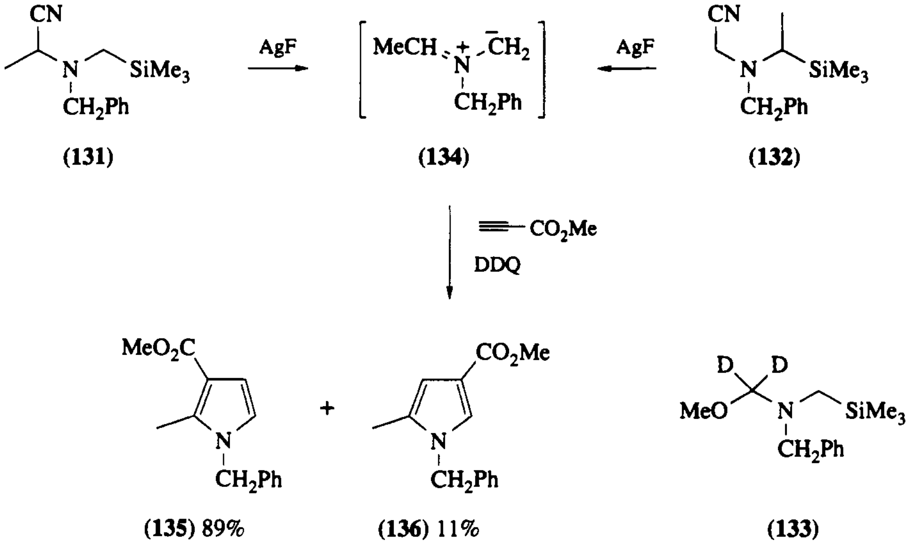

Scheme 30

Finally, the LDA deprotonation of amine *N*-oxides has been reported to generate azomethine ylides that can be trapped in [2 + 3] cycloadditions with simple alkenes.[126] For example, *N*-methylpyrrolidine *N*-oxide (**137**) reacts with LDA in the presence of cyclopentene to give adduct (**139**; Scheme 31). A variety of other *N*-oxides behave similarly. Interestingly, there are no examples published to date where nonstabilized azomethine ylides generated by the desilylation procedure can be trapped by simple, unactivated alkenes. It is not clear whether these discrepancies are due to some fundamental difference in the reactive intermediate being generated, or whether the differences in environment are responsible for differing behavior. Further work is needed to establish this point.

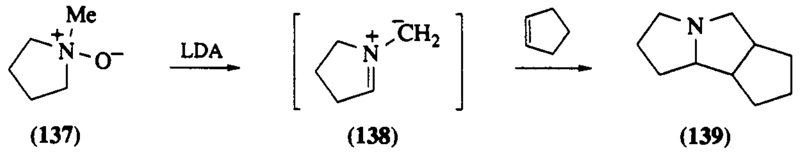

Scheme 31

### 4.9.6.6 Carbonyl Ylides

In recent years there has been a growing interest in the use of carbonyl ylides as 1,3-dipoles for total synthesis.[127–130] Their dipolar cycloaddition to alkenic, alkynic and hetero multiple bonded dipolarophiles has been well documented.[6] Methods for the generation of carbonyl ylides include the thermal and photochemical opening of oxiranes,[131] the thermal fragmentation of certain heterocyclic structures such as $\Delta^3$-1,3,4-oxadiazolines (141) or 1,3-dioxolan-4-ones[132–134] (**142**) and the reaction of carbenes or carbenoids with carbonyl derivatives.[135–138] Formation of a carbonyl ylide by attack of a rhodium carbenoid intermediate onto the lone pair of electrons of the carbonyl group represents a particularly useful approach to this dipole (Scheme 32).[137] The regiochemistry of the cycloaddition reaction of carbonyl ylides can be successfully predicted by FMO theory. Of the three categories described by Sustmann,[21] type 2 is particularly common for carbonyl ylides since they have one of the smallest HOMO–LUMO energy gaps of the common 1,3-dipoles. For carbonyl ylides, the HOMO of the dipole is dominant for reactions with electron-deficient dipolarophiles such as acrolein, while the LUMO becomes important for cycloaddition to electron-rich species such as ethyl vinyl ether.

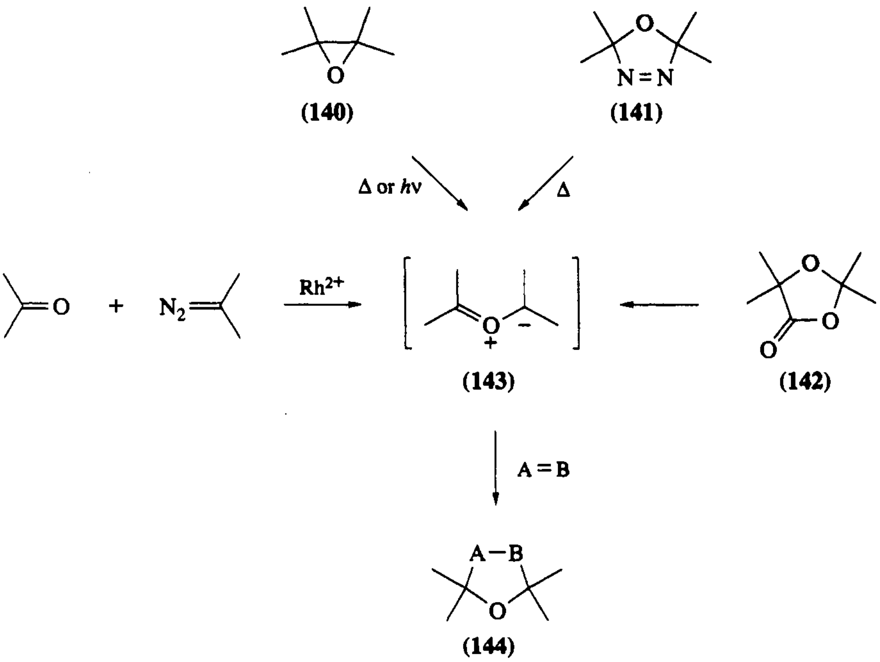

Scheme 32

Linn and Benson discovered in 1965 the ability of tetracyanoethylene oxide (**145**) to react with alkenes and alkynes at elevated temperatures in [3 + 2] cycloadditions.[139] The kinetics of the reaction of (**145**) with styrene revealed that the formation of (**147**) is preceded by a first-order step consisting of the electrocyclic ring opening to the carbonyl ylide (**146**; Scheme 33).

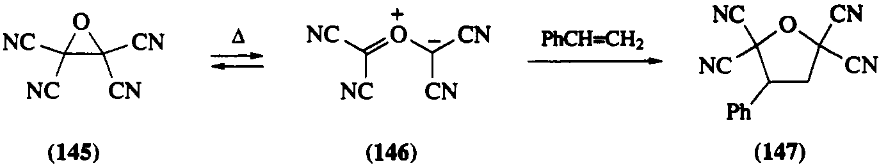

Scheme 33

1,2-Diaryloxiranes undergo a photofragmentation giving carbonyl compounds and a carbene.[140] Do-Minh, Trozzolo and Griffin noticed an orange color on irradiation of (**148**) at −196 °C and ascribed it to carbonyl ylide (**149**; Scheme 34)[141] Photogenerated carbonyl ylides can be captured *in situ* by α,β-unsaturated carboxylic esters as dipolarophiles.[142] Disrotation predicted by orbital symmetry control appears to be the predominant mode involved in the photoconversion of oxiranes to carbonyl ylides. An investigation of the thermal behavior of α-cyano-*trans*- and α-cyano-*cis*-stilbene oxide revealed that the symmetry-allowed conrotation is the favored pathway of electrocyclic ring opening (Scheme 34); however, steric hindrance can induce a partial switch to disrotation.[143]

The reaction of dimethyl diazomalonate with an excess of benzaldehyde with or without metal catalyst furnished the diastereomeric 1,3-dioxolanes (**156**) and the oxirane (**155**; Scheme 35). The reaction was proposed to proceed *via* the intermediacy of a carbonyl ylide dipole.[135] Benzaldehyde plays a double role

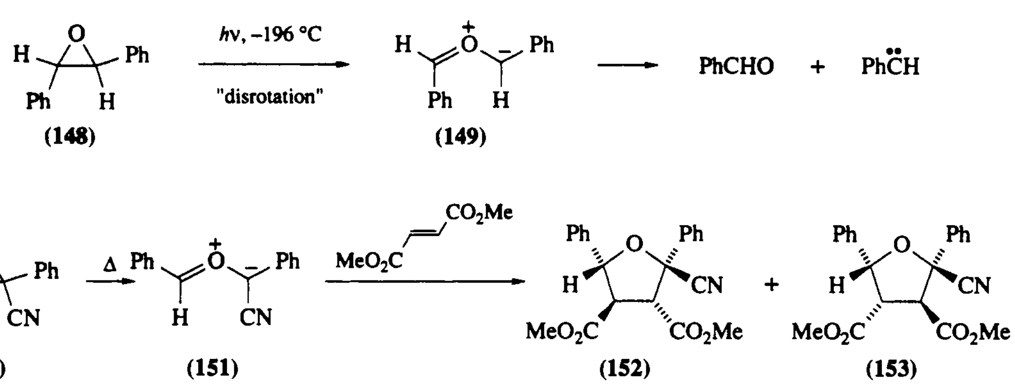

Scheme 34

here, first as a constituent of the carbonyl ylide and, subsequently, as a dipolarophile in the trapping of (**154**).

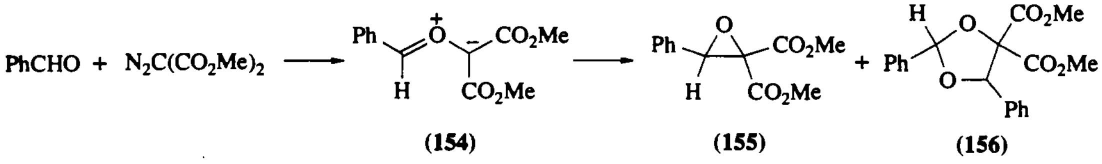

Scheme 35

The intramolecular reaction of carbenes with a neighboring carbonyl group results in the formation of cyclic carbonyl ylides. This approach, pioneered largely by Ibata and coworkers,[138] allows for the convenient generation of various five- or six-membered carbonyl ylides which can be trapped by π-bonds. Generation of the carbene center involves treating a diazo compound with an appropriate transition metal catalyst. An interesting example of this involves the tandem cyclization–cycloaddition reactions of α-diazoacetophenone derivatives which occur upon treatment of *O*-alkyl-2-enoxycarbonyl-α-diazoacetophenones (**157**) with rhodium(II) acetate. Initial cyclization gives a six-ring carbonyl ylide which undergoes a subsequent intramolecular dipolar cycloaddition across the neighboring double bond. The process is illustrated by the conversion of diazoketone (**157**) with rhodium(II) acetate to cycloadduct (**159**) in 87% yield (Scheme 36).[137] The initial work involved systems in which the ketorhodium carbenoid and the remote carbonyl were attached in a 1,2-fashion on a benzene ring. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. The conformationally unencumbered diazo ketone (**160**) was also found to undergo this same reaction when treated with a catalytic amount of rhodium(II) acetate. The cycloaddition proceeded quite smoothly in the presence of DMAD and produced cycloadduct (**161**; Scheme 37). The intermediate carbonyl ylide could also be trapped with benzaldehyde and methyl propiolate. The orientation observed with these systems can readily be rationalized in terms of maximum overlap of the dipole HOMO–dipolarophile LUMO. MNDO calculations of the carbonyl ylide derived from (**160**) clearly indicate that the largest coefficient in the HOMO resides on the enolate carbon.[137] This site becomes linked with the less-substituted carbon atom of the alkyne.

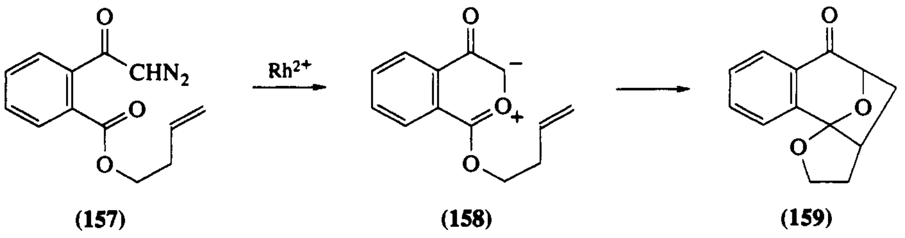

Scheme 36

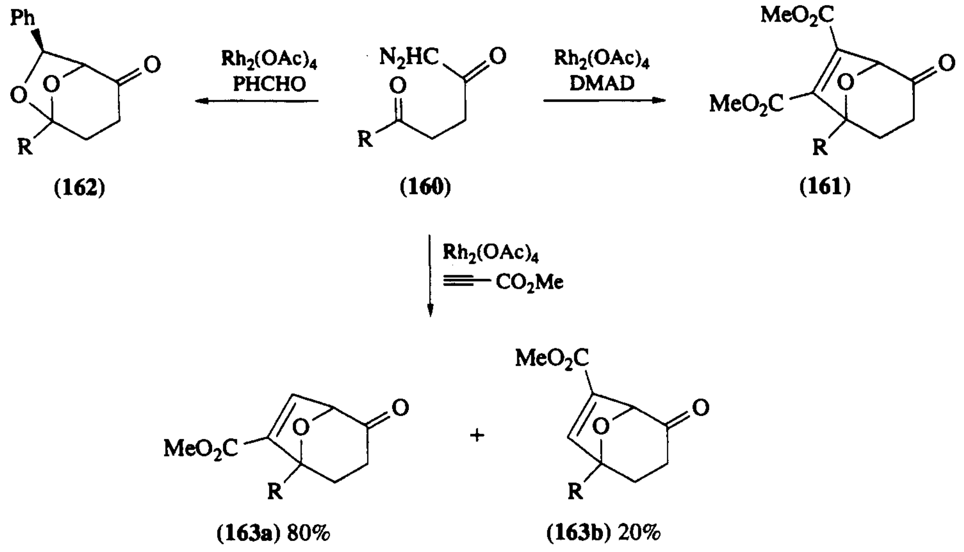

Scheme 37

The cycloaddition chemistry of the 3-oxidopyrylium system (**165**; Scheme 38) has been studied in some detail by Sammes and coworkers.[128] Pyranulose acetate (**164**) is readily available from simple furan derivatives and thus a route is available for the preparation of a variety of substituted 3-oxidopyrylium compounds.[127] These reactive species can be trapped with a wide range of unsaturated materials including alkenes, which cycloadd across the 2,6-positions. 3-Oxidopyrylium (**165**) reacts sluggishly with electron-deficient dipolarophiles giving reasonable yields of adducts (*i.e.* **166**) with only the most reactive traps (*i.e.* acrolein). Both experimental studies[144] and theoretical interpretations[21] have shown that 1,3-dipoles can behave as ambident species, reacting faster with either electron-deficient or electron-rich alkenes than neutral, unsubstituted ones. Huisgen, for example, obtained U-shaped curves when plotting

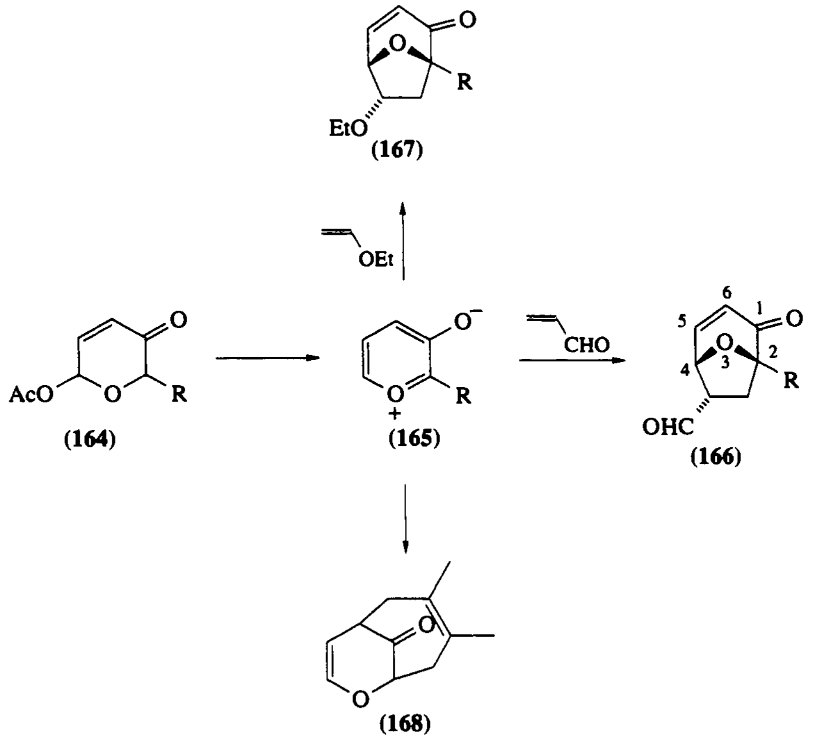

Scheme 38

reaction rates of a given dipole with different dipolarophiles against the ionization potential of the latter.[144] Thus, the formation of adduct (**167**) when ethyl vinyl ether was used as a trapping agent is perfectly understandable. Ylides of type (**165**) are also expected to undergo pericyclic additions across other centers depending on electronic demands. 4π-Electron systems such as dienes would be expected to add across the 2,4-positions, as observed with certain 3-oxidopyridinium derivatives.[145] In fact, 2,3-dimethylbutadiene reacted with (**165**) to give adduct (**168**) as the principal product. Sammes also studied the chemistry of oxidopyrylium ylides which contain an unsaturated side chain. These molecules (*i.e.* **169**) undergo an intramolecular dipolar cycloaddition reaction upon thermolysis to give bicyclic adducts which provide a simple entry into the perhydroazulene system (Scheme 39). This method was used to synthesize a number of natural products.[128]

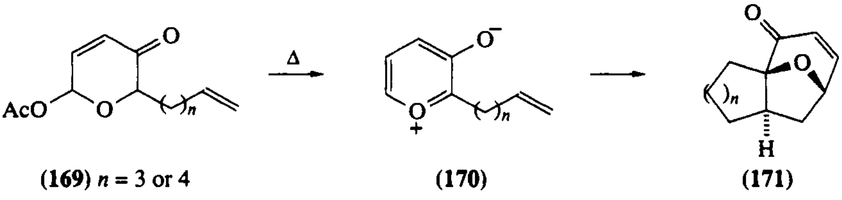

**Scheme 39**

### 4.9.6.7 Thiocarbonyl Ylides

The first recognition of the existence of the thiocarbonyl ylide appears to have been made by Knott in 1955 in conjunction with considerations of the contributions of this segment to the electronic make-up of certain dyestuffs.[146] Knott very likely generated the unstable thiocarbonyl ylide (**173**) *via* the route shown in Scheme 40.

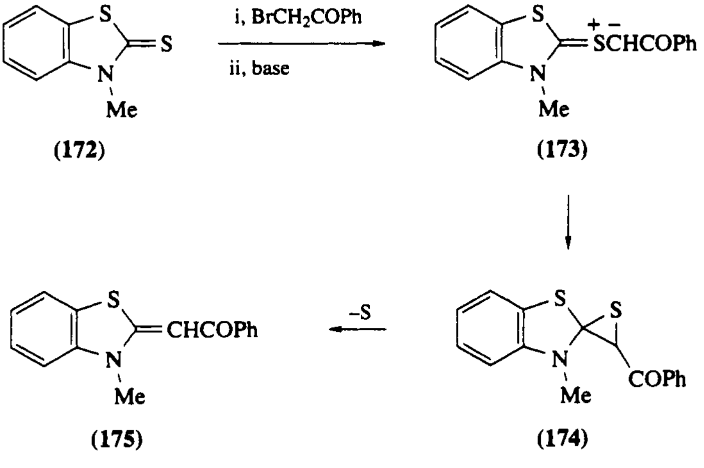

**Scheme 40**

The most flexible and general route to thiocarbonyl ylides involves the $\Delta^3$-1,3,4-thiadiazoline (**177**) ring system as the dipole precursor.[28] Mild thermolysis of (**177**) releases nitrogen and produces the thiocarbonyl ylide (**178**). The principle involved is that of a retro-1,3-dipolar cycloaddition.[147] Two generalized routes to the precursor (**177**) are shown in Scheme 41.[148–150] The thiocarbonyl ylide (**178**) generated as a reactive and short-lived intermediate can be trapped by various dipolarophiles. Kinetic analysis of the reaction establishes unambiguously the transitory existence of intermediate (**178**). The predicted conrotatory ring closure occurs to give thiirane (**180**) in the absence of trapping agents. Cycloaddition of (**178**) proceeds with retention of configuration as predicted.[10]

Thiocarbonyl ylides can also be generated *via* the electrocyclic ring closure of divinyl sulfides. Schultz has studied this transformation in some detail.[151] The formation of (**182**) from the irradiation of (**181**) has been rationalized in terms of an electrocyclic ring closure to generate thiocarbonyl ylide (**183**) which then undergoes a 1,4-hydrogen shift to give (**182**; Scheme 42). The successful trapping of the dipole intermediate with *N*-phenylmaleimide, to produce (**184**) provides strong support for the suggested mechan-

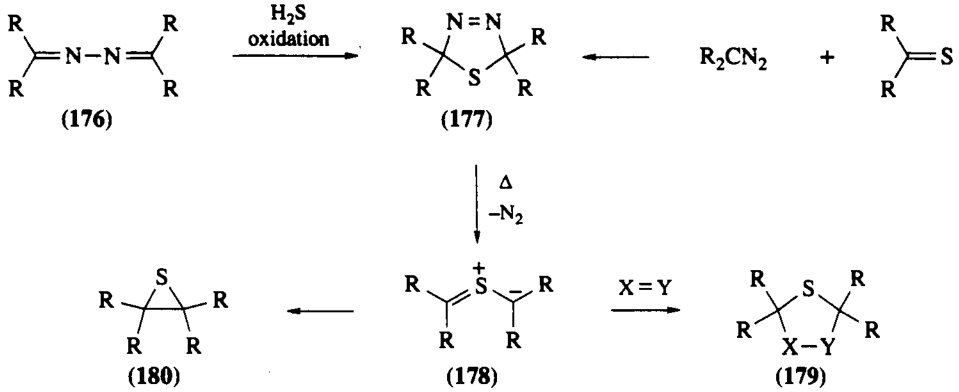
R
R
N–N
R
R
(176)
H₂S
oxidation
N=N
R
R
S
R
R
(177)
R₂CN₂
+
R
S
R
Δ
–N₂
S
R
R
R
R
(180)
R
S
+
–
R
R
R
(178)
X=Y
R
S
R
R
X–Y
R
(179)

Scheme 41

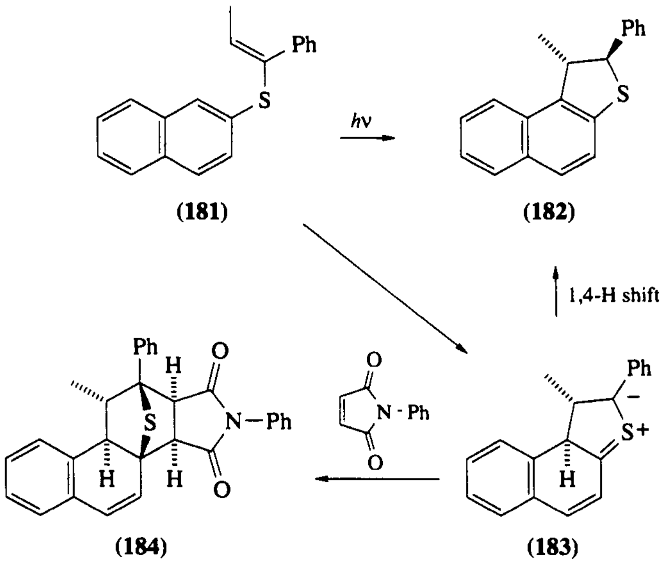
Ph
S
(181)
hν
Ph
S
(182)
1,4-H shift
Ph
H
O
S
N–Ph
H
H
O
(184)
O
N - Ph
O
Ph
–
S+
H
(183)

Scheme 42

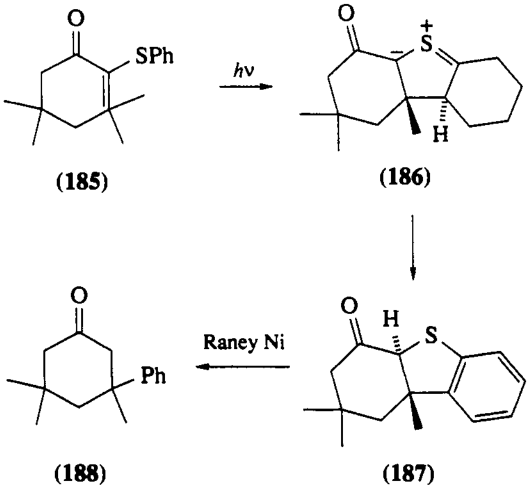
O
SPh
(185)
hν
O
S
+
–
H
(186)
O
Ph
(188)
Raney Ni
O
H
S
(187)

Scheme 43

ism. A clever variation of the above reaction was used by Schultz for the preparation of 3-phenylcyclohexanones.[151] Essentially the same reaction sequence was used here except that the final product was desulfurized. The overall effect is that an aryl group has been added in Michael fashion to an enone (Scheme 43).

Another route which has recently been used to generate thiocarbonyl ylides involves the bromodesilylation reaction of α-bromosilyl silyl sulfide (**189**). This process is related to the methodology first developed by Padwa for the preparation of azomethine ylides. Thus, heating a sample of (**189**) generates thiocarbonyl ylide (**190**) which can be trapped with various dipolarophiles to give cycloadducts of type (**191**; Scheme 44).

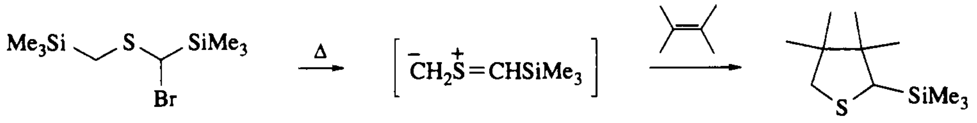

**(189)** **(190)** **(191)**

**Scheme 44**

Further work by the Achiwa group has demonstrated that this desilylation protocol can be used to generate the simple trimethylsilylthioaldehyde *S*-methylide (**193**).[152] The strategy employed the release of disiloxane from bis(trimethylsilylmethyl) sulfoxide (**192**) through a pathway related to a sila-Pummerer rearrangement. Heating a sample of sulfoxide (**192**) with a dipolarophile in HMPA at 100 °C gave the corresponding cycloadduct (**195**; Scheme 45) in 55–80% yield. Both alkenes and alkynes were used as dipolarophiles.

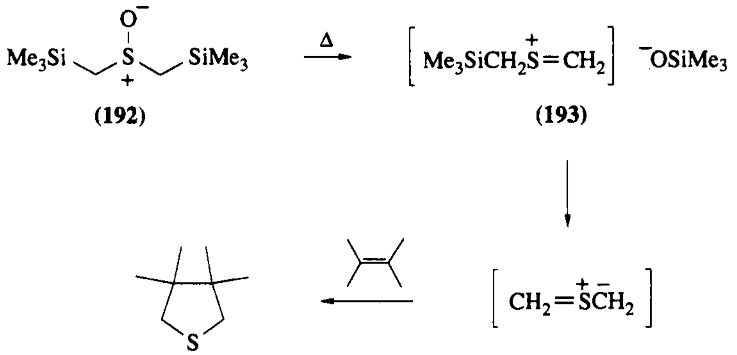

**(192)** **(193)**

**(195)** **(194)**

**Scheme 45**

### 4.9.6.8 Azomethine Imines

Azomethine imines possess the two-nitrogen 4π-dipolar system (**196**; equation 7) and therefore fall into the category of 1,3-dipoles without an orthogonal double bond.[153] The resonance form (**196a**) is expected to be more important as a result of the higher electronegativity of nitrogen relative to carbon. The condensation of aldehydes with *N*,*N*′-disubstituted hydrazines is a frequently employed method for generating azomethine imines.[154] Placing an acyl group on the nitrogen end of the dipole, as in (**197**), lowers both the HOMO and the LUMO of the unsubstituted azomethine imine. Reaction of (**197**) with conjugated alkenes like styrene turns out to be a dipole LUMO-controlled process, thereby accounting for the preferential formation of cycloadduct (**198**; Scheme 46).[155] When unsaturated aldehydes are used, the

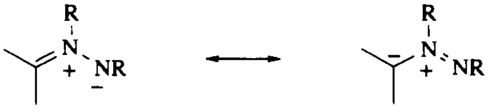

(7)

**(196a)** **(196b)**

reactions first give the 1,3-dipole, and are then followed by an intramolecular dipolar cycloaddition. An interesting application of this method involves the conversion of (**199**) to the diaza[3.2.1]octane system (**200**; equation 8) in 69% overall yield.[156]

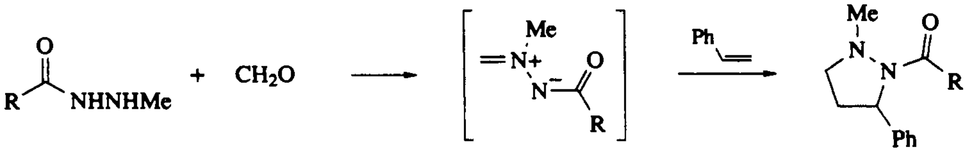

**(197)** **(198)**

**Scheme 46**

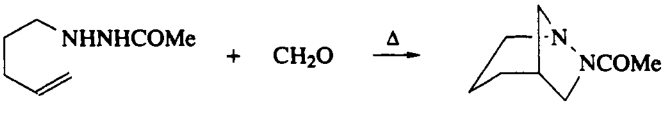

**(199)** **(200)** (8)

Hydrazones have also been used as azomethine imine precursors to achieve cycloadditions.[157] Protonated hydrazones act under suitable conditions as quasi-azomethine imines in polar [$3^+ + 2$] cycloadditions. Thus, acetaldehyde phenylhydrazone (**201**) was found to react with styrene in the presence of sulfuric acid in a regiospecific manner to give pyrazolidine (**203**; Scheme 47) as a diastereomeric mixture.[157] The most commonly used azomethine imine has a phenyl group attached to one end of the dipole and hence has a raised HOMO relative to the unsubstituted system. Because the coefficients at the terminal atoms of the dipole are smaller in the LUMO than they are in the HOMO, the phenyl group does not lower the energy of the LUMO as much as it raises the energy of the HOMO. With electron-deficient dipolarophiles like methyl acrylate, the reaction is dipole HOMO-controlled, and mixtures can be expected. In fact, a 1:1 mixture of regioisomers was obtained in the reaction of (**201**) with acrylonitrile (equation 9).[157]

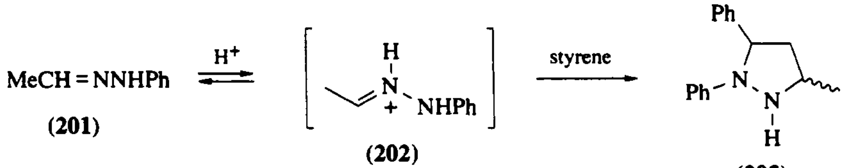

**(201)** **(202)** **(203)**

**Scheme 47**

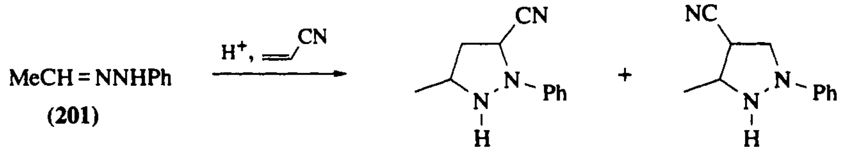

**(201)** **(204)** **(205)** (9)

### 4.9.6.9 Mesoionic Ring Systems

Mesoionic compounds have been known for many years and have been extensively utilized as substrates in 1,3-dipolar cycloadditions.[158–160] Of the known mesoionic heterocycles, munchnones and sydnones have generated the most interest in recent years. These heterocyclic dipoles contain a mesoionic aromatic system (*i.e.* **206**) which can only be depicted with polar resonance structures.[158] Although sydnones were extensively investigated after their initial discovery in 1935,[160] their 1,3-dipolar character was not recognized until the azomethine imine system was spotted in the middle structure of (**206**). *C*-Methyl-*N*-phenylsydnone (**206**) combines with ethyl phenylpropiolate to give the tetrasubstituted pyrrole (**208**; Scheme 48). Kinetic studies revealed that the rate-determining cycloaddition to give the bicyclic intermediate (**207**) is succeeded by a fast elimination of $CO_2$.[161] In the analogous reaction of *N*-phenylsydnone with styrene, the intermediate (**209**) suffers a 1,3-dipolar cycloreversion giving a new azomethine imine (**210**), which is no longer stabilized by aromaticity as was the case with the sydnone. This species either undergoes a 1,4-hydrogen shift to give 2-pyrazoline (**211**; Scheme 49), or adds a second molecule of the dipolarophile.[162]

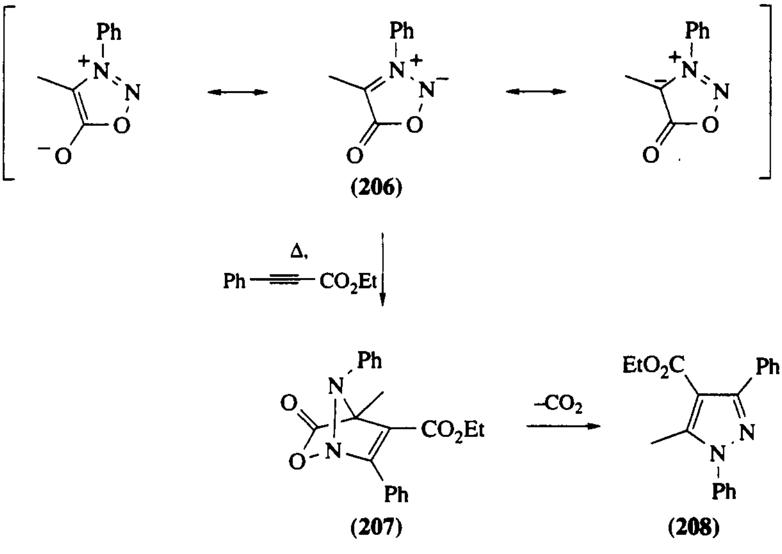

Scheme 48

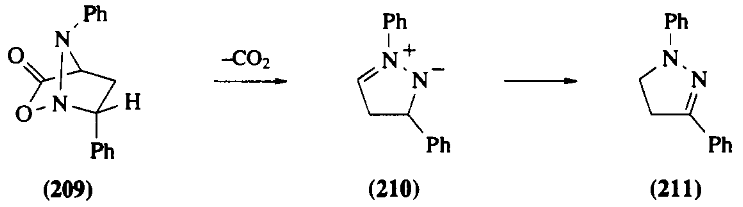

Scheme 49

When sydnones are used as 1,3-dipoles, the dipole LUMO and dipolarophile HOMO interaction has been suggested to be the controlling term.[163] Calculations by Houk indicate that the terminal coefficients of the azomethine imine system are almost identical in the LUMO.[164] Although LUMO control of reactivity will dominate, a decrease in regioselectivity of sydnone cycloaddition with respect to that observed with simpler azomethine imines is expected. In fact, sydnones do undergo regioselective reactions, but the degree of regioselectivity appears to be smaller than is observed with simpler azomethine imines.[163] For example, *N*-phenylsydnone is known to react with all three classes of dipolarophiles to give predominantly the products resulting from intermediate adduct (**212**).[165] Methyl propiolate gives a 4:1 mixture of adducts arising from (**212**) and the other regioisomer (**213**), respectively (Scheme 50).

Huisgen and coworkers have also described the cycloaddition behavior of the 'munchnones', unstable mesoionic $\Delta^2$-oxazolium 5-oxides with azomethine ylide character.[166] Their reactions closely parallel those of the related sydnones. These mesoionic dipoles are readily prepared by cyclodehydration of *N*-acyl amino acids (**216**) with reagents such as acetic anhydride. The reaction of munchnones with alkynic dipolarophiles constitutes a pyrrole synthesis of broad scope.[158-160] 1,3-Dipolar cycloaddition of alkynes to the $\Delta^2$-oxazolium 5-oxide (**217**), followed by cycloreversion of carbon dioxide from the initially formed adduct (**218**), gives pyrrole derivative (**219**; Scheme 51) in good yield. Cycloaddition studies of munchnones with other dipolarophiles have resulted in practical, unique syntheses of numerous functionalized monocyclic and ring-annulated heterocycles.[167-169]

Houk has suggested that unsymmetrically substituted azomethine ylides such as munchnones will react readily with both electron-deficient and electron-rich dipolarophiles due to the narrow frontier orbital

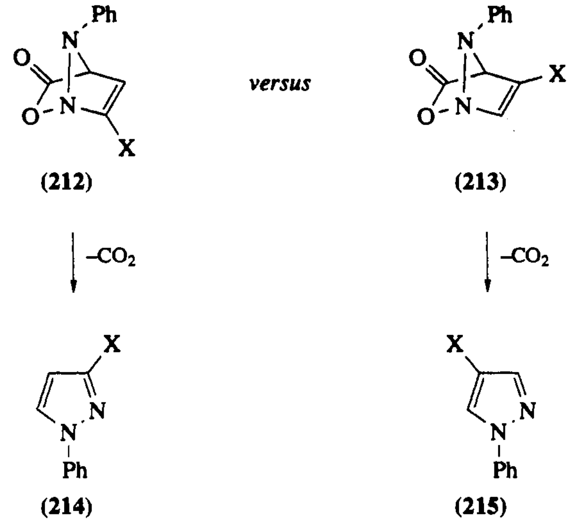

Scheme 50

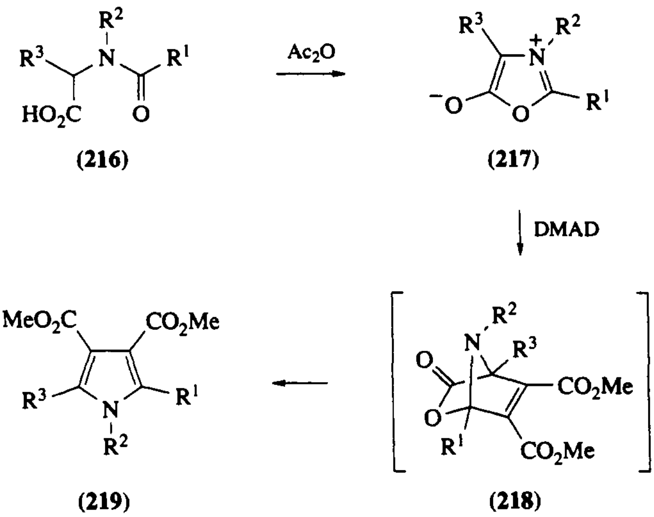

Scheme 51

separation[170] (*i.e.* Sustmann Type 2 classification).[21] The regiochemistry of the cycloaddition should be controlled by asymmetry in the dipole frontier orbitals caused by the substituent groups. Examples of dipolar cycloadditions of other mesoionic compounds can be found in several reviews.[158–160]

### 4.9.6.10 Ozone

Combination of an oxygen atom with the oxygen molecule yields the triatomic modification ozone. Despite the high oxidation potential of ozone, its reactions with organic compounds display considerable specificity. Reaction of ozone with alkenes has been formulated as a 1,3-dipolar cycloaddition.[7] The basic mechanism that describes the ozonolysis of an alkene to produce a secondary ozonide evolved during the 1950s and is now well recognized as the Criegee mechanism.[171–175] It consists of a 1,3-dipolar cycloaddition of ozone, a 1,3-dipolar cycloreversion to carbonyl oxide (**221**) and a carbonyl compound, followed by a renewed 1,3-cycloaddition producing the ozonide (Scheme 52). Criegee assumed a two-step cleavage of the 1,2,3-trioxolane (**220**) and formulated the carbonyl oxide as a zwitterion. Carbonyl oxides (Criegee zwitterions) have never been isolated, but indirect evidence for their existence is abundant. Although these species are usually generated by ozonolysis of a suitable alkene, evidence has been presented for their formation by reaction of a carbene with oxygen.[176] Carbonyl oxide reactions are LUMO-controlled and cycloadditions should be facile only with electron-rich species.

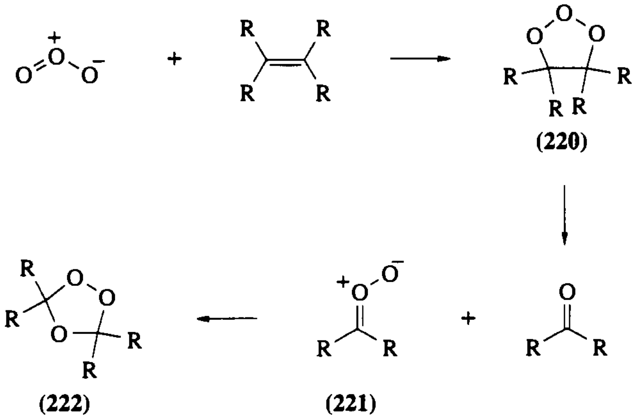

Scheme 52

Additional work by Criegee's group has shown that the ozonolysis of 1,2-disubstituted 1-cyclopentenes (*e.g.* **223**) containing different substituents in the 4-position of the ring produces carbonyl oxides such as (**224**) as reaction intermediates.[177] This dipole undergoes intramolecular 1,3-dipolar cycloaddition with each of the two functional groups present. Thus two different ozonides are formed, in the present case (**225**) and (**226**; Scheme 53). This reaction strategy was further pursued to evaluate the relative reactivity of nonequivalent carbonyls with the carbonyl oxide intermediate. In this way the 1,3-dipolarophilic character of carbonyl groups was estimated to be formyl > acetyl > benzoyl.[177]

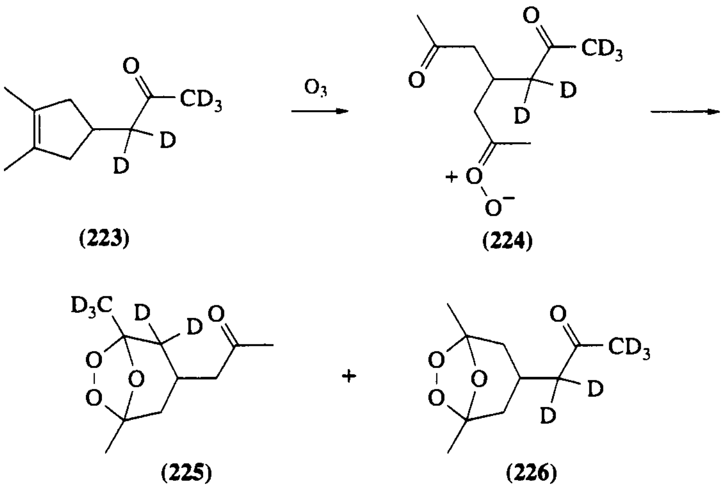

Scheme 53

### 4.9.6.11 Azides

The cycloaddition of azides to multiple π-bonds is an old and widely used reaction. Organic azides are well known to behave as 1,3-dipoles in thermal cycloaddition reactions.[178] The first example of this reaction was observed by Michael in 1893.[179] Since then the addition of azide to carbon–carbon double and triple bonds has become the most important synthetic route to 1,2,3-triazoles, -triazolines and their derivatives.[180–184] The cycloadditions of simple organic azides with electron-rich dipolarophiles are LUMO controlled.[3] Since the larger terminal coefficients are on the unsubstituted nitrogen in the azide and unsubstituted terminus in the dipolarophiles, the 5-substituted $\Delta^2$-triazolines are favored, in agreement with experiment.[185–187] Reactions with electron-deficient dipolarophiles are HOMO controlled, and union of the substituted azide N with the unsubstituted dipolarophile C leads to 4-substituted $\Delta^2$-triazolines (Scheme 54).[178] Sustmann correlated the reactivity of 21 alkenes with phenyl azide by means of the alkene ionization potentials.[188] The plot of the rate constants forms a curve, resembling a parabola, with a minimum at 9.8 eV. This is exactly what FMO theory predicts for a system in which the mechanism changes from dipole LUMO to dipole HOMO control.

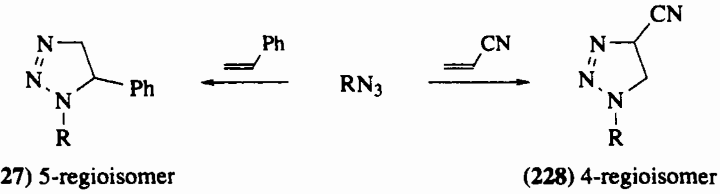

Scheme 54

Simple carbon–carbon double bonds react slowly with azides and frequently take more than a week to react at 25 °C. Increasing the reaction temperature is restricted by the thermal lability of most triazolines. In fact, some classes of triazolines decompose spontaneously at room temperature with the extrusion of nitrogen.[189] The principal decomposition modes involve the formation of aziridines and imines and are outlined in Scheme 55. Usually, just a few of these modes operate in any particular system.[190]

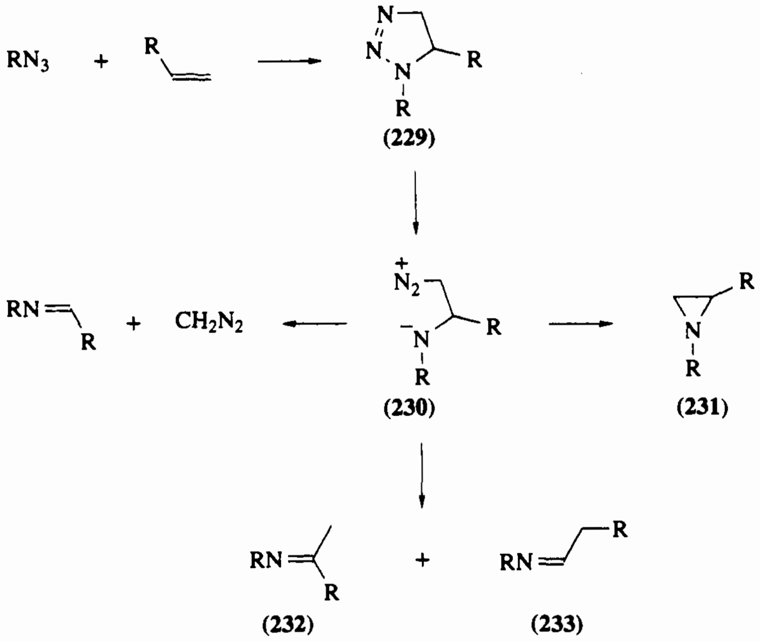

Scheme 55

Alkynes add to azides to form 1,2,3-triazoles (equation 10). In contrast to the azide additions to alkenes, the regioselectivity with alkynes is low and usually mixtures of triazoles are formed.[178] Alkynes have HOMO energy levels lower than those of the corresponding alkenes, although the LUMOs are ap-

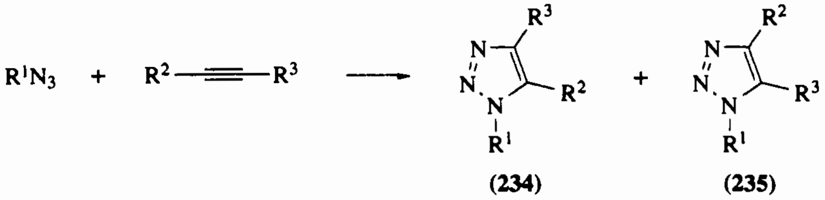

(10)

proximately at the same level. Consequently, most alkynes undergo simultaneously both azide LUMO- and azide HOMO-controlled cycloadditions.

Although less reactive than C—C triple bonds, C—N triple bonds are also known to undergo 1,3-dipolar cycloadditions with some organic azides. An interesting example of this reaction which occurs intramolecularly involves the conversion of 2′-azido-2-phenylcarbonitrile (**236**) into tetrazolophenanthridine (**237**; equation 11).[191]

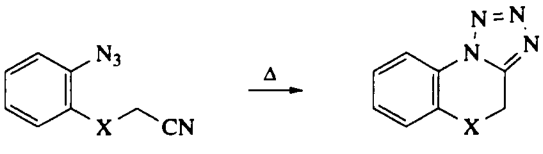

(**236**) X = O, $CH_2$ (**237**) (11)

The intramolecular 1,3-dipolar cycloaddition reaction of azides has become an increasingly useful process for the construction of natural products and molecules of theoretical interest.[192,193] For example, 2-substituted azido enone (**238**) was prepared from the corresponding bromide by treatment with sodium azide. Thermolysis of this material afforded aziridinyl ketone (**240**) presumably *via* a transient dipolar cycloadduct (**239**).[193] Ketone (**240**) was subsequently converted to an intermediate previously used to prepare histrionicotoxin (**241**; Scheme 56).

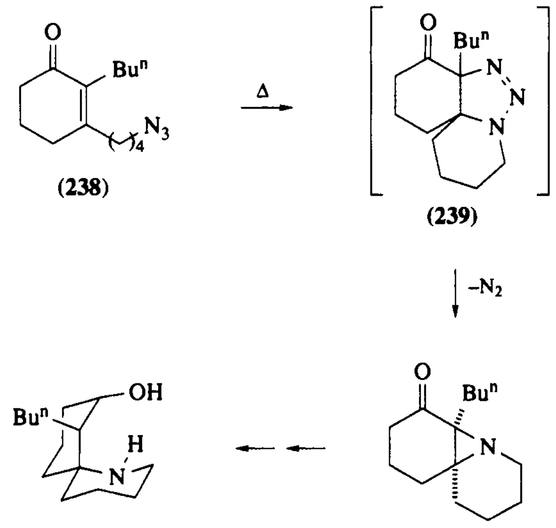

(**238**) (**239**) (**241**) (**240**)

Scheme 56

A very interesting sequence of intramolecular dipolar cycloaddition–nitrogen extrusion retro-Diels–Alder reactions that lead to pyrrole (**247**) was uncovered by Shultz and Sha.[194] These workers found that the thermolysis of azido dienone (**242**) in refluxing benzene gave triazoline (**243**) in high yield. Brief irradiation of (**243**) in methanol produced pyrrole carboxylic ester (**247**) in quantitative yield. The mechanism suggested for the formation of (**247**) involves homolytic extrusion of nitrogen from (**243**) to give diradical (**244**), from which recombination yields the bridged intermediate (**245**). Tricyclic (**245**) is formally an intramolecular pyrrole ketene Diels–Alder adduct and retro-Diels–Alder reaction of (**245**) would lead to the pyrrole ketene. Reaction of (**246**) with methanol nicely accounts for the formation of pyrrole carboxylic ester (**247**; Scheme 57).

### 4.9.6.12 Diazoalkanes

Apart from the significance of diazoalkanes for the generation of carbenes,[195] these compounds also play a dominant role in dipolar cycloaddition chemistry.[196,197] Recent advances in the synthesis of di-

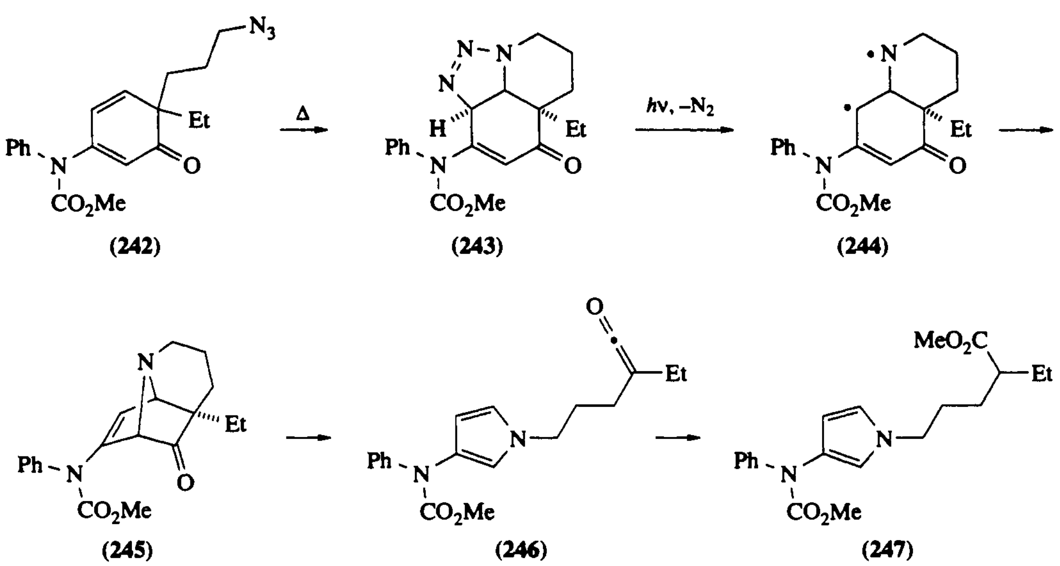

Scheme 57

azoalkanes have frequently led to new applications in cycloaddition chemistry.[198] The additions of diazoalkanes to alkenes are among the most thoroughly studied 1,3-dipolar cycloadditions. Tosylhydrazones are commonly used as precursors to generate diazoalkanes. The cycloadditions of simple diazoalkanes are HOMO (dipole)–LUMO(dipolarophile) controlled (equation 12).[196] Both conjugating and electron-attracting groups accelerate reactions of dipolarophiles with diazoalkanes as compared to ethylene. With these dipolarophiles, 3-substituted $\Delta'$-pyrazolines are favored, a result of the union of the larger diazoalkane HOMO coefficient on carbon with that of the larger dipolarophile LUMO coefficient on the unsubstituted carbon. Huisgen has shown that introduction of a methoxycarbonyl group into diazomethane shifts the 1,3-dipole to a Type 2 (Sustmann's classification)[21] in methyl diazoacetate and further toward a Type 3 for dimethyl diazomalonate and methyl diazo(phenylsulfonyl)acetate.[199] Electron-releasing substituents in the diazoalkane, on the other hand, raise the HOMO energy and enhance the cycloaddition rate.[200] 3-Substituted pyrazolines are formed as the major products in the 1,3-dipolar cycloaddition of diazomethane with 1-alkenes.[201,202] With these systems, the difference between the two frontier orbital interactions is quite small, but the nearly equal magnitude of the terminal coefficients in the diazomethane LUMO suggests that the diazomethane HOMO determines product regiochemistry. As is frequently observed for cycloadditions of diazo compounds to alkenes, the initial cycloadducts are unstable and readily undergo further reactions. Thus, the pyrazoline (**248**), generated from diazomethane and 3-cyanopropene, escapes isolation by undergoing a very facile hydrogen shift to give $\Delta^2$-pyrazoline (**249**; Scheme 58).[196]

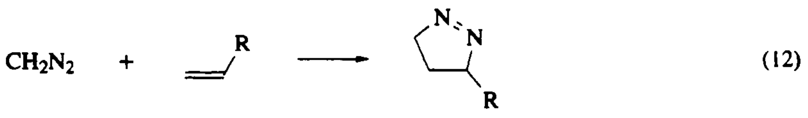

(12)

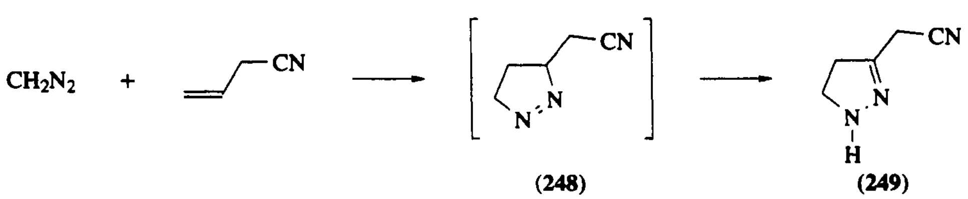

Scheme 58

Elimination of nitrogen from the $\Delta^1$-pyrazoline to give cyclopropanes frequently occurs, even during the cycloaddition step.[196] This reaction profits considerably from an increase in temperature. Thus, although $\Delta^1$-pyrazoline (**251**), which arises from 9-diazoxanthene (**250**) and methyl acrylate at –20 °C, can be isolated, it is transformed into a mixture of $\Delta^2$-pyrazoline (**252**) and the spirocyclopropane (**253**) on warming to room temperature (Scheme 59).[203]

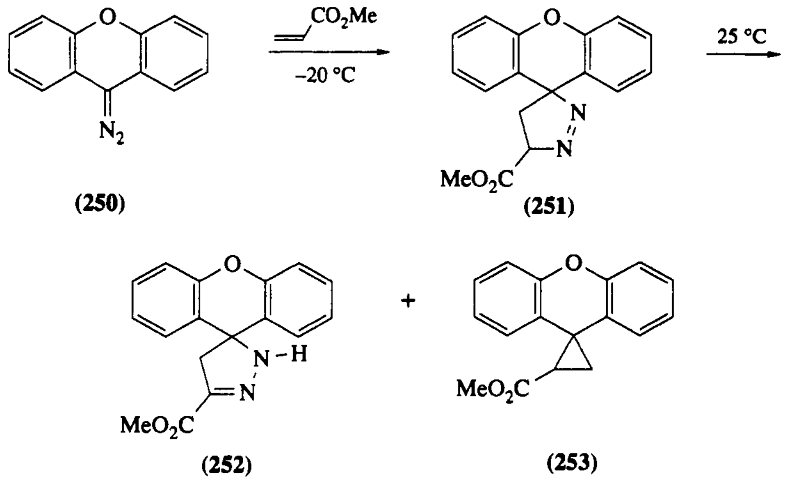

**Scheme 59**

Although it has been established that the HOMO (diazoalkane)–LUMO (alkene) controlled concerted cycloaddition occurs without intervention of any intermediate for the reactions of simple diazoalkanes with alkenes, Huisgen once proposed a mechanistic alternative;[4] namely an initial hypothetical nitrene-type 1,1-cycloaddition reaction of phenyldiazomethane to styrene followed by a vinylcyclopropane–cyclopentene-type 1,3-sigmatropic rearrangement. Control experiments, however, excluded this hypothesis for the bimolecular 1,3-dipolar cycloaddition reaction of diazomethane (Scheme 60).[204]

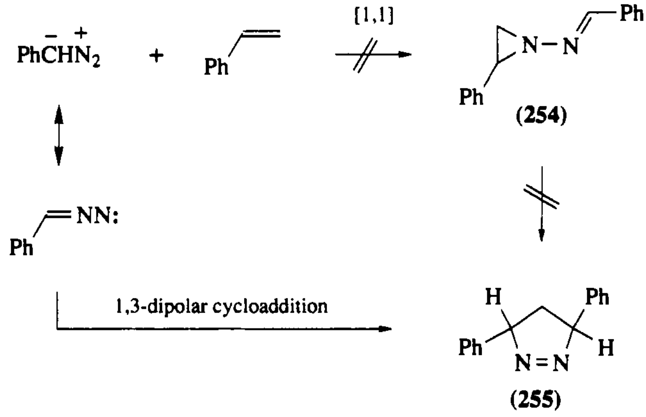

**Scheme 60**

The hypothetical nitrene reactivity of the terminal nitrogen of diazomethane was simultaneously uncovered by Miyashi[205] and Padwa.[206] Various allyl-substituted diazomethanes generated by pyrolyses of the sodium salts of the corresponding tosylhydrazones were found to undergo a reversible intramolecular nitrene-type 1,1-cycloaddition to give 1,2-diazabicyclo[3.1.0]hex-2-enes (Scheme 61). Further work established that these allyl-substituted diazoalkenes undergo the intramolecular 1,1-cycloaddition with complete retention of configuration. It was concluded by both groups that the 1,1-cycloaddition reaction occurs concertedly without intervention of a zwitterionic intermediate, being controlled by the electrophilic LUMO energy of diazomethane. The results parallel the stereospecific addition of singlet nitrenes[207] and the intramolecular 1,1-cycloaddition of nitrile ylides[87] and nitrile imines.[104] Formation of the 1,2-diazabicyclohexene ring seems to be limited to α-phenyl-substituted derivatives.

α-Diazo ketones represent an interesting subclass of diazoalkanes since several discrete modes of bimolecular cycloaddition are possible.[208] Among these are those involving the diazoalkane moiety or a re-

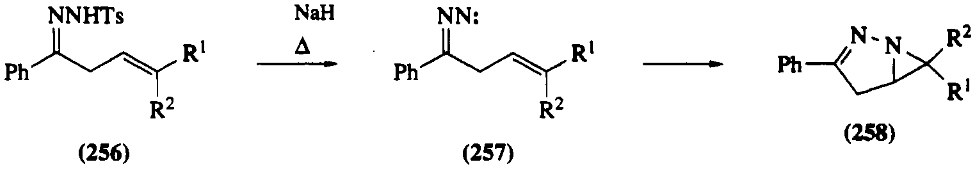

**Scheme 61**

active intermediate possessing the stoichiometry of a keto carbene species derived from an initial loss of nitrogen (Scheme 62). Much less common modes of addition involving the extended 6π-electron 1,5-dipolar system are also observed with certain quinonoid α-diazo ketones.[209] The use of extended diazoalkanes with six or more electrons has not received much attention despite the obvious synthetic and theoretical interest in such processes. When the diazoketone moiety is incorporated into a heterocyclic ring, dipolar cycloaddition processes can provide ready access to more elaborate and rare heterocyclic ring systems (Scheme 63).[210–213]

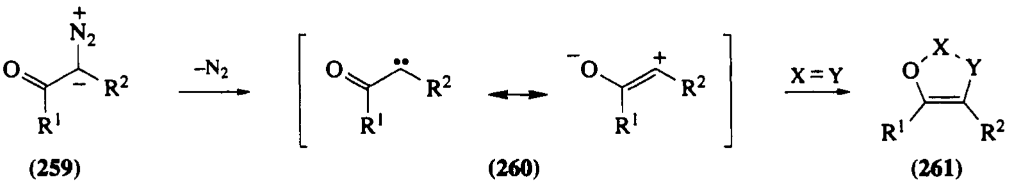

**Scheme 62**

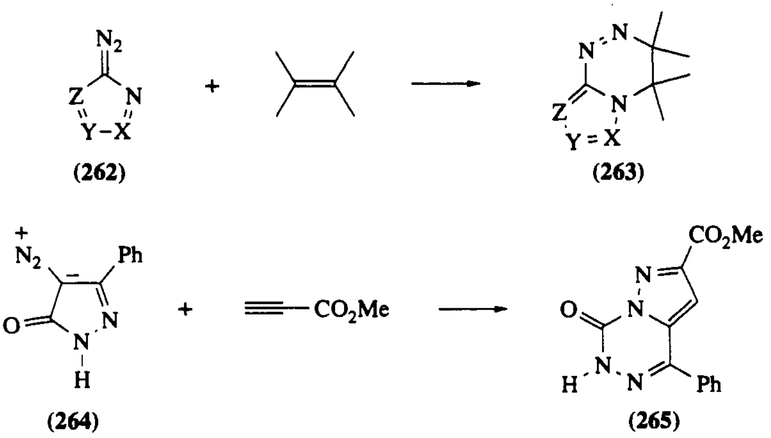

**Scheme 63**

## 4.9.7 CONCLUSION

The prominent role that 1,3-dipolar cycloaddition reactions play in the elaboration of a variety of organic molecules has become increasingly apparent in recent years. The ease of the cycloaddition, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereochemical control of the cycloaddition, and the fair predictability of its regiochemistry have contributed to the popularity of the reaction. In the realm of synthesis, in which a premium is put on the rapidity of construction of polyfunctional, highly bridged carbon and heteroatom networks, the dipolar cycloaddition reaction has now emerged as a prominent synthetic method. In the past decade, interest in the intramolecular 1,3-dipolar cycloaddition reaction, where the dipole and dipolarophile are constrained in the same molecule, has increased exponentially. When the reacting components are themselves cyclic or have ring substituents, complex multicyclic arrays, such as those contained in drugs and natural products, can be constructed in a single step. Often the syntheses of molecules of this complexity are more difficult and lengthy by other routes. Future developments will no doubt continue to enhance the synthetic utility of the dipolar cycloaddition reaction. After a century of research in this field, there is no end in sight.

## ACKNOWLEDGEMENT

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# 4.10

# Intramolecular 1,3-Dipolar Cycloadditions

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## 4.10.1 INTRODUCTION

The most general approach to synthesis of five-membered heterocyclic compounds involves cycloaddition of a 1,3-dipole to an appropriate unsaturated substrate, the dipolarophile. Intermolecular cycloadditions result in the formation of one new ring only. When the 1,3-dipole and the substrate are part of the same molecule, cycloaddition is intramolecular and leads to a new bicyclic system. Thus, intramolecular cycloadditions are amenable to the construction of inherently more complex products than intermolecular cycloadditions. Markedly different regioselectivity, controlled by the geometric constraints of bringing the 1,3-dipole into correct internal alignment for reaction with the dipolarophile, is often observed in an intramolecular cycloaddition. Sometimes these geometric constraints overwhelm the normal regiochemical preference dictated by electronic factors. The greater steric constraint inherent to intramolecular cycloaddition often affords higher diastereofacial discrimination: accordingly, these reactions can exhibit very high stereoselectivity. Periselectivity can also be different for an intramolecular cycloaddition, leading to formation of unusual bicyclic systems, containing other than five-membered heterocycles.

With all of these advantages, intramolecular cycloaddition is certainly a powerful synthetic tool. However, prior assembly of the 1,3-dipole and the dipolarophile within the same molecule is required. Careful consideration of transition state geometries is also essential: an accurate molecular model should always be constructed, preferably prior to carrying out the intramolecular cycloaddition. It is even better to do a calculational treatment prior to attempting the reaction. The recent development of routine molecular mechanics programs portends a much more accurate approach to predicting the outcome of an intramolecular cycloaddition.

There is an excellent recent review on intramolecular dipolar cycloadditions.[1] Reviews on mechanistic aspects of intermolecular 1,3-dipolar cycloadditions abound[2] and a treatise on intramolecular Diels–Alder cycloadditions is available.[3]

## 4.10.2 NITRONE CYCLIZATIONS

### 4.10.2.1 General

The earliest and to date most extensively studied class of intramolecular cycloadditions involves unsaturated nitrones.[4] These are most readily available from condensation of an unsaturated aldehyde with a hydroxylamine or an unsaturated hydroxylamine with an aldehyde. Another approach is simply to oxidize an unsaturated hydroxylamine. Nitronic esters are nitrones containing an alkoxy substituent attached to the N-atom: they can be prepared from nitro compounds. Frequently an unsaturated nitrone can be isolated and purified, although much work has been done with the nitrone generated *in situ*; eventual cyclization can provide three new contiguous chiral centers, often with only one diastereomer actually formed.

The outcome of cyclization depends on the intervening chain (bridge) separating the nitrone from the dipolarophile and whether this bridge is attached at C or N of the nitrone. Also important are the nonbonding interactions and entropic differences for competing cycloaddition pathways. Incorporation of the nitrone and/or dipolarophile in an existing ring system offers possibilities for the construction of a wide variety of polycyclics.

### 4.10.2.2 Open-chain Alkenylnitrones

#### *4.10.2.2.1 C-(5-Alkenyl)nitrones*

Cyclization of *C*-(5-alkenyl)nitrones typically produces an eight-membered 5,5-fused product and no bridged product as originally demonstrated by LeBel *et al.*[4] As a recent example, cyclization of the nitrone derived from aldehyde (**1**) led to isomeric fused isoxazolidines (**2**) and (**3**) in a 96:4 *anti*:*syn* ratio: no bridged isomers were detected (Scheme 1).[5,6] Similarly, aldehyde (**4**) afforded the fused isoxazolidines (**5**) and (**6**) in a 92:8 *anti*:*syn* ratio. These results illustrate three other important features of intramolecular nitrone cycloaddition. First, the stereochemistry of the alkenyl group is retained. Thus, (*Z*)-(**1**) led to *cis* products, whereas (*E*)-(**4**) led to *trans* products. Second, only *cis*-fused cyclization products were observed, presumably because a much higher energy transition state would be required to obtain *trans*-fused five-membered rings. Third, there was a high degree of asymmetric induction: the allylic chiral center, here outside of the incipient bicyclic system, controlled facial selectivity.

Intramolecular cycloaddition of nitrone (7) led to the diastereomeric fused isoxazolidines (**8a**) and (**8b**) in an 82:18 ratio (Scheme 2).[7a] The authors suggested cyclization through competing conformational isomers A and B as a rationale of the cyclization outcome. Notably, absence of the *trans*-alkenyl methyl

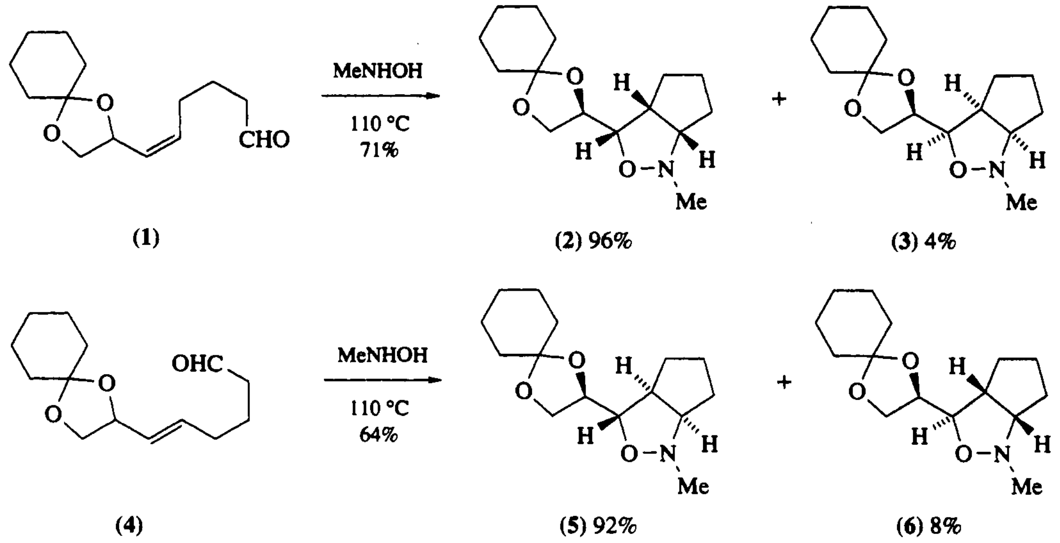

Scheme 1

group led to lower diastereoselection. The major product, isoxazolidine (**8a**) was transformed in three steps to acosamine. Reductive cleavage of the N—O bond is a very common transformation of isoxazolidines: γ-amino alcohols are typically obtained. Here hydrogenolysis over Pd—C was employed and concomitant debenzylation was accomplished. Nitrones are easily derived from sugars. For example, lactol (**9**) was prepared from D-ribose; reaction of (**9**) with *N*-methylhydroxylamine afforded the nitrone which cyclized *in situ* to the 5,5-fused bicyclic isoxazolidine (**10**).[7b]

### *4.10.2.2.2 C-(6-Alkenyl)nitrones*

Cyclization of *C*-(6-alkenyl)nitrones leads to competitive formation of the nine-membered 6,5-fused ring system and bridged bicyclo[4.2.1]nonyl system. For example, NMR analysis of nitrone-derived products obtained from ketone (**11**) indicated a 62:38 mixture of fused isoxazolidine (**12a**) and bridged isoxazolidine (**12b**), respectively (Scheme 3).[8] The preference for the 6,5-fused ring system is typical: it is entropic in nature. Frontier MO theory suggests a more developed C—C bond than C—O bond in the typical nitrone cycloaddition transition state. Formation of the fused product occurs through a six-membered carbocyclic transition state, whereas the bridged product is formed *via* a seven-membered carbocyclic transition state. This factor is usually, but not always, more important than opposing factors. Thus, nitrones (**13a**) and (**13b**) gave the 6,5-fused isoxazolidines (**14a**) and (**14b**) as the only detectable cyclization products.[9] Conversely, nitrones (**15a**) and (**15b**) gave the bridged 7-aza-8-oxabicyclo[4.2.1]nonanes (**16a**) and (**16b**) as the only detectable products. The major reason for the abrupt change in regiochemistry is presumably steric: the phenyl substituent in (**15a–b**) would interact unfavorably with the larger nitrone terminus, the substituted C- rather than the unsubstituted O-atom. Another contributory factor (with **15a** only) should be the electronic preference: nitrones prefer to cycloadd to alkenes affording five-rather than four-substituted isoxazolidines.

Whether *cis* or *trans* fusion is observed in nitrone cycloadditions can depend on reaction conditions as first determined by LeBel *et al.*[8] At lower temperature where cycloaddition is irreversible, kinetic control prevails and this usually favors *cis* fusion. However, at higher temperature equilibration can occur through retrocycloaddition and the more stable product will predominate (*i.e.* thermodynamic control). The nitrone may also undergo (*E*)/(*Z*) isomerization, particularly at elevated temperature, and this complicates the analysis: a different kinetically favored ratio might prevail. A recent example of temperature dependence involves formation of isoxazolidines (**18**) and (**19**) from aldehyde (**17a**; Scheme 4). At 90 °C *cis*-fused (**18**) and *trans*-fused (**19**) were formed in 74% and 9% yield, respectively. At 140 °C, however, (**18**) and (**19**) were formed in 31% and 34% yield.

The isoxazolidines derived from aldehydes (**17a–b**) were converted to eudesmane sesquiterpenes. Thus, quaternization of isoxazolidine (**18**) was followed by ring expansion *via* a Stevens rearrangement.

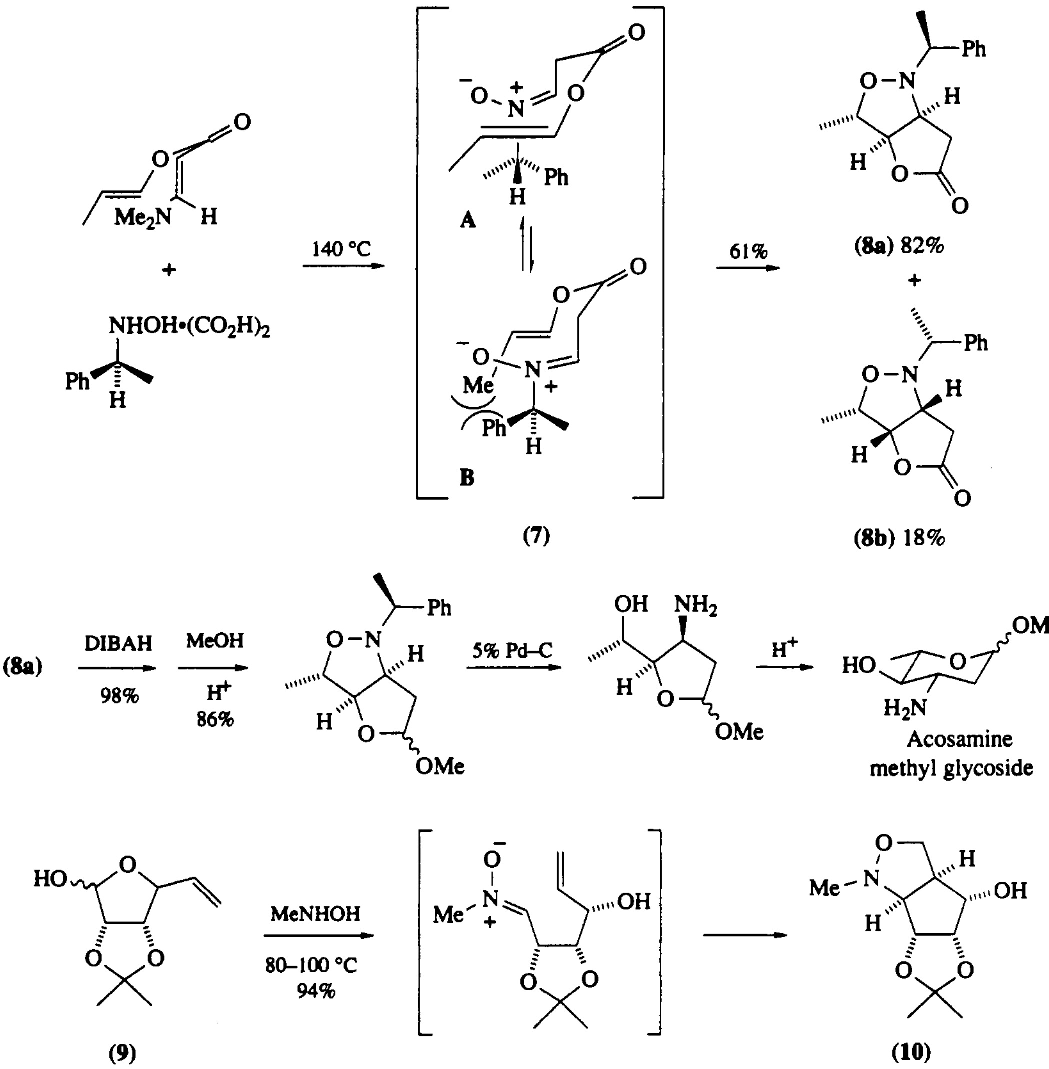

Scheme 2

Quaternization of the resulting tetrahydro-1,3-oxazine (**20**) and subsequent hydrogenolysis with lithium in liquid ammonia provided the nitrogen-free (±)-5-epi-α-eudesmol.

### *4.10.2.2.3 N-(Alkenyl)nitrones*

*N*-(Alkenyl)nitrones must always cyclize to give a new bridged bicyclic system. For example, nitrones (**21a–b**) gave the 1-aza-2-oxabicyclo[2.2.1]heptanyl derivatives (**22a–b**) in 76% and 85% yield, respectively (Scheme 5).[11] Regioselectivity depends heavily on the length of the intervening bridge. Thus, nitrones (**23a–b**) gave regioisomeric 1-aza-8-oxabicyclo[3.2.1]octanyl derivatives (**24a–b**) in 95% and 69% yield, respectively. In all of these cases, only one isomer was detected. Formation of (**22a–b**) occurred *via* a six-membered cyclic transition state avoiding angle strain inherent to formation of the other regioisomer. Formation of (**24a–b**) occurred *via* six-membered transition state A, entropically favored over seven-membered transition state B leading to the regioisomer. These rationalizations are predicated on the assumption that C—C bond formation is further developed in the transition state than C—O bond formation, in agreement with frontier molecular orbital theory. Accordingly, nitrone (**25**) with a longer bridge afforded a 75:25 mixture of isomers through competing seven- and eight-membered transition states, respectively.

Relatively low stereoselectivity in the cyclization of *N*-(alkenyl)nitrones (**26**) and (**27**) has been reported (Scheme 6).[12a] Cyclization of (**26**) led to an 80:11:9 ratio of the *exo,exo-*, *exo,endo-* and *endo,exo-*

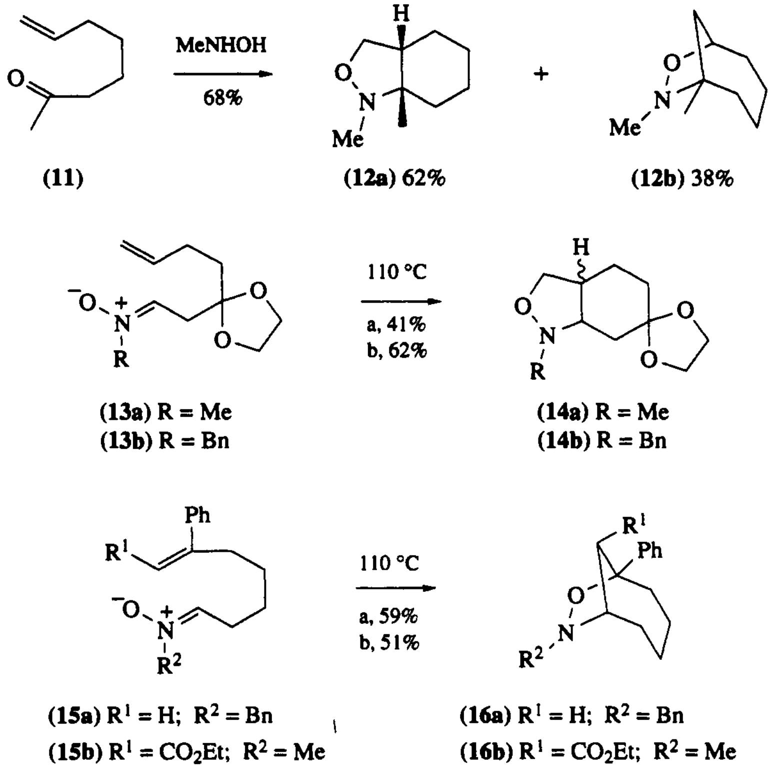
MeNHOH
68%
(11)
(12a) 62%
(12b) 38%
110 °C
a, 41%
b, 62%
(13a) R = Me
(13b) R = Bn
(14a) R = Me
(14b) R = Bn
110 °C
a, 59%
b, 51%
(15a) R1 = H; R2 = Bn
(15b) R1 = CO2Et; R2 = Me
(16a) R1 = H; R2 = Bn
(16b) R1 = CO2Et; R2 = Me

Scheme 3

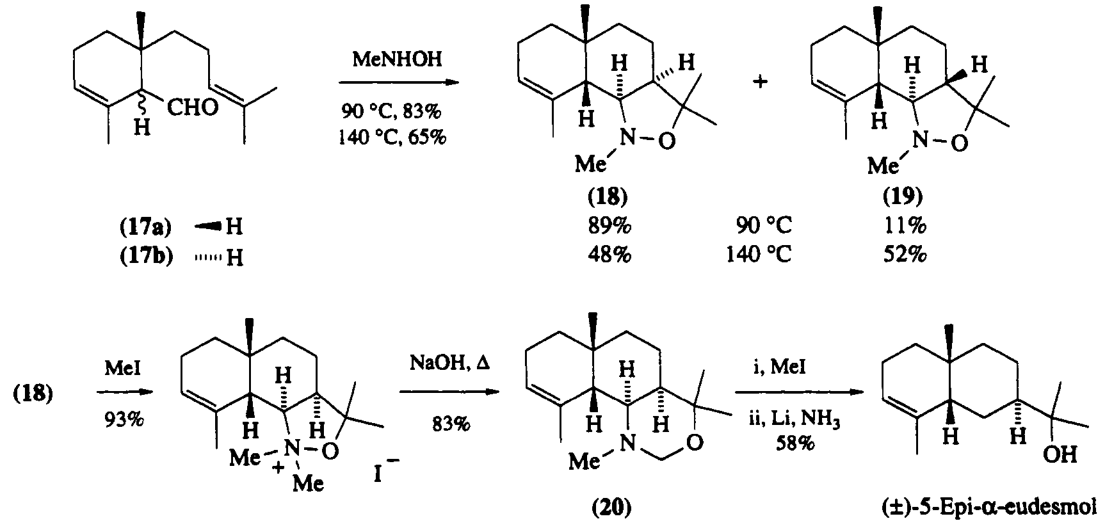
MeNHOH
90 °C, 83%
140 °C, 65%
(17a)
(17b)
(18)
89%
48%
90 °C
140 °C
(19)
11%
52%
(18)
MeI
93%
NaOH, Δ
83%
i, MeI
ii, Li, NH3
58%
(20)
(±)-5-Epi-α-eudesmol

Scheme 4

isoxazolidines. A very similar ratio was obtained for cyclization of nitrone (27). These results do not arise from product interconversion: the *exo,exo* product gave none of the isomers on heating. Perhaps interconversion of (26) and (27) occurred while heating *via* an aza-Cope rearrangement. The modest stereoselectivity could also have arisen simply from nitrone (*Z*)/(*E*) isomerization and competing cycloaddition, although in this case the nearly identical results are coincidental.

A synthesis of (±)-lasubine II was carried out by an analogous nitrone cyclization.[12a] The *exo,exo*, *exo,endo* and *endo,exo* ratio was 84:10:6 and the *exo,exo* product (28) was isolated pure in 60% yield.

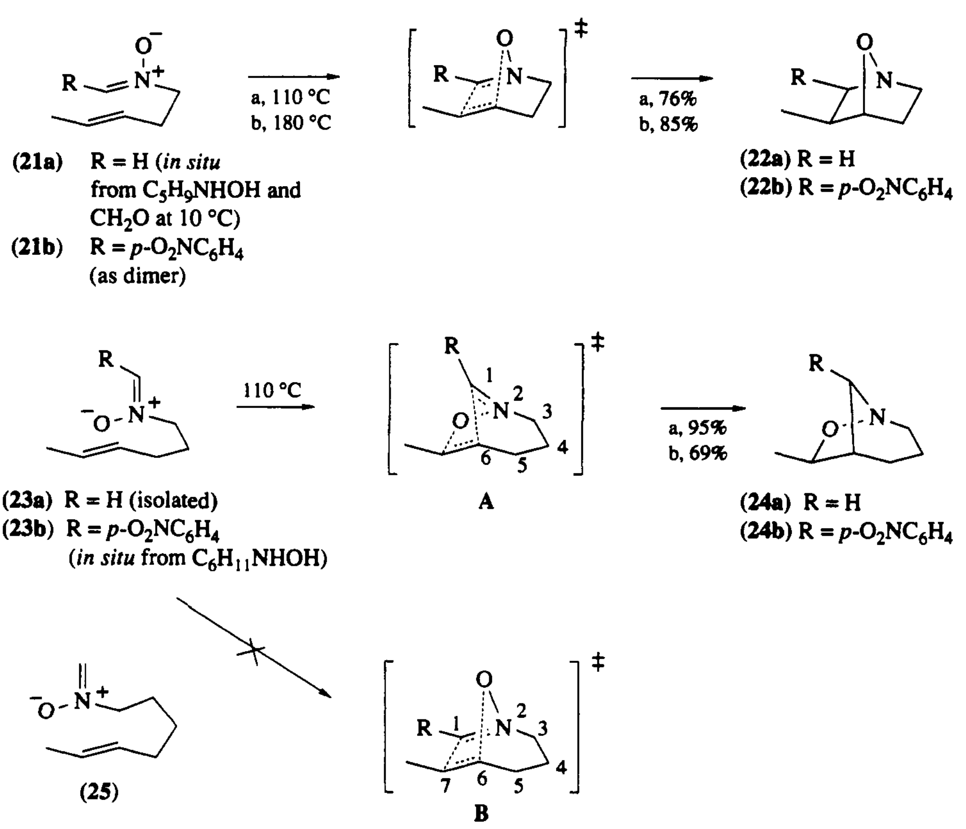
a, 110 °C
b, 180 °C
a, 76%
b, 85%
(21a) R = H (in situ from $C_5H_9NHOH$ and $CH_2O$ at 10 °C)
(21b) R = $p$-$O_2NC_6H_4$ (as dimer)
(22a) R = H
(22b) R = $p$-$O_2NC_6H_4$
110 °C
a, 95%
b, 69%
(23a) R = H (isolated)
(23b) R = $p$-$O_2NC_6H_4$ (in situ from $C_6H_{11}NHOH$)
A
(24a) R = H
(24b) R = $p$-$O_2NC_6H_4$
(25)
B

**Scheme 5**

Reduction of (**28**) with zinc–acetic acid provided the all-*cis*-piperidinol which was converted in several steps to (±)-lasubine II.

A very recent synthesis of (±)-pumiliotoxin C employed the nitrone cyclization product (**29**), obtained in 74% overall yield from the nitrone precursors.[12b] Reduction of (**29**) with zinc–acetic acid provided a trisubstituted piperidine which was converted in several steps to (±)-pumiliotoxin C.

### 4.10.2.3 Cyclic Alkenylnitrones

Cyclic substrates incorporating alkenyl and nitrone functional groups also undergo intramolecular cycloaddition. Examples of three simple types are known: the alkene may be part of a ring, the bridge only may include a ring or the nitrone may be part of a ring. Cyclizations involving complex combinations where more than one of the three elements are part of a ring are also numerous, including a case where all three elements are in rings. Typically, nonbonded interactions tend to be more severe in these cyclic substrates, often leading to greater selection of competing isomers and occasionally to unexpected preferences.

#### *4.10.2.3.1 C-(Cycloalkenyl)nitrones*

Cyclization of *C*-(cycloalkenyl)nitrones has been extensively investigated.[13–15] For example, the cyclohexenylnitrone (**30**) (an equilibrated 2:1 (*E*)/(*Z*) isomer mixture) afforded (**31**) in 56% yield (Scheme 7).[13] Presumably the (*Z*)-nitrone cyclized exclusively based on the strained transition state required for cyclization of the (*E*)-nitrone. None of the isomeric bridged [4.2.1] product (**32**) was formed: this is attributed to unfavorable nonbonded interaction between the carbonyl group and a ring methylene group in the required transition state.

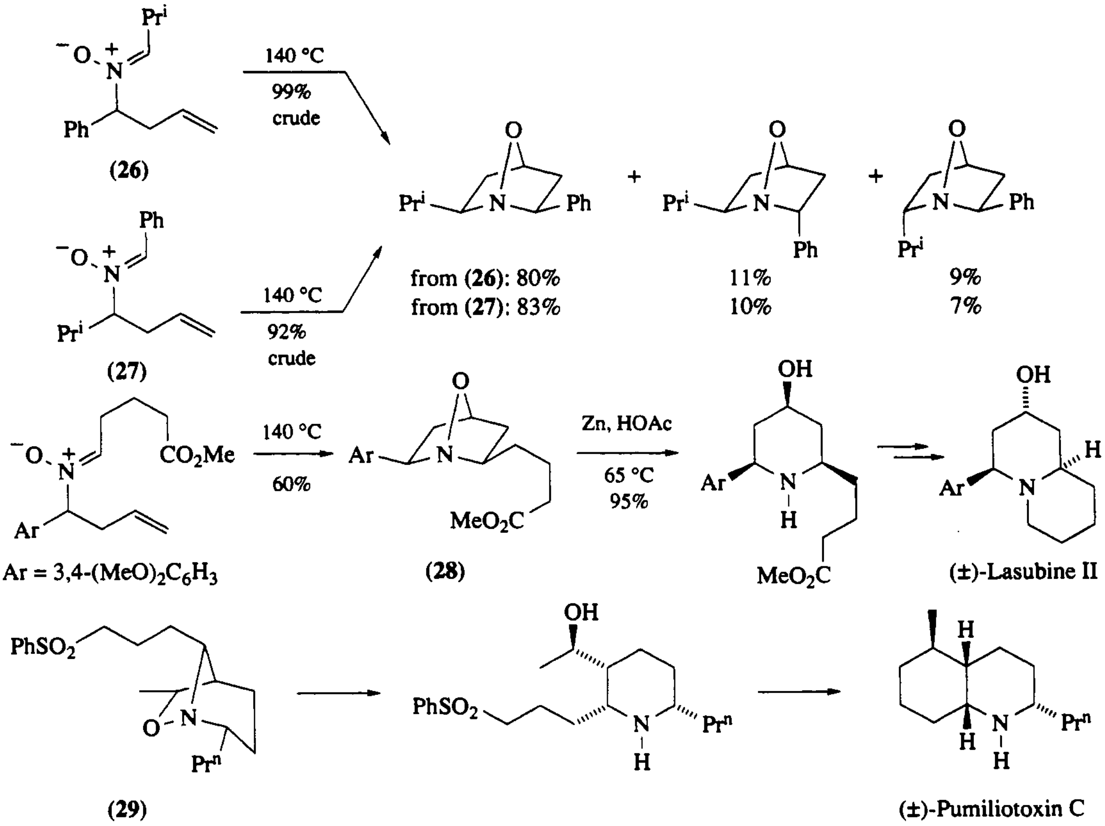
(26)
140 °C
99% crude
(27)
140 °C
92% crude
from (26): 80%
from (27): 83%
11%
10%
9%
7%
140 °C
60%
Ar = 3,4-(MeO)2C6H3
(28)
Zn, HOAc
65 °C
95%
(±)-Lasubine II
(29)
(±)-Pumiliotoxin C

Scheme 6

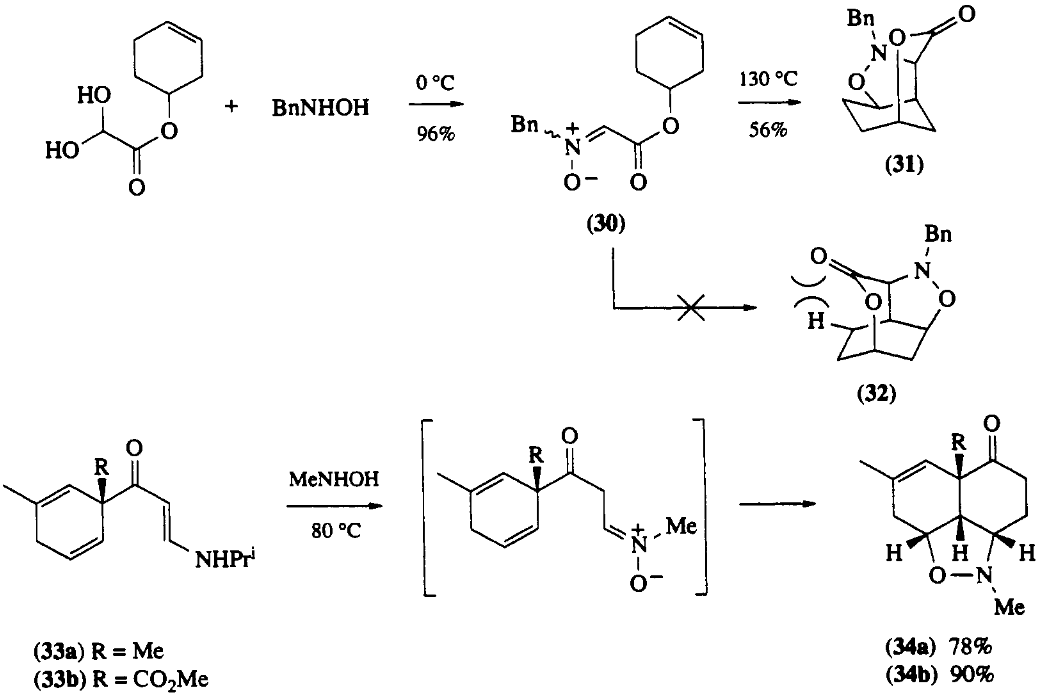
BnNHOH
0 °C
96%
(30)
130 °C
56%
(31)
(32)
MeNHOH
80 °C
(33a) R = Me
(33b) R = CO2Me
(34a) 78%
(34b) 90%

Scheme 7

The nitrones derived from dienes (**33a–b**) cyclize exclusively at the disubstituted double bond to give the isoxazolidines (**34a–b**) in 78% and 90% yield, respectively.[14] Chemoselection here arises from the marked rate difference in cycloaddition to di- *vs.* tri-substituted alkenyl double bonds.

Nitrones have been reported to undergo intramolecular cycloaddition to quinones[15a] and to thiophenes.[15b]

### *4.10.2.3.2 N-(Cycloalkenyl)nitrones*

Intramolecular cycloaddition of *N*-(cycloalkenyl)nitrones has also been extensively investigated. Thus, stepwise oxidation of the amine (**35**) and cyclization of the ensuing nitrone provided isoxazolidine (**36**) in 64% overall yield as the only observed regioisomer (Scheme 8).[16] Isoxazolidine (**36**) was then desulfonated with buffered sodium amalgam and further reduced with zinc–acetic acid to provide the corresponding γ-amino alcohol; subsequent dehydration provided (–)-hobartine.

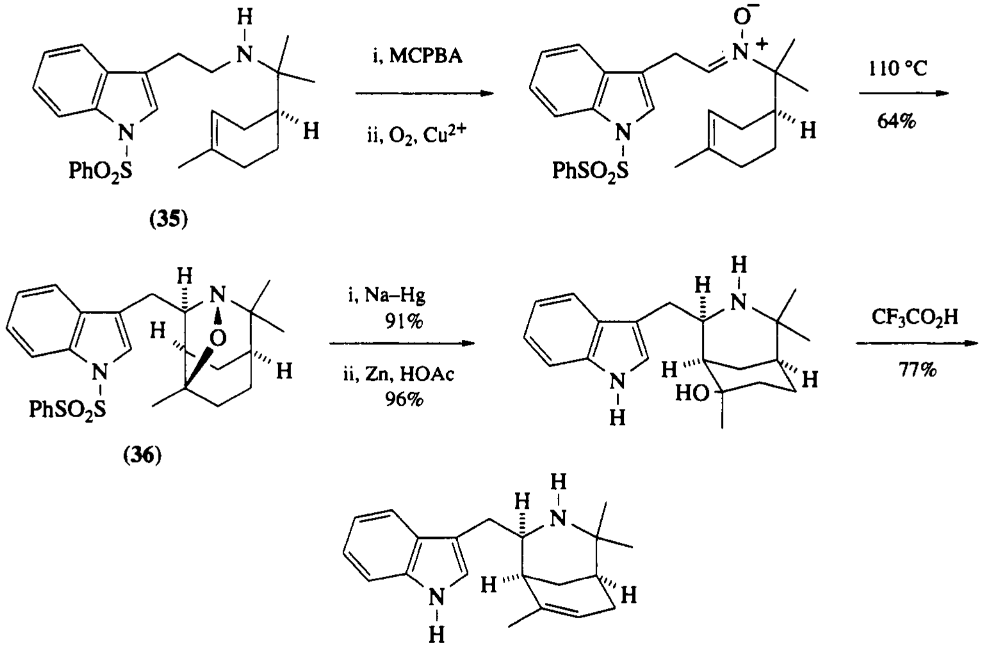

(–)-Hobartine

**Scheme 8**

The *N*-(bicycloalkenyl)nitrone (**37**) afforded the tetracyclic isoxazolidine (**38**) in 67% yield: none of the regioisomeric isoxazolidine was observed (Scheme 9).[17] The authors attributed this to non-bonded C—H interactions as shown, but the observed isoxazolidine was also entropically favored, forming *via* a six-membered, as opposed to a seven-membered, carbocyclic transition state. The *N*-(bicycloalkenyl)nitrone formed from (**39**) and furfural cyclized in 45% yield predominantly to the tetracyclic product (**40b**), but some (**41b**) was also produced (95:5 ratio).[18] Reaction of (**39**) and formaldehyde gave a mixture of (**40a**) and (**41a**) (62:38 ratio). The authors attribute the somewhat higher regioselectivity for (**40b**) in part to non-bonded interaction of the 2-furyl substituted methylene with the C-8 endocyclic C—H bond.

### *4.10.2.3.3 Aryl-bridged alkenylnitrones*

Many intramolecular nitrone cycloadditions have been carried out on substrates containing a cyclic intervening bridge. Perhaps the simplest possibility here is an *o*-disubstituted aromatic substrate, as, for example, the nitrone derived from aldehyde (**42**), which cyclizes to the 5,6-fused isoxazolidine (**43**; Scheme 10).[19] There are many additional possibilities: the nitrones derived from biphenyl aldehyde

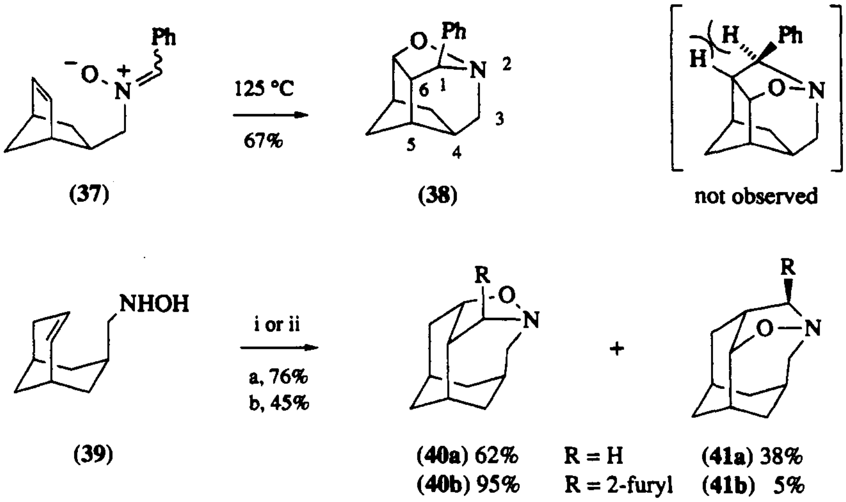

(37) (38)

(39)

(40a) 62% R = H (41a) 38%

(40b) 95% R = 2-furyl (41b) 5%

i, $(CH_2O)_n$, 100 °C; ii, furfural, 140 °C

**Scheme 9**

(44)[20] and indolyl nitrile (45)[21] cyclize uneventfully to fused isoxazolidines. Isoxazolidine (46) has been converted to (±)-chanoclavene I in a multi-step synthesis.

### *4.10.2.3.4 Alicylic-bridged alkenylnitrones*

The isoxazolidines (47) and (48) were obtained by cyclization of the corresponding ketone-derived exocyclic nitrones (Scheme 11).[22] Such reactions have been used for natural product sysnthesis, as in the conversion of isoxazolidine (49) to (±)-hirsutene. Methylation and catalytic hydrogenolysis provided a γ-dimethylamino alcohol, which underwent Cope elimination to provide an alkenyl alcohol in a key step. A related synthesis of (±)-7,12-sechoishwaran-12-ol is also reported.

### *4.10.2.3.5 Cyclic nitrones*

Cyclic nitrones also undergo intramolecular cycloaddition to an alkenyl group with very high regioselectivity. For example, (±)-cocaine was synthesized *via* cyclization of the cyclic nitrone (50), obtained from reduction of a nitroacetal or from thermolysis of an isoxazolidine, to isoxazolidine (51; Scheme 12).[23] Sequential methylation, reductive N—O cleavage and benzoylation of (51) provided (±)-cocaine.

Cyclic nitrone (52) has a cyclic bridge and cyclic enol ether dipolarophile: thus all three elements are present in rings (Scheme 13).[24a] Models show that direct cyclization of (52) is not possible because of the relative positions of the dipole and dipolarophile. However, a pentacyclic cage isoxazolidine was formed by heating (52); presumably epimerization at the phenyl-bearing bridgehead carbon preceded cycloaddition.

## 4.10.2.4 Oxime Cyclization Reactions

Unsaturated oximes can be cyclized simply by heating.[24b] It has been suggested that nitrone intermediates are involved in this process. Thus, oxime (53) on heating at 180 °C cyclized to a pyrrolizidine in 60% yield: presumably tautomerization to nitrone (54) first occurred followed by [3 + 2] cycloaddition (Scheme 14). Likewise, quinolizidine (55) was obtained in 69% yield from the corresponding oxime.

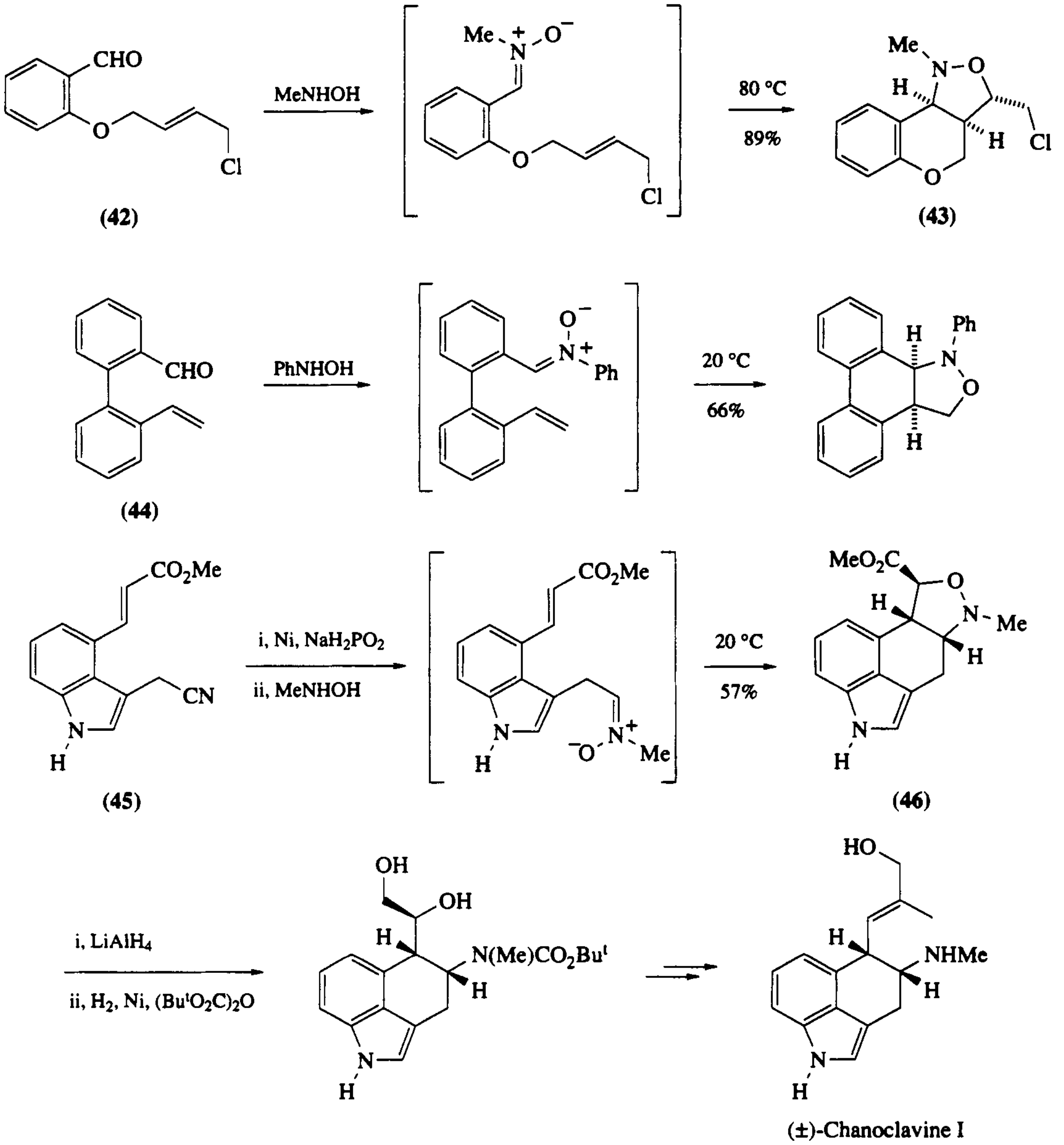

Scheme 10

### 4.10.2.5 Tandem Michael–Nitrone Cyclization Reactions

Nitrones can be generated by Michael reaction of oximes with appropriate conjugated substrates.[25] If a generated nitrone has a built-in dipolarophile, cyclization can ensue (Scheme 15). There are three synthetic variations on this theme.[25a,b] First, the oxime may contain the dipolarophile as in (**56**). Reaction of (**56**) with phenyl vinyl sulfone provided a quantitative yield of the tandem product as one stereoisomer. Alternatively, the dipolarophile can reside in the Michael substrate as in (**57**). Reaction of (**57**) with cyclohexanone oxime produced two isoxazolidines from competitive cyclization of the intermediate nitrone through six- and seven-membered carbocyclic transition states. It is also possible to carry out an intramolecular Michael addition followed by an intramolecular nitrone cyclization as in thermolysis of (**58**) to produce a tricyclic isoxazolidine. Very recently several examples of a tandem Diels–Alder, Michael addition, nitrone cyclization sequence have been reported.[25c]

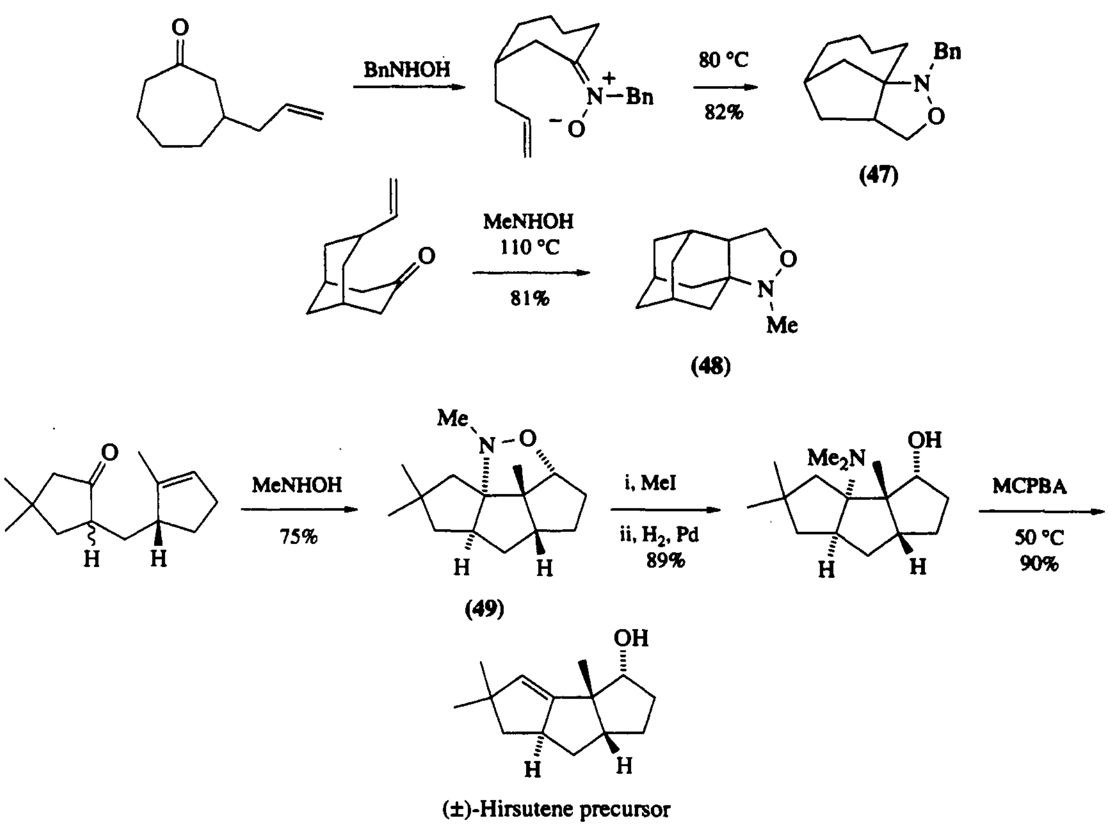
BnNHOH
80 °C
82%
(47)
MeNHOH
110 °C
81%
(48)
MeNHOH
75%
(49)
i, MeI
ii, $H_2$, Pd
89%
MCPBA
50 °C
90%
(±)-Hirsutene precursor

**Scheme 11**

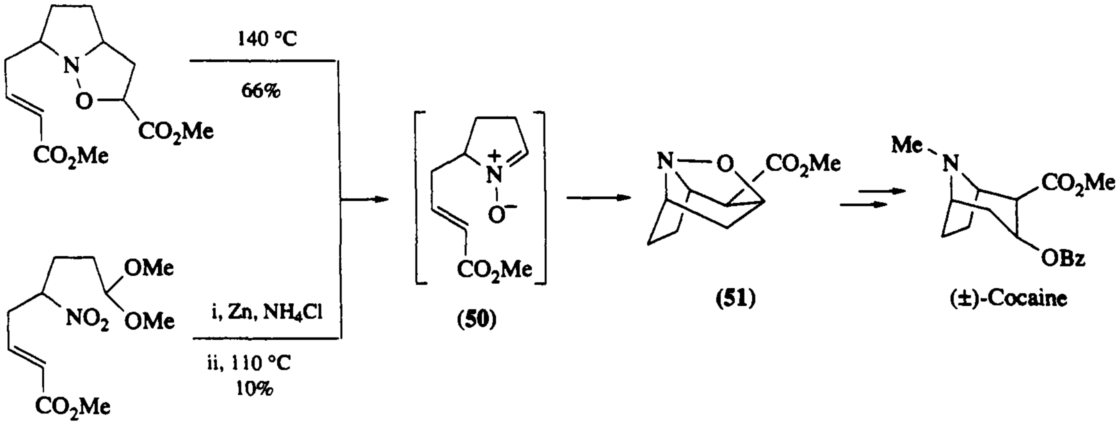
140 °C
66%
i, Zn, $NH_4Cl$
ii, 110 °C
10%
$CO_2Me$
OMe
$NO_2$
(50)
(51)
(±)-Cocaine
OBz

**Scheme 12**

### 4.10.2.6 Tandem Diels–Alder–Nitronic Ester Cyclization Reactions

Allylic nitro compounds containing a suitable dipolarophile undergo Diels–Alder cycloaddition to alkenes in the presence of tin(IV) chloride affording cyclic nitronic esters (Scheme 16).[26a] Nitronic ester (**59**) could not be isolated but spontaneously cyclized to the 5,5-fused cyclic product (**60**), isolated in 68% yield. The nitronic esters (**61a**) and (**61b**) were isolated from the Diels–Alder reaction and could be separated. Heating (**61a**) in refluxing benzene afforded the 5,6-fused dipolar cyclization product (**62a**) in 93% (68% overall) yield; (**61b**) likewise afforded (**62b**) in 62% (11% overall) yield. Either (**62a**) or (**62b**) could be converted to the tricyclic lactam (**63**) by catalytic hydrogenolysis followed by lactamiza-

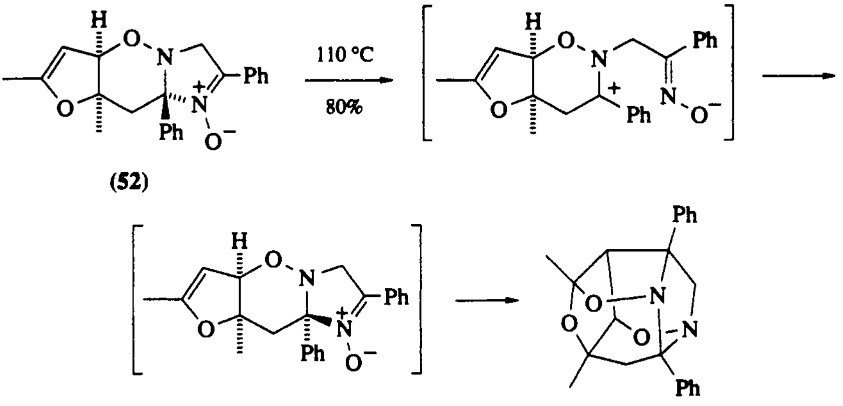

**Scheme 13**

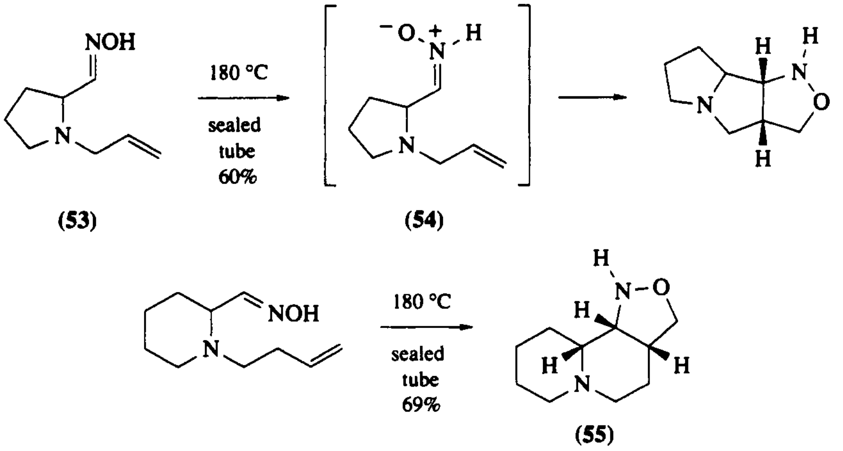
(53)
180 °C
sealed tube
60%
(54)
180 °C
sealed tube
69%
(55)

**Scheme 14**

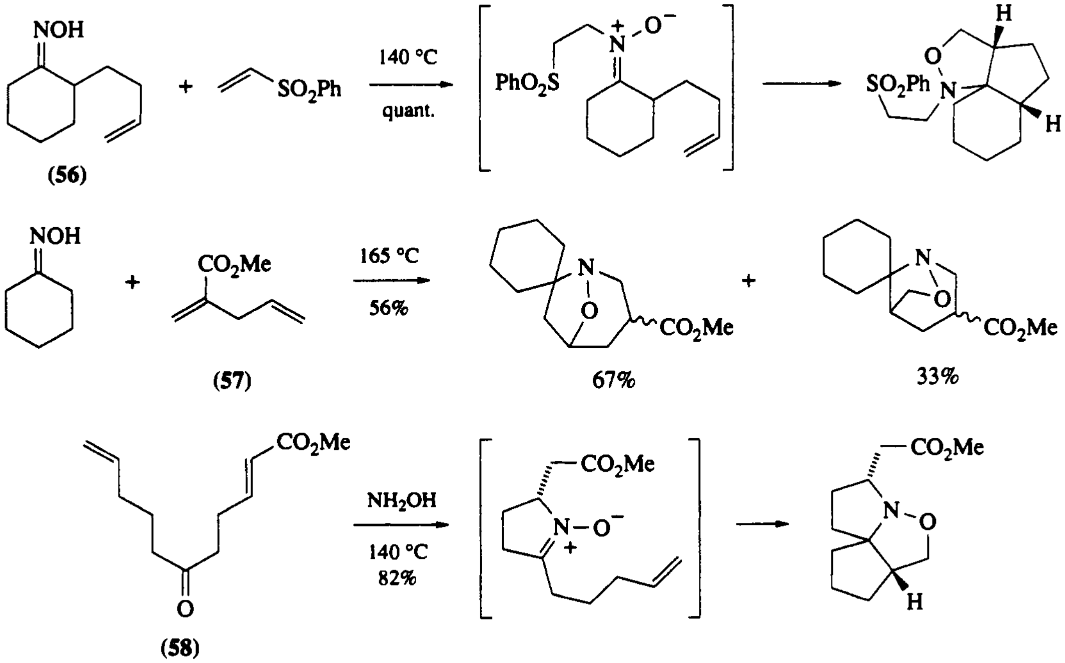
(56)
140 °C
quant.
(57)
165 °C
56%
67%
33%
(58)
NH₂OH
140 °C
82%

**Scheme 15**

tion. Nitronic ester (**64**) did not undergo intramolecular 1,3-dipolar cycloaddition, presumably because formation of the 5,7-fused product would be less favorable.

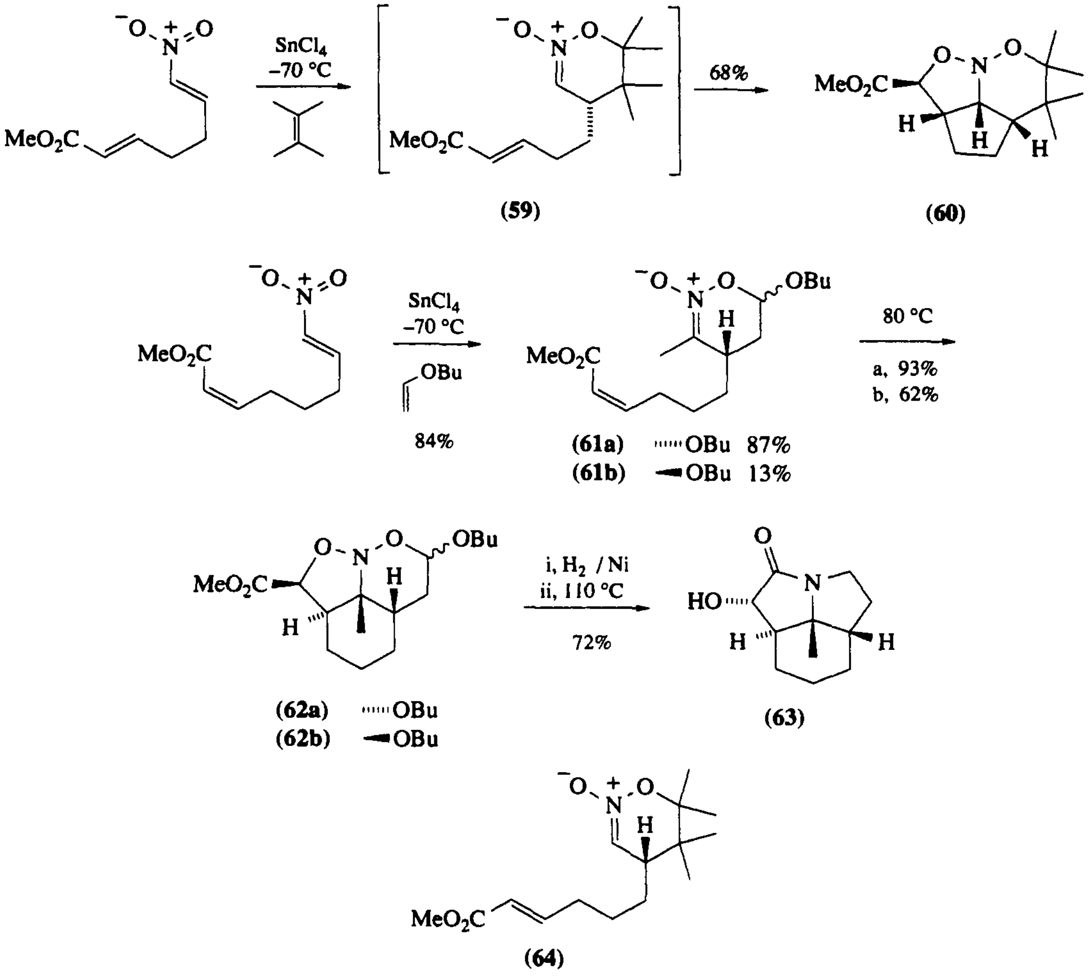

Scheme 16

### 4.10.2.7 Alkynylnitrones and Allenylnitrones

In constrast with intermolecular nitrone cycloadditions to alkynes and allenes, very little work has been done on the corresponding intramolecular cycloadditions. The bicyclic isoxazolidines (**65a–b**) were reported as products from reaction of an alkynone with methylhydroxylamine in ethanol.[26b] Presumably the initial strained bridgehead C—C double bond of the $\Delta^4$-isoxazoline added ethanol under the reaction conditions. Cyclization of an allenyl ketone with methylhydroxylamine in ethanol solution also led to isoxazolidines (**65a–b**) as the major products and isoxazolidine (**66**) as a minor product.[26b] Thus, preferential cyclization to the internal C—C double bond of the allene occurred followed by addition of ethanol to the exocyclic C—C double bond of the methyleneisoxazolidine intermediate.

## 4.10.3 NITRILE OXIDE CYCLIZATIONS

### 4.10.3.1 General

Intermolecular nitrile oxide cycloadditions have been known for a very long time.[27] However, it was not until the mid-1970s that intramolecular nitrile oxide cycloaddition (INOC) reactions were studied.[28]

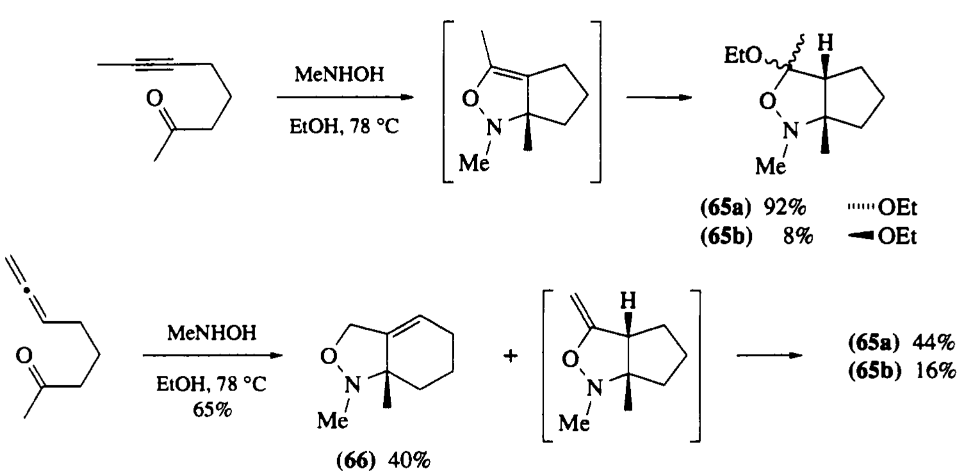

Scheme 17

Successful INOC reactions have typically been run on nitrile oxides generated *in situ*. It is necessary to avoid strong halogenating reagents to generate the nitrile oxide because of the presence of the dipolarophile. Consequently, an INOC procedure typically utilizes an isocyanate to generate the nitrile oxide from a nitro compound[29] or sodium hypochlorite to generate the nitrile oxide from an oxime.[30]

The entropically enhanced cycloaddition rate of an intramolecular cycloaddition permits alkenyl nitrile oxides to cyclize in the presence of free amino groups, in contrast to intermolecular reactions. Since nitrile oxides have a wide spectrum of possible intermolecular reactions, they also react well in macrocyclic cyclizations.

INOC reactions are occasionally synthetic alternatives to nitrone cyclizations. The isoxazolines produced can substitute for isoxazolidines in a number of further transformations. Thus, isoxazolines, like isoxazolidines, can be converted to $\gamma$-amino alcohols.[31] Isoxazolines can be converted to isoxazolidines and *vice versa*.[32]

Nitrile oxides are linear as opposed to nitrones which are planar with an approximately 120° C—N—O bond angle. Consequently, the cycloaddition transition states are rather different for these two dipoles. The nitrone usually, although not always, offers more promise of stereoselective cyclization; the nitrile oxide can offer more promise of regiospecific cyclization, especially in forming 5,6-, 5,7- and larger fused bicyclic systems.

## 4.10.3.2 Open-chain Alkenyl Nitrile Oxides

### *4.10.3.2.1 5-Alkenyl nitrile oxides*

Cyclization of nitrile oxides with a three-atom intervening chain to the alkene always leads to 5,5-fused bicylic isoxazolines possessing a bridgehead C—N double bond. Thus, the alkenyl oximes (**67**) and (**68**) cyclized exclusively to fused bicyclic isoxazoline products (Scheme 18).[33] These reactions illustrate other important features of nitrile oxide cyclizations. Like nitrone cyclizations, the C—C double bond stereochemistry is retained. Thus, (*Z*)-(**67**) gave only C(4)—C(5) *cis* products, while (*E*)- gave only C(4)—C(5) *trans* products. Yields in these reactions are moderate, and this is attributed to some difficulty in the dipole reaching the dipolarophile. The stereoselectivity of these reactions was moderate, determined by the chiral center which remains exocyclic to the developing ring system. Similar results were obtained using nitro compounds as the nitrile oxide precursors.

Higher stereoselectivity has been observed where the chiral center is included in the developing ring system. Thus, cyclization of (*Z*)-nitroalkene (**69**) led solely to *anti* isomer (**70**; Scheme 19).[34] This was explained based on the differing degree of $A^{1,3}$-strain in the transition state A leading to (**70**) and transition state B leading to the unobserved *syn* isomer. The much more severe Me—Me interaction in B precluded formation of the *syn* isomer.

Cyclizations of the nitrile oxide derived from nitroalkene (**71**) also led to bicyclic isoxazoline (**72**) as one stereoisomer, presumably through a transition state that minimized $A^{1,3}$-strain (Scheme 20).[35] Re-

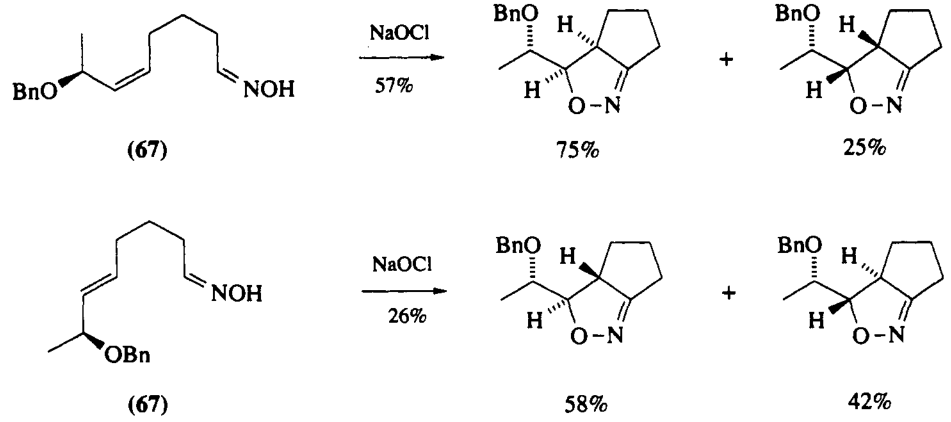
BnO
NOH
(67)
NaOCl
57%
BnO
H
H
O-N
75%
+
BnO
H
H
O-N
25%
NOH
OBn
(67)
NaOCl
26%
BnO
H
H
O-N
58%
+
BnO
H
H
O-N
42%

Scheme 18

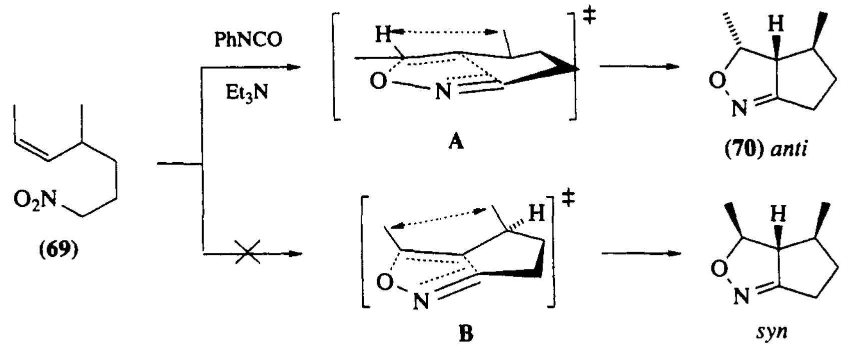
PhNCO
Et3N
O2N
(69)
H
O
N
‡
A
H
O
N
(70) anti
H
O
N
‡
B
H
O
N
syn

Scheme 19

ductive cleavage of (72) under hydrolytic conditions afforded a β-hydroxy ketone which underwent elimination to give (±)-sarkomycin on treatment with mesyl chloride.

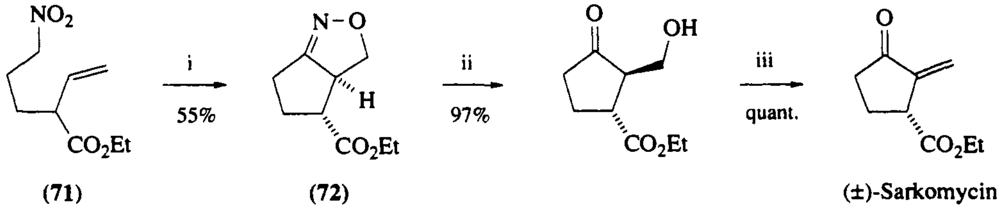
NO2
CO2Et
(71)
i
55%
N-O
H
CO2Et
(72)
ii
97%
O
OH
CO2Et
iii
quant.
O
CO2Et
(±)-Sarkomycin

i, $p$-$ClC_6H_4N{=}C{=}O$, $Et_3N$, 20 °C; ii, $H_2$, W-2 Raney Ni, $MeOH{-}H_2O$ (5:1), $B(OH)_3$; iii, MsCl, $Et_3N$

Scheme 20

### *4.10.3.2.2 6-Alkenyl nitrile oxides*

Cyclization of nitrile oxides with a four-atom intervening chain to the alkene always leads to 5,6-fused bicylic isoxazolines possessing a bridgehead C—N double bond. This is in contrast to nitrone cyclizations where competition to form bridged bicyclic isoxazolidines is observed. The alkenyl oximes (73) and (74) cyclize in typical fashion *via* nitrile oxide intermediates (Scheme 21).[33a,36] The stereochemistry of cyclization here was studied both experimentally and by calculation. The higher stereoselectivity observed with the (*Z*)-alkene is typical. (*Z*)-Alkenes cycloadd much slower than (*E*)-alkenes in intermolecular reactions: this is attributed to greater crowding in the transition state. Thus, intramolecular cycloaddition of (*Z*)-alkenes depends on a transition state that is heavily controlled by steric factors.

MM2 calculations suggest that transition state A where the small group (H) is on the 'inside' is favored for cyclization of (**73**); attack is then *anti* to the benzyloxy group. (*E*)-Alkenyl ethers in general undergo cycloaddition with the alkoxy group preferentially on the 'inside' arising from an electronic effect; it is suggested that transition state B is favored for cyclization of (**74**), although MM2 calculations were unable to substantiate this without modification of a torsional parameter.[33a] The additional transition state C with the benzyloxy group 'outside' was predicted to be second most stable (C also minimizes overlap of $\sigma_{C-O}*$ overlap with $\pi_{C-C}$, a major problem if the benzyloxy group were *anti*[37]) resulting in the lower stereoselectivity observed with (**74**) compared to (**73**).

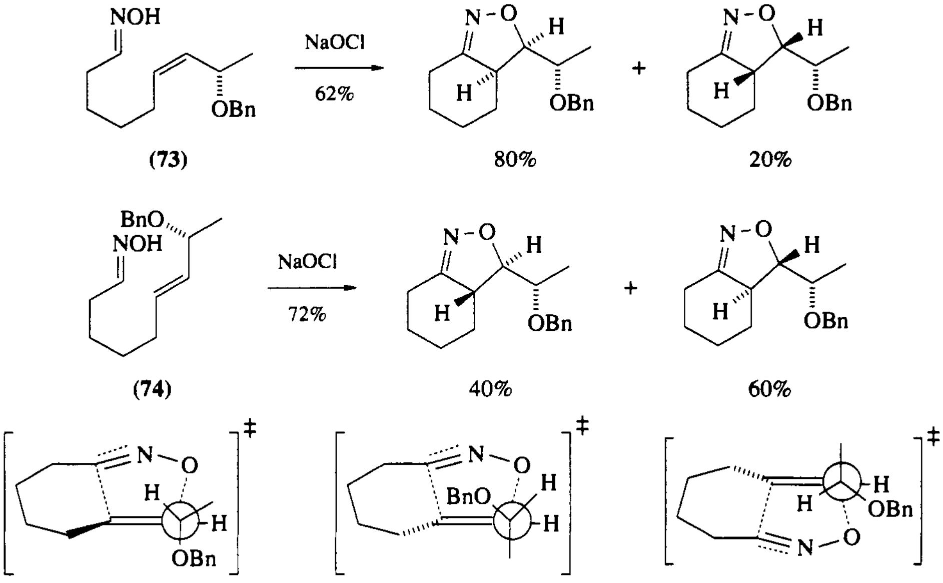

A (*Z*)-alkene most favored

B (*E*)-alkene most favored

C (*E*)-alkene 2nd most favored

**Scheme 21**

#### 4.10.3.2.3 *Long-chain alkenyl nitrile oxides*

Macro carbocyclic rings can be constructed by cyclization of nitrile oxides derived from ω-nitro-1-alkenes (Scheme 22). If the intervening bridge is not longer than seven atoms, only fused bicyclic products are obtained. Thus, the nitrile oxide derived from nitro compound (**75a**) is cyclized in 44% yield to the 5,9-fused bicyclic isoxazoline (**76a**).[38] 10-Nitro-1-decene (**75b**) also cyclized to (**76b**) in unspecified yield.[39] It should be noted that these results go counter to the usual regiochemistry of an intermolecular nitrile oxide cycloaddition where the five-substituted isoxazoline is usually,[27] although not always,[40] heavily preferred from reaction of a terminal alkene. Thus, geometric constraints have won out over the normal electronic control.

In the case of a longer intervening chain, a bridged bicyclic isoxazoline will form. Cyclization of the nitrile oxide derived from nitro compounds (**77a–b**) afforded only the bridged products (**78a–b**) in 67% and 50% yield, respectively.[38] None of the isomeric fused products were detected. Here the intervening chain has 13 atoms. Cases where the chain has 12 and 10 intervening atoms have also been studied: a mixture of bridged and fused bicyclic isoxazolines was obtained with the bridged product predominating in both cases. Isoxazoline (**78b**) was converted to an enone lactone and eventually to racemic antitumor agent A26771B.

### 4.10.3.3 Cyclic Alkenyl Nitrile Oxides

Intramolecular cycloaddition can be carried out on a variety of cyclic nitrile oxide substrates. Two simple possibilities exist: either the alkene may be part of a ring or the intervening bridge may include a ring. Both possibilities may also coexist.

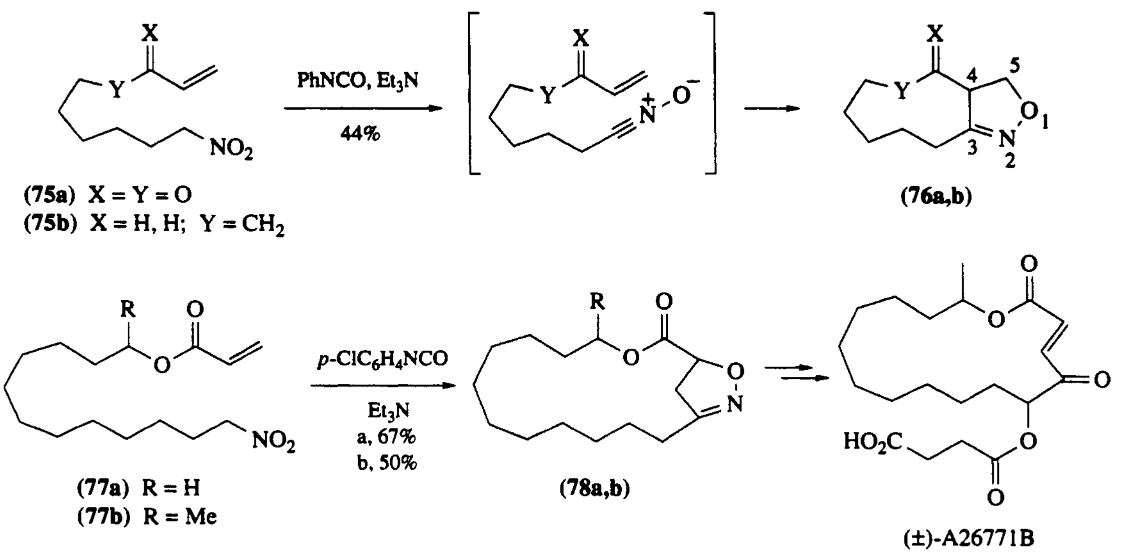

**(75a)** X = Y = O
**(75b)** X = H, H; Y = CH$_2$
**(76a,b)**
**(77a)** R = H
**(77b)** R = Me
**(78a,b)**
(±)-A26771B

**Scheme 22**

### *4.10.3.3.1 Cycloalkenyl nitrile oxides*

Cyclizations of nitrile oxides derived from the nitro compounds (**79**) and (**80**) are typical examples where the dipolarophile is part of a ring (Scheme 23).[41] In both cases only a fused polycyclic system was formed, typical of most nitrile oxide cyclizations. Nitro compound (**79**) led to tricyclic isoxazoline (**81**), which possesses a new 5,5-fused bicyclic system, doubly fused to the existing seven-membered ring. Isoxazoline (**81**) was the sole diastereomer obtained: all ring fusions were *cis*. Reductive cleavage of (**81**) afforded a γ-amino alcohol, which was converted to (±)-biotin in several additional synthetic steps.[41a] Nitro compound (**80**) led to tricyclic isoxazoline (**82**), which possesses a new 5,7-fused bicyclic system, doubly fused to the existing five-membered ring. Again, only one diastereomer, the all-*cis*-fused product, was obtained: models suggest that the transition state leading to *trans* fusion at the carbocyclic 5,7-ring junction would involve considerable nonbonded interaction absent in the transition state leading to *cis* fusion. Reductive cleavage of (**82**) with Raney nickel in the presence of water afforded a β-hydroxy ketone, which was dehydrated to provide a conjugated ketone in 80% yield. This procedure provides a good alternative to aldol strategies leading to polycyclic conjugated ketones.[41b]

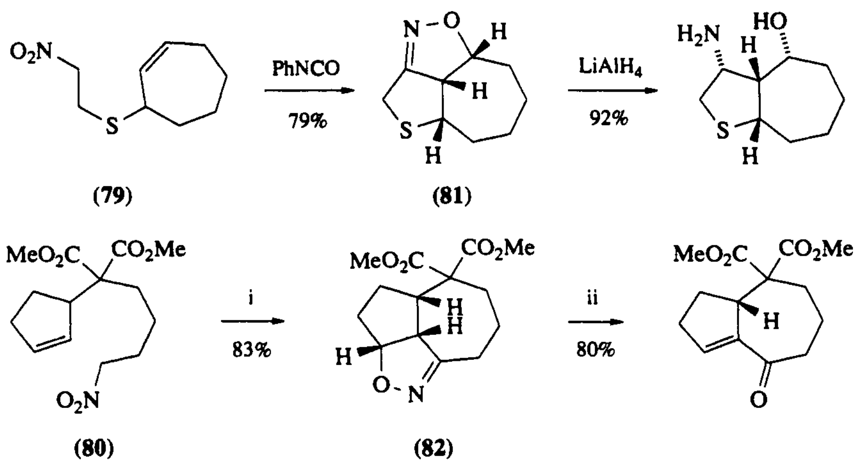

**(79)** **(81)**
**(80)** **(82)**

i, PhNCO added dropwise at 80 °C, cat. Et$_3$N; ii, O$_3$, –78 °C then TsOH, MeOH

**Scheme 23**

The hexahydronaphthalene ring system of compactin has been constructed by a nitrile oxide cyclization strategy (Scheme 24).[42] Thus, cyclization of either (**83**) or (**84**) *via* nitrile oxide intermediates led to the corresponding tricyclic isoxazoline in which a new 5,6-fused bicyclic system was appended to the existing six-membered ring. Again, the all-*cis*-fused diastereomer was obtained exclusively. These new isoxazolines were reductively cleaved with Raney nickel in the presence of water and the ensuing β-hydroxy ketones were dehydrated to provide conjugated ketones (**85a–b**). 1,2-Reduction then provided allylic alcohols that underwent dehydration to provide hexahydronaphthalenes (**86**) and (**87**). Using alumina for the dehydration provided dienes (**86a–b**) as major products, whereas other dehydrating agents gave more of the isomeric dienes (**87a–b**). The diene (**86b**) obtained from oxime (**84**) was converted in several steps to compactin.

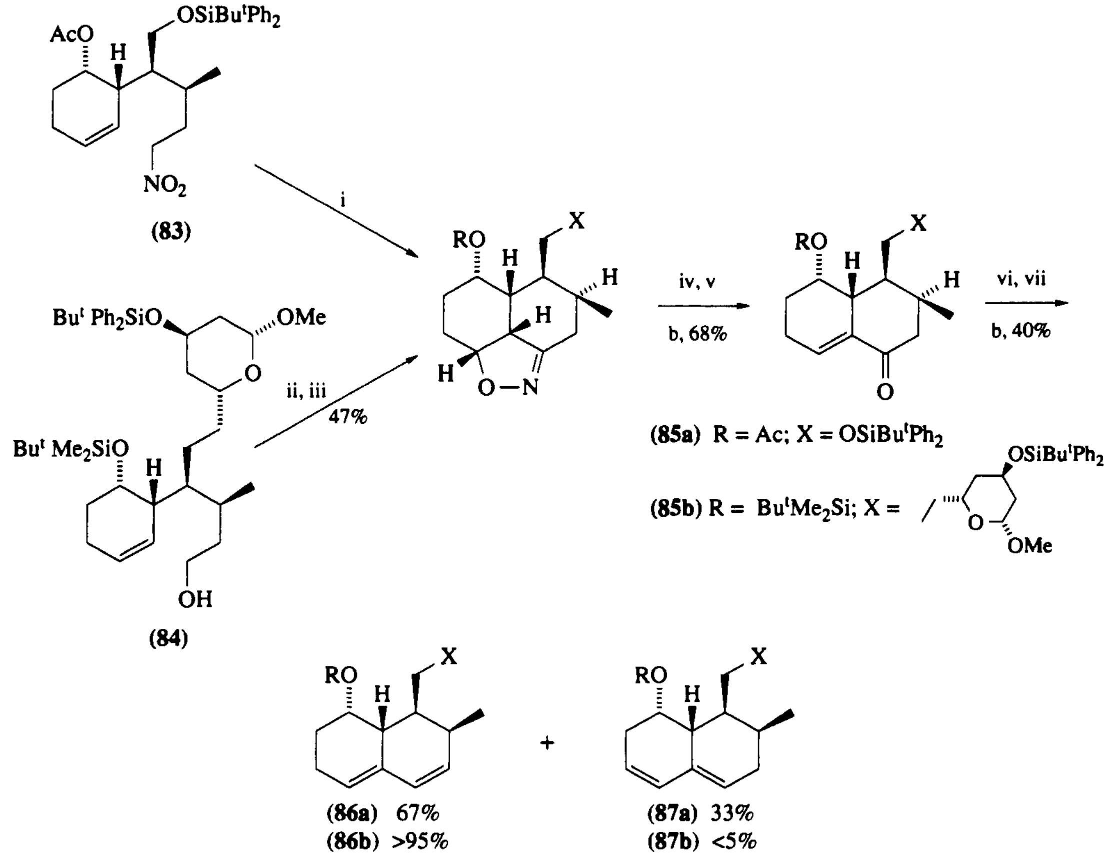

i, PhNCO, Et$_3$N; ii, DMSO, (COCl)$_2$, Et$_3$N then NH$_2$OH; iii, NaOCl, Et$_3$N; iv, H$_2$, Raney Ni, aq. MeOH;
v, Al$_2$O$_3$, 80 °C; vi, NaBH$_4$, CeCl$_3$; vii, Al$_2$O$_3$, 120 °C

Scheme 24

The spirocyclic alkaloid sibirine was prepared from the nitrile oxide cyclization product (**88**; Scheme 25).[43a] Here the intervening bridge of the nitrile oxide precursor is attached directly to the cycloalkenyl C—C double bond: cyclization to the new 5,6-fused bicyclic system afforded the azacarbocyclic ring attached spiro to the former cycloalkenyl ring. The furanylnitrile oxide (**89**), generated from the corresponding nitro compound, cyclized to (**90**) in 79% overall yield.[43b] Furan is typically sluggish in nitrile oxide cycloaddition reactions. Cycloaddition to the more substituted double bond of furan derivatives is highly atypical: therefore, the INOC reaction of (**89**) must be entropically driven.

### *4.10.3.3.2 Alicyclic-bridged nitrile oxides*

Many substrates containing a cyclic bridge have been investigated in intramolecular nitrile oxide cycloadditions. Typical examples include cyclization of the nitrile oxides derived from nitro compounds (**91**) and (**92**; Scheme 26).[44] MM2 calculations are consistent with these results: a chair-like transition state led to formation of the 5,6-fused product (**93**). Cyclization of (**92**) occurred through a more flexible

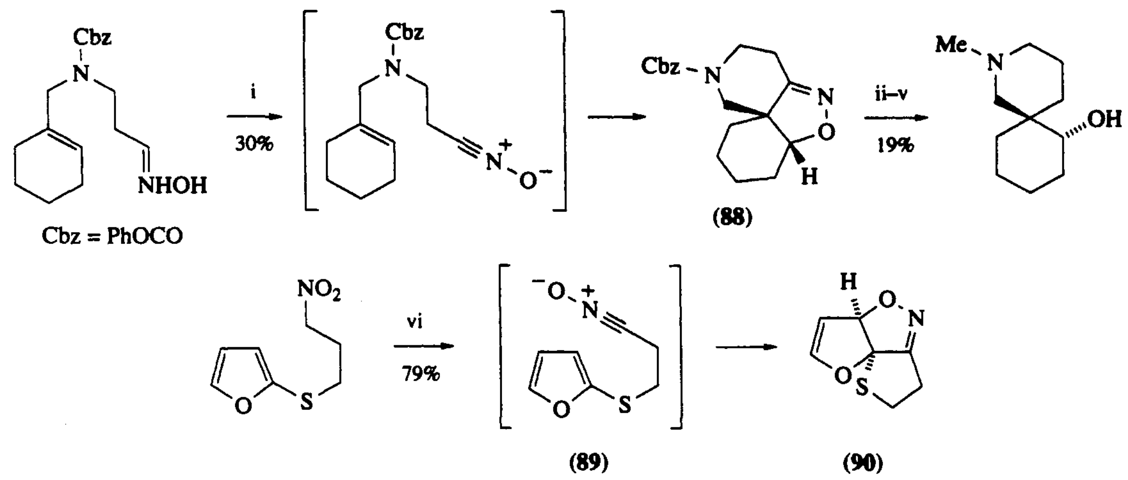

i, 30% aq. NaOCl; ii, $H_2$, Raney Ni, aq. MeOH, AcOH; iii, $HSCH_2CH_2SH$, $BF_3$; iv, $Bu_3SnH$, AIBN;
v, $H_2$, Raney Ni, MeOH; vi, $p$-$ClC_6H_4NCO$, $Et_3N$, 80 °C

**Scheme 25**

transition state, affording both *syn* and *anti* products. Cyclization of the nitrile oxide (**94**) (generated from nitro and oximino precursors) also led to a mixture of *syn* and *anti* products with the additional observation that only products with phenyl *cis* to methyl were obtained, although a 1:1 mixture of diastereomers was present in the precursor in both cases. It was suggested that $A^{1,3}$-strain present in the transition state leading to *syn* product (**95**) was responsible for the preferred formation of *anti* product. Presumably, the *cis* phenyl–methyl relationship arose from a severe nonbonded interaction between phenyl and one of the azetidine C(4)—H bonds. Interestingly, calculations based on product geometries were essentially equivalent to calculations based on transition state geometries: this is in accordance with a late transition state.

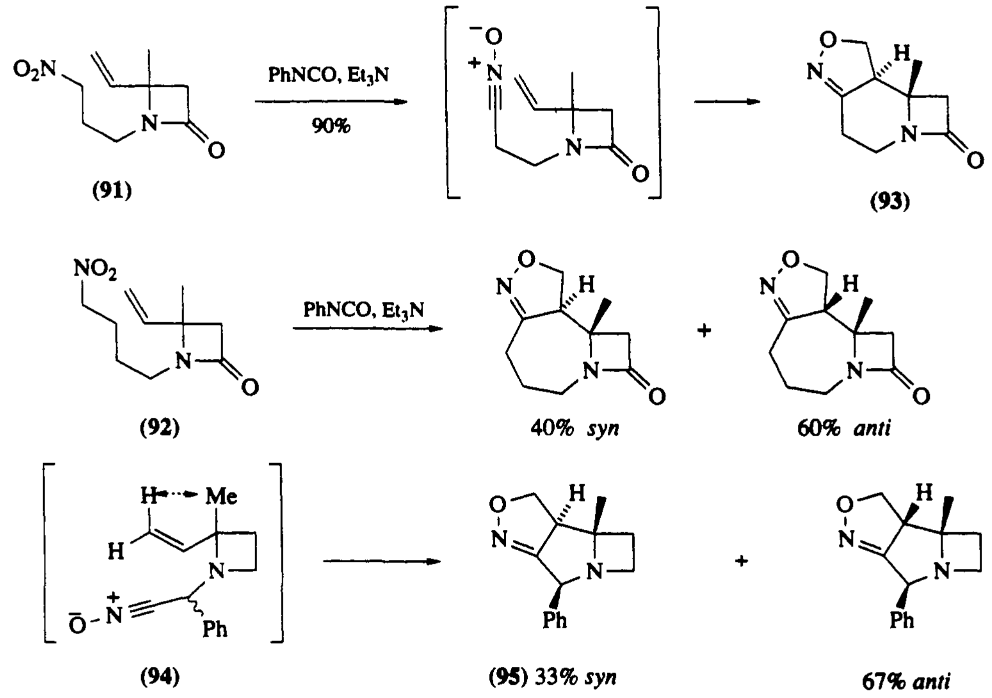

**Scheme 26**

The *cis*-dioxane (**97**) underwent cyclization to afford a single tricyclic isoxazoline in which the new 5,5-fused bicyclic system formed rapidly at 0 °C (Scheme 27).[45] The isomeric *trans*-dioxane also gave a single tricyclic isoxazoline (**96**) as product but only at 20 °C. The results were rationalized as follows: cyclization of the nitrile oxide derived from (**96**) occurred with the vinyl group equatorial, while the *cis* isomer required an axial vinyl group in the transition state. The isoxazoline (**96**) was converted in several steps to a known PGF$_{2\alpha}$ precursor.

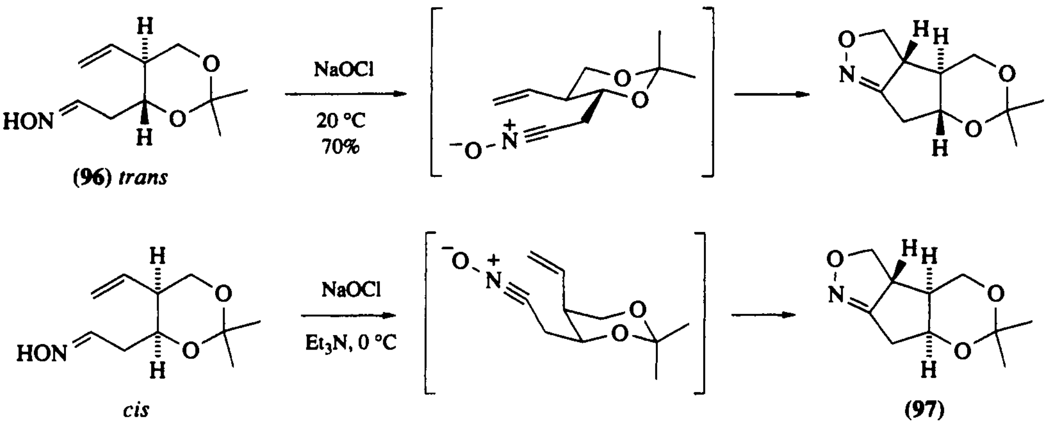

H
O
HON
O
H
(96) *trans*
NaOCl
20 °C
70%
O
O
$-O-\overset{+}{N}$
O
N
H
H
O
O
H
H
O
HON
O
H
*cis*
NaOCl
Et$_3$N, 0 °C
$^{-}O\overset{+}{N}$
O
O
O
N
H
H
O
O
H
(97)

Scheme 27

### 4.10.3.3.3 *Aryl-bridged nitrile oxides*

The indolyl nitro compound (**98**) was converted to the corresponding nitrile oxide, which cyclized to afford an inseparable mixture of isoxazolidines (**99**) and (**100**; Scheme 28).[46] These were acetylated and the THP group replaced by a mesyl group at which point the desired β-isomer could be separated. Elimination *via* a selenide intermediate provided the alkenylisoxazoline (**101**), which was converted to an isoxazolinium salt and reduced with LAH to give an *N*-methylisoxazolidine. Reductive cleavage with aluminum amalgam provided (+)-paliclavine.

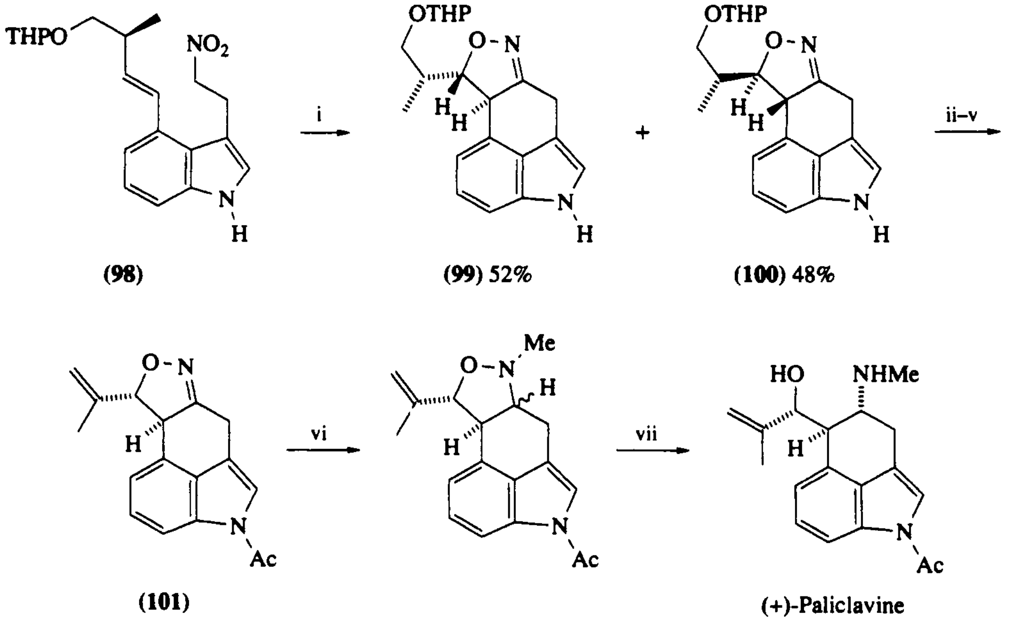

THPO
NO$_2$
N
H
(98)
i
OTHP
O-N
H
H
N
H
(99) 52%
+
OTHP
O-N
H
H
N
H
(100) 48%
ii–v
O-N
H
N
Ac
(101)
vi
Me
O-N
H
H
N
Ac
vii
HO
NHMe
H
N
Ac
(+)-Paliclavine

i, PhNCO, Et$_3$N; ii, Ac$_2$O, 4-DMAP, Et$_3$N then H$^+$; iii, MsCl, Et$_3$N then chromatography to separate mesylates; iv, Na$^+$ $^-$SePh then Ac$_2$O, 4-DMAP; v, NaIO$_4$; vi, MeO$_3$$^+$BF$_4$$^-$ then LiAlH$_4$; vii, Al–Hg

Scheme 28

In an early example of the INOC reaction, the oxime (**102**) with an *o*-aryl five-atom intervening bridge was cyclized to a tricyclic isoxazoline (Scheme 29).[47] The macrocylic bisisoxazoline (**103**) was formed as a byproduct, apparently *via* a tandem intermolecular–intramolecular cycloaddition sequence. The homologous oxime with a four-atom intervening bridge gave only intramolecular cycloaddition whereas from reaction of the homologs with six- and seven-atom intervening bridges, only the macrocyclic products corresponding to (**103**) were isolated. The effect of high-dilution conditions on cyclization was apparently not studied.

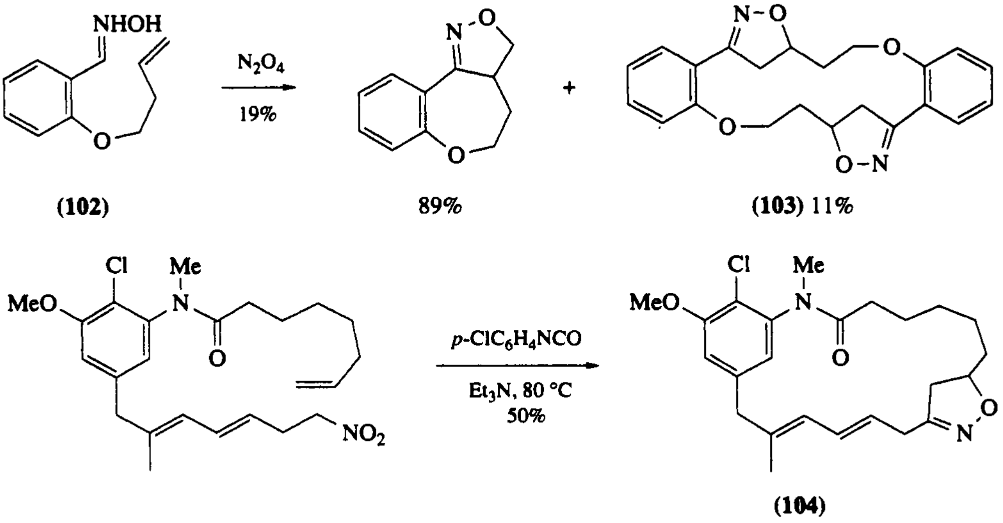

Scheme 29

Confalone and Ko have reported formation of the macrocyclic INOC product (**104**) in 50% yield from cyclization of an aryl-bridged nitrotriene containing a 17-atom intervening bridge.[48] Cyclization to the conjugated diene system did not occur, presumably because of geometric constraints and the fact that the more accessible double bond is trisubstituted. Isoxazoline (**104**) is a potential maytansine precursor.

## 4.10.3.4 Tandem Reaction Sequences Involving Nitrile Oxide Cyclizations

### *4.10.3.4.1 Tandem Diels–Alder–INOC reactions*

Nitrodienes undergo intermolecular Diels–Alder reactions with appropriate dienophiles. The resulting nitro compounds can then be cyclized *via* a nitrile oxide intermediate.[49] Thus, the 2-chloroacrylonitrile Diels–Alder adduct of 8-nitro-1,3-octadiene was prepared and cyclized to give (**105**) as a 3:1 mixture of diastereomers (Scheme 30). The Diels–Alder adduct of dimethyl acetylenedicarboxylate and 8-nitro-1,3-octadiene cyclized exclusively at the conjugated double bond, activated by the ester groups. Similarly, the quinone Diels–Alder adduct (**106**) cyclized at the conjugated double bond: reduction of the conjugated double bond permitted cyclization on the cycloalkenyl double bond.

### *4.10.3.4.2 Tandem Michael–INOC reactions*

Allylic stannanes condense with nitro dienes in the presence of titanium tetrachloride to give alkenyl α-chlorooximes; treatment of the α-chlorooximes with base then affords bicyclic isoxazolines.[50] Thus, cyclization of the intermediates (**107a–c**), obtained from appropriate 1-nitro-1,5-hexadienes and (3-propenyl)trimethyltin, gave bicyclic isoxazolines (Scheme 31). Cyclization occurred exclusively on the double bond with the longer (three-atom *vs.* two-atom) intervening bridge, even when that double bond was trisubstituted.

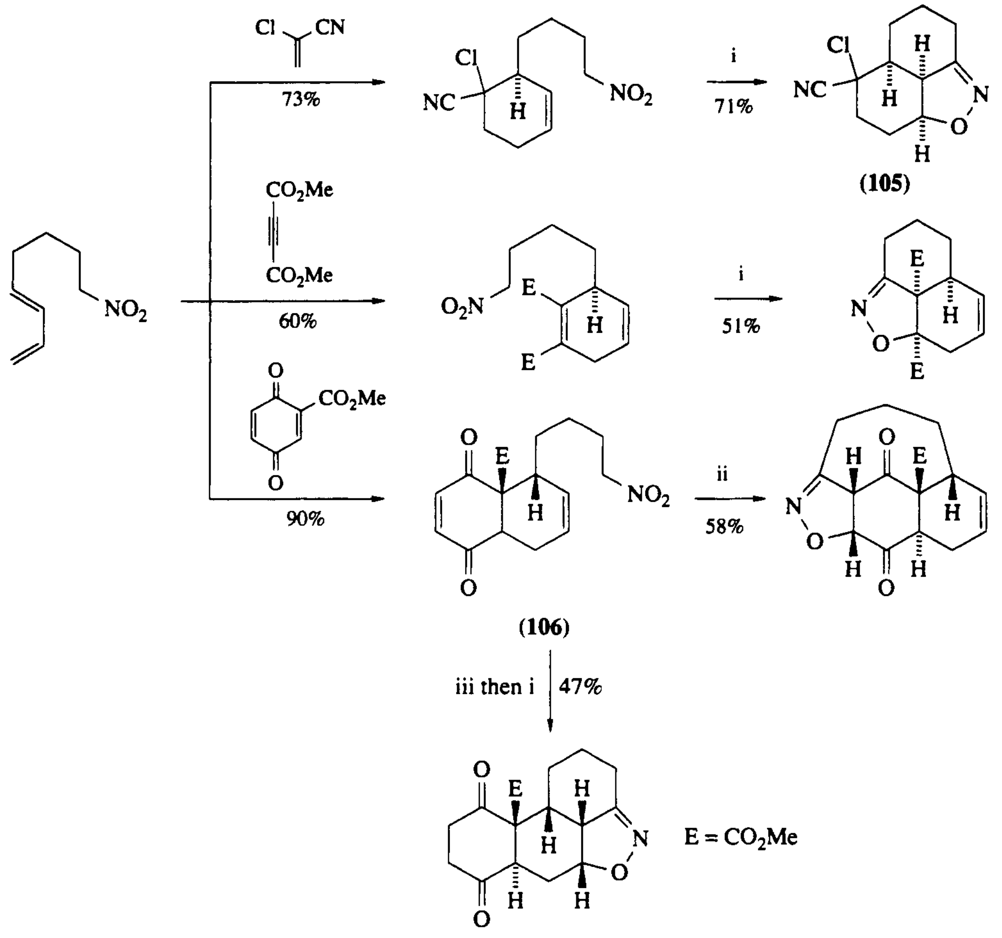

73%
71%
(105)
$CO_2Me$
$CO_2Me$
60%
51%
90%
58%
(106)
iii then i
47%
E = $CO_2Me$
i
ii

i, PhNCO, $Et_3N$, 80 °C; ii, *p*-$ClC_6H_4NCO$, $Et_3N$, 80 °C; iii, L-selectride, THF, −78 °C

Scheme 30

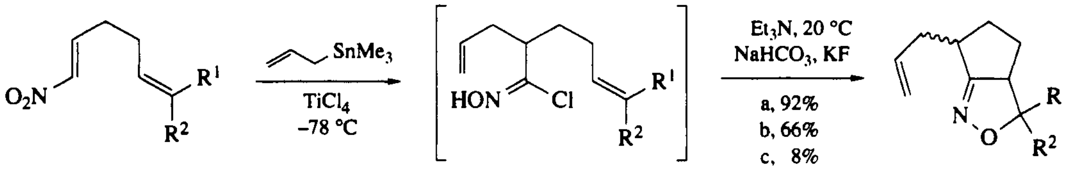

$SnMe_3$
$TiCl_4$
−78 °C
$Et_3N$, 20 °C
$NaHCO_3$, KF
a, 92%
b, 66%
c, 8%

**(107a)** $R^1 = R^2 = H$

**(107b)** $R^1 = H$; $R^2 = Ph$

**(107c)** $R^1 = R^2 = Me$

Scheme 31

### 4.10.3.5 Alkynyl Nitrile Oxides

Only a few INOC reactions have been run on alkynyl substrates.[51,52] The reactions do proceed well, as for example, cyclization of the alkynyl nitrile oxide (**108**), derived *in situ* from the corresponding oxime.[51] The oxime itself was formed *in situ* by reaction of an α-bromosilyloxime with propargyl alcohol, presumably *via* a vinylnitroso intermediate (Scheme 32). The alkynyl acylnitrile oxide (**109**) also cyclized to afford a bicyclic isoxazole.[52]

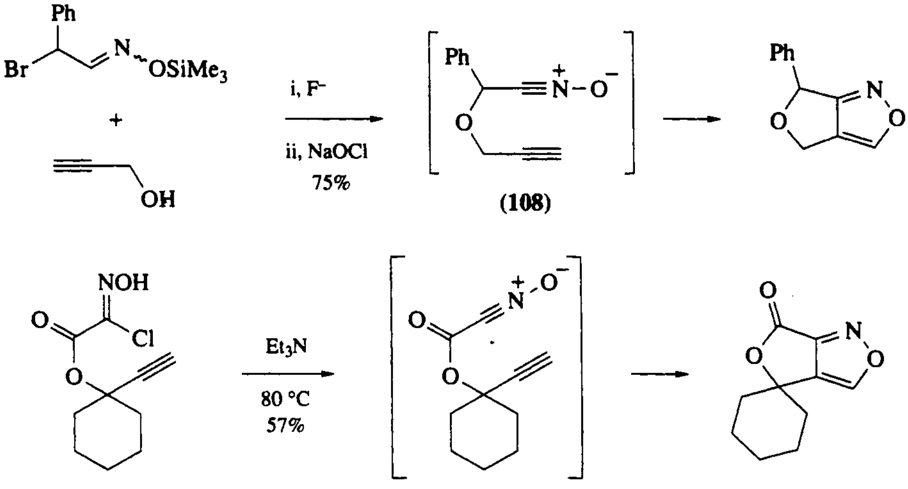

(108)

(109)

**Scheme 32**

## 4.10.4 AZOMETHINE YLIDE CYCLIZATIONS

### 4.10.4.1 General

Azomethine ylides are not typically isolable but must be used *in situ*. They undergo cycloaddition reactions that produce highly functionalized pyrrolidines, dihydropyrroles and pyrroles. The success of these reactions often depends on a judicious choice of dipole and dipolarophile. Azomethine ylides are reluctant to cycloadd to nonactivated alkenes, in large part owing to electronic considerations. The LUMO of most azomethine ylides is high in energy and there is a large gap with the HOMO of a nonactivated alkene.

Intramolecular cycloaddition of an azomethine ylide was first documented in 1977.[53] One frequently employed method for *in situ* generation of the azomethine ylide involves thermolysis of an aziridine, a reaction demonstrated to occur exclusively in a conrotatory fashion.[54] Other methods involve deprotonation of an iminium salt, either directly with base or preferably indirectly *via* desilylation.[55a] Oxazolium salts can be converted to 4-oxazolines, which undergo ring opening to afford azomethine ylides.[55b] Tautomerization of the imines of α-amino acid esters also gives azomethine ylides, presumably at low concentration.[56] Very recently it has been found that nonstabilized azomethine ylides can be generated by deprotonation of amine *N*-oxides.[57a] The ylides are formed in the absence of imines and have a wide reactivity range in intermolecular cycloadditions. This generation procedure has not yet been applied to intramolecular cycloadditions. Tandem Michael addition–intermolecular azomethine ylide cycloaddition to a tetrahydropyrazinone has also been carried out.[57b]

### 4.10.4.2 Alkenyl Azomethine Ylides

#### *4.10.4.2.1 Open-chain C-alkenyl azomethine ylides*

Independent thermolysis (80 °C) of the aziridines (**110a**) and (**110b**) led to the same 5,5-fused bicylic pyrrolidine (Scheme 33).[58] This was rationalized as follows: stereospecific conrotatory aziridine ring-opening afforded the doubly-stabilized azomethine ylides (**111a–b**). These azomethine ylides were in equilibrium but only (**111a**) was able to cyclize. The aziridines (**110c**) and (**110d**) underwent *cis–trans* isomerization, quite possibly *via* (**111c–d**), but gave no dipolar cyclization products. This was attributed to the lower reactivity of the unactivated dipolarophile. The doubly stabilized azomethine ylide (**112**), generated by thermolysis (140 °C) of the corresponding imine, did cyclize, affording a mixture of *cis*-

and *trans*-5,5-fused bicyclic pyrrolidines.[56] An attempt to form a homologous 5,6-fused bicyclic pyrrolidine was unsuccessful.

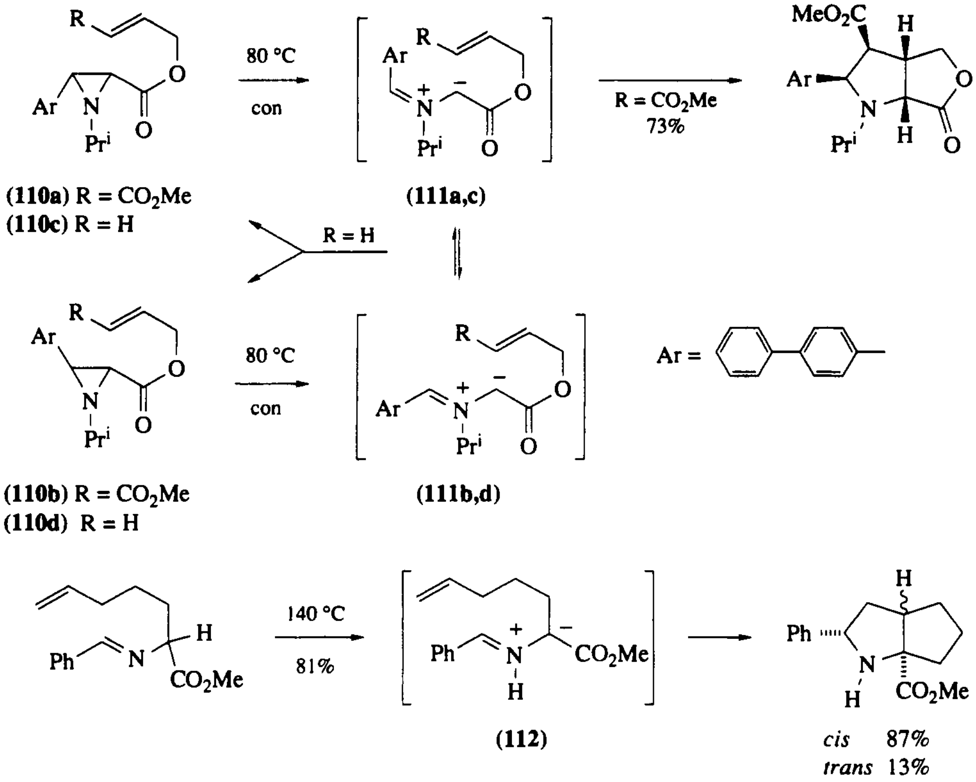
80 °C
con
R = CO2Me
73%
(110a) R = CO2Me
(110c) R = H
(111a,c)
R = H
80 °C
con
Ar =
(110b) R = CO2Me
(110d) R = H
(111b,d)
140 °C
81%
(112)
cis 87%
trans 13%

Scheme 33

Unactivated dipolarophiles readily participate in intramolecular azomethine ylide cycloadditions with a more reactive azomethine ylide. Thus, flash vacuum pyrolysis of aziridine (**113**) afforded a 67% yield of the 5,5-fused bicyclic pyrrolidine (Scheme 34).[59] A singly stabilized azomethine ylide was the apparent intermediate. Similarly, cyclization of the azomethine ylides derived from (**114a–c**) gave the corresponding *cis*-fused 6,6-bicyclic pyrrolidines in 69%, 26% and 16% yield, respectively; the original double bond stereochemistry was retained in the latter two cases.

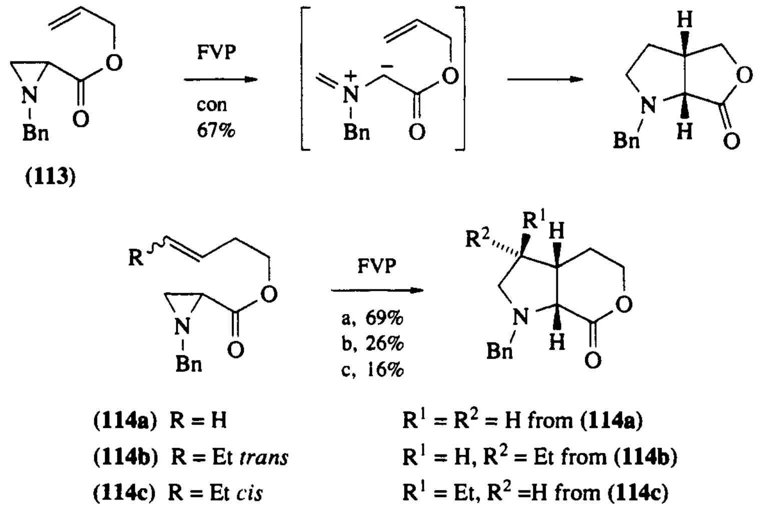
FVP
con
67%
(113)
FVP
a, 69%
b, 26%
c, 16%
(114a) R = H
(114b) R = Et trans
(114c) R = Et cis
R1 = R2 = H from (114a)
R1 = H, R2 = Et from (114b)
R1 = Et, R2 =H from (114c)

Scheme 34

Confalone and Earl have reported a series of intramolecular azomethine ylide cyclizations employing α-dithiolanyl aldehydes (Scheme 35).[60] Thus, reaction of the aldehydes (**115a–b**) with ethyl sarcosinate at 140 °C provided the 5,6-fused bicyclic pyrrolidines (**116a–b**), presumably *via* cyclization of the singly stabilized azomethine ylides. The dithiolanyl group could be removed by standard reactions: this route then provides bicyclic pyrrolidines which cannot be prepared directly from enolizable aldehydes.

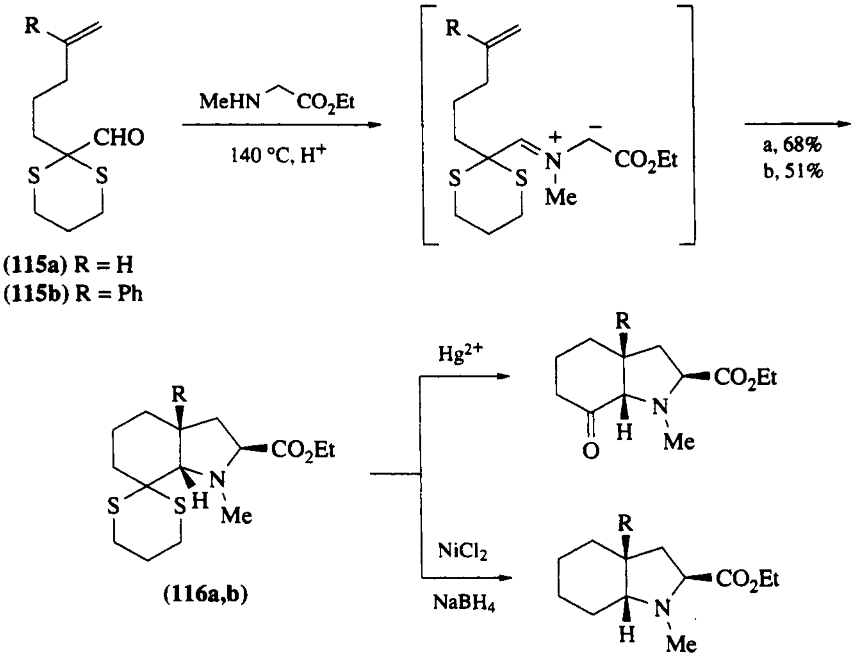

**(115a)** R = H
**(115b)** R = Ph

**(116a,b)**

Scheme 35

### *4.10.4.2.2 Cyclic C-alkenyl azomethine ylides*

A variety of cyclic azomethine ylides undergo cyclization. The intervening bridge may be part of an aryl ring system in the most common case. In principal, the alkene can be part of a ring, but there are no known examples. The azomethine ylide itself may also be cyclic.

A number of aryl-bridged azomethine ylides have been shown to undergo intramolecular cyclization. Thus, the imine (**117a**) was converted to a triflate salt and then desilylated to provide an azomethine ylide (Scheme 36).[61a] The ylide cyclized under high dilution to provide (±)-eserethole. Reaction of (**117b**) with benzoyl fluoride provided a similar cyclization product. These desilylation approaches to azomethine ylide generation show much promise for adaptation to intramolecular cycloadditions. The imine (**118**), containing an α-ester group, affords a tricyclic pyrrolidine on strong heating.[56] Presumably (**118**) tautomerizes to the corresponding azomethine ylide which then cyclizes. In similar fashion, the azomethine ylide (**119**) is presumably an intermediate in the formation of (**120a**), formed as a mixture of two isomers in 50% overall yield from the aldehyde and aminomethylphosphonate.[61b] Cycloadduct (**120a**) was converted to the corresponding lactam (**120b**) by sequential reaction with butyllithium and oxygen.

Cyclization of the azomethine ylide derived from aziridine (**121**) gave two diastereomeric pyrrolidinometacyclophanes (Scheme 37).[62a] Here an 11-atom chain separated the dipole from the dipolarophile. The homologous aziridine with an eight-atom intervening chain afforded (**122**) in 5% yield. Larger homologs were also studied: when a 17-atom chain was present, a small amount of bridged product accompanied the fused product. The stabilized cyclic azomethine ylide (**123**), formed *via* the desilylation route, afforded a pyrrolidine cyclization product in 70% yield as a single stereoisomer.[67b] This product possesses an erythrinane skeleton.

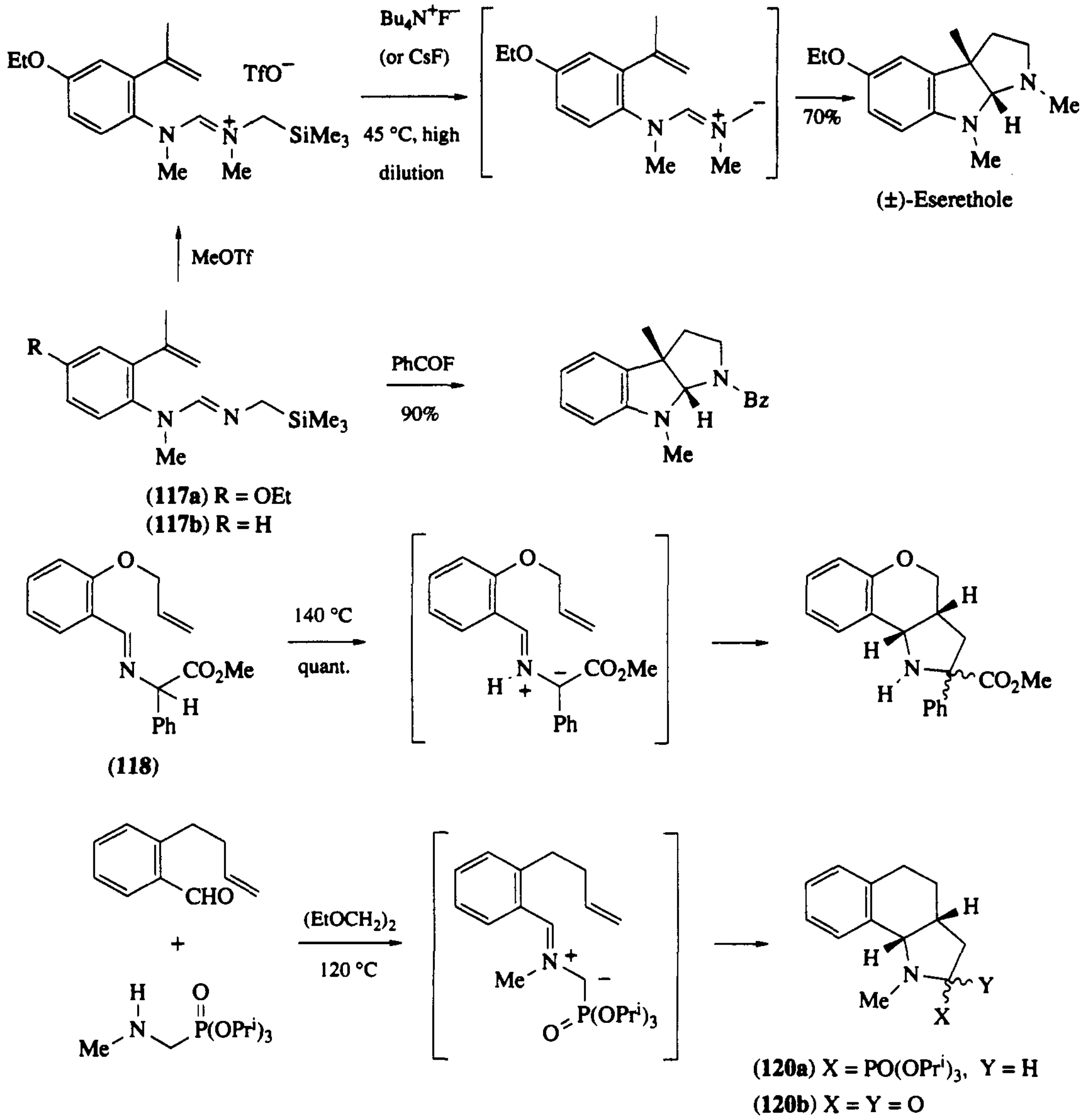
EtO
TfO⁻
SiMe3
Me
Bu4N+F⁻
(or CsF)
45 °C, high dilution
70%
(±)-Eserethole
MeOTf
R
PhCOF
90%
Bz
(117a) R = OEt
(117b) R = H
140 °C
quant.
CO2Me
Ph
(118)
CHO
(EtOCH2)2
120 °C
P(OPr^i)3
(120a) X = PO(OPr^i)3, Y = H
(120b) X = Y = O

Scheme 36

### 4.10.4.3 Tandem Michael–Azomethine Ylide Cyclization Reactions

Very recently examples of tandem Michael–azomethine ylide cyclization reactions have been presented.[62b] Thus, divinyl sulfone reacted with imine (**124**) in the presence of lithium bromide and triethylamine to give (**126**) in 40% yield (Scheme 38). Presumably formation of Michael adduct (**125**), tautomerization to an azomethine ylide and ensuing intramolecular [3 + 2] cycloaddition afforded (**126**). Indeed, (**125**) could be independently synthesized and converted to (**126**) under the reaction conditions. The preference for initial Michael addition, rather than cycloaddition, was variable. When (**124**) and divinyl sulfone were treated with silver acetate and triethylamine in DMSO, intermolecular azomethine cycloaddition occurred giving (**127**) in 27% yield.

### 4.10.4.4 Munchnones

The mesoionic heterocycles called munchnones function as cyclic azomethine ylides in cycloaddition reactions.[63] The alkenyl moiety can be attached at carbon or at nitrogen.

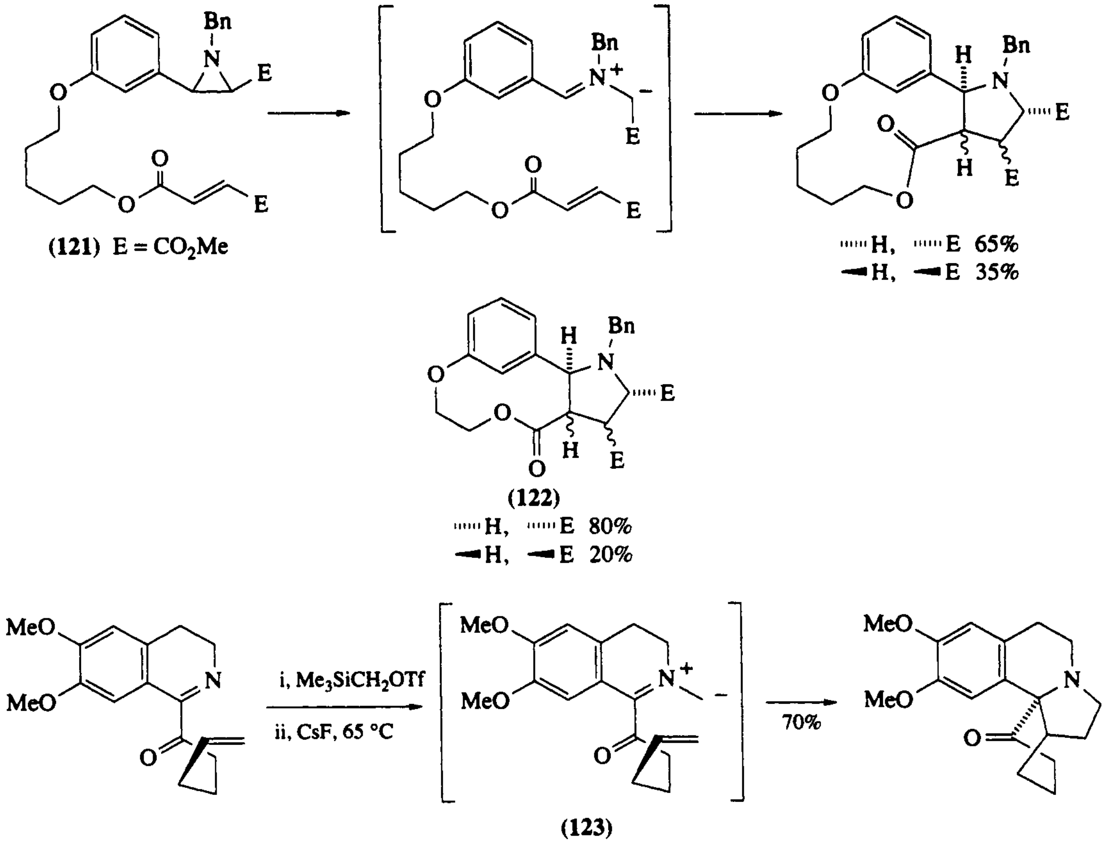
Bn
N
E
O
O
O
E
(121) E = CO$_2$Me
Bn
N+
E
O
O
O
E
H
Bn
N
E
O
O
H
E
O
H, E 65%
H, E 35%
H
Bn
N
E
O
O
H
E
O
(122)
H, E 80%
H, E 20%
MeO
MeO
N
O
i, Me$_3$SiCH$_2$OTf
ii, CsF, 65 °C
MeO
MeO
N+
O
(123)
70%
MeO
MeO
N
O

Scheme 37

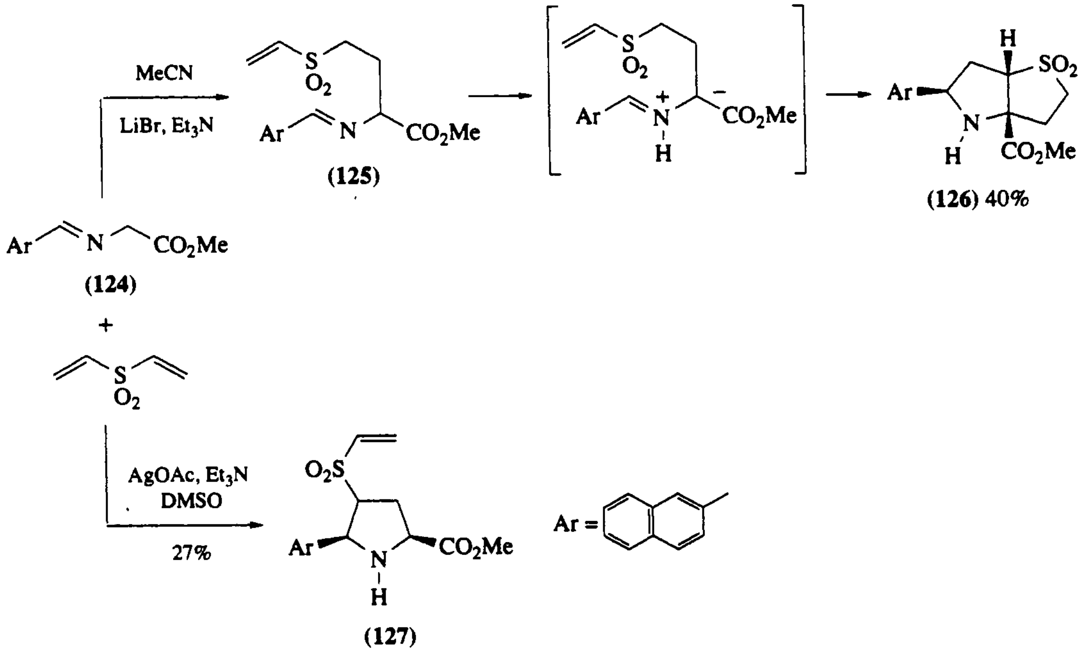
MeCN
LiBr, Et$_3$N
S
O$_2$
Ar
N
CO$_2$Me
(125)
S
O$_2$
Ar
N+
H
CO$_2$Me
H
SO$_2$
Ar
N
H
CO$_2$Me
(126) 40%
Ar
N
CO$_2$Me
(124)
+
S
O$_2$
AgOAc, Et$_3$N
DMSO
27%
O$_2$S
Ar
N
H
CO$_2$Me
(127)
Ar =

Scheme 38

#### 4.10.4.4.1 *C-Alkenyl munchnone azomethine ylides*

Acetylation of the amide (**128**) produced a fused tricyclic pyrrole in 17% yield (Scheme 39).[64] A munchnone intermediate was postulated and could be trapped *via* intermolecular cycloaddition with diethyl acetylenedicarboxylate. Presumably the direct cyclization product lost carbon dioxide, a known reaction of munchnone cycloadducts.[65] An homologous munchnone with an *o*-(propenyl)phenyl group, rather than *o*-(butenyl)phenyl group, failed to cyclize, although it could again be trapped with diethyl acetylenedicarboxylate.

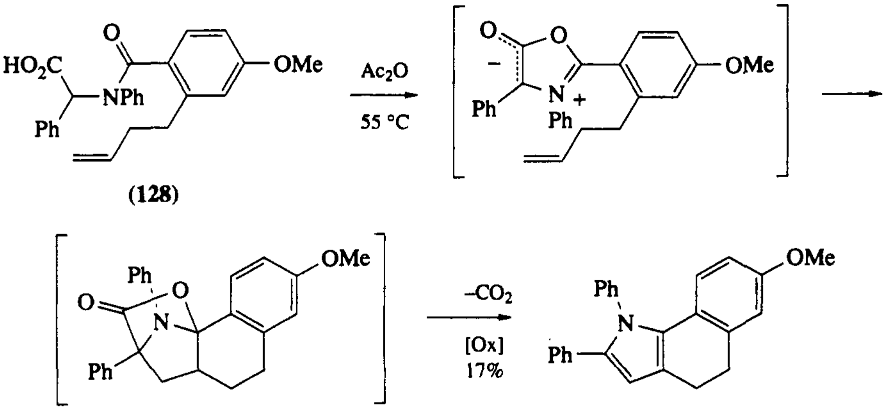

Scheme 39

#### 4.10.4.4.2 *N-Alkenyl munchnone azomethine ylides*

Munchnone (**129a**), prepared from the corresponding formamide and cyclized *in situ*, afforded a 75% yield of one product (Scheme 40).[66] Trifluoroacetylmunchnone (**129b**), formed directly from the corresponding amine *via* trifluoroacetylation, similarly gave a 70% yield of one cyclization product. The munchnone (**130a**) gave a mixture of two regioisomeric cyclization products in 92% yield, indicating the importance of substituent effects in determining regioselectivity. Munchnone (**130b**), presumably formed *via in situ* trifluoroacetylation of (**130a**), gave a 33% yield of one cyclization product, the opposite regioisomer to the one preferred from (**130a**). The homologous munchnones with a vinylic, rather than allylic, dipolarophile failed to undergo cyclization. However, munchnone (**131**), also with a vinylic dipolarophile but a one-atom longer bridge, did cyclize in 85% yield to afford two regioisomers.

### 4.10.4.5 Alkynyl and Allenyl Azomethine Ylides

Intramolecular cycloaddition can be carried out on a variety of alkynyl azomethine ylides analogous to reactions of the alkenyl azomethine ylides. There is also one report of cyclization with an allene.

#### 4.10.4.5.1 *Open-chain C-alkynyl azomethine ylides*

Flash vacuum pyrolysis of aziridine (**132**) led to a 35% yield of the bicyclic 2,5-dihydropyrrole, accompanied by varying amounts of the pyrrole and traces of a fused tricyclic pyrrole (Scheme 41).[59] The dihydropyrrole was easily converted to the pyrrole simply on exposure to oxygen. The homologous aziridine with a one-atom longer bridge directly afforded the aromatized product (**133a**) in 63% yield. Pyrrole (**133b**) was formed analogously but only in 34% yield. Very recently the generation of azomethine ylide (**135**) from oxazole (**134**) and its ensuing intramolecular cycloaddition have been reported.[67a] Thus, (**134**) was converted to the isoxazolium salt with methyl triflate. Reaction of the crude salt with trimethylsilyl cyanide/cesium fluoride afforded a mixture of (**136a**) and (**136b**); treatment with tetrabutylammonium fluoride prior to isolation afforded (**136b**) in 68% overall yield from (**134**).

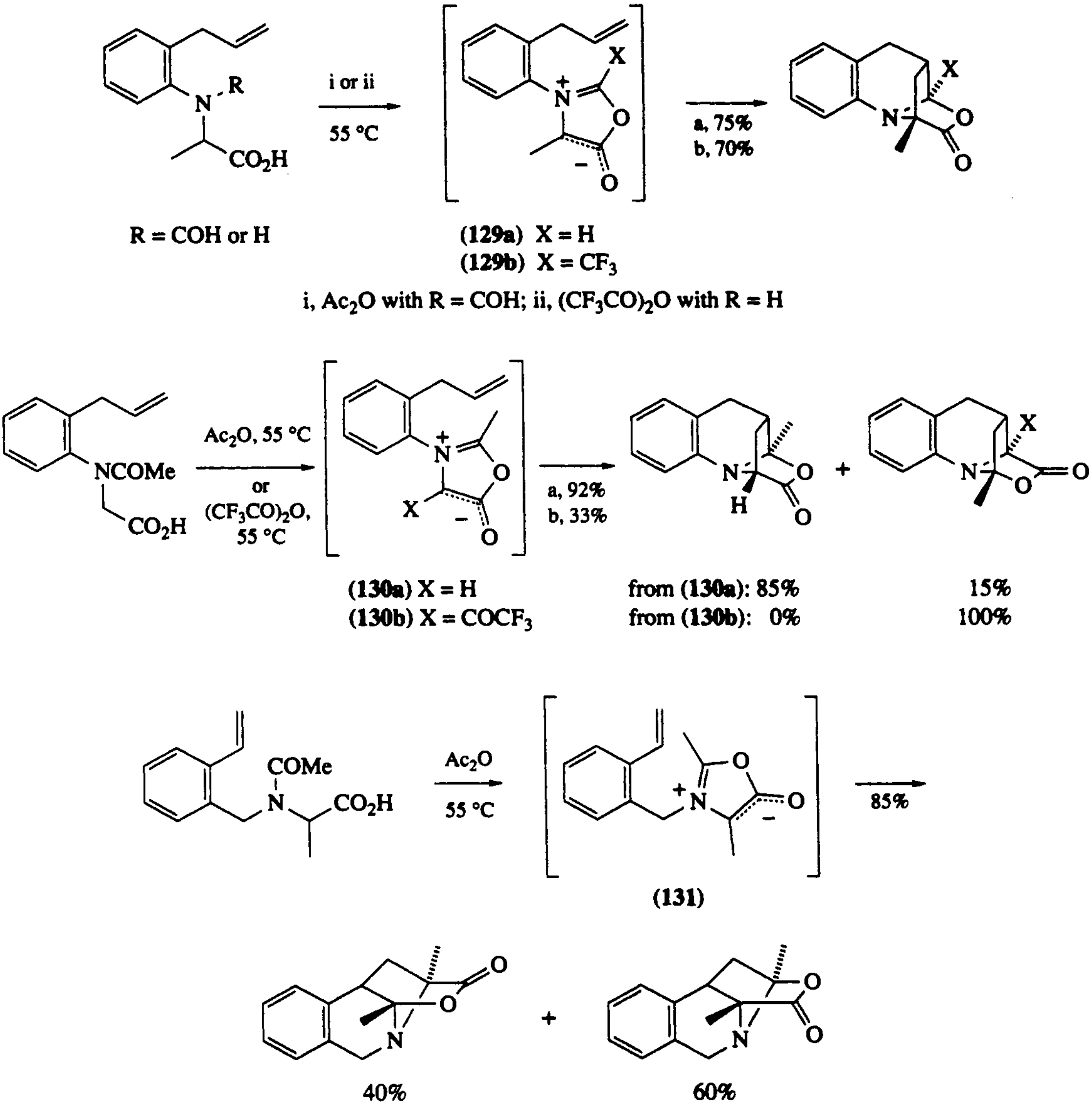
R = COH or H
i or ii
55 °C
(129a) X = H
(129b) X = CF3
a, 75%
b, 70%
i, Ac2O with R = COH; ii, (CF3CO)2O with R = H
NCOMe
CO2H
Ac2O, 55 °C
or
(CF3CO)2O,
55 °C
(130a) X = H
(130b) X = COCF3
a, 92%
b, 33%
from (130a): 85%
from (130b): 0%
15%
100%
COMe
Ac2O
55 °C
(131)
85%
40%
60%

Scheme 40

### 4.10.4.5.2 *Cyclic C-alkynyl azomethine ylides*

Alkynyl azomethine ylides containing an aryl bridge have been shown to undergo cyclization. Thus, tautomerization of imine (**137**) afforded an azomethine ylide which cyclized to give two diastereomeric dihydropyrroles and traces of aromatized product (Scheme 42).[56] The activated cyclic ylide (**138**), generated *via* the desilylation route, underwent cyclization to afford dihydropyrrole (**139**) in 42% yield.[67b] The structure of (**139**) is closely related to erythramine. The structurally related non-stabilized azomethine ylide (**140**) did not cyclize, tautomerizing to the corresponding enamine instead.

### 4.10.4.5.3 *C-Allenyl azomethine ylides*

Azomethine ylide (**141**), formed from condensation of the corresponding aldehyde with ethyl sarcosinate, gave a mixture of the regioisomeric cyclization products (Scheme 43).[60] The major product has two of the three aliphatic rings of lycorenine.

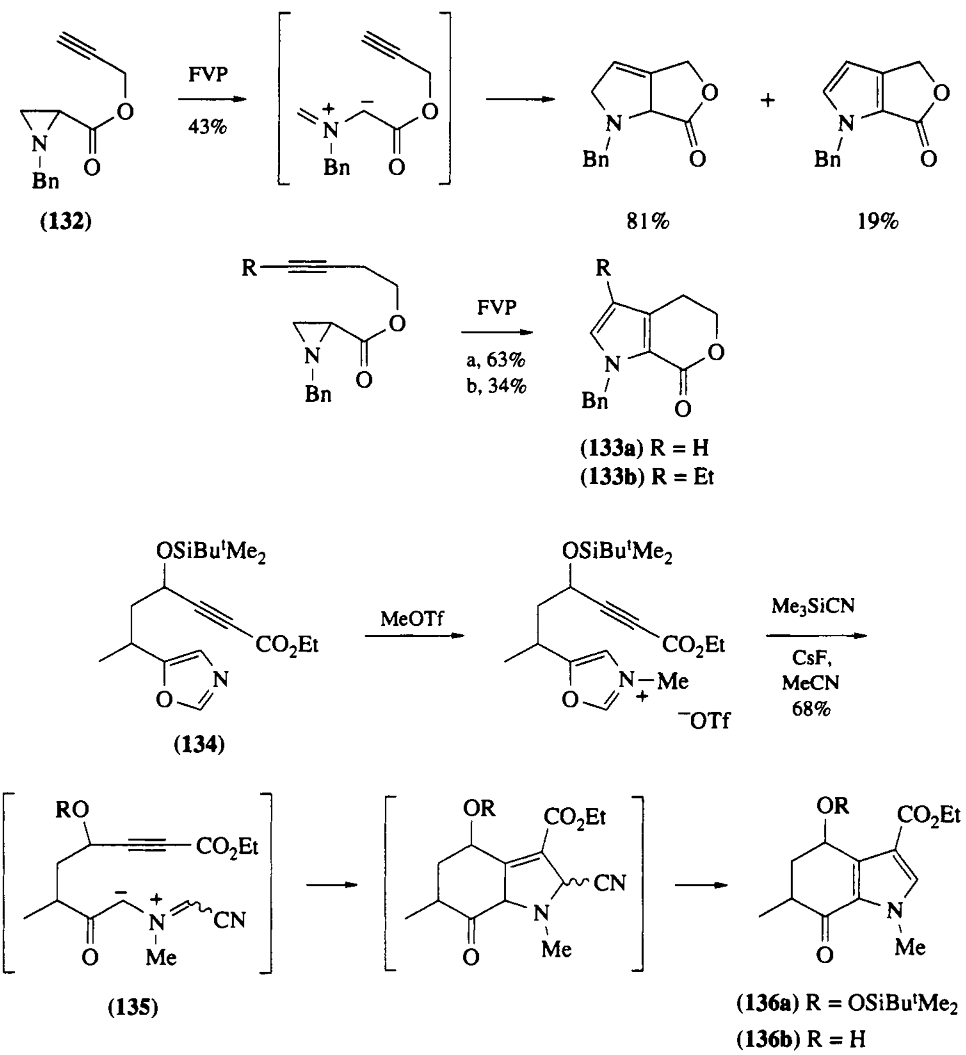

Scheme 41

## 4.10.5 NITRILE YLIDE CYCLIZATIONS

### 4.10.5.1 General

Nitrile ylides are not readily isolable but must be used *in situ*. They are typically bent, not linear like nitrile oxides.[68] As bent species containing six $\pi$-electrons, nitrile ylides have some carbene character. Consequently, they undergo both intramolecular 1,3- and 1,1-cycloaddition reactions. These lead to a variety of bicyclic dihydropyrroles, pyrroles and cyclopropanes. The LUMO of most azomethine ylides is high in energy. Consequently, the dipole LUMO–dipolarophile HOMO gap is large, leading to poor reaction with nonconjugated alkenes. Electron-attracting groups on the dipolarophile permit successful intermolecular cycloaddition.

Intramolecular azomethine ylide cycloaddition to the C—O double bond of an aldehyde was reported in 1973[69] and cycloaddition to the C—C double bond was first reported in 1975.[70] Competition between 1,1- and 1,3-cycloaddition is observed in intramolecular reactions, although intermolecular reactions give only 1,3-cycloaddition. Photolysis of 2*H*-azirines is one generation method of nitrile ylides applicable to intramolecular cycloaddition.[70] Another method involves the base-catalyzed 1,3-elimination of hydrogen halide from alkenyl imidoyl halides. Still other procedures involve thermolytic and photolytic cycloreversions of oxazolinones and dihydrooxazaphospholes.

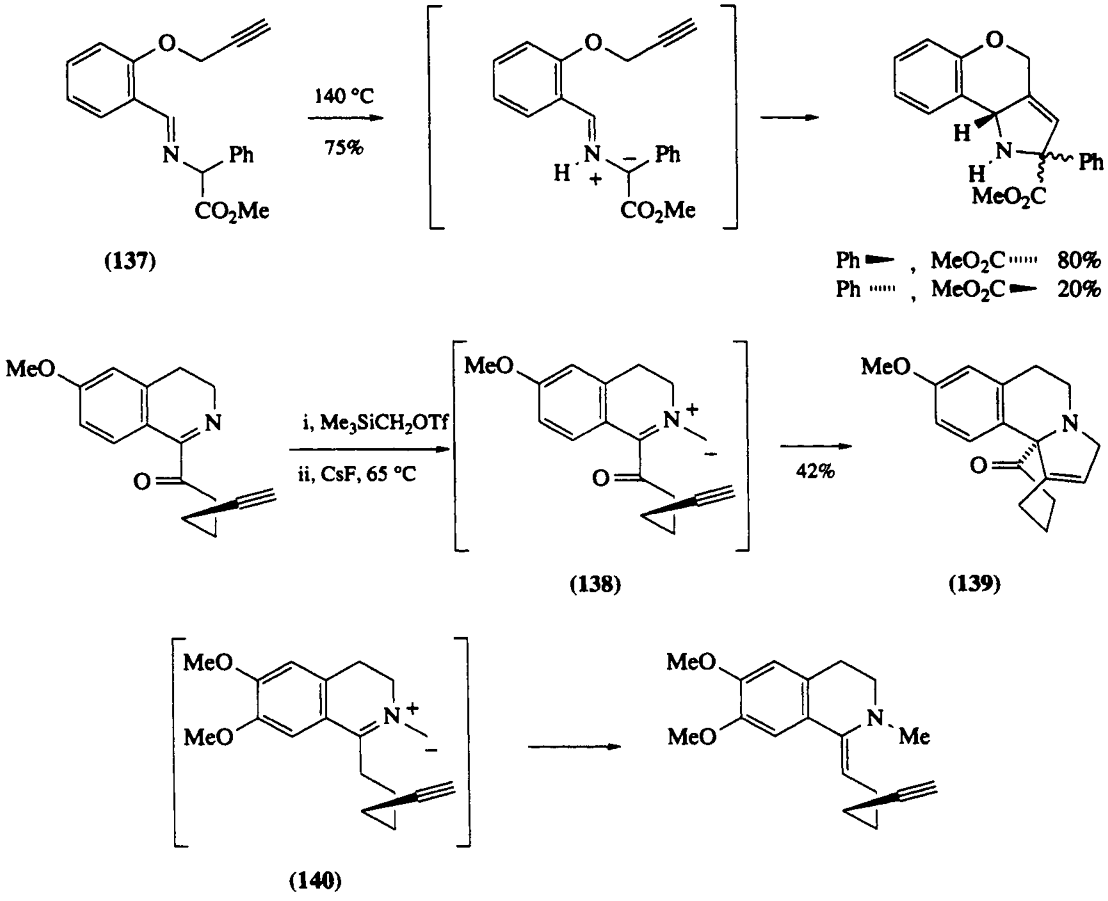
140 °C
75%
Ph ▬ , MeO$_2$C ⋯ 80%
Ph ⋯ , MeO$_2$C ▬ 20%
(137)
i, Me$_3$SiCH$_2$OTf
ii, CsF, 65 °C
42%
(138)
(139)
(140)

Scheme 42

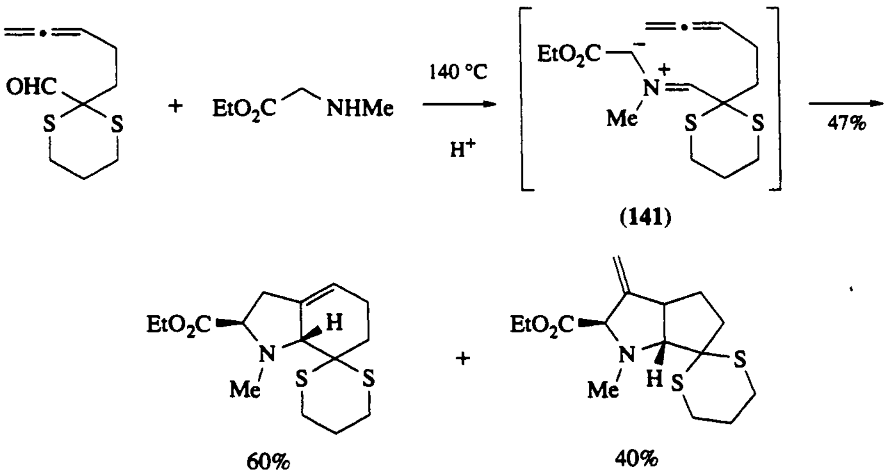
140 °C
H$^+$
47%
(141)
60%
40%

Scheme 43

### 4.10.5.2 Alkenyl Nitrile Ylides

Nitrile ylides can have the alkenyl group attached at either end, at the disubstituted or monosubstituted carbon.

#### 4.10.5.2.1 Open-chain nitrile ylides

Open-chain intramolecular systems have been examined with the chain attached at the disubstituted carbon. If the intervening bridge is sufficiently long (three atoms), only 1,3-cycloaddition is observed.[71] Thus, photolysis of azirine (**142**) gave a 5,5-fused bicyclic dihydropyrrole in 81% yield (Scheme 44). This result is rationalized based on the normal concerted cycloaddition of an intermediate azomethine ylide. Proof for the intermediate dipole was obtained by trapping as a pyrrole with dimethyl acetylenedicarboxylate. Approach of the dipole to the dipolarophile on parallel planes is geometrically possible. However, the regiochemistry normally dictated by electronic factors (which should favor a bridged product) was reversed, presumably by geometric constraints.

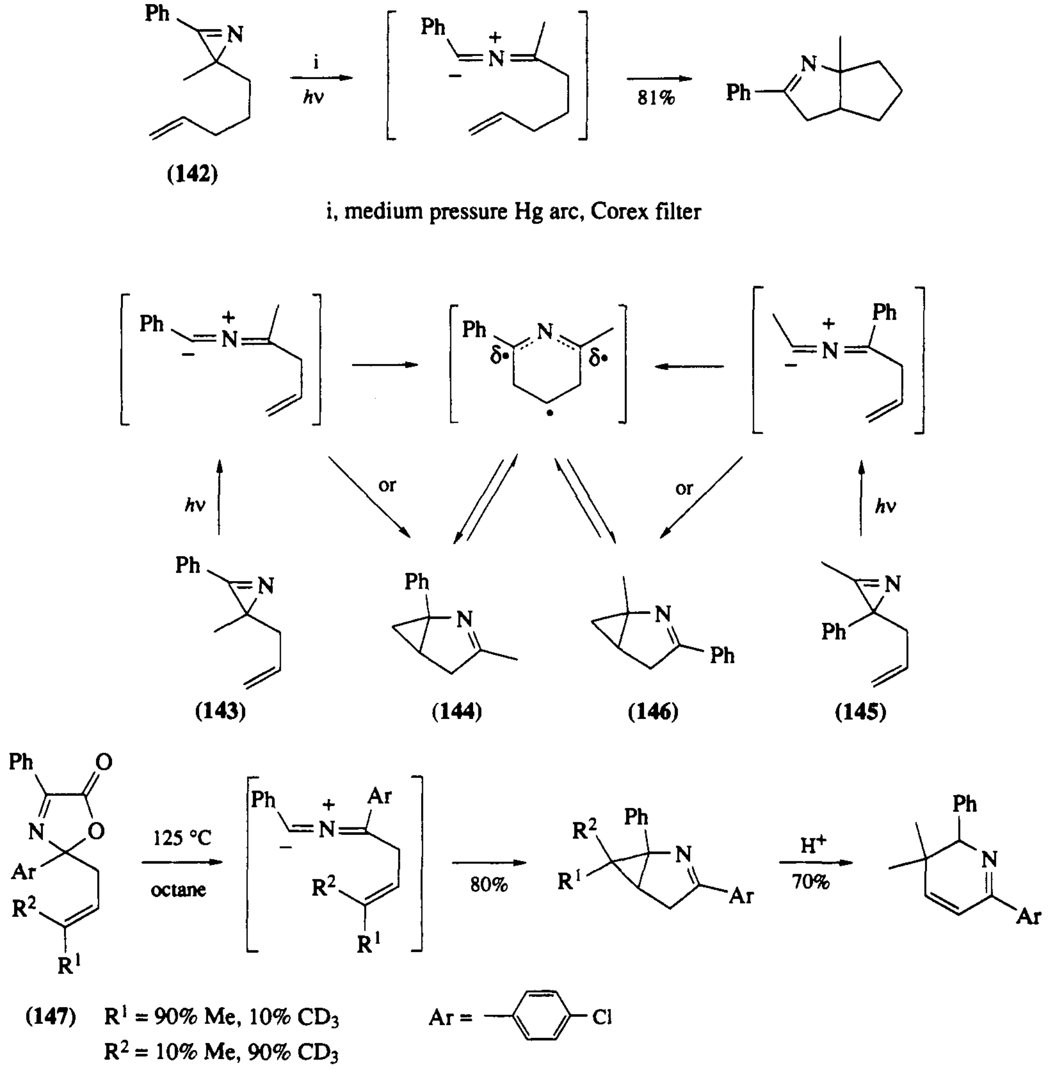

**Scheme 44**

The homologous azirine (**143**) with a one-atom bridge gave quite different results.[70] Photolysis led to the 3,5-fused bicyclic dihydropyrrole (**144**). The isomeric azirine (**145**) also led to (**144**), although the initial products included dihydropyrrole (**146**) which apparently converted to (**144**) as photolysis continued. Azirines (**143**) and (**145**) were shown to not interconvert and the postulated two discrete azomethine ylides were trapped with methyl trifluoroacetate. Formation of dihydropyrrole (**144**) was explained based on a two-step cycloaddition process involving a common diradical intermediate. The observation of (**146**) from photolysis of (**145**) but not (**143**) can be explained based on extinction coefficient differences. Azirine (**145**) has a high extinction coefficient as does (**146**). The initial product (**146**) can then be optically pumped to (**144**) with a low extinction coefficient. Azirine (**143**) also has a low extinction coefficient and any (**146**) that formed from it would be optically pumped to (**144**) before observation. It has also been suggested that the cycloaddition is concerted: according to this viewpoint the diradical is a secondary photoproduct, only formed from photolysis of (**146**) and (**144**).[72]

The complete change in periselectivity can be explained based on geometric constraints. The azomethine ylide generated from (**142**) can undergo approach of the dipole to the internal dipolarophile in parallel planes, the required geometry for a concerted [4π + 2π] process.[1a] However, the azomethine ylides generated from (**143**) and (**145**) *cannot* undergo approach of the dipole to the dipolarophile in parallel planes. Instead, it has been suggested that the dipolarophile HOMO must approach perpendicular to the nitrile ylide plane, interacting with the second LUMO, and resulting in a step-wise process.[73]

The 1,1-cycloaddition process also occurs in nonphotolytic reactions involving azomethine ylides. Thermolysis of oxazolinone (**147**) led to a 3,5-fused bicyclic dihydropyrrole in 80% yield.[72] The alkene stereochemistry was maintained in the product, although subsequent photolysis scrambled the methyl and trideuteromethyl groups. Nondeuterated oxazolinone gave the cyclization product which was converted to a dihydropyridine on warming with acid.[74]

#### *4.10.5.2.2 Aryl-bridged nitrile ylides*

The only cyclic nitrile ylides reported to undergo cyclization have been aryl-bridged species. The intervening bridge has typically been attached at the monosubstituted nitrile ylide carbon. Attachment at this site permits a large variation in the substituents attached at the disubstituted carbon. Changes in these groups lead to changes in periselectivity: the 1,1- *vs.* 1,3-cycloaddition ratio is altered.

The azomethine ylide (**148a**), formed by photolysis of the corresponding azirine, cyclized exclusively to the 1,3-cycloaddition product, obtained in 75% yield (Scheme 45).[75] The ylide (**148b**) cyclized exclusively to the 1,1-cycloaddition product, isolated in 55% yield as the amine. The azomethine ylide (**148c**) gave a 1:1 mixture of 1,1- and 1,3-cycloaddition products. These results apparently arise from electronic effects: electron-releasing groups at the disubstituted ylide carbon increase the amount of 1,1-cycloaddition while electron-attracting groups favor 1,3-cycloaddition. Thus, azomethine ylides (**148d–e**), generated from an imidoyl chloride and a dihydrooxazaphosphole, gave only the corresponding 1,3-cycloaddition products in 64% yield and quantitative yield, respectively. When the cyclization result for (**148b**) is compared to (**148d**), it is apparent that periselectivity was primarily controlled by electronic rather then steric factors.

The electronic effect has been rationalized based on the degree of linearity of the azomethine ylide.[75] Electron-donating groups should make the dipole more bent while electron-attracting groups should make it more linear. It has been reasoned that the more linear the dipole, the better the concerted 1,3-cycloaddition process. An electron-attracting group on the dipolarophile terminal carbon also favors 1,3-cycloaddition, presumably by speeding up the concerted process. Thus, azomethine ylide (**149a**) gave 1,1-cycloaddition while azomethine ylide (**149b**) gave 1,3-cycloaddition.[76]

### 4.10.5.3 Alkynyl Nitrile Ylides

Cyclization of the nitrile ylide generated from amide (**150a**) *via* an imidoyl chloride led to an 18% yield of a fused tricyclic pyrrole (Scheme 46).[77] Similarly, the nitrile ylide derived from (**150b**) cyclized in 6% yield.

## 4.10.6 AZOMETHINE IMINE CYCLIZATIONS

### 4.10.6.1 General

Azomethine imine cycloadditions provide access to pyrazolidines, pyrazolines and pyrazoles. Intramolecular cyclizations were first reported in 1970.[78] The main method for generation of azomethine imines involves reaction of a 1,2-disubstituted hydrazine with an aldehyde or an aldehyde precursor.

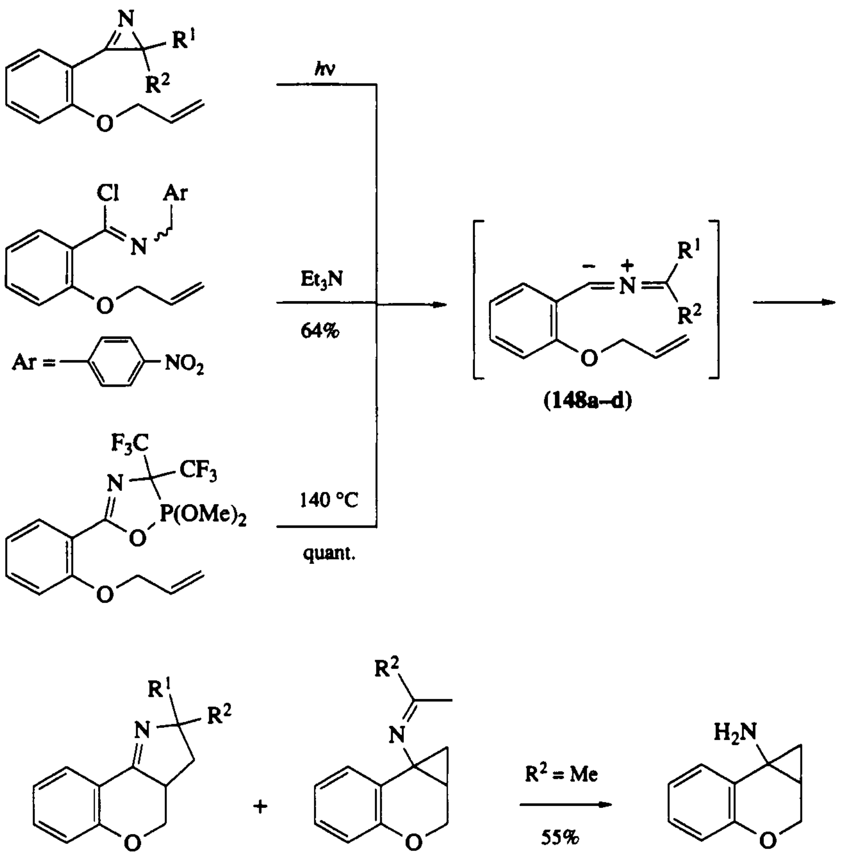
hv
Et$_3$N
64%
140 °C
quant.
Ar = —C$_6$H$_4$—NO$_2$
R$^2$ = Me
55%

**(148a–d)**

| | | |
|---|---|---|
| a: $R^1 = R^2 = H$ | 100% | 0% |
| b: $R^1 = R^2 = Me$ | 0% | 100% |
| c: $R^1 = Me, R^2 = H$ | 50% | 50% |
| d: $R^1 = Ar, R^2 = H$ | 100% | 0% |
| e: $R^1 = R^2 = CF_3$ | 100% | 0% |

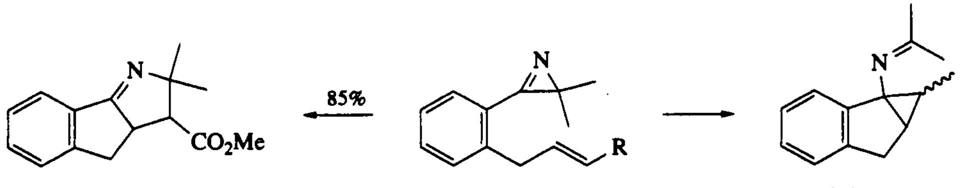
85%
80% *exo*
20% *endo*

**(149a)** R = Me
**(149b)** R = $CO_2Me$

Scheme 45

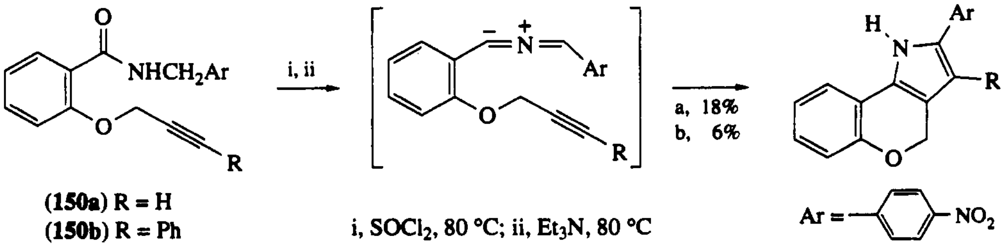
i, ii
a, 18%
b, 6%
Ar = —C$_6$H$_4$—NO$_2$

**(150a)** R = H
**(150b)** R = Ph

i, $SOCl_2$, 80 °C; ii, $Et_3N$, 80 °C

Scheme 46

### 4.10.6.2 Alkenyl Azomethine Imines

Azomethine imines can have the alkenyl group attached at carbon, the terminal nitrogen or the internal nitrogen.

#### *4.10.6.2.1 Open-chain azomethine imines*

The azomethine imine (**151**), having the alkene attached to the terminal dipole nitrogen, was generated *in situ* from the corresponding hydrazine by reaction with benzaldehyde (Scheme 47).[79] As is typical in these reactions, condensation at the more basic benzyl-substituted nitrogen occurred, rather than at the acyl-substituted nitrogen. Cyclization of (**151**) afforded the 5,5-fused pyrazolidine and no bridged product.

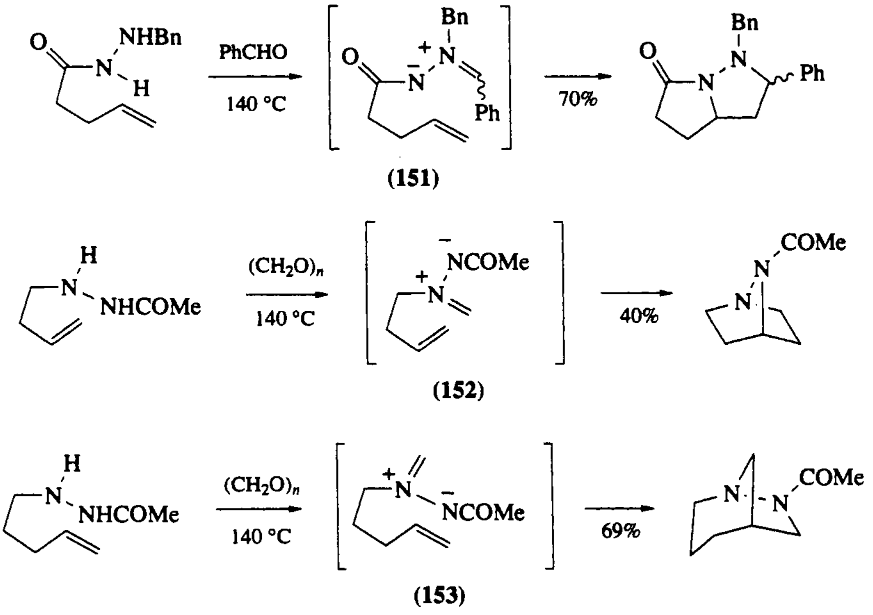

**Scheme 47**

Cyclization of azomethine imines substituted at the internal nitrogen with an alkenyl group must give bridged products. Thus, imines (**152**) and (**153**) cyclized to bridged pyrazolidines with a different regioisomer obtained as the sole reported product in each case: (**152**) cyclized with the dipole bonding through nitrogen to the terminal dipolarophile carbon whereas (**153**) cyclized in reverse fashion.[79] The imine corresponding to (**153**) but derived from benzaldehyde gave a mixture of regioisomers.

#### *4.10.6.2.2 Aryl-bridged azomethine imines*

Azomethine imines which contain an intervening aromatic ring between the dipole and dipolarophile are accessible from aryl aldehydes and readily undergo cyclization. Thus, imine (**154**), where the dipolarophile is attached at the carbon of the dipole, afforded *cis-* and *trans*-fused tricyclic pyrazolidines in which the alkene stereochemistry was retained (Scheme 48).[78a]

#### *4.10.6.2.3 Cycloalkenyl azomethine imines*

The azomethine imine (**155**), containing a cyclic dipolarophile, cyclized to a tetracyclic pyrazolidine in 48% yield.[78a] Aldehyde (**156**), containing a furan ring, reacted with *N*-methyl-*N*′-(phenylacetyl)hydrazine to afford an azomethine imine; the imine cyclized to one product, probably with the two new rings *cis* fused.[80]

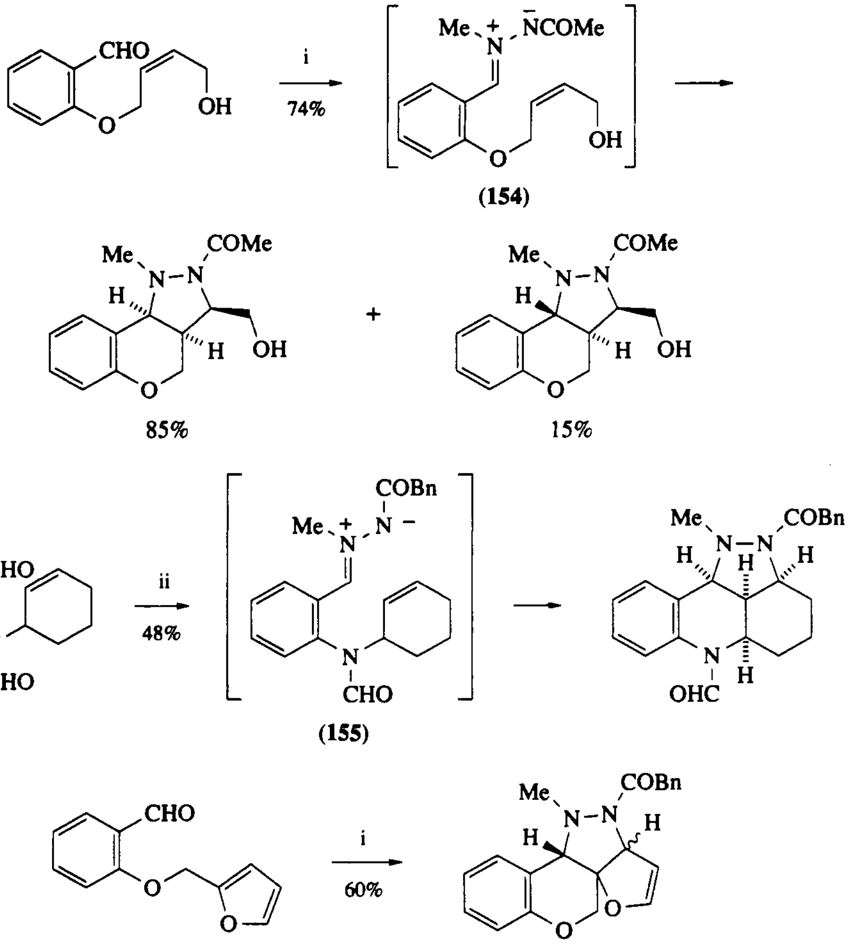
CHO
OH
O
i
74%
Me
+
N
NCOMe
OH
O
(154)
Me
COMe
N-N
H
H
OH
O
85%
+
Me
COMe
N-N
H
H
OH
O
15%
CHO
N
CHO
ii
48%
COBn
Me
+
N
N
N
CHO
(155)
Me
COBn
N-N
H
H
H
N
H
OHC
CHO
O
O
i
60%
Me
COBn
N-N
H
H
O
O

**(156)**

i, MeNHNHCOMe, 110 °C; ii, MeNHNHCOBn, 110 °C

**Scheme 48**

Jacobi *et al.* have reported the preparation of azomethine imines (**157a–b**) by the acid-catalyzed reaction of the corresponding hydrazines with acetals (Scheme 49).[81] The imine (**157a**) cyclized to a single product as did (**157b**). The stereochemistry of cyclization is apparently controlled by nonbonded interactions between the benzyl group and R group. The pyrazolidine obtained from (**157a**) was converted in several steps to (**160**) and hence to (±)-saxitoxin. First, it was necessary to epimerize the methoxycarbonyl group (thermodynamic control) which was then reduced *in situ* affording (**158**). Direct cleavage of the pyrazolidine ring of (**158**) could be accomplished with sodium in liquid ammonia. However, to complete the synthesis, it was found necessary first to prepare (**159**). Reductive cleavage of the pyrazolidine ring and *in situ* thioacylation afforded (**160**) with the requisite six-membered ring of saxitoxin.

### 4.10.6.3 Alkynyl Azomethine Imines

Azomethine imines can cycloadd to an internal C—C triple bond producing new bicyclic pyrazoline systems. Thus, imine (**161**), prepared *in situ* from the corresponding aldehyde, cyclized to a tricyclic pyrazoline (Scheme 50).[78a]

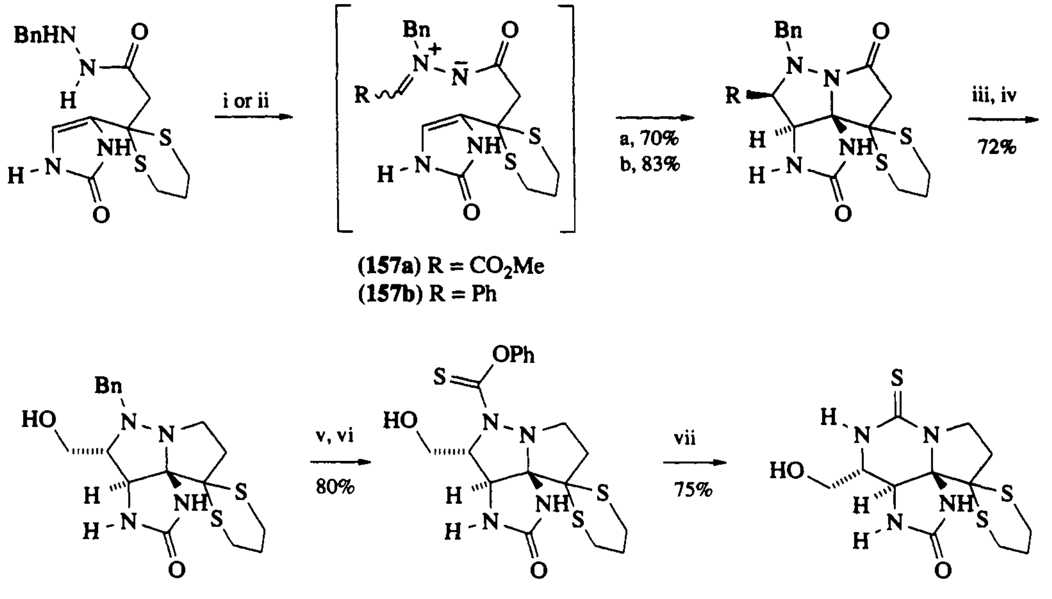

**(157a)** R = $CO_2Me$
**(157b)** R = Ph

**(158)** **(159)** **(160)**

i, $PhCH(OEt)_2$, TsOH, 80 °C; ii, $MeOCH(OH)CO_2Me$, $BF_3{\cdot}OEt_2$, 82 °C; iii, NaOMe; iv, $NaBH_4$ then $BH_3{\cdot}SMe_2$; v, Pd, $HCO_2H$; vi, PhOCSCl, pyridine; vii, Na, $NH_3$, −78 °C

Scheme 49

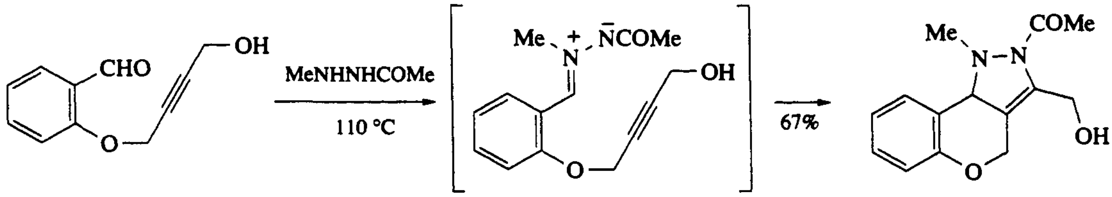

**(161)**

Scheme 50

### 4.10.6.4 Hydrazone Cyclization Reactions

Alkenyl hydrazones undergo cyclization to pyrazolines on heating, presumably *via* an azomethine imine tautomer; cyclization to a pyrazolidine is presumably followed by *in situ* oxidation.[82] Thus, **(162b)** afforded a 36% yield of the tricyclic pyrazoline (**163b**; Scheme 51). Several similar cyclizations have been reported.[82,83] However, a synthetically more useful procedure is to treat the hydrazone with strong acid.[84,82] Under these conditions **(162a)** was converted to a mixture of pyrazoline **(163a)** and pyrazolidine **(164a)**, which could be completely converted at 140 °C to the corresponding pyrazole. Hydrazone **(165)** cyclized to a tricyclic pyrazolidine under similar conditions. In these acid-catalyzed reactions, a protonated azomethine imine, rather then the free azomethine imine, is the likely intermediate and the process is formally a $[3^+ + 2]$ cycloaddition.

Aldehyde **(166)** reacted with excess hydrazine hydrochloride to afford a pyrazoline in 63% yield: a mixture of pyrazoline and pyrazolidine was obtained under an inert atmosphere.[85] This reaction presumably involves the hydrazone and protonated azomethine imine as intermediates. Using **(166)** in excess afforded a bisintramolecular adduct in 87% yield.

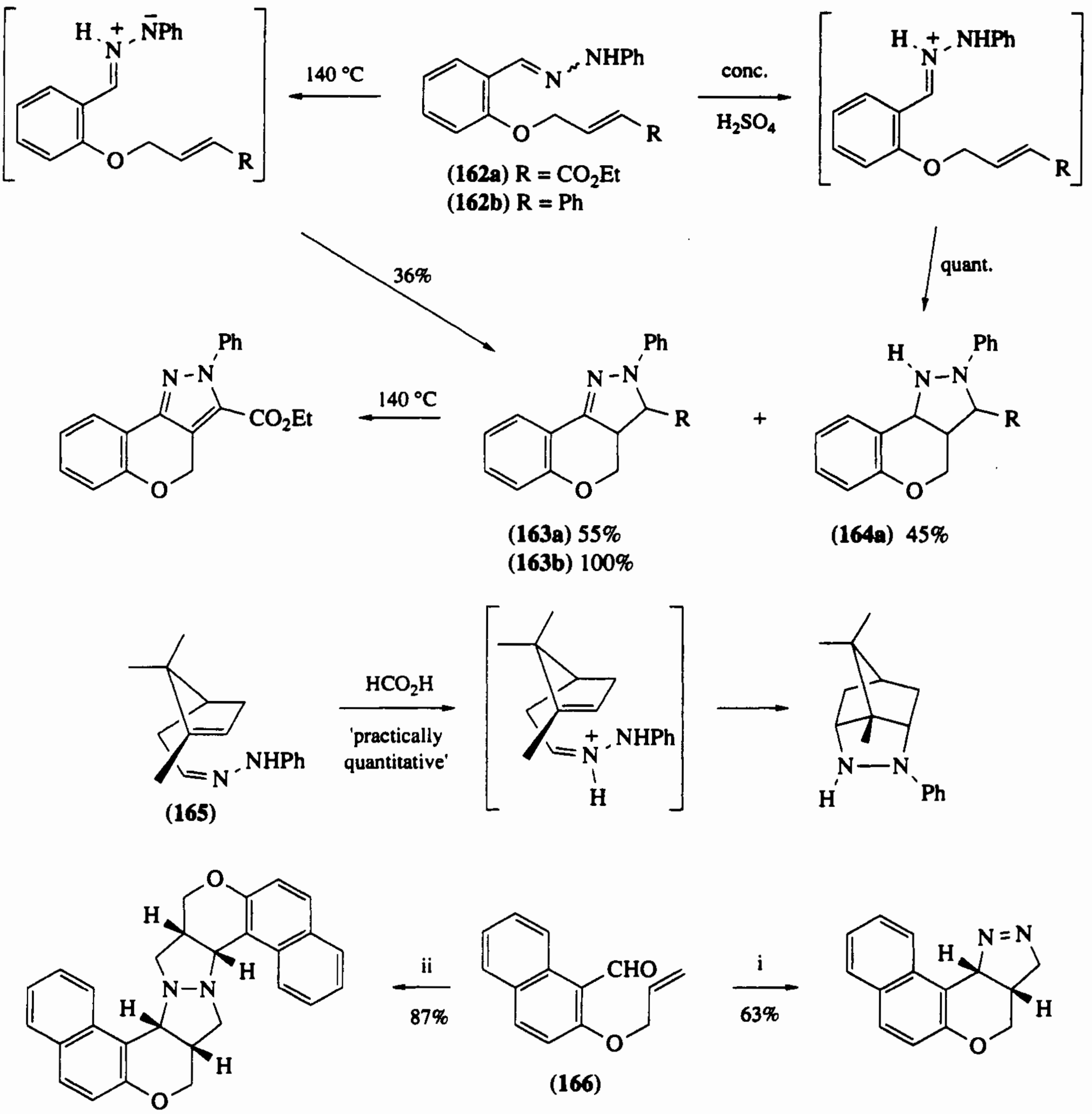

i, 20 equiv. $NH_2NH_2{\cdot}2HCl$, 78 °C; ii, 0.5 equiv. $NH_2NH_2{\cdot}2HCl$, 78 °C then $Et_3N$

Scheme 51

### 4.10.6.5 Azomethine Imine Cyclizations Employing Sydnones

The mesoionic compounds known as sydnones serve as cyclic azomethine imines. Thus, sydnone (**167**), isolable after preparation from the corresponding nitrosamine, underwent cyclization as an azomethine imine at 20–35 °C (Scheme 52).[86] Photolysis of sydnones also results in cyclization but through nitrile imine intermediates (*vide infra*).

### 4.10.6.6 Tandem Sydnone Intermolecular–Intramolecular Cycloadditions

The products derived from intermolecular cycloaddition of sydnones readily lose carbon dioxide. If the original cycloaddition is carried out on a diene, the resulting azomethine imine intermediate can be trapped intramolecularly. Thus, 1,5-cyclooctadiene cycloadded to a sydnone to afford the cycloadduct (**168**).[78b] It is theorized that the intermolecular monocycloadduct (**169**) was formed, lost carbon dioxide, and cycloadded as a cyclic azomethine imine to the remaining C—C double bond. Conjugated dienes have been shown to undergo a similar sequence.[87]

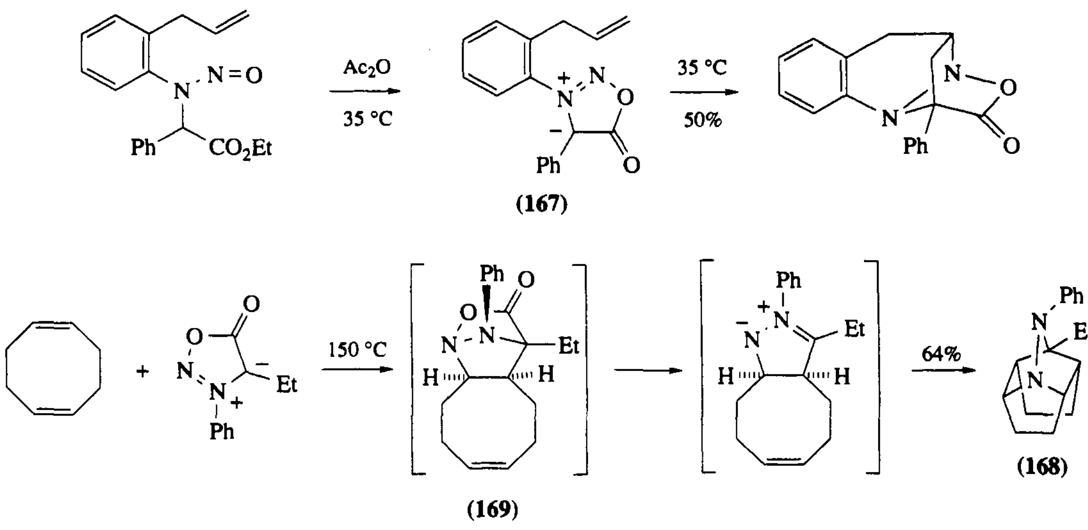

Scheme 52

## 4.10.7 NITRILE IMINE CYCLIZATIONS

### 4.10.7.1 General

Nitrile imine cycloadditions provide access to pyrazolines and pyrazoles. Intramolecular cyclizations to alkynes were first reported in 1974.[88] Perhaps the most useful method for generation of nitrile imines involves 1,3-elimination of hydrogen chloride from an α-chlorohydrazone. Tetrazoles and sydnones are also precursors to nitrile imines.

### 4.10.7.2 Alkenyl Nitrile Imines

Nitrile imines can have the alkenyl group attached at either end of the 1,3-dipole, through carbon or nitrogen. Predominantly 1,3-cyclizations have been observed although a few 1,1-cyclizations have been reported.

### *4.10.7.2.1 Open-chain nitrile imines*

The nitrile imines (**170a–b**), having the alkene attached to carbon, were generated *in situ* from the corresponding chlorohydrazone by reaction with triethylamine (Scheme 53).[89] Cyclization afforded the 5,5-fused pyrazolines and no bridged product. Alkene stereochemistry present in (**170b**) was retained in the cyclization product. It is noteworthy that nitrile imines typically fail to cycloadd intermolecularly to unactivated alkenes. The nitrile imine (**171**), presumably formed by reaction of the corresponding chlorohydrazone with base, failed to cyclize, probably owing to a reduced entropic advantage. The nitrile imine (**172**) also failed to cyclize, presumably because the dipole and dipolarophile could not approach on parallel planes.[90] Nor did (**172**) give a 1,1-cycloadduct, although it did undergo intermolecular cycloaddition.

### *4.10.7.2.2 Aryl-bridged nitrile imines*

A large number of nitrile imines which contain an intervening aromatic ring between the dipole and dipolarophile have been cyclized. Thus, the nitrile imines (**173a–b**), where the dipolarophile is attached at the nitrogen of the dipole, afforded tricyclic pyrazolines (Scheme 54).[89,86] Imine (**173a**) was generated from the chlorohydrazone, while (**173b**) was generated by photorearrangement of a sydnone. Nitrile imines (**174a–c**), where the dipolarophile is attached at the carbon of the dipole, also afforded tricyclic py-

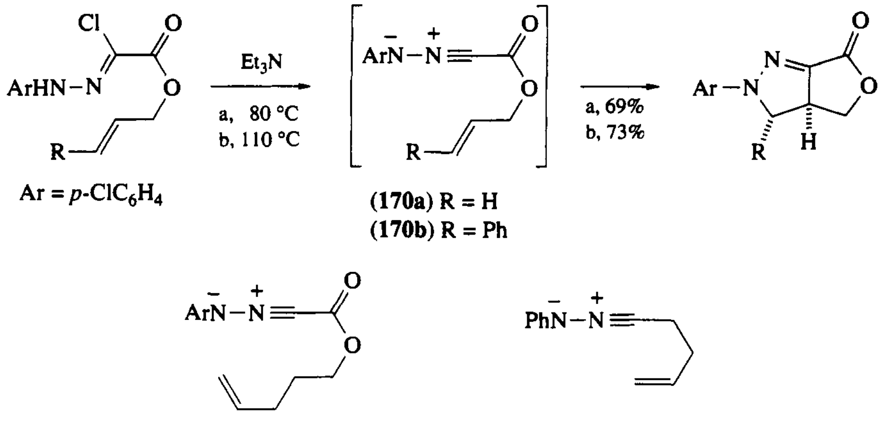

**(170a)** R = H
**(170b)** R = Ph

**(171)** **(172)**

Scheme 53

razolines.[91] Nitrile imine (**174a**) was formed from a tetrazole[91b] and (**174c**) by lead tetraacetate oxidation of a sulfonyl hydrazone.[91c] Other hydrazones also afford nitrile imines on lead tetraacetate oxidation but oxidation of the pyrazoline products to pyrazoles is a side reaction.[92]

Nitrile imines can cyclize to 1,1-cycloadducts if the dipole–dipolarophile parallel plane approach is unfavorable. Thus, cyclopropanes (**175a–b**) were independently obtained on short-term reaction of the chlorohydrazone precursors with silver carbonate (Scheme 55).[93] Longer reaction times afforded a 3:1 b:a ratio from either precursor: the products were shown to equilibrate. Heating of cyclopropanes (**175a–b**) afforded a benzodiazepine.

#### *4.10.7.2.3 Cycloalkenyl nitrile imines*

The nitrile imine (**176**), containing a cyclic dipolarophile, cyclized to a tricyclic pyrazoline in 73% yield.[89]

### 4.10.7.3 Alkynyl Nitrile Imines

Numerous alkynyl nitrile imines have been shown to undergo cyclization. Typical examples are the preparation of pyrazoles (**177**) and (**178**; Scheme 56).[90,94]

## 4.10.8 CYCLIZATION OF DIAZO COMPOUNDS

### 4.10.8.1 General

Diazomethane and its simple analogs undergo cycloaddition to unsaturated compounds both directly and after conversion to carbenes. The direct cycloadditions are 1,3-dipolar for the most part and provide access to pyrazolines and pyrazoles. Intramolecular cyclizations were recognized as early as 1965.[95] The two main methods used in generation of diazo compounds for subsequent intramolecular cycloaddition include thermolysis of tosylhydrazone salts and thermolysis of iminoaziridines. Decomposition of nitrosamines has also been employed.

### 4.10.8.2 Cyclization of Diazoalkenes

Diazoalkenes always have the intervening chain attached on carbon. The dipole HOMO–dipolarophile LUMO interaction is usually dominant in intermolecular cycloadditions. Consequently, nonactivated alkenes which have a relatively high-energy LUMO react poorly. Nevertheless, intramolecular cycloaddi-

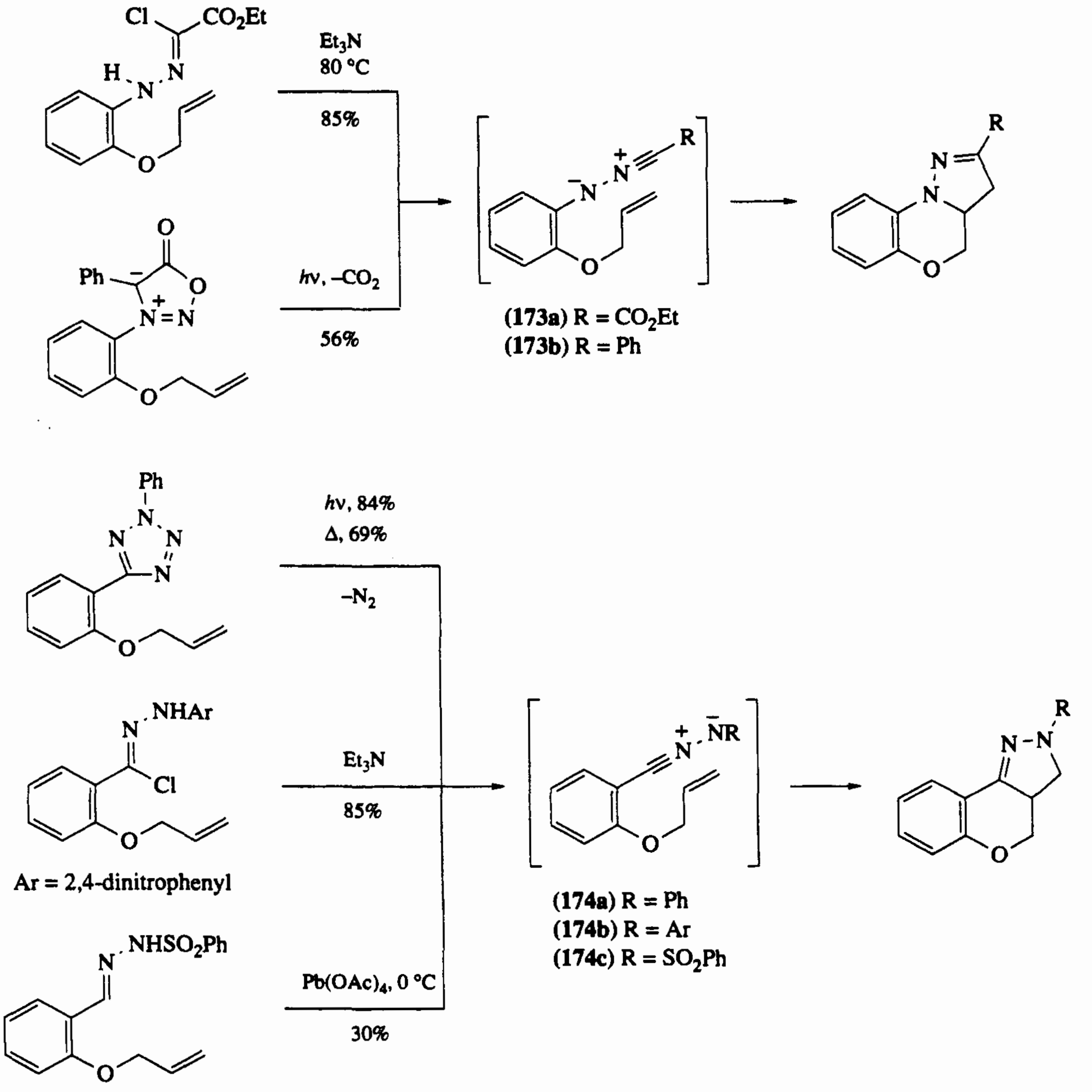

**Scheme 54**

tion of nonactivated alkenes does occur; indeed, activated alkenes have been largely ignored in intramolecular diazo cycloadditions.

Diazo compounds can often be isolated, although many intramolecular cycloadditions occur at room temperature. Thus, the diazo compounds have typically been treated as reactive intermediates. Both 1,3-cycloaddition and 1,1-cycloaddition reactions have been observed, depending on the substrate geometry.

### *4.10.8.2.1 Open-chain diazoalkenes*

Open-chain diazoalkenes can conceivably cyclize to give either fused or bridged bicyclic products. Only fused products have been reported. Thus, the diazoalkene (**179a**) cyclized to a 5,5-fused bicyclic pyrazoline in 76% overall yield when (**179a**) was formed from an iminoaziridine precursor (Scheme 57).[96] A tosylhydrazone salt was also cyclized in unstated yield *via* (**179a**). The analogous diazoalkene (**179b**), formed from a tosylhydrazone precursor, cyclized in 69% overall yield.[97] The homolog (**180**) with a two- rather than three-carbon intervening chain did not cyclize at room temperature: it was stable unless exposed to air. The homolog with a four-carbon intervening chain cyclized in only 16% yield. Longer intervening chains have not been investigated, but the reduced entropic activation would make these compounds unattractive candidates for high-yield cyclization.

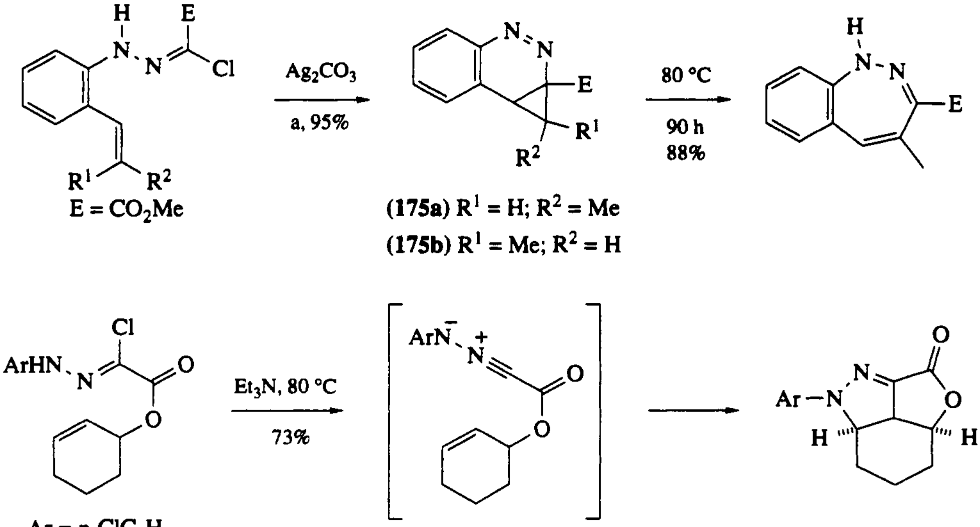

**(175a)** $R^1 = H; R^2 = Me$

**(175b)** $R^1 = Me; R^2 = H$

**(176)**

Scheme 55

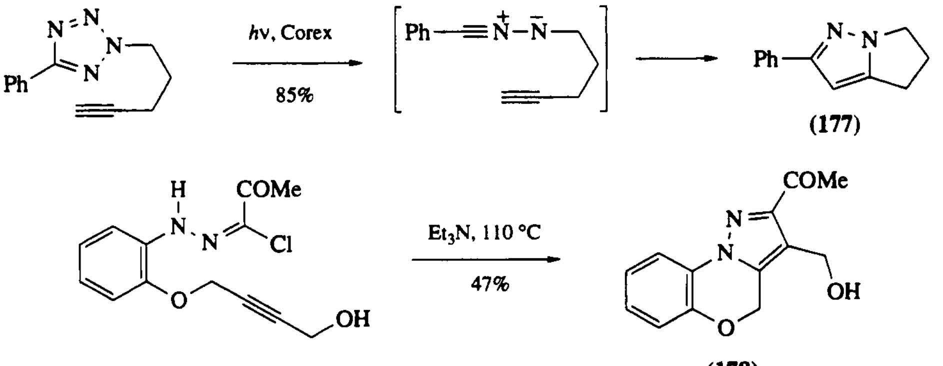

**(177)**

**(178)**

Scheme 56

The diazo compound (**181a**), prepared from the nitrosamine, cyclized to a pyrrolopyrazoline in 80% yield.[98] The diazo compound (**181b**), prepared from diethyl diazomalonate and allylamine, cyclized similarly but at a much more rapid rate. This is consistent with the lowered LUMO of the dipole of (**181b**), substituted with an ester group: here the dipole LUMO–dipolarophile HOMO is the likely dominant interaction. The N—N double bond of the pyrrolopyrazoline products was readily isomerized to afford $\Delta^2$-isomers.

In contrast to the above results, the diazo compounds (**182a–b**) with a one-carbon intervening chain underwent exclusive 1,1-cycloaddition.[97] These cyclizations were stereospecific: the alkene stereochemistry was retained.[97,99]

### *4.10.8.2.2 Aryl-bridged diazoalkenes*

A number of aryl-bridged diazoalkenes have been shown to undergo cyclization. Thus, (**183a**) cyclized to pyrazoline (**184a**) and (**183b**) cyclized to (**184b**; Scheme 58).[96] The alkene stereochemistry was retained in these cyclizations as in 1,1-cyclizations. The pyrazolines (**184a–b**) undergo nitrogen extrusion to afford cyclopropanes: this reaction, however, is nonstereospecific. Both (**184a**) and (**184b**) gave mixtures of the *endo*- and *exo*-methylcyclopropanes, although the product ratios differed (1:3 *endo:exo* from **184b** and 6:1 *endo:exo* from **184a**). These different ratios presumably reflect the rapid closure of the diradical intermediates and require a preference for inversion.

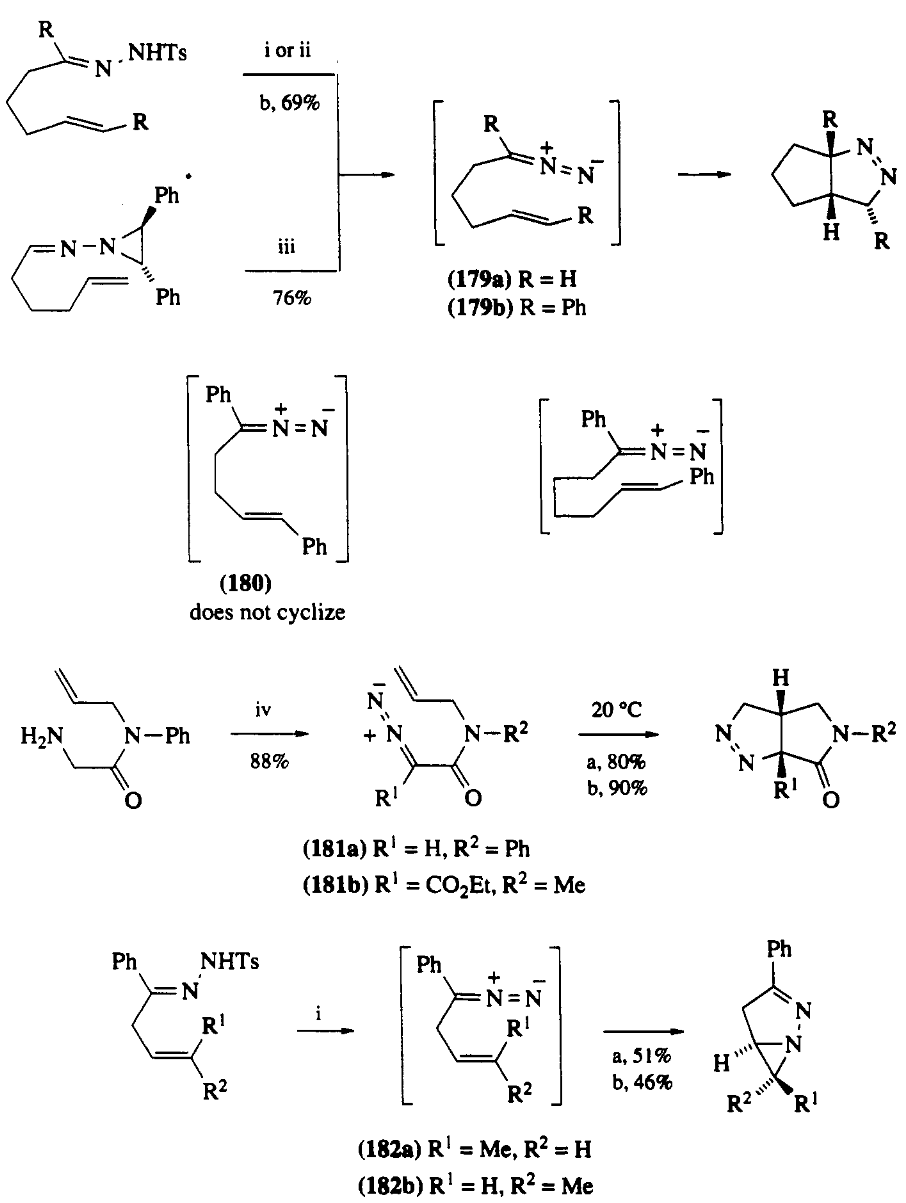
i or ii
b, 69%
iii
76%
(179a) R = H
(179b) R = Ph
(180)
does not cyclize
iv
88%
20 °C
a, 80%
b, 90%
(181a) R¹ = H, R² = Ph
(181b) R¹ = CO₂Et, R² = Me
i
a, 51%
b, 46%
(182a) R¹ = Me, R² = H
(182b) R¹ = H, R² = Me

i, NaH, 80 °C, $CCl_4$ then 20 °C; ii, NaH, THF then 80 °C, $C_6H_6$; iii, 80 °C, $C_6H_6$; iv, $NaNO_2$, HOAc, 20 °C

Scheme 57

### *4.10.8.2.3 Diazocycloalkenes*

A variety of cyclic diazo substrates have been shown to undergo cyclization. Thus, the diazodiene derived from thermolysis of iminoaziridine (**185**) underwent intramolecular 1,3-cycloaddition in 43% yield (Scheme 59).[100] A nitrile side product was formed by elimination of diphenylaziridine from (**185**). The cycloaddition product was converted in a number of steps to (–)-longifolene. The bicyclic tosylhydrazone salt (**186**) afforded a tetracyclic pyrazoline in 81% yield from which nitrogen could be extruded to afford (–)-cyclocopacamphene.[101] The diazocyclopentene (**187**), with a one-carbon intervening chain, underwent intramolecular 1,1-cycloaddition affording a tricyclic pyrazoline in 73% yield.[97] The cyclohexenyl and cycloheptenyl homologs of (**187**) reacted similarly to give 1,1-cycloadducts. Presumably the 1,1-cycloadduct (**188**) was formed from cycloheptatriene (**189**), but the actual product, isolated in 66% yield, was isomeric.[102,97] It was hypothesized that (**188**) underwent a 3,3-sigmatropic rearrangement and a subsequent 1,3-hydride shift.

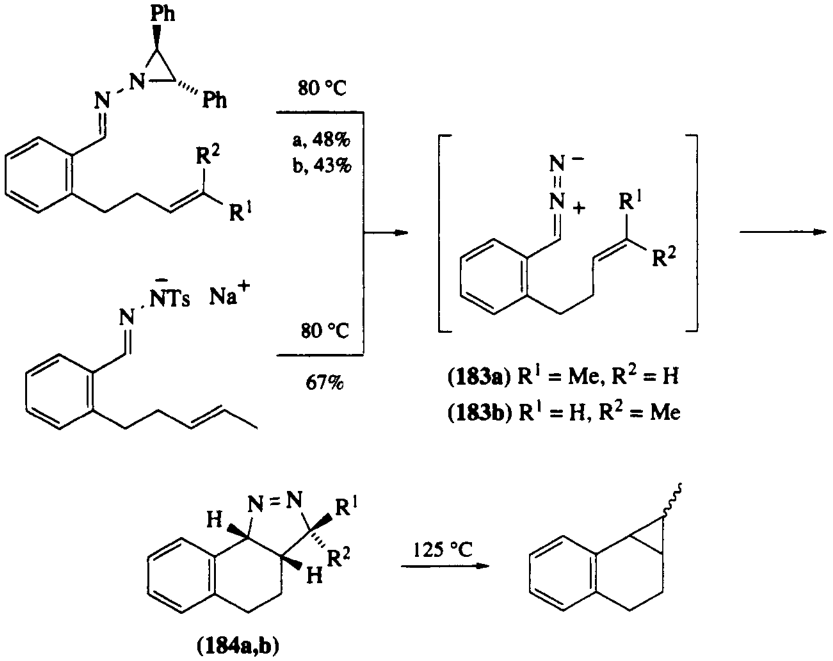
80 °C
a, 48%
b, 43%
80 °C
67%
(183a) R¹ = Me, R² = H
(183b) R¹ = H, R² = Me
125 °C
(184a,b)

Scheme 58

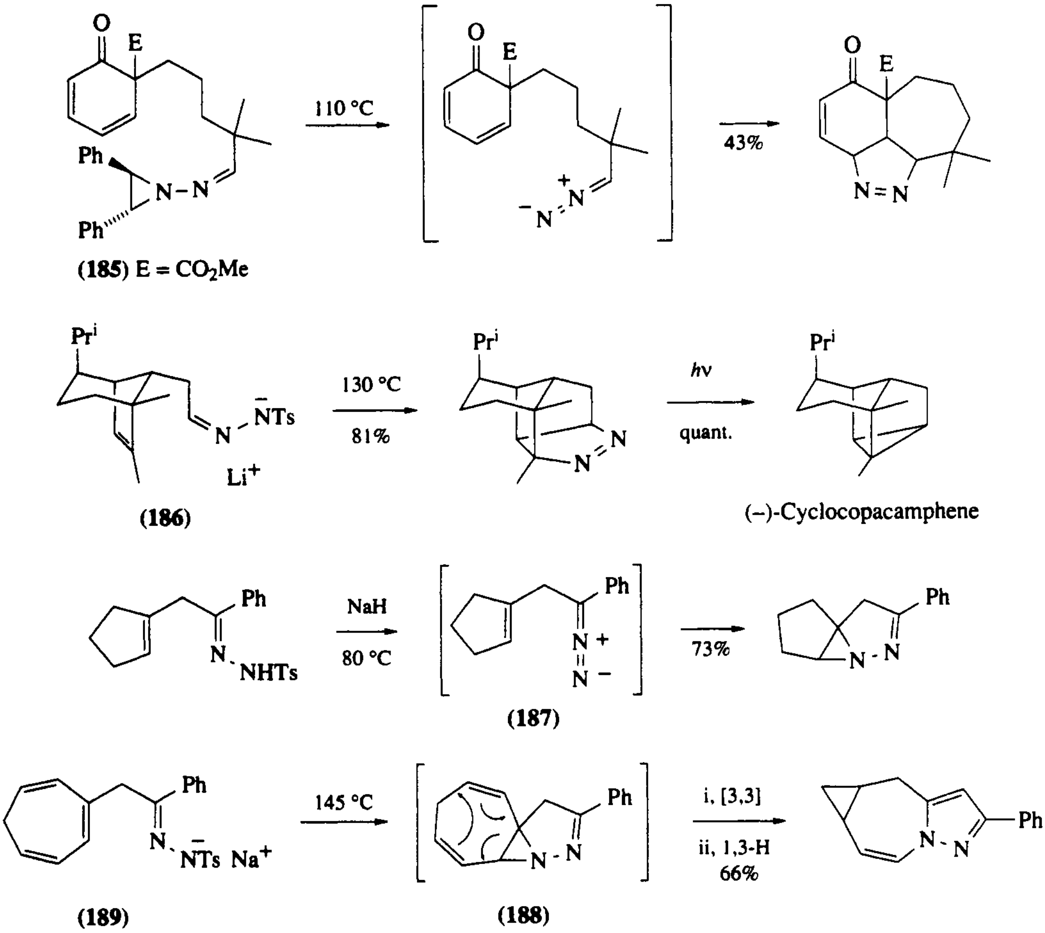
(185) E = CO₂Me
110 °C
43%
130 °C
81%
hv
quant.
(186)
(–)-Cyclocopacamphene
NaH
80 °C
73%
(187)
145 °C
i, [3,3]
ii, 1,3-H
66%
(189)
(188)

Scheme 59

### 4.10.8.3 Cyclization of 3-Diazoalkenes

3-Diazoalkenes have been known to cyclize to pyrazoles since 1935. This reaction has been rationalized as another variation of intramolecular 1,3-dipolar cycloaddition.[103] The 3-diazoalkenes, derived from nitrosamines (**190a–b**), gave typical results: cyclization afforded pyrazoles in 89% and 87% yield, respectively (Scheme 60).

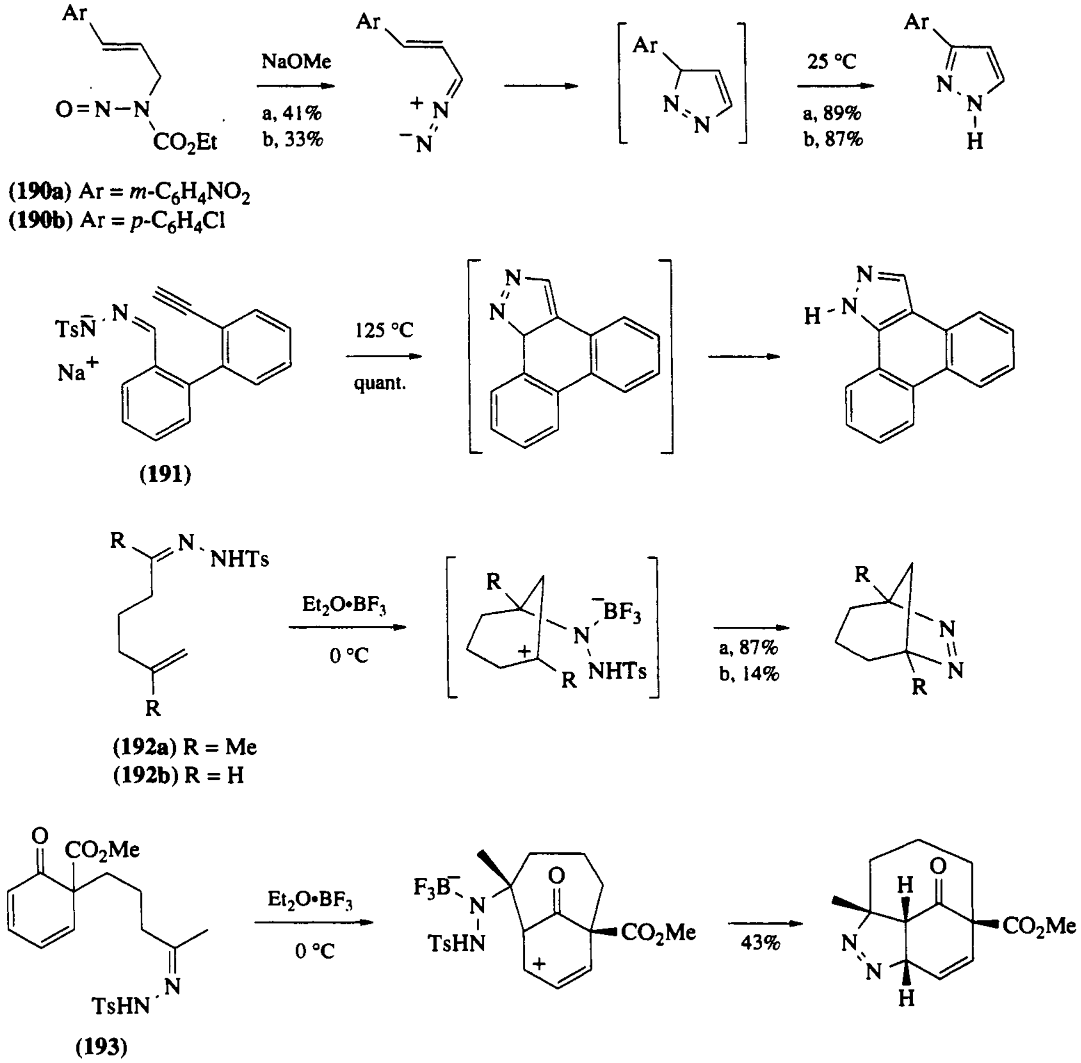

(**190a**) Ar = $m$-$C_6H_4NO_2$
(**190b**) Ar = $p$-$C_6H_4Cl$

(**191**)

(**192a**) R = Me
(**192b**) R = H

(**193**)

**Scheme 60**

### 4.10.8.4 Cyclization of Diazoalkynes

Intramolecular cycloaddition of diazoalkynes has been little studied. Cyclization of tosylhydrazone salt (**191**) illustrates the potential of these reactions (Scheme 60).[104] The actual product was isomeric with the expected 1,3-cycloadduct: presumably a 1,3-hydride shift followed the initial cyclization.

### 4.10.8.5 Acid-catalyzed Cyclization of Tosylhydrazones

A number of tosylhydrazones containing an alkene have been shown to undergo intramolecular cycloaddition in the presence of acid.[105,96] Boron trifluoride etherate appears to be the acid of choice.[105] Bridged, rather than fused, bicyclic pyrazolines are formed under these conditions. The mechanism almost certainly involves cationic intermediates. Thus, tosylhydrazone (**192a**) cyclized in 87% yield to the bridged bicyclic pyrazoline. Tosylhydrazone (**192b**), which lacks a methyl group on the C—C double bond, cyclized in only 14% yield while tosylhydrazone (**193**) cyclized in 43% yield.

## 4.10.9 AZIDE CYCLIZATIONS

### 4.10.9.1 General

Azides undergo both 1,3-dipolar cycloadditions and nitrene cycloadditions after loss of nitrogen. Triazolines and triazoles are the products of 1,3-dipolar cycloaddition. Triazoles are readily isolable, but triazolines differ markedly in stability as a function of substituents: their isolation sometimes provides an insurmountable challenge. Triazolines frequently lose nitrogen, giving aziridines: thus, the formal product of a nitrene cycloaddition can be obtained indirectly. Intramolecular cyclization of an azide to a nitrile was reported as early as 1958,[106] although it was not until 1965 that intramolecular azide–alkene cycloadditions (IAAC) were recognized.[107]

Azides are normally stable compounds and can be isolated prior to cycloaddition. Occasionally, intramolecular cycloaddition is so favored, however, that the azide cannot be isolated.

Azide cycloaddition to electron-deficient dipolarophiles is normally HOMO–dipole LUMO–dipolarophile controlled, whereas the reverse is true for electron-rich dipolarophiles. Products with an electron-deficient group at the 5-position or an electron-rich group at the 4-position are favored electronically; in intramolecular cycloadditions, steric constraints can be expected to outweigh these considerations.

### 4.10.9.2 Azidoalkenes

The alkenyl group of an azidoalkene is always attached to the end of the 1,3-dipole. Only 1,3-cyclizations have been observed with azides, typically giving fused bicyclic systems.

#### *4.10.9.2.1 Open-chain azidoalkenes*

Relatively few examples of aliphatic open-chain azide cyclizations have been reported in which the triazoline was isolated. In one example, the azidoalkene (**194a**) cyclized at 50 °C to give the 5,5-fused bicyclic triazoline (**195a**; Scheme 61).[107] At 80 °C, triazoline (**195a**) extruded nitrogen, affording a cyclic imine and a lesser amount of a bicyclic aziridine. The azidoalkene (**194b**) cyclized similarly, giving a diasteromeric mixture of (**195b–c**), which, however, was of very limited stability.[108] Silica gel chromatography converted (**195b–c**) to diastereomeric bicyclic aziridines. Thermolysis of (**195b–c**) at 80 °C afforded a $\Delta^3$-oxazoline. A zwitterionic intermediate (**196**) was presumably responsible for formation of the $\Delta^3$-oxazoline; the authors suggested a silica gel coordinated zwitterion as the intermediate in bicyclic aziridine formation.

#### *4.10.9.2.2 Aryl-bridged azidoalkenes*

Aryl azides to which an alkenyl group is attached can be readily cyclized. Thus, the azide (**197a**) afforded the tricyclic triazoline (**198a**) at 60 °C, which could be isolated in 12% yield by chromatography (Scheme 62).[109] Silica gel chromatography converted (**198a**) to diazo compound (**199**), used to synthesize a 1,2-dihydroisoquinoline. Azide (**197b**) was more reactive than (**197a**), cyclizing at 0 °C upon formation from bromide (**197b**).[110] At 50 °C, triazoline (**198b**) extruded nitrogen to afford a conjugated alkene.

The bromomethylindole (**200a**) cyclized on treatment with sodium azide to give a tetracyclic triazoline.[111] Treatment with a catalytic amount of *p*-toluenesulfonic acid afforded 2,4-dihydropyrrolo[3,4-*b*]indole (**201**), presumably *via* loss of diethyl diazomalonate by cycloreversion and subsequent tautomerization.

Kozikowski *et al.* have described a synthesis of clavicipitic acids where a key step involved preparation of the imine (**202**).[112] Azide cyclization at 190 °C presumably afforded a triazoline which, however, was nonisolable affording (**202**) in 62% yield.

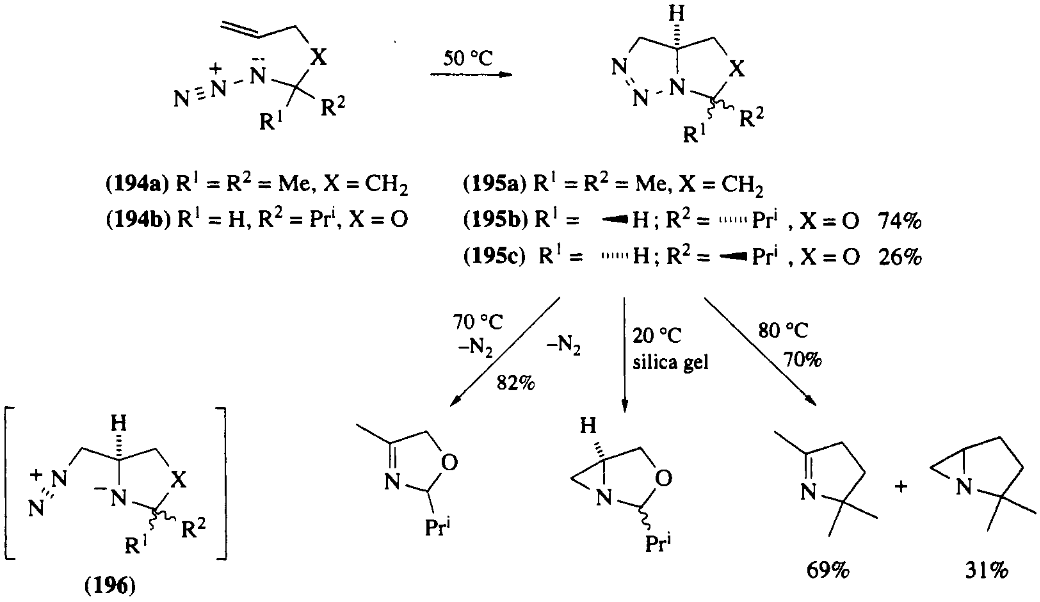

(194a) $R^1 = R^2 = Me, X = CH_2$

(194b) $R^1 = H, R^2 = Pr^i, X = O$

(195a) $R^1 = R^2 = Me, X = CH_2$

(195b) $R^1 =$ H; $R^2 =$ $Pr^i$, X = O 74%

(195c) $R^1 =$ H; $R^2 =$ $Pr^i$, X = O 26%

(196)

Scheme 61

### *4.10.9.2.3 Alicyclic-bridged azidoalkenes*

There have been a number of reports where alicyclic-bridged precursors underwent an IAAC reaction. Thus, the dioxolane (**203b**), formed from triflate (**203a**), cyclized *in situ* to a tricyclic triazoline (Scheme 63).[113] Treatment of this triazoline with sodium ethoxide converted it to a diazopyrrolidine in 86% yield, which underwent smooth catalytic hydrogenation in 89% yield. The (*Z*)-azidoalkene (**204**), bridged by a β-lactam, cyclized at 20 °C to triazoline (**205**).[114] The triazoline (**205**) extruded nitrogen at 80 °C providing a tricyclic aziridine. The (*E*)-isomer of (**204**) did not cyclize to a triazoline but instead produced an azirine, presumably *via* a nitrene intermediate.

### *4.10.9.2.4 Cycloalkenyl azides*

Azides undergo intramolecular cycloaddition to C—C double bonds present in rings to provide a variety of novel products. Schultz *et al.*, for example, reported thermolysis of azide (**206**) at 110 °C to afford an isolable triazoline as a single diastereomer (Scheme 64).[115] A related reaction, however, gave an isomer mixture. Photochemical nitrogen extrusion from the triazoline provided a dihydropyrrole in 97% yield.

Treatment of the bromide (**207a**) with sodium azide led to a mixture of the bicyclic products (**209**) and (**210**).[116] It was postulated that tricyclic triazoline (**208**) was formed *via* an IAAC reaction: cleavage of the strained system to a common zwitterion followed by competing rearrangement paths might then be responsible for product formation. The bromide (**207b**) presumably gave similar triazoline and zwitterion intermediates but extruded nitrogen to afford the tricyclic aziridine (**211**) without rearrangement. An approach to (±)-desamylperhydrohistrionicotoxin based on this chemistry was also presented.

The (azidofuranosyl)uracil (**212**) cyclized at 110 °C to afford a mixture of mostly a tricyclic triazole and lesser amounts of a tricyclic pyrimidine.[117] A triazoline intermediate was hypothesized; indeed, the triazoline could be intercepted by DDQ-effected aromatization to afford the corresponding tetracyclic triazole. Evidence was presented that the major product was in equilibrium with the triazoline at the reaction temperature.

### 4.10.9.3 Azidoalkynes

Intramolecular azide cycloaddition to an alkyne produces a triazole. Triazoles are typically much more stable than triazolines and are most often directly isolable. Thus, azide (**213**) cyclized in 89% yield to a triazole (Scheme 65).[118] The azido enyne (**214**) presents an interesting case: intramolecular cycloaddition

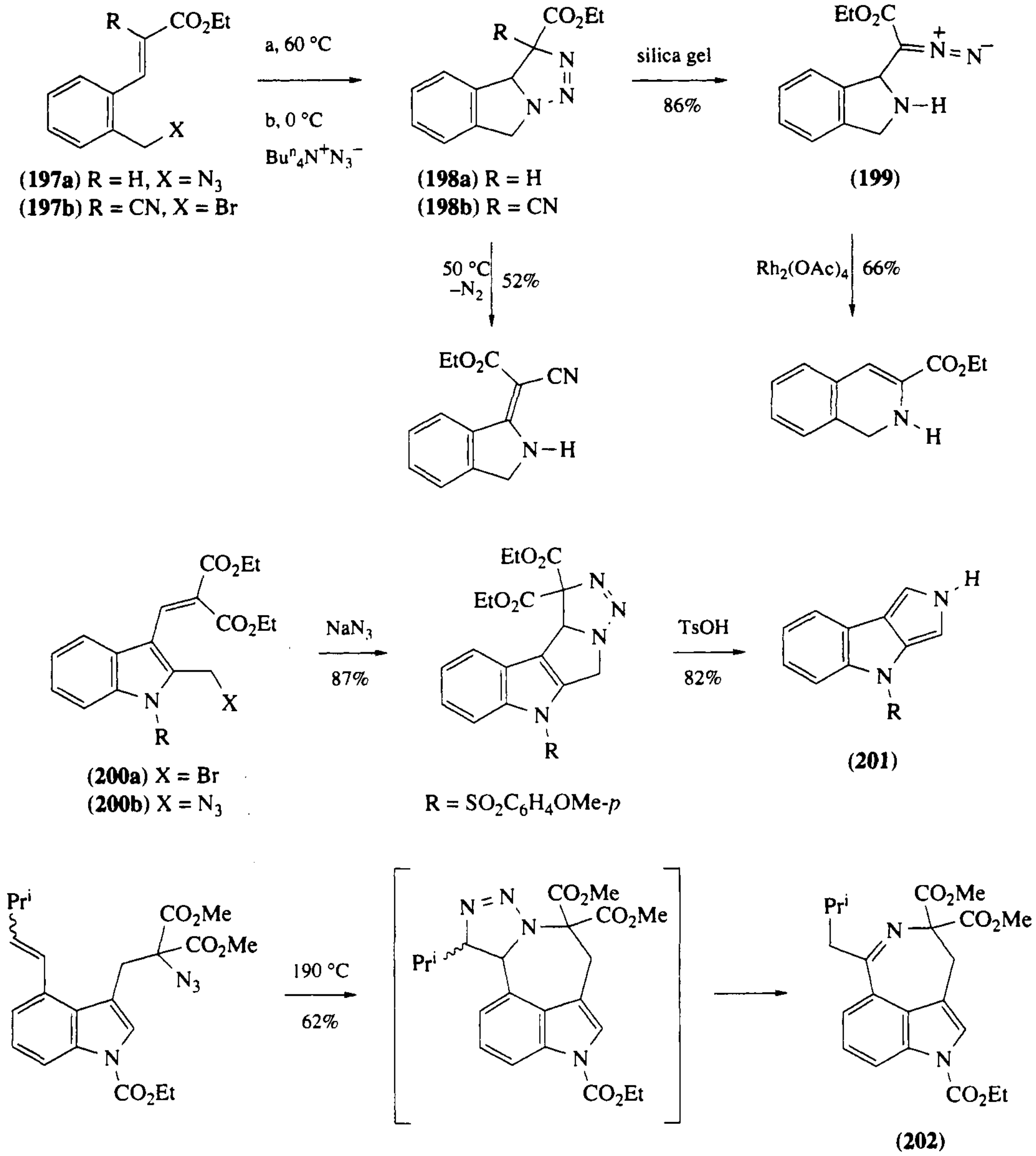
(197a) R = H, X = N3
(197b) R = CN, X = Br
a, 60 °C
b, 0 °C
Bun4N+N3−
(198a) R = H
(198b) R = CN
silica gel
86%
(199)
50 °C
−N2
52%
Rh2(OAc)4
66%
NaN3
87%
(200a) X = Br
(200b) X = N3
R = SO2C6H4OMe-p
TsOH
82%
(201)
190 °C
62%
(202)

Scheme 62

afforded the triazole where the C—C triple bond served exclusively as the dipolarophile, presumably because of geometric constraints.[119] The alkynyl β-lactam (**215**) cyclized to afford triazolocephem (**216**) in 49% yield and an azirine in 12% yield.[120] The authors suggested that (**216**) was derived from (*Z*)-isomer (**215a**), while the azirine was derived from (*E*)-(**215b**) *via* a nitrene. A triazolopenam was synthesized in similar fashion.

## 4.10.10 CARBONYL YLIDE CYCLIZATIONS

### 4.10.10.1 General

Carbonyl ylides were first reported to undergo intramolecular 1,3-dipolar cycloaddition to C—C double bonds in 1980.[121] New polycyclic ring systems containing a tetrahydrofuran are formed. Dipola-

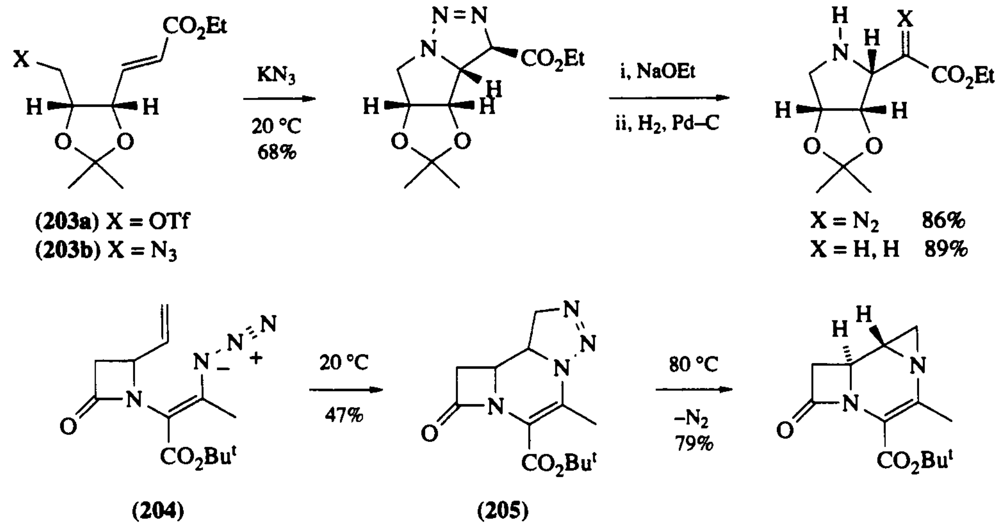
KN3
20 °C
68%
i, NaOEt
ii, H2, Pd–C
(203a) X = OTf
(203b) X = N3
X = N2 86%
X = H, H 89%
20 °C
47%
80 °C
–N2
79%
(204)
(205)

Scheme 63

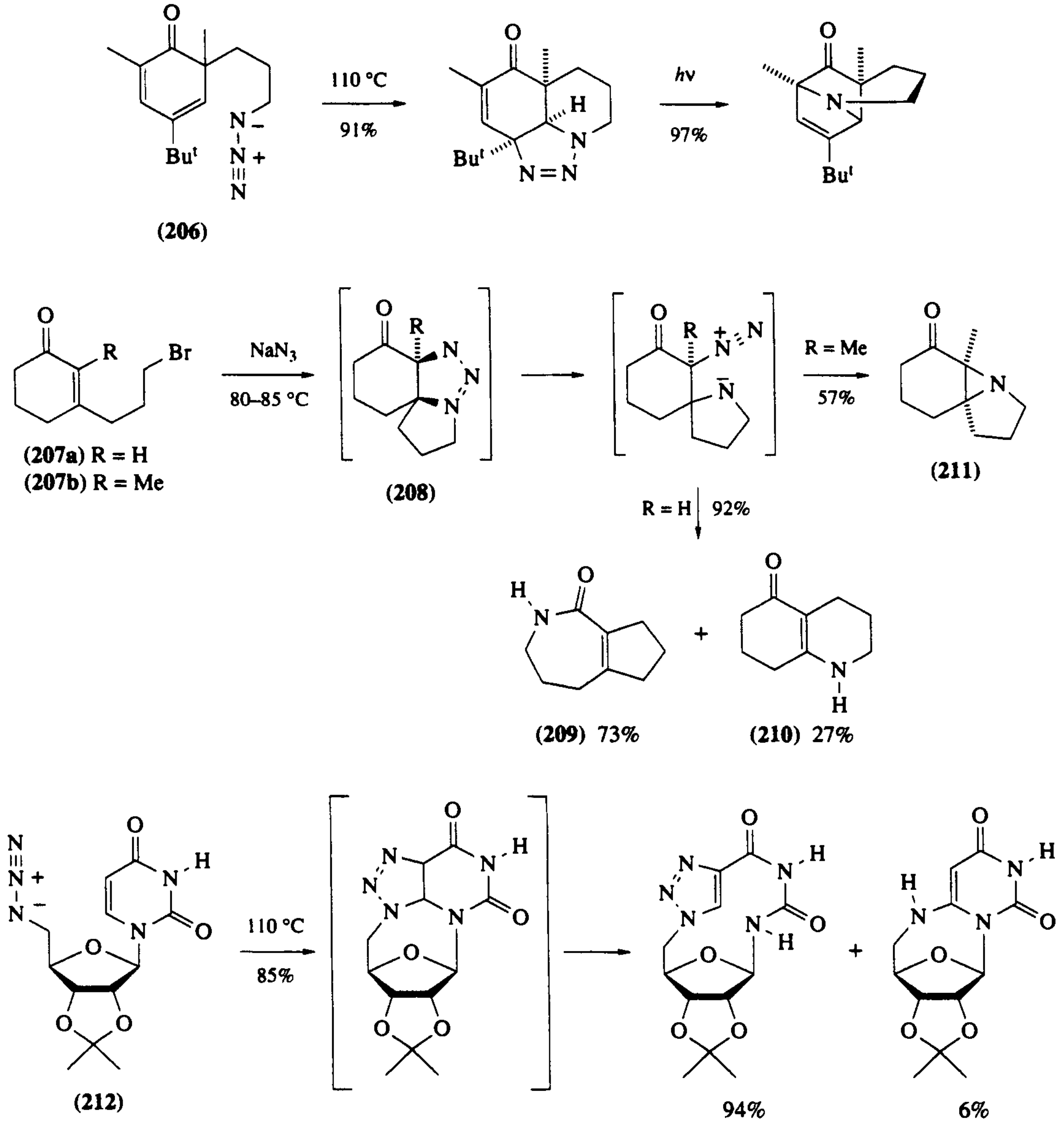
110 °C
91%
hν
97%
(206)
NaN3
80–85 °C
(207a) R = H
(207b) R = Me
(208)
R = Me
57%
(211)
R = H 92%
(209) 73%
(210) 27%
110 °C
85%
(212)
94%
6%

Scheme 64

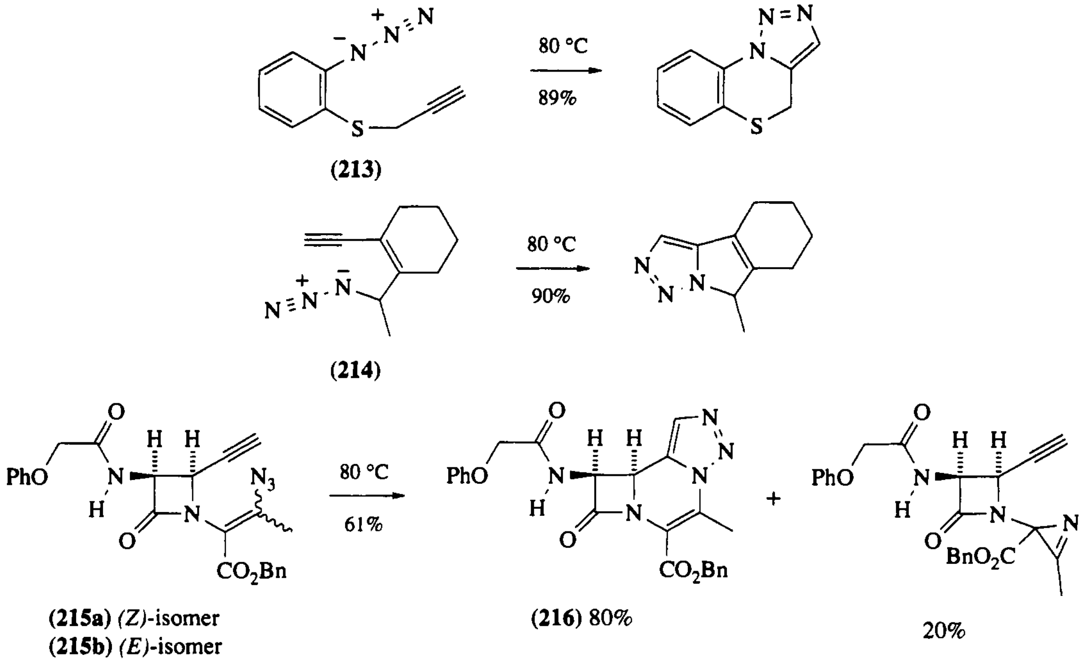

Scheme 65

rophiles activated by an electron-attracting group are somewhat more succesful than nonactivated dipolarophiles.

Carbonyl ylides are highly reactive and must be used only *in situ*. There are a number of procedures applicable to their generation. The most extensively studied approach involves thermal or photochemical cleavage of ene oxiranes, predominantly those with a cyano group on the ring. Rhodium acetate catalyzed decomposition of α-diazo ketones containing an additional carbonyl group can afford cyclic carbonyl ylides and has been applied to intramolecular cycloadditions. Oxazolin-4-ones are mesoionic carbonyl ylides: they have also been generated from α-diazo ketones containing an additional carbonyl group. Oxidopyrylium ylides can also be classified as carbonyl ylides and are available from pyranones.

### 4.10.10.2 Open-chain Carbonyl Ylide–Alkene Cyclizations

An alkenyl group can be attached at either carbon atom of the carbonyl ylide. Cyclization normally affords fused bicyclic tetrahydrofurans, although with large rings bridged products have been observed.

#### *4.10.10.2.1 Open-chain dipolarophiles*

Cyclization of aryl carbonyl ylides substituted in the *ortho* position with an open-chain alkenyl group has been systematically studied. Thus, the *exo,exo*-carbonyl ylide (**217**), generated by thermal conrotatory opening of an oxirane precursor, cyclized at 175 °C to afford the tricyclic tetrahydrofuran (**218**) as a single stereoisomer (Scheme 66).[121,122] Despite the presumed entropic advantage, (**217**) cycloadded only well above the temperature of its formation: when *N*-phenylmaleimide was added, intermolecular cycloaddition occurred at 120 °C in preference to formation of (**218**). The homologous carbonyl ylide with a one-carbon shorter chain gave a mixture of *cis*- and *trans*-fused (**219a–b**). The homolog with a one-carbon longer chain underwent cycloaddition only at higher temperature (240 °C) where the stereointegrity of the carbonyl ylide was lost: only 21% yield of a mixture of (**220a–b**) at 60% conversion was observed. A trace (1%) of the *cis*-fused isomer of (**220a**) was also noted.

A wider range of cyclizations occurred to conjugated ester dipolarophiles. Thus, (**221**) underwent thermolysis to the corresponding carbonyl ylide, which cyclized to give mainly bridged cycloadduct.[122] The homologous oxirane with a five-carbon chain was also studied and gave only the *trans*-fused product (**222**) in 73% yield at 55% conversion.

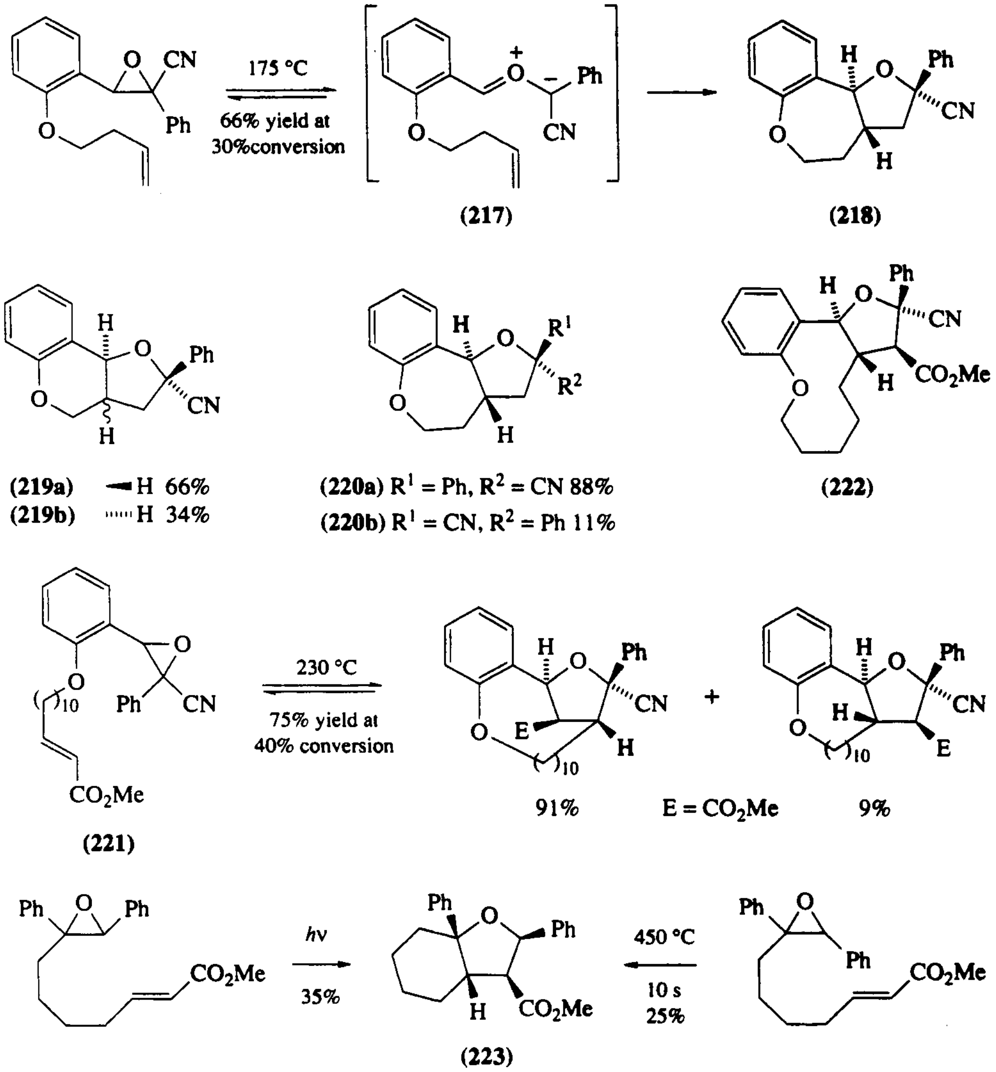
175 °C
66% yield at 30%conversion
(217)
(218)
(219a) H 66%
(219b) H 34%
(220a) $R^1$ = Ph, $R^2$ = CN 88%
(220b) $R^1$ = CN, $R^2$ = Ph 11%
(222)
(221)
230 °C
75% yield at 40% conversion
91%
E = $CO_2Me$
9%
hν
35%
450 °C
10 s
25%
(223)

Scheme 66

Photolysis of ene oxiranes not possessing an α-cyano group has also led to intramolecular carbonyl ylide cycloaddition, but in low yield.[123] Thus, bicyclic tetrahydrofuran (**223**) was formed in 35% yield by photolytic disrotatory opening of the corresponding *trans*-diphenyloxirane. Thermolytic conrotatory opening of the isomeric *cis*-oxirane also afforded tetrahydrofuran (**223**) in 25% yield accompanied by an aldehyde byproduct.

### *4.10.10.2.2 Cyclic dipolarophiles*

The diasteromeric tetracyclic products (**224a–b**) were formed from a cyclohexenyloxirane precursor (Scheme 67).[124] Similar cyclizations were carried out on cyclopentenyl, cycloheptenyl and cyclooctenyl substrates giving rise to diastereomeric mixtures in all cases. Interestingly, the cycloheptenyl substrate gave mostly (**225b**), corresponding to the minor product (**224b**).

## 4.10.10.3 Cyclic Carbonyl Ylide–Alkene Cyclizations

A variety of cyclic carbonyl ylides and related mesoionic species have been found to undergo intramolecular cycloaddition.

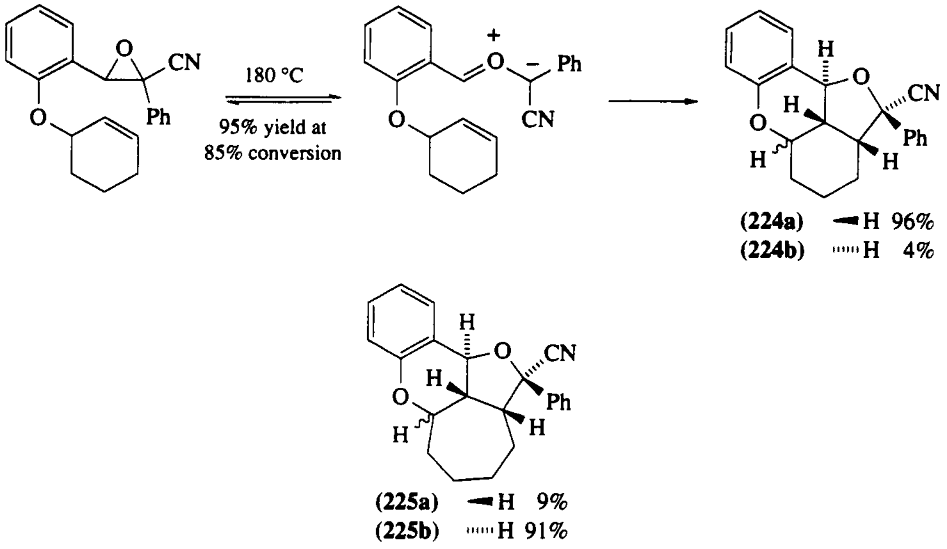

(224a) ◀H 96%
(224b) ⋯H 4%

(225a) ◀H 9%
(225b) ⋯H 91%

**Scheme 67**

#### *4.10.10.3.1 Oxidopyrylium ylide cycloadditions*

Rhodium acetate catalyzed cyclization of the diazo compounds (**226a–b**) led to the tetracyclic tetrahydrofurans (**227a–b**) in high yield (Scheme 68).[125] It was suggested that the reaction to produce (**227a–b**) involved a tandem carbene addition–carbonyl ylide intramolecular cycloaddition sequence. The carbonyl ylide here is actually an oxidobenzopyrylium ylide, formally a carbonyl ylide. The oxidobenzopyrylium ylide intermediate formed from (**226b**) was trapped by intermolecular cycloaddition to dimethyl acetylenedicarboxylate. A related tandem carbene addition–carbonyl ylide intramolecular cycloaddition sequence has been reported where the dipole is present in a five- rather than six-membered ring.[126]

Thermolysis of the pyranyl acetate (**228**) gave rise to the isomeric perhydroazulenes (**229a–b**), presumably *via* intramolecular cycloaddition of an intermediate oxidopyrylium ylide.[127] A similar cyclization occurred for the pyran-4-one (**230**), leading to (**231a**), which was isolated as the acetate (**231b**).[128] No evidence was presented for an oxidopyrylium intermediate and the timing of carbonyl–enol tautomerization is unknown. Thus, another mechanism may apply.

#### *4.10.10.3.2 Oxazolin-4-one (isomunchnone) cycloadditions*

A number of appropriate diazo precursors have been subjected to tandem carbene cyclization–isomunchnone intramolecular cycloaddition.[129] Thus, (**232a**) was cyclized with rhodium acetate to provide a tricyclic tetrahydrofuran; (**232b**) cyclized similarly and produced just one stereoisomer.

### 4.10.10.4 Carbonyl Ylide–Alkyne Cyclizations

Dihydrofurans are valuable synthetic compounds. Nevertheless, little is known about intramolecular cycloaddition of carbonyl ylides to alkynes. In one example, alkynyl pyran-4-one (**233**) was cyclized to dihydrofuran (**234**; Scheme 69).[128] Possibly this reaction proceeds *via* an oxidopyrylium ylide intermediate as shown.

## 4.10.11 THIOCARBONYL YLIDE CYCLIZATIONS

There are two mesoionic sulfur heterocycles which have been shown to undergo intramolecular cycloaddition as thiocarbonyl ylides: 1,3-dithiolones[130] and 1,3-thiazolones.[131] Thus, the alkenyl 1,3-dithiolone (**235**) gave a 90% yield of cyclization product (Scheme 70). The analogous alkynyl

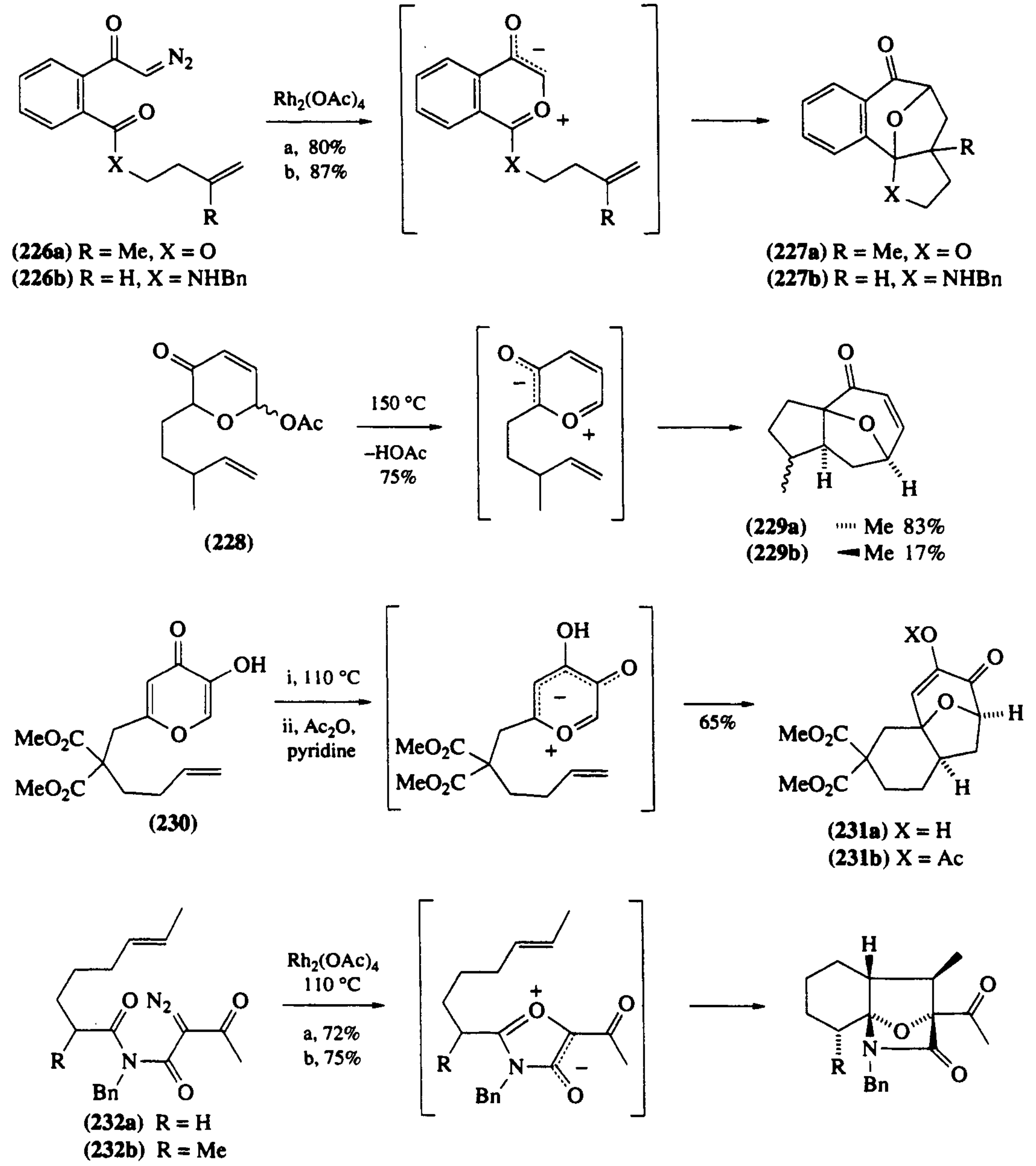

$N_2$
X
R
$Rh_2(OAc)_4$
a, 80%
b, 87%
(226a) R = Me, X = O
(226b) R = H, X = NHBn
(227a) R = Me, X = O
(227b) R = H, X = NHBn
OAc
150 °C
-HOAc
75%
(228)
(229a) Me 83%
(229b) Me 17%
OH
$MeO_2C$
$MeO_2C$
i, 110 °C
ii, $Ac_2O$, pyridine
65%
(230)
XO
(231a) X = H
(231b) X = Ac
$Rh_2(OAc)_4$
110 °C
a, 72%
b, 75%
Bn
(232a) R = H
(232b) R = Me

Scheme 68

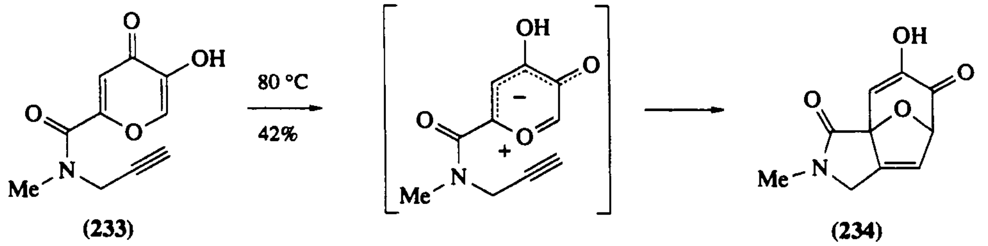

OH
Me
N
80 °C
42%
(233)
(234)

Scheme 69

1,3-dithiolone gave thiophene (**236**) in 92% yield, presumably formed from the corresponding cycloadduct after extrusion of carbonyl sulfide. The 1,3-thiazolone (**237**) reacted with 3-bromocyclohexene to afford pentacyclic (**238**) in 23% overall yield as a single isomer.[131] The intermediate alkylation product, tethered at the thiazolone 2-position, was partially cyclized to (**238**) during preparation. Similarly, thiazolone (**239**), tethered at the 5-position and generated from an α-hydroxy acid, also partially cyclized during preparation affording a 33% overall yield of (**240**). The thiazolone (**241**), tethered at the N-atom (3-position), was obtained pure: cyclization to (**242**) occurred only after eight days in refluxing xylene. Transition state analysis was consistent with the observed difference in reactivity depending on the position of the tether: 2-substituted > 5-substituted >> 3-substituted.

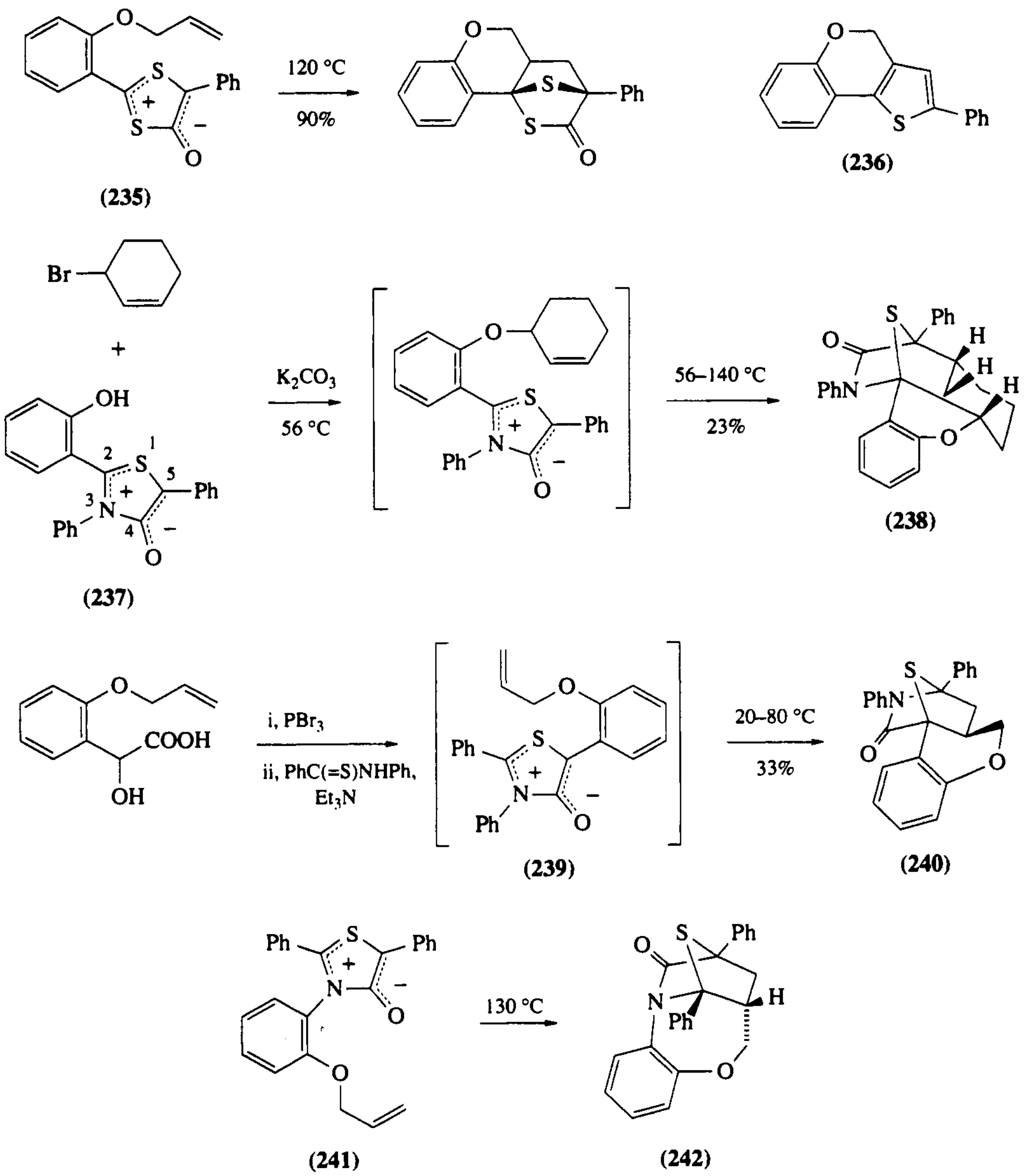

Scheme 70

## 4.10.12 NITRILE SULFIDE CYCLIZATIONS

Intermolecular nitrile sulfide cycloadditions have been known for some time but the first intramolecular cycloadditions have just been reported.[132] The oxathiazolone (**243**) gave (**244a**) in 70% yield when heated in refluxing xylene (Scheme 71). Extrusion of carbon dioxide presumably afforded the nitrile sulfide as an intermediate. The oxathiazolone (**245**) gave (**244b**) when heated in refluxing xylene; here, aromatization of the initial cycloadduct presumably occurred.

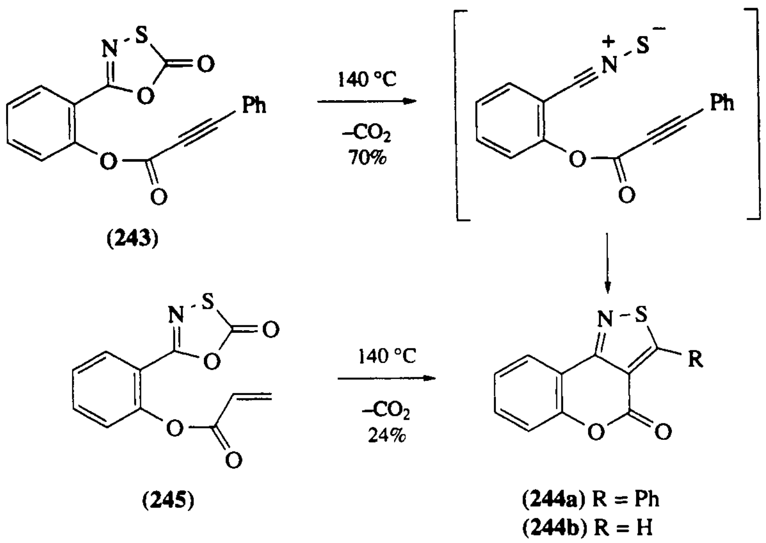

(243)

(245)

(244a) R = Ph
(244b) R = H

Scheme 71

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Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

*Abbott, D. E., 6[12,12c], 10[40], 573[53,54]*

The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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## Volume 5

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C $\pi$-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N'*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Ene Reactions with Alkenes as Enophiles

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## 1.1.1 INTRODUCTION

The thermal reaction of an alkene having an allylic hydrogen (an 'ene') with a compound containing a double or triple bond (enophile) to form a new bond with migration of the ene double bond and 1,5-hydrogen shift is referred to as the ene reaction (equation 1). The ene reaction is mechanistically related to the much better known Diels–Alder reaction since both reactions can be concerted, proceeding through cyclic transition states involving six electrons.[1–5] Stepwise ene reactions proceeding through either a diradical or zwitterionic intermediate are also known. Ene reactions proceed most readily when the enophile, like the dienophile in a Diels–Alder reaction, is electron deficient. Similarly, the ene, like the diene in the Diels–Alder reaction, should be electron rich. Although the exact order depends upon the enophile and reaction conditions, the relative reactivity of alkenes as ene components has typically been found to be 1,1-di- > tri- > tetra- >> mono- > 1,2-disubstituted. Unfortunately, ene reactions typically occur at higher temperatures than related Diels–Alder reactions, limiting the synthetic utility of the ene reaction.

As in the Diels–Alder reaction, Lewis acid catalysis dramatically increases the rates of some ene reactions. Complexation of a Lewis acid to an α,β-unsaturated ketone, aldehyde or ester makes the double bond more electron deficient, thereby accelerating the ene reaction and making these reactions more synthetically useful.[6,7] Recent investigations suggest that at least some of these Lewis acid catalyzed ene reactions are stepwise rather than concerted but that the intermediate bears more resemblance to a π-complex than to an open zwitterionic intermediate.[8–11]

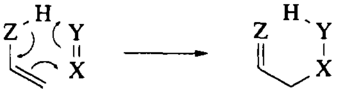

(1)

Coverage in this chapter is restricted to the use of alkenes or alkynes as enophiles (equation 1; X = Y = C) and to the use of ene components in which a hydrogen is transferred. Coverage in Sections 1.2 and 1.3 is restricted to ene components in which all three heavy atoms are carbon (equation 1; Z = C). Thermal intramolecular ene reactions of enols (equation 1; Z = O) with unactivated alkenes are presented in Section 1.4. Metallo-ene reactions are covered in the following chapter. Use of carbonyl compounds as enophiles, which can be considered as a subset of the Prins reaction, is covered in depth in Volume 2, Chapter 2.1. Addition of enophiles to vinylsilanes and allylsilanes is covered in Volume 2, Chapter 2.2, while addition of enophiles to enol ethers is covered in Volume 2, Chapters 2.3–2.5. Addition of imines and iminium compounds to alkenes is presented in Volume 2, Part 4. Use of alkenes, aldehydes and acetals as initiators for polyene cyclizations is covered in Volume 3, Chapter 1.9. Coverage of singlet oxygen, azo, nitroso, S=N, S=O, Se=N or Se=O enophiles are excluded since these reactions do not result in the formation of a carbon–carbon bond.

Intermolecular reactions will be presented first, followed by intramolecular reactions. Coverage will be organized by the nature of the enophile, The emphasis will be on material published since the field has been reviewed,[1–7,19,141] and on examples demonstrating the stereo-, regio- and chemo-selectivity of these reactions.

## 1.1.2 INTERMOLECULAR REACTIONS

### 1.1.2.1 Electron Deficient Alkenes as Enophiles

#### *1.1.2.1.1 Thermal reactions*

Alkenes are relatively unreactive as enophiles in thermal ene reactions.[1] Maleic anhydride is the most generally used enophile of this class. Arnold and Showell showed that β-pinene reacts at 140 °C with maleic anhydride, dimethyl maleate, dimethyl fumarate and methylenemalonic esters to form mixtures of ene adducts.[12] Berson and coworkers found that maleic anhydride reacts with *cis*-2-butene to give an 85:15 mixture of (**2a**) and (**5a**).[13] The major product (**2a**) is formed from *endo* transition state (**1a**) with the carbonyl groups toward the ene component. The minor product (**5a**) is formed from *exo* transition state (**4a**) with the carbonyl groups away from the ene component. Similar results are obtained with cyclopentene. On the other hand, *trans*-2-butene reacts with maleic anhydride to give a 57:43 mixture of (**5a**), formed from *endo* transition state (**6a**), and (**2a**) formed from *exo* transition state (**3a**). Hill and Rabinowitz demonstrated that ene reaction of an optically active ene component with maleic anhydride leads to optically active products, suggesting that the reaction is concerted.[14] Friedrich *et al.* established that the ene reaction of deuterated 2,3,3-trimethyl-1-butene with maleic anhydride proceeds through *cis* addition of the 'ene' component and deuterium to the maleic anhydride double bond.[15] Hill and coworkers found that a hydrogen is abstracted exclusively from the face opposite the *gem*-dimethyl bridge and that a 3:1 mixture of *endo* and *exo* isomers is formed in the thermal ene reaction of β-pinene with maleic anhydride.[16] The effect of substituents on maleic anhydride on the scope of the ene reaction has been examined,[17] and competing free-radical pathways have been proposed for ene reactions of maleic anhydrides with monounsaturated fatty acids.[18] As part of a comprehensive study of ene and retro-ene reactions of organosilanes and organogermanes, Dubac and Laporterie found that maleic anhydride undergoes thermal ene reactions with allyltrimethyl-silane or -germane at 200 °C to give vinyl-silanes or -germanes.[19]

Dwyer *et al.* have determined rates of reactions and energy and entropy of activation for the ene reactions of maleic anhydride with a series of terminal alkenes and *cis*- and *trans*-5-decene.[20] Nahm and

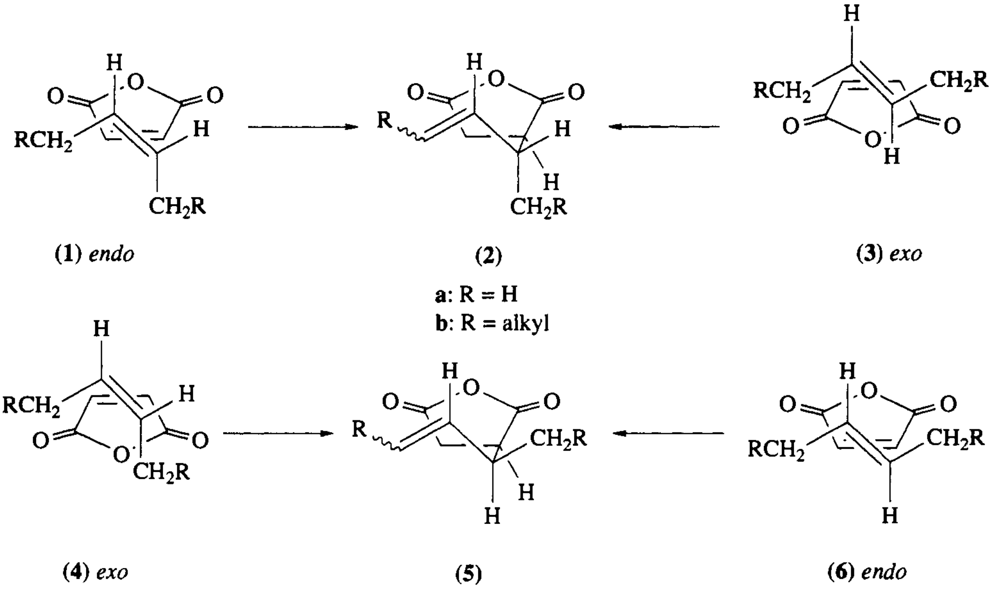

(1) *endo*

(2)

(3) *exo*

**a**: R = H
**b**: R = alkyl

(4) *exo*

(5)

(6) *endo*

Cheng have used $^{13}C$ NMR to determine the regioselectivity, *endo/exo* selectivity and *cis/trans* selectivity of the thermal ene reaction (200 °C, 16 h) of maleic anhydride with all nine decenes.[21] Their results, which are consistent with those of Berson described above,[13] can be summarized as follows: (1) maleic anhydride adds preferentially, but with only modest selectivity, to the less-hindered end of the double bond; (2) starting from a *cis*-alkene there is a > 6:1 preference for the *endo* transition state (**1b**) leading to the *threo* isomer (**2b**) with a *trans* double bond exclusively; (3) starting from a *trans*-alkene there is only a ~1.5:1 preference for the *endo* transition state (**6b**) leading to the *eyrthro* isomer (**5b**) as a 4.2:1 mixture of *trans* and *cis* isomers. Despite its reactivity, tetracyanoethylene has only rarely been used as an enophile.[22]

Alkenes containing only a single electron-withdrawing group have seen little use as enophiles in thermal reactions. A DuPont group demonstrated that thermal ene reactions occur between enophiles such as methyl vinyl ketone, methyl acrylate, methyl methacrylate and acrylonitrile and simple alkenes on heating at 200–300 °C for 0.15–9 h.[23] Reaction of methyl acrylate with isobutene gives the ene adduct in 46% yield, while reaction of methyl acrylate with 1-butene affords the ene adduct in only 8.5% yield. Under some conditions the initially formed ene adduct reacts as the ene component with a second molecule of enophile to give a 2:1 adduct. Alder and von Brachel found that reaction of excess propene with methyl acrylate at 230 °C for 40–50 h gives a 7:1 mixture of regioisomeric ene adducts (**7a**) and (**8a**) in 30% yield.[24] Similar reaction with 1-heptene provides a 3:1 mixture of ene adducts (**7b**) and (**8b**) in 35% yield. Monoactivated enophiles not only are relatively unreactive but give mixtures of regioisomers in thermal ene reactions.

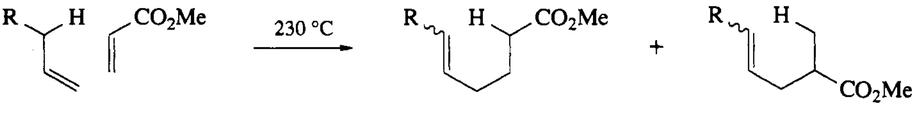

**a**: R = H
**b**: R = n-$C_4H_9$
c: R = n-$C_3H_7$
**d**: R = n-$C_5H_{11}$

(7)

(8)

More recently, Wolinsky has shown that acryloyl chloride reacts with β-pinene at only 70 °C for 2 d to give ene adduct (**9a**) in 84% yield.[25] These atypically mild conditions for a thermal ene reaction result from the powerfully electron-withdrawing chlorocarbonyl group making acryloyl chloride a reactive enophile and the strained electron-rich exomethylene double bond making β-pinene the most reactive readily available ene component. β-Pinene reacts with acrolein on heating at 140 °C to give ene adduct (**9b**) in 30% yield.[26] Nitroethylene polymerizes very readily but does undergo an ene reaction with β-pinene in low yield on heating at reflux in benzene for 16 h.[27] Mehta and Reddy report that limonene reacts with acrylonitrile and methyl acrylate at 200 °C for 12–24 h to give the ene adducts (**10a**) and (**10b**) in 25 and 45% yield, respectively.[28] Vinyltrichlorosilane reacts as an enophile with terminal alkenes and cycloalkenes at 250 °C for 48 h to give ene adducts in 60% yield.[19]

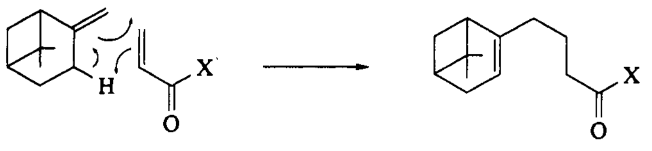

**(9a)** X = Cl
**(9b)** X = H

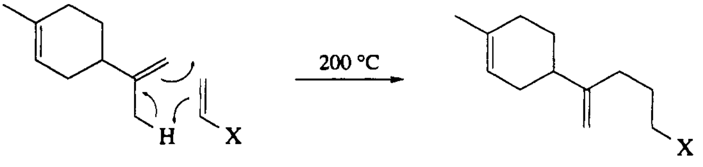

**(10a)** X = CN
**(10b)** X = $CO_2Me$

### *1.1.2.1.2 Lewis acid catalyzed reactions*

*(i) Acrylate esters*

Inukai[29] and Snider[30] first demonstrated that Lewis acids could be used to catalyze ene reactions of non-aldehyde enophiles. Inukai reported that reaction of 1-hexene, methyl acrylate and $AlCl_3$ for 3.5 h at 150 °C gives ene adduct (**7c**) in 39% yield.[29] Snider found that reaction of methylenecyclohexane than methyl acrylate in benzene in the presence of 0.1 equiv. of $AlCl_3$ for 48 h at 25 °C gives ene adduct (**11**) in 70% yield.[30] Ene adducts could be obtained from the $AlCl_3$ catalyzed reaction of methyl acrylate and reactive 1,1-disubstituted alkenes, although 2:1 adducts were also formed in some cases. Two groups[31,32] reexamined these Lewis acid catalyzed ene reactions in response to Sands' erroneous report that alkenes and methyl acrylate undergo Lewis acid catalyzed [2 + 2] cycloadditions.[33] Beckwith found that $AlCl_3$ catalyzed reaction of isobutene or 2,3-dimethyl-2-butene with methyl acrylate in benzene gives only the expected ene adducts.[32] In dichloroethane–nitromethane the initial products undergo isomerization or rearrangement. Greuter and Bellus obtained ene adducts from $AlCl_3$ catalyzed reaction of methyl acrylate with isobutene, 2-methyl-2-butene or 2,3-dimethyl-2-butene in dichloroethane–nitromethane with careful control of reaction conditions to prevent isomerization of the double bond in the initially formed products.[31] Åkermark and Ljungqvist found that ene reaction of 1-octene with methyl acrylate could be catalyzed by a $AlCl_3/NaCl/KCl$ eutectic at 100 °C for 16 h to give the expected ene adduct (**7d**) in 40% yield as an 86:14 (*E*):(*Z*) mixture.[34]

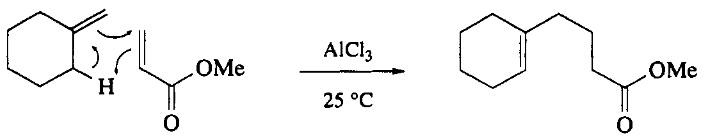

**(11)**

Lewis acid catalyzed ene reactions of methyl acrylate with alkenes are regiospecific, giving only adduct (**7**), in marked contrast to the thermal reactions which give mixtures of adducts (**7**) and (**8**). Complexation of a Lewis acid to the acrylate ester makes the double bond electron deficient and polarizes it so that reaction with the alkene occurs only at the more electron deficient β-carbon of methyl acrylate.

More highly functionalized products can be obtained, often in better yield, by the ene reaction of α-substituted acrylate esters.[35–37] $EtAlCl_2$ is a more effective catalyst than $AlCl_3$ for these reactions because it is a Brønsted base as well as a Lewis acid.[7] The $EtAlCl_2$ catalyzed reactions of methyl α-bromo- and α-chloro-acrylate with *trans*-1,2-disubstituted and trisubstituted alkenes are both regio- and stereo-specific.[35,36] The major product (**13a**; 85–95%) is formed *via* transition state (**12a**) in which the methoxycarbonyl group is *endo*.[35,36] The stereochemistry of the major adduct was established by the stereospecific conversion of (**13a**) to both diastereomers of (±)-2-amino-4-methyl-5-hexenoic acid[38] and confirmed by X-ray crystallographic analysis in a related system.[39]

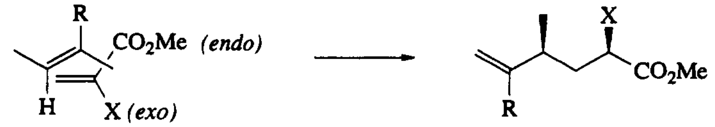

(**12a**) R = H
(**12b**) R = Et

X = Br, Cl

(**13a**) R = H
(**13b**) R = Et

The selective formation of the ene adduct with the methoxycarbonyl group *endo* is analogous to the *endo* selectivity usually observed in the Diels–Alder reaction, probably for similar electronic reasons. With 1,2-disubstituted and trisubstituted alkenes the *endo* selectivity of this ene reaction controls the relative stereochemistry of two centers in a 1,3-relationship. Since attempted thermal ene reactions of methyl α-haloacrylates give only polymer, the effect of the Lewis acid on the stereochemistry cannot be determined.

The ene reactions of α-haloacrylate esters with trisubstituted alkenes are also regiospecific. Transfer of a hydrogen occurs predominantly (90–100%) from the alkyl group *syn* to the vinylic hydrogen to give (**13b**). This appears to be due to steric interaction of the *exo* substituent on the acrylate with the substituent on the less-substituted end of the ene component, which is minimized if the substituent is hydrogen (**12b**) rather than carbon (**14**). This steric interaction is responsible for the failure of this ene reaction with *cis*-1,2-di- and tetra-substituted alkenes. This regioselectivity is general, although there is also a competing preference for the formation of the more stable, more highly substituted double bond.[35,36]

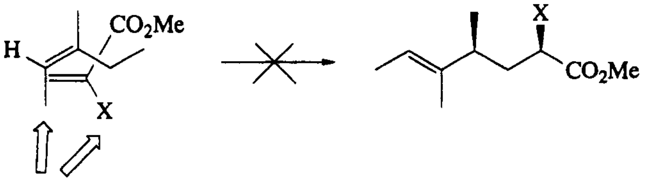

(**14**) (**15**)

Similar results are obtained with methyl methacrylate, methyl α-acetamidoacrylate, methyl α-bromomethylacrylate and dimethyl itaconate.[36] Those acrylates with electron-withdrawing α-substituents such as chloro or bromo are somewhat more reactive than methyl acrylate, while those with electron-releasing α-substituents such as methyl are less reactive with methyl acrylate. In an attempt to extend the scope of the ene reaction, acrylates containing a strongly electron-withdrawing α-substituent were examined. Trimethyl α-phosphonoacrylate undergoes $EtAlCl_2$ catalyzed ene reactions in high yield at 0 °C with most classes of alkenes.[40] The adducts are useful reagents for the phosphonate modification of the Wittig reaction. On the other hand, methyl α-cyanoacrylate undergoes $Me_2AlCl$ catalyzed reactions to give a zwitterion which reacts further to give a complex mixture of ene adducts, cyclobutanes, dihydropyrans and 2:1 adducts.[41]

A particularly elegant application of these ene reactions is the elaboration of functionalized steroid side chains with the natural stereochemistry at C-20 from (*Z*)-$\Delta^{17(20)}$-pregnenes (**16**) and (**18**) by Uskokovic and coworkers.[39,42] $EtAlCl_2$ catalyzed ene reaction of (**16**) with methyl acrylate occurs selectively from the α face to give 25-hydroxycholesterol precursor (**17**) with the natural stereochemistry at C-20.[39] An additional equivalent of $EtAlCl_2$ must be used to complex any basic functional groups, *e.g.* acetate, on the steroid nucleus. For instance, reaction of (**18**) with methyl acrylate and 3 equiv. of $EtAlCl_2$ in $CH_2Cl_2$ for 3 d at 25 °C gives chenodeoxycholic acid precursor (**19**) in 72% yield.[42] Lewis acid catalyzed ene reactions of methyl propiolate can also be used to introduced functionalized steroid side chains.[43,44] Reaction of methyl propiolate with (*E*)-$\Delta^{17(20)}$-pregnenes gives an ene adduct with the unnatural stereochemistry at C-20.[45]

### *(ii) α,β-Unsaturated ketones and aldehydes*

$ZnCl_2$ catalyzed ene reaction of methyl vinyl ketone and acrolein with β-pinene in ether at 25 °C gives the expected ene adducts in 62% and 32% yields, respectively.[30] Methyl vinyl ketone is reported to undergo $AlCl_3$ catalyzed ene reactions with limonene, carvone and perillaldehyde.[28] Although Lewis acid catalyzed ene reactions of acrolein and methyl vinyl ketone with alkenes are probably general, the initial products often cannot be isolated since the unsaturated carbonyl compound undergoes an intramolecular Lewis acid catalyzed type II ene reaction.[46,47]

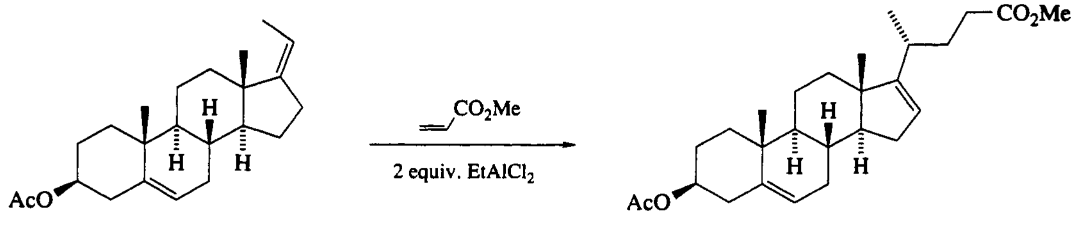

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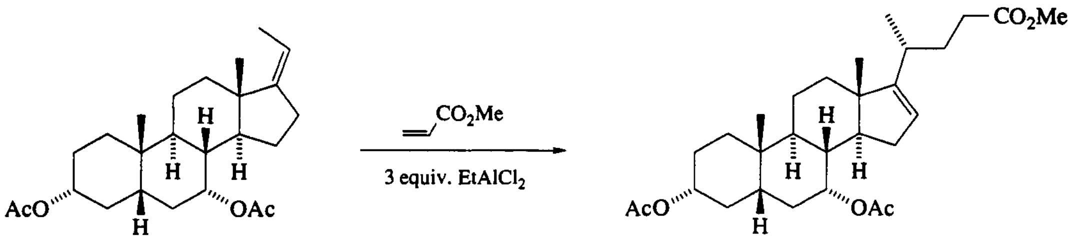

(18) (19)

Reaction of alkylidenecyclohexanes with acrolein derivatives and $Me_2AlCl$ generates unsaturated aldehydes (**20**; $R^1$ = H) which cannot be isolated but undergo type II intramolecular ene reactions to give (**21**; $R^1$ = H).[46] Reaction of alkylidenecyclohexanes with methyl vinyl ketone derivatives gives (**20**; $R^1$ = Me) which can be isolated if the reaction is carried out at –20 °C but cyclize at 25 °C to give (**21**; $R^1$ = Me).[46,47] Similar results have been obtained with alkylidenecyclopentanes[46] and 2- and 3-substituted methylenecycloalkanes.[47] 24-Oxocholesteryl acetate has been synthesized from (*Z*)-5,17(20)-pregnadienyl-3β-acetate by reaction with isopropyl vinyl ketone and 2 equiv. of $Me_2AlCl$ at 25 °C to give the ene adduct in 46% yield followed by hydrogenation of the C(16)—C(17) double bond over Pt/C.[46] In this case a type II intramolecular ene reaction is precluded by the absence of allylic ring hydrogens.

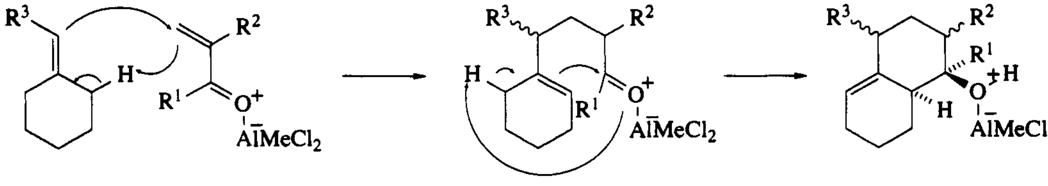

(20) (21)

Lewis acid complexes of β-substituted α,β-unsaturated ketones and aldehydes are unreactive toward alkenes. Crotonaldehyde and 3-penten-2-one cannot be induced to undergo ene reactions like acrolein and methyl vinyl ketone. The presence of a substituent on the β-carbon stabilizes the enal– or enone–Lewis acid complex and sterically retards the approach of an alkene to the β-carbon. However, Snider *et al.* have found that a complex of these ketones and aldehydes with 2 equiv. of $EtAlCl_2$ reacts reversibly with alkenes to give a zwitterion (**22**).[48] This zwitterion, which is formed in the absence of a nucleophile, reacts reversibly to give a cyclobutane (**23**) or undergoes two 1,2-hydride or alkyl shifts to generate irreversibly a β,β-disubstituted-α,β-unsaturated carbon compound (**24**).

## 1.1.2.2 Electron Deficient Alkynes as Enophiles

### *1.1.2.2.1 Thermal reactions*

Acetylenedicarboxylic ester, propiolic esters and dicyanoacetylene react with unactivated ene components below 200 °C.[1,24] Isobutene undergoes ene reactions with dimethyl acetylenedicarboxylate

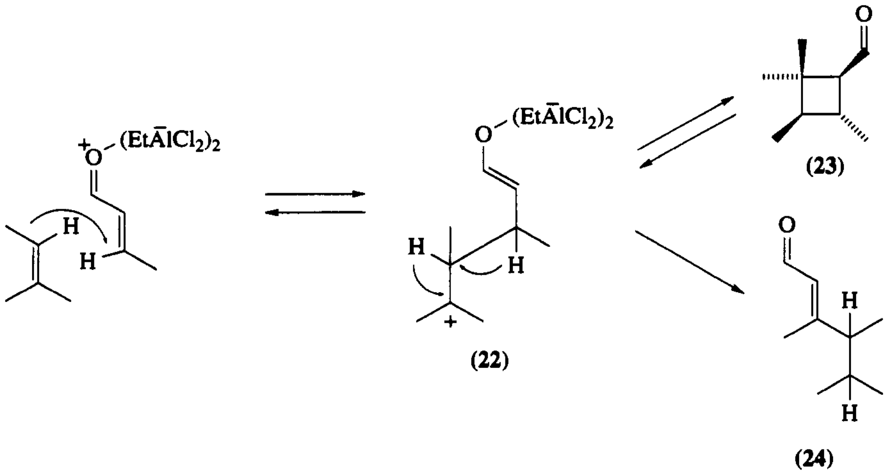

(DMAD), methyl propiolate or 1,1,1-trifluoropropyne or hexafluoro-2-butyne at 145–250 °C.[49] Ene reactions with DMAD give only one product, while reactions with methyl propiolate give mixtures of regioisomers.[24] Reaction of methyl propiolate with 1-heptene for 30 h at 200 °C gives a 4:1 mixture of (**25a**) and (**26a**) in 30% yield. Similar reaction with isobutene gives a 94:6 mixture of (**25b**) and (**26b**) in 50% yield.[24] Reaction of limonene with methyl propiolate for 24 h at 160 °C gives the ene adduct in 70–80% yield.[28]

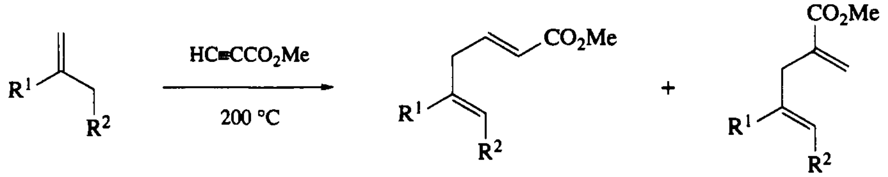

(25) a: $R^1$ = H, $R^2$ = Bu (26)
b: $R^1$ = Me, $R^2$ = H

Alder and Bong discovered a tandem ene/intramolecular Diels–Alder reaction in which 1,4-cyclohexadiene reacts with DMAD at 185 °C to give ene adduct (**27a**), which reacts further to give intramolecular Diels–Alder adduct (**28a**).[50,51] Recent studies by Giguere optimized the conditions for this reaction and extended it to monoactivated alkynes.[51] 1,4-Cyclohexadiene reacts with methyl propiolate, propiolic acid or 3-butyn-2-one at 350 °C (or at 220 °C in the presence of $ZnCl_2$) to give (**28b**) in 30–70% yield. The formation of (**28b**) indicates that ene adduct (**27b**), rather than the expected ene adduct (**29b**), is formed. This surprising result may be due to the formation of both ene adducts and competing retro-ene and Diels–Alder reactions. Alternatively, the selective formation of (**27b**) may result from a change in mechanism of the ene reaction. The second double bond of a diene does not lower the activation energy in a 'normal' concerted ene reaction, leading to (**29b**) in which carbon–carbon bond formation is more advanced than hydrogen transfer in the transition state. The second double bond of the diene will lower the activation energy for an 'abnormal' ene reaction in which hydrogen transfer is more advanced than carbon–carbon bond formation in the transition state. Adduct (**27b**) is the expected product of such an 'abnormal' ene reaction. Similar factors may be responsible for the selective formation of the unexpected regioisomer in the ene reaction of acrylonitrile with ergosteryl acetate.[52]

### *1.1.2.2.2 Lewis acid catalyzed reactions*

Snider demonstrated that $AlCl_3$ catalyzed reactions of methyl propiolate with a wide variety of alkenes give good yields of 1:1 adducts.[53–55] 1,1-Disubstituted, trisubstituted and tetrasubstituted alkenes give exclusively ene adducts (**30**) (equation 2). 1,2-Diubstituted alkenes give exclusively cyclobutenes formed by stereospecific [2 + 2] cycloaddition (equation 3). Monosubstituted alkenes give mixtures of ene adducts and cyclobutenes. $EtAlCl_2$ in $CH_2Cl_2$ was found to be a more effective catalyst for this reaction since it can act as a proton scavenger as well as a Lewis acid.[54] Optimal yields are usually obtained with

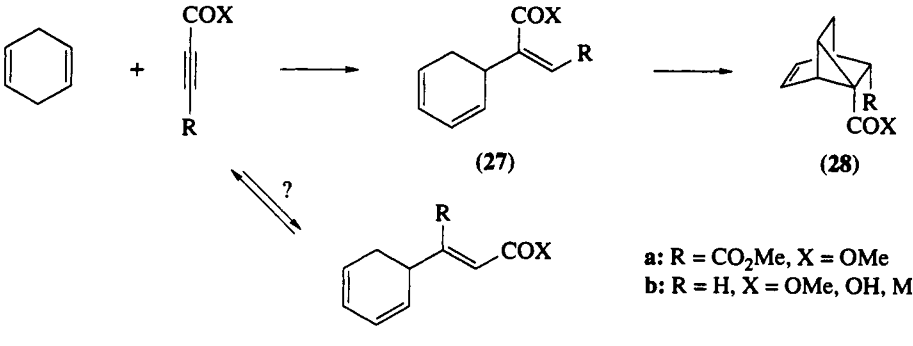

(27)

(28)

(29)

**a**: $R = CO_2Me$, $X = OMe$
**b**: $R = H$, $X = OMe, OH, Me$

close to 1 equiv. of catalyst since the product α,β-unsaturated ester is more basic than methyl propiolate and complexes preferentially to the Lewis acid. Functionalized alkenes containing nonbasic functional groups are suitable substrates. Alkenes containing more basic functional groups are suitable substrates if an additional equivalent of Lewis acid is used for every basic site.[54] Similar results are obtained in $ZnCl_2$ catalyzed reactions of 3-butyn-2-one,[56] and $EtAlCl_2$ catalyzed reactions of ethynyl *p*-tolyl sulfone[57] with alkenes.

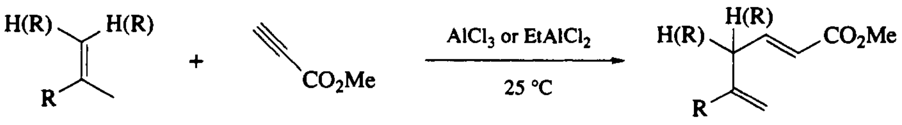

(30)

(2)

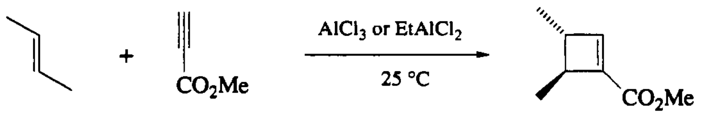

(3)

Lewis acid catalyzed ene reactions with methyl propiolate have been used for the construction of steroid side chains,[43–45] and for the synthesis of the A1 component of the female sex pheromone of the California red scale.[58] $AlCl_3$ catalyzed [2 + 2] cycloadditions of methyl propiolate have been used for the synthesis of inside-inside bicyclics and [10]paracyclophanes.[59] An intramolecular version of this cycloaddition has been used in the construction of coronofacic acid.[60]

Good yields of 1:1 adducts have also been obtained from Lewis acid catalyzed reactions of methyl chloropropiolate or DMAD with alkenes.[61–64] With methyl chloropropiolate, cyclobutenes are obtained exclusively from mono- and 1,2-di-substituted alkenes and mixtures of ene adducts and cyclobutenes are obtained with 1,1-di-, tri- and tetra-substituted alkenes.[61,62] With DMAD, ene adducts are obtained exclusively from 1,1-di-, tri- and tetra-substituted alkenes and mixtures of ene adducts and cyclobutenes are obtained from 1,2-disubstituted alkenes.[61–64] $EtAlCl_2$ is a more effective catalyst than $AlCl_3$ since it is a proton scavenger as well as a Lewis acid. With $AlCl_3$, lactone byproducts are also formed.[63,64] The relative reactivity of alkenes in these Lewis acid catalyzed reactions was found to be 1,1-di- > tri- > tetra- >> mono- > 1,2-di-substituted. With reactive ene components such as methylenecyclohexane, ethylidenecyclohexane and β-pinene, good yields of ene adducts can be obtained with DMAD by thermal reaction at 110–130 °C for 0.25–6 d.[64]

With trisubstituted alkenes the ene reaction with DMAD or methyl chloropropiolate, but not methyl propiolate, is regiospecific.[61,62] A hydrogen is transferred from the alkyl group *trans* to the alkenyl hydrogen to give (**32**). An examination of possible transition states indicates severe steric interactions between R and X (Cl or $CO_2Me$) in (**33**) leading to (**34**), while transition state (**31**) leading to the observed product (**32**) has no significant steric interactions.

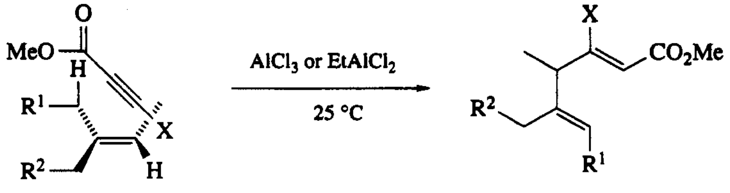

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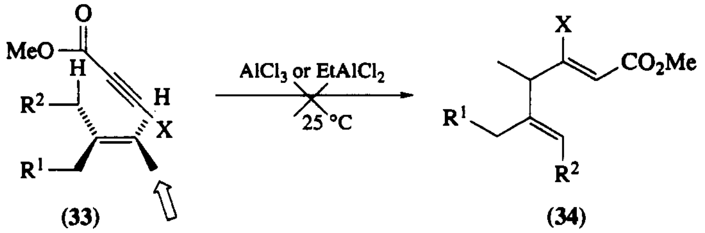

(33) (34)

### 1.1.2.3 Allenes as Enes or Enophiles

Surprisingly few examples of the use of allenes as the ene components in ene reactions have been reported. In a series of papers, Taylor and coworkers reported that alkylallenes undergo thermal ene reactions with DMAD, hexafluoro-2-butyne and 3,3,3-trifluoropropyne to give cross-conjugated trienes.[65,66] Similar reactions occur between allenes and hexafluoroacetone and electron-deficient azo compounds.[67–69]

Lewis acid catalyzed reactions of allenes with alkenes generally give cyclobutanes rather than ene adducts. $AlCl_3$ catalyzed reactions of alkylallenes with alkenes give alkylidenecyclobutanes.[70] Similarly, $AlCl_3$ catalyzed reactions of alkynes with alkenes give cyclobutenes.[71] These reactions are believed to occur by stereospecific cycloaddition of the alkene with the vinyl cation formed by complexation of $AlCl_3$ to the allene or alkyne.

2,3-Butadienoate esters undergo $AlCl_3$ and $EtAlCl_2$ catalyzed stereospecific [2 + 2] cycloadditions with a wide variety of alkenes to give alkyl cyclobutylideneacetates in good yield.[72,73] The stereospecificity and ratios of (*E*)- and (*Z*)-isomers suggest a $[_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition of the ester–Lewis acid complex to the alkene analogous to the cycloaddition of ketenes with alkenes. Similar results are obtained with methyl 2,3-pentadienoate, methyl 4-methyl-2,3-pentadienoate and methyl 2-methyl-2,3-butadienoate.[74]

## 1.1.3 INTRAMOLECULAR REACTIONS: ALKENES AS THE ENE COMPONENT

Intramolecular ene reactions are much more facile than their intermolecular counterparts due to the less negative entropy of activation for the intramolecular reaction. Even simple alkenes and alkynes are suitable enophiles in intramolecular reactions. Formation of cyclopentanes from 1,6-dienes or 1,6-enynes is a very facile process, providing some of the most impressive synthetic applications of the ene reaction. Formation of cyclohexanes from 1,7-dienes or 1,7-enynes is much less facile since the entropy of activation becomes more negative with the longer tether connecting the ene and enophile. For similar reasons, formation of larger rings by intramolecular ene reactions is rarely a synthetically useful reaction. Two comprehensive reviews of intramolecular ene reactions by Oppolzer and Snieckus[3] and by Taber[5] provide more complete coverage than is possible here.

Oppolzer has classified intramolecular ene reactions into type I, II and III depending on whether the tether is attached to carbon 1, 2 or 3 of the ene component (see equations 4, 5 and 6). Type IV reactions, which are a variation of type I in which the tether is attached to the terminal rather than internal end of the enophile, are occasionally observed (see equation 7). Type I reactions with alkenes or alkynes as enophiles have been extensively studied. Only a few examples of type II, III and IV reactions with alkenes or alkynes as enophiles are known. Numerous examples of intramolecular type I, II and III reactions with carbonyl compounds as enophiles are discussed in Volume 2, Chapter 2.1.

Type I

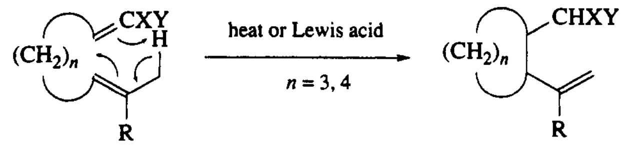

(4)

Type II

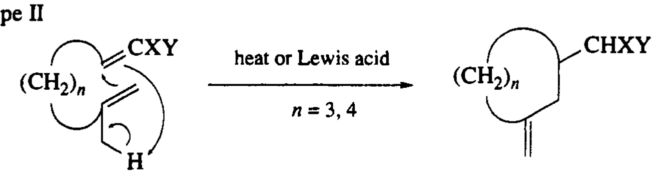

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Type III

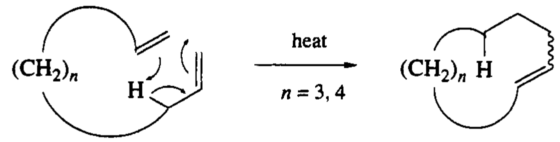

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Type IV

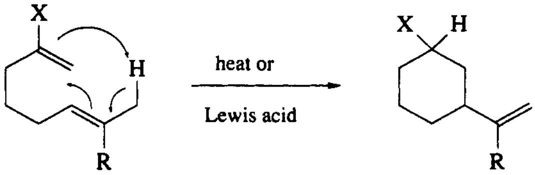

(7)

Type I intramolecular ene reactions give mixtures of *cis*- and *trans*-1,2-disubstituted cycloalkanes depending on whether the ene reaction proceeds through an *endo* or *exo* transition state. In general, steric rather than electronic effects determine which transition state is preferred. The reaction is often very selective, as indicated below.

### 1.1.3.1 Formation of 1-Vinyl-2-alkylcyclopentanes from 1,6-Dienes

#### *1.1.3.1.1 Unactivated enophiles*

Pioneering studies by Huntsman,[75] Ohloff[76] and others[77,78] demonstrated that cyclization of unactivated 1,6-dienes occurs in a flow system at 400–500 °C or on heating for longer times at 250–350 °C. Despite the apparently harsh conditions, good yields of product are usually obtained if no thermally sensitive functional groups are present. Lewis acid catalysis of these reactions is not possible since there is no basic site on the enophile.

A characteristic feature of these reactions is the selective or exclusive formation of *cis*-2-alkyl-1-vinylcyclopentanes (**36**). Intramolecular ene reaction with hydrogen transfer from an alkyl group *cis* to the tether containing the enophile must occur through *exo* transition state (**35**) to give (**36**) since the *endo* transition state (**37**), which would give (**39**), is too hindered. Intramolecular ene reaction with hydrogen transfer from an alkyl group *trans* to the tether containing the enophile occurs through *endo* transition state (**38**) to give (**36**) and through *exo* transition state (**40**) to give (**39**). The formation of (**36**) is usually strongly preferred in thermal ene reactions despite the possible formation of (**39**) from (**40**).

More recent studies have utilized more highly functionalized substrates to prepare synthetic intermediates. Oppolzer has shown that intramolecular ene reactions provide an efficient approach to substituted pyrrolidines.[79] Thermolysis of (**41**; $R^1$ = Me, OMe; $R^2$ = H, Me; $R^3$ = H, Ph) at 230–280 °C for 7–63 h gives pyrrolidine (**42**) in 55–90% yield. The *cis* isomer of (**41**) gives exclusively the *cis*-substituted pyrrolidine (**42**). The *trans* isomer of (**41**) affords 75–90% of *cis*-substituted (**42**). Oppolzer *et al.* have

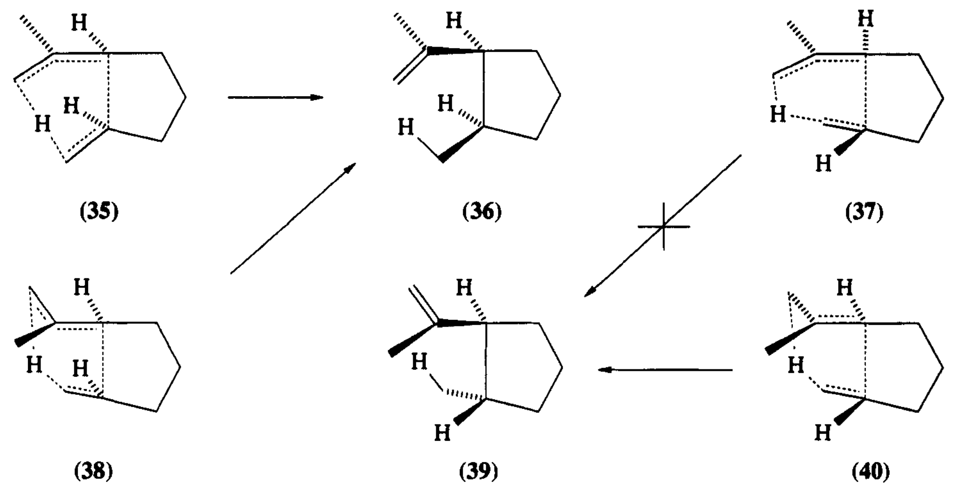

used an intramolecular ene reaction to prepare a spirocyclic precursor to β-acorenol, β-acoradiene, acorenone-B and acorenone.[80] Thermolysis of (**43**) in toluene at 290 °C for 72 h provides a 1.7:1 mixture of (**44**) and (**45**) in 68% yield. The methyl and vinyl are *cis* on the five-membered ring in both isomers. Adduct (**44**) was converted to β-acorenol and β-acorenone and adduct (**45**) was converted to acorenone-B and acorenone.

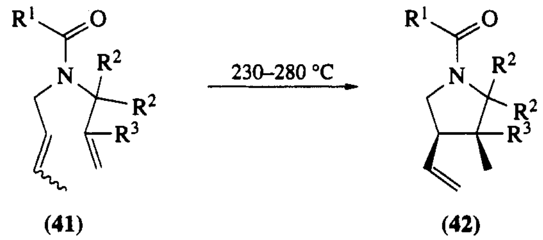

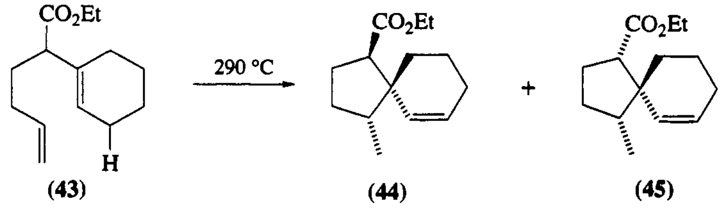

Oppolzer used an intramolecular ene reaction as the key step in a synthesis of isocomene.[81] Thermolysis of (**46**) in toluene at 280 °C for 24 h gives tricyclic ene adduct (**47**) in 17% yield. As required for the synthesis of isocomene, the methyl and vinyl substituents on the newly formed cyclopentane are *cis*. Oppolzer and coworkers developed two approaches to modhephene using intramolecular ene reactions to construct the [3.3.3]propellane system.[82,83] Pyrolysis of (**48a**) in toluene for 12 h at 250 °C gives (**49a**) in 73% yield. Pyrolysis of (**48b**) in toluene for 16 h at 250 °C gives a 76% yield of (**49b**) containing the *gem*-dimethyl group needed for the synthesis of modhephene. Once again, the methyl and vinyl substituents on the newly formed cyclopentane are *cis*. In model studies for the synthesis of pentalenolactone, Plavec and Heathcock developed routes to diquinanes based on intramolecular ene reactions.[84] Flash vacuum pyrolysis of (**50**) at 500 °C gives (**51**) in 93% yield. Thermolysis of (**52**) for 40 min at 345 °C gives the highly functionalized diquinane (**53**) in 71% yield.

Ziegler and Mencel have described tandem Claisen–ene rearrangements.[85] Thermolysis of vinyl ether (**54**) for 2 h at 330 °C gives a 1:1 mixture of aldehydes (**56**) and (**57**) in 75% yield. Claisen rearrangement gives (**55**), which undergoes intramolecular ene reactions with the side-chain double bond acting as the enophile to give (**56**) and the cyclopentene double bond acting as enophile to give (**57**). Ziegler and Mikami then introduced a trimethylsilyl group on to the side-chain double bond in an attempt to control the orientation of the ene reaction.[86] Pyrolysis of either (**58a**) or (**58b**) in benzene at 300 °C for 15 h pro-

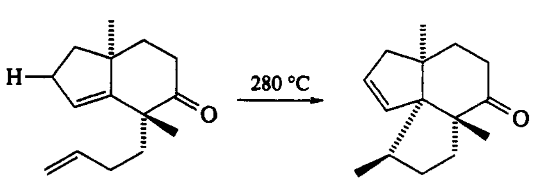

(46) (47)

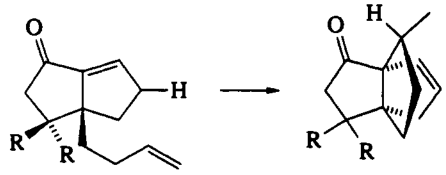

(48) (49)

a: R = H
b: R = Me

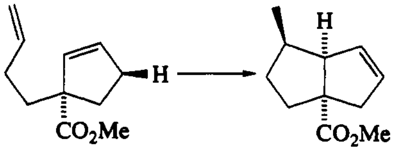

(50) (51)

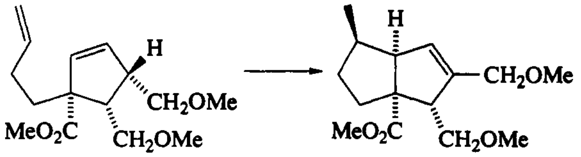

(52) (53)

vides a 1:1 mixture of (**59**) and (**60**), indicating that in this case the trimethylsilyl group does not perturb the orientation of the ene reaction. On the other hand, pyrolysis of (**61b**) at 300 °C gives only (**59b**), while pyrolysis of (**61a**) gives a 3:1 mixture of (**59a**) and (**60a**). Therefore steric interactions caused by the trimethylsilyl group in (**61b**) prevent the side-chain double bond from acting as the enophile.

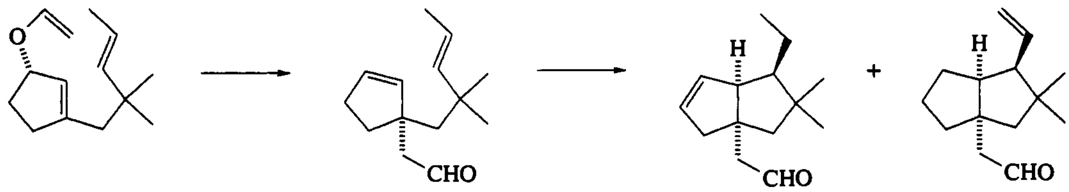

(54) (55) (56) (57)

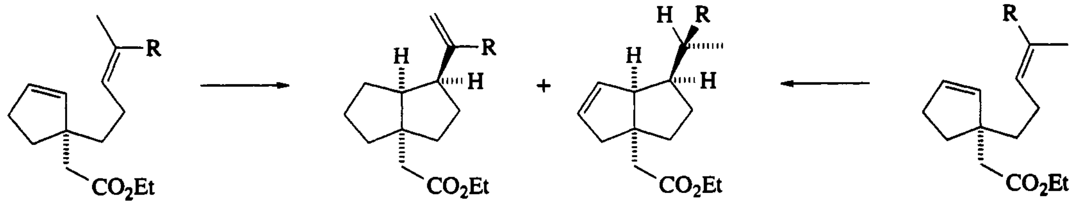

(58) (59) (60) (61)

a: R = H
b: R = $Me_3Si$

### *1.1.3.1.2 Activated enophiles*

As in intermolecular ene reactions, the presence of electron-withdrawing substituents, such as alkoxycarbonyl groups, on the enophile lowers the activation energy, permitting the ene reaction to occur under milder conditions. Type I intramolecular ene reactions with enophiles bearing two electron-withdrawing substituents on the terminal carbon occur under very mild conditions. Intramolecular ene reactions with enophiles bearing a single electron-withdrawing group on the terminal carbon sometimes proceed under mild conditions but, somewhat surprisingly, often proceed only at the elevated temperatures required for unactivated enophiles. Complexation of a Lewis acid to the electron-withdrawing group further activates the enophile, permitting these reactions to be carried out at or below room temperature.

Kelly found that intramolecular ene reaction of triester (**62**) occurs rapidly at room temperature to give (**63**).[87] Snider and coworkers investigated the scope of this reaction and found that 1-allylic 2,2-dimethyl ethylenetricarboxylates undergo intramolecular cyclization reactions at 80–140 °C to give mixtures of ene adducts and dihydropyrans resulting from inverse electron Diels–Alder reactions in which the α,β-unsaturated ester functions as the diene.[88] The *trans*-crotyl triester (**64a**) reacts at 135 °C for 200 h giving a 1:1 mixture of the *cis*-substituted ene adduct (**65**) and the Diels–Alder adduct (**66a**). The *cis*-crotyl triester (**64b**) reacts similarly giving a 9:1 mixture of (**65**) and (**66b**). Different products are formed with Lewis acid catalysis.[89] Treatment of (**64a**) with $FeCl_3$ in $CH_2Cl_2$ for 30 min at 25 °C gives chlorolactone (**67**), resulting from stereospecific *trans* addition of carbon and chlorine to the double bond in 85% yield. Similar treatment of (**64b**) gives chlorolactone (**68**) in 75% yield.

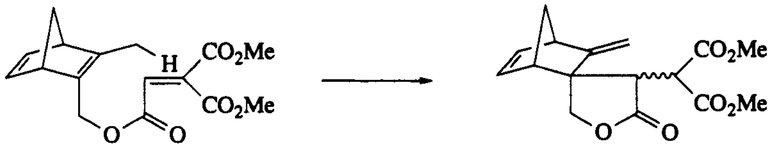

(**62**) (**63**)

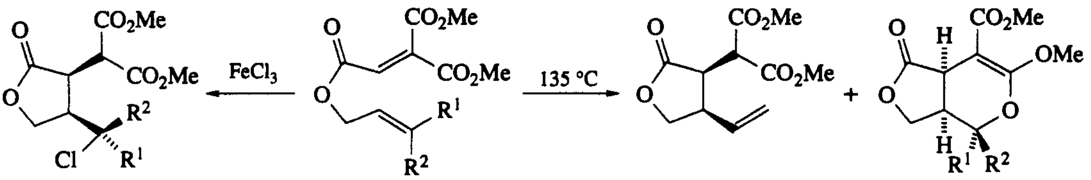

(**67**) $R^1$ = Me, $R^2$ = H
(**68**) $R^1$ = H, $R^2$ = Me

(**64**) a: $R^1$ = Me, $R^2$ = H
b: $R^1$ = H, $R^2$ = Me

(**65**) (**66**)

Oppolzer and Sammes independently developed a route to α-allokainic acid (**72**) based on the thermal ene reactions of (*Z*)-alkene (**69**) and (*E*)-alkene (**73**).[90–92] Pyrolysis of (**69**) for 5 min at 180 °C or 80 h at 70 °C gives a 3:1 mixture of (**70**) and (**71**). Reaction of (**73**) under similar conditions gives a 1:1 mixture of (**70**) and (**71**). The *trans* isomer (**70**) was converted to α-allokainic acid (**72**) by hydrolysis and decarboxylation. Oppolzer found that $EtAlCl_2$ catalyzed ene reactions of these esters proceed at very low temperature with improved selectivity for the desired *trans* isomer (**70**).[91] Treatment of (**69**) at –78 °C with 3 equiv. of $EtAlCl_2$ for 8 h or 20 equiv. of $EtAlCl_2$ for 5 min gives only (**70**). Treatment of (**73**) at –35 °C with $EtAlCl_2$ gives a 89:11 mixture of (**70**) and (**71**). At least three equiv. of $EtAlCl_2$ are needed to complex fully the ester groups in (**69**) and (**73**). The ene reactions of (**69**) and (**73**) differ from most ene reactions of 1,6-dienes in that *trans*-pyrrolidines are the exclusive or major products.

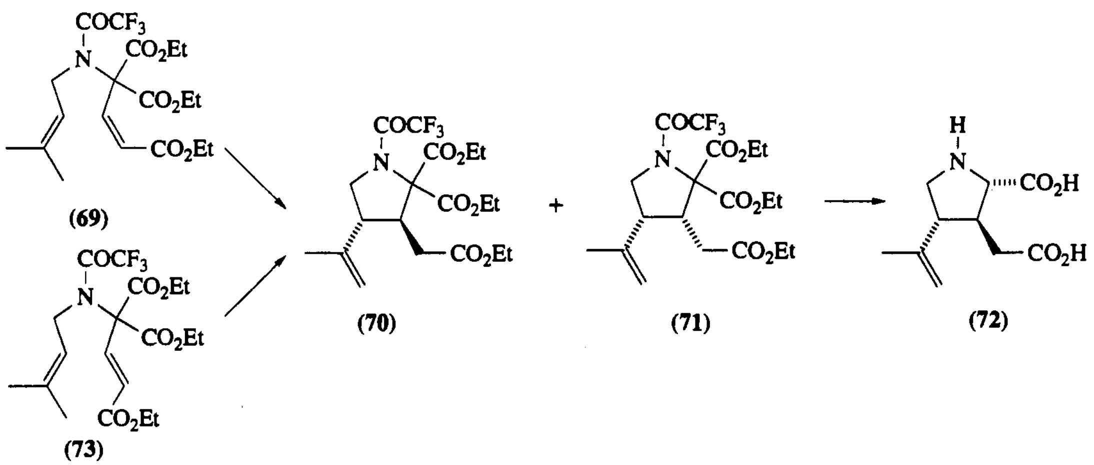

(**69**) (**73**) (**70**) (**71**) (**72**)

Oppolzer and coworkers have developed an enantioselective version of this reaction which permits the synthesis of (+)- and (–)-α-allokainic acid from (**76**) and (**77**), respectively.[93,94] Treatment of (–)-8-phenylmenthyl ester (**74**) with $EtAlCl_2$ at –78 °C gives a 95:5 mixture of (**76**) and (**77**). Treatment of (–)-8-phenylmenthyl ester (**75**) with $EtAlCl_2$ at –35 °C gives an 11:89 mixture of (**76**) and (**77**). Oppolzer and Mirza used $^{13}C$ labeling to establish that the hydrogen is transferred exclusively from the *trans*-methyl group of (**69**).[95] This result precludes a stepwise mechanism with a free cationic intermediate which should transfer hydrogen equally from both methyl groups.

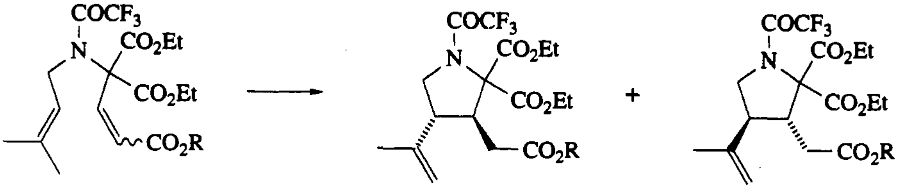
COCF3
N
CO2Et
CO2Et
CO2R
COCF3
N
CO2Et
CO2Et
CO2R
+
COCF3
N
CO2Et
CO2Et
CO2R

**(74)** *(Z)* R = (–)-8-phenylmenthyl **(76)** **(77)**
**(75)** *(E)*

Oppolzer and coworkers used an intramolecular ene reaction as the key step in the synthesis of α-kainic acid (**81**).[96] Thermolysis of diene (**78**) at 180 °C results in reversible isomerization to diene (**79**), which undergoes an intramolecular ene reaction to give the expected *cis*-substituted pyrrolidine (**80**) in 90% yield. Hydrolysis gives α-kainic acid (**81**) in 60% yield. This approach was extended to the synthesis of (–)-α-kainic acid.[97] Thermolysis of (**82**) for 40 h at 130 °C gives the key intermediate (**83**) in 75% yield.

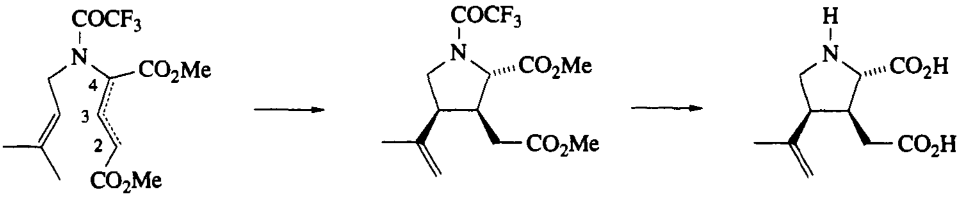
COCF3
N
CO2Me
4
3
2
CO2Me
COCF3
N
CO2Me
CO2Me
H
N
CO2H
CO2H

**(78)** $\Delta^{3,4}$ **(80)** **(81)**
**(79)** $\Delta^{2,3}$

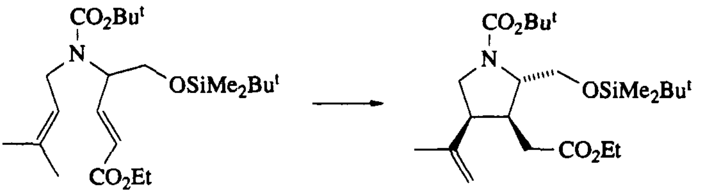
CO2Bu^t
N
OSiMe2Bu^t
CO2Et
CO2Bu^t
N
OSiMe2Bu^t
CO2Et

**(82)** **(83)**

Ghosh and Sarkar examined the effects of activating groups and geminal substitution on the rates and stereoselectivities of the thermal ene reactions of (**84**).[98] Cyclization of the (*E*)-isomer (**84**; X = $CO_2Me$; Y = H) gives a 3:1 mixture of (**85**) and (**86**), while cyclization of the (*Z*)-isomer (**84**; X = H; Y = $CO_2Me$) gives a 2:3 mixture of (**85**) and (**86**). Diester (**84**; X = Y = $CO_2Me$) gives a ~15:85 mixture of (**85**) and (**86**). Geminal substitution (R = Me) in (**84**) leads to a 3–4-fold rate enhancement over the unsubstituted case (R = H). The presence of a second ester on the dienophile (**84**; X = Y = $CO_2Me$) leads to a 13–17-fold rate enhancement over either the (*E*)- or (*Z*)-monoester. Tietze and coworkers found that $ZnBr_2$ catalyzed ene reactions of a series of malonates (**87**; X = OMe) at 25 °C proceed in excellent yield with high selectivity for the all-*trans* isomer (**88**).[99] Under these conditions the diketones (**87**; X = Me) give the inverse-electron Diels–Alder adduct (**89**).

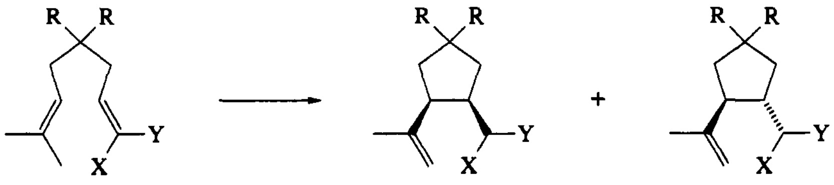
R R
Y
X
R R
Y
X
+
R R
Y
X

**(84)** **(85)** **(86)**

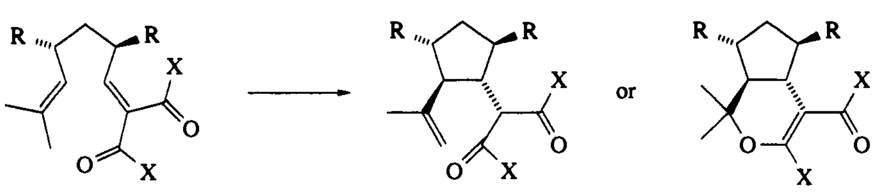

**(87)** R = H, Me **(88)** X = OMe **(89)** X = Me

Introduction of an electron-withdrawing group on the internal carbon of the enophile should favor bond formation between the terminal carbon of the enophile and the ene to give a type IV adduct (equation 7). Flash vacuum pyrolysis of **(90)** at 570 °C leads to a mixture of the type I adducts **(91)** and the type IV adduct **(92)**.[100] Lewis acid catalyzed cyclization of **(90)** should favor the formation of **(92)**, but a stepwise reaction leading to other products occurs.[48] Cyclohexenylacrylamides **(93)** cyclize only to the type I product **(94)** on heating above 200 °C.[101] However, the magnesium salt of hydroxyphenylacrylamides **(95)** undergoes intramolecular ene reactions at 140 °C to give mixtures of adducts **(96)** and **(97)** rich in the type IV adduct **(97)**.[102] Treatment of **(98)** with 0.9 equiv. of $EtAlCl_2$ at 40 °C for 5 d gives exclusively the type IV adduct **(99)**.[103]

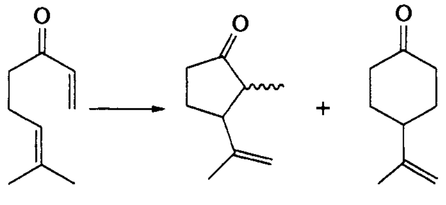

**(90)** **(91)** **(92)**

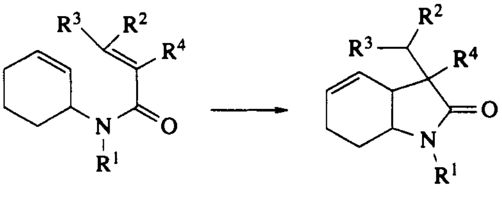

**(93)** **(94)**

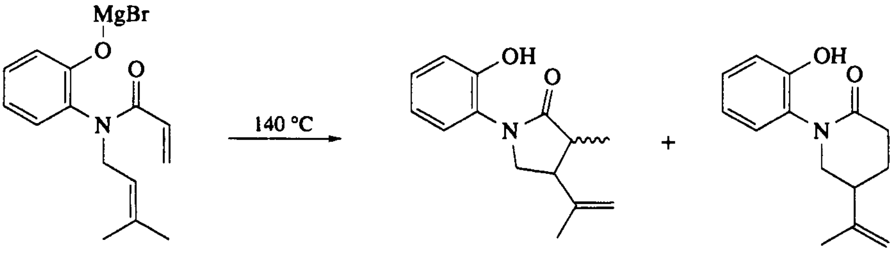

**(95)** **(96)** **(97)**

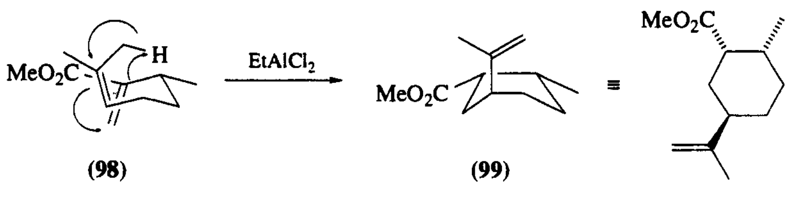

**(98)** **(99)**

### 1.1.3.2 Formation of 1-Vinyl-2-alkylidinecyclopentanes from 1,6-Enynes

Alkynes are generally more reactive than alkenes as enophiles in both inter- and intra-molecular ene reactions.[1,3] 6-Octen-1-yne **(100)** cyclizes to 1-methylene-2-vinylcyclopentane **(101)** on brief heating at 400 °C.[104,105] Dehydrolinalool **(102)** undergoes an ene reaction at 200 °C to give **(103)** in quantitative yield.[106,107] This ene reaction can also be carried by heating for 15 min in a microwave oven at 400–425 °C.[108] Arigoni has used an intramolecular ene reaction followed by a retro-ene reaction for the synthesis of chiral acetic acid.[109] Thermolysis of optically active **(104)** at 260 °C for 2.5 h gives **(105)**, which undergoes a retro-ene reaction to give **(106)**. Kuhn–Roth degradation of **(106)** gives (*R*)-[$^2$H,$^3$H]acetic acid. Stork and Kraus carried out a prostaglandin synthesis using the intramolecular ene reaction of **(107)** at 250 °C to give **(108)** in 60% yield as the key step.[110]

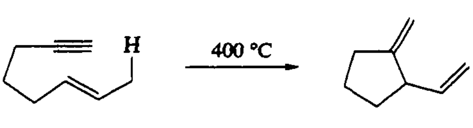

**(100)** **(101)**

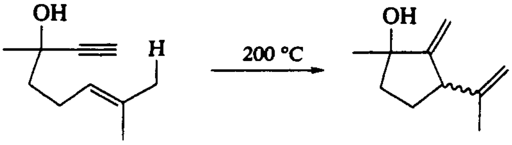

**(102)** **(103)**

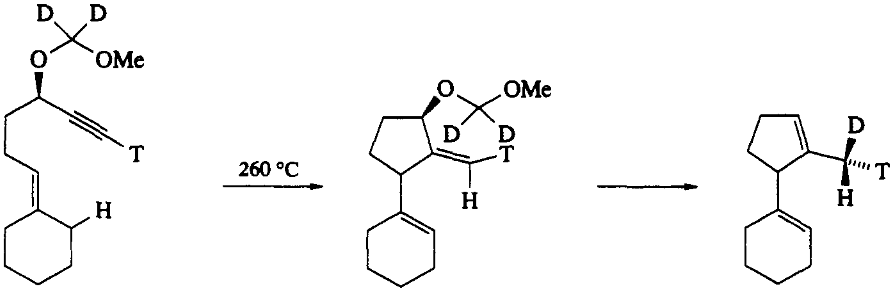

**(104)** **(105)** **(106)**

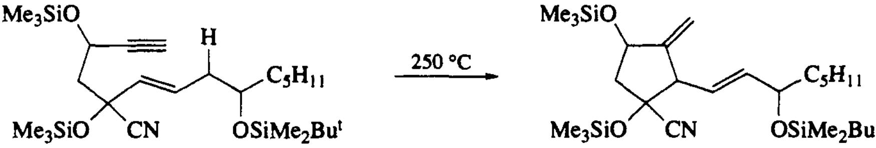

**(107)** **(108)**

Snider and Killinger have examined the intramolecular ene reaction of 1,6-enynes containing a hydrogen, methyl or methoxycarbonyl substituent on the alkyne.[111] Since the alkyne is acting as the enophile, a methyl substituent retards the reaction while a methoxycarbonyl group accelerates it. Pyrolysis of **(109)** for 62 h at 210 °C gives **(112)** in >95% yield. Pyrolysis of **(111)** for 48 h at 225 °C gives only 15% conversion to **(114)**. Pyrolysis of ester **(110)** for 24 h at 135 °C gives **(113)** in >95% yield. Nakai and coworkers have examined the intramolecular ene reactions of crotyl propargyl ethers **(115)** to give **(116)**.[112] As in the all carbon system, esters cyclize faster than terminal alkynes which cyclize faster than internal alkynes. High 1,2-*trans* diastereoselectivity is observed with α-alkylcrotyl systems, as shown in the formation of **(116)**.

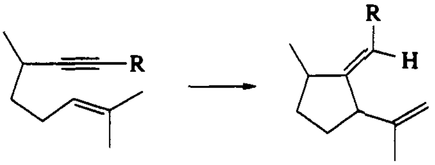

**(109)** R = H
**(110)** R = $CO_2Me$
**(111)** R = Me

**(112)** R = H
**(113)** R = $CO_2Me$
**(114)** R = Me

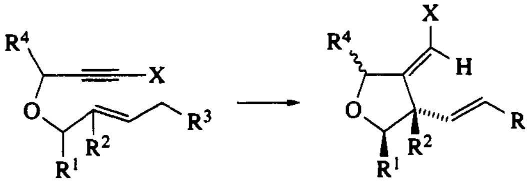

**(115)** X = H, $CO_2Me$, $Me_3Si$, Me **(116)**
R = H, alkyl or aryl

Trost has discovered that $Pd(OAc)_2$ and other $Pd^{II}$ compounds catalyze the cyclization of terminal 1,6-enynes to give ene-type adducts.[113] Treatment of **(117)** with 5 mol % $Pd(OAc)_2$ at 60–66 °C gives metallocyclopentene **(118)**, which reacts further to give a 6:94 mixture of **(119)** and **(120)** in 80% yield. Flash vacuum pyrolysis of **(117)** at 625 °C gives a 100:0 mixture of **(119)** and **(120)** in 83% yield. The palladium reaction not only occurs under much milder conditions but gives different isomer ratios. In many other cases the palladium-catalyzed cyclization gives products which are not available from a thermal ene reaction.

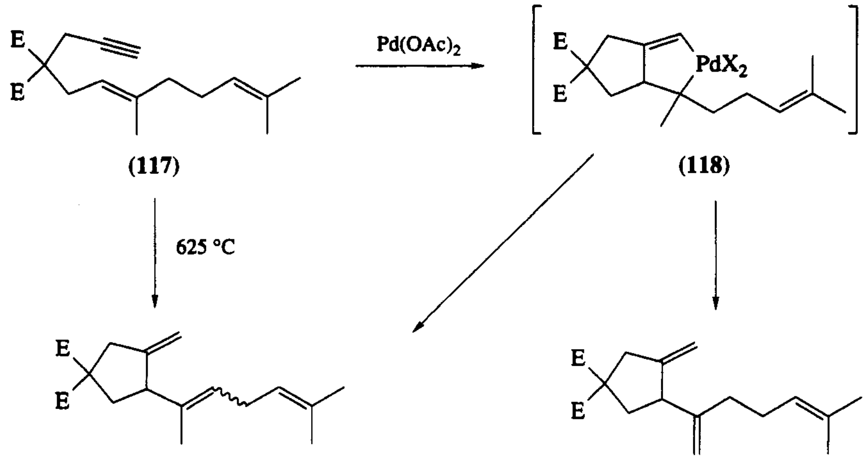

(117) (118)

(119) (120)

### 1.1.3.3 Formation of 1-Vinyl-2-alkylcyclohexanes from 1,7-Dienes

1,7-Dienes undergo intramolecular ene reactions much less readily than 1,6-dienes due to the more negative entropy of activation with the longer tether. These reactions require higher temperatures, proceed in lower yields and are not generally synthetically useful except in the case of 1,7-dienes containing two electron-withdrawing groups on the terminal carbon of the enophile. Flash vacuum pyrolysis of (**121a**) at 490 °C gives only 25% of (**122a**). Flash vacuum pyrolysis of (**121b**) with a monoactivated enophile at 400 °C gives an 82% yield of (**122b**).[114–116]

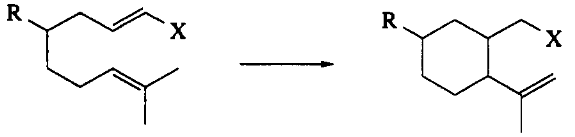

a: X = R = H
b: X = $CO_2Me$, R = Me

(121) (122)

Intramolecular ene reactions of 1,7-dienes with doubly activated enophiles (**123**; X, Y = $CO_2R$, CN, COMe) proceed readily either thermally or with Lewis acid catalysis to give (**124**) and stereoisomers.[115,117–121] In an elegant series of studies, Tietze and coworkers have explored the stereochemistry of these cyclizations.[118–121] Dienes (**123a**; X, Y = $CO_2Me$, CN) undergo thermal or $ZnBr_2$ catalyzed ene reactions, providing the *trans* isomer (**124a**) selectively in up to 89% yield.[118] Dienes (**123a**) in which one or both of the activating groups is a methyl ketone behave quite differently, giving mainly or exclusively the inverse electron demand intramolecular Diels–Alder adduct (**125a**).[118] Dienes (**123b**) behave similarly, giving adducts (**124b**) and (**125b**) with high selectivity for the fully equatorial diastereomer.[119,120] Anhydrous $FeCl_3$ on basic alumina proved to be the best catalyst for the cyclization of (**124b**; X = Y = $CO_2Me$) giving, at –78 °C, a 98.8:1.2 mixture of (**124b**) and the other diastereomer with *trans* isopropenyl and malonate substituents in 92% yield.[119] Malonate (**124b**) was converted to enantiomerically pure veticadinol by a six-step sequence.[121] Tietze has also exploited the inverse electron demand intramolecular Diels–Alder reaction of doubly activated 1,7-dienes.[122–124] This process, rather than an intramolecular ene reaction, is the main or exclusive reaction when the activating groups in (**123**) are diketones, Meldrum's acid or dimethylbarbituric acid.

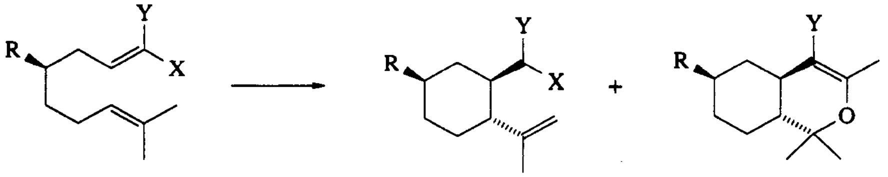

a: R = H
b: R = Me

(123) (124) (125)

Nussbaumer and Fráter have used a vinylogous carbonate as an enophile. Pyrolysis of a solution of (**126**) in toluene at 300 °C for 9 h gives (**127**), an intermediate in a synthesis of *cis*-γ-irone, in 25% yield as the only cyclization product.[125] Acid-catalyzed cyclization of (**126**) gives only the isomer of (**127**) with an endocyclic double bond. Thomas and Lander-Schouwey found that pyrolysis of (**128**) in decalin at 300 °C results in a retro-ene reaction to give propene and (**129**) which undergoes an intramolecular ene reaction to give (**130**).[126]

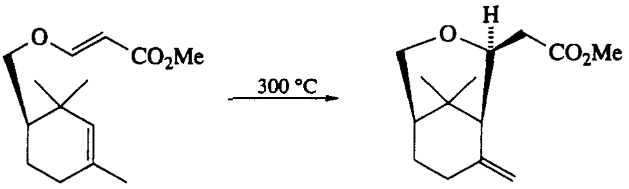

(**126**) (**127**)

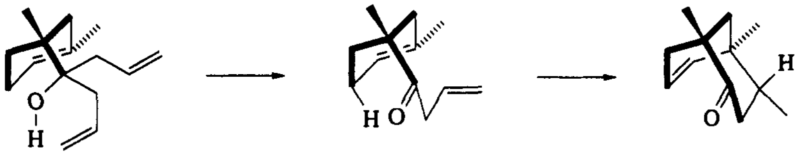

(**128**) (**129**) (**130**)

## 1.1.3.4 Formation of 1-Vinyl-2-alkylidinecyclohexanes from 1,7-Enynes

Only a few examples of intramolecular ene reactions of 1,7-enynes are known. Pyrolysis of terminal alkyne (**131**) in toluene for 48 h at 255 °C results in 17% conversion to ene adduct (**133**).[111] Ester (**132**) is more reactive, giving ene adduct (**134**) in 85% yield on heating for 62 h at 225 °C. Ficini and coworkers have found that similar reactions can be carried out conveniently by flash vacuum pyrolysis. Pyrolysis of (**135**) at 420 °C at 200 Torr gives 80% conversion to ene adduct (**136**), a model for the synthesis of the A ring of 1*S*,25-dihydroxycalciferol.[127] Dreiding found that flash vacuum pyrolysis of ynone (**137**) at 550 °C gives ene adduct (**138**) in 15% yield along with other products.[128]

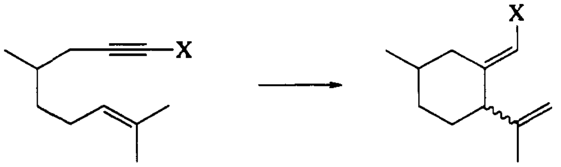

(**131**) X = H
(**132**) X = $CO_2Me$

(**133**) X = H
(**134**) X = $CO_2Me$

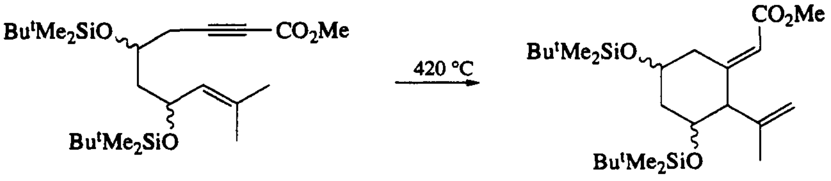

(**135**) (**136**)

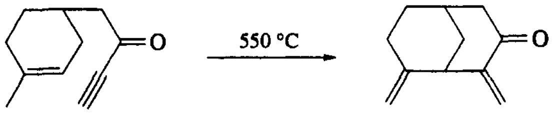

(**137**) (**138**)

### 1.1.3.5 Miscellaneous Reactions

Allenes have occasionally been used as enophiles in intramolecular ene reactions.[129] Thermolysis of (**139a**) at 200 °C gives ene adduct (**140a**) in >90% yield. Similar reaction occurs at 25 °C with $BF_3 \cdot Et_2O$ catalysis. Flash vacuum pyrolysis of allene (**139b**) at 380 °C at 200 Torr gives ene adduct (**140b**) in 80% yield. Treatment of allenic ester (**141**) with $EtAlCl_2$ for 12 d at 25 °C in $CH_2Cl_2$ gives ene adduct (**142**) in 49% yield, as a 2.9:1 mixture of α-methyl and β-methyl isomers, and cyclobutane (**143**) in 27% yield, as a 2:1 (*E*):(*Z*) mixture.[74] Only cyclobutanes are formed in related reactions with mono- or 1,2-di- rather than tri-substituted alkenes.

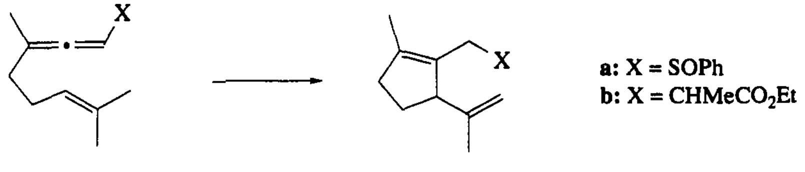

a: X = SOPh
b: X = $CHMeCO_2Et$

**(139)** **(140)**

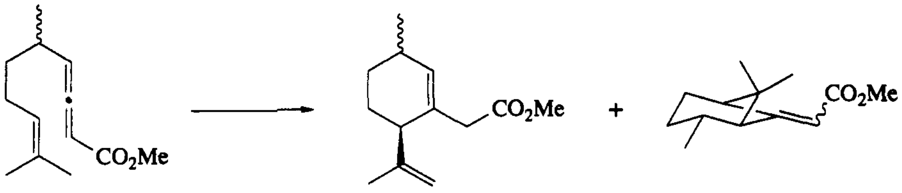

**(141)** **(142)** **(143)**

Allenes and alkynes occasionally react as ene components when other ene reactions are not possible. Pyrolysis of (**144**) for 2 h at 200 °C gives ene adduct (**145**) in 43% yield.[79] Flash vacuum pyrolysis of (**146**) at 490 °C gives a 3:1 mixture of cycloadduct (**147**) and ene adduct (**148**).[130]

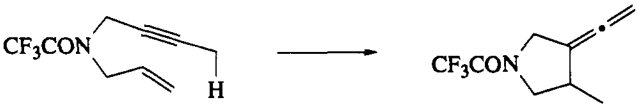

**(144)** **(145)**

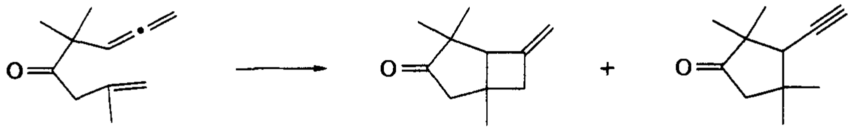

**(146)** **(147)** **(148)**

Type II reactions with carbonyl compounds as enophiles are well-known, synthetically useful reactions.[131] Type II reactions with alkenes as enophiles are very rare because competing type I reactions usually occur more readily. Thermolysis of (**149a**) at 280 °C gives ene adduct (**150a**) in 40% yield.[3] Thermolysis of (**149b**) at 230–280 °C leads to type I adduct (**151**) rather than type II adduct (**150b**).[79]

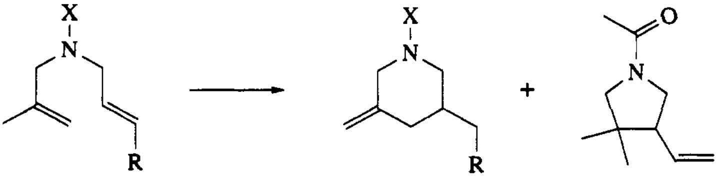

a: X = Ts, R = H
b: X = COMe, R = Me

**(149)** **(150)** **(151)**

Wender and Letendre have reported a series of transannular ene reactions.[132] Pyrolysis of (**152a**) for 2 h at 210 °C gives cyclodecadiene (**153a**) as a transient intermediate which undergoes a transannular ene reaction to give (**154a**) in 95% yield. Ester (**152b**) gives a quantitative yield of (**154b**) under similar conditions. Heating ether (**152c**) to 210 °C for 1 h gives (**153c**) which is stable at that temperature. Transannular ene reaction to give (**154c**) occurs in 60% yield on heating (**153c**) at 260 °C for 5 h.

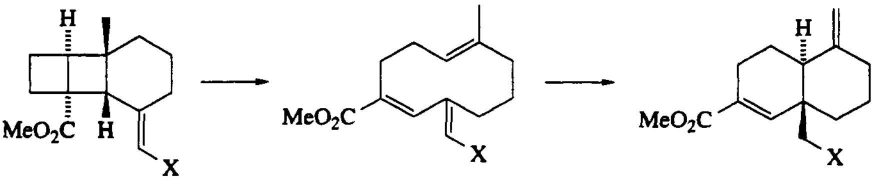

(**152**) (**153**) (**154**)

**a**: X = H
**b**: X = $CO_2Me$
**c**: X = OMe

Type III intramolecular ene reactions provide a route to medium sized rings.[133–136] Lambert found that heating (**155a**) for 24 h at 350 °C gives a quantitative yield of a 1:1 mixture of (**156a**) and (**157a**). Both benzocyclononadienes result from intramolecular ene reactions, with different double bonds acting as enophiles.[133,134] Pyrolysis of (**155b**) under similar conditions gives a 4:1 mixture of (**156b**) and (**157b**). Marvell found that pyrolysis of bis-silyl ether (**158a**) for 90 h at 300 °C gives (**159a**) in 80% yield.[135] The *cis* isomer reacts three times faster than the *trans* isomer. Monosilyl ether (**158b**) gives a 9:1 mixture of (**159b**) and (**160b**).

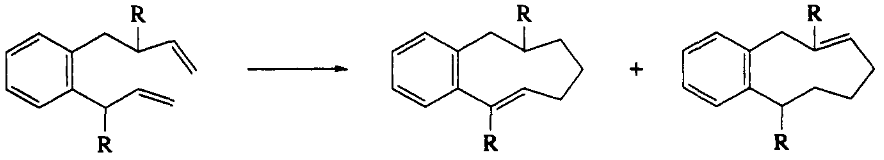

(**155**) (**156**) (**157**)

**a**: R = H
**b**: R = Me

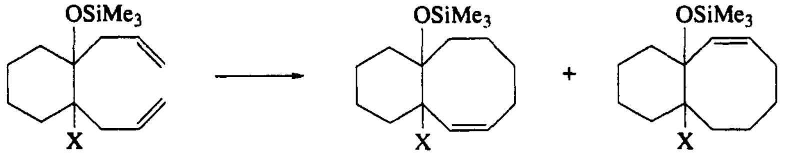

(**158**) (**159**) (**160**)

**a**: X = $OSiMe_3$
**b**: X = H

Lewis acid catalyzed intramolecular ene reactions with enones or enals sometimes occur in good yield. For instance, $MeAlCl_2$ catalyzed ene reaction of enone (**161**) at room temperature gives ene adduct (**162**) in 85% yield.[48] In many other cases, Lewis acid or proton catalyzed intramolecular additions of enones or enals to alkenes give zwitterions, which yield mixtures of products.[48,137–140]

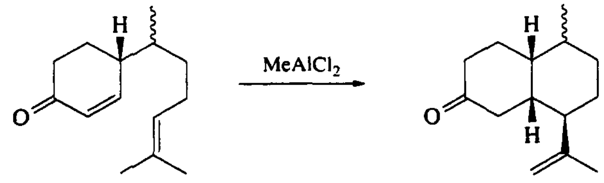

(**161**) (**162**)

## 1.1.4 INTRAMOLECULAR REACTIONS: ENOLS AS THE ENE COMPONENT; 'THE CONIA REACTION'

Conia and coworkers have developed an extensive series of thermal intramolecular ene reactions of unsaturated ketones which occur on extended heating (30 min to several hours) at 300–400 °C in pyrex.[141] The initial step of the reaction is reversible tautomerization of the ketone (**163**) to give enol

(**164**), which undergoes an intramolecular type I ene reaction with the enol as the ene component and the unactivated alkene as the enophile to give the *cis*-substituted adduct (**165**) selectively. If $R^2$ = H, equilibration with the more stable *trans*-substituted isomer (**166**) occurs rapidly under the reaction conditions. Related reactions with electron-deficient alkenes are Michael reactions rather than ene reactions.

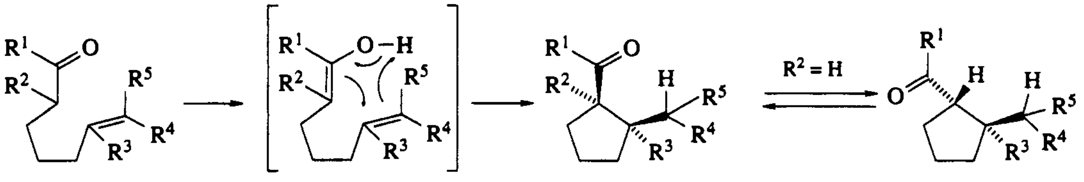

(**163**) (**164**) (**165**) (**166**)

As with other intramolecular ene reactions, this reaction is best suited to the preparation of cyclopentanes, but can also be used for the preparation of cyclohexanes. The reaction cannot be used for the formation of cyclopropanes or cyclobutanes since the unsaturated carbonyl compound is more stable than the ene adduct. δ,ε-Unsaturated ketones (**167**) do not give cyclobutanes (**171**) by enolization to give (**170**) followed by a type I reaction but instead give cyclohexanones (**169**) by enolization to give (**168**) followed by a type II reaction. Alkynes can replace alkenes as the enophile. Enols can be prepared from pyrolysis of enol esters, enol ethers and acetals and from β-keto esters and 1,3-dicarbonyl compounds. The reaction is well suited to the preparation of fused or bridged bicyclic and spirocyclic compounds. Tandem ene reactions in which two rings are formed in one pot from dienones have also been described. The examples discussed below[142–163] are restricted to those published since Conia and Le Perchec's 1975 review.[141]

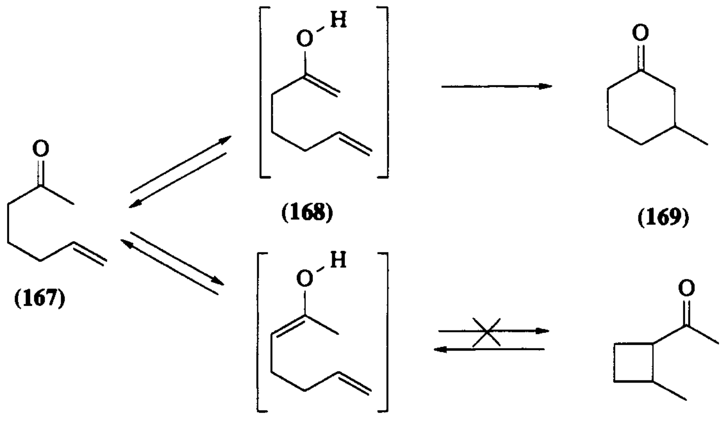

(**167**) (**168**) (**169**) (**170**) (**171**)

Conia and Lange[143] and Wolff and Agosta[144] have extended the reaction to the synthesis of bicyclo[2.2.1]heptanones and bicyclo[2.2.2]octanones. Cyclization of (+)-dihydrocarvone (**172**) at 400 °C for 20 h gives (+)-camphor (**173**) in 55% yield.[143] Pyrolysis of (**174**; R = H or Me) for 6 h at 375 °C gives *endo*-6-methylbicyclo[2.2.1]heptan-2-one (**175**; R = H, Me) in 60–70% yield.[144] Conia and coworkers have prepared [3.3.3]propellanes by tandem ene reactions. Pyrolysis of (**176**) for 2 h at 335 °C gives (**177**) in 50% yield.[147] Pyrolysis of (**178**) for 100 min at 290 °C gives (**179**) in 63% yield.[147] Pyrolysis of (**180**) for 6 h at 335 °C gives a 1:3 mixture of (**181**) and (**182**) in 40% yield.[146] Yates examined the pyrolysis of 5-vinylcholestan-3-ones.[145,148] The 5α-isomer (**183**) gives (**184**) in 41% yield.

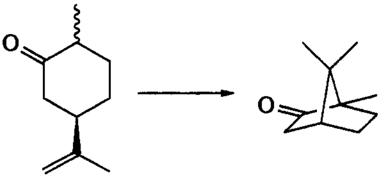

(**172**) (**173**)

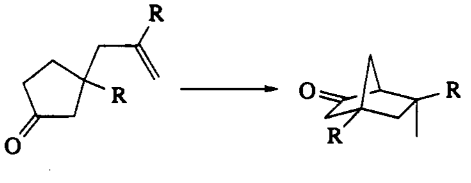

(**174**) (**175**)

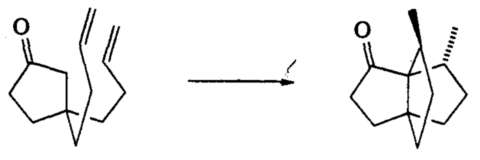

**(176)** **(177)**

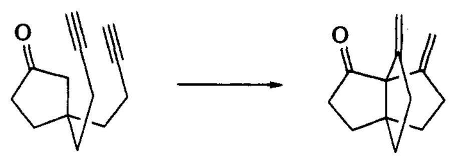

**(178)** **(179)**

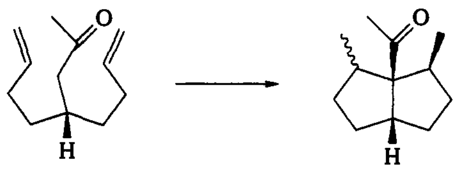

**(180)** **(181)** α-Me

**(182)** β-Me

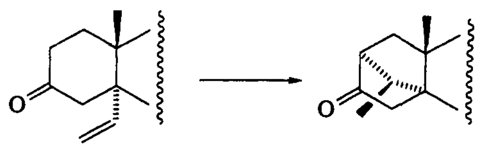

**(183)** **(184)**

Schostarez and Paquette used a 'Conia' ene reaction as a key step in their synthesis of modhephene.[149] Pyrolysis of (**185**) for 4 h at 360 °C gives (**186**) as a single stereoisomer in 85% yield, which was converted to epimodhephene. Cyclization of the corresponding alkyne gives an intermediate that was converted to modhephene. Paquette and coworkers examined the cyclization of (**187a–c**) as a part of a study directed toward the synthesis of proposed structures for senoxydene.[154] Enones (**187a**) and (**187c**) cyclize cleanly to give (**188a**) and (**188c**); (**187b**) does not give (**188b**). Mandville and Conia discovered that the enol intermediates could be prepared regioselectively from α-hydroxymethyl ketones.[151] Flash vacuum pyrolysis of (**189**) at 650 °C gives (**190**) which reacts further to give (**191**) in 99% yield.

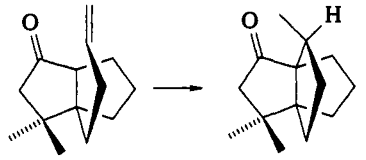

**(185)** **(186)**

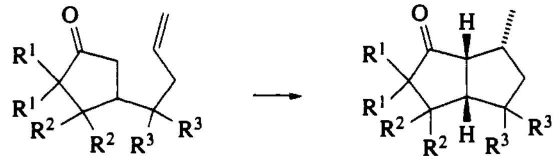

**(187)** **(188)**

a: $R^1 = R^3 = H$; $R^2 = Me$

b: $R^2 = R^3 = H$; $R^1 = Me$

c: $R^1 = R^2 = H$; $R^3 = Me$

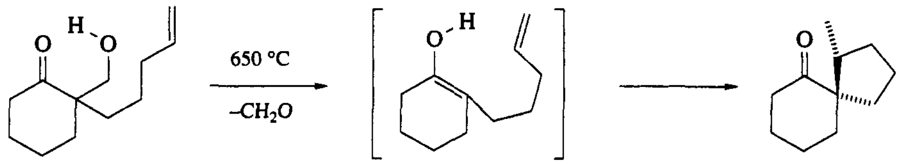

**(189)** **(190)** **(191)**

A major advance in the past decade has been the development of catalysts for the cyclization of alkynic ketones. Jackson and Ley found that (**192**) cyclizes to (**193**) in quantitative yield on heating at 280 °C, treatment with $ZnI_2$ in toluene at reflux or treatment with $SnCl_4$ in $CH_2Cl_2$ at 25 °C.[150] Conia has found that double catalysis by $H^+$ and $Hg^{2+}$ lowers the temperature necessary to achieve cyclization.[152] Treatment of (**178**) with hydrochloric acid and mercury(II) chloride in 1,1,2,2-tetrachloroethane at 110 °C gives the isomer of (**179**) with one endocyclic double bond in 43% yield and the monocyclized product in 23% yield. Improved results were obtained with $Hg^{2+}$ on a solid support.[157]

Drouin, Conia *et al.* have found that these reactions can be carried out under even milder conditions by cyclization of silyl enol ethers of alkynones.[153,155,156,158] Treatment of (**194**), as an (*E*)–(*Z*) mixture, with $HgCl_2$ in $CH_2Cl_2$ in the presence of hexamethyldisilazene for 30 min at 30 °C gives vinylmercurial (**195**; R = HgCl) in quantitative yield. Cleavage of the carbon–mercury bond can be carried out to give (**195**; R = H, D, $CO_2Me$, Br or COMe).

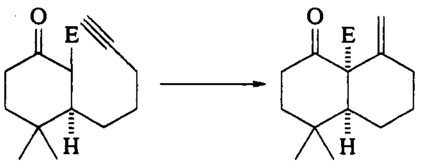

**(192)** E = $CO_2Et$ **(193)**

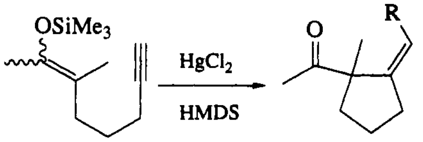

**(194)** **(195)**

Kende has examined a variant of this reaction using trimethylsilylalkynes. Pyrolysis of (**196**) neat at 300 °C for 2 h gives (**197**), which isomerizes to (**198**); the latter undergoes a 1,5-trimethylsilyl shift to give (**199**), which isomerizes to give (**200**) in 60–65% yield.[159] Kende has also developed a 'vinylogous Conia' rearrangement. Pyrolysis of (**201**) for 1.5 h at 285 °C gives (**202**) in 72% yield.[160]

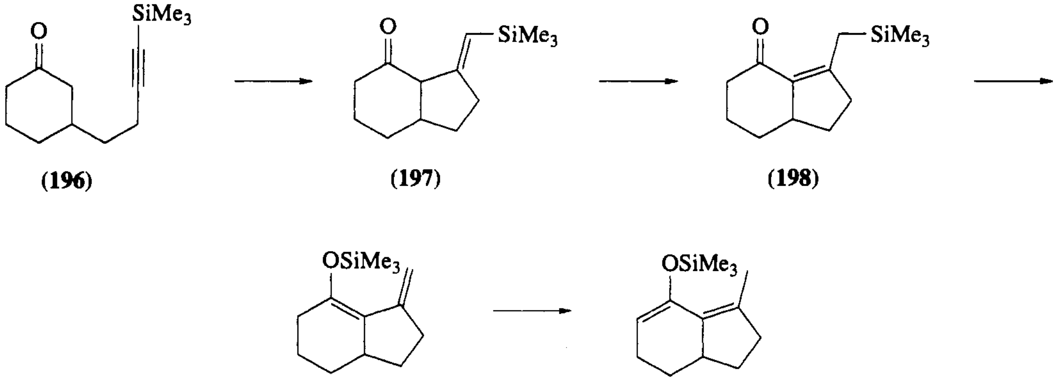

**(196)** **(197)** **(198)**

**(199)** **(200)**

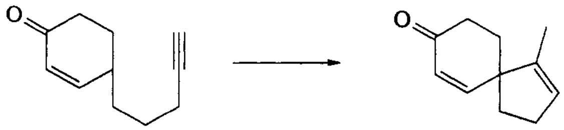

**(201)** **(202)**

Marples and coworkers have found that ene reactions of unsaturated acyloins occur under much milder conditions than for the corresponding unsaturated ketones.[161–163] Pyrolysis of (**203a**) at 110 °C for 18 h gives (**205a**) in 33% yield and (**206**) in 6% yield. Tautomerization of (**203a**) gives ene diol (**204a**) in which either enol can act as the ene component to give ene adducts (**205a**) and the isomer of (**206**) with the opposite stereochemistry at the methyl group. Apparently only ene adduct (**205a**) is formed; acyloin (**206**) is formed by isomerization of (**205a**). Ene reaction of the corresponding ketone requires much higher temperatures. Pyrolysis of the allyl ketone (**203b**) in decalin at 330 °C gives (**205b**) in 79% yield.

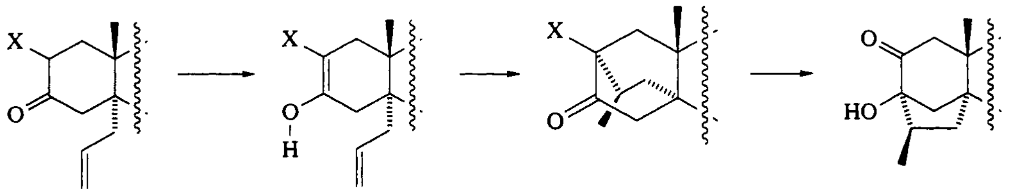

**(203)** **a**: X = OH **(204)** **(205)** **(206)**
**b**: X = H

## 1.1.5 ADDENDUM

*Section 1.1.2.1.2 (i) Acrylate esters.* Narasaka and coworkers found that *N*-acryloyloxazolidinone undergoes a [2 + 2] cycloaddition with 1,1-bis(methylthio)ethylene in the presence of $TiCl_2(OPr^i)_2$ and **(213)** to give 74% of the cyclobutane in 88% enantiomeric excess.[164]

*Section 1.1.2.1.2 (ii) α,β-Unsaturated ketones and aldehydes.* Engler and coworkers found that a 1:1 mixture of $TiCl_4$ and $Ti(OPr^i)_4$ catalyzes the addition of methoxymethyl vinyl ketone to styrenes and methylenecyclohexane to give cyclobutanes.[165]

*Section 1.1.3.1 Formation of 1-vinyl-2-alkylcyclopentanes from 1,6-dienes.* Nakai and coworkers found that **(207)** undergoes an ene reaction on heating in toluene for 20 h at 200 °C to give 97% of **(208)**.[166] The stereochemistry of the enophile does not affect the stereochemistry of the product. The isomer with an (*E*) double bond in the ene component gives mixtures of stereoisomers.

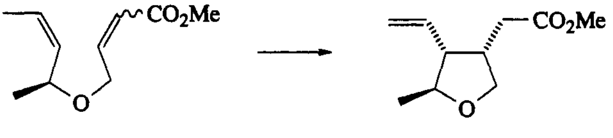

**(207)** **(208)**

*Section 1.1.3.2 Formation of 1-vinyl-2-alkylidinecyclopentanes from 1,6-enynes.* Nakai and coworkers reported that pyrolysis of **(209)** in toluene for 90 h at 170 °C gives 86% of a 4:1 mixture of ene adducts **(210)** and **(211)**.[167] The major isomer **(210)** was converted to a steroid C/D ring synthon.

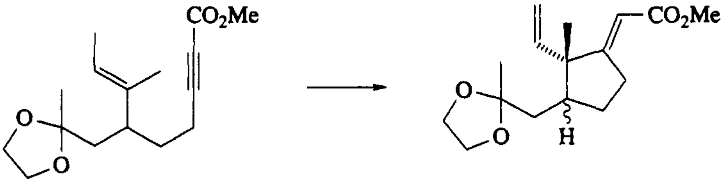

**(209)**

**(210)** α-H
**(211)** β-H

*Section 1.1.3.3 Formation of 1-vinyl-2-alkylcyclohexanes from 1,7-dienes.* Narasaka demonstrated that the chiral titanium alkoxide prepared from $TiCl_2(OPr^i)_2$ and **(213)** catalyzes the asymmetric intramolecular ene reaction of oxazolidinone **(212)** in Freon 113 at 0 °C to give 63% of ene adduct **(214)** in >98% enantiomeric excess and 25% of the hetero Diels–Alder adduct.[168]

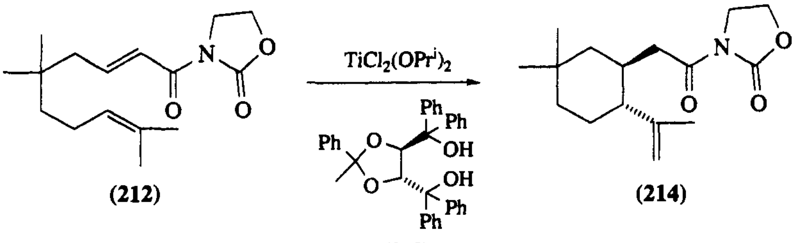

**(212)** **(213)** **(214)**

*Section 1.1.3.5 Miscellaneous reactions.* Takeshita and coworkers reported the remarkable use of intramolecular ene reactions to form cycloheptanes and cyclooctanes.[169] Pyrolysis of **(216)** in toluene at 200 °C gives 97% of the cycloheptane **(215)**. Reaction of **(216)** with $SnCl_4$ in THF gives 85% of cyclooctane **(217)**, which is an intermediate in the synthesis of cycloaraneosene.

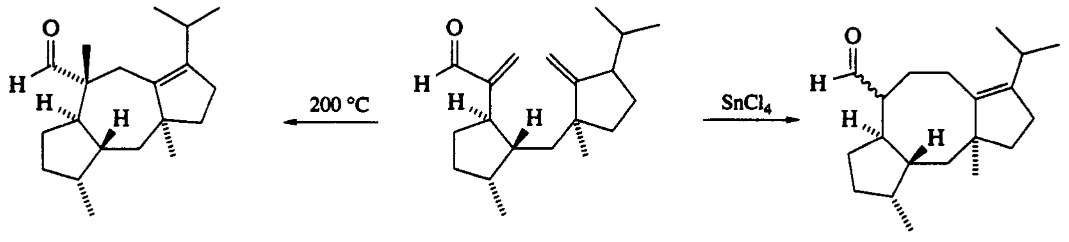

**(215)** **(216)** **(217)**

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# 1.2
# Metallo-ene Reactions

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## 1.2.1 INTRODUCTION

The ene reaction, discovered 45 years ago by Alder,[1] usually involves the thermal reaction of an alkene containing an allylic hydrogen (ene) with an electron-deficient unsaturated compound (enophile) to form 1:1 adducts *via* a cyclic six-electron transition state (*e.g.* **A** + **B** → $C^{\ddagger}$→ **D**; X = H; Scheme 1).

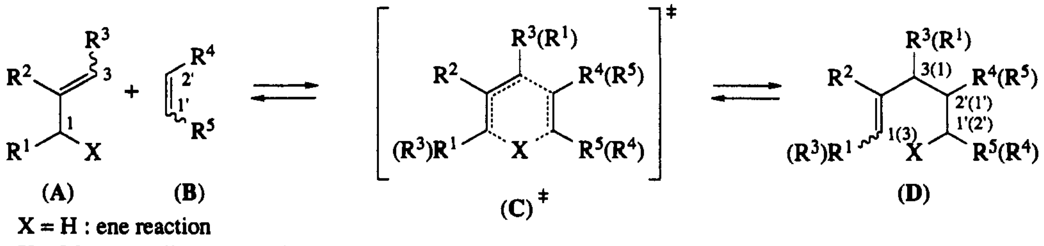

**Scheme 1**

Starting with a few reports in the early 1960s, additions of allylmetal compounds to alkenes and alkynes became increasingly acknowledged. These reactions resemble the classical ene process (Scheme 1), but involve a transfer of a metal instead of a hydrogen. This analogy prompted Oppolzer to classify transformations like (**A**) + (**B**) → (**D**), with X = metal, as metallo-ene reactions. However, allylmetal compounds (**A**) have specific properties mainly determined by the metal. This may profoundly influence their reactivity towards enophiles (**B**) and their compatibility with functional groups, as well as the final functionalization of the metallo-ene products (**D**). Furthermore, allylmetal species undergo relatively fast 1,3-metal migrations, ($\mathbf{A}^1$) ↔ ($\mathbf{A}^2$) ↔ ($\mathbf{A}^3$) ↔ ($\mathbf{A}^4$) and ($\mathbf{A}^1$) ↔ ($\mathbf{A}^4$), also resulting in (*E*)/(*Z*) equilibration (Scheme 2).

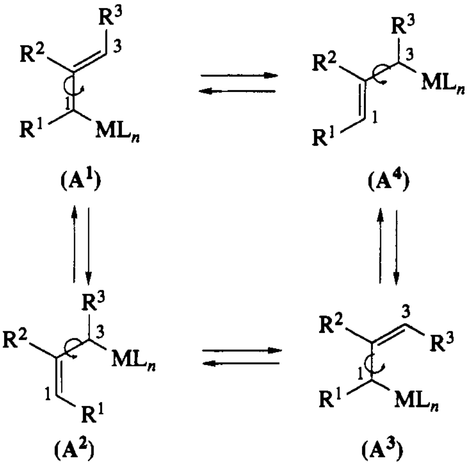

Scheme 2

This 1,3-metal shift usually precedes the metallo-ene reaction and thus obscures rationalizations and predictions of the regio- and stereo-chemistry. As to the regiochemistry of metallo-ene reactions involving nonsymmetrical ene (**A**) and enophile units (**B**), the question arises: which enophile (C-1′ or C-2′) or ene terminals (C-1 or C-3) will be joined by the new carbon–carbon bond? Regarding the stereochemistry, it is worth noting that inversion of metalated $sp^3$ centers C—M can occur either below (M = Mg, Zn, Al, Li) or above (M = Pd, Pt, Ni) the reaction temperature. Hence the suprafacial mode of allylmetal additions permits a C—Pd → C—C chirality transfer and, regardless of the metal, controls the (*E*)/(*Z*) configuration of the vinylmetal moiety which results from an alkyne enophile. Employing alkenic enophile components (**B**) often leads to the generation of stereogenic centers in (**D**) which are linked by the new carbon–carbon bond. These are difficult to control since they depend on the (rapidly equilibrating) (*E*)/(*Z*) configuration of the allylmetal component (**A**) as well as on its orientation towards the enophile unit in the transition state. Several of these problems may be efficiently overcome by employing intramolecular versions which, consequently, are far more attractive and useful in organic synthesis. Given the lack of any comprehensive information, intermolecular metallo-ene reactions will be reviewed in the first part of this chapter.

## 1.2.2 INTERMOLECULAR METALLO-ENE REACTIONS

### 1.2.2.1 Magnesium-ene Reactions

Starting in 1970, the addition of allylic Grignard reagents (**A**; X = MgCl) to alkenes or alkynes has been systematically studied.[2] Kinetic measurements showed negative activation entropies of $\Delta S^{\ddagger} = -18$ to $-24$ cal K−1 $\mathrm{mol}^{-1}$ ($-75$ to $-100$ J $\mathrm{K}^{-1}$ $\mathrm{mol}^{-1}$).[2b] Further evidence for a concerted suprafacial reaction *via* transition state ($\mathbf{C}^{\ddagger}$; X = $\mathrm{MgL}_n$) (Scheme 1) was provided by the addition of 2-alkenylmagnesium halides (**1**) to 3,3-dimethylcyclopropene (**2**) at 0–20 °C; subsequent carboxylation with $CO_2$ yielded *cis*-2-allylcyclopropanecarboxylic acids (**3**) (Scheme 3).[2c] Given that the configuration of a cyclopropyl–magnesium bond is stable and is carboxylated ($CO_2$) with retention,[3] it thus follows that the allyl unit and the metal are transferred to the same face of cyclopropene (**2**) to furnish intermediates (**3**).

In contrast, bimolecular additions of allylmagnesium halides (**5**) to nonstrained alkenes (**6**) (Scheme 4; Table 1) are notoriously inefficient due to low reaction rates and the formation of regio- and stereoisomer mixtures, as well as uncontrolled consecutive reactions of the metallated addition products (**7**) and (**8**).[2] Only trimethylsilylethylene showed a useful reactivity towards allylic Grignard reagents[2f]

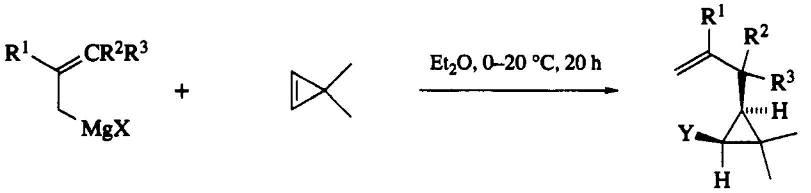

(1) $R^1, R^2, R^3$ = Me, H
X = Cl, Br

(2)

(3) Y = MgX
(4) Y = $CO_2H$
$CO_2$
51–67%

Scheme 3

(1,2-dialkyl-alkenes do not react at all). Therefore it is not surprising that the bimolecular magnesium-ene reaction has received little attention as a strategic tool in organic synthesis.

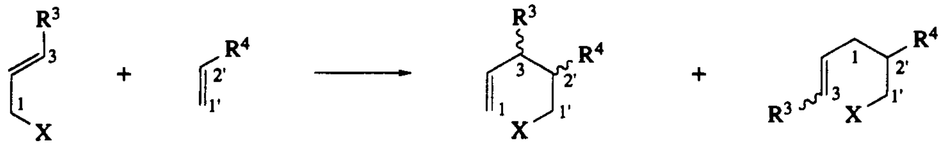

(5) (6)

(7) X = MgHal
(9) X = H
$H_2O$

(8) X = MgHal
(10) X = H
$H_2O$

Scheme 4

**Table 1** Additions of Allylmagnesium Halides to 1-Substituted Alkenes Followed by Protonolysis

| *Entry* | *$R^3$* | *$R^4$* | *Hal* | *Reaction temp. (°C) (time, h)* | *Yield*[a] *(9) + (10) (%)* | *Ratio (9):(10)* |
|---|---|---|---|---|---|---|
| 1 | H | $C_6H_{13}$ | Cl | 100 (48) | 2.5 (2) | 100:0 |
| 2 | Me | $C_6H_{13}$ | Cl | 100 (48) | 32 (11)[b] | 91:9[b] |
| 3 | H | CH=CH₂ | Br | 45 (96) | 25 (25)[c] | ~100:0[c] |
| 4 | H | Ph | Br | 100 (3) | 51 (25) | 28:72 |
| 5 | H | Ph | Br | 100 (6) | 39 (39) | 19:81 |
| 6 | H | $SiMe_3$ | Cl | 90 (48) | 47 (45) | 96:4 |
| 7 | Me | $SiMe_3$ | Cl | 90 (48) | 77 (77) | ~100:0 |

[a] Yield based on allylmagnesium halide (in parenthesis based on alkene). [b] (9) isolated as a stereoisomer mixture. [c] 2:1 mixture of 1,6- and 1,5-heptadienes.

### 1.2.2.2 Zinc- and Aluminum-ene Reactions

Preformed dicrotylzinc (**11**; $ML_n$ = Zn—CH=CHMe) underwent metallo-ene reactions with terminal alkenes under significantly milder conditions (20–50 °C) to give, after protonolysis, the alkenes (**14**) and (**15**) in 42–100% yield (Scheme 5; Table 2, entries 1–4). However, the regioselectivity was low on additions to 1,3-butadiene and styrene (entries 3, 4).[4]

Allylaluminum reagents, prepared *in situ* from triscrotylborane and triethylaluminum, showed a comparatively higher reactivity (–10 to 20 °C) and regioselectivity on additions to 1-butene, 1-hexene and styrene yielding, after methanolysis, alkenes (**14**) (entries 5–7, 50–55%).[5] Both zinc- and aluminum-ene reactions suffer from a lack of diastereochemical control.

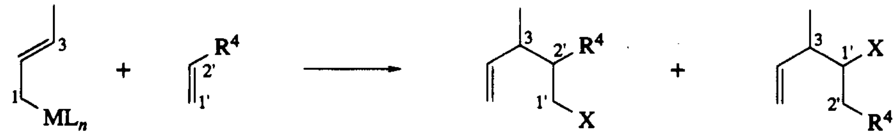

(11) (6)

(12) X = $ML_n$
(14) X = H
ROH

(13) X = $ML_n$
(15) X = H
ROH

Scheme 5

**Table 2** Metallo-ene Reactions of Dicrotylzinc and *In Situ* Prepared Allylaluminum Reagents with Alkenes Followed by Protonolysis

| *Entry* | *R* | *M* | *Reaction temp. (°C) (time, h)* | *Yield* (**14**) + (**15**) *(%)* | *Ratio* (**14**):(**15**) | *Diastereomer ratio of* (**14**) |
|---|---|---|---|---|---|---|
| 1 | H | Zn | 20 (20) | ~100 | 99.9:0.1 | — |
| 2 | $C_6H_{13}$ | Zn | 50 (20) | 85 | ~100:0 | 35:65 |
| 3 | Ph | Zn | 20 (66) | 42 | 33:67 | 75:25 |
| 4 | $CH{=}CH_2$ | Zn | 20 (43) | 81[a] | 42:58 | 52:48 |
| 5 | Et | Al | −10 | 50 | ~100:0 | 75:25 |
| 6 | Bu | Al | 0 (0.5) | 55 | ~100:0 | 67:33 |
| 7 | Ph | Al | 20 | 53 | 91:9 | 63:37 |

[a] Reaction mixture contains 3-methyl-1,5-heptadiene (10.2%).

Intermolecular additions of allylzinc halides (**16**) to silylated alkynes (**17**) are apparently facilitated by the silyl group (Scheme 6; Table 3). This substituent also governs the regiochemistry as it directs the metal transfer to the silylated carbon, yielding the non-isolated 1,1-dimetalloalkene products (**18**). Selective replacement of the zinc atom by iodination or protonolysis gave dienylsilanes (**19**) or (**20**).[6] These products may be useful in synthesis, as illustrated by the Pd-catalyzed carbon monoxide insertion sequence (**19a**) → (**21**).[6c] It is also worth mentioning that crotylzinc chloride (**16b**) formed the new C—C bond at the more substituted terminal C-3, in keeping with a six-centered transition state (C)[‡] (the presence of $Cp_2ZrCl_2$ led to exclusive C—C bond formation at C-1 which was attributed to a four-centered insertion mechanism[6a]). As to the (*E*)/(*Z*) configuration of the *gem*-dimetallated alkenic bond in (**18**), the products (**19**) and (**20**) indicate an initial *cis* addition process (entries 1–5); in contrast, the less-reactive branched enophiles (**17f–h**) require prolonged heating, which seems to result in a *cis*/*trans* isomerization of the intermediates (**18**) to furnish products corresponding to a net *trans* addition topicity (entries 6–8). The even more congested alkyne (**17i**) is completely unreactive (entry 9).

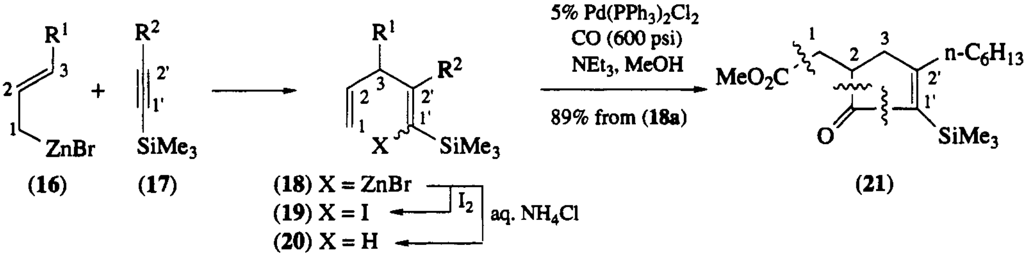

**Scheme 6**

**Table 3** Zinc-ene Reactions of 1-Trimethylsilylacetylenes

| *Entry* | *R¹* | *R²* | *Reaction temp. (°C)* | *Product* | *Yield*[a] *(%)* | *Stereoisomer ratio*[c] |
|---|---|---|---|---|---|---|
| 1 **a** | H | $(CH_2)_5Me$ | 60 | (**19a**) | 83 | 85:15 |
| 2 **b** | Me | $(CH_2)_5Me$ | —[b] | (**20b**) | 68 | 90:10 |
| 3 **c** | H | $(CH_2)_3Me$ | 67 | (**20c**) | 70 (85) | 85:15 |
| 4 **d** | H | $(CH_2)_3Cl$ | 67 | (**20d**) | 63 (80) | 81:19 |
| 5 **e** | H | Ph | r.t. | (**20e**) | (78) | >95:<5 |
| 6 **f** | H | $CH(OBn)(CH_2)_3Me$ | 67 | (**20f**) | (74) | <5:>95 |
| 7 **g** | H | $CH(OSiMe_3)(CH_2)_3Me$ | 67 | (**20g**) | (52) | <5:>95 |
| 8 **h** | H | $C(Me){=}CH_2$ | 67 | (**20h**) | (57) | <5:>95 |
| 9 **i** | H | $Bu^t$ | 67 | (**20i**) | 0 | — |

[a] Yields in parenthesis determined by GC. [b] Not reported. [c] $R^2/SiMe_3$ *cis:trans*.

A related approach to 1,1-dimetallated compounds relies on the allylation of 1-alkenyl-magnesium, -lithium, and -aluminum derivatives (**23**) with allylzinc bromides (**22**), which proceeds readily at 35 °C (Scheme 7; Table 4).[7] The resulting *gem*-dimetallic intermediates can be trapped by protonation (**24** → **26**, **25** → **29**), stannylation (**24** → **27**) or, more interestingly, with aldehydes in the presence of $BF_3{\cdot}OEt_2$ (*e.g.* **24a** → **28**). The dimetallated species (**24**) were also trapped with alkylidene malonates, $I_2/H_3O^+$, MeSSMe/$H_3O^+$ or MeSSMe/allyl bromides.[7c] Regarding the regioselectivity of the addition process, it appears that the nature of the C-3 substituent $R^2$ in the allylzinc bromides (**22**) may direct the enophile attack either to C-3 ($R^2$ = Me, OEt, entries 4, 5, 11) or to C-1 ($R^2$ = $SiMe_3$, entry 10).[7b]

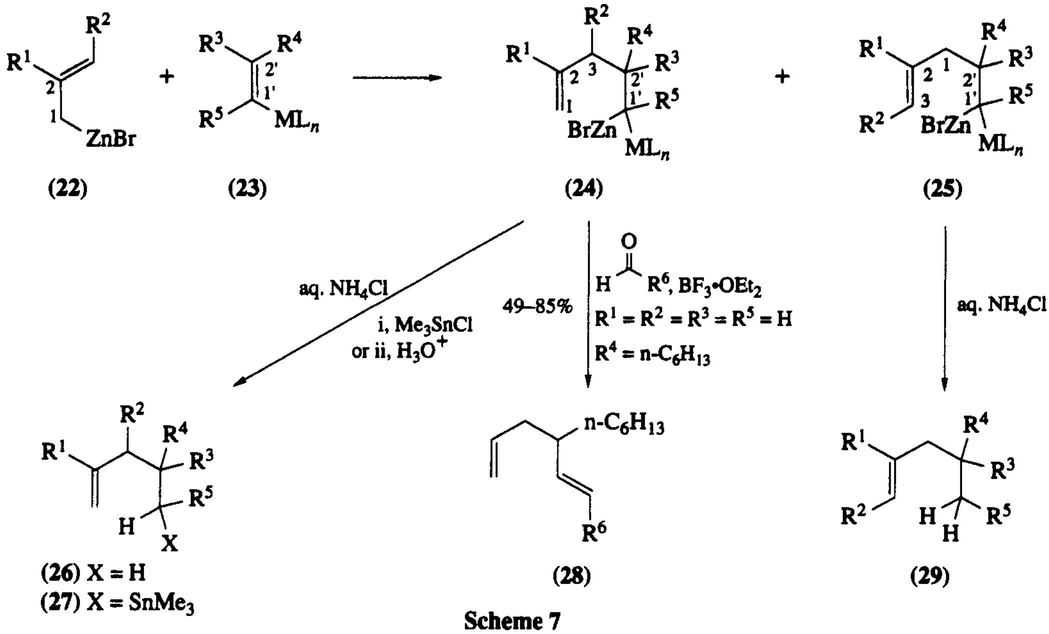
(22)
(23)
(24)
(25)
aq. NH4Cl
i, Me3SnCl
or ii, H3O+
49–85%
H(C=O)R6, BF3•OEt2
R1 = R2 = R3 = R5 = H
R4 = n-C6H13
aq. NH4Cl
(26) X = H
(27) X = SnMe3
(28)
(29)

**Scheme 7**

**Table 4** Additions of Allylzinc Bromides to 1-Alkenyl-magnesium, -lithium and -aluminum Derivatives

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *$R^4$* | *$R^5$* | *$ML_n$* | *Ratio* (**24**):(**25**) | *Final Product* | *Yield (%)* | *(E):(Z) ratio* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | H | $C_6H_{13}$ | H | MgBr | — | (**26**) = (**29**) | 93 | — |
| 2 **a** | H | H | H | $C_6H_{13}$ | H | MgBr | — | (**28**; $R^6$ = $C_5H_{11}$) | 75 | 94:6 |
| 3 **b** | Me | H | H | $C_6H_{13}$ | H | MgBr | — | (**26**) = (**29**) | 92 | — |
| 4 **c** | H | Me | H | $C_6H_{13}$ | H | MgBr | 100:0 | (**26**)[a] | 82 | — |
| 5 **d** | H | Me | H | H | $SiEt_3$ | MgBr | 100:0 | (**26**) | 83 | — |
| 6 **e** | H | H | Me | H | H | MgBr | — | (**26**) = (**29**) | 58 | — |
| 7 **f** | H | H | Me | Me | H | MgBr | — | (**27**) | 69 | — |
| 8 **g** | H | H | H | $C_6H_{13}$ | H | Li[b] | — | (**26**) = (**29**) | 90 | — |
| 9 **h** | H | H | $C_6H_{13}$ | H | H | $AlEt_2$ | — | (**26**) = (**29**) | 71 | — |
| 10 **i** | H | $SiMe_3$ | H | $C_6H_{13}$ | H | MgBr | 0:100 | (**29**) | 96 | 91:9 |
| 11 **j** | H | OEt | H | $C_6H_{13}$ | H | MgBr | 100:0 | (**26**)[a] | 65 | — |

[a] Diastereoisomer ratios of products (*E*:*Z* ratios of **23**): (**26c**), 70:30 (9:1); (**26j**), 86:14 (12:88). [b] Reaction conditions: 5 °C, 15 h.

### 1.2.2.3 Boron-ene Reactions

Triallylboranes (**30**) add to 1-methylcyclopropene (**31**) with participation of up to two allyl groups at low temperature in a *cis* fashion. The resulting isolable cyclopropylboranes (**32**) and (**33**) afforded *cis*-allylcyclopropanols (**34**) on methanolysis/oxidation (Scheme 8).[8]

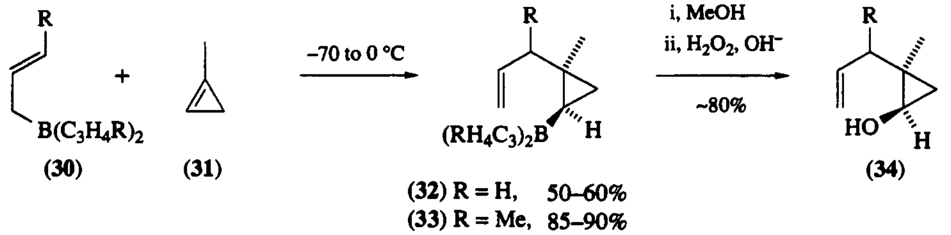
(30)
(31)
−70 to 0 °C
i, MeOH
ii, H2O2, OH−
~80%
(34)

(**32**) R = H, 50–60%
(**33**) R = Me, 85–90%

**Scheme 8**

Analogous boron-ene addition to enol ethers (**36**) requires 110–140 °C. Under these harsh conditions the initially formed 2-alkoxyboranes (**37**) undergo a spontaneous β-elimination to furnish 1,4-dienes (**38**) in good yields (Scheme 9; Table 5).[9] Application of this *cis*-metallo-allylation/*syn*-elimination sequence to cyclic enol ethers provides a stereocontrolled access to 1,4-dienols containing a trisubstituted alkenic bond, as illustrated by the transformation (**39**) + (**40**) → (**42**) (Scheme 9).

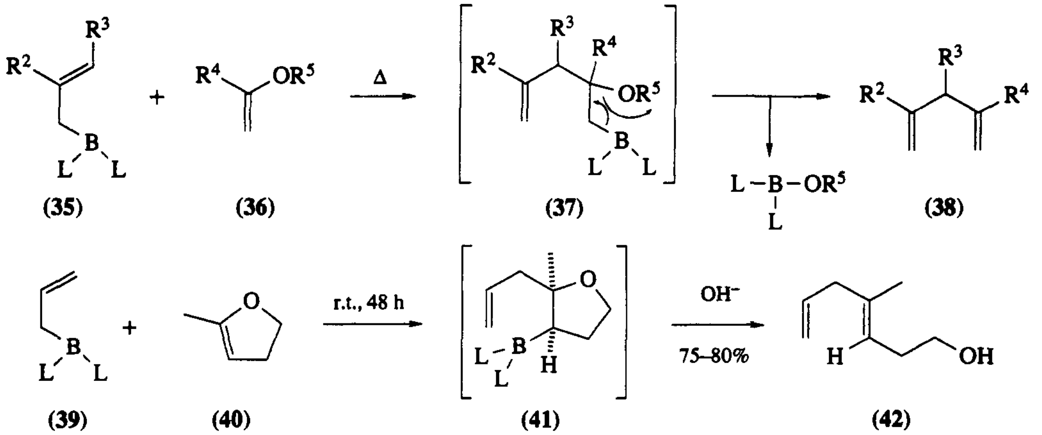

**Scheme 9**

**Table 5** Boron-ene Reactions of Enol Ethers: Preparation of 1,4-Dienes (**38**)

| *Entry* | $R^2$ | $R^3$ | $R^4$ | $R^5$ | *Reaction temp.* (°C) | *Yield (%)* |
|---|---|---|---|---|---|---|
| 1 **a** | H | H | H | Bu | 110–140 | 80 |
| 2 **b** | H | Me | H | Bu | 120–135 | 50 |
| 3 **c** | Me | H | H | Bu | 120–140 | 80–90 |
| 4 **d** | H | H | Me | Et | 135 | 75–85 |

Enophile activation by an alkoxy substituent was also observed with the particularly smooth and *cis* stereospecific additions of dialkylallylboranes (**43**) to ethoxyacetylene (**44**).[10] The resulting dienylboranes (**45**) are interesting polyfunctional building blocks and provide 2-ethoxy-1,4-dienes (**46**) or 1,4-enynes (**48**) (75–81%) by protonolysis or alumination/elimination (Scheme 10; Table 6).

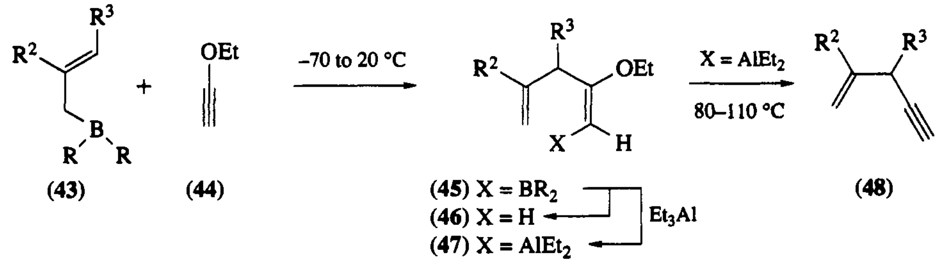

**Scheme 10**

**Table 6** Boron-ene Reactions of Ethoxyacetylene: Preparation of 2-Ethoxy-1,4-dienes and 1,4-Enynes

| *Entry* | $R^2$ | $R^3$ | *Reaction* (**43**) + (**44**) → (**45**) *temp.* (°C) | *Yield of* (**46**)[a] *(%)* | *Yield of* (**48**)[a] *(%)* |
|---|---|---|---|---|---|
| 1 **a** | H | H | −70 to 0 | 80–96 | 75 |
| 2 **b** | Me | H | −70 to 20 | 75–90 | 80 |
| 3 **c** | H | Me | 0 to 20 | 90–95 | 81 |

[a] Yield based on allylborane.

### 1.2.2.4 Palladium- and Nickel-ene Reactions

Metallo-ene reactions involving the transfer of palladium and nickel have been described since the early 1960s, mostly in connection with their crucial role in the Pd- and Ni-catalyzed polymerization of butadiene.[11] Hence, insertions of 1,3-dienes into allylpalladium compounds were extensively studied.[12] Thus preformed allylic complexes (**49**) underwent the metallo-ene reactions (**49**) → (**51**) at 20 °C (20 h) or 35 °C (<5 min) or 70 °C (1 h); the reaction rate depended on the substituents $R^1$ and $R^2$ as well as on the ligand L and decreased in the order $R^1$ = Cl > H > Me; $R^2$ = H > Me; L = $F_6$acac > acac > Cl. Further diene insertion into the resulting allylpalladium product (**51**) (polymerization) was generally slower than the initial step (**49**) → (**51**) and again relies on the nature of the ligand L (Scheme 11).[12b]

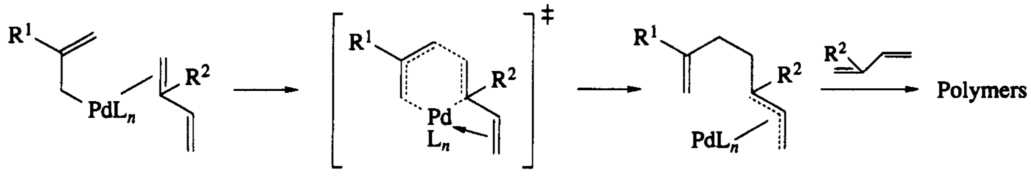

(**49**) (**50**)‡ (**51**)

Scheme 11

Additional regio- and stereo-chemical information was obtained from palladium-ene reactions of strained alkenes. An instructive example is the reaction of stoichiometric amounts of the allylpalladium species (**52**) which undergo rapid, reversible formation of the σ-allylpalladium–norbornadiene complexes (**53**) to give at 37 °C the *cis* insertion products (**54**) (Scheme 12). Carbon–carbon bond formation (at the least substituted allyl terminal) and palladium transfer from the same (*exo*) face of norbornadiene were ascribed[13] to a σ-allypalladium alkene insertion.

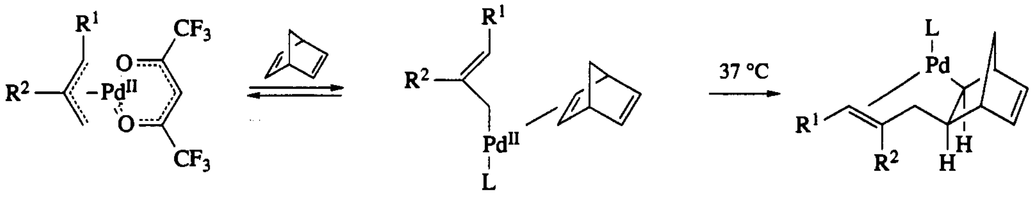

(**52**) (**53**) L = hexafluoroacetylacetonate (**54**)

Scheme 12

An analogous regio- and stereo-selectivity characterizes the palladium-ene reaction (**55**) + (**56**) → (**57**) which, *via* a coupling of the isolated σ-Pd product (**57**) with the lithium acetylide (**58**), afforded the prostaglandin endoperoxide analogue (**59**) (Scheme 13).[14]

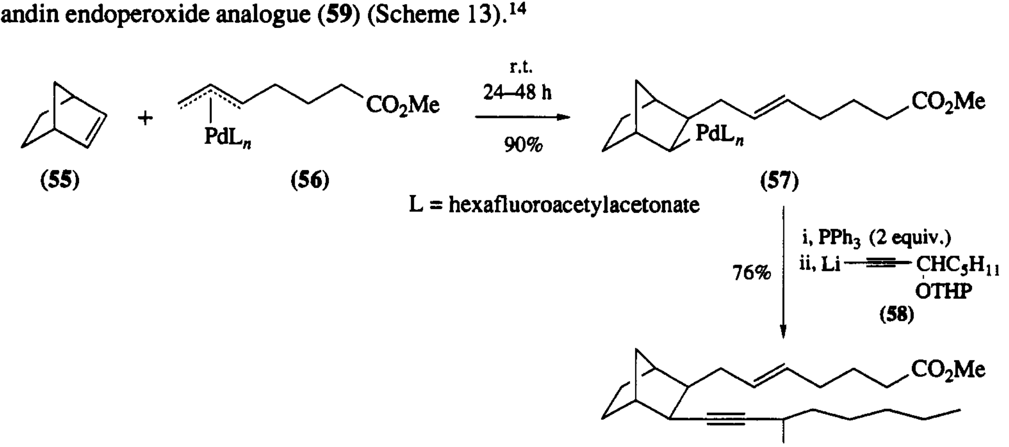

(**55**) (**56**) (**57**)

L = hexafluoroacetylacetonate

Scheme 13 (**59**)

Allylnickel species undergo analogous additions to strained alkenes, as exemplified by the *cis* stereospecific metallo-allylation/methoxycarbonylation of norbornene, **(60)** → **(61)** → **(62)**, employing a stoichiometric amount of 2-methallylnickel chloride (Scheme 14).[15] The nickel-catalyzed allylation **(60)** → **(61)** was accomplished on heating allyl acetate, norbornene and $Ni\{P(OPr^i)_3\}_4$ (2 mol %) in THF. The isolated products **(64)** and **(65)** (80% overall) result apparently from **(61)** *via* carbometallation, retrocarbometallation and β-elimination processes.[16]

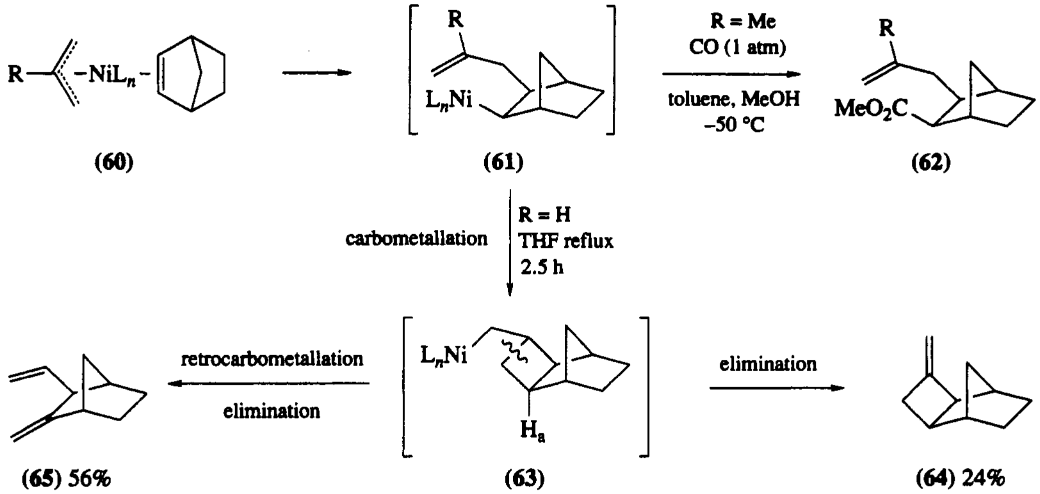

**Scheme 14**

Tetracarbonylnickel is an inexpensive (although toxic) source of $Ni^0$ and its use for the *in situ* generation of allylnickel intermediates dates back at least 25 years. In fact, the nickel allylation/methoxycarbonylation of alkynes with allyl chloride and an excess of $Ni(CO)_4$ in methanol has been reviewed (Scheme 15).[17] Accordingly, dienoates **(68)** (35–80%) were obtained in a regio- and stereo-selective manner corresponding to a metallo-ene *cis* addition of an allylnickel compound at the less-substituted terminal C-1 of **(67)**, followed by a CO insertion into the resulting vinylnickel species. The dienyl esters **(68)** were accompanied by variable amounts of cyclopentenones, indicating the possibility of consecutive CO insertion processes.

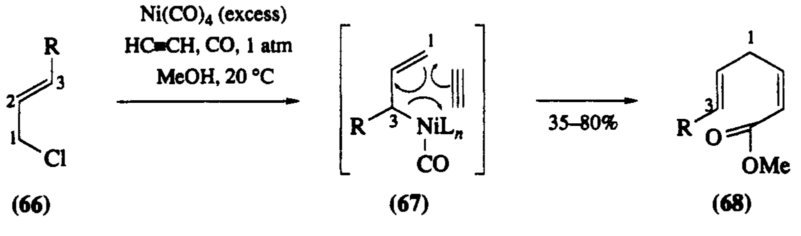

**Scheme 15**

A recent synthesis of methylenomycin-B **(74)**, based on these observations, features an allylation/carbonylation **(69)** → **(70)** followed by a C-1—C-2 bond/nickel acyl insertion **(70)** → **(71)** and a final methoxycarbonylation **(71)** → **(72)**. Thus 2-butyn-1-ol (1,2-dialkylacetylenes are inert) afforded in one synthetic operation a 1:4 mixture (78%) of regioisomeric cyclopentenones **(72)** and **(73)** which was converted to the antibiotic **(74)** (Scheme 16).[18]

An interesting example of anchimeric assistance is the catalytic isomerization of allyl 3-butenoate **(75)** to (*E*)-2,6-heptadienoic acid **(78)**, which proceeded at 20 °C with 4 mol % of an equimolar mixture of $Ni(COD)_2/P(OPr^i)_3$. It seems that the appropriately placed carboxylate substituent serves as a ligand for $Ni^{II}$, facilitating the transformation **(76)** → **(77)**; a subsequent β-elimination of $H_a$ leads to **(78)** with concomitant regeneration of the $Ni^0$ catalyst (Scheme 17).[19]

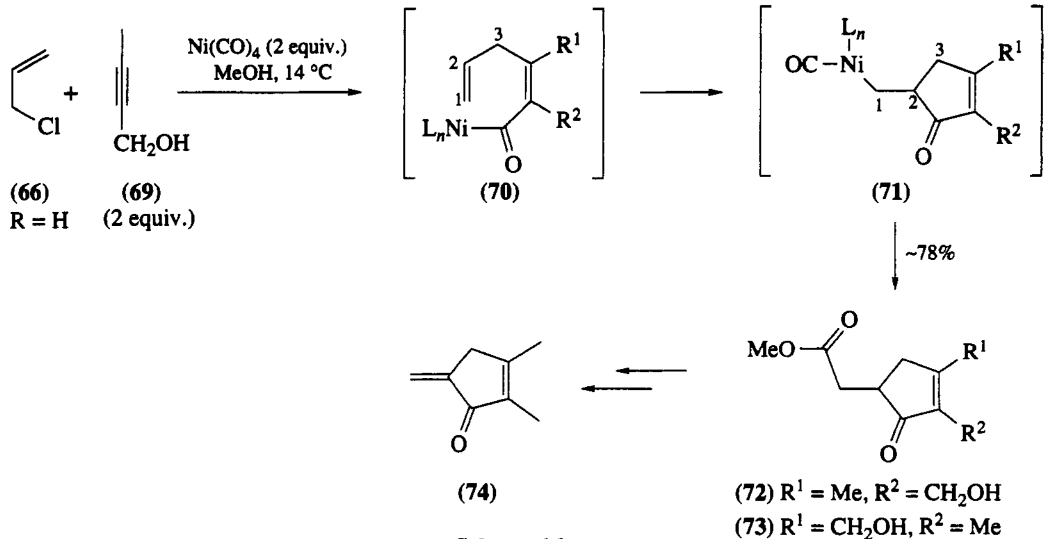

**Scheme 16**

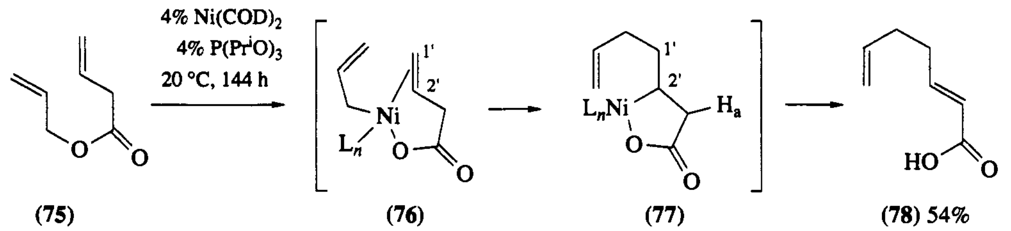

**Scheme 17**

## 1.2.3 INTRAMOLECULAR METALLO-ENE REACTIONS

### 1.2.3.1 General

Intermolecular metallo-ene reactions have received until now virtually no attention as a method in target-oriented organic synthesis despite the extensive work and interesting prospects. Problems of regio- and stereo-selectivity and overall efficiency seem to limit their applicability to specifically activated enophiles.

In contrast, intramolecular versions of the metallo-ene process may be regio- and stereo-selective as well as entropically favored and are thus more efficient, similar to intramolecular ene reactions (Volume 5, Chapter 1.1)[20] and [4 + 2] cycloadditions (Volume 5, Chapter 4.4).[21] This holds for two different modes of cyclization in which the enophile is linked by a suitable bridge, either to the terminal carbon atom C-3 (type I) or to the central carbon atom C-2 (type II) of the metallo-ene unit (Scheme 18). The propensity of the cyclized alkylmetal intermediates (**F**) and (**H**) for further functionalizations and cyclizations, involving the metallated and two alkenic sites, offers a considerable potential in organic synthesis.

### 1.2.3.2 Intramolecular Magnesium-, Zinc- and Lithium-ene Reactions

Essential for the practicality of (inter- and) intra-molecular magnesium-ene processes was a convenient preparation of the 2-alkenylmagnesium precursors (**E**) and (**G**) (Scheme 18, with metal = Mg). In particular, the conventional treatment of allylic halides with Mg turnings in Et$_2$O frequently led to coupling products, *e.g.* (**79**) → (**80**) (Scheme 19).

Magnesium, activated by evaporation[22a] or, much more conveniently, by sonication with anthracene (5%),[22b] usually accomplished the metallation of 2-alkenyl chlorides, *e.g.* (**79**) → (**81**), at –65 °C in THF

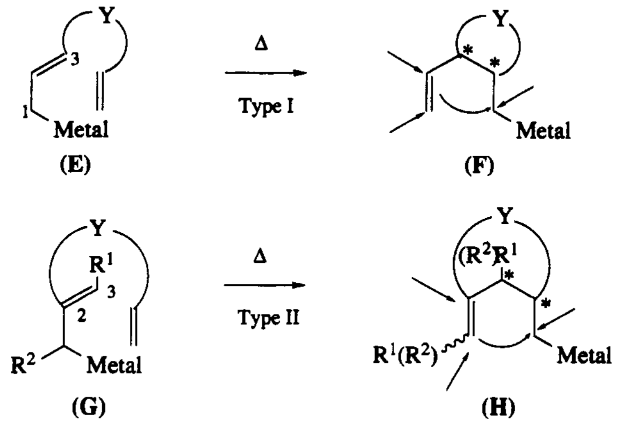
Y
3
1
Metal
(E)
Δ
Type I
Y
Metal
(F)
Y
R1
3
2
R2
Metal
(G)
Δ
Type II
Y
(R2)R1
R1(R2)
Metal
(H)

Type I : enophilic chain linked to terminal carbon of ene unit (C-3)
Type II : enophilic chain linked to central carbon of ene unit (C-2)

**Scheme 18**

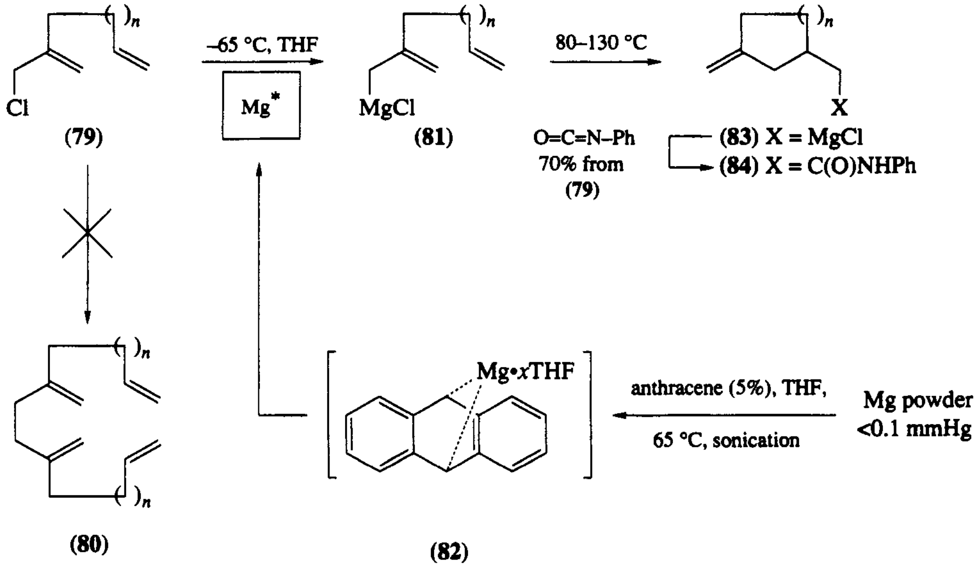
)n
Cl
(79)
–65 °C, THF
Mg*
)n
MgCl
(81)
80–130 °C
O=C=N-Ph
70% from
(79)
)n
X
(83) X = MgCl
(84) X = C(O)NHPh
)n
)n
(80)
Mg•xTHF
(82)
anthracene (5%), THF,
65 °C, sonication
Mg powder
<0.1 mmHg

**Scheme 19**

without significant coupling.[22c] The resulting clean, alkali metal and alkali halide free solutions of Grignard reagents (**81**) are compatible with the thermal cyclization/trapping sequence (**81**) → (**83**) → (**84**).[22c]

### *1.2.3.2.1 Type I cyclizations*

#### *(i) Initial Studies*

The first encouraging example of an intramolecular type I magnesium-ene reaction dates back to 1972. As described by Felkin *et al.*, [23a] 2,7-octadienylmagnesium bromide (**85**) cyclized in boiling $Et_2O$ to give, after aqueous work-up, selectively *cis*-2-methylvinylcyclopentane (**88**) in 67% yield (Scheme 20). Heating the solution of the transient Grignard product (**87**) to 110 °C (sealed tube, 24 h) furnished, after hydrolysis, mainly the thermodynamically more stable *trans*-cyclopentane (**90**) (**90**:**88** > 11:1), indicating the reversibility of the cyclization (**85**) ↔ (**87**) at a higher temperature.[23b] It is worth noting that (**85**) could be obtained *in situ* from 1,3-butadiene, $Pr^nMgBr$ and $(PPh_3)_2NiCl_2$ (2 mol %) and that (**87**) and (**89**) were also trapped by $D_2O$ or acetone. The conversion (**85**) → (**87**) was also reported in a patent.[23c]

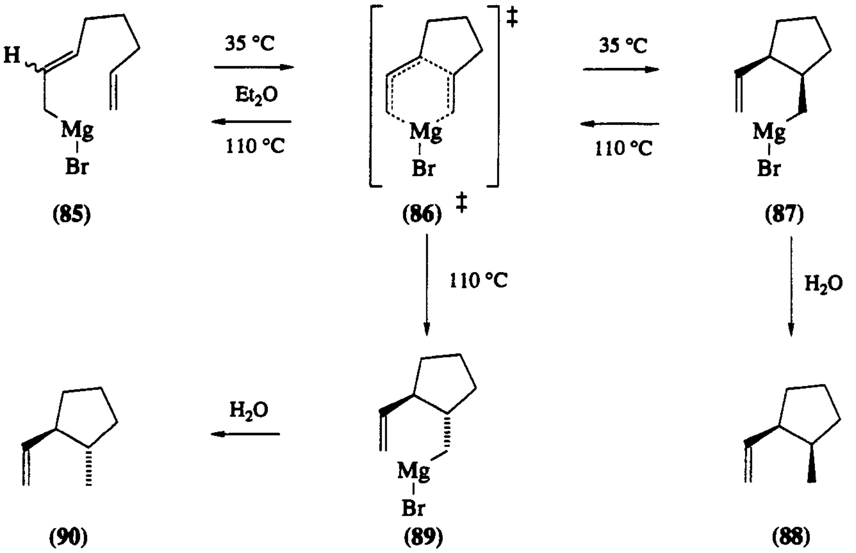
35 °C
Et$_2$O
110 °C
‡
35 °C
110 °C
110 °C
H$_2$O
H$_2$O
(85)
(86) ‡
(87)
(90)
(89)
(88)

Scheme 20

Two years later, the transformation of the isoprene dimer (**91**) to (**94**) (mixture of stereoisomers) was observed and interpreted as a conjugate addition of Bu$^n$Li to diene (**91**) followed by a (surprisingly smooth) intramolecular lithium-ene addition (**92**) → (**93**) (Scheme 21).[24]

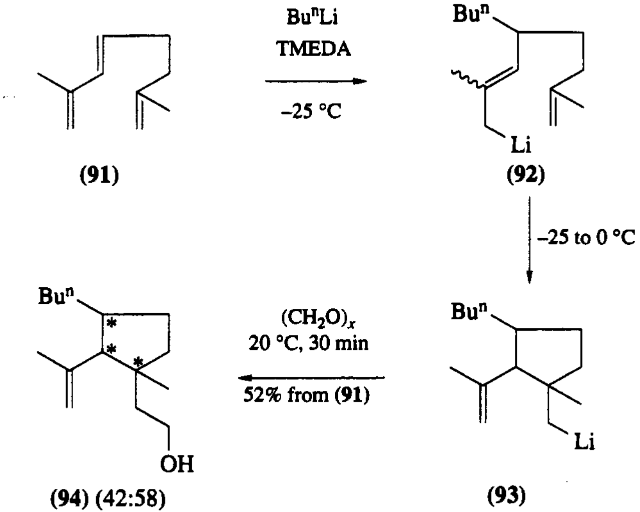
Bu$^n$Li
TMEDA
−25 °C
−25 to 0 °C
(CH$_2$O)$_x$
20 °C, 30 min
52% from (91)
(91)
(92)
(93)
(94) (42:58)

Scheme 21

A comparative study demonstrated the moderate efficiency of a metallation/cyclization/hydrolysis reaction sequence of enynyl bromides, (**95**) + (**96**) → (**97**), which obviously implies intramolecular zinc- and magnesium-ene additions to a terminal alkyne unit (Scheme 22; Table 7).[25]

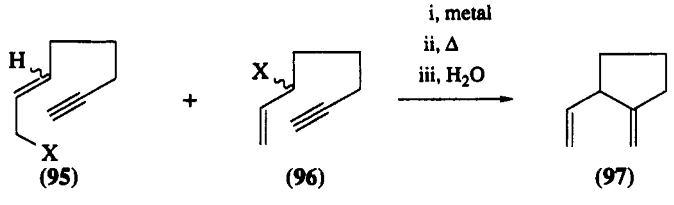
i, metal
ii, Δ
iii, H$_2$O
(95)
(96)
(97)

Scheme 22

**Table 7** Intramolecular Zinc- and Magnesium-ene Reactions of Alkynes

| *Leaving Group* *X* | *Metal* | *Solvent* | *Temp.* (°C) *(time,* h*)* | *Yield* (97) *(%)* |
|---|---|---|---|---|
| Br | Zn | THF | 20 (2) | 43 |
| Br | Mg | $Et_2O$ | reflux (2) | 15 |

*(ii) Applications to Syntheses of Natural Products*

After these more or less isolated reports it was the challenge of natural product synthesis that spurred the most relevant exploration and extensions of the intramolecular magnesium-ene reaction. Its strategic role in synthesis is also illustrated by the following examples.

The synthesis of $\Delta^{9(12)}$-capnellene (**103**), published in 1982,[26] addressed the issue of rendering this process iterative to assemble progressively polycyclopentanoid systems (Scheme 23). Thus in the first key step (**99**) → (**100**) the congested bond between C-4 and C-11 was formed with high stereochemical control, whilst trapping of the cyclized Grignard intermediate with acrolein set the stage for the second magnesium-ene cyclization which occurs at room temperature. Scavenging the bicyclic magnesium-ene product with oxygen furnished alcohol (**102**) as a 3:2 mixture of stereoisomers. This kinetically derived lack of diastereoselection was of minor importance since the remaining closure of ring c was accomplished by an intramolecular aldolization with thermodynamic control over the configuration at C-6 and/or at C-10. Hence the mixture (**102**) was channelled efficiently into the pure *cis-anti-cis*-triquinane (**103**).

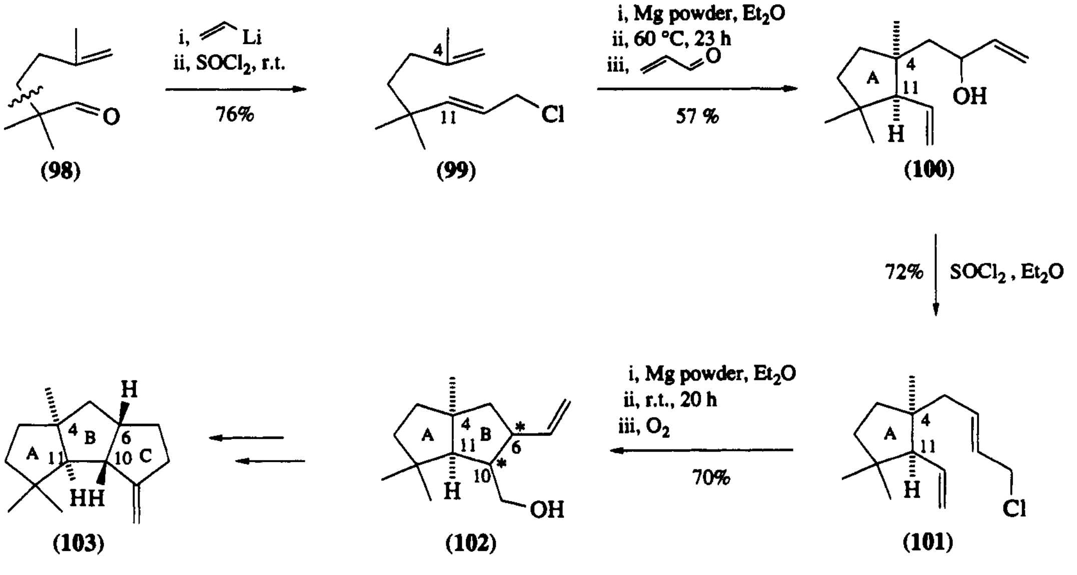

Scheme 23

Highly diastereocontrolled formation of a *cis*-1,2-disubstituted five-membered ring was again observed in the key step (**105**) → (**106**) of the synthesis of (±)-6-protoilludene (**111**) (Scheme 24).[27] Copper-promoted trapping of the cyclized organomagnesium species (**106**) by 1,4-addition to methyl 2-butynoate furnished the conjugated ester (**107**) in one synthetic operation from (**104**) (76%). The thus generated 1,2-*cis*-disposed functionalities in (**107**) were ideally suited to form the remaining six- and four-membered rings simultaneously by an intramolecular vinylketene/alkene cycloaddition (**108**) → (**109**) (*cf.* Volume 5, Chapter 2.1). The carbonyl group in (**109**) (chromatographically purified) furthermore directed the alkene bond into the 6/7-position (instead of the otherwise favored 7/8-position). Although the [2 + 2] addition (**108**) → (**109**) did not show the desired high stereoselectivity, this approach to the protoilludene skeleton (**109**) in only 2–3 synthetic operations from the readily available acyclic diene (**104**) exemplifies the general potential of magnesium-ene cyclizations when coupled with cycloaddition processes.

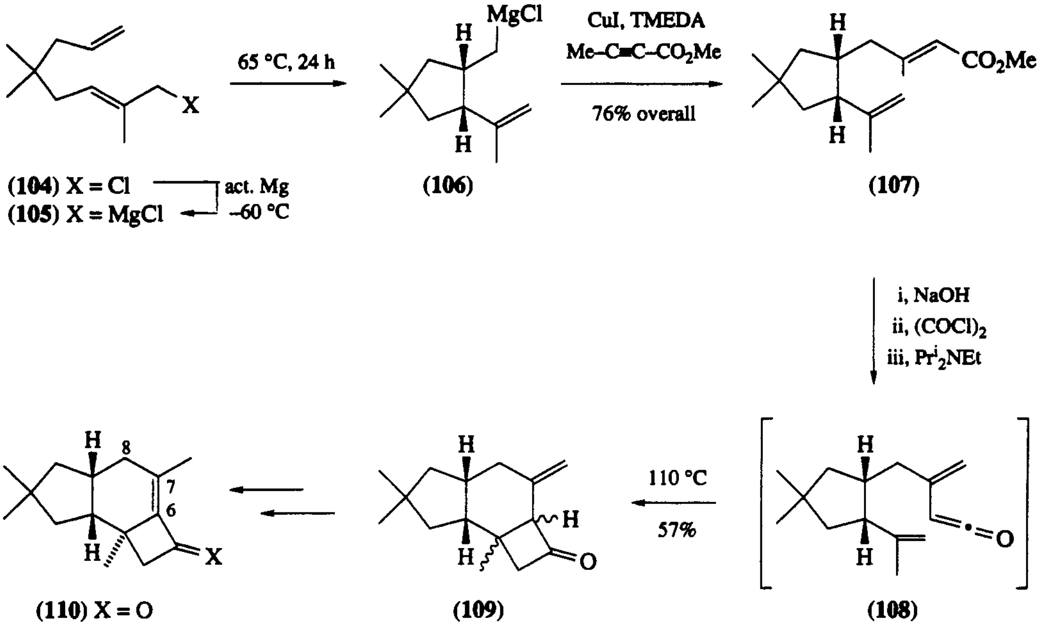

Scheme 24

Another approach to an unusual sesquiterpene, sinularene (**116**),[28] involves the diastereocontrolled formation of a six-membered ring by a magnesium-ene process (Scheme 25). Successive treatment of allylic chloride (**112**) with activated magnesium, heating to 50 °C and $CO_2$ trapping led to the formation of the bond between C-5 and C-6 as well as that between C-7 and C-15, giving the crystalline carboxylic acid (**115**) (47% overall) in a single operation. In this case, however, the kinetically controlled *cis* relation of magnesium donor and acceptor sites in (**114**) required an epimerization at C-5 at a later stage of the synthesis of the target molecule (**116**).

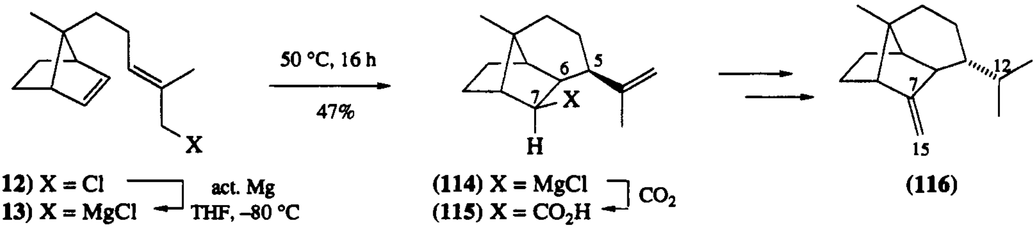

Scheme 25

A related synthesis of 12-acetoxysinularene (**122**)[29] differs in that the magnesium-ene unit is part of the norbornene skeleton which carries the enophilic chain at C-2 (Scheme 26). Hence, by reversing the relative position of the reaction partners the bond between C-5 and C-6 was closed in the key step (**119**) → (**120**) with simultaneous formation of both the C-7/C-15 methylene group and the C-12 Mg functionality. Accordingly, one synthetic operation provided alcohol (**121**) in 62% yield from allyl chloride (**118**) (again the initial *cis* relation of C-12/C-7 was altered thereafter by an epimerization at C-5).

The stereodirecting bias of a preexisting stereogenic center on the intramolecular magnesium-ene reaction is illustrated by the enantioselective syntheses of (+)-α-skytanthine (**130**) and (+)-δ-skytanthine (**131**), as well as of (+)-iridomyrmecine (**132**) (Scheme 27).[30] Allylic chloride (**123**), easily available in 94% enantiomeric purity, was metallated with commercial Mg powder. Heating of the resulting solution under reflux followed by oxidative trapping of (**125**) with MoOPH at –78 °C yielded an 88.4:5.9:3.0:1.4 stereoisomer mixture of cyclized alcohols (58%). The major isomer (**126**), isolated by flash chromatography (49% from (**123**), has the desired (4a*S*,7a*R*) configuration. This result is consistent with a favored transition state (**124**)‡ (with the C-7 methyl group oriented toward the convex face) assuming that 2,3-substituted 2-alkenylmagnesium halides react in their (*Z*)-form (*cf.* Section 1.2.3.2.2 (i)). Stereoconvergent control over the remaining center C-4 was achieved by hydroboration ($BH_3$)/oxidation of the free

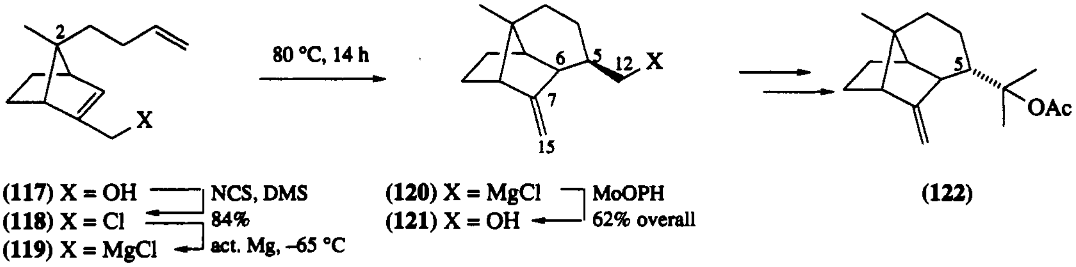
2
X
80 °C, 14 h
6
5
12
X
7
15
OAc
5
(117) X = OH
(118) X = Cl
(119) X = MgCl
NCS, DMS
84%
act. Mg, –65 °C
(120) X = MgCl
(121) X = OH
MoOPH
62% overall
(122)

Scheme 26

alcohol (**126**) to give diol (**128**), which was cyclized to give (+)-α-skytanthine (**130**); alternatively, hydroboration (BBN)/oxidation of the benzoate (**127**) furnished predominantly the C-4 epimer (**129**) which was transformed either to (+)-δ-skytanthine (**131**) or to (+)-iridomyrmecine (**132**).

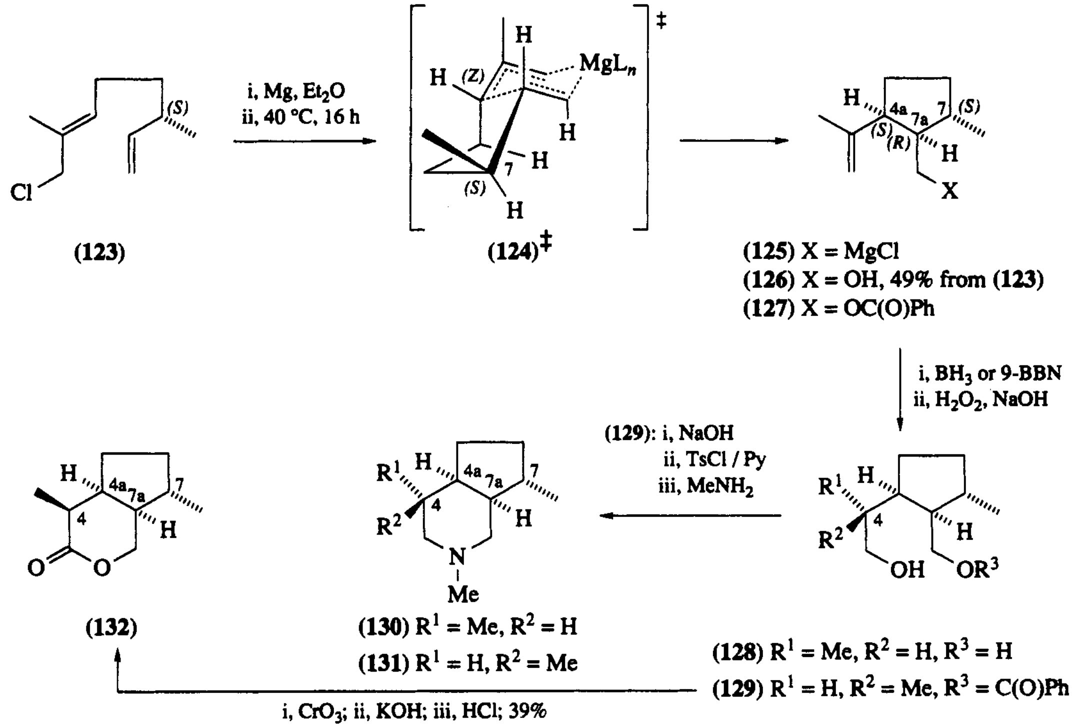
Cl
(S)
(123)
i, Mg, Et₂O
ii, 40 °C, 16 h
H
H
(Z)
MgLₙ
H
H
7
(S)
H
‡
(124)‡
H
4a
7a
7
(S)
(S)
(R)
H
X
(125) X = MgCl
(126) X = OH, 49% from (123)
(127) X = OC(O)Ph
i, BH₃ or 9-BBN
ii, H₂O₂, NaOH
R¹
H
R²
4
OH
OR³
H
(128) R¹ = Me, R² = H, R³ = H
(129) R¹ = H, R² = Me, R³ = C(O)Ph
(129): i, NaOH
ii, TsCl / Py
iii, MeNH₂
R¹
H
4a
7a
7
R²
4
H
N
Me
(130) R¹ = Me, R² = H
(131) R¹ = H, R² = Me
H
4a
7a
7
4
H
O
O
(132)
i, CrO₃; ii, KOH; iii, HCl; 39%

Scheme 27

Whereas all foregoing applications rely on a kinetically determined stereoselectivity of magnesium-ene cyclizations, it is apparently thermodynamic control which governs the cyclization (**134**) → (**135**) at 138 °C over 61 h to give, after oxidative quenching with $O_2$, an 83:8:9 mixture of stereoisomers. The major '*all-trans*' alcohol (**136**) was converted to the dimethyl ester of *trans,trans*-boschnialic acid (**137**) (Scheme 28).[31]

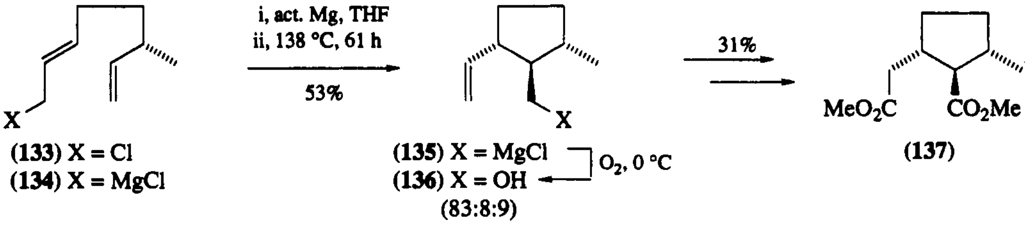
X
(133) X = Cl
(134) X = MgCl
i, act. Mg, THF
ii, 138 °C, 61 h
53%
X
(135) X = MgCl
(136) X = OH
(83:8:9)
O₂, 0 °C
31%
MeO₂C
CO₂Me
(137)

Scheme 28

### *1.2.3.2.2 Type II cyclizations*

#### *(i) Type II Magnesium-ene Cyclizations*

This version, in which the enophilic chain is attached to the central atom C-2 of the metallo-ene moiety, was not described until 1982. A systematic investigation dealing with the efficiency, regio- and stereo-selectivity of this reaction (Scheme 29; Table 8)[32] involved heating (2-alkenyl)allylmagnesium chlorides (**81**) followed by quenching of the cyclized Grignard reagents with phenyl isocyanate (entries 1–5) or water (entry 6). It is worth noting that a six-membered ring (entries 2, 5, 6) was formed more readily than a five-membered (entry 1) or a seven-membered ring (entry 4), reflecting the counterplay of entropic and angle strain factors.

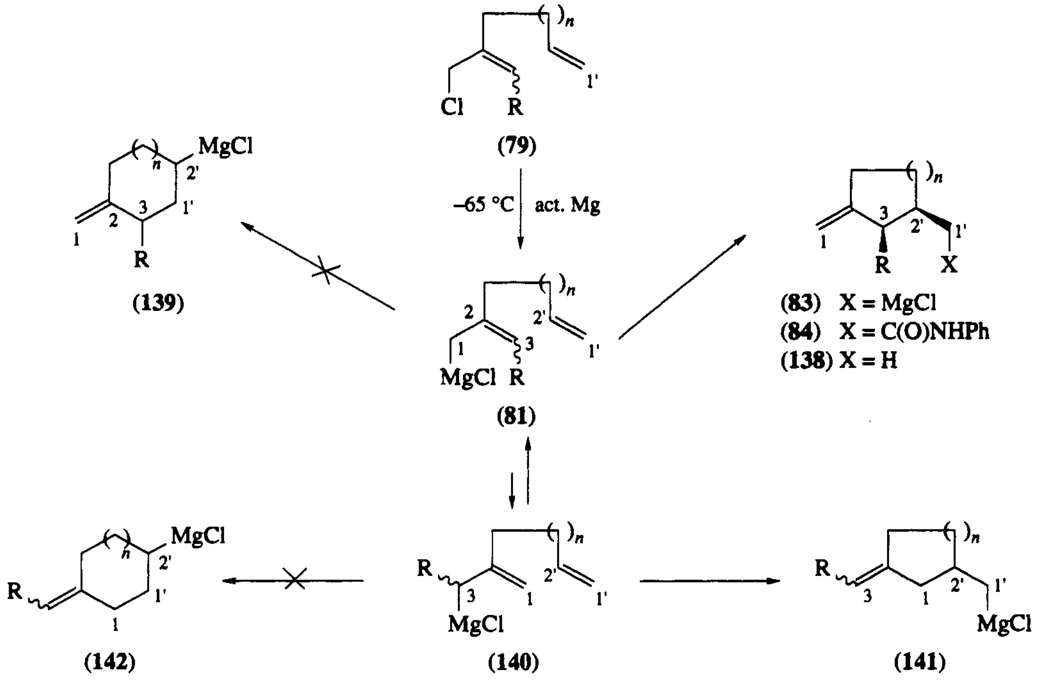

**Scheme 29**

**Table 8** Intramolecular Type II Magnesium-ene Reactions (**79**) → [(**81**) → (**83**)] → (**84**) or (**138**)

| *Entry* | *Bridge length* *n* | *R* | *Temp.* (°C) (*time*, h) | *Product* | *Yield* (*%*) |
|---|---|---|---|---|---|
| 1 **a** | 1 | H | 130 (23) | (**84**) | 71 |
| 2 **b** | 2 | H | 80 (17) | (**84**) | 72 |
| 3 **c** | 3 | H | 80 (17) | (**84**) | 71 |
| 4 **d** | 3 | Me | 90 (60) | (**84**) | 40[a] |
| 5 **e** | 2 | Me | 80 (17) | (**84**) | 86 |
| 6 **f** | 2 | n-$C_6H_{13}$ | 80 (17) | (**138**) | 81 |

[a] 20% of noncyclized dienylanilide isolated.

This study also revealed an astonishing regioselectivity insofar as only products (**84**) or (**138**) (but no isomers derived from **139** or **142**) were observed regardless of the distance between the reactive units. Accordingly, the magnesium was transferred to the distal site C-1′ of the enophile and the new C—C bond was formed at the proximal C-2′ site. As to type II cyclizations of nonsymmetrically substituted magnesium-ene species (entries 4–6), a rapid 1,3-metal migration (**81**) ⇌ (**140**) (*cf.* Scheme 2)[33] leaves two possibilities: C—C bond formation with either the more or less substituted ene terminal C-3 (**81** → **83**) or C-1 (**140** → **141**), of which only the former regiochemistry was observed. Also the 3,3-dimethyl-substituted magnesium-ene component of (**144**) underwent C—C bond formation only to C-3, generating a quaternary center to give (**146**; 80%) (Scheme 30).

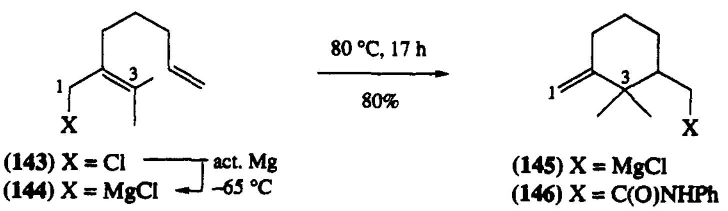
1
3
X
80 °C, 17 h
80%
1
3
X
(143) X = Cl
(144) X = MgCl
act. Mg
–65 °C
(145) X = MgCl
(146) X = C(O)NHPh

Scheme 30

Focusing on the stereochemistry, it is interesting to note that only *cis* isomers (**84**) and (**138**) were observed; this indicates highly selective alkene 'insertion' into a (*Z*)-ene unit (**81**) (Scheme 31) which is in a rapid equilibrium with (*E*)-(**81**) (*via* the 1,3-Mg shift, **81** ⇌ **140**).

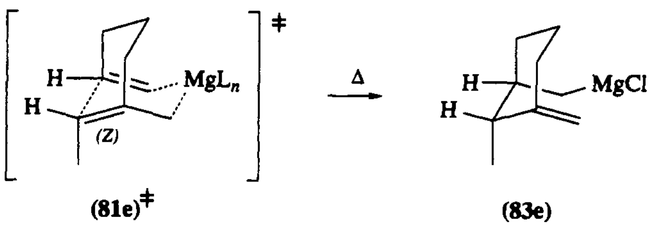
H
H
MgL$_n$
(Z)
‡
Δ
H
H
MgCl
(81e)‡
(83e)

Scheme 31

This type of stereocontrol is featured in a synthesis of the fungitoxin (±)-chokol-A (**156**) (Scheme 32).[34] Alcohol (**147**) (easily prepared from 1-hexen-5-one in two steps) efficiently gave the allyl chloride (**148**) ($CCl_4/PBu_3$). The metallation/cyclization/oxidation step (**148**) → (**149**)‡→ (**150**) → (**151**) (described in detail) furnished *cis*-cyclopentylmethanol (**151**) (64% from **148** together with 2% of its *trans* epimer and 6% of a positional isomer derived from **141**) which was oxidized to *cis*-carboxylic acid (**152**). Iodolactonization/reduction (**152**) → (**153**) → (**154**) secured the desired *cis* disposition of the *t*-hydroxy (C-1) and *s*-methyl (C-2) groups. Basic methanolysis of lactone (**154**), accompanied by C-3 epimerization, furnished (**155**) with a *trans*-related C-3 methoxycarbonyl substituent which was transformed into the pentenol side chain of (**156**).

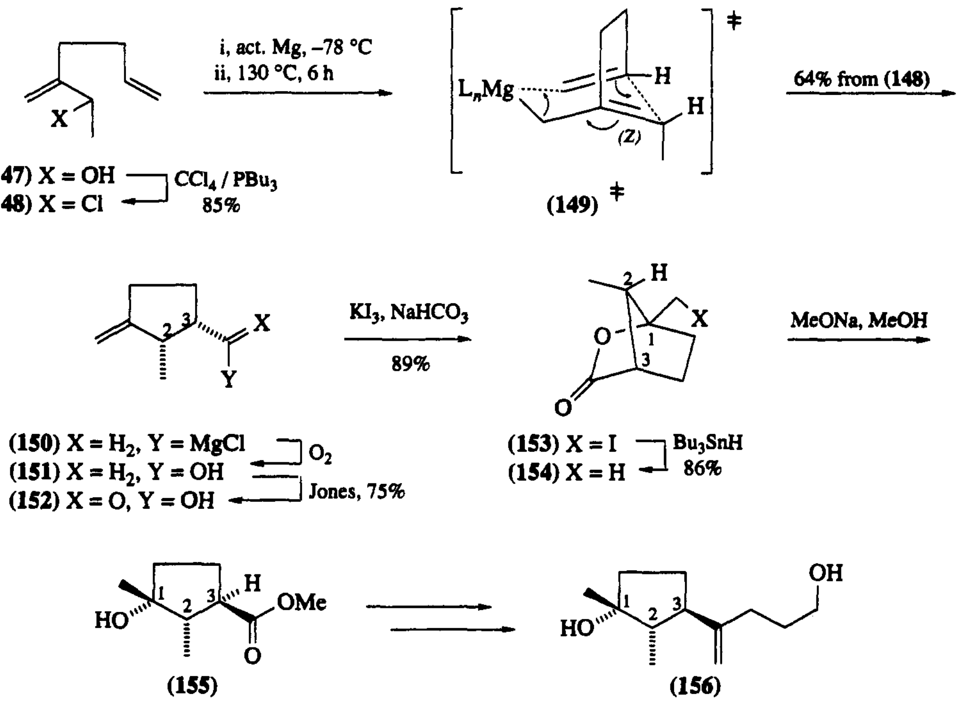
X
i, act. Mg, –78 °C
ii, 130 °C, 6 h
L$_n$Mg
H
H
(Z)
‡
64% from (148)
(147) X = OH
(148) X = Cl
CCl$_4$ / PBu$_3$
85%
(149) ‡
2
3
X
Y
KI$_3$, NaHCO$_3$
89%
2
H
X
O
1
3
O
MeONa, MeOH
(150) X = H$_2$, Y = MgCl
(151) X = H$_2$, Y = OH
(152) X = O, Y = OH
O$_2$
Jones, 75%
(153) X = I
(154) X = H
Bu$_3$SnH
86%
HO
1
2
3
H
OMe
O
HO
1
2
3
OH
(155)
(156)

Scheme 32

By contrast, no diastereoselectivity was found in the type II magnesium-ene cyclization/oxidation **(158)** → **(159)** → **(160)**, which afforded the carrion beetle defense compound β-necrodol **(160a)** together with its C-1 epimer **(160b)** (61%, 1:1 mixture) (Scheme 33).[35] This is not surprising since the corresponding transition states suffer similar steric crowding due to the *gem*-dimethyl substitution. Nevertheless, (*R*)-**(157)**, obtained in enantiomerically pure form *via* a methylcopper addition/Mannich reaction of a chiral *N*-crotonoylsultam, provided, after separation from **(160b)**, optically pure β-necrodol **(160a)**, thus enabling an assignment of the absolute configuration of the natural product.

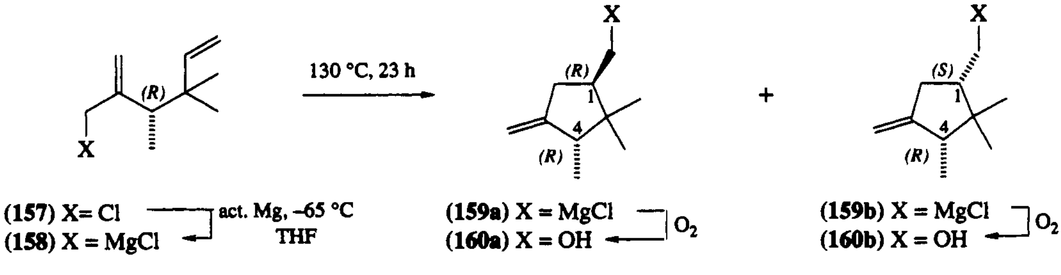
(R)
X
130 °C, 23 h
X
(R)
1
4
(R)
+
X
(S)
1
4
(R)
(157) X= Cl
(158) X = MgCl
act. Mg, –65 °C
THF
(159a) X = MgCl
(160a) X = OH
O₂
(159b) X = MgCl
(160b) X = OH
O₂

Scheme 33

A culmination of the type II magnesium-ene cyclization methodology is its ideal application to the regio-, diastereo- and enantio-selective synthesis of the otherwise elusive, odoriferous norsesquiterpene (+)-khusimone **(168)** (Scheme 34).[36] Conjugate addition of a chiral dienolate **(161)** to cyclopentenone, coupled with enolate trapping by allyl bromide, chromatography and crystallization, directly gave enantiomerically pure **(162)** (37% from cyclopentenone), which was readily converted into allylic chloride **(164)**. Slow addition of **(164)** to Mg powder in THF, heating the solution at 60 °C for 17 h and quenching with $CO_2$ gave, after crystallization, bicyclic carboxylic acid **(167)** (85% from **164**). No regio- or stereo-isomer of **(167)** was found in the mother liquor. This particularly strong bias of the preexisting centers C-5 and C-1 in **(164)** on the generation of stereogenic center C-8 conforms with the sterically least congested transition state **(165)**‡. Hence the magnesium-ene step provided the thermodynamically unstable, encumbered 7,7-dimethyl-6-methylene moiety with perfect control over the chirality at C-8.

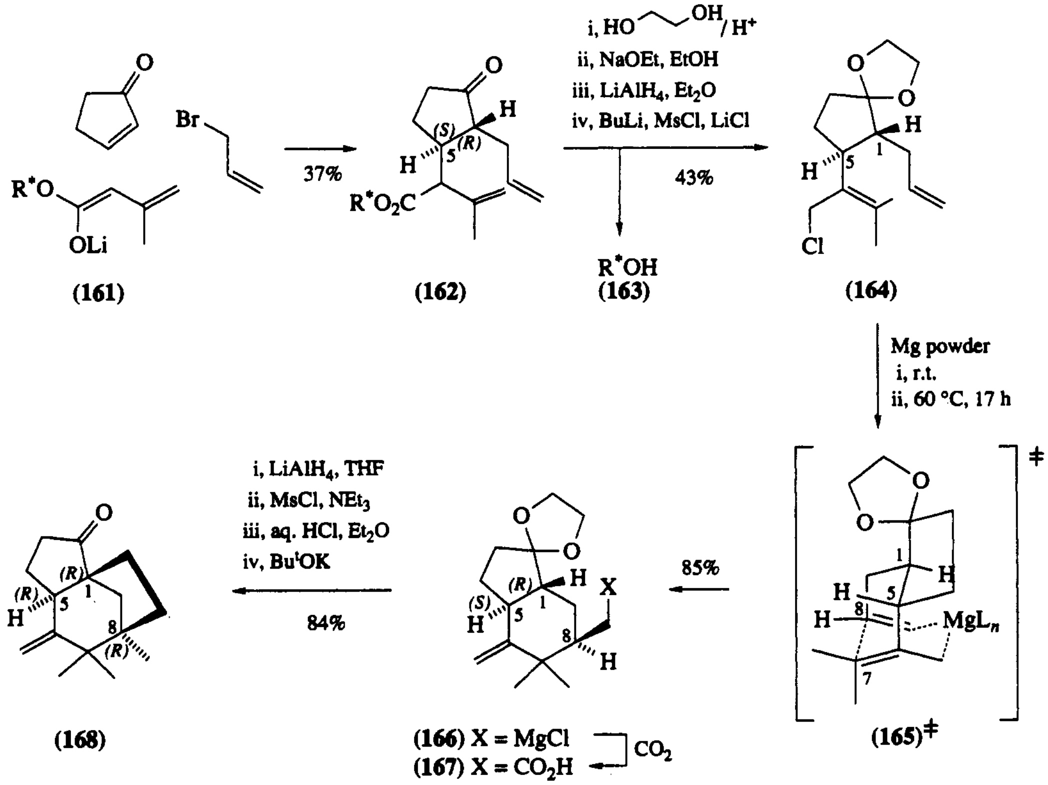
O
Br
R*O
OLi
(161)
37%
O
H
(S)
5
(R)
H
R*O₂C
(162)
i, HO⁀⁀OH / H⁺
ii, NaOEt, EtOH
iii, LiAlH₄, Et₂O
iv, BuLi, MsCl, LiCl
43%
R*OH
(163)
O
O
H
1
H
5
Cl
(164)
Mg powder
i, r.t.
ii, 60 °C, 17 h
‡
O
O
1
H
H
5
H
8
MgLₙ
7
(165)‡
85%
O
O
(R)
H
X
(S)
H
5
1
8
H
(166) X = MgCl
(167) X = CO₂H
CO₂
i, LiAlH₄, THF
ii, MsCl, NEt₃
iii, aq. HCl, Et₂O
iv, BuᵗOK
84%
O
(R)
(R)
H
5
1
8
(R)
(168)

Scheme 34

### *(ii) Type II Zinc-ene Cyclizations*

The thermal type II cyclizations of alkenic allylzinc bromides (**171**) show interesting possibilities; the latter were prepared *in situ* from chlorides (**169**) *via* transmetalation of the Grignard intermediates (**170**) with $ZnBr_2$ (1.5 equiv). Quenching of the cyclized alkylzinc species (**172**) with $H_2O$ (→ **173**) or $ClSnMe_3$ (→ **174**) provided oxygen and nitrogen heterocycles (Scheme 35; Table 9).[37] Analogous attempts to cyclize the allylmagnesium chlorides (**170**) failed except for the transformation (**170g**) → (**174g**) (76%). However, the less nucleophilic zinc derivatives (**171**) cyclized readily at 80 °C even with a terminally methyl-substituted alkenyl (although at 130 °C, entry 3) but not with a cyclohexenyl enophile unit (entry 6).

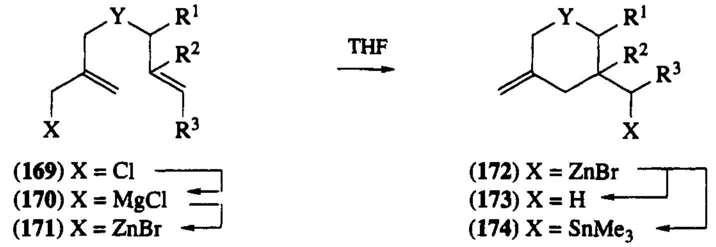

Scheme 35

**Table 9** Intramolecular Type II Zinc-ene Reactions Followed by Trapping (**171**) → (**172**) → (**173**) or (**174**) in THF

| *Entry* | *Y* | *R*$^1$ | *R*$^3$ | *R*$^2$ | *Temp.* (°C) (*time*, h) | *Product* | *Yield*$^a$ (%) |
|---|---|---|---|---|---|---|---|
| 1 **a** | O | H | H | H | 80 (23) | (**174**) | 57 |
| 2 **b** | O | H | H | Me | 80 (45) | (**173**) | 80 |
| 3 **c** | O | H | Me | H | 130 (22) | (**173**) | 50 |
| 4 **d** | O | Ph | H | H | 80 (48) | (**173**) | 76$^b$ |
| 5 **e** | $OCH_2$ | H | H | H | 80 (24) | (**174**) | 62 |
| 6 **f** | O | —$(CH_2)_3$— | | H | 130 (24) | (**173**) | 0 |
| 7 **g** | NMe | H | H | H | 80 (24) | (**174**) | 64 |

$^a$ Based on (**169**). $^b$ 2:1 *trans*/*cis* mixture.

## 1.2.3.3 Intramolecular Palladium- and Nickel-ene Reactions

### *1.2.3.3.1 Catalytic type I palladium-ene cyclizations*

Whereas stoichiometric additions of allylpalladium species to norbornene and 1,3-dienes are known (*cf.* Section 1.2.2.4), simple alkenes (*e.g.* styrene, cyclohexene, 1,4-cyclohexadiene and 1,5-cyclooctadiene) did not undergo this reaction.[13] However, it can be assumed that the intramolecular ene process (L) → (M) (Scheme 36) is entropically favored and that a subsequent irreversible β-elimination (M) → (N) withdraws the ene product (M) from the equilibrium (L) ⇌ (M). Further options are insertion/reductive elimination processes (M) → (O). The thereby regenerated $Pd^0$ species should continue the catalytic cycle by oxidative addition to allyl derivatives (I) or (J) (*e.g.* X = OR), thus providing *in situ* the alkenic allylpalladium intermediates (K).

The first example of this concept was published in 1987.[38] Acetoxydienes (**176**) were readily obtained, predominantly as their (*E*) isomers, *via* $Pd(PPh_3)_4$ catalyzed alkylation[39] of disulfones (**175a**; Y = $SO_2Ar$) or malonates (**175b**; Y = $CO_2Me$) with 4-acetoxy-2-butenyl methyl carbonate. Heating diene (**176a**; Y = Ts) with $Pd(dba)_2$ (0.07 equiv)/$PPh_3$ (0.2 equiv) in THF at 70 °C for 2 h gave the expected cyclized 1,4-diene (**177a**; Y = Ts) in 82% yield. Even more conveniently, product (**177a**; Y = Ts) was obtained (76% yield) in one operation from (**175a**) *via* $Pd^0$ catalyzed alkylation/cyclization (Scheme 37; Table 10, entry 2).[38]

Solvent effects significantly influence this novel ene process, as illustrated by the cyclization of malonate (**176b**) → (**177b**; Y = $CO_2Me$). Whereas no reaction took place in toluene, dichloromethane or DMF, the rate and yield increased on proceeding from THF (20%) to methanol (65%) to acetic acid (77%; entries 3–5). Interestingly, the presence of the phosphine turned out to be indispensable for the transformation (**176b**) → (**177b**).[38]

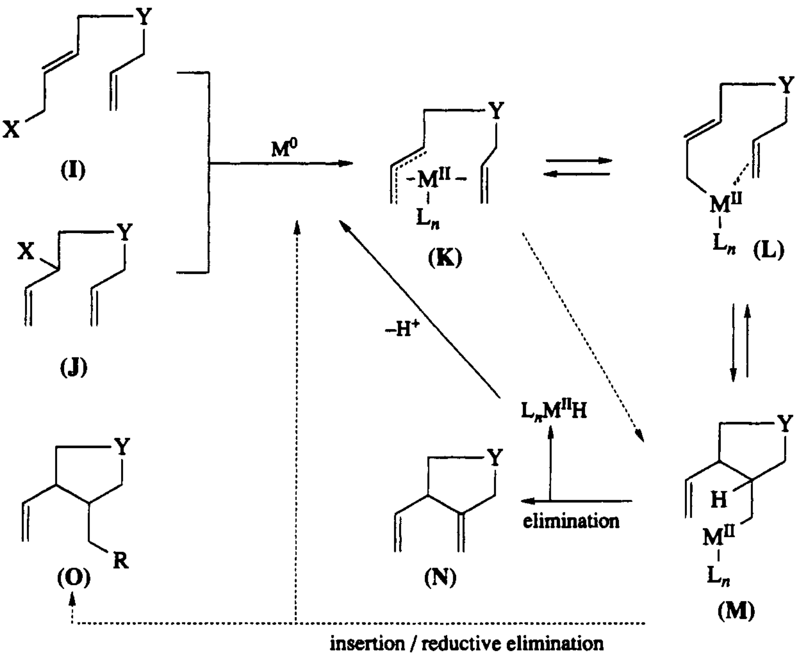
(I)
(J)
X
Y
$M^0$
$-M^{II}-$
$L_n$
(K)
(L)
$M^{II}$
$L_n$
-H+
$L_nM^{II}H$
elimination
(M)
H
(N)
(O)
R
insertion / reductive elimination

X = OAc, OH, OTHP; Y = $C(SO_2Ar)_2$, $C(CO_2Me)_2$, $CH_2$, NR, O

Scheme 36

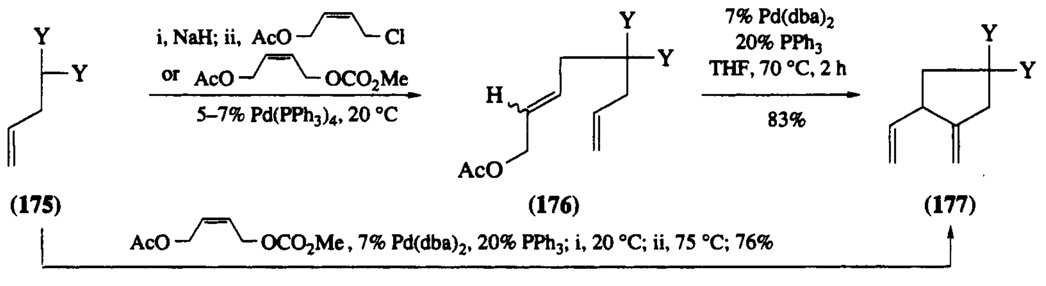
i, NaH; ii, AcO–CH₂CH=CHCH₂–Cl
or AcO–CH₂CH=CHCH₂–OCO₂Me
5–7% Pd(PPh₃)₄, 20 °C
7% Pd(dba)₂
20% PPh₃
THF, 70 °C, 2 h
83%
AcO–CH₂CH=CHCH₂–OCO₂Me, 7% Pd(dba)₂, 20% PPh₃; i, 20 °C; ii, 75 °C; 76%
(175)
(176)
(177)
Y
H
AcO

Scheme 37

**Table 10** $Pd(dba)_2/PPh_3$ Catalyzed Cyclizations (176) → (177)

| *Entry* | *Y* | *Solvent* | *Reaction temp. (°C) (time, h)* | *Yield of (177) (%)* |
|---|---|---|---|---|
| 1 a | $SO_2C_6H_4Me$-*p* | THF | 70 (2) | 82 |
| 2 a | $SO_2C_6H_4Me$-*p* | THF | '1-pot'[a] | 76 |
| 3 b | $CO_2Me$ | THF | 80 (40) | 20 |
| 4 b | $CO_2Me$ | MeOH | 80 (8) | 65 |
| 5 b | $CO_2Me$ | AcOH | 80 (1.5) | 77 |

[a] '1-pot' from (175a).

The significance of the medium for this type of reaction accounts also for unsuccessful attempts to achieve $Pd^0$ catalyzed cyclizations of various 2,7-octadienyl acetates in aprotic solvents. Nevertheless, $Pd^0$ catalyzed cyclization of 4-alkyl-4-hydroxy-2,7-octadienyl acetates such as **(178)**, **(181)** and **(184)** were readily accomplished in boiling acetonitrile.[40] Some of these (presumably hydroxy assisted) ring closures led preferentially to products with *cis*-related hydroxy and vinyl groups, *e.g.* **(179)** and **(182)** (Scheme 38).

Intramolecular insertion of a 1,1-dialkylalkene into an allylpalladium unit **(188)** → **(189)** proceeded under the usual conditions, as illustrated by the cyclization **(187)** → **(192)** (Scheme 39).[41] It appears that the cyclized alkylpalladium intermediate **(189)**, unable to undergo β-elimination, carbometallates the ad-

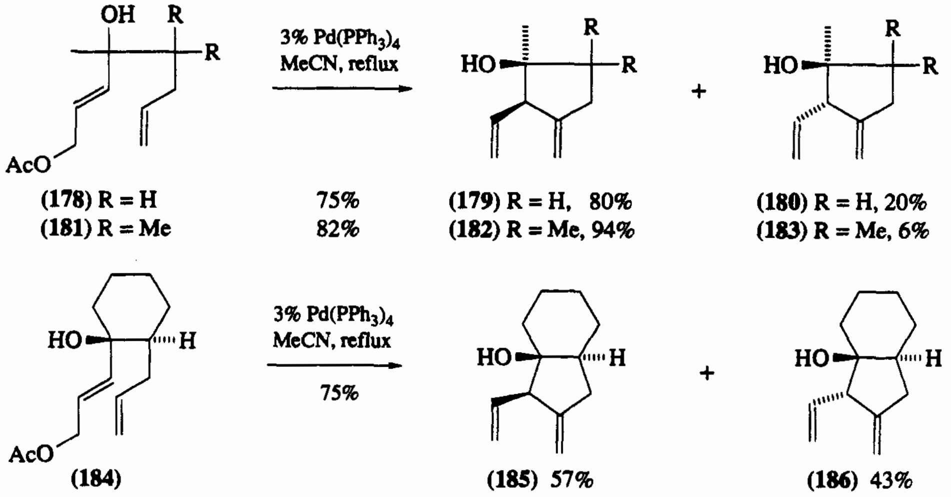
3% Pd(PPh3)4
MeCN, reflux
(178) R = H
(181) R = Me
75%
82%
(179) R = H, 80%
(182) R = Me, 94%
(180) R = H, 20%
(183) R = Me, 6%
3% Pd(PPh3)4
MeCN, reflux
75%
(184)
(185) 57%
(186) 43%

Scheme 38

jacent vinyl group to give the transient cyclobutane (**190**) which undergoes retro-carbometallation/β-elimination, (**190**) → (**191**) → (**192**).

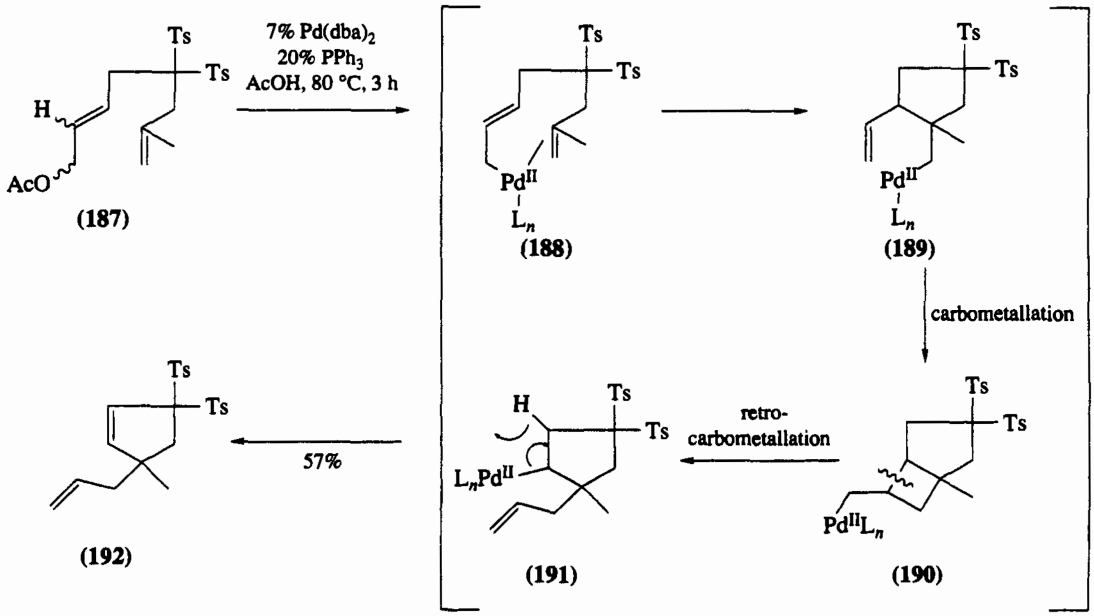
7% Pd(dba)2
20% PPh3
AcOH, 80 °C, 3 h
(187)
(188)
(189)
carbometallation
(190)
retro-carbometallation
(191)
57%
(192)

Scheme 39

In striking contrast to 8-alkyl-substituted 2,7-dienylmagnesium halides that did not cyclize (*cf.* Section 1.2.3.2), the allylpalladium unit of (**194**) inserted readily into a terminally mono- and even di-methyl-substituted alkenic bond, (**194**) → (**195**) (Scheme 40; Table 11).[38] The efficient $Pd^0$ catalyzed cyclizations (AcOH, 75 °C, 1, 5 h) of acetoxydienes (**193a**) and (**193b**) gave, in each case, a single 1,5-diene product (**196a**; 91%) and (**196b**; 71%), respectively. It follows that the cyclic alkylpalladium intermediate (**195**) eliminates the exocyclic $H_b$ preferentially over $H_a$, in agreement with the conformational constraints of a *syn* β-elimination process. Again acetic acid proved to be a better solvent than THF (*cf.* entries 1, 2 and 3, 4).

A study of the stereochemistry of the cyclization (**197**) → (**198**) + (**200**) showed a kinetically controlled 2:1 preference for the formation of the *trans*-divinylcyclopentane (**200**) (independent of the ene *E*/*Z* configuration, *cf.* Scheme 48) which increased to 9:1 when more catalyst and a longer reaction time were employed (Scheme 41, Table 12).[41] This useful predominance of the thermodynamically more stable

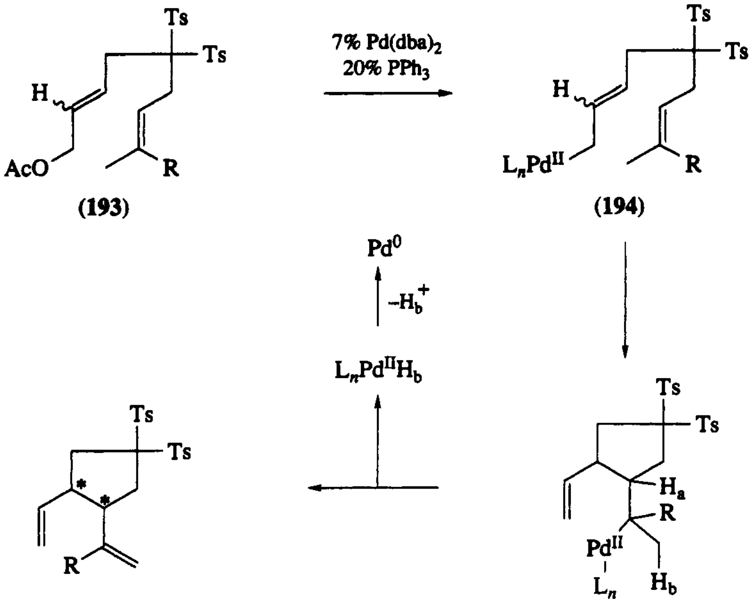
Ts
Ts
H
AcO
R
(193)
7% Pd(dba)$_2$
20% PPh$_3$
Ts
Ts
H
L$_n$Pd$^{II}$
R
(194)
Pd$^0$
$-H_b^+$
L$_n$Pd$^{II}$H$_b$
Ts
Ts
R
(196)
Ts
Ts
H$_a$
R
Pd$^{II}$
L$_n$
H$_b$
(195)

**Scheme 40**

**Table 11** Pd(dba)$_2$/PPh$_3$ Catalyzed Cyclizations **(193)** → **(196)**

| *Entry* | *R* | *Solvent* | *Reaction temp. (°C) (time,* h*)* | *Yield of* **(196)** *(%)* |
|---|---|---|---|---|
| 1 **a** | H | THF | 75 (15) | 80 |
| 2 **a** | H | AcOH | 75 (1.5) | 91 |
| 3 **b** | Me | THF | 85 (40) | 40 |
| 4 **b** | Me | AcOH | 75 (1.5) | 71 |

*trans* product **(200)** (entry 4) presumably involves a palladium-catalyzed 'Cope-type' equilibration **(198)** $\rightleftharpoons$ **(199)** $\rightleftharpoons$ **(200)**.

As expected, Pd(PPh$_3$)$_4$ also proved to be a suitable catalyst for intramolecular palladium-ene reactions (Scheme 42). Conversion **(201)** → **(202)** illustrates the feasibility of this method for six-membered ring formation.[38] Acetoxydiene **(203)**, containing a cyclic enophile unit, furnished stereoselectively the bicy-

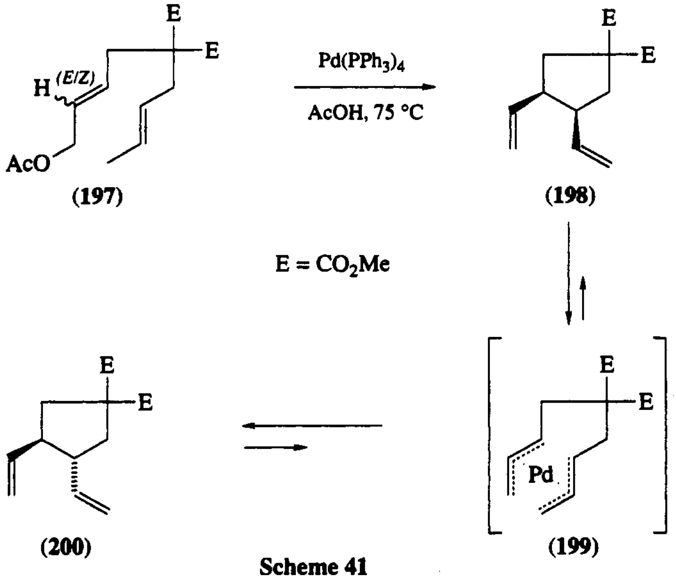
E
E
H
(E/Z)
AcO
(197)
Pd(PPh$_3$)$_4$
AcOH, 75 °C
E
E
(198)
E = CO$_2$Me
E
E
(200)
E
E
Pd
(199)

**Scheme 41**

**Table 12** Stereochemistry of $Pd(PPh_3)_4$ Catalyzed Cyclizations[a] (**197**) → (**198**) + (**200**)

| *Entry* | *Educt* (**197**) *(E):(Z)* | *Equiv.* $Pd(PPh_3)_4$ | *Reaction time* (h) | *Yield of* (**198**) + (**200**) (%) | *Ratio* (**198**):(**200**) |
|---|---|---|---|---|---|
| 1 | 0:100 | 0.05 | 5 | 70 | 36:64 |
| 2 | 60:40 | 0.05 | 5 | 67 | 36:64 |
| 3 | 60:40 | 0.07 | 2 | 26 (80)[b] | 32:68 |
| 4 | 60:40 | 0.10 | 24 | 52 | 10:90 |

[a] 75 °C, AcOH. [b] Yield in parenthesis based on recovered (**197**).

clic product (**204**) in 86% yield. The palladium-ene unit may be also part of a ring, as shown by the stereoselective formation of a spiro system, (**205**) → (**206**).[38c,42]

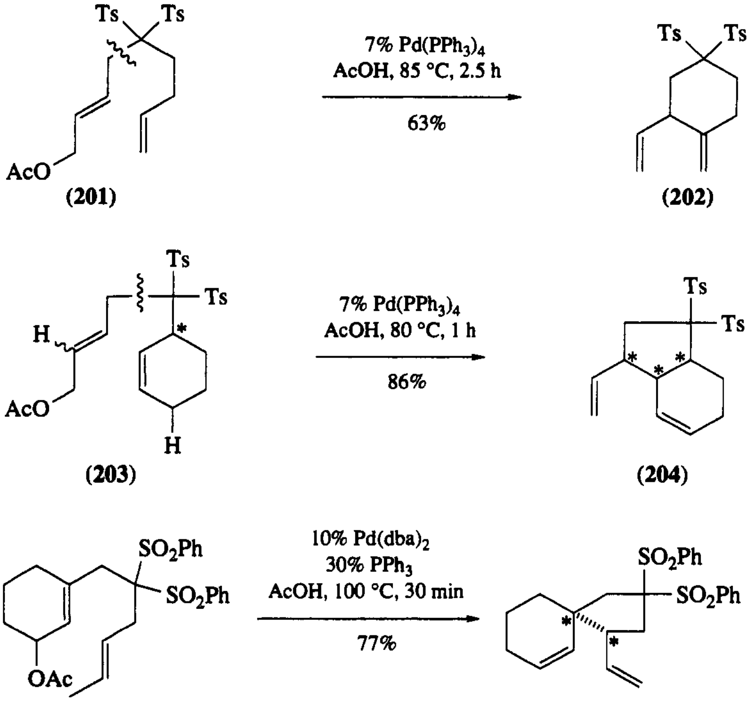

**Scheme 42**

Stereochemically even more striking are the cyclizations depicted in Scheme 43 and Table 13. Comparison of entries 1 and 2 shows that the *trans* or *cis* alkenic cyclohexenyl acetates (**208a**) or (**211a**) gave the same *cis*-annulated hexahydroindene (**210a**).[38] However, the conversion (**211a**) → (**210a**) is significantly slower and presumably implies a relatively slow *trans*/*cis* isomerization (**212a**) → (**209a**). It appears that in initially formed (**212a**) the coordination of the Pd atom with the *trans*-disposed enophile is highly unfavorable, which prevents its conversion to (**213a**). However, a longer bridge or a larger preexisting ring should permit allylpalladium alkene coordination even in the *trans* intermediates (**212**). Indeed, the *trans*-acetoxydiene (**208b**) furnished exclusively the *cis*-fused octahydronaphthalene (**210b**), whereas the *cis*-acetoxydiene (**211b**) gave, with 95% stereospecificity, the *trans*-annulated product (**213b**) (entries 3, 4).[42,43] This interesting C—O → C—Pd → C—C chirality transfer also provides selective routes to *cis*- or *trans*-fused hexahydroazulenes (**210c**) or (**213c**) (entries 5, 6).[41,43] These findings confirm that the alkene inserts predominantly into the $\sigma$-(or $\pi$-)allylpalladium unit *cis* relative to the Pd atom (*i.e.* in a suprafacial manner).

Scheme 44 exemplifies the analogous enantiospecific preparation of a hexahydropentalene (**217**) from a readily available, optically pure hydroxyacetate (**214**).[43]

The *gem*-disulfone and malonate functionalities described above facilitate the preparation of the 'palladium-ene' precursors (**I**) (Scheme 36) and can be readily removed or modified, but they are not essential for the cyclization process. Thus 3-acetoxy-1,7-octadienes (**J**) (*e.g.* **218**) containing simple carbon bridges are very easily accessible and undergo smooth Pd-catalyzed cyclizations (Scheme 45).[41,44] Only

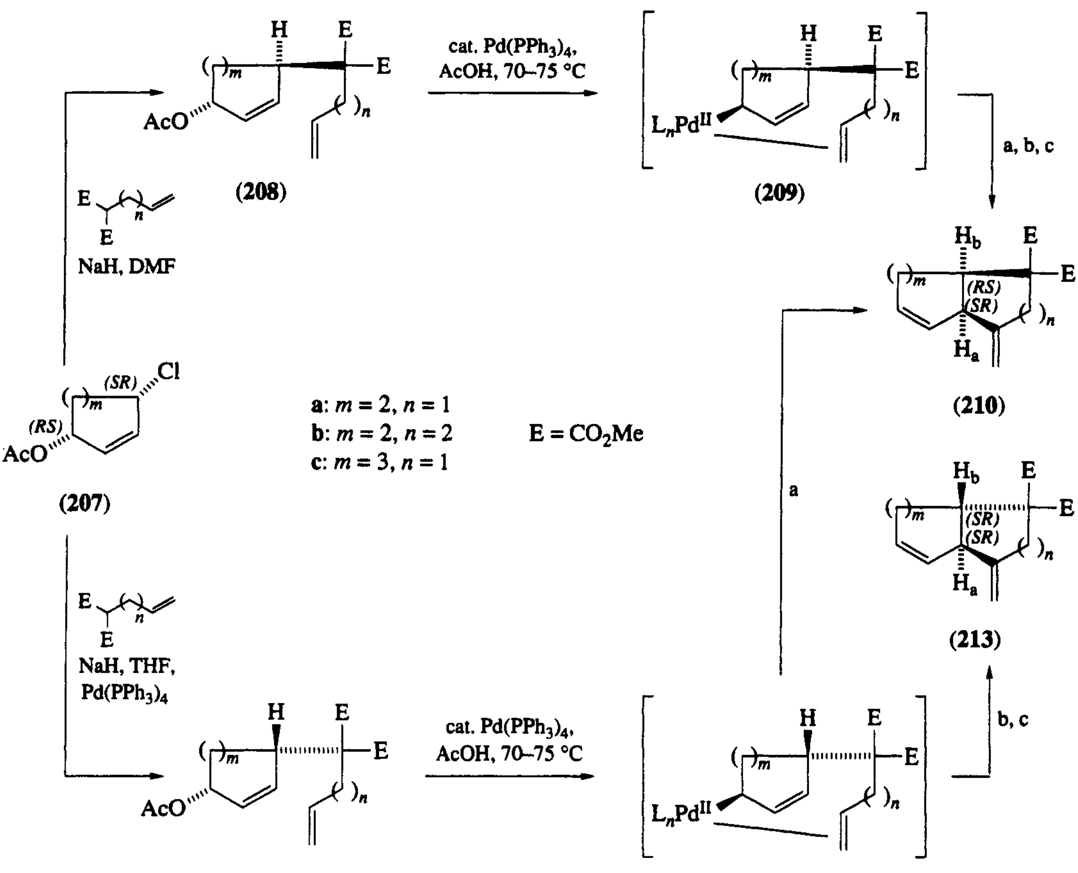

Scheme 43

**Table 13** Stereocontrolled Syntheses of [4.3.0], [4.4.0] and [5.3.0] Ring Systems by Pd-catalyzed Cyclizations of Acetoxydienes (**208**) and (**211**)

| *Entry*[a] | *Starting material* | *m* | *n* | *Reaction time* (h) | *Yield (%)* (**210**) + (**213**) | *Ratio* (**210**):(**213**) |
|---|---|---|---|---|---|---|
| 1 a | (**208**) | 2 | 1 | 1.1 | 84 | ≥98:≤2 |
| 2 a | (**211**) | 2 | 1 | 4 | 55 | ≥98:≤2 |
| 3 b | (**208**) | 2 | 2 | 3 | 60 | >99:<1 |
| 4 b | (**211**) | 2 | 2 | 3 | 69 | 5:95 |
| 5 c | (**208**) | 3 | 1 | 4 | 73 | 99:1 |
| 6 c | (**211**) | 3 | 1 | 1.8 | 80–92 | 2:98 |

[a] Entries 1–4: 7 mol % Pd(PPh$_3$)$_4$, 75 °C; entry 5: 10 mol % Pd(PPh$_3$)$_4$, 70 °C; entry 6: 5 mol % Pd(PPh$_3$)$_4$, 70 °C.

products (**220**) containing an (*E*)-alkenic bond were found, indicating the ene-type reaction of (*E*)-allylpalladium intermediates.

Catalytic palladium-ene cyclizations may also open new perspectives in alkaloid synthesis, considering the smooth formation of pyrrolidines and piperidines.[42,45] Scheme 46 and Table 14 illustrate the cyclizations of 'palladium-ene' precursors (**I**) (**221**; *entries 1–4*) and (**J**) (**223**; *entries 5, 6*) containing a nitrogen atom as part of the bridge. The leaving group in (**223**) can even be a simple hydroxy group (entry 6).[45a]

Stereospecific formation of a *cis*-fused octahydroquinoline (**226**; 85%) is depicted in Scheme 47, which also shows the conversion of diallyl ether (**227**) into a 1:1 *cis/trans* mixture of tetrahydrofurans (**228**; 75%).[45a] It is worth noting that analogous nickel(0)-catalyzed cyclization of the corresponding acetate gave exclusively the *trans* isomer of (**228**).[45b]

Pd$^0$ catalyzed cyclizations of (*E,Z*)-, (*Z,Z*)-, (*E,E*)- and (*Z,E*)-*N*-trifluoroacetamides (**229**) and (**232**) again represent the insertion of terminally methyl-substituted alkenic bonds into (*E*)-allylpalladium components followed by β-elimination of a methyl-hydrogen atom (Scheme 48; Table 15).[45a]

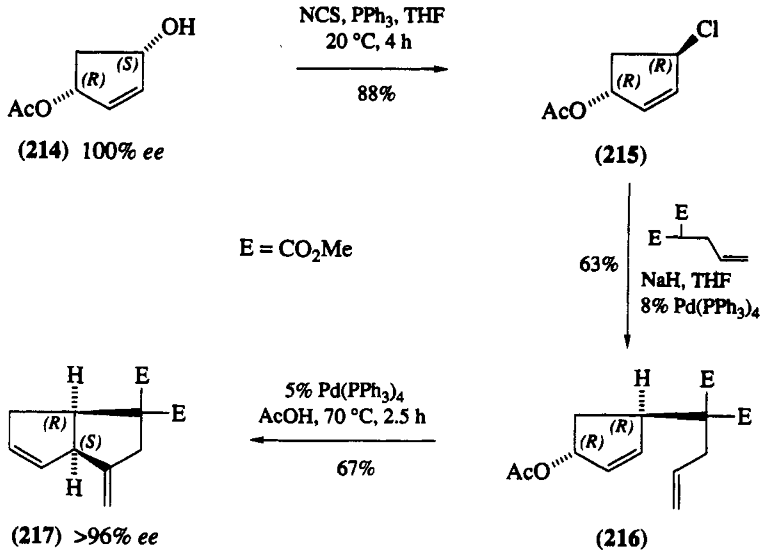

OH
(R)
(S)
AcO
(214) 100% ee
NCS, PPh3, THF
20 °C, 4 h
88%
Cl
(R)
(R)
AcO
(215)
E = CO2Me
63%
E
E
NaH, THF
8% Pd(PPh3)4
H
E
E
(R)
(R)
AcO
(216)
5% Pd(PPh3)4
AcOH, 70 °C, 2.5 h
67%
H
E
E
(R)
(S)
H
(217) >96% ee

**Scheme 44**

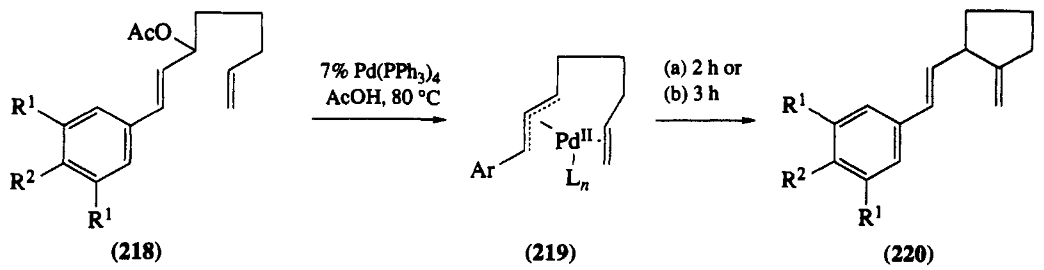

AcO
R1
R2
R1
(218)
7% Pd(PPh3)4
AcOH, 80 °C
PdII
Ar
Ln
(219)
(a) 2 h or
(b) 3 h
R1
R2
R1
(220)

(a) $R^1 = H, R^2 = CF_3$; 67%

(b) $R^1 = OMe, R^2 = H$; 94%

**Scheme 45**

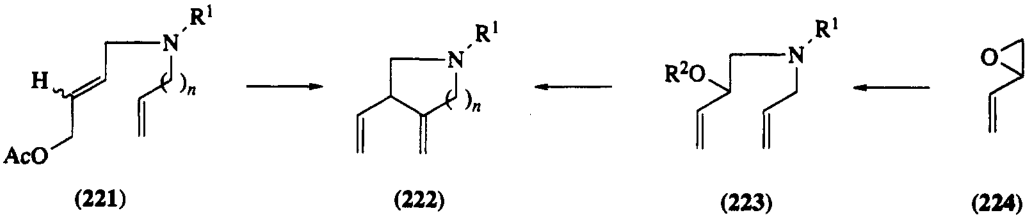

R1
N
H
( )n
AcO
(221)
R1
N
( )n
(222)
R1
R2O
N
(223)
O
(224)

**Scheme 46**

**Table 14** Pyrrolidines and Piperidines by Pd$^0$ Catalyzed$^a$ Cyclizations (221) → (222) and (223) → (222)

| *Entry* | *Starting material* | *R$^1$* | *n* | *R$^2$* | *Reaction time* (h) | *Yield (%)* |
|---|---|---|---|---|---|---|
| 1 a | (221) | $CH_2Ph$ | 1 | — | 3 | 72 |
| 2 b | (221) | $CO_2$ $CH_2Ph$ | 1 | — | 1 | 69 |
| 3 c | (221) | $SO_2C_6H_4Me$-*p* | 1 | — | 0.5 | 72 |
| 4$^b$ d | (221) | $SO_2C_6H_4Me$-*p* | 2 | — | 4 | 77 |
| 5 e | (223) | C(O)Ph | 1 | C(O)Ph | 0.5 | 81 |
| 6$^b$ f | (223) | $SO_2C_6H_4Me$-*p* | 1 | H | 3.5 | 78 |

$^a$AcOH, 80 °C, $Pd(PPh_3)_4$ (5 mol %). $^b$7 mol % of $Pd(PPh_3)_4$ used.

Entries 2 and 5 in Table 15 exemplify the use of a polymer-supported palladium(0)–phosphine catalyst which may offer practical advantages for carrying out palladium-catalyzed ene-type cyclizations.[46] As to the stereochemistry, dienes (229) containing a (*Z*)-enophile gave, under kinetic control, predominantly

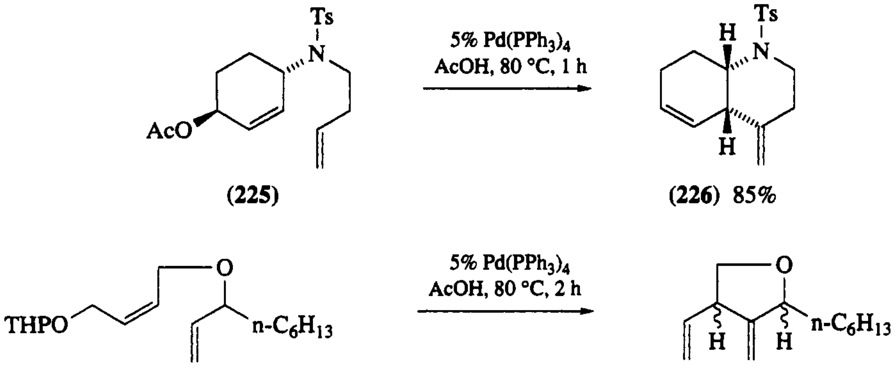

**Scheme 47**

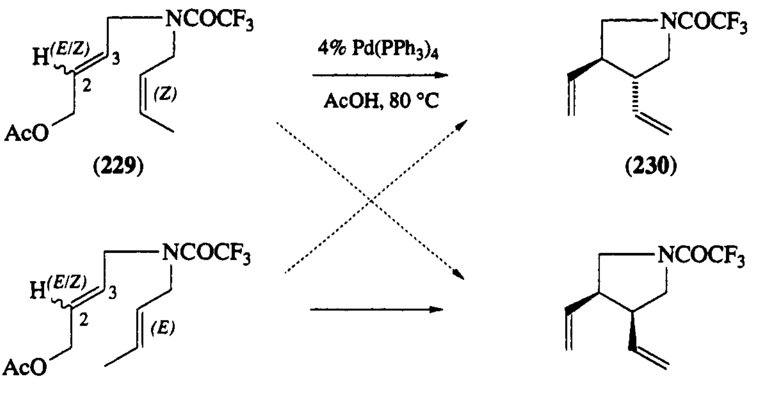

**Scheme 48**

**Table 15** Pd$^0$ Catalyzed Cyclizations (**229**) → (**230**) + (**231**) and (**232**) → (**230**) + (**231**)

| *Entry* | *Starting material* | *E/Z C(2)—C(3)* | *Reaction time* (h) | *Yield* (%) (**230**) + (**231**) | *Ratio* (**230**):(**231**) |
|---|---|---|---|---|---|
| 1 | (**229**) | *E* | 0.6 | 76 | 88:12 |
| 2$^a$ | (**229**) | *E* | 20 | 75 | 88:12 |
| 3 | (**229**) | *Z* | 1.9 | 59 | 91:9 |
| 4 | (**232**) | *E* | 2 | 67 | 28:72 |
| 5$^a$ | (**232**) | *E* | 52 | 62 | 30:70 |
| 6 | (**232**) | *Z* | 2.5 | 51 | 30:70 |

$^a$10 mol % of (polymer-$C_6H_4$-$PPh_2)_4Pd$ (Fluka).

the *trans*-divinylpyrrolidine (**230**) (~8:1, *entries 1–3*) whereas dienes (**232**) containing an (*E*)-enophile afforded, less selectively (2.5:1), the *cis* product (**231**) (*entries 4–6*). This stereochemical outcome was independent of the (*E*/*Z*) configuration of the allyl acetates (**229**) and (**232**), in agreement with a (*Z*)- → (*E*)-allylpalladium isomerization prior to the insertion (indeed, isomerizations (*Z*)-(**229**) → (*E*)-(**229**) and (*Z*)-(**232**) → (*E*)-(**232**) were observed under the cyclization conditions).

By contrast, if the (*Z*) configuration of the allylpalladium unit (*e.g.* in **233**$^‡$) is enforced by incorporation into a ring, only cis-substituted insertion products were expected, as confirmed by the annulation (**233**) → (**235**) (Scheme 49).[45a]

A recent report described analogous palladium(0)-catalyzed cyclizations of allyl acetates containing a conjugated dienyl-enophile component.[47] Thus heating trienes (**236**) with acetic acid and lithium or sodium acetate in acetonitrile under reflux furnished mixtures of *trans* and *cis* cyclization products (**238**) and (**239**). It appears that the cyclized allylpalladium species (**237**) is trapped by acetate (*via* reversal of the oxidative addition (**I**) → (**K**), Scheme 36) which results in an overall isomerization (**236**) → (**238**) + (**239**). As previously observed (*cf.* Scheme 37), the presence of triphenylphosphine was required for the corresponding transformation of the malonate (**236e**). Cyclizations of the monodesulfonated substrates

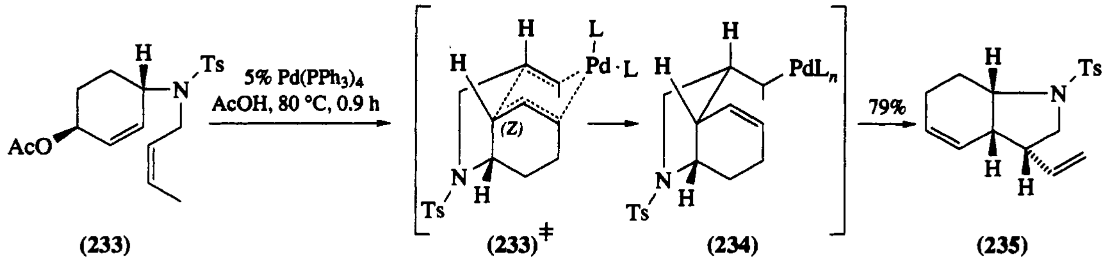
5% Pd(PPh3)4
AcOH, 80 °C, 0.9 h
79%
(233)
(233)‡
(234)
(235)

**Scheme 49**

(**236c**) and (**236d**) provided exclusively the all-*cis* products (**239c**) and (**239d**), respectively (Scheme 50, Table 16).

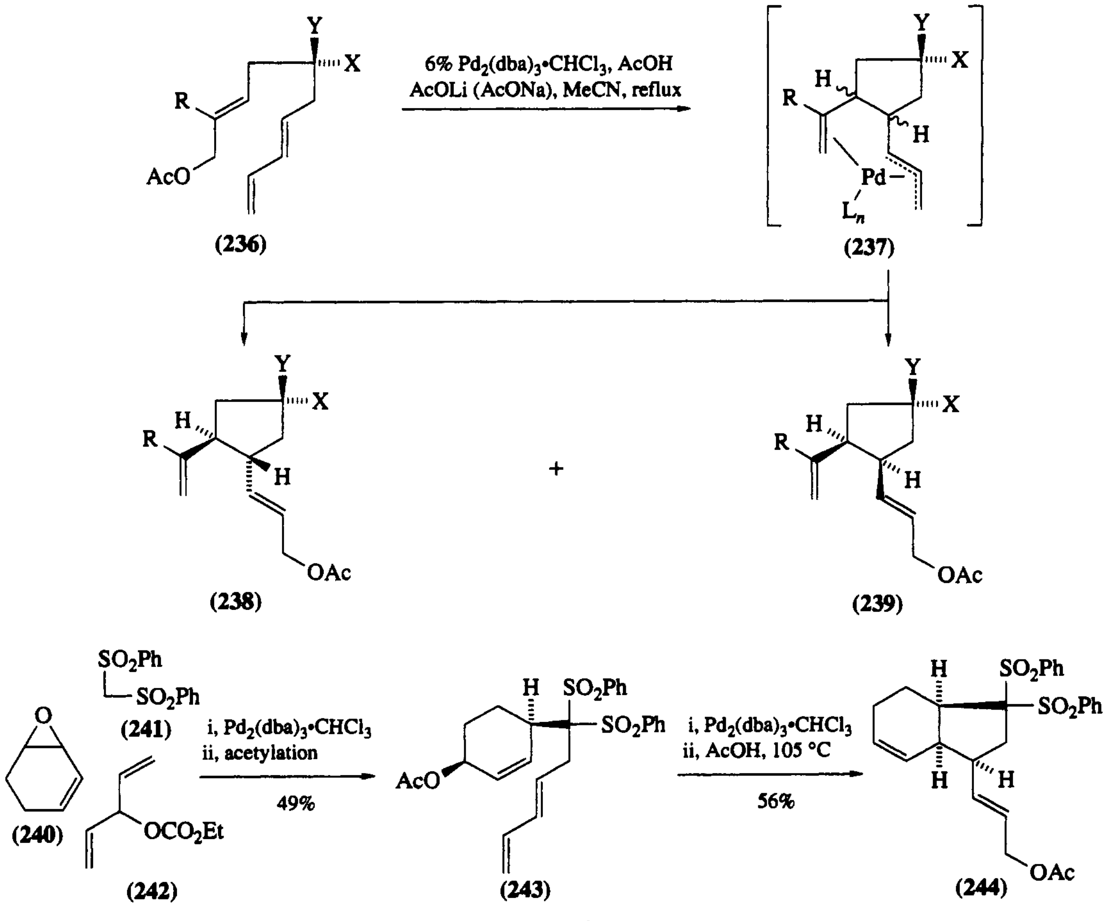
6% Pd2(dba)3•CHCl3, AcOH
AcOLi (AcONa), MeCN, reflux
(236)
(237)
(238)
(239)
(240)
(241)
(242)
i, Pd2(dba)3•CHCl3
ii, acetylation
49%
(243)
i, Pd2(dba)3•CHCl3
ii, AcOH, 105 °C
56%
(244)

**Scheme 50**

**Table 16** Pd$^0$ Catalyzed Cyclizations *via* Isomerizations of α-Dienyl-ω-allyl Acetates

| *Entry* | *R* | *Y* | *X* | *PPh*$_3$ (mol %) | *Yield* (**238**) +(**239**) | *Ratio* (**238**):(**239**) |
|---|---|---|---|---|---|---|
| a | H | $SO_2Ph$ | $SO_2Ph$ | — | 60–70 | 70:30 |
| b | Me | $SO_2Ph$ | $SO_2Ph$ | — | 62 | 58:42 |
| c | H | $SO_2Ph$ | H | — | 68 | 0:100 |
| d | Me | $SO_2Ph$ | H | — | 62 | 0:100 |
| e | H | $CO_2Et$ | $CO_2Et$ | 24 | 75 | —[a] |

[a] Ratio not reported.

Direct palladium(0)-catalyzed bisalkylation of disulfone (**241**) by (**240**) and (**242**) and acetylation furnished the cyclohexenyl precursor (**243**) with a *cis*-related acetoxy group and dienyl chain. This configuration is, however, unfavorable for the cyclization step (*cf.* Scheme 43), which explains the high reaction temperature (AcOH, 105 °C). The all-*cis* configuration of (**244**) parallels that one of (**235**) (*cf.* Scheme 49).

Trapping of the cyclized σ-alkylpalladium species by carbon monoxide (2 atm) is exemplified by Scheme 51.[48] Again the use of acetic acid as a solvent was essential for the cyclization of the butadiene telomer (**245**) giving initially σ-Pd species (**246**). Subsequent C—Pd/CO insertion (**246**) → (**247**) + (**248**) was followed more readily an alkene/acylpalladium insertion–β-elimination sequence (**248** → **251**) when the two adjacent moieties were *cis* disposed, whereas the *trans* intermediate (**247**) mainly provided the *trans*-vinylcyclopentane acetic acid (**249**) (50% from **245**). Ligand variations have so far failed to increase the diastereoselectivity of these cyclizations.

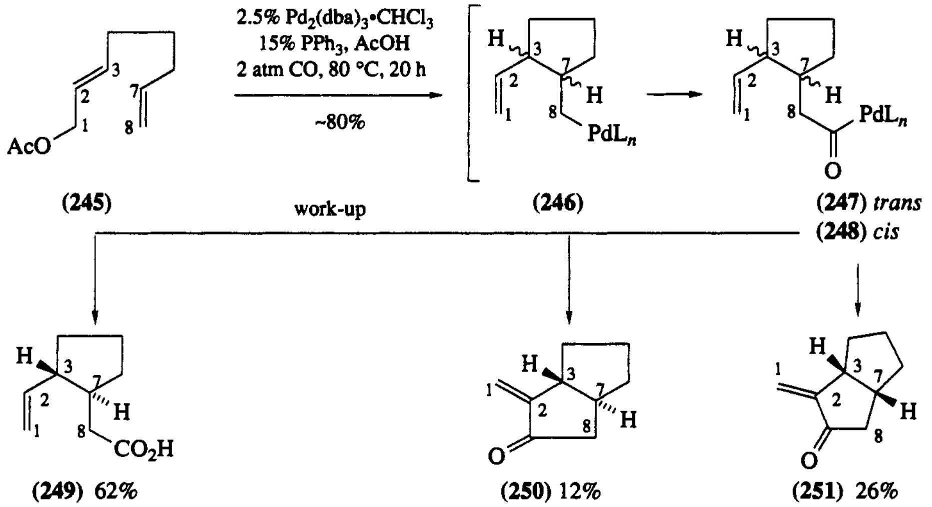
2.5% $Pd_2(dba)_3$•$CHCl_3$
15% $PPh_3$, AcOH
2 atm CO, 80 °C, 20 h
~80%
work-up
(**245**)
(**246**)
(**247**) *trans*
(**248**) *cis*
(**249**) 62%
(**250**) 12%
(**251**) 26%

**Scheme 51**

### *1.2.3.3.2 Catalytic type II palladium-ene cyclizations*

Scheme 52 illustrates the feasibility of carrying out catalytic type II palladium-ene cyclizations; for example, the transformation (**252**) → (**253**) (118 °C, 8 h, 66% yield).[42,49] Cyclization of (**254**) proceeded under milder conditions (80 °C, 6 h) to give piperidine (**255**; 63%).[49]

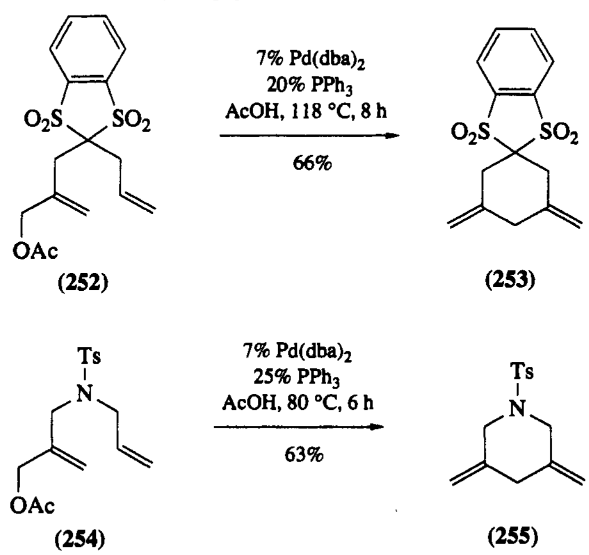
7% $Pd(dba)_2$
20% $PPh_3$
AcOH, 118 °C, 8 h
66%
(**252**)
(**253**)
7% $Pd(dba)_2$
25% $PPh_3$
AcOH, 80 °C, 6 h
63%
(**254**)
(**255**)

**Scheme 52**

Dienyl acetate (**256**) (readily prepared from 1-hepten-6-one and lacking the disulfone moiety) was also easily transformed to (*E*)-1,4-diene (**259**; 87%) (Scheme 53).[42,49] This regiochemistry parallels that of stoichiometric additions of allylpalladium complexes to norbornadiene,[13] but was subject to uncertainty in view of the relatively fast 1,3-Pd migration within the allyl component.[39] Therefore the conversion (**256**) → (**259**) demonstrates a new stereocontrolled access to exocyclic trisubstituted alkenes which implies C—C bond formation at the less-substituted allylpalladium terminal and thus shows a regio- and stereo-chemistry both opposite to the type II magnesium-ene process (*cf.* Section 1.2.3.2.2; **81** → **83**).

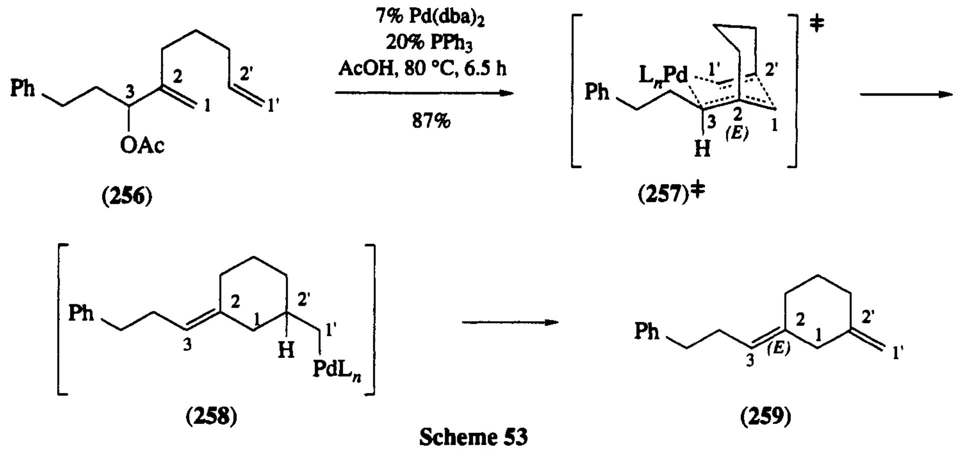

Scheme 53

### 1.2.3.3.3 Catalytic platinum- and nickel-ene cyclizations

The above concept of catalytic metallo-ene cyclizations (Scheme 36) may also be extended to platinum and nickel, as one would expect in view of previous work on intermolecular nickel-ene reactions (*cf.* Section 1.2.2.4).

Recently, a platinum-catalyzed cyclization/elimination was accomplished on heating dienyl acetate (**260a**) with 3.5 mol % of $Pt(PPh_3)_4$ in acetic acid at 80 °C, which furnished the expected cyclopentane (**261a**) in 84% yield (Scheme 54; Table 17, *entry 1*).[42,50a]

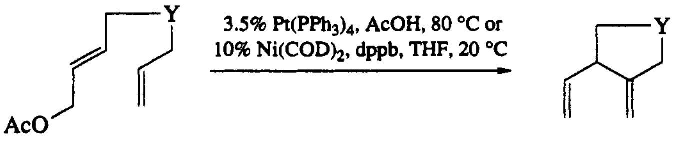
Y
AcO
3.5% Pt(PPh3)4, AcOH, 80 °C or
10% Ni(COD)2, dppb, THF, 20 °C
(260)
(261)

Scheme 54

Table 17 $Pt(PPh_3)_4$ ($Pt^0$) or $Ni(COD)_2$/dppb (1:1) ($Ni^0$) Catalyzed Cyclizations (**260**) → (**261**)

| *Entry* | *Bridge* *Y* | *Catalyst* (mol %) | *Solvent* | *Reaction temp.* (°C) (*time*, h) | *Yield* (*%*) |
|---|---|---|---|---|---|
| 1 a | $C(SO_2Ph)_2$ | $Pt^0$ (3.5) | AcOH | 80 (5) | 85 |
| 2 a | $C(SO_2Ph)_2$ | $Ni^0$ (10) | THF | 20 (3) | 83 |
| 3 b | $NSO_2C_6H_4Me$-*p* | $Ni^0$ (10) | THF | 20 (12) | 76 |
| 4 c | N—$CPh_3$ | $Ni^0$ (10) | THF | 20 (0.7) | 92 |

The first indication, reported in 1971, for a nickel-catalyzed intramolecular allylation of an alkenic bond was the dimerization of butadiene to 2-methylvinylcyclopentane (**263**).[51] This efficient transformation (90%) proceeded with 1.2 mol % of a $Ni^0$ catalyst (prepared *in situ* from $(Bu_3P)_2NiBr_2$ and BuLi) in the presence of methanol and presumably involves a nickel-ene reaction of (**262**) followed by a β-elimination of $H_a$ (Scheme 55).

The feasibility of $Ni^0$ complexes as catalysts for intramolecular metallo-ene reactions was, despite the encouraging precedents, not straightforward and depended strongly on their ligands. Systematic studies showed that a 1:1 mixture of $Ni(COD)_2$/1,4-bis(diphenylphosphino)butane catalyzes (10 mol %) the

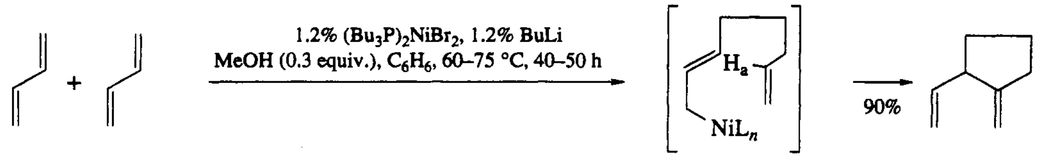
1.2% (Bu$_3$P)$_2$NiBr$_2$, 1.2% BuLi
MeOH (0.3 equiv.), C$_6$H$_6$, 60–75 °C, 40–50 h
H$_a$
NiL$_n$
90%
(262)
(263)

Scheme 55

allylation/elimination (**260**) → (**261**) at 20 °C in THF with a synthetically useful efficiency (76–92%) (Scheme 54; Table 17, entries 2–4).[50a]

The catalyst Ni(COD)dppb, formed *in situ*, also induced smooth conversion of monocyclic *trans*-acetoxydiene (**264**) to the *cis*-fused 3-methylenehexahydroindole (**266**; 88%), which is also formed much more slowly (12 h, 58%) from the *cis* precursor (**267**) (Scheme 56).[50a] This indicates a preferred *cis*-allylnickel/alkene insertion (**265**) → (**266**) analogous to the closely related palladium-catalyzed annulations (**209a**) or (**212a**) → (**210a**).

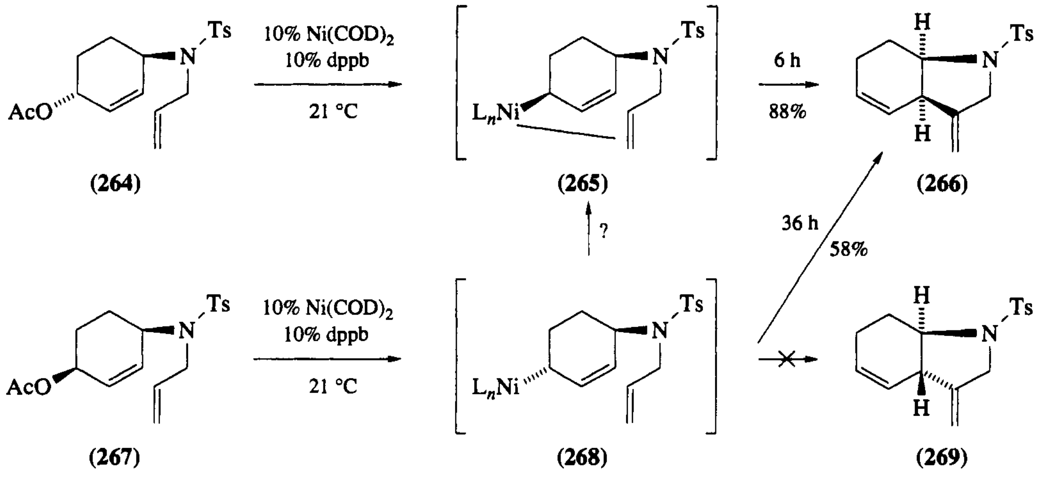

Scheme 56

The nickel/chromium-catalyzed cyclizations of 1,2,7-trienes (**270**) to (**272**) were postulated to proceed *via* a metal hydride addition to the allene unit of (**270**), generating an allylmetal intermediate (**271**) which undergoes a metallo-ene/β-elimination sequence.[52] It is worth noting that these cyclizations can be stereocontrolled by the presence of resident stereogenic centers, as demonstrated by the transformations (**273**) → (**274**) and (**275**) → (**276**) (Scheme 57).

Coupling of an intramolecular nickel-ene process with a methoxycarbonylation shows a striking preference for products with *cis*-related metal donor (C-1) and acceptor (C-8) sites.[50] Thus tricarbonyl(triphenylphosphine)nickel (25 mol %),[53] a stable, easy-to-handle solid [compared with the highly volatile and toxic Ni(CO)$_4$], readily catalyzed the conversion of dienyl iodide (**278**) (THF/MeOH 4:1, 1 atm CO, r.t.) into monocyclic *cis*-substituted pyrrolidine (**280**; 29%) and the bicyclic cyclopentanone (**281**; 47%, 4:1 isomer mixture) (Scheme 58).[50a]

It follows that a *cis* stereoselective nickel-ene process yields (**279**) and that (**279**) forms a *C*-acylnickel intermediate which inserts into either methanol (→ **280**) or the internal alkenic bond affording, after final methoxycarbonylation, keto ester (**281**). It is interesting to note that the bidentate ligand dppb favored the latter process and that no β-elimination of (**279**) was observed. Thus a catalyst, prepared *in situ* from Ni(COD)$_2$/dppb (1:1) under CO, effected complete bicyclization of (**278**) to give only (**281**; 80%, 10:1 epimer mixture).[50b]

Direct β-elimination cannot interfere with allylnickel/alkyne insertion–carbonylation sequences. In extension of previous work (*cf.* Scheme 16) the bicyclization of (*E*)- and (*Z*)-(**282**) to (**283**; 50%), promoted by 200 mol % of Ni(CO)$_4$ at 40 °C, has been reported (Scheme 59).[54]

Using 25 mol % of the more practical Ni(CO)$_3$PPh$_3$ catalyst under CO (1 atm, THF/MeOH 4:1, r.t.), exclusive monocyclization of iodoenyne (**284a**) → (**286a**) was accomplished (Scheme 60; Table 18, entry 1).[50] This unusual stereocontrolled approach to an exocyclic trisubstituted alkenic bond is consistent with a suprafacial allylnickel/alkyne insertion, (**284**; X = NiL$_n$) → (**285**). Malonate (**284b**; X = I) yielded, under similar reaction conditions, monocyclized ester (**286b**; 41%) and bicyclo[3.3.0]octenone

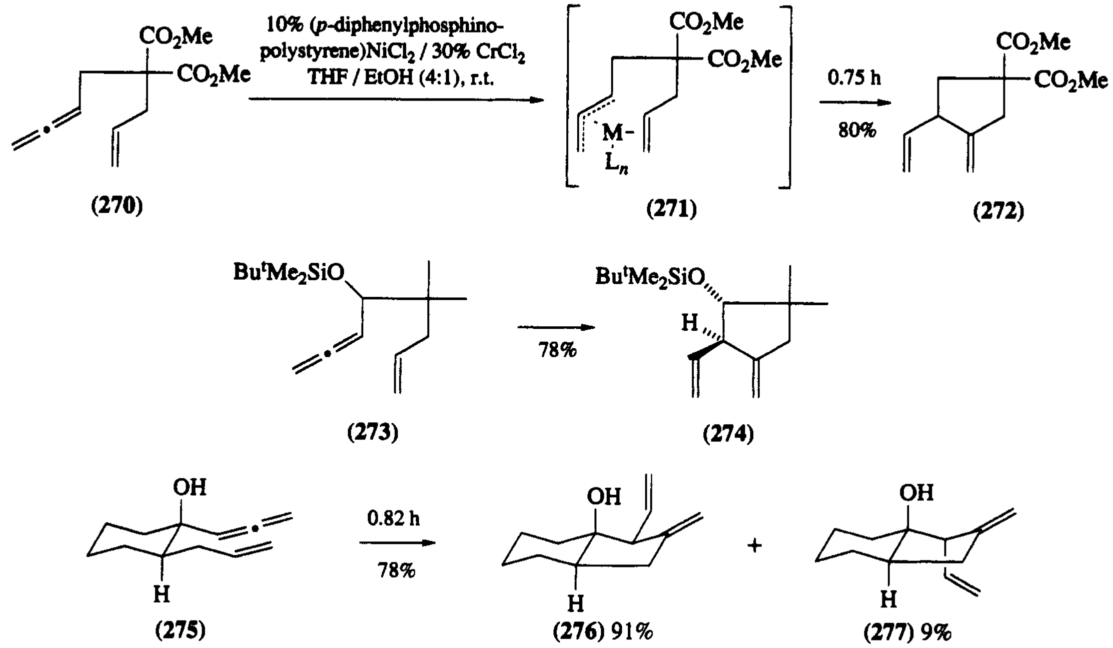
CO2Me
CO2Me
(270)
10% (p-diphenylphosphino-polystyrene)NiCl2 / 30% CrCl2
THF / EtOH (4:1), r.t.
CO2Me
CO2Me
M-
Ln
(271)
0.75 h
80%
CO2Me
CO2Me
(272)
ButMe2SiO
(273)
78%
ButMe2SiO
H
(274)
OH
H
(275)
0.82 h
78%
OH
H
(276) 91%
+
OH
H
(277) 9%

Scheme 57

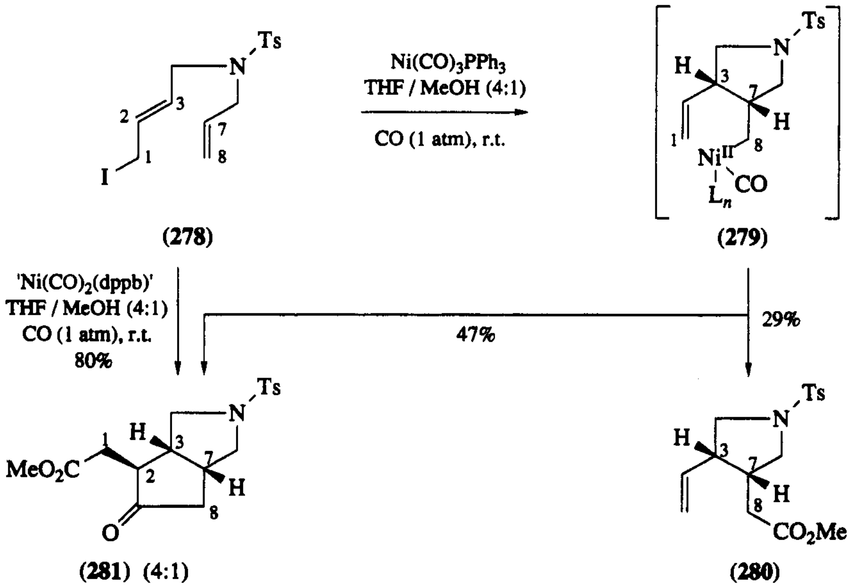
Ts
N
2
3
1
7
8
I
(278)
Ni(CO)3PPh3
THF / MeOH (4:1)
CO (1 atm), r.t.
Ts
N
H
3
7
H
1
8
NiII
CO
Ln
(279)
'Ni(CO)2(dppb)'
THF / MeOH (4:1)
CO (1 atm), r.t.
80%
47%
29%
Ts
N
H
3
1
MeO2C
2
7
H
8
O
(281) (4:1)
Ts
N
H
3
7
H
8
CO2Me
(280)

Scheme 58

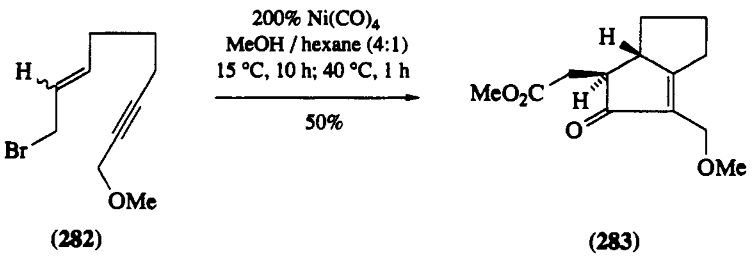
H
Br
OMe
(282)
200% Ni(CO)4
MeOH / hexane (4:1)
15 °C, 10 h; 40 °C, 1 h
50%
H
MeO2C
H
O
OMe
(283)

Scheme 59

(**287**; 36%) in a stereospecific manner (*entry 2*). Exclusive bicyclization (**284b**) → (**287**; 87%) was observed in the presence of the bidentate ligand dppb (entry 3).[50b]

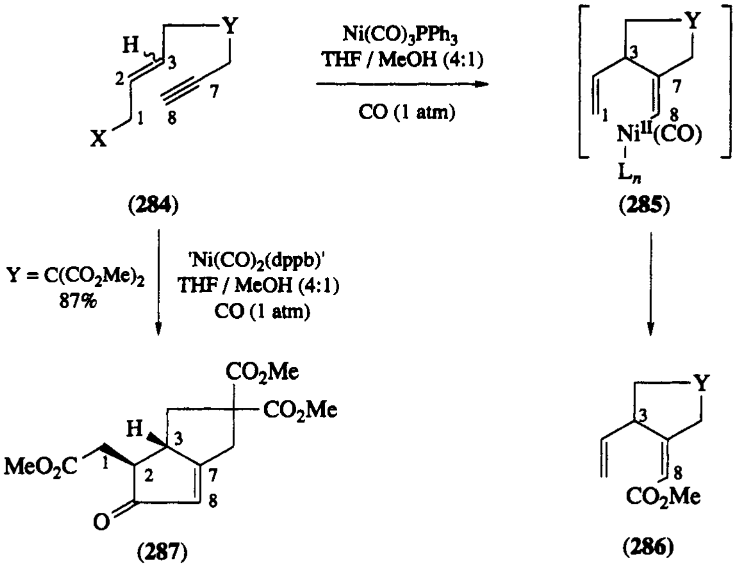

Scheme 60

Table 18 Nickel(0)-catalyzed Intramolecular Allylation/Carbonylation of Iodoenynes (**284**)

| *Entry* | *Bridge* *Y* | *Catalyst* (mol %) | *Reaction temp.* (°C) (*time*, h) | *Monocyclic product* (*yield*, %) | *Bicyclic product* (*yield*, %) |
|---|---|---|---|---|---|
| 1 a | $NSO_2C_6H_4Me$-*p* | $Ni(CO)_3PPh_3$ (25) | r.t. (20) | (**286**) (69) | — |
| 2 b | $C(CO_2Me)_2$ | $Ni(CO)_3PPh_3$ (25) | r.t. (20) | (**286**) (41) | (**287**) (36) |
| 3 b | $C(CO_2Me)_2$ | $Ni(CO)_2dppb$ (25)[a] | r.t. (15) | — | (**287**) (87) |

[a]Addition of dppb to $Ni(COD)_2$ (1:1) under CO (1 atm), THF/MeOH (4:1).

## 1.2.4 SUMMARY

Intermolecular metallo-ene reactions show interesting prospects when applied to strained or strongly polarized enophiles. Intramolecular versions, however, have proved to be far more powerful in the hands of synthesis-oriented chemists. Based on the criteria of (established and/or potential) utility in organic synthesis the following summary is focused on intramolecular magnesium-, palladium- and nickel-ene reactions.

Stoichiometric, intramolecular magnesium-ene reactions involving terminal or strained alkene enophile units have served extensively as a cornerstone in efficient syntheses of natural products. One of the reasons is the propensity of the cyclized Grignard intermediates to be trapped by a vast array of electrophiles. On the other hand, the use of Mg is incompatible with several functionalities such as certain heteroatoms in the acyclic precursor (zinc-ene cyclizations seem to surmount some of these limitations).

However, palladium and nickel catalyzed versions promise, at the moment, an even wider range of possibilities. The need to maintain the catalytic cycle by continuous regeneration of the zerovalent metal catalyst limits, nevertheless, the functionalizability of the metallated center in the cyclized intermediate. For the same reason, the readily accessible starting materials may contain various functional groups which are compatible with the reaction conditions and which may be of value for the syntheses of complex heterocycles such as alkaloids. Carbon monoxide insertion reactions of the cyclized $\sigma$-metal intermediates were shown to afford monocyclic methyl carboxylates and/or annulated cyclopentanones (cyclopentenones) with concomitant stereocontrolled formation of up to four carbon–carbon bonds.

The following further trends can be seen from the available evidence.

*Ring size*. The ease of cyclization decreases in the following order relative to the size of the developing ring: type I, 5 > 6 >> 7; type II, 6 > 5 ~ 7 >> 8.

*Regioselectivity.* Carbon–carbon bonds are preferentially formed between the proximal sites of ene and enophile in the type I process and between the more (Mg-ene reaction) or less substituted (Pd-ene reaction) ene terminal and the proximal enophile site in the type II version.

*Stereoselectivity.* All described metallo-ene reactions proceed apparently in a suprafacial manner. Other stereochemical features depend strongly on the metal as summarized below.

Type I magnesium-ene cyclizations usually furnish under kinetic control predominantly five- and six-membered rings carrying *cis*-disposed magnesium-donor and -acceptor units even when a quaternary center is generated. 2,3-Dialkyl-substituted allylmagnesium moieties react preferentially in their (*Z*)-form, inducing a *cis* relation of the C-3 alkyl substituent and the magnesium-acceptor site in type II cyclization products. However, the stereoselectivity of type I and type II magnesium cyclizations can be greatly diminished by severe steric hindrance, *e.g.* by critically placed *gem*-dimethyl groups (*cf.* **101** → **102**; **158** → **160**).

Related palladium-catalyzed ring closures permit simple and selective either *cis* or *trans* annulation processes *via* an almost 100% stereospecific C—O → C—Pd → C—C transfer. The diastereoselectivity of the palladium-ene cyclizations depends on the (*E*)/(*Z*) configuration of the enophile units and becomes exclusively *cis* when the (*Z*)-ene geometry is secured by incorporation into a ring. However, even acyclic allylnickel intermediates add to internally bound alkene units to form five-membered rings with *cis*-disposed nickel-donor and -acceptor sites.

As to our own work, mentioned in this chapter, it is a privilege to acknowledge the crucial contributions of my coworkers whose names are cited in the appropriate references. We thank the Swiss National Science Foundation, Sandoz AG, Basel, and Givaudan SA, Vernier, for generous support of this work. We are grateful to Professors E. Negishi and J. Tsuji for kindly communicating their results prior to publication.

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# 2.1

# Thermal Cyclobutane Ring Formation

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## 2.1.1 INTRODUCTION

This chapter reviews thermal [2 + 2] cycloadditions of alkenes to form cyclobutanes, extending the coverage provided by earlier summaries of the literature.[1–8] It does not deal with [2 + 2] cycloadditions that are achieved photochemically, or that utilize allenes, arynes or ketenes, or that are deliberately catalyzed,[9–14] or that result in heterocyclic four-membered rings, even though these other varieties of [2 + 2] cycloaddition reactions are important and of substantial interest.

Thermal [2 + 2] cycloadditions of alkenes are both well known and often overlooked or underutilized in synthetic practice. Yet a maturing mechanistic understanding of these reactions, and the growing importance of cyclobutane structures and of cyclobutanes as synthetic intermediates,[15] may soon lead to more widespread applications of this synthetic method.

## 2.1.2 DIMERIZATIONS OF ALKENES *VIA* 1,4-DIRADICALS

Dimerizations of monosubstituted ethylenes were among the earliest recognized examples of thermal [2 + 2] cycloadditions; the fact that acrylonitrile (**1**) gives 1,2-dicyanocyclobutanes (**3**, **4**) led to postulation of reaction by way of a tetramethylene diradical intermediate (**2**).[16]

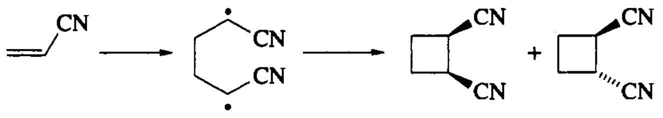

(**1**) (**2**) (**3**) (**4**)

Styrene,[17–19] butadiene[20] and divinylacetylene[21] similarly give [2 + 2] cycloadducts of head-to-head regiochemistry as mixtures of *cis* and *trans* 1,2-disubstituted cyclobutanes. The tetramethylene diradical hypothesis accounts for the regiochemistry: these [2 + 2] cycloadditions take place through an initial carbon–carbon bond-forming step to give the most stable 1,4-disubstituted 1,4-diradical. This view was extended to explain why the reaction lacked generality (why some alkenes did not dimerize efficiently when heated) and to interpret relative rates of dimerization. The dimerization of ethylene itself, for example, is kinetically well behaved[22] but quite difficult to realize, for the diradical intermediate involved has a much higher heat of formation[23] than tetramethylene diradical systems having good radical-stabilizing groups at C-1 and C-4, and the reaction is associated with a very unfavorable change in entropy. Relative rates of cycloadditions may be correlated qualitatively with the relative potency of substituents as radical-stabilizing groups: styrene dimerizes at 240 °C faster than acrylonitrile, for phenyl is a better radical-stabilizing group than cyano.[24]

The diradical mechanism for such reactions was substantially bolstered through the theoretical insights of the Woodward–Hoffmann theory and through a number of telling stereochemical studies. Orbital symmetry considerations led Woodward and Hoffmann[25] to a recognition that the [2 + 2] cycloaddition of two ethylenes would not be a favored process: the $[_{\pi}2_s + {}_{\pi}2_s]$ option is not thermally allowed, and the $[_{\pi}2_s + {}_{\pi}2_a]$ alternative is ordinarily geometrically inaccessible. This analysis reinforced the view that such reactions must proceed by way of tetramethylene diradicals, or possibly zwitterionic intermediates. The theoretically based generalizations and the experimental facts are mutually reinforcing, thus providing firm guidance as to when [2 + 2] cycloadditions are likely to occur at rates and with sufficient selectivity to be synthetically useful. Structural features destabilizing an alkene and stabilizing a 1,4-diradical (or 1,4-zwitterionic) intermediate should facilitate such reactions, and regiochemistry may then be predicted with considerable confidence. More quantitative techniques for predicting or rationalizing regiochemistry based on this simple idea have been developed;[26] alternative approaches based on perturbational molecular orbital theory are also quite successful.[27]

Cyclobutanes may be converted to alkenes thermally, the reverse of the [2 + 2] cycloaddition reaction. These retroaddition or cycloreversion reactions have important synthetic applications[28] and offer further insights into the chemical behavior of the 1,4-diradical intermediates involved:[29] they may proceed to product alkenes or collapse to starting material with loss of stereochemistry.[30,31] Both observations are readily accommodated by the diradical mechanism. Generation of 1,4-tetramethylene diradicals in other ways, such as from cyclic diazo precursors, results in formation of both alkenes and cyclobutanes, with stereochemical details consistent with kinetically competitive bond rotations before the diradical gives cyclobutanes or alkenes. From the tetraalkyl-substituted systems (**5**) and (**6**), cyclobutane products are formed with very high retention stereospecificity,[32] while the diradicals generated from the azo precursors (**7**) and (**8**) lead to alkene and cyclobutane products with some loss of stereochemical definition.[33–35]

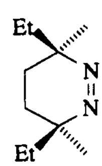

**(5)**

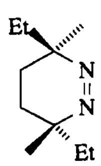

**(6)**

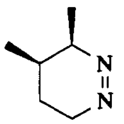

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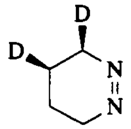

**(8)**

Diradical intermediates may occur in other types of cycloadditions and cycloreversions. Kinetic data for the thermal transformation of *cis,cis*-1,5-cyclooctadiene to butadiene and 4-vinylcyclohexene are consistent with a diradical intermediate;[36] the same intermediate may be involved in the reaction of butadiene leading to [2 + 2] adducts and to the Diels–Alder product 4-vinylcyclohexene.[37,38] That a Diels–Alder product may arise from a stepwise path is not as unimaginable today as may have been the case just a few years ago.[39–42] In more elaborate contexts as well, regiochemistry may be successfully rationalized through estimations of the relative stabilities of diradical intermediates.[43]

When 1,1-disubstituted ethylenes are dimerized, the same regiochemistry is observed. Alkenes (**9**),[44,45] (**10**)[46–49] and (**11**)[50] all dimerize with head-to-head regiochemistry and give *cis/trans* mixtures of 1,1,2,2-tetrasubstututed cyclobutanes. In more highly substituted systems the same pattern is followed: the trifluorostyrene (**12**) gives the head-to-head dimers (**13**) and (**14**),[51] and the cyanodihydropyridine (**15**) gives the tricyclic structure (**16**).[52]

One may see [2 + 2] cycloadditions of alkenes even when radical-stabilizing groups are lacking if the alkene is of relative high energy: cyclopropenes,[53] methylenecyclopropenes, bridgehead alkenes[54] and *trans*-cycloalkenes exemplify the point.

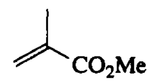
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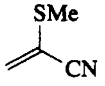
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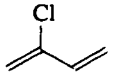
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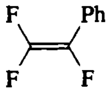
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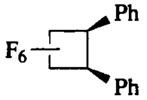
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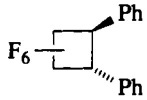
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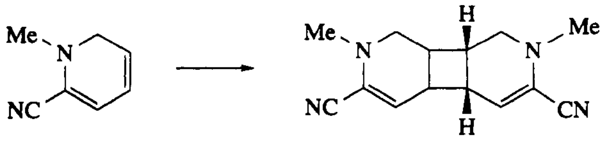
**(15)** **(16)**

3,3-Dicyclopropylcyclopropene$^{55}$ and 3,3-dimethoxycyclopropene$^{56,57}$ both dimerize readily (**17** → **18**). Cyclopropenes having a hydrogen at C-3 often give dimers generated through ene reactions, rather than from [2 + 2] cycloadditions.

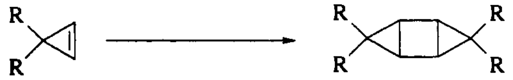
(**17**) R = cyclopropyl or methoxy (**18**)

Methylenecyclopropene (**19**) dimerizes to give (**20**) and (**21**) in a 92:8 ratio.$^{58-61}$ Bicyclopropylidene (**22**) is converted in 35% yield to dimer (**23**);$^{62}$ a competitive methylenecyclopropane rearrangement forming (**24**) is the major side reaction.

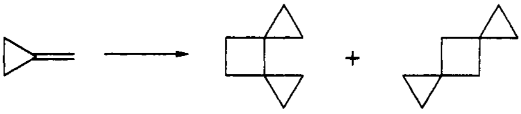
**(19)** **(20)** **(21)**

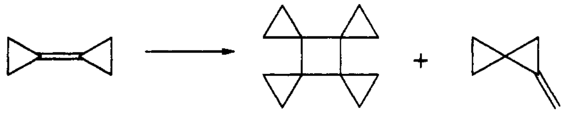
**(22)** **(23)** **(24)**

7-Methylenenorbornadiene and tetracyanoethylene give a [2 + 2] adduct, even though the methylene double bond is not directly conjugated with the other two double bonds;$^{63}$ the formal [2 + 2] cycloadditions of pentalenes are probably best viewed as allowed [2 + 8] reactions.$^{64}$

Bridgehead alkenes such as adamantene$^{65-70}$ and 3-homoadamantene (**25**)$^{71}$ dimerize to give mixtures of head-to-head and head-to-tail [2 + 2] cycloadducts. 3-Homoadamantene reacts to form five dimers, four of which have been assigned as structures (**26**) and (**27**). The diradical intermediates corresponding to the regiochemical alternatives are apparently of comparable energy, and the intermediates show competitive rotations about carbon–carbon single bonds and cyclobutane bond-forming reactions. 1-Norbornene$^{72}$ and bicyclo[2.2.2]oct-1-ene$^{73}$ react similarly.

Bicyclo[4.4.1]undec-1(11)-ene (**28**), however, exhibits different behavior, for it dimerizes in 95% yield to form structure (**29**).$^{74}$ Whether this process involves hydrogen atom transfer from a tetramethylene diradical, or an unusual pericyclic reaction reminiscent of an ene reaction, remains unclear.

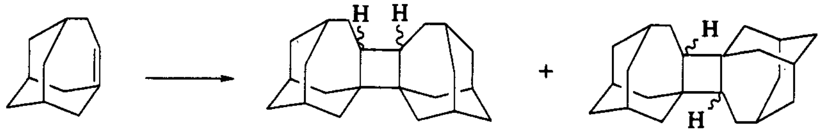

**(25)** **(26)** **(27)**

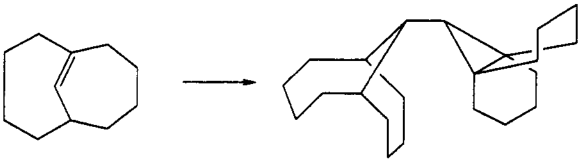

**(28)** **(29)**

Bicyclo[2.2.0]hex-1(4)-ene (**30**) dimerizes cleanly at 0 °C in very dilute solution; the products eventually isolated plausibly stem from a [2 + 2] cycloaddition to form (**31**), followed by [2 + 2] retroadditions in two different ways to give (**32**) and (**33**).[75,76]

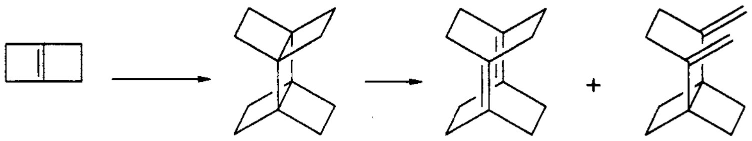

**(30)** **(31)** **(32)** **(33)**

The [2 + 2] dimerizations of *cis,trans*-1,5-cyclooctadiene (**34**), uncovered by Ziegler and coworkers in 1954,[77] have been studied more recently by other groups; Leitich[78] showed that three stereoisomers are formed, and assigned them as (**35**), (**36**) and (**37**).

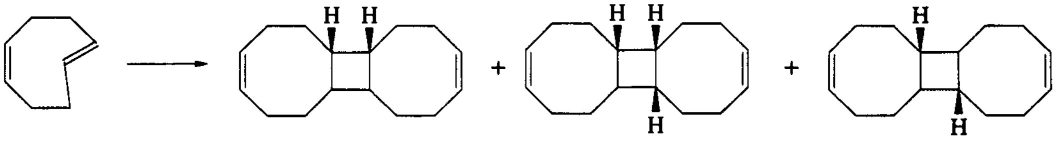

**(34)** **(35)** **(36)** **(37)**

When (*R*)-(−)-(**34**) is dimerized, only the second and third isomers are formed (26%, 74%), both in dextrorotatory form, suggesting that the first isomer obtained with racemic starting material stems from a pair of enantiomers. Even though the monoinversion product (the $[_{\pi}2_s + {}_{\pi}2_a]$ product) is not the major product with either racemic or optically active *cis,trans*-diene, the fact that it is formed at all has been read as an indication that Woodward–Hoffmann theory has some predictive validity even for reactions which are not concerted.[78] The normal diradical formulation rationalizes this outcome differently.

Largely similar behavior is evident in the dimerizations of *cis,trans*-1,3-cyclooctadiene (**38**),[79] *trans,cis*-2,4-cyclooctadienone (**39**)[80] and bicyclo[4.2.2]deca-3-*trans*,7,9-triene (**40**).[81]

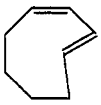

**(38)**

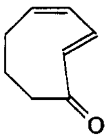

**(39)**

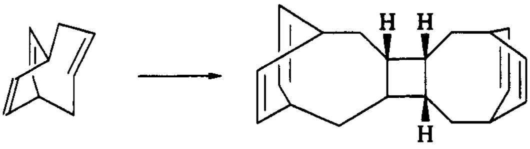

**(40)** **(41)**

The dimers from the bridged *trans*-cyclooctene (**40**) include the $[_{\pi}2_s + {}_{\pi}2_a]$ product (**41**), a result which in 1969 was seen as a beautiful example of a $[_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition,[25] a characterization amplified in the secondary literature.[82] The same nomenclature is legitimately and conveniently used here for two different purposes, once to designate the stereochemistry of a product and again to describe a reaction mechanism; but the product here, as elsewhere, does not inevitably signal the mechanism. The Woodward–Hoffmann theory fails to account for the other two dimers, one of which is the major isomer at 40 °C. Perhaps all three could be rationalized in a uniform and unexceptional fashion through a diradical formulation, and special treatment for the $[_{\pi}2_s + {}_{\pi}2_a]$ product could be unnecessary.

Stereochemical studies add great support to the proposition that [2 + 2] cycloadditions involve tetramethylene diradical intermediates, for these additions take place with partial or complete loss of *cis*/*trans* stereochemical relationships present in alkene reactants. The dimerization of acrylonitrile, for example, studied with *cis*-1,2-dideuteriocyanoethylene (**42**), gives six distinct [2 + 2] adducts:[83] the distribution of deuterium labels in the *cis*-1,2-dicyanocyclobutane products are given in structures (**43**), (**44**) and (**45**); an analogous set of three *trans* stereoisomers is formed. Recovered starting material shows partial loss of stereochemical integrity.

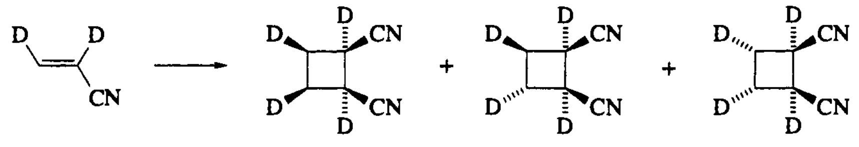

(**42**) (**43**) (**44**) (**45**)

## 2.1.3 INTRAMOLECULAR AND MIXED [2 + 2] CYCLOADDITIONS

Several fascinating intramolecular [2 + 2] cycloadditions of cyclopropenes have been explored by Padwa and coworkers;[84–92] a typical example is 1,2-diphenyl-3-methyl-3-*o*-vinylphenylcyclopropene, which gives a [2 + 2] intramolecular product in 100% yield. The analogous *o*-*trans*-propenyl system (**46**) reacts to yield isomers (**47**; 82%) and (**48**; 18%).

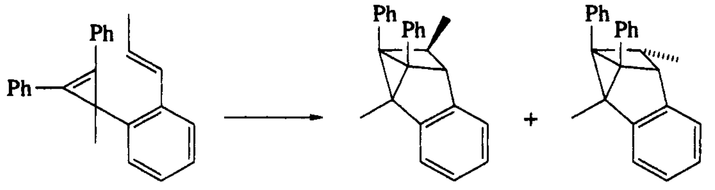

(**46**) (**47**) (**48**)

If this reaction is initiated through formation of a cyclopropylbenzylic/benzylic diradical, then product regiochemistry is set when the first bond is made to generate (**49**) or (**50**). The former leads to the major product while the latter gives the *endo* isomer (**48**), following a conformational isomerization involving substantial rotations about several carbon–carbon bonds. The substituted tetramethylene diradical (**50**) may then have a substantial lifetime, and formation of diastereoisomeric diradicals may lead to diastereoisomeric products; such product mixtures need not derive from partitioning of a single, common intermediate, though in many cases they undoubtedly do.

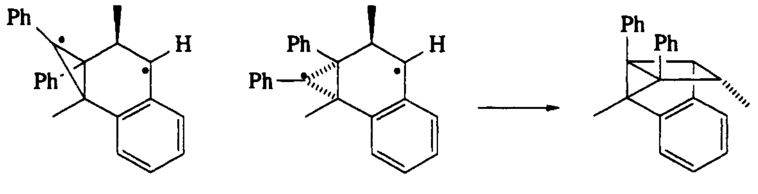

(**49**) (**50**) (**48**)

The *cis*-propenyl analog (**51**) gives exclusively an ene reaction product, (**52**).

Intramolecular [2 + 2] cycloaddition of acyclic substrates take place when some activating substituent is present; for hydrocarbons, conjugating vinyl or phenyl groups are sufficient. Tetraene (**53**) gives products (**54**) and (**55**),[93] and the diphenylheptadiene (**56**) is converted thermally to the bicyclo[3.2.0] system (**57**).[94]

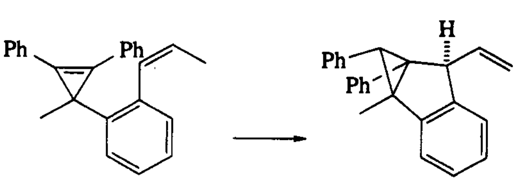

(51) (52)

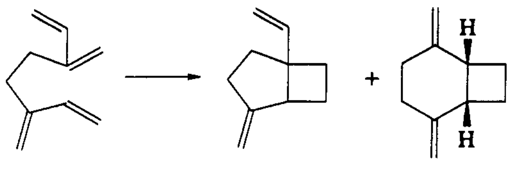

(53) (54) (55)

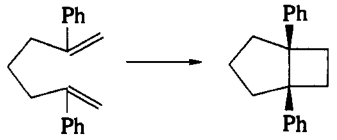

(56) (57)

The regiochemistry of intramolecular [2 + 2] cycloadditions depends on the relative stabilities of alternative 1,4-diradical intermediates, which may depend both on C-1/C-4 substituents in the tetramethylene and on geometrical constraints. 1,8-Divinylnaphthalene (**58**) isomerizes at 150 °C to cyclobutane products (**59**) and (**60**) in a 75:25 ratio, implying that diradicals (**61**) and (**62**) have similar heats of formation.[95,96] The dibenzylic diradical intermediate (**62**), presumably, is restricted geometrically so that both radical centers may not simultaneously be in full conjugation with the π-system of the naphthylene moiety. The analog (**63**) gives just one isomeric product (**64**), formally corresponding to a [${}_{\pi}2_s + {}_{p}2_a$] cycloaddition. The diradical involved has ample time to achieve this stereochemical result.

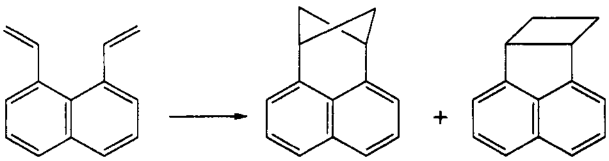

(58) (59) (60)

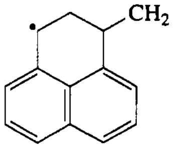

(61)

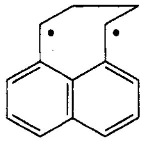

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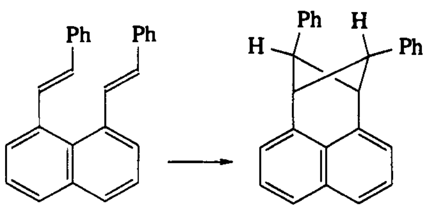

(63) (64)

The styrene derivatives studied by Oppolzer are less constrained, and the regiochemistry is governed by the placement of substituents (**65** → **66**; **67** → **68**).[97]

A variation on these themes allowed Alder and Bellus to realize a thermal head-to-tail [2 + 2] addition of two acrylic units (**69** → **70**).[98]

Annulated polyenes like (**71**) and (**72**) isomerize at 180–200 °C to give [2 + 2] intramolecular cycloadducts, with yields and stereochemical details dependent upon the structure and stereochemistry of the

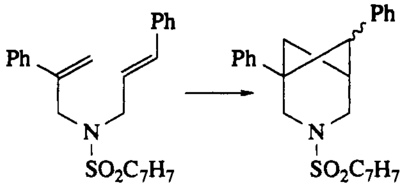

**(65)** **(66)**

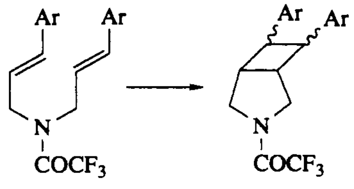

**(67)** Ar = $p$-ClC$_6$H$_4$ **(68)**

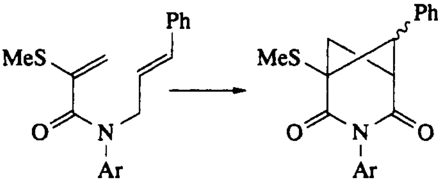

**(69)** Ar = 3,5-Cl$_2$C$_6$H$_3$ **(70)**

starting material.[99–102] At higher temperatures one obtains products derived from a cycloaddition–cycloreversion sequence, such as phenanthrene (from **71** and **72**) and acenaphthalene (from **72**).

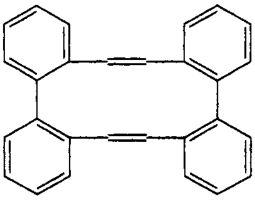

**(71)**

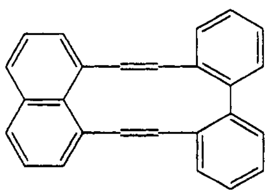

**(72)**

Pairs of similar alkenes may give useful yields of cycloadducts when one may be employed in large excess: the isomers of 2-butene will add to ethylene at 360–430 °C, giving 1,2-dimethylcyclobutanes showing some but not complete loss of stereochemistry.[103,104]

Pairs of alkenes with complementary donor–acceptor properties often give good yields of [2 + 2] cycloadducts. The relatively electron-deficient fluoro- and fluorochloro-alkenes, such as tetrafluoroethylene and 1,1,2,2-difluorodichloroethylene, are excellent participants in thermal [2 + 2] cycloadditions, providing efficient access to many novel and valuable compounds.[3] Mechanistic investigations with these alkenes sustained the credibility of the diradical intermediate mechanism, and attributed heightened reactivity both to destabilization of the ethylene reactant and stabilization of the intermediate by substituents.

In a series of classic papers, Bartlett and coworkers determined regiochemistry and reaction stereochemistry for additions of 1,1-dichloro-2,2-difluoroethylene with conjugated dienes.[5,6] These cycloadditions invariably proceed with the first new bond made between one end of the diene and the difluoro-substituted carbon of the halogenated alkene.[105] For the isomers of 2,4-hexadiene, all cycloaddition products were formed with this regiochemistry, one consistent with formation of the more stable allyl dichloro-substituted diradical intermediate; from each isomeric 2,4-hexadiene the adducts observed were consistent with competitive rates of rotation about carbon–carbon single bonds and formation of the cyclobutane adduct through bond making.[106] The *trans,trans* isomer gave rise to cyclobutanes (**73**) and (**74**), while the *cis,cis* diene gave only isomers (**75**) and (**76**). *cis,trans*-2,4-Hexadiene gave a mixture of all four adducts (**73**)–(**76**).

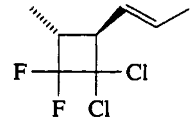

**(73)**

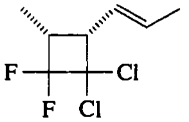

**(74)**

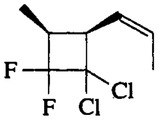

**(75)**

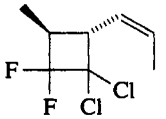

**(76)**

Loss of stereochemical relationships present in starting alkenes in product cyclobutanes was demonstrated as well for additions involving ethylene or the 2-butenes with tetrafluoroethylene (TFE). The *cis* and *trans* isomers of 1,2-dideuterioethylene and TFE gave a mixture of both (**77**) and (**78**) in comparable proportions.[107] The isomers of 2-butene give (**80**) and (**81**) (42:58 from *cis*-2-butene, 28:72 from *trans*-2-butene).[108]

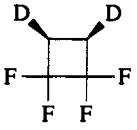

(**77**)

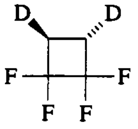

(**78**)

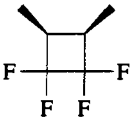

(**79**)

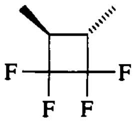

(**80**)

The loss of stereochemistry possible at the diradical stage, and the possible reversion of the diradical to alkenes, may lead to some loss of stereochemical integrity in recovered starting material. This occurrence is consistent with the mechanistic model, and it may be exploited by employing a reagent capable of reacting with an alkene to form a diradical, but reluctant to give a [2 + 2] adduct. 9-(Difluoromethylene)fluorene (**81**) serves well in this capacity: it will catalyze the isomerization of, but does not give cycloaddition products with, the 2,4-hexadienes.[5]

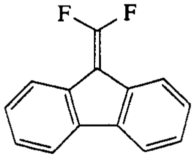

(**81**)

Fluorine and hydrogen appear comparable as radical-stabilizing groups, for both 1,1-difluoroethylene and trifluoroethylene react with butadiene to give mixtures of [2 + 2] regioisomers, as well as some [2 + 4] products.[109,110] Captodative substituted alkenes, not surprisingly, are well suited to [2 + 2] cycloadditions.[111-113]

For alkene–diene or diene–diene reactions, [2 + 2] additions are often in competition with Diels–Alder reactions: the balance is extremely system dependent. Only [2 + 2] products will be formed when the diene is restricted to the *(S)-trans* geometry, as in the reactions of dienes (**82**)[114] and (**84**)[115] with TCNE to give [2 + 2] adducts (**83**) and (**85**). Other conformationally mobile dienes give [2 + 2] rather than [2 + 4] adducts when reacting intramolecularly because the Diels–Alder alternative would lead to relatively unstable products, as in the isomerizations of (**86**) to (**87**)[116] and of (**88**) to (**89**).[117]

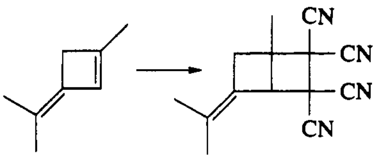

(**82**) (**83**)

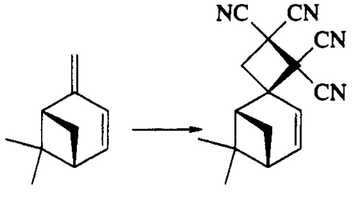

(**84**) (**85**)

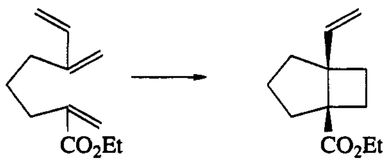

(**86**) (**87**)

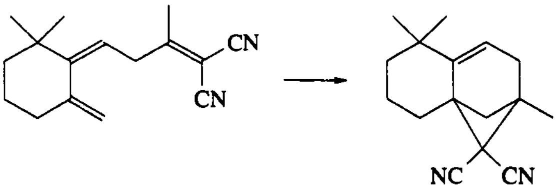

(**88**) (**89**)

When the tetramethylene intermediate involved in [2 + 2] cycloadditions lacks stabilizing functionality at both termini, and the diene is free to assume, or is locked into, the *(S)-cis* conformation, the Diels–Alder process dominates: ethylene and butadiene give vinylcyclobutane and cyclohexene in 1:5000 proportions.[5] While 4-methylpenta-1,3-diene[118] or bicyclopropylidene and TCNE give both [2 + 2] and [2 + 4] addition products,[119,120] only [2 + 2] cycloaddition is seen with 2,5-dimethylhexa-2,4-diene.[121]

For dienes existing as mixtures of *(S)-cis* and *(S)-trans* conformational isomers, reaction in the *(S)-trans* form will lead to [2 + 2] adducts, while reaction to generate a diradical from the *(S)-cis* form may lead to either [2 + 2] or [2 + 4] products. Temperature-dependent product ratios correlate with temperature-dependent *(S)-cis/(S)-trans* conformer populations for the reactions between 1,1-difluoro-2,2-dichloroethylene and butadiene.[122]

This competition between [2 + 2] and [2 + 4] cycloaddition modes presents both a fascinating mechanistic topic[123–126] and an occasionally daunting synthetic hazard, especially since many alkenes that are particularly reactive in [2 + 2] additions are also excellent dienophiles in Diels–Alder reactions. Frontier molecular orbital analysis provides useful insight regarding this parallelism in relative reactivity. Houk and others[127–129] have developed this treatment, especially for reactions between a substituted ethylene and another $\pi$-system, finding that cycloaddition rates may be increased when strong electron-withdrawing groups are present on the ethylene. Correlations between reaction rates for Diels–Alder reactions of 9,10-dimethylanthracene[130] and the ionization potentials (or LUMO energies) of cyano- and polycyanoethylenes as dienophiles validate this view. According to the FMO model, when substitution reduces the donor–acceptor HOMO–LUMO energy separation, the transition state energy may be reduced through configuration interaction. Although Diels–Alder reactions may be symmetry allowed, they still may be facilitated through configuration interaction between ground state and charge-transfer configuration. Evidence of other sorts indicative of significant charge-transfer configuration involvement in Diels–Alder reactions continues to accrue.[131–136]

For [2 + 2] cycloadditions of electron-poor and electron-rich pairs of alkenes, configuration interaction is not just marginally helpful: it is of dominant importance. Without it, activation energies would ordinarily be not just a bit higher, but drastically higher. Interestingly, the nucleophilicities of the cyanoethylenes as two-bond nucleophiles in Diels–Alder reactions and as one-bond nucleophiles in [2 + 2] cycloadditions going by way of 1,4-dipolar intermediates are projected to be approximately the same.[128]

Careful product and kinetic studies for selected electron-deficient alkenes, electron-rich dienes and vinyl-substituted aromatic systems have provided some clarification of the [2 + 2] *versus* [2 + 2] cycloaddition issue. The thermodynamically favored product can often be anticipated on structural grounds. Reactions of TCNE with vinyl-substituted benzenoid aromatics,[5] protoporphorins[137] or heteroaromatics[138] give [2 + 2] products, but for some styrenes the [2 + 4] addition may be kinetically favored. *p*-Methoxystyrene and TCNE react to form a charge-transfer complex which leads reversibly to the Diels–Alder product, and eventually to the finally isolated [2 + 2] adduct.[139–142] An isomer of dicyclopentadiene shows the same pattern, with the initially formed Diels–Alder adduct giving rise to a [2 + 2] adduct.[143]

It is not known with firm assurance if products in these reactions come directly from a charge-transfer complex. Under normal reaction conditions the kinetic behavior of these systems is not sensitive to whether the complex is on the reaction path or is just the product of a dead-end side-equilibrium process.[144] For one Diels–Alder reaction, Kiselev and Miller have demonstrated that the donor–acceptor complex is on the reaction path.[145] Similar studies for representative [2 + 2] additions remain on the agenda, for the issue is of fundamental importance even though it has proven to be a very difficult one to resolve.

Other [2 + 2] cycloadditions based on electron-rich and electron-poor alkenes, such as alkoxyethylenes and TCNE, an extremely electron-deficient alkene, were reported in the late 1950s. Dienes restricted to an *(S)-trans* geometry, thus obviating competitive [2 + 4] additions, and electron-rich alkenes of all sorts give [2 + 2] adducts with TCNE.[146–148] The scope of such additions has continued to develop impressively: TCNE has been added successfully to hundreds of substituted alkenes, and other pairs of alkenes having complementary substituents, making one electron-rich (donor substituents), the other electron-poor (acceptor substituents), have been shown to give similar facile [2 + 2] cycloadditions. Vinylcyclopropanes,[149–152] enamines,[153–157] ketene acetals[158–162] and other activated alkenes[163–165] will combine with alkenes substituted with electron-withdrawing groups. Ketene acetal (**90**), for instance, reacts with acrylic ester (**91**) to give adduct (**92**).[158]

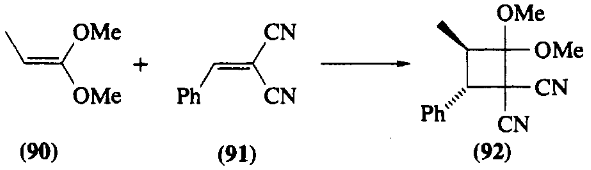

(**90**) (**91**) (**92**)

Substituent effects for typical [2 + 2] cycloadditions between electron-rich and electron-poor alkenes demonstrate a high degree of dipolar character in the transition structure; for *p*-substituted styrenes and TCNE[6] the first-order rate constants for disappearance of the π-complexes and for formation of cyclobutane products correlates well in a Hammett treatment with $[\sigma + 1.21(\sigma^+ - \sigma)]$, and $\rho = -7.1 \pm 0.5$; there is a high degree of charge transfer in the transition structure. For aryl alkenyl sulfides reacting with TCNE the ρ-value of the Hammett correlation is similarly large and negative, –5.5.[166] These and other studies lead naturally enough to consideration of whether 1,4-zwitterionic intermediates might be involved.

### 2.1.4 DIRADICAL *VERSUS* ZWITTERIONIC INTERMEDIATES

The 1,4-tetramethylene diradical has been subjected to numerous theoretical investigations using a full range of calculational methods[167–172], from the most rudimentary to the most computationally sophisticated. The dimerization of ethylene to generate the diradical has also been modeled theoretically. The diradical mediated path is strongly favored over the orbital symmetry allowed but geometrically awkward $[{}_{\pi}2_s + {}_{\pi}2_a]$ concerted cycloaddition.

From the perspective of theory, a tetramethylene intermediate substituted with a donor such as methoxy and an acceptor such as cyano is viewed as a resonance hybrid of a singlet diradical canonical form (**93**) and a zwitterionic form (**94**).[173–178] Alternatively, the state wavefunction for the substituted tetramethylene may be derived through configuration interaction which mixes the molecular orbital electronic configurations appropriate to forms (**93**) and (**94**). (Another, higher-energy zwitterionic configuration could be included in the calculation, but would contribute relatively little). Such tetramethylene systems would then in principle span a full range of possibilities from diradicals at one extreme to real zwitterions at the other. In between these extremes the resonance hybrid form, neither a perfectly pure diradical nor a true zwitterion, would be of lower energy than either canonical form would have by itself, and one may validly consider there to be a continuous range of possibilities between diradical and zwitterionic forms. The relative weights of diradical and zwitterionic forms will depend upon the donor and acceptor substituents, other structural factors, and probably on conformation and solvent.[179–182]

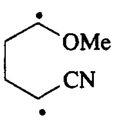

**(93)**

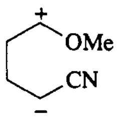

**(94)**

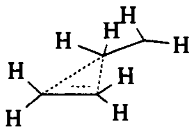

**(95)**

The issue here is not merely semantic, or of interest only to theoreticians, for the representations (**93**) and (**94**) imply different chemical propensities and properties to a synthetic organic chemist, and one or another style of representation will influence synthetic planning and rationalizations of observed reaction product mixtures.

Interestingly, some polar character may even be involved in what would seem to be a purely diradical mediated cycloaddition, the dimerization of ethylene. The transition structure for the first step in this addition, according to some calculations,[183] is of tricentric geometry (**95**) and it involves transfer of 0.11 electron unit of charge from the ethylene moiety in the three-membered ring to the distant $CH_2$ of the other ethylene, a reminder that the diradical/zwitterion dichotomy need not be absolute. Other calculations suggest other geometries for this transition structure.[171,184,185]

Calculations for substituted tetramethylene systems, using both semiempirical and *ab initio* methodologies, have been reported for several representative [2 + 2] cycloaddition reactive intermediates one might expect to have some dipolar character. Hydroxyethylene and acrolein lead to a 1-formyl-4-hydroxytetramethylene (**96**) having high diradical character and low zwitterionic character, according to spin density and charge transfer criteria.[186,187] The net transfer of electric charge from hydroxyethylene to acrolein is only 0.09 of one electron unit, suggesting that there is no essential theoretical difference between the diradical character of the intermediate of a polar and of a nonpolar [2 + 2] cycloaddition. Hydroxyethylene and TCNE similarly react to give, according to MNDO with CI calculations, an intermediate of extended conformation (**97**) that is essentially a diradical.[188]

For the [2 + 2] cycloaddition of hydroxyethylene to 1,1-dicyanoethylene the intermediate exists in a very shallow potential well and has largely diradical, but some zwitterionic, character: the charge transfer amounts to 0.2 electrons.[183] The overall transition state for the reaction, which is the transition state

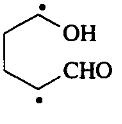

**(96)**

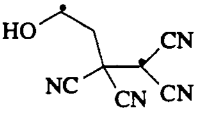

**(97)**

leading from intermediate to product, has more zwitterionic character, with 0.53 electrons transferred, as the second bond is just beginning to be formed.

Similar calculations of acid-catalyzed [2 + 2] cycloadditions between hydroxyethylene and acrolein show drastic alterations in reaction profile, with the catalyst lowering the overall energy requirements and changing the rate-determining step.[189,190] For the reaction catalyzed by $BF_3$, $NH_4^+$ or $H^+$, the formation of the first bond to give the tetramethylene becomes rate limiting; for the uncatalyzed cycloaddition the second bond formation is the slow step. The catalyst stabilizes both intermediate and second transition state as it 'amplifies' charge transfer between the cycloaddition partners. The first transition state is only slightly lowered, so by default it becomes the rate limiting step.

Other theoretical studies have been concerned with diradical or zwitterionic tetramethylenes approached from [2 + 2] cycloreversions. For 1,1-dicyano-2-methoxycyclobutane, cleavage of C-1—C-2 gives a *gauche* intermediate (**98**) which may isomerize to the *trans* intermediate (**99**). They are nearly isoenergetic, and both have predominant diradical character.[191,192]

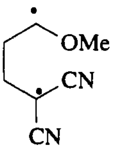

**(98)**

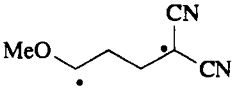

**(99)**

Hall has introduced an empirical test to estimate the relative importance of diradical and zwitterionic forms in tetramethylene intermediates: *trans*-1,4-tetramethylene diradical intermediates may initiate alternating radical copolymerizations if they add to another alkene faster than they undergo conformational isomerization to the *gauche* form and give a cyclobutane product through carbon–carbon bond formation, while zwitterionic 1,4-tetramethylene intermediates may initiate ionic homopolymerizations.[193–204] This empirical yardstick draws a boundary between [2 + 2] cycloadditions that occur through essentially diradical or essentially zwitterionic tetramethylenes; the resonance hybrid view which encompasses a continuous range of more or less dipolar intermediates is neglected in favor of a more decisive either/or discrimination.

Application of this postulate to a wide variety of reactions demonstrates that diradical behavior persists even with substitutents one might have expected to support zwitterionic behavior. Vinyl ethers and 1-cyano-1-alkoxycarbonylethylenes, for instance, according to the Hall hypothesis, react to give [2 + 2] adducts by way of diradical intermediates (**100**), and dimethyl cyanofumarate and *p*-methoxystyrene show the behavior expected of a reaction mediated by diradical (**101**), even though both reactions might well have been plausibly represented as involving 1,4-zwitterionic intermediates. Diradical (**101**) was successfully trapped using the 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.

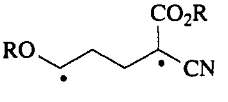

**(100)**

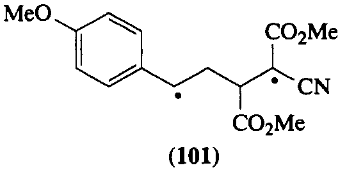

**(101)**

A matrix display of reactive alkenes, with more and more powerful donor and acceptor substituents arrayed in columns and rows, affords a visual representation of the transition between diradical and zwitterionic additions;[199] this 'periodic chart' of thermal [2 + 2] cycloadditions of alkenes makes vivid the wide range of acceptor- and donor-substituted alkenes which show these additions and the demarcation, as derived from the empirical rule or hypothesis given above, between diradical and zwitterionic behavior. The chart contains mostly diradical entries; zwitterionic intermediates are inferred, according to the criterion adopted, for only a few very strong donor-substituted–strong acceptor-substituted pairs of reactants. When the donor–acceptor potency of reactants becomes somewhat more extreme, electron transfer processes intervene and products derived from radical ion pair intermediates are formed.

While this empirical approach has undeniable merits, its application through experimentation poses some potential limitations, since any extraneous initiation of an ionic homopolymerization could be misinterpreted as indicating the presence of a zwitterionic intermediate. This concern is underscored by reported instances of polymerization initiated by TCNE or by impurities in TCNE,[205,206] or by acidic products derived from an electron-poor alkene and adventitious water,[207] and by other manifestations of acid-catalyzed chemistry accompanying attempted cycloaddition reactions. The isomerization of *trans,trans*-2,4-hexadiene to 1,3-hexadiene in the presence of 1,10-difluoro-2,2-dichloroethylene,[5] and the catalyzed addition of methanol to *anti*-sesquinorbornene (**102**) to afford ether (**103**)[208] are illustrative.

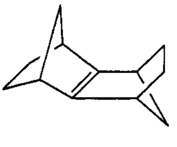

**(102)**

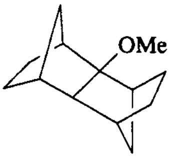

**(103)**

For a series of 10 donor–acceptor substituted *trans*-tetramethylenes, calculations[209,210] have shown a trend paralleling the empirical diradical/zwitterionic test proposed by Hall. Three of the ten cases, (**104**), (**105**) and (**106**), were predicted to have zwitterionic ground states.

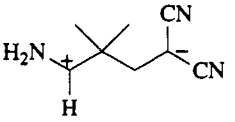

**(104)**

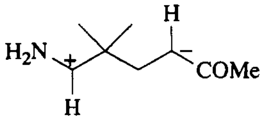

**(105)**

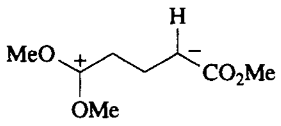

**(106)**

Some cases found empirically by Hall to fall in the zwitterionic category were redesignated as diradicals through these calculational findings, but the overall trends of the empirical scheme were duplicated.

Reviewing the various sorts of evidence employed as mechanistic criteria for cycloadditions involving dipolar intermediates, Gompper[211] concluded that detection of such intermediates through spectroscopic or kinetic methods, or through interception reactions, offers the most generally valid proof. Alternative grounds for mechanistic deductions, based on stereochemical tests, substituent effects, solvent effects on rates, kinetic isotope effects, and activation parameter comparisons, all suffer from a lack of wide-ranging applicability: they may be used only in special cases.

This cautionary attitude toward the standard enumeration of mechanistic criteria seems fully justified when one reflects on the sorts of evidence advanced in support of 1,4-tetramethylene zwitterionic intermediates in thermal [2 + 2] cycloadditions.

Numerous [2 + 2] cycloadditions which may proceed through dipolar intermediates (tetramethylenes which may be represented as resonance hybrids of singlet diradical and zwitterionic forms) react with partial or even complete loss of the stereochemical relationships present in starting materials. Reactions between the *cis* and *trans* isomers of 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*- and *trans*-propenyl *n*-propyl ether are not completely stereoselective. The *trans* electrophilic alkene (**107**) and the *cis* isomer of the enol ether (**108**), for instance, give rise to products (**109**), (**110**) and (**111**), the last having trifluoromethyl groups in *cis* relationship one to the other.[212]

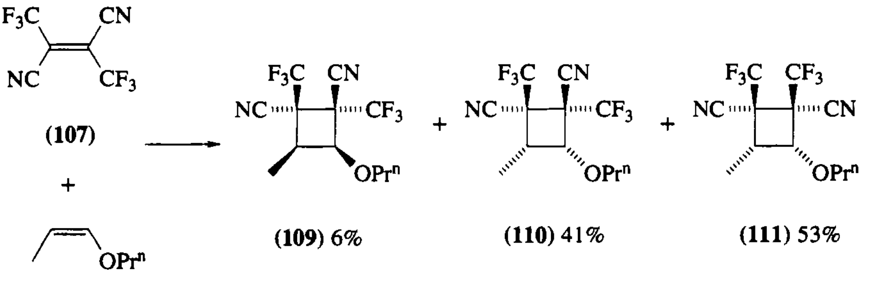

**(107)**

**(108)**

**(109)** 6%

**(110)** 41%

**(111)** 53%

A thorough stereochemical study of a very similar reaction with *cis*- and *trans*-propenyl methyl ether as electron-rich alkenes provides comparable findings.[213] The *trans* isomer of 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*-propenyl methyl ether (**112**) gave adducts (**113**), (**114**) and (**115**). In some cases, adducts revealing some loss of stereochemistry in the enol ether component were detected and identified.

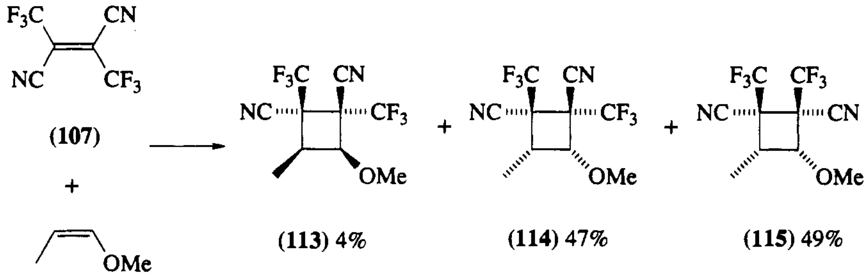

(**107**)

(**112**)

(**113**) 4%

(**114**) 47%

(**115**) 49%

For other examples of ostensibly similar cycloadditions, however, quite different stereochemical results have been obtained, ranging from complete loss (**116** + **117** → **118**; the *trans*-propenyl enamine also gives adduct **118**!)[214,215] to complete retention of stereochemistry: tetramethoxyethylene reacts with (**107**) to give only the [2 + 2] adduct (**119**).[216,217]

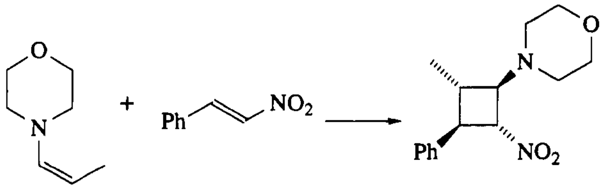

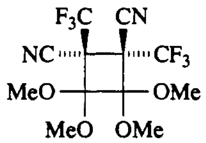

(**116**) (**117**) (**118**) (**119**)

Loss of stereochemistry may be plausibly rationalized either through postulation of a diradical intermediate, or a zwitterionic intermediate, or a dipolar intermediate; an observed loss of stereochemistry in [2 + 2] cycloadditions does not help one determine the relative importance of diradical and zwitterionic forms. Complete preservation of stereochemistry, as in the reactions between the 1,2-bis(trifluoromethyl)-1,2-dicyanoethylenes and tetramethoxyethylene, does not necessarily imply a concerted reaction, one with no intermediate on the potential energy surface. There are cogent theoretical reasons for believing that [2 + 2] cycloadditions between very electron-rich and very electron-poor alkenes might be concerted pericyclic processes;[218–225] the Woodward–Hoffmann rules presuppose that a reaction under consideration may be modeled adequately from start to finish with single configuration wavefunctions, and they may be quite irrelevant here, where strong mixing of a charge-transfer configuration is probably involved.[226–230] These reactions could also involve an intermediate that collapses to product faster than it can suffer rotations about carbon–carbon single bonds. This situation may obtain in the decomposition of (**120**) to (**121**) with high stereoselectivity, even though the reaction is believed to proceed in a step-wise fashion.[231]

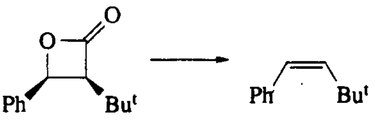

(**120**) (**121**)

Early work on dipolar [2 + 2] cycloadditions showed that some were extremely sensitive to solvent effects. Qualitative observations for the reaction between *p*-methoxystyrene and TCNE showed that it was faster the more polar the solvent; it proceeded about $10^5$ times faster in acetonitrile than in cyclohexane![232,233]

More systematic studies with *trans*-β-methyl-*p*-methoxystyrene and with alkyl vinyl ethers confirmed and extended these remarkably large solvent effects on reaction rates; the reactions of such alkenes with TCNE show large solvent effects and good correlations between solvent polarity, as represented by the $E_T$ parameter, and reaction rates. These large effects were interpreted as support for the intervention of zwitterionic intermediates.[232–238]

The significance of such observations may be inferred from comparisons with solvent effects on the rates of other types of reactions, or on the rates of other reactions believed to be within the same mechanistic category; or one can undertake the thermochemical work necessary to determine changes in heats of solvation for reactants in various solvents and deduce then how much of the observed solvent effect on reaction rates is due to variations in ground-state energies and how much to solvent-sensitive changes in the enthalpy of solution of the transition structure.

For the reaction of (**122**) with TCNE to form (**123**) the rate increase in going from carbon tetrachloride as solvent to acetonitrile is about 4900, while for the reaction of (**124**) with (**125**) to produce (**126**) there is only about a factor of six increase in rate for reaction in acetonitrile relative to reaction in toluene;[239] there is no spectacular solvent effect. Does the latter reaction have a fundamentally different mechanism than is operative in [2 + 2] cycloadditions of enol ethers with TCNE? Are the tetramethylene intermediates of quite different dipolar character?

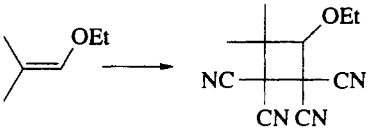

**(122)** **(123)**

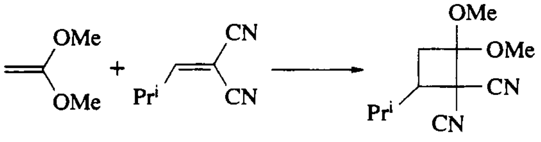

**(124)** **(125)** **(126)**

The [2 + 2] adduct from propenylidenecyclopropane and TCNE undergoes a cycloreversion at 100 °C to give 1,1-dicyanoethylene; the solvent effect on this reaction is quite modest, a result not readily interpretable in terms of a zwitterionic transition state.[240]

Some Diels–Alder reactions have only modest rate responses to changes in solvent,[130,241] and when contrasted with a [2 + 2] addition exhibiting a strong dependence on solvent polarity, a neat mechanistic demarcation may be drawn; distinctions between concerted *versus* nonconcerted reactions, and between early and late transition states,[242] may be advanced. The large solvent effect in the [2 + 2] addition may be ascribed to solvent stabilization of a zwitterionic intermediate. However, when similar reactants, one set giving Diels–Alder product, the other [2 + 2] product, are examined for solvent effects on reaction rates, the dependencies may be virtually identical. A case in point is provided by the reactions of TCNE with 9,10-dimethylanthracene (Diels–Alder reaction) and with 2,5-dimethylhexa-2,4-diene ([2 + 2] cycloaddition).

The solvent effects on rates shown by these two reactions were determined employing the solvents chloroform, dichloromethane, acetonitrile, ethyl acetate, benzene, tetrahydrofuran and dioxane.[243,244] Solvents which react with TCNE, such as nitromethane, dimethylformamide and protic solvents, as well as cyclohexane, carbon tetrachloride and tetrachloroethylene, in which the reactants have very low solubility, were deliberately excluded from the study. The observed solvent effects were virtually identical for both Diels–Alder and [2 + 2] cycloaddition processes. Statistical correlations of rate data using a multiparameter equation with dependencies based on acceptor properties, polarizability and inherent polarity of the solvents gave nearly identical coefficients through the regression analyses for each term for both reactions, and excellent linear fits to the rate data.

Thermochemical studies on the reaction between anthracene and TCNE in various solvents show that solvent-dependent changes in reactivity are largely determined by changes in the enthalpies of solvation of the reactants.[246,247] The same is true for the [2 + 2] cycloadditions between TCNE and *n*-butyl vinyl ether, and TCNE with *trans*-β-methyl-*p*-methoxystyrene.[248] Experimental values for heats of solution and heats of sublimation of reactants allow one to calculate enthalpies of solvation of the reactants in different solvents; plots of $\Delta H^\ddagger$ against $\Delta H$(solvation of reactants) determined for different solvents are linear with slopes of –0.8 and –0.9. The observed changes in enthalpies of solution for the transition structures in these [2 + 2] cycloaddition reactions hardly exceed experimental uncertainties. Only carbon tetrachloride gives points well off the correlation lines, which may be related to the fact that kinetic measurements defining $\Delta H^\ddagger$ values were made in carbon tetrachloride solutions containing high concentrations of enol ether.[249]

Since solvent effects are so variable, and when studied rigorously provide no support for the involvement of solvent stabilization of zwitterionic intermediates, definite mechanistic and synthetic implications follow: observed rate effects in response to changes in solvent must be interpreted with great caution, and heats of solution studies are highly desirable to distinguish solvent-induced variations in ground-state *versus* transition-state energies. At least in the immediate future, new [2 + 2] cycloadditions required to attain given synthetic objectives may be optimized most expeditiously with respect to yield and selectivity through an empirically determined choice of solvent. The importance of solvent effects for the practical exploitation of such reactions can hardly be overemphasized, even though the theoretical explanation of such effects must be approached with discretion.

There are instances when a loss of stereochemistry accompanying a [2 + 2] cycloaddition, as well as the overall rate of reaction, may change with solvent, and typically there is more loss in more polar solvents.[6,249–251] This may reflect a longer lifetime of a tetramethylene species, thus advantaging rotations about carbon–carbon single bonds relative to ring closures, which in turn could be associated with a growing importance of zwitterionic character for the intermediate. Alternatively, the effect might be the outcome of small shifts in relative importance of initial bond-making to form *gauche versus* extended *trans* tetramethylenes. The latter, whether formulated as diradical or zwitterion, should have better prospects of losing stereochemical integrity prior to forming a cyclobutane product. This possibility may be compared with the cycloaddition chemistry of cyclopropene (**47**) discussed above.

When [2 + 2] cycloadditions are followed as a function of pressure, the volume of activation, $\Delta V^\ddagger$, may be deduced. A number of representative [2 + 2] additions have been investigated in this way: the reactions take place with very large negative activation volumes, ranging from –25 to –45 $cm^3\ mol^{-1}$.[252–265] Intermolecular Diels–Alder reactions typically exhibit large negative volumes of activation also: from –25 to –45 $cm^3\ mol^{-1}$.[266,267] As mechanistically discriminating indicators for concerted *versus* stepwise cycloadditions, then, $\Delta V^\ddagger$ values are not especially telling; nor, incidentally, are $DH^\ddagger$ or $\Delta S^\ddagger$ parameters.[245]

The most curious point respecting volume of activation considerations, however, relates to synthetic applications. While high pressure is now often employed to secure intermolecular Diels–Alder adducts that could not otherwise be formed in reasonable yields, there has been little application of the same tactic to recalcitrant [2 + 2] cycloadditions. The opportunities for synthetic exploitations of the mechanistically oriented $\Delta V^\ddagger$ determinations for [2 + 2] cycloadditions seem essentially untapped (and enormous).

When donor-substituted and acceptor-substituted alkenes complex and suffer a one-electron transfer, the cation radical of the radical cation–radical anion pair may suffer rearrangement at rates competitive with back electron transfer or with radical ion pair recombination. Some vinylcyclopropanes show this phenomenon (**127** → **128** → **129** → **130**);[268] TCNE and the diphenylbenzocyclobutene (**131**) react similarly to form (**134**) by way of (**132**) and (**133**).[269]

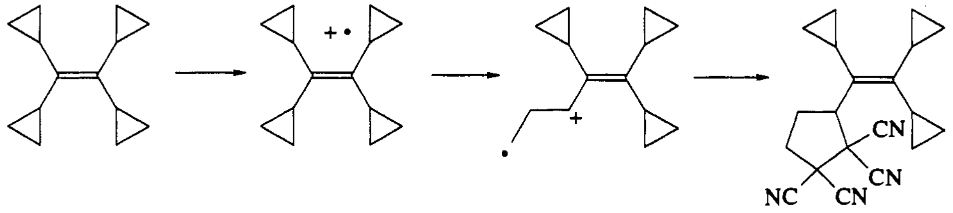

(**127**) (**128**) (**129**) (**130**)

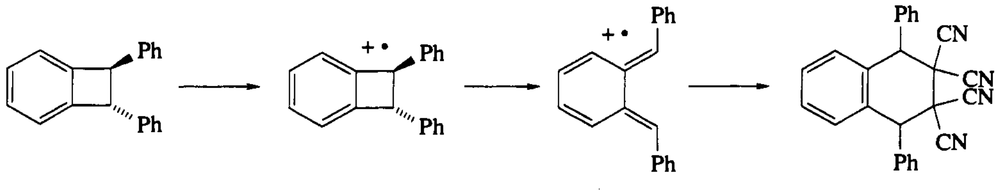

(**131**) (**132**) (**133**) (**134**)

In other cases the one-electron transfer mediated mechanism for rearrangement and final adduct formation is only a conjecture, a possibility, an alternative interpretation. Might it be involved in the reaction of **(135)** with dimethyl methylenemalonate leading to **(136)**[270,271] or of dimethyl fumarate with **(137)** to give **(138)**?[272]

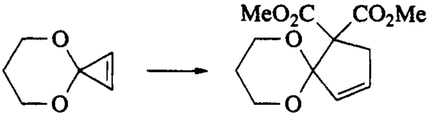

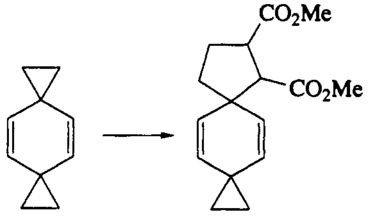

**(135)** **(136)** **(137)** **(138)**

The case for 1,4-zwitterionic intermediates based on chemical trapping experiments depends on obtaining such products using reagents reactive toward the tetramethylene and unreactive toward both addends and the [2 + 2] cycloadduct.

There have been a number of unsuccessful attempts to trap 1,4-zwitterionic intermediates,[217,273–275] but there have also been some reported successes. At best, then, such trapping experiments are not uniformly diagnostic for zwitterionic intermediates. *trans*-Propenyl ethyl ether reacts with TCNE in ethanol solvent at 25 °C to give product **(140)**.[276–279] The normal [2 + 2] adduct **(139)** gives this same product when allowed to react in ethanol, but at a slower rate. Just how fast this solvolysis might take place under the conditions of the cycloaddition reaction, with enol ether and TCNE present, is not clear. Acetone does not interfere with the addition of ethyl vinyl ether to TCNE, but the adduct **(141)** is converted over one week at room temperature to the six-membered ring product **(142)**, which may be postulated as being derived from capture of a 1,4-zwitterionic intermediate in equilibrium with the cyclobutane structure. Alternatively, since acetone like ethanol is known to react with TCNE,[147] it may be a case of acid-catalyzed solvent-assisted solvolysis.

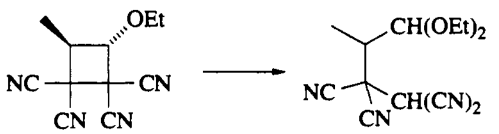

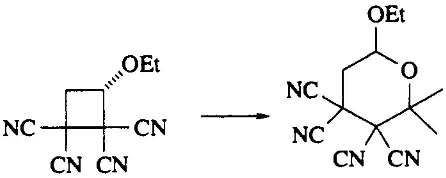

**(139)** **(140)** **(141)** **(142)**

Solvolyses of structures containing relatively polar C—C(CN)₂ bonds have been found by other workers, when the bond cleaved is in a four-membered ring[280] and in larger ring structures: adduct **(143)** gives **(144)** in methanol.[281] Acid catalysis may play a role; it may too in other cases involving cleavage of other kinds of bonds.[282]

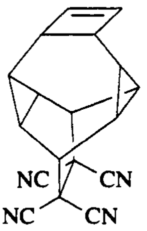

**(143)**

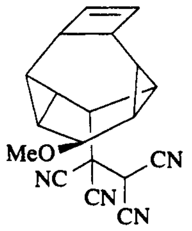

**(144)**

Bicyclopropylidene and TCNE give rise to structures corresponding to trapping of a zwitterionic intermediate by such agents as acetonitrile.[283]

Whatever the difficulties associated with attempts to demonstrate the intervention of 1,4-zwitterionic intermediates, there are undoubtedly reactions for which the zwitterionic formalism provides a convenient model for accounting for the unexpected products sometimes observed,[284–288] and this fact should assure some continuing efforts toward trapping and kinetic experiments designed to test that model.

## 2.1.5 STEREOCHEMISTRY AND SUMMARY

The stereochemistry of thermal [2 + 2] cycloadditions of alkenes is fairly predictable: which of two double bonds in a molecule, and the regiochemistry of addition, may be anticipated with confidence; the extent to which *cis/trans* relationships in alkene reagents will be lost in the adduct is in general not known in advance, and this factor must be taken into account in synthetic planning. The normal expedients (limiting geometrical options through employing cyclic substructures, or using reagents without *cis/trans* stereochemistry, such as 1,1-dimethoxyalkenes) can often obviate this limitation. While solvent effects on loss of stereochemistry during cycloadditions are potential variables to be utilized, the effects are often minor, and the stereochemical objectives have to be balanced against other considerations, including reaction time and yield. The great augmentation in scope of [2 + 2] thermal cycloadditions to be attained through the use of high-pressure reaction conditions may also have a benefit for stereochemical concerns: at higher pressures there may be less loss of stereochemistry accompanying the addition.

The diastereofacial selectivity of [2 + 2] cycloadditions can be quite high, as in the reaction of TCNE with diene (**82**)[115] or with the chiral alkene (**145**) which gives product (**146**) in 94% yield.[289]

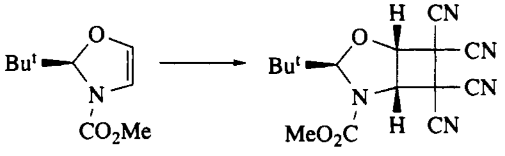

(**145**) (**146**)

Substituents on the carbon atoms involved in the first bond-making step give rise to stereochemical relationships in the product with fairly high selectivity; the larger substituents are disposed in a *trans* orientation in the product, as in the reaction (**90**) + (**91**) → (**92**). Models and theoretical rationales for this favored mode of combination of the two trigonal centers have been advanced.[290–292]

In summary, then, the diradical *versus* zwitterionic issue seems to have shifted in recent years, away from an either/or dichotomy and toward a more integrated view, one seeing tetramethylene intermediates as more or less dipolar diradicals. A small amount of zwitterionic character does not obviate the essentially diradical nature of these intermediates, any more than monoradicals forego radical character if they are more or less electrophilic or nucleophilic.

A little bit of zwitterionic character goes a long way energetically, especially in transition states for cyclobutane formation. 1,4-Zwitterionic tetramethylene intermediates in [2 + 2] cycloadditions may well be important in some reactions, where donor and acceptor substituents are so strong that diradical character is overshadowed and yet one-electron transfer does not take over, but they do not at this point seem common.

The stereochemical characteristics of thermal [2 + 2] cycloadditions of alkenes seem fairly well defined, but substantial further developments and elaborations on stereochemical aspects of the reaction may be anticipated. The ground work has been done, but full development of the potential of the reaction for stereocontrolled synthetic operations still lies ahead.

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# 2.2

# Formation of Four-membered Heterocycles

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## 2.2.1 INTRODUCTION

Among the four-membered heterocycles, 2-azetidinones have received considerable attention due to the presence of a β-lactam ring as an important structural feature for the biological activity of penicillins, cephalosporins and related antibiotics.[1,2] Recent reviews of β-lactam syntheses have been given by Sammes,[3] Isaacs,[4] Mukerjee,[5,6] Hegedus,[7] Labia[8] and Barrett.[9] The most complete and exhaustive accounts covering the chemistry of small heterocyclic rings are found in the well-known series edited by Weissberger[10] and Hassner.[11]

The replacement of carbon atoms of cyclobutane by heteroatoms introduces functionalities which show increased reactivity resulting from the ring strain. This often leads to unusual properties which make four-membered heterocycles useful as synthetic intermediates.[12–18] However, it also adds a new dimension of difficulty concerning the synthesis of these heterocycles. A valuable source of four-membered heterocycles uses the combination of π-bonds. This section is devoted to a survey of these reactions with special focus on selectivity in all of its forms. Photochemical cycloadditions are not discussed here since they are covered elsewhere. In several instances, reactions will be described which can formally be considered as combinations of π-systems but probably take alternate pathways. However, since the real mechanisms are often unknown, these very useful reactions will be discussed here.

## 2.2.2 2-OXETANONES FROM KETENES AND CARBONYL COMPOUNDS

2-Oxetanones (β-lactones)[19,20] are useful synthetic intermediates which have been most often prepared by cyclization[21,22] of β-halo or β-hydroxy acid derivatives or by addition of ketenes[23–26] to carbonyl compounds. They are starting materials for useful polymers and copolymers[27,28] and have been used for the synthesis of alkenes[26,29] and carboxylic acid derivatives.[30,31] β-Lactones possessing antimicrobial activity have recently been found in bacterial cultures.[32–34]

### 2.2.2.1 Chemo- and Regio-selectivity

The carbonyl π-bond has been found to add chemo- and regio-selectively across the alkenic π-bond of ketenes.[24] Thus diphenylketene readily reacts with benzoquinone to yield a stable [2 + 2] adduct (equation 1).[25] With an excess of diphenylketene the bis-adduct is formed, which decomposes into tetraphenylquinodimethane and carbon dioxide (equation 2).[25] With the less stable ketene, thermal [2 + 2] cycloadditions are observed with highly electrophilic carbonyl compounds (equation 3).[25] With unactivated aldehydes and ketones, yields are much lower due to a faster oligomerization of the ketene reagent. However, in the presence of a Lewis acid catalyst, most aldehydes or ketones form β-lactones with ketene (equation 4).[35] Cycloadditions with ketones usually require more active catalysts than with aldehydes. The catalyzed reaction of ketene with methyl vinyl ketone is chemoselective,[25] yielding a 10:1 ratio of [2 + 2] *versus* [4 + 2] adducts (equation 5). In the absence of catalyst, methyl vinyl ketone reacts with ketene to give exclusively the [4 + 2] adduct.

A practical extension of the reaction uses ketenes generated *in situ*[36] in the presence of a carbonyl compound. Thus the highly reactive dichloroketene generated *in situ* from the reaction of dichloroacetyl chloride with triethylamine has been trapped by aldehydes (equation 6) or activated ketones (equation 7)

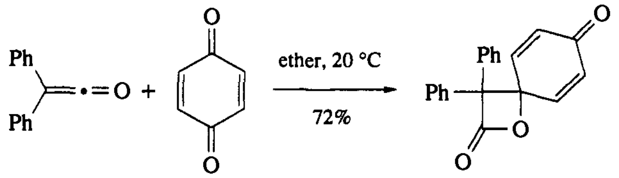

(1)

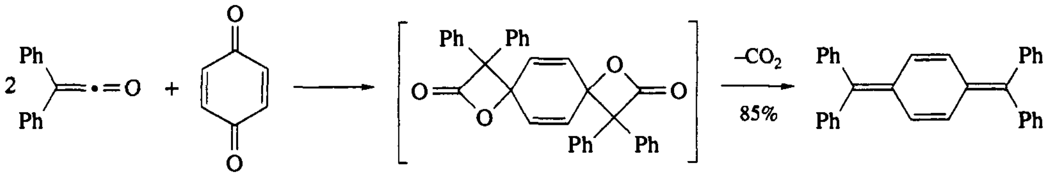

(2)

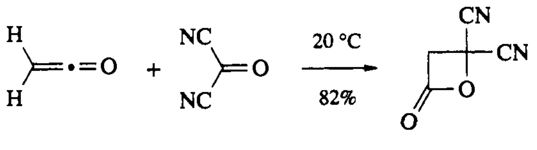

(3)

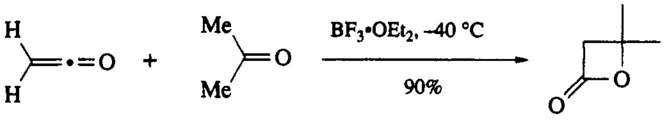

(4)

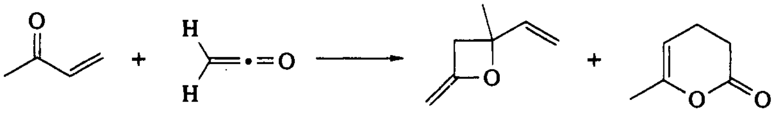

(5)

| | | |
|---|---|---|
| $ZnCl_2$ (20 °C) | 91 | 9 |
| no catalyst (Δ) | 0 | 100 |

to give β-lactones.[37–39] Simple ketones do not react under these conditions. However, β-lactones are formed when ketones are reacted with dichloroketene generated from trichloroacetyl chloride and zinc (equation 8). Zinc chloride formed *in situ* activates the ketone partner.

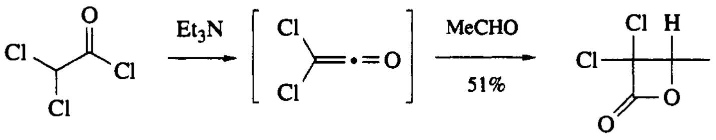

(6)

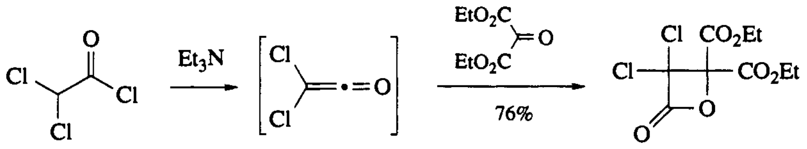

(7)

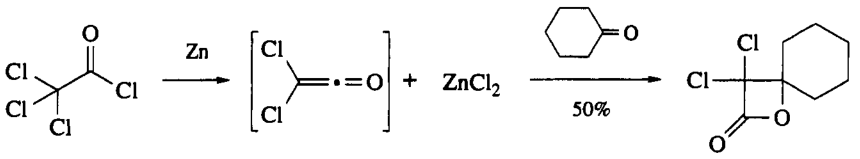

(8)

There is ample evidence[40] that, in these reactions, the ketene is behaving as the nucleophilic partner. Ketenes are ambiphilic molecules[41] which are characterized by a low-energy LUMO but also by a high-energy HOMO resulting from the interaction of an oxygen lone pair with the alkenic π- bond. Thus the dominant interaction between the two partners occurs *via* the highest occupied molecular orbital of the ketene and the lowest unoccupied molecular orbital of the carbonyl compound. This readily accounts for the regiochemistry of the reaction, the C-2 carbon atom of the ketene being always linked to the carbon atom of the carbonyl compound. From the information available it is not possible to ascertain whether these reactions are stepwise or concerted cycloadditions. Formation of the β-lactone could well occur in a single step involving a transition state (**1**) similar to that of the ketene–alkene reaction[41] but in which bonding is more advanced between C-2 of the ketene and the carbon of the carbonyl compound. However, the formation of a 1,4-dipolar intermediate (**2**) cannot be rejected. Complexation of the carbonyl compound with a Lewis acid catalyst will lower the LUMO, thus favoring the reaction.

Alternatively, when the ketene is generated in the presence of triethylamine, one cannot exclude the formation of a nucleophilic intermediate (**3**) which would then add to the carbonyl compound (Scheme 1).[42]

### 2.2.2.2 Stereoselectivity

The diastereoselectivity of addition of ketenes to carbonyl compounds is moderate (equations 9 and 10). Mixtures of *cis* and *trans* β-lactones are usually formed.[43,44]

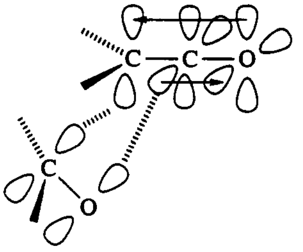

**(1)**

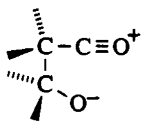

**(2)**

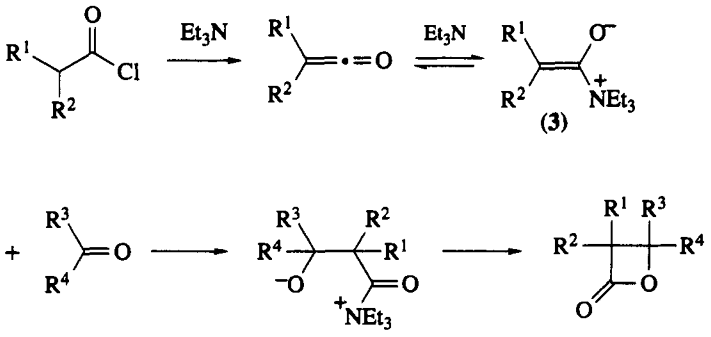
R1
O
Cl
R2
Et3N
R1
R2
=•=O
Et3N
R1
O−
R2
+NEt3
(3)
(3)
+
R3
R4
=O
R3
R2
R4
R1
−O
=O
+NEt3
R1 R3
R2
R4
O
O

**Scheme 1**

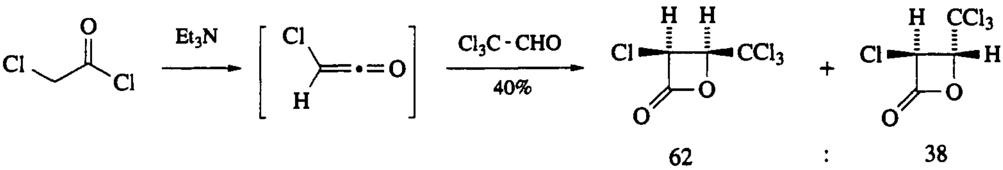
Cl
O
Cl
Et3N
Cl
H
=•=O
Cl3C-CHO
40%
H H
Cl
CCl3
O
O
+
H CCl3
Cl
H
O
O
62
:
38

(9)

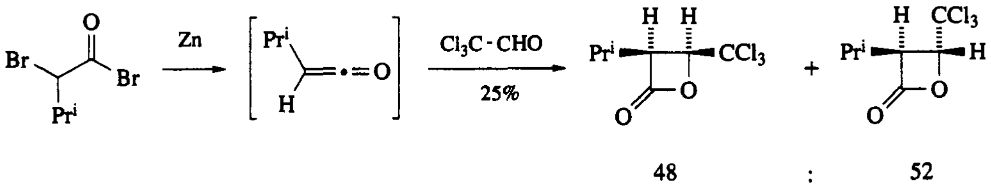
Br
O
Br
Pri
Zn
Pri
H
=•=O
Cl3C-CHO
25%
H H
Pri
CCl3
O
O
+
H CCl3
Pri
H
O
O
48
:
52

(10)

Enantiopure β-lactones have been obtained from the reaction of acid chlorides[45] or ketene[30,46–49] with aldehydes in the presence of optically active tertiary amines. The reaction of ketene with chloral has been studied in considerable detail (Scheme 2). In the presence of 2 mol % of quinidine at –50 °C the β-lactone is formed in virtually quantitative chemical and optical yield.[47] By proper choice of the catalyst, either enantiomer of the β-lactone can be obtained. The transition state picture (4) has been proposed[50] for the ketene–chloral addition in the presence of quinidine. Hydrolysis converts the β-lactone to malic acid with inversion of configuration (Scheme 2).[47]

Similarly, the quinidine-catalyzed cycloaddition of ketene to 2,2-dichloro aldehydes gives β-lactones of high optical purities which are easily converted to the corresponding methyl (3*S*)-hydroxyalkanoates (Scheme 3).[30]

In the presence of catalysts such as $ZnEt_2/H_2O$ or $AlEt_3/H_2O$, optically active 2-substituted β-propiolactones readily polymerize[48,49] to give optically active stereoregular polyesters exhibiting quite unique properties compared with the corresponding racemic polymers (Scheme 4).

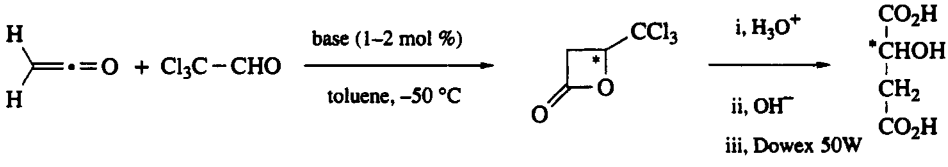
base (1–2 mol %)
toluene, −50 °C
i, $H_3O^+$
ii, $OH^-$
iii, Dowex 50W

| *Base* | *Yield (%)* | *ee (%)* | *Configuration* |
|---|---|---|---|
| *(R)*-1,2-Dimethylpyrrolidine | 87 | 60 | *(S)*-(+) |
| *(S)*-*N*,*N*-Dimethyl-α-phenylethylamine | 90 | 77 | *(R)*-(−) |
| Quinine | 89 | 76 | *(S)*-(+) |
| Quinidine | 95 | 98 | *(R)*-(−) |

**Scheme 2**

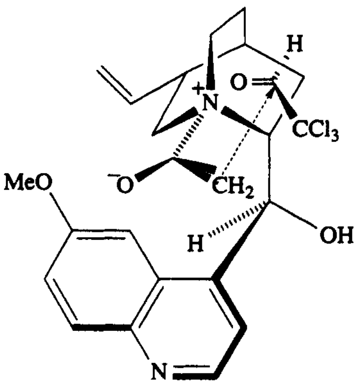

**(4)**

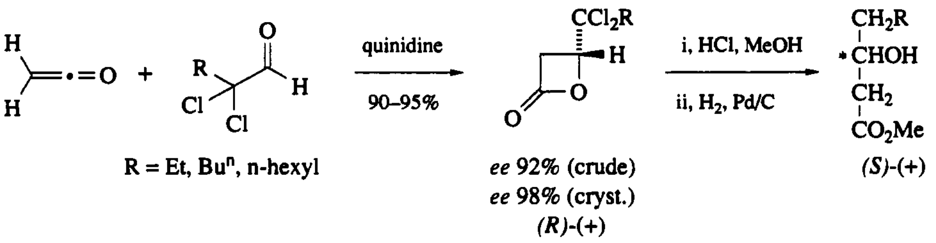
quinidine
90–95%
i, HCl, MeOH
ii, $H_2$, Pd/C
R = Et, $Bu^n$, n-hexyl
*ee* 92% (crude)
*ee* 98% (cryst.)
*(R)*-(+)
*(S)*-(+)

**Scheme 3**

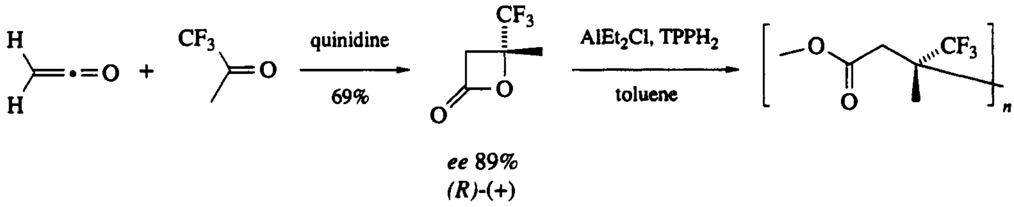
quinidine
69%
$AlEt_2Cl$, $TPPH_2$
toluene
*ee* 89%
*(R)*-(+)

**Scheme 4**

## 2.2.3 2-THIETANONES FROM KETENES AND THIOCARBONYL COMPOUNDS

These reactions, first described by Staudinger,[24] have received little attention. A more recent investigation shows[51] that the C=S bond of the thiones regioselectively adds across the C=C bond of the ketenes (equation 11) to form 2-thietanones (β-thiolactones). Primary adducts have been isolated only in a few cases. Most often they spontaneously decompose to yield an alkene and COS (equation 12).

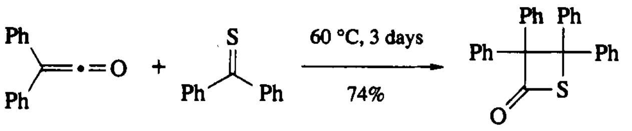

(11)

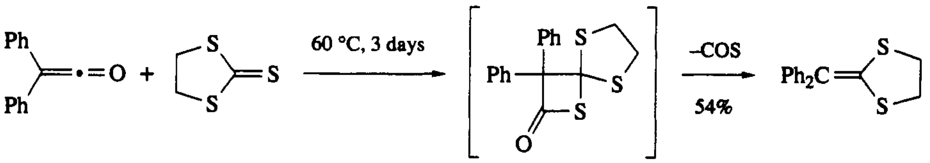

(12)

## 2.2.4 2-AZETIDINONES FROM KETENES AND IMINES

### 2.2.4.1 Direct Combination of Ketenes with Imines

The first 2-azetidinone (β-lactam) was obtained by Staudinger[52] from the reaction of diphenylketene with benzylideneaniline (equation 13). Most of the β-lactams prepared by this method have been made from imines derived from aromatic carbonyl compounds and ketoketenes.[23-26,53-55] The reaction of ketene itself with imines has been recently reinvestigated.[56] Good yields of β-lactams are obtained when a stream of ketene gas is passed through the imine in the absence of solvent (equations 14 and 15). No [4 + 2] cycloadduct is formed with *N*-cinnamylideneaniline.

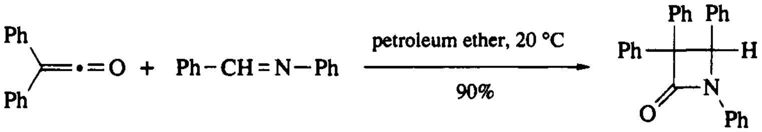

(13)

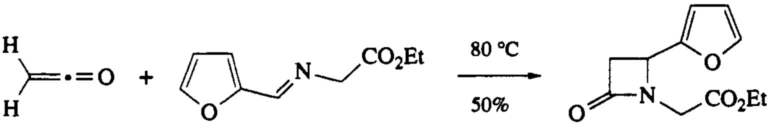

(14)

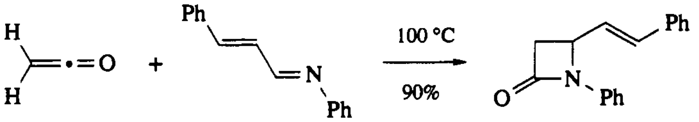

(15)

Cyanoketenes are conveniently prepared[54,57] by thermolysis of 2,5-diazido-1,4-quinones or 4-azido-3-halo(or phenoxy)-5-methoxy-(5*H*)-furan-2-ones in refluxing benzene (Scheme 5).

With the exception of *t*-pentyl- and *t*-butyl-cyanoketenes, which are stable to self-condensation, cyanoketenes are generally generated *in situ*.[54] Reactions with imines, formimidates and thioformimidates yield the corresponding 3-cyano-2-azetidinones (equations 16–18). The reactions proceed stereoselectively, yielding β-lactams having the 3-cyano and 4-protio substituents in a *trans* relationship.[57]

There is ample evidence[57] that these cycloadditions involve the initial formation of a dipolar intermediate (**5**; Scheme 6). Conrotatory cyclization of (**5**) leads to the β-lactam. Intermediates of type (**5**) can be trapped by another molecule of ketene to yield (**6**)[24] or by sulfur dioxide to yield sulfone (**7**).[58] This mechanism also explains the formation of [4 + 2] adducts (**8**) which are sometimes observed with conjugated imines.[57,59]

Intermediates of type (**5**) have been independently generated[54] and found to yield β-lactams (Scheme 7). The stereochemistry of the β-lactams has been rationalized[57] on the basis of a conrotatory ring closure of the intermediate dipole in a way which minimizes steric interactions (equations 19 and 20). However, this explanation is weakened by the fact that configurations proposed for dipoles are purely speculative.

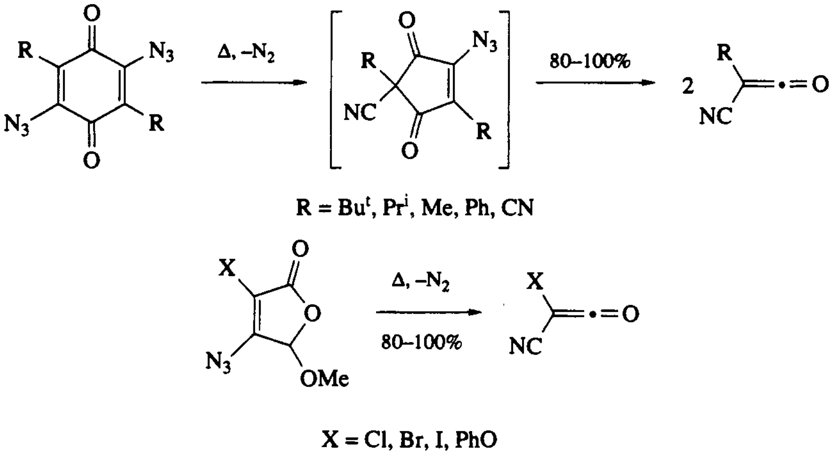
Δ, –N$_2$
80–100%
2
R = Bu$^t$, Pr$^i$, Me, Ph, CN
Δ, –N$_2$
80–100%
X = Cl, Br, I, PhO

**Scheme 5**

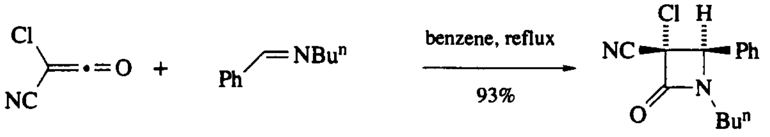
benzene, reflux
93%

(16)

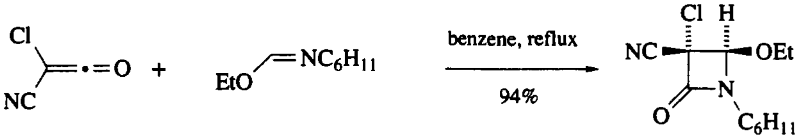
benzene, reflux
94%

(17)

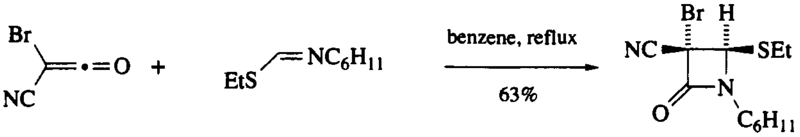
benzene, reflux
63%

(18)

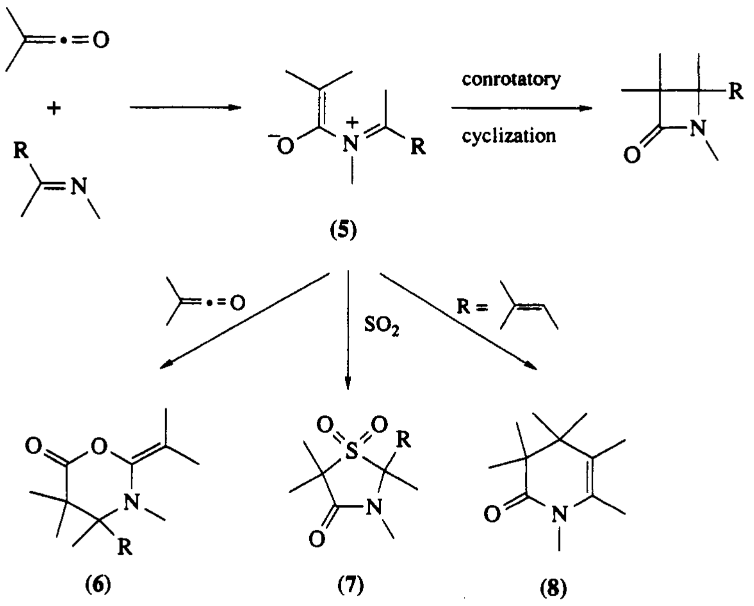
conrotatory
cyclization
(5)
SO$_2$
R =
(6)
(7)
(8)

**Scheme 6**

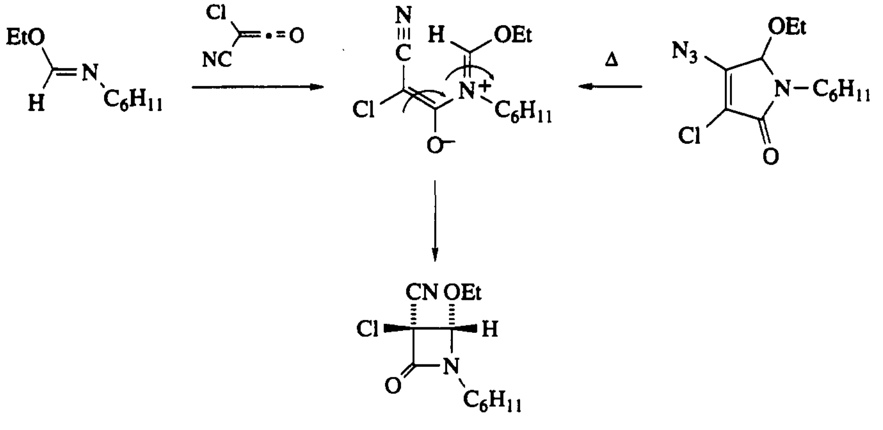

Scheme 7

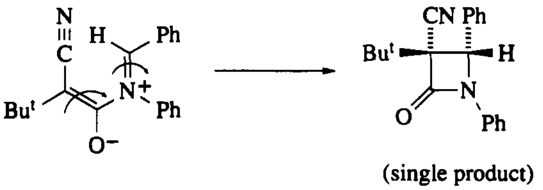

(19)

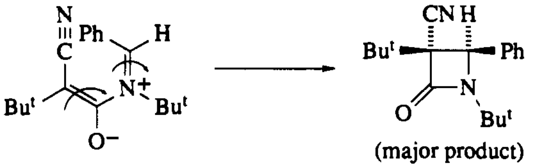

(20)

The preparation of β-lactams by the direct combination of isolated ketenes with imines is severely limited by the instability of monosubstituted and heterosubstituted ketenes, which show a great tendency to polymerize.[41] The discovery that ketenes can be readily generated by the reaction of an acid chloride with tertiary amines offers a practical solution to this problem.[60]

## 2.2.4.2 Reactions with Ketene Precursors

### *2.2.4.2.1 Chemo- and regio-selectivity*

β-Lactams are readily prepared by reaction of acid chlorides or bromides with imines in the presence of a tertiary base, usually triethylamine. The method is extremely versatile. Conditions are very mild (inert solvent, room temperature) and sensitive functional groups are tolerated on both the imine and acid chloride partners (equations 21–24).[61–64]

Particular attention has been focused on cycloadditions of acid chlorides bearing a masked amine function[65–75] since they are potential precursors of penicillin or cephalosporin analogs (equations 25–27).

Thiazines have been successfully used as cycloaddition partners (equation 28)[76] but only thiazolines bearing a substituent at C-2 were found to yield β-lactams.[77,78] In this context, thio and, even better, seleno groups are useful as precursors of a protio group in the resulting β-lactams (Scheme 8).[79–81]

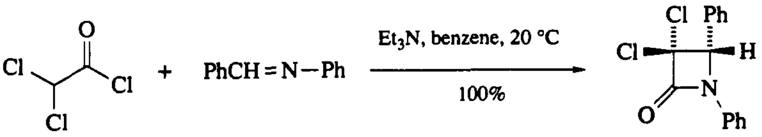

(21)

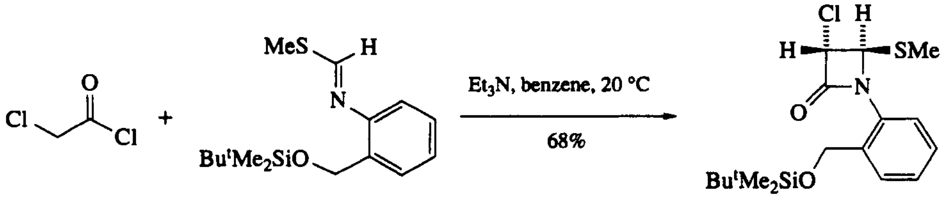
Et$_3$N, benzene, 20 °C
68%

(22)

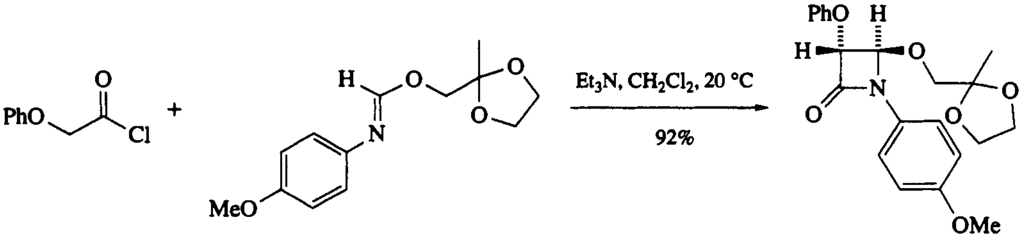
Et$_3$N, CH$_2$Cl$_2$, 20 °C
92%

(23)

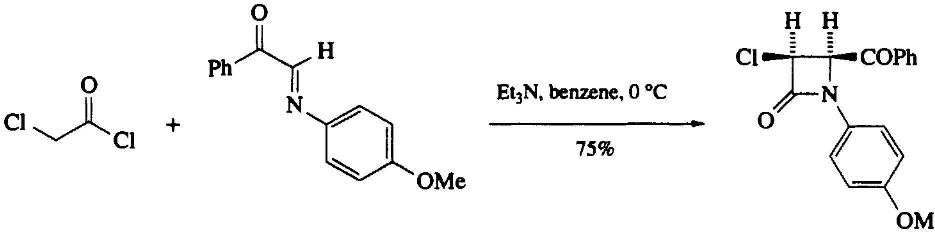
Et$_3$N, benzene, 0 °C
75%

(24)

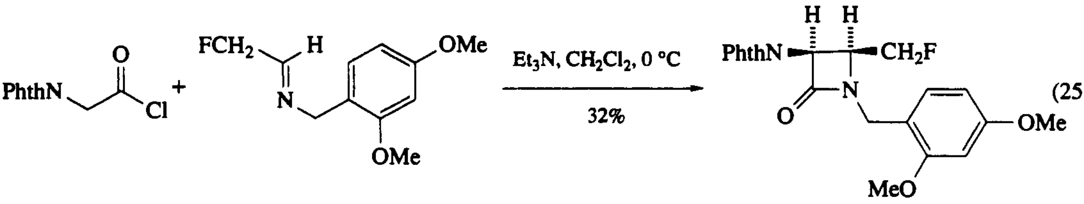
Et$_3$N, CH$_2$Cl$_2$, 0 °C
32%

(25)

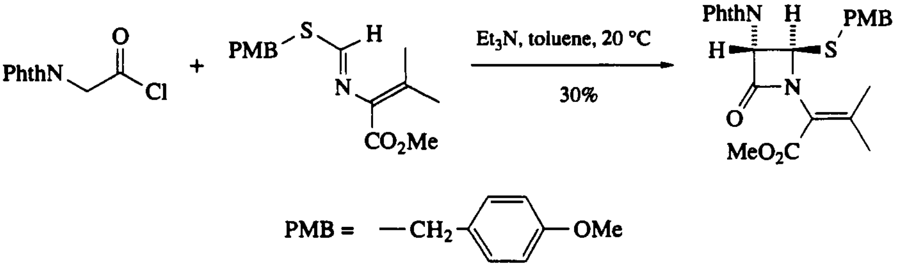
Et$_3$N, toluene, 20 °C
30%
PMB = —CH$_2$—◯—OMe

(26)

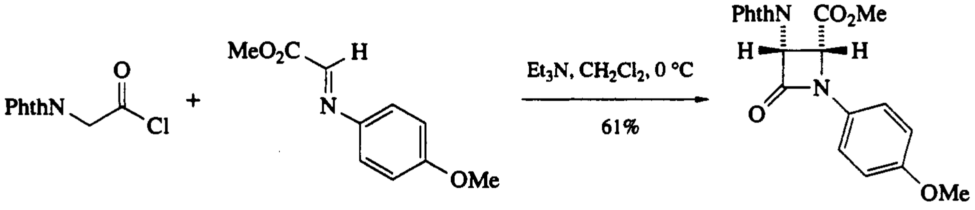
Et$_3$N, CH$_2$Cl$_2$, 0 °C
61%

(27)

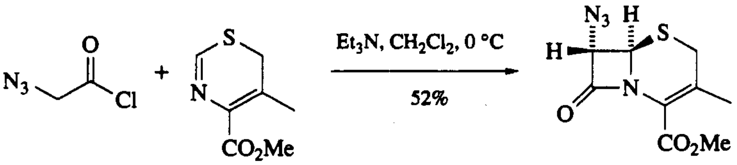
Et$_3$N, CH$_2$Cl$_2$, 0 °C
52%

(28)

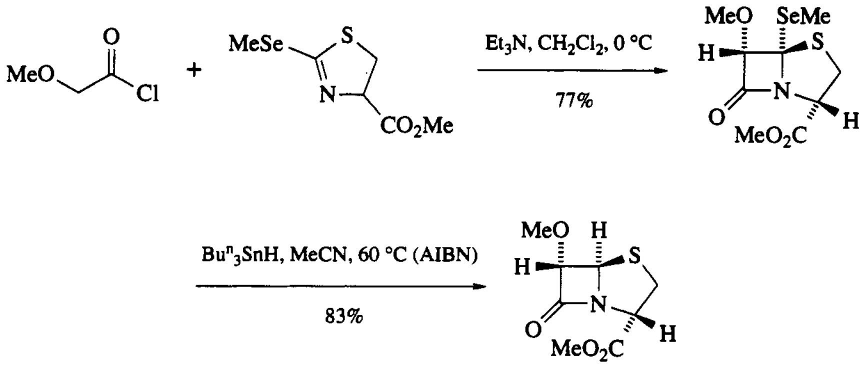
MeO
Cl
+
MeSe
S
N
CO2Me
Et3N, CH2Cl2, 0 °C
77%
MeO SeMe
H
S
N
O
MeO2C
H
Bun3SnH, MeCN, 60 °C (AIBN)
83%
MeO H
H
S
N
O
MeO2C
H

**Scheme 8**

Imines derived from glyoxylic acid derivatives[66,82] successfully lead to β-lactams which are potential precursors of various antibiotics (equation 29). Conjugated imines have also been used in this context: they give exclusively [2 + 2] cycloadducts with azido-,[66,83–86] phthalimido-,[87] phenoxy-[87] and vinylketene[88] precursors (equations 30 and 31). However, [4 + 2] adducts are the only observed products with haloketene precursors (equation 32).[59,61]

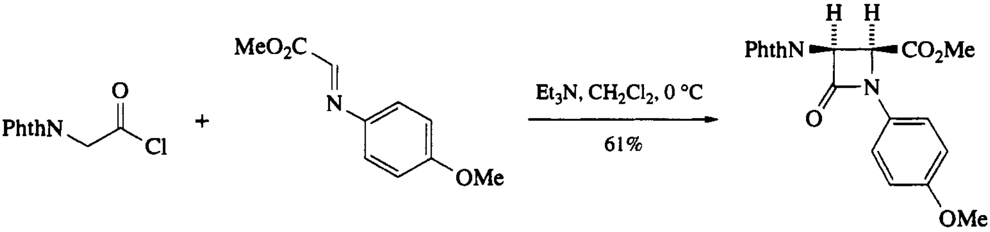
PhthN
O
Cl
+
MeO2C
N
OMe
Et3N, CH2Cl2, 0 °C
61%
H H
PhthN
CO2Me
N
O
OMe

(29)

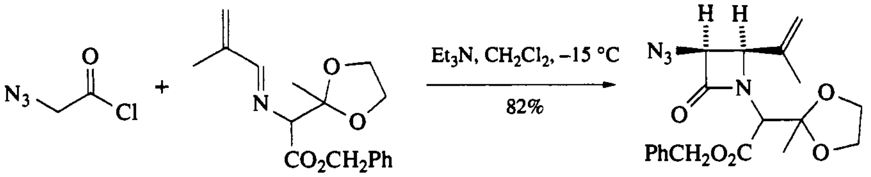
N3
O
Cl
+
N
O
O
CO2CH2Ph
Et3N, CH2Cl2, -15 °C
82%
H H
N3
N
O
PhCH2O2C
O
O

(30)

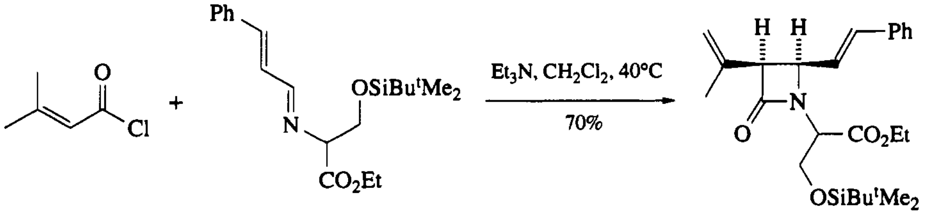
O
Cl
+
Ph
N
OSiButMe2
CO2Et
Et3N, CH2Cl2, 40°C
70%
H H
Ph
N
O
CO2Et
OSiButMe2

(31)

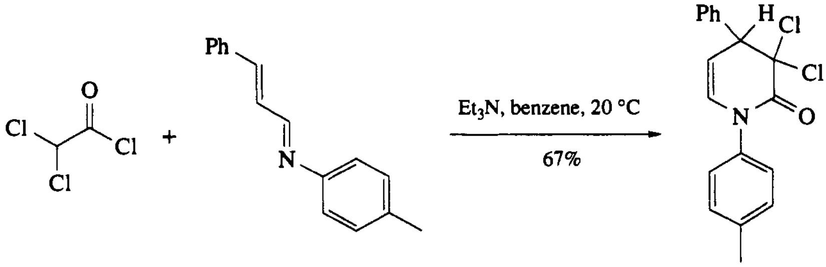
Cl
O
Cl
Cl
+
Ph
N
Et3N, benzene, 20 °C
67%
Ph
H
Cl
Cl
N
O

(32)

Alternative syntheses of β-lactams which circumvent the use of acid halides involve carboxyl group activating reagents (equations 33–35).[89–98] These are more practical when the corresponding acid chlorides are unstable or unsafe.[89]

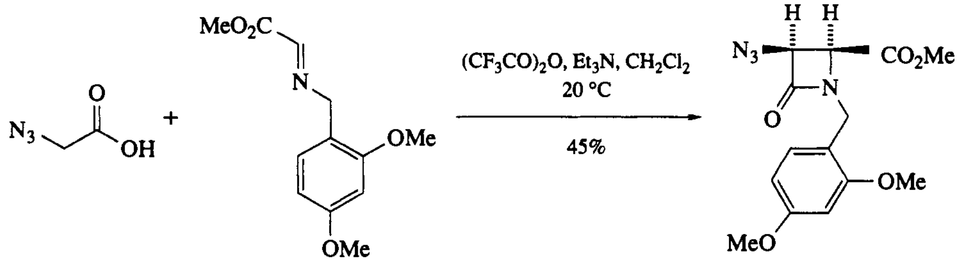
$N_3$
OH
O
+
$MeO_2C$
N
OMe
OMe
$(CF_3CO)_2O$, $Et_3N$, $CH_2Cl_2$
20 °C
45%
H H
$N_3$
$CO_2Me$
N
O
OMe
MeO

(33)

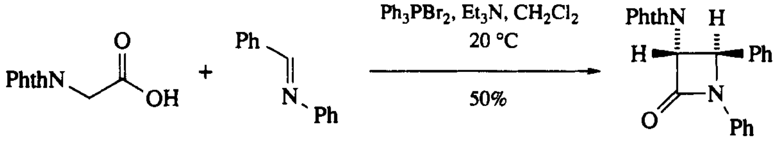
PhthN
O
OH
+
Ph
N
Ph
$Ph_3PBr_2$, $Et_3N$, $CH_2Cl_2$
20 °C
50%
PhthN H
H
Ph
N
O
Ph

(34)

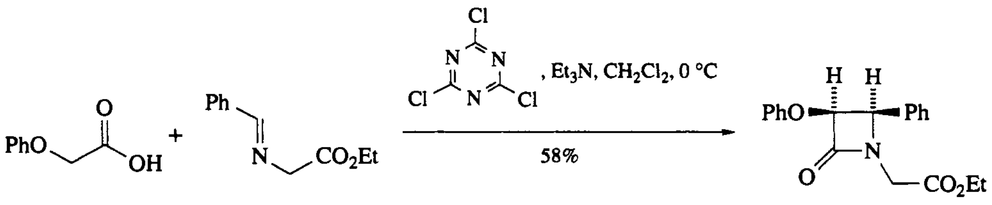
PhO
O
OH
+
Ph
N
$CO_2Et$
Cl
N
N
Cl
N
Cl
, $Et_3N$, $CH_2Cl_2$, 0 °C
58%
H H
PhO
Ph
N
O
$CO_2Et$

(35)

A practical synthesis of α-amido β-lactams uses a 'Dane salt' (**9**) formed by the reaction of a methanolic solution of the potassium salt of glycine with methyl acetoacetate (Scheme 9). The salt (**9**) readily reacts with a Schiff base in the presence of triethylamine and *e.g.* a chloroformate ester.[89] Other activating agents such as phenyl dichlorophosphate[90,99,100] or phosphorus oxychloride[101,102] have also been successfully used.

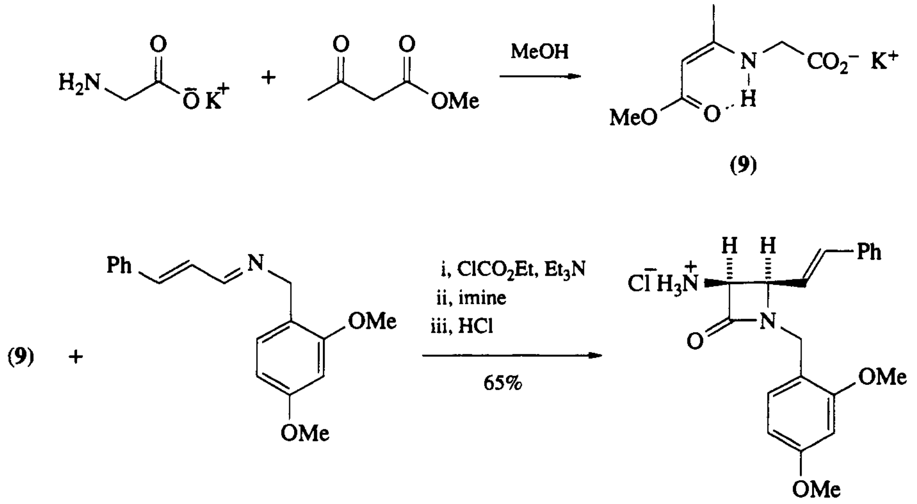
$H_2N$
O
$\bar{O}\,K^+$
+
O
O
OMe
MeOH
N
$CO_2^-$ $K^+$
H
MeO
O
(9)
(9)
+
Ph
N
OMe
OMe
i, $ClCO_2Et$, $Et_3N$
ii, imine
iii, HCl
65%
H H
$Cl^-H_3N^+$
Ph
N
O
OMe
OMe

**Scheme 9**

### *2.2.4.2.2 Stereoselectivity*

The stereochemical course of the reaction varies with the nature of the substituents on both the ketene precursors and imines and also with experimental conditions.[57,68,73,88] Under the usual conditions (addition of the acid chloride to a solution of imine and $Et_3N$, in $CH_2Cl_2$ at 0–20 °C), α-functionalized acetyl chlorides yield *cis* β-lactams as major or often single stereoisomer (equations 24, 25, 27, 29, 30, 31, 33 and 35) except with imidates or thioimidates (equations 22, 23, 26 and 28). The sequence of addition of the reactants can also influence the isomer ratios (Scheme 10).[68] Both *cis* and *trans* β-lactams appear to be stable under the experimental conditions.

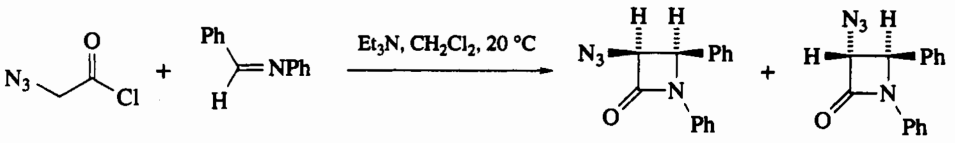

| | *cis* | *trans* |
|---|---|---|
| addition of acid chloride (to imine + $Et_3N$) | 66% | 34% |
| addition of $Et_3N$ (to imine + acid chloride) | 33% | 67% |

**Scheme 10**

Tentative rationalizations of these stereochemical results have been offered on the basis of a mechanism involving a ketene intermediate reacting with an imine.[103–107] However, it is by no means proven that all these reactions involve an intermediate ketene. Several pathways can lead from an acid chloride, an imine and triethylamine to a β-lactam (Scheme 11). Thus the origin of the stereochemical selection in these multistep processes is not very well understood.

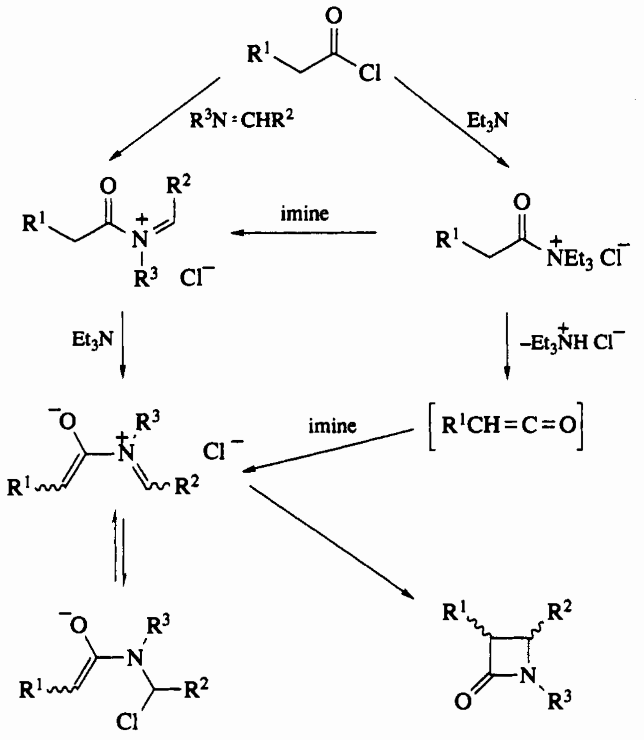

**Scheme 11**

Enantiopure β-lactams have been prepared using chiral ketene precursors or chiral imines.[103,107,108] Acyclic imines derived from optically active α-amino acid derivatives have been used in the Staudinger reaction.[105,106,109,113,114,117,118] Variable levels of diastereoselection have been reported (equations 36 and 37). In several cases the poor diastereoselectivity has been shown to result from some racemization of the imine synthon under the experimental conditions.[109,110] Only a few examples of high levels of diastereoselection have been reported (equations 38 and 39).[111,112,115,116]

The condensation of imines derived from glyceraldehyde acetonide[104,119–121] or α,β-epoxy aldehyde[122] with phthalimidoacetyl chloride proceed with high diastereoselection. Thus the addition of phthalimido acetyl chloride to the aldimine (**10**) derived from (*S*)-glyceraldehyde acetonide in the presence of triethylamine yields a β-lactam (**11**) which possesses the (3*S*,4*S*) configuration (Scheme 12). Compound

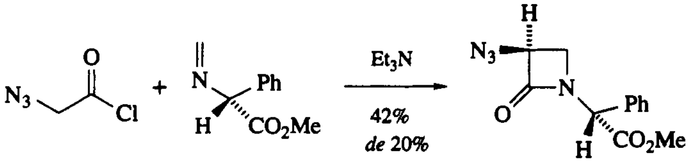
Et$_3$N
42%
de 20%

(36)

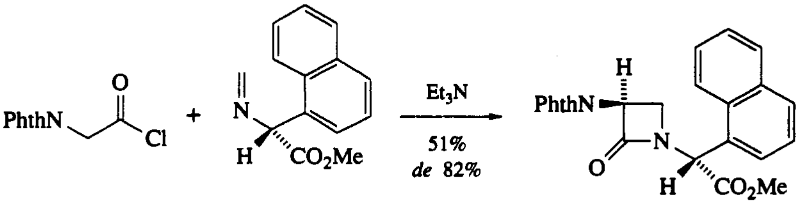
Et$_3$N
51%
de 82%

(37)

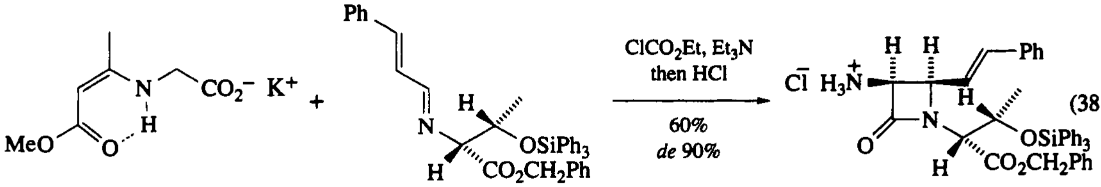
ClCO$_2$Et, Et$_3$N
then HCl
60%
de 90%

(38)

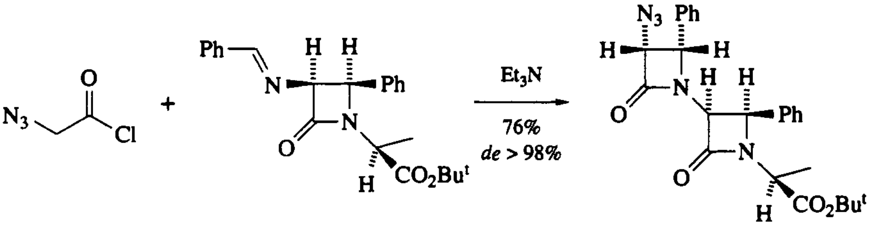
Et$_3$N
76%
de > 98%

(39)

**(11)** is readily transformed into β-lactam (**12**), a useful chiral synthon for the production of new analogs of β-lactam antibiotics (Scheme 12).[104]

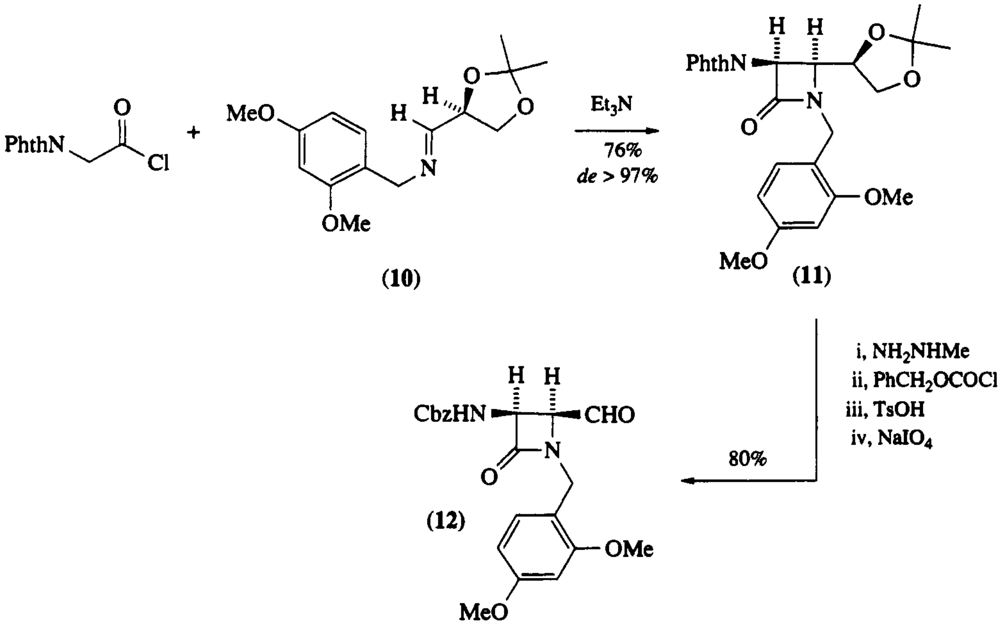
Et$_3$N
76%
de > 97%
(10)
(11)
i, NH$_2$NHMe
ii, PhCH$_2$OCOCl
iii, TsOH
iv, NaIO$_4$
80%
(12)

**Scheme 12**

Sharpless asymmetric epoxidation provides direct access to epoxy alcohols which are precursors of the required epoxy imines for the cycloaddition process.[122] Reaction of (**13**) with a protected glycine acid chloride yields the *cis* azetidinone which can be isolated in >98% diastereoisomeric purity by either chromatography or crystallization. Oxidation gave aldehyde (**14**; Scheme 13). The mode of asymmetric induction correlates with that of the corresponding reaction from (*S*)-glyceraldehyde acetonide. The π-facial discrimination imposed by the α-oxygen substituent of the imine is at least in part stereoelectronic in nature.[121] Accordingly, the preferred orientation of the C—O bond should be antiperiplanar to the forming C(3)—C(4) β-lactam bond for transition state stabilization by delocalization into the C—O antibonding orbital. In addition, 1,3-allylic strain interactions might be expected to force the electrocyclization to be initiated from a nonplanar reactant conformation (Scheme 14).[103] These effects appear to be maximal when the C—O bond is part of a ring since lower levels of diastereoselection are usually obtained with imines derived from chiral α-alkoxy aldehydes.[104,123,124]

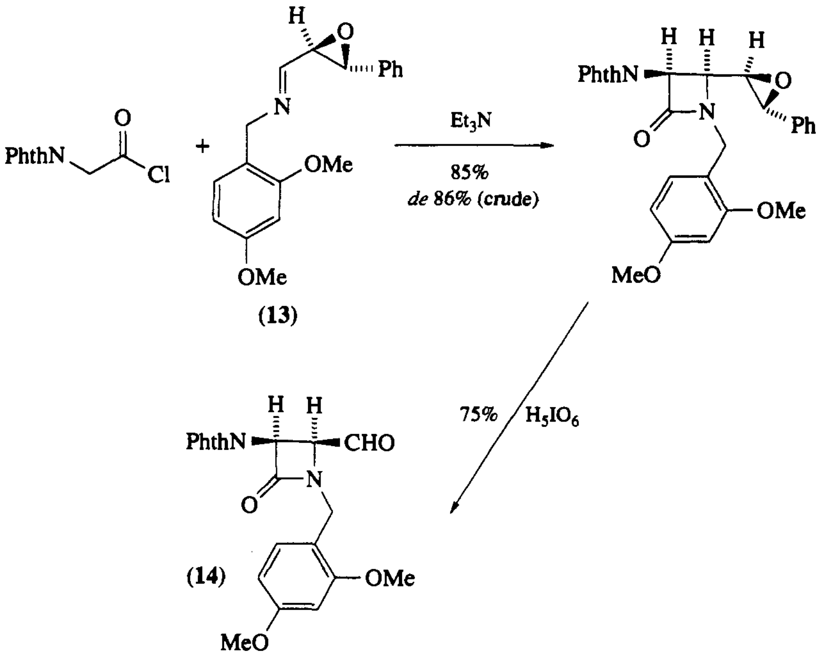

Scheme 13

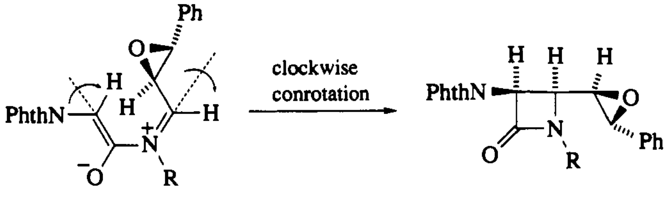

Scheme 14

Significant progress has been made in the development of asymmetric syntheses of the biologically important 3-amino-β-lactams from homochiral ketene precursors.[103,123–128] High levels of diastereoselection have been observed with chiral 1,3-oxazolidinones. Thus (4*R*)-phenyloxazolidylacetyl chloride, readily prepared from (*S*)-phenylglycine, reacts with *N*-benzylaldimines in the presence of triethylamine to yield the *cis* β-lactams in high diastereoisomeric excesses (Scheme 15).[126]

In addition to providing excellent diastereoselection in the cyclocondensation process, the chiral oxazolidinone auxiliary can be reductively removed to give the enantiomerically pure 3-amino-β-lactam in good overall yields (Scheme 16).[126] Homochiral 1,4-imidazolidinones also give *cis* β-lactams with excellent induction when the asymmetric carbon atom is next to the nitrogen atom (**15** in Scheme 17).[129] High inductions can also be observed with a γ-lactam (**16**),[125] but the cycloaddition yields a mixture of *cis* and *trans* isomers. The level of diastereoselection is much lower with imide synthons (**17**).[103,125]

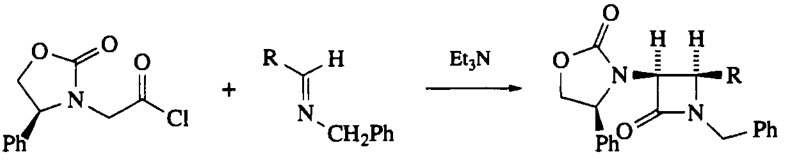

| *R* | *Yield (%)* | *de (%)* |
|---|---|---|
| Ph | 90 | 94 |
| *trans*-PhCH=CH– | 82 | 90 |
| 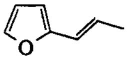 | 80 | 94 |

**Scheme 15**

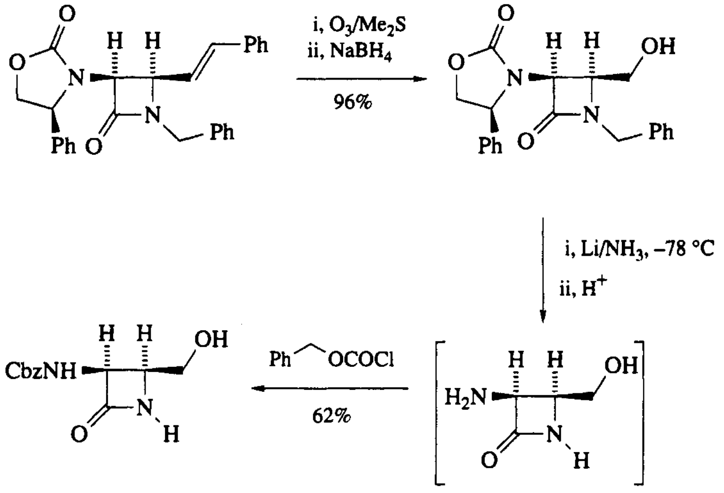

**Scheme 16**

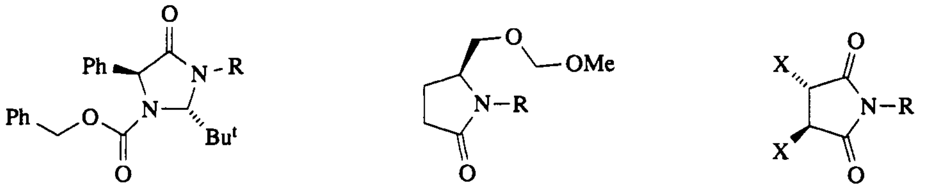

(**15**) R = $CH_2COCl$ (**16**) R = $CH_2COCl$ (**17**) R = $CH_2COCl$
X = OMe, $OCOCH_2Ph$, OCOMe

**Scheme 17**

A good level of diastereoselection has also been obtained with (3*S*)-triisopropylsilyloxybutyric acid chloride as chiral precursor (equation 40).[130]

Finally, all attempts to develop an asymmetric cyclocondensation of an acid chloride with an imine in the presence of a chiral tertiary base have failed.[103] No induction was observed when the reaction between diphenylketene and benzylideneaniline was effected in cholesteric liquid crystals.[131]

### 2.2.4.3 Cycloadditions of Ketenes to Carbodiimides

Ketenes readily react with carbodiimides[132–139] to yield 1:1 adducts (equation 41). The formation of 2:1 adducts (**18**) is observed[139] when the C=N double bond of the 1:1 adduct is activated by strain

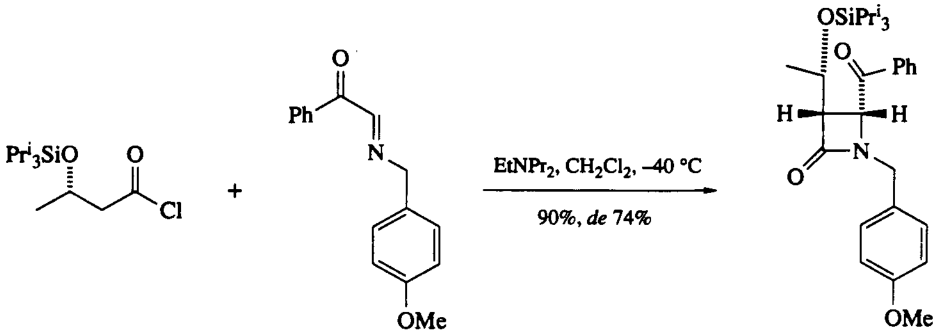

(40)

(Scheme 18). The reaction occurs at the most nucleophilic imine bond:[136,138] C═NMe > C═NBu$^t$ > C═N-aryl > C═NSiR$_3$ (equation 42). The reaction takes place by an ionic mechanism[133,135] in which ring closure is the slowest step. In the reaction of prochiral ketenes with chiral carbodiimides,[137] ring closure creates a new chiral center with good selectivity (equation 43).

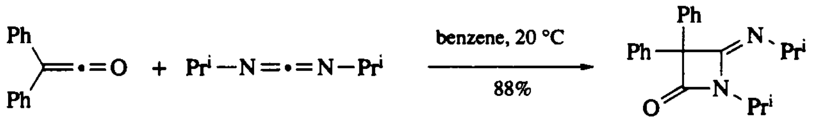

(41)

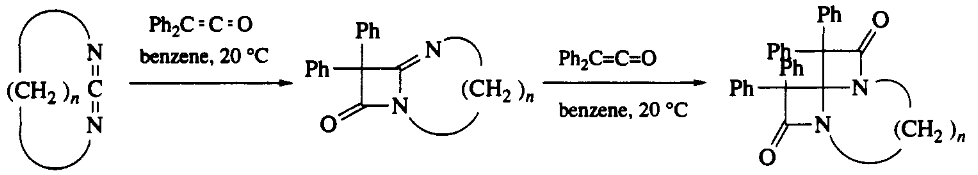

**(18)**

| | | |
|---|---|---|
| $n = 5$ | – | 91% |
| $n = 11$ | 90% | – |

**Scheme 18**

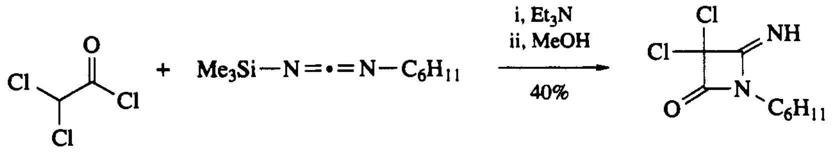

(42)

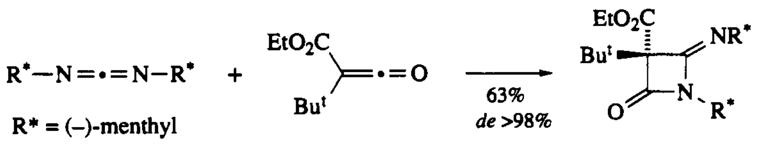

(43)

### 2.2.5 2-AZETIDINONES FROM ENOLATES OR ENOL ETHERS AND IMINES

Zinc enolates (Reformatsky reagents), generated from α-bromo esters and zinc, react with imines derived from aromatic amines to yield β-lactams (Scheme 19).[140–142] The stereoselectivity of the reaction varies[143–146] with the nature of ester substituents R$^1$ and R$^2$: the bulkier the groups, the more *trans* isomer is produced.

A useful variation of this reaction involves lithium enolates derived from esters.[147,148] They react with imines derived from non-enolizable aldehydes to form β-lactams (equations 44 and 45).[149–158]

The *cis* stereoselectivity can be explained[150] by a six-membered chair-like transition state model (**19**) resulting from the interaction of an (*E*)-enolate with an imine in its *trans* configuration (Scheme 20). Conditions favoring (*E*)-enolate formation (LDA, THF) predominantly yield *cis* β-lactams.[150,152,155,156,158] Addition of HMPA[152,159] or reactions at higher temperature[151,160] favor the forma-

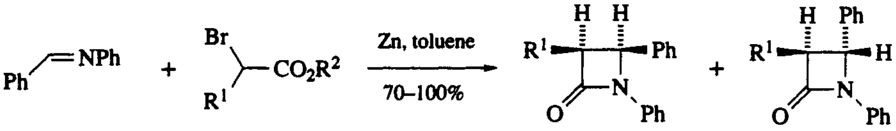

| *R*$^1$ | *R*$^2$ | *% cis* | *% trans* |
|---|---|---|---|
| Me | Me | 73 | 27 |
| Bu$^t$ | Me | 25 | 75 |
| Bu$^t$ | Pr$^i$ | 2 | 98 |

**Scheme 19**

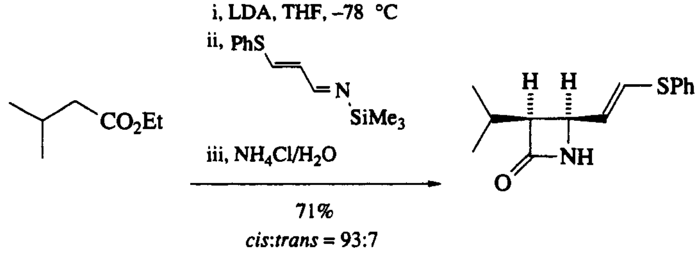

(44)

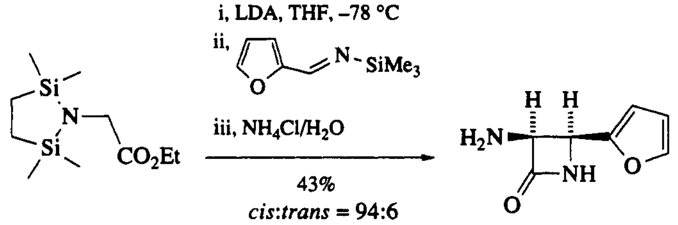

(45)

tion of *trans* β-lactams. In several cases this has been shown to result from a change in enolate geometry but in other cases, *e.g.* with imines derived from aromatic amines, isomerization of the β-lactam occurred under the reaction conditions.[150,160] *Trans* β-lactams were also obtained in the presence of ZnCl$_2$[161] or Et$_2$AlCl[162] while AlMe$_3$[163] was reported to enhance *cis* selectivity.

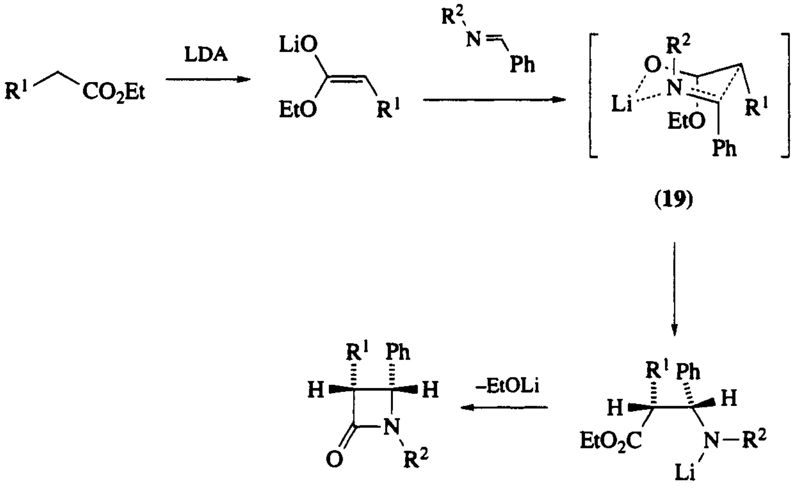

**Scheme 20**

Attempts to prepare homochiral β-lactams using chiral reactants under Reformatsky conditions described above gave poor results.[143,164] Good diastereoselectivities are observed in the reaction of lithium enolates with imines bearing a chiral group on either a nitrogen (equation 46)[154] or carbon atom (equation 47).[165] Esters derived from isoborneol-10-diisopropylsulfonamide give enolates which condense with cinnamaldimines to yield *cis* β-lactams with excellent enantioselectivity (equation 48).[166]

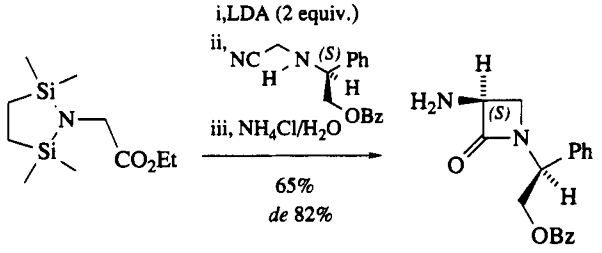
Si
N
Si
CO2Et
i,LDA (2 equiv.)
ii, NC N (S) Ph H H OBz
iii, NH4Cl/H2O
65%
de 82%
H
H2N
(S)
N
O
Ph
H
OBz

(46)

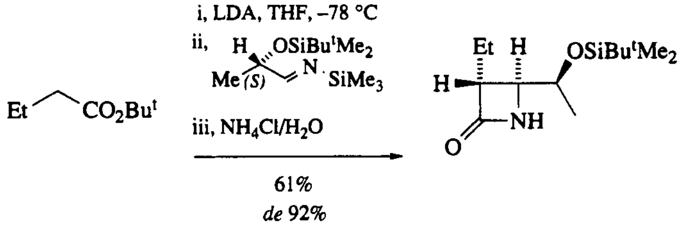
Et
CO2Bu^t
i, LDA, THF, –78 °C
ii, H OSiBu^tMe2 Me (S) N SiMe3
iii, NH4Cl/H2O
61%
de 92%
Et H
OSiBu^tMe2
H
NH
O

(47)

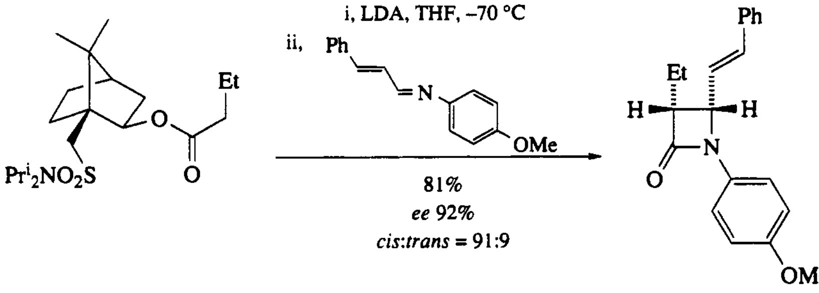
Pr^i2NO2S
O
Et
O
i, LDA, THF, –70 °C
ii, Ph N OMe
81%
ee 92%
cis:trans = 91:9
Ph
Et
H
H
N
O
OMe

(48)

Using (3*R*)- or (3*S*)-hydroxybutyric esters as chirons, it was possible to construct β-lactams with some control on three contiguous asymmetric centers.[165,167–174] Chelation maintains the dilithium derivative of ethyl (3*S*)-hydroxybutyrate in the (*Z*) configuration (Scheme 21). Approach of the imine from the less-hindered β-face leads to the (3*S*)-β-lactam with a high degree of facial selectivity but to a much lower degree of diastereoselectivity at C-4. The corresponding reaction using ethyl (3*R*)-hydroxybutyrate gave, as expected, high diastereofacial selection in favor of the (3*R*)-β-lactam.

Silylketene acetals react with imines under acidic conditions (Scheme 22). With *N*-alkylimines in the presence of a stoichiometric amount of $TiCl_4$, β-lactams are formed[175] in good yields. *N*-Aryl-[176–178] and *N*-trimethyl-silylimines[179] also react under acidic conditions but yield only open-chain products. On the other hand, bis(trimethylsilyl)ketene acetals yield β-lactams with both *N*-alkyl- and *N*-aryl-imines (Scheme 22).[180]

High diastereoselectivities have been observed[181] for the reaction of dimethylketene methyl trimethylsilyl acetal with imines derived from (2*S*)-amino esters (equation 49). However, the scope of this method must be further investigated.

## 2.2.6 2-AZETIDINONES FROM ISOCYANATES AND ALKENES

### 2.2.6.1 Scope

The cycloaddition of an alkene across the C═N bond of an isocyanate is a useful method of synthesis of β-lactams (equation 50).[24,182] The reaction requires the activation of the alkene by electron-releasing

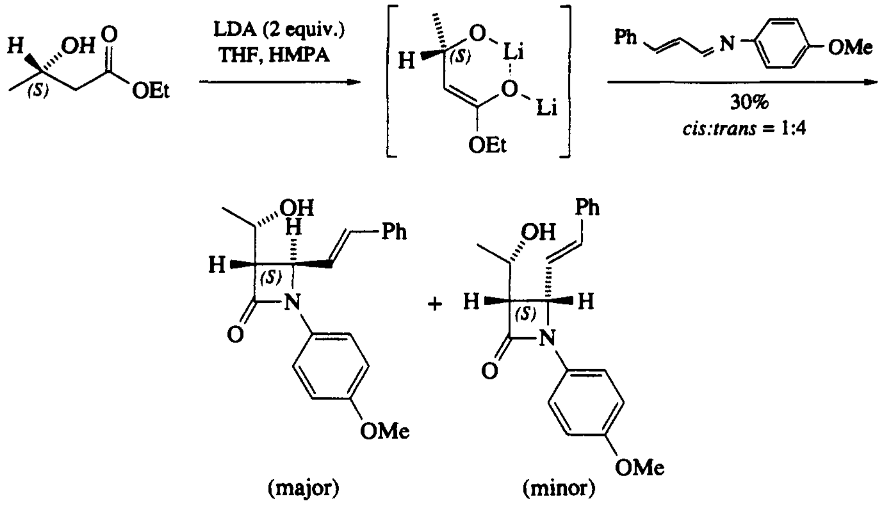
LDA (2 equiv.)
THF, HMPA
OEt
Ph
OMe
30%
cis:trans = 1:4
(major)
(minor)

**Scheme 21**

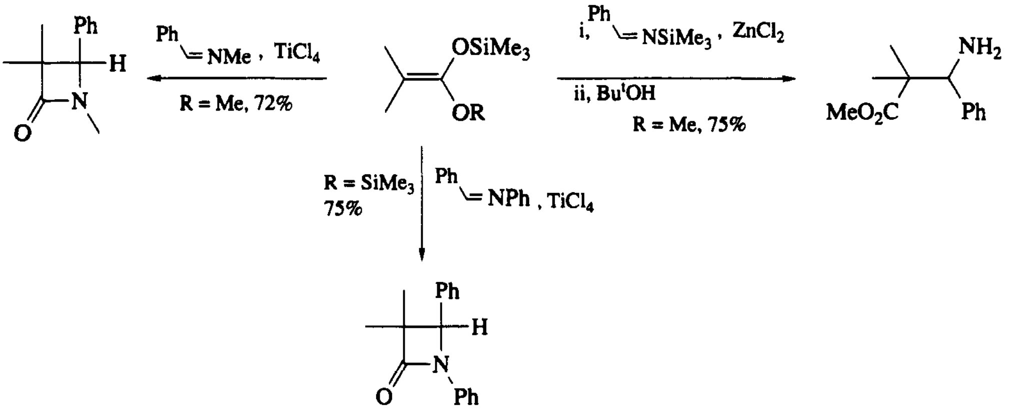
Ph
=NMe, TiCl4
R = Me, 72%
OSiMe3
OR
i, Ph =NSiMe3, ZnCl2
ii, ButOH
R = Me, 75%
NH2
MeO2C
Ph
R = SiMe3
75%
Ph =NPh, TiCl4

**Scheme 22**

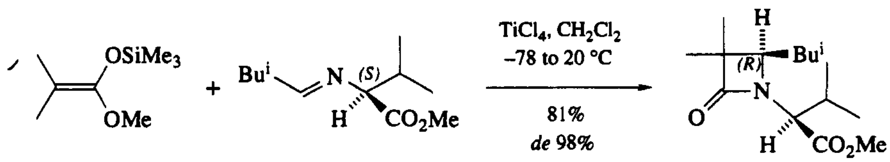
OSiMe3
OMe
Bui
CO2Me
TiCl4, CH2Cl2
−78 to 20 °C
81%
de 98%

(49)

substituents or that of the isocyanate by electron-withdrawing groups. Alkyl and aryl isocyanates do not react with alkenes or enol ethers but cycloadd to enamines, ketene acetals and ketene aminals. The initial product is a β-lactam (**20**) which is stable when there is no available hydrogen at C-3 (Scheme 23). However, when $R^2$ = H, enolization yields intermediate (**21**) which undergoes a fast electrocyclic rearrangement to give the open-chain isomer (**22**). Ketene acetals behave similarly (Scheme 24). In both cases the rearrangement is driven by the release of strain and the presence of an electron-releasing group at C-4.

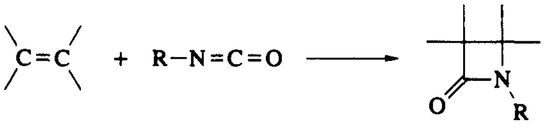

(50)

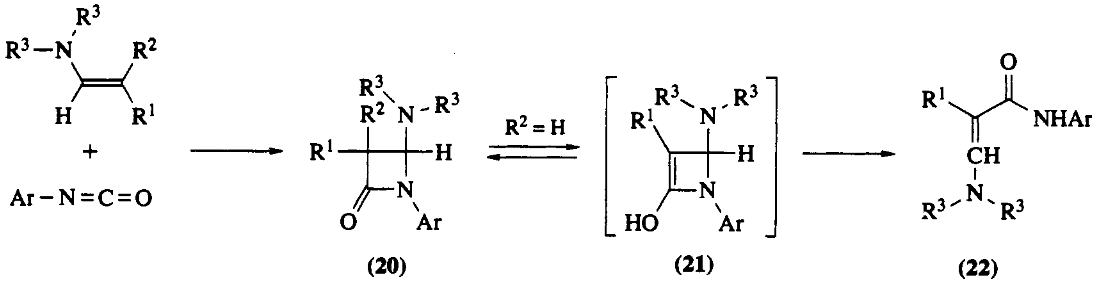

Scheme 23

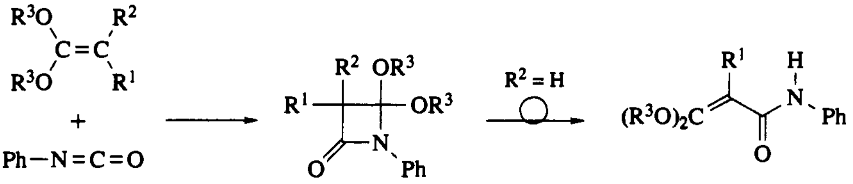

Scheme 24

Acyl isocyanates[183–185] are more reactive than alkyl or aryl isocyanates. However, the presence of an additional π-bond conjugated to the C═N bond of the isocyanate opens the possibility for [4 + 2] cycloadditions to compete with normal [2 + 2] additions. Reactions with alkyl and aryl substituted alkenes are rather slow. Propene, *trans*-2-butene, styrene and conjugated dienes give only β-lactams, albeit in moderate yields (Scheme 25). The strained double bond of norbornene, a reactive dienophile, adds across the conjugated 4π-system of trichloroacetyl isocyanate (equation 51).

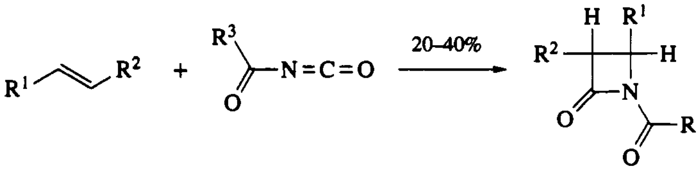

$R^1$ = Me, Ph, CH=CH$_2$; $R^2$ = H, Me; $R^3$ = $Cl_3C$, Ph

Scheme 25

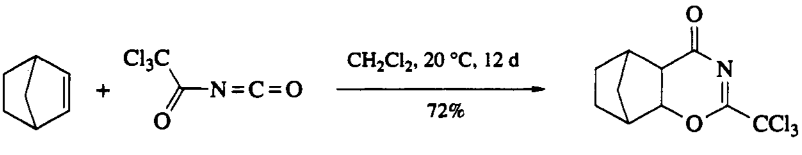

(51)

More nucleophilic alkenes such as enamines or enol ethers react faster with acyl isocyanates but the reaction is of little value for the preparation of β-lactams since it often produces [4 + 2] or open-chain adducts. The chemoselectivity apparently varies with subtle changes in the structures of the reactants as well as experimental conditions (equations 52–55).

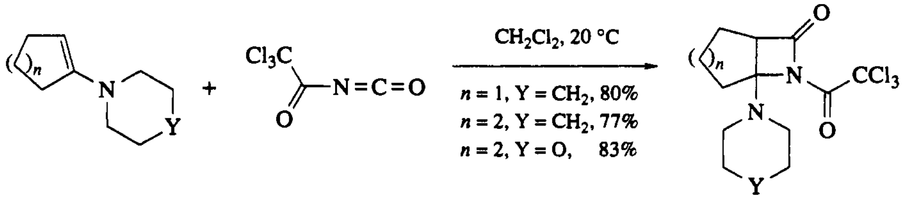

(52)

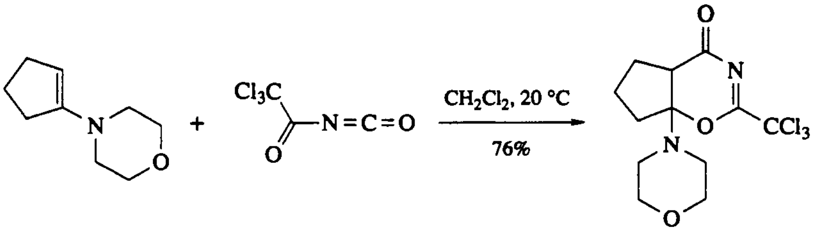

(53)

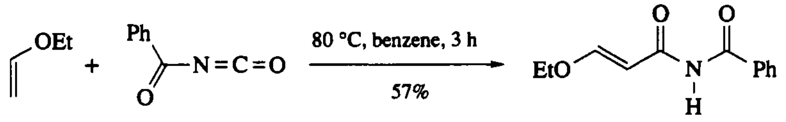

(54)

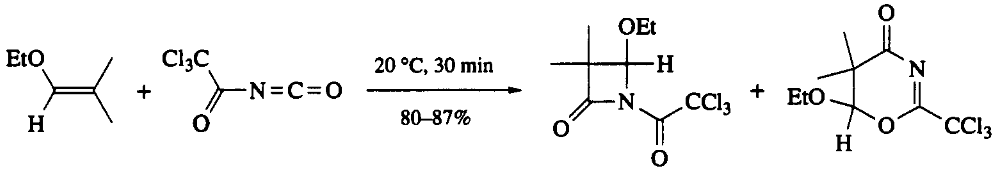

(55)

60% (in $CCl_4$) 40%
40% (in MeCN) 60%

These results are best explained by the formation of 1,4-dipolar intermediates which can cyclize from two conformations (**23**) or (**24**) leading respectively to a β-lactam or to a six-membered heterocycle (Scheme 26). When $R^1$ or $R^2$ = H, open-chain adducts can also be formed.

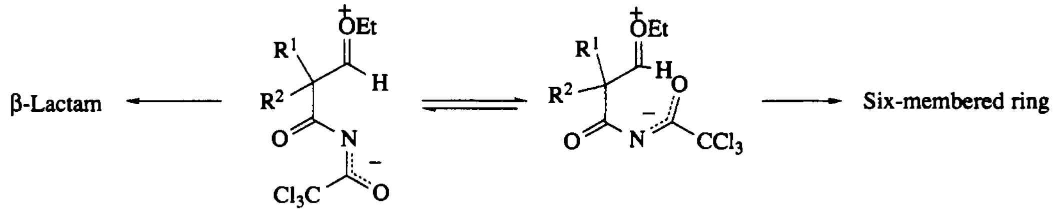

(**23**) (**24**)

**Scheme 26**

A more general and practical approach towards β-lactams utilizes the cheap chlorosulfonyl isocyanate (CSI),[186–191] which was first described by Graf[192] more than 35 years ago. The chlorosulfonyl group offers several advantages over the acyl groups described above: (a) it has a stronger activating effect on the isocyanate function; (b) it does not offer the possibility for competing [4 + 2] cycloadditions; (c) it can be smoothly removed by simple basic hydrolysis or even more effectively *via* unstable sulfinic acids produced by reduction with zinc dust, iron powder or sodium sulfite. A two-phase system consisting of an organic solvent and aqueous sodium sulfite kept slightly basic by addition of KOH has been recommended.[193]

Chlorosulfonyl isocyanate reacts with a wide range of alkenes under mild conditions to produce β-lactams (**25**) accompanied[186,189] by variable but usually minor amounts of open-chain adducts (**26**; Scheme 27). In most cases, β-lactams and open-chain products are formed independently. Thus *N*-chlorosulfonyl amide by-products are not formed by further reaction of *N*-chlorosulfonyl-β-lactams.

A large number of β-lactams have been prepared[188,189,191] by this method (equations 56–61). Cycloadditions of CSI with 1,5-hexadiene,[194] allyl iodide[195] and vinyl acetate[196,197] yield azetidinones which have been used as starting materials in the synthesis of carbapenems and penems. In some cases the cycloaddition must be conducted at low temperature to avoid open-chain products (equations 61 and 62).

Conjugated dienes react with CSI to yield[198] *N*-chlorosulfonyl-β-lactams as the primary products (Scheme 28). These [2 + 2] adducts undergo stepwise thermal rearrangements with variable degrees of ease to thermodynamically more stable [2 + 4] adducts, cyclization occurring at oxygen or nitrogen of the intermediate ambident zwitterion. These rearrangements can be avoided by *in situ* reduction of the *N*-

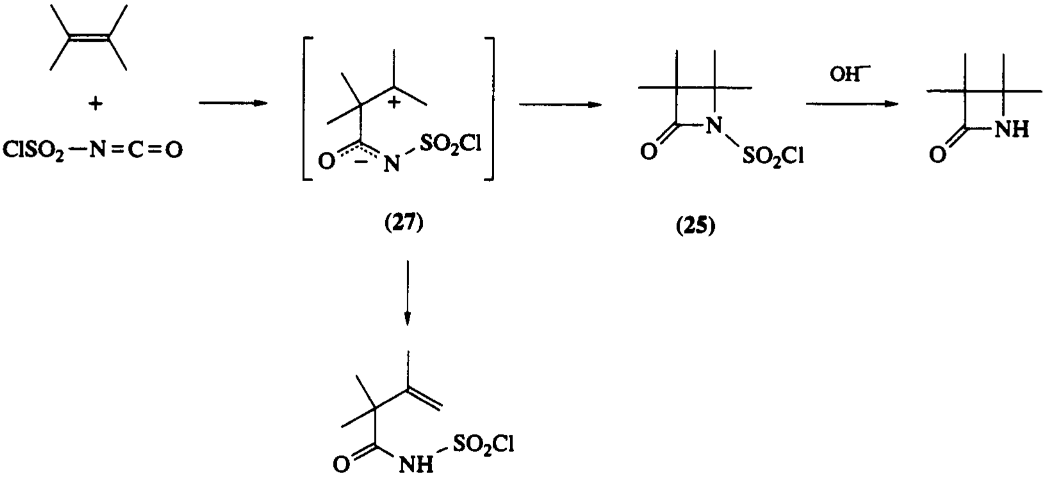
+
$ClSO_2-N=C=O$
+
$SO_2Cl$
O
N
OH⁻
O
N
$SO_2Cl$
O
NH
O
NH
$SO_2Cl$

(27) (25)

(26)

**Scheme 27**

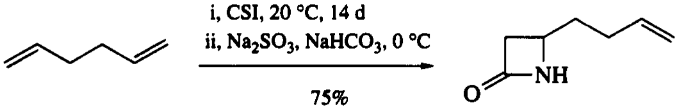

i, CSI, 20 °C, 14 d
ii, $Na_2SO_3$, $NaHCO_3$, 0 °C
75%

(56)

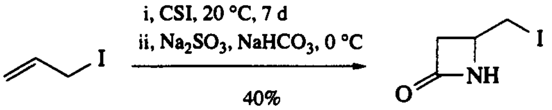

i, CSI, 20 °C, 7 d
ii, $Na_2SO_3$, $NaHCO_3$, 0 °C
40%

(57)

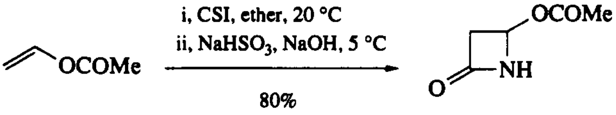
OCOMe
OCOMe
NH
O
i, CSI, ether, 20 °C
ii, $NaHSO_3$, NaOH, 5 °C
80%

(58)

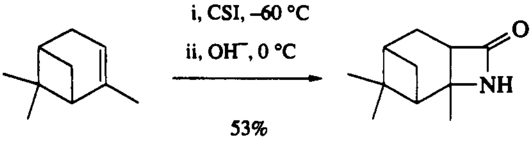

i, CSI, –60 °C
ii, OH⁻, 0 °C
53%

(59)

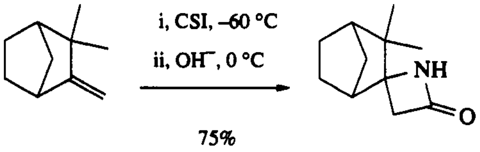

i, CSI, –60 °C
ii, OH⁻, 0 °C
75%

(60)

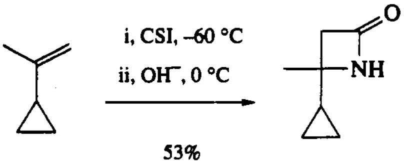

i, CSI, –60 °C
ii, OH⁻, 0 °C
53%

(61)

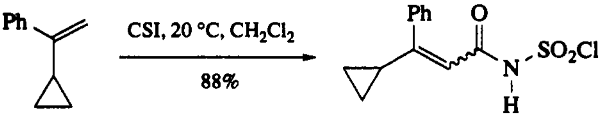
Ph
Ph
O
N
H
$SO_2Cl$
CSI, 20 °C, $CH_2Cl_2$
88%

(62)

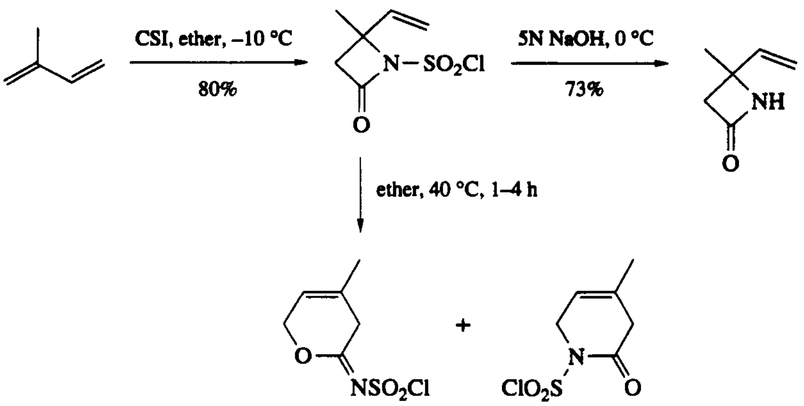
CSI, ether, −10 °C
80%
N−SO2Cl
O
5N NaOH, 0 °C
73%
NH
O
ether, 40 °C, 1–4 h
+
O
NSO2Cl
N
ClO2S
O

Scheme 28

chlorosulfonyl-β-lactams to the more stable NH β-lactams.[199,200] CSI reacts with allenes[201–203] to give 3-alkylidene-β-lactams accompanied by variable amounts of 2-vinylacrylamides when the $R^2$ substituent is a methyl group (Scheme 29).

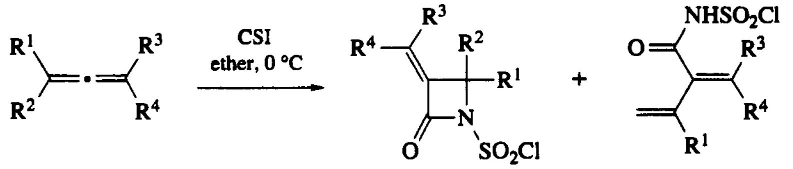
R1
R3
R2
R4
CSI
ether, 0 °C
R3
R4
R2
R1
N
O
SO2Cl
+
NHSO2Cl
O
R3
R4
R1

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | % | % |
|---|---|---|---|---|---|
| Me | Me | Me | Me | 67 | 28 |
| Me | Me | H | H | 23 | 36 |
| H | Ph | H | H | 60 | 0 |
| H | OAc | Me | Me | 50 | 0 |

Scheme 29

Both concerted[204] and stepwise[192] mechanisms have been proposed for these reactions although the experimental facts can be readily accounted for by the formation of a 1,4-dipolar intermediate (**27**; Scheme 27). The reaction rates are markedly increased in polar solvents.[188] The cycloadditions of isocyanates to alkenes are always regiospecific, the reaction taking place so as to form the most stable 1,4-dipole.

### 2.2.6.2 Stereochemical Aspects

Reactions of activated isocyanates with alkenes are highly stereospecific (equations 63 and 64).[183,187,201]

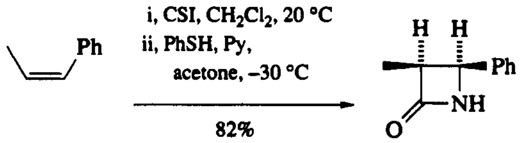
Ph
i, CSI, CH2Cl2, 20 °C
ii, PhSH, Py,
acetone, −30 °C
82%
H H
Ph
NH
O

(63)

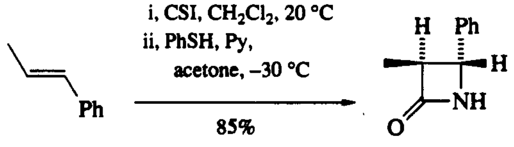
Ph
i, CSI, CH2Cl2, 20 °C
ii, PhSH, Py,
acetone, −30 °C
85%
H Ph
H
NH
O

(64)

In a few cases it was found that the primary adduct epimerized[205] under the reaction conditions (Scheme 30).

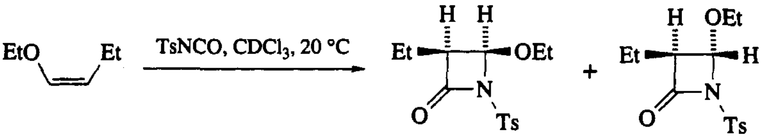
EtO
Et
TsNCO, $CDCl_3$, 20 °C
H H
Et
OEt
N
O
Ts
+
H OEt
Et
H
N
O
Ts

| *Reaction time* (min) | *cis* | *trans* |
|---|---|---|
| 1 | >95% | <5% |
| 18 | 65 | 35 |
| 1440 | 27 | 73 |

**Scheme 30**

Excellent stereoselectivity is also obtained in the cycloaddition of CSI with the optically active enol ether (**28**).[206] The reaction gives the *trans* β-lactams (**29**) and (**30**) in a 10:1 ratio (equation 65).

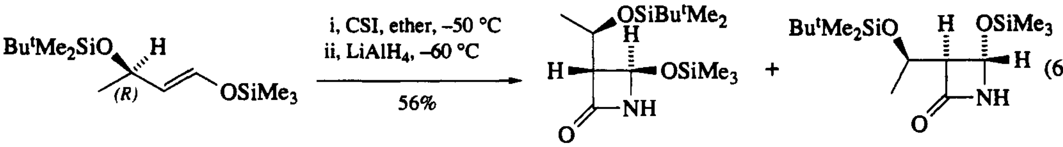
$Bu^tMe_2SiO$
H
(R)
$OSiMe_3$
i, CSI, ether, –50 °C
ii, $LiAlH_4$, –60 °C
56%
$OSiBu^tMe_2$
H
H
$OSiMe_3$
NH
O
+
$Bu^tMe_2SiO$
H $OSiMe_3$
H
NH
O

(65)

(**28**) (**29**) 91% (**30**) 9%

[2 + 2] Cycloadditions of activated isocyanates to 3,4-dihydro-2*H*-pyran derivatives are highly sensitive to the nature of substituents attached to the dihydropyran ring.[207,208] Thus, at normal pressure, the reaction of tosyl and trichloroacetyl isocyanates to give acetylated glycals is entirely shifted toward starting materials. Application of 10 kbar ($10^6$ kPa) pressure led to the formation of unstable β-lactams (equation 66). The cycloadditions proceed regio- and stereo-specifically, yielding adducts resulting from a *trans* addition relative to the acetoxy group at C-3. Glycals having nonpolar blocking groups react at normal pressure. Again the cycloadditions proceed regio- and stereo-specifically with formation of the β-lactam ring *anti* to the C-3 substituent (equation 67).

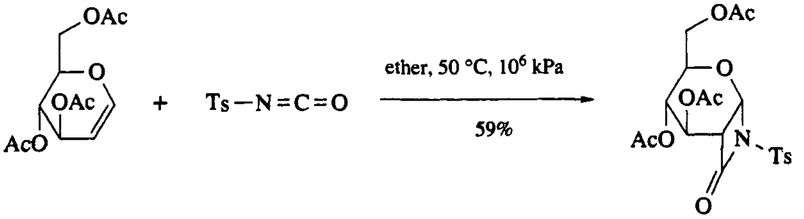
OAc
O
OAc
AcO
+
Ts–N=C=O
ether, 50 °C, $10^6$ kPa
59%
OAc
O
OAc
AcO
N
Ts
O

(66)

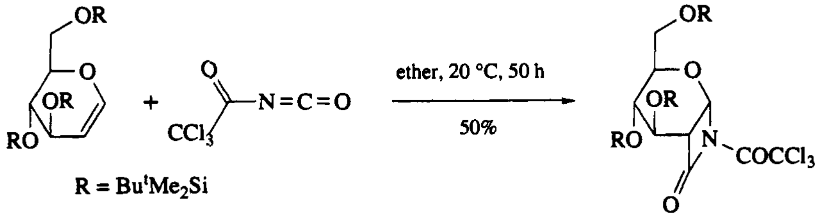
OR
O
OR
RO
+
O
N=C=O
$CCl_3$
R = $Bu^tMe_2Si$
ether, 20 °C, 50 h
50%
OR
O
OR
RO
N
$COCCl_3$
O

(67)

## 2.2.7 2-AZETIDINIMINIUM SALTS FROM KETENIMINIUM SALTS AND IMINES

### 2.2.7.1 Scope

2-Azetidiniminium salts[209,210] are available from the reaction of imines with iminium salts derived from tertiary carboxamides. These smoothly react with phosgene[211,212] to yield α-chloroiminium chlorides (**31**; Scheme 31). Elimination of HCl with a tertiary base forms[213,214] the corresponding α-chloroenamines (**32**) in good yields. These are ambiphilic molecules[215] which exhibit nucleophilic reactivity at C-2 and electrophilic reactivity at C-1 (Scheme 31). Thus they can react either as enamines or as keteniminium chlorides. Consequently, they readily undergo self-condensation reactions and have often to be prepared *in situ*. However, when they bear no hydrogen at C-2, their nucleophilic reactivity is reduced and they are stable enough to be purified by distillation.[214]

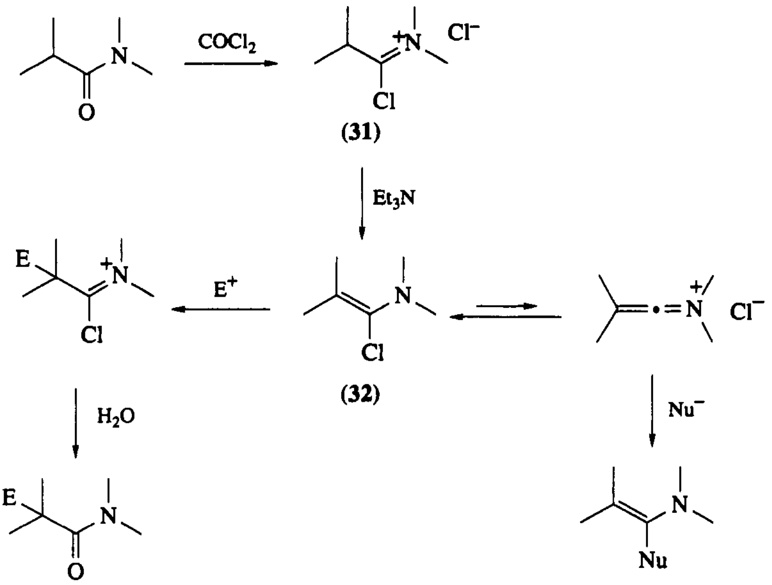

**Scheme 31**

β-Disubstituted α-chloroenamines are readily converted into the corresponding keteniminium salts (**33**)[216,217] in the presence of a Lewis acid (equation 68). Silver tetrafluoroborate, zinc, tin and aluminum chlorides have been successfully used. β-Disubstituted keteniminium salts have been isolated and characterized.[211] Unlike the corresponding ketenes, they do not dimerize or polymerize. However, they readily undergo [2 + 2] cycloaddition reactions with unsaturated substrates.[41]

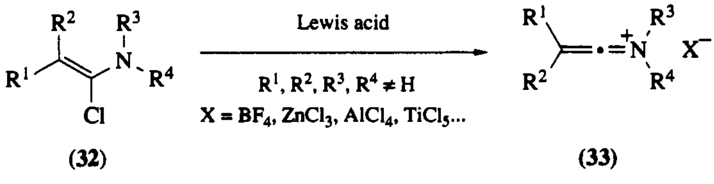 (68)
Lewis acid
R$^1$, R$^2$, R$^3$, R$^4$ ≠ H
X = BF$_4$, ZnCl$_3$, AlCl$_4$, TiCl$_5$...
(32)
(33)

While alkenes and alkynes only react with the most reactive keteniminium salts, imines are nucleophilic enough to cycloadd[210,218,219] to α-chloroenamines (**32**) which then behave as keteniminium chlorides (Scheme 32). The latter are often conveniently prepared *in situ* from the corresponding α-chloroiminium chlorides (**31**). A wide variety of 2-azetidinimimium salts (**34**) has been prepared by this method.[222] They are conveniently purified as perchlorates (Scheme 33). Paths A and B (Scheme 32) usually give similar results. In general, path B, which does not involve the isolation of (**32**), is more practical. However, neither path A nor path B allows the preparation of 4-alkyl substituted azetidiniminium salts: open-chain products are formed. This limitation is overcome by using a keteniminium salt generated from the corresponding α-chloroenamine and a Lewis acid (path C).[222]

Basic hydrolysis[209,210] of azetidiniminium salts proceeds *via* a tetrahedral intermediate which can fragment in two ways (Scheme 34): cleavage of the exocyclic C–N bond yields a β-lactam; alternatively, cleavage of the endocyclic C–N bond leads to an open-chain product devoid of any strain. Experimentally it is found[220–222] that β-lactams are the major hydrolysis products of 2-azetidiniminium salts bearing alkyl groups on the endocyclic nitrogen. When this substituent is an aryl group, the course of hydrolysis is pH dependent: at pH ≤ 10, β-lactams are the major products; at higher pH, β-amino amides are formed predominantly (Scheme 35).

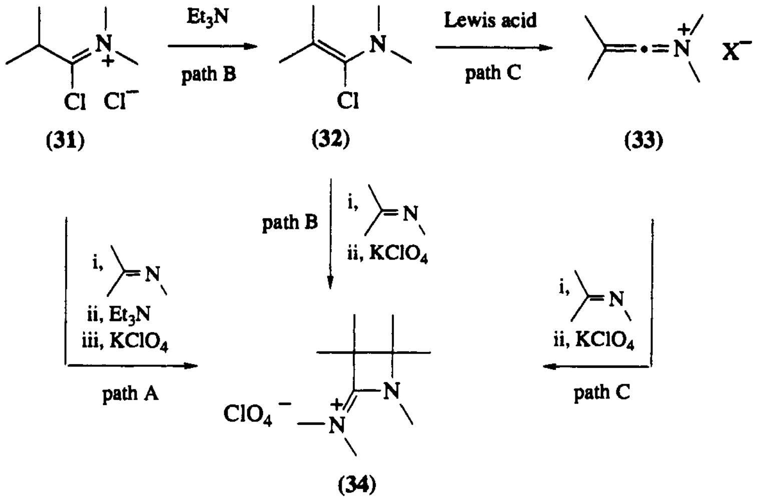
Et$_3$N
path B
Lewis acid
path C
X$^-$
Cl Cl$^-$
Cl
(31)
(32)
(33)
path B
i,
ii, KClO$_4$
i,
ii, Et$_3$N
iii, KClO$_4$
path A
i,
ii, KClO$_4$
path C
ClO$_4$$^-$
(34)

**Scheme 32**

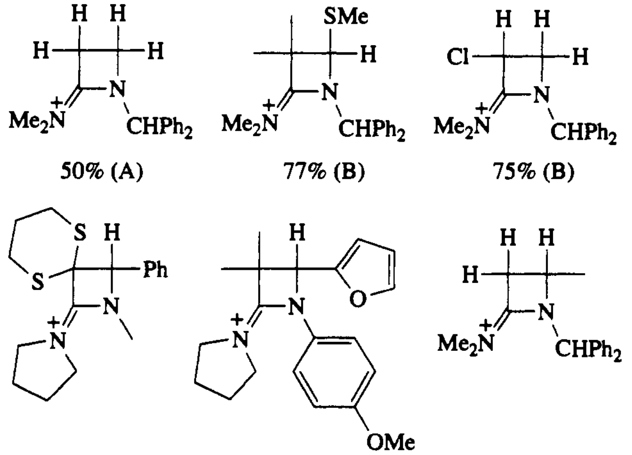
H H
H
H
Me$_2$N
CHPh$_2$
SMe
H
Me$_2$N
CHPh$_2$
H H
Cl
H
Me$_2$N
CHPh$_2$
S H
S
Ph
H
O
OMe
H H
H
Me$_2$N
CHPh$_2$

50% (A) 77% (B) 75% (B)

60% (A) 70% (B) 0% (A); 70% (C)

**Scheme 33**

Azetidiniminium salts have also been converted[222,223] into azetidine-thiones, -imines or -hydrazones (Scheme 36). Yields of imine derivatives are high when the azetidiniminium salts bear no hydrogen atom at C-3. Otherwise the reaction is best effected by first forming the corresponding 2-azetidinethione which is further treated[223] with an amine in the presence of mercury(II) acetate (Scheme 37).

The high reactivity of these strained amidinium salts (**34**) is further illustrated by their unusual ability to react with nucleophilic peroxides (equation 69).[210,222] None of the above transformations is observed with the corresponding 2-azetidinones.

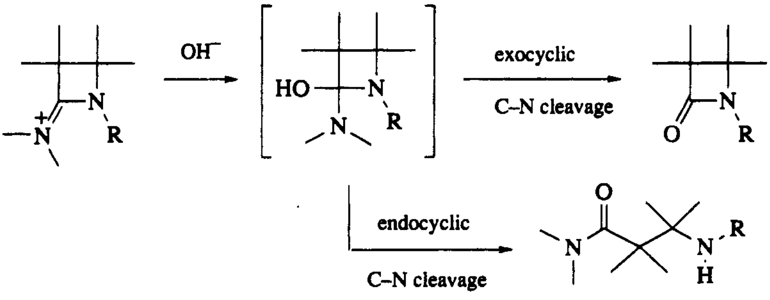
OH$^-$
HO
R
R
exocyclic
C–N cleavage
O
R
endocyclic
C–N cleavage
O
R
H

**Scheme 34**

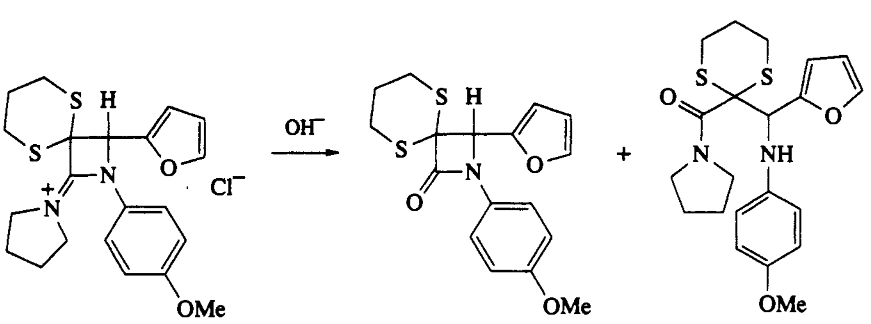

| pH | | |
|---|---|---|
| 9.5 | 48% | 0% |
| 13 | 0% | 60% |

**Scheme 35**

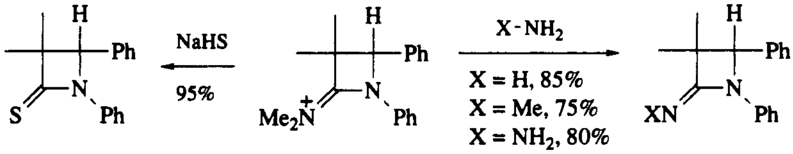
NaHS
95%
X-NH₂
X = H, 85%
X = Me, 75%
X = NH₂, 80%

**Scheme 36**

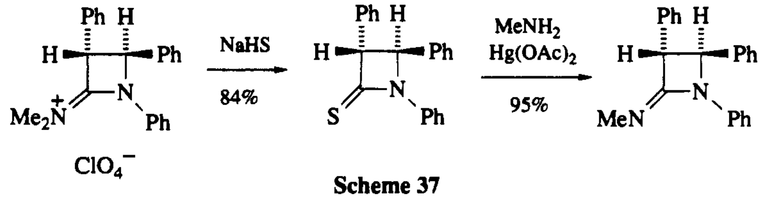
NaHS
84%
MeNH₂
Hg(OAc)₂
95%
ClO₄⁻

**Scheme 37**

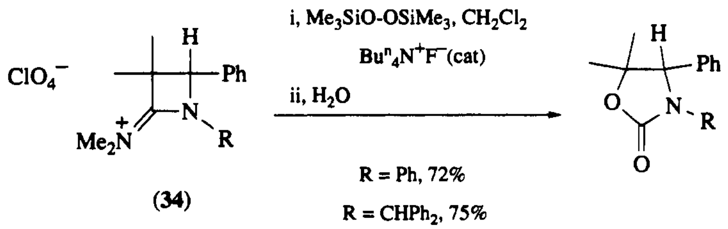
ClO₄⁻
i, Me₃SiO-OSiMe₃, CH₂Cl₂
Buⁿ₄N⁺F⁻(cat)
ii, H₂O
R = Ph, 72%
R = CHPh₂, 75%

(34)

(69)

## 2.2.7.2 Stereochemistry

While cycloadditions of imines with ketenes or their precursors often produce *cis* β-lactams, the corresponding reactions of keteniminium salts are *trans* stereoselective (equations 70 and 71).[210,222] It is not clear whether the *trans* stereoselectivity is kinetic or results from an equilibration of 2-azetidiniminium salts under the basic conditions used in both cycloaddition and hydrolysis steps.

Use of chiral imines[224,225] produces β-lactams with low diastereoselection (Scheme 38).

A potentially more interesting application of the method for asymmetric synthesis[210,222] uses chiral α-chloroiminium chlorides as starting material. Best results are obtained with iminium salts derived from (2*S*)-(methoxymethyl)pyrrolidine. They react with imines in the presence of triethylamine to give opti-

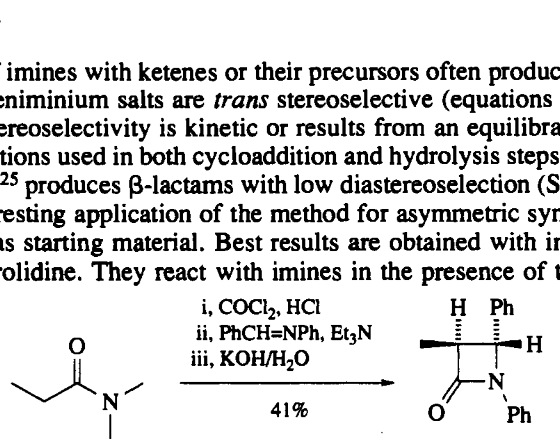
i, COCl₂, HCl
ii, PhCH=NPh, Et₃N
iii, KOH/H₂O
41%

(70)

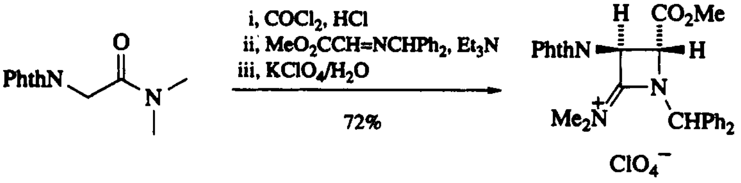
PhthN
O
N
i, $COCl_2$, HCl
ii, $MeO_2CCH{=}NCHPh_2$, $Et_3N$
iii, $KClO_4/H_2O$
72%
H
$CO_2Me$
PhthN
H
N
$Me_2\overset{+}{N}$
$CHPh_2$
$ClO_4^-$

(71)

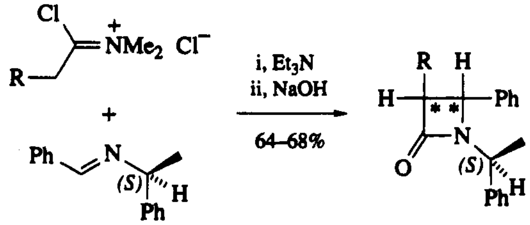
Cl
R
$\overset{+}{N}Me_2$ $Cl^-$
+
Ph
N
(S)
H
Ph
i, $Et_3N$
ii, NaOH
64–68%
R
H
H
Ph
* *
N
O
(S)
Ph
H

| *R* | *trans* (%) | | *cis* (%) | |
|---|---|---|---|---|
| | (3*S*,4*R*) | (3*R*,4*S*) | (3*R*,4*R*) | (3*S*,4*S*) |
| Me | 35 | 32 | 22 | 11 |
| Ph | 30 | 50 | 5 | 15 |

**Scheme 38**

cally active β-lactams after hydrolysis (Scheme 39). The bulk of the C-3 substituents $R^1$ and $R^2$ plays a decisive role in the diastereoselectivity. When $R^1$ and $R^2$ are different from hydrogen, the diastereoselection is very high. However, it drops dramatically when $R^1$ and/or $R^2$ are hydrogens.

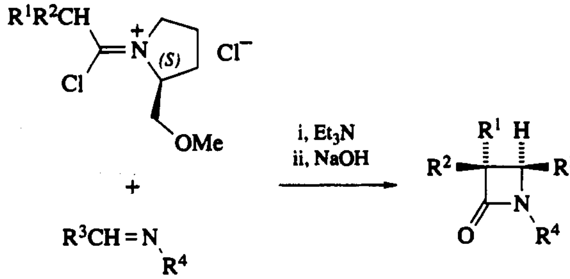
$R^1R^2CH$
Cl
+
N
(S)
$Cl^-$
OMe
+
$R^3CH{=}N$
$R^4$
i, $Et_3N$
ii, NaOH
$R^1$
H
$R^2$
$R^3$
N
O
$R^4$

| *R¹* | *R²* | *R³* | *R⁴* | *Yield* (%) | *cis/trans* | *ee* (%) |
|---|---|---|---|---|---|---|
| Me | Me | Ph | 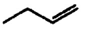 | 42 | – | 98 |
| Me | Me | SPh | $CH_2Ph$ | 65 | – | 99 |
| Ph | Me | Ph | Me | 29 | 0/100 | 97 |
| Me | H | Ph | Me | 30 | 20/80 | 40 |
| H | H | Ph | Me | 47 | – | 4 |

**Scheme 39**

A notable exception is found in the reaction of iminium salt (**35**) derived from *N*-phthaloylglycinamide with imines (Scheme 40). The presence of the phthalimido substituent requires a modification of the procedure[222,223] converting the adduct (**36**) into the β-lactam (**38**). While basic hydrolysis destroys compound (**36**), treatment with sodium hydrogensulfide smoothly gives the azetidinethione (**37**) which is readily oxidized to the corresponding β-lactam (**38**) with modest overall chemical yield but high enantiomeric purity.

The nature of the anion associated with the iminium salt appears to play an important role in the diastereoselectivity of the reaction.[222] Thus while tetramethyl-α-chloroenamine (**39**) gives a β-lactam in high optical purity, the corresponding tetramethylketeniminium tetrafluoroborate (**40**) reacts with almost no diastereoselection (Scheme 41).

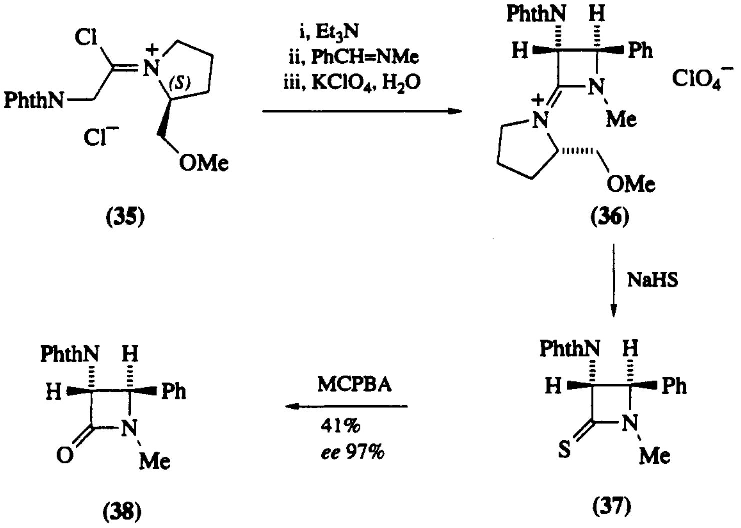
(35)
i, $Et_3N$
ii, PhCH=NMe
iii, $KClO_4$, $H_2O$
(36)
$ClO_4^-$
NaHS
(37)
MCPBA
41%
*ee* 97%
(38)

Scheme 40

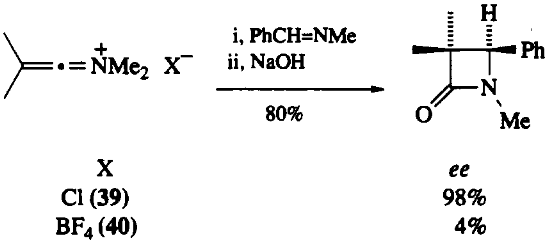
i, PhCH=NMe
ii, NaOH
80%
X
Cl (39)
$BF_4$ (40)
*ee*
98%
4%

Scheme 41

## 2.2.8 CYCLOADDITIONS OF KETENIMINES

There are only few reports of [2 + 2] cycloadditions with ketenimines.[226–232] In most cases, reactions occur across the C=C bond. Only ynamines[233] and polyfluorinated alkenes[234] cycloadd to the C=N bond.

### 2.2.8.1 2-Iminoazetidines from Ketenimines and C=N Bonds

The nucleophilic C=C bond of ketenimines reacts[235] with isocyanates to yield a single [2 + 2] adduct (equation 72).

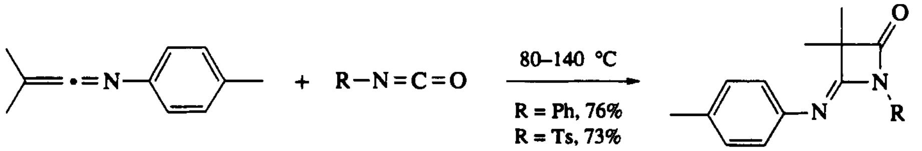
R–N=C=O
80–140 °C
R = Ph, 76%
R = Ts, 73%

(72)

*N*-Alkyl- and *N*-aryl-ketenimines are poor electrophilic partners and do not react with benzylideneaniline[236] or dicyclohexylcarbodiimide.[237] The introduction of an electron-withdrawing substituent (tosyl[236,238] or cyano[239]) on the nitrogen atom enhances the electrophilic character of the cumulene and cycloadditions to imines occur under very mild conditions (Scheme 42). In most cases, the reactions are *trans* stereoselective.

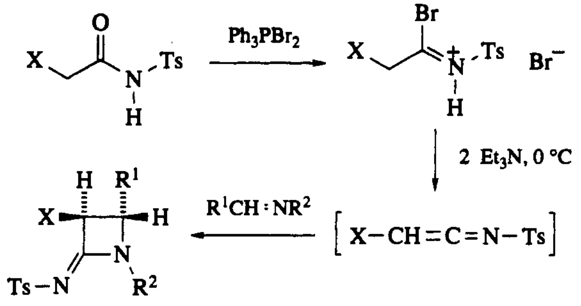

| *X* | *R$^1$* | *R$^2$* | *Yield* (%) | *cis:trans* |
|---|---|---|---|---|
| H | Ph | Ph | 50 | - |
| Cl | Ph | Ph | 38 | 0/100 |
| $N_3$ | $CO_2Me$ | $CHPh_2$ | 47 | 50/50 |
| Phth | 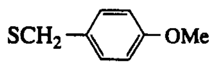 | 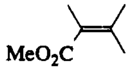 | 57 | 0/100 |

Scheme 42

### 2.2.8.2 2-Iminooxetanes from Ketenimines and C=O Bonds

Thermal cycloadditions of ketenimines to carbonyl compounds requires activation of the C=O bond. The highly electrophilic bis(trifluoromethyl) ketone reacts[240] at high temperature with diphenyl-*N*-tolylketenimine (equation 73). Lanthanide shift reagents[241] such as tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium or -ytterbium [Eu(fod)$_3$ or Yt(fod)$_3$] are efficient catalysts for the cycloaddition of ketenimines with aldehydes (equation 74). The use of chiral catalysts such as tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium or -ytterbium [Eu(hfc)$_3$ or Yt(hfc)$_3$] has been found to generate only moderate enantiomeric excesses (20–40%).[241]

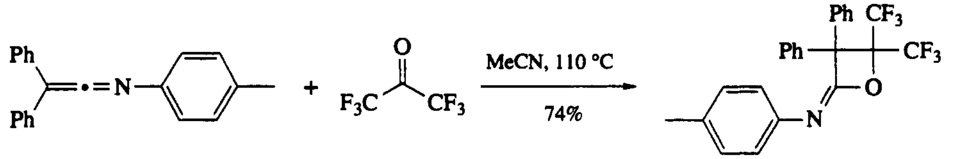

(73)

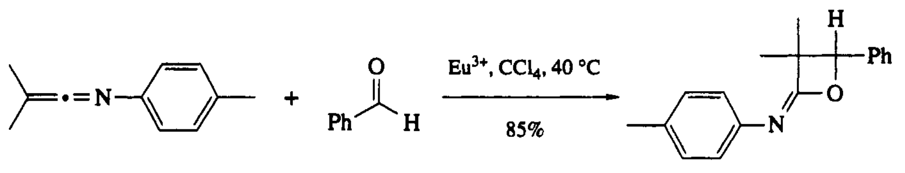

(74)

### 2.2.8.3 2-Iminothietanes from Ketenimines and C=S Bonds

Thermal reactions of ketenimines with thiobenzophenone have been investigated in detail.[242–245] Trisubstituted ketenimines bearing an alkyl or an *o,o'*-disubstituted aryl group on nitrogen give 2-iminothietanes (equation 75). When there are no *ortho* substituents on the aromatic ring, the C=S bond adds across the conjugated system involving the C=N bond of the cumulene and one C=C bond of the aromatic ring (equation 76). With aldoketenimines, and irrespective of the nature of the nitrogen substituent, the initially formed 2-iminothietanes isomerize to give the more stable conjugated thioamides (equation 77).

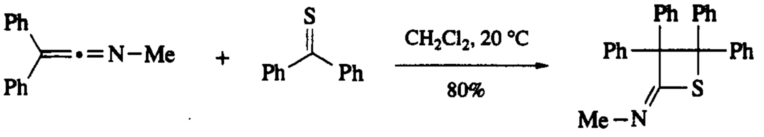

(75)

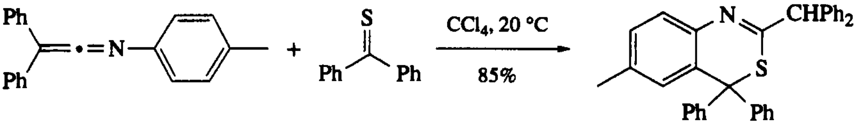

(76)

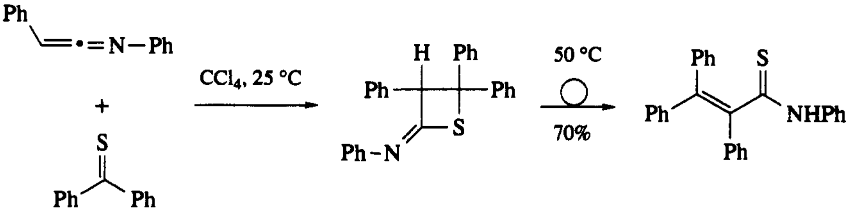

(77)

### 2.2.9 CYCLOADDITIONS OF THIOKETENES

Thioketenes are generally unstable and difficult to prepare. Therefore only few compounds have been studied.[246] Bis(trifluoromethyl)thioketene reacts[247] with a wide range of C═C and C═X bonds (equations 78–80). The products always result from addition across the C═S bond of the cumulene.

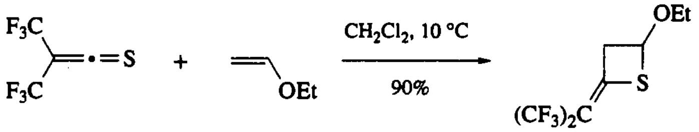

(78)

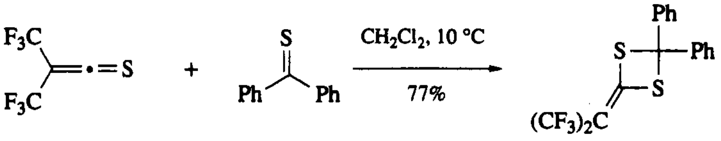

(79)

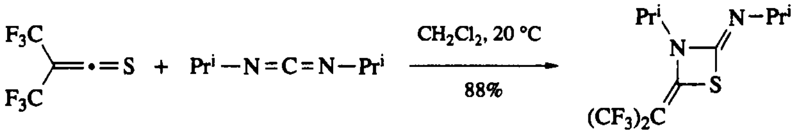

(80)

2-Azetidinethiones are formed[248,249] in the reaction of imines with dialkylthioketenes (equation 81). These also react across the C═N bond of electrophilic isocyanates (equation 82).[250,251]

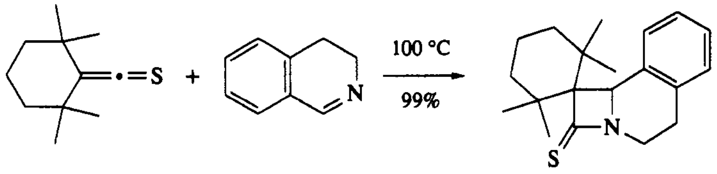

(81)

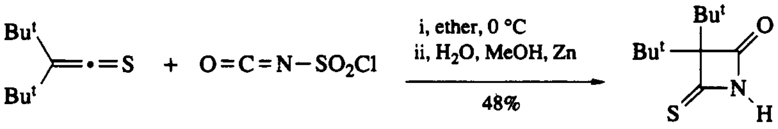

(82)

## 2.2.10 FOUR-MEMBERED HETEROCYCLES FROM ACTIVATED ALKYNES AND C=X BONDS

Few reactions of alkynes with C=X bonds are valuable for the preparation of four-membered heterocycles. Ynamines[252,253] react with aldehydes and ketones in the presence of Lewis acids to give unstable oxetene derivatives[254] which undergo electrocyclic opening (Scheme 43). Open-chain products are also obtained with thiocarbonyl compounds,[255] Schiff bases[256] and iminium salts.[257] Reactions of ynamines with carbon dioxide,[258] ketenes,[259,260] ketenimines[261,262] and isocyanates[263–266] often give mixtures of products and are of little preparative value.

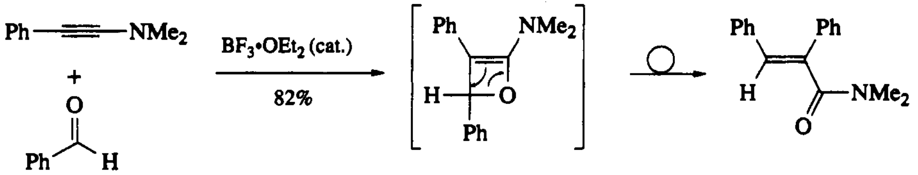
Ph
NMe2
+
O
Ph
H
BF3•OEt2 (cat.)
82%
Ph
NMe2
H
O
Ph
Ph
Ph
H
NMe2
O

Scheme 43

Lithium phenylethynolate (**41**), which is readily obtained from 3,4-diphenylisoxazole and butyllithium, reacts[267,268] with aldehydes and ketones to yield 2-oxetanones after protonation (Scheme 44).

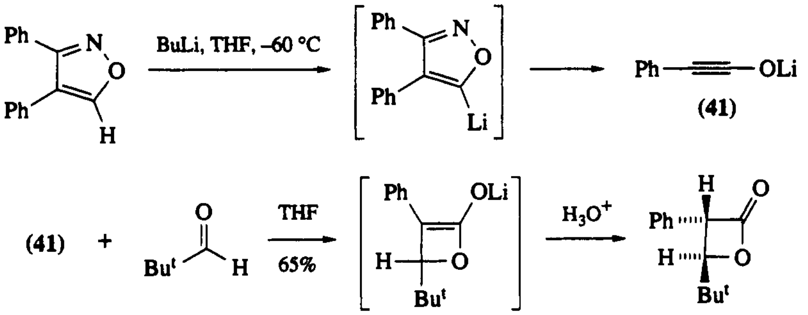
Ph
N
O
Ph
H
BuLi, THF, –60 °C
Ph
N
O
Ph
Li
Ph
OLi
(41)
(41)
+
O
Bu^t
H
THF
65%
Ph
OLi
H
O
Bu^t
H3O+
H
O
Ph
H
O
Bu^t

Scheme 44

The reaction of (**41**) with electron-deficient imines yields 2-azetidinones resulting from a 1:2 addition (Scheme 45).[269,270] The total stereoselectivity of the reaction has been explained on the basis of steric approach control and chelation in transition state (**43**). The intermediate β-lactam enolate (**42**) is more nucleophilic than the starting ynolate. This unfavorable nucleophilicity ratio is responsible for the formation of a 1:2 adduct. This represents a severe limitation of the reaction as a general route toward β-lactams.

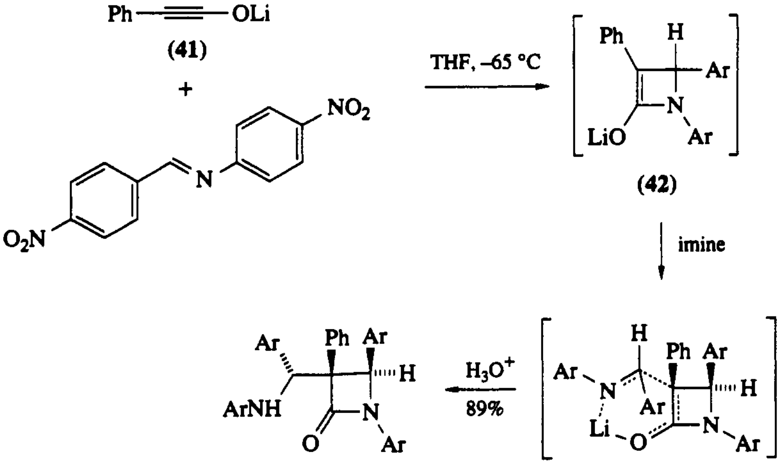
Ph
OLi
(41)
+
NO2
N
O2N
THF, –65 °C
Ph
H
Ar
N
LiO
Ar
(42)
imine
Ar
Ph
Ar
H
ArNH
N
O
Ar
H3O+
89%
H
Ph
Ar
Ar
N
H
Ar
Li
O
N
Ar
(43)

Scheme 45

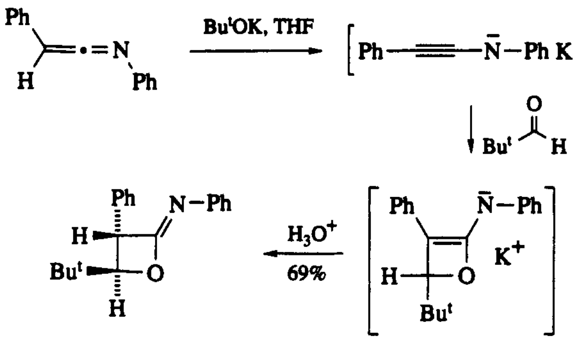
Bu$^t$OK, THF
H$_3$O$^+$
69%
K$^+$

Scheme 46

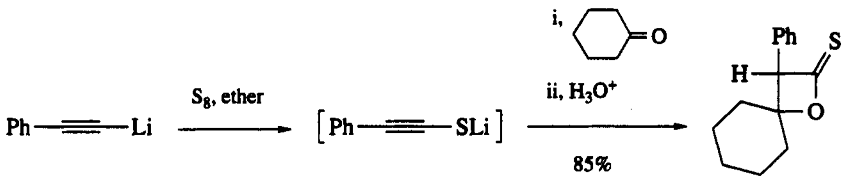
S$_8$, ether
i,
ii, H$_3$O$^+$
85%

Scheme 47

2-Iminooxetanes have been prepared from aldehydes and lithium (*N*-phenyl)phenylethynamide (Scheme 46).[271,272] 2-Thionooxetanes are similarly formed from carbonyl compounds and lithium thioalkynolates (Scheme 47).[273] None of these reactions is of general preparative value.

## 2.2.11 MISCELLANEOUS

There are many other cases of combination of π-bonds leading to four-membered heterocyclic rings. Few of these are of great preparative value and most have been little studied. Some representative examples are shown in equations (83),[274] (84),[275] (85),[276] (86)[277] and (87).[278]

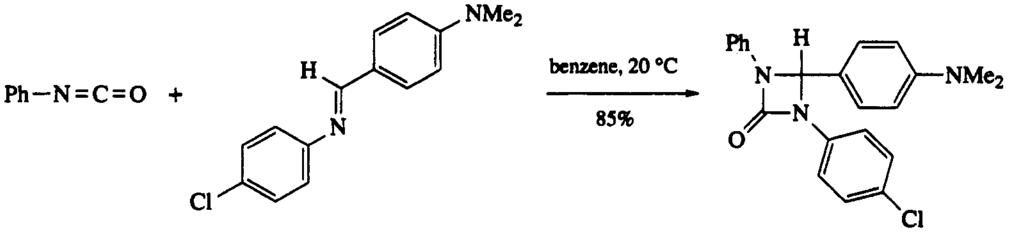
benzene, 20 °C
85%

(83)

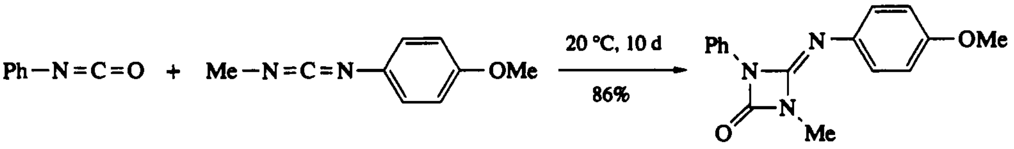

(84)

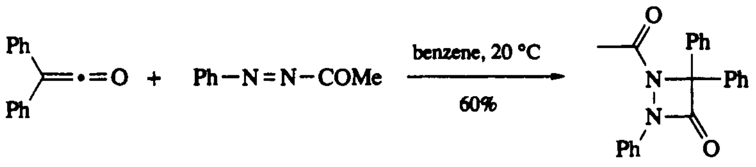
benzene, 20 °C
60%

(85)

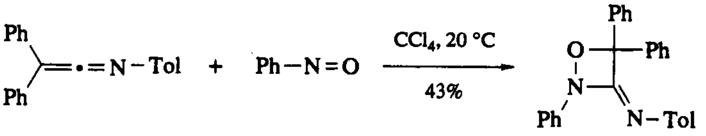

(86)

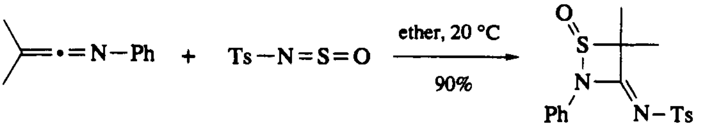

(87)

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# 2.3
# Photochemical Cycloadditions

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## 2.3.1 INTRODUCTION

The photochemical [2 + 2] cycloaddition reaction of alkenes, the light-induced cycloaddition of two carbon–carbon π-bonds to produce a cyclobutane, is a potentially highly useful reaction in organic synthesis since two new carbon–carbon bonds are formed and a maximum of four new stereocenters are introduced in the process.[1] Ciamician reported the first example in 1908 when he observed the formation of carvone camphor (**2**) on prolonged exposure of carvone (**1**) to Italian sunlight (equation 1).[2]

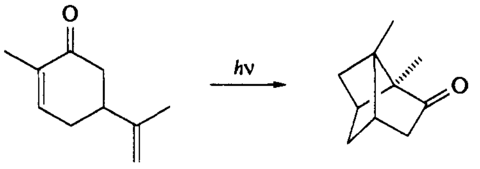

(1)

(1) (2)

After Buchi confirmed this finding in the 1950s,[3] numerous other investigators immediately recognized the rapidity with which complex molecular architectures could be constructed by this reaction. Cookson irradiated the Diels–Alder adduct (**3**) of cyclopentadiene and benzoquinone to produce the caged diketone (**4**) (equation 2)[4] while Eaton utilized a photochemical cycloaddition of diene (**5**) in a synthesis of the platonic solid cubane (**6**) (equation 3).[5]

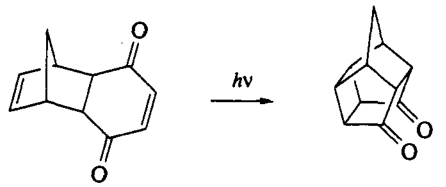

(3) (4)

(2)

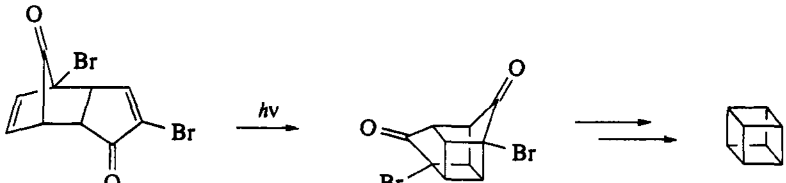
Br
Br
hν
Br
Br

(5)

(6) Cubane

(3)

Corey,[6] Eaton,[7] de Mayo[8,9] and many others began to investigate the various synthetic and mechanistic ramifications of the photocycloaddition which resulted in the total synthesis of caryophyllene[10] and bourbonene[11] as well as a proposed mechanistic rationale for the reaction.[6] Subsequently, numerous natural and unnatural products have been prepared by synthetic routes which have a [2 + 2] photocycloaddition as a crucial step in their synthesis, and the reaction has become recognized as an important transformation in the repertoire of the synthetic organic chemist.

## 2.3.2 MECHANISM

While there is still much which is not well understood about the mechanism of the photochemical cycloaddition, several points about a working hypothesis (Scheme 1)[6,8-10] are worthy of note and serve as a basis for the discussions which follow.

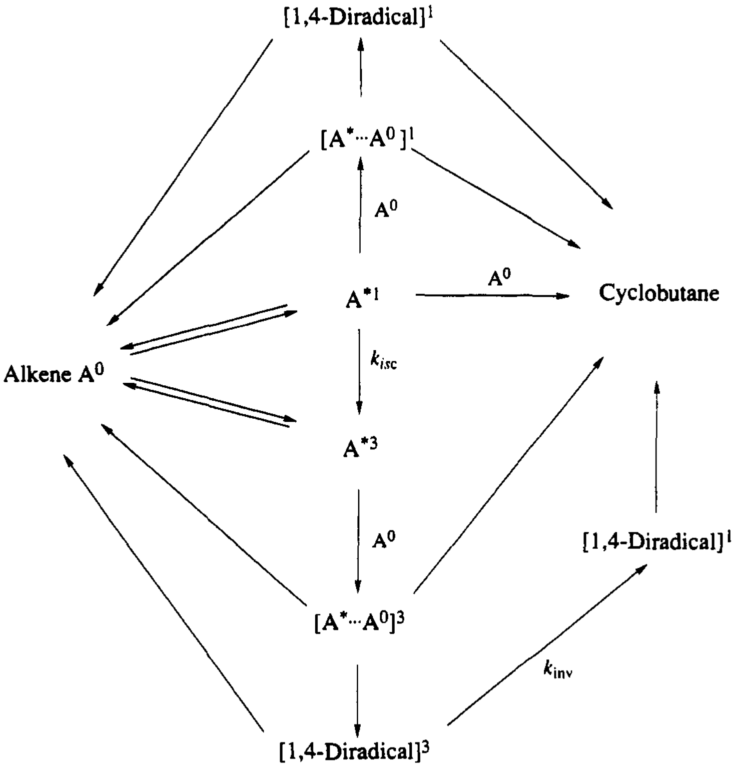
[1,4-Diradical]$^1$
[A*···A$^0$]$^1$
A$^0$
A*$^1$
A$^0$
Cyclobutane
Alkene A$^0$
$k_{isc}$
A*$^3$
A$^0$
[1,4-Diradical]$^1$
[A*···A$^0$]$^3$
$k_{inv}$
[1,4-Diradical]$^3$

**Scheme 1**

Excitation of the ground-state alkene $A^0$ (either $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$)[12,13] normally produces the excited singlet $A^{*1}$ which can (1) combine with a ground-state alkene $A^0$ to form a singlet exciplex $[A^{*}...A^0]^1$, (2) undergo a concerted cycloaddition with $A^0$ to form a cyclobutane, (3) intersystem cross to an excited triplet $A^{*3}$, or (4) collapse back to the ground state. The singlet is fairly short lived, particularly in enone systems, and will decay back to the ground state if *cis–trans* isomerization can occur.[14] The singlet exciplex can decay back to the ground state or generate a cyclobutane directly, or produce a 1,4-diradical which can also collapse to the ground state or proceed to cyclobutane. The triplet $A^{*3}$, which can result from the singlet $A^{*1}$ or from sensitized excitation of the ground state $A^0$, can either decay to the ground state or combine with a ground-state alkene to generate a triplet exciplex $[A^{*}...A^0]^3$.[6] The exciplex can then form a carbon–carbon bond and produce a triplet 1,4-diradical which can undergo spin inversion to the singlet diradical followed by production of the cyclobutane. Additionally, at any point along the path to cyclobutane, *i.e.* (1) the triplet exciplex $[A^{*}...A^0]^3$, (2) the triplet diradical or (3) the singlet diradical, the ground-state alkenes can be regenerated. While it is convenient to invoke the intermediacy of exciplexes in photocycloadditions, Schuster has recently presented kinetic evidence which is inconsistent with exciplex formation.[15]

In the majority of cases the pathway which leads to cyclobutane adducts is most likely excitation to a short-lived singlet $A^{*1}$, followed by crossing to the longer-lived triplet $A^{*3}$ which forms an exciplex and then a triplet diradical. The triplet diradical spin inverts to the singlet and closes to the cyclobutane. If the singlet can undergo rotation, energy wasting *cis–trans* isomerization will compete with intersystem crossing and subsequent photocycloaddition. This occurs primarily in acyclic systems which are not rigidly held by hydrogen bonding or in cyclic systems which are larger than six members.[16]

## 2.3.3 INTERMOLECULAR PHOTOCYCLOADDITIONS

### 2.3.3.1 Regiochemical Control

When two unsymmetrical alkenes undergo [2 + 2] photocycloaddition, two regiochemical isomers, the head-to-head and head-to-tail isomers, can result. For example, when cyclohexenone is irradiated in the presence of isobutene the head-to-head product (**8**) is produced along with the head-to-tail isomer (**7**) (equation 4). The preponderence of the head-to-tail isomer (**7**) is generally thought to be controlled by electronic interactions. The excited enone is assumed to have a charge distribution which is the opposite of its ground-state configuration and thus the enone β-carbon bears a partial negative charge.[6,17] During the exciplex formation the ground-state alkene and the excited-state enone are oriented to maximize electrostatic interactions. This interpretation is supported by results with more highly polarized alkenes and enones which both show significantly higher regioselectivity (equations 5–7).[6,18,19] While this electrostatic interpretation is a useful predictive tool, regioselectivity may be greatly influenced by the rate with which each initially formed exciplex proceeds to products or reverts to the ground state.

Steric interactions can dramatically affect regioselectivity as well. This is demonstrated by the result that cyclohexenone reacts with vinyl acetate to give exclusively the head-to-tail regioisomer (**9**)[20] while 3-methylcyclohexenone produces a 1:4 mixture of the head-to-head:head-to-tail isomers (**10**):(**11**) (equation 8).[21] Additionally, 3-*n*-butylcyclopentenone undergoes photocycloaddition with vinyl acetate to give a 3:1 mixture of head-to-tail:head-to-head photoadducts while 1-acetoxy-1-hexene gives rise to exclu-

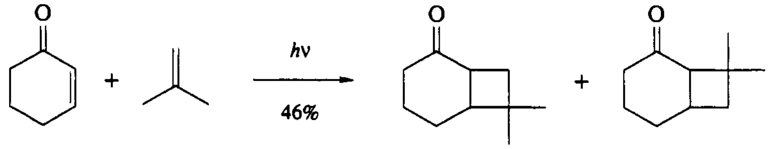

(4)

(**7**) 86:14 (**8**)

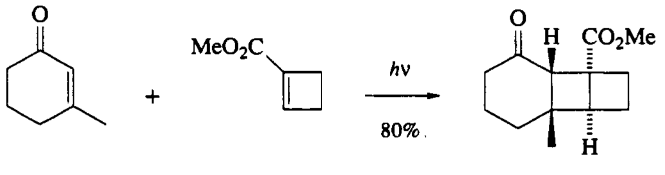

(5)

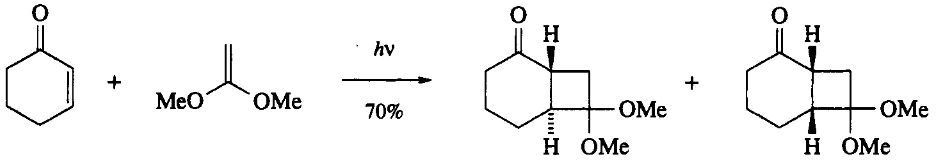

70:30

(6)

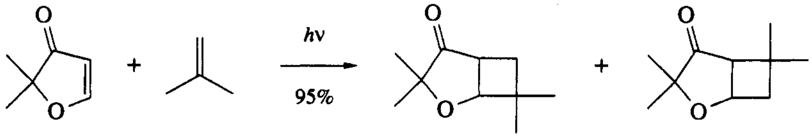

98:2

(7)

sively the head-to-tail adduct, presumably due to the steric interaction between the two alkyl chains (equation 9).[22]

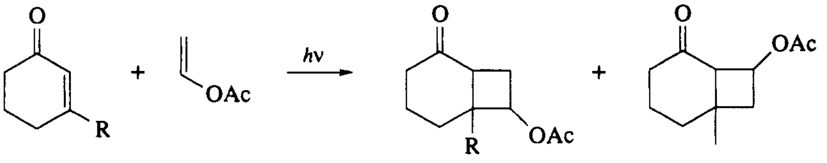

(8)

R = H 90%; 100:0 **(9)**
R = Me 68%; 20:80 **(10)** **(11)**

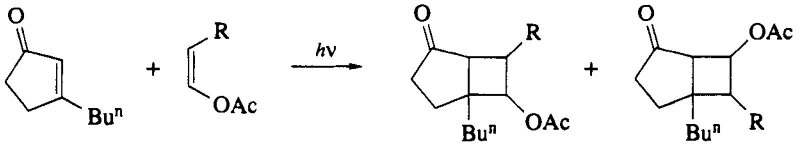

(9)

R = H 75:25
R = $Pr^n$ 100:0

Regioselectivity in photocycloadditions may also depend on the production and partitioning of various 1,4-diradicals as has been proposed by Bauslaugh (equation 10).[1] In this treatment, unstable 1,4-diradicals are presumed not to form to any appreciable extent while the more stable diradicals are presumed to revert to starting alkenes preferentially. The diradicals of intermediate stability thus determine the selectivity of the reaction. While the product ratio may clearly depend in some instances on the rates of partitioning of the diradicals to cyclobutane *versus* ground-state alkenes, it is often very difficult even qualitatively to determine which diradicals are more or less stable, making this interpretation somewhat difficult. Overall, the polar exciplex theory serves as a useful model for predicting regioselectivity in most photocycloadditions.

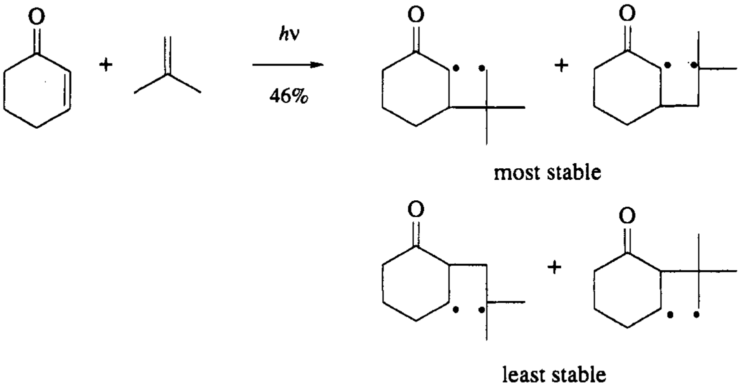

(10)

The observed regioselectivity can be perturbed to varying degrees by choice of reaction parameters. Solvent polarity can play a role in the control of regioselectivity, as would be predicted by the polar exciplex model. The regioselectivity of the dimerization of cyclopentenone (equation 11) produces a larger proportion of the head-to-head adduct in more polar solvents.[23] The photoaddition of enone (**11**) to alkene (**12**) also displays a pronounced solvent dependence (equation 12).[24] A consequence of the solvent effect is that nonpolar solvents tend to produce products which would be predicted from the polar exciplex model, while more polar solvents result in somewhat more of the minor product but do not cause complete reversal of the regioselectivity.

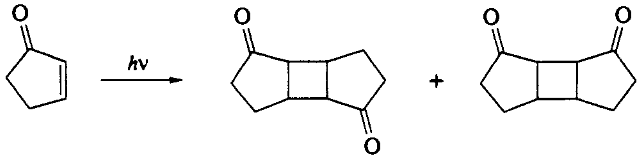

(11)

| | |
|---|---|
| neat | 57:43 |
| cyclohexane | 85:15 |

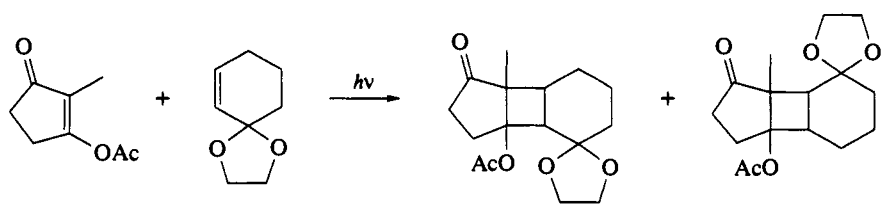

(12)

(**11**) (**12**)

| | |
|---|---|
| cyclohexane | 2:98 |
| methanol | 55:45 |

Organized media have also been used to influence the regiochemical outcome in the reactions.[22] Photoaddition of 3-*n*-butylcyclopentenone with various terminal alkenes has shown a pronounced preference for the alignment of the enone and the alkenes with their polar groups toward the surface of the micelle. This effect is most pronounced in the case of 1-acetoxy-1-heptene, which gives exclusively the head-to-tail adduct in cyclohexane solvent but a 2.3:1 mixture in favor of the head-to-head isomer in the presence of potassium dodecyl sulfate (equation 13).

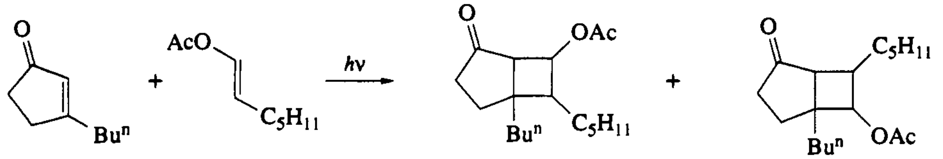

(13)

| | |
|---|---|
| cyclohexane | 0:100 |
| potassium dodecyl sulfate | 70:30 |

Varying the temperature of the photoaddition reaction can also produce minor changes in the regioselectivity. Typically, lowering the temperature tends to enhance the selectivity in favor of the major regioisomer, as seen in equation (14).[25]

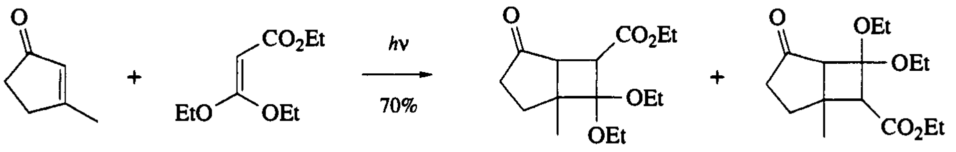

(14)

| | |
|---|---|
| 25 °C | 29:71 |
| –40 °C | 0:100 |

### 2.3.3.2 Stereochemical Control

Since up to four new stereogenic centers can be produced in a photocycloaddition reaction, prediction of stereoselectivity becomes extremely important with regard to the use of [2 + 2] photoadditions in synthesis. Stereoisomerism in the products of photoaddition can manifest itself in several different ways. First of all there is the question of geometry about the cyclobutane ring. In the addition of acyclic alkenes to cyclic enones, the geometry of the alkene is normally scrambled during the cycloaddition as a result of the rotational freedom in the intermediate long-lived 1,4-diradical. Thus *cis*- and *trans*-2-butene produced the same mixture of three stereoisomeric photoadducts when irradiated with cyclohexenone.[6] Similarly, cyclopentenone and 1,2-dichloroethylene produced all four possible *cis* photoadducts when either the *cis* or *trans* alkene was used.[26] Here the ratios of the products are somewhat different depending on the geometry of the alkene, but this may simply be a result of different rates of cyclobutane closure of the initially formed diradicals (equation 15).

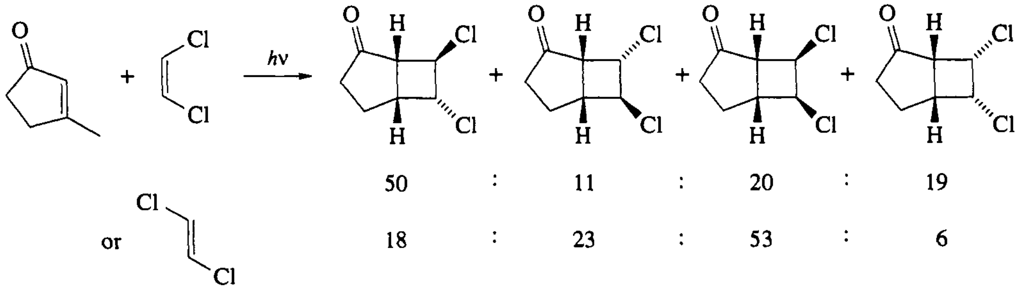

(15)

Loss of geometric integrity is not observed with cyclic alkenes which have ring sizes of five members or less since *cis–trans* isomerization is inhibited. Larger rings, however, can result in loss of alkene stereochemistry (equations 16, 17).[22,27] The cyclobutane ring juncture derived from the excited-state alkene is always *cis* if the enone is contained in a five-membered ring (or smaller), since the excited state is not substantially twisted (equations 7, 15–17).[19,22,26,27] Conversely, cyclohexenones often produce significant amounts of *trans* products at the cyclohexane–cyclobutane ring juncture (equations 6, 18, 19).[6,28,29] This has been attributed to the spectroscopic observation that some cyclohexenone triplets are substantially twisted, allowing bond formation on one side of the ring at the α-carbon and bond formation from the opposite face at the β-carbon.[13] Cyclohexenones which are conformationally more rigid tend to produce predominantly or exclusively *cis* ring fusions (equations 20–22).[21,30] The *cis* product is also obtained with cyclohexenones if the product cyclobutane contains an unusual amount of ring strain, *e.g.* with cyclobutenes, alkynes or allenes as the ground state alkene (equations 5, 23, 24).[18,31,32] As can be seen in equations (5), (11), (12) and (20), if the *cis* product is obtained the *cis-anti-cis* geometry as opposed to the *cis-syn-cis* geometry is by far the dominant product, presumably as a result of the steric interactions between the two rings.

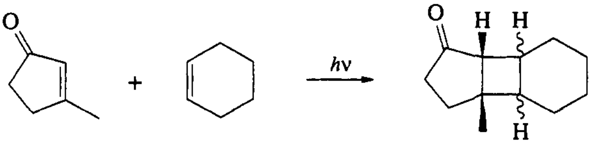

(16)

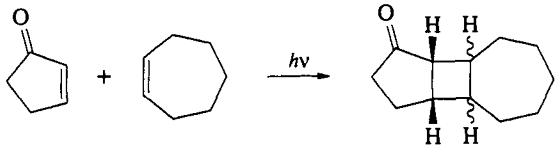

(17)

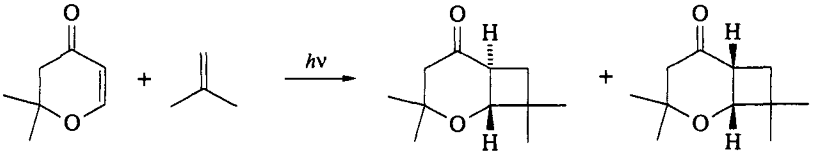

(18)

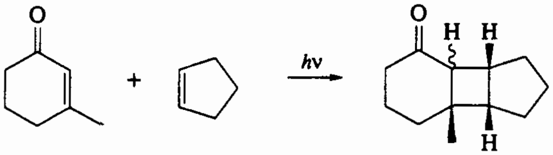

(19)

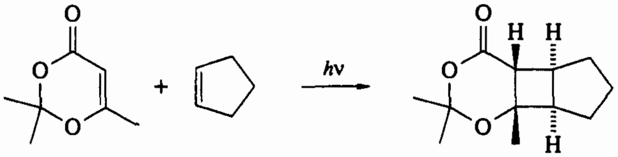

(20)

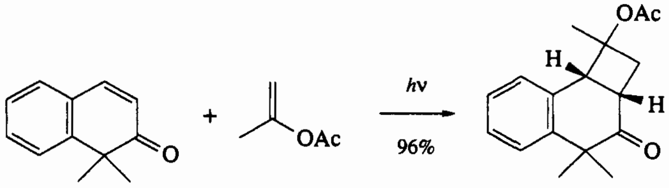

(21)

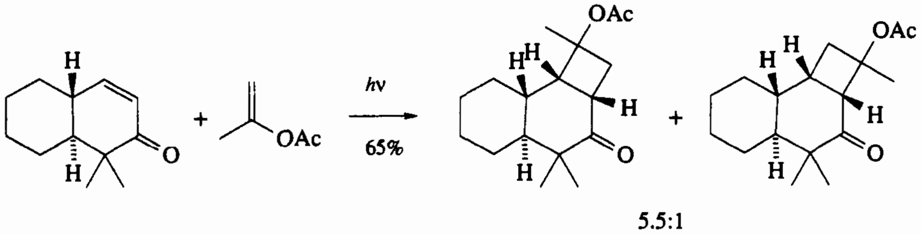

(22)

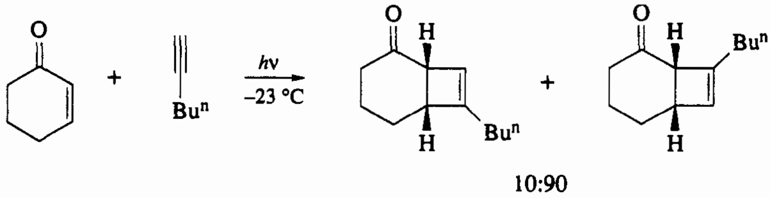

(23)

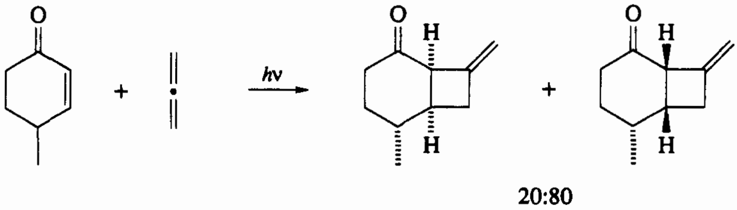

(24)

The remaining stereochemical point which must be addressed is the effect of a preexisting stereogenic center on either the excited-state or ground-state alkene. As a general rule, a stereogenic center in the ground-state alkene will affect the stereochemical outcome of a photocycloaddition reaction much as it would be expected to affect any other chemical reaction. That is, the excited state enone normally adds to the sterically most accessible face of the ground-state alkene, as in the photoadditions utilized in the syntheses of loganin (equation 25),[33] sarracenin (equation 26),[34] acorenone (equation 27)[35] and bourbonene (equation 28).[11] The addition of the dimethylfuranone (**13**) to enol derivatives (**14–18**) (equation 29) produces the product which would appear to result from approach from the more hindered face of the alkene.[36] This can perhaps be rationalized by $A_{1,2}$ strain in a similar manner to the epoxidation of 1,5-dimethylcyclopentene.[37]

Stereochemical induction by a stereogenic center on the excited state enone, particularly cyclohexenones, has been rationalized by Wiesner as resulting from attack of the ground-state alkene on the most

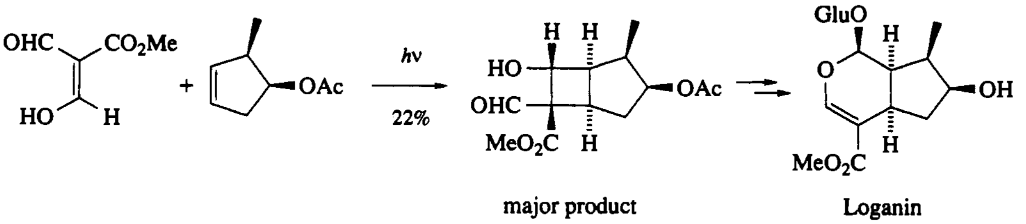
OHC
CO2Me
HO
H
OAc
hv
22%
HO
OHC
MeO2C
H H
OAc
major product
GluO
O
H
OH
MeO2C
Loganin
(25)

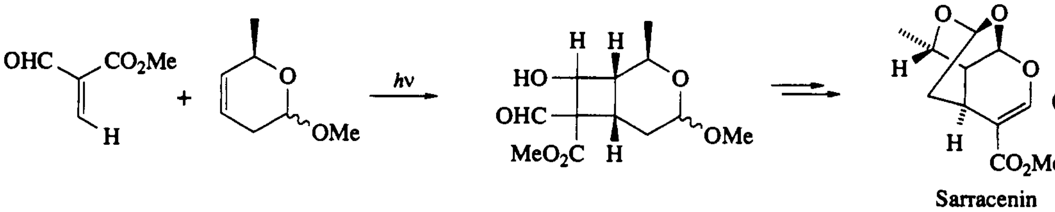
OHC
CO2Me
H
O
OMe
hv
HO
OHC
MeO2C
H H
O
H
CO2Me
Sarracenin
(26)

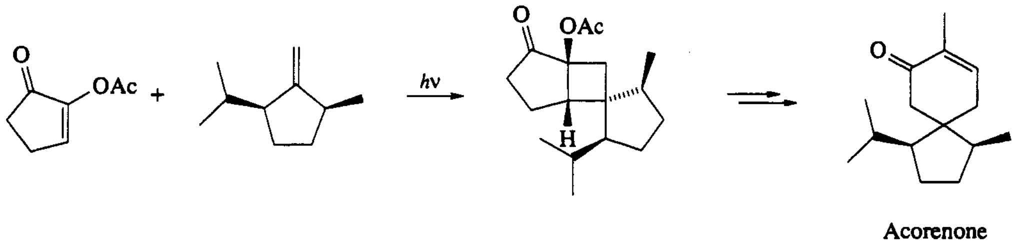
O
OAc
hv
H
Acorenone
(27)

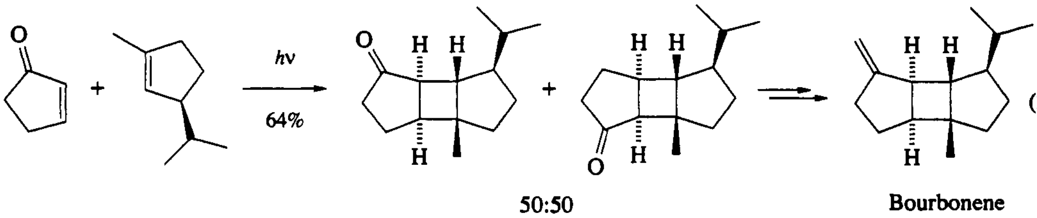
O
hv
64%
H H
H
50:50
Bourbonene
(28)

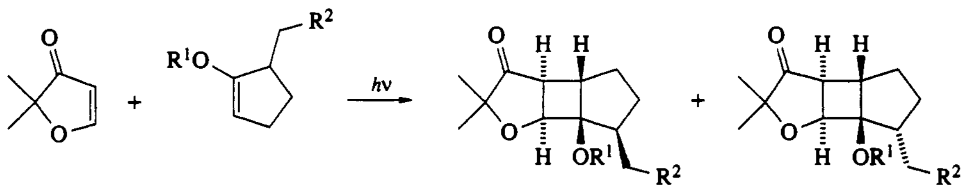
O
R1O
R2
hv
H H
H OR1
R2
(29)

(13)

| | | |
|---|---|---|
| (14) | $R^1 = SiMe_3$, $R^2 = H$ | 1:5 |
| (15) | $R^1 = SiMe_3$, $R^2 = OCH_2Ph$ | 1:5 |
| (16) | $R^1 = SiMe_3$, $R^2 = OSiMe_3$ | 1:10 |
| (17) | $R^1 = Ac$, $R^2 = H$ | 1.8:1 |
| (18) | $R^1 = Ac$, $R^2 = OCH_2Ph$ | 1.8:1 |

stable conformation of an excited enone which has a substantially pyramidalized β-carbon.[38,39] For example, addition of allene to octalone (**19**) produces (**20**) which results from addition of allene opposite the angular substituent (equation 30).[39] Similar results are obtained in the dissolving metal reductions of (**19**), which are presumed to proceed through a species in which the β-carbon is pyramidalized.[40] Results for the addition of allene to 3,4-dimethylcyclohexenone (equation 31) support this model since the predicted product should arise from *cis* approach to the C-4 methyl.[32] However, an alternative explanation which invokes $A_{1,2}$ strain, as in the epoxidation of 1,6-dimethylcyclohexene, is also plausible. Conversely, 4-isopropylcyclohexenone shows no selectivity[10,41] while 4-*t*-butylcyclohexenone yields the *trans* adduct as the major isomer,[42] albeit with ethylene as the ground-state alkene (equations 32, 33). Thus it would appear that most examples might be better rationalized as proceeding through an excited state with a trigonal β-carbon with pyramidalization occurring during the reaction with the ground-state alkene, which conforms more closely to theory, and that cases such as 3,4-dimethylcyclohexenone are somewhat distorted due to torsional strain induced in a conformation with a trigonal β-carbon. It should also be noted that Dauben has recently proposed that photoadditions involving allenes as ground-state alkenes may be very different mechanistically from ordinary alkenes, at least in intramolecular cases.[43]

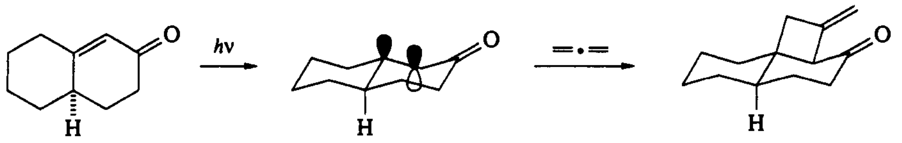

**(19)** **(20)**

(30)

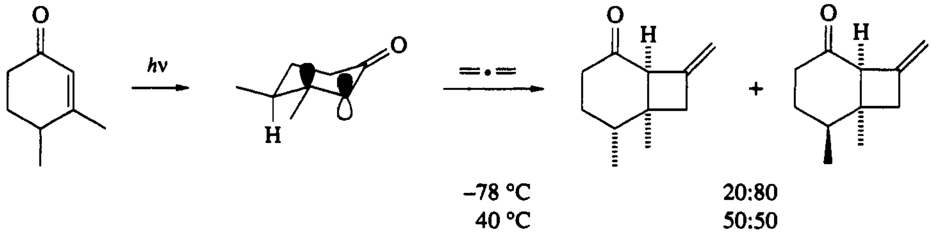

(31)

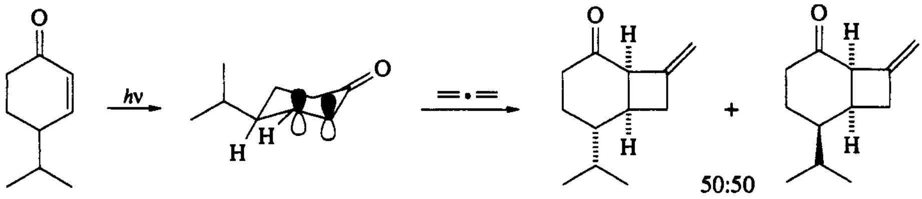

(32)

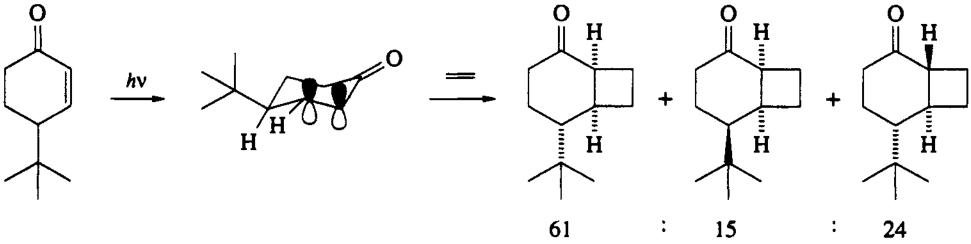

(33)

Cyclohexenones with substituents at the 5- and 6-positions tend to give the product which would be predicted by steric approach control to an excited state with a trigonal β-carbon (equations 34–36).[44–46] As a final cautionary note, while these hypotheses are often useful for prediction of stereochemical results, the true source of the selectivity may involve the rates of cleavage of the intermediate diradicals to the ground state *versus* rates of cyclobutane ring closure. Insufficient data are currently available to explain these results completely.

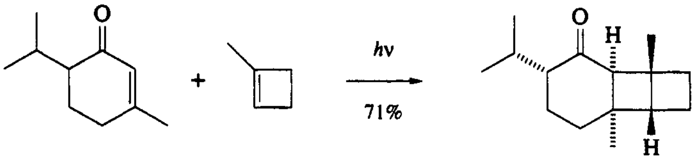

(34)

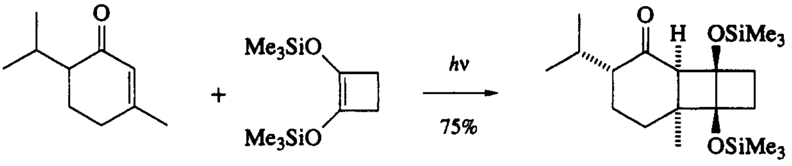

O
Me3SiO
Me3SiO
hν
75%
H
OSiMe3
OSiMe3

(35)

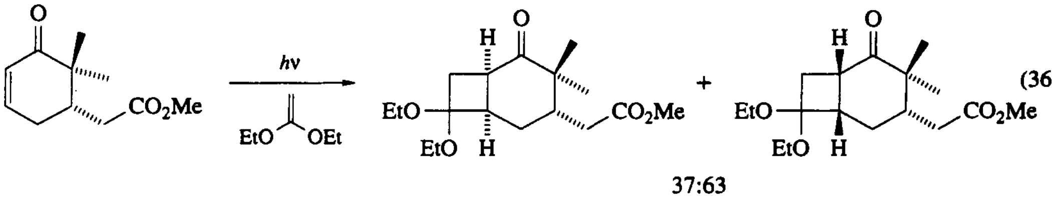

O
CO2Me
hν
EtO
OEt
H
EtO
EtO H
37:63

(36)

### 2.3.3.3 Enantioselectivity

Control of absolute asymmetry is a relatively untouched area for [2 + 2] photochemical cycloaddition reactions despite the recent advances in the field of asymmetric synthesis. The first example of the use of a 'removable' chiral auxiliary was reported by Tolbert,[47] who obtained impressive enantioselectivity in the photocycloaddition of bornyl fumarate to stilbenes (equation 37). More recently, Lange[48] has shown that menthyl cyclohexenonecarboxylates are useful in control of absolute stereochemistry (equation 38). Baldwin[49] and Meyers[50] have also obtained excellent facial selectivity in systems where the stereogenic center which controls the diastereoselectivity can be excised to afford products of high enantiomeric purity (equations 39, 40).

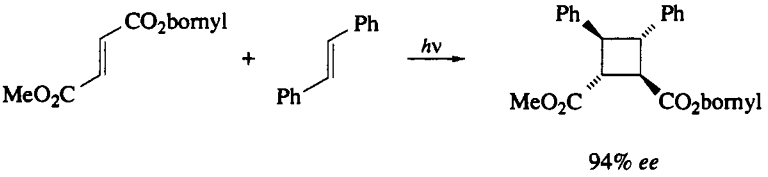

CO2bornyl
MeO2C
Ph
Ph
hν
Ph
Ph
MeO2C
CO2bornyl
94% ee

(37)

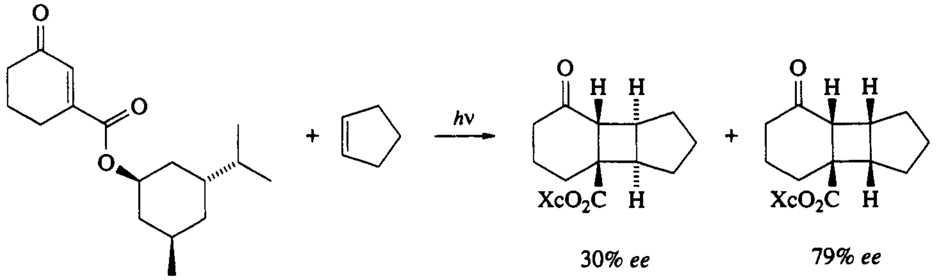

O
O
O
hν
O
H H
XcO2C H
O
H H
XcO2C H
30% ee
79% ee

(38)

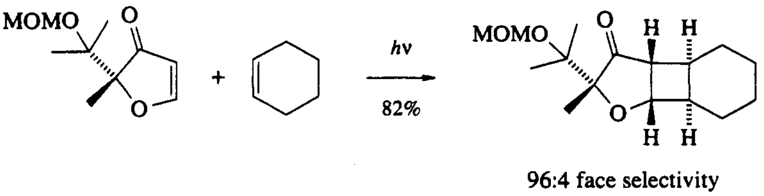

MOMO
O
O
hν
82%
MOMO
O
H H
O
H H
96:4 face selectivity

(39)

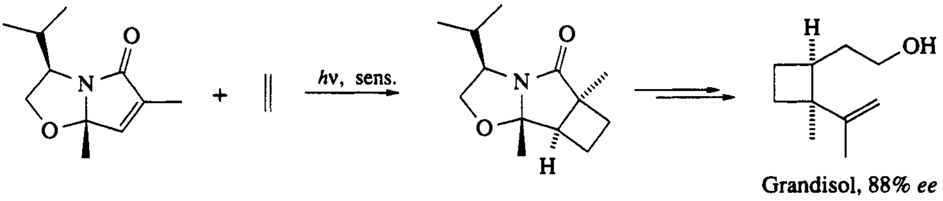

O
N
O
hν, sens.
O
N
O
H
H
OH
Grandisol, 88% ee

(40)

## 2.3.4 INTRAMOLECULAR PHOTOCYCLOADDITIONS

Regiochemical and stereochemical control can be excellent in many examples of the intermolecular photochemical [2 + 2] cycloaddition, but the frequency of cases where selectivity is low, or worse, unpredictable, has inhibited the use of this powerful reaction. While the major disadvantage of the *inter*molecular photocycloaddition is its low selectivity in some systems, this problem can be substantially overcome by incorporating the two sites of unsaturation into the same molecule. Although many of the early examples of the [2 + 2] photocycloaddition were *intra*molecular, this variation of the reaction saw only limited use until the 1970s when its potential for the rapid construction of complex polycyclic carbon skeleta was recognized by Oppolzer, Pattenden and others.

### 2.3.4.1 Regioselectivity

Regioselectivity in the intramolecular photocycloaddition reaction is generally higher and more predictable than in the intermolecular version. This derives primarily from the geometric constraints which are placed on the transition states during initial ring closure. Formation of five-membered rings, if possible, is favored in the initial ring formation by attack of the excited-state on the ground-state alkene. This empirical observation was termed 'the rule of five' by Hammond and Srinivasan[51] and is similar to the observation by Beckwith[52] that the 5-hexenyl radical undergoes cyclization to the cyclopentylmethyl radical 75 times faster than to the cyclohexyl radical. An excellent illustration of this model is seen in the cyclization of enol ether (**21**) to the crossed adduct (**22**), presumably proceeding through the intermediate diradical formed by the closure of a five-membered ring (equation 41).[53] The system (**23**), with a three-atom tether, produces exclusively the straight adduct (**24**) also by initial formation of a five-membered ring (equation 42).[54] While there are exceptions to this generalization, systems with two- and three-atom tethers give either exclusively or predominantly the product predicted by the 'rule of five' (equations 43–47).[55–59] Cyclohexenones and cyclopentenones with tethers of two and three atoms attached at C-2 or C-3 are particularly reliable with respect to their regiochemistry. Of particular note is the interesting case of the furan (**25**), which cyclizes to (**26**) in accord with the above rule while completely overcoming the normal electronic preference observed for intermolecular photocycloadditions (equation 47).[59] The major exceptions to the 'rule of five' in these systems have an allene as the ground-state alkene and Dauben has presented convincing evidence which indicates that photocycloadditions involving allenes may be quite different mechanistically.[43]

When the two alkenes are tethered by four or more atoms, the favored product is typically the straight adduct. For example, systems with a four-atom tether give products derived from initial formation of a

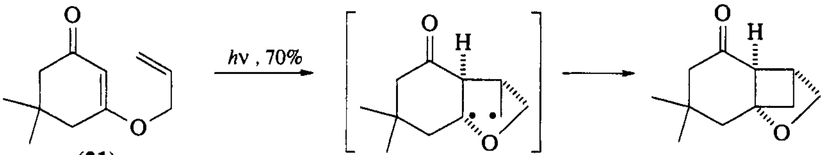

(**21**) (**22**) (41)

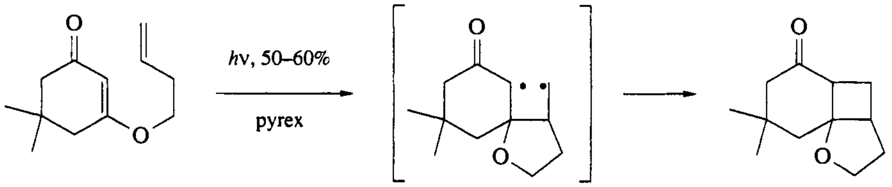

(**23**) (**24**) (42)

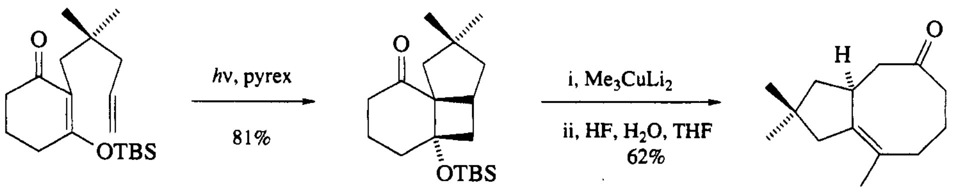

(43)

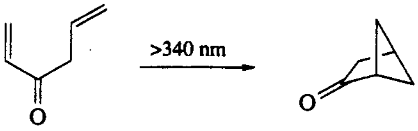

(44)

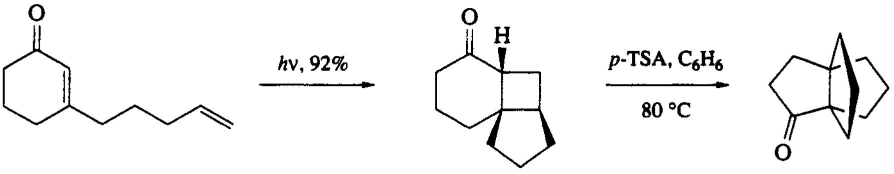
O
hv, 92%
O
H
p-TSA, C6H6
80 °C
O

(45)

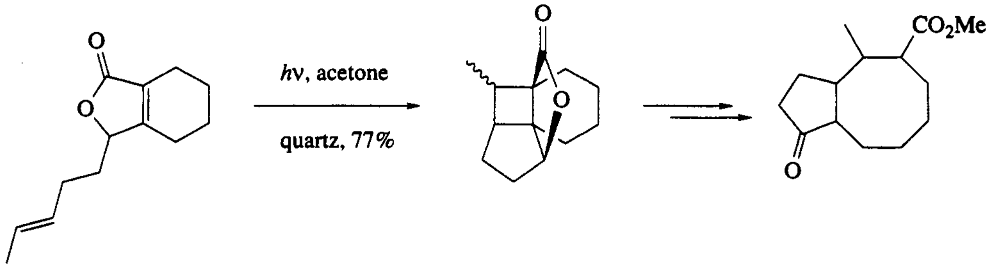
O
O
hv, acetone
quartz, 77%
O
O
CO2Me
O

(46)

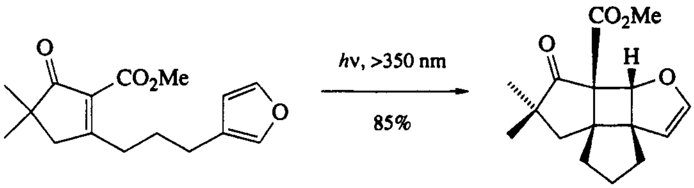
O
CO2Me
O
hv, >350 nm
85%
CO2Me
O
H
O

**(25)** **(26)**

(47)

six-membered ring, as in equations (48)–(53).[60–65] Winkler has studied a variety of tether lengths in the photocycloadditions of dioxolenones and observed only the straight adduct in all cases (equations 54, 55).[66] However, Baldwin has pointed out that the regiochemistry in these dioxolenone systems is particularly sensitive to subtle steric and electronic effects (equations 56–58).[30]

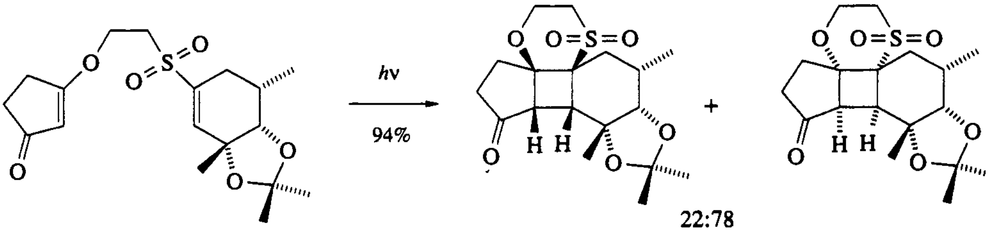
O
O=S=O
O
O
O
hv
94%
O O=S=O
O
H H
O
O
+
O O=S=O
O
H H
O
O
22:78

(48)

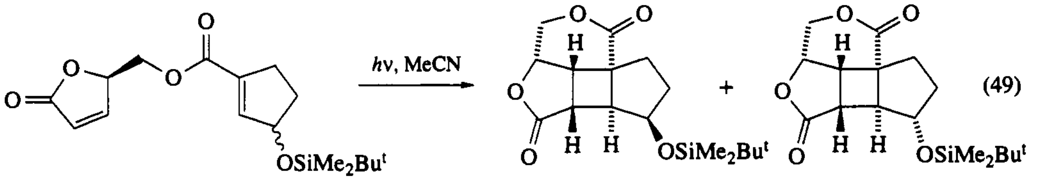
O
O=
O
O
OSiMe2Bu^t
hv, MeCN
O
O
H
O
O
H H
OSiMe2Bu^t
+
O
O
H
O
O
H H
OSiMe2Bu^t

(49)

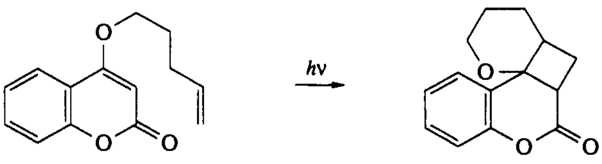

(50)

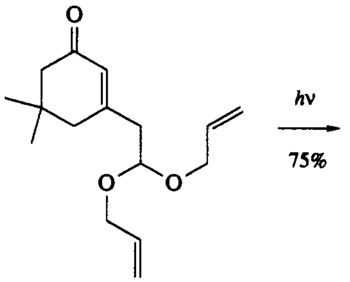

(51)

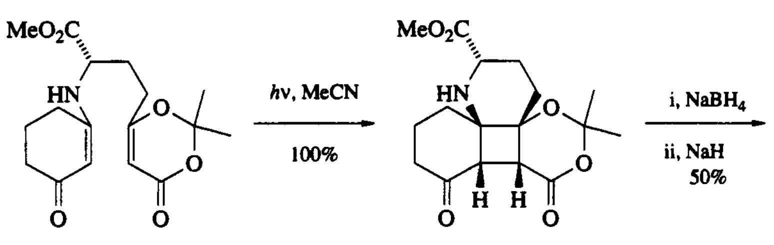
hν, MeCN
100%
i, NaBH$_4$
ii, NaH
50%
MeO$_2$C
HN
H H

(52)

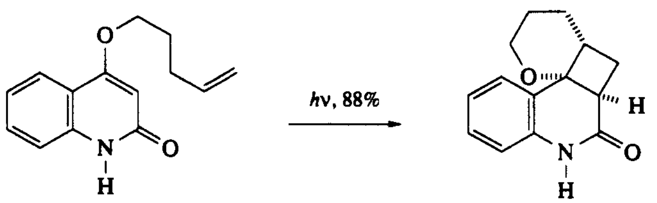

(53)

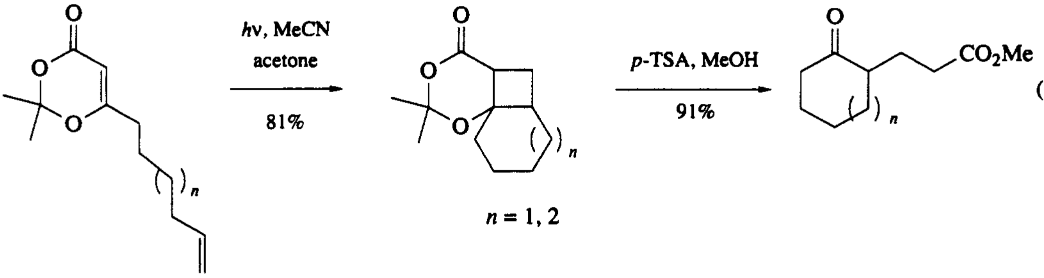
hν, MeCN
acetone
81%
p-TSA, MeOH
91%
CO$_2$Me
n
n = 1, 2

(54)

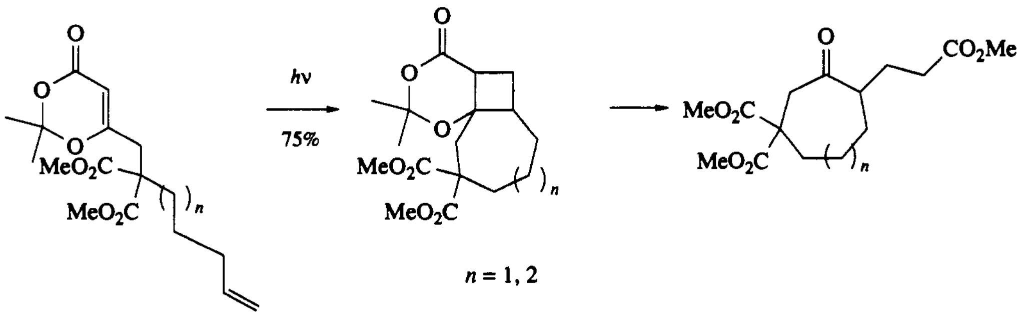
hν
75%
MeO$_2$C
MeO$_2$C
CO$_2$Me
n
n = 1, 2

(55)

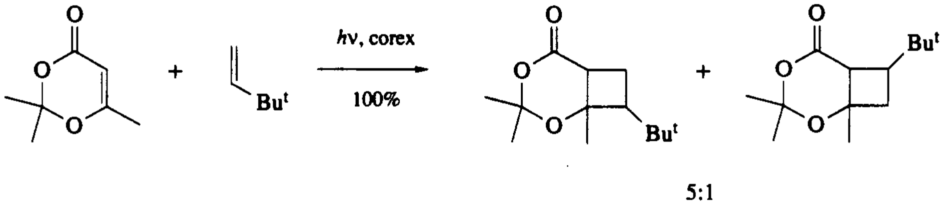
hν, corex
100%
Bu$^t$
Bu$^t$
Bu$^t$
5:1

(56)

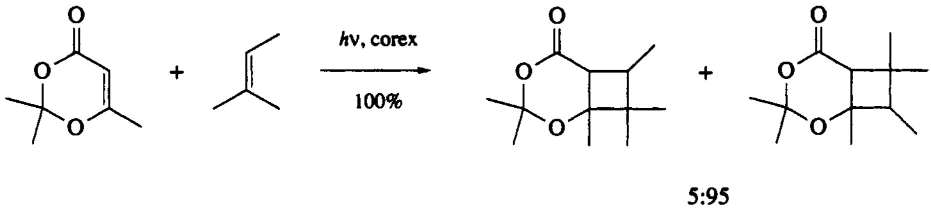

(57)

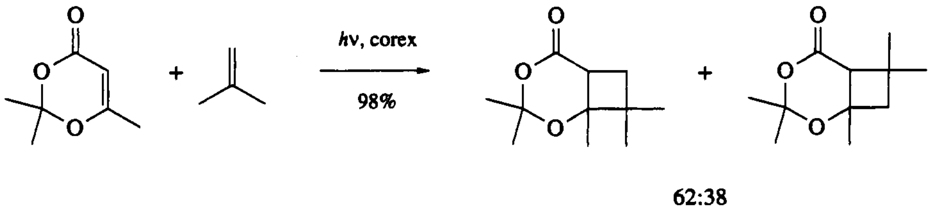

(58)

One very unusual case which does not follow the 'rule of five' is shown in equation (59). Enone (**27**) produced a 1:1 mixture of straight and crossed adducts at 65 °C and a 9:1 ratio in favor of the crossed adduct at –50 to –60 °C. The result was completely reversed when the methyl substituted alkene (**28**) was utilized, producing exclusively the straight adduct (**29**) (equation 60).[67,68]

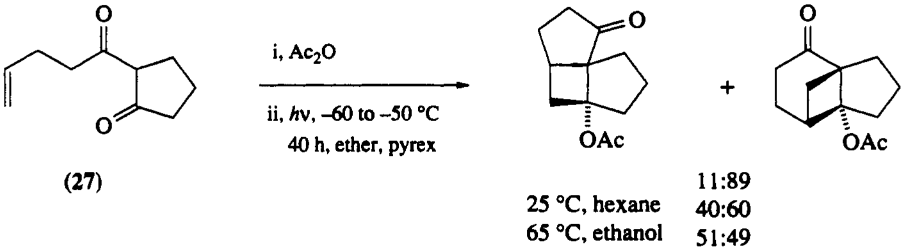

(59)

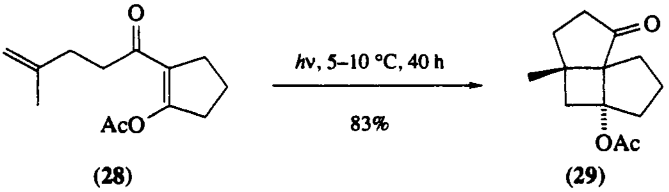

(60)

Wolff and Agosta have taken advantage of a similar result in the photocycloaddition of 1,5-dienes in an efficient approach to substituted fenestranes.[69,70] The unsubstituted system (**30**) yielded a mixture of photoadducts (equation 61) while enone (**31**), containing a methyl group on the internal carbon of the double bond, gave excellent yields of a single regioisomer (**32**) which was transformed to the [4.4.4.5]fenestrane (**33**) (equation 62). The photocycloadditions of 1,5-hexadienes have been carefully studied by Wolff and Agosta, who note important structural features for the reversal of regiochemistry in these systems.[56,69–72] Alkyl substitution at C-5 and incorporation of the enone double bond into a ring, particularly a five-membered ring, appear to effect a change in the mechanism for the cyclization. The simple systems such as (**34**) (equation 63; also equation 44) appear to cyclize initially from C-1 to C-5, in accord with the 'rule of five', and as substitution is added at C-5 the rate of cyclization is retarded. This is very similar to the steric effect observed in the cyclization of 5-substituted 5-hexenyl radicals, which show a depressed rate for the formation of the cyclopentylmethyl radical and an increase in the rate of formation of the cyclohexyl radical. Incorporation of the conjugated double bond into a ring reduces the twisting of the excited triplet and can severely alter the geometry for the cyclization. When both effects are combined, as in enone (**31**), the result is exclusive 1,6-cyclization.

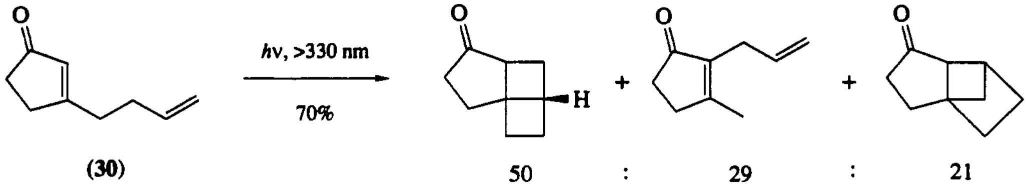
(30)
hν, >330 nm
70%
50 : 29 : 21

(61)

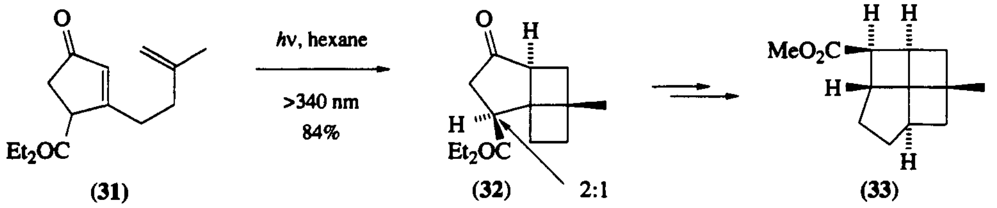
(31)
hν, hexane
>340 nm
84%
(32)
2:1
(33)
MeO2C
Et2OC

(62)

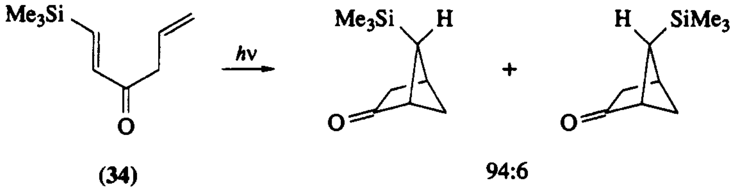
Me3Si
hν
(34)
94:6

(63)

### 2.3.4.2 Stereoselectivity

Some of the most important recent advances in the use of [2 + 2] photocycloadditions in synthesis have been in the control of stereochemistry in complex polycyclic systems. The geometric constraints involved in the cyclizations to the photoadducts often result in extremely stereoselective cycloadditions. Additionally, preexisting stereogenic centers in the photocycloaddition substrate can be utilized to induce relative stereochemistry in the cycloadduct. The resident stereogenic center of the diene can be on the tethering chain, on the ring containing the excited state partner or on a ring containing the ground-state alkene.

First of all, the stereochemistry about the cyclobutane in the photoadducts is *cis* in almost all cases (equations 64–68).[66,73–77] There are rare exceptions, but these usually result from systems where the cycloalkenone is larger than six members or when the tethering chain can easily accommodate the *trans* cyclobutane (equations 69–72).[78–81] The most noteworthy exception is the recent example reported by Winkler in which dioxolenone (**35**) produced exclusively the *trans* cycloadduct (**36**) which was readily converted to the smallest known inside-outside bicycloalkanone (**37**).[82] This photoproduct presumably arises from initial cyclization in the chair-like conformation (**38**) (equation 73). Similarly, (**39**) has been converted to the carbon skeleton of the naturally occurring inside-outside bicyclic compound ingenol (equation 74).[83]

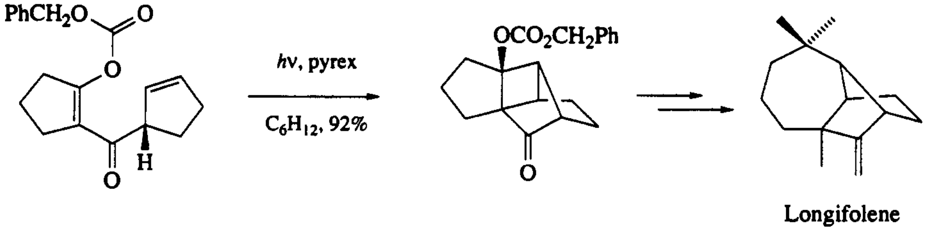
PhCH2O
hν, pyrex
C6H12, 92%
OCO2CH2Ph
Longifolene

(64)

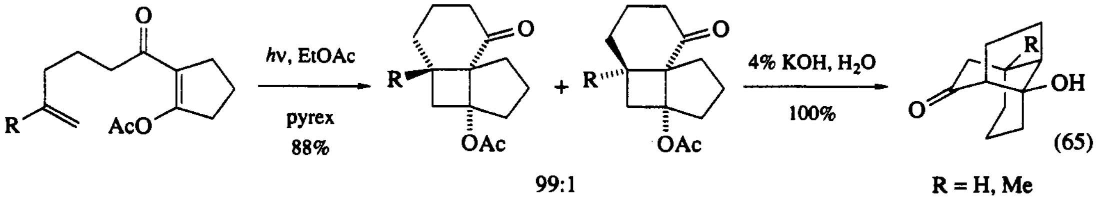
hν, EtOAc
pyrex
88%
AcO
OAc
99:1
4% KOH, H2O
100%
OH
(65)
R = H, Me

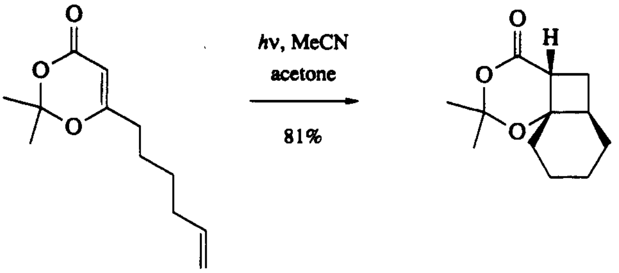
*h*ν, MeCN
acetone
81%

(66)

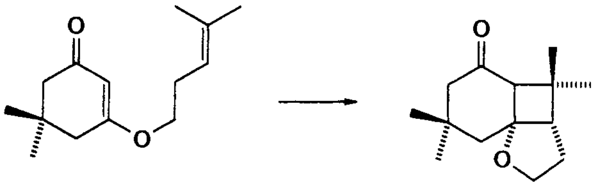

(67)

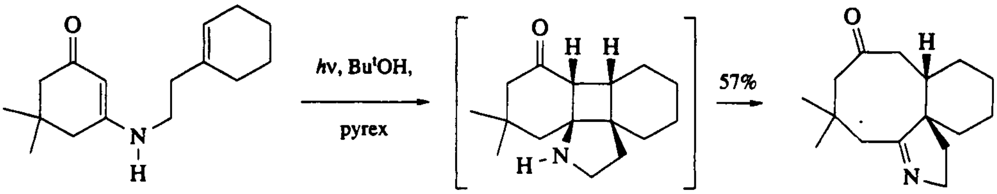
*h*ν, Bu$^t$OH,
pyrex
57%

(68)

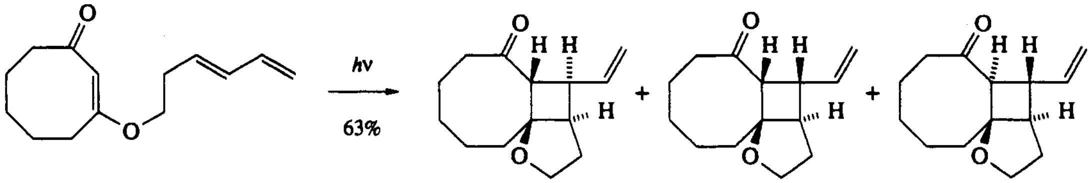

33 : 40 : 27 (69)

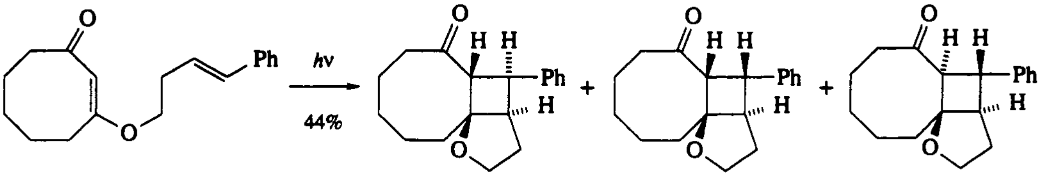

(70)

14 : 47 : 39

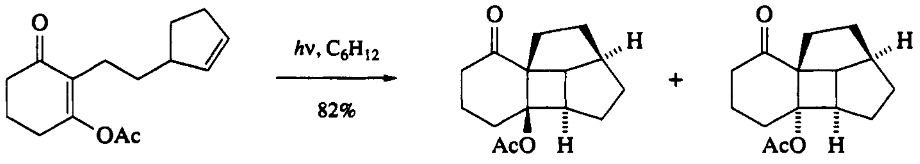

(71)

85 : 15

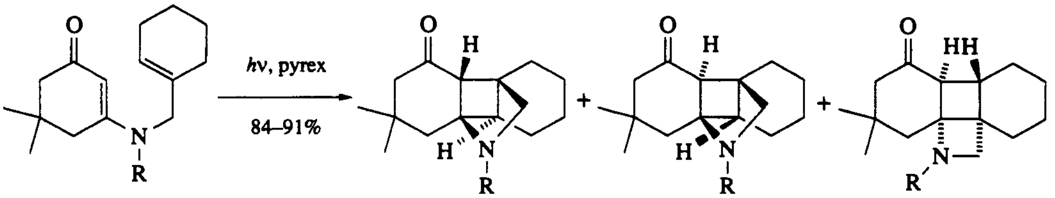

(72)

| | | | | | |
|---|---|---|---|---|---|
| R = CHO | 77 | : | 9 | : | 14 |
| R = Ac | 71 | : | 11 | : | 18 |

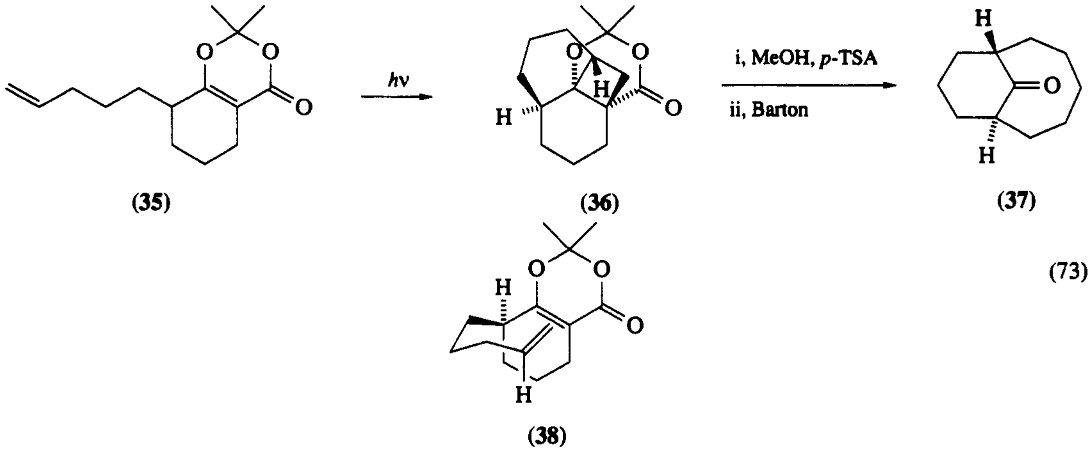

**(35)** **(36)** **(37)**

(73)

**(38)**

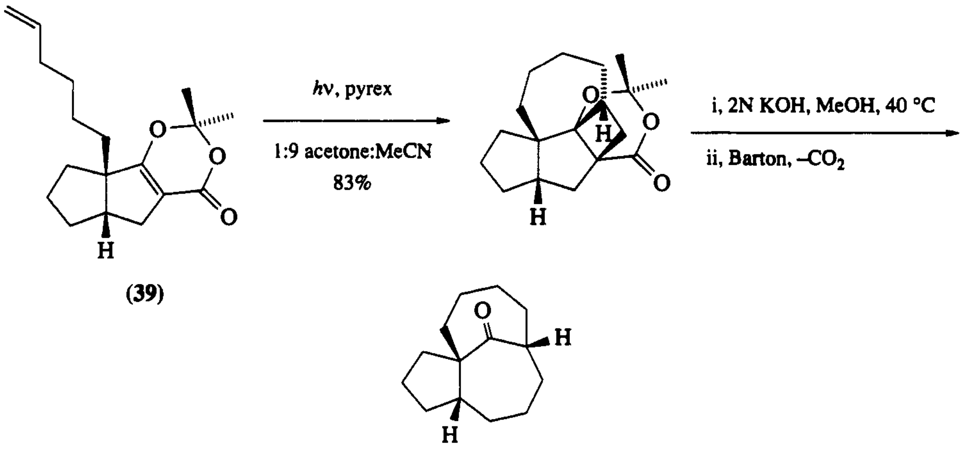

**(39)**

(74)

Stereochemical induction by a stereocenter on the tethering chain has been used effectively in the total synthesis of several natural products. In a synthesis of acoradiene, Oppolzer irradiated cyclohexenone (**40**) and obtained a 5:1 mixture of the β:α methyl diastereomers (**41**) in 76% yield together with some starting diene which had partially isomerized at the isolated alkene (Scheme 2).[84] The stereoselectivity was attributed to radical reversion of the 1,4-diradical (**42**) leading to the minor product due to a steric interaction between the secondary methyl group and the carbonyl α-hydrogen during the final cyclobutane closure. The resulting product ratio was presumed, therefore, to be a result of the thermodynamic preference for the major product. An alternative explanation is that the major product arises from a kinetic preference for the formation of the 1,4-diradical (**43**) because of the difference in energy of the two diastereomeric exciplexes (**44**) and (**45**). There is an $A_{1,3}$ interaction between the secondary methyl and the α-vinyl hydrogen in exciplex (**45**) while the equivalent interaction in (**44**) is between two hydrogens. Becker has recently presented evidence that there is no radical reversion in some closely related systems.[85]

Which of these two pathways is operative is unclear at this time, but it is clear that the vinyl substituent on the cycloalkenone plays an important role in the selectivity. Pattenden, in a synthesis of epipre-

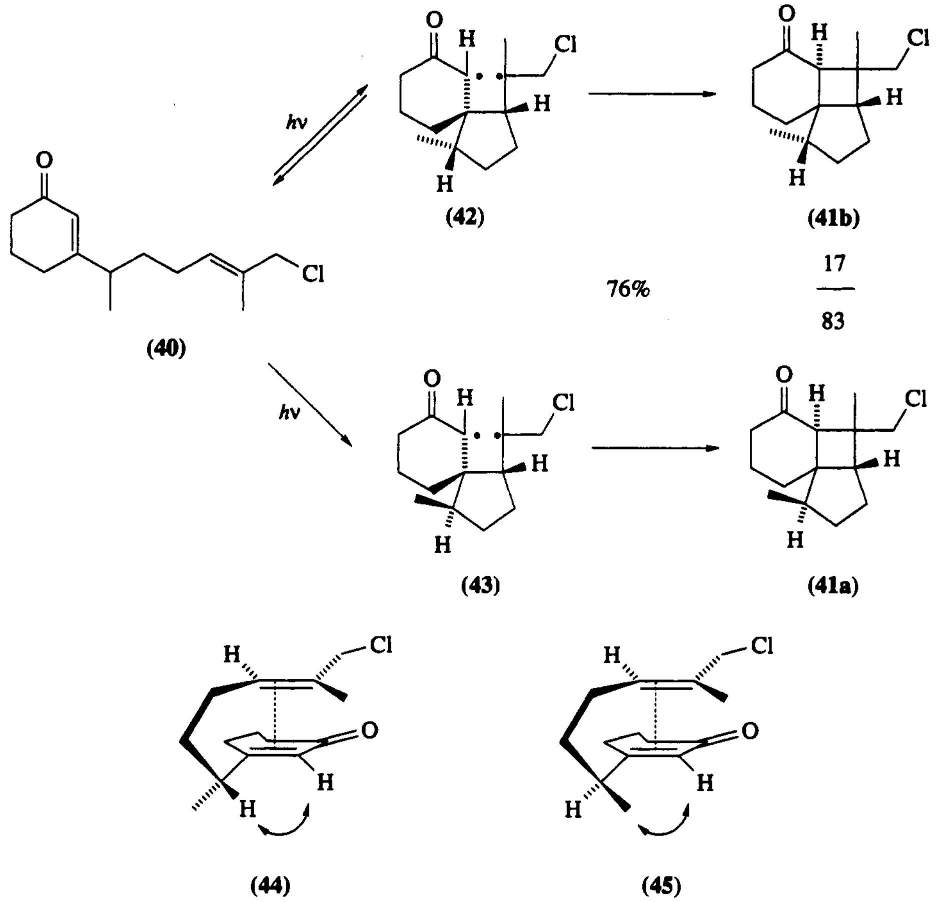
hν
(40)
(42)
(41b)
76%
17
83
hν
(43)
(41a)
(44)
(45)

Scheme 2

capnelladiene,$^{86}$ carried out the photocycloaddition of enol acetate (**46**) and obtained a 92:8 mixture of diastereomers (equation 75). However, when the corresponding enol benzoate was utilized a single diastereomer was produced, presumably due to the increased steric interaction between the methyl group and the vinyl substituent. Similarly, Crimmins noted a sequential increase in stereoselectivity in the photocycloaddition of esters (**47**)–(**49**) from 93:7 with the methyl ester to >97:3 with the isopropyl ester (equation 76).$^{87}$ A similar case (**50**) gave a single cycloadduct in high yield (equation 77).$^{88}$

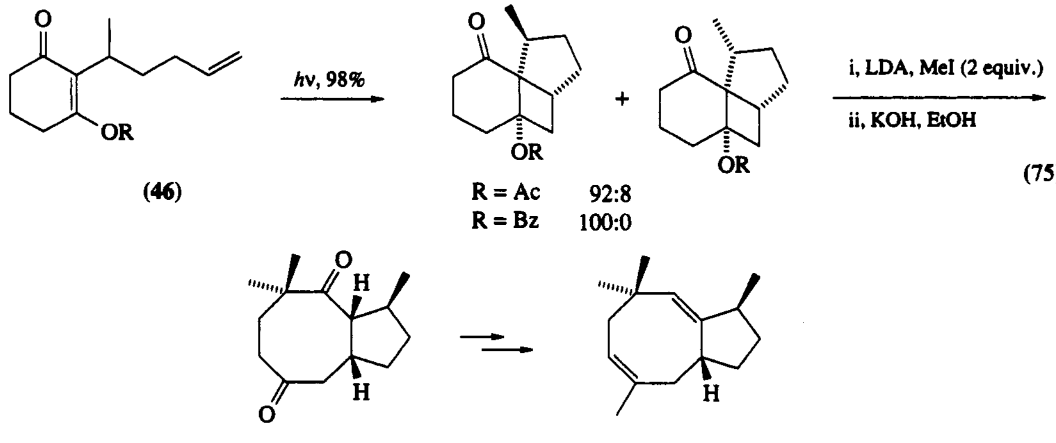
hν, 98%
(46)
R = Ac 92:8
R = Bz 100:0
i, LDA, MeI (2 equiv.)
ii, KOH, EtOH
(75)

Epiprecapnelladiene

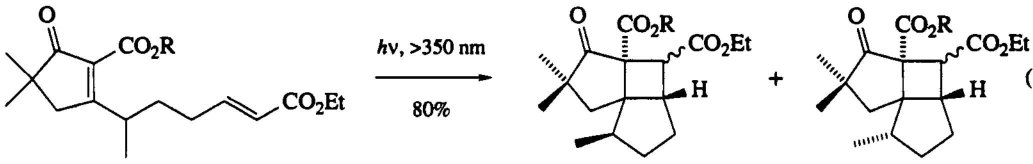

CO2R
CO2Et
hv, >350 nm
80%
CO2R
CO2Et
H
+
CO2R
CO2Et
H

(76)

(47) R = Me
(48) R = Et
(49) R = Pr$^i$

93:7
94:6
>97:3

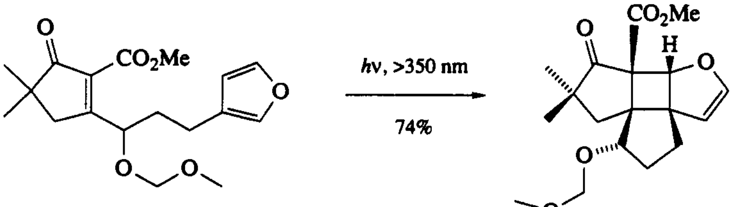

CO2Me
O
hv, >350 nm
74%
CO2Me
H
O
O
O

(50)

(77)

When the substituent is placed adjacent to the ground-state alkene in these systems, similar levels of stereoselectivity are observed as seen in equations (78)–(81).[89–91] Interestingly, diene (**51**), with a methyl group on the alkenic carbon adjacent to the isopropyl, is nonstereoselective while the system lacking the methyl group proceeds with complete stereoselectivity.[91] Apparently the $A_{1,2}$ strain between the methyl and the isopropyl groups in exciplex (**52**) counterbalances the $A_{1,3}$ strain between the hydrogen and isopropyl group in exciplex (**53**).

Modest asymmetric induction was seen in the cycloaddition of dioxolenone (**54**) to produce the eight membered photoadducts (**55**) and (**56**) (equation 82). The major product can be seen to arise from an exciplex in chair-like conformation with the silyloxy group in a pseudoequatorial position, while the minor isomer would require the silyloxy substituent to occupy a pseudoaxial site and would create a steric interaction between the OTBS and the ring oxygen.[56] Similar explanations can be put forth for the examples in equation (83).[92]

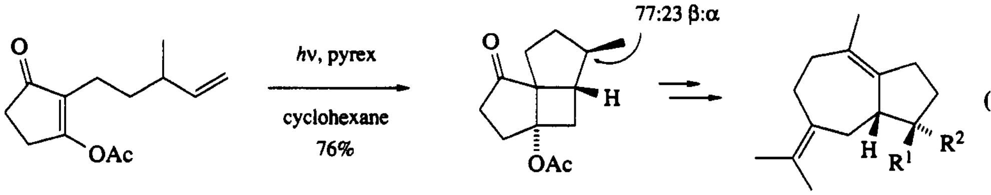

O
OAc
hv, pyrex
cyclohexane
76%
77:23 β:α
O
H
OAc
H
R1
R2

(78)

3.3:1 Epibulnesene:bulnesene

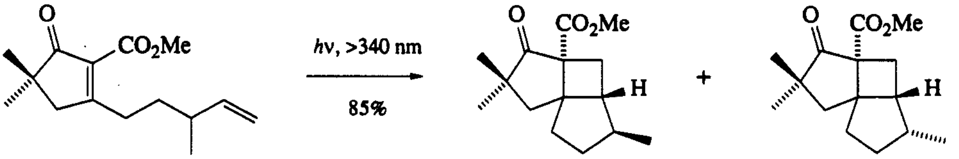

O
CO2Me
hv, >340 nm
85%
O
CO2Me
H
+
O
CO2Me
H

(79)

89:11

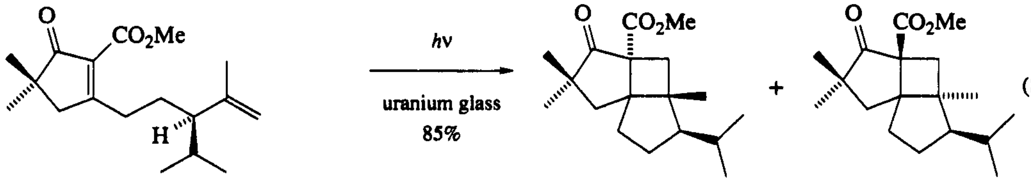

O
CO2Me
H
hv
uranium glass
85%
O
CO2Me
+
O
CO2Me

(80)

(51)

51:49

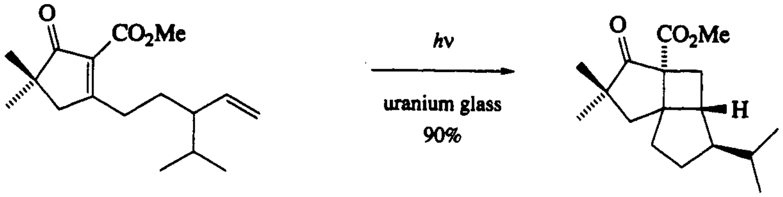
CO2Me
hv
uranium glass
90%
O
CO2Me
H
only product

(81)

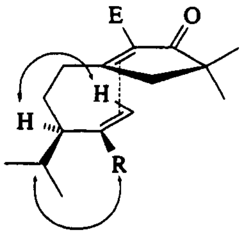

(52) $A_{1,2}$ strain if R = Me

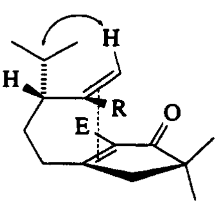

(53)

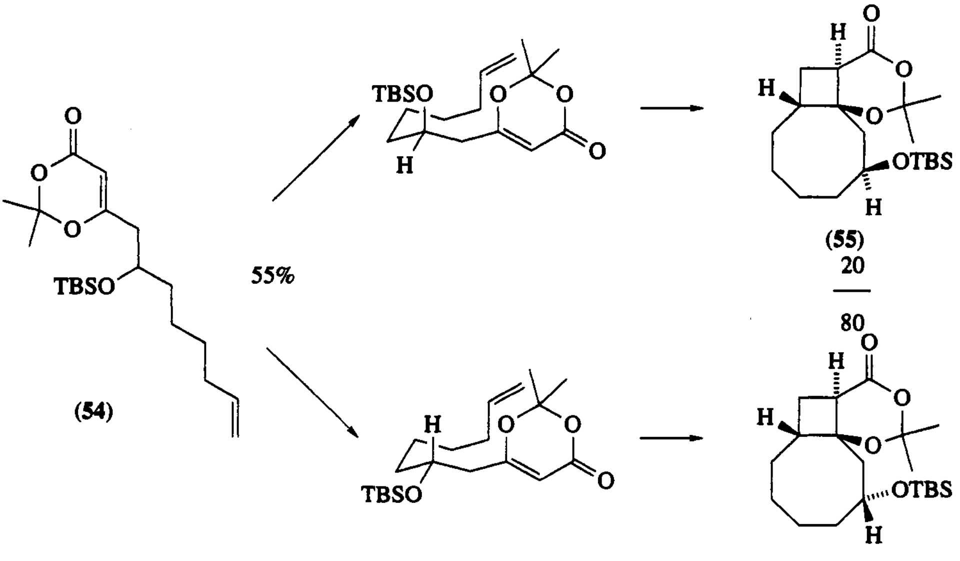
O
O
O
TBSO
55%
TBSO
H
O
O
O
H
O
O
TBSO
O
H
O
O
OTBS
H
H
O
H
O
O
OTBS
H
H

(54)

(55)

20
—
80

(56)

(82)

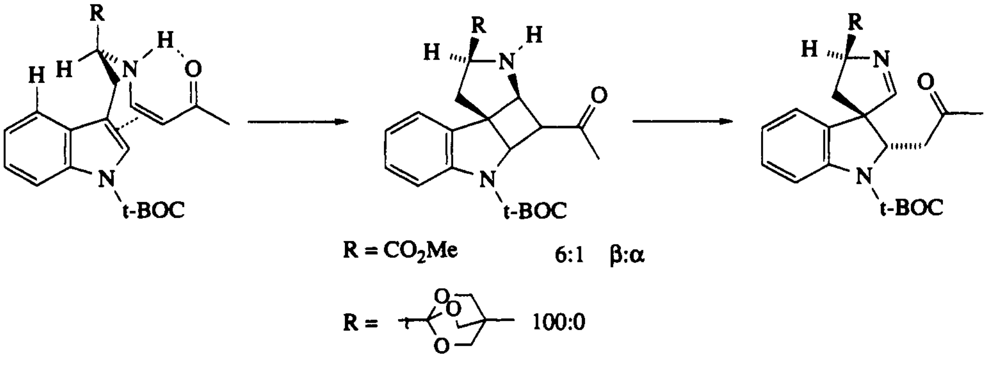
R
H
H H
N
O
N
t-BOC
R
H
H
N
O
N
t-BOC
R
H
N
O
N
t-BOC
R = CO2Me
6:1 β:α
R =
O
O
O
100:0

(83)

Becker has carried out a careful study of the effects of positioning a preexisting stereogenic center at the 4-position of cyclohexenones with the tethering chain attached at the 2-position.[93] Substitution at the 4-position generally influenced the alkene to approach the enone from the face opposite the alkyl group (equation 84) and increasing the steric bulk of the C-4 substituent resulted in a modest increase in stereoselectivity (equation 85). The selectivity increased from 2.3:1 to 2.7:1 when a methyl group was placed on the internal carbon of the alkene (equation 86), but the improvement is most notable when either one (equation 87) or two methyl groups (equation 88) are added to the terminal carbon of the ground-state alkene. These results can be explained by comparing the energies of the diastereomeric exciplexes or by invoking a radical reversion explanation (Scheme 3). However, Becker has presented evidence in very closely related systems (equation 89) that no radical reversion is operative since the quantum yields are quite high and no alkene isomerization could be detected in recovered starting material.[85] In a similar case, Pirrung irradiated (**57**) to produce a single cycloadduct (**58**) which was converted to isocomene in two steps (equation 90).[94,95]

Several additional examples of stereochemical control in [2 + 2] photocycloadditions which include systems containing preexisting stereogenic centers on the ground-state alkene are shown in equations (91)–(97).[75,76,96–103] The stereoselectivity in these systems is typically controlled by the nonbonded inter-

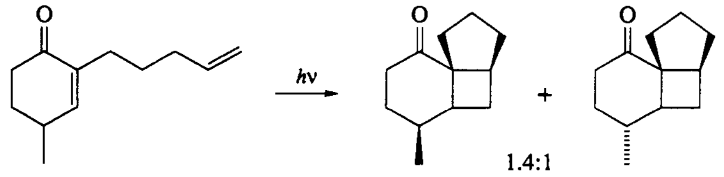

(84)

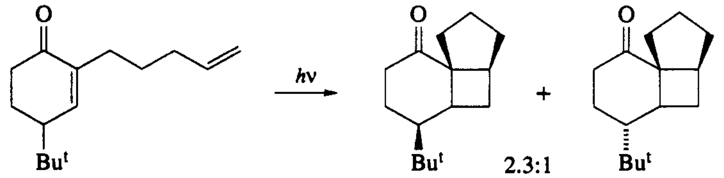
O
Bu$^t$
hν
O
Bu$^t$
+
2.3:1
O
Bu$^t$
(85)

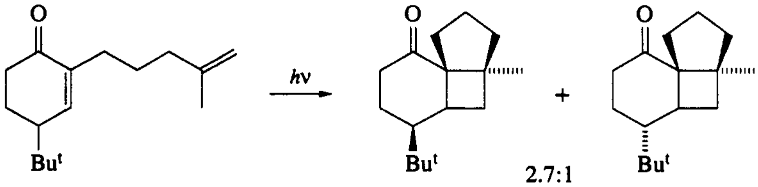
O
Bu$^t$
hν
O
Bu$^t$
+
2.7:1
O
Bu$^t$
(86)

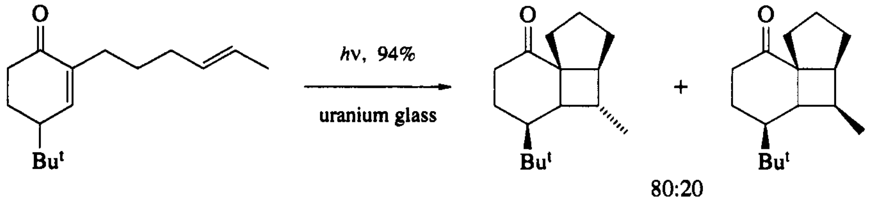
O
Bu$^t$
hν, 94%
uranium glass
O
Bu$^t$
+
O
Bu$^t$
80:20
(87)

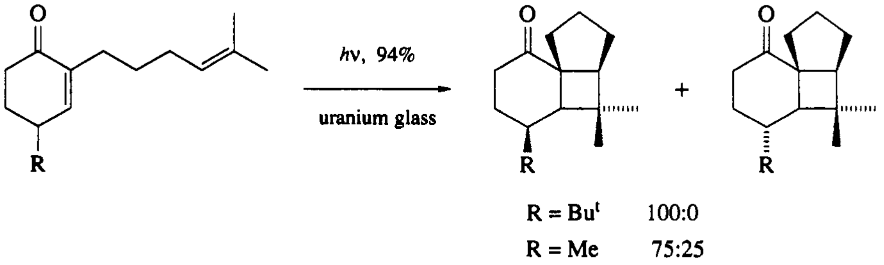
O
R
hν, 94%
uranium glass
O
R
+
O
R
R = Bu$^t$ 100:0
R = Me 75:25
(88)

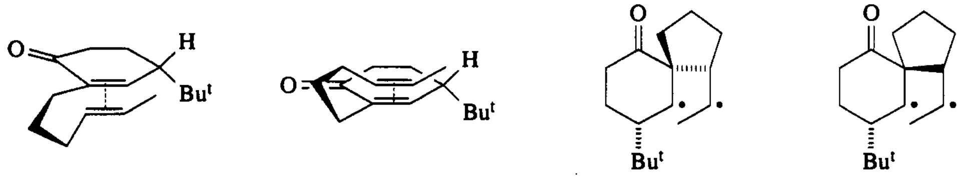
O
H
Bu$^t$
O
H
Bu$^t$
O
Bu$^t$
O
Bu$^t$

**Scheme 3**

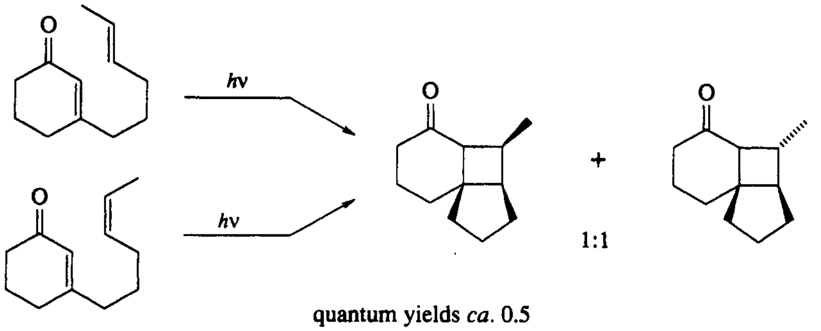

(89)

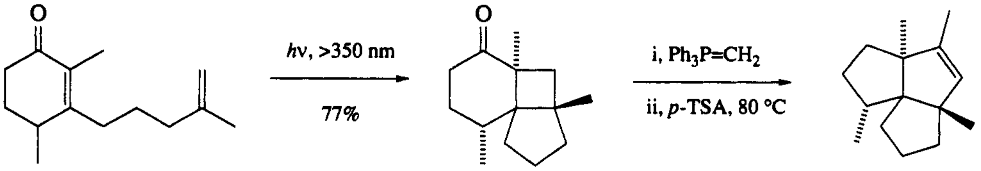

(90)

**(57)** **(58)** Isocomene (5 steps, 48%)

actions between the two alkene portions and the tethering chain, as in the previously discussed cases. Of particular note is the diquinane enone (**59**), which produced only recovered starting material upon irradiation in hexane at 25 °C, but underwent smooth cycloaddition to (**60**) when irradiated at 110 °C in chlorobenzene at 350 nm (equation 96).[101,102] There is a severe nonbonded interaction between the angular and vinyl methyls in the transition state for initial cyclization in this system. The success of the higher temperature may be a result of accessing the reactive conformation by overcoming this steric interaction, or it is possible that there is a thermal barrier between two excited states of different reactivities. The photoadduct (**60**) has been elaborated to the naturally occurring fenestrane laurenene.

Also of interest are cyclohexenones with the tether attached at the 4-position, which have not been as widely applied as the 2- and 3-substituted cycloalkenones. Croft and Jeffries irradiated the diastereomeric enones (**61**) and obtained two cycloaddition products and two products from intramolecular hydrogen atom abstraction (equation 98).[104] All the products contained a *trans* decalin, however. This re-

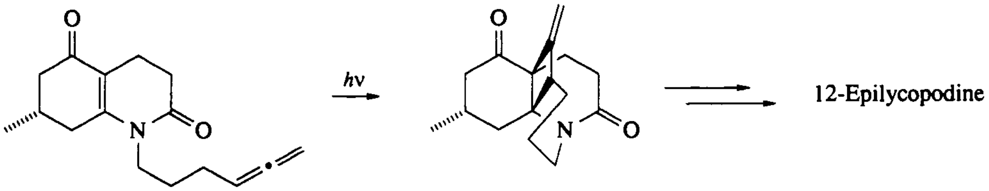

(91)

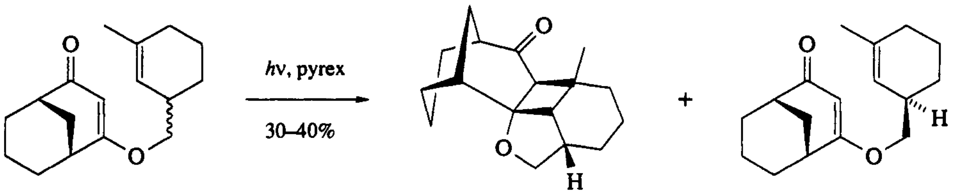

(92)

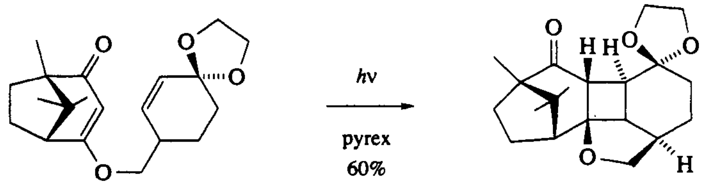

(93)

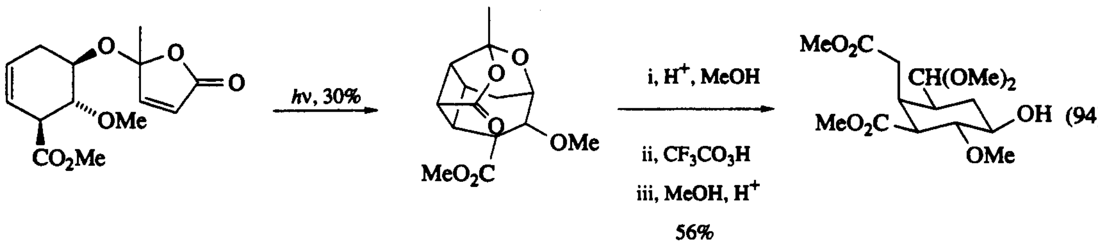

O
O
O
'''OMe
CO2Me
hν, 30%
O
O
O
OMe
MeO2C
i, H+, MeOH
ii, CF3CO3H
iii, MeOH, H+
56%
MeO2C
CH(OMe)2
MeO2C
OH
OMe

(94)

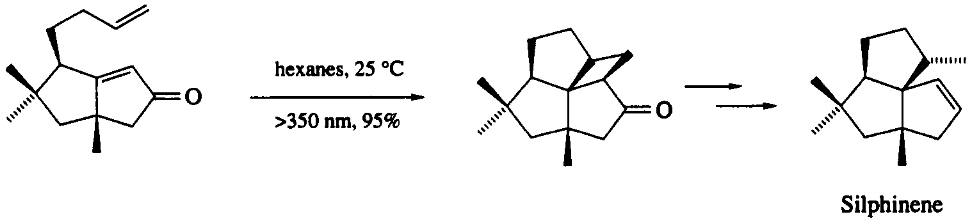

O
hexanes, 25 °C
>350 nm, 95%
O
Silphinene

(95)

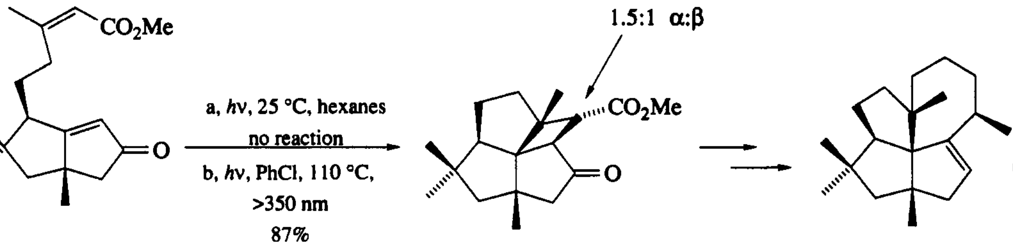

CO2Me
O
a, hν, 25 °C, hexanes
no reaction
b, hν, PhCl, 110 °C,
>350 nm
87%
1.5:1 α:β
CO2Me
O

(59) (60) Laurenene

(96)

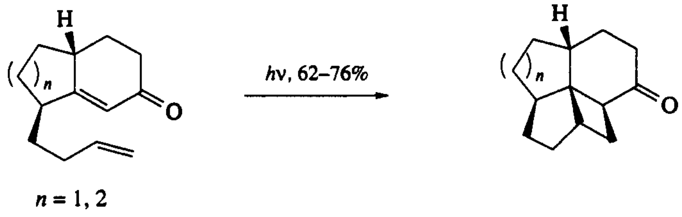

H
( )n
O
n = 1, 2
hν, 62–76%
H
( )n
O

(97)

sult can be rationalized by assuming the excited triplet enone is twisted, with the tether occupying a pseudoequatorial site on the cycloalkenone as in (**62**). Smith[105] also saw predominantly *trans* products in the cycloaddition of (**63**) (equation 99), but obtained some *cis* product (**64**) probably due to the reduced degrees of freedom in the alkyne which would destabilize the transition state for the initial formation of the *trans* decalin. Both photoadducts were converted to hibiscone C. Dauben[43,106,107] has studied a variety of allenes attached to cyclohexenones and cyclopentenones at the 4-position. These all produce predominantly or exclusively the *cis* decalin products, in contrast to the cases above. This result (equation 100) in combination with some anomalous results (equations 101, 102) have prompted Dauben to suggest that intramolecular [2 + 2] photocycloadditions involving allenes as the ground-state partner (with the allene tethered at the 3- or 4-position) are likely proceeding through initial cyclization at C-2 of the enone rather than C-3.[43] This could explain the different stereochemical result with these systems. If allenes in general proceed through a different mechanistic pathway, this might also explain some inconsistencies in the intermolecular photocycloadditions with allenes.

## 2.3.5 UNACTIVATED ALKENES

Synthetic applications of [2 + 2] photocycloadditions of unactivated alkenes have been limited due to the low regioselectivity and stereoselectivity observed in this process. However, Wender recently reported an intramolecular example of a diene–diene photochemical [2 + 2] which provides rapid access to *cis*-fused 5–8 ring systems and subsequently linearly fused triquinanes.[108] Sensitized irradiation of (**65**) produced the *cis*-fused 5–4 product. This product is a result of the initial formation of a five-membered ring from the more stable conformer (**65**). The *cis* diradical (**66**) presumably closes rapidly to product while the *trans* diradical (**67**) cannot form the cyclobutane because of the inherent strain in the product and thus reverts back to the diene. Thermolysis of the product (**68**) produced the cyclooctadiene (**69**) which was converted to coriolin (Scheme 4).

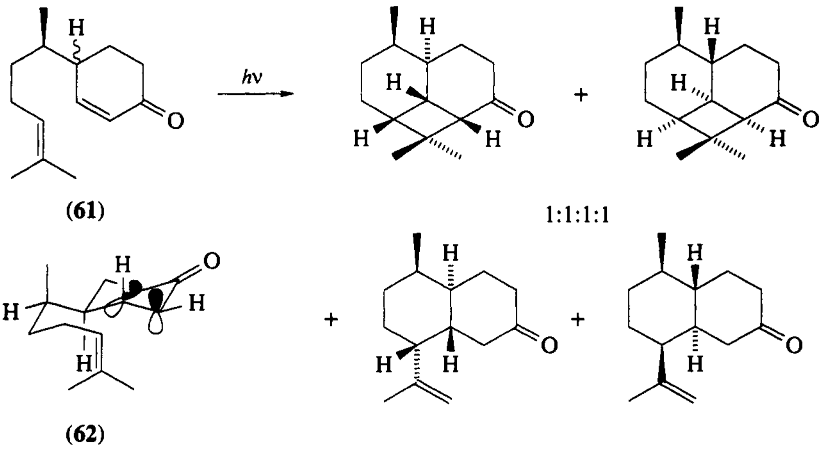
H
*h*ν
H
H
O
H
H
+
H
H
O
H
H
**(61)**
1:1:1:1
H
O
H
H
H
H
+
H
O
H
H
+
H
O
H
**(62)**

(98)

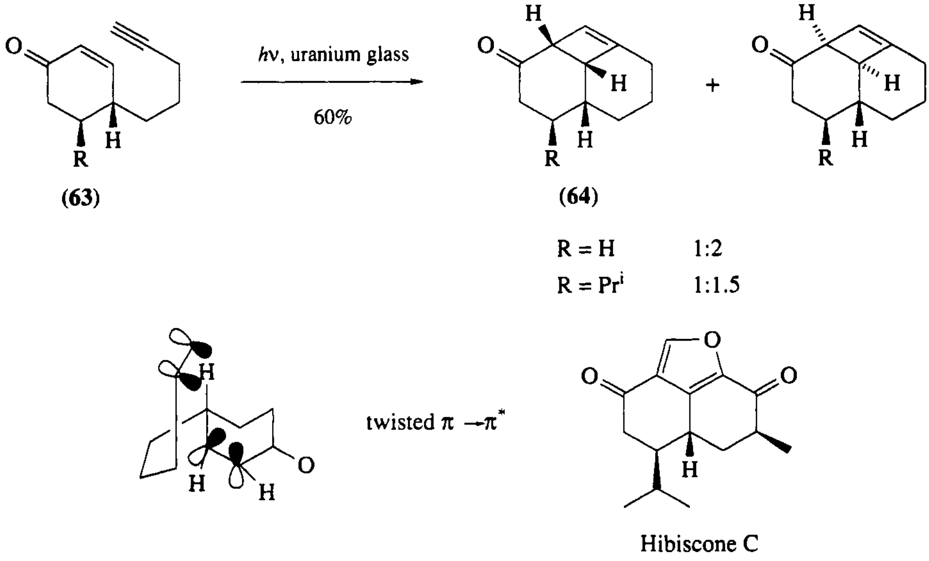
O
H
R
**(63)**
*h*ν, uranium glass
60%
H
O
H
H
R
**(64)**
+
H
O
H
H
R
H
O
H
H
twisted π →π*
O
O
O
H
Hibiscone C

(99)

R = H 1:2

R = Pr$^i$ 1:1.5

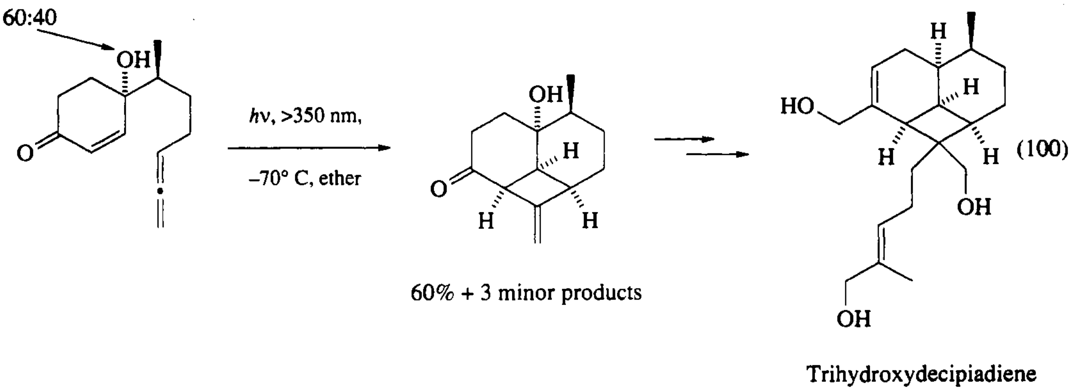
60:40
OH
O
*h*ν, >350 nm,
−70° C, ether
OH
H
O
H
H
60% + 3 minor products
H
H
HO
H
H
OH
OH
Trihydroxydecipiadiene

(100)

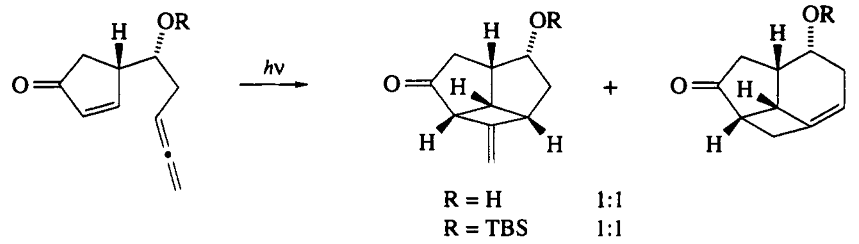

(101)

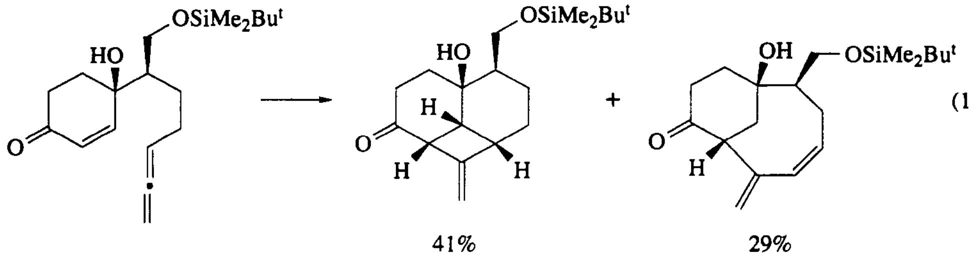

(102)

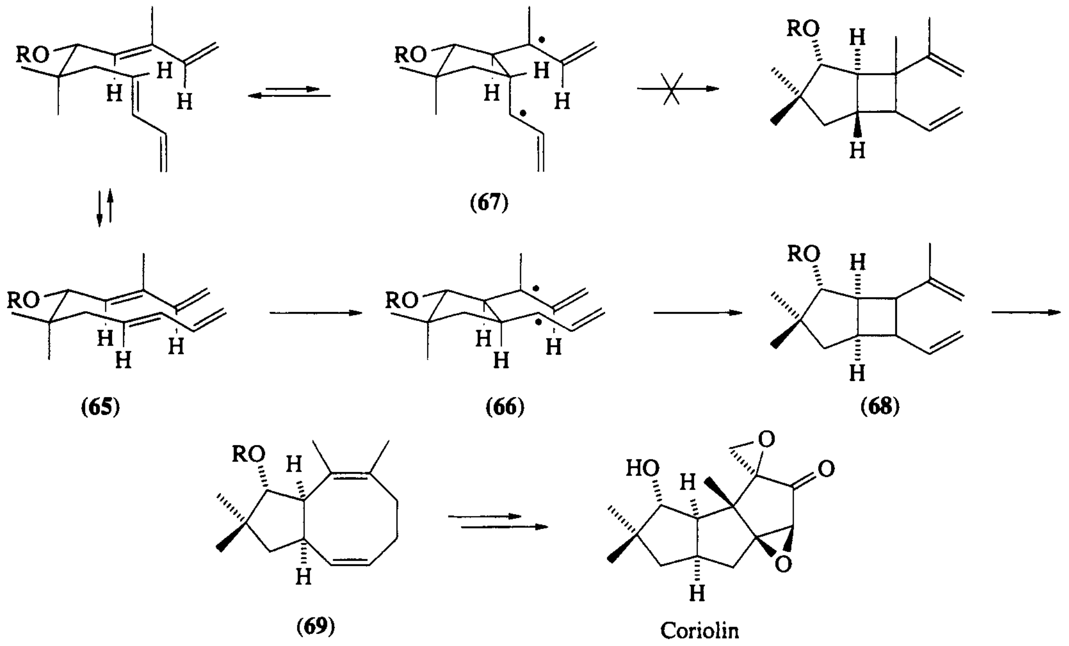

Scheme 4

## 2.3.6 COPPER CATALYZED [2 + 2] PHOTOCYCLOADDITIONS

Salomon has recently investigated the copper(I) triflate catalyzed photocycloadditions of allylic alcohols and allylic ethers in an effort to improve the selectivity in photocycloadditions of unactivated alkenes (equations 103–105,108).[109] One particularly interesting case is illustrated in equation (104), where the more sterically hindered product is produced as a result of the photocycloaddition of a rigidly held tridentate copper complex. McMurry has also utilized a copper(I) catalyzed [2 + 2] photocycloaddition in the synthesis of β-panisene (equation 106).[110] Interestingly, the noncatalyzed cycloaddition shown in equation (107), which might also produce a precursor for β-panisene, was unsuccessful.

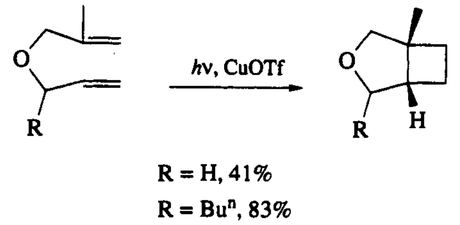
O
R
hv, CuOTf
O
R
H
R = H, 41%
R = Bu$^n$, 83%

(103)

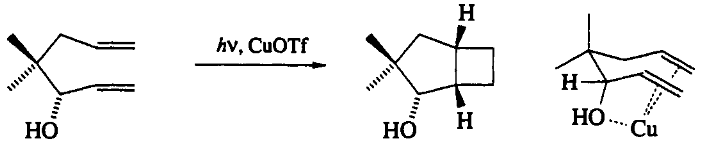
HO
hv, CuOTf
H
HO
H
H
HO
Cu

(104)

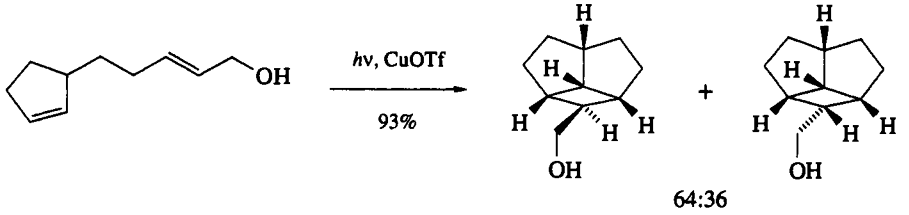
OH
hv, CuOTf
93%
H
H
H
H
H
OH
+
H
H
H
H
H
OH
64:36

(105)

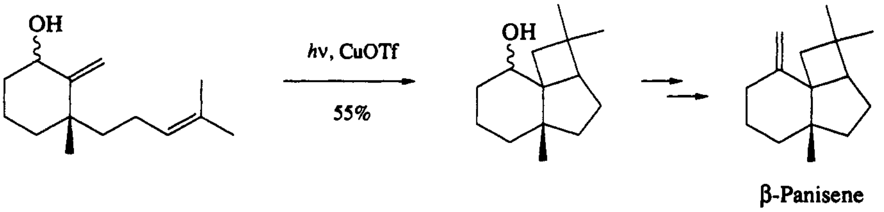
OH
hv, CuOTf
55%
OH
β-Panisene

(106)

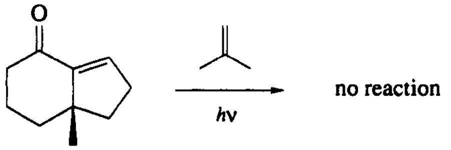
O
hv
no reaction

(107)

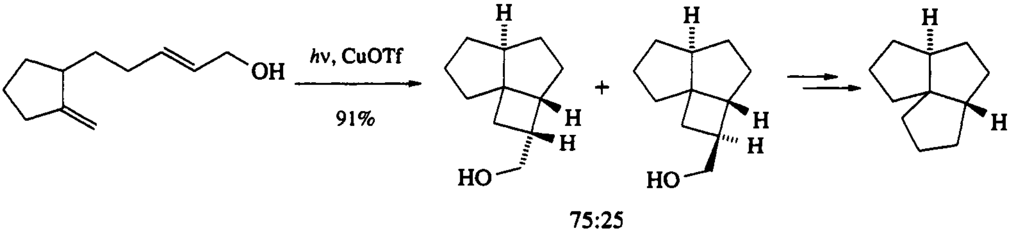
OH
hv, CuOTf
91%
H
H
H
HO
+
H
H
H
HO
H
H
75:25

(108)

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# 2.4

# The Paterno–Büchi Reaction

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## 2.4.1 INTRODUCTION

In the 80 years since the original report[1] of a photochemical addition to form an oxetane, the Paterno–Büchi reaction[2] has become increasingly familiar to chemists engaged in the synthesis of complex molecules. Existing reviews[3–6] have summarized mechanistic considerations and defined the scope and limitations of the photocycloaddition reactions. In confluence with the widespread advances in synthetic methods and asymmetric synthesis, the Paterno–Büchi reaction has prospered and led to significant developments in the area of organic synthesis.

The chemical and biological relevance of oxetane-containing materials is illustrated (*vide infra*) by compounds such as thromboxane $A_2$ (**1**),[7] oxetanocin (**2**)[8] and the unique amino acid antibiotic oxetin (**3**).[9] The elusive thromboxane $A_2$ molecule, for example, is unstable owing to its strain from the acetal linkage of the four-membered ring oxetane unit. While there are many useful methods for oxetane formation, including ring expansion,[10] ring contraction[11,17] and alkylation,[12] oxetane synthesis from the 'quenching' of photochemically excited carbonyl compounds and alkenes is perhaps the most direct and flexible. In addition, both the thermal[13] and Lewis acid catalyzed[14] [2 + 2] cycloadditions of electron-rich alkenes with carbonyl compounds are known and generally occur with regioselectivity complementary to that of the photochemical process. For example, the photochemical reaction of biacetyl with ketene diethyl acetal provides solely the 3-alkoxyoxetane (**4**), whereas the thermal reaction gives the more labile 2-alkoxyoxetane (**5**).[14,15]

This photochemical umpolung is useful from the perspective of chemoselectivity in synthetic transformations. In addition, oxetane-containing products, prepared regioselectively, can be valuable synthetic intermediates. Both oxetane and vinyloxetane derivatives react with nucleophiles in intermolecular and intramolecular condensations and with transition metals[18] and carbenoids.[19] A second feature of oxetane-containing photoproducts, which has important implications, is that they can act as vehicles for subsequent manipulations and stereocontrolled synthesis. For example, the oxetane photoproduct (**6**)

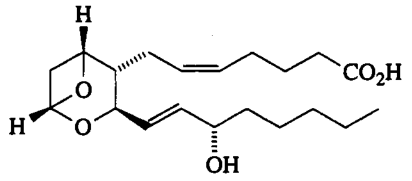

**(1)**

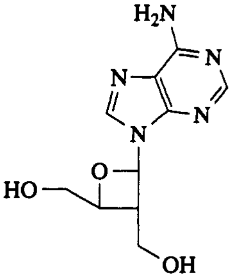

**(2)**

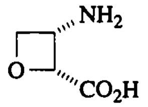

**(3)**

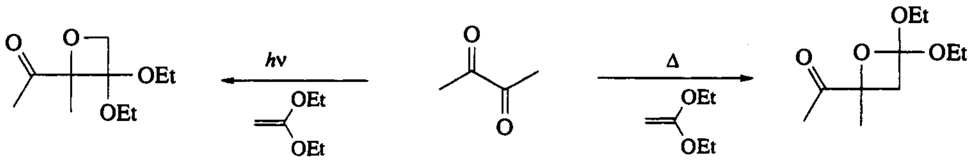

**(4)** **(5)**

undergoes consecutive hydrogenolysis and hydrogenation to form stereospecifically the tetrahydrofuran compound (7),[20] a precursor to hybrid platelet activating factor (PAF) antagonist ligands.[21]

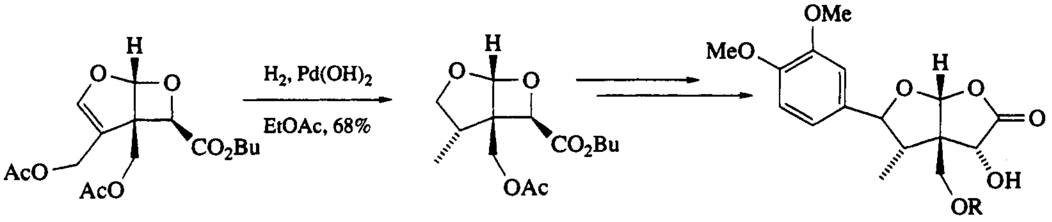

**(6)** **(7)**

The chemo-, regio- and stereo-selectivity observed in the Paterno–Büchi photocycloaddition make the reaction a valuable synthetic method as its numerous applications to targets in synthesis attest. This review will summarize the important mechanistic and synthetic advances. Knowledge of these precedents will likely initiate further scrutiny and applications of the reaction to the synthesis of architecturally complex targets.

## 2.4.2 MECHANISTIC CCONSIDERATIONS

The Paterno–Büchi reaction has been studied mechanistically ever since Paterno and Chieffi[1] first reported that the photoreaction of ketones and alkenes produced, unexpectedly, the corresponding oxetane. Indeed, a recent surge of studies of the photoreaction mechanism has stimulated numerous applications in organic synthesis.

Early mechanistic studies by Arnold[3] supported the Schlenk mechanism, in which a putative 1,4-diradical intermediate resulted from the addition of the *n*,π* triplet state of benzophenone to *cis*- and *trans*-2-butene. The preoxetane diradical led to the same mixture of *cis* and *trans* oxetanes (1:6), suggesting the existence of a 'most stable' diradical species in which rotation occurred prior to oxetane ring closure. Further support for the existence of diradical intermediates came from work by Nishida,[21] in which irradiation of benzophenone with 1,1-dicyclopropylethylene gave 81% of product (**8**) at room temperature, but 65% of the tetrahydroxepin (**9**) at 160 °C. The thermal stability of oxetane (**8**) at 160 °C suggests the cyclopropyl–carbinyl rearrangement of an intermediate diradical. Subsequently, Caldwell[22] refined the Schlenk mechanism to include an initial charge transfer, generating an exciplex intermediate. In the reaction of benzophenone with both deuterated and nondeuterated *cis*- and *trans*-2 butene, a negligible product isotope effect of 1.03 ± 0.01 was obtained. This observation is contrary to the prediction of a small inverse isotopic effect as a result of the rehybridization from $sp^2$ to $sp^3$ at the labeled site in oxetane formation. A π-bonded charge transfer complex that aligns the orbital of the carbonyl symmetrically with respect to the alkene double bond was formulated (Figure 1) to account for the observed isotope effects. Additionally, product isotope effects for the *cis–trans* photoisomerization of 3-methyl[2-$^2$H]-2-pentene (1.003 ± 0.007 for the *trans* isomer) indicate that the preference for intermediate diradical (**10**) *versus* (**11**) is negligible. Therefore the 'most stable diradical' hypothesis[23] is apparently not applicable in certain cases, and other factors such as charge distribution and polarizability can be significant.

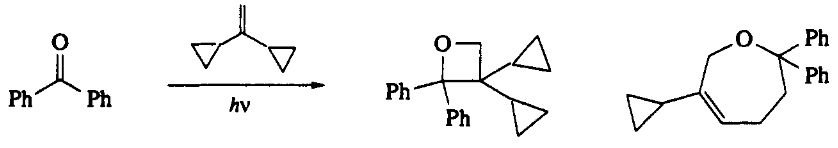

(**8**) (**9**)

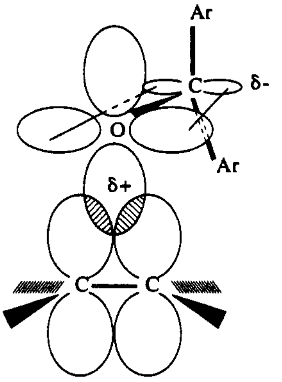

**Figure 1**

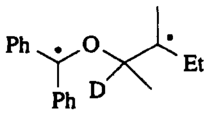

(**10**)

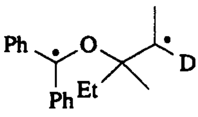

(**11**)

Further support for the prior generation of electron transfer complexes has come from recent investigations by Turro.[24] It was found through fluorescence and phosphorescence quenching studies of enol ethers with both singlet and triplet ketones that charge transfer occurred to the extent of 10 or 15%; in the case of electron-rich alkenes, donation of charge from the alkene *p*-orbitals to the ketone *n*-orbital produced an 'invisible' exciplex. This mechanism successfully accounted for the low regioselectivity observed in oxetane formation from enol ethers, since the 'best diradical' model would suggest higher regioselectivity. However, the involvement of triplet exciplexes in [2 + 2] photocycloadditions of cyclic enone π,π* triplets to alkenes has been recently found to be inconsistent with kinetic data.[25] The greater rate of quenching of enone triplets by electron-poor alkenes was seemingly inconsistent with polar exciplex formation, but the implication of the formation of triplet exciplex precursors in oxetane formation to the 'fundamentally different case of photoannulation' was found to be inappropriate.

The nature of the intermediates in the Paterno–Büchi reaction has been inferred largely from indirect measurements. However, recently the reaction course has been monitored through spectroscopic methods. The first observation of a 1,4-diradical intermediate was claimed by Hayashi,[26] who used a nanosecond laser-photolysis technique to monitor the time dependence of the intermediate 1,4-diradical absorption produced by the irradiation of benzophenone and *cis*-3-methyl-2-pentene. Experiments involving methyl viologen dication quenching indicate that a transient absorbing at 530 nm had a lifetime of 6–25 μs. Scaiano[27] has recently pointed out that the spectrum reported by Hayashi is indentical with the UV band of the ketyl radical of benzophenone ($\lambda_{max}$ = 332 nm) and that the lifetime of the putative diradical is implausibly long. These conclusions have received further support from recent work by Caldwell.[28] A study of the transient spectroscopy of benzophenone in the presence of both tetramethylethylene and ethyl vinyl ether found UV absorptions ($\lambda_{max}$ = 330 nm) with lifetimes of 1.5–4 ns. Similar results have been obtained in recent studies by Peters.[29] In an effort to determine the pathway for formation of the 1,4-diradical, a picosecond dynamics study monitoring the quenching of the triplet state of benzophenone with 1,4-dioxene was undertaken. The transient triplet spectrum is quenched with a half-life of 175 ± 25 ps to form a new species, $\lambda_{max}$ = 535 nm, which is assigned as the 1,4-diradical. As the diradical decays, intersystem crossing of the triplet to the singlet occurs concomitant with oxetane ring closure. In addition, a new species appears ($\lambda_{max}$ = 690 nm in MeCN) whose absorbance corresponds to that of the radical anion of benzophenone. It has been postulated that this species arises from heterolysis of the 1,4-diradical to generate a radical anion and an alkene radical cation. To determine whether exciplexes are formed prior to diradical formation, the photolysis of 4-phenylbenzophenone in 1,4-dioxene was examined and a transient absorption ($\lambda_{max}$ = 520 nm) was found to persist at least 250 ns following irradiation. Since both benzophenone and 4-phenylbenzophenone undergo similar rates of electron transfer with DABCO,[30] a polar transition state best describes any pre-diradical intermediate. Scheme 1 summarizes a mechanism for the Paterno–Büchi reaction which accommodates the available data.

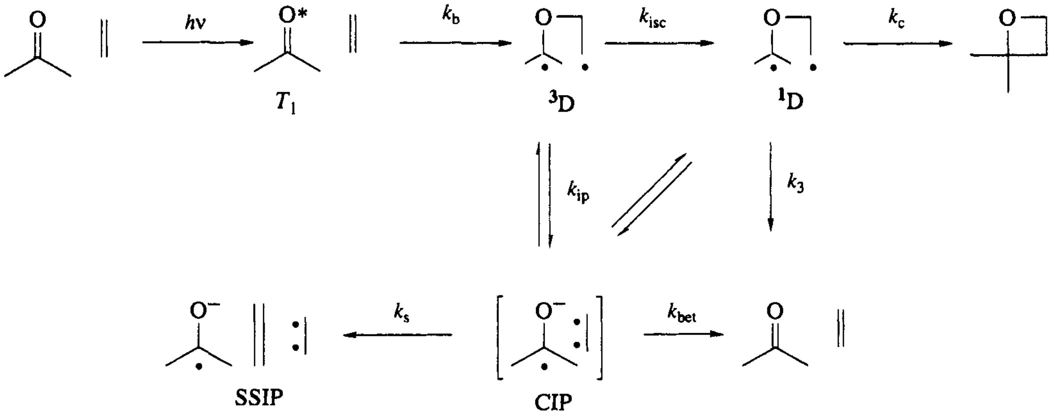

Scheme 1

Recent investigations of the solution photochemistry of biacetyl lend further support to the polar exciplex hypothesis. Luminescence quenching studies reveal the donor–acceptor nature of biacetyl triplet quenching and stereochemical scrambling in the product oxetane and recovered alkene.[31] An extension of the basic exciplex mechanism was recently reported by Mattay and coworkers.[32] ESR measurements of the reaction of biacetyl with electron-rich 1,3-dioxoles with *in situ* irradiation led to the observation of both the biacetyl radical anion and the dioxene radical cation. This 'ionic photo-association' process contrasts with Peters[29] observation of a diradical transient that was postulated to exist in equilibrium with a contact ion pair. Scheme 2 shows some typical photoproducts which result from photolysis of 1,3-dioxoles in the presence of biacetyl. Oxetane-containing products are obtained in all cases, and dioxoles containing allylic hydrogens readily form addition products. In the case of the parent unsubstituted 1,3-dioxole, one-third of the product mixture results from 1,4-addition. Calculated exciplex lifetimes (0.2–0.5 ns) and nonvariance of this lifetime with the alkene quencher led to extension of the exciplex mechanism to include electron transfer as shown in Scheme 3. Insofar as the ESR measurement supports both the radical anion and cation structures, clear differentiation between an exciplex with charge transfer and a contact ion pair may not be possible. However, the theory is a powerful tool for predicting photoreaction chemoselectivity. In the previously described photochemical addition of biacetyl and 1,1-diethoxyethylene, spin densities obtained from ESR measurements indicate that the 1,1-diethoxyethylene radical cation contains 80% of the spin density at the β-carbon (Scheme 4). This explains the regioselective joining observed with biacetyl to form exclusively the 3-alkoxyoxetane, a useful photochemical 'umpolung' of the reactivity of biacetyl.[14,32]

To probe further the nature and reactivity of the transient species produced in the Paterno–Büchi reaction, trapping experiments have been recently performed. Putative diradical intermediates have been trapped with many reagents, including molecular oxygen[33] and sulfur dioxide.[33,34] A mechanistic study of trioxane formation from quinones has implicated both quinone–alkene CT exciplexes and preoxetane diradicals as intermediates. For example, in the laser photolysis of tetramethylallene and benzoquinone, irradiation under a high pressure of oxygen gave oxetane (**15**), which arises from the less-stable vinyl diradical (**14**), and the 1,2,4-trioxane (**13**) which results from oxygen trapping of the longer-lived allyl diradical (**12**). However, in the analogous reaction with *t*-butylethylene it was found that the oxetane ratio (**17**):(**16**) was relatively insensitive to the oxygen pressure. Increased pressure should increase the ratio (**17**):(**16**) by trapping out the more stable preoxetane diradical leading to (**16**). These results may require that another intermediate precedes the preoxetane diradical intermediate and dominates in the trapping process.

Adam and coworkers have recently trapped laser-generated Paterno–Büchi intermediates on a preparative scale in the synthesis of synthetically and medicinally useful peroxides.[35,36] Artemisinin, or qinghaosu (**18**), is a potent antimalarial drug of low toxicity and is effective against chloroquine-resistant malaria.[37] The necessity of the peroxy group for the biological action of the drug has been established. Dioxygen trapping of diradical intermediates in the Paterno–Büchi reaction affords 1,2,4-trioxanes. For

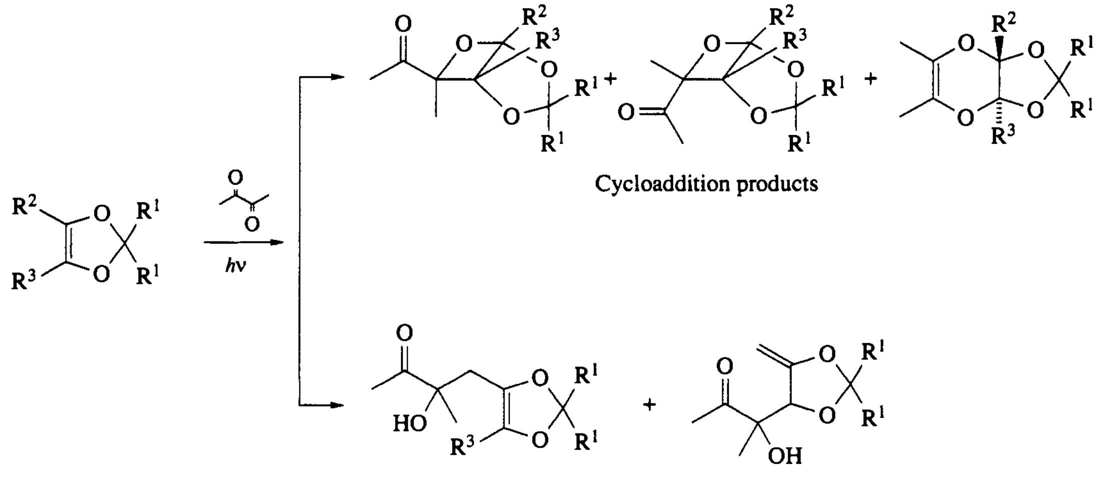
hν
Cycloaddition products
Addition products

**Scheme 2**

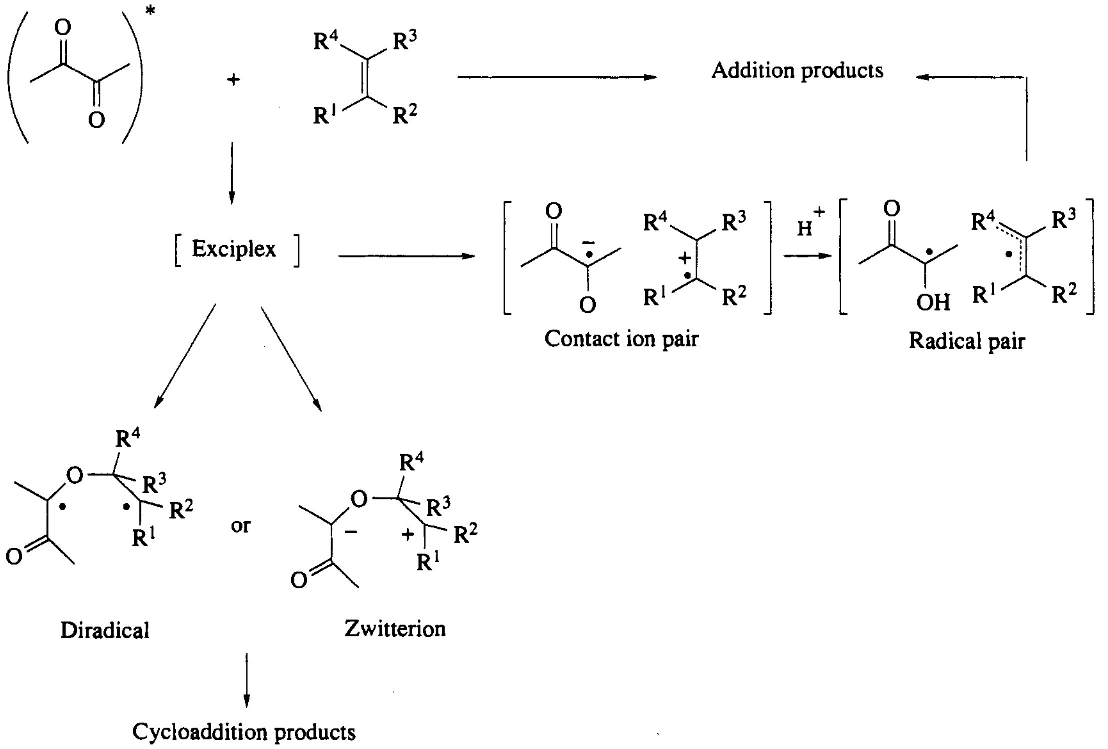
Addition products
Exciplex
Contact ion pair
Radical pair
Diradical
or
Zwitterion
Cycloaddition products

**Scheme 3**

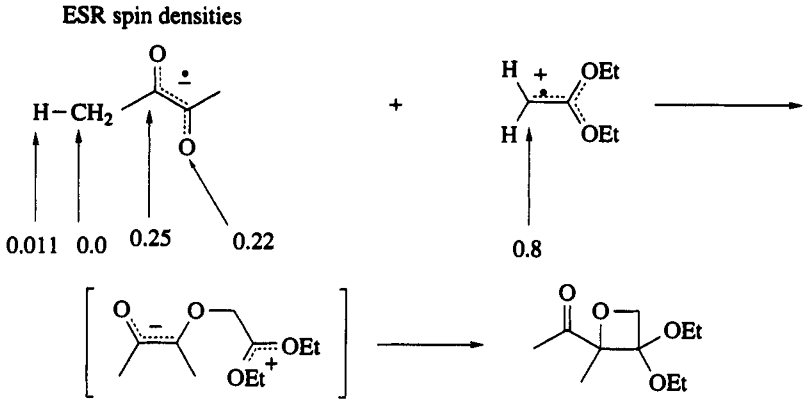

**Scheme 4**

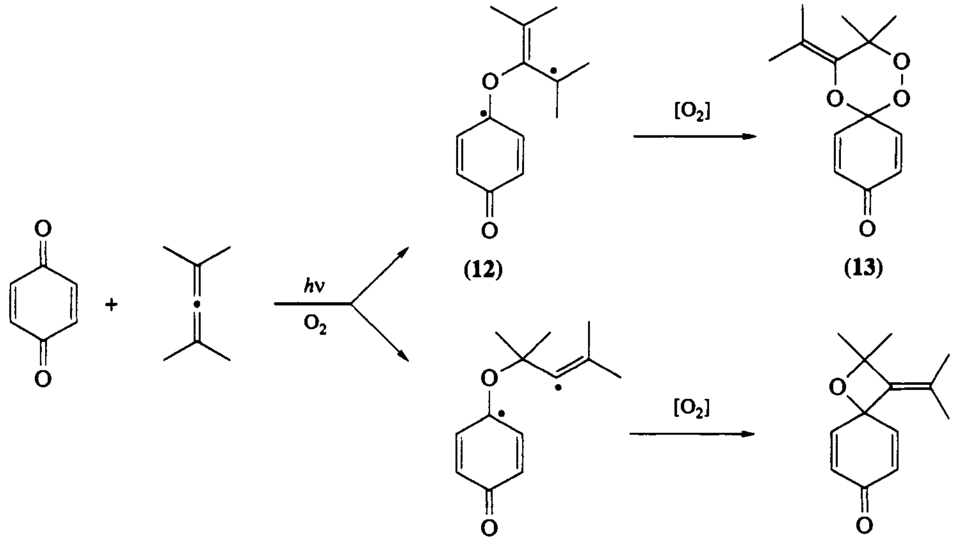

**(12)** **(13)** **(14)** **(15)**

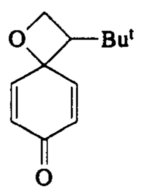

**(16)**

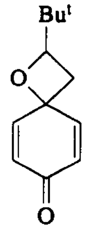

**(17)**

example, the previously described triplet of the preoxetane diradical derived from benzophenone and 1,4-dioxene (lifetime approximately 1.5 ns)[29] can be trapped by molecular oxygen (10 atm) to form the *cis*-fused 1,2,4-trioxane (**19**) in 7% isolated yield. Similarly, argon ion laser irradiation of dioxene and benzoquinone provided the trioxane (**20**) in 20% isolated yield. In a more recent study, qinghaosu-like 1,2,4-trioxanes have been synthesized.[36] Visible laser irradiation of 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**21**) with benzoquinone gave *trans*-(**22**), *cis*-(**22**) and *cis*-(**23**) in a 29:9:18 ratio, as well as small amounts of regioisomeric oxetane products. However, under the same conditions, phenanthraquinone (**24**) yielded only oxetane-containing photoproducts. The differences in trapping reactivity were attributed to either the existence of zwitterionic intermediates or short lifetimes for triplet diradical intermediates. The construction of novel lactone trioxanes of the qinghaosu class has demonstrated the utility of trapping, and yields spiro-annulated lactone trioxanes as potentially active artemisinin analogues. The Paterno–Büchi reaction thus offers an alternative to other available methods for 1,2,4-trioxane synthesis.[36,38,39] In addition, the recently reported conversion of 1,2,4-trioxanes to *syn*-1,2-diols[39] and electrophile-induced rearrangements of trioxane systems[40] bode well for continued interest in the preparative trapping of transient intermediates and illustrates how the study of reaction mechanism has produced new and useful synthetic methods.

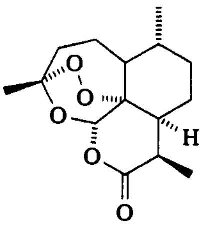
**(18)**

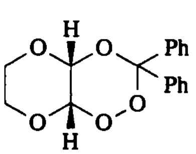
**(19)**

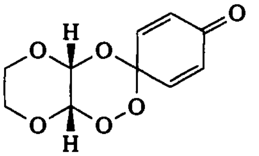
**(20)**

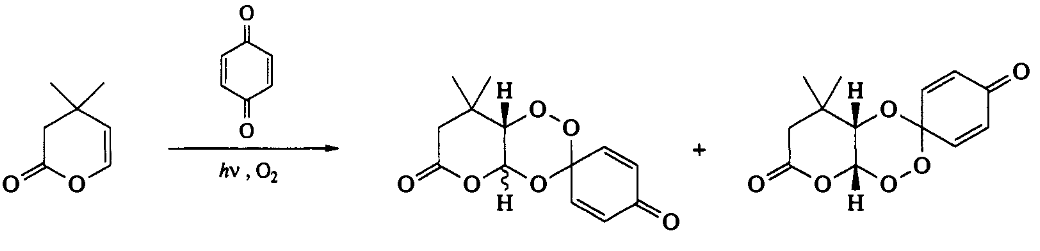

**(21)** **(22)** **(23)**

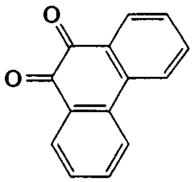
**(24)**

## 2.4.3 PHOTOCHEMICAL SYNTHESIS USING ALKENYL AND ALKYNYL ADDENDS

The synthesis of oxetanes from alkenic precursors has been demonstrated and the range and scope of Paterno–Büchi photocycloadditions are broad. In general, both the reaction regioselectivity and stereoselectivity can often be predicted by considering the reaction mechanism (Section 2.4.2); for example, the directing effects of alkene substituents are readily understood. Synthetic applications are numerous owing to the rapid stereocontrolled assembly of multifunctional targets.

A photochemical approach towards prostaglandin analogs relied on stereoselective use of the Paterno–Büchi reaction.[40] The analog (**25**), which possesses the natural prostaglandin configuration, was shown to be a potent inhibitor of ADP-induced platelet aggregation *in vitro*.[41] Irradiation of a benzene solution of (**26**) and *m*-acetoxybenzaldehyde, followed by benzylic hydrogenolysis of the oxetane ring, gave (**27**) in 30% overall yield from (**26**). Further analysis of the product mixture revealed the formation of 10–20% of a regioisomeric oxetane. However, the predominant formation of (**27**) in the reaction possibly reflects the ability of the cyclopropyl group to stabilize an incipient radical.

A similar application of a vinylcyclopropane in a stereoselective photoreaction has been reported by Dürr and coworkers.[42] Scheme 5 shows the addition of a bicyclo[3.1.0]hexenol derivative and acetophenone, which afforded the strained 7-oxatricyclo[4.2.0.0]octane and a comparable amount of tetraphenylcyclopentadiene. Since the vinylcyclopropane is known to undergo photochemical isomerization and photofragmentation to the cyclopentadiene, it is conceivable that these reactions precede photocycloaddition. If this is the case, the major oxetane (4:1 selectivity) arises from addition of the alkoxy radical to

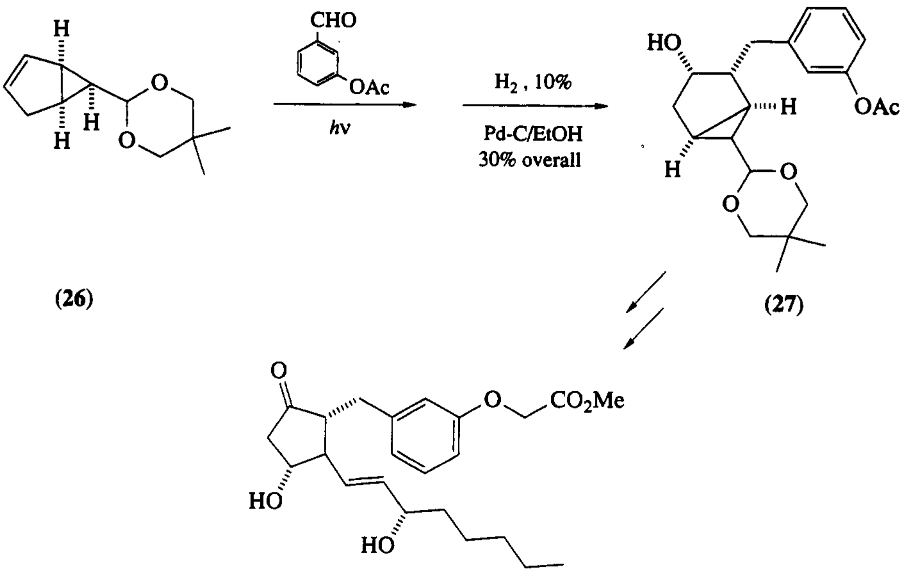

(26)

(27)

(25)

produce a cyclopropyl–carbinyl radical. The photoreaction thus demonstrates the trapping of a photofragmentation intermediate and the formation of a strained oxetane structure.

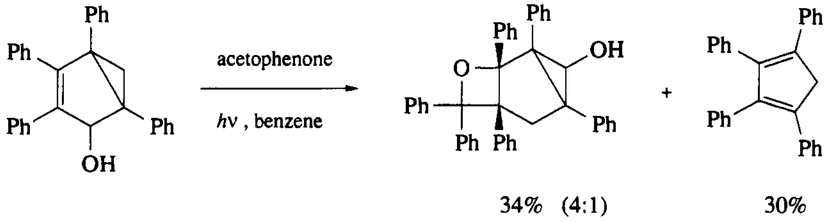

**Scheme 5**

Araki has made use of the Paterno–Büchi reaction in the synthesis of C-glycosyl compounds and branched-chain sugars. For example, irradiation of a benzene solution of 1,3-diacetoxyacetone (**28**) and vinylene carbonate gave the oxetane photoproduct (**31**) in 55% yield. This adduct was subsequently hydrolyzed to (±)-apiose (**32**) in 60% yield.[43] Photocycloaddition of (**28**) with (*Z*)-vinylene diacetate gave mixtures of *cis*- and *trans*-photoproducts (46% and 49% yield, respectively). An independent control experiment established that the excited ketone promotes equilibration of the alkene. The higher overall yield of open-chain ethylenediol derivatives compared with vinylene carbonate in the photocycloaddition was attributed to the photolability of (**31**). A limitation of the cycloaddition process was uncovered with the use of carbonyl compounds (**29**) and (**30**); competitive Norrish type II photoprocesses formed alternative oxetane products (**33**) and (**34**). A similar problem has been noted for benzyl glyoxalate as a carbonyl addend in Paterno–Büchi photoadditions.[44] In a related series of experiments, the more easily prepared silyl enol ethers[45] reacted with (**28**) to form the 3-siloxyoxetane (**35**).[4,45] The 2-alkoxyoxetane was not isolable, but careful derivatization of the crude reaction mixture revealed that it was a significant side-product (22% *vs.* 46%). This is consistent with the modest regiochemistry in the Paterno–Büchi reaction of enol ethers and the lability of 2-alkoxyoxetane observed by Schroeter and coworkers.[16]

A similar approach to branched-chain aldonolactone sugars has been recently reported by Mattay.[46] Lithium aluminum hydride reduction of photoproduct (**36**) afforded the desired alcohol which rearranged under acidic conditions to the deoxygenated apiose derivative (**38**). This process is notable since such reductions usually proceed with cleavage of the oxetane moiety. Also noteworthy are the rapid assemblage of highly oxygenated functionality and the ease of the synthetic procedure.

Carbohydrate templates have provided interesting applications of the Paterno–Büchi reaction. In a series of papers, Araki has demonstrated the feasibility of oxetane formation from glucals.[47,48] Photocy-

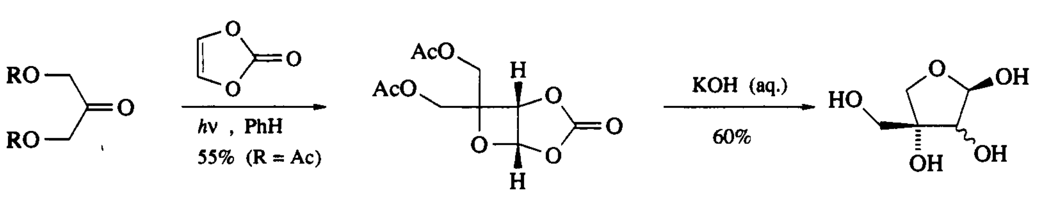
RO
RO
O
O
O
O
hν , PhH
55% (R = Ac)
AcO
AcO
H
O
O
O
O
H
KOH (aq.)
60%
HO
O
OH
OH
OH

**(28)** R = Ac
**(29)** R = Bn
**(30)** R = Me

**(31)**

**(32)**

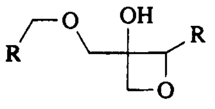

**(33)** R = H
**(34)** R = Ph

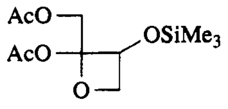
AcO
AcO
OSiMe3
O

**(35)**

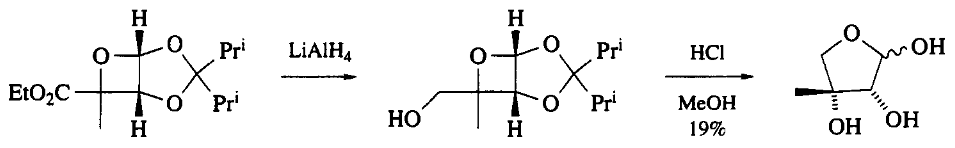
H
O
O
Pri
EtO2C
O
Pri
H
LiAlH4
H
O
O
Pri
HO
O
Pri
H
HCl
MeOH
19%
O
OH
OH
OH

**(36)**

**(37)**

**(38)**

cloaddition of acetone to 3,4,6-tri-*O*-acetyl-D-glucal was found to exhibit a remarkable solvent effect, providing oxetane (**39**) when acetone was employed as solvent in addition to varying amounts of ring-opened product (**40**) depending on the chromatographic conditions.[49] *C*-Glycoside (**41**) was the major product when the photolysis was performed in isopropanol. The general mode of oxetane formation was believed to occur as shown in Scheme 6. Since the carbonyl oxygen in the *n*,π* triplet state is electron deficient,[50] attack occurs at the β-carbon of the glucal to form an anomerically stabilized glucopyranosyl radical.[51] Stereochemical control is thus exerted by the adjacent β-acetoxy group. Additionally, an electronic effect may be operative, in which the axial β C—O bond[52] is aligned synplanar to the singly occupied *p*-orbital, providing for SOMO(*p*)–LUMO(σ*) stabilization.[51] The high orientational selectivity is in accord with the results of Carless[53] in which cyclic enol ethers give rise to 3-alkoxyoxetanes predominantly. This is contrary to the case of acyclic enol ethers where only modest regioselectivity is observed.[16,54] Oxetane formation did not occur in benzene, thus illustrating the need for hydrogen donating solvents such as isopropanol. Acetone-sensitized formation of glycoside (**41**) from isopropanol can be explained by addition of an electron-donating radical to the less electron-rich glycal carbon in an equatorial fashion.

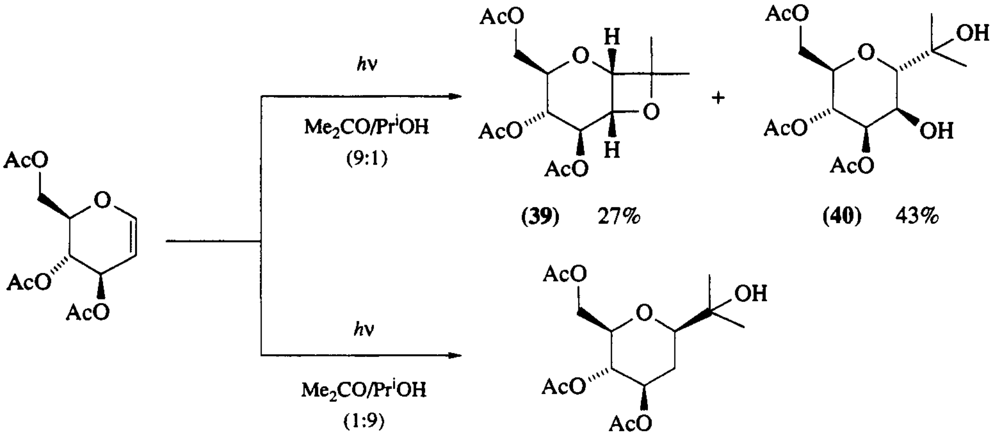
AcO
O
AcO
AcO
hν
Me2CO/PriOH
(9:1)
AcO
O
H
O
AcO
AcO
H
+
AcO
O
OH
AcO
OH
AcO
hν
Me2CO/PriOH
(1:9)
AcO
O
OH
AcO
AcO

**(39)** 27%

**(40)** 43%

**(41)**

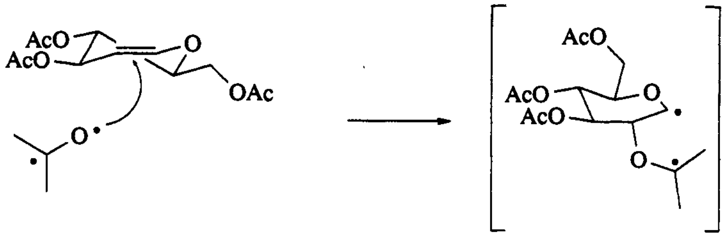

(39)

Scheme 6

A recent effort to improve the modest regioselectivity observed in photochemical additions to enol ethers was recently reported by Smith and coworkers.[55] Vinyl sulfide (**42**) was prepared using a standard Homers–Emmons alkenation reaction and irradiated with benzophenone in degassed benzene. A high selectivity for *trans*-4-alkyl-3-methylthiooxetanes (**43**) was observed, as shown by analysis of the product using X-ray diffractometry. In addition, reaction times were reduced approximately eight-fold relative to similar enol ether substrates, which indicates possible radical stabilizing and electronic effects.

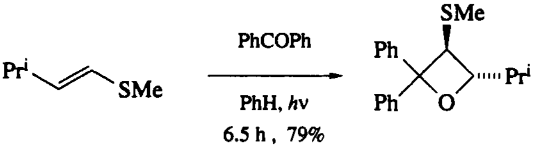

(**42**) (**43**) *trans*

The photochemistry of more complex and highly substituted alkenic partners has been studied. In 1978, Hartmann and coworkers reported the photocycloaddition of 4-oxazolin-2-one with acetone, used as a photosensitizer in the reaction of 4-oxazolin-2-one with alkenyl and alkynyl partners, to form oxetane (**44**).[56] Recently, Scharf has described the photochemistry of 3-acetyl-2,3-dihydro-2,2-dimethyloxazole (**45**).[57] Irradiation of (**45**) in the presence of acetophenone produced the oxetane (**46**) with the phenyl group *endo* (17%), in addition to 21% of a ring-opened derivative. The stereoselectivity is in agreement with the high *exo* carboxyl selectivity observed in the photocycloaddition of methyl phenylglyoxylate with 2,2-dimethyl-1,3-dioxole to produce oxetane (**47**).

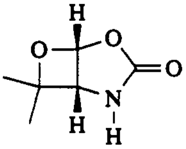

(**44**)

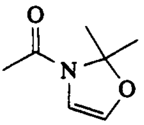

(**45**)

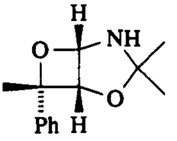

(**46**)

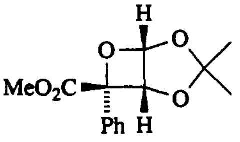

(**47**)

In a related study, 2,2-diisopropyl-1,3-dioxole was found to undergo cycloaddition with ethyl pyruvate to form a 4:1 mixture of regioisomeric oxetanes (**48**) and (**49**).[14] However, the strongly accepting diethyl mesoxalate fails to undergo photocycloaddition, whereas cyclopentene forms oxetane photoproducts with this carbonyl compound. Mattay has demonstrated[14,46] that 2,2-diisopropyl-1,3-dioxole can be irradiated with trimethylpyruvic acid ethyl ester to form a single (unassigned) stereoisomer of oxetane (**50**). It would be interesting to determine the stereochemistry of this transformation since this information is relevant to the issue of the relative importance of steric and electronic effects in the photocycloaddition reaction.[58]

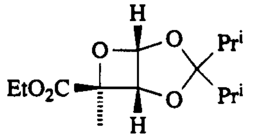

(**48**)

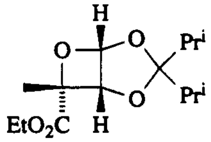

(**49**)

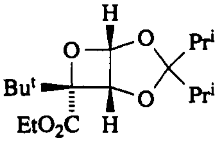

(**50**)

A recent application of the Paterno–Büchi reaction involved the synthesis of novel polymeric structures. Guillet and coworkers have described the photolysis of benzophenone and *cis*-1,4-polyisoprene (natural rubber) that forms a copolymer (**51**) of isopropene and isomeric isoprene–diphenyloxetane adducts.[59] NMR analysis indicates incorporation of about 25 mol % oxetane rings, giving a stiffer polymer with a higher glass transition, the result of inclusion of motionally restricting ring structures and bulky phenyl groups in the polymer chain. Another type of 'photopolymerization' that uses alternatively the photoexcited group as the polymerization template involves the solid-phase photocycloaddition of alkenes to poly(vinylbenzophenone) (Scheme 7).[60] In addition, polyfunctional alkenes such as squalene have been utilized in photocrosslinking of poly(vinylbenzophenone). Further studies of polymeric systems offer much potential, especially in areas of polymer modification and in the development of novel macromolecular materials.

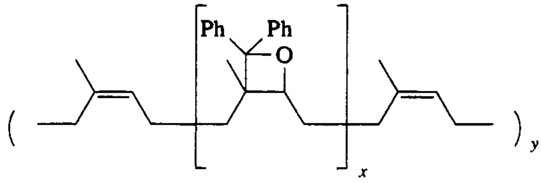

(**51**)

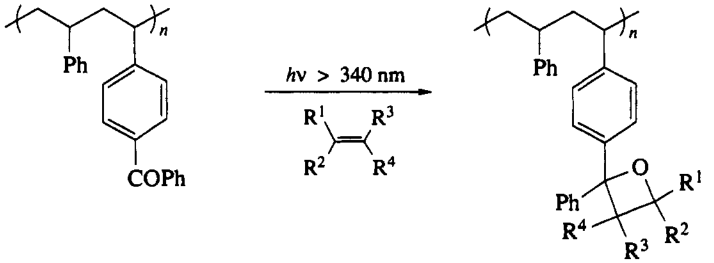

**Scheme 7**

While most of the previously described photochemical reactions of alkenes have centered on aldehyde and ketone partners, there have been recent reports on the behavior of nitriles and carboxylic acid derivatives. Cantrell has reported the photochemical cycloadditions of benzonitrile to alkenes.[61] A dramatic dependence of alkene structure on the chemoselectivity of benzonitrile addition was noted. For example, Scheme 8 shows that 2,3-dimethyl-2-butene reacts under photolytic conditions to give mainly the azabutadiene product (66%) plus 8% of the thermally stable azetine valence isomer, suggesting that the azabutadiene isomer results from a photochemical ring opening. Photolysis of 2-methyl-2-butene with benzonitrile, on the other hand, gave as a major product the 1-cyanobicyclo[4.2.0]octadiene derivative. While the reasons for this divergent photochemical behavior are not clear, it has been proposed that singlet exciplexes or charge transfer complexes of benzonitrile with alkenes are generated with various geometries. Thus electron-poor alkenes locate themselves over the high electron density of the benzene ring (A), whereas electron-rich alkenes such as enol ethers will form an exciplex oriented over the electron-poor cyano group (B).

In a recent study, Mattay and coworkers[62] have studied the photoreactions of benzonitrile with cyclic enol ethers. Both methoxycyclohexene and methoxycyclopentene show a preference for type II cycloaddition, giving the azabutadiene derivatives (**52**) and (**53**), respectively. The regioselectivity of the process, although in disagreement with the assignment reported by Cantrell,[61] was proven by hydrolysis of (**53**) to the methyl 7-phenyl-7-oxoheptanoate derivative. In addition, irradiation of benzonitrile and dihydrofuran produced a 20% yield of the type I *ortho* adduct (**54**), while photoreaction of 1,3-dioxole produced 4-phenyloxazole (**55**), presumably by hydrolysis of an incipient azabutadiene derivative. The formation of 2-azabutadiene derivatives is of considerable interest in both the construction of medium-membered ring nitrogen-containing heterocycles and in the synthesis of 5,6-dihydro-2*H*-1,3-oxazine[63] and pyridine[64] structures.

The photochemical reactions of arenecarboxylic acid esters with alkenes has received recent attention by Cantrell.[65,66] For example, irradiation of 2,3-dimethyl-2-butene and methyl benzoate gave a mixture of alkoxyoxetane (**56**), carbonyl–alkene metathesis[4] product (**57**) and ketone (**58**), resulting from alkoxy radical allylic hydrogen abstraction and radical recombination. Such alkoxyoxetane photoproducts are

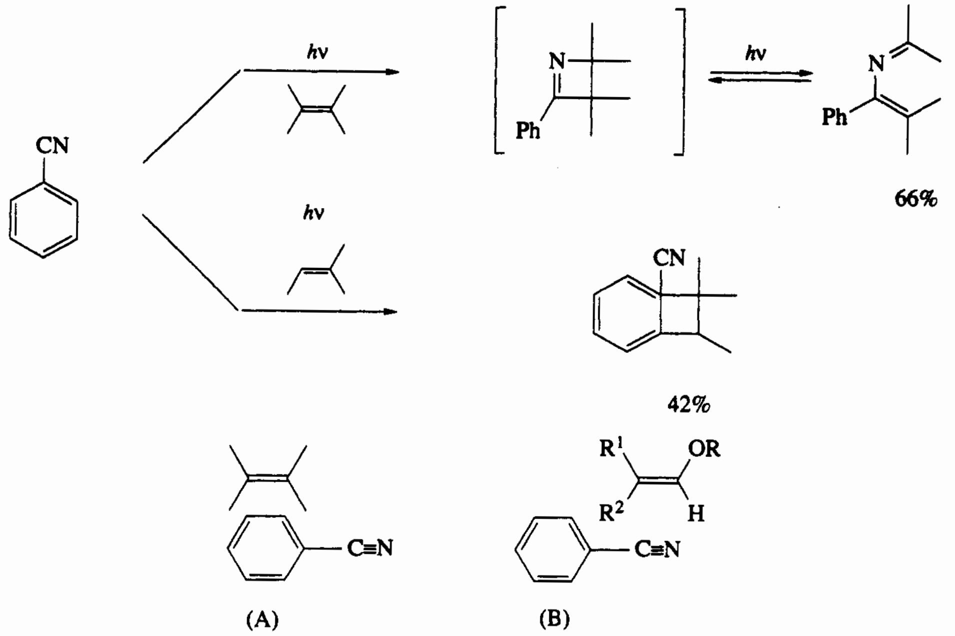

**Scheme 8**

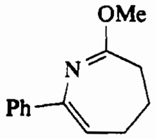

**(52)**

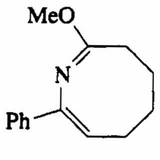

**(53)**

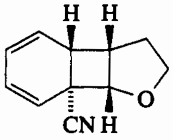

**(54)**

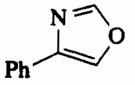

**(55)**

useful synthons, as shown by the acid-catalyzed hydrolysis of acetal (**59**) to the diketone (**60**), a useful precursor to the tricarbonyl functional unit.[67]

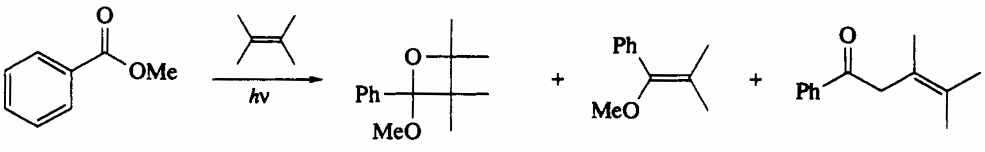

(**56**) 52% (**57**) 7% (**58**) 9%

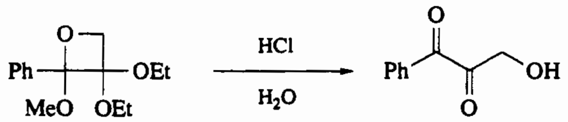

(**59**) (**60**)

Numerous papers have been published describing the photochemical production of enones from carbonyl compounds and alkynes.[68] The first detection of an oxetene intermediate involved low-temperature (–78 °C) photolysis of 2-butyne and benzaldehyde to form the photoproduct (**61**), which was observed by NMR. The oxetene undergoes further photoreaction with benzaldehyde to form the novel fused oxetane (**62**). Recently, Friedrich has reported further studies on the reactivity of oxetenes and developed alternative syntheses of the parent compound and 3-phenyloxete (**64**).[69] The parent oxetene is found to have a thermal half-life of approximately 8 h in solution at room temperature. The phenyl-substituted derivative (**64**) underwent slow ring-opening under acidic conditions to form 2-phenylpropenal and air oxidation to yield a formate derivative, probably *via* a radical process.

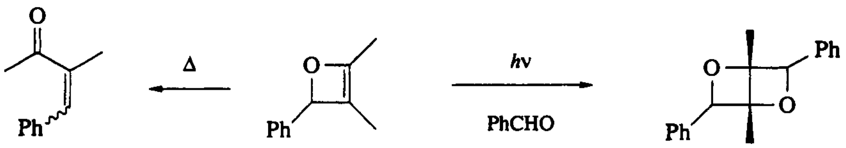

**(63)** **(61)** **(62)**

*(Z)*:*(E)* = 2 : 1 at 20 °C (photostationary state)
*(E)* only at –78 °C

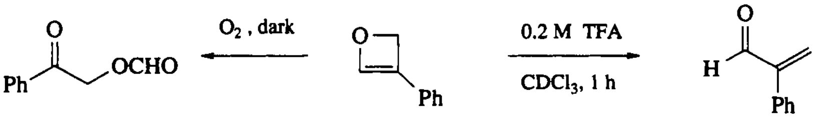

**(64)**

A related photochemical process in which an oxetene intermediate may not be involved is the photolysis of benzaldehyde and 1-hexyne,[70] yielding as major products (**65**) and (**66**). Since no ring-opening products derived from regioisomeric oxetanes could be observed, it was proposed that benzoyl radicals were adding to the alkyne from the unsubstituted terminus. Further photoreaction of (**65**) to (**66**) was observed upon prolonged irradiation. This result is in contrast to the original report by Büchi,[71] in which irradiation of benzaldehyde and 5-decyne produced 6-benzylidene-5-decanone (13%), presumably from electrocyclic oxetene ring opening.

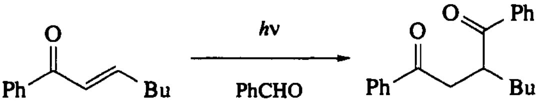

**(65)** **(66)**

Bos and coworkers have developed several applications of alkyne–ketone photoadditions to organic synthesis.[72] Irradiation of a solution of acetone and 1-methylthio-1-propyne gives as a major product the cycloadduct (**67**); this results from selective oxetane formation due to radical stabilization by the methylthio group, followed by electrocyclic ring opening. Similarly, photoreaction of benzil and 1-*t*-butylthio-1-propyne gave the adduct (**68**) in 45% yield, which was transformed in 90% yield to the furan (**69**).

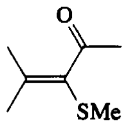

**(67)**

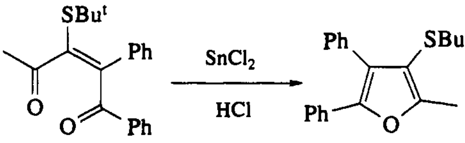

**(68)** **(69)**

Photoaddition of carboxylate esters to diphenylacetylene has also been reported.[73] For example, irradiation of methyl *p*-cyanobenzoate and diphenylacetylene gave in 86% overall yield the enol ether (**71**), presumably a result of carbonyl *n*,π* triplet addition to the alkyne to form the unstable oxetene, which rapidly ring opens. This complements the utility of aromatic esters in the Paterno–Büchi reaction with alkenes as discussed by Cantrell.[65,66]

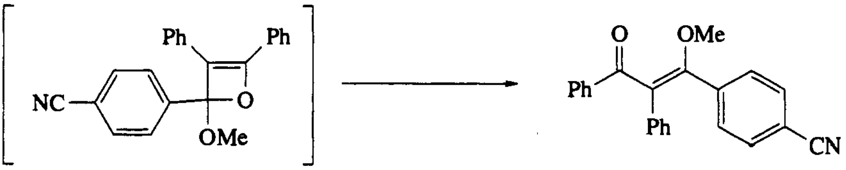

**(70)** **(71)**

Preliminary investigations describing the photoadditions of ynones to alkenes[74] have determined that these species may react through *n*,π* excitation to produce alkynic oxetanes. Irradiation of 3-butyn-2-one with isobutene gave a 46% isolated yield of (**72**) and (**74**) (14:86). 3-Octyn-2-one analogously provided a 50% isolated yield of (**73**) and (**75**) (15:85), a regioselectivity predicted on the basis of the 'best' diradical intermediate.

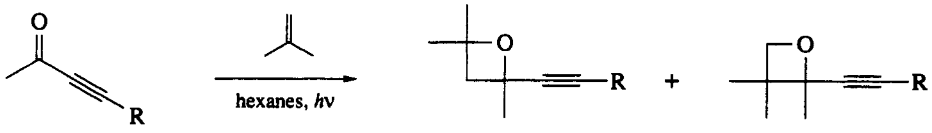

(**72**) R = H
(**73**) R = Bu

(**74**) R = H
(**75**) R = Bu

In a related series of experiments, Agosta[75] and coworkers have discovered alternative pathways for 1,4-diradicals generated from addition of photoexcited ynones to alkenes. For example, in the photolysis of 3-pentyn-2-one with tetramethylethylene, products arising from both [3 + 2] and [2 + 2] cycloaddition have been noted (Scheme 9). It is proposed that oxetane formation proceeds from the short-lived first excited singlet state of the alkynone, since addition of triplet quenchers to the reaction has no effect on oxetane formation. On the other hand, the [3 + 2] mode of cyclization is quenched by triplet scavengers such as naphthalene, which suggests the existence of a longer-lived quenchable state that can add to tetramethylethylene to form a carbenoid. The intermediacy of the carbene has been implicated by deuterium and alcohol-trapping experiments; however, attempts to observe this species *via* laser flash photolysis and ESR were unsuccessful.[76]

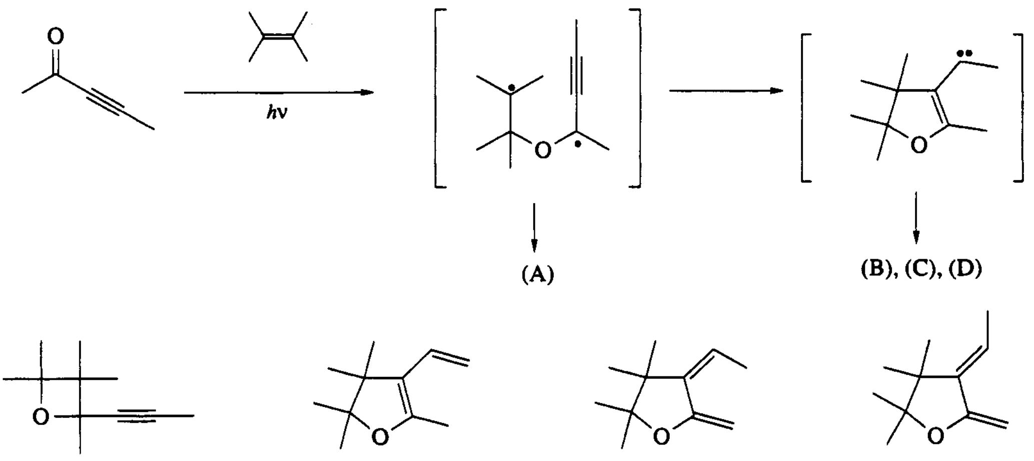

(A) 7% (B) 2% (C) 27% (D) 49%

**Scheme 9**

An example in which the chemoselective photoaddition of carbonyl compounds to a conjugated enyne becomes an important issue has been reported by Carless.[77] A solution of 2-methylbut-1-en-3-yne and benzophenone was irradiated to form in 58% yield the oxetane (**76**), which was converted under acid catalysis to conjugated enyne (**77**). Surely the synthetic utility of such a process, as well as further applications of alkynyl–carbonyl photocycloadditions, will be forthcoming.

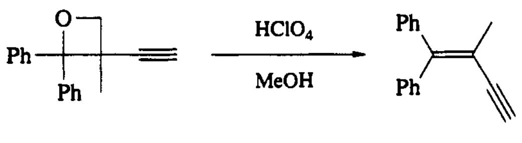

(**76**) (**77**)

## 2.4.4 PATERNO–BÜCHI REACTION OF DIENYL AND ALLENYL SYSTEMS

The use of dienes such as piperylene in the quenching of triplet states of carbonyl compounds is well known.[78] However, in many photochemical studies, attempts to quench the carbonyl $T_1$ state are often complicated by the formation of oxetane photoproducts.[79] Since the photosensitized dimerization of diene triplets is well known,[80] synthetic applications utilizing dienes in the Paterno–Büchi photocycloaddition are rather limited. However, the diene addend not only allows for rapid assemblage of functionality but remains a continuing challenge in terms of experimental efficiency and generality.

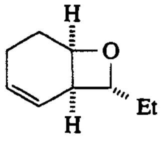

**(78)**

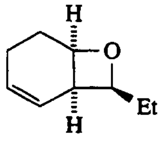

**(79)**

Perhaps the earliest use of a conjugated diene system was the photoaddition of propionaldehyde to cyclohexa-1,3-diene, first reported by Kubota and coworkers.[81] Oxetanes (**78**) and (**79**) were obtained in a 4:1 ratio, presumably through attack of excited singlet propionaldehyde on the diene,[82] whereas diene dimers are thought to originate *via* attack of triplet diene on another ground-state diene molecule. The use of Pyrex filters in these experiments suggests that propanal is excited to its *n*,π* singlet state. The case of endocyclic *versus* exocyclic alkene selectivity has been considered by Duthaler and coworkers.[83] Irradiation of diene (**80**) and acetaldehyde gave a 45.5:11:43.5 mixture of isomeric oxetanes (**81**), (**82**) and (**83**), which indicates low site-selectivity in oxetane formation but preferential *endo* stereoselectivity for spirooxetane (**83**).

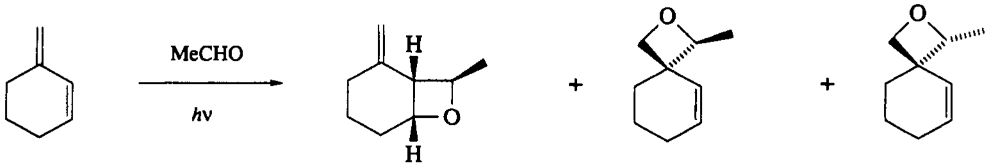

**(80)** **(81)** **(82)** **(83)**

Likewise, photocycloaddition of acetaldehyde to (*E*)-penta-1,3-diene gave oxetanes (**84**) and (**85**) as major products (51%, 25%), indicating that attack at the more substituted double bond is preferred with high orientational selectivity.[84] The formation of (**86**) and (**87**) from (*Z*)-penta-1,3-diene (48%, 27%) implicates a singlet intermediate because of the observed retention of stereochemistry.[79,85]

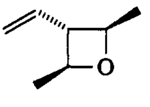

**(84)**

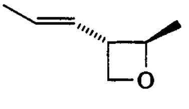

**(85)**

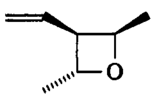

**(86)**

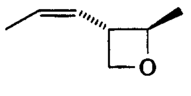

**(87)**

Further evidence for singlet 1,4-diradical intermediates has been obtained in the case of photocycloaddition of cyclopropanecarbaldehyde with (*E*)-penta-1,3-diene, in which the formation of the cyclopropyloxetane (**88**) dominated. This is in contrast to the case of aromatic carbonyl compounds and cyclopropylethylene in which the formation of considerable amounts of ring-opened products and oxepins, formed by cyclopropylcarbinyl–allylcarbinyl rearrangement, implicates the intermediacy of a triplet 1,4-diradical.[23]

Jones and coworkers have utilized a carbonyl–alkene metathesis sequence in the synthesis of insect pheromones.[86] Oxetane (**89**) was synthesized efficiently from adduct (**78**) by hydrogenation ($PtO_2$, EtOH) since direct irradiation of cyclohexene and propionaldehyde gave photoreduction products, possibly owing to the greater availability of allylic hydrogens. Pyrolysis of (**89**) (270 °C) or treatment with $\{Rh(CO)_2Cl\}_2$ in benzene gave *trans*-non-6-enal (**90**; 89%). $LiAlH_4$ reduction of (**90**) provided *trans*-non-6-en-1-ol, a sex attractant of the Mediterranean fruit fly. Similar thermal[87] or catalyzed[88] cyclorever-

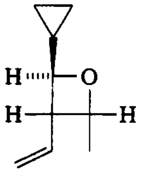

**(88)**

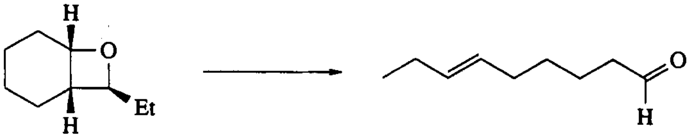

**(89)** **(90)**

sions were noted previously to be both stereoselective and favor the formation of metathesis products instead of regenerated carbonyl–alkene pairs.

Several applications of the Paterno–Büchi reaction in medium-membered ring functionalizations have been documented. Sakurai and coworkers[89] have reported the photoaddition of acetone to 1,3-cyclooctadiene to produce a 4:1 mixture of *cis* and *trans* oxetanes (**91**) and (**92**). Interestingly, acetone adds stereorandomly to cyclooctene to give a 1:1 mixture of *cis* and *trans* oxetanes. These results have been interpreted in terms of a mechanism in which diradicals are generated from ketone triplets. Jones and coworkers[90] have recently uncovered a critical dependence of the photoaddition stereoselectivity on the concentration of the alkene component. Irradiation of butanal and cyclooctene in acetonitrile resulted in a 65:17:18 mixture of adducts (**93**), (**94**) and (**95**). A different (2.8:47.5:49.7) mixture results when irradition was performed in neat alkene. At low concentrations of alkene a more stereorandom triplet path may be operative. At higher alkene concentrations, addition of aldehyde singlets leads predominantly to *cis* isomers, most likely by formation of a singlet exciplex in which the $n,\pi^*$ electrophilic carbonyl attacks the alkene in an 'edge-on' arrangement.[91]

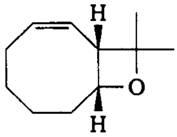

**(91)**

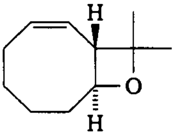

**(92)**

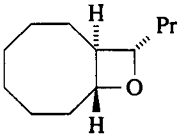

**(93)**

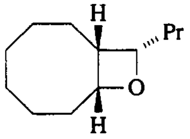

**(94)**

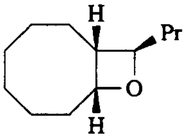

**(95)**

A recent synthesis of the tricyclic secoiridoid (±)-sarracenin (**98**) relied on the Paterno–Büchi addition of acetaldehyde and cyclopentadiene as the initial step.[92] Irradiation of cyclopentadiene and acetaldehyde provided a 5:1 mixture of bicyclic oxetanes (**97**) and (**96**) in 5–10% yield. Treatment of the crude photolysate with CSA and methanol followed by tosylation of the crude product gave (**99**), which represents the toluenesulfonate ester derived from the major oxetane (**97**).[93] The tosylate was displaced by the anion prepared from dimethyl β-styrenylmalonate to afford the substituted malonate (**100**) in 84% yield (Scheme 10). Attempts to effect ring opening of the oxetane mixture were unsuccessful.[17] Decarboxylation and demethylation gave the alcohol (**102**) which was subjected to ozonolysis and reductive work-up to afford (±)-sarracenin in 60% yield. The oxetane-based synthesis is noteworthy due to its brevity and use of a biosynthetically postulated trialdehyde equivalent.

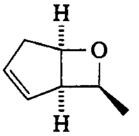

**(96)**

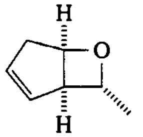

**(97)**

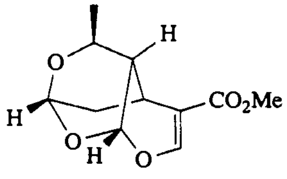

**(98)**

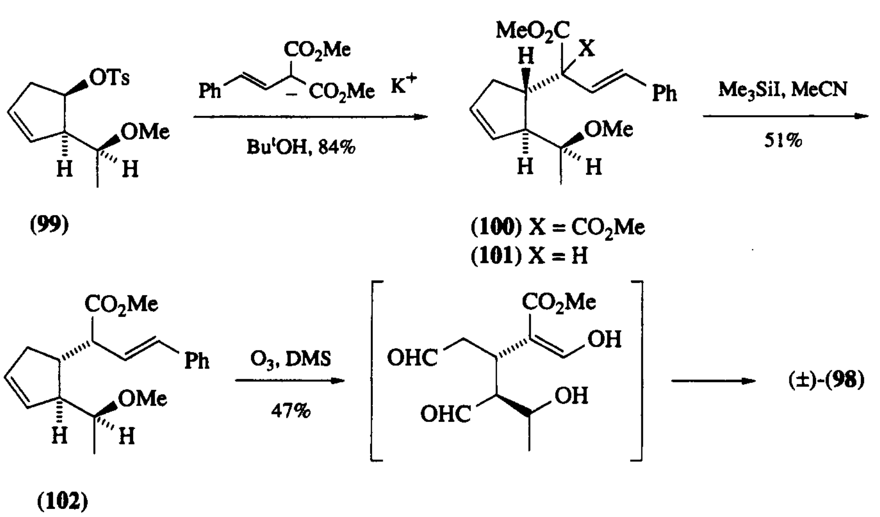

**Scheme 10**

In studies directed towards the synthesis of the fungal isonitrile antibiotic isonitrin B (**103**),[94] a cyclopentanoid metabolite related to trichoviridine (**104**),[95] various trialkylsilyl enol ethers were irradiated with propionaldehyde to produce equimolar amounts of stereoisomeric bicyclic oxetanes (**105**).[96] The corresponding silyl dienol ethers, however, gave little oxetane product owing to preferential diene photopolymerization. The use of vinyl epoxide derivatives such as (**106**), however, offers a possible access to the epoxycyclopentanoid system with simultaneous control of the face selectivity of the photoaddition by the epoxide moiety.

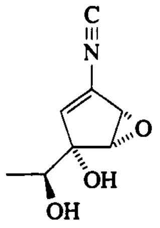

**(103)**

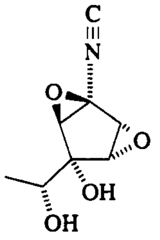

**(104)**

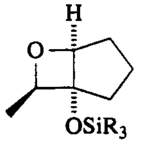

**(105)**

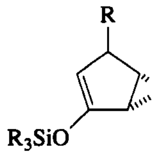

**(106)**

Even more rare are photocycloadditions involving carbonyl compounds to allenes.[5] Arnold[97] has found that acetone and tetramethylallene can be irradiated to form a mixture of 2-alkylideneoxetane and 1,5- and 1,6-dioxaspiro[3,3]heptane products (**107**:**108**:**109** = 8:51:27), all resulting from initial attack of the carbonyl *n*,π* state on the central carbon linkage. Hammond[98] subsequently reported a study in which alkylideneoxetane derivatives (**111**) were photoisomerized to cyclobutanes (**110**).

Similarly, it was found that (**111**) rearranged to a 78:22 mixture of cyclobutanes (**112a**) and (**112b**), presumably through a cyclopropylcarbinyl cation.[99] Extension of the alkene photocycloaddition to ketenimines has been reported by Singer and coworkers.[100] Iminooxetane (**113**) was formed by irradiation of an acetone/dimethyl-*N*-phenylketenimine mixture and was found to possess a 21.8 kcal mol$^{-1}$ barrier to *syn–anti* imine exchange determined from variable-temperature NMR experiments. An effort to use the allene–carbonyl photocyclization in a photopolymerization reaction has been described by Andrews and

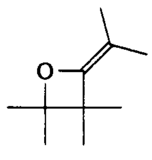

**(107)**

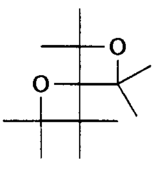

**(108)**

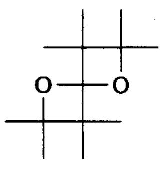

**(109)**

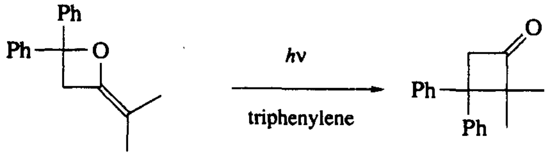

**(111)** **(110)**

Feast.[101] Dibenzoylbenzene derivative (**114**) was irradiated with tetramethylallene for 3.5 minutes in benzene to produce a polymeric structure in which there were 90% oxetane structures incorporated along the backbone. This process constitutes an example of step-growth photopolymerization *via* the triplet state of an aromatic carbonyl moiety. The products are thermally unstable and readily degraded by acids, but are quite soluble in organic solvents and may possess useful properties as new materials.

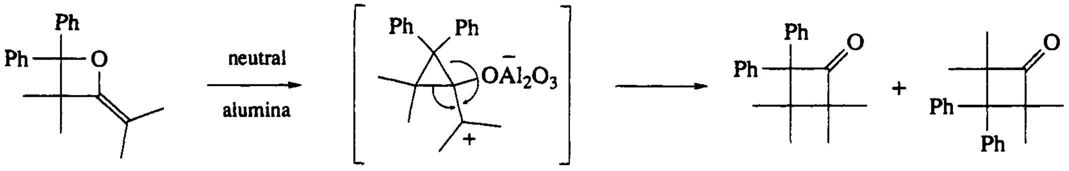

**(111)** **(112a)** **(112b)**

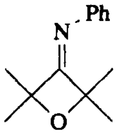

**(113)**

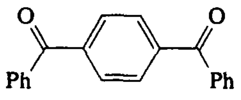

**(114)**

## 2.4.5 THE FURAN–CARBONYL PHOTOCYCLOADDITION

The Paterno–Büchi photocycloaddition reaction[4,5] of various carbonyl compounds to furans was initially investigated by Sakurai[102] in 1965 and was found to afford only the head-to-head photoproducts with high *exo* relative face selectivity. An NMR study by Whipple and Evanega[103] later confirmed the *exo* mode of cycloaddition. Since the time of the original report the photoreaction has been systematically studied by several groups and the 2,7-dioxabicyclo[3.2.0]hept-3-ene ring system has been exploited in several facets of synthesis.

A recent synthesis of 3-substituted furan derivatives illustrates an important application of the furan–carbonyl photocycloaddition.[104] Zamojski has reported the rearomatization of oxetane (**115**) in the presence of *p*-toluenesulfonic acid to 3-furylmethanol derivative (**116**). Synthesis of (**117**), itself a substrate for the intramolecular photocycloaddition reaction (Section 2.4.6), involved a similar rearomatization process (PPTS/$CH_2Cl_2$) and capitalized upon the chemoselectivity observed in the ketone–furan photocycloaddition.[105] Similarly, a synthesis of perillaketone (**118**) by Kawanisi[106] involved irradiation of a carbonyl compound and furan. A complication in the rearomatization is that acid also catalyzes the reversion of the photoadduct to starting materials; to circumvent this problem the photoreaction was run in the presence of acid, so that rearomatization would occur *in situ* and the products of competitive reversion would promptly recombine.

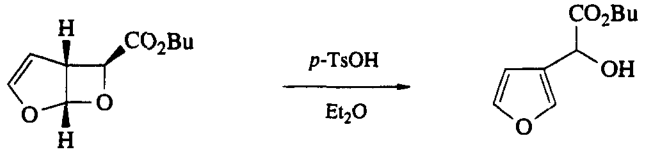

**(±)-(115)** **(±)-(116)**

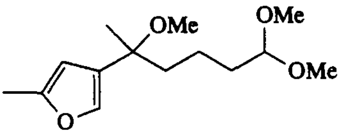

**(117)**

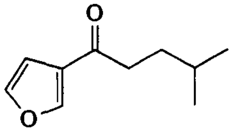

**(118)**

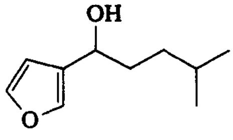

**(119)**

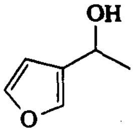

**(120)**

Irradiation of furan with 4-methylpentanal in the presence of methanesulfonic acid gave 3-substituted furans (**119**) and (**120**), the latter formed by Norrish type II cleavage of the starting aldehyde to acetaldehyde and subsequent photocycloaddition and rearomatization. Oxidation of (**119**) with Collins reagent gave the desired perillaketone (**118**).[104] Isomerization of furan–carbonyl photoproducts with Lewis acids, on the other hand, is a more complicated process.[107] Jarosz and Zamojski have found that treatment of bicyclic oxetane (**121**) with $BF_3 \cdot Et_2O$ gave a 16:36:48 mixture of substituted furans (**122**), (**123**) and (**124**), the latter two compounds arising from Lewis acid catalyzed reversion to and subsequent reaction of 2-methylfuran and butyl glyoxylate.

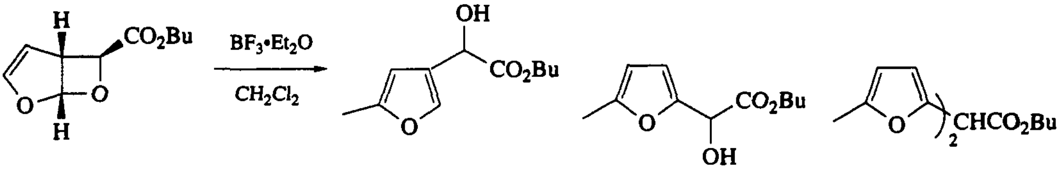

**(121)** **(122)** **(123)** **(124)**

An effort to use the methods of asymmetric synthesis to obtain substituted 3-furylmethanol derivatives in optically active form has been reported by Zamojski.[108] Irradiation of (*R*)-(–)-menthyl glyoxylate and furan gave the *exo* photoproduct (*R*)-(–)-menthyl 2,7-dioxabicyclo[3.2.0]hept-3-ene-6-carboxylate (**125**), which was determined by degradation and comparison with (–)-dimenthyl maleate to have the (*S*)-configuration at C-6. Similarly, irradiation of 8-phenylmenthyl glyoxylate gave oxetane of 15% *ee*.[109] An explanation for the low enantioselectivity has been advanced[108] and is summarized in Scheme 11. Photocycloaddition between furan and alkyl glyoxylates probably occurs in both *exo* and *endo* fashions; however, in the *endo* diradical intermediate (B) a 180° rotation around the C—O bond must occur before oxetane closure occurs. In addition, the *s-trans* (C) and *s-cis* (D) conformations of the glyoxylate system

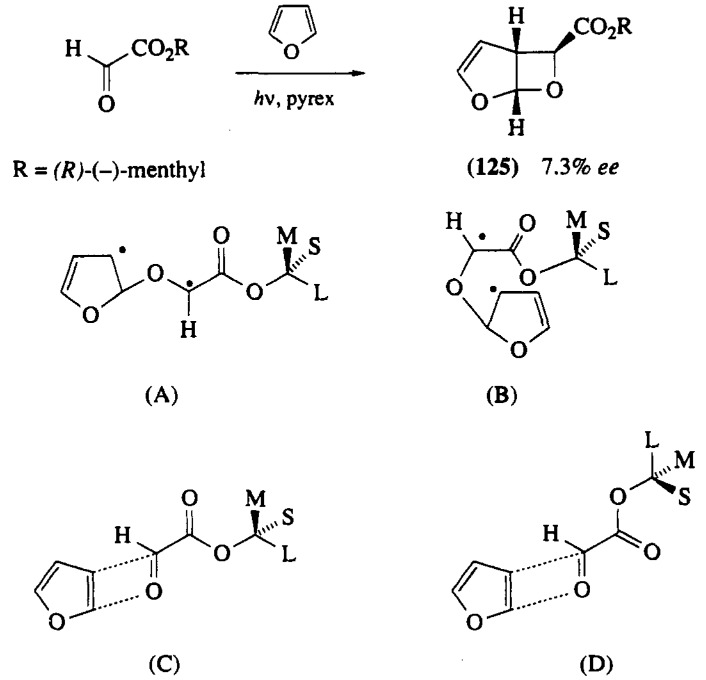

**Scheme 11**

should lead to opposite enantiomers of the bicyclic oxetane if the glyoxylate enters in an *exo* fashion. Although the use of chelation to produce entirely *s-cis* conformers of chiral glyoxylate derivatives may hold promise for asymmetric synthesis in the Paterno–Büchi reaction, the high 'non-chelation' selectivity achieved with chiral phenylmenthyl glyoxylates may suggest alternative explanations for asymmetric induction (Section 2.4.7).

The use of conformationally rigid carbonyl compounds in an attempt to enhance the asymmetric induction in the photocycloaddition has been reported by Zamojski.[110] Irradiation of (*R*)-(–)-menthone (**126**) and subsequent acid-catalyzed rearomatization gave a 2:1 mixture of diastereomeric 3-furyl alcohol derivatives (**127**) resulting from Norrish type I photoisomerization and subsequent Paterno–Büchi cyclization with furan. The major stereoisomer was assigned as in structure (**127**), indicating 1,3-asymmetric induction in accord with Cram's model.[111] The conformationally restricted hexofuranose (**128**) gave four diastereomeric adducts upon irradiation in the presence of furan. Photoproducts (**129**) and (**130**), which result from attack of the furan molecule from the less hindered β-face of (**128**), constituted approximately 75% of the product mixture. The authors suggest the importance of steric factors in this reaction and show how conformationally restricted systems may in certain cases be useful for obtaining asymmetric photoproducts.

The relationship of the furan–carbonyl photocycloaddition to the aldol condensation[16] has been noted in studies by Schreiber and coworkers.[112,121] Scheme 12 shows that the furan is equivalent to a (*Z*)-enolate and that hydrolytic unmasking of the 'photoaldol' adducts affords *threo* aldols of 1,4-dicarbonyl compounds.[113] The cup-shaped *cis*-dioxabicyclo[3.2.0]heptene skeleton of the photoaldol lends control to a variety of reactions wherein electrophilic reagents add to the enol ether on its convex face (Scheme 13). Hydroboration–oxidation [$BH_3$·THF (inverse addition); $H_2O_2$/NaOH] of the photoaldol (**131**) (Scheme 14) gave the 1,3-diol (**132**) in 82% yield, resulting in total stereocontrol over five contiguous chiral centers in a two-step procedure. The stereochemistry of (**132**) was verified by single-crystal X-ray diffractometry of the corresponding bis(*p*-bromobenzoate) derivative (Figure 2).

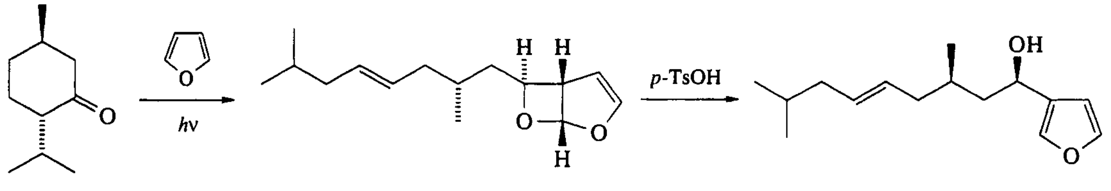

**(126)** **(127)**

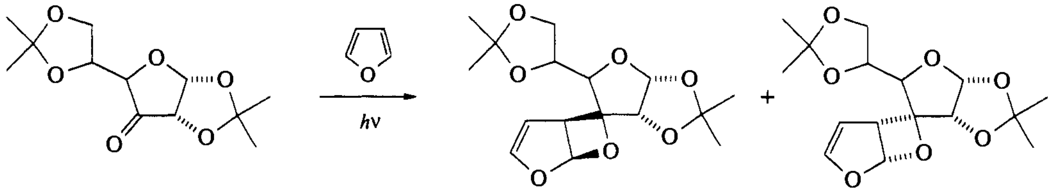

**(128)** **(129)** **(130)**

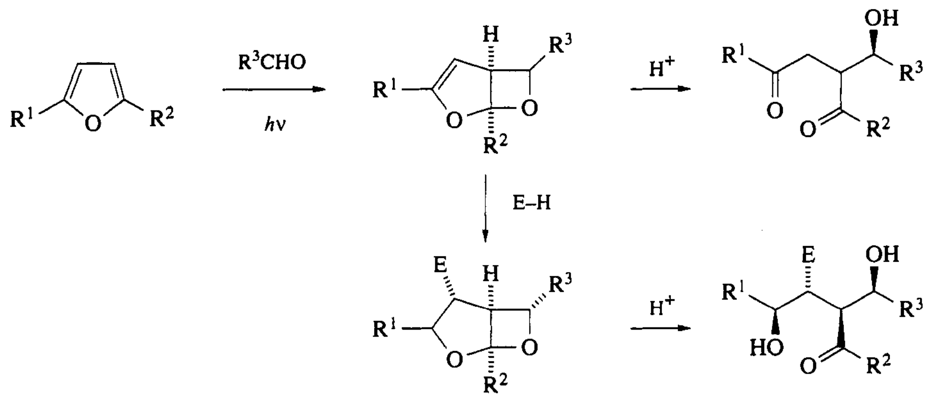

**Scheme 12**

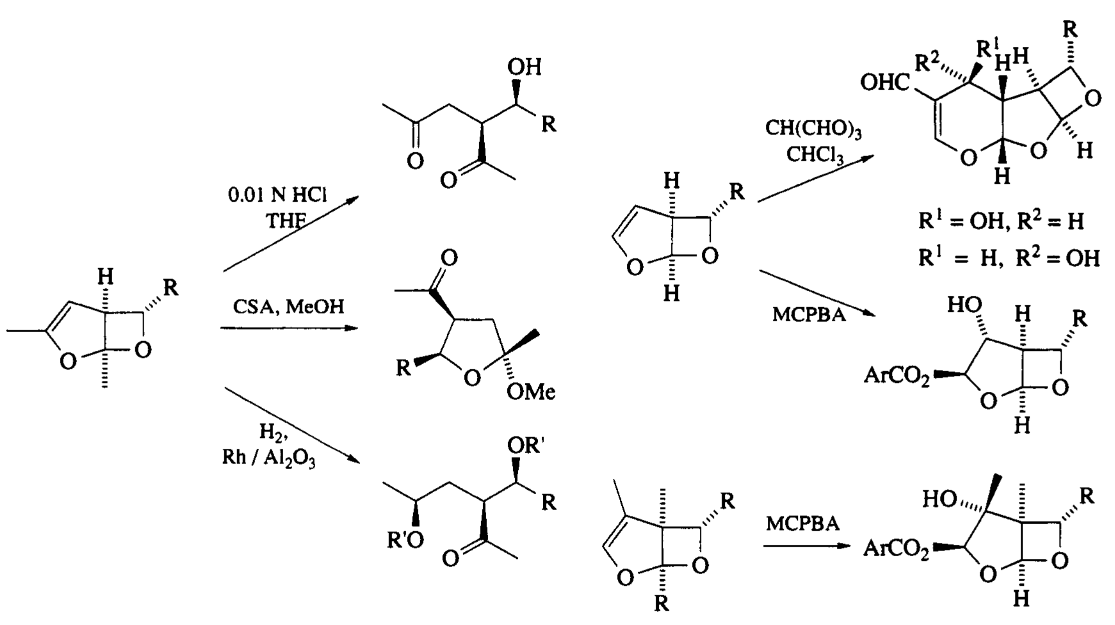

Scheme 13

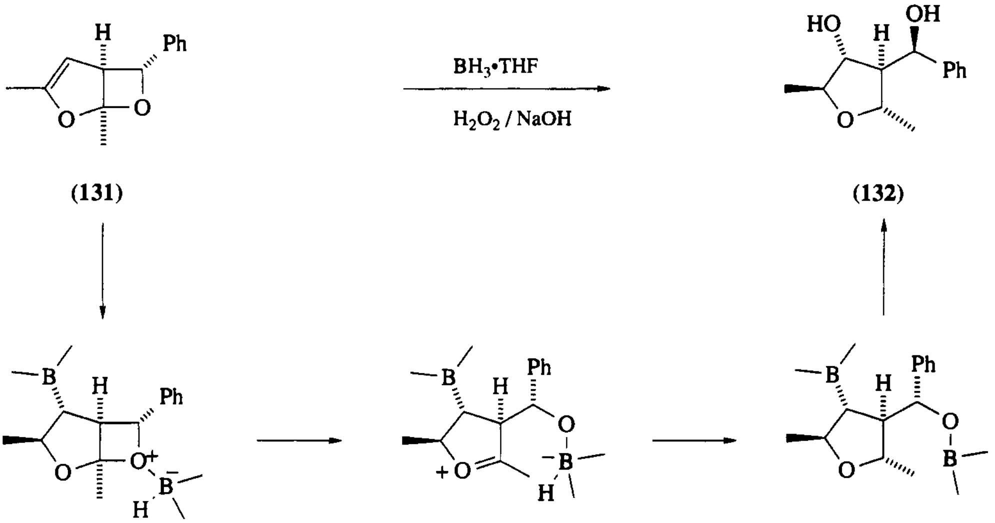

Scheme 14

In addition to the functionalization protocols of Schemes 13 and 14, vinylic substitution reactions involving metalation and palladium-mediated carbon–carbon bond formation have been formulated,[114] which further broaden the variety of structural types available from the Paterno–Büchi reaction. For example, deprotection and stannylation of photoaldol (**133**), followed by refunctionalization of the α-enol ether position of vinylstannane (**134**), gave the substituted oxetane (**135**) in good overall yield. Similar functionalization of bicyclic oxetane (**136**) *via exo*-face dihydroxylation and acid-catalyzed reorganization of the acetal to the protected 3-deoxy-(±)-streptose (**137**) has been reported, which illustrates the synthetic utility of such processes in the synthesis of polyoxygenated materials.[115]

An application of the furan–carbonyl photocycloaddition to the synthesis of the antifungal metabolite (±)-avenaciolide (**146**)[116,121] involved as the first step the photocycloaddition of nonanal to furan on a multigram scale (Scheme 15). Hydrogenation and hydrolysis of the resulting bicyclic oxetane (**138**) gave a butyrolactol derivative (**139**) which was reacted with vinylmagnesium bromide to give a 5:1 mixture of stereoisomeric allyl alcohols (**140**). The two proximal, secondary hydroxy groups were engaged as an acetonide that upon oxidation (PCC, NaOAc) provided aldehyde derivative (**141**). Ozonolysis of (**141**) in MeOH and reductive work-up produced dialdehyde (**142**) that was epimerized *via* 'ancillary stereocontrol' to the equatorial isomer (**143**).[117] Acidification of the dialdehyde acetonide in the same pot de-

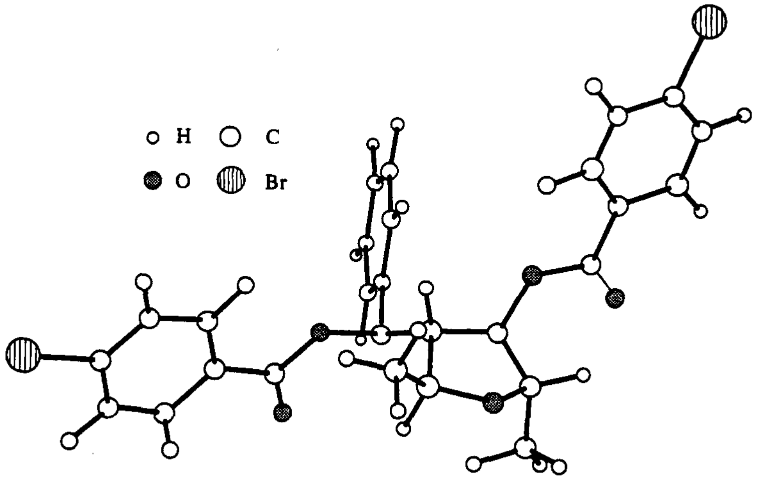

Figure 2

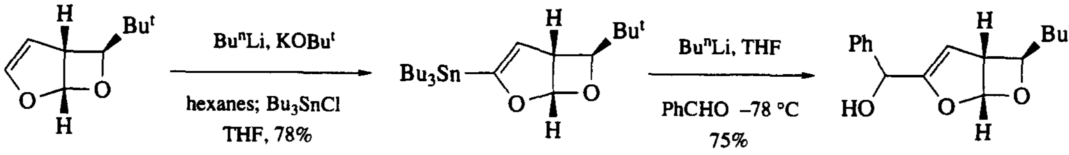

(133) (134) (135) (1:1)

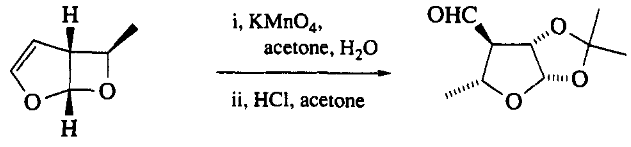

(136) (137)

livered the bis-methoxy lactol (**144**), which was oxidized using Grieco's procedure[118] to the bis-lactone (**145**) in 80% yield. Methylenation of (**145**) gave (±)-avenaciolide (**146**) in 10 steps.

A recent application of the furan–carbonyl photocycloaddition involved the synthesis of the mycotoxin asteltoxin (**147**).[119–121] Scheme 16 shows the synthetic procedure that began with the photoaddition of 3,4-dimethylfuran and β-benzyloxypropanal to furnish photoaldol (**148**), which was epoxidized with MCPBA to afford the functionalized product (**149**) in 50% overall yield. Hydrolysis (THF, 3N HCl) provided the monocyclic hemiacetal which was protected as its hydrazone (**150**). Chelation-controlled addition of ethylmagnesium bromide to the latent α-hydroxy aldehyde (**150**) and acetonide formation produced compound (**151**), which was transformed through routine operations to aldehyde (**152**). Chelation-controlled addition of the lithium salt of pentadienyl sulfoxide (**153**) followed by double 2,3-sigmatropic rearrangement provided (**154**) as a 3:1 mixture of isomers (Scheme 17). Acid-catalyzed cyclization of (**154**) (CSA/$CH_2Cl_2$) gave the bicyclic acetal (**155**), which was transformed in several steps to (±)-asteltoxin (**147**).[120]

The furan–carbonyl photocycloaddition reaction has also been used in the determination of the absolute stereostructure of asteltoxin.[122] The photocycloaddition of D-glyceraldehyde acetonide and 3,4-dimethylfuran gave a 1.2:1.0 mixture of photoproducts (**156**) and (**157**) each obtained in about 54% enantiomeric excess, reflecting the lability of the aldehyde towards racemization under the reaction conditions. The relative configurations of (**156**) and (**157**) were proven by converting the major photoproduct (**156**) (MCPBA/$CH_2Cl_2$ followed by hydrolysis) to the bis-tetrahydrofuran (**159**) (Scheme 18). The *cis* relationship of hydroxyl and acetoxymethyl substituents at C-5 and C-6 was proved by comparison of the coupling constant ($J_{5,6}$ = 2.2 Hz) with related compounds prepared in the racemic synthesis.[120] Treatment of (**158**) under previously described conditions gave bis-tetrahydrofuran (**160**); comparison of opti-

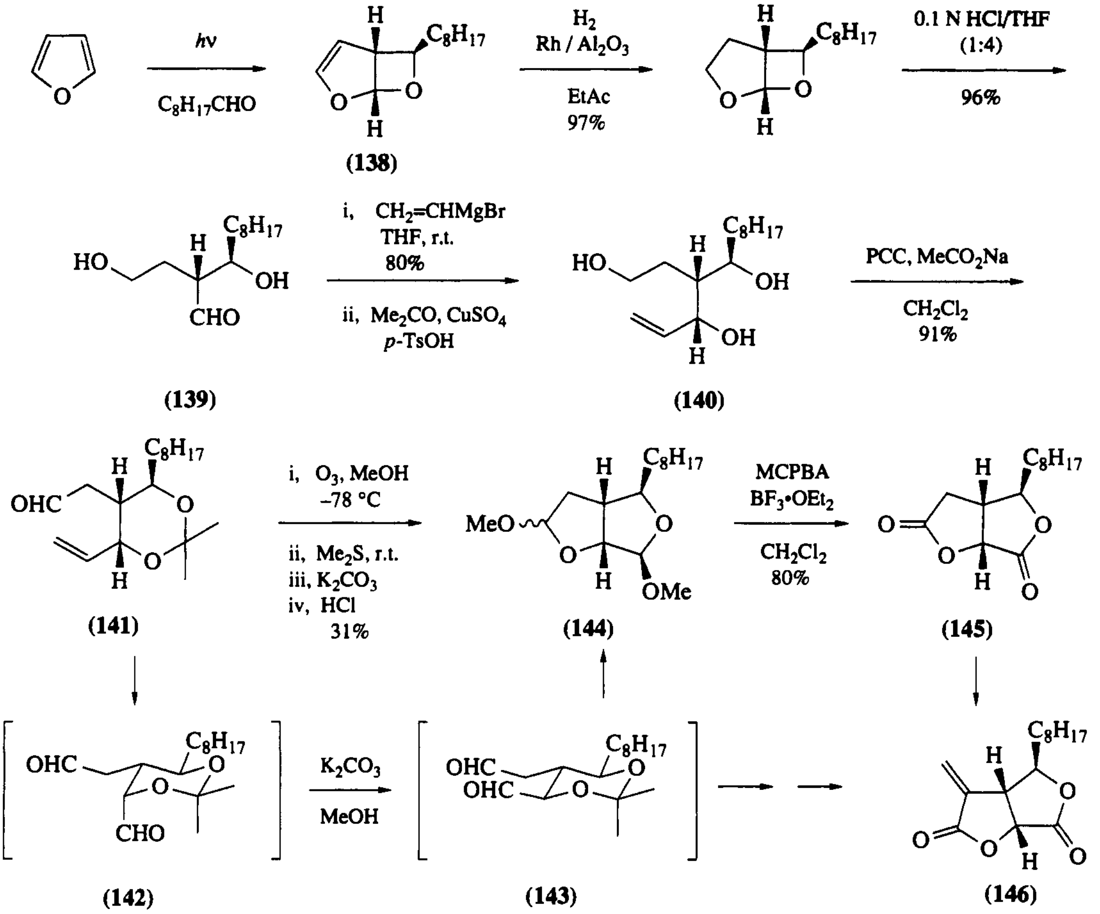
hv
C8H17CHO
(138)
H2
Rh / Al2O3
EtAc
97%
0.1 N HCl/THF
(1:4)
96%
(139)
i, CH2=CHMgBr
THF, r.t.
80%
ii, Me2CO, CuSO4
p-TsOH
(140)
PCC, MeCO2Na
CH2Cl2
91%
(141)
i, O3, MeOH
-78 °C
ii, Me2S, r.t.
iii, K2CO3
iv, HCl
31%
(144)
MCPBA
BF3•OEt2
CH2Cl2
80%
(145)
(142)
K2CO3
MeOH
(143)
(146)

Scheme 15

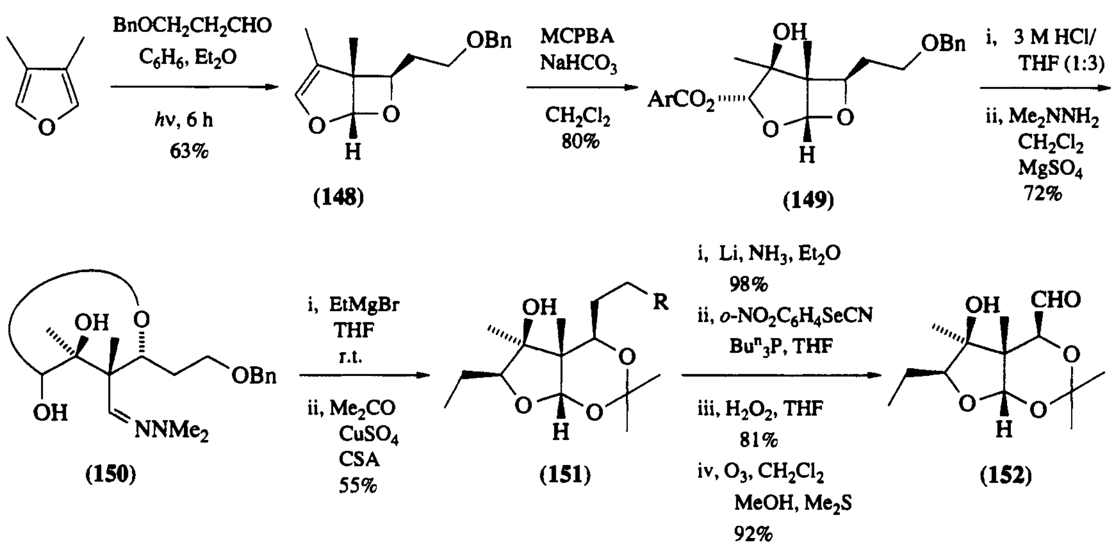
BnOCH2CH2CHO
C6H6, Et2O
hv, 6 h
63%
(148)
MCPBA
NaHCO3
CH2Cl2
80%
ArCO2
(149)
i, 3 M HCl/
THF (1:3)
ii, Me2NNH2
CH2Cl2
MgSO4
72%
(150)
i, EtMgBr
THF
r.t.
ii, Me2CO
CuSO4
CSA
55%
(151)
i, Li, NH3, Et2O
98%
ii, o-NO2C6H4SeCN
BunP3, THF
iii, H2O2, THF
81%
iv, O3, CH2Cl2
MeOH, Me2S
92%
(152)

Scheme 16

cal rotation values with an identical sample prepared by degradation of asteltoxin demonstrated that the absolute configuration of asteltoxin is as drawn in structure (**161**).

In synthetic studies directed toward the synthesis of the antileukemic cembranolide isolobophytolide (**162**),[123] the photocycloaddition of 2,5-bis(hydroxymethyl)furan and β-*t*-butyldimethylsiloxybutanal

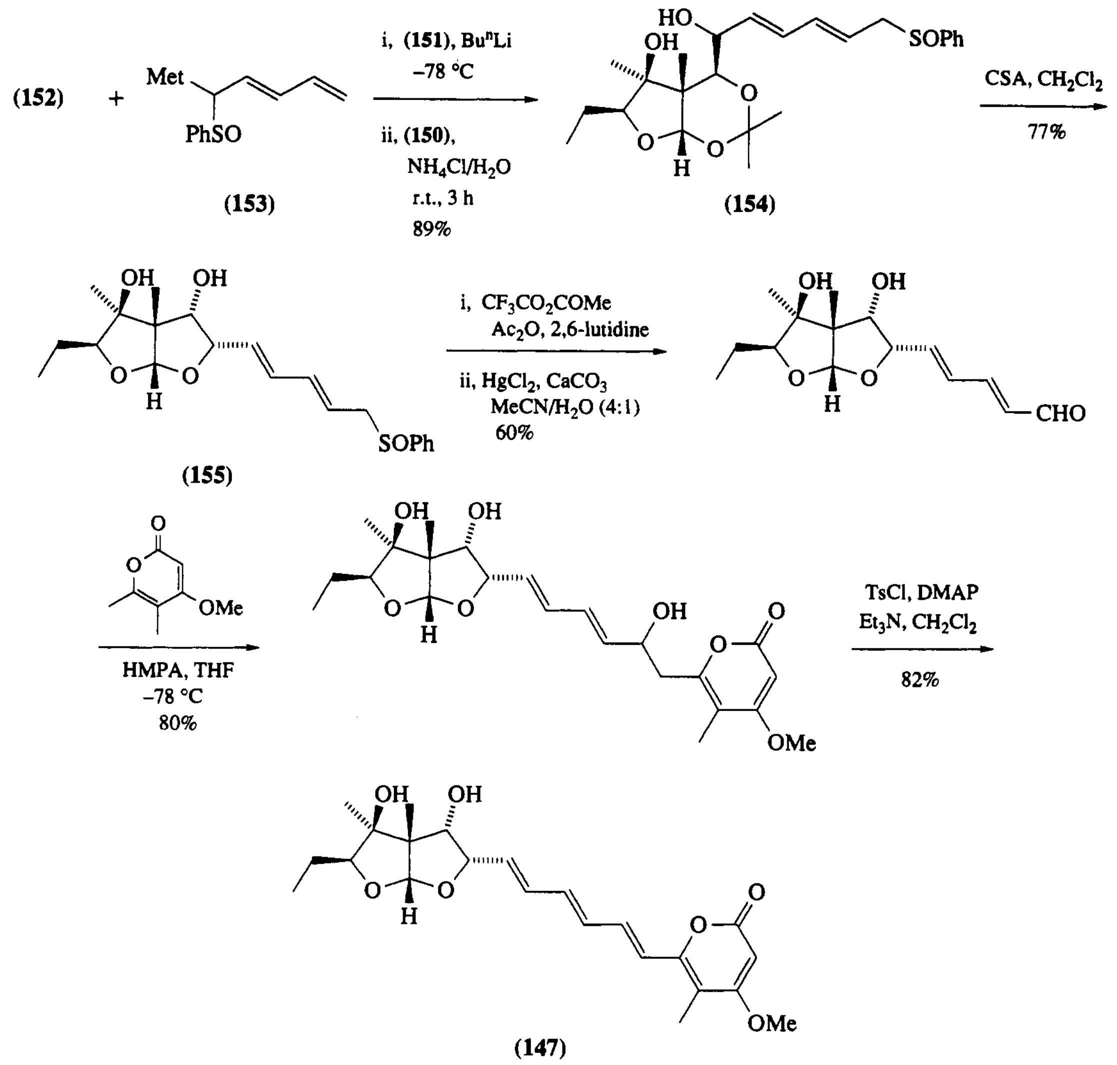
(152)
+
Met
PhSO
(153)
i, (151), BunLi
-78 °C
ii, (150),
NH4Cl/H2O
r.t., 3 h
89%
HO
OH
SOPh
O
O
O
H
(154)
CSA, CH2Cl2
77%
OH
OH
O
O
H
SOPh
(155)
i, CF3CO2COMe
Ac2O, 2,6-lutidine
ii, HgCl2, CaCO3
MeCN/H2O (4:1)
60%
OH
OH
O
O
H
CHO
O
O
OMe
HMPA, THF
-78 °C
80%
OH
OH
O
O
H
OH
O
O
OMe
TsCl, DMAP
Et3N, CH2Cl2
82%
OH
OH
O
O
H
O
O
OMe
(147)

Scheme 17

proceeded smoothly (53%) in tetrahydrofuran on multigram scale and provided, after acetylation, the photoaldol product (**163**) (Scheme 19).[105,124] The reaction proceeds with normal *exo* selectivity but results in a mixture of diastereomers by virtue of the lack of facial selectivity in the addition of chiral aldehydes. Hydrogenation of the enol ether from the convex face using Rh/$Al_2O_3$ minimized competing hydrogenolysis of the allylic acetate, a process that was problematic when palladium- and platinum-based catalysts were used. Subsequent hydrolysis of the photoproduct, acetylation and Wittig methylenation afforded the acyclic derivative (**164**), which contains three of the four stereocenters present in isolobophytolide. A series of protecting group interconversions and routine transformations parlayed (**164**) into epoxy bromide (**165**), which was alkylated with an allylic selenide anion to afford epoxy selenide (**166**). The seco derivative (**166**) contains all the carbons and stereocenters present in the natural

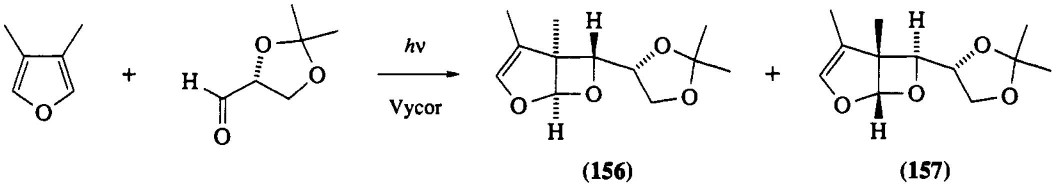
O
+
H
O
O
O
hν
Vycor
H
O
O
O
O
H
(156)
+
H
O
O
O
O
H
(157)

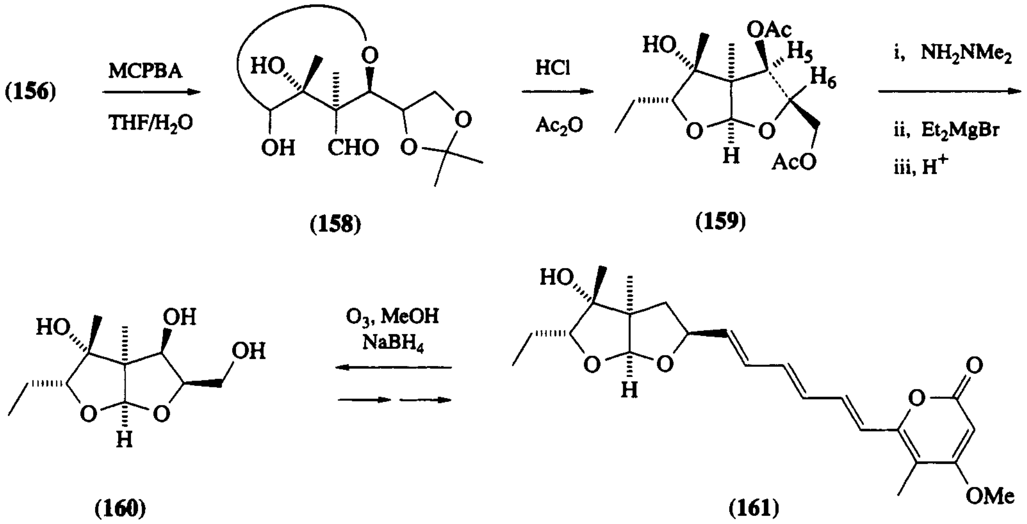
(156)
MCPBA
THF/H$_2$O
HO
O
OH
CHO
O
O
(158)
HCl
Ac$_2$O
HO
OAc
H$_5$
H$_6$
O
O
H
AcO
(159)
i, NH$_2$NMe$_2$
ii, Et$_2$MgBr
iii, H$^+$
HO
OH
OH
O
O
H
(160)
O$_3$, MeOH
NaBH$_4$
HO
O
O
H
O
O
OMe
(161)

**Scheme 18**

product. Unfortunately, conditions to effect the ring closure that will be required in order to complete the cembranolide synthesis have not yet been discovered.

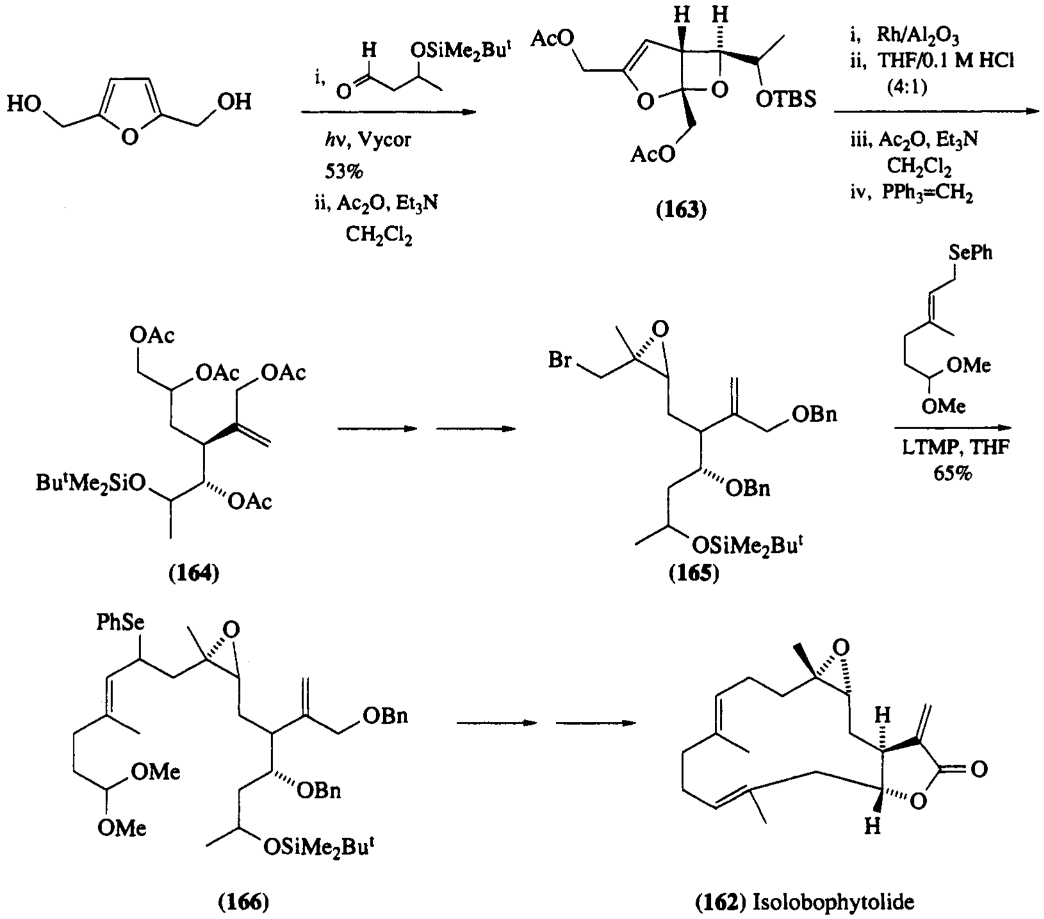
HO
O
OH
i, H OSiMe$_2$Bu$^t$
O
*hv*, Vycor
53%
ii, Ac$_2$O, Et$_3$N
CH$_2$Cl$_2$
AcO
H H
O
O
OTBS
AcO
(163)
i, Rh/Al$_2$O$_3$
ii, THF/0.1 M HCl
(4:1)
iii, Ac$_2$O, Et$_3$N
CH$_2$Cl$_2$
iv, PPh$_3$=CH$_2$
OAc
OAc
OAc
Bu$^t$Me$_2$SiO
OAc
(164)
Br
O
OBn
OBn
OSiMe$_2$Bu$^t$
(165)
SePh
OMe
OMe
LTMP, THF
65%
PhSe
O
OBn
OMe
OMe
OBn
OSiMe$_2$Bu$^t$
(166)
O
H
O
O
H
(162) Isolobophytolide

**Scheme 19**

One limitation encountered in synthetic studies of this reaction is the lack of chemoselectivity in the addition of aldehydes to unsymmetrically substituted furans. For example, the photochemical addition of benzaldehyde to 2-methylfuran provides a 1:3:1 mixture of oxetanes resulting from the *exo* addition of aldehyde to the more and less substituted alkenes, respectively. Ketone photocycloadditions are more selective. For instance, irradiation of 2-butanone and furan forms a 7:1 mixture of regioisomeric oxetanes (**167**) and (**168**) (1:1 mixture of epimers).

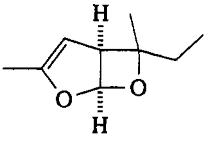

**(167)**

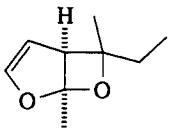

**(168)**

A recent use of silyl- and stannyl-substituted furans[125] in the photocycloaddition reaction has resulted in the short synthesis of a ginkgolide B–kadsurenone hybrid, potential antagonists of the platelet activating factor (PAF) (Scheme 20). Photoaddition of 2-tributylstannylfuran and *n*-butyl glyoxylate resulted in the formation of a single photoproduct (**169**). A Stille coupling[126] of bromoveratrole [$Pd(PPh_3)_4$/THF] produced the arylated dihydrofuran (**170**), which was hydrolyzed[112] to an unstable keto-aldehyde. Chemoselective reduction of this species using conditions described by Luche[127] resulted in the formation of a mixture of lactol isomers (**171**). Treatment of this mixture with Otera's distannoxane transesterification catalyst (toluene, 50 °C)[128] afforded a separable mixture of bicyclic compounds (**172**) and (**173**). These studies illustrate the use of a main group metal both to direct the site of addition and to participate in a transition metal catalyzed coupling reaction. In this fashion, the inherent lack of chemoselectivity of photochemically excited aldehydes in their addition to unsymmetrical furans can be overcome.

The stereoselective synthesis of unsaturated oxetanes has recently been achieved by Feigenbaum and coworkers.[129] Previous studies have indicated that photochemical *cis–trans* isomerization of enals is rapid and results in the formation of equivalent amounts of stereoisomeric alkene adducts.[105,116] For example, irradiation of *trans*-crotonaldehyde and 2,6-dimethylfuran produced a 1:1 mixture of alkenic isomers (**174**) and (**175**) in 64% yield. Irradiation of 4-trimethylsilylbutyn-2-one and furan[129] provided with 5:1 stereoselectivity the bicyclic oxetane (**176**) in which the methyl group occupies the *exo* position, presumably because of the small steric requirement of the triple bond. Desilyation of the protected alkyne produced an alkynic oxetane which was hydrogenated under Lindlar conditions to bicyclic vinyloxetane (**177**); attempts to use the unprotected butyn-2-one gave low isolated yields of oxetane because of extensive polymerization. The stereochemical outcome thus broadens previous alkynyloxetane syntheses[75,78] and makes possible the preparation of new oxetane structures that may be synthetically useful.

Recent work by Cantrell[130] extends the range of possible carbonyl addends in the furan–carbonyl photocycloaddition to include arenecarboxylic acid esters. For example, irradiation through Vycor of methyl benzoate and excess furan gave a mixture of alkoxyoxetane (**178**) and enol formate (**179**). Prolonged irradiation led to the predominant formation of product (**179**), most likely through a photo-induced [2 + 2] cycloreversion process. In the reaction of 2,5-dimethylfuran with methyl benzoate, an (*E*/*Z*) mixture of product (**181**) amounted to 44% of the product mixture, indicating possible intervention of a photochemically allowed suprafacial 1,7-sigmatropic rearrangement of (**180**).

Andrews and Feast[131] have described a further application of the Paterno–Büchi reaction in which furans are used in step-growth polymerization. Irradiation of *m*-dibenzoylbenzene and furan produced the monomeric 2:1 adduct (**182**), which was polymerized further with *m*-dibenzoylbenzene to produce polymers containing isomeric oxetane units. The step-growth polymerization in this case was limited by low monomer solubility, slow oxetane formation, and hydrogen abstraction processes that led to crosslinking.

In addition to furan, other heterocycles have been examined.[105] Thiophene undergoes efficient photocycloaddition with benzaldehyde to afford a single *exo* photoproduct (**183**) in 60% yield. As reported by Jones and coworkers,[132] the photolysis of *N*-methylpyrrole in the presence of aldehydes or ketones yields the corresponding 3-hydroxyalkyl derivative (**184**), even when the reaction mixture is free from any trace of acid. In order to use the pyrrole nucleus for stereoselective alkaloid synthesis (*cf.* caesalpinine, **185**)[133] in the fashion developed with the furan nucleus, pyrrole substituents that stabilize the presumed intermediate bicyclic oxetane must be discovered.

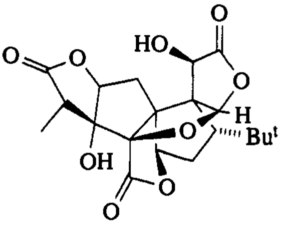

Ginkgolide B

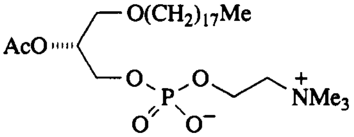
AcO
O(CH$_2$)$_{17}$Me
P
O$^-$
$\overset{+}{N}$Me$_3$

Platelet activating factor

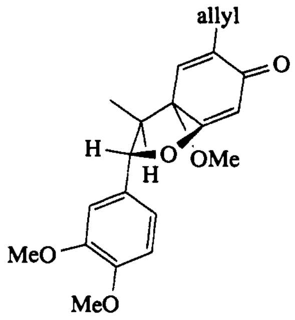
allyl
O
H
OMe
MeO
MeO

Kadsurenone

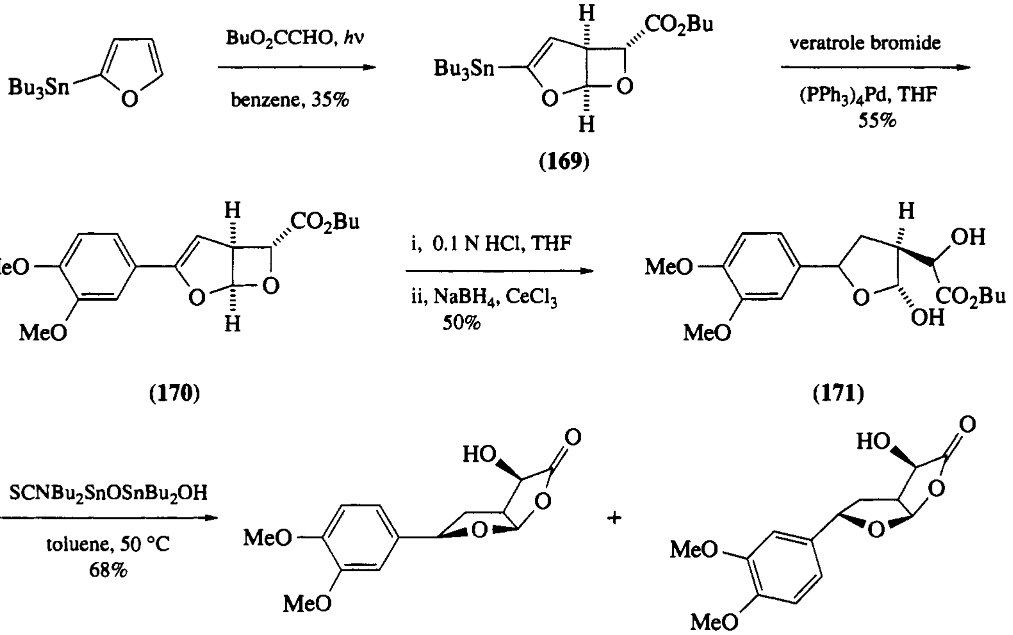
Bu$_3$Sn
BuO$_2$CCHO, *h*ν
benzene, 35%
CO$_2$Bu
veratrole bromide
(PPh$_3$)$_4$Pd, THF
55%
MeO
i, 0.1 N HCl, THF
ii, NaBH$_4$, CeCl$_3$
50%
OH
SCNBu$_2$SnOSnBu$_2$OH
toluene, 50 °C
68%
HO
+

(169)

(170)

(171)

(172)

(173)

**Scheme 20**

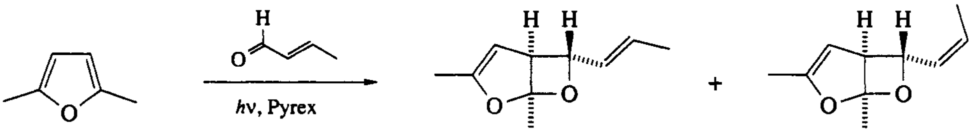
H
O
*h*ν, Pyrex
H H
+

(174)

(175)

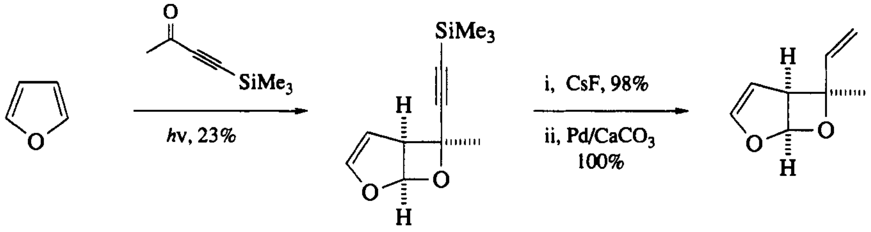
O
SiMe$_3$
*h*ν, 23%
H
i, CsF, 98%
ii, Pd/CaCO$_3$
100%

(176)

(177)

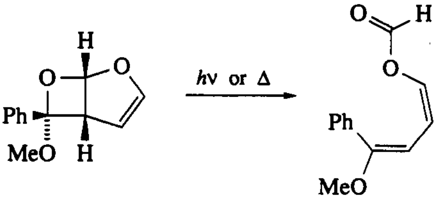

(178) (179)

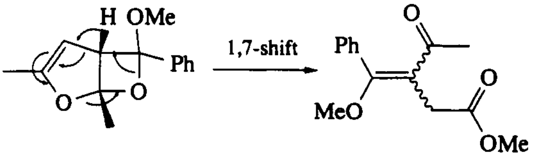

(180) (181)

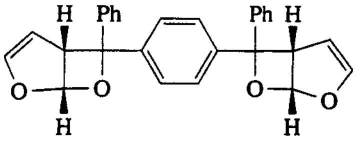

(182)

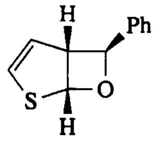

(183)

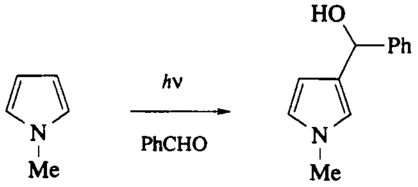

(184)

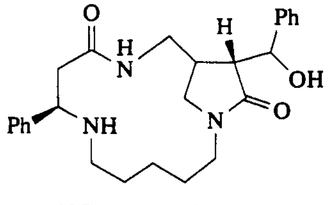

(185) Caesalpinine

### 2.4.6 THE INTRAMOLECULAR PATERNO–BÜCHI PHOTOCYCLOADDITION

The intramolecular attack of an excited carbonyl on an alkene can occur to provide oxetane products, even in cases when the corresponding intermolecular reaction is unsuccessful. Thus the intramolecular reaction surely benefits from favorable entropic considerations. Jones[4] and Carless[5] have summarized the scope and utility of intramolecular Paterno–Büchi photocycloadditions. There is general agreement that successful implementation of an intramolecular reaction requires that the Norrish type II photoreactions[134] and other hydrogen abstraction processes be overcome. In addition, the intramolecular reaction provides access to polyoxygenated ring systems that can exhibit remarkable properties because of their strain.

Early reports by Kossanyi and coworkers[135] illustrate the variety of strained products that can be obtained from intramolecular photoreactions. For example, irradiation of 2-allylcyclohexanone gave a mixture of (**186**; 32%), (**188**; 22%) and (**189**; 14%), the latter two arising presumably from decomposition of the strained tricyclic oxetane (**187**). In a related azulene synthesis,[136] Kossanyi obtained high yields of oxetanes (**190**) and (**191**), the latter comprising 80% of the reaction mixture. When thermolyzed, compound (**191**) formed a mixture of isomeric dihydroazulene compounds that could be dehydrogenated ($Pd/Al_2O_3$) to form azulenes.

Engel has reported[137] the synthesis of the strained oxetane (**193**) from the β,γ-unsaturated ketone (**192**), the reaction being facilitated by the high π-electron density of the alkene and a flexible tether, which allows the alkene π- and oxygen *n*-orbitals to become coplanar. A similar oxetane product (**194**) has been made by Cookson and Rogers.[138] Smith and Dieter[139] have reported the chemoselective formation of oxetane (**196**) from ketoalkene precursor (**195**), in which geometrical constraint leads to selective

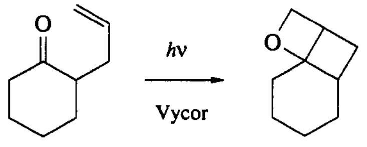

**(186)**

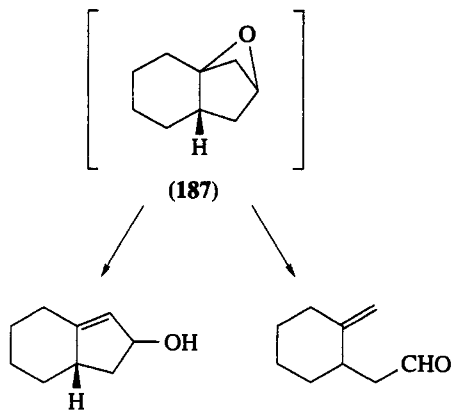
O
H
(187)
OH
H
CHO

**(188)** **(189)**

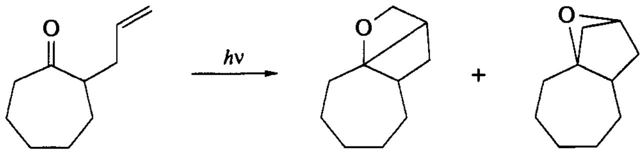

**(190)** **(191)**

reaction at the remote γ,δ-alkenic site. The curious formation of oxetane (**198**) in the course of a synthesis of 2,4-methanoproline derivative (**197**)[140,141] further attests to the ability of the intramolecular Paterno–Büchi reaction to form oxetane rings more strained than could likely be formed in an intermolecular reaction.

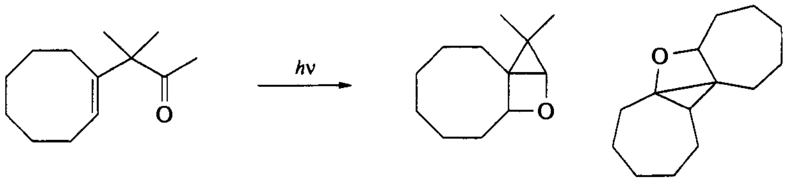

**(192)** **(193)** **(194)**

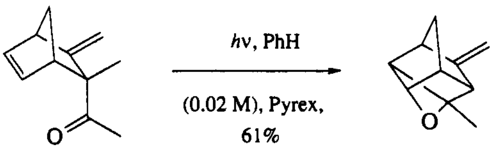
O
hv, PhH
(0.02 M), Pyrex,
61%
O

**(195)** **(196)**

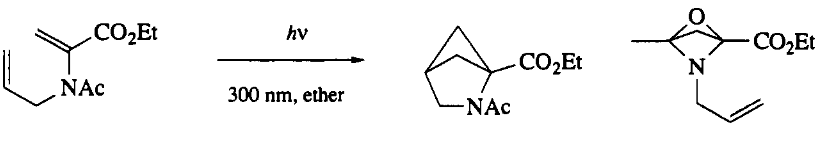
CO2Et
NAc
hv
300 nm, ether
CO2Et
NAc
O
CO2Et
N

**(197)** **(198)**

Several reports of transannular Paterno–Büchi photocyclizations have been documented.[142,143] Mihailovi has demonstrated that cholesterol can be hydroxylated indirectly but stereoselectively at C-1 through a Paterno–Büchi reaction, thus allowing access to vitamin $D_3$ analogues.[143] Scheme 21 illustrates the procedure in which the A–B ring fusion of alcohol (**199**) was first cleaved *via* photochemical hypoiodite fragmentation to give ketone (**200**). This material was then irradiated in acetone to provide in 42% overall yield the oxetane (**201**), which was converted directly to 1α-hydroxycholesterol 3-acetate (**202**) by acid-catalyzed ring openings. The sequence is notable for its ability to functionalize cholesterol efficiently and with useful chemoselectivity. On a related terpenoid system, Adam and Sung[144] used Norrish type I photocleavage and subsequent photocycloaddition of gibberellin C derivative (**203**) to construct the strained oxetane (**204**). Acid-catalyzed ring opening of (**204**) delivers the C-11 hydroxylated gibberellin derivative (**205**), in which nucleophilic attack has occurred stereospecifically with inversion at C-8.

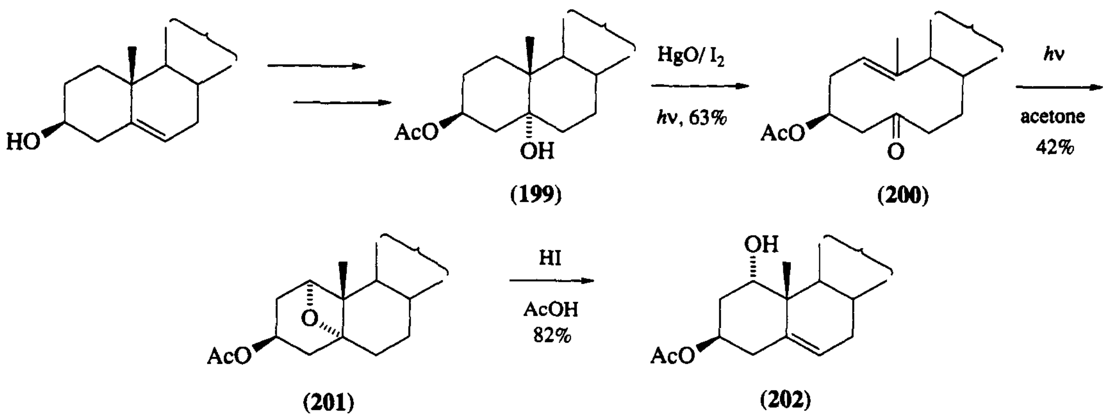

Scheme 21

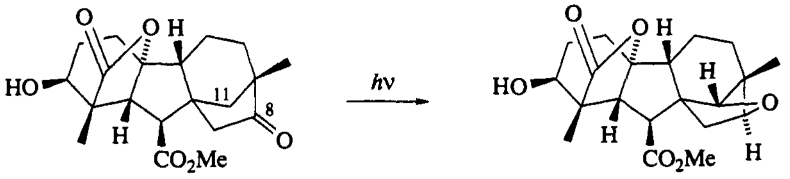

**(203)** **(204)**

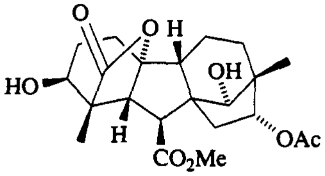

**(205)**

The intramolecular photocycloaddition has been used in the synthesis of medium and large ring compounds. Carless has described a photochemical route[145] to an analog of the thromboxane $A_2$ ring system.[146] Irradiation of vinyloxy ketone (**206**) in benzene gave 11% of (**207**) and 54% of the orientational isomer (**208**). Unlike thromboxane $A_2$,[7] the dioxaoctane (**207**) was stable towards methanol but reacted readily with nucleophiles under acidic conditions. The need for *gem*-disubstitution γ to the carbonyl group for a successful photoreaction was established by irradiation of the demethyl version (**206**), in which Norrish type II photoreactions dominated, illustrating a further limitation of the intramolecular process. In a similar manner, Carless[147] has synthesized the cyclic acetal (**211**) by irradiating seco derivative (**209**) to give the 2-alkoxyoxetane (**210**) which undergoes rapid reaction with MeOH/TFA. Photoaddition of shorter-chain ketone (**212**), on the other hand, gave a 1:1 mixture of oxetane products (**213**) and (**214**) in high yield. In these examples it is worth noting that there are no γ hydrogens, which precludes any Norrish type II photocleavage process. However, a related photochemical synthesis of tetrahydrofuranol and tetrahydrapyranol derivatives uses the Norrish type II photoreaction in the abstraction of δ and ε hydrogens to form useful oxygen heterocycles.[148]

The secochamigrane sesquiterpene laureacetal-C (**215**)[149] provides a fitting introduction to the synthetic applications available to the intramolecular furan–carbonyl photocycloaddition. Initial investigations by Schreiber and Hoveyda used 3-substituted furans as substrates, and many of these were available themselves through the intermolecular photoaldol reaction (Section 2.4.5).[105] For example, irradiation of

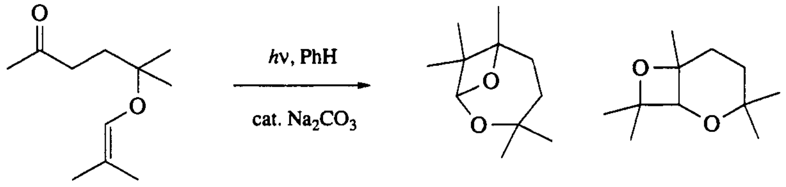

**(206)** **(207)** **(208)**

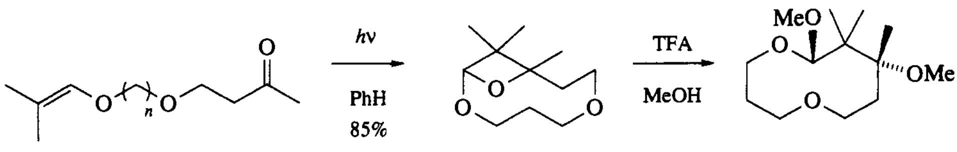

**(209)** $n = 3$ **(210)** **(211)**
**(212)** $n = 2$

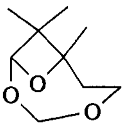

**(213)**

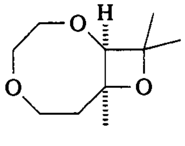

**(214)**

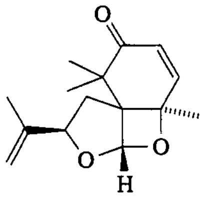

**(215)**

a 0.1 M solution of furyl aldehyde (**217**) in Pyrex gave as major products the oxetanes (**218**) and (**219**) in a 3:2 mixture (Scheme 22), with Norrish cleavage occurring to the extent of only about 10%. Aldehyde (**216**), on the other hand, gave solely Norrish type II cleavage, illustrating the dramatic effect of substitution. In a study of five-membered ring carbocycle formation, aldehyde (**220**) was irradiated and formed a single stereoisomeric photoadduct (**221**) in 42% yield (*ca.* 5% Norrish cleavage). By comparing the expected diradical intermediates (eight- *versus* seven-membered rings), the increased yield (**221**) relative to (**219**/**218**) can be understood. Even the highly strained product (**223**) could be obtained by irradiation of (**222**), presumably because of the ready formation of a six-membered ring intermediate diradical.

Synthesis of similarly strained β-lactam products has been reported by Aoyama and coworkers.[150] Asymmetric induction by an α-furyl stereocenter was demonstrated by irradiation of compound (**224**) in benzene to form photoproduct (**227**) as a single stereoisomer (Scheme 23). Molecular models indicate that the transition state leading to the alternative stereochemistry (**228**) would be destabilized by steric interaction between the MOM ether and ketal hydrogen,[151] which may explain the high degree of facial selectivity in the reaction. The suggestion was made that the initial carbon–oxygen bond formation is reversible.[105] Although diradicals (**225**) and (**226**) may be formed with little selectivity, the rate of coupling of diradical (**226**) is expected to be considerably slower than that of diradical (**225**).

In contrast to intermolecular photoaldols, which can be manipulated with facility, intramolecular cycloadducts undergo retro-[2 + 2] cycloaddition when subjected to hydrolytic conditions. In an alternative protocol, oxymercuration of (**229**) afforded α-mercurio ketone (**230**; 42%) which was acetylated under standard conditions to provide 1,4-diketone (**231**) quantitatively.[152] Similarly, epoxidation of (**229**) provided functionalized photoaldol (**232**), which was hydrolyzed and acetylated to form α-acetoxy derivative (**233**). Finally, hydrolysis of (**234**) (4:1 THF/0.1 N HCl) gave lactol (**235**) in nearly quantitative yield, illustrating the utility of the intramolecular furan carbonyl photocycloaddition in spirocycle formation.

Intramolecular Paterno–Büchi reactions of imides with alkenes provide some interesting examples of oxetane formation and rearrangement.[153] Photolysis of cyclic imide (**236**) gave quantitatively oxetane (**237**) which, upon treatment with aqueous acid, underwent fragmentation to amide (**238**), illustrating a potentially useful medium-membered ring synthesis.[154] Mazzocchi has reported[155] that irradiation of an acetonitrile solution of the phthalimide (**239**) produces (**240**), possibly through an oxetane intermediate. A similar photolysis[156] of substrate (**241**) in 8:1 MeCN/$H_2O$ gave, in a 17:43 ratio, δ H-abstraction product (**243**) and spiroazepinedione (**244**), both resulting from initial intramolecular formation of an oxe-

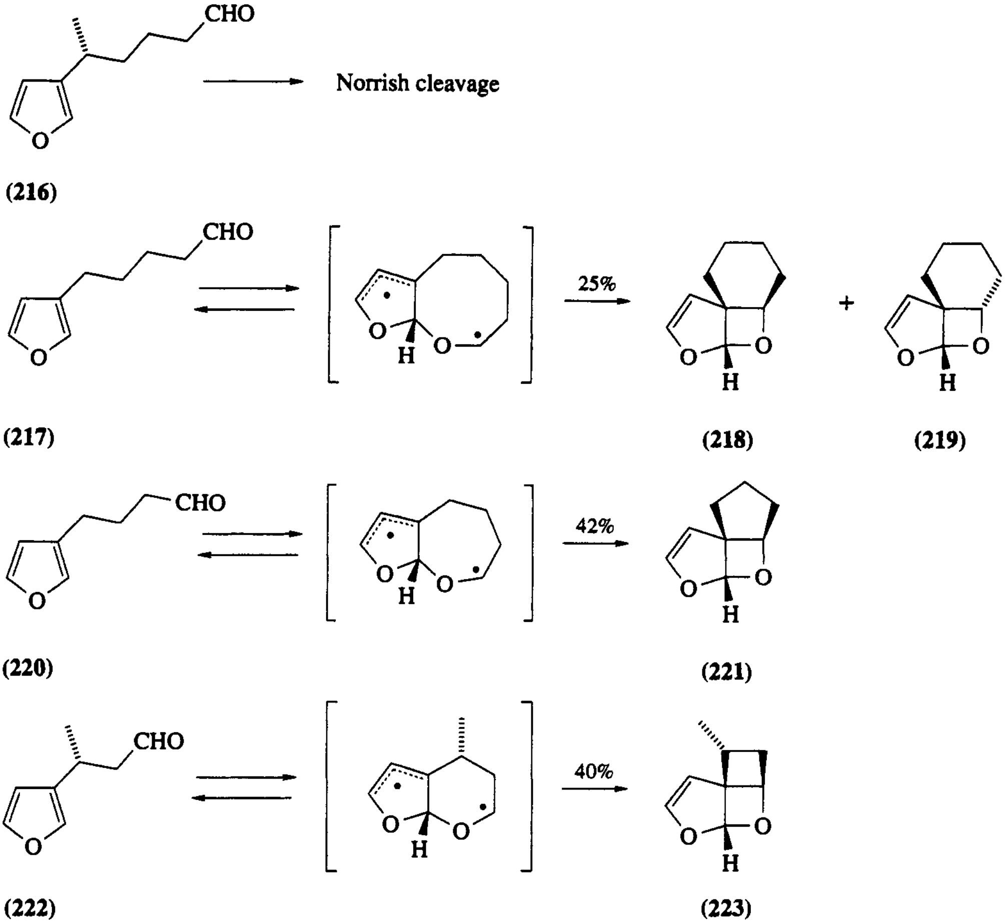
CHO
Norrish cleavage
(216)
CHO
25%
+
(217)
(218)
(219)
CHO
42%
(220)
(221)
CHO
40%
(222)
(223)

Scheme 22 Efficiency of intramolecular photocycloadditions

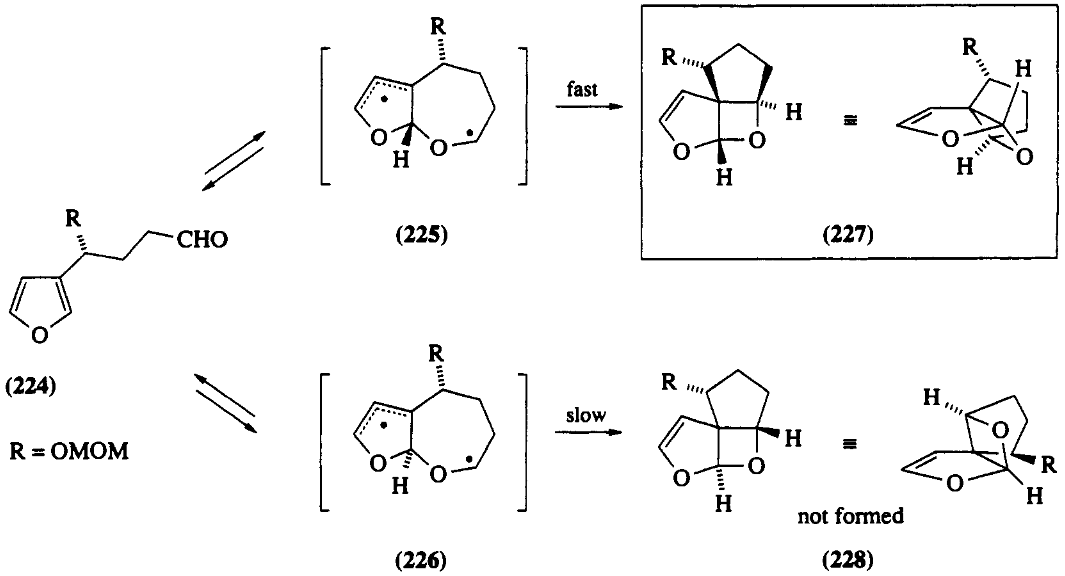
R
fast
R
H
(225)
(227)
R
CHO
(224)
R = OMOM
slow
not formed
(226)
(228)

Scheme 23 Intramolecular photocycloaddition: asymmetric induction

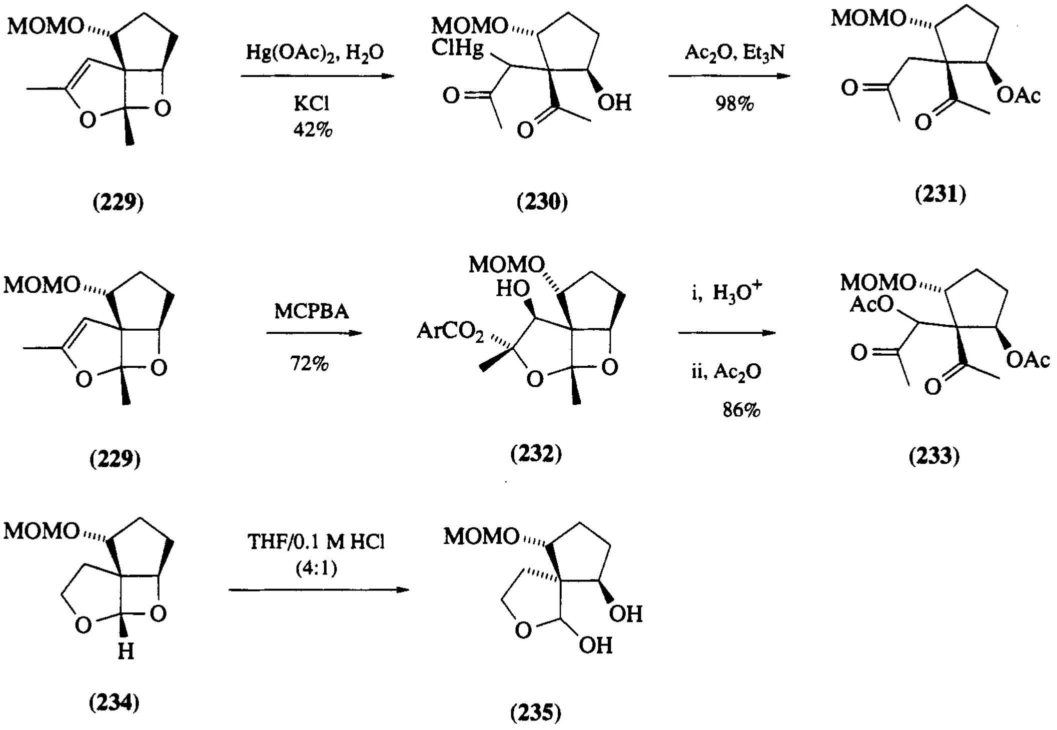
(229)
Hg(OAc)2, H2O
KCl
42%
(230)
Ac2O, Et3N
98%
(231)
(229)
MCPBA
72%
(232)
i, H3O+
ii, Ac2O
86%
(233)
(234)
THF/0.1 M HCl
(4:1)
(235)

**Scheme 24** Functionalization of intramolecular photoproducts

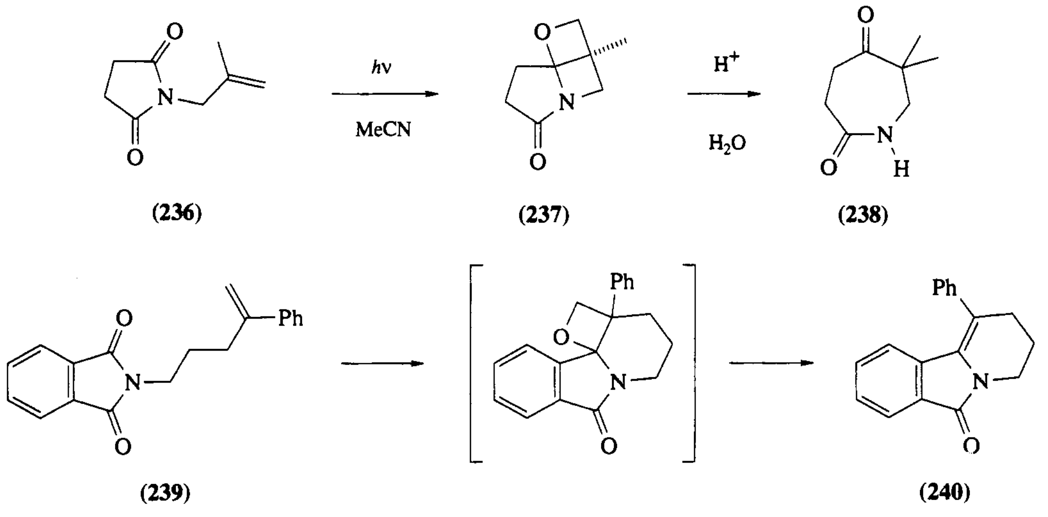
hν
MeCN
H+
H2O
(236)
(237)
(238)
(239)
(240)

tane, followed by heterolytic cleavage and transannular ring-opening of spiroazetidine intermediate (**242**).

## 2.4.7 EXCITED-STATE ASYMMETRIC SYNTHESIS[157] USING THE PATERNO–BÜCHI PHOTOCYCLOADDITION

In a previous section (Section 2.4.5), it was noted that the photoreaction of aldehydes containing an asymmetric center adjacent to the carbonyl with furan results in the production of a 1:1 ratio of two *exo* photoproducts. Irradiation of 2-phenylpropanal and furan results in a nearly quantitative yield of *exo* photoproducts (**245**) and (**246**) in approximately a 1:1 ratio. This suggests a mechanism that is insensitive to the substitution pattern of the aldehyde; one such mechanism is depicted in Scheme 25. Reaction of an excited carbonyl and the electron-rich furan proceeds with initial carbon–oxygen bond formation to pro-

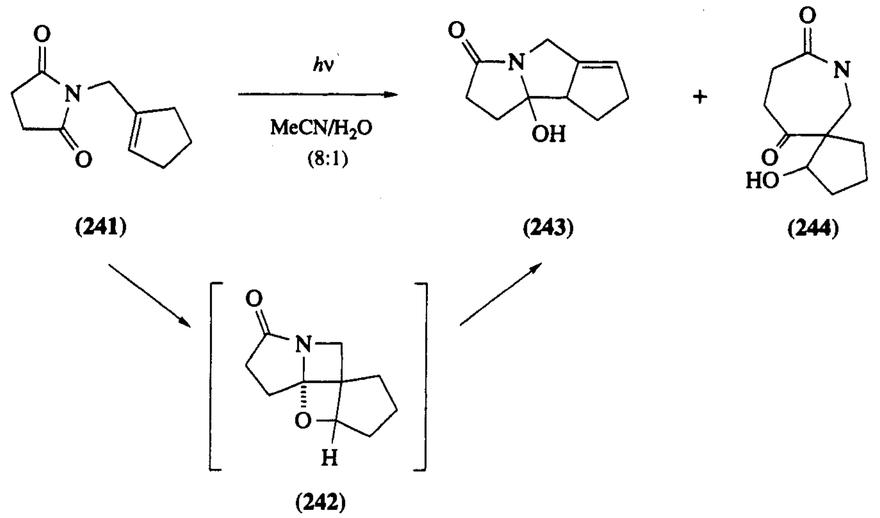

duce either of two diradical species. The newly formed asymmetric center is now in a 1,4-relationship the stereocenter α to the carbonyl and is not expected to exert much influence as a stereocontrol device. Since each cyclization produces a *cis* ring fusion with an *exo*-substituted side chain, the reaction proceeds to form photoproducts in which the stereocenter on the side chain is of no consequence in initial acetal formation or the final diradical ring closure. The site-selectivity of diradical ring closure may be related to the free valency index of the incipient diradical intermediate.[121] The free valency index provides an indication of the amount of π-bonding that is available at each atom of the π system. Scheme 25 also shows a simple Hückel molecular orbital calculation for the 1-methoxyallyl radical and the values of the free valency index at the three carbon centers. The calculation indicates that bond formation with carbon-based radicals would be favored at the C-3 position (oxetane formation), since bonding at C-1 would involve a greater loss of the π-bonding character present in the furanyloxyallyl radical intermediate.

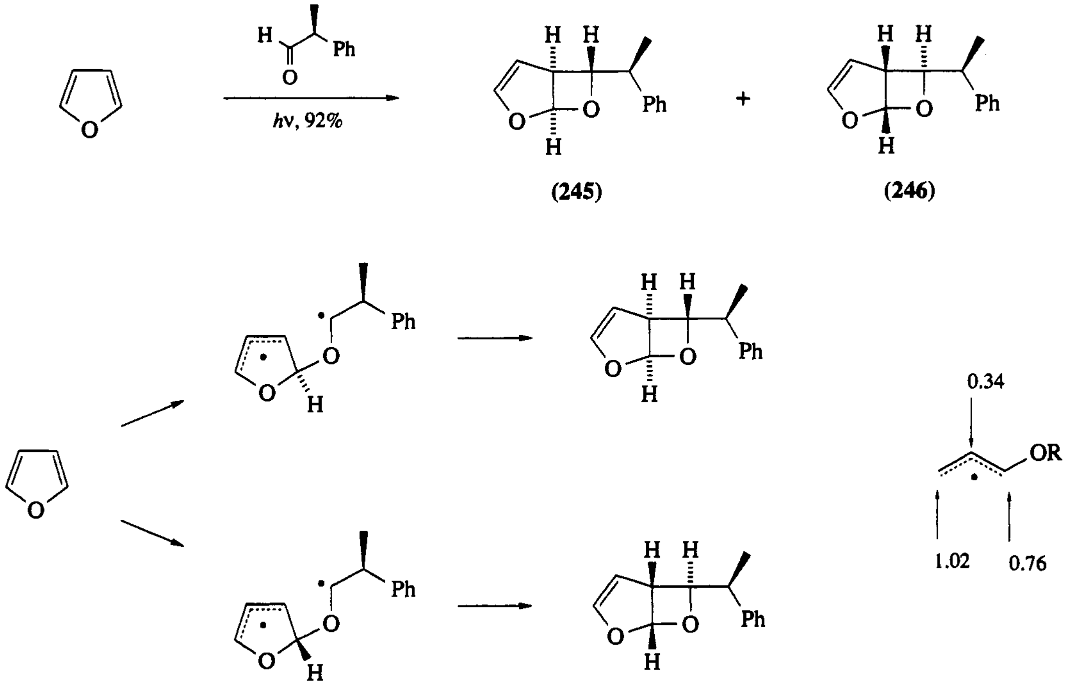

Scheme 25

A direct solution to the problem of enantioselective furan–carbonyl photoproduct synthesis would require a photoaddition that proceeded with enantiofacial selectivity in the aldehyde or furan component and maintained the relative face selectivity that is intrinsic to the reaction. Preliminary work used host–guest chemistry to achieve this objective.[124,158] In aqueous dioxane, a 1:1:1 inclusion complex of unmodified β-cyclodextrin, furan and benzaldehyde is formed. Upon irradiation (Hanovia 450 W lamp, Vycor filter), a rapid photoaddition occurs to afford a photoproduct of 10–20% *ee*.

Despite the limited number of examples available on asymmetric induction in the furan–carbonyl photocycloaddition, workers have nonetheless been interested in learning to apply the methods of asymmetric synthesis to the Paterno–Büchi reaction. An early report by Gotthardt and Lenz[159] of optical induction in thietane synthesis using a chiral menthyl methacrylate derivative encouraged examination of the Paterno–Büchi reaction.[160] Optically active phenylglyoxylic (–)-menthyl ester undergoes cycloaddition to 2,3-dimethyl-2-butene to form a diastereomeric mixture, which upon hydrolysis of the chiral auxiliary gave oxetane product with 53% enantiomeric excess. Scharf and coworkers[161] have investigated the effect of chiral auxiliaries on the diastereoselectivity of oxetane formation. Among the cases studied, the phenylglyoxylic acid derivative (**247**) was optimal and gave high *endo* phenyl selectivity.[162] The *endo* selectivity is not a result of the chirality of the ester, as it is also observed in the achiral methyl ester case. Lithium aluminum hydride reduction of adduct (**248**) allows complete recovery of the auxiliary; subsequent acid-catalyzed transacetalization forms furanose (**249**), which is oxidized under the conditions of Sharpless[163] ($RuCl_3 \cdot xH_2O/NaIO_4$) and then reduced with $LiAlH_4$ in ether to form β-1-apiofuranoside derivative (**250**). Side reactions due to the chiral auxiliary were uncovered when attempted use of keto ester (**251**) resulted in competitive transannular photochemical cyclization, indicating a favorable stereochemical arrangement of keto carbonyl and benzylic hydrogens. A similar process has been noted by Araki and coworkers in the photoreaction of hexafuranos-5-ulose derivative (**252**) to form cyclized derivative (**253**).[164]

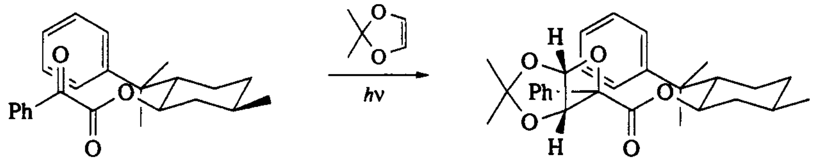

**(247)** **(248)**

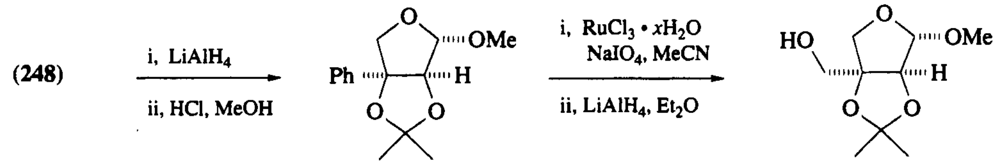

**(249)** **(250)**

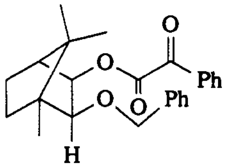

**(251)**

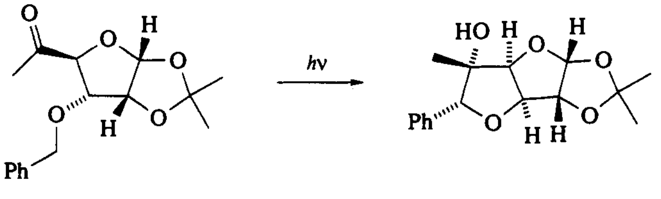

**(252)** **(253)**

Chiral induction in the photochemical reactions of phenylglyoxylic ester (**247**) can be explained by *re* face addition of the alkene to the keto carbonyl in a roughly *s-trans* conformation (**254**).[165] The conformational mobility of the α-keto ester subunit has been implicated by the readiness with which these compounds undergo Norrish type II cleavage, a carbonyl–carbonyl torsional angle of 180° being optimal.[166] In order to understand better the role of the phenyl group in photoreactions of (–)-8-phenylmenthyl glyoxylate derivatives, a crystal structure (–)-(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl phenylglyoxylate was obtained (Figure 3).[167] In the solid state the molecule adopts a conformation wherein the phenyl group is rotated away from the reactive α-keto ester. In addition, the keto carbonyl points towards the C-8 methyl group of the phenyl menthyl moiety (torsional angle −103.3°), while the ester carbonyl is nearly parallel to the C-1—H bond (deviation 23.2°). The twisting of alicyclic diketocarbonyl derivatives is well studied,[168] and the UV absorption of the carbonyls has been found to depend on the angle between carbonyl planes. The crystal structure of the (−)-menthyl *p*-bromophenylglyoxylate, shown in Figure 4 for comparison,[169] reveals a similar conformation, except for the reversed sign of the dihedral angle between carbonyl groups (+104°, average of four independent molecules in the unit cell) with the keto carbonyl pointing away from the isopropyl hydrogen.

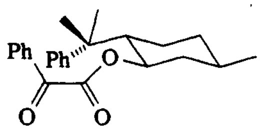

**(254)**

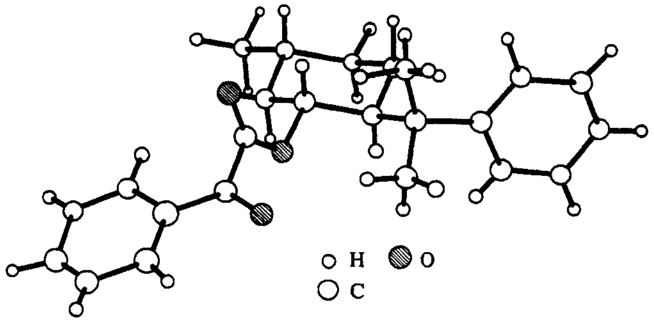

**Figure 3**

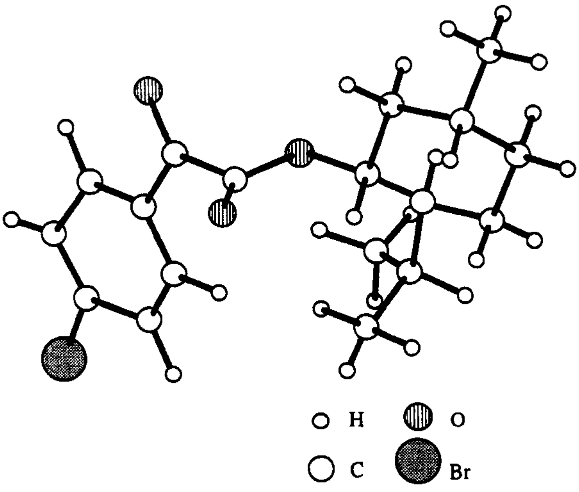

**Figure 4**

A combination of $^1H$ and $^{13}C$ NMR showed that a mixture of solution conformations exists. The relative proportion of conformer (**255a**) ($P_a$) is found to be increased by adding hydrogen-donating solvents and lowered by hydrophobic solvents such as benzene, which indicates that conformation (**255a**) allows for maximum dipole–induced-dipole interaction between keto and aromatic moieties.[170] Although the solid-state conformation of these glyoxylates may not be relevant to solution photochemistry, a difference in solid-state keto orientation may provide insight into the origin of the observed decrease in diastereoselectivities obtained with nonaromatic face-differentiating groups.

A model for stereoselection that has been developed from the analyses of face-discriminating Paterno–Büchi reactions has been reported by Scharf and coworkers.[171] Isoselective relationships[172] were ob-

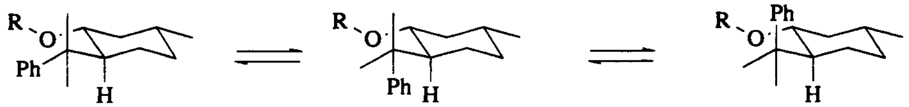

**(255a)** **(255b)** **(255c)**

served in Eyring plots to change considerably with different chiral auxiliaries and alkenes. Figure 5 shows the isoselective relationship for three phenylglyoxylates (**256a–c**) in photochemically induced oxetane formation with furan. The rate constants $k$ and $k'$ for the formation of diastereomeric oxetanes were found to be highly temperature dependent. In all cases a characteristic inversion temperature ($T_{\mathrm{inv}}$) was noted, and the plots were strictly linear on either side thereof. The existence of inversion temperatures implies that a different selection step dominates in each temperature region. In the low-temperature region, $T < T_{\mathrm{inv}}$, entropy-determined selection for the formation of 1,4-diradicals was noted. In the diradical intermediate, energetically unfavorable conformations undergo predominantly retrocleavage instead of ring closure, which results in diastereoselectivity. For $T < T_{\mathrm{inv}}$, increase in temperature increases the rate of heterocleavage. In the high-temperature region, $T > T_{\mathrm{inv}}$, selection is determined largely by enthalpy. The diastereomeric excess in this region is controlled predominantly by the steric effects of the chiral auxiliaries.

In a related study, Scharf and coworkers have studied isoselectivity relationships in the asymmetric Paterno–Büchi reaction using carbohydrates as chiral auxiliaries.[173] D-Glucofuranose derivative (**257**) underwent photocycloaddition with furan to give an oxetane product in 79% chemical yield, and the stereoselectivity depended linearly on temperature (48% *de* at 20 °C, 70% *de* at –78 °C). The reaction with benzylidene derivative (**258**), on the other hand, gave an oxetane photoproduct in 80% chemical yield and 80% diastereomeric excess upon irradiation at room temperature, but showed linear isoselectivity to produce photoadduct of approximately 75% diastereomeric excess at –78 °C. Cyclohexylidene (+)-galactopyranose compound (**259**) gave an oxetane product of only 6% *de*; previous use of this auxiliary in asymmetric amino acid synthesis[174] involved the use of metal ion chelation to enforce conformational rigidity in the system. The discovered competition between enthalpy- and entropy-determined partial selection steps is very likely general; thus consideration of mechanism may allow for rational optimization of photocycloaddition diastereoselectivity, which bodes well for the future of asymmetric photocycloadditions.

## 2.4.8 SUMMARY

The Paterno–Büchi [2 + 2] photocycloaddition is becoming increasingly popular as a method for the synthesis of chiral molecules with multiple functionality. Investigations of reaction mechanism have been fruitful and have led quickly to improved procedures and interesting applications. For example, it is through these studies that radical intermediate trapping techniques were developed, and that the temperature dependence of reaction diastereoselectivity was explained. Since photoreactions can be performed on multigram scale and often proceed in high yield and with stereocontrol, these reactions are quite useful and merit special consideration in the early steps of a complex molecule synthesis. Stereocontrolled syntheses of four-membered ring photoproducts have provided efficient, concise syntheses for a number of chemical transformations resulting in the synthesis of naturally occurring substances and analogs, including of carbohydrates and mycotoxins. Further advancements in the Paterno–Büchi process will surely come from the exploitation of the entropic favorability of intramolecular photocycloadditions and a more widespread knowledge of the potential of photochemical, asymmetric synthesis. As an entry point in complex molecule synthesis, the Paterno–Büchi reaction offers the possibility of concise and economic solutions to problems in synthesis involving naturally occurring molecules and also target systems containing modified functionality.

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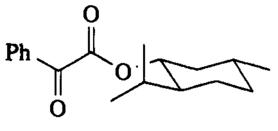

**(256a)**

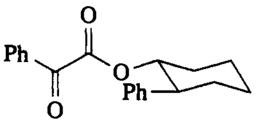

**(256b)**

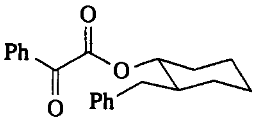

**(256c)**

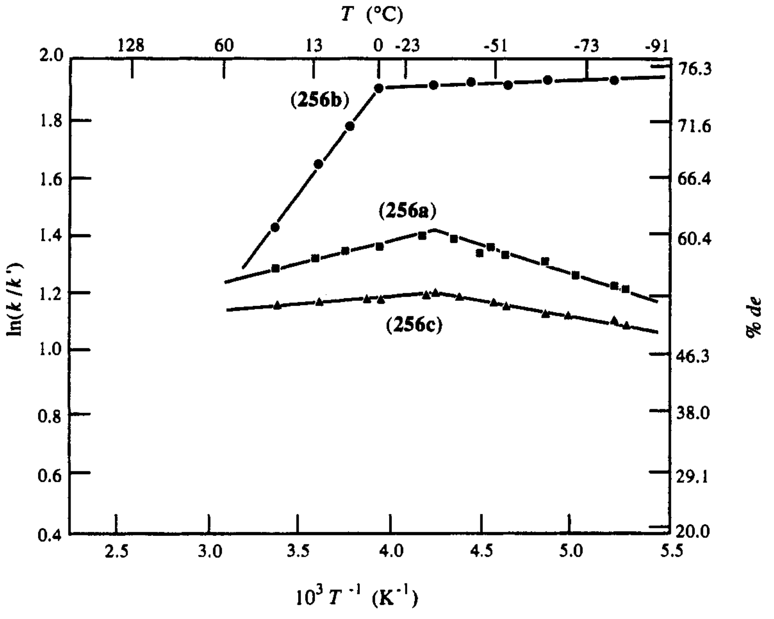

**Figure 5**

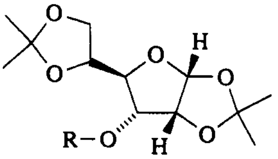

**(257)**

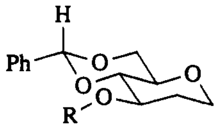

**(258)**

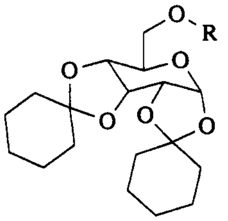

**(259)**

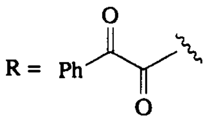

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# 2.5

# Di-π-methane Photoisomerizations

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## 2.5.1 INTRODUCTION

### 2.5.1.1 Historical Remarks

The term di-π-methane rearrangement is meant to describe the photoisomerization of 1,4-dienes (*i.e.* two π-systems separated by a methane unit) leading to vinylcyclopropanes. The reaction can be generalized in schematic form as in equation (1). As will be discussed more specifically in the section dealing with mechanism, such a simplistic presentation is not intended as the actual reaction path, but it greatly helps in predicting the reaction products.

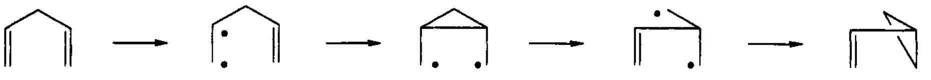

(1)

The di-π-methane rearrangement was discovered and conceptually developed by H. E. Zimmerman (University of Wisconsin), one of the earliest examples being the photoisomerization of barrelene (**1**) into semibullvalene (**2**) (equation 2). Through intensive subsequent work, this photoreaction was shown to be quite general for 1,4-dienes. In view of the major contributions by the original author, the rearrangement is also referred to as the Zimmerman rearrangement.

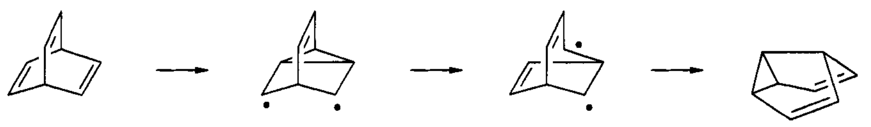

(**1**) (**2**) (2)

The 1,4-diene moiety can include atoms other than carbon. Particularly common are oxygen and nitrogen (see later in this chapter and in Chapter 2.6).

Prior to Zimmerman's recognition of the generality of the reaction scheme outlined in equation (1), other photorearrangements falling into the di-π-methane category had been observed. Most of these examples have already been reviewed.[1] The mechanism of the reaction has also been studied in detail for several systems and carefully scrutinized.[2-4]

### 2.5.1.2 Nomenclature

Owing to the numerous possibilities in which a 1,4-diene can be assembled, especially when heteroatoms are included, a nomenclature issue arises that needs to be addressed from the outset. According to the Hantzsch–Widman nomenclature system in combination with the IUPAC rules,[5] hetera-di-π-methane reactions are those transformations in which a particular heteroatom replaces the carbon atom of the 1,4-diene moiety; the position is specified by means of a numerical prefix. We will use this suggested nomenclature for the di-π-methane photorearrangement as indicated for the substrates shown in Scheme 1.

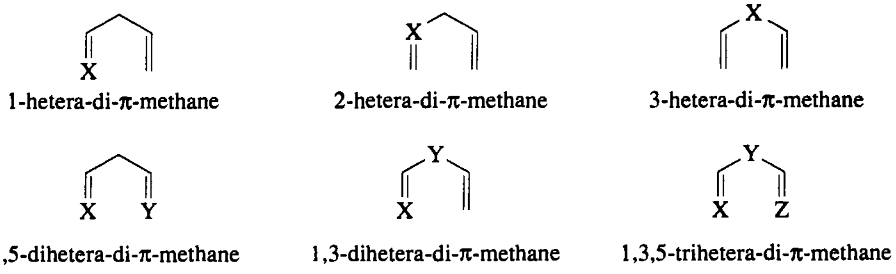

1-hetera-di-π-methane 2-hetera-di-π-methane 3-hetera-di-π-methane

1,5-dihetera-di-π-methane 1,3-dihetera-di-π-methane 1,3,5-trihetera-di-π-methane

**Scheme 1**

## 2.5.2 SCOPE

### 2.5.2.1 Acyclic 1,4-Dienes

Study of the di-π-methane rearrangement of the parent system is hampered by the low extinction coefficient of the 1,4-pentadiene chromophore. In the practical wavelength ranges, this substrate does not possess a useful chromophore besides the unconjugated π-bonds. The effective wavelength is too energetic so that side products, usually arising from radical chemistry with the solvent, are observed. For this reason the original photoreaction of the parent system was carried out under conditions of mercury sensitization and vapor phase irradiation.[6]

Sensitization by mercury is useful for performing the photoreaction on all those 1,4-dienes that lack chromophoric groups, *e.g.* alkyl and/or cycloalkyl substituted systems. These reactions appear to proceed by triplet energy transfer from the mercury to give vibrationally exited diene triplets. Thus, at variance with solution phase photoreactions, the exited states possess greater vibrational energy and substantially different products are possible. While such comparison is impossible for the parent system because no solution phase photochemistry has been reported, the di-π-methane product (**4**) was not observed when irradiation of the 3,3-dimethyl-substituted diene (**3**) (equation 3) was carried out under acetone sensitization in solution. Hydrocarbon (**4**) was the major component under mercury-sensitized conditions in the vapor phase.[7]

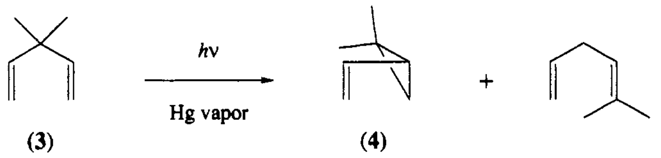

(3)

More recently, the parent system has been investigated under radio frequency plasma conditions. The plasma generated by an electric discharge provides an unusual medium for reactions in the gas phase. The free electrons that are present in the plasma are responsible for the chemical reactions that take place. The electrons are accelerated by an applied electric field and collide with the molecule, thereby activating it for the reaction. Most procedures employ radio frequency (RF) discharges so as to keep the pressure, temperature and energy of the system relatively low. The substrate is usually volatilized into the plasma zone with residence times of the order of a second. Because there is no need of chromophores, the technique has been used to activate those cases that are inert to the normal photoexcitation in solution, *e.g.* the parent 1,4-pentadiene.[8]

It is worth mentioning that direct irradiation of molecules possessing low extinction coefficients at standard wavelengths ($\lambda < 250$ nm) can be accomplished at 185 nm.[9]

Aryl substitution produces a bathochromic shift on 1,4-pentadienes so that standard reaction conditions (in solution at $\lambda > 250$ nm) can be applied. The reaction of equation (4) shows one of the latest examples aimed at understanding the effect of an hydroxy or alkoxy function at the 3-position on the photorearrangement.[10] In the case of the free hydroxy group, two secondary photoproducts were observed besides the two expected vinylcyclopropanes. At variance with this observation, no secondary photoproducts were detected for the phenyldimethylsilyloxy substituent. Direct or benzophenone-sensitized irradiation did not cause significant variation in the reaction products.

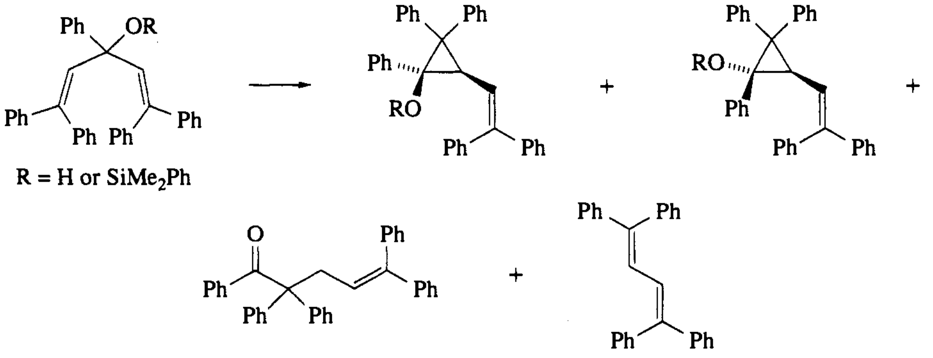

(4)

### 2.5.2.2 Cyclic Dienes

By cyclic dienes are implied those systems in which at least one of the two π-bonds is part of a ring, excluding aromatic rings which will be treated in Sections 2.5.2.4 and 2.5.3.2.

Unsubstituted cyclic dienes, such as 1,4-cyclohexadiene, which contain both double bonds in the same ring, possess very low extinction coefficients at standard wavelengths. The reaction can be carried out by mercury sensitization[11] or under direct irradiation at 185 nm (equation 5).[12] The next higher homolog, *i.e.* 1,4-cycloheptadiene, can be generated in the photolysis of bicyclo[4.1.0]hept-3-ene (**5**) and further transformed into the expected di-π-methane product (**6**) at 185 nm (equation 6).[13]

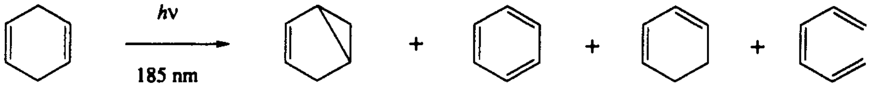

(5)

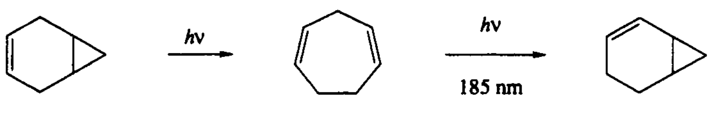

(**5**) + other products (**6**)

(6)

When only one of the two double bonds is part of a ring, there are many possible combinations; these have already been reviewed.[1–4] A recently reported representative example involves the photochemistry of (**7**), which contains both the aryl and the acetyl chromophores (equation 7).[14] The observed products arise both from the standard di-π-methane and oxa-di-π-methane rearrangements.

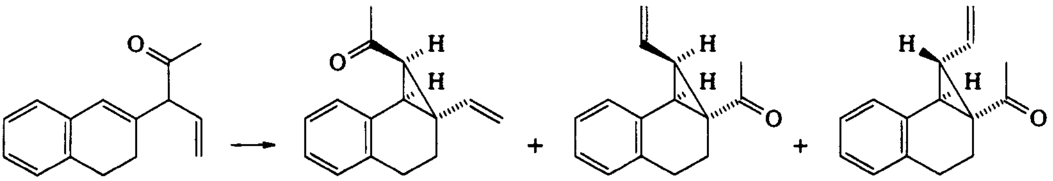

(**7**)

(7)

### 2.5.2.3 Polycyclic Dienes

Polycyclic dienes are probably the best represented class of substrates for the di-π-methane rearrangement. The rigid geometry of these molecules places the reacting double bonds in closer proximity, thus allowing for more efficient through-space interaction than is present in acyclic or monocyclic dienes due to conformational mobility. Among the latest examples, the photoisomerization of bicyclo[3.2.2]nona-2,6,8-triene (homobarrelene; **8**) and its dihydro derivatives, which lead to the products illustrated in equation (8), has been reported.[15] The absence of valence tautomer (**9**) in the photoreaction of (**8**) has been attributed to geometrical causes.

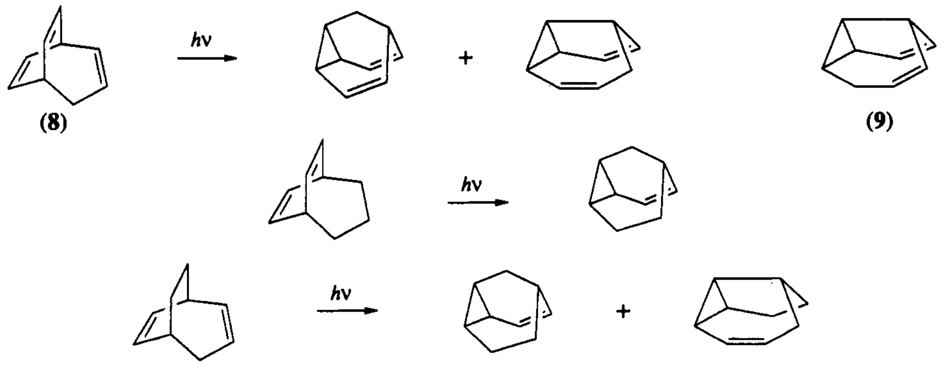

(8)

The di-π-methane photoisomerization also occurs with high efficiency when one of the two double bonds is exocyclic.[1–5] A significant effect is exhibited by dicyano substitution on the exocyclic double bond.[16,17] For example, 5,5-dicyanomethylenebicyclo[2.2.2]oct-2-ene (**10**) gives upon direct irradiation good yields of the highly strained di-π-methane product (**11**).[16] Upon heating or in the presence of catalysts (*e.g.* $SiO_2$), the latter is quantitatively isomerized back to the starting diene (equation 9).

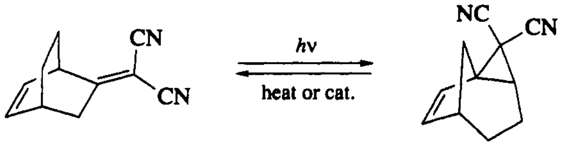

(9)

**(10)** **(11)**

When both the endocyclic and exocyclic systems are present as in (**12**), reaction occurs only at the endocyclic di-π-unit to afford (**13**) (equation 10).[18] Deuterium labeling experiments revealed that this di-π-methane product can be rationalized by postulating the cyclopropyldicarbinyl diradical (**14**) as intermediate.

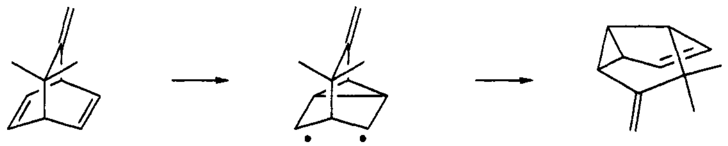

(10)

**(12)** **(14)** **(13)**

### 2.5.2.4 Benzo and Dibenzo Systems

The di-π-methane rearrangement readily occurs when one of the two π-bonds is part of an aromatic ring. The aromatic ring substantially increases the extinction coefficient of the substrate and, as expected, these reactions are usually quite efficient, except for the parent system 3-phenylpropene. Indeed, 3-phenylpropene is reported not to photorearrange to di-π-methane products under standard photochemical conditions in solution, but to give the expected vinylcyclopropyl product under RF-generated plasma reaction conditions (equation 11).[8] In the plasma reaction, indene is also produced. The 2-deuterio-substituted analog gave 1-phenyl-1-deuteriocyclopropane, suggesting a reaction pathway consistent with the di-π-methane rearrangement, and thus ruling out the possibility of a 1,2-hydrogen shift.

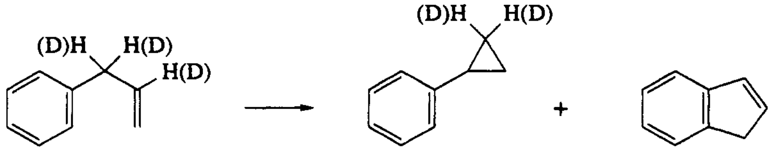

(11)

Methyl-substituted arylpropenes afford the expected cyclopropanes, but the latter undergo facile ring opening to the corresponding aryl-substituted butenes (equation 12).[19]

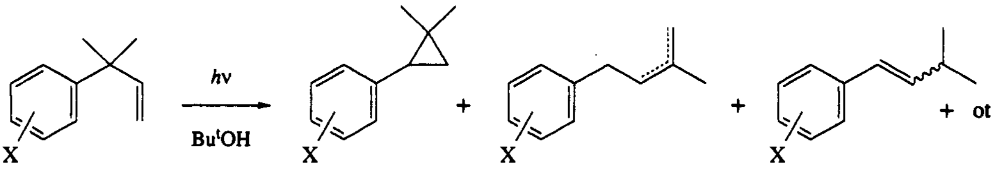

(12)

X = *p*-MeO, *m*-MeO, *p*-CN, *m*-CN

A minimal structural feature for di-π-methane rearrangement of acyclic arylpropenes to occur in solution appears to be the presence of an additional phenyl group.[1-5] A similar requisite seems valid also for cyclic 1,4-systems such as indenes, while the scope for 1,4-dihydronaphthalenes is uncertain.[1-5]

In comparison with acyclic and cyclic substrates, polycyclic systems are far more reactive. The di-π-methane unit *par excellence* is benzonorbornadiene, which affords on triplet sensitization the tricyclic product (**15**) (equation 13).[20] The favorable geometry of this substrate, which by virtue of the methylenic bridge possesses the two π-bonds fixed at an optimal interacting distance, is largely responsible for the increased reactivity. Interestingly, this di-π-methane photoisomerization can be achieved thermally in the presence of 1,2-dioxetanes.[21] Since the latter decompose thermally to give preferentially triplet state carbonyl fragments (equation 14), such a chemically energized transformation provides rigorous confirmation that the di-π-methane rearrangement of benzonorbornadiene[20] is triplet sensitized.

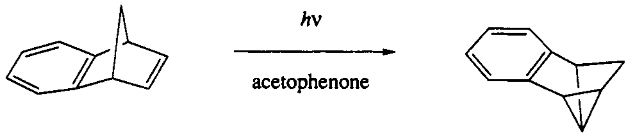

(15)

(13)

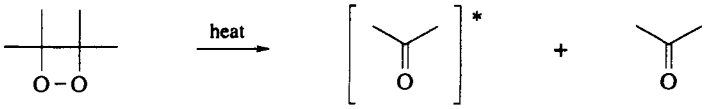

(14)

Bridges other than methylene, *e.g.* those present in benzobarrelene and its dihydro derivative, also provide for reactive di-π-methane systems.[1-5] In the benzobarrelene case, aryl–vinyl or vinyl–vinyl bonding is possible. As shown in equation (15), the products derived from these two pathways are distinctive for the labelled substrate. This aspect has been studied for several barrelenes containing different aromatic groups, including naphthalene (both at the 1,2- and 2,3-positions), anthracene, *etc.*[2] The observed products are rationalized most frequently *via* vinyl–vinyl bridging.[2] Similar behavior is exhibited by dibenzobarrelene[22] and related systems.[2,3]

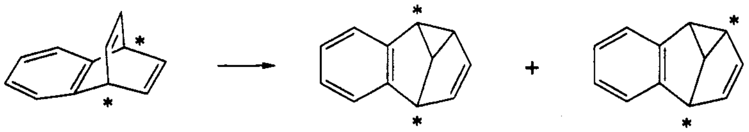

(15)

Di-π-methane products arising from aryl–aryl bonding are much more rarely observed. In these cases, the aromaticity of one aryl group has to be sacrificed in the final di-π-methane product. A well studied system is shown in equation (16).[23]

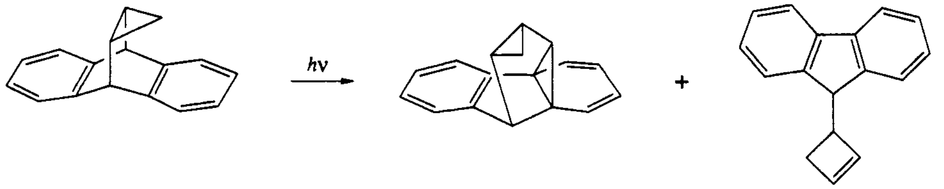

(16)

## 2.5.2.5 Cyclopropyl-π-methane Rearrangements

In this case, one of the two π-bonds is a cyclopropane unit and a vinyl cyclobutane is formed (equation 17), the photorearrangement still resembling closely the di-π-methane process of equation (1). Such an unsymmetric substrate should in principle afford, besides the cyclobutane (path b), also dicyclopropane (path a) by opening of the other σ-bond in the cyclopropyl diradical intermediate; this pathway has not been observed so far.

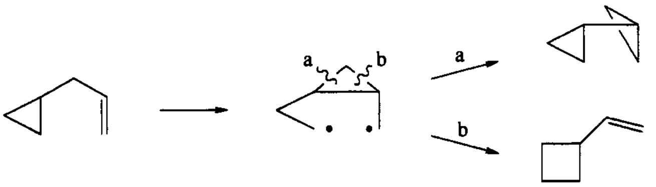

(17)

An example of the photoisomerization of a cyclopropyl-π-methane system is depicted in equation (18). Five products are observed, the first three of which are primary products, while the last two derive from secondary photochemical fragmentation of the vinylcyclobutane.[24]

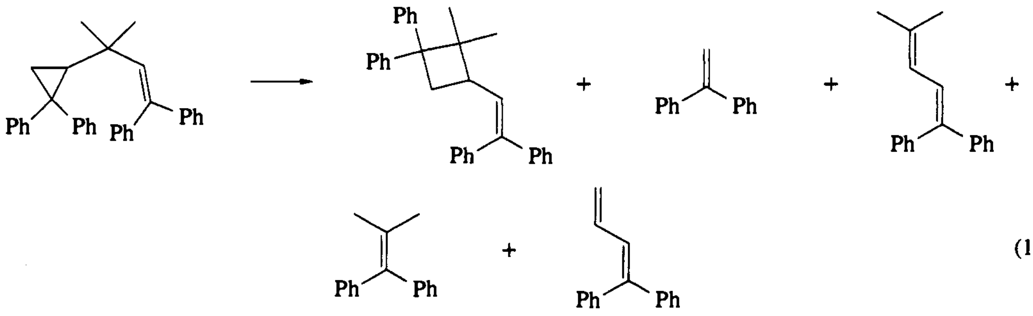

(18)

The benzo version of the cyclopropyl-π-methane rearrangement has been reported for substrate (**16**).[25] The products are shown in equation (19), of which cyclobutane (**17**) corresponds to the cyclopropyl-π-methane product. The two alkenes are secondary products from the cyclobutane, while the last two products derive from photocycloreversion of the starting material (Griffin fragmentation),[26] the diphenylcarbene being trapped by the solvent (Bu$^t$OH) in the form of the ether.

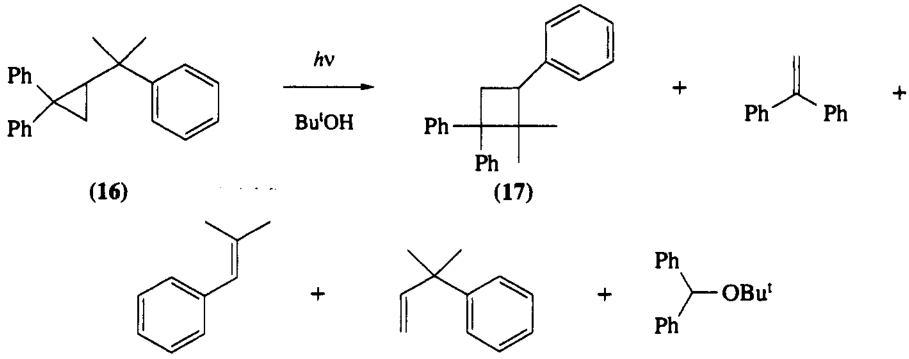

(**16**) (**17**)

(19)

## 2.5.2.6 Hetera-substituted Systems

The hetera-substituted di-π-methane rearrangement is currently an active area of investigation. So far, most examples have been reported for oxa and aza substitution. From the available data, it appears that the rearrangement is operative only when the heteroatom is in the 1-position. Replacement of the $sp^2$ carbon at the 2-position or the $sp^3$ carbon at the 3-position by heteroatoms such as O, N, S, Se, B, P, *etc.* entails systems which have not been investigated or which have proved incapable of giving di-π-methane products.

An exception is given by silicon as heteroatom. The silabarrelene (**18**) undergoes photorearrangement very similar to barrelene, affording the silasemibullvalene in quantitative yield (equation 20).[27]

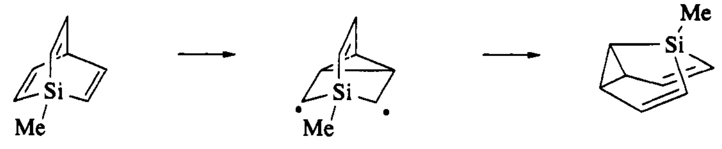

(**18**)

(20)

Other types of sila systems also give di-π-methane products. In the case of (**19**), irradiation at 10 K in an argon matrix or at 77 K in a 3-methylpentane glass affords the di-π-methane product (**20**), which on further irradiation or upon heating reverts to the starting material (equation 21). Photolysis of (**19**) at room temperature gives instead retro Diels–Alder fragmentation to tetramethyldisilene, whose intermediacy was established by means of [4 + 2] cycloaddition with 2,3-dimethyl-1,3-butadiene.[28]

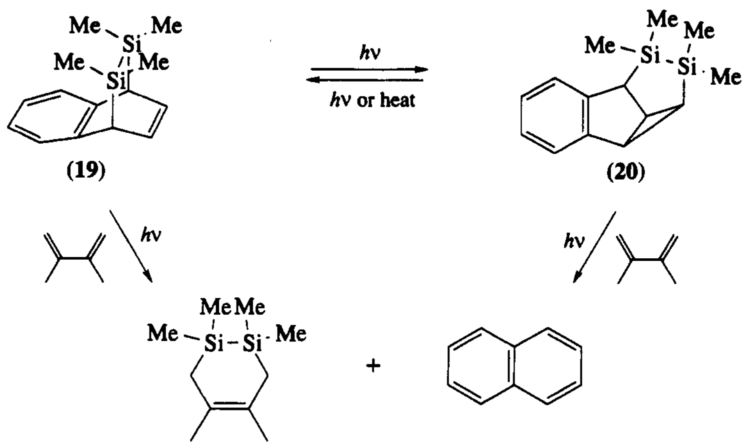

(21)

### 2.5.2.6.1 *Oxa-di-π-methane rearrangements*

The chemistry of the oxa-di-π-methane rearrangement is covered in Chapter 2.6, so that here, for the sake of completeness, only a few remarks on its more salient features are presented.

Of the two possible oxa-di-π-methane systems, only the 1-oxa has been extensively studied. The presence of the carbonyl group significantly alters the photophysical characteristics of the 1,4-diene moiety, *e.g.* the type of excitation (from π,π* to *n*,π*), level ordering, spin state, and extinction coefficients. Other reaction pathways such as Norrish type fragmentations become operative and such products often accompany the di-π-methane ones. Of the two possible reaction paths arising from cleavage of the cyclopropyldicarbinyl diradical, usually the one leading to the carbonyl-substituted cyclopropane is observed. An illustrative example is given in equation (22).[29] The triplet sensitized oxa-di-π-methane rearrangement of pure enantiomers of bicyclo[2.2.2]oct-5-en-2-one affords enantiomeric tricyclo[3.3.0.0$^{2,8}$]octan-3-ones, which have been used as building blocks for the synthesis of natural products.

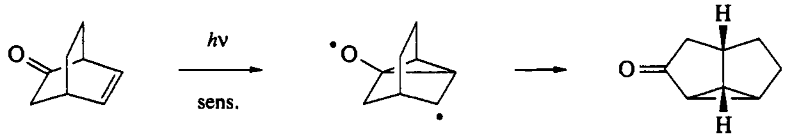

(22)

The 3-oxa-di-π-methane rearrangement is far less common. As a symmetrical system, the product should be a vinyl epoxide (equation 23). So far, no 3-oxa-di-π-methane products have been observed from the divinyl ethers depicted in the equation.[30] It was shown that the solution photochemistry of (**21a**) derives from its singlet π,π*-state and parallels that of the unsubstituted divinyl ether (**21d**) and of furan in the gas phase. All products could be rationalized in terms of the initial formation of a singlet vinyl–vinyloxy radical pair (equation 24). Triplet sensitization brings about *cis–trans* isomerization and consequent deactivation. Had the 3-oxa-di-π-methane product, *i.e.* the vinyloxirane (**22**), been formed, it would have decomposed *via* Griffin fragmentation[26] as confirmed by irradiation of an authentic sample.

An explanation for the lack of formation of 3-oxa-di-π-methane products is offered in terms of Zimmerman's bond order control.[4] Thus, while the 1,4-diene is a four-electron system with bonding between

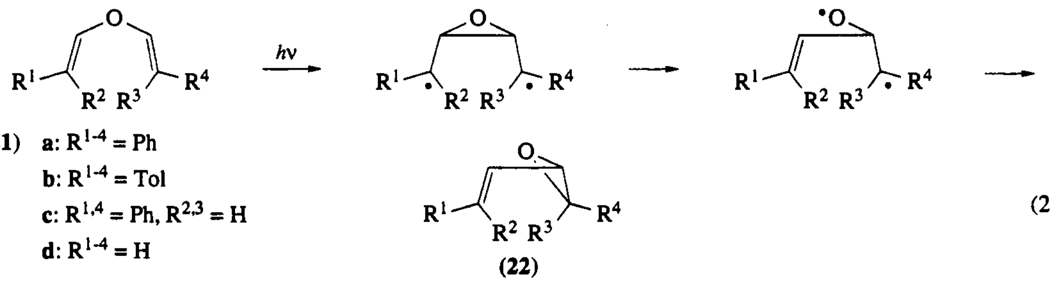

(**21**) a: $R^{1-4}$ = Ph
b: $R^{1-4}$ = Tol
c: $R^{1,4}$ = Ph, $R^{2,3}$ = H
d: $R^{1-4}$ = H

(23)

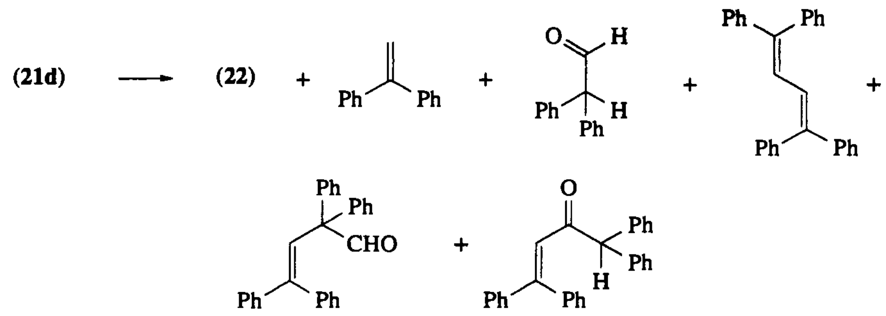

(24)

C-2 and C-4 in the reacting LUMO, the divinyl ether is a six-electron system with antibonding between C-2 and C-4 in the reacting LUMO of the excited states species. Presumably on account of this, the divinyl ether substrate is di-π-methane inactive. This rationalization is shown in Scheme 2.

1,4-Pentadiene

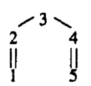

| | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|
| MO 4 | + | − | + | − | |
| MO 3 | + | − | − | + | LUMO $h\nu$ |
| MO 2 | + | + | − | − | HOMO |
| MO 1 | + | + | + | + | |

Divinyl ether

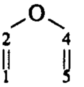

| | 1 | 2 | 3 | 4 | 5 | |
|---|---|---|---|---|---|---|
| MO 4 | + | − | 0 | + | − | LUMO $h\nu$ |
| MO 3 | + | 0 | − | 0 | + | HOMO |
| MO 2 | + | + | 0 | − | − | |
| MO 1 | + | + | + | + | + | |

**Scheme 2**

Of mechanistic interest in this context is the independent generation of di-π-methane diradicals of 3-oxa-di-π-methane systems which do not give the rearrangement, in order to probe whether such diradicals at least in principle are prone to give di-π-methane products. For this purpose, the cyclopropyldicarbinyl diradical in equation (25) was generated *via* photochemical carbon monoxide extrusion.[31] Indeed, the expected oxa-di-π-methane product 2,5-dimethyl-4,5-epoxy-2-hexene was formed, as well as other products.

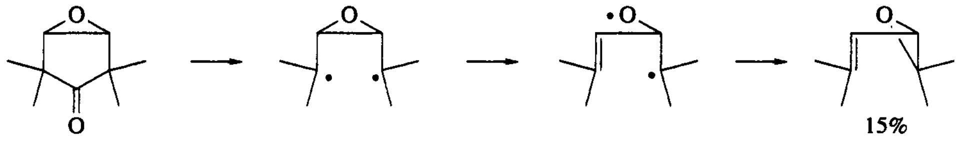

(25)

### *2.5.2.6.2 Aza-di-π-methane rearrangements*

In nitrogen systems, all three arrangements are in principle possible, *i.e.* the 1-, 2- and 3-aza-di-π-methane rearrangements. Only the first of them has recently been investigated, while examples of the 2- and 3-aza-di-π-methane rearrangement appear still missing from the literature.

The first aza-di-π-methane rearrangement to be reported is illustrated in equation (26). The product of the reaction is the imine and not the aziridine; the latter could have formed upon rupture of the alternative bond of the cyclopropyldicarbinyl diradical intermediate.[32] In this regard, the aza-di-π-methane resembles the 1-oxa case, with reestablishment of the imine bond.

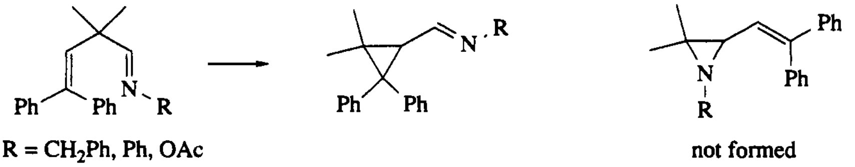

R = $CH_2Ph$, Ph, OAc

not formed

(26)

The 1-aza-di-π-methane rearrangement depends on the type of substitution of the nitrogen atom.[33] For example, aza-di-π-methane rearrangement occurs with aryl-substituted imines and with oxime acetates, but not with the oxime (**23**) or the nitrile (**24**).[34]

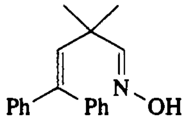

**(23)**

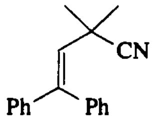

**(24)**

The 1-aza-5-oxa-di-π-methane rearrangement of (**25**) does not occur. Instead, *cis–trans* isomerization and photoelimination of methanol are observed for this oxime (equation 27).[35] Finally, the 1-oxa-4-aza-di-π-methane rearrangement of compound (**26**) also did not take place. This substrate gave rise to the photo-induced 1,5-benzoyl migration shown in equation (28).[36]

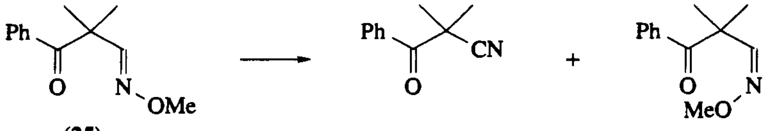

**(25)** (27)

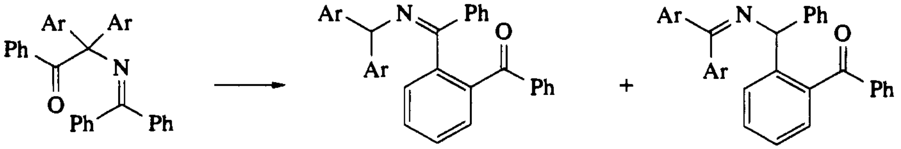

**(26)** (28)

## 2.5.3 MECHANISM

### 2.5.3.1 General Aspects

The mechanism of the reaction has been extensively reviewed on several occasions.[2–4] We intend, therefore, to highlight only the essential features. Moreover, it should be kept firmly in mind that, in most instances, diradical intermediates have been postulated for mechanistic convenience and rigorous experimental confirmation of their intervention is often lacking.

Recent achievements in the elucidation of the mechanism have been obtained by computational methods. The results of a SINDO1 study[37] are in agreement with the general mechanistic pathway suggested by Zimmerman.[2] For the parent 1,4-pentadiene system the calculated correlation diagrams suggest that opening of the cyclopropyldicarbinyl diradical is prevented by a high barrier on the singlet surface. Thus the rate of formation of the parent vinylcyclopropane should be negligible under direct irradiation. However, the singlet-state reaction becomes efficient where no barriers appear in the first excited singlet state, *e.g.* the case of *gem*-dimethyl substitution at the central carbon atom. For this substrate, calculations predict that the cyclopropyldicarbinyl diradical is not an intermediate.[37]

On the other hand, these calculations suggest that the triplet-state process can be efficient only if the cyclopropyldicarbinyl triplet intermediate is avoided during the reaction because of high vibrational energy. If the ground-state triplet cannot be circumvented, back reaction to the ground-state reactants should be observed.[37] However, the existence of the cyclopropyldicarbinyl diradical on the triplet energy surface has been advanced by Borden *et al.*,[38] who compared the calculated geometries and energies of reactants, intermediates and products.

The general impression of the present computational status on this complex photochemical rearrangement is that the results are still contradictory. Presumably the mechanistic details depend on the system under consideration, so that a spectrum of possibilities applies. More intensive efforts should be invested in the future to resolve this perplexing situation.

### 2.5.3.2 Divinyl *versus* Benzo–Vinyl Bridging

The question arises whether there is any need for formation of the cyclopropyldicarbinyl diradical in the aryl di-π-methane rearrangement. In the event that this intermediate is indeed formed, one has to keep in mind that the aromaticity of the aryl moiety has to be sacrificed along the reaction coordinate. Alternatively, a 1,2-aryl shift with direct formation of the 1,3-diradical may operate, which irreversibly cyclizes to the di-π-methane product. In Scheme 3 these mechanistic alternatives are illustrated for benzonorbornadienes, which have been studied in great detail by Paquette *et al.*[39]

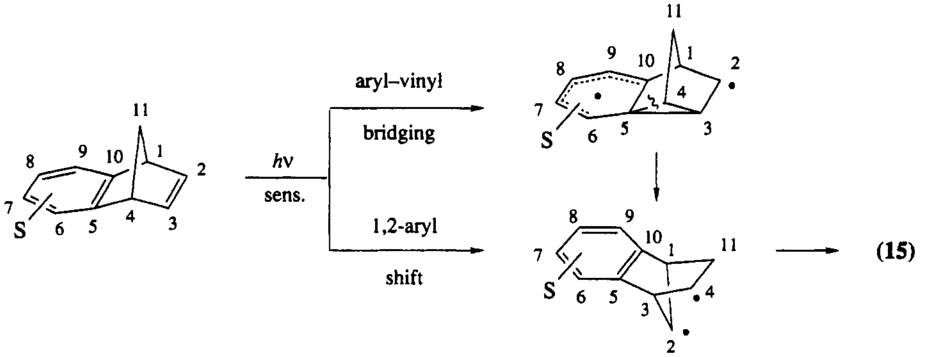

**Scheme 3**

Experimental scrutiny of this mechanistic problem has been approached from several points of view; substituent effects on the aromatic ring have been investigated with special intensity (Scheme 3). The significant features can be summarized as follows.

(a) Substitution at C-7 by electron-acceptor groups (S = EA) results in rebonding *via* the *para* position in the rearrangement (equation 29),[39a,b] while electron-donor groups (S = ED) at C-7 favor rebonding *via* the *meta* position (equation 30).[39a,b]

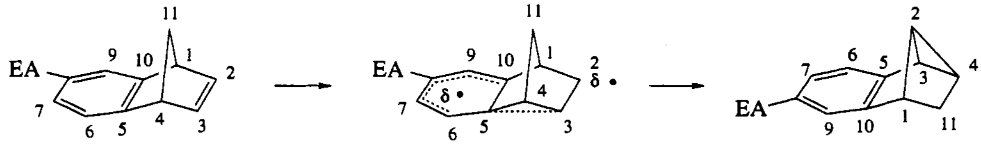

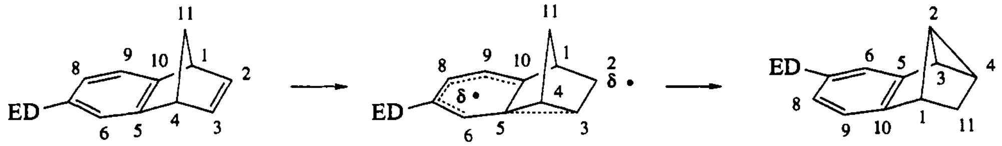

(b) Substitution at C-6 favors rebonding *via* the *ortho* carbon atom, irrespective of the electronic nature of the group (equation 31).[39c,d]

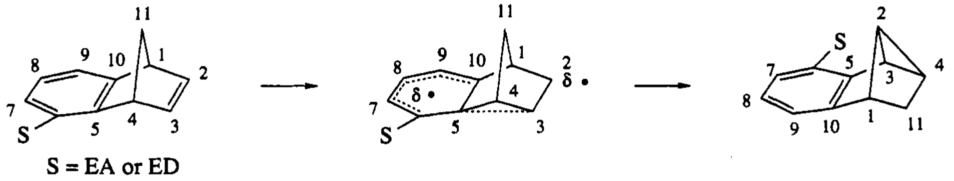

(c) Bridgehead substitution at C-1 promotes regiospecific migration of the proximate aryl site (equation 32), except for Br (heavy atom effect) and D (isotopic control).[39e,f]

(d) In the case of 1-methoxy-4-substituted benzonorbornadienes, with few exceptions the reaction channel involving the aryl carbon atom proximate to the substituent is favored.[39g]

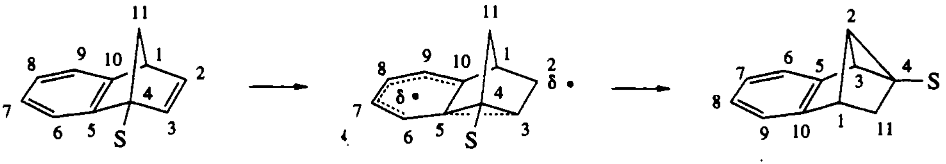

S = EA or ED

(32)

(e) A cyano group in the 2-position strongly induces migration of the distant aryl site;[39h,i] the effect of a methyl group at the same position is less pronounced (equation 33).[39j]

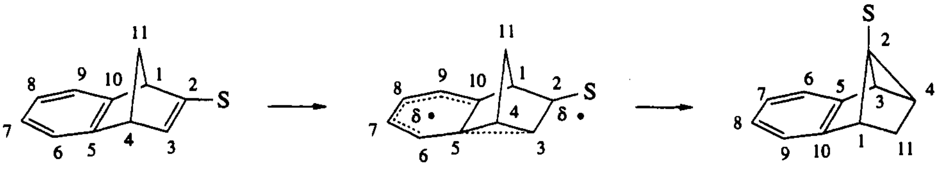

S = CN or Me

(33)

(f) In 1,2-dimethyl- and 1,2-bis(trimethylsilyl)-benzonorbornadienes, both the possible reaction channels operate, showing that the substituent effects in the two positions are matched. Bridgehead cyano substitution overwhelms the effect of a vinylmethyl group, while bridgehead bromine augments the ratio of product derived from rebonding at the distal site of the methyl group (equations 34 and 35).[39k]

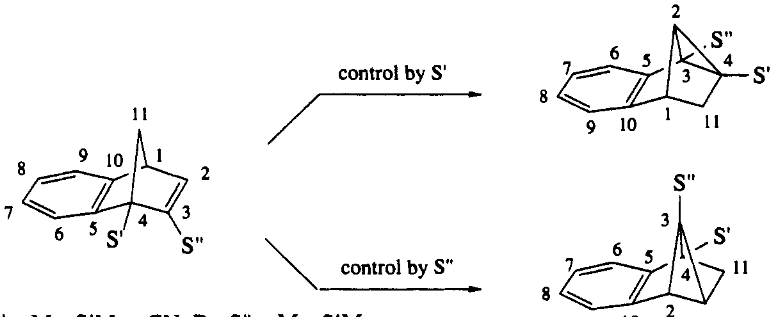

S' = Me, SiMe$_3$, CN, Br; S" = Me, SiMe$_3$

(34)

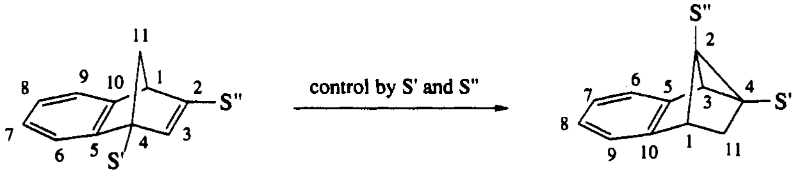

S' = CN, Br; S" = Me

(35)

(g) In bridgehead-substituted 6-methoxybenzonorbornadienes, electron acceptors have a dominant effect over the methoxy substituent; for electron donors, competition with the directing control by the methoxy group in the aryl ring is observed.[39l]

(h) The deuterium isotope effect associated with the triplet state di-π-methane rearrangement of [1-D]- and [2-D]-benzonorbornadiene has been determined to be quite large, *i.e.* $k_H/k_D = 1.27$ and 1.34, respectively.[39l] These findings strongly support a mechanistic pathway *via* 1,2-aryl migration (Scheme 3).

### 2.5.3.3 Independent Generation of the Diradical Intermediates

A useful mechanistic probe for the diradical intermediates postulated in the di-π-methane rearrangement entails generating them *via* authentic routes and elucidating their chemical behavior. One of the early examples concerns the cyclopropyldicarbinyl diradical postulated in the photoisomerization of barrelene into semibullvalene by nitrogen extrusion from the appropriate azoalkane.[40] Indeed, as shown in equation (36), beside the expected semibullvalene, barrelene and cyclooctatetraene were also formed, thereby suggesting that the postulated cyclopropyldicarbinyl diradical is a reasonable intermediate in this photoreaction.

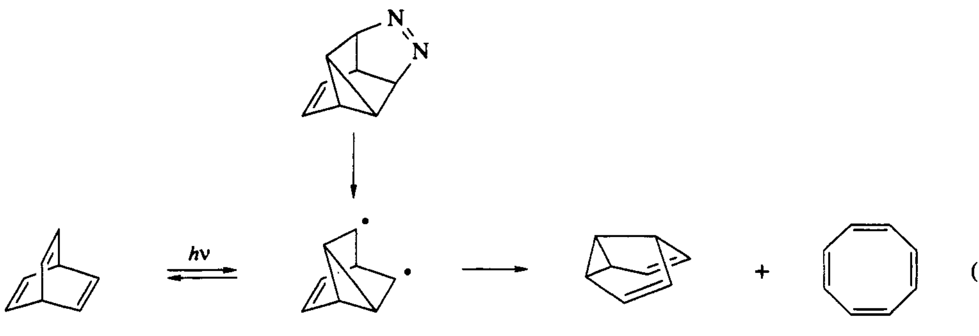

(36)

In a similar way, the 1,3-diradicals postulated in the di-π-methane rearrangement of several benzonorbornadienes and related species have been produced *via* denitrogenation of the appropriate azoalkanes (**27**)–(**30**).[41] The products obtained in the thermal and photochemical denitrogenation of (**27**), for example, are the norbornadiene and the tricyclic di-π-methane product (occasionally other products not derived from denitrogenation have been observed).[42] The latter hydrocarbon, which derives from direct collapse of the 1,3-diradical, is formed almost exclusively (equation 37).

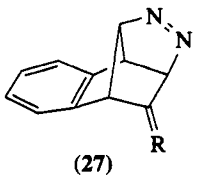

**(27)**

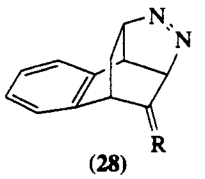

**(28)**

$R = H_2$
$R = (CH_2)_2$
$R = CPh_2$

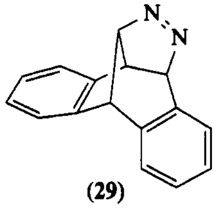

**(29)**

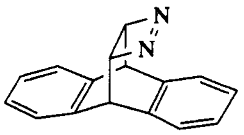

**(30)**

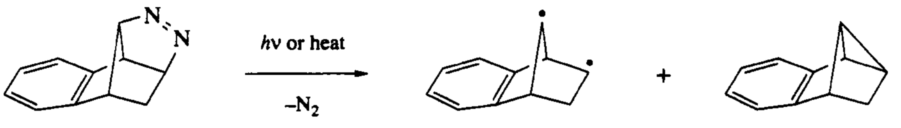

(37)

The question arises whether the generated diradicals are indeed the same as the ones involved in the photoreaction. Recent investigations on bicyclo[3.2.1]octa-2,6-diene (Scheme 4) and its benzo analog[43] have brought into focus a more complicated picture. The product compositions derived from thermal and photochemical denitrogenation of the three azoalkanes (**31**)–(**33**) and of some deuterated species, all potential entry points into the same diradical manifold, suggest that the di-π-methane rearrangement and the photochemical denitrogenation of the azoalkanes are disjointed chemical events.[43] The retro di-π-methane product (the octadiene) obtained in the azoalkane photolyses is better explained by postulating diazenyl diradicals (stepwise bond cleavage of the azoalkane). However, the major pathway leading to the di-π-methane products unquestionably involves cyclization of the 1,3-diradicals postulated in the di-π-methane rearrangement, so that their intermediacy is secured. In this context, it is immaterial whether the 1,3-diradical is formed directly or *via* the diazenyl diradical in the photolysis of the azoalkane. Nonetheless, caution should be exercised in using azoalkanes as mechanistic probes for elucidating the diradical manifolds postulated in photochemical reactions because the intermediate diazenyl diradical may lead to unexpected products.

Although the utility of azoalkanes as mechanistic probes is being questioned, their utilization in synthesis is well documented.[44] The sequence of reactions shown in equation (38) is definitely a useful alter-

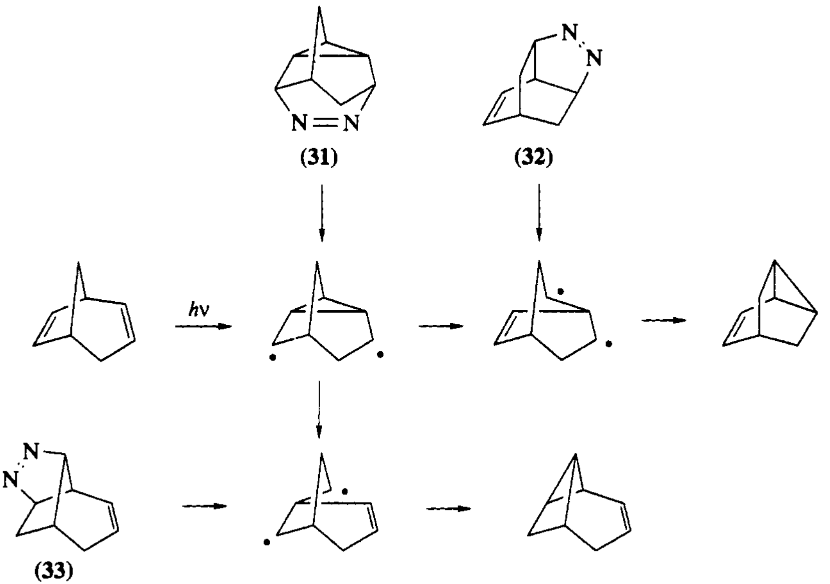

Scheme 4

native for preparing unusual di-π-methane products. This fact rests on the interesting feature that triazolinediones cycloadd to polycyclic dienes *via* the same skeletal modifications that occur in the di-π-methane rearrangement.[45] In this sense, triazolinedione cycloaddition, coupled with hydrolysis of the resulting urazole to the azoalkane and subsequent denitrogenation (thermal or photochemical), represents a synthetic equivalent to the di-π-methane rearrangement. An illustrative example is given in equation (39), in which the di-π-methane product was prepared *via* these two distinct routes.[46]

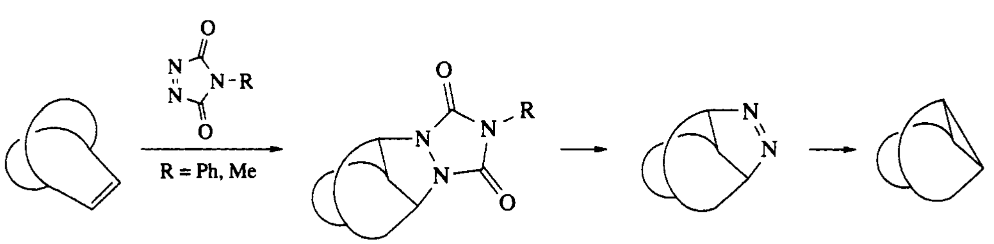

(38)

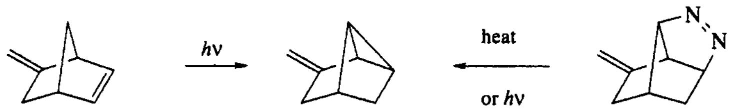

(39)

## 2.5.4 SELECTIVITY

### 2.5.4.1 Chemoselectivity

Several processes are known to be capable of competing with the di-π-methane rearrangement. The following list is, however, by no means exhaustive and refers only to those side reactions that are more frequently encountered.

#### *2.5.4.1.1 [2 + 2] Photocycloadditions and/or photoreversions*

[2 + 2] Photocyclizations are usually observed with symmetric systems. Indeed, when vinyl–vinyl bridging is equally possible for the four alkenic carbons, a [2 + 2] photocyclization can occur. As an example, norbornadiene prefers to give quadricyclane *via* photocyclization rather than the tricyclic di-π-methane product.[47] The latter, however, has been generated from the appropiate azoalkane as shown in

Scheme 5.[48] It should be noted that for this substrate all three possible diradical species have been prepared from the respective azoalkanes.[49]

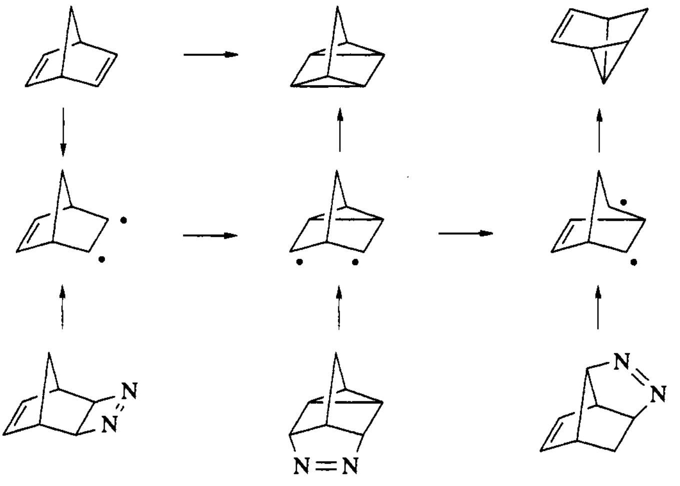

**Scheme 5**

More complicated nonsymmetric systems can sometimes produce [2 + 2] cycloadducts, although this is usually a very minor process. The example of equation (40) illustrates one such case where [2 + 2] cycloaddition (product **34**) as well as [2 + 2] cycloreversion (formation of naphthalene) are observed simultaneously with the di-π-methane rearrangement.[50] Cycloreversion can usually only be observed when one of the double bonds of the 1,4-diene is part of a cyclobutene.

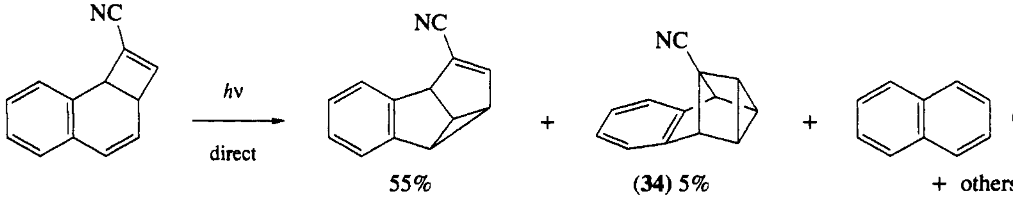

(40)

The possibility must be considered as well that triplet sensitization with carbonyl sensitizers can lead to competition by the Paterno–Büchi reaction, *i.e.* the [2 + 2] cycloaddition of the sensitizer to the substrate. To the best of our knowledge this possibility has not yet been observed.

### *2.5.4.1.2* Cis–trans *isomerizations*

Such isomerizations can only be observed in open-chain structures and, of course, medium–large ring systems. The mode of irradiation is important, as illustrated in the representative example of equation (41),[51] *i.e* the direct and sensitized irradiation of the 1,4-diene (**35**). While direct photolysis leads to the expected di-π-methane product, sensitized irradiation brings about *cis–trans* isomerization before cyclization, resulting in products with inverted stereochemistry at the double bond.[51]

### *2.5.4.1.3 1,3-Sigmatropic shift*

This photochemical transformation, shown in equation (42), is a process that occurs especially frequently in the oxa-di-π-methane rearrangement. This isomerization may proceed *via* a Norrish type I reaction.

An extension of the simplistic but practical diradical mechanism of equation (1) leads to the generalized di-π-methane process given in equation (43).[41] Thus, the initial 1,3-diradical, instead of cyclizing across C-3 and C-5 to the final vinylcyclopropane, bonds across C-2 and C-5 to generate a cyclopropyldicarbinyl diradical, which on opening of the C-2/C-4 bond affords the isomerized 1,4-diene. A num-

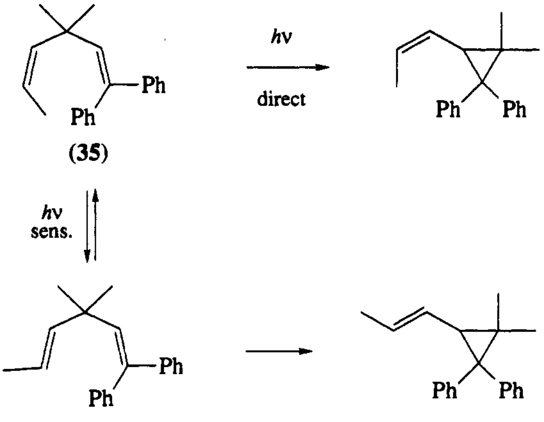

(41)

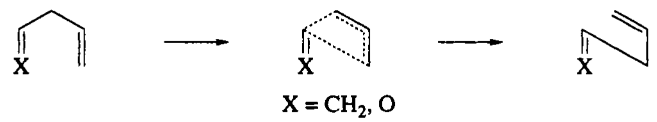

(42)

ber of photochemical transformations may be rationalized *via* the reversible generalized di-π-methane process of equation (43), but have so far not been scrutinized from this mechanistic perspective. As a significant example the photoisomerization of the $C_8H_8$ hydrocarbon series, depicted in Scheme 6, is illustrated. The mechanistic postulate in equation (43) helps to predict and to rationalize photoisomerized 1,4-diene products in the di-π-methane process.

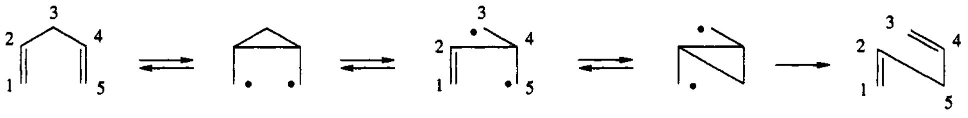

(43)

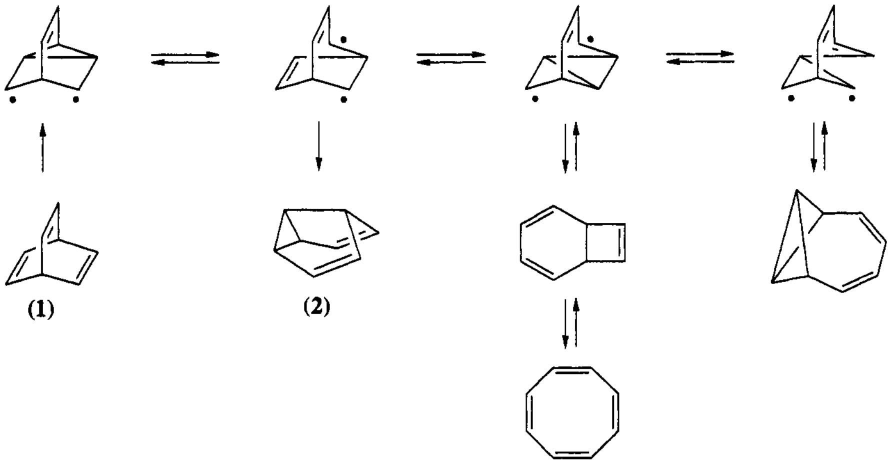

Scheme 6

### 2.5.4.1.4 *Radical-type rearrangements*

Such processes have been encountered in the photolysis of highly aryl-substituted systems. Representatively, 1-phenylindane is formed in the photolysis of *trans*-1,3-diphenylpropene (equation 44).[52] To the best of our knowledge, no cases have as yet been reported in which radical-type hydrogen abstractions compete with the di-π-methane rearrangement.

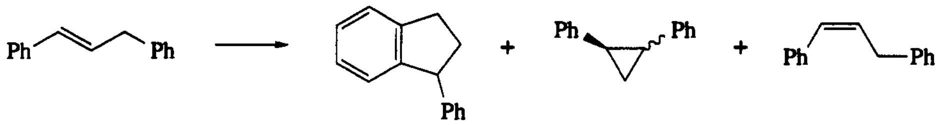

(44)

### *2.5.4.1.5 Fragmentations*

In some cases the initial cyclopropyldicarbinyl diradical fragments into a carbene. Such diradical–carbene fragmentations are quite common in the 185 nm photochemistry of alkenes,[9] but seldom in photolyses under long wavelength conditions. An example, however, is given in equation (45), in which the driving force of the fragmentation is rearomatization.[53] An analogous process constitutes the photofragmentation of triptycenes.[54]

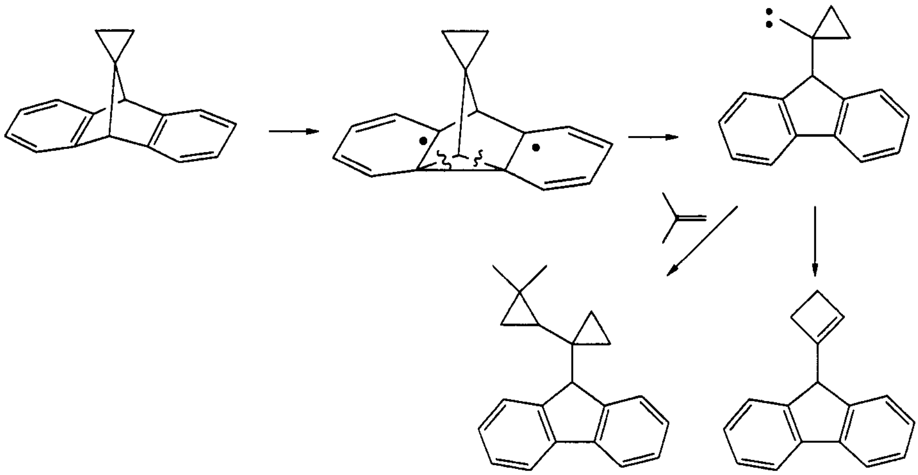

(45)

### 2.5.4.2 Regioselectivity

The regioselectivity that arises from unsymmetrically substituted dienes has already been discussed for several systems in the cited reviews.[2–4] For acyclic 1,4-dienes substituted with alkyl and/or aryl groups, the general rule applies that the product with the less substituted vinyl moiety (conversely the higher substituted cyclopropane) is formed. This type of regiochemistry derives from the need for producing the more stable 1,3-diradical intermediate. In the arylpropene cases the resultant regiochemistry is mandated by the need for maintaining the aromaticity of the aryl ring.

The general trend for acyclic 1,4-dienes substituted with functional groups possessing electron donor or acceptor characteristics is highlighted by the examples shown in equation (46).[55] The polarity of the intermediates plays a major role in determining the regiochemistry. From an empirical viewpoint, the more electron-rich double bond in the substrate remains as the double bond in the product.

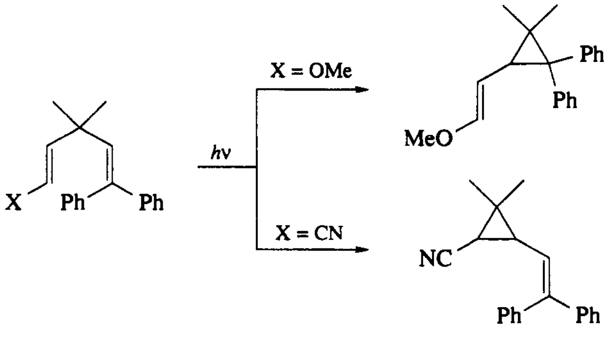

(46)

The regioselectivity associated with *ortho,meta*-substituted, bridgehead- and alkene-substituted benzonorbornadienes has already been discussed in Section 2.5.3.2. These studies by Paquette *et al.*[39] have provided valuable insights into the mechanism of the complex di-π-methane process. Latest reports concern the regioselectivity exhibited by the pyridine ring in the heterobenzonorbornadiene series (equation 47).[56] The ring nitrogen atom in the parent system favors migration of the distal carbon. The '*meta*' chloro and methoxy substituents act cooperatively with the ring nitrogen atom and cause a higher proportion of the same product. An '*ortho*' methoxy group acts in an antagonist fashion and the only observed product reflects total control by the methoxy substituent. These results consolidate the mechanistic rationales developed in the study on the substituted benzonorbornadienes.[39] The regioselectivities associated with substituted benzo-[57] and dibenzo-barrelene[58] systems are also in line with these mechanistic notions.

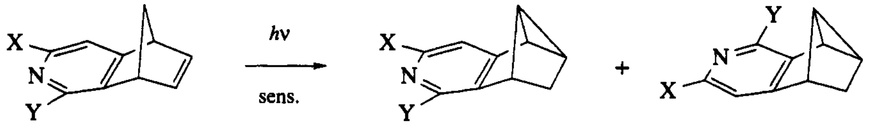

(47)

X = Y = H; X = OMe, Y = H; X = Cl, Y = H; X = H, Y = OMe

### 2.5.4.3 Stereoselectivity

The stereochemistry of the di-π-methane photorearrangement has been reviewed in detail.[1,2] The general trend is that configuration at C-1 is retained, while that at C-3 and C-5 is inverted (equation 48). The disrotatory motion at C-3 and C-5 is responsible for inversion, provided that no untoward geometric factors operate.

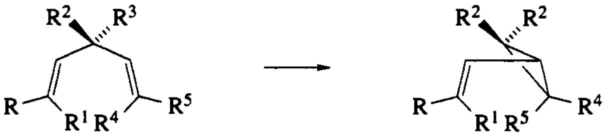

(48)

The retention of stereochemistry at C-1, as, for example, in the direct photolysis in equation (41), implies that rotation between C-1 and C-2 in the cyclopropyldicarbinyl diradical does not occur. Study of the stereochemical event at the central carbon atom requires optically active substrates containing an asymmetric C-3 carbon atom. The example of equation (49)[59] and all other cases studied[2] demonstrate that in the two diastereomeric vinylcyclopropanes which form, the central carbon atom has inverted its configuration. Knowledge of the stereochemical fate of C-5 can be gained by inspection of the examples shown in equation (50).[60] Rearrangement of the *cis* and *trans* isomers of the diene gave the *cis* and *trans* vinylcyclopropanes, respectively.[60]

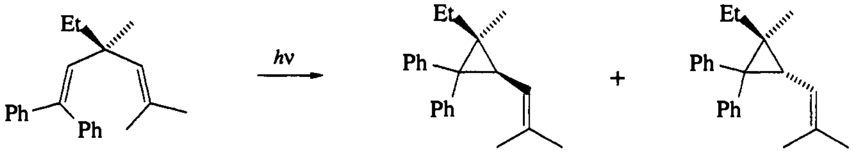

(49)

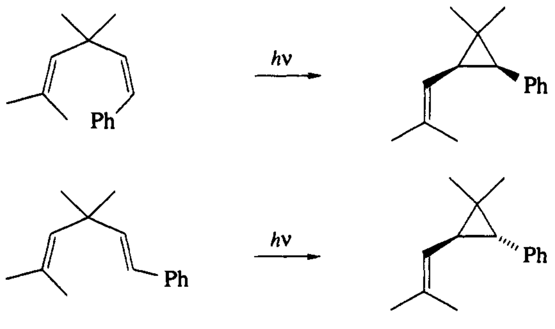

(50)

Recent efforts have focused also on the possible realization of enantioselective reactions. The use of organized chiral media has met with some success. Benzonorbornadiene forms stoichiometric complexes with β-cyclodextrin. These β-cyclodextrin–benzonorbornadiene complexes, either in solution or in the solid state, gave on acetophenone sensitization optically active tricyclic product (**15**).[61] No quantitative data are available, however. In view of the rapid equilibrium between the free substrate and its complexed form, the major problem with such experiments is the difficulty of ascertaining whether the photoreaction has occurred for the complexed or free substrate. Another problem is the difficulty experienced by the sensitizer in approaching the complexed substrate.

Finally, a few di-π-methane reactions have been reported to occur in the solid state using chiral crystals. The success of such experiments rests on the fact that racemic, but more significantly nonchiral, compounds form chiral crystalline lattices. An example is the dibenzobarrelene (**36**) (equation 51).[62] The enantioselective photoreaction occurs on the crystal surface with a high degree of asymmetric induction. It is worth noting that reactions within the crystalline state also exhibit a marked regioselectivity as the result of augmented steric interactions in the lattice compared with isotropic liquid media.[63]

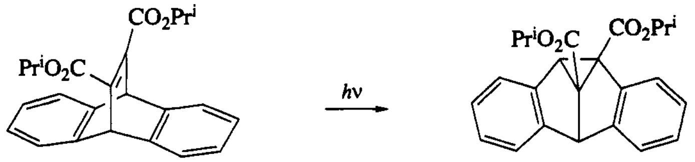

(**36**) $P2_1P2_1P2_1$ crystals    100% *ee*    (51)

## 2.5.5 SYNTHETIC UTILITY

So far the di-π-methane photoisomerization has found few applications in synthesis, despite the fact that vinylcyclopropanes are versatile intermediates. Several reviews discuss these compounds from a general point of view.[64] For example, vinylcyclopropanes are prone to rearrange to cyclopentenes. Hence, in sequence, these two rearrangements may serve as a way to produce cyclopentenes from 1,4-dienes.[65]

It is perhaps worth pointing out that the di-π-methane rearrangements of 1,4-cycloheptadienes produce bicyclo[4.1.0]alkenes which are present in several natural products (*e.g.* in carenes). However, the most striking utility is perhaps evident in polycyclic transformations. The di-π-methane rearrangement remains the most efficient and effective method for synthesizing semibullvalene and its benzo and dibenzo derivatives. It is, indeed, surprising that this synthetic protocol has found so little utilization, especially in the subsequent transformation of products into useful complex target molecules.

For synthetic applications, the stability of the di-π-methane product is very important. Generally, vinylcyclopropanes exhibit different extinction coefficients from the starting dienes, but frequently they are not inert photochemically. This is especially crucial in aryl vinyl systems where the radiation wavelength excites the aryl chromophore and hence both reagent and products. For example, arylcyclopropane photochemistry affords alkenes and indane, as illustrated by 1,2-diphenylcyclopropane (equation 52).[66]

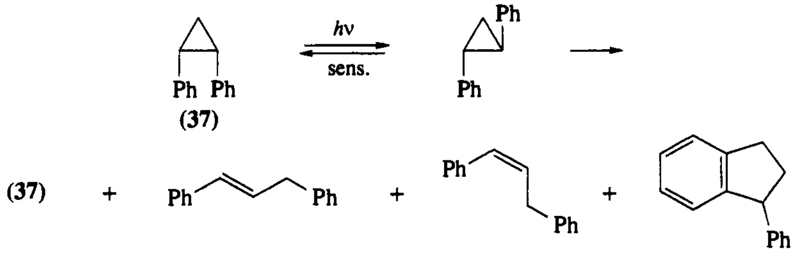

(52)

In other cases the addition of the ketone sensitizer to the cyclopropane moiety has been observed (equation 53).[67] This secondary reaction is probably occurring because of the notably stable benzyl radical center that results upon rupture of the cyclopropane.

On the other hand, retro-di-π-methane rearrangements have been observed. For example, the rearrangement of (**38**) has been rationalized in terms of a reverse di-π-methane reaction, followed by 1,3-hydrogen shift (equation 54).[68]

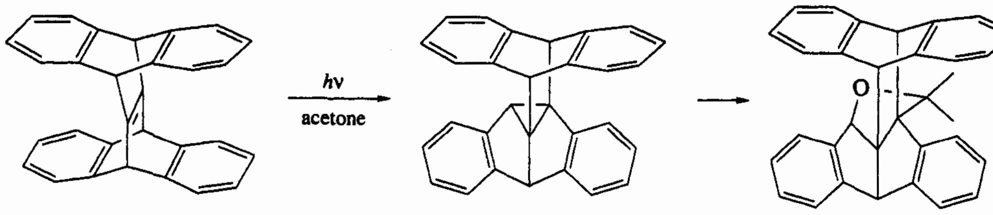

(53)

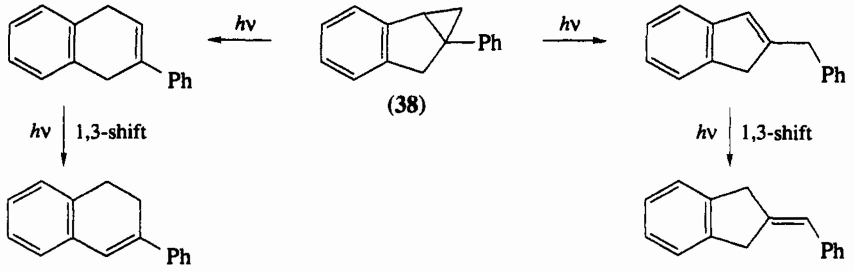

(38)

(54)

Even more complex is the mixture of products which arises from the direct irradiation of benzotricyclo[3.1.0.0$^{2,6}$]hex-3-ene (**15**), the di-π-methane product of benzonorbornadiene (equation 12). In cyclohexane as solvent, 2-vinylindene and benzonorcaradiene are the major primary products (equation 55).[69]

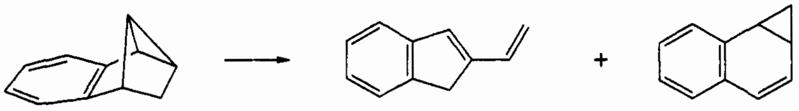

(15)

(55)

## 2.5.6 PRACTICAL ASPECTS

The di-π-methane rearrangement, being a photochemical process, is subject to all basic practical considerations important in routine photochemical work. These are well described in books dealing with this topic.[70] General considerations which are possibly valid for classes of substrates are given in this section.

*Apparatus.* Exploratory and mechanistic photochemistry does not need large quantities of material (up to 1 g) and can be accomplished with external light sources. The Rayonet photoreactor is a typical apparatus. The merry-go-round device allows for more uniform irradiation and simultaneous photolysis of larger amounts (10–100 g) of material. In this simple photoreactor, the radiation intensity can be augmented or diminished by removing light bulbs. Another advantage is the possibility of directly irradiating NMR tubes in order to monitor the progress of the reaction.

Problems arise with this apparatus when low temperatures are needed and when stirring of larger quantities of material is necessary. In these cases, immersion-well photoreactors are more useful. Cooling jackets permit the use of low temperatures and external magnetic stirring can provide good agitation. The latter can be also achieved by passage of a vigorous inert gas stream, most usually pure, dry nitrogen gas, into the solution.

*Lamps and filters.* The combination of radiation source and filter accounts for the actual radiation wavelength to which the reaction mixture is exposed. An unavoidable filter is the glass type of the reaction vessel. In the direct irradiation of substrates not containing functionality other than the phenyl groups, wavelengths in the 280 nm region are needed. Typically a Hanovia 450 W medium-pressure mercury lamp and a 2 mm Corex cylindrical filter ($\lambda > 270$ nm) are employed. Triplet-sensitized reactions need a higher cut-off, which can be obtained by the use of the same lamp with a 2 mm Pyrex filter ($\lambda > 300$ nm). The Rayonet photoreactor can be equipped with 254, 300 and 350 nm lamps.

*Solvents, concentration and sensitizers.* Purity standards for solvents to be used in photoreactions may differ substantially from those in usual preparative chemistry. It is of outmost importance that absorbing impurities and radical initiators are avoided. Furthermore, the reaction mixtures should be purged with pure, dry nitrogen before and during the irradiation.

Common solvents for direct di-π-methane reactions are hexane, cyclohexane or acetonitrile. The substrate concentrations depend on the extinction coefficient of the substrate.

Acetone and acetone–benzene are standard solvent systems for triplet-sensitized reactions. Alternatively, acetophenone or benzophenone (depending upon the triplet energy required) can be used in hydrocarbon solvents, acetonitrile or benzene. The presence of benzene is particularly useful to avoid adsorbance by aryl groups present in the substrate. For example, in the reaction of the benzonorbornadienes, in order to guarantee triplet sensitization the irradiation should be carried out in dilute benzene solutions (*ca.* $10^{-2}$ M) containing acetophenone (*ca.* $10^{-2}$ M) and using a 3500 Å light source. The excited triplet energy of benzophenone ($E_T$ = 73.6 kcal $mol^{-1}$) ensures sufficient energy for most rearrangements. In all cases the isomerizations for these substrates are rapid (complete within 20–40 min) and essentially quantitative.

*Hazards.* Eyes and skin can be severely injured by ultraviolet radiation. One should avoid looking at the reaction mixture when the irradiation source is activated. The photochemical apparatus, especially when using immersion set-ups, must be wrapped appropriately to avoid exposure to the ultraviolet radiation. In view of the high temperatures produced by the lamp, efficient cooling is mandatory. Special care must be exercised when flammable solvents are used. Ozone is also produced, so that working in an efficient hood is essential. Furthermore, proper electrical safety is necessary to avoid high voltage shocks.

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# 2.6

# Oxa-di-π-methane Photoisomerizations

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## 2.6.1 INTRODUCTION

The knowledge and body of β,γ-enone photochemistry have continued to grow rapidly during the past decade following the last comprehensive reviews.[1–4] One main interest in this area is the oxa-di-π-methane (ODPM) photoisomerization, a reaction that has become a powerful synthetic tool and has hence served successfully in natural product synthesis.[5–11] Based on detailed investigations, a convincingly consistent picture of the mechanistic events of the reaction has evolved and predictions of the reactivity of new substrates can nowadays be made with reasonable assurance.

ODPM rearrangements can be readily controlled by the use of appropriate triplet sensitizers and selection of the wavelength. Excellent reproducibility is assured since the optimum reaction conditions are not sensitive to small changes of the experimental parameters (light source, concentration, irradiation time, and temperature). In this context it should be pointed out that the ODPM reaction is typically run at ambient temperature, bringing about rearrangements even of substrates with complex functionality patterns. Very often the rearrangement can be achieved with unprotected functional groups, an aspect which is certainly not restricted to the area of ODPM chemistry but is a valuable bonus for a large number of phototransformations compared with most ground-state processes. This offers a solution to a very prominent goal of modern synthetic methodology.

The chemical yields of ODPM transformations are generally high, *i.e.* yields of 80–95% are achieved in several cases together with quantum efficiencies of 0.5–1.0. In summary, the title reaction has the essential characteristics of a general synthetic method permitting easy and safe handling and has the potential to be employed in medium- to large-scale applications, at least on a multigram to kilogram scale.

## 2.6.2 MECHANISTIC ASPECTS

Most β,γ-unsaturated ketones rearrange upon triplet sensitization to cyclopropyl ketones *via* the so-called oxa-di-π-methane (ODPM) rearrangement, the result of which is an overall 1,2-acyl shift as schematically shown for **(1)** → **(2)**.[1] β,γ-Enone arrangements in which the alkene moiety is further conjugated to either phenyl or C═O sites also undergo this transformation upon direct excitation, *i.e.* *via* the singlet excited state.

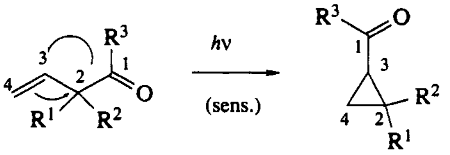
R$^3$
3
1
2
4
O
R$^1$
R$^2$
$h\nu$
(sens.)
R$^3$
O
1
3
R$^2$
4
2
R$^1$

**(1)** **(2)**

### 2.6.2.1 Correlation of Excited States and Reactivity

As shown for the transformations of the cyclopentenyl methyl ketones **(3a–d)** to mixtures of **(4a–d)** and **(5a–d)** (Scheme 1), the ODPM rearrangement occurs from the lowest electronically excited β,γ-enone triplet state.[12,13] The π,π* configuration has been assigned to this state on the basis of CNDO-MO calculations,[12,14] phosphorescence studies at 77 K,[15,16] and mechanistic examinations.[16,17] The phosphorescence data together with sensitization experiments have revealed a $T_1$ energy range of 289–310 kJ mol$^{-1}$ (4.18 kJ = 1.0 kcal) for **(3a–c)** and a much lower $T_1$ of 253 kJ mol$^{-1}$ for **(3d)**.[16]

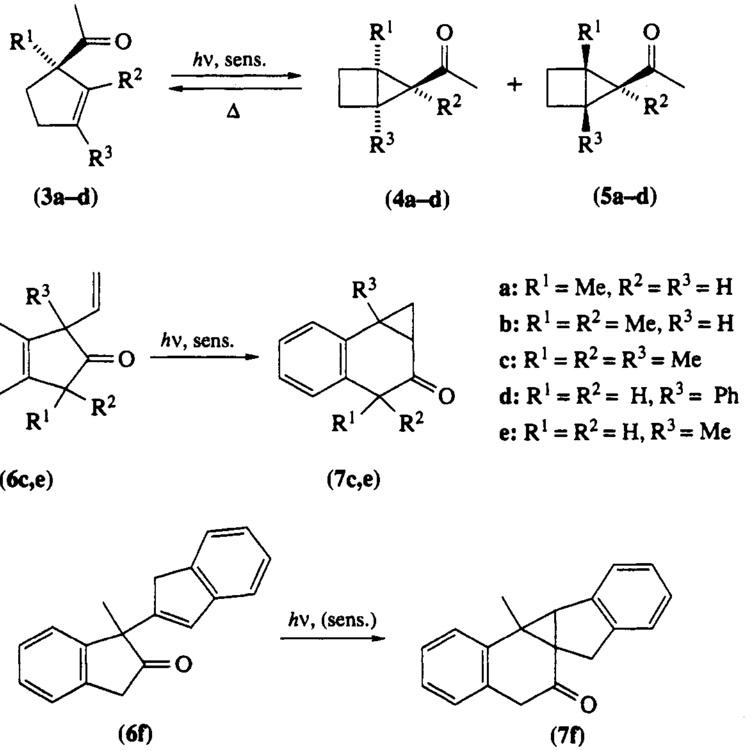
R$^1$
O
R$^2$
R$^3$
$h\nu$, sens.
Δ
R$^1$
O
R$^2$
R$^3$
+
R$^1$
O
R$^2$
R$^3$
(3a–d)
(4a–d)
(5a–d)
R$^3$
O
R$^1$
R$^2$
$h\nu$, sens.
R$^3$
O
R$^1$
R$^2$
a: R$^1$ = Me, R$^2$ = R$^3$ = H
b: R$^1$ = R$^2$ = Me, R$^3$ = H
c: R$^1$ = R$^2$ = R$^3$ = Me
d: R$^1$ = R$^2$ = H, R$^3$ = Ph
e: R$^1$ = R$^2$ = H, R$^3$ = Me
(6c,e)
(7c,e)
O
$h\nu$, (sens.)
O
(6f)
(7f)

**Scheme 1**

Further detailed information on the reactive excited states of β,γ-unsaturated ketones has been acquired with (**3a–c**). Inefficient intersystem crossing from the singlet to the triplet state precedes population of $T_2(n,\pi^*)$ from which the 1,3-acyl shift, induced by Norrish type I cleavage, occurs more readily than internal conversion to $T_1$.[2] $T_2$ has been estimated to lie within 8 kJ mol$^{-1}$ of the acetone triplet (335 kJ mol$^{-1}$).[18] That the 1,3-acyl shift is coupled not only with singlet-state but also $T_2$-state reactivity has been unequivocally shown by two methods. Thermal decomposition of a dioxetane, a derivative of (**3a**), generates predominantly the $T_2$ state from which the 1,3-acyl shift product is formed concurrently with the ODPM products (**4a**) and (**5a**) *via* $T_1(\pi,\pi^*)$.[17] A photo-CIDNP study has independently demonstrated that the 1,3-shift with (**3a–c**) originates from both excited states, $S_1$ and $T_2$, on direct excitation.[19,20] This correlation of excited-state multiplicity and electronic configuration, at least with regard to the ODPM reaction, has recently been supported by more examples such as the rearrangements of (**6c,e**) to the corresponding cyclopropyl ketones (**7c,e**).[21] Furthermore, this latter investigation has uncovered a novel facet of ODPM photochemistry. Whereas (**6c**) rearranges exclusively to (**7c**) upon direct irradiation, the analogs (**6e**) and (**6f**) afford, under the same conditions, products derived from multiple reaction paths, *i.e.* three reaction channels: decarbonylation, 1,3-migration, and the ODPM rearrangement to (**7e,f**). Interestingly, the formation of (**7f**), but not of (**7c**) and (**7e**), is efficiently suppressed by triplet quenchers, a finding that parallels the results of experiments employing triplet sensitizers in which (**6f**) cleanly undergoes the rearrangement to (**7f**) but, in contrast, no reaction occurs with (**6c,e**). The authors conclude that on direct excitation of (**6f**) the ODPM product (**7f**) is formed from the $T_1(\pi,\pi^*)$ state *via* intersystem crossing from $S_1(n,\pi^*)$. Both (**7c**) and (**7e**), however, are thought to originate from the $S_2(\pi,\pi^*)$ state. A reason for the selective $S_2(\pi,\pi^*)$ reactivity of (**7c**) and (**7e**) may be that triplet excitation of (**6c**) and (**6e**) does not extend to the vinyl group, *i.e.* is preferably localized on the benzo ketone part.

Scheme 2 summarizes all the knowledge available up to the present time of the energetic order, spin multiplicity, and configuration of excited states involved in the photochemistry of β,γ-enones.

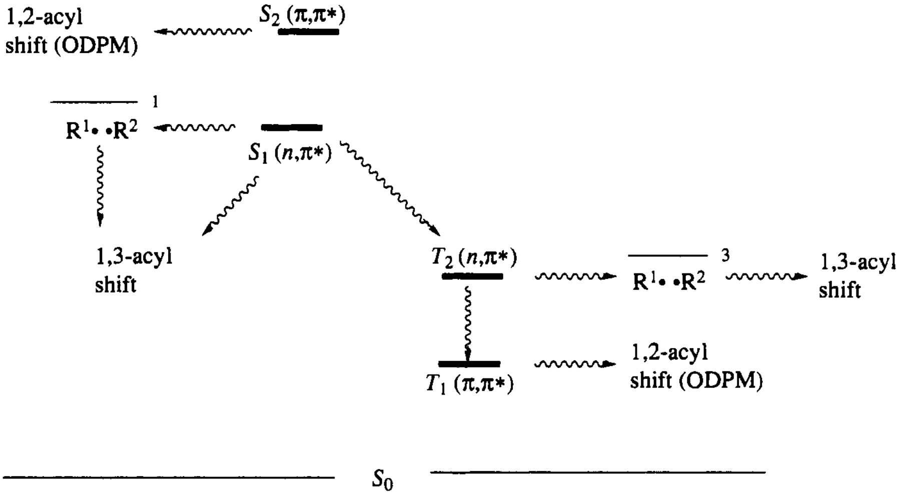

**Scheme 2**

In sole conflict with this coherent picture of the correlation of excited states and reactivity in the ODPM context is the claim that a representative of the 1-methoxy-substituted bicyclo[2.2.2]octenones [*cf.* (**66a**) in Scheme 13, Section 2.6.3.4.2] may not necessarily rearrange from the $T_1$ state but rather from $T_2$.[22,23]

Evidence in favor of a stepwise rather than a concerted mode of rearrangement is gained from the three examples (**8**) → (**11**) (Scheme 3),[24] (**12**) → (**14**) + (**15**) (Scheme 4),[25] and (**16**) → (**18**) + (**19**) (Scheme 4),[26,27] in which the reaction paths can most satisfactorily be described by a sequence of diradical intermediates. In the first case, complete stereochemical scrambling of the isotopically labelled geminal methyls of the products (**11a,b**; 1:1 ratios) during the ODPM rearrangement requires the formulation of a stepwise reaction mode. The depicted sequences of diradicals *via* (**9a,b**) and (**10a,b**) are proposed as the likely reaction cascades fitting the experimental findings. Similarly, the ODPM products resulting from the rearrangements of (–)-(**12**) and (+)-(**16**) demand, by analogy with the previously postulated intermediacy of (**10**), transients such as (**13**) and (**17**), respectively, to account for scrambling of the substituents prior to permanent bond formation, *i.e.* the assembly of the cyclopropane [→ (–)-(**14**) + (–)-

(**15**) and (±)-(**18**) + (±)-(**19**)]. In summary, one may suggest that the majority of ODPM reactions be classified as stepwise processes.

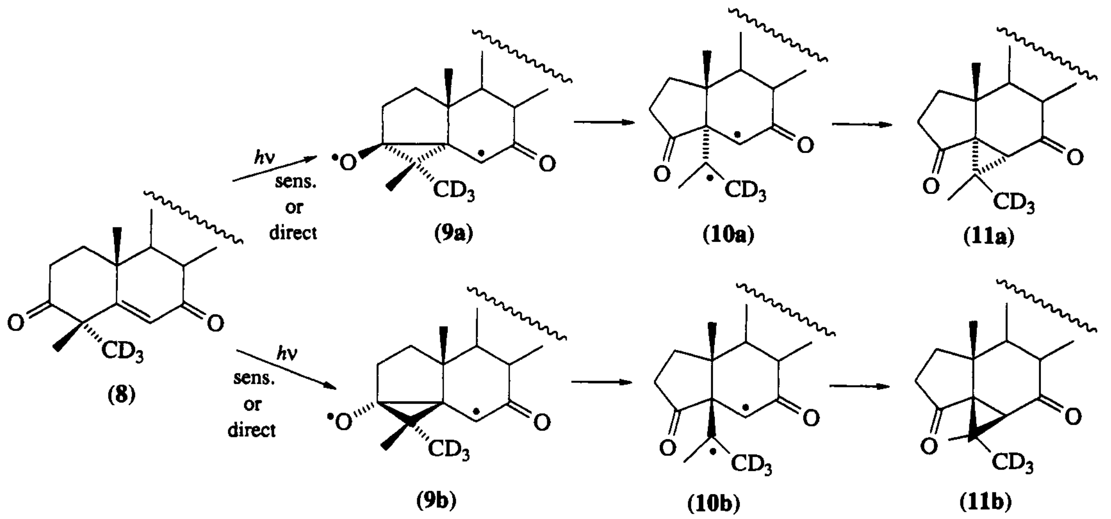

Scheme 3

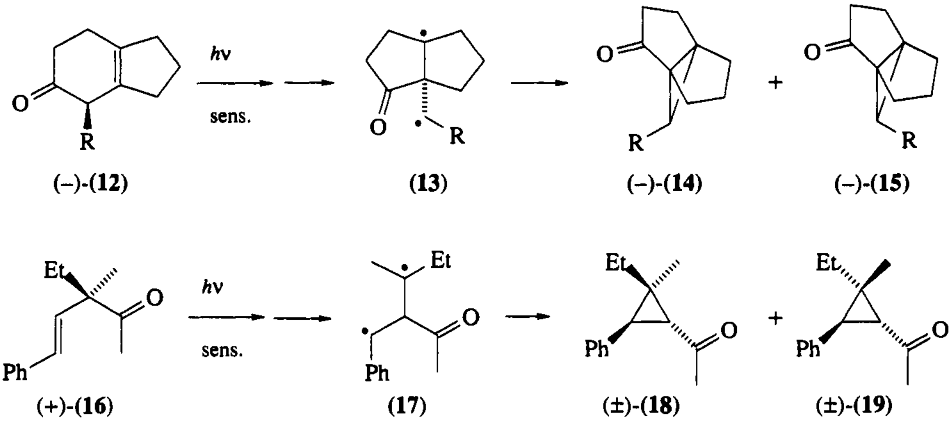

Scheme 4

Nevertheless, several examples are interpreted to be in accord with either of the two allowed concerted modes of the rearrangement, a $[_{\sigma}2_a + {}_{\pi}2_a]$ or $[_{\sigma}2_s + {}_{\pi}2_s]$ process. Whereas the suprafacial case involves retention[28] of the methane carbon, the antarafacial variant gives rise to inversion[29–35] of this center. However, serious doubts[1,36] about the interpretation of some of the results must be raised since geometrical restrictions may also lead to a stereoselective reaction course in the case of stepwise pathways.

### 2.6.2.2 Selective Population of Excited States: The Clue to Reaction Selectivity

High quantum and chemical yields of ODPM rearrangements are obtained with substrates in which the β,γ-enone chromophore is part of a conformationally rigid molecular assembly which at the same time guarantees adequate orbital overlap of the C=C and C=O π-bonds. Whereas in bicyclic and bridged β,γ-unsaturated ketones these prerequisites are widely met, acyclic β,γ-unsaturated ketones usually rearrange inefficiently since other channels of energy dissipation from the triplet state predominate. Exceptions to this rule are substrates in which the C=C π-bond is part of a styrene or an α,β-enone moiety (Section 2.6.3.1). In this context it should also be noted that β,γ-unsaturated aldehydes, except for one case, are ODPM unreactive (Section 2.6.3.2).

The principle of efficiency and selectivity control of the 1,2-acyl shift can best be demonstrated by the bicyclo[2.2.2]octenone transformations given in Scheme 5.

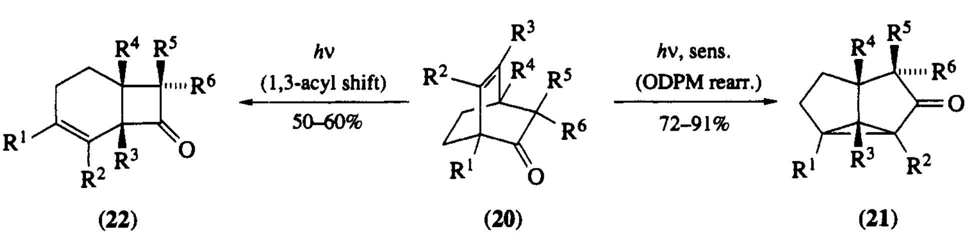

**a**: $R^{1-6}$ = H (refs. 5–11, 39, 40; available enantiomerically pure)
**b**: $R^1$ = Me, $R^{2-6}$ = H (refs. 5–11, 39)
**c**: $R^{1,4}$ = Me, $R^{2,3,5,6}$ = H (ref. 5)
**d**: $R^1$ = $CH_2CH(OMe)_2$, $R^{2,3,5,6}$ = H, $R^4$ = OMe (refs. 8, 41)

**Scheme 5**

As mentioned previously, the energy of the lowest and, at the same time, ODPM-reactive triplet state of structurally plain β,γ-unsaturated ketones is in the range of 289–310 kJ mol$^{-1}$.[12–17] This means that sensitization of the 1,2-acyl shift starts to be effective with acetophenone or acetophenone-type donors, known to possess a $T_1$ energy of 302–310 kJ mol$^{-1}$.[37,38] Most efficient energy transfer is guaranteed with sensitizers transferring their energy exothermically, *e.g.* a quantum yield close to unity is determined for the conversion (**20a**) → (**21a**) in 1–2% acetone solution [$E(T_1)$ of acetone approx. 335 kJ mol$^{-1}$] when irradiating at $\lambda_{irr}$ 300 nm; $\Phi = 0.3$ is found for the same transformation when sensitized by acetophenone [20% of acetophenone added to acetone, benzene or cyclohexane solutions of (**20a**); $\lambda_{irr} > 340$ nm].[39] The chemical yields are uniformly high, 86–91%, under either condition at 94–96% conversions of starting enone. The reaction run in pure acetone solution at $\lambda_{irr}$ 300 nm is, in addition to its efficiency, very attractive from a practical viewpoint. Acetone serving both as solvent and sensitizer renders the work-up and purification preparatively easy: no separation procedure is required. It should be noted, however, that the substrate concentration under the latter conditions should not exceed 2–4% because another reaction path, the 1,3-shift induced by Norrish type I cleavage, becomes noticeably competitive, affording the cyclobutanone (**22a**). This side reaction is a consequence of direct light absorption by (**20a**) competing increasingly with absorption by the acetone at the wavelength employed. For the same reason, even greater direct absorption of light renders the yield of (**21a**) much lower (34%) when the acetone solution of (**20a**) is irradiated with 254 nm light.[40]

Cyclobutanone formation becomes more bothersome in the acetone-sensitized rearrangements of the homologs (**20b–d**) to (**21b–d**) in which approximately 10% of (**22b–d**) are already formed as by-products when 1–2% acetone solutions are irradiated. For these substrates, and generally for all 1-substituted bicyclooctenones of type (**20**), it is therefore advantageous to employ acetophenone sensitization at >340 nm, where the absorbance of the enone chromophore is negligible. Preparatively attractive high substrate concentrations of up to 10% of (**20**) can be employed under the latter conditions.

## 2.6.3 CLASSES OF ODPM-REACTIVE SUBSTRATES

Semicyclic, bicyclic and among these especially bridged β,γ-unsaturated ketones give rise to ODPM products in good to excellent yields. This does not only apply to the simplest case of ODPM chromophores, but also to those which are conjugated additionally either at the ketonic or at the alkenic site. These latter two arrangements undergo efficient singlet to triplet intersystem crossing and hence also 1,2-acyl migration upon direct excitation. Besides exclusive ODPM arrangements, mixed chromophores have been investigated in which additional di-π-methane (DPM) reactive sites[42] are present. Such combinations, however, react highly selectively *via* the DPM route rather than following the ODPM option (Section 2.6.4.3).

With respect to the preparative usefulness of the ODPM reaction, it should be noted that the chemical yields depend strongly on the skeletal arrangement and substituents of the reactants; the yields increase, at least as a general trend, in the order of Sections 2.6.3.1–2.6.3.4.

### 2.6.3.1 Acyclic β,γ-Unsaturated Carbonyls

Acyclic β,γ-unsaturated aldehydes do not undergo the ODPM reaction and acyclic β,γ-unsaturated ketones rearrange efficiently only if the C═C π-bond is further conjugated, *e.g.* part of a styrene moiety. In all the other cases where the vinyl group is less favorably substituted, other channels of deactivation from the triplet state are more important than the ODPM path. The main process then becomes twisting around the carbon–carbon double bond, resulting in *cis–trans* isomerization. This form of energy dissipation has been called the 'free rotor effect' for β,γ-unsaturated ketones, adopting an earlier formulation made for unconstrained DPM arrangements.[43–45] This process is the main event in the case of irradiation of the isomers (**23**) and (**24**) (R = D) (Scheme 6), which interconvert with a quantum efficiency of 0.12; the potential ODPM product (**25**) is not formed at all.[46] Successful competition of the 1,2-acyl migration with the free rotor effect is suggested to depend on the degree of orbital mixing in the $T_1$ state, which in turn is reflected by an enhanced $n \rightarrow \pi^*$ absorption.[1] If the vinyl group is part of a styrene moiety, ODPM reactivity, in competition with *cis–trans* isomerization, is again encountered. One example of this type is the transformation of the *cis*/*trans* isomers (**26**)/(**27**), which affords the sole product (**28**) in 93% yield.[47]

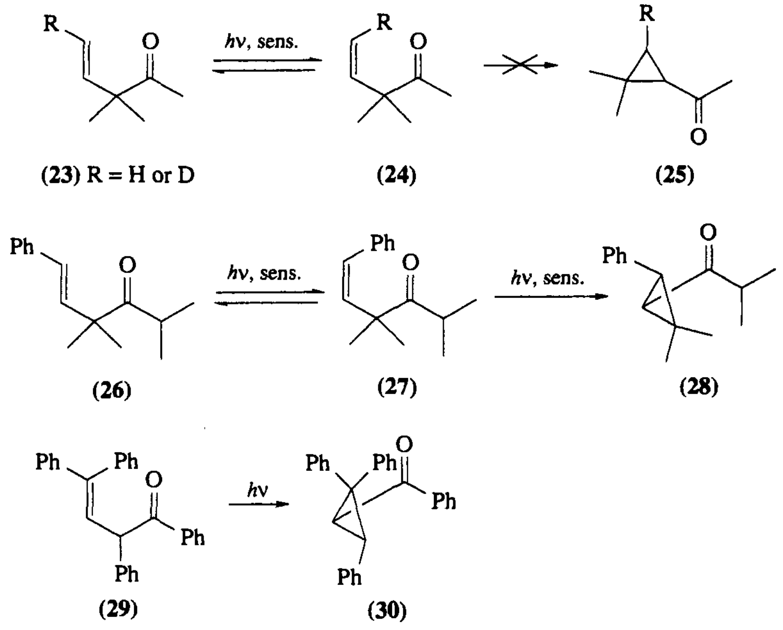

**Scheme 6**

A number of cases have been found where the ODPM rearrangement also occurs on direct excitation, *e.g.* compounds in which the alkene is further conjugated to either C═O or phenyl sites. It should be noted that the first example of an ODPM reaction belongs to the latter category: (**29**) rearranges without sensitizer to (**30**) in 7% yield[48] (for further examples of ODPM reactions on direct excitation, see the following Sections 2.6.3.2 and 2.6.3.3). Introduction of a $^{14}C$ label has shown that the rearrangement to (**30**) proceeds by migration of the benzoyl group. A closely related analog of (**29**) that bears a methyl ketone instead of the benzoyl group also undergoes *cis–trans* isomerization exclusively from the triplet state,[49] a result that may reflect enhanced susceptibility of the methyl derivative to vibrational energy dissipation.

The reluctance of the acyclic substrates to undergo the ODPM reaction, apart from the few exceptions cited above, represents a methodological gap, at least from a synthetic viewpoint; it can, however, be overcome by resorting to the respective imine derivatives of such β,γ-unsaturated aldehydes and ketones (Section 2.6.3.1.1).

#### *2.6.3.1.1 Aza-di-π-methane rearrangement*

Specific imine derivatives of otherwise reluctant (see preceding section) β,γ-unsaturated aldehydes and ketones are again photochemically reactive and cyclize in high yields when irradiated in the presence of a triplet sensitizer: they undergo the aza-di-π-methane rearrangement, typical examples of which are shown for (**31**) → (**32**) ($R^1$ = alkyl or phenyl).[50,51]

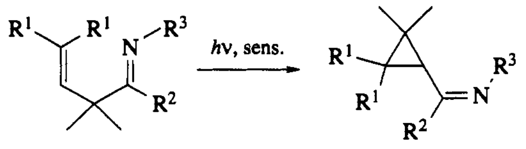

**(31)** **(32)**

**a:** $R^1$ = Ph, $R^2$ = H or Me, $R^3$ = OAc
**b:** $R^1$ = Me, $R^2$ = H, $R^3$ = OAc

no reaction (*h*ν, direct or sens.) in case of $R^1$ = Ph, $R^2$ = H or Me, $R^3$ = OH or OMe

This reaction depends on the type of nitrogen substitution and it is proposed that the reactivity may correlate with the ionization potential of the imine.[52] Oxidized derivatives, *i.e.* the oxime (**31**; $R^3$ = OH)[53] and the oxime ether (**31**; $R^3$ = OMe),[54] fail to undergo the aza-di-π-methane reaction. Instead, isomerizations around the C=N and C=C bonds are the main paths of deactivation. Only for one oxime, a cyclic and additionally constrained derivative, has aza-di-π-methane reactivity been reported.[55]

In order to increase the ionization potential of the oxime group, oxime acetates have been prepared and investigated recently.[56] The acetophenone-sensitized rearrangement of (**31a**) turns out to be highly efficient, providing the cyclopropane (**32a**) in 79% yield in addition to the nitrile derivative, which derives from elimination of acetic acid, to the extent of 11%. The aza-di-π-methane reaction also proceeds in benzene; direct excitation, on the other hand, fails to trigger this process. The authors suggest that initial energy transfer to the 1,1-diphenylalkene moiety may be responsible for the success of cyclization. This notion is substantiated in the same work[56] by the lack of rearrangement of (**31b**) in the presence of acetophenone. The sole product formed under these conditions is an oxetane. The aza-di-π-methane reaction path, on the other hand, is again activated when (**31b**) receives the energy from acetone to form (**32b**), a result which confirms the necessity for exothermic energy transfer to the alkene moiety of the starting material.

In a synthetic context, it is important to note that liberation of the carbonyl from the respective imine photoproducts has so far not yet been probed. A potential 'drawback' of this step could be simultaneous cleavage of the cyclopropane[57,58] under the necessary hydrolytic conditions, a transformation which is, however, by itself part of the synthetic strategy in many instances.[59]

### 2.6.3.2 Semicyclic β,γ-Unsaturated Carbonyls

In cases where either the C=C, the C=O or both moieties of a β,γ-unsaturated enone are part of a cyclic system, the ODPM reactivity is noticeably enhanced and less substituent-dependent compared with the previously discussed acyclic arrangement of the chromophore. Two examples of this category have already been given earlier in Section 2.6.2.1 (Scheme 1): the transformations of (**3a–d**) to a mixture of (**4a–d**) + (**5a–d**)[12,13,16,30] and (**6c,e,f**) to (**7c,e,f**)[21] which proceed in yields as high as 65% and 84%, respectively.

Efficiency and limitation of the ODPM reaction are strongly coupled to the degree of flexibility of the alkene moiety. The energy dissipation from the triplet state *via* twisting of the C=C bond is indicated by a comparison of the following examples. When the C=C bond is geometrically constrained, for example being part of a five-membered ring, the rearrangement proceeds smoothly, as documented by the representative reactions of (**3a–d**) and (**6f**), cited above, as well as (**33**) → (**34**)[46] and (**35**) → (**36**) (Scheme 7).[35,59] On the other hand, no rearrangement occurs when the vinyl group is embedded in a six-membered ring such as in (**37**).[46] In this connection it should be pointed out that strong evidence for the existence of alkene twisting has recently been gained in a closely related field, the photochemistry of α,β-unsaturated cyclohexenones.[60]

Substrates in which the methane carbon is not fully substituted, for example in (**35**; R = H), are similarly ODPM unreactive, irrespective of the ring size of the alkene moiety; β,γ → α,β isomerization of the C=C bond appears to constitute a major path of chemical energy dissipation.[61] One exception in this category is, however, the earlier cited (**3d**) in which the alkene is part of a styrene moiety.[16]

When the C=C bond is part of an α,β-unsaturated ketone moiety as in (**38**) (Scheme 8), direct (*i.e.* π,π* excitation) triggers the ODPM reaction: a stereoisomeric mixture of (**39**) and the 1,3-shift product (**40**) is formed in 93% and 6% yield, respectively, at 91% conversion of starting material.[62] Compounds (**40**) and (**39**) are suggested to be generated from the singlet and triplet state, respectively.[62] This finding

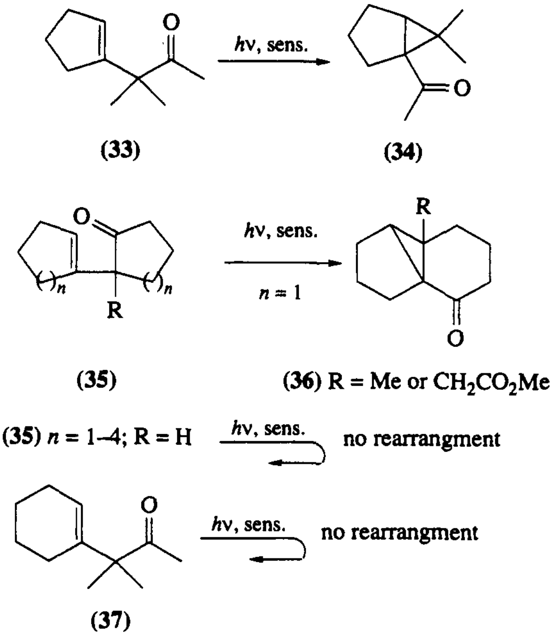
hν, sens.
(33)
(34)
hν, sens.
n = 1
R
(35)
(36) R = Me or CH2CO2Me
(35) n = 1–4; R = H
hν, sens.
no rearrangment
hν, sens.
no rearrangment
(37)

Scheme 7

of 1,2-acyl migration *via* the singlet state seems to be characteristic for various categories of substrates with an extended chromophore (additional conjugation of the vinyl group to either phenyl or C=O sites). Examples of this type are also encountered with bicyclic (**8** and **16** in Schemes 3 and 4, respectively), acyclic (**29** in Scheme 6) and bridged chromophores (**201** in Scheme 11).

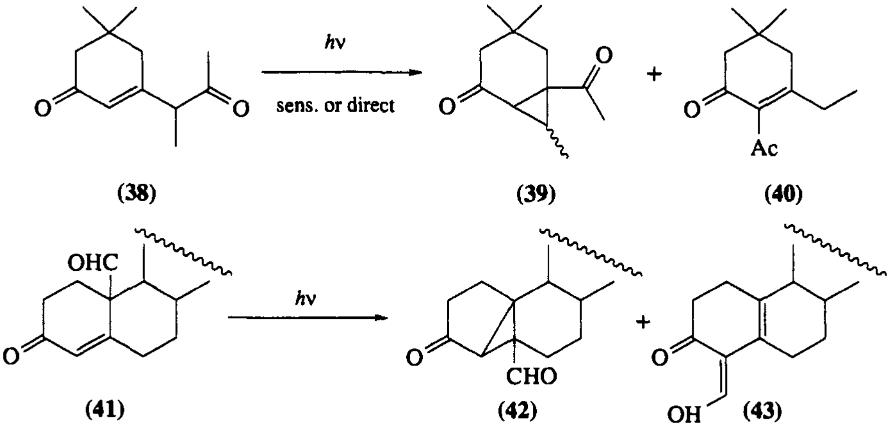
hν
sens. or direct
Ac
(38)
(39)
(40)
OHC
hν
CHO
OH
(41)
(42)
(43)

Scheme 8

A concluding result, albeit of little synthetic value, should still be mentioned because of its uniqueness. One congener (**41**) of the otherwise ODPM-resistant β,γ-unsaturated aldehyde class exhibits ODPM reactivity on direct excitation, giving rise to the formation of (**42**), albeit in moderate yield, besides decarbonylation and 1,3-acyl migration (→ **43**) as the major reactions (Scheme 8).[63]

### 2.6.3.3 Mono-, Bi- and Spiro-cyclic β,γ-Unsaturated Ketones

Representative examples of conversions of bicyclic β,γ-enones have previously been cited in the mechanistic context: the efficient transformation of (**8**) into (**11**) (Scheme 3),[24] the reaction of an analog of (**8**) lacking the C-7 carbonyl,[64,65] and ultimately the preparation of (**14**) and (**15**) from (**12**) (Scheme 4).[25]

In agreement with the findings concerning the reactivity of (**38**) and (**41**) (Scheme 8), the $\mathrm{O{=}C{-}C{-}C{=}C{-}C{=}O}$ chromophore in (**8**) also undergoes the 1,2-acyl shift on direct excitation.[24,66] This rearrangement has been shown to occur from the lowest triplet state (π,π*) in the energy range typical of α,β-enones.[66]

Two unusual findings concern ODPM reactions encountered on direct excitation of structurally simple β,γ-enone chromophores as in (**44**; R = H; Scheme 9) and in the steroidal analog (**46**), which rearrange to (**45**)[67–69] and (**47**),[68,69] respectively. Intriguingly, a number of closely related compounds do not rearrange to ODPM products in the absence of a sensitizer,[64,65,70] two examples of which are (**44**; R = Me)[68] and the 2-keto isomer of (**46**).[68,69] It has been suggested that the dihedral angle between the carbonyl and the vinyl group in the enones controls the efficiency by which the $^3$(π,π*) state is populated on direct irradiation; hence the reaction selectivity of 1,2- *vs.* 1,3-acyl migration.[1,71]

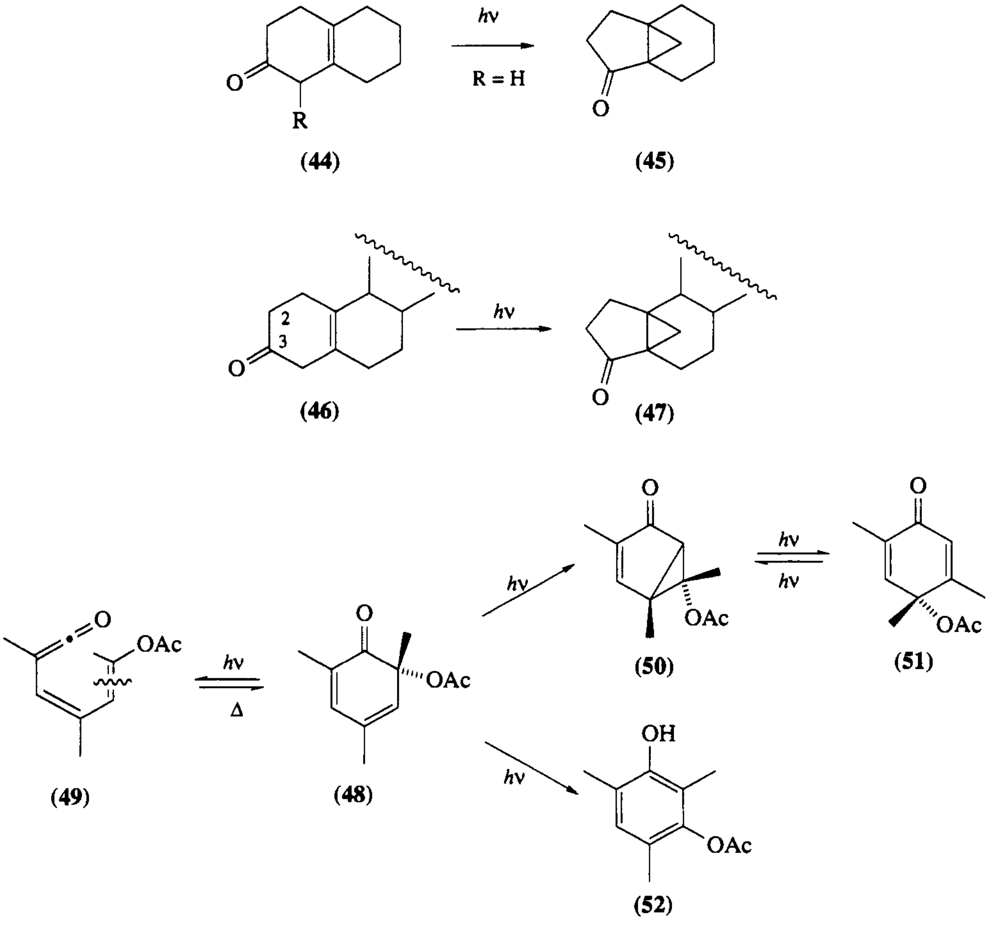

Scheme 9

In the monocyclic series, the 2,4-cyclohexadienones rearrange to photoproducts of potential synthetic value.[72] However, for efficient 1,2-acyl migration, only a relatively small number of substrates are suitable. These must be highly substituted, for example (**48**). Whereas on direct excitation in methanol, cleavage to the isomeric ketenes (**49**) ($\Phi \geq 0.42$) predominates,[73] the remarkably stereoselective 1,2-acyl shift to the bicyclohexenone (**50**) is found either in trifluoroethanol or when the dienone is adsorbed on silica gel.[74] The conversion to (**50**) is followed by a reversible phototransformation to the cross-conjugated dienone (**51**)[75,76] and accompanied by aromatization to (**52**) to a minor extent.[77] Such reactivity has also been verified for tetra- and penta-methylated 2,4-cyclohexadienones.[78,79] The only photoreaction of the hexamethylated homolog, on the other hand, is ketene formation.[78,80,81]

In a third category of cyclic β,γ-enones of synthetic potential, the chromophore moieties are linked by a spiro carbon; typical examples are a β,γ-unsaturated δ-diketone[82] and β,γ;δ,ε-unsaturated spirocyclic ketones.[83–86] A representative of the latter category is (**53**), which upon triplet sensitization with Michler's ketone affords the isomers (**54**) and (**55**) in a ratio of about 2:1 and a total yield of 82% (Scheme

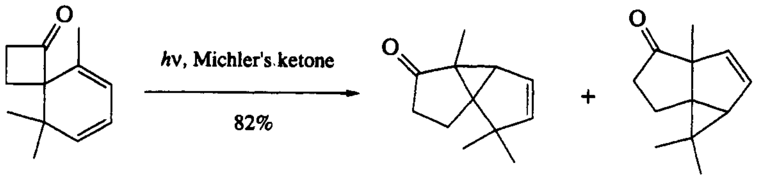

**(53)** **(54)** 71% **(55)** 29%

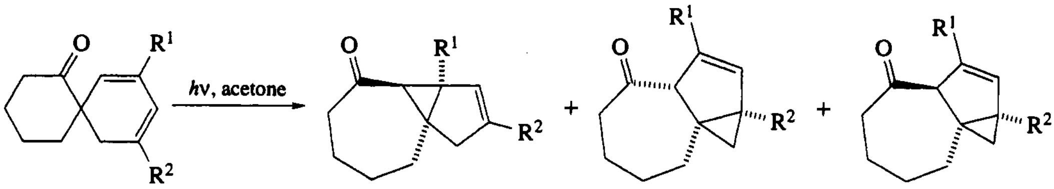

**(56)** **(57)** **(58)** **(59)**

| total yield: | | **(57)** | **(58)** | **(59)** |
|---|---|---|---|---|
| 74% | **a**: $R^1$ = Me, $R^2$ = H | 75% | 20% | 5% |
| 60% | **b**: $R^1$ = H, $R^2$ = Me | 68% | 24% | 8% |
| 51% | c: $R^1$ = $R^2$ = H | 33% | 55% | 12% |
| 95% | **d**: $R^1$ = $CO_2Me$, $R^2$ = H | 100% | 0% | 0% |

**Scheme 10**

10).[83] Analogous homoconjugated spirocyclobutanones in which the diene moiety is part of a seven- or eight-membered ring have similarly been rearranged.[83] Analogously, the acetone-sensitized rearrangement of (**56a,b**) leads to a mixture of vinyl cyclopropyl ketones, the major isomers of which are (**57a,b**) besides two minor components (**58a,b**) and (**59a,b**).[84] Reduced selectivity and yield have been found for the conversion of (**56c**).[84] However, a preparatively attractive result is reported for the sensitized reaction when $R^1$ is an electron-withdrawing group such as the methyl ester in (**56d**): the *trans* isomer (**57d**) is obtained exclusively in 95% yield.[85] The rearrangement of (**56d**) is also highly selective when direct irradiation is employed (>340 nm light): the *trans* product (**57d**) is formed solely.[85] Interestingly, if the irradiation is conducted with 254 nm light, other reaction channels are activated, *i.e.* electrocyclic opening of the diene moiety predominates.[84,85] With regard to potential synthetic exploitation of this chemistry, the smooth thermal isomerization of (**57d**) to (**59d**) is worth mentioning.[85] The photochemical results with (**56a–d**), *i.e.* the striking wavelength dependence of the reactions, are interpreted as being indicative of the mechanistic involvement of more than one excited state with exceptionally high selectivity.[86]

## 2.6.3.4 Bridged β,γ-Enones

### *2.6.3.4.1 General*

Since the efficiency of the ODPM reaction depends strongly on the degree of potential twisting of the C═C moiety of the β,γ-enone in the excited state (*cf.* Sections 2.6.3.1 and 2.6.3.2), the conformationally rigid [2.2.1]- and especially the [2.2.2]-bridged skeletons are generally excellent candidates for good performance. Synthetically very useful examples of bicyclo[2.2.2]octenone transformations *via* the ODPM path have already been given in Scheme 5; for the extension of the list, further analogous conversions are cited in Scheme 11 (for older examples, consult refs. 1–4).

The rearrangement of bicyclo[2.2.1]heptenone (**60a**) in acetone affords mainly the 1,2-acyl shift product (**61a**) accompanied by a small amount of the 1,3-shift isomer (**62a**),[32,99] the latter being convertible to (**61a**) photochemically by acetone sensitization (Scheme 12).[99] In accord with the results discussed in Section 2.6.2, formation of (**62a**) can be suppressed if acetophenone ($\lambda_{irr}$ > 340 nm) is employed as the sensitizer. Identical photoreactivity has been found for the two higher-substituted congeners (**60b**)[100] and the spiro-2-norbornenone (**60c**).[31,32] A mechanistic study has revealed that (**60a**) and (**62a**) both give (**61a**) on triplet sensitization and that the triplet diradical (**63**), generated independently by benzophenone-sensitized nitrogen extrusion from the parent ketoazoalkane, is a common intermediate.[101]

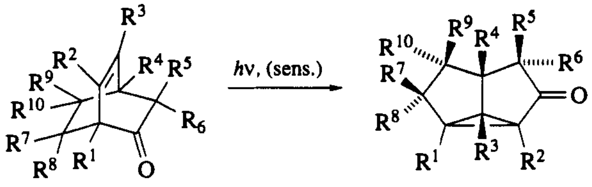

(20) (21)

a–d: *cf.* Scheme 5

e: $R^{1,4,7-10} = H$, $R^{2,3} = CO_2Me$, $R^{5,6} = Me$ (76% yield) (refs. 87, 88)

f: $R^{1,2,4,7-10} = H$, $R^3 = CO_2Me$, $R^{5,6} = OMe$ (ref. 89)

g: $R^{1-6,9-10} = H$, $R^7 = Me$, $R^8 = CH_2OH$ (91% yield) (ref. 90)

h: $R^{1-6,8,10} = H$, $R^{7,9} = CH{=}CH$ (66% yield) or $CBr{=}CH$ (80% yield) (ref. 91)

i: $R^{1-3,5-8} = H$, $R^{4,9}$ = cycle, $R^{10} = Me$ (structure *cf.* Scheme 21, 70% yield) (refs. 92–94)

j: $R^{1-7} = H$, $R^{8,10}$ = cycle, $R^9 = Me$ (structure *cf.* Scheme 21, 72% yield) (refs. 92–94)

k: $R^1 = Me$, $R^2 = H$, $R^{3,4}$ = cycle, $R^{5-10} = H$ (structure *cf.* Scheme 21, 50% yield) (ref. 95)

l: $R^{1,4-8} = H$, $R^{2,3} = CMe_2(CH_2)_2CO$, $R^{9,10} = Me$ (direct or sens., 78% yield) (ref. 96)

m: $R^{1,4,7-10} = H$, $R^{2,3,5 \text{ or } 6} = CO_2Me$, $R^{5 \text{ or } 6} = Me$ or $CH_2Ph$ (51–65% yield) (ref. 97)

n: $R^{1-4,7-9} = H$, $R^5 = CO_2Me$, $R^{6,10}$ = four-, five- or six-membered cycles (66–89% yield) (ref. 98)

Scheme 11

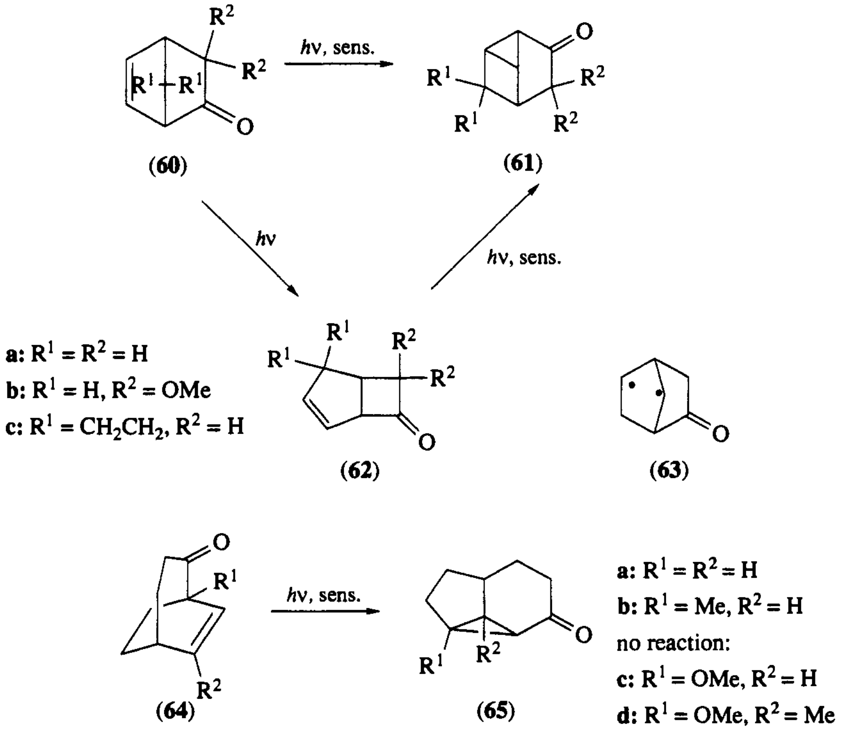

(60) (61)

a: $R^1 = R^2 = H$

b: $R^1 = H$, $R^2 = OMe$

c: $R^1 = CH_2CH_2$, $R^2 = H$

(62) (63)

(64) (65)

a: $R^1 = R^2 = H$

b: $R^1 = Me$, $R^2 = H$

no reaction:

c: $R^1 = OMe$, $R^2 = H$

d: $R^1 = OMe$, $R^2 = Me$

Scheme 12

While the bicyclo[2.2.1]heptenones and bicyclo[2.2.2]octenones are both excellent ODPM reactants, the higher homolog bicyclo[3.2.2]nonenones (**64**)[102–104] are rather reluctant regarding the 1,2-shift. In acetone solution ($\lambda_{irr} > 290$ nm), (**64a**) and (**64b**) rearrange in moderate yields of 18% and 23%, respectively, to the cyclopropyl ketones (**65a,b**) besides formation of the 1,3-shift products in about equal amounts.[104] Surprisingly, the 1-methoxy derivatives (**64c,d**) do not undergo the 1,2-shift at all.[104] Specific patterns of substituents in the enone can sterically control or even alter the course of ODPM reactions. Similarly, additional unsaturation in the starting enone gives rise to competitive reaction modes

(DPM reaction), yielding products which are of great synthetic value as well. The following classes of substrates exhibit such reaction properties: 1-methoxy-substituted β,γ-unsaturated ketones (Section 2.6.3.4.2), β,γ-unsaturated ε-diketones (Section 2.6.3.4.3), β,γ;β′,γ′- and α,β;β′,γ′;δ,ε-unsaturated ketones (Section 2.6.4.3).

### *2.6.3.4.2 1-Methoxy-substituted cyclic β,γ-unsaturated ketones*

The rearrangement of 1-methoxy-substituted bicyclo[2.2.2]octenones (**66a–d**) follows a mechanistic variant of the ODPM reaction, which includes two consecutive single-step phototransformations, *i.e.* the ODPM path to (**67a–d**), again triplet sensitized, and conversion to the final 1,4-diketones (**68a–d**) (*cf.* Scheme 13).[5–11,105–108] The second step involves cleavage of the transient cyclopropane in (**67a–d**) accompanied by loss of the methoxy methyl, most likely *via* methyl radicals, and transfer of a hydrogen atom from the solvent.[107]

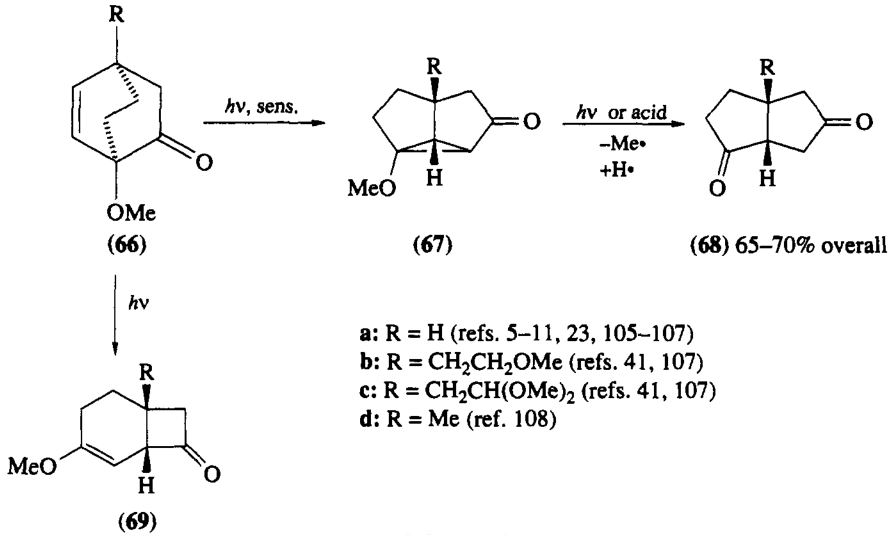

**a**: R = H (refs. 5–11, 23, 105–107)
**b**: R = $CH_2CH_2OMe$ (refs. 41, 107)
**c**: R = $CH_2CH(OMe)_2$ (refs. 41, 107)
**d**: R = Me (ref. 108)

**Scheme 13**

Notably, diquinane products of type (**68**) are of particular synthetic interest. Firstly, their rings are conveniently functionalized by keto groups that can be chemically distinguished and allow further individual elaboration of the functionality pattern into polyquinanes (*cf.* Section 2.6.6). Secondly, the starting materials (**66a–d**) are readily available, each in about 30% yield, from anisole, *p*-methoxytoluene, *p*-methoxyphenylacetic acid and *p*-methoxybenzyl cyanide, respectively.[41,105–108] The optimum reaction conditions, resulting from detailed mechanistic studies,[107] are as follows. Irradiation with 300 nm light (Rayonet) of argon-flushed 1% solutions of (**66a–d**) in 2:1 mixtures of acetone and isopropyl alcohol at room temperature affords 65–70% yields of (**68a–d**) and 5–10% of cyclobutanones (**69a–d**). The latter 1,3-shift products are accessible as the main components in yields of 50–60% on direct irradiation of the starting enones.[41]

It has been proposed that the sensitized conversion (**66a**) → (**68a**) proceeds *via* the 1,2-acyl shift product (**67a**).[105,106] The three-membered ring in (**67a**) is photolytically cleaved,[109,110] followed by loss of the methoxy methyl and addition of a hydrogen atom to give (**68a**).[105–107] In neat acetone, serving both as solvent and triplet sensitizer of the homologous (**66b**), and in benzene containing acetophenone, the formation of a transient in low concentration has actually been observed.[41,107,108] The analytical data and chemical behavior are clearly in favor of the proposed tricyclic structure (**67b**).[41,107] However, the donor/acceptor substitution of the three-membered ring[58,111,112] renders the compound too labile to allow its isolation. Compound (**67b**) reacts not only photochemically to give (**68b**) but also undergoes this transformation in protic media.[41,107]

The ODPM reactivity of higher homologs in the series of bridged 1-methoxy compounds, *i.e.* bicyclo[3.2.2]nonenones, has also been investigated.[104] In contrast to the nor-methoxy analogs (**64a,b**) (*cf.* Scheme 12), which undergo the 1,2-migration in moderate yield, a 1,3-shift is observed exclusively for the derivatives (**64c,d**) [note: the substituents Y and Z in structure (**4**) of ref. 104 are erroneously interchanged].

### *2.6.3.4.3 β,γ-Unsaturated ε-diketones*

The ODPM rearrangement has been very successfully probed with extended chromophores such as β,γ-unsaturated ε-diketones (Table 1). The ε-diketones (**70**), (**72**) and (**75**) afford the tricyclo[3.3.0.0$^{2,8}$]octane-4,7-diones (**71**),[113,114] (**73**) + (**74**)[113–115] and (**76**),[116] respectively, upon triplet sensitization. The rearrangements of (**70**) and (**72**) have been carried out in acetone at $\lambda_{irr}$ = 300 nm and the conversion of (**75**) to (**76**) has been achieved in acetophenone employing 350 nm light. These rearrangements proceed efficiently with quantum yields of 0.17–0.93 and deliver the products in 60–95% yield.[114]

**Table 1**

| *β,γ-Unsaturated ε-diketone* | *Photoproduct* | *Quantum yield (Φ)* | *Chemical yield (%)* | *Ref.* |
|---|---|---|---|---|
| 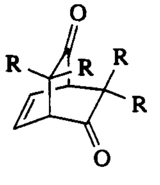<br>(**70**) | 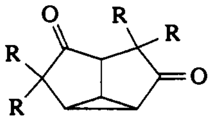<br>(**71**) | | | |
| R = H | | 0.93 | 75 | 113, 114 |
| R = Me | | 0.34 | 60–75 | 113, 114 |
| 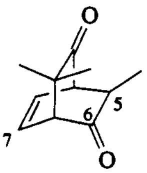<br>(**72a**) | 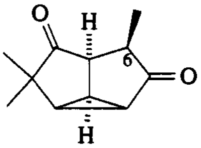<br>(**73a**) | 0.36 | 70–74 | 113, 114 |
| 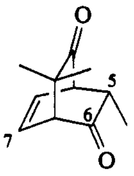<br>(**72b**) | 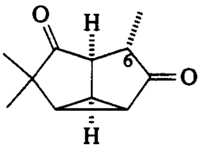<br>(**73b**) | 0.17 | | |
| 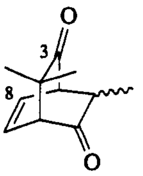<br>(**72a,b**) | 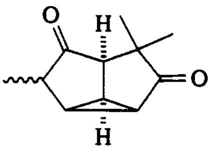<br>(**74a,b**) | — | Minor product | 113, 114 |
| 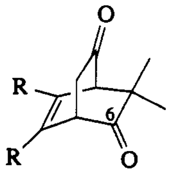<br>(**75**) R = $CO_2Me$ | 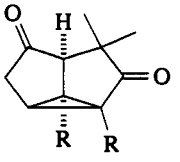<br>(**76**) | — | 95 | 116 |

A preparatively attractive aspect of this chemistry is the exceptionally high enone concentration of more than 20%, as shown with (**72**), at which the transformations can still be run without noticeable formation of side products. In the case of the trimethyl derivative (**72**), a regioselective photochemical rearrangement favoring the formation of (**73**) over (**74**) has been encountered. The course of the reaction seems to be sterically controlled by the methyls. *In situ* photochemical equilibration of the C-5 epimers (**72a,b**) allows preferential rearrangement involving the C-6 (→ **73a,b**) rather than the C-3 (→ **74a,b**) keto group.[114,115]

It has been argued that bridging in the primary photochemical step between C-6 and C-7 of (**72a**), on the way to (**73a**), should be the sterically least-hindered ODPM path since the C-5 methyl occupies the '*exo*' position with respect to the bonding sites.[114] In contrast, the corresponding bridging in (**72b**) should be impeded by the secondary methyl now occupying the '*endo*' position. The same argument should apply to the bridging process between C-3 and C-8 of (**72a,b**) which leads to (**74a,b**). Quantum yield measurements indeed support the notion of steric hindrance exerted by the '*endo*' methyls; decreasing values are found in the order of the reactions (**70**) → (**71**; R = H), (**72a**) → (**73a**) and (**72b**) → (**73b**). The efficiency of the tetramethyl homolog (**70**) → (**71**; R = Me), that has the option of two identical bridgings yielding a single product, is greater than for (**72b**) → (**73b**) which competes with the process (**72a,b**) → (**74a,b**).

In conflict with this coherent picture of steric control of the ODPM rearrangement of the ε-diketones (**72a,b**) is the course of the transformation of (**75**).[110] This compound is reported to yield cleanly the 1,4-diketone (**76**) which is the isomer derived from bridging between the vinyl and C-6 in (**75**). In the previously described examples this reaction path has been shown to be unfavorable — an open mechanistic riddle!

## 2.6.4 LIMITATIONS OF THE METHOD

### 2.6.4.1 General

Skeletal arrangements, substituents and ring size of the β,γ-enones are key parameters controlling the ODPM reactivity. As outlined in Section 2.6.3.1, the reactivity of acyclic β,γ-unsaturated carbonyls depends strongly on the pattern of substituents since *cis–trans* isomerization of the C═C bond is often competitive, disfavoring ODPM reactions. They are even suppressed in cases where no phenyl group is attached to the enone γ-position, such as in (**23**) of Scheme 6. The semicyclic arrangements, discussed in Section 2.6.3.2, suffer from ODPM inertness under two circumstances: incorporation of an isolated vinyl moiety in a ring of size larger than a five-membered one (**37** in Scheme 7) or absence of a quaternary methane carbon as in example (**35**; R = H).

### 2.6.4.2 Bridged Bicyclic β,γ-Enones

Generally excellent ODPM substrates are encountered in the classes of mono-, bi- and spiro-cyclic as well as bridged α,β-unsaturated ketones (Sections 2.6.3.3 and 2.6.3.4). In the latter category, the bicyclo[2.2.1]heptenones and bicyclo[2.2.2]octenones, with the exceptions (**20o–q**) (Scheme 14), undergo the 1,2-acyl shift much more readily than the homologous bicyclo[3.2.2]nonenones (**64**) in Scheme 12. The enones of type (**64a,b**) rearrange in moderate yields to (**65a,b**), but most interestingly the 1-methoxy derivatives (**64c,d**) do not give any ODPM product, a result which is yet difficult to rationalize. The switch of reactivity from the [2.2.1] and [2.2.2] skeletons to the [3.2.2] homologs, however, could reasonably be explained by enhanced skeletal flexibility (see the discussion of the acyclic series) or unfavorable orbital overlap, or both.

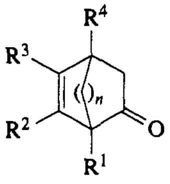

(**20**)

o: $n = 2$, $R^1$ = Me, $R^{2,3}$ = H, $R^4$ = OMe (refs. 8, 41)
p: $n = 2$, $R^1$ = $CO_2Me$, $CO_2H$ or $CO_2Na$, $R^{2,3,4}$ = H (ref. 5)
q: $n = 1$, $R^{1,2,4}$ = H, $R^3$ = OMe (ref. 124)

**Scheme 14** ODPM unreactive substrates

Only with compounds (**20o–q**) are bicyclooctenones found which are unreactive either on direct excitation ($\lambda_{irr}$ = 300 nm) or by triplet sensitization (acetone or acetophenone as sensitizer).[5,8,41,124] On comparison of these exceptional cases with the substrates in Schemes 5 and 11, it becomes apparent that ODPM reactivity *vs.* inertness is influenced by very subtle differences in the substitution pattern. For example, shortening of the acetal chain of (**20d**) to $R^1$ = Me for (**20o**) renders a photoreactive substrate (**20d** → **21d**; 90% yield) photochemically inert.[8,41]

A model has been proposed which allows an empirical prediction of reactivity for this class of compound.[7] Accordingly, if $R^1$ or $R^2$ are donor-type substituents or $R^3$ or $R^4$ acceptors, the substrates (**20**) are ODPM reactive. The complementary pattern of substituents ($R^1$ or $R^2$ = acceptors or $R^3$ or $R^4$ = donors) is characteristic of the unreactive enones. Bicyclo[3.2.2]nonenones (**64c,d**; no reaction, Scheme 12, Section 2.6.3.4.1) and mixed bicyclo[2.2.2]octenones (**20e** → **21e**; Scheme 11, Section 2.6.3.4.1) need not fit into this reactivity scheme.

### 2.6.4.3 β,γ;β′,γ′- and α,β;β′,γ′;δ,ε-Unsaturated Ketones

Besides parent ODPM arrangements, mixed chromophores have also been investigated in which DPM-reactive sites can compete with the ODPM reaction. β,γ;β′,γ′-Unsaturated ketones, *i.e.* barrelenones of type (**77**), rearrange to the corresponding unsaturated cyclopropyl ketones (**78**) upon acetophenone sensitization *via* a highly regioselective DPM process, rather than the optional ODPM variant, in 42–73% yields.[117,118] These results contrast with the observations in a benzobarrelenone series[119,120] but are in full agreement with the following mechanistic investigation. The question as to which of the two possible mechanisms is operative has been answered by the acetone-sensitized reaction of labelled material (**77**; $R^{2,3}$ = D, $R^{4,5}$ = Me).[121] The products must derive from a DPM process rather than from the alternative ODPM reaction paths.

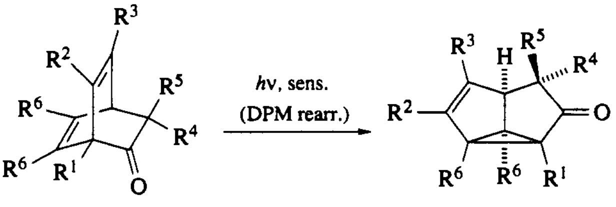

(**77**) (**78**)

$R^{1-3}$ = H, Me or Bu$^t$

$R^{4,5}$ = oxirane

$R^6$ = $CO_2Me$

In summary, the above results reveal relative bridging 'rates' between the optional chromophoric sites in bicyclo[2.2.2]octadienone-type substrates (**77**) in the following order: vinyl–vinyl > keto–vinyl > benzo–vinyl bridging.[117–121]

Similarly, α,β;β′,γ′;δ,ε-unsaturated ketones react in a DPM fashion as shown for the rearrangement of steroidal dienones, *e.g.* (**79**) → (**80**).[122,123]

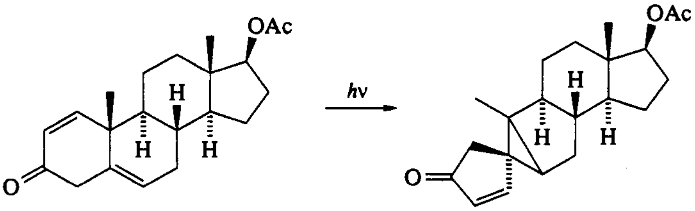

(**79**) (**80**)

## 2.6.5 APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

The search for efficient methods for the construction of five-membered rings with the aim of gaining access to polycondensed cyclopentanoids, which are also found in nature, has been a major concern in synthesis during the past 15 years.[125,126] Preparatively attractive routes to a remarkable number of structural variants of such natural products have been established by the use of tricyclooctanone-type building blocks and congeners thereof, all products of high-yield ODPM transformations.

A considerable number of ODPM products have been made available in optically pure form. Resolution techniques prior to the photorearrangement as well as the use of enantiomerically pure starting materials in general provide ready access to such building blocks. In contrast, enantioselection *via* sensitization has so far turned out to be preparatively of little value. The latter possibility has been probed with a racemate of (**20a**), the rearrangement of which has been sensitized by an optically active hexahydrofluorenone.[39] The enantiomeric excess of (–)-(**21a**) after 7–44% conversion of (±)-(**20a**) reaches 4.5% in benzene or in ethyl acetate at ambient temperature, and 10% in ethyl acetate at low temperature. Interestingly, the same degree of induction can be achieved when racemic sensitizer is employed for the rearrangement of (**20a**) in optically active solvent, *i.e.* in diethyl (+)-tartrate (Scheme 15).[39]

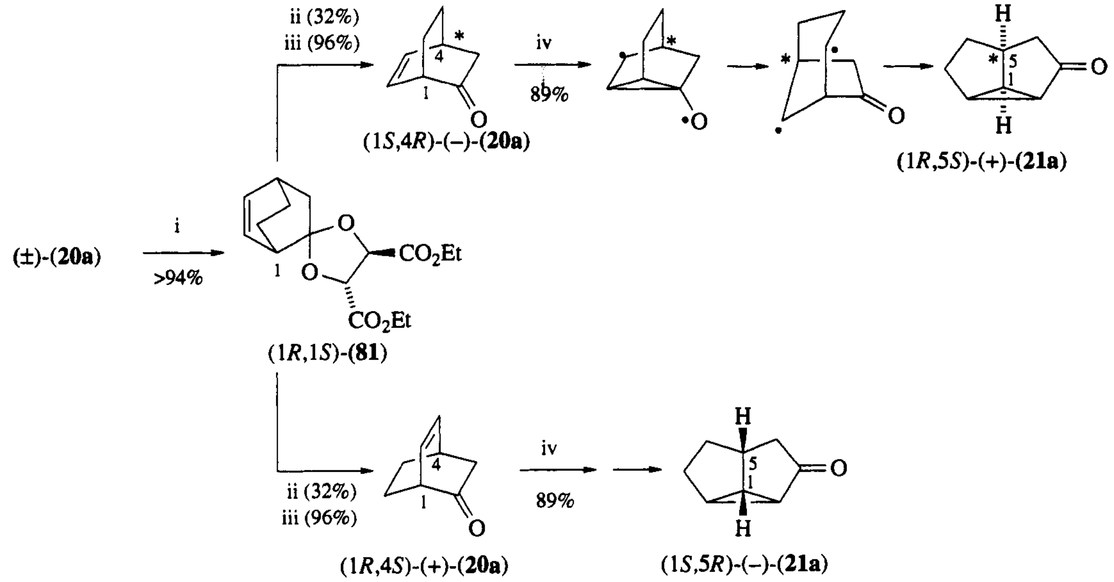
ii (32%)
iii (96%)
iv
89%
(1*S*,4*R*)-(–)-(**20a**)
(1*R*,5*S*)-(+)-(**21a**)
(±)-(**20a**)
i
>94%
CO$_2$Et
CO$_2$Et
(1*R*,1*S*)-(**81**)
ii (32%)
iii (96%)
iv
89%
(1*R*,4*S*)-(+)-(**20a**)
(1*S*,5*R*)-(–)-(**21a**)

i, diethyl (*R*,*R*)-tartrate, *p*-TsOH, toluene, reflux; ii, chromatography; iii, 1N HCl, THF, 40 °C; iv, *h*ν (300 nm), acetone

**Scheme 15**

The ODPM transformation of bridged β,γ-unsaturated ketones is, as expected on mechanistic grounds, enantiospecific. This aspect has been first documented by the production of (+)-(**21a**) and (–)-(**21a**) from the pure enantiomers (–)-(**20a**) and (+)-(**20a**), respectively, without loss of optical activity; this implies that the configuration of the starred carbon (see scheme above) is retained throughout the reaction cascade.[39] This circumstance has paved the way to ready access to enantiomeric target materials simply by the choice of the appropriate optically pure precursors of the photochemical step or starting materials. The enantiomers of (**20a**)[127–129] and (**70**)[114,115] are obtained in >98% enantiomeric excess and in multigram amounts *via* a resolution step which involves ready chromatographic separation of diethyl tartrate derivatives such as (**81**), followed by their hydrolysis to the enantiomers. The use of the photoproducts (**21a**), (**71**) and (**73**), which can be functionalized in a manifold manner by cleavage of the cyclopropane, *e.g.* reductively, *via* nucleophile addition or rearrangement,[57,114,115,130,131] offers a conceptually new approach to the synthesis of enantiomerically pure cyclopentanoid natural products.[5–11]

Four basic structural arrangements as shown in Scheme 16 have so far proven to be of broad utility in synthesis: a parent type (I), with a minimal but very variable set of functionalities, and three more target-oriented complexer units (II)–(IV). The bold lines in the formulae depicted emphasize the functionality pattern characteristic of each representative, constituting in sum a fully flexible and complementary set of possible synthetic modifications at the diquinane core.

Among the first synthetic achievements, based on the use of tricyclooctanones, are the following preparations of mono- and sesqui-terpenes. Four members of the monoterpene iridoid family have been obtained by a single approach (Scheme 17). The disadvantage of the stereo*non*selective reduction of (**21b**), affording (**82**) and (**83**) in a 1:1 ratio, is compensated for by the benefit of simultaneous access to four natural products: (±)-boschnialactone and the epimer (**84**), this being a suitable precursor to attain (±)-al-

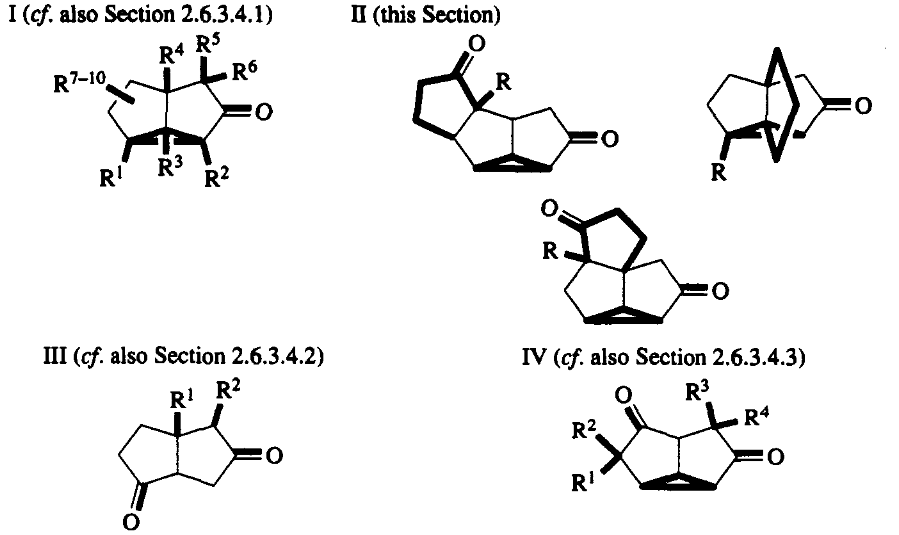
I (*cf.* also Section 2.6.3.4.1)
II (this Section)
III (*cf.* also Section 2.6.3.4.2)
IV (*cf.* also Section 2.6.3.4.3)
R$^4$
R$^5$
R$^6$
R$^{7-10}$
R$^1$
R$^3$
R$^2$
O
R

**Scheme 16**

lodolicholactone, (±)-iridomyrmecin and (±)-isoiridomyrmecin.[5] The sesquiterpene cedrol and more highly oxygenated cedranoids, in racemic form, have been accessed from the Stork–Clarke β-diketone (**85**), which in turn can be assembled in a novel way *via* the 76% yield rearrangement of (**20e**) to (**21e**) (*cf.* Scheme 11).[87,88,132] In 10 steps and in a 15% overall yield, a synthesis of (±)-forsythide aglucone dimethyl ester has recently been accomplished by similarly exploiting the potential of ODPM photochemistry for the key step.[133]

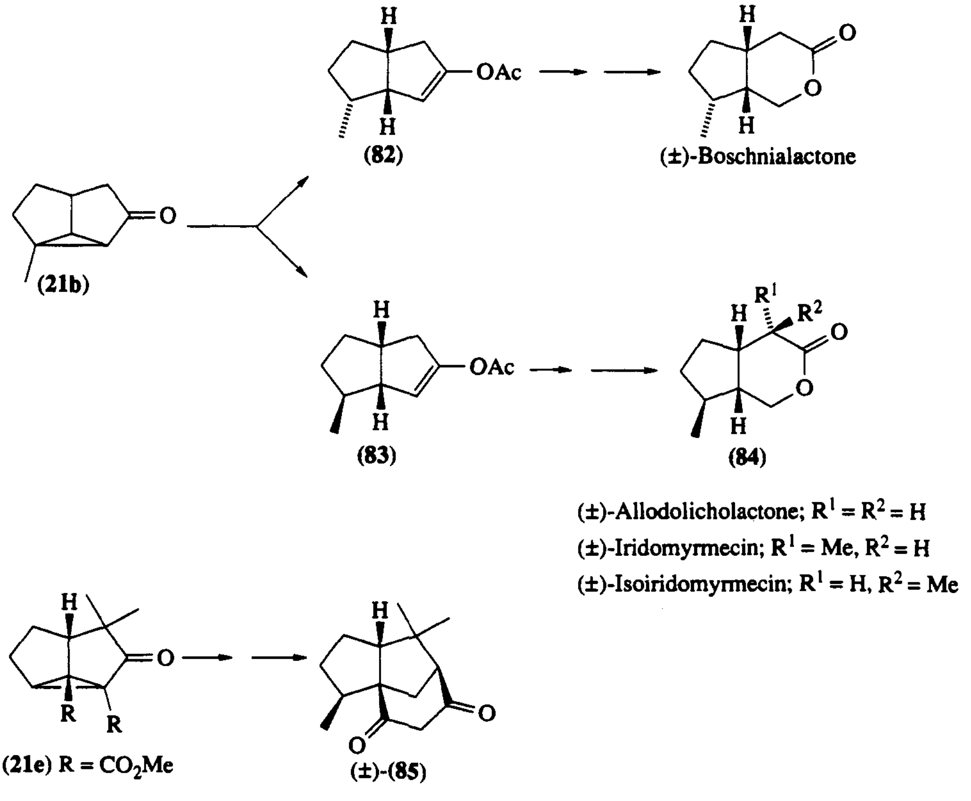
H
OAc
(82)
(±)-Boschnialactone
(21b)
(83)
(84)
R$^1$
R$^2$
O
R
(21e) R = CO$_2$Me
(±)-(85)

(±)-Allodolicholactone; R$^1$ = R$^2$ = H
(±)-Iridomyrmecin; R$^1$ = Me, R$^2$ = H
(±)-Isoiridomyrmecin; R$^1$ = H, R$^2$ = Me

**Scheme 17**

An enantioselective access to a number of different structural variants of the cyclopentanoids is given by the use of the tricyclooctanone building blocks (–)-(**21a**) and (+)-(**21a**), both of which are available in optically pure form as mentioned previously. These particular photoproducts offer an alternative to earlier exercised principles aiming at individually designed target-oriented syntheses. The enantiomers (**21a**) exhibit structural features allowing for a multitude of synthetic transformations of predictable regio- and stereo-selectivity.[57,130,131] As part of this concept, the first stereocontrolled assembly of natural iridodial has been achieved from (–)-(**86**) *via* oxidative ring B cleavage in the last step of the sequence (Scheme 18).[129] Five steps are required for the elaboration of the target material from the intermediate (–)-(**86**), which is the product of exclusive *exo* methylation of (–)-(**21a**). Rearrangement of the cyclopropane moiety of the latter intermediate constitutes the basis for extensive ring A functionalizations, including oxidative enlargement, on the way to (+)-loganin aglucone 6-acetate.[127] This synthesis is distinguished by a higher overall yield of 7%, starting from 1,3-cyclohexadiene and acrylonitrile, than previous efforts and the lack of separation problems.

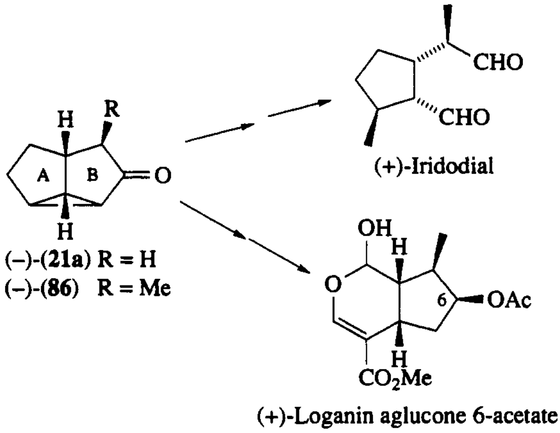

**Scheme 18**

The cleavage of all rings of (**21a**) has led to stereocontrolled access to (**88**; Scheme 19), which is viewed as a segment to serve in the construction of the 16-membered lactone carbamycin B.[134] The numbered carbons in the target derive from the respective centers of the intermediate (**87**), which has been prepared from (**21a**) in a high-yield sequence involving consecutive rearrangement of the cyclopropane, Baeyer–Villiger oxidation and methylation. Evidently the correct absolute configuration, as depicted for (**88**), should derive from (–)-(**21a**) in the final version of the synthesis.

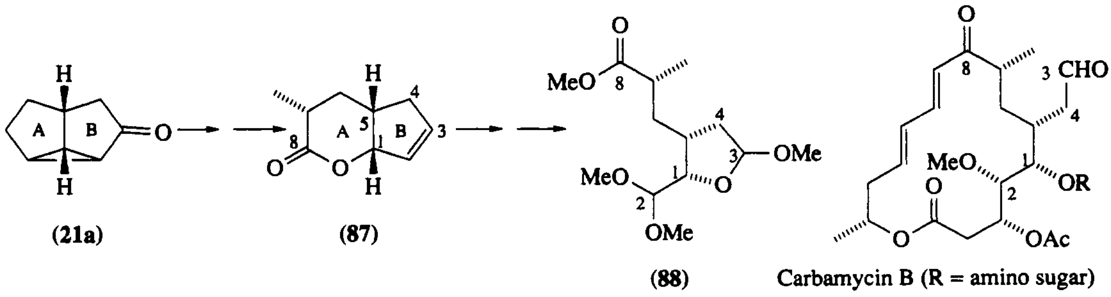

**Scheme 19**

The enantiomer (+)-(**21a**) has been considered configurationally suited as starting material to approach *cis,anti,cis* tricycloundecane-type targets, *e.g.* the antitumor and antibacterially active coriolin, a potential progenitor (**89**) of which has been synthesized, at first in racemic form (Scheme 20).[135,136] However, this route has been abandoned in favor of a much shorter synthesis outlined later (see Scheme 22). Two-step transformations from (+)-(**21a**) to a number of C,18-bisnor-13α,17α-dehydroestrone derivatives (–)-(**90**; R = OTs, OCOCF$_3$, Cl) have been elaborated;[131,137] these are intermediates from which ring C enlargement to (**91**) can be achieved in three further steps which are all realized in high yields (Scheme 20).[138]

In an extension of the previous concept, starting materials which are readily available in enantiomerically pure form have served for the construction of bridged β,γ-enones with an additional five-membered ring.[92,93] In this way the first total synthesis of enantiomerically pure (–)-silphiperfol-6-en-5-one

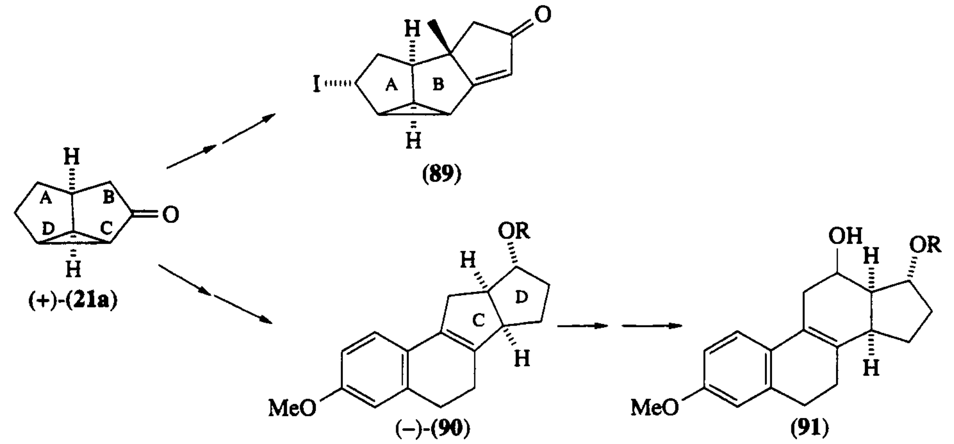

Scheme 20

has been accomplished.[92,94] The acetone-sensitized photorearrangement at $\lambda_{irr}$ = 300 nm of (+)-(**20i**) cleanly furnishes the angularly fused (–)-(**21i**; 72% yield of purified product), the structural features of which have allowed economic elaboration into the silphiperfolenone target (Scheme 21). A by-product, which results from a 1,3-acyl migration, is formed to a negligible extent (4%) under the reaction conditions employed. Such a smooth rearrangement of (+)-(**20i**) is *a priori* not predictable in view of some β,γ-enones bearing bridgehead substituents known to be unreactive under ODPM conditions (see Section 2.6.4.2). Similarly efficient is the conversion of (**20j**) to the linearly arranged *cis,syn,cis* tetracycloundecanone (**21j**), for which the initially wrongly assigned *cis,anti,cis* structure[93] has later been revised on the basis of an X-ray analysis.[92,94] *Cis,anti,cis* fusion of the five-membered rings in tetracycloundecanone-type skeletons has been achieved by the rearrangement of appropriately assembled tricyclo[5.2.2.$0^{2,6}$]undecanediones in racemic form.[139] A very economic preparation of racemic modhephene, a unique natural product with [3.3.3]propellane structure, has been prepared from (**21k**), which in turn is obtained in 50% yield upon irradiation of (**20k**) in acetone solution.[95] These results are complementary in that three types of important cyclopentanoid ring fusions, *i.e.* the [3.3.3]propellane assembly, linearly and angularly fused skeletons (*cf.* Scheme 16: structures type II), can be attained by resorting to a common class of bridged β,γ-enones (**20i,j,k**). These enones are accessible *via* thermal [4 + 2] cycloadditions in an efficiently regio- and stereo-controlled manner. Whereas the stereochemical result of the addition of the etheno bridge is responsible for the ultimate *syn*/*anti* relation of the rings in the photoproducts, the regiochemical location of the C═C bond in the enones determines whether a propellane, a linearly or angularly fused photoproduct results.

The acetone-sensitized ($\lambda_{irr}$ = 300 nm) preparation of a mixture of enantiomerically pure (–)-(**73a,b**) in 70–74% yield (*cf.* Table 1), besides the minor regioisomers (**74a,b**), has opened access to the first total synthesis of the antitumor agent coriolin in its natural configuration (Scheme 22).[113–115] The key step is characterized by a novel facet of ODPM photochemistry, steric control by the methyls in (**72a,b**) giving rise to a site selective rearrangement to (**73a,b**) (*cf.* Section 2.6.3.4.3). Both epimeric photoproducts (–)-(**73a,b**) are equally suitable for the A + B → ABC building-up principle of the target. Concurrent with the ODPM reaction and favoring the most efficient ODPM channel, a second and fast photoreaction results in a 5:1 equilibration of the epimers (**72a**) and (**72b**). Although the mechanism of this process has not been fully identified, it has at least been shown that Norrish type I cleavage and reclosure is unlikely to be responsible for the epimerization.[114] The earlier mentioned, preparatively attractive, high substrate concentrations of more than 20% at which the transformation of (**72a,b**) can still be run without noticeable side reactions (1,3-acyl shift) have to be stressed again at this point. This preparation of (–)-coriolin comprises 14 steps in all, entirely from readily available starting materials; the sequence compares favorably with the shortest synthesis of the racemate achieved earlier.

Similarly, the photorearrangement of β,γ-unsaturated ε-diketone (**75**) (*cf.* Table 1) has been probed in view of its potential application as a key step for the synthesis of cedranoids.[116] Although the tricyclooctanedione (**76**) is cleanly accessible, the scheme has been abandoned in view of difficulties in assembling the ultimately required functionalities; routine β,γ-enone photochemistry has been employed instead.

In a final example, use has been made of a mechanistic variant of the ODPM reaction: the conversion of a 1-methoxy-substituted bicyclo[2.2.2]octenone (**92**) to the bicyclo[3.3.0]octadione (**94**; Scheme 23). The highly substituted β,γ-enone (**92**) is accessible *via* hydroxymethylation of (**66c**), a compound which

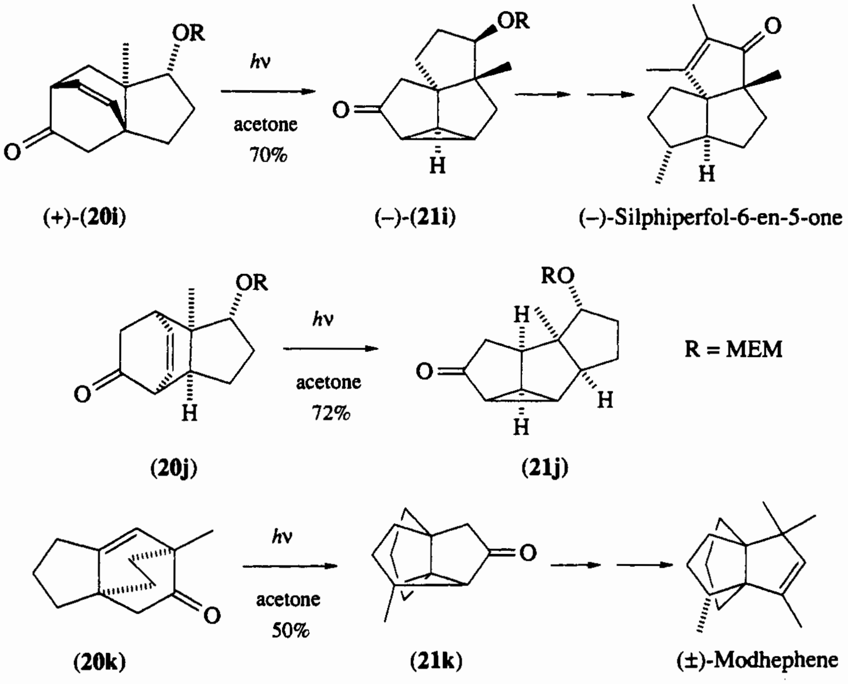
OR
hν
acetone
70%
O
H
(+)-(20i)
(–)-(21i)
(–)-Silphiperfol-6-en-5-one
OR
hν
acetone
72%
RO
H
R = MEM
(20j)
(21j)
hν
acetone
50%
O
(20k)
(21k)
(±)-Modhephene

Scheme 21

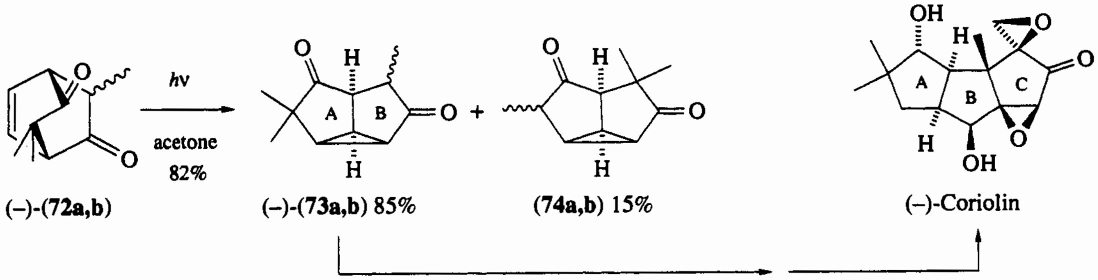
O
hν
acetone
82%
H
A
B
C
OH
(–)-(72a,b)
(–)-(73a,b) 85%
(74a,b) 15%
(–)-Coriolin

Scheme 22

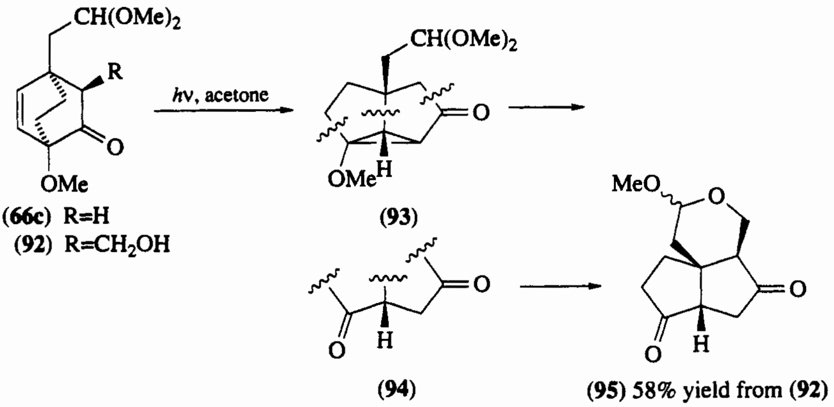
CH(OMe)₂
R
O
OMe
hν, acetone
H
MeO
(66c) R=H
(92) R=CH₂OH
(93)
(94)
(95) 58% yield from (92)

Scheme 23

itself is photoreactive (*cf.* Scheme 13). Enone (**92**) rearranges in two consecutive single-step photoreactions to (**94**) *via* (**93**). The photoproduct (**94**) cyclizes smoothly upon purification on silica gel, affording a potential progenitor (**95**) of pentalenolactone G in good yield.[9,10,41,140] This natural product is a member of a family of antibiotic and tumor inhibitory agents. The photorearrangement (**92**) → (**94**), which is mechanistically in accord with the reactions (**66a–d**) → (**68a–d**), can be performed either in acetone with 20% acetophenone added ($\lambda_{irr} \geq 340$ nm) or by following the procedure described in Section 2.6.3.4.2.[41]

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# 3.1

# Thermal Cycloadditions

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## 3.1.1 INTRODUCTION

The past 15–20 years have witnessed a tremendous growth in the number and type of reactions which are applicable to the synthesis of five-membered rings. The underlying reasons for the growth, and for the continued activity one finds in this area of research, have been elegantly described by others and will not be recounted here.[1] The material which follows focuses primarily upon the use of derivatives of a very reactive diradical, trimethylenemethane (TMM), to construct carbocyclic systems through use of the 1,3-diyl trapping reaction, and upon the use of 1,3-dipolar cycloaddition reactions to synthesize both carbocyclic and heterocyclic ring systems. The latter field is, of course, very rich, intricate and extensive. The present treatment provides only a brief overview of it and, unfortunately, many elegant pieces of work have not been discussed.

## 3.1.2 TRIMETHYLENEMETHANE (TMM)

### 3.1.2.1 Regioselectivity

### *3.1.2.1.1 Fused* versus *bridged (intermolecular 1,3-diyl trapping)*

Both the thermally and the photochemically initiated extrusion of nitrogen from bicyclic diazene (**1**) leads to the formation of a 1,3-diradical (diyl) which is structurally related to trimethylenemethane.[2] As shown in the cascade mechanism illustrated, two forms of the diyl can be intercepted by alkenes bearing electron-withdrawing groups (diylophiles), *viz.* the open form of the singlet diyl and the triplet diyl which is formed *via* intersystem crossing from the singlet (Scheme 1).[2]

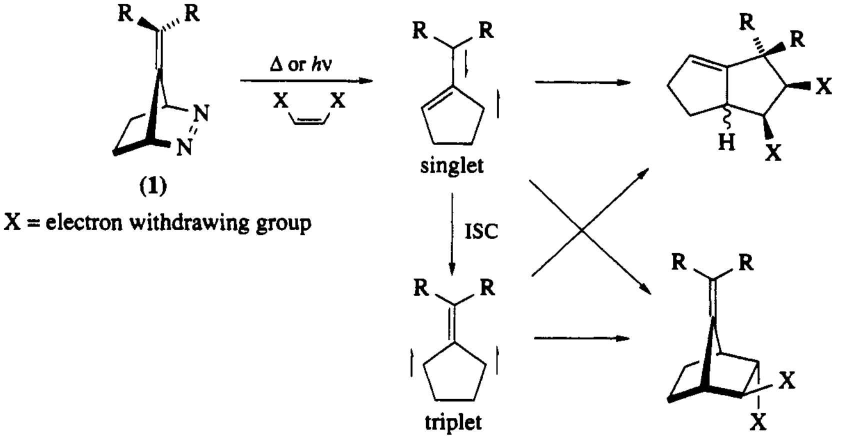

**Scheme 1**

Fortunately, for synthetic purposes, the diyls are sufficiently long lived to be trapped in high yield.[2,3] Of equally good fortune, the singlet undergoes cycloaddition with maintenance of diylophile stereochemistry and with a marked regiochemical preference for formation of fused adducts. The triplet, on the other hand, undergoes cycloaddition with loss of the diylophile stereochemistry and with the formation of both bridged and fused cycloadducts; little preference is expressed for the formation of either product type (Table 1).[2a,b]

**Table 1** Product Composition as a Function of Diyl Spin State

| *Diyl spin state*[a] | *Diylophile* | *Fused bridged ratio* | *Trans:cis ratio*[b] |
|---|---|---|---|
| Singlet | Dimethyl fumarate | 65.7 | *Trans* only |
| Triplet | Dimethyl maleate | 0.72 | 88:12 |
| Triplet | Dimethyl fumarate | 0.72 | 92:8 |

[a] From diazene (1) when R = Me. [b] Refers to relationship between esters in the product.

Frontier orbital theory has been used successfully to rationalize the regiochemical course of the singlet diyl chemistry (Table 2).[2a] To do so, the assumption is made that the formally degenerate nonbonding molecular orbitals of TMM are perturbed, placing the symmetric form below the antisymmetric and making the former the HOMO. Only when the exocyclic carbon of the diyl is substituted with two strongly electron-donating methoxy groups is it suggested that the antisymmetric orbital lies below the symmetric. In this case, bridged cycloadducts are formed preferentially, in accord with expectations based upon this ordering of frontier molecular orbitals.

**Table 2** Frontier Molecular Orbital Analysis of Intermolecular Diyl Trapping

| *TMM nonbonding molecular orbitals (symmetry)* | *HOMO/LUMO combination* | *Predicted product* |
|---|---|---|
| | Symmetric diyl HOMO with diylophile LUMO | |
| 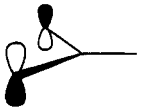 (Antisymmetric, *a*) | 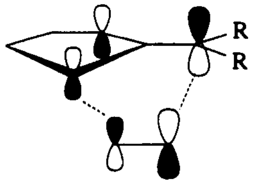 | Fused cycloadduct |
| | Antisymmetric diyl HOMO (R = OMe) with diylophile LUMO | |
| 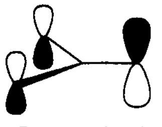 (Symmetric, *s*) | 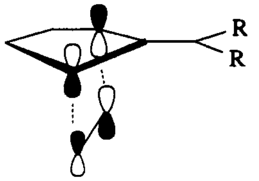 | Bridged cycloadduct |

### *3.1.2.1.2 Linear* versus *bridged (intramolecular 1,3-diyl trapping)*

Like its intermolecular counterpart, the intramolecular diyl trapping reaction can, in principle, afford either fused or bridged cycloadducts.[4] Because of the geometric constraints imposed by the intramolecular variety, however, one might anticipate that bridged products, strictly analogous to those produced in the intermolecular cycloaddition, would form only when the length of the tether is long enough to minimize the angle strain which would be associated with maintaining a double bond at C-7 of the bicyclo[2.2.1] cycloadduct. When the length of the tether is three or less, therefore, one might safely dismiss from consideration the formation of products of this type, the type II bridged products. Indeed, no evidence is available to suggest that these products have ever been produced (Figure 1).

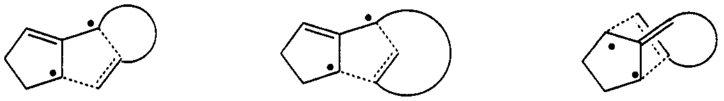

Linear Type I bridged Type II bridged

**Figure 1**

Both linear and type I bridged cycloadducts can be produced selectively and by design.[5] The regioselective formation of linearly fused cycloadducts occurs from the singlet state of the diyl when the diylophile is substituted with an electron-withdrawing group at either the internal or terminal carbon, and also when the diylophile bears the tether as its only substituent. It has recently been firmly established that type I bridged cycloadducts arise from the triplet diyl and that they can be formed regioselectively when the internal carbon of the diylophile is substituted with a large alkyl group.[5] The mere presence of an alkyl group at this carbon is sufficient to ensure the formation of the bridged cycloadduct. However, it is not sufficient to ensure the formation of synthetically useful amounts. Table 3 clearly indicates[5] that the selectivity increases as the size of the substituent increases, and eventually to a value where synthetically useful amounts of the bridged cycloadduct are obtained. The trend is reminiscent of the way in which the *6-endo,trig* to *5-exo,trig* cyclization ratio increases as the size of the substituent on the internal carbon of the 5-hexenyl monoradical increases.[6]

These results suggest that when an electron-withdrawing substituent is placed on the internal carbon of the diylophile, then the diyl HOMO–diylophile LUMO energy gap is small enough such that the singlet form of the diyl is trapped at a rate which significantly exceeds the rate of intersystem crossing to the

**Table 3** Influence of Diylophile Substituents Upon Bridged *versus* Linear Regioselectivity

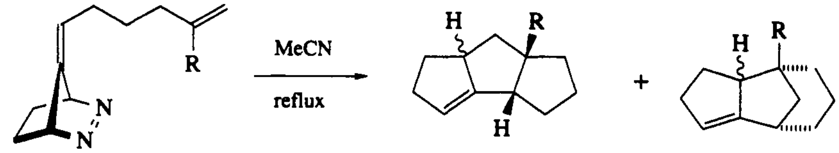

| *R* | *Bridged:linear ratio* | *Yield (%)* |
|---|---|---|
| $CH_2OH$ | 1.2:1 | 90 |
| $CH(OMe)_2$ | 2:1 | 93 |
| $CMe(OMe)_2$ | 16:1 | 83 |
| COMe | 1:7 | 98 |
| $CO_2Me$ | 1:19 | 85 |

triplet manifold. On the other hand, when an alkyl group occupies the same site, then the rate of trapping of the singlet decreases sufficiently to allow intersystem crossing and the expression of triplet diyl chemistry. Provided the alkyl group is large enough, type I bridged cycloadducts form regioselectively. This discovery promises to be of utility in a variety of synthetic endeavors.

### 3.1.2.2 Stereoselectivity (Intramolecular)

#### *3.1.2.2.1 Diylophile stereochemistry*

Diylophile stereochemistry is nearly always maintained. This generalization is adequately exemplified by the chemistry of the diradicals derived from diazenes (**2**) and (**3**), the former possessing a diylophile with (*E*) geometry, the latter (*Z*) (Table 4).[7] The observed stereospecificity suggests either that the two new σ-bonds are formed in concert or, assuming a nonconcerted process wherein the σ-bond is formed first between the exocyclic carbon of the diyl and the β-carbon of the diylophile, that rotation about the $C_\alpha$—$C_\beta$ bond with concurrent loss of diylophile stereochemistry is not competitive with formation of the second σ-bond.

**Table 4** Maintenance of Diylophile Stereochemistry

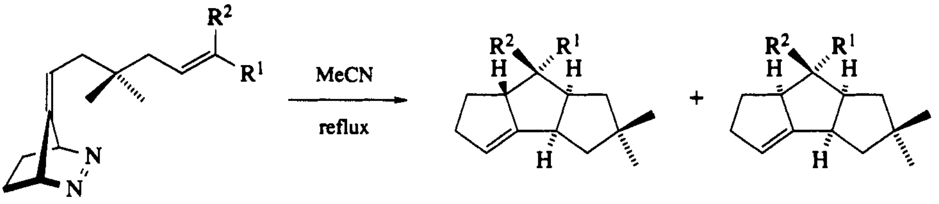

(**2, 3**)   *cis,anti*   *cis,syn*

| | *R*¹ | *R*² | *Cis,anti:cis,syn ratio*[a] | *Yield (%)* |
|---|---|---|---|---|
| (**2**) | $CO_2Me$ | H | 87:13 | ≥85 |
| (**3**) | H | $CO_2Me$ | 75:25 | 87 |

[a] Both the *cis,anti* and the *cis,syn* products are formed with retention of diylophile stereochemistry.

The only instance wherein the diylophile stereochemistry is lost was recorded upon examination of the chemistry of the diyl derived from diazene (**4**), one possessing a two-carbon tether.[8] In this case, four products were isolated in an 83% yield and in the ratio 16:5:1.5:1. Formation of tricycle (**5**) as the major product, as well as the diene (**6**), argue convincingly for the existence of a stepwise pathway where rotation about the $C_\alpha$—$C_\beta$ bond with loss of diylophile stereochemistry and hydrogen atom abstraction occur in competition with formation of the second σ-bond (Scheme 2).

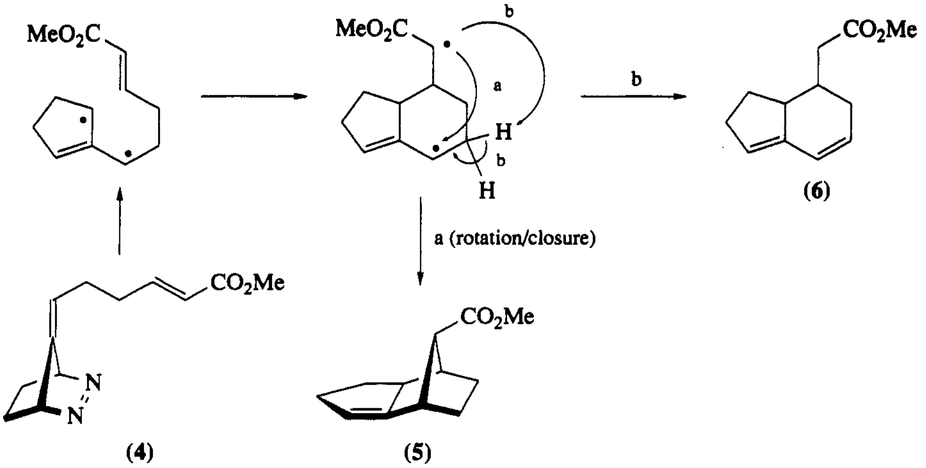

**Scheme 2**

### 3.1.2.2.2 *Ring junction stereochemistry*

Linearly fused tricycles are produced stereoselectively, the major product corresponding to one with the *cis,anti* ring junction stereochemistry. This selectivity made the intramolecular diyl trapping reaction well-suited for the synthesis of several natural products, including the mold metabolite hirsutene,[7,9] the marine natural product $\Delta^{9(12)}$-capnellene,[10] and the antitumor agents coriolin and hypnophilin.[4b,11] Table 5 shows how the degree of stereoselection, expressed by the *cis,anti*/other products ratio, is a function of the temperature at which the diyl trapping reaction is conducted;[11] the highest selectivity is obtained when the diyl is generated photochemically at temperatures below 0 °C.

**Table 5** Ring Junction Stereoselectivity in Intramolecular Diyl Trapping Reactions

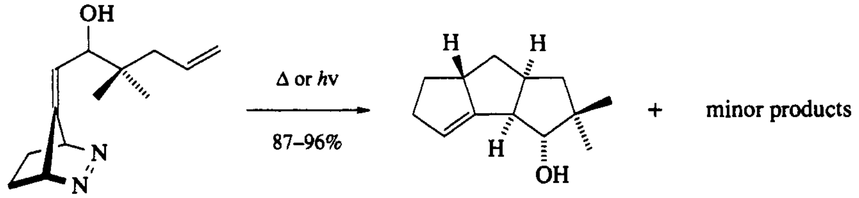

| *Solvent* | *Temp. (°C)* | *Δ or hν* | *cis,anti:minor products* |
|---|---|---|---|
| MeCN | 81 | Δ | 3.8:1 |
| MeCN | 6 | hν | 9.1:1 |
| MeOH | 61 | Δ | 4.7:1 |
| MeOH | 6 | hν | 9.1:1 |
| MeOH | –60 | hν | 30:1 |

Both the relative and the absolute stereochemical outcome of the intramolecular diyl trapping reaction can be predicted by assuming that the cycloaddition is kinetically controlled. The objective, then, is to formulate a model of the alternative transition states and to choose among them the one of lowest energy. Two examples, each dealing with optically active diazenes, are illustrated in Schemes 3 and 4. In the first case,[12] the major diastereomer arises *via* the extended pseudochair transition-state formulation wherein the diylophile and tether coil to the rear, in a manner which places the OR unit in a pseudoequatorial orientation. Coiling to the front forces OR to assume an energy-raising pseudoaxial orientation (Scheme 3).

In the second example the diazene possesses a four-carbon tether with two stereogenic centers.[13] The major product can be viewed as arising *via* a pathway where the tether coils to resemble a chair form of cyclohexane with the methyl, silyl ether and five-membered ring occupying pseudoequatorial positions. That the observed stereospecificity is due to the preference for the substituents to orient themselves pseudoequatorially is exemplified by the failure to observe any stereoselection in the diyl trapping reaction originating from a diazene possessing an unsubstituted four-carbon tether (Scheme 4).[13,14]

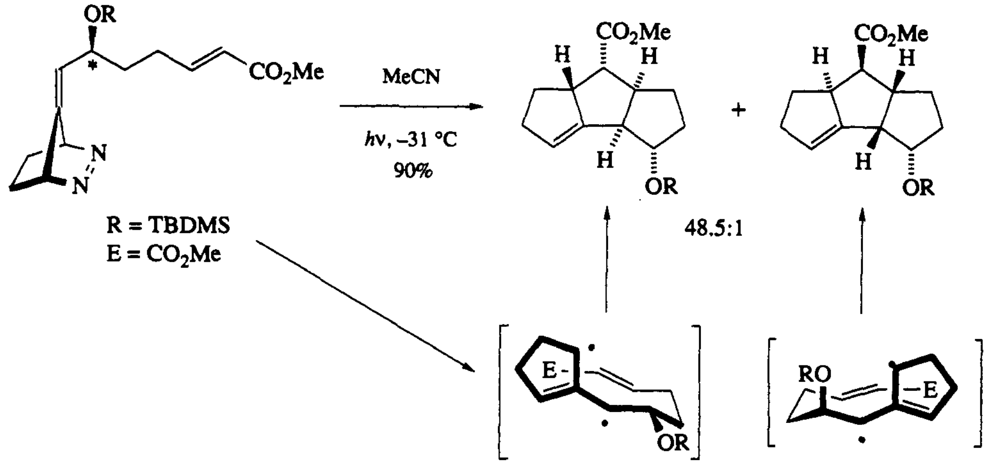
OR
CO2Me
N
N
R = TBDMS
E = CO2Me
MeCN
hν, −31 °C
90%
CO2Me
H
H
H
OR
+
48.5:1
E
OR
RO
E

Scheme 3

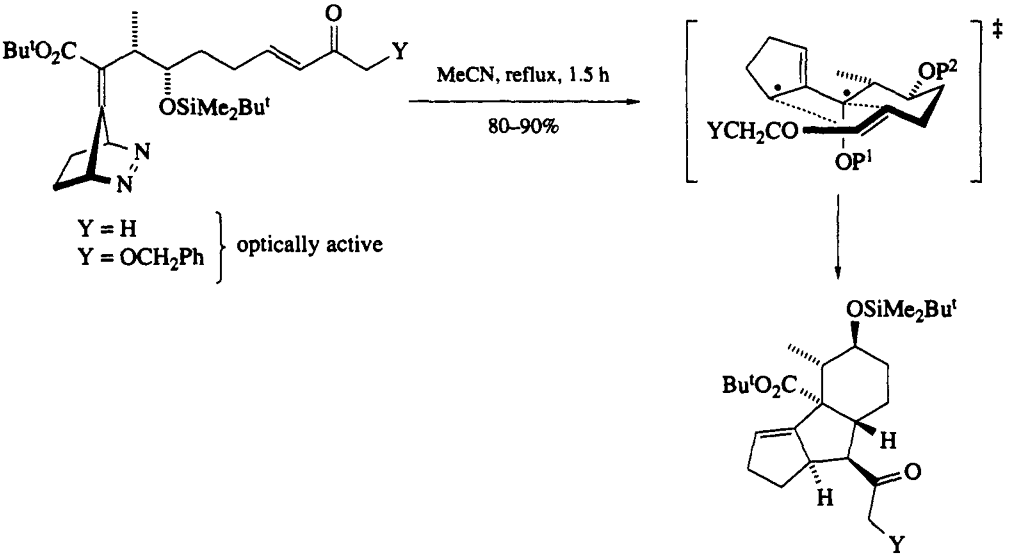
Bu^tO2C
O
Y
OSiMe2Bu^t
N
N
Y = H
Y = OCH2Ph
optically active
MeCN, reflux, 1.5 h
80–90%
OP2
YCH2CO
OP1
‡
OSiMe2Bu^t
Bu^tO2C
H
O
H
Y

Scheme 4

## 3.1.3 TRIMETHYLENEMETHANE SYNTHETIC EQUIVALENTS[15]

### 3.1.3.1 Palladium Trimethylenemethane Complex [($\eta^3$-TMM)PdL$_2$]

An exceptionally powerful means of constructing five-membered rings surfaced in 1979 with the report of the reaction between 2-acetoxymethyl-3-allyltrimethylsilane and electron-deficient alkenes in the presence of Pd$^0$.[16] Through this process, one can conduct the equivalent of a [3 + 2] cycloaddition between trimethylenemethane and an alkene,[17] a reaction which otherwise occurs in low yield.[2c,18] Several sources of Pd$^0$ have been utilized including (a) $(Ph_3P)_4Pd/Ph_2PCH_2CH_2PPh_2$ (DPPE) and (b) $Pd(OAc)_4/(Pr^iO)_3P$, the latter generating Pd$^0$ *in situ* and often leading to higher yields. Typically, 0.1–10 mol % of the resulting catalyst, $\{(Pr^iO)_3P\}_nPd$, is used in a 'typical' laboratory-scale reaction. Table 6 provides several examples of the cycloaddition.[17]

Evidence clearly indicates that trimethylenemethane (TMM) is not an intermediate in these reactions and establishes, instead, the existence of a trimethylenemethane–palladium complex with dipolar character, *viz.* ($\eta^3$-TMM)PdL$_2$ (7).[16,19]

**Table 6** Examples of Cycloaddition with ($\eta^3$-TMM)PdL$_2$

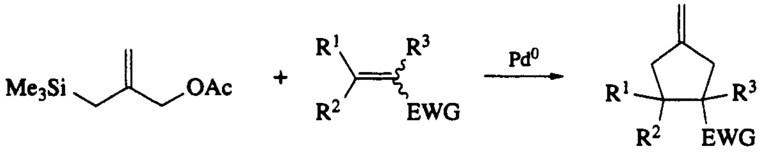

Me3Si
OAc
+
R1
R3
R2
EWG
Pd0
R1
R3
R2
EWG

| *R¹R²C═CR³EWG* | *Solvent* | *Temp. (°C)* | *Time (h)* | *Yield (%; comment)* |
|---|---|---|---|---|
| Methyl acrylate | PhMe | 85–90 | 43 | 68 |
| Acrylonitrile | PhMe | 60 | 150 | 35 |
| Coumarin | PhMe | 115 | 14 | 52 |
| Cyclohexenone | THF | reflux | 20 | 17 (*cis* fused) |
| Chalcone | PhMe | 115 | 11 | 85 (with retention of alkene geometry) |
| 1-(Phenylsulfonyl)cyclopentene | THF | reflux | 40 | 58 (*cis* fused) |

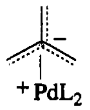

(7)

The cycloadditions proceed stereoselectively with the geometry of (*E*)-alkenes being preserved, but that for (*Z*)-alkenes being partially lost (equations 1 and 2).[20] Excellent diastereofacial selectivity has been observed in cycloadditions to cyclic alkenes,[17] the major product resulting from the addition of the TMM–PdL$_2$ complex to the least-hindered face of the alkene (equations 3–5). Modest (4:1) to high (>99:1) diastereoselectivity is also observed when enantiomerically pure acyclic alkenes are used (equations 6, 7).[21]

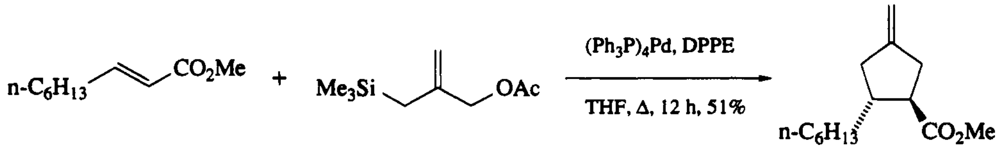

n-C6H13
CO2Me
+
Me3Si
OAc
(Ph3P)4Pd, DPPE
THF, Δ, 12 h, 51%
n-C6H13
CO2Me

(1)

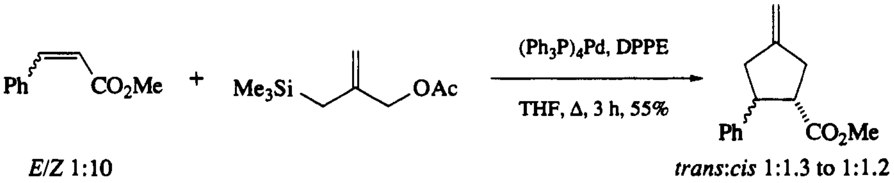

Ph
CO2Me
+
Me3Si
OAc
(Ph3P)4Pd, DPPE
THF, Δ, 3 h, 55%
Ph
CO2Me
E/Z 1:10
trans:cis 1:1.3 to 1:1.2

(2)

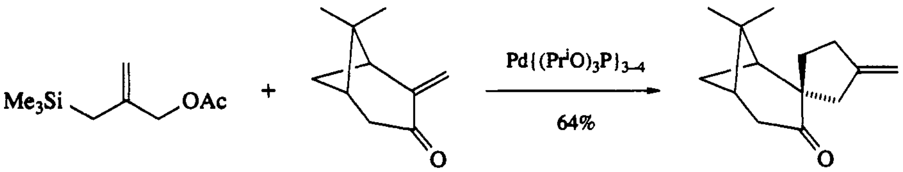

Me3Si
OAc
+
O
Pd{(PriO)3P}3–4
64%
O

(3)

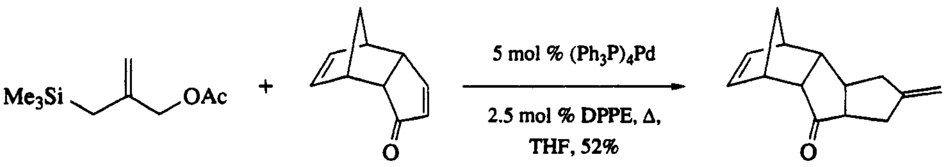

Me3Si
OAc
+
O
5 mol % (Ph3P)4Pd
2.5 mol % DPPE, Δ,
THF, 52%
O

(4)

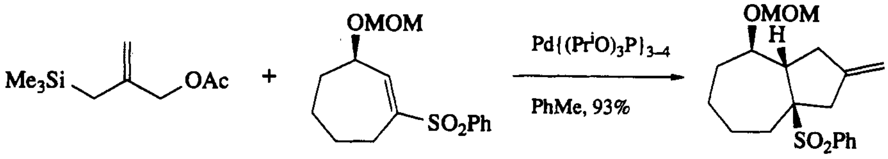
Me3Si
OAc
+
OMOM
SO2Ph
Pd{(PriO)3P}3–4
PhMe, 93%
OMOM
H
SO2Ph

(5)

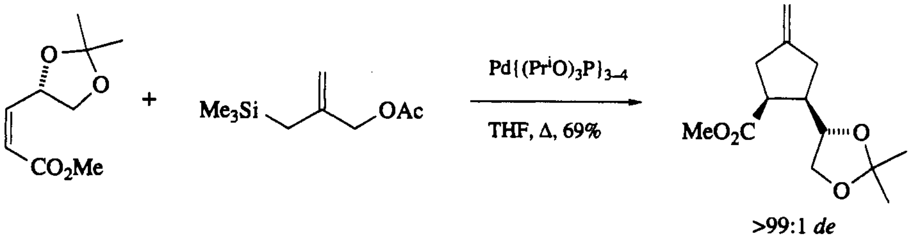
O
O
CO2Me
+
Me3Si
OAc
Pd{(PriO)3P}3–4
THF, Δ, 69%
MeO2C
O
O
>99:1 de

(6)

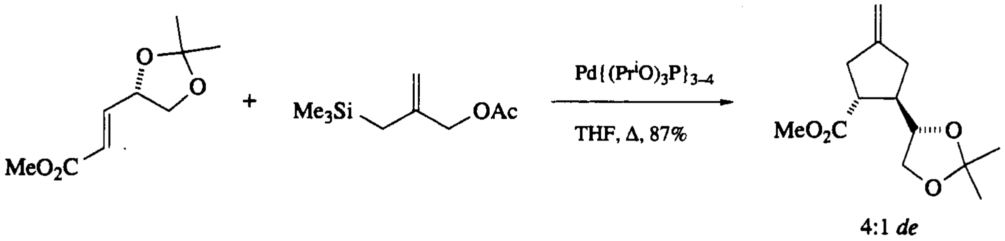
O
O
MeO2C
+
Me3Si
OAc
Pd{(PriO)3P}3–4
THF, Δ, 87%
MeO2C
O
O
4:1 de

(7)

A nonconcerted mechanism, involving a least-hindered approach of the cycloaddends and a stepwise addition of the palladium complex to the β-carbon of the α,β-unsaturated alkene, followed by cyclization without loss of alkene geometry and/or competitive rotation about the $C_\alpha$–$C_\beta$ bond prior to cyclization with loss of stereochemistry, provides a reasonable account of the cycloaddition (Scheme 5).[22]

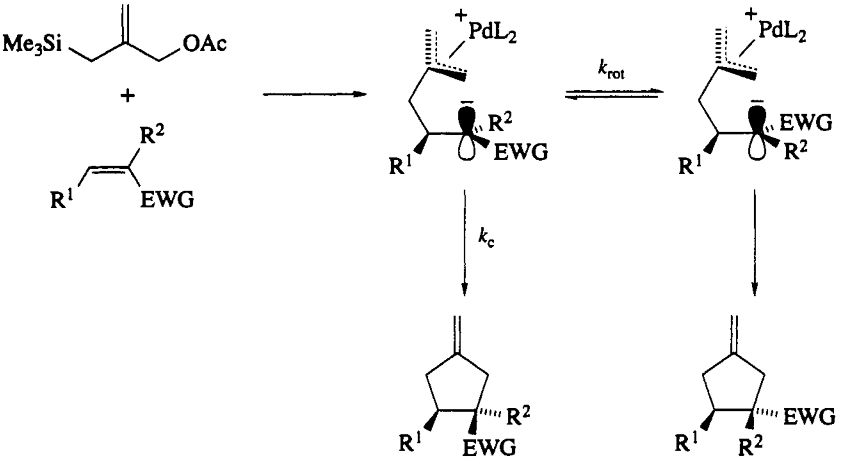
Me3Si
OAc
+
R2
R1
EWG
+
PdL2
R2
R1
EWG
krot
+
PdL2
EWG
R1
R2
kc
R2
R1
EWG
EWG
R1
R2

Scheme 5

### 3.1.3.2 Organo-tin and -zinc Reagents Derived from 3-Iodo-2-[(trimethylsilyl)methyl]propene

Addition of bifunctional conjunctive organometallic reagents derived from 3-iodo-2-[(trimethylsilyl)methyl]propene to 1,2-diones provides a stereoselective pathway to *cis*-4-methylenecyclopentane-1,2-diols.[23] Both zinc and tin(II) fluoride have been used to generate the organometallic. The latter has proven more advantageous, presumably because the $Sn^{4+}$ generated during the reaction serves more effectively than $Zn^{2+}$ to complex with the carbonyl group of the initially formed ketolate, thereby increasing the electrophilicity of the carbonyl carbon toward nucleophilic addition. The observed *cis* stereoselectivity is believed to result as a consequence of chelation control, as illustrated in Table 7.[23a]

**Table 7** Diastereoselectivity in Cycloaddition to 1,2-Diones

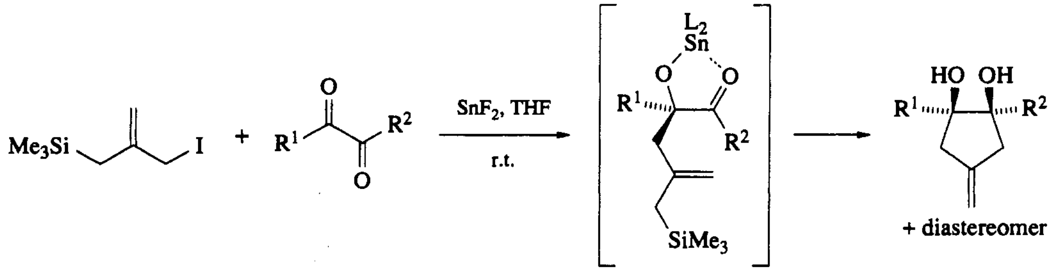

| *R*¹ | *R*² | *Yield (%)* | *Diastereoselectivity* |
|---|---|---|---|
| Me | Me | 72 | >75:1 |
| Me | Et | 88 | >32:1 |
| Me | Ph | 72 | >28:1 |
| Bu$^n$ | $Cl(CH_2)_4$ | 73 | >50:1 |

Reasonable diastereofacial selectivity has also been observed in the addition of the allylstannane referred to above to 2-acetoxy-3,4-octanedione (equation 8).[23] Chemoselective Felkin–Anh addition to the more reactive carbonyl carbon located α to the stereocenter is presumed to occur first, followed by an intramolecular chelation-controlled addition of the allylsilane to the second ketone.

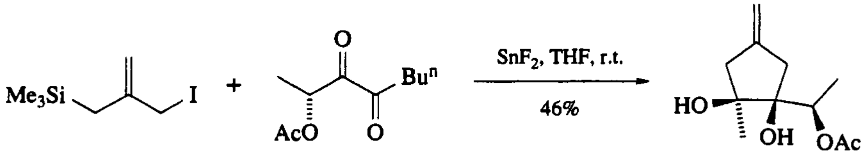

(8)

7.5:1 mixture of diastereomers

β-Keto esters and β-keto amides, each substituted between the two carbonyl units with a 2-[2-(trimethylsilyl)methyl] group, also undergo Lewis acid catalyzed, chelation-controlled cyclization.[24] When titanium tetrachloride is used, only the product possessing a *cis* relationship between the hydroxy and ester (or amide) groups is produced; yields range from 65 to 88% (Table 8). While loss of stereochemistry in the product and equilibration of diastereomers could have occurred *via* a Lewis acid promoted retro aldol–aldol sequence, none was observed. Consequently, it is assumed that the reactions occur under kinetic, rather than thermodynamic, control. In contrast to the titanium tetrachloride promoted process, fluoride-induced cyclization produces a 2:1 mixture of diastereomeric products, and the nonchelating Lewis acid $BF_3 \cdot OEt_2$ leads to a 1:4.8 mixture of diastereomers.

## 3.1.4 1,3-DIPOLAR CYCLOADDITIONS[25]

### 3.1.4.1 Regioselectivity

The ability to use a given reaction in synthesis depends heavily upon understanding the nature of the factors controlling regiospecificity/regioselectivity. A rationale for the regiochemical outcome of [2 + 3] cycloaddition reactions became available in the early 1970s through the use of frontier molecular orbital (FMO) theory.[26] With it, a further sense of order was established in an area where an understanding of the factors responsible for regiochemical control was absent. Since that time, nearly all practitioners of organic synthesis have developed a fundamental grasp of this matter, and it is commonplace to find predictions couched in terms of FMO arguments.

**Table 8** Diastereoselection in Cycloadditions Promoted by Titanium Tetrachloride

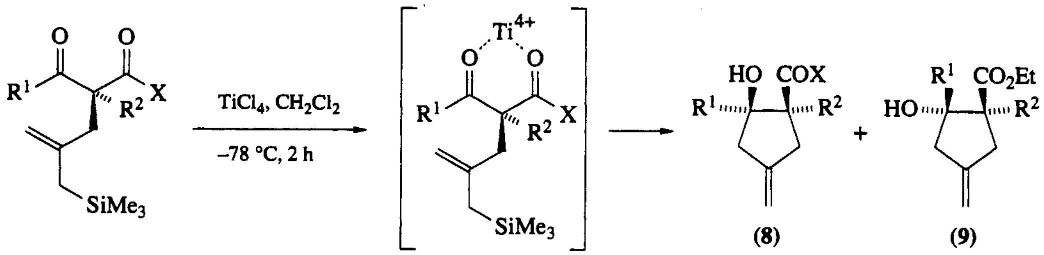

| $R^1$ | $R^2$ | $X$ | Yield (%) | (8):(9) |
|---|---|---|---|---|
| Me | Me | OEt | 88 | 100:1 |
| $Pr^i$ | Me | OEt | 66 | 100:1 |
| Ph | Me | OEt | 73 | 100:1 |
| Me | $Pr^i$ | OEt | 65 | 100:1 |
| $Pr^i$ | H | $NMe_2$ | 56 | 100:1 |
| $Bu^t$ | H | $NMe_2$ | 75 | 100:1 |
| Me | Me | OEt | — | 2:1[a] |
| Me | Me | OEt | — | 1:4.8[b] |

[a] $Bu^n_4NF$, THF; [b] $BF_3{\cdot}OEt_2$, $CH_2Cl_2$.

Dipolar cycloaddition reactions are generally classified into three types, dipole HO controlled, dipole LU controlled or HO,LU controlled, depending upon the relative energies of the dipole and dipolarophile frontier molecular orbitals.[27] If the energy gap separating the dipole HOMO from the dipolarophile LUMO is smaller than that between the dipole LUMO and the dipolarophile HOMO, then the reaction is said to be dipole HO controlled. If the dipole LUMO–dipolarophile HOMO energy gap is smaller, then dipole LU control prevails. If the energy difference between the dipole HOMO and the dipolarophile LUMO is about the same as that between the dipole LUMO and the dipolarophile HOMO, then neither interaction dominates and HO,LU control is operable.

Substituents placed on either the dipole or the dipolarophile affect the energy of the frontier orbitals in a manner which leads to either an acceleration or a deceleration depending upon whether the pertinent FMO energy gap increases or decreases, respectively, as a consequence of the substitution. In general, electron-withdrawing groups lower the level of both the HOMO and the LUMO, electron-donating groups raise the energy of both, and conjugating groups raise the HOMO but lower the LUMO energy.[28]

Once the dominant FMO interaction has been identified, then a choice as to which regiochemical outcome is preferred is based upon a comparison of the sizes of the coefficients at the atomic orbital centers involved in the formation of the new bonds. Consequently, at least a qualitative knowledge of the form of the FMOs is useful in assessing the relative merits of one over the other regiochemical outcome. If, as is usually but not always (*vide infra*) the case, the coefficients in both the HOMO and the LUMO differ in size, then the new overlap can occur in either of two ways. It can readily be shown, however, that overlap between the atomic orbitals with the larger coefficients (and, by default, the two centers with the smaller atomic orbital coefficients overlap at the other site of bond formation) is preferred over the alternative.[28,29]

Table 9 illustrates the direction of polarization of the HOMO and the LUMO of simple monosubstituted alkenes ($CH_2{=}CHC,Z,X$) and dipoles ($a{=}^{+}b{-}^{-}c$); the atom with the larger coefficient is marked with a star.[26a] Except in cases where $C_2$ symmetry exists (*e.g.* the azomethine ylide,

**Table 9** Direction of Polarization of Dipole and Dipolarophile FMO's

| Dipolarophile |  | Dipole |  |
|---|---|---|---|
| HOMO | LUMO | HOMO | LUMO |
| 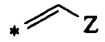 | 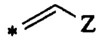 |  |  |
| 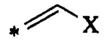 | 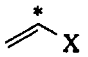 | a = b — c* | *a = b — c |
| 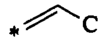 | 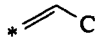 |  |  |

$CH_2{=}^{+}NH{-}^{-}CH_2$), or for the parent nitrone, $CH_2{=}^{+}NH{-}^{-}O$, where the coefficients are nearly the same at both termini, dipole HOMOs are polarized toward the 'anionic' terminus c, the LUMO toward a. Use of this information, in accord with the principles put forth above, allows one to make the predictions illustrated in Scheme 6.[26a]

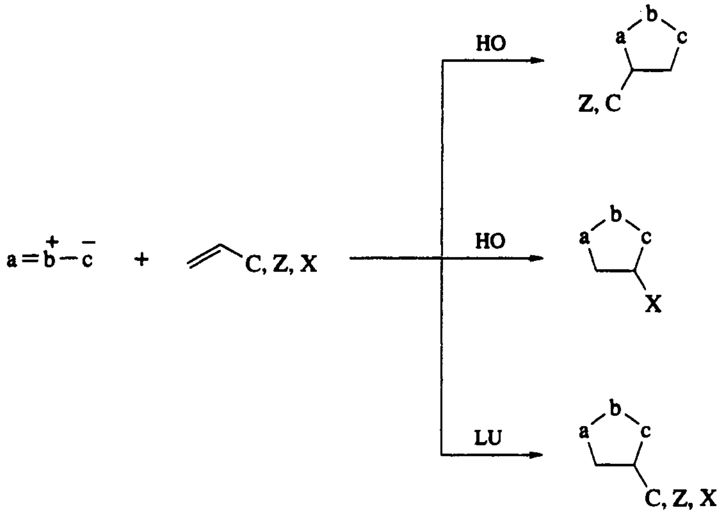

a=b−c
+
C, Z, X
HO
HO
LU
a
b
c
Z, C
X
C, Z, X

**Scheme 6**

These generalizations are applicable to a large number of cycloadditions, particularly to the intermolecular variety. The examples in equations (9)–(13)[30–34] and Schemes 7–9[31,35,36] illustrate these points and also highlight the tremendous power of [2 + 3] dipolar cycloaddition reactions in the rapid and selective construction of a rich array of both carbo- and hetero-cyclic ring systems.

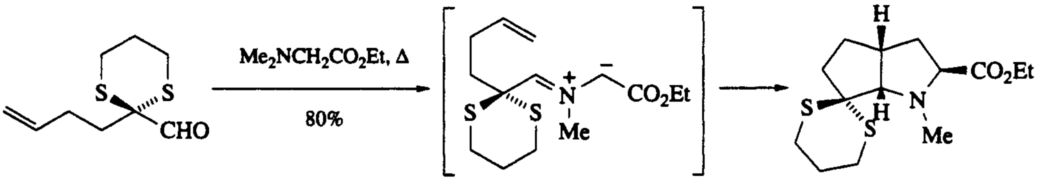

S
S
CHO
Me2NCH2CO2Et, Δ
80%
N
Me
CO2Et
H
H
N
Me
CO2Et

(9)

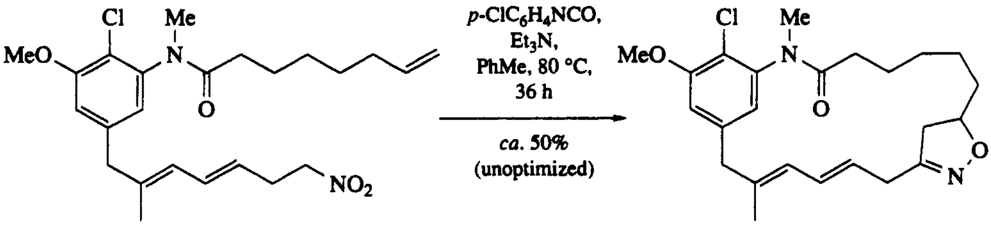

Cl
Me
MeO
N
O
NO2
p-ClC6H4NCO,
Et3N,
PhMe, 80 °C,
36 h
ca. 50%
(unoptimized)
Cl
Me
MeO
N
O
O
N

(10)

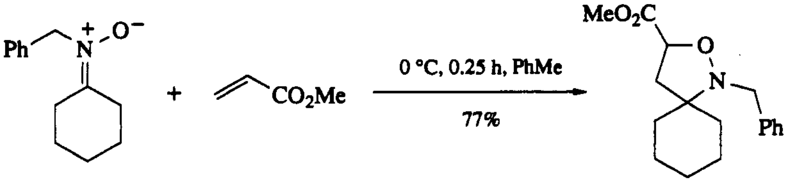

Ph
N
O−
+
CO2Me
0 °C, 0.25 h, PhMe
77%
MeO2C
O
N
Ph

(11)

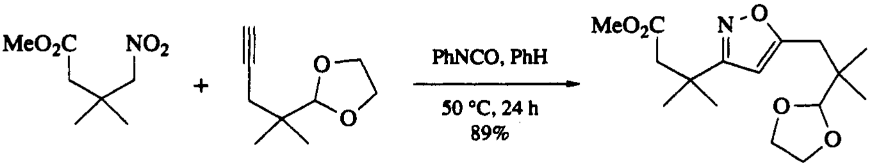

MeO2C
NO2
+
O
O
PhNCO, PhH
50 °C, 24 h
89%
MeO2C
N
O
O
O

(12)

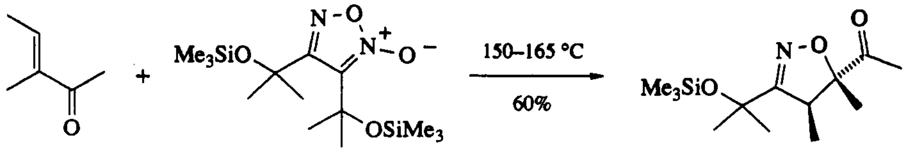

(13)

Exceptions do exist, however, and one must be particularly alert to substituent-induced changes in the direction of polarization, as well as to their affect upon the energy of the frontier molecular orbitals.[37] For example, nitrone cycloaddition regiochemistry is generally LU controlled,[37,38] leading to the production of C-5 substituted isoxazolines in excellent yield. However, as the ionization potential of the nitrone decreases or the electron affinity of the dipolarophile increases, there exists an increased propensity for formation of the C-4 regioisomer. Eventually, a switch from LU to HO control occurs and substantial amounts of the C-4 isomer are produced (equation 14).

A substituent-induced change in the direction of polarization of one of the FMOs can also lead to a change in regiochemistry. Thus, in contrast to acrylates, crotonates undergo nitrone cycloaddition to afford the regioisomer where the alkyl, rather than the ester, unit is attached to the carbon linked to the nitrone oxygen atom (Scheme 10). While the coefficient at the β-carbon in the HOMO of an acrylate is larger than at the α, the reverse is apparently true for crotonates.[39] This result has been put to exceptionally elegant use in the construction of a number of alkaloids.[39a]

As indicated above, the parent azomethine ylide possesses $C_2$ symmetry. When the symmetry is reduced by placing a substituent at either end of the dipole, the FMOs polarize. Assuming HO control, the example in Scheme 11 suggests that the largest coefficient of the dipole HOMO resides on the unsubstituted carbon to which the silyl group was attached.[40]

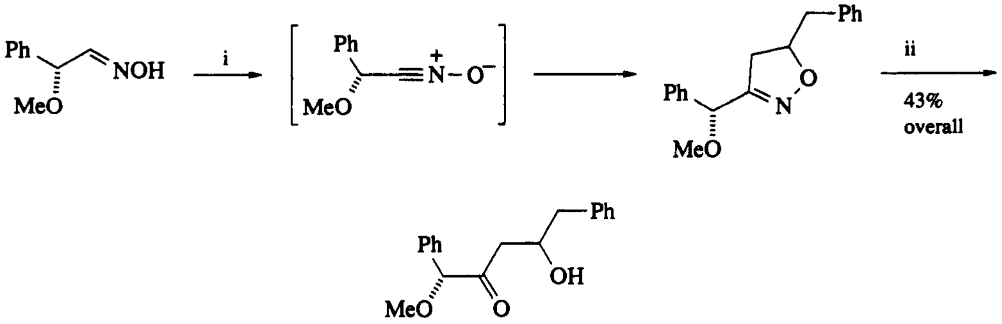

i, Chlorox, $\diagup\!\!\diagdown$Ph, $Et_3N$, $CH_2Cl_2$, r.t., 1 h: ii, $H_2$, Raney Ni, $MeOH/H_2O/AcOH$, r.t., 16 h

Scheme 7

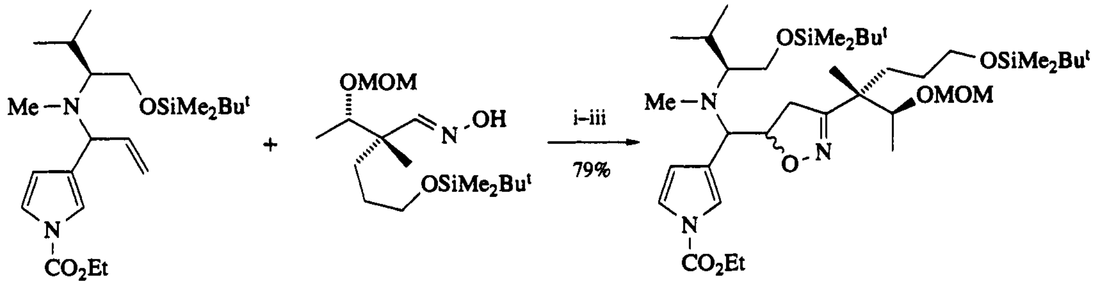

2.5:1 mixture of diastereoisomers

i, $Bu^tOCl$, −78 °C; ii, $Et_3N$, −78 °C to r.t.; iii, PhH, 80 °C, 20 h

Scheme 8

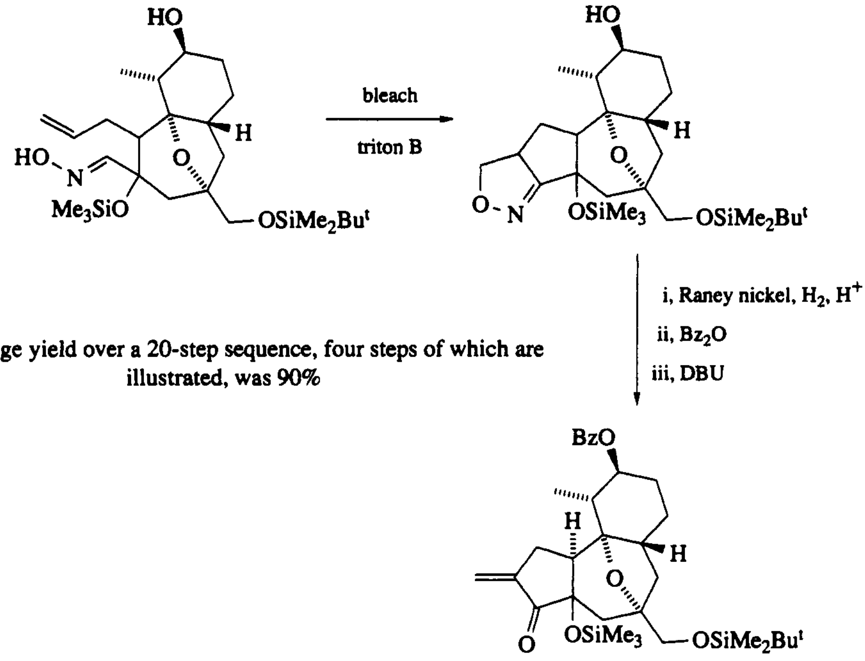
HO
HO
bleach
triton B
Me3SiO
OSiMe2Bu<sup>t</sup>
OSiMe3
i, Raney nickel, H2, H+
ii, Bz2O
iii, DBU
BzO
H
O
OSiMe2Bu<sup>t</sup>

The average yield over a 20-step sequence, four steps of which are illustrated, was 90%

**Scheme 9**

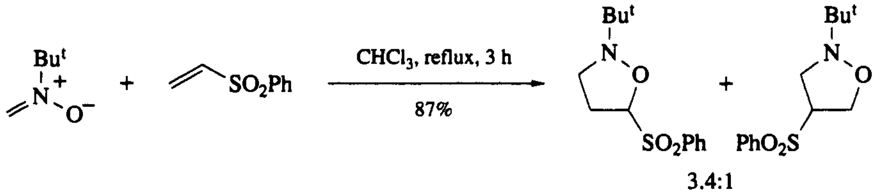 (14)
Bu<sup>t</sup>
SO2Ph
CHCl3, reflux, 3 h
87%
SO2Ph
PhO2S
3.4:1

Highly regioselective cycloaddition to monosubstituted 1,3-dienes has been observed, the preferred product corresponding to one formed *via* addition to the less-substituted double bond (equations 15, 16).[39a] Here again, the regiochemical outcome is in accord with simple FMO arguments.

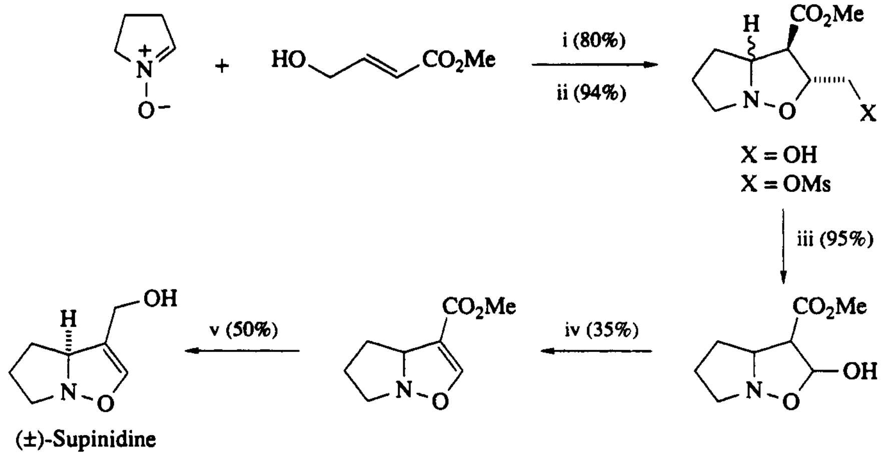
HO
CO2Me
i (80%)
ii (94%)
X = OH
X = OMs
iii (95%)
iv (35%)
v (50%)
OH
(±)-Supinidine

i, $CHCl_3$, 4 h, 25 °C, then reflux, 12 h; ii, MsCl, $C_5H_5N$, 0 °C, 3 h; iii, $H_2$, 10% Pd/C, MeOH, 24 h; iv, $POCl_3$, $C_5H_5N$, 0 °C, 12 min; v, $LiAlH_4$, $Et_2O$, r.t., 15 min

**Scheme 10**

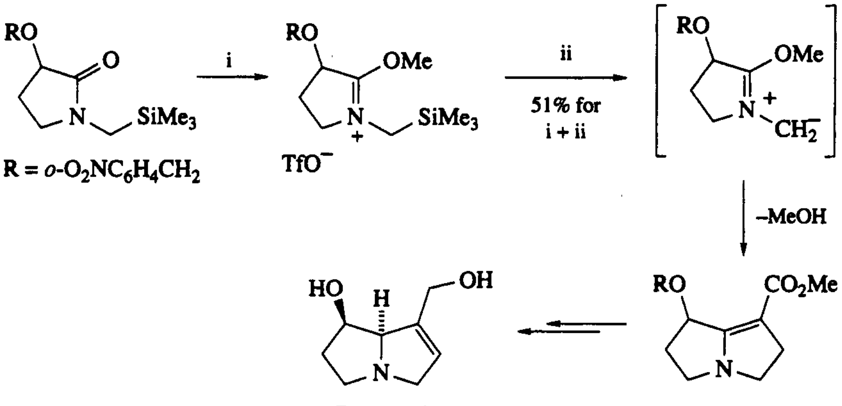
RO
O
N
SiMe3
R = o-O2NC6H4CH2
i
RO
OMe
N
+
SiMe3
TfO−
ii
51% for
i + ii
RO
OMe
N
+
CH2−
−MeOH
RO
CO2Me
N
HO
H
OH
N

Retronecine

i, MeOTf, $CH_2Cl_2$, overnight; ii, $\diagup\!\!\diagdown CO_2Me$, CsF, DME, 20 °C, 24 h

**Scheme 11**

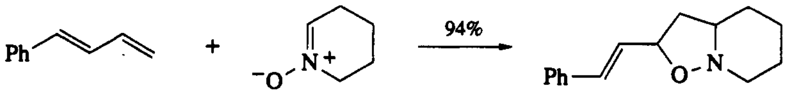
Ph
+
N+
−O
94%
Ph
O
N

(15)

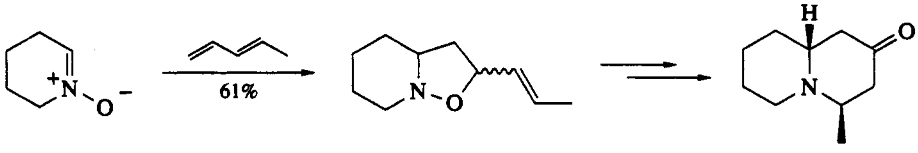

(±)-Myrtine

(16)

Occasionally, molecular mechanics calculations provide a rationale when FMO theory fails to account for a given regiochemical outcome.[37,41–45] For example, cycloaddition of *C*-phenyl-*N*-methyl nitrone to methyl 2-methyl-2,3-butadienoate leads exclusively to the 5-*exo*-methylene cycloadduct, as one would expect based upon FMO theory. In contrast, *C*-phenyl-*N*-*t*-butyl nitrone affords only the 4-*exo*-methylene isoxazolidine, a result which clearly cannot be in accord with the same principles (Scheme 12). Molecular mechanics calculations, carried out under the assumption that the relative energy differences between the products parallel the energy differences between transition states, were in accord with the experimental results, suggesting that the difference in behavior between the two nitrones may have a steric rather than an electronic origin (Table 10).[37]

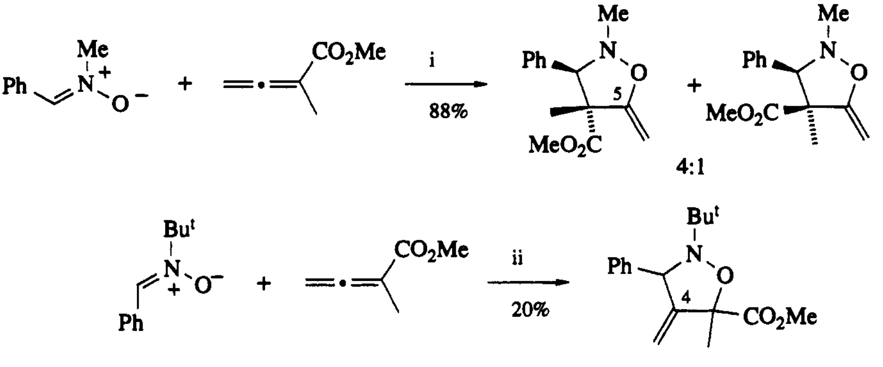
Me
Ph
N+
O−
+
CO2Me
i
88%
Me
Ph
N
O
5
MeO2C
+
Me
Ph
N
O
MeO2C
4:1
Bu^t
N
+
O−
Ph
+
CO2Me
ii
20%
Bu^t
Ph
N
O
4
CO2Me

only regioisomer isolated

i, PhH, 45 °C, 10 h; ii, PhH, 80 °C, 8 h, sealed tube

**Scheme 12**

**Table 10** Results of Molecular Mechanics Calculations[a]

| 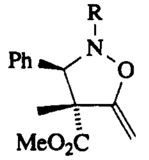 | 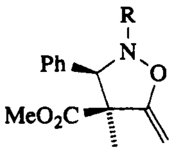 | 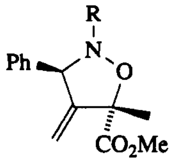 | 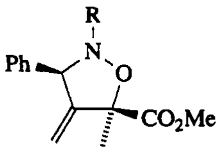 |
|---|---|---|---|
| R = Me, 24.48 | R = Me, 25.40 | R = Me, 26.67 | R = Me, 27.65 |
| R = Bu$^t$, 28.96 | R = Bu$^t$, 29.05 | R = Bu$^t$, 27.73 | R = Bu$^t$, 27.84 |

[a] Energy in kcal mol$^{-1}$.

While the cycloadditions illustrated thus far involve polarized dipolarophiles, regiospecificity can also occur in instances where the alkene is unpolarized. For example, the *N*-alkenyl nitrone (**10**), an important intermediate in an elegant synthesis of the lycopodium alkaloid (+)-luciduline,[46] undergoes intramolecular cycloaddition to afford only the tetracyclic heterocycle (**11**; Scheme 13). Nitrones (**12a**; *n* = 2) and (**12b**; *n* = 3), two compounds which differ only by the length of the chain linking dipole to dipolarophile, also undergo regiospecific cycloaddition, but do so to produce precisely opposite regiochemical outcomes (Scheme 14). The next higher homolog, nitrone (**12c**; *n* = 4), affords a 3:1 mixture of regioisomeric products, as shown.

Clearly, FMO arguments do not assist in understanding the nature of the preferences expressed above. Instead, attention has been directed toward differences in the geometry of the presumed transition-state structures for each mode of cycloaddition.[46c,d] In each case it was assumed that the C—C bond is more fully developed than the C—O bond in the transition state. From models it is clear that when two methylene units separate dipole from dipolarophile, the preferred transition state is the one suffering least from angle strain. When the length of the chain link is three, the preferred product arises *via* formation of the entropically favored six-membered ring, instead of the alternative seven-membered ring.

Interestingly, the balance can be tipped toward formation of the seven-membered ring by simply placing an electron-withdrawing group on the terminal carbon of the dipolarophile (Scheme 15). This leads to polarization of the alkene and to an FMO-controlled process. Incidentally, the reaction shown proved critical in a total synthesis of anatoxin *a*, the so-called 'very fast death factor'.[47]

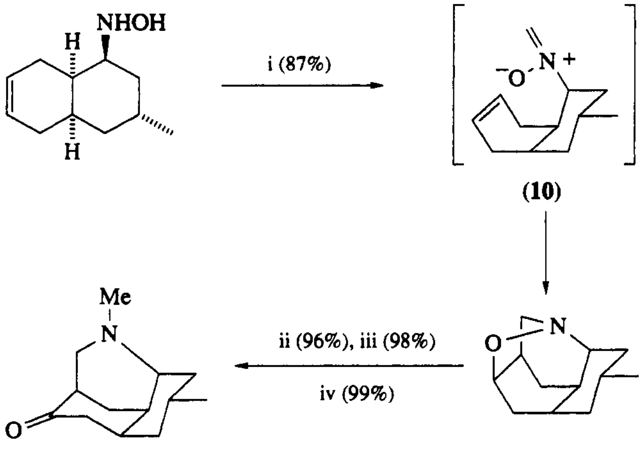

i, $(CH_2O)_n$, 4 Å molecular sieves, PhMe, sealed tube, 115 °C, 4 h; ii, $MeOSO_2F$, $Et_2O$, 0 °C, 30 min; iii, $LiAlH_4$, THF, 25 °C, 4.5 h; iv, Jones reagent, $Me_2CO$, 0 to 25 °C, 1 h

**Scheme 13**

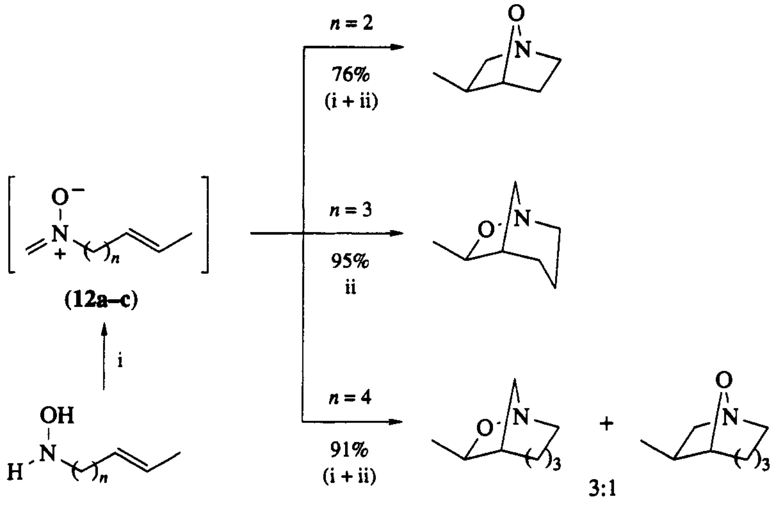

$n$ = 2: i, $CH_2O$, PhMe, 10 °C, 12 h; ii, PhMe, reflux, 6 h; $n$ = 3: i, $CH_2O$, PhMe, –20 °C, 15 min, quant; ii, PhMe, reflux, 3 h; $n$ = 4: i, $CH_2O$, PhMe; ii, PhMe, reflux

**Scheme 14**

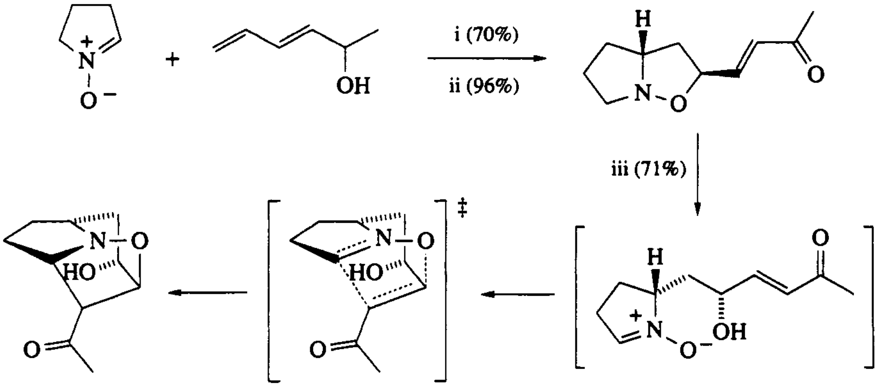

i, HgO, PhH, reflux, 3 h; ii, $MnO_2$, Celite, $CH_2Cl_2$, r.t., 24 h; iii, MCPBA, 0 °C, 20 min; $K_2CO_3$, $H_2O$; reflux, 18.5 h (in the dark), $CH_2Cl_2$

**Scheme 15**

### 3.1.4.2 Stereoselectivity

### *3.1.4.2.1 Relative stereoselection*

Dipolar cycloaddition reactions proceed with preservation of dipolarophile stereochemistry,[29b] a result which is obviously of synthetic utility. The dipole and dipolarophile approach one another in parallel planes with the substituents attached to the dipolarophile oriented in either an *endo* or an *exo* relationship with respect to the dipole in the transition state. Depending upon which orientation is of lower energy, varying degrees of diastereoselectivity result (*vide infra*).[29b] The consequences of these generalizations are expressed repeatedly in the chemistry described below.

Synthetically useful amounts of *endo* selectivity have been observed in the intermolecular cycloaddition reactions of some acyclic nitrones. For example, the reaction between *C*,*N*-diphenyl nitrone and dimethyl maleate leads to a 9:1 mixture of products, the major arising *via* the (*Z*)-nitrone and *endo* transition state (equation 17).[48] The *endo* but not the *exo* transition state experiences an energy-lowering secondary orbital interaction between the coefficient on nitrogen in the LUMO of the nitrone and the coefficient on the carbonyl carbon in the HOMO of the dipolarophile, thereby making it the kinetically preferred product.

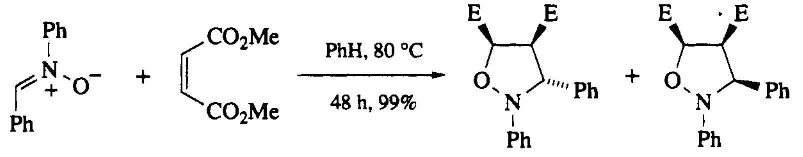

90:10

E = $CO_2Me$

(17)

The possible existence of such an interaction by no means ensures that *endo* selectivity will be observed. Table 11 makes this point abundantly clear.[49] Notice particularly how changes in substituents on the carbon and nitrogen of the nitrone can lead to a complete reversal of *endo*/*exo* selectivity.

**Table 11** Influence of Nitrone Substitution Upon *endo*/*exo* Stereoselectivity

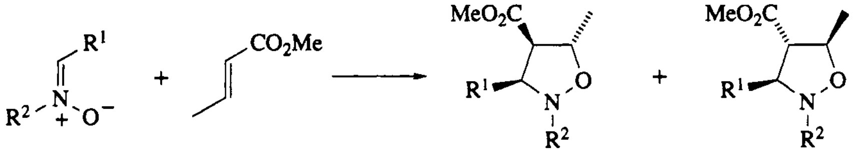

| *R*$^1$ | *R*$^2$ | *endo*:*exo* |
|---|---|---|
| Ph | Ph | 87:13 |
| Ph | Me | 50:50 |
| Pr$^i$ | Ph | 100:0 |
| Pr$^i$ | $CH_2Ph$ | 33:67 |
| Me | $CH_2Ph$ | 0:100 |

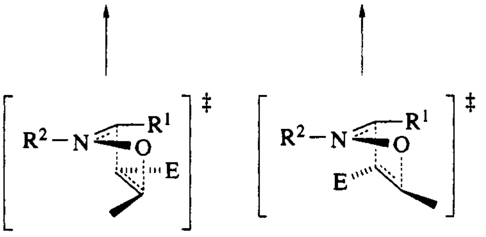

E = $CO_2Me$

*exo* transition state *endo* transition state

Nitrones are known to undergo (*E*/*Z*) isomerization;[50] both forms may therefore be available for reaction. For example, the heats of formation for the (*E*)- and (*Z*)-forms of *N*-methyl-*C*-phenyl nitrone place the latter 1.46 kcal mol$^{-1}$ lower in energy than the former.[37,50] This implies that approximately 10% of the (*E*)-form is present in solution even at room temperature. On the other hand, the (*E*)-form of *N*-*t*-butyl-*C*-phenyl nitrone is 6.3 kcal mol$^{-1}$ less stable and only the (*Z*)-isomer exists in solution.[37] For steric reasons the (*E*)-isomer has been proposed to undergo cycloaddition at a faster rate than the (*Z*).[37] Interestingly, cycloaddition of the (*E*)-isomer *via* an *exo* transition state leads to the same product as that from the (*Z*)-isomer through an *endo* transition state. This factor must obviously be considered when interpreting experimental results.

The reaction of methyl 1,2-butadienoate with *C*-methyl-*N*-phenyl nitrone (Scheme 16) leads to a single diastereoisomer and is believed to take place through a transition state (**13**) which places the methoxycarbonyl and phenyl groups above one another,[37,51] thereby allowing maximal π-overlap (attractive van der Waals interaction). To do so requires that the (*E*)-form of the nitrone exist in solution and that it react faster than the (*Z*), both being reasonable suggestions (*vide supra*).

Vinyl ethers and esters display a marked preference for undergoing cycloaddition through an *endo* rather than an *exo* transition state. The sole product isolated from the reaction of nitrone (**14**) with ethyl vinyl ether and vinylene carbonate arises in this manner (equation 18).[52] This selectivity has been attributed to stabilization of the *endo* transition state by developing anomeric and *gauche* interactions which are absent in the *exo* transition state.[53] Thus, it is assumed that the transition-state structure resembles the product in its lowest-energy conformation, one which places both the dipolarophile OR unit and the alkyl group attached to nitrogen in pseudoaxial orientations. In this manner, a stabilizing anomeric interaction between OR and the nitrone oxygen develops, as does a *gauche* interaction between the latter and the developing lone-pair electrons on nitrogen. By assuming the *gauche* relationship, the system avoids the alternative energy-raising *anti*- and *syn*-periplanar arrangement of lone pairs shown in **(15)**.

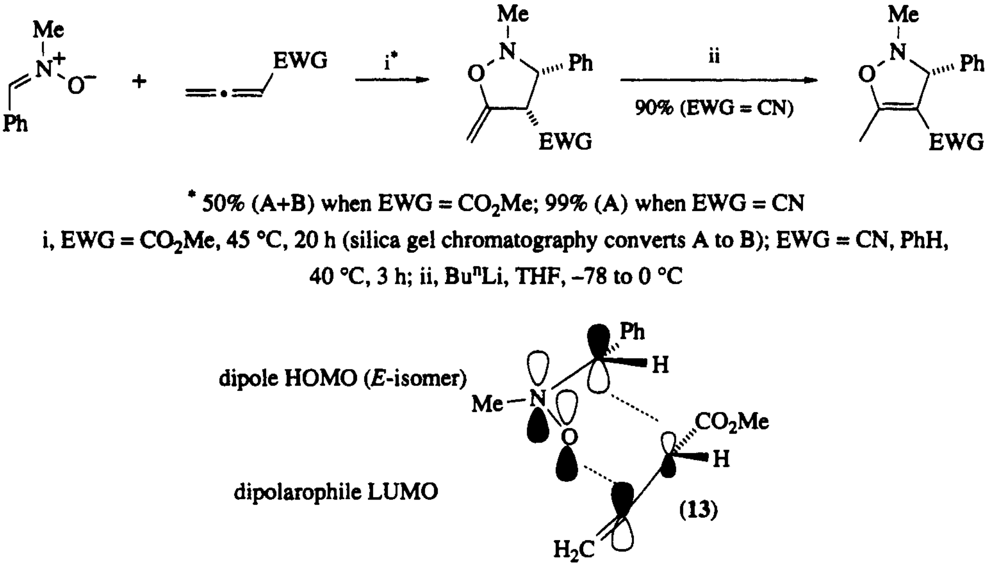
Me
EWG
i*
Ph
ii
90% (EWG = CN)
EWG
dipole HOMO (*E*-isomer)
Me
H
$CO_2Me$
dipolarophile LUMO
$H_2C$
(13)

* 50% (A+B) when EWG = $CO_2Me$; 99% (A) when EWG = CN

i, EWG = $CO_2Me$, 45 °C, 20 h (silica gel chromatography converts A to B); EWG = CN, PhH, 40 °C, 3 h; ii, $Bu^nLi$, THF, –78 to 0 °C

**Scheme 16**

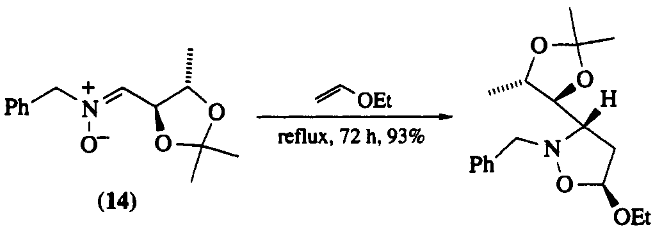
Ph
O
OEt
reflux, 72 h, 93%
H
N
OEt

**(14)** (18)

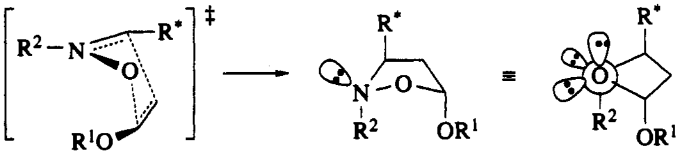

**(15)**

With cyclic nitrones, where (*E*/*Z*) isomerization is not possible, the *exo* transition state is usually sterically preferred (equation 19–21).[54–56] When steric factors in the *endo* and *exo* transition states are nearly the same, however, the existence of bonding secondary orbital interactions in the *endo* transition state can tip the balance in its favor; this appears to be the case for the reaction of methyl crotonate and 1-pyrroline 1-oxide (equation 22).[57]

Nitrone cycloaddition reactions are reversible,[58] thereby offering the opportunity to change stereoselection from that of kinetic to thermodynamic control, should the selectivities associated with these path-

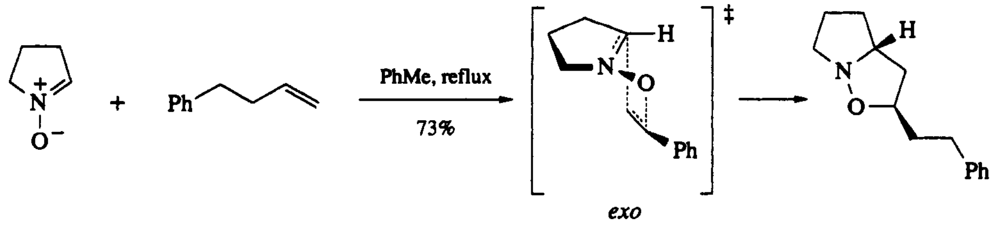
Ph
PhMe, reflux
73%
H
Ph
‡
exo

(19)

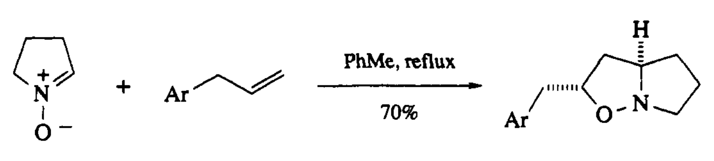

(20)

Ar = $p$-MeOC$_6$H$_4$

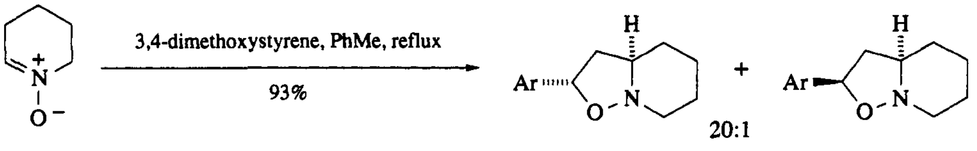

(21)

Ar = 3,4-(MeO)$_2$C$_6$H$_3$

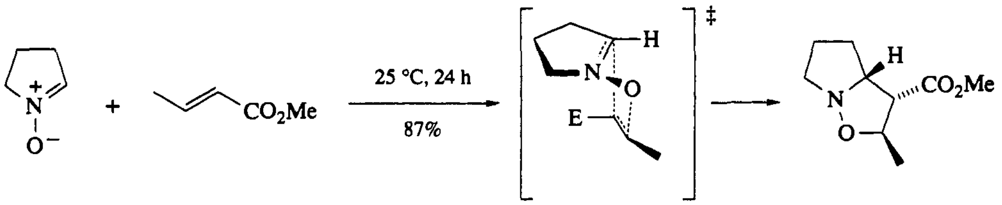

(22)

E = CO$_2$Me

ways differ. To illustrate, consider the cycloaddition portrayed in Table 12; it served as a key step *en route* to 1α,25*S*,26-trihydroxycholecalciferol.[58b] Unfortunately, a 36:45:7:12 ratio of four diastereomeric isoxazolidines was produced when the reaction was conducted at room temperature, albeit with complete regiochemical control and in high yield. The required 23*S*,25*S*-isomer was separated from the other three and the latter were heated overnight (refluxing xylene) in the presence of an excess of methyl methacrylate to effect cycloreversion and equilibration. After four cycles, the total yield of the 23*S*,25*S*-isomer reached 71%.

The two major products, the 23*S*,25*S*- and the 23*R*,25*S*-isomers, arise *via* the sterically less encumbered *exo* transition state, the minor products (23*S*,25*R* and 23*R*,25*S*) from an *endo* transition state. The analogous *N*-benzyl and *t*-butyl nitrones, on the other hand, display high *endo* selectivity, further attesting to how the group attached to nitrogen can play an important role in determining stereoselectivity (*vide supra*). In this case, the larger the group on nitrogen, the larger the *endo*/*exo* ratio (Scheme 17).

Molecular mechanics calculations have recently been used to assist in explaining the stereochemical course of several intramolecular cycloaddition reactions.[43,59] In one case,[59a] calculations were carried out to determine the relative energies of four diastereomeric products which could have been produced in the intramolecular azomethine cycloaddition reaction displayed (equation 23). A single product was isolated, though in only 25% yield. The assumption was made that the calculated differences in product stability were reflected by similar, but smaller, energy differences in the transition states.

Both ground state and transition state molecular mechanics calculations have been used to account for the stereochemical outcome of intramolecular nitrile oxide cycloadditions involving a series of vinylazetidinones and azetidines (Scheme 18).[43] Qualitative accord with the experimental results was observed once again (Table 13). Given the good agreement between theory and experiment, and the ease with which these calculations can be carried out, one is certainly tempted to use them (cautiously) in a predictive sense.

The preferred mode of addition to *cis*-3,4-disubstituted cyclobutenes varies from one where the dipole adds exclusively *anti* to the substituents, to instances where exclusive *syn* cycloaddition is observed (Table 14).[60] The latter observation is true particularly when the substituents are electron donating (*e.g.* Cl, OR), and is intriguing in that it is clearly opposite to that predicted solely on steric grounds. Several theories have been put forth to explain the results and the reader is directed to the original literature for a detailed account.[61] The tendency for the π-bond of these systems to distort toward a pyramidal geometry in the ground state, even by as little as *ca.* 1–5°, is generally believed to be associated with the selectivity; distortion reduces the torsional interaction between vicinal substituents.[61c] Thus the trigonal hydrogens move out-of-plane, away from the electron-donating substituents[61a] and, as the reaction progresses, away from the dipole. The movement is toward a geometry which allows attainment of a staggered

**Table 12** Influence of Reaction Conditions Upon Product Composition

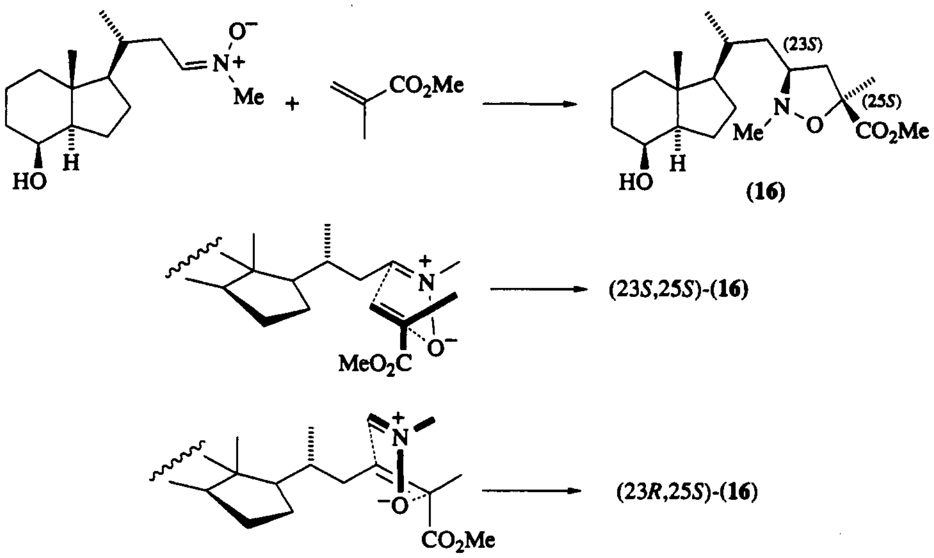
O⁻
N+
Me
+
CO2Me
HO
H
(23S)
(25S)
N
O
Me
CO2Me
(16)
+
N
O⁻
MeO2C
(23S,25S)-(16)
+
N
-O
CO2Me
(23R,25S)-(16)

| Solvent, temp. (°C) | Product composition | | | |
|---|---|---|---|---|
| | 23*S*,25*S* | 23*R*,25*S* | 23*S*,25*R* | 23*R*,25*S* |
| $CH_2Cl_2$, 22 | 35 | 45 | 7 | 12 |
| PhMe, 90 | 34 | 38 | 11 | 16 |
| Xylenes, 140 | 31 | 22 | 26 | 20 |

arrangement between the trigonal C—H bonds as well as the bonds which are being formed to the dipole, and the C—X and C—H bonds at the allylic carbon. It has been suggested that 'the tendency for staggering of vicinal bonds with respect to partially formed bonds is greater than for fully formed bonds'.[61b] Perhaps the *syn*-facial selectivity observed in these cycloadditions reactions is an expression of this idea.

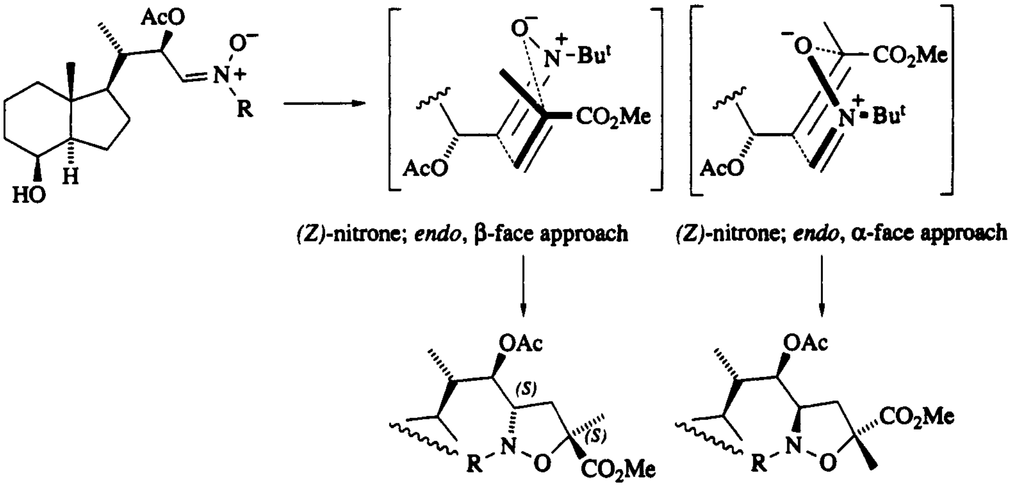
AcO
O⁻
N+
R
HO
H
O⁻
+
N-Bu^t
CO2Me
AcO
⁻O
CO2Me
+
N•Bu^t
AcO
(Z)-nitrone; endo, β-face approach
(Z)-nitrone; endo, α-face approach
OAc
(S)
(S)
R
N
O
CO2Me
OAc
CO2Me
R
N
O

| | | *endo*:*exo* | *yield* (%) *SS-isomer* |
|---|---|---|---|
| Methyl methacrylate, r.t., 15 h | R = $CH_2Ph$ | 83:17 | 72 |
| Methyl methacrylate, 50 °C, 42 h | R = $Bu^t$ | >99:<1 | 81 |

**Scheme 17**

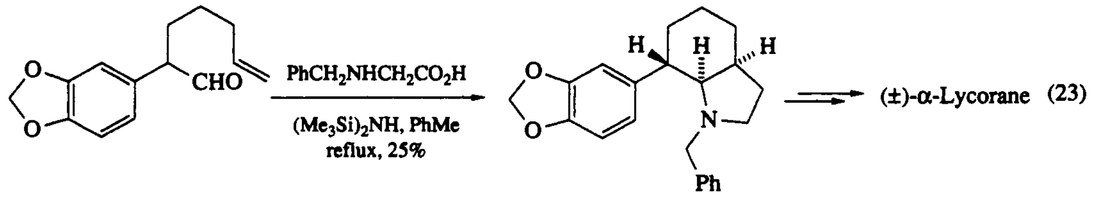

CHO
PhCH$_2$NHCH$_2$CO$_2$H
(Me$_3$Si)$_2$NH, PhMe
reflux, 25%
H
H
H
N
Ph
(±)-α-Lycorane

(23)

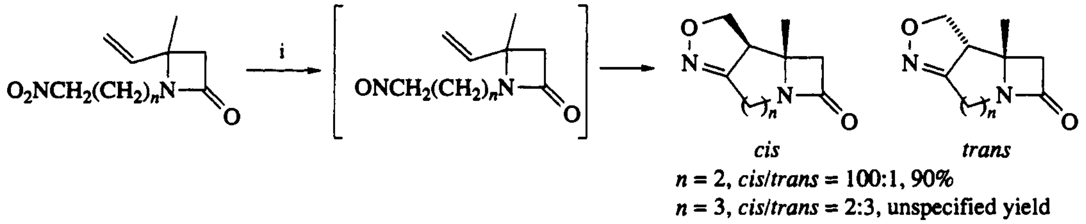

O$_2$NCH$_2$(CH$_2$)$_n$N
i
ONCH$_2$(CH$_2$)$_n$N
O
N
n
cis
trans

$n$ = 2, *cis*/*trans* = 100:1, 90%

$n$ = 3, *cis*/*trans* = 2:3, unspecified yield

i, $n$ = 2: PhNCO, Et$_3$N, CHCl$_3$, r.t., 10 h; $n$ = 3: PhNCO, Et$_3$N, CHCl$_3$, r.t., 6 h

**Scheme 18**

**Table 13** Results of Molecular Mechanics Calculations for Nitrile Oxide Cycloaddition

| | | *Total energy* (kcal mol$^{-1}$) | | | |
|---|---|---|---|---|---|
| | | *Cis* | *Trans* | *Energy difference* | *Cis:trans*[a] |
| 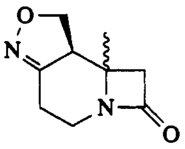 | Ground state<br>Transition state | 53.93<br>43.13 | 56.94<br>44.67 | 3.01<br>1.54 | 100:1 |
| 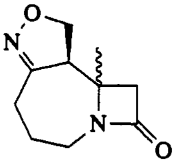 | Ground state<br>Transition state | 64.82<br>53.81 | 65.43<br>54.04 | 0.61<br>0.23 | 2:3 |

[a] Experimental ratio determined by NMR.

**Table 14** Diastereofacial Selectivity in Additions to 3,4-Disubstituted Cyclobutenes

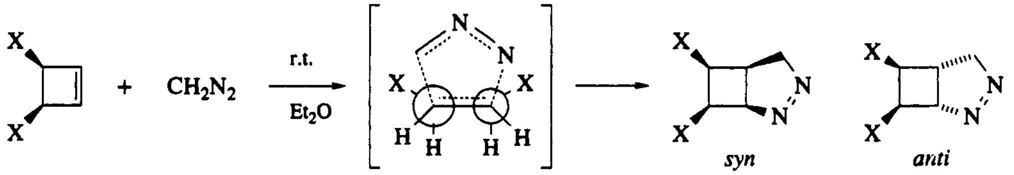

X
X
+
CH$_2$N$_2$
r.t.
Et$_2$O
N
N
X
X
H
H
H
H
syn
anti

| *X* | *θ* (°)[a] | *Yield (%)* | *Product(s)* |
|---|---|---|---|
| —(CH$_2$)$_3$— | 5.1 (toward X) | 70 | *anti* only |
| —O(C═O)O— | nearly coplanar | 82 | 1.8:1 *anti*/*syn* |
| —OC≡CMe | 3.1 (away from X) | 95 | *syn* only |

[a]Deviation of trigonal C—H bonds from planarity based on STO-3G calculations.

### *3.1.4.2.2 Absolute stereoselection*

There is no doubt that the field of asymmetric induction occupies a very important place in modern synthetic methodology. Elegant protocols designed to carry out dipolar cycloadditions have been developed and important advances in the theoretical description of these processes have taken place as a consequence (*vide infra*).[25] Diastereoselective cycloadditions have been carried out between optically active nitrile oxides,[62] nitrones,[52,63a–d] azomethine ylides[64] and achiral dipolarophiles, and between optically active dipolarophiles and achiral nitrile oxides[65–70] and achiral nitrones.[71] The products have been put to good use, either by 'translating' the cycloaddition diastereoselectivity to the construction of useful optically active acyclic intermediates, or in the total synthesis of natural products (*vide infra*).[25,39a,66,69b]

The 'inside alkoxy effect' is useful for predicting the stereoselectivity of nitrile oxide cycloaddition reactions with chiral allylic ethers.[65] The hypothesis states that 'allylic ethers adopt the inside position and alkyl substituents prefer the sterically less-crowded *anti* conformation in transition states for these electrophilic cycloadditions'. The terms 'inside' and 'outside' are defined in (**17**) for a hypothetical nitrile oxide cycloaddition transition state. Both *ab initio* (Gaussian 80 with 3-21G basis set) and molecular mechanics calculations agree, each predicting the lowest-energy transition state to be the one described, *i.e.* (**18***; H outside); just above it lies one where the alkyl group is *anti*, OR outside and H inside (**19***).[65] As illustrated, the former leads to a product wherein OR and the nitrile oxide oxygen are *anti*, the latter to one with them *syn* (Scheme 19).

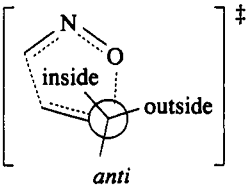

(**17**)

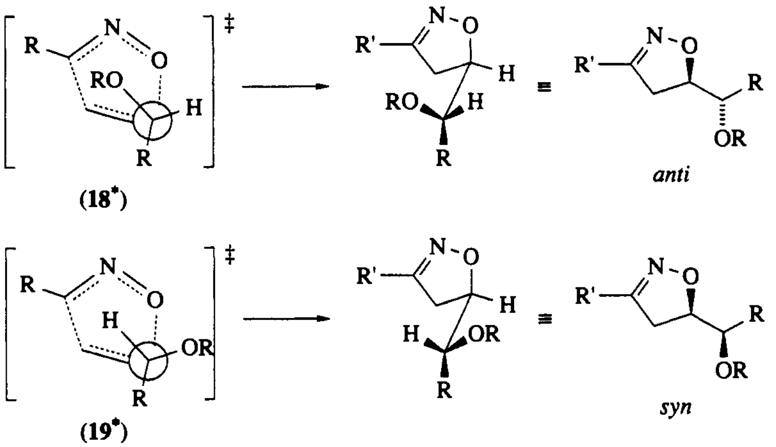

Scheme 19

It is argued that if the OR unit occupied the *anti* position, then the electron withdrawal by the $\sigma^*_{CO}$-orbital from the $\pi$-orbital of the dipolarophile would destabilize the electrophilic transition state.[65] By assuming the inside (or outside) position, $\sigma^*_{CO}$–$\pi$ interaction is minimized and overlap of the electron-donating $\sigma_{CH}$ and $\sigma_{CR}$ orbitals with the *p*-orbital is maximized.

The model correctly predicts (rationalizes) the observed preference for formation of the *anti* rather than the *syn* product in the cycloaddition reactions of a wide variety of chiral allylic ethers, thus successfully laying to rest years of frustrated discussion.[65,66] It also correctly predicts that as the size of R increases (Me ~ Ph < Et < $Pr^i$ < $Bu^t$), the preference for transition state structure (**18***) should increase leading to enhanced *anti* stereoselectivity (Table 15).[65] At first, this prediction seems strange. However, once it is realized that, like the Felkin-Anh model for nucleophilic addition to a carbonyl,[72] the outside position is actually more sterically demanding than the inside, then the prediction is sensible on purely steric grounds. Thus, the angle of approach of the nitrile oxide oxygen to the alkene actually places it nearer the outside than the inside substituent located at the allylic carbon.[67]

**Table 15** *Anti/syn* Stereoselectivity in Nitrile Oxide Cycloadditions to Chiral Allylic Ethers[a]

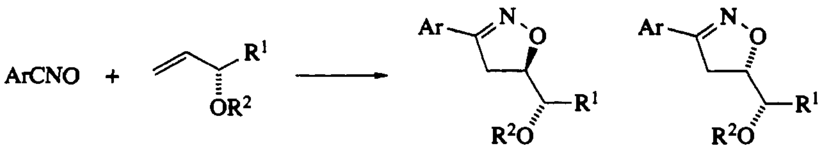

| *Ar* | *$R^1$* | *$R^2$* | *Anti:syn* |
|---|---|---|---|
| $p$-$O_2NC_6H_4$ | Me | OMe | 64:36 |
| $p$-$O_2NC_6H_4$ | Ph | OMe | 67:33 |
| $p$-$O_2NC_6H_4$ | $Bu^t$ | OMe | >95:5 |
| Ph | Me | OTMS | 71:29 |
| $p$-$O_2NC_6H_4$ | Ph | OTMS | 69:31 |
| $p$-$O_2NC_6H_4$ | $Bu^t$ | OTMS | >95:5 |
| $p$-$O_2NC_6H_4$ | Me | $OSiMe_2Ph$ | 65:35 |
| $p$-$O_2NC_6H_4$ | Et | $OSiMe_2Ph$ | 80:20 |
| $p$-$O_2NC_6H_4$ | $Pr^i$ | $OSiMe_2Ph$ | 91:9 |

[a]Conditions: $CH_2Cl_2$, 25 °C when Ar = $p$-$O_2NC_6H_4$; $Et_2O$, 20 °C when Ar = Ph.

On the other hand, the ratio varies little with changes in electronic or steric demands of either the nitrile oxide substituent or the alkyl group attached to the oxygen of the allyl ether (Table 16).[65,66,68,69] Similar observations have been made when $R^2$ = Me, THP, OAc and $SiR_3$.[65,66]

**Table 16** Insensitivity of Cycloaddition Stereoselectivity to Ether Substituent[a]

| | *$R^2$* | *Yield (%)* | *Anti:syn* |
|---|---|---|---|
| ArCNO + 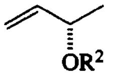 | Me | 63 | 64:36 |
| | $C_6H_4OMe$-$p$ | 89 | 66:34 |
| Ar = $p$-$NO_2C_6H_4$ | Ph | 93 | 60:40 |
| | $C_6H_4NO_2$-$p$ | 91 | 60:40 |

[a]$CH_2Cl_2$, 25 °C.

In contrast to allylic ethers, chiral allylic alcohols give rise to a modest preference for the *syn* product, presumably a reflection of stabilization through hydrogen bonding between the incoming nitrile oxide oxygen and the allylic alcohol.[67] *Ab initio* calculations agree that the outside OH position is favored over the inside. Additional support for this idea comes from the fact that in good hydrogen-bonding acceptor solvents like DMF, the 40:60 *anti/syn* ratio observed in diethyl ether becomes 60:40, nearly the same value as that found for the corresponding allyl ether (Table 17).[67]

**Table 17** Influence of Hydrogen Bonding and Solvent Upon Stereoselectivity

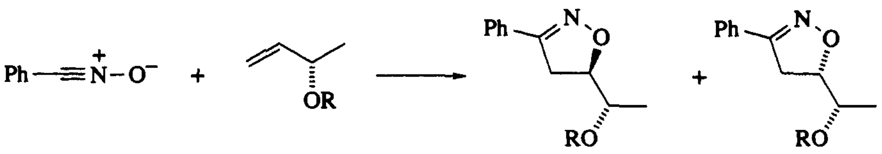

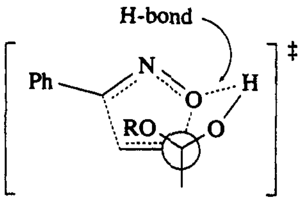

| *R* | *anti:syn* | *Solvent* |
|---|---|---|
| H | 40:60 | $Et_2O$ |
| H | 60:40 | DMF |
| $CH_2Ph$ | 64:36 | $Et_2O$ |

Studies dealing with the general case where the groups attached to the stereogenic center of the allylic framework differ in size have only recently been performed. Remarkably good agreement between the results of MM2 calculations and experiment were evident and are summarized in Table 18.[68] The major product arises from a staggered transition state (**20**) similar to those shown above, with the largest group (L) *anti*, the medium-sized group (M) inside, and the small group (S) outside.

**Table 18** Comparison of Calculated and Experimentally Determined Diastereoselectivity

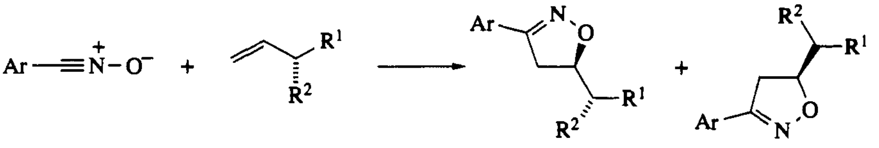

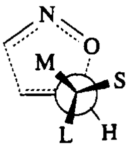

(**20**)

| *$R^1$* | *$R^2$* | *Total yield (%)* | *Experimental (±3%)* | *Calculated* |
|---|---|---|---|---|
| Et | Me | 72 | 50:50 | 50:50 |
| Ph | Me | 70 | 59:41 | 53:47 |
| $Pr^i$ | Me | 50 | 65:35 | 72:28 |
| $C(OMe)Me_2$ | Me | 93 | 80:20 | 87:13 |
| $Bu^t$ | Me | 82 | 77:23 | 97:3 |
| Me | OMe | 63 | 64:26 | 68:32 |
| $Bu^t$ | OMe | 64 | >97:3 | 96:4 |

Interestingly, the transition states are calculated to be relatively early in terms of bond making and breaking, but are product-like in terms of conformational preferences about the bonds to the alkene.[67] For example, the X-ray crystal structure for the product of the reaction between *p*-nitrobenzonitrile oxide and 3,4,4-trimethyl-1-pentene resembles the transition-state model. Similarly, comparison of the ORTEP plot resulting from a single-crystal X-ray analysis of the major product resulting from the reaction of benzonitrile oxide with a chiral (α-oxyallyl)silane, $CH_2{=}CHCH(OTBDMS)SiEt_3$, closely resembles the predicted, preferred transition-state model, one which places the large trialkylsilyl group *anti*, the medium-size alkyl or oxy group inside, and the small hydrogen outside. The minor product apparently arises from a transition state where the location of the medium and small groups is reversed (Scheme 20).

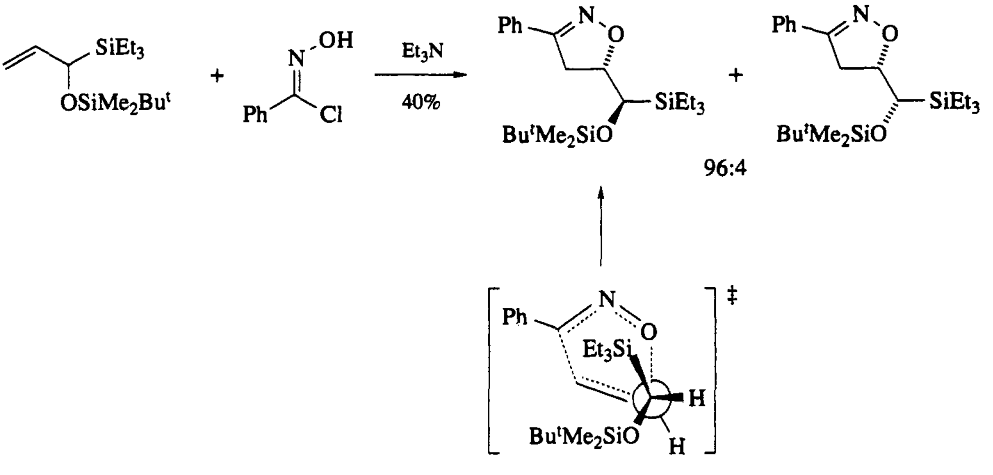

**Scheme 20**

The addition of (ethoxycarbonyl)formonitrile oxide to (+)-(*S*)-isopropylidene-3-butene-1,2-diol led to an 80:20 mixture (60% diastereomeric excess) of diastereomers in *ca.* 70% yield (Scheme 21); the major product was converted to 2-deoxy-D-ribose to illustrate the utility of the process.[69] The observed diastereoselectivity was explained using a different transition-state model than the one discussed thus far. In particular, it was assumed that cycloaddition occurred preferentially *via* a transition state where the nitrile oxide oxygen adds *anti* to the C—O bond in the dipolarophile as shown.[72] This approach does appear to minimize steric interactions. However, it maximizes $\sigma^*_{CO}$ electron withdrawal from the alkene in a process which is, like most other nitrile oxide cycloadditions, LU controlled. The 'inside alkoxy' transition-state model invoked previously also accounts for the observed diastereoselectivity *via* a transition state which minimizes the $\sigma^*_{CO}$–$\pi$ interaction.

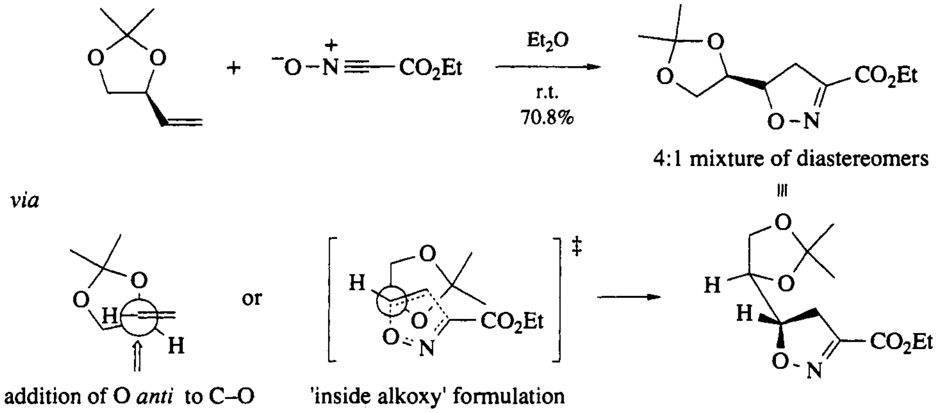

Et₂O
r.t.
70.8%
CO₂Et
4:1 mixture of diastereomers
via
or
addition of O anti to C–O
'inside alkoxy' formulation
‡

**Scheme 21**

Poor (<4% *de*) to modest (56% *de*) amounts of diastereofacial selection is observed in the cycloaddition of nitrile oxides to optically active acrylates.[70] The plan in each case, of course, was to use a chiral auxiliary which would preferentially shield one of the two $\pi$-faces of the dipolarophile. Of the auxiliaries used, the sulfonamide esters derived from (+)-camphorsulfonyl chloride worked best, the menthyl esters derived from (–)-menthol the poorest (<4% *de*). As illustrated in Table 19, changes in both temperature and solvent had either no or little affect on the product ratios. Unlike Diels–Alder reactions, the addition of Lewis acids, specifically $Et_2AlCl$, $EtAlCl_2$ and $TiCl_4$, resulted in significant decreases in both the rate of cycloaddition and isolated yield, without an appreciable change in diastereomer ratio.[70]

Examination of the structure of the major diastereomer suggests that it is derived from a cycloaddition between the nitrile oxide and the *s-cis* conformer of the acrylate. Calculations performed on simple transition-state models for the process do indeed place the formulation involving the *s-cis* conformer at lower energy than the alternative *s-trans* form.[70]

**Table 19** Influence of Conditions Upon Diastereoselectivity in Cycloadditions to Chiral Acrylates

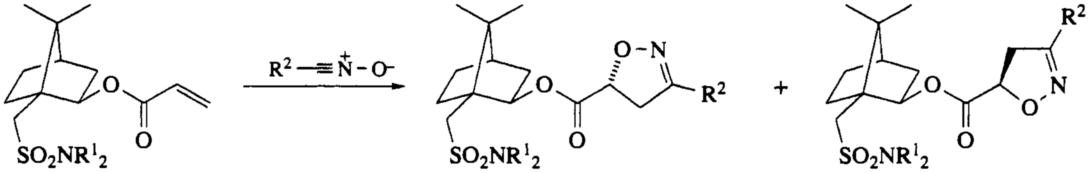

R = cyclohexyl **(21)** **(22)**

| $R^2$ | *Solvent* | *Temp. (°C)* | *Diastereomer ratio (% de;* **21**:**22***)* |
|---|---|---|---|
| Ph | PhH or PhMe | Ambient | 77:23 (54) |
| Ph | a | 0 | b |
| Ph | a | –20 | b |
| Ph | Hexane | Ambient | 76:24 (52) |
| Ph | $Et_2O$ | Ambient | 72:28 (44) |
| Ph | $CH_2Cl_2$ | Ambient | 70:30 (40) |
| $Bu^t$ | PhMe | Ambient | 77:23 (54) |
| $Bu^t$ | a | 185 | 66:34 (32) |

[a] Not specified. [b] No detectable change.

A variety of elegant experiments serve to highlight the nature of the subtle factors which control diastereofacial selectivity in dipolar cycloaddition reactions between optically active nitrones, of the type illustrated, and electron-rich dipolarophiles.[52,53,63b] In general, facial selectivity is found to be influenced by the nature of the substituent on nitrogen and by the presence of a second stereogenic center. As illustrated, selectivities ranging from zero to 'complete' have been observed (Scheme 22). Notice also the preference for formation of the *endo* transition state derived product.

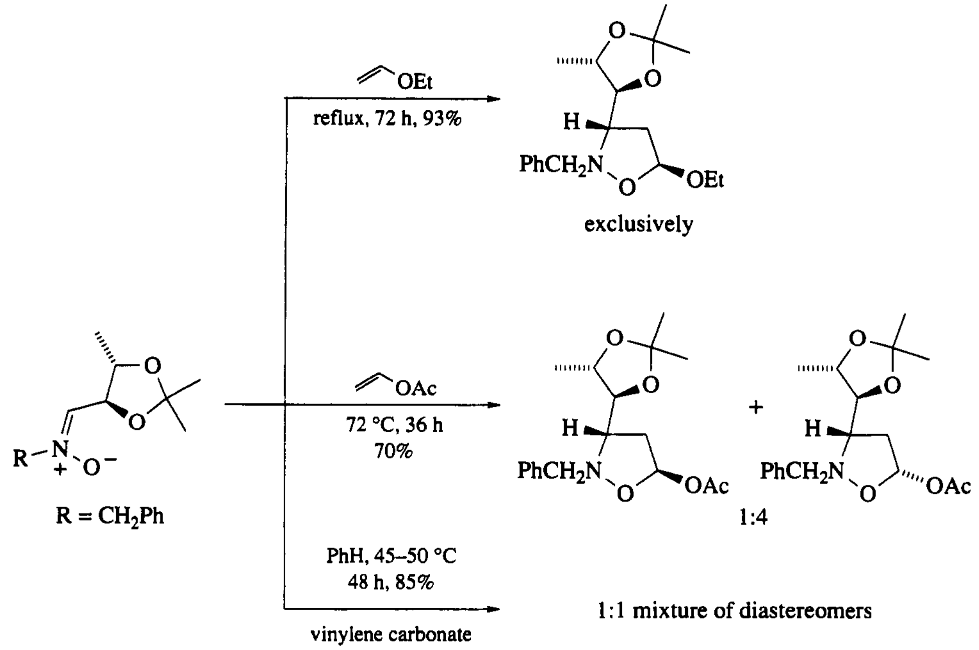

**Scheme 22**

To rationalize the stereochemical outcome of the reactions illustrated as well as a host of other examples, the following arguments have been put forth.[53] Firstly, since the cycloaddition reactions are exothermic and have an early, reactant-like transition state, those factors which influence the relative energy of the equilibrating rotamers (**23**)–(**25**) also influence the transition-state energies. Examination of (**23**)–(**25**) reveals that (**23**) is sterically most congested, suggesting that the equilibrium should lie toward (**24**) and (**25**). Yet (**23**) could be the highest-energy and most reactive form of the nitrone. However, molecular mechanics calculations place it 8–10 kcal mol$^{-1}$ higher in energy than (**24**), making it only a minor contributor to the conformational equilibrium during cycloaddition. Of (**24**) and (**25**), rotamer (**25**) finds one of the ketal CO bonds located *anti* to the $\pi$ framework of the nitrone, thereby stabilizing it through an energy-lowering $\sigma^*_{CO}$–$\pi_{CC}$ interaction. Secondly, attack of the dipolarophile is assumed to occur on to the face of the nitrone indicated by the double arrow. One concludes that cycloaddition should occur to give the major diastereomer *via* (**24**) and the minor diastereomer *via* (**25**), as observed (Scheme 23).

Diastereofacial selectivity is also expressed in the cycloaddition reactions of optically active nitrones bearing stereogenic centers on nitrogen, rather than on carbon.[50b,63c,63d,73] For example,[63d] formylation of *trans*-propenyl acetate with Brederick's reagent led to acrylate (**26**) in 91% yield. The latter was converted to nitrone (**27**) by heating it with the oxalate salt of (*S*)-(–)-*N*-hydroxy-α-methylbenzenemethanamine. Under these conditions the nitrone undergoes intramolecular cycloaddition leading to a 68% yield of an 82:18 mixture of diastereomers (Scheme 24). While the dipolarophile stereochemistry is preserved in the usual manner, this example is the first recorded instance of preferential addition of the nitrone oxygen to the non-oxygen bearing carbon of an enol ether.[74] In contrast, intermolecular nitrone cycloadditions with enol ethers and esters shows a marked preference for the opposite regiochemical outcome (*vide supra*).

A working model, which may account for the results, proposes that transition state (**28***) leads to the major and (**29***) to the minor diastereomer. Notice that, in each, the α-methylbenzyl group is oriented with the small hydrogen atom directed toward the dipolarophile.[63d] As anticipated from this model, the degree of diastereoselection is dependent upon the substituents R$^2$ and R$^3$ located on the dipolarophile

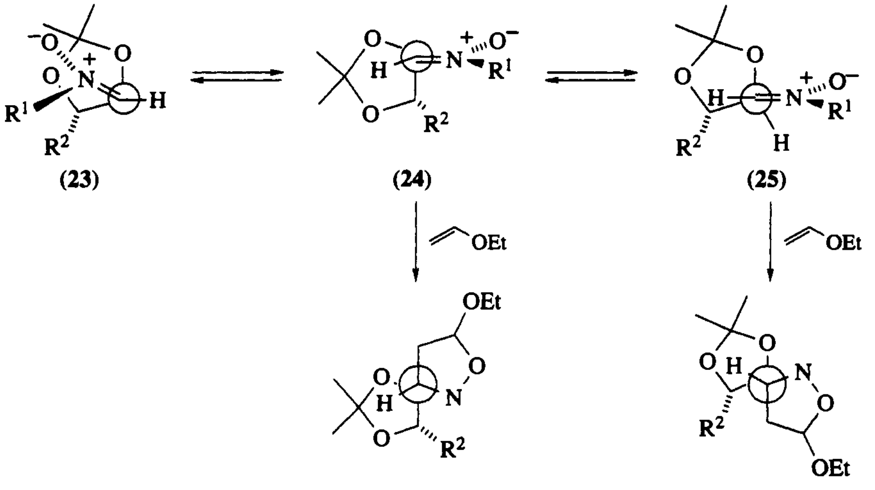

Scheme 23

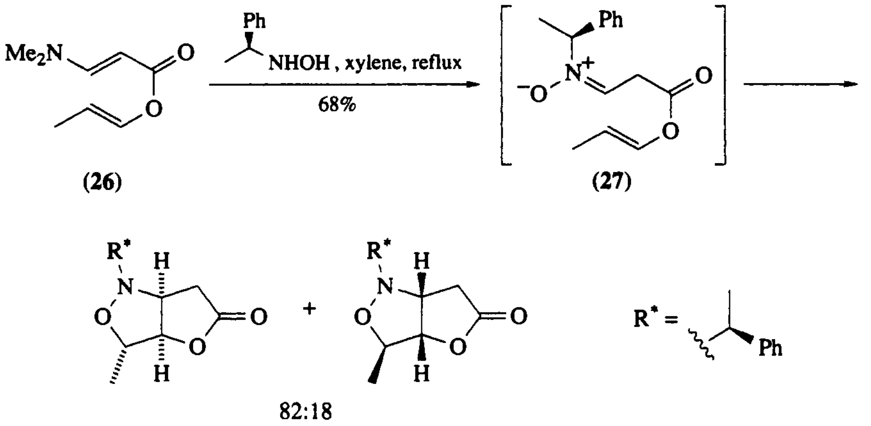

Scheme 24

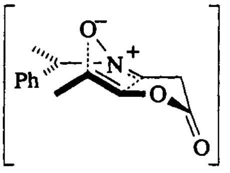

(28*)

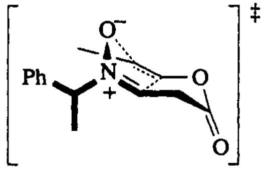

(29*)

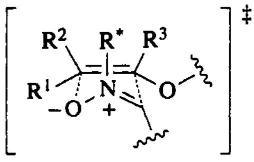

(30)

since each is in position to interact with the other and with R* in the transition state (**30**). The largest selectivity is observed when $R^2$ or $R^3$ = Me, the smallest when both are hydrogen (Table 20).[63d]

The same chiral auxiliary has been used in the cycloaddition of an optically active azomethine ylide to benzaldehyde and to 1-nitro-2-(3,4-methylenedioxyphenyl)ethylene; the ylide was generated *in situ* by treating (*R*)-(+)-*N*-(1-phenylethyl)-*N*-cyanomethyl-*N*-trimethylsilylmethylamine (**33**) with silver fluoride.[64] Unfortunately, no selectivity was observed in the first case and only a 3:2 preference was expressed in the second. Use of the azomethine ylide derived in the same manner from (*R*)-(−)-*N*-(1-phenyl-2-methoxyethyl)-*N*-cyanomethyl-*N*-trimethylsilylmethylamine (**34**) displayed a modest, but potentially useful, 4:1 diastereofacial selectivity in its reaction with 1-nitro-2-(3,4-methylenedioxyphenyl)ethylene. The precise structure of the major and minor product was not determined (Scheme 25).

**Table 20** Diastereoselectivity in Intramolecular Nitrone Cycloaddition Using a Chiral Nitrone

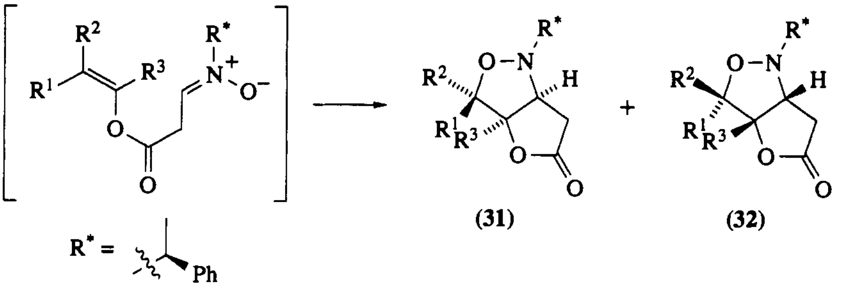
R2
R*
R1
R3
N+
O−
O
O
R* =
Ph
R2
O−N
R*
H
R1
R3
O
O
+
(31)
(32)

| | (31):(32) |
|---|---|
| $R^1 = R^3 = H, R^2 = Me$ | 82:18 |
| $R^1 = Me, R^2 = R^3 = H$ | 53:47 |
| $R^1 = R^2 = R^3 = H$ | 60:40 |
| $R^1 = R^2 = H, R^3 = Me$ | 73:27 |
| $R^1 = R^2 = Me, R^3 = H$ | 73:27 |

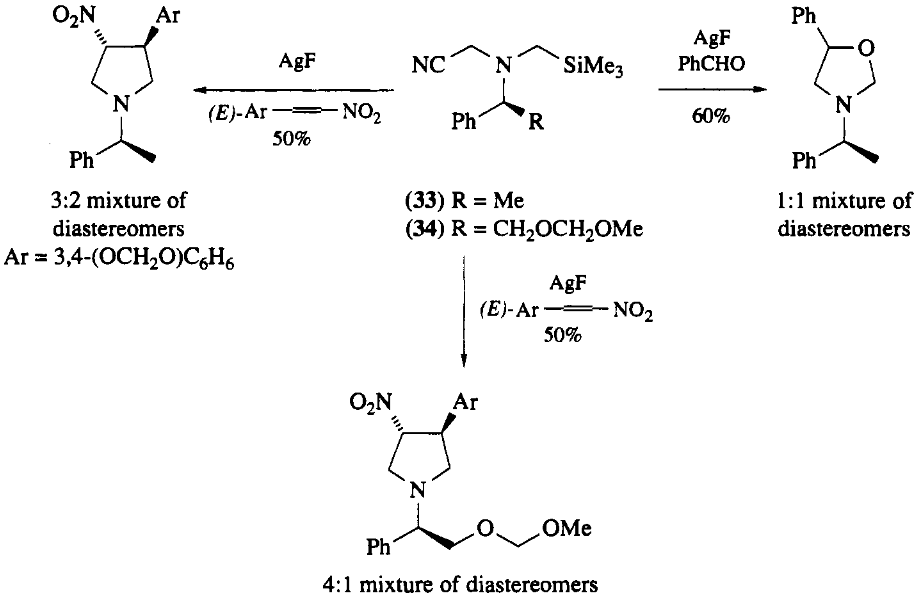
O2N
Ar
N
Ph
AgF
(E)-Ar—NO2
50%
NC
N
SiMe3
Ph
R
AgF
PhCHO
60%
Ph
O
N
Ph
3:2 mixture of diastereomers
Ar = 3,4-(OCH2O)C6H6
(33) R = Me
(34) R = CH2OCH2OMe
1:1 mixture of diastereomers
AgF
(E)-Ar—NO2
50%
O2N
Ar
N
Ph
O
OMe
4:1 mixture of diastereomers

**Scheme 25**

## 3.1.5 1,3-DIPOLAR SYNTHETIC EQUIVALENTS[75]

### 3.1.5.1 Polarized Cyclopropanes

#### *3.1.5.1.1 Cyclopropenone ketals*

In 1984, the facile [3 + 2] cycloaddition of cyclopropenone ketals to alkenes bearing geminal electron-withdrawing groups was reported.[76] The reaction proceeds regiospecifically, always placing the ketal adjacent to the carbon bearing the electron-withdrawing group. The reactions are typically run at temperatures of 70–80 °C in benzene or acetonitrile. Isolated yields range from *ca.* 40 to 80%. Representative examples of this mechanistically interesting and synthetically useful process are shown in Table 21.[75]

**Table 21** Reaction of Cyclopropenone Ketal With Electron Deficient Alkenes

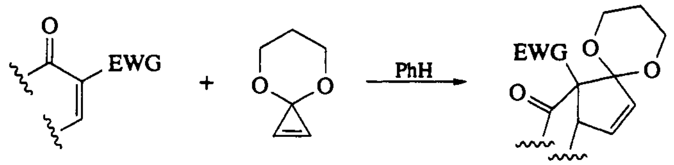

| *Substrate* | *Equiv. of ketal* | *Conditions* | *Product* | *Yield (%)* |
|---|---|---|---|---|
| 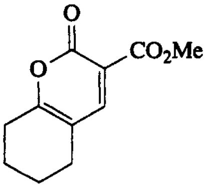 | 1.0–2.0 | 80 °C, 12 h | 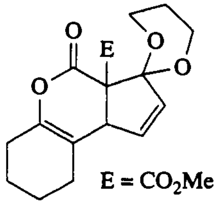 | 42 |
| 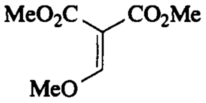 | 2.0 | 80 °C, 5 h | 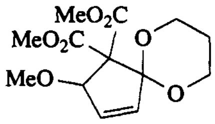 | 84 |
| 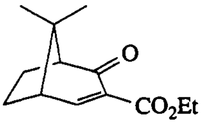 | 1.0 | 75 °C, 13 h | 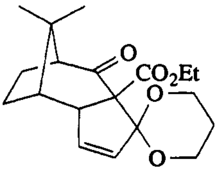 | 45 |
| 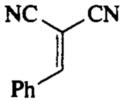 | 2.0 | 80 °C, 4 h | 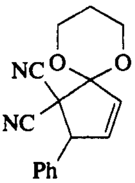 | 86 |

The synthetic utility is restricted somewhat by the failure of alkenes activated by only one electron-withdrawing group to undergo the cycloaddition. Instead, vinylcyclopropanes, corresponding to [1 + 2] cycloadducts, are formed. Unfortunately, attempts to affect a vinylcyclopropane–cyclopentane rearrangement were unsuccessful. 2-Acetoxyacrylonitrile fails to participate in either [1 + 2] or [2 + 3] cycloaddition (Schemes 26, 27).[76b]

The cyclopropenone ketal behaves as the 1,3-dipolar equivalent (**35**; Scheme 28). Yet attempts to detect it, or to affect the rate of the process by varying solvent polarity, indicate that little discernible dipolar character is associated with the intermediate involved in the rate-determining step.[76] Detailed

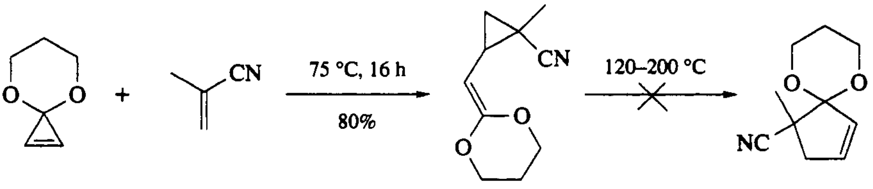

9:1 *cis*:*trans*

**Scheme 26**

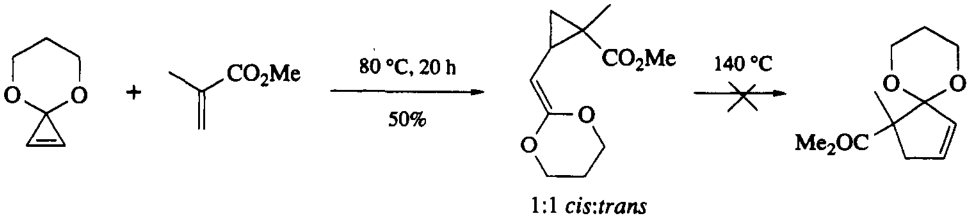
CO2Me
80 °C, 20 h
50%
CO2Me
140 °C
Me2OC
1:1 cis:trans

Scheme 27

mechanistic studies have ruled out several potentially viable mechanisms. It has been suggested that a π-delocalized singlet vinylcarbene is formed *via* a reversible, thermal process and is followed by single electron transfer from it to the electron-deficient doubly activated alkene to generate a π-delocalized cation radical–radical anion pair; their combination leads to the product.[76]

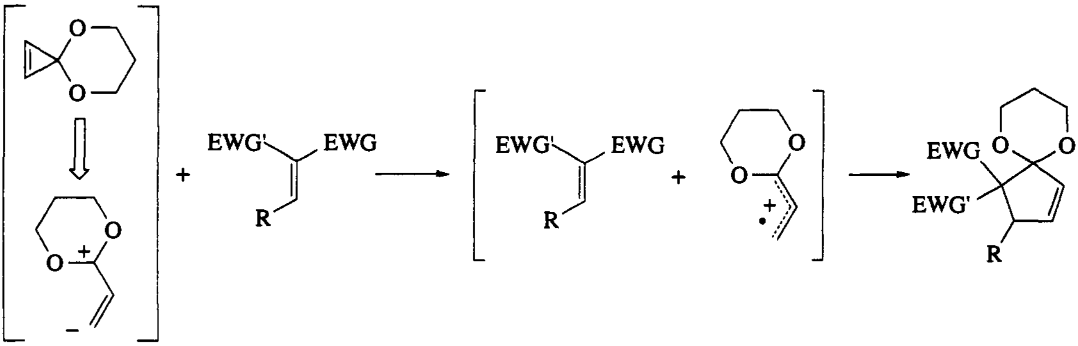
EWG'
EWG
R
EWG'
EWG
R
EWG
EWG'
R

(35)

Scheme 28

### 3.1.5.1.2 Cyclopropylphosphonium salts

It is well known that cyclopropane rings, activated toward reaction by the existence of geminal electron-withdrawing groups, can be opened by nucleophiles.[77] One such system is ethoxycarbonylcyclopropyltriphenylphosphonium tetrafluoroborate.[75,78] When allowed to react with an enolate derived from a β-keto ester or a 1,3-diketone, the salt suffers ring opening to generate an ylide which subsequently undergoes an intramolecular Wittig cyclization on to the ketone, leading to the creation of a five-membered ring.[78] In so doing the phosphonium salt clearly behaves as a synthon for a 1,3-dipolar reagent.[75] Equations (24)–(26) provide an indication of the scope of the reaction.

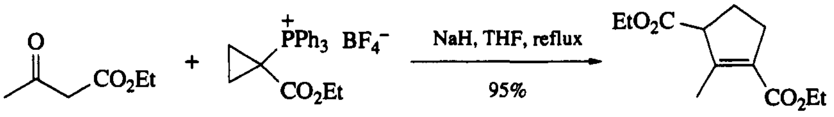
CO2Et
PPh3 BF4-
CO2Et
NaH, THF, reflux
95%
EtO2C
CO2Et

(24)

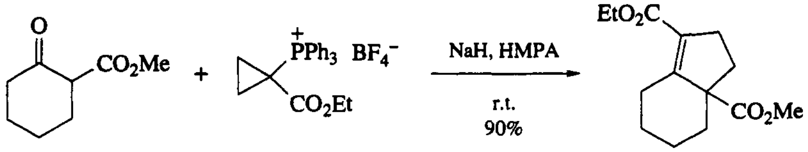
CO2Me
PPh3 BF4-
CO2Et
NaH, HMPA
r.t.
90%
EtO2C
CO2Me

(25)

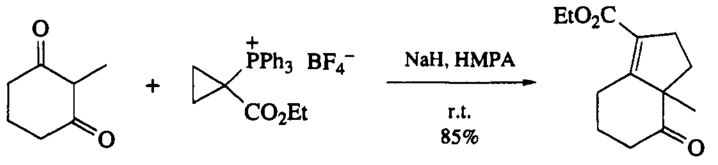
PPh3 BF4-
CO2Et
NaH, HMPA
r.t.
85%
EtO2C

(26)

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# 3.2
# Transition Metal Mediated Cycloadditions

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## 3.2.1 GENERAL INTRODUCTION

Five-membered ring systems are rapidly emerging as important structural features in a large number of natural products and theoretically interesting molecules. The development of methodologies for the construction of these systems has thus become a subject of great interest and intense effort for synthetic chemists. In recent years, one has seen a number of $C_5$ annulation procedures, with the majority focusing on multistep sequences based on 1,4-dicarbonyl compounds or their functional equivalents.

One particularly attractive and logical approach to a five-membered ring is the [3 + 2] cycloaddition. This reaction couples a three-carbon $4\pi$ unit directly with a two-carbon $2\pi$ unit, forming two C—C bonds in one operation. The net result is rapid and efficient construction of complex cyclic structures from simple building blocks. This direct method is analogous to the highly effective and popular [4 + 2]

Diels–Alder reaction. The [3 + 2] methodology has the promise and the potential to achieve similar success if one can likewise control the chemo-, regio- and diastereo-selectivity of these reactions.

The ready availability of starting materials, such as dienes and alkenes, has contributed to the popularity of the Diels–Alder reaction. Unfortunately, this is not true in [3 + 2] cycloadditions. While the $C_2$ unit is well represented by simple unsaturated molecules as in the Diels–Alder reactions, the source of the odd-numbered $4\pi$ fragment is less obvious because it is not a common stable entity. Hence, the success of using the [3 + 2] methodology in a synthetic sequence depends critically on the effective generation, reactivity and selectivity of this $C_3$ synthon.

Thermal [3 + 2] cycloadditions have been discussed in the previous chapter. Transition metals also play a critical role in mediating such reactions.[1] Reaction of a commercially available or readily synthesized organic substrate with an appropriate transition metal reagent or catalyst can generate a reactive intermediate which can function as the three-carbon synthon. One can view this as the stabilization of the $C_3$ fragment by ligation to the transition metal center. One unique advantage of these transition metal mediated reactions is the ability to modulate the selectivity of the cycloaddition by the judicious selection of the metal and its ancillary ligands. The opportunity to use chiral ligands to effect enantioselective synthesis is another useful feature. In addition, the properties of this three-carbon unit can be so markedly altered by the metal that the resulting complex may undergo completely different types of reaction from those of the thermally generated systems. This may open up new synthetic avenues not available before. The transition metal complexes described in this section are not esoteric, but are either commercially available or readily prepared. In most cases, these transition metal-mediated reactions require only routine oxygen- and moisture-free laboratory techniques.

## 3.2.2 CLASSIFICATION OF REACTIONS

The main research efforts in transition metal mediated [3 + 2] cycloaddition can be categorized into the development of three important types of $C_3$ synthon: dimethylenemethane, 2-oxyallyl, and trimethylenemethane. This review summarizes some recent achievements up to the first quarter of 1989, and centers around these three synthons. Emphasis will be placed on the chemo-, regio- and stereo-selectivity of these reactions, their preparative aspects, and their synthetic potential.

## 3.2.3 THE DIMETHYLENEMETHANE SYNTHONS

A [3 + 2] cycloaddition involving a dimethylenemethane (**1**) and an unsaturated receptor is depicted in equation (1). A number of these three-carbon synthons has been developed. They include stable and easily prepared organometallic species, as well as the activation of an organic precursor with a transition metal reagent or catalyst. The discussion on the generation and reactions of this three-carbon synthon will be organized according to precursor types: allylic, alkynyl, allenylic, cyclopropyl and others.

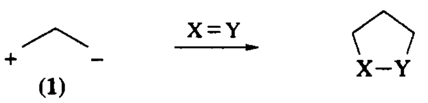

(1)

### 3.2.3.1 Allylic Precursors

Cycloaddition reactions of 18-electron transition metal $\eta^1$-allyl complexes with unsaturated electrophiles to form five-membered rings have been extensively investigated. These transformations constituted a family of metal-assisted cycloaddition reactions in which the metal functions as an electron-donor center. These are typically two-step processes that involve the initial formation of a dipolar metal $\eta^2$-alkene intermediate (**2**) and subsequent internal cyclization (equation 2).[2–4] The most extensively investigated application of this methodology has been with dicarbonyl-$\eta^5$-cyclopentadienyliron (Fp) complexes from the laboratory of Rosenblum.[3,4] These ($\eta^1$-allyl)Fp complexes are available either by metallation of allyl halides or tosylates with a Fp anion, or by deprotonation of (alkene)Fp cations.[4,5]

The parent ($\eta^1$-allyl)Fp (**3**) reacts readily with a highly activated electron-deficient alkene such as dimethyl methylenemalonate at room temperature to give the Fp-cyclopentane (**4**) (equation 3).[4] As discussed previously, the mechanism apparently involves the initial Michael addition of (**3**) to the

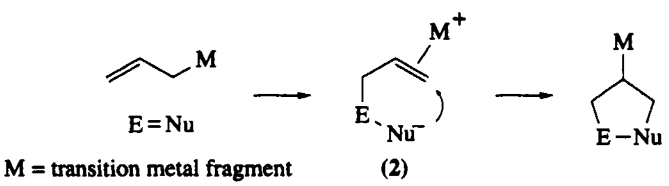
M
E=Nu
M = transition metal fragment
M+
E
Nu−
(2)
M
E−Nu

(2)

electron-deficient alkene to produce the intermediate complex (**5**). Ring closure is achieved *via* the attack of the stabilized anion on the Fp-coordinated (and thus activated) alkene.

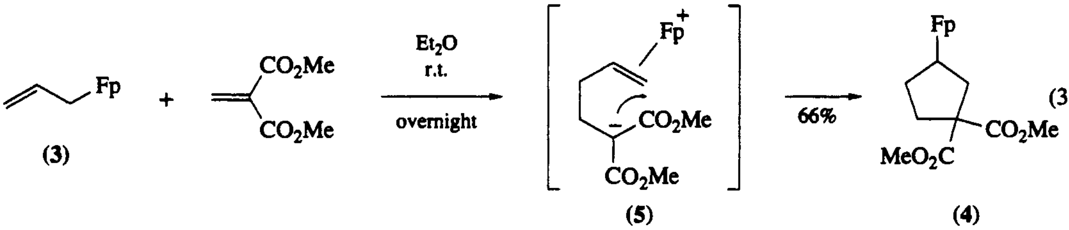
Fp
(3)
+
CO2Me
CO2Me
Et2O
r.t.
overnight
Fp+
CO2Me
CO2Me
(5)
66%
Fp
CO2Me
MeO2C
(4)

(3)

The cycloadditions of ($\eta^1$-allyl)Fp complexes to alkenes proceed with high chemoselectivity. Only highly activated alkenes such as methylenemalonates, benzylidenemalononitrile,[6] TCNE[4] or 1,2-dicyano-4,5-dichloroquinone[4] will participate in the reaction. With the less electrophilic α,β-unsaturated systems, cycloaddition can only be effected with Lewis acid activation. Thus the cycloadduct (**6**) is formed in reasonable yield (as a mixture of stereoisomers) from (**3**) and cyclohexenone using freshly sublimed $AlBr_3$ (equation 4). The same reaction gives only a 8% yield with $AlCl_3$. The exclusive formation of a *cis*-hydrindanone system can be explained by suprafacial attack of the enone on the allyl unit, which is then followed by another suprafacial ring closure of the dipolar intermediate, affording the thermodynamically preferred cyclic system (**7a**) and (**7b**).[6]

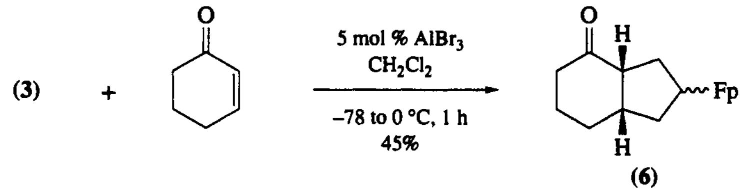
(3)
+
O
5 mol % AlBr3
CH2Cl2
−78 to 0 °C, 1 h
45%
O
H
Fp
H
(6)

(4)

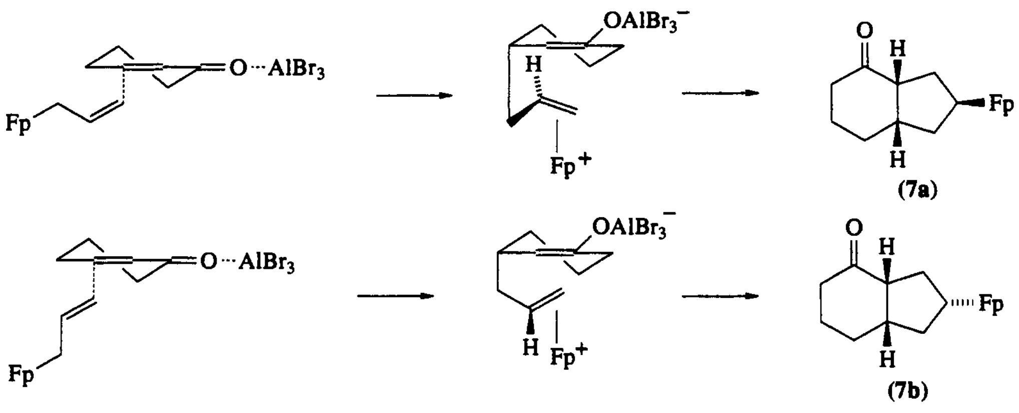
O···AlBr3
Fp
OAlBr3−
H
Fp+
O
H
Fp
H
(7a)
O···AlBr3
Fp
OAlBr3−
H
Fp+
O
H
Fp
H
(7b)

The more sterically demanding ($\eta^1$-2-butenyl)Fp cycloadds to diethyl methylenemalonate to give adduct (**8**) as a mixture of stereoisomers (equation 5).[6] In this case the poor stereoselectivity may be due to the fact that the starting butenyl complex is a mixture of *cis* and *trans* isomers. Formation of the bicyclic ketone (**9**) from the reaction of ($\eta^1$-2-methallyl)Fp and 2-ethoxycarbonylcyclopentenone suggests that alkyl substituents can also be tolerated at C-2 of the (allyl)Fp unit (equation 6).[6] The corresponding ($\eta^1$-2-methoxyallyl)Fp fails to produce any cycloadduct with 2-ethoxycarbonylcyclohexenone or 2-cyclohexenone in the presence of AlBr$_3$. In this case it appears that closure of the zwitterionic intermediate is impeded by the electron-donating methoxy group.

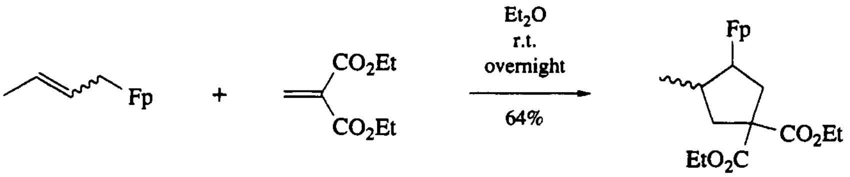

**(8)**

(5)

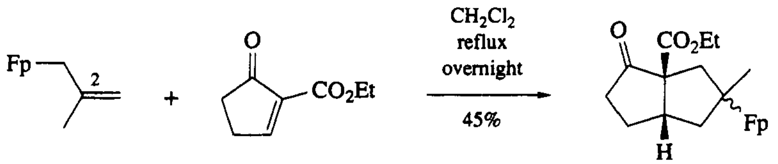

**(9)**

(6)

The construction of hydroazulenes using (allyl)Fp chemistry exemplifies a synthetic application of this [3 + 2] cycloaddition and illustrates some rather interesting regioselectivity of these reagents. The tropyliumiron tricarbonyl (**10**) reacts with ($\eta^1$-allyl)Fp (**3**) to give the dinuclear *cis*-hydroazulene complex (**11**) as a mixture of C-2 epimers (equation 7).[7] With 1-substituted (allyl)Fp complexes such as ketal (**12**), reaction with (**10**) affords exclusively the 1-substituted hydroazulene complexes (**13**) in good yield (equation 8).[7] Another remarkable regioselectivity of the (allyl)Fp cycloaddition is manifested in the reaction with substituted tropyliumiron tricarbonyls. The readily available troponeiron tricarbonyl can be activated for the [3 + 2] cycloaddition by trimethylsilyl or di-*n*-butylboryl triflate at low temperature. Treatment of the resulting trimethylsilyloxy- or di-*n*-butylboryloxy-tropylium salt with a number of (allyl)Fp complexes yields the *cis*-4-ketohydroazulene as the sole product (equation 9).[8] These reactions are likely to proceed *via* intermediate (**14**), which is derived from attack of the allyl organometallic nucleophile at the least sterically hindered position of the pentadienyl ligand, *i.e.* on the opposite side of the Fe(CO)$_3$ moiety. The formation of a single regioisomer is remarkable in view of the known dynamic equilibrium of structural isomers of a substituted tropyliumiron tricarbonyl. The oxygen substituents (Z = TMS or BBu$_2$) on the tropylium unit appear to exert the regiocontrol. Reaction of the corresponding 2-methyltropone system with the parent ($\eta^1$-allyl)Fp (**3**) also results in a single regioisomer (equation 10).[9] Likewise, the hydroazulene complex (**15**) is formed in the reaction of 4-methyltroponeiron tricarbonyl and (**3**) (equation 11).[9]

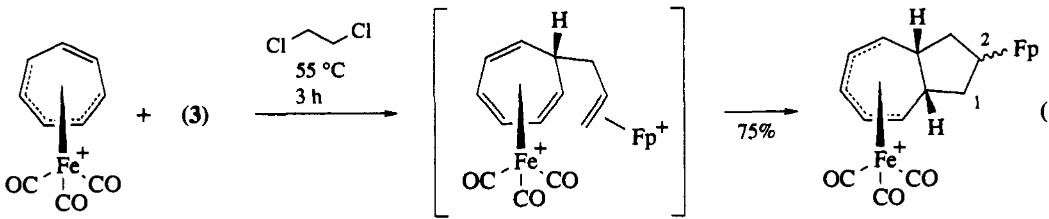

**(10)**

**(11)**

(7)

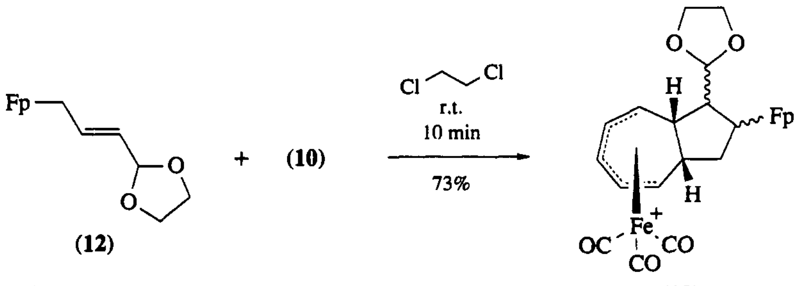

**(12)**

**(13)**

(8)

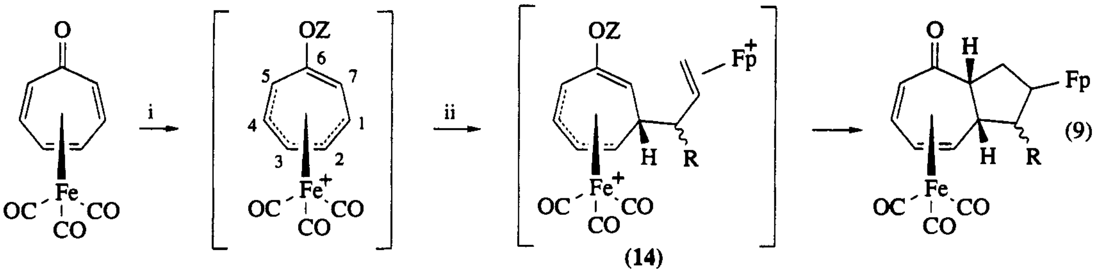

(9)

| Nucleophile | R | Activator | Z | Yield |
|---|---|---|---|---|
| 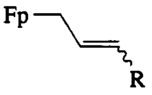 | H | $Me_3SiOTf$ | $Me_3Si$ | 58% |
| | H | $Bu^n{}_2BOTf$ | $Bu^n{}_2B$ | 60% |
| | Me | $Bu^n{}_2BOTf$ | $Bu^n{}_2B$ | 62% |

i, 1 equiv. of activator added at –78 °C, $CH_2Cl_2$, 3 h;
ii, nucleophile at –78 °C, 2 h, then reflux 2 h, then EtOH, $K_2CO_3$

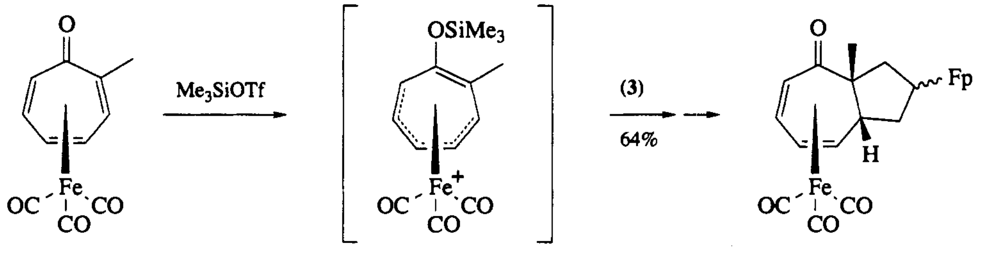

(10)

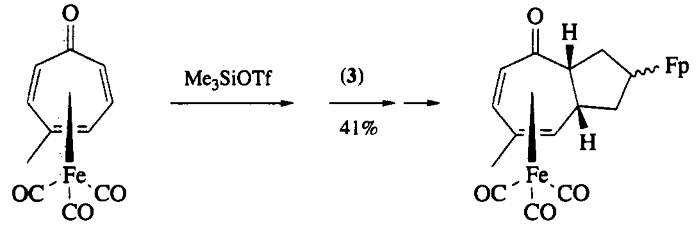

(15)

(11)

The subsequent transformation of these cycloadducts further illustrates the versatility of this approach in the construction of guaianolide sesquiterpenes (Scheme 1).[7] The Fp moiety incorporated in the adduct allows for the introduction of diverse functionalities at C-5 and C-2. For example, reduction of the cycloadduct (**11**) with sodium borohydride produces a good yield of the iron complex (**16**). Oxidation of this complex with cerium ammonium nitrate gives methyl ester (**17**). In addition, (**11**) reacts with nucleophiles such as lithium dimethylmalonate and methanol to give the alkylated complex (**18**) and the methoxylated complex (**19**), respectively. Oxidative demetallation of (**11**) with bromine leads to selective replacement of the Fp moiety at C-2 by bromide.[7]

This [3 + 2] strategy can also be extended to include other heteroatom substrates. The ($\eta^1$-allyl)Fp (**3**) reacts smoothly with toluenesulfonyl isocyanate to afford butyrolactam (**20**) (equation 12).[10]

Other $\eta^1$-allyl transition metal complexes have also been investigated, but mostly they are less effective than the corresponding Fp system. For example, the tungsten, cobalt, chromium and molybdenum analogs of (**3**) cycloadd with the highly electron deficient TCNE at indistinguishable rates;[4] however, with the less reactive *o*-chlorodicyanostyrene there is a distinct difference in their reactivity. The tungsten $\eta^1$-allyl complex affords only 6% of the adduct after 4 h in refluxing THF, whereas the chromium complex fails to react even after prolonged heating. For comparison, the iron complex (**3**) cyclizes smoothly with the same styrene in only 3 h at room temperature (equation 13).[4]

Cycloaddition of the analogous 16-electron ($\eta^1$-allyl)$Pt^{II}$ complexes (**21**) with TCNE proceeds at –78 °C for three days to give the adduct (**22**) (equation 14).[2] The reaction of $\eta^1$-allylpalladium complexes (**23**) with maleic anhydride has also been reported (equation 15).[11] This reaction is sensitive to the nature

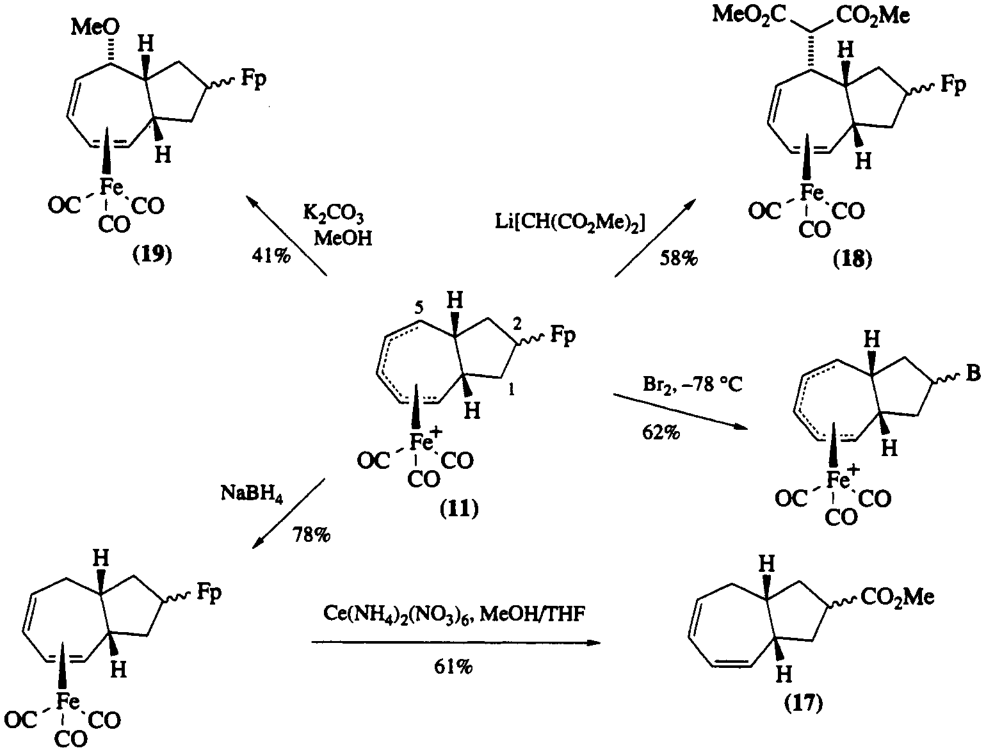
(19)
K$_2$CO$_3$
MeOH
41%
Li[CH(CO$_2$Me)$_2$]
58%
(18)
(11)
Br$_2$, −78 °C
62%
NaBH$_4$
78%
(16)
Ce(NH$_4$)$_2$(NO$_3$)$_6$, MeOH/THF
61%
(17)

**Scheme 1**

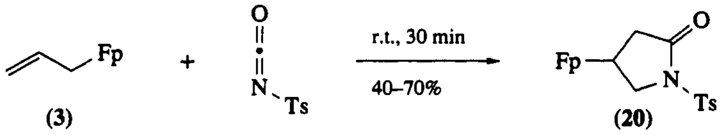
(3)
r.t., 30 min
40–70%
(20)

(12)

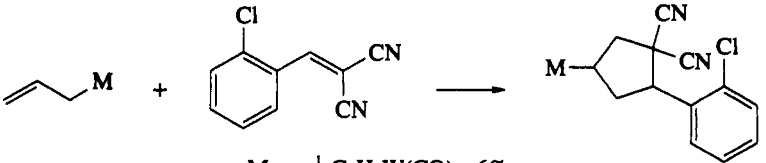

(13)

M = $\eta^1$-$C_5H_5W(CO)_3$ 6%
= $\eta^1$-$C_5H_5Cr(NO)_2$ 0%
= Fp 40%

of the aryl ligand on the metal. Replacing the pentafluorophenyl ligand with a 2,3,5,6-tetrachlorophenyl group gives propene as the main product. No reaction is observed with (23) and dimethyl fumarate or maleate.

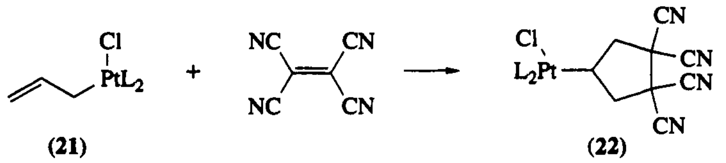

(14)

| *L* | *Yield* |
|---|---|
| $Ph_3P$ | 70% |
| $Ph_2PMe$ | 54% |
| $Ph_2PCH{=}CHPPh_2$ | 64% |

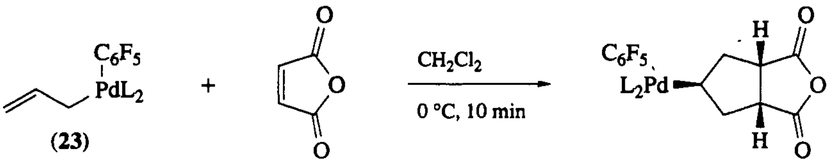

(23)

(15)

| $L_2$ | *Yield* |
|---|---|
| $Ph_2PCH_2CH_2PPh_2$ | 60% |
| $Ph_2PCH{=}CHPPh_2$ | 30% |

A novel [3 + 2] cycloaddition of allylstannanes to α,β-unsaturated (acyl)Fp complexes in the presence of a Lewis acid has been reported. Allyltributyltin reacts smoothly with an (acryloyl)Fp complex at low temperature with a stoichiometric amount of $AlCl_3$ to give the bimetallic cyclopentane (equation 16).[12] It should be noted that allyltrimethylsilane fails to produce any cycloadduct under similar conditions.

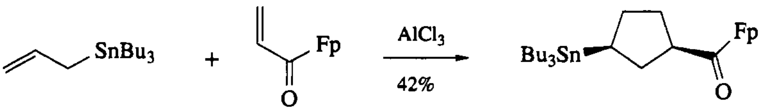

(16)

### 3.2.3.2 Alkynyl Precursors

Alkynyl organometallic reagents based on the Fp system have also been used in [3 + 2] cycloadditions to give cyclopentene systems. The mechanism is similar to the allyl case (equation 17). Reaction of ($\eta^1$-butynyl)Fp (**24**) with cyclohexenone activated with aluminum bromide generates the bicyclic adduct (**25**) in moderate yield (equation 18).[6] The same butynyl complex cycloadds to the tropyliumiron tricarbonyl (**10**) and its oxo derivative to give good yields of iron carbonyl adducts (equation 19).[7,8] The Fp group in adduct (**26**) is readily removed by exposure to dilute sulfuric acid. The cycloadditions of $FpCH_2C{\equiv}CR$ (R = Me, Ph, $CH_2Fp$) with unsaturated substrates such as toluenesulfonyl isocyanate, sulfonylurethane, diarylketene and *N*-sulfinylaniline in variable yields have been reported.[13] The butynyl complex (**24**) reacts with diphenylketene and *N*-sulfinylaniline to give cyclopentanone (**27**)[13] and γ-sultam (**28**),[10] respectively (equation 20).

### 3.2.3.3 Allenylic Precursors

A novel nucleophilic cyclopentene annulation with (trimethylsilyl)allene mediated by titanium tetrachloride has been developed by Danheiser and coworkers.[14–17] One powerful feature of this one-step cycloaddition is its capability to generate substituted five-membered rings regiospecifically. As illustrated in equation (21), the reaction proceeds with high stereoselectivity *via* effective suprafacial addition of the allenylic unit to the electron-deficient alkene. This [3 + 2] annulation methodology is most effective with 1-substituted TMS-allenes, which are available from propargyl alcohols (equation 22).[14,15] Methyl vinyl ketone reacts smoothly with 1-methyl-1-(trimethylsilyl)allene (**29**) at –78 °C to give a good yield of the

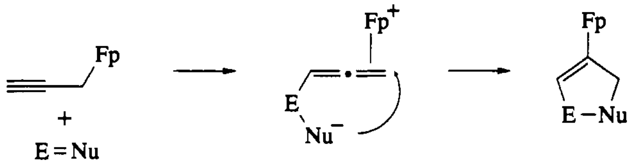

(17)

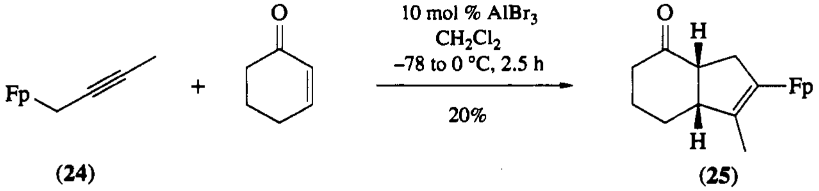

(24)

(25)

(18)

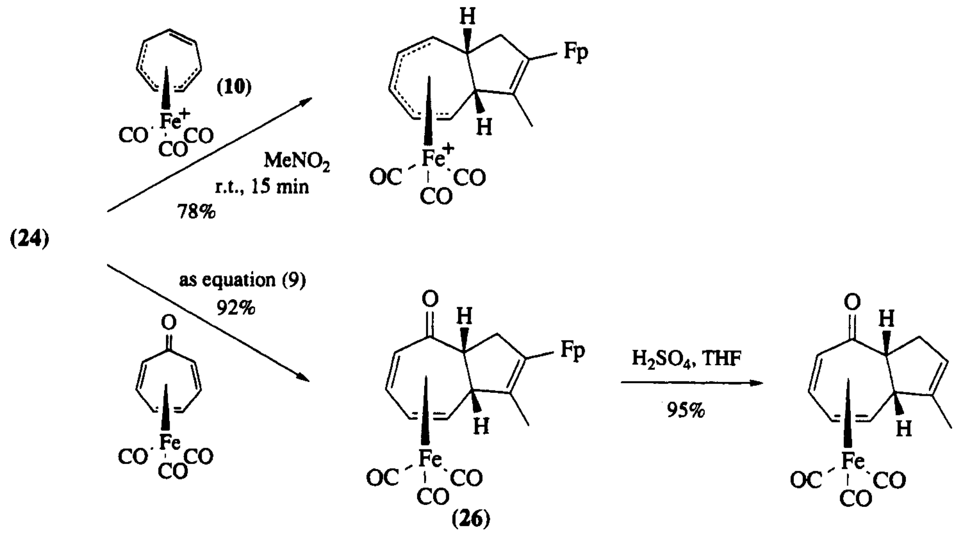
(10)
MeNO$_2$
r.t., 15 min
78%
(24)
as equation (9)
92%
Fp
H$_2$SO$_4$, THF
95%
(26)

(19)

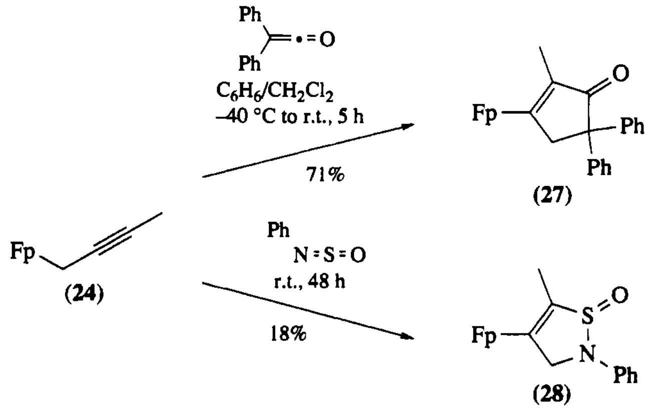
Ph
Ph
C$_6$H$_6$/CH$_2$Cl$_2$
–40 °C to r.t., 5 h
71%
Ph
N=S=O
r.t., 48 h
18%
Fp
(24)
(27)
(28)

(20)

annulation product (**32**) (equation 23).[15] The reaction is likely to involve initial complexation of the enone with TiCl$_4$. Regiospecific electrophilic substitution at the least-hindered end of the allene by the activated enone produces a stabilized vinyl cation (**30**). A 1,2-shift of the TMS group isomerizes (**30**) to cation (**31**), which is then intercepted internally by the titanium enolate to produce the cyclic product. Alkynoic ketones, such as 3-butyn-2-one, also undergo smooth annulation to generate a cyclopentadiene system (equation 24).[15] Isopropylidenecyclohexanone gives the spiro adduct with the silyl allene (**29**) only at room temperature (equation 25).[15] The low yield formation of the highly sterically congested cyclopentene adduct (**33**) (equation 26), and the failure of annulation with the more hindered isophorone,[14] demarcates the steric limit of this cycloaddition.

The reactions of (*E*) and (*Z*)-3-methyl-3-penten-2-one demonstrate the high stereoselectivity of this cycloaddition. From the (E)-isomer a single cyclopentene (**34**) is observed. The reaction of the correspond-

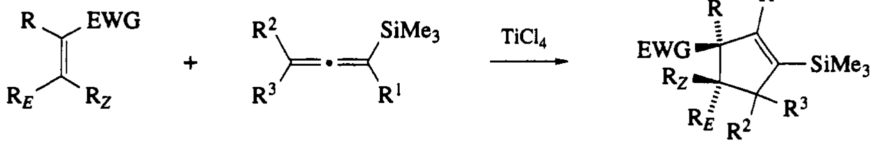
R
EWG
R$_E$
R$_Z$
+
R$^2$
SiMe$_3$
R$^3$
R$^1$
TiCl$_4$

(21)

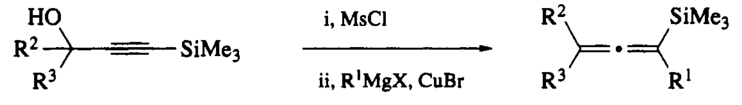
HO
R$^2$
R$^3$
SiMe$_3$
i, MsCl
ii, R$^1$MgX, CuBr

(22)

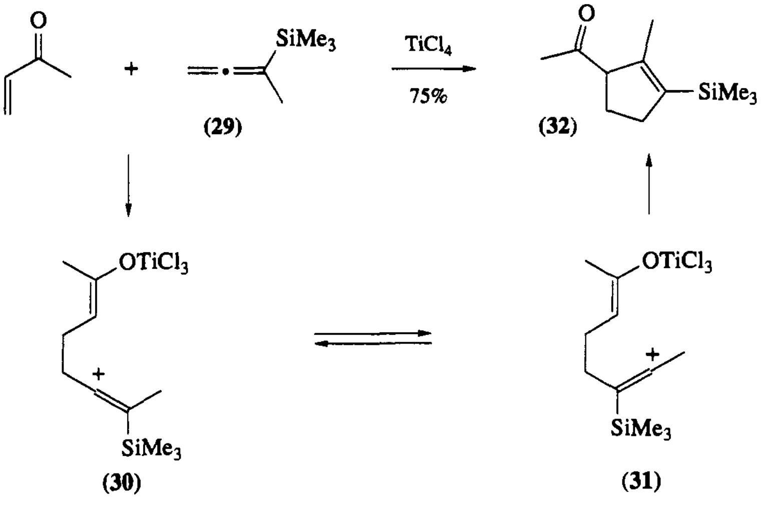

(23)

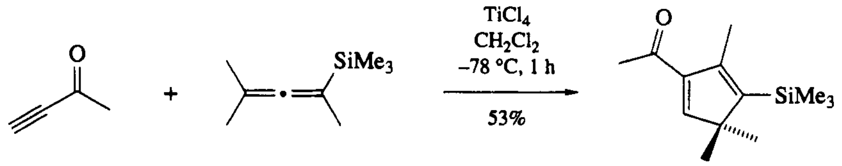

(24)

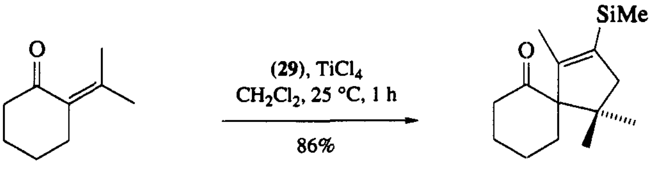

(25)

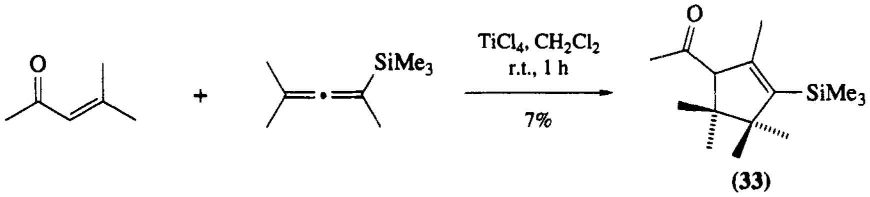

(26)

ing (*Z*)-isomer generates mainly the other diastereomer (**35**) (equation 27).[15] Cyclopentenone and cyclohexenone yield exclusively *cis*-fused adducts with (**29**). Cycloheptenone also gives predominantly the *cis*-fused bicyclic system (equation 28).[15] The stereoselectivity of this [3 + 2] annulation is further shown in the formation of a single stereoisomer (**36**) from the reaction of carvone (**37**) with (**29**) (equation 29).[15] The vinylsilane moiety incorporated in these cyclic products can serve as the basis for a variety of useful transformations. Regiospecific electrophilic substitution reactions of vinylsilanes are well documented. For example, TMS-cyclopentene (**32**) can be readily converted to the diacetyl derivative (**38**) in high yield under mild conditions (equation 30).[15]

This $TiCl_4$-promoted allene cycloaddition has also been extended to the synthesis of five-membered ring heterocycles.[16] In this case, increasing the steric shielding about the silicon atom seems to improve the cyclization process by suppressing the unproductive desilylative alkylation. For example, 1,3-dimethyl(*t*-butyldimethylsilyl)allene (**39**) reacts smoothly with cyclohexanecarbaldehyde to give in high yield the dihydrofuran predominantly as one stereoisomer (equation 31). Similar reaction with an *N*-acyliminium ion precursor (**40**) produces the pyrrolizidine system as a mixture of bicyclic isomers (equation 32).[16]

(Allenyl)Fp complexes have also been used successfully in cycloaddition reactions. Thus ($\eta^1$-allenyl)Fp cycloadds to tropyliumiron tricarbonyl (**10**) to give the hydroazulene complex (**41**) (equation 33).[7] However, reaction of the same allenyl organometallic species with cyclohexenone generates only the four-membered ring cycloadduct (**42**) (equation 34).[6] In the latter case it is likely that the ($\eta^1$-alle-

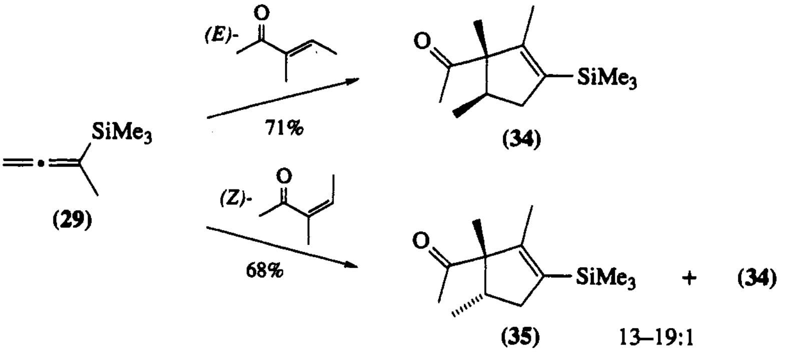
(E)-
71%
(Z)-
68%
SiMe3
(29)
(34)
(35)
+ (34)
13–19:1

(27)

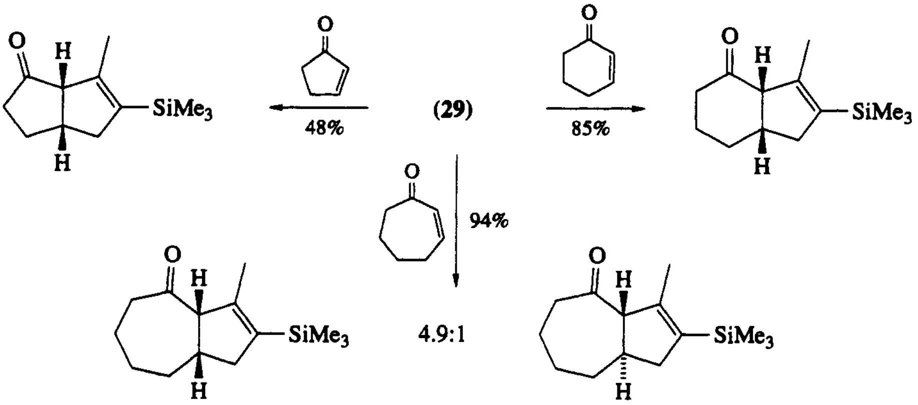
48%
85%
94%
(29)
SiMe3
H
4.9:1

(28)

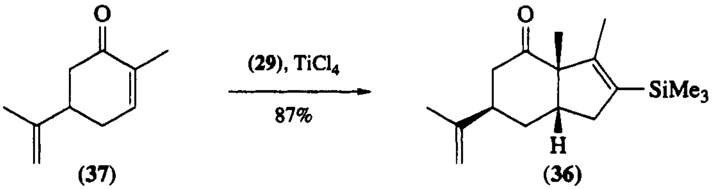
(29), TiCl4
87%
(37)
(36)
SiMe3
H

(29)

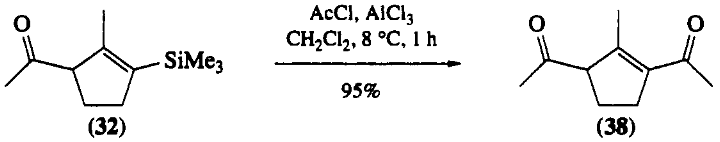
AcCl, AlCl3
CH2Cl2, 8 °C, 1 h
95%
SiMe3
(32)
(38)

(30)

nyl)Fp complex is initially isomerized by traces of acid to ($\eta^1$-1-propynyl)Fp, which is then responsible for the observed product.

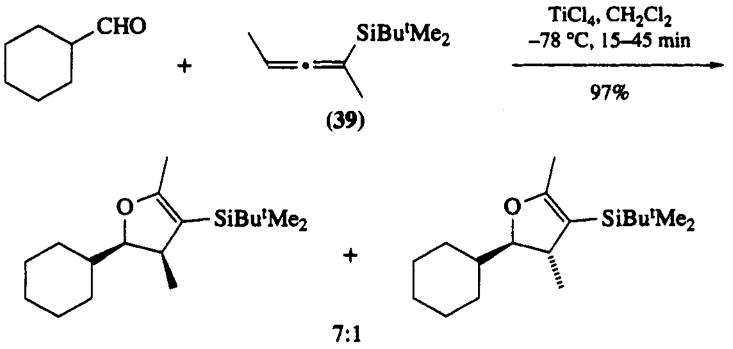
CHO
+
SiBu^tMe2
(39)
TiCl4, CH2Cl2
–78 °C, 15–45 min
97%
+
7:1

(31)

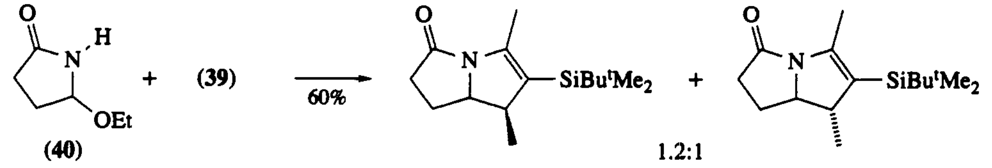

(40)
OEt
(39)
60%
SiBu$^t$Me$_2$
1.2:1

(32)

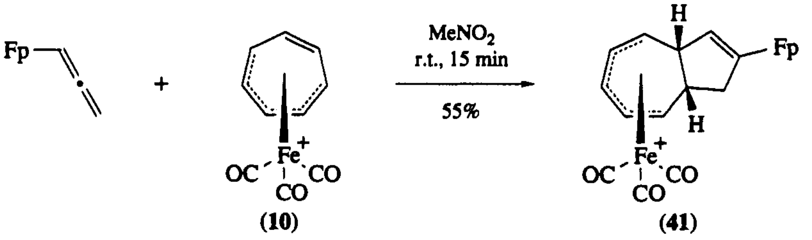

Fp
(10)
MeNO$_2$
r.t., 15 min
55%
Fe$^+$
OC CO CO
(41)
H

(33)

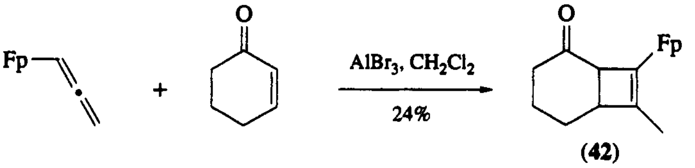

Fp
AlBr$_3$, CH$_2$Cl$_2$
24%
(42)

(34)

### 3.2.3.4 Cyclopropyl Precursors

While simple unactivated cyclopropanes have yet to be used for [3 + 2] cycloaddition, Tsuji and coworkers have developed a palladium-catalyzed cycloaddition reaction using electron-deficient vinylcyclopropanes.[18,19] Thus, vinylcyclopropane (**43**) undergoes smooth cyclization with methyl acrylate in the presence of a palladium catalyst to give vinylcyclopentane (**44**) as a mixture of diasteroisomers (equation 35).[18] The cycloaddition probably proceeds through the zwitterionic (π-allyl)palladium intermediate (**45**) and its stepwise reaction with the acrylate (equation 36). Enones such as cyclopentenone and methyl vinyl ketone will also react. Reaction of the same vinylcyclopropane with phenyl isocyanate produces vinyllactam (**46**) (equation 37).[19] Some cycloaddition reactions with (cyclopropyl)Fp complexes have also been reported. However, the substrates are limited to $SO_2$ and TCNE and the yields have not been disclosed (equation 38).[20]

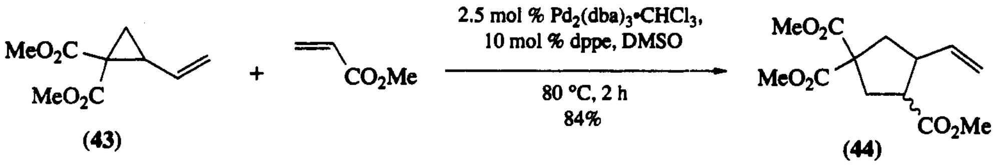

MeO$_2$C
MeO$_2$C
(43)
CO$_2$Me
2.5 mol % Pd$_2$(dba)$_3$•CHCl$_3$,
10 mol % dppe, DMSO
80 °C, 2 h
84%
(44)

(35)

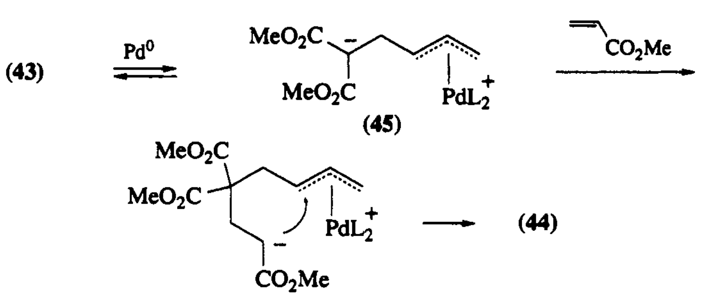

(43)
Pd$^0$
MeO$_2$C
MeO$_2$C
PdL$_2^+$
(45)
CO$_2$Me
(44)

(36)

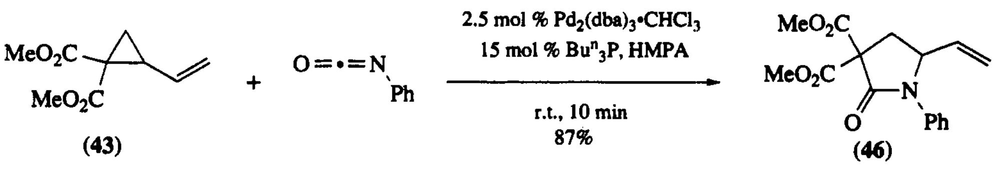

MeO$_2$C
MeO$_2$C
(43)
O=•=N Ph
2.5 mol % Pd$_2$(dba)$_3$•CHCl$_3$
15 mol % Bu$^n_3$P, HMPA
r.t., 10 min
87%
(46)

(37)

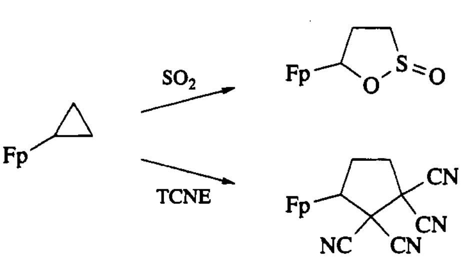
Fp
SO2
TCNE
Fp
O
S
O
Fp
CN
CN
NC
CN

(38)

### 3.2.3.5 Other Precursors

The isolation of cyclopentanecarboxylates from 1,3-diiodopropane and an acrylate in the presence of metallic copper and an alkyl isonitrile has been reported by Saegusa and coworkers (equation 39).[21,22] The reaction is proposed to involve formation of a transient 3-iodopropylcopper–isonitrile complex (**47**) from the diiodopropane, which then adds to the unsaturated ester in a Michael fashion (equation 40). The nonconcertedness of this reaction results in stereoselective cycloaddition. For example, both diethyl maleate and fumarate produce the same cyclopentane adduct in identical yields (equation 41). The generality of this cycloaddition has not been explored.

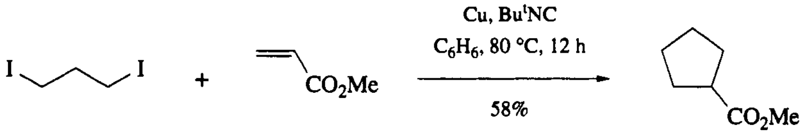
I
I
+
CO2Me
Cu, ButNC
C6H6, 80 °C, 12 h
58%
CO2Me

(39)

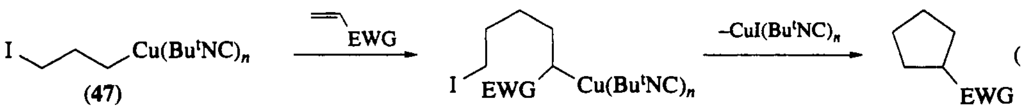
I
Cu(ButNC)n
(47)
EWG
I
EWG
Cu(ButNC)n
–CuI(ButNC)n
EWG

(40)

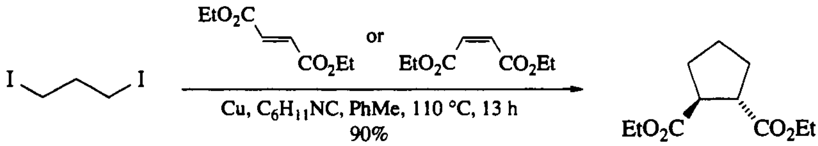
I
I
EtO2C
CO2Et
or
EtO2C
CO2Et
Cu, C6H11NC, PhMe, 110 °C, 13 h
90%
EtO2C
CO2Et

(41)

Another $TiCl_4$-mediated electrophilic annulation using acetal stannane (**48**) has also been developed recently.[23] As an example, the silyl enol ether of 2-methylcyclohexanone has been shown to form the *cis*-fused bicyclic alcohol (**49**) in reasonable yield with this tin reagent (equation 42).[24]

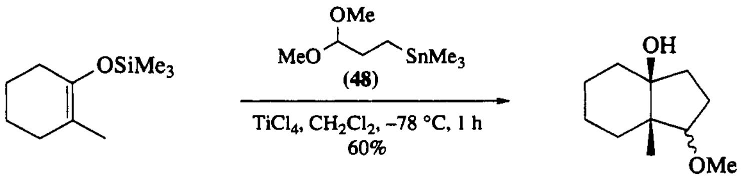
OSiMe3
OMe
MeO
SnMe3
(48)
TiCl4, CH2Cl2, –78 °C, 1 h
60%
OH
OMe

(49)

(42)

## 3.2.4 THE 2-OXYALLYL SYNTHONS

2-Oxyallyl (**50**) is a useful $C_3$ synthon in [3 + 2] cycloadditions because it generates a five-membered ring containing a carbonyl moiety (equation 43).[24] Although oxyallyl zwitterions can be generated from the ring-opening reaction of cyclopropanones, they have only limited synthetic utility. A transition metal-stabilized system (**51**), which can be generated *in situ* from readily accessible organic precursors, provides an alternative approach. An electrophilic version of the 2-oxyallyl synthon derived from a $\alpha,\alpha'$-dibromo ketone–diiron nonacarbonyl system has been developed by Noyori and coworkers.[25–33]

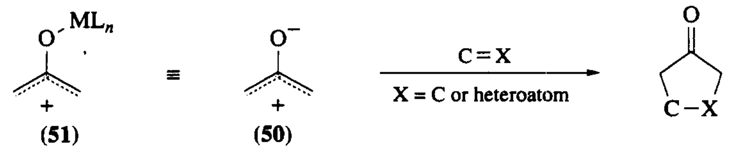

(43)

### 3.2.4.1 Cyclopentanone and Cyclopentenone Syntheses

Reaction of styrene with the commercially available 2,4-dibromopentan-3-one (**52**) in the presence of a stoichiometric amount of $Fe_2(CO)_9$ gives a 65% yield of cyclopentanone (**53**) as a mixture of two diastereoisomers (equation 44).[25] The cycloadduct is formed in a stepwise fashion *via* electrophilic attack of the incipient (oxyallyl)$Fe^{II}$ complex (**54**) on the alkene to form the zwitterionic species (**55**). Ring closure of this intermediate affords the cyclopentanone product (equation 45).[26] In light of this mechanism, it is not surprising that the reaction is highly chemoselective, *i.e.* only electron-rich alkenes will participate in the cycloaddition. One is also limited to alkyl-substituted oxyallyl systems since both α,α′-dibromo- and α,α,α′,α′-tetrabromo-acetone fail to yield any cycloadduct. $Fe_2(CO)_9$ is the most efficient reagent, although $Fe(CO)_5$ can also be used. The dibromo ketones are either commercially available or easily prepared by simple procedures.[30]

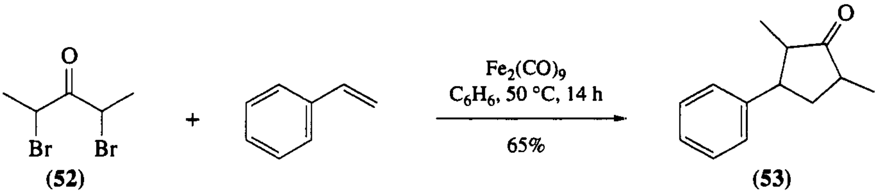

(44)

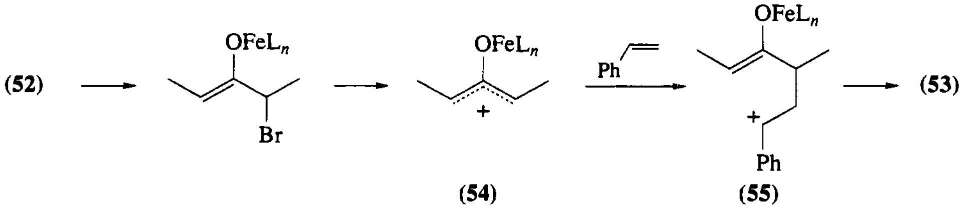

(45)

The yield of this cycloaddition depends primarily on the stability of the intermediary carbocation, such as (**55**).[27] Thus α-cyclopropylstyrene reacts smoothly with (**52**) under similar conditions to produce unrearranged cyclopentanone (**56**) in high yield (equation 46).[25] The facility of this reaction is due to the cation-stabilizing property of the phenyl and cyclopropyl groups. In addition to the electronic effect, the steric environment of the alkenic partner is also important. These two controlling factors can at times counteract each other. In the iron carbonyl-activated cycloaddition involving (**52**), the more electron-rich α-methylstyrene reacts five times faster than styrene, while styrene cycloadds very much faster than *trans*-β-methylstyrene. In the latter case the rate deceleration is presumably due to the sizeable steric hindrance to electrophilic attack in the transition state.[27] Cycloaddition with more sterically hindered oxyallyl systems also gives lower yields and other side products. The iron carbonyl-mediated reaction of tetramethyldibromo ketone (**57**) and α-methylstyrene gives only a poor yield of the expected cyclopentanone (**58**) together with a mixture of other 1:1 adducts (equation 47).[25] The alkylidenetetrahydrofuran (**59**) is formed from the ring closure at the oxygen site of intermediate (**60**), promoted by steric crowding of the carbon terminus. The acyclic products are formed from proton migration within the same intermediate.

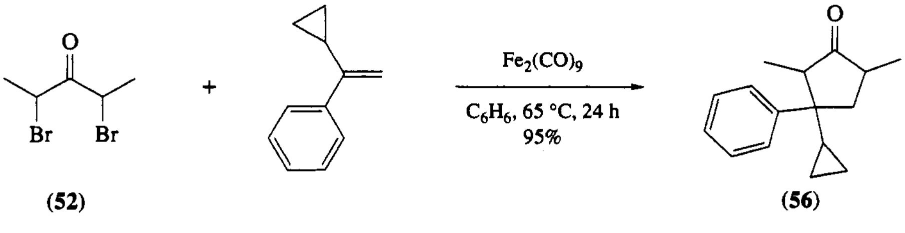

(46)

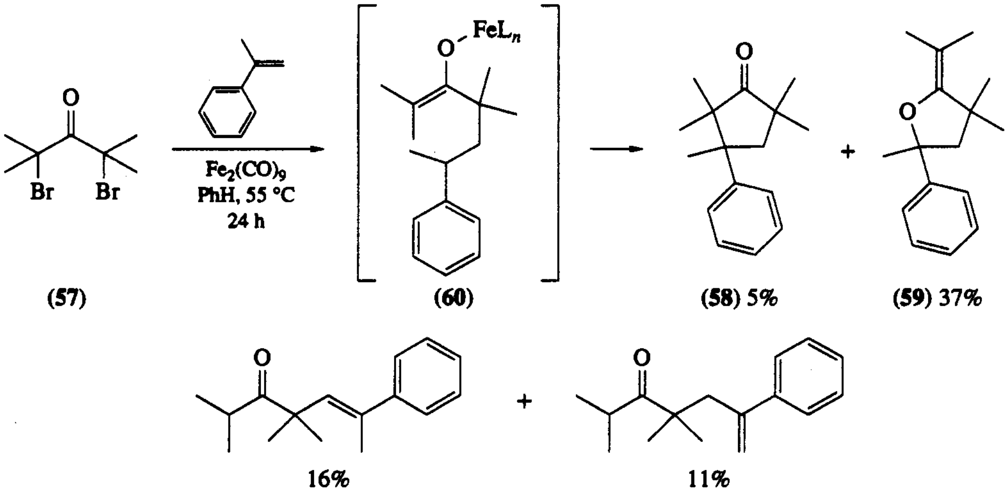
Fe$_2$(CO)$_9$
PhH, 55 °C
24 h
FeL$_n$
(57)
(60)
(58) 5%
(59) 37%
16%
11%

(47)

The high regioselectivity of this [3 + 2] cycloaddition is illustrated in equation (48).[28] The prime controlling factor is the relative stability of the zwitterionic intermediates, which in this case is determined by the number and the type of substituents on the iron enolate moiety. In this case it appears that a phenyl group on the dibromo ketone precursor exerts greater regiocontrol than the combination of two alkyl groups. This regioselective cycloaddition of an unsymmetrically substituted 2-oxyallyl has been utilized in a one-step synthesis of (±)-α-cuparenone (**61**) from dibromo ketone (**62**) and styrene (**63**) (equation 49).[29,30]

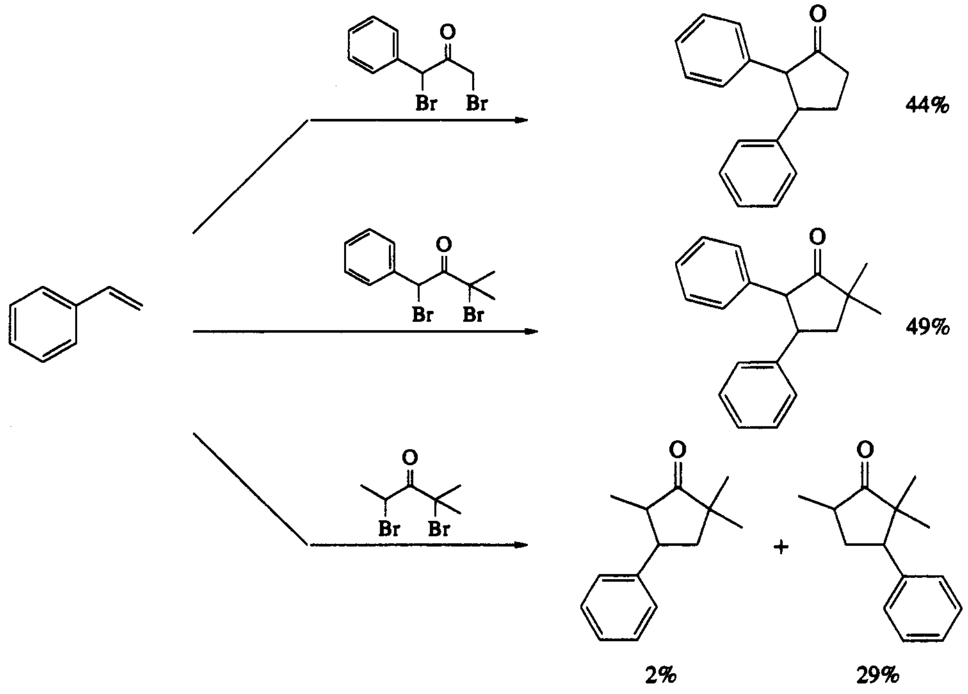

(48)

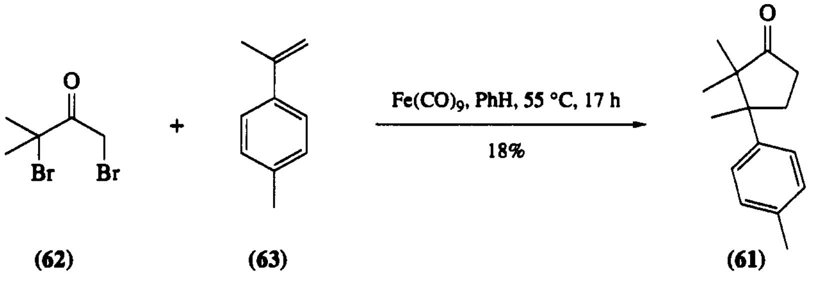
Fe(CO)$_9$, PhH, 55 °C, 17 h
18%
(62)
(63)
(61)

(49)

The iron carbonyl-mediated cycloaddition is also highly stereospecific despite a nonconcerted mechanism. In the reaction of dibromo ketone (**57**) with *cis*-β-deuteriostyrene, only the *cis* stereoisomer of the adduct is detected at low conversion (equation 50).[27,31] This stereospecificity is attributed to the formation of a U-shaped intermediate, in which the bonds are fixed rigidly by charge-transfer or coulombic attraction between the iron enolate and the cationic center. The result can also be explained by rapid bond formation between the two termini before bond rotation can occur. *Trans*-anethole also couples stereospecifically with (**57**) (equation 51).[25]

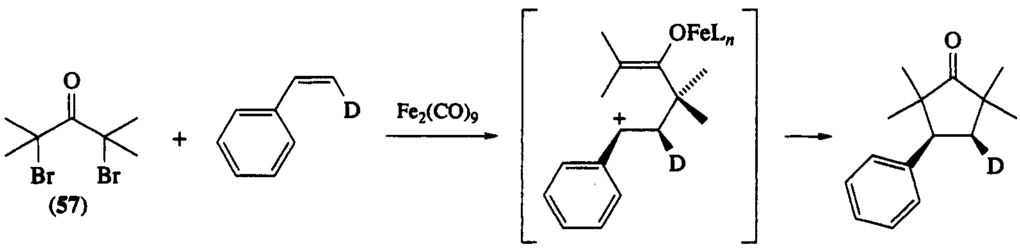

(**57**)

(50)

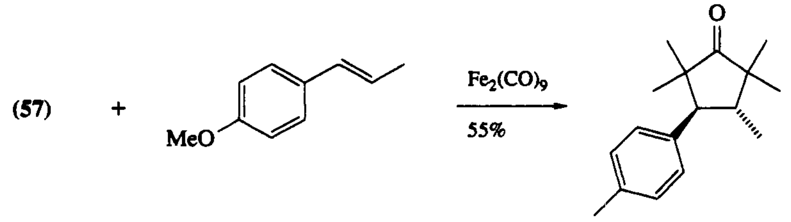

(**57**)

(51)

Enamines are excellent substrates for the cycloaddition. The $Fe_2(CO)_9$-activated dibromo ketone (**57**) reacts with the morpholinoenamine of cylcohexanone (**64**) to afford a good yield of bicyclic adduct (**65**) (equation 52).[32] A facile synthesis of cyclopentenones can be achieved using secondary dibromo ketones. For example, dibromo ketone (**52**) reacts with the same enamine (**64**) to give a quantitative yield of bicylic enone (**66**) after chromatography on silica gel (equation 53).[32] For bulky α-substitutents on the oxyallyl unit, *e.g.* an isopropyl group, the elimination of morpholine can be effected by treatment of the initial adduct with NaOH in ethanol. The [5,7] bicyclic enones resulting from [3 + 2] cycloaddition of cycloheptanone enamines are useful intermediates in the synthesis of azulenes, *e.g.* adduct (**67**) can be easily converted to 1,3-dimethylazulene in reasonable yield (equation 54).[32] Another application of this enamine cycloaddition is the construction of spiro[*n*.4]alkenones. A synthesis of spiro[4.11]hexadecenone (**68**) from cyclododecanone is presented in equation (55).[32] The iron carbonyl-promoted cyclocoupling between secondary dibromo ketones and enamines provides a general route to α,α′-dialkyl cyclopentenones. Some attractive features are the availability of the starting materials, high yields, simple procedures, and ease in which α-substituents are incorporated. However, one limitation of this methodology is its inability to produce cyclopentenones without α-alkyl groups.

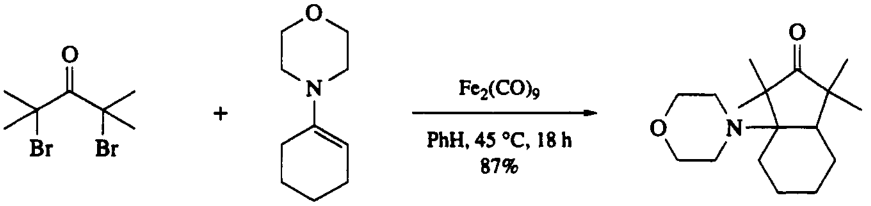

(**57**) (**64**) (**65**)

(52)

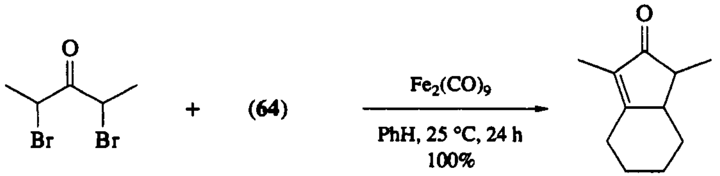

(**52**) (**66**)

(53)

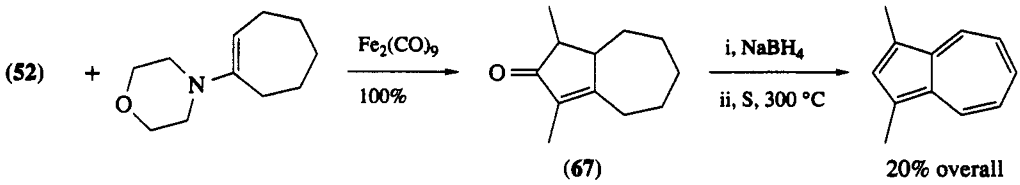
(52)
+
Fe2(CO)9
100%
(67)
i, NaBH4
ii, S, 300 °C
20% overall

(54)

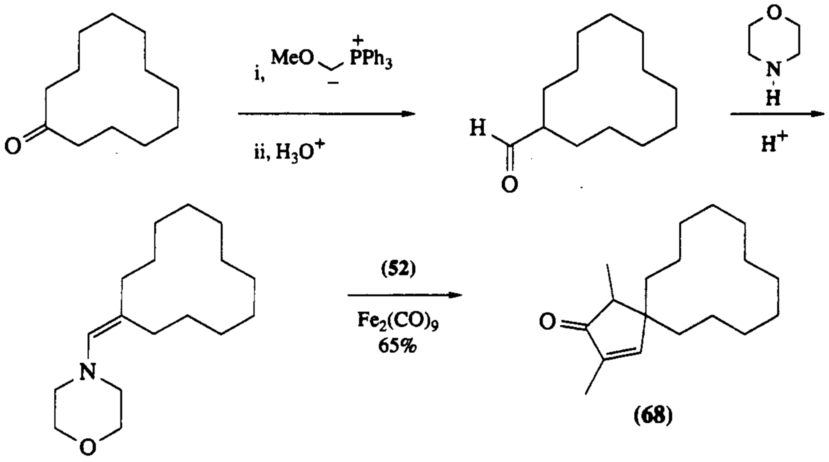
i, MeO PPh3
ii, H3O+
H
O
H+
(52)
Fe2(CO)9
65%
(68)

(55)

### 3.2.4.2 Furanone Synthesis

The iron carbonyl-promoted reaction of secondary dibromo ketones and an amide produces 3(2*H*)-furanone derivatives (**69**) (equation 56).[33] This cyclocoupling reaction has some useful applications, such as the synthesis of a muscarine analog (**70**) from furanone (**71**) (equation 57). Reaction of the dibromo ketone (**72**) with *N*-methylpyrrolidinone results in formation of the aminofuranone (**73**) *via* an intramolecular deamination (equation 58).

### 3.2.4.3 Intramolecular Reactions

The intramolecular version of this [3 + 2] process provides an entry into terpenes with a bicyclo[2.2.1]heptane skeleton.[30] Treatment of the $C_{10}$ dibromo ketone (**74**) with $Fe_2(CO)_9$ produces (±)-camphor in reasonable yield (equation 59). The corresponding $C_{15}$ analog (**75**) yields a 2:1 mixture of (±)-campherenone (**76**) and (±)-epicampherenone (**77**) (equation 60). The product ratio is reversed if the (*Z*)-isomer of the dibromo ketone precursor is used.

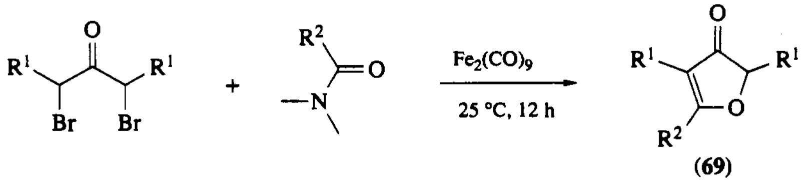
R1
R1
Br
Br
+
R2
O
N
Fe2(CO)9
25 °C, 12 h
R1
R1
R2
O
(69)

(56)

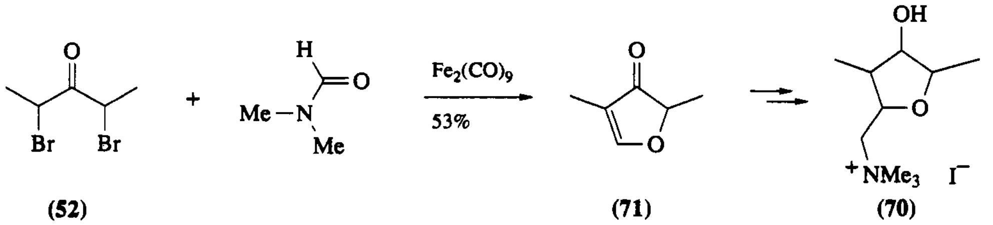
Br
Br
(52)
+
H
Me—N
Me
Fe2(CO)9
53%
(71)
OH
+NMe3 I−
(70)

(57)

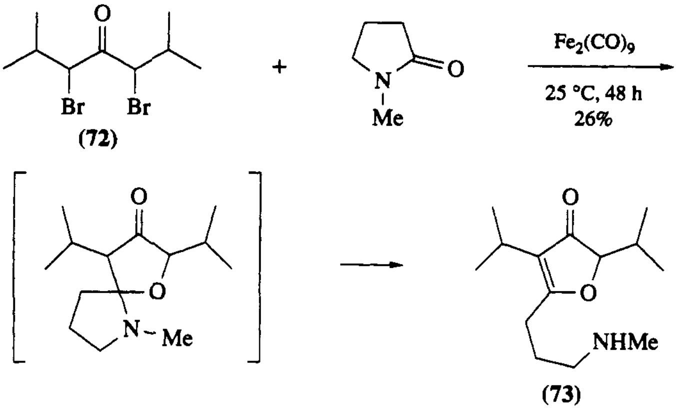

(58)

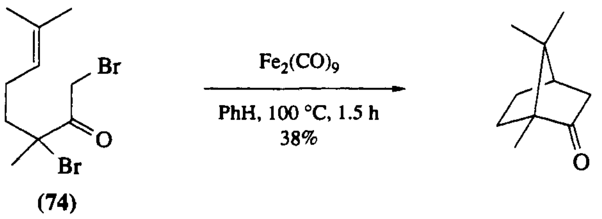

(59)

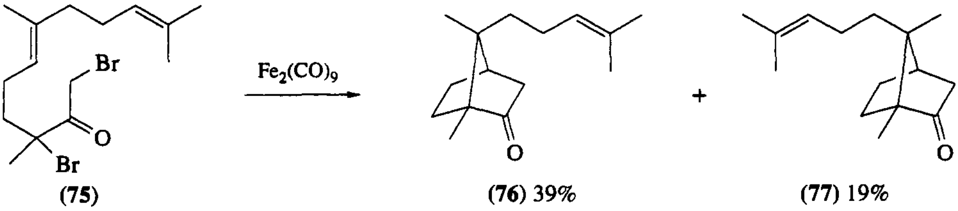

(60)

### 3.2.5 THE TRIMETHYLENEMETHANE SYNTHONS

Trimethylenemethane (TMM; **78**) represents a very useful synthon in the [3 + 2] cycloaddition approach to cyclopentanoids. In addition to contributing the three-carbon unit necessary for ring formation, it also generates a methylene moiety useful for further synthetic elaboration (equation 61). For example, the exocyclic alkene can be cleaved to generate a ketone carbonyl, or it can be transformed into a methyl group or a *gem*-dimethyl unit. The effectiveness of this [3 + 2] approach for the construction of methylenecyclopentanes depends critically on finding efficient systems for generating the TMM synthon. As presented in the previous section, the synthetic utility of substituted 2-methylene-1,3-propanediyls from the thermal decomposition of azo precursors has its limitations. A transition metal mediated system can be a practical alternative if suitable reagents can be identified. Stable TMM–metal complexes, although known for a long time, are generally too unreactive to be of any synthetic value. The combination of a stable and readily available organic precursor and a transition metal catalyst is an ideal solution. In recent years, tremendous progress has been made in a number of laboratories in the development of such systems and their chemistry. The two major types of precursors that have been identified are methylenecyclopropanes[34] and bifunctional conjunctive reagents (BCRs).[35] With these new methodologies, a TMM [3 + 2] cycloaddition strategy has become a very powerful tool in the synthesis of cyclopentanoids.

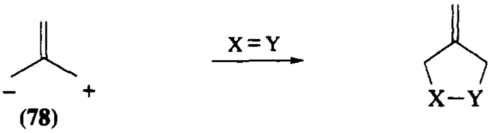

(61)

### 3.2.5.1 TMM from Methylenecyclopropanes

Methylenecyclopropane (**79**), and its substituted derivatives, have been shown to function as TMM equivalents in the presence of a transition metal catalyst. These cyclic materials are useful synthetic reagents because they are quite stable at ambient temperature and are also readily available. For example, parent compound (**79**) can be prepared from methallyl chloride on a kilogram scale with high yield (equation 62).[36] Other efficient syntheses of various substituted derivative systems are outlined in Scheme 2.[34]

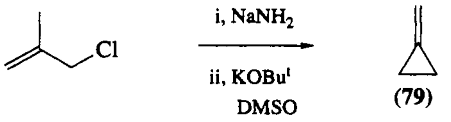

(62)

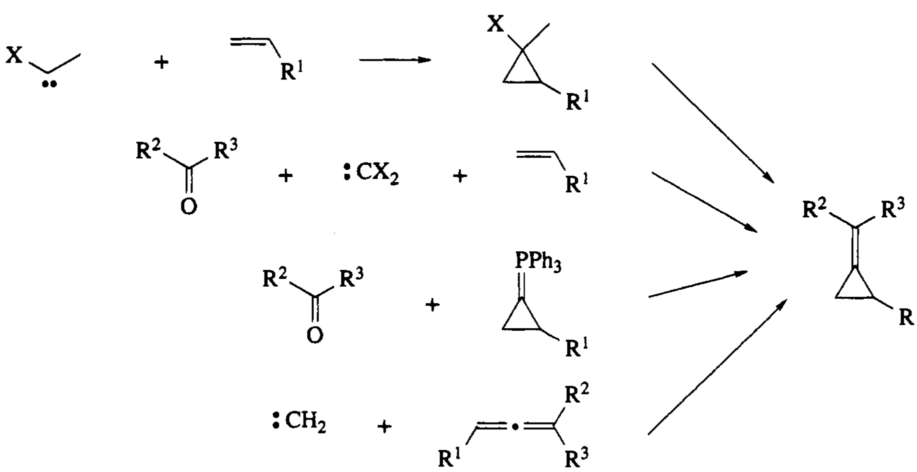

Scheme 2

There are two possible modes of methylenecyclopropane cycloaddition: the distal ring-opening and the proximal ring-opening (Scheme 3). The former generates a functional equivalent of a TMM. However, interconversion between isomeric structures may lead to scrambling of the three methylene termini of the synthon. This can present a problem in controlling the regioselectivity of substituted systems since nonsymmetrical TMM synthons are involved. While the proximal ring-opening mode does not formally constitute a TMM cycloaddition, it does however generate a methylenecyclopentane. Zerovalent nickel and palladium species are the two types of catalyst most effective for methylenecyclopropane activation. The choice of the catalyst system can have a profound effect in determining the reaction pathway, *e.g.* distal *vs.* proximal ring-opening, as well as the regioselectivity of substituted systems. The ensuing discussion of [3 + 2] reactions involving methylenecyclopropanes is divided into these two catalyst systems.

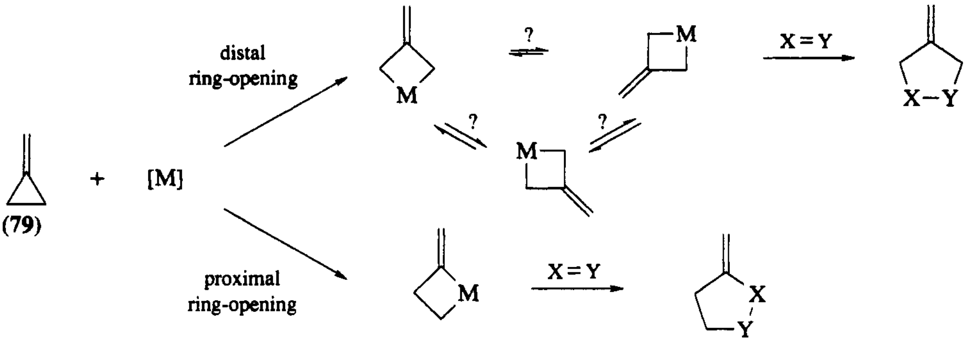

Scheme 3

### 3.2.5.1.1 Cycloaddition with a palladium catalyst: parent system

Palladium(0) catalysts promote exclusive distal ring-opening cycloaddition of (**79**) with alkenes (equation 63). The reaction is normally performed in an autoclave at elevated temperature in benzene or THF. The most effective catalyst system is a 1:1 mixture of a palladium(0) species and a hindered trialkylphosphine ligand, *e.g.* $Pr^i_3P$.[34] Thermally stable complexes, such as bis(dibenzylideneacetone)palladium, can be employed as a source of $Pd^0$. The catalyst can also be generated by the *in situ* reduction of $Pd^{II}$ salts, *e.g.* $Pd(acac)_2$ + $Et_2AlOEt$, although ($\eta^3$-allyl)CpPd functions as a catalyst without any external reducing agent. The efficiency of the cycloaddition is sometimes improved by pumping a mixture of the reactants into a preheated catalyst solution.[34]

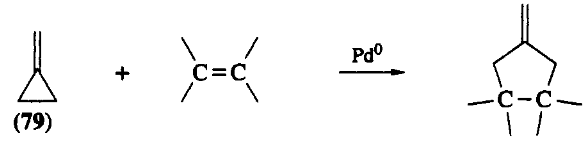

(63)

A variety of alkenes can participate in the cycloaddition. Simple alkenes such as ethylene and allene will react to form methylenecyclopentane adducts. Facile cycloadditions with strained alkenes are also observed.[37,38] For example, norbornene reacts smoothly with (**79**) to give only the *exo* adduct (**80**) in good yield (equation 64).[37] Electron-deficient alkenes, having an ester, ketone or sulfone activating group, are also substrates. However, the methylenecyclopropane cycloaddition does not appear to be very chemoselective. This is demonstrated by the Pd-catalyzed reaction of (**79**) with 2,3-dimethoxycarbonylnorbornadiene, where both double bonds of the norbornadiene react to an almost equal extent (equation 65).[34]

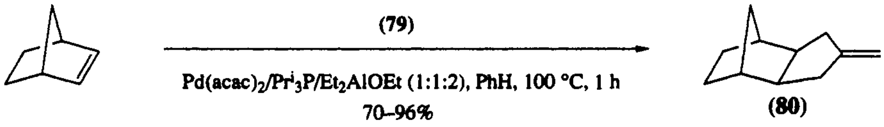

(64)

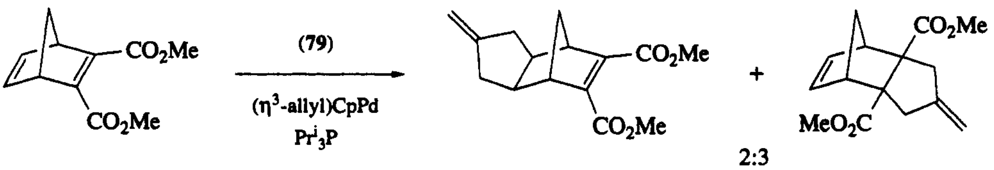

(65)

The mechanism for methylenecyclopentane formation is believed to involve prior coordination of both (**79**) and the reacting alkene to the metal. Subsequent coupling of these two units generates the cycloadduct (Scheme 4). The success of the reaction thus depends critically on the extent of interaction of the alkenic substrate with the palladium center. Weak alkene coordination will not produce efficient cycloaddition. On the other hand, too strong a binding can prevent methylenecyclopropane activation. This may account for the failure to prepare cycloadducts of highly electron-deficient alkenes, such as maleic anhydride, acrolein and acrylonitrile, which are all excellent ligands. While cyclopentenone gives a satisfactory yield (78%) of the adduct, larger-ring analogs such as 2-cyclohexenone give mainly simple alkylation products.[34,40]

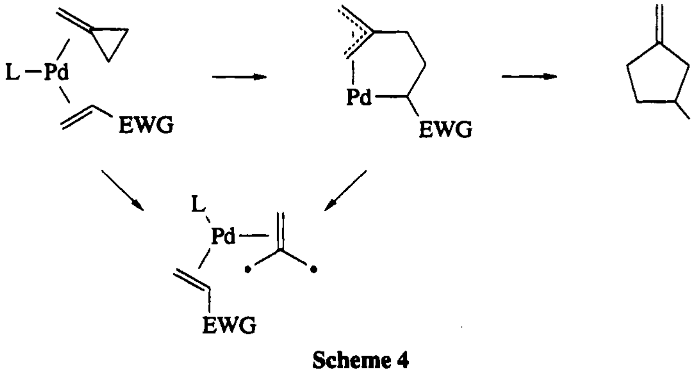

**Scheme 4**

The stereospecificity of this codimerization is only moderate. While diethyl fumarate gives essentially only the *trans* adduct, the alkene geometry is not preserved in the maleate system (equation 66).[39] In the latter case the concomitant isomerization of the starting material may contribute to the loss of alkene geometry. The slow introduction of reactants by the pumping technique can significantly enhance the stereospecificity of the cycloaddition. Dimethyl maleate has been shown to yield up to 90% of the *cis* adduct under these conditions. The diastereoselectivity of the methylenecyclopropane reaction has not been fully explored. In the few cases where a nonsymmetrical alkene such as the norbornene in equation (64) has been used, the exclusive formation of a single product suggests that the cycloaddition of (**79**) is sensitive to steric effects.

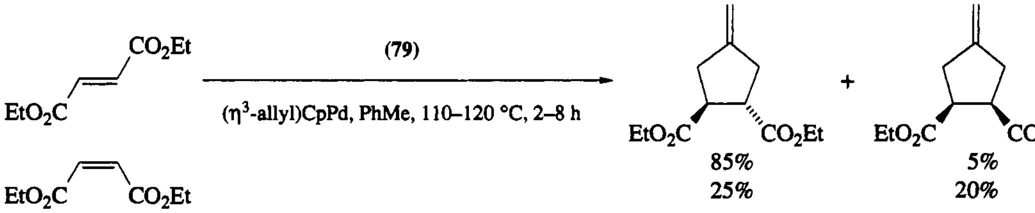

(66)

### 3.2.5.1.2 Cycloaddition with a palladium catalyst: substituted systems

The palladium-catalyzed cycloaddition of substituted methylenecyclopropanes also proceeds *via* distal ring-opening. There is also a propensity to form alkylidenecyclopentane adducts, regardless of the substituent location. This preference is most prominent with precursors having two alkyl or aryl groups on the exocyclic methylene.[34] For example, dimethylidenecyclopropane (**80**) gives exclusively dimethylidenecyclopentanes with a number of alkenes, which include fumarate and norbornene (equations 67, 68). With diethyl maleate, partial loss of alkene stereochemistry is also observed (1:2 *cis*/*trans* mixture). The diphenyl derivative (**81**) also shows excellent regioselectivity and yields (equations 69, 70).[41] These two cyclopropanes also codimerize smoothly with cyclic alkenones, even with the sluggish 2-cycloheptenone (equation 71). With these enones the enhanced activity of the dialkylidene derivatives is a considerable improvement over that of the parent compound (**79**).[40] An intramolecular [3 + 2] version of the diphenyl system has been utilized in the construction of bicyclo[3.3.0]octanes (equations 72, 73).[42]

Monosubstituted alkylidenecyclopropanes show lower regioselectivity. While *n*-hexylidenecyclopropane (**82**) and the corresponding phenyl analog (**83**) cycloadd to cyclopentenone, acrylate or crotonate to produce mostly alkylidenecyclopentanes, a mixture of adducts is observed with diethyl fumarate (equations 74–77).[34] Nonetheless, compared to the parent compound (**79**), these mono- and di-substituted alkylidenecyclopropanes often give better cycloaddition reactions with a wider range of alkenes, and are also less susceptible to self-oligomerization.

The regioselectivity associated with ring-substituted methylenecyclopropanes is not as distinct. The 2-methyl derivative (**84**) shows only a small preference for ethylidenecyclopentane formation with diethyl

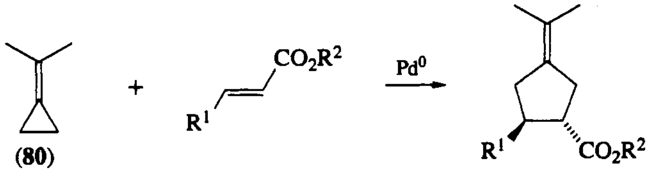

(67)

| $R^1$ | $R^2$ | |
|---|---|---|
| H | Me | 48% |
| Me | Me | 71% |
| $C_5H_{11}$ | Me | 61% |
| $CO_2Et$ | Et | 83% |

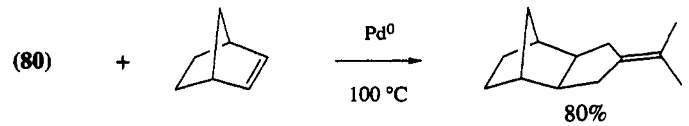

(68)

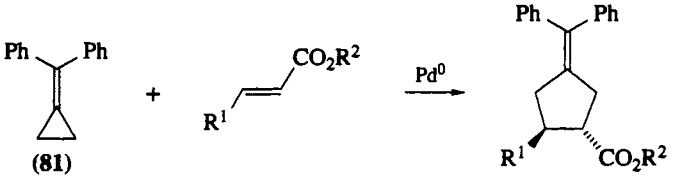
Ph
Ph
$CO_2R^2$
$R^1$
$Pd^0$
Ph
Ph
$R^1$
$CO_2R^2$

(81)

(69)

| $R^1$ | $R^2$ | |
|---|---|---|
| H | Me | 86% |
| Me | Me | 94% |
| $C_6H_{13}$ | Me | 98% |
| $CO_2Et$ | Et | 100% |

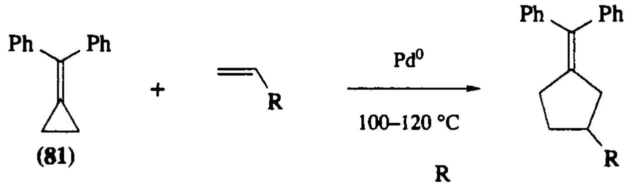
Ph
Ph
R
$Pd^0$
100–120 °C
Ph
Ph
R

(81)

(70)

| R | |
|---|---|
| H | 83% |
| Me | 83% |
| Ph | 88% |
| $(CH_2)_8CO_2Me$ | 50% |
| $CH{=}CH_2$ | 48% |

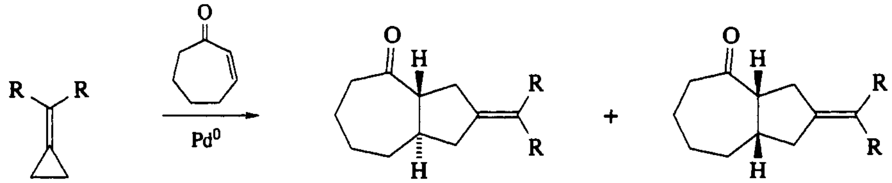
R
R
O
$Pd^0$
O
H
R
R
H
O
H
R
R
H

(71)

| | | |
|---|---|---|
| R = Me (**80**) | 45% | 5% |
| R = Ph (**81**) | 67% | 13% |

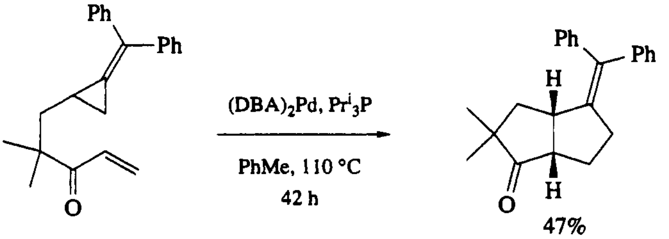
Ph
Ph
O
$(DBA)_2Pd, Pr^i_3P$
PhMe, 110 °C
42 h
Ph
Ph
H
O
H

47%

(72)

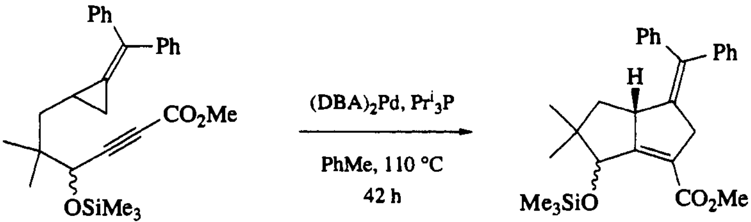
Ph
Ph
$CO_2Me$
$OSiMe_3$
$(DBA)_2Pd, Pr^i_3P$
PhMe, 110 °C
42 h
Ph
Ph
H
$Me_3SiO$
$CO_2Me$

79%

(73)

fumarate. The phenyl system (**85**) has a high regioselectivity, but its preference for alkylidenecyclopentane formation is greatly suppressed by increasing the amount of phosphine ligand (equation 78).[34] The alkylidene cycloadduct is also highly favored in the 2-trimethylsilyl system (**86**) (equations 79, 80).[43]

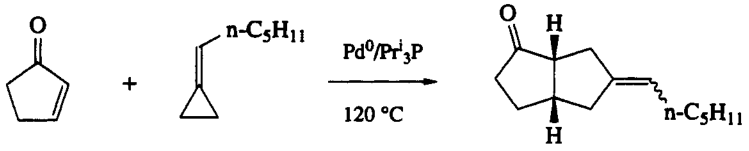
n-$C_5H_{11}$
$Pd^0/Pr^i_3P$
120 °C
O
H
H
n-$C_5H_{11}$

(82) 61% (1:1) (74)

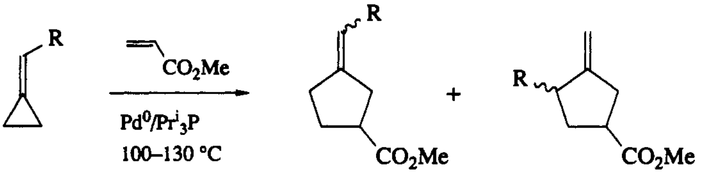
R
$CO_2Me$
$Pd^0/Pr^i_3P$
100–130 °C
R
$CO_2Me$
+
R
$CO_2Me$

(75)

| | | |
|---|---|---|
| R = n-$C_5H_{11}$ (**82**) | 49% | 4% |
| R = Ph (**83**) | 81% | 7% |

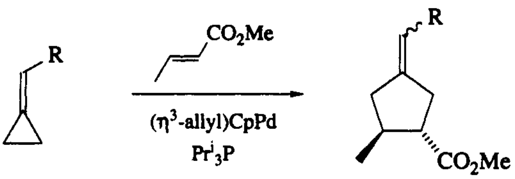
R
$CO_2Me$
($\eta^3$-allyl)CpPd
$Pr^i_3P$
R
$CO_2Me$

(76)

| | |
|---|---|
| R = n-$C_5H_{11}$ (**82**) | 51% |
| R = Ph (**83**) | 52% |

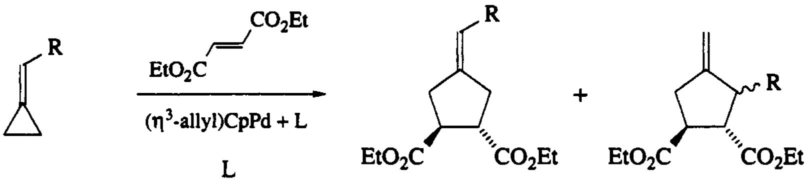
R
$CO_2Et$
$EtO_2C$
($\eta^3$-allyl)CpPd + L
R
$EtO_2C$
$CO_2Et$
+
R
$EtO_2C$
$CO_2Et$

(77)

| | L | | |
|---|---|---|---|
| R = n-$C_5H_{11}$ (**82**) | $Pr^i_3P$ | 31% | 27% |
| R = Ph (**83**) | 4 $Pr^i_3P$ | 37% | 30% |

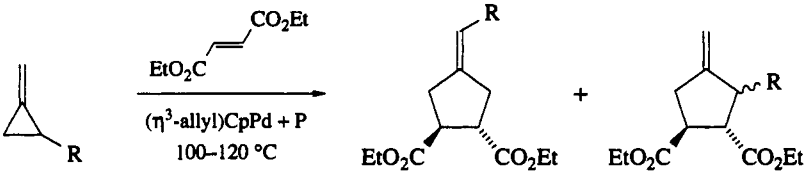
R
$CO_2Et$
$EtO_2C$
($\eta^3$-allyl)CpPd + P
100–120 °C
R
$EtO_2C$
$CO_2Et$
+
R
$EtO_2C$
$CO_2Et$

(78)

| R | P | | |
|---|---|---|---|
| Me (**84**) | $Pr_3P$ | 40% | 27% |
| Ph (**85**) | $Pr_3P$ | 60% | 25% |
| Ph (**85**) | 4 $Pr_3P$ | 10% | 76% |

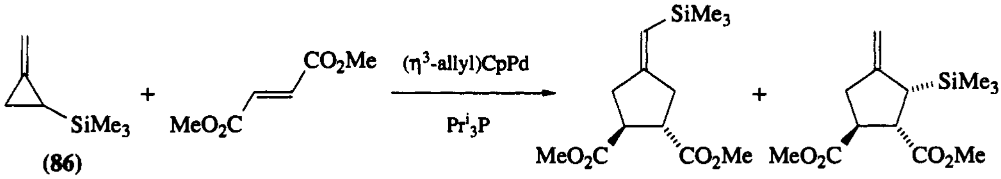
$SiMe_3$
+
$CO_2Me$
$MeO_2C$
($\eta^3$-allyl)CpPd
$Pr^i_3P$
$SiMe_3$
$MeO_2C$
$CO_2Me$
+
$SiMe_3$
$MeO_2C$
$CO_2Me$

(86) 78% 9% (79)

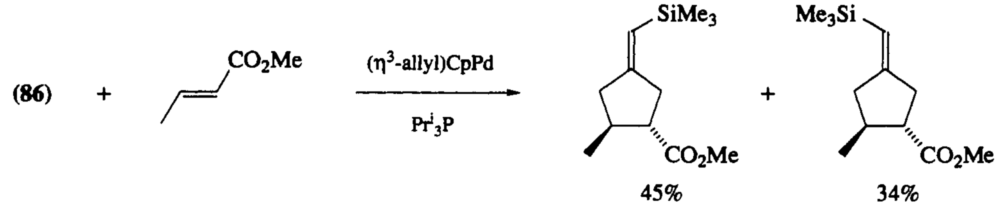
(86)
+
CO2Me
(η3-allyl)CpPd
Pri3P
SiMe3
CO2Me
45%
+
Me3Si
CO2Me
34%
(80)

### *3.2.5.1.3 Cycloaddition with a nickel catalyst: parent system*

The reactions of (**79**) with a Ni$^0$ catalyst are very sensitive to the nature of the ancillary ligands and that of the reacting alkene. A 'naked' nickel catalyst, such as Ni(COD)$_2$, produces proximal ring-opening adducts with high stereospecificity (equations 81, 82).[44–46] The proposed mechanism involves nickel-promoted reductive coupling of the methylenecyclopropane and the alkene, which is then followed by a cyclopropylmethyl–3-butenyl rearrangement (equation 83).[46] Dialkyl fumarates and maleic anhydride do not participate in the cycloaddition, but simply function as control ligands to increase dimer formation of (**79**).[47] With bis(acrylonitrile)nickel as the catalyst, both types of ring-opening adducts can be observed with dimethyl fumarate as the alkenic receptor (equation 84). In this case, a deuterium-labelling study at low product conversion suggests that a TMM–Ni intermediate (**87**), or a related rapidly equilibrating σ-complex (**88**), is responsible for the complete scrambling of the label in the distal ring-opening cycloadduct. On the other hand, the proximal ring-opening mode appears to involve a non-equilibrating 2-methylenemetallocyclobutane (**89**), since very little scrambling of the deuterium label is detected.[48]

Reactions with phosphine- or phosphite-modified catalysts, *e.g.* Ni(COD)$_2$ + PPh$_3$, show lower stereospecificity and require higher reaction temperature. In the case of fumarate and maleate this catalyst system promotes only distal ring-opening cycloaddition (equation 85).[49]

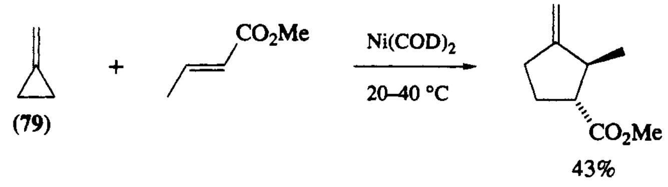
+
CO2Me
(79)
Ni(COD)2
20–40 °C
CO2Me
43%
(81)

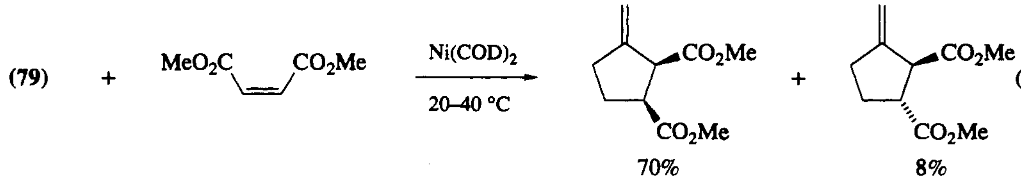
(79)
+
MeO2C
CO2Me
Ni(COD)2
20–40 °C
CO2Me
CO2Me
70%
+
CO2Me
CO2Me
8%
(82)

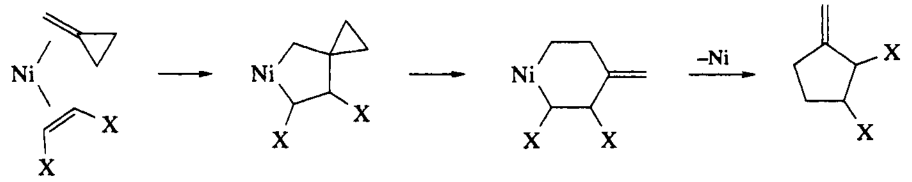
Ni
X
X
Ni
X
X
Ni
X
X
–Ni
X
X
(83)

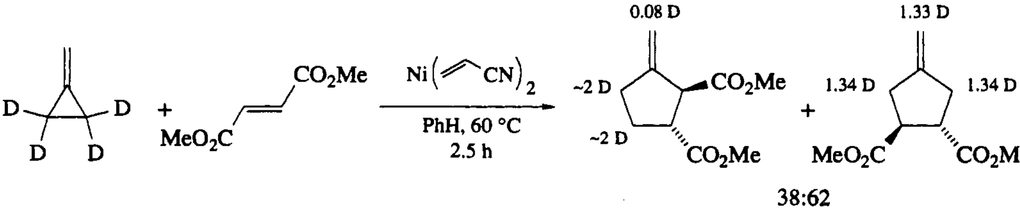
D
D
D
D
+
CO2Me
MeO2C
Ni(CN)2
PhH, 60 °C
2.5 h
0.08 D
~2 D
~2 D
CO2Me
CO2Me
+
1.33 D
1.34 D
1.34 D
MeO2C
CO2Me
38:62
(84)

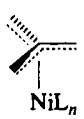

**(87)**

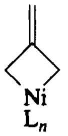

**(88)**

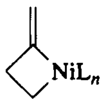

**(89)**

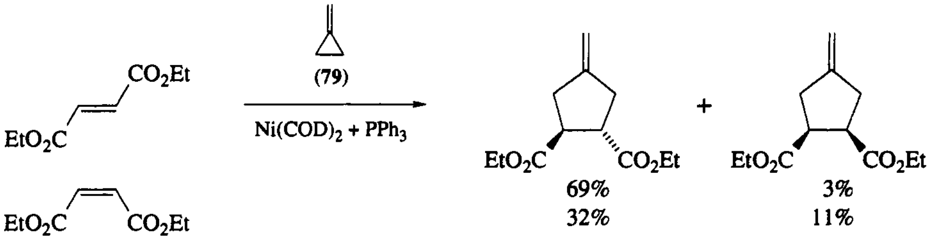

(85)

### 3.2.5.1.4 *Cycloaddition with a nickel catalyst: substituted system*

The regiochemistry of Ni$^0$-catalyzed cyloadditions of substituted methylenecyclopropanes is influenced by many factors. Only diphenylidenecyclopropane (**81**) maintains the strong preference and high yields for alkylidenecyclopentane formation (equation 86).[50] This diphenyl derivative is one of the few TMM precursors that shows this exclusive regioselectivity regardless of reaction conditions. The regiochemistry of dimethyl analog (**80**) is determined by the nature of the ligand as well as that of the reacting alkene (equations 87, 88).[50] The phosphine- and phosphite-modified Ni$^0$ catalysts also produce a methylenecyclopentane adduct (**90**) with a regiochemistry complementary to that of the corresponding adduct obtained from the Pd$^0$-catalyzed reactions (see equation 75). This regioisomer has the activating group of the alkene immediately adjacent to the substituents of the methylenecyclopropane precursor. With monoalkylidenecyclopropanes and a nickel phosphite catalyst, this regioisomer can be the only product. Such is the case in the formation of (**91**) from (**82**) and methyl crotonate (equation 89). However, most other reactions generate isomeric mixtures (equations 90, 91).[34]

The highly regioselective Ni$^0$-catalyzed codimerization of 2,2-dimethylmethylenecyclopropane (**92**) and acrylates is presumed to occur *via* proximal ring-opening of the cyclic precursor.[34,51] In addition, excellent asymmetric induction in the synthesis of a dimethyl(methylene)cyclopentane adduct is achieved using an acrylamide with a chiral auxiliary (equation 92).[52] This strategy to make chiral methylenecyclopentanes also works well with the parent system (**79**). Monoalkyl methylenecyclopropanes, such as (**84**), yield only proximal ring-opening cycloadducts with a Ni$^0$/PPh$_3$ catalyst, whereas the corresponding phenyl system (**85**) undergoes both types of ring-opening reactions (equations 93, 94).[34]

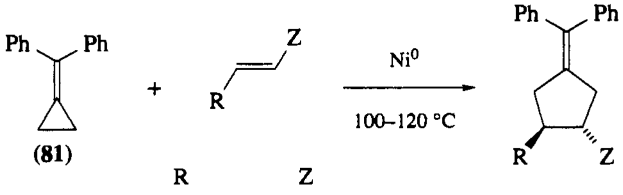

(86)

| R | Z | |
|---|---|---|
| H | Bu | 80% |
| H | CN | 82% |
| Me | CO$_2$Me | 75% |
| CO$_2$Et | CO$_2$Et | 98% |

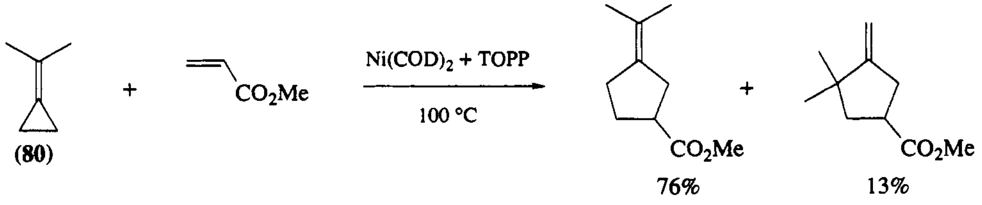

(87)

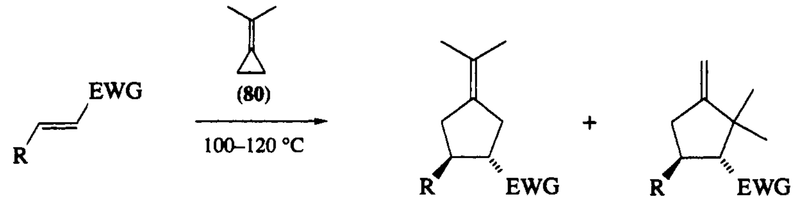
EWG
R
(80)
100–120 °C
+
R
EWG
R
EWG
(90)

(88)

| R | EWG | | | (90) |
|---|---|---|---|---|
| Me | $CO_2Me$ | $Ni(COD)_2 + PPh_3$ | 31% | 17% |
| Me | $CO_2Me$ | $Ni(COD)_2$ + TOPP | 8% | 36% |
| $CO_2Et$ | $CO_2Et$ | $Ni(COD)_2$ + TOPP | 31% | 52% |

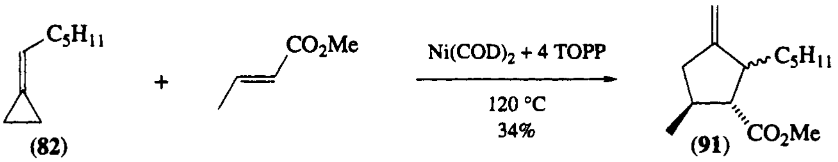
$C_5H_{11}$
(82)
+
$CO_2Me$
$Ni(COD)_2$ + 4 TOPP
120 °C
34%
$C_5H_{11}$
(91)
$CO_2Me$

(89)

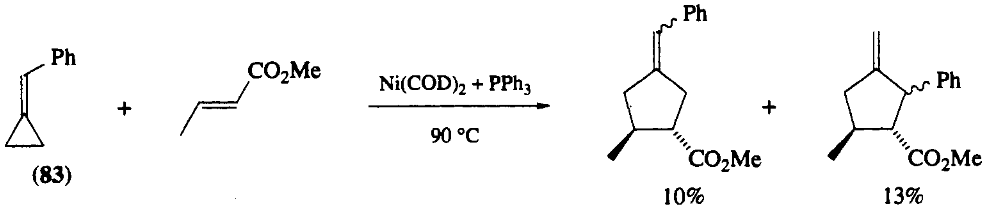
Ph
(83)
+
$CO_2Me$
$Ni(COD)_2 + PPh_3$
90 °C
Ph
$CO_2Me$
10%
+
Ph
$CO_2Me$
13%

(90)

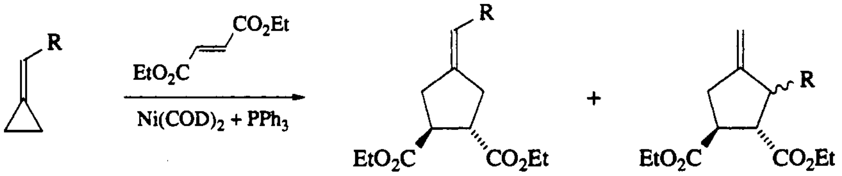
R
$CO_2Et$
$EtO_2C$
$Ni(COD)_2 + PPh_3$
R
$EtO_2C$
$CO_2Et$
+
R
$EtO_2C$
$CO_2Et$

(91)

| | | |
|---|---|---|
| R = n-$C_5H_{11}$ (**82**) | 50% | 37% |
| R = Ph (**83**) | 75% | 7% |

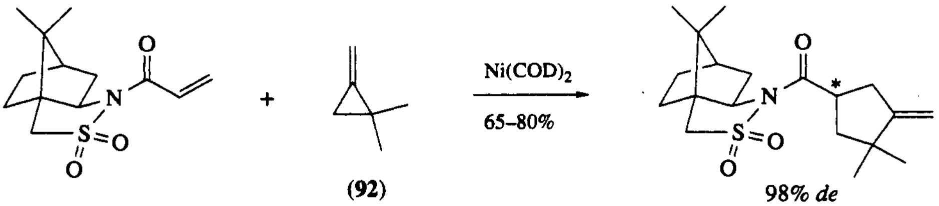
O
N
S=O
O
+
(92)
$Ni(COD)_2$
65–80%
O
N
*
S=O
O
98% de

(92)

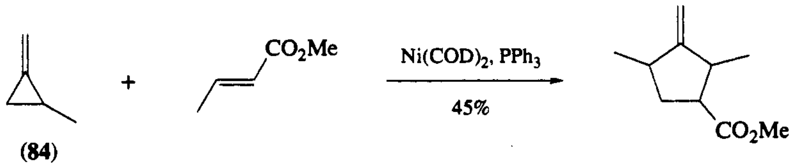
(84)
+
$CO_2Me$
$Ni(COD)_2$, $PPh_3$
45%
$CO_2Me$

(93)

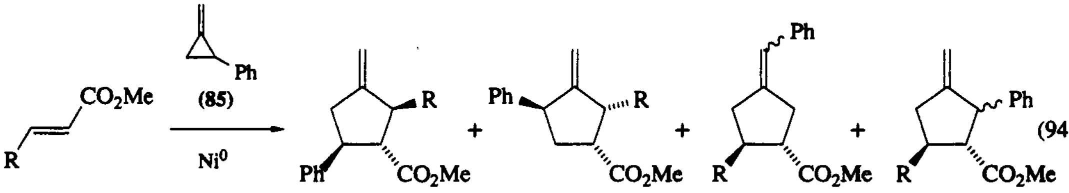

(94)

| | | | | |
|---|---|---|---|---|
| R = H | 33% | - | 30% | 20% |
| R = Me | 26% | 8% | 5% | 5% |

The yields and regioselectivity of the reactions of substituted methylenecyclopropanes with 2-cyclopentenone are improved with the use of triethylborane as a Lewis acid co-catalyst (equations 95, 96).[53] No reaction with cyclopentenone is observed in the case of (**82**) without this co-catalyst.[34]

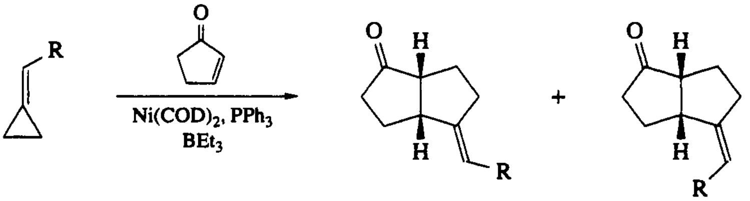

(95)

| | | |
|---|---|---|
| R = n-$C_5H_{11}$ (**82**) | 58% | 10% |
| R = Ph (**83**) | 72% | - |

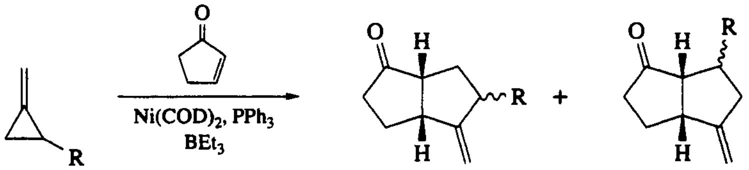

(96)

| | | |
|---|---|---|
| R = Me (**84**) | 73% | - |
| R = Ph (**85**) | - | 75% |
| R = $SiMe_3$ (**86**) | 50% | - |

The use of alkynes in transition metal catalyzed reactions is often complicated by their tendency to undergo cyclo-trimerization and -tetramerization. Thus, it is useful to note that a phosphite-modified catalyst, $Ni(COD)_2$/tris(*o*-phenylphenyl) phosphite (TOPP), promotes codimerization of alkynes with methylenecyclopropane and its alkylidene analogs.[34,54] Both electron-rich and electron-poor alkynes participate in cycloaddition with moderate regioselectivity. Opposite regiochemistry is sometimes observed with disubstituted alkylidene systems (equations 97–99).

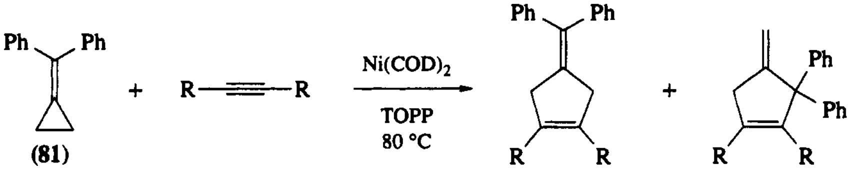

(97)

| | | |
|---|---|---|
| R = Me | 6% | 89% |
| R = $CH_2OSiMe_3$ | 49% | 37% |
| R = $Me_3Si$ | 34% | 37% |
| R = $Me_3Si$, $CO_2Me$ | 63% | - |

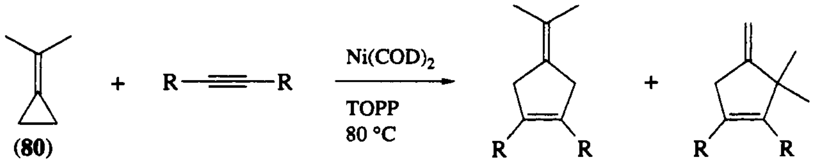

(80)

| | | |
|---|---|---|
| R = Me | 4% | 62% |
| R = Me$_3$Si | - | 50% |
| R = Me$_3$Si, CO$_2$Me | 26% | 38% |

(98)

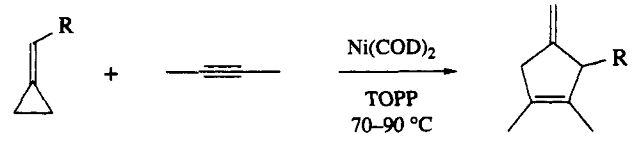

| | |
|---|---|
| R = H (79) | 34% |
| R = Ph (85) | 57% |

(99)

### *3.2.5.1.5 Diene, C=O and C=N cycloadditions*

Conjugated dienes are a special substrate for the TMM synthon because they can potentially undergo [3 + 2] as well as [4 + 3] cycloaddition. While dimethyl (*E*,*E*)-muconate gives only seven-membered ring [4 + 3] adducts, methyl 2,4-pentadienoate reacts exclusively at the terminal double bond with (**79**) to give a vinylmethylenecyclopropane (equation 100).[55] The diphenyl system (**81**) also reacts with simple 1,3-dienes to produce only diphenylidenecyclopentanes in the presence of Ni$^0$ or Pd$^0$ catalysts (equation 101).[34]

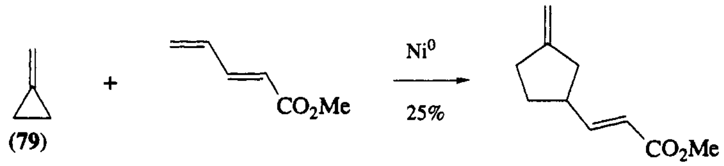

(79)

(100)

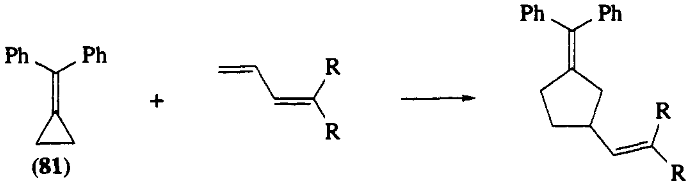

(81)

| | | |
|---|---|---|
| R = H | Pd$^0$ | 48% |
| R = Ph | Ni$^0$ | 79% |

(101)

The ketenimine (**93**) reacts only at the C=N bond to give pyrroles and pyrrolines with methylene migration (equations 102, 103).[34,56] Carbon dioxide codimerizes smoothly with methylenecyclopropanes to yield lactones with alkene isomerization (equations 104, 105).[57,58] The Pd$^0$-catalyzed rearrangement of γ-butyrolactone (**94**) to butenolide (**95**) indicates that this CO$_2$ insertion reaction is reversible. This is further supported by the observation that lactone (**94**) can serve as a TMM precursor in the codimerization with aldehydes and electron-deficient alkenes (equations 106, 107).[59] No cycloaddition to ketenes or simple ketone carbonyls has ever been reported.

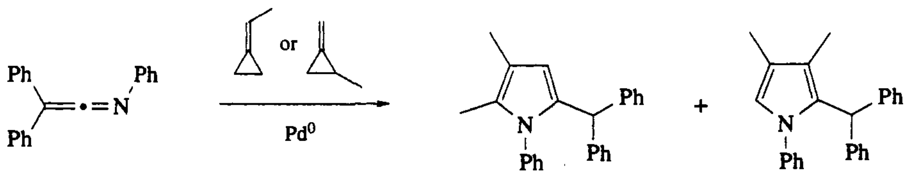

(93) 45% 31%

(102)

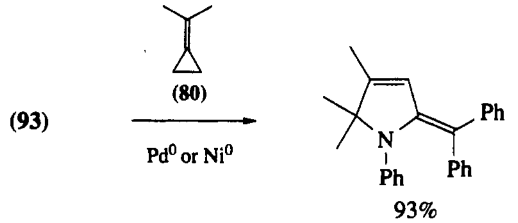
(93)
(80)
Pd⁰ or Ni⁰
N
Ph
Ph
Ph
93%

(103)

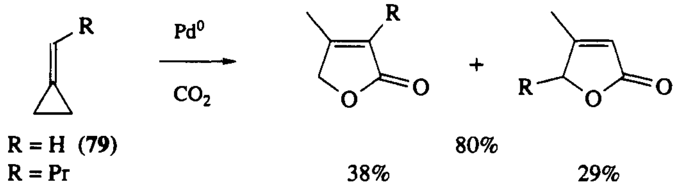
R
Pd⁰
CO₂
R = H (79)
R = Pr
R
O
O
+
R
O
O
80%
38%
29%

(104)

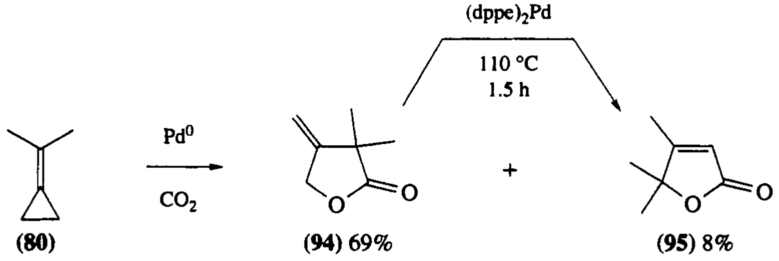
Pd⁰
CO₂
(80)
(dppe)₂Pd
110 °C
1.5 h
O
O
(94) 69%
+
O
O
(95) 8%

(105)

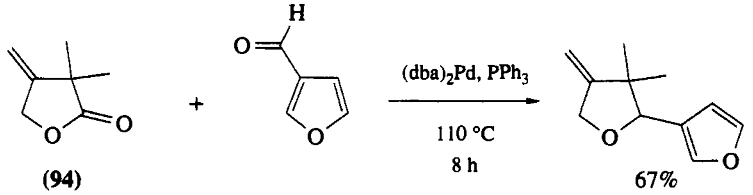
O
O
(94)
+
H
O
O
(dba)₂Pd, PPh₃
110 °C
8 h
O
O
67%

(106)

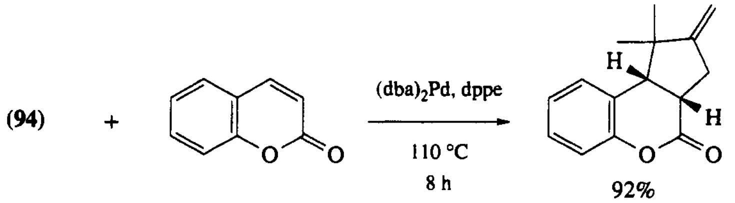
(94)
+
O
O
(dba)₂Pd, dppe
110 °C
8 h
H
H
O
O
92%

(107)

### 3.2.5.2 TMM from Bifunctional Conjunctive Reagents

Bifunctional conjunctive reagents (BCRs), such as a 1,3-substituted 2-methylenepropane (**96**), can serve as effective TMM synthons *via* transition metal catalysis. In this case, the transition metal complex can promote the elimination of the elements X—Y from (**96**) to form a coordinated TMM species. Cyclization of this intermediate with an alkene thus produces the methylenecyclopropane product and also regenerates the catalyst (Scheme 5). In the last decade a number of BCRs utilizing this concept, or some modifications thereof, has been developed for various TMM synthons.[35]

#### *3.2.5.2.1 Cycloaddition with the parent system*

The use of BCR methodology for the present TMM synthon was first demonstrated by Trost and Chan using a Pd$^0$ catalyst and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**97**) as the bifunctional prototype.[60–63] In this system the trimethylsilyl and the acetoxy moieties provide the carbanion and the carbocation equivalents, producing TMSOAc as the by-product. Silyl acetate (**97**) and some of its precursors,

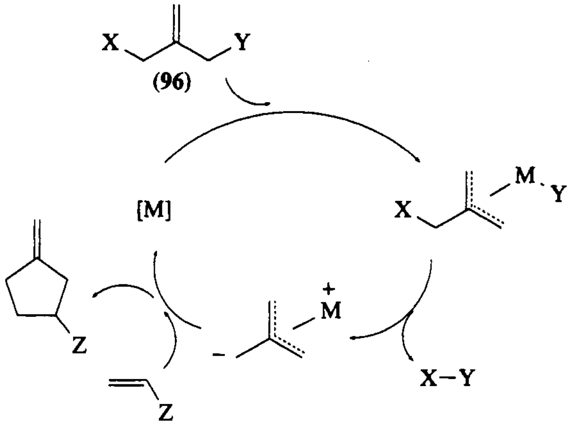

**Scheme 5**

2-[(trimethylsilyl)methyl]-2-propen-1-ol and 2-chloromethyl-3-trimethylsilyl-1-propene, are commercially available.[64] Alternatively, it can be readily prepared from methallyl alcohol in high yield.[65,66] Other synthetic routes to this bifunctional reagent, starting with 2-(chloromethyl)-3-chloropropene, or trimethylsilyl ethyl glycolate, have also been reported (equation 108).[67,68]

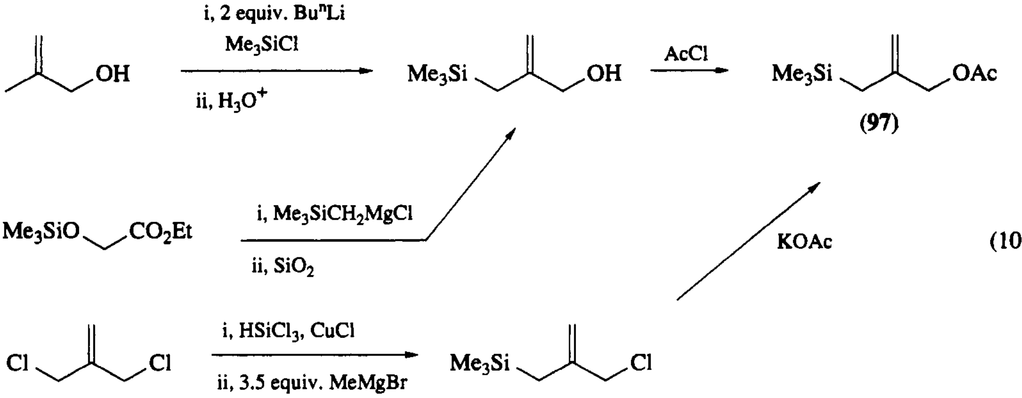

(108)

The Pd$^0$-catalyzed [3 + 2] cycloaddition reactions of (**97**) exhibit very different selectivities from those of the corresponding methylenecyclopropane codimerizations. One major distinction is the chemoselectivity: only electron-deficient alkenes will react to form methylenecyclopentane. The nucleophilic nature of this TMM synthon is indicated in the exclusive annulation of the electron-poor double bond of 2,3-dimethoxycarbonylnorbornadiene (equation 109).[35,62] No such differentiation of alkenes is evident in the methylenecyclopropane codimerization with the same diene (equation 65).

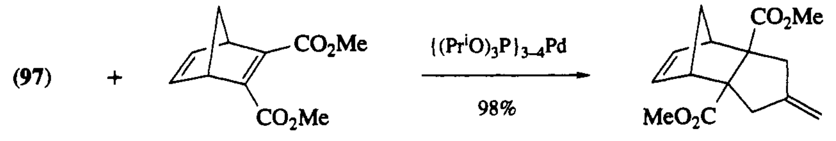

*exo*:*endo* = 4:1

(109)

The cycloaddition is normally performed by heating a solution of the silyl acetate with the electron-deficient alkene in the presence of 0.1–9 mol % of a palladium catalyst in an aprotic solvent, such as THF, toluene, DME, DMF or acetonitrile.[69] The commercially available $(PPh_3)_4Pd$ is a good catalyst for this reaction. Other effective catalysts can also be generated *in situ* by the reduction of a Pd$^{II}$ salt in the presence of at least two equivalents of a phosphorus-containing ligand. For example, a highly active catalyst is obtained by simply mixing $Pd(OAc)_2$ with 6–8 equivalents of triisopropyl phosphite.[70] In this case the phosphite ligand also serves as the reducing agent. The alkenic substrate for this BCR cycloaddition has properties parallel to that of a dienophile in Diels–Alder reactions. A wide range of alkenes possessing a ketone, ester, cyano, sulfoxide or sulfone function have been shown to react.[62] Thus, this annulation procedure is compatible with many reactive functional groups, with even a broader scope of reactivity than the methylenecyclopropane codimerization. Some examples of methylenecyclopentane formation from (**97**) are depicted in equation (110).

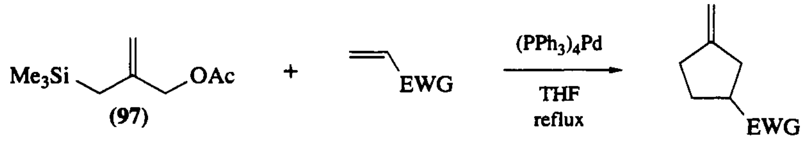

(110)

| | |
|---|---|
| EWG = $CO_2Me$ | 68% |
| = COMe | 30% |
| = CN | 35% |

The cycloaddition of (**97**) appears to involve an ($\eta^3$-TMM)palladium intermediate (**98**), which is generated from the desilylation of the initially formed ($\eta^3$-allyl)Pd complex (**99**) (Scheme 6).[63] The non-symmetrical nature and the nucleophilic/basic character of this TMM species are predicted by theorectical calculations,[63,71–73] and further deduced from reactions with nucleophiles containing a proton source.[63] Although the bonding nature of (**98**) implies a nonequivalence of the carbon termini on the TMM ligand, there is rapid equilibration among the three $\eta^3$ structures (**98-I**, **-II**, **-III**), which results in a functionally symmetrical synthon. This fast interconversion would account for complete scrambling of the deuterium label in the cycloaddition with the dideuterated derivative (**100**) (equation 111).[63] The isolation of stable TMM complexes of Ir, Ru, Os and Rh from analogs of (**97**) further supports the validity of this proposed mechanism.[74] The methylenecyclopentane adduct is presumed to form in a stepwise fashion *via* a Michael addition of the (TMM)Pd intermediate (**98**) to the alkene, which is then followed by ring closure of intermediate (**101**) (Scheme 6). This nonconcertedness of product formation is reflected in the moderate stereospecificity of the cycloaddition.[63,75] It is not surprising that dimethyl maleate gives a mixture of *cis* and *trans* adducts, whereas the corresponding fumarate yields virtually all *trans* material (equation 112).[62] As in the case with methylenecyclopropane codimerization, annulations with *cis* alkenic substrates are frequently complicated by their isomerization during the reaction.[69]

The Pd-catalyzed BCR cycloaddition is highly diastereoselective. For example, exclusive addition at the least-hindered face of the δ-oxaeneone (**102**) is observed (equation 113).[76] Similarly, the six-membered ring sulfone (**103**) also gives essentially a single adduct (**104**).[35] This compound can be readily transformed, *via* ozonolysis and sulfone elimination, to a bicyclic enone that is equivalent to a cyclopen-

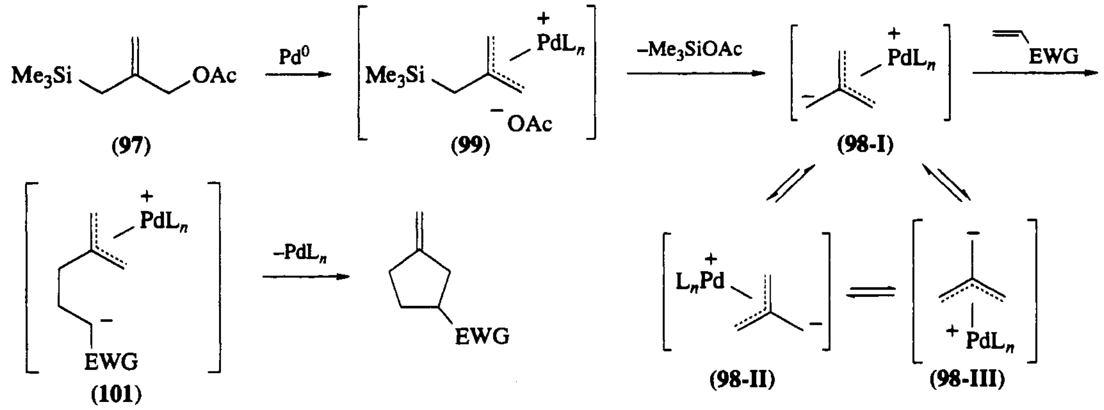

**Scheme 6**

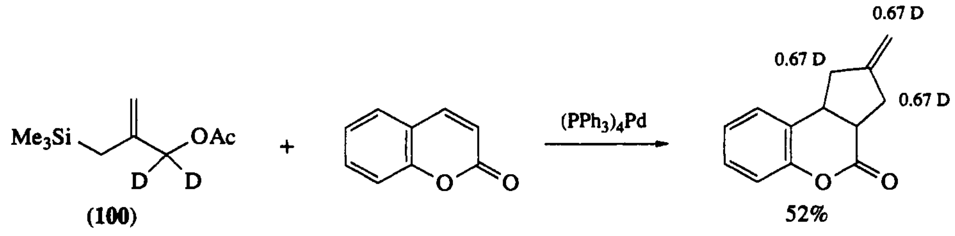

(111)

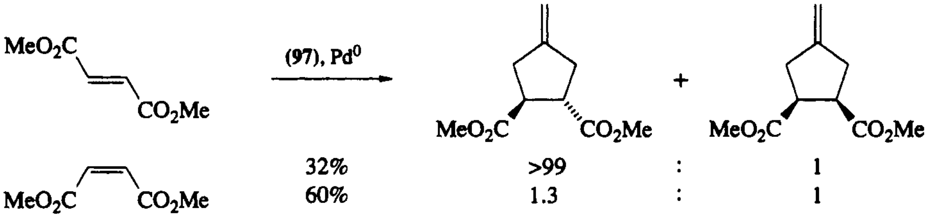
MeO2C
CO2Me
(97), Pd0
32%
60%
MeO2C
CO2Me
>99 : 1
1.3 : 1

(112)

tenone annulation procedure (equation 114). Alternatively, it is easily converted into a product that would have derived from the theoretical 2-cyclohexynone (equation 115). Good asymmetric induction is noted in the cycloaddition of (97) with a chiral vinyl sulfoxide (equation 116).[77]

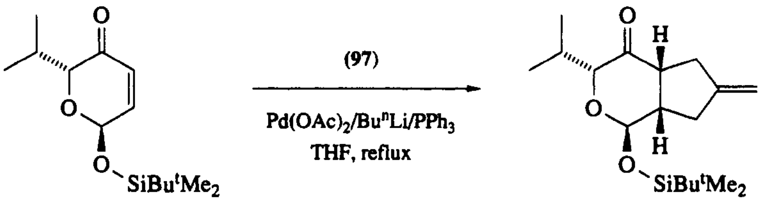
O
O
O
SiBu$^t$Me$_2$
(97)
Pd(OAc)$_2$/Bu$^n$Li/PPh$_3$
THF, reflux
H
H
94%

**(102)**

(113)

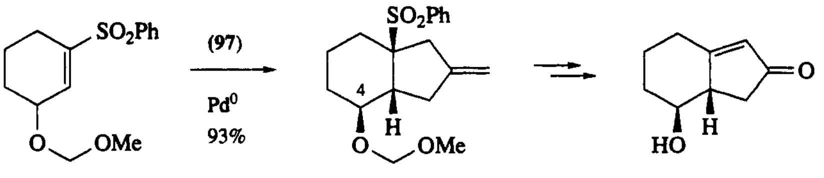
SO2Ph
OMe
(97)
Pd0
93%
4
H
HO
O

**(103)** **(104)** 4β:4α > 9:1

(114)

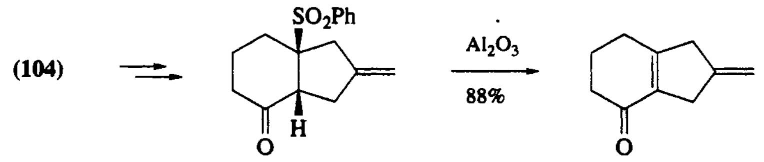
(104)
SO2Ph
H
O
Al2O3
88%

(115)

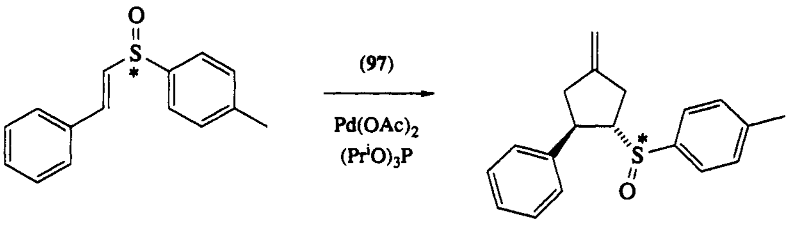
O
S
*
(97)
Pd(OAc)2
(Pr$^i$O)$_3$P

72% (+ 8% Z-isomer)
80% *de*

(116)

Although 2-cyclopentenone reacts smoothly with this BCR, cyclohexenone and 2-methylcyclohexenone produce low yields of the bicyclic adduct, and cycloheptenone does not react at all.[62,78] The introduction of an ester function at the α-position significantly improves the reactivity of these sluggish cyclic alkenones toward cycloaddition.[78] In an eight-membered ring case, the [5,8] cycloadduct (**105**) is obtained in excellent yield (equation 117). Considering the synthetic versatility of an ester function, this particular strategy to improve the reaction efficiency is very useful.

### *3.2.5.2.2 Cycloaddition with substituted systems*

The Pd$^0$-catalyzed [3 + 2] reactions of substituted BCRs are highly regioselective. There is a particularly strong preference for formation of the cyclic adduct having a 1,3 relationship between the activating

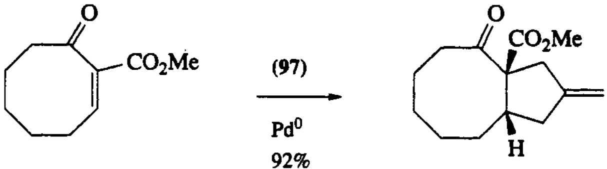
O
CO$_2$Me
(97)
Pd$^0$
92%
O
CO$_2$Me
H

**(105)**

(117)

group of the alkene and the substituent of the precursor. Furthermore, this preference is independent of the substitution pattern in the precursors because of the facile equilibration of the initially formed TMM intermediate to the other isomeric forms. The substituted silyl acetate derivatives are readily prepared, as outlined in Scheme 7.[35]

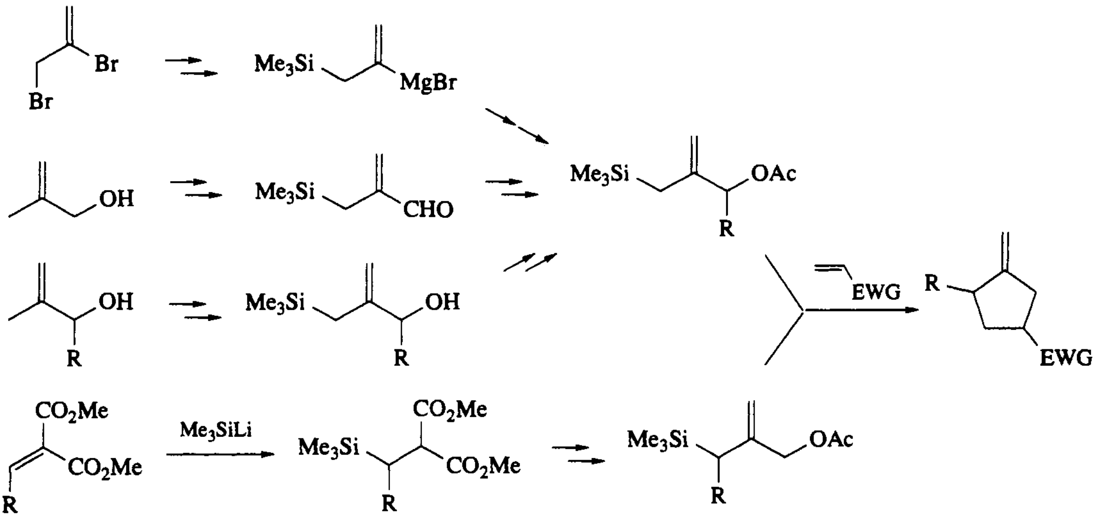
Br
Br
Me$_3$Si
MgBr
OH
Me$_3$Si
CHO
Me$_3$Si
OAc
R
OH
R
Me$_3$Si
OH
R
EWG
R
EWG
CO$_2$Me
CO$_2$Me
R
Me$_3$SiLi
Me$_3$Si
CO$_2$Me
CO$_2$Me
R
Me$_3$Si
OAc
R

**Scheme 7**

Cycloaddition of either of the methyl-substituted precursors (**106**) or (**107**) to 2-cyclopentenone produces the same regioisomer (**108**) with very high selectivity (equation 118).[79] This cycloadduct apparently originates from the TMM intermediate (**109**) according to the proposed mechanism. Thus it appears that TMM intermediate (**111**), which is formed initially from the precursor (**106**), equilibrates to the more reactive isomer (**109**) faster than it undergoes cycloaddition. Theorectical calculations also suggest that (**109**) is the thermodynamically preferred isomer.[73] Regioselectivity can be influenced by the nature of the alkene receptor. For example, the reaction of (**106**) or (**107**) with dimethyl benzylidenemalonate produces more of the minor regioadduct (equation 119).

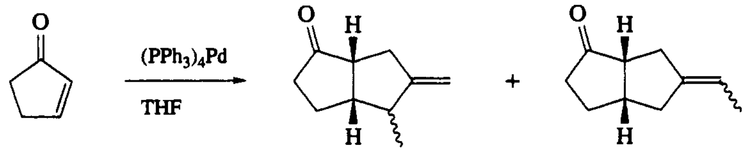
O
(PPh$_3$)$_4$Pd
THF
O
H
H
+
O
H
H

(118)

| | (108) | |
|---|---|---|
| (106) | 43% | 2% |
| (107) | 49% | 3% |

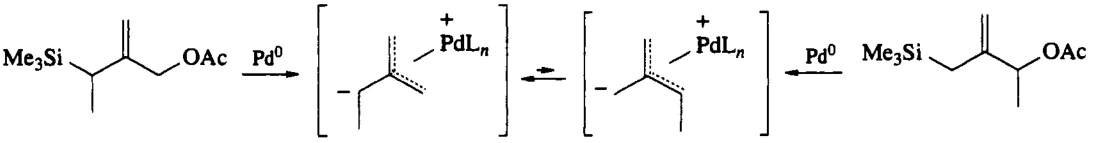
Me$_3$Si
OAc
Pd$^0$
+
PdL$_n$
+
PdL$_n$
Pd$^0$
Me$_3$Si
OAc

**(106)** **(109)** **(111)** **(107)**

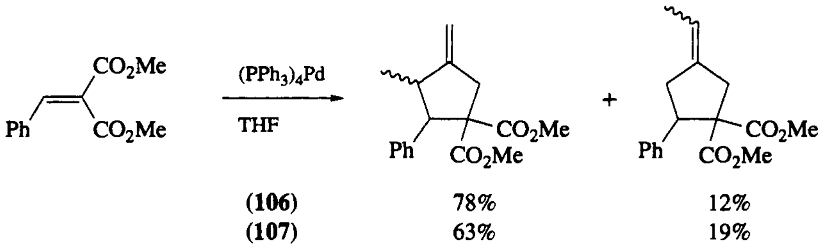
CO2Me
Ph
CO2Me
(PPh3)4Pd
THF
Ph
CO2Me
CO2Me
+
Ph
CO2Me
CO2Me
(106)
(107)
78%
63%
12%
19%

(119)

The regioselectivity is even better with other BCR systems. Thus only one regioisomer is obtained with substituted silyl acetate (**112**) and the same benzylidenemalonate (equation 120).[80] The successful cycloaddition with these substituted bifunctional reagents indicates that this TMM synthon can again accommodate a number of reactive functional groups such as cyano, keto and alkoxycarbonyl. It is remarkable that the regioselectivity remains the same despite the tremendous electronic pertubation produced by these substituents, *i.e.* electron-withdrawing, electron-donating and π-conjugation. In addition, the mildness of the reaction conditions is responsible for product stability with respect to potential alkene isomerization (R = Ph), and possible further reaction with the catalyst (R = OAc).

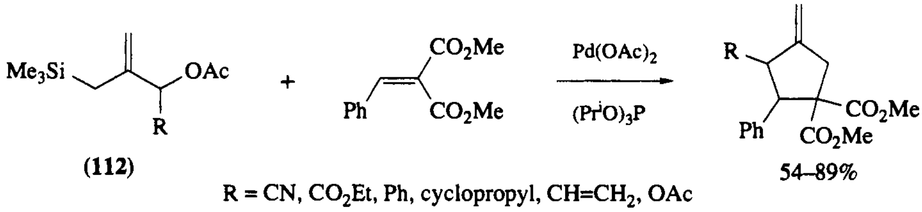
Me3Si
OAc
R
(112)
+
CO2Me
Ph
CO2Me
Pd(OAc)2
(PriO)3P
R
Ph
CO2Me
CO2Me
54–89%
R = CN, CO2Et, Ph, cyclopropyl, CH=CH2, OAc

(120)

Carbonate analogs of the corresponding silyl acetates are also good TMM synthons. In this case the carbonate leaving group from initial π-complex formation undergoes decarboxylation to give an alkoxide, which then initiates the desilylation. The type of BCR is employed in the annulation can be critical in determining the reaction pathway. The bis(silyl) acetate (**113**) generates a trimethylsilyl-substituted adduct (**114**), whereas the corresponding carbonate (**115**) yields exclusively a carboxylic methylenecyclopentane (**116**) (equation 121).[66] The latter is presumably derived from trapping of the (TMM)Pd intermediate by the incipient CO2, which is the by-product of carbonate decarboxylation.

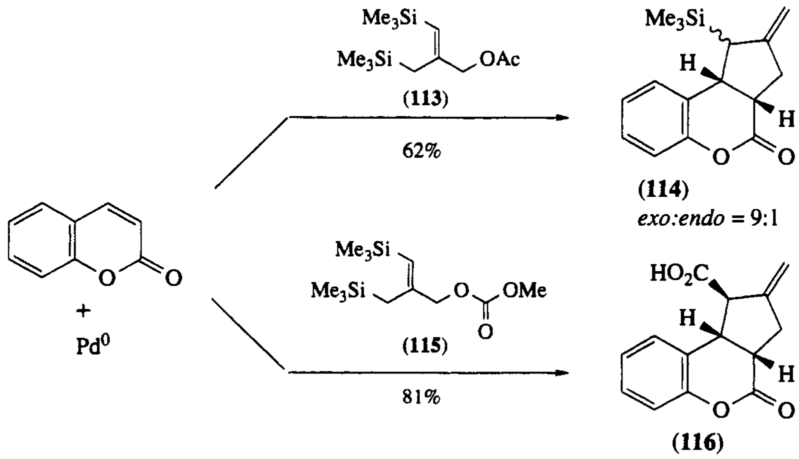
Me3Si
Me3Si
OAc
(113)
62%
Me3Si
H
H
O
O
(114)
exo:endo = 9:1
O
O
+
Pd0
Me3Si
Me3Si
O
OMe
O
(115)
81%
HO2C
H
H
O
O
(116)

(121)

The BCR cycloaddition is diastereoselective with respect to the TMM unit, with the alkene approaching from the side opposite to the metal center. This accounts for an overall net retention of configuration of the starting material in the cycloadducts obtained from the silyl carbonates (**117**) and (**118**) (equations 122, 123).[81] Thus, no prior coordination of the electron-deficient alkene to the Pd center is necessary for reaction. This is quite different from the methylenecyclopropane mechanism as depicted in Scheme 5. It would also explain the need for a higher ligand-to-metal ratio of the catalyst.

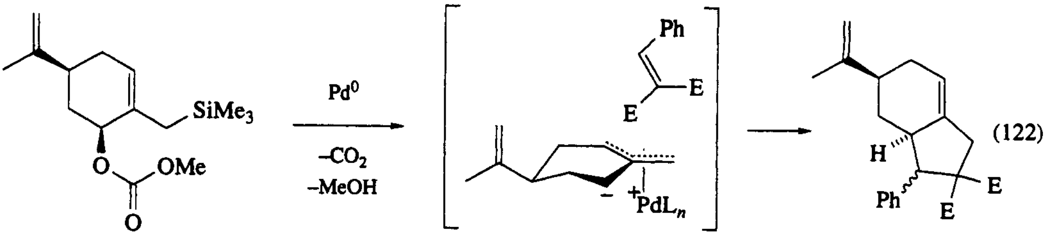
SiMe$_3$
OMe
Pd$^0$
–CO$_2$
–MeOH
Ph
E
E
PdL$_n$
H
Ph
E
E

(117)

(122)

E = CO$_2$Me; 86%

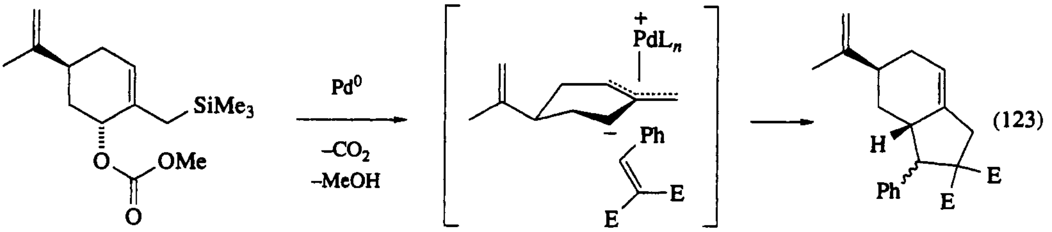
SiMe$_3$
OMe
Pd$^0$
–CO$_2$
–MeOH
PdL$_n$
Ph
E
E
H
Ph
E
E

(118)

(123)

E = CO$_2$Me; 88%

The regioselective cycloadditions can generate useful synthetic intermediates. Conversion of adduct (**119**) to (**120**) provides the equivalent of an α-phenylcyclopentanone annulation (equation 124).[80] The allylsilane moiety generated by the bis(silyl) acetate (**113**) is a useful entity. For example, the cycloadduct (**121**) can be easily transformed to (**122**), which is a regioisomer of the adduct resulting from reaction with (**112**; R = OAc) (equation 125).[66]

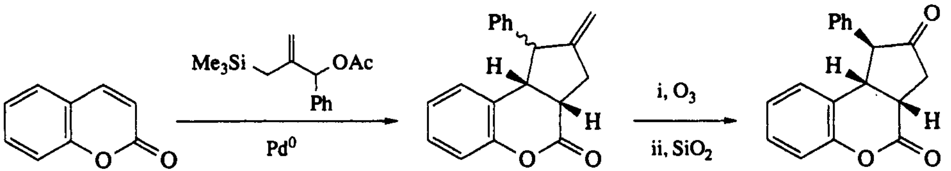
Me$_3$Si
OAc
Ph
Pd$^0$
76%
Ph
H
H
i, O$_3$
ii, SiO$_2$
Ph
H
H

(119)

(120) 98%

(124)

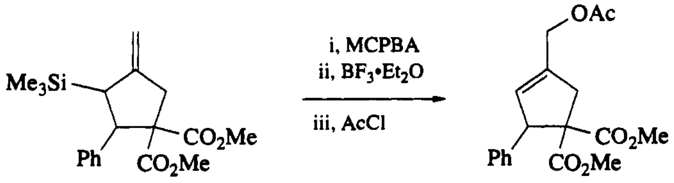
Me$_3$Si
CO$_2$Me
Ph
CO$_2$Me
i, MCPBA
ii, BF$_3$•Et$_2$O
iii, AcCl
OAc
CO$_2$Me
Ph
CO$_2$Me

(121)

(122)

(125)

Extension of the TMM strategy to intramolecular reactions greatly expands the scope of this BCR methodology. The precursors are readily available, *e.g.* from the silyl Grignard reagent (**123**) and ω-oxo-α,β-unsaturated substrates (equation 126). Ester- and sulfonyl-substituted bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems are readily constructed in a single step from acyclic material (equations 127, 128).[82]

Silyl carbonates (**124**) possessing an anion-stabilizing function have been developed by Tsuji and coworkers as TMM synthons in [3 + 2] reactions.[83] In this case the *in situ* generated alkoxide serves as a

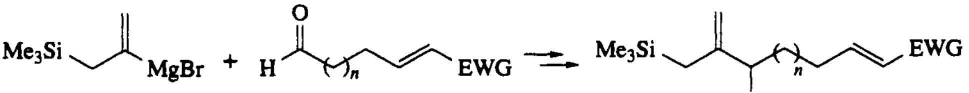
Me$_3$Si
MgBr
+
O
H
n
EWG
Me$_3$Si
n
EWG
OAc

(123)

(126)

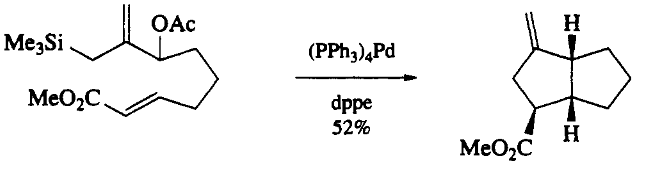
Me3Si
OAc
MeO2C
(PPh3)4Pd
dppe
52%
H
MeO2C
H

(127)

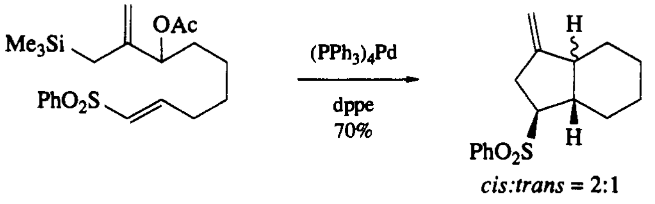
Me3Si
OAc
PhO2S
(PPh3)4Pd
dppe
70%
H
PhO2S
H
cis:trans = 2:1

(128)

base to effect proton abstraction from the π-allyl intermediate (equation 129). These bifunctional reagents can be prepared from 2-methylene-1,3-propanediol, or methallyl phenyl sulfone in the case of the sulfonyl precursor (Scheme 8). The Pd-catalyzed cycloaddition with (**124**) is similar in scope and regioselectivity to the silyl acetate system. However, alkene migration does occur in the cyano system (equations 130, 131).[84] The sulfonyl(methylene)cyclopentanes resulting from this reagent are useful synthetic intermediates. Some further elaborations of an acrylate adduct are summarized in Scheme 9.[85] A sulfone-substituted BCR has also been successfully generated with aqueous hydroxide for cycloaddition under phase-transfer conditions (equation 132).[86]

The use of chiral ligands to facilitate asymmetric synthesis with these TMM synthons is difficult because the bond-formation process occurs away from the metal center. None the less, an enantioselective synthesis using a Tsuji TMM synthon has been achieved with a catalyst containing a chiral phosphine ligand (equation 133).[87] While the enantiomeric excess is not very high in this case, the fact that one can achieve asymmetric induction at all is quite remarkable.

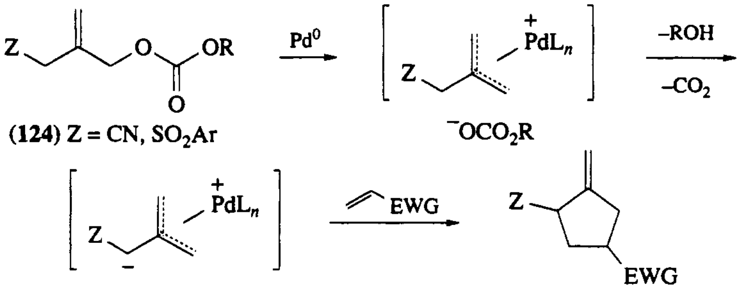
Z
O
OR
O
(124) Z = CN, SO2Ar
Pd0
Z
+
PdLn
−OCO2R
-ROH
-CO2
Z
+
PdLn
−
EWG
Z
EWG

(129)

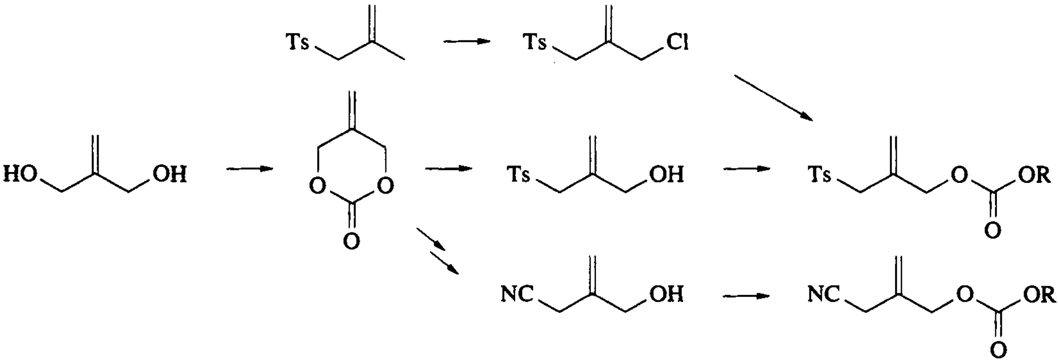
Ts
Ts
Cl
HO
OH
O
O
O
Ts
OH
Ts
O
OR
O
NC
OH
NC
O
OR
O

**Scheme 8**

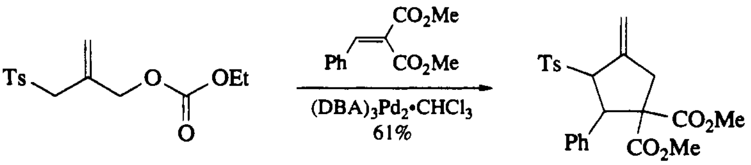
Ts
O
OEt
O
CO2Me
Ph
CO2Me
(DBA)3Pd2•CHCl3
61%
Ts
Ph
CO2Me
CO2Me

(130)

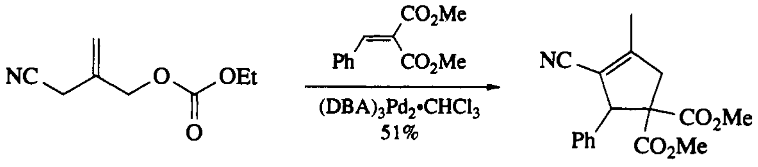
NC
O
OEt
O
CO2Me
Ph
CO2Me
(DBA)3Pd2•CHCl3
51%
NC
CO2Me
Ph
CO2Me

(131)

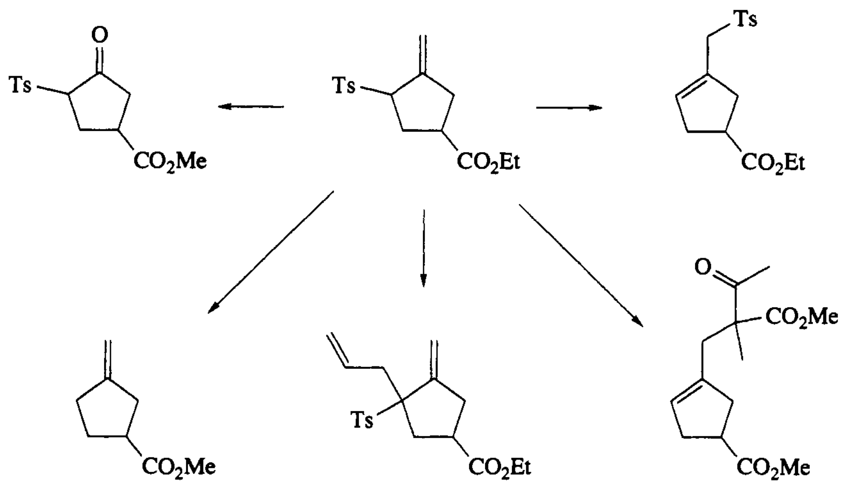
O
Ts
CO2Me
Ts
CO2Et
Ts
CO2Et
O
CO2Me
CO2Me
Ts
CO2Et
CO2Me

**Scheme 9**

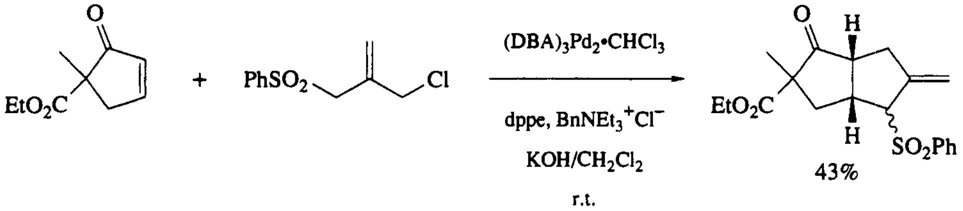
O
EtO2C
+
PhSO2
Cl
(DBA)3Pd2•CHCl3
dppe, BnNEt3+Cl−
KOH/CH2Cl2
r.t.
O
H
EtO2C
H
SO2Ph
43%

(132)

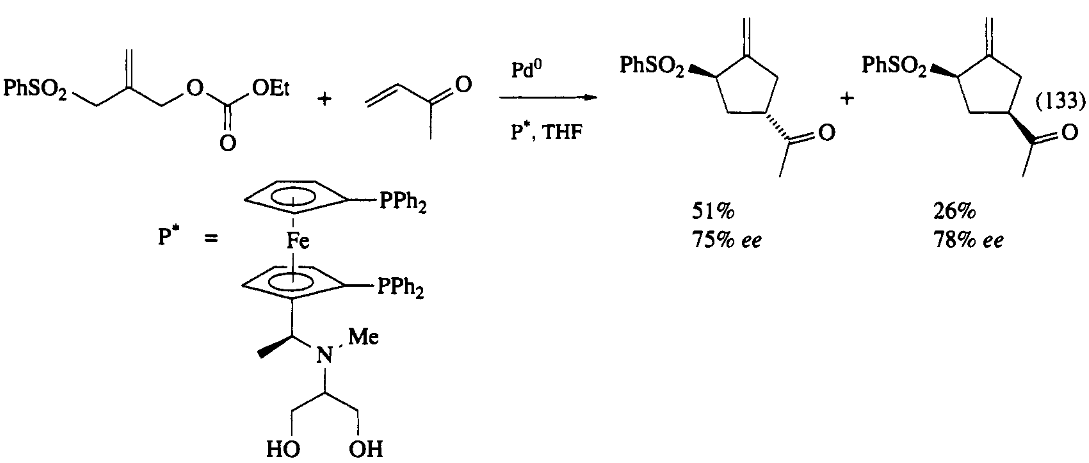
PhSO2
O
OEt
O
+
O
Pd0
P*, THF
PhSO2
O
+
PhSO2
O
51%
75% ee
26%
78% ee
P* =
PPh2
Fe
PPh2
Me
N
HO
OH

(133)

The highly regioselective cycloadditions of the substituted BCRs can be contrasted to the [3 + 2] reactions employing the corresponding methylenecyclopropanes. While the latter can provide a complementary regiochemistry, *i.e.* formation of alkylidenecyclopentanes, they often give lower selectivity and are very sensitive to the catalyst systems, as well as the substitution pattern of the three-membered ring precursors.

### *3.2.5.2.3 Diene, C=O and C=N cycloadditions*

The relative amount of [3 + 2] and [4 + 3] product in the annulation of dimethyl (*E,E*)-muconate with the parent silyl acetate (**97**) depends critically on the reaction conditions (equation 134).[88] The most notable effect on the ratio of the seven- to five-membered rings is the temperature of the reaction, with a higher temperature favoring methylenecyclopentane formation. Steric factors are also important, as a phenyl-substituted BCR (**124**; R = Ph) generates only [3 + 2] cycloadducts with the same diene. It should be noted that the corresponding reaction using methylenecyclopropane as the TMM synthon produces only the seven-membered ring [4 + 3] adduct. Pyrones are also interesting conjugated dienyl substrates. While the parent and alkyl-substituted system yield only [4 + 3] adducts with (**97**), introduction of a methoxycarbonyl group on the 2-position promotes the exclusive formation of the [3 + 2] adduct (equation 135).[89] However, a 4-methoxycarbonyl function results in a mixture of products from both types of cycloaddition.

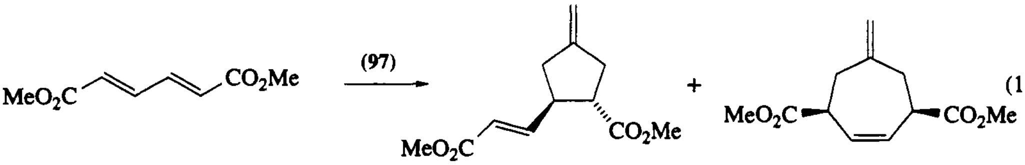

(134)

| | | |
|---|---|---|
| $(PPh_3)_4Pd$, dppe, dioxane | 77% | 21% |
| $(PPh_3)_4Pd$, dppe, THF | 29% | 18% |
| $Pd(OAc)_2$, $4(Pr^iO)_3P$, THF | 47% | 42% |

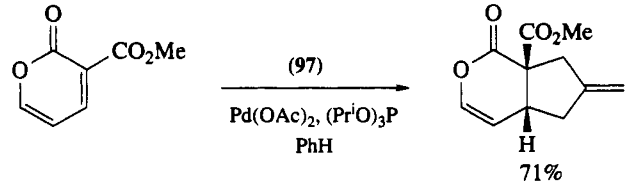

(135)

Annulation to carbonyl functions has also been achieved with Trost's bifunctional reagents.[35] Whereas the parent silyl acetate (**97**) yields only simple alkylation products with aldehydes under normal conditions, addition of only a few mole % of trimethyltin acetate to the reaction mixture results in facile formation of methylenetetrahydrofurans![90] Furthermore, excellent diastereoselectivity is observed in the cycloaddition to a galactose-derived aldehyde (**125**) (equation 136). The tin acetate co-catalyst also promotes addition to relatively unreactive ketone carbonyls, such as in the case of benzofuran (**126**) and the acetylenic ketone (**127**) (equations 137, 138). It is remarkable that even the sterically hindered enone (**128**) reacts preferentially at the ketone function (equation 139). A tributyltin analog (**129**) of (**97**) has been used in the stepwise formation of a methylenetetrahydrofuran from aldehydes.[91,92] Similarly, pyrrolidines can be prepared from the corresponding imines in two steps *via* a Lewis acid-catalyzed 1,2-addition of the tin reagent, which is then followed by a Pd-catalyzed cyclization (equation 140).[91] Direct formation of pyrrolidine from the imine is possible if one uses a mesylate analog of (**97**) and a nickel(0) catalyst (equation 141).[93]

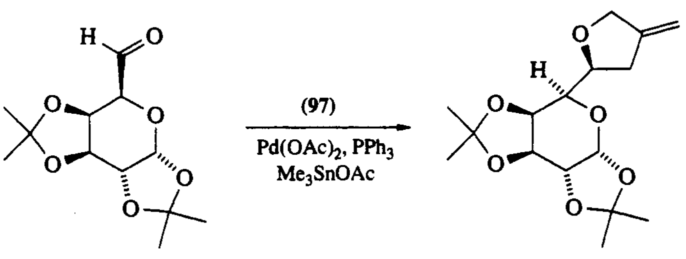

**(125)**

84%

(136)

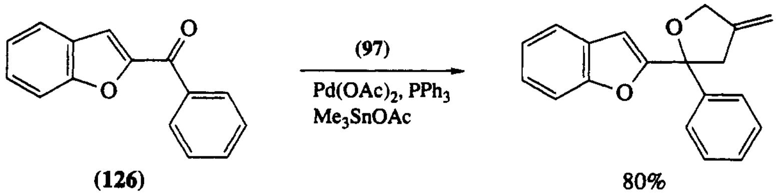
(126)
(97)
Pd(OAc)$_2$, PPh$_3$
Me$_3$SnOAc
80%

(137)

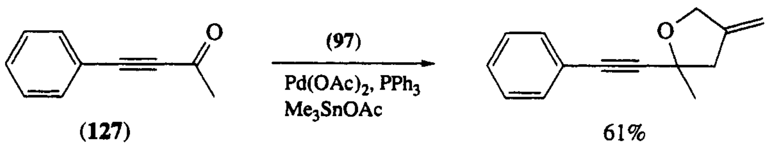
(127)
(97)
Pd(OAc)$_2$, PPh$_3$
Me$_3$SnOAc
61%

(138)

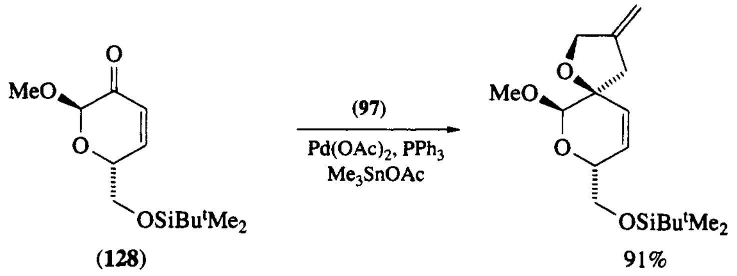
MeO
O
OSiBu$^t$Me$_2$
(128)
(97)
Pd(OAc)$_2$, PPh$_3$
Me$_3$SnOAc
91%

(139)

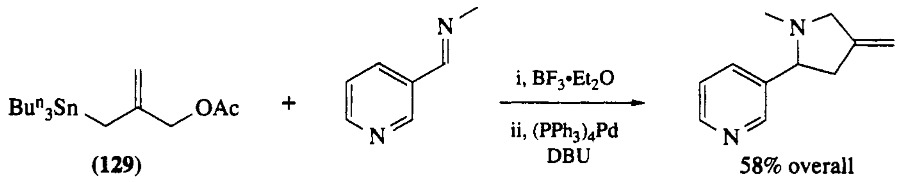
Bu$^n_3$Sn
OAc
(129)
N
i, BF$_3$•Et$_2$O
ii, (PPh$_3$)$_4$Pd
DBU
58% overall

(140)

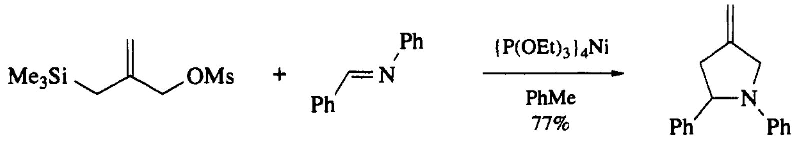
Me$_3$Si
OMs
Ph
N
Ph
{P(OEt)$_3$}$_4$Ni
PhMe
77%
N
Ph
Ph

(141)

### 3.2.5.3 TMM Cycloaddition in Natural Product Synthesis

The TMM cycloaddition has been applied to a number of total syntheses and synthetic studies of various natural products.[34,35] The main advantage of this methodology is the stereoselective construction of a five-membered ring in one step from readily available starting materials. The exocyclic alkene of the cycloadduct is another crucial element of this strategy because of its synthetic versatility. The following examples illustrate some of the applications of this [3 + 2] strategy in the area of cyclopentanoid syntheses.

The cycloadduct of methyl acrylate undergoes smooth oxidative cleavage to the cyclopentanone (**130**), which is a useful starting material in the synthesis of dihydrojasmone, *cis*-jasmone and sarkomycin (Scheme 10).[34] *trans*-Diester (**131**),[94] likewise derived from a TMM adduct of dimethyl fumarate, provides a starting point for two total syntheses of (±)-brefeldin A (**132**) (equation 142).[95,96] The same diester has also been used in a prostaglandin synthesis. An enantioselective synthesis of (+)-brefeldin A has also been achieved *via* diastereoselective annulation of (**97**) to the chiral α,β-unsaturated ester (**133**). The product from this reaction is easily elaborated into the key intermediate (**134**), which possesses all but one chiral center of the target molecule (equation 143).[97] Cycloaddition of methylenecyclopropane (**79**) or BCR (**97**) occurs only at the *exo* face of 1,2-dimethoxycarbonylnorbornene to produce the adduct (**135**), a starting material for a short synthesis of (±)-albene (**136**) (equation 144).[70] In this case the methylene group provides a latent function for the requisite internal alkene of the natural product.

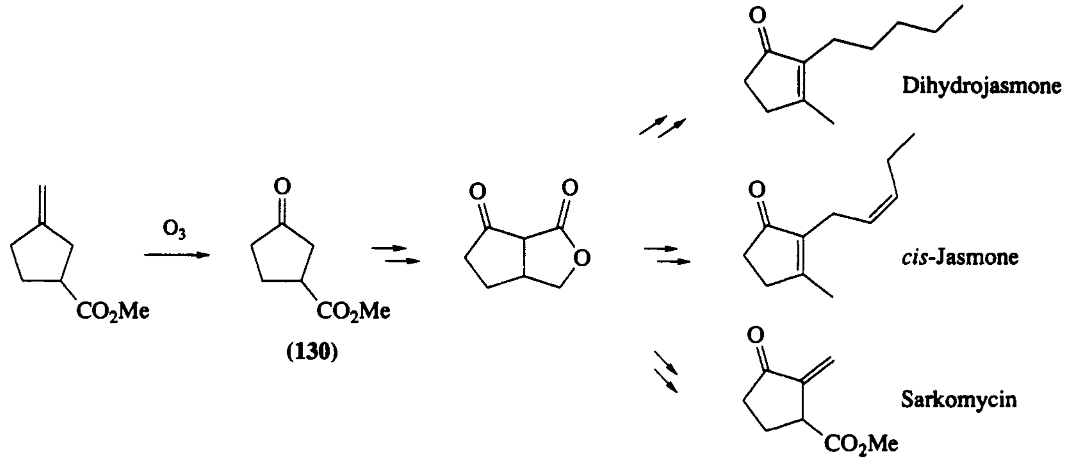
O₃
(130)
Dihydrojasmone
*cis*-Jasmone
Sarkomycin

Scheme 10

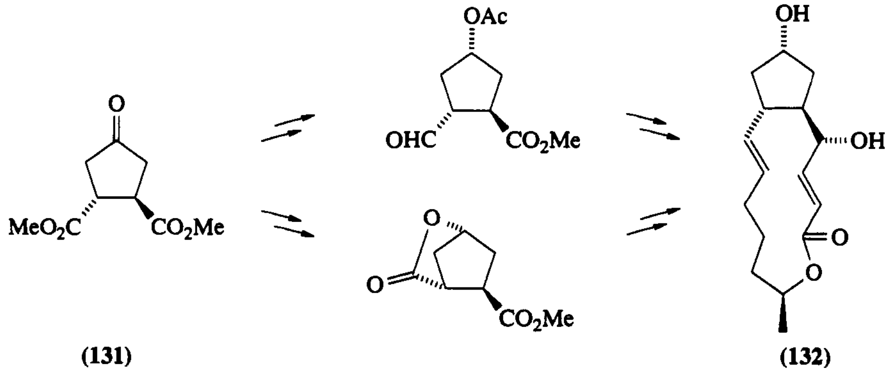

(142)

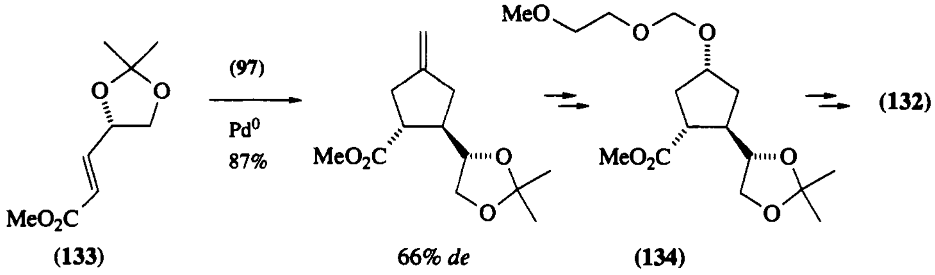
(97)
Pd⁰
87%
(133)
66% *de*
(134)
(132)

(143)

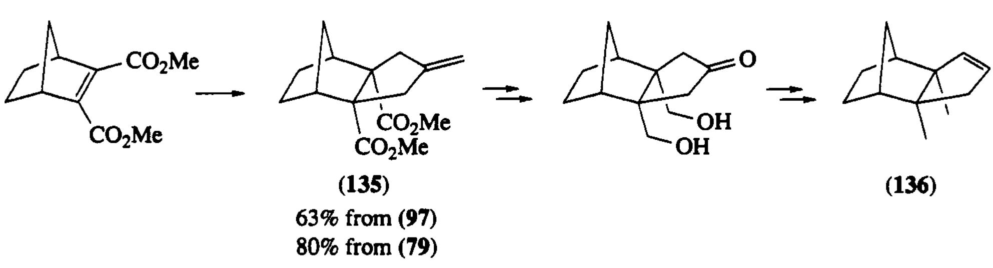
(135)
63% from (97)
80% from (79)
(136)

(144)

The methyl-substituted BCR is useful for the construction of some iridoid cyclopentanoids. Keto alcohol (**137**), a crucial intermediate for a synthesis of (±)-chrysomelidial (**138**), can be prepared from the cycloadduct (**108**) of cyclopentenone and the methyl-TMM synthon (equation 145).[79] This expedient approach to the keto alcohol, four steps and 83% overall yield from the bifunctional reagent (**107**), is a considerable improvement over a previous 14-step sequence using conventional methodologies. Although the initial bicyclic ketone (**108**) is a 1:1 epimeric mixture, base-catalyzed equilibration of the products from ozonolysis results in only one epimer, having the required stereochemistry. This epimerization strategy is again employed in an efficient formal synthesis of (±)-loganin (**139**) (equation 146).[98] In this case the cyclopentanone ring of adduct (**108**) becomes a latent function for the 1,5-dialdehyde unit present in the loganin aglucon (**140**). The TMM approach to these two seco-iridoids, chrysomelidial and loganin, is made possible only through the unique regioselectivity of the BCR cycloaddition. It would be difficult to effect the same syntheses using the methylenecyclopropane strategy because of the very different regiochemistry.

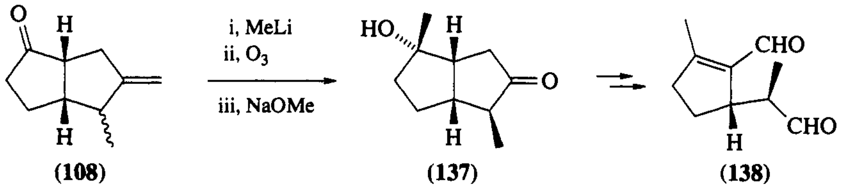
O
H
H
(108)
i, MeLi
ii, O3
iii, NaOMe
HO
H
O
H
(137)
CHO
CHO
H
(138)

(145)

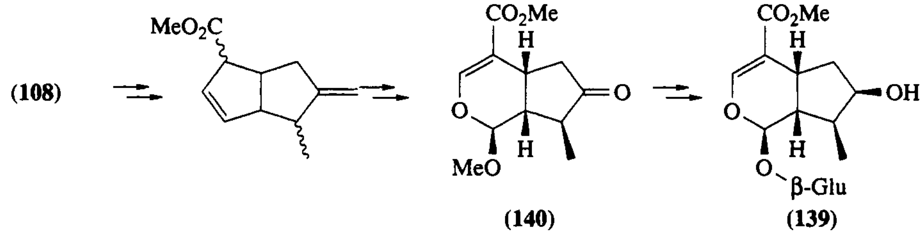
(108)
MeO2C
CO2Me
H
O
O
H
MeO
(140)
CO2Me
H
OH
O
H
O
β-Glu
(139)

(146)

The pentalenene precursor (**141**) can be derived from a TMM cycloadduct (**142**) (equation 147).[99] This synthetic approach is expedited by the facile conversion of the methylene unit of (**142**) to a *gem*-dimethyl function found in (**141**). This is normally accomplished by a simple cyclopropanation–hydrogenolysis sequence.[100] The two reported TMM-based syntheses of the linear triquinane (±)-hirsutene (**143**) also utilize this particular strategy for the *gem*-dimethyl formation (equation 148).[35,101]

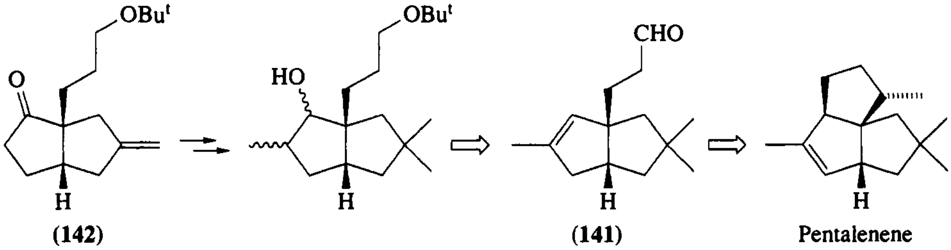
OBu^t
O
H
(142)
OBu^t
HO
H
CHO
H
(141)
H
Pentalenene

(147)

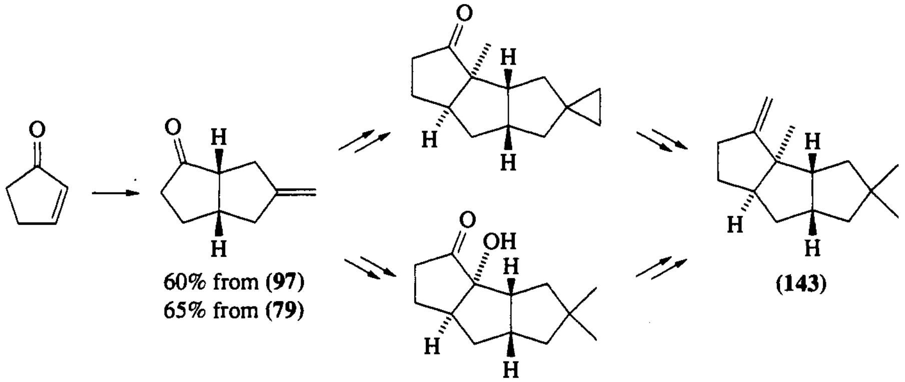
O
O
H
H
60% from (97)
65% from (79)
O
H
H
H
O
OH
H
H
H
H
H
H
(143)

(148)

Intramolecular exocyclic transannular cycloaddition of TMM can provide a viable route to propellanes, such as the sesquiterpene modhephene (**144**). This methodology is demonstrated in an efficient synthesis of a [3.3.3]propellane (**145**) (equation 149).[101] The methylenecyclopropane approach is preferred in this case because it works well with dialkyl-substituted systems.

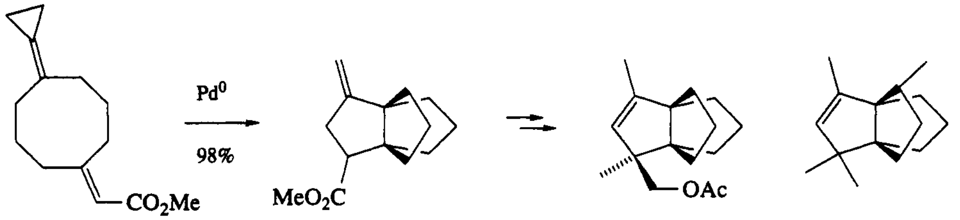
Pd$^0$
98%
CO$_2$Me
MeO$_2$C
OAc

(145) (144) (149)

The TMM cycloaddition has also been applied successfully in the synthetic studies of various types of cyclopentanoid natural products, such as ginkolides,[102] phyllanthocin[103] and 2β-hydroxyjatrophone[35] (equations 150–152). The last case employs an equivalent of an alkyne cycloaddition using a retro Diels–Alder strategy.[104] This is a viable alternative for the formation of methylenecyclopentenes from BCRs because electron-deficient alkynes fail to cycloadd with the silyl acetate (**97**).[69] A highly diastereoselective annulation of the (*p*-anisyl)silyl acetate (**146**) to a benzylidenemalonate possessing a chiral auxiliary has been reported.[105] The resulting adduct can be converted to an enantiomerically pure ketone (**147**), which serves as a starting point for an asymmetric synthesis of the antileukemic (–)-rocaglamide (**148**) (equation 153).[106] The exomethylene unit of the BCR cycloadduct provides the crucial dienophile unit in an intramolecular Diels–Alder reaction (equation 154).[106] This novel approach to the phyllocladane ring system is an interesting example of complementarity between [4 + 2] and [3 + 2] cycloaddition strategies.

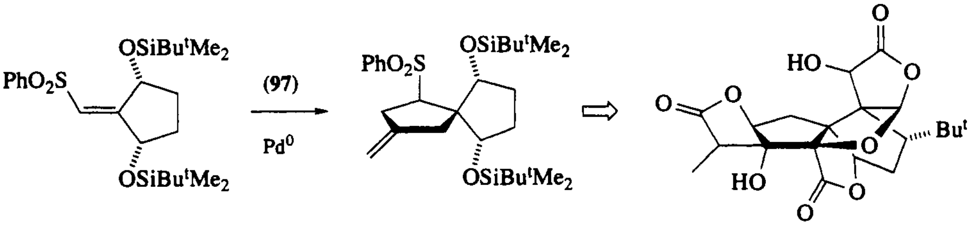
OSiBu$^t$Me$_2$
PhO$_2$S
OSiBu$^t$Me$_2$
(97)
Pd$^0$
PhO$_2$S
OSiBu$^t$Me$_2$
OSiBu$^t$Me$_2$
O
HO
O
O
O
Bu$^t$
O
HO
O
O

Ginkgolide A

(150)

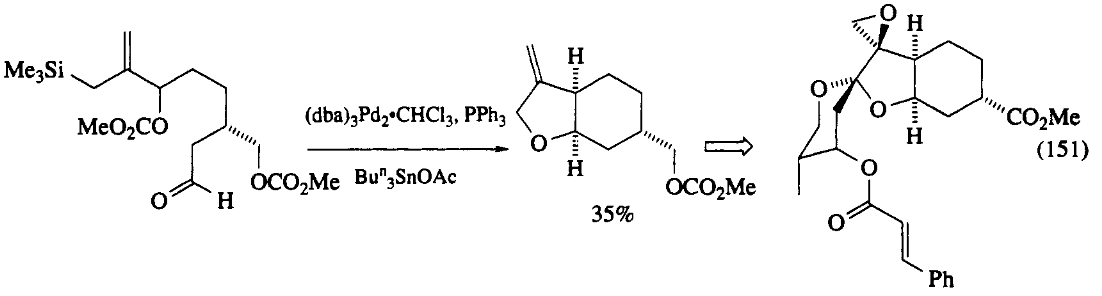
Me$_3$Si
MeO$_2$CO
O
H
OCO$_2$Me
(dba)$_3$Pd$_2$•CHCl$_3$, PPh$_3$
Bu$^n_3$SnOAc
H
O
H
OCO$_2$Me
35%
O
H
O
O
H
CO$_2$Me
O
O
Ph

(151)

Phyllanthocin

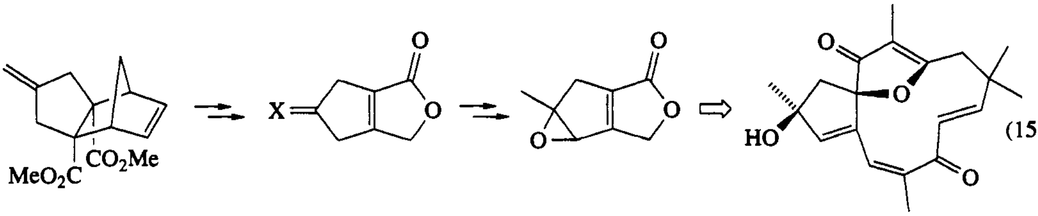
MeO$_2$C
CO$_2$Me
X
O
O
O
O
O
O
O
HO
O

(152)

2β-Hydroxyjatrophone

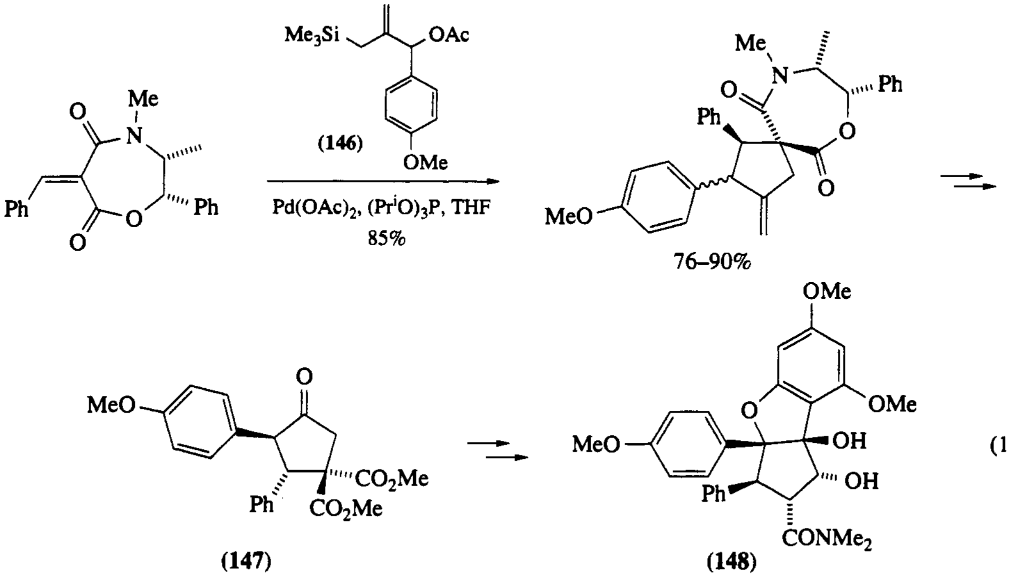

(153)

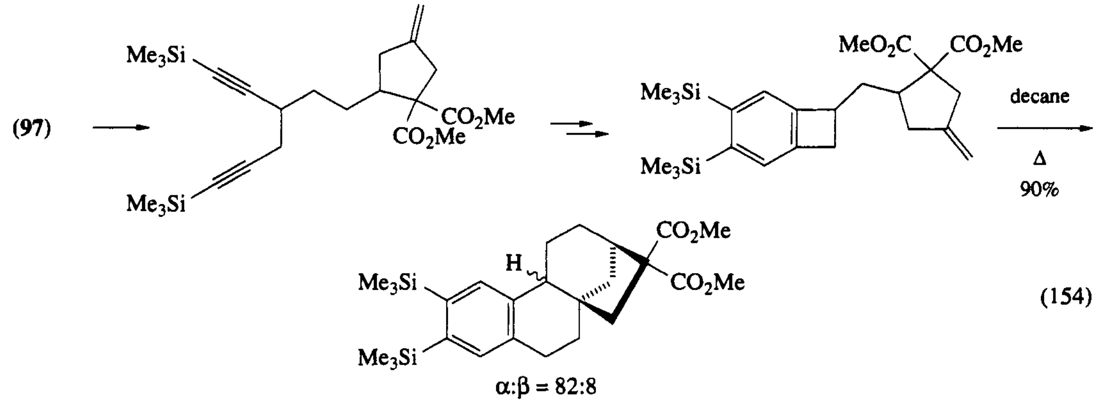

(154)

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# 4.1

# Intermolecular Diels–Alder Reactions

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## 4.1.1 INTRODUCTION

### 4.1.1.1 Definition, Background and Thermodynamics

Discovered in 1928,[1] the Diels–Alder reaction, *i.e.* the [4 + 2] cycloaddition of a diene (**I**) and a dienophile (**II**) or (**IV**) (Scheme 1), has become, arguably, the most powerful carbon–carbon bond forming process. It is therefore surprising that the last comprehensive survey of the Diels–Alder reaction dates back to 1972.[2] Since then, substantial gains in insight and methodology have been accomplished hand-in-hand with a body of creative and conceptually new applications in organic synthesis. In view of the extensive literature, this chapter is limited to the formation of 'all-carbon' six-membered rings *via* bimolecular additions of 1,3-dienes to alkenes and alkynes.

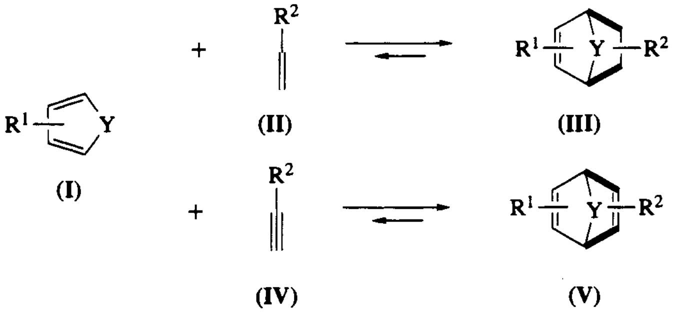

Scheme 1

During this reaction (Scheme 1), two new carbon–carbon single bonds are formed at the expense of two double bonds or one triple bond, which usually provides a significant driving force ($\Delta G°$). Diels–Alder reactions involving benzynes as dienophiles (Section 4.1.7) or, alternatively, *o*-quinodimethanes as dienes (Section 4.1.8) are even more exothermic owing to a restoration of aromaticity. Only some aromatic dienes such as furans show unfavorable reaction equilibria which, nevertheless, can be shifted toward the cycloadducts by employing high pressure (Section 4.1.4.2) or by reaction with a high-energy dienophile (*e.g.* benzyne; Section 4.1.7).

Owing to their exergonic nature, Diels–Alder reactions are mostly run in an irreversible manner, resulting in kinetically determined regio- and stereo-chemistry. Therefore it is the successful control of its kinetics (featuring values of $\Delta H^{\ddagger} \approx 16$ to 18 kcal mol–1 and $\Delta S^{\ddagger} \approx -30$ to –40 kcal K–1 mol$^{-1}$) which is fundamental to the pivotal role of the Diels–Alder reaction in organic synthesis.

### 4.1.1.2 Reactivity

To react with the majority of dienes, the dienophilic double or triple bond needs to be strained (*e.g.* benzynes; Section 4.1.7) or electron deficient. Recently, transient allyl cations have been introduced as highly reactive, electron-poor dienophiles (Section 4.1.4.1). However, dienophile activation is most often achieved by substitution with at least one electron-withdrawing substituent (*e.g.* C=O, $CO_2R$, CN, $NO_2$ or $SO_2Ar$). Molecular orbital considerations[3] provide the following rationalization. In a 'normal' Diels–

Alder reaction of an electron-poor dienophile with an electron-rich diene, the main interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied orbital (LUMO) of the dienophile. Electron-attracting substituents lower the frontier orbital energies of the dienophile, thereby decreasing the dienophile-LUMO/diene-HOMO energy difference and, consequently, the activation enthalpy ($\Delta H^{\ddagger}$) of the reaction. The remarkable Lewis acid induced acceleration of Diels–Alder reactions (Section 4.1.4.1) is also in agreement with a lowering of the frontier orbital energies of the dienophile by coordination with the Lewis acid. Furthermore, consistent with this reasoning, the reaction rate of Diels–Alder reactions is often increased by electron-donating substituents in the diene (*e.g.* $NR_2$, OR, SR, Section 4.1.3).

There is also a small number of [4 + 2] cycloadditions involving electron-rich dienophiles (*e.g.* enamines, vinyl ethers and vinyl sulfides) and electron-deficient dienes. These 'inverse-electron-demand' Diels–Alder reactions correspond to a predominant dienophile-HOMO/diene-LUMO overlap.

Isolated alkenes and alkynes, such as ethylene and acetylene, are notoriously poor dienophiles. This limitation has been largely overcome by the development of dienophiles containing an 'activating' moiety (*e.g.* $NO_2$, $SO_2Ar$) which is readily removed after cycloaddition, with or without introduction of further functionality. These reactive dienophiles can, accordingly, be regarded as synthetic equivalents of unreactive or inaccessible species (Section 4.1.2).

An entirely different type of rate enhancement relies on rendering the activation entropy ($\Delta S^{\ddagger}$) less negative. In this sense, advantage can be taken of using high pressure, ultrasound, aggregation effects in water, adsorption on dry SiO2, or clays and zeolites (Section 4.1.4.2).

#### 4.1.1.3 Regiochemistry

A question of regioselectivity arises when both the diene (VI) and the dienophile (VII) are nonsymmetrically substituted as this can give a mixture of two regioisomers (VIII) + (IX). Their relative proportions depend on the individual nature of, and on the interplay between, substituent effects (Scheme 2).

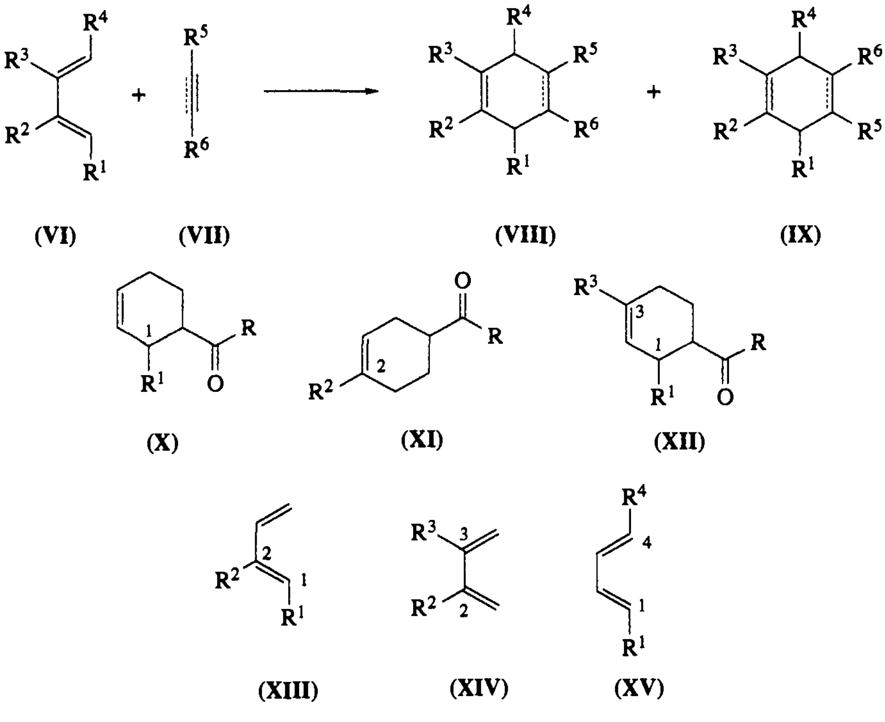

Scheme 2

In frontier orbital terms, the regiochemistry is governed largely by the atomic orbital coefficients at the termini of the reaction partners, which are altered by the substituents.[3] Hence, in 'normal' Diels–Alder reactions a diene substituent at C-1 has the tendency to direct the addition of a carbonyl-conjugated alkene towards the '*ortho*' product (X), whereas a substituent at C-2 favors the '*para*' product (XI). The individual directive effects of substituents are synergistic with 1,3-disubstituted dienes (*e.g.* favoring more strongly the formation of regioisomer XII), but antagonistic with 1,2- (XIII), 2,3- (XIV) and 1,4-disubstituted dienes (XV). The magnitude of the directing effect differs from one substituent to another (*e.g.* SAr > OR > $SiR_3$) and also with their position on the diene.

Similar arguments hold for the dienophile partner. Thus, the regiocontrolling effect of a substituent $R^5$ can outweigh that of $R^6$ in 1,2-disubstituted dienophiles (VII) (*e.g.* Me < $SO_2Ar$ < $NO_2$ > C=O > Me).

This hierarchy of substituent effects can be exploited to obtain adducts with predictable and high regioselectivity through the use of dienes and dienophiles containing 'temporary' substituents which control the regiochemistry of the addition and are removed thereafter. Sulfide (diene) and nitro (dienophile) groups can serve in this manner as powerful regiocontrol elements (Sections 4.1.3.3 and 4.1.2.1).

Lewis acid coordination of carbonyl-conjugated dienophiles usually results in vastly improved regioselectivities on [4 + 2] cycloadditions to nonsymmetrical dienes (Section 4.1.4.1). Medium effects can also be usefully applied to achieve better regiochemical control (Section 4.1.4.2).

### 4.1.1.4 Stereochemistry

It is accepted that in the majority of Diels–Alder reactions the two new σ-bonds are formed in a concerted, although not necessarily synchronous, manner as depicted by transition state (A) (Scheme 3).

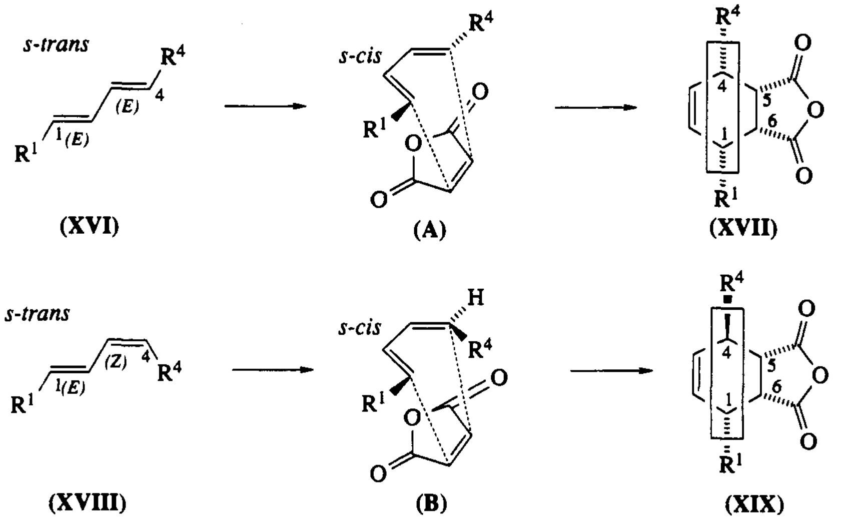

Scheme 3

This requires the diene to adopt the *s-cis* (cisoid) conformation. Consistent with this supra/supra/facial mode of addition,[4] Diels–Alder reactions are generally stereospecific, *i.e.* the configurations of both dienes and dienophiles are 'retained' in the adducts. Thus (*E,E*)-dienes (XVI) afford specifically adducts (XVII) with a $R^1/R^4$ *cis* relation, and (*E,Z*)-dienes (XVIII) give rise to a *trans* disposition of $R^1$ and $R^4$ in their adducts (XIX). Similarly, (*Z*)-dienophiles (XX) provide adducts (XXII) and (XXIII) showing a $R^5/R^6$ *cis* disposition, whereas (*E*)-dienophiles (XXI) yield adducts (XXIV) and (XXV) with *trans* related substituents $R^5/R^6$ (Scheme 4).

That each of the (*Z*)- or (*E*)-dienophiles yields a set of two diastereoisomers [(XX) → (XXII)/(XXIII) and (XXI) → (XXIV)/(XXV)] reflects the *endo* and *exo* orientations of the dienophile substituents in the transition states. Thus starting from a (*Z*)-dienophile (XX), both substituents $R^5$ and $R^6$ can be *endo* (C) or *exo* oriented (D) whereas an (*E*)-dienophile (XXI) entails transition states (E) and (F) featuring either an *endo* oriented $R^6$ or $R^5$, respectively.

Alder's *endo* rule[2] specifies a preference for *endo* (C) over *exo* (D) addition. However, this rule appears to be strictly applicable only to the addition of cyclic dienophiles (*e.g.* maleic anhydride, *p*-quinones) to cyclic dienes (*e.g.* cyclopentadienes).

The '*endo* preference' of substituents varies, and can be selectively and dramatically increased by coordination with a Lewis acid (Section 4.1.4.1). Medium effects also help to improve the *endo*/*exo* product ratio (Section 4.1.4.2). This becomes an essential selectivity issue when the individual *endo* preferences of substituents are opposed, as in transition states (E) and (F).

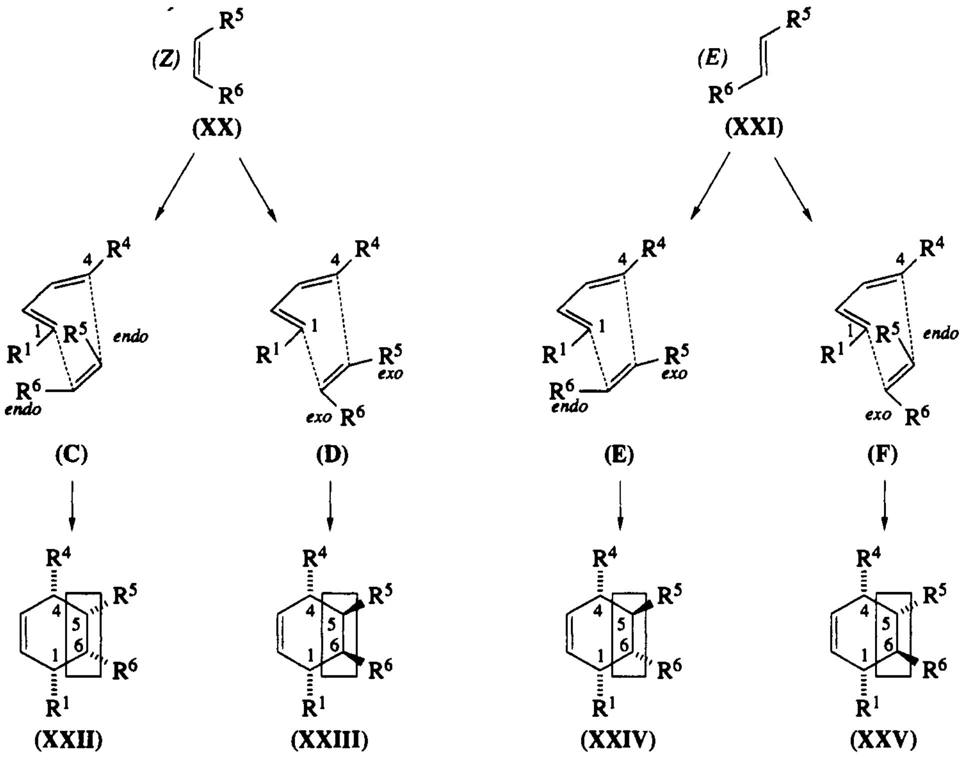
(Z)
R5
R6
(XX)
(E)
R5
R6
(XXI)
4 R4
1 R1
R5 endo
R6 endo
(C)
R5 exo
exo R6
(D)
R6 endo
R5 exo
(E)
R5 endo
exo R6
(F)
R4
4
5
6
1
R5
R6
R1
(XXII)
(XXIII)
(XXIV)
(XXV)

Scheme 4

Finally, the most recently addressed stereochemical issue is that of π-facial control (Scheme 5). In the previous discussion, absolute configurations were depicted arbitrarily to describe relative configurations. Hence, in the absence of a π-facial control element, [4 + 2] cycloaddition of a dienophile occurs at the same rate to the top and bottom faces of a diene (*cf.* situation G) to give a 50:50 mixture of enantiomers (XXVI) and (XXVII).

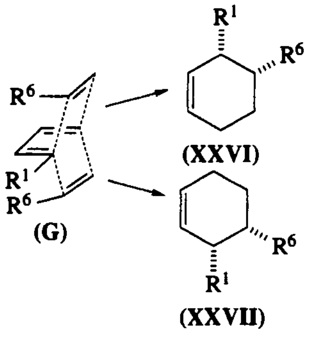
R6
R1
R6
(G)
R1
R6
(XXVI)
R6
R1
(XXVII)

Scheme 5

Recent years have witnessed remarkable progress in directing Diels–Alder additions with up to 99.5% selectivity to either face, thereby controlling the absolute configuration of the newly generated stereogenic centers. This chapter therefore culminates by dealing with this highly relevant topic in Sections 4.1.5 and 4.1.6.

No doubt the Diels–Alder reaction will lend itself to further extensions of scope and selectivity. Nevertheless, the current 'state of the art' and the pivotal applications of Diels–Alder adducts (**XXX**) for the efficient chemo-, regio- and stereo-selective syntheses of complex structures, *e.g. via* annulation processes (a, b) and/or cleavage reactions (c, d, e) speak for themselves (Scheme 6). An adequate treatise would vastly exceed the limits of this chapter.

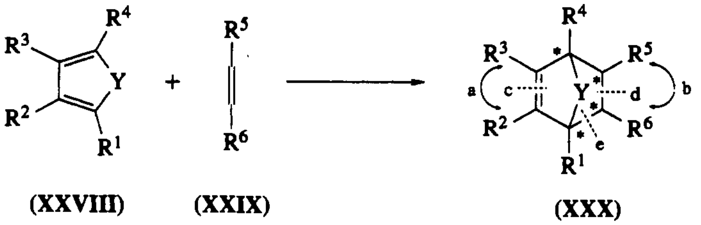

Scheme 6

## 4.1.2 HETEROATOM-SUBSTITUTED DIENOPHILES

Dienophiles substituted with appropriate heteroatoms may offer a number of advantages such as: (1) provide dienophilic equivalents of C═C and C≡C moieties which do not undergo [4 + 2] cycloadditions to 1,3-dienes because of low (*e.g.* isolated alkenes, alkynes, allenes) or different reactivities (*e.g.* ketenes); (2) enhance or invert the regiochemistry of the Diels–Alder process; (3) permit facile removal of the activating and/or regiocontrolling group after cycloaddition with or without introduction of further functionalities. The use of nitroalkenes as dienophiles demonstrates these issues most strikingly.

### 4.1.2.1 Nitroalkenes

Nitroethylene undergoes rapid cycloaddition to 1,3-dienes; subsequent conversion of the nitro to a carbonyl group, *e.g.* (**1**) → (**2**) → (**3**), exemplifies its application as a dienophilic ketene equivalent (Scheme 7).[5]

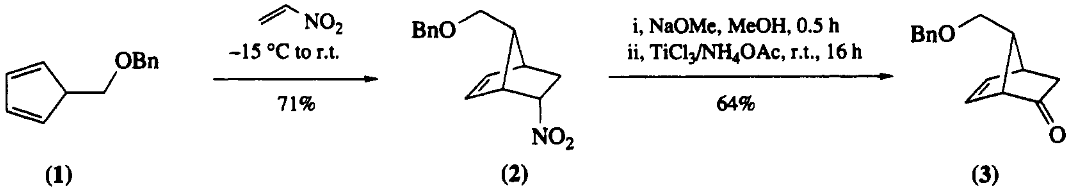

Scheme 7

Furthermore, a pronounced regiochemical control has been recognized with nitroalkenes. For example, (*E*)-methyl β-nitroacrylate (**5**) is an outstanding dienophile. Its cycloadditions to 1,3-dienes display a high regioselectivity dominated by the nitro group, as illustrated by the synthesis of the cyclohexadiene-amino acid (**8**).[6] This involves Diels–Alder reaction with 1-(*N*-acylamino)-1,3-diene (**4**) followed by removal of the nitro group from cycloadduct (**6**) *via* DBU-induced elimination of nitrous acid, (**6**) → (**7**) (Scheme 8). A similar cycloaddition/desilylation/elimination sequence, starting from 2-(trimethylsilyloxy)l-1,3-butadiene, afforded the unusual cyclohexenone (**10**).[7]

The capacity of the nitro substituent to override the directing influence of the carbonyl group, providing 1,4-cyclohexadiene products with unconventional substitution patterns, is further demonstrated in Scheme 9. The [4 + 2] cycloaddition of diene (**11**) to ethyl propiolate (**11** → **12** + **13**) or, alternatively, to ethyl β-nitroacrylate (**11** → **15**) clearly reveals that these two dienophiles are regiochemical counterparts.[8]

Scheme 10 illustrates an analogous regioselective Diels–Alder reaction with 3-nitrocyclohexenone (**17**) serving as a 'cycloalkynone' dienophile equivalent.[9]

Nitroalkenes can also be regarded as dienophilic alkene equivalents owing to the recently reported substitution of the nitro group by a hydrogen atom. Thus treatment of the cycloadducts with $Bu_3SnH$ in the presence of AIBN opens a new regioselective (but stereo-random) access to cyclohexenes (Scheme 11).[10]

β-Sulfonylnitroalkenes or β-sulfinylnitroethylene are excellent dienophiles and correspond to alkyne or nitroalkyne equivalents (Scheme 12).[11] Bisactivated dienophile (**26**) reacts with 1,3-dienes in a highly regioselective manner to give, on subsequent reductive elimination of the nitro and sulfonyl groups, cyclohexadienes, *e.g.* (**16**) + (**26**) → (**27**) → (**28**). β-Sulfinylnitroethylene (**30**) offers a regioselective

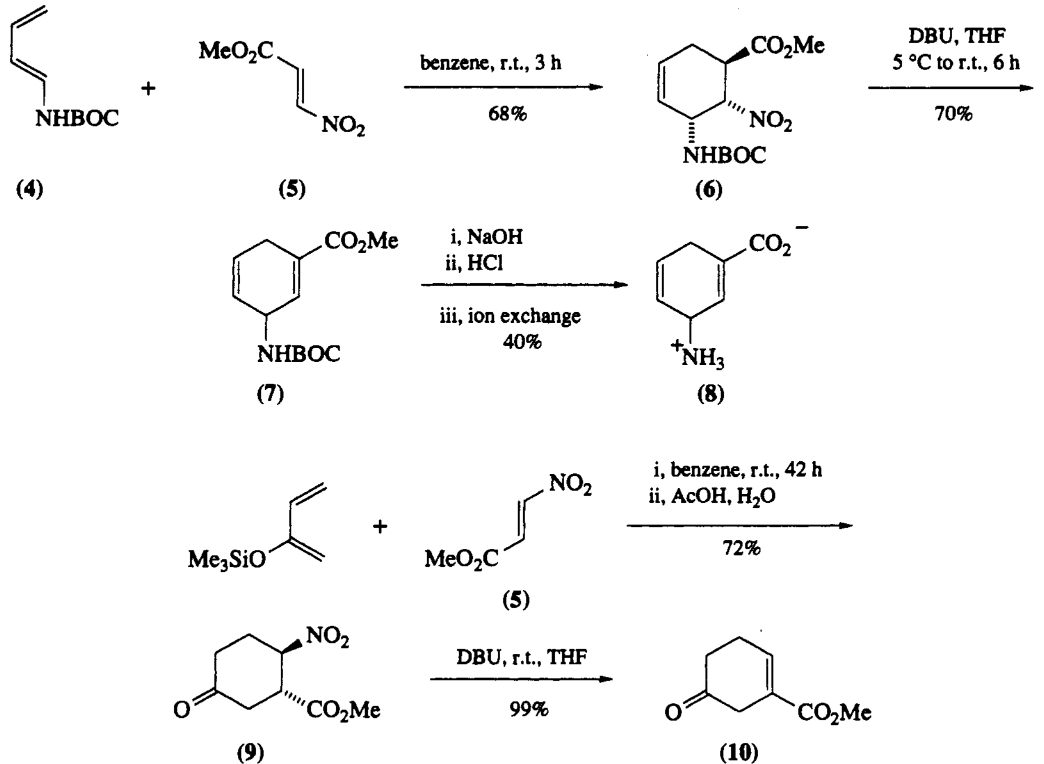
NHBOC
(4)
+
$MeO_2C$
$NO_2$
(5)
benzene, r.t., 3 h
68%
$CO_2Me$
$NO_2$
NHBOC
(6)
DBU, THF
5 °C to r.t., 6 h
70%
$CO_2Me$
NHBOC
(7)
i, NaOH
ii, HCl
iii, ion exchange
40%
$CO_2^-$
$^+NH_3$
(8)
$Me_3SiO$
+
$NO_2$
$MeO_2C$
(5)
i, benzene, r.t., 42 h
ii, AcOH, $H_2O$
72%
$NO_2$
O
$CO_2Me$
(9)
DBU, r.t., THF
99%
O
$CO_2Me$
(10)

**Scheme 8**

approach to nitrobenzenes, as illustrated by its addition to diene (**29**) followed by the $SiO_2$-promoted hydrolysis/sulfenic acid elimination yielding pure *p*-nitrophenol (**32**; 51%).

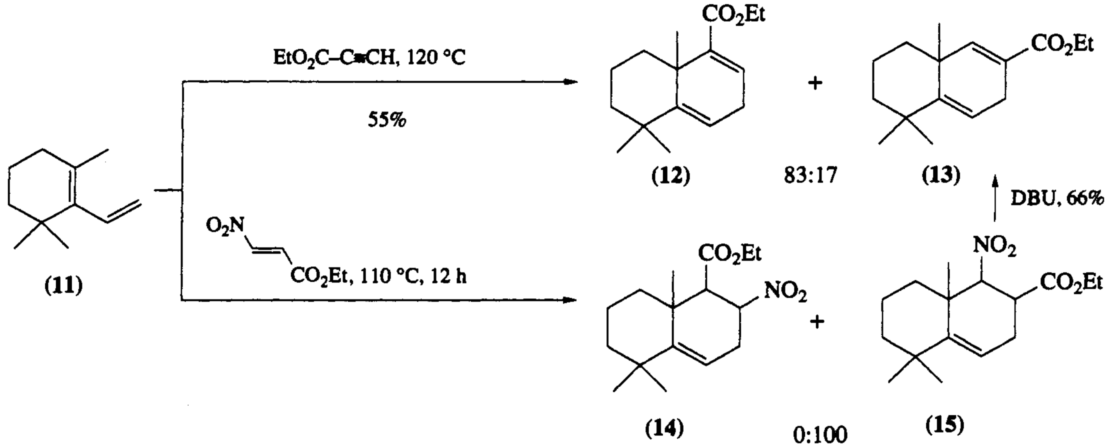
$EtO_2C-C≡CH$, 120 °C
55%
$CO_2Et$
+
$CO_2Et$
(12)
83:17
(13)
DBU, 66%
(11)
$O_2N$
$CO_2Et$, 110 °C, 12 h
$CO_2Et$
$NO_2$
+
$NO_2$
$CO_2Et$
(14)
0:100
(15)

**Scheme 9**

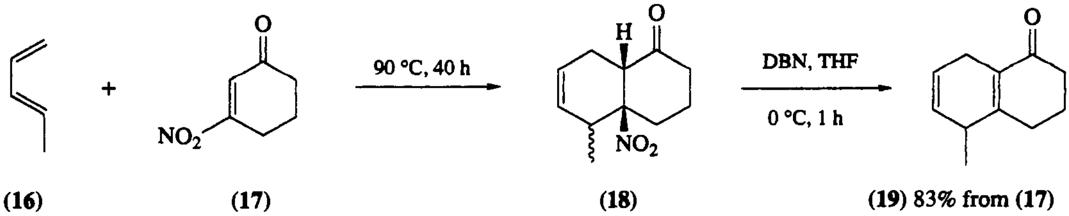
+
O
$NO_2$
90 °C, 40 h
H
O
$NO_2$
DBN, THF
0 °C, 1 h
O
(16)
(17)
(18)
(19) 83% from (17)

**Scheme 10**

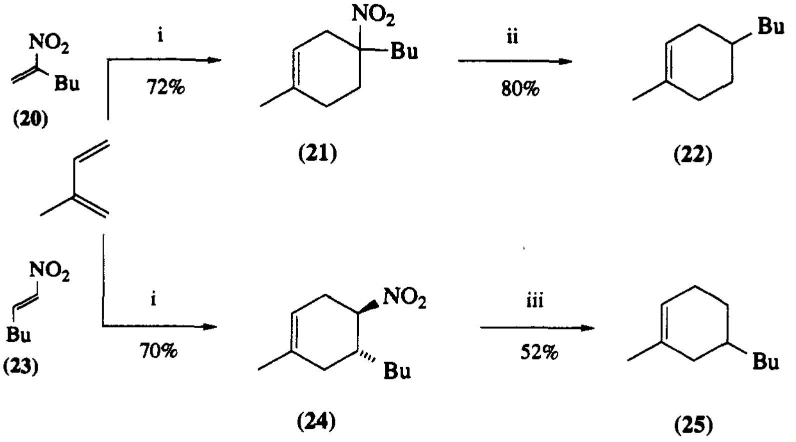

(20)
(21)
(22)
(23)
(24)
(25)
i
72%
ii
80%
i
70%
iii
52%

i, $CHCl_3$, reflux, 72 h; ii, $Bu_3SnH$ (1.2 equiv.), AIBN (0.2 equiv.), benzene, 80 °C, 2 h; iii, $Bu_3SnH$ (5 equiv.), AIBN (0.5 equiv.), toluene, 110 °C, 0.5 h

Scheme 11

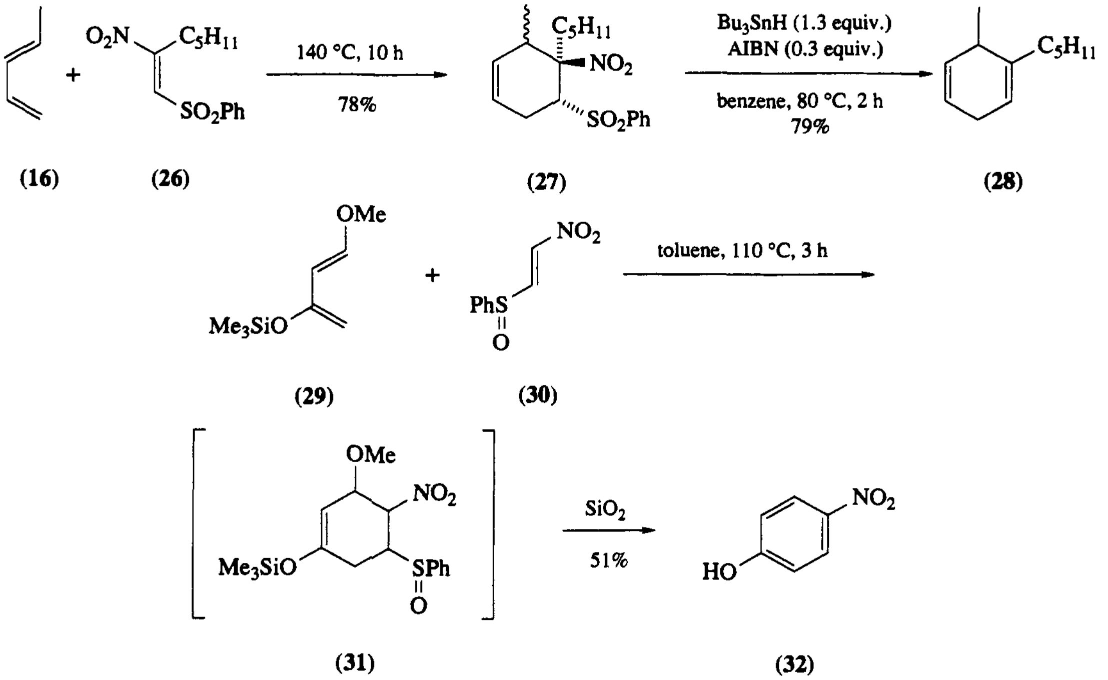

(16)
(26)
140 °C, 10 h
78%
(27)
Bu3SnH (1.3 equiv.)
AIBN (0.3 equiv.)
benzene, 80 °C, 2 h
79%
(28)
(29)
(30)
toluene, 110 °C, 3 h
(31)
SiO2
51%
(32)

Scheme 12

### 4.1.2.2 Enamines and Enamides

Lowering the oxidation state of the nitrogen substituent has a dramatic effect on its electronic properties. In marked contrast to nitroalkenes, enamines are electron-rich reagents and thus undergo 'inverse-electron-demand' Diels–Alder reactions with the electron-poor β-vinylacrylic esters. Acidic work-up gave 1,3-cyclohexadienecarboxylates as illustrated by the cycloaddition/elimination sequence (**33**) + (**34**) → (**35**) → (**36**) (Scheme 13).[12] Under analogous reaction conditions, including a Pd-catalyzed dehydrogenation step, the heterocyclic enamine (**37**) was transformed into (**38**; 87%), which represents an interesting route to tetrahydroisoquinolines.[13]

Diels–Alder addition of the endocyclic enamine (**40**) to the moderately electron-deficient (±)-1,3-dienyl sulfoxide (**39**) proceeded smoothly without loss of the nitrogen atom. Subsequent 2,3-sigmatropic

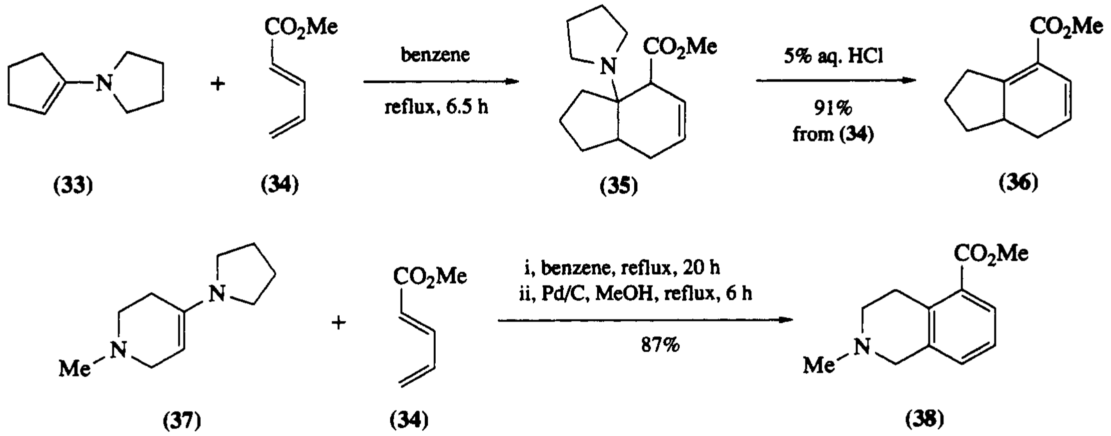
CO2Me
benzene
reflux, 6.5 h
CO2Me
5% aq. HCl
91%
from (34)
CO2Me
(33)
(34)
(35)
(36)
CO2Me
i, benzene, reflux, 20 h
ii, Pd/C, MeOH, reflux, 6 h
87%
CO2Me
Me
N
Me
N
(37)
(34)
(38)

Scheme 13

rearrangement of the allyl sulfoxide (**41** → **42**) offered an elegant synthetic entry into derivatives of the hasubanan alkaloid family (Scheme 14).[14]

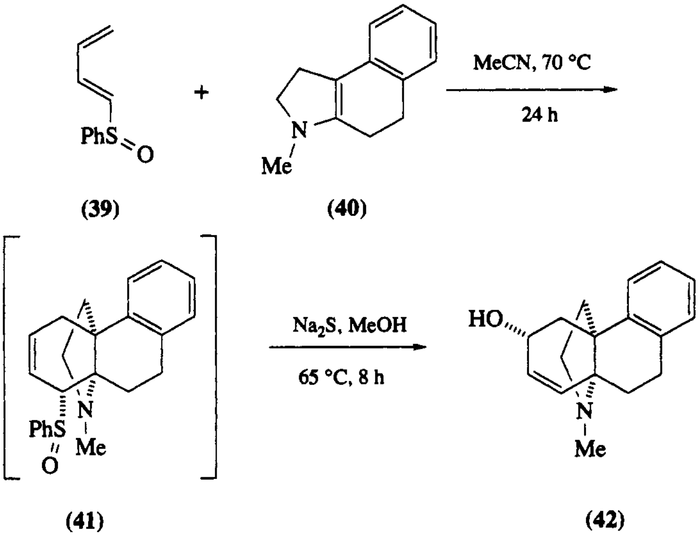
PhS
O
N
Me
MeCN, 70 °C
24 h
(39)
(40)
PhS
O
N
Me
Na2S, MeOH
65 °C, 8 h
HO
N
Me
(41)
(42)

Scheme 14

More recently, dioxopyrrolines have been introduced as 'classical', electron-deficient dienophiles. For example, the addition of (*in situ* prepared) 3-aryldioxopyrroline (**43**) to butadiene afforded the hexahydroindole (**44**), a key precursor in a synthesis of Amaryllidaceae alkaloids (Scheme 15).[15] Similarly, highly regioselective [4 + 2] cycloaddition of isoquinolinodioxopyrroline (**46**) to 1,3-bis(trimethylsilyloxy)butadiene (**45**) afforded the tetracyclic adduct (**47**) with excellent control over the relative configuration of two quaternary and one tertiary stereogenic centers. Cycloadduct (**47**) served as a pivotal intermediate in erythrina alkaloid synthesis.[16]

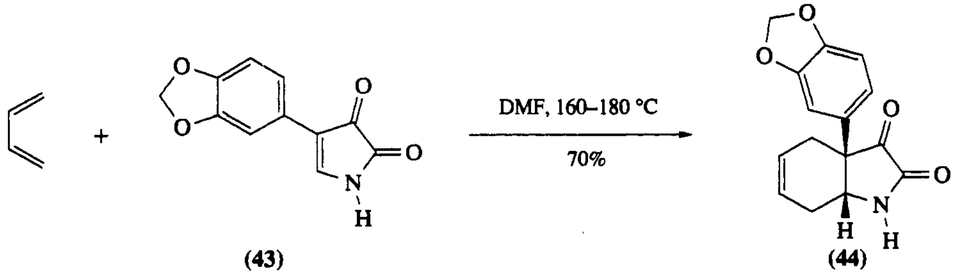
O
O
O
O
N
H
DMF, 160–180 °C
70%
O
O
O
O
N
H
H
(43)
(44)

Scheme 15

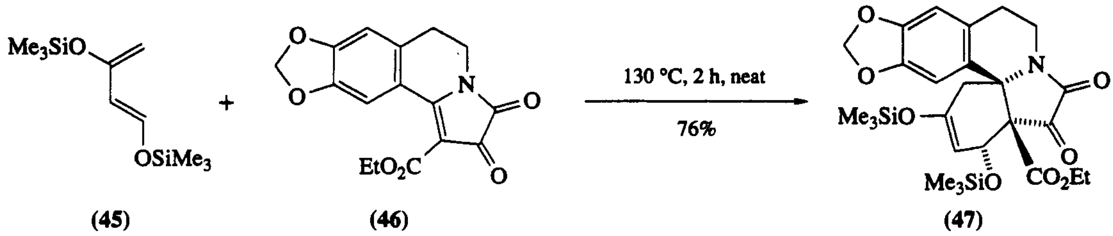

**Scheme 15** ***(continued)***

### 4.1.2.3 Alkenyl Sulfur Derivatives

The role of sulfur functionalities in activating alkenic and alkynic dienophiles, and directing their cycloadditions to 1,3-dienes, has been recently reviewed[17] and only some essential points are outlined here. Depending on the oxidation state of sulfur, its vinyl derivatives range from strongly or weakly electron-deficient (sulfones or sulfoxides) to electron-rich (sulfides) dienophiles.

Vinyl sulfones are the most versatile and widely used sulfur substituted dienophiles. They may serve as both activated ethylene and terminal alkene equivalents in highly regioselective Diels–Alder additions to 'classical', *i.e.* electron-rich, 1,3-dienes. The sulfonyl moiety facilitates the introduction of further functionality into the cycloadducts and can be easily removed by mild reduction (Scheme 16).[18a] These features have been exploited in a synthesis of the terpenoid zingiberenol (**56**) (Scheme 17).[18b]

The 'temporary' functionalization of cyclic or acyclic alkenes with a phenylsulfonyl group, followed by [4 + 2] cycloadditions of 1,3-bis-oxygenated dienes, opens a regiocontrolled route to annulated or 5-substituted cyclohexenones (Scheme 18).[18b,19]

Methyl α-bromovinyl sulfone (**64**) corresponds to an activated allene equivalent when subjected to a Diels–Alder/Ramberg–Bäcklund reaction sequence providing, for example, *exo*-methylenenorbornene (**66**) (Scheme 19).[18b,20]

Tolylsulfonylacetylene (**68**) has found use as a dienophilic substitute for acetylene, as exemplified by the synthesis of the structurally unique hydrocarbon [4]-peristylane (**71**) (Scheme 20).[21]

Vinyl sulfoxides mostly require a second electron-withdrawing group to increase their dienophilic character. Thus vinyl sulfoxides bearing a carbonyl moiety at $C_\beta$ undergo 'carbonyl-directed' diene addition followed by a spontaneous elimination of sulfenic acid, as applied to a synthesis of disodium prephenate (**74**) (Scheme 21).[22]

The chirality at sulfur also confers to (*Z*)-β-carbonylmenthoxy vinyl sulfoxides a useful topological bias which will be discussed in context with asymmetric Diels–Alder reactions (Section 4.1.6.2.1 (vi)).

A $C_\alpha$-positioned sulfoxide (as well as a sulfide) group enhances significantly the dienophilicity of α,β-unsaturated carbonyl compounds in Diels–Alder reactions with 'standard' dienes. Moreover, the synergistic influence of the two functional groups secures a high regiochemical control, *e.g.* (**75**) + (**76**) → (**77**) (Scheme 22).[23]

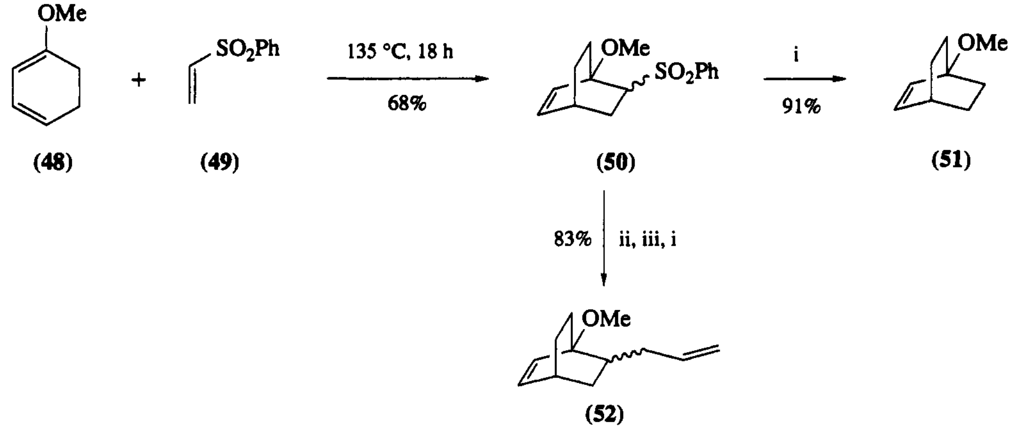

i, Na/Hg excess, $Na_2HPO_4$/MeOH, –20 °C; ii, BuLi, THF/HMPA (9:1); iii, $BrCH_2CH{=}CH_2$

**Scheme 16**

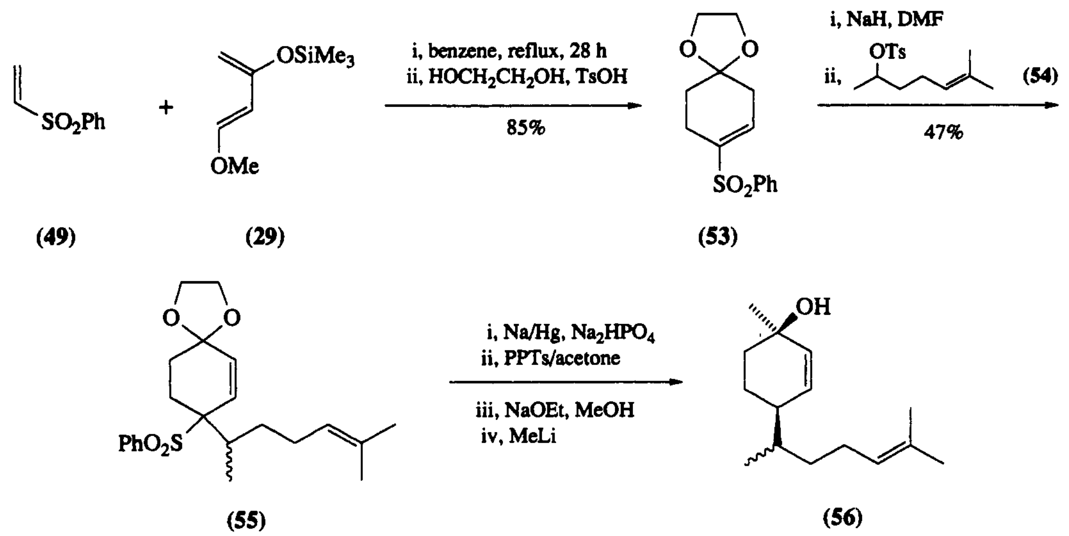
OSiMe3
SO2Ph
OMe
+
i, benzene, reflux, 28 h
ii, HOCH2CH2OH, TsOH
85%
SO2Ph
i, NaH, DMF
ii, OTs (54)
47%
(49)
(29)
(53)
PhO2S
i, Na/Hg, Na2HPO4
ii, PPTs/acetone
iii, NaOEt, MeOH
iv, MeLi
OH
(55)
(56)

**Scheme 17**

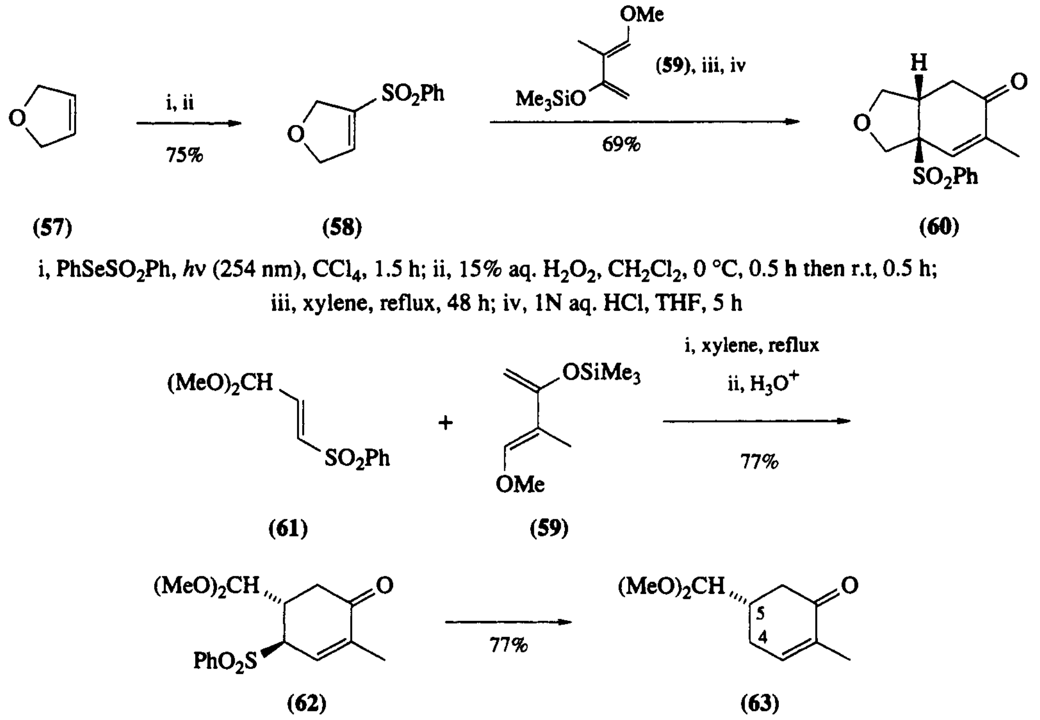
OMe
(59), iii, iv
Me3SiO
i, ii
75%
SO2Ph
69%
H
O
SO2Ph
(57)
(58)
(60)
(MeO)2CH
SO2Ph
+
OSiMe3
OMe
i, xylene, reflux
ii, H3O+
77%
(61)
(59)
(MeO)2CH
PhO2S
77%
5
4
(62)
(63)

i, PhSeSO$_2$Ph, *h*ν (254 nm), CCl$_4$, 1.5 h; ii, 15% aq. H$_2$O$_2$, CH$_2$Cl$_2$, 0 °C, 0.5 h then r.t, 0.5 h;
iii, xylene, reflux, 48 h; iv, 1N aq. HCl, THF, 5 h

**Scheme 18**

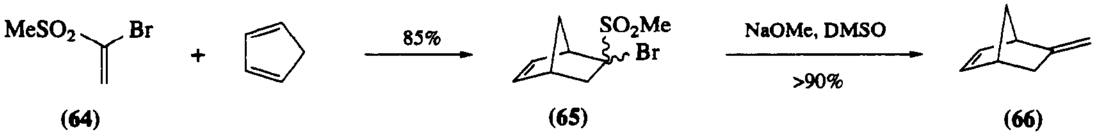
MeSO2
Br
+
85%
SO2Me
Br
NaOMe, DMSO
>90%
(64)
(65)
(66)

**Scheme 19**

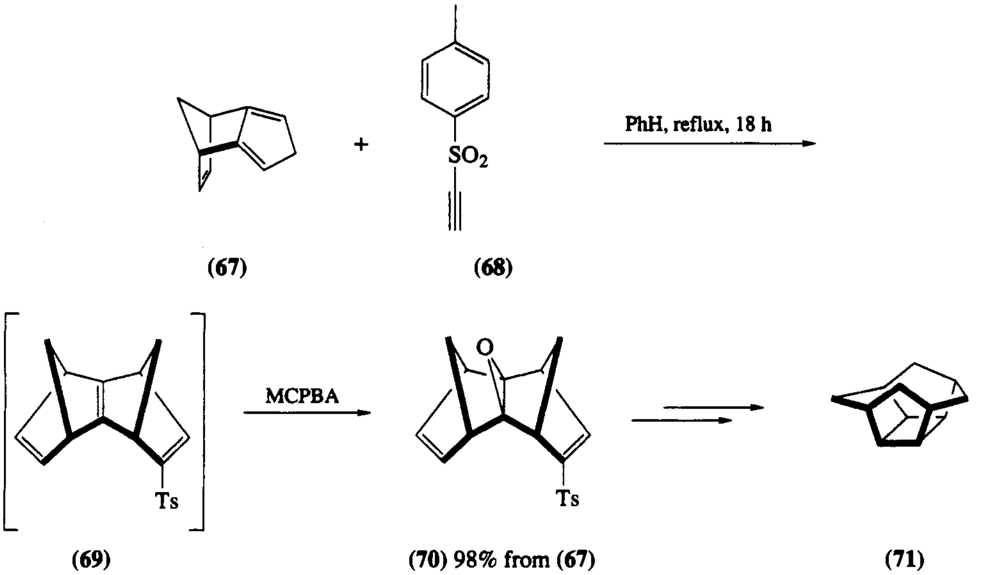
+
SO2
PhH, reflux, 18 h
(67)
(68)
MCPBA
O
Ts
Ts
(69)
(70) 98% from (67)
(71)

Scheme 20

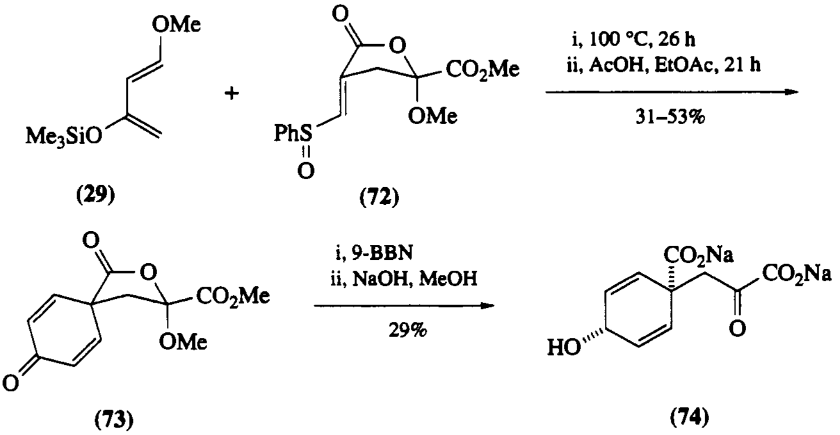
OMe
Me3SiO
+
O
O
CO2Me
OMe
PhS
O
i, 100 °C, 26 h
ii, AcOH, EtOAc, 21 h
31–53%
(29)
(72)
O
O
CO2Me
OMe
O
i, 9-BBN
ii, NaOH, MeOH
29%
CO2Na
CO2Na
O
HO
(73)
(74)

Scheme 21

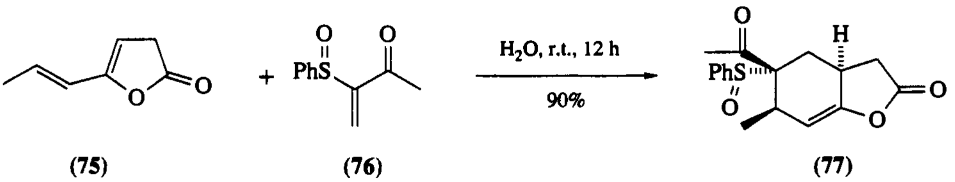
O
O
+
O
O
PhS
H2O, r.t., 12 h
90%
O
H
PhS
O
O
O
(75)
(76)
(77)

Scheme 22

As already mentioned, vinyl sulfides are electron-rich dienophiles and react, therefore, preferentially with electron-poor dienes, *i.e.* in 'inverse-electron-demand' processes such as those depicted in Scheme 23.[24,25] The auxiliary sulfur substituent may be removed at some stage after the cycloaddition, either by hydrogenolysis (*e.g.* → **81**)[24] or oxidation/sulfenic acid elimination (*e.g.* → **84**),[25] illustrating the potential of vinyl sulfides as ethylene or acetylene equivalents.

However, enones carrying a sulfide group at $C_\alpha$ react (similar to sulfoxide **76**) much more rapidly with 'classical' dienes than the corresponding $C_\alpha$-unsubstituted enones (Scheme 24).[26]

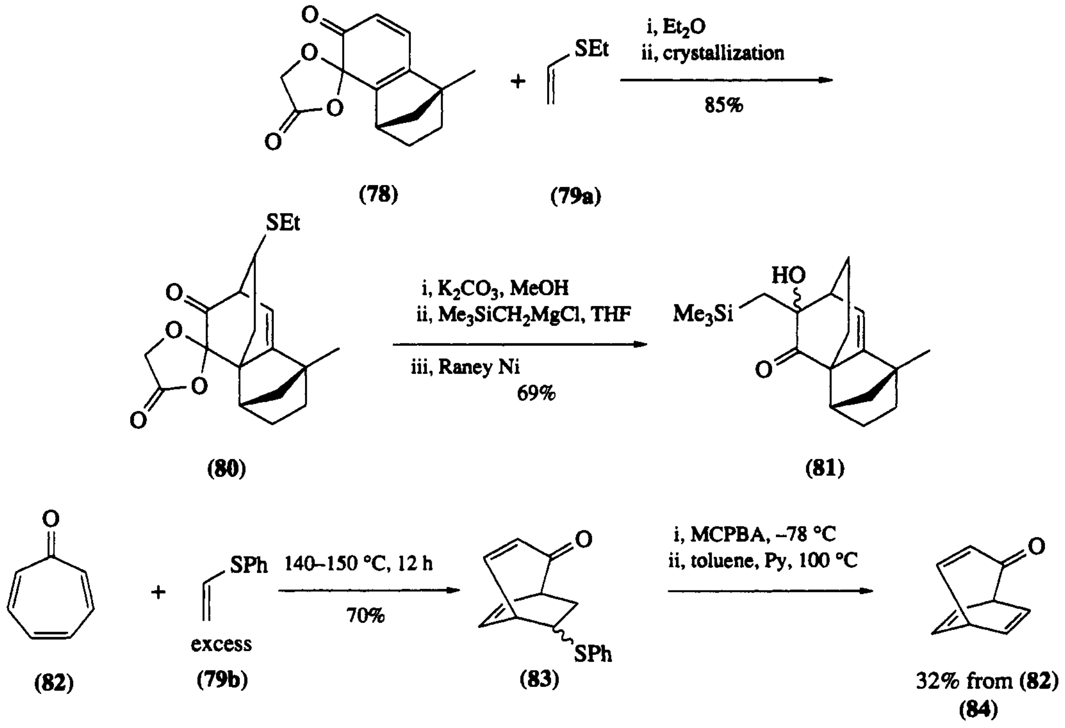
i, $Et_2O$
ii, crystallization
85%
(78)
(79a)
SEt
i, $K_2CO_3$, MeOH
ii, $Me_3SiCH_2MgCl$, THF
iii, Raney Ni
69%
HO
$Me_3Si$
(80)
(81)
SPh
140–150 °C, 12 h
70%
excess
i, MCPBA, –78 °C
ii, toluene, Py, 100 °C
SPh
(82)
(79b)
(83)
32% from (82)
(84)

**Scheme 23**

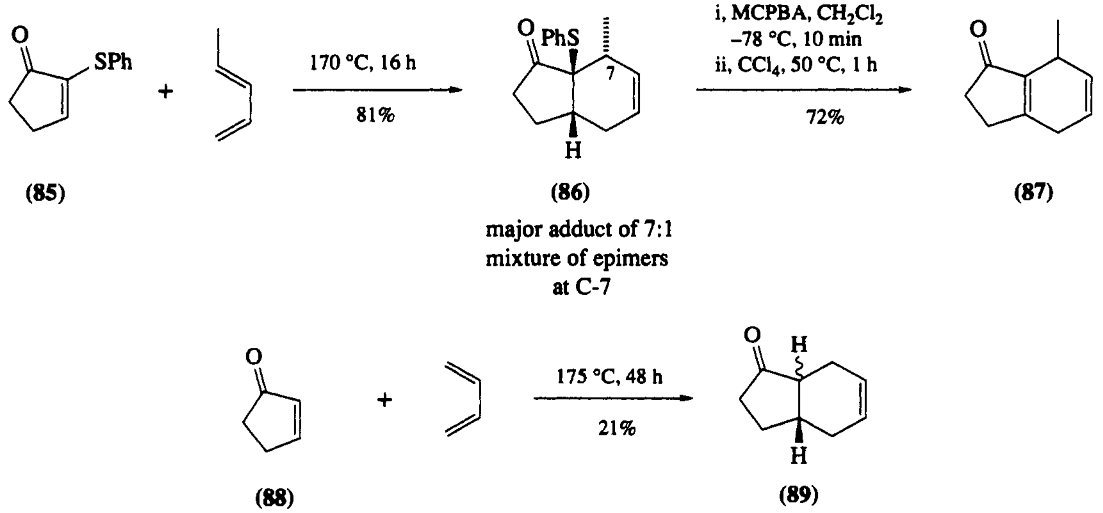
SPh
170 °C, 16 h
81%
PhS
7
H
i, MCPBA, $CH_2Cl_2$
–78 °C, 10 min
ii, $CCl_4$, 50 °C, 1 h
72%
(85)
(86)
(87)
major adduct of 7:1
mixture of epimers
at C-7
175 °C, 48 h
21%
H
H
(88)
(89)

**Scheme 24**

The regiochemical control provided by the sulfide moiety is a further asset, most strikingly exploited in the synthesis of anthracyclines (*cf.* Scheme 25).[27] The phenylthio group in cycloadduct (**92**) also prevents aromatization of the newly formed ring c, allowing its appropriate functionalization *via* enone (**93**).

### 4.1.2.4 Alkenyl Halogen Derivatives

Kishi's synthesis of aklavinone (**625**) (Section 4.1.8.4) exploits the regiodirecting bias of a bromide substituent in dienophile (**94**) (which parallels that of the phenylthio group in **90**) (Scheme 26).[28] The initially formed cycloadduct underwent spontaneous elimination of HBr (neutralized by $SrCO_3$) and oxidation (air, $Pr^i_2NEt$) to give the anthraquinone product (**97**) as the exclusive regioisomer.

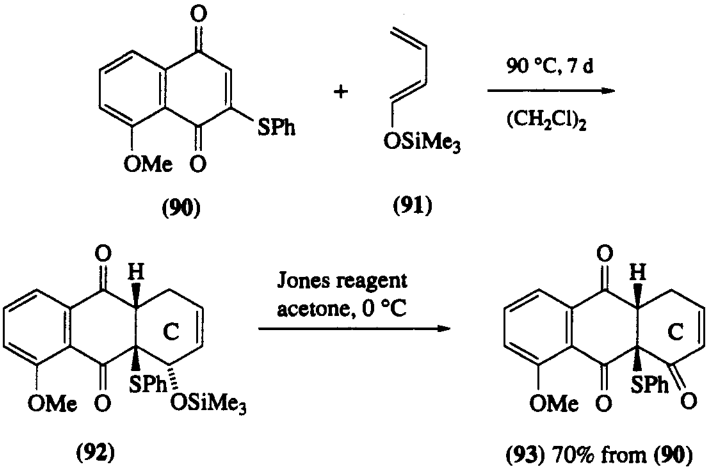
OMe
SPh
OSiMe$_3$
(90)
(91)
90 °C, 7 d
(CH$_2$Cl)$_2$
H
C
SPh
(92)
Jones reagent
acetone, 0 °C
(93) 70% from (90)

Scheme 25

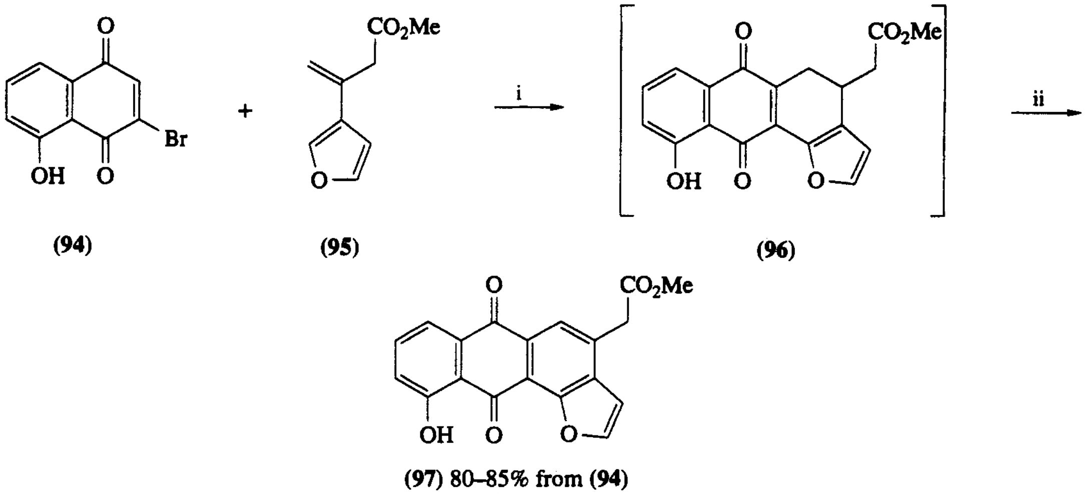
Br
OH
CO$_2$Me
(94)
(95)
i
ii
(96)
(97) 80–85% from (94)

i, (94) + (95) (3 equiv.), $C_6H_6$, $SrCO_3$, 4,4'-thiobis(6-t-butyl-3-methylphenol), reflux;
ii, air, $Pr^i_2NEt$, $CHCl_3$, r.t.

Scheme 26

### 4.1.2.5 Vinylphosphonium Salts

Vinyltriphenylphosphonium bromide (98) reacted with a number of dienes to form cyclic phosphonium salts which afford *exo*-methylene compounds *via* a subsequent Wittig reaction (Scheme 27).[29]

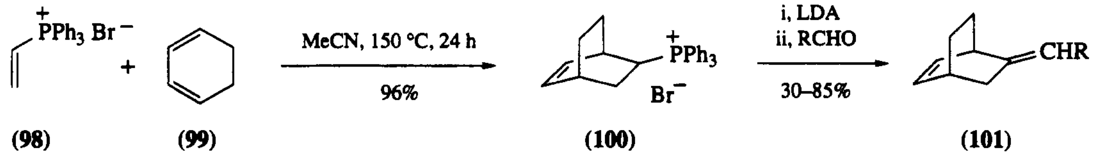
$\overset{+}{P}Ph_3$ Br$^-$
MeCN, 150 °C, 24 h
96%
$\overset{+}{P}Ph_3$
Br$^-$
i, LDA
ii, RCHO
30–85%
CHR
(98)
(99)
(100)
(101)

Scheme 27

## 4.1.3 HETEROATOM-SUBSTITUTED DIENES

The efficiency and regioselectivity of intermolecular [4 + 2] cycloadditions can be improved by placing heteroatom substituents not only on the dienophile but also on the diene partner, as already illustrated by several examples in the foregoing section. Heteroatom-substituted dienes and their use in the Diels–Alder reaction were reviewed extensively in 1981;[30] therefore discussion here will be limited to representative examples and some more recent developments.

### 4.1.3.1 Oxygen-substituted Dienes

Monoalkoxy- and trimethylsilyloxy-1,3-butadienes are electron-rich dienes and have been extensively used in Diels–Alder reactions with electron-poor dienophiles, as already shown in Section 4.1.2 (Schemes 8 and 25). A very recent example is the synthesis of the labdane diterpenoid (±)-erigerol (**105**), which centers on the key step (**102**) + (**103**) → (**104**) (Scheme 28).[31] Diene (**102**) features, apart from the regiodirecting ethoxy group, a cyclopropylidene moiety and, thus, serves as an equivalent for the much less reactive 1-ethoxy-4-methyl-1,3-pentadiene. Indeed, the depicted Diels–Alder reaction proceeded efficiently under mild conditions in a highly regio- and 'C═O *endo*'-selective manner.

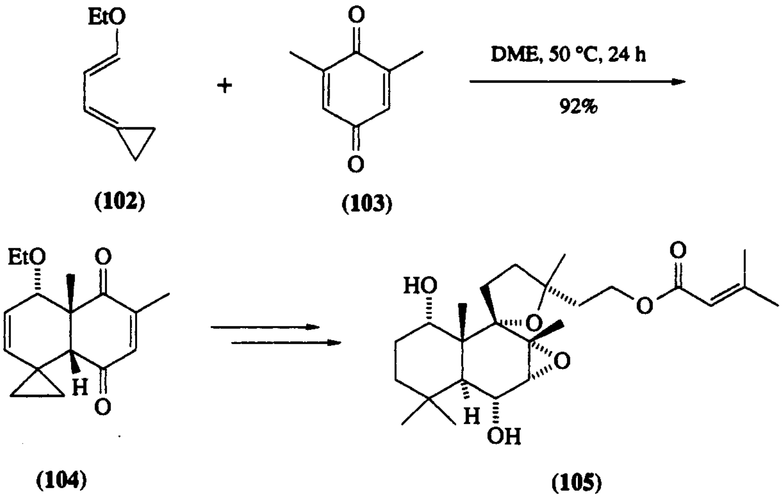

Scheme 28

[4 + 2] Cycloaddition of the endocyclic 2-silyloxydiene (**106**) to methyl vinyl ketone gave the bicyclo[2.2.2]octenes (**107**) with a silyloxy-directed regiochemistry. The major *endo* product was then transformed into the tricyclic sesquiterpene (±)-seychellene (**108**) (Scheme 29).[32]

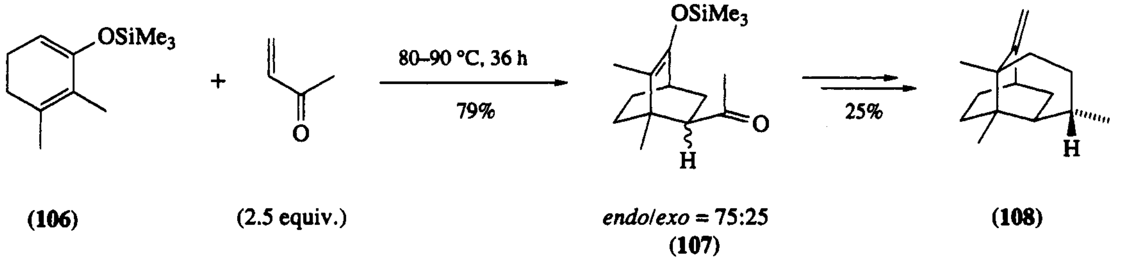

Scheme 29

One of the most popular dioxygenated dienes is 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**109**), the so-called 'Danishefsky diene' (Scheme 30). The elegant application of this and related polyoxygenated dienes in synthesis was reviewed in 1981.[30,33] [4 + 2] Cycloadditions of diene (**109**), with typical electron-poor dienophiles, display increased reactivity and regiochemical control owing to the synergism of the two oxygen atoms. Acidic hydrolysis of the initial cycloadducts readily affords cyclohexenones, phenols or cyclohexadienones (*cf.* Section 4.1.2, Schemes 12, 17, 18 and 21). A pertinent example is the addition of (**109**) to the relatively unreactive dienophile (**110**) to yield the angularly substituted cyclohexenone (**112**), an intermediate for a synthesis of vernolepin.[34] The related 1,1-dimethoxy-3-trimethylsilyloxybutadiene (**113**) reacts readily with alkynic dienophiles to give, after treatment with aqueous acid, polysubstituted phenols. This highly regioselective type of transformation was applied to a synthesis of the macrolide lasiodiplodin (**116**).[35]

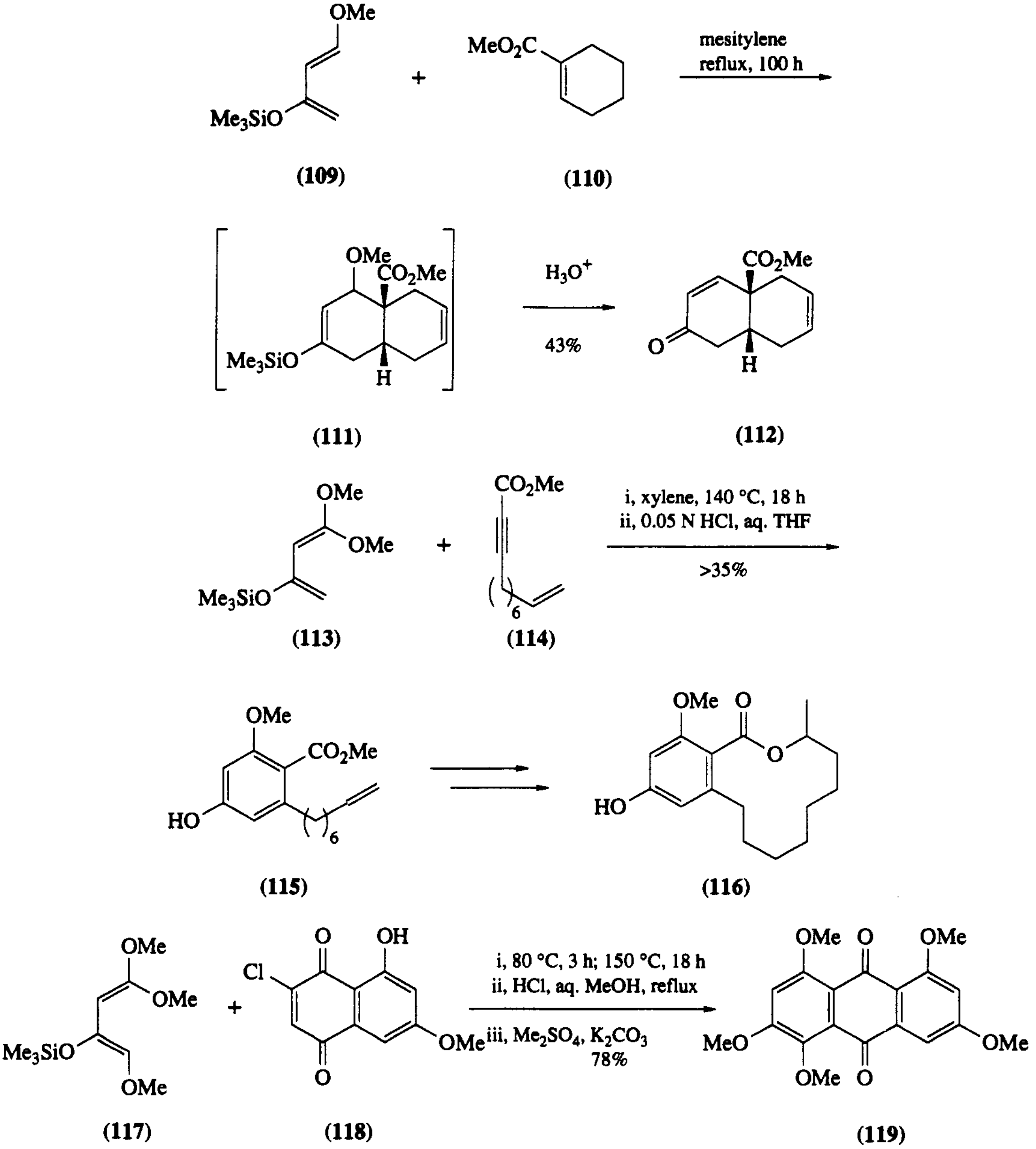
OMe
Me3SiO
+
MeO2C
mesitylene
reflux, 100 h
(109)
(110)
OMe
CO2Me
Me3SiO
H
H3O+
43%
CO2Me
O
H
(111)
(112)
OMe
OMe
Me3SiO
+
CO2Me
6
i, xylene, 140 °C, 18 h
ii, 0.05 N HCl, aq. THF
>35%
(113)
(114)
OMe
CO2Me
HO
6
OMe O
O
HO
(115)
(116)
OMe
OMe
Me3SiO
OMe
+
O
OH
Cl
OMe
O
i, 80 °C, 3 h; 150 °C, 18 h
ii, HCl, aq. MeOH, reflux
iii, Me2SO4, K2CO3
78%
OMe O OMe
MeO
OMe
OMe O
(117)
(118)
(119)

**Scheme 30**

Even the tetrasubstituted diene (**117**) underwent smooth cycloaddition to *p*-quinones, thereby opening a convenient route to polyoxygenated anthraquinone pigments, *e.g.* (**117**) + (**118**) → (**119**).[36]

Diels–Alder reactions of furans were the subject of a recent review (1986).[37] Their intermolecular versions profit notably from high-pressure conditions (Section 4.1.4.2.1) or the use of benzynes as dienophiles (Section 4.1.7).

Another type of oxacyclic diene are the pyrones, *e.g.* (**120**),[38] which react with typical dienophiles at temperatures ranging from 80 to 205 °C with spontaneous loss of carbon dioxide (Scheme 31).

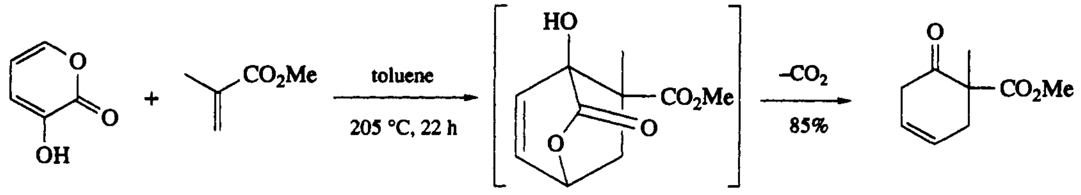

**(120)** **(121)** **(122)** **(123)**

**Scheme 31**

### 4.1.3.2 Nitrogen-substituted Dienes

Acyclic dienamines are relatively unstable, but very reactive towards electron-poor dienophiles as described in a review article (1984).[39] A more recent example shows the preparation of sterically encumbered 1-amino-1,3-diene (**125**) and its, nevertheless, efficient and highly stereoselective [4 + 2] cycloaddition to dimethyl fumarate (Scheme 32).[40] Elimination of pyrrolidine, by heating the non-isolated cycloadduct with acetic anhydride, afforded hexahydronaphthalene (**126**), a key intermediate for a synthesis of drimane-type sesquiterpenes.

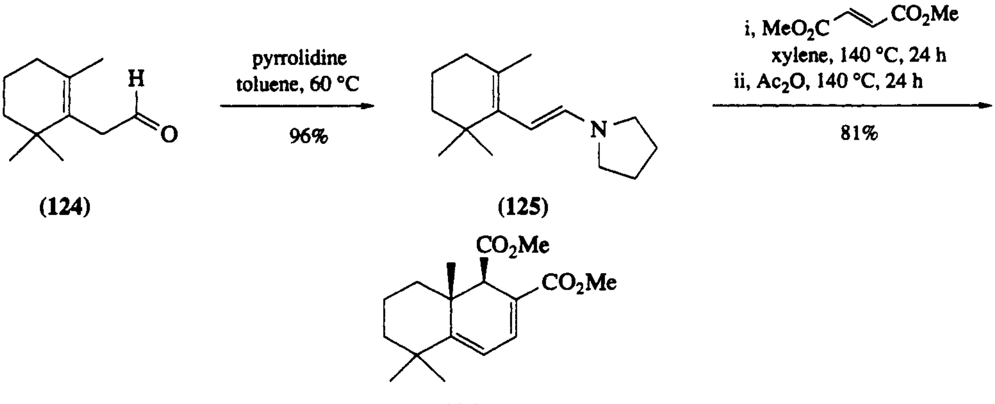

**(124)** **(125)** **(126)**

**Scheme 32**

2-Dialkylamino-1,3-dienes are even less stable, but may react at low temperature, *e.g.* with nitroalkenes. The exclusive formation of one regio- and stereo-isomer, (**127**) + (**128**) → (**129**), resulting from *endo* orientation of the nitro group, is exemplified in Scheme 33.[41]

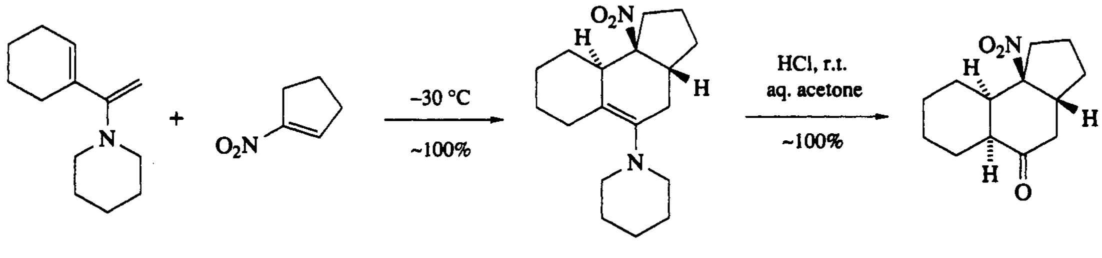

**(127)** **(128)** **(129)** **(130)**

**Scheme 33**

*N*-Acylaminodienes are more stable than the corresponding dienamines and are easily accessible in one synthetic operation from conjugated enals, (**131**) → (**132**) → (**133**),[42] or alternatively from dienoic acids, (**134**) → (**135**) (Scheme 34).[43]

Dienamides (**133**) readily undergo intermolecular [4 + 2] cycloadditions, as exemplified by the highly *endo*-selective reaction of (**136**) with maleic anhydride giving (**137**) (Scheme 35).[42b] However, the main advantage of the simple diene preparation (**131**) → (**133**) is the facile 'introduction' of an alkenic chain,

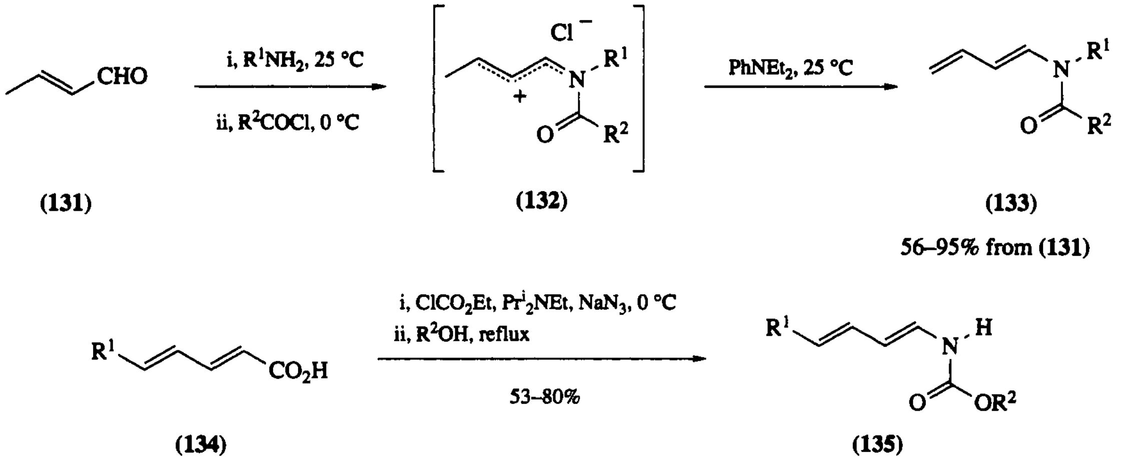
CHO
(131)
i, R1NH2, 25 °C
ii, R2COCl, 0 °C
Cl−
+
N
R1
O
R2
(132)
PhNEt2, 25 °C
N
R1
O
R2
(133)
56–95% from (131)
R1
CO2H
(134)
i, ClCO2Et, Pri2NEt, NaN3, 0 °C
ii, R2OH, reflux
53–80%
R1
N
H
O
OR2
(135)

Scheme 34

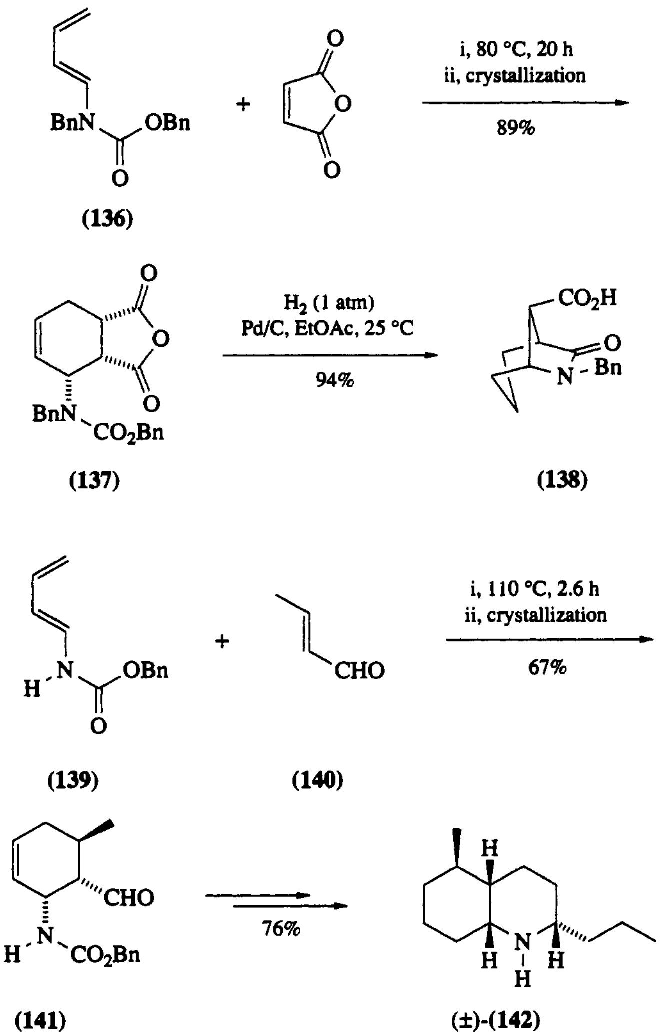
BnN
OBn
O
(136)
+
O
O
O
i, 80 °C, 20 h
ii, crystallization
89%
O
O
O
BnN
CO2Bn
(137)
H2 (1 atm)
Pd/C, EtOAc, 25 °C
94%
CO2H
O
N - Bn
(138)
H
N
OBn
O
(139)
+
CHO
(140)
i, 110 °C, 2.6 h
ii, crystallization
67%
CHO
H
N
CO2Bn
(141)
76%
H
N
H
H
H
(±)-(142)

Scheme 35

either as substituent $R^1$ or $R^2$. Hence dienamides (**133**) are versatile precursors for intramolecular Diels–Alder reactions (Chapter 4.4), *e.g.* as applied to the stereoselective conversion of (*S*)-norvaline into enantiomerically pure (–)-pumiliotoxin C (**142**).[42c] A synthesis of the racemic alkaloid (**142**) features the regio- and 'CHO *endo*'-selective intermolecular Diels–Alder reaction (**139**) + (**140**) → (**141**).[43b] An enantioselective version of this approach is presented in Section 4.1.6.2.1(ii) (Scheme 84).

### 4.1.3.3 Sulfur-substituted Dienes

1-(Phenylthio)-1,3-butadienes undergo sulfur-directed Diels–Alder reactions to form adducts from which the sulfur moiety can be removed by reduction, or (after oxidation to the sulfoxide) by elimination or 2,3-sigmatropic rearrangement (*cf.* Section 4.1.2, Schemes 12, 14).[30]

(*Z*)-2-Methoxy-1-(phenylthio)-1,3-butadienes react with methyl vinyl ketone and with 2-cyclohexen-1-one under catalysis by magnesium bromide or ethylaluminum dichloride. This provides exclusively the 'C=O *endo*' adducts in which the regiochemistry is completely controlled by the sulfur substituent despite the juxtaposed influence of the OMe group, *e.g.* (**143**) → (**144**) (Scheme 36).[44a]

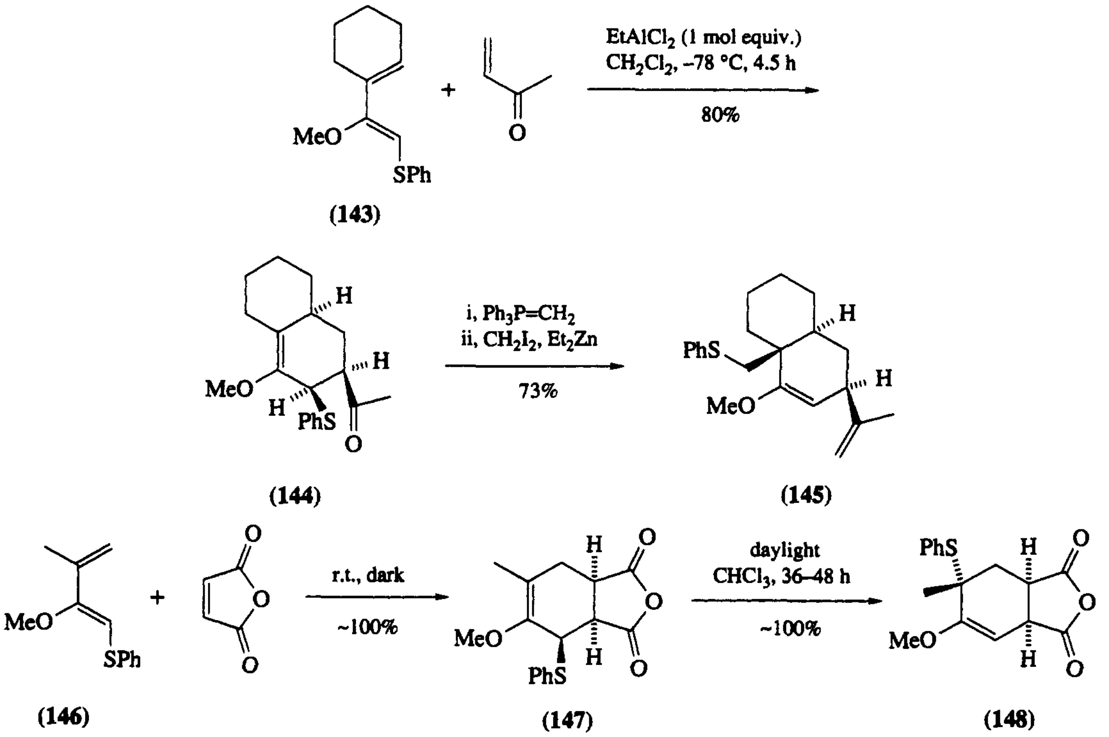

Scheme 36

The allylic position of the sulfide group in the cycloadducts may be employed for 2,3-sigmatropic reactions, as demonstrated by the alkenation/sulfur ylide rearrangement sequence (**144**) → (**145**).[44a] A noteworthy allyl rearrangement (**147**) → (**148**) was observed on exposing the related Diels–Alder adduct (**147**) to daylight; the thiophenyl group underwent a formal 'antarafacial migration' consistent with a free-radical chain mechanism.[44b]

1,3-Butadienes carrying an aryl sulfide substituent at C-2 also display a sulfur-dominated regiochemistry which overrides the influence of a C-3 positioned OMe, OAc or $SO_2Ph$ group (Scheme 37, Table 1).[45] Dienes (**151**), prepared by electrocyclic ring opening or chelotropic $SO_2$ extrusion, reacted with methyl vinyl ketone, methacrolein or methyl acrylate to give, preferentially, regioisomers (**153**). Table 1 highlights the Lewis acid reinforced regioselectivity, provided that the competing substituent (X) is a relatively weak Lewis base (*cf.* entries 4/5, 6/7).

2-(Phenylsulfonyl)-1,3-dienes, *e.g.* (**155**) and (**159**), show an interesting 'dual-electron-demand' reactivity, *i.e.* they react with both electron-deficient and electron-rich alkenes (Scheme 38).[46] Adduct (**156**) can be transformed to its elimination product (**158**) or, more interestingly, to nitrile (**157**) *via* simple treatment with KCN.

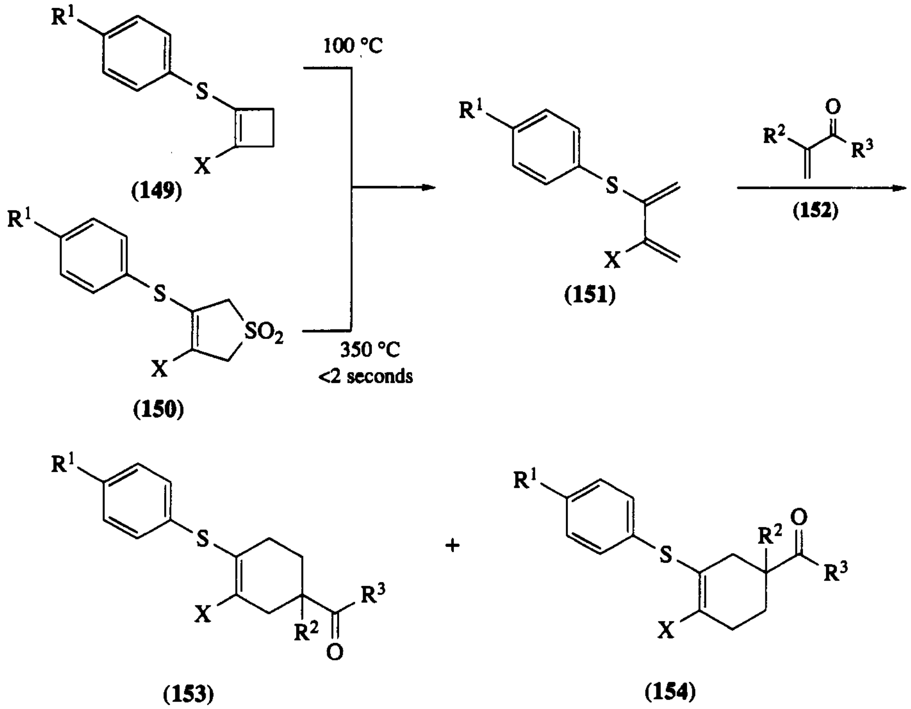
(149)
(150)
100 °C
350 °C
<2 seconds
(151)
(152)
(153)
(154)
R1
R2
R3
X
S
SO2
O

Scheme 37

Table 1 Diels–Alder Reactions of 2-Substituted 3-Arylthiobuta-1,3-dienes (Scheme 37)

| *Entry* | *Diene* $R^1$ | *Diene* $X$ | *Dienophile* $R^2$ | *Dienophile* $R^3$ | *Solvent* | *Lewis acid* | *Temp.* (°C) (*time*, h) | *Yield* (%) (**153**) + (**154**) | *Ratio* (**153**)/(**154**) |
|---|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | H | Me | Toluene | None | 110 | 97 | 91:9 |
| 2 **b** | H | OMe | Me | H | Methacrolein | None | Reflux | 72 | 89:11 |
| 3 **c** | H | OAc | Me | H | Methacrolein | None | Reflux (18) | 84 | 90:10 |
| 4 **d** | OMe | OAc | Me | H | Methacrolein | None | Reflux (17) | 82 | 93:7 |
| 5 **d** | OMe | OAc | Me | H | Methacrolein | $BF_3 \cdot OEt_2$ | r.t. (1.6) | 94 | >98:<2 |
| 6 **e** | H | $SO_2Ph$ | H | OMe | *p*-Xylene | None | 200 (8) | 98 | 75:25 |
| 7 **e** | H | $SO_2Ph$ | H | OMe | *p*-Xylene | $ZnCl_2$ | r.t. (72) | 85 | ~100:0 |

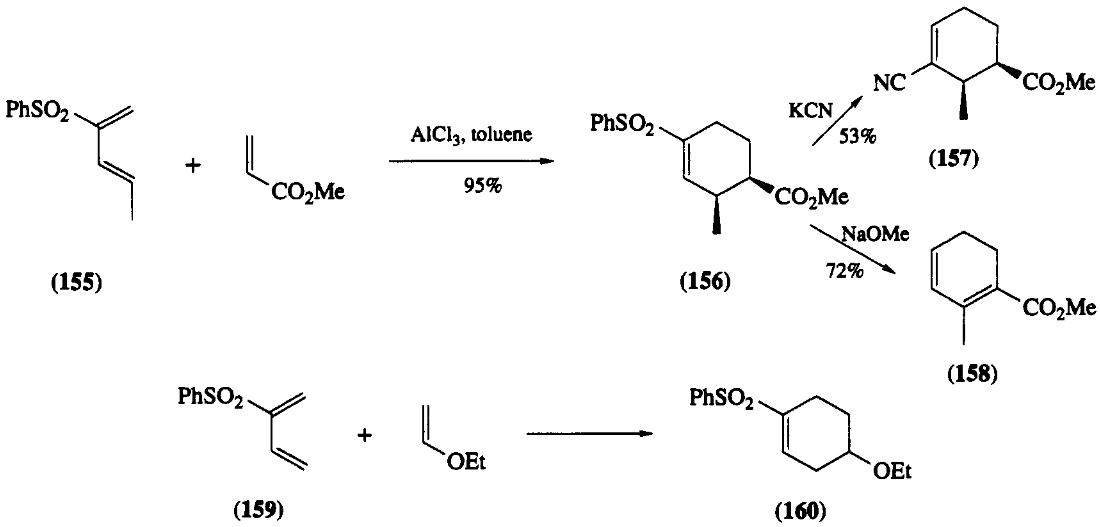
PhSO2
+
CO2Me
AlCl3, toluene
95%
(155)
PhSO2
CO2Me
(156)
KCN
53%
NC
CO2Me
(157)
NaOMe
72%
CO2Me
(158)
PhSO2
+
OEt
(159)
PhSO2
OEt
(160)

Scheme 38

### 4.1.3.4 Silicon-, Tin- and Boron-substituted Dienes

1-Silylated 1,3-butadienes, *e.g.* **(161)**, are potentially attractive reaction partners in [4 + 2] cycloadditions since the adducts are prone to various functionalizations of the allylsilane. For example, addition product **(162)** gave allylic alcohol **(163)** on hydrolysis/oxidation (Scheme 39).[47] However, addition of diene **(161)** to methyl acrylate is inefficient and largely devoid of regio- and stereo-chemical control.

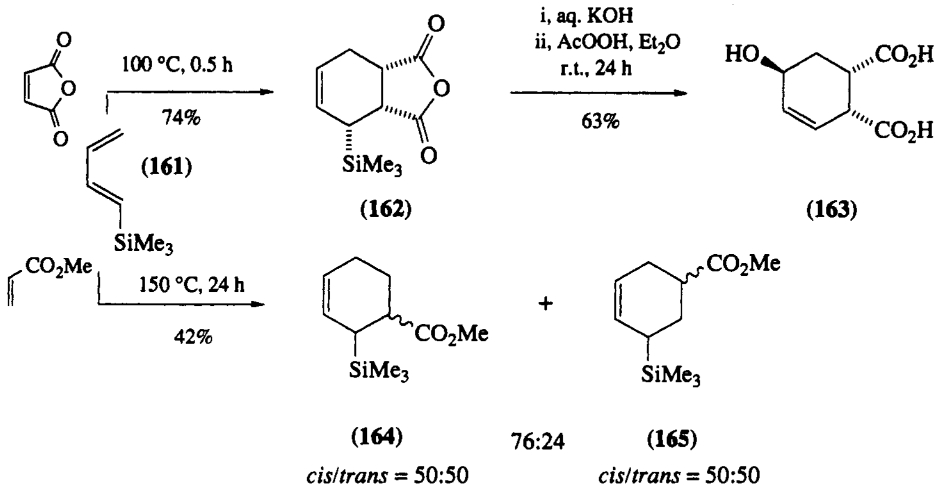
100 °C, 0.5 h
74%
(161)
SiMe₃
(162)
i, aq. KOH
ii, AcOOH, Et₂O
r.t., 24 h
63%
HO
CO₂H
CO₂H
(163)
CO₂Me
150 °C, 24 h
42%
CO₂Me
SiMe₃
+
CO₂Me
SiMe₃
(164)
76:24
(165)
cis/trans = 50:50
cis/trans = 50:50

**Scheme 39**

Nevertheless, because of its weak influence, the silyl substituent hardly interferes with more potent regiochemical control elements, as demonstrated by the acetoxy-directed Diels–Alder reaction of diene **(166)** with methyl acrylate (Scheme 40).[48] The major *endo* product **(168)** was then converted to (±)-shikimic acid **(171)**.

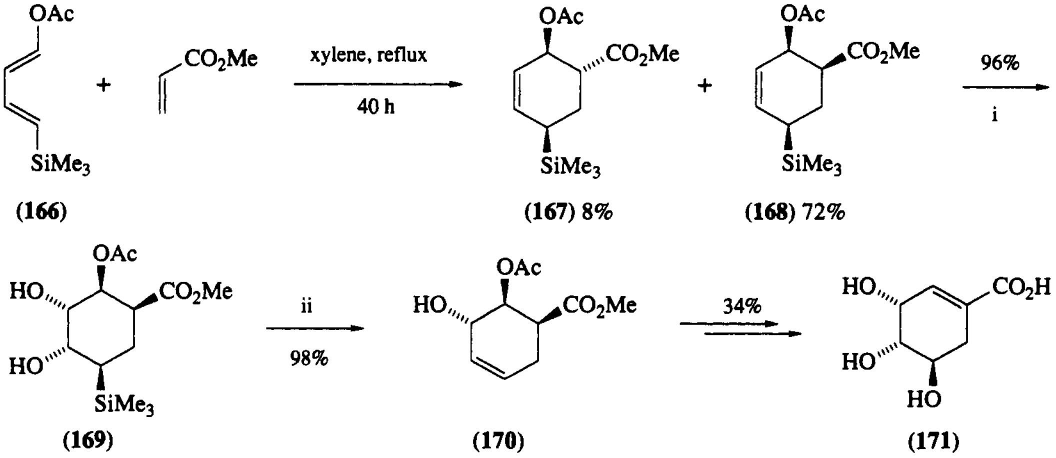
OAc
SiMe₃
(166)
+
CO₂Me
xylene, reflux
40 h
OAc
CO₂Me
SiMe₃
(167) 8%
+
OAc
CO₂Me
SiMe₃
(168) 72%
96%
i
OAc
HO
CO₂Me
HO
SiMe₃
(169)
ii
98%
OAc
HO
CO₂Me
(170)
34%
HO
CO₂H
HO
HO
(171)

i, $OsO_4$ (cat.)/*N*-methylmorpholine *N*-oxide, $Bu^tOH$, $Me_2CO$, $H_2O$;

ii, *p*-TsOH (benzene), reflux, 20 min

**Scheme 40**

[4 + 2] Cycloadditions of 2-triethylsilyl- and 2-tributylstannyl-1,3-butadienes **(172)** to ethyl acrylate and methyl vinyl ketone also proceeded with moderate regioselectivities which could be significantly enhanced by Lewis acid catalysis in favor of products **(174)** (Scheme 41, Table 2).[49] The resulting cyclohexenylstannanes (**174**; M = $SnBu_3$) show potential for C—C coupling reactions.

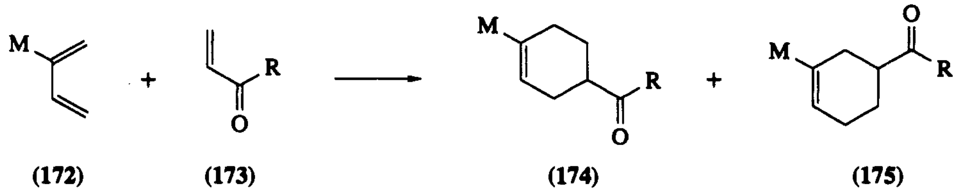
M
R
O
M
R
+
M
O
R
+
(172)
(173)
(174)
(175)

Scheme 41

**Table 2** Diels–Alder Reactions of 2-Triethylsilyl- and 2-Tributylstannyl-1,3-butadienes with Conjugated Enoyl Compounds (Scheme 41)

| *Entry* | *Diene* *M* | *Dienophile* *R* | *Solvent* | *Lewis acid*$^a$ | *Temp.* (°C) (*time*, h) | *Yield* (%) (**174**) + (**175**) | *Ratio* (**174**)/(**175**) |
|---|---|---|---|---|---|---|---|
| 1 a | $SiEt_3$ | OEt | Benzene | None | Reflux (6) | 77 | 77:23 |
| 2 a | $SiEt_3$ | OEt | Benzene | $BF_3{\cdot}Et_2O$ | b | 90 | 88:12 |
| 3 b | $SnBu_3$ | Me | Benzene | None | Reflux (12) | 50 | 75:25 |
| 4 b | $SnBu_3$ | Me | $CH_2Cl_2$/hexane | $Et_2AlCl$ | r.t. | 75 | 94:6 |
| 5 b | $SnBu_3$ | Me | $C_2H_4Cl_2$ | $Et_2BCl$ | r.t. (12) | 69 | 95:5 |
| 6 b | $SnBu_3$ | Me | $CH_2Cl_2$ | $TiCl_4$ | −78 to 0 | 31 | 98:2 |

$^a$0.1–0.3 mol equiv. of Lewis acid used. $^b$ Not reported.

1,3-Dienylboronate (**176**), easily available by hydroboration of 2-methylbut-1-en-3-yne, underwent a highly regiocontrolled, but only moderately *exo*-selective, Diels–Alder addition to methyl acrylate, yielding a mixture of *cis*/*trans* isomers (**177**) (Scheme 42).[50] The corresponding [4 + 2] cycloaddition of diene (**179**) to maleic anhydride gave only the *endo* product (**180**). Adducts (**177**) were oxidized to afford

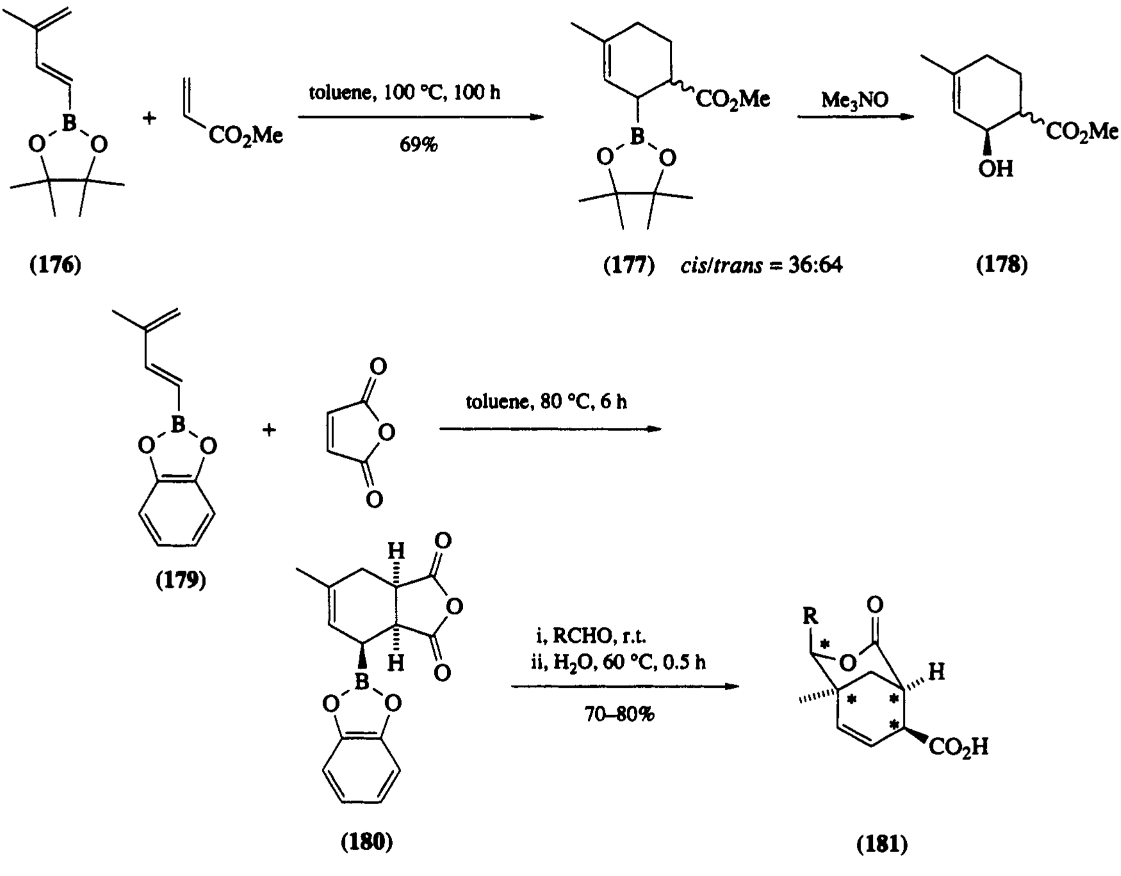
B
O
O
+
$CO_2Me$
toluene, 100 °C, 100 h
69%
$CO_2Me$
B
O
O
$Me_3NO$
$CO_2Me$
OH
(176)
(177) *cis*/*trans* = 36:64
(178)
B
O
O
+
O
O
O
toluene, 80 °C, 6 h
(179)
H
O
O
O
H
B
O
O
i, RCHO, r.t.
ii, $H_2O$, 60 °C, 0.5 h
70–80%
R
O
O
H
$CO_2H$
(180)
(181)

Scheme 42

allylic alcohols (**178**). More spectacular is the stereoselective addition of aldehydes to the allylboronate unit of adduct (**180**) followed by a lactonization. The resulting lactones (**181**) contain four stereogenic centers with perfectly controlled relative configuration.

### 4.1.3.5 2-[(Silyl-, Stannyl- and Thio-)methyl]-1,3-dienes

2-Trimethylsilylmethyl-1,3-butadiene (**182**; M = $SiMe_3$) is an excellent diene for highly regio- and stereo-selective Diels–Alder reactions with nonsymmetrical dienophiles (Scheme 43, Table 3).[51] Although the silicon atom is not directly attached to the diene system, the '*para*' selectivity of Diels–Alder reactions with methyl acrylate is more pronounced with (**182**; M = $SiMe_3$) than with isoprene (**182**; M = H) (*cf.* entries 1/3, 2/4). Stannylisoprene (**182**; M = $SnMe_3$) shows an even higher regiodirecting influence on thermal [4 + 2] cycloadditions to methyl vinyl ketone (*cf.* entries 5, 7). However, under catalysis by $AlCl_3$, virtually 100% regiochemical control was observed on Diels–Alder reactions of (**182**; M = $SiMe_3$) (entries 4, 6).

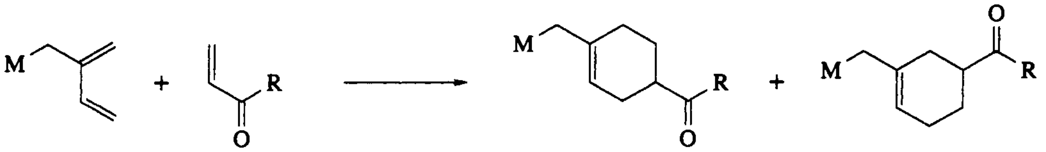

**(182)** **(173)** **(183)** **(184)**

**Scheme 43**

**Table 3** Diels–Alder Reactions of Isoprene, 2-Trimethylsilylmethyl- and 2-Trimethylstannylmethyl-1,3-butadienes with Conjugated Enoyl Compounds (Scheme 43)

| *Entry* | *Diene* *M* | *Dienophile* *R* | *Lewis acid*[a] | *Temp.* (°C) (*time*, h) | *Yield* (%) (**183**) + (**184**) | *Ratio* (**183**)/(**184**) |
|---|---|---|---|---|---|---|
| 1[b] **a** | H | OMe | None | 120 (6) | 83 | 70:30 |
| 2[b] **a** | H | OMe | $AlCl_3$ | 10–20 (3) | 50 | 95:5 |
| 3 **b** | $SiMe_3$ | OMe | None | 80 (46) | 58 | 84:16 |
| 4 **b** | $SiMe_3$ | OMe | $AlCl_3$ | 50–60 (2) | 75 | 99.5:0.5 |
| 5 **c** | $SiMe_3$ | Me | None | 80 (36) | 83 | 83:17 |
| 6 **c** | $SiMe_3$ | Me | $AlCl_3$ | 15–20 (3.5) | 64 | 100:0 |
| 7 **d** | $SnMe_3$ | Me | None | 80 (69) | 94 | 92:8 |

[a] 0.1 equiv. of $AlCl_3$ in benzene. [b] Ref. 57b.

The exclusively obtained adduct (**183c**) has been converted to monoterpenes by simple reaction sequences involving protodesilylation of the allylsilane unit either by HCl/MeOH (→ **185**) or by fluoride/DMSO (→ **186**) (Scheme 44).

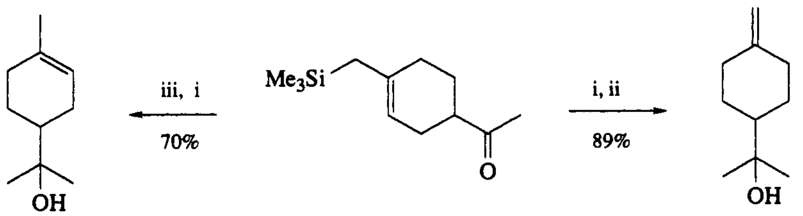

**(186)** **(183c)** **(185)**

i, MeMgBr, $Et_2O$; ii, HCl, MeOH; iii, KF, DMSO, 120 °C, 12 h

**Scheme 44**

As an extension of this work, the use of 2-(*N*-dimethylaminomethyl)-3-(trimethylsilylmethyl)-1,3-butadiene (**187**) as a '2,2′-biallyl radical' equivalent has been demonstrated (Scheme 45).[52] For example, the initial cycloadduct (**189**), obtained from 3-acetoxy-3-buten-2-one, afforded on 1,4-elimination (*cf.* Scheme 127) 1,2-dimethylenecyclohexane (**190**) which reacted with a second dienophile to give the demethoxyanthracycline precursor (**192**) (*cf.* Scheme 140).

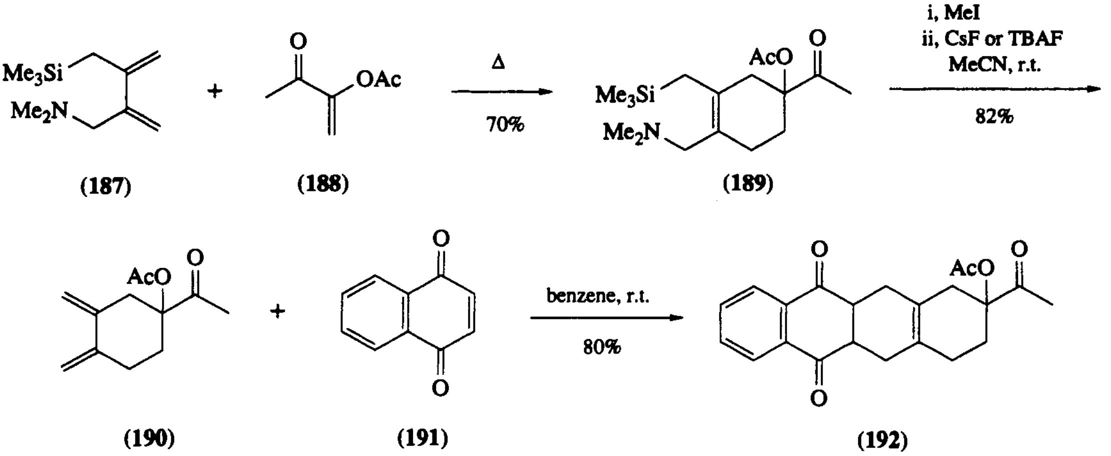

**Scheme 45**

Independently, 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene (**193**) was shown to be a similar 'conjunctive' reagent for tandem Diels–Alder reactions (Scheme 46).[53] In this case the initial cycloadducts were subjected to an oxidative bis-desilylation with NBS and the resulting 1,2-dimethylenecyclohexanes were directly submitted to the second Diels–Alder step, as demonstrated by the reaction sequence (**193**) → (**194**) → (**195**).

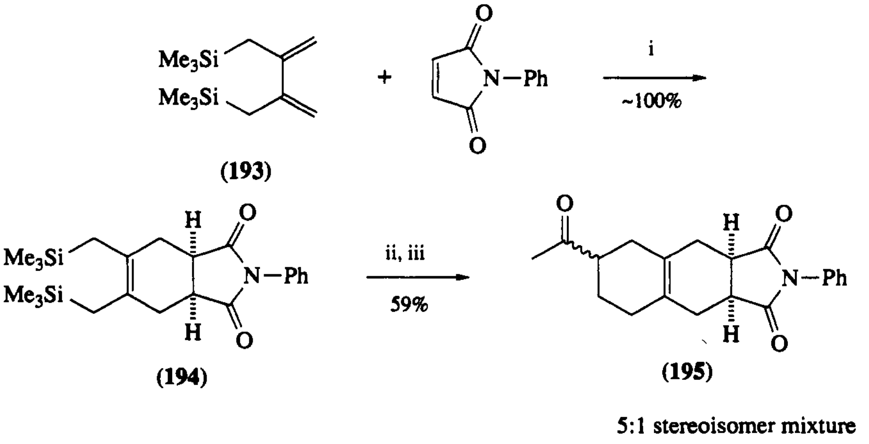

i, toluene, reflux; ii, NBS, THF, propylene oxide, −100 to −78 °C, 1 h; iii, MVK, −78 °C to r.t., 16 h

**Scheme 46**

An elegant diastereocontrolled synthesis of the sesquiterpene trichodiene (**201**) relies on a smooth regio- and stereo-selective Diels–Alder reaction of 2-[(phenylthio)methyl]-1,3-butadiene (**197**) with the α-methylenelactone (**198**), giving the '*para*' adduct (**199**) in 89% yield (Scheme 47).[54]

Analogous additions of isoprene or 2-[(trimethylsilyl)methyl]-1,3-butadiene (**182**; M = $SiMe_3$) to dienophile (**198**) resulted in 75:25 or 95:5 mixtures of '*para*' and '*meta*' adducts, respectively. Although obtained with good selectivity, the major silyl-substituted adduct furnished, on protodesilylation, an inseparable mixture of endo- and exo-cyclic alkenes. In favorable contrast, the exclusively formed adduct (**199**) allowed a quantitative reductive removal of the sulfur auxiliary without migration of the alkenic bond.

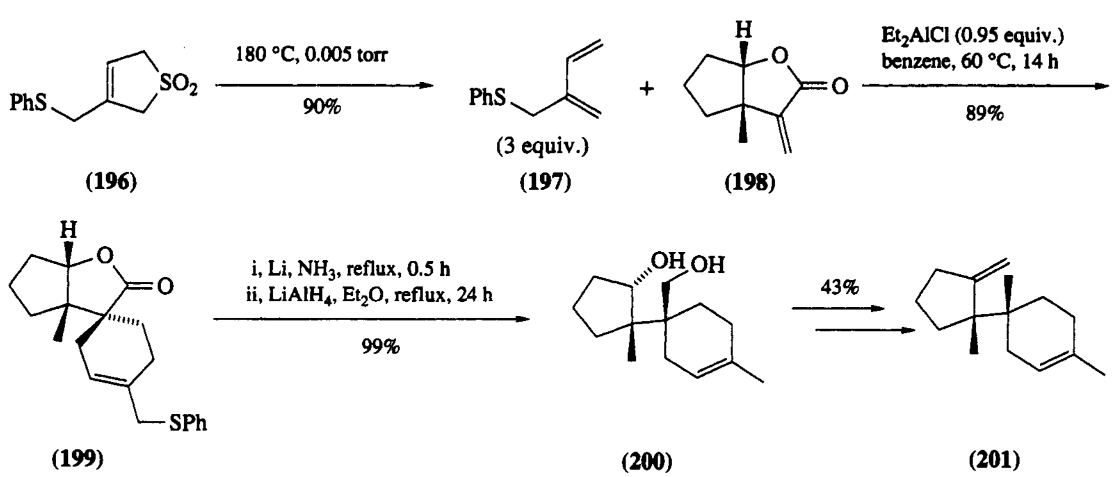

**Scheme 47**

## 4.1.4 LEWIS ACID AND MEDIUM PROMOTED DIELS–ALDER REACTIONS

### 4.1.4.1 Lewis Acids

The discovery by Yates and Eaton (1960) that $AlCl_3$ dramatically accelerates [4 + 2] cycloadditions of maleic anhydride, dimethyl fumarate and *p*-benzoquinone to anthracene[55] had a remarkable impact on the scope and selectivity of the Diels–Alder reaction. Since then, it has been found that a plethora of Lewis acids, such as $EtAlCl_2$, $Et_2AlCl$, $BF_3{\cdot}OEt_2$, $TiCl_4$, $TiCl_2(OR)_2$, $SnCl_4$, $ZnCl_2$, $MgBr_2$, *etc.*, increase not only the rate but, moreover, the regio, *endo* and π-face selectivities of this process *via* coordination with the dienophile partner (*e.g.* to a conjugated C═O or C═N moiety). The latter issue, namely the outstanding role of Lewis acids in π-facially controlled Diels–Alder reactions, will be discussed in Sections 4.1.5 and 4.1.6. The effects of Lewis acids on the rate and regiochemistry of the Diels–Alder reaction are ascribed to a lowering of the frontier orbital energies and an alteration of the atomic orbital coefficients in the dienophile.[3]

A well-known example which underlines the vital advantage of this rate acceleration is the $Cu(BF_4)_2$catalyzed [4 + 2] cycloaddition of α-chloroacrylonitrile (**203**) to the 5-substituted cyclopentadiene (**202**).[56] Owing to the selective coordination of the copper(I) ion with the nitrile group of (**203**), the desired adduct (**204**) was formed readily at 0 °C, thus avoiding the otherwise dominating 1,5-rearrangement (**202**) → (**205**) (Scheme 48).

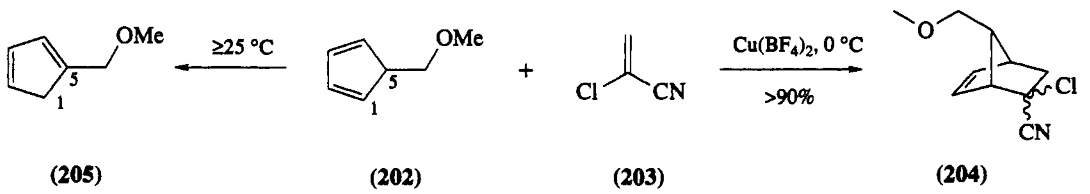

**Scheme 48**

The general Lewis acid induced enhancement of rates, regio- and *endo*-selectivities is clearly demonstrated by the [4 + 2] cycloaddition of (*E*)-2,4-pentadiene (**16**) to methyl acrylate (Scheme 49, Table 4).[57a] The uncatalyzed reaction at 120 °C shows an 84:16 regiochemical preference in favor of the '*ortho*' products (**206**) and (**207**), but almost no *endo* selectivity. These values improve only marginally at a reaction temperature of 25 °C (requiring 70 days) but rise sharply to ratios of 98:2 ('*ortho*/*meta*') and 95:5 (*endo*/*exo*) in the presence of $AlCl_3$ (0.15 mol equiv.) at 10–20 °C (3 h). Similar regiochemical improvements were observed on the corresponding additions of isoprene and its derivatives to methyl acrylate, methyl vinyl ketone and acrolein (Scheme 43, Table 3; Scheme 61, Table 10).[57b]

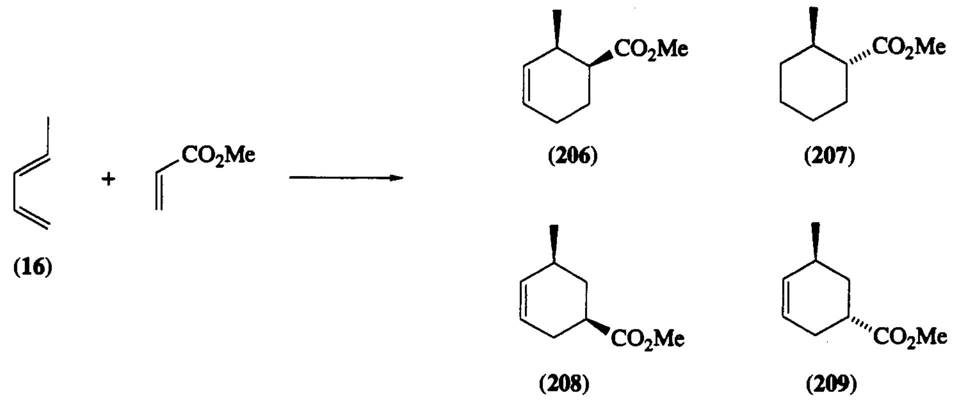

**Scheme 49**

**Table 4** Influence of $AlCl_3$ on the Regio and *Endo* Selectivity of the Diels–Alder Reaction between (*E*)-2,4-Pentadiene and Methyl Acrylate in Benzene (Scheme 49)

| *Entry* | *Temp.* (°C) (*time*, h) | *$AlCl_3$* (mol equiv.) | *Yield (%)* *(206) + (207) + (208) + (209)* | *Ratio* *(206)/(207)/(208)/(209)* |
|---|---|---|---|---|
| 1 | 120 (6) | 0 | 53 | 45.4:38.6:10.6:5.4 |
| 2 | 25 (1680) | 0 | 39 | 51.3:38.7:7.3:2.7 |
| 3 | 10–20 (3) | 0.15 | 50 | 93.1:4.9:1.9:0.1 |

Alkene dienophiles bearing two different substituents at C-1 or, *trans* related, at C-1 and C-2 often react with low *endo*/*exo* selectivities (*cf.* Scheme 50, Table 5). For example, the thermal Diels–Alder reactions of cyclopentadiene with methyl (*E*)-crotonate (**210b**) (entry 4) and methyl methacrylate (**210c**) (entry 6) show approximately equal proportions of products with an *endo*-oriented methoxycarbonyl or methyl group.[57c] Coordination of the $CO_2Me$ unit clearly favors its *endo* orientation in the reaction of acrylate (**210a**) (entry 3) and crotonate (**210b**) (entry 5). However, the *endo*-directing influence of the $C_\alpha$-methyl group was only poorly counteracted in the $AlCl_3$-promoted addition of methyl methacrylate (**210c**) (entry 7). Nevertheless, even dienophiles with 'competing' geminal substituents can react in a highly *endo*/*exo* selective manner depending on the substituents and the type of Lewis acid (*cf.* Scheme 111, Table 32). This reference to Section 4.1.6.3.3 may underline the vital importance of an almost complete *endo*/*exo* selectivity as a prerequisite for achieving useful asymmetric Diels–Alder reactions.

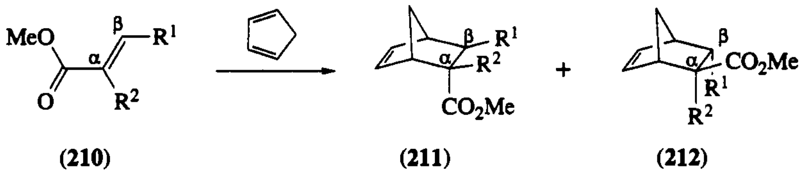

**Scheme 50**

**Table 5** Influence of $AlCl_3$ on the *Endo*/*Exo* Selectivity of Diels–Alder Reactions between Cyclopentadiene and Methyl Enoates (Scheme 50)

| *Entry* | *$R^1$* | *$R^2$* | *Lewis acid* (mol equiv.) | *Solvent* | *Temp.* (°C) | *Yield (%)* *(211) + (212)* | *Ratio* *(211)/(212)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | — | $CH_2Cl_2$ | 0 | 22–51 | 82:18 | 57d |
| 2 **a** | H | H | $AlCl_3·OEt_2$ (0.1) | $CH_2Cl_2$ | 0 | 79–91 | 96:4 | 57d |
| 3 **a** | H | H | $AlCl_3·OEt_2$ (0.1) | $CH_2Cl_2$ | –70 | 67–72 | 99:1 | 57d |
| 4 **b** | Me | H | — | $C_6H_6$ | 30 | — | 54:46 | 57c |
| 5 **b** | Me | H | $AlCl_3$ (0.9) | $C_6H_6$ | 30 | — | 94:6 | 57c |
| 6 **c** | H | Me | — | $C_6H_6$ | 30 | — | 31:69 | 57c |
| 7 **c** | H | Me | $AlCl_3$ (0.9) | $C_6H_6$ | 30 | — | 60:40 | 57c |

Scheme 51 presents an entirely different mode of catalyzed [4 + 2] cycloadditions. Thus trimethylsilyl triflate or triflic acid apparently transform vinyl orthoesters and acrolein acetals to powerful transient allyl cation dienophiles (**214**) and (**219**), respectively. The 'ionic' Diels–Alder reactions (**213**) → (**216**) and (**218**) → (**220**) proceed at low reaction temperatures in a remarkably regio- and *endo*-selective manner.[58]

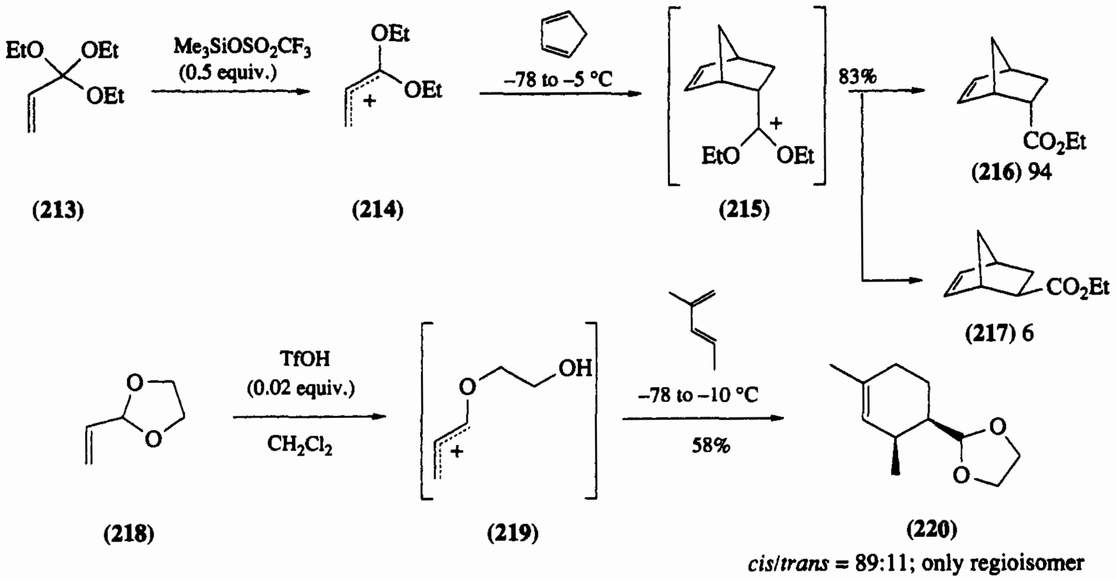
EtO
OEt
OEt
(213)
$Me_3SiOSO_2CF_3$
(0.5 equiv.)
OEt
OEt
+
(214)
−78 to −5 °C
+
EtO
OEt
(215)
83%
$CO_2Et$
(216) 94
$CO_2Et$
(217) 6
O
O
(218)
TfOH
(0.02 equiv.)
$CH_2Cl_2$
O
OH
+
(219)
−78 to −10 °C
58%
O
O
(220)
*cis*/*trans* = 89:11; only regioisomer

Scheme 51

## 4.1.4.2 Medium Effects

### *4.1.4.2.1 High pressure and ultrasound*

Intermolecular [4 + 2] cycloadditions exhibit strongly negative activation volumes and reaction volumes. High pressure, therefore, can be applied to accelerate Diels–Alder reactions and to shift the reaction equilibrium towards the cycloadducts. These effects are of particular advantage to: (1) promote otherwise slow [4 + 2] cycloadditions involving heat or Lewis acid sensitive educts or products; (2) suppress cycloreversion processes which are either thermodynamically favored or would interfere with a kinetically controlled stereochemistry. In view of a recent review (1985)[59] only a few examples are presented here.

Scheme 52 and Table 6 emphasize the beneficial influence of high pressure on the Diels–Alder reactions of (Lewis acid sensitive) nitrogen- or oxygen-substituted dienes (**221**) to acrylates (**222**) (*cf.* entries 1/2 and 3/4).[60]

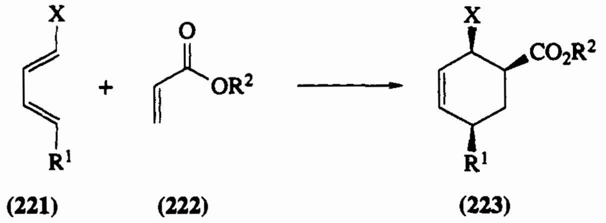
X
$R^1$
(221)
+
O
$OR^2$
(222)
X
$CO_2R^2$
$R^1$
(223)

Scheme 52

A serious drawback of [4 + 2] cycloadditions to *p*-quinones is the aromatization of the cycloadducts, affording hydroquinones. Hence, the first step, (**224**) + (**225**; R = H) → (**226**; R = H), of Woodward's landmark synthesis of reserpine, carried out in benzene under reflux (10 h), gave the desired adduct (**226**; R = H) in only 18% yield because of its facile tautomerization to (**227**; R = H) (Scheme 53).[61a]

**Table 6** Influence of High Pressure on the Diels–Alder Addition of Heteroatom-substituted Dienes to Acrylates (Scheme 52)

| *Entry* | *Diene* | | *Dienophile* | *Solvent* | *Temp.* (°C) (*time*, h) | *Pressure* (kbar) | *Yield* (%) *of* (223) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| | *X* | $R^1$ | $R^2$ | | | | | |
| 1 **a** | $NEt_2$ | H | Et | Benzene | 20 (144) | 0.001 | 94 | 60a |
| 2 **a** | $NEt_2$ | H | Et | $Et_2O$ | r.t. (0.5) | 13.6 | 95 | 60a |
| 3 **b** | OMOM | $CO_2Me$ | Me | Toluene | 110 (72) | 0.001 | 0 | 60b |
| 4 **b** | OMOM | $CO_2Me$ | Me | $CH_2Cl_2$ | r.t. (24) | 15 | 70 | 60b |

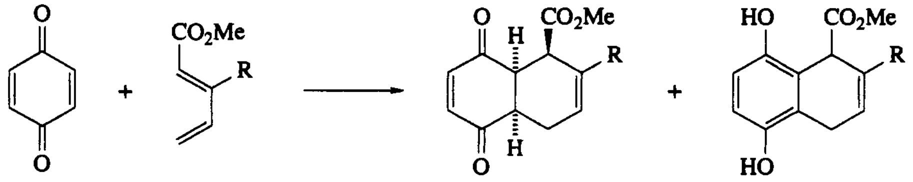

**(224)** **(225)** **(226)** **(227)**

**Scheme 53**

In contrast, this reaction, when run at room temperature under a pressure of 15 kbar (18 h), afforded bicyclic dienedione (**226**; R = H) in 64% yield.[61b] Similarly, the Diels–Alder reaction of *p*-benzoquinone (**224**) with dienyl ester (**225**; R = Et) was significantly improved by high pressure (15 kbar, r.t., 3 h), providing product (**226**; R = Et) in 60% yield; dione (**226**; R = Et) served as a key intermediate for a synthesis of (±)-aklavinone (**625**).[61c]

High pressure has been applied successfully to Diels–Alder reactions of furans, which are notoriously troublesome due to low activation barriers and low or even negative $\Delta G°$ values. For example, attempts to synthesize the potent vesicant cantharidin (**232**) *via* reaction of furan (**228**) with dimethylmaleic anhydride (**234**) date back to 1928. The failure of this approach has been attributed to a thermodynamic preference for cycloreversion over cycloaddition.[62a] More than 50 years later the problem was solved by employing high pressures and either a modified dienophile (**229**)[62b] or diene partner (**233**).[62c] Interestingly, product (**235**) reverts to 'reactants' (**233**) and (**234**) in solution at atmospheric pressure and room temperature (Scheme 54).

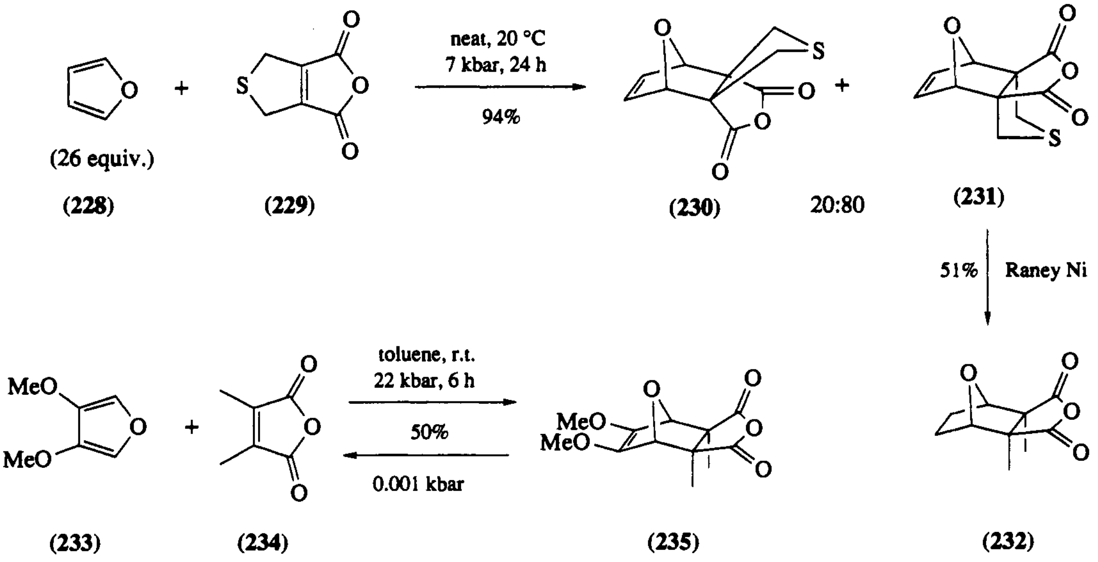

**Scheme 54**

A pressure of 5 kbar was also essential to accomplish the [4 + 2] cycloaddition of furan (**236**) to enone (**237**), the key step in a synthesis of the diterpenes jatropholones A and B (Scheme 55).[63]

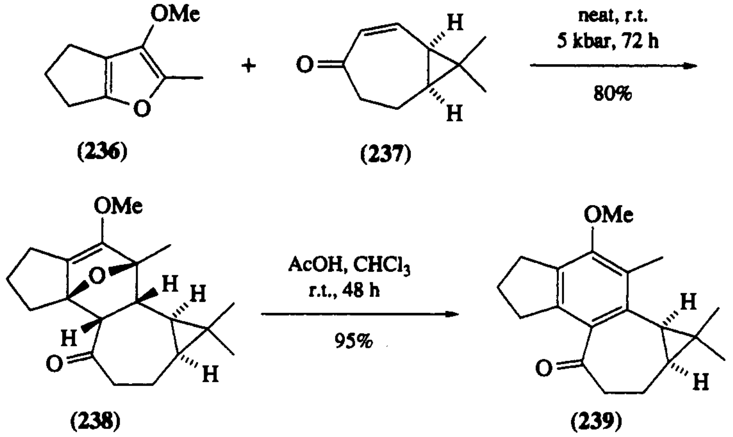
OMe
O
+
H
H
neat, r.t.
5 kbar, 72 h
80%
(236)
(237)
OMe
O
H
H
H
H
O
AcOH, CHCl3
r.t., 48 h
95%
OMe
H
H
O
(238)
(239)

Scheme 55

Ultrasound was reported to promote Diels–Alder reactions as well as improve their regioselectivity similarly to high pressure, but much more conveniently (Scheme 56, Table 7).[64] Comparison of entries 2/3 indicates the similarity of the yields and product ratios (**242**)/(**243**), obtained at 10 kbar (entry 2) and on sonication (entry 3). The latter were attributed to the implosion of the ultrasound-induced cavities which locally generate high pressures and temperatures (up to 1 kbar and 5000 K). Deacetalization of the major aromatized regioisomer (**242**) gave the natural product tanshindiol B.

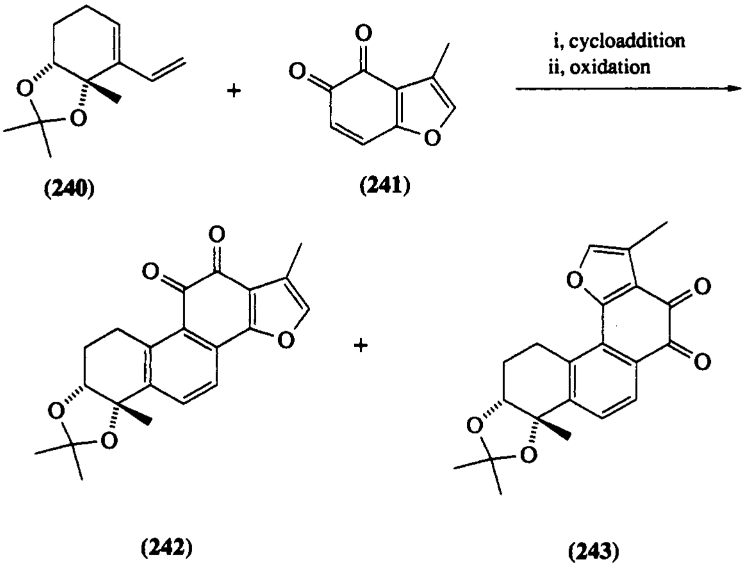
O
O
+
O
O
O
i, cycloaddition
ii, oxidation
(240)
(241)
O
O
O
O
O
+
O
O
O
O
O
(242)
(243)

Scheme 56

Table 7 Ultrasound Promoted Diels-Alder Reactions: Influence on Yield and Regiochemistry[a] (Scheme 56)

| *Entry* | *Reaction conditions* | *Yield (%)*<br>*(242) + (243)* | *Ratio (242)/(243)* |
|---|---|---|---|
| 1 | Benzene, reflux, 8 h | 15 | 50:50 |
| 2 | Toluene, 10 kbar, r.t., 1 h | 73 | 87:13 |
| 3 | Neat, ultrasound, 45 °C, 2 h | 76 | 83:17 |

[a] Aromatization of the initial Diels–Alder products occurred under oxygen with $SiO_2$ or on heating with DDQ in benzene.

### *4.1.4.2.2 Water*

The beneficial effect of water as a reaction medium for Diels–Alder reactions was first described in 1939,[65] but was not generally recognized for more than 40 years. In the early 1980s, Breslow and coworkers reported that the [4 + 2] cycloaddition of cyclopentadiene to methyl vinyl ketone is accelerated by a factor of 700 when carried out in water compared with isooctane.[66] This rate enhancement, paralleled by an increase of the *endo*/*exo* selectivity from 80:20 to 96:4, was ascribed to a hydrophobic association of the diene with the dienophile in water.

In context with synthetic work on quassinoids, Grieco and coworkers found an even more striking rate enhancement of aqueous Diels–Alder reactions when the diene partner contains a suitably placed ionic substituent (Scheme 57, Table 8).[67a] The concentration-dependent increase of rate, yield and *endo* selectivity observed, particularly, with the sodium salt of dienoic acid (**245b**) in water (entry 3) was assigned to an entropically favorable interaction of the reactants within an aggregate.

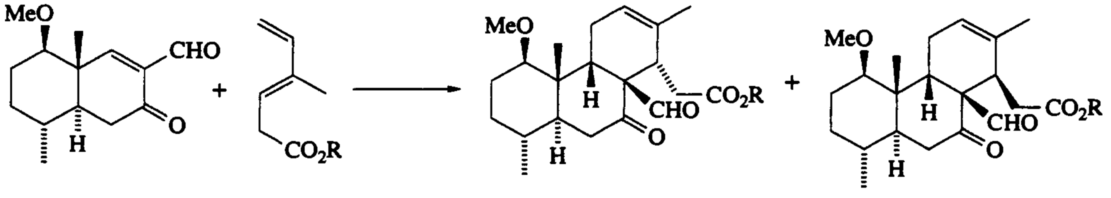

**(244)** **(245)** **(246)** **(247)**

**Scheme 57**

**Table 8** Aqueous, Aggregation-promoted Diels–Alder Reactions of Quassinoid Intermediates at Room Temperature (Scheme 57)

| *Entry* | *R* | *Solvent* | *Concentration of diene* | *Time* (h) | *Yield* (%) *(246) + (247)* | *Ratio (246)/(247)* |
|---|---|---|---|---|---|---|
| 1 **a** | Et | $C_6H_6$ | 1.0 M | 288 | 52 | 46:54 |
| 2 **a** | Et | $H_2O$ | 1.0 M | 168 | 82 | 57:43 |
| 3 **b** | Na | $H_2O$ | 2.0 M | 5 | ~100 | 75:25 |
| 4 **b** | Na | $H_2O$ | 0.1 M | 120 | 46 | 47:53 |

Under analogous aqueous reaction conditions, the sodium salts of (*E*)-3,5-hexadienoic, (*E*,*E*)-6-methoxy-3,5-hexadienoic and (*E*)-4,6-heptadienoic acid underwent high-yielding [4 + 2] cycloadditions to a variety of dienophiles,[67b] *e.g.* to the $C_\alpha$-substituted enal (**248**) (Scheme 58).[67c] The crude Diels–Alder

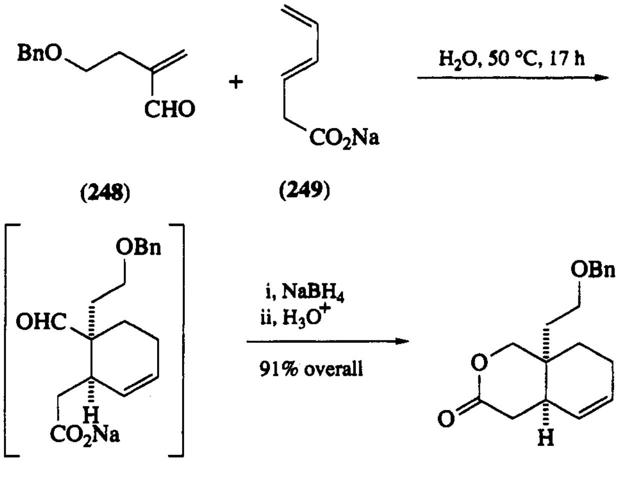

**(250)** **(251)**

**Scheme 58**

adduct (**250**), formed from (**248**) and (**249**) with a 91:9 *endo*/*exo* selectivity, was directly reduced with $NaBH_4$ and lactonized. This afforded, in 91% overall yield, bicyclic lactone (**251**), a precursor in a synthesis of vernolepin.

The aqueous addition of conjugated allene carboxylate (**252**) to typical dienophiles proceeded smoothly between 20 and 50 °C to yield predominantly, if not exclusively, 'C=O *endo*' adducts containing a conjugated *exo*-methylene group, *e.g.* the methyl vinyl ketone adduct (**253**) (Scheme 59).[67e] Also diene (**255**), featuring a sodium carboxylate unit attached *via* a nitrogen atom, reacted efficiently at 25 °C with various, even acid-sensitive, dienophiles as exemplified by the [4 + 2] cycloaddition of (**255**) to methacrolein (→ **256**).[67d]

Applications of the water-promoted aggregation effects in diastereoface controlled or 'iminium' Diels–Alder reactions will be discussed in Section 4.1.5.2 (Scheme 66) and in Chapter 4.2, respectively.

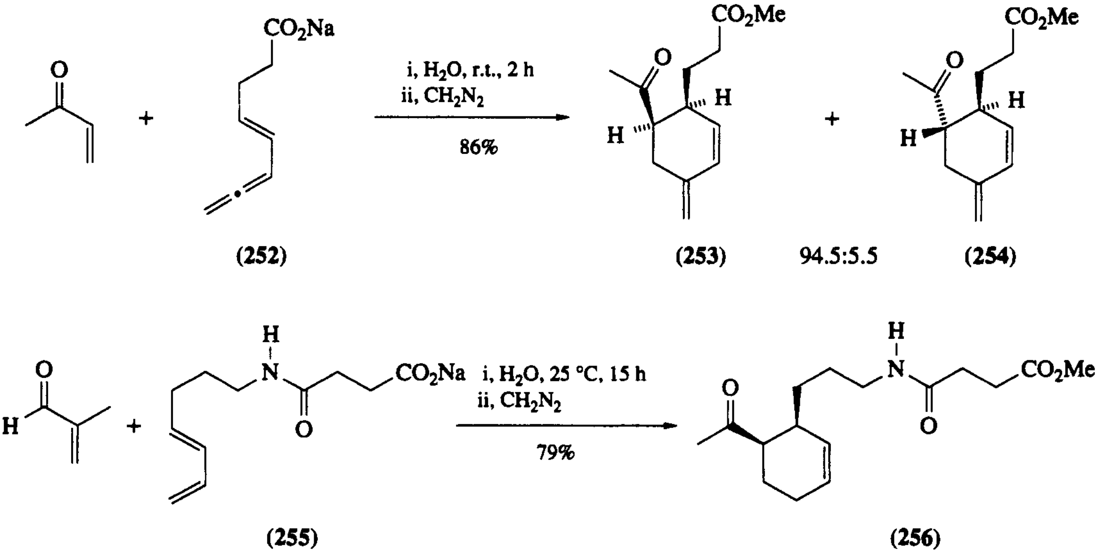

Scheme 59

#### 4.1.4.2.3 *Clays, zeolites and silica gel*

Diels–Alder reactions showed a pronounced increase of rate, *endo*- and regio-selectivity when carried out in organic solvents in the presence of modified clays[68] or zeolites.[69] Similar improvements could be accomplished by co-adsorption of the reactants on dry $SiO_2$ in the absence of organic solvents.[70] These trends are summarized below and compared with the results obtained by employing the 'classical-thermal',[71a] Lewis acid catalyzed,[57,68a,71b] 'high pressure'[71c] or 'aqueous'[66] reaction conditions.

For this comparison the [4 + 2] cycloadditions of methyl vinyl ketone to cyclopentadiene and to furan are chosen as reference reactions (Scheme 60, Table 9). Smectile clays, with the interlayer cations exchanged by $Cr^{III}$ or $Fe^{III}$ ions, catalyzed the addition of cyclopentadiene in providing the *endo* product (**258**; Y = $CH_2$) at a drastically reduced reaction temperature in high yield together with $\leqslant$10% of the *exo* product (**259**; Y = $CH_2$) (entries 3, 4). These results are comparable with those obtained under 'aqueous' reaction conditions (entry 2), which supports the idea that the presence of water pockets in clays could account for their catalytic activity. The Lewis acidity as well as one-electron-transfer processes, involving the internal $Fe^{III}$ or $Cr^{III}$ cations, have also been invoked as possible explanations.

On the other hand, the enhancements of rate and *endo* selection caused by adsorption of the reactants on dry silica gel (entry 5) seem to arise from an association of the nonsolvated reacting partners at the $SiO_2$ surface, which acts as a matrix.

Entries 6–10 deal with the Diels–Alder reactions of methyl vinyl ketone with furan and also include the use of $AlCl_3$ (entry 6), high pressure (entry 7) and $Cu^I$ ion-exchanged Y-zeolite (entry 9). This series, however, displayed only modest *exo* selectivities. The highest product ratio (**258**; Y = O)/(**259**; Y = O) = 20:80 was found on adsorption of the educts on dry $SiO_2 \cdot MgO$ (entry 10).

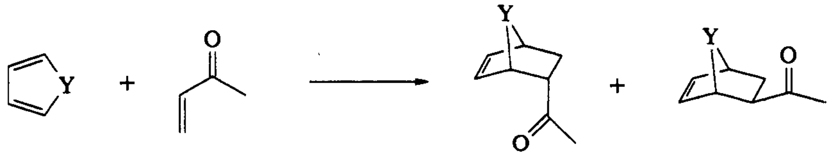

**(257)** **(258)** **(259)**

**Scheme 60**

**Table 9** Diels–Alder Reactions of MVK with Cyclopentadiene and Furan: Influence of Reactions Conditions (Scheme 60)

| *Entry* | *Y* | *Solvent* | *Catalyst or support* | *Temp.* (°C) *(time,* h*)* | *Yield (%)* *(***258***) + (***259***)* | *Ratio* *(***258***)/(***259***)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | $CH_2$ | Benzene | None | 80 | 80 | 83:17 | 71a |
| 2 | $CH_2$ | $H_2O$ | None | 25 (3) | 80 | 95.5:4.5 | 66 |
| 3 | $CH_2$ | $CH_2Cl_2$ | K10-$Fe^{III}$ | –24 (4) | 96 | 95.5:4.5 | 68a |
| 4 | $CH_2$ | CH2Cl2 | $Cr^{III}$ montmorillonite | 22 (0.3) | 91 | 90:10 | 68b |
| 5 | $CH_2$ | None | $SiO_2$ | –20 (1) | 90 | 96:4 | 70 |
| 6 | O | $CH_2Cl_2$ | $AlCl_3$ (0.15) | –43 (0.25) | 81 | 44:56 | 68a |
| 7 | O | $CH_2Cl_2$ | 15 kbar | r.t. (4) | 48 | 50:50 | 71c |
| 8 | O | $CH_2Cl_2$ | K10-$Fe^{III}$ | –43 (6) | 60 | 31:69 | 68a |
| 9 | O | $CH_2Cl_2$ | $Cu^I$ zeolite | 0 (48) | 73 | 29:71 | 69 |
| 10 | O | none | $SiO_2{\cdot}MgO$ | 20 (70) | 48 | 20:80 | 70 |

Scheme 61 and Table 10 illustrate the influence of $SnCl_4$ or solid supports on the Diels–Alder reactions of methyl vinyl ketone or acrolein with isoprene. Apart from the reaction rate, the regiochemical control was substantially increased, *e.g.* from 59:41 to 99.5:0.5 (entries 5/7) in favor of the '*para*' products (**260**).

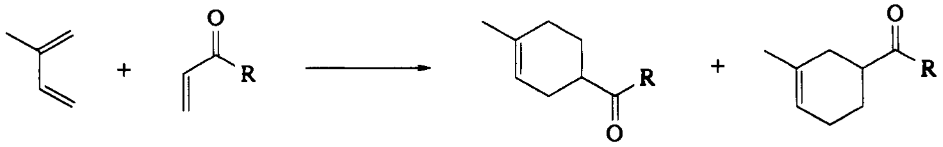

**(173)** **(260)** **(261)**

**Scheme 61**

**Table 10** Influence of Lewis Acid and Solid Support on the Diels–Alder Reactions of MVK and Acrolein with Isoprene (Scheme 61)

| *Entry* | *Dienophile* | *Solvent* | *Catalyst or support* | *Temp.* (°C) *(time,* h*)* | *Yield* (%) *(***260***) + (***261***)* | *Ratio* *(***260***)/(***261***)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | MVK | Toluene | None | 120 (15) | — | 71:29 | 71b |
| 2 | MVK | Benzene | $SnCl_4{\cdot}5H_2O$ (0.18) | <25 (1) | — | 93:7 | 71b |
| 3 | MVK | $CH_2Cl_2$ | $Cu^I$ zeolite | 0 (3) | 83 | 96:4 | 69 |
| 4 | MVK | None | $SiO_2$ | 20 (0.5) | 70 | ≥95:≤5 | 70 |
| 5 | Acrolein | None | None | 150 | — | 59:41 | 71b |
| 6 | Acrolein | Benzene | $SnCl_4{\cdot}5H_2O$ (0.18) | <25 (1) | 54 | 96:4 | 71b |
| 7 | Acrolein | $CH_2Cl_2$ | $Cu^I$ zeolite | 0 (12) | 65 | 99.5:0.5 | 69 |
| 8 | Acrolein | None | $SiO_2$ | 20 (0.5) | 56 | ≥95:≤5 | 70 |

## 4.1.5 DIASTEREOFACE-SELECTIVE DIELS–ALDER REACTIONS WITHOUT REMOVAL OF THE INDUCING MOIETY

As discussed previously, the Diels–Alder reactions of alkenic dienes and dienophiles involve the simultaneous formation of two carbon–carbon bonds and up to four contiguous stereogenic centers. Their relative topicity derives from the (*E,Z*) geometry of the diene and dienophile units coupled with the *endo*/*exo* mode of addition. A further stereochemical issue arises in directing the addition process to only one (diastereo- or enantio-topic) π-face of either reaction partner. This π-facial differentiation governs the relation between pre-existent and newly developing centers of chirality and/or the absolute configuration of the latter ones. These two aspects of facial differentiation will be emphasized separately in the following subsections.

### 4.1.5.1 Induction by a Prochiral Center: 5-Substituted Cyclopentadienes

[4 + 2] Cycloadditions to C-5 substituted 1,3-cyclopentadienes (**262**) represent a particular type of face discrimination owing to the potential of a prochiral center (C-5) to alter the reactivity of the two diene faces (Scheme 62, Table 11). Hence some attention has been devoted to whether a dienophile (**263**) would preferably add *syn* or *anti* relative to a substituent X.[72] Entries 1–3 show a predominant addition of $Cu(BF_4)_2$-coordinated 2-chloroacrylonitrile (or of acrylic acid and nitroethylene) *anti* to the $CH_2OMe$ group, *i.e.* *syn* to $R^2 = H$. A similar *anti*-directing influence was shown (in decreasing order) for C-5 substituents $X = CH_2OH > Me$ (entries 4, 5). Also, the methylthio and methylsulfonyl groups direct maleic anhydride to the *anti* face of cyclopentadienes (entries 8, 9). In contrast, C-5 substituents X = Cl,OH, OMe and NHAc exert a *syn*-directing bias on (**262**) (entries 6, 7, 10–12), the origin of which is subject to debate.

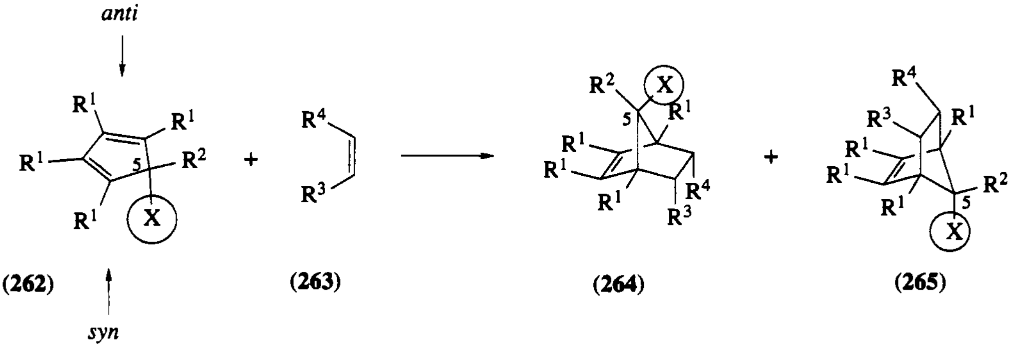

(**262**) (**263**) (**264**) (**265**)

**Scheme 62**

**Table 11** Diels–Alder Reactions of C-5 Substituted 1,3-Cyclopentadienes (Scheme 62)

| *Entry* | *R*$^1$ | *R*$^2$ | *X* | *Dienophile* | *Lewis acid* (mol equiv.) | *Temp.* (°C) (*time*, h) | *Yield (%)* (**264**) + (**265**) | *Ratio* (**264**)/(**265**) | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | $CH_2OMe$ | 2-Chloroacrylonitrile | $Cu(BF_4)_2$ | 0 | >90 | <10:>90 | 56 |
| 2 **b** | H | H | $CH_2OMe$ | Acrylic acid | None | −7 | a | <3:>97 | 72a |
| 3 **c** | H | H | $CH_2OMe$ | Nitroethylene | None | −15 to r.t. | 68 | <5:>95 | 5 |
| 4 **d** | H | Me | $CH_2OH$ | *N*-Phenylmaleimide | None | r.t. (120) | 87 | 13:87 | 72b |
| 5 **e** | Me | H | Me | Maleic anhydride | None | r.t. | a | 21:79 | 72c |
| 6 **f** | Cl | H | Cl | Maleic anhydride | None | 105 (3) | 73 | 91:9 | 72d |
| 7 **f** | Cl | H | Cl | Maleic anhydride | $AlCl_3$ (1) | 100 (2.5) | 80 | 99:1 | 72e |
| 8 **g** | Me | Me | SMe | Maleic anhydride | None | 22 (27.5) | >90 | 10:90 | 72f |
| 9 **h** | Me | Me | $SO_2Me$ | Maleic anhydride | None | 22 (216) | >90 | <5:>95 | 72f |
| 10 **i** | Me | Me | OH | Maleic anhydride | None | 22 (<0.01) | >90 | >95:<5 | 72f |
| 11 **j** | Me | Me | OMe | Maleic anhydride | None | 22 (<0.2) | >90 | >95:<5 | 72f |
| 12 **k** | Me | Me | NHAc | Maleic anhydride | None | 22 (3.5) | >90 | >95:<5 | 72f |

[a] Yield not reported.

On the other hand, a C-5 cyclopentadiene moiety induced almost no face discrimination on addition of dimethyl acetylenedicarboxylate to 9,10-dihydrofulvalene (**266**) (Scheme 63).[73a] Products (**268**) and (**270**) result from a tandem inter-/intra-molecular Diels–Alder reaction (domino Diels–Alder reactions).

This seminal concept for the construction of polycyclic systems, developed by Paquette and coworkers, is highlighted by the conversion of product (**270**) into dodecahedrane.[73b]

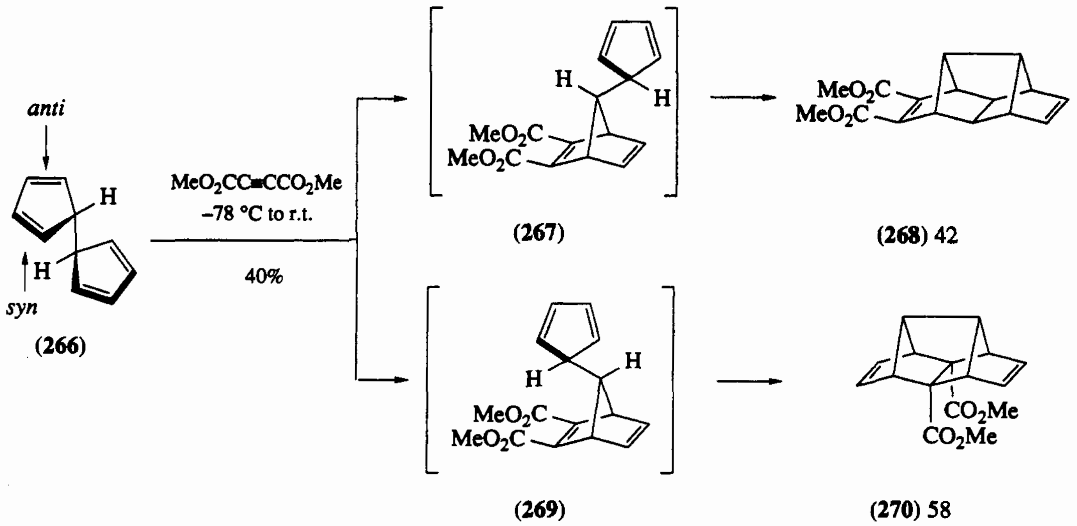

**Scheme 63**

### 4.1.5.2 Induction by Resident Stereocenter(s)

#### *4.1.5.2.1 Chiral dienes*

Acyclic 1,3-dienes containing an allylic stereogenic center may display a useful π-facial differentiation on addition of dienophiles. For example, 1,3-dienes (**271**) bearing an allylic oxygenated center of chirality at C-1 gave, on addition of *N*-phenylmaleimide, mixtures of diastereoisomers (**272**) and (**273**) in ratios from 63:37 ($R^1$ = H) up to 88:12 ($R^1$ = TMS) (Scheme 64, Table 12).[74a] This trend significantly increased with 2-alkoxydiene (**271d**), giving exclusively adduct (**272d**) (entry 4).[74b] The improved selectivity observed with (**271d**) was attributed to the 2-alkoxy substituent $R^2$ which restricts the rotational freedom of the bond between C-1 and the stereogenic center.

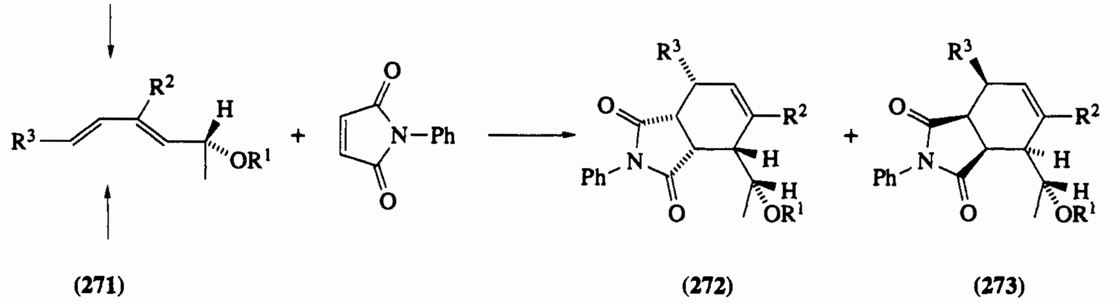

**Scheme 64**

**Table 12** [4 + 2] Cycloadditions of *N*-Phenylmaleimide to Acyclic 1,3-Dienes Bearing an Oxygenated Allylic Center of Chirality (Scheme 64)

| *Entry* | $R^1$ | $R^2$ | $R^3$ | *Solvent* | *Temp.* (°C) (*time*, h) | *Yield* (%) (**272**) + (**273**) | *Ratio* (**272**)/(**273**) |
|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | Me | Benzene | r.t. (120) | 78 | 63:37 |
| 2 **b** | Me | H | Me | Benzene | 55 (72) | a | 83:17 |
| 3 **c** | TMS | H | Me | Benzene | r.t. (240) | 74.5 | 88:12 |
| 4 **d** | TMS | OMOM | $Pr^i$ | Benzene | r.t. (12) | a | ~100:0 |

[a] Yield not reported.

To remove the conformational ambiguity which obscures interpretations of these results, additions of various dienophiles to 3-substituted 1-vinylcyclopentenes (**274**) were studied.[75] Preferential cycloaddition from the diene face *anti* to the Me, OMe and, particularly, the OTBDMS group was observed (Scheme 65, Table 13). Cycloaddition of the hydroxy-substituted diene (**274b**) occurred with a weak *syn* preference in toluene (entry 2), but with an *anti* preference in more polar solvents.

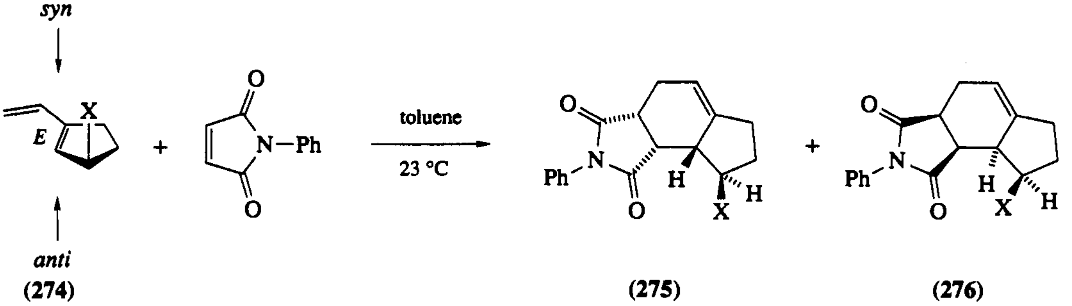

**Scheme 65**

**Table 13** [4 + 2] Cycloadditions of *N*-Phenylmaleimide to C-3 Substituted 1-Vinylcyclopentenes in Toluene at Room Temperature (Scheme 65)

| *Entry* | *X* | *Ratio (275)/(276)* |
|---|---|---|
| 1 a | Me | 83:17 |
| 2 b | OH | 36:64 |
| 3 d | OMe | ≥97:≤3 |
| 4 d | OTBDMS | 100:0 |

A pertinent example of π-face differentiation by means of the 'aqueous Diels–Alder methodology' is the addition of dienyl sodium carboxylate (**277**; R = Na) to methacrolein in water, yielding adducts (**278**; R = Na) and (**279**; R = Na) in a ratio of 18:82 (85%) (Scheme 66, Table 14, entry 1).[76] This useful induction of centers C-13 and C-17 by the pre-existing center C-20 is essential for a synthesis of the vitamin $D_3$ precursor (**280**). It contrasts with the inefficient [4 + 2] cycloaddition of dienyl methyl ester (**277**; R = Me) in neat methacrolein, which showed no facial selectivity (entry 2).

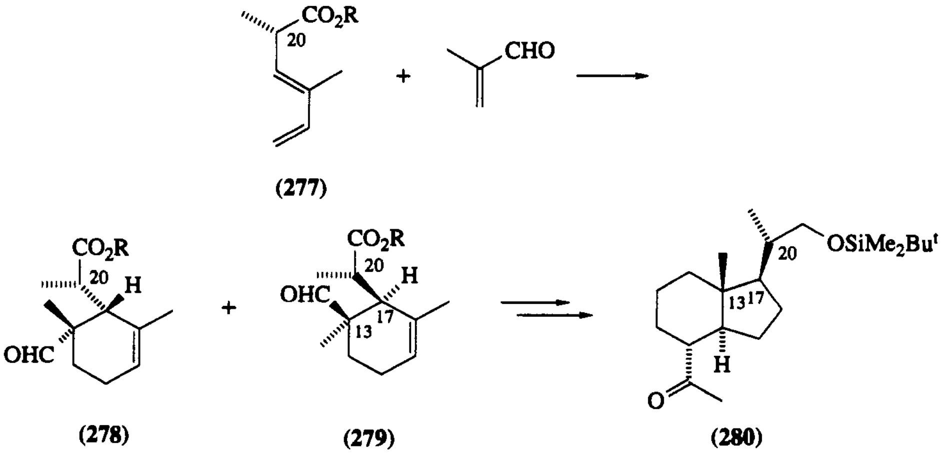

**Scheme 66**

**Table 14** Diene with an Allylic Stereogenic Center: Medium-assisted Face Differentiation on Addition to Methacrolein (Scheme 66)

| *Entry* | *R* | *Solvent* | *Temp. (°C) (time, h)* | *Yield (%) (278) + (279)* | *Ratio (278)/(279)* |
|---|---|---|---|---|---|
| 1 a | Na | $H_2O$ | 55 (16) | 85 | 18:82 |
| 2 b | Me | Methacrolein | 55 (63) | 10 | 50:50 |

A synthesis of the hypocholesterolemic agent (+)-compactin centers around the Diels–Alder reaction of the chiral diene (**282**) with the chiral dienophile (**281**), which provided in a single operation the carbon framework of the target molecule (Scheme 67).[77] However, facial and regiochemical selectivities of the additions were only moderate, giving rise to the formation of two regioisomers (**283**) and (**284**); the major product (**283**) was transformed into (+)-compactin.

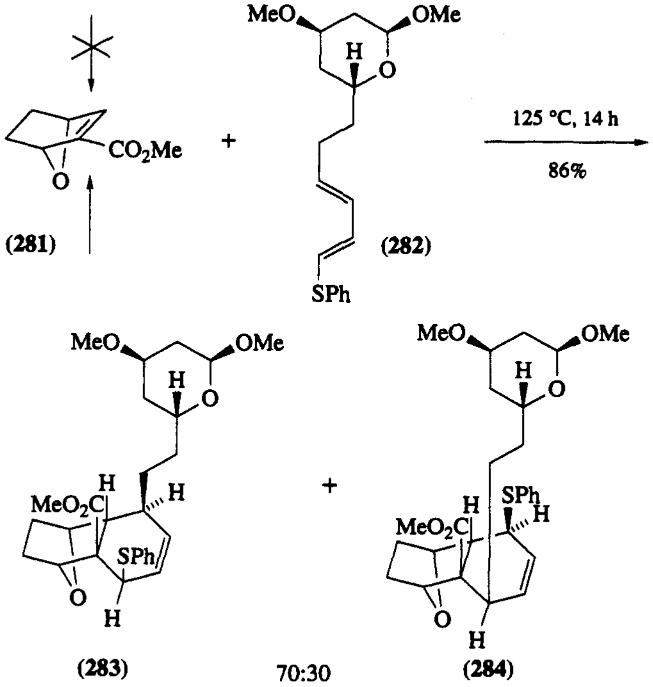

Scheme 67

### 4.1.5.2.2 *Chiral dienophiles*

Cyclic enones carrying an endocyclic stereogenic center reliably undergo cycloadditions of 1,3-dienes to the sterically less-hindered face, as exemplified by the $AlCl_3$-catalyzed reaction of (**285**) with butadiene which yielded (**286**; 84%) as the sole cycloadduct (Scheme 68).[78]

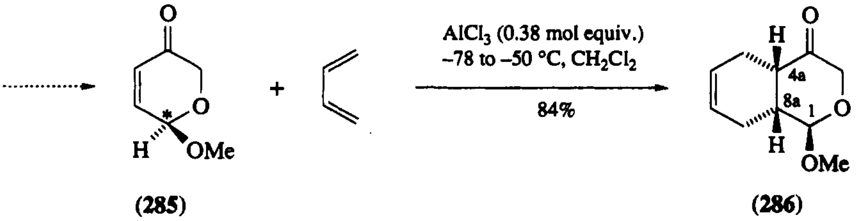

Scheme 68

Levoglucosenone (**287**), readily available by the pyrolysis of cellulose, when heated with a variety of dienes in the absence of a Lewis acid provided exclusively products (**289**) resulting from cycloaddition to its convex face (Scheme 69, Table 15).[79]

$AlCl_3$-promoted Diels–Alder addition of butadiene to another sugar-derived dienophile (**290**) proceeded, as expected, only from the face opposite to the allylic ethoxy substituent, giving cycloadduct (**291**) (Scheme 70).[80]

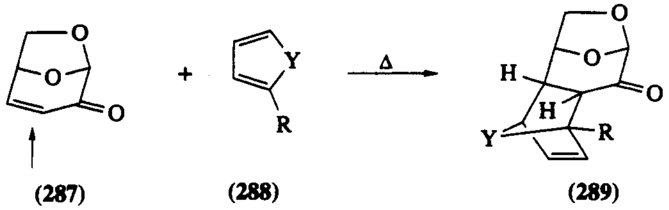
O
O
O
Y
R
Δ
H
H
O
O
O
Y
R
(287)
(288)
(289)

**Scheme 69**

**Table 15** [4 + 2] Cycloadditions to Levoglucosenone (Scheme 69)

| *Entry* | *Diene* *Y* | *R* | *Temp.* (°C) (*time*, h) | *Yield* (%) (**289**) |
|---|---|---|---|---|
| 1 **a** | $H_2$ | H | 160 (3) | 95 |
| 2 **b** | $CH_2$ | H | 168 (3) | 48 |
| 3 **c** | $(CH_2)_2$ | H | 200 (3) | 96 |
| 4 **d** | $H_2$ | OAc | 80 (7) | 63 |

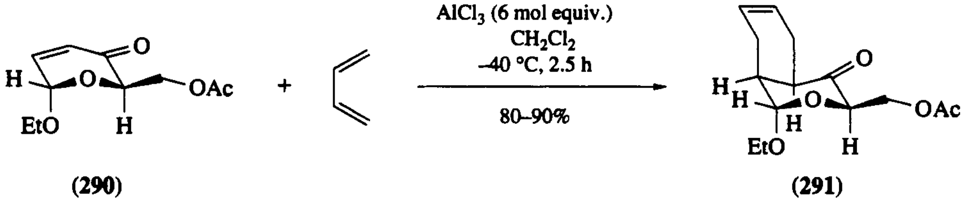
H
O
O
OAc
EtO
H
+
$AlCl_3$ (6 mol equiv.)
$CH_2Cl_2$
−40 °C, 2.5 h
80–90%
O
H
H
O
OAc
H
EtO
H
(290)
(291)

**Scheme 70**

A synthesis of (±)-quassin relies on the $AlCl_3$-catalyzed Diels–Alder reaction (**292**) + (**293**) → (**294**), where the angular allylic methyl group of the dienophile directs the diene to its less-hindered face (Scheme 71).[81]

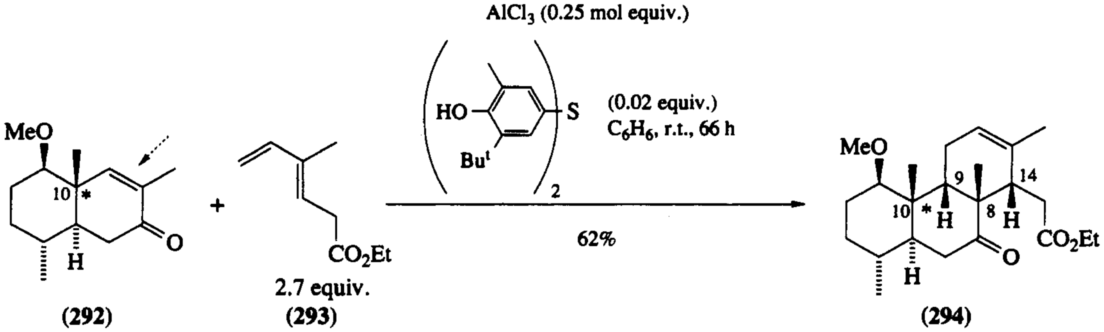
$AlCl_3$ (0.25 mol equiv.)
HO
S
Bu$^t$
2
(0.02 equiv.)
$C_6H_6$, r.t., 66 h
62%
MeO
10
*
H
O
+
$CO_2Et$
2.7 equiv.
MeO
9
14
10
*
H
8
H
$CO_2Et$
O
H
(292)
(293)
(294)

**Scheme 71**

The non-catalyzed [4 + 2] cycloaddition of the chiral pyrrolone (**295**) to triene (**296**) occurred with π-facial selection owing to the allylic benzyl substituent of dienophile (**295**) affording two regioisomers (Scheme 72).[82] The major product (**297**) is a key intermediate in a synthesis of cytochalasin B.

A particularly short and efficient synthesis of the lycopodium alkaloid (+)-luciduline (**303**) features as the first step the [4 + 2] cycloaddition of butadiene to optically pure cyclohexenone (**299**) opposite to the homoallylic methyl group (Scheme 73).[83] To achieve this excellent face discrimination the presence of $SnCl_4$ was required which, however, provoked an epimerization at C-8a yielding mainly the undesired *trans*-fused product (**301**). Oximation, under epimerizing conditions, easily rectified this problem by channelling both isomers (**300**) and (**301**) to a single *cis*-fused oxime (**302**) which was converted to the enantiomerically pure alkaloid (**303**).

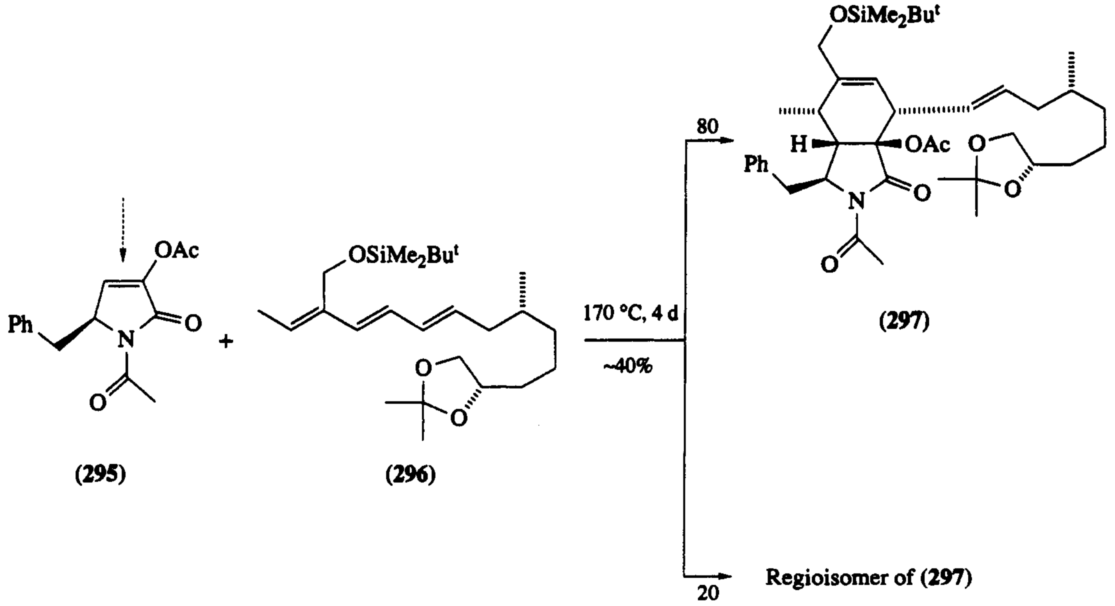
OAc
Ph
N
O
+
OSiMe$_2$Bu$^t$
O
(295)
(296)
170 °C, 4 d
~40%
80
20
OSiMe$_2$Bu$^t$
H
OAc
Ph
N
O
(297)
Regioisomer of (297)

Scheme 72

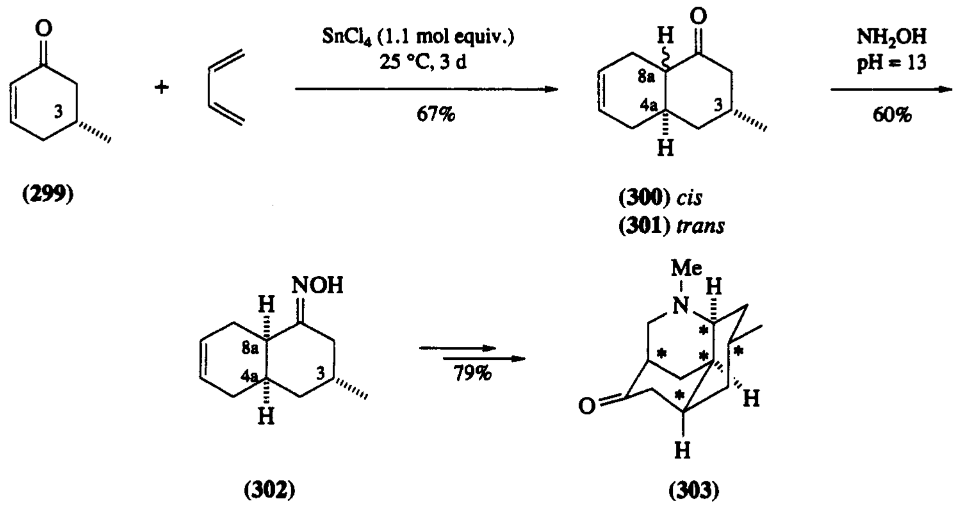
O
3
(299)
+
SnCl$_4$ (1.1 mol equiv.)
25 °C, 3 d
67%
H
O
8a
4a
3
H
(300) *cis*
(301) *trans*
NH$_2$OH
pH = 13
60%
NOH
H
8a
4a
3
H
(302)
79%
Me
N
H
O
H
H
(303)

Scheme 73

## 4.1.6 STEREOFACE-SELECTIVE DIELS–ALDER REACTIONS WITH REMOVAL OF THE INDUCING MOIETY

### 4.1.6.1 Background

Studies on the control of the absolute topicity of the Diels–Alder reaction started in 1961, but it is only during the last decade that substantial progress has been achieved. The development of this challenging field up to 1984 is the subject of several review articles.[84] A more specialized account on chiral enoate dienophiles appeared in 1986.[85] Some of this 'earlier' work will stand the test of time; some of it laid the foundations for new methods and concepts and will be put into perspective with today's panorama of possibilities.

### 4.1.6.2 Covalently Bound Auxiliary Groups

The first use of an asymmetric Diels–Alder reaction in enantioselective synthesis, reported by Corey and Ensley (1975), involved both diene and dienophile face differentiations (Scheme 74).[86] Addition of 5-(methoxymethyl)cyclopentadiene (**304**) to acrylic acid (**305a**) proceeded *endo* selectively and *anti* with respect to the diene substituent. Consequently, the relative configuration of the four new chiral centers in (**306a**) was determined and, of four possible diastereoisomers, one was formed selectively.[72a] As expected, the diene added at the same rate to the two enantiotopic dienophile π-faces, affording a 1:1 mixture of the enantiomers (1*R*)-(**306a**) and (1*S*)-(**306a**).

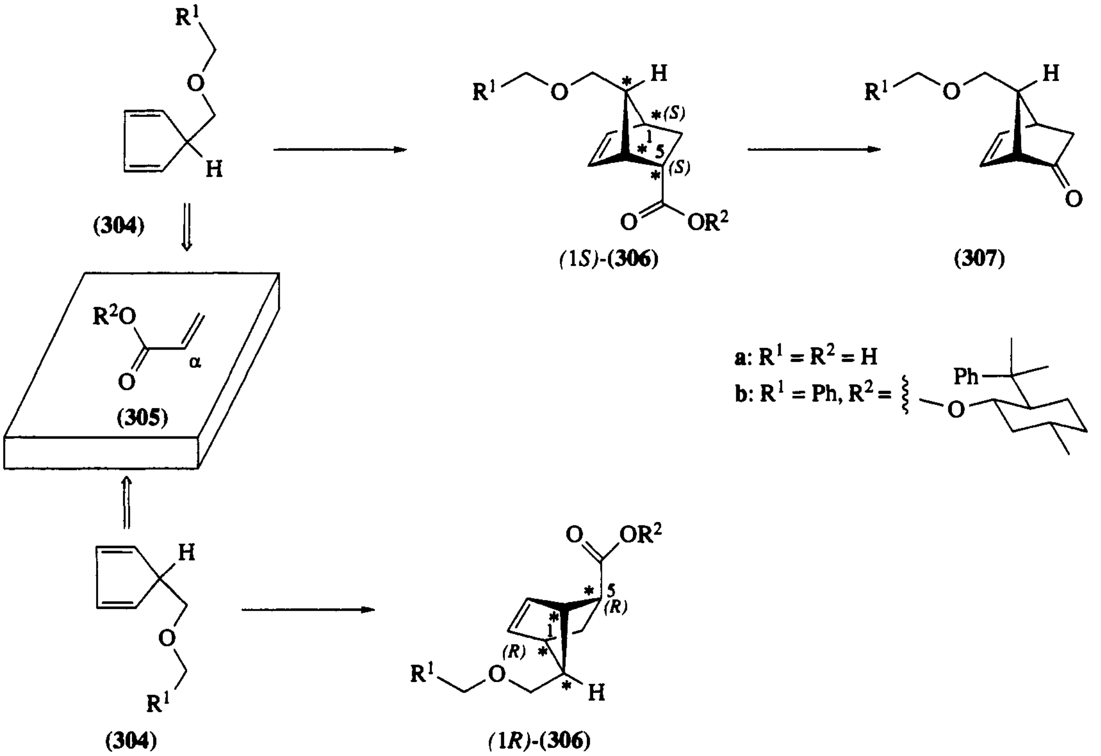

**Scheme 74**

Since only the (1*S*)-enantiomer is suitable for the synthesis of prostaglandins, exclusive diene addition from the $C_\alpha$ *re*-face was required. Indeed, attachment of an appropriate chiral ester group $R^2$ to the dienophile caused steric shielding of the now diastereotopic $C_\alpha$ *si*-face of (**305b**), thereby directing the $AlCl_3$-promoted diene addition to the $C_\alpha$ *re*-face. As a result of the π-face differentiation, the desired (1*S*)-(**306b**) was obtained from (**305b**) in significant excess over the undesired (1*R*)-isomer. This mixture was then transformed into enantiomerically pure ketone (**307**) involving cleavage of the chiral control element $R^2$.[86]

The above example demonstrates the addition of a prochiral diene to a dienophile bearing a removable chiral auxiliary. Further options for π-topological differentiation in Diels–Alder reactions include the temporary attachment of a chiral control group to the diene or, more elegantly, the employment of a chiral catalyst. So far the stoichiometric use of covalently bound chiral control groups has proved to be more efficient and predictable. In practical terms, the ideal prosthetic group should meet the following criteria. (1) Provide a wide range of Diels–Alder adducts in high chemical yield with virtually quantitative and predictable π-face stereodifferentiation and a high *endo*/*exo* as well as regio-selectivity. (2) Both enantiomers or alternative topological counterparts should be readily available. (3) Be capable of efficient attachment to the dienophile or diene and nondestructive removal from the adduct with complete retention of the induced configuration. (4) Permit direct facile and reliable assessment of induction by direct analysis of the reaction mixture (NMR, GC, HPLC). (5) Enable facile purification of the major cycloadduct to almost 100% *de*. (6) Impose crystallinity on intermediates and cycloaddition products.

#### *4.1.6.2.1 Chiral dienophiles*

The vast majority of work on asymmetric Diels–Alder reactions deals with additions of 1,3-dienes to α,β-alkenic carbonyl derivatives (XXXI) where the chirophore R* is attached to the carbonyl group either directly or *via* a heteroatom X, permitting subsequent removal of the auxiliary (*e.g.* by attack of a nucleophile Nu⁻; Scheme 75).

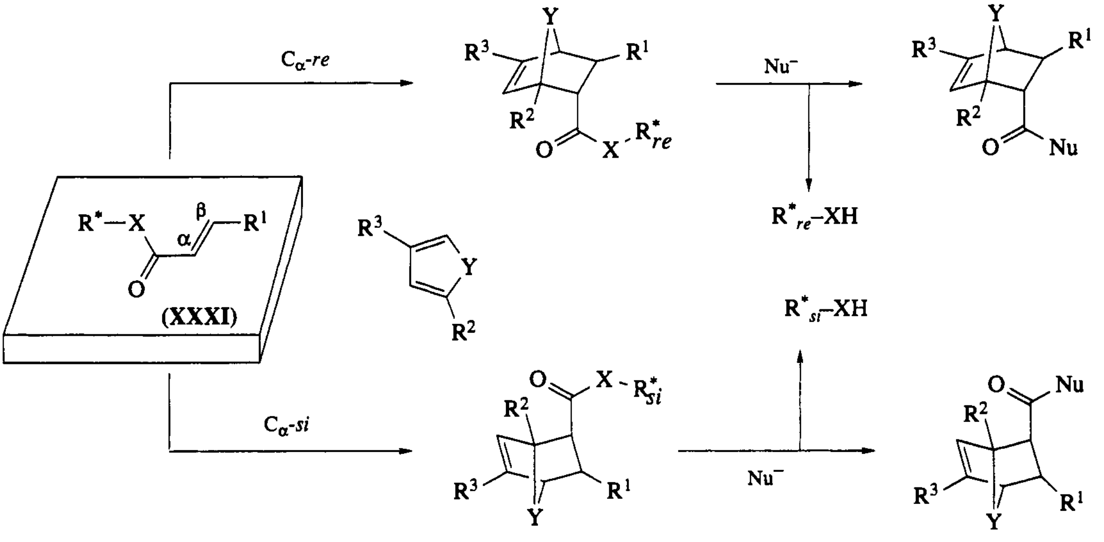

Scheme 75

The factors which direct the diene to the top (Cα *re*) or bottom face (Cα *si*) of dienophile (XXXI) may be of steric and/or stereoelectronic origin. Moreover, the overall stereofacial bias is intrinsically dependent on the conformation of (XXXI). Thus the rotational freedom around the single bonds which link the chiral and prochiral centers in (XXXI) needs to be restricted in a well-defined manner.

*(i) Non-chelated Enoates Derived from Secondary Alcohols*

In conjunction with the above arguments, the relevant conformers of acrylates derived from secondary alcohols are now discussed briefly (Scheme 76).[84a]

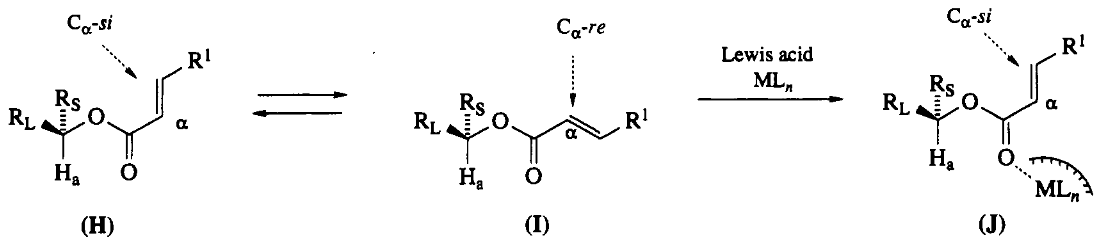

Scheme 76

According to X-ray data, such acrylates or (*E*)-$C_\beta$-substituted enoates exhibit a synperiplanar C—$H_a$/C=O relationship in the solid state which also seems to predominate in solution. In solution, however, spectroscopic evidence indicates an equilibrium between conformers (H) and (I), where the synplanar C=O/C=C disposition of the latter is disfavored by only $\Delta H = 0.32$ kcal mol$^{-1}$. If the diene adds exclusively to the π-face opposite the larger substituent, conformers (**H**) and (**I**) display a reversed topicity. Consistent with this element of unpredictability, no thermal Diels–Alder reactions of acrylates have ever surpassed a face selectivity of 80:20. However, the situation changes dramatically when the acrylate coordinates to a Lewis acid. Supported by the results of X-ray and spectroscopic studies, we assume predominant coordination of various Lewis acids (notably $TiCl_4$ and $SnCl_4$) with the carbonyl oxygen *anti* to the ester oxygen. This secures the C=O/C=C *s-trans* conformation (**J**). Moreover, Lewis acid coordination to acrylates increases the regio- and *endo*-selectivity as well as the rate of their [4 + 2] cycloaddition to 1,3-dienes. As a result of this advantageous coincidence of effects, most asymmetric Diels–Alder reactions are carried out at low temperatures in the presence of a Lewis acid.

In 1963, Walborsky and coworkers published the addition of bis(menthyl) fumarate (**308a**) to 1,3-butadiene promoted by Lewis acids, affording the cyclohexene derivative (**311a**) (Scheme 77, Table 16).[87a]

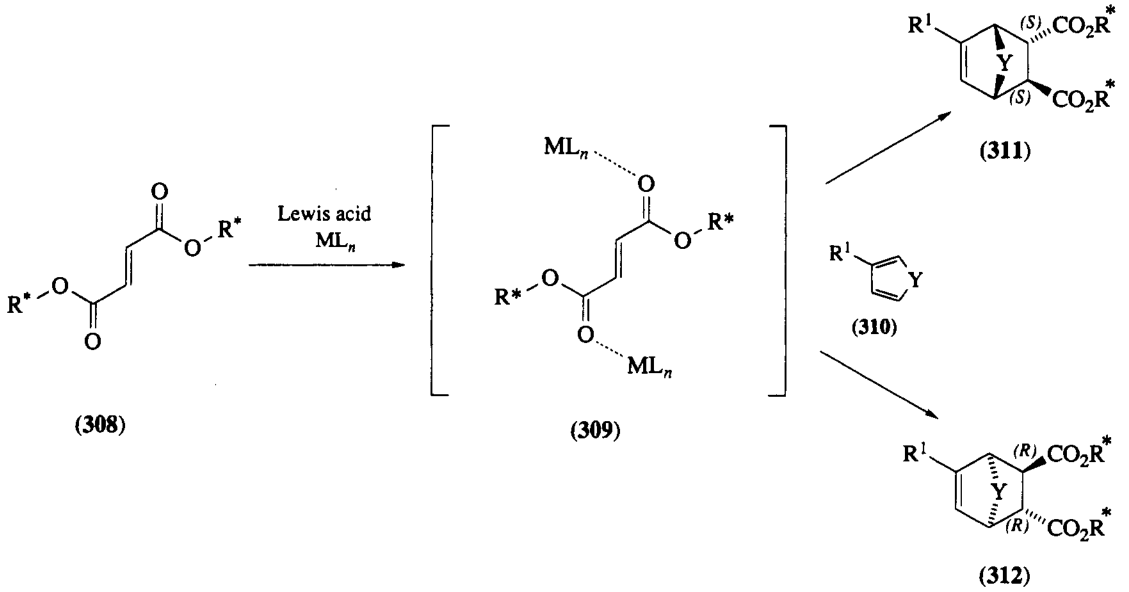

Scheme 77

Table 16 Asymmetric Diels–Alder Additions of 1,3-Dienes to Fumarates Derived from Chiral Secondary Alcohols (Scheme 77)

| Entry | Dienophile | Diene | | Lewis acid | Solvent | Temp. | Yield (%) | Ratio | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | *R** | *Y* | *R*$^1$ | (mol equiv.) | | (°C) | (**311**) + (**312**) | (**311**)/(**312**) | |
| 1 a | (1*R*)-Menthyl | $H_2$ | H | $TiCl_4$ (1.0) | Toluene | 25 | 80 | 89:11 | 87a |
| 2 a | (1*R*)-Menthyl | $H_2$ | H | $Bu^i_2AlCl$ (2.0) | Hexane | –40 | 56 | 97.5:2.5 | 87b |
| 3 b | (1*R*)-Menthyl | $H_2$ | Me | $Bu^i_2AlCl$ (1.0) | Hexane | –20 | 94 | 97.5:2.5 | 87b |
| 4 c | (1*R*)-Menthyl | $H_2$ | $OSiMe_3$ | $Et_2AlCl$ (2.0) | Toluene | –20 | 92 | 97:3 | 87b |
| 5 d | (1*R*)-Menthyl | $CH_2$ | H | $Et_2AlCl$ (1.0) | Toluene | –78 | 100 | 99.5:0.5 | 87b |
| 6 e | (*S*)-CH(Me)$CO_2$Et | $H_2$ | H | None | Hexane | 130 | 96 | 25:75 | 87c |
| 7 f | (*S*)-CH(Me)$CO_2$Et | $CH_2$ | H | None | Hexane/$CCl_4$ | –54 | 99 | 2:98 | 87c |
| 8 g | (*S*)-CH(Me)$CO_2$Et | $(CH_2)_2$ | H | None | $CCl_4$ | 77 | 96 | 10:90 | 87c |

Optimal results (product ratio (**311a**)/(**312a**) = 89:11, entry 1) were obtained using $TiCl_4$ (1 mol equiv.) in toluene at 25 °C. This relatively high induction is not surprising since fumarate (**309a**) profits from a cooperative influence of two chiral *O*-acyl groups which increase its dienophilicity and direct the diene to the π-face opposite of two large groups $R_L$ in the coordinated dienophile (**309**). More recent studies showed improved π-face differentiations by the use of $Bu^i_2AlCl$ and the more popular (*vide infra*) $Et_2AlCl$ as the Lewis acid.[87b] Acyclic dienes furnished cyclohexenes (**311a**)–(**311c**) in ratios of (**311**)/(**312**) = 97.5:2.5 (entries 2–4, 56–94% yield) whereas addition of cyclopentadiene at –78 °C yielded quantitatively a 99.5:0.5 mixture of norbornenes (**311d**)/(**312d**). Furthermore, it appears that the two acyl groups stabilize the C=O/C=C *s-trans* conformation of the (*E*)-alkene (**308**) even in the absence of Lewis acids. Hence fumaric acid esters of the *re*-face-directing ethyl (*S*)-lactate gave [4 + 2] cycloaddition products (**311**) and (**312**) in 96–99% yield and in ratios which increase (25:75 → 2:98) with decreasing reaction temperature (130 → –54 °C, entries 6–8).[87c]

The utility of the asymmetric fumarate/butadiene addition in synthesis is highlighted by the conversion of the (*R*,*R*)-cyclohexene (**313a**) (derived from (+)-(1*S*)-menthol) to enantiomerically pure (–)-bilobalide (**317**) (Scheme 78).[88] This conversion involves particularly the annulation of a cyclopentenone ring to (**313a**) at the acylated centers which govern the topicity of the acylation (**313a**) → (**314**) and internal 'Michael reaction' (**314**) → (**315**). Ozonolysis of the cyclohexene moiety sets the stage for the formation of two γ-lactone rings.

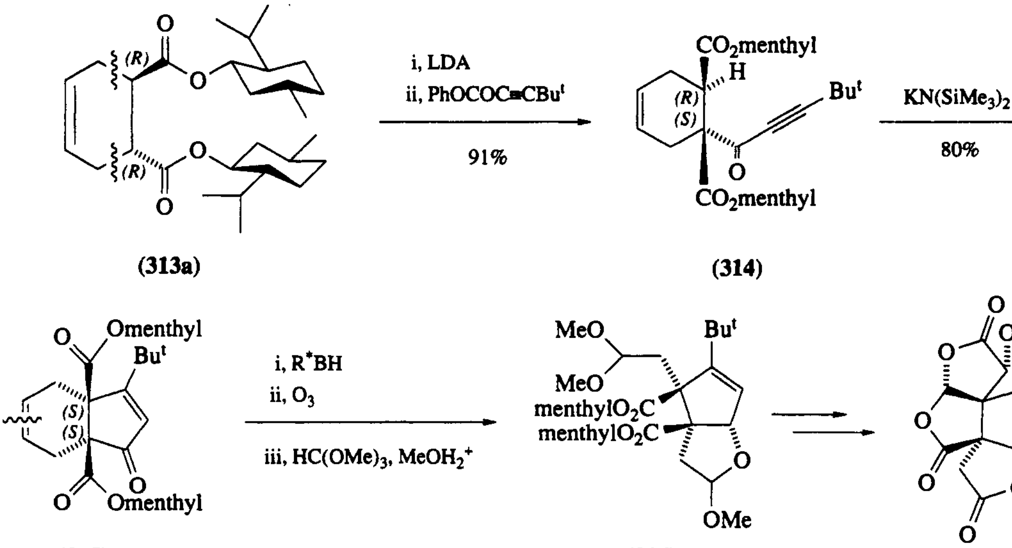

(**313a**) (**314**)

(**315**) (**316**) (**317**)

Scheme 78

Two menthyloxycarbonyl groups attached to the same alkenic terminal may also govern the topicity of diene additions, as exemplified by the $TiCl_4$-catalyzed (0.1 mol equiv., –78 °C) addition of cyclopentadiene to di-(1*R*)-menthyl methylenemalonates (**318**) (Scheme 79).[89] Under these conditions, (**318**; R = H) gave a <10:>90 mixture of norbornenes (**320**; R = H) and (**321**; R = H) in 93% yield. Crystallization of (**321**; R = H) followed by reductive cleavage ($LiAlH_4$) afforded enantiomerically pure diol (**322**). Analogous Diels–Alder reaction of (**318**; R = OAc) provided a 3:1 *endo*/*exo* mixture of (**321**; R = OAc) (83% yield, containing less than 5% of **320**; R = OAc), which was transformed into the optically pure *C*-nucleoside precursor (**323**) *via* a C–C bond cleavage by retroaldolization–reduction.

Comparison of Schemes 77 and 79 reveals that the topological interaction of the two menthyl ester groups is fundamentally different in [4 + 2] additions of fumarates (**308**) compared with those of methylenemalonates (**318**). In the latter, both ester auxiliaries cooperate in terms of activating the dienophile through formation of a stable chelate (**319**) but their individual stereoface biases in (**319**) are reversed. However, the observed π-face discrimination can be rationalized by assuming that the C-2,C-3 moiety of cyclopentadiene is more bulky than the 5-$CH_2$ group so that orientations c and d are favored over orientations a and b. Consistent with this hypothesis, no asymmetric induction could be achieved on addition of (**318**; R = H) to cyclohexadiene, which has comparably bulky C-2,C-3 and C-5,C-6 moieties.

The modest stereoface directing influence of one menthyl auxiliary in the addition of cyclopentadiene to the acrylate of (1*R*)-menthol (**324**) led to the development of improved alcohol auxiliaries, *e.g.* (**325**) to (**329**) (Scheme 80).

Without going into detail (see ref. 84), the use of neopentyl ether (**328**) is outlined here as a representative example (Scheme 81, Table 17).[90] Its acrylate (**330a**) underwent $TiCl_2(OPr^i)_2$-promoted addition of cyclopentadiene with >20:1 *endo*/*exo* selectivity and outstanding π-face discrimination to give norbornene (**331a**) in almost quantitative diastereoisomeric purity (entry 1); reductive cleavage regenerated the auxiliary (**328**) and afforded virtually pure alcohol (**332a**) in excellent overall yield. The less reactive butadiene required more stringent reaction conditions ($TiCl_4$, –8 °C, 112 h) but still proceeded with high chiral efficiency (entry 2). In contrast, crotonate (**330c**), deactivated by the $C_\beta$-positioned methyl group, failed to give the cyclopentadiene adduct (**331c**) in yields of >7% (entry 3).

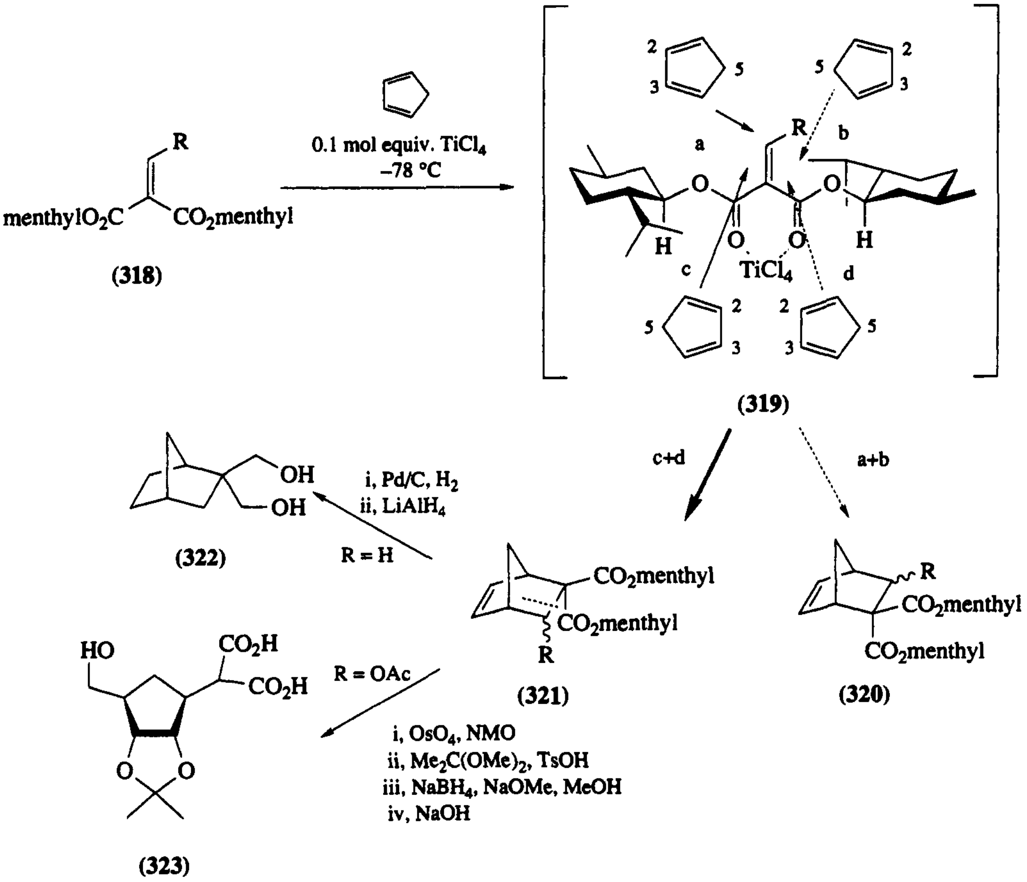
R
menthylO2C
CO2menthyl
(318)
0.1 mol equiv. TiCl4
-78 °C
2
3
5
a
b
c
d
R
O
O
H
TiCl4
(319)
c+d
a+b
i, Pd/C, H2
ii, LiAlH4
R = H
OH
OH
(322)
CO2menthyl
CO2menthyl
R
(321)
R
CO2menthyl
CO2menthyl
(320)
HO
CO2H
CO2H
R = OAc
i, OsO4, NMO
ii, Me2C(OMe)2, TsOH
iii, NaBH4, NaOMe, MeOH
iv, NaOH
(323)

**Scheme 79**

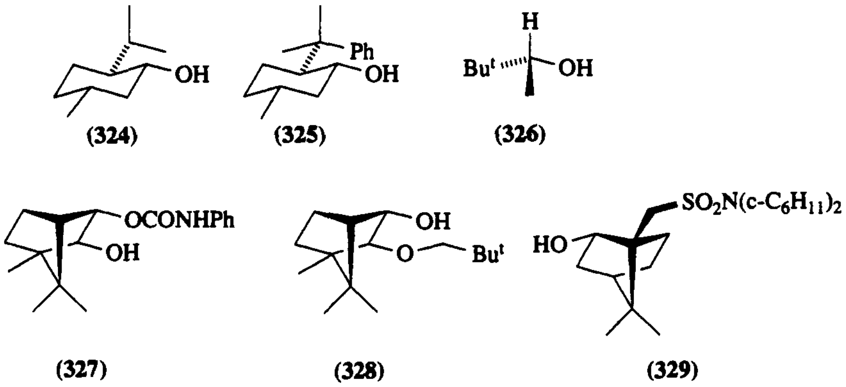
OH
(324)
Ph
OH
(325)
H
Bu^t
OH
(326)
OCONHPh
OH
(327)
OH
O
Bu^t
(328)
SO2N(c-C6H11)2
HO
(329)

**Scheme 80**

These observations are consistent with a steric shielding of the $C_\alpha$,$C_\beta$-face in coordinated (**330**) by the Bu$^t$ group which directs the diene to the opposite face. However, the addition process still suffers from steric hindrance due to the tetragonalization of the $C_\alpha$ and $C_\beta$ centers, and slows down with crotonate (**330c**) to such an extent that polymerization predominates.

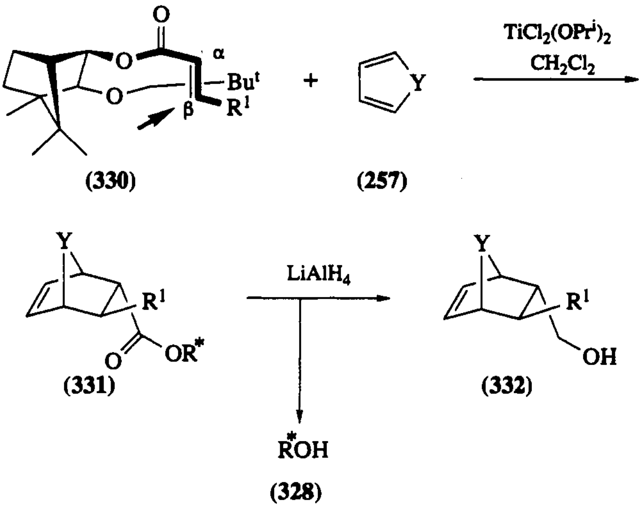
α
β
Bu$^t$
R$^1$
Y
TiCl$_2$(OPr$^i$)$_2$
CH$_2$Cl$_2$
(330)
(257)
LiAlH$_4$
OR*
OH
(331)
(332)
R*OH
(328)

Scheme 81

Table 17 Asymmetric Diels–Alder Reactions of Neopentyl Ether Shielded Acrylates (Scheme 81)

| *Entry* | *Dienophile* *R*$^1$ | *Diene* *Y* | *Lewis acid* | *Temp. (°C)* *(time,* h*)* | *Yield (%)* *(331)* | *ee (%)* *(332)* |
|---|---|---|---|---|---|---|
| 1 **a** | H | CH$_2$ | TiCl$_2$(OPr$^i$)$_2$ | −20 (4) | 95 | 99.2 |
| 2 **b** | H | H$_2$ | TiCl$_4$ | −8 (112) | 98 | 96 |
| 3 **c** | Me | CH$_2$ | TiCl$_2$(OPr$^i$)$_2$ or TiCl$_4$ | −20 to 20 (4–150) | <10 | — |

Allenic ester (**334**), nevertheless, displayed a sufficiently high dienophilicity towards cyclopentadiene to give, in the presence of TiCl$_2$(OPr$^i$)$_2$, *exo*-methylenenorbornene (**335**) in high yield and stereochemical purity (Scheme 82).[90b] The Diels–Alder process (**334**) → (**335**) served as the key step for a synthesis of enantiomerically pure (–)-β-santalene (**337**). The conversion of (**335**) into the natural product involved notably intermediate (**336**) which, owing to the attached auxiliary, could be efficiently purified by crystallization.

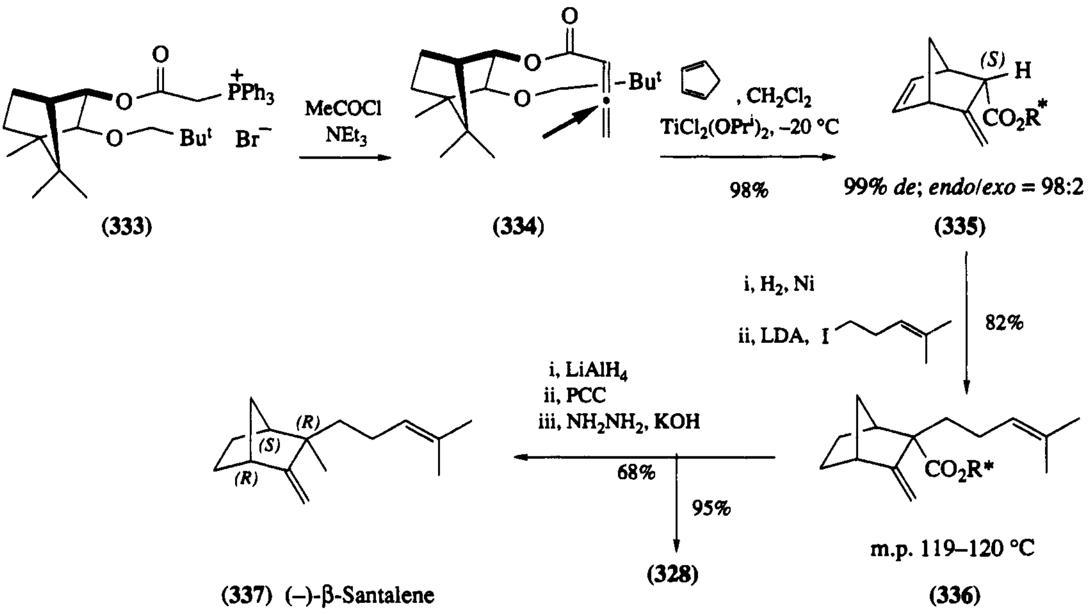
PPh$_3$
Bu$^t$ Br$^-$
(333)
MeCOCl
NEt$_3$
Bu$^t$
(334)
, CH$_2$Cl$_2$
TiCl$_2$(OPr$^i$)$_2$, −20 °C
98%
(S)
H
CO$_2$R*
99% de; endo/exo = 98:2
(335)
i, H$_2$, Ni
ii, LDA, I
82%
CO$_2$R*
m.p. 119–120 °C
(336)
i, LiAlH$_4$
ii, PCC
iii, NH$_2$NH$_2$, KOH
68%
95%
(328)
(R)
(S)
(R)
(337) (–)-β-Santalene

Scheme 82

In the following phase of development (*vide infra*) the scope of asymmetric Diels–Alder reactions was extended to include β-alkyl-substituted dienophiles and less-reactive dienes by means of 'activating' dienophile auxiliaries.

### (ii) α,β-Unsaturated Hydroxy Ketones

The crucial role of chelation in terms of increasing rigidity and reactivity of chiral dienophiles was first demonstrated (1983) with α-hydroxy ketone derivatives (Scheme 83, Table 18).[91] Conjugated α-hydroxy ketones (**340**) and their enantiomers were prepared *via* separation of acid (**338**) from its enantiomer, followed by successive treatment with $Bu^nLi$ and the appropriate vinyllithium reagent (**339**).

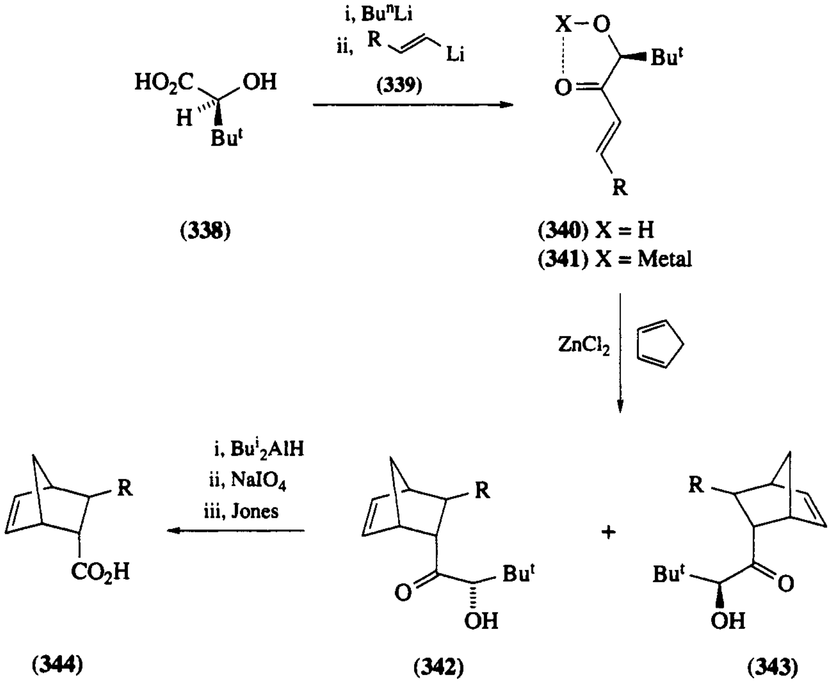
HO2C
OH
H
Bu^t
(338)
i, Bu^nLi
ii, R Li
(339)
X–O
Bu^t
O
R
(340) X = H
(341) X = Metal
ZnCl2
i, Bu^i2AlH
ii, NaIO4
iii, Jones
R
CO2H
(344)
R
O
Bu^t
OH
(342)
+
R
Bu^t
O
OH
(343)

**Scheme 83**

**Table 18** Diels–Alder Reactions of α,β-Unsaturated Hydroxy Ketones with Cyclopentadiene (Scheme 83)

| *Entry* | *R* | *Lewis acid* (1 mol equiv.) | *Temp.* (°C) (*time*, h) | *Yield* (%)[a] | *endo/exo* (C=O) | *Ratio* (**342**)/(**343**) |
|---|---|---|---|---|---|---|
| 1 **a** | H | — | −20 (24) | 90 | 89:11 | 99:1 |
| 2 **a** | H | $ZnCl_2$ | −43 (1) | 95 | 94:6 | >99:<1 |
| 3 **b** | Me | — | r.t. (72) | 84 | 83:17 | 98.5:1.5 |
| 4 **b** | Me | $ZnCl_2$ | −20 (16) | 90 | 94:6 | >99:<1 |

[a] Combined yield of *endo* and *exo* adducts.

Addition of cyclopentadiene to (**340a**) occurs readily at −20 °C even in the absence of a Lewis acid (Table 18, entry 1) to give adducts (**342a**) and (**343a**) in a ratio of 99:1. This high diastereotopic $\pi$-face differentiation undoubtedly derives from hydrogen bonding, which constrains the chiral center within a rigid five-membered ring. The bulky *t*-butyl group enforces the C=O/C=C *syn* conformation and directs the diene to the opposite enone face. The unusually high reaction rate can also be assigned to hydrogen bonding. In the presence of $ZnCl_2$ or $Ti(OPr^i)_4$, Diels–Alder additions to (**340**) proceed at even lower temperatures with improved *endo* and $\pi$-face selectivities (entries 2, 4). Apparently the dienophile system becomes more conformationally rigid and 'activated' in the chelate (**341**), permitting efficient asymmetric Diels–Alder addition of a less-reactive dienophile (entry 4) and of acyclic dienes, as exemplified by Scheme 84.

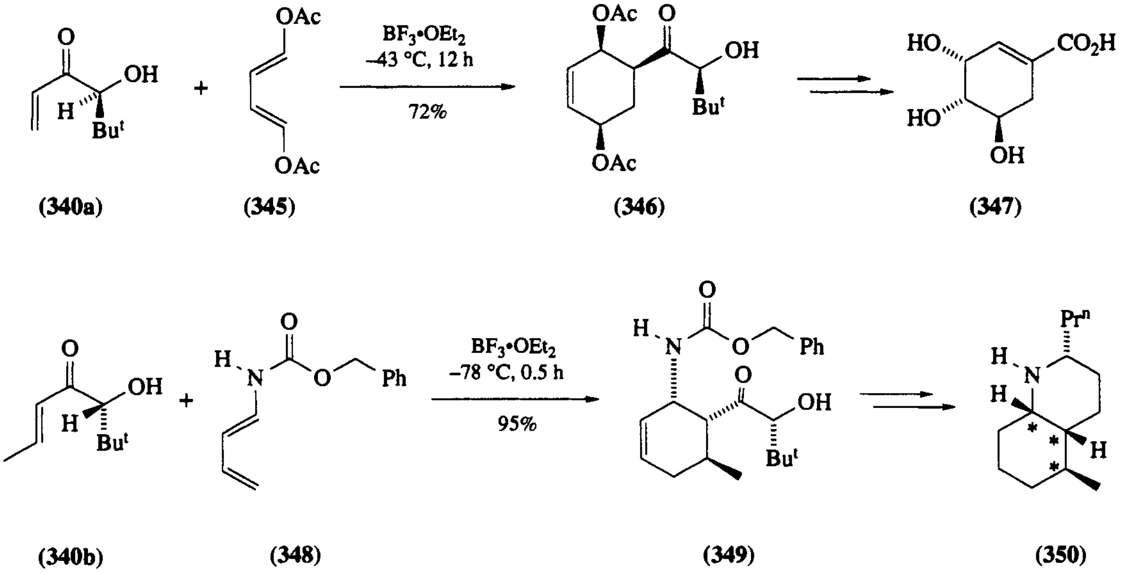

**(340a)** **(345)** **(346)** **(347)**

**(340b)** **(348)** **(349)** **(350)**

**Scheme 84**

Thus optically pure shikimic acid (**347**) has been synthesized *via* the addition of 1,4-diacetoxybutadiene (**345**) to (**340a**), whereas the Diels–Alder reaction of *N*-dienylcarbamate (**348**) to hydroxy enone (**340b**) served as the key step for a synthesis of the enantiomer (**350**) of naturally occurring pumiliotoxin C (**142**) (*cf.* Scheme 35).

Regardless of these impressive applications, the preparation of chiral dienophiles remains relatively laborious. A further shortcoming is the inevitable destruction of the valuable chiral auxiliary on oxidative removal, (**342**) → (**344**) (Scheme 83).

### *(iii) Chelated N-Acyl-N-enoyl Derivatives*

In contrast to nonchelated enoates, $\alpha,\beta$-alkenic amide derivatives prefer a $C{=}O/C_\alpha{=}C_\beta$ *s-cis* arrangement (**L**) over (**K**) to avoid repulsions between $C_\beta/XR^*$ or $C_\beta/R^2$ (Scheme 85). This also holds for the chelated dienophiles (**M**) where rotation around the (C=O)—N and (X=Z)—N bonds is further inhibited. Such a chelation also increases the dienophilicity of (**M**), which contributes to the versatility of this concept.

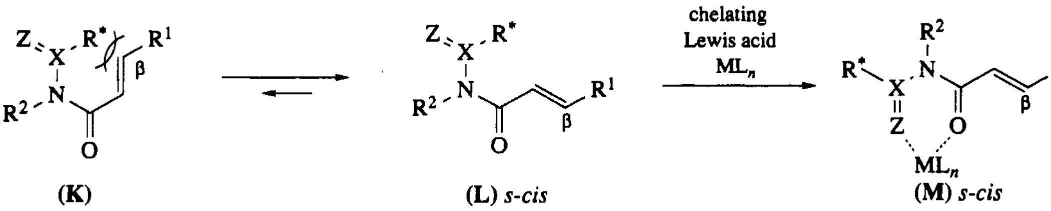

**(K)** **(L)** *s-cis* **(M)** *s-cis*

**Scheme 85**

As an extension of the elegant applications of chiral *N*-acyloxazolidinones to asymmetric aldolizations and enolate alkylations, Diels–Alder reactions of the unsaturated derivatives (**351**) and (**355**) were first described in 1984 (Scheme 86, Table 19).[92]

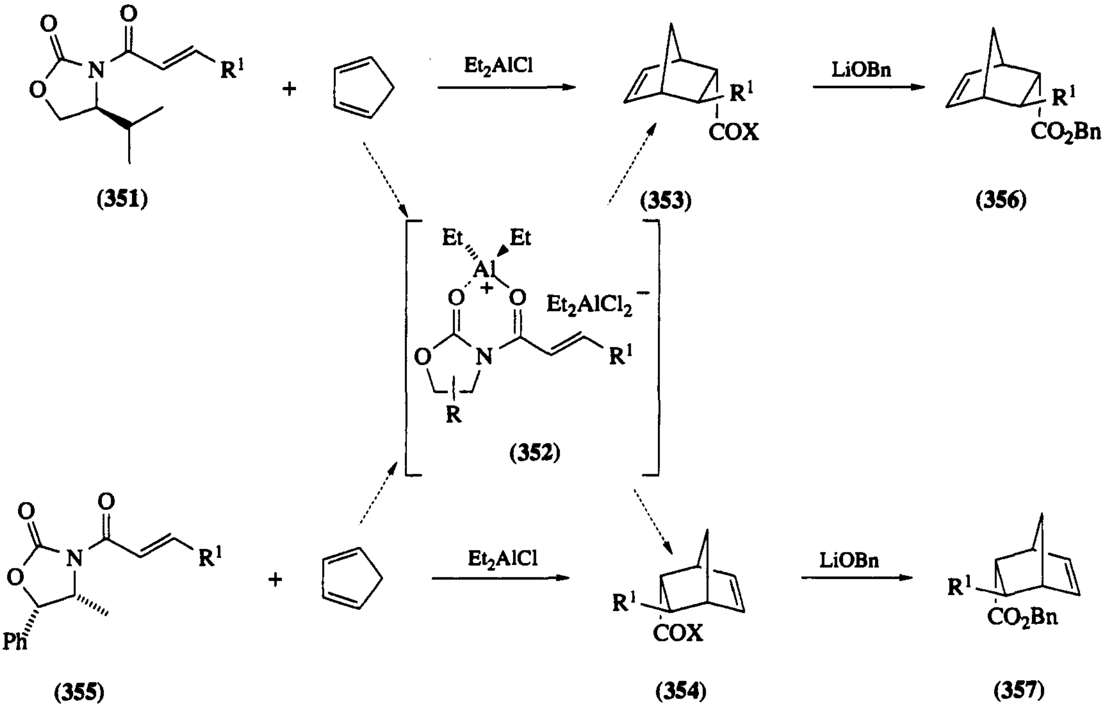

**Scheme 86**

**Table 19** Asymmetric Diels–Alder Additions of Cyclopentadiene to α,β-Unsaturated *N*-Acyloxazolidinones[a] (Scheme 86)

| *Entry* | *Dienophile* | *R*¹ | *endo/exo (C=O)* | *Ratio*[b] *(353)/(354)* | *Purification* | *Pure product*[c] | *Yield (%)* |
|---|---|---|---|---|---|---|---|
| 1 a | (**351**) | H | >100:1 | 93:7 | Chrom. | (**353a**) | 81 |
| 2 b | (**355**) | H | 100:1 | 5:95 | Chrom. | (**354b**) | 82 |
| 3 c | (**351**) | Me | 48:1 | 95:5 | Cryst. | (**353c**) | 82 |
| 4 d | (**355**) | Me | 60:1 | 2:98 | Chrom. | (**354d**) | 88 |
| 5 e | (**351**) | Ph[d] | >50:1 | 93:7 | Chrom. | (**353a**) | 83 |

[a]Conditions: 1.4 mol equiv. of $Et_2AlCl$, $CH_2Cl_2$, −100 °C, 5 min. [b]Crude reaction mixture. [c]*ds* ≥99:1. [d]At −20 °C, 2.5 h.

Comparative studies of several Lewis acids revealed the essential advantage of using more than 1 equivalent of $Et_2AlCl$, whereas $TiCl_4$ or $SnCl_4$ gave poor inductions. Thus $Et_2AlCl$-induced (1.4 equivalent) additions of the valinol derivatives (**351**) to cyclopentadiene were complete within 2 min at −100 °C and gave, with 98–99% *endo* selection, norbornenes (**353**) and (**354**) in ratios of >93:<7 (entries 1, 3, 5). Inverse π-face topicity was displayed with similar efficacy by the norephedrine-derived dienophiles (**355**) (entries 2, 4). After recrystallization or chromatography the resulting major cycloadducts (**353**) or (**354**) were obtained in 81–88% yield and >98% diastereoisomeric purity. Nondestructive cleavage of the oxazolidinone auxiliaries from the adducts (**353**) and (**354**) by 'transesterification' with lithium benzyloxide furnished the benzyl esters (**356**) or their enantiomers (**357**). Sterically hindered addition products were preferably 'saponified' with LiOH/30% $H_2O_2$ in THF, *e.g.* (**360d**) → (**361d**) (Scheme 87).

The influence exerted by $Et_2AlCl$ on the Diels–Alder additions of dienophiles (**351**) and (**355**) was ascribed to the intermediacy of the chelates (**352**) which exhibit C=C/C=O *syn* planarity. The electron deficiency and rigid structure of (**352**) account for the high reactivity and good π-face differentiation. Even less reactive acyclic dienes add smoothly to such chelated dienophiles (Scheme 87, Table 20). Interestingly, in this case the (*S*)-benzyl derivatives (**358**) displayed much higher diastereoselectivity than the isopropyl derivatives (**351**). Good stereoface selectivities were achieved on additions to (*E*)-C$_\beta$-substituted *N*-enoyloxazolidinones at temperatures between −100 and 0 °C (Table 19, entries 3–5; Table 20, entries 2, 4). Additions to (*Z*)-*N*-crotonoyl or β,β-dimethylacryloyl dienophiles were less useful due to (*Z*/*E*) equilibration or insufficient reactivity. It is worth noting that the chiral oxazolidinone moiety also efficiently directed intramolecular Diels–Alder reactions of 2,7,9-decatrienoyl- and 2,8,10-undecatrienoyl derivatives.[92b]

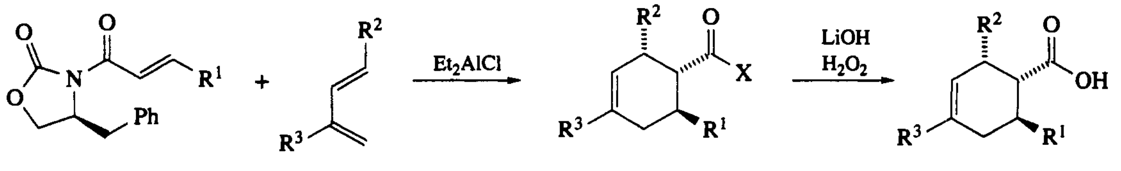

(**358**) (**359**) (**360**) (**361**)

**Scheme 87**

**Table 20** Asymmetric Diels–Alder Additions of Acyclic Dienes to α,β-Unsaturated *N*-Acyloxazolidinones[a] (Scheme 87)

| *Entry* | *Dienophile* *$R^1$* | *Temp.* (°C) (*time*, h) | *Diene* *$R^2$* | *Diene* *$R^3$* | *Purification* | *Yield* (%) *pure* (**360**) |
|---|---|---|---|---|---|---|
| 1 **a** | H | −100 (0.3) | H | Me | Chrom. | 85 |
| 2 **b** | Me | b | H | Me | Cryst. | 83 |
| 3 **c** | H | −100 (0.3) | Me | H | Chrom. | 84 |
| 4 **d** | Me | −30 (6) | Me | H | Cryst. | 77 |

[a]Conditions: 1.4 mol equiv. of $Et_2AlCl$, $CH_2Cl_2$. [b]−40 °C, 10 h, then 0 °C, 0.5 h.

Bornane-10,2-sultam (**362**) and its antipode, accessible from inexpensive (+)- and (−)-camphorsulfonic acid in two simple operations, were introduced[93] in 1984 and rank today among the most practical auxiliaries (Scheme 88).[94] Both chirophore enantiomers are commercially available in kg quantities.[93f] Almost all of their *N*-acyl derivatives are stable and can be (1) readily purified by crystallization, (2) directly analyzed by $^1$H NMR and/or GC to determine their stereochemical purity, and (3) cleaved (*e.g.* with $LiAlH_4$, LiOH, LiOOH, MeOMgI, *etc.*) under mild conditions without loss of the induced chirality and with excellent recovery of the auxiliary.

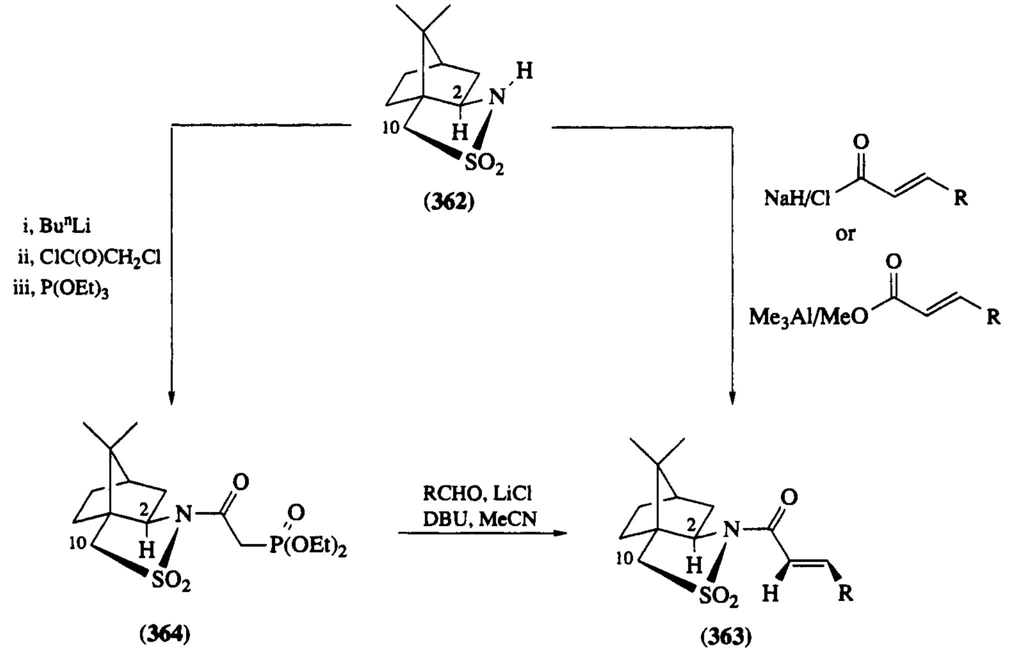

(**362**) (**364**) (**363**)

**Scheme 88**

The strongly dienophilic N-enoyl compounds (**363**) are readily prepared by direct *N*-acylation (NaH, RCOCl or $Me_3Al$, $RCO_2Me$)[94b] or *via* phosphonates (**364**)[93d] by means of a modified Wittig–Horner reaction.

In the presence of $TiCl_4$, $EtAlCl_2$, $Et_2AlCl$ or $Me_2AlCl$, cyclopentadiene added smoothly to the acryloyl sultam (**363a**) at –130 °C and to the less reactive crotonoyl sultam (**363b**) at –78 °C (Scheme 89, Table 21).[93a,93b,93g] Adducts (**366**) were formed with excellent *endo* as well as π-face selectivities and obtained pure in good yields after crystallization.

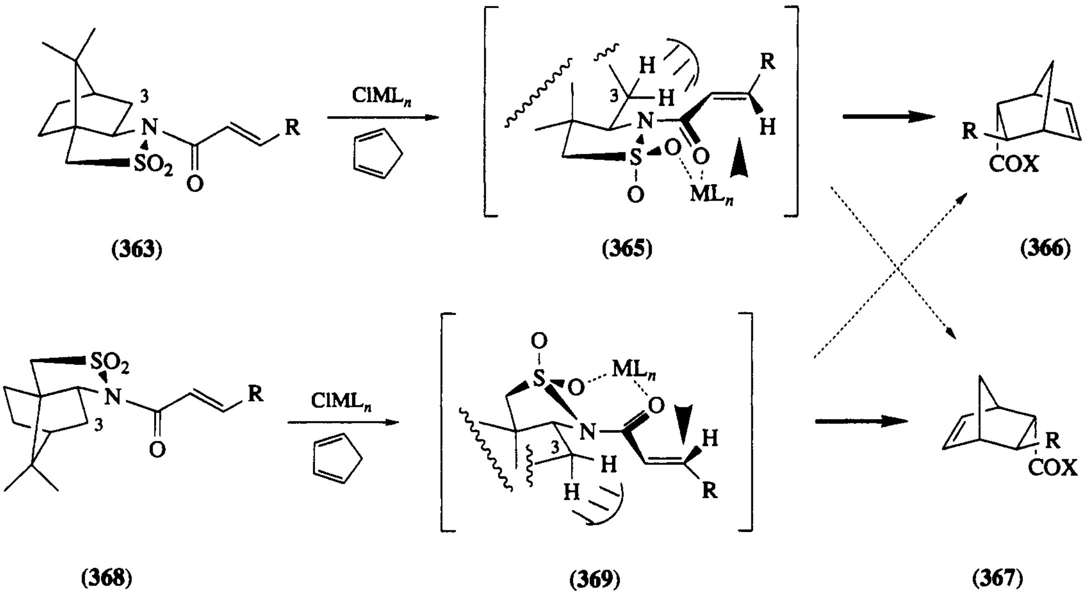

**Scheme 89**

**Table 21** Asymmetric Diels–Alder Additions of Cyclopentadiene to *N*-Enoylbornane 10,2-Sultams (Scheme 89)

| *Entry* | *Dienophile* | *R* | *Lewis acid* (mol equiv.) | *Temp.* (°C) (*time*, h) | *endo/exo* (C=O) | *Ratio*[a] (**366**)/(**367**) | *Purification* | *Pure product*[b] | *Yield* (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 a | (**363**) | H | $EtAlCl_2$ (1.5) | –130 (6) | 200:1 | 97.5:2.5 | Cryst. | (**366a**) | 83 |
| 2 a | (**363**) | H | $TiCl_4$ (0.5) | –130 (6) | 25:1 | 97:3 | — | — | — |
| 3 b | (**363**) | Me | $TiCl_4$ (0.5) | –78 (1) | 100:1 | 96.5:3.5 | Cryst. | (**366b**) | 83 |
| 4 b | (**363**) | Me | $EtAlCl_2$ (1.5) | –78 (18) | 24:1 | 99:1 | — | — | — |
| 5 b | (**363**) | Me | $Et_2AlCl$ (2) | –78 (18) | — | — | Cryst. | (**366b**) | 80 |
| 6 c | (**368**) | Me | $TiCl_4$ (0.5) | –78 (20) | 50:1 | 3:97 | Cryst. | (**367c**) | >57 |
| 7 c | (**368**) | Me | $EtAlCl_2$ (1.5) | –78 (18) | 50:1 | 3:97 | — | — | — |

[a] Mixtures of (**366**) + (**367**) obtained in 88–98% yield from dienophile. [b] Diastereomeric purity ≥99%.

$EtAlCl_2$- or $Me_2AlCl$-promoted Diels–Alder addition of butadiene or isoprene to (**363a**) also proceeded readily at –78 or –94 °C to give, after recrystallization, ~100% pure (*S*)-cyclohexenes (**370**) (Scheme 90, Table 22, entries 8–10). Reductive cleavage of the cycloadducts (**370**) with $LiAlH_4$ refurnished the sultam (**362**) (89–95% after crystallization) and gave the pure alcohols (**372**) on simple bulb-to-bulb distillation. Alternatively, saponification of adduct (**370a**) with LiOH afforded acid (**373a**) (a potential precursor for a synthesis of (–)-shikimic acid, **347**) without epimerization.

The sense of asymmetric induction could be easily reversed (Schemes 89, 90; Tables 21, 22, entries 6, 7, 11) by exploiting the readily available enantiomeric dienophiles (**368**). It is worth noting that several of these sultam-controlled [4 + 2] cycloadditions were smoothly carried out with 10 g, 15 g and 112 g batches of dienophile (Tables 21, 22; entries 5,[93g] 10,[93h] 11,[93i] respectively).

Crystallized cyclopentadiene adduct (**367c**) was transformed into enantiomerically pure (–)-1-*O*-methylloganin aglucone (**378**) (Scheme 91).[93b] This synthesis illustrates the potential of asymmetric Diels–Alder reactions which in one step created four stereogenic centers of which all but C-1 (requiring C,O inversion) possess the desired absolute configuration. Extension of the sultam-directed bias to intra-

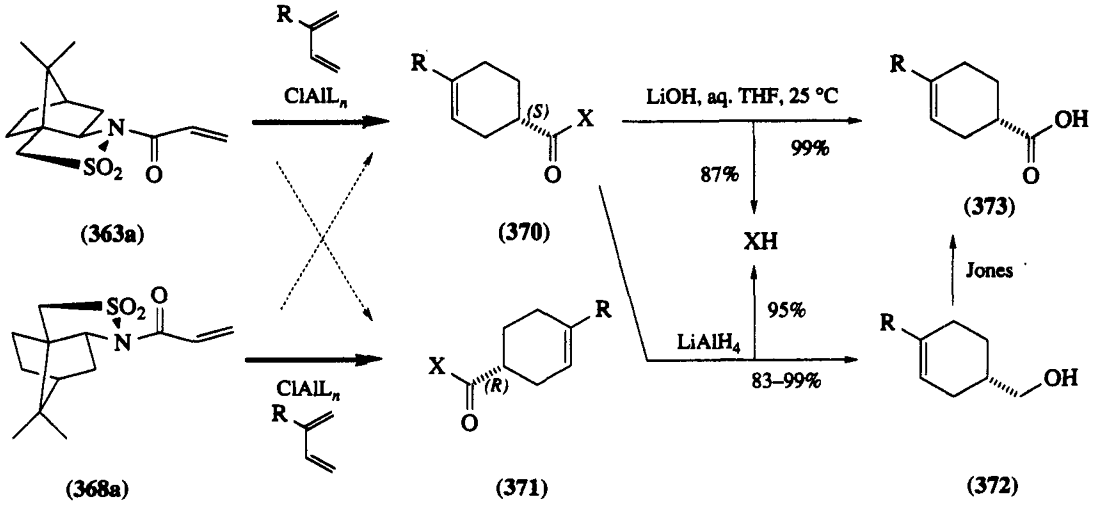
R
ClAlL$_n$
N
SO$_2$
O
(363a)
SO$_2$
N
(368a)
ClAlL$_n$
R
R
(S)
X
O
(370)
X
(R)
O
R
(371)
LiOH, aq. THF, 25 °C
99%
87%
XH
95%
LiAlH$_4$
83–99%
R
OH
O
(373)
Jones
R
OH
(372)

Scheme 90

**Table 22** Asymmetric Diels–Alder Additions of Butadiene and Isoprene to *N*-Acryloylbornane 10,2-Sultams in $CH_2Cl_2$ (Scheme 90)

| *Entry* | *Dienophile* | *Diene* *R* | *Lewis acid* (mol equiv.) | *Temp.* (°C) (*time*, h) | *Ratio* (**370**)/(**371**) | *Product* *cryst.* | *Yield* (%) |
|---|---|---|---|---|---|---|---|
| 8 a | (**363a**) | H | $EtAlCl_2$ (1.5) | −78 (6 ) | 98.5:1.5 | (**370a**) | 81[a] |
| 9[b] b | (**363a**) | Me | $EtAlCl_2$ (1.5) | −94 (6) | 97.2:2.8 | (**370b**) | 64[a] |
| 10 a | (**363a**) | H | $Me_2AlCl$ (1.5) | −78 (44) | 95:5 | (**370b**) | 53–60[a] |
| 11 c | (**368a**) | H | $EtAlCl_2$ (1.5) | −78 (—) | 3.5:96.5 | (**371a**) | 95.9[c] |

[a] Diastereomeric purity ≥99%. [b] Ref. 93j. [c] Not crystallized.

molecular Diels–Alder reactions proved equally successful[93c] and was exploited for the enantioselective total synthesis of the marine natural product (–)-pulo'upone.[93d]

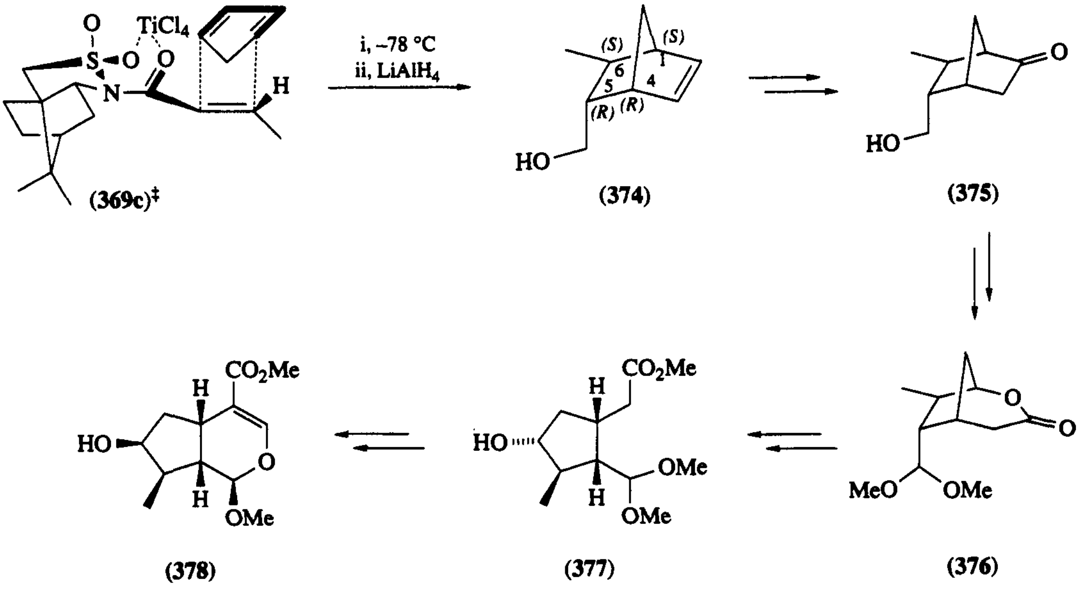
O
TiCl$_4$
S
O
O
N
H
(369c)‡
i, –78 °C
ii, LiAlH$_4$
(S)
(S)
6
1
5
4
(R)
(R)
HO
(374)
O
HO
(375)
O
O
MeO
OMe
(376)
H
CO$_2$Me
HO
OMe
H
OMe
(377)
H
CO$_2$Me
HO
O
H
OMe
(378)

Scheme 91

The remarkable $TiCl_4$- and $EtAlCl_2$-enhanced rate and π-face differentiation of [4 + 2] cycloadditions to *N*-enoylsultams was rationalized in terms of chelates (**365**) and (**369**) (Scheme 89) involving the dicoordinating Lewis acid $ML_n$, the carbonyl O-atom and the upper sulfonyl O-atom which are attacked by dienes from the π-face opposite to the C-3 methylene group.[93a] Indeed, X-ray crystal-structure analyses of noncoordinated[93a] or $TiCl_4$-chelated *N*-crotonylsultam[93c] show in both cases *s-cis* disposed $C{=}O/C_\alpha{=}C_\beta$ bonds but an $NSO_2/C{=}O$ *s-trans* arrangement of (**363b**) in the absence of $TiCl_4$ (Scheme 92).

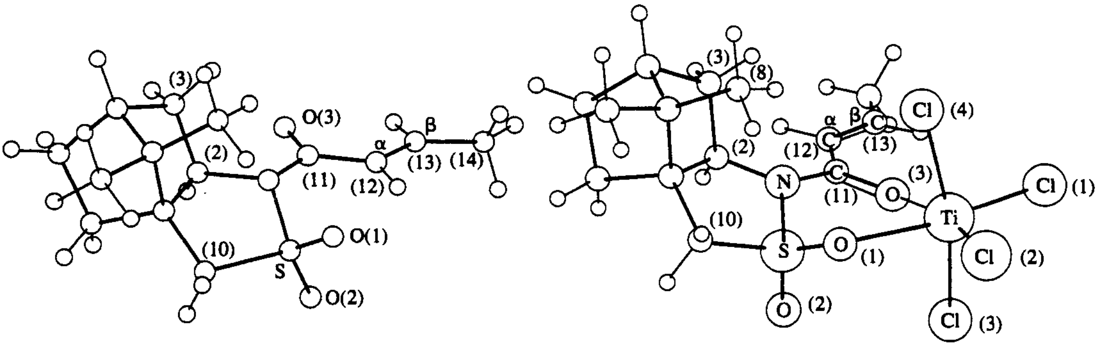

**(363b)** **(365b)** $ML_n = TiCl_4$

Scheme 92

In the $TiCl_4$ chelate (**365b**) the $NSO_2$ and C=O groups are locked into a rigid *s-cis* conformation where, compared with $H_{exo}$ of C-3, the Cl atoms play only a minor role in blocking the $C_\alpha$-*si* face (*cf.* Scheme 93).

### *(iv) α,β-Unsaturated Chelated Esters and Amides*

The concept of using an ester auxiliary which also contains a 'handle' suitable for chelation was first disclosed in 1984/1985.[95] Thus $TiCl_4$-promoted addition of cyclopentadiene to the acrylate of ethyl (*S*)-lactate (**379**) proceeded readily at –63 °C to give (with a 39:1 *endo*/*exo* preference) a 93:7 mixture of norbornenes (**381a**) and (**382a**), from which the major product (**381a**) was isolated by MPLC (Scheme 93, Table 23, entry 1). Mild saponification of adduct (**381a**) with LiOH in aqueous THF and purification *via* iodolactonization/elimination provided pure (1*R*,2*R*)-5-norbornene-2-carboxylic acid.

A highly significant X-ray crystal-structure analysis of the isolated $TiCl_4$ complex (**380a**) revealed the following features: chelation of the two ester carbonyl groups by the titanium atom with one of its chloride ligands shielding the $C_\alpha$-*re* face of the alkenic bond which is *s-cis* relative to the adjacent C=O bond.[95b] It thus appears that during the Diels–Alder process the diene is directed to the $C_\alpha$-*si* face of the chelated dienophile (**380a**) to avoid the steric bulk of the Cl ligand. Analogous reaction conditions but using $EtAlCl_2$ as a Lewis acid resulted in a similar *endo*/*exo* selectivity but a reversed face differentiation in favor of product (**382a**) (entry 2). A maximal ratio (**381a**)/(**382a**) = 22:78 attained with 2.5 mol equiv. of $EtAlCl_2$ indicates the 1:2 complex (**383**) to be the reactive species. The critical influence of $TiCl_4$ also shows on additions of 1,3-dienes to the (more reactive) fumarate of ethyl (*S*)-lactate.[87c] The dienes approach predominantly the *si* face of the dienophile in the presence of $TiCl_4$ (1.4–1.5 mol equiv.) (Table 23, entries 3–5), but the opposite *re* face in the absence of Lewis acids (Table 16, entries 6–8).

Prompted by the X-ray studies of the acryloyl lactate–$TiCl_4$ complex (**380a**), commercially available pantolactone was chosen as an auxiliary aiming to facilitate entropically the formation of a seven-membered titanium chelate (**385**). Indeed, using 0.1–0.75 mol equiv. of $TiCl_4$ the acrylate and crotonate of (*R*)-pantolactone (**384**) underwent smooth addition of cyclopentadiene, butadiene and isoprene to give adducts (**386**) and (**387**) in ratios of >93:<7 (Scheme 94, Table 24, entries a–d).[96a,96c] Opposite product ratios were obtained using dienophiles (**388**) derived from (*S*)-pantolactone (entry e)[96b] or (**390**) derived from the more readily available *N*-methyl-2-hydroxysuccinimide (entries f, g).[96c] The major products were purified by crystallization and saponified without epimerization (LiOH, THF/water, r.t.) to furnish the corresponding carboxylic acids.

In close relation to the work on acrylates derived from lactate, pantolactone and 2,5-disubstituted pyrrolidines (*vide infra*), *N*-acryloylproline benzyl ester (**391**) has been studied as a chiral dienophile

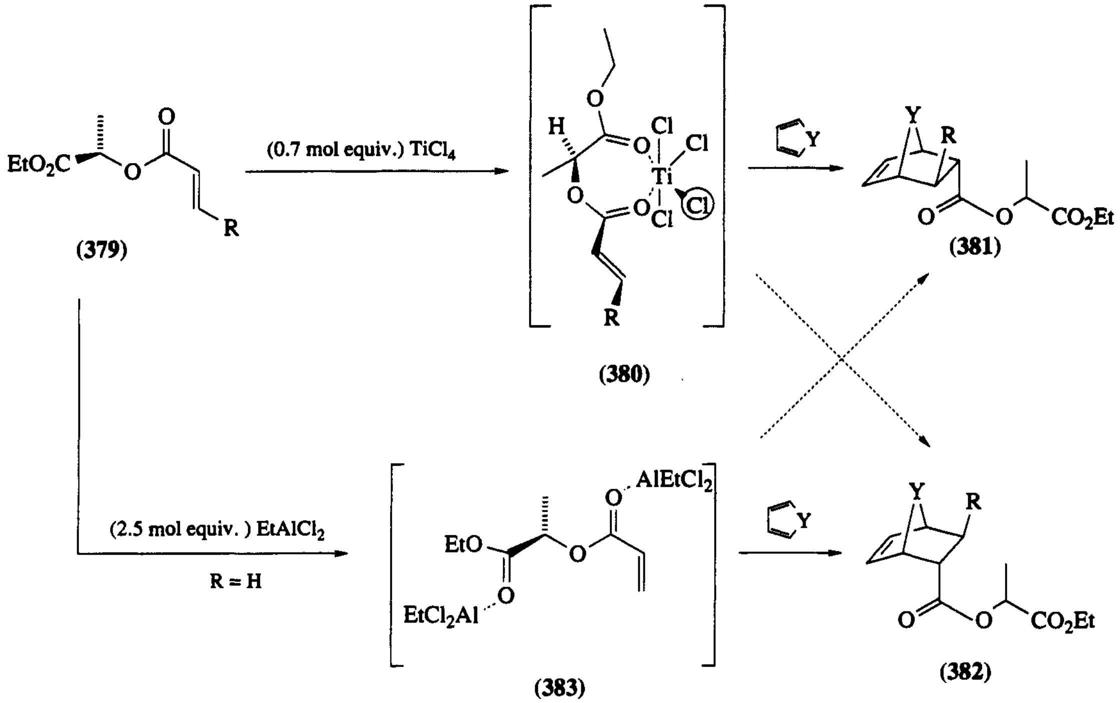

Scheme 93

**Table 23** Lewis Acid Promoted Diels–Alder Additions of 1,3-Dienes to Acrylates and Fumarates Derived from Ethyl (*S*)-Lactate (Scheme 93)

| *Entry* | *R* | *Y* | *Lewis acid* (mol equiv.) | *Solvent* | *Temp.* (°C) | *Yield (%)* (**381**) + (**382**) | *Ratio* (**381**)/(**382**) |
|---|---|---|---|---|---|---|---|
| 1 **a** | H | $CH_2$ | $TiCl_4$ (0.75) | $CH_2Cl_2$/hexane | –63 | 88 | 93:7 |
| 2 **a** | H | $CH_2$ | $AlEtCl_2$ (2.5) | $CH_2Cl_2$ | –63 | —[a] | 22:78 |
| 3 **b** | (*S*)-$CO_2CH(Me)CO_2Et$ | $CH_2$ | $TiCl_4$ (1.5) | $CH_2Cl_2$ | –40 | 99 | 95:5 |
| 4 **c** | (*S*)-$CO_2CH(Me)CO_2Et$ | $(CH_2)_2$ | $TiCl_4$ (1.4) | $CH_2Cl_2$/hexane | –24 | 97 | 92:8 |
| 5 **d** | (*S*)-$CO_2CH(Me)CO_2Et$ | $H_2$ | $TiCl_4$ (1.4) | $CH_2Cl_2$ | –50 | 95 | 90:10 |

[a] Yield not reported.

(Scheme 95, Table 25).[97] Diels–Alder reaction of (**391**) with cyclopentadiene, mediated by $TiCl_4$ (1 mol equiv.) at 0 °C, gave adducts (**394a**) and (**395a**) in a ratio of 96.5:3.5 (85%, entry 1). Analogous to the reaction of the *O*-acryloyl lactate it is assumed that the diene adds preferentially from the $C_\alpha$-*si* face of the complex (**392**) which is shielded at the $C_\alpha$-*re* side by a chloride ligand. Again replacement of $TiCl_4$ by $EtAlCl_2$ resulted in a reversal of stereoface selection, yielding a 10:90 mixture of stereoisomers (**394a**) and (**395a**), attributed to the reaction of a monocoordinated dienophile (**396**) (entry 2). $TiCl_4$-promoted reaction of dienophile (**391**) with less reactive dienes (entries 3–7) had to be carried out at 20 °C but still gave products (**394**) + (**395**) (24–75%) in ratios of >90:<10. Comparing the $TiCl_4$-chelated *N*-acryloylproline (**392**) with the *O*-acryloyl analogs (**380**) and (**385**) shows that the amide derivative is less dienophilic but sufficiently rigid to permit good topological differentiation at a relatively high temperature. However, purification of the major product could only be achieved with (**394a**) (chromatography + crystallization) and cleavage of the amide bond required *O*-alkylation ($Me_3O^+BF_4^-$) prior to hydrolysis.

Similar, but less easily accessible, dienophiles (**397**) were reported to undergo preferential *si* face additions of cyclopentadiene at 0 °C when mediated by $AlCl_3$ or $Et_2AlCl$ (Scheme 96, Table 26).[98] This diastereodifferentiation was most significant with $AlCl_3$-coordinated (**397c**) (entry 3) and still good, but much less *endo* selective, in the absence of $AlCl_3$ (entry 5). Treatment of *endo* products (**398**) with $I_2$ in aqueous DME and reduction of the iodolactone with Zn/MeOH furnished (1*R*,2*R*,4*R*)-5-norbornenecarboxylic acid (68%) and the recovered pyrrolidine auxiliary (63%).

Dienophiles carrying a sugar moiety as a face-directing element may also benefit from chelation. Two recent examples are depicted in Scheme 97.[99] Treatment of the 5-*O*,6-*O*-disilylated 3-*O*-acryloyl-1,2-*O*-isopropylidene-α-glucofuranose (**400**) with $TiCl_4$ gave a complex which was assigned chelate structure

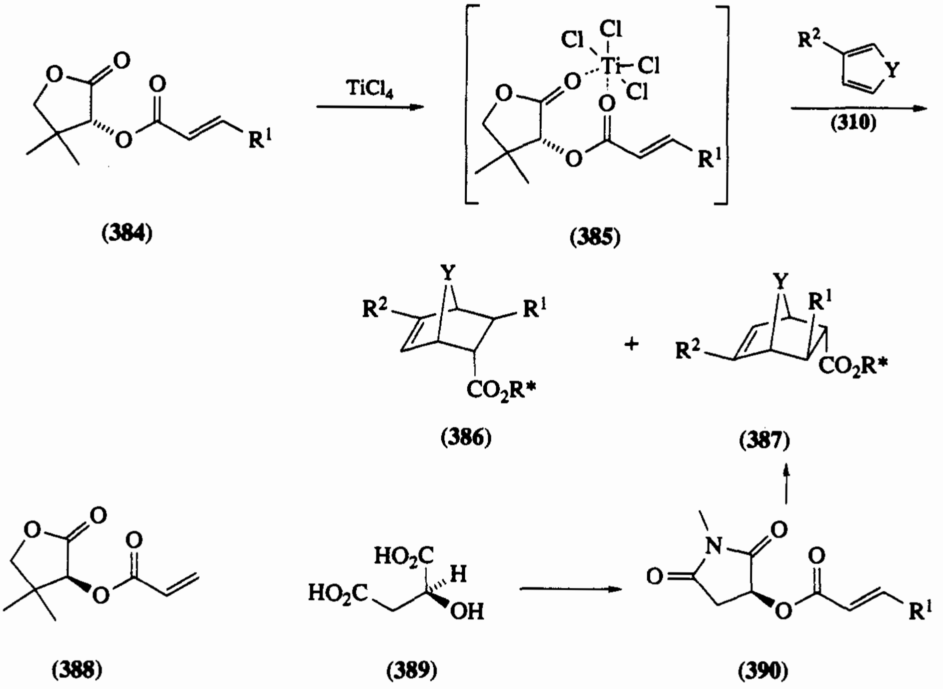

Scheme 94

**Table 24** $TiCl_4$-catalyzed Additions of 1,3-Dienes to *O*-Enoylpantolactone and *N*-Methyl-2-enoyloxysuccinimide (Scheme 95)

| *Entry* | *Dienophile* | *Diene* $R^2$ | *Diene* *Y* | *Temp.* (°C) | *Ratio* **(386)**/**(387)** *crude* | *Ratio* **(386)**/**(387)** *cryst.* | *Yield (%)* *major prod.* *cryst.* |
|---|---|---|---|---|---|---|---|
| **a** | **(384)** $R^1 = H$ | H | $CH_2$ | −10 | 97:3[a] | ≥99.9:0.1 | **(386)** 81 |
| **b** | **(384)** $R^1 = H$ | H | $H_2$ | 0 | 93:7 | >99.5:0.5 | **(386)** 73 |
| **c** | **(384)** $R^1 = H$ | Me | $H_2$ | 0 | 97:3 | >99.5:0.5 | **(386)** 76 |
| **d** | **(384)** $R^1 = Me$ | H | $CH_2$ | −24 | 97.5:2.5[b] | >99:1 | **(386)** 74 |
| **e** | **(388)** — | H | $H_2$ | −32 | 4.5:95.5 | — | **(387)** >61[c] |
| **f** | **(390)** $R^1 = H$ | H | $CH_2$ | −10 | 3:97[a] | 1:>99 | **(387)** 86 |
| **g** | **(390)** $R^1 = Me$ | H | $CH_2$ | −24 | 3:97[b] | 1:>99 | **(387)** 62 |

[a] *Endo*/*exo* = 20–52:1. [b] *Endo*/*exo* = 13–14:1. [c] Crystallized product after subsequent saponification/epoxidation/lactonization.

**(401)** featuring an *s-trans* $C{=}O/C_\alpha{=}C_\beta$ arrangement. Addition of cyclopentadiene at −78 °C gave exclusively the *endo* products (**402**; R = $CH_2OH$) and (**403**; R = $CH_2OH$) in a ratio of 93:7, which corresponds to a preferred diene attack from the less-hindered $C_\alpha$-*si* face. Reactions of (**400**) with 1,3-cyclohexadiene, 1,3-butadiene and anthracene were less efficient (r.t., 12 d, yields <30%) and less diastereoselective. The analogous α-xylofuranose-derived complex (**405**) was expected to be more dienophilic. Cyclopentadiene reacted with (**404**) at −78 °C to afford (**402**; R = H) in 73% yield. No stereoisomeric product could be detected ($^1H$ and $^{13}C$ NMR).

### (v) α,β-Unsaturated Iron Acyl Complexes

Chiral iron acyl complexes $[(C_5H_5)Fe(CO)(PPh_3)COR]$ undergo an impressive range of face-selective carbon–carbon bond-forming processes which also includes the $ZnCl_2$-mediated [4 + 2] addition of cyclopentadiene to the acryloyliron dienophile (**406**) (Scheme 98).[100] The *re*-face-directing bias of the auxiliary apparently relies on a predominant C=O/CO *s-trans* and a $C{=}O/C_\alpha{=}C_\beta$ *s-cis* disposition, resulting in a blocking of the $C_\alpha$-*si* face by a phenyl substituent. The reaction mixture containing (**407**) and two minor products (84:12:4) was treated with ammonium cerium(IV) nitrate and then with $I_2/NaHCO_3$ to give iodolactone (**408**) in >95% *ee* (57% yield from **406**).

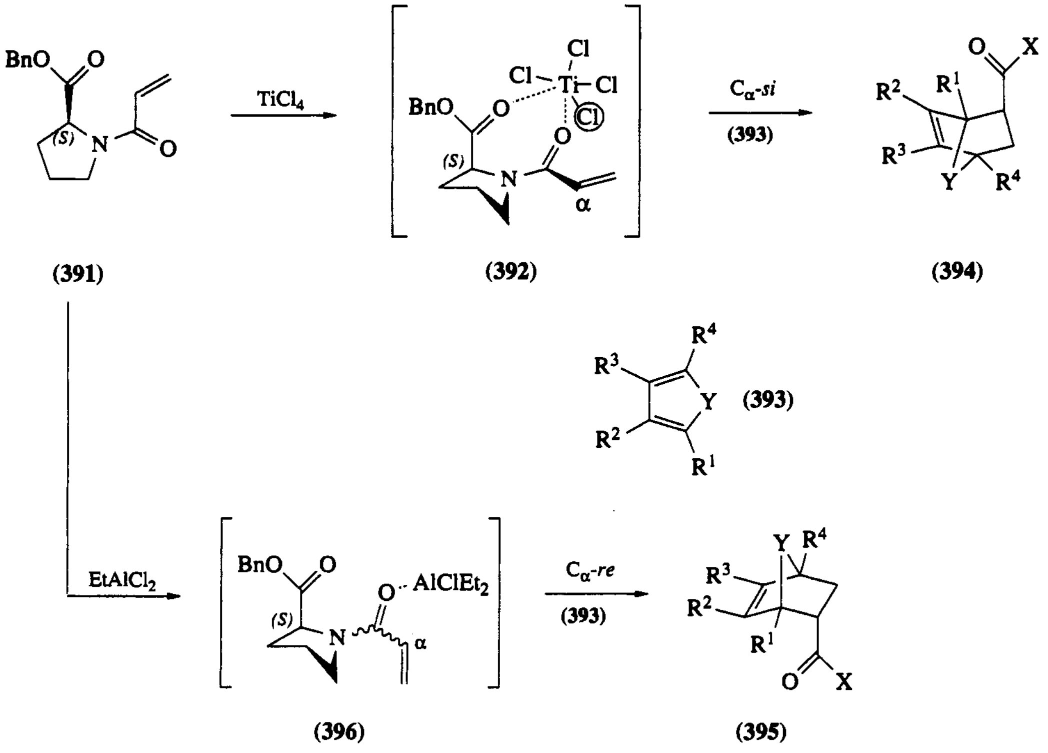

**Scheme 95**

**Table 25** Lewis Acid Catalyzed Diels–Alder Reactions of Dienes to *N*-Acryloyl-(*S*)-proline Benzyl Ester (**391**) (Scheme 95)

| *Entry* | *R*$^1$ | *R*$^2$ | *Diene (393)* *R*$^3$ | *R*$^4$ | *Y* | *Lewis acid* | *Temp. (°C)* | *Yield (%)*[a] | *Ratio (394)/(395)* | *Ratio endo/exo* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | H | H | $CH_2$ | $TiCl_4$ | 0 | 85 | 96.5:3.5 | 92:8 |
| 2 **a** | H | H | H | H | $CH_2$ | $EtAlCl_2$ | 0 | 96 | 10:90 | 92:8 |
| 3 **b** | H | H | H | H | $(CH_2)_2$ | $TiCl_4$ | 20 | 24 | 94:6 | —[b] |
| 4 **c** | Me | H | H | H | $H_2$ | $TiCl_4$ | 20 | 41 | 89:6.5:2.7:1.8[c] | — |
| 5 **d** | Me | H | H | Me | $H_2$ | $TiCl_4$ | 20 | 42 | 90:10 | — |
| 6 **e** | H | H | Me | H | $H_2$ | $TiCl_4$ | 20 | 72 | 92:8 | — |
| 7 **f** | H | Me | Me | H | $H_2$ | $TiCl_4$ | 20 | 75 | 90:10 | — |

[a] Combined yield of *endo* and *exo* products. [b] *Endo*/*exo* ratio not reported. [c] Minor isomers not assigned.

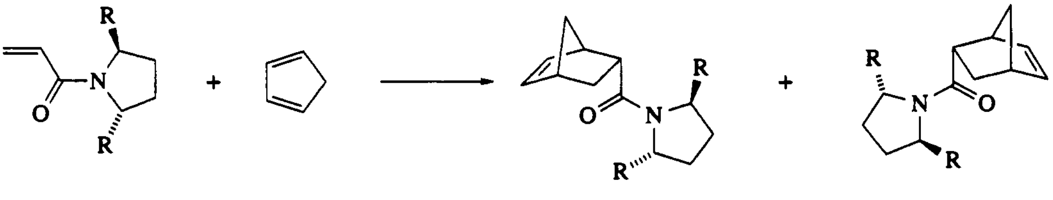

**(397)** **(398)** **(399)**

**a**: R = $CO_2Me$; **b**: R = $CH_2OMe$; **c**: R = $CH_2OCH_2OMe$

**Scheme 96**

**Table 26** Addition of Cyclopentadiene to *N*-Acryloyl *trans*-2,5-Disubstituted Pyrrolidines (**397**) (Scheme 96)

| *Entry* | *R* | *Lewis acid*[a] | *Temp.* (°C) (*time*, h) | *Yield*[b] | *endo/exo* | *Ratio* (**398**)/(**399**) |
|---|---|---|---|---|---|---|
| 1 a | $CO_2Me$ | $AlCl_3$ | 0 (2) | 85 | 87:13 | 97:3 |
| 2 b | $CH_2OMe$ | $AlCl_3$ | 0 (1) | 71 | 89:11 | 99:1 |
| 3 c | $CH_2OCH_2OMe$ | $AlCl_3$ | 0 (1) | 76 | 95:5 | 99:1 |
| 4 c | $CH_2OCH_2OMe$ | $Et_2AlCl$ | 0 (1) | 73 | 86:14 | 99:1 |
| 5 c | $CH_2OCH_2OMe$ | None | r.t. (42) | 75 | 69:31 | 95:5 |

[a] 1.2 mol equiv. [b] Combined yield of *endo* and *exo* adducts.

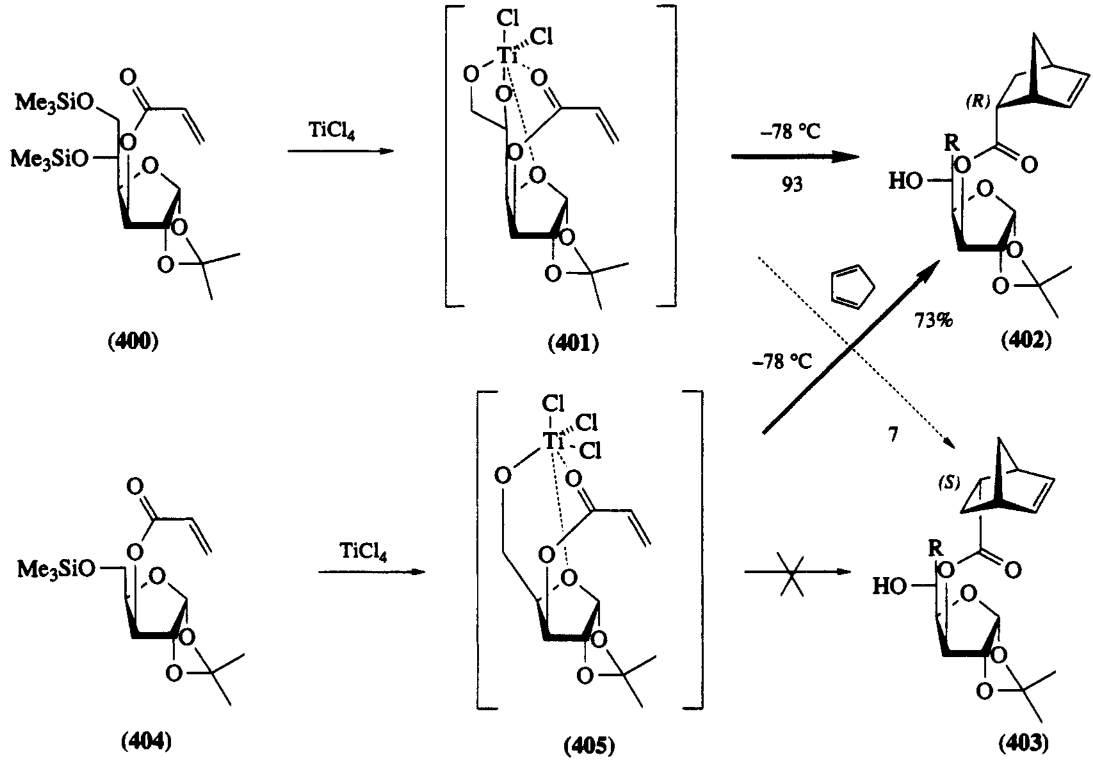
Me3SiO
Me3SiO
TiCl4
Cl
Cl
Ti
-78 °C
93
(R)
R
HO
(400)
(401)
-78 °C
73%
(402)
7
Me3SiO
TiCl4
Cl
Cl
Ti
Cl
(S)
R
HO
(404)
(405)
(403)

**Scheme 97**

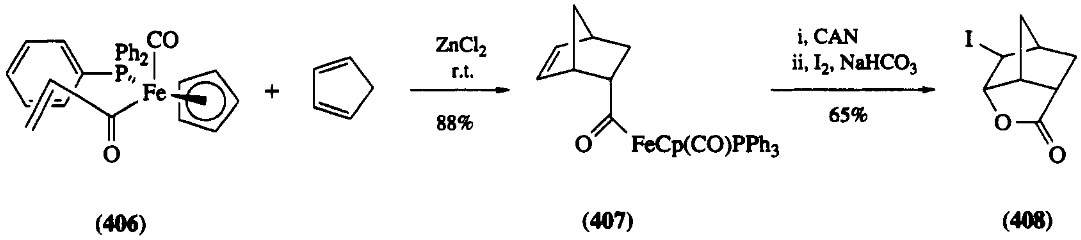
Ph2
P
CO
Fe
ZnCl2
r.t.
88%
FeCp(CO)PPh3
i, CAN
ii, I2, NaHCO3
65%
I
(406)
(407)
(408)

**Scheme 98**

### *(vi) Vinyl Sulfoxides*

The chirality of a sulfoxide moiety may be also exploited for asymmetric [4 + 2] additions of 1,3-dienes to vinyl sulfoxides. However, the latter are poor dienophiles and thus require an additional 'activating' group.

Hence the menthyloxycarbonyl group in (**409**) facilitates the separation of its pure enantiomers as well as their *endo*-selective addition to 1,3-dienes.[101] (The *endo*-directing influence of (*E*)- or C-1-positioned carbalkoxycarbonyl substituents opposes that of the sulfoxide). The *cis*-related ester group, furthermore, favors a conformation of (**409**) where the sulfur lone pair and the C═C bond are *syn* periplanar (Scheme 99, Table 27).[101a]

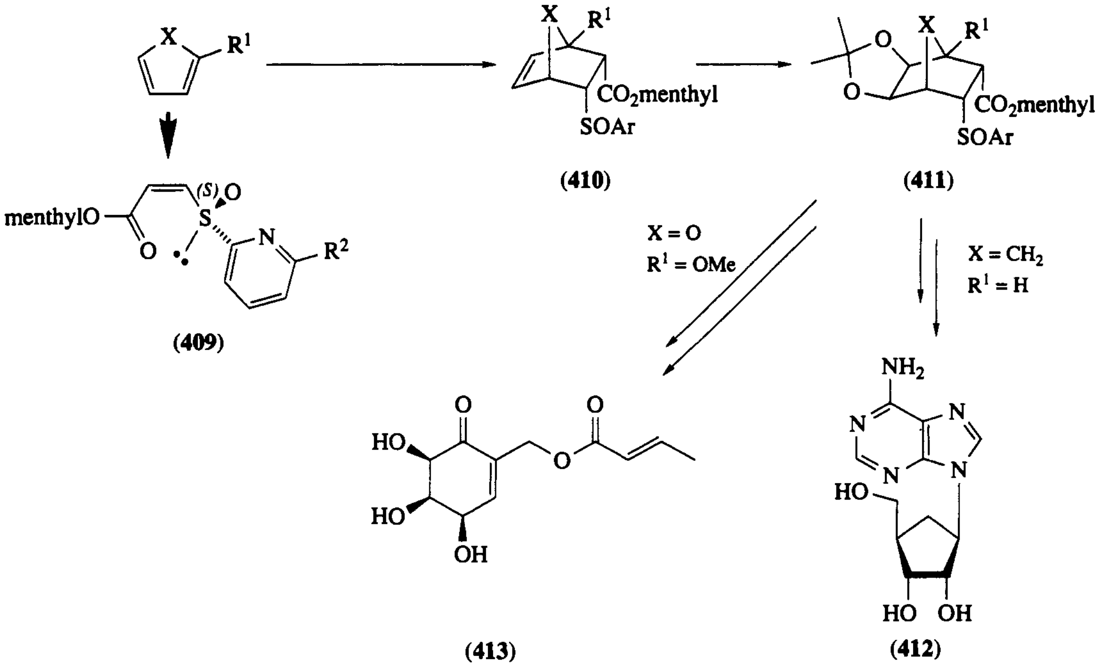

Scheme 99

Table 27 Sulfoxide Directed Asymmetric Diels–Alder Additions to (*Z*)-3-Arylsulfinylacrylates (Scheme 99)

| *Entry* | *Diene* *X* | *R*¹ | *Dienophile* *R*² | *Temp.* (°C) (*time*, h) | *Lewis acid* | *Yield* (%) (**410**) |
|---|---|---|---|---|---|---|
| 1 **a** | $CH_2$ | H | H | –78 (3) | $Et_2AlCl$ | 96 |
| 2[a] **b** | $(CH_2)_2$ | H | H | r.t. (96) | $ZnBr_2$ | ~100 |
| 3 c | O | OMe | $CF_3$ | 0 (144) | None | >72 |

[a] Conditions: $CH_2Cl_2$, 1.1–1.2 equiv. Lewis acid.

$Et_2AlCl$-promoted reaction of (**409**; $R^2$ = H) with cyclopentadiene (–78 °C) gave almost exclusively the cycloadduct (**410a**) in 96% yield, consistent with a diene approach *syn* to the sulfoxide oxygen atom (entry 1). Transformation of the Diels–Alder product (**410a**) into the carbocyclic nucleoside (–)-aristeromycine (**412**) involved dihydroxylation of the alkenic bond, removal of the sulfur moiety by elimination, and ozonolysis of the resulting ester-conjugated double bond.[101b] [4 + 2] Cycloaddition of the less-reactive cyclohexa-1,3-diene to (**409**; $R^2$ = H) proceeded efficiently in the presence of $ZnBr_2$ (entry 2), providing product (**410b**) in quantitative yield.[101c] A synthesis of glyoxalase inhibitor I (**413**) relied on the analogous addition of 2-methoxyfuran which is incompatible with the presence of a Lewis acid. To this end the more reactive dienophile (**409**; $R^2$ = $CF_3$) was treated with 2-methoxyfuran under nonacidic conditions (0 °C, 6 d) to give (**410c**; X = O, $R^1$ = OMe) in high purity (entry 3).[101d] Conversion of the resulting crude product to acetal (**411**; X = O, $R^1$ = OMe) (72% from **409**; 98:2 stereoisomer mixture by HPLC) followed by crystallization provided pure (**411**; X = O, $R^1$ = OMe) which was transformed into the natural product (**413**).

Instead of preparing the sulfoxide chirophore *via* a separation of diastereoisomers, the diastereoselective oxidation of a sulfide offers an interesting alternative. Thus Michael addition of 10-mercaptoisoborneol (**414**) to methyl propiolate furnished (*Z*)-vinyl sulfide (**415**) which underwent a hydroxy-directed oxidation (MCPBA) to give the (sulfur-*R*)-vinyl sulfoxide (**416**) in a highly selective manner (Scheme 100).[102]

Diels–Alder addition of cyclopentadiene (1.3 mol equiv., $CH_2Cl_2$) to the purified dienophile (**416**) proceeded smoothly at 5 °C in a virtually quantitative *endo* fashion *syn* to the H-bonded sulfoxide oxygen atom (assuming that formula **416** depicts the reactive conformation). Stereoisomerically pure adduct

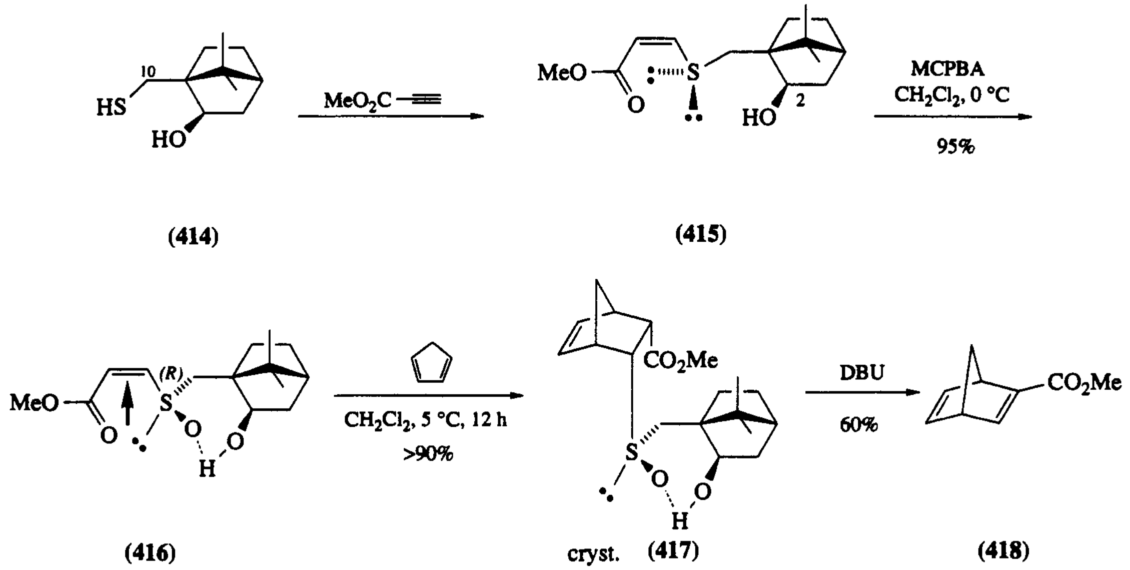
10
HS
HO
MeO$_2$C—≡
MeO
O
S
HO
2
MCPBA
CH$_2$Cl$_2$, 0 °C
95%
(414)
(415)
MeO
(R)
S
O
O
H
CH$_2$Cl$_2$, 5 °C, 12 h
>90%
CO$_2$Me
S
O
O
H
DBU
60%
CO$_2$Me
(416)
cryst. (417)
(418)

Scheme 100

(417) was subjected to DBU-induced elimination, affording norbornadiene (418) in high enantiomeric purity.[102]

### (vii) *Endocyclic Dienophiles*

Covalent incorporation of the dienophile into a ring procures an additional rigidity and, as a consequence, the potential of *endo* and stereoface selective cycloadditions of 1,3-dienes in the absence of Lewis acids at high temperatures. On the other hand, this requires well-defined structural elements which are difficult to remove but can be put to advantage within a synthetic scheme.

Optically pure menthyloxybutyrolactone (421) was obtained by crystallizing a mixture of both epimers (420) (prepared from racemic 419) under equilibrating conditions. Cycloadditions of dienes occurred at 110–120 °C exclusively to the much less hindered 'bottom' face of (421) with >97% *endo* selectivity to give adducts (423) (Scheme 101, Table 28).[103]

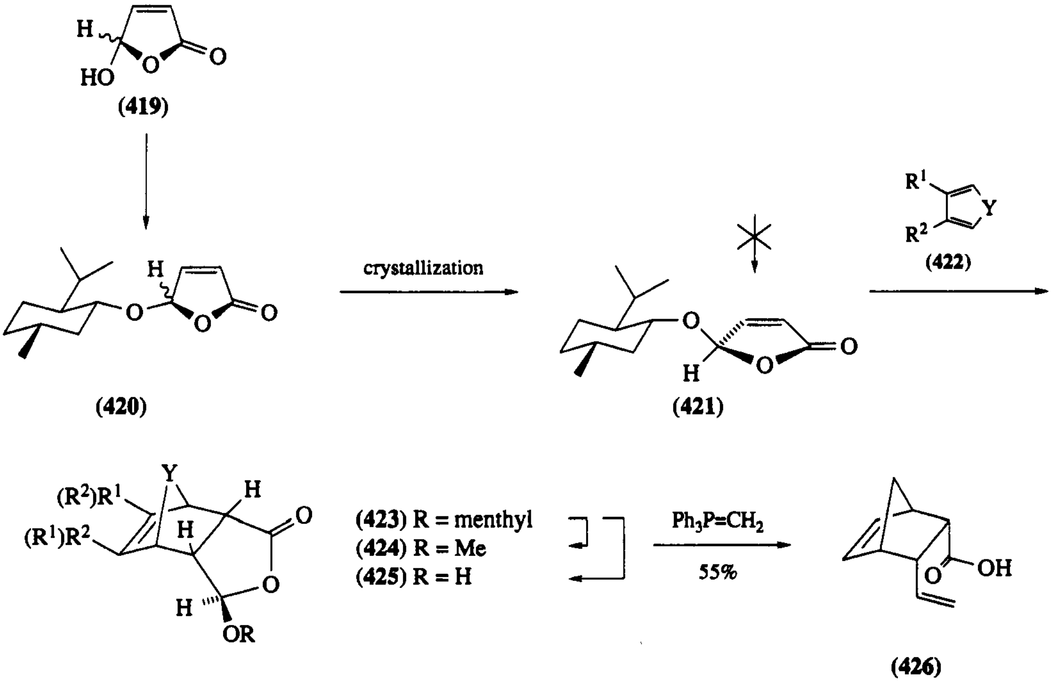
H
HO
O
O
(419)
H
O
O
O
crystallization
O
O
H
O
R$^1$
R$^2$
Y
(422)
(420)
(421)
Y
(R$^2$)R$^1$
(R$^1$)R$^2$
H
H
O
O
H
OR
(423) R = menthyl
(424) R = Me
(425) R = H
Ph$_3$P=CH$_2$
55%
O
OH
(426)

Scheme 101

**Table 28** Noncatalyzed Diels–Alder Reactions of 5-(Menthyloxy)-2(5*H*)-furanone with 1,3-Dienes (Scheme 101)

| *Entry* | $R^1$ | $R^2$ | *Y* | *Temp.* (°C) | *Yield (%) of* (**423**)[a] |
|---|---|---|---|---|---|
| 1 **a** | H | H | $CH_2$ | 110 | 65 |
| 2 **b** | H | H | $(CH_2)_2$ | 120 | 47 |
| 3 **c** | H | H | $H_2$ | 120 | 45 |
| 4 **d** | Me | H | $H_2$ | 120 | 56[b] |
| 5 **e** | Me | Me | $H_2$ | 120 | 44 |

[a] 96% diastereomeric excess ($^1H$, $^{13}C$ NMR). [b] 50:50 mixture of regioisomers.

However, the addition of isoprene (entry 4) reveals a serious lack of regiochemical control under these noncatalyzed reaction conditions. Removal of menthol by methanolysis or hydrolysis ($SiO_2$, $H_2O$) afforded enantiomerically pure methoxy- or hydroxy-substituted lactones (**424**) or (**425**). Wittig reaction of (**425a**) provided carboxylic acid (**426**), a key intermediate for a synthesis of 6,7-dehydroaspidospermidine.

The versatile functionality pattern of bicyclic *N,O*-acetal-γ-lactams (found in conjunction with their π-face-selective alkylation) can also be applied to Diels–Alder reactions of the corresponding alkenic methoxycarbonyl-activated derivative (**427**) (Scheme 102).[104] Noncatalyzed addition of 2,3-dimethylbutadiene to dienophile (**427**) (60 °C, 8 h) proceeded exclusively from the π-face opposite the isopropyl substituent. The reactivities of the latent immonium and carbonyl groups in adduct (**428**) were exploited during transformation into [1,3,4]propellane (**434**).

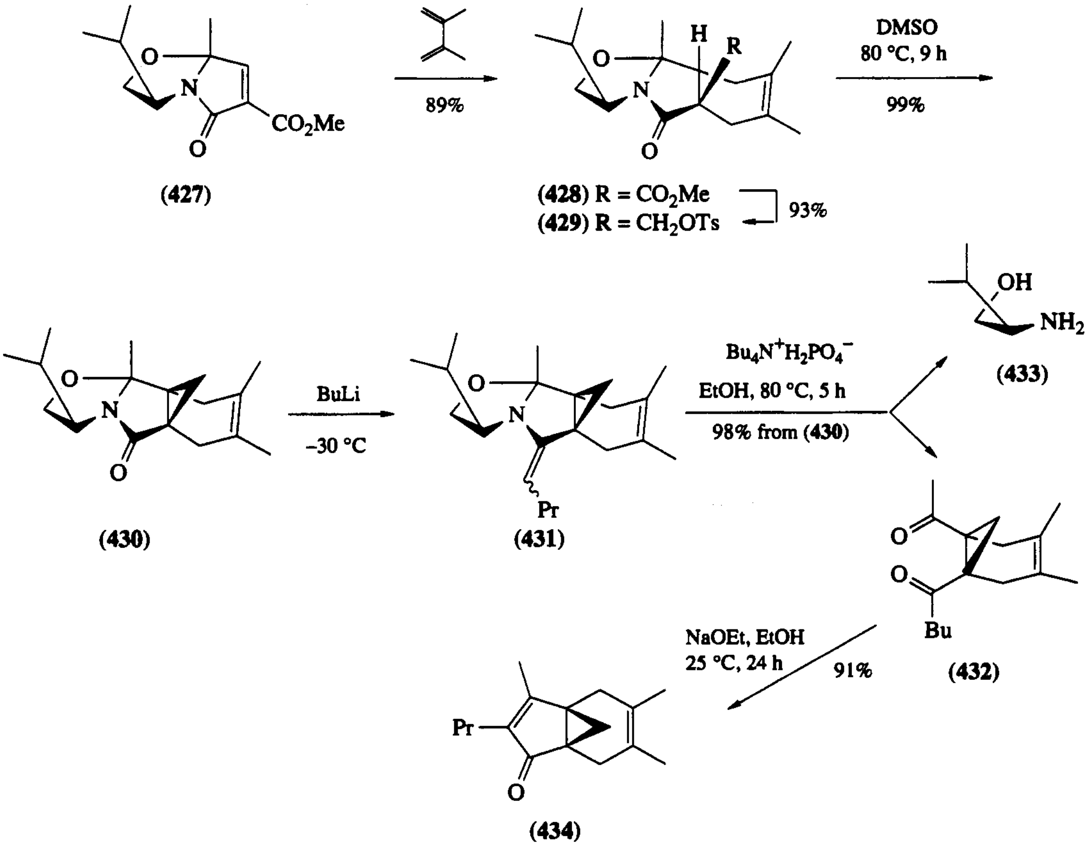

**Scheme 102**

### (viii) Vinyl Ether

An interesting example of an asymmetric 'inverse-electron-demand' Diels–Alder reaction is the smooth addition of chiral vinyl ether (**436**) (readily accessible from **435**) to the electron-deficient 3-toluenesulfonyl pyrone (**437**) (Scheme 103).[105] The pure adduct (**438**), isolated by chromatography in 84% yield, was transformed into the (–)-4-epishikimic acid derivative (**440**) *via* cyclohexene intermediate (**439**).

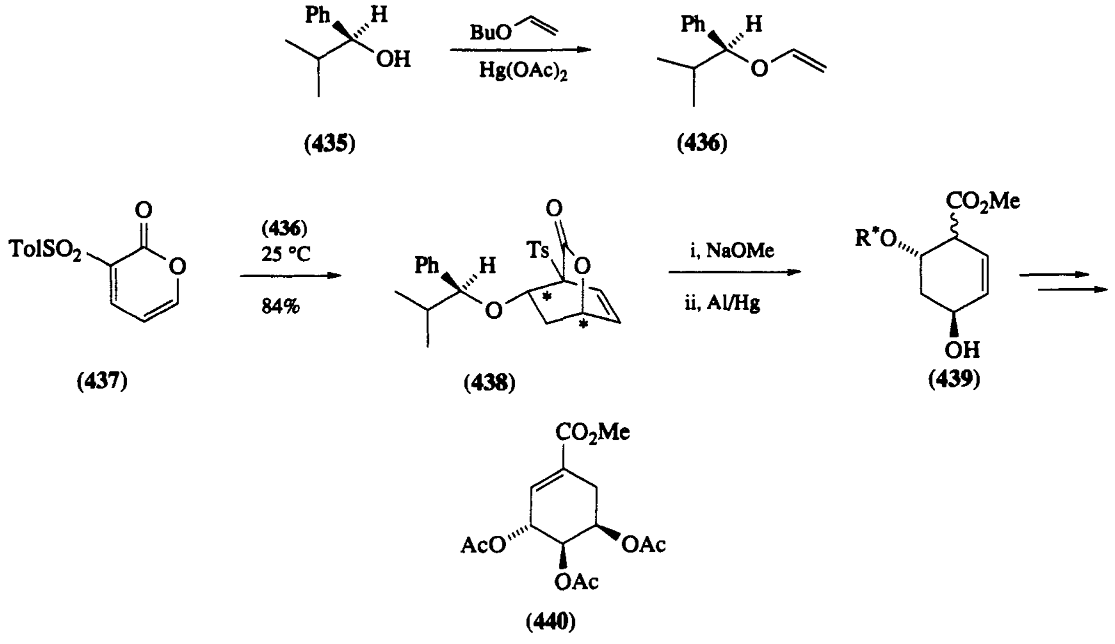

Scheme 103

#### 4.1.6.2.2 Chiral dienes

Asymmetric Diels–Alder reactions of dienes substituted with a removable chiral moiety with prochiral dienophiles have been much less extensively studied. The few successful examples involve ester or ether derivatives of 1,3-dienols.

##### *(i) 1-(O-Methylmandeloxy)dienes*

Dienyl esters (**442**; $R^3$ = Ph), available *via* a retro-Diels–Alder reaction of norbornene (**441**; $R^3$ = Ph), underwent $BF_3 \bullet Et_2O$-catalyzed additions of conjugated aldehydes, ketones and quinones (Scheme 104, Table 29).[106]

The π-face differentiation in favor of adducts (**443**) was more pronounced with increasing amounts of the Lewis acid and at lower reaction temperatures (*cf.* entries 3/4 and 8/9). The cooperative effect of chiral auxiliaries at the diene and at the dienophile units is exemplified by the double diastereoface selective addition presented in entry 2.[91] Particularly noteworthy is the outstanding π-face selectivity, observed in the [4 + 2] cycloaddition of juglone (**445**).[106b] Removal of the prosthetic group from adducts (**443**) was accomplished *via* hydrogenolysis or allylic displacement, as illustrated by the key step (**447**) → (**448**) of a synthesis of enantiomerically enriched (+)-ibogamine (Scheme 105).[106a]

This asymmetric induction was first rationalized in terms of a binding diene/aryl π-orbital overlap (Scheme 104).[106b] In this π-stacking model, methoxy/diene repulsion favors conformer (**O**) which undergoes preferential dienophile addition opposite to the phenyl-shielded diene face. More recently a different transition state conformation (**P**) was proposed based on X-ray studies of adducts (**443**).[106c] Distinctive characteristics of this model are a perpendicular disposition of phenyl and ester-carbonyl groups and a synperiplanarity of the latter with the methoxy substituent. A similar asymmetric induction was achieved with the diene (**442d**) (entry 5), where the phenyl is replaced by a cyclohexyl group, which indicates that π-stacking is not of major relevance here. A dienophile approach opposite to the sterically encumbering phenyl (or cyclohexyl), *i.e.* from the top face of (**P**), may be a reason for the observed topicities.

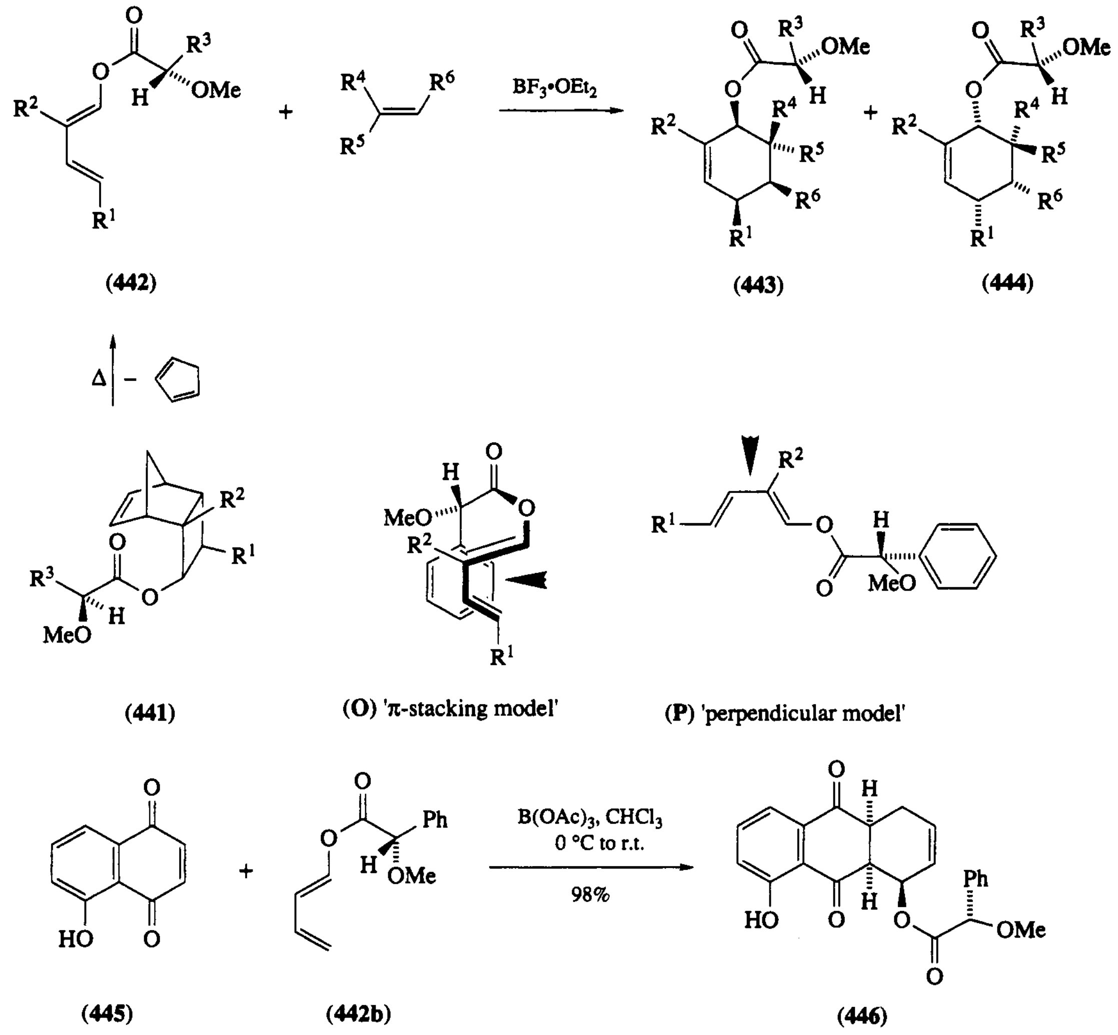
(442)
BF3•OEt2
(443)
(444)
Δ
(441)
(O) 'π-stacking model'
(P) 'perpendicular model'
(445)
(442b)
B(OAc)3, CHCl3
0 °C to r.t.
98%
(446)

Scheme 104

Table 29 Additions of Dienophiles to Chiral 1-Acyloxy-1,3-dienes (**442**)[a] (Scheme 104)

| *Entry* | *Diene* $R^1$ | $R^2$ | $R^3$ | *Dienophile* | *Mol equiv.* $BF_3{\cdot}OEt_2$ | *Temp.* (°C) | *Ratio* (**443**)/(**444**) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 **a** | Et | H | Ph | $CH_2{=}CHCHO$ | 0.1 | −10 | 80:20 | 106a |
| 2 **b** | H | H | Ph | (*S*)-$CH_2{=}CHC(O)CH(OH)Bu^t$ | 0.3 | −78 to −45 | 99.2:0.8 | 91 |
| 3 **c** | H | H | Ph | $CH_2{=}CHCHO$ | 0.15 | −20 | 82:18 | 106c |
| 4 **c** | H | H | Ph | $CH_2{=}CHCHO$ | 0.3 | −78 | 94:6 | 106c |
| 5 **d** | H | H | c-$C_6H_{11}$ | $CH_2{=}CHCHO$ | 0.3 | −78 | 89:11 | 106c |
| 6 **e** | H | H | Ph | $CH_2{=}C(Me)CHO$ | 0.3 | −78 | 98:2 | 106c |
| 7 **f** | H | Me | Ph | $CH_2{=}CHCHO$ | 0.3 | −78 | 97:3 | 106c |
| 8 **g** | H | H | Ph | *p*-Benzoquinone | 0.15 | −78 | 96:4 | 106c |
| 9 **h** | H | H | Ph | *p*-Benzoquinone | None | 20 | 80:20 | 106c |

[a] Yields of (**443**) + (**444**): 46–94%.

### *(ii) 1,3-Dienyl Tetraacetyl-β-glucopyranosides*

Glucose-derived diene (**451**) displays a notable diastereofacial bias on addition to dienophiles.[107] Its preparation relies on the alkylation of tetraacetylglucopyranosyl bromide (**450**) with sodium salt (**449**) followed by *O*-silylation of the resulting enone (Scheme 106).[107a]

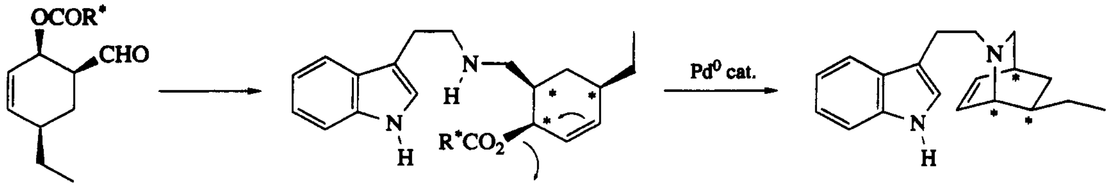
OCOR*
CHO
N
H
N
H
R*CO2
Pd0 cat.
N
N
H

**(443a)** **(447)** **(448)**

**Scheme 105**

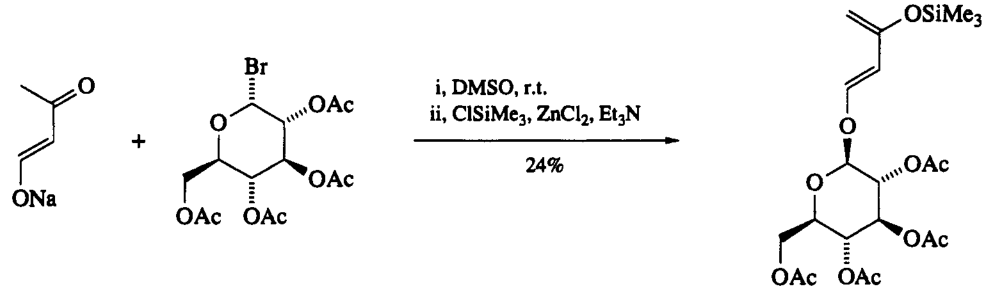
O
ONa
+
Br
O
OAc
OAc
OAc OAc
i, DMSO, r.t.
ii, ClSiMe3, ZnCl2, Et3N
24%
OSiMe3
O
O
OAc
OAc
OAc OAc

**(449)** **(450)** **(451)**

**Scheme 106**

Serving as the key step for an anthracycline synthesis, addition of the epoxytetrone dienophile (**452**) to diene (**451**) gave a mixture of adducts (**453**) and (**454**) in ratios of 4:1 ($C_6H_6$, 5 °C) up to 7:1 (acetone, 5 °C) (Scheme 107). The major isomer (**453**), isolated by crystallization (74% yield from **451**), was then converted into (+)-4-demethoxydaunomycinone (**641**) (Scheme 142) *via* glycoside cleavage with 0.5N

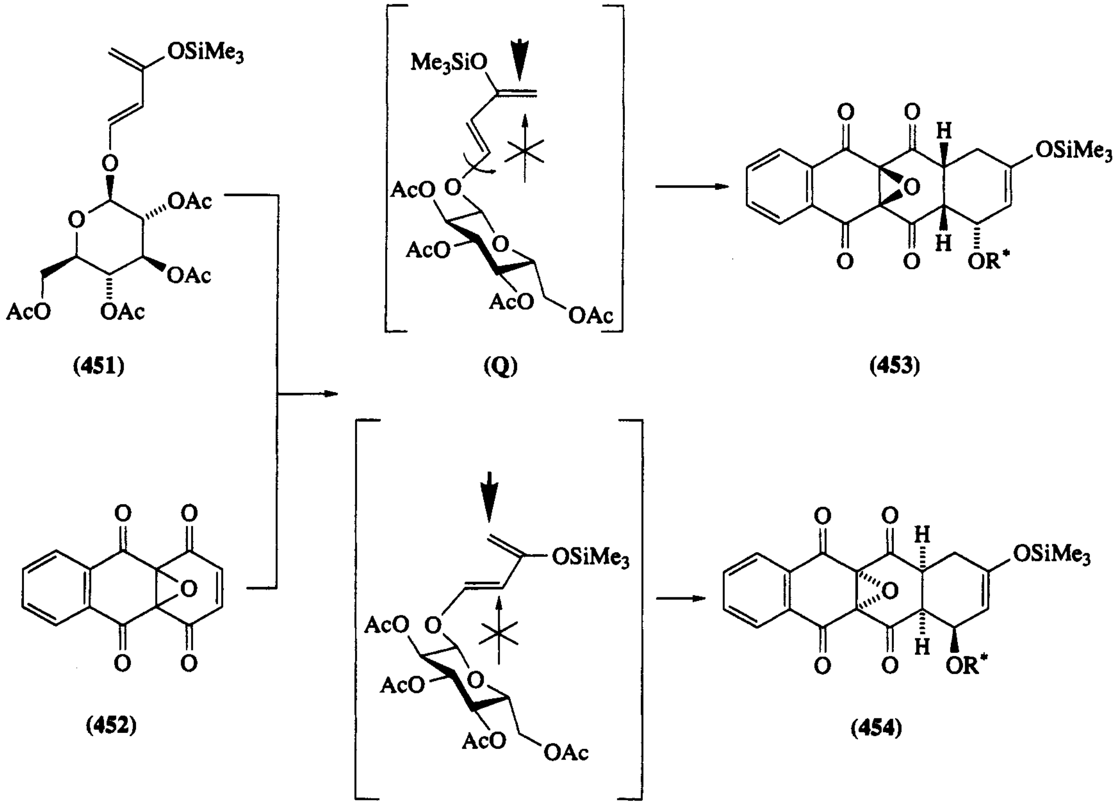
OSiMe3
O
O
OAc
OAc
AcO
OAc
(451)
Me3SiO
AcO
O
AcO
O
AcO
OAc
(Q)
O
O
H
OSiMe3
O
O
O
H
OR*
(453)
O
O
O
O
O
(452)
OSiMe3
AcO
O
AcO
O
AcO
OAc
(R)
O
O
H
OSiMe3
O
O
O
H
OR*
(454)

**Scheme 107**

HCl in EtOH/$H_2O$ (1:1, reflux, 30 h). In agreement with X-ray and NOE measurements of (**451**) and consistent with the assumed operation of an *exo* anomeric effect, reactive diene conformations (**Q**) and (**R**) were proposed.[107b] It was therefore inferred that the major cycloaddition pathway involves attack of the dienophile (**452**) at the least-hindered 'top face' of conformer (Q).

### 4.1.6.3 Chiral Catalysts

At first sight, the use of a chiral catalyst appears to be the potentially most attractive method to achieve asymmetric Diels–Alder reactions of prochiral dienes and dienophiles. Compared to the stoichiometric use of a covalently attached auxiliary, two synthetic steps would be avoided. However, analysis of the resulting enantiomer mixture and purification of the major product may be more laborious.

#### *4.1.6.3.1 Chiral alkoxyaluminum dichlorides*

As early as 1979 it was reported that addition of cyclopentadiene to methacrolein, catalyzed by (–)-menthyloxyaluminum dichloride (**455**; R = Me) (0.14 mol equiv., –78 °C, 3 h) furnished[108a] a mixture of enantiomeric adducts (**456**) and (**457**) (56%) in a ratio of 86:14 which was subsequently corrected to a more modest value of 78.5:21.5 (Scheme 108).[84a,108b]

This isolated report encouraged preparation of a host of chiral Lewis acids throughout the world to test their capacity to induce asymmetric Diels–Alder reactions catalytically. However, until very recently (*vide infra*) only disappointing face selectivities (<50%) were found on [4 + 2] cycloadditions of alkenic diene and dienophile partners.

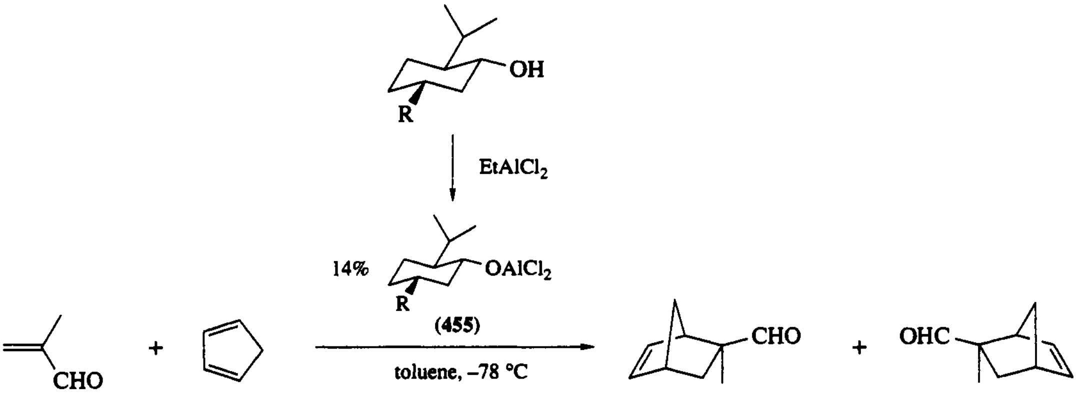

Scheme 108

#### *4.1.6.3.2 Chelation of prochiral dienophiles by chiral boron, aluminum and titanium Lewis acids*

In view of previous positive experience with chelated chiral dienophiles (Section 4.1.6.2.1 (iii)), it was plausible to expect that nonchiral dienophiles would also profit from chelation in terms of increased reactivity and decreased conformational mobility. This would enhance the π-face directing influence of a chiral ligand attached to the same chelating metal.

Successive treatment of (*S*)-binaphthol (**459**) with equimolar amounts of $BH_3$.THF and AcOH gave a non-isolated Lewis acid. Reaction of the latter with juglone (**458a**) provided a complex, assigned structure (**460a**), in which one phenyl substituent shields the top face of the dienophilic bond (Scheme 109, Table 30).[109] Indeed, a fast and efficient addition of 1-methoxycyclohexa-1,3-diene to the complex (**460a**) provided adduct (**462a**) as the only enantiomer within the limits of detection (entry 1). Analogous 'bottom face' additions to complexes (**460**) were observed with 2-methyl-4-trimethylsilyloxybuta-1,3-diene (entry 2) and 1-acetoxybuta-1,3-diene (entry 3).[109] It appears that the initially formed adducts remain strongly chelated, which prevents dissociation of the binaphthoxyboron Lewis acid and necessitates its stoichiometric application.

Chiral titanium and aluminum Lewis acids (**465**), prepared *in situ* from (**463**) or (**464**), promote the addition of cyclopentadiene to *N*-acryolyl- and *N*-crotonoyl-oxazolidinones (**466**) (Scheme 110, Table

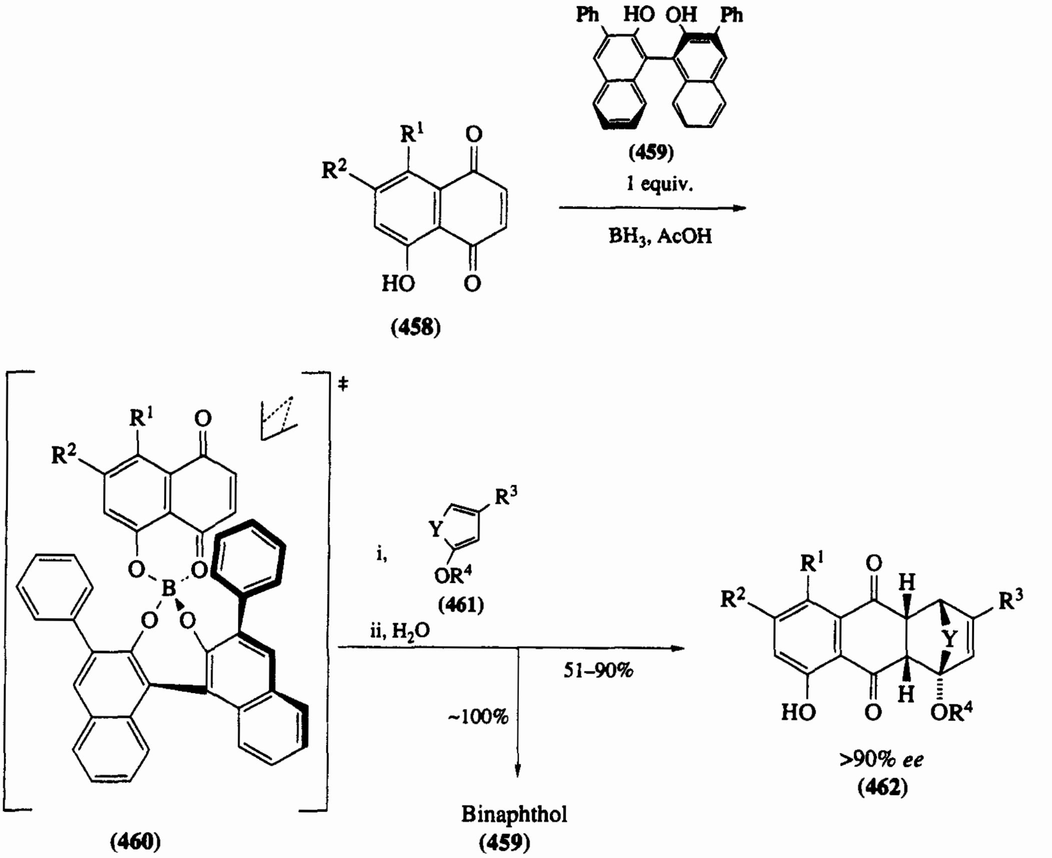

**Scheme 109**

**Table 30** Diels–Alder Reactions of *peri*-Hydroxyquinones: Asymmetric Induction by Chiral Lewis Acid (Scheme 109)

| *Entry* | *Dienophile* $R^1$ | $R^2$ | $R^3$ | *Diene* $R^4$ | *Y* | *Temp.* (°C) | *Yield (%)* (**462**) | *ee (%)* (**462**) |
|---|---|---|---|---|---|---|---|---|
| 1 **a** | H | H | H | Me | $(CH_2)_2$ | –78 | 70–90 | >98 |
| 2 **b** | O—$CPh_2$—O | | Me | $SiMe_3$ | $H_2$ | 20 | >51 | >90 |
| 3 **c** | H | H | H | C(O)Me | $H_2$ | 20 | >68 | >98 |

31).[110] The titanium Lewis acid derived from diol (**463**) could be employed in catalytic amounts (0.1 mol equiv.) when molecular sieves were present (entries 2, 3). Under these conditions, cycloaddition of the crotonoyl dienophile was significantly more enantioselective compared with that of the acryloyl analog. On the other hand, both adducts (**467a**) as well as (**467b**) were obtained in ≥92% *ee* using the Lewis acid (**465**) (0.1–0.2 mol equiv.), prepared *in situ* from bis-sulfonamide (**464**) and $AlMe_3$ (entries 4, 5).[110b]

#### *4.1.6.3.3 Tartrate-derived chiral acyloxyborane catalysts*

So far the most promising chiral 'Diels–Alder catalyst' has been obtained *in situ* by treatment of monoacylated tartaric acid (**470**) with $BH_3$·THF (1 mol equiv.).[111] The resulting non-isolated acyloxyborane was assumed to feature a five-membered ring derived from the α-hydroxy acid moiety of (**470**) with the boron atom bound to the carboxylate and $C_\alpha$-positioned oxygen atoms (*cf.* formula **471**) (Scheme 111, Table 32).

It is remarkable that 0.1 mol equiv. of this chiral acyloxyborane complex induced fast (–78 °C) and highly enantioselective Diels–Alder reactions of cyclic or acyclic 1,3-dienes with simple acrylic acid (entry 1),[111a] or α,β-unsaturated aldehydes (entries 2–9).[111b] Table 32 reveals a striking stereodirecting

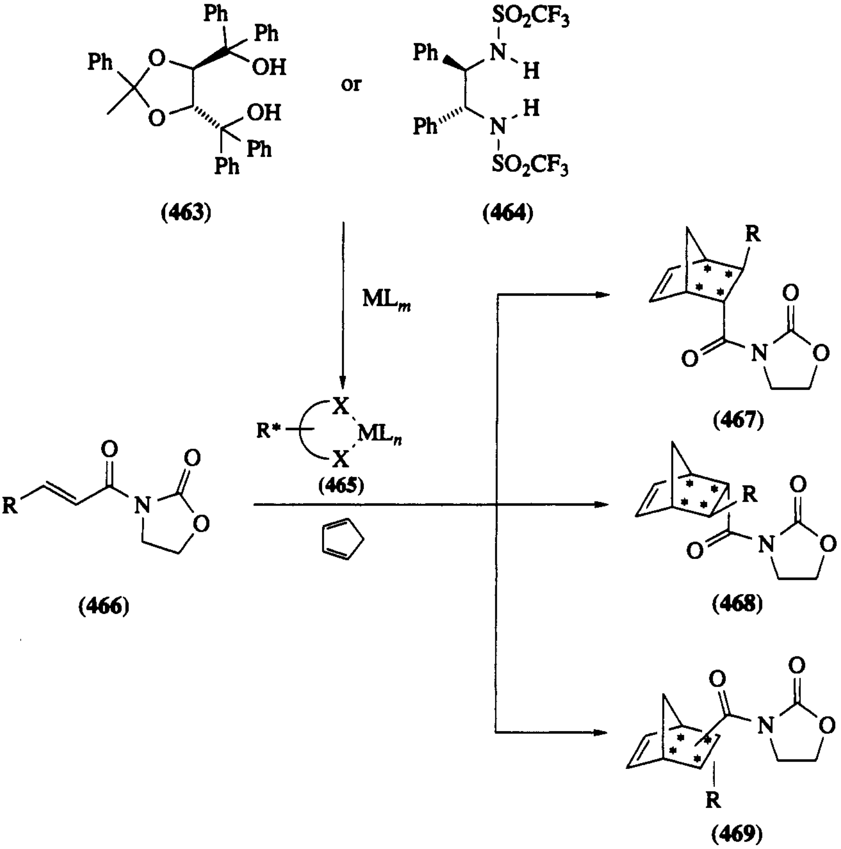

**Scheme 110**

**Table 31** Asymmetric Diels–Alder Reactions of Cyclopentadiene and *N*-Enoyloxazolidinones Mediated by Chiral Lewis Acids (Scheme 110)

| *Entry* | *Dienophile* | *Lewis acid precursors* | | *Molecular* | *Temp.* | *Yield* | *Ratio* | *Ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| | *R* | *ligand* (mol equiv.) | $ML_m$ (mol equiv.) | *sieves* | (°C) | (%)[a] | (467) + (468) /(469) = *endo*/*exo* | (467)/(468) | |
| 1 a | Me | (463) (2.2) | $TiCl_2(OPr^i)_2$ (1) | None | −15 | 93 | 90:10 | 96:4 | 110a |
| 2 a | Me | (463) (0.1) | $TiCl_2(OPr^i)_2$ (0.1) | 4 Å | 0 | 87 | 92:8 | 95.5:4.5 | 110a |
| 3 b | H | (463) (0.1) | $TiCl_2(OPr^i)_2$ (0.1) | 4 Å | −40 | 93 | 96:4 | 82:18 | 110a |
| 4 a | Me | (464) (0.2) | $AlMe_3$ (0.1) | None | −78 | 88 | 96:4 | 97:3 | 110b |
| 5 b | H | (464) (0.1) | $AlMe_3$ (0.2) | None | −78 | 92 | >98:2 | 95.5:4.5 | 110b |

[a] Combined yield of *endo* and *exo* products.

influence of $C_\alpha$ and $C_\beta$ substituents in the enal dienophiles. Hence, acrolein gave specifically products (**477**; $R^1 = R^2 = H$) with an *endo* positioned CHO unit and in high enantiomeric purity resulting from diene additions to the $C_\alpha$-*si* face (entries 2, 3). Methacrolein carrying a $C_\alpha$-methyl group selectively provided products (**474**; $R^1$ = Me, $R^2$ = H) which again reflect a predominant $C_\alpha$-*si* face attack to the enal but an *exo*-oriented aldehyde group in the transition state (entry 6). The $C_\beta$ substituent of crotonaldehyde does not interfere with the 'CHO-*endo* preference' but dramatically decreases the face differentiation of the addition process (entry 5). In the case of (*E*)-2-methyl-2-butenal, having substituents at both $C_\alpha$ and $C_\beta$ positions, high CHO-*exo* as well as $C_\alpha$-*si* face selectivities were observed (entry 9); thus the effect of the $C_\alpha$-methyl overcomes that of the $C_\beta$-methyl moiety. As expected, transformation of methacrolein to (**476**; $R^1 = R^2 = H$) was equally efficient and selective when catalyzed by the readily available enantiomer of (**471**). However, it should be noted that the absolute configuration of several cycloadducts is only tentatively assigned (entries 4, 5, 7–9). Further understanding, extensions and applications of this principle may attract substantial interest in the future.

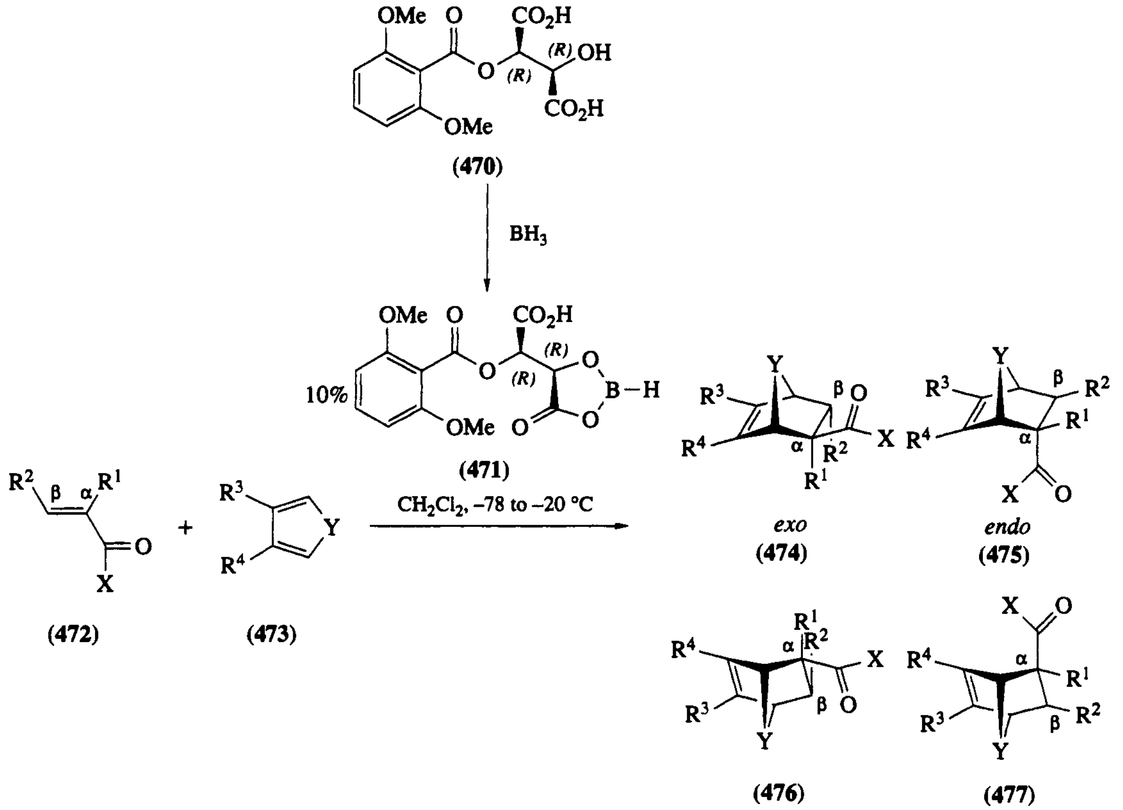

**Scheme 111**

**Table 32** Asymmetric Diels–Alder Reaction of Acrylic Acid and of Conjugated Aldehydes Catalyzed by a Chiral Acyloxyborane (Scheme 111)

| *Entry* | *Dienophile* | | | *Diene* | | | *Temp.* (°C) | *Yield*[a] | *Ratio endo/exo* | *Major* | *ee* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *$R^1$* | *$R^2$* | *X* | *$R^3$* | *$R^4$* | *Y* | *(time,* h*)* | *(%)* | *(C=O)* | *adduct* | *(%)* |
| 1 **a** | H | H | OH | H | H | $CH_2$ | -78 (24) | 93 | 96:4 | (**477**) | 78 |
| 2 **b** | H | H | H | H | H | $CH_2$ | -78 (14.5) | 90 | 88:12 | (**477**) | 84 |
| 3 **c** | H | H | H | H | H | $(CH_2)_2$ | -78 (10) | 46 | >99:<1 | (**477**) | 80 |
| 4 **d** | H | H | H | Me | Me | $H_2$ | -78 (10.5) | 53 | — | (**477**) | 84[c] |
| 5 **e** | H | Me | H | H | H | $CH_2$ | -78 (10) | 53 | 90:10 | (**477**) | 2[c] |
| 6 **f** | Me | H | H | H | H | $CH_2$ | -78 (6) | 85 | 11:89 | (**474**) | 96 |
| 7 **g** | Me | H | H | Me | Me | $H_2$ | -78 (7.5) | 61 | — | (**474**) | 97[c] |
| 8 **h** | Me | H | H | Me | H | $H_2$ | -40 (10.5) | 65[b] | — | (**474**) | 91[c] |
| 9 **i** | Me | Me | H | H | H | $CH_2$ | -78 (9.5) | 91 | 3:97 | (**474**) | 90[c] |

[a] Combined yield of *endo* and *exo* adducts. [b] Contains 2% of the '*meta*' regioisomer. [c] Absolute configuration not reported

## 4.1.7 BENZYNES AS DIENOPHILES

### 4.1.7.1 Background and Preparation

The chemistry of benzyne (dehydrobenzene), pioneered by Wittig and coworkers, was reviewed between 1967 and 1981.[112] Benzyne (**478**) (Scheme 112) is a 'high-energy', extremely reactive species and oligomerizes rapidly in the absence of other reaction partners.

To apply (**478**) as a dienophile in Diels–Alder reactions it is, therefore, prepared *in situ* in the presence of a suitable diene, while maintaining its stationary concentration as low as possible. The most popular methods of preparation (Scheme 112) include dehydrohalogenations of halobenzenes, *e.g.* (**479**),[113a] metallation of *o*-dihalobenzenes, *e.g.* (**480**),[113b] as well as thermal decompositions of benzenediazonium-2-

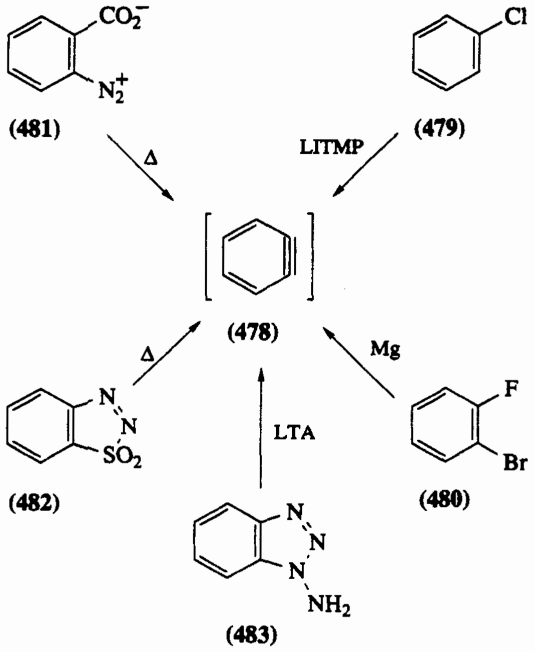

Scheme 112

carboxylate (**481**)[113c] and 1,2,3-benzothiadiazole 1,1-dioxide (**482**).[113d] Precursors (**481**) and (**482**) are explosive and are best prepared *in situ*. Oxidation of 1-aminobenzotriazole (**483**) with lead tetraacetate provides another relatively safe access to (**478**).[113e]

Reaction of benzynes with acyclic dienes generally gives Diels–Alder products in poor yields because of competitive [2 + 2] cycloadditions and ene-type processes (Scheme 113). The product distribution, obtained from 2,3-dimethyl-1,3-butadiene (**484**),[114] is more characteristic of a two-step mechanism than of a concerted addition. Without pursuing this argument, it appears that the extremely poor yield of [4 + 2] cycloadduct (**485**) results from the very fast reaction of benzyne with the 'transoid' diene (**484**). Bond formation at C-1 coupled with a hydrogen transfer (→ **487**) or cyclobutane ring closure (→ **486**) seeds to occur rapidly before diene (**484**) can adopt the *s-cis* conformation.

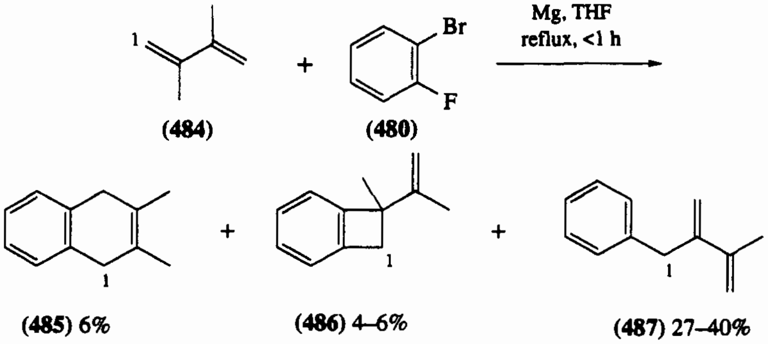

Scheme 113

## 4.1.7.2 Reactions with Cyclopentadiene and Furan Derivatives

Cyclic 1,3-dienes (with an inherent *s-cis* conformation) can react with benzyne to afford Diels–Alder adducts in high yields (Scheme 114). The addition to furan (**228**), reported by Wittig and Pohmer in 1955,[115] is so efficient that it has become a diagnostic test for the formation of benzyne. Cyclopentadiene[113b] and tetracyclone (**492**)[113e] also serve as standard assay reagents.

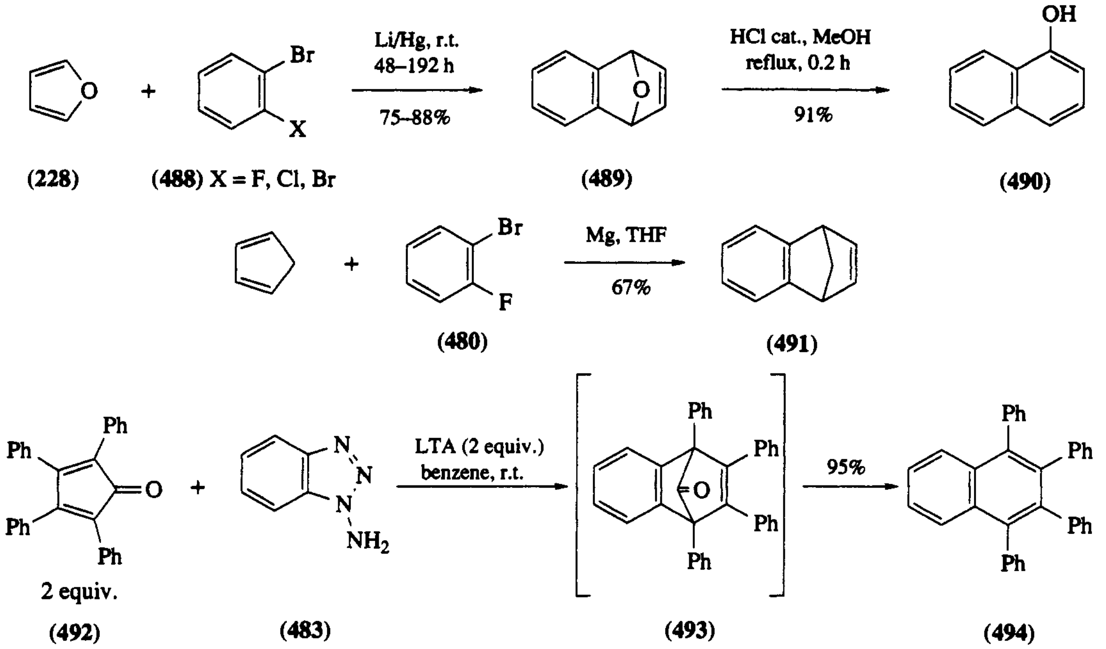
Br
X
Li/Hg, r.t.
48–192 h
75–88%
O
HCl cat., MeOH
reflux, 0.2 h
91%
OH
Br
F
Mg, THF
67%
Ph
O
N
NH2
LTA (2 equiv.)
benzene, r.t.
95%
2 equiv.

**(228)** **(488)** X = F, Cl, Br **(489)** **(490)**

**(480)** **(491)**

**(492)** **(483)** **(493)** **(494)**

Scheme 114

The propensity of furans for benzyne cycloadditions is illustrated by its fourfold application to the four furan units of (**495**), providing the unusual macrocycle (**496**) in 84% yield in one synthetic operation (Scheme 115).[116] The benzyne/furan adducts are also useful precursors for naphthalene derivatives. For example, adduct (**489**) (Scheme 114) was readily converted into α-naphthol (**490**) by treatment with acid.[115]

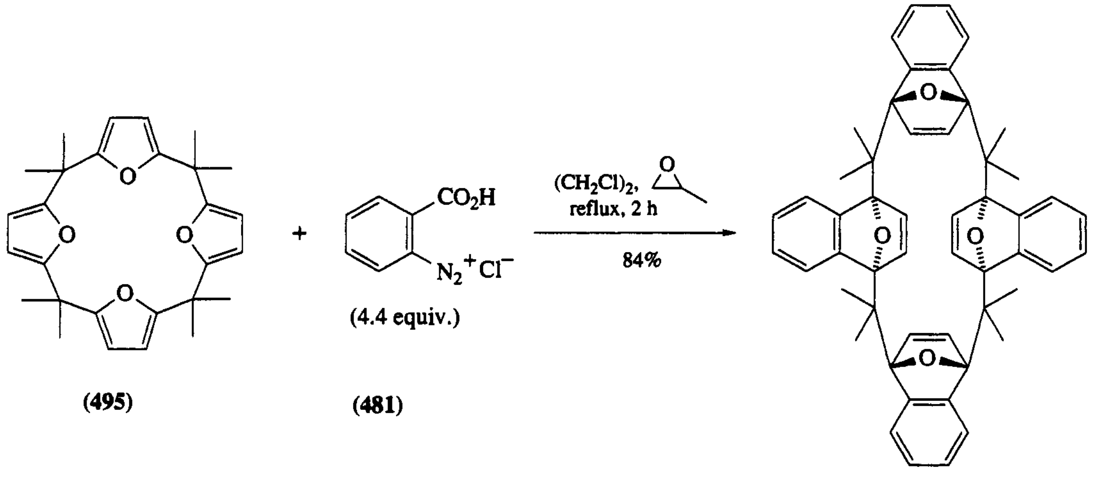
O
CO2H
N2+Cl−
(CH2Cl)2,
reflux, 2 h
84%
(4.4 equiv.)

**(495)** **(481)** **(496)**

Scheme 115

Additions of (**478**) to furans which contain an appropriately placed aryl or vinyl bromide unit permit the construction of polycyclic systems by a Diels–Alder/radical cyclization/aromatization sequence (Scheme 116).[117]

A route to partially hydrogenated phenanthrenes relies on the Diels–Alder reaction of a benzyne to an annulated furan, *e.g.* (**501**) → (**503**) (Scheme 117).[118] However, regiochemistry 'raises its ugly head' when both the furan and the benzyne are nonsymmetrically substituted (Scheme 118). Hence, the [4 + 2] cycloaddition of 3-methylbenzyne with 2-substituted furans (**504**) gave the *anti* and *syn* adducts (**506**)

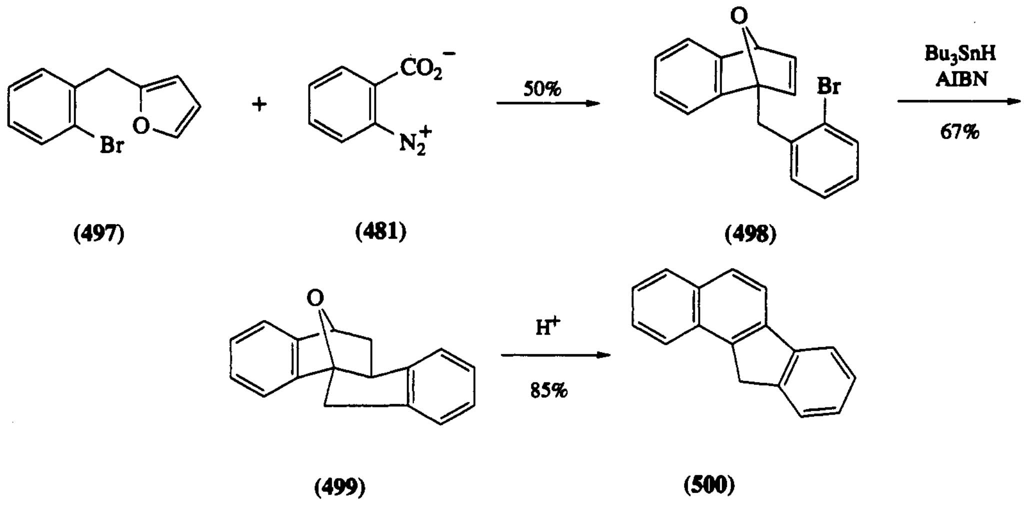

**(497)** **(481)** **(498)**

**(499)** **(500)**

**Scheme 116**

and (**507**) in comparable proportions, irrespective of the size of R and irrespective of the method of benzyne generation.[119a] Analogous addition of the more polarized 3-fluorobenzyne to 2-*t*-butylfuran gave preferentially (90:10) the corresponding, more crowded, *syn* product.[119b]

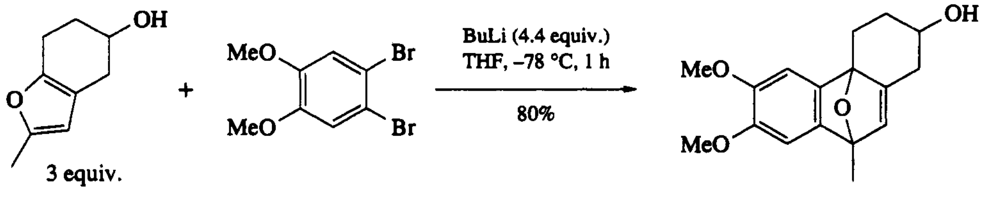

**(501)** **(502)** **(503)**

**Scheme 117**

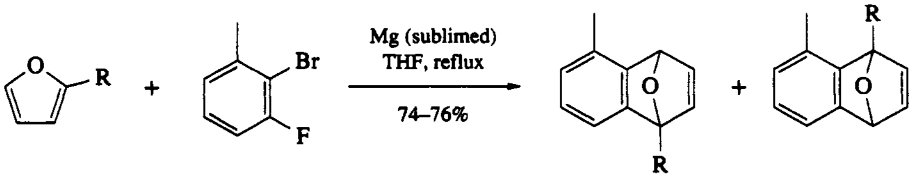

**(504)** **(505)**

| | **(506)** | | **(507)** |
|---|---|---|---|
| R = Bu$^t$ | 62 | : | 38 |
| R = Me | 58 | : | 42 |

**Scheme 118**

Bistriazole (**508**) served as a formal 1,4-benzadiyne equivalent in a sequence of two Diels–Alder additions to 2-methoxycarbonylfuran (**509**), which yielded (**511**) as the sole regio- and (tentatively assigned) stereo-isomer (Scheme 119).[120] It appears, therefore, that the $CO_2Me$ group, in the transient monoadduct (**510**), controls the orientation in the second step.

Pyrroles have also been subjected to [4 + 2] cycloadditions of benzynes. *N*-Trimethylsilylpyrrole (**512**) is particularly suitable for such additions; subsequent mild desilylation furnished 1,4-dihydronaphthalen-1,4-imines, *e.g.* (**514**), in yields ranging from 30 to 53% (Scheme 120).[121]

Oxazoles are another class of heteroaromatic dienes which readily undergo Diels–Alder reactions with benzynes. For example, slow, simultaneous injection of solutions of triazole (**483**) and lead tetraacetate to a solution of oxazole (**515**) in $CH_2Cl_2$ at 0 °C afforded cycloadduct (**516**) in essentially quantitative yield.[122] The latter is a convenient source for the unstable isobenzofuran (**517**), which can be trapped by [4 + 2] cycloaddition to a variety of dienophiles, *e.g.* by *N*-methylmaleimide (Scheme 121).

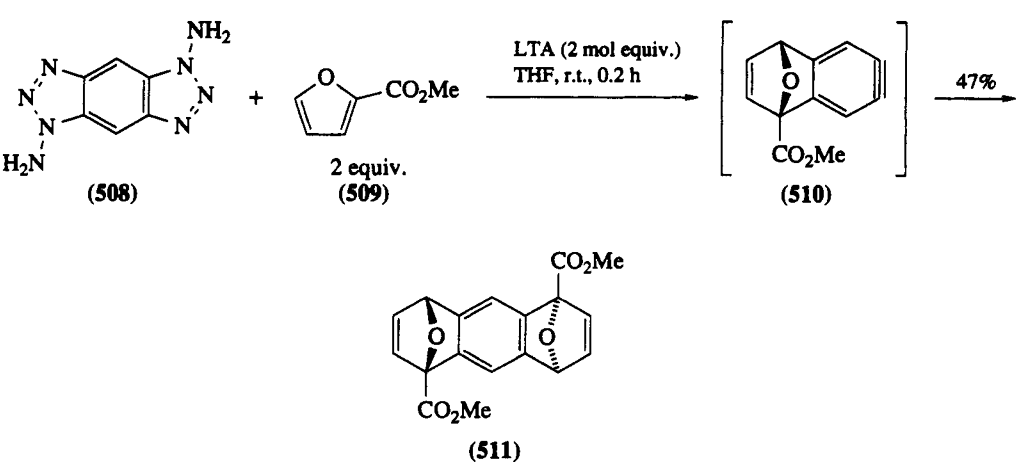
(508)
2 equiv.
(509)
LTA (2 mol equiv.)
THF, r.t., 0.2 h
(510)
47%
(511)

Scheme 119

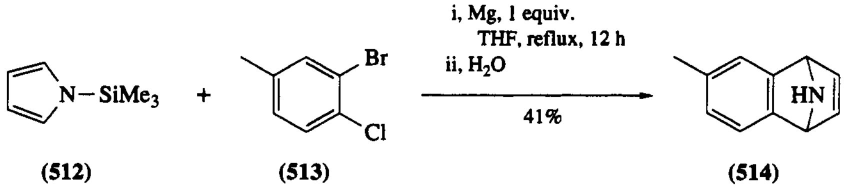
(512)
(513)
i, Mg, 1 equiv.
THF, reflux, 12 h
ii, H2O
41%
(514)

Scheme 120

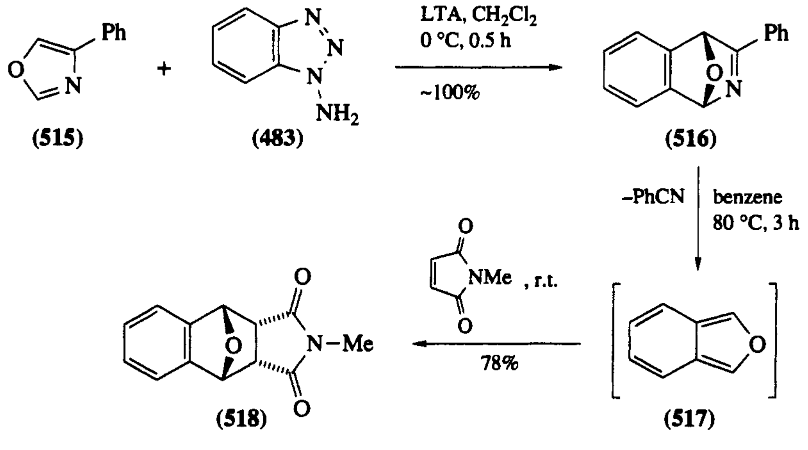
(515)
(483)
LTA, CH2Cl2
0 °C, 0.5 h
~100%
(516)
-PhCN
benzene
80 °C, 3 h
(517)
, r.t.
78%
(518)

Scheme 121

### 4.1.7.3 Reactions with Benzenes and Anthracenes

The outstanding dienophilicity of benzynes is highlighted by their Diels–Alder additions to benzenes. Tetrachlorobenzyne (**520**), easily generated by lithiation of hexachlorobenzene (**519**), smoothly reacted with benzene to afford tetrachlorobenzobarrelene (**521**) in ~60% yield (Scheme 122).[123] The parent benzyne (**478**) underwent similar addition to benzene, although not so efficiently.[112]

[4 + 2] Cycloaddition of benzyne (**478**) to (the less aromatic) anthracene provides a well-known approach to triptycene (**524**).[124] More recently, this type of reaction was extended to elegant syntheses of iptycenes, *e.g.* (**526**), using 1,2,4,5-tetrabromobenzene (**525**) as a 1,4-benzadiyne equivalent (Scheme 123).[125]

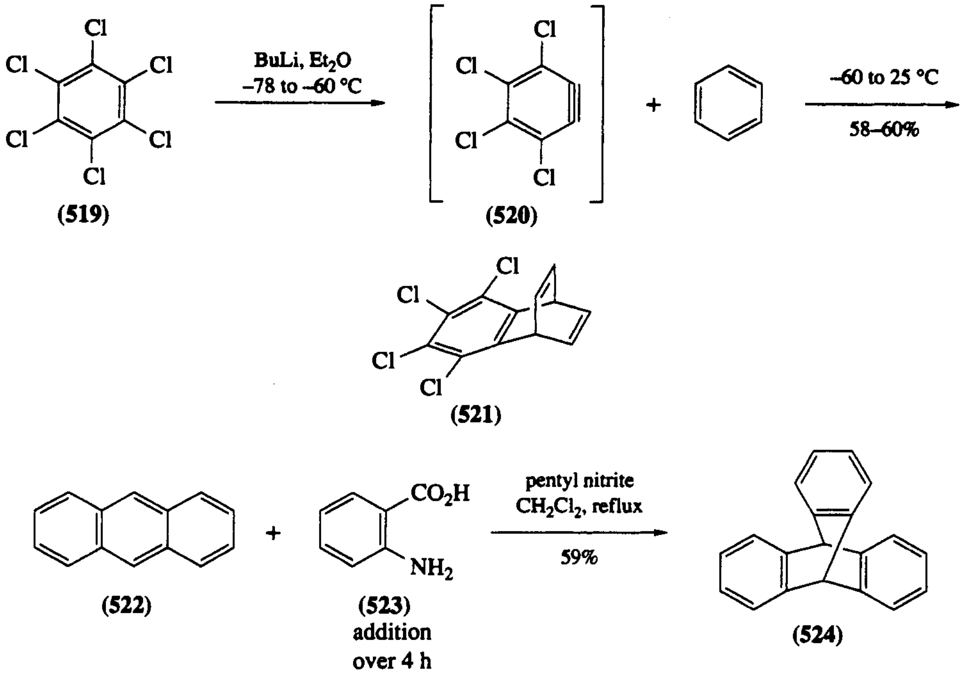
Cl
BuLi, Et$_2$O
−78 to −60 °C
(519)
(520)
−60 to 25 °C
58–60%
(521)
CO$_2$H
NH$_2$
pentyl nitrite
CH$_2$Cl$_2$, reflux
59%
(522)
(523)
addition
over 4 h
(524)

**Scheme 122**

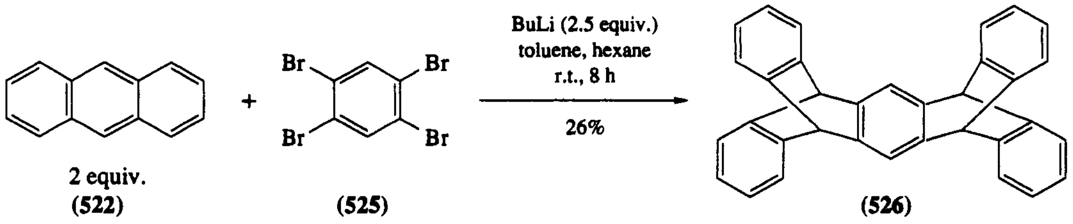
Br
BuLi (2.5 equiv.)
toluene, hexane
r.t., 8 h
26%
2 equiv.
(522)
(525)
(526)

**Scheme 123**

### 4.1.7.4 Reactions with Exocyclic or Partially Cyclic 'Cisoid' Dienes

The tetrakis(methylidene)-7-oxabicyclo[2.2.1]heptane (**527**) offers an interesting route to linear polyannulated ring systems, e.g. 4-demethoxydaunomycinone (**641**), *via* a sequence of two Diels–Alder reactions (Scheme 124). Monoadduct (**528**) could be isolated and subjected to the [4 + 2] cycloaddition of benzyne.[126a] An alternative synthesis of anthracyclinone analogs starts with the Diels–Alder addition of 3-methoxybenzyne to a derivative of the 'bis-cisoid' tetraene (**527**).[126b]

A synthetic approach to the class of aporphine alkaloids centers on [4 + 2] cycloadditions of benzynes to the 'cisoid' 1,3-diene (**531**), which contains one double bond as part of a benzene ring (Scheme 125).[127]

### 4.1.7.5 3,4-Pyridyne as a Dienophile

Hetarynes (dehydroaromatic heterocycles) can also act as dienophiles in Diels–Alder reactions.[112] This capacity and the inherent regiochemical problems are illustrated by two syntheses of the alkaloid ellipticine, which both feature a [4 + 2] cycloaddition of 3,4-pyridyne (**533**) (Scheme 126).[128] The first approach used the triazenylcarboxylic acid (**534**) as a precursor for hetaryne (**533**), which then underwent an addition to pyranoindolone (**535**); spontaneous $CO_2$ extrusion of the initial cycloadducts (**536**; X = N, Y = CH) and (**536**; X = CH, Y = N) gave directly a 50:50 mixture of ellipticine (**537**) and its undesired regioisomer (**538**).[128a]

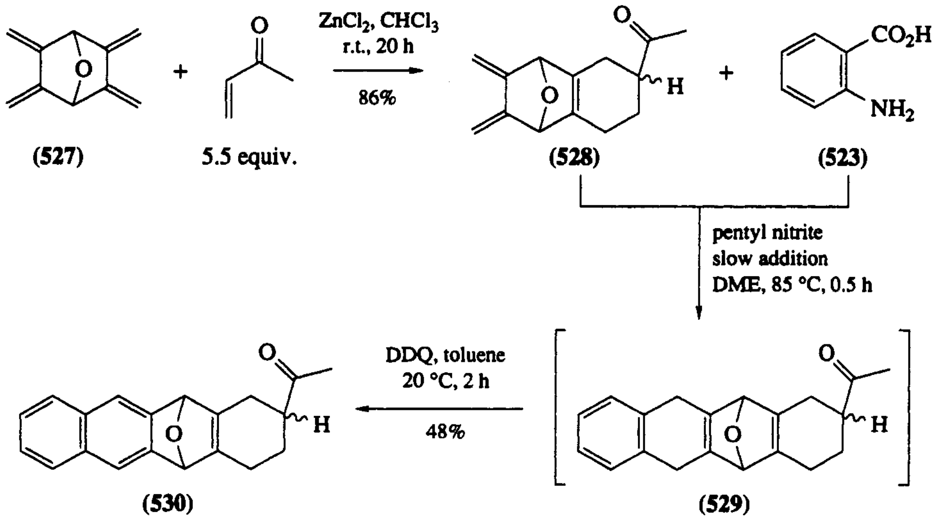

Scheme 124

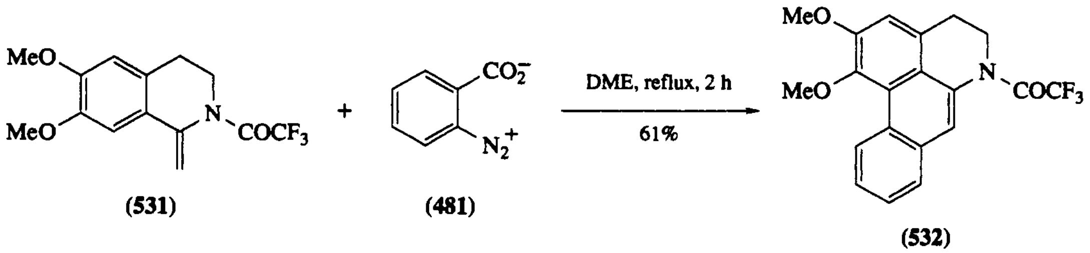

Scheme 125

A similar lack of regiochemical control also hampers the [4 + 2] cycloaddition of pyridyne (**533**) (prepared from **539**) to furoindole (**540**). Desulfonylation and 'deoxygenation' of the cycloadduct mixture of (**541**; X = N, Y = CH) and (**541**; X = CH, Y = N) afforded ellipticine (**537**) and isoellipticine (**538**) in a 45:55 ratio.[128b]

## 4.1.8 *ORTHO*-QUINODIMETHANES AS DIENE COMPONENTS

### 4.1.8.1 Background

*ortho*-Quinodimethanes (*o*-xylylenes), represented by the prototype (**542**), are very reactive dienes. When generated in the presence of a dienophile they afford [4 + 2] cycloadducts, *e.g.* (**543**), with a concomitant restoration of aromaticity (Scheme 127). In fact, species (**542**) and its derivatives were first recognized by Cava and coworkers[129a,c,d] and, independently, by Jensen and Coleman[129b] (1957–1959) *via* trapping by maleic anhydride or *N*-phenylmaleimide, and identification of cycloadducts (**543**).

Several reviews have dealt with Diels–Alder reactions of *o*-quinodimethanes,[130] emphasizing the more powerful, selective and thus extensively used intramolecular versions (*cf.* Scheme 135) introduced in 1971.[131] The most recent survey also tackled the issue of asymmetric induction by means of a chiral auxiliary group attached to the *o*-quinodimethane precursor.[130i] This section aims at a complementary coverage of intermolecular Diels–Alder reactions of *o*-quinodimethanes, underlining synthetically relevant aspects.

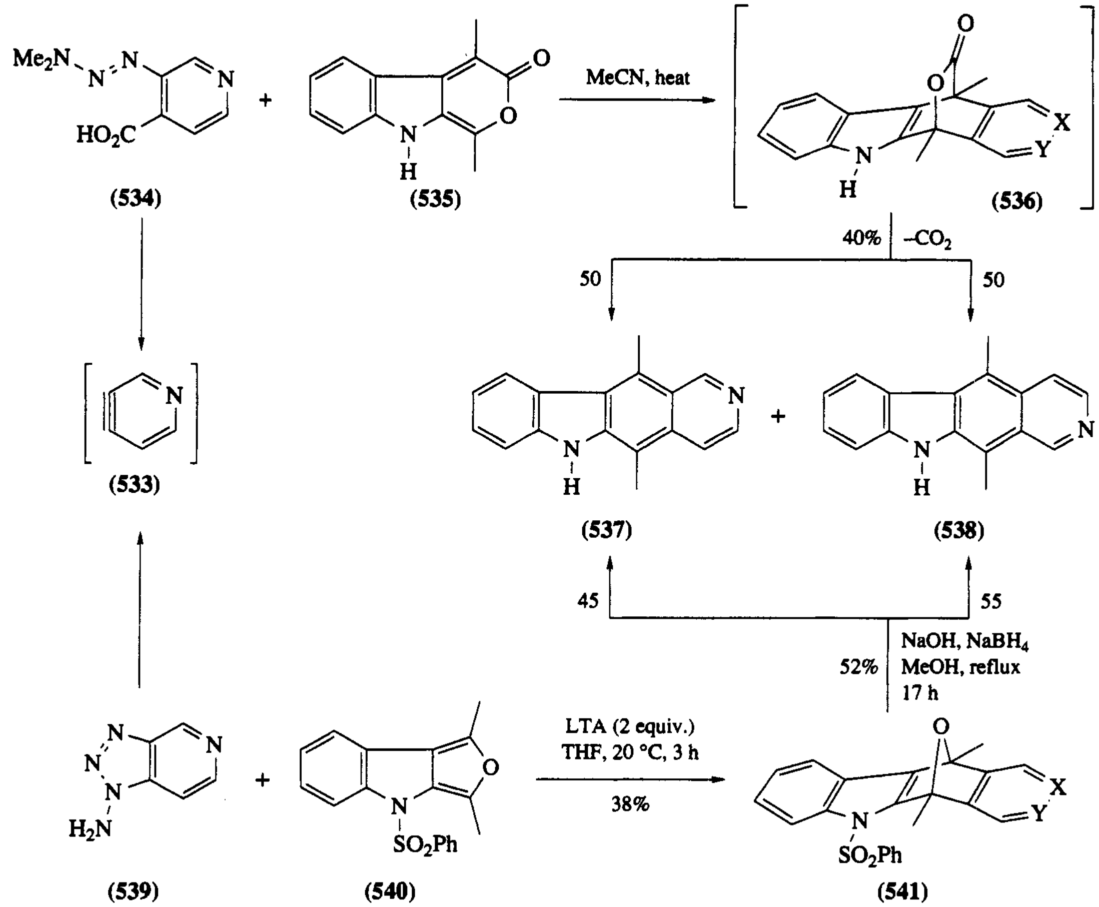

Scheme 126

### 4.1.8.2 Preparation

The preparation of this class of dienes has received considerable attention during the last few years. Scheme 127 depicts the current approaches, such as 1,4-eliminations of *o*-xylene derivatives *via* reduction (**544**) → (**542**),[132] thermal dehydrohalogenation (**545**) → (**542**),[133] and fluoride-induced desilylation (**546**) → (**542**).[134] The last procedure is particularly noteworthy because of the mild reaction conditions, which are compatible with various functional groups. The chelotropic, thermal elimination of sulfur dioxide, (**547**) → (**542**), one of the oldest routes to *o*-quinodimethanes,[129c] remains attractive owing to the easy functionalization of (**547**) at $C_\alpha$.[130c,135] This advantage also holds for 3-isochromanones (**548**), which provide (**542**) on Diels–Alder cycloreversion with loss of carbon dioxide.[130c] Without doubt, the most established source of *o*-quinodimethanes are the derivatives of benzocyclobutene (bicyclo[4.2.0]octa-1,3,5-triene) (**549**), which on heating undergo a clean and reversible electrocyclic ring opening (**549**) $\rightleftharpoons$ (**542**).[129b] Consequently, when *o*-quinodimethanes are generated by an independent route, in the absence of a reaction partner, benzocyclobutenes can be obtained in high yields (*vide infra*).

Recently, the occasionally capricious reduction of α,α'-dibromo-*o*-xylenes (**550**) has been improved by the use of Zn/ultrasound, zinc/silver couple, reactive nickel (0) or $CrCl_2$, as assayed by *in situ* trapping of (**551**) with typical dienophiles (Scheme 128, Table 33).[132]

These methods still show limitations. The reduction of (**550a**) with activated nickel in the presence of diethyl maleate gave a 50:50 mixture of *cis* and *trans* adducts (entry 4), probably due to a nickel-promoted *cis*/*trans* isomerization of the dienophile prior to cycloaddition. Homogeneous reduction using $CrCl_2$ failed with a dibromide precursor containing a quinone moiety.[132d]

The preparatively attractive approach to benzocyclobutenes by flash pyrolytic 1,4-dehydrohalogenation, (**545**) → (**542**) → (**549**),[133a] was extended to the even more remarkable conversion of *o*-methylbenzal chlorides to 1-chlorobenzocyclobutenes e.g. (**554**) → (**555**) (Scheme 129).[133b]

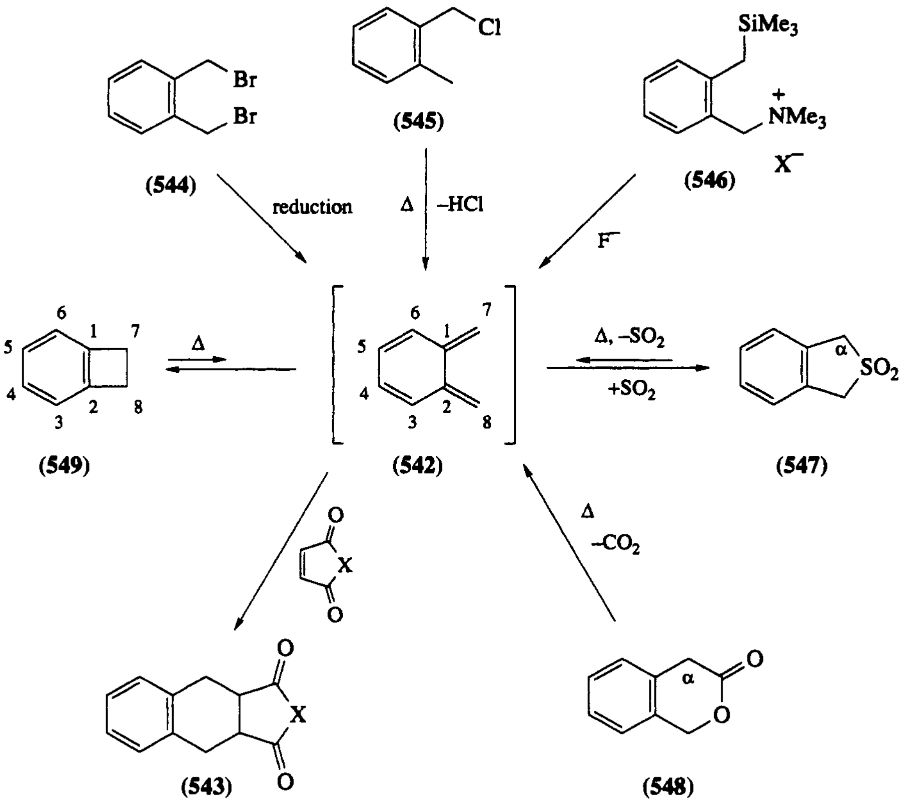
(544)
Br
Br
(545)
Cl
(546)
SiMe3
+
NMe3
X⁻
reduction
Δ
−HCl
F⁻
(549)
Δ
(542)
Δ, −SO2
+SO2
α
SO2
(547)
O
X
O
Δ
−CO2
(543)
(548)
α
O
O
1
2
3
4
5
6
7
8

Scheme 127

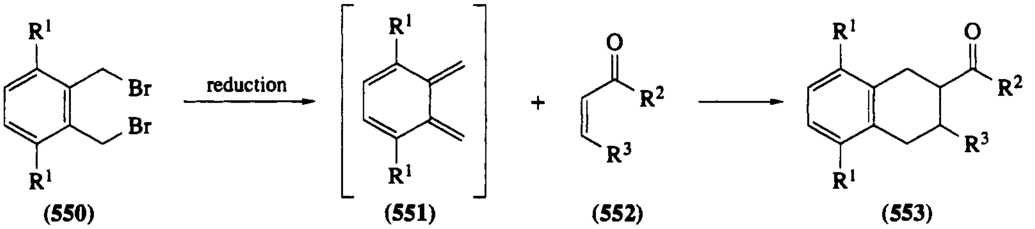
R1
Br
Br
R1
(550)
reduction
R1
R1
(551)
+
O
R2
R3
(552)
R1
O
R2
R3
R1
(553)

Scheme 128

Table 33 Reduction of α,α′-Dibromo-*o*-xylenes and Diels–Alder Reactions of the Resulting *o*-Quinodimethane Intermediates (Scheme 128)

| *Entry* | *$R^1$* | *$R^2$* | *$R^3$* | *Reduction method* | *Yield (%) of (553)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 a | H | Me | H | Zn/ultrasound[a] | 87 | 132a |
| 2 b | Me | Me | H | Zn/Ag[b] | 74 | 132b |
| 3 a | H | OMe | H | Ni[d] | 67 | 132c |
| 4 a | H | OEt | $CO_2Et$ | Ni[d] | 90[e] | 132c |
| 5 a | H | OEt | H | $CrCl_2$[c] | 84 | 132d |
| 6 c | OMe | Me | H | $CrCl_2$[c] | 85 | 132d |

[a] Activated zinc (2.3 equiv.), dioxane, ultrasound, $N_2$, 20–25 °C, 12 h. [b] Zn(Ag) (2 equiv.), DMF, stirring, $N_2$, r.t., 6 h. [c] Addition of dibromide + dienophile (3–5 equiv.) to $CrCl_2$ (3–5 equiv.) in THF/HMPA, $N_2$, 20 °C, 0.5 h. [d] (i) $NiI_2$ (1.25 equiv.), Li (3 equiv.), naphthalene (0.13 equiv.), r.t., 12 h; (ii) dienophile (2 equiv.), slow addition of dibromide, r.t., 7 h. [e] 50:50 mixture of *cis*/*trans* products.

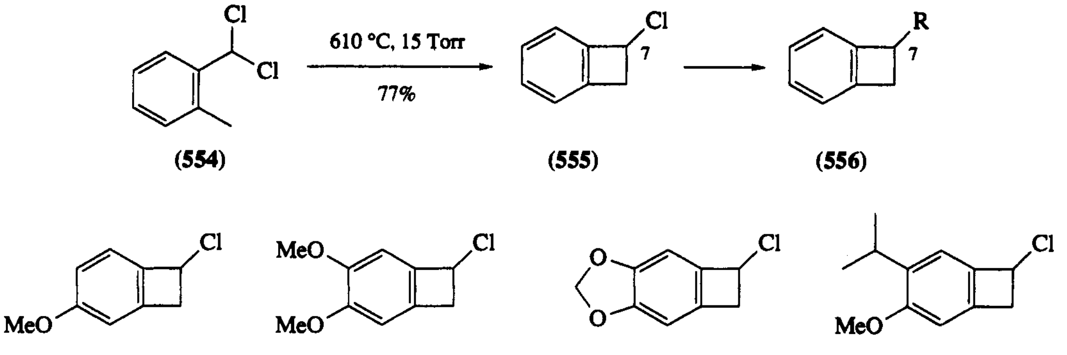

**(554)** **(555)** **(556)**

**(557)** 68% **(558)** 64% **(559)** 68% **(560)** 55%

**Scheme 129**

Treatment of *o*-tolualdehyde with $PCl_5$, followed by thermal HCl elimination, afforded **(555)** in 77% overall yield. The halogen in **(555)** can be replaced by substitution with nucleophiles and, *via* the Grignard reagent, with electrophiles, providing an easy access to variously 7-substituted benzocyclobutenes **(556)**. This sequence is compatible with aromatic substituents, as exemplified by the range of useful building blocks **(557)**–**(560)**, obtained in good yields.

Similar flash vacuum pyrolysis of *o*-toluic acid chloride **(561)** lends itself to the easy preparation of benzocyclobutenone **(563)** (76% at a laboratory scale of 250 g).[133b] Variations of the aromatic nucleus are easy, as demonstrated by the preparation of derivatives **(564)**–**(567)** (Scheme 130).

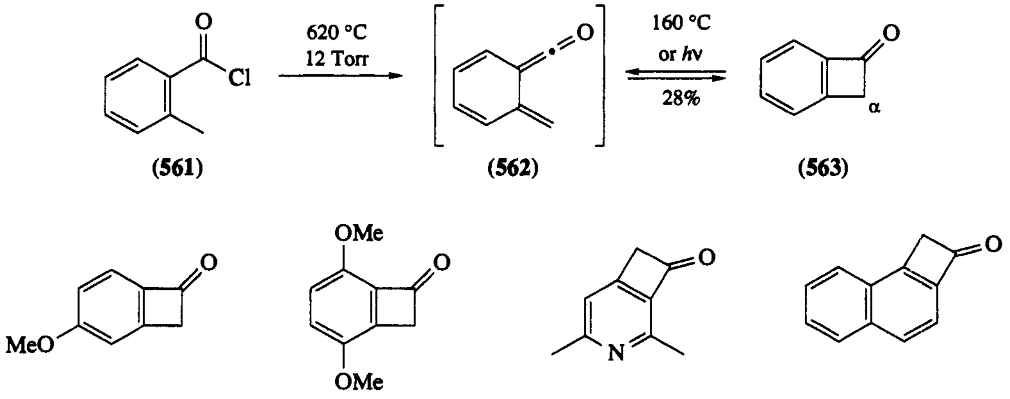

**(561)** **(562)** **(563)**

**(564)** 68% **(565)** 63% **(566)** 53% **(567)** 66%

**Scheme 130**

As to the underlying reaction mechanism, it appears that vacuum thermolysis of **(545)**, **(554)** and **(561)** generates in each case, initially, a transient *o*-quinodimethane which cyclizes in the highly dilute gas phase. *o*-Quinoid vinylketene intermediate **(562)** could be regenerated in solution from the isolated benzocyclobutenone **(563)** on heating or irradiation and trapped by electron-poor dienophiles, *e.g.* **(632)** (Scheme 141).[133c,146] Alternatively, benzocyclobutenones can be easily functionalized at the carbonyl group or at $C_\alpha$, affording further *o*-quinodimethane precursors.

For example, 7-phenylbenzocyclobuten-7-ol **(568)** (obtained from **563**) when heated with maleic anhydride in toluene gave acid lactone **(571)** in 75% yield (Scheme 131).[136] This result is consistent with an *endo*-[4 + 2] cycloaddition of the dienophile to the (*E*)-dienol **(569)** followed by lactonization of cycloadduct **(570)**. The cycloadduct **(570)** was, furthermore, obtained in 80% yield by the 'photoenolization' of *o*-methylbenzophenone **(572)** in the presence of maleic anhydride at room temperature.[137] It follows that the photoinduced 1,5-hydrogen shift of **(572)** must have generated the same (*E*)-dienol **(569)** as that obtained by the thermal ring opening of **(568)**. This and other aspects of 'photoenolization' have been reviewed.[136]

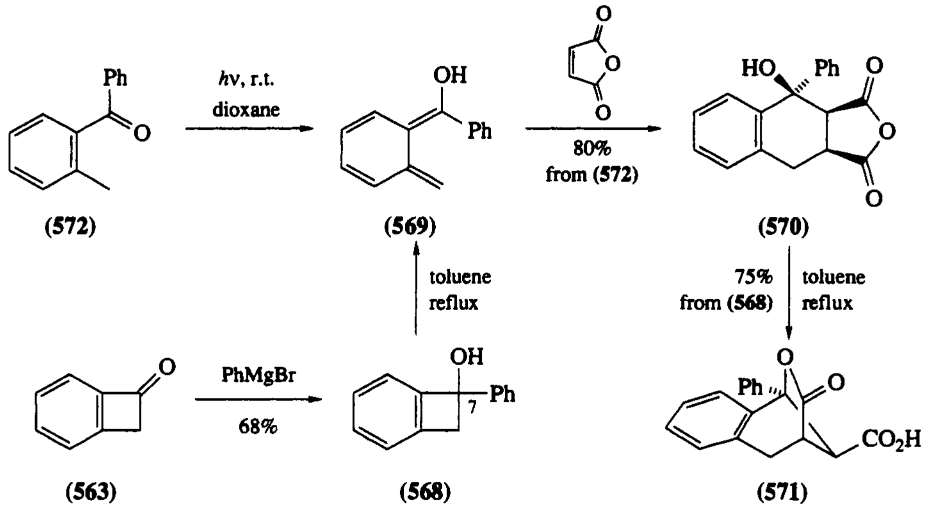
Ph
O
(572)
hν, r.t.
dioxane
OH
Ph
(569)
O
O
O
80%
from (572)
HO
Ph
O
O
O
(570)
toluene
reflux
75%
from (568)
toluene
reflux
O
(563)
PhMgBr
68%
OH
Ph
7
(568)
O
Ph
O
CO2H
(571)

Scheme 131

Analogous irradiation of *o*-tolualdehyde forms apparently (*E*)-dienol (**574**), which was trapped directly with maleic anhydride (→ **575**)[136] or $SO_2$ (→ **576**) (Scheme 132).[138] α-Hydroxysulfones such as (**576**) could be transformed into α-methoxy and α-acetoxy sulfones and then used, *per se*, as *o*-quinodimethane precursors.[138] The advantage of thermal benzocyclobutenol ring opening (**577** → **574**) over photoenolization (**573** → **574**) is illustrated by the efficient formation of Diels–Alder product (**579**) on heating (**577**) with (**578**).[136] The corresponding photogeneration/trapping technique failed due to the photosensitivity of the quinone dienophile (**578**). Another drawback of *in situ* photoenolizations is the facile light-induced *cis*/*trans* isomerization of acyclic dienophiles.

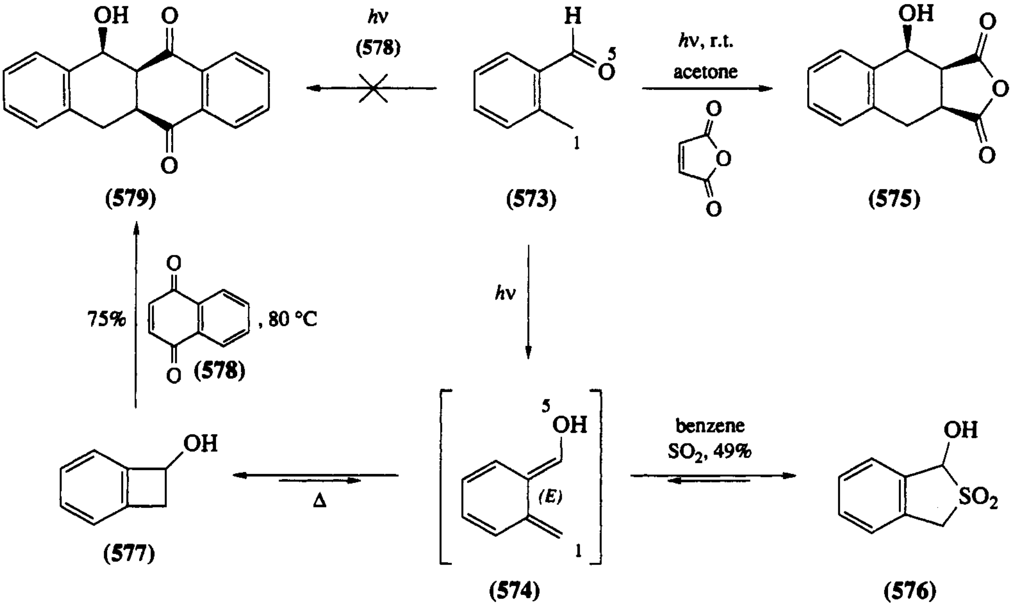
OH
O
O
(579)
hν
(578)
H
5
O
1
(573)
hν, r.t.
acetone
O
O
O
OH
O
O
O
(575)
75%
O
O
(578)
, 80 °C
hν
OH
(577)
Δ
5
OH
(E)
1
(574)
benzene
SO2, 49%
OH
SO2
(576)

Scheme 132

A relatively new route to benzocyclobutenes, without the involvement of *o*-quinodimethanes, is the cobalt-catalyzed co-oligomerization of bis(trimethylsilyl)acetylene with 1,5-hexadiynes, (**580**) + (**581**) → (**582**) (Scheme 133).[139] Despite its elegance, and the potential to modify the silyl groups, this method suffers from limitations in providing benzocyclobutenes with well-defined substitution patterns. In this respect, it is the 'older', more general, base-induced cyclization of *o*-halodihydrocinnamonitriles (or esters), *e.g.* **(583)** → **(585)**, which currently enjoys much wider practical use.[140]

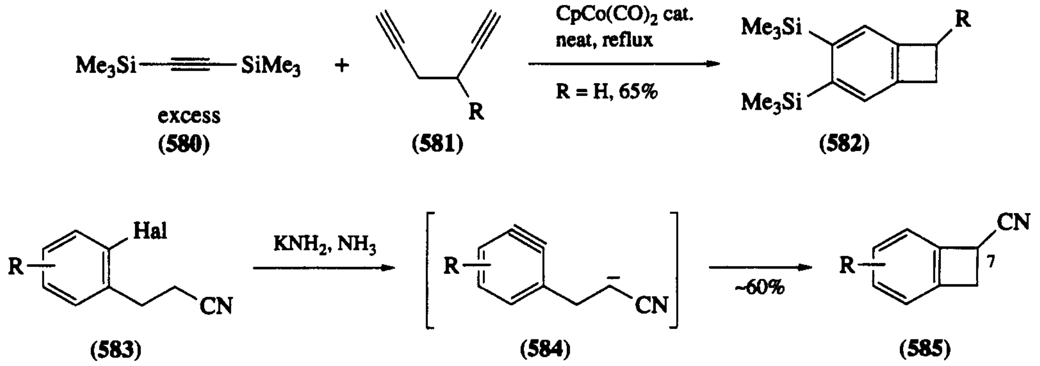
$Me_3Si$—≡—$SiMe_3$
excess
(580)
+
R
(581)
$CpCo(CO)_2$ cat.
neat, reflux
R = H, 65%
$Me_3Si$
$Me_3Si$
R
(582)
R
Hal
CN
(583)
$KNH_2$, $NH_3$
R
–
CN
(584)
~60%
R
CN
7
(585)

Scheme 133

### 4.1.8.3 Regio- and Stereo-chemistry

It thus follows that benzocyclobutenes are readily accessible, relatively inert and reliable 'masked' *o*-quinodimethane equivalents. With 7-substituted derivatives **(586)**, thermal 'unmasking' takes place at a rate which varies widely with the nature of the substituent R (Scheme 134, Table 34).[130a]

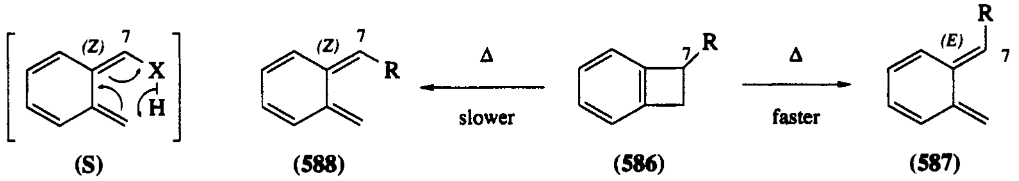
(Z)
7
X
H
(S)
(Z)
7
R
(588)
Δ
slower
7
R
(586)
Δ
faster
R
(E)
7
(587)

Scheme 134

**Table 34** Approximate Temperature for Complete Ring Opening of 7-Substituted Benzocyclobutenes[a] (Scheme 134)

| *Substituent R* | $NH_2$ | OH | NH(C=O)R′ | C=O | $CH_2$ | H |
|---|---|---|---|---|---|---|
| *Temp.* (°C) | 25 | 80 | 111 | 150 | 180 | 200 |

[a] Reaction time: 18 h.

This thermal ring opening favors the formation of (*E*)-*o*-quinodimethanes **(587)** over that of (*Z*)-dienes **(588)** which, when the substituent R bears a hydrogen atom (R = XH), undergo a 1,5-H shift. For this and other reasons, the (*E*)-configuration of terminally substituted *o*-quinodimethanes is relevant for their use in Diels–Alder reactions.[130a]

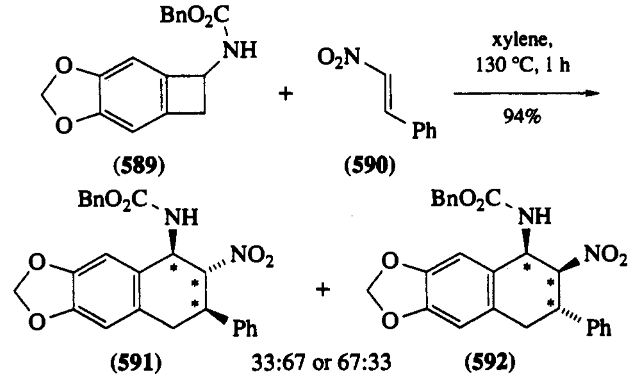
$BnO_2C$
NH
O
O
(589)
+
$O_2N$
Ph
(590)
xylene,
130 °C, 1 h
94%
$BnO_2C$
NH
$NO_2$
O
O
Ph
(591)
+
$BnO_2C$
NH
$NO_2$
O
O
Ph
(592)
33:67 or 67:33

Scheme 135

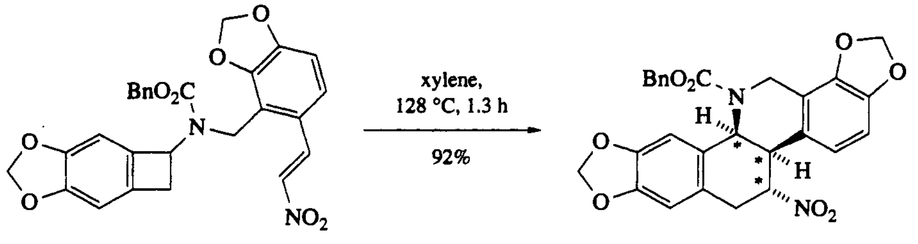

**(593)** **(594)**

**Scheme 135** ***(continued)***

Hence, no 1,5-hydrogen shift was observed on heating benzocyclobutenylcarbamate (**589**) with nitrostyrene (**590**) at 130 °C, which furnished cycloadducts (**591**) + (**592**) in 94% yield (Scheme 135).[141] The strong regio-directing effects of the *N*-$CO_2Bn$ (diene) and $NO_2$ groups (dienophile) secured their 'ortho' disposition in the products. However, the observed product ratio (**591**)/(**592**) reflects a stereospecific, but only poorly *endo*/*exo*-selective, [4 + 2] cycloaddition step.

This result contrasts sharply with that of the intramolecular transformation (**593**) → (**594**) (a key step in a synthesis of chelidonine). The exclusive formation of (**594**) (isolated in 92% yield) shows here an opposite regiochemical control and a strong preference for an *exo*-oriented nitro group in the transition state, dictated by the constraints of intramolecularity.[141]

Intermolecular thermal addition of 7-methylbenzocyclobutene (**595**) to propyne (→ **596** + **597**) displayed only modest regioselectivity (Scheme 136).[142] [4 + 2] Cycloadditions of the more polarized methyl acrylate to 7-*n*-butyl-*o*-quinodimethane, generated from (**598**) at room temperature *via* the desilylation technique, was more selective, giving the '*ortho*'/'*endo*' isomer (**599**) as the major product.[134] A methoxy substituent or a nitrogen atom as part of the developing aromatic ring has virtually no regiodirecting influence, as demonstrated by the corresponding reactions of (**601**) and (**604**).[134]

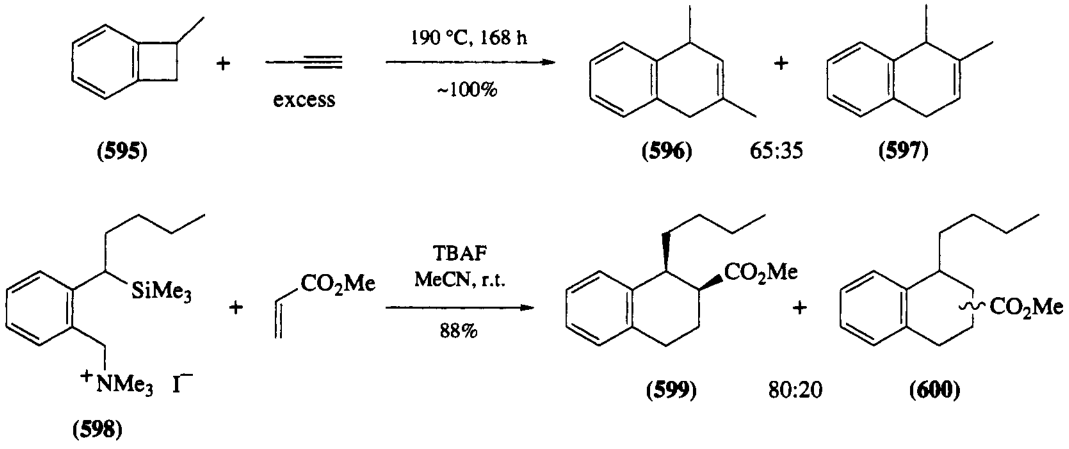

**(595)** **(596)** **(597)** **(598)** **(599)** **(600)**

**Scheme 136**

Several stereochemical facets show up on Diels–Alder reactions of 7,8-disubstituted *o*-quinodimethanes. A seminal study of addition reactions of 7,8-diphenylbenzocyclobutenes provided strong evidence for a conrotatory opening of the four-membered ring, followed by a supra-supra-facial *endo*-selective Diels–Alder reaction with *N*-phenylmaleimide, as exemplified by the transformation (**607**) → (**609**) (Scheme 137).[143] Based on this result, it is now generally agreed that the *trans* relation of substituents at C-7 and C-8 in benzocyclobutenes translates, *via* the transient (*E*,*E*)-*o*-quinodimethanes, *e.g.* (**608**), into the *cis* disposition in the corresponding cycloadducts.

The corresponding transformation of *cis*-benzocyclobutene (**610**) to (**612**) proceeded slower (by a factor of 27), in keeping with the involvement of an (*E*,*Z*)-intermediate (**611**).[143] Attempts to generalize the latter type of stereochemistry met with only limited success due to the propensity of (*E*,*Z*)-*o*-quinodimethanes for 1,5-shifts (*e.g.* S, Scheme 134) and cyclizations.

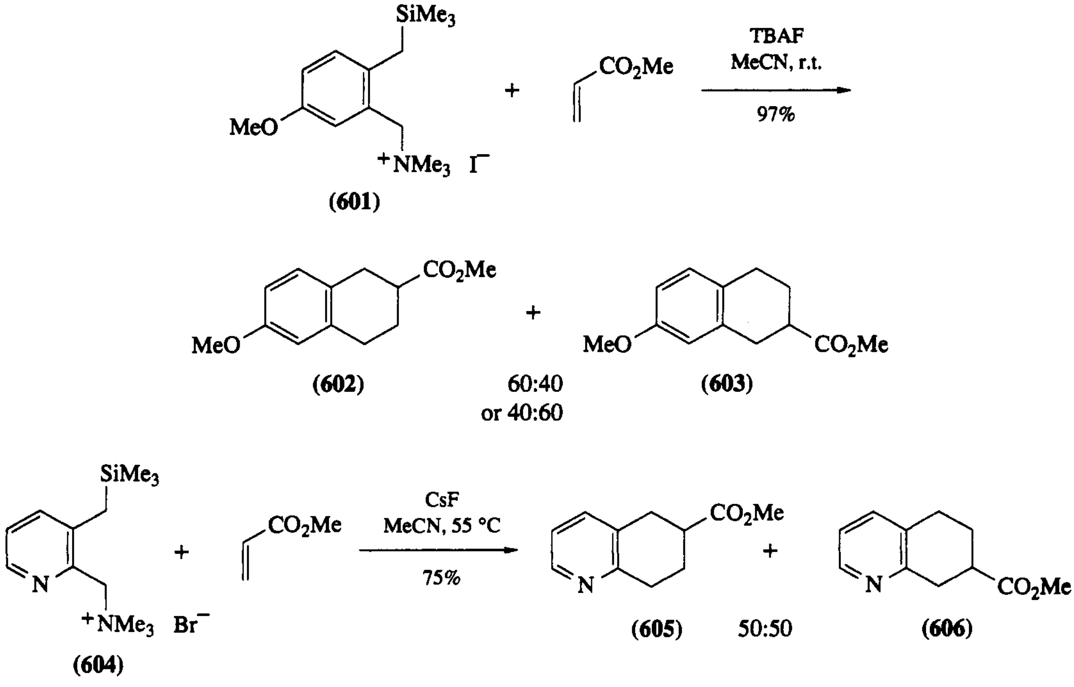
SiMe3
MeO
+NMe3 I−
(601)
+
CO2Me
TBAF
MeCN, r.t.
97%
CO2Me
MeO
(602)
+
60:40
or 40:60
MeO
CO2Me
(603)
SiMe3
N
+NMe3 Br−
(604)
+
CO2Me
CsF
MeCN, 55 °C
75%
CO2Me
N
(605)
+
50:50
N
CO2Me
(606)

Scheme 136 *(continued)*

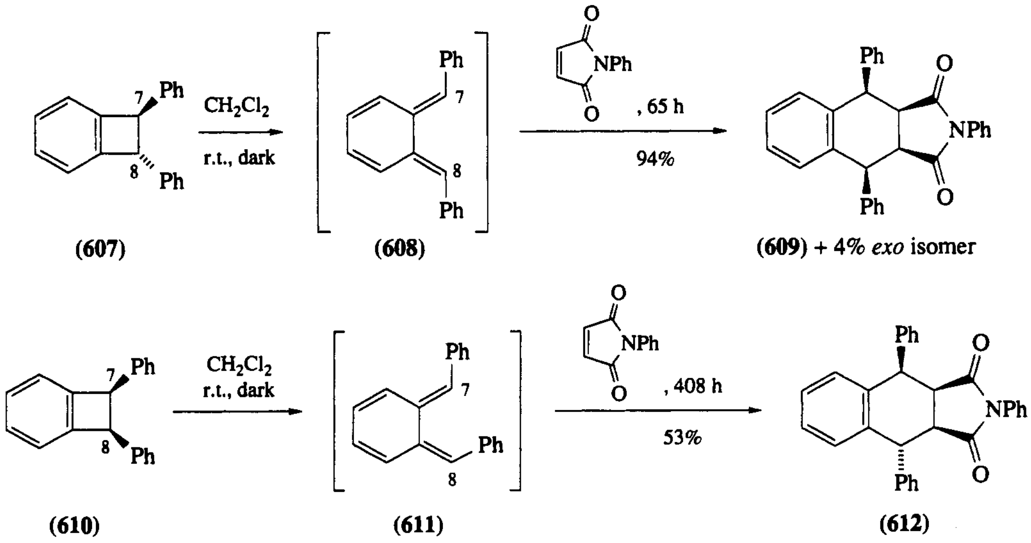
Ph
7
8
Ph
(607)
CH2Cl2
r.t., dark
Ph
7
8
Ph
(608)
O
NPh
O
, 65 h
94%
Ph
O
NPh
Ph
O
(609) + 4% exo isomer
Ph
7
8
Ph
(610)
CH2Cl2
r.t., dark
Ph
7
Ph
8
(611)
O
NPh
O
, 408 h
53%
Ph
O
NPh
Ph
O
(612)

Scheme 137

One reported exception is the thermal stereospecific $SO_2$ extrusion of *trans*-acetoxyphenyl sulfone (**613**), coupled with the Diels–Alder reaction of the postulated (*E,Z*)-diene (**614**) to dimethyl fumarate, yielding (**615**; 94%) (Scheme 138).[138b]

As expected, *cis*-sulfone (**616**) afforded fumarate adduct (**618**; 90%) under milder conditions. Both examples display a complete 'retention' of diene and dienophile configurations in the cycloadducts. Moreover, each product (**615**) and (**618**) shows a *trans* disposition of the phenyl and adjacent ('*ortho*') methoxycarbonyl groups; the latter is apparently *exo* oriented on addition to (*E,E*)-diene (**617**).[138b]

[4 + 2] Cycloadditions of dimethyl maleate to (*E,E*)-*o*-quinodimethanes exhibit only modest *endo*/*exo* selectivities (in contrast to maleic anhydride) (Scheme 139).[134,138b]

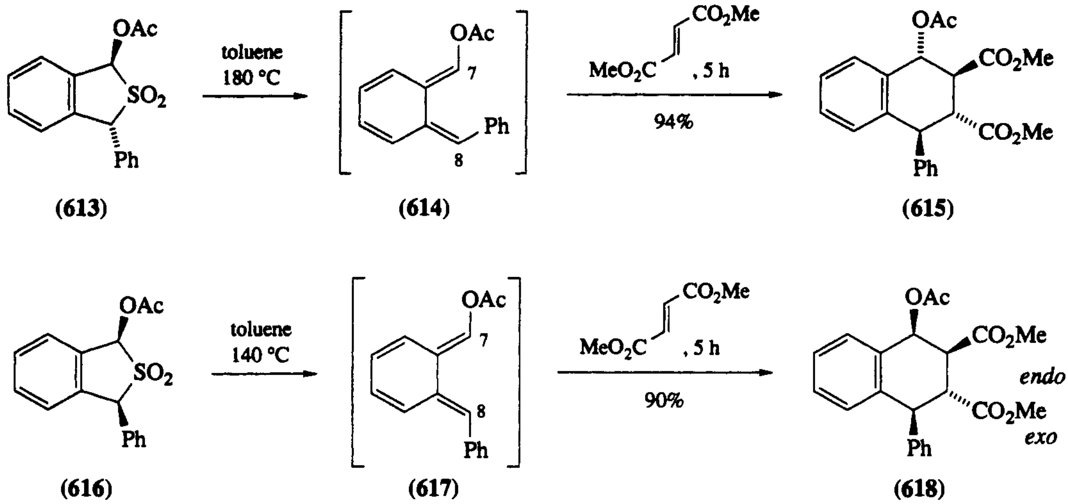
OAc
SO2
Ph
(613)
toluene
180 °C
OAc
7
Ph
8
(614)
CO2Me
MeO2C
, 5 h
94%
OAc
CO2Me
CO2Me
Ph
(615)
OAc
SO2
Ph
(616)
toluene
140 °C
OAc
7
8
Ph
(617)
CO2Me
MeO2C
, 5 h
90%
OAc
CO2Me
endo
CO2Me
exo
Ph
(618)

Scheme 138

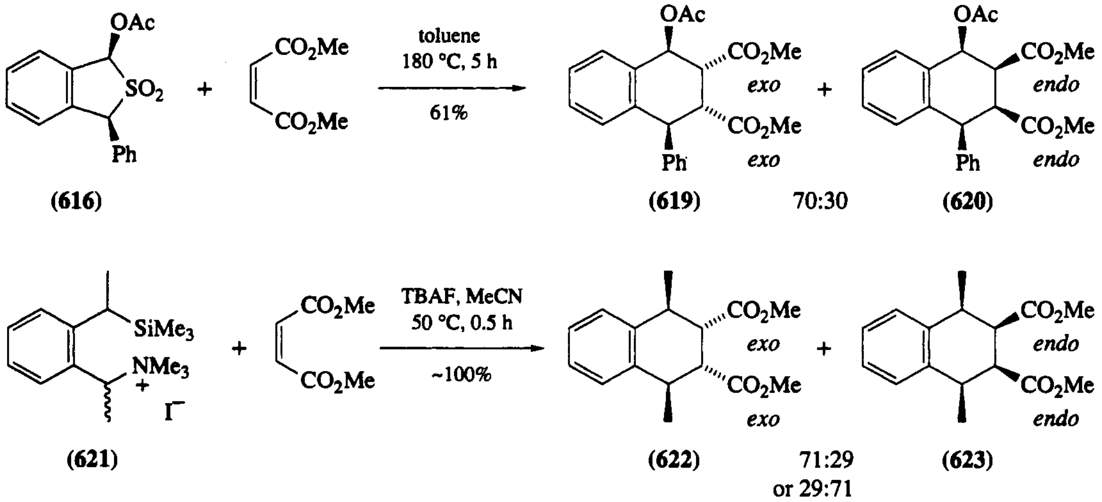
OAc
SO2
Ph
(616)
+
CO2Me
CO2Me
toluene
180 °C, 5 h
61%
OAc
CO2Me
exo
CO2Me
exo
Ph
(619)
70:30
+
OAc
CO2Me
endo
CO2Me
endo
Ph
(620)
SiMe3
NMe3
+
I−
(621)
+
CO2Me
CO2Me
TBAF, MeCN
50 °C, 0.5 h
~100%
CO2Me
exo
CO2Me
exo
(622)
71:29
or 29:71
+
CO2Me
endo
CO2Me
endo
(623)

Scheme 139

### 4.1.8.4 Applications in Synthesis

Diels–Alder reactions have played an eminent role (*cf.* Schemes 25, 26, 45, 53, 107, 109 and 124) in the synthesis of analogs of daunomycinone (**624**) and aklavinone (**625**), two representative aglycones of the tumor-inhibiting anthracyclines (Scheme 140).[144]

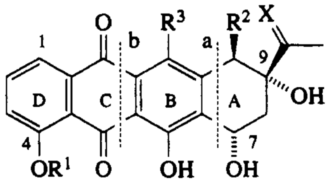
O
R3
R2
X
1
b
a
9
OH
D
C
B
A
4
7
OR1
O
OH
OH

(**624**) $R^1 = Me, R^2 = H, R^3 = OH, X = O$ Daunomycinone

(**625**) $R^1 = H, R^2 = CO_2Me, R^3 = H, X = H_2$ Aklavinone

Several approaches to this linearly annulated ring system make use of *o*-quinodimethanes to form either ring A ('disconnection' a) or ring C ('disconnection' b). The first strategy is illustrated by the treatment of bis(bromomethyl)anthraquinone (**626**) with NaI in DMA and trapping of transient diene (**627**) with methyl vinyl ketone, which gave tetracyclic ketone (**628**) (Scheme 140).[145a] The generation of the same diene (**627**) by heating benzocyclobutene (**629**) is more efficient and compatible with the less-reactive dienophile (**630**) to afford the 9-oxygenated product (**631**) in one step.[145b]

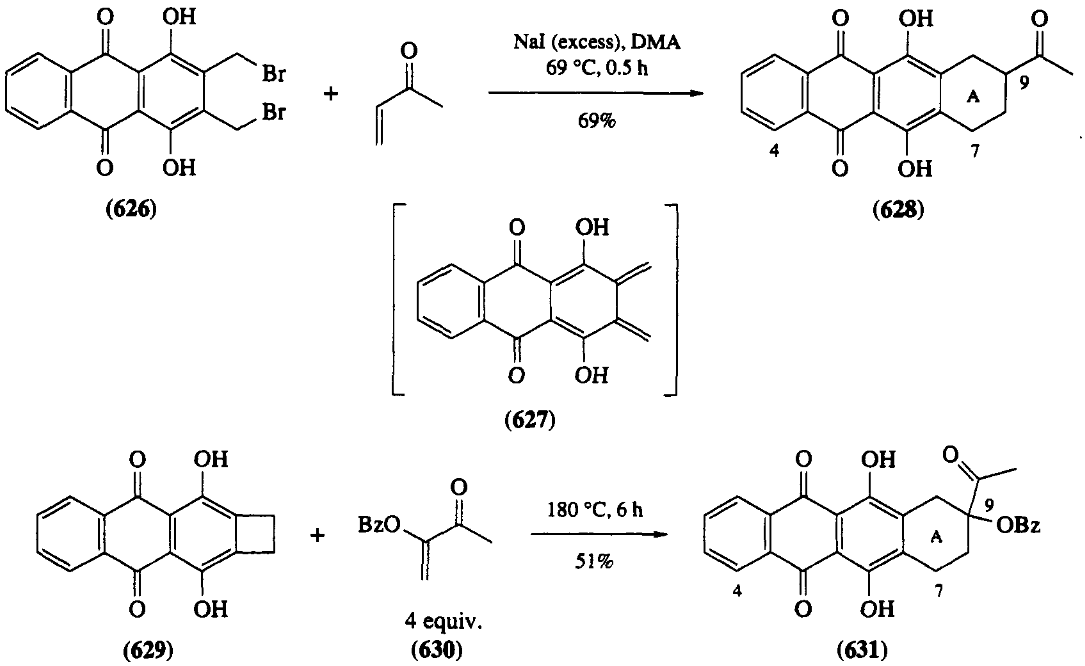
NaI (excess), DMA
69 °C, 0.5 h
69%
(626)
(627)
(628)
180 °C, 6 h
51%
4 equiv.
(629)
(630)
(631)

Scheme 140

Formation of ring C ('disconnection' b) was readily accomplished by addition of *o*-quinodimethane intermediates, e.g. (**562**)[146] or 7,8-dibromo-*o*-quinodimethane,[147] to tetrahydronaphthoquinones such as racemic or enantiomerically pure (**632**) (Scheme 141).

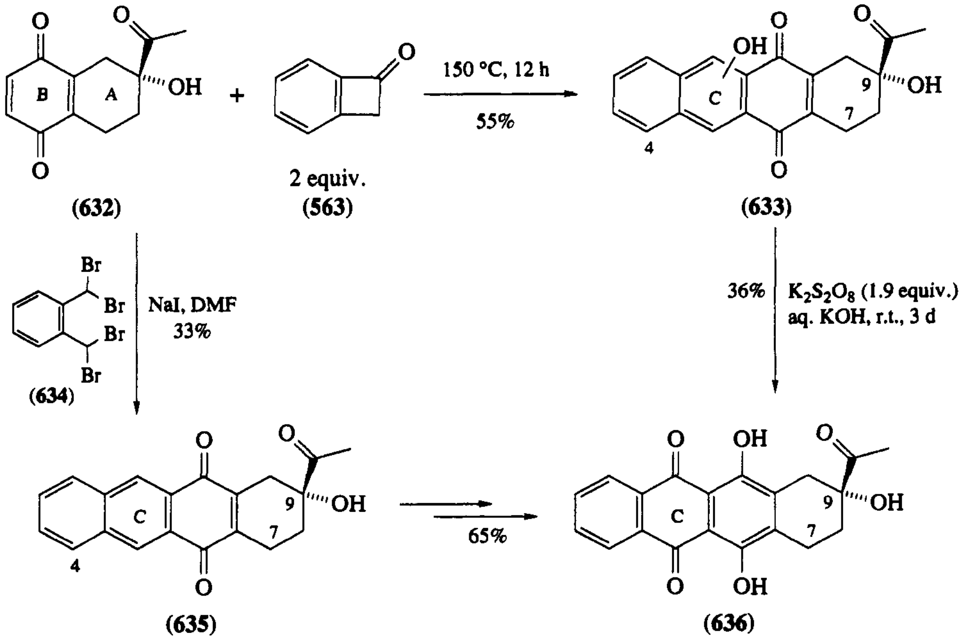
150 °C, 12 h
55%
2 equiv.
(632)
(563)
(633)
NaI, DMF
33%
(634)
36%
K₂S₂O₈ (1.9 equiv.)
aq. KOH, r.t., 3 d
65%
(635)
(636)

Scheme 141

Resulting adducts (**633**) and (**635**) require further manipulation involving oxidation of ring C and introduction of a hydroxy group at C-7. The latter problem was elegantly solved by using enantiomerically pure, fully functionalized, phenylboronate (**638**) as an 'A,B-dienophile' (Scheme 142).[148] Thermal generation and cycloaddition of (*E,E*)-diacetoxy-*o*-quinodimethane furnished adduct (**639**) in 81% yield. The remaining five steps served mainly to adjust the oxidation levels of rings B and C.

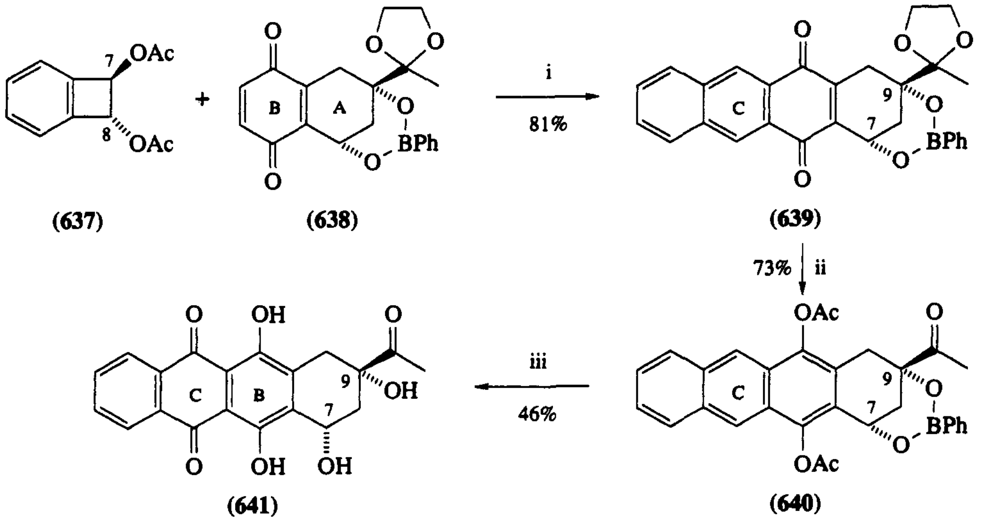
(637)
(638)
(639)
(640)
(641)
i
81%
73%
ii
iii
46%

i, xylene, reflux, 3 h; ii, 6 N HCl, dioxane, 25 °C, 4 h; $H_2$, Pd/C; $Ac_2O$, pyridine, 25 °C, 0.7 h; iii, $CrO_3$, $Ac_2O$, AcOH, 25 °C, 20 h; $BCl_3$, $CH_2Cl_2$, –70 to 10 °C, 1.5 h; $Me_2C(OH)CH_2CH(OH)Me$, AcOH, $CH_2Cl_2$, 25 °C

**Scheme 142**

This approach was dramatically shortened (from six to two operations) by providing the required oxidation level *via* the *o*-quinodimethane partner (Scheme 143).[146] Benzocyclobutenedione (**643**), readily available through flash vacuum pyrolysis of phthalide (**642**), furnished 'divinylketene' (**644**) on photo-

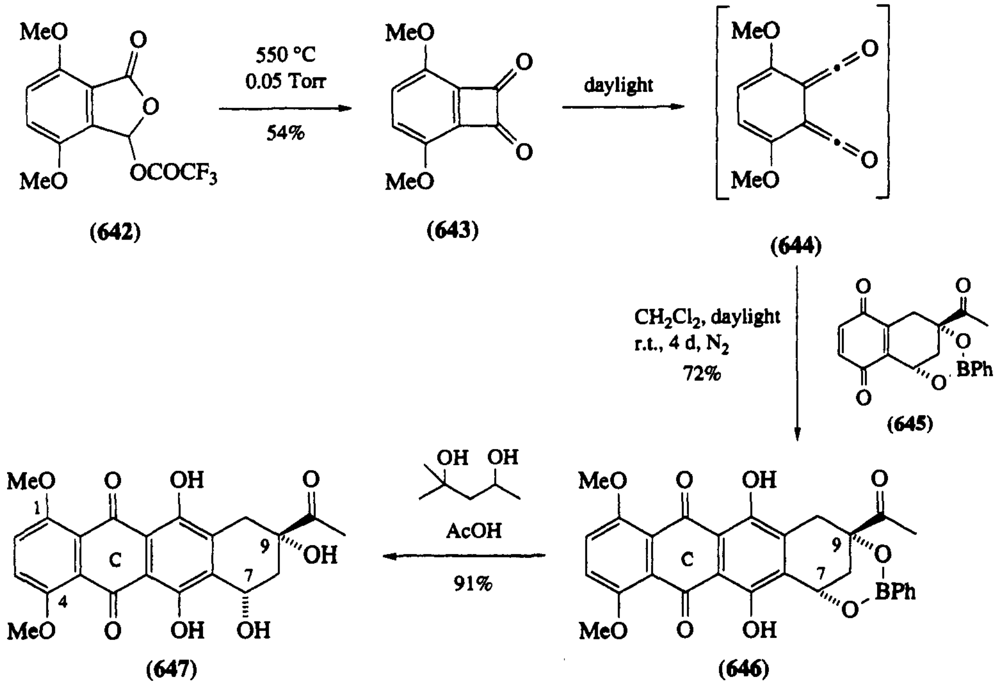
(642)
(643)
(644)
(645)
(646)
(647)
550 °C
0.05 Torr
54%
daylight
CH2Cl2, daylight
r.t., 4 d, N2
72%
AcOH
91%

**Scheme 143**

lytic ring opening. Transient species (**644**) underwent a smooth addition to enantiomerically pure quinone (**645**) to give adduct (**646**) which, on simple deprotection, yielded (+)-1-methoxydaunomycinone (**647**) in 66% overall yield.

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# 4.2

# Heterodienophile Additions to Dienes

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## 4.2.1 INTRODUCTION

Diels–Alder reactions of heterodienophiles have been known for decades, but only recently has this methodology become widely accepted by the synthetic community. There is enormous diversity in the structural types of compounds which can act as heterodienophiles, and a wide array of heterocyclic adducts can be prepared *via* these [4 + 2] cycloadditions. It seems clear that hetero Diels–Alder reactions span a range of mechanism from concerted to stepwise ionic processes. In many instances, mechanistic information is totally lacking. The discussion below therefore classifies heterodienophiles by structural rather than mechanistic class. Only the major types of synthetically useful heterodienophiles have been included. Moreover, the significant regio- and stereo-chemical features of the reactions have been exemplified as much as possible using recently reported cases. Other more comprehensive and more specialized reviews[1] should be consulted for older material and more obscure hetero Diels–Alder cycloadditions.

## 4.2.2 IMINO DIENOPHILES

The initial report of an imine acting as a heterodienophile was briefly mentioned by Alder almost five decades ago.[2] Since that time an ever increasing number of examples of this type of cycloaddition have appeared. The large preponderance of imino Diels–Alder reactions have utilized electron-deficient imines, although a few cases of inverse electron demand cyclizations exist. Detailed reviews of this subject have previously been published.[1]

### 4.2.2.1 *N*-Sulfonyl Imines

Although some of the earliest reported examples of imino Diels–Alder reactions have involved *N*-sulfonyl imines,[1d,3] these dienophiles have not been widely utilized in synthesis. These cycloadditions appear to be generally efficient and show excellent regiochemical control.[4] For example, imine (**1**) derived from chloral adds to unsymmetrical dienes to give single regioisomeric products as shown in Scheme 1.[4,5] Similarly, glyoxylate-derived imine (**2**) shows good regioselectivity in its cycloadditions (equation 1),[3b] as does cyclic *N*-sulfonyl imine (**3**) (equation 2).[6]

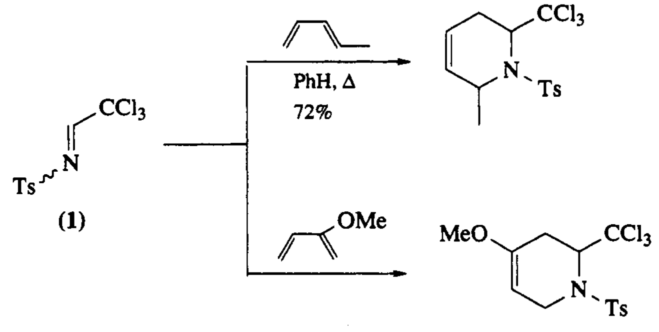

**Scheme 1**

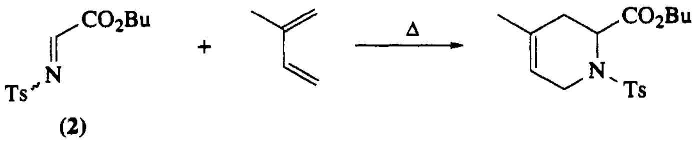

(1)

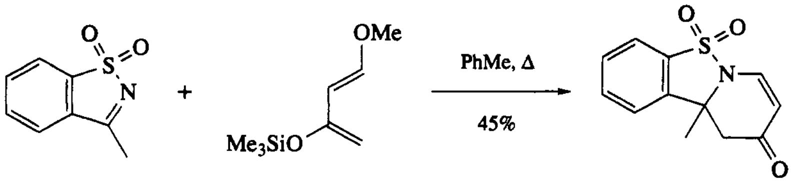

(3)

(2)

It has been suggested that the regioselectivity observed in these cycloadditions is due to a reaction mechanism involving concerted bond forming and breaking in an unsymmetrical, highly polarized transition state.[1,4] Such a postulate seems reasonable, but at present there is little supporting evidence for it.

Krow *et al.* have investigated the stereochemistry of the addition of imines (**1**) and (**2**) to various cyclic dienes.[7] With cyclopentadiene, dienophile (**1**) produces a kinetic 43:57 mixture of *endo* (**4**)/*exo* (**5**) adducts (Scheme 2). Interestingly, fluorinated dienophile (**6**) gives a 78:22 mixture of *endo* (**7**)/*exo* (**8**) as the kinetic cycloaddition products. The observed stereochemical results may be largely due to steric factors, although ambiguities in interpretation arise since one cannot ascertain the reacting geometry (*E* or *Z*) of these dienophiles.

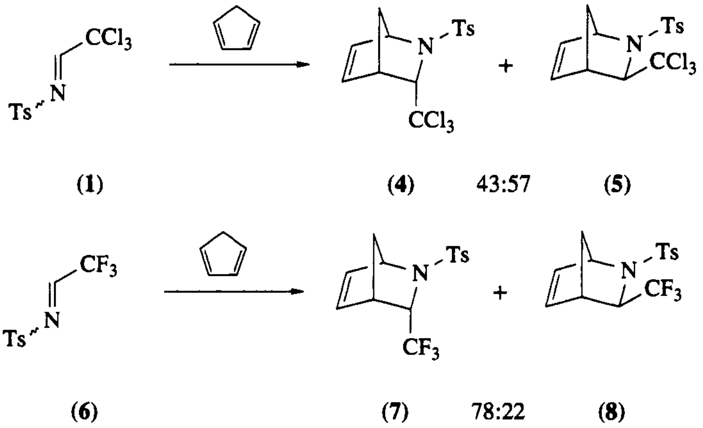

**Scheme 2**

The carboxyl-substituted dienophile (**2**) shows excellent stereoselectivity with cyclopentadiene, affording solely *exo* adduct (**9**) (equation 3).[8] This somewhat surprising result can be rationalized if one assumes that the cycloaddition involves an (*E*)-imine which reacts *via* a transition state having the bulky tosyl group *endo* to avoid steric interactions with the methylene bridge of the diene. Such a transition state, however, precludes secondary orbital interactions of the carbonyl group with the diene.

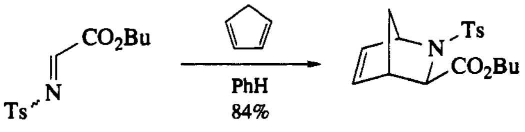

(2) (9)

(3)

Some results described by Holmes and coworkers are consistent with the stereochemical outcome of equation (3).[9] Cycloaddition of imine (**10**) with 2-trimethylsiloxy-1,3-cyclohexadiene afforded a mixture of adducts (**11**) and (**12**) with the *exo* isomer predominating (equation 4). In this example, only a single regioisomer was detected.

Recently, Sisko and Weinreb have developed a new, *in situ* procedure for effecting *N*-sulfonyl imine Diels–Alder reactions.[10] The method consists of treating an aldehyde with an *N*-sulfinyl sulfonamide/boron trifluoride etherate in the presence of a diene (Scheme 3). Under these conditions the *N*-sulfinyl sulfonamide reacts with the aldehyde to produce an *N*-sulfonyl imine. This reaction, developed by Kresze,[3b,11] has been used previously for preparing imines from simple, non-enolizable aldehydes (*cf.* **1**,**2**), but had not been applied to more complex aldehydes. As can be seen from the scheme, the cycloaddition is effective with a variety of aldehyde precursors and 1,3-dienes. The process shows the usual high regioselectivity associated with [4 + 2] cycloadditions of *N*-sulfonyl imines (*vide supra*) but proceeds with only marginal stereoselectivity.

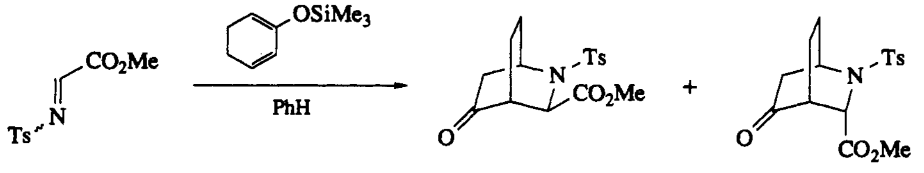

(4)

**(10)** **(11)** 57%:24% **(12)**

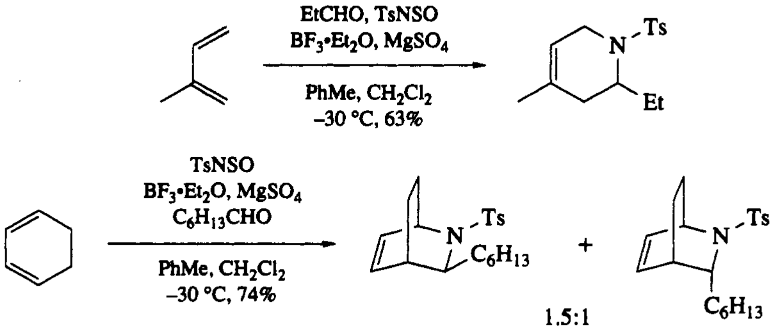

Scheme 3

### 4.2.2.2 *N*-Acyl Imines

Since the initial report in 1962 by Merten and Muller of the cycloaddition of an *N*-acyl imine with a conjugated diene,[12] a number of examples of this type of reaction have appeared.[1] In general, *N*-acyl imines are highly reactive, unstable species which are rarely isolated,[13] but rather are generated *in situ* from stable precursors. Depending upon the method of formation of the particular dienophile and the reaction conditions, a neutral *N*-acyl imine or a protonated (or Lewis acid complexed) *N*-acyl immonium ion may be involved in the Diels–Alder reaction.

#### *4.2.2.2.1 Acyclic dienophiles*

As a rule, cycloadditions with acyclic *N*-acyl imino dienophiles are useful synthetic reactions which demonstrate excellent regio- and stereo-selectivity. A commonly used source of *N*-acyl immonium dienophiles are bis-urethanes[12,14–17] such as (**13**) (equation 5), which upon treatment with a Lewis acid and a diene afford Diels–Alder adducts. In this case, (**13**) reacts with boron trifluoride etherate to afford immonium ion (**14**) which adds to diene (**15**), yielding tetrahydropyridine (**16**).[17]

Krow has in fact studied the involvement of immonium intermediates like (**14**) in these reactions and has made important contributions in understanding the mechanism of the process.[7,18] The available data are consistent with a concerted cycloaddition mechanism, perhaps involving a polarized transition state. With substituted bis-carbamates such as (**17**) (Scheme 4), a protonated (*E*)-*N*-acyl immonium dienophile (**18**) is probably the reactive species. Krow has investigated the cycloaddition of various substituted dienophiles (**18**) with 1,3-cyclohexadiene and the stereochemical results are summarized in Scheme 4.[18] It was found that in most cases there is about a 3–4:1 preference for *exo* (**19**)/*endo* (**20**) cycloadducts. Thus immonium ion (**18**) generally reacts *via* a transition state in which the *N*-acyl group is *endo* to the diene. The exceptions to this rule occur when group R is very bulky and/or α-branched, leading to an increase in isomeric adduct (**20**). In these cases, R in (**18**) prefers an *endo* orientation to avoid severe steric interactions with the ethano bridge of the diene.

A few instances of neutral acyclic *N*-acyl imino dienophiles have been reported.[8b,19,20] Some of these imines can be prepared and isolated, but often they are generated *in situ*. For example, Wittig chemistry has been used to synthesize *N*-acyl imines of glyoxylate and mesoxylate which can be trapped regioselectively by dienes to give Diels–Alder adducts (Scheme 5).[19]

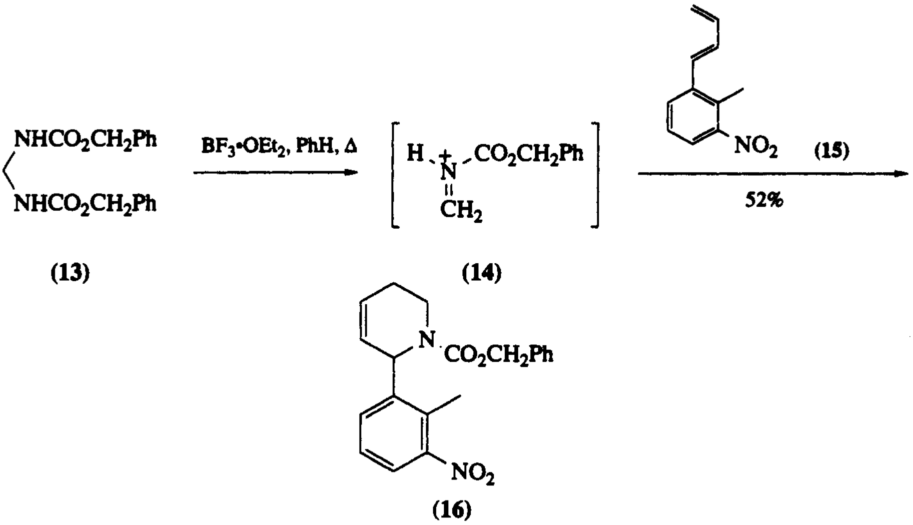
NHCO$_2$CH$_2$Ph
NHCO$_2$CH$_2$Ph
(13)
BF$_3$•OEt$_2$, PhH, Δ
H N CO$_2$CH$_2$Ph CH$_2$
(14)
NO$_2$
(15)
52%
N CO$_2$CH$_2$Ph
NO$_2$
(16)

(5)

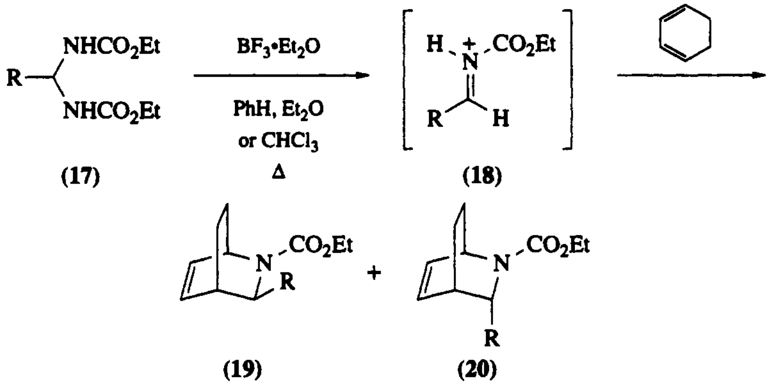
R
NHCO$_2$Et
NHCO$_2$Et
(17)
BF$_3$•Et$_2$O
PhH, Et$_2$O or CHCl$_3$ Δ
H N CO$_2$Et R H
(18)
N CO$_2$Et R
+
N CO$_2$Et R
(19)
(20)

| | | |
|---|---|---|
| R = CO$_2$Et | 70% | 30% |
| CO$_2$Me | 80% | 20% |
| Ph | 80% | 20% |
| COMe | 67% | 33% |
| Me | 82% | 18% |
| Et | 81% | 19% |
| Pr | 81% | 19% |
| Bu$^i$ | 79% | 21% |
| Pr$^i$ | 36% | 64% |
| CCl$_3$ | 38% | 62% |
| cyclohexyl | 54% | 46% |

Scheme 4

Alternatively, an α-chlorocarbamate (21) has been used to produce an imine which cycloadds to cyclopentadiene (equation 6).[20] Interestingly, only the *exo* adduct was formed.

In some related work, trinitrile (22) (equation 7) has been prepared and was found to react with cyclopentadiene to afford (23) in unspecified yield.[21] No other examples of cyanamid-derived imino dienophiles seem to have been reported to date.

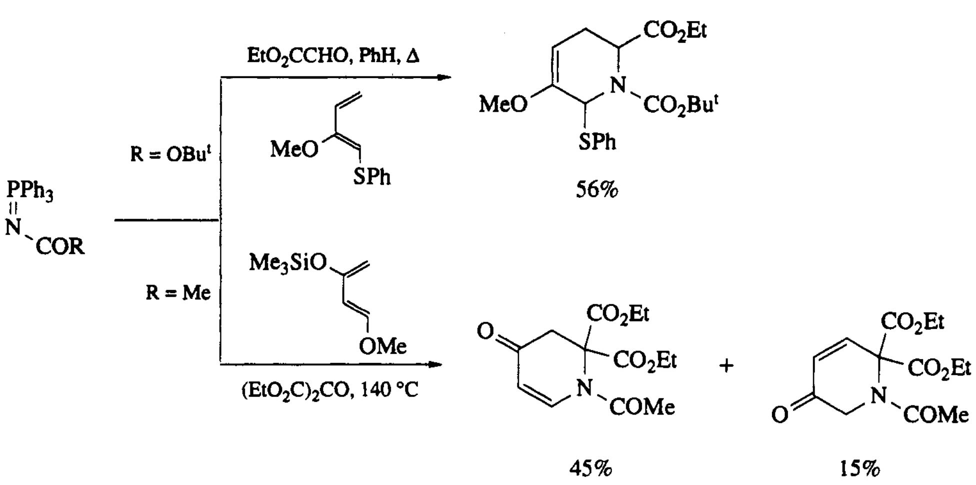
PPh3
N
COR
R = OBu^t
R = Me
EtO2CCHO, PhH, Δ
MeO
SPh
CO2Et
N
CO2Bu^t
56%
Me3SiO
OMe
(EtO2C)2CO, 140 °C
O
CO2Et
CO2Et
N
COMe
+
45%
15%

Scheme 5

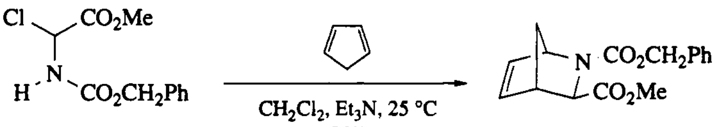
Cl
CO2Me
H
N
CO2CH2Ph
CH2Cl2, Et3N, 25 °C
56%
N CO2CH2Ph
CO2Me

**(21)**

(6)

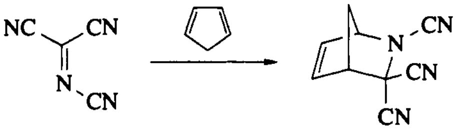
NC
CN
N
CN
N
CN
CN
CN

**(22)** **(23)**

(7)

### *4.2.2.2.2 Cyclic dienophiles*

A number of diverse structural types of cyclic imino dienophiles have been used in cycloadditions. For instance, dehydrohydantoins are useful partners in hetero Diels–Alder reactions. Two methods have been developed for *in situ* generation of these species. In one approach, methoxyhydantoins such as (**24**) (equation 8) are heated or are treated with acid to promote elimination of methanol, affording dienophile (**25**).[22,23] This intermediate can be trapped regio- and stereo-selectively with 1,3-dienes. For example, with 1,3-cyclohexadiene only *endo* adduct (**26**) is formed. There is no ambiguity in this case concerning the dienophile configuration, and thus product (**26**) clearly derives from an *endo* transition state.

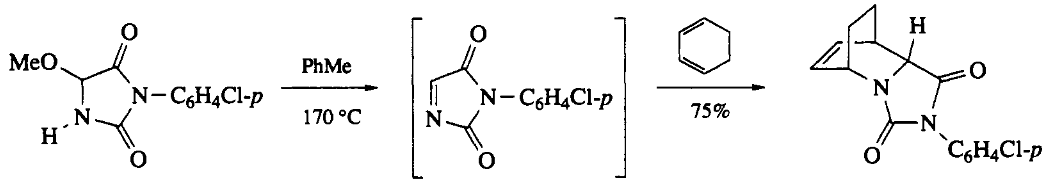
MeO
O
N-C6H4Cl-p
H
N
O
PhMe
170 °C
O
N-C6H4Cl-p
N
O
75%
H
O
N
N
O
C6H4Cl-p

**(24)** **(25)** **(26)**

(8)

Another method for producing dehydrohydantoins involves *N*-chlorination of a compound such as (**27**) followed by dehydrohalogenation to give (**28**) which reacts with 1-methoxybutadiene forming adduct (**29**) (equation 9).[24] As can be seen, this cycloaddition is both regio- and stereo-selective.

The Diels–Alder cycloaddition of a dehydrohydantoin has been utilized as a key step in a total synthesis of the antitumor antibiotic streptonigrin (**33**) (equation 10).[23b] Addition of diene (**30**) to hydantoin (**24**) afforded a 1:3 mixture of the tetrahydropyridines (**31**) and (**32**). The desired regioisomer (**32**) was converted in several steps to the natural product.

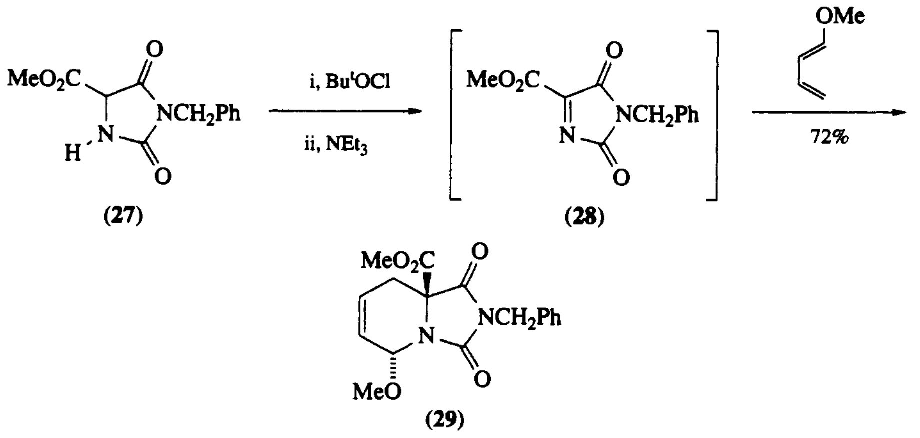

(9)

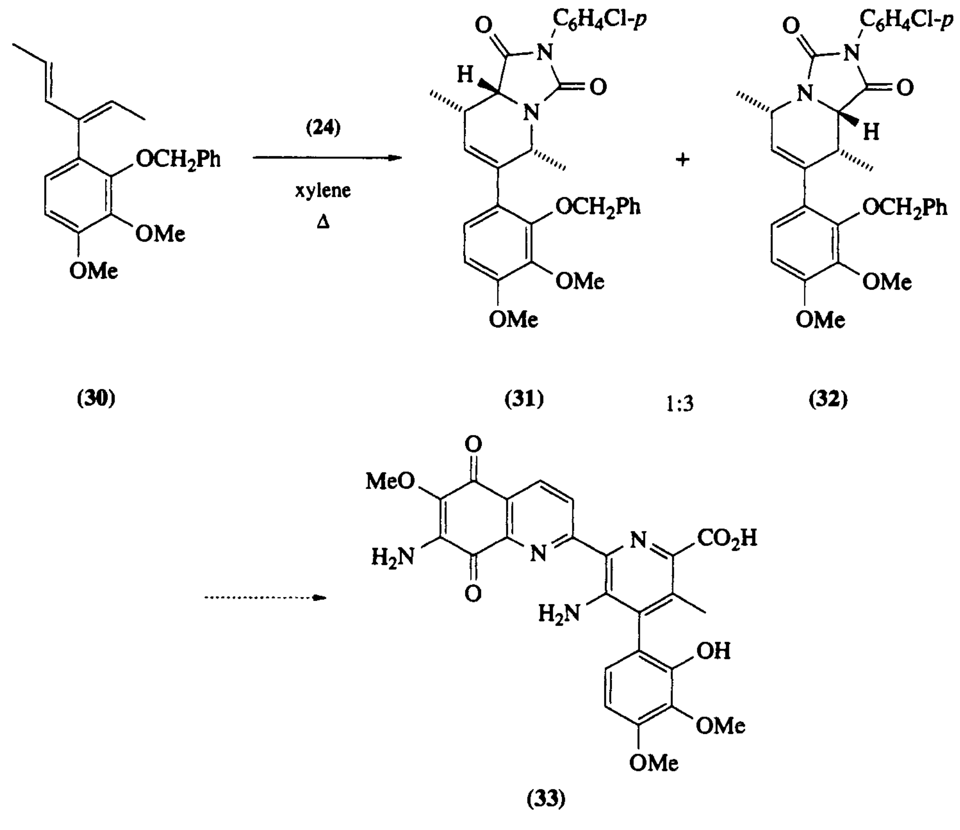

(10)

There are some scattered reports of other cyclic *N*-acyl imines which have been used as dienophiles.[25–27] In particular, the group of Ben-Ishai has described the cycloadditions shown in Scheme 6, along with several other systems.[25] These dienophiles have not been used in synthesis to any significant extent.

Recently, a few examples of imino Diels–Alder reactions using azetinones as dienophiles have been described in work aimed at synthesis of carbapenems.[28] In one sequence of reactions, acetate (**34**) was treated with a Lewis acid in the presence of a siloxy diene to afford adduct (**36**) (equation 11).[28b] This transformation presumably involves imine (**35**) which reacts both regio- and stereo-selectively with the diene. Adduct (**36**) was converted in a few steps to carbapenem (**37**).

Edwards and coworkers have investigated the cycloaddition chemistry of cyclic immonium ion (**39**) produced from ethoxy lactam (**38**) (Scheme 7).[29] It was found that under a variety of acidic reaction conditions (**38**) usually produced complex mixtures of Diels–Alder adducts along with 'one bond' solvolysis products. Some representative examples are shown in Scheme 7. It was concluded that these results are more consistent with a stepwise ionic mechanism than a concerted one.

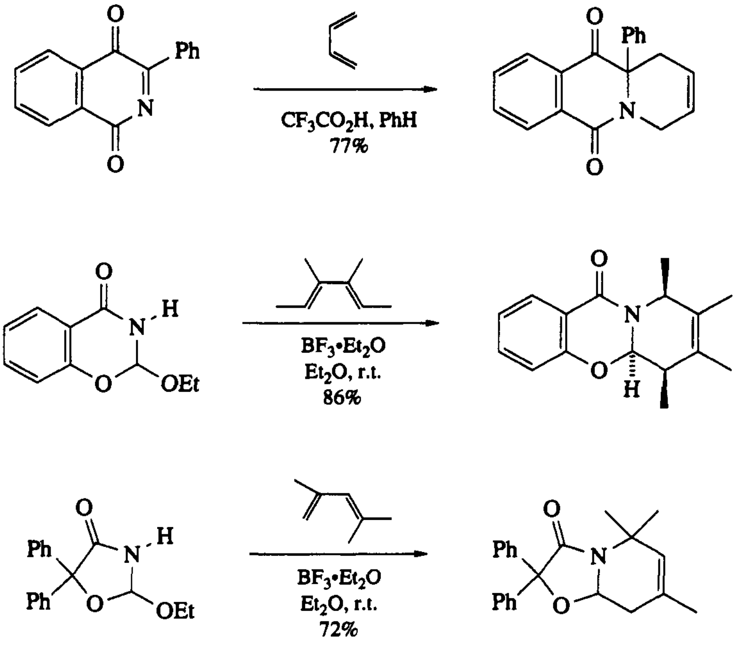

**Scheme 6**

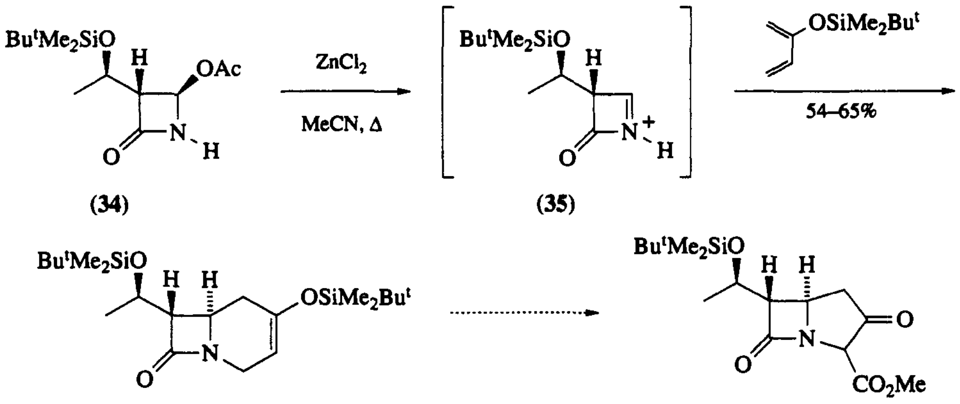

(34) (35) (36) (37) (11)

### 4.2.2.3 *C*-Acyl Imines

Simple *C*-acyl imines have been used rarely in Diels–Alder reactions, and little is presently known about the structural features necessary to make these species useful dienophiles.[30–34]

Indolones such as (**40**) have been exploited on a few occasions as heterodienophiles (equation 12).[30] Cycloaddition of (**40**; R = Ph) with several dienes was regioselective (*cf.* equation 12). The reactions with (*E,Z*)- and (*E,E*)-2,4-hexadiene were *syn* stereoselective with respect to the diene but *exo*/*endo* selectivity was not determined.[30b] With the related dienophile (**40**; R = $CO_2Et$), regioselectivity deteriorated in the cycloadditions.

Acyclic *C*-acyl imines have recently been studied as dienophiles.[32–34] For example, Prato and coworkers examined the reaction of imines (**41**) (equation 13) with several cyclic and acyclic 1,3-dienes.[33] Under neutral conditions, (**41**) is unreactive as a dienophile. However, under Lewis acid catalysis these imines react to afford mixtures of adducts. With 1,3-cyclohexadiene, bicyclic adducts (**42**) and (**43**) are produced along with (**44**) in which the imine has acted as an azadiene.[35] The ratios of these sorts of products are dependent upon the particular imine and diene used. The formation of adducts of type (**43**) proved to be both regio- and stereo-selective. Product formation in these cases can be rationalized both by concerted and by stepwise ionic mechanisms.[33]

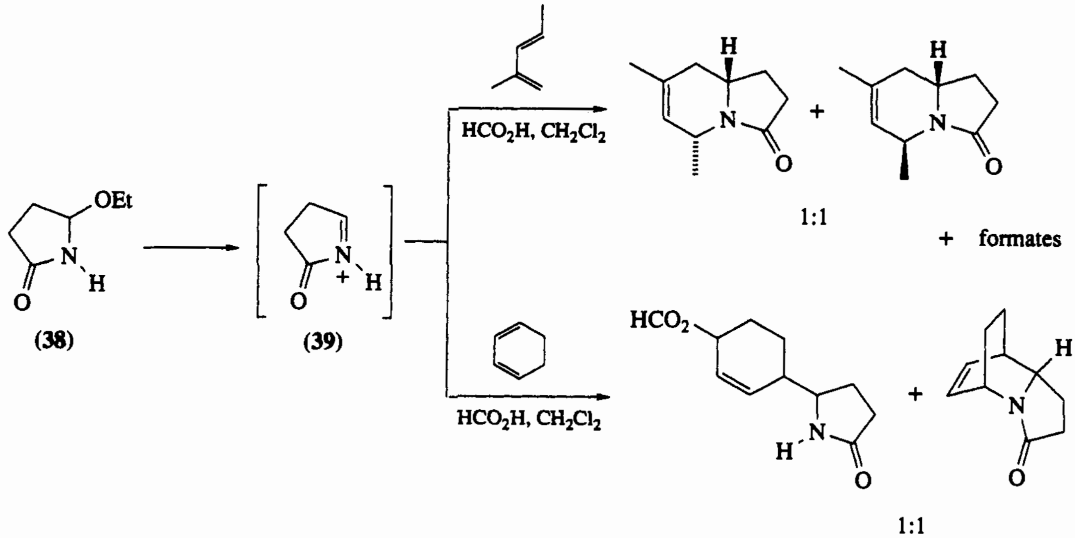
OEt
N
H
O
(38)
N
+
H
O
(39)
HCO₂H, CH₂Cl₂
H
N
O
+
H
N
O
1:1
+ formates
HCO₂H, CH₂Cl₂
HCO₂
N
H
O
+
H
N
O
1:1

**Scheme 7**

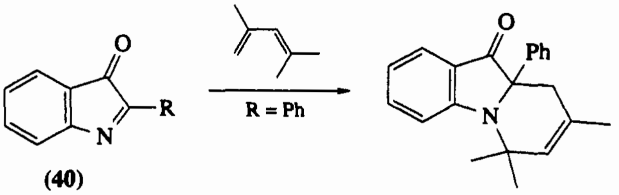
O
N
R
(40)
R = Ph
O
Ph
N

(12)

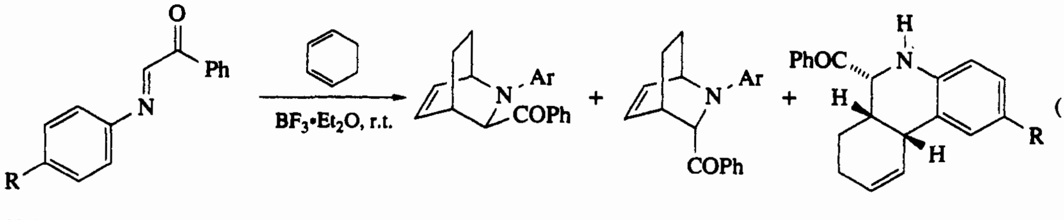
O
Ph
N
R
BF₃•Et₂O, r.t.
N
Ar
COPh
+
N
Ar
COPh
+
H
PhOC
N
H
H
R

(13)

(41) R = NO$_2$, Cl, Me, OMe (42) (43) (44)

In another recent study, Grieco *et al.* have found that *C*-acyl immonium ions formed *in situ* under aqueous conditions undergo [4 + 2] cycloadditions as shown in equation (14).[34] This group has utilized similar methodology for other immonium Diels–Alder reactions (see Sections 4.2.2.4 and 4.2.2.8).

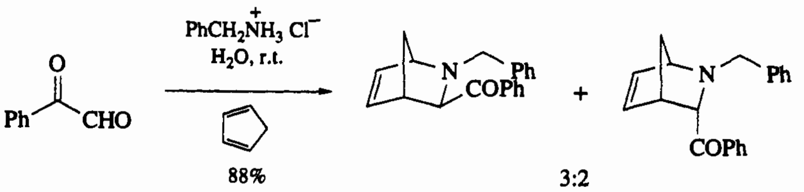
O
Ph
CHO
$PhCH_2\overset{+}{N}H_3$ Cl$^-$
H₂O, r.t.
88%
N
Ph
COPh
+
N
Ph
COPh
3:2

(14)

### 4.2.2.4 Alkyl and Aryl Imines and Immonium Salts

Simple, neutral electron-rich imines are generally not useful dienophiles unless appropriately reactive dienes are used. Thus it is possible to effect cycloadditions of neutral imines with some electron-deficient dienes.[36,37] In a series of papers, Langlois and coworkers[37] have described Diels–Alder reactions of cyclic imines and methyl 2,4-pentadienoate to afford adducts used in alkaloid synthesis. For example, the cycloaddition shown in equation (15) was used in a total synthesis of the indole alkaloid vincamine (**45**).

Neutral imines also add to *o*-quinodimethanes.[38] Kametani's group has reported several cycloadditions of the type shown in equation (16).

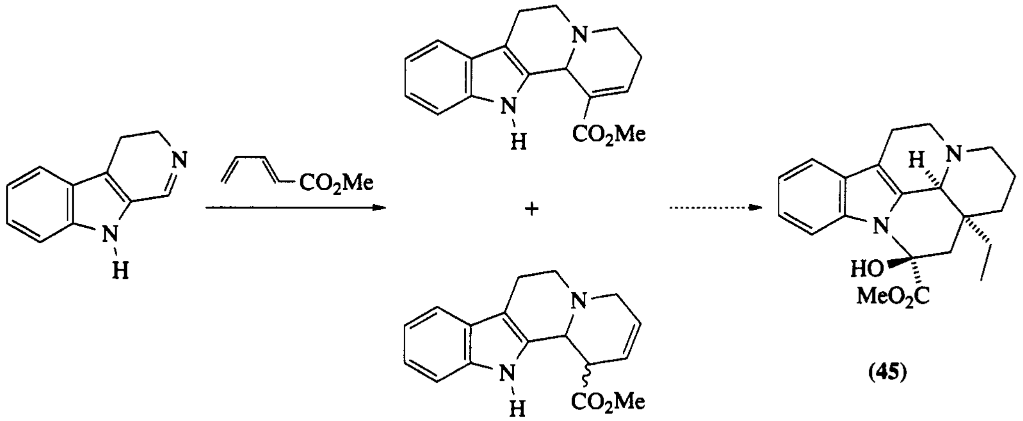

(15)

**(45)**

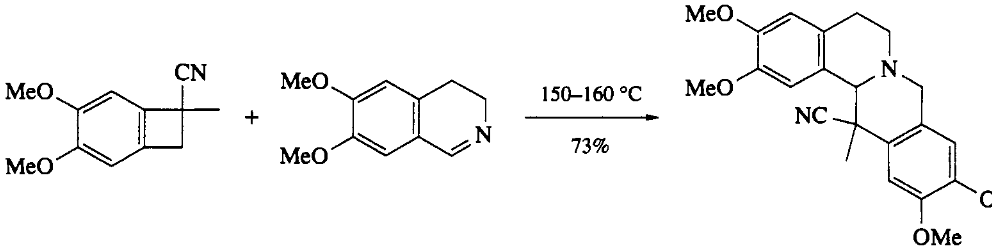

(16)

Another type of reactive electron-deficient diene which combines with neutral imines is disulfone (**46**) (equation 17).[39] Interestingly, this diene rearranges under the reaction conditions to isomer (**47**) which undergoes regioselective [4 + 2] cycloadditions with neutral imines to give initial adducts such as (**48**). However, this product suffers a subsequent 1,3-hydrogen shift to provide isolable adduct (**49**). Independent synthesis and cycloaddition of (**47**) provided good evidence for the overall reaction pathway shown.

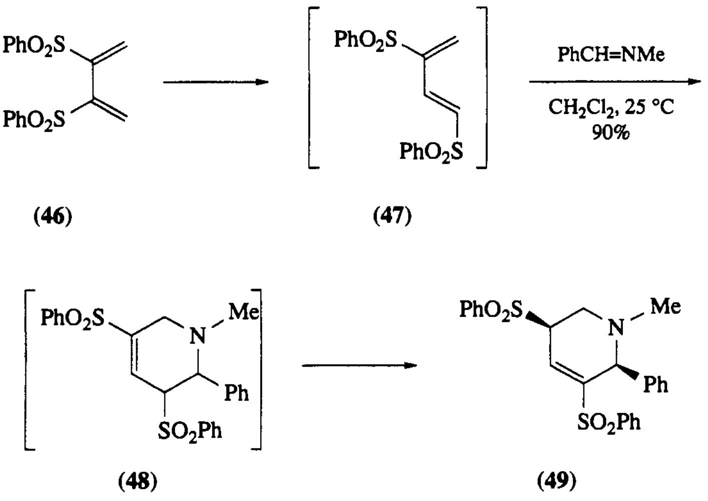

(17)

Immonium salts constitute a class of generally reactive hetero dienophiles.[1,40] During the past several years a number of examples have been described of [4 + 2] cycloadditions of imines with oxygenated dienes under Lewis acid catalysis.[41,42] These reactions probably involve intermediate immonium salts which react regio- and often stereo-selectively with these electron-rich 1,3-dienes. Danishefsky and coworkers have provided several instances of this type of process.[41a,b,f] Equation (18) shows an approach to the indolizidine alkaloid ipalbidine (**52**) which utilized a regioselective [4 + 2] cycloaddition of diene (**50**) with 1-pyrroline to afford lactam (**51**).[41f]

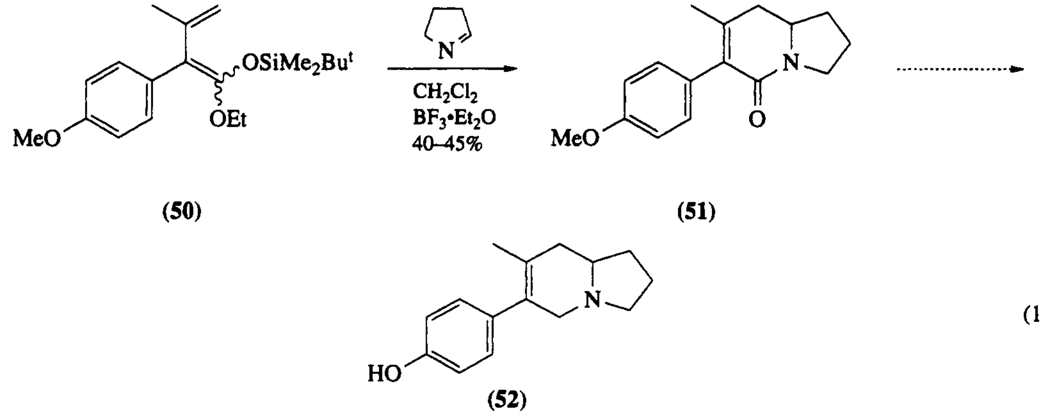

(18)

Another example of this process is delineated in equation (19).[41i] In this case, chiral imine (**53**) was found to react under Lewis acid catalysis with diene (**54**) to provide adduct (**55**) stereoselectively *via* a Cram 'chelation controlled' process. This cycloadduct was transformed in a few steps to amino sugar (**56**).

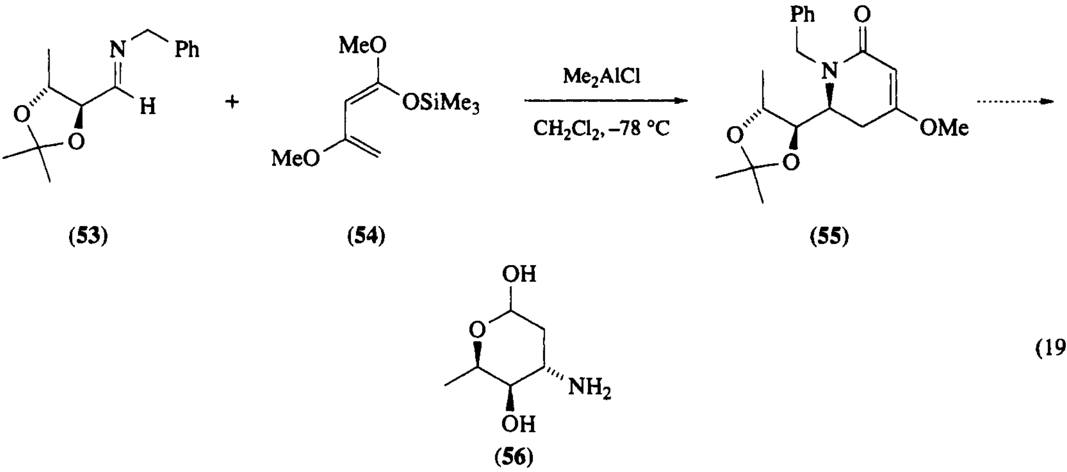

(19)

In related work, Barluenga *et al.* have reported that electron-rich dienamine (**57**) reacts with imine (**58**) in the presence of zinc chloride to afford adduct (**60**) regio- and stereo-selectively (equation 20).[42] It was suggested that the stereochemical outcome is due to involvement of a chelated intermediate (**59**).

An important advance in immonium Diels–Alder methodology has been reported by Grieco and coworkers[34,43] (*cf.* Sections 4.2.2.3 and 4.2.2.8). The procedure consists of treating a 1,3-diene with an amine hydrochloride and an aldehyde under aqueous conditions to produce a Diels–Alder adduct, presumably *via* an *in situ* produced immonium salt. Conversion of (*E*,*E*)-hexadiene to adduct (**61**) (Scheme 8) exemplifies the method. Waldman[43c] has recently applied the Grieco approach to various α-amino acid methyl ester derivatives. It was found that condensation of the immonium intermediates with various cyclic and acyclic 1,3-dienes gave mixtures of diastereomers (*cf.* **62** and **63**) ranging from 93:7 to 63:37 depending upon the particular substrates utilized.

### 4.2.2.5 Cycloadditions with Heterocyclic Azadienes

A limited number of examples of this class of reactions exist. One heteroaromatic compound which has been used as an azadiene in inverse electron demand reactions with electron-rich imines is tetrazine

(**64**).[44,45] Scheme 9 outlines two cycloadditions of this substance. As can be seen, the intermediate adduct cannot be isolated but, rather, triazines are produced.

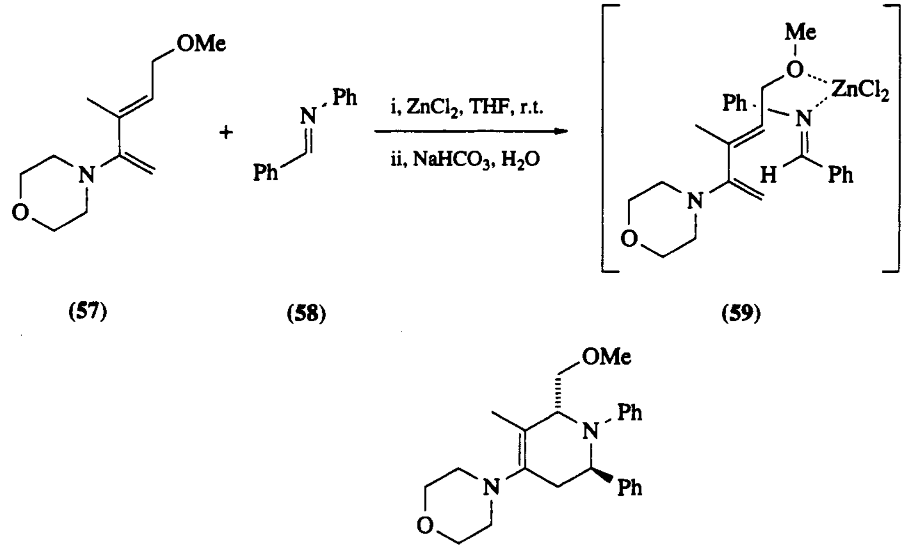

(**57**) (**58**) (**59**)

(**60**)

(20)

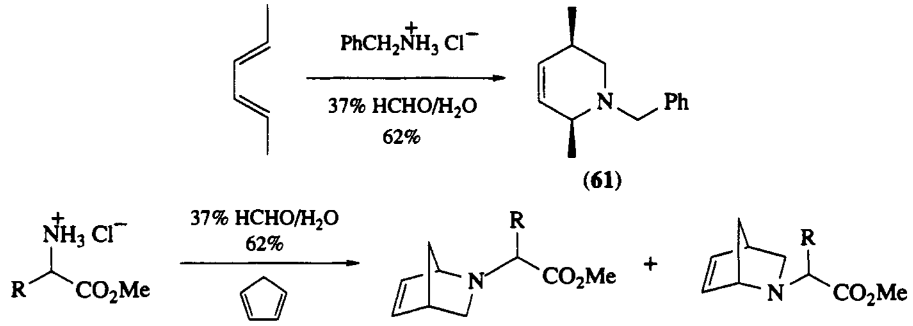

(**61**)

(**62**) (**63**)

**Scheme 8**

### 4.2.2.6 Oximino Dienophiles

Oximes bearing electron-withdrawing substituents on both carbon and oxygen have been used upon occasion as imino dienophiles. Fleury and coworkers, in an extensive study, investigated cycloadditions of oxime derivatives (**65**) with cyclopentadiene to afford adducts (**66**) (equation 21). It was found that groups X and Y on the dienophile impart reactivity in the order CN >> $CO_2R$ > $CONH_2$. The oxygen substituent R has a reactivity sequence Ts > Ms > COAr. Carbonyl substituents as X or Y have a preference over cyano for being *endo* in the cycloaddition but a complication is that *exo*/*endo* equilibration often occurs in the products. The cycloaddition is not totally general, and is only successful with relatively reactive 1,3-dienes. Butadiene and 1,4-diphenylbutadiene, for instance, do not react with (**65**). The process does show good regioselectivity with unsymmetrical dienes (*vide infra*) in the few cases reported.

The cycloaddition does provide a useful route to certain pyridine derivatives.[46,47] For example, oxygenated dienes (**67**) add to oximino dienophile (**68**) to afford adducts (**69**)[47b] in a totally regioselective manner (equation 22). Treatment of this adduct with base provides the pyridine amide (**70**).

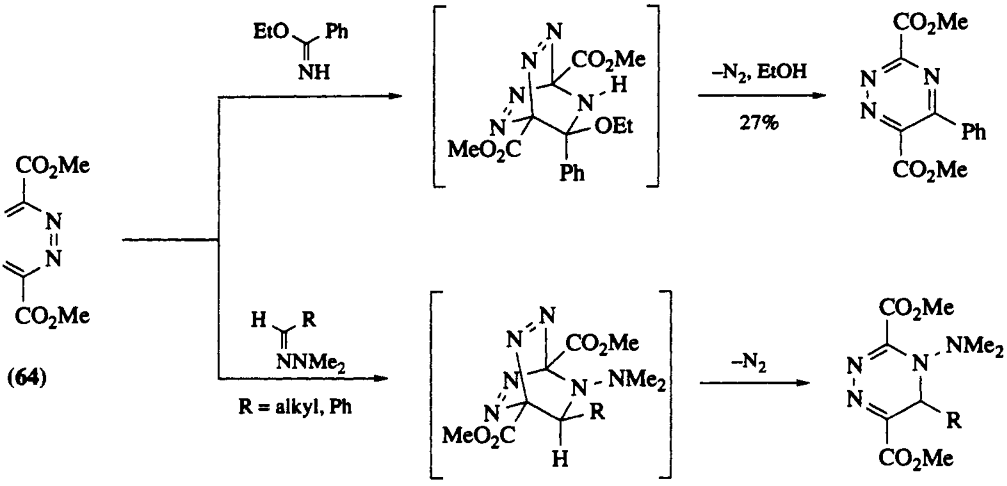

Scheme 9

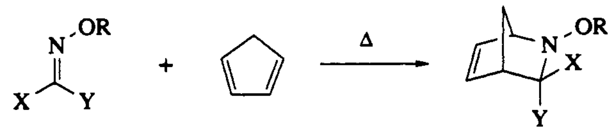

(65)
X, Y = CN, CO$_2$Et, CONH$_2$
R = Ts, Ms, COAr

(66)

(21)

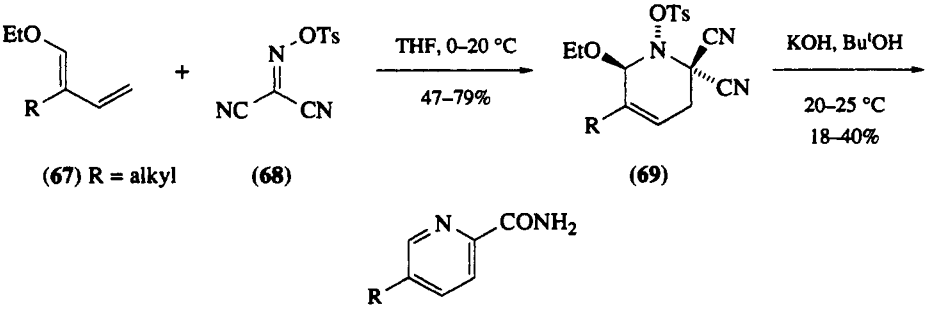

(67) R = alkyl (68) (69)

(70)

(22)

### 4.2.2.7 Azirines

Several reports of the participation of azirines as hetero dienophiles have appeared, and this subject has been reviewed.[1,48] Simple alkyl and aryl azirines react with cyclopentadienones to afford azepines as the ultimate products (equation 23). This type of azirine does not react with cyclopentadiene, but the benzoyl azirine shown in equation (24) does to afford an isolable Diels–Alder adduct.[49] Azirines have also been shown to react stereoselectively in [4 + 2] fashion with tetrazines such as (64) and isobenzofuran.

### 4.2.2.8 Intramolecular Cycloadditions

Over the past ten years, intramolecular imino Diels–Alder reactions have become a useful tool for alkaloid synthesis. This subject has been thoroughly reviewed[1b,c,50] and the discussion below is intended to exemplify various important aspects of the methodology.[51]

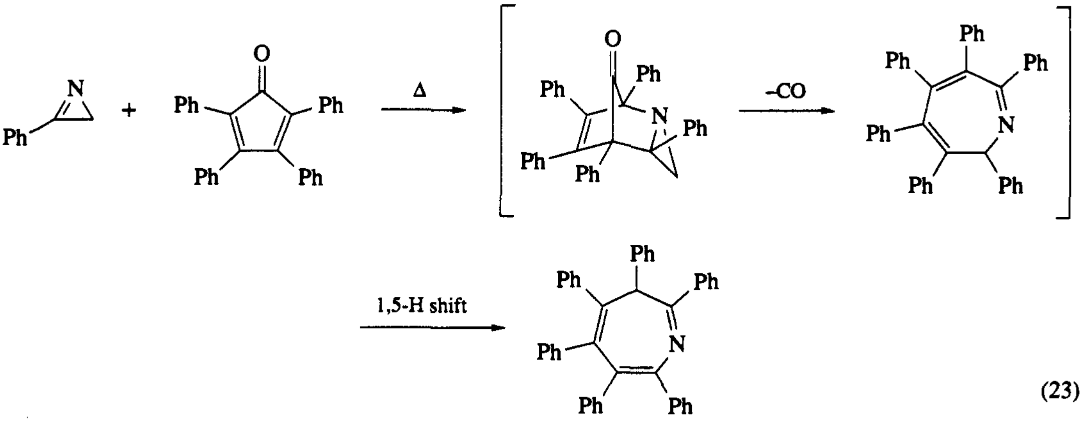
N
Ph
+
O
Ph
Ph
Ph
Ph
Δ
O
Ph
Ph
N
Ph
Ph
Ph
-CO
Ph
Ph
Ph
N
Ph
Ph
Ph
1,5-H shift
Ph
Ph
Ph
N
Ph
Ph
Ph

(23)

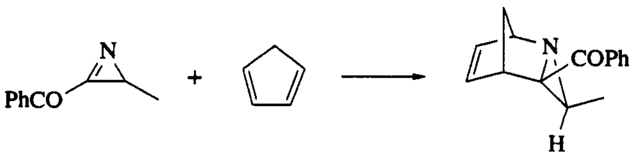
N
PhCO
+
N
COPh
H

(24)

The Weinreb group has used an intramolecular imino Diels–Alder cycloaddition as the key step in a total synthesis of the fungal neurotoxin slaframine (**74**) (equation 25).[52] Thus, thermolysis of acetate (**71**) produced an intermediate *N*-acyl imine (**72**) which underwent [4 + 2] cycloaddition to afford bicyclic lactam (**73**) as a 1.8:1 mixture of epimers. Both compounds were converted to the natural product in a few steps.

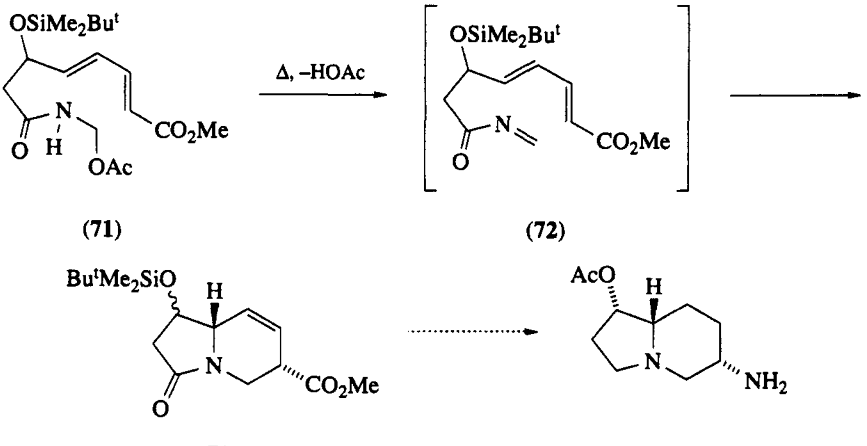
OSiMe2Bu^t
N
O H
OAc
CO2Me
Δ, -HOAc
OSiMe2Bu^t
N
O
CO2Me
Bu^tMe2SiO
H
N
O
CO2Me
AcO
H
N
NH2

(**71**) (**72**) (**73**) (**74**)

(25)

A clever approach to lysergic acid (**78**) has been described by Oppolzer and coworkers (equation 26).[53] Their approach involved an initial retro Diels–Alder reaction of (**75**) to give diene (**76**). This compound then underwent intramolecular cycloaddition with the oxime ether to afford adduct (**77**) as a 3:2 mixture of diastereomers (67% yield). This mixture could be converted to lysergic acid by a short sequence of reactions.

In a study directed towards total synthesis of the spermidine-derived alkaloid anhydrocannabisativine (**82**), Weinreb and coworkers investigated the intramolecular cyclizations of azafumarates.[54] It was found that, upon heating, acetate (**79**) provided Diels–Alder adduct (**81**) as a single stereoisomer (equation 27). The suggestion was made that (**79**) loses acetic acid to produce azafumarate (**80**), which cyclizes *via* the conformation shown. This conformation is favored over other possibilities since it has the *N*-carbonyl group *endo* to the diene and the connecting chain is chair-like with the large alkyl group quasi-equatorial.[54]

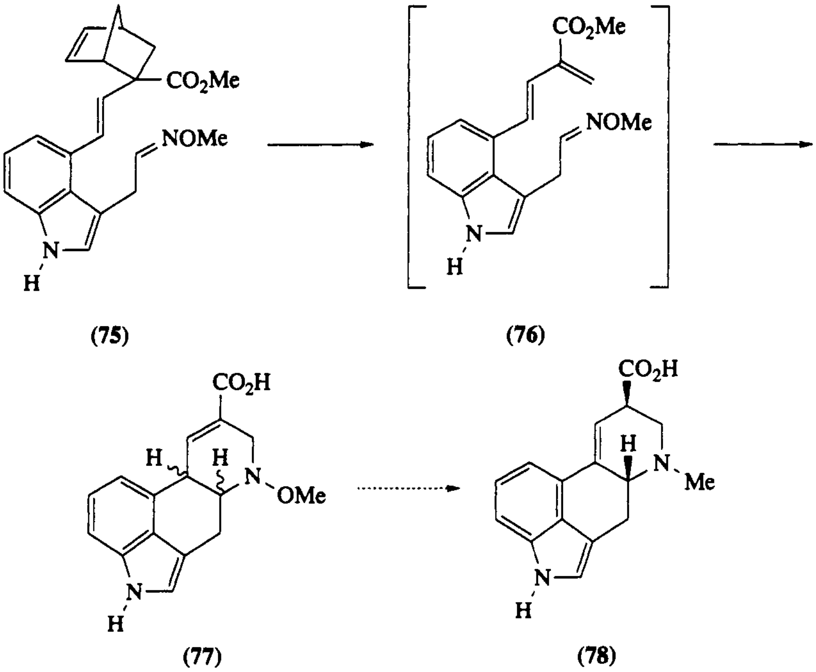
CO2Me
NOMe
N
H
(75)
CO2Me
NOMe
N
H
(76)
CO2H
H
H
N
OMe
N
H
(77)
CO2H
H
N
Me
N
H
(78)

(26)

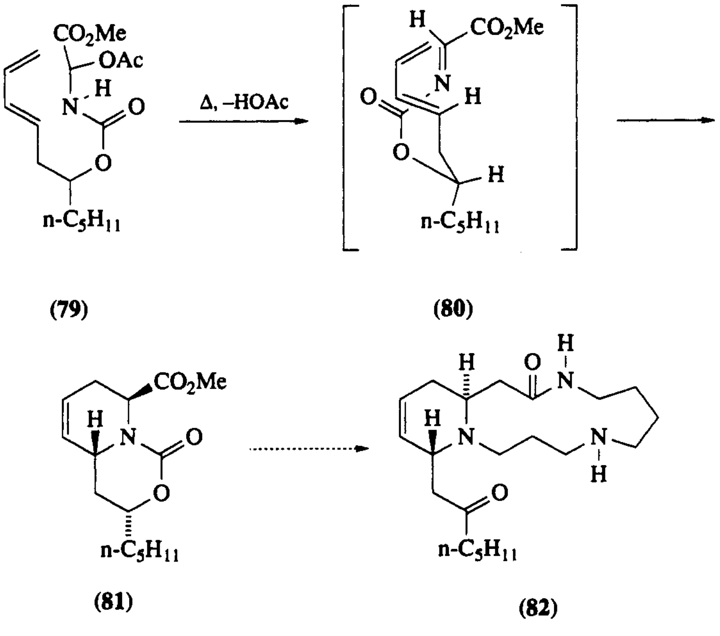
CO2Me
OAc
N
H
O
O
n-C5H11
Δ, -HOAc
(79)
H
CO2Me
O
N
H
O
H
n-C5H11
(80)
CO2Me
H
N
O
O
n-C5H11
(81)
H
O
H
N
H
N
N
H
O
n-C5H11
(82)

(27)

Grieco has used his aqueous immonium Diels–Alder procedure to effect a number of intramolecular reactions.[51b–d] In one case, diene aldehyde (**83**) was treated with ammonium chloride to afford a 2.2:1 mixture of isomeric Diels–Alder adducts (**87**) and (**85**) (Scheme 10). Since intermediate immonium ions (**84**)/(**86**) cannot participate in secondary orbital effects as is the case with *N*-acyl imines (*cf.* **80**),[55] these results are probably due to steric factors. It was suggested that adduct (**85**) derives from conformation (**84**) and adduct (**87**) comes from (**86**). Conformer (**84**) is favored since there is a severe eclipsing of $H_a/H_b$ in (**86**). A more detailed account of the stereochemical aspects of intramolecular Diels–Alder reactions can be found in Chapter 4.4.

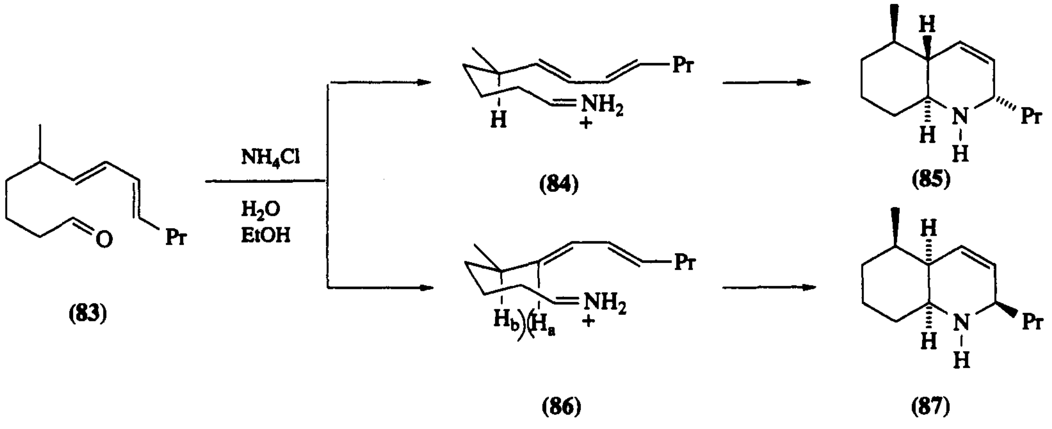
NH4Cl
H2O
EtOH
Pr
O
(83)
H
NH2
+
(84)
Hb
Ha
(86)
H
N
H
H
Pr
(85)
(87)

Scheme 10

### 4.2.3 NITRILES

There is only sparse literature on [4 + 2] cycloadditions of nitriles with 1,3-dienes. In general, simple alkyl and aryl nitriles will only react at high temperatures and under these conditions the product dihydropyridines usually disproportionate.[1d] However, certain types of electron-deficient nitriles appear to be reactive dienophiles under milder conditions. For example, arylsulfonyl cyanides cycloadd to 1,3-dienes to afford adducts as shown in Scheme 11.[56,57] This methodology has not been widely explored and little is known about the regiochemistry of the process.

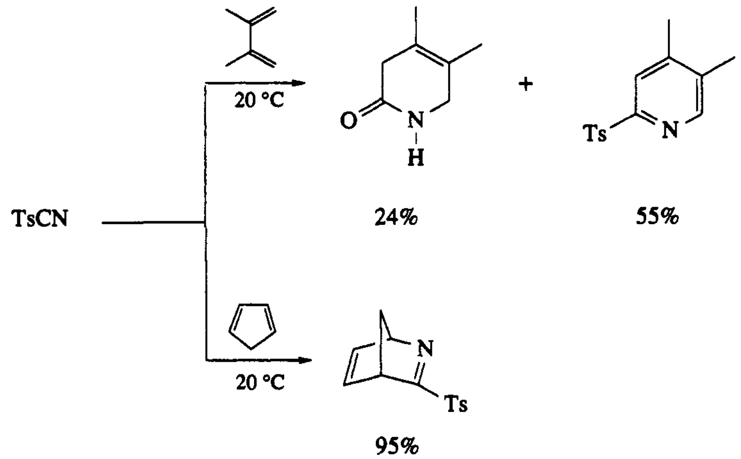
TsCN
20 °C
O
N
H
+
Ts
N
24%
55%
20 °C
N
Ts
95%

Scheme 11

More recently, Potthoff and Breitmaier found that alkoxy dienes (83) react with cyanoformate (84) under mild conditions if a cobalt catalyst is used (equation 28).[58] The products of the reaction are pyridines (85) and/or (86) depending upon the 2-alkyl substituent in the diene. Thus, if R = methyl, only isomer (85) is formed. When R = ethyl, a mixture of pyridines is produced, whereas when R is large only (86) is detected. The origin of these results is not clear.

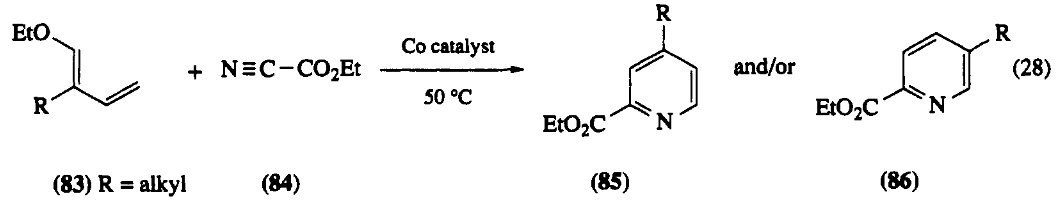
EtO
R
+ N≡C−CO2Et
Co catalyst
50 °C
R
EtO2C
N
and/or
(28)
(83) R = alkyl
(84)
(85)
(86)

Inverse demand Diels–Alder cycloadditions of electron-rich nitriles with electron-deficient heteroaromatic dienes are also known. Typical examples of inter-[59] and intra-molecular[60] instances of this process are shown in equations (29) and (30), respectively.

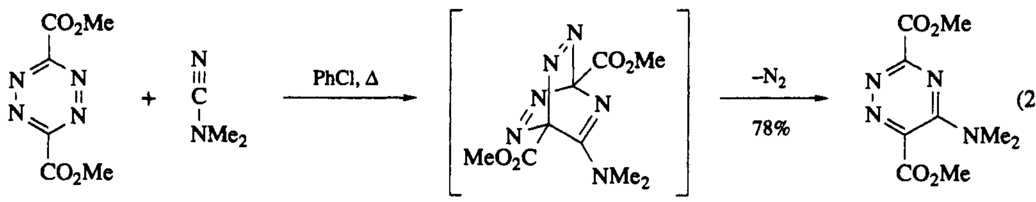

(29)

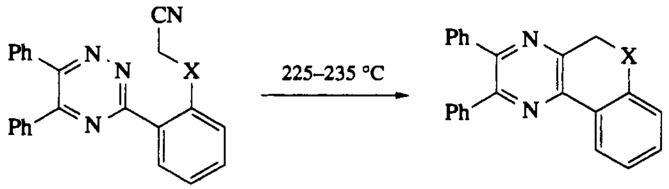

X = O, NCOCF$_3$

(30)

## 4.2.4 NITROSO COMPOUNDS

A wide range of *C*-nitroso compounds have proven to be useful dienophiles in [4 + 2] cycloadditions.[1,61] On the other hand, *N*-nitroso compounds and nitrosyl chloride do not act as dienophiles. In general, this class of cycloadditions proceeds with excellent regioselectivity.

A unified picture of the mechanism of this cycloaddition for various structural types of nitroso dienophiles is not available. Depending upon the electronic and steric nature of the particular nitroso compound, the reaction apparently may vary from a concerted pericyclic process to one involving discrete dipolar intermediates.[61–63] The net result of this mechanistic diversity is a few 'anomalous' regiochemical results in the cycloaddition.

### 4.2.4.1 Aryl Nitroso Compounds

Aryl nitroso compounds, which are readily available synthetic intermediates, react regioselectively with most 1,3-dienes.[1,61,64] Scheme 12 shows two examples of cycloadditions with unsymmetrical dienes, affording single isomeric 3,6-dihydro-1,2-oxazines in each case.[61] Kresze and coworkers have examined the cycloaddition of aromatic nitroso compounds in some detail and have rationalized the orientational results of this process. It appears that, depending upon the specific nitroso compound used, the reaction transition state varies from nonpolar to dipolar.[64]

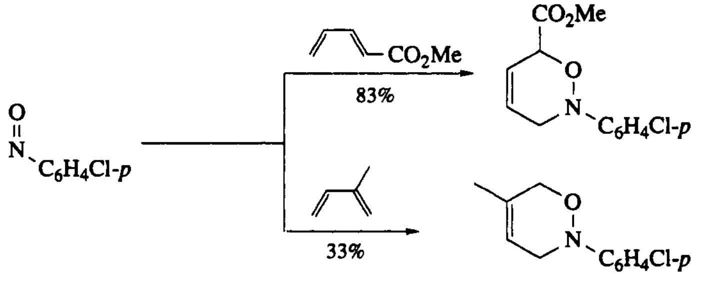

**Scheme 12**

The dihydrooxazines which are produced from aryl nitroso compounds have not found wide use in synthesis.[65] One application to the syntheses of an *N*-aryl-3-pyrrolidone is shown in equation (31).[66] The initial Diels–Alder reaction in this sequence was totally regioselective.

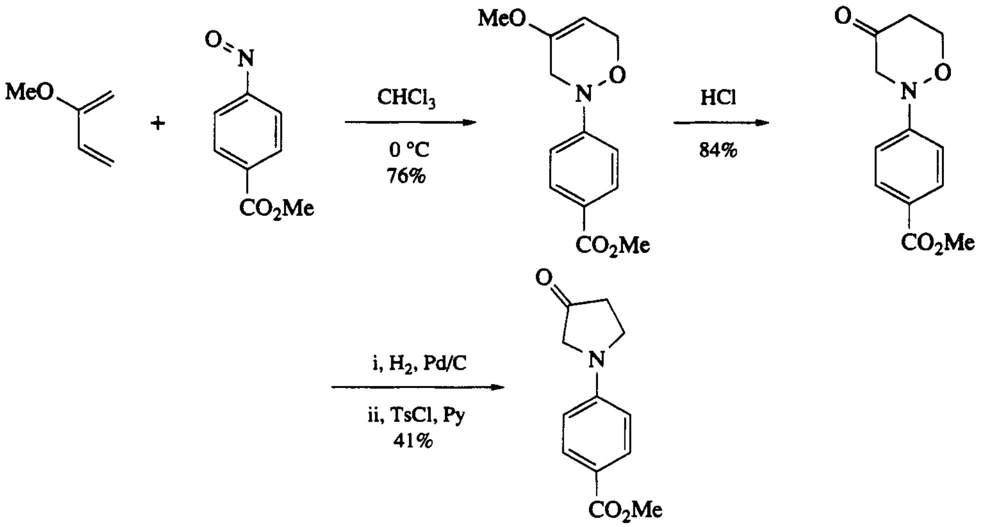
MeO
O
N
CO2Me
CHCl3
0 °C
76%
MeO
O
N
CO2Me
HCl
84%
O
N
O
CO2Me
i, H2, Pd/C
ii, TsCl, Py
41%
O
N
CO2Me

(31)

A number of cases of additions of aryl nitroso compounds to 1,2-dihydropyridine derivatives have been effected.[67] For instance, compound (**87**) reacts with nitrosobenzene regioselectively and *anti* to the C-2 methyl group to afford adduct (**88**) (equation 32).

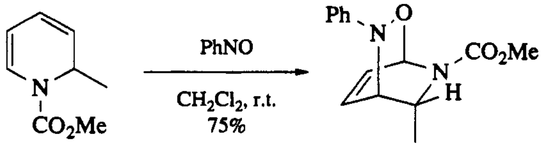
N
CO2Me
PhNO
CH2Cl2, r.t.
75%
Ph
N
O
N
CO2Me
H

(**87**) (**88**)

(32)

### 4.2.4.2 α-Chloro Nitroso Compounds

Readily available α-chloro nitroso compounds have been used on a number of occasions as heterodienophiles since the first report appeared in 1947.[68] The initial adduct of this reaction is unstable and if alcohol solvent is used a dihydrooxazine hydrochloride (**89**) is produced (equation 33). The cycloadditions proceed under very mild conditions with most 1,3-dienes and, as outlined in Scheme 13, the regioselectivity is excellent.[61,69]

Kresze and coworkers have used nitroso Diels–Alder reactions in synthesis of a variety of inosamines and related compounds.[70] One example of this work is the synthesis of conduramine-F1 (**92**) as shown in equation (34). In this case, diene (**91**) reacted with α-chloro nitroso cyclohexane to afford adduct (**91**) as the only product. Just why this stereoisomer was formed is not obvious. Compound (**91**) could be converted to the conduramine in a few steps.

In a series of interesting papers, Kresze has explored chiral nitroso Diels–Alder reactions.[71] Several different chiral α-chloro nitroso substrates have been examined and mannose derivative (**93**) proved to be one of the best auxiliaries. This dienophile is very reactive with both cyclic and acyclic dienes, affor-

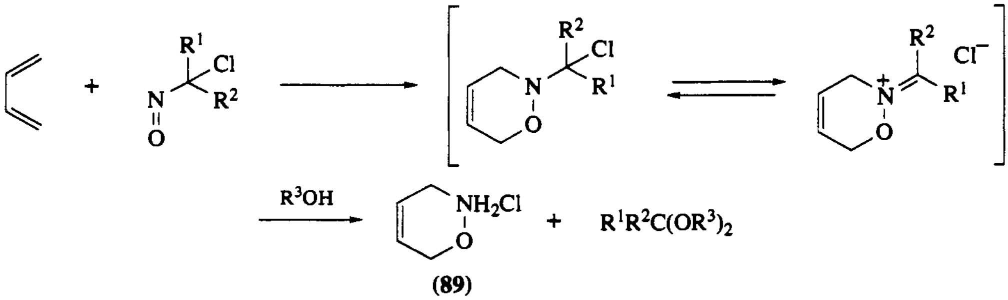
+
R1
Cl
N
R2
O
R2
Cl
N
R1
O
R2
Cl−
N+
R1
O
R3OH
NH2Cl
O
+
R1R2C(OR3)2

(**89**)

(33)

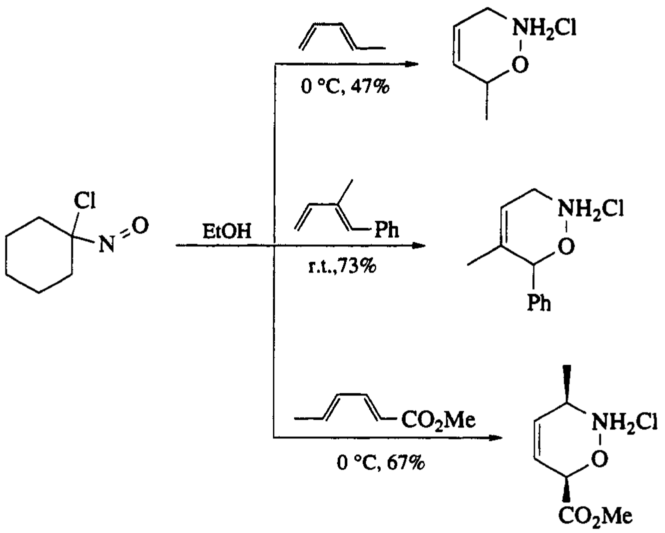
Cl
N
O
EtOH
0 °C, 47%
r.t.,73%
Ph
CO2Me
0 °C, 67%
NH2Cl
O

**Scheme 13**

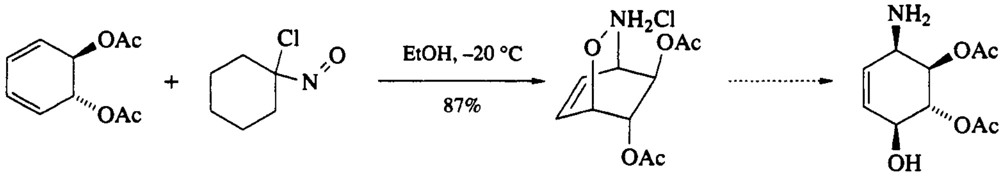
OAc
Cl
N
O
+
EtOH, -20 °C
87%
NH2Cl
NH2
OH

(34)

**(90)** **(91)** **(92)**

ding adducts with high enantiomeric excesses. For example, dienophile (**93**) reacts with 1,3-cyclohexadiene as depicted in equation (35) to afford (**94**) with >96% *ee*.

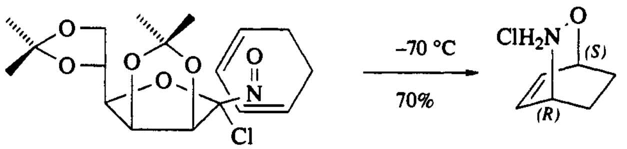
O
N
Cl
-70 °C
70%
ClH2N
(S)
(R)

(35)

**(93)** **(94)**

### 4.2.4.3 Acyl Nitroso Compounds

The use of acyl nitroso compounds as dienophiles was first described by Kirby.[72] The primary method for generating these highly reactive, unstable species is by periodate oxidation of hydroxamic acids.[73] The acyl nitroso compounds can be trapped in a Diels–Alder reaction with 9,10-dimethylanthracene to give adduct (**95**) (equation 36) which can act as an alternative source of the dienophile, since retro [4 + 2] cycloaddition occurs under mild thermal conditions.

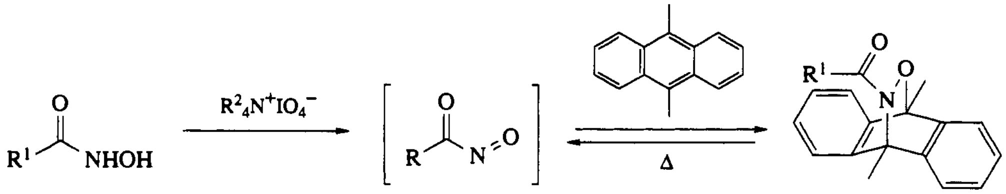
O
R1
NHOH
R24N+IO4−
R
N
O
Δ

(36)

**(95)**

A few examples of cycloadditions of acyl nitroso compounds with unsymmetrical dienes have been described[74] and it generally appears that the process shows good regioselectivity. Boger *et al.* found that dienes (**96a**) and (**96b**) cycloadd to afford regioisomeric adducts (**97a/98a**) and (**97b/98b**), respectively in 3:1 ratios (equation 37).[62] It was suggested that the results with (**96a**) are consistent with a HOMO-diene/LUMO-dienophile cycloaddition, whereas in the case of (**96b**) this same situation or an inverse electron demand (LUMO-diene/HOMO-dienophile) process may apply.

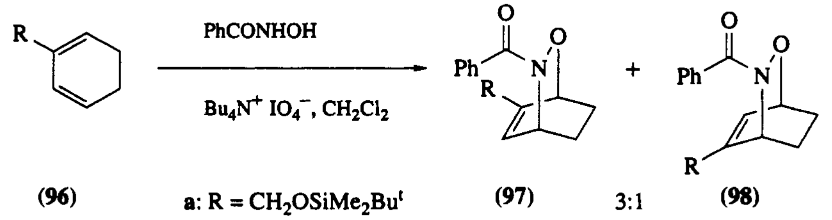

(37)

**(96)** a: R = $CH_2OSiMe_2Bu^t$ **(97)** 3:1 **(98)**

b: R = $CO_2Me$

Studies on the addition of acyl nitroso compounds to 1,2-dihydropyridine derivatives have been described,[75] and some of the results are shown in equation (38). It was found that the nitroso dienophiles produced from hydroxamic acids (**100**) reacted with dihydropyridine (**99**) at different rates and afforded the ratios of regioisomeric products indicated. Both the relative reaction rates and orientation are in accord with a HOMO-diene/LUMO-dienophile controlled process.

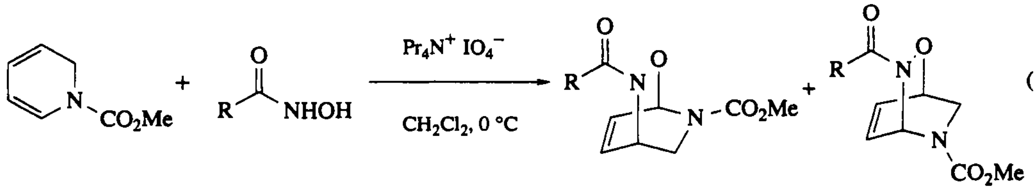

(38)

| R = | |
|---|---|
| PhCO | 0:100 |
| $PhCH_2CO$ | 0:100 |
| MeOCO | 50:50 |
| $PhCH_2OCO$ | 50:50 |
| $Me_2NCO$ | 75:25 |

Brief reports of cycloadditions with chiral acyl nitroso dienophiles have recently appeared.[75,76] In one study, acyl nitroso compound (**101**) derived from the corresponding hydroxamic acid was added to cyclohexadiene to afford a 3.5:1 mixture of diastereomeric adducts (**102**) and (**103**).[76] It was proposed that dienophile (**101**) reacts in the cyclic chelated form shown, since the related methyl ether which cannot internally hydrogen bond shows much lower diastereoselectivity.[75,76]

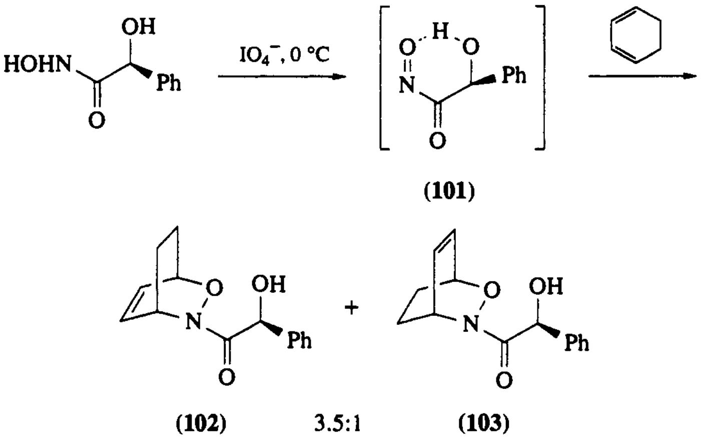

(39)

Intramolecular acyl nitroso Diels–Alder reactions have been utilized as key steps in some elegant alkaloid total syntheses. Keck has prepared compound (**104**) (equation 40) which upon thermolysis gave an intermediate acyl nitroso species leading to adduct (**105**) as a mixture of epimers.[77] This mixture was converted to the pyrrolizidine alkaloids heliotridine (**106**) and retronecine (**107**). Kibayashi and coworkers have used the intramolecular cycloaddition shown in equation (41) to synthesize the neurotoxic alkaloid gephyrotoxin 223AB (**108**).[78]

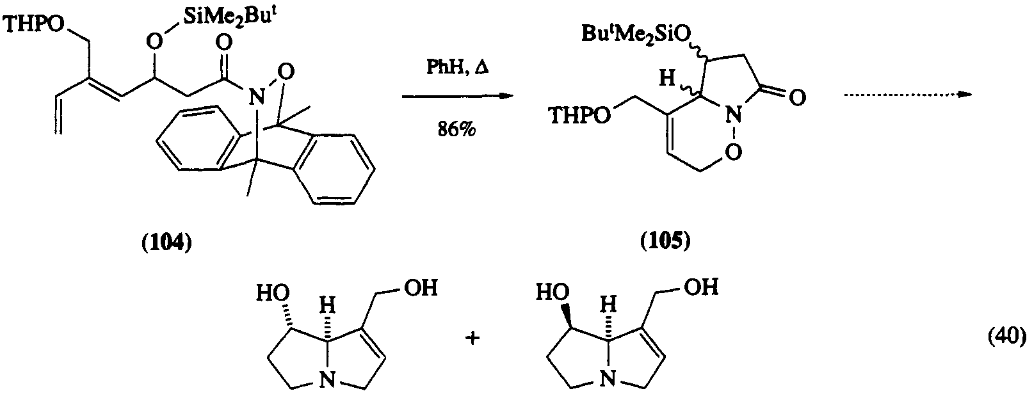
THPO
SiMe₂Buᵗ
PhH, Δ
86%
BuᵗMe₂SiO
H
THPO
N
O
HO
H
OH
+

**(104)** **(105)** **(106)** **(107)** (40)

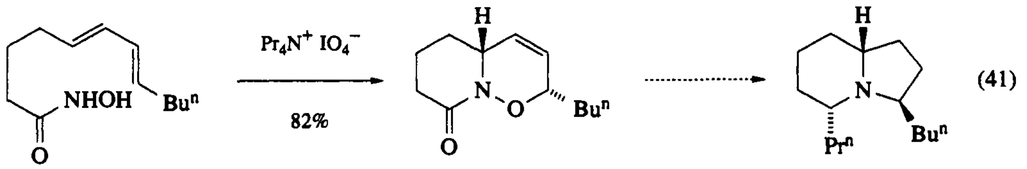
NHOH
Buⁿ
Pr₄N⁺ IO₄⁻
82%
H
N
O
Buⁿ
Prⁿ

**(108)** (41)

### 4.2.4.4 Cyano and Sulfonyl Nitroso Compounds

Nitrosyl cyanide (**109**) has been briefly examined as a dienophile by Kirby *et al.*[79] This intermediate can be generated from nitrosyl chloride and silver cyanide (equation 42) and trapped with 9,10-dimethylanthracene to yield adduct (**110**). As with acyl nitroso compounds, this adduct can be used as a stable source of (**109**) *via* a retro Diels–Alder reaction.

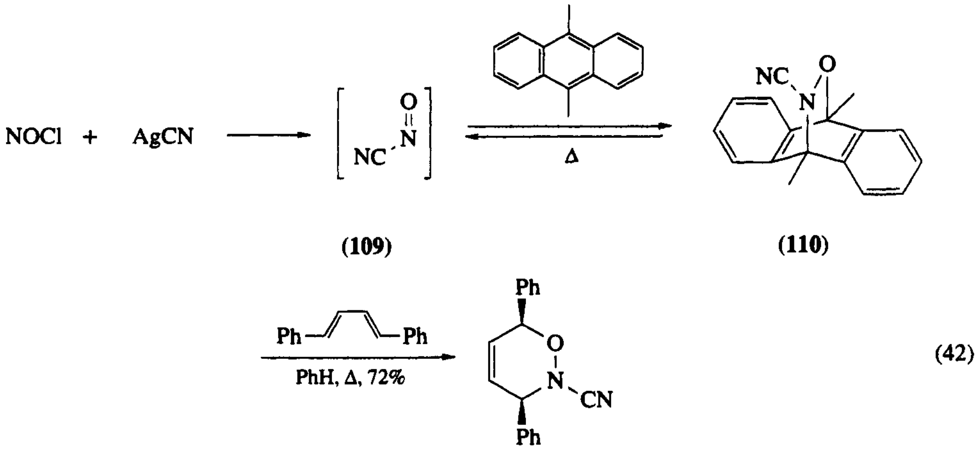
NOCl + AgCN
NC
N
O
Δ
Ph
PhH, Δ, 72%
CN

**(109)** **(110)** (42)

Sulfonyl nitroso compounds have been used only rarely as dienophiles.[80] One source of these species is from arylsulfinic acids and alkyl nitrites (equation 43). These compounds probably warrant further investigation.

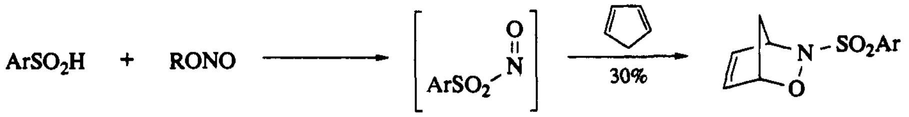
ArSO₂H + RONO
ArSO₂
N
O
30%
N - SO₂Ar

(43)

### 4.2.4.5 Vinyl Nitroso Compounds

Vinyl nitroso compounds have proven to be rather interesting species since they can act as either 2π or 4π components in Diels–Alder cycloadditions.[81] The particular reaction which occurs is dependent upon the structure of the vinyl nitroso compound and the diene which are used. For example, vinyl nitroso compound (**112**), prepared from oxime (**111**), reacts as a dienophile (equation 44). On the other hand, nitroso compound (**113**) (equation 45) reacts with cyclopentadiene to give oxazine (**114**). Not enough data are presently available to interpret these results satisfactorily.

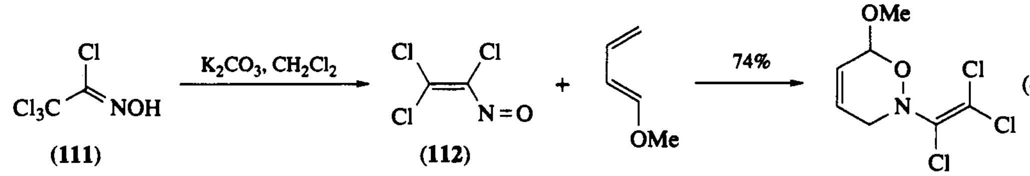

(**111**) (**112**) (44)

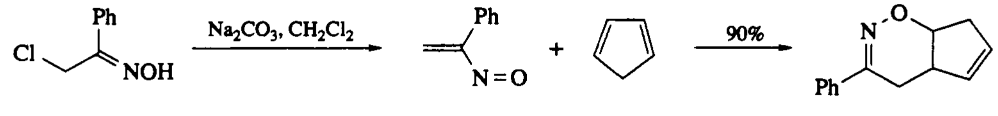

(**113**) (**114**) (45)

## 4.2.5 THIONITROSO COMPOUNDS

Thionitroso compounds are reactive, unstable species which have been used upon occasion as dienophiles.[1,82] The scant activity in this area is probably due to a lack of general methods for preparing these compounds. Recent examples of some cycloadditions of thionitroso dienophiles are shown in equations (46),[83] (47)[84] and (48).[85]

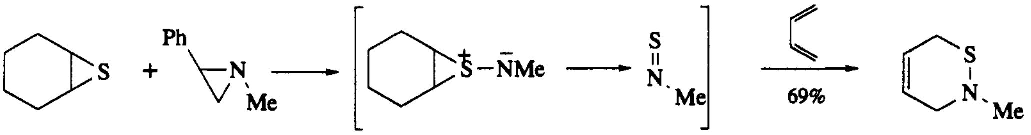

(46)

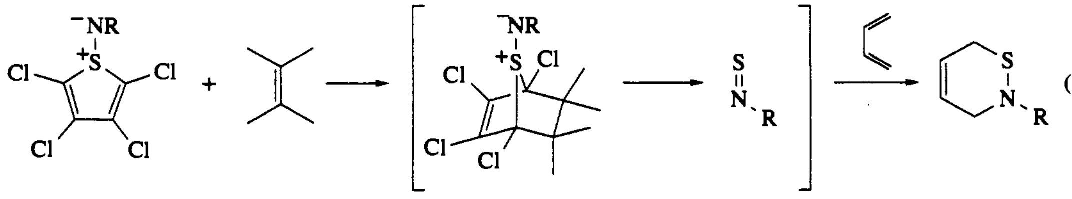

(47)

R = $CO_2Ph$, Ts

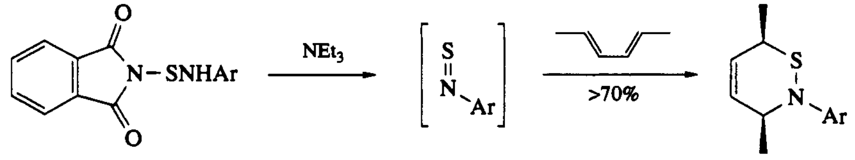

(48)

Ar = $p$-$MeOC_6H_4$, $p$-$MeC_6H_4$, $p$-$BrC_6H_4$, $p$-$ClC_6H_4$

## 4.2.6 *N*-SULFINYL DIENOPHILES

Two general classes of *N*-sulfinyl compounds have been employed as dienophiles. The most widely utilized type are *N*-sulfinyl species (**115**), formally monoimines of sulfur dioxide, which produce 3,6-dihydrothiazine 1-oxides (**116**) (Scheme 14) upon cycloaddition.[1,86–88] The analogous bis-imines of sulfur dioxide (**117**) have also been used upon occasion as dienophiles to yield the 3,6-dihydrothiazine 1-imines (**118**). Both processes show excellent regioselectivity and are *syn* stereoselective with respect to the diene. In both cycloaddition products (**116**) and (**118**) sulfur is chiral, but the factors controlling stereochemistry at this center are not understood (*vide infra*).

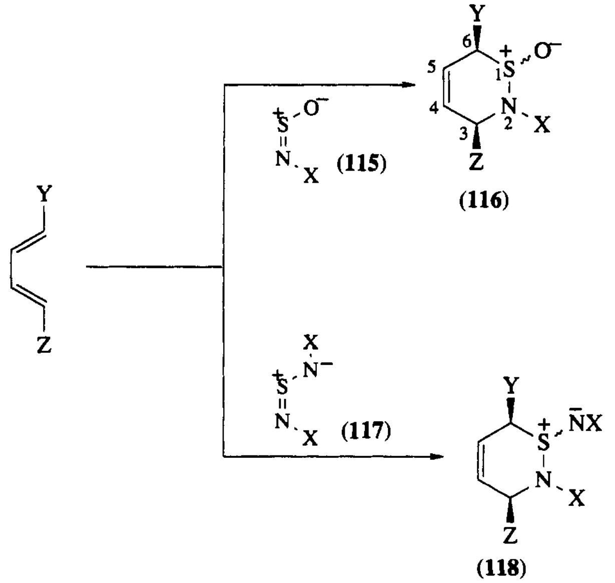

X = Ar, COR, $CO_2R$, $SO_2R$, $\overset{+}{S}Me_2$, CN, $(RO)_2PO$, $NMe_2$

**Scheme 14**

### 4.2.6.1 Monoimines

*N*-Sulfinyl compounds (**115**) are very reactive as dienophiles provided they bear an electron-withdrawing substituent. Several of the structural types of *N*-sulfinyl dienophiles which have been used are indicated in Scheme 14. In general, these cycloadditions proceed at room temperature or below, and are highly regioselective as shown in equations (49),[88] (50)[89] and (51).[90] *N*-Sulfinyl compounds which are substituted with an electron-donating group do not react under these conditions. However, a recent study by Bell and Weinreb has shown that *N*-alkyl sulfinyl compounds undergo [4 + 2] cycloaddition provided a Lewis acid catalyst or high pressure is utilized.[91] Some results of this work are compiled in Scheme 15. As can be seen, with (*E,E*)-2,4-hexadiene the reactions are *syn* selective with regard to the 4π component, but sulfur stereochemistry varies depending upon conditions. The best yields were obtained at 12 kbar pressure in most of the systems investigated.

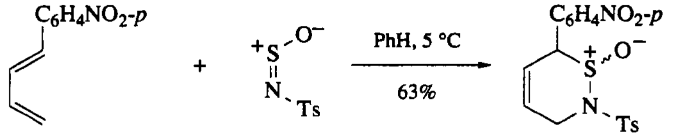

(49)

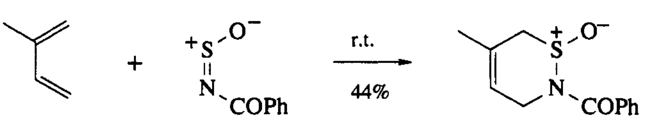

(50)

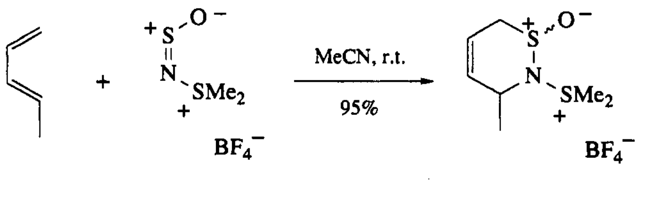

(51)

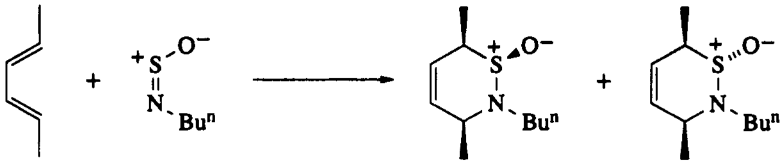

| *Conditions* | *Isomer ratio* | *Isolated yield* |
|---|---|---|
| $TiCl_4$, $CH_2Cl_2$, –78 °C (1.0 equiv.) | 100:0 | 27% |
| $SnCl_4$, $CH_2Cl_2$, –78 °C (0.5 equiv.) | 40:60 | 47% |
| $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, –78 °C (1.0 equiv.) | 100:0 | 54% |
| 12 kbar, $Et_2O$, r.t. | 11:89 | 56% |
| 12 kbar, hexane, r.t. | 12:88 | 66% |
| 12 kbar, $CH_2Cl_2$, r.t. | 18:82 | 80% |

**Scheme 15**

The high pressure reaction also works well with *N*-silyl dienophile (**119**).[92] This process allows easy access to 3,6-dihydrothiazine 1-oxides which are unsubstituted on nitrogen.

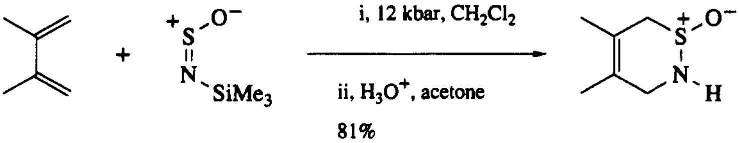

**(119)**

Two studies on the mechanism of this type of [4 + 2] cycloaddition which have led to very different interpretations have appeared.[93,94] Mock and Nugent suggested that the Diels–Alder reactions of *N*-sulfinyl-*p*-toluenesulfonamide are stepwise, ionic processes.[93] On the other hand, Hanson and Stockburn prefer a concerted, pericyclic mechanism in accord with frontier molecular orbital theory.[94] Both proposals satisfactorily rationalize the observed regioselectivity of these reactions.

As noted above, the stereochemical outcome at sulfur in these cycloadditions is not yet understood. Relatively few systems, particularly among the older examples, have been well characterized with respect to sulfur stereochemistry and thus existing data are sparse. Moreover, although *N*-sulfinyl compounds prefer to exist as the (*Z*)-isomers, it is not clear if they always undergo cycloaddition in this geometrical form. It is also known that the Diels–Alder reactions of *N*-sulfinyl compounds are sometimes reversible, which complicates the issue.[95]

Two groups have recently examined enantioselective *N*-sulfinyl dienophile Diels–Alder reactions.[96,97] In one case, Whitesell *et al.* found that a phenylmenthol derived *N*-sulfinyl carbamate adds to (*E*,*E*)-2,4-hexadiene under Lewis acid catalysis to afford a single diastereomer (equation 52).[96] If the Lewis acid was omitted, a complex mixture of cycloaddition products was obtained. Attack of the diene on the *N*-sulfinyl dienophile as shown in the equation would rationalize the observed results. The site of Lewis acid complexation, however, is unknown.

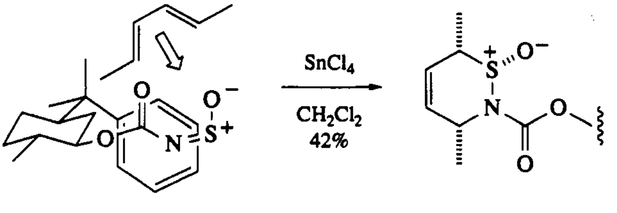

(52)

Until recently, dihydrothiazine oxides had not found much use in synthesis. Recently, Weinreb and coworkers have exploited some of the known reactions of these adducts, along with some new transformations, in stereoselective preparation of some complex nitrogen-containing molecules.[87] One useful transformation of these adducts is the hydrolysis/retro-ene elimination of sulfur dioxide shown in equation (53).[98] Thus dihydrothiazine oxide (**120**), prepared from (*E*,*E*)-tetramethylbutadiene, underwent hydrolysis to allylic sulfinic acid (**121**) which suffered a retro-ene reaction *via* the chair-like conformation shown to give exclusively homallylic sulfonamide (**122**). The diastereotopic face of the alkenic double bond in (**121**) to which the proton is transferred is controlled by the pseudo-equatorial methyl substituent adjacent to the sulfur. The isomer of (**120**) derived from (*E,Z*)-tetramethylbutadiene affords the epimer of sulfonamide (**122**) stereoselectively.

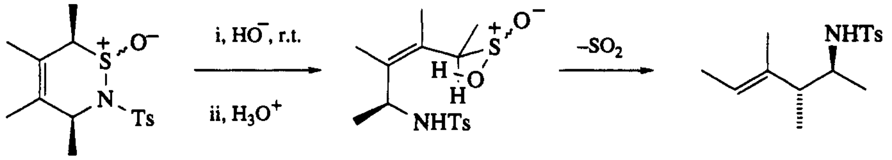

(**120**) (**121**) (**122**)

(53)

Another useful reaction of these Diels–Alder adducts is shown in equation (54).[99] Dihydrothiazine oxide (**123**) from (*E,E*)-2,4-hexadiene can be opened with a Grignard reagent to allylic sulfoxide (**124**) which undergoes a stereoselective 2,3-sigmatropic rearrangement *via* the envelope-like transition state conformation shown, having a quasi-equatorial methyl group to afford sulfenate ester (**125**). Desulfurization of (**125**) provides (*E*)-*threo*-amino alcohol derivative (**126**) in excellent overall yield. If (*E,Z*)-2,4-hexadiene is used, the (*E*)-*erythro* epimer of (**126**) is formed cleanly.

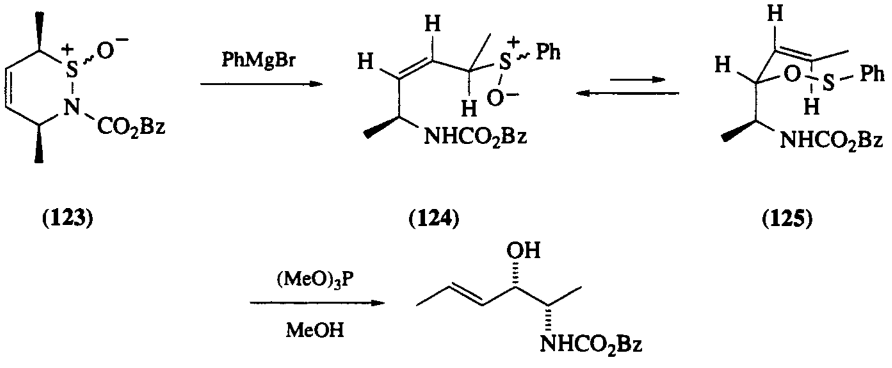

(**123**) (**124**) (**125**)

(**126**)

(54)

### 4.2.6.2 Intramolecular Cycloadditions

The Weinreb group has reported the only examples of intramolecular [4 + 2] cycloadditions of *N*-sulfinyl compounds.[87,99,100] For example, diene carbamate (**127**) could be converted to an *N*-sulfinyl compound which cyclized intramolecularly to dihydrothiazine oxide (**128**) (Scheme 16). Using the chemistry outlined in equation (54), (**128**) was transformed stereoselectively to *threo*-sphingosine (**129**). Similarly, (*E,Z*)-diene carbamate (**130**) was transformed *via* adduct (**131**) to *erythro*-sphingosine (**132**).

One other example of an intramolecular *N*-sulfinyl carbamate cycloaddition is depicted in Scheme 17. In this case, diene carbamate (**133**) was converted to a sulfinyl compound which cyclized to give exclusively adduct (**135**).[100] It was suggested that the cycloaddition occurs *via* an *endo* boat-like *N*-sulfinyl carbamate conformation (**134**). The alternate *endo* chair-like conformation (**137**) leading to isomeric adduct (**138**) is destabilized relative to (**134**) due to an eclipsing interaction between $H_a$ and $H_b$. Adduct (**135**) was converted to amino sugar (**136**) in a few steps.

### 4.2.6.3 Bis-imines

Bis-imines (**117**) have been used far less than the monoimines as dienophiles. However, there are enough examples of these cycloadditions to indicate clearly that they are regioselective and, provided at least one electron-withdrawing group is present on nitrogen, that they proceed under mild reaction conditions.[1] As with the monoimines, little is known with regard to the establishment of sulfur stereochemistry in the dihydrothiazine imines (**118**). Equations (55),[101] (56)[102] and (57)[103] demonstrate both the regioselectivity of the process and some of the structural types of bis-imino compounds which have been

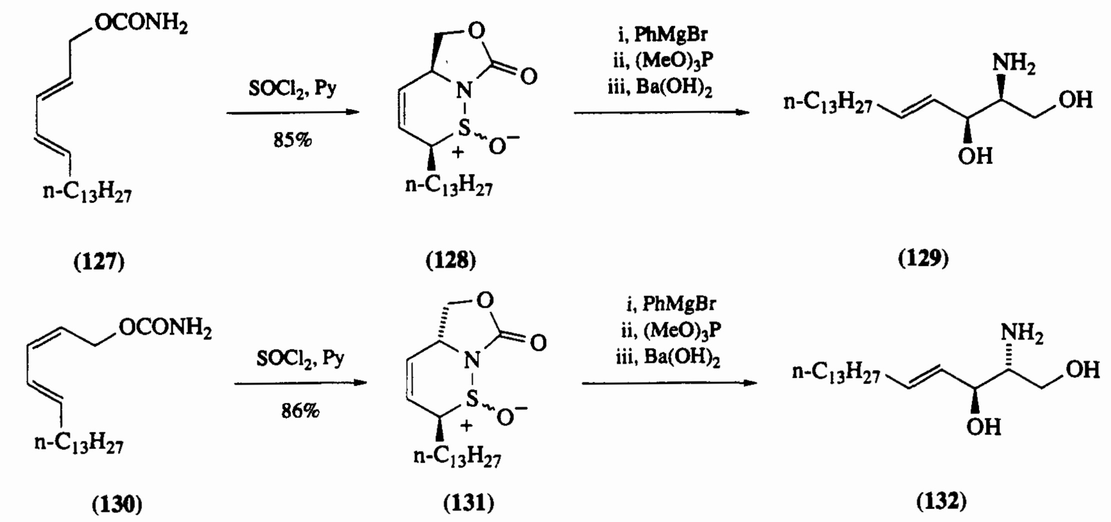

**Scheme 16**

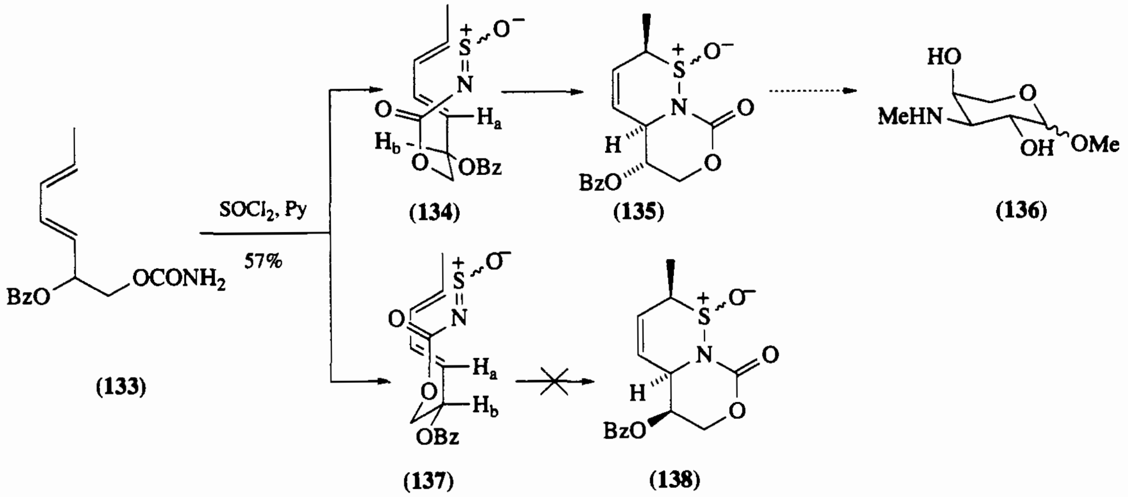

**Scheme 17**

used. It should be noted that unsymmetrical *N*-sulfinyl compound (**139**) reacts regioselectively at the N═S double bond bearing the least electron-withdrawing substituent. This is apparently a general phenomenon which has not been satisfactorily rationalized.

Weinreb and coworkers have examined some reactions of dihydrothiazine imines and have developed a new approach to vicinal diamines using these intermediates.[87,104] Their method is outlined in Scheme 18. Cycloaddition of (*E,E*)-2,4-hexadiene with the tosyl bis-imine gives a 1.1:1 mixture of epimeric dihydrothiazine imines (**140**) and (**144**). Subsequent transformations of these adducts took two different courses. In one, adduct (**140**) could be opened to allylic sulfilimine (**141**) which underwent a stereoselective 2,3-sigmatropic rearrangement to sulfenamide (**142**) (*cf.* equation 54). Desulfurization of (**142**) yielded (*E*)-*threo* vicinal sulfonamide (**143**). Adduct (**144**), which presumably exists in conformation (**145**), suffers a unique stereoselective transannular 2,3-sigmatropic rearrangement to thiadiazolidine (**146**) which can also be converted to bis-sulfonamide (**143**).

## 4.2.7 AZO DIENOPHILES

The reaction of diethyl azodicarboxylate with cyclopentadiene reported by Diels in 1925 is of historical significance since it is one of the first examples of a Diels–Alder [4 + 2] cycloaddition (equation 58).[1,105,106] These cycloadditions usually proceed under mild conditions and are *syn* selective with

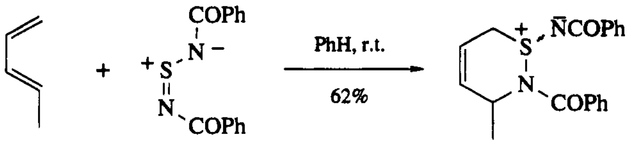
COPh
N
S
N
COPh
PhH, r.t.
62%
NCOPh
S
N
COPh

(55)

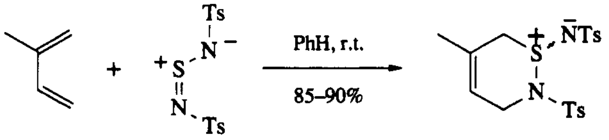
Ts
N
S
N
Ts
PhH, r.t.
85–90%
NTs
S
N
Ts

(56)

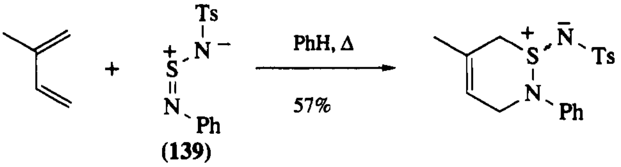
Ts
N
S
N
Ph
(139)
PhH, Δ
57%
N
Ts
S
N
Ph

(57)

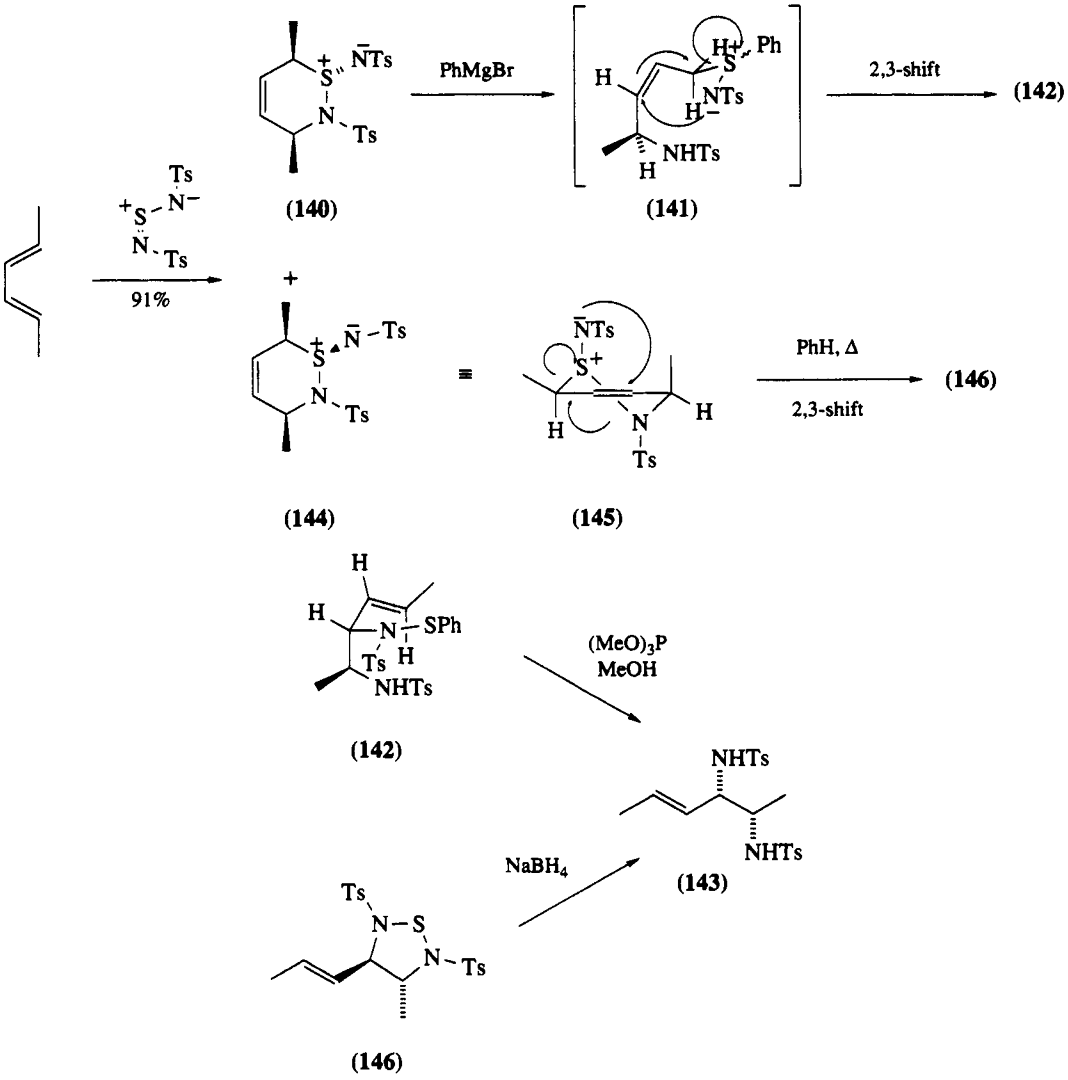
NTs
S
N
Ts
(140)
PhMgBr
H
H
Ph
S
NTs
H
NHTs
H
(141)
2,3-shift
(142)
Ts
S
N
N
Ts
91%
+
N
Ts
S
N
Ts
(144)
≡
NTs
S+
H
N
H
Ts
(145)
PhH, Δ
2,3-shift
(146)
H
H
N
SPh
Ts
H
NHTs
(142)
(MeO)3P
MeOH
NHTs
NHTs
(143)
NaBH4
Ts
N
S
N
Ts
(146)

**Scheme 18**

respect to the diene. Cycloadditions of azo dienophiles are among the most widely utilized hetero Diels–Alder reactions and examples of these cycloadditions abound in the literature.

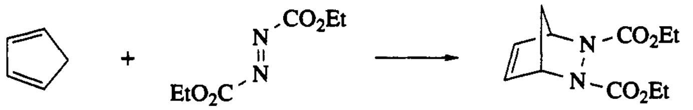
(58)

The mechanism of this type of reaction has received some attention.[105,107] It has been suggested that these reactions are pericyclic processes, and since N=N dienophiles have lower lying LUMOs than C=C compounds, they are more reactive. Cyclic N=N species have an even lower LUMO energy.[105] However, a recent investigation of the cycloadditions of 4-phenyl-1,2,4-triazoline-3,5-dione (*vide infra*) indicates that in at least some cases the Diels–Alder reactions involve discrete intermediates.[107] It would appear that a range of mechanisms may be available to azo dienophiles.

### 4.2.7.1 Acyclic Azo Systems

Azodicarboxylates and related compounds have been widely used as dienophiles over the last six decades.[108] A thorough description of these reactions is beyond the scope of this review. In a recent representative example of such a cycloaddition, Schmidt and coworkers found that diene (**147**) adds to diethyl azodicarboxylate to yield (**148**).[109] This product was used in synthesis of aminoxylose derivative (**149**) (equation 59).

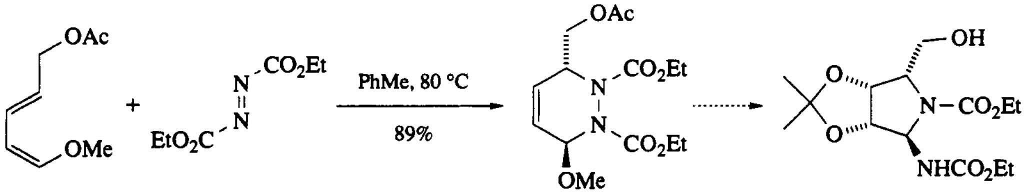
(59)

**(147)** **(148)** **(149)**

Another example of a cycloaddition of this type is shown in equation (60), in which Kresze *et al.* used adduct (**150**) to prepare a highly substituted pyrrole.[110]

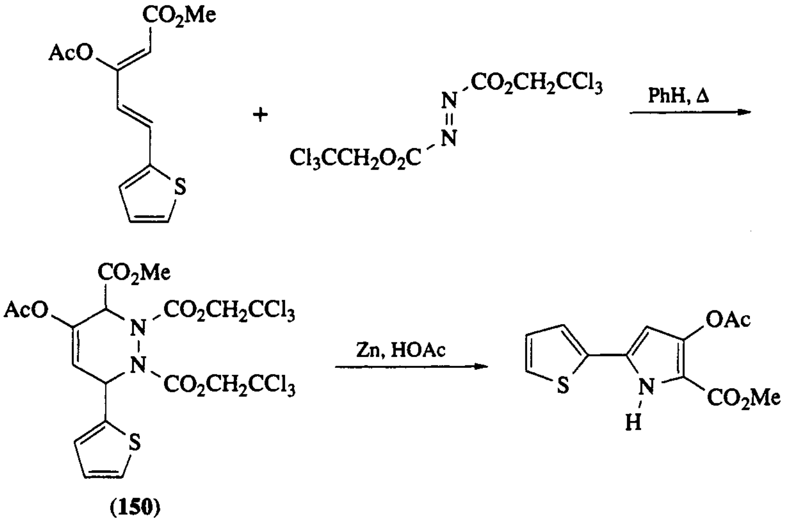
(60)

**(150)**

A structural variation of azodicarboxylate is arenediazocyanide (**151**) prepared from the corresponding diazonium salt (equation 61).[111] Dienophiles of this class add regioselectively to 1,3-dienes in a Diels–Alder sense. This selectivity is consistent with both stepwise polar and concerted pericyclic mechanisms.

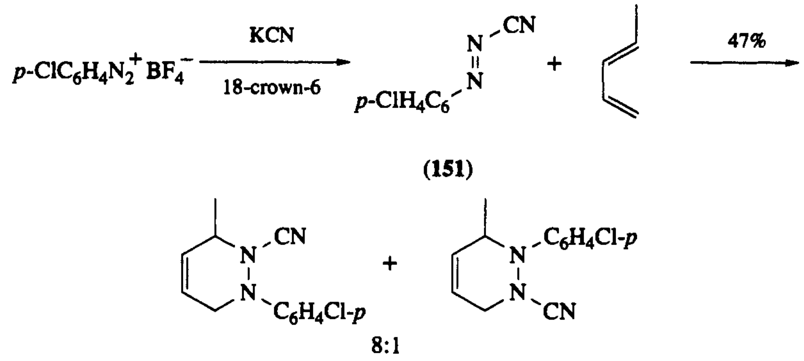

(61)

### 4.2.7.2 Cyclic Azo Systems

Since their introduction by Cookson *et al.* in 1962,[112] 4-substituted 1,2,4-triazoline-3,5-diones have been used extensively as dienophiles (equation 62).[1,105] These dienophiles are highly reactive towards most 1,3-dienes and undergo cycloadditions under very mild conditions. In general, these Diels–Alder reactions are *syn* selective with respect to the diene, although with some (*Z*)-dienes this selectivity is lost. As noted above, it has been found that these cycloadditions are stepwise reactions in (*Z*)-dienes which cannot achieve an *s-cis* conformation.[107] However, it is not clear if all cycloadditions of triazolinediones with 1,3-dienes proceed this way.

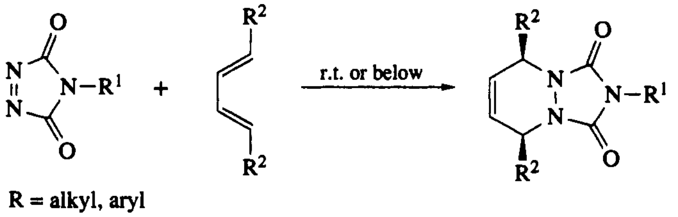

(62)

The triazolinedione adducts in equation (62) are often difficult to hydrolyze to the parent cyclic hydrazine derivatives and therefore a modified dienophile (152) was developed independently by Corey[113a] and by Beak[113b] (equation 63). The adducts of this compound are readily converted to the hydrazine by mild basic hydrolysis.

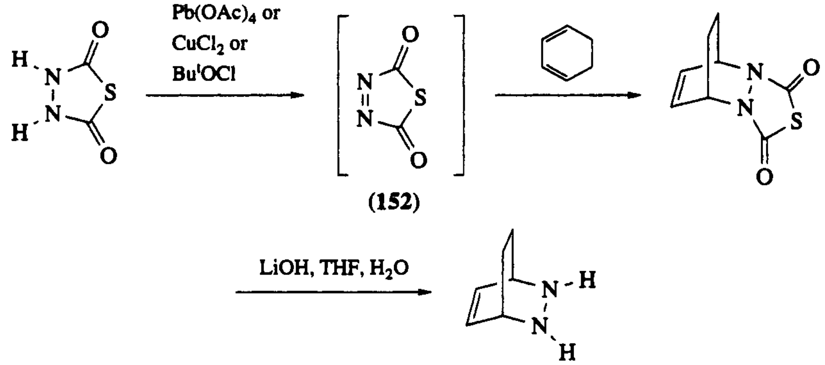

(63)

Two interesting examples of intramolecular Diels–Alder reactions of azo dienophiles have recently been published. In the first, Kyler and coworkers oxidized systems such as (**153**) to an intermediate azo compound which underwent cycloaddition to afford adduct (**154**) (equation 64).[114] In another case, Kahn *et al.* found that diacylhydrazide (**155**) could be oxidized to yield Diels–Alder adduct (**156**) (equation 65).[115]

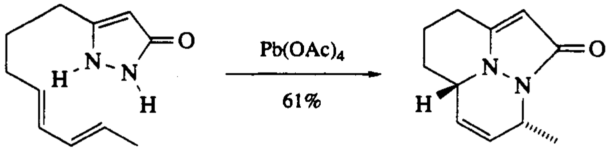

**(153)** **(154)**

(64)

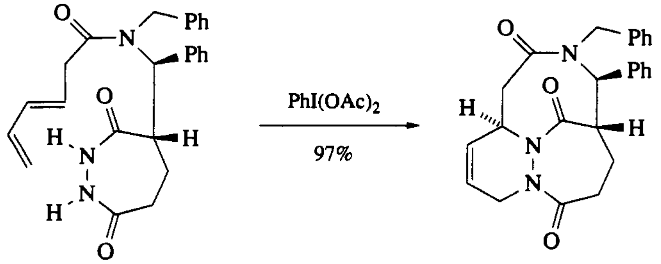

**(155)** **(156)**

(65)

### 4.2.7.3 Charged Dienophiles

Diazonium salts have been briefly investigated as hetero dienophiles.[116] It appears that electron-rich dienes and electron-deficient diazonium compounds are the best partners in this cycloaddition. The reactions are usually regioselective (equation 66). It has been proposed that these cycloadditions are one-step pericyclic processes.[116b]

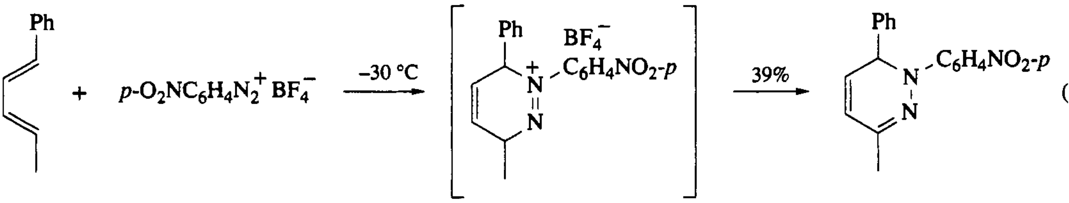

(66)

Nelsen *et al.* have discovered that simple alkyl diazo compounds, which are normally not dienophiles, will react in a Diels–Alder fashion if protonated (equation 67).[117] It was suggested that protonation facilitates the reaction thermodynamically, since hydrazines are much stronger bases than azo compounds.

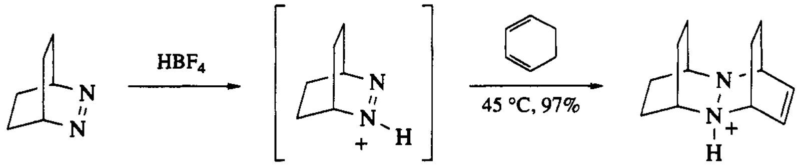

(67)

## 4.2.8 CARBONYL DIENOPHILES

Diels–Alder cycloadditions of carbonyl compounds with aldehydes and ketones provide a powerful method for synthesis of 5,6-dihydropyrans, which are useful synthons for a variety of purposes.[1,118] This methodology was slow to develop since early work indicated that simple carbonyl compounds react poorly with most alkyl and aryl substituted 1,3-dienes. However, with the understanding that [4 + 2] cycloadditions are facilitated by Lewis acid catalysts and high pressure, along with the recent availability of highly reactive oxygenated dienes, this chemistry has been increasingly exploited in total synthesis.

Cycloadditions with these heterodienophiles are usually regioselective and are in accord with FMO theory. The reactions are *syn* selective with the diene component. Other stereochemical features of the process are outlined in some of the examples described below, as well as in previous reviews.[1,118] It should also be mentioned that only aldehydes and some ketones act as dienophiles. Except for rare exceptions, other types of carbonyl compounds apparently do not participate in Diels–Alder cycloadditions.

### 4.2.8.1 Electron-deficient Aldehydes

Aldehydes bearing electron-withdrawing substituents are reactive as heterodienophiles under mild conditions with a range of 1,3-dienes. In particular, glyoxylate derivatives have been widely used in these cycloadditions. Some examples of Diels–Alder reactions of this type are shown in equations (68),[119] (69)[120] and (70).[121] As can be seen, these reactions occur at relatively low temperatures and are regioselective.[122]

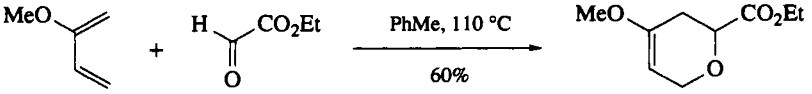
MeO
H
CO2Et
O
PhMe, 110 °C
60%
MeO
CO2Et
O

(68)

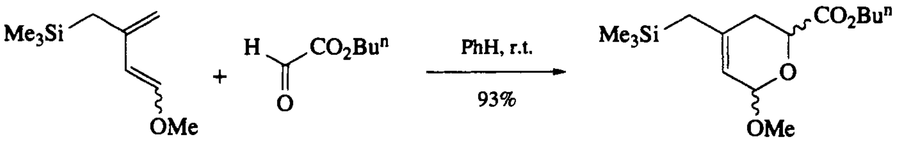
Me3Si
OMe
H
CO2Bun
O
PhH, r.t.
93%
Me3Si
CO2Bun
O
OMe

(69)

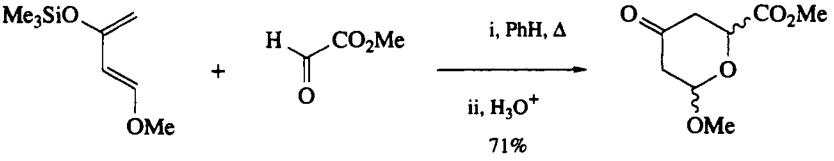
Me3SiO
OMe
H
CO2Me
O
i, PhH, Δ
ii, H3O+
71%
O
CO2Me
O
OMe

(70)

Some very interesting stereo- and regio-chemical features of the cycloaddition can be seen in the work of Schmidt and Wagner outlined in Scheme 19.[123] They found that the unsymmetrically 1,4-substituted diene (**157**) reacts with methyl glyoxylate regioselectively to afford adducts (**158**), (**159**) and (**160**).[123a] Compounds (**158**) and (**159**) result from *exo* and *endo* transition states, respectively, and (**160**) presumably arises from (**158**) *via* isomerization at the anomeric center. When siloxy diene (**161**) was used in a cycloaddition with glyoxylate (**162**), *exo* and *endo* adducts (**163**) and (**164**), respectively, were produced.[123b] However, the regiochemistry here is completely reversed relative to diene (**157**). It was proposed that these results occur since the magnitude of the C-1 and C-4 HOMO coefficients of benzoyl-substituted diene (**157**) are reversed in the siloxy diene (**161**).[123b]

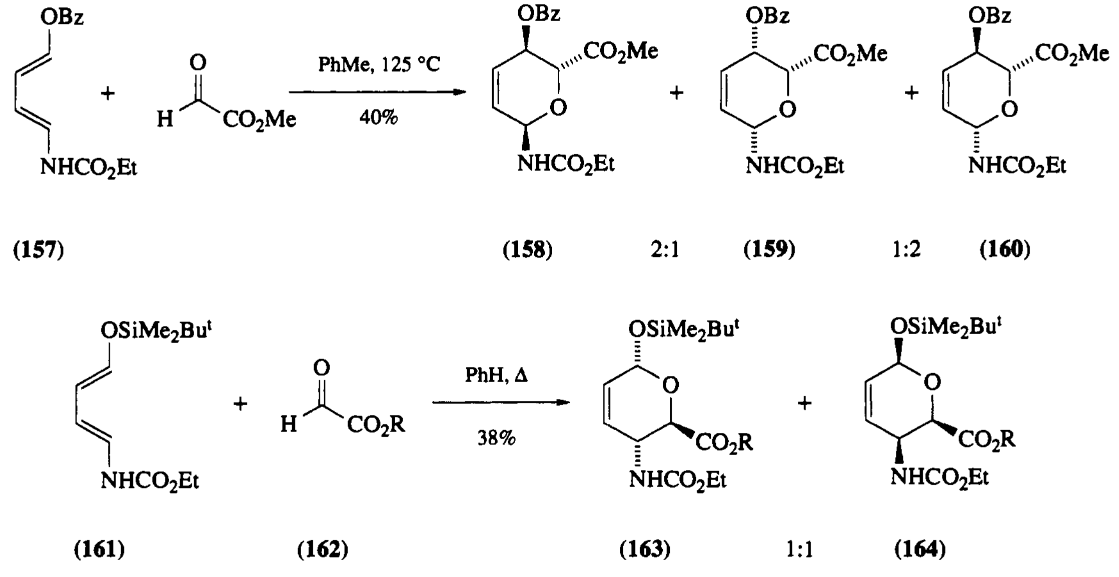
OBz
NHCO2Et
O
H
CO2Me
PhMe, 125 °C
40%
OBz
CO2Me
O
NHCO2Et
OBz
CO2Me
O
NHCO2Et
OBz
CO2Me
O
NHCO2Et
OSiMe2But
NHCO2Et
O
H
CO2R
PhH, Δ
38%
OSiMe2But
O
CO2R
NHCO2Et
OSiMe2But
O
CO2R
NHCO2Et

**(157)** **(158)** 2:1 **(159)** 1:2 **(160)**

**(161)** **(162)** **(163)** 1:1 **(164)**

R = $CH_2C_6H_4NO_2$-*p*

**Scheme 19**

Several reports of Diels–Alder cycloadditions of chiral glyoxylate esters have been published.[124–126] In general, reactions with menthyl esters of glyoxylate do not show very high selectivities either thermally or under high pressure.[124,125] Better results have been obtained by David and coworkers using (*E*)-1-oxygenated butadienes attached to chiral sugars.[126] In a nice application of this methodology to the synthesis of a blood group antigenic determinant, the principle of double diastereoselection was used.[127] Thus chiral diene (**165**) was combined with L-menthyl glyoxylate to afford a mixture of epimeric pyrans, which was equilibrated at the anomeric center to yield (**166**) (equation 71).

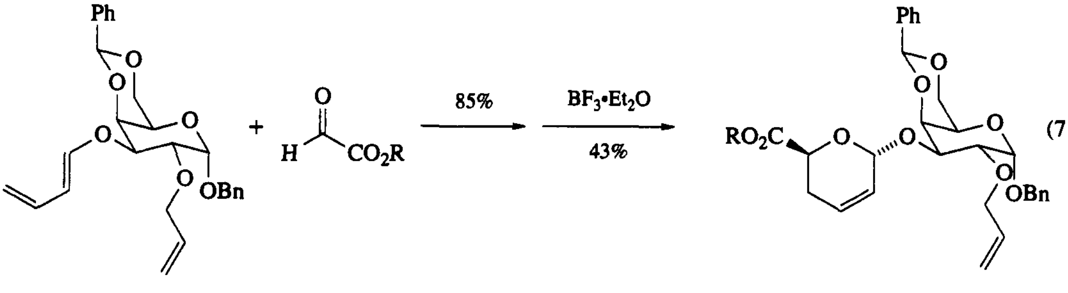
Ph
O
O
O
O
O
OBn
+
O
H
CO2R
85%
BF3•Et2O
43%
RO2C
O
O
Ph
O
O
O
O
OBn

(71)

(**165**) R = L-menthyl (**166**)

It should also be noted that it has recently been found that chiral Lewis acid catalysts promote glyoxylate Diels–Alder reactions, but enantiomeric excesses are usually low.[128,129]

### 4.2.8.2 Electron-deficient Ketones

The large majority of cycloadditions of keto dienophiles have involved mesoxylate. Some typical examples of this process are shown in equations (72),[130] (73)[131] and (74).[132] The cycloaddition appears to be regioselective in most cases.[133]

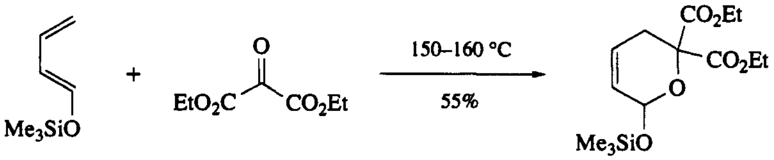
Me3SiO
+
O
EtO2C
CO2Et
150–160 °C
55%
CO2Et
CO2Et
O
Me3SiO

(72)

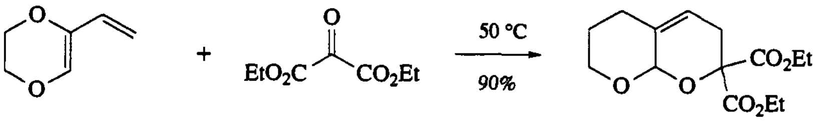
O
O
+
O
EtO2C
CO2Et
50 °C
90%
O
O
CO2Et
CO2Et

(73)

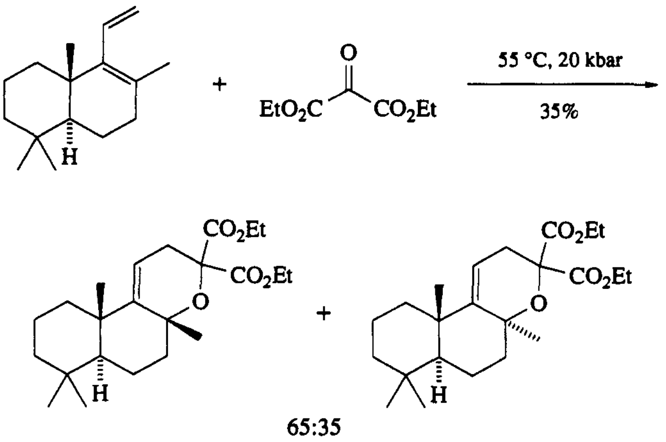
H
+
O
EtO2C
CO2Et
55 °C, 20 kbar
35%
CO2Et
CO2Et
O
H
+
CO2Et
CO2Et
O
H
65:35

(74)

One very useful transformation of these adducts is given in equation (75). Hydrolysis of the diester to the diacid, followed by bis-decarboxylation either by a double Curtius rearrangement[134] or oxidatively with ceric ammonium nitrate,[133a] yields an unsaturated lactone. This overall sequence is equivalent to effecting a Diels–Alder reaction with carbon dioxide, which is unreactive as a dienophile.

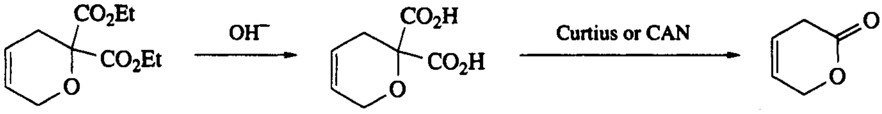

(75)

A few examples of cycloadditions with other electron-deficient ketones have appeared.[130b,135,136a] Two such systems are shown in equations (76)[135a] and (77).[135b] However, this chemistry has not been widely applied to date.

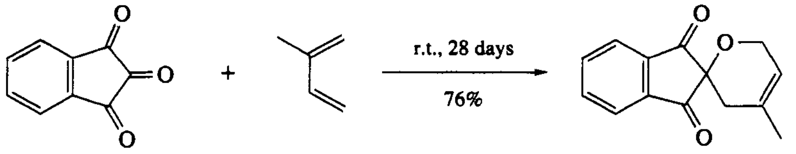

(76)

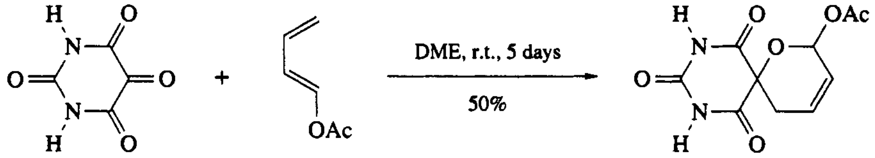

(77)

### 4.2.8.3 Aliphatic and Aromatic Aldehydes

Until recently, relatively little work had been reported on Diels–Alder reactions of simple aromatic and aliphatic aldehydes with 1,3-dienes.[1] It was initially thought that these reactions did not work well. However, a better understanding of the factors governing the cycloaddition has led to important methodological advances. This section and the following one briefly outline work in this area.

Few examples of [4 + 2] cycloadditions of aromatic aldehydes with simple alkyl-, halo- and alkoxy-substituted 1,3-dienes exist. Ansell and Charalambides found that benzaldehydes substituted with electron-withdrawing groups such as nitro and cyano undergo thermal cycloaddition.[136b] Other benzaldehydes were found to cycloadd only in the presence of *p*-toluenesulfonic acid.

Formaldehyde reacts thermally with 1-alkoxybutadienes, but not with most simple alkyl-substituted dienes.[137a] However, in the presence of a Lewis acid this type of cycloaddition is synthetically useful.[137b,c] A recent example of this reaction is shown in equation (78).[138b]

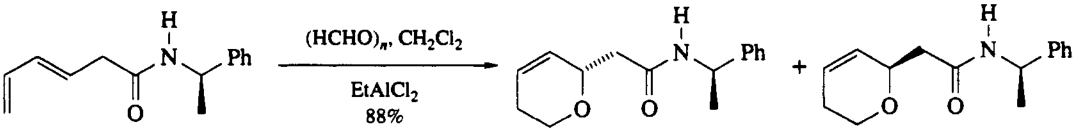

1:1 (78)

In an extensive study, Jurczak and coworkers have looked at the high pressure induced cycloaddition of (*E*)-1-methoxybutadiene with various aliphatic aldehydes.[138,139] An example is shown in equation (79).[139a] If a lanthanide catalyst is used the pressure can be reduced from 20 to 10 kbar, but yields appear to be somewhat lower.[139f]

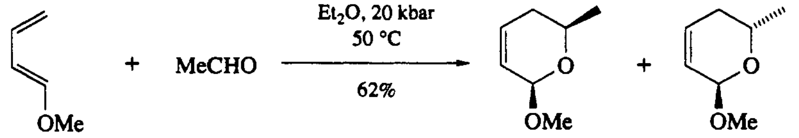

(79)

70:30

These workers have also examined asymmetric induction in the process in some detail. For instance, cycloaddition of sugar aldehyde (**167**) occurred to afford only adduct (**169**) at high pressure (equation 80). It was suggested that the Diels–Alder reaction proceeds *via* diene attack on the aldehyde conformation shown in (**168**) from the least congested face.[139i] Other chiral aldehydes have been investigated by this group, as has the effect of lanthanide catalysts upon the extent of asymmetric induction. Summaries of this work have recently been published.[138]

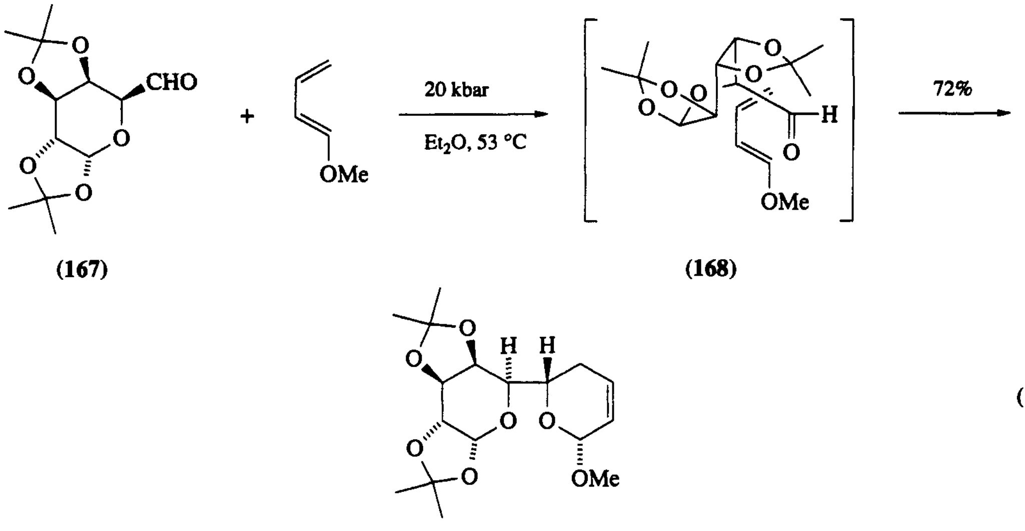

**(167)** **(168)** **(169)**

(80)

## 4.2.8.4 Cycloadditions with Highly Oxygenated Dienes

An important discovery in the area of carbonyl cycloadditions is that highly oxygenated 1,3-dienes are excellent 4π components.[1,140] These reactions occur at low temperatures with a wide range of aldehydes provided Lewis acid catalysts are used.[121b,141,142] This general type of reaction is shown by the example in equation (81). It was also found by Danishefsky and coworkers that lanthanide shift reagents are effective catalysts for the cycloaddition.[143] An example of one of these cycloadditions is outlined in equation (82).[121d]

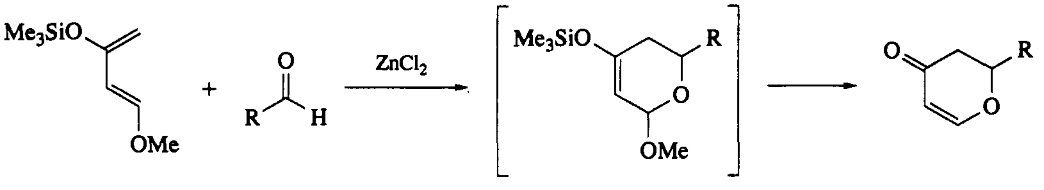

R = H, aryl, alkyl, alkenyl, *etc.*

(81)

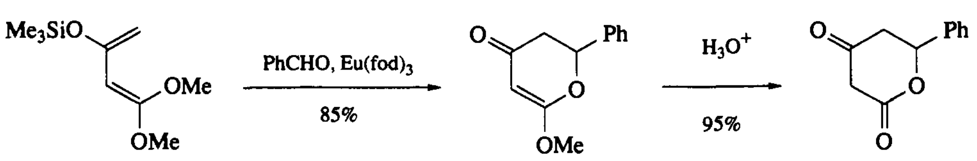

(82)

The Danishefsky group has investigated the mechanism of this process in some detail.[144] It has also been found that the cycloadditions show excellent diastereofacial selectivity with many chiral aldehydes.[144,145] Moreover, chiral catalysts have proven effective in controlling the enantioselectivity of the cycloaddition.[146–148] These features of the reaction, along with applications to natural product total syntheses, are discussed in detail in Volume 2, Chapter 2.5.

### 4.2.8.5 Intramolecular Reactions

Surprisingly few examples of intramolecular carbonyl Diels–Alder reactions exist. Two recent cases are shown in equations (83)[149] and (84).[150,151]

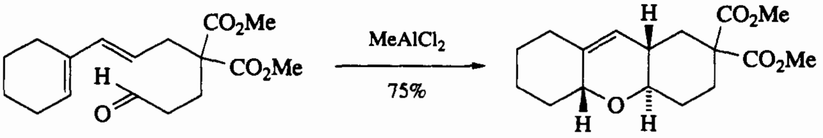

$CO_2Me$
$CO_2Me$
H
O
$MeAlCl_2$
75%
H
$CO_2Me$
$CO_2Me$
O
H
H

(83)

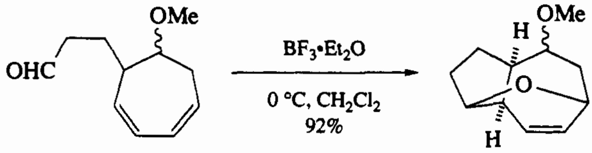

OMe
OHC
$BF_3•Et_2O$
0 °C, $CH_2Cl_2$
92%
OMe
H
O
H

(84)

In a clever piece of work, Snider *et al.* have used a 'quasi' intramolecular carbonyl Diels–Alder cycloaddition to produce a key intermediate for syntheses of pseudomonic acid A (**175**) (Scheme 20).[137c] Thus a Lewis acid catalyzed ene reaction of alkene (**170**) and formaldehyde afforded (**171**), which complexed with additional formaldehyde to give (**172**). Intramolecular [4 + 2] cycloaddition of (**172**) gave adduct (**173**) which produced dihydropyran (**174**) upon hydrolysis.

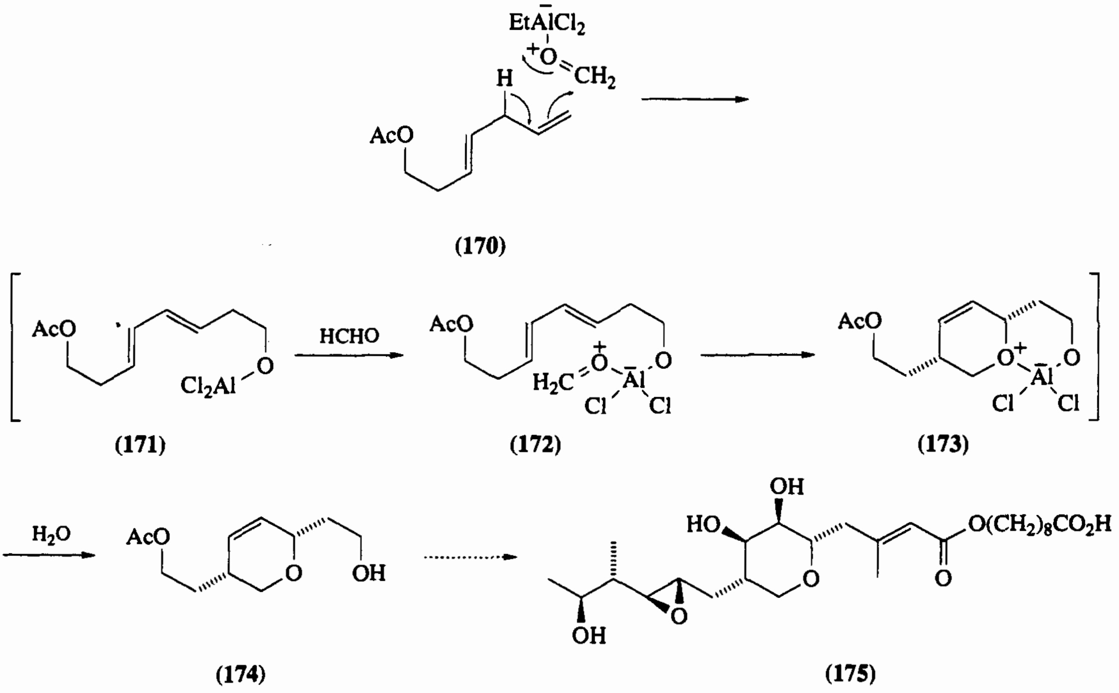

$Et\bar{A}lCl_2$
$^+O$
H
$CH_2$
AcO
(170)
AcO
$Cl_2Al$
O
(171)
HCHO
AcO
$H_2C$
O
Al
O
Cl
Cl
(172)
AcO
O
Al
O
Cl
Cl
(173)
$H_2O$
AcO
O
OH
(174)
OH
HO
O
$O(CH_2)_8CO_2H$
O
O
OH
(175)

Scheme 20

## 4.2.9 THIOCARBONYL DIENOPHILES

Thiocarbonyl compounds of all kinds are excellent heterodienophiles.[1,152] There has not been much systematic study of this class of reaction but it seems that such cycloadditions are generally regioselective. One difference between carbonyl and thiocarbonyl Diels–Alder reactions is that the dihydrothiopyran adducts from the latter dienophiles often undergo cycloreversion. The slow development of this field is perhaps mainly due more to lack of methods for generating certain thiocarbonyl compounds than with difficulties in effecting cycloadditions.

### 4.2.9.1 Thioketones

Thioketones are generally readily available and undergo [4 + 2] cycloadditions under mild thermal conditions. Representative examples of this process are shown in equations (85),[153] (86)[154] and (87).[155]

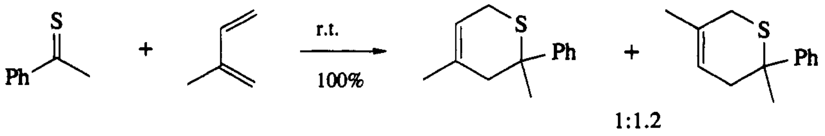
S
Ph
+
r.t.
100%
S
Ph
+
S
Ph
1:1.2

(85)

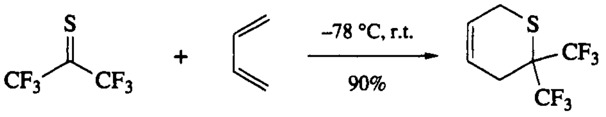
S
CF3
CF3
+
−78 °C, r.t.
90%
S
CF3
CF3

(86)

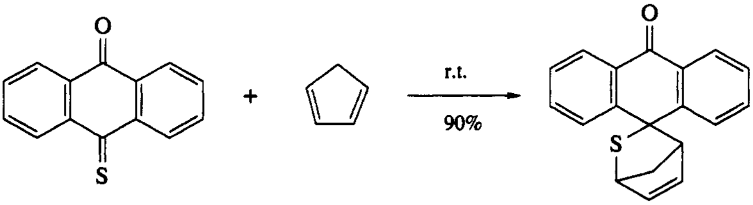

(87)

Larsen has recently described an interesting synthetic use for the cycloadducts of thiooxomalonate (Scheme 21).[156] Bunte salt (176) can be converted *in situ* to thiooxomalonate (**177**)[157] which undergoes regioselective [4 + 2] cycloaddition with 1,3-dienes at 25–70 °C to afford adducts. Thus with 1,3-dimethylbutadiene a 1:12 mixture of (**178**) and (**179**) are formed in excellent yield. It was found that treatment of major isomer (**179**) with base, followed by methyl iodide, yielded a 16:1 mixture of epimeric thiomethylcyclopentenes (**180**) and (**181**). Some mechanistic possibilities for formation of these products have been offered.[156]

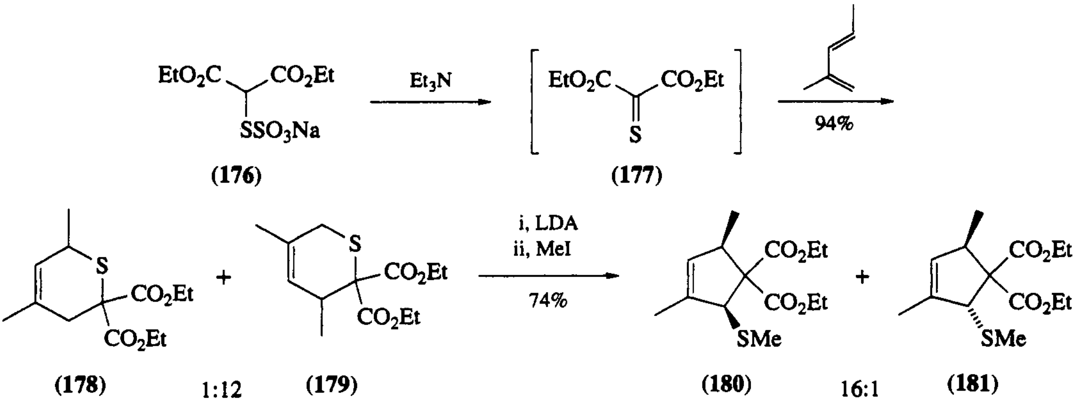
EtO2C
CO2Et
SSO3Na
(176)
Et3N
EtO2C
CO2Et
S
(177)
94%
S
CO2Et
CO2Et
(178)
+
1:12
S
CO2Et
CO2Et
(179)
i, LDA
ii, MeI
74%
CO2Et
CO2Et
SMe
(180)
+
16:1
CO2Et
CO2Et
SMe
(181)

Scheme 21

### 4.2.9.2 Thioaldehydes

Until recently, few reliable methods were available for preparation of thioaldehydes, which are usually very unstable, and little had been done with these species as dienophiles. However, this problem has now been remedied and there has been considerable interest in using thioaldehydes in [4 + 2] cycloadditions.[1]

Vedejs and coworkers have developed a general procedure for generation and trapping of transient thioaldehydes with 1,3-dienes.[158] They found that photolysis of phenacyl sulfides (**182**) produced thioaldehydes which gave [4 + 2] cycloadducts in good yields (Scheme 22). Some regiochemical results using siloxybutadiene (**183**) and variously substituted thioaldehydes are shown in Scheme 22.[158a,b,g] This regioselectivity is in accord with molecular orbital calculations.[158b]

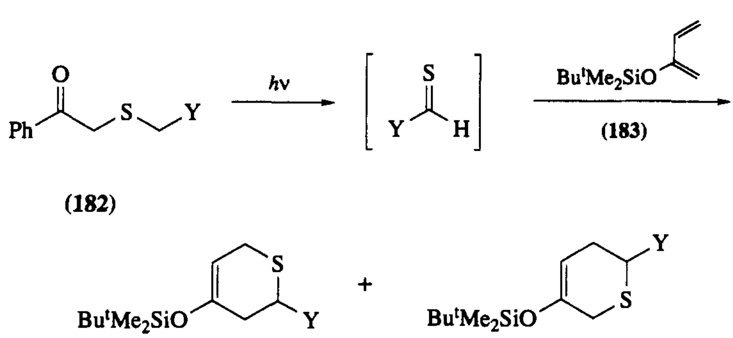

| Y = | |
|---|---|
| CN | 18:1 |
| COPh | 12:1 |
| $CH_2CH_2Ph$ | 0:100 |
| H | 1:11 |
| Ph | 1:2 |
| $SO_2Ph$ | 9.5:1 |
| $SiMe_3$ | 1:10 |

Scheme 22

Several groups have examined the *exo*/*endo* stereoselectivity of thioaldehyde cycloadditions.[158f,159,160] Scheme 23 outlines some of the methods used for *in situ* generation of thioaldehydes and selected stereochemical results with cyclopentadiene. As can be seen, these reactions generally give a predominance of *endo* products kinetically. Vedejs has rationalized this outcome as arising from steric factors.[158f]

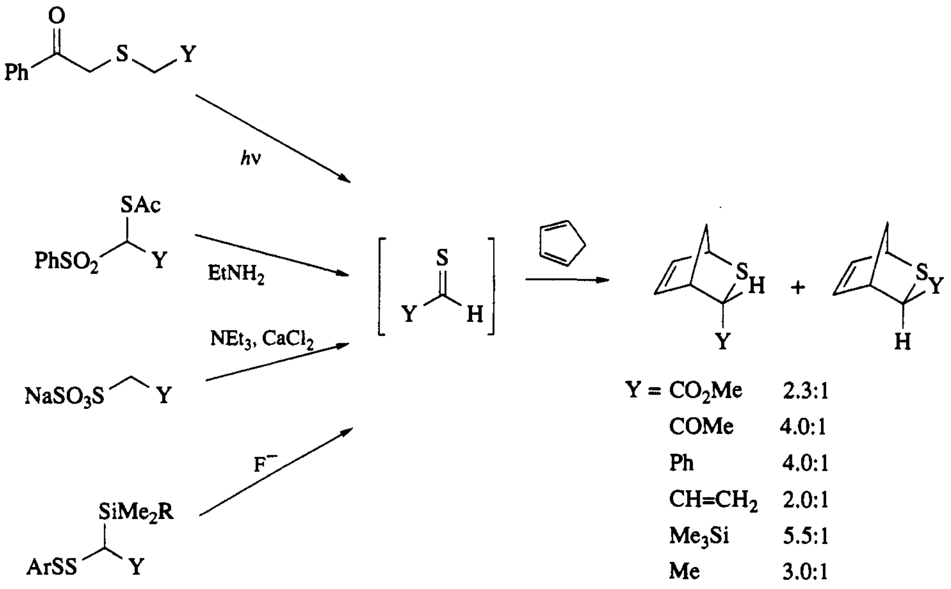

| Y = | |
|---|---|
| $CO_2Me$ | 2.3:1 |
| COMe | 4.0:1 |
| Ph | 4.0:1 |
| $CH{=}CH_2$ | 2.0:1 |
| $Me_3Si$ | 5.5:1 |
| Me | 3.0:1 |
| $Pr^i$ | 16:1 |
| $Bu^t$ | >50:1 |

Scheme 23

Another stereochemical aspect of these Diels–Alder reactions which has been studied by the Vedejs group is the facial selectivity in cycloadditions of chiral thioaldehydes.[158f] For instance, thioaldehyde (**184**), generated by the photochemical method, added to cyclopentadiene to give *exo* adducts (**185**) and (**186**) along with *endo* isomers (**187**) and (**188**) (Scheme 24). As was the case for achiral thioaldehydes, the *endo* adducts predominated (~9:1). The facial selectivity obtained can be rationalized *via* a Felkin–Anh or Cornforth model for asymmetric induction.[158f]

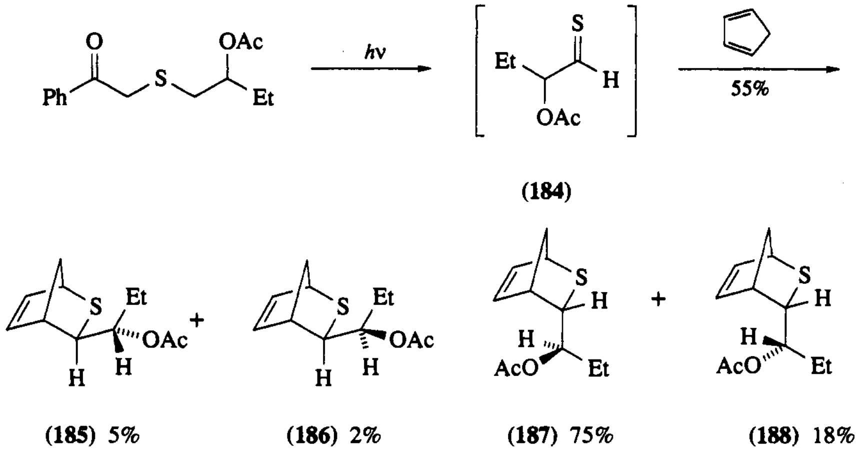

Scheme 24

Only a few intramolecular thioaldehyde [4 + 2] cycloadditions have been executed to date. Vedejs *et al.* have looked at systems such as that shown in equation (88).[158d] Their photochemical method is useful in effecting intramolecular reactions but stereoselectivity in the process was only moderate. Baldwin and Lopez have described the single intramolecular cycloaddition shown in equation (89) which involves a new thermal method for generating thioaldehydes from alkyl thiosulfinates.[161,162]

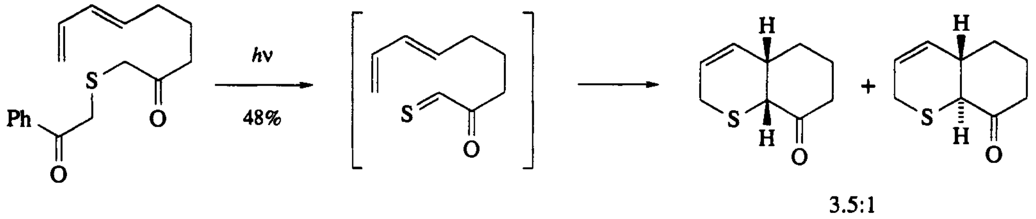

(88)

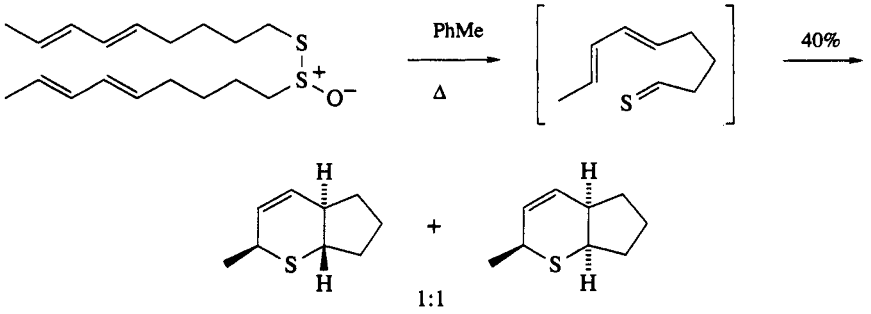

(89)

### 4.2.9.3 Thioesters, Dithioesters and Related Compounds

A number of thiocarbonyl compounds in the carboxylic acid oxidation state have been utilized in Diels–Alder reactions, but no systematic study in this area has been done. Some of the various structural types of thiocarbonyls which are reactive dienophiles are indicated in equations (90),[163] (91)[164] and (92).[165] Reactions of this class show good to moderate regioselectivity, but relatively little is known with regard to stereoselectivity. Additional examples can be found in earlier reviews.[1]

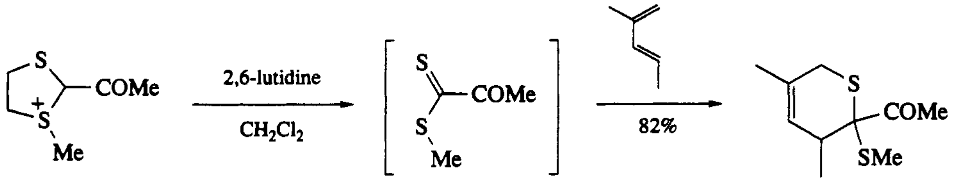

(90)

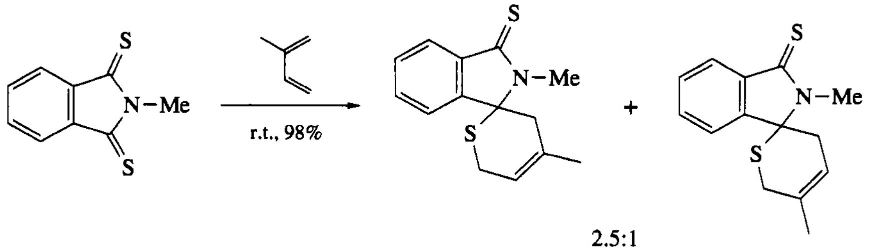

(91)

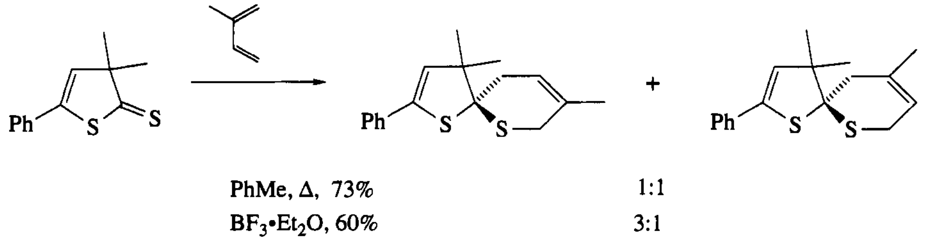

(92)

### 4.2.9.4 Thiophosgene and Related Compounds

Although carbon disulfide is not reactive as a heterodienophile, thiophosgene and its derivatives do participate in Diels–Alder reactions.[154,166] One example is shown in equation (93).

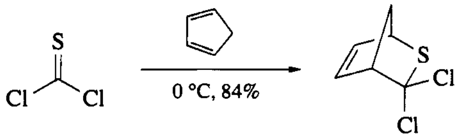

(93)

A few examples of cycloadditions with the thiophosgene equivalent (**189**) have been reported (equation 94).[167] In addition, methyl cyanodithioformate (**190**) has also been utilized several times as a heterodienophile (equation 95).[168]

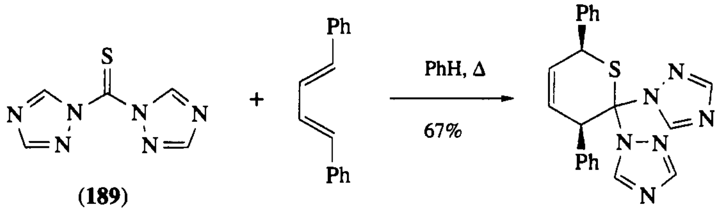

(94)

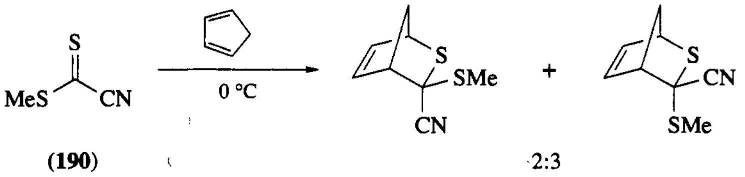

(95)

### 4.2.9.5 Thienium Salts and Related Cations

There are several scattered instances of [4 + 2] cycloadditions with charged thienium dienophiles.[169–171] The first reported example of this type of Diels–Alder reaction was by Corey and Walinsky, who used dithienium compound (**191**) in cycloadditions.[169] For instance, (**191**) reacts at low temperature with isoprene regioselectively to afford adduct (**192**) (equation 96). This compound can be converted to cyclopropane (**193**) and thermally rearranged to cyclopentanone derivative (**194**). The overall process is equivalent to addition of carbon monoxide to a 1,3-diene.

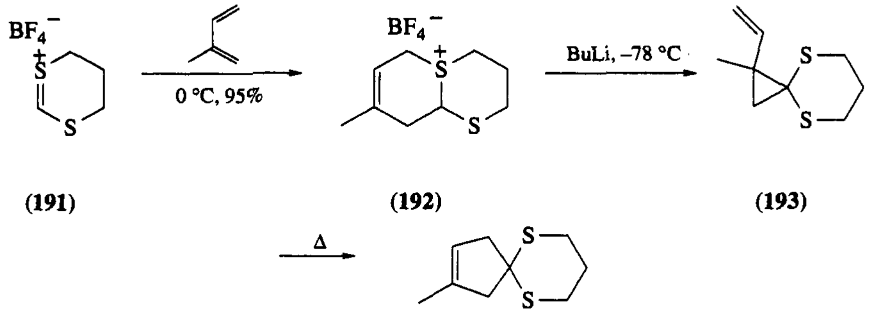

**(191)** **(192)** **(193)**

**(194)**

(96)

Another interesting use of a thienium dienophile is outlined in equation (97).[171] The initial Diels–Alder adduct was not isolated in these systems but was inferred based upon the nitro sulfide actually produced.

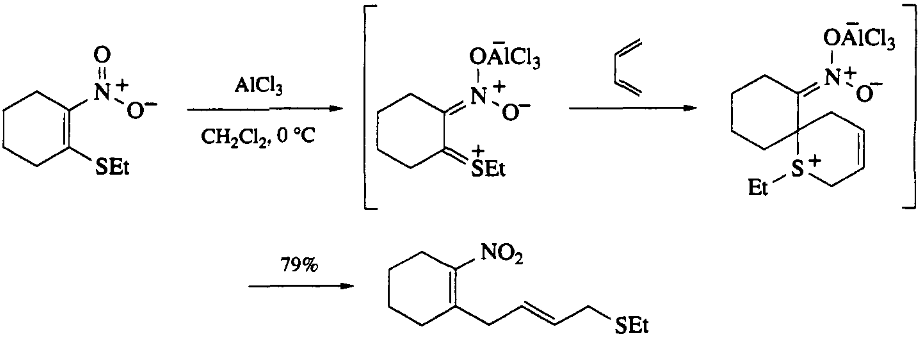

(97)

#### 4.2.9.6 Sulfines and Sulfenes

Sulfines, which are thiocarbonyl *S*-oxides, have been used many times as heterodienophiles.[1,172] As with thioaldehydes, the development of this field has been limited more by the availability of these often unstable species rather than by problems with the Diels–Alder chemistry. It should be noted that sulfines can exist as configurationally stable (*E*)- or (*Z*)-isomers and this stereochemistry can play a role in the outcome of the cycloaddition reactions.

Two recent examples of cycloadditions with simple sulfines are shown in equations (98)[173] and (99).[174] Surprisingly, the first case is nonstereospecific, a feature unique to this particular reaction. The example shown in equation (100), which involves retention of dienophile configuration, is more typical.[175]

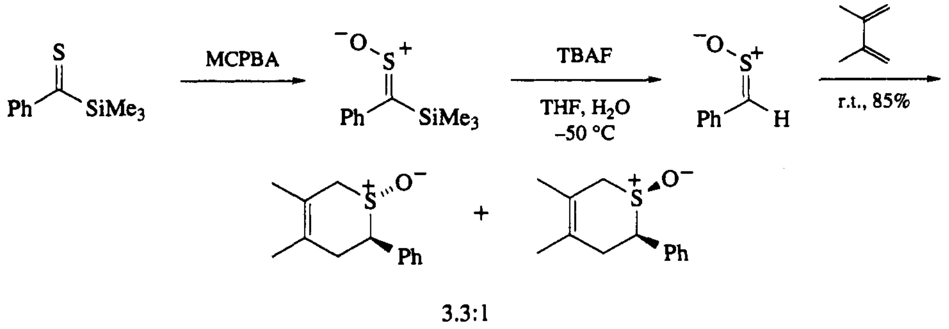

(98)

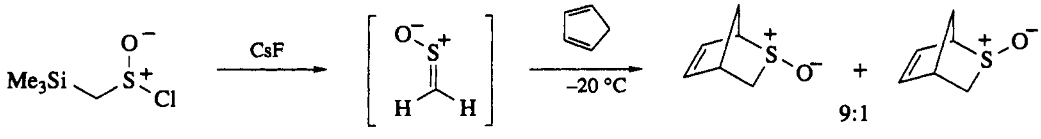

(99)

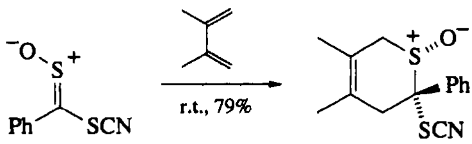

(100)

α-Oxosulfines have been the object of some research during recent years and these compounds have proven to be excellent dienophiles.[176] Two cases are shown in equations (101)[176d] and (102).[176f] It should be noted that sulfine geometry is retained in these cycloadditions. The former example shows a preference for an *endo* methoxycarbonyl group.

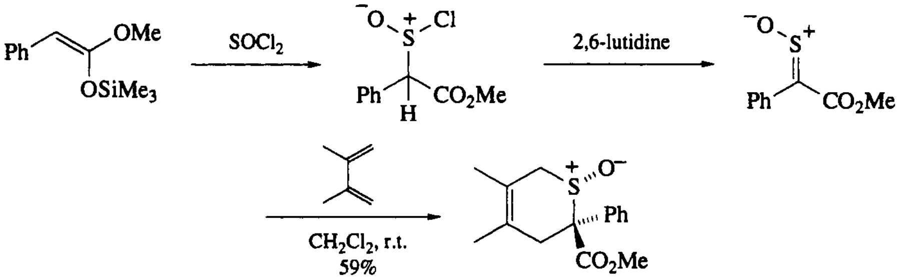

(101)

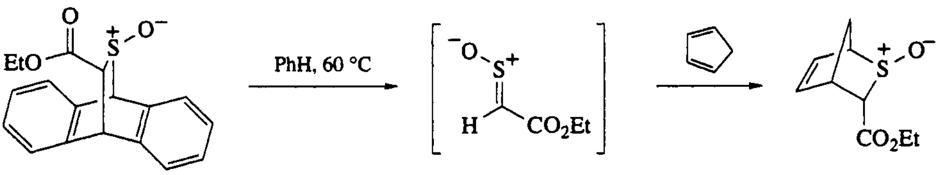

(102)

Zwanenburg and coworkers have examined the diastereoselectivity of chiral sulfine systems in Diels–Alder reactions.[177] In one case, α-chlorosulfine (**195**) derived from camphor reacts with 2,3-dimethylbutadiene *via* attack on the sulfine conformer indicated in equation (103) to afford adduct (**196**) as a single diastereomer.

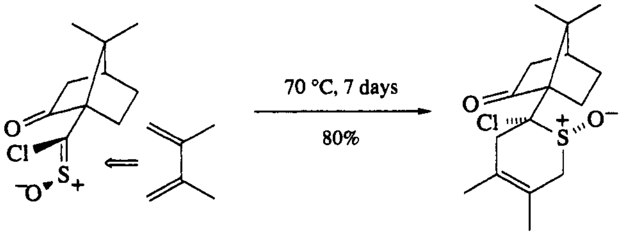

(103)

**(195)** **(196)**

One example exists of a thione imine (*i.e.* the nitrogen analog of a sulfine) acting as a dienophile.[178] Saito and Motoki have found that (**197**) reacts regioselectively with 1,3-dienes in a Diels–Alder sense (equation 104). This potentially useful reaction seems worthy of further exploration, provided general methods for generation of these imines can be developed.

Sulfenes have received little attention to date as dienophiles.[174,179] These reactive species undergo [4 + 2] cycloadditions with certain dienes upon occasion, but [2 + 2] cycloadditions and electrophilic reactions are also common (*cf.* Scheme 25).[179b] In addition, the mode of reaction of a sulfene may depend upon its method of formation.[174]

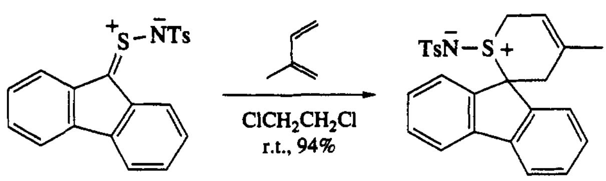

**(197)**

(104)

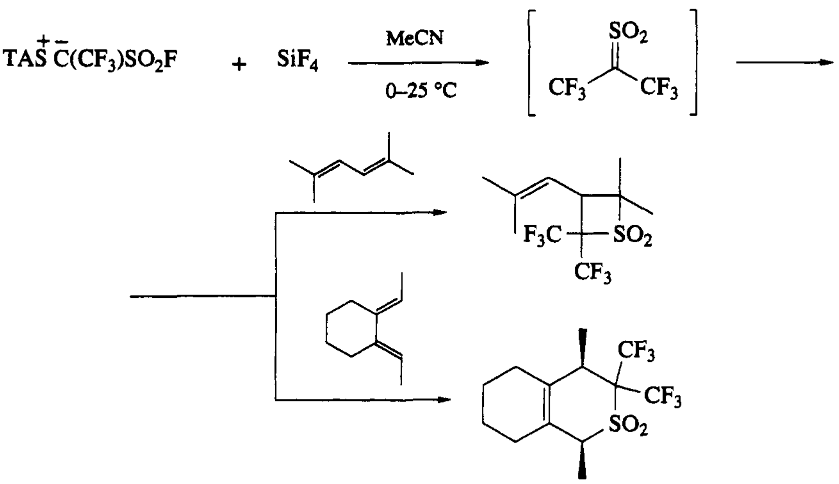

Scheme 25

### 4.2.10 SELENOCARBONYL DIENOPHILES

Essentially all of the work on [4 + 2] cycloadditions of selenocarbonyl compounds has been reported within the past five years.[180–185] Krafft and coworkers have developed a novel method for producing seleno-aldehydes and -ketones, and have investigated in some detail the Diels–Alder chemistry of these species.[180] Alkyl- and aryl-substituted selenocarbonyl compounds could be formed from silyl selenocyanates (**198**) (equation 105). As is the case with thioaldehydes,[158] selenoaldehydes react with cyclopentadiene to afford predominantly *endo* cycloadducts. This stereochemical preference has also been observed by Segi *et al.*[185a] using a different method for generating selenoaldehydes.

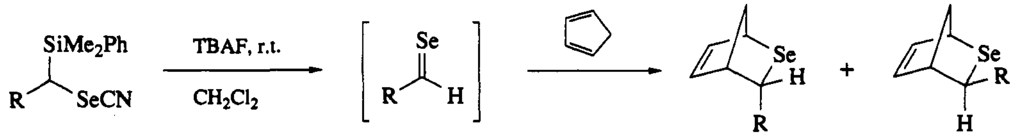

(**198**) R = alkyl, aryl

2.3–9.0:1

(105)

Alkyl-substituted selenoaldehydes only cycloadd to certain reactive dienes such as cyclopentadiene or 1,3-diphenylisobenzofuran. On the other hand, selenoaldehydes bearing electron-withdrawing groups react with a wide range of electron-rich dienes. One method of formation of this type of dienophile and some regiochemical results with an unsymmetrical 1,3-diene are shown in equation (106). The orientation observed here is in accord with a dienophile-LUMO/diene-HOMO controlled process.[180d]

Another selenoaldehyde preparation has been developed by Kirby and Trethewey (equation 107).[184] Dienophile (**199**) can be trapped directly by 1,3-dienes or by anthracene to give adduct (**200**). Retro Diels–Alder reaction of (**200**) in the presence of another diene affords a new cycloadduct.

Segi and coworkers have invented a direct method for converting aldehydes to selenoaldehydes.[185] This procedure can be used to effect intermolecular reactions as well as intramolecular selenoaldehyde Diels–Alder reactions as outlined in equation (108).

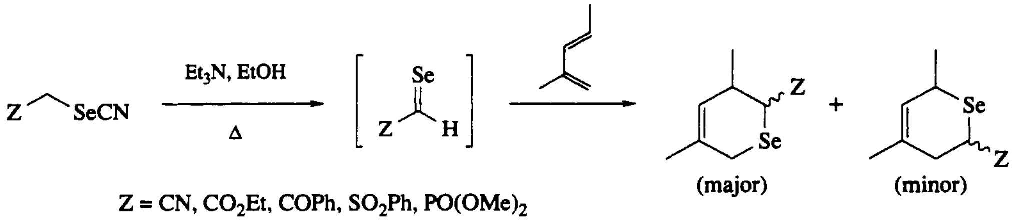
Z
SeCN
$Et_3N$, EtOH
Δ
Se
Z
H
Z
Se
+
Se
Z
(major)
(minor)

(106)

Z = CN, $CO_2Et$, COPh, $SO_2Ph$, $PO(OMe)_2$

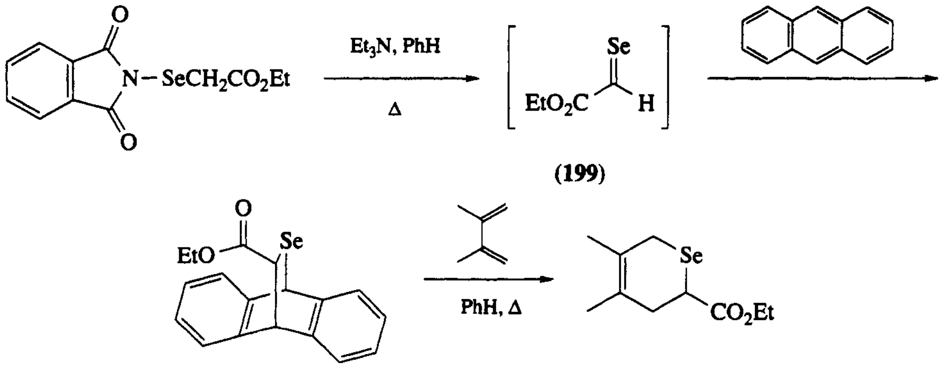
O
N
$-SeCH_2CO_2Et$
O
$Et_3N$, PhH
Δ
Se
$EtO_2C$
H
(199)
O
EtO
Se
PhH, Δ
Se
$CO_2Et$

(200)

(107)

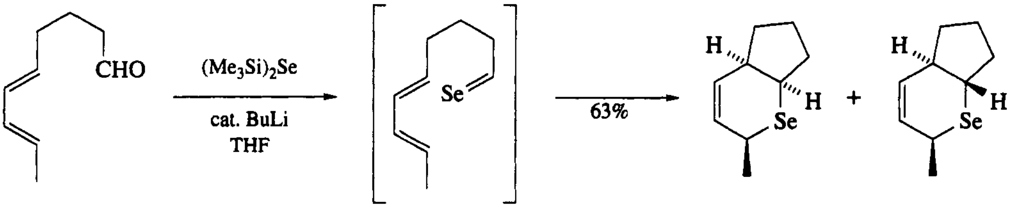
CHO
$(Me_3Si)_2Se$
cat. BuLi
THF
Se
63%
H
H
Se
+
H
H
Se
65:35

(108)

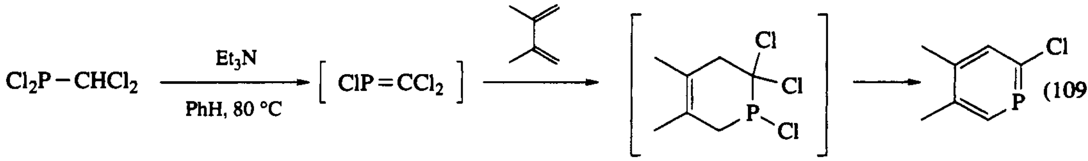
$Cl_2P-CHCl_2$
$Et_3N$
PhH, 80 °C
$ClP=CCl_2$
Cl
Cl
P
Cl
Cl
P

(109)

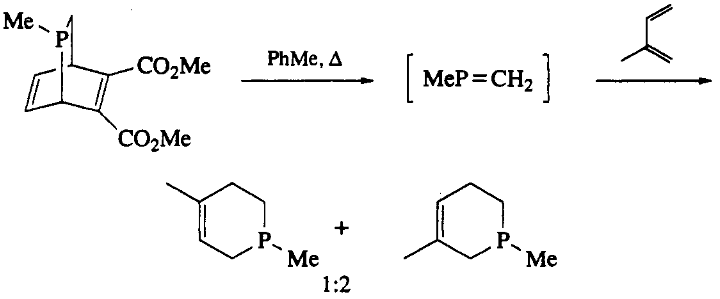
Me
P
$CO_2Me$
$CO_2Me$
PhMe, Δ
$MeP=CH_2$
P
Me
+
P
Me
1:2

(110)

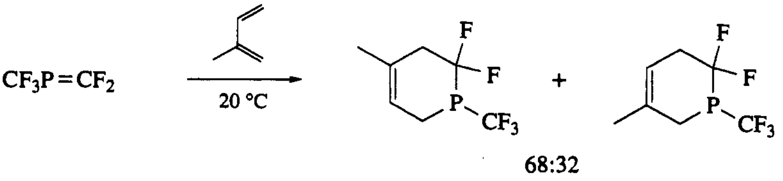
$CF_3P=CF_2$
20 °C
F
F
P
$CF_3$
+
F
F
P
$CF_3$
68:32

(111)

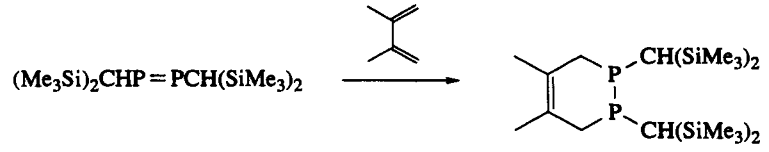
(112)

### 4.2.11 PHOSPHORUS-CONTAINING DIENOPHILES

Multiply bonded phosphorus compounds are often reactive as heterodienophiles. However, this is a diffuse area of research and little systematic study of these Diels–Alder reactions has been done. A complete listing of the various types of phosphorus dienophiles is beyond the scope of this review. Some of this material is available in previous summaries.[1] Selected representative examples of recent activity in this area is given in equations (109),[186] (110),[187] (111)[188] and (112).[189]

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# 4.3
# Heterodiene Additions

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## 4.3.1 INTRODUCTION

In 1906, Wieland described the formation of 1:1 dimerization products of selected conjugated dienes under thermolysis conditions in the first report of a [4 + 2] cycloaddition reaction.[1] Albrecht's concurrent investigation of the reaction of cyclopentadiene with *p*-benzoquinone resulted in the observed formation of a 1:1 as well as a 2:1 diene:quinone adduct,[2] the structures of which were determined by Diels and Alder.[3] As a consequence of subsequent comprehensive studies,[7,9] Diels and Alder defined the fundamental structural,[3,4] regiochemical (*ortho/para* effect),[5] and stereochemical (*endo* addition, *cis* principle)[5,6,9] features of this reaction that now bears their names.[7–9] In the intervening time, the Diels–Alder reaction has been the continued subject of extensive preparative,[10–45] mechanistic,[44–49] and theoretical studies[50–54] that have led to the detailed understanding of the factors governing the rate, regioselectivity, and diastereoselectivity of the pericyclic [4 + 2] cycloaddition reaction. Perhaps more than any single reaction in organic chemistry, the Diels–Alder reaction has served to demand mechanistic studies and theoretical models of sufficient accuracy to accommodate the experimental observations; the widespread use of the Diels–Alder reaction in organic synthesis has continued to demonstrate the elegance and efficiency with which it may be employed in the stereocontrolled preparation of substituted six-membered carbocyclic and heterocyclic systems.

The Diels–Alder reaction may be subclassified into three types of [4 + 2] cycloaddition reactions: (1) the normal Diels–Alder reaction appropriately referred to as a $\mathrm{HOMO_{diene}}$-controlled [4 + 2] cycloaddition reaction; (2) the neutral Diels–Alder reaction; and (3) the inverse electron demand or $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reaction (Figure 1). Historically, it has been the normal or $\mathrm{HOMO_{diene}}$-controlled Diels–Alder reaction comprised of the [4 + 2] cycloaddition reaction of an electron-rich diene and an electron-deficient dienophile that has serviced the preparative needs of organic chemistry and has occupied the central focus of mechanistic and theoretical studies. Pertinent to the topic of this chapter and the inherent electron-deficient nature of all fundamental heterodienes (Table 1), the $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reaction possesses a characteristic rate acceleration and high levels of predictable regio- and diastereo-control comparable with those observed in the $\mathrm{HOMO_{diene}}$-controlled Diels–Alder reaction.

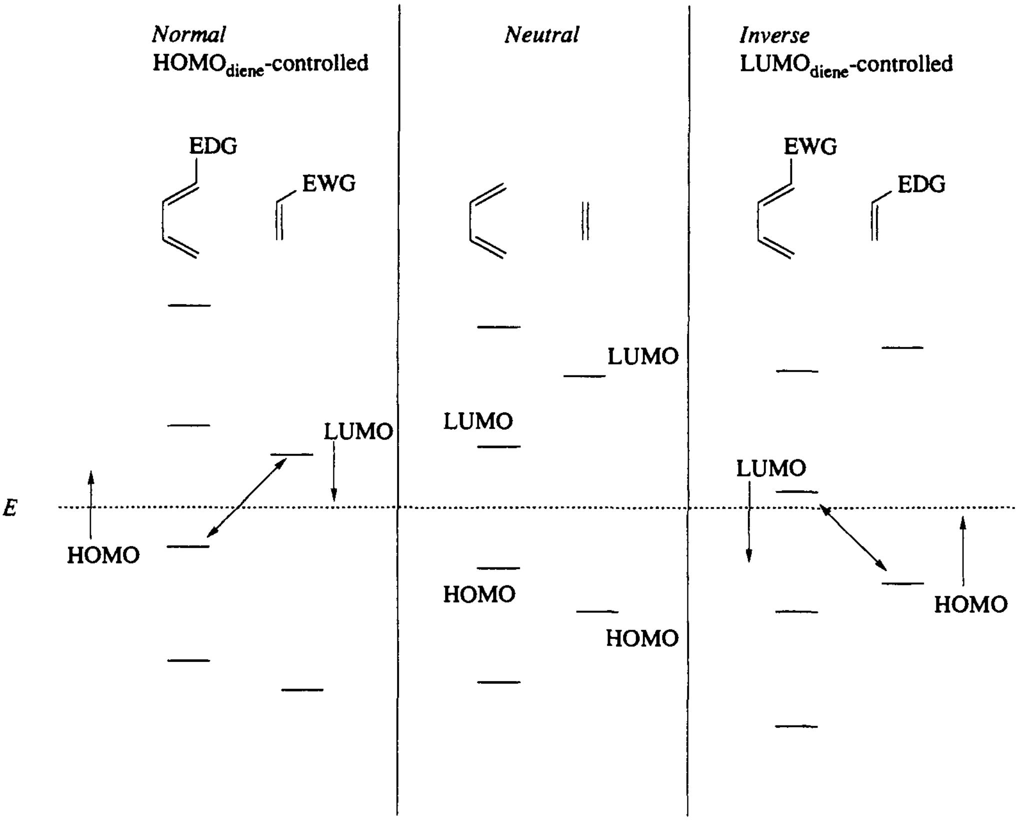

Figure 1

Table 1 Experimental Ionization Potentials (IP), Theoretical Highest Occupied π Orbital (HOMO), Experimental Electron Affinities (EA), and Theoretical Lowest Unoccupied π Orbital (LUMO) of Fundamental Heterodienes[a]

| *Diene* | *IP*[b] | *HOMO (3-21G)*[c] | *–EA*[d] | *LUMO (3-21G)*[c] |
|---|---|---|---|---|
| $H_2C{=}CH{-}CH{=}CH_2$ | –9.2 | –8.9 | 0.6 eV | 3.4 |
| $H_2C{=}CH{-}CH{=}O$ | –10.8 | –10.8 | <0.0 | 2.6 |
| $H_2C{=}CH{-}CH{=}OH^+$ | — | –23.7[e] | — | –6.5[e] |
| $H_2C{=}CH{-}CH{=}NH$ | — | –9.9 | — | 2.9 |
| $H_2C{=}CH{-}CH{=}S$ | — | –9.4 | — | 0.7 |
| $H_2C{=}CH{-}N{=}CH_2$ | — | –9.2 | — | 2.9 |
| $H_2C{=}CH{-}N{=}O$ | — | –11.0 | — | 1.6 |
| $O{=}CH{-}CH{=}O$ | –13.9 | –14.1 | — | 1.5 |

[a] All values in eV. [b] Taken from ref. 55. [c] Taken from ref. 56. [d] Taken from ref. 57. [e] Protonated acrolein; taken from ref. 58; CINDO/2 values are reported.

Although the early examples of the 4π participation of heterodienes in [4 + 2] cycloaddition reactions describe their reactions with electron-deficient alkenes, *e.g.* the thermal dimerization of α,β-unsaturated carbonyl compounds,[55] the introduction of one or more heteroatoms into the 1,3-butadiene framework does convey electrophilic character to the heterodiene. Consequently, such systems may be expected to participate preferentially in $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions with electron-rich, strained, or simple alkene and alkyne dienophiles. The complementary substitution of the heterodiene with one or more electron-withdrawing substituents further lowers the heterodiene $E_{\text{LUMO}}$, accelerates the rate of heterodiene participation in the $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reaction, and enhances the observed regioselectivity of the [4 + 2] cycloaddition reaction.[15]

The noncomplementary substitution of the heterodiene with electron-withdrawing substituents significantly lowers the heterodiene $E_{\text{LUMO}}$, accelerates its rate of reaction in a $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reaction, and in selected instances enhances the *endo* selectivity of heterodiene Diels–Alder reaction.[15,60,61]

The complementary substitution of the heterodiene with one or more strongly electron-donating substituents raises the heterodiene $E_{\text{HOMO}}$ and in selected instances has proven sufficient to promote its 4π participation in $\text{HOMO}_{\text{diene}}$-controlled Diels–Alder reactions.[15] The combined use of a nucleophilic heterodiene and reactive, electrophilic alkenes, *e.g.* ketenes, permits the observation of Diels–Alder products often formed in competition with [2 + 2] cycloaddition products and represents examples of stepwise [4 + 2] cycloaddition reactions proceeding with zwitterionic intermediate generation.

The entropic assistance provided in the intramolecular Diels–Alder reaction often is sufficient to promote heterodiene 4π participation in poorly matched [4 + 2] cycloaddition reactions, including those with unactivated and electron-deficient dienophiles.[15,30–34]

The use of a range of modified reaction conditions including the use of protic acids or conventional and nonconventional Lewis acid catalysts,[62] pressure-promoted reaction conditions,[63,64] cation-radical catalysts,[65] and dry-state adsorption reaction conditions[66] has been employed to accelerate the 4π participation of sensitive heterodienes in thermally slow or problematic Diels–Alder reactions. The former two techniques have proven useful for promoting the typically poor reactions of simple, unactivated 1-oxa-1,3-butadienes or acyclic azadienes.

## 4.3.2 OXABUTADIENES

### 4.3.2.1 1-Oxa-1,3-butadienes

Since the disclosures that the thermal dimerizations of acrolein and methyl vinyl ketone provide the 3,4-dihydro-2*H*-pyrans (**1**, **2**)[59] derived from 4π and 2π participation of the α,β-unsaturated carbonyl compound in a Diels–Alder reaction, an extensive series of related observations have been detailed. This work has been the subject of several comprehensive reviews[15,24,27,44] including the Desimoni and Tacconi extensive tabular compilation of work through 1974. Consequently, the prior reviews should be consulted for thorough treatments of the mechanism, scope, and applications of the [4 + 2] cycloaddition reactions of α,β-unsaturated carbonyl compounds. The [4 + 2] cycloaddition reactions of 1-oxa-1,3-butadienes with their 4π participation in the Diels–Alder reaction exhibit predictable regioselectivity with the preferential or exclusive formation of 2-substituted 3,4-dihydro-2*H*-pyrans (equation 1). The exceptions to the predicted regioselectivity that have been observed involve the poorly matched [4 + 2] cycloaddition reaction of an electron-deficient 1-oxa-1,3-butadiene with an electron-deficient dienophile, *e.g.* methyl crotonate or methacrolein.[24,68,69] Rigorous or simplified theoretical treatments of the [4 + 2] cycloaddition reaction of 1-oxa-1,3-butadienes predict the preferential formation of 2-substituted 3,4-dihydro-2*H*-pyrans and accommodate the preferred *endo* approach of the reactants in which the carbon–carbon bond formation is more advanced than carbon–oxygen bond formation, *i.e.* a concerted but nonsynchronous [4 + 2] cycloaddition reaction.[67]

Simple α,β-unsaturated aldehydes, ketones, and esters ($R = CO_2Me \gg H > \text{alkyl, aryl} \gg OR$; equation 1)[15,60] preferentially participate in $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions with electron-rich, strained, and selected simple alkene and alkyne dienophiles,[15,24] although the thermal reaction conditions required are relatively harsh (150–250 °C) and the reactions are characterized by the competitive dimerization and polymerization of the 1-oxa-1,3-butadiene. Typical dienophiles have included enol ethers, thioenol ethers, alkynyl ethers, ketene acetals, enamines, ynamines, ketene aminals, and selected simple alkenes; representative examples are detailed in Table 2.[15,24] The most extensively studied reaction in the series is the [4 + 2] cycloaddition reaction of α,β-unsaturated ketones with enol ethers and Desimoni,

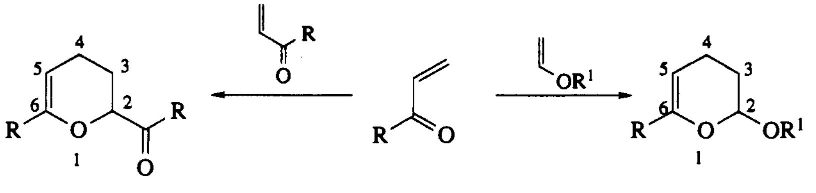

(1)

(1) R = H
(2) R = Me

Tacconi and coworkers have conducted the most thorough studies to date.[70] Characteristic of the [4 + 2] cycloadditions of enol ethers with α,β-unsaturated carbonyl compounds, the Diels–Alder reactions of 4-arylidene-5-pyrazolones proceed with the maintenance of dienophile alkene geometry preferentially through an *endo* cycloaddition transition state (equation 2). Good correlations of the $\text{LUMO}_{\text{pyrazolone}}$ with kinetic cycloaddition rates were observed, thereby confirming the 1-oxa-1,3-butadiene 4π participation in $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions under FMO control, although Sustmann's approximations of perturbation theory did not adequately accommodate the experimental observations. As can now be intuitively anticipated, pyrazolone C-3 substituents ($R^2$) have no effect on the rate of reaction; increasing the electron-withdrawing character of the substituent $X^2$ increased the rate of reaction and a good correlation between log *k* (reaction rate) and $\sigma(X^2)$ was observed; increasing the electron-withdrawing character of the substituent $X^1$ increased the reaction rate and a good correlation between log *k* and $\sigma^+(X^1)$ was observed; and increasing the electron-donating ability of $R^1$ increased the rate of [4 + 2] cycloaddition and a good correlation between log *k* and $\sigma^*(R^1)$ was observed.

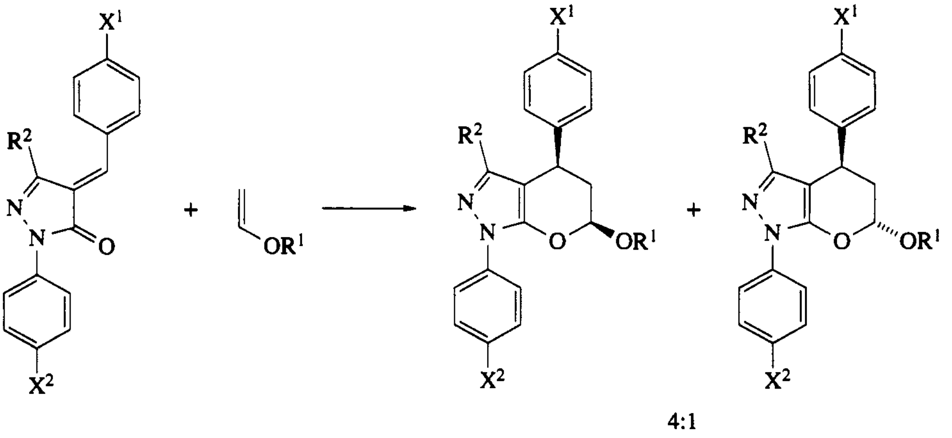

(2)

A number of experimental techniques have been employed to compensate for the poor conversions and include the use of a substantial excess of diene, addition of a free radical inhibitor, Lewis acid catalysis,[15] and pressure-promoted reaction conditions.[63] The latter two techniques have been used to conduct successfully the [4 + 2] cycloaddition reactions under mild thermal conditions (25–100 °C) and it is surprising that these techniques have not been applied more extensively. Representative results are summarized in Table 3 and common problems accompanying the use of Lewis acid catalysts have been cycloadduct C-2 epimerization or decomposition, as well as the intervention of stepwise addition–cyclization reactions with the interception of zwitterionic intermediates. Lewis acid coordination of the α,β-unsaturated carbonyl nonbonding electrons will result in the lowering of the energies of its π-orbitals (*cf.* Table 1) and redistribution of its orbital electron densities. In instances where C-2 epimerization has been avoided, the Lewis acid-catalyzed [4 + 2] cycloaddition reaction of 1-oxa-1,3-butadienes with electron-rich dienophiles proceeds at a substantially faster rate than the uncatalyzed reaction ($\leq 10^6$ acceleration), with increased regio- and diastereo-selectivity that may be attributed to a decrease in the $\text{LUMO}_{\text{diene}}$–$\text{HOMO}_{\text{dienophile}}$ energy separation (*cf.* Table 1 and Table 5, rate), the increased polarization of the diene (Δ C-4/O-1 coefficient, regioselectivity), and the enhanced secondary orbital overlap achieved with cycloaddition through an *endo* transition state (increased C-2 coefficient, diastereoselectivity) (Figure 2).[58] Similarly, liquid high-pressure techniques have proven useful in increasing the rate and diastereoselectivity of the [4 + 2] cycloaddition reaction of simple or activated

**Table 2** Representative [4 + 2] Cycloaddition Reactions of Simple 1-Oxa-1,3-butadienes

| *Reactants* | | *Conditions* | *Product* | *Yield (%)* | *Natural product* | *Ref.* |
|---|---|---|---|---|---|---|
| 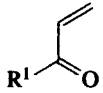 | 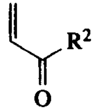 | | 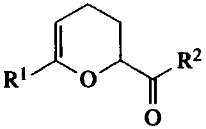 | | 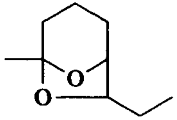 Brevicomin | |
| $R^1$ = Me | $R^2$ = H | — | | — | | 74 |
| $R^1$ = H | $R^2$ = H | — | | | | 75 |
| $R^1$ = Me | $R^1$ = Me | — | | | | 69, 76 |
| $R^1$ = Me | $R^2$ = Me | 185 °C, 2 h | | | 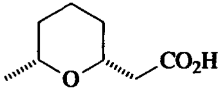 | 77 |
| $R^1$ = H | $R^2$ = H | — | | | 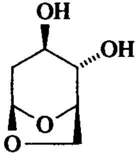 | 78 |
| $R^1$ = Me | $R^2$ = Me | — | | | 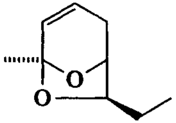 | 69, 79 |
| $R^1$ = H | $R^2$ = H | — | | | | 75 |
| 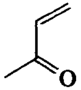 | 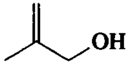 | | 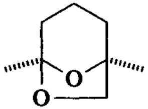 | | 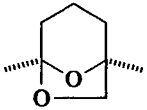 Frontalin | |
| | | | | 6–7 | | 80 |
| | | | | 35–40 | | 81 |

**Table 2** *(continued)*

| *Reactants* | | *Conditions* | *Product* | *Yield (%)* | *Natural product* | *Ref.* |
|---|---|---|---|---|---|---|
| 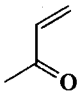 | 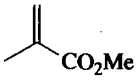 | PhH, 200 °C, 2 h | 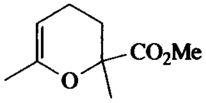 | | 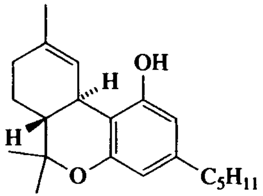 | 82 |
| 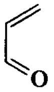 | 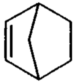 | 190 °C | 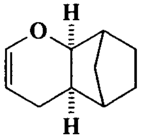 | 44 | 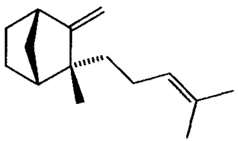<br>β-Santalene | 83 |
| 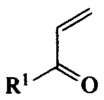 | 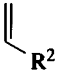 | | 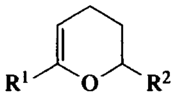 | | 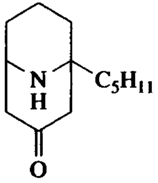<br>Adaline | |
| $R^1$ = Me | $R^2$ = SPh | 160 °C, 1 h | | 73 | Brevicomin | 84 |
| $R^1$ = H | $R^2$ = $C_5H_{11}$ | 190 °C, 25 h | | 50 | Massoia lactone | 85 |
| $R^1$ = $C_5H_{11}$ | $R^2$ = OMe | 180 °C, 40 h | | *ca.* 60 | Adaline | 86 |
| $R^1$ = Me | $R^2$ = $OPr^i$ | — | | | β-L-Boivinoside | 87 |

**Table 2** *(continued)*

| *Reactants* | *Conditions* | *Product* | *Yield (%)* | *Natural product* | *Ref.* |
|---|---|---|---|---|---|
| 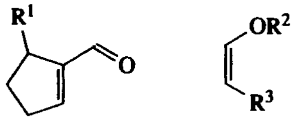 | | 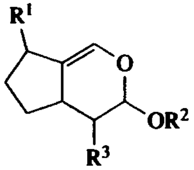 | | 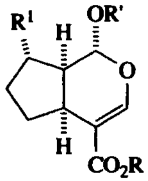 R1<br>H<br>OR'<br>O<br>H<br>CO2R | |
| $R^1 = H, R^2 = Et, R^3 = H$ | 185 °C | | 95 | Iridoids | 88 |
| $R^1 = Me, R^2 = Pr^i, R^3 = Me$ | 130 °C, 48 h | | 42 | Iridomymecin | 89 |
| $R^1 = Me, R^2 = Me, R^3 = CH_2OMe$ | 200 °C | | 47 | (–)-Valerainine<br>(–)-Tecostidine, (–)-actinidine | 90 |

α,β-unsaturated carbonyl compounds (Table 3). The rate acceleration of the pressure-promoted intermolecular Diels–Alder reaction can be attributed to the substantial decrease in the volume of activation that accompanies the formation of the [4 + 2] cycloaddition transition state ($-\Delta V^{\ddagger} > 30$ cm3 $\text{mol}^{-1}$, all-carbon Diels–Alder reaction; $-\Delta V^{\ddagger} = 20\text{–}26\ \text{cm}^3\ \text{mol}^{-1}$, heterodiene Diels–Alder reaction, rate);[63,71,72] the increased diastereoselectivity may be attributed to the added difference in the activation volume for formation of the *endo versus exo* transition state ($-\Delta\Delta V^{\ddagger}$ *endo:exo* = $5.8 \pm 0.5\ \text{cm}^3\ \text{mol}^{-1}$, diastereoselectivity).[73] Recent observations have suggested that this increased *endo* diastereoselectivity is enhanced further with *cis*-1,2-disubstituted dienophiles and the accompanying additional difference in the volume of activation between the reaction paths leading to the *endo* and *exo* diastereomers due to the additional dienophile C-2 substituent.[61] This effect overrides the rate deceleration due to the presence of the added destabilizing steric interactions that accompany the *endo* cycloaddition.

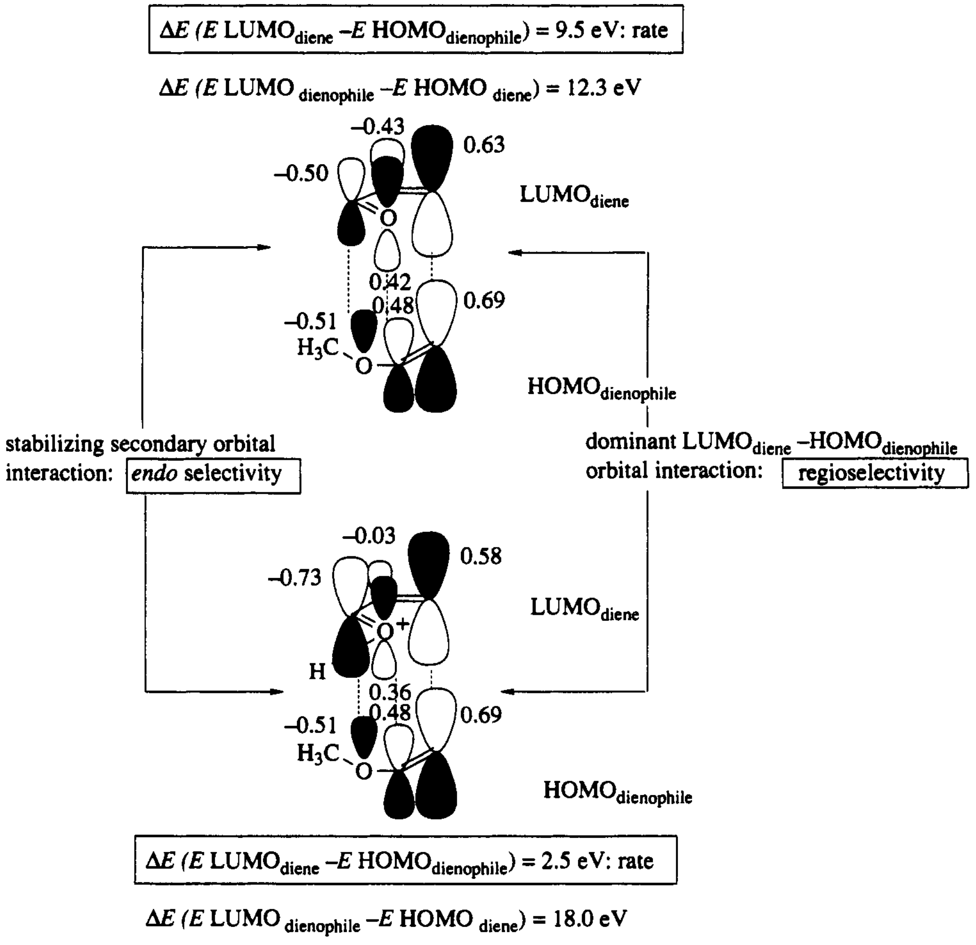
ΔE (E LUMO$_{\text{diene}}$ –E HOMO$_{\text{dienophile}}$) = 9.5 eV: rate
ΔE (E LUMO$_{\text{dienophile}}$ –E HOMO$_{\text{diene}}$) = 12.3 eV
–0.43
0.63
–0.50
O
LUMO$_{\text{diene}}$
0.42
0.48
–0.51
0.69
H$_3$C
O
HOMO$_{\text{dienophile}}$
stabilizing secondary orbital interaction: endo selectivity
dominant LUMO$_{\text{diene}}$ –HOMO$_{\text{dienophile}}$ orbital interaction: regioselectivity
–0.03
0.58
–0.73
O+
LUMO$_{\text{diene}}$
H
0.36
0.48
–0.51
0.69
H$_3$C
O
HOMO$_{\text{dienophile}}$
ΔE (E LUMO$_{\text{diene}}$ –E HOMO$_{\text{dienophile}}$) = 2.5 eV: rate
ΔE (E LUMO$_{\text{dienophile}}$ –E HOMO$_{\text{diene}}$) = 18.0 eV

**Figure 2** Thermal and (Lewis) acid catalyzed LUMO$_{\text{diene}}$-controlled [4+2] cycloaddition reaction of acrolein and methyl vinyl ether; AM1 results (Table 5)

### 4.3.2.2 Electron-deficient 1-Oxa-1,3-butadienes

The most successful approach to implementing the 4π participation of α,β-unsaturated carbonyl compounds in intermolecular Diels–Alder reactions has employed dienes substituted with a C-3 electron-withdrawing group. The additional C-3 electron-withdrawing substituent substantially lowers the 1-oxa-1,3-butadiene $E_{\text{LUMO}}$, thereby increasing the [4 + 2] cycloaddition reaction rate, increases the magnitude of the differences in the O-1/C-4 LUMO coefficients, thereby enhancing the regioselectivity of the cycloaddition reaction, and maintains a large C-2 LUMO coefficient, thus maintaining the diastereoselectivity (*endo* addition) of the cycloaddition reaction (Table 5). In addition, C-3 substitution of the heterodiene may increase the relative stability of the cisoid *versus* transoid diene conformation and in

**Table 3** Representative Lewis Acid Catalyzed and Pressure-promoted [4 + 2] Cycloaddition Reactions of 1-Oxa-1,3-butadienes

| *Reactants* | *Conditions* | *Product(s)* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|
| 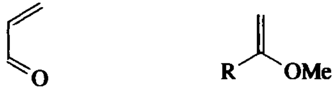 | | 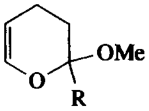 | | | 91 |
| R = H | 140 °C, 12 h | | 44 | | |
| R = H | 90 °C, 0.5 h, cat. $ZnCl_2$ | | 55 | | |
| R = Me | 60 °C, 1.5 h, cat. $ZnCl_2$ | | 61 | | |
| 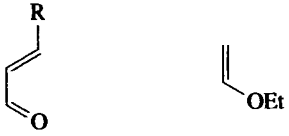 | Yb(fod)$_3$, 25 °C, neat | 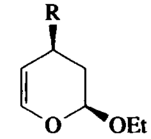 | 60–80 | *endo* product only | 92 |
| 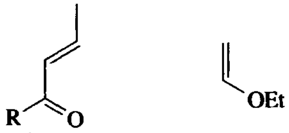 | | 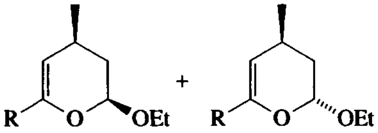 | | | 93 |
| R = H | $Et_2O$, 75 °C, 15 kbar | | 89 | 100% endo | |
| R = Me | $Et_2O$, 110 °C, 15 kbar | | 68 | 10:1 | |
| 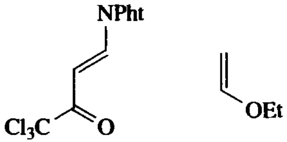 | | 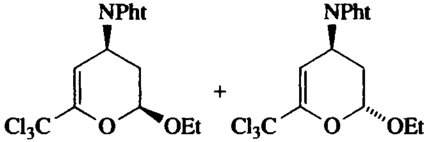 | | | 72 |
| | $CH_2Cl_2$, 90 °C, 1 atm | | | 1.7:1 | |
| | $CH_2Cl_2$, 60 °C, 1 atm | | | 2.2:1 | |
| | $CH_2Cl_2$, 60 °C, 6.5 kbar | | | 6.1:1 | |
| | $CH_2Cl_2$, 0 °C, 6.5 kbar | | | 13.6:1 | |

Table 3 *(continued)*

| *Reactants* | *Conditions* | *Product(s)* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|
| 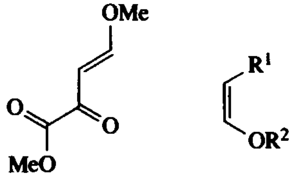 OMe<br>O<br>O<br>MeO<br>R1<br>OR2 | | 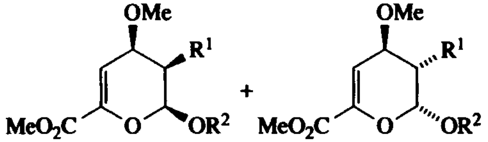 OMe<br>R1<br>MeO2C<br>O<br>OR2<br>+<br>OMe<br>R1<br>MeO2C<br>O<br>OR2 | | | 61 |
| $R^1 = H, R^2 = Et$ | 110 °C, 1 atm | | 48 | 1.8:1 | |
| | 25 °C, 13 kbar | | 82 | 5.7:1 | |
| | −78 °C, <5 min, cat. $EtAlCl_2$ | | 75 | 0.8:1 | |
| | 25 °C, florisil (DSAC) | | [a] | >45:1 | 94 |
| $R^1 = H, R^2 = CH_2Ph$ | 25 °C, 13 kbar | | 69 | 6.5:1 | |
| $R^1 = Me, R^2 = CH_2Ph$ | 80 °C, 1 atm | | 11 | 3.0:1 | |
| | −78 °C, <5 min, cat. $EtAlCl_2$ | | 50 | 6.0:1 | |
| | 25 °C, 9.5 kbar | | 56 | 19.0:1 | |
| $R^1 = OAc, R^2 = CH_2Ph$ | 110 °C, 1 atm | | 0 | — | |
| | 25 °C, 13 kbar | | 50 | >45:1 | |

[a] Yield not determined.

turn further increase the Diels–Alder reactivity of such dienes. These observations first pursued by Tietze[95–98] and Schmidt[110] and subsequently employed by a number of groups[15,99–101] have found considerable application (Scheme 1, Table 4). The [4 + 2] cycloaddition reaction of such dienes with electron-rich dienophiles proceeds under mild reaction conditions (0–100 °C) with: (1) exclusive regiocontrol; (2) excellent to modest diastereocontrol with preferential cycloaddition through an *endo* transition state in the absence of destabilizing steric interactions; (3) complete maintenance of the dienophile alkene geometry; and (4) little rate dependency on the solvent polarity.[102] The *endo* diastereoselectivity, the preservation of dienophile alkene geometry, and the increased reactivity of (*E*)-1-ethoxypropene *versus* (*Z*)-1-ethoxypropene $[k(E)/k(Z) = 35]$[100] toward 2-acetylcyclohex-2-enone (Table 4) have been interpreted to be consistent with and characteristic of a concerted $\mathrm{LUMO}_{\mathrm{diene}}$-controlled Diels–Alder reaction.

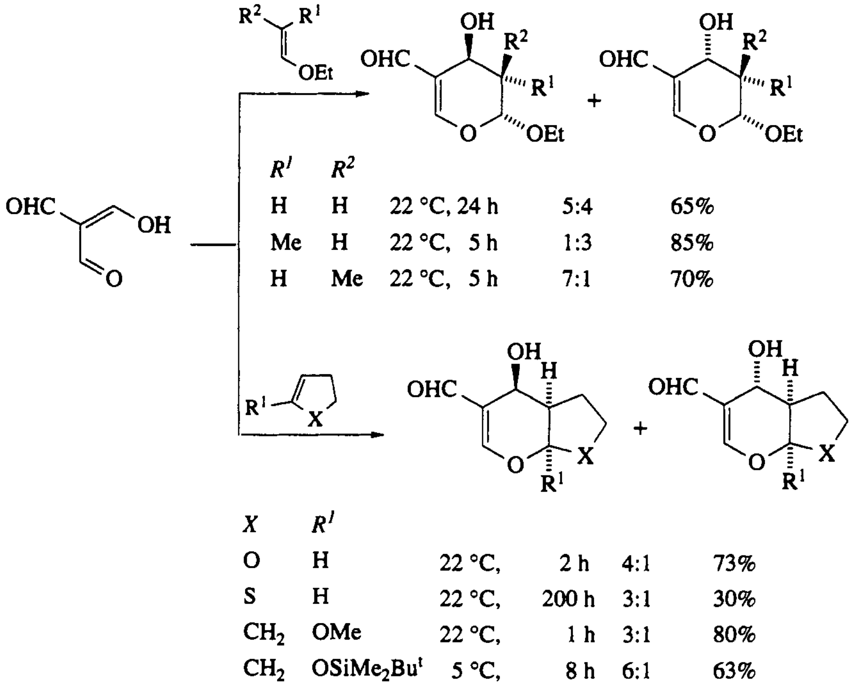

**Scheme 1**

Until recently, the reaction of α,β-unsaturated esters with electron-rich alkenes has been reported to provide cyclobutane [2 + 2] cycloaddition products. Amice and Conia first proposed the intermediacy of [4 + 2] cycloadducts in the reaction of ketene acetals with methyl acrylate,[103] and the first documented example of the 4π participation of an α,β-unsaturated ester in a Diels–Alder reaction appears to be the report of Snider and coworkers in their description of the reversible, intramolecular [4 + 2] cycloaddition reaction of 1-allylic-2,2-dimethyl ethylenetricarboxylates.[104] Subsequent efforts have demonstrated that substitution of an α,β-unsaturated ester with a C-3 electron-withdrawing substituent may permit their well-behaved 4π participation in $\mathrm{LUMO}_{\mathrm{diene}}$-controlled Diels–Alder reactions (equation 3).[15,105]

Similarly, the noncomplementary C-2[60,61,106,107] or C-4[15] addition of an electron-withdrawing substituent to the 1-oxa-1,3-butadiene serves to lower substantially the 1-oxa-1,3-butadiene $E_{\mathrm{LUMO}}$, accelerates its 4π participation in a $\mathrm{LUMO}_{\mathrm{diene}}$-controlled [4 + 2] cycloaddition reaction, maintains the *endo*-derived diastereoselectivity through the maintenance (C-4) or enforcement (C-2) of a large LUMO C-2 coefficient, and does not alter the observed [4 + 2] cycloaddition regioselectivity, although such substitution may decrease the magnitude of the difference between the O-1/C-4 LUMO coefficients (Table 5).

Characteristic of such dienes, α-keto-β,γ-unsaturated esters such as (**3**; see also Table 3 and Table 5) exhibit good thermal reactivity toward simple vinyl ethers in [4 + 2] cycloaddition reactions that proceed with exclusive regiocontrol predominately through an *endo* transition state. The *endo* selectivity increases as the reaction temperature is decreased and both the reaction rate and the *endo* selectivity increase as the reaction pressure is increased (Figure 3, Table 3). The substantial increase in the diastereoselectivity of the pressure-promoted [4 + 2] cycloaddition reaction of (**3**) with a *cis* 1,2-disubstituted dienophile has been attributed to the additional differences in the volume of activation between the reaction paths leading to the *endo* and *exo* diastereomers due to the additional *cis* C-2 dienophile sub-

**Table 4** Representative Diels–Alder Reactions of Electron Deficient 1-Oxa-1,3-butadienes

| *Reactants* | *Conditions* | *Products* | *Yield (%)* | *Product ratio* | *Ref. (application)* |
|---|---|---|---|---|---|
| 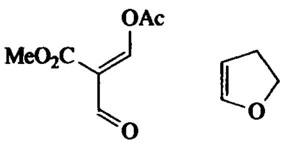 | 25 °C, 4 h | 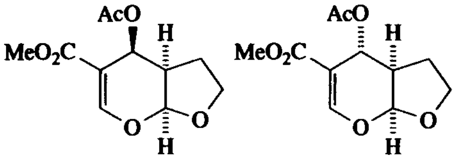 | 85 | 1:2 | 97 |
| 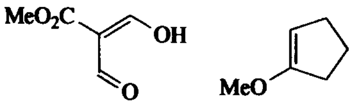 | 25 °C, 200 h | 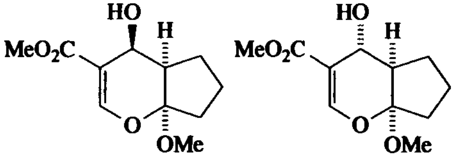 | 82 | 3:1 | 97 |
| 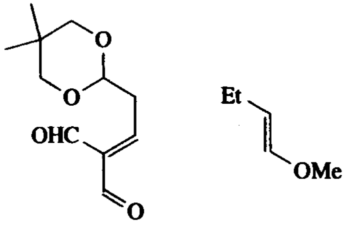 | 25 °C, 2 h | 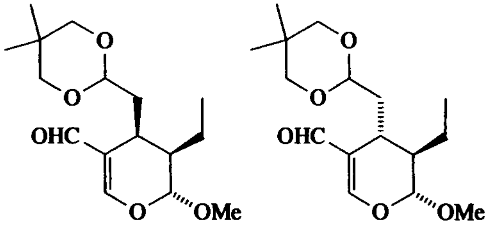 | 62 | 3:1 | 98 Secoiridoids |
| 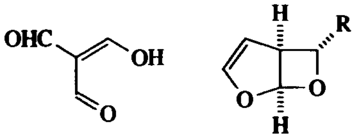 | CHCl$_3$, 4 h, 67 °C | 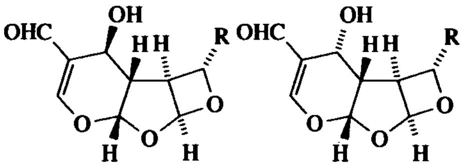 | 45 | 7:1 | 99 |

**Table 4** *(continued)*

| *Reactants* | | *Conditions* | *Products* | | *Yield (%)* | *Product ratio* | *Ref. (application)* |
|---|---|---|---|---|---|---|---|
| 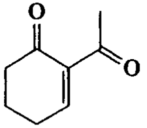 | 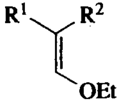 | | 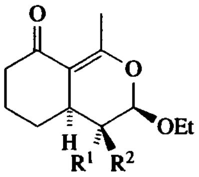 O<br>O<br>OEt<br>H<br>$R^1$<br>$R^2$ | 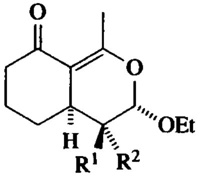 O<br>O<br>OEt<br>H<br>$R^1$<br>$R^2$ | | | 100 |
| $R^1$ = H, $R^2$ = H | | 25 °C, 24 h | | | 75 | >20:1 | |
| $R^1$ = H, $R^2$ = Me | | 25 °C, 28 d | | | 30 | 3:1 | |
| $R^1$ = Me, $R^2$ = H | | 25 °C, 48 h | | | 70 | 7:1 | |
| 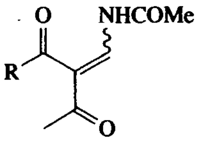 | 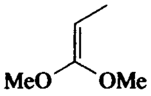 | | 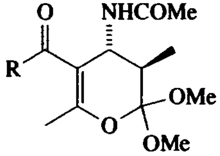 O<br>NHCOMe<br>R<br>OMe<br>O<br>OMe | 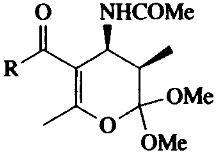 O<br>NHCOMe<br>R<br>OMe<br>O<br>OMe | | | 101 Carbapenems |
| R = OMe | | | | | 90 | 1.2:1 | |
| R = $NHC_6H_4$-4-Cl | | | | | 90 | 20:1 | |

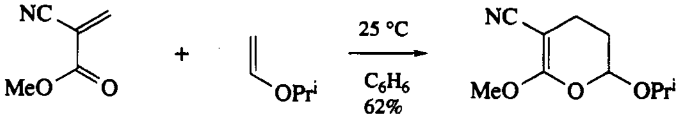

(3)

stituent, and this effect overrides the inherent rate deceleration imposed by destabilizing steric interactions that accompany the *endo* cycloaddition (Figure 3).[61]

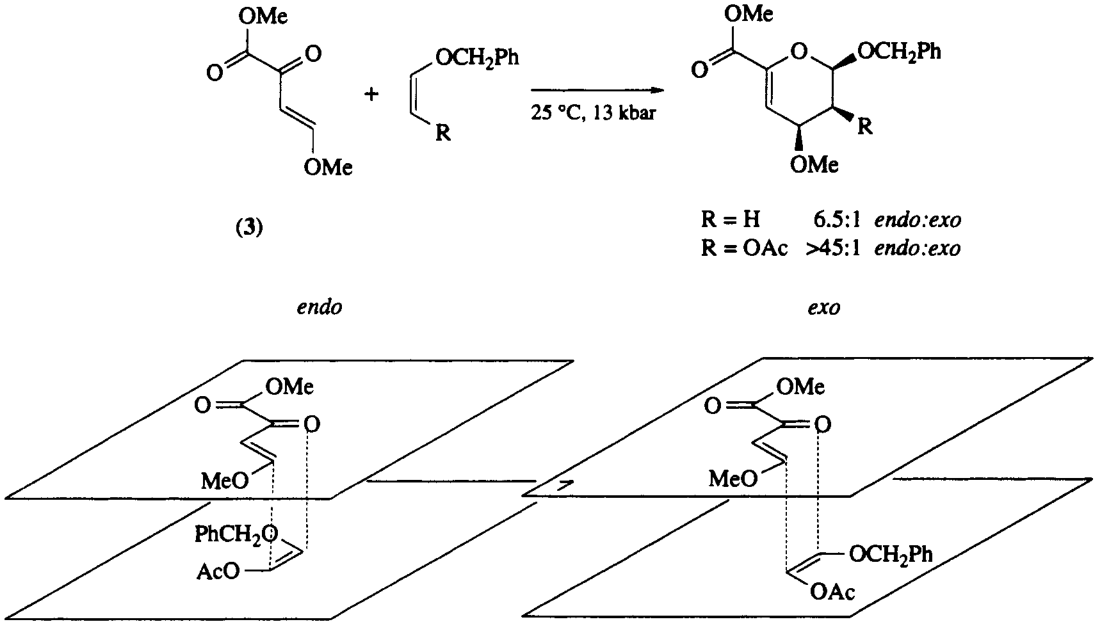

Figure 3

### 4.3.2.3 1-Oxa-1,3-butadienes Substituted with C-3, C-4 Electron-donating Substituents

The addition of a C-2 (equation 1; R = H > alkyl, aryl > OMe >> $NR_2$), C-3, or C-4 electron-donating substituent to a 1-oxa-1,3-butadiene electronically decreases its rate of $4\pi$ participation in a $LUMO_{diene}$-controlled Diels–Alder reaction (*cf.* Table 5). Nonetheless, a useful set of C-3 substituted 1-oxa-1,3-butadienes have proven to be effective dienes[107–113] and have been employed in the preparation of carbohydrates (Table 6).[114] The productive use of such dienes may be attributed to the relative increased stability of the cisoid *versus* transoid diene conformation that in turn may be responsible for the Diels–Alder reactivity of the dienes. Clear demonstrations of the anticipated [4 + 2] cycloaddition rate deceleration of 1-oxa-1,3-butadienes bearing a C-4 electron-donating substituent have been detailed (Table 6; entry 4).[114,115] In selected instances, the addition of a strong electron-donating substituent (OR, $NR_2$) to the C-4 position provides sufficient nucleophilic character to the 1-oxa-1,3-butadiene to permit the observation of [4 + 2] cycloaddition reactions with reactive, electrophilic alkenes including ketenes and sulfenes, often in competition with [2 + 2] cycloaddition reactions.[15]

### 4.3.2.4 Intramolecular 1-Oxabutadiene Diels–Alder Reactions

One of the most effective approaches to implementing the Diels–Alder $4\pi$ participation of 1-oxa-1,3-butadienes is through the use of an intramolecular [4 + 2] cycloaddition reaction.[15,30–34,95] A select set of thermal and Lewis acid-catalyzed intramolecular cycloaddition reactions of unactivated and electron-rich alkenes with α,β-unsaturated aldehydes and ketones has been detailed.[15] Two examples of the poorly matched intramolecular Diels–Alder reaction of an α,β-unsaturated aldehyde ($4\pi$ component) with an α,β-unsaturated amide ($2\pi$ component) have proven successful (190–160 °C) and may be attributed to the entropic assistance provided by the intramolecular reaction. These observations have been applied in

**Table 5** 1-Oxa-1,3-butadiene Substituent Effects on the π HOMO and LUMO[a]

| | | | Coefficients | | | | |
|---|---|---|---|---|---|---|---|
| | *E(LUMO)* | *E(HOMO)* | *O-1* | *C-2* | *C-3* | *C-4* | *CHO* |
| $H_2C{=}CH{-}CH{=}O$ | −0.04 | −10.9 | LUMO: 0.42 | −0.50 | −0.43 | 0.63 | — |
| | | | HOMO: −0.35 | −0.05 | 0.68 | 0.65 | — |
| $H_2C{=}CH{-}CH{=}OH^+$ | −7.0 | −16.6 | LUMO: 0.36 | −0.73 | −0.03 | 0.58 | — |
| | | | HOMO: −0.36 | −0.23 | 0.73 | 0.53 | — |
| $H_2C{=}C(CHO){-}CH{=}O$[b] | −0.8 | −11.3 | LUMO: 0.26 | −0.27 | −0.41 | 0.69 | −0.34 |
| | | | HOMO: −0.32 | −0.05 | 0.64 | 0.61 | −0.05 |
| $H_2C{=}CH{-}C(CHO){=}O$[c] | −0.9 | −11.1 | LUMO: 0.47 | −0.51 | −0.20 | 0.43 | −0.40 |
| | | | HOMO: −0.34 | −0.03 | 0.68 | 0.65 | 0.00 |
| $HC(CHO){=}CH{-}CH{=}O$[b] | −1.1 | −11.3 | LUMO: 0.33 | −0.34 | −0.50 | 0.52 | 0.35 |
| | | | HOMO: −0.32 | −0.05 | 0.64 | 0.62 | −0.06 |
| | *E(LUMO)* | *E(HOMO)* | *O-1* | *C-2* | *C-3* | *C-4* | *$CO_2Me$* |
| $HC(OMe){=}CH{-}CH{=}O$ | 0.05 | −9.9 | LUMO: 0.39 | −0.46 | −0.38 | 0.66 | — |
| | | | HOMO: −0.32 | 0.00 | 0.69 | 0.43 | — |
| $HC(OMe){=}CH{-}C(CO_2Me){=}O$ | −0.7 | −10.2 | LUMO: 0.46 | −0.52 | −0.22 | 0.52 | −0.28 |
| | | | HOMO: −0.31 | 0.02 | 0.69 | 0.41 | −0.01 |
| | *E(LUMO)* | *E(HOMO)* | *C-1* | *C-2* | *O-Me* | | |
| $H_2C{=}CH{-}OMe$ | 1.4 | −9.5 | LUMO: 0.72 | −0.66 | 0.21 | | |
| | | | HOMO: 0.48 | 0.69 | −0.51 | | |

[a] AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π orbital; values in eV. [b] *cis,trans* conformation. [c] *cis,trans* (dione) conformation (ref. 94).

**Table 6** Representative [4 + 2] Cycloaddition Reactions of Electron-rich 1-Oxa-1,3-butadienes

| *Reactants* | | *Conditions* | *Product* | *Yield (%)* | *Endo:exo ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| 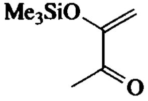 | | | 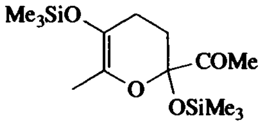 | 59 | | 107 |
| 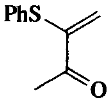 | 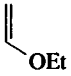 | 180 °C, 3 h | 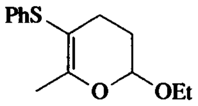 | 95 | | 109 |
| 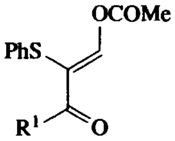 | 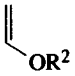 | 70–80 °C | 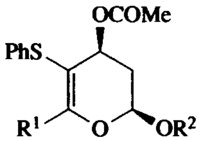 | | | 110–114 |
| $R^1 = Me$ | $R^2 = Et$ | | | 98 | >10:1 | |
| $R^1 = Me$ | $R^2 = Bn$ | | | 96 | >10:1 | |
| $R^1 = CH_2OBn$ | $R^2 = Et$ | | | 96 | >10:1 | |
| $R^1 = CH_2OPh$ | $R^2 = Et$ | | | 68 | 12.5:1 | |
| $R^1 = CO_2Me$ | $R^2 = Et$ | | | 57 | *endo* only | |
| 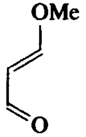 | 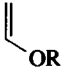 | | 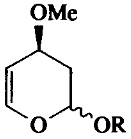 | | | |
| | R = Me | 240 °C | | 60 | | 119 |
| | R = Bu$^i$ | | | 45 | | 120 |

the total syntheses of heteroyohimboid and corynantheiod indole alkaloids (Scheme 2).[116,117] In a useful comparison, the intramolecular reaction of an electron-deficient α,β-unsaturated aldehyde (4π component) with an electron-rich enamine provided the [4 + 2] cycloadduct at room temperature (25 °C).[118] Use of an optically active amine provided predominantly one cycloadduct possessing the *cis* bicyclic dihydropyran relative stereochemistry and the absolute stereochemistry depicted in Scheme 3 derived from *si* face addition to the enamine.[119]

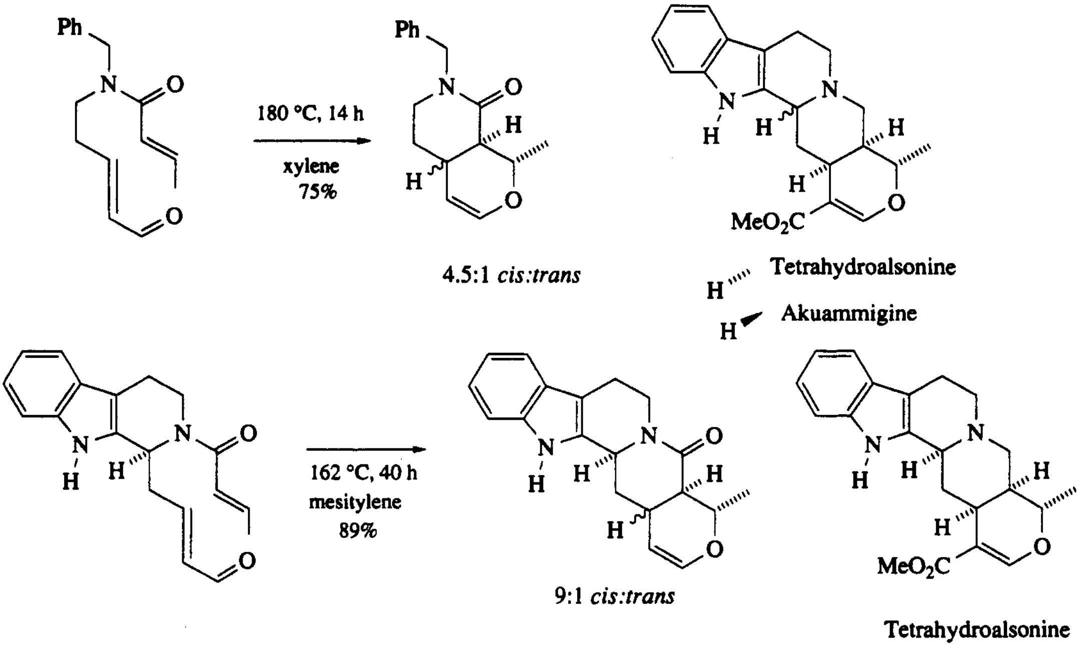
180 °C, 14 h
xylene
75%
4.5:1 cis:trans
Tetrahydroalsonine
Akuammigine
162 °C, 40 h
mesitylene
89%
9:1 cis:trans
Tetrahydroalsonine

Scheme 2

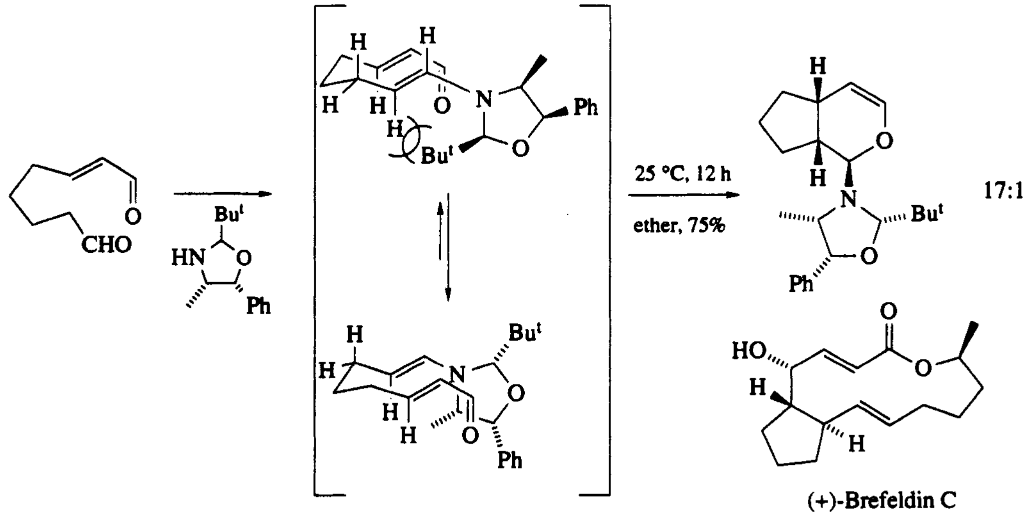
25 °C, 12 h
ether, 75%
17:1
(+)-Brefeldin C

Scheme 3

The combined use of the intramolecular version of the 1-oxa-1,3-butadiene [4 + 2] cycloaddition reaction with the use of α,β-unsaturated carbonyl compounds bearing a C-3 electron-withdrawing substituent provides effective room temperature, regio- and diastereo-selective [4 + 2] cycloaddition reactions. In a series of investigations, Tietze and coworkers have shown that alkylidene- or arylidene-1,3-dicarbonyl compounds may be obtained *in situ* through a Knoevenagel condensation (0–25 °C) catalyzed by ethylenediammonium diacetate. Without isolation, the resulting heterodienes undergo [4 + 2] cycloaddition at room temperature to provide Diels–Alder products with high or exclusive diastereocontrol ($\geq$ 90%).[95] Asymmetric induction can be effected by a stereogenic center in the connecting chain[121–123] or in the dicarbonyl compound[124,125] with high induced diastereoselectivity, *i-de* > 90%. The intramolecular cycloaddition reactions proceed with full (100%) maintenance of the alkene geometry,[126] the rate of reaction increases as the nucleophilic character of the dienophile is increased, and the rate of cycloaddition does not show a pronounced dependency on the solvent polarity, demonstrating that such cycloadditions may be regarded as concerted.[95,126] The *E*/*Z* stereochemistry of the diene carbon–carbon double bond, the length and nature of the diene–dienophile linking chain, and the alkene substitution have a pronounced effect on the rate, diastereoselectivity and regioselectivity (fused *versus* bridged cycloadduct) of the intramolecular [4 + 2] cycloaddition reaction.[15] In cases with substrates bearing a definable diene (*E*/*Z*)-alkene geometry,[127] isomerization to the (*E*)-alkene precedes cycloaddition and 6,6-*trans*-fused [4 + 2] cycloaddition products are favored with preferential cyclization through an *exo-E-anti* transition state. When unfavorable steric interactions between the diene and the connecting chain preclude formation of the *exo-E-anti* transition state, cycloaddition proceeds through an *endo-E-syn* transition state, providing the 6,6-*cis*-fused [4 + 2] cycloaddition product (Scheme 4). In such instances the lack of observation of cycloaddition through the *exo-E-anti* transition state has been attributed principally to stereoelectronic effects in which dienophile approach to the diene along a trajectory angle of approximately 109° is not permitted.[128]

Application of these observations to the total synthesis of (–)-(3*R*)- and (+)-(3*S*)-hexahydrocannabinol (Scheme 5)[123] and (3*S*)-3-hydroxyhexahydrocannabinol (Scheme 6)[95] has been described.

Although far less explored, the studies have been extended to the preparation of 6,5-fused cycloadducts. At present, the limited observations suggest that substrates bearing dienophile C-1 disubstitution or an *E*-1,2-disubstituted dienophile provide 6,5-*cis*-fused cycloaddition products with preferential cyclization through an *endo-E-syn* transition state. In contrast, substrates bearing a *Z*-1,2-disubstituted dienophile have been found to provide 6,5-*trans*-fused cycloadducts with preferential cyclization through an *exo-E-anti* transition state. Exceptions have been observed and have been related to the nature of the diene–dienophile linking chain.[128–131] The former observations have been applied in total syntheses of deoxyloganin from (*S*)-citronellal (Scheme 7),[128] (–)-kainic acid (Scheme 8)[129] and (–)-sesamolin, (–)-sesamin and (–)-acuminatolide (Scheme 9). In addition, these and related observations[132] have suggested that the biosynthesis of the loganins may proceed through a diastereoselective [4 + 2] cycloaddition reaction of the *E*-enol of a recognized biosynthetic precursor (equation 4).[133]

### 4.3.2.5 *o*-Quinones, *o*-Quinone Methides

The generation and subsequent [4 + 2] cycloaddition reactions of *o*-quinones (4π 1,4-dioxabutadiene participation)[14,24,44,134] and *o*-quinone methides[14,24,44,134] have been extensively reviewed.[15] Perhaps the most spectacular demonstration of the potential of such cycloadditions rests with the Chapman biomimetic total synthesis of carpanone (equation 5).[135] Palladium(II)-catalyzed generation and subsequent oxidation of an *o*-alkylphenol with intermediate generation of an *o*-quinone methide and *in situ* [4 + 2] cycloaddition through an *endo* transition state provided carpanone. The propensity for methide-substituted *o*-quinone methides to undergo rapid 1,5-hydrogen shift and rearomatization with *o*-hydroxystyrene generation has restricted their use to nontautomerizable *o*-quinone methides.[15] Even then the dimerization of the reactive *o*-quinone methides has proven problematic. In contrast, *in situ* generated *o*-quinone methides capable of tautomerization have been successfully employed in intramolecular [4 + 2] cycloaddition reactions,[15] and the observations have found application in the total synthesis of optically active cannabinoids (Scheme 10)[136,137] and citrans.[15] The exclusive generation of a single diastereomer possessing the *trans* ring fusion is consistent with [4 + 2] cycloaddition through an *exo-E-anti* transition state from a chair conformation possessing an equatorial methyl substituent.

### 4.3.2.6 Hetero 1-Oxabutadienes

An extensive range of hetero 1-oxabutadiene systems containing nitrogen (Section 4.3.4) and sulfur (Section 4.3.3) have been investigated and found to function as 4π components of Diels–Alder reactions.[15] In general, the incorporation of an additional heteroatom into the 1-oxabutadiene system increases its electrophilic character and facilitates its 4π participation in $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reactions with electron-rich dienophiles. Examples of such systems are presented in Figure 4.[15]

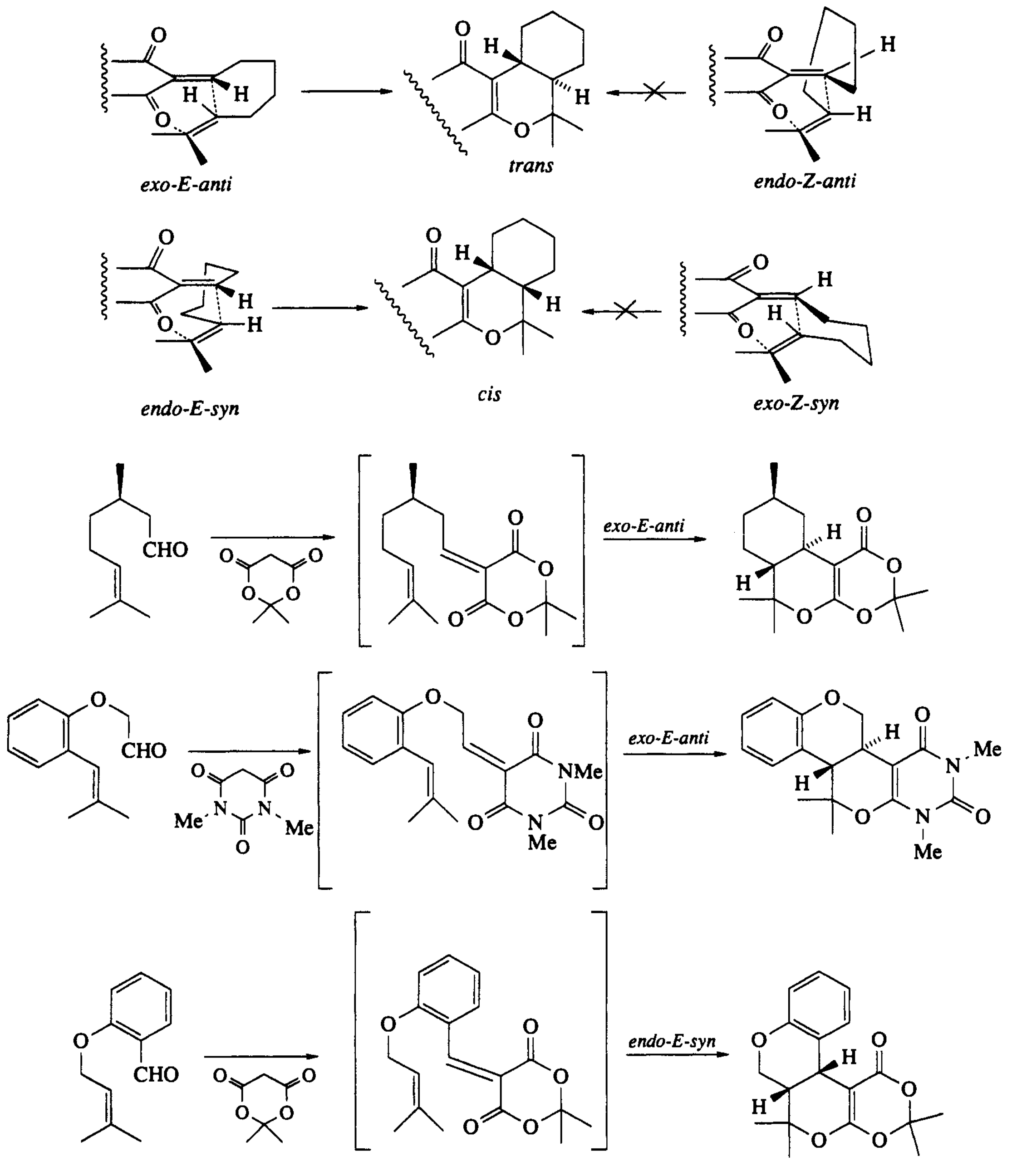

Scheme 4

### 4.3.3 THIABUTADIENES

In contrast to the thorough studies of the Diels–Alder reactions of oxa- and aza-butadienes, the [4 + 2] cycloaddition reactions of 1-thia-1,3-butadienes have not been studied extensively.[15,17,138] Although the general participation of thiabutadienes in LUMO$_{diene}$-controlled [4 + 2] cycloaddition reactions has been recognized and experimentally verified,[15] most investigations have detailed their 4π participation in HOMO$_{diene}$-controlled reactions with typical electron-deficient dienophiles. In such instances, the complementary C-2 or C-4 addition of electron-donating substituents to the 1-thia-1,3-butadiene increases the rate and regioselectivity of its 4π participation in HOMO$_{diene}$-controlled Diels–Alder reactions. With notable exceptions,[15] the LUMO$_{diene}$-controlled Diels–Alder reactions provide the expected 2-substituted 3,4-dihydro-2*H*-thiopyrans and, unlike simple 1-oxa-1,3-butadienes, the HOMO$_{diene}$-controlled Diels–

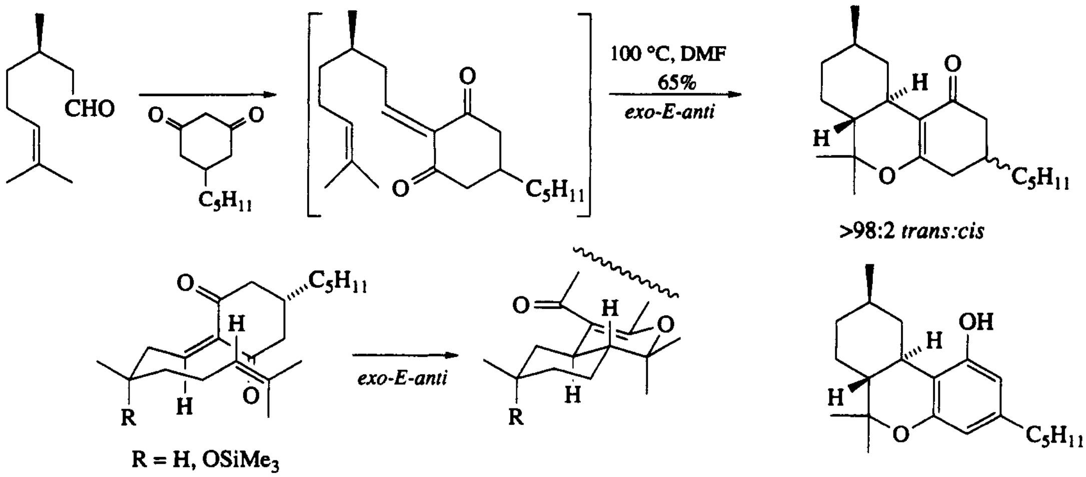

(–)-(3R)-Tetrahydrocannabinol

Scheme 5

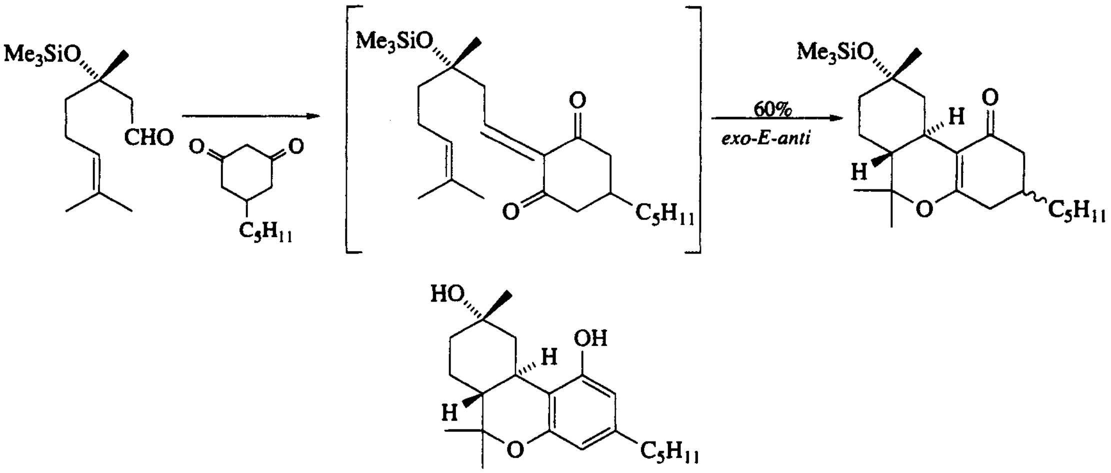

(3S)-3-Hydroxytetrahydrocannabinol

Scheme 6

Alder reactions of 1-thia-1,3-butadienes with electron-deficient or conjugated dienophiles provide 3-substituted 3,4-dihydro-2*H*-thiopyrans (equation 6). Representative Diels–Alder reactions of 1-thia-1,3-butadienes are presented in Table 7 and hetero-1-thiabutadienes that have been demonstrated to participate in [4 + 2] cycloaddition reactions are summarized in Figure 4.[15]

## 4.3.4 AZABUTADIENES

Comparable to the 1-oxabutadienes, the azabutadienes constitute a class of widely investigated heterodienes capable of productive 4π participation in [4 + 2] cycloaddition reactions. This work has been the subject of several comprehensive reviews[13–18,39–41] including recent accounts[15,21–23] that should be consulted for a thorough treatment of the mechanism, scope and applications of the [4 + 2] cycloaddition reactions of azabutadienes. Conjugated systems containing nitrogen characteristically are electron-deficient π-systems (Table 8) and exhibit an expected diminished Diels–Alder reactivity toward representative electron-deficient dienophiles and a modest Diels–Alder reactivity toward electron-rich dienophiles.

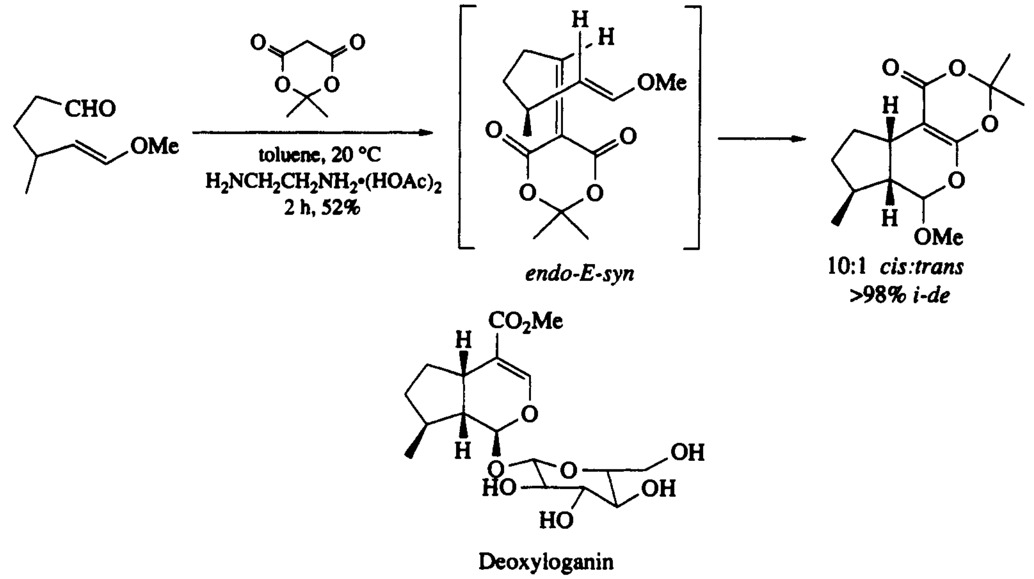
CHO
OMe
toluene, 20 °C
$H_2NCH_2CH_2NH_2{\cdot}(HOAc)_2$
2 h, 52%
endo-E-syn
10:1 cis:trans
>98% i-de
$CO_2Me$
Deoxyloganin

**Scheme 7**

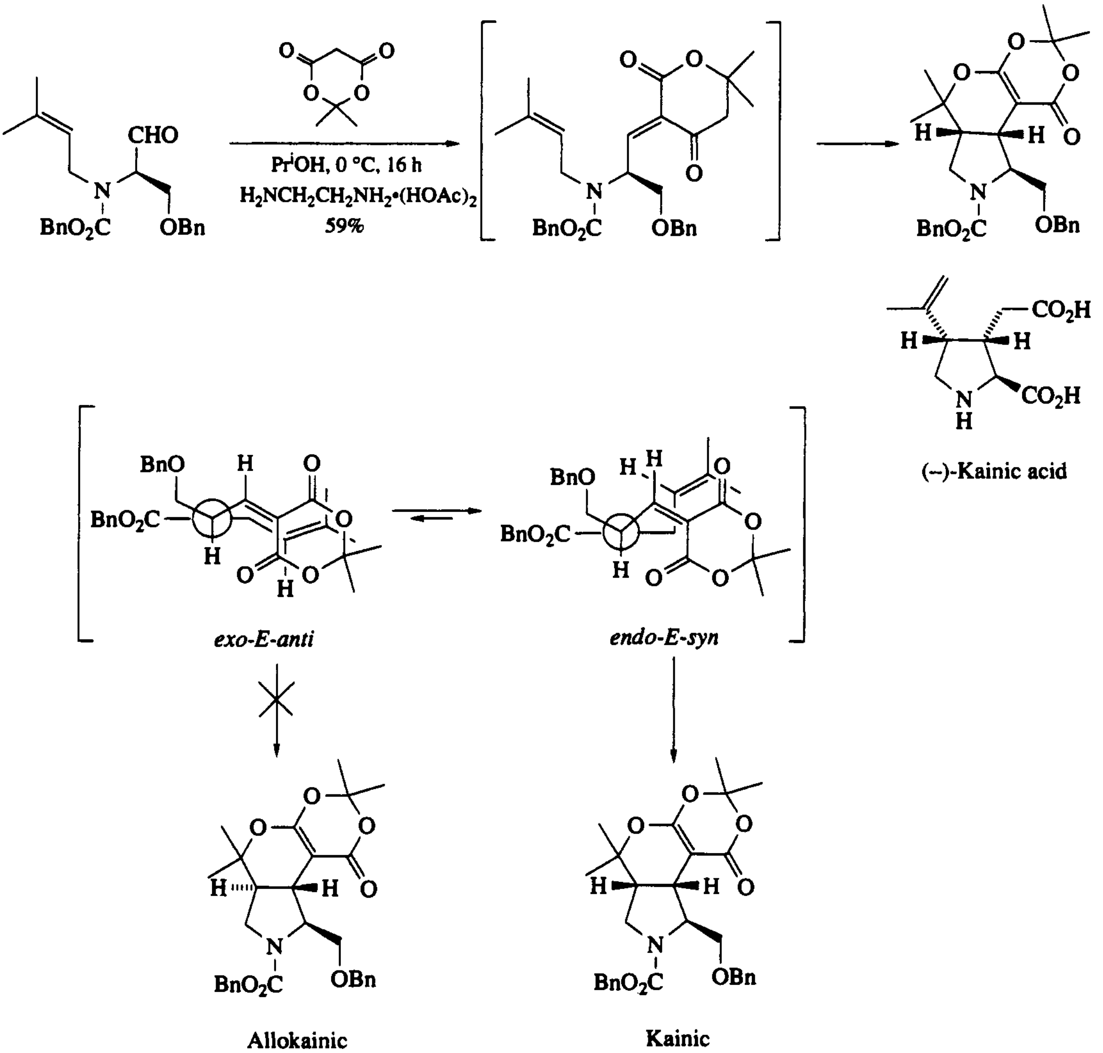
CHO
$BnO_2C$
OBn
$Pr^iOH$, 0 °C, 16 h
$H_2NCH_2CH_2NH_2{\cdot}(HOAc)_2$
59%
(–)-Kainic acid
exo-E-anti
endo-E-syn
Allokainic
Kainic

**Scheme 8**

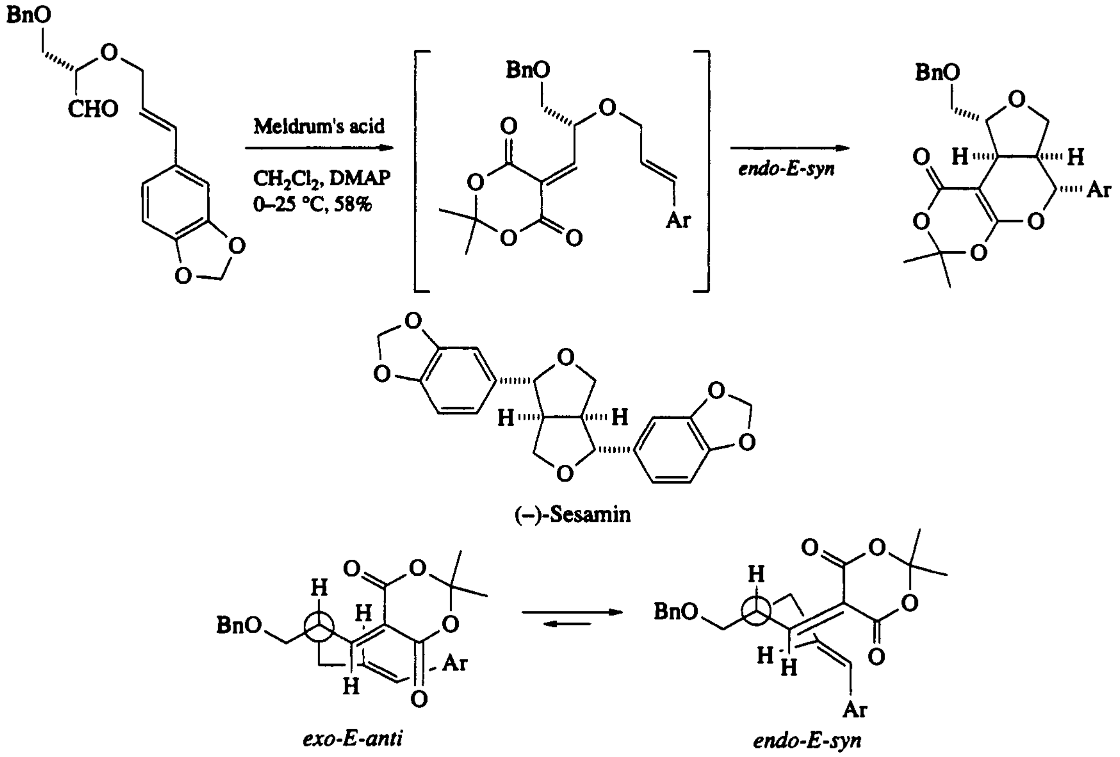
BnO
CHO
O
Meldrum's acid
CH₂Cl₂, DMAP
0–25 °C, 58%
endo-E-syn
Ar
H
(–)-Sesamin
exo-E-anti
endo-E-syn

**Scheme 9**

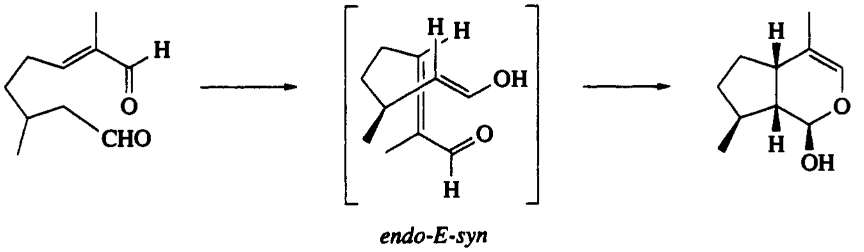
H
O
CHO
OH
endo-E-syn

(4)

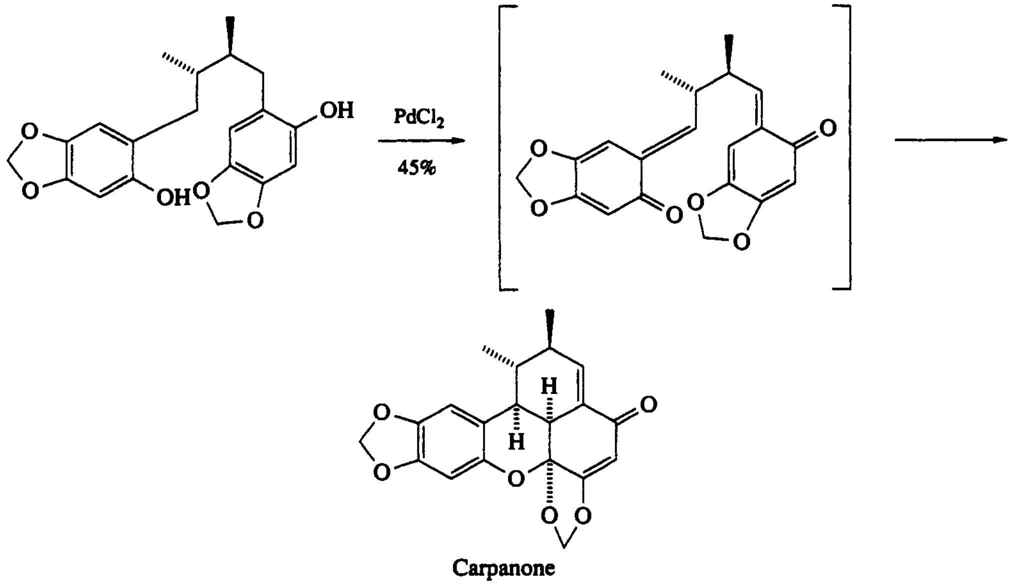
OH
PdCl₂
45%
O
H
Carpanone

(5)

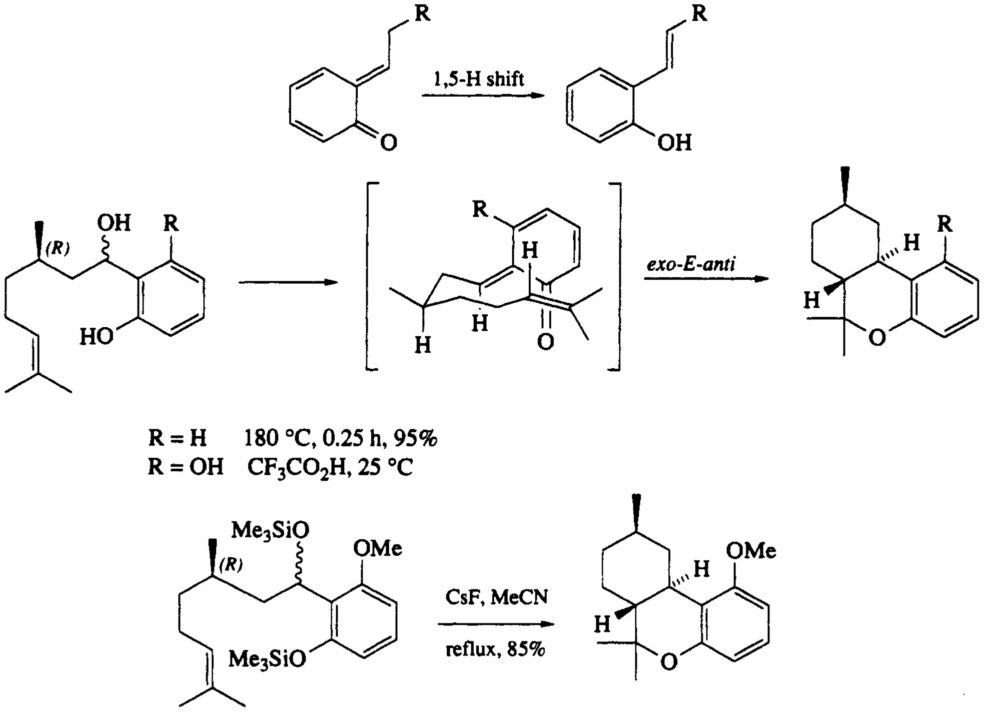

**Scheme 10**

### 4.3.4.1 1-Aza-1,3-butadienes

α,β-Unsaturated imines, simple 1-aza-1,3-butadienes, participate in Diels–Alder reactions with typical electron-deficient dienophiles preferentially through their enamine tautomer;[149] in instances where tautomerization is not accessible, [2 + 2] cycloaddition usually intervenes (equation 7).[15] Consequently, the Diels–Alder 4π participation of simple α,β-unsaturated imines rarely is observed and typically suffers low conversions, competitive imine addition, and/or imine tautomerization precluding [4 + 2] cycloaddition. A limited number of 1-aza-1,3-butadiene structural variations and modified reaction conditions have been introduced that have permitted the productive 4π participation of 1-aza-1,3-butadienes in [4 + 2] cycloaddition reactions and include the intramolecular [4 + 2] cycloaddition reactions of *in situ* generated *N*-acyl-1-aza-1,3-butadienes[150] and *in situ* generated *o*-quinomethide imines,[151] the HOMO$_{\text{diene}}$-controlled Diels–Alder reactions of α,β-unsaturated *N,N*-dimethylhydrazones,[152,153] the Lewis acid-catalyzed intramolecular [4 + 2] cycloaddition reactions of *in situ* generated 2-*t*-butyldimethylsilyloxy- and 2-trimethylsilyloxy-1-aza-1,3-butadienes,[154] and the recently detailed general 4π participation of α,β-unsaturated *N*-phenylsulfonylimines in LUMO$_{\text{diene}}$-controlled Diels–Alder reactions.[155] Table 9 summarizes recent descriptions of the use of 1-aza-1,3-butadienes in [4 + 2] cycloaddition reactions.

The complementary N-1 or C-3 substitution of an α,β-unsaturated imine with an electron-withdrawing substituent accentuates the electron-deficient nature of the 1-aza-1,3-butadiene (Table 10), accelerates the rate of its [4 + 2] cycloaddition reaction with electron-rich dienophiles in LUMO$_{\text{diene}}$-controlled [4 + 2] cycloaddition reactions through substantial lowering of the 1-aza-1,3-butadiene $E_{\text{LUMO}}$, maintains the expected regioselectivity of the cycloaddition reaction, and enhances the *endo* selectivity of the cycloaddition reaction through a substantial increase in the LUMO C-2 coefficient. In addition, a bulky electron-withdrawing N-1 azabutadiene substituent preferentially decelerates 1,2-imine addition relative to [4 + 2] cycloaddition and conveys [4 + 2] cycloaddition product stability to the reaction conditions (deactivated enamine) while enhancing the electron-deficient nature of the diene. These expectations have been realized in the [4 + 2] cycloaddition reactions of *N*-phenylsulfonyl-1-aza-1,3-butadienes in which: (1) the Diels–Alder reactions have been shown to proceed predominately if not exclusively (≥ 95%) through an *endo* transition state (Figure 5); (2) there is full preservation of the dienophile alkene geometry; (3) the cycloaddition rate exhibits little solvent dependency; (4) *trans*-1,2-disubstituted dienophiles react more rapidly than *cis*-1,2-disubstituted dienophiles [$k(E)/k(Z)$ = 6–13 for (*E*)- and (*Z*)-1-ethoxypropene]; and (5) the diastereoselectivity of the reaction increases as the pressure of the reaction is increased and the re-

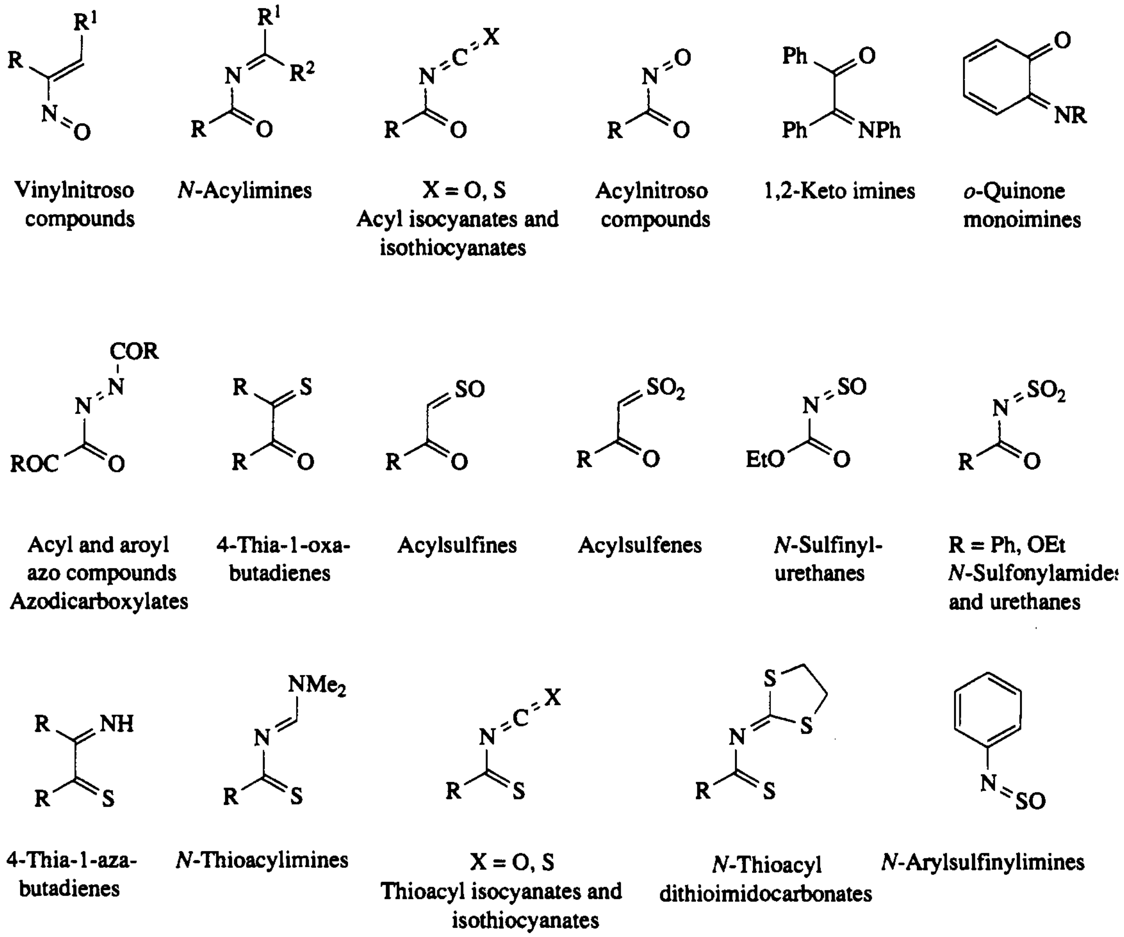

Vinylnitroso compounds

*N*-Acylimines

X = O, S
Acyl isocyanates and isothiocyanates

Acylnitroso compounds

1,2-Keto imines

*o*-Quinone monoimines

Acyl and aroyl azo compounds
Azodicarboxylates

4-Thia-1-oxa-butadienes

Acylsulfines

Acylsulfenes

*N*-Sulfinyl-urethanes

R = Ph, OEt
*N*-Sulfonylamides and urethanes

4-Thia-1-aza-butadienes

*N*-Thioacylimines

X = O, S
Thioacyl isocyanates and isothiocyanates

*N*-Thioacyl dithioimidocarbonates

*N*-Arylsulfinylimines

**Figure 4**

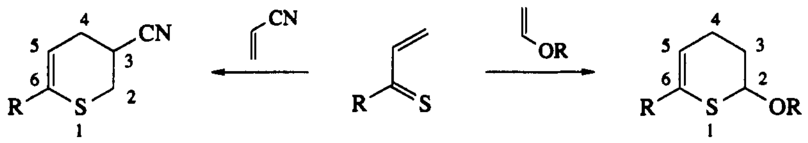

(6)

action temperature is decreased.[155,156] The observations are consistent with the 4π participation of the *N*-phenylsulfonyl-1-aza-1,3-butadiene in a concerted $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reaction (Scheme 11). *N*-Phenylsulfonyl aldimines ($R^1$ = H) have proven more reactive than *N*-phenylsulfonyl ketimines ($R^1$ = Me > $R^1$ = Ph), the complementary addition of a C-3 electron-withdrawing substituent ($R^2 = CO_2R$ >> $R^2$ = H) further accelerates the *N*-phenylsulfonyl-1-aza-1,3-butadiene participation in the $\text{LUMO}_{\text{diene}}$-controlled [4 + 2] cycloaddition reaction, and the observations have been successfully extended to include α,β-unsaturated *N*-phenylsulfonylimines that exist preferentially in the extended (*s*-*E*)-diene conformation.[155]

Similarly, the noncomplementary addition of a C-2 electron-withdrawing substituent to the *N*-phenylsulfonyl-1-aza-1,3-butadiene substantially lowers the 1-aza-1,3-butadiene $E_{\text{LUMO}}$ (Table 10), accelerates its 4π participation in a $\text{LUMO}_{\text{diene}}$-controlled [4 + 2] cycloaddition reaction, maintains the expected regioselectivity of the cycloaddition reaction, and potentially enhances the *endo* diastereoselectivity of the [4 + 2] cycloaddition reactions through the introduction of a substantial increase in the magnitude of the LUMO C-2 coefficient (Table 10; equation 8).[157,158]

**Table 7** Representative [4 + 2] Cycloaddition Reactions of Thiabutadienes

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 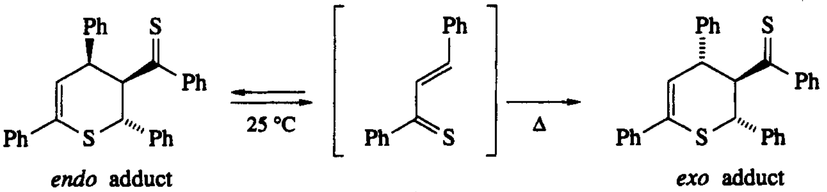 Ph<br>S<br>Ph<br>Ph<br>Ph<br>25 °C<br>Ph<br>Ph<br>S<br>Δ<br>Ph<br>S<br>Ph<br>Ph<br>Ph<br>*endo* adduct<br>*exo* adduct | 139 |
| 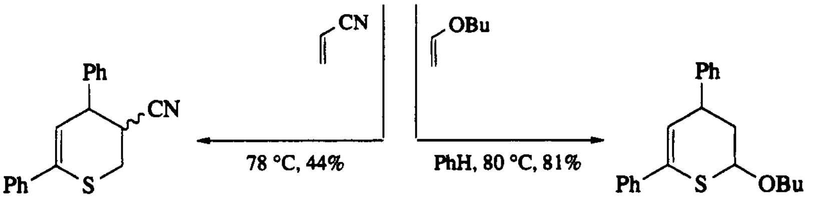 CN<br>OBu<br>Ph<br>CN<br>78 °C, 44%<br>PhH, 80 °C, 81%<br>Ph<br>Ph<br>S<br>Ph<br>S<br>OBu | 140, 141 |
| 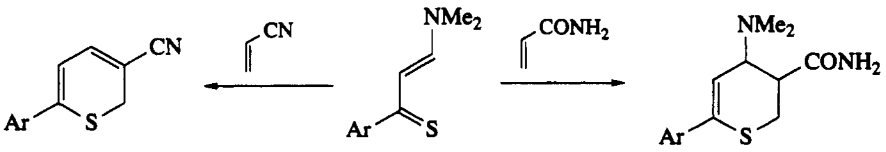 CN<br>CN<br>NMe2<br>CONH2<br>NMe2<br>CONH2<br>Ar<br>S<br>Ar<br>S<br>Ar<br>S | 142 |
| 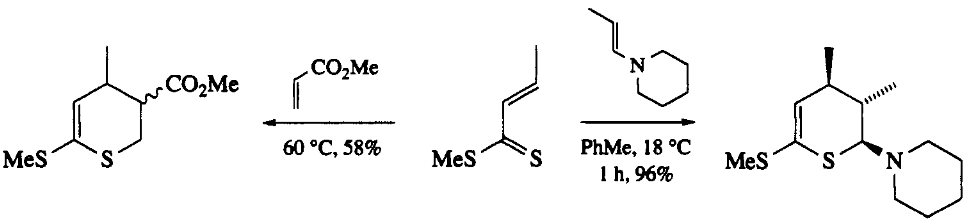 CO2Me<br>CO2Me<br>60 °C, 58%<br>N<br>PhMe, 18 °C<br>1 h, 96%<br>MeS<br>S<br>MeS<br>S<br>MeS<br>S<br>N | 143 |
| 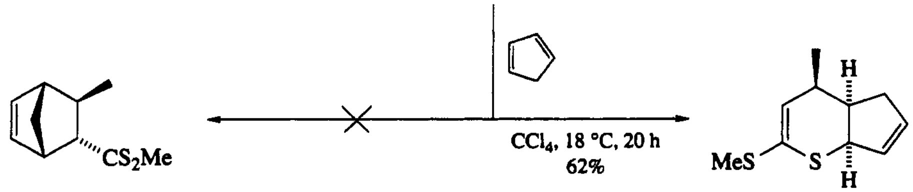 CS2Me<br>CCl4, 18 °C, 20 h<br>62%<br>H<br>MeS<br>S<br>H | |
| 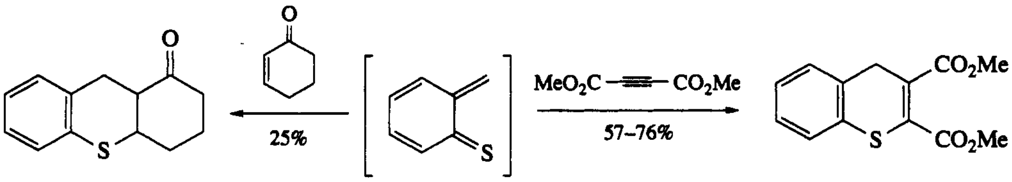 O<br>O<br>S<br>25%<br>S<br>MeO2C — CO2Me<br>57–76%<br>CO2Me<br>S<br>CO2Me | 144 |
| 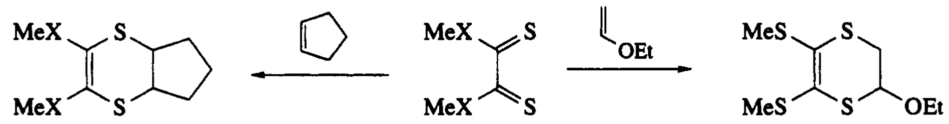 MeX<br>S<br>MeX<br>S<br>MeX<br>S<br>MeX<br>S<br>OEt<br>MeS<br>S<br>MeS<br>S<br>OEt<br>X = O, 67%, 3 days, 43 °C<br>X = S, 95%, 3 days, 25 °C<br>X = S, neat, 30 min, 25 °C<br>95% | 145, 146 |

**Table 7** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 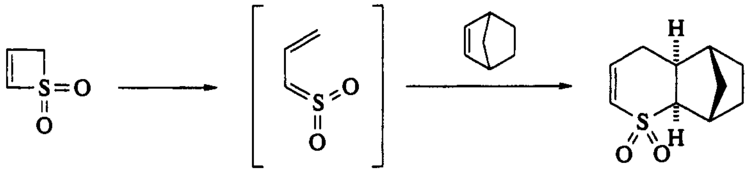 | 147 |

**Table 8** Theoretical Highest Occupied π Orbital (HOMO) and Lowest Unoccupied π Orbital (LUMO) of the Fundamental Aza-1,3-butadienes[a]

| *Azadiene* | *E*(eV) | *Coefficients* | | | |
|---|---|---|---|---|---|
| $H_2C{=}CH{-}CH{=}NH$ | | *N-1* | *C-2* | *C-3* | *C-4* |
| LUMO | 0.4 | 0.50 | −0.45 | −0.43 | 0.60 |
| HOMO | −10.1 | 0.46 | 0.24 | −0.59 | −0.62 |
| $H_2C{=}CH{-}CH{=}NH_2^+$ | | | | | |
| LUMO | −6.3 | 0.47 | −0.70 | −0.11 | 0.53 |
| HOMO | −15.9 | 0.41 | 0.05 | −0.70 | −0.59 |
| $H_2C{=}CH{-}N{=}CH_2$ | | *C-1* | *N-2* | *C-3* | *C-4* |
| LUMO | 0.3 | 0.58 | −0.38 | −0.43 | 0.56 |
| HOMO | −9.8 | 0.36 | 0.41 | −0.49 | −0.62 |
| $H_2C{=}CH{-}\overset{+}{N}H{=}CH_2$ | | | | | |
| LUMO | −6.2 | 0.78 | −0.49 | −0.11 | 0.38 |
| HOMO | −15.5 | 0.35 | 0.22 | −0.66 | −0.63 |
| $H_2C{=}N{-}CH{=}NH$ | | *N-1* | *C-2* | *N-3* | *C-4* |
| LUMO | 0.1 | 0.51 | −0.46 | −0.38 | 0.62 |
| HOMO | −11.1 | 0.62 | 0.40 | −0.45 | −0.49 |
| $H_2C{=}N{-}N{=}CH_2$ | | *C-1* | *N-2* | *N-3* | *C-4* |
| LUMO | 0.8 | 0.52 | −0.43 | −0.43 | 0.52 |
| HOMO | −12.4 | 0.45 | 0.44 | −0.44 | −0.45 |
| $HN{=}CH{-}CH{=}NH$ | | *N-1* | *C-2* | *C-3* | *N-4* |
| LUMO | 0.2 | 0.52 | −0.37 | −0.37 | 0.52 |
| HOMO | −11.5 | 0.57 | 0.41 | −0.44 | −0.56 |
| $HN{=}N{-}CH{=}CH_2$ | | *N-1* | *N-2* | *C-3* | *C-4* |
| LUMO | −0.1 | 0.55 | −0.44 | −0.40 | 0.60 |
| HOMO | −10.5 | 0.38 | 0.17 | −0.63 | −0.66 |
| $HN{=}N{-}N{=}CH_2$ | | *N-1* | *N-2* | *N-3* | *C-4* |
| LUMO | 0.2 | 0.54 | −0.49 | −0.38 | 0.53 |
| HOMO | −12.4 | 0.46 | 0.33 | −0.60 | −0.55 |
| $HN{=}N{-}CH{=}NH$ | | *N-1* | *N-2* | *C-3* | *N-4* |
| LUMO | 0.1 | 0.42 | −0.50 | −0.40 | 0.45 |
| HOMO | −12.2 | 0.60 | 0.62 | −0.57 | −0.65 |
| $HN{=}N{-}N{=}NH$ | | *N-1* | *N-2* | *N-3* | *N-4* |
| LUMO | 0.0 | 0.52 | −0.46 | −0.46 | 0.52 |
| HOMO | −13.6 | 0.52 | 0.44 | −0.44 | −0.52 |

[a] AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π-orbital.[148]

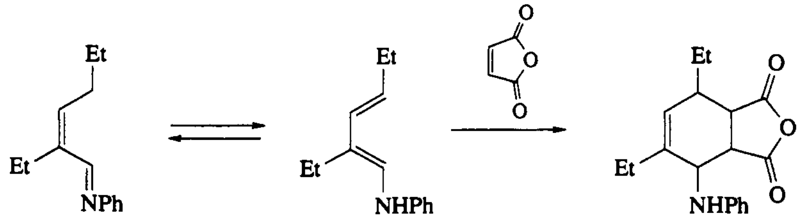

(7)

**Table 9** Representative [4 + 2] Cycloaddition Reactions of 1-Aza-1,3-butadienes

| *Diels–Alder reaction* | *Ref. (application)* |
|---|---|
| 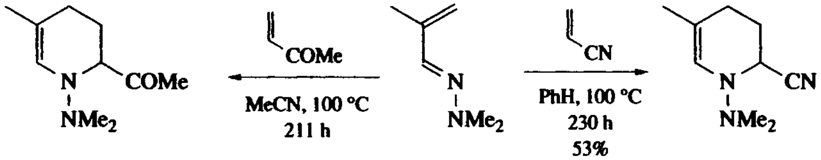 COMe<br>MeCN, 100 °C<br>211 h<br>N<br>NMe2<br>COMe<br>CN<br>PhH, 100 °C<br>230 h<br>53%<br>CN | 152, 153 |
| 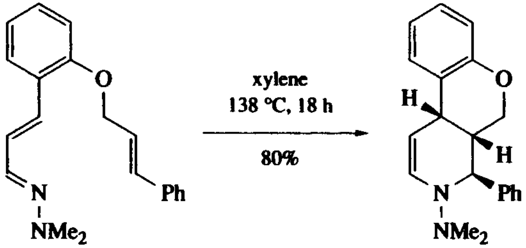 O<br>N<br>NMe2<br>Ph<br>xylene<br>138 °C, 18 h<br>80%<br>H<br>O<br>H<br>Ph<br>N<br>NMe2 | 159 |
| 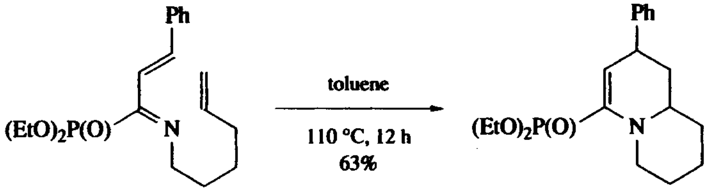 Ph<br>(EtO)2P(O)<br>N<br>toluene<br>110 °C, 12 h<br>63%<br>Ph<br>(EtO)2P(O)<br>N | 160 |
| 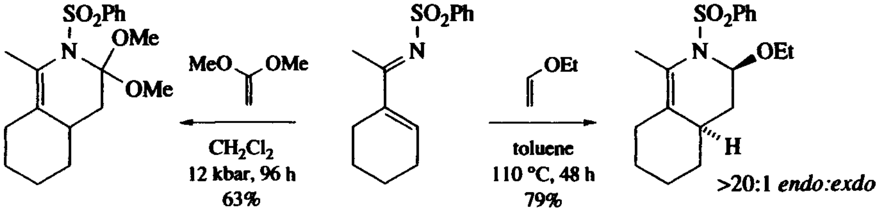 SO2Ph<br>N<br>OMe<br>OMe<br>MeO<br>OMe<br>CH2Cl2<br>12 kbar, 96 h<br>63%<br>SO2Ph<br>N<br>OEt<br>toluene<br>110 °C, 48 h<br>79%<br>SO2Ph<br>N<br>OEt<br>H<br>>20:1 endo:exdo | 155 |

**Table 9** *(continued)*

| *Diels–Alder reaction* | *Ref. (application)* |
|---|---|
| 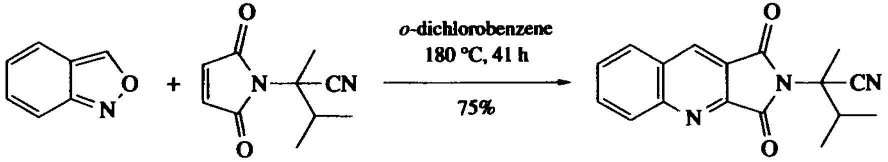 o-dichlorobenzene<br>180 °C, 41 h<br>75% | 161, 162 |
| 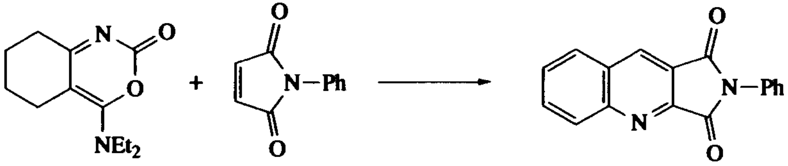 | 163 |
| 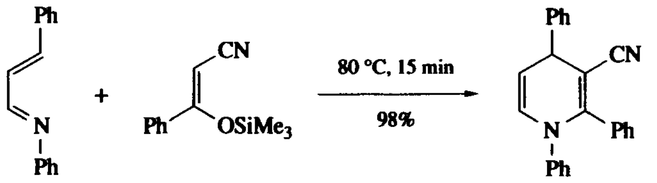 80 °C, 15 min<br>98% | 164 |
| 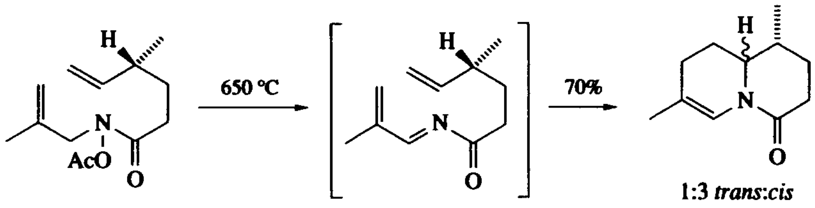 650 °C<br>70%<br>1:3 trans:cis | 150 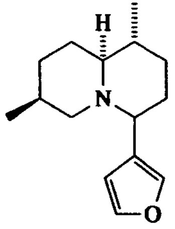 Deoxynupharidine |

**Table 9** *(continued)*

| *Diels–Alder reaction* | *Ref. (application)* | |
|---|---|---|
| 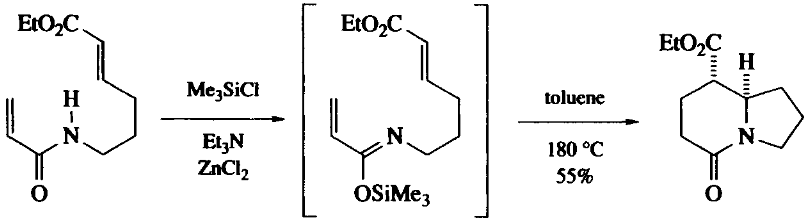 EtO$_2$C<br>H<br>N<br>O<br>Me$_3$SiCl<br>Et$_3$N<br>ZnCl$_2$<br>OSiMe$_3$<br>toluene<br>180 °C<br>55% | 154 | 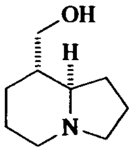 <br>**Epilupinine** |
| 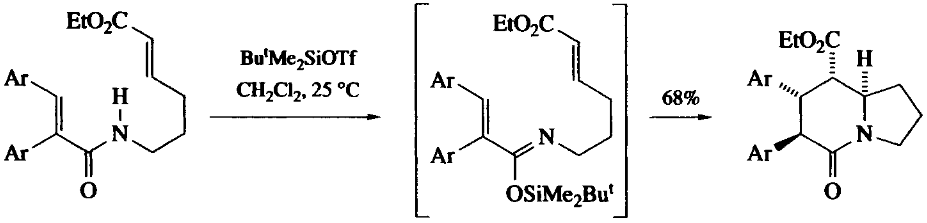 EtO$_2$C<br>Ar<br>H<br>N<br>O<br>Bu$^t$Me$_2$SiOTf<br>CH$_2$Cl$_2$, 25 °C<br>OSiMe$_2$Bu$^t$<br>68% | 154 | 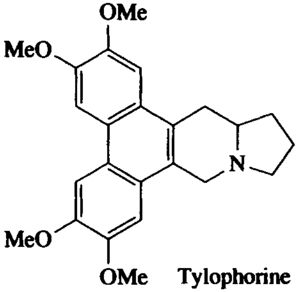 <br>**Tylophorine** |
| 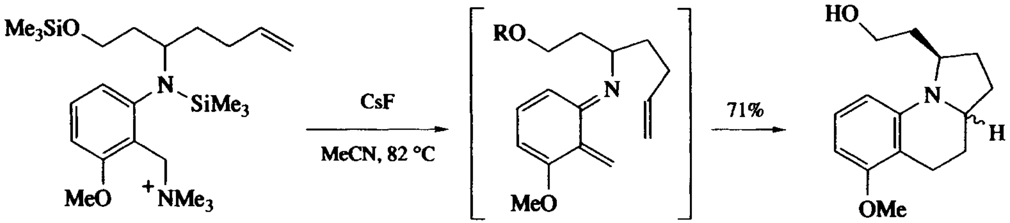 Me$_3$SiO<br>N<br>SiMe$_3$<br>MeO<br>$^+$NMe$_3$<br>CsF<br>MeCN, 82 °C<br>RO<br>71%<br>HO<br>H<br>OMe<br>4:1 *cis:trans* | 151 | 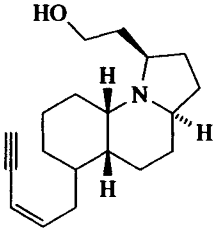 <br>**Gephyrotoxin** |

**Table 10** 1-Aza-1,3-butadiene Substituent Effects on the π HOMO and LUMO[a]

| Azadiene | E (eV) | Coefficients N-1 | C-2 | C-3 | C-4 | |
|---|---|---|---|---|---|---|
| $H_2C{=}CH{-}CH{=}NH$ | | | | | | |
| LUMO | 0.4 | 0.50 | −0.45 | −0.43 | 0.60 | |
| HOMO | −10.1 | 0.46 | 0.24 | −0.59 | −0.62 | |
| $H_2C{=}CH{-}CH{=}NSO_2Ph$ | | | | | | |
| LUMO | −0.9 | 0.50 | −0.58 | −0.30 | 0.53 | |
| HOMO | −11.1 | 0.32 | 0.11 | −0.47 | −0.46 | |
| $H_2C{=}C(CHO){-}CH{=}NSO_2Ph$ | | | | | | *CHO* |
| LUMO | −1.3 | 0.39 | −0.37 | −0.34 | 0.63 | 0.23 |
| HOMO | −11.5 | 0.36 | 0.12 | −0.52 | −0.48 | −0.10 |
| $H_2C{=}CH{-}C(CO_2Me){=}NSO_2Ph$ | | | | | | *CO2Me* |
| LUMO | −1.1 | 0.53 | −0.60 | −0.21 | 0.47 | −0.10 |
| HOMO | −11.2 | 0.32 | 0.12 | −0.55 | −0.55 | 0.05 |

[a] AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π orbital[148]

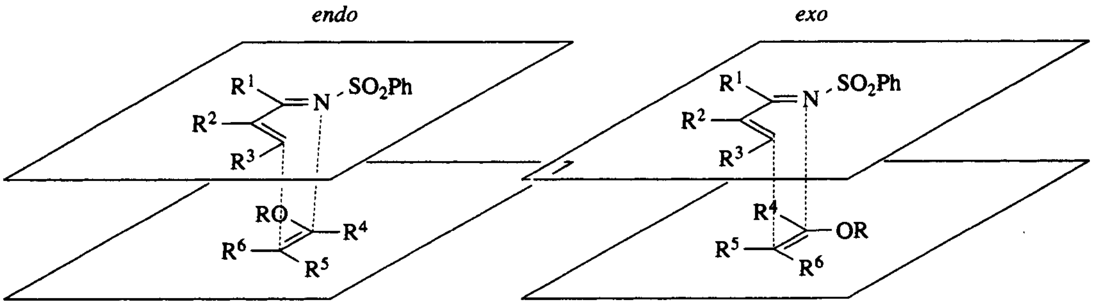

**Figure 5**

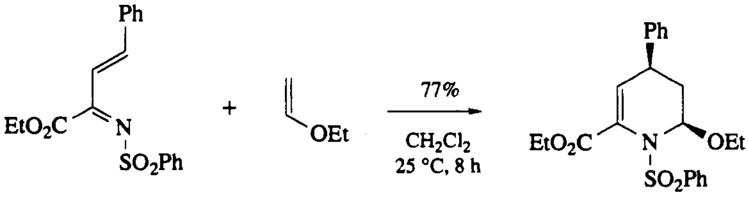

(8)

>20:1 *endo*:*exo*

### 4.3.4.2 2-Aza-1,3-butadienes

A select set of useful [4 + 2] cycloaddition reactions of simple 2-aza-1,3-butadienes have been detailed (Table 11),[170–176] and in most instances the 2-azadienes employed are substituted with strong electron-donating substituents responsible for enhancing its Diels–Alder reactivity toward electron-deficient dienophiles. The ease with which the 1,3-bis(t-butyldimethylsilyloxy)-2-aza-1,3-butadienes may be prepared from imides, and the demonstrated facility with which they participate in $HOMO_{diene}$-controlled [4 + 2] cycloaddition reactions, may prove exceptionally useful; their use constitutes the most general approach to implementing the 4π participation of 2-aza-1,3-butadienes (Scheme 12).[165–168] With the recent introduction of a convenient preparation of 3-trimethylsilyloxy-2-aza-1,3-butadienes, their comparable synthetic utility may be anticipated.[169]

The protic acid and Lewis acid-catalyzed [4 + 2] cycloaddition reactions of electron-rich alkenes with imines derived from anilines and aryl aldehydes constitute an extensively explored class of 2-azadienes capable of providing the products of a formal Diels–Alder reaction (equation 9).[15,27,177] In a useful extension of these studies and in efforts to increase the rate of the 4π participation of simple 2-aza-1,3-butadienes in [4 + 2] cycloaddition reactions, Mariano and coworkers have examined the Lewis acid-catalyzed intermolecular reactions of (1*E*,3*E*)-1-phenyl-2-aza-1,3-pentadiene with electron-rich dienophiles, including enol ethers.[178] Reductive work-up of the cycloaddition reactions provided the pro-

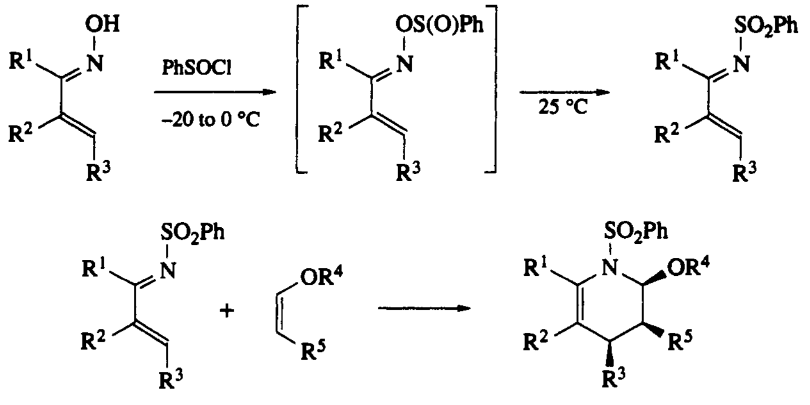

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | *Equiv. of dienophile, temp. or pressure (time, h), solvent* | *% Yield (endo:exo)* |
|---|---|---|---|---|---|---|
| Me | H | H | Et | H | 10, 60 °C (12), neat | 73% (>20:1) |
| Me | H | Ph | Et | H | 5, 12 kbar (80), $CH_2Cl_2$ | 69% (>20:1) |
| Ph | H | Ph | Et | H | 5, 12 kbar (45), $CH_2Cl_2$ | 77% (>20:1) |
| H | H | Ph | Et | H | 5, 12 kbar (45), $CH_2Cl_2$ | 72% (>20:1) |
| H | H | Ph | $CH_2Ph$ | Me | 5, 6 kbar (144), $CH_2Cl_2$ | 54% (>20:1) |
| H | Me | H | Et | H | 5, 12 kbar (45), $CH_2Cl_2$ | 72% (>20:1) |
|  |  |  |  |  | 10, 40 °C (11), $CH_2Cl_2$ | 82% (>20:1) |

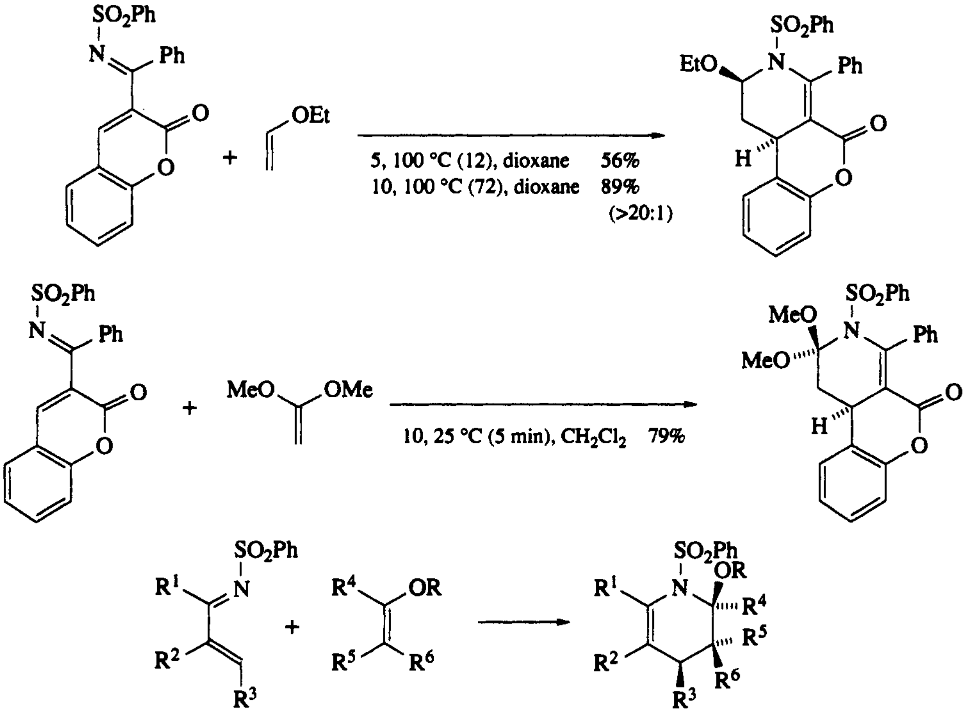
5, 100 °C (12), dioxane 56%
10, 100 °C (72), dioxane 89% (>20:1)
10, 25 °C (5 min), CH2Cl2 79%

**Scheme 11**

ducts of regio- and diastereo-selective [4 + 2] cycloaddition reactions derived from predominant cycloaddition through an *endo* transition state with full preservation of the dienophile and diene alkene geometries (equation 10). Although further studies are required to develop the scope of such reactions, the N-2 Lewis acid coordination or protic acid protonation of a 2-aza-1,3-butadiene would be expected to: (1) substantially lower the diene $E_{\text{LUMO}}$ and thereby accelerate the rate of a $\text{LUMO}_{\text{diene}}$-controlled cycloaddition; (2) substantially increase the magnitude of LUMO N-2 coefficient and consequently enhance the

**Table 11** Representative [4 + 2] Cycloaddition Reactions of 2-Aza-1,3-butadienes

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 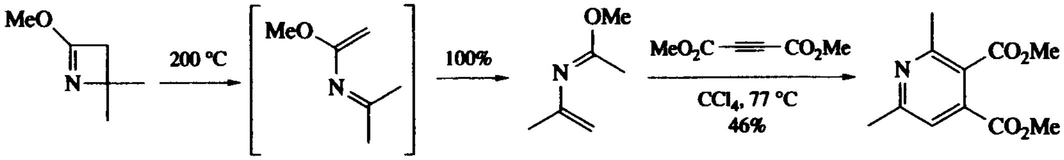 | 170 |
| 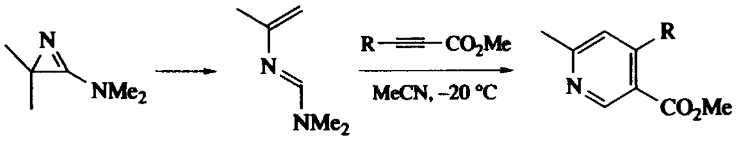 R = H, 72%<br>R = $CO_2Me$, 57% | 171 |
| 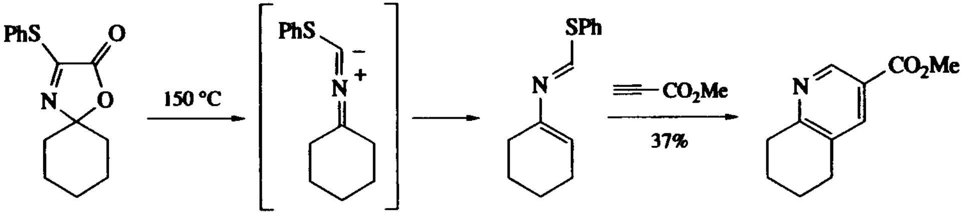 | 172 |
| 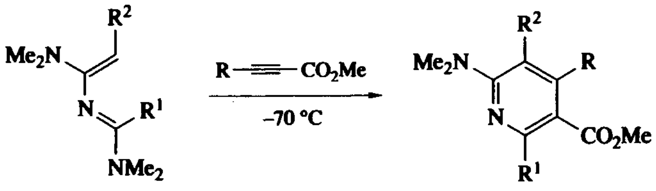 | 173 |

| *R¹* | *R²* | *R* | *Yield (%)* |
|---|---|---|---|
| H | H | $CO_2Me$ | 16 |
| H | Ph | $CO_2Me$ | 50 |
| H | Ph | H | 29 |
| Ph | H | H | 12 |
| Ph | H | $CO_2Me$ | 27 |

**Table 11** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 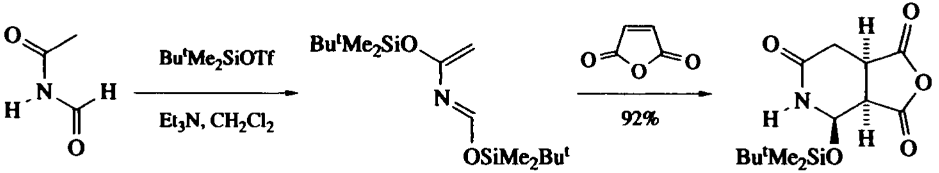 Bu<sup>t</sup>Me<sub>2</sub>SiOTf<br>Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub><br>92% | 165 |
| 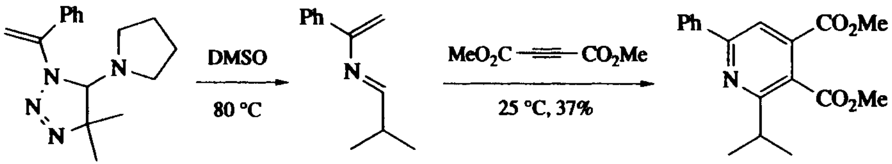 DMSO<br>80 °C<br>MeO<sub>2</sub>C—≡—CO<sub>2</sub>Me<br>25 °C, 37% | 174 |
| 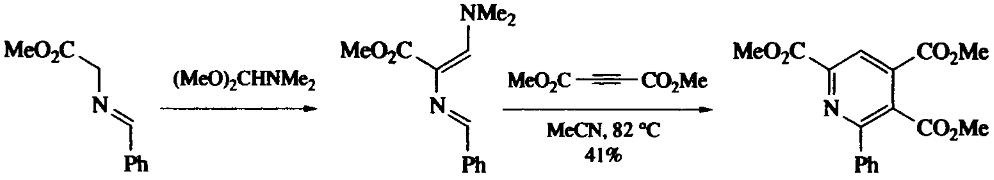 (MeO)<sub>2</sub>CHNMe<sub>2</sub><br>MeO<sub>2</sub>C—≡—CO<sub>2</sub>Me<br>MeCN, 82 °C<br>41% | 175 |
| 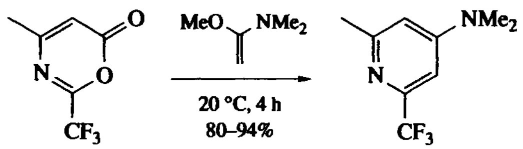 ref. 176 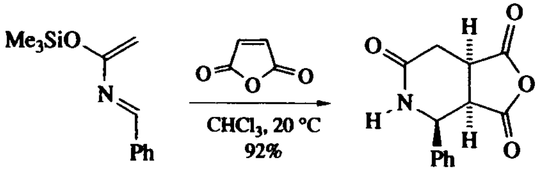 CHCl<sub>3</sub>, 20 °C<br>92% 100% *endo* | 169 |

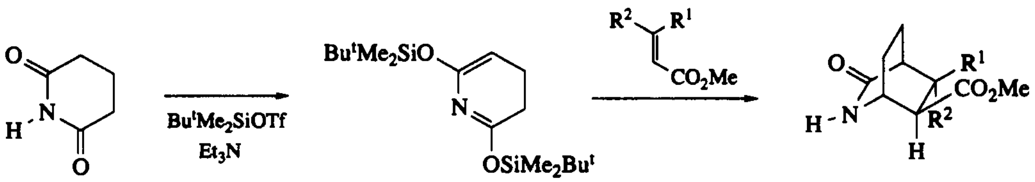
Bu$^t$Me$_2$SiOTf
Et$_3$N
Bu$^t$Me$_2$SiO
OSiMe$_2$Bu$^t$
R$^2$
R$^1$
CO$_2$Me
H-N
H

| Conditions[166] | exo:endo | $R^1$ | $R^2$ |
|---|---|---|---|
| 60 °C, 72 h, 74% | 92:8 | H | H |
| 60 °C, 10 d, 67% | 100:0 | $CO_2Me$ | H |
| 60 °C, 35 h, 84% | 100:0 | H | $CO_2Me$ |
| 120 °C, 21 h, 67% | 97:3 | H | Me |

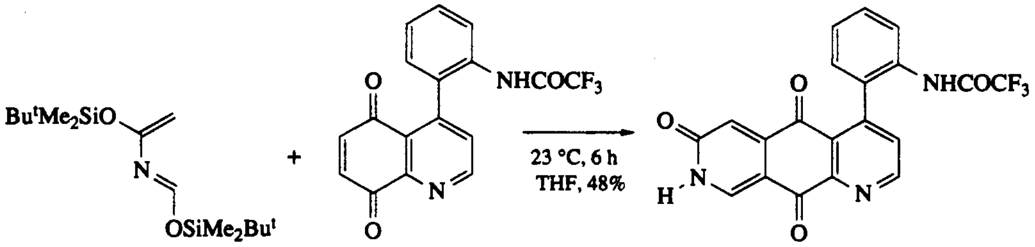
Bu$^t$Me$_2$SiO
OSiMe$_2$Bu$^t$
NHCOCF$_3$
23 °C, 6 h
THF, 48%
NHCOCF$_3$

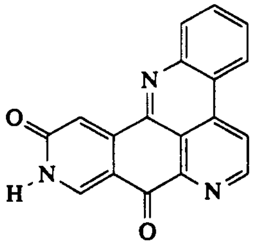

Amphimedine[167]

**Scheme 12**

*endo* diastereoselectivity; and (3) substantially increase the magnitude of the difference in the C-1/C-4 LUMO coefficients and thereby control the regioselectivity of the [4 + 2] cycloaddition reaction (*cf.* Table 8).[179] Additional discussion of this topic may be found in Section 4.3.6.1.

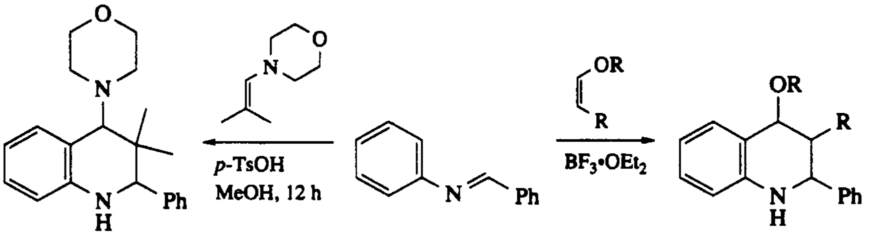
p-TsOH
MeOH, 12 h
OR
R
BF$_3$•OEt$_2$
Ph

(9)

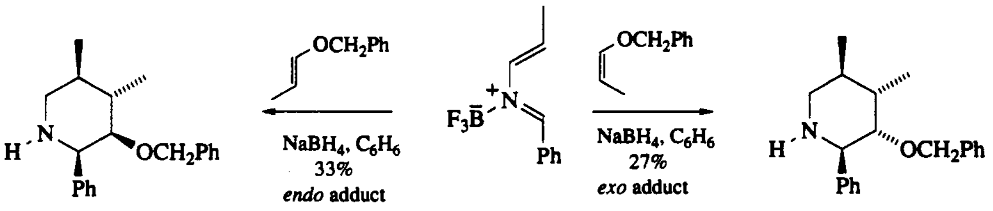
OCH$_2$Ph
NaBH$_4$, C$_6$H$_6$
33%
endo adduct
F$_3$B
Ph
OCH$_2$Ph
NaBH$_4$, C$_6$H$_6$
27%
exo adduct

(10)

### 4.3.4.3 Hetero 2-Aza-1,3-butadienes

A wide range of hetero 2-aza-1,3-butadienes have been shown to participate as 4π components of Diels–Alder reactions (Figure 4). Perhaps the most widely recognized class of hetero 2-aza-1,3-butadienes is the *N*-acylimines (1-oxa-3-aza-1,3-butadiene)[15,24,39–43,180] and comprehensive reviews of their 4π participation in $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions are available. The recent disclosure of the 4π participation of *N*-acylimines in intramolecular [4 + 2] cycloaddition reactions (equation 11),[181] and the use of optically active *N*-acylimines in productive $\text{LUMO}_{\text{diene}}$-controlled [4 + 2] cycloaddition reactions, illustrate applications of the systems that have not been explored fully (equation 12).[182]

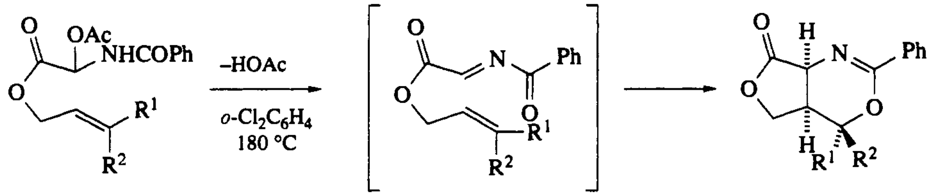

(11)

$R^1 = Me, R^2 = H$; 62%
$R^1 = H, R^2 = Me$; 75%

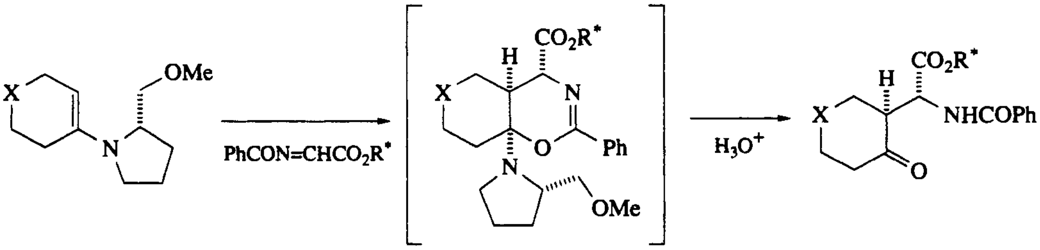

(12)

The Diels–Alder reactions of vinylnitroso compounds have been investigated extensively and they have been shown to participate productively as 4π components of $\text{LUMO}_{\text{diene}}$-controlled [4 + 2] cycloaddition reactions. The complementary C-3 substitution of the vinylnitroso compound with an electron-withdrawing substituent has proven sufficient to permit the observation of $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions with neutral dienophiles (equation 13).[183] In addition, vinylnitroso compounds may participate as 2π or 4π components in competitive [4 + 2] cycloadditions with typical dienes (Scheme 13). Experimentally it has been shown that vinylnitroso compounds possessing C-4 substituents react as 2π components in [4 + 2] cycloaddition reactions with dienes (path a) and that vinylnitroso compounds lacking C-4 substituents react as 4π components in [4 + 2] cycloaddition reactions with dienes (path b). To date, the potential that the 4π participation of vinylnitroso compounds in Diels–Alder reactions with dienes (path b) may be derived from the all-carbon Diels–Alder reaction (path d), followed by 3,3-sigmatropic rearrangement to the oxazine product, has not received experimental verification.

Similarly, acylnitroso compounds are recognized for their 2π participation in Diels–Alder reactions with dienes and these observations have found substantial application (Chapter 4.2). In addition, recent efforts have detailed the apparent 4π participation of an acylnitroso compound in a Diels–Alder reaction with a cyclopentadiene that suggests their potentially useful 4π participation in $\text{LUMO}_{\text{diene}}$-controlled Diels–Alder reactions (equation 14).[184]

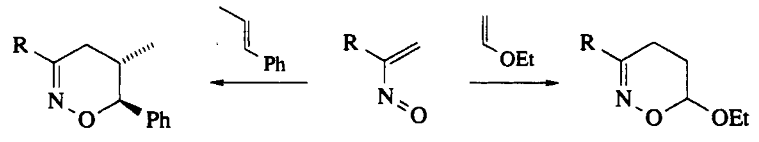

(13)

R = Ph; 26%
$R = CO_2Et$; 43%

R = Ph; 87%
$R = CO_2Et$; 82%

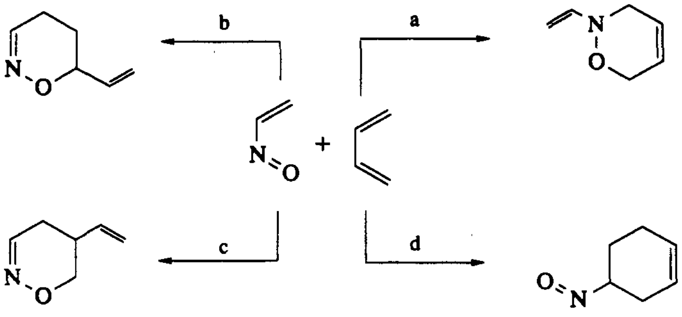

Scheme 13

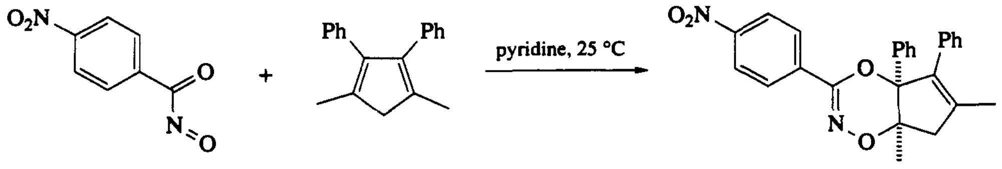

(14)

### 4.3.4.4 1,2-Diaza-1,3-butadienes

Electron-deficient azoalkenes, 1,2-diaza-1,3-butadienes, participate as 4π components in regiospecific LUMO$_{\text{diene}}$-controlled [4 + 2] cycloaddition reactions with selected dienes or electron-rich and selected simple alkene dienophiles. The reactions studied in detail exhibit no rate dependency on the solvent polarity, proceed predominantly through an *endo* transition state, and have been suggested to represent concerted [4 + 2] cycloaddition reactions.[185] Table 12 summarizes representative examples of the inter- and intra-molecular [4 + 2] cycloaddition reactions of 1,2-diaza-1,3-butadienes.

### 4.3.4.5 Hetero 1,2-Diaza-1,3-butadienes

Azodicarboxylates are recognized for their ability to participate as 2π components of HOMO$_{\text{diene}}$-controlled Diels–Alder reactions with dienes and for their participation in ene reactions with reactive alkenes.[15,189] In addition, electron-rich or reactive simple alkenes that do not contain a reactive allylic hydrogen atom have been shown to participate in competitive [2 + 2] and [4 + 2] cycloaddition reactions with azodicarboxylates in which the observed course of the reaction is dependent upon the solvent polarity and nucleophilic character of the alkene (Table 13). As may be anticipated, alkoxycarbonylaroyldiimides (**4**), diaroyldiimides (**5**), and arylaroyldiimides (**6**) participate with increasing selectivity as 4π components of [4 + 2] cycloaddition reactions.

### 4.3.4.6 1,3-Diaza-1,3-butadienes

A surprisingly small group of 1,3-diaza-1,3-butadienes have been shown to participate in [4 + 2] cycloaddition reactions and the lack of additional efforts reflects the current difficulty in securing stable 1,3-diaza-1,3-butadienes for study (Table 12).

### 4.3.4.7 1,4-Diaza-1,3-butadienes

A select group of 1,4-diaza-1,3-butadienes have been demonstrated to participate as 4π components of Diels–Alder reactions (Table 12). Perhaps the most successful system described to date is the LUMO$_{\text{diene}}$-controlled [4 + 2] cycloaddition reaction of diiminosuccinonitrile, a 1,4-diaza-1,3-butadiene substituted with C-2 and C-3 electron-withdrawing groups, with electron-rich dienophiles (equation 15).[196] A common and competitive reaction of the α-diimines is [2 + 2] cycloaddition to afford azetidine cycloaddition products and many of the early reports of the [4 + 2] cycloaddition reactions are incorrect.

**Table 12** Representative [4 + 2] Cycloaddition Reactions of Diaza-1,3-butadienes

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 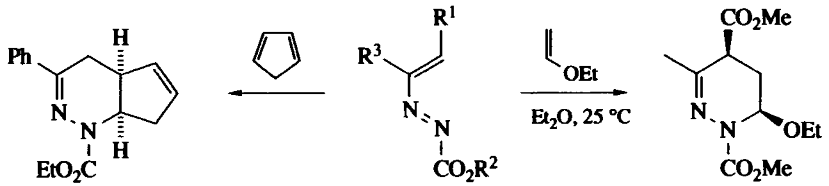<br>$R^1 = H, R^2 = Et, R^3 = Ph$; 96% <br>$R^1 = CO_2Me, R^2 = Me, R^3 = Me$; 70% | 185, 186 |
| 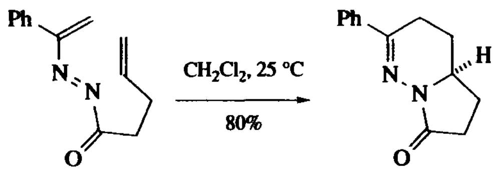 | 187 |
| 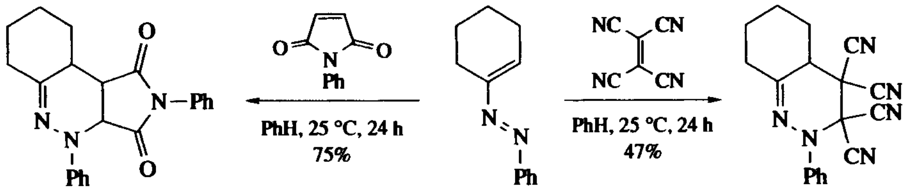 | 188 |
| 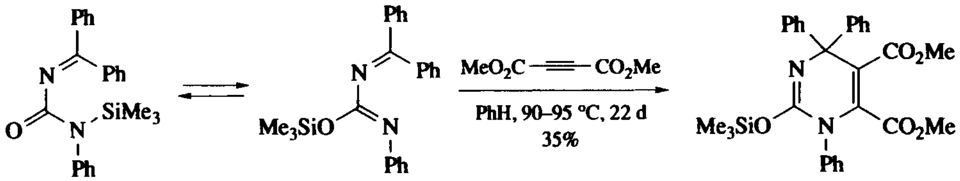 | 193 |

**Table 12** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 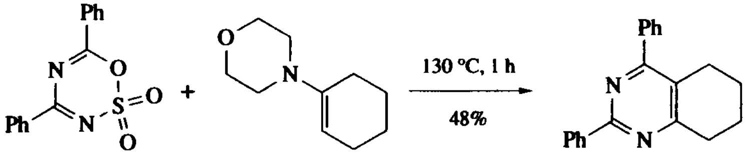 | 194 |
| 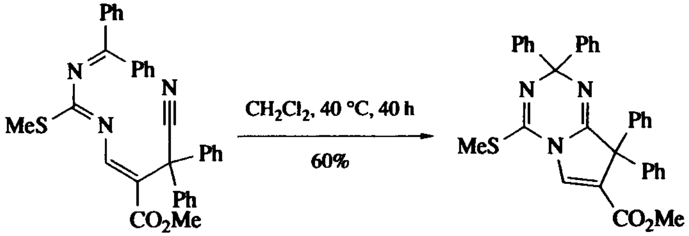  CH₂Cl₂, 40 °C, 40 h 60% | 195 |
| 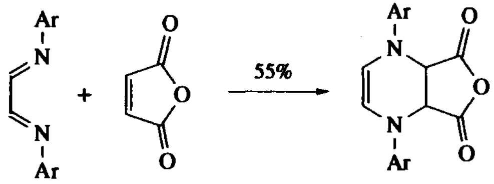 <br>Ar = 4-MeOC$_6$H$_4$ | 197 |
| 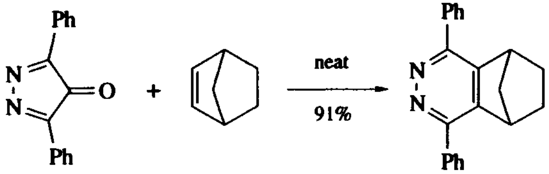 | 198 |

**Table 12** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| 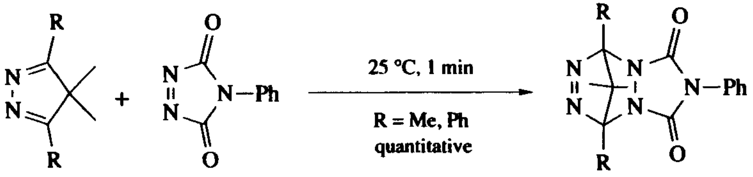  25 °C, 1 min<br>R = Me, Ph<br>quantitative | 199 |
| 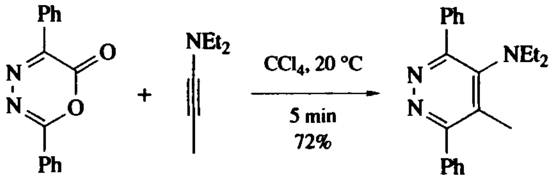  CCl4, 20 °C<br>5 min<br>72% | 200 |

**Table 13**

| *Diels–Alder reaction* | *Ref. (application)* |
|---|---|
| 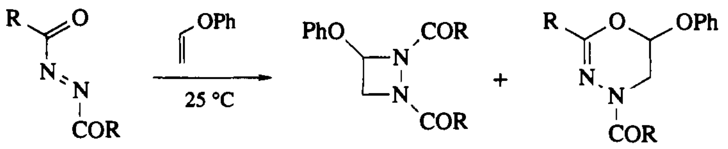 | 190 |

| *R* | *Solvent* | *Yield (%)* | *Product ratio* |
|---|---|---|---|
| OMe | neat | 73 | 77:23 |
| Ph | neat | 66 | <5:95 |
| OMe | MeCN | — | 80:20 |
| OMe | PhH | — | 33:67 |

| *Diels–Alder reaction* | *Ref. (application)* |
|---|---|
| 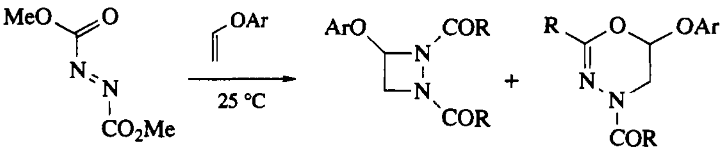 | 191 |

| *Ar* | *Solvent* | *Yield (%)* | *Product ratio* |
|---|---|---|---|
| Ph | neat | 73 | 77:23 |
| $4\text{-}NO_2C_6H_4$ | neat | 40 | 5:95 |

| *Diels–Alder reaction* | *Ref. (application)* |
|---|---|
| 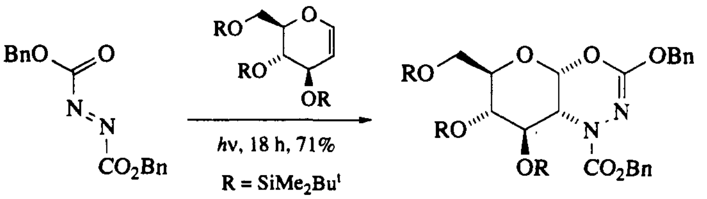 | 192 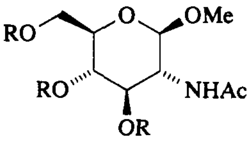 |

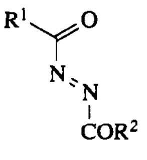

(4) $R^1 = Ar$, $R^2 = OR$

(5) $R^1 = R^2 = Ar$

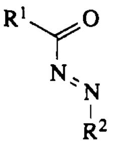

(6) $R^1 = R^2 = Ar$

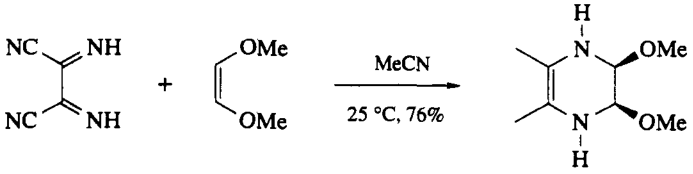

(15)

#### 4.3.4.8 2,3-Diaza-1,3-butadienes

The examples of 2,3-diaza-1,3-butadienes participating as $4\pi$ components of Diels–Alder reactions are rare, and each successful case constitutes the reaction of a cyclic diene confined to an *s-Z* (cisoid) diene conformation (Table 12). Typical efforts to promote the Diels–Alder reactions of 2,3-diaza-1,3-butadienes provide simple imine addition products, *e.g.* 2:1 adducts, or [3 + 2] criss-cross products[26] that may be attributed to the strong preference for simple acyclic 2,3-diaza-1,3-butadienes to adopt an *s-E* (transoid) diene conformation.

## 4.3.5 HETEROAROMATIC AZADIENES

Since the initial demonstrations of the participation of substituted 1,2,4,5-tetrazines[201] and oxazoles[202,203] in [4 + 2] cycloaddition reactions with alkene and alkyne dienophiles, the investigation and application of the Diels–Alder reactions of heteroaromatic systems possessing reactive azadienes have been pursued extensively. A number of general reviews[15,21–23] have treated the spectrum of heteroaromatic azadienes that participate in [4 + 2] cycloaddition reactions and many of the individual heteroaromatic systems have been reviewed separately.[206,207] An extensive account was published recently and should be consulted for descriptions of the [4 + 2] cycloaddition reactions of the common heteroaromatic azadienes that have been observed to date.[15]

As with the simple heterodienes, the electron-deficient heteroaromatic azadienes have proven ideally suited for $4\pi$ participation in $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reactions. In fact, it was the recognition of this electron-deficient nature of heteroaromatic azadienes that led to the proposed[204] and demonstrated[205] rate acceleration that may accompany the reversal of the electronic properties of the Diels–Alder diene–dienophile partners and subsequently led to the full investigation of the $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reaction.

### 4.3.5.1 Five-membered Ring Heteroaromatic Azadienes

Oxazoles represent the most widely recognized heteroaromatic azadiene capable of [4 + 2] cycloaddition reactions.[206] The course of the oxazole Diels–Alder reaction and the facility with which it proceeds are dependent upon the dienophile structure (alkene, alkyne), the oxazole and dienophile substitution, and the reaction conditions. Alkene dienophiles provide pyridine products derived from fragmentation of the [4 + 2] cycloadducts which subsequently aromatize through a variety of reaction pathways to provide the substituted pyridines (Scheme 14). In comparison, alkyne dienophiles provide substituted furans that arise from the retro Diels–Alder reaction with loss of $R^1CN$ from the initial [4 + 2] cycloadduct (Scheme 14).[15,206] Representative applications of the [4 + 2] cycloaddition reactions of oxazoles are summarized in Table 14. Selected examples of additional five-membered heteroaromatic azadienes participating in [4 + 2] cycloaddition reactions have been detailed and include the Diels–Alder reactions of thiazoles,[15,208] 1,3,4-oxadiazoles,[209] isoxazoles, pyrroles and imidazoles.[15]

### 4.3.5.2 Six-membered Ring Heteroaromatic Azadienes

Six-membered heteroaromatic azadienes, including pyridazines (1,2-diazines), pyrimidines (1,3-diazines), pyrazines (1,4-diazines), 1,2,3-triazines, 1,3,5-triazines, 1,2,4-triazines and 1,2,4,5-tetrazines, participate in characteristic $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reactions (Table 15), and this topic has been recently reviewed.[15] The regioselectivity and mode of the [4 + 2] cycloaddition reaction are dependent upon the heteroaromatic substitution pattern (electronic and steric substituent effects), the electronic and steric properties of the dienophile employed, as well as the reaction conditions. In most instances the proper selection of a matched diene–dienophile pair will permit the observation of a single cycloaddition product. The complementary substitution of the heteroaromatic azadiene with electron-withdrawing substituents accelerates its $4\pi$ participation in $\mathrm{LUMO_{diene}}$-controlled Diels–Alder reactions, enhances or may control the observed regioselectivity of the [4 + 2] cycloaddition reaction, and in extreme cases will govern the mode of [4 + 2] cycloaddition, *e.g.* 1,2,4-triazine C-3/C-6 *versus* C-5/N-2 cycloaddition. The inherent reactivity of some heteroaromatic azadienes, *e.g.* 1,2,4,5-tetrazine and 1,3,5-triazine, or substitution of selected heteroaromatic azadienes with strong electron-donating substituents (OR, $NR_2$) are sufficient to overcome the characteristic electron-deficient nature of the heteroaromatic azadiene and permit the use of conventional electron-deficient dienophiles, presumably in $\mathrm{HOMO_{diene}}$-controlled Diels–Alder

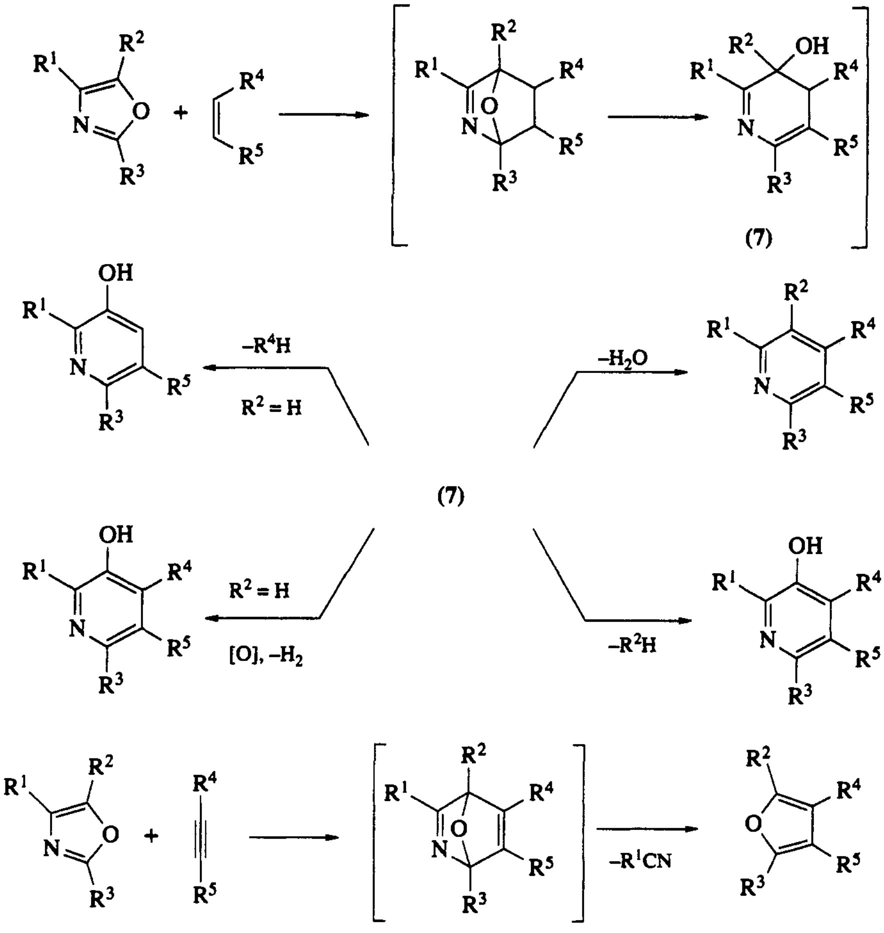

Scheme 14

reactions. In addition, the entropic assistance provided by the intramolecular Diels–Alder reaction has proven effective in promoting a number of heteroaromatic azadiene Diels–Alder reactions and selected examples of this widely used process may be found in the following schemes. Representative examples of the application of heteroaromatic azadiene Diels–Alder reactions include the total syntheses of streptonigrin (Scheme 15),[239] lavendamycin (Scheme 16),[240] OMP (Scheme 17),[238] prodigiosin (Scheme 18),[241] PDE-I, PDE-II and (+)-CC-1065 (Scheme 19),[242–244] pyrimidoblamic acid/bleomycin $A_2$ (Scheme 20),[245] actinidine (Scheme 21),[246] fabianine (Scheme 22),[247] guaipyridine (Scheme 23)[248] and DDATHF (Scheme 24)[249] and are summarized below.[22,23]

## 4.3.6 CATIONIC HETERODIENES, [4⁺ + 2] CYCLOADDITIONS

The past classification of the $[4^+ + 2]$ cycloaddition reactions involving the $4\pi$ participation of a cationic heterodiene among the 'polar' cycloadditions is derived not from an implied stepwise addition–cyclization reaction mechanism but was terminology introduced to distinguish cycloadditions employing cationic or anionic components from those employing dipolar or uncharged components.[29] Herein the reactions are simply referred to as $[4^+ + 2]$ cycloaddition reactions.

### 4.3.6.1 Cationic Azadienes

The preparation or *in situ* generation of azabutadienes bearing a formal positive charge, *i.e.* an immonium cation, provides a substantial enhancement of the electron-deficient character of the azadiene and in many instances such systems have proven to be effective $4\pi$ components in Diels–Alder reactions with electron-rich or neutral dienophiles. The most widely recognized class of cationic azadienes shown

**Table 14** Representative [4 + 2] Cycloaddition Reactions of Oxazoles

| *Diels–Alder reaction* | *Application* | *Ref.* |
|---|---|---|
| 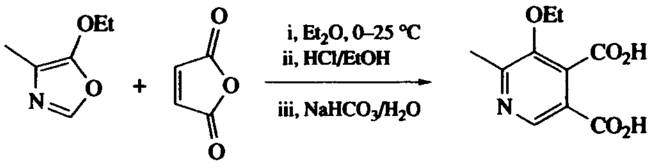 OEt<br>O<br>N<br>+<br>O<br>O<br>O<br>i, Et$_2$O, 0–25 °C<br>ii, HCl/EtOH<br>iii, NaHCO$_3$/H$_2$O<br>OEt<br>CO$_2$H<br>N<br>CO$_2$H | 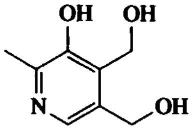 <br>Pyridoxol | 210 |
| 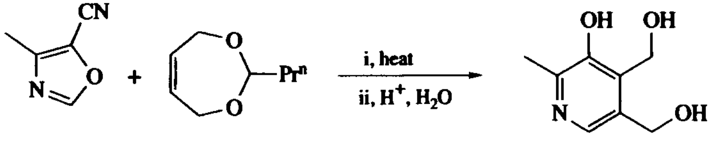 CN<br>O<br>N<br>+<br>O<br>O<br>Pr$^n$<br>i, heat<br>ii, H$^+$, H$_2$O<br>OH<br>OH<br>N<br>OH | Pyridoxol | 211 |
| 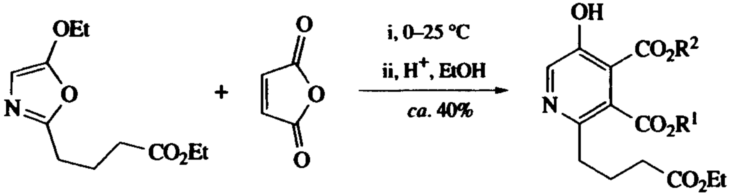 OEt<br>O<br>N<br>CO$_2$Et<br>+<br>O<br>O<br>O<br>i, 0–25 °C<br>ii, H$^+$, EtOH<br>ca. 40%<br>OH<br>CO$_2$R$^2$<br>N<br>CO$_2$R$^1$<br>CO$_2$Et<br>R$^1$, R$^2$ = H, Et | 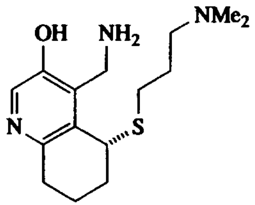 OH<br>NH$_2$<br>NMe$_2$<br>N<br>S | 212 |
| 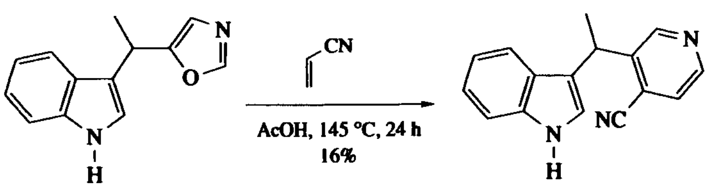 N<br>O<br>N<br>H<br>CN<br>AcOH, 145 °C, 24 h<br>16%<br>N<br>NC<br>N<br>H | 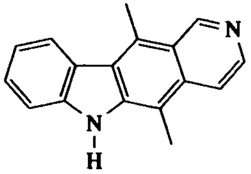 <br>Ellipticine | 213 |

**Table 14** *(continued)*

| *Diels–Alder reaction* | *Application* | *Ref.* |
|---|---|---|
| 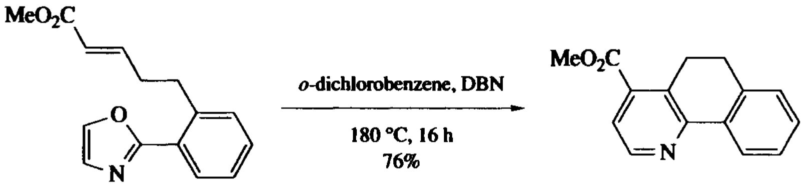 o-dichlorobenzene, DBN<br>180 °C, 16 h<br>76% | 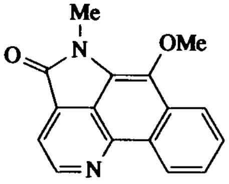<br>Eupolauramine | 214 |
| 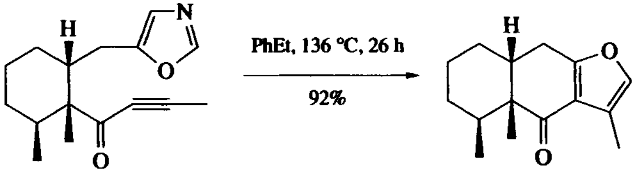 PhEt, 136 °C, 26 h<br>92% | 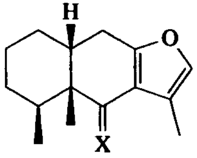<br>X = O, Ligularone<br>X = *cis* OH, H; Petasalbine | 215<br>216 |
| 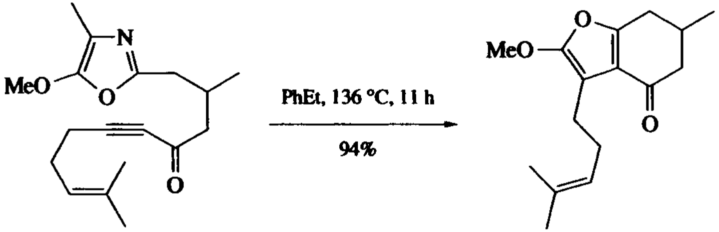 PhEt, 136 °C, 11 h<br>94% | 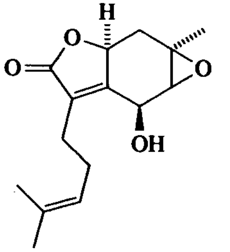<br>Paniculide-A | 217 |

**Table 14** *(continued)*

| *Diels–Alder reaction* | *Application* | *Ref.* |
|---|---|---|
| 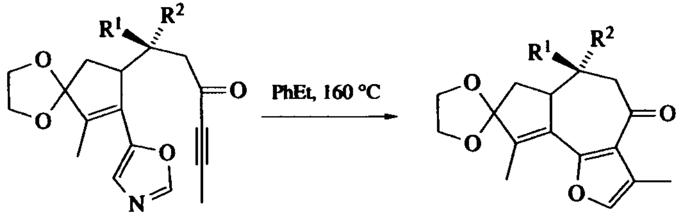 <br>$R^1$ = Me, $R^2$ = H; 45%<br>$R^1$ = H, $R^2$ = Me; 57% | 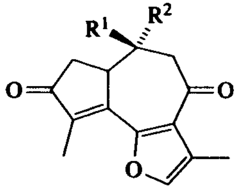Gnididione<br>Isognididione | 218 |

**Table 15** Representative [4 + 2] Cycloaddition Reactions of Six-membered Heteroaromatic Azadienes

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| *1,2-Diazines (pyridazines)* | |
| 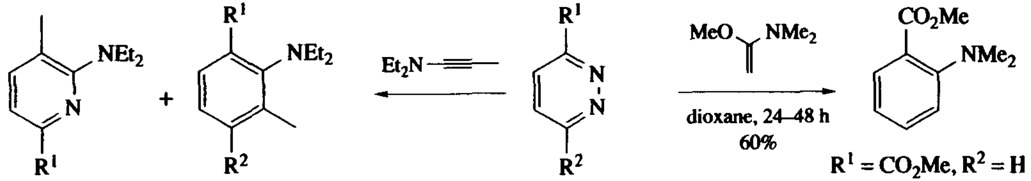 | 219 |

| | | *R¹* | *R²* | |
|---|---|---|---|---|
| 23% | – | $CO_2Me$ | H | xylene, 140 °C, 40 h |
| – | 75% | $CO_2Me$ | $CO_2Me$ | dioxane, 101 °C, 50 h |

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| *1,3-Diazines (pyrimidines)* | |
| 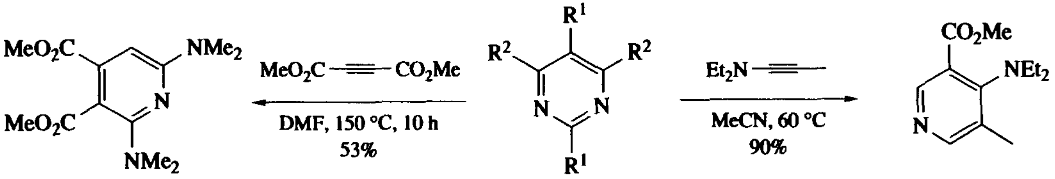 | 220, 221 |

$R^1 = H, R^2 = NMe_2$

$R^1 = CO_2Me, R^2 = H$

**Table 15** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| *1,4-Diazines (pyrazines)* | |
| 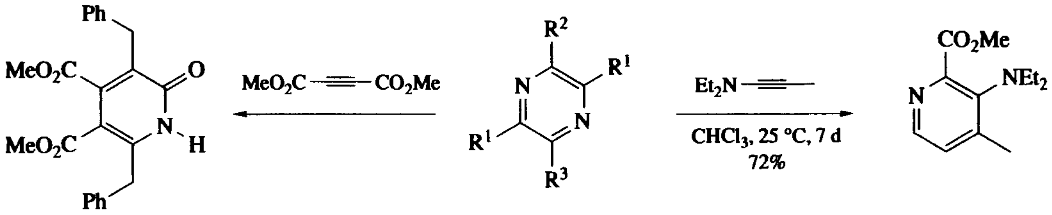  Ph<br>MeO$_2$C<br>MeO$_2$C<br>O<br>N<br>H<br>Ph<br>MeO$_2$C—≡—CO$_2$Me<br>R$^2$<br>R$^1$<br>N<br>N<br>R$^1$<br>R$^3$<br>Et$_2$N—≡—<br>CHCl$_3$, 25 °C, 7 d<br>72%<br>CO$_2$Me<br>NEt$_2$<br>N<br>R$^1$ = OH, R$^2$ = R$^3$ = CH$_2$Ph<br>R$^1$ = CO$_2$Me, R$^2$ = R$^3$ =H | 222, 223 |
| *1,2,3-Triazines* | |
| 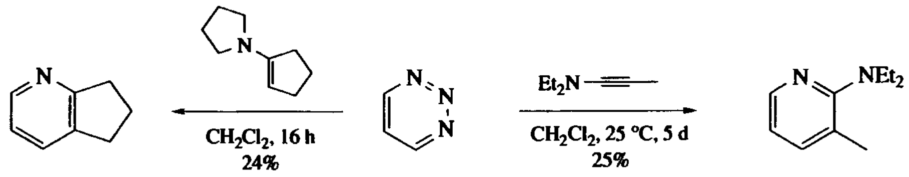  N<br>N<br>CH$_2$Cl$_2$, 16 h<br>24%<br>N<br>N<br>N<br>Et$_2$N—≡—<br>CH$_2$Cl$_2$, 25 °C, 5 d<br>25%<br>N<br>NEt$_2$ | 224, 225 |
| *1,3,5-Triazines* | |
| 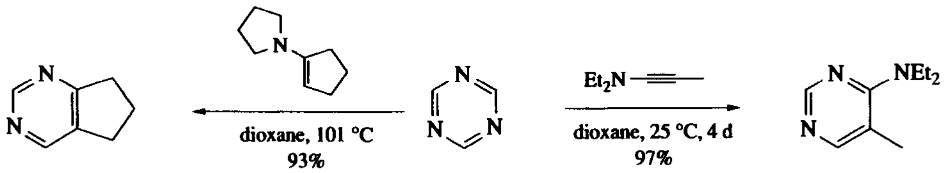  N<br>N<br>N<br>dioxane, 101 °C<br>93%<br>N<br>N<br>N<br>Et$_2$N—≡—<br>dioxane, 25 °C, 4 d<br>97%<br>N<br>N<br>NEt$_2$ | 226, 227 |

**Table 15** *(continued)*

| *Diels–Alder reaction* | *Ref.* |
|---|---|
| *1,2,4-Triazines* | |
| 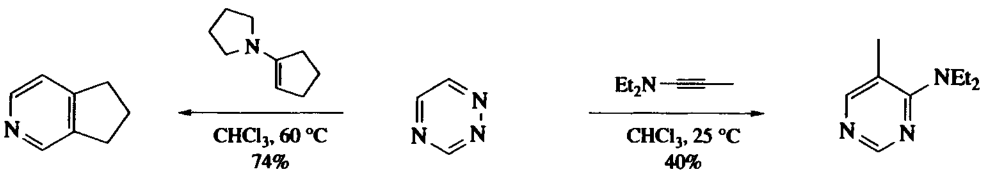 N<br>CHCl$_3$, 60 °C<br>74%<br>N<br>N<br>N<br>Et$_2$N<br>CHCl$_3$, 25 °C<br>40%<br>NEt$_2$<br>N<br>N | 228–235 |
| *1,2,4,5-Tetrazines* | |
| 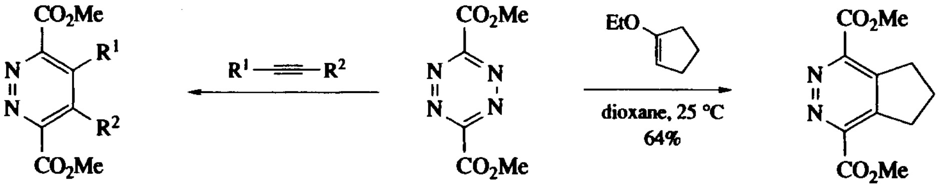 CO$_2$Me<br>R$^1$<br>N<br>N<br>R$^2$<br>CO$_2$Me<br>R$^1$—≡—R$^2$<br>CO$_2$Me<br>N<br>N<br>N<br>N<br>CO$_2$Me<br>EtO<br>dioxane, 25 °C<br>64%<br>CO$_2$Me<br>N<br>N<br>CO$_2$Me<br>R$^1$ = NEt$_2$, R$^2$ = Me; 25 °C; 73%<br>R$^1$ = R$^2$ = CO$_2$Me; 140 °C; 53% | 236–238 |

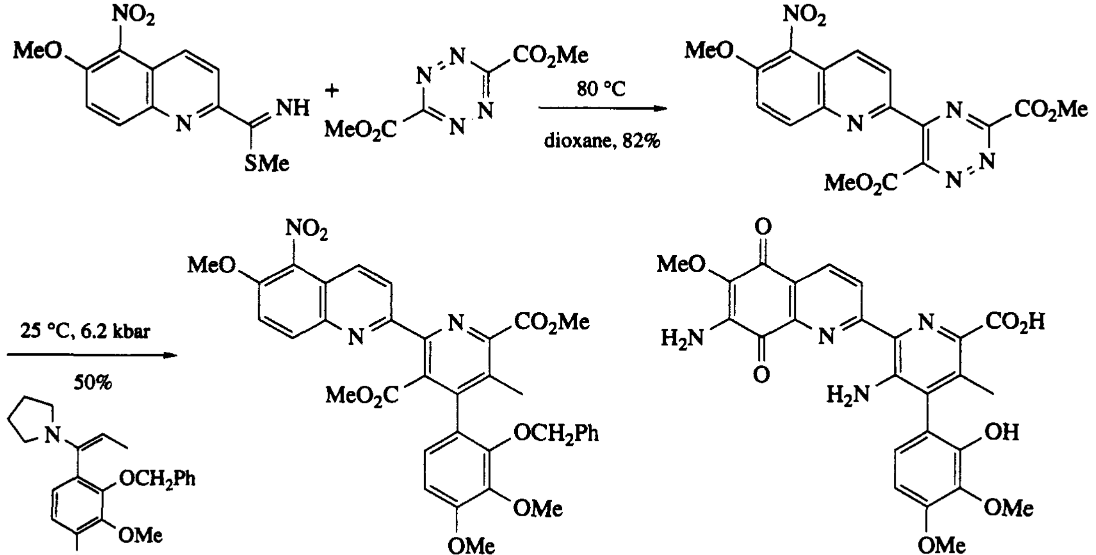

Streptonigrin

**Scheme 15**

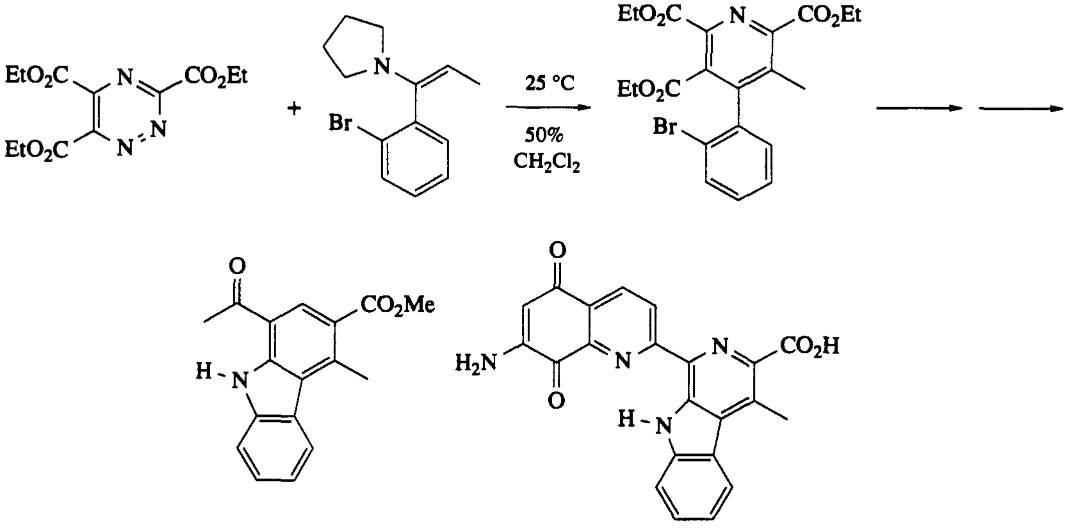

Lavendamycin

**Scheme 16**

to participate in effective $[4^+ + 2]$ cycloadditions is the heteroaromatic quaternary salts including the acridizinium and isoquinolinium cations.[15] The extensive studies of Bradsher and Fields and more recently Falck[250,251] and Franck[252] have been reviewed.[15,253–255] Nucleophilic alkenes including ketene acetals or enol ethers react at room temperature with the acridizinium or isoquinolinium cations but typical electron-deficient dienophiles require more vigorous reaction conditions (100–160 °C, 10–90 h) (Scheme 25). The reactions proceed with complete regiocontrol with the nucleophilic carbon of an electron-rich dienophile attaching to the expected aromatic quaternary salt electrophilic site (acridizinium C-6, isoquinolinium C-1). The rate of the reaction expectedly increases as the nucleophilic character of the dienophile is increased. The observed high diastereoselectivity may be best rationalized by developing electrostatic interactions at or *en route* to the transition state for the $[4^+ + 2]$ cycloaddition where dienophile electron-withdrawing substituents are found *cis* to the quaternary nitrogen in the cycloaddition products and dienophile electron-donating, alkyl or alkenyl substituents are found *trans* to the quaternary nitrogen, and the dienophile alkene geometry is maintained in the $[4^+ + 2]$ cycloaddition products. In addition, the recent interception of simple addition products, albeit under modified reaction conditions, and

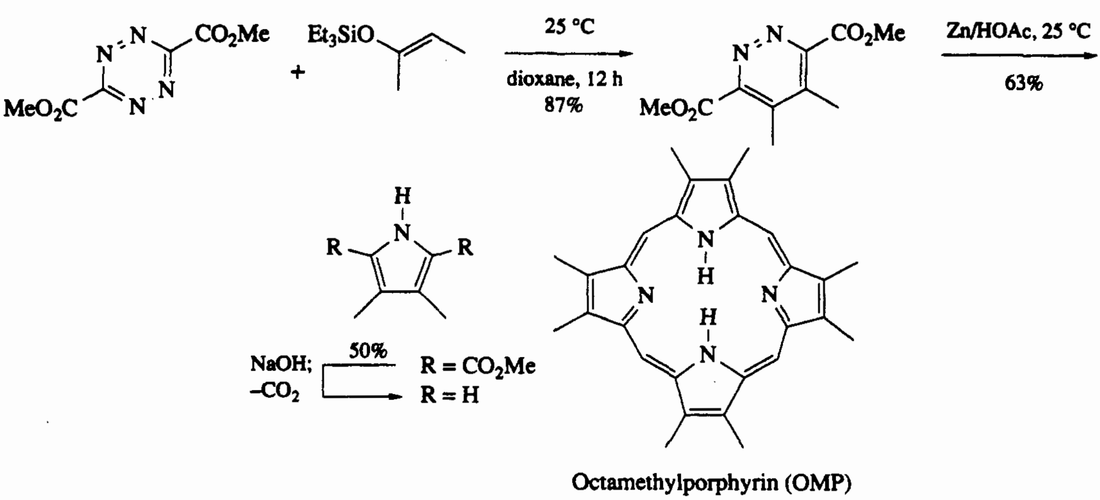

Scheme 17

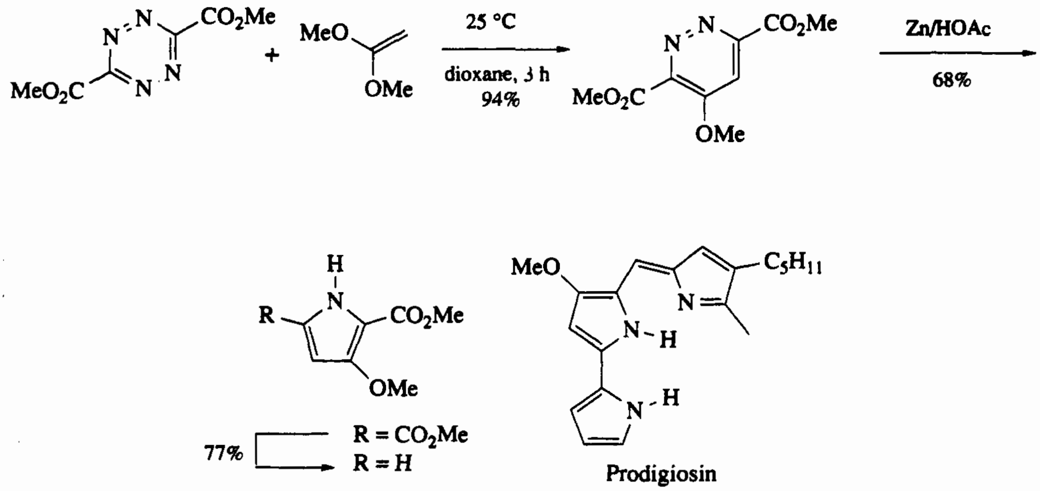

Scheme 18

their subsequent diastereoselective conversion to the observed [$4^+$ + 2] cycloadducts[252] suggest the mechanism for the reaction may be represented as a stepwise addition–cyclization reaction in which the second bond formation need not proceed at a rate that exceeds that of simple bond rotation and in which electrostatic interactions control the regio- and diastereo-selectivity of the cycloaddition reaction.

The use of 2,4-dinitrophenyl aromatic quaternary salts prepared directly from the parent isoquinoline compound and 2,4-dinitrophenyl bromide or chloride enhances the electron-deficient nature of the isoquinolinium salts, accelerates the rate of their [$4^+$ + 2] cycloaddition reactions with electron-rich alkenes, and has permitted the use of isoquinolinium salts previously regarded as unmanageable. The application of these observations in the total syntheses of methylarnottianamide and 14-epicorynoline is summarized in Scheme 26.[250,251]

The preparation of *N*-vinyl-2-ethoxypyrrolidinium tetrafluoroborate and its cycloaddition reactions with terminal alkenes, including electron-rich enol ethers, have been detailed. At present, the reported regioselectivity of this [$4^+$ + 2] cycloaddition is not easily rationalized (equation 16).[256]

The acid-catalyzed or Lewis acid-catalyzed ($TiCl_4$, $BF_3{\cdot}OEt_2$; −78 °C) *in situ* generation of *N*-alkylarylimmonium ions in the presence of electron-rich or neutral alkenes has been shown to provide [$4^+$ + 2] cycloadducts (*N*-methyltetrahydroquinolines) in excellent yields (Scheme 27).[257–260] More recent efforts have demonstrated that immonium ions derived from the condensation of aryl amines and aldehydes in the presence of cyclopentadiene participate as effective 4π components of [$4^+$ + 2] cycloadditions and complement their demonstrated 2π participation in related [4 + $2^+$] cycloaddition reactions (Scheme 27).[261] Additional examples of the participation of cationic azadienes in [$4^+$ + 2] cycloaddition reactions

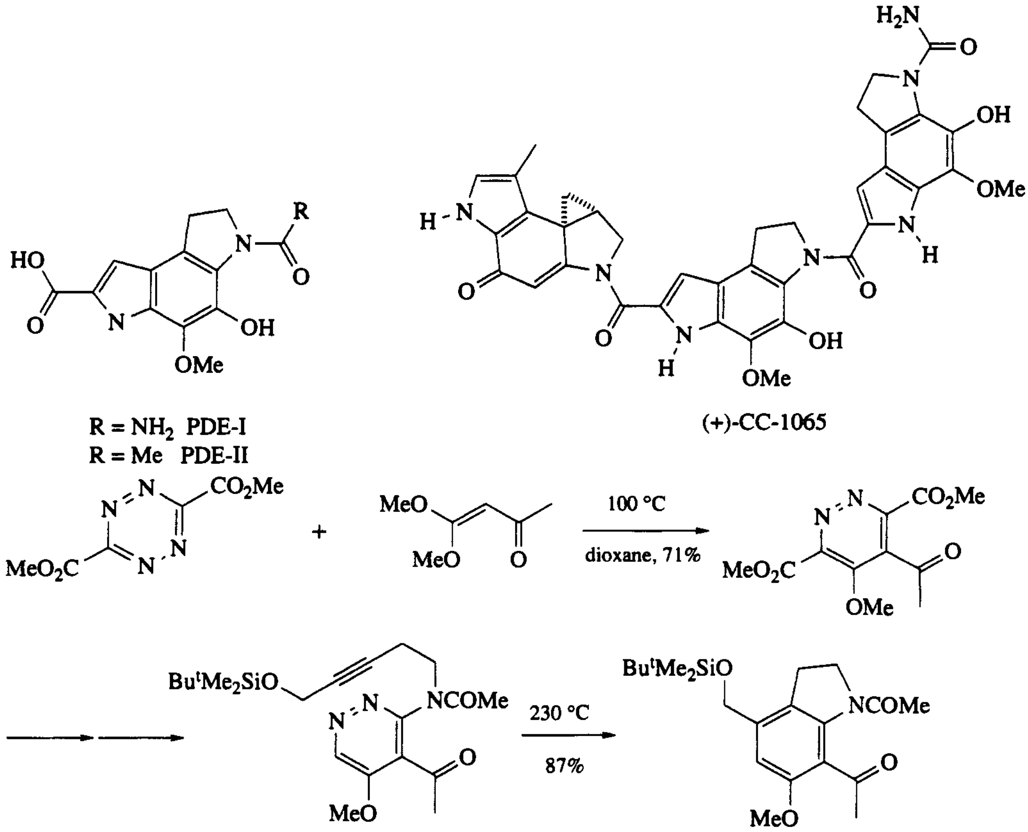

Scheme 19

may be found in recent reviews[15,28] and within the discussion of the Lewis acid-catalyzed [4 + 2] cycloaddition reactions of azabutadienes (Section 4.3.4).

Two classes of cationic heteroazadienes have been shown to participate in effective [4$^+$ + 2] cycloaddition reactions: (1) *N*-methyl-*N*-methylenium amide[262] cations and simple *N*-methylenium amides[263–267] and (2) vinyl nitrosonium cations[268–270] (Scheme 28). *N*-Methyl-*N*-methylenium cations and the simple *N*-methylenium benzamide cation have been shown to participate in regio- and stereo-specific [4$^+$ + 2] cycloaddition reactions with a range of representative electron-rich, neutral or electron-deficient dienophiles in which the alkene geometry is maintained in the cycloaddition products. As noted by investigators in this area, the clean preservation of dienophile alkene geometry, and the lack of observed rearrangement products potentially derived from polar intermediates susceptible to carbocation rearrangement, satisfy important criteria required of a concerted cycloaddition reaction but do not exclude a two-step addition–cycloaddition reaction in which the subsequent cyclization of a polar intermediate is more rapid than carbon–carbon bond rotation or carbocation rearrangement.[29,253]

Similarly, *in situ* generation of *N*-vinyl-*N*-cyclohexylnitrosonium cations and their 4π participation in regio- and stereo-specific [4$^+$ + 2] cycloaddition reactions with the full range of electron-rich, neutral and electron-deficient alkenes continue to be extensively investigated.[15,268–270]

### 4.3.6.2 Cationic Oxabutadienes

The most extensively explored class of cationic oxabutadienes are the 3-aza- and 2-aza-1-oxabutadienes including the *N*-methyl-*N*-methylenium and simple *N*-methylenium amides and *N*-vinyl-*N*-cyclohexylnitrosonium cation detailed in the preceding section.[15] In addition, the *o*-hydroxybenzyl carbocation generated *in situ* has been shown to participate in regio- and stereo-specific [4$^+$ + 2] cycloaddition reactions in which the alkene geometry of the dienophile is maintained in the cycloaddition reaction (Scheme 29).[271] Schmidt has described the presumed 4π participation of *in situ* generated

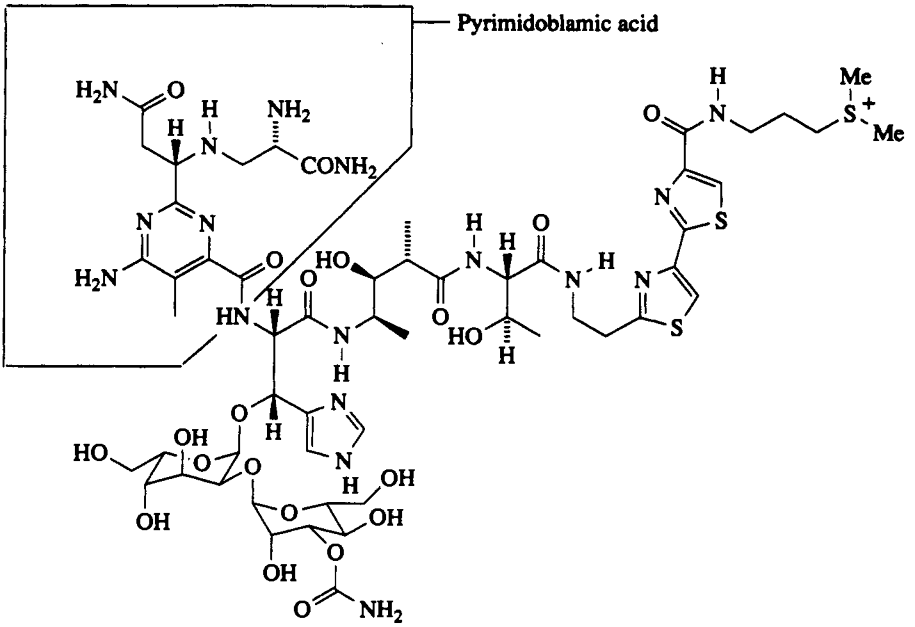
Pyrimidoblamic acid

Bleomycin $A_2$

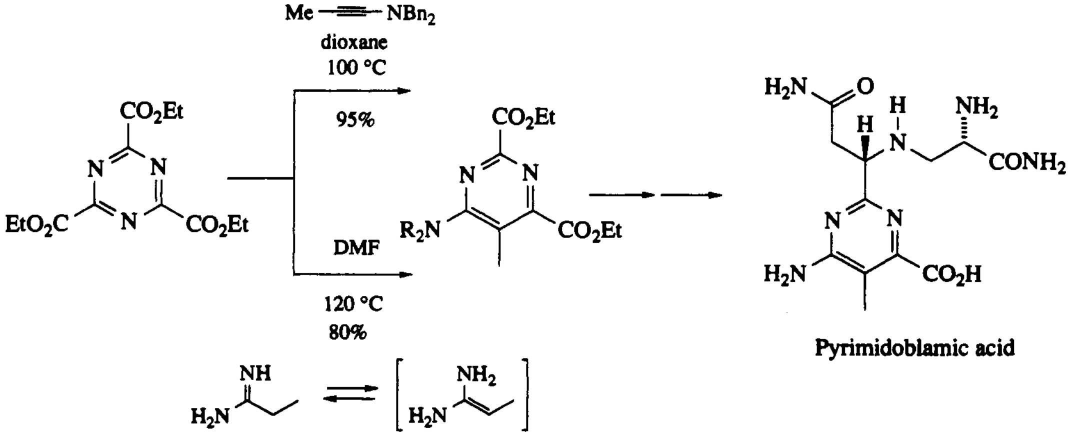
Me—≡—NBn2
dioxane
100 °C
95%
DMF
120 °C
80%
Pyrimidoblamic acid

**Scheme 20**

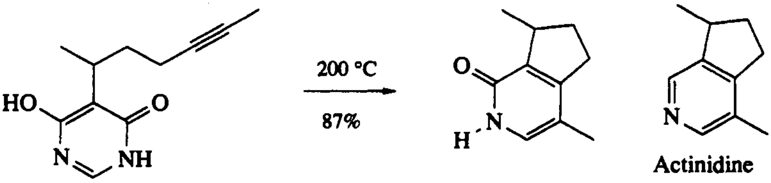
200 °C
87%
Actinidine

**Scheme 21**

β-acylvinyl carbocations in a [4⁺ + 2] cycloaddition reaction providing pyrylium salts (equation 17).[272,273]

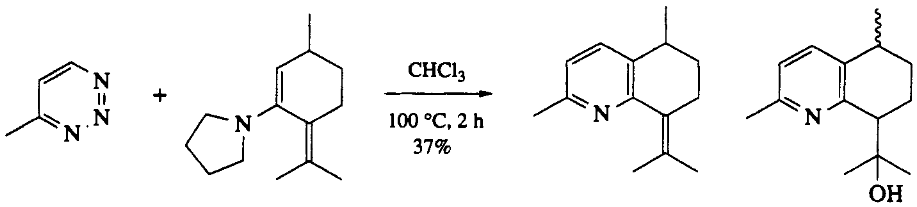
CHCl3
100 °C, 2 h
37%
OH
Fabianine

**Scheme 22**

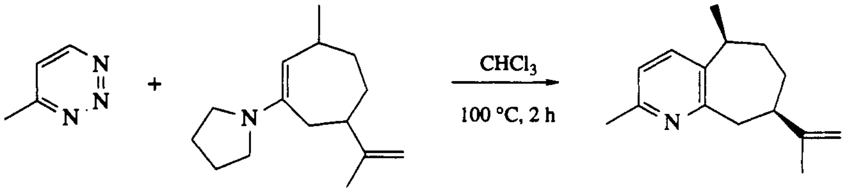
CHCl3
100 °C, 2 h
Guaipyridine

**Scheme 23**

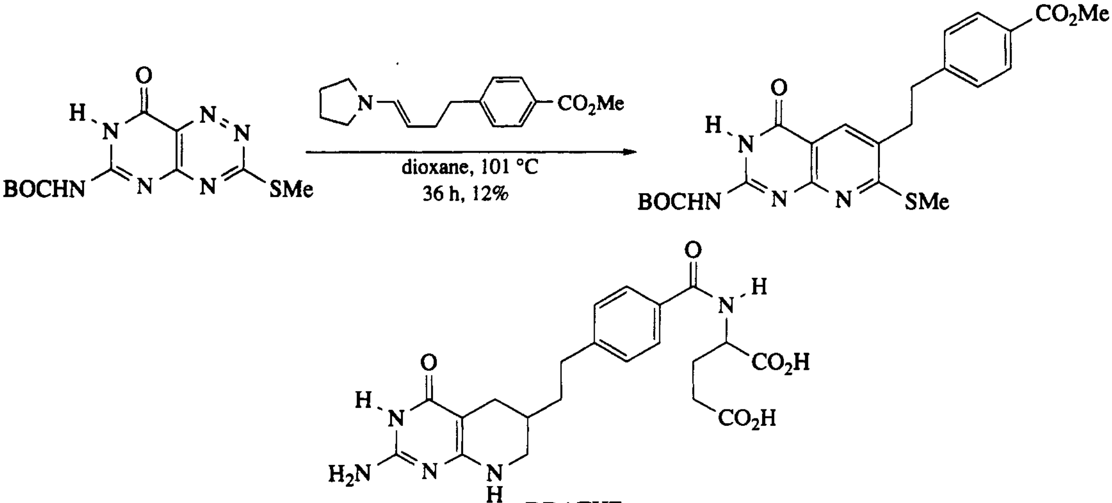
BOCHN
SMe
CO2Me
dioxane, 101 °C
36 h, 12%
CO2H
H2N
DDATHF

**Scheme 24**

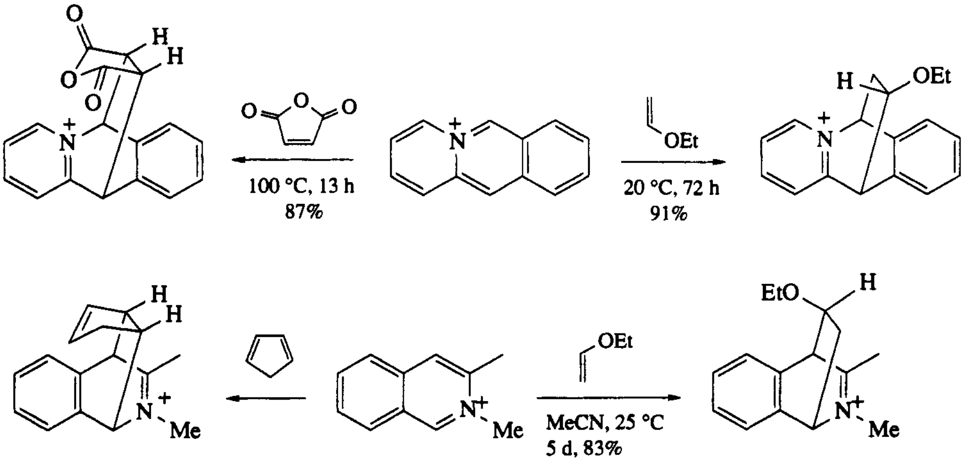
100 °C, 13 h
87%
OEt
20 °C, 72 h
91%
Me
MeCN, 25 °C
5 d, 83%
EtO

**Scheme 25**

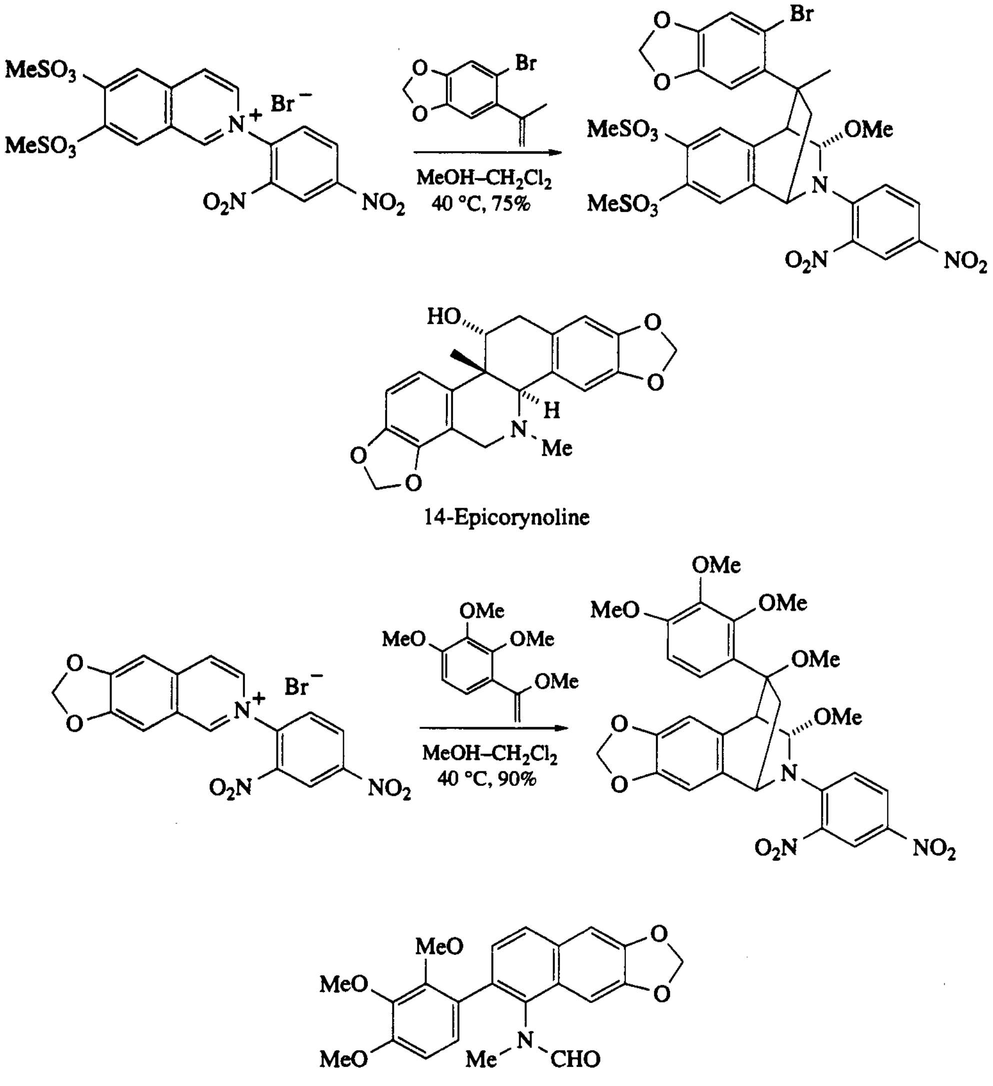
MeSO3
MeSO3
Br−
O2N
NO2
Br
MeOH–CH2Cl2
40 °C, 75%
OMe
MeOH–CH2Cl2
40 °C, 90%
CHO

14-Epicorynoline

Methylamottianamide

**Scheme 26**

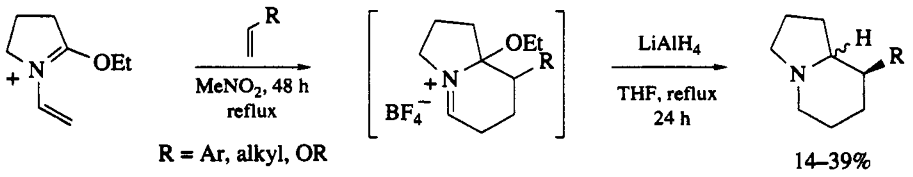
OEt
R
MeNO2, 48 h
reflux
R = Ar, alkyl, OR
BF4−
LiAlH4
THF, reflux
24 h
H
14–39%

(16)

### 4.3.6.3 Cationic Thiabutadienes

A growing class of useful [$4^+ + 2$] cycloadditions based on the use of *in situ* generated 2-thieniumbutadienes have been detailed.[274–277] The 4π participation of arylthienium salts in [$4^+ + 2$] cycloaddition reactions with alkenes, alkynes and nitriles[274–276] complements the 2π participation of simple thienium salts in [$4 + 2^+$] cycloadditions (Scheme 30). Thioamidomethylenium cations generated *in situ* from hydroxymethylthioamides have been shown to participate in regio- and stereo-specific [$4^+ + 2$] cycloadditions to provide 5,6-dihydro-4*H*-1,3-thiazinium salts, although the conversions are lower than that observed with amidomethylenium cations (equation 18).[277]

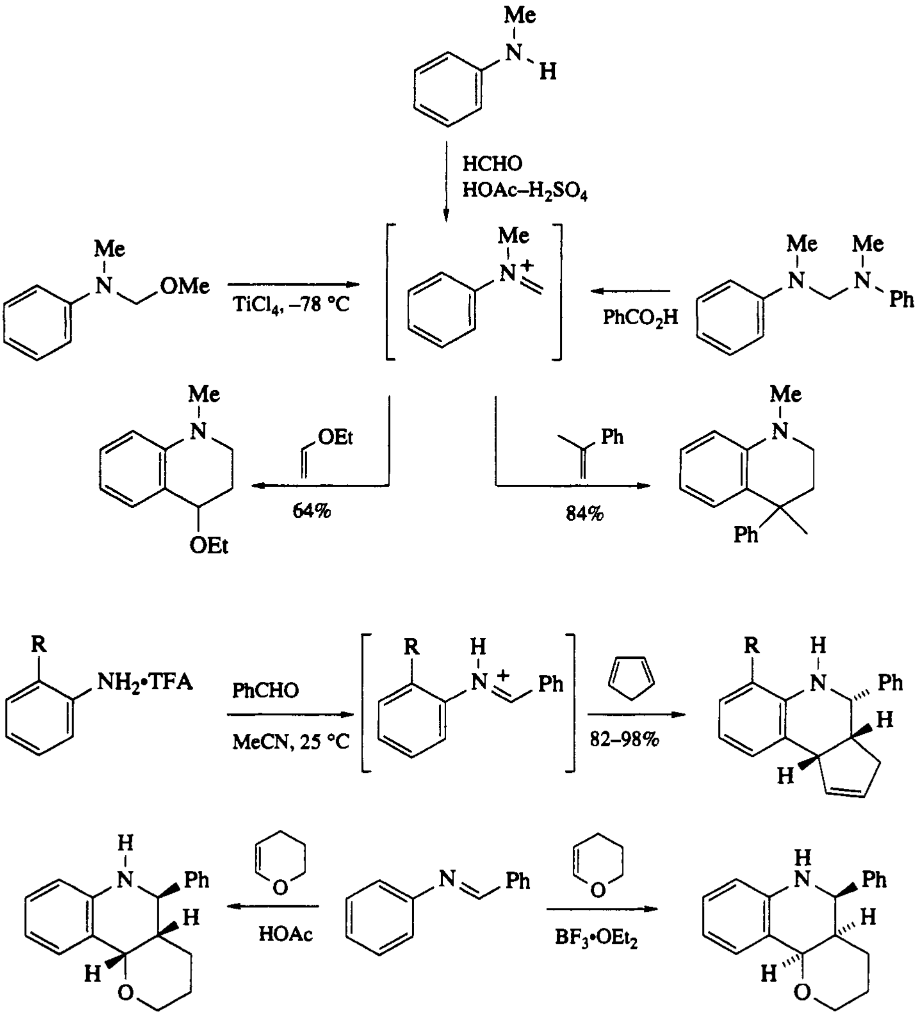
Me
N
H
HCHO
HOAc–$H_2SO_4$
Me
N
OMe
$TiCl_4$, –78 °C
Me
N+
Me
Me
N
N
Ph
$PhCO_2H$
Me
N
OEt
OEt
64%
Ph
84%
Me
N
Ph
R
$NH_2$•TFA
PhCHO
MeCN, 25 °C
R
H
N+
Ph
82–98%
R
H
N
Ph
H
H
H
N
Ph
H
H
O
O
HOAc
N
Ph
O
$BF_3$•$OEt_2$
H
N
Ph
H
H
O

**Scheme 27**

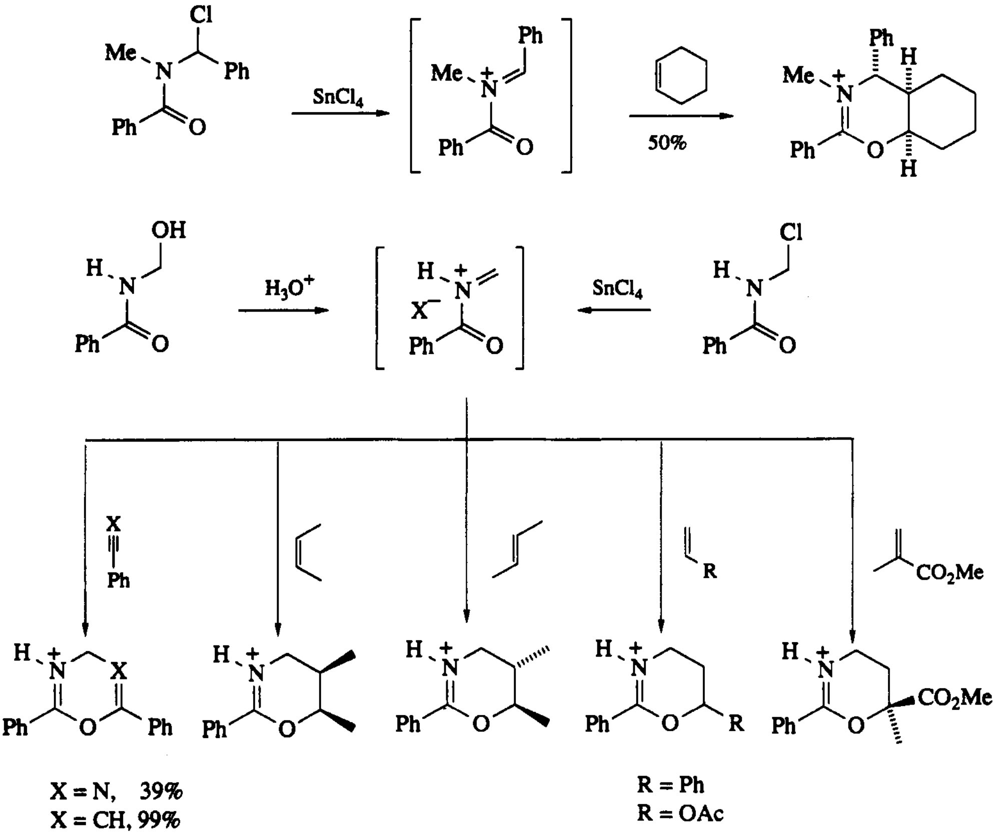
SnCl$_4$
50%
H$_3$O$^+$
SnCl$_4$
X$^-$
X = N, 39%
X = CH, 99%
R = Ph
R = OAc
CO$_2$Me

Scheme 28

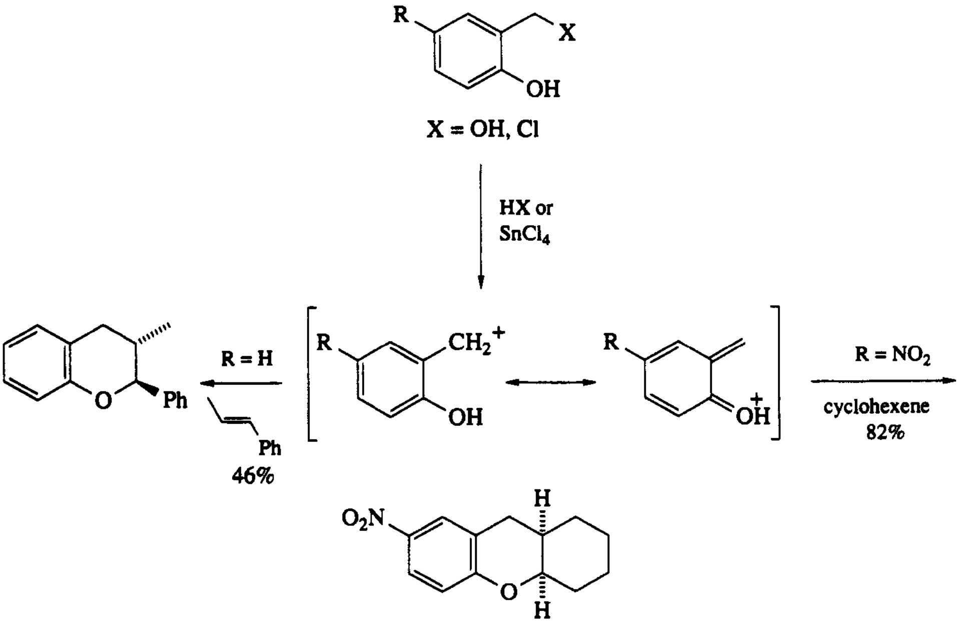
X = OH, Cl
HX or
SnCl$_4$
R = H
46%
R = NO$_2$
cyclohexene
82%

Scheme 29

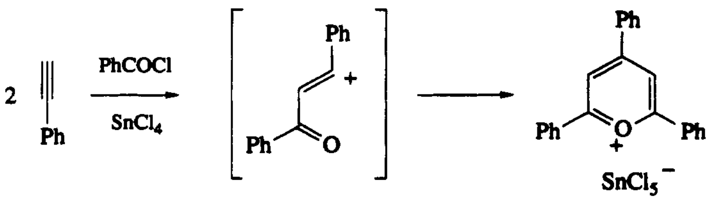

(17)

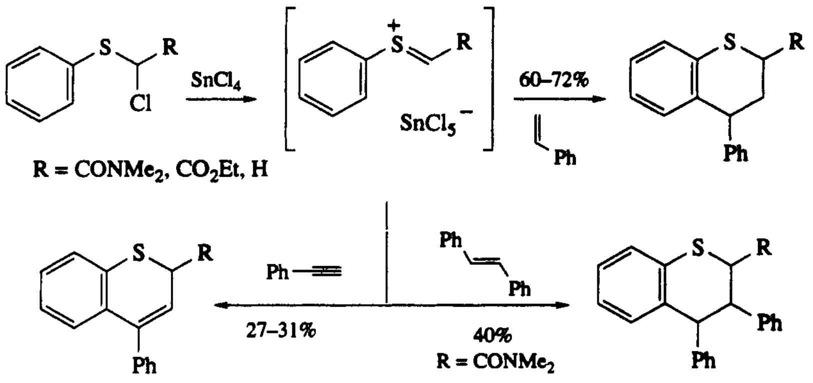

**Scheme 30**

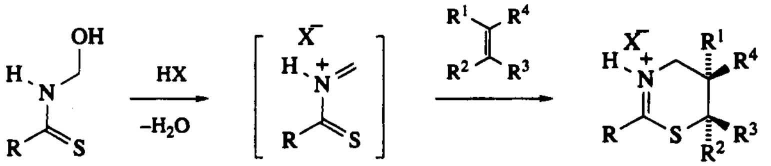

(18)

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# 4.4

# Intramolecular Diels–Alder Reactions

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## 4.4.1 INTRODUCTION

The Diels–Alder reaction, first described in 1928,[1] has enjoyed widespread use in organic synthesis.[2] This [4 + 2] cycloaddition is particularly valuable in that it forms two bonds in a cyclohexenyl system with simultaneous creation of up to four new stereocenters. Curiously, the intramolecular version in which the diene and dienophile are tethered by a connecting chain was not investigated for many years. Alder and Schumaker reported the first example of the intramolecular reaction in 1953,[3] but it was not until the early 1960s that additional examples began to appear in the literature.[4] Since the mid-1970s, however, a virtual explosion of interest in this reaction has occurred.[5] The increased reactivity (due to favorable entropy considerations) and heightened regioselectivity (due to constraints posed by the connecting chain), as well as the potential for the synthesis of stereochemically complex polycyclic ring systems, account for the growth of applications of this reaction in organic and particularly natural products synthesis.

Two major classes of intramolecular Diels–Alder (IMDA) reactions may be identified based on the point of connection of the diene to the dienophile (Figure 1). Type I reactions involve trienes with the connecting chain attached to the diene terminus, while type II substrates have the dienophile tethered *via* one of the internal diene positions.

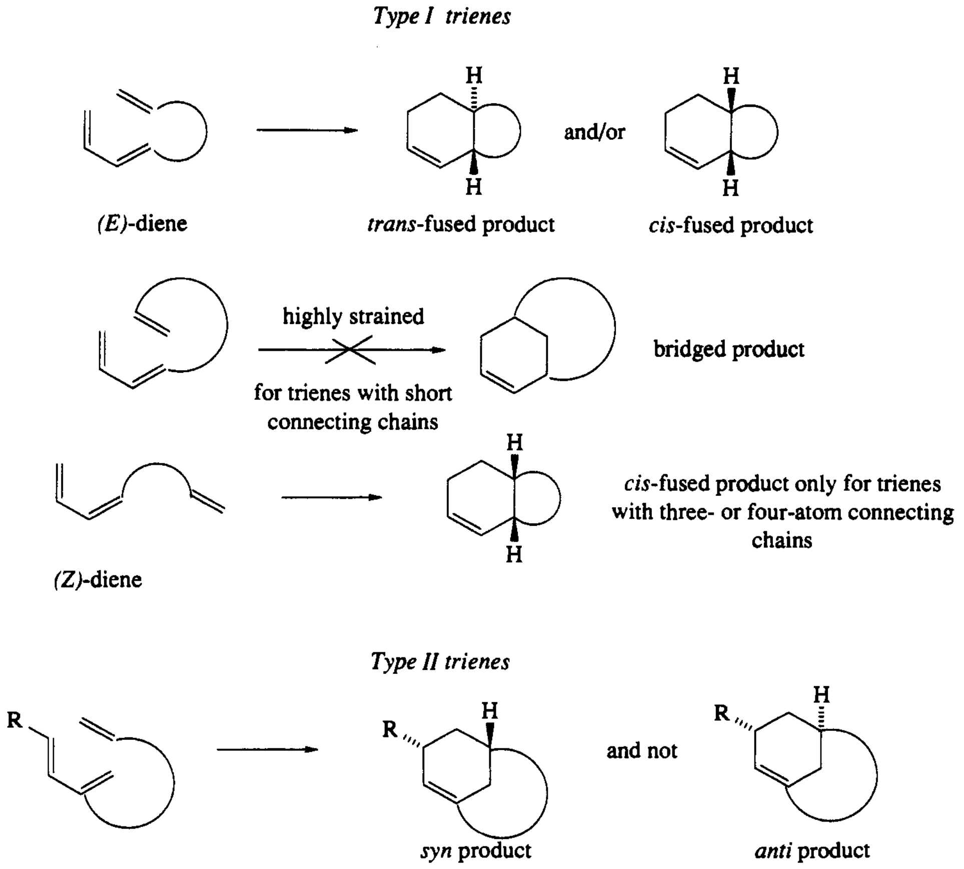

**Figure 1**

The ability to control the stereo- and regio-selectivity of these cycloadditions is critical for their successful application in synthesis. Except for some specialized cases,[3,6] type I IMDA reactions are feasible only if the connecting chains contain three or more atoms.[4c] In the vast majority of successful cases the fused rather than the bridged product is obtained, even when (*Z*)-dienes are employed. The only reported examples of bridged product formation involving type I (*E*)-diene substrates occur with connecting chains of 10 or more atoms.[7] The most significant issue with type I trienes is that of stereoselectivity, as mixtures of *cis* and *trans*-fused cycloadducts are accessible from (*E*)-dienes, the most frequently encountered class of substrates. This problem of simple diastereoselection is not an issue with type I (*Z*)-dienes with three or four atom connecting chains, however, as the transition states leading to the *trans*-fused products are highly strained.[4c,8]

Simple diastereoselection is also a potential concern for type II IMDA reactions. However, type II substrates with bridging chains of three or four members cyclize exclusively to the *syn* cycloadduct, since the transition state leading to the *anti* diastereomer is more strained than that leading to the *syn* diastereomer.[9] It should be noted as well that type II cycloadditions are restricted to substrates with bridging chains of at least three members owing to the strain that develops in the transition state.[10]

Another selectivity issue that influences the applicability of all IMDA reactions in synthesis is that of relative diastereoselection if the substrate is chiral. This problem is encountered whenever the substrate contains one or more stereocenters on the chain linking the diene and dienophile, or is chiral by virtue of stereocenters associated with a substituent anywhere else in the Diels–Alder substrate. Conventional asymmetric synthesis involving removable chiral auxiliaries falls into the latter category.

The purpose of this review is to assess critically the stereoselectivity of the IMDA reaction. Owing to the number of exhaustive reviews that have appeared,[5] no effort has been made to provide yet another comprehensive survey here. Rather, our focus is on the selectivity issues that define the utility of this reaction in synthesis, and only a carefully selected number of examples will be provided to illustrate each point. Attempts have been made, however, to include examples published since 1987, the date that the last major review appeared.[5i] The literature coverage extends through the end of 1988.

This chapter is organized along three distinct stereoselectivity issues: (i) simple diastereoselection, (ii) relative diastereoselection and (iii) absolute stereochemical induction. Because the greatest number of examples involve type I trienes with three- or four-atom connecting chains, the review is heavily slanted towards the IMDA reactions of functionalized 1,6,8-nonatrienes and 1,7,9-decatrienes. Factors that are examined include the role of dienophile activating groups, the influence of nonbonded interactions involving substituents on the diene or the connecting chain, and the influence of heteroatom substituents on IMDA diastereoselectivity.

## 4.4.2 SIMPLE DIASTEREOSELECTION

### 4.4.2.1 All-carbon Nona- and Deca-trienes

#### *4.4.2.1.1 Effect of dienophile activating group*

It has been recognized for many years that the presence of a dienophile activating group has a significant effect on the stereoselectivity of IMDA reactions. The results in Figure 2 show that *trans*-fused cycloadducts are favored in the cyclizations of terminally activated nonatrienes such as (**1**) or (**2**),[11] while with internally activated systems such as (**5**)–(**7**) it is the *cis*-fused cycloadduct that is favored.[12–15] While the results with (**1**), (**6**) and (**7**) are superficially consistent with *endo* stabilization of the predominant reaction transition state, the results with (**2**) and (**5**) are not; in these cases the major product diastereomers arise *via* transition states in which the dienophile activating group occupies an *exo* orientation relative to the diene. In contrast to these results in the nonatriene series, introduction of a terminal $CO_2Me$ activating group in the 1,7,9-decatriene system has a very minor effect on stereoselectivity relative to the unsubstituted triene (**10**).[13a,16] A significant shift in stereoselectivity favoring the *cis*-fused product, however, occurs with internal dienophile activation, *e.g.* (**11**) (Figure 3).[17,18]

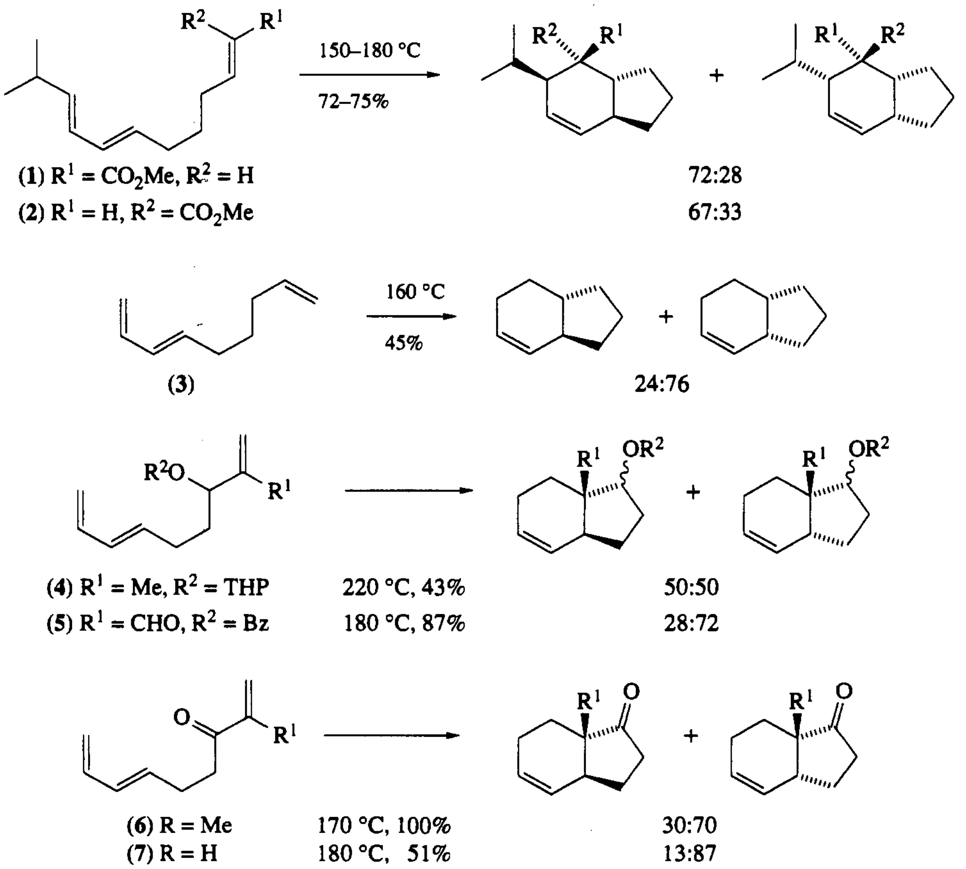

**Figure 2** 1,6,8-Nonatriene cyclizations

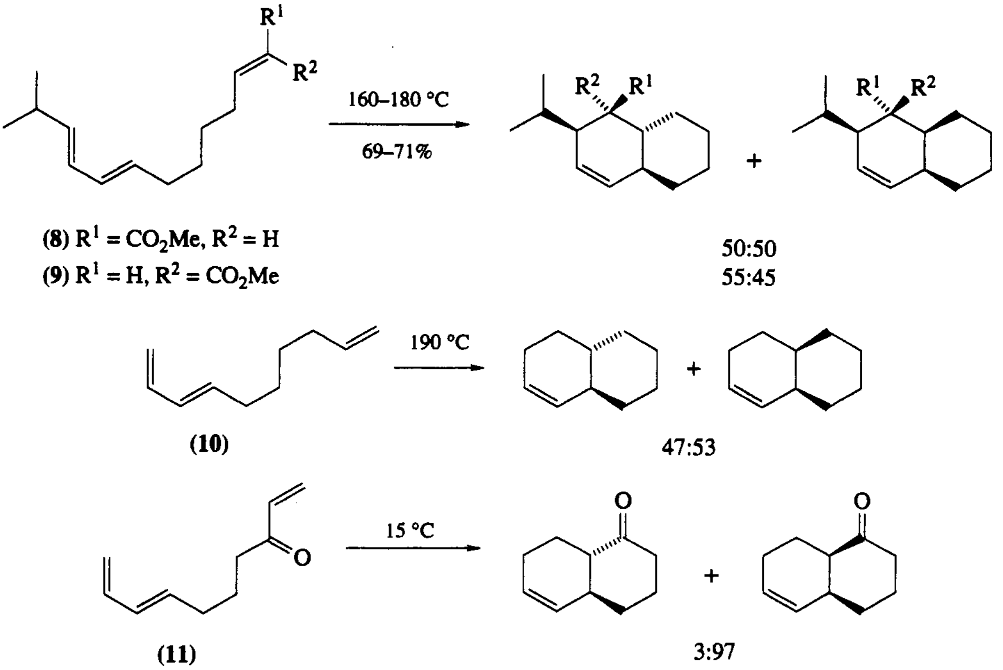

**Figure 3** 1,7,9-Decatriene cyclizations

The currently accepted interpretation of these data involves the concept of concerted but asynchronous transition states.[2i,19] Boeckman was first to apply this idea to IMDA reactions,[20] but shortly thereafter White,[21] Taber[12b] and Roush[12a] also invoked this model to rationalize stereochemical results. Houk further expanded this theory by introducing the concept of 'twist asynchronicity' to rationalize differences between pairs of similarly substituted nona- and deca-trienes.[22]

According to this model, stereoselectivity is governed by the timing of bond formation in the transition states. It is clear that in the absence of overriding steric or substituent effects the *cis*-fused nonatriene transition state (for **3**) is favored enthalpically by *ca.* 1 kcal mol$^{-1}$.[13a] The parent nonatriene transition states, further, are assumed to be rather symmetrical.[22] Addition of a terminal dienophile activating group, $CO_2Me$ for (**1**) or (**2**) (Figure 2), shifts selectivity by at least 1.3 kcal mol$^{-1}$ relative to (**3**) and the *trans*-fused product is then favored by 0.3–0.5 kcal mol$^{-1}$. This effect is attributed to the polarization of the dienophilic C=C bond that causes the LUMO coefficient at C(2) to be larger than at C(1). Consequently, bonding between C(2) and C(6) will be somewhat more advanced than between C(1) and C(9) in the transition state. Under these circumstances, steric or other nonbonded interactions involving the chain separating diene and dienophile develop at an early stage of the reaction, and the transition state that has more *trans*-disubstituted cyclopentanoid character becomes the more stable one (due to 'twist asynchronicity' resulting from torque applied to the developing C(2)—C(6) bond by the three-carbon connecting chain).[22] Similarly, introduction of a substituent at the diene terminus C(9) that increases the HOMO coefficient at C(6) should also lead to increased *trans* stereoselectivity in the Diels–Alder reaction (Figure 4).

For trienes like (**5**)–(**7**) with dienophile activating groups located at C(2) ('internally' activated systems), however, the situation is reversed. The LUMO coefficient at C(1) is greater than at C(2) and so bonding between C(1) and C(9) should be more advanced early in the transition state. This form of twist asynchronicity, however, is probably less significant than that involving the C(2)—C(6) bond for terminally activated nonatrienes (**1**,**2**) since the selectivity of the IMDA reactions of (**5**)–(**7**) is comparable with that obtained with the unsubstituted nonatriene (**3**) (also compare results with (**4**), Figure 2).

This model also predicts that selectivity for the *trans*-fused cycloadducts in nonatriene ($n = 0$) or decatriene ($n = 1$) cyclizations should increase as size of the coefficients at C(2)/C($6 + n$) are increased relative to those at C(1)/C($9 + n$), that is, as the polarization of the dienophile or diene is increased.[23] Tables 1 and 2 summarize results of intramolecular Diels–Alder reactions that provide a test of this proposal.[24,25] First, it is clear that an electron-releasing $Et_2N$ group at C(9) of the nonatrienoate system leads to a substantial increase in selectivity for the *trans*-fused product (compare entries 4–6, Table 1).[26] Increased *trans* stereoselectivity also occurs with C(9)-alkoxy-substituted nonatrienes.[28] A similar effect

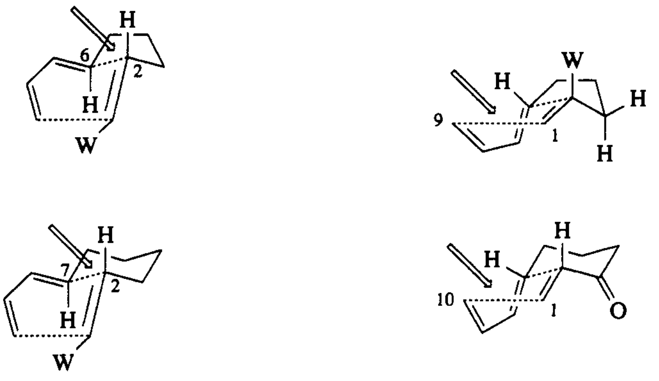

Terminally activated nona- and deca-trienes

Bonding is more advanced at the indicated position in the transition state; *trans*-fused product is favored

Internally activated nona- and deca-trienes

Bonding is more advanced at the indicated position in the transition state; *cis*-fused product is favored

**Figure 4** Asynchronous transition states

may be involved in the increased selectivity of triene (**1**) in entry 5 compared with the C(9)-unsubstituted triene in entry 4, since the alkyl substituent at C(9) of (**1**) is expected to increase the size of the HOMO coefficient at C(6).[23,25c] Second, for trienes with *trans* dienophiles, stereoselectivity for the *trans*-fused cycloadduct increases as the dienophile activating group is changed along the series $CONR_2 < CO_2Me <$ $COMe < CHO$;[24,29] further increases in selectivity occur when Lewis acid catalysis is employed.[11a,24] This trend exactly parallels the ability of these groups to activate alkenes towards β-nucleophilic attack, and is consistent with the predictions made above regarding the increased polarization of the dienophile double bond.

Similar trends, albeit less pronounced in several instances, are apparent in the data summarized in Table 2 for (*E,E,E*)-decatrienes. Houk has attributed the smaller effect of the $Et_2N$ substituent in the deca- compared to the nona-triene series to the smaller requirement for twist asynchronicity in the decatriene transition state. It is argued that this transition state is essentially unstrained by the four-carbon connecting chain and that less torque is applied to the developing C(2)—C(7) bond.[22,26] Although the

**Table 1** Substituent Effects in Cyclizations of Terminally Activated Nonatrienes

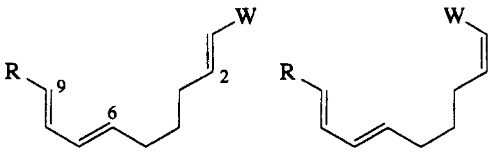

| *Entry* | *R* | *W* | *Temp.* (°C) | *trans:cis* | *Temp.* (°C) | *trans:cis* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | H | 160 | 24:76 | — | — | 13a |
| 2 | $EtO_2C$ | H | 180 | 43:57 | — | — | 13b |
| 3 | $Pr^i$ | $CO(NC_4H_8)$ | 150 | 51:49 | — | — | 24 |
| 4 | H | $CO_2Me$ | 150 | 60:40 | 180 | 65:35 | 11a |
| 5 | $Pr^i$ | $CO_2Me$ | 150 | 72:28 | 180 | 67:33 | 11a |
| 6 | $Et_2N$ | $CO_2Et$ | 60 | 85:15 | — | — | 26 |
| 7 | $Pr^i$ | COMe | 120 | 85:15 | — | — | 24 |
| 8 | Me | $NO_2$ | 80 | 89:11 | 23 | 53:47 | 27 |
| 9 | $Pr^i$ | CHO | 110 | 92:8 | — | — | 24 |
| 10 | H | $CO_2Me\cdot AlEtCl_{2AlEtCl}$ | 23 | >99:1 | 23 | 52:48 | 11a |
| 11 | $Pr^i$ | $CO_2Me\cdot AlEtCl_{2AlEtCl}$ | 23 | >99:1 | 23 | 63:37 | 11a |
| 12 | $Pr^i$ | $COMe\cdot AlEt_{2AlEt}Cl$ | −78 | >99:1 | — | — | 24 |
| 13 | $Pr^i$ | $CHO\cdot AlEt_{2AlEt}Cl$ | −78 | >99:1 | — | — | 24 |

**Table 2** Substituent Effects in Cyclizations of Terminally Activated Decatrienes

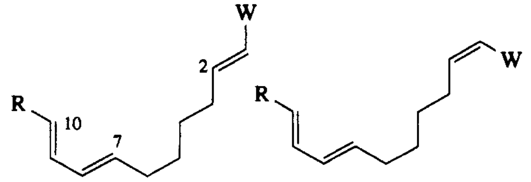

| *Entry* | *R* | *W* | *Temp.* (°C) | *trans:cis* | *Temp.* (°C) | *trans:cis* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | H | 190 | 47:53 | — | — | 13a |
| 2 | $EtO_2C$ | H | 180 | 50:50 | — | — | 13b |
| 3 | H | $CO_2Me$ | 155 | 51:49 | 155 | 51:49 | 16b |
| 4 | $Pr^i$ | $CO_2Me$ | 160 | 50:50 | 180 | 55:45 | 16a |
| 5 | $Et_2N$ | $CO_2Et$ | 40 | 55:45 | — | — | 26 |
| 6 | $Pr^i$ | COMe | 150 | 67:33 | — | — | 24 |
| 7 | $Pr^i$ | CHO | 150 | 75:25 | — | — | 24 |
| 8 | $Pr^i$ | $CO_2Me\cdot AlEtCl_{2AlEtCl}$ | 23 | 88:12 | 23 | <8:92 | 16a |
| 9 | $Pr^i$ | $COMe\cdot AlEtCl_{2AlEtCl}$ | 23 | 97:3 | — | — | 24 |
| 10 | $Pr^i$ | $COMe\cdot AlEtCl_{2AlEtCl}$ | −78 | >99:1 | — | — | 24 |
| 11 | $Pr^i$ | $CHO\cdot AlEtCl_{2AlEtCl}$ | 23 | >98:2 | — | — | 24 |
| 12 | $Pr^i$ | $CHO\cdot AlEtCl_{2AlEtCl}$ | −78 | >99:1 | — | — | 24 |

$CO_2Me$ group increases *trans* selectivity by only 0.1 kcal $mol^{-1}$ in the decatriene series (compare entries 1–3, Table 2) *versus ca.* 1.3 kcal $mol^{-1}$ with the nonatrienes, the additional increases in selectivity due to the COMe and CHO activating groups are comparable in the two series: 0.6–0.7 kcal $mol^{-1}$ for COMe and 0.3–0.4 kcal $mol^{-1}$ for CHO.[24]

The behaviors of the (*Z,E,E*)-nona- and deca-trienes are different, however. The data in Table 1 indicate that (*Z,E,E*)-nonatriene stereoselectivity is unaffected by changes in the dienophile activating group, while the more limited data available for (*Z,E,E*)-decatrienes in Table 2 suggest that increased dienophile activation increases selectivity for the *cis*-fused, and not the *trans*-fused, product. Two factors presumably contribute to these results: twist asynchronicity and Alder *endo* stabilization that undoubtedly becomes increasingly important as the dienophile activation increases. It is a well established trend in bimolecular Diels–Alder reactions that increased amounts of *endo* product are obtained as dienophile activation is increased.[2] Although *endo* stabilization is apparently not an important stereochemical control element of the IMDA reactions of $CO_2Me$ activated trienes like (**1**), (**2**), (**8**) and (**9**) (Figures 2, 3), it is necessary to invoke this factor in order to develop an internally consistent rationalization of the data summarized in Tables 1 and 2:

For terminally activated (*E,E,E*)-trienes in both series, twist asynchronicity and *endo* stabilization of the transition state are cooperative and increased selectivity for the *trans*-fused product occurs with increased dienophile activation. The dienophile activating group occupies an *endo* position in the transition state as long as the dienophile geometry is (*E*).

For (*Z,E,E*)-nonatrienes, however, twist asynchronicity favors the *trans*-fused adduct and Alder *endo* stabilization favors the *cis*-fused product. These effects evidently cancel such that no significant change in selectivity occurs with increased dienophile activation.

Increased *endo* stabilization of the *cis*-fused transition state must be invoked to account for the increased selectivity in the Lewis acid catalyzed cyclization of the (*Z,E,E*)-decatrienoate recorded in Table 2, entry 8.[16a] Because twist asynchronicity is believed to be less important in the decatriene transition state,[22,26] Alder *endo* stabilization apparently dominates twist asynchronicity in this case.

The increased stereoselectivity of decatrien-3-ones relative to the nonatrien-3-ones[14,15,17] may also be the consequence of cooperativity between twist asynchronicity and *endo* stabilization that both favor the *cis*-fused product. The decatrien-3-one transition state is considerably less strained than the nonatrien-3-one transition state, and the uncatalyzed decatrienone cyclizations occur at or near ambient temperature.[17] Consequently, one expects greater *endo* stabilization, and hence also greater *cis* stereoselectivity, in the decatrienone intramolecular Diels–Alder reactions.

#### *4.4.2.1.2 Lewis acid and other catalyzed intramolecular Diels–Alder reactions*

The use of Lewis acid catalysis is a powerful method of increasing the rates and diastereoselectivity of many IMDA reactions. Several examples involving terminally activated nona- and deca-trienes are summarized in Tables 1 and 2. Examples illustrating rate and stereoselectivity improvements in the cyclizations of functionalized decatrien-3-ones appear in Figure 5.[30–32] The most striking of these is the cyclization of (**12**) when performed in the presence of trifluoroacetic acid at –78 °C, providing (**13**) with 94% stereoselectivity.[30]

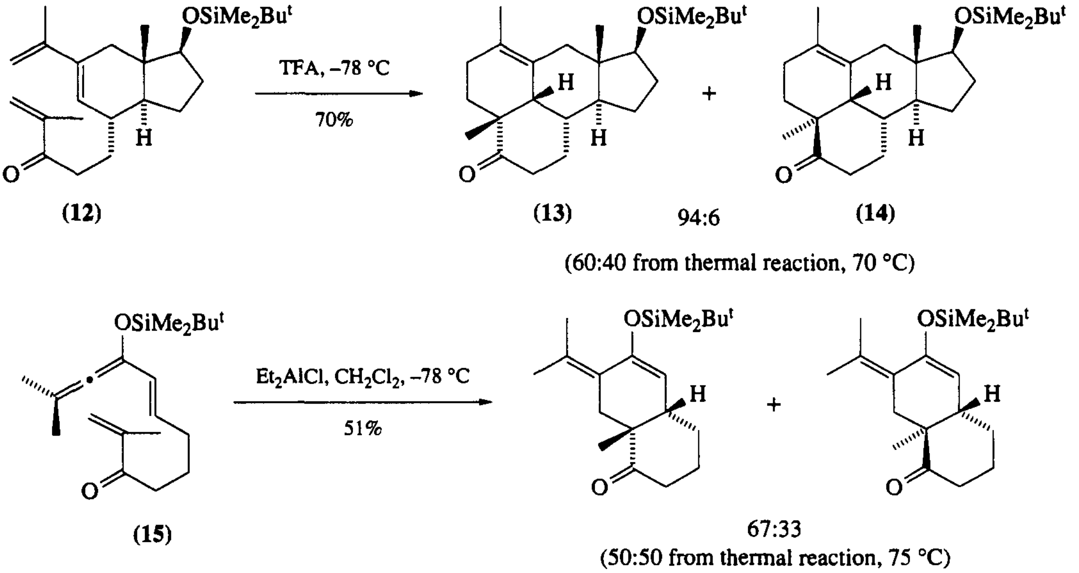

(**12**) (**13**) 94:6 (**14**)

(60:40 from thermal reaction, 70 °C)

(**15**) 67:33

(50:50 from thermal reaction, 75 °C)

**Figure 5**

Several examples of IMDA reactions that are successful with Lewis acid or alumina catalysis, but which are not preparatively useful or fail altogether under thermal conditions, have been reported.[15,33,34] Among the former group are trienones such as (**16**).[15,33] More frequently encountered, however, are substrates that fail to cyclize in the presence of Lewis acids. Polymerization of the diene is a frequently encountered problem, and consequently relatively mild Lewis acids such as the alkylaluminum chlorides (*e.g.* $EtAlCl_2$ or $Et_2AlCl$) are generally recommended.[35] Another group of problematic functionality are alkoxy substituents allylic to the diene that readily ionize to pentadienyl carbonium ions upon exposure to Lewis acids.[11a] In such cases it is necessary to use a highly activated dienophile so as to accelerate the rate of cycloaddition relative to the pentadienyl carbonium ion decomposition pathway. This point has been demonstrated in several studies by Marshall, who has shown that alkoxy-substituted trienals such as (**17**) smoothly cyclize in the presence of Lewis acids,[29] whereas the corresponding methoxycarbonyl activated triene (**18**) fails to cyclize under analogous conditions.[16b] Comparison of the stereoselectivities of the IMDA reactions of (**17**) and (**18**) provides another set of data that demonstrates the tendency of terminally activated 1,7,9-decatrienes to cyclize with increasing selectivity to *trans*-fused cycloadducts upon increased dienophile activation (Figure 6). Lewis acid catalysis may be used with alkoxy-substituted trienoates, however, as long as the alkoxy substituent is not in a dienylic position (see cyclization of **21**[102]).

The reactive species in Lewis acid catalyzed IMDA reactions of α,β-unsaturated ester dienophiles is formally a Lewis acid stabilized dioxolenium ion. It stands to reason that other allylic species bearing positive charges, such as dioxolenium ion (**22**) and allyl cations (**23**), should also function as highly reac-

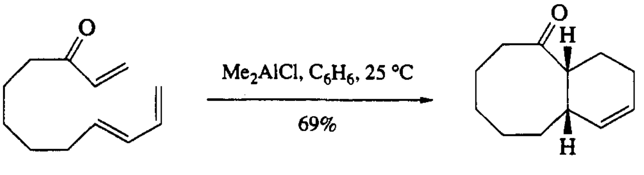

(**16**) *cis* isomer only

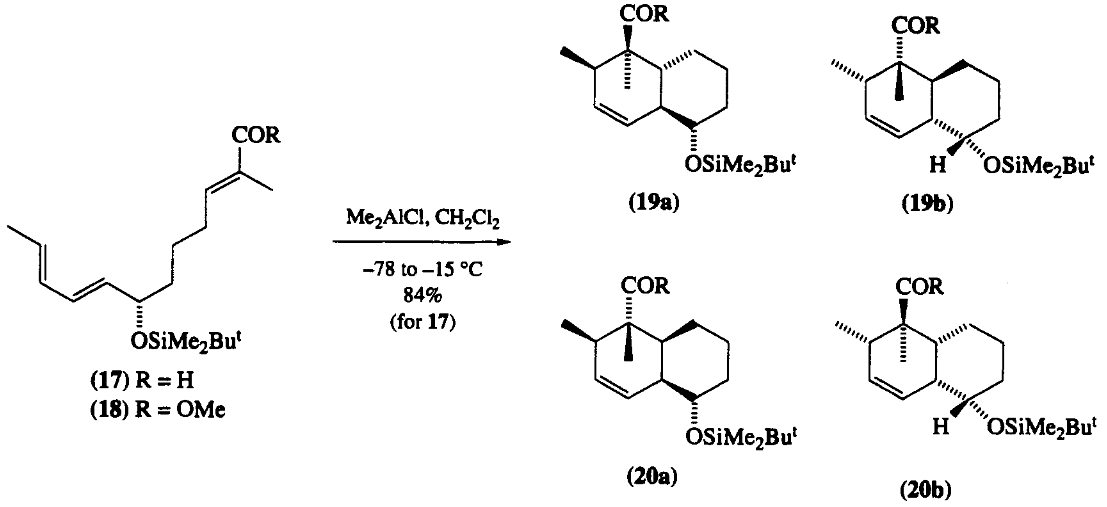
COR
OSiMe$_2$Bu$^t$
(17) R = H
(18) R = OMe
Me$_2$AlCl, CH$_2$Cl$_2$
–78 to –15 °C
84%
(for 17)
COR
OSiMe$_2$Bu$^t$
(19a)
COR
H
OSiMe$_2$Bu$^t$
(19b)
COR
OSiMe$_2$Bu$^t$
(20a)
COR
H
OSiMe$_2$Bu$^t$
(20b)

| *Substrate* | *Conditions* | **(19a)** | **(19b)** | **(20a)** | **(20b)** | *trans:cis* |
|---|---|---|---|---|---|---|
| **(17)** | Me$_2$AlCl, as above | 15 | 75 | 10 | 0 | 90:10 |
| **(17)** | thermal (150 °C) | 27 | 27 | 33 | 13 | 54:46 |
| **(18)** | thermal (150 °C) | 15 | 13 | 49 | 23 | 28:72 |

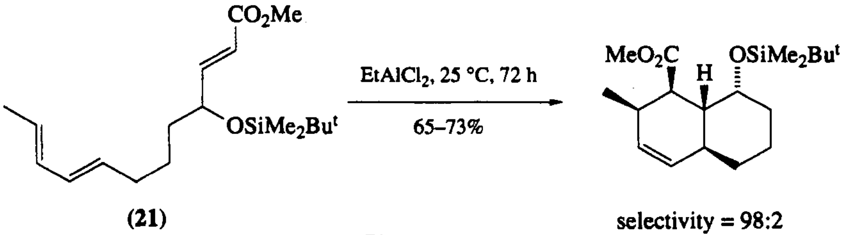
CO$_2$Me
OSiMe$_2$Bu$^t$
(21)
EtAlCl$_2$, 25 °C, 72 h
65–73%
MeO$_2$C
H
OSiMe$_2$Bu$^t$
selectivity = 98:2

**Figure 6**

tive dienophiles. Dioxolenium ions (**22**) were encountered as reactive intermediates in studies of trienes such as (**24**) and (**25**) (Figure 7).[36] Recent studies by Gassman have shown that α,β-unsaturated dioxolenium ions, generated by treatment of triethyl orthoacrylate with trimethylsilyl triflate in CH$_2$Cl$_2$ at –78 °C, are excellent dienophiles for intermolecular Diels–Alder reactions.[37] Similarly, acetals of α,β-unsaturated aldehydes are precursors to alkoxy-substituted allyl cations that are also excellent ionic Diels–Alder dienophiles.[38]

Gassman first observed the intermediacy of allyl cations as dienophiles in connection with efforts to extend the aminium cation-radical catalyzed Diels–Alder reaction[39] to intramolecular cases.[40] It was found that the cyclization of tetraene (**26**) performed in the presence of 0.2 equiv. of tris(*p*-bromophenyl)aminium hexachloroantimonate [$Ar_3N^{+}\cdot Cl_6Sb^{-}$] was in fact catalyzed by protic acid.[40,41] A better means of catalyzing the cyclization of (**26**) involves use of 4 mol % trifluoromethanesulfonic acid at –23 °C for 6 min, which provides the *trans*-fused cycloadduct in 88% yield (98% isomeric purity). Similar treatment of (**27**), however, provided a mixture of *cis*- and *trans*-fused products. A subsequent report revealed that allylic alcohols and allylic ethers are useful precursors to the allyl cation dienophiles with

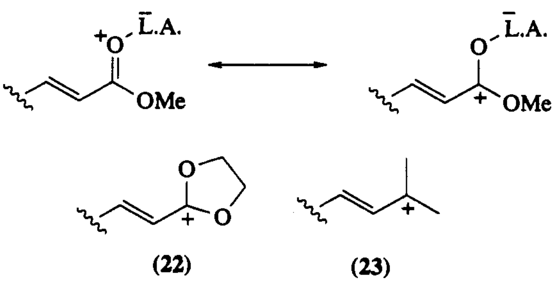
+O
L.A.
OMe
O
L.A.
+
OMe
O
O
+
+

**(22)** **(23)**

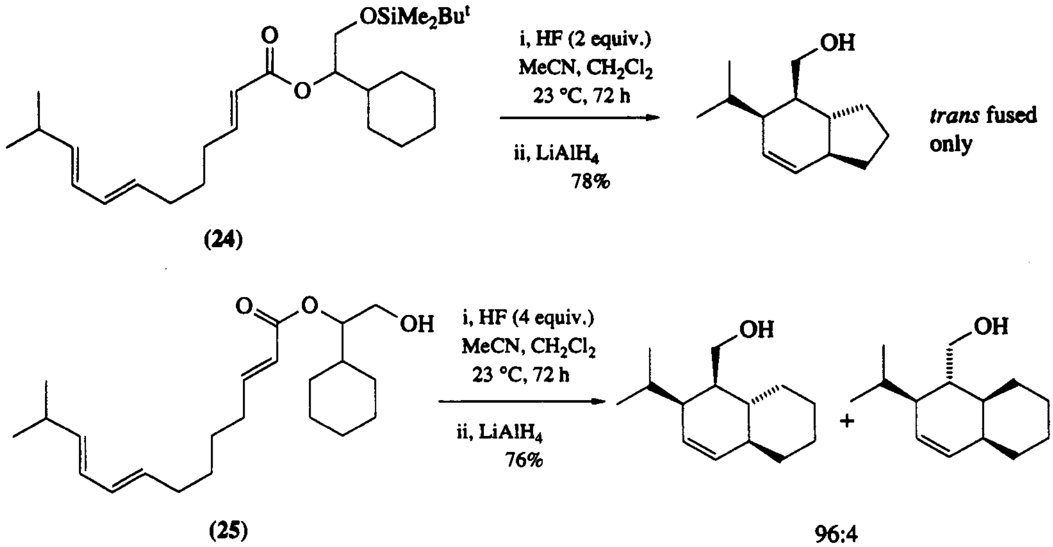
OSiMe$_2$Bu$^t$
O
O
i, HF (2 equiv.)
MeCN, CH$_2$Cl$_2$
23 °C, 72 h
ii, LiAlH$_4$
78%
OH
*trans* fused only
(24)
O
O
OH
i, HF (4 equiv.)
MeCN, CH$_2$Cl$_2$
23 °C, 72 h
ii, LiAlH$_4$
76%
OH
+
OH
(25)
96:4

**Figure 7** Dioxolenium ion mediated IMDA reactions

$CF_3SO_3H$ as catalyst.[42] This method has been applied successfully to several highly functionalized trienes including (**29**) (Figure 8). While the outcome of these reactions is consistent with the IMDA paradigm, it is unclear whether these reactions are actually concerted or stepwise. For example, the acid catalyzed cyclization [$Ar_3N^{+}{\cdot}Cl_6Sb^{-}$ conditions] of the (*E*,*Z*)-isomer of (**27**) provided the same products as obtained from (*E*,*E*)-(**27**), albeit in altered ratio, suggesting that the cyclization of (*E*,*Z*)-(**27**) is not concerted.

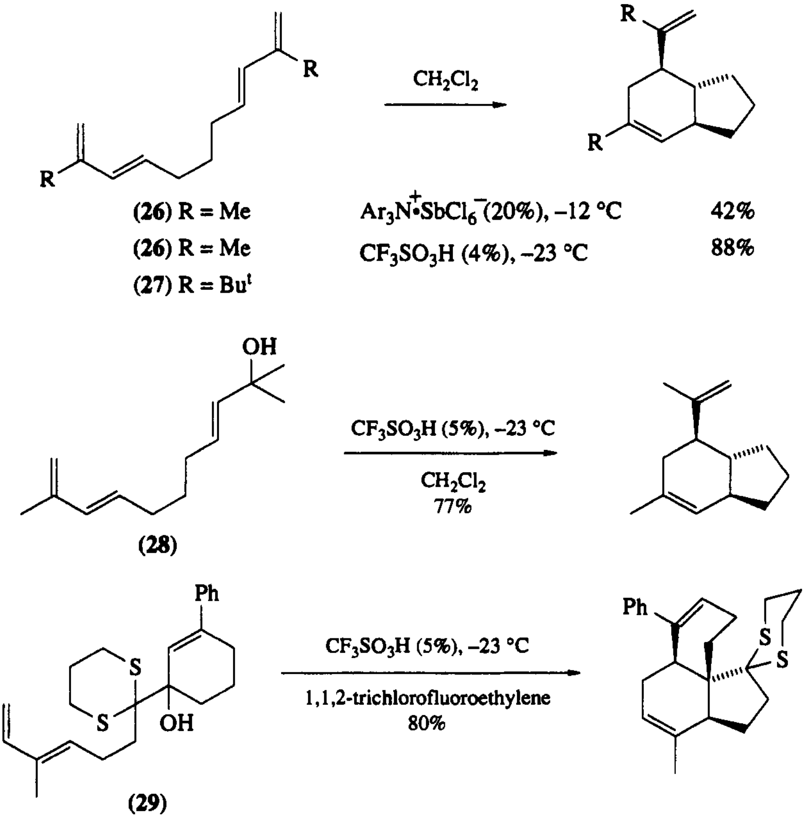
R
CH$_2$Cl$_2$
R
R
R
(26) R = Me
(26) R = Me
(27) R = Bu$^t$
$Ar_3\overset{+}{N}{\bullet}SbCl_6^-$(20%), –12 °C
CF$_3$SO$_3$H (4%), –23 °C
42%
88%
OH
CF$_3$SO$_3$H (5%), –23 °C
CH$_2$Cl$_2$
77%
(28)
Ph
S
S
OH
CF$_3$SO$_3$H (5%), –23 °C
1,1,2-trichlorofluoroethylene
80%
Ph
S
S
(29)

**Figure 8** Allyl cation mediated IMDA reactions

Cation radical[14a] Diels–Alder reactions catalyzed by $Ar_3N^{+\cdot}Cl_6Sb^-$ occur when the reactions are performed in the presence of 2,6-di-*t*-butylpyridine (in excess, based on aminium cation salt) to scavenge protic acids generated either from loss of protons from initially generated cation radicals or from dimerization of cation radical intermediates.[41] Bauld has applied these modified conditions to the cyclizations of (**30**) and (**31**), and both show very high selectivity for the *trans*-fused product.[43] The (*Z*)-dienophile isomer of (**30**) also undergoes cyclization, but with prior isomerization of the dienophile from (*Z*) to (*E*). Attempts to apply this method to trienes with less easily ionized dienophiles, *e.g.* (*E,E*)-1,6,8-decatriene or (*E,E*)-2-methyl-2,7,9-undecatriene, were unsuccessful. Nevertheless, in combination with the acid catalyzed cyclizations *via* allyl cation intermediates and conventional Lewis acid mediated cyclizations of carbonyl activated trienes, a wide range of trienic systems are viable substrates for catalyzed, rate accelerated cyclizations with impressive increases of selectivity relative to the uncatalyzed, thermal cycloadditions.

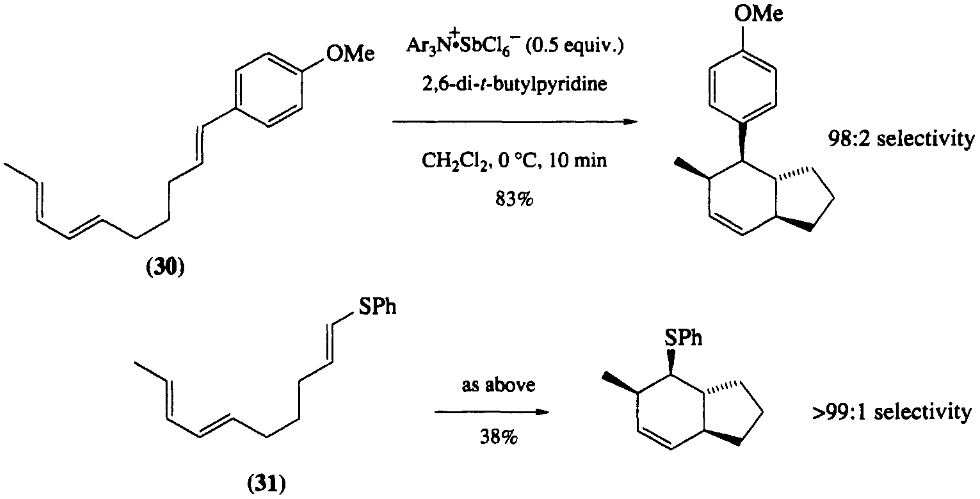

**Figure 9** Cation radical catalyzed IMDA reactions

### *4.4.2.1.3 Influence of steric effects on diastereoselectivity*

While the electronic effects discussed in Section 4.4.2.1.1 certainly play a significant role in determining the stereochemical outcome of IMDA reactions, steric and conformational effects, discussed in Section 4.4.2.1.4, also exert a significant influence on the course of these reactions. Figure 10 summarizes two sets of data that illustrate that steric effects are capable of overriding the usual preference of terminally activated nona- and deca-trienes to cyclize to *trans*-fused products.[44,45] Sulfonyl activated 1,7,9-decatriene (**32**) cyclizes exclusively to the indicated *cis*-fused octalin, while the nonatriene analogue provides a 1:1 mixture of *trans*- and *cis*-fused products.[44] The bulky $PhSO_2$ group apparently experiences repulsive nonbonded interactions with the diene in the *trans*-fused ($PhSO_2$ *endo*) transition state for (**32**), thereby prompting this cyclization to proceed by way of a *cis*-fused transition state with the $PhSO_2$ unit in a less sterically demanding *exo* position. The twist asynchronicity encountered in the cyclizations of terminally activated nonatrienes (Table 1), however, is sufficient to counterbalance the $PhSO_2$ steric effect in the IMDA reactions of the analogous sulfonyl activated 1,6,8-nonatriene.[44] Steric effects evidently are much more serious with substituted nonatriene (**33**), which provides the indicated *cis*-fused cycloadduct as a single stereoisomer.[45] The ordinarily favored (*cf.* Table 1) *trans*-fused transition state (**34**) is destabilized by nonbonded interactions between the diene and the cyclopentenone unit, and the IMDA reaction thus proceeds *via* the less sterically crowded *cis*-fused transition state (**35**).

Geminal substitution at C(3) introduces destabilizing nonbonded interactions in the *cis*-fused transition states for both nona- and deca-trienes (Figure 11), resulting in enhanced selectivity for the *trans*-fused diastereomer.[14a,46,47] These examples are instructive particularly when compared with the results discussed previously for (**6**) and (**11**) (Figures 2, 3). The destabilizing nonbonded interactions are presumably more significant in the 1,7,9-decatriene series (**36**) owing to the greater conformational flexibility of the nonatriene transition state (developing five-membered ring).

Substituents on C(8) of the decatriene skeleton also enhance selectivity for the *trans*-fused cycloadduct by destabilizing the *cis*-fused transition state (Figure 12). A classic example is provided by Wilson, who

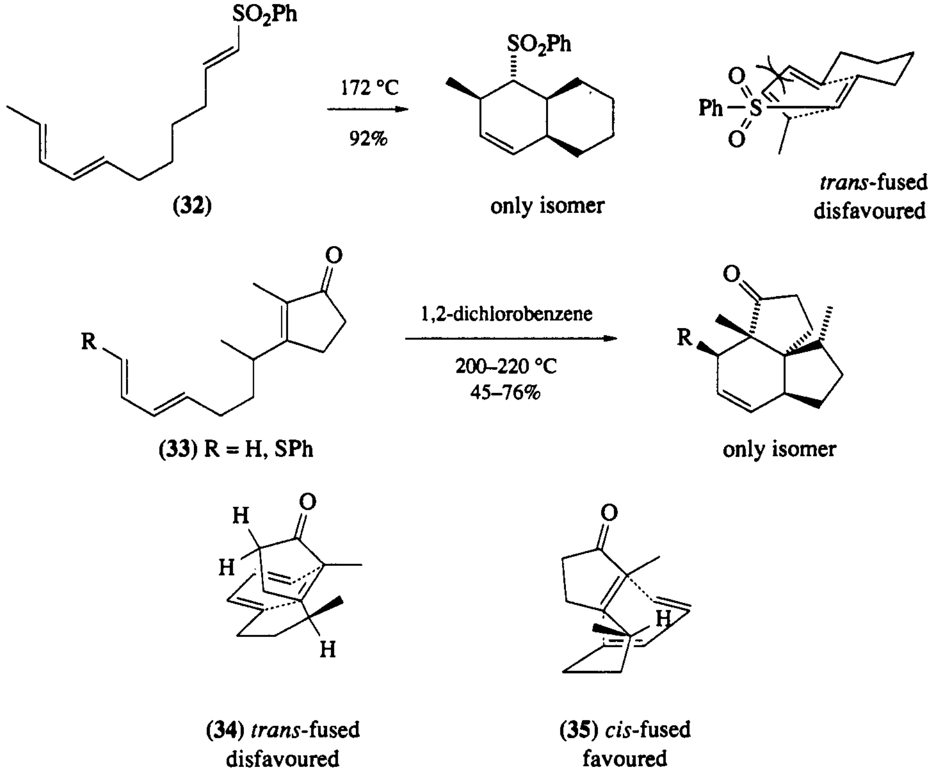
SO2Ph
172 °C
92%
SO2Ph
Ph
S
O
O
1,2-dichlorobenzene
200–220 °C
45–76%
R
O
H
H
H
O
O
H
(32)

only isomer

*trans*-fused disfavoured

(33) R = H, SPh

only isomer

(34) *trans*-fused disfavoured

(35) *cis*-fused favoured

Figure 10

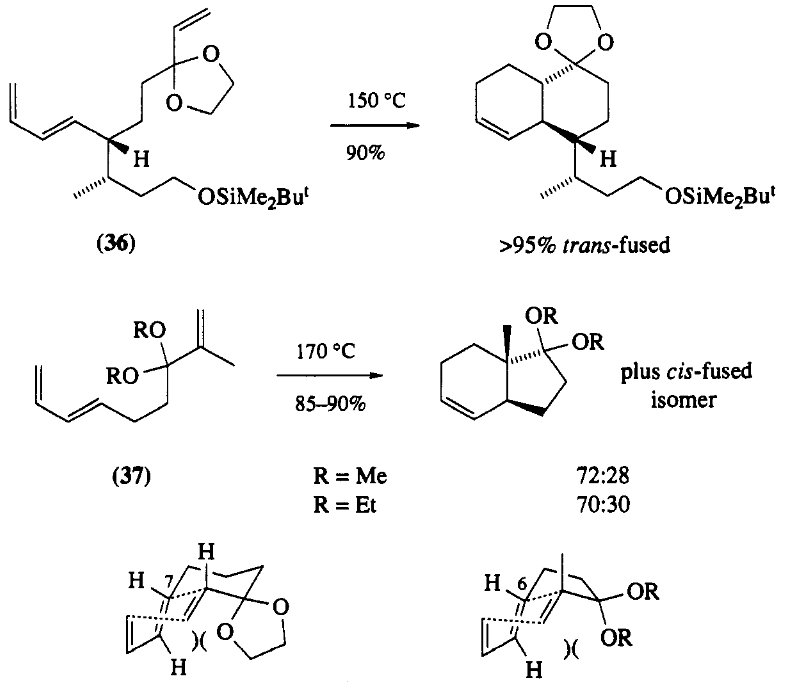
O
O
150 °C
90%
H
OSiMe2Bu$^t$
RO
RO
170 °C
85–90%
OR
OR
H
7
H
O
O
H
H
6
OR
OR
H
(36)

>95% *trans*-fused

plus *cis*-fused isomer

(37)

R = Me 72:28

R = Et 70:30

Figure 11

observed that (**38**) with a C(8)-Me substituent cyclized almost exclusively to *trans*-fused products, while the C(8) unsubstituted triene (**39**) provided a 55:45 mixture of the *trans*- and *cis*-fused products.[48] The increased selectivity with (**38**) is attributable to interactions between the C(8)-Me group and the axial C(5)-H that prohibitively destabilize the *cis*-fused transition state. In fact, the majority of unactivated

1,7,9-decatrienes that cyclize with high selectivity to *trans*-fused products, including most IMDA reactions involving *o*-diquinomethanes,[5c,e] possess substituents at C(8). With this effect in mind, several groups have explored the use of removable C(8) substituents (so called steric directing groups) as a strategy to enhance the diastereoselectivity of otherwise poorly selective IMDA reactions.[49,50] One example involves the $Me_3Si$-substituted triene (**40**) that undergoes a thermal IMDA reaction with 95% *trans* selectivity (compare results with (**8**), Figure 3).[51] Although a C(8)-$Me_3Si$ substituent exerts a greater influence than a C(8)-Br group,[50] the C(8)-Br substituted trienes are more easily synthesized, especially in structurally complex cases, and thus are likely to find numerous applications in synthesis.[50b,52]

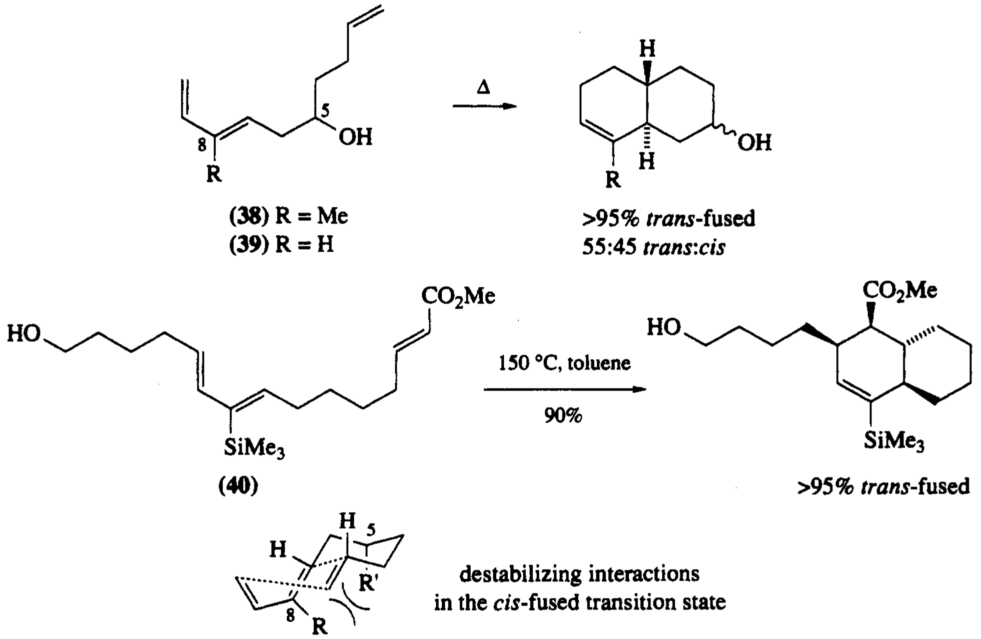

**Figure 12**

1,7,9-Decatrienes with geminal substituents at C(5), or C(5)-monosubstituted trienes constrained to cyclize *via* transition states with the C(5) substituent in an axial position, also display excellent stereoselectivity for the *trans*-fused product, *e.g.* triene (**41**).[53]

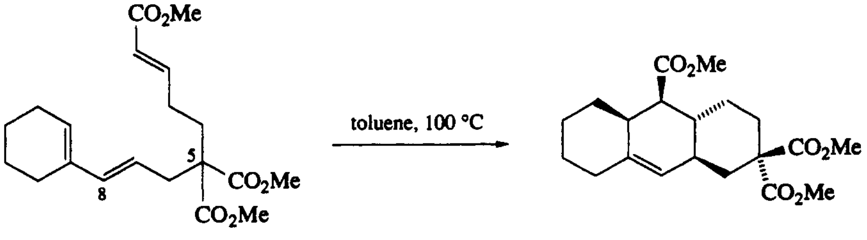

(**41**)

*trans*-fused only

Similar nonbonded interactions occur between C(4) and C(7) substituents in the *cis*-fused 1,6,8-nonatriene transition state (Figure 13).[20,53,54] The very high *trans* selectivity exhibited by trienes (**42**), (**43**), (**44**) and (**46**) is striking in view of the data summarized in Figure 2 for less highly substituted systems. The results with (**44**) and (**45**) imply that the extent of destabilization of the *cis*-fused transition state depends on the steric requirements of the C(7) substituent, a conclusion also supported by other examples cited in the references.[54e–g] Nevertheless, these interactions are large enough to reverse the stereoselectivity of the IMDA reactions of internally activated nonatrienes (**44**) and (**47**)[55] relative to the usually observed *cis* manifold (compare (**5**) and (**7**), Figure 2).

Finally, it is worthy of brief mention that the presence of C(6)-alkoxy substituents in decatriene substrates leads to an increase in selectivity for the *cis*-fused products, *e.g.* (**48**) (Figure 14).[16] This effect may result from eclipsing interactions involving H(8) in the *trans*-fused transition state, an interaction

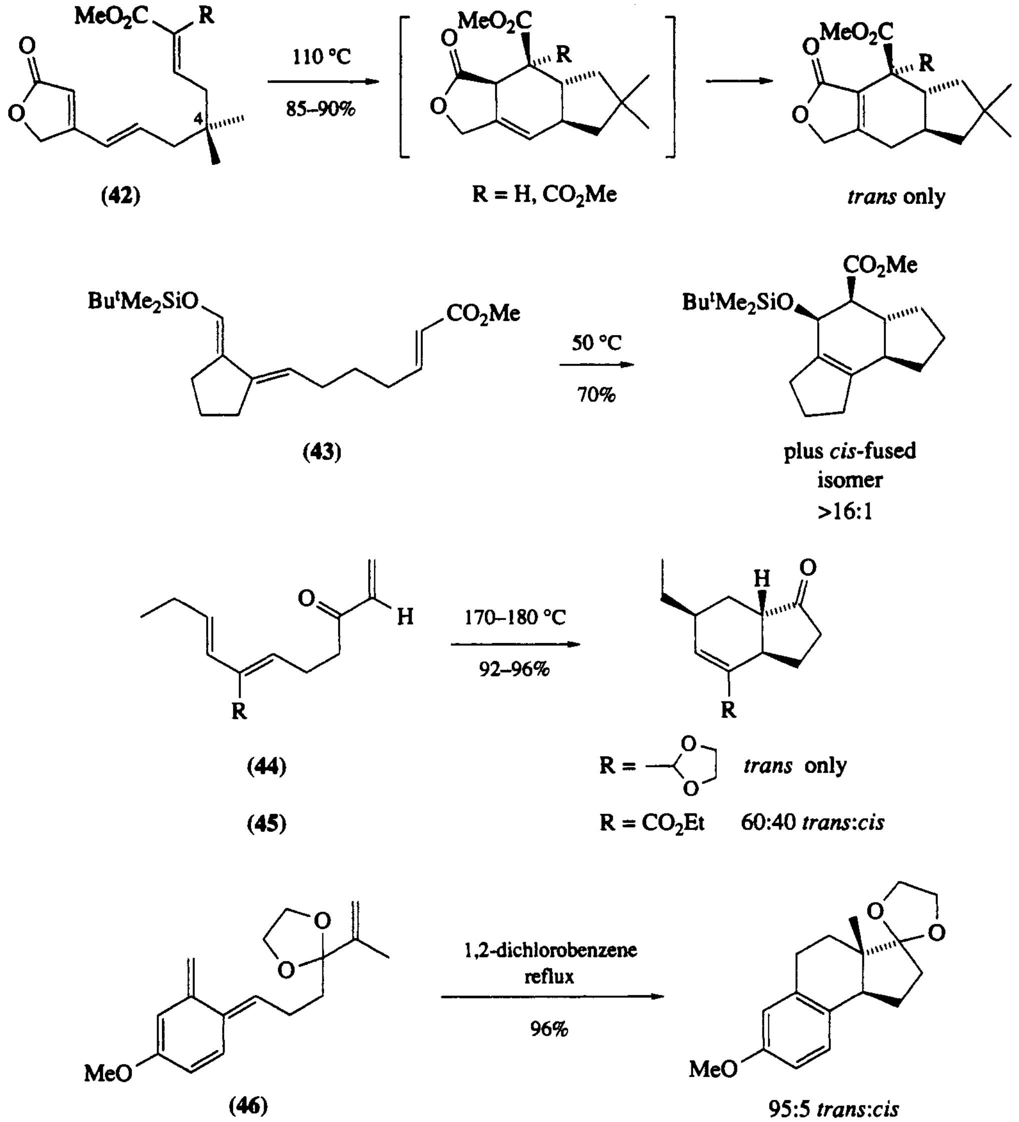
110 °C
85–90%
50 °C
70%
170–180 °C
92–96%
1,2-dichlorobenzene
reflux
96%
4

(42)

R = H, $CO_2Me$

*trans* only

(43)

plus *cis*-fused isomer >16:1

(44)

(45)

R = $CO_2Et$ 60:40 *trans*:*cis*

*trans* only

(46)

95:5 *trans*:*cis*

**Figure 13**

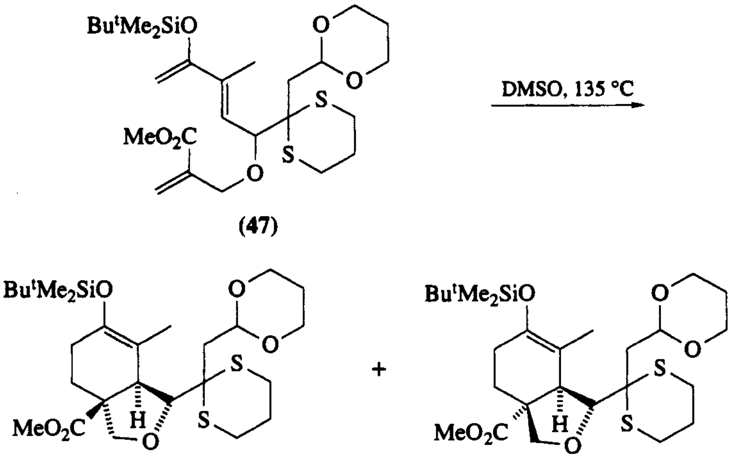

(47)

*trans*:*cis* 71:29

that is less severe in the *cis*-fused transition structure. A single C(6)-alkoxy substituent also increases selectivity for the *cis*-fused product, so the effect may not be entirely steric in origin.[16b,56] Interestingly, the same substitution pattern leads to a slight increase in *trans* stereoselectivity with nonatriene substrates.[11]

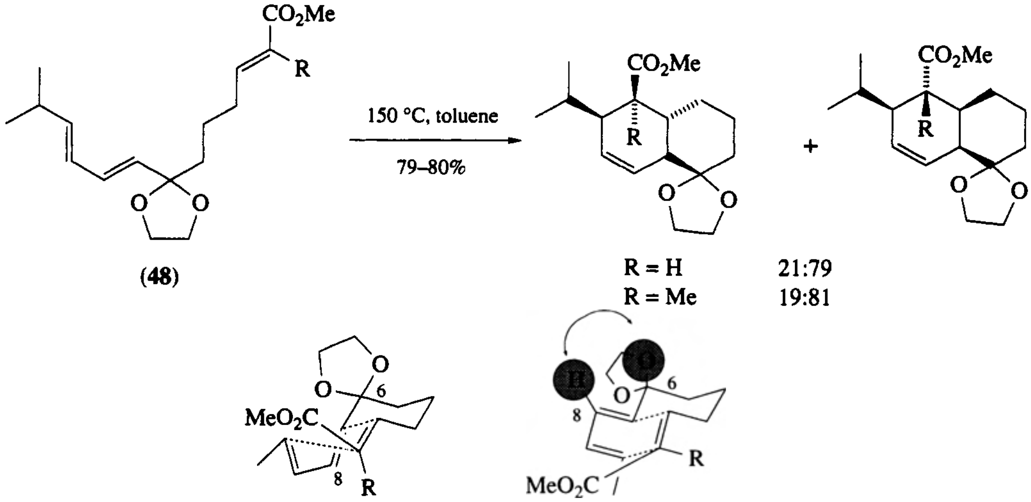

**(48)**

R = H 21:79
R = Me 19:81

**Figure 14**

### 4.4.2.1.4 *Influence of conformational effects on diastereoselectivity*

Conformational effects also play an important role in determining IMDA diastereoselectivity. For example, trienes like (**49**) and (**50**) with two $sp^2$ hybridized atoms within the connecting chain cyclize preferentially to *cis*-fused rather than the *trans*-fused products that would be expected based on the presence of the C(8)-methyl substituent (Figure 15).[57] The benzo fusion forces the bridging chain to adopt boat-like conformations in the transition states, and the 1,3-diaxial interactions that the C(8)-methyl ordinarily experiences in the *cis*-fused, chair-like transition state are thus relieved (refer to Figure 12). The preferential formation of the *cis*-fused diastereomer may then be the consequence of a favored skew butene rotamer at C(6)—C(7) in (**51**) compared with a less favorable *gauche* butene rotamer at this position in the *trans*-fused transition state.[58] This effect is discussed in more detail in Section 4.4.3.2 concerning relative diastereoselection in the IMDA reactions of substituted decatrienones.

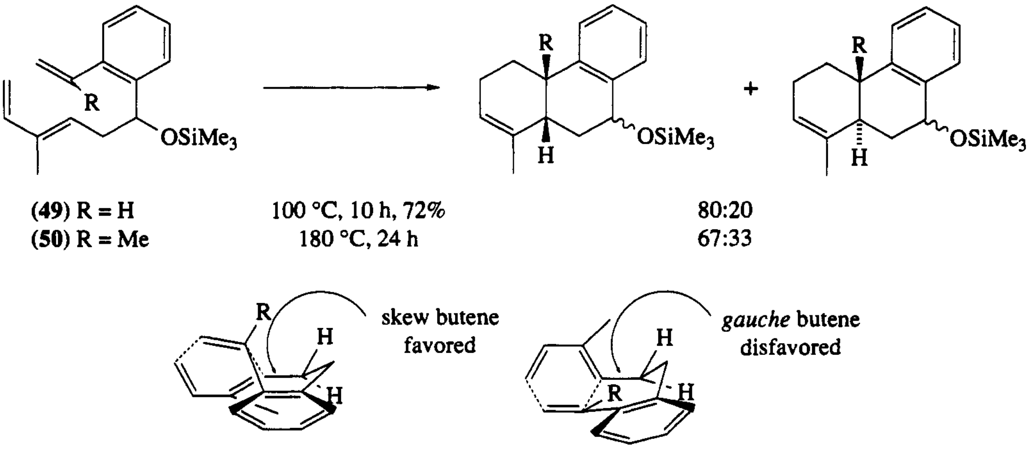

(**49**) R = H 100 °C, 10 h, 72% 80:20
(**50**) R = Me 180 °C, 24 h 67:33

(**51**) *cis* transition state *trans* transition state

**Figure 15**

A variety of IMDA reactions have been reported for which only one set of transition states are accessible due to strain in the other. This factor is responsible for the exclusive production of *cis*-fused cycloadducts in the IMDA reactions of (*Z*)-nona- and deca-trienes,[4c,8] and of the *syn* cycloadducts in type II IMDA cycloadditions (refer to Figure 1).[9] This conformational effect is probably also involved in the thermal isomerizations of allenic tetraenes (**52**)[59] and (**53**)[60] that cyclize *via* the same transition state even though the two substrates differ in terms of internal (**52**) *vs.* external (**53**) dienophile activation (Figure 16). An *exo* folding of the connecting chain in transition state (**54**) is much more easily accommodated than the *endo* folding in (**55**) owing to strain in the connecting chain that develops as C(2) and C(7) approach reasonable bonding distances.

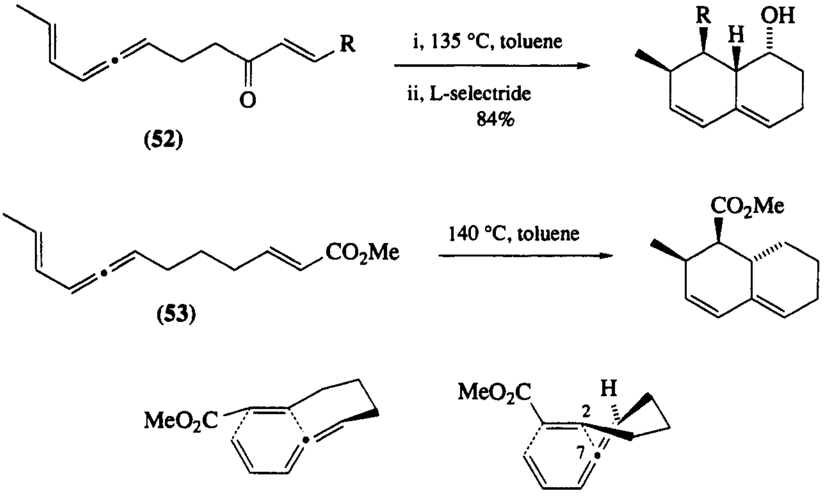

(**52**)

(**53**)

(**54**) *exo* fold

(**55**) *endo* fold, strained

**Figure 16**

### 4.4.2.2 Heteroatom-substituted Nona- and Deca-trienes

Numerous IMDA reactions of heteroatom-substituted systems have been described.[5] In this section we provide an overview of the factors that influence diastereoselectivity of these cycloadditions, in comparison with the behavior of similarly functionalized all-carbon nona- and deca-trienes.

#### *4.4.2.2.1 Heteroatom substituents on the bridging chain*

Replacement of one of the $CH_2$ groups of the chain bridging the diene or dienophile with an amine, ether or thioether unit has a relatively minor effect on the IMDA diastereoselectivity, at least with relatively simple trienes such as (**56**)–(**58**) (Figure 17). Thus the stereoselectivities of the IMDA cyclizations of (**56**)[8b] and (**57**)[61] are comparable with that for (**8**) (Figure 3 and Table 2), and the cyclizations of (**58**) and (**59**) also give very similar product mixtures.[61]

A significant alteration of diastereoselectivity occurs with C(8)-substituted trienes like (**60**), however, since replacement of the C(5)-methylene by an NH group greatly reduces steric interactions in the *cis*-fused transition state that are important in enhancing stereoselectivity for the *trans*-fused product (refer to Figure 12). The results with (**61**) are more typical of all-carbon cases (Figure 18).[62]

Stereoselectivity in the IMDA reactions of heteroatom-substituted nonatrienes series sometimes shows a much greater departure relative to all-carbon analogs (Figure 19).[63–65] This is especially so in the case of (**63**)[64] compared to (**3**) in Figure 2, perhaps due to the reduced 1,3-interactions between C(7)-H and N(4) in the *cis*-fused transition state. The more highly activated triene (**64**), however, displays excellent selectivity for the *trans*-fused product, a result that may be due to the presence of the two dienophile activating groups and the electron-releasing *p*-methoxyphenyl unit at the diene terminus (nonsynchronous transition state hypothesis).[65]

The presence of an amide linkage on the connecting chain exerts a significant influence on IMDA diastereoselectivity (Figures 20 and 21). These effects, first observed by Oppolzer,[62,66] are related to conformational preferences exerted by the amide unit. Thus urethane (**65**) presumably cyclizes exclusively through transition state (**71**$_{cis}$) since (**71**$_{trans}$) is destabilized by an eclipsing interaction between H(8) and

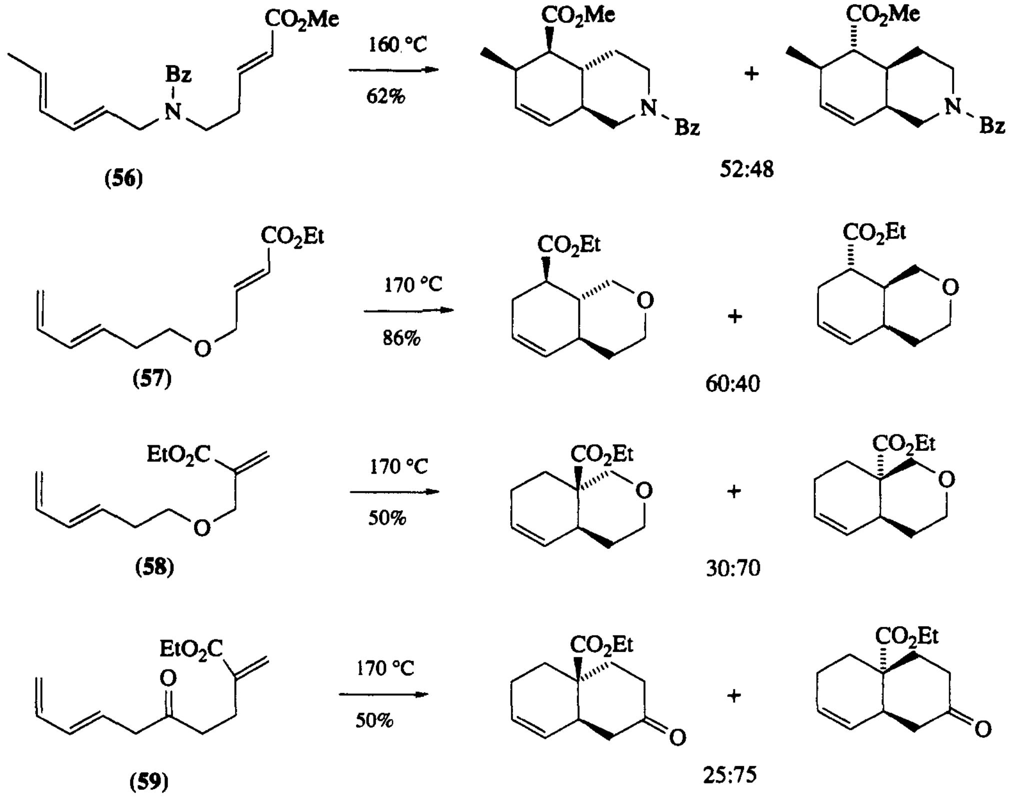

Figure 17

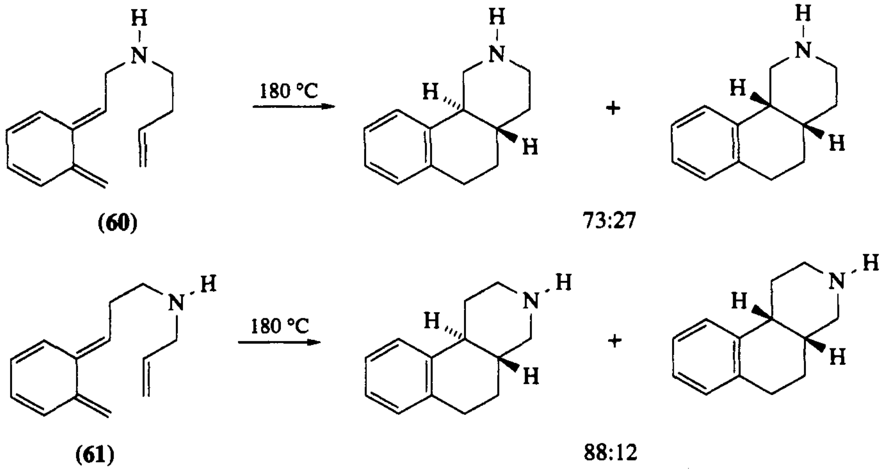

Figure 18

the $CO_2Me$ unit.[66a] Triene (**66**), on the other hand, exhibits a modest preference for the *trans*-fused cycloadduct.[66a] Comparison of this result with the exclusive *trans* selectivity observed with (**67**)[67] supports the thesis that transition state (**72**$_{trans}$) is intrinsically favored over (**72**$_{cis}$) because the amide unit remains coplanar with the diene in (**72**$_{trans}$),[66a] and because the C(3)-methylene unit interacts strongly with the diene in (**72**$_{cis}$). Stereoselectivity with (**66**) is lower than with (**67**) presumably since (**72**$_{trans}$) for (**66**) is destabilized by a 1,3-interaction between H(8) and the *N*-propyl unit. The only other triene that exhibits significant stereoselectivity in this series is (**70**),[68] and this IMDA reaction most likely proceeds through a boat-like transition state analogous to (**51**) of Figure 15. Consistent with this analysis is the report that a triene related to (**70**) but containing a C(8)-OTBDMS substituent also cyclizes to a 4:1 mixture of *cis*- and *trans*-fused products.[69] A C(8) substituent is not expected to influence significantly the relative en-

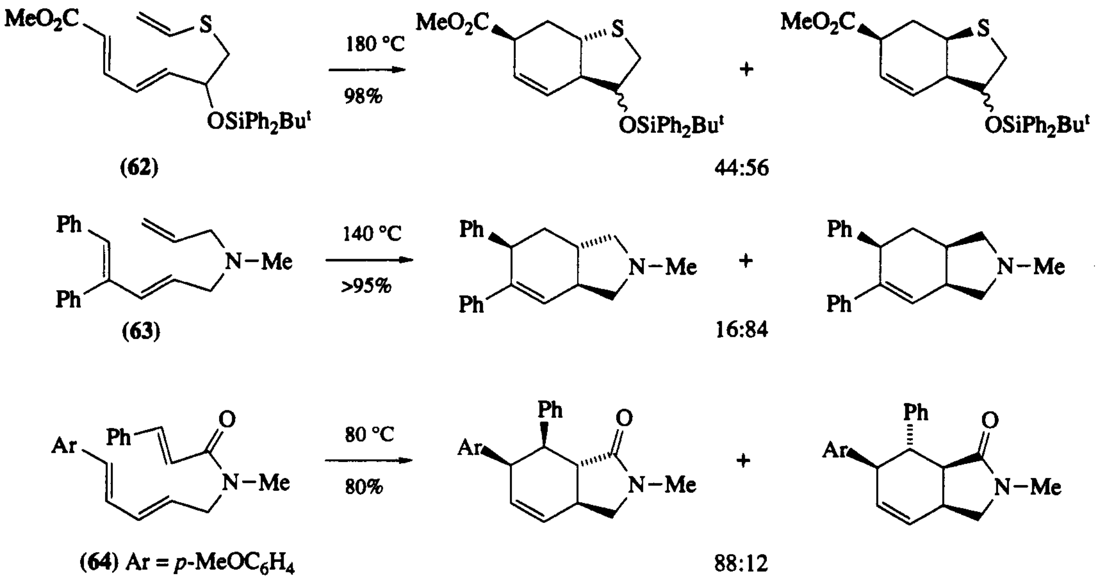

**(62)** 44:56

**(63)** 16:84

**(64)** Ar = $p$-MeOC$_6$H$_4$ 88:12

**Figure 19**

ergies of the *cis* and *trans* transition states if the connecting chain is in a boat conformation (refer to **51**; Figure 15).

Nonatrienes with amide linkages on the connecting chain generally exhibit a preference for the *cis*-fused product as long as a terminal dienophile activating group is not present (Figure 22). The *cis* stereoselectivity of (**73**)[66a] and (**74**)[70] is undoubtedly the result of eclipsing interactions involving H(7) and the nitrogen substituent in the *trans*-fused transition state (*cf.* **71**$_{trans}$) since stereoselectivity in the cyclization of (**74**) increases as the steric bulk of R increases.[70] Other results have been reported that are also consistent with this analysis.[66b,c] *Cis* stereoselectivity also is realized with (**75**), although with (**76**) a mix-

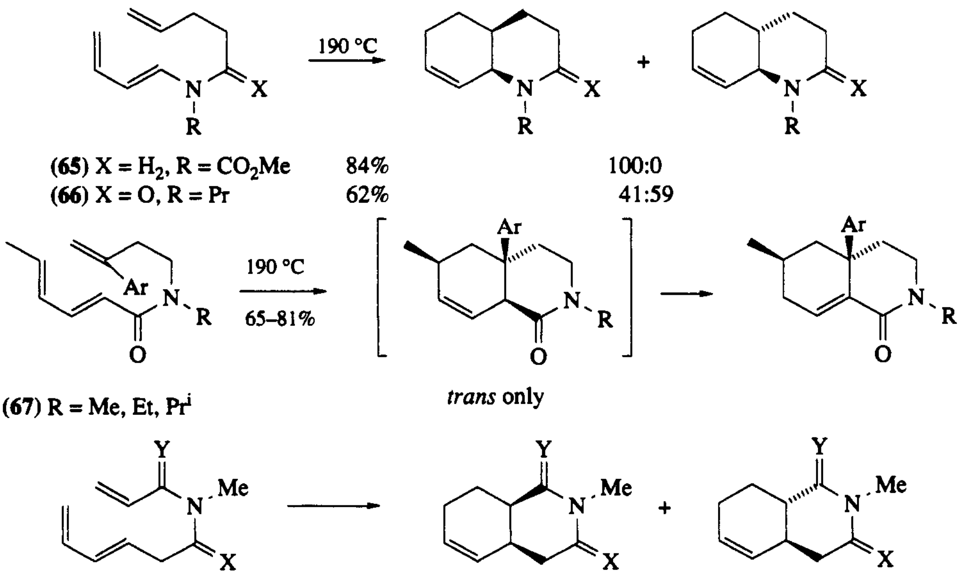

(**65**) X = H$_2$, R = CO$_2$Me 84% 100:0

(**66**) X = O, R = Pr 62% 41:59

(**67**) R = Me, Et, Pr$^i$

*trans* only

| *Triene* | *X* | *Y* | *Temp.* (°C) | *cis*:*trans* |
|---|---|---|---|---|
| (**68**) | O | H$_2$ | 185 | 67:33 |
| (**69**) | H$_2$ | H$_2$ | 140 | 52:48 |
| (**70**) | H$_2$ | O | 80 | 89:11 |

**Figure 20**

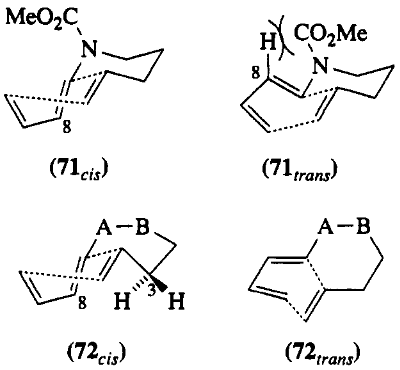

$MeO_2C$
N
8
$CO_2Me$
H
N
8
A−B
8
H
3
H
A−B

($71_{cis}$) ($71_{trans}$) Transition states for (**65**)

($72_{cis}$) ($72_{trans}$) Transition states for (**66**) A = NPr, B = CO, and (**67**) A = CO, B = NR

**Figure 21**

ture of *cis*- and *trans*-fused products is obtained.[71] These results have been rationalized in terms of the nonsynchronous transition state hypothesis. This theory also helps to explain the very high *trans* stereoselectivity exhibited by terminally activated trienes (**78**) and (**79**) compared with (**77**) (see also **64**; Figure 19).[64,65]

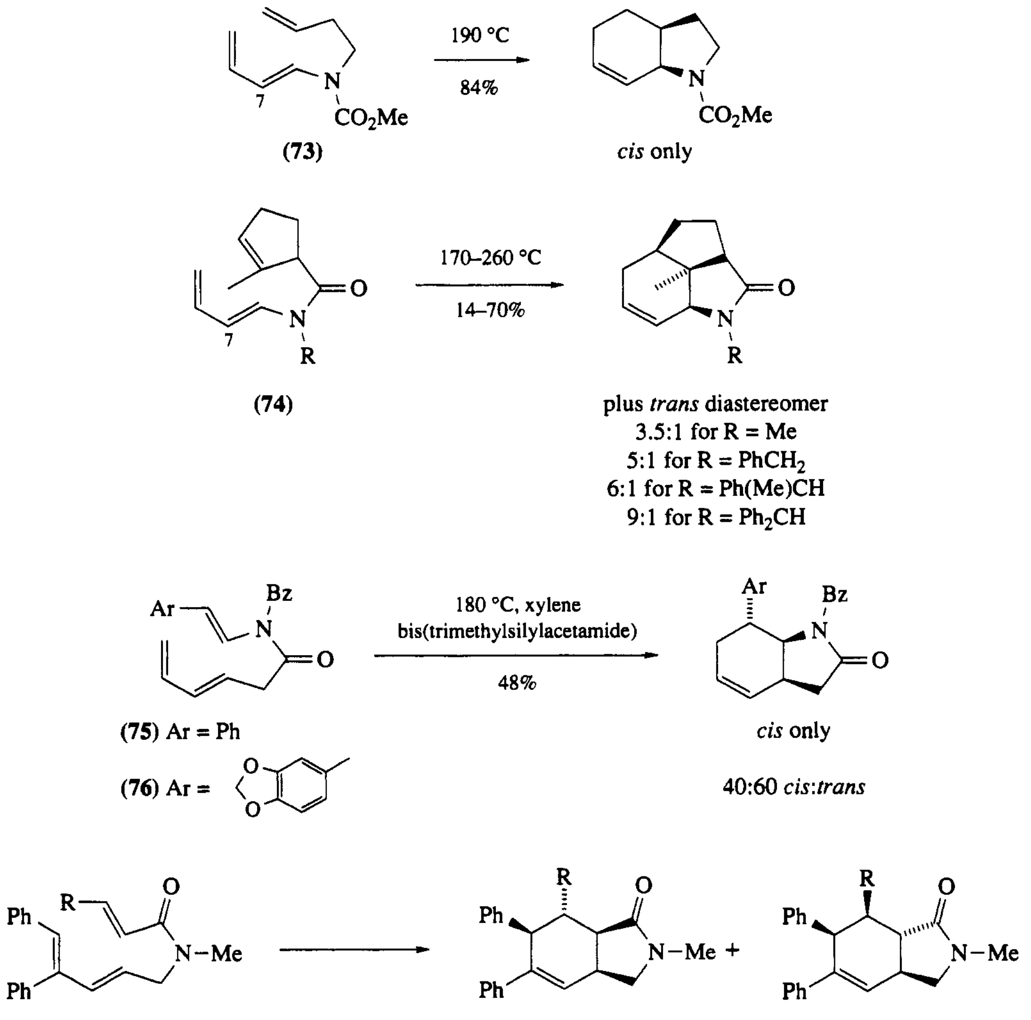

7
N
$CO_2Me$
190 °C
84%
N
$CO_2Me$
7
O
N
R
170–260 °C
14–70%
O
N
R
Ar
Bz
N
O
180 °C, xylene
bis(trimethylsilylacetamide)
48%
Ar
Bz
N
O
O
O
Ph
R
O
N−Me
Ph
R
O
Ph
N−Me +
Ph
R
O
Ph
N−Me
Ph

(**73**) *cis* only

(**74**) plus *trans* diastereomer
3.5:1 for R = Me
5:1 for R = $PhCH_2$
6:1 for R = Ph(Me)CH
9:1 for R = $Ph_2CH$

(**75**) Ar = Ph
(**76**) Ar =
*cis* only
40:60 *cis*:*trans*

| | | |
|---|---|---|
| (**77**) R = H | 110 °C, 82% | 49:51 |
| (**78**) R = Ph | 90 °C, 61% | 11:89 |
| (**79**) R = $CO_2Me$ | 0 °C, 63% | *trans* only |

**Figure 22**

In contrast to carboxamide substitution, the presence of an ester linkage on the bridging chain often introduces problems due to the generally poor reactivity of the resulting trienic system. For example, trienes (**81**) and (**82**) fail to cyclize even when heated at temperatures up to 275 °C.[68] Triene (**80**) similarly fails to cyclize at 200 °C, but when heated at 220–225 °C migration of the diene occurs to give (**83**) that cyclizes to the indicated product mixture (Figure 23).[61] A triene related to (**83**) but lacking the diene methyl and the dienophile MeO2C substituents required a temperature of 250 °C (120 h) for cyclization to occur.[68] The low reactivity of systems such as these has been attributed to poor overlap of the nonbonding electrons of the ethereal oxygen and the carbonyl group in the transition state,[61] and use of an acetal linkage in place of the reactivity deadening ester unit has been recommended as a solution to this problem.[72]

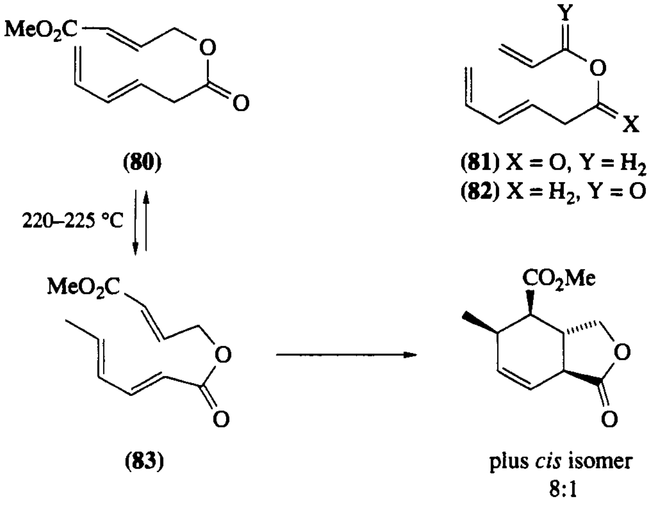

**Figure 23**

A second means of increasing the reactivity of trienes of general structure (**82**) is to add an additional activating group to the terminus of the diene.[73] The *trans*-fused product is generally favored in these reactions, except when a carboxylic acid is employed as the terminal dienophile activating group (Figure 24).[21,74–76] White has speculated that the aberrant behavior of acid (**87**) relative to ester (**86**) may be due to thermodynamic control.[21] On the other hand, it may be that the carboxylic acid is hydrogen bound to the adjacent ester carbonyl, thereby activating the internal ester such that it dominates the stereoelectronics of a nonsynchronous transition state. Additional examples illustrating the reversal of stereoselectivity by using a terminal carboxylic acid function have appeared, *e.g.* (**88**) *vs.* (**89**).[74]

### *4.4.2.2.2 Heterodienes and dienophiles*

The use of heterodienes and dienophiles, particularly systems containing nitrogen and oxygen substituents, has found increased application in natural products synthesis.[77] Replacement of a carbon atom by a heteroatom on the diene appears to have little effect on the IMDA diastereoselectivity; several representative examples are summarized in Figure 25[78–81] that are in excellent agreement with all carbon diene cases discussed earlier. A particularly interesting case is (**94**) that exhibits a modest preference for the *trans*-fused product when R = H, but which strongly favors the *cis*-fused cycloadduct when R = Me.[81d] This is due to nonbonded interactions between R and the phenyl unit that are more serious in the *trans* transition state; note that in this case the benzo fusion prevents the bridging chain from adopting the usual chair-like conformation that is ordinarily invoked with trienes with all $sp^3$ hybridized atoms on the connecting chain. The transition state in this case is probably better described as boat-like (see Figure 44 for one representation).

Introduction of heteroatom substituents in the dienophile has a significant effect on diastereoselectivity of the IMDA cyclization owing to electronic effects. For example, trienes (**96**) generated by thermolysis of (**95**) cyclize with excellent stereoselectivity to cycloadduct (**97**) with a *trans* relationship between the two stereocenters on the ring (Figure 26).[82] Assuming that the dienophile has (*E*) geometry as suggested

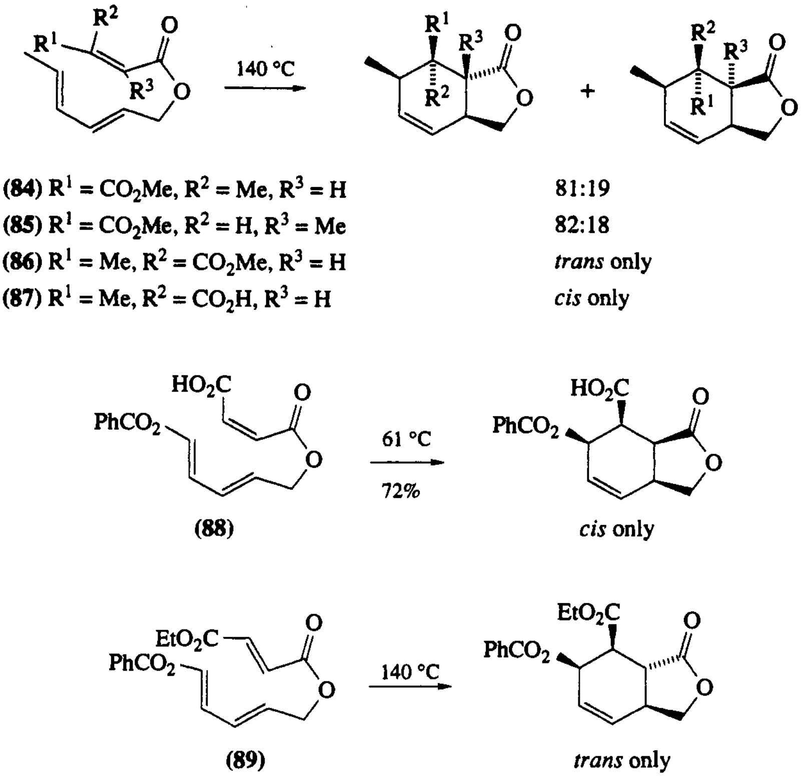

| | |
|---|---|
| (**84**) $R^1 = CO_2Me, R^2 = Me, R^3 = H$ | 81:19 |
| (**85**) $R^1 = CO_2Me, R^2 = H, R^3 = Me$ | 82:18 |
| (**86**) $R^1 = Me, R^2 = CO_2Me, R^3 = H$ | *trans* only |
| (**87**) $R^1 = Me, R^2 = CO_2H, R^3 = H$ | *cis* only |

(**88**) *cis* only

(**89**) *trans* only

**Figure 24**

by Weinreb, then it is necessary that (**96**) cyclize *via* transition states in which the internal acyl imine is *endo* and the terminal methoxycarbonyl group is *exo*. This is exactly the opposite of the stereochemistry realized with analogous all carbon dienophiles, *cf.* (**86**) and (**89**) (Figure 24).[74a,c] This difference may be rationalized, however, by invoking a nonsynchronous transition state in which the highly electrophilic acyl imine function dominates the stereoelectronics. Heteroatom substitution at the dienophile terminus also influences IMDA diastereoselectivity, as illustrated by the results summarized in Figure 26 for N, Se and S substituted trienes (**98**)–(**100**).[83–85]

### 4.4.2.3 Transannular Cycloadditions

Several detailed investigations of transannular IMDA cycloadditions have appeared in recent years.[86,87] This transformation promises to become an important synthetic method owing to the potential for the rapid efficient construction of complex polycyclic ring systems.[88] Other potential strategic benefits include increased reactivity due to diminished entropic requirements ($\Delta S^{\ddagger}$). This is nicely illustrated by the facile cyclization of (**101**) with a tetrasubstituted dienophile, compared with the unsuccessful IMDA reaction of (**102**) (Figure 27).[86c] Although the cyclization of (**101**) proceeds with only moderate diastereoselection, many other examples have been reported that exhibit outstanding selectivity, *e.g.* cyclization of (**103**).[87] It is conceivable that conformational constraints imposed by the macrocyclic system may lead to improved IMDA stereoselectivity relative to conventional acyclic trienes, but this point has not yet been demonstrated in any published examples.

## 4.4.3 RELATIVE DIASTEREOSELECTION

Relative diastereoselection is an issue that is confronted most frequently in the IMDA reactions of trienes with one or more stereocenters on the chain connecting the diene and dienophile. As a general rule, trienes with saturated connecting chains cyclize *via* transition states with chair-like conformations, while boat-like transition states are frequently encountered with the 1,7,9-decatrienones as well as with

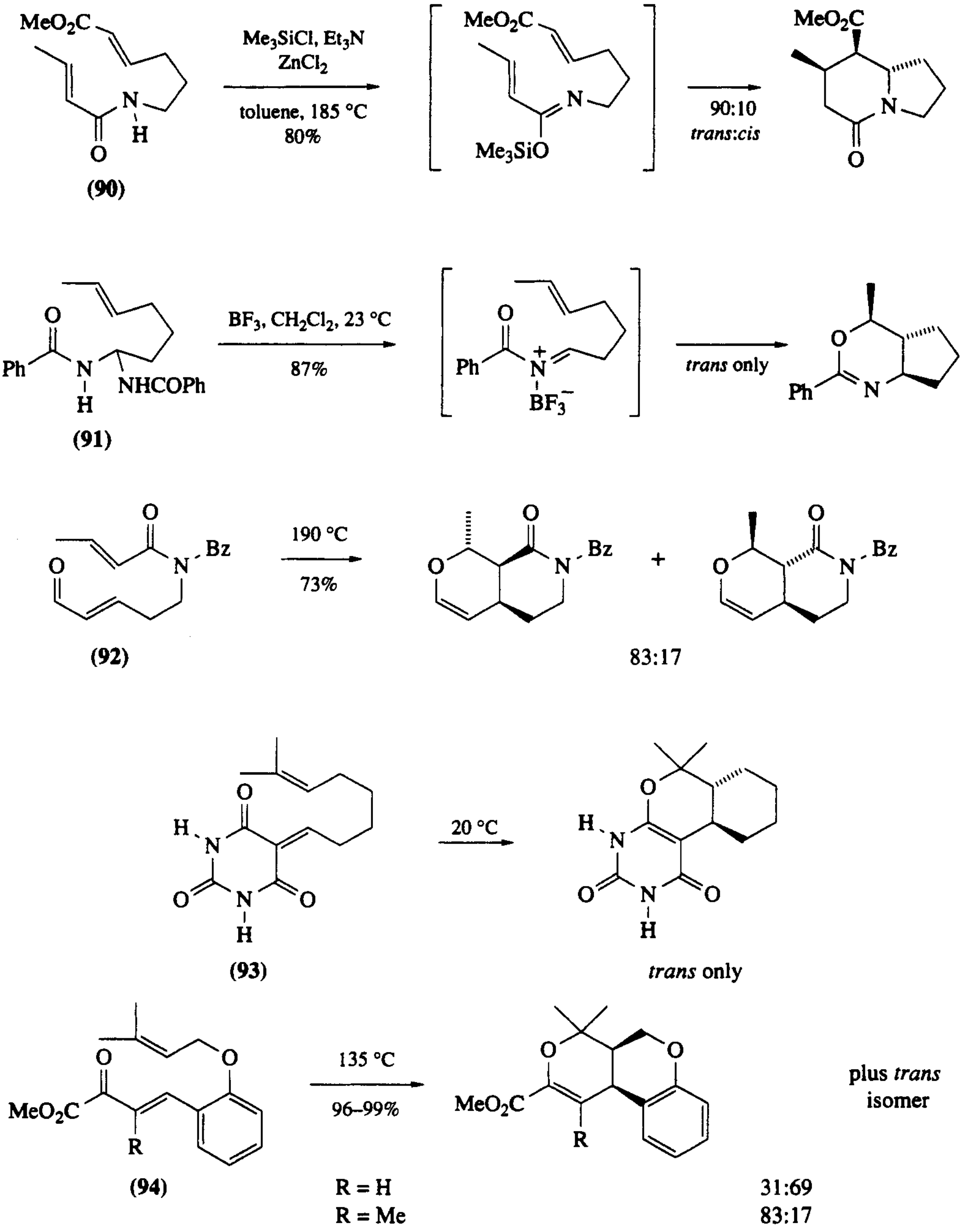
MeO2C
(90)
Me3SiCl, Et3N
ZnCl2
toluene, 185 °C
80%
Me3SiO
90:10
trans:cis
Ph
NHCOPh
(91)
BF3, CH2Cl2, 23 °C
87%
BF3
trans only
Bz
(92)
190 °C
73%
83:17
(93)
20 °C
trans only
(94)
135 °C
96–99%
plus trans isomer
R = H
R = Me
31:69
83:17

Figure 25

trienes such as (49) (Figure 15) that contain one or more $sp^2$ hybridized atoms on the connecting chain. The stereochemical consequences of these transition states are considered in the following sections.

### 4.4.3.1 Trienes with Saturated Connecting Chains

Figure 28 defines the sterically preferred orientation of substituents in the *trans*- (**104**) and *cis*-fused (**105**) transition states for conformationally mobile monosubstituted 1,7,9-decatrienes. Substituents at $R^1$, $R^2$ and $R^3$ will preferentially occupy the sterically less demanding equatorial positions in both transition states. Dienylic $R^4$ substituents generally adopt an equatorial position in the *trans*-fused transition state (**104**), while an axial orientation appears to be sterically favored in the *cis* transition state (**105**) (for example, refer to cyclizations of (**17**) and (**18**), Figure 6). Equatorial placement of $R^4$ in (**105**) introduces

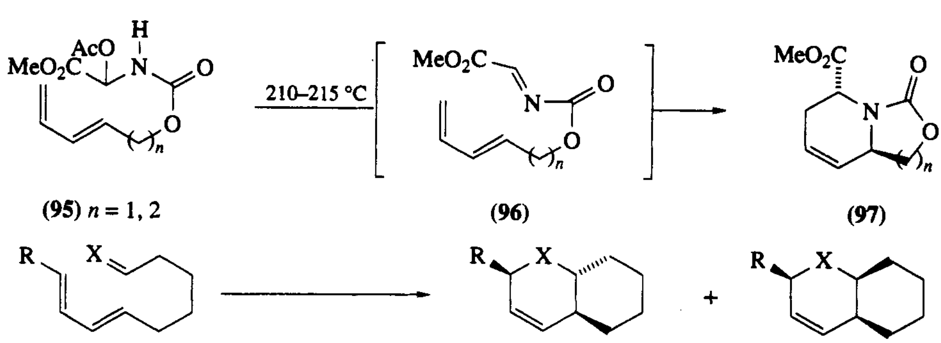

**(95)** $n = 1, 2$ **(96)** **(97)**

| | $X$ | $R$ | *Conditions* | *Selectivity* |
|---|---|---|---|---|
| **(98)** | NBz | Me | 70 °C, 63% | 71:29 |
| **(99)** | Se | Me | 55 °C, 70% | 45:55 |
| **(100)** | S | H | 25 °C, 71% | 33:67 |

**Figure 26**

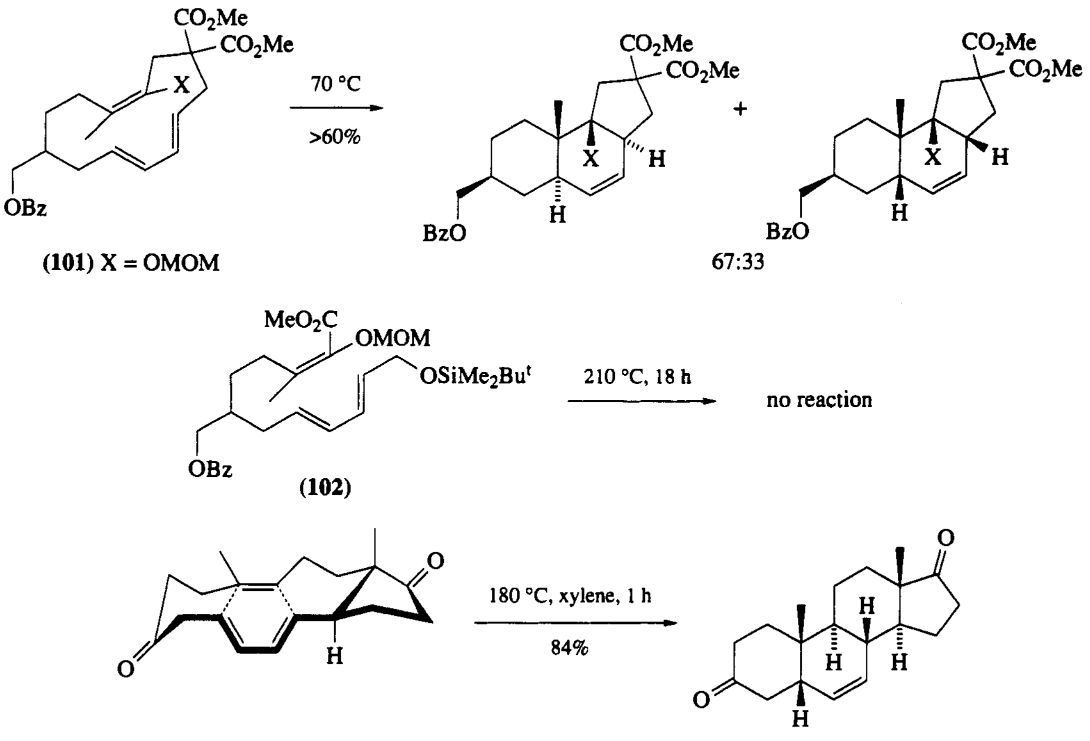

**(101)** X = OMOM

**(102)**

**(103)**

**Figure 27**

nonbonded allylic interactions with C(8), and thus is often disfavored relative to the axial position.[95h] Similar considerations apply in the nonatriene series, particularly with respect to the two allylic substituents (transition states (**106**) and (**107**), respectively).

The examples presented in Figures 29[29,89,90] and 30,[54,91–94] along with other cases discussed earlier, *e.g.* (**33**), (**47**), (**101**) and (**103**), plus numerous additional ones described in the literature,[29,95] are supportive of this analysis. This discussion of course applies explicitly to trienes with a single substituent on the chain linking the diene and dienophile. When two or more substituents are present, then the observed diastereoselectivity will depend on the relative stereochemistry and the individual preferences for equatorial *vs.* axial placement in the various diastereomeric transition states. In this respect, the very high *cis* ring-fusion selectivity exhibited by (**114**) is noteworthy.[94] The excellent stereoselectivity in this case may be due to the fact that both allylic alkoxy substituents can occupy sterically preferred positions in the *cis*-fused transition state (**107**), even though the preference for each alkoxy group to do so is not large (*vide*

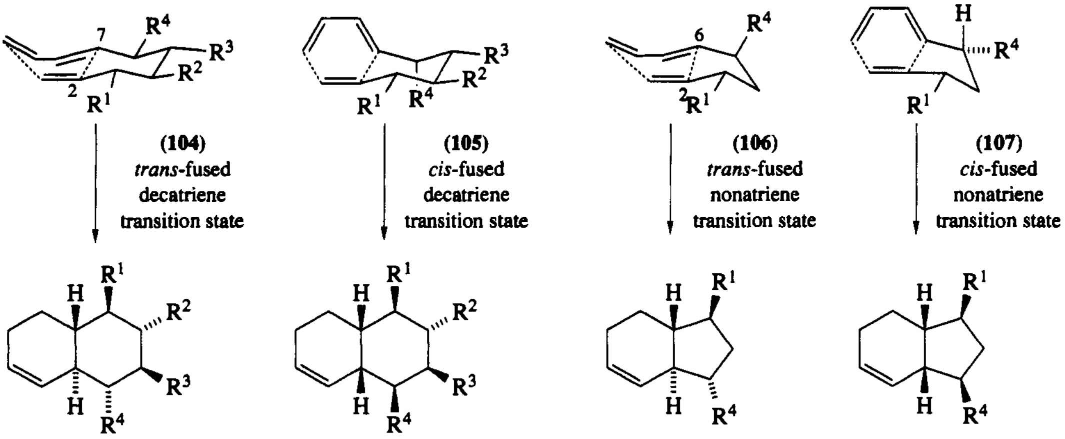
7
R4
R3
R2
2
R1
R1
R4
R3
R2
6
R4
2
R1
H
R4
R1
H
R1
R2
R3
H
R4
H
R1
R2
R3
H
R4
H
R1
H
R4
H
R1
H
R4

**(104)** *trans*-fused decatriene transition state

**(105)** *cis*-fused decatriene transition state

**(106)** *trans*-fused nonatriene transition state

**(107)** *cis*-fused nonatriene transition state

**Figure 28** Diastereoselectivity in IMDA reactions of conformationally mobile, monosubstituted 1,7,9-decatrienes and 1,6,8-nonatrienes: sterically favored transition states

*infra*). This is not possible, however, in the *trans*-fused transition state (**108**). The effect of solvent on stereoselectivity in the cyclizations of (**110**)[90] and (**113**)[54g] is also worthy of note.

Exceptions to these generalizations occur if the system is constrained to cyclize *via* transition states with substituents in axial positions. Two examples appear in Figure 31. The IMDA cyclization of (**115**)

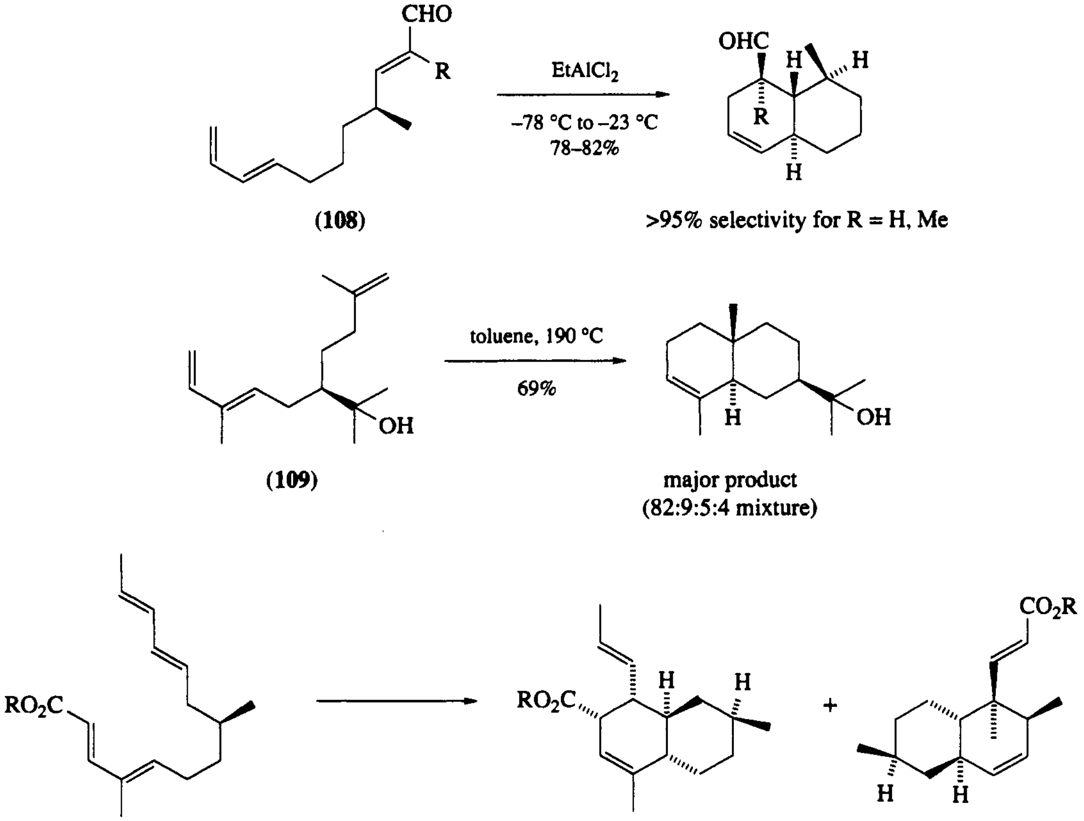
CHO
R
EtAlCl$_2$
−78 °C to −23 °C
78–82%
OHC
H
H
R
H
toluene, 190 °C
69%
OH
H
OH
RO$_2$C
RO$_2$C
H
H
CO$_2$R
H
H

**(108)**

>95% selectivity for R = H, Me

**(109)**

major product
(82:9:5:4 mixture)

| | | | |
|---|---|---|---|
| **(110)** | R = Et | toluene, 165°C, 80% | 75:25 |
| | R = Et | $H_2O$, 100 °C, 60% | 40:60 |
| | R = Na | $H_2O$, 100 °C | 11:89 |

**Figure 29**

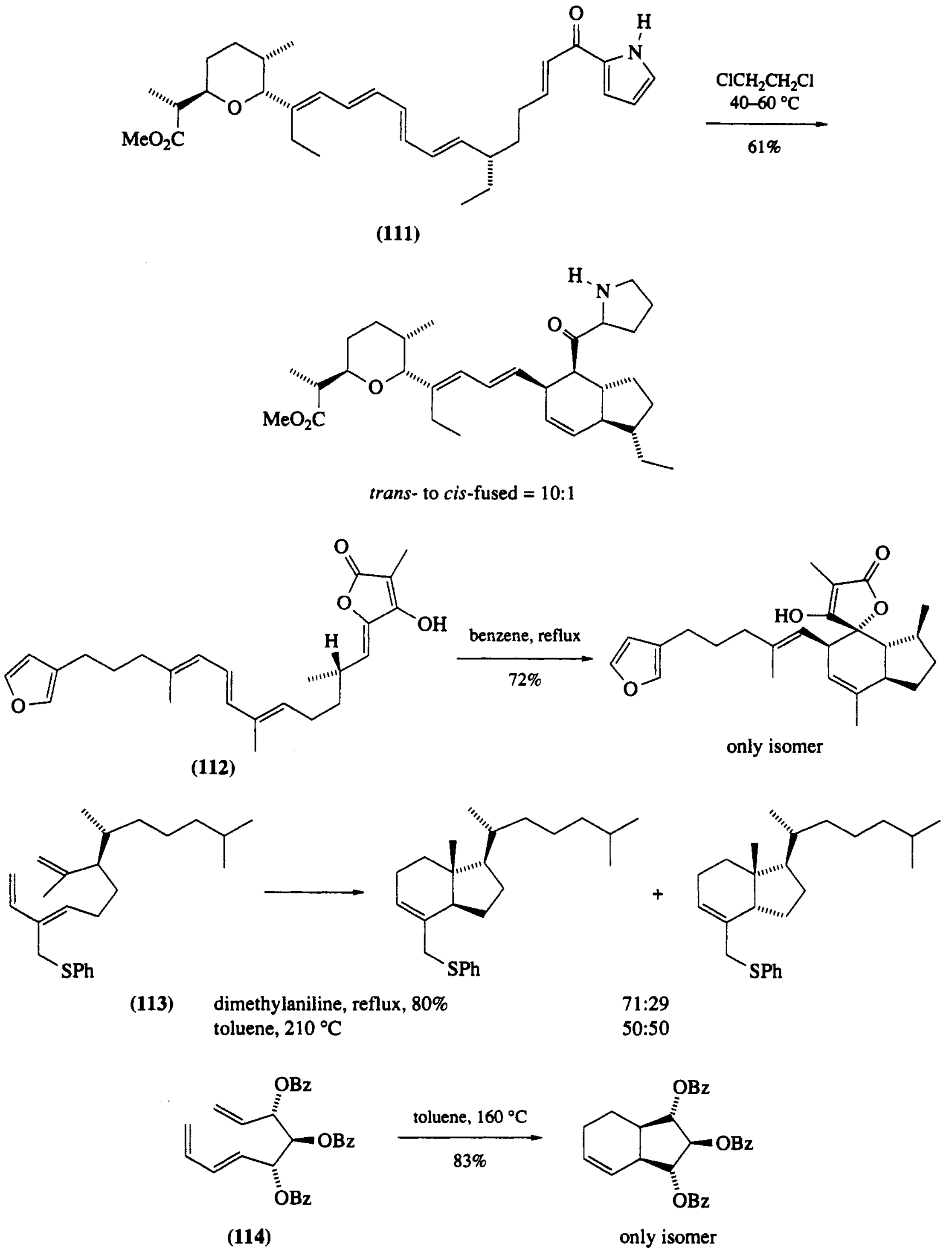

MeO2C
ClCH2CH2Cl
40–60 °C
61%
(111)
MeO2C
trans- to cis-fused = 10:1
OH
benzene, reflux
72%
(112)
HO
only isomer
SPh
(113)
dimethylaniline, reflux, 80%
toluene, 210 °C
71:29
50:50
OBz
toluene, 160 °C
83%
(114)
only isomer

**Figure 30**

nicely illustrates the strategic consequences of linking two substituents into axial positions in the transition state, in this case as a lactone, since in addition to obtaining products with stereochemical relationships not accessible from trienes lacking the lactone bridge, competition from *cis*-fused transition states was also effectively eliminated, *e.g.* refer to Figure 12.[96] Triene **(116)** cyclizes *via* a chair-like transition state with two substituents, the C(3)-methylene and C(6)-$OSiMe_3$ groups, in axial positions even though the latter interacts strongly with the diene C(8) substituent.[97] The major stereochemical control elements in this system are the C(3) stereocenter that restricts the diene to approach only one face of the cyclopentenone dienophile, and the substitution pattern of the diene that precludes transition states leading to *cis*-fused products (Figure 12). Consequently, only a single transition state is available to **(116)** and the C(6)-OSiMe3 group has no choice but to occupy an axial position where it eclipses the diene.

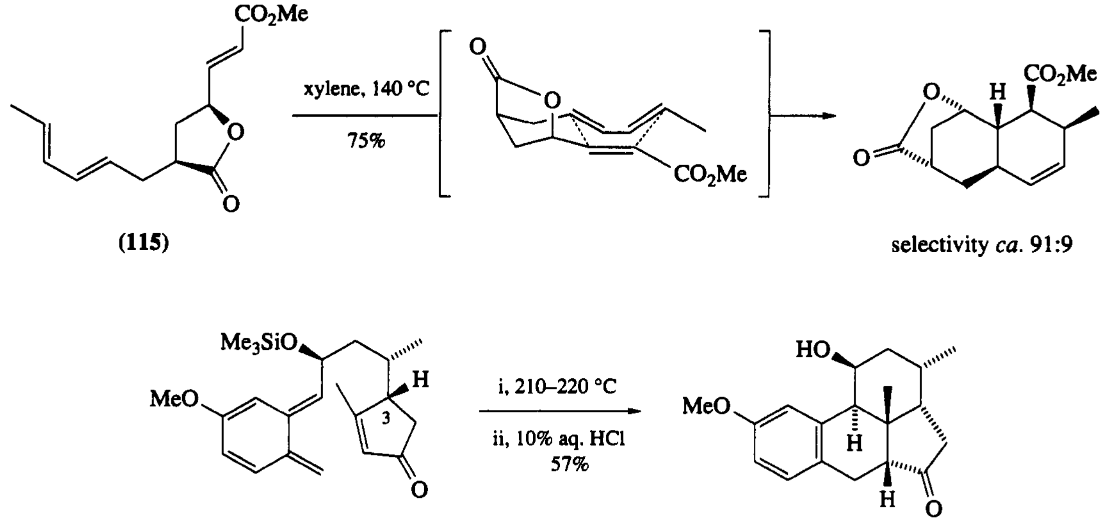

**(115)**

selectivity *ca.* 91:9

**(116)**

Figure 31

The addition of a ring between the diene and the bridging chain also has an influence on IMDA diastereoselectivity. This structural feature restricts the number of degrees of conformational freedom that are accessible, and in the vast majority of cases the dienophile approaches the diene from the same face as the stereocenter, *e.g.* **(117)** (Figure 32).[98,99] One exception, however, occurs with triene **(118)** that cyclizes preferentially *via* a transition state with the dienophile approaching from the face opposite to the anchor position of the tether.[100] The factors responsible for this unusual result remain to be clarified.

Numerous exceptions to the stereochemical picture presented in Figure 28 occur with trienes possessing allylic heteroatom $R^1$ and $R^4$ substituents, particularly allylic alkoxy groups. These substituents are considerably less sterically demanding than methyl or other alkyl groups,[101] and electronic effects may

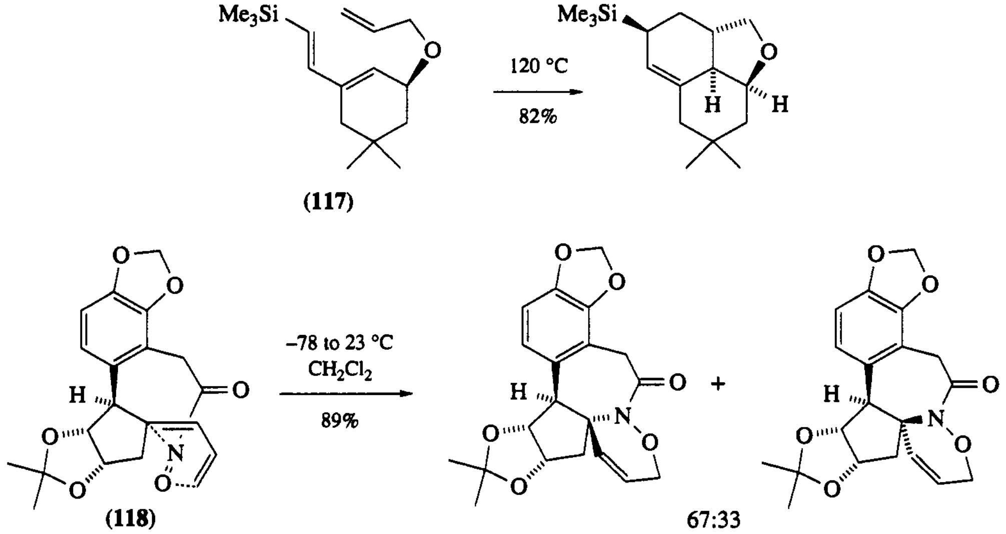

**(117)**

**(118)**

67:33

Figure 32

also intervene such that an axial orientation in the transition state is sometimes favored. The examples presented in Figure 33 serve to illustrate these points. The alkoxy group of (**119**) exhibits only a slight preference for orientation in the pseudoequatorial $R^1$ position in transition states (**106**) and (**107**), and diastereoselectivity is much lower than with alkyl substituted trienes like (**113**) (Figure 30).[12a] With triene (**120**), however, diastereoselectivity is much higher owing to $A_{1,3}$ interactions between the benzyloxy and $CO_2Me$ groups in the transition state, with the former in a pseudoaxial position.[12a] A slightly greater preference for equatorial placement of the hydroxy group occurs in the thermal IMDA reaction of (**121**), but this preference disappears if the cycloaddition is catalyzed with $EtAlCl_2$ or if the hydroxy is protected as a *t*-butyldimethylsilyl (TBDMS) ether; the effects appear to be additive in this case.[102] The preference for pseudoaxial placement of the TBDMSO group in this reaction has been ascribed to a hyperconjugative interaction ($\sigma_{C—O}$–$\pi^*_{C=C}$) that lowers the dienophile LUMO and thereby increases the rate of reaction *via* this transition state.

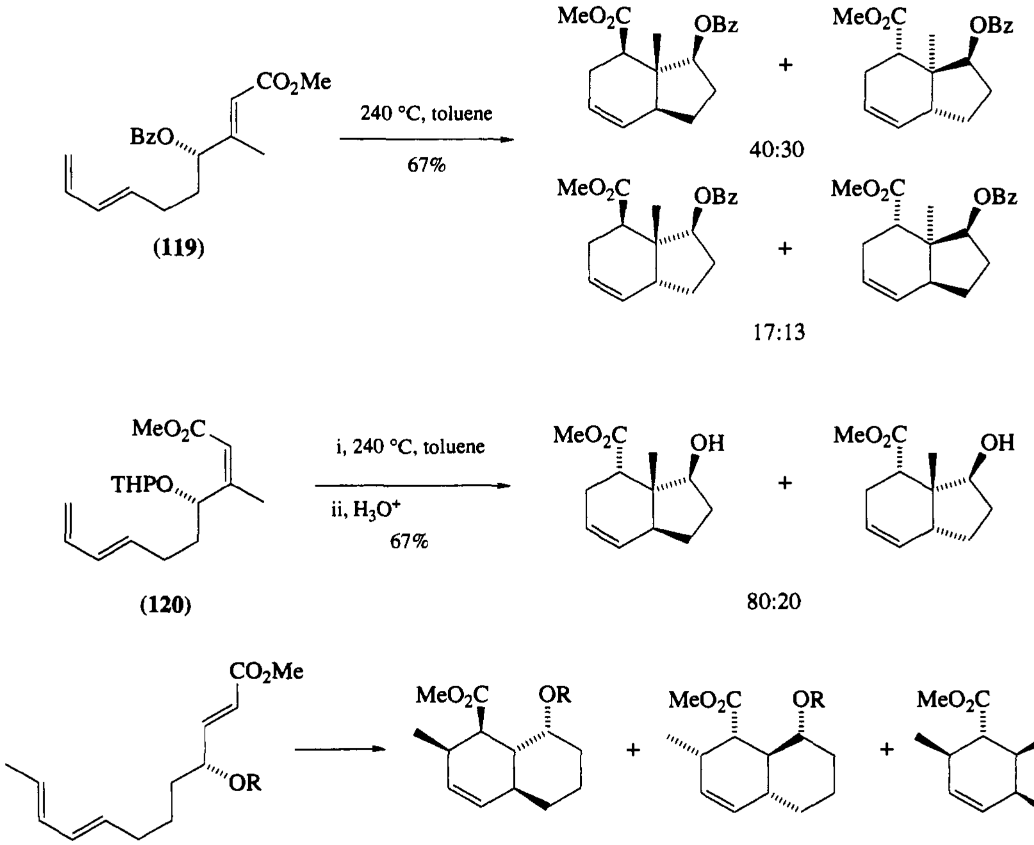

(**119**)

(**120**)

| | | |
|---|---|---|
| (**121**) R = H | 155 °C, 53% | 12:41:47 |
| (**121**) R = H | $EtAlCl_2$, 23 °C, 55% | 55:45:1 |
| (**21**) R = $Bu^tMe_2Si$ | 140 °C, 65% | 65:13:22 |
| (**21**) R = $Bu^tMe_2Si$ | $EtAlCl_2$, 23 °C, 65–73% | 98:2:0 |

**Figure 33**

Alkoxy groups at the $R^4$ position allylic to the diene also generally exhibit a modest preference for either the equatorial or axial placement in the transition state, and the dependence of stereoselectivity on the protecting group has been noted.[29e,103] Larger allylic heteroatom substituents such as a benzenesulfonyl group, however, exhibit a much greater preference for the less sterically demanding pseudoequatorial position.[27] Marshall has made the interesting observation that the axial alkoxy diastereomer is favored in Lewis acid catalyzed cyclizations as long as a silyl ether protecting group is employed; the silyloxy substituent necessarily eclipses the diene in the transition state. Diastereoselectivity is much lower with MOM ether protected substrates, suggesting a stereoelectronic component to these results (compare data for (**17**) and (**122**), Figure 34).[29e] A similar preference for production of axial silyloxy diastereomers in the IMDA cyclizations of vinylnitrosonium cations has been noted by Denmark, who has provided a detailed discussion of the steric and stereoelectronic factors that presumably contribute to this stereochemical preference.[104] IMDA cycloadducts with equatorial alkoxy groups at the dienylic position can be prepared with good selectivity by application of the steric directing group strategy that also amplifies the selectivity for the *trans*-fused product (for example, trienes (**123**)–(**126**), Figure 34).[50b] The production of significant quantities of *cis*-fused products in these IMDA reactions, especially in the IMDA reactions of (**123**) and (**124**) where X = $SiMe_3$, suggests that the *cis*-fused diastereomers probably arise *via* a boat-like, and not a chair-like, transition state as is usually assumed (Figure 35).[49,50]

### 4.4.3.2 Decatrienones and Other Trienes with Unsaturated Connecting Chains: Intervention of Boat-like Transition States

While most decatrienes cyclize *via* transition states with chair-like conformations of the connecting chain (*vide supra*), a growing body of evidence indicates that conformationally unrestricted decatrienones preferentially cyclize *via* boat-like transition states.[58] The stereochemical consequences of this are significant, particularly since the cycloadduct obtained *via* the the lowest-energy boat transition state (**127**) is not always the same as the one obtained from the lowest-energy chair conformation (**128**) (Figure 36). Three unambiguous cases that proceed either exclusively, *e.g.* (**129**),[58] or at least preferentially, *e.g.* (**130**)[105] and (**131**),[106] by way of boat transition states are summarized in Figure 37.[107] The IMDA reaction of (**131**) is particularly interesting in that the kinetic product (**132**) derives from a boat transition state, while the thermodynamic product (**133**) is produced *via* the higher-energy chair transition state.[106]

Boat-like transition states have also been implicated in the IMDA cyclizations of heteroatom substituted trienes such as (**134**), (**135**)[108] and (**137**)[109] (Figure 38). Additional support for the involvement of a boat transition state in the cyclization of (**135**) derives from studies of the corresponding immonium ion substituted triene [lacking the carbonyl unit of (**136**)] that presumably cyclizes by way of chair-like transition states and is considerably less diastereoselective.[95g]

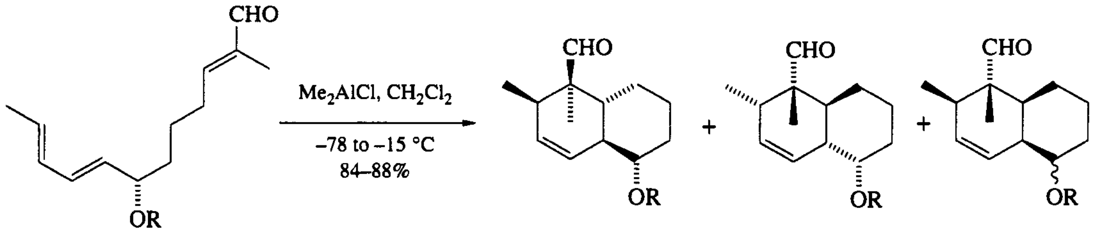

(**122**) R = MOM
(**17**) R = $Bu^tMe_2Si$

56:40:4
15:75:10

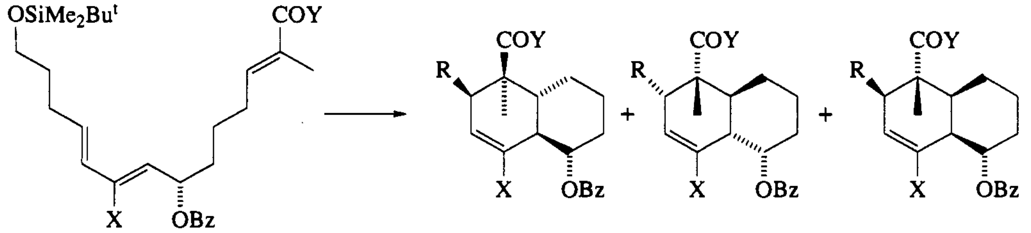

| | | | | |
|---|---|---|---|---|
| (**123**) | X = $SiMe_3$ | Y = OMe | 160 °C, 85% | 78:8:14 |
| (**124**) | X = $SiMe_3$ | Y = H | 160 °C, 82% | 79:9:12 |
| (**124**) | X = $SiMe_3$ | Y = H | $Et_2AlCl$, –15 °C, 77% | 89:5:6 |
| (**125**) | X = Br | Y = OMe | 160 °C, 80% | 62:4:34 |
| (**126**) | X = Br | Y = H | 160 °C, 86% | 75:3:22 |
| (**126**) | X = Br | Y = H | $EtAlCl_2$, –15 °C, 24% | 90:1:9 |

**Figure 34**

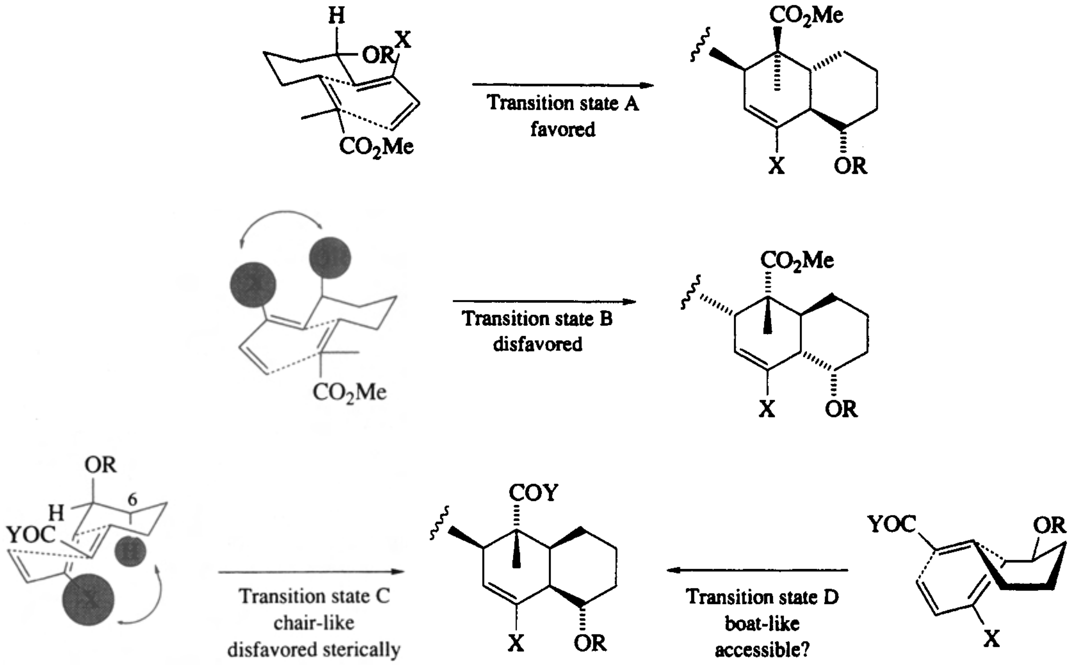
H
OR
X
CO2Me
Transition state A
favored
CO2Me
X
OR
Transition state B
disfavored
CO2Me
CO2Me
X
OR
OR
H
6
YOC
Transition state C
chair-like
disfavored sterically
COY
X
OR
Transition state D
boat-like
accessible?
YOC
OR
X

**Figure 35** The steric directing group stategy

A rationalization of the preference of boat-like decatrienone transition states has been presented.[58] In the absence of overriding substituent effects, the boat-like transition state is free of destabilizing eclipsing or other unfavorable nonbonded steric interactions, and the C(4)—C(6) segment adopts staggered conformations in both the boat-like (**127**) and chair-like (**128**) arrangements (Figure 36). The principal difference between them is that in (**127**) the C(6)—C(7) unit exists in a favored skew butene conformation and the C(3)—C(4) unit in a favored eclipsed ethanone conformation, while in the chair-like arrangement (**128**) these *sp*$^3$–*sp*$^2$ rotamers exist in higher-energy *gauche* butene and *gauche* ethanone conformations, respectively. The presence of both stabilizing eclipsing *sp*$^3$–*sp*$^2$ interactions is unique to the *cis*-fused boat decatrienone transition state; all other decatrienone transition states have no more than one such stabilizing allylic conformation and the available experimental evidence suggests that they are each higher in energy than the *cis*-fused boat transition state.[58]

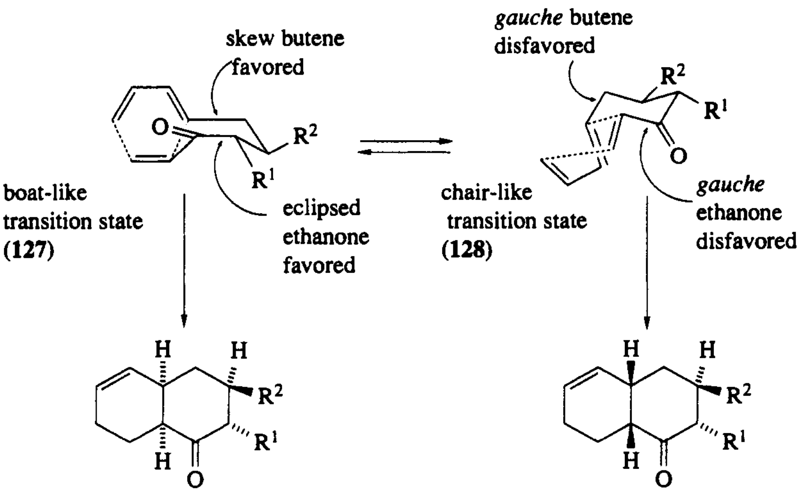
skew butene
favored
O
R2
R1
boat-like
transition state
(127)
eclipsed
ethanone
favored
gauche butene
disfavored
R2
R1
O
chair-like
transition state
(128)
gauche
ethanone
disfavored
H
H
R2
R1
H
O
H
H
R2
R1
H
O

**Figure 36**

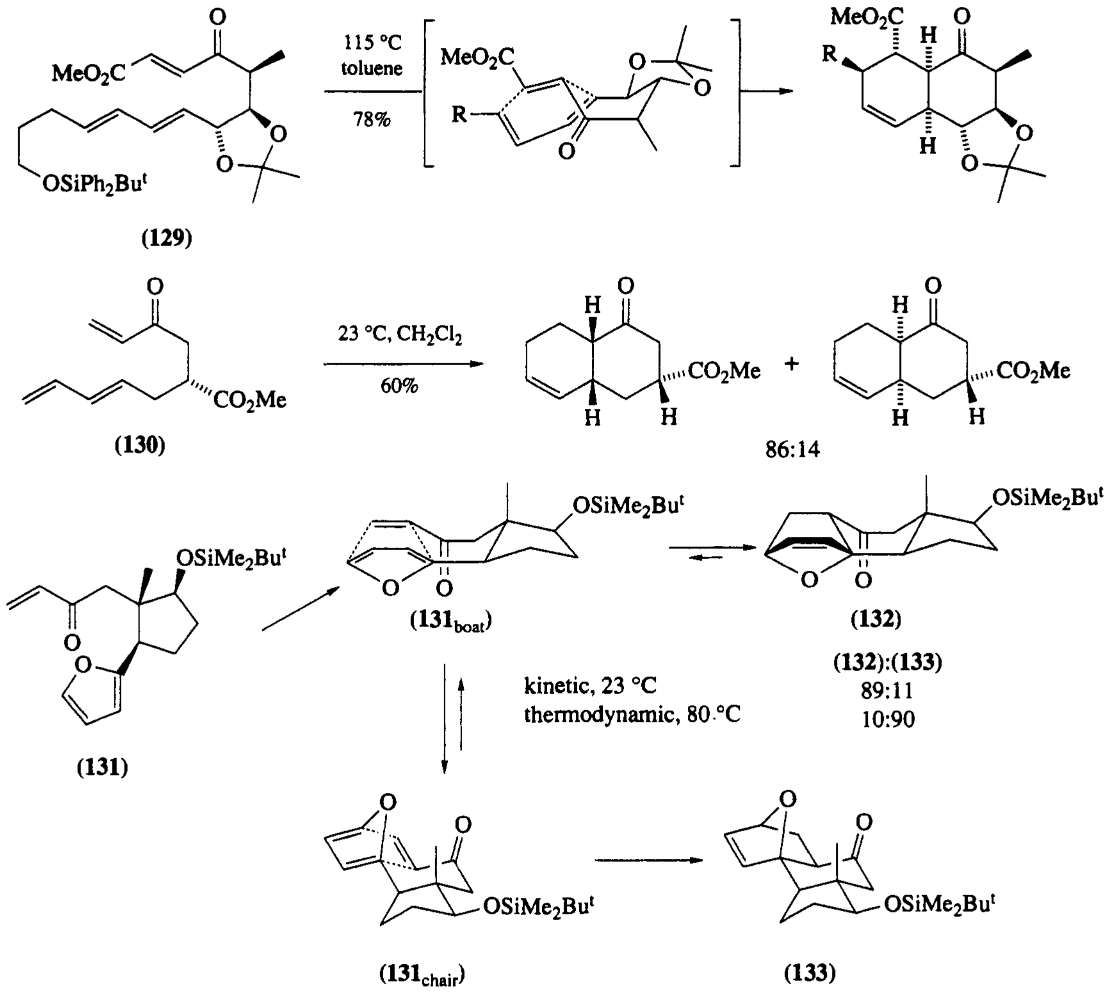

Figure 37

The preference for decatrienones to cyclize by way of boat-like transition states, while significant in the cases cited above, is not so great that competition from chair-like structures is precluded, especially in highly substituted systems. This is nicely illustrated by comparing the diastereoselectivity of the IMDA reactions of **(138)**[110] and **(139)**[111] (Figure 39). Thus triene **(138)** undoubtedly cyclizes by way of boat-like transition state **(140)** since the alternative *cis*-fused chair **(141)** is significantly destabilized by the indicated 1,3-interaction, while *trans*-fused transition state **(142)** is destabilized by the eclipsing interaction between the C(6)-OMe and C(8)-Me units. Examination of models, however, suggests that the two-atom bridge introduces strain into **(140)** relative to the unconstrained boat-like transition structure **(127)** in Figure 36. This is relevant, since replacement of the C(8)-Me with a hydrogen atom in **(139)** causes a reversal of stereoselectivity such that the *trans*-fused product is the only cycloadduct when the IMDA reaction of **(139)** is performed with Lewis acid catalysis. A chair-like transition state resembling **(142)**, but lacking the C(8)-Me group, appears to be the most favorable one in this case. Additional examples have been reported that demonstrate that nonbonded interactions may be sufficient to tip the balance such that a chair-like decatrienone transition state is populated in preference to the otherwise favored boat-like arrangement.[58] Thus all possible interactions must be carefully analyzed when attempting to predict the diastereoselectivity of decatrienone (and other) IMDA cyclizations.

While boat-like transition states are frequently observed in decatrienone IMDA reactions, they are only rarely observed in decatriene IMDA reactions. Undoubtedly, this is due to the fact that boat-like conformations of the bridging chain when all atoms are $sp^3$ hybridized have one eclipsed ethane interaction not present in the chair-like arrangement. Consequently, the boat transition states are intrinsically higher in energy than the chair-like structures.[58] Products deriving from boat decatriene transition states have been observed only in circumstances where the chairs are destabilized by substituent effects or strain, *etc.* One example was presented in Figure 35 concerning the production of *cis*-fused dia-

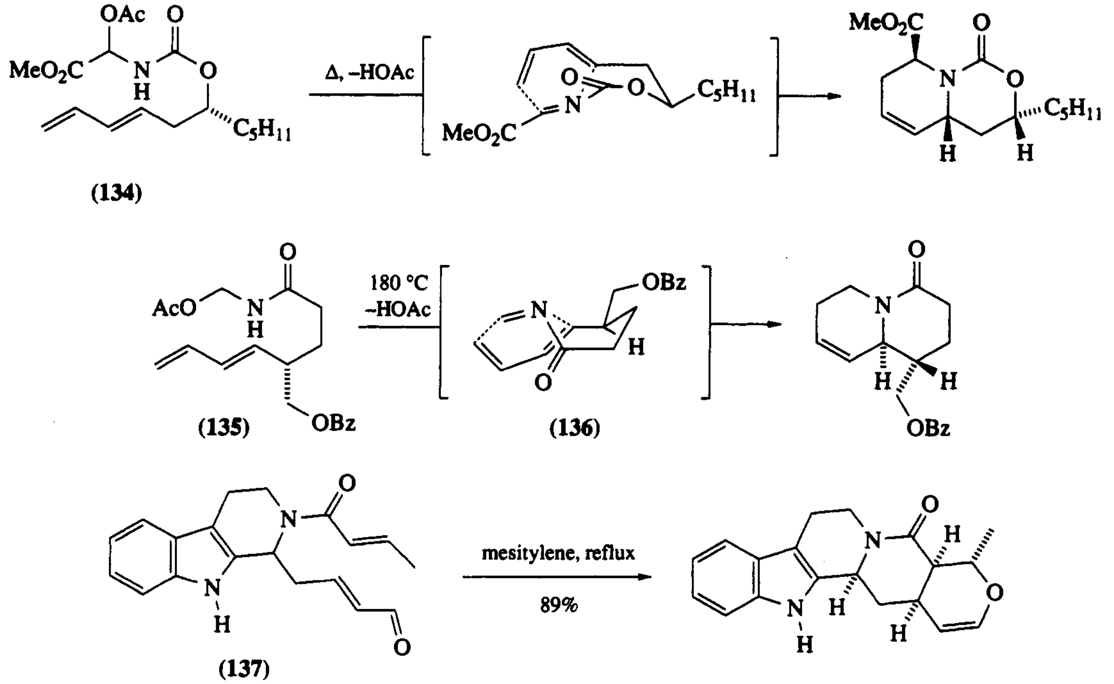
(134)
Δ, -HOAc
(135)
180 °C
-HOAc
(136)
(137)
mesitylene, reflux
89%

Figure 38

stereomers from the IMDA reactions of (**123**)–(**126**); a second example appears in Figure 40.[112] Koreeda has argued that transition state (**143**$_{\text{chair}}$) is strained and therefore higher in energy than (**143**$_{\text{boat}}$) since the chair conformation of bicyclo[3.2.1]octane, a model for the developing [3.2.1] bicyclic system in the cycloadducts, is considerably less stable than the boat conformation.[112]

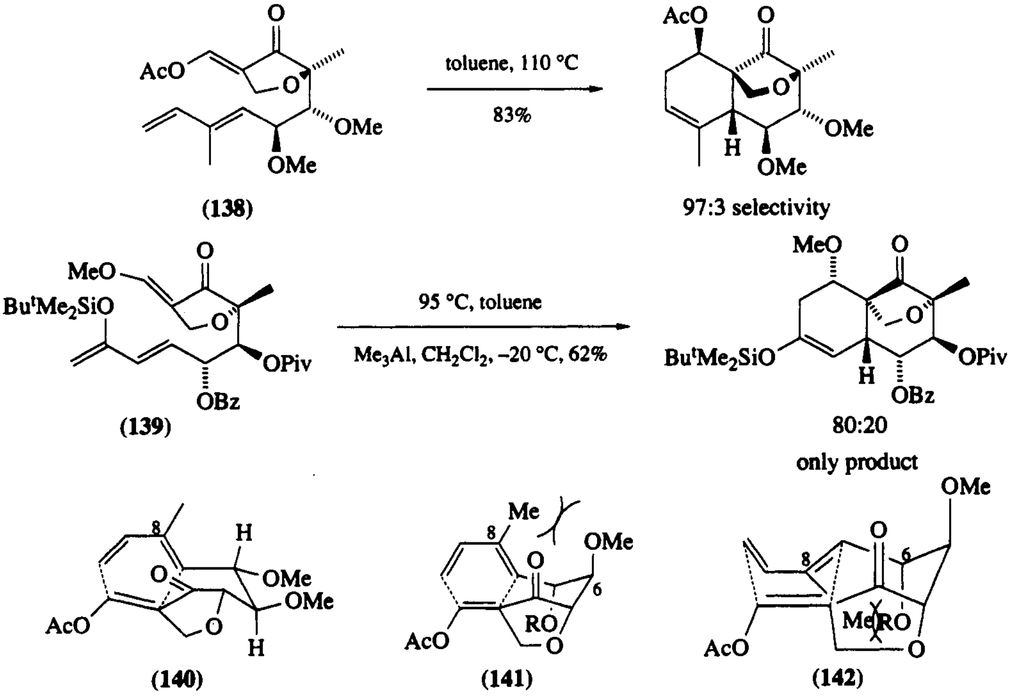
(138)
toluene, 110 °C
83%
97:3 selectivity
(139)
95 °C, toluene
Me3Al, CH2Cl2, -20 °C, 62%
80:20
only product
(140)
(141)
(142)

Figure 39

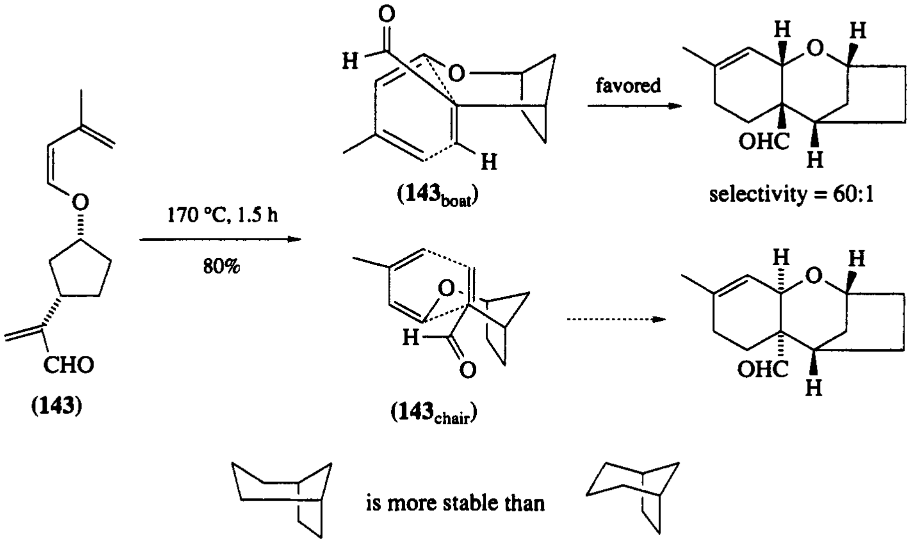

**Figure 40**

### 4.4.4 ASYMMETRIC INTRAMOLECULAR DIELS–ALDER REACTIONS

Reactions that involve asymmetric synthesis are traditionally classified separately from other diastereoselective transformations of chiral substrates, even though there is little fundamental difference between them. The degree of success realized in both categories depends on the ability of the chemist to distinguish between competing, diastereomeric transition states; the critical objective is to maximize $\Delta\Delta G^{\ddagger}$. This classification system undoubtedly evolved since the chiral auxiliary used in asymmetric reactions, whether it is introduced as part of a catalyst or is covalently bound to the substrate, is not destined to be an integral structural component of subsequent transformation products, while the reverse situation obviously pertains in the more frequently encountered diastereoselective transformations of chiral substrates. Work that has been reported for asymmetric IMDA reactions is summarized in this section.[113]

The first example illustrating the use of a removable chiral auxiliary in IMDA reactions was reported by Mukaiyama.[114] The Diels–Alder reaction of (**144**) was slow and showed no diastereofacial selectivity. Conversion of (**144**) to the magnesium alkoxide (**145**), in which the dienophile is activated by chelation to the magnesium ion, however, increased the rate of cyclization and provided the indicated cycloadduct with 76% diastereomeric excess (*de*; 88:12 mixture of diastereomers).

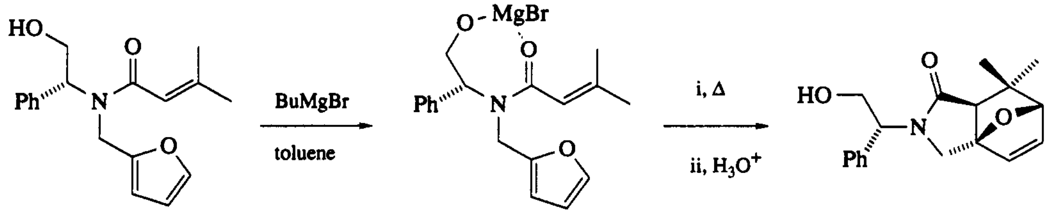

**(144)** **(145)** 76% *de*

A number of trienes with auxiliaries associated with the dienophile activating group have been studied (Figure 41). The 8-phenylmenthyl auxiliary, that generally affords very good levels of asymmetric induction in bimolecular Diels–Alder reactions,[115] gives relatively poor results with trienes (**146**) and (**147**), probably due to the low reactivity of these trienoates that precludes cycloaddition at temperatures below 0 °C.[11a] Much better results have been achieved with trienes (**148**)–(**155**) incorporating the *N*-acyloxazolidinone, *N*-acyl sultam and α-hydroxy ketone auxiliaries developed by Evans,[116] Oppolzer[117] and Masamune,[118] respectively. Trienes (**148**)–(**153**) are considerably more reactive than (**146**) and (**147**) and their Lewis acid catalyzed cyclizations are complete typically within several hours at −20 °C or −30 °C.[116b,c,117b] *Trans*-fused cycloadducts are obtained with >99:1 selectivity from nonatrienes (**148**)–(**150**),

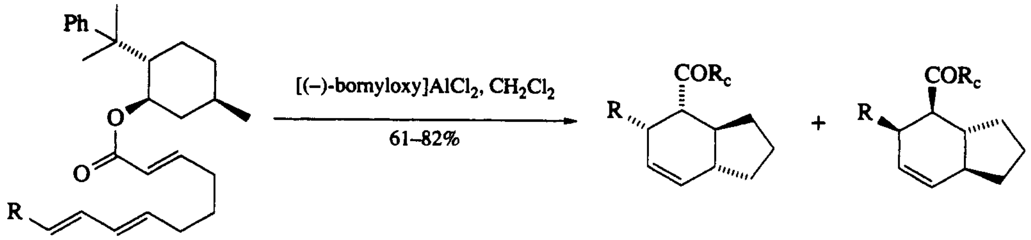
Ph
O
O
R
[(–)-bornyloxy]AlCl$_2$, CH$_2$Cl$_2$
61–82%
COR$_c$
R
+
COR$_c$
R

| | | |
|---|---|---|
| **(146)** R = Pr$^i$ | 23 °C, 92 h | 67:33 |
| **(147)** R = H | 23 °C, 36 h | 82:18 |
| **(147)** R = H | 8 °C, 330 h | 86:14 |

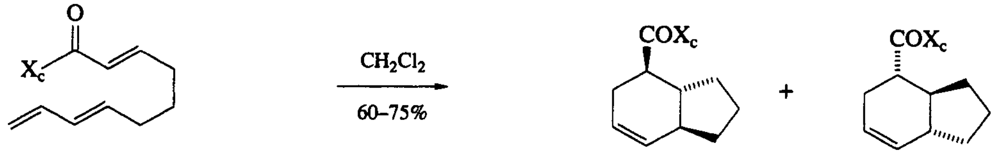
O
X$_c$
CH$_2$Cl$_2$
60–75%
COX$_c$
+
COX$_c$

| | | |
|---|---|---|
| **(148)** X$_c$ = X$_P$ | Me$_2$AlCl, –30 °C | 5:95 |
| **(149)** X$_c$ = X$_{PPG}$ | Me$_2$AlCl, –30 °C | 97:3 |
| **(150)** X$_c$ = X$_S$ | Et$_2$AlCl, –20 °C | 97.5:2.5 |

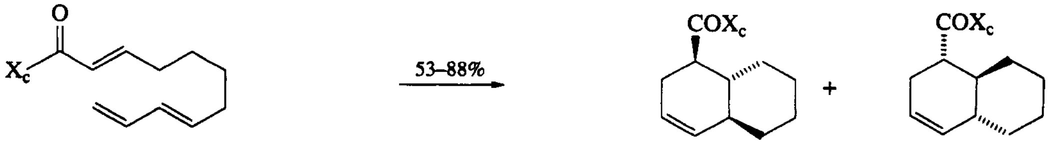
O
X$_c$
53–88%
COX$_c$
+
COX$_c$

| | | |
|---|---|---|
| **(151)** X$_c$ = X$_P$ | Me$_2$AlCl, –30 °C | 3:97 |
| **(152)** X$_c$ = X$_{PPG}$ | Me$_2$AlCl, –30 °C | 94:6 |
| **(153)** X$_c$ = X$_S$ | Et$_2$AlCl, –20 °C | 94:2.6:3.4 (*cis*-fused) |

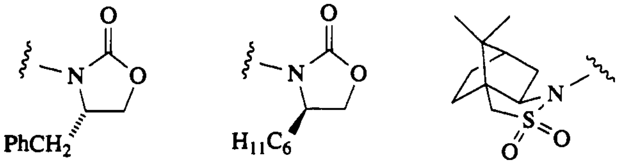
O
N
O
PhCH$_2$
O
N
O
H$_{11}$C$_6$
N
S
O
O

X$_P$ X$_{PPG}$ X$_S$

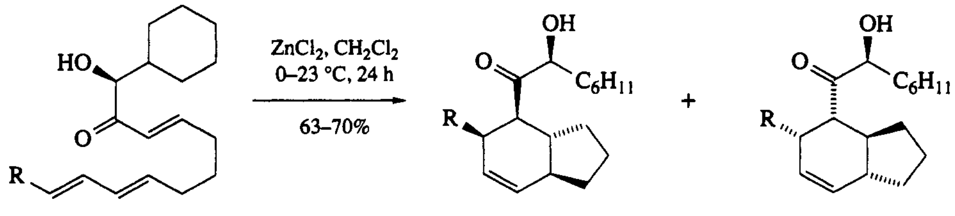
HO
O
R
ZnCl$_2$, CH$_2$Cl$_2$
0–23 °C, 24 h
63–70%
OH
O
C$_6$H$_{11}$
R
+
OH
O
C$_6$H$_{11}$
R

**(154)** R = H, Pr$^i$

97:3

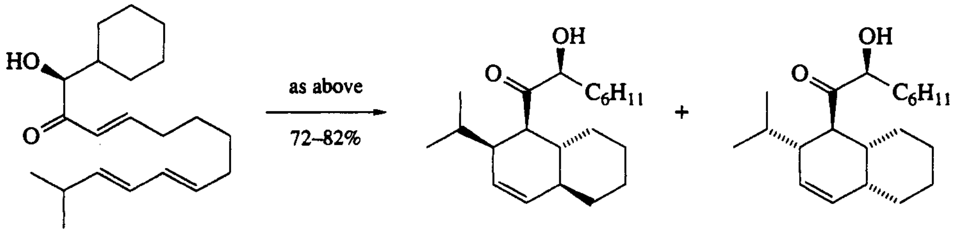
HO
O
as above
72–82%
OH
O
C$_6$H$_{11}$
+
OH
O
C$_6$H$_{11}$

**(155)**

96:4

**Figure 41**

while simple diastereoselection with the decatriene substrates (**151**)–(**153**) is >30:50:1. The major products of these reactions are readily purified by crystallization or chromatography. Comparable levels of diastereoselection have also been realized with trienes (**154**) and (**155**).[119] The sense of relative diastereoselection realized in these cycloadditions can be rationalized by inspection of the transition states depicted in Figure 42 for the IMDA reactions (**149**), (**150**) and (**154**).

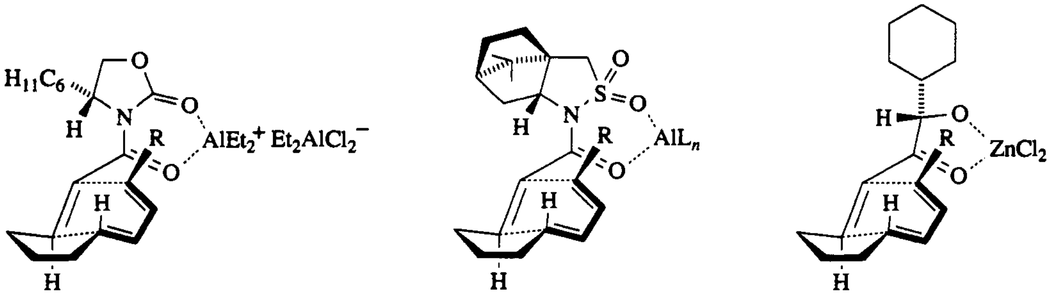

**(149)** **(150)** **(154)**

**Figure 42**

Of these three highly diastereoselective methods for accomplishing asymmetric IMDA reactions, the α-hydroxy ketone protocol[118,119] [trienes (**154**) and (**155**)] is the least convenient owing to the greater difficulty of triene preparation, the moderate reactivity of the trienes, and the destructive removal of the auxiliary. Consequently, the auxiliary systems developed by Evans and Oppolzer are more likely to find application in natural products synthesis. Indeed, Oppolzer has recently applied the *N*-acyl sultam methodology to the asymmetric total synthesis of (–)-pulo'upone (Figure 43).[120]

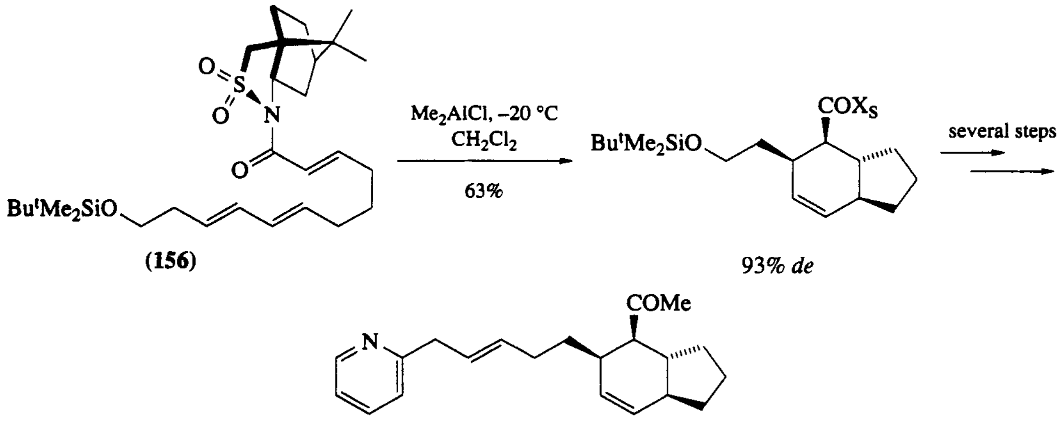

**(156)**

93% *de*

(–)-Pulo'upone

**Figure 43**

Two strategies for accomplishing asymmetric hetero-IMDA reactions have been reported (Figure 44). First, Tietze has shown that (**157**), that includes an ephedrine auxiliary as a component of the heterodiene unit, undergoes a highly diastereoselective Lewis acid catalyzed cycloaddition, providing cycloadduct (**158**) with >97% selectivity.[121] Second, Schreiber has shown that (**161**), prepared *in situ* by treatment of (**159**) with the ephedrine-derived aminal (**160**), provides cycloadduct (**162**) with 94% selectivity.[122] In both instances the auxiliaries are readily removed in subsequent transformations.

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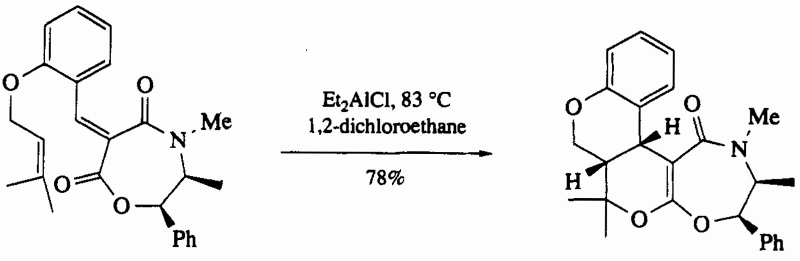

**(157)** **(158)**

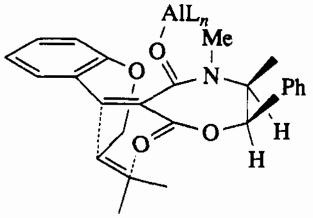

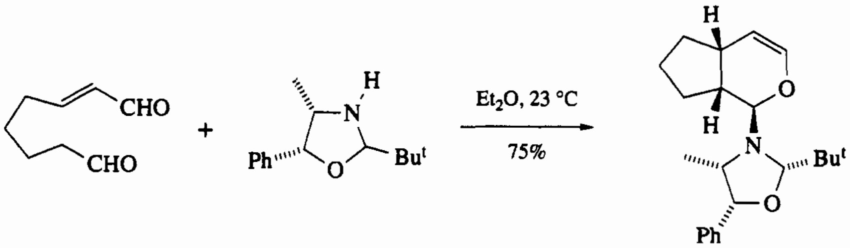

**(159)** **(160)** **(162)** 94% diastereoselection

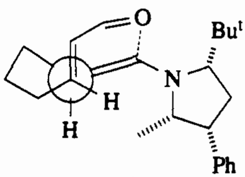

**(161)**

**Figure 44**

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# 4.5

# Retrograde Diels–Alder Reactions

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## 4.5.1 INTRODUCTION

The retro Diels–Alder (rDA) reaction is a ${}_{\pi}2_s + {}_{\sigma}2_s + {}_{\sigma}2_s$ electrocyclic process that, as the name implies, is the reverse of the familiar Diels–Alder cycloaddition reaction. A kinetic study of the prototypical rDA reaction, conversion of cyclohexene to 1,3-butadiene and ethylene (equation 1), has been studied in the temperature range of 541–629 °C.[1] Some early observations of rDA reactions were made in 1906 by Albrecht, who reported that the DA adducts of cyclopentadiene with benzoquinone dissociate at their melting points,[2] and in 1929 by Diels and Alder, who reported the dissociation of a furan–maleic anhydride adduct at its melting point.[3] Alder used the reaction as a test to differentiate between acetylenedicarboxylic ester adducts of cyclopentadiene and of cyclohexadiene;[4] heating the latter adduct eliminates ethylene, while heating the former yields only the starting diene and dienophile (the Alder–Rickert rule). Perhaps the earliest use of the rDA reaction in a synthetic mode was in the preparation of acetylenedicarbonyl chloride,[5] in which an anthracene adduct was used as a removable acetylene protecting group. Use of the rDA reaction in achieving selective synthetic conversions has been reviewed several times to date.[6–9]

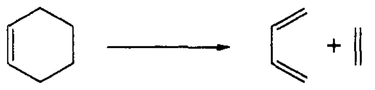
(1)

As the focus of this chapter is on the synthetic utility of the rDA reaction, an overview of mechanism is beyond the scope of this review; however, the subject has been reviewed previously.[10–12] Structural and medium effects on the rate of the rDA reaction are of prime importance to their synthetic utility, and therefore warrant discussion here. A study of steric effects on the rate of cycloreversion was the focus of early work by Bachmann[13] and later by Vaughan.[14] The effect of both diene and dienophile substitution on the rate of the rDA reaction in anthracene cycloadducts has been reported in a study employing 45 different adducts.[15] If both cycloaddition and cycloreversion processes are fast on the time scale of a given experiment, reversibility in the DA reaction is observed. Reversible cycloaddition reactions involving anthracenes,[16,17] furans,[18–22] fulvenes[23] and cyclopentadienes[24–26] are known. Herndon has shown that the well-known exception to the '*endo* rule' in the DA reaction of furan with maleic anhydride (equation 2) occurs not because *exo* addition is faster than *endo* addition (it is not), but because cycloreversion of the *endo* adduct is about 10 000 times faster than that of the *exo* adduct.[18]

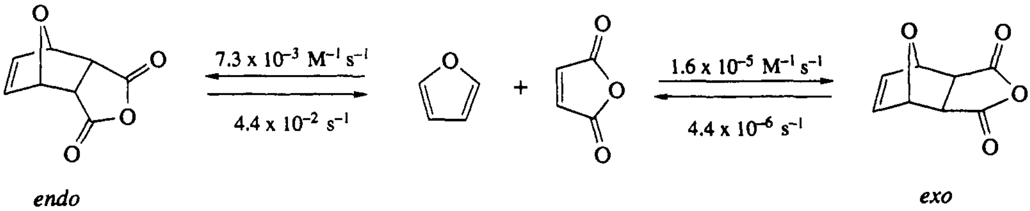

(2)

Many rDA reactions are carried out at temperatures of 150 °C or more in solution phase and often at temperatures of 400–600 °C using the flash vapor pyrolysis (FVP) method; individual conditions are referenced throughout the text. However, an accelerating effect by anionic, cationic and radical substitution on either the dienophile or at the termini of the diene fragments has been predicted by Carpenter.[27] Experimentally, this prediction has been substantiated only for anionic substitution. In 1967, Hart reported what is likely the first example of an oxyanion-accelerated rDA reaction.[28] Both oxyanionic[29–35] and carbanionic[36,37] substituents accelerate the cycloreversion reaction such that they proceed rapidly at room temperature (for example, equation 3). In addition, acid-catalyzed rDA reactions have been reported in which protonation effectively makes the dienophile fragment of the adduct more electron deficient.[38,39] Grieco has utilized a room temperature retro aza DA reaction useful for the *N*-methylation of dipeptides and amino acid derivatives (equation 4).[40]

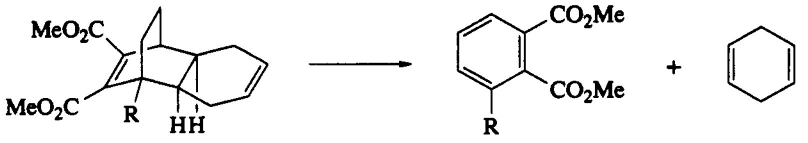

(3)

$R = H, t_{1/2} = 176$ min at 100 °C

$R = OSiMe_3, t_{1/2} = 236$ min at 60 °C

$R = O^- \overset{+}{N}Bu^n{}_4, t_{1/2} = <1$ min at 25 °C

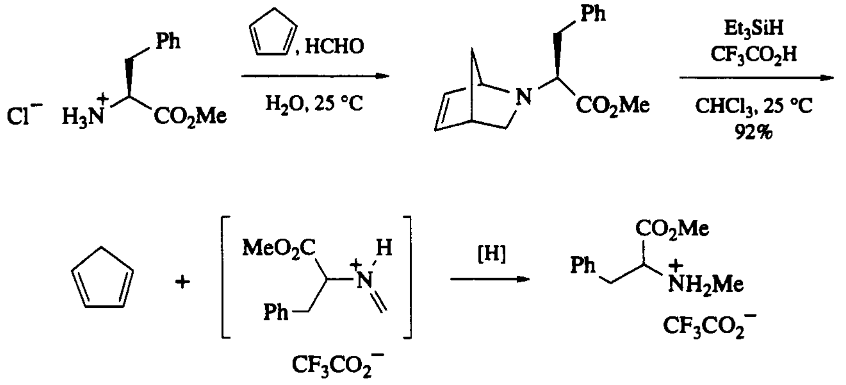

(4)

## 4.5.2 PREPARATION OF SUBSTITUTED ALKENES

### 4.5.2.1 α,β-Unsaturated Esters

Numerous acyclic ethylenes with oxygen-containing substituents have been obtained *via* the rDA reaction. A series of methylidenemalonic acid diesters (**1a–1s**) was prepared using a synthetic scheme based on the rDA reaction (equation 5).[41] Contamination by anthracene was avoided by performing the thermolytic retrodiene step in the presence of maleic anhydride, which consumes the anthracene produced in a DA reaction. Another series of acrylate esters, methyl 2-alkyl-2-alkenoates (**3**), was prepared by the rDA reaction of adduct (**2**) (equation 6).[42] The thermal cleavage occurs under relatively mild conditions by dissolving (**2**) in diphenyl ether and distilling the products directly from the solution at 170–190 °C. This simple preparation is preferable to various multistep methods for the synthesis of methyl 2-alkyl-2-alkenoates.[43,44]

### 4.5.2.2 α,β-Unsaturated Aldehydes and Ketones

The preparation of acyclic alkenic ketones and aldehydes has been shown to be operable *via* methods based on the rDA elimination. A DA–rDA scheme was used to convert methyl vinyl ketone (**4**) into various alkenic ketones (**5**) as shown in equation (7).[45] Yields for the cycloreversion step are reported to be >90%. A similar DA–rDA path has been applied to terpenoid synthesis using cyclopentadiene to protect the double bond. The synthesis of (–)-turmenone (**7**) was accomplished by distilling ketone (**6**) as given in equation (8).[46] Ethylenic hydroxy ketones, which are useful synthetic intermediates for polyhydroxylated natural products, are obtained by rDA reactions. Adduct (**8a**) was flash thermolyzed at 500 °C to give ethylenic ketone (**9a**) (equation 9);[47] however, a competing retro aldol complicated this reaction. Protection of the alcohol with trimethylsilyl chloride followed by thermolysis of protected aldol (**8b**) gave siloxy ketone (**9b**) in 80% yield. The preparation of *cis*-crotonaldehyde (**12**) has been described *via* a three-step synthesis as outlined in equation (10);[48] protection of the double bond is accomplished by DA addition in the initial step giving adduct (**10**), followed by nitrile transformation to aldehyde (**11**). The sequence is completed by regeneration of the double bond by a rDA thermolysis to give *cis*-crotonaldehyde (**12**).

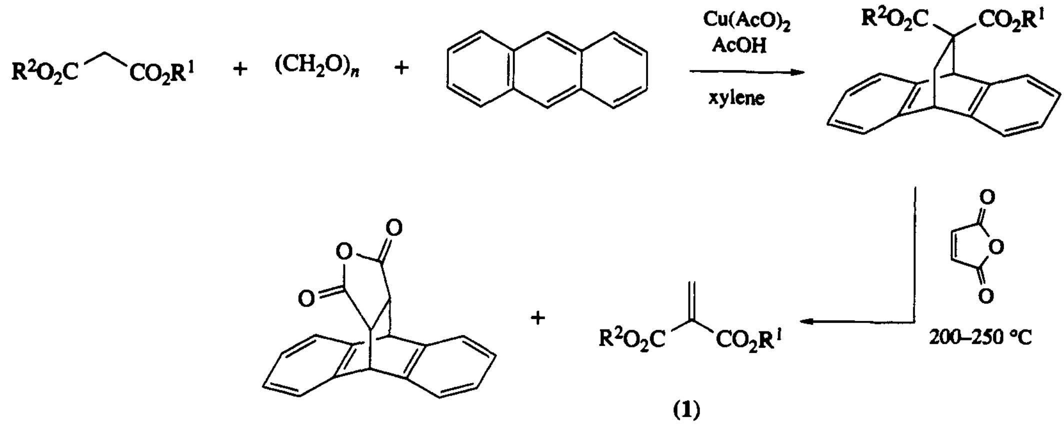

(5)

| *Compound* | *R¹* | *R²* | *Yield (%)* |
|---|---|---|---|
| **(1a)** | Me | Me | 54 |
| **(1b)** | Et | Et | 67 |
| **(1c)** | $Pr^n$ | $Pr^n$ | 81 |
| **(1d)** | $Bu^n$ | $Bu^n$ | 68 |
| **(1e)** | $Pr^i$ | $Pr^i$ | 64 |
| **(1f)** | $Bu^i$ | $Bu^i$ | 61 |
| **(1g)** | n-$C_5H_{11}$ | n-$C_5H_{11}$ | 46 |
| **(1h)** | $CH_2CH{=}CH_2$ | $CH_2CH{=}CH_2$ | 48 |
| **(1i)** | Me | $Bu^n$ | 75 |
| **(1j)** | Me | n-$C_6H_{13}$ | 77 |
| **(1k)** | Et | $Pr^n$ | 63 |
| **(1l)** | Et | $Bu^n$ | 71 |
| **(1m)** | Et | $CH_2CH{=}CH_2$ | 48 |
| **(1n)** | Et | $CH_2C{\equiv}CH$ | 20 |
| **(1o)** | Et | $CH_2CH_2OEt$ | 43 |
| **(1p)** | Et | $CH_2CO_2Et$ | 62 |
| **(1q)** | Et | $(CH_2)_3CO_2Et$ | 32 |
| **(1r)** | $Pr^n$ | $Bu^n$ | 53 |
| **(1s)** | $Bu^n$ | n-$C_5H_{11}$ | 78 |

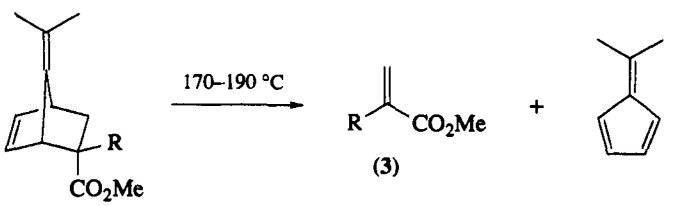

(6)

**(2)** R = Me, Et, $CH_2CH{=}CH_2$, $CH_2CH{=}CHMe$, $CH_2Ph$, $CH_2CO_2Et$

### 4.5.2.3 Acyclic Allylic Alcohols

The preparation of alkenic alcohols based on rDA processes has found application in the synthesis of natural products. Matsutake alcohol (**14a**; (–)-(*R*)-1-octen-3-ol), an important flavor component of mushrooms, can be prepared in high enantiomeric purity by a method that includes rDA cleavage as a key step. Asymmetric DA addition gave enantiomerically pure adducts that were modified dia-

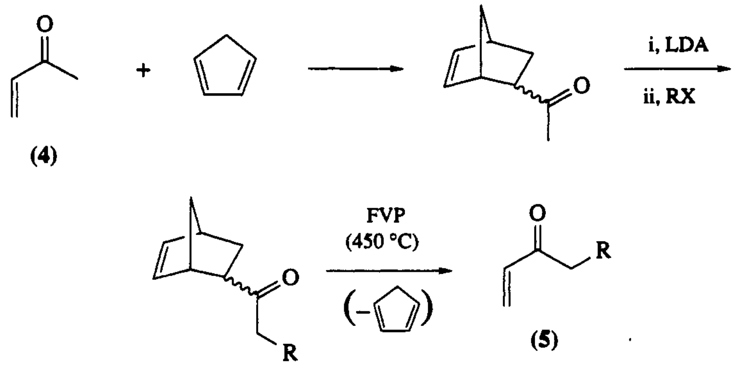
i, LDA
ii, RX
FVP
(450 °C)
O
R

(4) (5) (7)

R = Me, Et, n-$C_5H_{11}$, $CH_2CH{=}CH_2$, $CH_2CH{=}CMe_2$

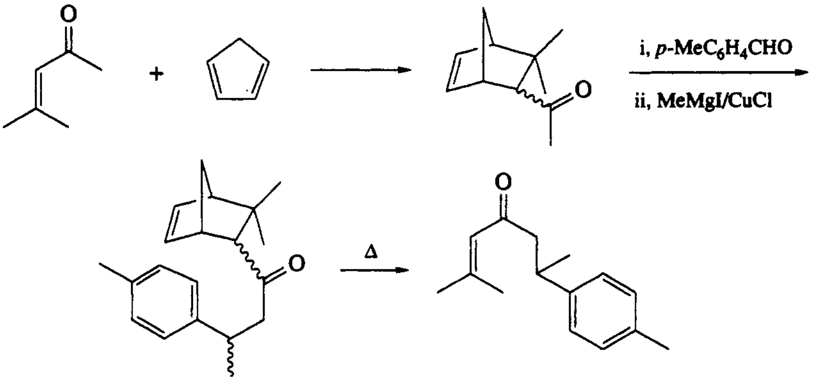
i, p-MeC6H4CHO
ii, MeMgI/CuCl
Δ
O

(6) (7) (8)

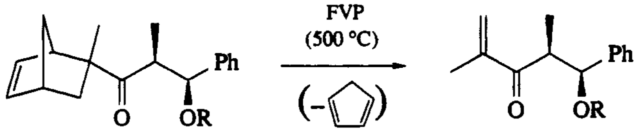
FVP
(500 °C)
Ph
O
OR

(8a) R = H
(8b) R = $SiMe_3$

(9) (9)

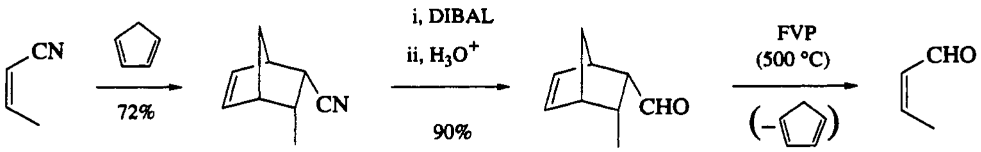
CN
72%
i, DIBAL
ii, H3O+
90%
CHO
FVP
(500 °C)

(10) (+ *exo*) (11) (+ *exo*) (12) (10)

stereoselectively to give isomeric adducts (**13a**) and (**13b**).[49] The isomers were individually *O*-silylated, subjected to FVP and desilylated to give (–)-(*R*)-1-octen-3-ol (**14a**) and (*S*)-1-octen-3-ol (**14b**). The rDA reaction yielding these sensitive allylic alcohol derivatives was not accompanied by racemization. A DA–rDA scheme has been applied to the high yield syntheses of linalool and nerolidol.[45] A similar scheme involving DA protection of a double bond with final rDA regeneration of an alkenic alcohol was used to prepare (±)-ipsenol (**16**). The final step of the synthesis was rDA thermolysis of adduct (**15**) at 450 °C to give (±)-ipsenol in quantitative yield (equation 12).[50]

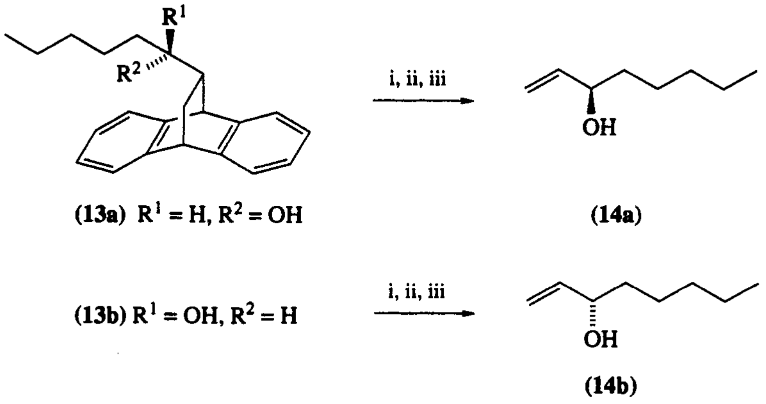

**(13a)** $R^1 = H, R^2 = OH$ **(14a)**

**(13b)** $R^1 = OH, R^2 = H$ **(14b)**

(11)

i, $MeCON(Me)SiMe_3$, $CH_2Cl_2$; ii, FVP, 660 °C/0.005 Torr; iii, AcOH, $MeOH/H_2O$

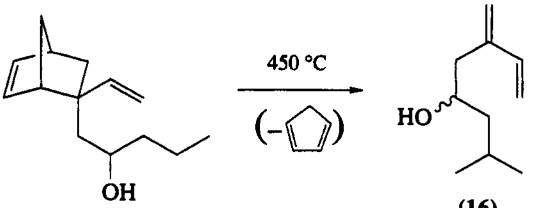

**(15)** **(16)**

(12)

### 4.5.2.4 α,β-Unsaturated Thio Compounds

Acyclic alkenic sulfur compounds have also been obtained *via* pyrolytic rDA reactions. A general route to thioacrylamides utilizing rDA reactions under FVP conditions has been developed. The rDA reaction of the appropriate adducts yields thioacrylamide, *N*-methylthioacrylamide and *N*,*N*-dimethylthioacrylamide in approximately quantitative yield (equation 13).[51] The high reactivity of these α,β-unsaturated thioamides had previously limited their availability. α,β-Unsaturated acyclic thioketones such as **(17)** were prepared *via* a rDA reaction using a FVP technique. These highly reactive species dimerize to 4*H*-1,3-dithiins **(18)** on warming to −60 °C (equation 14).[52]

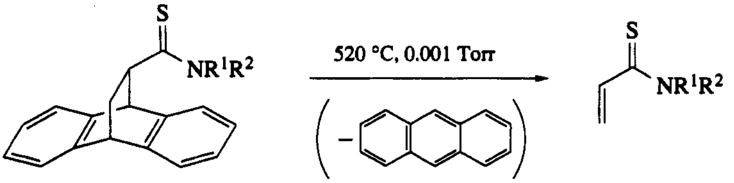

(13)

$R^1, R^2$ = H or Me

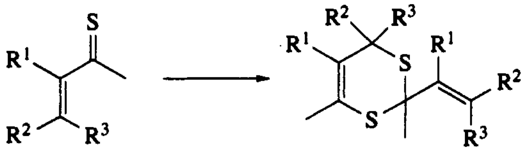

**(17)** **(18)**

(14)

$R^1, R^2$ = H or Me

### 4.5.2.5 Alkenic Nitrogen Species

A few syntheses of alkenic nitrogen compounds based on the rDA reaction are known. For example, ynamine (**19**), *via* rDA decomposition under FVP conditions, gives 1-*N*,*N*-diethylamino-3-buten-1-yl (**20**).[53] 2-Vinylimidazoles had previously been obtained by lengthy reaction schemes with low yields;[54,55] however, a practical laboratory synthesis of 2-vinylimidazoles based on a DA–rDA scheme has been developed. The DA adduct of acrolein and cyclopentadiene was converted to 2-(5-norbornen-2-yl)imidazole (**21**), which was readily transformed into 2-vinylimidazole (**22**) as depicted in equation (16).[56] Glyoxal gave the best result, but other α-dicarbonyl compounds could be substituted to obtain various 2-vinylimidazoles.

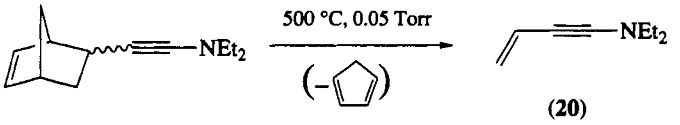

**(19)** **(20)** (15)

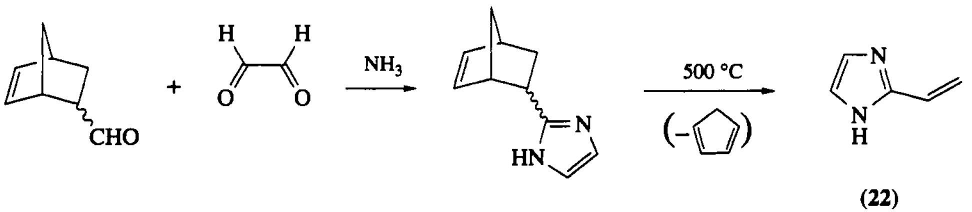

**(21)** **(22)** (16)

### 4.5.2.6 Vinyl Alcohols, Ethers and Esters

The preparation of enols of simple aldehydes and ketones has been achieved by rDA reactions under FVP conditions. Equation (17) illustrates the formation of enols by this method.[57] The percentage of enol reported shows that the enols of aldehydes appear to be isolated more readily than those of the ketones. The last two entries are preparations of the simplest enediols, (*E*)- and (*Z*)-ethylene-1,2-diols. A very similar process was used to unmask the 'protected' ethylene cycloadduct (**23**) and produce 2-hydroxybutadiene (**24**), an elusive enol form of the more stable unsaturated ketone, as given by equation (18).[58]

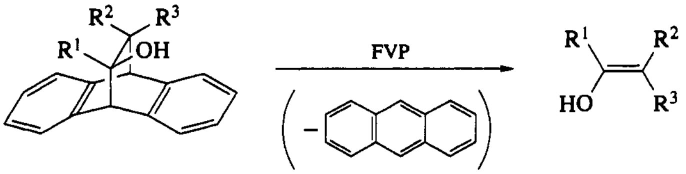

(17)

| *R¹* | *R²* | *R³* | *FVP conditions* | *Enol (%)* |
|---|---|---|---|---|
| H | H | H | 550 °C, $10^{-4}$ Torr | 55 |
| H | H | Me | 550 °C, $10^{-4}$ Torr | 80 |
| H | Me | H | 550 °C, $10^{-4}$ Torr | 75 |
| H | Me | Me | 550 °C, $10^{-4}$ Torr | 100 |
| Me | H | H | 550 °C, $10^{-4}$ Torr | – |
| Me | H | Me | 550 °C, $10^{-4}$ Torr | 5 |
| Me | Me | H | 550 °C, $10^{-4}$ Torr | – |
| Me | Me | Me | 550 °C, $10^{-4}$ Torr | – |
| H | H | OH | 600 °C, $10^{-5}$ Torr | – |
| H | OH | H | 600 °C, $10^{-5}$ Torr | – |

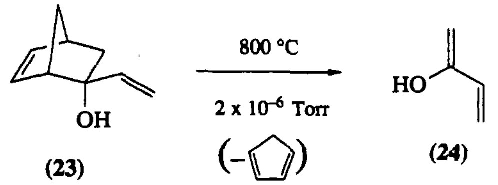

(18)

A series of metalated alkoxymethyl vinyl ethers has been prepared by the thermolysis of substituted bicyclo[2.2.1]hept-5-enes, one example of which is shown in equation (19).[59]

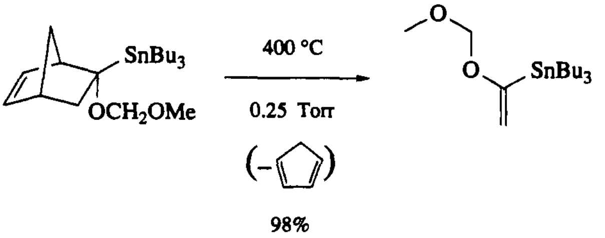

(19)

The rDA route to isopropenyl acetoacetate and to vinyl acetoacetate was apparently the first synthesis of acetoacetate esters of enols. The reaction between diketene (**26**) and norbornenols (**25a**) and (**25b**) generated the 'protected' ethylene cycloadducts (**27**), which upon FVP gave the desired isopropenyl acetoacetate (**28a**) in 48% yield and vinyl acetoacetate (**28b**) in 61% yield (equation 20).[60]

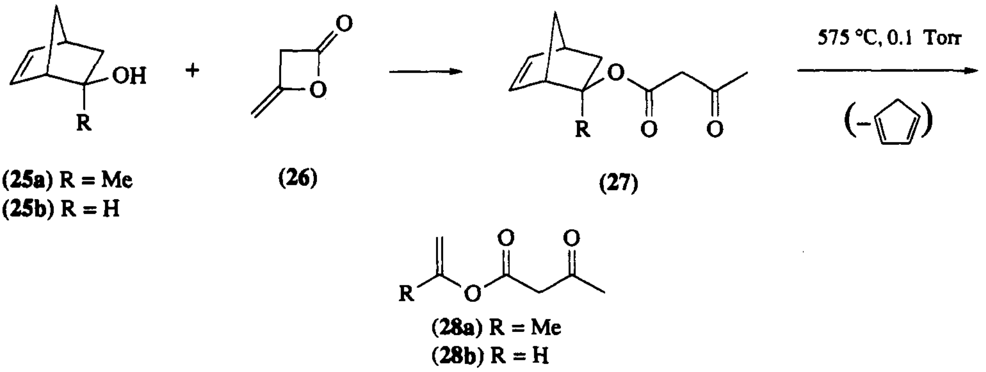

(20)

### 4.5.2.7 Ketenes

Ketenes are generated by rDA pathways; however, most examples are not hetero retrodiene processes. Instead, ketenes are most often produced by the rDA reaction of a 'masked' ethylene cycloadduct generating the carbon–carbon double bond of the ketene. One of the simplest ketenes, dimethylketene (**30**), can be produced by thermal or photochemical elimination of bicyclo[2.2.1]octadienone (**29**) as given in equation (21).[61] The ease with which the ketene is formed by the photolytic retrodiene extrusion process stands in contrast to the high temperature, 450–550 °C, required for the corresponding thermolytic cleavage. Ketenes have also been generated by intramolecular rDA reactions. Upon photolysis of ketone (**31**), intermediate ketene (**32**) formed that reacted with methanol to give cyclooctadiene diester (**33**) (equation 22).[62] In an enantioselective process, the photochemically generated ketene (**34**) reacted with (+)-ephedrine with induction of optical activity (equation 23).[63]

### 4.5.2.8 Enamines

Generation of the double bond of enamines is possible *via* a rDA reaction. Ethylenamine and its methyl derivatives have been prepared by FVP of the corresponding anthracene adducts (equation 24).[62] Identification of the primary enamines in a pure state has been accomplished at −80 °C, while the less stable secondary enamines are accompanied by the corresponding tautomeric imines. The preparation of 2-aza-1,3-dienes has been achieved by rDA reaction on imine adducts as outlined in equation (25).[64] 2-Aza-1,3-dienes are compounds with utility in the synthesis of six-membered N-heterocycles.

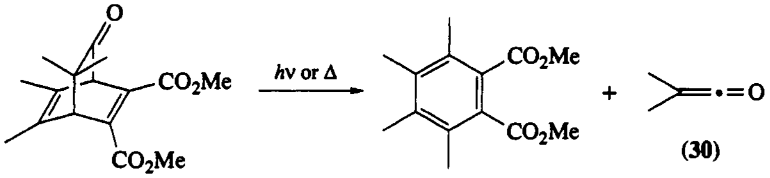
CO2Me
hν or Δ
CO2Me
CO2Me
CO2Me
+

(29) (30)

(21)

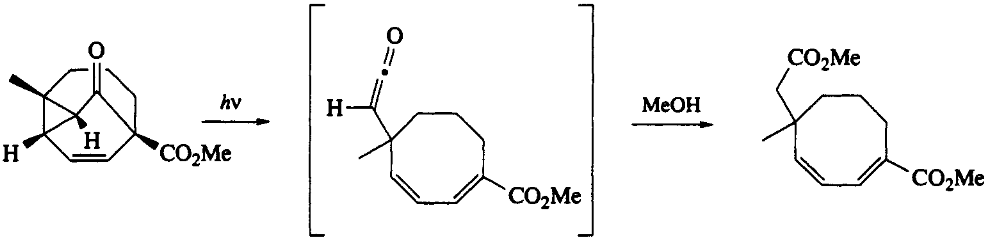
H
H
CO2Me
hν
H
CO2Me
MeOH
CO2Me
CO2Me

(31) (32) (33)

(22)

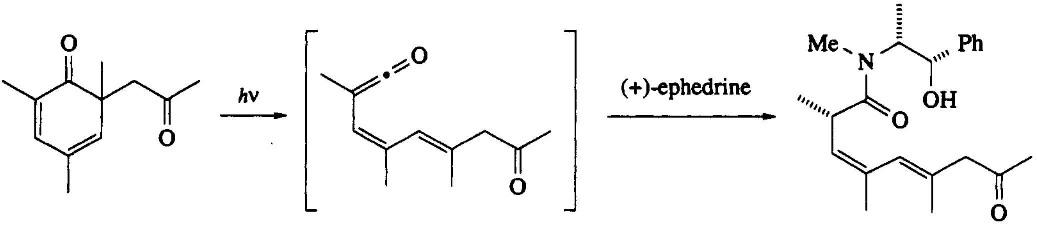
hν
(+)-ephedrine
Me
N
Ph
OH

(34)

(23)

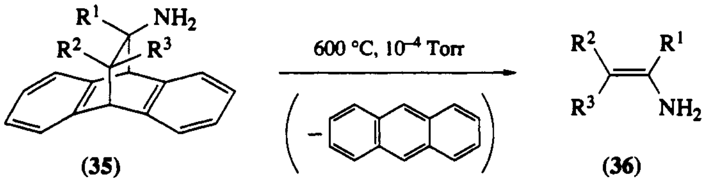
R1
NH2
R2
R3
600 °C, 10−4 Torr
R2
R1
R3
NH2

(35) (36)

(24)

$R^1, R^2, R^3$ = H or Me

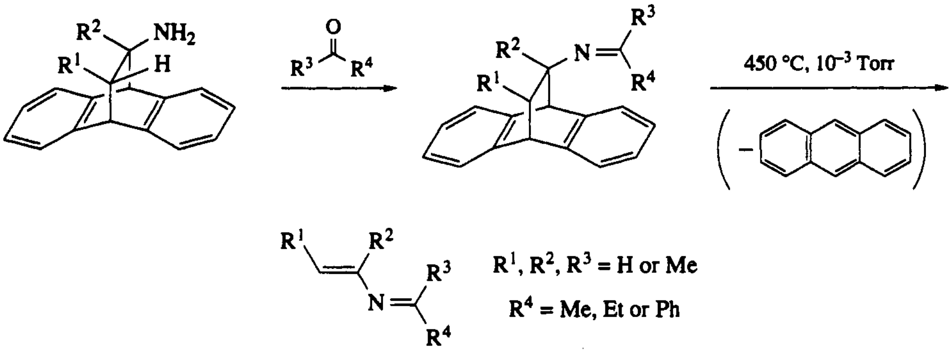
R2
NH2
R1
H
R3
R4
R2
N
R3
R1
R4
450 °C, 10−3 Torr
R1
R2
R3
N
R4

$R^1, R^2, R^3$ = H or Me

$R^4$ = Me, Et or Ph

(25)

### 4.5.2.9 Vinylphosphines

The synthesis of primary alkenylphosphines has been accomplished utilizing the same rDA method that was used to synthesize primary enamines.[62] The synthesis of primary alkenylphosphines had been an unsolved problem owing to the high reactivity of the phosphine group under acidic, basic and neutral conditions.[65] The preparation of vinylphosphine (**38a**) and isopropenylphosphine (**38b**) by FVP of the appropriate anthracene (**37**) or 1,3-diphenylbenzofuran (**39**) adduct has been accomplished as shown in equation (26).[66] (*E*)-Prop-1-enylphosphine was synthesized by a similar rDA route.[66] These phosphines were found to be surprisingly stable, with a half-life of approximately 8 d for (**38a**).

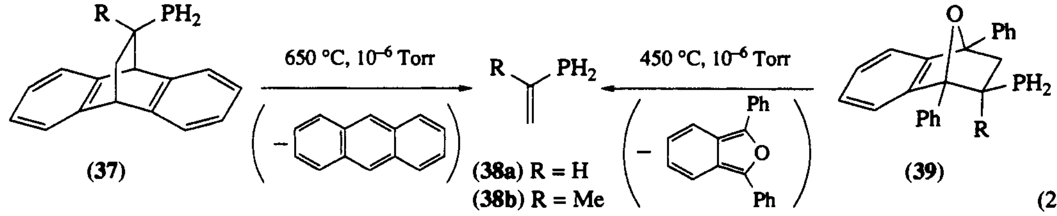

(**37**) (**38a**) R = H (**38b**) R = Me (**39**) (26)

### 4.5.2.10 Exocyclic Alkenes

Exocyclic alkenes have been generated *via* rDA processes. The antibiotic sarcomycin, an antitumor agent, and its methyl ester (**40**) have been the goals of many synthetic efforts. Generation of the exocyclic carbon–carbon double bond by a rDA reaction was the final step to the preparation of ester (**40**).[67] An acid-catalyzed rDA reaction has been used to generate the exocyclic double bond of dione (**41**).[68] The rDA reaction has found further use in the synthesis of α-methylenecyclopentenone antibiotics. FVP of spirocyclopentenone precursors yields the corresponding α-methylenecyclopentenones (**42**) in quantitative or nearly quantitative yield.[69]

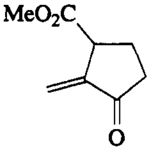

(**40**)

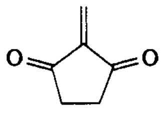

(**41**)

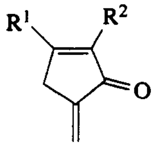

(**42**)

### 4.5.2.11 Endocyclic Alkenes

The rDA reaction has been applied as well to the synthesis of a wide range of compounds containing endocyclic carbon–carbon double bonds. For example, adduct (**43**) as a mixture of *syn* and *anti* isomers yields 3,3-difluorocyclopropene (**44**) and naphthalene upon heating at 200 °C (equation 27).[70] One of the first syntheses of the methylenecyclobutenone moiety was accomplished by a rDA process. The pyrolysis of (**45**) gave approximately 25% conversion to isopropylidenecyclobutenone (**46**) as shown in equation (28).[71] Similarly, the pyrolysis of adduct (**47**) at 425 °C produced the endocyclic double bond of dimethylenecyclobutene (**48**) as shown in equation (29).[69]

rDA processes have been used extensively to generate the endocyclic carbon–carbon double bond of cyclopentene derivatives. Functionalized cyclopentenones are important synthetic intermediates in the synthesis of many quinane natural products.[72–77] The synthesis of optically active cyclopentenones with a predetermined absolute configuration has been achieved. Conjugate addition to enone (**49**) gives adducts (**50a–f**) stereospecifically, which upon FVP yield cyclopentenones (**51a–f**) (equation 30).[78] The development of a general method to prepare 4,5-disubstituted 2-cyclopentenones (**52**) is of value owing to the

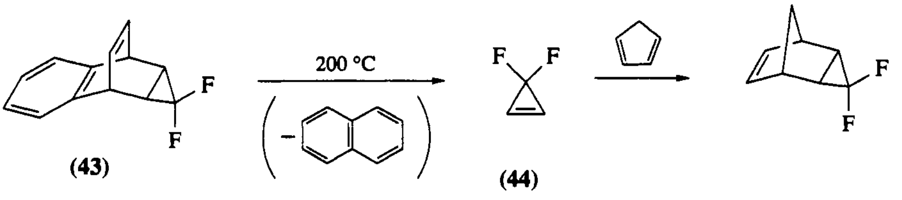

(**43**) *syn* + *anti* (**44**) (27)

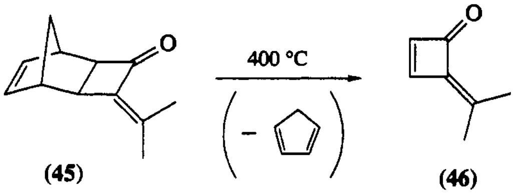

**(45)** **(46)** (28)

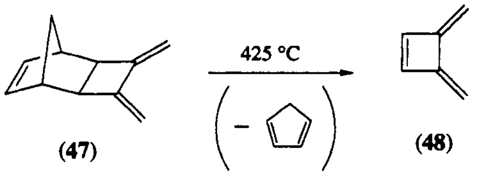

**(47)** **(48)** (29)

occurrence of this system in a variety of natural products. Such systems have been synthesized with a rDA reaction as the key step; the method is outlined in equation (31).[79]

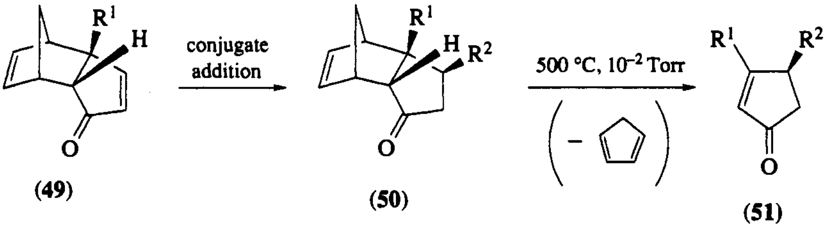

**(49)** **(50)** **(51)** (30)

a: $R^1 = H, R^2 = Me$  d: $R^1 = CO_2Et, R^2 = Me$

b: $R^1 = H, R^2 = C_7H_{15}$  e: $R^1 = CO_2Et, R^2 = C_7H_{15}$

c: $R^1 = H, R^2 = CH(CO_2Me)_2$  f: $R^1 = CO_2Et, R^2 = CH(CO_2Me)_2$

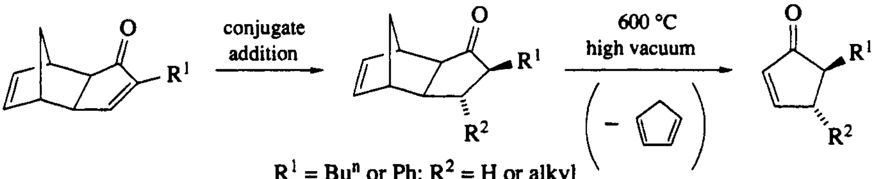

$R^1 = Bu^n$ or Ph; $R^2 = H$ or alkyl

**(52)** (31)

Generation of the endocyclic double bond of cyclopentanoids has been accomplished frequently by rDA reaction of the appropriate cyclopentadiene. FVP has been used as the last step of the synthesis of the antibiotic (±)-pentenomycin (**53**) in 50% yield.[80] Other cyclopentanoid natural products that are synthesized by procedures based upon a nearly quantitative rDA reaction are jasmone (**54**)[81] and alkyne (**55**), a precursor to methyl jasmonate.[82] This same procedure has been applied to the synthesis of intermediates of prostaglandins such as (**56**).[83]

A facile synthesis of cyclopentadienone epoxides *via* thermal rDA cycloreversion of a tricyclodecenone epoxide and its acetal derivatives has been applied to the preparation of cyclopentanoid antibiotics.[84,85] This procedure has been used in an efficient synthesis of terrein, a mould metabolite from *Aspergillus terreus*, by rDA synthesis of cyclopentadiene epoxide intermediate (**57**).[85] FVP conditions for these reactions typically involve temperatures of 420–600 °C. Furan-derived DA adducts have also been used to generate cyclopentadienone epoxides. The thermal rDA reaction of the furan-derived DA adduct (**58**) proceeds at temperatures as low as 330 °C with complete cycloreversion and generation of epoxide (**59**) in nearly quantitative yield (equation 32).[84] Subsequent elaboration led to epipentenomycin derivatives such as (**60**).

A facile synthesis of enol lactones was achieved by a process dependent upon successful rDA decomposition. The tricyclic (*E*)-enol lactones (**61**) thermally decomposed to the corresponding (*E*)-enol lactones (**62**) in excellent yield as shown in equation (33).[86] Tricyclic (*E*)-enol lactones (**61**) could be photoisomerized to the corresponding (*Z*)-enol lactones, which were also thermally cleaved to the (*Z*)-enol lactones (**62**).

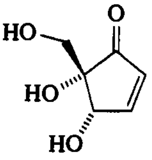

**(53)**

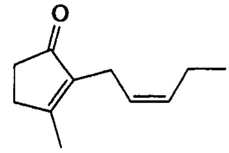

**(54)**

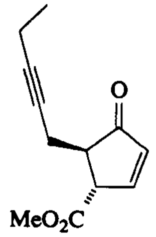

**(55)**

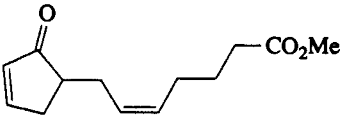

**(56)**

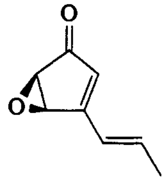

**(57)**

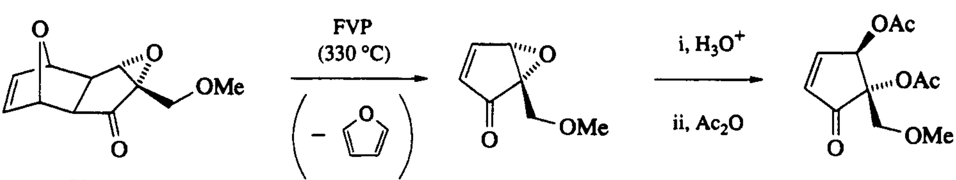

**(58)** **(59)** **(60)** (32)

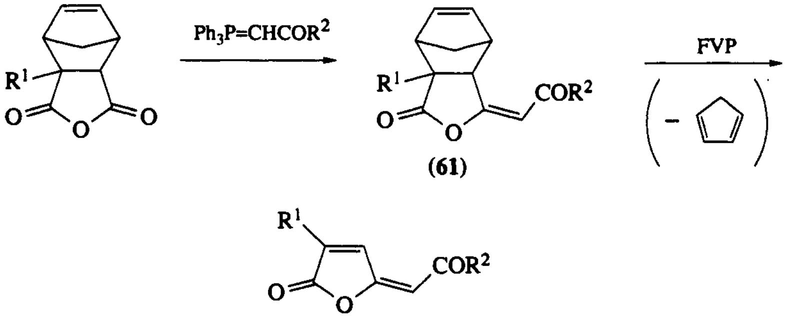

**(61)** **(62)** (33)

| *Compound* | *R$^1$* | *R$^2$* | *FVP conditions* | *Yield of (62) (%)* |
|---|---|---|---|---|
| **(61a)** | H | OEt | 450 °C, 0.3 Torr | 95 |
| **(61b)** | Me | OEt | 310 °C, 0.3 Torr | 93 |
| **(61c)** | H | OBu$^t$ | 490 °C, 0.3 Torr | 88 |
| **(61d)** | H | Me | 310 °C, 0.3 Torr | 92 |
| **(61e)** | Me | Me | 300 °C, 0.3 Torr | 89 |

Many rDA processes exist for the generation of cyclopentene units not possessing a carbonyl in the cyclic framework. The previously unknown alkylidenecyclopentenols have been accessed by a procedure dependent upon a rDA cycloreversion. Reaction of lithium aluminum hydride with 4-*p*-tolylsulfonylmethyloxatricyclo[5.2.1.0]decadienone (**63**) gave the *exo*-methylene tricyclodecenols (**64**) regioselectively and stereospecifically, which upon FVP yielded the *exo*-methylene cyclopentenols (**65**) (equation 34).[87] These cyclopentenols in turn serve as precursors for prostanoid natural products such as clavulones and punaglandins.[88]

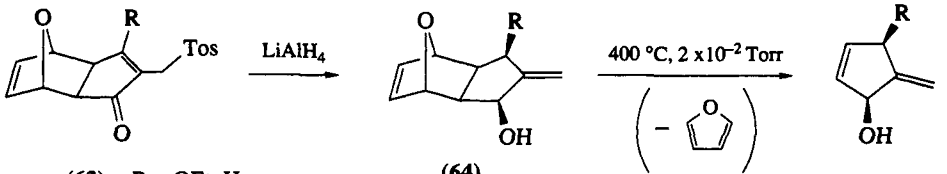

(63) R = OEt, H (64) (65) (34)

The development of syntheses for highly functionalized cyclopentanes has been enhanced by the isolation of numerous cyclopentanoid natural products. 4-Methylene-1-cyclopentenes (**67**) are interesting and versatile building blocks for such species. The preparation of these cyclopentenes has been accomplished by a three-step synthesis, the last of which is rDA cycloreversion under FVP conditions (equation 35).[89] This final rDA step simply involves distillation of the adducts (**66a–h**), which yields cyclopentenes (**67a–h**) in a virtually pure state.

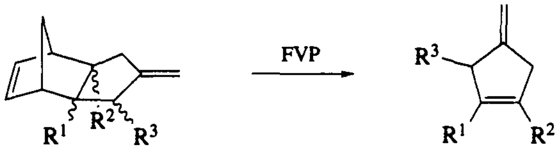

(66) (67) (35)

| *Compound* | *$R^1$* | *$R^2$* | *$R^3$* | *rDA conditions* | *Yield of (67) (%)* |
|---|---|---|---|---|---|
| (**66a**) | $CO_2Me$ | $CO_2Me$ | H | 550 °C, 2 Torr | 100 |
| (**66b**) | $CO_2Me$ | $CO_2Me$ | Me | 530 °C, 0.1 Torr | 94 |
| (**66c**) | H | $CO_2Me$ | H | 600 °C, 2 Torr | 89 |
| (**66d**) | H | $CO_2Et$ | H | 755 °C, 0.03 Torr | 58 |
| (**66e**) | H | COPh | H | 560 °C, 0.03 Torr | 52 |
| (**66f**) | H | $SO_2Ph$ | H | 560 °C, 0.03 Torr | 72 |
| (**66g**) | —$CH_2OCO$— | | H | 580 °C, 0.03 Torr | 95 |
| (**66h**) | $CH_2OH$ | $CH_2OH$ | H | 575 °C, 0.03 Torr | 100 |

Multifidene (**69**), a major constituent of the essential oil of *Cutleria multifida*,[90] has been prepared by a method based upon rDA cleavage of adduct (**68**) (equation 36).[91] The synthesis of (**69**) combines a high degree of stereoselectivity with broad variability, giving easy access to analogs of multifidene.

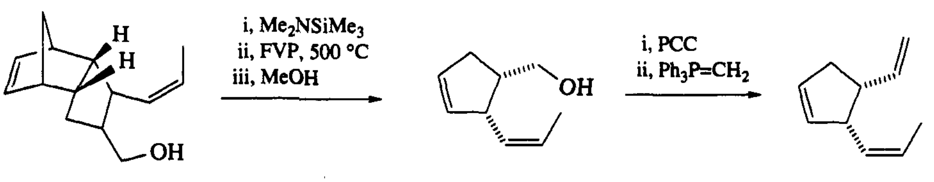

(68) (69) (36)

The rDA reaction has been applied to the synthesis of quinone epoxides and α-epoxycyclohexenones. Dimethylfulvene was used as the diene since the rDA cycloreversion of these adducts proceeds at much lower temperatures than do the corresponding cyclopentadiene adducts. The rDA reaction of these epoxide adducts was performed by two procedures involving heating at 150–190 °C in (a) high-boiling solvents such as diphenyl ether, xylene or diglyme, or (b) low-boiling solvents such as benzene, THF or toluene in a sealed tube.[92] This process is illustrated by the two similar synthetic schemes (equation 37) used to generate (±)-senepoxyde (**72**), isolated from the fruits of *Uvaria catocarpa*, and (±)-crotepoxide (**75**), a tumor inhibitor isolated from the fruits of *Croton macrostachys*.[93] The rDA reaction of adducts (**70**) and (**73**) gave the epoxycyclohexenones (**71**) and (**74**), respectively, and each was subsequently transformed into the natural product. This process has been used for the preparation of many bioactive natural products, including epoxydon (**76**), epiepoxydon (**77**), phyllostine (**78**), epoformine (**79**) and epi-epoformine (**80**).[94]

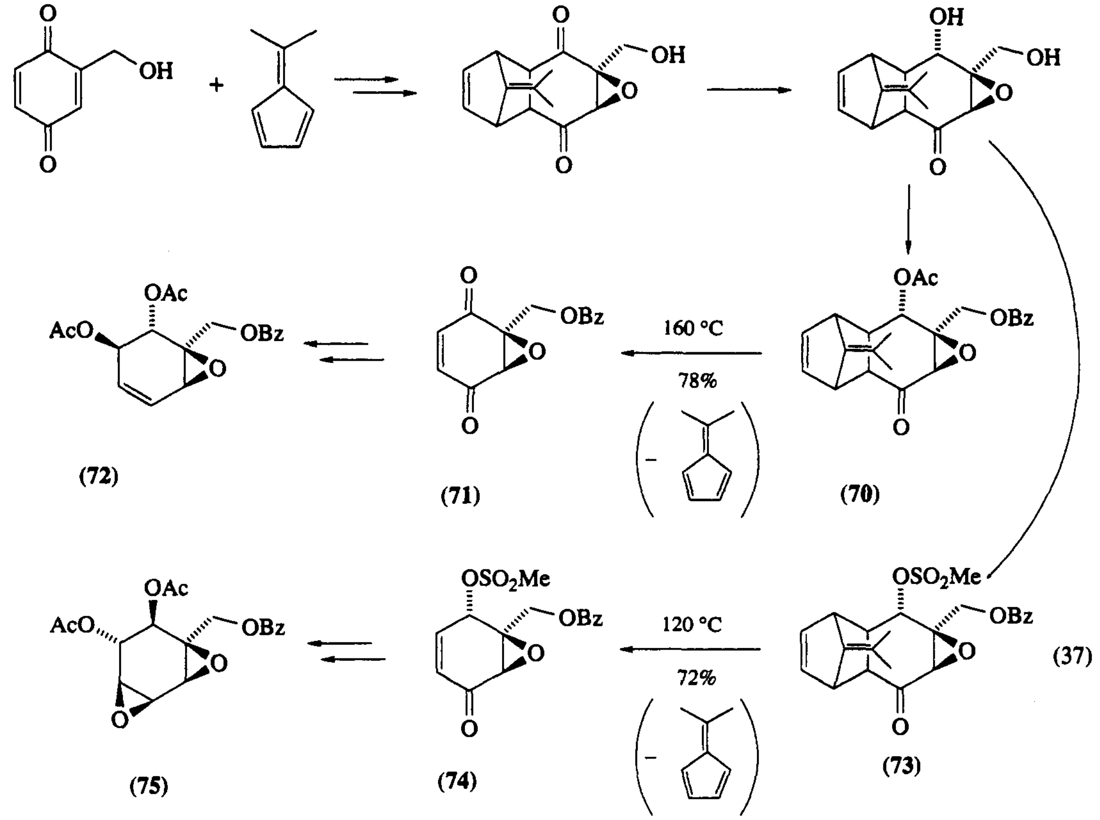

(37)

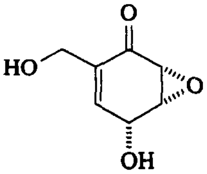
(**76**)

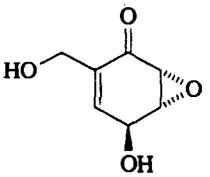
(**77**)

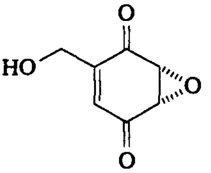
(**78**)

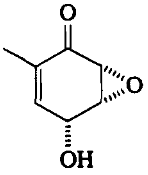
(**79**)

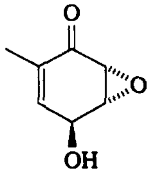
(**80**)

Knapp has used the oxyanion-accelerated rDA reaction to advantage in the synthesis of conduritol A. The masked dienol used was 9-[(benzyloxy)methoxy]anthracene (**81**), which upon reaction with benzoquinone (**82**) gave the protected adduct (**83**) (equation 38).[31] Further transformations yielded (**84**), which upon treatment with potassium hydride caused rDA fragmentation to occur at 35 °C. Two subsequent steps produced conduritol A (**86a**), a naturally occurring cyclitol, in 39% overall yield from (**82**). The room-temperature DA activity of anthranol reported by Rickborn,[95] coupled with the observed low-temperature rDA reactivity of its adducts, makes anthranol a highly useful alkene protecting group *via* a DA/rDA sequence.

Alkylated naphthoquinones can be generated by the rDA strategy that has been used in natural products synthesis. Plumbagin (**89**), an alkylated naphthoquinone that has antimicrobial and antineoplastic activities, has been obtained by an alkylation of juglone (**86b**) based on a DA/rDA reaction sequence (equation 39).[96] This method enabled alkylation of C-2 in juglone by alkylation of cycloadduct (**87**) with methyl iodide. The subsequent rDA reaction of (**88**) followed by oxidation gave plumbagin (**89**). A similar alkylation scheme based on the rDA reaction has been applied to the synthesis of α-caryopterone (**90**), a red pyranojuglone from *Caryopteis clandonensis*.[97]

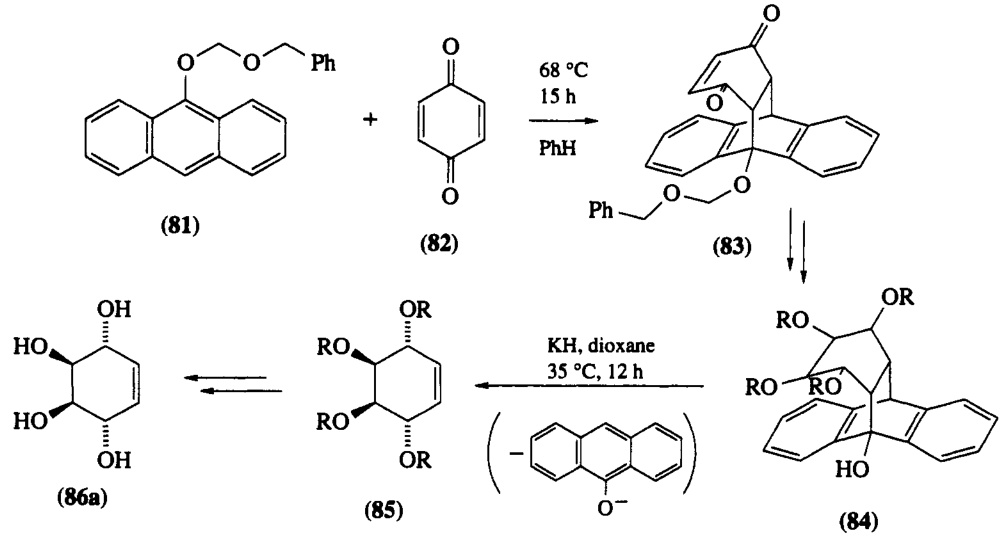

(38)

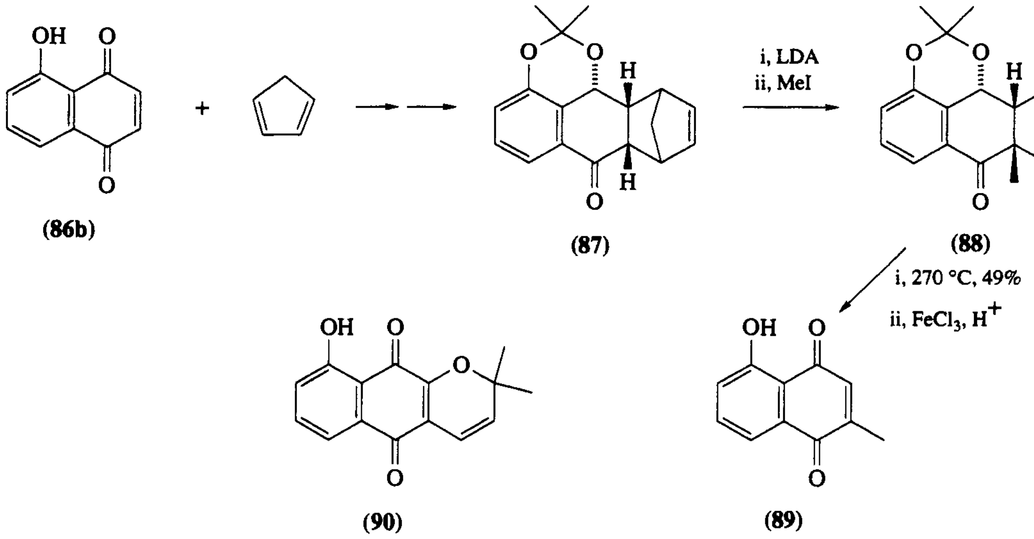

(39)

#### 4.5.2.12 Alkynes

Functionalized alkynes are made *via* rDA cycloreversion of cycloadducts that act as 'protected' alkynes. Substituted alkynes (**93a–h**) are obtained from adducts (**92a–h**) *via* FVP-induced rDA cycloreversion as shown in equation (40).[98] This method, based on the rDA reaction, provides an alternative route to the alkynic bond, which is more commonly formed *via* elimination reactions.

Substituted alkynic compounds result when two cycloreversions are carried out on the same carbon–carbon bond of a bis-DA adduct. Thermolysis of bis-adduct (**94**) produced alkyne (**95**) and anthracene *via* two rDA cycloreversions as shown in equation (41).[99]

## 4.5.3 PREPARATION OF POLYUNSATURATED HYDROCARBONS

### 4.5.3.1 Substituted Acyclic Butadienes

The generation of variously substituted butadienes has been accomplished *via* the thermal rDA reaction of substituted cyclohexene derivatives. Derivatives of 1,3-butadiene-2,3-dicarboxylic acid, which are otherwise difficult to prepare, have been obtained by the vapor-phase pyrolysis of cyclohexene-1,2-

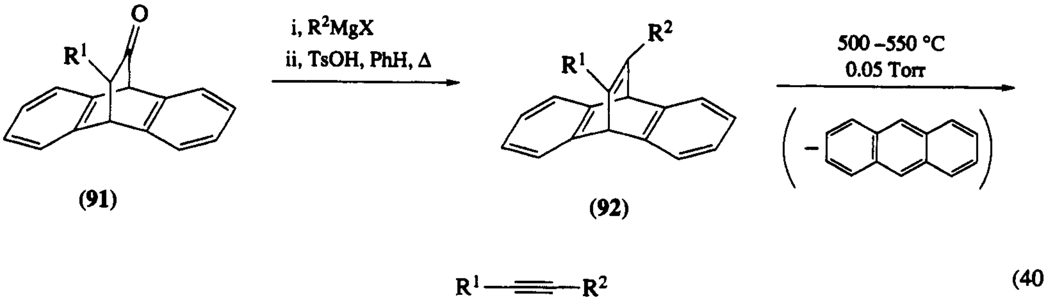
O
R1
i, R2MgX
ii, TsOH, PhH, Δ
R2
R1
500-550 °C
0.05 Torr
R1—≡—R2

(91) (92) (93) (40)

| *Compound* | *R¹* | *R²* | *% of* (**93**) *from* (**92**) |
|---|---|---|---|
| **(91a)** | H | Ph | ~100 |
| **(91b)** | Me | Ph | ~100 |
| **(91c)** | Et | Ph | ~100 |
| **(91d)** | $CH_2Ph$ | Et | ~100 |
| **(91e)** | Me | Et | 82 |
| **(91f)** | Et | Et | 80 |
| **(91g)** | $CH_2Ph$ | Me | 60 |
| **(91h)** | $CH_2Ph$ | Et | 72 |

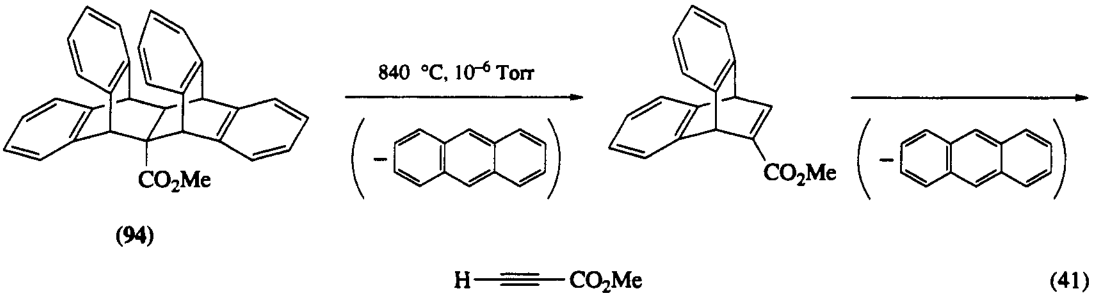
$CO_2Me$
840 °C, $10^{-6}$ Torr
$CO_2Me$
H—≡—$CO_2Me$

(94) (95) (41)

dicarboxylic acid analogs. Thus cyclohexene-1,2-dicarboxylate yielded dimethyl 1,3-butadiene-2,3-dicarboxylate as shown in equation (42), and cyclohexene-1,2-dicarbonitrile produced 1,3-butadiene-2,3-dicarbonitrile as given in equation (43).[100] The synthesis of 4-alkyl-2-amino-4-(substituted amino)-1,1,3-tricyano-1,3-butadienes has been accomplished *via* selective thermal decomposition of the corresponding amino adducts as shown in equation (44).[101] An interesting aspect of the synthesis of these dienes is the mild rDA conditions used, simple refluxing in xylene or decalin.

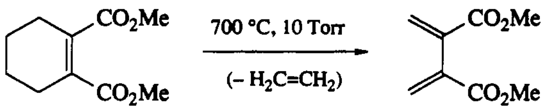
$CO_2Me$
$CO_2Me$
700 °C, 10 Torr
(– $H_2C{=}CH_2$)
$CO_2Me$
$CO_2Me$

(42)

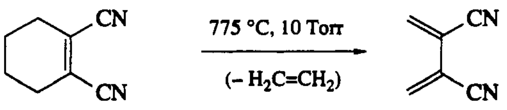
CN
CN
775 °C, 10 Torr
(– $H_2C{=}CH_2$)
CN
CN

(43)

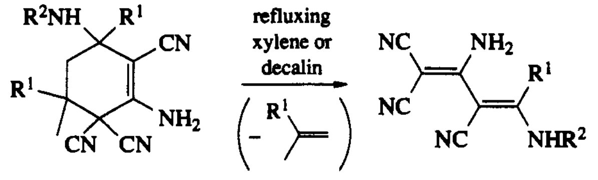
R2NH
R1
CN
R1
NH2
CN
CN
refluxing xylene or decalin
R1
NC
NH2
R1
NC
NC
NHR2

(44)

### 4.5.3.2 Extrusion of Sulfur Dioxide

The thermolysis of 2-substituted 2,5-dihydrothiophene 1,1-dioxides leads to (*E*) conjugated dienes *via* cycloreversion followed by the concerted cheletropic extrusion of sulfur dioxide. The thermolysis of the α,β-alkylated sulfone (**96**) gives the intermediate, which loses $SO_2$ to give (*E*)-9,11-dodecadien-1-yl acetate (**98**), a component of the sex pheromone of the red bollworm moth.[102] This procedure has been extended to the thermolysis of α,β-dialkylated sulfones in order to obtain (*E*,*E*)-1,4-disubstituted-1,3-dienes (equation 46).[103] Similar processes have been used for the syntheses of alkaloids. The synthesis of an Elaeocarpus alkaloid, elaeokanine A (**100**), makes use of the retrodiene extrusion of sulfur dioxide to give the 1,3-diene intermediate (**99**) that is subsequently consumed by an intramolecular imino DA reaction (equation 47).[104] *o*-Xylylene (**102**) has been generated by rDA expulsion of $SO_2$ from benzo-fused 3,6-dihydro-1,2-oxathiin 2-oxide (**101**).[105]

### 4.5.3.3 Extrusion of Molecular Nitrogen

Model studies of rDA reactions exhibit a high degree of stereoselectivity. This fact is evidenced by the oxidation of the *cis* hydrazo compound (**103**), which gives nearly a quantitative yield of nitrogen *via* the

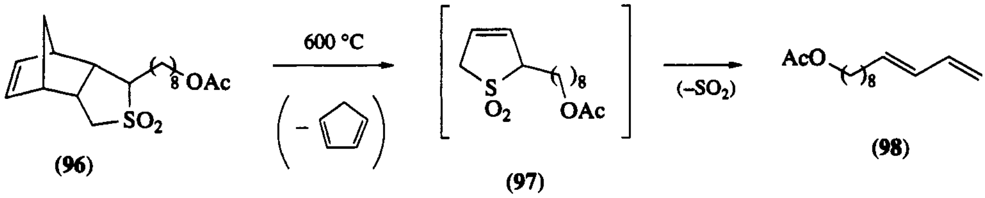
8 OAc
SO2
600 °C
S
O2
8
OAc
(–SO2)
AcO
8

(**96**) (**97**) (**98**) (45)

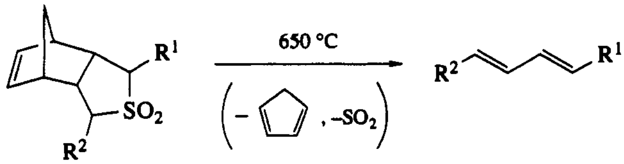
R1
SO2
R2
650 °C
, –SO2
R2
R1

(46)

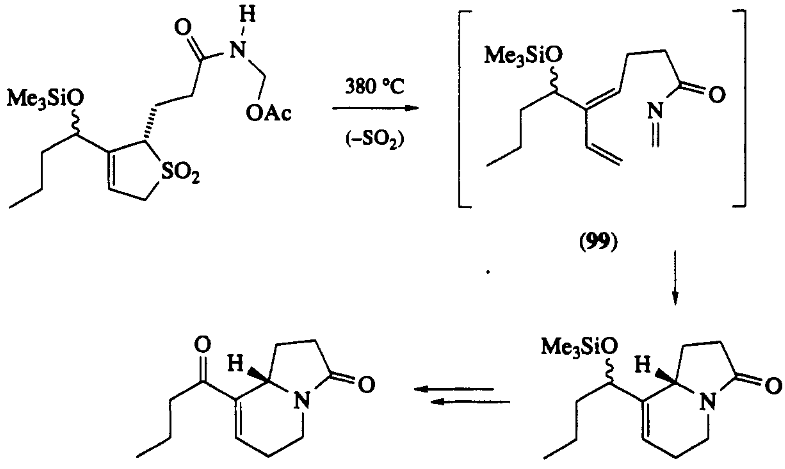
O
H
N
OAc
Me3SiO
SO2
380 °C
(–SO2)
Me3SiO
N
O
O
H
N
O
Me3SiO
H
N
O

(**99**) (**100**) (47)

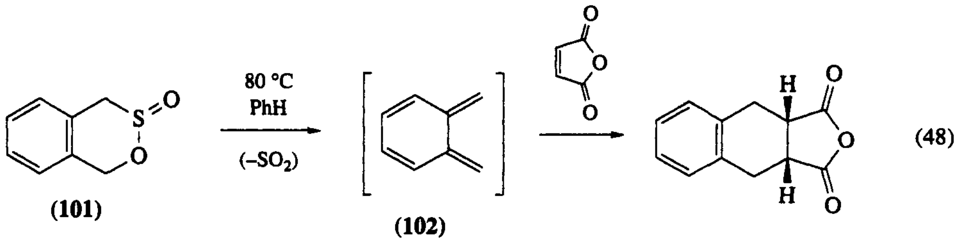

(101) (102) (48)

unstable azo compound (**104**) (equation 49).[106] The process has been extended to cyclopropane (**105**), which upon oxidation gives the azo intermediate (**106**) that extrudes nitrogen at room temperature producing *cis,trans*-2,5-heptadiene (**107**).[106]

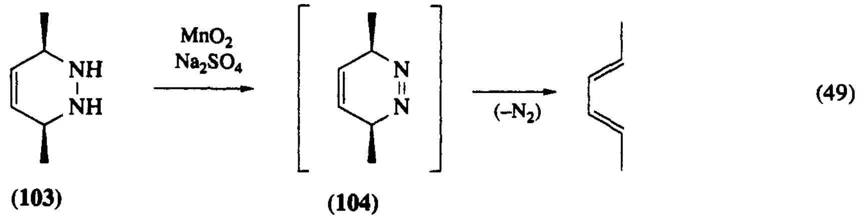

(103) (104) (49)

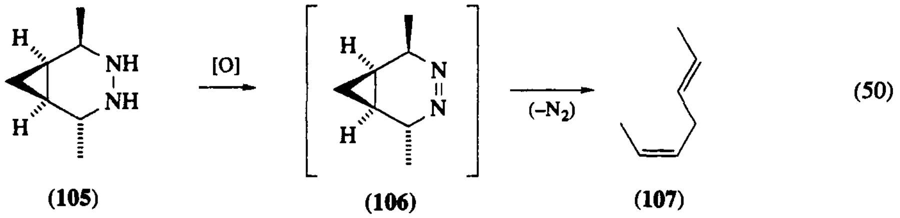

(105) (106) (107) (50)

### 4.5.3.4 Cyclobutadiene and Cyclopentadienes

The formation of 1,3-dienes within a cyclic framework has been accomplished *via* extrusion of molecular nitrogen. Cyclobutadiene has been obtained by nitrogen extrusion from 2,3-diazo-Dewar benzene, which is generated by mild oxidation of 2,3-dioxybicyclo[2.2.0]hex-5-ene. Other cyclic dienes that have been similarly obtained are cyclopentadiene and cyclohexa-1,3-diene from the corresponding diazo compounds.[107,108]

Substituted cyclopentadienones have been generated *via* rDA thermolyses. Thermolysis of adduct (**108**) unmasks dienone (**109**) as shown in equation (51).[109] The generation of (**109**) was followed by trapping with cyclopentadiene to produce the tricyclic enones (**110**), which are used as synthons for sarkomycin derivatives.[109] The presence of the alkyl group at the 6-position in ester (**108**) enhances fragmentation *via* a rDA process, while in its absence (R = H) fragmentation occurs by decarbonylation.

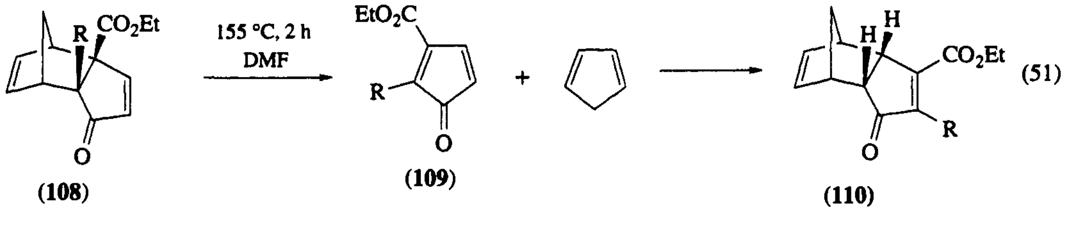

(108) (109) (110) (51)

The reaction of stannylated dicyclopentadiene (**111**) with methyllithium gave dicyclopentadiene (**113**) and cyclopentadienyllithium (**114**) even at –78 °C.[110] The intermediate can be trapped by addition of iron(II) chloride to give intermediate (**115**), which then cleaves off cyclopentadiene from one of the two dicyclopentadiene ligands in a rDA process to give (**116**) as the isolated product. It therefore appears that the rDA decomposition is only partially blocked by trapping with iron(II) chloride.

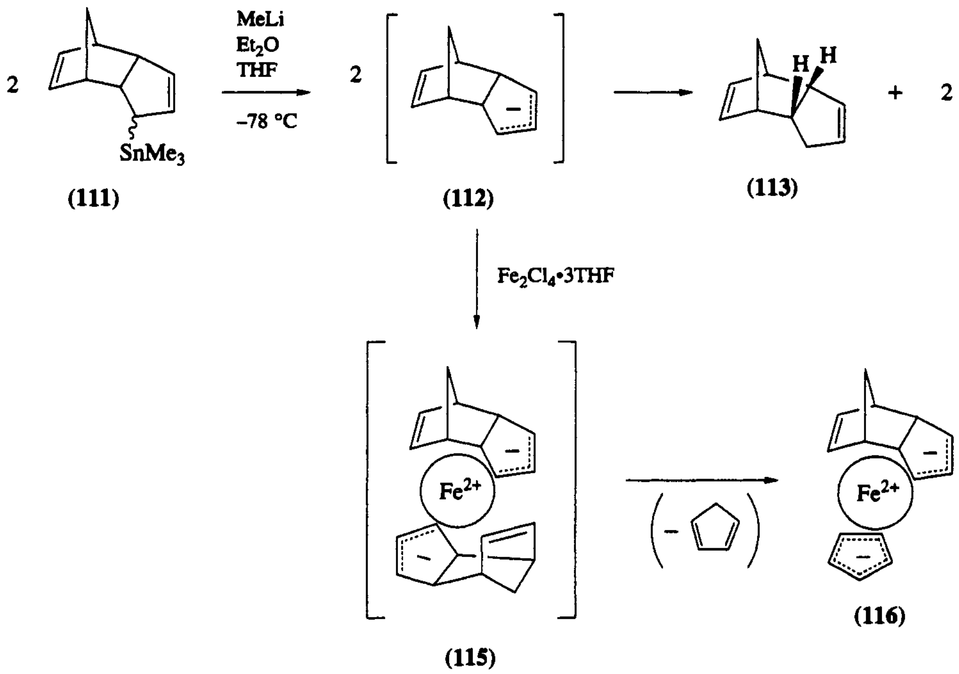

(111) (112) (113) (114)

(115) (116)

(52)

### 4.5.3.5 Cyclohexadiene Derivatives

Cyclohexadiene generation by the rDA reaction has been used in the synthesis of natural products. The reaction of pyrone (**117**) with 4-methyl-3-cyclohexenone provides keto ester (**118**) regio- and stereoselectively (equation 53).[111] Fixation of both the correct ring fusion and the *cis*-diene functionality in a single step makes the keto ester a useful intermediate for the synthesis of natural products such as occidentalol (**119**).[111] The unmasking of DA adducts of steroidal ring-B dienes that are protected by cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (**121**) has been accomplished by a rDA process. In the synthesis of 22,23-epoxyvitamin $D_2$ (**123**) the protected steroidal adduct (**120**) was heated with base in dimethyl sulfoxide to give the corresponding steroidal 5,7-diene (**122**) as shown in equation (54).[112] This rDA method is useful because it can be applied to compounds having groups that are sensitive to lithium aluminum hydride, which had been previously used for regenerating the protected steroidal ring-B diene system. The rDA reaction of the neolignan asatone (**124**) produces dienone intermediate (**125**), which reacts with 1-allyl-3,4,5-trimethoxybenzene (**126**) to give the two novel neolignans heterotropanone (**127**) and isoheterotropanone (**128**) as shown in equation (55).[113]

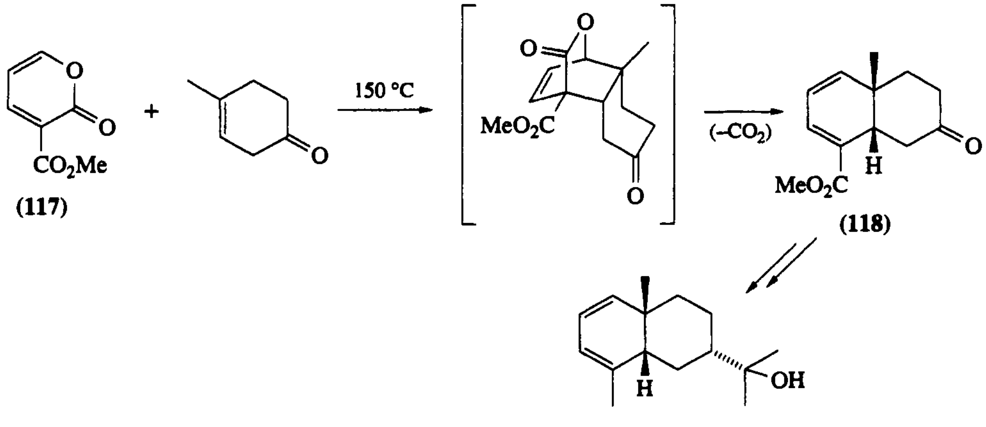

(117) (118) (119)

(53)

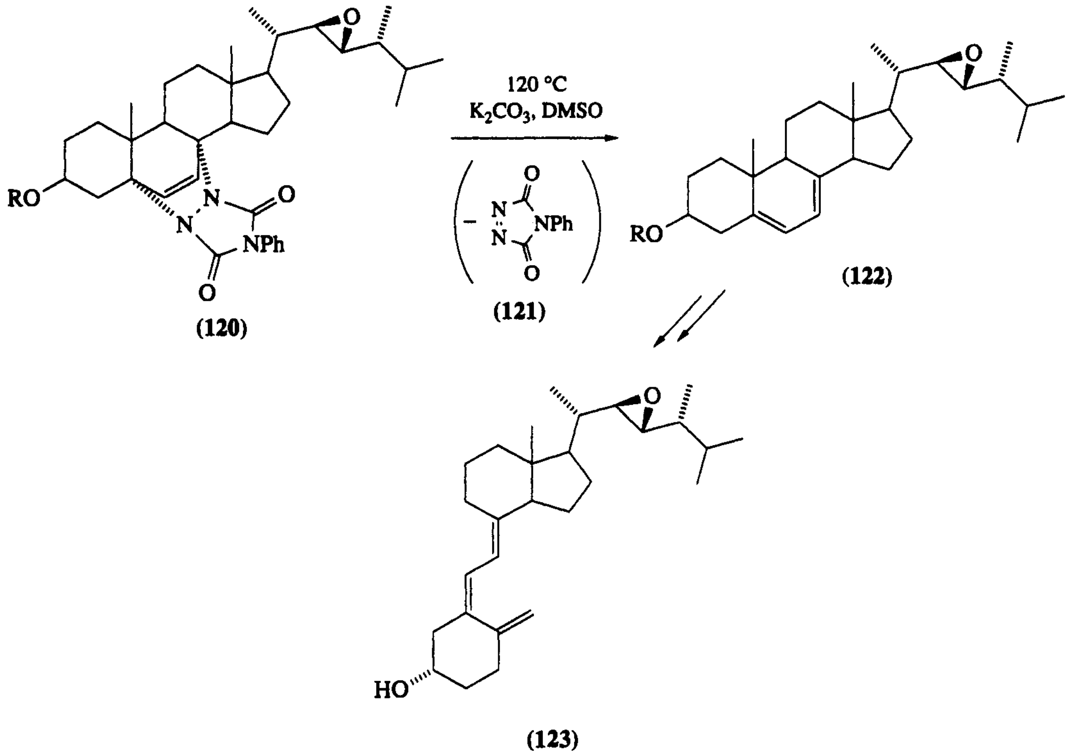
120 °C
K2CO3, DMSO
RO
NPh
O
HO
(120)
(121)
(122)
(123)

(54)

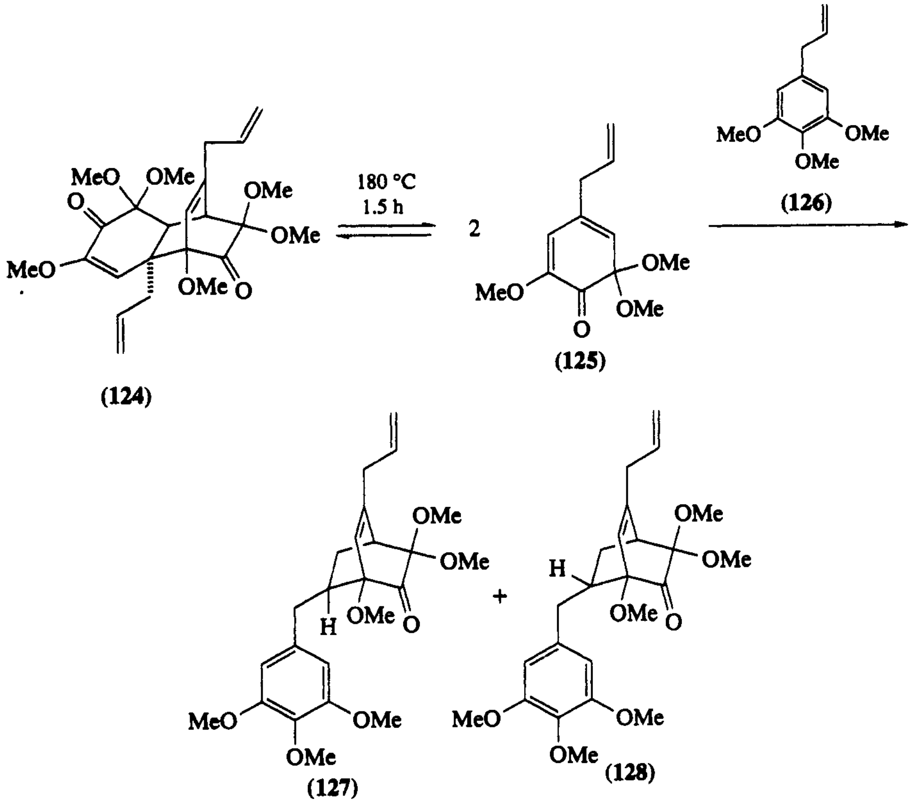
180 °C
1.5 h
2
MeO
OMe
O
H
+
(124)
(125)
(126)
(127)
(128)

(55)

### 4.5.3.6 Benzene and Benzene Derivatives

Many cycloadducts produce aromatic rings *via* rDA processes. The generation of benzene has been obtained by the FVP of bicyclo[2.2.2]octa-2,5-diene[114] and of barrelene[115] in the gas phase. Dimethyl terephthalate was generated by the thermolysis of 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene as depicted in equation (56).[116] This cycloreversion has been shown to proceed even at room temperature, and readily occurs at temperatures as low as 50 °C. Sulfene extrusion *via* the rDA reaction also yields benzene derivatives: dimethyl phthalate was obtained by the thermolysis of the bicyclo adduct shown in equation (57).[117] Sulfene extrusion *via* a rDA route competes with the predominant process of sulfur dioxide extrusion. The presence of a phenyl group at C-4 can suppress the alternate route to norcaradiene formation by sulfur dioxide elimination and force the reaction to proceed exclusively *via* the rDA sulfene extrusion path.[118] *N*-Aminopyrroles are used in a versatile DA–rDA sequence to produce substituted benzenes in high yields. Diels–Alder reaction of *N*-aminopyrrole (**129a**) with DMAD produces benzene derivative (**131**) *via* rDA nitrene extrusion from adduct (**130**) (equation 58).[119] It is of interest that the rate of DA addition increases in the order (**129a**) > (**129b**) > (**129c**), whereas adduct rDA decomposition to (**131**) increases in the order (**130c**) > (**130b**) > (**130a**). A series of phthalate esters was prepared by the rDA reaction of the adduct between substituted pyridones and DMAD (equation 59).[120]

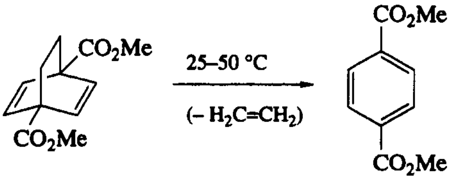

(56)

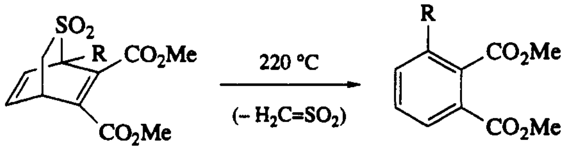

R = H, Ph

(57)

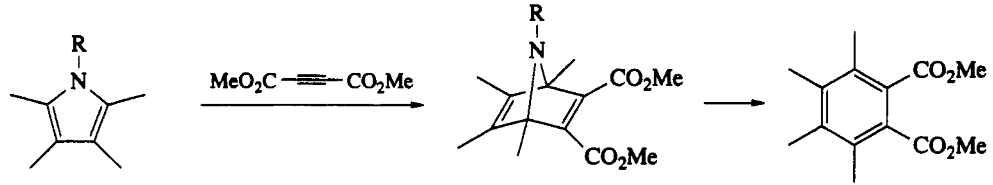

(**129a**) R = $NH_2$
(**129b**) R = NHMe
(**129c**) R = $NMe_2$

(**130**)

(**131**)

+ R–N̈:

(58)

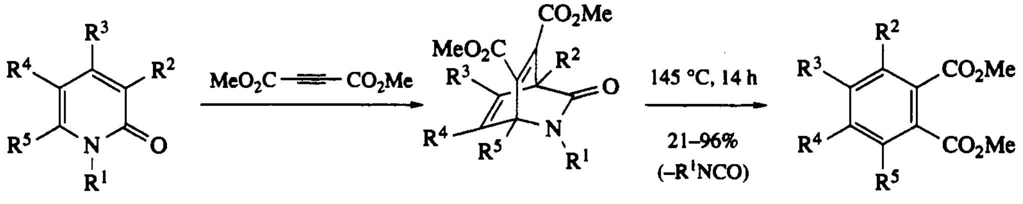

$R^n$ = H, Me or Ph

(59)

The formation of aromatic rings *via* rDA processes has found application in the synthesis of many natural products; only a representative set can be presented here. Pyrenochaetic acid A (**134**), a phytotoxic metabolite, was synthesized by a process involving a rDA reaction as a key step. The DA reaction of pyrone (**132**) with ethyl propiolate gave, after isolation, benzoate (**133**) *via* a rDA reaction evolving carbon dioxide (equation 60).[121] A synthesis of α-cartopterone (**137**) has been achieved that involves the rDA elimination of ethylene. The key step is rDA decomposition of adduct (**135**) to naphthoquinone

**(136)** as in equation (61).[122] Hydrindane derivatives **(140a)** and **(140b)** are formed by the reaction of 2,4-cholestadiene **(138a)** and 2,4-androstadien-17-one **(138b)**, respectively, with DMAD in boiling xylene (equation 62).[123] The products, **(140a)** and **(140b)**, are formed *via* DA addition of the steroid diene followed by subsequent rDA decomposition of adduct **(139)**. The rDA reaction of these adducts provides a simple method for the simultaneous cleavage of rings A and B in steroids.[123] The synthesis of the cytotoxic phytoalexin juncusol **(143)** has been accomplished *via* two pathways based upon different rDA processes. One pathway involves the previously described reaction of *N*-aminopyrroles. The reaction of *N*-aminopyrrole **(141)** with methyl propiolate gave dihydrophenanthrene **(142)**, after HPLC isolation. Formation of **(142)** occurred by a DA addition–rDA extrusion of *N*-aminonitrene pathway (equation 63),[124] and the product was subsequently transformed into juncusol. The second pathway to juncusol based on a rDA step involved the use of 3-methoxycarbonyl-2-pyrones. The formation of the aromatic ring C is obtained by DA addition of 1,1-dimethoxyethylene to the 3-methoxycarbonyl-2-pyrone **(144)** followed by subsequent rDA extrusion of carbon dioxide to give the 9,10-dihydrophenanthrene **(145)** (equation 64),[125,126] which is also a precursor of juncusol.

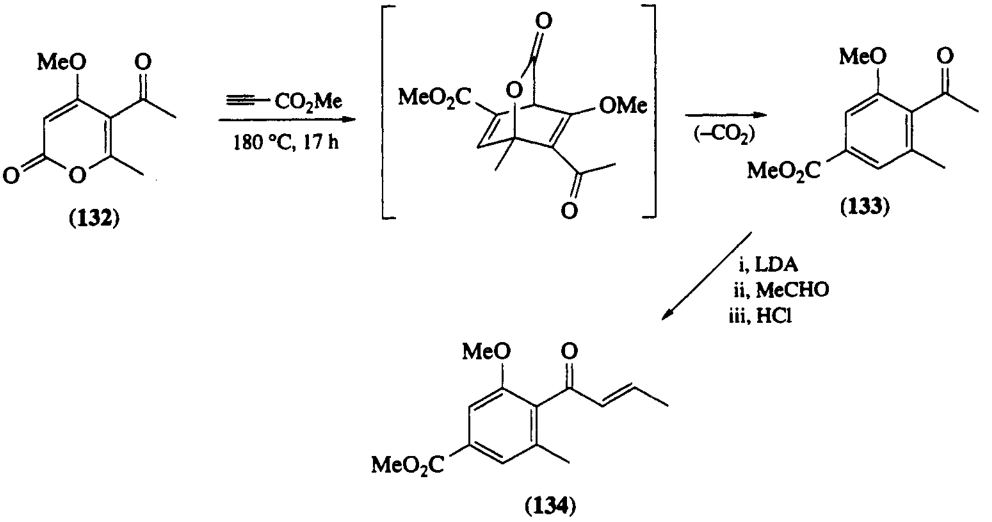
MeO
O
O
O
(132)
≡—CO2Me
180 °C, 17 h
O
MeO2C
O
OMe
O
(–CO2)
MeO
O
MeO2C
(133)
i, LDA
ii, MeCHO
iii, HCl
MeO
O
MeO2C
(134)

(60)

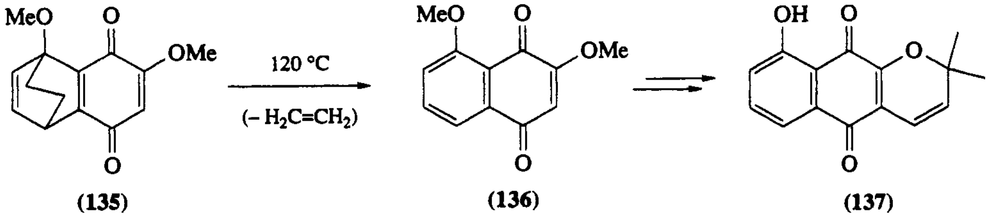
MeO
O
OMe
O
(135)
120 °C
(– H2C=CH2)
MeO
O
OMe
O
(136)
OH
O
O
O
(137)

(61)

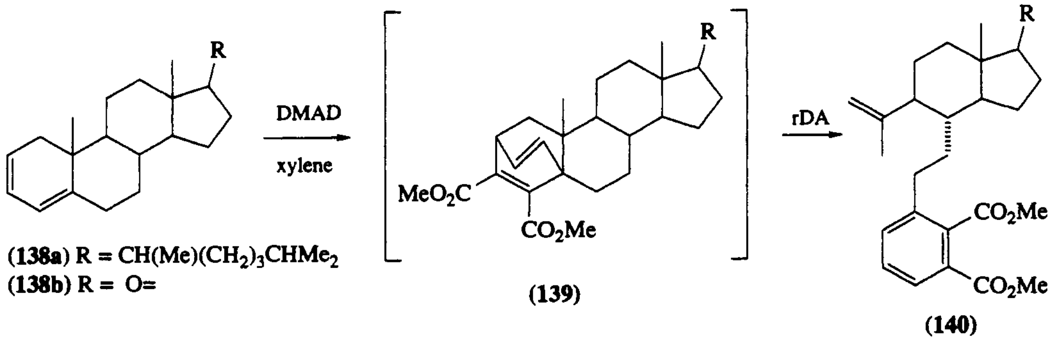
R
(138a) R = CH(Me)(CH2)3CHMe2
(138b) R = O=
DMAD
xylene
R
MeO2C
CO2Me
(139)
rDA
R
CO2Me
CO2Me
(140)

(62)

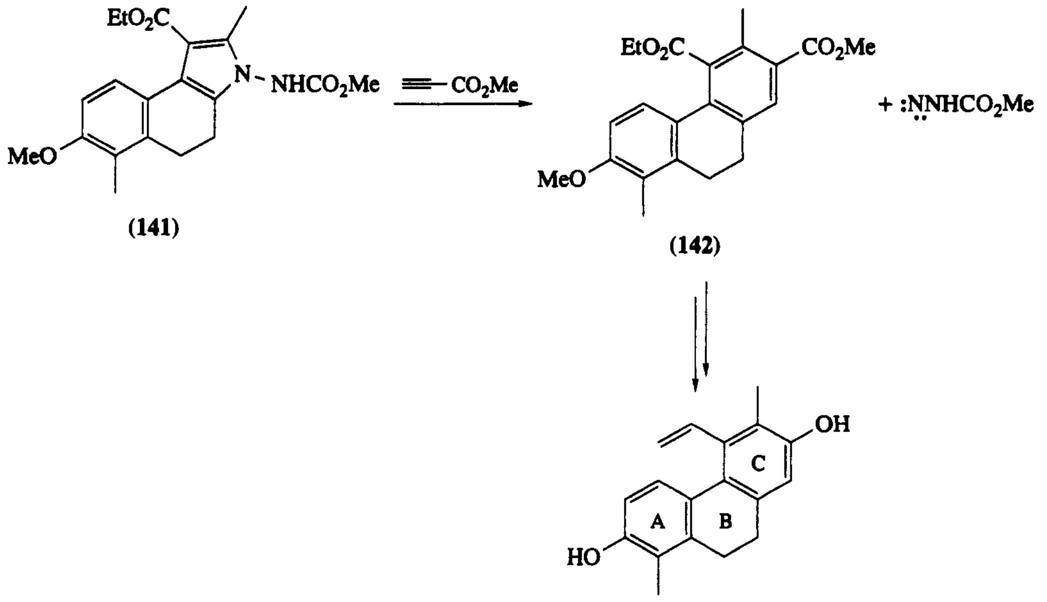

(141) (142) (143)

(63)

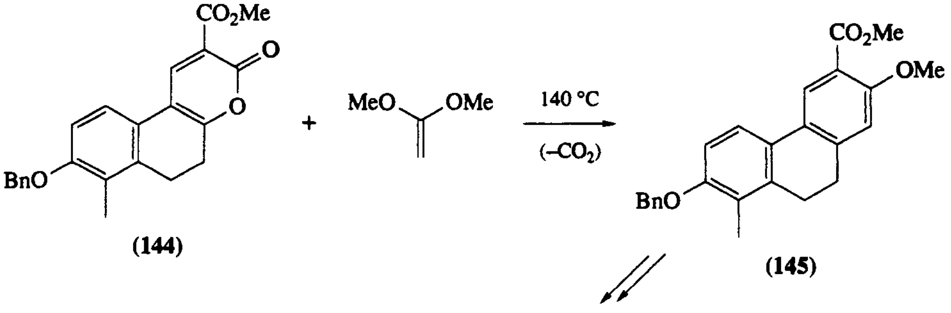

(144) (145) (143)

(64)

### 4.5.3.7 Cyclic Trienes in Non-aromatic Systems

A final example of a rDA cycloreversion of a cycloadduct that acts as a ‘protected’ butadiene illustrates the generation of extended conjugation in a non-aromatic cyclic system. Equation (65) shows that the addition of cyclopropene (**147**) to (146) can yield either (**148**) or (**149**), and both adducts undergo rDA extrusion of carbon dioxide to produce a triene.[127] Hydrolysis of the triene ketals gives access to substituted tropones (**150**).

## 4.5.4 FORMATION OF DOUBLY BONDED HETEROATOMS

### 4.5.4.1 Acyclic Aldehydes, Ketones and Carboxylic Esters

Formation of a double bond between carbon and a heteroatom or between two heteroatoms can be accomplished by a hetero retro-Diels–Alder reaction. Aldehydes, ketones and carboxylic esters can be obtained by this retrodiene process. A series of α,β-unsaturated aldehydes (**152**) was prepared by Funk using the facile bis-hetero retro-Diels–Alder reaction of 4-alkyl-4*H*-1,3-dioxins (**151**) as shown in equation (66).[128] This retrodiene process involves exceptionally mild conditions, refluxing in toluene, in order to unmask the α,β-unsaturated aldehyde. The diversity of this process is illustrated by the partial list of reactions shown.[128] The same mild conditions can be used to prepare α,β-unsaturated ketones by refluxing the appropriate 4,6-dialkyl-1,3-dioxins in toluene.[129] During the synthesis of the 'right-wing' equivalent (**156**) of the ionophore antibiotic indanomycin, an unexpected hetero retro-Diels–Alder reaction preempted the planned Claisen 3,3-shift. However, a subsequent intramolecular Diels–Alder reaction of intermediate (**154**) gave the desired product (**155**) of the planned Claisen 3,3-shift (equation 67).[130]

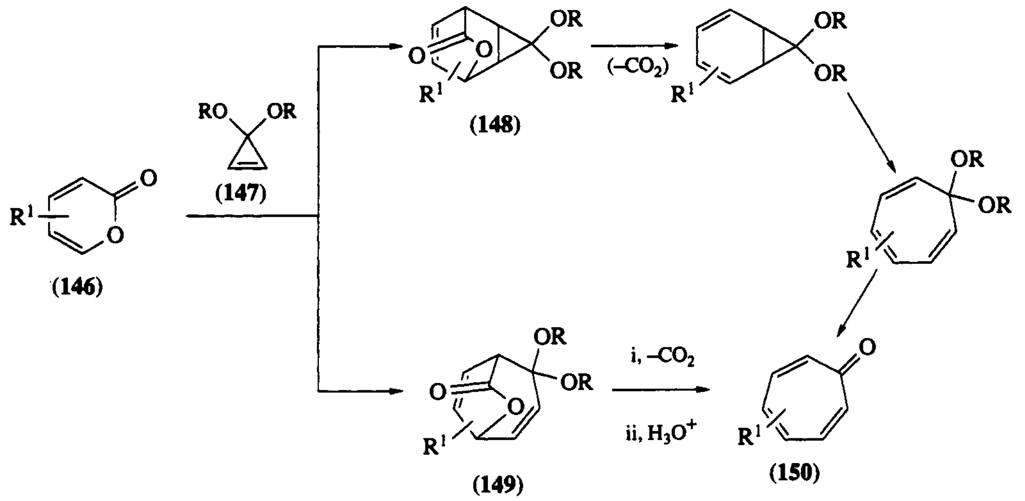
RO
OR
(147)
(146)
(148)
(−CO2)
(149)
i, −CO2
ii, H3O+
(150)
R1
OR
O

(65)

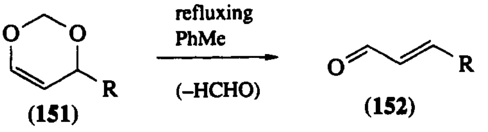
(151)
refluxing
PhMe
(−HCHO)
(152)
R

(66)

| *Compound* | *R* | *Yield (%)* |
|---|---|---|
| (**151a**) | $(CH_2)_7Me$ | 74 |
| (**151b**) | $CH(Me)(CH_2)_2CH{=}CMe_2$ | 73 |
| (**151c**) | $CH_2Ph$ | 83 |
| (**151d**) | $CH_2C(O)Me$ | 45 |
| (**151e**) | $CH(OH)CH{=}CHMe$ | 70 |

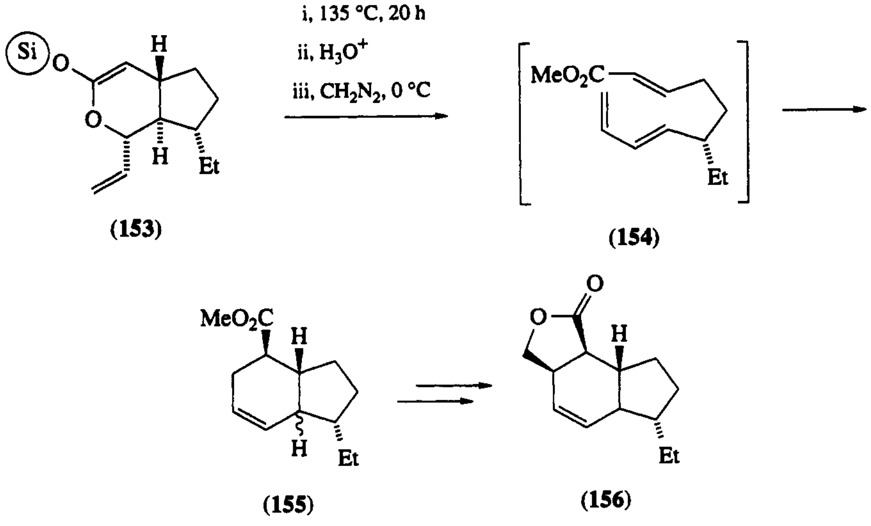
Si
H
H
Et
(153)
i, 135 °C, 20 h
ii, H3O+
iii, CH2N2, 0 °C
MeO2C
Et
(154)
MeO2C
H
H
Et
(155)
O
O
H
Et
(156)

(67)

### 4.5.4.2 Thio Analogs

The types of compounds containing carbon–sulfur double bonds that can be generated *via* a retro-Diels–Alder reaction are quite varied. Thioacrolein (**157**), a vinyl thioaldehyde, once generated forms a Diels–Alder dimer mixture of (**158**) and (**159**). By thermal retrodiene splitting of the dimer mixture at 400 °C, thioacrolein has become available for preparative use (equation 68).[131] The simplest thioaldehyde, thioformaldehyde, can be obtained by the FVP of the anthracene adduct as shown in equation (69).[132] The most reactive and labile class of sulfines, the thioaldehyde *S*-oxides, are generated by heating the cycloadduct of the sulfine with anthracene or cyclopentadiene. The liberated sulfine can be trapped *in situ* by cycloaddition to a conjugated diene, for example 2,3-dimethylbuta-1,3-diene as illustrated in equation (70).[133] The thioamide vinylog (**161**) has been obtained by the thermally induced cycloreversion of 4*H*-1,3-thiazine (**160**) as given in equation (71).[134] By prolonged heating in the presence of dimethyl acetylenedicarboxylate the 4*H*-thiopyran (**162**) was formed. Thioketenes, when devoid of bulky substituents, are very reactive species with few available methods for synthesis. Propadienethione has been produced by the FVP of a ketene dithioacetal as shown in equation (72).[135]

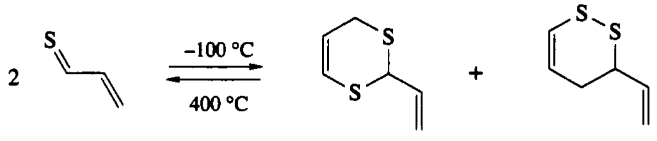
2
S
-100 °C
400 °C
S
S
+
S
S

(**157**) (**158**) (**159**)

(68)

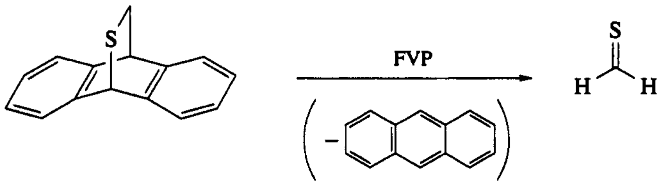

(69)

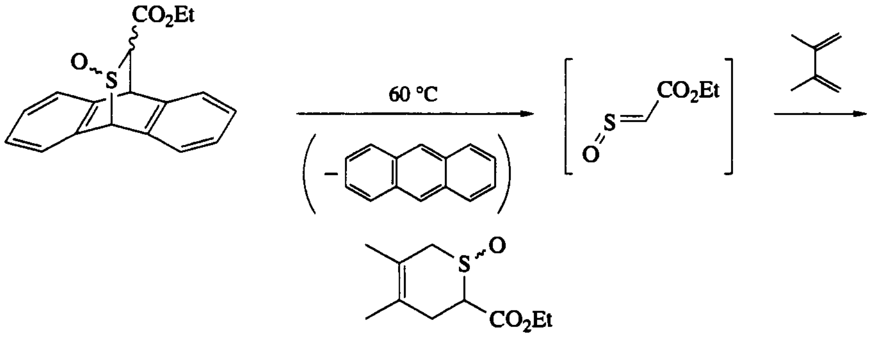
CO2Et
O
S
60 °C
-
S
O
CO2Et
S
O
CO2Et

(70)

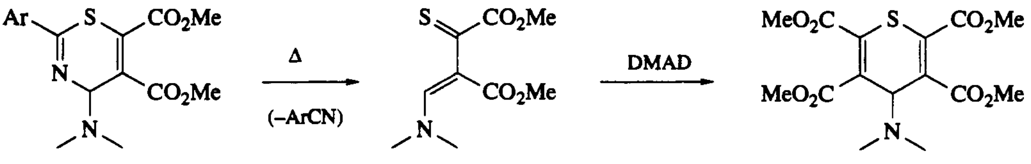
Ar
S
CO2Me
N
CO2Me
N
Δ
(-ArCN)
S
CO2Me
CO2Me
N
DMAD
MeO2C
S
CO2Me
MeO2C
CO2Me
N

(**160**) (**161**) (**162**)

(71)

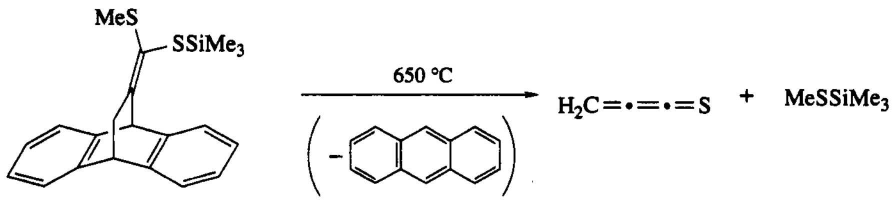
MeS
SSiMe3
650 °C
-
H2C=•=•=S
+
MeSSiMe3

(72)

### 4.5.4.3 Nitrogen Analogs

Use of the rDA reaction has been applied to the preparation of numerous compounds containing nitrogen double bonded to carbon or another heteroatom. The simplest compound possessing a carbon–nitrogen double bond is methanimine (**163**), which has been generated by the FVP of 2-azabicyclo[2.2.*n*]alkenes in almost quantitative yields (equation 73).[136] Application of the method for the synthesis of methanimine has led to the preparation of several *N*-acylmethanimines and *N*-methylenemethanesulfonamide.[137] The high reactivity of *N*-acylimino groups towards 1,3-dienes was evidenced by the production of lactam (**165**) *via* intramolecular cycloaddition of the intermediate acylimine (**164**) (equation 74).[137] Vinylideneamine was obtained *via* a rDA reaction of the anthracene adduct as shown in equation (75).[214]

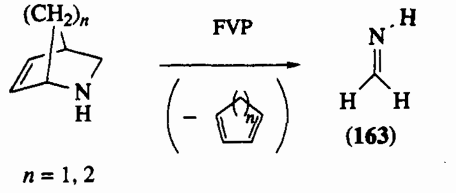

(73)

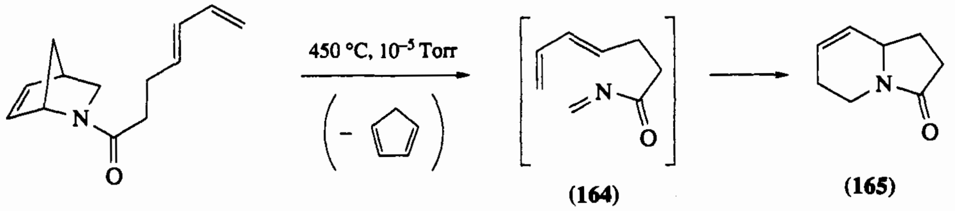

(74)

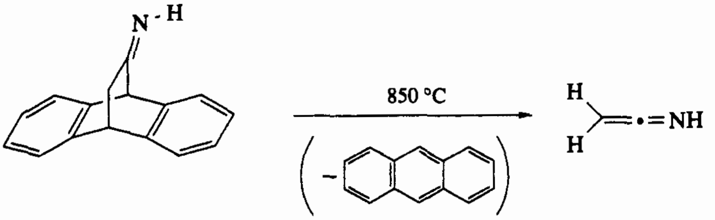

(75)

Acylnitroso alkenes produced *via* rDA reactions are key intermediates in the synthesis of alkaloids.[138–144] The acylnitroso alkene intermediate (**167**) that is generated from anthracene adduct (**166**) can react by an intramolecular ene reaction, resulting in the formation of hydroxamic acid (**168**).[138] If the acylnitroso alkene is produced in the presence of a diene, an intramolecular Diels–Alder reaction can occur to give a 1,2-oxazine derivative such as (**170**) as shown in equation (76).[143]

The preparation of compounds containing nitrogen double bonded to another heteroatom has been accomplished by a rDA pathway. *Cis*- and *trans*-azomethane have been synthesized from tetrahydropyridazine (**171**) by thermal retrodiene extrusion (equation 77).[145] The *anti* conformation of (**171**) is presumed to give *trans*-azomethane and the *syn* conformations yields the *cis*-isomer. Preparation of nitrosyl hydride (**173**) has been accomplished under mild nonphotochemical conditions, unlike conditions used in previous preparations. The extrusion of nitrosyl hydride from anthracene adduct (**172**) as shown in equation (78),[146] which occurs at a very mild temperature, was followed by microwave detection of (**173**).

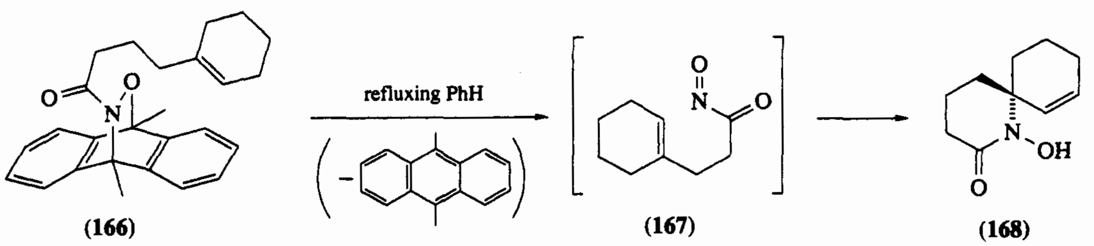

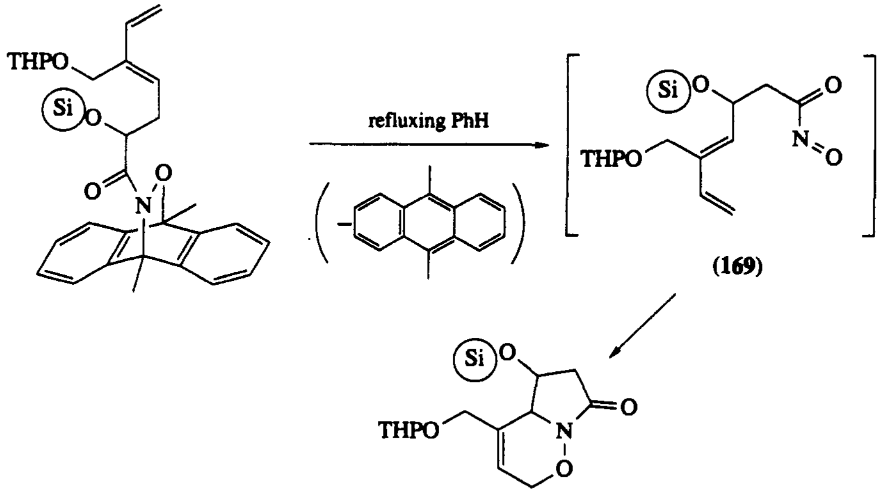

(169)

(170)

(76)

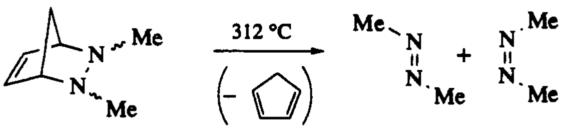

(171)

(77)

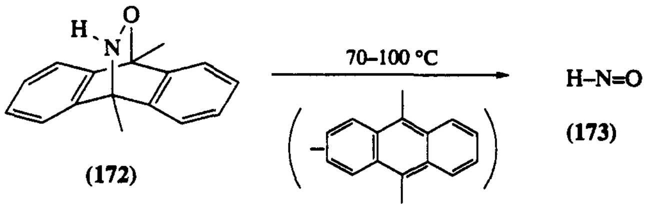

(172)

(173)

(78)

### 4.5.4.4 Phosphaalkene

Phosphaalkene (174) has been generated from two different adducts (equation 79).[147]

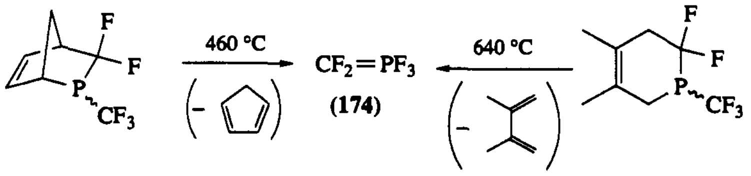

(79)

## 4.5.5 PREPARATION OF UNSATURATED HETEROCYCLES

### 4.5.5.1 Oxygen Heterocyclics Generated by Ethylene Formation

The preparation of many unsaturated heterocyclic compounds can be achieved *via* rDA processes. The vast majority of these compounds are either oxygen or nitrogen containing heterocyclics, preparation of which is most often accomplished by the expulsion of an ethylene or a butadiene moiety. α-Methyleneoxetane (**175a**) and β-methyleneoxetane (**175b**) are obtained by a rDA process from the anthracene cycloadducts.[148]

The generation of exocyclic double bonds by rDA cycloreversion is useful for the synthesis of unsaturated lactones, which are an important part of many natural products. The α-methylenebutyrolactone tuli-

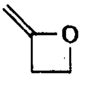

**(175a)**

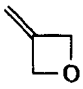

**(175b)**

palin A (**176**), an antifungal phytotoxic compound isolated from tulip bulbs, has been prepared by two independent syntheses *via* rDA reactions.[149,150] The syntheses of α-methylene-γ-butyrolactones (**177**) and (**178**) were achieved in good yield by rDA cycloreversion of the corresponding anthracene adducts.[151]

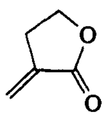

**(176)**

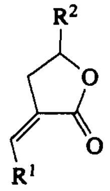

**(177)**

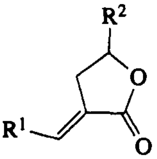

**(178)**

The formation of the endocyclic double bonds of unsaturated lactones has been accomplished *via* the rDA reaction. The preparation of 2-alkyl-2-butenolactones, such as (**179**), by a method that incorporates the rDA reaction as a key step has been applied to the synthesis of butyrolactone lignans such as (±)-hinokinin (**180**) as shown in equation (80).[152] An extensive study of the preparation of substituted 2-butenolides (**183**) has been reported. The mono-, di- and tri-alkyl bicyclobutenolides are prepared by reacting adducts (**181**) with Grignard reagents or with LDA followed by alkyl halides. Alkylated adducts (**182**) were then either directly distilled under vacuum or heated in a sealed tube to give the alkylated 2-butenolides (**183**) (equation 81).[153–157]

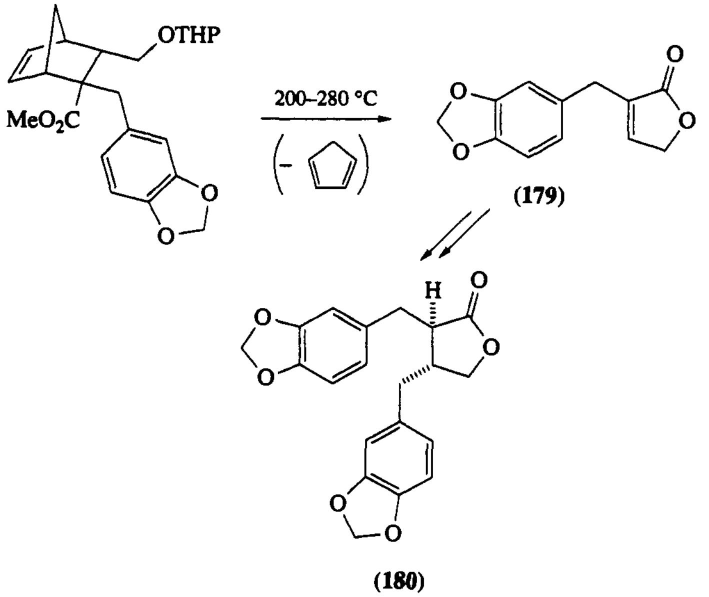

**(180)**

(80)

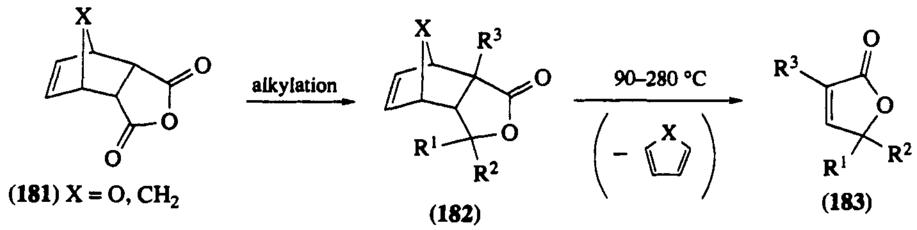

(81)

$R^1$ = H, alkyl, aryl, benzyl; $R^2$ = H, alkyl, aryl, benzyl; $R^3$ = H, alkyl, allyl, aryl, benzyl

The generation of a carbon–carbon double bond from a protected ethylene cycloadduct by rDA cycloreversion has been used for the preparation of 2,5-dihydrofurans. The syntheses of 3,4-dimethyl-2,5-dihydrofuran (**184**) and 3,7-dioxabicyclo[3.3.0]oct-1(5)-ene (**185**) were accomplished in high yield using FVP conditions to effect cycloreversion of the anthracene adducts at 550 and 800 °C, respectively.[158,159]

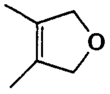
**(184)**

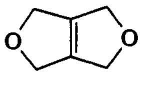
**(185)**

### 4.5.5.2 Oxygen Heterocyclics Generated by Butadiene Formation

The rDA cycloreversion of a 'protected' butadiene adduct has been applied to the synthesis of unsaturated oxygen heterocycles. The very unstable 2,3-dihydro-2,3-bis(methylene)furan and its 4-methyl derivative have been generated by rDA reaction of 4,5,6,7-tetrahydrobenzofuran and its dimethylated derivative (equation 82).[160] Characterization of these dienes was accomplished by trapping with various dienophiles. This method was extended to a two-step rDA synthesis of tetramethylenetetrahydrofuran as shown in equation (83).[161]

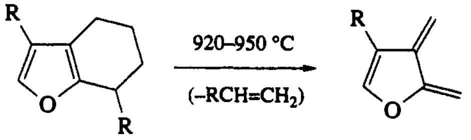

R = H, Me (82)

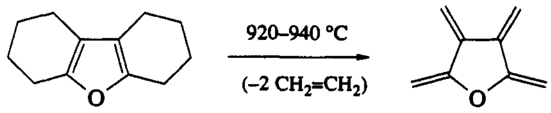

(83)

Another 3,4-disubstituted furan, compound (**189**), was prepared by an interesting one-pot DA–rDA process. The reaction of methyl 10-oxodec-8-ynoate (**187**) with 4-phenyloxazole (**186**) produced disubstituted furan (**189**), which was subsequently converted into the 3,4-disubstituted furan prostanoid (**190**). The method of furan formation based upon the intramolecular DA addition between oxazoles and alkynes, followed by subsequent rDA reaction extruding an alkyl nitrile, has been extended to the synthesis of several natural products. Upon refluxing in ethylbenzene, oxazole (**191**) gave evodone (**193**), the simplest member of the naturally occurring furanoterpenes.[162] This method has been used similarly to prepare the furanoeremophilanes (±)-petasalbine (**194**), (±)-ligularone (**195**)[163] and (±)-paniculide A (**196**),[164] and the furanosesquiterpenes gnididione (**197a**) and isognididione (**197b**).[165]

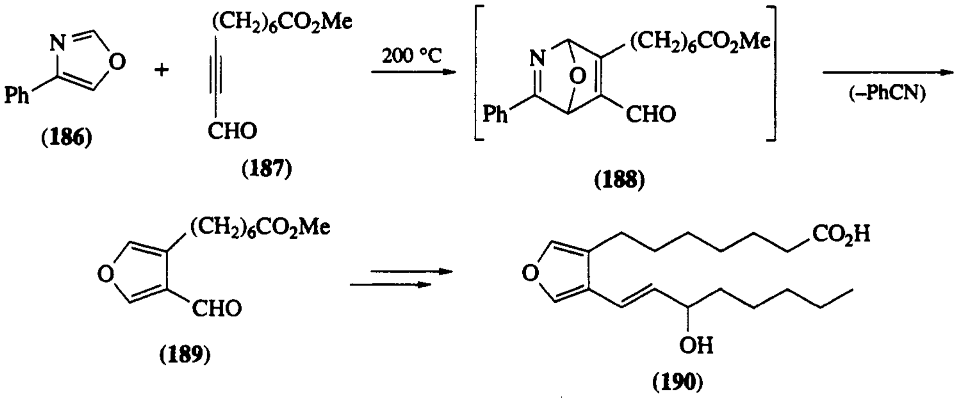

**(186)** **(187)** **(188)** **(189)** **(190)**

(84)

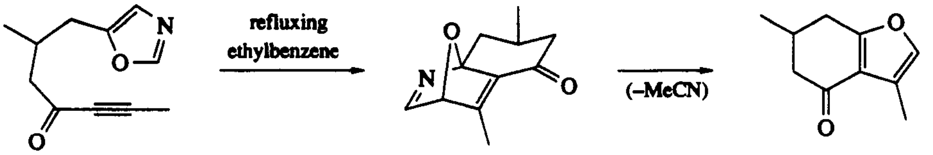

**(191)** **(192)** **(193)** (85)

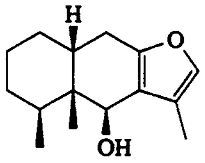

**(194)**

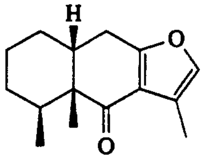

**(195)**

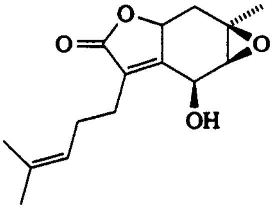

**(196)**

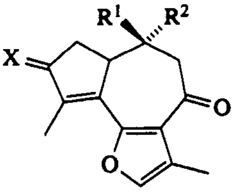

**(197a)** X = 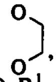, $R^1 = Me, R^2 = H$
**(197b)** X = O, $R^1 = H, R^2 = Me$

Isobenzofuran (**198**; $R^1 = R^2 = H$) and substituted isobenzofurans have been formed *via* rDA cycloreversions from many adducts. Depicted are some of the various adducts that have been used for this purpose.[166–170]

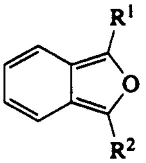

**(198)**

| *Adduct* | *rDA temp.* (°C) | *Yield of isobenzofuran* (%) |
|---|---|---|
| 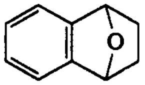 | 650 | 100 |
| 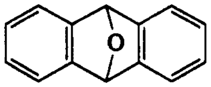 | 170 | 100 |
| 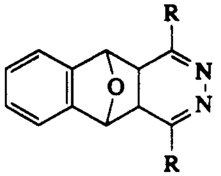 | 120 | – |
| 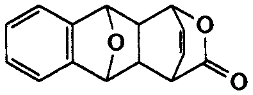 | 130 | 30 |
| 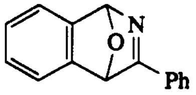 | 80 | 78 |
| 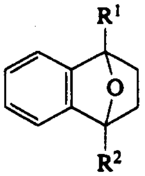 | 600 | 100 |

### 4.5.5.3 Nitrogen Heterocyclics Generated by Ethylene Formation

The generation of the carbon–carbon double bond of unsaturated nitrogen heterocycles by the rDA reaction of cycloadducts that act as 'protected' ethylenes has been accomplished. Azetines have been prepared by this method.[171] Another example is the synthesis of 1-methyl-3-pyrroline (**201**). By protecting the ethylene of *N*-methylmaleimide (**199**) with furan and then reducing with lithium aluminum hydride, adduct (**200**) was obtained (equation 86).[172] Pyrolysis of adduct (**200**) at 250–300 °C gave 1-methyl-3-pyrroline (**201**) in 60% isolated yield. The ethylene moiety of *N*-substituted maleimides can also be generated *via* rDA reactions. Examples include the generation of *N*-phenylmaleimide (equation 87)[173] and of *N*-acetoxymaleimide (equation 88).[174]

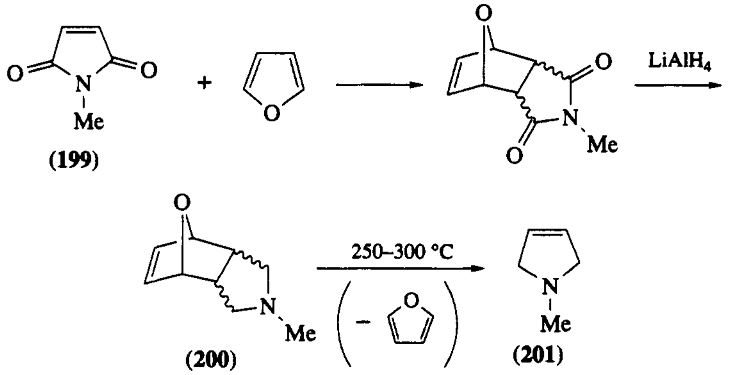

(86)

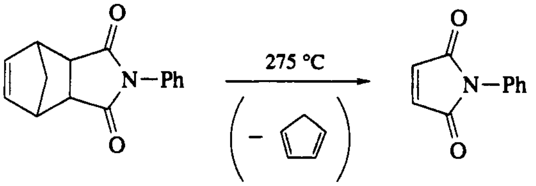

(87)

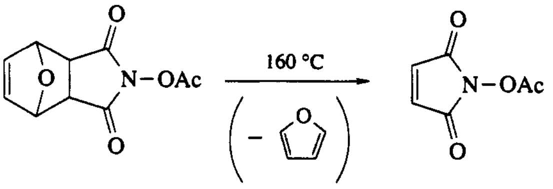

(88)

Generation of an ethylene unit from a 'protected' cycloadduct has found application in the synthesis of the α,β-unsaturated lactam moiety of indole alkaloids. The formation of lactam (**203**) occurs by pyrolysis at 180–190 °C *via* rDA extrusion from (**202a**) in 120 hours (67% yield) or from (**202b**) in seven hours (100% yield) as shown in equation (89).[175] Acceleration of the rDA process in (**202b**) is due to the trimethylsilyl group, which lowers the activation energy of the extrusion process by charge, radical or double bond stabilization β to the trimethylsilyl group. This 7-trimethylsilyl accelerated rDA process is useful for regeneration of the ethylene moiety under mild conditions. Lactam (**203**) was subsequently converted to the pentacyclic deethylaspidosperma-type alkaloid (**204**).[175]

### 4.5.5.4 Nitrogen Heterocyclics Generated by Butadiene Formation

Substituted pyrroles such as verrucarine E (**208**), an antimitotic agent, have been synthesized by methods that incorporate a rDA reaction as a key step. In order to prepare 3,4-disubstituted pyrroles in reasonable yields, an electron-withdrawing *N*-substituent must be present. Therefore, as shown in equation (90), *N*-benzoylpyrrole (**205**) was subjected to a DA–rDA sequence with acetylene elimination to produce diester (**207**), which was transformed into verrucarine E (**208**).[176]

The photochemical generation of pyrroles has been accomplished *via* intramolecular rDA reactions. Irradiation of azatricyclodecenone (**209**) in methanol resulted in a photoinitiated retrograde reaction that

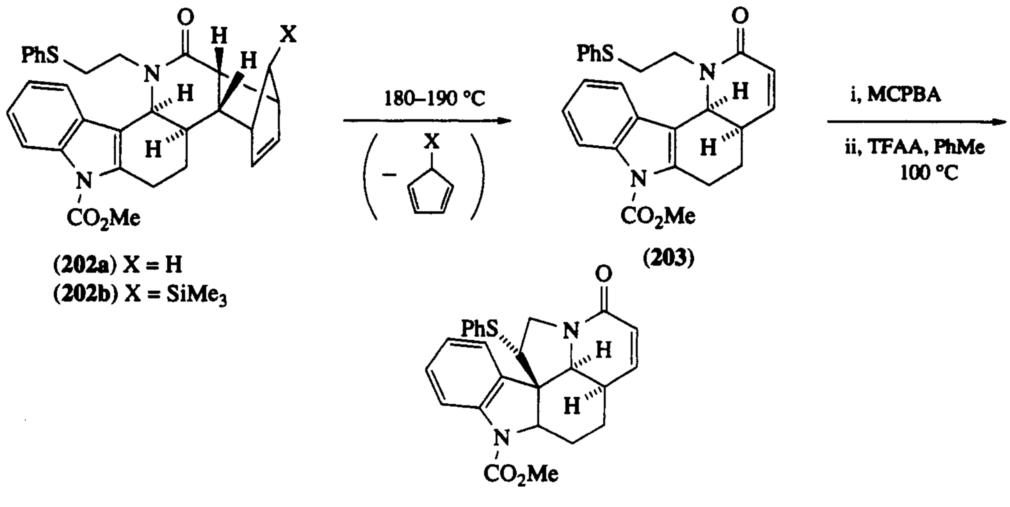
PhS
O
H
X
H
N
H
H
N
CO2Me
(202a) X = H
(202b) X = SiMe3
180–190 °C
(– X-cyclopentadiene)
(203)
i, MCPBA
ii, TFAA, PhMe
100 °C
(204)

(89)

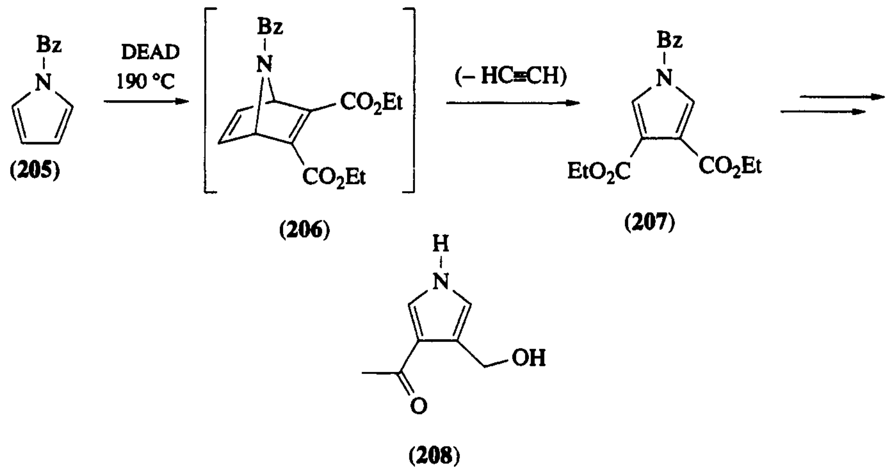
Bz
N
(205)
DEAD
190 °C
CO2Et
CO2Et
(206)
(– HC≡CH)
EtO2C
CO2Et
(207)
H
N
OH
O
(208)

(90)

yielded pyrrole ketene (**210**). The final product, pyrrole methyl ester (**211**), was obtained by reaction of (**210**) with methanol (equation 91).[177]

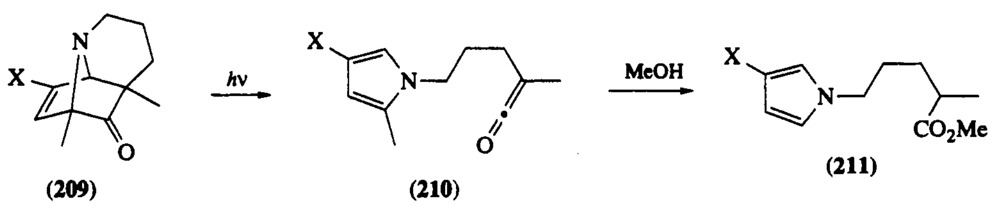
N
X
O
(209)
hν
X
N
O
(210)
MeOH
X
N
CO2Me
(211)

(91)

The generation of pyrazole has been effected by thermal rDA decomposition of diazatricycle (**212**) (equation 92), while photolysis resulted in nitrogen elimination.[178] The formation of 4-(3-butenyl)-1,2-pyrazole (**214**) occurred *via* rDA reaction of adduct (**213**) (equation 93).[179] Apparently the rigidity of the tricyclic azoalkane (**213**) prevented nitrogen extrusion under the usual thermolysis conditions. Again, photolysis resulted in nitrogen elimination rather than cycloreversion.

Isoindole was formed in essentially quantitative yield by rDA reaction of its ethylene adduct under FVP conditions (equation 94).[180] Substituted isoindoles (**215**)[181] and (**216**)[182] have been obtained by a similar rDA extrusion process.

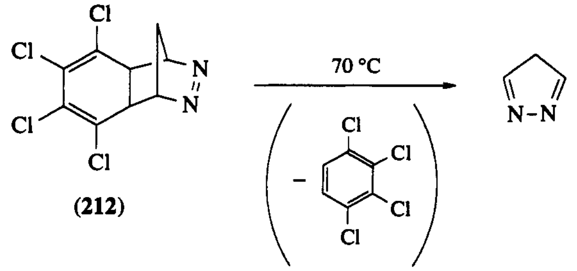
Cl
N
N
70 °C
-
Cl
N-N

**(212)**

(92)

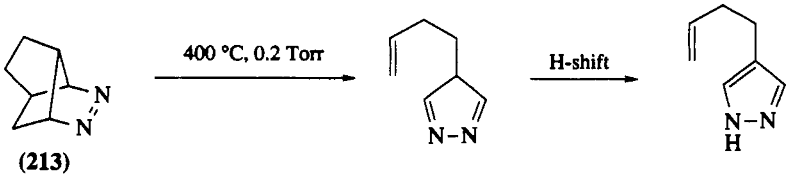
N
N
400 °C, 0.2 Torr
N-N
H-shift
N-N
H

**(213)** **(214)**

(93)

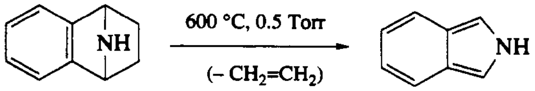
NH
600 °C, 0.5 Torr
(- CH2=CH2)
NH

(94)

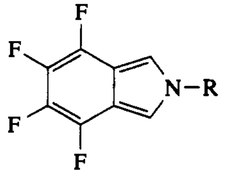

**(215a)** R = H
**(215b)** R = $CH_2Ph$

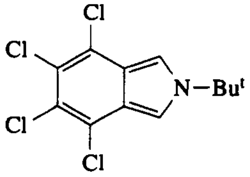

**(216)**

### 4.5.5.5 Six-membered Nitrogen Heterocyclics

A vast array of six-membered nitrogen heterocyclics has been synthesized by rDA methods. Pyridine,[183] 1,4-dihydropyridine,[184] 5,6-dihydropyridine[185] and pyrimidinone[186] syntheses have all been reported.

Boger has devised numerous synthetic schemes for the synthesis of six-membered nitrogen heterocycles based upon DA addition with subsequent rDA extrusion, and has reviewed the subject.[187,188] Representative examples are shown for the synthesis of substituted pyridines (equation 95),[189] substituted pyrimidines (equation 96)[190] and substituted 1,2-diazines (equation 97).[191]

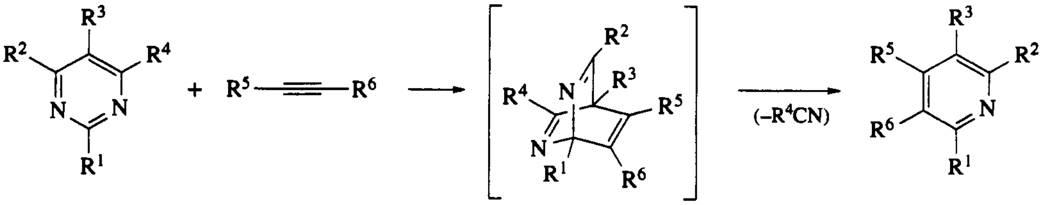
R3
R2
R4
N
N
R1
+ R5 ≡ R6
R2
R4
N
R3
R5
N
R1
R6
(-R4CN)
R3
R5
R2
R6
N
R1

(95)

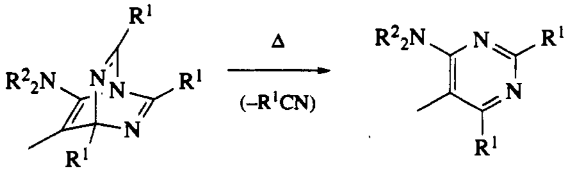
R1
R2₂N
N
N
R1
N
R1
Δ
(-R1CN)
R2₂N
N
R1
N
R1

(96)

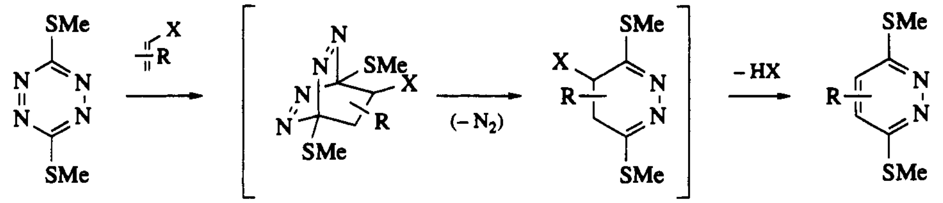

(97)

### 4.5.5.6 Heterocycles with Two Different Heteroatoms

The synthesis of heterocycles *via* rDA processes includes the preparation of heterocycles with two different heteroatoms. Furo[3,4-*c*]pyridine (**218**), a previously unknown polyheterocyclic, has been achieved by FVP of adduct (**217**) (equation 98).[192] The heteropentalene thieno[3,4-*b*]furan (**220**) has been synthesized by a reaction pathway based upon rDA formation of polyheterocycle (**219**) (equation 99).[193] Other heterocycles prepared *via* rDA reactions that contain two different heteroatoms include 6*H*-1,3-oxazin-6-one (**221**)[194] and 3-arylisoxazoles (**222**).[195]

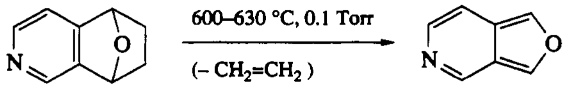

(98)

**(217)** **(218)**

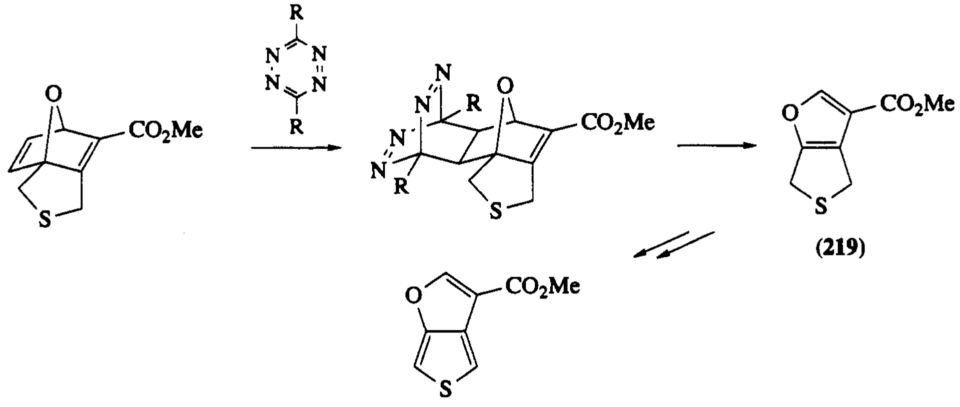

**(219)**

(99)

**(220)**

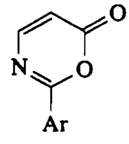

**(221)**

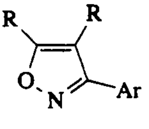

**(222)** R = H or $CO_2Me$

## 4.5.6 INTRAMOLECULAR CYCLOREVERSIONS

### 4.5.6.1 Cyclic Compounds

Intramolecular rDA processes have been used to produce a variety of cyclic compounds. Thermolysis of azoalkane (**223**) followed by tautomerization gives 4-(2′-styryl)pyrazole (**224**) as shown in equation (100).[196] Apparently the C-1—C-6 and C-4—C-5 bonds are sufficiently weakened compared with the C-1—N-2 and N-3—C-4 bonds in strained (**223**) that the rDA process is preferred over expected molecular nitrogen extrusion. An investigation of the thermal stability of (**225**) led to production of 2-vinylindene (**227**) *via* an intramolecular cycloreversion to intermediate (**226**), which underwent a 1,5-hydrogen shift to yield the more stable aromatized product (equation 101).[197]

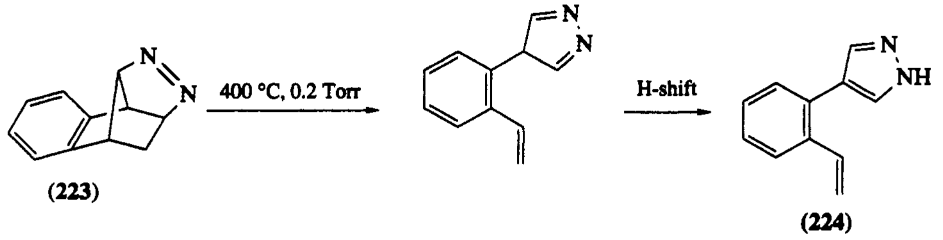

(100)

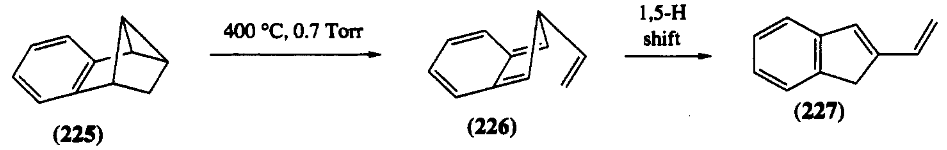

(101)

### 4.5.6.2 Isomerizations

Often an intramolecular rDA cycloreversion is involved in a series of DA–rDA reactions in an isomerization or an automerization process. In the automerization of [4.2.2]propella-2,4,7,9-tetraene (**228**), a DA–rDA sequence occurred twice to produce bicyclic (**230**) (equation 102).[198] A remarkable facet of this thermal molecular rearrangement process is the formation of the highly energetic cyclobutadiene intermediate (**229**), whose presence was evidenced by trapping with methanol. Another isomerization involving a series of rDA reactions is observed for the thermal decomposition of tricyclo[6.4.2.0.2$^{3,6}$]tetradeca-1(8),4,13-triene (**231**). This thermal decomposition produces 1,2-dimethylenecyclohexane (**235**), tetralin (**237**), benzene (**236**) and butadiene (**238**) as shown in equation (103).[199] The mechanism shown was based on thermal decomposition of the hexadeutero analog of (**231**) (asterisks are deuterated positions). The suspected driving force for this molecular rearrangement is the aromatization occurring during the rDA reactions of (**232**) and (**234**). Tricyclic acetate (**239**) is converted to acetate (**240**) by a thermally initiated intramolecular rDA reaction (equation 104).[200] Relief of ring strain is cited as contributing to the low temperature required for this rDA reaction.

### 4.5.6.3 Solvolysis Reactions

Very few well-documented cases of intramolecular rDA reactions are known that occur during solvolysis. Three examples that exist are: the aqueous ethanolysis of (**241**) in excess sodium cyanide (equation 105),[201] the hydrolysis of a related *p*-nitrobenzoate in aqueous acetone,[202] and a related tosylate in TFA.[203] In each case a cyclopentadienyl derivative is formed by an intramolecular rDA process, which can then be trapped as a DA adduct, tautomerize or dimerize.

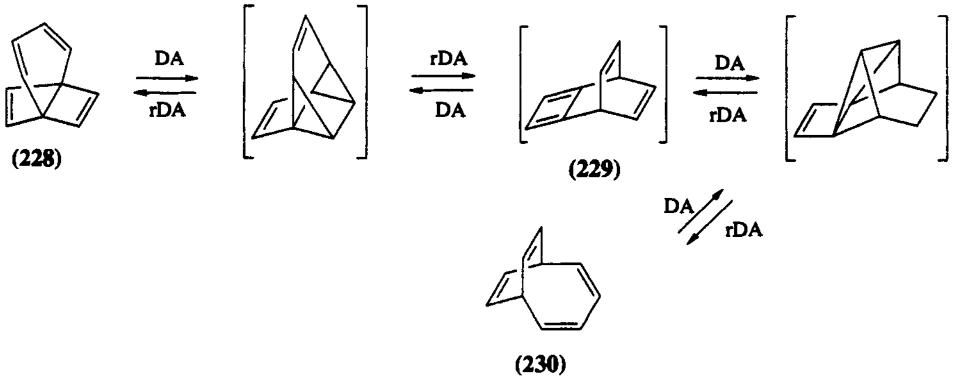

(102)

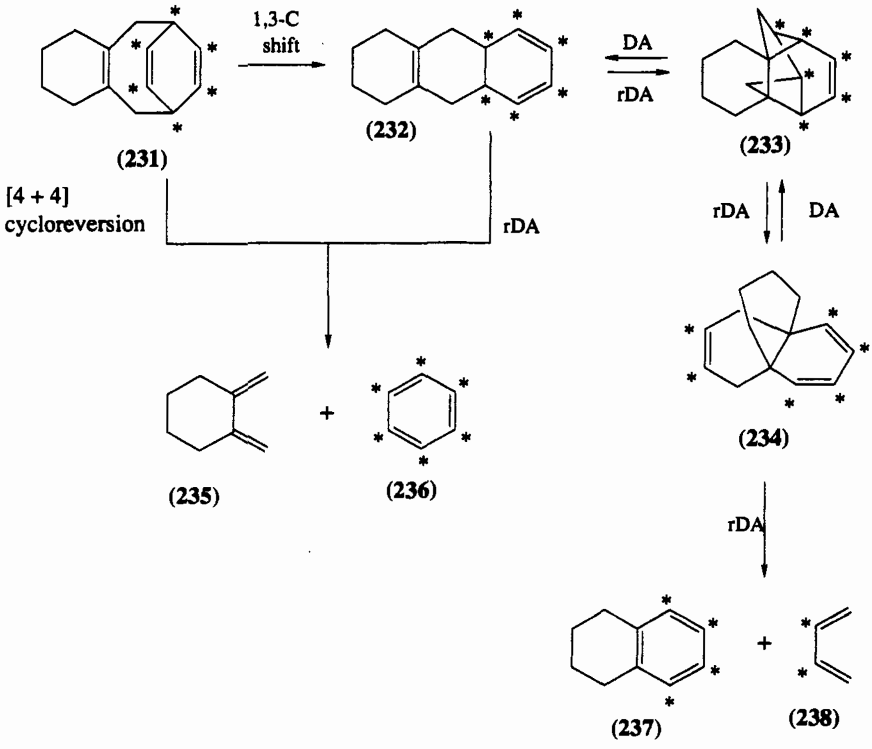

(231) (232) (233) (234) (235) (236) (237) (238)

(103)

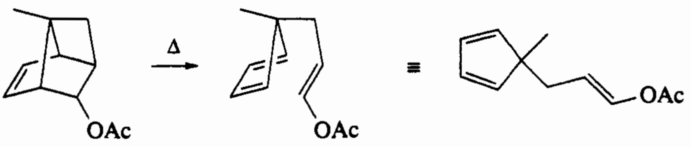

(239) (240)

(104)

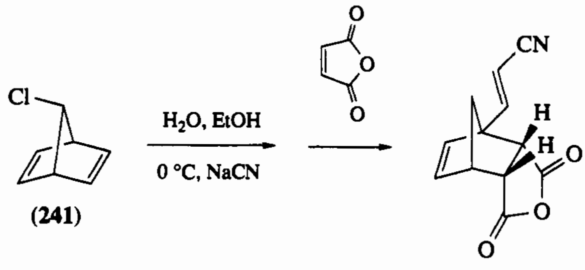

(241)

(105)

### 4.5.6.4 Acyclic Species

Intramolecular rDA reactions are also known that generate acyclic compounds. The thermal isomerizations of bicyclo[4.1.0]hept-2-enes (**242**) and (**243**) were found to occur *via* an intramolecular rDA process as depicted in equations (106) and (107), respectively;[204] *gem*-difluoro substituents of (**242**) and the spiropentyl substituent of (**243**) give rise to similar kinetic enhancements of ring cleavage and an incremental strain of the ring system.[204] The kinetic parameters for these reversible intramolecular rDA processes demonstrate that almost all of the entropy lost upon product formation is lost on reaching the transition state. A final example of the formation of acyclic species by an intramolecular rDA cycloreversion involves the photochemistry of tropidine (**244**). Irradiation of tropidine in pentane with 185 nm light (6.7 eV photons) gave only product (**245**) in greater than 90% yield (equation 108).[205]

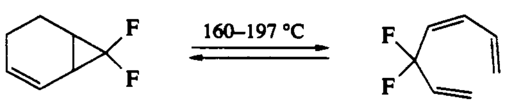

**(242)**

(106)

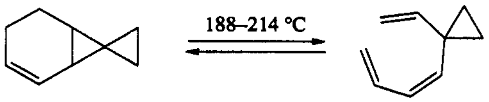

**(243)**

(107)

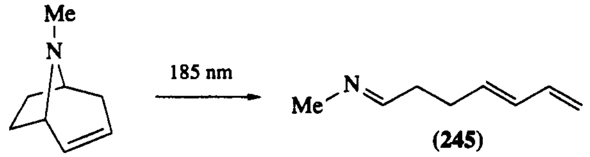

**(244)** **(245)**

(108)

## 4.5.7 GENERATION OF REACTIVE INTERMEDIATES

### 4.5.7.1 Silenes, Disilenes and Silanones

The generation of reactive species by a retrograde Diels–Alder pathway has proven a powerful tool for the study of chemical intermediates. The generation of intermediates containing doubly bonded silicon, such as silenes, disilenes and silanones, has been achieved. Silenes, molecules containing a silicon–carbon double bond, can be obtained by the thermolysis or photolysis of an appropriate adduct. A very efficient silaalkene generator is the 7-silabicyclo[2.2.2]octadiene (**246**), which upon thermolysis or photolysis yields 2-methyl-2-silapropene (**247**) as shown in equation (109).[206] Disilenes, compounds with a silicon–silicon double bond, have been similarly obtained. The disilene intermediate tetramethyldisilene (**249**) has been produced by the thermal decomposition of 7,8-disilabicyclo[2.2.2]octa-2,5-dienes such as (**248**). The existence of these reactive intermediates is often substantiated by trapping with an appropriate diene. To be suitable, the diene must be stable at the decomposition temperature and the product formed after the reaction with the diene must also be thermally stable at this temperature. Direct evidence for the existence of tetramethyldisilene was obtained by trapping with anthracene as shown in equation (110).[207]

Silanones, the silicon analogs of ketones, are produced *via* rDA reactions. One attempt to prepare a suitable DA precursor for retrograde decomposition to a silanone met with unexpected results. The desired DA reaction between 2,2-dimethyl-1-oxa-2-silacyclohexa-3,5-diene (**251**) and perfluoro-2-butyne was complete in one day at room temperature. The observed product was *o*-bis(trifluoromethyl)benzene, as the initial adduct apparently underwent retrodiene decomposition to yield the intermediate dimethylsilanone (**252**) (equation 111). The occurrence of this retrodiene process at room temperature was not consistent with the analogous extrusions of silenes and disilenes that require elevated temperatures. However, the reaction sequence was substantiated by comparison with its carbon analog in which tetramethylpyran and dimethyl acetylenedicarboxylate react at room temperature to afford only acetone and the corresponding phthalate.[208] Stable adducts that extrude silanones are also known. Reactions of 2-silapyrans and maleic anhydride provide stable adducts, such as (**253**), that decompose upon thermolysis

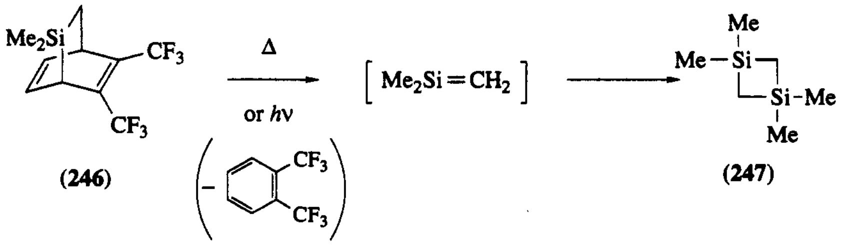

**(246)** **(247)**

(109)

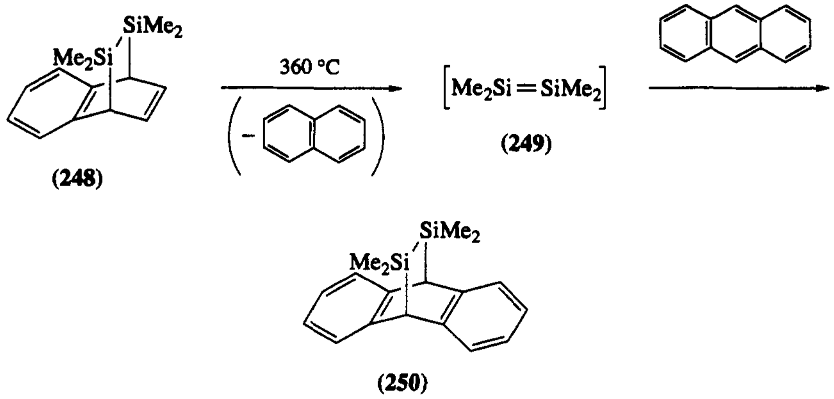
SiMe2
Me2Si
(248)
360 °C
(-naphthalene)
[Me2Si=SiMe2]
(249)
SiMe2
Me2Si
(250)

(110)

or photolysis to yield silanones. The existence of these reactive intermediates is based on the formation of cyclosiloxanes, for example (**254**), from the cyclic oligomerization of the silanone in the absence of a trapping agent. The product of silanone insertion is obtained when a suitable trap such as dimethoxydiphenylsilane is present.[208]

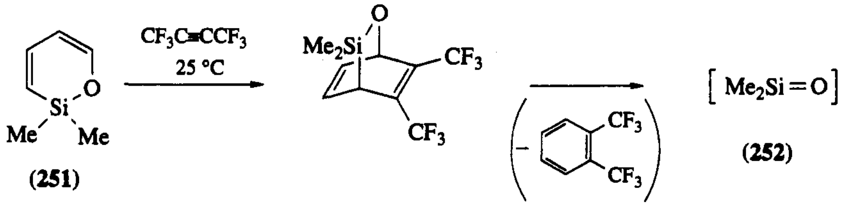
O
Si
Me
Me
(251)
CF3C≡CCF3
25 °C
O
Me2Si
CF3
CF3
CF3
CF3
[Me2Si=O]
(252)

(111)

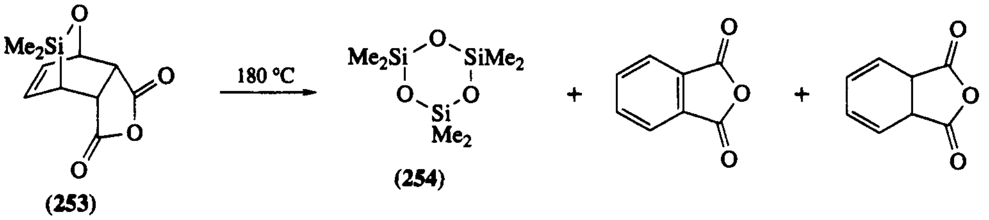
O
Me2Si
O
O
O
(253)
180 °C
Me2Si
O
SiMe2
O
O
Si
Me2
(254)
+
O
O
O
+
O
O
O

(112)

### 4.5.7.2 *o*-Xylylene *via* Retro-dimetalla-DA Reaction

An interesting variation of the rDA reaction is the retro-dimetalla-Diels–Alder reaction that generates two reactive intermediates, *o*-xylylene (**257**) and the metal–metal double bonded dimer (**256**), *via* a dinuclear elimination. Performing this equilibrium reaction in the presence of reagents that react with (**256**), such as trialkylphosphines, yields the dinuclear monophosphine adducts. Consumption of (**256**) allows the *o*-xylylene to dimerize as shown in equation (113).[209]

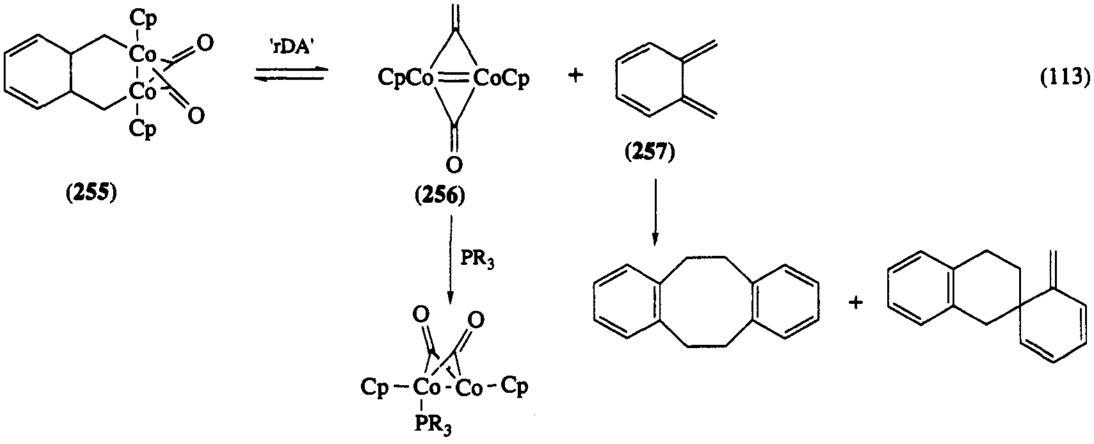
Cp
Co
O
Co
O
Cp
(255)
'rDA'
O
CpCo=CoCp
O
(256)
+
(257)
PR3
O
O
Cp–Co–Co–Cp
PR3
+

(113)

### 4.5.7.3 Cumulenes

Cumulenes, generally regarded as difficult to prepare, can be obtained readily *via* rDA methods. Allenes, the most basic cumulenes, with a wide range of substituents on the allenic carbon, can be obtained by FVP of anthracenic DA adducts as shown in equation (114).[210] Butatriene (**258**), the next in the series of cumulenes, has been produced by FVP of a variety of adducts that includes 9,10-ethano-9,10-dihydroanthracene,[211] cyclohexyne[212] and fulvene, furan and benzene cycloadducts.[213] Pentatetraene (**260**), a compound that is stable enough to be purified by GLC at room temperature, has also been obtained by the FVP of vinylallene (**259**).[214]

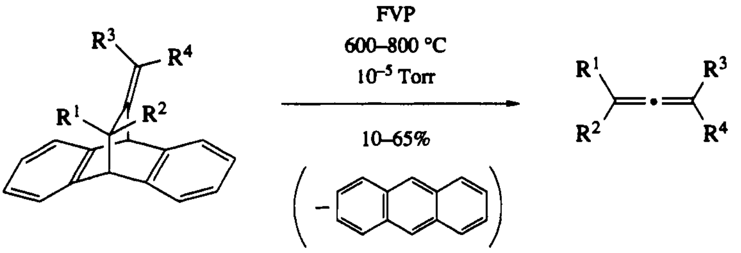

(114)

$R^1$ = H, Me; $R^2$ = H, Me, CHO; $R^3$ = H, Me, CN, $CO_2R$; $R^4$ = H, alkyl, CHO, CN, $CO_2R$, $OSiMe_3$, $NH_2$

$CH_2{=}\bullet{=}\bullet{=}CH_2$

**(258)**

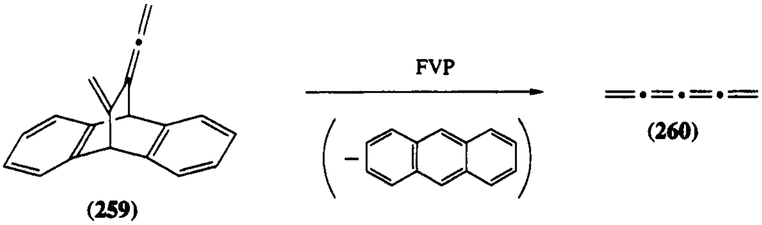

(115)

**(259)**

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# 5.1

# [4 + 3] Cycloadditions

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## 5.1.1 INTRODUCTION

Seven-membered carbocycles are an important class of organic compounds that are of practical and theoretical interest. They are more elusive and have been studied less in depth than their lower homologs, probably because of entropy reasons, ring strain, and synthetic difficulties. Before discovery of the [4 + 3] cycloaddition reaction, methods for preparing seven-membered carbocycles were limited to enlargement of six-membered rings and some cyclization reactions. However, [4 + 3] cycloadditions of reactive three-carbon species with dienes should prove to be the most convenient and straightforward method for the synthesis of a wide range of seven-membered rings. Recently, various routes to reactive three-carbon species have rapidly developed and therefore [4 + 3] cycloadditions using these species have come to be widely investigated, although not yet to the level of [4π (4C) + 2π (2C)] cycloadditions. The latter processes constitute one of the most useful and successful processes in organic synthesis, leading to six-membered carbocycles.[1]

## 5.1.2 PREPARATION OF REACTIVE THREE-CARBON UNITS

In 1962, Fort first reported the preparation of an 8-oxabicyclo[3.2.1]oct-6-en-3-one derivative (**1**) by reaction of α-chlorodibenzyl ketone (**3**) with furan in the presence of 2,6-lutidine as a base.[2] The 2-oxyallyl unit (**2**) coupled with furan in this reaction (Scheme 1). Soon after, Cookson and his coworkers reported an improved method for the synthesis of (**1**).[3]

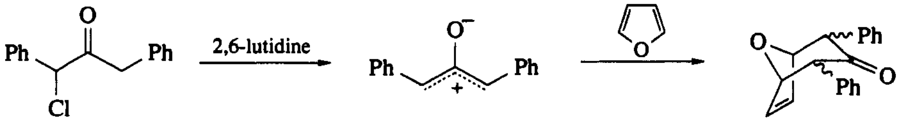

(**3**) (**2**) (**1**)

**Scheme 1**

The discovery of allyl cations (**2**) that serve as 2π components in [4π (4C) + 2π (3C)] cyclocoupling reactions provides considerable innovation for the elaboration of seven-membered ring carbocycles. The [4 + 3] cyclocoupling reaction of allyl cations with 1,3-dienes is an efficient and easy method for the stereoselective synthesis of seven-membered ring compounds. New methodology for generating allyl cation species continues to evolve and annulations using these species have opened easy access to a wide range of organic frameworks that have been utilized for preparing natural products, pharmacologically active compounds, and key intermediates for various useful organic molecules. These reactive species also undergo [3 + 2] cycloadditions across simple alkenic bonds, thereby giving rise to five-membered carbocycles. Mechanistic and synthetic aspects of the [4 + 3] and [3 + 2] cycloaddition reactions using allyl cations have been elegantly reviewed by Hoffmann,[4] Noyori[5] and Mann.[6] Recently, vinylcarbenes and 1,3-dipolarophiles consisting of three-carbon species have also been used as 2π components in [4 + 3] cycloaddition reactions.[7]

### 5.1.2.1 β-Heteroatom-substituted Allylic Cations

Much attention has been directed to the chemistry of β-heteroatom-substituted allylic cations (**5**), especially oxyallyl cations (**7**), from both synthetic and mechanistic viewpoints. One of the characteristic reactions of oxyallyls (**7**) is their [4 + 3] → 7 cycloadditions with conjugated dienes, which provide a unique and important route to seven-membered rings (Schemes 2 and 3).

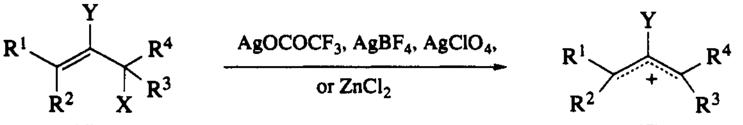

(**4**) (**5**)

X = Cl, Br, OH, OCOCF$_3$,; Y = OSiMe$_3$, OR, NR$_2$, alkyl

| | *R*¹ | *R*² | *R*³ | *R*⁴ |
|---|---|---|---|---|
| a: | H | H | H | H |
| b: | Me | Me | H | H |
| c: | H | H | Me | Me |
| d: | H | Me | Me | Me |
| e: | Me | Me | Me | Me |
| f: | H | -(CH$_2$)$_2$- | | H |
| g: | H | -(CH$_2$)$_3$- | | H |

**Scheme 2**

#### *5.1.2.1.1 α,α′-Dihalo ketones and reducing agents*

One of the most useful routes to 2-oxyallyl cations (**7**) is the reaction of α,α′-dihalo ketones (**9**) with reducing agents (Scheme 3). Initially, halogenated metal enolates of type (**8**) are formed and oxyallyl cations (**7**) are then generated by subsequent elimination of the halide ion. Copper–sodium iodide in ace-

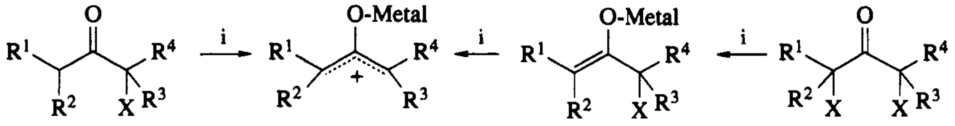

(6) (7) X = Cl, Br (8) (9)

i, $Fe_2(CO)_9$ and related iron carbonyl species, Zn–Cu couple ($Me_3SiCl$), Zn–Ag couple, Zn/$(EtO)_3B$, or Cu/NaI

| | *R¹* | *R²* | *R³* | *R⁴* |
|---|---|---|---|---|
| **a:** | Me | H | H | H |
| **b:** | Pr$^i$ | H | H | H |
| **c:** | Pr$^i$ | H | H | Pr$^i$ |
| **d:** | Ph | H | H | H |
| **e:** | Ph | H | Me | H |
| **f:** | H | Me | Me | H |
| **g:** | H | Ph | Ph | H |
| **h:** | Me | Me | H | H |
| **i:** | Me | Me | Me | H |
| **j:** | Me | Me | Ph | H |
| **k:** | Me | Me | Me | Me |
| **l:** | H | –$(CH_2)_2$– | | H |
| **m:** | H | –$(CH_2)_3$– | | H |
| **n:** | H | Br | H | H |
| **o:** | H | Br | Br | H |
| **p:** | H | Cl | Cl | H |
| **q:** | I | H | Me | Me |

**Scheme 3**

tonitrile,[8] zinc dust–triethyl borate in THF,[9] zinc–copper couple in DME or acetone,[10] diiron enneacarbonyl [$Fe_2(CO)_9$] in benzene,[11] and sodium iodide in acetone or acetonitrile[3] have seen use. In addition, copper–isonitrile complexes,[12] Grignard reagents,[13] organocuprates,[13] and dissolved electrons[14] are also capable of promoting the reaction with open-chain dibromides. The reaction of (**9**) with zinc–copper couple has been accelerated by the addition of chlorotrimethylsilane. Moreover, the yield of cycloadduct dramatically increases, presumably due to formation of an α-haloalkyl-substituted silyl enol ether (**8**; M = $SiMe_3$) followed by a cation of type (**7**), which is more electrophilic than (**8**; M = ZnBr).[15] A summary of the main features of various methods for preparing 2-oxyallyl cations is given in Table 1.

### *5.1.2.1.2 α-Halo ketones and base*

After Fort's and Cookson's reports, a variety of combinations between α-halo ketones (**6**) and bases has evolved for the generation of 2-oxyallyl cations (**7**). Simple α-bromobenzyl and α-bromoalkyl ketones can be converted to the corresponding oxyallyl cations, which are trapped with 1,3-diene derivatives. Reactions using triethylamine proceed smoothly in methanol and 2,2,2-trifluoroethanol.[16] The dehalogenation can also be efficiently promoted by silver tetrafluoroborate and triethylamine in acetonitrile, or in furan which serves as both solvent and trapping agent.[17] Readily available, inexpensive lithium perchlorate–triethylamine in diethyl ether is also effective for reaction with α-chloro and α-bromo ketones, owing to the formation of insoluble triethylammonium halide.[18] The base-induced reaction of α-halo ketones turns out to generate weakly electrophilic 2-oxyallyl intermediates (**7**), which react specifically with furan and other nucleophilic dienes.[19]

The more acidic γ-bromo-β-oxonitriles (**10**) have been easily dehydrohalogenated with $Ag_2O$ (Scheme 4).[20]

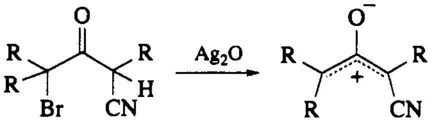

(10) (11)

**Scheme 4**

**Table 1** Preparation of Reactive Three-carbon Units

| *Section* | *Stating material* | *Reagent* | *Solvent* | *Reaction time* | *Reaction temp.* | *Ref.* |
|---|---|---|---|---|---|---|
| 5.1.2.1.1 | α,α′-Dihalo ketone | Cu, NaI | MeCN | 4–24 h | r.t. → 60 °C | 3, 8b, 15 |
| | | Zn/(EtO)$_3$B | THF | 24 h | r.t. | 9 |
| | | Zn–Cu | DME or acetone | | −10 °C → r.t. | 15, 53 |
| | | Zn–Ag | THF | 4–12 h | r.t. | 11b |
| | | $Fe_2(CO)_9$ or $Fe(CO)_5$ | Benzene | 2–48 h | r.t. | 11a, 49 |
| | | Cu, Bu$^t$NC | Benzene | | | 12 |
| | | Grignard or cuprate reagent | | | | 13 |
| | | Electron reduction | | | | 14 |
| 5.1.2.1.2 | α-Bromo ketone | $AgBF_4/Et_3N$ | $CH_2Cl_2$ or MeCN | 5–6 h | r.t. | 17 |
| | γ-Bromo-β-oxonitrile | $Ag_2O$ | $CH_2Cl_2$ or ether | 3–64 h | r.t. | 20 |
| | α-Chloro and α-bromo ketone | $LiClO_4/Et_3N$ | Ether | 2 h–117 days | r.t | 18 |
| | | $Et_3N$ | $MeOH/CF_3CH_2OH$ | 1 h–29 days | −20 °C → r.t. | 16 |
| | | NaH | Ether | | | 19 |
| 5.1.2.1.3 | Siloxyallyl chloride | $LiClO_4$ | MeOH | | | 21 |
| | | $AgClO_4$ | $MeNO_2$ | 1 h | 0–20 °C | 21 |
| | | $AgClO_4$ | THF/ether | 1 h | 0 °C | 21 |
| | Siloxyallyl bromide | $ZnCl_2$ | $CH_2Cl_2$ | 50 min | −78 °C → r.t. | 22 |
| | Siloxyvinyl aldehyde | $SnCl_4$ | $CH_2Cl_2$ | 5 h | −78 °C | 23a |
| | Siloxyvinyl ketone | $TiCl_4$ | $CH_2Cl_2$ | 1 h | −78 °C | 23b |
| | Alkoxyallyl bromide | $CF_3COOAg$ or $ZnCl_2$ | Benzene | 10 hr | r.t. | 24, 25 |
| | Aminoallyl chloride | $AgBF_4$ | $CH_2Cl_2$ | | −60 °C | 26 |
| 5.1.2.1.4 | Cyclopropanone allenoxide | | $CH_2Cl_2$ | 5–6 days | r.t. | 27, 28 |
| 5.1.2.2.1 | Allyl iodide | $CCl_3COOAg$ | Liquid $SO_2$ | 3 h | −60 °C → r.t. | 31 |
| | | | $CH_2Cl_2$ | 1.5 h | −50 °C → r.t. | 32 |
| | | $CF_3COOAg$ | Isopentene | 6 h | −78 °C | 32 |
| 5.1.2.2.2 | Allyl alcohol | $H_2O$–TsOH | Pentane | 24 h | 0 °C → r.t. | 34 |
| | | $(CF_3CO)_2O$ | $EtNPr_2$ | | | 36 |
| | | $PhNHMe/TiCl_4$ | $CH_2Cl_2$ | | −20 °C | 37 |

### *5.1.2.1.3 β-Heteroatom-substituted allylic halides and silver salts or Lewis acids*

2-(Trimethylsiloxy)allyl cations (**5**; Y = $OSiMe_3$) are obtained by the reaction of 2-(trimethylsiloxy)allyl chlorides (**4**; X = Cl, Y = $OSiMe_3$) with silver perchlorate in nitromethane (Scheme 2).[21] These intermediates are also obtained with the aid of a Lewis acid.[22] It has been reported that 2-siloxyacrolein (**12a**; R = H), but not the less electrophilic (**12b**; R = Me), when activated by an equimolar amount of $SnCl_4$ serves as a 1-hydroxy-2-oxidoallyl synthon (**13**) (Scheme 5).[23]

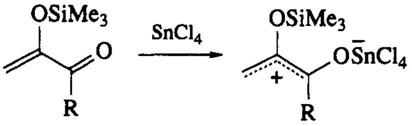

(**12a**) R = H
(**12b**) R = Me

(**13a**) R = H
(**13b**) R = Me

**Scheme 5**

2-Methoxyallyl cation (**5a**; Y = OMe), derived from 2-methoxyallyl bromide (**4a**; X = Br, Y = OMe) and silver trifluoroacetate in the presence of sodium carbonate, reacts with benzene, toluene, *p*-xylene or mesitylene.[24] 2-Ethoxyallyl alcohol (**4c**; X = OH, Y = OEt) in the presence of trifluoroacetic anhydride generates the 2-ethoxyallyl cation (**5c**; Y = OEt).[25] 2-Ethoxyallyl alcohol (**4c**) is probably more advantageous than the corresponding 2-methoxyallylic species (**4a**; Y = OMe) because dealkylation of the intermediary oxonium ion seems to be less facile, and the ethyl enol ether is more nucleophilic than the methyl enol ether. Treatment of cyclic α-chloroenamines (**4f**; X = Cl, Y = morpholino) and (**4g**; X = Cl, Y = pyrrolidino) with $AgClO_4$ or $AgBF_4$ in THF or dichloromethane generates 2-aminoallyl cations (**5f**; Y = morpholino) and (**5g**; Y = pyrrolidino).[26]

### *5.1.2.1.4 Cyclopropanones and related compounds*

Cyclopropanones act as three-carbon sources in [4 + 3] cycloadditions. However, these small-ring compounds are impractical for preparative scale experiments, because they are generally inaccessible and also must be handled with special precautions, in contrast to other oxyallyl species. One of the early descriptions of the synthesis of cyclopropanones appeared in 1932.[27] Nevertheless, the development of the chemistry of cyclopropanones proceeded at quite a slow pace until the late 1960s when Turro reported their utilization in [4 + 3] cycloaddition reactions.[28] 2,2-Dimethylcyclopropanone (**14**) adds to furan, cyclopentadiene, 6,6-dimethylfulvene and the relatively nucleophilic *N*-methylpyrrole to give the corresponding cycloproducts, but fails to react with anthracene and 1,3-butadiene. Parent cyclopropanone cannot be used.

Irradiation of tetramethylcyclobutanedione (**16**) in furan gives an 8-oxabicyclo[3.2.1]oct-6-en-3-one derivative *via* oxyallyl cation (**17**).[29] This reaction is the first example of the cycloaddition of cyclopropanones. Although the syntheses of a few seven-membered ring compounds have been subsequently carried out by means of this photoreaction, interest in cyclopropanone chemistry has been directed to structure and reactivity relationships, but not to organic synthesis.[30]

Allenoxide (**18**) also reacts with 1,3-dienes to give seven-membered ring adducts (**19**) (Scheme 6).[31]

## 5.1.2.2 Other Allylic Cations

### *5.1.2.2.1 Allylic halides and Lewis acids or silver salts*

Treatment of β-methallyl iodide (**4a**; X = I, Y = Me) with a silver salt gives a methallyl cation (**5a**; Y = Me) which reacts with 1,3-dienes such as 1,3-butadiene, 1,3-cyclopentadiene or 1,3-cyclohexadiene to give the corresponding seven-membered ring compounds (**20**) and (**21**) and their isomers.[32] However, cycloaddition of the parent allyl cation (**5a**) with 1,3-dienes generally produces satisfactory results. In fact, (**5a**; Y = H) derived from allyl iodide (**4a**; X = I, Y = H) and silver trifluoroacetate reacts with 1,3-cyclopentadiene to yield bicyclo[3.2.1]octa-2,6-diene (**21**; Y = H, *n* = 1) though in poor yield, along with

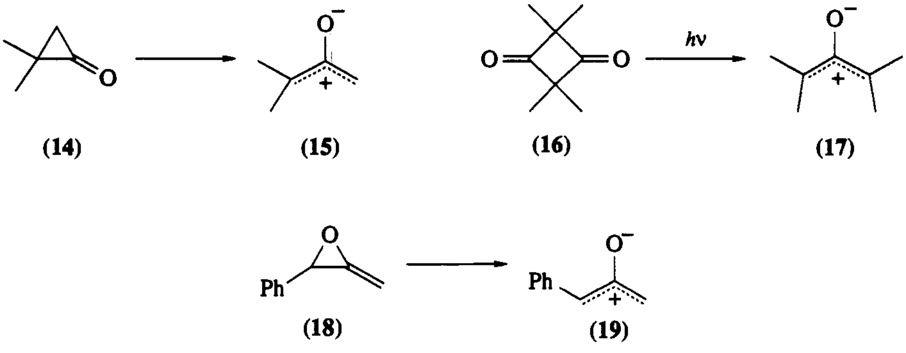

Scheme 6

2-propenyl trifluoroacetate as a major product.[32b] Similarly, propargyl cation (**23**) also gives a seven-membered ring product (**24**) (Scheme 7).[33]

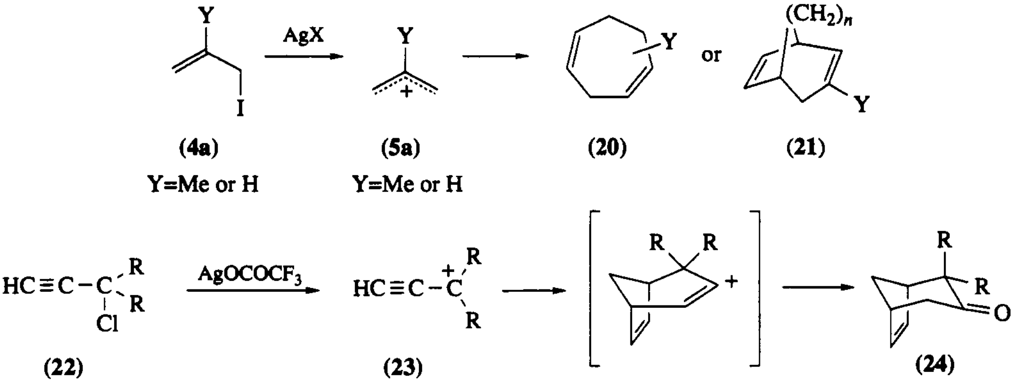

Scheme 7

### 5.1.2.2.2 Activation of allylic alcohols and allylsilanes

Allyl alcohol with three terminal methyl groups, such as (**4c**; X = OH, Y = Me), reacts with cyclopentadiene under two-phase conditions (in an aqueous *p*-toluenesulfonic acid/pentane solution) to give a seven-membered ring product (**26**) (Scheme 8).[34]

Allylsilanes are important synthetic reagents for the introduction of allyl groups and act as otherwise inaccessible synthetic equivalents.[35] Although allylsilanes are relatively stable and isolable, they react with a variety of electrophiles in the presence of a Lewis acid. When 2-(trimethylsilylmethyl)allyl alcohol or its trifluoroacetate is treated with a Lewis acid, the 2-(trimethylsilylmethyl)allyl cation that can participate in [4 + 3] cyclization is formed.[36] The reaction proceeds in a symmetry-allowed suprafacial manner. For example, when a highly substituted 1,3-bifunctional silyl alcohol (**4d**; X = OH, Y = $CH_2SiMe_3$) is exposed to a Lewis acid, the intermediate 2-(trimethylsilylmethyl)allyl cation (**27**) reacts with cyclopentadiene and furan to give the corresponding cycloadduct (**28**), though the yields are modest (Scheme 8).[36]

Recently, Trost reported on [4 + 3] cycloadditions of trimethylenemethane fragments by palladium-catalyzed reaction of 2-(trimethylsilylmethyl)allyl acetate (**4a**; X = OAc, Y = $CH_2SiMe_3$) and related compounds with electron-deficient alkenes. An exciting approach to methylenecycloheptenes (**30**) is realized.[37] These interesting reagents have been elegantly reviewed by Trost.[38] The reaction of trimethylenemethane-palladium intermediate (**29**) with dimethyl (*E*,*E*)-muconate gives as cyclized products a 1:1 mixture of the five- and seven-membered carbocycles. Treatment of exocyclic diene (**30**) with (**29**) in the presence of a $Pd^0$ catalyst leads to perhydroazulenes (**31**) in good yields. Best results are obtained by using *N*,*N*′-benzylideneethylenediamine as a ligand. The *exo* methylene group of the adduct is chemoselectively oxidized to a ketone (**32**) by the portion-wise addition of benzyltriethylammonium permanganate. The ketone (**32**) corresponds to the [4 + 3] cycloadduct of the 2-oxyallyl zwitterion.[37]

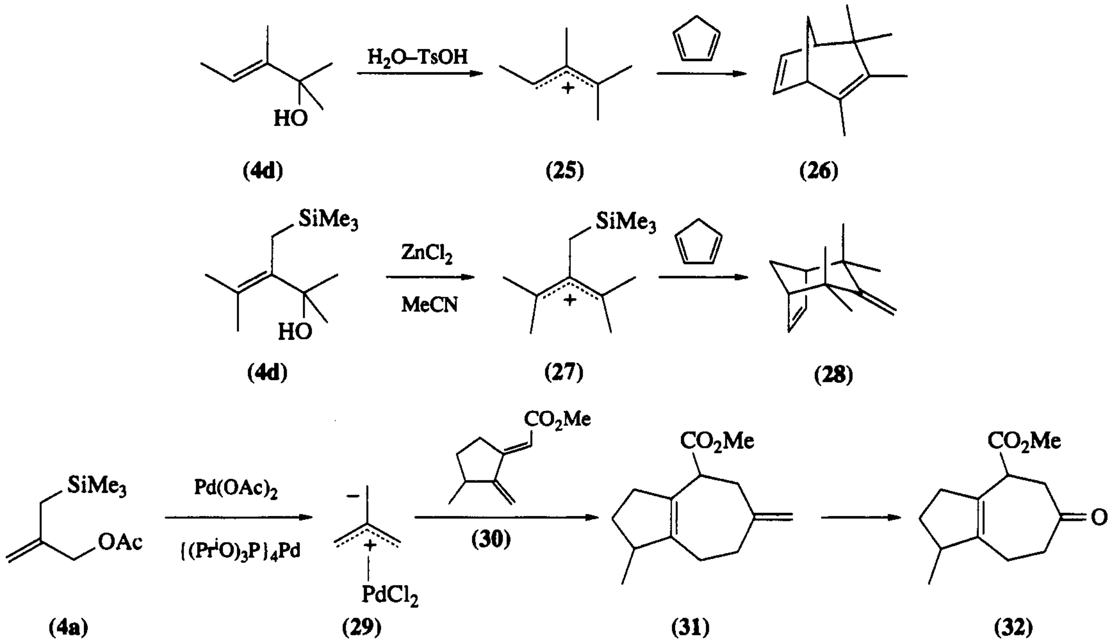
HO
(4d)
H2O–TsOH
(25)
(26)
SiMe3
HO
(4d)
ZnCl2
MeCN
SiMe3
(27)
(28)
SiMe3
OAc
(4a)
Pd(OAc)2
{(PriO)3P}4Pd
PdCl2
(29)
CO2Me
(30)
CO2Me
(31)
CO2Me
O
(32)

**Scheme 8**

Molander *et al.* have reported on the dianionic [4 + 3] annulation reaction of 1,4-dicarbonyl compounds with 3-iodo-2-[(trimethylsilyl)methyl]propene (**4a**; X = I, Y = $CH_2SiMe_3$) promoted by tin(II) fluoride.[39] The extraordinary efficiency of this novel stereoselective seven-membered ring forming process, coupled with the simplicity of the procedure, promises to provide an expedient route to innumerable cyclic organic molecules (Scheme 9).

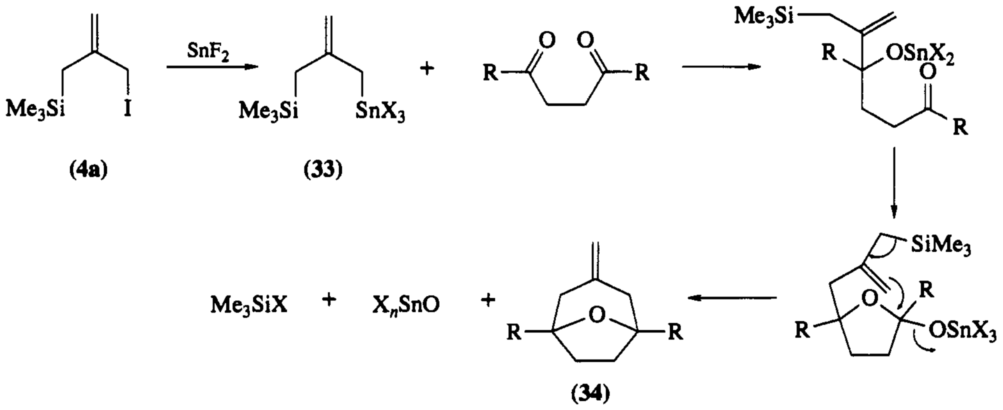
Me3Si
I
(4a)
SnF2
Me3Si
SnX3
(33)
+
O O
R R
Me3Si
R OSnX2
O
R
SiMe3
R
O
R
OSnX3
R O R
(34)
Me3SiX + XnSnO +

**Scheme 9**

### 5.1.2.3 Singlet Vinylcarbenes and Vinylcarbenoids

Cyclopropenone ketals (**35**) on thermal reaction give π-delocalized singlet vinylcarbenes (**36c**), which serve as three-carbon 1,1-/1,3-dipoles (**36a**) lacking octet stabilization that cycloadd to α-pyrones effectively.[7]

Davies *et al.* have reported that the formal [4 + 3] cycloaddition reaction of vinylcarbenoids (**38**) with furan to give (**39**) *via* (**40**) proceeds satisfactorily (Scheme 10).[40]

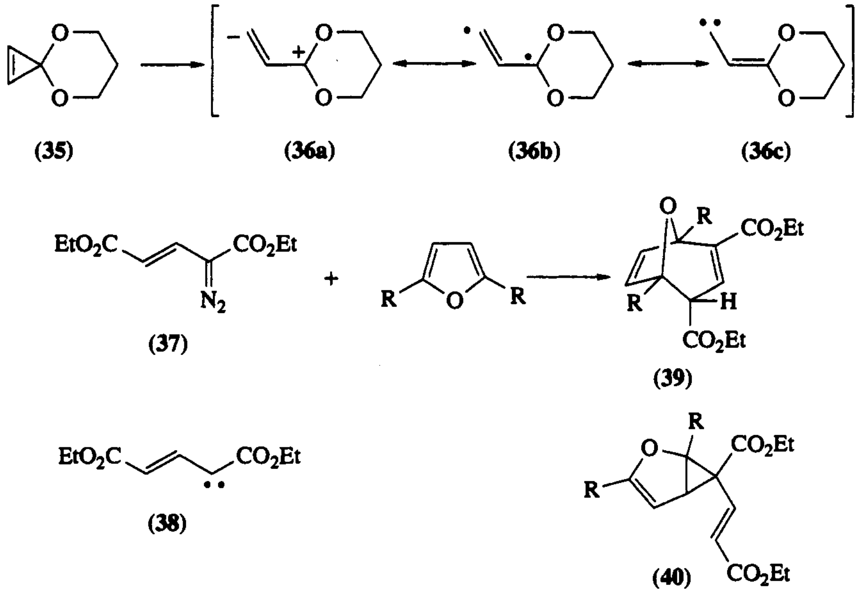
(35)
(36a)
(36b)
(36c)
EtO2C
CO2Et
N2
(37)
R
O
R
CO2Et
H
CO2Et
(39)
(38)
(40)

Scheme 10

### 5.1.2.4 Miscellaneous Methods

The dehydrogenation of bis(α-bromobenzyl) sulfide (**41**) with $Fe_2(CO)_9$ in the presence of furan affords (**43**). The iron-stabilized sulfur ylide (**42**) has been proposed as intermediate.[41] Reaction of *C,N*-diphenylnitrone (**44**) with 1,2-bis(methylene)-3,3,4,4,5,5-hexamethylcyclopentane (**45**) in benzene at 80 °C gives a [4 + 3] cycloadduct (**46**; 18%), along with some other products.[42] Landor *et al.* have shown that the dehydrobromination of allenyl bromide (**47**) in the presence of furan affords bicyclic ketone (**49**) in 9% yield.[43] Apparently, a strained alkyne intermediate reacts with *t*-butyl alcohol to afford an enol ether (**48**), which is then converted to (**49**) (Scheme 11).

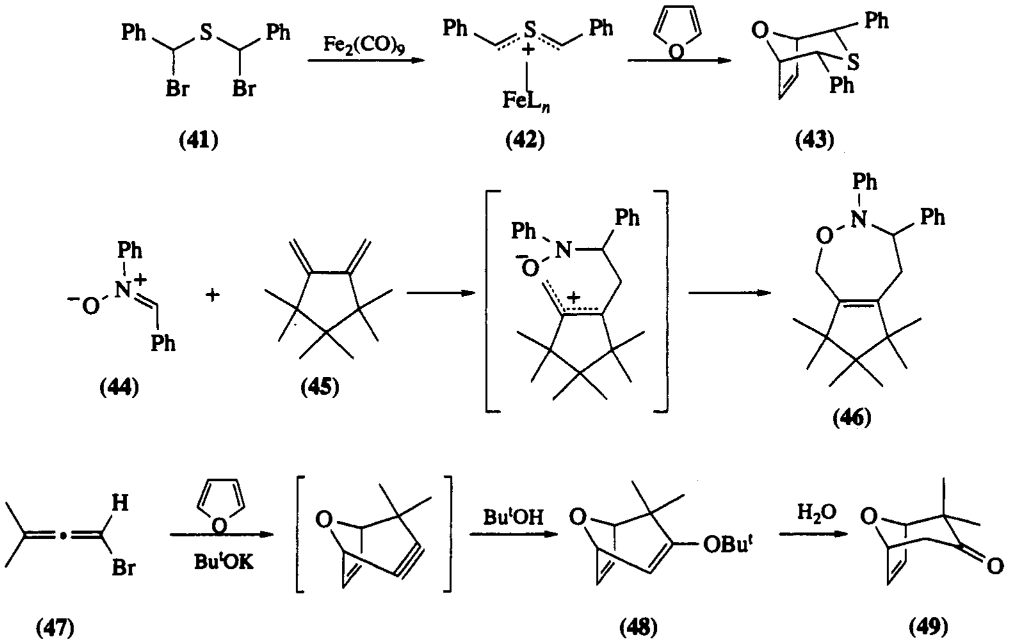
Ph
S
Ph
Br
Br
(41)
Fe2(CO)9
FeLn
(42)
O
(43)
(44)
(45)
(46)
H
Br
(47)
Bu'OK
Bu'OH
OBu'
(48)
H2O
(49)

Scheme 11

### 5.1.3 REACTIONS WITH DIENES

The β-heteroatom-substituted allylic cations shown in Section 5.1.2 serve as active three-carbon units toward 1,3-dienes to afford the corresponding seven-membered ring compounds selectively, though five-membered rings are obtained in some cases.[21,44]

[4 + 3] Annulations of allylic cation species with diene moieties are formally classified according to a mechanistic descriptor (Class A and B), where Class A is a concerted mechanism and Class B is the stepwise one as shown in Scheme 12.

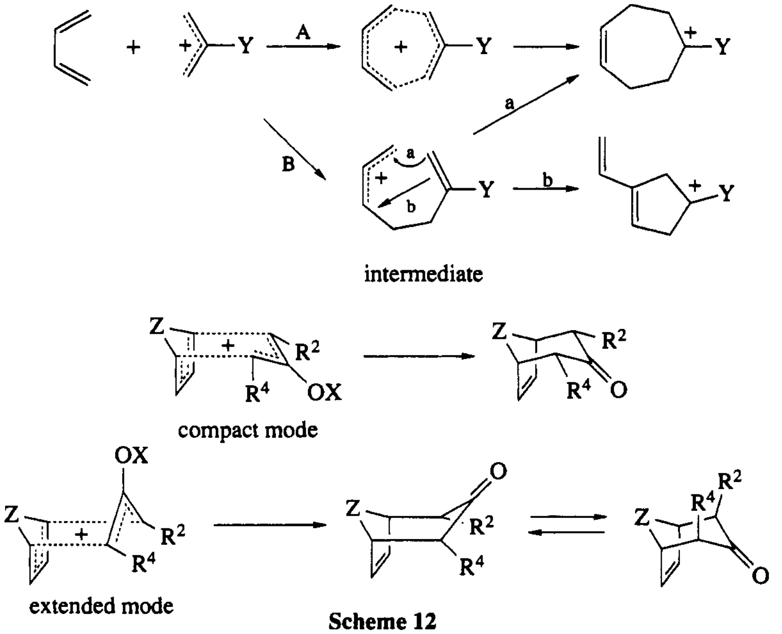

**Scheme 12**

The precise mechanism of [4 + 3] cycloadditions involving allyl cations depends upon the nucleophilicity of the dienes, the electrophilicity of the allyl cations, and the electronic property of the substituent Y on the allylic moiety. For example, the cycloaddition of 2-oxyallyliron(II) cation species (7), generated from a dibromo ketone and iron carbonyl, with 1,3-dienes is classified as a [4π (4C) + 2π (3C)] process.[44] This cationic cycloaddition, which is symmetry allowed, proceeds in a concerted manner *via* the cyclic transition state, and the regioselectivity should be controlled by frontier molecular orbitals (FMOs) of the cycloaddends. Indeed, the experimental findings by Noyori *et al.* are not consistent with the stepwise mechanism *via* zwitterions but agree with the concerted process that occur *via* a cyclic transition state (Class A).[45] Thus the reaction of 1-phenyl-2-oxyallyl (**7d**) with 3-methylfuran generates a mixture of (**50**)–(**53**), in which the ratio of both (**50a**)/(**51a**) and (**52a**)/(**53a**) is 56:44. Similarly, the addition of (**7d**) and ethyl 3-furoate leads to a 55:45 mixture of (**50b**)/(**51b**). The observed regioselectivity is best accounted for by considering the primary interaction between the FMOs of each cycloaddend, namely the LUMO of the electron-accepting oxyallyl and the HOMO of the electron-donating furan substrates. Thus the transition state formed through dominant interaction between the termini with the larger MO coefficient (primary MO interaction) results in the production of the major isomer. Interesting is the behavior displayed by 2-furoates that have comparable MO coefficients at the two reaction sites, C-2 and C-5. The trend toward the production of the major regioisomer (**54**) is far greater than that expected from the degree of MO inclination. This bias is presumably due to the presence of secondary MO interactions between the substituents of each cycloaddend in the transition state. There exists only a narrow energy gap between the FMOs of the cationic oxyallyl and furans. Therefore the two cycloaddends can achieve pericyclic interaction even at a long distance. Consequently, such secondary MO interactions become much more significant than in the ordinary nonpolar [4π (4C) + 2π (C2)] process (Scheme 13).[1]

The unsymmetrically substituted oxyallyl intermediates (**7i**) and (**7j**), generated from the corresponding dibromo ketones, are trapped by styrene to give a regioisomeric mixture of 3-phenylcyclopentanones (**56a,b**) and (**57a,b**), respectively.[46] The results are summarized in Scheme 14.

Apparently the preferred orientation in the cationic [3 + 2] cycloaddition is the one that realizes the maximum stabilization within the zwitterionic intermediates (Class B, route b). The same trend has been observed in the reaction that employs enamines.[47]

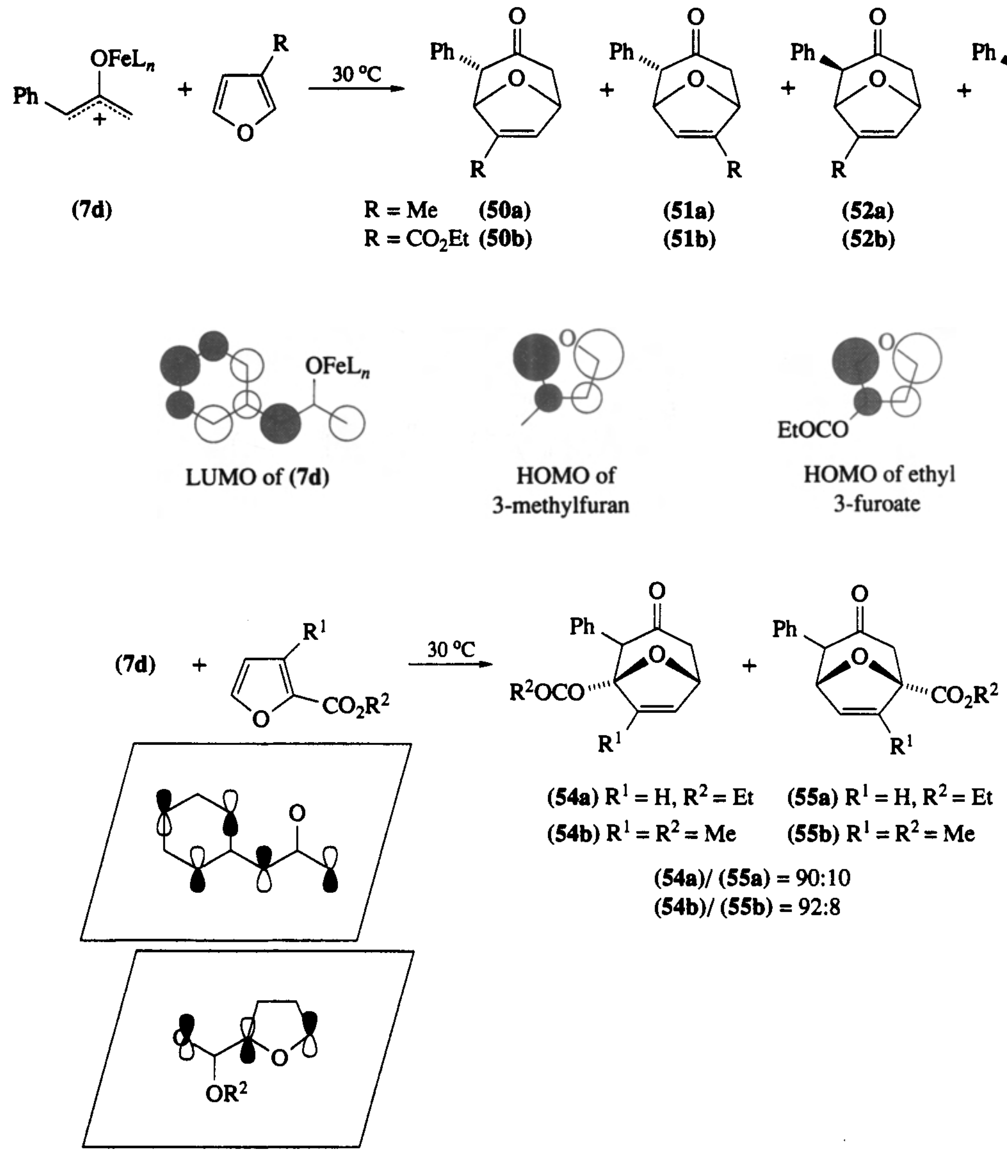
OFeLn
Ph
R
30 °C
O
(7d)
R = Me (50a)
R = CO2Et (50b)
(51a)
(51b)
(52a)
(52b)
(53a)
(53b)
LUMO of (7d)
HOMO of 3-methylfuran
EtOCO
HOMO of ethyl 3-furoate
R1
CO2R2
R2OCO
OR2
(54a) R1 = H, R2 = Et
(54b) R1 = R2 = Me
(55a) R1 = H, R2 = Et
(55b) R1 = R2 = Me
(54a)/ (55a) = 90:10
(54b)/ (55b) = 92:8

**Scheme 13**

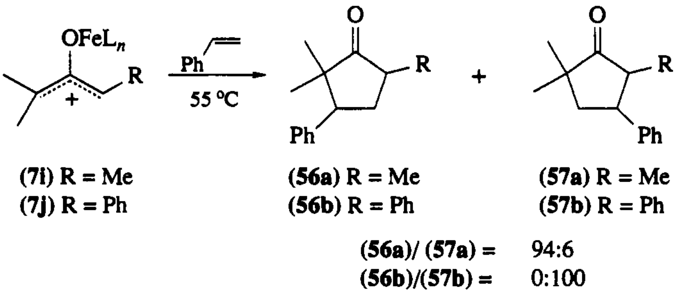
OFeLn
R
Ph
55 °C
O
(7i) R = Me
(7j) R = Ph
(56a) R = Me
(56b) R = Ph
(57a) R = Me
(57b) R = Ph
(56a)/ (57a) = 94:6
(56b)/(57b) = 0:100

**Scheme 14**

Since mechanistic considerations in these areas have been discussed in detail by Hoffmann,[4] a variety of regio- and stereo-selective [4 + 3] cycloaddition and cyclization reactions are described in this section.

### 5.1.3.1 Open-chain 1,3-Dienes

Oxyallyl cations give cycloadducts (**58**) in the presence of a variety of open-chain 1,3-dienes in generally good yields, provided that the diene exists primarily in an *s-cis* conformation. Noyori and his coworkers found that the reaction of α,α′-dibromo ketones and $Fe_2(CO)_9$ in the presence of 1,3-dienes afforded the corresponding 4-cycloheptenones in moderate to good yield.[47] This simple one-step procedure reveals wide applicability for the regioselective synthesis of seven-membered ketones in preparative scale experiments. Although reactions of 1,3-dienes with α,α′-dibromoacetone fail to give cycloheptenone adducts, unlike dibromides that possess long alkyl side chains, condensation with tetrabromoacetone proceeds smoothly.[48] Thus the iron carbonyl-promoted reaction of polybromoacetone and 1,3-dienes, followed by zinc–copper reduction, formally corresponds to [4 + 3] cyclocoupling of dibromoacetone to dienes.[48] This modification has wide applicability and can also be used for reactions involving other methyl ketone polybromides. Thus 2-oxyallyls with various kinds of substitution patterns can be obtained in a formal sense. Additionally, tetrasubstituted dibromo ketones and disubstituted dibromo ketones such as 2,4-dibromopentan-3-one (**9f**) and 3,5-dibromo-2,6-dimethylheptan-4-one (**9c**) can be employed. A variety of 1,3-dienes, including 1,3-butadiene, isoprene and 2,3-dimethyl-1,3-butadiene, can serve as open-chain 1,3-dienes.

Since the present [4 + 3] → 7 reaction can be regarded as a concerted [4π + 2π] cycloaddition, it is expected that dienes having high equilibrium concentrations of the *s-cis* conformer should serve as efficient acceptors of the reactive three-carbon unit. As expected, 1,2-dimethylenecyclohexane is recognized to be one of the most effective dienes.[22,48] It should be further noted that the use of diene–iron carbonyl complexes in place of the free dienes results in remarkable increases in the yields of cycloadducts, presumably owing to fixing the *s-cis* conformation within the diene.[48]

Compound (**4c**; X = Cl, Y = $OSiMe_3$) reacted with isoprene to give a mixture of karahanaenone (**59**) and its regioisomer (**60**), irrespective of the reaction conditions.[21] The regioselectivity is slightly higher in THF-ether or benzene than in nitromethane. 2-Siloxyallyl cation (**5c**), generated from 2-siloxyallyl bromide (**4c**; X = Br, Y = $OSiMe_3$) with the aid of zinc chloride in dichloromethane, adds to isoprene regioselectively to give karahanaenone (**59**) and its regioisomer (**60**) in a ratio of *ca.* 2:1.[22] With *p*-methylstyrene the aromatic sesquiterpene α-cuparenone is obtained. These results strongly suggest that the reaction proceeds in a stepwise manner in rather nonpolar solvent systems. These two monoterpenoids may also be obtained from the appropriate α,α′-dihalo ketone and zinc–copper[49] or zinc dust–triethyl borate.[9]

Compound (**13a**) also reacts with butadiene in the presence of $SnCl_4$ to give 2-hydroxy-4-cycloheptenone (**61**) directly (Scheme 15).[23]

### 5.1.3.2 Cyclic 1,3-Dienes

#### *5.1.3.2.1 Cyclopentadienes and related compounds*

Cyclopentadiene gives rise to bicyclo[3.2.1]oct-6-en-3-ones (**62**) upon reaction with 2-oxyallyl cations (**7**) in generally high yields. The adducts are important precursors to natural products, as discussed in a later section. The 2,4-disubstituted products (**64a,b**), obtained stereoselectively *via* the extended and compact mode, respectively, are usually a mixture of two *cis* isomers except for the diphenyl adduct.[3] A similar conformational change can be seen for cycloadducts involving oxyallyl cation (**7f**) from 2,4-dibromopentan-3-one (**9f**; X = Br) and cyclohexa-1,3-diene. A tricyclic ketone (**63**) is obtained by a reaction using 2,5-dibromocyclopentanone (**91**; X = Br).[50] Tri- and tetra-bromo ketones (**9n**) and (**9o**) also react with cyclopentadiene with the assistance of $Fe(CO)_5$ in benzene or THF–benzene.[48a,e,51] The extra bromine atoms in the resulting cycloadducts are quantitatively removed by treatment with zinc–copper couple in ammonium chloride-saturated methanol.[48,52] In this case, less satisfactory results are obtained with $Fe_2(CO)_9$ or zinc–copper couple–triethyl borate. Compound (**4c**) also reacts with 1,3-cyclopentadiene to give a cyclized product (**66**), which is the key intermediate for the synthesis of camphenic acid (Scheme 16). Iron carbonyl-promoted reactions of α,α′-dibromo ketone (**9**) with various substrates, including alkenes, enamines and 1,3-dienes have been reviewed in detail by Noyori.[5]

Hoffman *et al.* have reported that reaction of the 2-methylallyl cation with cyclopentadiene affords seven-membered ring products.[32]

Cycloadditions of cyclopentadienones (**67a–d**) with (**9f**) and (**9k**) in the presence of $Fe_2(CO)_9$ in dry benzene has given the corresponding [4 + 3] cycloadducts (**68a–d**) and (**69a–d**) in moderate yields.[53]

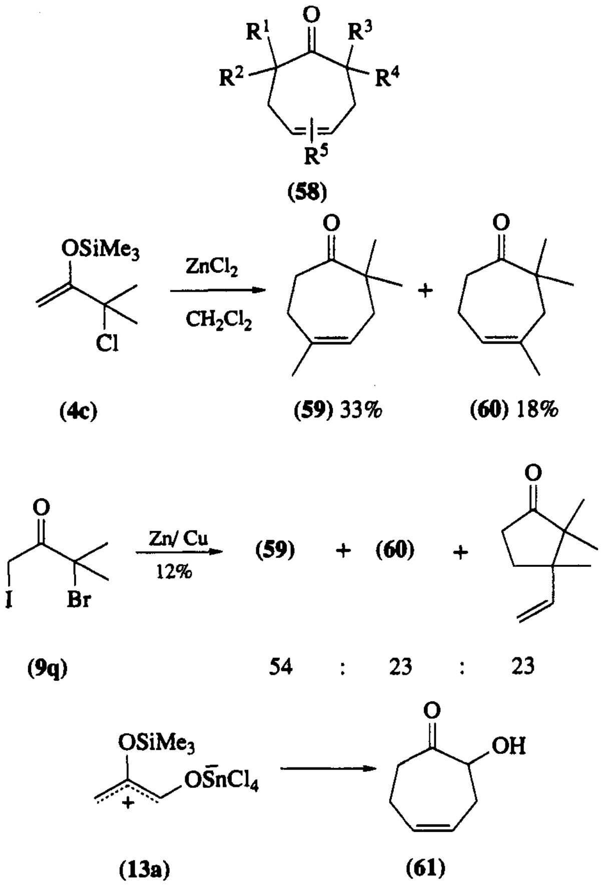

Scheme 15

However, a similar cycloaddition reaction of (**9f**) with tetraphenylcyclopentadienone (**67e**) did not take place even under more drastic conditions, presumably owing to the steric hindrance of the phenyl groups at the 2,5-positions in the cyclopentadienone moiety. Adducts (**68**) and (**69**) probably arise *via* a half-boat conformation.[53] The rate constants of these reactions are second order and reveal low sensitivity to the ionizing power of the reaction medium, suggesting that a concerted mechanism may be involved. Fulvenes also enter into cyclocoupling with dibromo ketones (**9f**) aided by copper–sodium iodide in acetonitrile,[52] zinc–copper couple in DME,[8b] or sodium iodide in acetonitrile,[52] giving 8-alkylidenebicyclo[3.2.1]oct-6-en-3-ones (**70**) (Scheme 17). Reactions with 6,6-dialkylfulvenes generally give good results, though hetero substituents at the C-6 position depress the yields. 6-(Dimethylamino)fulvene acts as a 6π component, giving a different type of cyclic adduct (**71**) in the presence of $Fe_2(CO)_9$.[53]

### *5.1.3.2.2 Cyclohexadiene and other cyclic dienes*

Diels–Alder reactions of 2-pyrone with various dienophiles are well known to give the corresponding [4 + 2] cycloadducts in good yields.[1,54] Although the reaction of allyl cations with 2-pyrones has not, to our knowledge, been reported, Boger *et al.* have recently described the reaction of delocalized singlet vinylcarbenes with 2-pyrones to give [4 + 3] cycloaddition products.[7] Vinylcarbene species (**36**) acts as a 2π component in [4π (4C) + 2π (3C)] cycloadditions with selected dienes, suitable for the preparation of functionalized cycloheptadienes that are capable of further elaboration to tropones (**73**).[7b] This reaction has been applied to the formal total synthesis of colchicine (**74**) (Scheme 18).

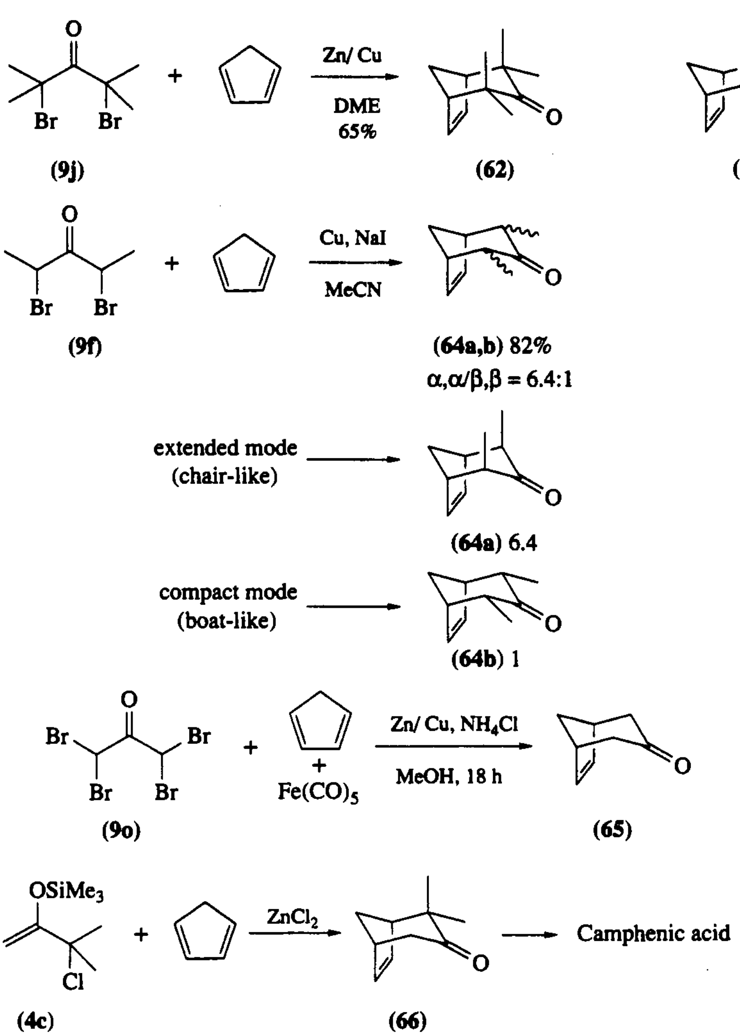

O
Br Br
(9j)
+
Zn/ Cu
DME
65%
(62)
O
(63)
O
Br Br
(9f)
Cu, NaI
MeCN
(64a,b) 82%
α,α/β,β = 6.4:1
extended mode
(chair-like)
(64a) 6.4
compact mode
(boat-like)
(64b) 1
Br Br
Br Br
(9o)
Fe(CO)5
Zn/ Cu, NH4Cl
MeOH, 18 h
(65)
OSiMe3
Cl
(4c)
ZnCl2
(66)
Camphenic acid

**Scheme 16**

### 5.1.3.3 Heterocycles

#### *5.1.3.3.1 Furans*

Cycloaddition reactions of allylic cations with furans (**76**) have been extensively studied for the preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**75**), which have served widely as starting materials for the synthesis of a number of natural products and their congeners such as thromboxane $A_2$[55] and $B_2$[56] analogues, *C*-nucleosides,[57] muscarine analogues,[58] pyrrolizidine alkaloids,[59] and troponoids,[49e,60] as well as theoretically interesting molecules (Scheme 19).[60a,b,61]

For the cyclocouplings of open-chain dibromo or polybromo ketones and cyclic bromo ketones with furans, iron carbonyls and zinc–copper couple are the most widely used reducing agents to afford the corresponding adducts, generally in fair to high yields and significantly high stereoselectivity. Thus (**75**) can be prepared by reductive cyclocoupling of dibromo or polybromo ketones with furan or its alkyl, alkoxycarbonyl or halogeno derivatives. For example, the stereochemical outcome in the reaction of (**9f**) with furan was 48:10:0 for the α,α/β,β/α,β-isomers of (**75d**).[62] Cyclic dibromides undergo somewhat erratic transformation accompanied by α-substitution reactions to give 2-substituted furans. Reactions using α,α′-dibromomethyl alkyl ketones are generally efficient. When cyclocoupling reactions of 1,3-dibromo-1-phenylpropan-2-one (**9d**; X = Br) with substituted furans are promoted by $Fe_2(CO)_9$ and zinc–copper couple, regioisomeric mixtures of [4 + 3] adducts are obtained (Scheme 19).[5,46,63] The

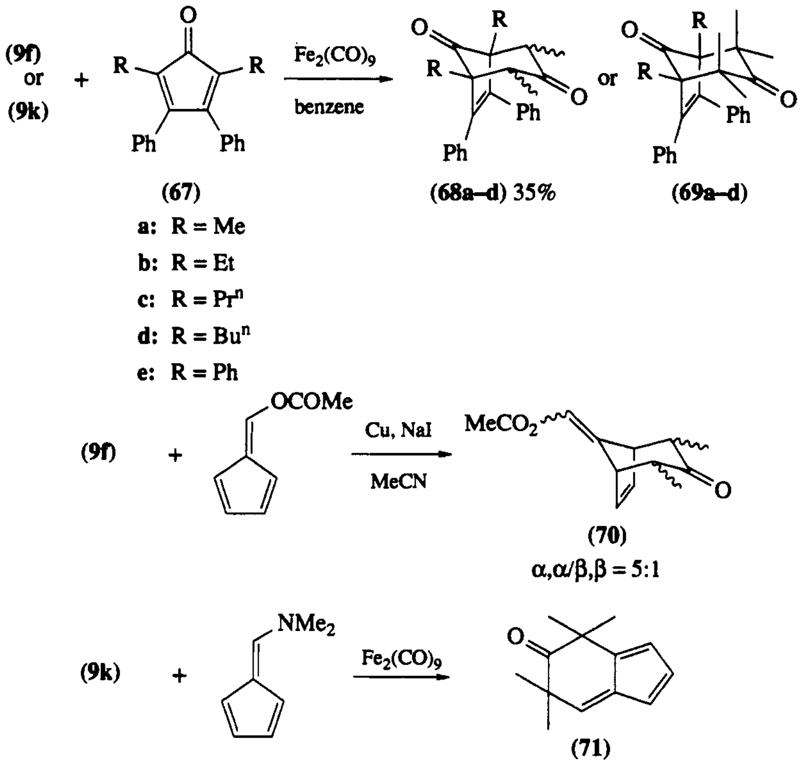

Scheme 17

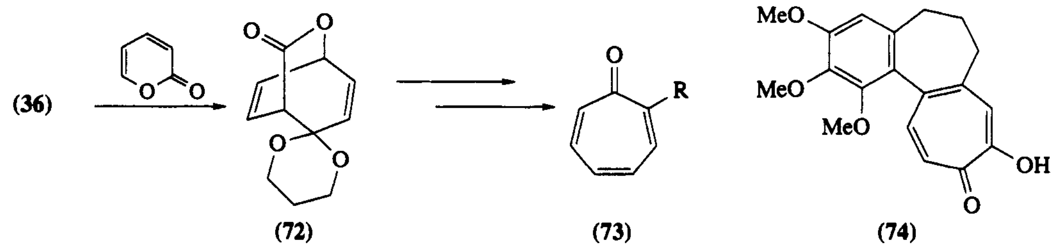

Scheme 18

regioselectivity, which is moderately good, is controlled by the FMOs of the intermediary oxyallyl species (LUMOs) and furan (HOMOs) (see Section 5.1.3).[45]

It has been recently reported that 2-(trimethylsiloxy)acrolein (**12a**; R = H), but not the less electrophilic (**12b**; R = Me), can serve as a 1-hydroxy-2-oxidoallyl synthon (**13**) in the presence of an equimolar amount of $SnCl_4$.[23] Interestingly, furan affords only the *exo* adduct (**77**). This stereoselectivity can be explained by postulating that the cycloaddition belongs to Class B, the formation of the second σ-bond being late or product-like and assisted by chelation to oxygen.

2-(Trimethylsiloxy)allyl cations (**5**; Y = $OSiMe_3$), generated from the corresponding siloxyallyl chlorides (**4**; X = Cl, Y = $OSiMe_3$) and silver perchlorate, smoothly react with furan and cyclopentadiene in nitromethane to give [4 + 3] cycloadducts in good yields.[21] The cycloaddition with furan proceeds in a stereospecific manner with retention of the allyl cation configuration, in accord with the concerted mechanism (Class A). In contrast, the reactions in THF–ether are nonstereospecific and the yields strongly dependent upon the structure of the allyl cation (**5**; Y = $OSiMe_3$) because of competition with electrophilic substitution. The reaction of (**4c**; Y = $OSiMe_3$, X = Cl) with 2-methylfuran proceeds in a highly regioselective manner in THF–ether, giving (**78a**) overwhelmingly, compared with nitromethane where two regioisomers (**78a**) and (**78b**) are formed in comparable amounts. The findings in THF–ether are reasonably explained by a stepwise mechanism (Class B, route a) (Scheme 20).

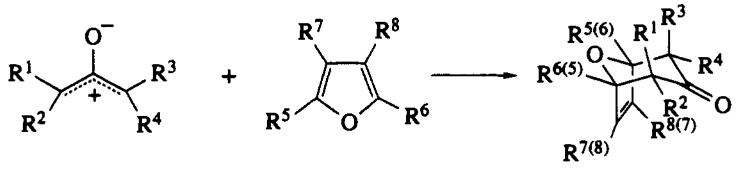
O⁻
R1
R3
R2
R4
+
R7
R8
R5
O
R6
R5(6)
R1
R3
O
R6(5)
R4
R2
O
R8(7)
R7(8)

**(5)** or **(7)** **(76)** **(75)**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | $R^7$ | $R^8$ |
|---|---|---|---|---|---|---|---|---|
| **75a:** | H | H | H | H | H | H | H | H |
| **b:** | H | H | Me | Me | H | H | H | H |
| **c:** | H | H | Me | Me | H | Me | H | H |
| **d:** | H | Me | Me | H | H | H | H | H |
| **e:** | H | Me | Me | H | 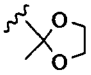 | H | H | H |
| **f:** | H | $Pr^i$ | H | H | H | H | H | H |
| **g:** | H | H | H | H | H | $Pr^i$ | H | H |
| **h:** | H | H | H | H | H | H | $Pr^i$ | H |
| **i:** | H | H | Cl | Cl | Cl | H | H | H |

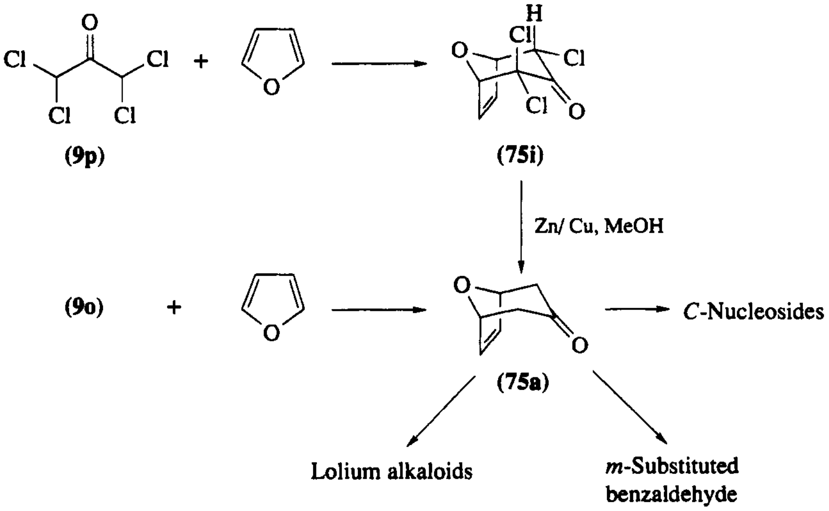
O
Cl
Cl
Cl
Cl
+
O
H
Cl
O
Cl
Cl
O
Zn/ Cu, MeOH
+
O
O
O
C-Nucleosides
Lolium alkaloids
m-Substituted
benzaldehyde

**(9p)** **(75i)** **(9o)** **(75a)**

**Scheme 19**

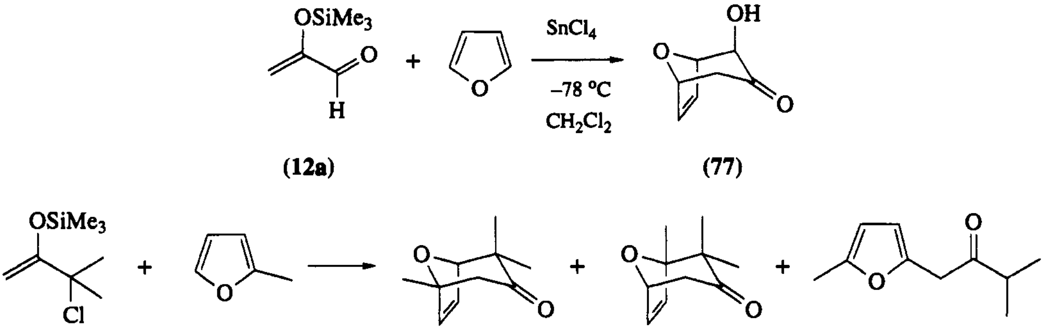
OSiMe3
O
H
+
O
SnCl4
−78 °C
CH2Cl2
OH
O
O
OSiMe3
Cl
+
O
O
O
+
O
O
+
O
O

**(12a)** **(77)**

**(4c)** **(78a)** **(78b)** **(79)**

**Scheme 20**

### *5.1.3.3.2 Pyrroles*

Pyrrole and its *N*-alkyl derivatives can be employed as diene components for the copper–sodium iodide promoted [4 + 3] cyclocoupling reaction of open-chain dibromo ketones.[8b,64] Reactions with cyclic dibromo ketones such as 2,6-dibromocyclohexanone (**9m**; X = Br) afford only substitution products. Treatment of both acyclic and cyclic dibromo ketones with zinc or iron carbonyls only results in substitution.[49c,e,64] In contrast, pyrrole derivatives bearing an electron-withdrawing substituent such as acetyl or methoxycarbonyl on the nitrogen atom undergo the cyclocoupling reaction with di- or more highly brominated ketones (**9**; X = Br).[65] As a reducing agent, $Fe_2(CO)_9$ is used since $Fe(CO)_5$ or zinc–copper couple give less satisfactory results in these cases. Attempts to use copper–sodium iodide were unsuccessful (Scheme 21). Allenoxide also reacts with *N*-methylpyrrole to give the corresponding seven-membered adducts.[31]

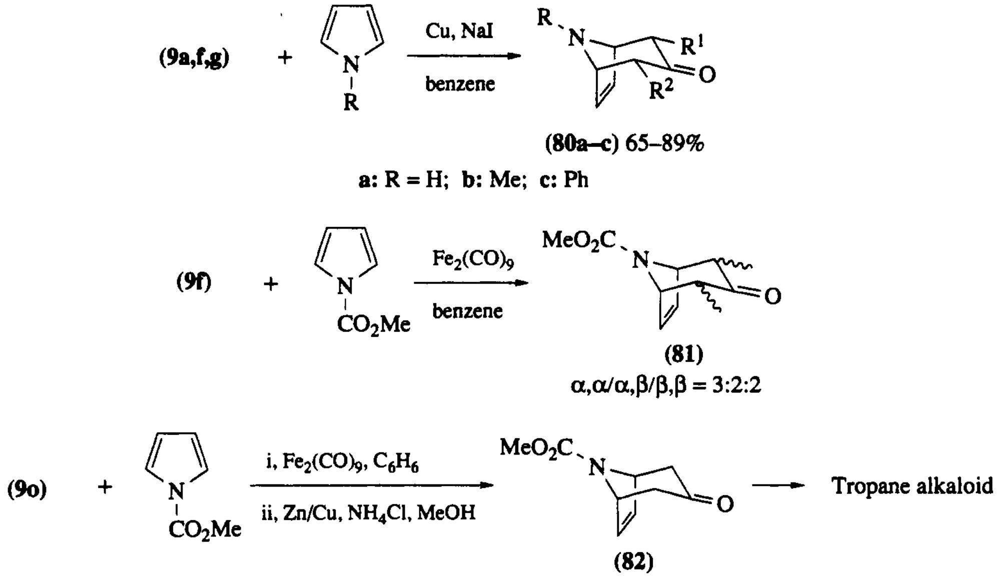

**Scheme 21**

### 5.1.3.4 Arenes

Oxyallyl, alkoxyallyl, siloxyallyl, aminoallyl and alkylallyl cations react with arenes to give cycloadducts (**83**)–(**87**). Methoxyallyl bromide (**4a**) reacts with benzene in the presence of $CF_3COOAg$ to give bicyclo[3.2.2]nona-6,8-dien-3-one (**83**), though the yield is not always good.[24a] The reactive species obtained from (**4c**) is captured by naphthalene to give a small amount of 1,4-addition product (**84**) together with a substitution product.[21] The reduction of α,α′-dibromo ketones (**9**; X = Br) with zinc–copper couple in dioxane containing anthracene affords 6,7,8,9-dibenzobicyclo[3.2.2]nonan-3-one (**85**) in 3–25% yields.[66] However, the addition of chlorotrimethylsilane to the system along with a solvent change to benzene results in substantially increased yields of (**85**) (71–97%).[66] Schmid *et al.* have shown that in the presence of $AgBF_4$ and naphthalene, cyclic α-chloroenamine (**4g**; X = Cl, Y = pyrrolidino) affords (**86**) and (**87**), in 24 and 0.4% yields, respectively (Scheme 22).[26a]

## 5.1.4 SYNTHETIC APPLICATIONS

There now exist many procedures for the generation of allyl cations, and various reactions of these with 1,3-dienes are known. The products have been conveniently applied as precursors in synthesis of important naturally occurring products, inaccessible by other methods.[4–6]

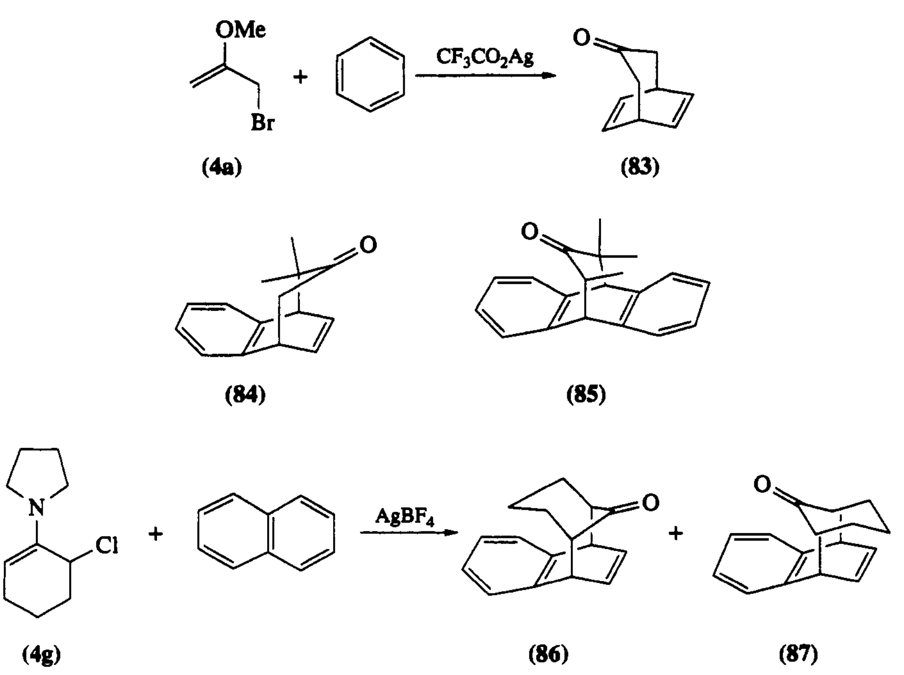

Scheme 22

### 5.1.4.1 Intramolecular Cyclization

Despite the copious literature dealing with bimolecular [4 + 3] cycloaddition reactions, intramolecular reactions are not plentiful. Probably the most attractive feature of the internal cycloaddition is the opportunity to control the stereochemistry of the products at several centers. Polybromo ketones bearing a functional group are extremely important substrates for the synthesis of novel seven-membered fused-ring compounds. The first example of such a process was reported for the synthesis of **(89)** from **(88)** by Paquette *et al.* in 1973,[67] though they did not isolate the intermediate. Noyori *et al.* have reported that the intramolecular dibromo ketone–iron carbonyl reaction permits the direct synthesis of an oxidoperhydroazulenone **(91)**, a ring system found in naturally occurring daucon.[68] Thus treatment of dibromo ketone **(90)** with $Fe_2(CO)_9$ produced **(91**; 38%). A similar conversion of **(92)** to **(93)** was carried out by Föhlisch and Herter.[69] Hoffmann *et al.* have also reported an intramolecular variant to generate **(95)** and **(96)** by starting from **(94)** (Scheme 23).[70]

### 5.1.4.2 Troponoid Compounds

2,7-Dialkylated 4-cycloheptenones such as **(58)** are utilized as key intermediates in the preparation of various kinds of troponoid compounds, including 2,7-dialkylated tropones **(97)**,[49a,60c] γ-tropolones **(98)** and 4,5-homotropones **(99)**,[49a,60c] which exist as hydrohomotropylium ions **(100)** in concentrated sulfuric acid.[60,61]

8-Oxabicyclo[3.2.1]oct-6-en-3-ones **(75)** are also readily transformed to tropones **(97)** or γ-tropolones **(98)** in a few steps. The tricyclic adduct (**75**; R = $(CH_2)_9$) can be readily converted to troponophane **(101)**. Successful use of tetrabromoacetone and tribromo derivatives of methyl alkyl ketones in these reactions opens a new route to various naturally occurring troponoid compounds, *viz.* nezukone **(102)**,[60b,c] α-thujaplicin **(103)**[49d,60] and hinokitiol (β-thujaplicin) **(104)**,[49d,60c] respectively (Scheme 24).

### 5.1.4.3 Tropane Alkaloids

The synthesis of a variety of tropane alkaloids has been achieved *via* 6,7-dehydrotropines **(105)**, derived from **(82)** by stereoselective reduction with diisobutylaluminum hydride. Subsequent appropriate modification of the double bond leads to several naturally occurring tropane alkaloids, including tropine **(106)**, scopine **(107)**, tropanediol **(108)** and teloidine **(109)** (Scheme 25).[49,64]

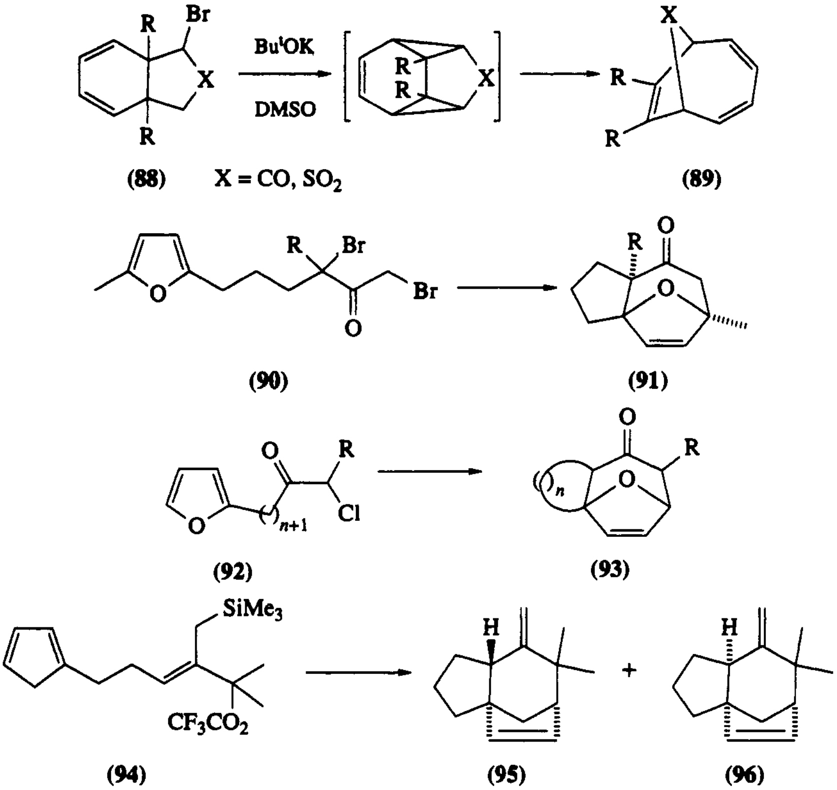
Bu$^t$OK
DMSO
X = CO, SO$_2$
(88)
(89)
(90)
(91)
(92)
(93)
(94)
(95)
(96)

**Scheme 23**

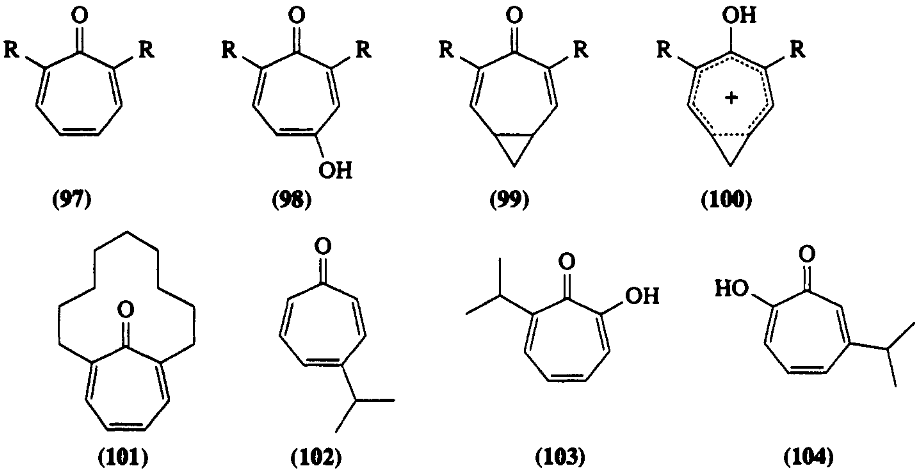
(97)
(98)
(99)
(100)
(101)
(102)
(103)
(104)

**Scheme 24**

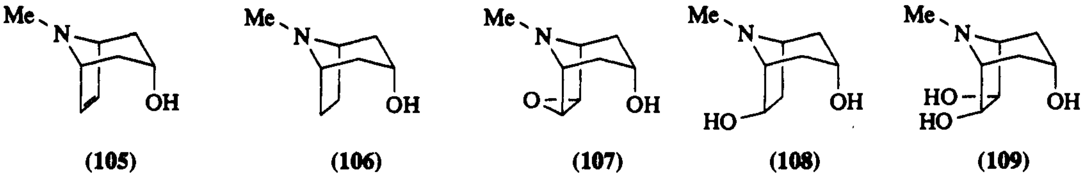
(105)
(106)
(107)
(108)
(109)

**Scheme 25**

### 5.1.4.4 *C*-Nucleosides

The oxabicyclic ketone (**75a**) is converted to (**110**) with high stereoselectivity, the methodology providing an efficient entry into *C*-nucleosides.[5b,57] The stereocontrolled synthesis of natural products such as pseudouridine (**111**), pseudocytidine (**112**) and showdomycin (**113**) has been accomplished along with a number of unnatural analogs such as pseudoisocyctidine (**114**) and 2-thiopseudouridine (**115**). Apparently the efficiency of this direct approach to *C*-nucleosides is based on the ready availability of (**75a**) from tetrabromoacetone and furan (Scheme 26).[5b]

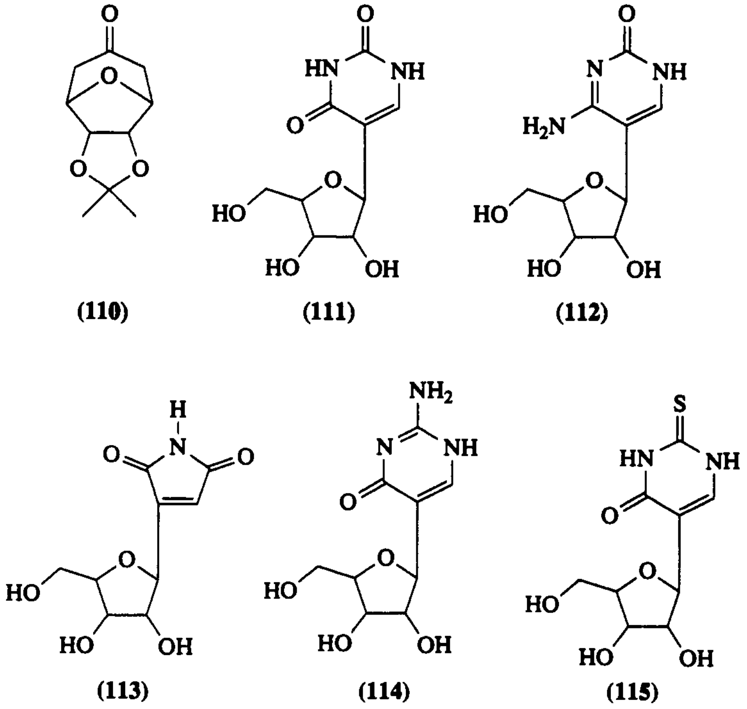

**Scheme 26**

### 5.1.4.5 Nonactic Acid, Lilac Alcohol and Prelog–Djerassi Lactone

The cycloadduct (**75d**) has been utilized for the synthesis of nonactic acid (**116**) and lilac alcohol (**119**) *via* (**118**).[71] The Prelog–Djerassi lactone (**117**), a pivotal intermediate in Masamune's methymycin synthesis, has been prepared from the key compound (**75e**) (Scheme 27).[72]

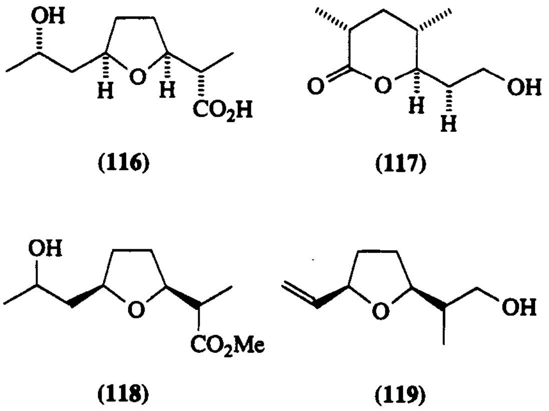

**Scheme 27**

### 5.1.4.6 Pederin

The bicyclic ketone (**75b**) has been used as a starting material for a multi-step synthesis of the ‘eastern half’ of pederin (**120**), which is the most complex, nonproteinaceous insect defensive compound known (Scheme 28).[73]

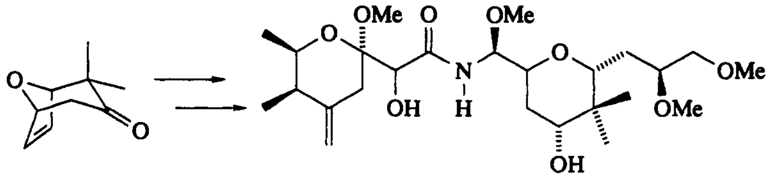

(**75b**) (**120**)

Scheme 28

### 5.1.4.7 Noncyclic Ionophore and Barbaralanes

The parent bicyclic compound (**65**), prepared from (**9o**) and cyclopentadiene, has been elaborated in only a few steps into the noncyclic ionophore (**121**), which transports $Ca^{2+}$ efficiently.[74] Its 2,4-dimethylated homolog (**64**) has been used by Wierenga *et al.* as the starting material to prepare functionalized barbaralanes (**124**) (Scheme 29).[75]

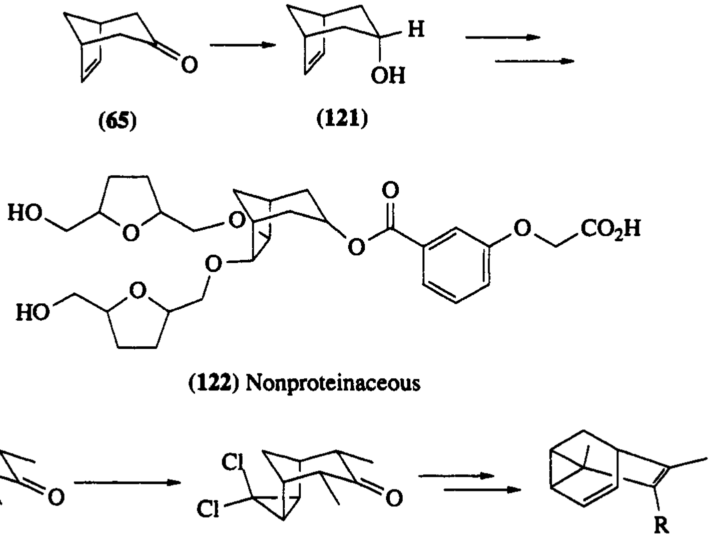

(**65**) (**121**)

(**122**) Nonproteinaceous

(**64**) (**123**) (**124**) Barbaralanes

Scheme 29

### 5.1.4.8 Thromboxane $A_2$ and $B_2$

Thromboxane families (**125**) and (**126**) were prepared from the cycloadduct (**128**) between a bromo ketone (**127**) and 2-furfural dimethyl acetal, though the yields were not good (Scheme 30).[76,77]

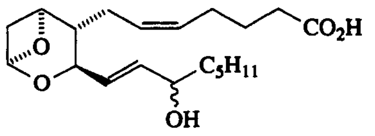

**(125)** Thromboxane $A_2$

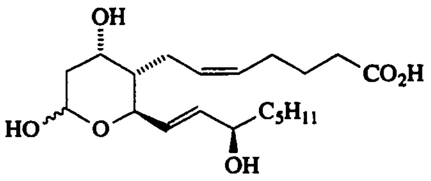

**(126)** Thromboxane $B_2$

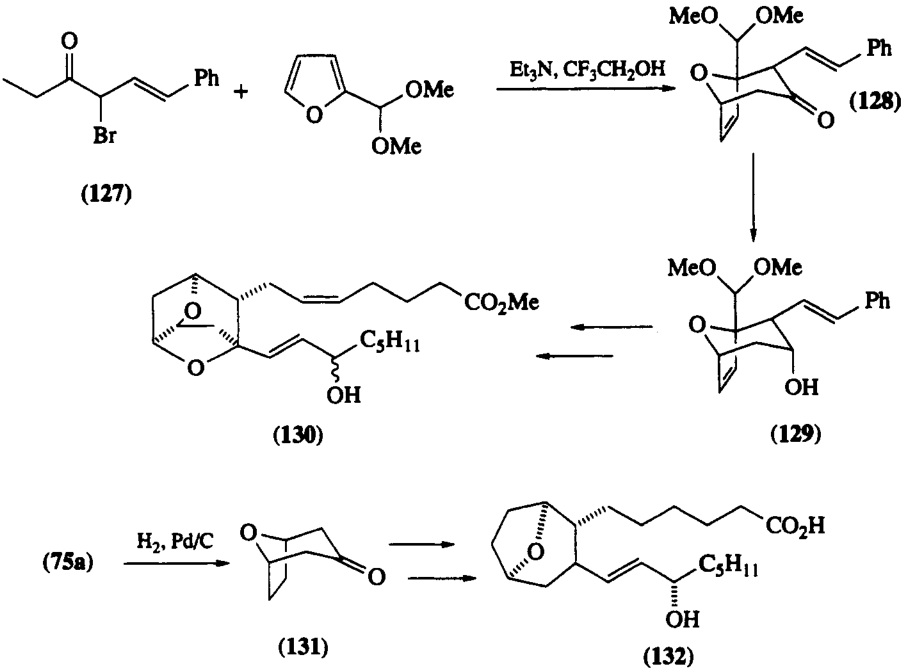

**Scheme 30**

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# 5.2

# [4 + 4] and [6 + 4] Cycloadditions

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## 5.2.1 INTRODUCTION

The potential utility of higher-order cycloaddition reactions in complex syntheses has only been recognized relatively recently. To a large extent, cycloaddition processes involving the interaction of two polyene addends have been restricted to somewhat specialized molecular systems selected for examining particular mechanistic and theoretical issues. This has been a very fruitful endeavor since the observations concerning the behavior of higher-order cycloaddition reactions have been instrumental in providing insight into the underlying principles of the cycloaddition reaction in a general sense.

Various early studies in this area have provided a sound and fundamental comprehension of the basic mechanistic tenets and limitations of the [6 + 4] and [4 + 4] cycloaddition reactions. However, the scope of this broad class of reactions has yet to be fully established, particularly within the context of preparative chemistry. A number of these reactions display qualities that are traditionally desirable in synthetically useful transformations. Typically, many examples proceed with attendant high levels of predictable stereoselectivity; furthermore, the nature of these cycloadditions is such that they are eminently suitable for rapid and efficient assembly of complex polycyclic carbon systems.

The fundamental variable that must be addressed to employ profitably either the [6 + 4] or [4 + 4] cycloaddition in a synthetic scheme is the general propensity for systems that possess extensive conjugated unsaturation to participate in multiple, competitive pericyclic reactions. The ability to control which of several thermally or photochemically allowed processes will prevail in a given situation is the principal challenge confronting successful synthetic design based on a higher-order cycloaddition reaction as the key bond-forming step. A number of interesting and effective themes for manipulating both [6 + 4] and [4 + 4] cycloaddition processes in a predictable fashion have emerged. These include the well-established technique of tying the reacting centers together to exploit the advantages of intramolecularity. A particularly powerful approach for controlling periselectivity has been to employ the templating effect of complexation to transition metals. This strategy has resulted in a number of useful advances in the synthetic application of these cycloaddition reactions and points the way for future investigations in this area.

## 5.2.2 [6 + 4] CYCLOADDITION REACTIONS

### 5.2.2.1 2,4,6-Cycloheptatrien-1-one (Tropone) as the 6π Addend

#### *5.2.2.1.1 Dienes as 4π addends*

The thermally induced [6 + 4] cycloaddition of 2,4,6-cycloheptatrien-1-one (tropone) (**1**) with a variety of diene partners has played a central role in the development of the mechanistic precepts and preparative utility of the entire class of higher-order pericyclic processes. The relatively well-defined reaction parameters for these cycloadditions render them particularly well-suited for the rapid assembly of relatively complex polycyclic carbon arrays.

Tropone (**1**) and cyclopentadiene form a single 1:1 adduct (**2**) in high yield when heated together at 80 °C.[1,2] Of particular note in this transformation is the production of the *exo* oriented adduct to the virtual exclusion of the corresponding *endo* product (**3**). This experimentally established preference for the *exo* mode of addition was one of the early triumphs of the Woodward–Hoffmann orbital symmetry rules, which correctly predicted this stereoselectivity a year earlier.[3,4]

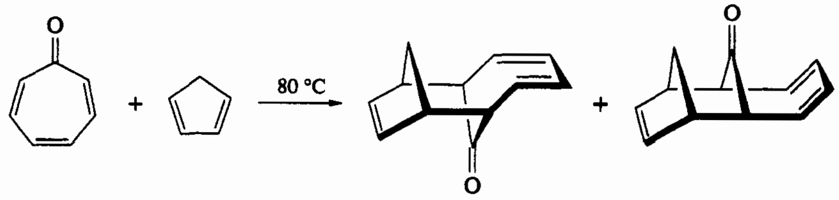

(**1**) (**2**) 100% (**3**) 0%

Numerous examples of *exo* selective cycloadditions employing a diversity of diene partners attest to the generality of this manner of combination. Isodicyclopentadiene can be added to tropone to give principally ketone (**4**)[5] and *in situ* generated 2-benzopyran-3-one provided *exo*-lactone (**5**) in 28% yield.[6] 1-Substituted butadienes have proven to be particularly useful 4π partners, which give the *exo* adducts (**6**) exclusively when reacted with tropone at moderate temperatures.[7,8] Furthermore, the intramolecular vari-

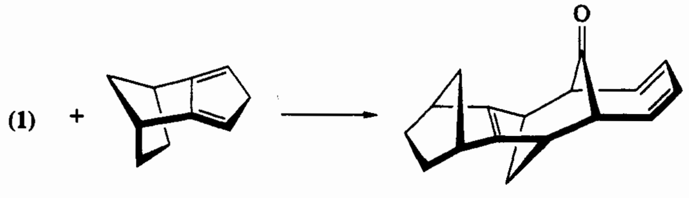

(**4**)

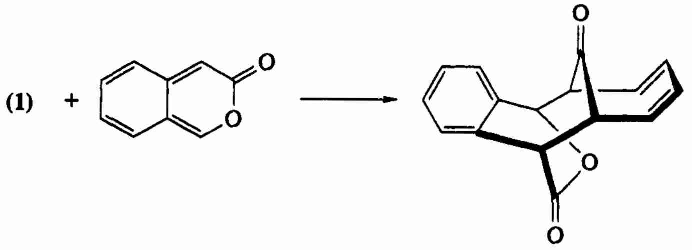

(**5**)

ant of the diene–tropone [6 + 4] cycloaddition also proceeds smoothly at temperatures between 80–110 °C to generate *exo* products (7) in high yields.[8,9]

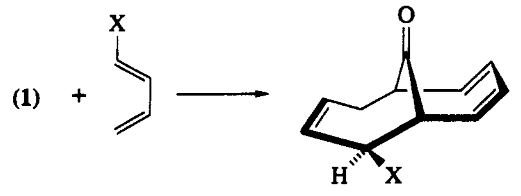

(6)

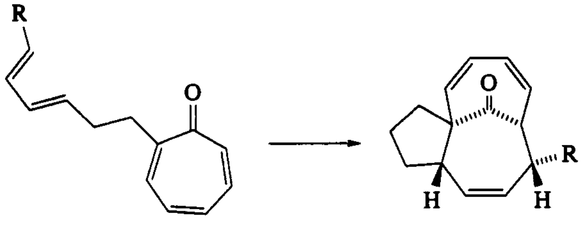

(7)

The observed stereochemical course of the [6 + 4] diene–tropone cycloaddition has been explained by consideration of the interactions of the HOMO and LUMO of the diene and triene participants, respectively. The appropriate orbital combinations for the *exo* transition state and the alternative *endo* transition state are depicted in Figure 1.[3] A repulsive secondary orbital interaction develops when the diene engages the tropone triene system in an *endo* fashion. This unfavorable situation is avoided in the *exo* transition state; hence the experimentally observed preference for production of the *exo* stereoisomer in these reactions. An intriguing recent study of the reaction of tropone and cyclopentadiene at high pressure indicated that the transition state of the cycloaddition is somewhat smaller than the final state, a result paralleling observations in certain Diels–Alder reactions in which favorable secondary orbital interactions were operative.[10] From these results it was concluded that an attractive interaction between the diene LUMO and the carbonyl portion of the tropone HOMO may be partially responsible for the high degree of *exo* stereoselectivity exhibited by these transformations. Work from other laboratories, however, has suggested only a minimal contribution by attractive secondary orbital interactions in these reactions.[11–13]

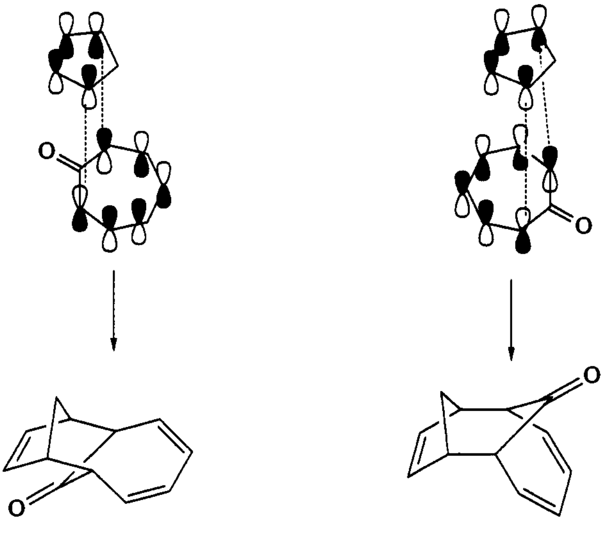

*Exo* transition state

*Endo* transition state

**Figure 1** Frontier molecular orbitals for the cycloaddition of cyclopentadiene to tropone

The relative complexity of the extended π-systems present in these reactants suggest that a variety of potentially competitive pericyclic processes could be operative in the thermal reaction of a given diene with tropone. Consequently, the question of periselectivity in these reactions has been examined in some detail in recent years and a number of useful generalizations have been enumerated for predicting products in a variety of circumstances.

From the earliest investigations it was noted that tropone in combination with a number of dienes would provide the *exo* [6 + 4] cycloadduct at relatively low reaction temperatures (≤80 °C), whereas higher temperatures and prolonged reaction times produced, in most cases, the corresponding *endo* [4 + 2] species with tropone serving as the 4π reactant and the diene participating as the 2π partner.[14,15] For example, heating tropone (**1**) and 2,5-dimethyl-3,4-diphenylcyclopentadienone together at 60 °C in THF or acetone gave a 95% yield of the *exo* [6 + 4] product (**8**). In contrast, performing the same reaction at 100 °C or higher provided only the *endo* [4 + 2] product (**9**) in high yield.[15] A qualitatively similar observation had been made with cyclopentadiene and tropone.[14] Formation of these two adducts has been attributed to the operation of concerted *exo* [6 + 4] (kinetic) and *endo* [4 + 2] (thermodynamic) pathways, respectively. A number of kinetic studies on the tropone–diene [6 + 4] cycloaddition have concluded that the reaction possesses a late transition state, which is consistent with a concerted process and mechanistically resembles the classical Diels–Alder reaction.[10–13]

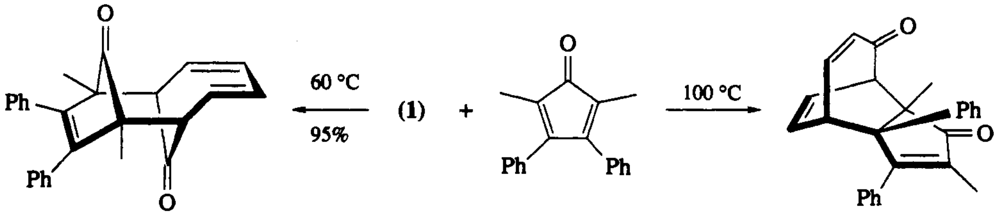

**(8)** **(9)**

The periselectivity of the reaction of a given diene with tropone is critically dependent on temperature. The variable course of the cycloaddition of (*E*)-1-trimethylsilyloxybutadiene with tropone as a function of reaction temperature is a dramatic illustration of this phenomenon. At 80 °C the major adduct is bicyclo[4.4.1]undecenone (**10**), whereas in refluxing xylene the [4 + 2] cycloadduct (**11**) prevails as a mixture of regioisomers.[7] A further example of the dichotomy between [6 + 4] and [4 + 2] reaction pathways can be seen with (*Z*)-1-acetoxybutadiene, which provides some [6 + 4] cycloadduct along with larger quantities of various [4 + 2] products as depicted in equation (1).[7] In contrast to these results, dienes such as ethyl 2,4-hexadienoate and furan do not yield any [6 + 4] or [4 + 2] products when heated with tropone.[7] The latter result, in particular, may be reflective of the reversibility of the furan cycloadducts. Various furan derivatives do provide modest yields of mixtures of *endo* and *exo* [4 + 2] cycloadducts with tropone when reacted together at 3 kbar and 130 °C.[16]

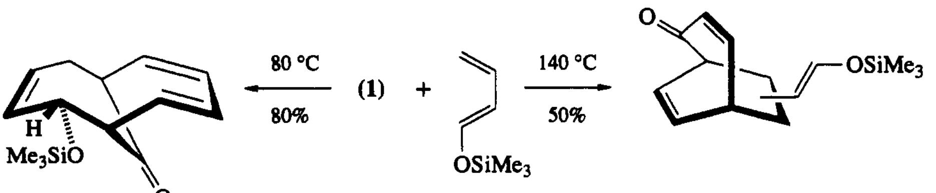

**(10)** **(11)**

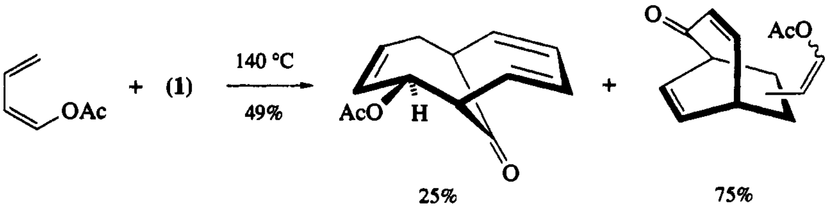

(1)

Another important generalization in these systems is that the course of cycloaddition between tropone and dienes appears to be particularly sensitive to substitution patterns in either addend. 2-Chlorotropone

**(12)**, for example, gives rise to a mixture of four 1:1 adducts when exposed to cyclopentadiene at 105 °C for 3 h. In this instance the *endo* [4 + 2] species **(14)** and **(15)** were produced in excess.[17] A further interesting observation in this particular reaction was the prevalence of the regioisomer in which bonding occurred at the troponoid carbon bearing the chlorine substituent. Diene substitution also plays a significant role in determining the course of these reactions. None of the expected [6 + 4] products were detected in the reaction of spiro[2.4]hepta-4,6-diene with tropone. Regioisomeric *endo* [4 + 2] adducts **(16)** and **(17)** were the principal materials isolated in this case.[18,19] Apparently, the steric congestion provided by the quaternary center in the diene is sufficient to suppress the [6 + 4] option. In contrast, certain highly substituted but quite reactive dienes have been reported to undergo reasonably efficient [6 + 4] cycloaddition with tropone in selected situations. The formation of adduct **(8)** from a cyclopentadienone addend is a case in point.[15,20]

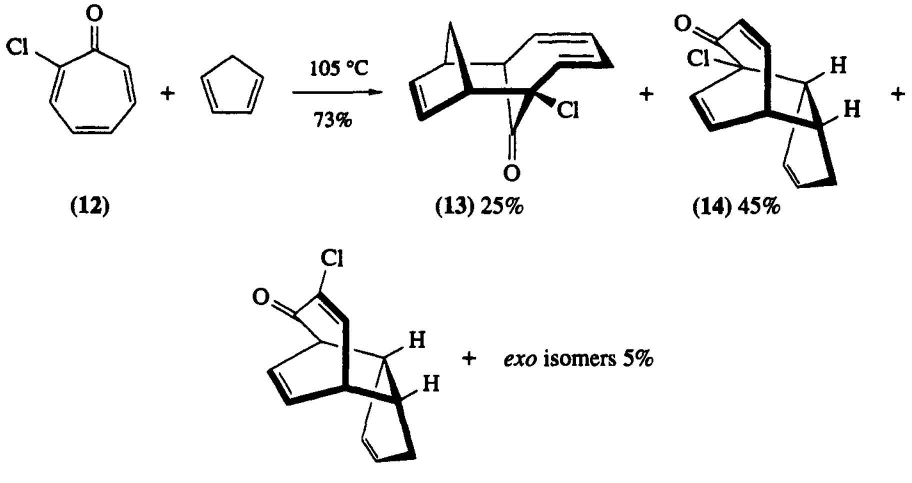

**(12)** **(13)** 25% **(14)** 45%

**(15)** 25%

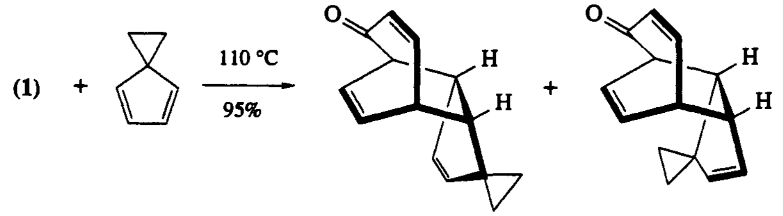

**(16)** 17% **(17)** 83%

Unsymmetrically substituted tropones wherein the substitution is remote from the actual bonding centers have also been the subject of regioselectivity studies.[21] Modest chemical yields accompanied high regioselectivities in the resultant products isolated from the addition of various dienes to 3- and 4-ethoxycarbonyltropones, **(18)** and **(21)**. So-called 'even' regioselectivity, which completely parallels the regioselectivity observed in the Diels–Alder reaction, prevailed in these cases. Lower selectivities characterized the reactions of 3- and 4-methoxytropones with the same set of electron-rich diene partners.

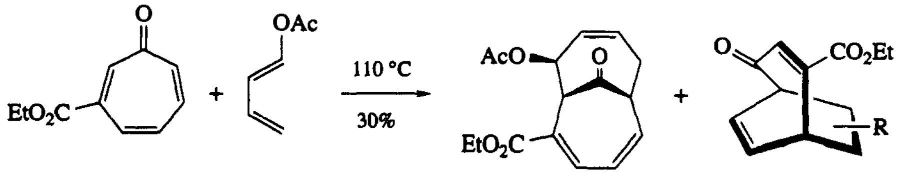

**(18)** **(19)** 67% **(20)** 33%

While the primary modes of cycloaddition between tropone and a given diene can normally be classified as following one of two distinct pathways, in which tropone serves either as the $6\pi$ or as the $4\pi$

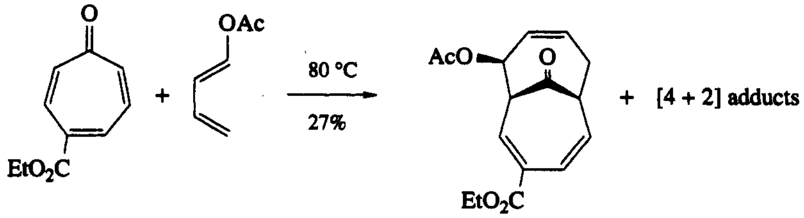

(21) (22) 81%

partner, a few cases have been reported in which other reactivities have been revealed. *o*-Xylylene has been described as giving two products, (**23**) and (**24**), when reacted with tropone (**1**) at room temperature.[22] The major product (**23**) was the normal [6 + 4] adduct. On the other hand, the minor species appeared to arise from a [2 + 4] cycloaddition process with tropone participating as the $2\pi$ component. A similar phenomenon was observed in the reaction of isobenzofuran and tropone to give (**25**)–(**27**)[23] and an [8 + 2] adduct has been observed in the reaction of 2,5-dimethyl-3,4-diphenylcyclopentadienone with tropone.[15] While mechanistically interesting, these latter examples appear to be exceptions to the dual pathways normally available to tropone in its reactions with dienes.

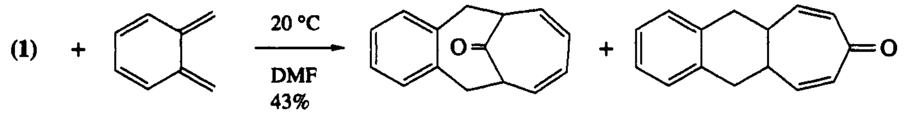

(**23**) 67% (**24**) 33%

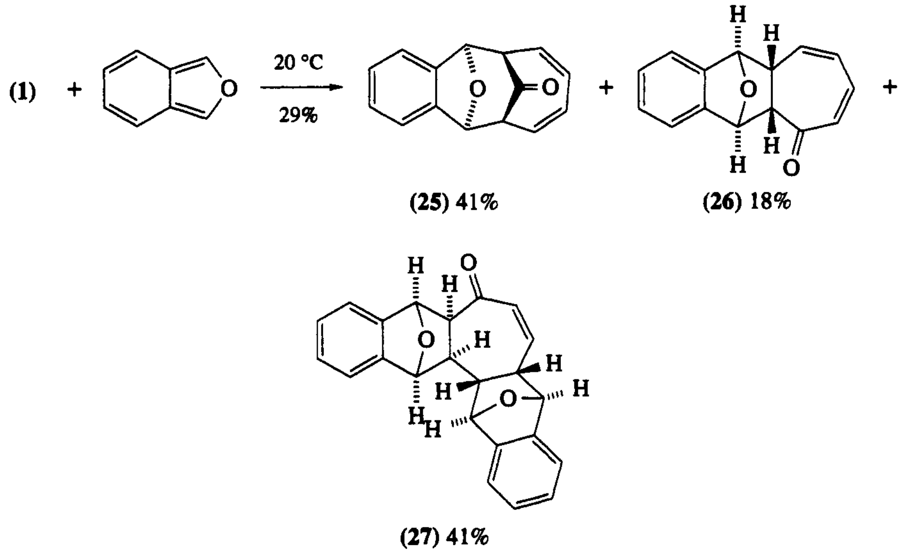

(**25**) 41% (**26**) 18%

(**27**) 41%

Although the characteristics of the thermal reaction of tropone with dienes can be accommodated by the operation of concerted *exo* [6 + 4] and *endo* [4 + 2] pathways, an alternative mechanistic scenario that would lead with equal stereoselectivity to the observed [4 + 2] and [6 + 4] products can be envisioned as depicted in Scheme 1. This pathway would involve initial [2 + 4] cycloaddition of cyclopentadiene to tropone to give dienone (**28**) followed by thermally allowed 1,5- and 3,3-sigmatropic carbon migrations which would lead to the *exo* [6 + 4] adduct (**2**) and *endo* [4 + 2] adduct (**29**), respectively. Recently a test of this scheme was conceived and executed by Franck-Newmann and Martina.[24] Cycloaddition of cyclopentadiene to tricarbonyl(tropone)iron provided access to the critical [2 + 4] intermediate (**28**) after metal decomplexation. Heating of the resultant cycloadduct at 60–75 °C led exclusively to compound (**29**) *via* a Cope rearrangement. No evidence for the production of the [6 + 4] product (**2**) in this reaction was indicated. These results suggest that ketone (**2**) probably arises directly from a concerted [6 + 4] cycloaddition. In an interesting contrast, compound (**26**) has been reported to rearrange to [6 + 4] adduct (**25**) when heated at 160–165 °C for several hours.[23]

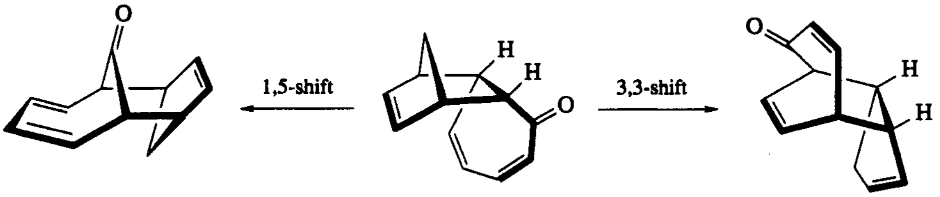

**(2)** **(28)** **(29)**

**Scheme 1**

Application of the *exo* [6 + 4] tropone–diene cycloaddition protocol to the construction of specific target molecules has begun to receive attention only recently. The high level of stereocontrol and ease of assembling polycyclic carbon frameworks afforded by this technology is particularly appealing for complex synthesis. Several members of the highly strained troponophane series have been efficiently assembled by the use of tropone–diene [6 + 4] cycloaddition.[25] Cycloadduct (**30**), derived from tropone and 1-acetoxybutadiene, can be converted into the dehydro analog of [4](2,7)troponophane (**31**) through the action of a remarkable base-mediated double bond migration[26] as depicted in Scheme 2.

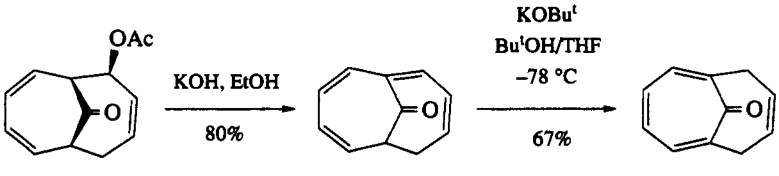

**(30)** **(31)**

**Scheme 2**

Other highly distorted troponoid species have been accessed through related [6 + 4] cycloaddition–dehydrohalogenation protocols as well. For instance, bridged troponophane (**33**) was prepared from cycloadduct (**32**) in 68% yield.[27] An interesting aspect of this particular work is the remarkable efficiency of the cycloaddition between 2-chlorotropone and cyclohexadiene, which proceeded smoothly to form ketone (**32**) in 58% yield.

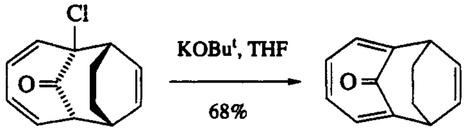

**(32)** **(33)** (2)

Ito and coworkers have employed the simple cycloadduct of butadiene and tropone to prepare the theoretically interesting 1,6-methano[10]annulen-11-one (**34**).[28] Although a number of dehydrogenation procedures were examined, direct treatment of the cycloadduct with DDQ was of only modest value in delivering the desired [10]annulene derivative.

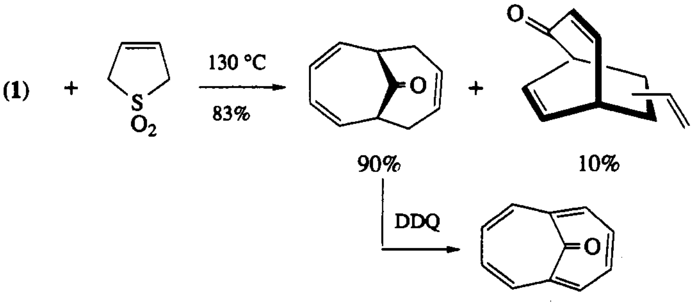

**(34)**

**Scheme 3**

The potential utility of the stereocontrol available through *exo* [6 + 4] cycloaddition in the tropone series can be seen in Garst's stereoselective cyclodecene synthesis.[29] This methodology is predicated on the efficient translation of the double bond geometry from stereochemically homogeneous (*E*)- and (*Z*)-1-acetoxybutadiene *via* cycloadducts (**30**) and (**35**) into (*E*)-cyclodecene (**36**) and (*Z*)-cyclodecene (**37**), respectively. Reduction of cycloadducts (**30**) and (**35**) to the corresponding fully saturated ketoacetates, followed by conversion to the mesylates and hydride reduction, led to the desired 10-membered ring products (**36**) and (**37**) in 78% and 40% yields, respectively.

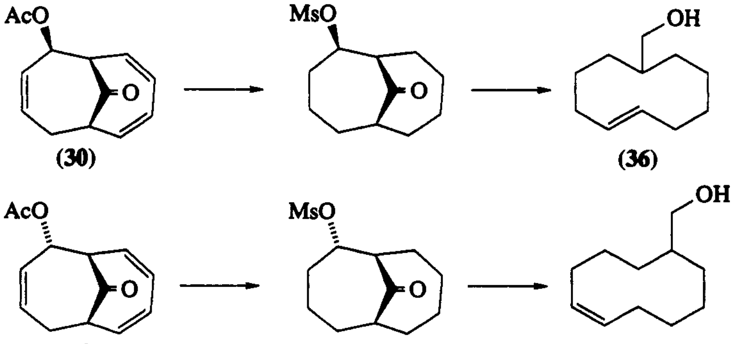

(**30**) (**36**)

(**35**) (**37**)

Scheme 4

The [6 + 4] cycloaddition strategy is ideally suited for constructing the basic bicyclo[4.4.1]undecanone carbon skeleton (**38**) which is characteristic of the potent co-carcinogenic diterpene ingenol (**39**). This cycloaddition strategy rapidly assembles the requisite bicyclo[4.4.1]undecanone system which is initially epimeric to the naturally occurring ingenol at the C-8 position. Thus this technology is particularly useful for the construction of the important so-called 'isoingenol' series. The resultant cycloadducts afford further advantages by retaining a number of strategically located functional handles for subsequent elaboration of the ample array of substituents displayed throughout this target molecule. Both inter-[8] and intra-molecular[8,9] approaches into this complex natural product have been developed that employ a [6 + 4] tropone–diene cycloaddition as the key ring-forming step. Initial efforts to assemble the basic tricycle through [6 + 4] cycloaddition of 1-acetoxybutadiene with a substituted tropone bearing the elements of the A ring at the 2-position were thwarted by the production of only [4 + 2] cycloadducts in modest yields, a result that is in complete concurrence with established precedent in these reactions. Cycloaddition with the parent tropone gave adduct (**30**) which was smoothly transformed into enone (**40**) through a routine oxidation level adjustment protocol (Scheme 6).[8] Bridgehead enolate alkylation with 2-methoxyallyl bromide, conjugate addition of a methyl substituent and enol ether hydrolysis gave dione (**41**) in good yield. Subsequent base-mediated cyclopentannulation provided the key tricycle (**42**) after deprotection and oxidation at the one-carbon bridge.

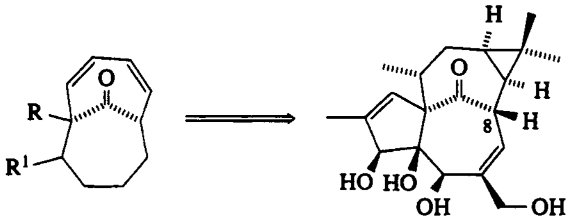

(**38**) (**39**)

Scheme 5

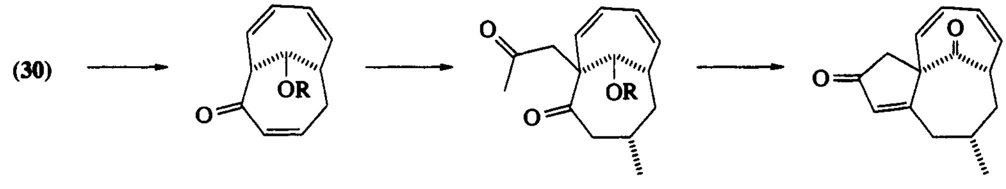

(**40**) (**41**) (**42**)

Scheme 6

A complementary strategy into the ingenane skeleton exploited the first reported intramolecular [6 + 4] tropone–diene cycloaddition[8] for the one-step construction of an intermediate with the A, B and C rings of the target molecule intact.[8] The successful implementation of the intramolecular version was made possible by tethering the diene partner to the tropone moiety in straightforward fashion. This accomplishment was achieved by incorporating the requisite diene side-chain *via* an addition–elimination sequence starting with 2-chlorotropone (Scheme 7).[8] Subsequent to this initial disclosure, a second report of a similar strategy appeared which featured an alternative addition–elimination protocol for constructing the tethered diene species.[9]

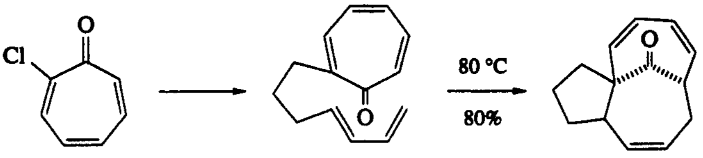

**(43)**

**Scheme 7**

Clearly, the utilization of the [6 + 4] tropone–diene cycloaddition for synthetic applications has just begun to develop and many new opportunities for exploiting the unique combination of stereocontrol and synthetic convergency afforded by these reactions is certain to be forthcoming in the near future.

### *5.2.2.1.2 1,3-Dipoles as 4π addends*

In stark contrast to the relative abundance of dienes that are known to provide synthetically useful yields of [6 + 4] cycloaddition products when reacted with tropone, relatively few examples of viable [6 + 4] additions have been documented in which the 4π addend has been a 1,3-dipolar species. This situation is somewhat surprising since 1,3-dipoles and dienes are normally quite similar in their respective cycloaddition behavior.

The initial disclosure of a [6 + 4] cycloaddition between tropone (1) and a 1,3-dipole involved diphenylnitrilimine as depicted in Scheme 8.[30,31] In this instance the [6 + 4] pathway competed rather poorly with various alternative [4 + 2] pathways and only a small quantity of the adduct in which the dipole added across the 2- and 7-positions of (1) was recovered. The three [4 + 2] adducts (45)–(47) that were isolated from the reaction mixture presumably arose from a base-catalyzed hydrogen shift that occurred subsequent to the initial cycloaddition. Efforts to account for the divergent behavior of dienes and 1,3-dipolar species in their reactions with tropone have included invoking a dipole repulsion between the large positive charge located on the central atom of the 1,3-dipole and the partial positive charge on tropone, which must come into close proximity in the transition state of a concerted [6 + 4] cycloaddition.[32] A ca-

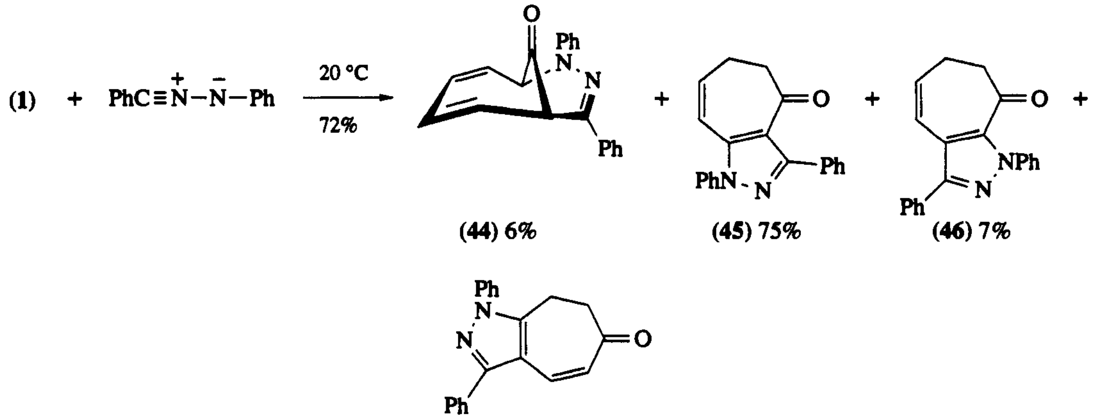

**(44)** 6% **(45)** 75% **(46)** 7%

**(47)** 7%

**Scheme 8**

veat to this argument has been issued, however, since the energetics of this repulsion appear insufficient to explain the almost total lack of [6 + 4] adducts in these reactions. The regioselectivity observed in the formation of the corresponding [4 + 2] adducts can be satisfactorily interpreted based on the interaction of the LUMO of the electron-deficient nitrilimine with the HOMO of tropone.[32]

Nitrile oxides have also been reported to combine with tropone in a [6 + 4] fashion.[33] Again this mode of addition does not compete well with various [4 + 2] alternatives as can be seen from inspection of equation (3). The room temperature addition of benzonitrile oxide to tropone (**1**) provided the [6 + 4] adduct in quite low yield and at least five [4 + 2] cycloadducts of various structures were also formed during this reaction. In contrast, the hindered mesitonitrile oxide displayed somewhat greater periselectivity than did the parent nitrile oxide in combination with tropone. Almost no [6 + 4] adduct was isolated, however, and a single [4 + 2] species (**49**) emerged as the principal product of this reaction. The higher periselectivity exhibited by the more hindered mesityl derivative was rationalized as reflecting a higher steric demand in the [6 + 4] transition state relative to the [4 + 2] process.[33]

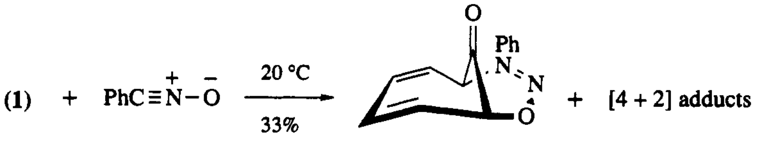

(**48**) 11% 89% (3)

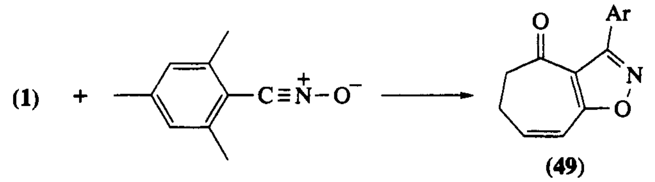

(**49**)

Based on the existent data, it appears that the reaction of 1,3-dipolar species with tropone in a [6 + 4] sense does not hold much promise as a viable tool for applications to synthetic problems.

### 5.2.2.2 Fulvenes as 6π Addends

#### *5.2.2.2.1 Dienes as 4π addends*

Fulvenes, like their troponoid counterparts, are capable of engaging dienes in a number of different pericyclic reactions. A reasonably well-defined reactivity profile of these systems has emerged as the result of extensive scrutiny of the cycloaddition behavior of the fulvene nucleus. To a large extent, fulvenes undergo concerted cycloadditions to dienes as either the 6π or 2π participant and the factors governing which of these reactivities is expressed in a particular circumstance has been elucidated employing frontier molecular orbital considerations.[34]

The reactions of electron-deficient dienes with fulvenes tend to favor addition across one of the endocyclic double bonds where the fulvene is the 2π component, as illustrated in the cycloaddition of 6,6-dimethylfulvene with 2,5-dimethyl-3,4-diphenylcyclopentadienone in refluxing THF to give adduct (**50**).[35] Cyclopentadiene exhibited a similar periselectivity in its reactions with several fulvenes. In contrast, [6 + 4] adducts are the major products when electron-rich dienes are used in these reactions. For example, hydroazulene (**51**) was isolated in good yield from the combination of 1-diethylaminobutadiene and 6,6-dimethylfulvene subsequent to the elimination of diethylamine from the initially formed cycloadduct.[36]

Reversing the polarity of the reacting partners has also proven to be an effective ploy for promoting [6 + 4] periselectivity.[37–39] The room temperature reaction of 6-dimethylaminofulvene with 3,4-dichlorothiophene dioxide is typical, giving azulene (**52**) in 60% yield.[37,38] 6-Aminofulvenes have also been successfully added in a [6 + 4] sense to α-pyrones, resulting in low yields of azulenes.[39]

The variations of periselectivity exhibited in the cycloadditions of fulvenes to dienes have been rationalized by application of frontier molecular orbital theory. The fulvene orbitals of interest in these reactions are depicted in Figure 2.[34,40] The controlling orbitals in the reaction of fulvene with an

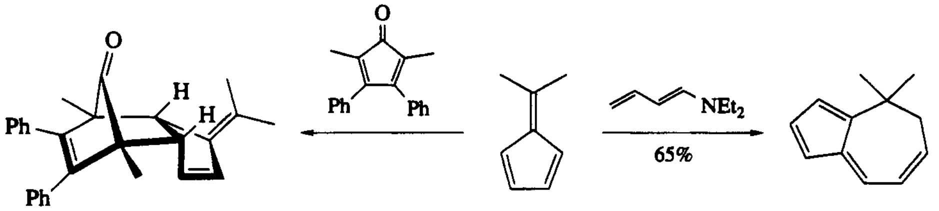

**(50)** **(51)**

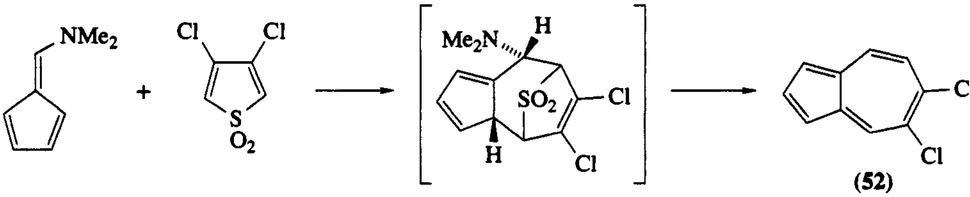

**(52)**

electron-deficient diene are the fulvene HOMO and the diene LUMO. The relatively large coefficients at C-2 and C-3, as well as the node through positions 1 and 6 in the fulvene HOMO, dictate that this species will participate as the 2π component in this case. HOMO-controlled electron-rich diene partners should add to fulvene at C-6 and to either C-1 or C-2 since the LUMO of this type of species possesses large coefficients at these locations. In the event, fulvene derivatives are indeed observed to react with dienamines as the 6π addend. Finally, strongly electron-donating substituents at the C-6 position on fulvene elevate the next highest occupied molecular orbital (NHOMO) sufficiently to permit the [6 + 4] mode of cycloaddition to prevail in reactions with electron-deficient 4π systems.

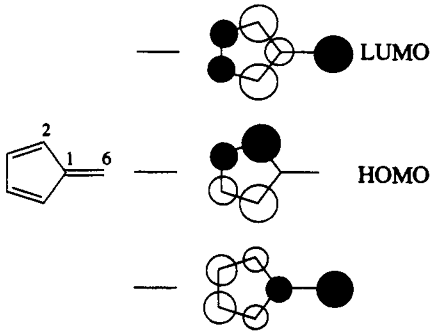

**Figure 2** The frontier molecular orbitals of fulvene

An interesting example of the influence of electron-donating substituents at C-6 on reactivity in the fulvene series is the contrast in periselectivity displayed by 6-dimethylaminofulvene and 6,6-diphenylfulvene when exposed to the electron-deficient heterodiene 3,6-diphenyltetrazine.[41] The electron-rich fulvene derivative yielded only diazaazulene (**53**), which arose from an initial [6 + 4] cycloaddition followed by spontaneous loss of the elements of nitrogen and dimethylamine. The corresponding aryl-substituted system reacted exclusively as a 2π species to give compound (**54**). It has been suggested in some studies, however, that steric hindrance at C-6 in fulvenes can serve to inhibit reaction at that center.[42]

A series of interesting cycloadditions of substituted benzocyclobutenes with 6,6-dimethylfulvene has been detailed in regard to additional periselectivity effects.[43] The readily available cyano-substituted benzocyclobutene led exclusively to the endocyclic [4 + 2] adduct (**55**; R = CN) in 67% yield when exposed to 6,6-dimethylfulvene (Scheme 9), while the corresponding [(methoxycarbonyl)amino]benzocyclobutene gave a mixture of adducts, (**55**; R = $NHCO_2Me$) and (**56**; R = $NHCO_2Me$), in yields of 28% and 66%, respectively. Interestingly, pyrolysis of the methyl-substituted compound in the presence of the same fulvene resulted in the generation of a small quantity of [6 + 4] adduct (**57**; R = Me) along with the previously described [4 + 2] products.

The influence of intramolecularity on the benzocyclobutene–fulvene cycloaddition was illustrated in dramatic fashion when the two reactive units were tethered together by a three-carbon chain. Heating nitrile (**58**) gave only the [6 + 4] cycloadduct (**59**) as an inseparable mixture of cyclopentadiene isomers in

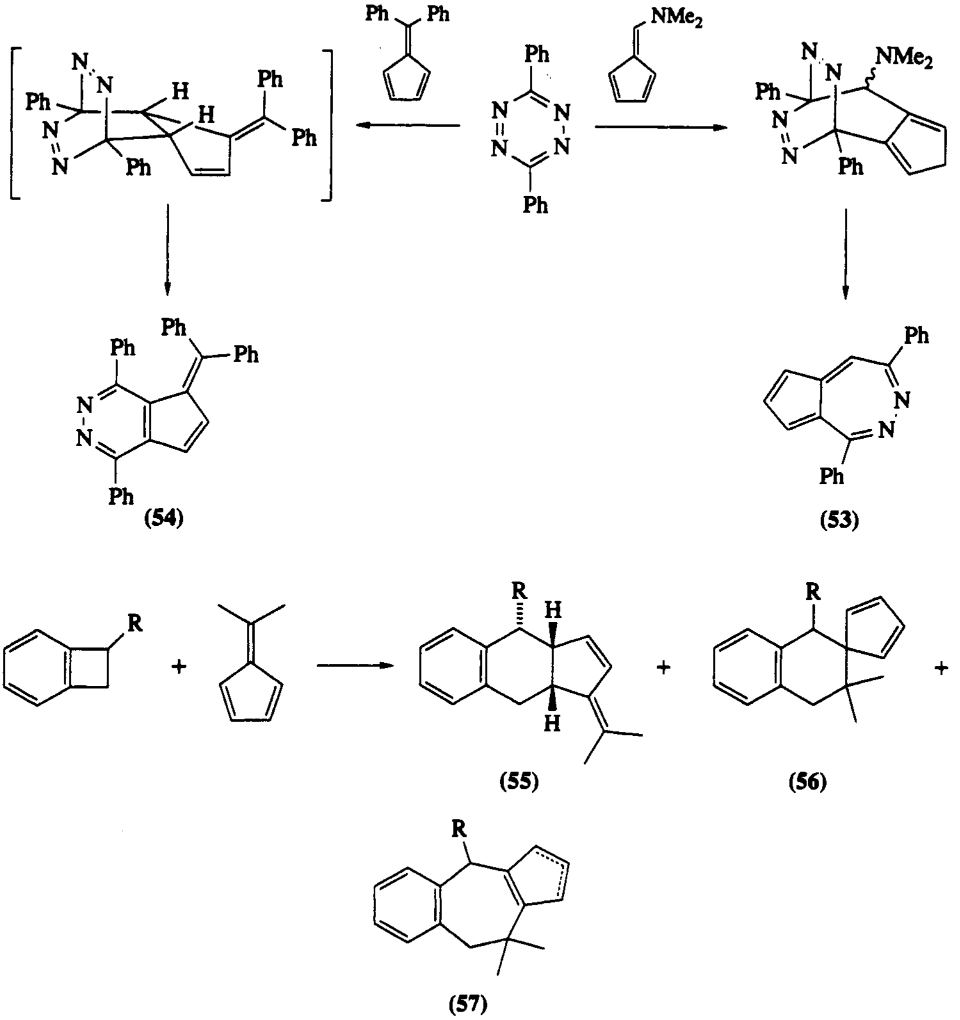

(54) (53)

(55) (56)

(57)

Scheme 9

60% yield.[44] This change of periselectivity relative to the intermolecular series stems from conformational restrictions due to the carbon chain connecting the two addends. A further consequence of these constraints is that the reaction is proposed to occur through an *endo* transition state. A similar cycloaddition performed without the benefit of the cyano substituent on the benzocyclobutene moiety exhibited somewhat diminished periselectivity although the [6 + 4] mode still predominated.[44]

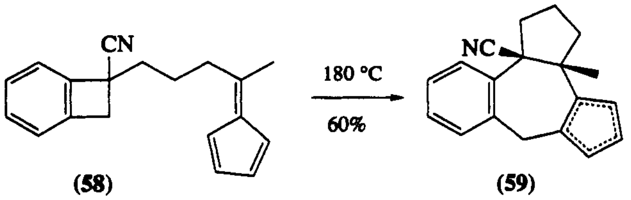

(58) (59)

An important ancillary study with significant synthetic implications revealed that electron-rich dienes attached to fulvenes by a multicarbon chain also exhibited a high degree of preference for forming the corresponding [6 + 4] adducts.[45] For example, when substituent X in compound (**60**) was either diethylamino or trimethylsiloxy, the [6 + 4] adduct (**61**) was the major product-type isolated. However, if no substituent was present on the diene portion of the molecule, a mixture consisting of [6 + 4], exocyclic [4 + 2] (**62**) and endocyclic [4 + 2] (**63**) cycloadducts was obtained.[45]

The regioselectivity of the reaction of unsymmetrical diene addends to various fulvene systems has also been explored in some detail. Heating 2-ethyl-5-methylthiophene dioxide in the presence of 6-di-

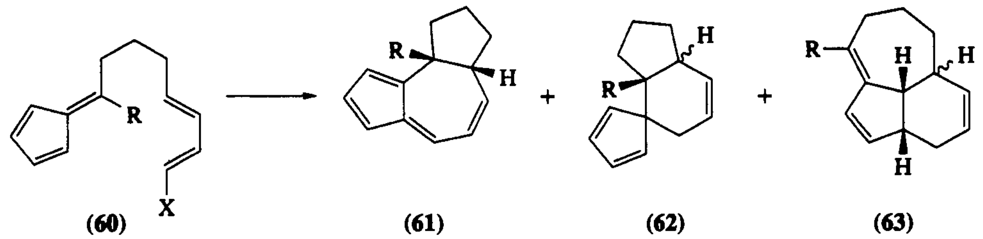

**(60)** **(61)** **(62)** **(63)**

X = NEt$_2$, OTMS, H
R = H, Me

**Scheme 10**

methylaminofulvene at 80 °C gave a 4:1 mixture of azulenes (**64**) and (**65**) in low overall yield. Steric effects appear to be the critical factor for controlling the observed regioselectivity in this case.[46] However, electronic effects seem to be more potent in directing the course of these reactions. When 6-methylfulvene was reacted with 2-ethyldiethylaminobutadiene, a single hydroazulene (**66**) was obtained in 52% yield. In this situation the most nucleophilic end of the diene reacted with the most electrophilic center on the fulvene partner, as predicted by frontier molecular orbital theory.[47]

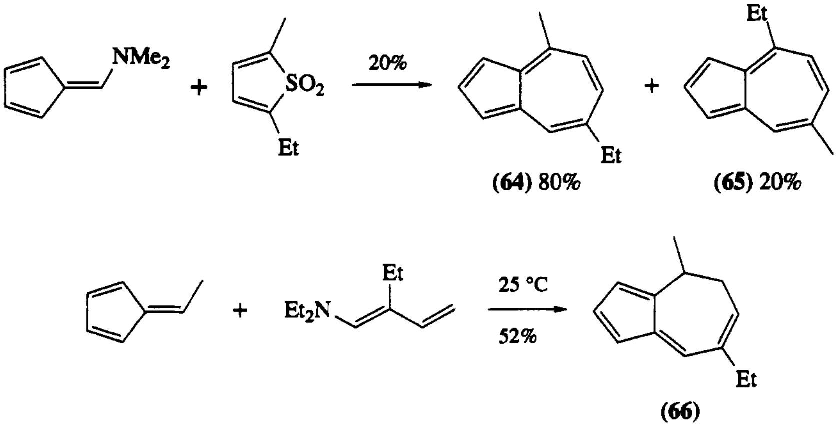

**Scheme 11**

The synthetic utility of the [6 + 4] cycloaddition of dienes to the fulvene system has been amply demonstrated by providing strategies which have greatly improved the available technology for accessing various substituted azulenes and related natural products.[36,38,46–48] A recent development in this area, which is particularly illustrative of the advantages offered by fulvene cycloaddition technology, involved the assembly of a hydroazulene lactone system in a one-step sequence (equation 4). Heating ester (**67**) gave hydroazulene (**68**) as a mixture of cyclopentadiene isomers in good yield along with lesser amounts of the spiro compound (**69**).[49] The general structural type exemplified by compound (**68**) is commonly observed in a variety of sesquiterpene lactones of medicinal interest.

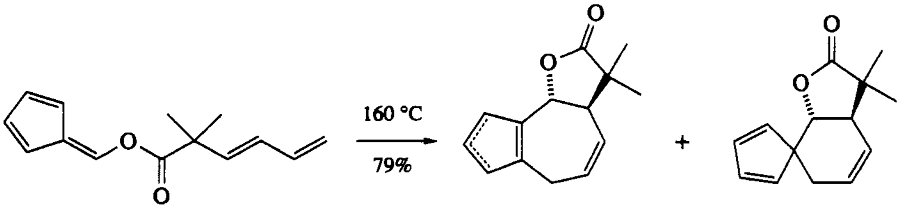

(4)

**(67)** **(68)** 71% **(69)** 29%

An important feature, characteristic of virtually all fulvene-mediated strategies thus far described in the literature, is the relative ease with which the addends can be assembled from readily available starting materials prior to cycloaddition. Customarily, a simple base-catalyzed condensation of an appropriate ketone substrate with a cyclopentadienide anion will suffice to provide good yields of the requisite fulvenes. As a consequence, these reaction schemes lend themselves very nicely to synthetic applications and should be useful for the construction of a number of terpenoid natural products.

### *5.2.2.2.2 1,3-Dipoles as $4\pi$ addends*

Cycloadditions between substituted fulvenes and 1,3-dipolar reagents have been the subject of considerably less study than the corresponding diene-mediated chemistry, paralleling the situation seen in the tropone series. For the most part, however, the reactivity patterns formulated in the fulvene–diene studies are repeated in the analogous 1,3-dipole reactions.

Diazomethane, a 1,3-dipole with well-established nucleophilic character, adds to 6,6-dimethylfulvene exclusively in a [6 + 4] fashion to give compound (**70**) after rapid tautomerism of the initially formed cycloadduct.[50] This observation is in complete accord with frontier orbital predictions for the interaction of a strongly HO-controlled $4\pi$ species with the LUMO of the fulvene partner.[40] Electron-rich nitrile ylides also are known to react primarily in a [6 + 4] fashion with substituted fulvene derivatives. A case in point is the irradiation of a 1:1 mixture of azirine (**71**) and 6,6-dimethylfulvene, which provided cycloadducts (**72**) and (**73**) in a ratio of 3:1.[51] The major adduct was quite labile and rapidly rearranged to two new species that were simply isomeric to the original cycloadduct with respect to the cyclopentadiene double bond regiochemistry. The orientation of the two reaction partners in adduct (**72**) is consistent with the preferential bonding of the position with the highest orbital coefficient in the fulvene LUMO to the position with the highest orbital coefficient in the dipole HOMO. 6-Dimethylaminofulvene was observed to be totally inert when exposed to a nitrile ylide in an effort to induce a cycloaddition between the two reactants.[51] This lack of reactivity was attributed to a significant raising of the fulvene LUMO energy, resulting in a decreased frontier orbital interaction.

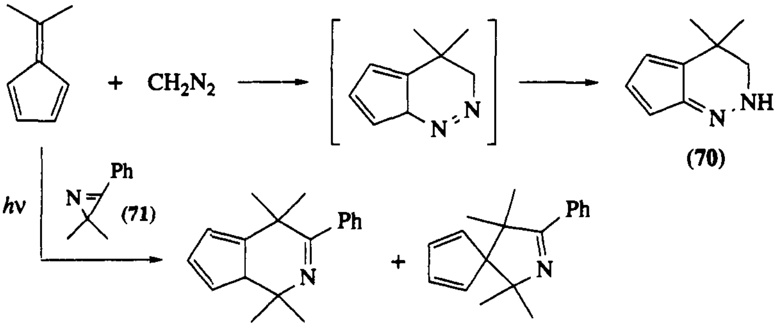

(**70**)

(**72**) 75% (**73**) 25%

An interesting electron-rich 1,3-dipole, nitropyridyl betaine (**74**), smoothly cycloadded across positions 2 and 6 of 6,6-dimethyfulvene to generate the relatively unstable [6 + 4] cycloadduct. This labile intermediate experienced the now familiar 1,5-hydrogen shift to give the corresponding cyclopentadiene isomer (**75**) as the product which was, in fact, isolated from the reaction.[52] The reversed regioselectivity (the HOMO coefficient at the betaine C-2 was calculated to be slightly larger than at C-6) observed in this particular process has been rationalized in terms of attractive secondary orbital interactions.

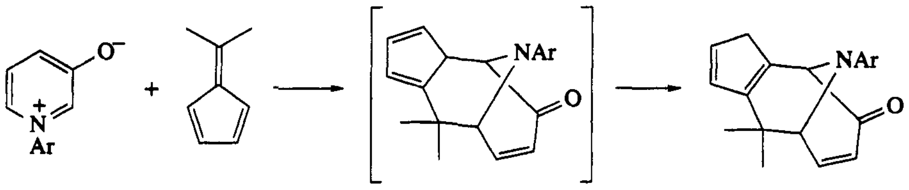

(**74**) Ar = 5-NO$_2$-2-pyridyl

(**75**)

A further illustration of the electronic influence of substituents on the course of reactions with 1,3-dipoles can be seen in the cycloaddition of an amino-substituted fulvene to benzonitrile oxide. Adduct (**76**) was obtained in 60% yield when the electron-rich dipolarophile 6-dimethylaminofulvene was exposed to benzonitrile oxide.[53] The structure of the resultant product can be conveniently explained by an initial [6

+ 4] cycloaddition followed by eliminative loss of dimethylamine. In contrast, benzonitrile oxide gave only products derived from various [4 + 2] cycloaddition processes when reacted with 6,6-dimethyl- and 6,6-diphenyl-fulvenes.[53]

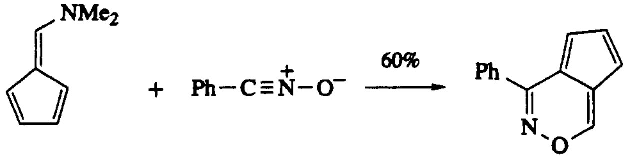

**(76)**

### 5.2.2.2.3 *Tropone as the 4π addend*

Among the earliest [6 + 4] reactions of fulvene to be studied involved tropone ostensibly participating as the 4π partner. Heating a solution of tropone and 6,6-dimethylfulvene in THF at 50 °C yielded the novel double [6 + 4] adduct (**77**) in up to 88% yield.[54,55] Performing the same reaction at room temperature provided relatively small quantities of several 1:1 adducts along with the 2:1 adduct (**77**) in 66% yield. Unfortunately, from a synthetic perspective, efforts to suppress the addition of the second molecule of tropone have met with limited success in this series. The primary course of this novel reaction was presumed to proceed *via* an initial [6 + 4] cycloaddition in which tropone participated as the 4π addend to give intermediate (**78**) which rapidly rearranged to the more stable cyclopentadiene isomer (**79**). This compound then experienced an apparently quite facile *exo* [6 + 4] cycloaddition with a second molecule of tropone to provide the isolated 'double' cycloadduct. When mono-substituted fulvenes were employed in this reaction, only the corresponding stereoisomer of the 2:1 adduct displaying the fulvene substituent oriented toward the three-carbon bridge of the tropone moiety was observed. This result was rationalized in terms of the fulvene addend approaching tropone so as to avoid unfavorable nonbonding interactions that were present during the production of the alternative stereoisomer.[56,57]

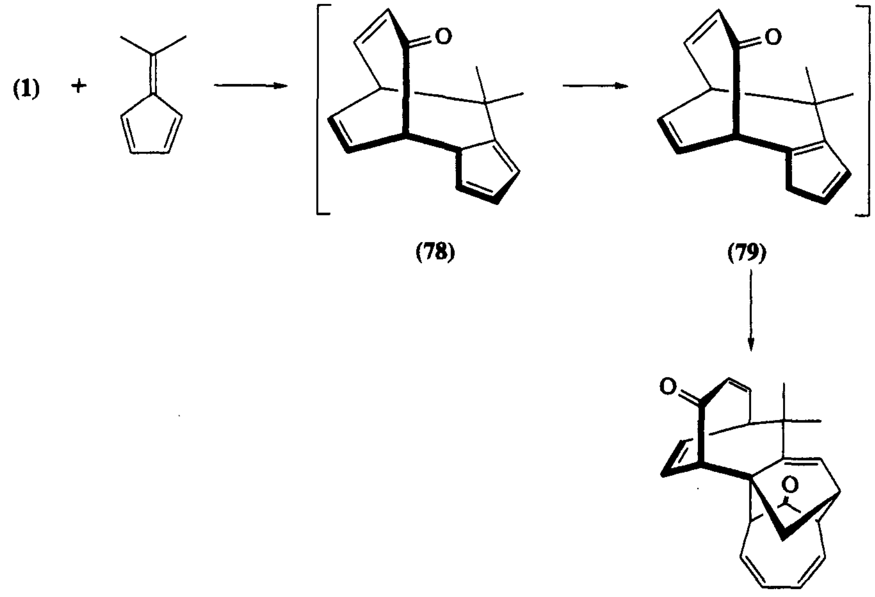

**(77)**

The steric consequences of substitutents at various locations on the tropone addend have also been described for this reaction. Substituents at the 2-position apparently provided sufficient steric hindrance to the approach of the fulvene addend that cycloaddition proceeded so as to completely avoid this center. Thus 2-chlorotropone gave cycloaddition products in which the chlorine substituent was always situated on the three-carbon bridge remote from the fulvene moiety in the initial [6 + 4] cycloadducts.[58] Furthermore, 2,7-dichlorotropone failed to cycloadd to substituted fulvenes under any conditions. From these results it is clear that steric hindrance plays a crucial role in determining the course of fulvene–tropone cycloaddition much as it did in the corresponding cycloadditions of dienes to tropone (see Section 5.2.2.1.1).

Although many of the observed products from the [6 + 4] cycloaddition of tropone to various fulvenes can be explained by the concerted reaction of tropone as the 4π addend with fulvene participating as the 6π addend, an alternative mechanistic scheme for the production of species such as (**78**) and (**79**) can be envisioned. This pathway would necessitate the intervention of an *exo* [6 + 4] cycloadduct in which the fulvene behaved as the 4π addend. In this pathway, bond formation at the two termini of the tropone–triene system would initially occur across the C-2 and C-5 positions of the fulvene participant. Several reports have surfaced noting that some fulvene derivatives dimerize thermally in a [6 + 4] fashion in which one of the fulvene molecules reacts as a 4π species across the C-2 and C-5 positions, as required in this mechanistic scenario.[59,60] Subsequent, rapid 3,3-sigmatropic rearrangement of the thermodynamically unstable [6 + 4] adduct would deliver the products observed experimentally. The first substantive evidence for the operation of this alternative pathway in a cycloaddition was observed in the reaction of 8,8-dimethylisobenzofulvene with tropone in which the postulated [6 + 4] intermediate (**80**) was actually isolated.[61] This transient material rearranged rather rapidly to the final adduct (**81**) as required in the alternative mechanistic scheme. Other cycloadditions of substituted isobenzofulvenes have also been observed to proceed *via* the pathway depicted in Scheme 12.[62] Since the *exo* [6 + 4] tropone (6π)–fulvene (4π) adduct has not been observed to date in other examples of cycloadditions of tropone and substituted fulvenes, the question still remains open as to whether this intriguing tandem [6 + 4] cycloaddition–3,3-sigmatropic rearrangement process actually prevails in all fulvene–tropone cycloadditions.

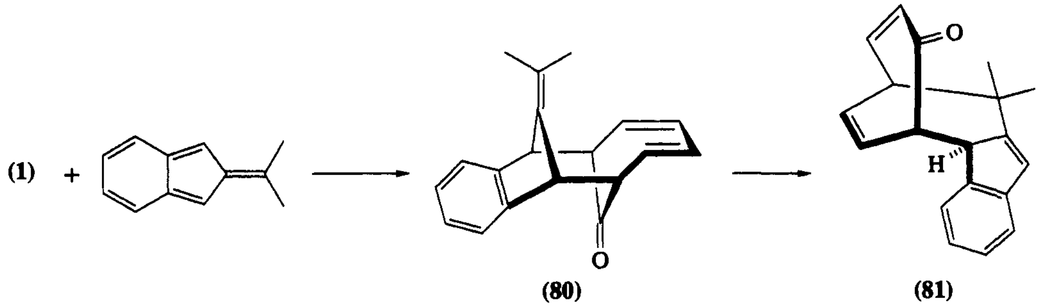

Scheme 12

### 5.2.2.3 Cyclic Trienes as 6π Addends

Cycloheptatriene and related heterocyclic analogs have been examined to some extent with regard to their reactivity with various conjugated diene partners. Characteristically, higher-order cycloaddition pathways often suffer relative to alternative modes of reaction in these systems and usually a select type of highly reactive diene partner is a prerequisite for viable cycloaddition to occur. Selectivity in these species can also be compromised by the intervention of the corresponding norcaradiene tautomer in certain circumstances. Modest periselectivity coupled with low chemical yields limit the potential synthetic utility of these cycloadditions.

The reaction of cycloheptatriene with 2,5-dimethyl-3,4-diphenylcyclopentadienone is typical for this class of compounds, resulting in the formation of six distinct products.[63] Equation (5) displays the major products of interest, which include a modest quantity of the *exo* [6 + 4] adduct (**82**). The mechanistic details of this process were gleaned from monitoring an equimolar mixture of the two reactants maintained at 120 °C. This experiment revealed that both the [2 + 4] adduct (**83**) and the [6 + 4] adduct (**82**) were formed from the outset of the reaction. However, adduct (**83**) was subsequently converted quantitatively into the [4 + 2] cycloadduct (**84**) *via* a Cope rearrangement. This interconversion is reminiscent of a similar transformation in the tropone–diene series (see Section 5.2.2.1.1 and ref. 24).

The thermal cycloaddition of phencyclone (**85**) with cycloheptatriene offers additional mechanistic insight into these reactions (Scheme 13). In this case a 57% yield of the corresponding *endo* [2 + 4] adduct was isolated. Further pyrolysis of this material at 170 °C provided the decarbonylated pentacyclic material (**86**) along with an *exo* [6 + 4] adduct (**87**).[64] The course of this reaction can be contrasted with the thermolysis of compound (**83**). While neither of these examples is of great potential synthetic value, they do serve to illustrate some of the typical mechanistic themes which characterize these reactions.

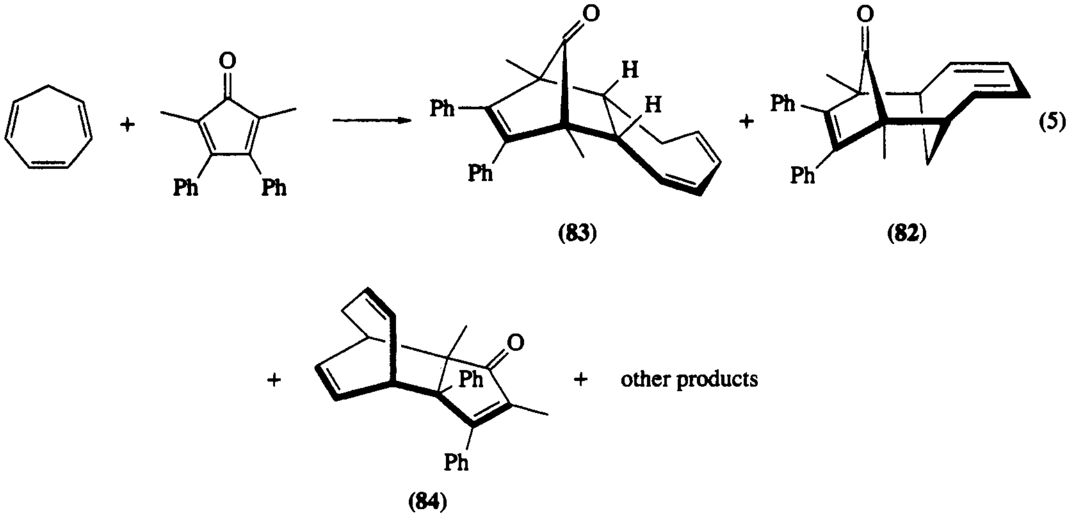

**(83)** **(82)** **(84)**

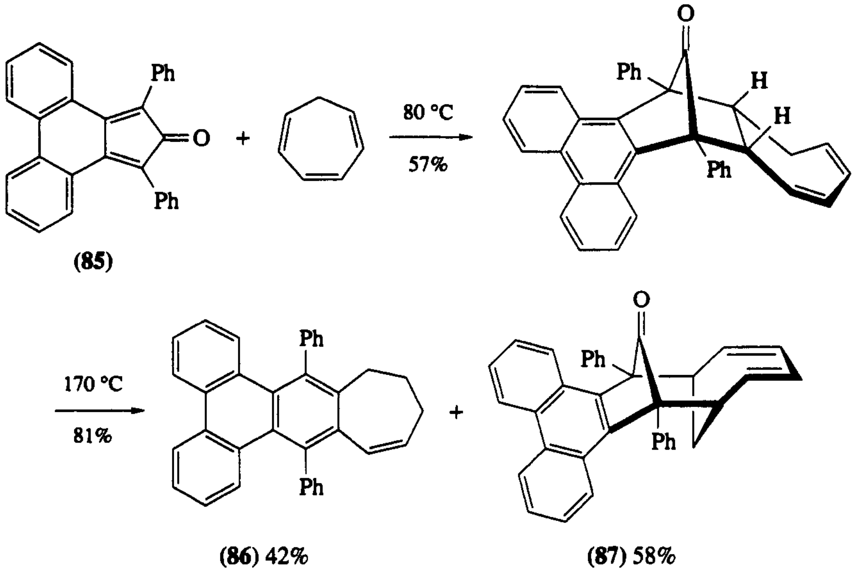

**(85)**

**(86)** 42% **(87)** 58%

Scheme 13

In dramatic contrast to the normal course of higher-order cycloadditions with most cyclic triene substrates, the photochemically induced [6 + 4] cycloaddition reactions exhibited by tricarbonyl(η-1,3,5-cycloheptatriene)chromium(0) complexes appear to be quite suitable for preparative applications. Yields of the resultant diene cycloadducts are usually good and the metal can be removed in high yield on treatment of the cycloadduct complex with triethylphosphine.[65–67] Scheme 14 shows the results of several cycloadditions between the complex and substituted diene addends. While not specifically delineated in the original work, these reactions provide the corresponding *endo* adducts exclusively.[67]

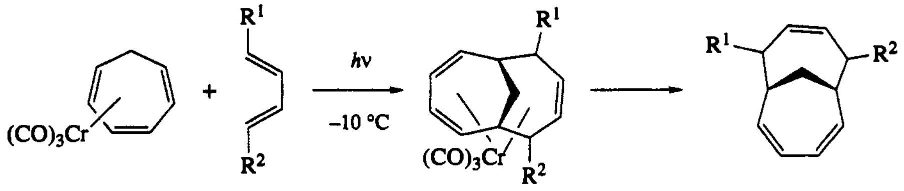

| | **(88)** | **(89)** |
|---|---|---|
| $R^1$ = vinyl, $R^2$ = H | 65% | 63% |
| $R^1$ = Me, $R^2$ = $CO_2Me$ | 40% | 85% |

Scheme 14

The nitrogen and oxygen analogs of cycloheptatriene offer attractive potential 6π substrates for higher-order cycloadditions. Unfortunately, the reactions of these compounds with a variety of dienes usually result in low yields of [6 + 4] adducts. The mechanistic details of many of these processes are intriguing, however, and merit some attention. The dimerization of *N*-substituted azepines, for example, has provided numerous clues as to the actual pathways involved in these and related reactions.[68–70] Thermolysis of *N*-ethoxycarbonylazepine at 130 °C gave initially an *exo* [6 + 4] cycloadduct (**90**) and a small amount of a dimer ostensibly derived from a 'thermally forbidden' [6 + 6] cycloaddition process.[68] At 200 °C the azepine was converted into the [6 + 6] product in 83% yield. Apparently the [6 + 4] product isolated under milder conditions is an intermediate in the formation of the [6 + 6] dimerization product.

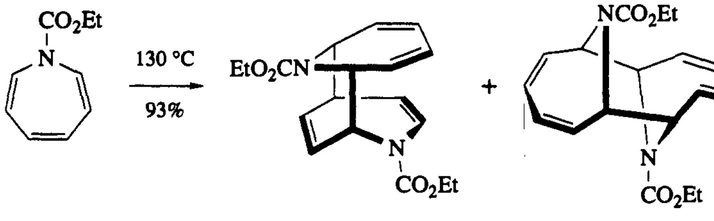

(**90**) 91% (**91**) 9%

A typical example of the reaction of *N*-ethoxycarbonylazepine with a reactive diene is illustrated by the addition of 2,5-dimethoxycarbonyl-3,4-diphenylcyclopentadienone. Heating a mixture of these reactants at 80 °C for several hours gave *exo* [6 + 4] adduct (**92**) and *endo* [4 + 2] adduct (**93**) in yields of 18% and 82%, respectively.[71,72] Alternatively, heating diene (**94**) in the presence of the same azepine gave only the [2 + 4] adduct (**95**).[73] Low-temperature examination of the cyclopentadienone reaction revealed the intervention of a cycloadduct similar in structure to compound (**95**), which rapidly led to the [4 + 2] adduct (**93**) *via* a facile 3,3-sigmatropic rearrangement.[71]

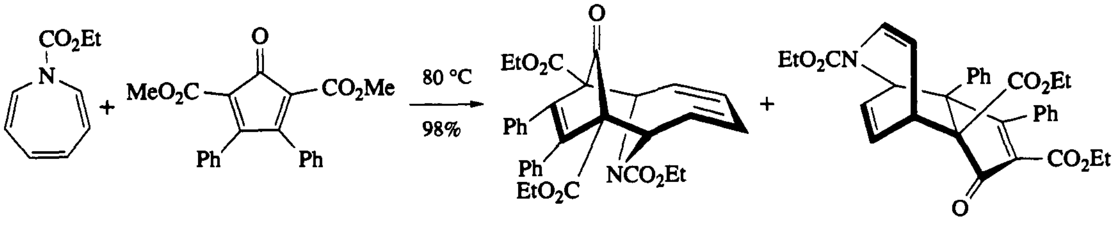

(**92**) 18% (**93**) 82%

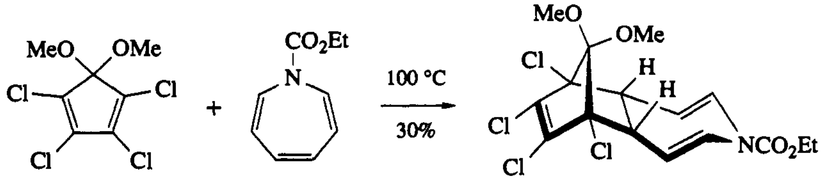

(**94**) (**95**)

Heating *N*-ethoxycarbonylazepine with the electron-deficient diene (**96**) provided [2 + 4] adduct (**97**) and [6 + 4] adduct (**90**) in nearly equal quantities.[74] Other examples of relatively low conversion [6 + 4] cycloadditions of substituted azepines and various dienes have been reported but are of little synthetic consequence due to low periselectivity and modest chemical yields.[75,76] Oxepin heterocycles display a range of reactions with dienes which are similar in scope to the azepine series and, as such, will not be dealt with specifically in this review.[77–79] Other cyclic polyenes such as cyclooctatetraene are known to yield some [6 + 4] adducts when exposed to highly reactive diene species. For example, the potent electron-deficient diene 2,5-dimethoxycarbonyl-3,4-diphenylcyclopentadienone gives a modest amount of the corresponding [6 + 4] cycloadduct when reacted with cyclooctatetraene.[80,81]

In a very exciting series of studies, Kreiter and coworkers have established the viability of photochemically induced [6 + 4] cycloadditions of dienes to the chromium tricarbonyl complex of 8,8-dimethylheptafulvene.[82–84] These potentially useful transformations appear to be general with a wide range

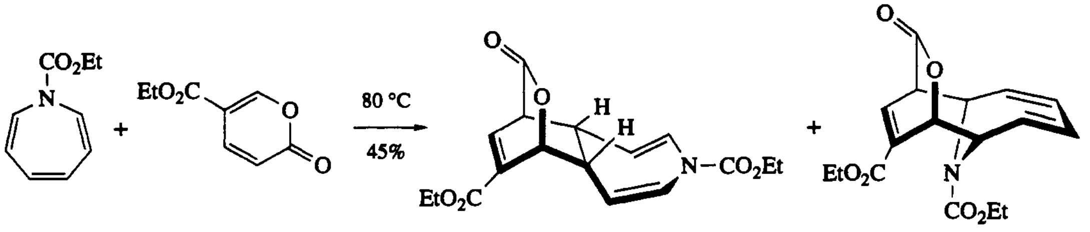

(96) (97) 55% (98) 45%

of diene structures and, depending on the identity of the particular diene employed, proceed either through a direct cycloaddition pathway or alternatively *via* a novel π-allyl complex that subsequently collapses efficiently to the corresponding [6 + 4] adduct on addition of excess carbon monoxide. Decomplexation with trimethyl phosphite provided the free hydrocarbon product in good yields. In general, the peri- and stereo-selectivity of these reactions have been observed to be very high, making them particularly attractive for preparative applications. The stereochemistry of the resultant cycloadducts is derived from an *endo* approach of the diene to the complex. This selectivity is presumably a consequence of a metal-diene interaction prior to covalent bond formation. A typical cycloaddition using this chemistry is illustrated in the preparation of bicyclo[4.4.1]undecene (**100**). In this case the heptafulvene complex is photolyzed in the presence of (*E,E*)-2,4-hexadiene. The resulting cycloadduct is then liberated from the metal by decomplexation using trimethyl phosphite.[84] Table 1 displays the results of several cycloaddition reactions in this series. Clearly, this methodology offers numerous opportunities for preparative applications.

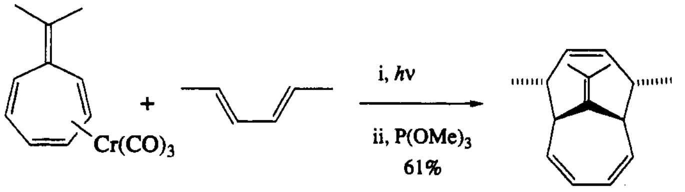

(99) (100)

**Table 1** Photocycloadditions of Conjugated Dienes with Tricarbonyl[1–6-η-(8,8-dimethylheptafulvene)]chromium(0)[84]

| *Diene* | *Yield of complex (%)* | *Yield of free cycloadduct (%)* |
|---|---|---|
| Butadiene | 65 | 76 |
| 2,4-Pentadiene | 73 | 85 |
| 2,4-Hexadiene | 71 | 86 |
| 1,3-Cyclohexadiene | 81 | 92 |
| 2-Methylbutadiene | 56 | 90 |
| 4-Methyl-2,4-pentadiene | 61 | 84 |

A number of interesting [6 + 4] cycloaddition processes involving ionic reactants have also surfaced recently. The bulk of examples reported to date involve charged heterocyclic systems with various reaction partners.[85–87]

## 5.2.3 [4 + 4] CYCLOADDITION REACTIONS

### 5.2.3.1 Photocycloaddition Reactions of 1,3-Dienes and Arene Substrates

Reactions in which two 4π addends engage in a suprafacial cycloaddition process are generally photochemically allowed transformations.[3] The [4π + 4π] cycloaddition is an attractive strategy-level reaction from the perspective of the rapid construction of functionalized eight-membered carbocycles. The development of new methodology for eight-membered ring formation has been stimulated by the identification of numerous natural products of medicinal interest that display a cyclooctane ring as a prominent structural feature.[88,89] [4 + 4] Cycloaddition-based strategies could play a significant role in this synthetic endeavor if appropriate protocols that proceed efficiently could be brought to bear on the problem. In practice, however, the photoinduced [4π + 4π] cycloaddition process is most frequently characterized by relatively low yields of adducts and by production of a plethora of different photoproducts. For example, the photoinduced intermolecular [4 + 4] cycloadditions of acyclic dienes in general provide low yields of cyclooctane products and are of little preparative value.[90] Competitive [2 + 2] processes prevail in these cases and in certain systems can be of considerable synthetic utility.[91]

Photocycloaddition of dienes to benzene and most other arenes offer little respite from the low yields and complex product mixtures that plague the simple diene cycloadditions.[92,93] Typical of this genre of reaction is the photoaddition of butadiene to benzene which gives the corresponding *trans* cycloadduct (**101**) as the primary photoproduct in low yield. In an interesting contrast, the *cis* adduct (**102**) is a major product from the light-induced cycloaddition of benzene and 2,4-dimethyl-1,3-pentadiene. Based on these results, the ground-state conformation of the diene has been suggested as the controlling factor in determining the structure of the resultant adduct in these reactions.[94] Similarily, when anthracene was irradiated in the presence of 2,5-dimethyl-2,3-hexadiene, a metastable [4 + 4] adduct (**103**) exhibiting a *trans* double bond was initially isolated in 'high yield.' This compound was smoothly isomerized to the more stable *cis* isomer (**104**) by photosensitization. The observed stereospecificity of this cycloaddition is suggestive of a concerted process in which the diene participates in the *s-trans* conformation.[95] Cyclohexadiene also provides the corresponding [4 + 4] adduct in good yields.[95]

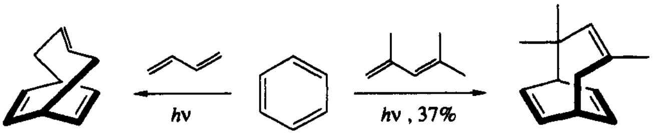

**(101)** **(102)**

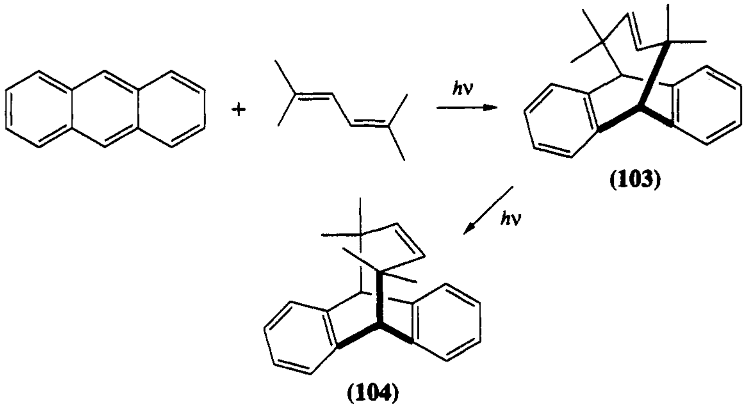

**(103)**

**(104)**

In contrast to the course of reaction with the parent anthracene, 2,5-dimethyl-2,4-hexadiene has been reported to yield chiefly the photochemically 'forbidden' [4 + 2] cycloadduct (**105**) when exposed to 9-cyanoanthracene.[96] The remarkable variability in periselectivity displayed by these systems has been rationalized in terms of the [arene*:1,3-diene] exciplex which is presumably involved in these transformations.[96,97] Polar exciplexes are described as leading to [4 + 2] products while less polar exciplexes are believed to be the precursors of [4 + 4] adducts. Of interest is the observation that cyclohexadiene provides principally the corresponding [4 + 4] adduct when reacted with both anthracene and 9-cyanoanthracene; thus it has been proposed that a less polar exciplex is involved in both of these reactions.[96]

Other results in this area point to an initial [4 + 4] cycloaddition step followed by a thermally or photochemically initiated rearrangement of the initial cycloadduct to give a '[4 + 2]' species as the final observed product. Irradiation of 9-cyanoanthracene and cycloheptatriene at low temperature initially produced the [4 + 4] adduct (**106**) which promptly rearranged to (**107**) at temperatures exceeding 0 °C.[98] Related diene–arene photocycloadditions have been reported in which comparable tandem processes were apparently operative.[99–101]

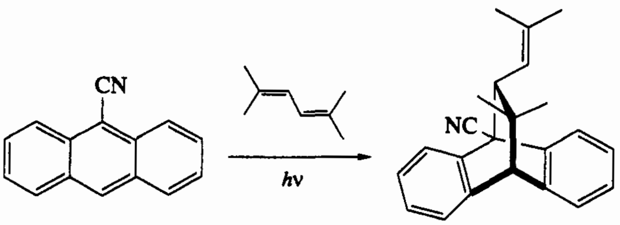

**(105)**

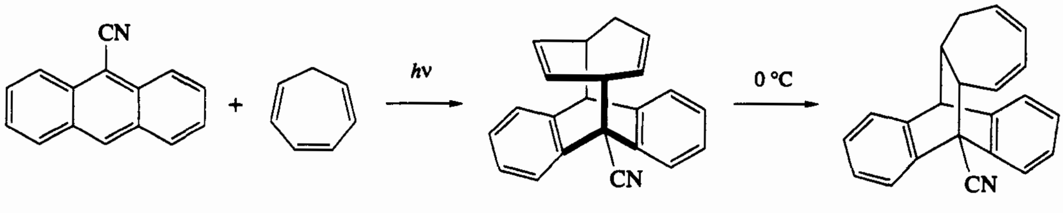

**(106)** **(107)**

A number of interesting studies have appeared in which somewhat more complex and highly substituted addends have been shown to participate in [4 + 4] photocycloadditions. As with the majority of [4 + 4] photocycloaddition reactions, the yields of adducts, *e.g.* (**108**), in these examples are, at best, modest.[102,103]

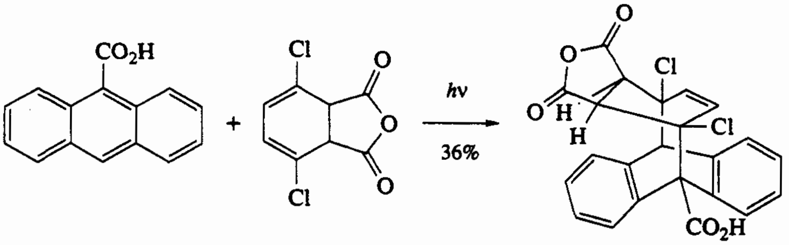

**(108)**

Photochemically excited arenes are also known to cycloadd to other aromatic species in a few cases. Furthermore, a growing body of literature attests to the relative ease of photoinduced dimerization of numerous aromatic species. Irradiation of benzene in furan as solvent provided cycloadduct (**109**) as the major isolable product.[104–106] The process was quite inefficient from a preparative perspective since a mixture of six products was formed during this reaction, of which (**109**) represented only 50% of this complex mixture.

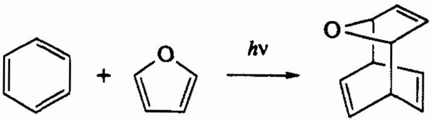

**(109)**

[4 + 4] Photodimers have been reported as the principal products from irradiation of numerous arene substrates.[107] While there is little selectivity to be considered in most of these reactions, it has been reported that almost all photolyses of 9-substituted anthracenes give head-to-head dimers as depicted in (**110**).[108] An intramolecular version of these photodimerizations has also been reported. Irradiation of di(α-2-naphthylmethyl) ether gave a mixture of the *endo* cyclomer (**111**) and the *exo* cyclomer (**112**).[109]

The photodimerization of 2-pyridones has been the subject of extensive investigation for a number of years.[110–114] In most instances the 'head-to-tail' or *trans-anti* isomer was the major or exclusive product in these reactions. Irradiation of *N*-methyl-2-pyridone for 15 h provided the *trans-anti* dimer (**113**) in 51% yield.[115] This material was accompanied by much smaller quantities of other dimeric species. Vari-

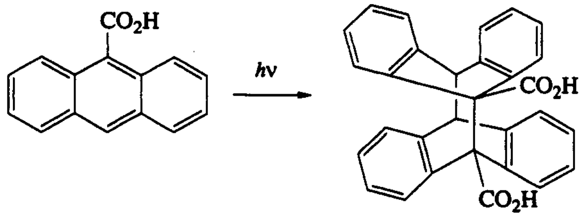

**(110)**

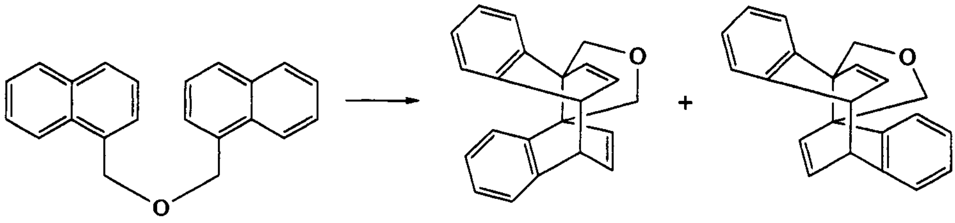

**(111)** **(112)**

ous substituted 2-pyrones have also been subjected to photoinduced dimerization and yield primarily the *trans* isomers as well.[116]

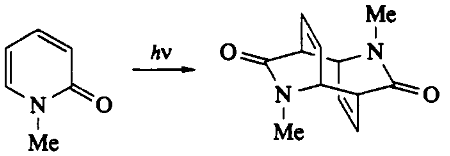

**(113)**

Intramolecular photodimerization of 2-pyridones provides a series of primary photoproducts, the structures of which were a function of the chain length connecting the two reactive centers.[117] The initially formed dimers were characterized as being derived from a photochemically allowed [2 + 2] cycloaddition process in each case examined. A particularly interesting example from this study in terms of [4 + 4] cycloaddition chemistry is the conversion of dipyridone (**114**) into the net [4 + 4] dimer (**115**) *via* a facile thermal rearrangement.[117] Further irradiation of the [4 + 4] species (**115**) produced a second [2 + 2] adduct that was isomeric with the initially formed metastable species.

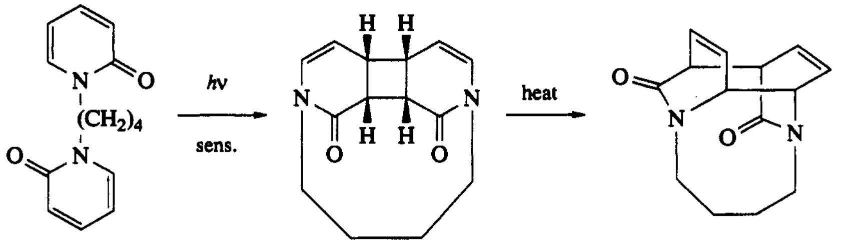

**(114)** **(115)**

Although a number of novel and mechanistically significant reactions have been reported in the area of polyene photocycloaddition, the inefficiency of these processes generally precludes their use for preparative applications.

### 5.2.3.2 Dimerization of *o*-Xylylene and 2,3-Dimethylenefurans

Ultrasound has been employed to promote the formation of *o*-xylylene from the reaction of zinc metal with α,α′-dibromo-*o*-xylene.[118] In the absence of reactive dienophiles, the transient diene produced in this reaction dimerizes to generate the 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctadiene (**116**) in 5% yield. Dimer (**116**) can be produced in 80% yield from the same dibromide when it is treated with lithium and exposed to sonication. No [4 + 2] cycloadducts were observed in this reaction when it was performed in the presence of relatively reactive dienophiles, suggesting that *o*-xylylene is not an intermediate in the dimerization process.[119]

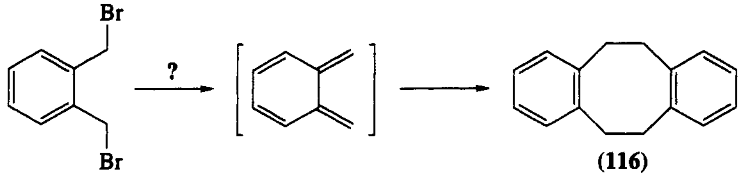

**(116)**

Similar [4 + 4] dimers have been reported during the flash vacuum pyrolysis of 2-methyl-3-furylmethyl benzoate in which 4*H*,5*H*,9*H*,10*H*-cycloocta[1,2-*b*:6,5-*b'*]difuran (**117**) is produced in virtually quantative yield.[120] A stepwise mechanism has been forwarded to rationalize the high-yield formation of the corresponding head-to-head [4 + 4] dimer.[121] Other examples of the [4 + 4] dimerization of 2,3-dimethylene furan[122] and 2,3-dimethylene thiophene[123] have been reported as well.

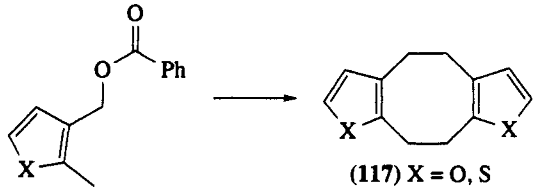

**(117)** X = O, S

It is apparent that these types of [4 + 4] dimerization, while normally high-yielding processes, are of limited potential for application to complex synthetic problems.

### 5.2.3.3 Applications of 'Indirect' [4 + 4] Cycloadditions to Synthesis

Direct application of [4 + 4] cycloaddition chemistry to problems in natural product synthesis is rare due to the general inefficiency of these processes. However, several variations on the theme of direct [4 + 4] cycloaddition have been developed and will be considered in this section.

As alluded to in Section 5.2.3.1, the intermolecular photoinduced [$2\pi + 2\pi$] cycloaddition of dienes is an efficient reaction in only a relatively few instances.[91] However, many of the liabilities normally associated with the intermolecular cycloaddition process can, in principle, be circumvented by employing the intramolecular version of the coupling. The requisite eight-membered ring could then be accessed from thermal rearrangement of the resultant divinylcyclobutane photoproduct.[124]

Wender and Correia have brought this concept to practice by tethering two 1,3-diene units together with a three-carbon chain.[125] Sensitized irradiation of the resultant tetraene provided a quantitative yield of two *cis*-fused bicyclo[3.2.0]heptane products that were isomeric with respect to the relative spatial disposition of the two vinyl side-chains. Thermolysis of the *cis*-divinylcyclobutane isomer at 130 °C for several hours gave a quantitative conversion to *cis*-cyclooctadiene (**118**). The *trans*-divinylcyclobutane, which proved to be more reluctant to rearrange, required higher temperatures (200 °C) and longer reaction times to give (**118**) as the major product. A modest quantity of a six-membered ring rearrangement product accompanied cyclooctadiene formation in this case. This reaction sequence was shown to be both versatile and general in scope. Tetraene analogs displaying heteroatom tethers, four-carbon connecting chains and functionalization all gave the corresponding products in good yields. Furthermore, the sequence has been employed as the key ring-forming step in a formal total synthesis of the antitumor and antibiotic triquinane coriolin.

In an extension of the indirect intramolecular [4 + 4] cycloaddition concept, Wender and coworkers have also developed a very powerful $Ni^0$ catalyzed cyclodimerization variant which is quite efficient at delivering cyclooctadiene products.[126] Exposure of the appropriate tetraene to catalytic amounts of $Ni^0$ in the presence of $Ph_3P$ at 60 °C gave a mixture of two cyclooctadienes (**119**) and (**120**) in 70% total yield. In this instance the *cis*-fused isomer (**119**) prevailed in a ratio of 19:1 over the corresponding *trans* material. The proclivity for formation of the *cis*-cyclooctadiene, the result of a formal *endo* addition, was a

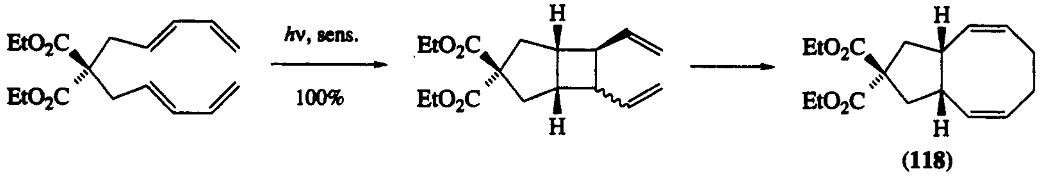

(118)

Scheme 15

general phenomenon for tetraenes joined by a three-carbon chain. It is clear that the overall process described here, while formally a [4 + 4] cycloaddition reaction, proceeds mechanistically through a series of intermediates.[127]

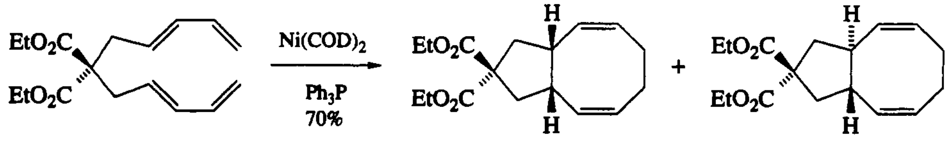

(119) 95% (120) 5%

A particularly significant aspect of this reaction is the level of stereoinduction observed when certain substituents were appended to the carbon tether. When tetraene (**121**; R = $CO_2Me$) was treated with the standard $Ni(COD)_2/Ph_3P$ catalyst, cyclization proceeded smoothly to give (**122**; R = $CO_2Me$) in 84% yield along with a small amount of (**123**) and traces of *cis*-fused products. The equatorially substituted diastereomer (**122**) was formed with a preference of ≥70:1 over epimer (**123**), which exhibited an axially oriented methoxycarbonyl group. The *exo*/*endo* selectivity of the reaction was established as >95:5, now favoring formation of the *trans*-fused ring system. In contrast to the three-carbon analog, dienes connected by a four-carbon tether were found to display a high selectivity for formation of the *trans*-fused product.

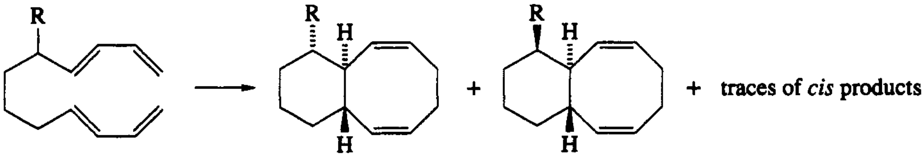

(121) (122) (123)

A number of different substituents (R) were positioned on tetraene (**121**) to evaluate the origins of the remarkable level of diastereoselection observed in these reactions. Table 2 summarizes the results of this study. The small cyano group had only a minor stereoinductive effect while the bulkier, noncomplexing methyl group showed a more pronounced effect. The influence of the acetoxymethyl group was essentially identical to the methyl group despite the possibility of coordination. Thus, it was concluded that the diastereoinduction observed was predominently steric in origin.[128]

**Table 2** Substitutent Effects on the Diastereoselectivity of the Nickel(0) Catalyzed Intramolecular [4 + 4] Cycloaddition of (**121**)[128]

| *Substituent (R)* | *Yield (%)* | *Ratio (eq:ax)* |
|---|---|---|
| CN | 66 | 1.5:1 |
| Me | 88 | 20:1 |
| $CH_2OAc$ | 92 | 21:1 |
| $CO_2Me$ | 84 | ≥70:1 |

The nickel-catalyzed intramolecular [4 + 4] cycloaddition strategy has been successfully applied to the construction of both the AB and BC ring systems of the taxane diterpenes.[129] These studies additionally served to establish the viability of this chemistry for the construction of angularly alkyl-substituted bicyclo[6.4.0]dodecanes. In an example typical of this class of transformations (Scheme 16), cyclooctadiene (**125**) was produced with greater than 97% diastereoselectivity and in 92% chemical yield when tetraene

**(124)** was subjected to the standard $Ni^0$ cyclodimerization conditions. The complementary strategy for construction of the AB taxane ring system proceeded somewhat less effectively to give adduct **(127)** in 52% yield as a 1.3:1 mixture of *t*-butyldimethylsilyloxy epimers. Merging of these two sequences could, in principle, provide rapid entry into the taxane skeleton itself in a very efficient fashion.

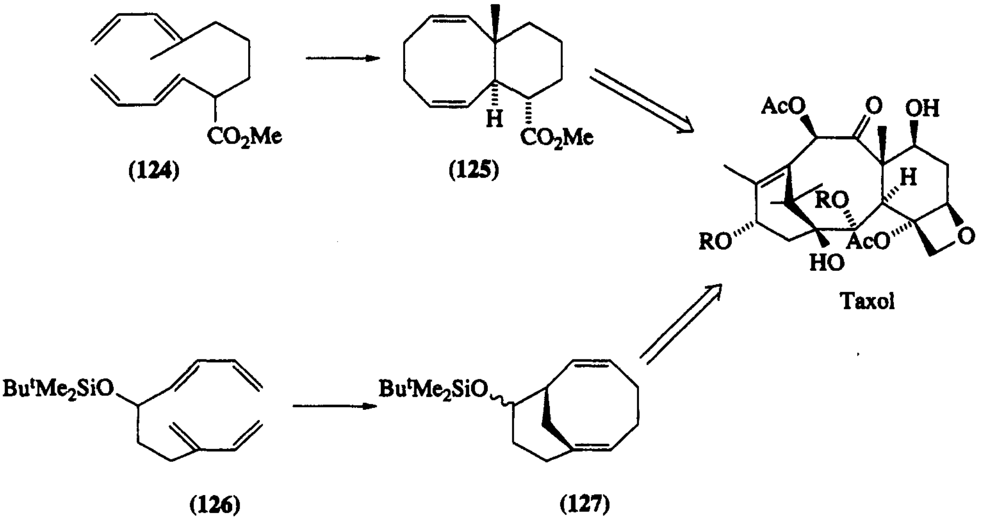

**Scheme 16**

The nickel-mediated [4 + 4] cycloaddition strategy has also provided a concise and stereocontrolled route into the sequiterpene lactone (+)-asteriscanolide **(128)**.[130] The basic features of this approach are outlined in Scheme 17. The critical [4 + 4] cycloaddition step occurred under standard conditions to give the key intermediate in 67% yield. Clearly, the intramolecular version of the nickel-catalyzed diene cyclodimerization has been established as a powerful and highly-selective protocol for the synthesis of cyclooctane ring systems and should find extensive application to natural product synthesis.

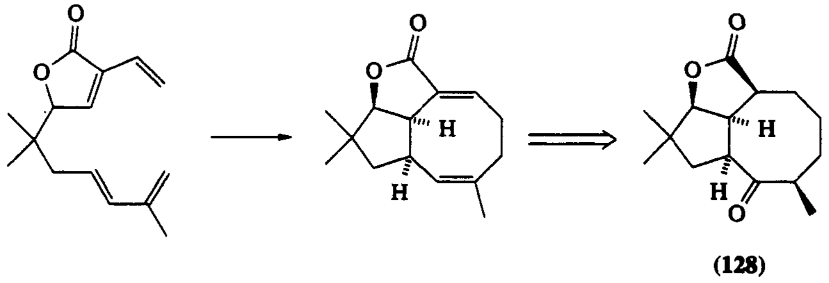

**Scheme 17**

The corresponding intermolecular nickel-catalyzed [4 + 4] cyclodimerization has not proven to be a useful synthetic tool, due primarily to low selectivities with unsymmetrical dienes and the general inefficiency of the reaction with dienes more complex than butadiene.[131,132] Several exceptions to this generalization do exist, however, as exemplified by the regio- and stereo-selective cyclodimerization of 1-trimethylsilyloxybutadiene in equation (6).[133,134] The presence of a substituent at the terminus of the diene is critical to the success of this reaction. However, 1,4-disubstitution on the diene completely suppresses the reaction. Methyl sorbate, for example, is recovered intact when exposed to the *in situ* generated $Ni^0$ catalyst used in these reactions. These few examples notwithstanding, it is clear that the intramolecular version of this coupling holds the most promise as a general synthetic method.

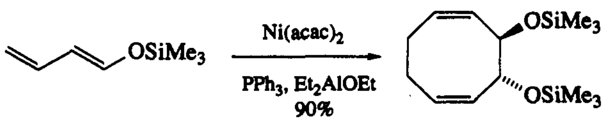

(6)

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# 5.3

# [3 + 2] and [5 + 2] Arene–Alkene Photocycloadditions

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## 5.3.1 INTRODUCTION

Arene–alkene cycloadditions (Scheme 1) are among the most theoretically intriguing and synthetically promising recent discoveries in organic chemistry, providing particularly efficient synthetic access to a range of natural and non-natural compounds from simple, readily available precursors.[1] Reflecting their enormous versatility and their consequent designation in this series as higher order cycloadditions, these reactions have the unique capability of producing from three- to nine-membered rings through [2C + 2C], [3C + 2C], [4C + 2C], [5C + 2C], [6C + 2C], [4C + 3C], [4C + 4C] and [5C + 4C] conjunctions of arenes with various π-systems. In this chapter, an overview of this fascinating class of reactions will be

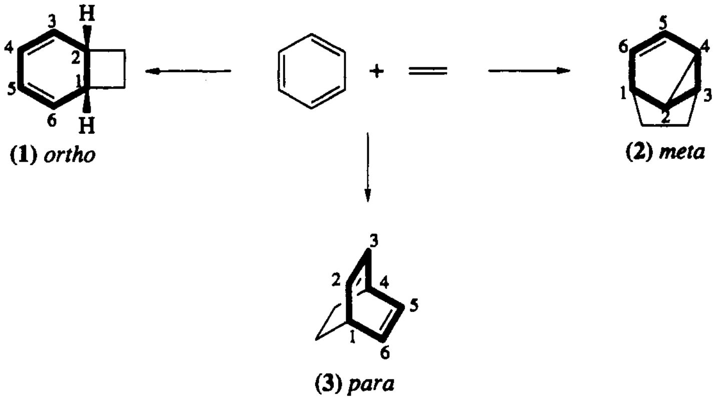

**Scheme 1**

presented. In accord with the goals and focus of this series, emphasis will be placed on developments of the last decade and on the unique role of these reactions in organic synthesis. Primary attention will be given to the *meta* cycloaddition reaction due to its more extensive development and use in synthesis. As a consequence of the inexorable relationship between synthesis and mechanism, this treatment will start with a brief historical perspective and mechanistic analysis.

## 5.3.2 HISTORICAL PERSPECTIVE

The genesis of contemporary arene–alkene photochemistry is marked in large measure by the 1957 publication of Bryce-Smith and Blair[2] in which irradiation of benzene is reported to give fulvene (equation 1). Serving to dispel the long-held view that benzene and its derivatives are photochemically inert, this finding did much to attract further interest to this unexplored field, leading in turn to the discovery of new rearrangement processes[3] and eventually the arene–alkene cycloadditions.

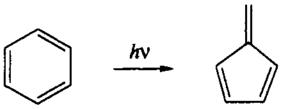

(1)

Of particular note in these early studies is the work of Bryce-Smith and Angus,[4] in which an attempt was made to trap the fulvene produced during the irradiation of benzene by conducting the reaction in the presence of a powerful dienophile, maleic anhydride. Instead of the expected Diels–Alder cycloadduct of fulvene, this reaction (equation 2) was found to yield a novel 2:1 adduct (5), which was subsequently shown[5] to form through initial photocycloaddition of maleic anhydride to the 1,2- or *ortho*-related positions of benzene, giving cycloadduct (4), which then provides (5) through a Diels–Alder cycloaddition. Analogous results were subsequently reported for the photo-mediated reactions of other dienophiles with benzene.[6] Contemporaneous work in the Büchi group[7] demonstrated that benzene derivatives are also capable of cycloaddition to alkenes. These seminal contributions, along with later reports from these and other investigators, served to illustrate the generality of the 1,2- or *ortho*-cycloaddition reaction and seeded the field for an even richer harvest.

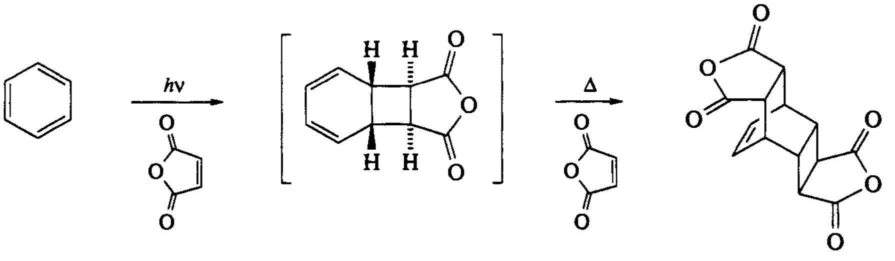

(4) (5)

(2)

Stimulated by these early discoveries, interest in the photochemistry of other arene–alkene systems grew rapidly, leading in 1966 to the co-discovery by Wilzbach and Kaplan[8] and by Bryce-Smith, Gilbert and Orger[9] of a second type of cycloaddition, involving bonding of an alkene to the 1,3- or *meta*-related positions of an arene (equation 3). Shortly thereafter, the first examples of a third type of cycloaddition were reported,[10] involving bonding of dienes and allenes to the 1,4- or *para*-related positions of the original arene ring (equation 4).

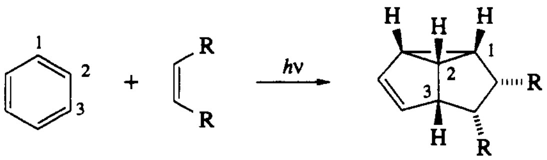

(6)

(3)

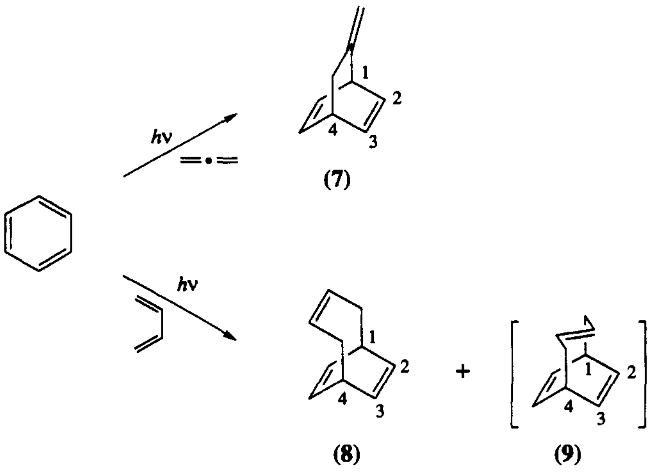

(4)

Following this exciting period of rapid discovery, investigations of arene–alkene cycloadditions focused more heavily on their scope and mechanism(s). Bryce-Smith and Longuet-Higgins[1f,11] were the first to present a theoretical treatment, providing an orbital symmetry analysis of the three types of cycloaddition. In connection with the possible role of charge transfer in these reactions, a mnemonic was introduced later by Bryce-Smith and Gilbert[12] for predicting the type of reaction an arene–alkene pair will undergo, based on the difference in their ionization potentials. In 1969, Morrison and Ferree[13] reported the first examples of an intramolecular arene–alkene cycloaddition (equation 5), discovered in the course of their exciting studies on bichromophoric compounds. Subsequent studies by the groups of Morrison,[1h] Srinivasan[14] and Yang[10c] implicated an exciplex intermediate in the cycloaddition process. More recently, Mattay and coworkers[1m–p] have provided direct spectroscopic evidence supporting such an intermediate, at least for some arene–alkene cycloadditions. Further studies in the 1970s, particularly by the Reading group and by Srinivasan and coworkers, served to test and refine previous mechanistic proposals, thereby substantially extending the generality of these reactions.[1a–f]

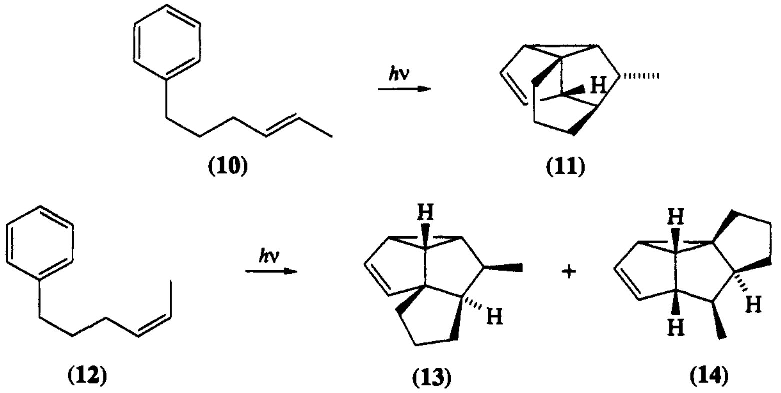

(5)

In 1981, Wender and Howbert[15] reported the first application of an arene–alkene cycloaddition in complex molecule synthesis. Heralding the spectacular synthetic efficacy offered by these reactions, this report provided a general protocol for the use of the *meta* cycloaddition in total synthesis, demonstrating its merit in a four-step total synthesis of (±)-cedrene (**17**; equation 6). In 1982, Houk[16] developed a significant extension of earlier mechanistic analyses based on a frontier molecular orbital treatment. Providing through calculations a better description of the energies of interacting orbitals than that derived from ionization potential differences alone, this treatment added a much-needed enhancement of predictive capability to the rapidly growing field. Efforts by the Sheridan group[17] on another aspect of these cycloadditions served for the first time to provide much needed information on the intermediacy of a diradical species in the latter stage of the *meta* cycloaddition. Concurrent experimental studies, highlighted in particular by the contributions of the Cornelisse group,[18] suggested that in the early stages of this process considerable charge transfer occurs between the arene and alkene. In recent years the Cornelisse[19] and Mattay[1m–p] groups have independently and collaboratively provided a rather impressive and appealing

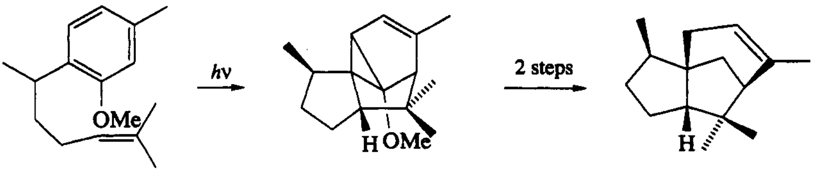

(15) (16) (17) Cedrene

(6)

general mechanistic treatment of the arene–alkene cycloadditions. Thus in a period of three decades the chemical community has witnessed the evolution of a new class of reactions, from an admittedly 'strange process'[1e] to one which is becoming better understood mechanistically and which has proven to be exceedingly effective for complex molecule synthesis.[1i,j,r]

## 5.3.3 MECHANISTIC CONSIDERATIONS

When an arene is irradiated in the presence of an alkene a number of processes can take place, including exciplex formation, excitation transfer, isomerization, addition, and cycloaddition. Of these, the pathways involving covalent association of the arene and alkene can lead to ene addition products as well as *ortho*, *meta* and *para* cycloadducts (equation 7).

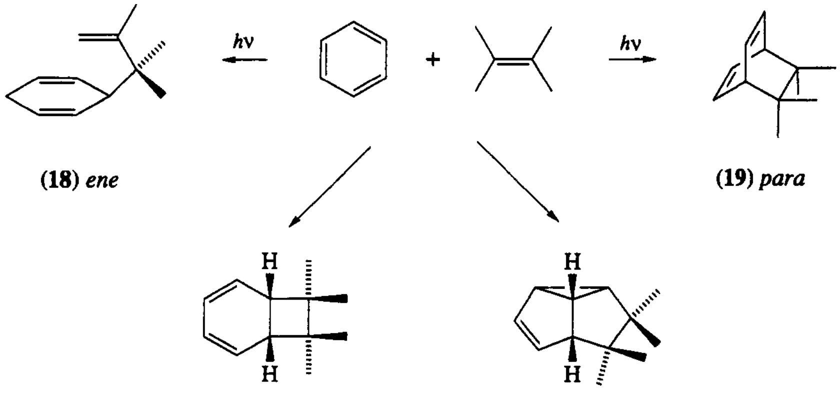

(18) *ene* (19) *para*

(20) *ortho* (21) *meta*

(7)

As noted above, Bryce-Smith and Longuet-Higgins[11,20] were the first to provide a theoretical treatment of these reactions. Using orbital symmetry arguments, they proposed that *ortho* and *para* cycloadditions of alkenes to benzene (and by analogy other arenes) are forbidden from the $^1B_{2u}$ ($S_1$) state, unless charge transfer is involved. *Meta* cycloadditions are considered to be allowed from this state with or without charge transfer. In a sequel to this contribution, which elaborated the charge transfer aspect of this analysis, attention was drawn to the relationship of the ionization potential difference (ΔI.P.) between the arene and alkene and the relative quantum efficiencies for their *meta* and *ortho* cycloadditions.[12] It was noted that reactions of benzene (I.P. = 9.24 eV) with alkenes having I.P.'s between 8.6 and 9.6 eV proceed generally with *meta*-mode selectivity. In contrast, when the ΔI.P. difference between the arene and alkene is greater than 0.6 eV, a situation which would favor charge transfer, *ortho* cycloaddition is preferred. While exceptions to these 'rules' have been noted,[1m–p] this analysis provided a much-needed organization of the field and the basis for further theoretical developments. As revealed in these subsequent studies, the main limitation of the ionization potential analysis rests on the fact that it is based solely on the energies of filled orbitals. The energies of unoccupied orbitals, derivable from electron affinity data, are not included even though they would figure in charge transfer interactions. These limitations were subsequently addressed by other workers and in a particularly effective fashion by Mattay.[1m–p]

While the orbital symmetry analysis of the arene–alkene cycloadditions addresses their 'allowedness', it does not specify a sequence for bond formation. It was recognized, however, that these cycloadditions could proceed stepwise and that in the specific case of the *meta* cycloaddition, three temporally distinct pathways are possible (Scheme 2): (a) a fully concerted path (A) where all bonds are formed simultaneously; (b) cyclization of the arene (B) to a prefulvene species (22), followed by addition of the alkene to carbons 2 and 4 (or 6) of this intermediate; and (c) complexation of the alkene to the excited arene (exciplex formation) or excitation of a ground-state complex, followed by bonding of the alkene to the *meta*-related carbons of the arene, and subsequent cyclopropane formation (C). Of these possibilities, the concerted process (A) has received little attention, in part because the extensive bond reorganization and nuclear motion is considered to be unlikely. This pathway also does not allow a simple rationalization of the regioselectivity observed in the cycloaddition. The prefulvene mechanism (B), on the other hand, was strongly favored in some early and even more recent discussions.[1f] Support for this mechanism was not unreasonably encouraged by the observation that while irradiation of arenes alone gives fulvenes, a *meta* cycloadduct is obtained when the same reaction is conducted in the presence of an alkene. Both results are in accord with the intermediacy of a prefulvene (22). However, as additional information on this reaction was obtained, it became increasingly apparent that its selectivity, particularly regioselectivity, could not be explained by a prefulvene intermediate. Deuterium labelling studies also revealed that bond formation between the arene and alkene occurs much in advance of cyclopropane bond formation,[18] which is opposite to what would be expected for a prefulvene mechanism. Finally, while not emphasized in these earlier discussions, it is also apparent that the addition of an alkene to a prefulvene would require bond formation to the sterically less-accessible concave face of the prefulvene.

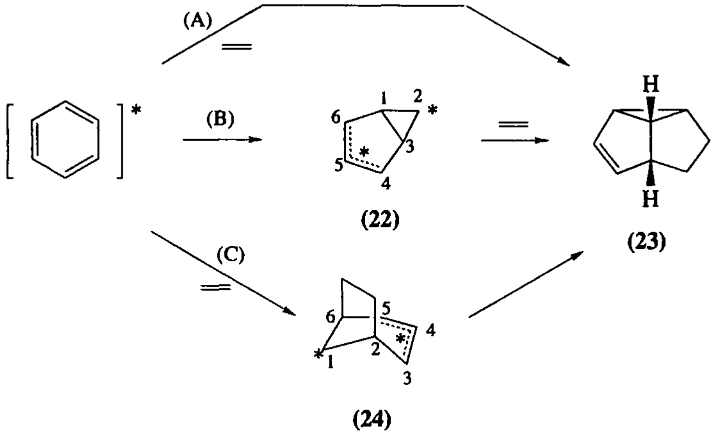

Scheme 2

Support for the third mechanism, the exciplex pathway (C), came initially from the studies of Morrison[1h] and of Srinivasan.[14] Morrison was able to show that quenching of the intramolecular cycloaddition of 6-phenyl-2-hexene is only about one-half as efficient as fluorescence quenching for this substrate, a result consistent with a short-lived, unquenchable cycloaddition precursor. While less direct, the stereoselectivities observed by Srinivasan[14,21] in studies on anisole derivatives are also interpretable in terms of an exciplex intermediate. Extensive studies by Cornelisse and coworkers[18,22] on substituent effects also suggest that the arene is already polarized at the stage when bond formation to the alkene begins, as would be expected for an exciplex involving charge transfer. More recently, Mattay[1m–p] has reported the observation of long-wavelength emission attributable to an exciplex and additionally has found that quenching of this emission and of product formation have identical rate constants.

In 1982, Houk[16] provided a frontier molecular orbital analysis for rationalizing the partitioning between *ortho*, *meta* and *para* modes of cycloaddition. In this treatment the HOMO and LUMO energies of the alkene were explicitly considered along with the energies of the singly occupied molecular orbitals (SOMO) of the excited arene. For the simple case of benzene and ethylene the relevant electronic configurations and their energies are given in Scheme 3. The actual orbitals for benzene are combinations of these; the lowest excited singlet is $^1B_{2u}$ (SA*–AS*). Consideration of the symmetry-determined mixing of these frontier molecular orbitals indicates that the ethylene HOMO can mix with the benzene S orbital to stabilize a *meta* cycloaddition and with the benzene A orbital to stabilize an *ortho* cycloaddition. Alkene interaction with A* is possible for both *ortho* and *meta* modes of cycloaddition.

Interactions leading to *para* cycloaddition (S + ethylene LUMO) are only weakly stabilized. *Para* cycloadditions are also disfavored by the distance-determined (2.79 Å) poor overlap between interacting orbitals of the arene with those of the alkene. From this analysis it is predicted that an *ortho* mode of cycloaddition will be favored for an arene AS* transition while *ortho* but preferentially *meta* cycloaddition will be stabilized in the SA* transition. In addition to symmetry considerations, the effectiveness of the

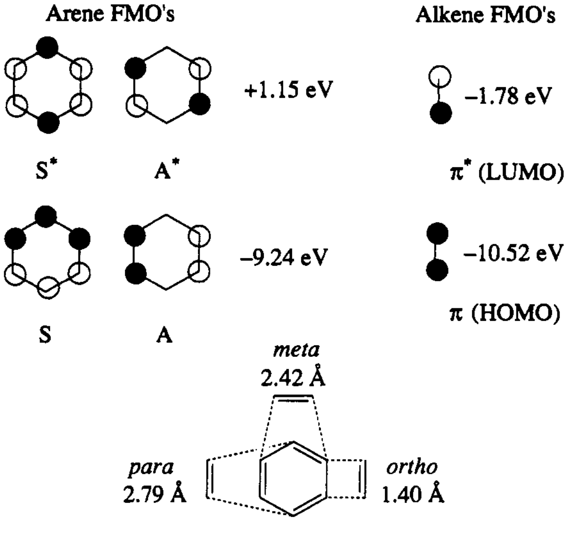

**Scheme 3**

indicated mixings are also related to the relative energies of the interacting orbitals. In order to obtain these energies, calculations at the STO-3G level (GAUSSIAN 82 program) were performed for the case of benzene and ethylene, fixed in parallel planes and separated by 2.5 Å (*i.e.* in a reasonable approximation of the exciplex).[23] The results indicate that the *meta* approach is favored slightly over the *ortho* approach (−1.32 *vs.* −1.25 eV, respectively), in agreement with experimental observations.[24]

In the case of donor-substituted arenes, this FMO analysis indicates that *meta* cycloaddition is favored over the *ortho* mode due to the preferential stabilization of the SA* transition (Scheme 4). This mode selectivity is indeed observed in numerous cycloadditions involving simple alkenes and alkoxy- or alkyl-substituted arenes.[1q] However, as the difference in energy between interacting orbitals is increased due to substituent effects, charge transfer becomes more important. In such cases, both *ortho* and *meta* modes of cycloaddition are possible but the former is usually preferred on the basis of its better orbital overlap.

FMO analysis further indicates that the magnitude of the coefficients of the interacting orbitals determines the regioselectivity of a cycloaddition. Thus for *meta* cycloadditions the increased size of the *ortho* coefficients relative to the *meta* in the S orbital of the arene leads to the expectation that the alkene will add across the donor group, *i.e.* to positions 2 and 6 or *ortho* and *ortho′* related to the donor-bearing atom (**25**, **26**; Scheme 4). The regioselectivity of the *ortho* and *para* cycloadditions can also be deduced through a similar analysis of orbital coefficients. Finally, the *exo*/*endo* selectivities of the *meta* and *ortho* cycloadditions are also rationalized in the FMO treatment by secondary orbital interactions. The *endo* selectivity observed in many *meta* cycloadditions is thus attributed to stabilizing secondary orbital interactions arising from mixing of the S and A* arene orbitals with the HOMO and LUMO orbitals of the alkene. The frequently observed *exo* selectivity of *ortho* cycloadditions is similarly treated by interaction between the arene S orbital and the alkene HOMO.

Recognizing the limitations of previous treatments, Mattay[1m–p] recently reported an analysis of arene–alkene cycloadditions which is noteworthy in its capacity to accommodate the observed polarization and steric effects and data supporting an exciplex intermediate. In this treatment, an empirical 'rule', derived from a correlation of reaction selectivity and the degree of excited state charge transfer,[25] is used to predict reaction mode selectivity for a wide range of arene–alkene reactions. The degree of excited-state charge transfer is estimated in this analysis from the free enthalpy of electron transfer ($\Delta G_{\mathrm{ET}}$), which in turn is calculated, using the Rehm–Weller equation (equation 8),[26] from the oxidation potential of the donor (D), the reduction potential of the acceptor (A), and the excitation energy of the reactant excited state. When $\Delta G_{\mathrm{ET}}$ is negative or nearly zero, addition is expected to predominate over cycloaddition, as is indeed observed in the reactions of certain electron-rich alkenes with excited-state arenes. When $\Delta G_{\mathrm{ET}}$ is positive, cycloaddition is expected, with *ortho* cycloaddition favored for values up to approximately 1.4–1.6 eV and *meta* cycloaddition is favored for more positive values.[19]

In 1987, Cornelisse and coworkers[19] reported a semi-empirical calculation for the *meta* cycloaddition of benzene with ethylene, which impressively consolidates many experimental aspects of this reaction and fits well with the Mattay analysis. This calculation, performed at the CNDO/S and MNDO levels, supports an exciplex mechanism with charge polarization, in accord with Mattay's treatment and a related mechanism developed earlier in the Cornelisse laboratories.[22] According to this mechanism (equa-

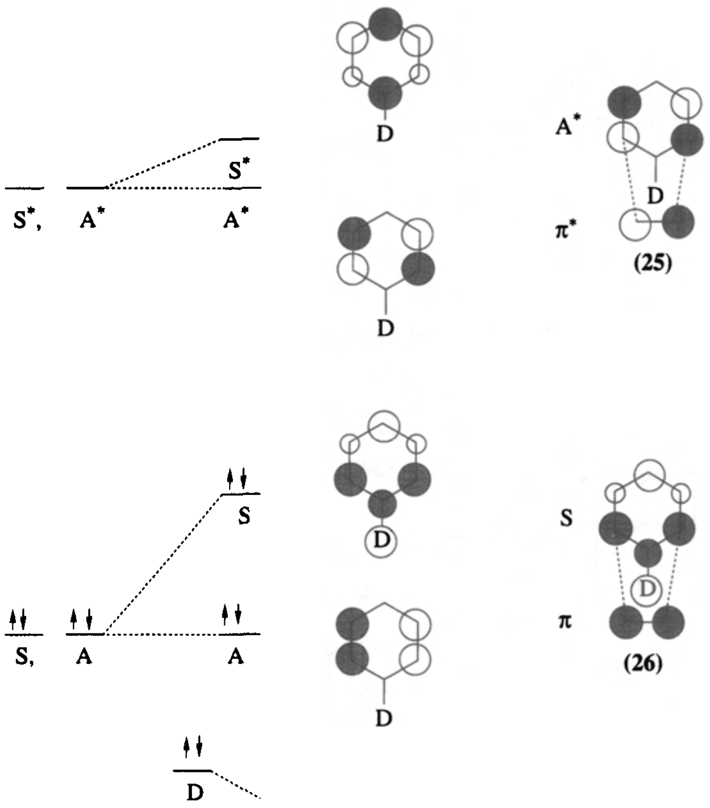

**Scheme 4**

$$\Delta G_{\mathrm{ET}} = F\left[E_{1/2}^{\mathrm{Ox}}(\mathrm{D}) - E_{1/2}^{\mathrm{Red}}(\mathrm{A})\right] - \Delta E_{\mathrm{excit}} + \frac{e^2N}{4\pi\varepsilon_0 a}\left[\frac{1}{\varepsilon} - \frac{2}{37.5}\right] \tag{8}$$

where $E_{1/2}^{\mathrm{Ox}}(D)$ and $E_{1/2}^{\mathrm{Red}}(\mathrm{A})$ = oxidation (reduction) potential of the donor (acceptor) molecule in acetonitrile; $E_{\mathrm{excit}}$ = excitation energy; $F = 96490$ Coulomb;

tion 9a), bonding between the arene and alkene precedes cyclopropane bond formation and occurs with appreciable polarization (see **27**) in the early stage of the reaction. As will be discussed shortly, this polarization effect allows one to rationalize the regio and *exo*/*endo* stereoselectivities of the *meta* cycloaddition. Importantly, the calculations further indicate that as the reaction proceeds, dipolar character dissipates and the system evolves along the reaction coordinate toward the cycloadduct (**29**) directly or through a nonpolar diradical (**28**) which then undergoes cyclopropane formation to provide the cycloadduct. Such a polarization–depolarization pathway explains the solvent and the deuterium-isotope effects associated with the reaction. It also can be used to rationalize the regiochemistry for at least the *meta* cycloaddition, since association of the arene and alkene would be expected to proceed in a fashion in which charge is stabilized by the arene substituents. This treatment also accommodates the intermediacy of a diradical species which has been implicated by several studies. Of particular note on this point are the impressive investigations of the Sheridan group (equation 10),[17] in which irradiation of either diazoalkene (**34**) or (**36**) is found to give the same product ratio as that observed in the direct irradiation of *m*-xylene (**37**) with cyclopentene. That such diradical species have never been observed in *meta* cycloadditions can be attributed to the large energy difference (22.9 kcal mol$^{-1}$), but the small energy barrier (7.5 kcal mol$^{-1}$) between the diradical and the cycloadduct.

In 1987, Mattay[1m] provided a rather comprehensive analysis of regioselectivity and *exo*/*endo* selectivity based on his previously developed charge transfer treatment and on a mechanistic treatment similar to that proposed by Cornelisse. This work incorporates many findings of earlier studies.[1] According to this treatment, these reactions are proposed to proceed through an exciplex which is polarized in proportion

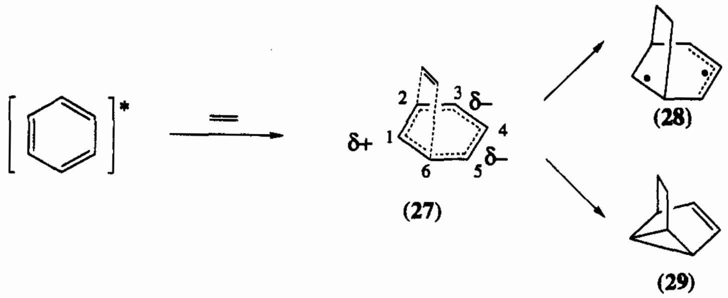

(9a)

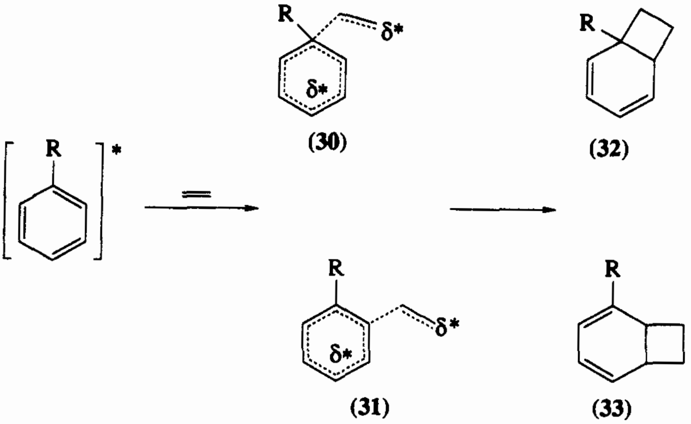

(9b)

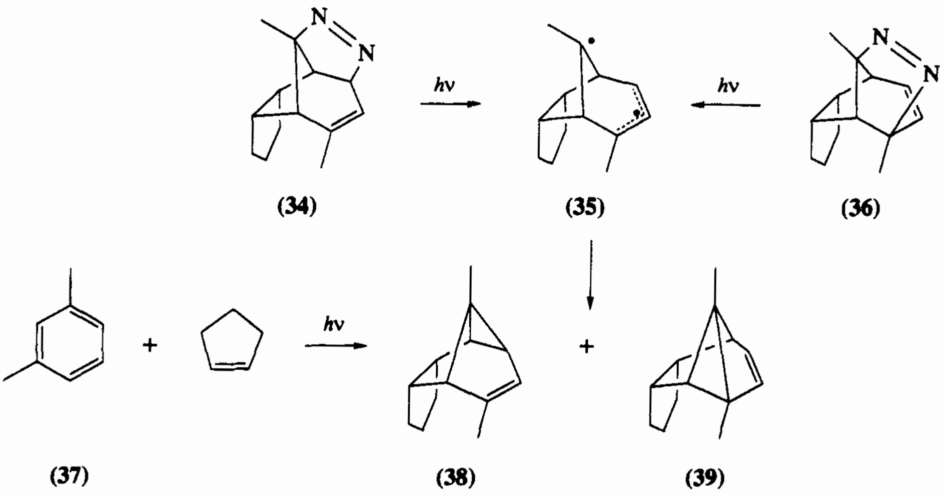

(10)

to the degree of charge transfer between the donor and the acceptor. Evolution of this species along the *meta* cycloaddition path occurs with polarization within the arene subunit (**27**; equation 9a) in advance of σ-bond formation, in accord with calculations[19] and experimental evidence.[18] As discussed in previous studies by Cornelisse, bond formation between the arene and alkene then proceeds in a fashion which maximizes charge stabilization by substituents on the arene ring in the early stage of the reaction (equation 9a). Consequently, donor groups at C-1 in (**27**) direct alkene bonding to positions C-2 and C-6 of the arene subunit since such groups would stabilize partial positive charge developing at C-1 in the early stage of the cycloaddition process. Conversely, acceptor groups at C-3 (or C-5 as numbered in **27**) would direct alkene bonding to positions C-2 and C-6 of the arene since such groups would stabilize partial negative charge build-up in the C-3—C-4—C-5 allyl subunit in the early stage of the reaction. This analysis is supported by experimental results: for alkoxy- and alkyl-substituted arenes, alkene addition occurs preferentially to positions C-2 and C-6 relative to the C-1 donor, while for acceptor-substituted arenes, such as trifluoromethylbenzene or cyanobenzene, alkene addition is preferentially directed to positions C-2 and C-6 relative to the C-3 acceptor group (as numbered in **27**).[18] Furthermore, for arenes bearing two substituents, addition is preferentially directed by the stronger donor or acceptor. The regioselectivity observed in *ortho* cycloadditions, while generally lower, is explained in a similar fashion involving species (**30**) and/or (**31**) (equation 9b), depending on the charge stabilization provided by R.

*Exo*/*endo* selectivity can also be rationalized on the basis of this treatment. An interesting example is provided by the *meta* cycloadditions of anisole with vinylene carbonate (**41**) and dioxole (**44**) (equation 11). Reactions of (**41**) give an *exo*/*endo* cycloadduct ratio of 0.5, while for the latter alkene a reversed preference is found, *i.e. exo*/*endo* = 3.2. In contrast to what would be expected on the basis of steric effects alone, a larger arene substituent, trimethylsilyloxy, gives even greater *exo* selectivity (9.3). This behavior can be explained if allowance is made for charge transfer. Thus polarization arising during the cycloaddition with (**41**) would electrostatically stabilize the *endo* addition mode (**43**) and destabilize the *exo* mode (**42**), the latter due to charge repulsion between the vinylene carbonate subunit and the alkoxy group of the arene. On the other hand, the more electron-rich dioxole (**44**) can serve as a donor in the cycloaddition, in which case charge repulsion is minimized along with steric effects in the *exo* orientation (**45**).

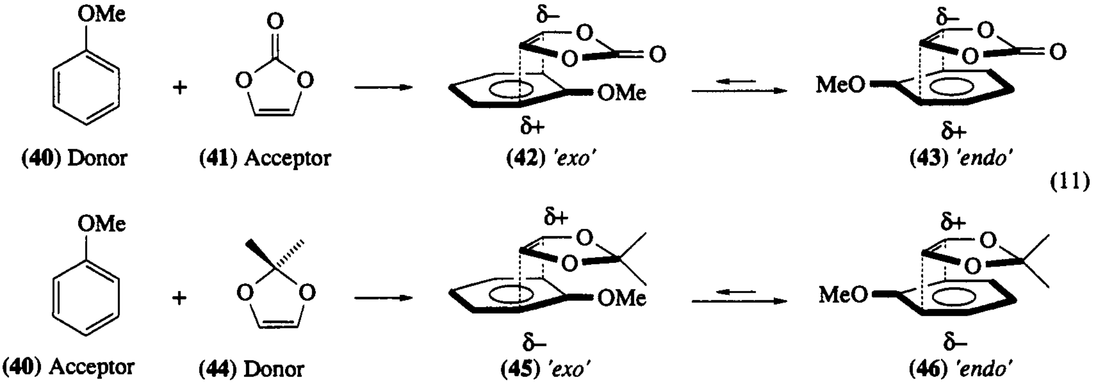

(**40**) Donor (**41**) Acceptor (**42**) *'exo'* (**43**) *'endo'*

(11)

(**40**) Acceptor (**44**) Donor (**45**) *'exo'* (**46**) *'endo'*

While the aforementioned electronic effects provide the basis for understanding many aspects of reaction selectivity, a complete analysis must also include orbital alignment and steric effects since in many cases these factors are dominant. For example, while most intermolecular *meta* cycloadditions involving alkyl- or alkoxy-substituted arenes and simple alkenes proceed with *endo* selectivity, the intramolecular *meta* cycloadditions generally give high, if not complete, *exo* selectivity.[1r] This difference in selectivity has been rationalized in numerous studies by Wender's group on the basis of steric effects associated with the formation and reaction of an exciplex. In this analysis (Scheme 5),[15] the plane of the alkene and that of the excited-state arene are oriented in a parallel fashion and separated by a distance of approximately 2.5 Å, in reasonable agreement with previous studies on exciplex systems[23] and the more recent calculations[16,19] noted above. The intermolecular reaction would then involve exciplex (**47**), in which an *endo* orientation is preferred due to secondary orbital interactions and, depending on substitution, electrostatic effects. In the corresponding intramolecular exciplexes, the favorable orbital alignment for *meta* cycloaddition is preserved only if an *exo* orientation (**48**) is adopted, as the *endo* exciplex (**49**) is poorly aligned. Moreover, *meta* cycloaddition proceeding *via* (**49**) would lead to the formation of a pro-

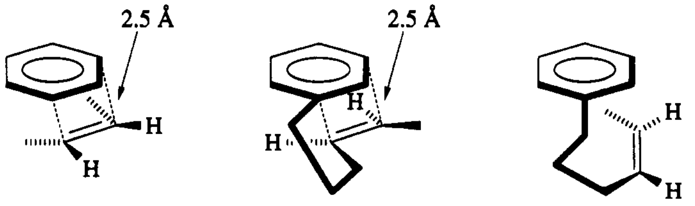

(**47**)
Intermolecular
exciplex model
(*endo* orientation)
Favored

(**48**)
Intramolecular
exciplex model
(*exo* orientation)
Favored

(**49**)
Intramolecular
exciplex model
(*endo* orientation)
Disfavored

**Scheme 5**

duct with a highly strained *trans*-fused bicyclo[3.3.0]octane subunit. In contrast, the corresponding *exo* cycloaddition process proceeds to a less-strained *cis*-fused bicyclo[3.3.0]octane product.

Steric effects on reaction selectivity are also interpretable in terms of this exciplex model. For example (Scheme 6), the cycloaddition of (*E*)-6-phenyl-2-hexene (**10**) proceeds as expected through exciplex (**50**) with addition of the alkene subunit to positions C-2 and C-6 of the C-1 donor-substituted arene.[1h] In contrast, irradiation of the (*Z*)-isomer (**12**) occurs with addition to positions C-1 and C-3 to give cycloadducts (**13**) and (**14**). This contrasting behavior provided an important starting point for studies in Wender's group, as it indicated that the seemingly abnormal behavior of the (*Z*)-isomer is simply a result of destabilizing nonbonded interactions which would arise in exciplex (**51**) if addition were to occur across the donor (alkyl) group. This interpretation was tested and figured significantly in several studies in total synthesis, as will be described below. Since this effect arises in intramolecular cycloadditions involving alkenes bearing a substituent which is (*Z*) related to the tether connecting the alkene and arene, it is commonly referred to as the (*Z*)-alkene effect.

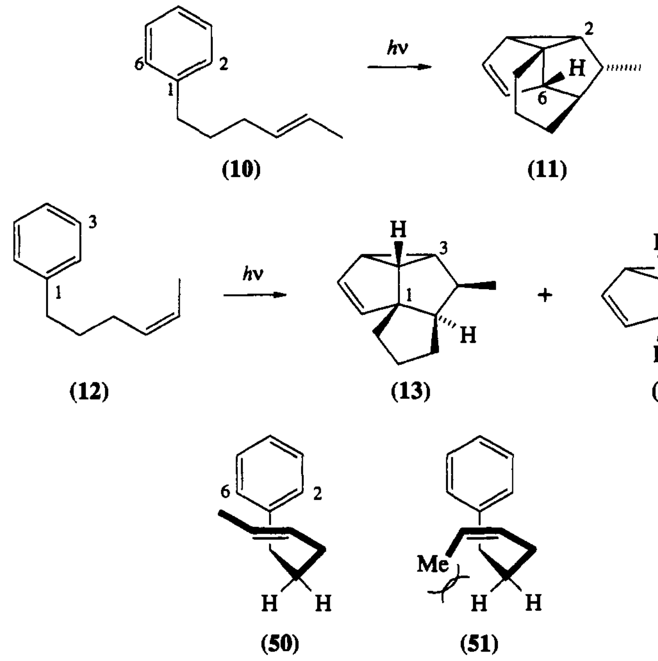

**Scheme 6**

Finally, steric effects have been observed to play a significant role in controlling the diastereoselectivity of the arene–alkene cycloadditions. Elaboration of this aspect of the reaction again rests on an exciplex model and will be provided in the context of synthetic applications where it has been most frequently encountered.

## 5.3.4 SUMMARY OF MECHANISM AND REACTION SELECTIVITY

The pathway depicted in Scheme 7 represents a consolidation of some of the more recent contributions noted above and is provided along with the following summary as a guideline for the implementation of this class of reactions in synthesis. Based on existing information, irradiation of an arene in the presence of an alkene appears to be a singlet process leading to an exciplex intermediate (**52**). The overall course (mode) of any ensuing photochemistry can then be predicted on the basis of this proposed intermediate. Based on the aforementioned charge transfer analysis, this species will be polarized in proportion to the donor and acceptor abilities of the arene and alkene. When charge transfer is highly favored (*i.e.* when $\Delta G_{\mathrm{ET}}$ for electron transfer is negative), substitution or ene reactions are expected (**52** to **53**). When charge transfer is relatively weaker, cycloaddition occurs, with *ortho*-mode selectivity (**54**) for $0 < \Delta G_{\mathrm{ET}} <$ 1.4–1.6 and with *meta*-mode selectivity (**27**) for $\Delta G_{\mathrm{ET}} >$ 1.4–1.6. *Para* cycloadditions are possible but disfavored by poor orbital overlap and primarily restricted to reactions of arenes with allenes, dienes and extended arenes.[27] Owing to the limited study of *para* cycloadditions, further generalization is at present inappropriate. Mode selectivity for *ortho* and *para* cycloadditions can also be rationalized on the basis of FMO analysis, although limitations have been noted.

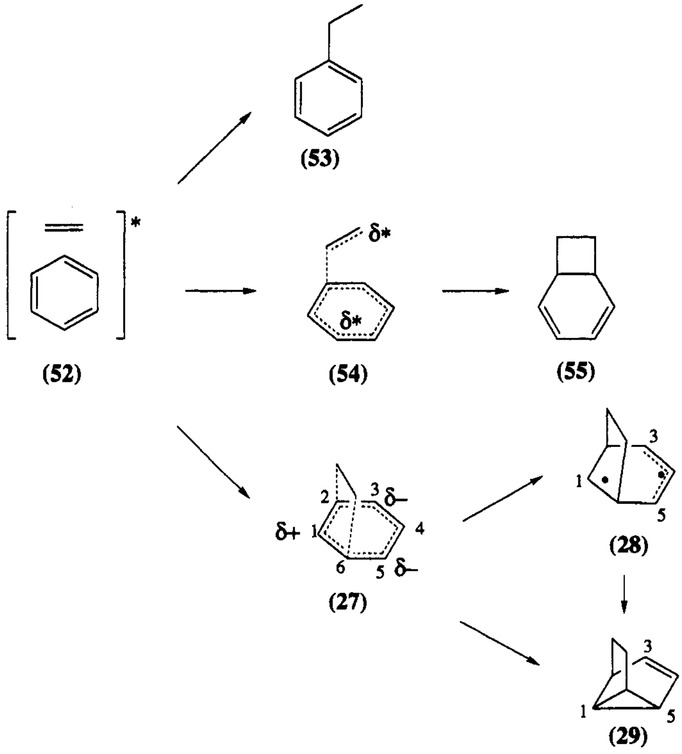

Scheme 7

In the next stage of the cycloaddition process, the weakly polarized exciplex is thought to evolve to polarized species (**54**) and/or (**27**), putatively involved in the *ortho* and *meta* cycloadditions, respectively. These species can be used to predict reaction regioselectivity. In the *ortho* mode of cycloaddition, regioselectivity is influenced by the degree of electron transfer and therefore the extent of polarization of (**54**), as well as the stabilizing effect of arene substituents and steric factors. Consequently, *ortho* addition to positions C-1 and C-2 of a C-1-substituted arene is preferred when $\Delta G_{\mathrm{ET}}$ of electron transfer is low (*i.e.* approximately zero) and when the arene substituent at C-1 is charge stabilizing. When electron transfer is less likely, the regioselectivity of the cycloaddition is low. In the *meta* mode of cycloaddition, regioselectivity can be similarly predicted on the basis of the effectiveness of substituents in stabilizing charge in species (**27**). Thus bond formation to positions C-2 and C-6 of the arene would be favored when a donor group is at C-1, where it could stabilize positive charge, and/or when acceptor groups are at C-3 and/or C-5 where they could stabilize negative charge. As bond formation progresses, steric effects on regioselectivity become more pronounced and occasionally override these electronic directing effects. For example, the *meta* cycloaddition of cyclooctene to toluene proceeds with essentially exclusive addition of the alkene to positions C-2 and C-6 of the arene, as would be expected for a C-1 donor-substituted arene.[28] However, when the arene methyl group is replaced by a sterically more-demanding *t*-butyl group, alkene addition to positions C-3 and C-5 is favored.[29] Similarly, as noted for the dramatically contrasting behavior of (*E*)- and (*Z*)-6-phenyl-2-hexenes (Scheme 6), steric and orbital alignment effects imposed by the intramolecularity of certain cycloadditions can override electronic effects.

The next selectivity issue, *exo/endo* preferences, can be predicted for both the *ortho* and *meta* modes of cycloaddition on the basis of secondary orbital interactions (FMO treatment) and by electrostatic considerations involving polarized species (**54**) and (**27**). In general, intermolecular reactions with simple alkenes proceed with *endo* selectivity. Heteroatom-substituted or polarized alkenes (equation 11) give *exo/endo* mixtures, whose composition can be explained by electrostatic considerations. Intramolecular cycloadditions of simple alkenes and arenes joined by a three-atom tether generally proceed with high *exo* selectivity due in part to orbital alignment effects. In all cases, alkene geometry is preserved, except for sterically encumbered alkenes, in which case excitation transfer from the arene to the alkene can occur.

As alkene bonding progresses in the *meta* cycloaddition, calculations[19] and experimental evidence[17,18] suggest that dipolar character dissipates, resulting in one scenario in the direct formation of cycloadduct (**29**) or in another in the intermediacy of diradical species (**28**) (Scheme 7). For the latter, closure to the cycloadduct(s) would then proceed with bond formation between C-1 and C-3 and/or C-5. Factors contributing to the selectivity of this closure have not been fully investigated and indeed they are frequently obscured by the fact that many *meta* cycloadducts can be photoisomerized. For example, irradiation of arene-alkene (**56**) (equation 12) gives two cycloadducts (**57**) and (**58**) in a ratio of 1:4.5, respectively, at short reaction times whereas prolonged irradiation produces a 1:2.6 mixture.[30] Either isomer can be photoequilibrated. While caution is thus required, it would appear on the basis of many studies that the final closure favors formation of the less-strained cycloadduct. Cycloadduct (**58**) is thus favored over (**57**) because the alkyl groups at C-1 and C-8 are less sterically congested in the former as a result of its longer C-1—C-8 (cyclopropane) bond. Electronic factors are also expected to play a role in the final closure due to the differing interactions of substituents attached to normal *versus* cyclopropane bonds. Examples of this selectivity will be presented in the next section.

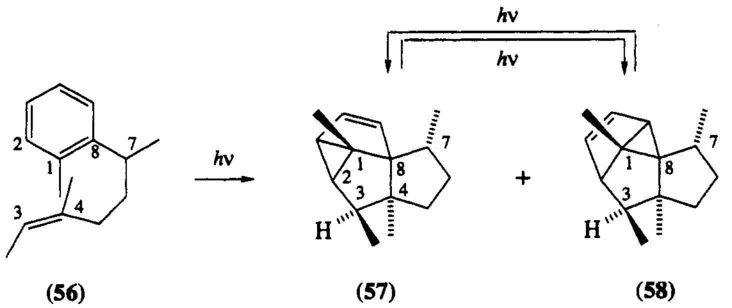

(12)

The final major selectivity issue associated with the arene–alkene cycloadditions pertains to the influence of preexisting stereogenic centers on the course of the reaction. This selectivity has been rationalized by Wender's group in numerous studies on the basis of the aforementioned exciplex model for *meta* cycloaddition, from which steric interactions can be determined for all possible cycloadditions. For example, arene-alkene (**59**) (equation 13) could in principle produce cycloadducts (**61**) and (**62**) with a β-oriented C-2 methyl group and/or (**64**) and (**65**) with an α-oriented C-2 methyl group. Examination of the exciplex (**63**) leading to the latter pair, however, clearly reveals a destabilizing nonbonded interaction involving the benzylic methyl group and the methoxy group of the arene. Formation of the diastereomerically related exciplex (**60**) is thus favored, in agreement with the observed highly selective, if not exclusive, formation of cycloadducts (**61**) and (**62**).[15]

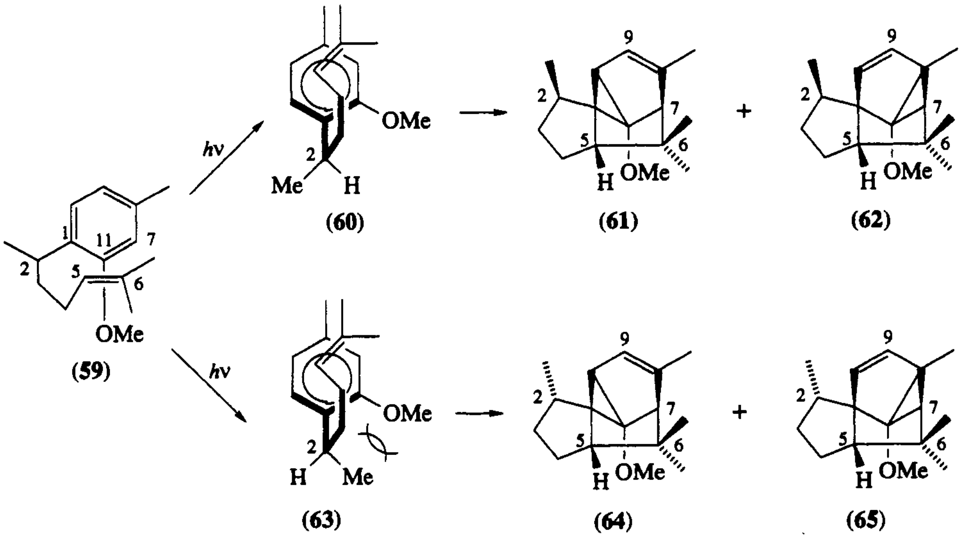

(13)

## 5.3.5 GENERAL SYNTHESIS DESIGN CONSIDERATIONS

Organic synthesis has evolved rapidly and impressively since its genesis in the nineteenth century, with each generation defining an ever-more demanding set of goals. As empiricism gave way to mechanistic understanding, a foundation was laid for the realization of greater control over reaction selectivity and thereby the advent of complex molecule synthesis. The past three decades have witnessed impressive successes in the synthesis of complex structures. Indeed, the problems posed by many synthetic targets are now 'solved' at a practical level. However, for the majority of synthetic problems, solutions either do not exist or are not practical. In general, few solutions approach the ideal, wherein the target is prepared from readily available starting materials in one step which proceeds in 100% yield and which is operationally safe and simple and ecologically acceptable. Obviously, this is a rather demanding but not unrealistic objective. While it is unlikely to be commonly realized, attempts to achieve this level of sophistication are of great importance as they are likely to produce fundamentally new and practical solutions which will clearly have a profound impact on the ways in which total synthesis will be used in the future.

The relationship of the arene–alkene cycloadditions and other strategy level reactions of this calibre to this goal of simplifying complex molecule synthesis can be appreciated from an analysis of a typical synthesis. Generally, a total synthesis proceeds from simple starting materials to a complex target. While 'simple' and 'complex' are frequently intuitive or at best qualitative descriptors of molecules, it is possible to determine more quantitatively these relative attributes of structure through the use of simple graph theory.[31] In essence, the atoms and bonds of a molecule can be related to the points and lines of a graph. The relative complexity of a graph (molecule) is therefore a function of the number of points (atoms) in the graph (molecule) and of the nature and number of their connections (bonds). It necessarily and objectively follows from this consideration that the average complexity increase per step in a synthesis determines the total number of steps needed to produce the target (complexity level), provided that the increase is relevant to the target. From a chemical viewpoint, this is equivalent to stating that the average number of target bonds formed per step necessarily determines the number of steps needed to complete a synthesis. Consequently, the incorporation of reactions like the arene–alkene *meta* cycloaddition, the Diels–Alder cycloaddition, or polyene cyclizations into a synthetic plan will generally produce a greater increase in average complexity per step in the synthetic sequence, thereby leading to a shorter synthesis. The ramifications of these considerations will become apparent as this analysis turns to synthetic applications.

From another viewpoint, the value of the arene–alkene *meta* cycloaddition arises from its capacity to produce a cycloadduct (**66**; equation 14) with three new rings and up to six new stereocenters, an impressive feat even when compared with the highly regarded Diels–Alder cycloaddition. Moreover, the cycloadduct can be used in the synthesis of a variety of commonly encountered structural types including cyclopentanes, cycloheptanes, bicyclo[3.2.1]octanes and bicyclo[3.3.0]octanes. While frequently overlooked in some discussions of reaction classification, the overall processes leading to cycloheptanes, bicyclo[3.2.1]octanes and bicyclo[3.3.0]octanes are clearly classifiable as [5C + 2C], [3C + 2C] and [3C + 2C] cycloadditions, respectively. Examples of these types will be given in the following section.

While providing less of a complexity increase than the *meta* cycloaddition, the *ortho* and *para* modes of cycloaddition (equation 15) nevertheless offer a significant increase, not unlike that attending the Diels–Alder reaction. In both, a new ring and up to four contiguous stereocenters are formed. From a synthetic view, the *ortho* cycloaddition offers access to four- and six-membered rings, bicyclo[4.2.0]octanes, and eight-membered rings, the last through cleavage of the ring fusion bond. These processes are formally examples of [2C + 2C] and [6C + 2C] cycloadditions. The *para* cycloaddition also affords access to six-membered rings as well as bicyclo[2.2.2]octanes through a [4C + 2C] connection. *Para* cycloadditions involving dienes or a second arene additionally provide access to eight-membered rings through a [4C + 4C] cycloaddition.

## 5.3.6 SYNTHETIC APPLICATIONS

With the above synthetic considerations as a backdrop, the use of the arene–alkene cycloaddition in complex molecule total synthesis can now be examined. The emphasis here will be on the *meta* cycloaddition process since it has received the most study. It will become apparent, however, that even this reaction has received relatively little attention in synthesis in spite of its enormous potential. This situation is likely to change rapidly as recent theoretical and synthetic advances are assimilated.

The first example of the application of the arene–alkene *meta* cycloaddition in complex molecule synthesis was the total synthesis of the sesquiterpene cedrene (**82**; Scheme 8).[15] This target was selected for

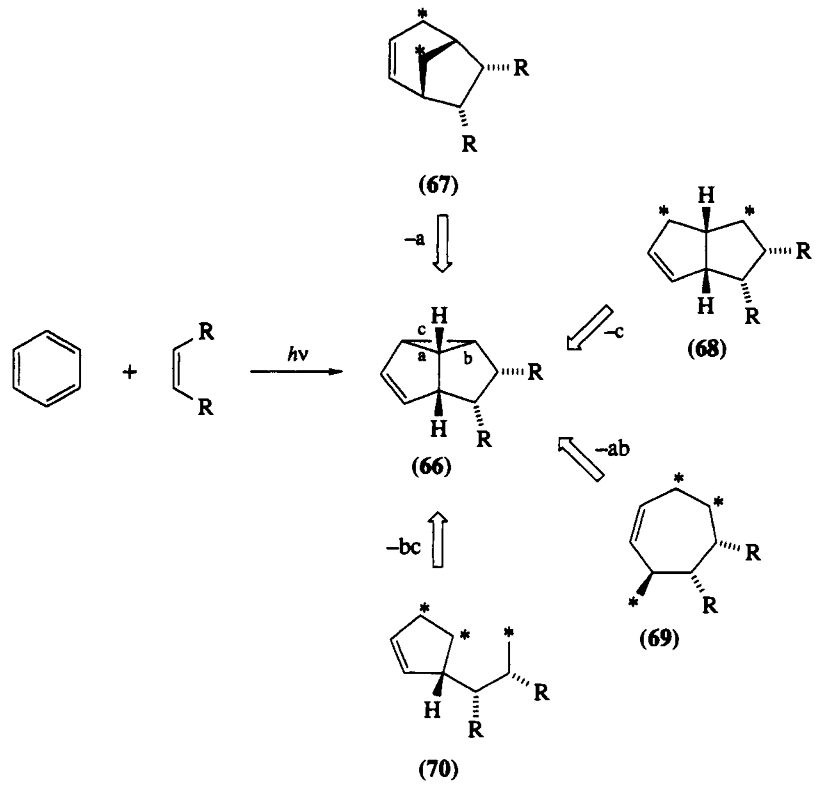

(14)

study because it offered the opportunity to investigate several issues of crucial importance to the broader implementation of this reaction in synthesis, including mode, regio and *exo*/*endo* selectivity and, for the first time, stereoinduction. From a retrosynthetic analysis, it is seen that the bicyclo[3.2.1]octane subunit of cedrene could arise from a [3C + 2C] cycloaddition, allowing for the connection of carbons 1 with 5 and 7 with 6, respectively. This connectivity is exactly that which would arise from the *meta* cycloaddition of arene-alkene (**59**). While not required in the product, the oxidation (methoxy group) at C-11 in this precursor was expected, for reasons discussed above, to control regioselectivity and to simplify the task of transforming the cycloadduct into the desired target.

That arene-alkene (**59**) would give the desired cycloadducts rested on several assumptions which can now be presented in terms of the previous discussion. Thus, with respect to mode selectivity, it is seen that the substitution of the arene and alkene in (**59**) is that which would be expected on the basis of FMO and charge transfer treatments to lead to a *meta*-selective process. This is further supported by earlier studies showing that alkyl-substituted anisoles give *meta* cycloadducts with simple alkenes.[21] While these studies also indicate that *ortho*-substituted anisoles give low yields of cycloadducts, the intramolecularity of the proposed route to cedrene would favor the cycloaddition. The regioselectivity of the key step in the cedrene synthesis (**59** to **61** and **62**) is predictable from two considerations: a methoxy group is known to be a stronger director (donor) than an alkyl group in intermolecular *meta* cycloadditions[21] and should therefore be the dominant director in (**59**), and *meta* addition across the C-1 alkyl group would be disfavored by the (*Z*)-alkene effect (Scheme 9), *i.e.* by nonbonded interactions of the type which were previously invoked to explain the contrasting regioselectivities observed in the cyclizations of (*E*)- and (*Z*)-6-phenyl-2-hexenes. With regard to *exo*/*endo* selectivity, cycloaddition of (**59**) should favor *exo* addition (**84** > **85**) since such a process allows for better orbital overlap in the precursor and for the formation of a less-strained cycloadduct (with a local *cis*-fused bicyclo[3.3.0]octane subunit). The influence of the benzylic stereogenic center on the stereochemical course of the reaction can be predicted from a consideration of the remaining exciplex possibilities, (**86**) and (**87**). A nonbonded interaction between the benzylic methyl group and the methoxy group of the arene would destabilize exciplex (**87**), thereby favoring formation of cycloadducts (**61**) and (**62**) *via* the alternative exciplex (**86**). Molecular mechanics calculations place the steric energy difference between these exciplexes at approximately 1.5 kcal mol$^{-1}$. Finally, since the regioselectivity of cyclopropane formation could not be predicted at the time of this analysis, the synthesis design allowed for the use of both possible cycloadducts as cedrene precursors. This analysis set the stage for the experimental evaluation of its underlying assumptions.

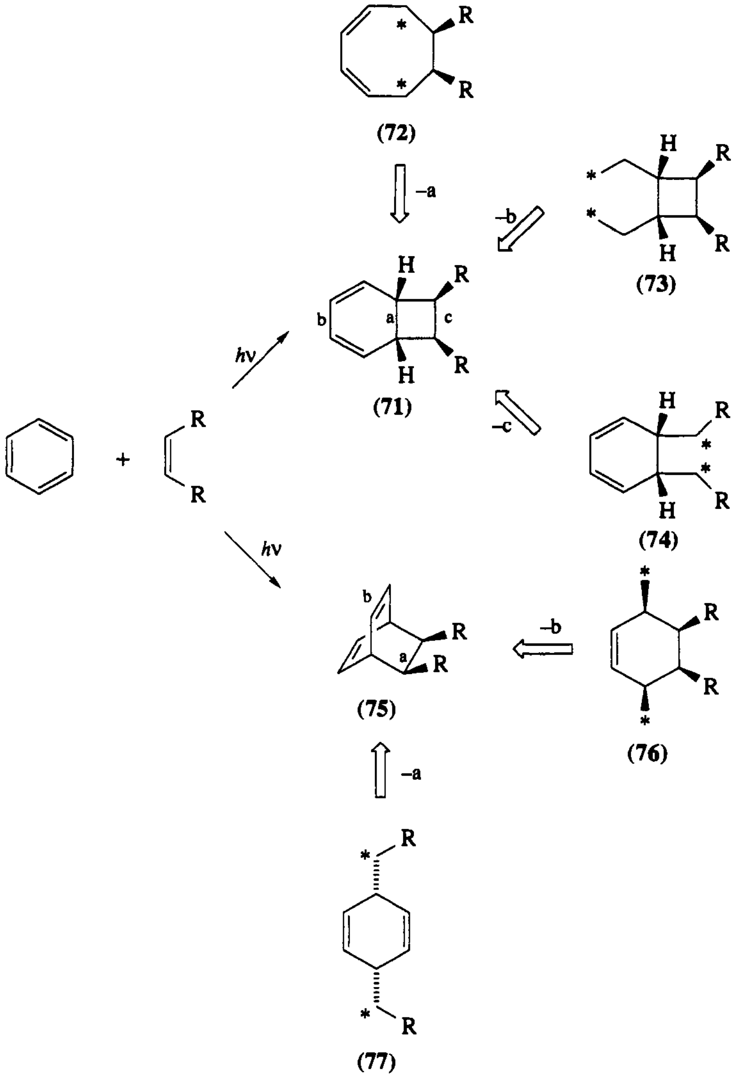

(15)

The design of many syntheses evolves from an analysis of the suitability of certain strategy level reactions for solving target-related problems, as exemplified in the preceding paragraph. The overall efficacy of a design is also, however, a function of how easily the starting materials for key steps can be made and how readily the products of these steps can be converted to the desired target. Arene–alkene cycloadditions fare rather well when judged by these criteria. Typically, the cycloaddition precursors are readily prepared through a variety of processes which allow coupling of an arene to an alkene, a notable example being the reductive condensation procedure developed by the Hall group.[32] According to this procedure (Scheme 8) the starting material for the key step in the cedrene synthesis was prepared by treating bromoanisole (**79**) with excess lithium metal (high sodium content) to provide an aryllithium intermediate which was then treated with commercially available ketone (**78**). Addition of ammonia to this reaction mixture resulted in reduction of the initial addition product and the formation of arene-alkene (**59**) in high yield.

In accord with the above analysis and its underlying assumptions, irradiation of arene-alkene (**59**; Scheme 8) results in the highly selective formation of cycloadducts (**61**) and (**62**) (70% yield), differing only by the regiochemical sense of cyclopropane formation. The isomeric nature of these cycloadducts is demonstrated by their photointerconversion and by their subsequent conversion to cedrene. Cleavage of the cycloadducts to cedrenone (**80**) is accomplished directly with acid. However, a brominative cleavage is more reproducible, giving bromocedrenone as an intermediate which is readily reduced with tri-*n*-butyltin hydride to afford (**80**). The selectivity of these cleavages is thought to be governed by formation of a cyclopropylcarbinyl cation (or its equivalent) at C-9 and by the stabilization provided by the methoxy group during the cleavage of the proximate cyclopropane bond. Subsequent deoxygenation of C-11 pro-

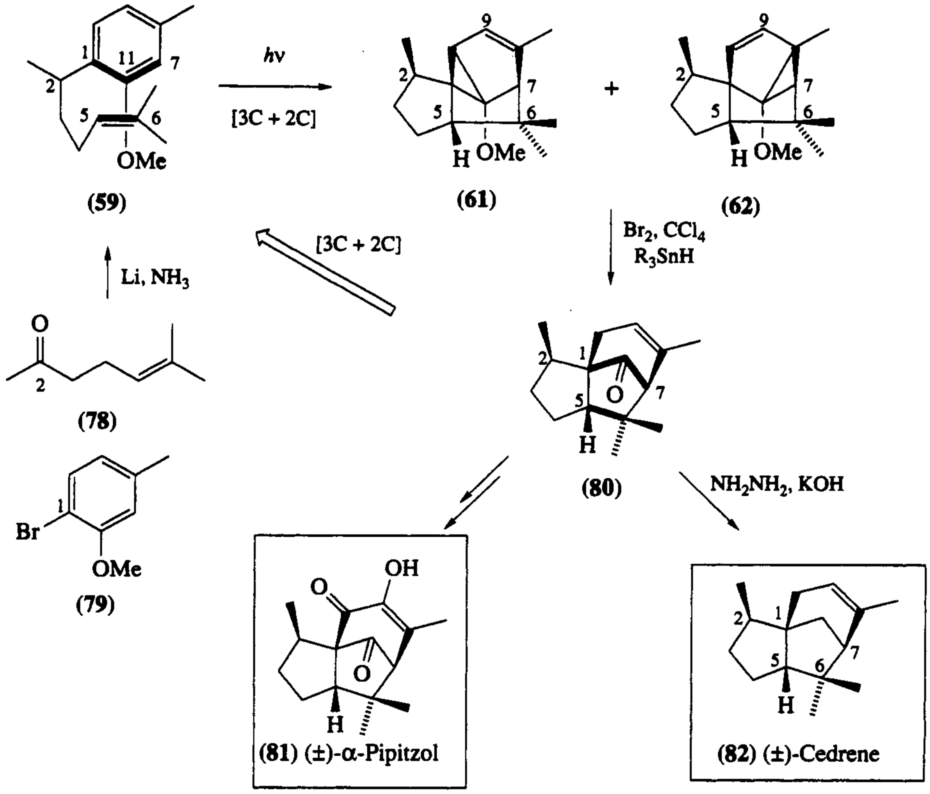
(59)
hν
[3C + 2C]
(61)
+
(62)
Li, NH3
[3C + 2C]
Br2, CCl4
R3SnH
(78)
(79)
(80)
NH2NH2, KOH
(81) (±)-α-Pipitzol
(82) (±)-Cedrene

Scheme 8

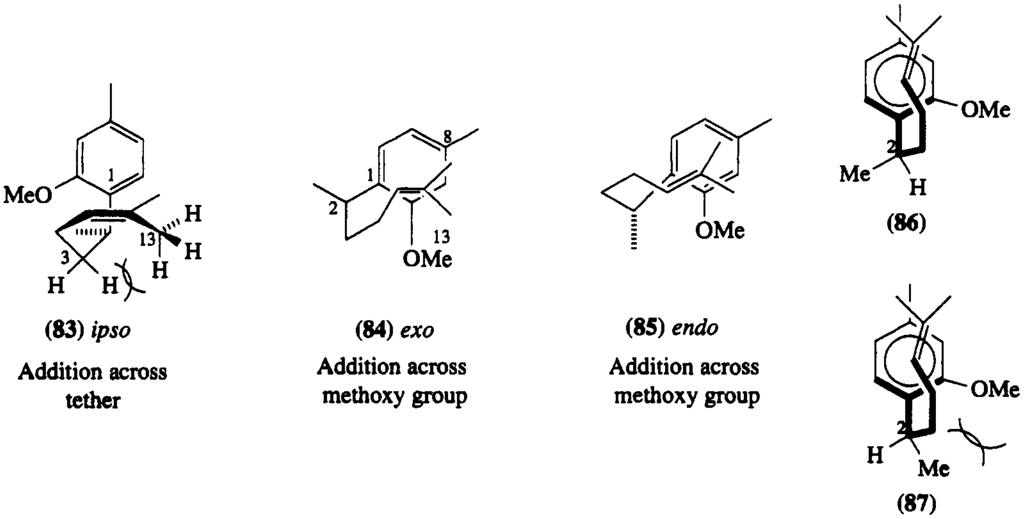
(83) ipso
Addition across tether
(84) exo
Addition across methoxy group
(85) endo
Addition across methoxy group
(86)
(87)

Scheme 9

vides cedrene (**82**) in a total of four steps from commercially available starting materials. The effectiveness of this synthesis, when compared with other syntheses of this molecule, is a predictable consequence of the aforementioned relationship of reaction complexity to brevity of synthesis design. Cycloadducts (**61**) and (**62**) have also been used in a comparably efficient synthesis of α-pipitzol (**81**), a more highly oxidized member of the cedrene family.

The synthesis of cedrene served to establish a firm foundation for the implementation of the *meta* cycloaddition in complex molecule synthesis and allowed also for a comparison of the effectiveness of an arene–alkene based strategy with the many impressive approaches to this well-known target. On the other hand, the next application of the *meta* cycloaddition was directed at isocomene (**90**; Scheme 10),[30] a relatively new structural motif but one which has been found with increasing frequency in new natural products of biological interest. The retrosynthetic analysis of isocomene derives from the recognition that its ring system is composed of two bicyclo[3.3.0]octanes, either representing a substructure of a *meta* cycloadduct. While a synthesis could thus be fashioned around either subunit, the sequence selected for study allowed for an evaluation of the stereochemical fate of the alkene subunit as well as a further examination of synthetic issues tested up to that point only in the cedrene synthesis. The success of this sequence rests in part on the expectation that the target could be derived from the partial hydrogenation of diene (**89**), which in turn could be obtained from cycloadduct (**57**) *via* a sigmatropic 1,5-H shift. The effectiveness of this strategy for selectively cleaving this cycloadduct is completely dependent on the configuration of C-3, since as required by mechanistic considerations and supported in work on simple cycloadducts reported by Srinivasan,[33] only an α-oriented hydrogen at C-3 could participate in the required rearrangement. The stereogenesis of C-3 occurs during the cycloaddition and can be controlled only if the geometry of the starting alkene is retained during the course of the reaction. Previous studies of inter-[34] and intra-molecular[1h] cycloadditions involving simple disubstituted alkenes support such an expectation, but the fate of more sterically encumbered alkenes was uncertain since loss of stereochemistry could occur through a sterically less-demanding excitation transfer process.

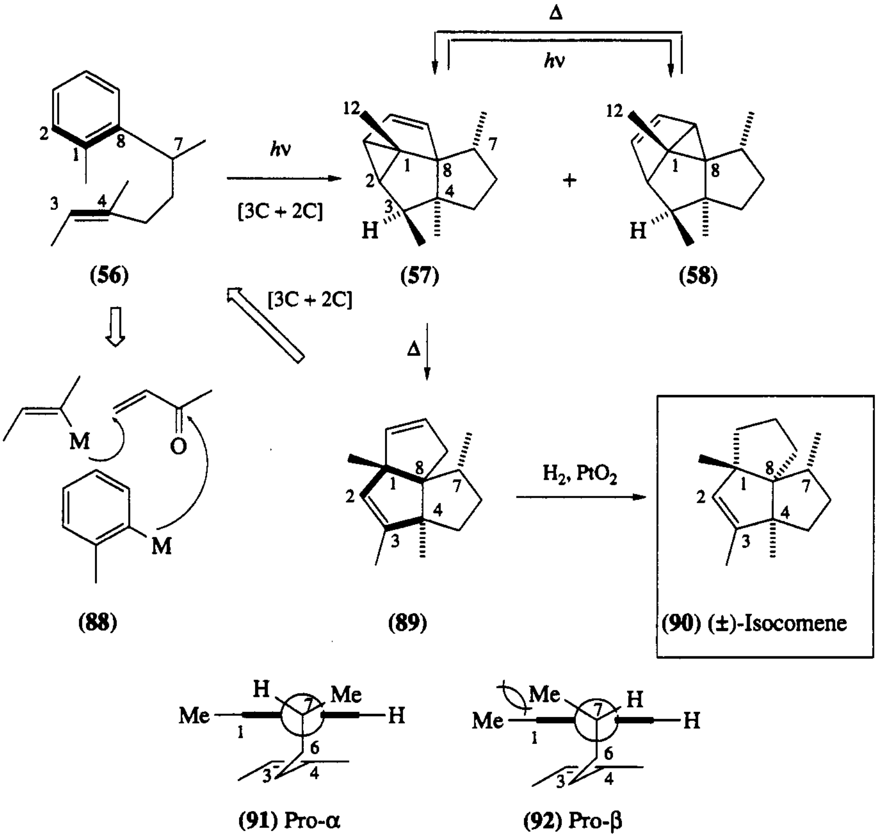

**Scheme 10**

Along with the above issues, the design for the synthesis of isocomene incorporated a further test bearing on the interplay of steric and electronic effects. Specifically, the *meta* cycloaddition of arene-alkene (**56**) would be expected to proceed regio-randomly with alkene addition directed equally well by the C-1 methyl (donor) and the C-8 alkyl (donor) groups, based on electronic considerations alone. However, if the previously discussed (*Z*)-alkene effect were to be manifested in the cycloaddition, the reaction would be expected to proceed in only the desired regiochemical sense. Resolution of the remaining issues of selectivity draw heavily on the cedrene work, leading to the expectation of an *exo*-selective addition based on orbital overlap considerations and of high stereoinduction favoring the pro-α exciplex (**91**) due to steric destabilization which would inhibit formation of the pro-β exciplex (**92**). This analysis proved to be in agreement with the experimental results, as irradiation of arene-alkene (**56**) gives cycloadducts (**57**) and (**58**) (1:2.5) in 72% yield, each ostensibly arising from exciplex (**91**). In connection with a caveat made earlier, it is important to note that at shorter irradiation times these cycloadducts are produced in a 1:4.5 ratio and each cycloadduct can be photoisomerized to the other, suggesting that caution be exercized in evaluating literature data which does not discriminate between kinetic and photo-equilibrated mixtures.

The conversion of the cycloadducts (**57**) and (**58**) to isocomene proceeds according to plan. Thermolysis of the former provides diene (**89**), which is also obtained from cycloadduct (**58**), presumably *via* a 1,3-alkyl shift which produces (**57**) as an intermediate. Partial hydrogenation of diene (**89**) affords isocomene in six steps from commercially available starting materials. The brevity of this approach to such angularly-fused triquinanes is a further manifestation of the synthetic benefit arising from the complexity increase associated with the *meta* cycloaddition.

Perhaps the best example of the efficacy of the arene–alkene cycloaddition in the synthesis of angularly fused tricyclopentanoids is seen in the three-step total synthesis of silphinene (**98**; Scheme 11).[35] As in isocomene, the key to this synthesis is again based on the recognition that the bicyclo[3.3.0]octane subunit of the target could be derived through the [3C + 2C] connectivity established in a *meta* cycloaddition. Silphinene (**98**) is thus related to cycloadduct (**96**), which in turn is the cyclization product of arene-alkene (**95**). As discussed above, this arene-alkene would be expected to undergo *meta* cycloaddition across the C-3 methyl group, since addition across the C-8 alkyl group would be disfavored by the aforementioned (*Z*)-alkene effect. Furthermore, *exo* addition would be favored over *endo* on the basis of orbital overlap considerations. Finally, stereoinduction should be high, comparable with that obtained in the isocomene synthesis, since the basis for control remains relatively unchanged.

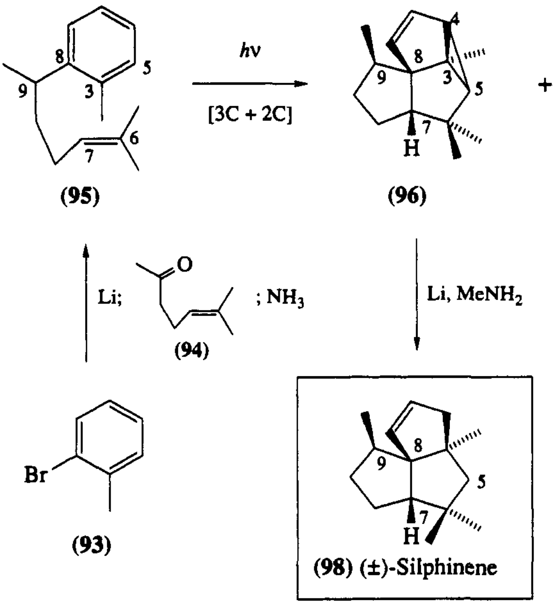

Scheme 11

The key precursor in the silphinene synthesis, arene-alkene (**95**), is obtained in one step from commercial materials and provides, in accord with the above analysis, cycloadducts (**96**) and (**97**) (1:1) in 70% yield. Mode, regio-, *exo*/*endo*- and stereo-selectivity are essentially complete. Transformation of cycloadduct (**96**) to silphinene involves reduction with lithium in methylamine, which proceeds with formation of the alkene radical anion and subsequent rupture of the better aligned cyclopropane bond (C-4—C-5 > C-3—C-4). Requiring only three steps from commercial materials, this synthesis dramatically illustrates how complexity can be rapidly built up through strategies based on the *meta* cycloaddition.

The successful elaboration of isocomene and silphinene provides the basis for the general application of the arene–alkene *meta* cycloaddition to targets incorporating an angularly fused tricyclopentanoid ring system. A further and significant illustration of the exquisite effectiveness of this process for this structural class is seen in the synthesis of laurenene (**102**; Scheme 12),[36] the first naturally occurring rosettane. As determined by other contemporaneous efforts, the synthesis of laurenene can require in excess of 30 steps, but as few as 13 steps when derived through the *meta* cycloaddition. The key to simplifying this structure centers again around the recognition of the relationship between its bicyclo[3.3.0]octane subunits and the structure of a *meta* cycloadduct. For reasons relating to the execution of this plan, the specific *meta* cycloadduct which figures in this effort is **(100)**, which is seen to be a product derivable from arene-alkene **(99)**. The expectation that **(100)** should be the major or exclusive cycloadduct follows largely from the silphinene synthesis. Thus the (*Z*)-alkene effect precludes *meta* addition across C-8 while addition across C-1 would incur greater steric interaction with the cycloheptyl ring than would be expected for addition across C-4 involving the hydropyranyl ring. In accord with this analysis, irradiation of **(99)** does indeed give cycloadduct **(100)** in 51% yield. Significantly, unlike many other types of cycloaddition, *meta* cycloaddition proceeds efficiently even when three contiguous quaternary centers are developed. Furthermore, only one vinylcyclopropane isomer is produced. As previously discussed, the factors determining this (cyclopropane formation) selectivity are not generally understood, although strain minimization appears to be important. Thus cycloadduct **(100)** is calculated to be less strained than its vinylcyclopropane isomer by some 5 kcal $mol^{-1}$.[37] Completion of the laurenene synthesis from the cycloadduct exploits the cyclopropane bond cleavage employed in the silphinene synthesis, allowing for the conversion of **(100)** to diol **(101)**. Reduction of this diol gives laurenene **(102)**, in 13 steps overall.

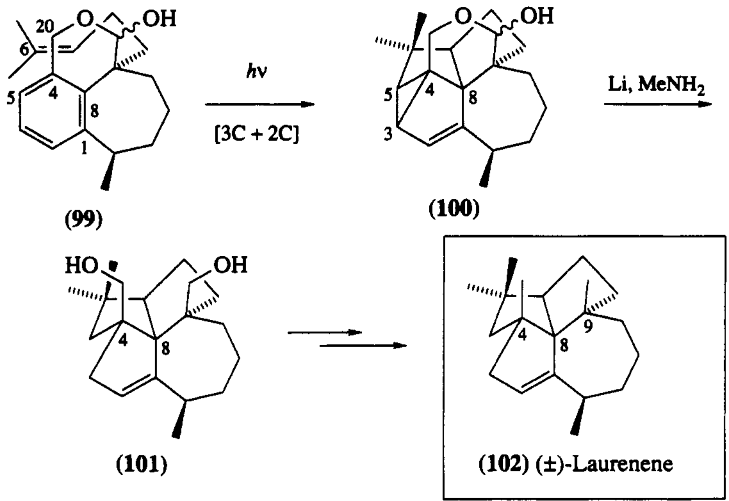

Scheme 12

A novel strategy for rosettane synthesis is also seen in the work of Keese and coworkers.[37] As illustrated in Scheme 13, the tricyclopentanoid subunit of the rosettane target **(106)** is assembled through a *meta* cycloaddition, after which the fourth target ring is elaborated through conventional cyclization

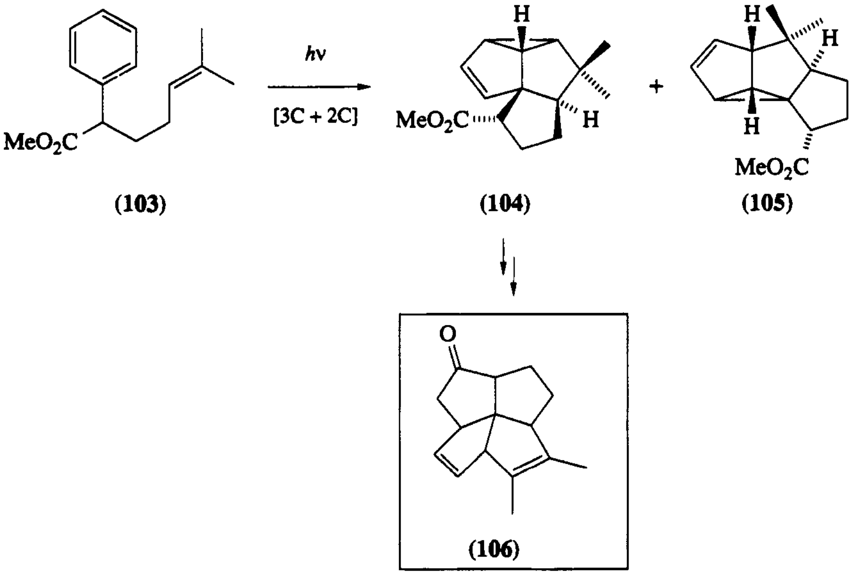

Scheme 13

techniques. The regioselectivity of the *meta* cycloaddition process can be attributed to the aforementioned (*Z*)-alkene effect, which would disfavor addition across what is otherwise a donor (alkyl)substituted center. The diastereoselectivity of this cycloaddition is that expected from steric considerations, as the larger benzylic substituent (ester > H) emerges on the sterically less-encumbered face of the local bicyclo[3.3.0]octane subunit of the products (**104** and **105**).

A further example of the arene–alkene *meta* cycloaddition in angularly fused tricyclopentanoid synthesis is seen in the syntheses of the silphiperfolenes, which were designed, in part, to evaluate the influence of an allylic stereogenic center on the cycloaddition and thereby to extend the aforementioned exciplex model.[38] For these syntheses, illustrated here in the case of silphiperfol-5-ene (**113**; Scheme 14), it was expected that the target would arise through cyclopropane cleavage of cycloadduct (**110**), which in turn would be derived from arene-alkene (**109**). The cycloaddition was expected to proceed through exciplex (**114**), as formation of the diastereomeric exciplex (**115**) would be destabilized by the indicated methyl–methyl interaction. In practice, irradiation of (**109**) produces cycloadducts (**110**) and (**111**), each arising from addition across the C-4 methyl group. Isomers arising from addition across the C-8 alkyl group are also presumably formed. With respect to the key issue in this study and in accord with the exciplex model, allylic stereoinduction (*i.e.* by the C-9 stereogenic center) appears to be complete. A further finding of this study is a new cyclopropane cleavage reaction which involves addition of an acetyl radical to the convex face of the C-6—C-7 double bond of cycloadduct (**110**), thereby controlling C-7 stereochemistry and producing a C-6 radical which then induces rupture of the adjacent C-3—C-5 bond. C-4—C-5 cleavage is disfavored due to the poor orbital alignment of this bond with the C-6 radical center.

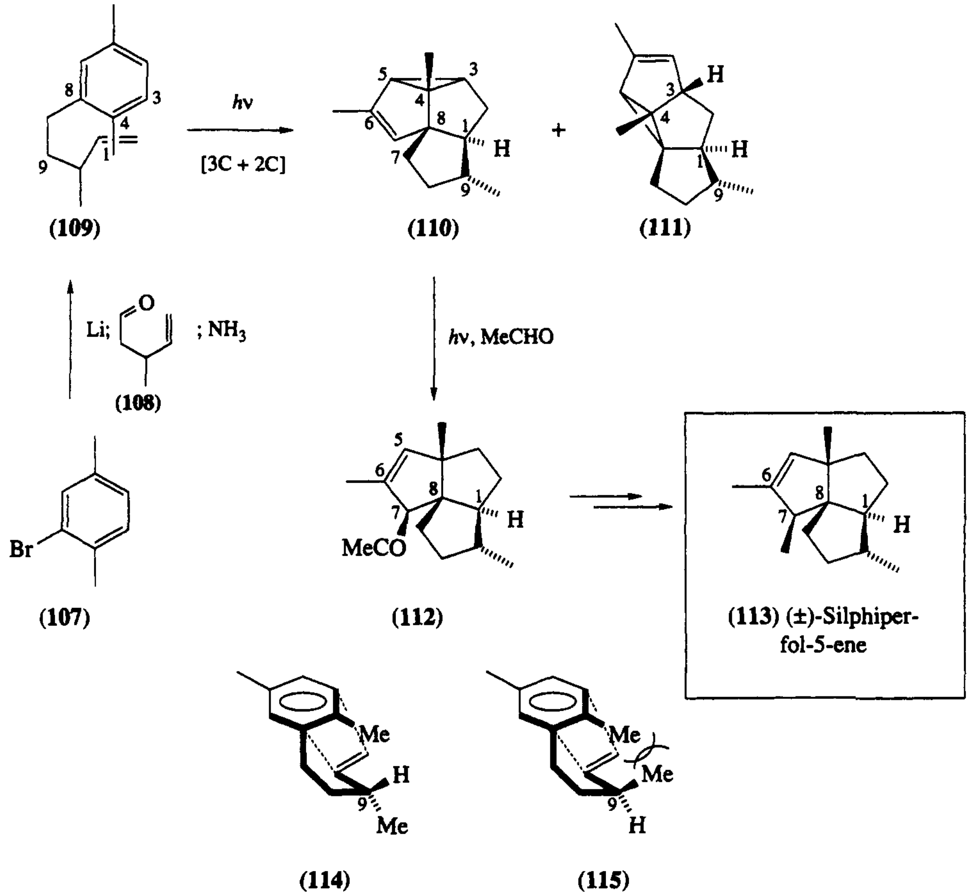

Scheme 14

The strategy explored in the syntheses of the siphiperfolenes has more recently proven effective in the asymmetric total synthesis of (–)-retigeranic acid (**122**),[39] as illustrated in Scheme 15.

Another major tricyclopentanoid structural motif, the tricyclo[6.3.0.0$^{2,6}$]undecane skeleton of the so-called linearly fused triquinanes, is also readily accessed by using the *meta* cycloaddition process, as

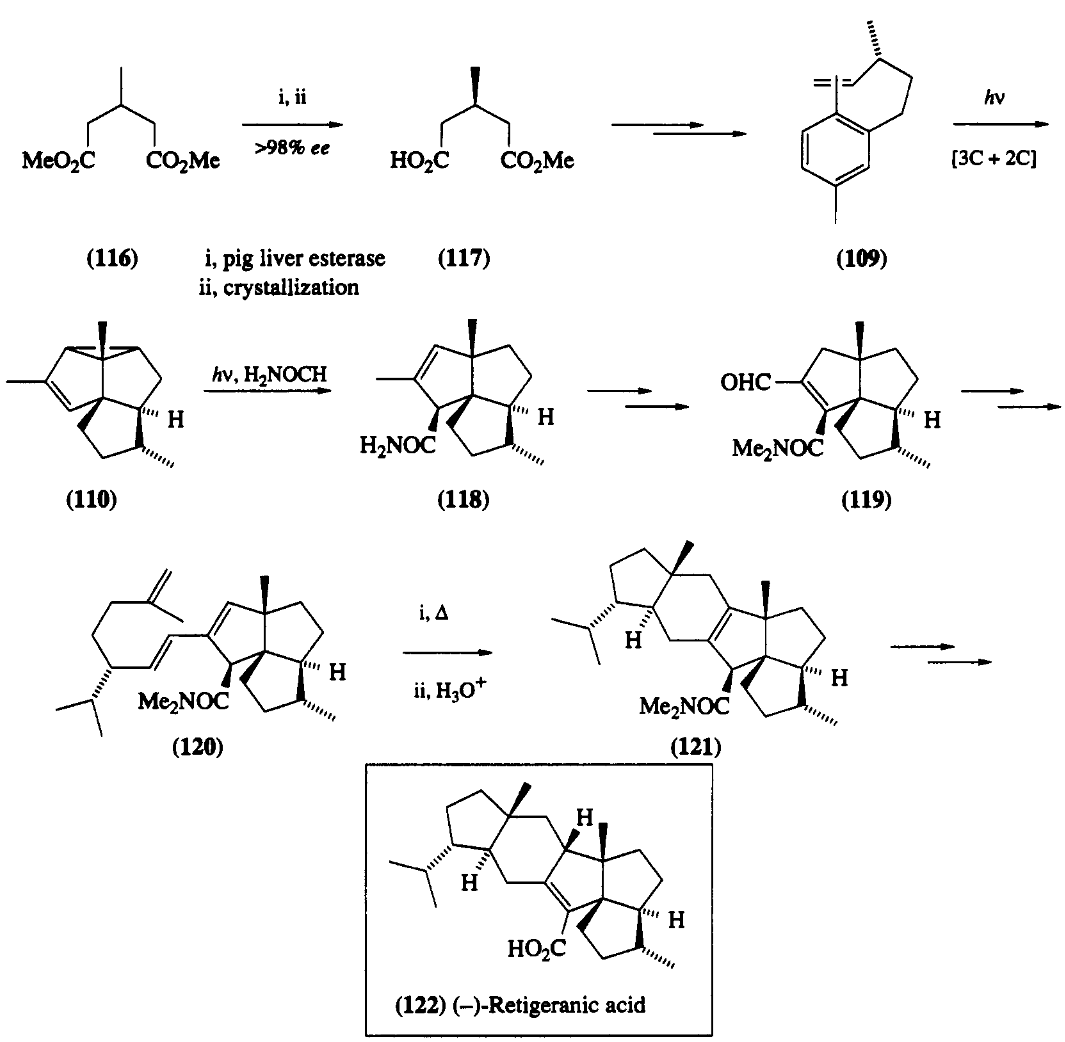

**Scheme 15**

exemplified in the syntheses of hirsutene (**129**; Scheme 16)[40] and coriolin (**135**; Scheme 17).[41] Examination of the *cis-anti-cis* ring fusion stereochemistry of hirsutene reveals that it is concealed within a cycloadduct (*e.g.* **126**) arising from a *meta* cycloaddition of a 5-aryl-1-pentene (*e.g.* **125**). An important feature of this cycloaddition is that its *exo*/*endo* selectivity as the target requires the hydrogen at C-9 in the cycloadduct to be *anti* to the hydrogen at C-7 as well as to the C-3 methyl group (see exciplex **130**). Stereochemistry arising at C-2 after cleavage of (**126**) can be expected to favor formation of the less-strained *cis*-fused ring system relative to the corresponding *trans*-fused bicyclo[3.3.0]octane. In the specific case of hirsutene, this stereochemistry was expected to arise through hydrogenation of a protected form of triene (**128**). The formation of this triene in turn illustrates another method available for the deconvolution of *meta* cycloadducts, specifically that in which a leaving group (at C-1 in **126**) external to the cycloadduct core is used to trigger opening of the cyclopropane system. While two cyclopropane bonds could participate in such a process, C-2—C-4 cleavage is expected to be favored over C-2—C-3 cleavage since the former would proceed with formation of a tertiary allylic carbonium ion. Given the role of the C-1 leaving group, the configuration of C-1 is not necessarily significant. However, the stereochemistry arising in the cycloaddition of (**125**) would reveal new information about the intrinsic stereo preference of a benzylic group, since in contrast to previous studies this group is flanked in (**125**) by equivalent *ortho* substituents. A further feature of interest in this study is the regioselectivity of the cycloaddition, since arene-alkene (**125**) possesses neither a dominant director group nor a (*Z*)-alkene. However, models do indicate that addition across the C-2 alkyl group would result in the development of a more congested (strained) cycloadduct than that arising from addition across the C-3 methyl group. Of course, these arguments are based on an expectation that cycloaddition will be *meta selective, which* is not unreasonable given the substitution of the arene and alkene subunits.

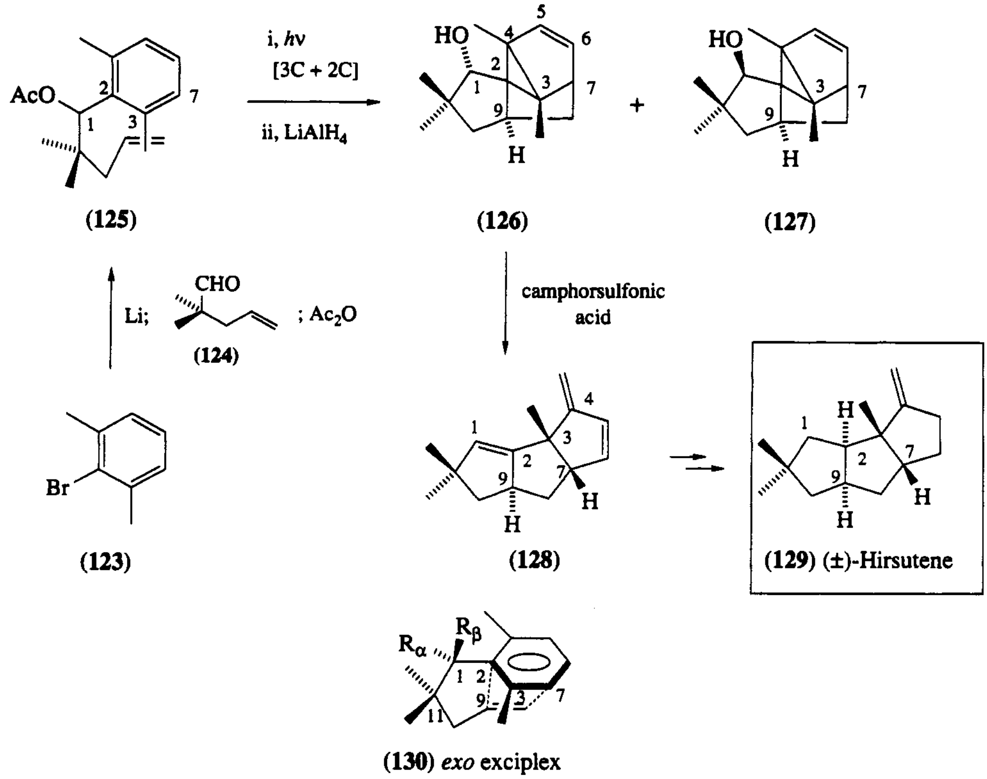

Scheme 16

The arene-alkene (**125**) required in the synthesis of hirsutene is easily prepared through the condensation of the aryllithium derived from (**123**) with aldehyde (**124**) and quenching of the addition product with acetic anhydride. Photolysis of (**125**) is followed by the reductive removal of the acetate group, which provides products (**126**) and (**127**) (3:1, respectively) in 33% yield along with minor amounts (7% and 2%) of the vinylcyclopropane isomers corresponding to the angularly fused cycloadducts. The preference for the α-acetoxy epimer in this cycloaddition is attributable to product development control, since in this epimer the acetoxy group is on the sterically less-congested face of the local bicyclo[3.3.0]octane subunit. This result is also in accord with the aforementioned work reported by Keese.[37] As discussed previously, solvolysis of (**126**) affords triene (**128**) which upon selective reduction provides hirsutene (**129**).

Drawing heavily on the 'model' studies with hirsutene, the synthesis of coriolin (**135**; Scheme 17) requires that provision be made for the additional oxygenation of the target and that an alternative cycloadduct cleavage method be employed. The key cycloaddition step involves the irradiation of arene-alkene (**131**) which gives the desired cycloadduct (**133**), albeit in low yield (15%), presumably due to enhanced steric congestion arising from the positioning of the bulky acetal group in the vicinity of the three developing, contiguous quaternary centers (C-2, C-3 and C-4). This congestion is further reflected in the fact that, in this reaction, starting material undergoes (*E*)–(*Z*) isomerization. However, the (*Z*)-isomer reacts preferentially to give the desired product. While otherwise problematic, the steric effects operating in this cycloaddition work to increase stereoselectivity since the benzylic (C-1) acetoxy group is now more strongly directed to the less-congested α-face than is found in the cyclization of arene-alkene (**125**). The completion of this synthesis involves a novel method for cycloadduct cleavage (**133** to **134**) in which the addition of a thiophenoxy radical leads to the formation of a cyclopropylcarbinyl radical, triggering homolytic rupture of the better aligned (C-2—C-4 > C-3—C-4) cyclopropane bond and generation of a C-2 radical. Hydrogen abstraction by this radical proceeds with the formation of the thermodynamically preferred *cis*-fused product (**134**), from which coriolin is derived.

A third general, structural motif of the tricyclopentanoids, the propellane system, is exemplified by modhephene (**140**; Scheme 18).[42] Retrosynthetically, the core ring system of modhephene is seen to be

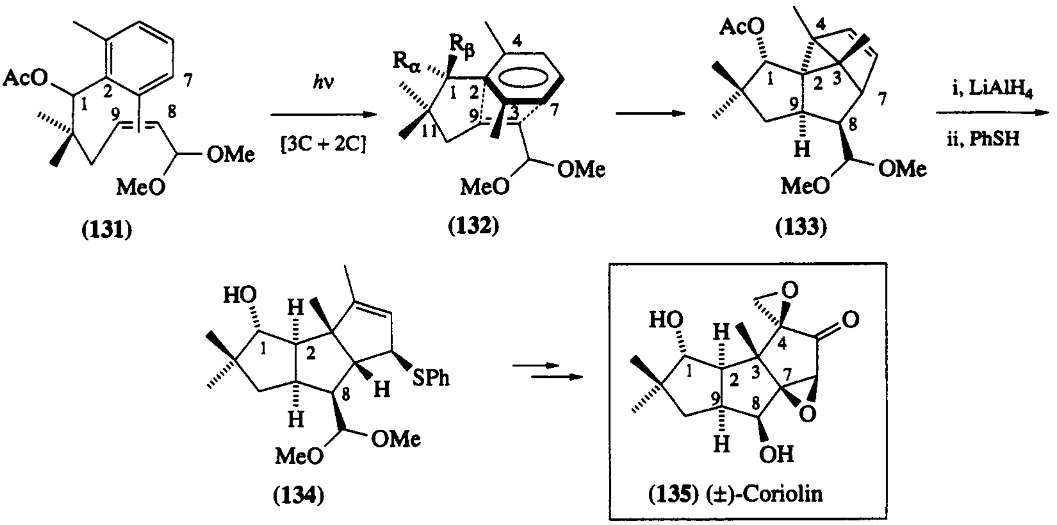

Scheme 17

related to *meta* cycloadduct (**136**), which in turn is derivable from the intermolecular *meta* cycloaddition of vinyl acetate to indane. The formation of this cycloadduct would be favored by the directing influence of the donor (alkyl) group and by charge transfer, which would stabilize the *endo* exciplex. While not the only reaction product, cycloadduct (**136**) is indeed the major cycloadduct obtained in this process. Subsequent conversion of (**136**) to modhephene involves a novel permethylation of a fluxional enolate derived from (**137**) and a potentially general cleavage process based on the 'conjugate addition' of dimethylcopper lithium to vinylcyclopropyl ketone (**138**).

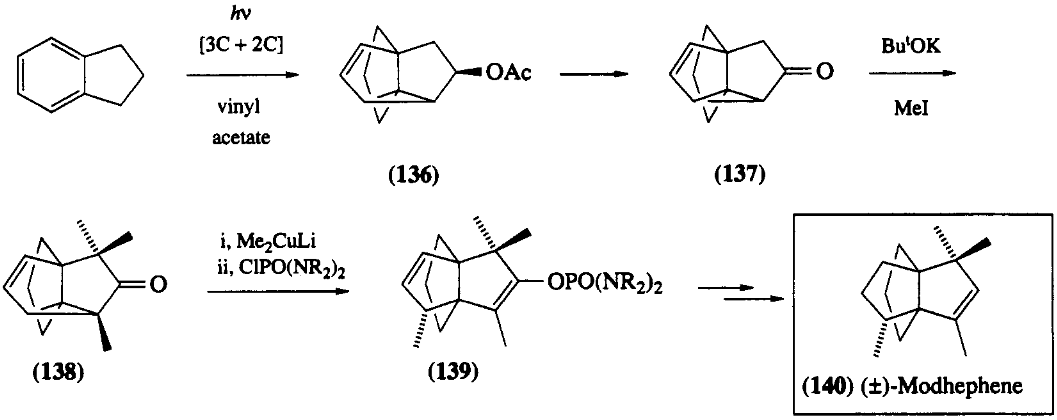

Scheme 18

The cycloadduct of indane and vinyl acetate (**136**) has also figured in a clever synthesis of decarboxyquadrone (**145**; Scheme 19) reported by Mehta.[43] For this target the cycloadduct is reduced and solvolyzed to provide alcohol (**142**). Dimethylation and rearrangement provides the required tricyclic subunit of the target.

An analogous cycloaddition involving benzene and vinyl acetate (Scheme 20) also provides rapid access to simple bicyclo[3.3.0]octanes, which have many synthetic uses as illustrated in part by their value in a straightforward synthesis of isoiridomyrmecin (**150**).

A final example of a [3C + 2C] connection based on the *meta* cycloaddition merits special mention as it demonstrates a new regioselectivity for the process, which in turn provides access to a new structural class. In the preceding studies of the intramolecular process, regioselectivity is controlled by a strong director group at a position *ortho* to the alkene tether and/or by the (*Z*)-alkene effect. As illustrated in a study directed at the synthesis of a quadrone analog, namely dedimethylquadrone (**156**; Scheme 21),[44] the absence of these control elements in arene-alkene (**151**) leads to the formation of cycloadduct (**152**) arising from addition across the tether as well as cycloadducts (**153**) and (**154**) from addition across the

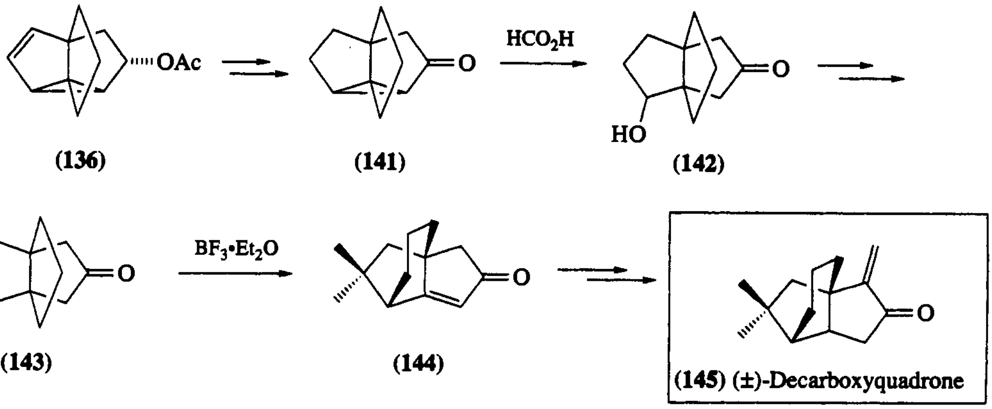
OAc
O
HCO$_2$H
O
HO
(136)
(141)
(142)
O
HO
(143)
BF$_3$•Et$_2$O
O
(144)
O
(145) (±)-Decarboxyquadrone

Scheme 19

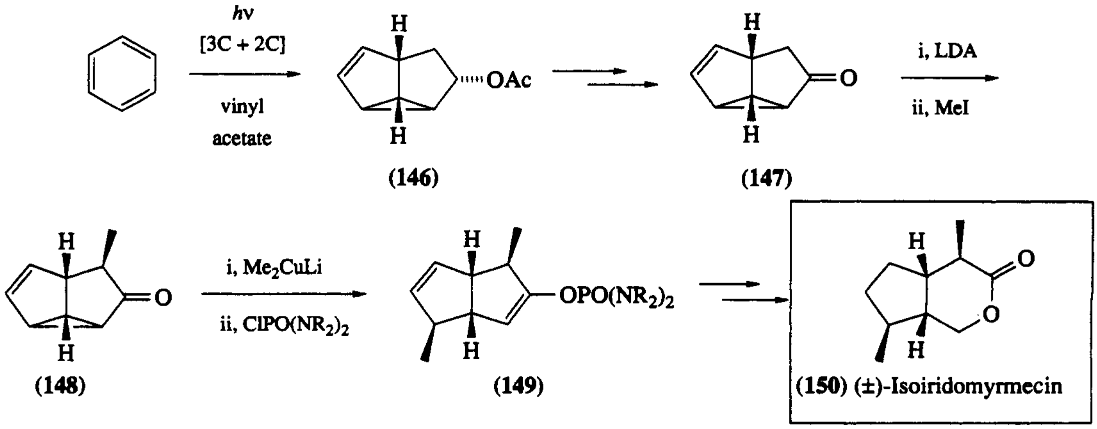
*h*v
[3C + 2C]
vinyl
acetate
H
OAc
H
(146)
H
O
H
(147)
i, LDA
ii, MeI
H
O
H
(148)
i, Me$_2$CuLi
ii, ClPO(NR$_2$)$_2$
H
OPO(NR$_2$)$_2$
H
(149)
H
O
O
H
(150) (±)-Isoiridomyrmecin

Scheme 20

unactivated *ortho* position (5.8:1:1.1, respectively). This result reflects the intrinsic regiochemical preference for the intramolecular *meta* cycloaddition. Another noteworthy point of this study is the exclusive formation of one vinylcyclopropane isomer (**152**), corresponding to addition across the tether. This finding is in accord with the previous discussion regarding the influence of strain on the final cyclopropane

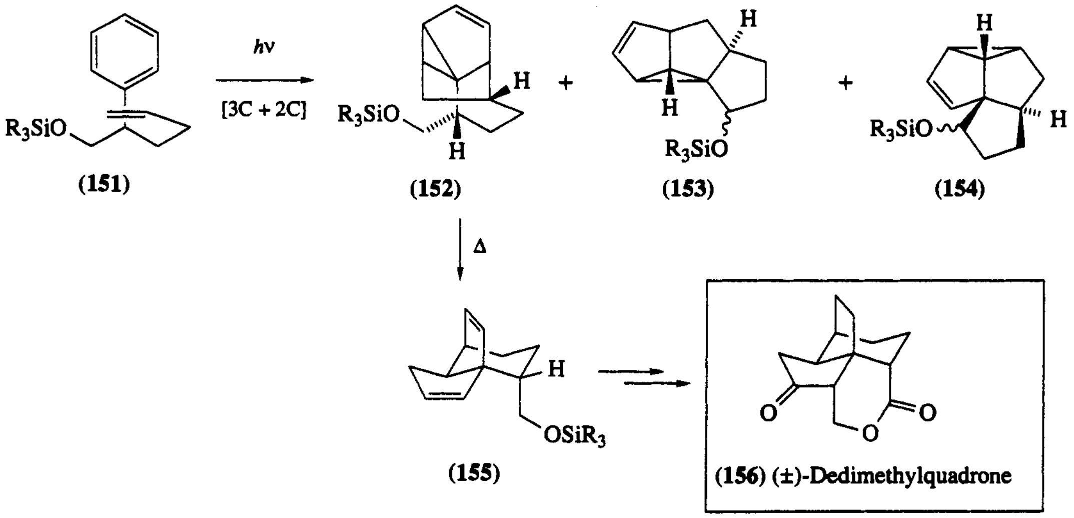
R$_3$SiO
(151)
*h*v
[3C + 2C]
R$_3$SiO
H
H
(152)
+
H
H
R$_3$SiO
(153)
+
H
R$_3$SiO
H
(154)
Δ
H
OSiR$_3$
(155)
O
O
O
(156) (±)-Dedimethylquadrone

Scheme 21

closure, as the vinylcyclopropane isomer of (**152**) would possess a highly strained *trans*-fused bicyclo[4.1.0]heptane subunit. This study also provides another example of the effectiveness of the homosigmatropic 1,5-hydrogen shift, as thermolysis of cycloadduct (**152**) furnishes diene (**155**), which possesses the tricyclic core of quadrone.

In all of the aforementioned studies, an arene–alkene *meta* cycloaddition is used to establish a five-membered ring through a [3C + 2C] connection. The obvious value of this process in five-membered ring synthesis can be readily extended to a [5C + 2C] approach to the synthesis of seven-membered rings through modification of the cycloadduct cleavage procedure. For example, rudmollin (**163**; Scheme 22), a pseudoguaiane with antileukemic activity, possesses the bicyclo[5.3.0]decane subunit of cycloadducts (**158**) and (**159**), which in turn are related to arene-alkene (**157**) by a *meta* cycloaddition reaction. The selectivity of the cycloaddition follows directly from previous considerations. Thus the arene and alkene substituents should favor a *meta* mode of addition, directed by the stronger donor (methoxy) and proceeding through the less-strained *exo* exciplex (**164**). Stereoinduction should be high and controlled by nonbonded interactions, which would destabilize exciplex (**165**), and by product development control, which favors positioning of the larger benzylic substituent on the less-encumbered cycloadduct face.

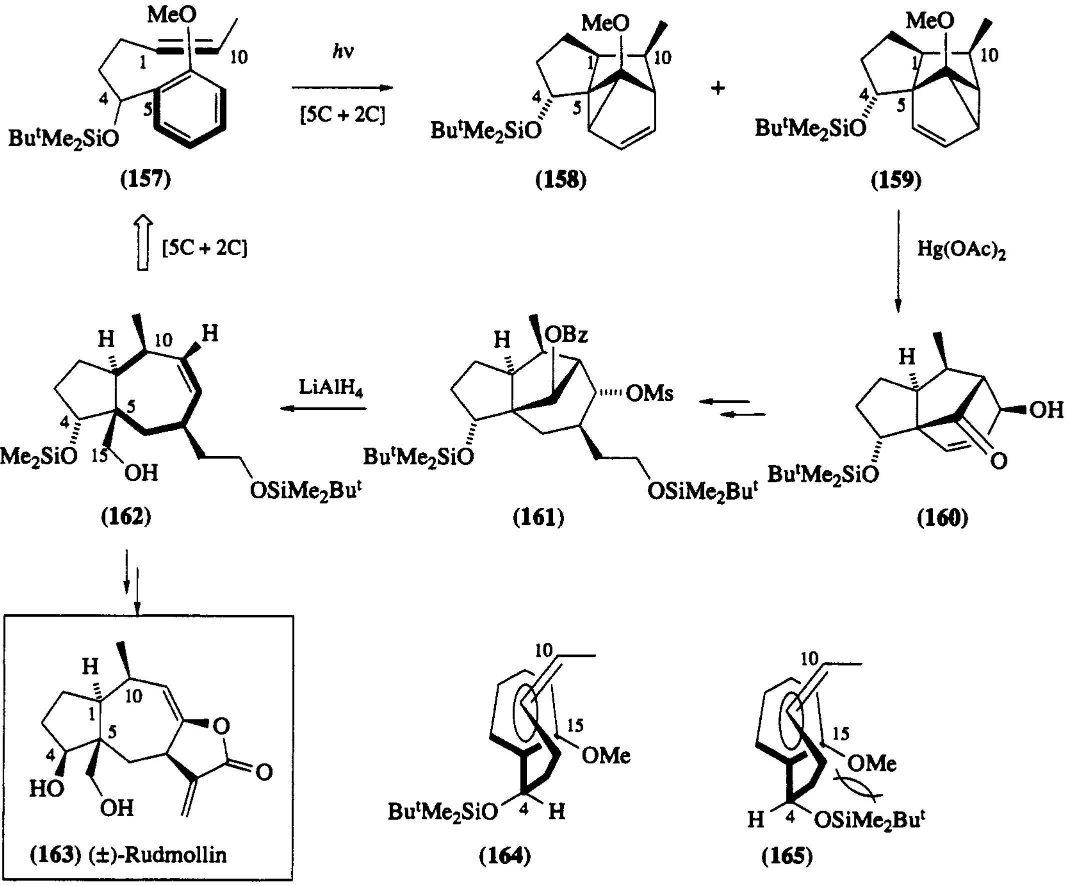

**Scheme 22**

Illustrative of the effectiveness of this [5C + 2C] approach to seven-membered rings, irradiation of arene-alkene (**157**) indeed affords two cycloadducts (**158**) and (**159**) (2:1) in 62% yield, each possessing a highly functionalized cycloheptanoid subunit.[45] At this point the key to the synthesis of rudmollin rests on the success of two bond cleavages. The first is accomplished by treatment of either or both cycloadducts with mercury(II) acetate. This reaction produces a common product (**160**). The next cleavage is based on mesylate (**161**), which is derived from ketone (**160**) and gives upon fragmentation bicyclo[5.3.0]decane (**162**), an immediate precursor to rudmollin (**163**). The control of stereochemistry at centers C-1, C-4, C-5 and C-10 in the key cycloaddition provides the basis for the general application of this strategy to guaiane and pseudoguaiane syntheses.

A further demonstration of the ring forming capabilities of the *meta* cycloaddition are seen in the investigation of its use for the synthesis of grayanotoxins, such as grayanotoxin II (**169**; Scheme 23).[46] Noteworthy in this effort is the use of a tetralin as an arene component. This study also involves the first examination of stereoinduction by a homobenzylic stereogenic center. Importantly, irradiation of arene-alkene (**166**) provides pentacycle (**167**) as the only detectable cycloadduct. Mode, regio- and *exo*- selectivity associated with this reaction are in accord with previous considerations, while stereoinduction can be rationalized from an examination of exciplexes (**170**) and (**171**). The latter would be expected to be destabilized by the indicated C-18 methyl/methoxy interaction, thereby favoring reaction *via* exciplex (**170**). The formation of only one vinylcyclopropane isomer is a predictable consequence of strain, which is minimized when the methoxy and C-18 methyl groups are on a cyclopropane bond rather than the shorter σ-bond of the isomer of (**167**). Overall, this transformation is a rather dramatic demonstration of the synthetic capabilities of the *meta* cycloaddition as it allows the one-step conversion of a simple bicyclic material to a pentacyclic product with seven stereogenic centers.

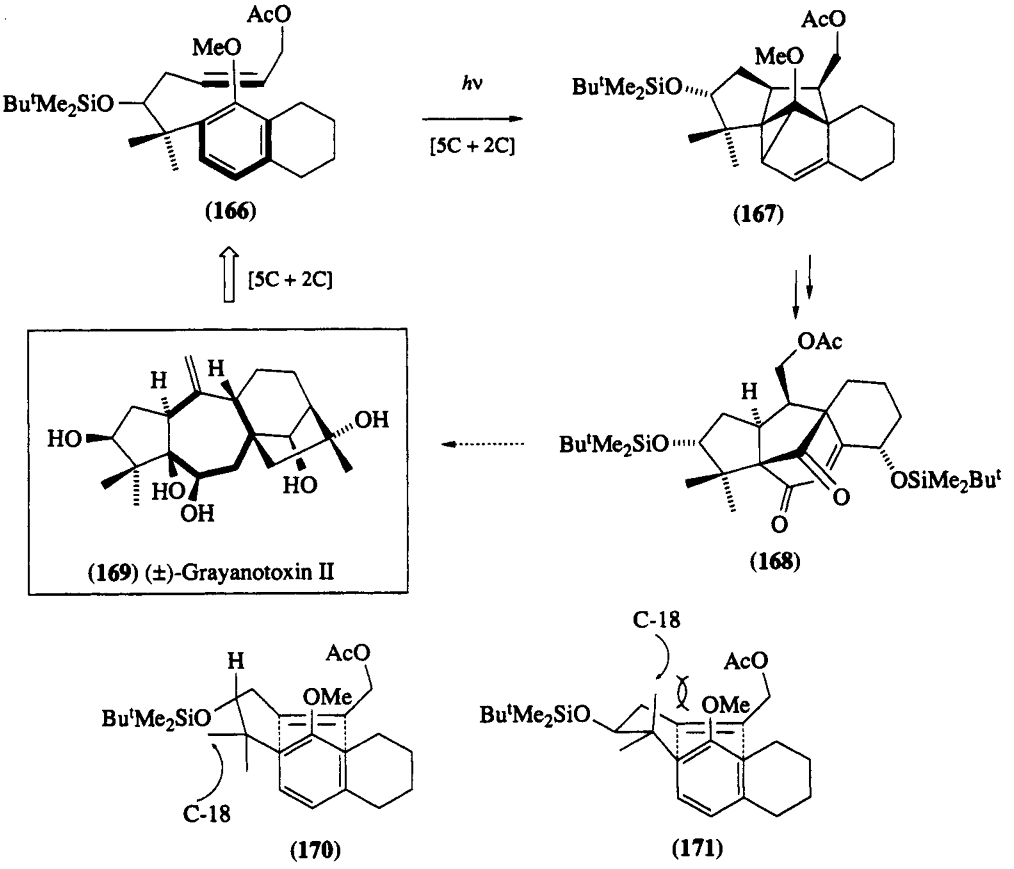

**Scheme 23**

Intermolecular *meta* cycloadditions provide yet another option for the facile [5C + 2C] construction of seven-membered rings, as illustrated in Srinivasan's pioneering studies (Scheme 24).[47] The availability of simple arenes and alkenes and of numerous methods as discussed above for the modification of *meta* cycloadducts makes this a particularly effective stategy for cycloheptanoid synthesis.

In contrast to the major developments in the use of [3C + 2C] and [5C + 2C] cycloadditions based on the arene–alkene *meta* cycloaddition, relatively less is known about the use of the *meta* cycloaddition as a means to achieve [3C + 4C] and [5C + 4C] connections. Nevertheless, these processes have great potential, provided that the factors determining their selectivity could be elucidated. For example, benzene and diene (**176**) (equation 16) undergo cycloaddition to furnish a [3C + 4C] (or [5C + 4C]) cycloadduct (**177**) and a [4C + 4C] cycloadduct (**178**).[48] Cleavage of the former adduct as in the aforementioned cases would provide access to seven- or nine-membered rings. While most dienes react with arenes to give [4C + 4C] cycloadducts, the range of dienes and arenes studied thus far is too limited to rule out the development of [3C + 4C] and [5C + 4C] cycloadditions as useful synthetic processes.

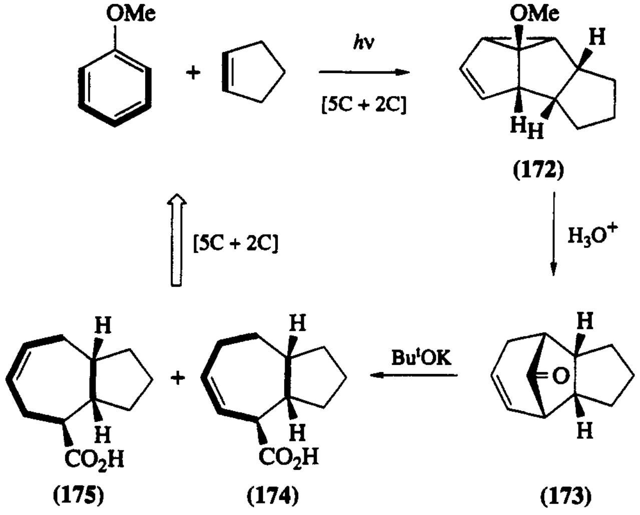

**Scheme 24**

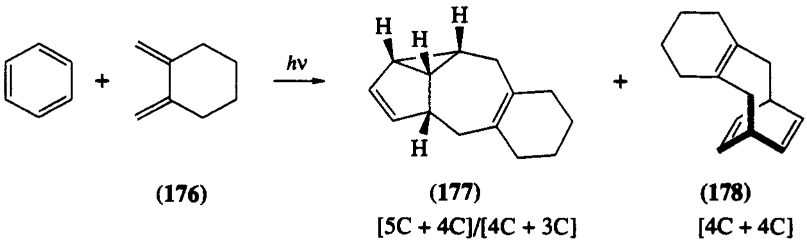

(16)

In summary, this chapter has highlighted the mechanistic and synthetic advances which have been realized in studies on arene–alkene cycloadditions, primarily during the past decade. Much is now understood but far more remains to be done. Critical tests of the leading mechanisms are necessary to establish their generality. It would also be highly desirable to determine how the available mechanistic insight might be put to practical use in, say, increasing the yield of inefficient cycloadditions. Many simple additions, for example, proceed in only 60–70% yield. Another major but as yet unexplored aspect of these cycloadditions relates to control of absolute stereochemistry. Given the sophistication of mechanistic models, such studies could be very valuable, from both mechanistic and synthetic considerations.[49] A further area of great importance pertains to the development of the *ortho* and *para* modes of cycloaddition as methods for complex molecule synthesis. Given the ways in which such cycloadducts can be formed and manipulated, the synthetic potential of these processes is vast. The past decade has witnessed an exciting and significant surge of research on the arene–alkene cycloadditions. It is clear that these reactions will continue to be a highly significant subject for future mechanistic and synthetic research.

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49. Studies related to this point are under way at Stanford University.

# 6.1

# Cyclobutene Ring Opening Reactions

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## 6.1.1 INTRODUCTION

Cyclobutenes and 1,3-butadienes can be interconverted by either thermal or photochemical means. The thermal conversion of a number of simple cyclobutenes to the corresponding 1,3-dienes was first noted in the early 1950s.[1] Typically, simple cyclobutenes are thermodynamically less stable than the open-chain dienes due to the considerable ring strain. For the parent pair, cyclobutene → 1,3-butadiene (equation 1), the energy difference is 28.5 kcal $\text{mol}^{-1}$.[2] In contrast, the 1,3-diene isomer is generally considerably less stable than the ring form when the double bond of the ring is part of an aromatic system, for example in benzocyclobutene, since ring opening in this case results in loss of aromaticity (equation 2).

The generality of the thermal ring opening of cyclobutenes and the ease with which it often takes place has made this reaction an important route to 1,3-dienes of defined structure. More important however is the *in situ* generation of reactive 1,3-dienes, especially short-lived dienes such as *o*-quinodimethane (**1**) or vinylketene (**2**) (equation 3). *o*-Quinodimethanes typically undergo subsequent [4 + 2] cycloaddition or ene reactions. In contrast, both [2 + 2] and [4 + 2] cycloadditions have been observed for the vinylketenes. In addition, both species partake in six-electron electrocyclic reactions if an additional vinyl or aryl group is present. Such tandem sequences represent powerful strategies for the synthesis of complex target molecules.

This chapter is restricted to a short, but by no means complete, review of key synthetic routes to cyclobutenes, benzocyclobutenes and cyclobutenones and a generally qualitative discussion of the way in which substituents control both the ease of ring opening and the stereochemistry of the products obtained. The reader should thus be in position to make useful predictions. Finally we have included pertinent synthetic applications which illustrate in useful and often very imaginative ways the value of the

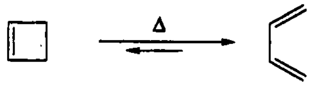

(1)

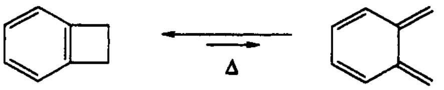

**(1)**

(2)

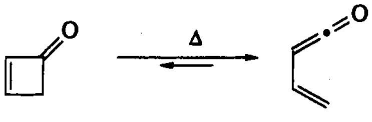

**(2)**

(3)

thermal cyclobutene ring opening reaction in organic synthesis. The photochemical ring opening of cyclobutenes is rarely useful in a synthetic strategy and will not, except for one or two examples, be addressed in this review.

## 6.1.2 PREPARATION OF CYCLOBUTENES

A summary of most of the available routes to cyclobutenes and cyclobutenones is given in equations (4)–(7). These approaches can be divided into two major strategies. (a) Cycloaddition between an alkyne and an alkene to give directly a cyclobutene. In the case where the alkene partner is a ketene, cyclobutenones are obtained (see Section 6.1.5). (b) Introduction of a double bond into a preformed cyclobutane derivative, typically *via* an elimination reaction.

Owing to space restrictions only a few general comments will be made concerning these methods. The photochemical [2 + 2] cycloaddition utilizes simple alkynes (acetylene and mono- or di-alkyl derivatives) and alkenes bearing at least one strongly electron-withdrawing group (equation 4a).[3] Yields are usually above 50%, often higher than 80%. Bicyclic cyclobutenes can be prepared by irradiation of cyclic or heterocyclic 1,3-dienes or 1,3,5-trienes, as exemplified by the photolysis of *N*-ethoxycarbonyl-1*H*-azepine (equation 4b).[3]

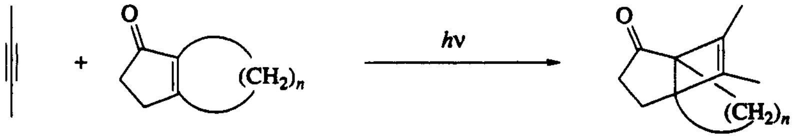

(4a)

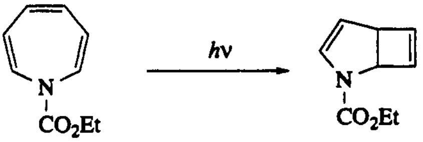

(4b)

Thermal [2 + 2] cycloadditions proceed to give cyclobutenes either when an alkyne bearing an electron-withdrawing group is reacted with an electron-rich alkene such as an enamine[4] or enol ether (equation 5), or when the alkyne substituted with an electron-donating group, such as dimethylamino, is heated with electron-poor alkenes (equation 6).[5] Good to excellent yields of cyclobutenes are generally obtained.

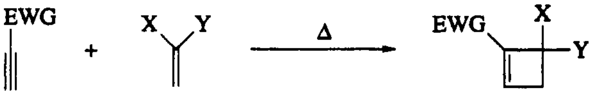

(5)

$X = H, Y = OR; X = NR_2, Y = alkyl$

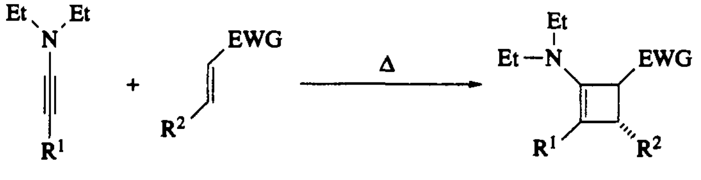

(6)

$R^1 = R^2$ = alkyl or aryl

Intact cyclobutanes, especially cyclobutanones, can serve as obvious precursors to many cyclobutenes. For example, cyclobutanones have been converted to their silylated enol ethers by standard methodology.[6] Thermolysis of these intermediates gives rise to 1-alkoxysilyl-1,3-butadienes (equation 7).

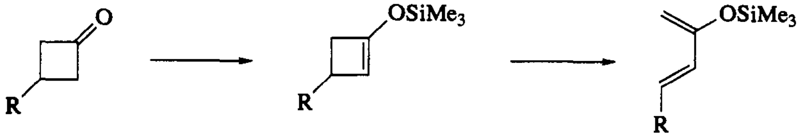

(7)

Halazy and Krief[7] have converted cyclobutanone into 1-lithio-1-selenophenylcyclobutane (**3**) by treating 1,1-diselenophenylcyclobutane with Bu$^n$Li. The lithio derivative can be trapped with a variety of electrophiles including alkyl halides, epoxides and aldehydes or ketones to yield the selenides (**4**). Unsaturation is introduced into the ring *via* a *cis* elimination from the *in situ* formed selenoxide or by β-elimination from the methylselenonium salt (**5**). Control of the regiochemistry in the elimination steps to give cyclobutenes rather than methylenecyclobutanes is possible. For example, the use of NaH or Bu$^t$O$^-$ in DMF to affect the β-elimination of MeSePh from (**5**) leads only to the cyclobutenes (**6**) since under these strongly basic conditions alkylidenecyclobutanes are cleanly isomerized to 1-alkylcyclobutenes. The yields are typically in the range 70–90% in steps (a) and (b) and 60–65% for either (d) or (e) (Scheme 1).

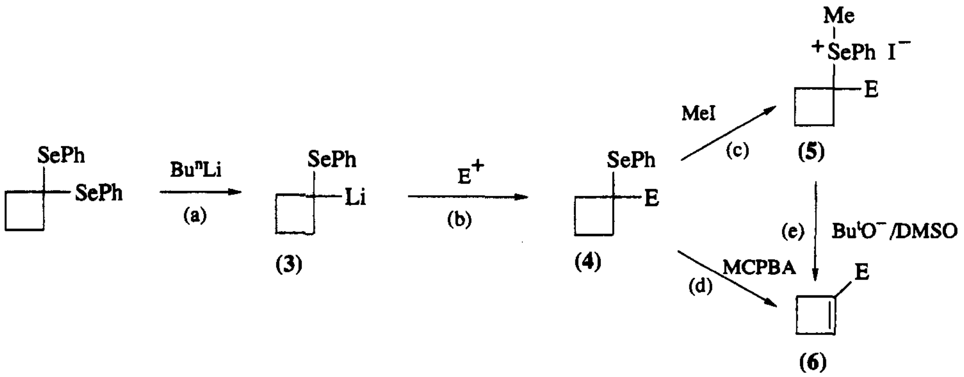

**Scheme 1**

A number of less general routes to cyclobutenes have also been described. These include the ring enlargement of cyclopropyl substituted carbenes[8] and the acid-catalyzed ring enlargement of both 3-hydroxymethylcyclopropenones[9] and 3-acylcyclopropenones.[10] Finally, mention should be made of the large-scale preparation of *cis*-3,4-dichlorocyclobutene (**7**) *via* a retro Diels–Alder reaction of the cyclobutane (**8**), prepared in two steps from cyclooctatetraene.[11] 3,3-Dimethoxycyclobutene has also been prepared *via* a retro Diels–Alder reaction.[12]

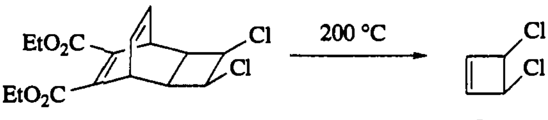

(**8**) (**7**) 43%

## 6.1.3 RULES PERTAINING TO THE THERMAL CYCLOBUTENE RING OPENINGS

The thermally activated conversion of cyclobutenes to 1,3-butadienes is controlled by orbital symmetry. Woodward and Hoffman[13] and Fukui[14] described the allowed thermal process as conrotatory, *i.e.* one in which the substituents at C-3 and C-4 both move in the same direction, either in a clockwise (equation 8) or counter-clockwise fashion (equation 9). In the photochemical process the motion of the same substituents is in the opposite direction, resulting in the formation of either a *trans,trans* or a *cis,cis* 1,3-diene (equations 10 and 11).

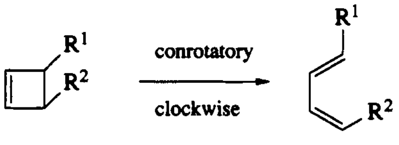

(8)

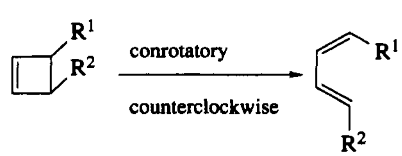

(9)

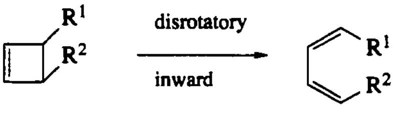

(10)

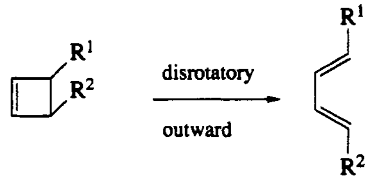

(11)

It has been demonstrated that the thermally allowed conrotatory process is 15 kcal mol$^{-1}$ more favorable than the disrotatory mode.[15] It should be noted that the 'disallowed' process can be observed for molecules in which the allowed conrotatory process is structurally denied. Such a situation exists for the series of *cis*-[*n*.2.0] bicyclics when $n < 3$ since the monocycle formed upon ring opening cannot accomodate a *trans* double bond.[16] Ring opening in these molecules to yield the observed *cis,cis*-1,3-dienes could occur *via* the forbidden disrotatory mode, the allowed conrotatory mode followed by isomerization, or by a nonconcerted diradical process. Bicyclo[2.1.0]pent-2-ene converts to 1,3-cyclopentadiene at room temperature, bicyclo[2.2.0]hex-2-enes typically require temperatures above 150 °C for isomerization to 1,3-cyclohexadienes, while the corresponding bicycloheptenes are stable to nearly 400 °C. Lower temperatures (250 °C) are again found for the bicyclo[4.2.0]oct-7-enes, where a conrotatory ring opening to a *cis,trans*-1,3-cyclooctadiene becomes sterically feasible. These temperatures should be compared with the 175–180 °C range necessary to isomerize *cis*-3,4-dimethylcyclobutene to *cis,trans*-2,4-hexadiene.[17]

### 6.1.3.1 Substituent Effects on the Cyclobutene Ring Opening Reaction

A number of authors have recently reported detailed studies on the cyclobutene → 1,3-butadiene ring opening reaction in order to gain a better understanding of the many diverse results which have been compiled over the past 40 years. An excellent compilation of data, including various thermodynamic perameters, is available in the 1980 monograph by Marvell.[1]

In a lengthy theoretical paper, Rondan and Houk considered the available data, described *ab initio* calculations and discussed earlier explanations concerning the stereochemical aspects of the ring openings of substituted cyclobutenes.[18] These authors came to the following conclusions. The stereochemistry of the thermal electrocyclic conrotatory ring opening of 3- and 4-substituted cyclobutenes is controlled by electronic effects. Electron-donating substituents prefer to rotate outward, with the preference increasing as the electron donor ability of the substituent increases. Conversely, powerful electron-withdrawing substituents were predicted to have the opposite effect and rotate inward (equation 12).

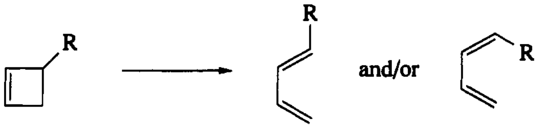

(12)

For the 3,3-disubstituted and *cis*-3,4-disubstituted cyclobutenes it was predicted that the stronger electron donor would rotate outwards while the weaker donor rotates inward. In the case of the *trans*-3,4-isomers, outward rotation of both substitutions would normally be expected; however, calculations have predicted that the in-in rotation is preferred for two *trans* 3,4-$BH_2$ substituents.[18]

The above generalizations should be sufficient to serve most of the needs of the synthetic chemist. Those interested in obtaining a more detailed understanding of the theoretical basis of the arguments are referred to the Rondan and Houk paper and the references therein.[18] Some examples which illustrate the application of these guidelines are shown below for 3,4-disubstituted cyclobutenes and benzocyclobutenes.

The thermolysis of 3,3-, 3,4-*cis*- and 3,4-*trans*-disubstituted cyclobutenes can provide useful comparisons of the propensity of two substituents to rotate either inward or outward. Frey and his colleagues[19] were amongst the first to note that the simple notion of the larger the substituent the greater the tendency for outward rotation, was incorrect. They showed that the activation energy for isomerization to the 1,3-diene was less for 3,3-diethylcyclobutene than for the 3,3-dimethyl analog and thereby inferred that an ethyl group rotates inward more readily than a methyl group. This conclusion was verified by the observation that 3-ethyl-3-methylcyclobutene (**9**) gave a 68:32 mixture of the dienes (**10**) and (**11**) when heated in the gas phase at 180 °C. In a subsequent study, Curry and Stevens[20] showed that the preferred inward rotation of the sterically larger group was also observed for 3-methyl-3-propylcyclobutene and the 3-methyl-3-isopropyl analog. Even in the competition between methyl and *t*-butyl, the bulky *t*-butyl group rotated inward to a surprisingly large (32%) extent. Replacement of the alkyl group by phenyl, substituted phenyl or cyclopropyl groups resulted in a mixture of products in which these groups rotated inward to the extent of 30–50%. These data are summarized in Table 1. Rationalization of the results in terms of extra stabilization of the transition state for an aryl group rotating inward, and destabilization of transition state relative to methyl when the alkyl group rotates outward, were put forward.[20] Some of these arguments were later questioned by Houk.[18]

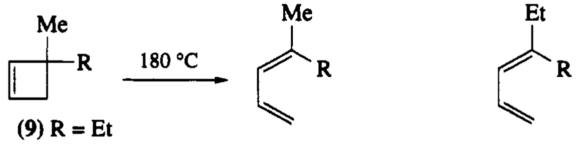

(**9**) R = Et

(**10**) 68%

(**11**) 32%

**Table 1** Gas-phase Thermolysis of 3,3-Disubstituted Cyclobutenes (9)

| *R in* (**9**) | *Diene* (**10**) (%) | *Diene* (**11**) (%) |
|---|---|---|
| Ethyl | 68 | 32 |
| Isopropyl | 66 | 34 |
| *n*-Propyl | 62 | 38 |
| *t*-Butyl | 32 | 68 |
| Cyclopropyl | 43 | 57 |
| Phenyl | 30 | 70 |
| 4-Methoxyphenyl[a] | 52 | 48 |
| 4-Cyanophenyl[a] | 45 | 55 |

[a] At 161 °C.

Perhaps the most spectacular illustrations of the above 'rules' come from the Houk group. For example, these authors were able to show that heating 3-*t*-butyl-3-methoxycyclobutene (**12**), or the 3-trimethylsilyloxy analog (**13**) in $C_6D_6$ (90–95 °C) or $CDCl_3$ (reflux), respectively, afforded only the dienes

(**14**) and (**15**).[21] Clearly, the direction of rotation of the substituents is not dominated by the steric interactions encountered by the inward rotating substituent. Steric interactions encountered by the outward rotating substituent are also readily overcome if it is strongly electron donating, as shown by the clean conversion of (**16**) to (**17**).

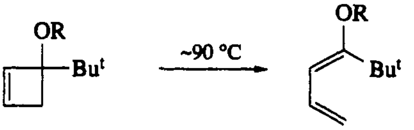

(**12**) R = Me
(**13**) R = SiMe$_3$

(**14**) R = Me
(**15**) R = SiMe$_3$

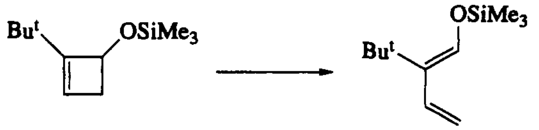

(**16**)

(**17**)

The preferred, predicted inward rotation of the strongly electron-withdrawing formyl group was also verified experimentally.[22] Thus cyclobutene-3-carbaldehyde (**18**) undergoes ring opening at room temperature with a half-life of about 50 h to give (*Z*)-2,4-pentadienal (**19**) accompanied by less than 2% of the (*E*)-isomer. The preference for inward rotation by the formyl group is thus greater than 2.7 kcal mol$^{-1}$. Based on these findings, a chlorocarbonyl group is expected to follow this trend. As predicted, the methyl ester (**20**) undergoes selective ring opening (at room temperature!) to give the diene (**21**). Less electrophilic carbonyl functions such as ketones and, even more so, carboxylic acids, esters and amides, show an increased tendency to rotate outward. Thus the ketoester (**22**) gave a 2:1 mixture of two (*E*,*Z*) products (**23**) and (**24**). The major product resulted from inward rotation of the keto and outward rotation of the ester group.[23]

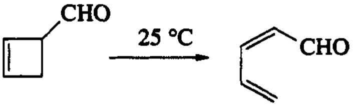

(**18**)

(**19**)

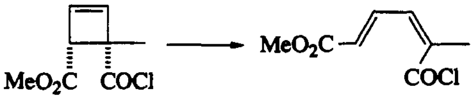

(**20**)

(**21**)

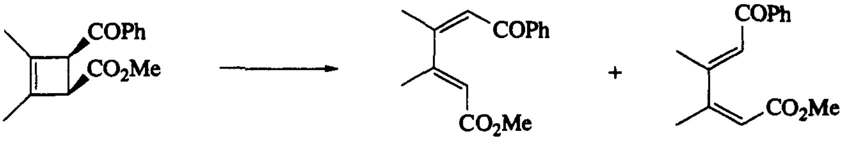

(**22**)

(**23**)

(**24**)

Halogen substiuents show a strong tendency for outward rotation.[24] The particularly strong tendency by fluorine to rotate outward has been demonstrated by the work of Dolbier *et al.*,[24a,b] who have shown that ring opening of the perfluorinated cyclobutene (**25**) gives (**26**) in which preference for outward rotation of the two *trans* 3,4-fluorine substituents forces the relatively large trifluoromethyl substituents to rotate inward. The activation energy for the ring opening of (**25**) to (**26**) is approximately 18 kcal mol$^{-1}$ lower than that leading to (**27**). These results are consistent with the Rondan and Houk calculations which showed that strong *p*-electron donating substituents rotate preferentially outward.[18] Interestingly, in the perfluorinated series studied by Dolbier *et al.* the 1,3-dienes are generally less stable than the corresponding cyclobutenes, in contrast to most 1,3-diene–cyclobutene equilibria.

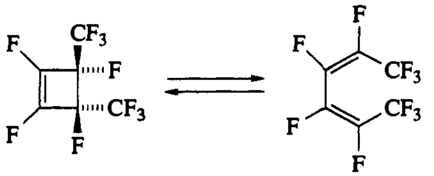

(**25**)

(**26**)

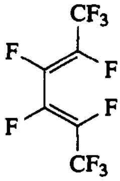

(**27**)

Inward rotation by substituents which normally prefer outward motion can be observed when the ring opening reaction is reversible, as in the case of benzocyclobutene → *o*-quinodimethane (equation 2), and the less favored isomer is further transformed by an irreversible reaction. For example, 1-vinylbenzocyclobutene (**28**) when heated in the absence of a dienophile yields 1,2-dihydronaphthalene *via* inward rotation of the vinyl group to give (**29**), followed by an electrocyclic ring closure.[25]

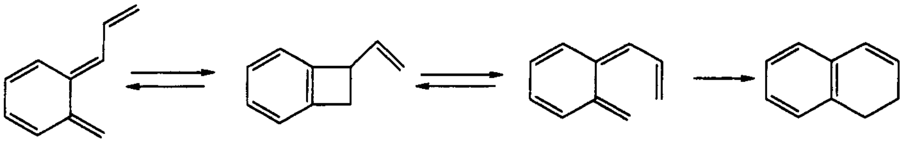

(**28**) (**29**)

Under flash vacuum thermolysis conditions (550–600 °C/0.01 mmHg), even an acetoxy group can be induced to rotate inward, as shown by the conversion of (**30**) to the ketoaldehyde (**31**).[26] The presence of a suitably placed dienophile, even the weak terminal vinyl group as in (**30a**), results only in the intramolecular Diels–Alder product (**32**), thereby demonstrating the large preference for outward motion by an acyloxy derivative.[26] Similar thermolysis of 1-acetoxy-1-methylbenzocyclobutene (**30**; $R^1 = R^2 = Me$) afforded a 96:4 mixture of the vinyl acetate (**33**) and the diketone (**34**); these products arise from outward and inward rotation of the acetoxy group, respectively (Scheme 2).

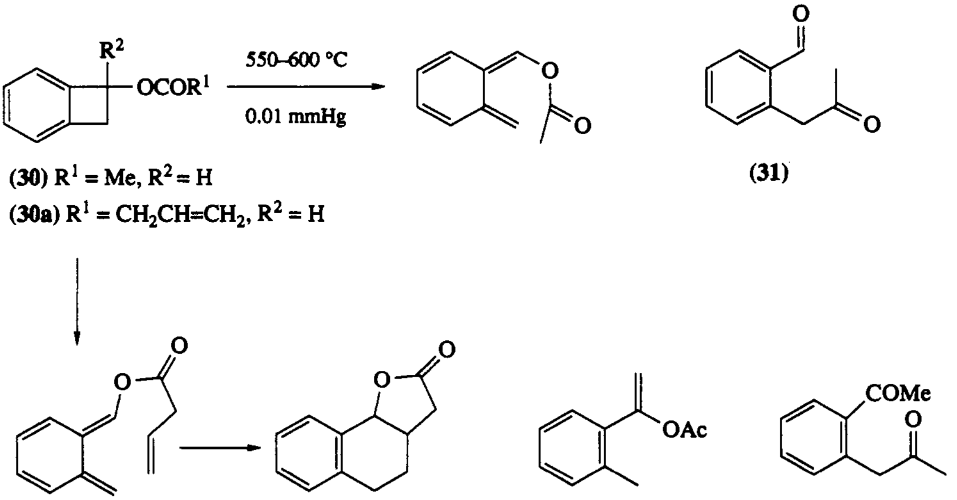

(**30**) $R^1 = Me$, $R^2 = H$

(**30a**) $R^1 = CH_2CH{=}CH_2$, $R^2 = H$

(**31**)

(**32**) (**33**) (**34**)

**Scheme 2**

Based on the Houk predictions regarding cyclobutene-3-carbaldehyde,[18] the easy isomerization of 1-acetylbenzocyclobutene to the benzopyran (**35**),[27] which proceeds *via* inward rotation of the acetyl group and a subsequent cyclizations, is not surprising.

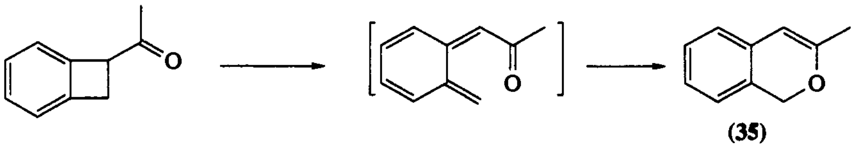

(**35**)

Fukumoto *et al.*[28] have taken advantage of the propensity for inward rotation of an acyl group to prepare the isochroman-3-one (**36**), an intermediate in their synthesis of geneserine, a constituent of the calabar bean. The conversion of the benzocyclobutene (**37**) to (**36**) proceeds *via* ring opening to the *o*-quinodimethane (**38**) followed by cyclization and a 3,3-sigmatropic rearrangement.

Oppolzer,[29] in a series of key papers in 1974, showed that the amide substituents in the benzocyclobutenes (**39**) can rotate outward to give the dienamides (**40**) as intermediates. Intramolecular trapping by the remote alkene groups afforded the tricyclic derivatives (**41**) in very good to excellent yields. This work clearly established the value of benzocyclobutenes in the preparation of complex polycyclic target

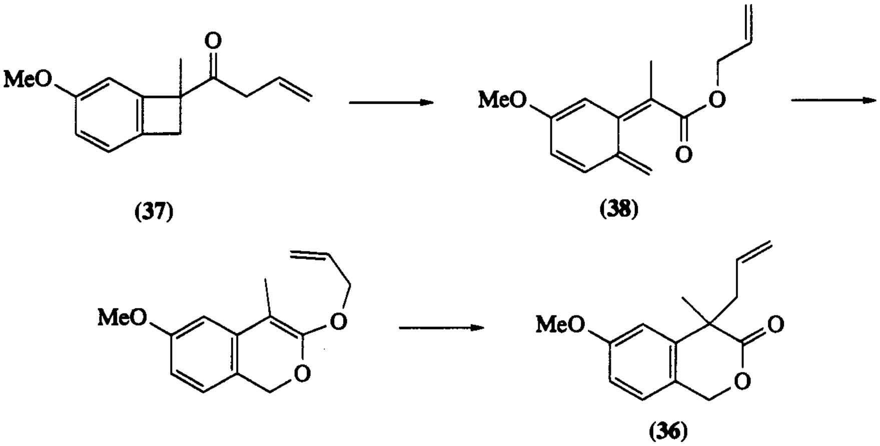

molecules. No evidence of inward rotation of the CONHR group, which could have resulted in a 3-amino substituted benzopyran, was reported.

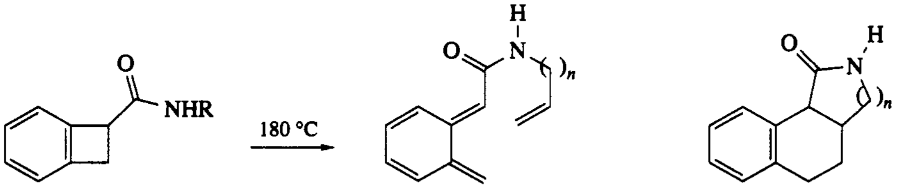

**(39)** **(40)** $n = 1, 2$ **(41)** $n = 1, 2$

From a synthetic point of view it is useful to know not only the direction of rotation of the substituents, *i.e.* the stereochemistry of the diene produced, but also the temperatures at which cyclobutenes open at synthetically useful rates. Much of the early work in this area has been done without the synthetic aspect in mind and some of the temperatures quoted below may be of value only for comparison purposes.

For the synthetic chemist the following should serve as useful guidelines. If an electron-donating substituent at the $sp^3$ carbons is able to rotate outward it lowers significantly the temperature required for cyclobutene ring opening. The stronger the electron-donating ability, especially *via* resonance effects, the lower the temperature for isomerizations.

This conclusion is nicely illustrated by the series 1-phenylbenzocyclobutene (**42**), *trans*-acetoxy-2-phenylbenzocyclobutene (**43**) and the *trans*-1-methoxy (**44**) and *trans*-1-alkoxy (**45**) analogs. These compounds undergo synthetically useful rates of ring opening to the corresponding *o*-quinodimethanes at approximately 190–210 °C for (**42**),[30] 150–170 °C for (**43**),[31] 100 °C for (**44**)[32] and <0 °C for (**45**).[33] In each of the latter three cases, both substituents rotate outward.

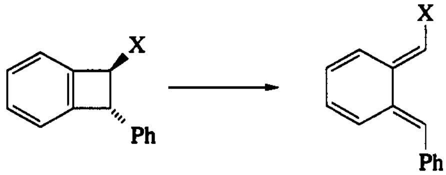

| *Compound* | *Reaction Temp.* ( °C) |
|---|---|
| (**42**) X = H | >200 |
| (**43**) X = OAc | 150 |
| (**44**) X = OR | 80–110 |
| (**45**) X = $O^-$ | <0 |
| (**46**) X = Ph | 20 |

A similar trend can be found in the monocyclic series. As expected, the difference between cyclobutene itself and a 3-alkyl substituted cyclobutene is relatively minor. For 3-phenylcyclobutene (**47**) the extra stabilization of the transition state for either the in or out rotation is sufficient to lower the ring opening temperature to approximately 100 °C.[34a] An even more dramatic lowering to 30–50 °C is observed for the isomerization of (**48**) to (*E*)-1-methoxy-1,3-butadiene.[34b] The difference between (**48**) and *cis*-1,2-diethoxycyclobutene (**49**) can be ascribed to the fact that in (**49**) one of the methoxy groups is forced to undergo an unfavorable inward rotation. A similar differential exists for *cis*- and *trans*-1,2-dimethoxybenzocyclobutenes (**50**) and (**51**). These compounds, together with others bearing representative substituents and the 'best estimate' of the temperature required for a reasonable rate of ring opening, are collected in Table 2; many further examples can be found in the Marvell monograph.[1] Further comments concerning reaction conditions, and propensity for outward or inward rotation during ring opening, will be made at appropriate places during the discussion of synthetic applications of the cyclobutene ring opening reactions.

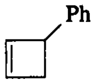
(**47**)

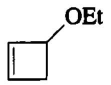
(**48**)

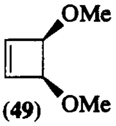
(**49**)

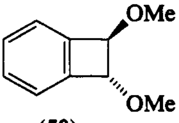
(**50**)

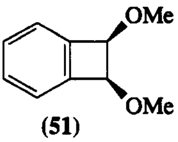
(**51**)

**Table 2** Ring Opening Temperatures of Representative Cyclobutenes

| *Compound* | *Temp. (°C)* | *Ref.* |
|---|---|---|
| *cis*-3,4-Dimethylcyclobutene | 175 | 1 |
| Cyclobutene | 150 | 1 |
| 3-Methylcyclobutene | 150 | 1 |
| *cis*-3,4-Dichlorocyclobutene | 135–165 | 24c |
| *cis*-3,4-Di(methoxycarbonyl)cyclobutene | 120 | 1 |
| 3-Phenylcyclobutene (**47**) | 98 | 34a |
| *trans*-3,4-Dichlorocyclobutene | 90 | 24c |
| *cis*-3,4-Dimethoxycyclobutene (**49**) | >80 | 38 |
| *cis*-3,4-Bis(hydroxymethyl)cyclobutene | 60–70 | 39 |
| 3-Ethoxycyclobutene (**48**) | 30–50 | 34b |
| *cis*-3,4-Diphenylcyclobutene | 27 | 1 |
| 3-Formylcyclobutene | 25 | 22 |
| 3-Formyl-4-hydroxymethylcyclobutene | <0 | 39 |
| *trans*-1,2-Dimethoxybenzocyclobutene (**50**) | 80 | 115 |
| *cis*-1,2-Dimethoxybenzocyclobutene (**51**) | >110 | 115 |
| 2,3-Dimethylcyclobutenone | 120 | 82 |

## 6.1.4 SYNTHESIS *VIA* CYCLOBUTENES

### 6.1.4.1 Preparation of Reactive 1,3-Dienes

One of the more obvious synthetic uses of cyclobutenes which has already been mentioned is for the preparation of specifically substituted 1,3-dienes, often to be used in subsequent [4 + 2] cycloaddition reactions.

The synthetic value of highly oxygenated 1,3-dienes in both the Diels–Alder and hetero Diels–Alder reaction is evident from the outstanding work of the Danishefsky group.[35] They typically prepared such compounds, *e.g.* (**52**), by converting the appropriate ketone into its enol silyl ether.

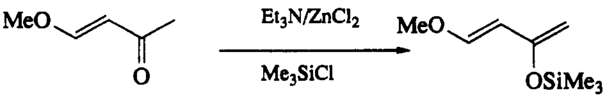

(**52**)

A number of authors have shown that, in addition to the above route, highly oxygenated 1,3-dienes can be prepared from the corresponding cyclobutene enol silyl ethers. For example, 2-methoxy-3-phenylthiobuta-1,3-diene (**53**) was obtained in essentially quantitative yield by rapid passage of a hexane solution of 1-methoxy-2-phenylthiocyclobut-1-ene (**54**) through a column containing glass helices at 340 °C.[36a]

Diene (**53**) undergoes Diels–Alder reactions with unsymmetrical dienophiles such as methyl vinyl ketone to give preferentially the adduct (**55**). Further manipulations of (**55**), such as acid hydrolysis to an α-phenylthiocyclohexanone (**56**), were carried out.

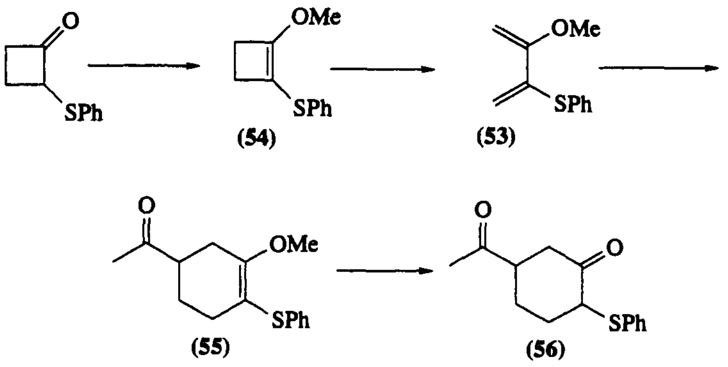

(**54**) (**53**) (**55**) (**56**)

2,3-Bis(trimethylsilyloxy)-1,3-butadiene (**58**) has been obtained from the cyclobutene (**57**) in 84% yield (6 h, 180 °C). This compound, as expected, reacted with dimethyl acetylenedicarboxylate to furnish adduct (**59**) in 82% yield after a 24 h reflux in toluene; oxidation yielded the substituted phthalate (**60**).[36b]

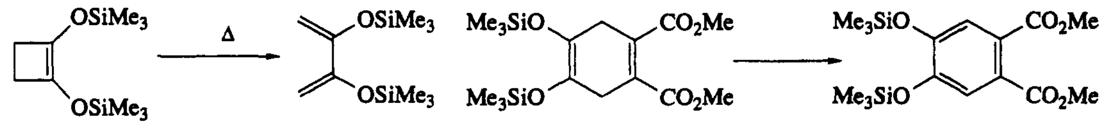

(**57**) (**58**) (**59**) (**60**)

Aben and Scheeren[37] have described a rather general approach to even more highly oxygenated 1,3-dienes based on the reaction of vinyl ethers or ketene acetals with ethoxyketene generated *in situ* from ethoxyacetyl chloride and triethylamine. Thus the cyclobutanone (**61**), obtained in 80% yield from ethoxyvinyl ether and ethoxyketene, was converted into a mixture of enol silyl ethers (**62**) and (**63**) with $Me_3SiCl$ and $ZnCl_2$ in benzene. Since the *trans*-3,4-diethoxy derivative (**63**) undergoes ring opening at considerably lower temperature (<25 °C), because of the preferred out-out rotation of both ethoxy groups, than the isomeric cyclobutene (**62**) (>80 °C), and since (**62**) and (**63**) are in equilibrium in benzene in the presence of $ZnCl_2$, essentially pure diene (**64**) can be obtained. The preparation of the ethoxy analog of the Danishefsky diene (**52**) in 85% yield from the thermolysis of 3-ethoxy-1-trimethylsiloxycyclobut-1-ene at 50 °C in MeCN was also described.

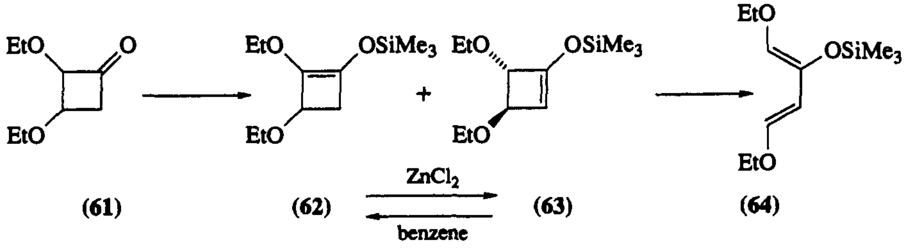

(**61**) (**62**) (**63**) (**64**)

*cis*-3,4-Dichlorocyclobutene (**65**) reacts cleanly with 1 equivalent of NaOMe in MeOH *via* an $S_N2'$ mechanism to yield *cis*-3-methoxy-4-chlorocyclobutene (**66**).[38] In the presence of excess methoxide the dimethoxy derivative (**67**) is obtained. When heated above 80 °C, both compounds undergo ring opening and furnish the (*E,Z*)-dienes (**68**) and (**69**), respectively.

The functionalized dienals (**70**) and (**71**), potentially of value as the $C_5$–$C_{10}$ and $C_7$–$C_{12}$ segments, respectively, in the synthesis of lipoxygenase derived metabolites of arachadonic acid, have been prepared in high purity as shown in Scheme 3.[39] The expected aldehyde (**72**) obtained by Swern oxidation of (**73**) underwent ring opening below room temperature to yield exclusively (**70**; 90%). Both the stereochemistry of the product which results from the electron-withdrawing formyl group preferentially rotating in-

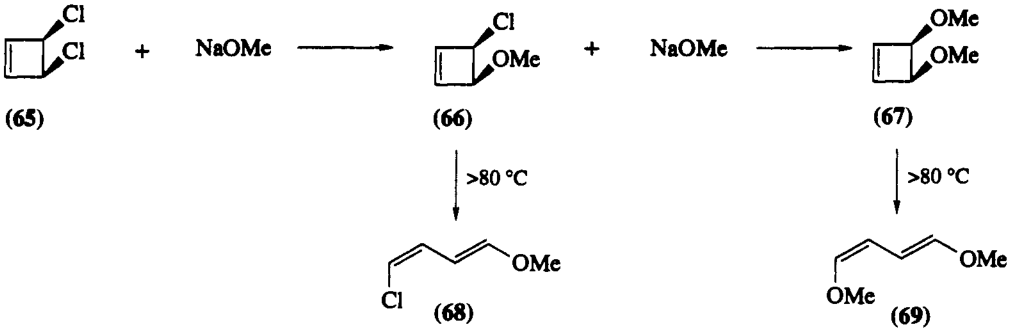
Cl
Cl
+
NaOMe
(65)
Cl
OMe
+
NaOMe
(66)
OMe
OMe
(67)
>80 °C
>80 °C
Cl
OMe
(68)
OMe
OMe
(69)

ward while the *p*-methoxybenzyloxymethyl group rotates outward, and the low activation energy for the ring opening, are predicted by the Rondan and Houk[18] calculations. Acid treatment of (70) caused isomerization to the thermodynamically more stable (71). The mono ethylenedithiol protected (*E*,*E*)-hexa-2,4-dienediol (74) was obtained when the hemiacetal (73) was reacted with 1,2-ethanedithiol/$TiCl_4$ at −15 °C followed by PCC oxidation. Presumably the initial ring opened product isomerized to (74) under the reaction conditions.

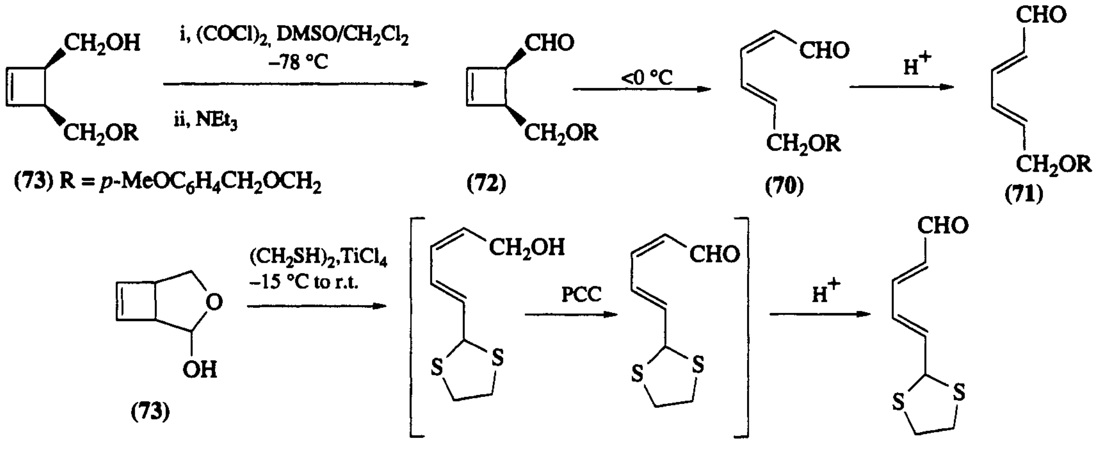
CH2OH
CH2OR
i, (COCl)2, DMSO/CH2Cl2
-78 °C
ii, NEt3
(73) R = p-MeOC6H4CH2OCH2
CHO
CH2OR
(72)
<0 °C
CHO
CH2OR
(70)
H+
CHO
CH2OR
(71)
O
OH
(73)
(CH2SH)2,TiCl4
-15 °C to r.t.
CH2OH
S
S
PCC
CHO
S
S
H+
CHO
S
S
(74)

Scheme 3

Thermolysis of the half esters (75a,b) obtained upon reaction of the cyclobutene anhydride (76) with *n*-butanol or 2-trimethylsilylethanol and DMAP in DMSO at 110 °C gave approximately 1:1 mixtures of the dienoic acid esters (77a,b). Obviously there is no strong preference for outward (or inward) rotation of a carboxylic acid *vs.* a typical ester function. Interestingly, when the solvent was changed from DMSO to 1,2-dichloroethane a 3:1 ratio of (77a) to (77b) was formed. The variation in the isomer ratio can be rationalized by assuming that the effective size of the carboxylic acid group is larger in DMSO than in $ClCH_2CH_2Cl$ due to hydrogen bonding with the solvent and thus has a greater tendency to rotate outward in that solvent.[40] Alternatively, one could argue that in the presence of a hydrogen bond accepting solvent, the carboxylic acid function becomes more electron rich and thus shows a greater tendency to outward rotation compared with $CO_2R$.

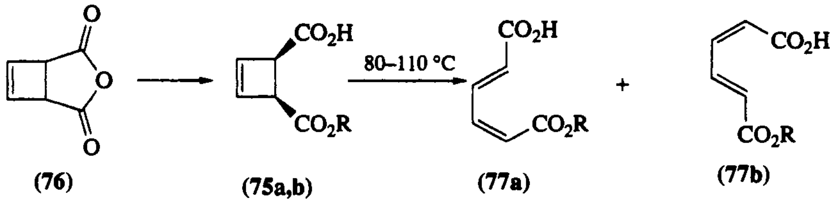
O
O
O
(76)
CO2H
CO2R
(75a,b)
80–110 °C
CO2H
CO2R
(77a)
+
CO2H
CO2R
(77b)

**a**: R = Me; **b**: R = $CH_2SiMe_3$

Replacement of C-3 or C-4 hydrogen by a methyl group in (**75**) leads to both a lowering of the temperature required for ring opening and stereospecific formation of the diene (**78**) due to the outward rotation of the methyl group.$^{41}$ The very dramatic lowering of the temperature for ring opening by an aldehyde substituent and its preference for inward rotation is illustrated by the inability to trap the hemiacetal-aldehyde (**79**), obtained upon DIBAL reduction of the corresponding lactone at –78 °C, with methoxymethylenetriphenylphosphorane.$^{42}$

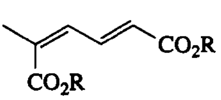

(**78**)

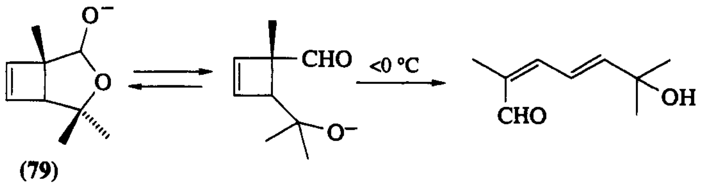

(**79**)

### 6.1.4.2 Two-carbon Ring Expansion *via* Cyclobutene Ring Openings

The possibility of a two-carbon ring enlargement *via* opening of a cyclobutene ring which is part of a bicyclo[*n*.2.0]alkene is shown schematically below. Assuming that the ring fusion is *cis* and that the number of atoms in the enlarged ring of the product is >8, the expected product should have both a *trans* and a *cis* double bond, *e.g.* (**80** → **81**).$^{43}$ Smaller ring final products cannot accommodate *trans* double bonds and thus cyclobutene ring openings producing, for example, (**82** → **83**) must occur either *via* a concerted symmetry forbidden$^{16,44}$ or a diradical pathway.$^{16}$ The ring expansion of bicyclobutenes such as (**80**; $n = 6$) occurs in the same temperature range, 160–200 °C, as found for most monocyclic *cis*-3,4-disubstituted cyclobutenes. Thus *cis*-bicyclo[6.2.0]cyclodec-2-ene is converted in 95% yield in 1 h at 200 °C to *cis,trans*-1,3-cyclodecadiene.$^{43}$

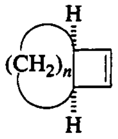

(**80**)

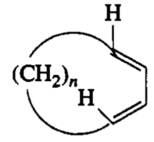

(**81**)

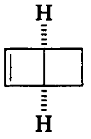

(**82**)

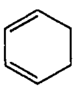

(**83**)

Dauben and Michno$^{45}$ studied the ring expansion of analogs such as (**84**). The double bond adjacent to the ring fusion reduced the thermolysis temperature to 140–160 °C. Typically similar amounts of the products (**85**) and (**86**) resulting from both the allowed modes of rotation of both substituents were observed. The *trans,cis,trans*-diene (**86**), formed by the inward rotation of the vinyl group, underwent a subsequent 6π-electrocyclic cyclization to the cyclohexadiene (**87**). The starting bicyclobutenes were prepared by ring expansion of the appropriate bicyclic cyclopropylmethylcarbenes.

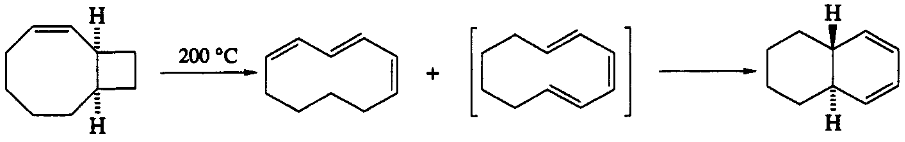

(**84**) (**85**) (**86**) (**87**)

Bicyclobutenes which carry dialkylamino substituents at a bridgehead position have proved to be excellent synthetic intermediates. Such compounds are readily prepared by reaction of enamines of cyclic ketones (**88**) with alkynes bearing one or two electron-withdrawing groups, typically in apolar solvents such as ether. The presence of the strongly electron-donating dialkylamino group facilitates the ring opening such that it is sometimes difficult to isolate the bicyclobutene. The definitive work in this area has been carried out by Reinhoudt and coworkers.$^{46-49}$ Contrary to earlier studies, both experimental$^{50,51}$ and theoretical,$^{52}$ these authors have shown that ring opening of (**89**) occurs *via* the symmetry allowed conrotatory process when $n > 3$. As expected, the dialkylamino group rotates outward to yield the *trans,cis* ring-expanded diene (**90**).$^{46-48,53}$ This reaction is reversible in the case where $n = 3$.$^{46,47}$ Prolonged standing at room temperature typically converts (**90**) into the thermodynamically more stable *cis,trans*-diene (**91**) *via* a 1,5-hydrogen shift. The isomeric *cis,cis*-dienes (**92**), which had previously been regarded as reaction products of enamines of cyclic ketones and DMAD, are a result of two consecutive 1,5-hydrogen shifts from (**90**) or, in some cases, simple isomerization of the strained *trans* double bond.[48] Compound (**91**) has reactivity which is comparable with that of (**88**) and thus a ring expansion sequence can be reiterated.[48]

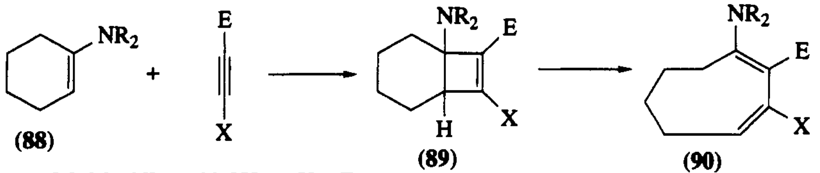

(**88**) (**89**) (**90**)

E = $CO_2Me$; $NR_2$ = $N(CH_2)_4$; X = E or Me

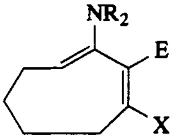

(**91**)

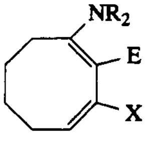

(**92**)

Variations in the ring opening process with enamines derived from five- and six-membered ring ketones, such as tetralone (**93**), have been documented. When the bicyclic adduct (**94**) is warmed with pyrrolidine in chloroform, excellent yields of the diene (**96**) are obtained. This interesting transformation involves Michael addition of pyrrolidine to the cyclobutene (**94**) followed by elimination of the bridgehead pyrrolidine ($S_N2'$) to generate a new cyclobutene (**95**) which undergoes a facile ring opening to (**96**).[46,49]

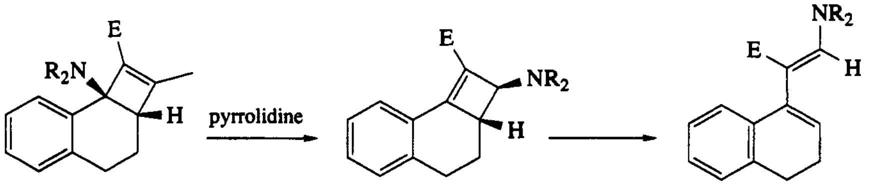

(**94**) E = $CO_2Me$; $NR_2$ = $N(CH_2)_4$ (**95**) (**96**)

The enamine–acetylenedicarboxylate or ethyl propiolate ring expansion reaction has been used effectively in the synthesis of several natural products which contain medium or large rings, including steganone,[54] muxone,[55] velleral and related compounds.[56] The relevant sequence typically involves treatment of the appropriate enamine with DMAD or ethyl propiolate followed by hydrolysis of the ring expansion product with acid. The latter treatment regenerates the carbonyl group and causes decarboxylation of the carboxyl function α to the carbonyl group, eventually leading to a ring expanded enone. Five- and six-membered heterocyclic rings containing an electron-rich double bond react with DMAD, and also often with ethyl propiolate, to give [2 + 2] cycloaddition products. The initial addition products are usually isolable or verifiable spectroscopically, but generally they are converted directly into ring expanded heterocycles. A wide variety of heterocycles has been prepared by this route, including azepines from pyrroles,[57] 2,3-dihydroazepines from 2,3-dihydro-1*H*-pyrroles,[58] and 1,2-dihydroazocines from 1,2-dihydropyridines.[59] Indoles have been converted to 1*H*-benzo[*b*]azepines.[60] Replacement of the nitrogen in the above heterocycles by oxygen or sulfur is generally feasible and leads to acceptable results. An excellent review of the pioneering work in this area is available.[61] Several representative examples of such ring expansions are shown in Scheme 4.[51,58b,62,63]

The temperatures required for these expansions are typically below 100 °C if one or two electron-donating heteroatom substituents is attached to the bridgehead positions. Considerably higher temperatures are required in the absence of such substituents. For example, thermolysis of (**97**) requires 180–200 °C,[64] the amide (**98**) must be heated to over 450 °C in order to achieve ring expansion,[65] and the cyclobutene (**99**) is reported to be thermally stable.[66]

3,4-Dihydropyrans have been found to react with DMAD in refluxing xylene, affording useful yields of dihydrooxocines.[67] Ring expansion of the parent derivative (**100**) occurs only slowly at 180 °C in toluene but can be catalyzed with $EtAlCl_2$ (80%, 25 °C, toluene). The formation of (**101**) from 5-methyl-

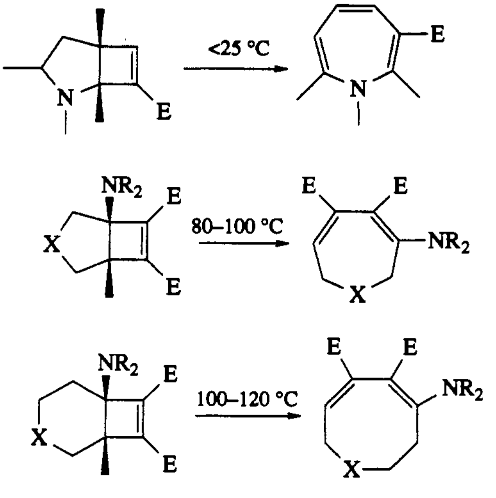

(ref. 62)

X = S (ref. 58b)
X = O (ref. 51)

X = N, S (ref. 63)

E = $CO_2Me$; R = alkyl

**Scheme 4**

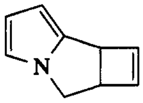

**(97)**

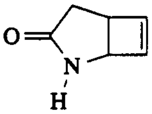

**(98)**

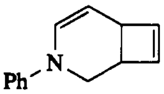

**(99)**

2,3-dihydrofurans and DMAD is favored in polar solvents such as DMF compared with toluene. Thermolysis of (**101**) to (**102**) requires 200 °C.

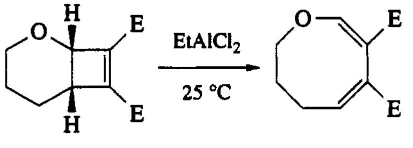

(**100**) E = $CO_2Me$

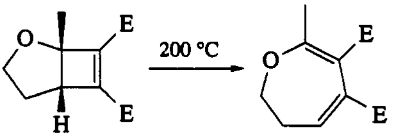

**(101)** **(102)**

Reaction of DMAD with the enolates of keto esters results in a two-carbon ring expansion,[68,69] an example being the preparation of (**103a**) from (**103**). These latter results suggest a general sequence of ring expansions involving cyclic β-diketones, β-keto esters or β-keto sulfones and alkynes.

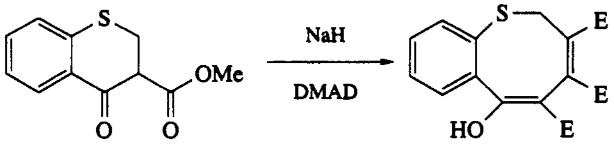

**(103)** **(103a)**

## 6.1.5 CYCLOBUTENONE RING OPENINGS

The ring opening of cyclobutenone derivatives leads to the formation of vinylketenes (equation 3). The potential of these compounds in the synthesis of complex molecules has been investigated in the 1980s by a number of research groups, most notably those of Moore, Liebeskind and Danheiser. An excellent review describing work in this area prior to 1986 is available.[70]

Cyclobutenones can be prepared by several routes including the reaction of ketenes, generally prepared *in situ* by dehydrohalogenation of acyl chlorides, with electron-rich alkynes such as alkoxyacetylenes,[71,72] alkylthioacetylenes[73] or ynamines.[71,74]

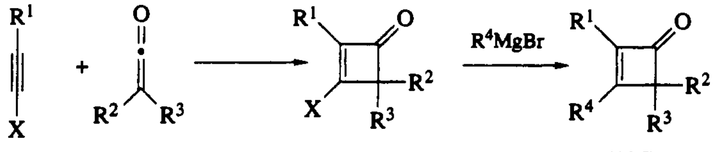

**(104)** **(105)**

X = OR, SR, NR$_2$; R$^1$, R$^2$, R$^3$ = H, alkyl, aryl; R$^4$ = alkyl, aryl

Typically, reaction of **(104)** with Grignard reagents leads to replacement of X by an alkyl or aryl substituent and gives rise to **(105)**. Such reactions appear to occur *via* a Michael addition to **(104)** followed by elimination of the alkoxide;[72] 1,2-addition followed by loss of $H_2O$ and hydrolysis of the intermediate enol ether leads to the same result. Dialkyl squarates **(106)** have recently become a favorite starting material for the preparation of a variety of substituted cyclobutenones, in particular those bearing one or more oxygen substituents. Liebeskind and coworkers have carefully reviewed both this and earlier approaches to cyclobutenones and concluded that diisopropyl squarate, a stable crystalline solid, offers the most versatility.[75] For example, reaction of (**106**; R = Pr$^i$) with alkyllithiums at –78 °C gives the 1,2-adducts **(107)**, usually in >90% yield.[75,76] These substances are cleanly hydrolyzed to the enediones **(108)**. The use of LiAl(OBu$^t$)$_3$H in place of RLi affords the isopropyl ester of semisquaric acid (**108**; R$^1$ = H) in >60% overall yield.[75] Protection of the hydroxyl group in **(107)** as its TBDMS derivative and repetition of the alkylation–hydrolysis sequence affords differentially 3,4-disubstituted 1,2-cyclobut-3-enediones **(109)**.[75] Reaction of **(108)** with aryl- or alkynyl-lithiums gives selective addition to the more reactive, nonvinylogous ester carbonyl group to yield **(110)**.[77]

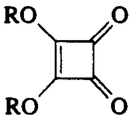

**(106)**

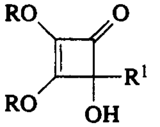

**(107)**

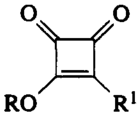

**(108)**

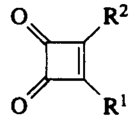

**(109)**

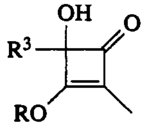

**(110)**

The synthetic value of the various cyclobutenones rests with their ready thermal opening to vinylketenes and subsequent reactions of these intermediates. Depending on the structure of the ketene generated, and the nature of any additional reagents present, a series of subsequent electrocyclic cyclizations, cycloadditions followed by further ring opening and again electrocyclic cyclizations can occur which lead to a marvellous variety of highly substituted phenols, resorcinols, quinones and annulated quinones, 2-alkylidene-1,3-cyclopentanediones and cycloocta-2,6-dien-1-ones.[70]

Those applications that make use of alkenyl derivatives such as **(112)** are particularly attractive since these compounds can themselves be generated from simpler cyclobutenenones.[78,79] Thus heating a cyclobutenone such as **(111)** above 80 °C results in a reversible electrocyclic cleavage to generate a vinylketene **(113)** which can combine with an electron-rich alkyne. Further electrocyclic cleavage of the vinylcyclobutenone **(112)** thus obtained furnishes a dienylketene **(114)** which undergoes a six-electron cyclization to afford, after tautomerization, a highly substituted phenol **(115)**. This sequence provides an efficient, regiocontrolled route to a variety of selectively protected resorcinol and phloroglucinol derivatives and has been used to synthesize a number of natural products, including the antifungal derivative DB 2073 **(116)**,[78a] grifolin **(117)**,[78a] mycophenolic acid[78b] and khellinone.[79]

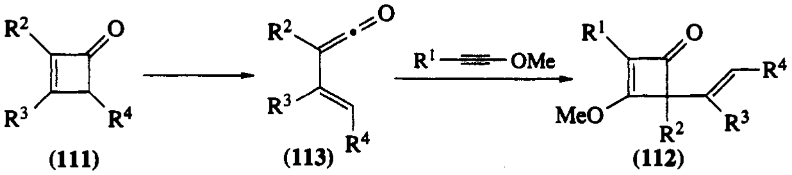

**(111)** **(113)** **(112)**

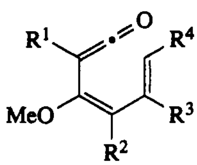
**(114)**

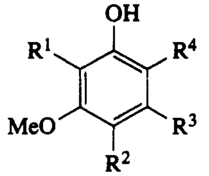
**(115)**

$R^1 = R^2 = R^3 = R^4 =$ H or alkyl

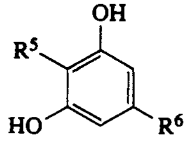
**(116)** $R^5 = C_6H_{13}$, $R^6 =$ Pr

**(117)** $R^5 =$ farnesyl, $R^6 =$ Me

4-Aryl-4-hydroxycyclobut-2-enones rearrange upon heating in refluxing xylene (2 h) to hydroquinones which can be oxidized with $Ag_2O$, $Ce^{IV}/SiO_2$ or $FeCl_3/O_2$ to the corresponding quinones. A wide combination of substituents and heteroannulated rings have been prepared in excellent overall yield from the addition of lithio arenes to **(106)**, **(108)** or **(109)** followed by thermolysis. Several examples are shown in Scheme 5. In these reactions the outward rotation of the hydroxyl group during the ring opening of intermediate **(110)** occurs, which places the aryl group in the ideal position for electrophilic attack on the carbonyl group of the ketene (or electrocyclization) necessary for cyclization.

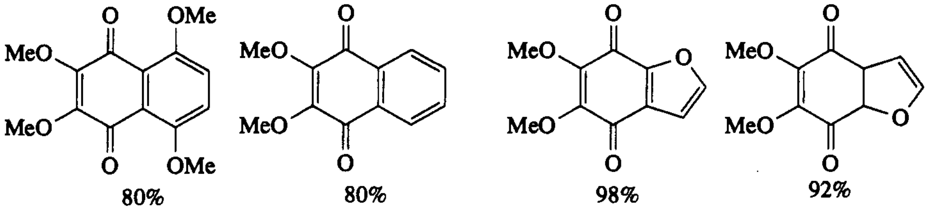

**Scheme 5**

The same sequence when applied to benzocyclobutene-1,2-diones such as **(118)** afforded the adduct (**119**; 80%), which was rearranged upon heating at 160 °C and air oxidation to the anthraquinone **(120)**.[77a]

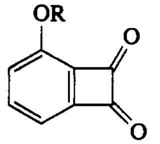
**(118)** R = $OSiMe_2Bu^t$

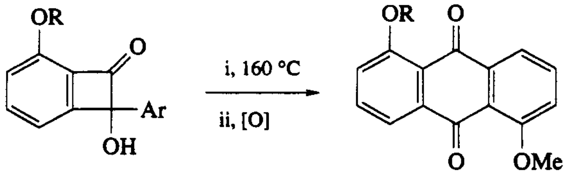

**(119)** Ar = 2-methoxyphenyl

**(120)**

Benzoquinones **(121)** also result from the thermolysis of 4-alkynylcyclobut-2-enones **(122)** in refluxing xylene.[80] This conversion proceeds *via* the alkynylketene (123), and possibly *via* the zwitterionic intermediate **(124a)** or the corresponding diradical **(124b)**.[80c] The conversion of **(123)** to **(121)** is occasionally competitive with the formation of 2-alkylidenecyclopent-4-ene-1,3-diones **(125)**, the result of an alternate alkyne–ketene cyclization. This latter route becomes the major pathway when $R^1$ = Ph, $SiMe_3$ or OEt in **(126)**.[80c] Liebeskind and coworkers[81] have generalized the formation of **(125)** for a large variety of substituents by heating **(122)** with 10 mol % of $Pd(OCOCF_3)_2$ in THF at 60 °C for 1 h. All the above reactions have been applied to benzo analogs of **(122)**, thus yielding naphthaquinones including nanaomycin A and deoxyfrenolicin.[80]

If the cyclobutene–vinylketene equilibrium is established in the presence of a 1,3-diene such as cyclopentadiene, cyclohexadiene or (*E*)-1,3-pentadiene, the ketene is trapped *via* a [4 + 2] cycloaddition reaction to furnish a 2,3-divinylcyclobutanone **(127)**. When such reactions are carried out above 120 °C a further 3,3-sigmatropic rearrangement takes place to yield cyclooctadienones **(128)** in overall yields ranging from 30–90%. The intermediate divinylcyclobutanes can also be obtain by dehydrohalogenation of crotyl chloride in the presence of the dienes.[82]

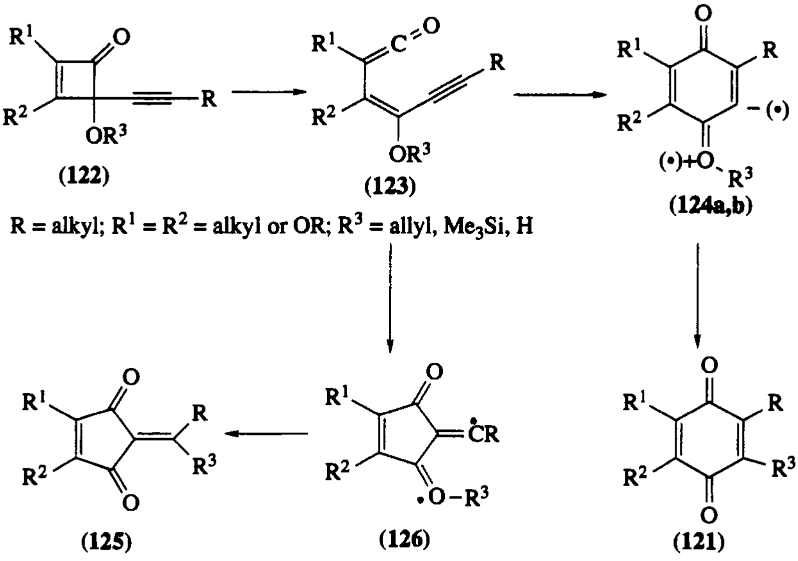

**(122)** **(123)** **(124a,b)** **(125)** **(126)** **(121)**

R = alkyl; $R^1 = R^2$ = alkyl or OR; $R^3$ = allyl, $Me_3Si$, H

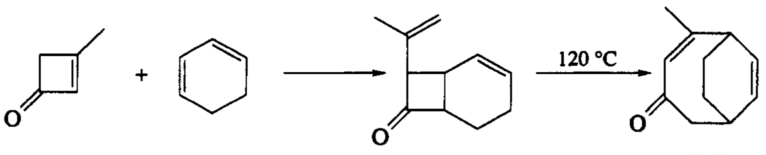

**(127)** **(128)**

## 6.1.6 BENZOCYCLOBUTENES AND DERIVATIVES

Benzocyclobutenes are one of a number of starting materials which can serve as precursors of *o*-quinodimethanes (**129** → **130**). This route to these reactive 1,3-dienes often has considerable advantage over others, despite the fact that occasionally temperatures in excess of 200 °C are required for ring opening, since no other reagents which might interfere with subsequent reactions of (**129**) are required. Thus remarkably clean and efficient transformations are often obtained.

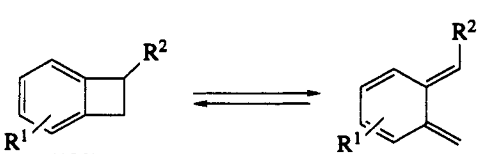

**(129)** **(130)**

The temperature required to set up the equilibrium between (**129**) and (**130**) is highly dependent upon R. Typical values are: R = $O^-$, 0 °C;[33] R = $NR_2$, 25–50 °C; R = OH, O-alkyl, 80–110 °C; R = O-acyl or NH-acyl, 110–140 °C; R = $CONHR^1$, $COR^1$, $CO_2R^1$, 150–180 °C; R = alkyl, phenyl, 180–210 °C; R = H, >210 °C.[83b] The value of *o*-quinodimethanes in organic synthesis rests with their outstanding reactivity as 1,3-dienes in both inter- and intra-molecular Diels–Alder reactions.[83] Even relatively unreactive dienophiles such as terminal vinyl groups and internal alkenes such as cyclopentene have been successfully combined with various derivatives of (**130**) either in an inter-[83b,85] or intra-molecular mode.[84] Imines[86] and aldehydes[83b,87] also react efficiently with (**130**), yielding dihydroquinolines and dihydrobenzopyrans, respectively. Nitriles[83b,87] and alkynes[83b,88] have also been employed as dienophiles. The vast potential of these intermediates for the synthesis of polycyclic compounds began to be realized in the 1970s, mainly due to the efforts of the research groups led by Oppolzer and Kametani. Only a limited number of examples illustrating the key role of benzocyclobutenes (and *o*-quinodimethanes) will be described. Excellent reviews covering the various years of development, including analysis of the relative regio- and stereo-chemistry observed in the cycloadditions reactions, are available.[83] Asymmetric induction in the intermolecular Diels–Alder reactions of (**130**) has also begun to be investigated.[83a,89]

A major initial limitation of the benzocyclobutene approach to *o*-quinodimethanes was the lack of efficient, large-scale syntheses for many specifically substituted derivatives. Fortunately, recent developments have removed much of this impediment. Conceptually, the synthesis of benzocyclobutenes from aromatic precursors can be envisaged in only a limited number of ways. These include [2 + 2] cycloadditions involving benzynes and alkenes, intramolecular cyclization on to a benzyne, cyclizations involving arene anions, and electrocyclic closure of *o*-quinodimethanes. Benzocyclobutene derivatives can also be prepared by aromatization of bicyclo[4.2.0]octanes. Detailed discussion of variations to these approaches can be found in the cited reviews.[83] The cobalt catalyzed co-oligomerization of 1,5-hexadiynes with alkynes, especially bis(trimethylsilyl)acetylene, has also been employed for the preparation of specifically substituted benzocyclobutenes.[90] In the latter case the cyclobutenes are often not isolated but converted directly to *o*-quinodimethanes and subsequent products.[90]

Stevens and Bisacchi[91] have carefully examined the trapping of benzynes, generated from a number of aryl bromides and sodium amide in THF, with 1,1-dimethylethylene and report procedures which afford 64–86% yields of 1,1-dimethoxycyclobutenes, *e.g.* (**131**). These compounds are hydrolyzed quantitatively to the corresponding benzocyclobutenones (**132**). Excellent regioselectivity was obtained with unsymmetrical benzynes derived from methoxy substituted bromobenzenes due to the polarized nature of the benzyne intermediate. Steric effects also influence regioselectivity: *o*-bromotoluene afforded a 3:1 mixture of 3-methyl- and 6-methyl-benzocyclobutene.

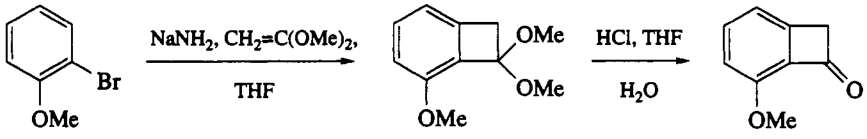

(**131**) 70%  (**132**) ~100%

The diazotization of anthranilic acid, a classic route to benzyne, when carried out in the presence of vinyl acetate,[92] vinyl ethers[92] or 1,1-dichloroethylene gives the expected benzocyclobutenes in about 40% yield. Despite the rather moderate yields this method represents a convenient route to multigram quantities of the parent compounds, benzocyclobutenol and benzocyclobutenone. The latter is easily converted to benzocyclobutene-1,2-dione.[93] The diazotization sequence applied to 2-amino-3,6-dimethoxybenzoic acid and 1,1-dichloroethylene results in a 80% yield of 3,6-dimethoxycyclobuten-1-one.[94] Trapping of benzynes with other ethylene derivatives, and especially more substituted alkenes, has given generally poorer, variable results.[95]

The Kametani group has made considerable use of the intramolecular trapping of benzynes by pendant carbanion centers. The nitrile (**133**) is a key and versatile intermediate in many of the Kametani studies, including the preparation of optically pure estradiol.[83c,84,96] The ester of the benzocyclobutenecarboxylic acid (**134**) was prepared by a similar benzyne cyclization.[97] The acid (**134**) was converted *via* oxidative decarboxylation and HCl hydrolysis to the very labile *trans*-2-arylbenzocyclobutenol (**135**), which was used in the preparation of podophyllotoxin.[98]

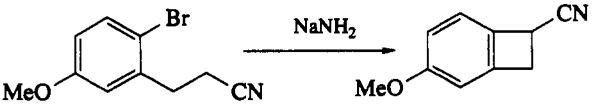

(**133**)

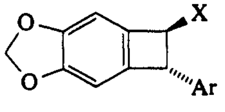

(**134**) X = CO$_2$H
(**135**) X = OH
Ar = 3,4,5-trimethoxyphenyl

Intermolecular benzyne–enolate cycloadditions have been studied in detail by Caubere *et al.*[99] Benzocyclobutenols (**136**) were obtained with enolates derived from five-, six- and seven-membered ring ketones. Larger ring enolates and acyclic enolates results in ring expanded ketones and *o*-disubstituted benzenes. The stability of the intermediate alkoxy anions (**137**) is rather high when $n < 3$ since the preferred outward rotation of the O$^-$ group results in the formation of a *trans* double bond in a seven- or eight-membered ring. The preparation of analogs of (**136**) bearing additional functionality in the enolate ring has been described.[100]

Intramolecular cyclizations *via* aryl anions have been used to prepare benzocyclobutenes (**138**) from *o*-bromo-β-phenethyl bromides[101] and benzocyclobutenols (**139**) from *o*-bromostyrene oxides.[102]

Flash vacuum thermolysis of *o*-methylbenzyl halides (**140**) at 500–600 °C gives benzocyclobutenes.[103,104] This reaction has recently been extended to the preparation of cyano and chloro sub-

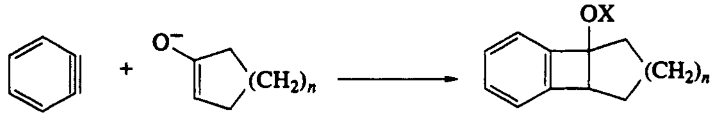

**(136)** X = OH

**(137)** X = $O^-M^+$

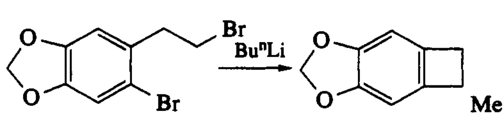

**(138)**

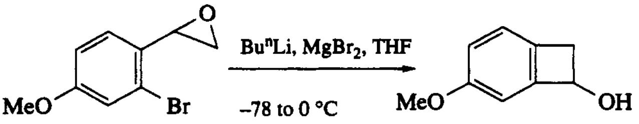

**(139)**

stituted benzocyclobutenes.[105] Benzocyclobutene[106] and *trans*-2-phenyl-1-acetoxybenzocyclobutene (**141**)[107] have been obtained *via* thermolysis of the corresponding 2,5-dihydrobenzothiophene 2,2-dioxides. These reactions presumably occur by ring closure of thermally generated *o*-quinodimethane intermediates.

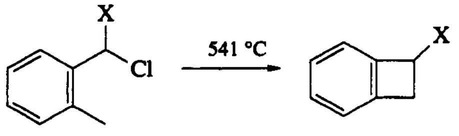

**(140)** X = H, Cl, CN

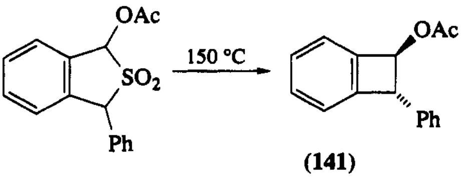

**(141)**

The bicyclo[4.2.0]octane approach has proved valuable in particular situations. South and Liebeskind[93] have converted the adduct obtained from 3-methyl-1-trimethylsilyloxy-1,3-butadiene and 1,4-dichloro-3,3,4-trifluorocyclobutene into 3-hydroxy-5-methylbenzocyclobutene-1,2-dione in 72% yield.[93]

Target molecules which have six-membered rings fused to an aromatic nucleus are obvious candidates for synthesis *via* *o*-quinodimethane intermediates which are potentially accessible by benzocyclobutene ring openings. Early targets included a variety of steroids such as estrone, homoestrone, estradiol, various alkaloids, anthraquinones and anthracyclines. These applications in which the *o*-quinodimethane precursor is readily recognized have been often reviewed.[83] They are shown in a general scheme (Scheme 6). Application of *o*-quinodimethane intermediates generated from benzocyclobutenes to the synthesis of targets such di-[107] and tri-terpenes,[108] diterpene alkaloids,[109] morphinans[110] and norsteroids,[111] in which the aromatic ring has been substantially modified and thus the precursor is no longer readily apparent, have also been reported. Recently the use of alternate precursors to *o*-quinodimethanes especially the $F^-$ catalyzed desilylation of *o*-substituted benzyltrimethylsilanes, has received considerable attention.[112]

The synthetic use of benzocyclobutenes bearing a single substituent on the cyclobutene ring is well established and quite predictable since one generally finds that most useful substituents prefer to rotate outward during the ring opening to give *o*-quinodimethanes having structure (**130**), which are reliably trapped as such by good external and even weak internal dienophiles. The fact that the benzocyclobutene ring opening is reversible, as shown for example by the racemization of optically active benzocyclobutenol,[113] does allow the possibility of observing products from the less favorable ring opening, especially in the absence of efficient dienophilic trapping reagents. Several such examples have been discussed (see Section 6.1.3.1).

Synthetic applications involving 1,1- and 1,2-disubstituted benzocyclobutenes are more rare. Inward rotation of an alkyl group in the ring opening of 1,1-disubstituted benzocyclobutenes leads to an intermediate which is prone to 1,5-hydrogen shift.[114] Such a pathway is obviously detrimental to an application which requires trapping of the *o*-quinodimethane in the typical Diels–Alder format. The situation is particularly serious when one of the two groups is OR, due to the powerful tendency of the oxygen substituent for outward rotation. Benzocyclobutenol when heated alone is isomerized to 2-methylbenzaldehyde[115] either *via* a 1,5-hydrogen shift from a small amount of the isomer resulting from inward rotation of the hydroxy group, or by an intermolecular hydrogen transfer mechanism. From a synthetic point of view it is often worthwhile to protect the hydroxy group and thus avoid this competing process.

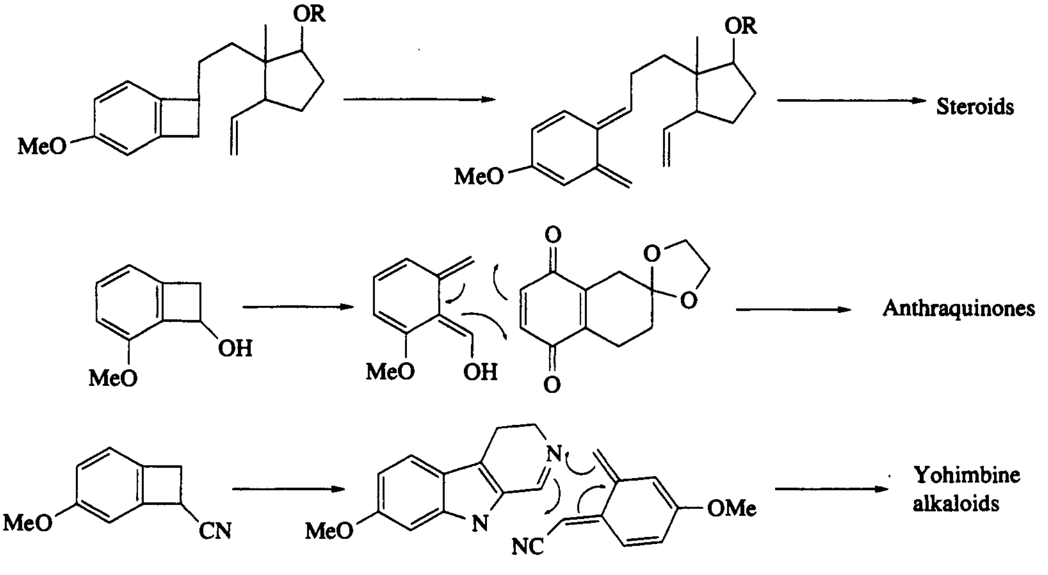

Scheme 6

In 1,2-disubstituted series such as *cis*- and *trans*-2-alkyl-1-alkoxybenzocyclobutenols, the *trans* isomer is more likely to lead to a high yield of cycloaddition product than the *cis* since the 1,5-hydrogen shift is precluded. The forced inward rotation of an aryl substituent in 1-methoxy-1-phenylbenzocyclobutene is potentially advantageous and leads to anthracene derivatives.[115] See also the anthraquinone synthesis from the corresponding benzocyclobutenones (Section 6.1.5).

The Kametani group has made considerable use of 1-alkyl-1-cyanobenzocyclobutenols. Ring opening of benzocyclobutenol (**142**) appears to form preferentially the intermediate (**143**) resulting from the outward rotation of the alkyl group and inward rotation of the electron-withdrawing (and small) cyano group which 'protects' against the unwanted 1,5-hydrogen shift.[114] The product obtained from this ring opening–cyclization sequence was elaborated into morphinan derivatives.[110]

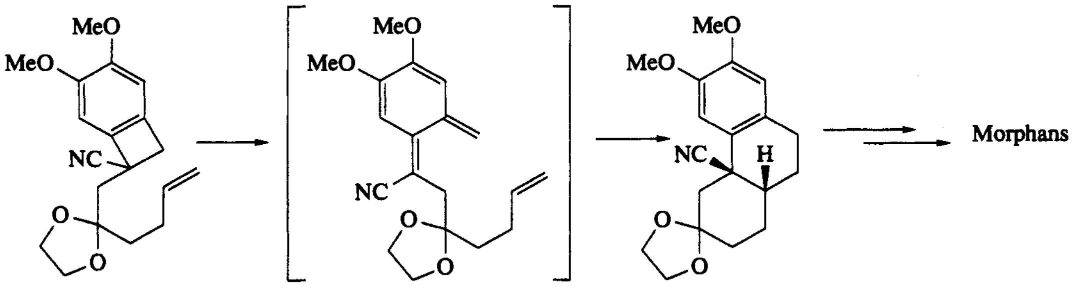

(**142**) (**143**)

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# 6.2

# 1,3-Cyclohexadiene Formation Reactions

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## 6.2.1 INTRODUCTION

### 6.2.1.1 Scope

The (3*Z*)-1,3,5-hexatriene (**1**) to 1,3-cyclohexadiene (**2**) interconversion is the prototypical example of the six-electron (6e$^-$) electrocyclization reaction as defined by Woodward and Hoffmann (WH).[1,2] Among the early observations, the complementary stereochemical results (Figure 1) obtained for thermal (disrotatory, dis) and photochemical (conrotatory, con) processes in the vitamin D system (*vide infra*) provided experimental bases leading to the formulation of the WH rules. Despite its theoretical significance, the thermal variant of the 6e$^-$ electrocyclization[3] has found relatively little use in synthesis. By contrast, the photochemical counterpart (photocyclization of stilbenes and analogs) constitutes a powerful synthetic procedure for the formation of aromatic compounds.[4] More recently, new ways of inducing electrocyclic processes have been discovered, such as those which proceed by reductive electron transfer[5] or by electrical discharge.[6] The former appears to mimic stereochemically the photochemical process while the latter is considered to involve vibrationally excited (thermal) ground states. The potential utility of these new methods for inducing 6e$^-$ electrocyclizations remains virtually unexplored.

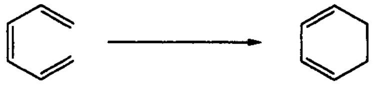

(1) (2)

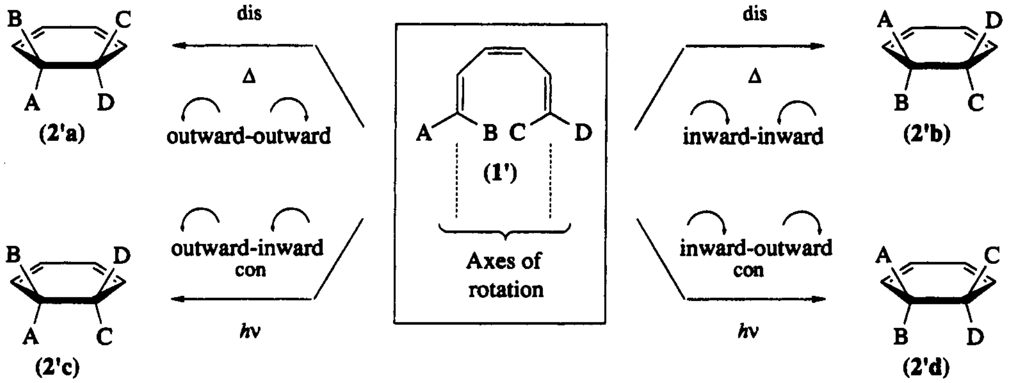

**Figure 1** The four stereochemically distinct modes of electrocyclic ring closure wherein the notations 'inward' and 'outward' refer to the axes of rotation as viewed with respect to (1'). The principle of the conservation of orbital symmetry predicts disrotatory (dis) or conrotatory (con) ring closure for the thermally or photochemically induced processes, respectively. The same modes (dis or con) are predicted for the reverse ring opening processes

Several excellent reviews and monographs have been devoted to the topic of electrocyclizations,[3,4] but little attempt has been made at systematically describing the utility of 6e$^-$ electrocyclizations from a synthetic point of view. The aim of this chapter is to highlight the unique features of this intramolecular formation of six-membered rings in synthesis, a capability primarily only shared by the Diels–Alder reaction and the cyclotrimerization of alkenes among the variety of pericyclic reactions.[7] The emphasis is on selectivity and the resulting 1,3-cyclohexadienes have been classified (Figure 2) in terms of fused and bridged structures according to the position of the cycle with respect to the diene array. Thus this chapter is organized according to the 1,3-cyclohexadiene structural type, independent of their mode of formation, whether photochemically, thermally or otherwise induced.

It is not possible within the restrictions of this review to treat all carbocyclic frameworks (*e.g.* spirocyclics) and a conscious decision was also made specifically to exclude the heterocyclic version of this electrocyclization. The number and variety of heteroatoms and the possible permutations along the hexatriene system that can *a priori* be considered would justify a separate treatment. The reader is referred to the excellent monograph by Marvell[3a] for references to the treatment of electrocyclizations leading to heterocycles. However, in order to provide at least a few leading references, several selected examples of hetero electrocyclizations are included in this chapter together with comments concerning retro electrocyclizations and higher-order electrocyclic processes.

### 6.2.1.2 Historical Perspective

The investigations by Havinga and coworkers[8] disclosing the detailed stereochemical consequences of the thermal and photochemical interconversions in the vitamin D field provided an important impetus for the elaboration of the WH rules. The reversible photochemical ring opening of provitamin D (**5**) to precalciferol (**3**) and the photochemical ring closure of precalciferol (**3**) to lumisterol (**6**) can be explained by consecutive conrotatory processes (*vide infra*). Thermal treatment of precalciferol (**3**) below 100 °C generates calciferol (**4**) by a 1,7-sigmatropic hydrogen shift, which constitutes the second pericyclic reaction involved in vitamin D biosynthesis. By increasing the temperature to 100–200 °C, a new electrocyclization takes place, resulting in formation of pyrocalciferol (**7**) and isopyrocalciferol (**8**). The configuration of the latter pair of stereoisomers requires a disrotatory motion (Figure 1) of the ends of the

**hexatriene. The occurrence of complementary processes, thermal disrotatory ring closure of (3) to (7) and (8) and photochemical conrotatory ring closure of (3) to (5) and (6), is striking, and these results among others led to the development of the concept of the conservation of orbital symmetry and the WH rules.**

(a) CYCLIC AND ANNULATED HEXATRIENES: MONO-ANNULATED TRIENES

*Ortho*-condensed systems: [*i*,*j*]-annulated systems with *j* – *i* = 1 or 5. *Types I–IV*

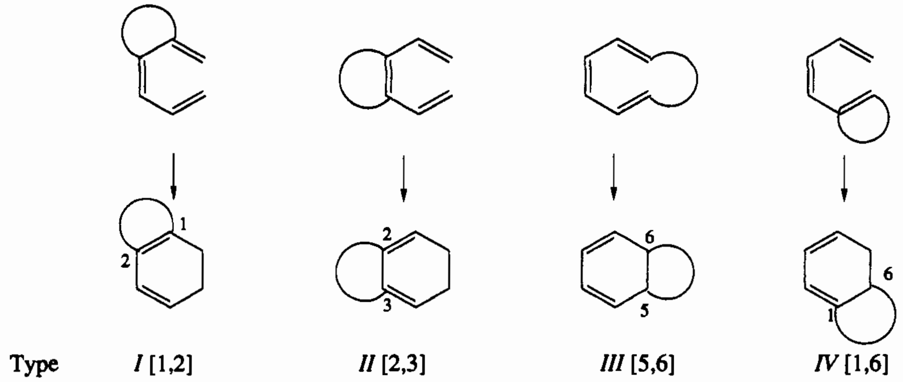
1
2
2
3
6
5
6
1
Type
*I* [1,2]
*II* [2,3]
*III* [5,6]
*IV* [1,6]

Bridged systems: [*i*, *j*]-annulated systems with *j* – *i* = 2–4. *Types V–IX*

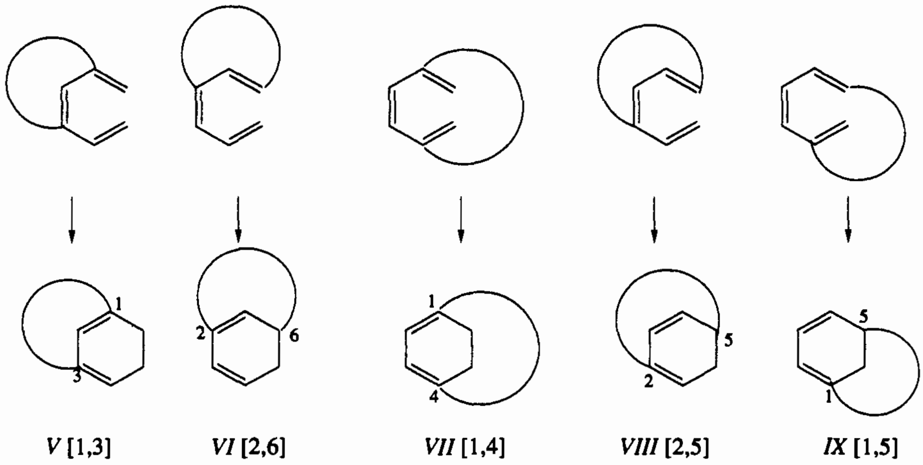
1
3
2
6
1
4
5
2
5
1
*V* [1,3]
*VI* [2,6]
*VII* [1,4]
*VIII* [2,5]
*IX* [1,5]

(b) CYCLIC AND ANNULATED HEXATRIENES: BIS-ANNULATED TRIENES

Only *ortho*-condensed systems: [*i*,*j*:*k*,*l*]-annulated systems with *j* – *i* = 1 or 5, *l* – *k* = 1. *Types X–XV*

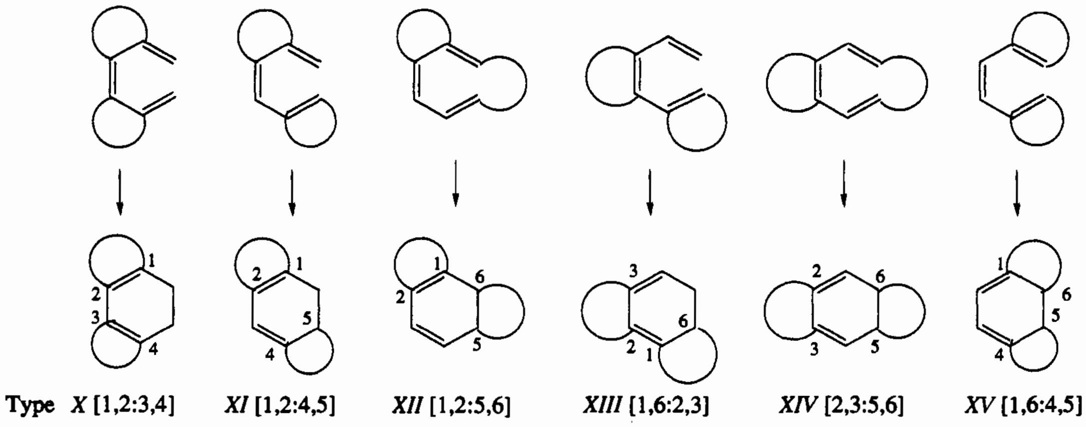
1
2
3
4
2
1
5
4
1
6
2
5
3
6
2
1
2
6
3
5
1
6
5
4
Type *X* [1,2:3,4]
*XI* [1,2:4,5]
*XII* [1,2:5,6]
*XIII* [1,6:2,3]
*XIV* [2,3:5,6]
*XV* [1,6:4,5]

**Figure 2**

(c) HIGHER ORDER ANNULATED SYSTEMS

Only *ortho*-condensed systems: [*i,j*:*k,l*:*m,n*]-annulated systems with *j* – *i* = 1 or 5, *l* – *k* = *n* – *m* = 1.
*Types XVI–XVII*

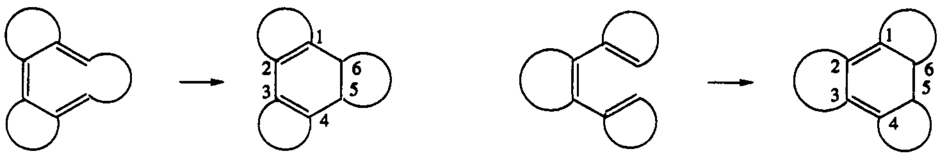

Type *XVI* [1,2:3,4:5,6] *XVII* [1,6:2,3:4,5]

**Figure 2** Classification of the six-electron (6e⁻) electrocyclizations is based on the structure of the resulting cyclohexadiene derivatives (Types I–XVII) irrespective of the method of ring closure, whether thermally, photochemically or otherwise induced

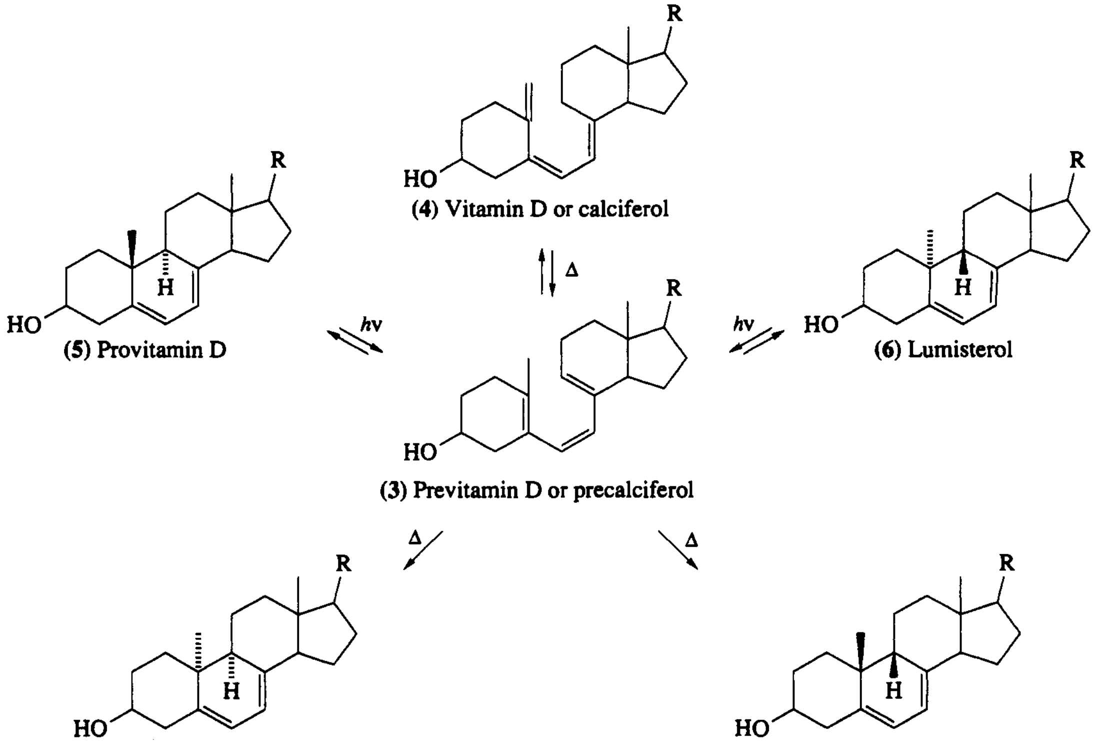

(4) Vitamin D or calciferol

(5) Provitamin D

(6) Lumisterol

(3) Previtamin D or precalciferol

(7) Pyrocalciferol

(8) Isopyrocalciferol

A definitive confirmation of the disrotatory nature of the thermal 6e⁻ electrocyclization was based on studies of the stereoisomers of 2,4,6-octatriene[9] and (*Z,Z,Z*)-1,3,5-cyclononatriene.[10] Heating (*E,Z,E*)-isomer (**9**) at 132 °C gave *cis*-5,6-dimethylcyclohexadiene (**10**) with a diastereomeric purity of 99.5%. Although the (*Z,Z,Z*)-(**11**) and (*E,Z,Z*)-(**12**) isomers are in mobile equilibrium above 100 °C, the complementary *trans*-5,6-dimethylcyclohexadiene (**13**) was formed at 178 °C from the (*E,Z,Z*)-isomer (**12**). The interconversion (**11**) to (**12**) was postulated[9b] to involve the intermediacy of (*Z,Z*)-1,3,5-octatriene (**14**) through a 1,7-sigmatropic hydrogen (1,7-H) shift. A more recent reexamination of this process[11] conclusively demonstrated the intermediacy of (**14**). Similar results were obtained for the (*Z,Z,Z*)-1,3,5-cyclononatriene.[10] The conrotatory nature of the photochemical ring closure was demonstrated by irradiation of (**9**),[12] resulting in a photostationary state consisting of a small amount of *trans* isomer (**13**) as the only significant electrocyclized material (for the stereochemistry of the ring opening process, see Section 6.2.4.1).

An even more detailed mechanistic scrutiny of photochemical and thermal 6e⁻ electrocyclizations of the parent system (**1, 2**) has recently emerged using resonance Raman spectroscopic[13] and isotopic labeling[14] techniques, respectively.

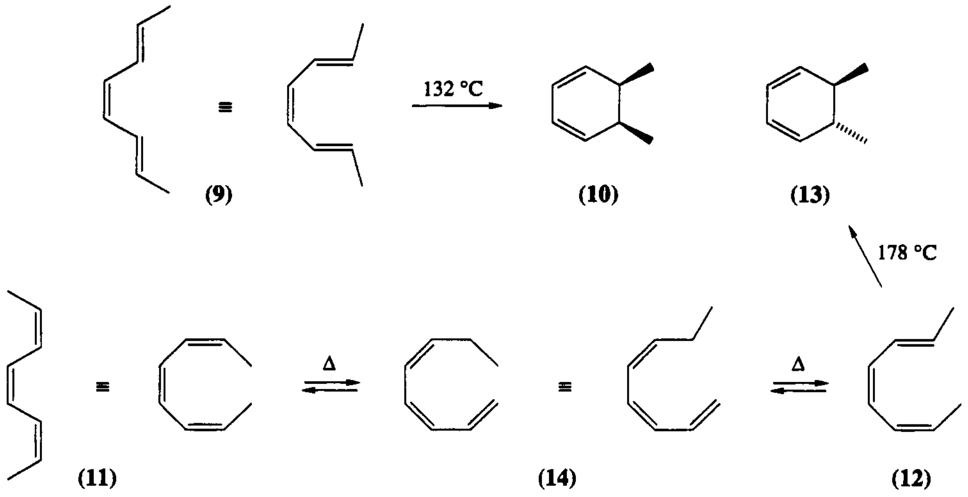

### 6.2.1.3 Theoretical Treatment of Electrocyclic Processes: Stereochemistry

Theoretical analysis of the interconversion of hexatriene (**1**) to cyclohexadiene (**2**) has eluded a thorough *ab initio* study similar to that carried out for the corresponding 4e$^-$ process, the interconversion of butadiene and cyclobutene.[15] Early predictions[16a] using the Polanyi–Evans method of interacting potential energy surfaces predicted that the thermal 6e$^-$ cyclization would proceed in a conrotatory sense; similarly the same prediction was obtained using calculations based on the principle of least motion (PLM).[16b] The failure of these methods amply illustrates the power of orbital symmetry requirements in overcoming the steric disadvantage of the thermal disrotatory motion. However, later theoretical evaluations at the MINDO/2 and *ab initio* SCF/6-31G* levels have provided a more satisfactory congruence between experiment and theory.[14,17] There are a number of theoretical approaches which have become popular among experimentalists to treat electrocyclizations and other pericyclizations.[18,19] These approaches include the orbital and/or state correlation diagram method, the transition state aromaticity model, the perturbation molecular orbital method and various other methods. The correlation diagram approach has been selected here for describing how the principle of the conservation of orbital symmetry leads to the WH selection rules.

To depict these symmetry requirements leading to the stereospecificity of the interconversion of (**1**) to (**2**), consider the orbital correlation diagram involving the six $\pi$-orbitals of the hexatriene and the four $\pi$-orbitals and two $\sigma$-orbitals of cyclohexadiene (Figure 3). In the thermal disrotatory process, which maintains a mirror plane of symmetry (or $\sigma$-symmetry), ground state reactant (**1**) orbitals ($\pi_a{}^2\pi_b{}^2\pi_c{}^2$) correlate with the corresponding product (**2**) orbitals ($\sigma^2\pi_1{}^2\pi_2{}^2$). This suggests that the disrotatory thermal process should possess a relatively low activation barrier (compared to the thermal conrotatory process) and the process is said to be allowed. For the thermal conrotatory process, in which a $C_2$ axis of symmetry is preserved (ignoring substituents), ground state reactant (**1**) orbitals ($\pi_a{}^2\pi_b{}^2\pi_c{}^2$) correlate with product (**2**) excited state orbitals ($\sigma^2\pi_1{}^2\pi_3{}^{*2}$). A relatively high activation barrier is therefore predicted and the 6e$^-$ thermal conrotatory closure of (**1**) to (**2**) is considered to be forbidden.

An analysis of the thermal ring opening process (**2**) to (**1**) affords the same prediction. The ground state of (**2**) ($\sigma^2\pi_1{}^2\pi_2{}^2$) correlates with the ground state of (**1**) ($\pi_a{}^2\pi_b{}^2\pi_c{}^2$) in the disrotatory mode, but with an excited state of (**1**) ($\pi_a{}^2\pi_b{}^2\pi_d{}^{*2}$) in the conrotatory process. Thus the same prediction obtains for both the forward and reverse process.

A similar analysis of the first excited state of the hexatriene (**1**) closing to (**2**) leads to the opposite prediction, namely that the conrotatory ring closure process should be allowed and that the disrotatory mode should be forbidden (*i.e.* the former should have a lower activation barrier than the latter in the excited state manifold). Thus, for example, the first excited state of (**1**) ($\pi_a{}^2\pi_b{}^2\pi_c{}^1\pi_d{}^{*1}$) correlates in the disrotatory mode with an excited state of (**2**) ($\sigma^2\pi_1{}^1\pi_2{}^2\pi_4{}^{*1}$) higher in energy than that of (**2**) ($\sigma^2\pi_1{}^2\pi_2{}^1\pi_3{}^{*1}$) when (**1**) undergoes conrotatory closure. That the conrotatory mode is preferred over the disrotatory mode in the first excited state is also predicted for the reverse, the ring opening process (**2**) to (**1**). It is also possible to consider other excited states undergoing electrocyclizations.[18b]

With respect to the electrocyclic reactions of spin doublets (such as cation and anion radicals), the situation is more complex and an extended orbital correlation diagram approach or the Zimmermann orbital topology criterion have been suggested to be more satisfactory theoretical approaches to the observed stereoselectivities.[20] Except for the electrocyclic ring closure of the hexatriene anion-radical mentioned earlier,[5] all of the corresponding processes involving cation-radicals examined thus far involve ring opening processes.[21] It remains for future experiments to delineate whether electron transfer processes can be utilized for inducing electrocyclic processes at a practical level. In this connection it should be mentioned that certain other cation-radical pericyclic processes (*e.g.* the Diels–Alder reaction) have already been demonstrated to exhibit impressively high regio- and stereo-selectivity and to be synthetically useful.[22]

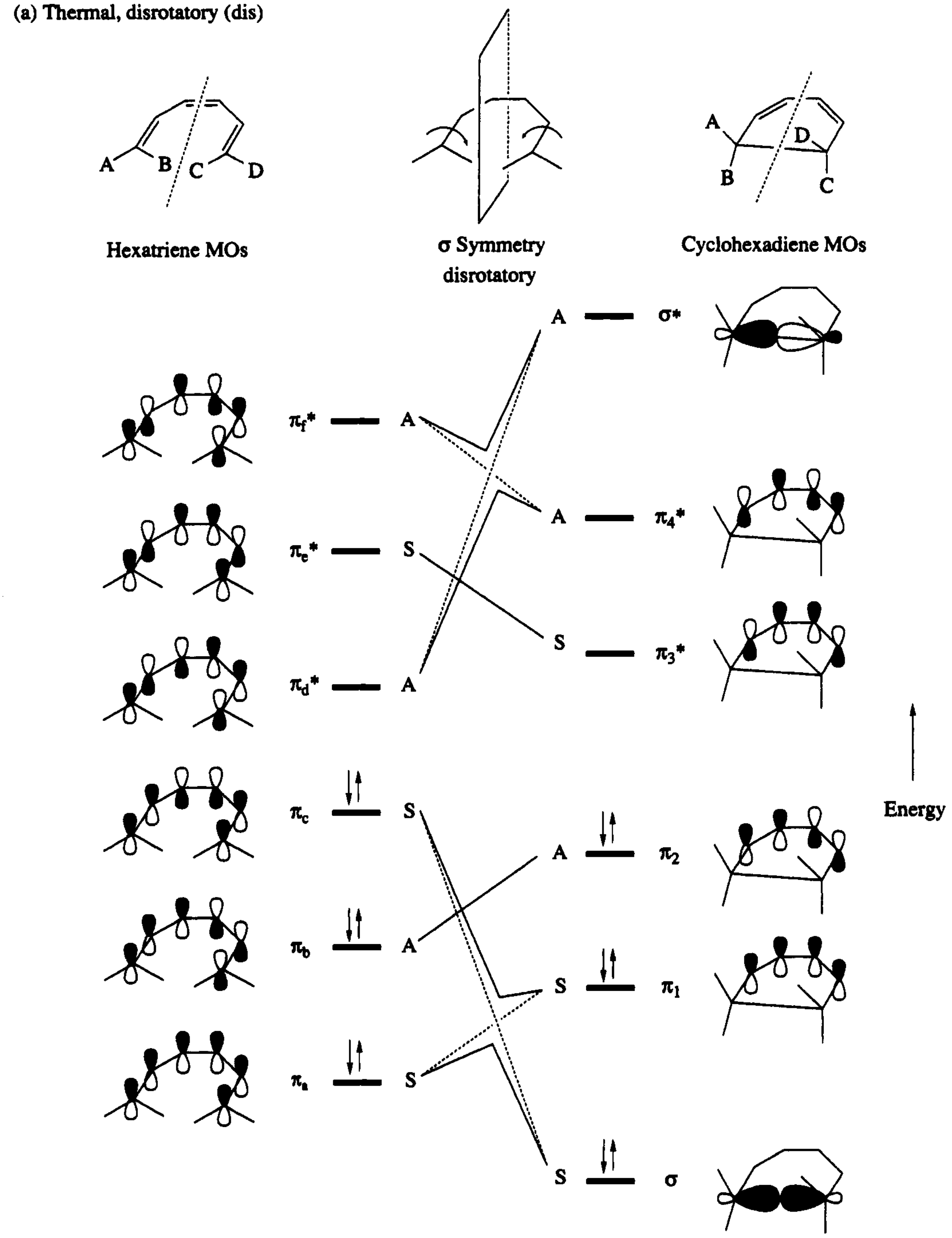
(a) Thermal, disrotatory (dis)
A
B
C
D
Hexatriene MOs
σ Symmetry
disrotatory
Cyclohexadiene MOs
$\pi_f$*
$\pi_e$*
$\pi_d$*
$\pi_c$
$\pi_b$
$\pi_a$
A
S
A
S
A
S
A
A
S
A
S
S
σ*
$\pi_4$*
$\pi_3$*
$\pi_2$
$\pi_1$
σ
Energy

**Figure 3**

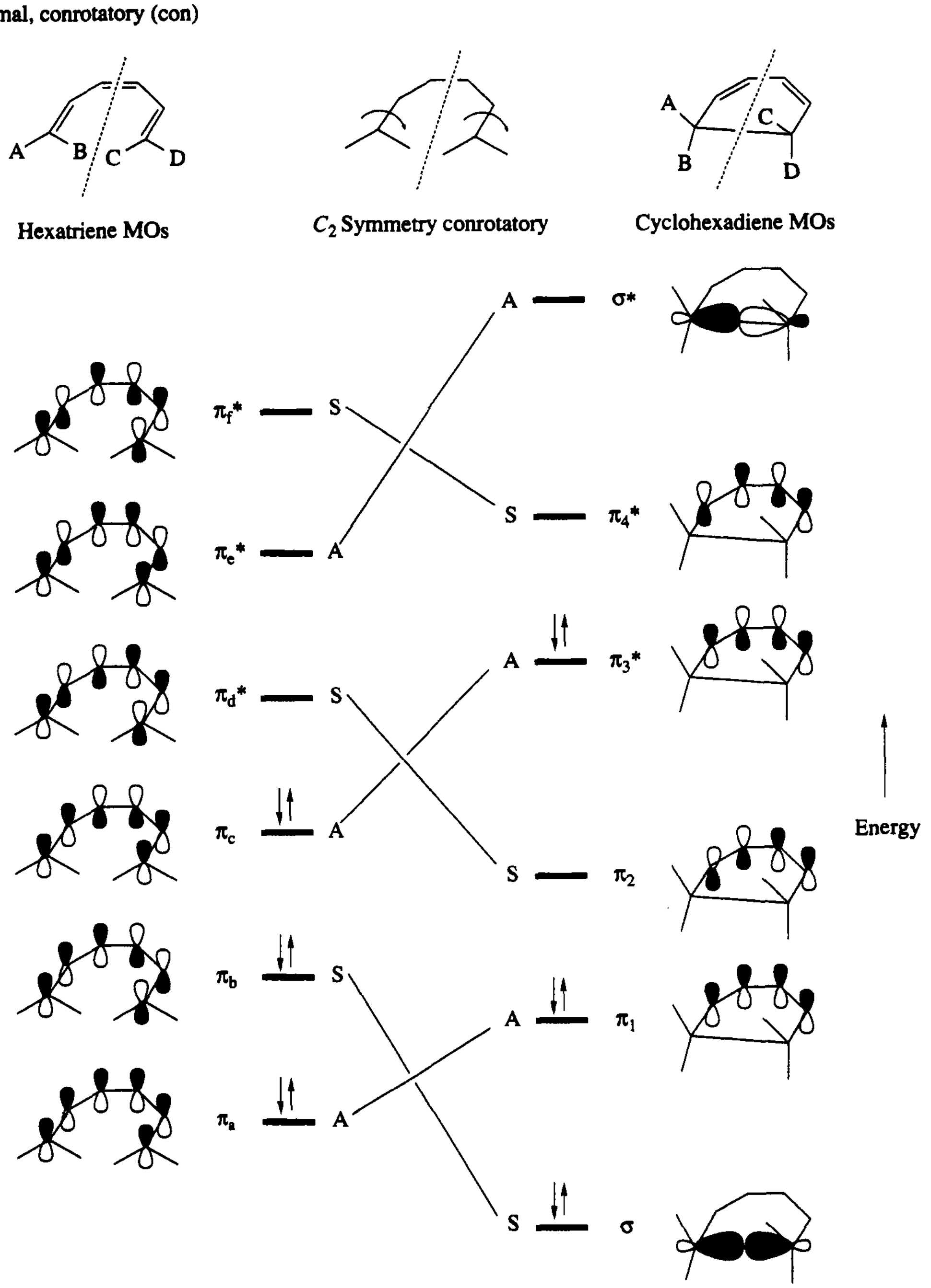
(b) Thermal, conrotatory (con)
A
B
C
D
Hexatriene MOs
$C_2$ Symmetry conrotatory
A
C
B
D
Cyclohexadiene MOs
$\pi_f$*
S
$\pi_e$*
A
$\pi_d$*
S
$\pi_c$
A
$\pi_b$
S
$\pi_a$
A
A
σ*
S
$\pi_4$*
A
$\pi_3$*
S
$\pi_2$
A
$\pi_1$
S
σ
Energy

**Figure 3** Comparison of the orbital correlation diagrams for the thermal dis (a) and con (b) 6e⁻ electrocyclic ring closures. Note that the electronic configuration is shown in each case only for the ground state of the hexatriene reverting to the cyclohexadiene *via* the dis and con modes. These diagrams can also be used directly for qualitatively describing other states in either forward (ring closure) or reverse (ring opening) processes. Alternative methods of theoretical analyses lead to similar predictions as the orbital (and/or state) correlation approach

Orbital-symmetry-disallowed energetically concerted reactions[23] can take place when the allowed reaction is made energetically prohibitive due to geometrical constraints. A more rigorous theoretical analysis including configuration interaction,[19,24] avoiding the crossing of states of the same symmetry, has been invoked to account for the extremely facile (~50 °C) thermal conrotatory interconversion of 15,16-dimethyldihydropyrene (**16**) and the 15,16-dimethyl[2,2]metacyclophane-4,9-diene (**15**).[25] A second example of a thermal, conrotatory reaction is provided by the bridged triene (**17**),[26] which is converted at room temperature to the cyclohexadiene (**18**) in a thermally forbidden process.

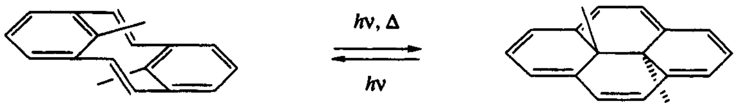

**(15)** **(16)**

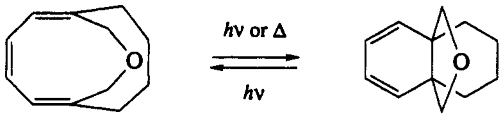

**(17)** **(18)**

The preservation of chiral integrity of the dissymmetric (*E,Z,E*)-1,3,5-cyclodecatrienes obtained by conrotatory photoisomerization of *trans*-Δ$^{1,3}$-hexalins has been addressed recently.[27] The photogenerated hexatrienes (+)-(**20**) and (–)-(**23**) were found to preserve their (*R*) and (*S*) chirality, respectively, at 193 K (only ring closure from (+)-(**20**) and (–)-(**23**) to the starting hexalins (–)-(**19**) and (+)-(**22**) was observed). However, above 205 K they lose chiral integrity by competitive ring closure to the achiral *cis*-Δ$^{1,3}$-hexalins (**21**) and (**24**). Similar behavior was observed for 5α-cholesta-1,3-diene [(–)-(**25**)] with formation of (–)-(**26**), which gave 5β-cholesta-1,3-diene [(+)-(**27**)] upon warming to 233 K.[27]

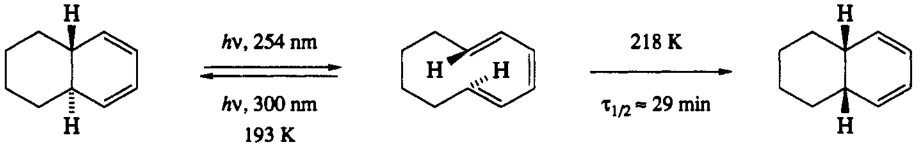

**(19)** **(20)** **(21)**

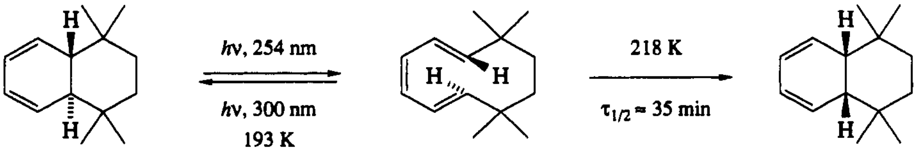

**(22)** **(23)** **(24)**

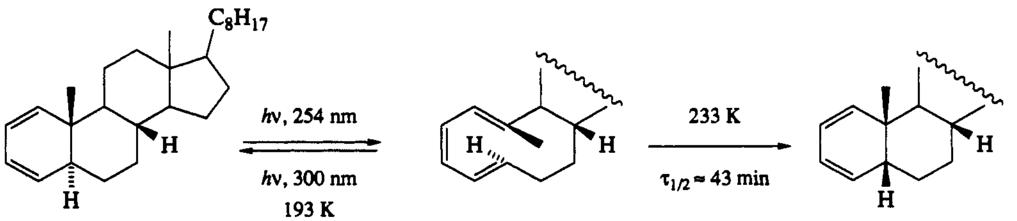

**(25)** **(26)** **(27)**

## 6.2.2 ELECTROCYCLIZATIONS OF 1,3,5-HEXATRIENES

### 6.2.2.1 General Considerations Including Acyclic Hexatrienes and Selected Ring Fused Systems

The limitation to the widespread synthetic use of the thermal or photochemical cyclization of trienes are twofold: the difficulty in preparing the starting, geometrically correct triene array; and the periselectivity[28] (*i.e.* the competition with other reactions occurring from the same substrate). Much of the following discussion is limited to the latter topic although it must be recognized that an efficacious synthesis of hexatrienes with appropriate geometry can be a major obstacle in considering $6e^-$ electrocyclizations in a synthesis.

The main competing processes resulting from the thermal treatment of hexatrienes are sigmatropic hydrogen shifts, specifically 1,5- and 1,7-H shifts. Related 1,3- and 1,5-alkyl shifts are uncommon in acyclic trienes and cyclohexadienes. The competition[29] between ring closure and 1,7-H shifts[30] has been clarified from an exhaustive study of the ground state isomerization behavior of alloocimene (**28**).[31] It was concluded that the fastest thermal reaction in unhindered 1,3,5-heptatrienes is the 1,7-H shift, interconverting the (*Z,Z*)- and the (*E,Z*)-isomers (**28**) and (**30**) *via* (**29**), followed by the ring closure. The transformation of (**11**) to (**12**) and then (**13**) represents a related example. Higher temperatures were required for the 1,5-H shift and for direct isomerization of the central and terminal double bonds. Ring opening could be observed on further heating. Similarly, an aromatic 1,7-H shift has been postulated[32] to explain the thermal isomerization of (**31**) to (**32**). At equilibrium (225 °C), 89% (**32**) and 11% (**31**) are present and they do not experience disrotatory electrocyclization unless heated for prolonged periods. The latter condition ultimately leads to (**34**). The (*E,E*)-isomer (**33**) experiences cyclization followed by 1,5-H shift under similar conditions to afford the dihydronaphthalene (**34**). The abnormal stereochemistry of the decalin (**35**) obtained from either (**36**) or its isomer (**37**) may also be explained by a reversibly produced 1,7-H shifted intermediate.[33]

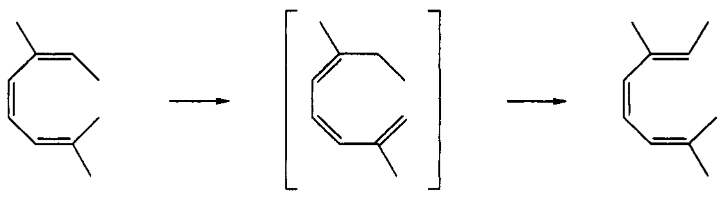
(**28**) (**29**) (**30**)

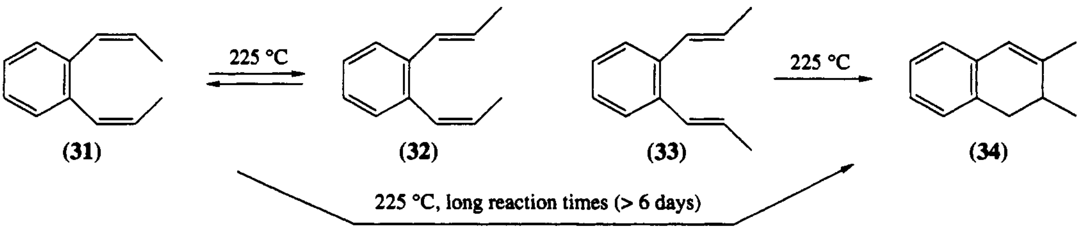

(**31**) (**32**) (**33**) (**34**)

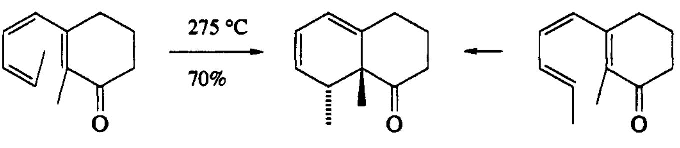

(**36**) (**35**) (**37**)

Both 1,5- and 1,7-H shifts have been invoked in the thermal rearrangement of the diketone (**38**).[34] In xylene (138 °C, 24 h), (**38**) isomerized quantitatively to the (*E,E*)-trienedione (**40**), probably *via* intramolecular hydrogen transfer from (**39**). Under flash vacuum pyrolysis (FVP) conditions (740 °C), the indan-1-one (**43**) was the only product observed. Its genesis may involve an initial 1,7-H sigmatropic shift to give (**41**) followed by cyclization to (**42**) and elimination of acetone to give (**43**).

For a vinylallene variant[35] of the $6e^-$ electrocyclization process, a comprehensive study of the effect of substituents at the terminal position of the triene system in (**45**), generated from the propargylic alcohol (**44**) *via* a 2,3-sigmatropic rearrangement, was undertaken. For relatively small groups (R = Me or Et), electrocyclization afforded (**46**) and (**47**), in spite of their sterically congested nature. For the bulkier *t*-butyl group however, only tetraene products (**48**) and (**49**) derived from 1,7-H shifts were observed. Products derived from both electrocylization and 1,7-H shift are observed for the case R = $\mathrm{Pr}^i$ in (**45**). The topic of polyene units possessing *sp* hybridized carbon centers will be discussed further in Section 6.2.3.

The photochemically induced ring closure of (**1**) to (**2**) has also found relatively little synthetic use due to the seemingly complex nature of the photoproducts obtained upon irradiation of a hexatriene.[36–40] Some of the following principles or factors which can affect the course of a photochemical process have been reviewed by Laarhoven[36] and these include the following. (a) The NEER (non-equilibration of excited state rotamers) principle indicates that each conformer of a polyene yields its own characteristic

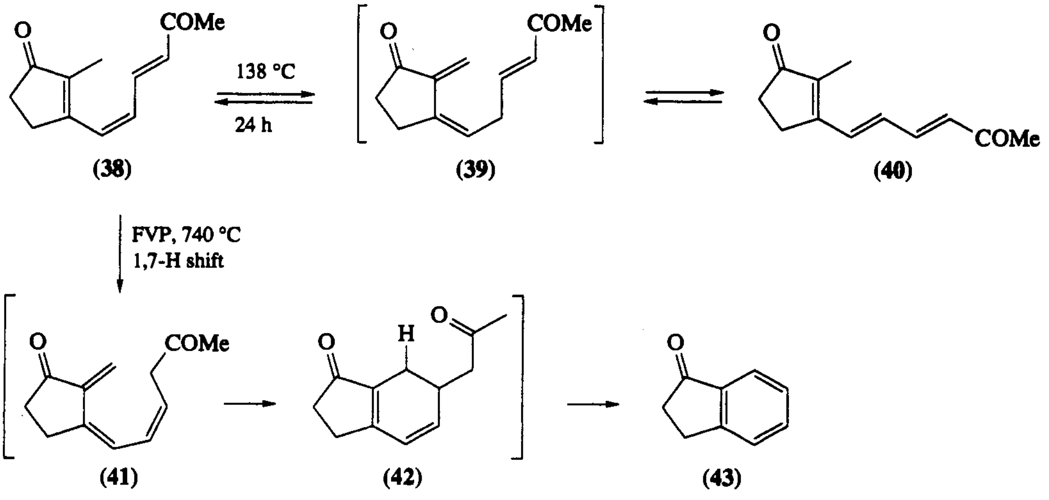

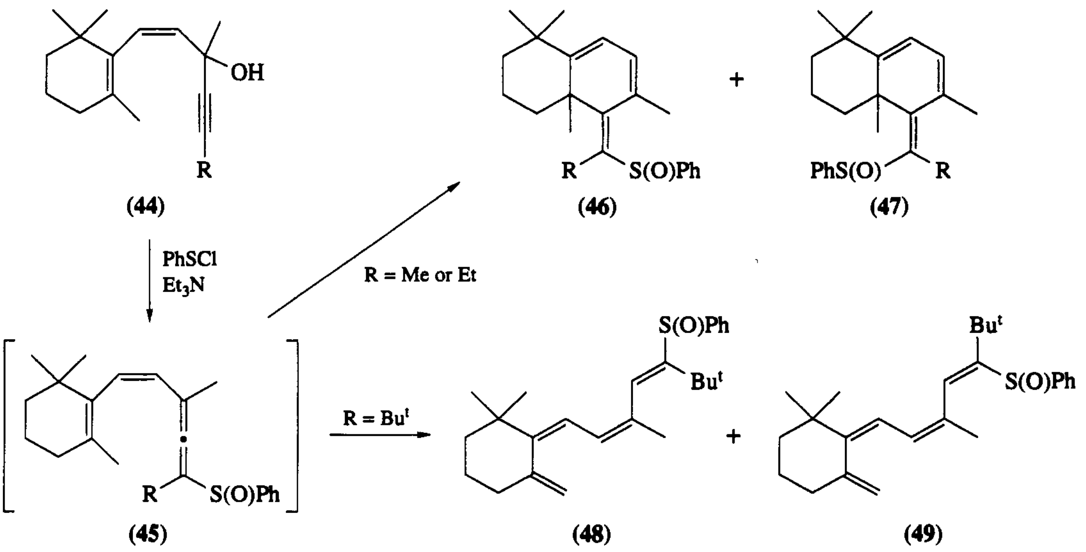

photoproduct. In other words, there is a direct correlation between the composition of a photoproduct mixture and the conformational equilibria of the starting material in its ground state. (b) The principle of least motion, especially important in the photochemical opening of cyclohexadienes, assumes that the geometry of the resulting triene is a function of the position (pseudoaxial or pseudoequatorial) of the bulky substituent on the cyclohexadiene. Related to this, the 'accordancy principle' (see Section 6.2.4.1 for further discussion) states that the mode of conrotatory opening follows the chirality (twist) of the diene. (c) The change in the wavelength of irradiation can affect the selectivity on the excitation of specific conformers as well as change the composition of the photoproducts by giving secondary photoproducts from the primary ones. (d) The temperature and the solvent can influence the course of the photoreaction, as can (e) the influence of substituents (which can cause large changes in the equilibrium position of the different conformers).

For the parent (*Z*)-1,3,5-hexatriene (**1**), the main pathways competing with the desired electrocyclization to (**2**) are the isomerization of the central double bond to give the (*E*)-triene (**50**) as well as the formation of other cyclized products (**51**) and (**52**) and the vinylallene (**53**).[41] The sensitized irradiation of isomeric trienes results primarily in rapid (*Z*)–(*E*) isomerization about the central double bond and dimerization.[42] By contrast to singlet state photochemistry, no electrocyclic or sigmatropic rearrangements occur under sensitized conditions.[41a]

The importance of conformational effects on photoreaction pathways are clearly seen with substituted hexatrienes. For the opening of hexalins (**54**), the ratio of vinylcyclobutenes (**56**) to bicyclo[3.1.0]hexanes (**57**) depends on the size of the substituent R in accordance with a preponderance of one or the other conformer of the photogenerated hexatriene (**55**).[43] In addition, when the (*cZc*) conformer is favored, the

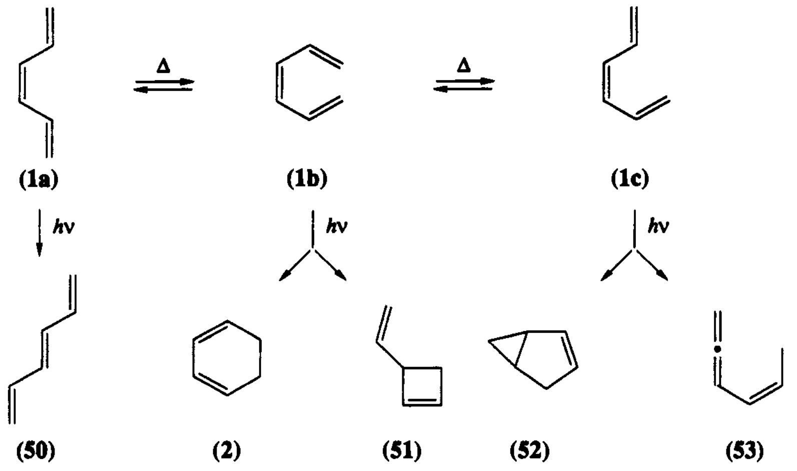

back reaction (ring closure to cyclohexadiene) is more likely to occur, which explains the longer lifetimes of the starting (**54**) possessing the bulkiest substituents. Sigmatropic hydrogen shifts also account for some of the products, which probably result from over-irradiation. The (*E,Z,Z*)-1,3,5-cyclononatriene (**59**) (formed from the corresponding *cis*-tetrahydroindene **58**) affords a vinylcyclobutene, bicyclo[5.2.0]nona-2,8-diene (**60**), together with 1,3,6-cyclononatriene (**61**) resulting from a 1,3-H shift.[44] Photochemical sigmatropic 1,*j*-H shifts when substitution patterns and geometric factors are favorable, can be a major undesirable pathway in attempts to induce 6e⁻ electrocyclizations.[39,45]

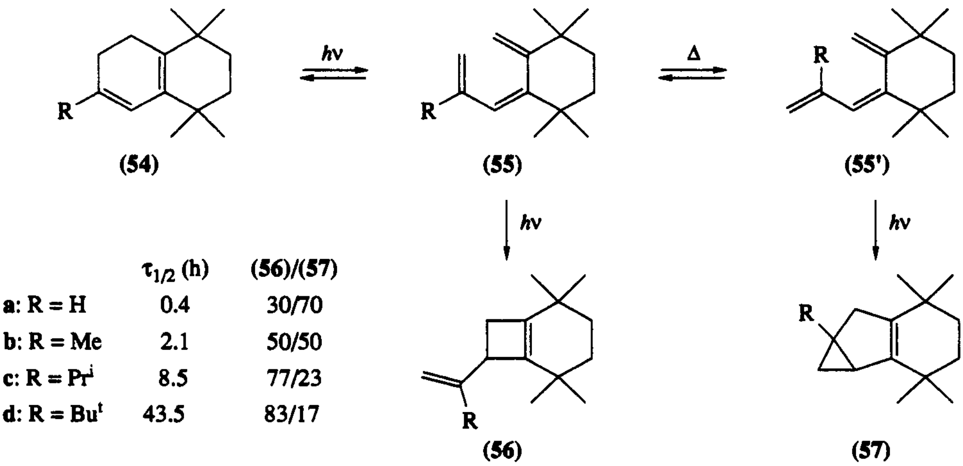

| | $\tau_{1/2}$ (h) | (**56**)/(**57**) |
|---|---|---|
| **a**: R = H | 0.4 | 30/70 |
| **b**: R = Me | 2.1 | 50/50 |
| **c**: R = Pr$^i$ | 8.5 | 77/23 |
| **d**: R = Bu$^t$ | 43.5 | 83/17 |

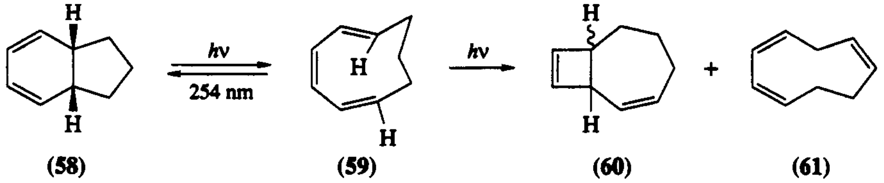

From a thermodynamic standpoint, one can expect that for the thermal conversion of (**1**) to (**2**) and related derivatives, unless the temperature is sufficiently high or strain factors become predominant, cycloreversion will not be observed. A more complete discussion of the factors affecting the thermal equilibration of strained hexatrienes and cyclohexadienes will be discussed in Section 6.2.2.2.1. A kinetic study of the pericyclic transformation of the parent triene (**1**) to 1,3-cyclohexadiene (**2**) provided an activation energy of 29.9 kcal mol$^{-1}$.[16a] Taking into account the heats of formation of reactant and product (40.6 kcal mol$^{-1}$ for (*Z*)-1,3,5-hexatriene and 25.4 kcal mol$^{-1}$ for 1,3-cyclohexadiene),[46] the reverse process (*i.e.*, the thermal ring openings of the 1,3-cyclohexadiene) requires a significantly higher activation energy (~44.2 kcal mol$^{-1}$).

That the thermal ring opening of cyclohexadienes proceeds at sufficiently high temperatures has been demonstrated by the observation of complete scrambling of the labels in the automerization of cyclohexadiene (**62**) at 560 °C in the gas phase.[47–49] The thermal ring opening of cyclohexadienes is thus not generally useful for synthesizing hexatrienes. By contrast, the photochemical ring openings of cyclohexadienes are rather facile processes, and have found at least some synthetic use as will be discussed in Section 6.2.4.1.

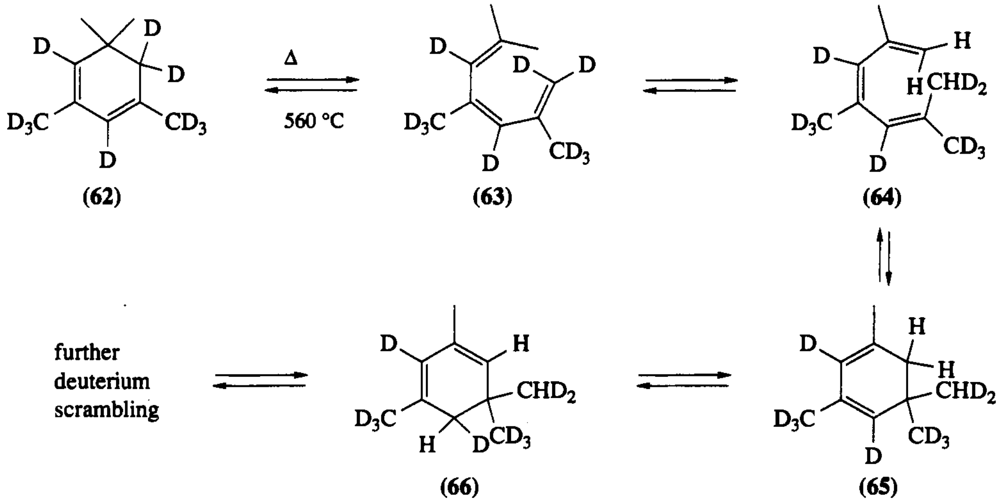

With the transition state geometries deduced from semi-empirical approaches,[17] several correlations with experimental results have been developed for different substitution patterns of the hexatriene.[50–55] Structure–reactivity data which have been tabulated[3a] are important considerations in synthesis applications. The general trends which emerge from these studies are the following. Substituents at the C-1 (or C-6) position have moderate (*Z*) or negligible (*E*) effects on the rate of electrocyclization. Substituents at C-2 (or C-5) can cause a two-fold rate increase effect, either at the ground state level (by increasing its energy as a result of deviation from planarity and by increasing the population of the *s-cis* conformation) or by stabilizing a presumed radical character developed at the transition state. For the substituents at C-3 (or C-4) the same effects are operative, although to a lesser extent. These trends parallel the experimental results. For example, for simple hexatrienes substituted at C-2, the ability of phenyl and ethoxycarbonyl substituents as radical stabilizers facilitates (room temperature) electrocyclization.[52]

The electrocyclization of certain 1-dialkylamino-1,3,5-hexatrienes is followed by elimination of dialkylamine to afford benzene derivatives.[56] If the double bond of the 1-aminohexatriene is part of an aromatic or heteroaromatic system, smooth cyclization ensues to give benzannulated derivatives (a topic to be discussed further in Section 6.2.2.2.1 and later sections). The starting aminohexatrienes (**68**) have been conveniently prepared, for example by Knoevenagel condensation of carbonyl compounds (carbanion equivalents) with pentamethynium salts (**67**) (pentadienyl cation equivalents). Aminoheptatrienones (**68**) typically cyclize at temperatures below 50 °C to the benzoyl derivative (**70**) accompanied in some cases by (**71**) (resulting from elimination of the *cis* substituents)[56c] when (**69**) is sterically congested. With other carbanions, the condensation–cyclization–elimination sequence also occurs, as exemplified by the conversion of chromone (**72**) into flavone (**73**) and azulene (**74**) into its derivative (**76**). An alternative benzannulation sequence is exemplified by the condensation of crotonitriles (**77**) with vinylamidinium salt (**78**) to afford (**80**) as shown. With the possibility of using different substituents in both components, this synthetic approach to aromatic compounds is highly versatile.

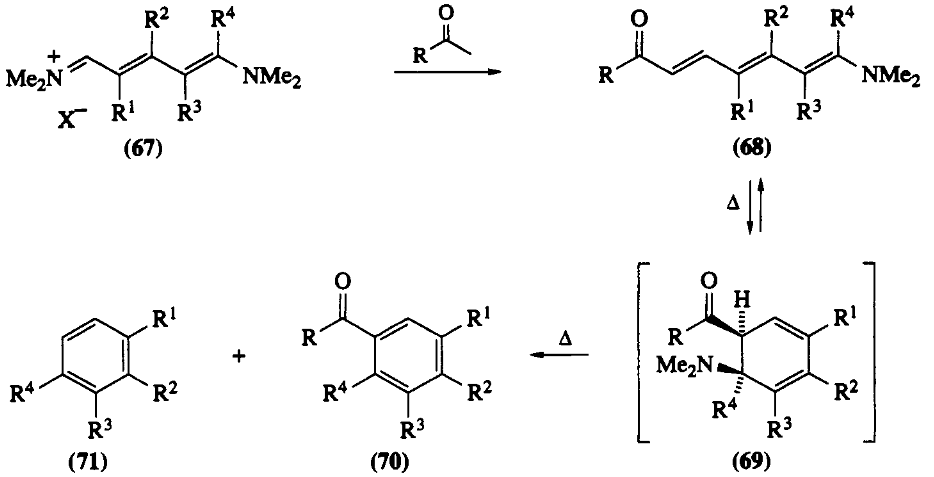

(67) (68) (69) (70) (71)

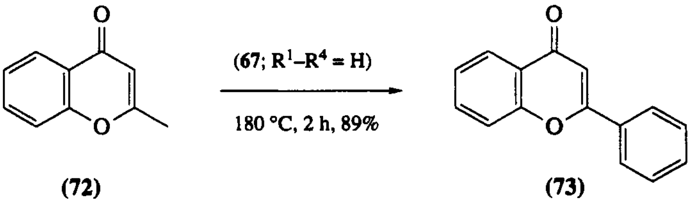

(72) (73)

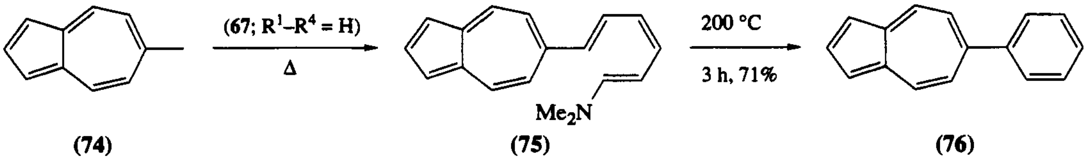

(74) (75) (76)

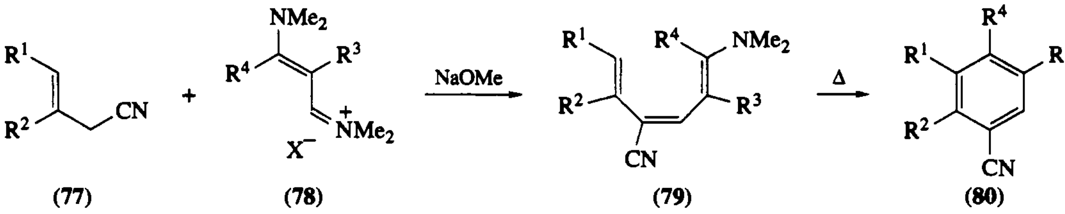

(77) (78) (79) (80)

### 6.2.2.2 Cyclic and Annulated Hexatrienes

### *6.2.2.2.1 Mono-annulated trienes*

Mono-annulated 1,3,5-hexatrienes leading to *ortho*-condensed 1,3-cyclohexadienes of the types I–IV (see Figure 2) have been well studied. By contrast, bridged trienes leading to 1,3-cyclohexadienes of types V–IX are rare. This section is organized sequentially according to the 1,3-cyclohexadiene type.

*(i) Type I: Ortho-condensed [1,2]-Annulated Systems*

The synthesis of a [1,2]-annulated cyclohexadiene requires a relatively less common bis-exomethylene ring-fused hexatriene precursor. Indirect procedures take advantage of other facile thermal or photochemical rearrangements leading to *in situ* generation of the necessary triene substrate. As an example, a reaction initiated by a thermal conrotatory ring opening of vinylcyclobutenol (**81**) gave a quantitative yield of α-tetralone (**84**), which can be considered to involve a disrotatory electrocyclization of the dienol (**82**) followed by enol–keto tautomerism of (**83**).[57a] Other cyclizations of dienol ethers have been reported,[57b–e] including those promoted by transition metal catalysts.[57d] Note that formation of the aromatic ring on (**83**) facilitates the 6e$^-$ electrocyclization process as indicated by the low temperature (25 °C) at which thermal cyclization of (**85**) to (**86**) occurs, thus suggesting that the transformation of (**82**) to (**83**) must be fast.[45d] A 1,5-H sigmatropic shift of cyclohexenone (**87**) also generates the desired bis-exomethylene subunit in (**88**). Under the reaction conditions the presumed (**88**) affords as the main product tetrahydronaphthalenone (**89**) *via* electrocyclization.[58]

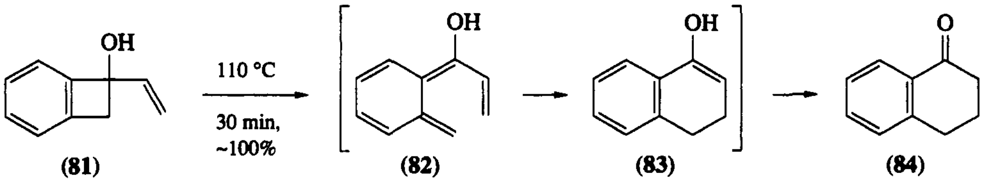

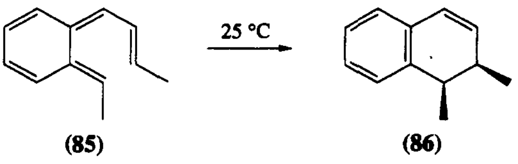

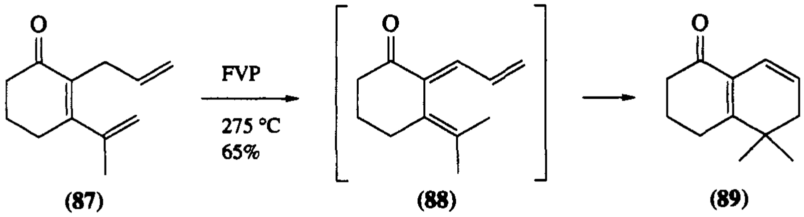

The photochemical ring opening of palustric ester (**90**), an example of a [1,2]-annulated cyclohexadiene, has been achieved wherein a ~1:1 photostationary state mixture of diene (**90**) and triene (**91**) was obtained. Upon heating for 4 h (162 °C), the photo-mixture regenerates palustric ester (**90**).[59] A related interconversion was observed for a series of photochromic cyclohexadienes of the xanthenone, dibenzofuran and acridone types, exemplified by (**92**) → (**93**).[60]

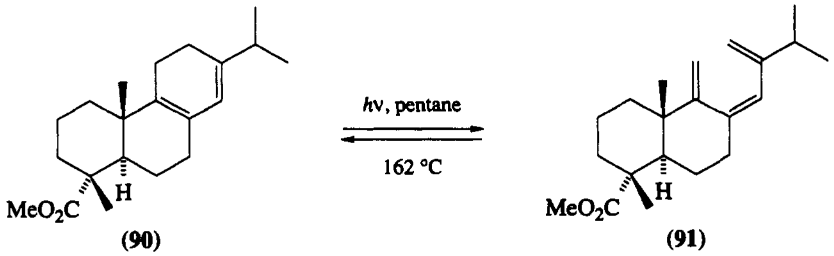

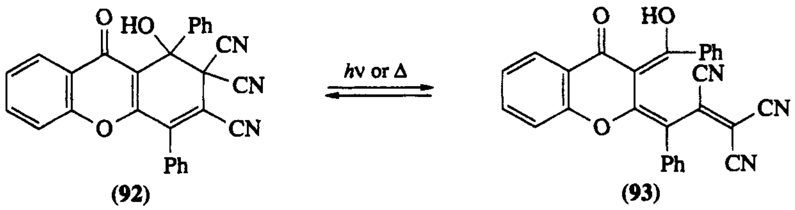

*(ii) Type II: Ortho-condensed [2,3]-Annulated Systems*

The synthetic advantage of using a triene with the central double bond locked in a (*Z*) configuration by virtue of ring fusion has provided a series of 1,2-divinylcyclohexenes (**94**) used for structure–reactivity studies.[51,61] While the parent system (**94a**) cyclizes upon heating at 125 °C, higher temperatures are required for the cyclization of the derivatives (**94b–g**), irrespective of their location and/or stereochemistries. Prolonged heating of (**94c**) led to the rearranged diene (**96**).

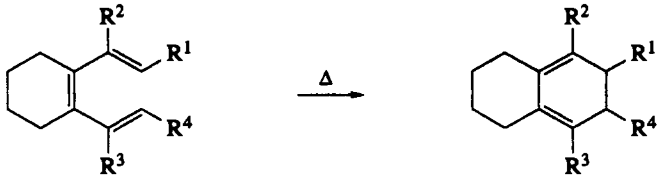

**(94)** **(95)**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| a: | H | H | H | H |
| b: | $CO_2Et$ | H | H | H |
| c: | H | H | H | $CO_2Et$ |
| d: | (*E*)-Ph | H | H | (*E*)-Ph |
| e: | (*E*)-Ph | (*Z*)-Ph | H | H |
| f: | Ph | $CO_2Et$ | H | H |
| g: | *p*-An | $CO_2Et$ | H | H |

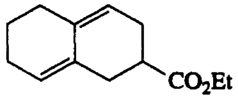

**(96)**

When the central double bond is part of an aromatic ring, the ring closure is retarded and is accompanied by regeneration of the aromatic nucleus. Thus, as described earlier in this review, the dihydronaphthalene (**34**) was obtained upon thermolysis of compound (**33**), a product obtained by an initial electrocyclization followed by a 1,5-H shift.[32] Similarly, a synthesis of the dihydroindole nucleus (**99**) makes use of the thermal (216 °C) or photochemical electrocyclic ring closure of 2,3-dienylpyrroles (**97**) to intermediate (**98**) followed by a 1,5-H shift.[62]

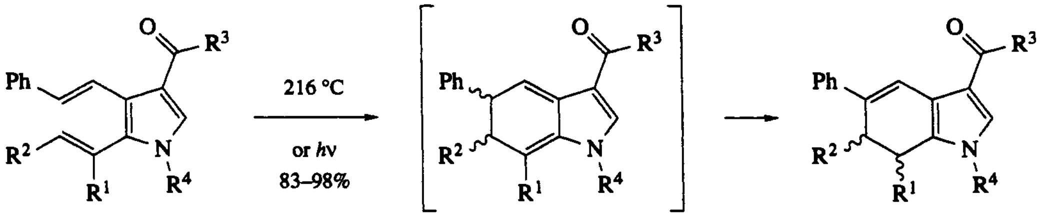

**(97)** **(98)** **(99)**

### (iii) Type III: Ortho-condensed [5,6]-Annulated Systems

The cycloheptatriene (CHT)–norcaradiene (NCD) valence tautomerism, or CHT–NCD equilibrium (**100**)–(**101**), has captivated the interest of the scientific community for about a century[63] and considerable theoretical and experimental evidence has clarified the factors favoring one or the other tautomer. A direct experimental observation of NCD (**101**) has recently been reported, together with the kinetics of its conversion into CHT (**100**).[64] NCD was interpreted to be the unstable intermediate generated by low-temperature (77 K) irradiation of solutions of tricyclo[3.2.2.0$^{2,4}$]non-6-ene-8,9-dione (**102**) in a hydrocarbon glass with light of wavelength 240–400 nm. Upon brief warming to ~110 K and recooling, the $\lambda_{max}$ changed from 265 nm (attributable to **101**) to 261 nm, the absorption maximum corresponding to (**100**). These differences in the UV spectra allowed the measurement of the kinetics for the isomerization of NCD (**101**) to CHT (**100**). The rate constant for the process at 25 °C was estimated to be 1 × $10^7 s^{-1}$.

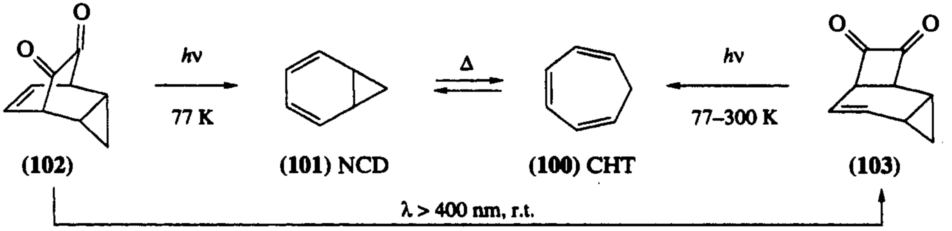

**(102)** **(101)** NCD **(100)** CHT **(103)**

Excellent reviews concerning the NCD problem have appeared describing more than 80 compounds with different substitution patterns.[3a,63] From these data and recent experimental findings, the following factors contributing to the displacement of the isomerization equilibrium towards the NCD form have been proposed: (a) placement of a π-acceptor group at the C-7 position;[65–67] (b) extension of conjugation at appropriate positions in the NCD form[68] as in (**104**) and (**105**); (c) shortening of the C-1–C-6 distance by bridging these positions by a chain of carbon atoms as in (**106**);[69] (d) the nonbonding interactions between the C-7 substituent and proximal π-bonds or substituents as in (**107**).[70,71]

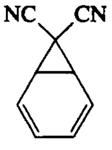

(**104**)

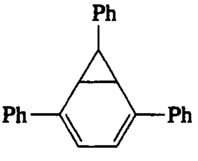

(**105**)

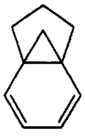

(**106**)

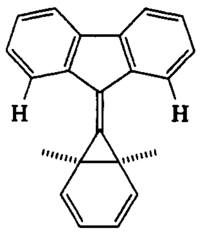

(**107**)

The sensitivity of the CHT–NCD equilibrium towards the substitution pattern is nicely illustrated by the equilibrium between (**108**) and (**109**),[72] noting for reference that the parent system (**108a**)–(**109a**) is displaced towards the CHT (**108a**). Introduction of *t*-butyl groups at the C-3, C-2, C2,4 or C2,5 positions progressively shifts the equilibrium towards the NCD form (**109**). Nonbonding interactions between the C-3 *t*-butyl group and H-2 and between the C-2 *t*-butyl and H-1 are relieved by structural change from CHT to NCD. The synergistic effect of placing *t*-butyl groups at C-2 and C-5 on shifting the equilibrium to the NCD form has been used to study the effect of the π-acceptor strength of the C-7 substituent.[73] At room temperature, ~30% of NCD (**111**) is observed, which allowed the determination of the equilibrium constant by $^{13}$C NMR. As expected, the NCD form (**111**) is stabilized in the order of π-acceptor strength of substituents (OMe < H < $CF_3$). Several other related studies have been reported.[74]

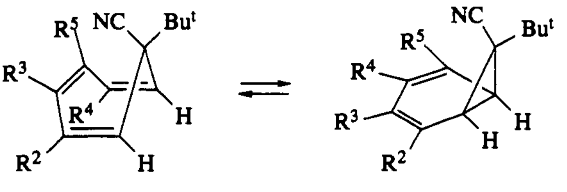

(**108**) (**109**)

| | $R^2$ | $R^3$ | $R^4$ | $R^5$ | % (**109**) |
|---|---|---|---|---|---|
| a: | H | H | H | H | 19 |
| b: | Bu$^t$ | H | H | H | 88 |
| c: | H | Bu$^t$ | H | H | 46 |
| d: | Bu$^t$ | H | Bu$^t$ | H | 97.4 |
| e: | Bu$^t$ | H | H | Bu$^t$ | 99.7 |

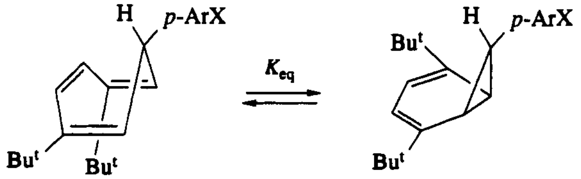

(**110**) X = OMe, H, $CF_3$ (**111**)

From a synthetic point of view, the CHT–NCD equilibrium has been exploited in a total synthesis of colchicine[75a] and, more recently, in syntheses of tropones (**115**) and tropolones (**119**) from 7-halobicyclo[4.1.0]heptenones (**112**) or 7-halobicyclo[4.1.0]heptane-3,4 diones (**116**), respectively.[75b] Keto–enol tautomerism of (**112**) to (**113**) followed by ring opening to the cycloheptatrienols (**114**) and loss of HX would explain the formation of the tropone (**115**). The tropolone (**119**) probably results from a similar sequence. These examples represent one of few cases that exemplify 6e$^-$ retro electrocyclizations presented thus far in this review. Additional examples will be presented later in Section 6.2.4.1.

For the related tautomerism between the higher homologues, 1,3,5-cyclooctatriene (**120**) and bicyclo[4.2.0]octa-2,4-diene (**121**),[76] a tabulation of a series of derivatives including thermodynamic data is presented in the treatise by Marvell.[3a] The data reveal a large variation in equilibrium constants by introducing seemingly small changes in the structure. While the electronic effects of the substituents at C-7

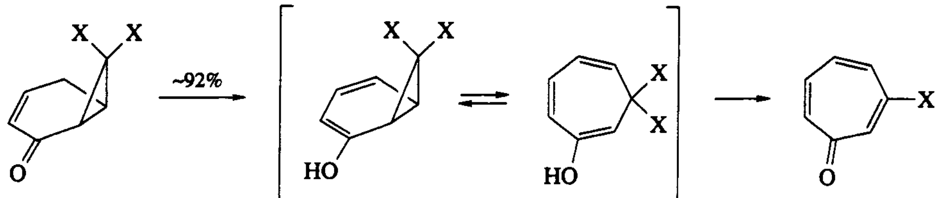

(112) X = Cl, Br (113) (114) (115)

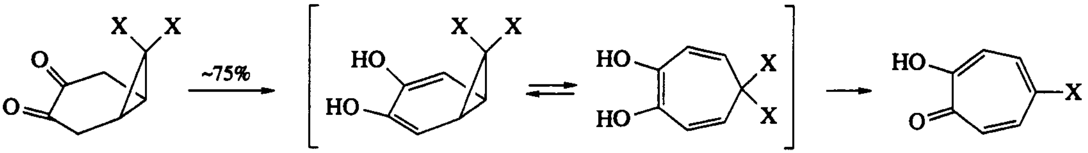

(116) (117) (118) (119)

and C-8 do not reveal a striking trend, the effect of adding a bridge between C-7 and C-8 is more clear. Small ring fusion as in (**122**)–(**123**) ($n$ = 1, 2) imparts an increase in the strain to the tautomer (**123**), leading to a shift in equilibrium towards (**122**). Larger cycles tend to be more stable in bicyclic form (**123**).[77] Interestingly, while the equilibrium between (**120**) and (**121**) favors the former open triene form (ratio 85:15 at 100 °C), the iron complex (**124**) exists in the bicyclic form.[78]

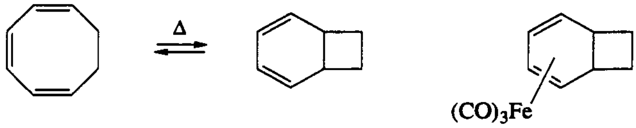

(120) (121) (124)

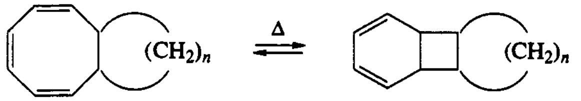

(122) (123)

For the cyclooctatetraene (COT)–bicyclo[4.2.0]octa-2,4,7-triene system (**125**)–(**126**), earlier studies using an indirect method afforded an equilibrium composition at 100 °C containing 0.01% of the bicyclic form (**126**) ($\Delta G° \approx 6.8$ kcal mol$^{-1}$ less stable).[79] The bicyclic form (**126**) has been prepared, however, by low-temperature dehalogenation of dibromide (**127**) and found to rearrange to COT at 0 °C ($E_a \approx 18.7$ kcal mol$^{-1}$).[80] Recently, a high-temperature thermal trapping technique has been utilized to assess more completely the transformation between (**126**) and (**125**) in a quantitative manner.[81]

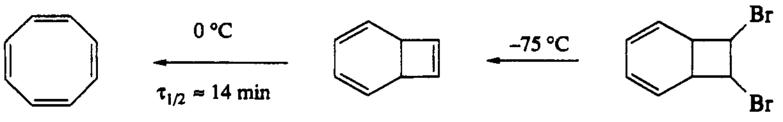

(125) (126) (127)

For monocyclic conjugated trienes with a (*Z*) central double bond such as (*E*,*Z*,*E*)-1,3,5-cyclodecatriene (**20**) discussed earlier, allowed disrotatory ring closure to a 5,6-fused cyclohexadiene (**21**) is a common isomerization pathway. Methyl substituents at positions C-1 and C-6 of (*E*,*Z*,*E*)-1,3,5-cyclodecatriene attenuates the rate of ring closure, probably due to the steric hindrance for approaching the disrotatory transition state.[82] The disrotatory pathway is also reported to be followed in trienes with a putative (*E*,*Z*,*E*) geometry, such as (**129**) believed to be formed by base-promoted dehydration of dienol (**128**).[83] The coiled geometry of (**129**) was thought to be kinetically favored over the alternative, more congested all-(*Z*) isomer, the cyclization of which could also explain the formation of the observed bicyclic isomer (**130**).

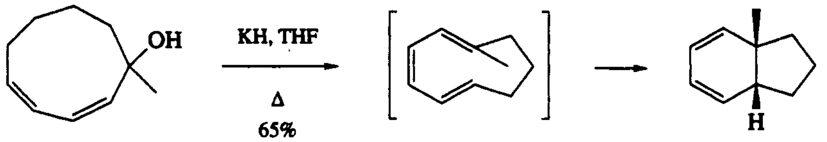

**(128)** **(129)** **(130)**

When the central double bond of the hexatriene is (*E*), new pathways are followed and the product distribution shows a structure–reactivity correlation with the size of the ring.[84] The thermal rearrangement of the cyclononatriene (**131**) afforded the *trans*-bicyclo[4.3.0]nona-2,4-diene (**132**). By contrast, the larger 11-membered-ring triene (**135**) yielded a different structure, the *trans*-tricyclo[5.4.0.$0^{4,6}$]undec-2-ene (**136**). The 10-membered ring (*Z,E,Z*)-triene (**133**) exhibited intermediate behavior between these two pathways, affording a *ca.* 1:1 mixture of both derivatives (**19**) and (**134**).[84] A most plausible explanation for the formation of (**134**) and (**136**) involves an initial 1,5-H migration to a partially nonconjugated (*E,Z,Z*)-triene (**137**) followed by an intramolecular Diels–Alder reaction. To rationalize the formation of the cyclohexadienes (**132**) and (**19**), two successive 4e⁻ conrotatory electrocyclizations *via* a vinylcyclobutene intermediate (**138**) was proposed to interconvert the (*Z,E,Z*)-trienes (**131**) and (**133**) to the corresponding (*E,Z,Z*)-trienes, from which the observed cyclohexadienes (**132**) and (**19**), respectively, could be generated by normal disrotatory ring closure.

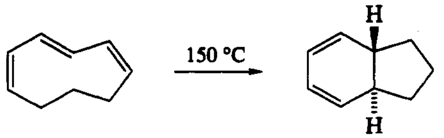

**(131)** **(132)**

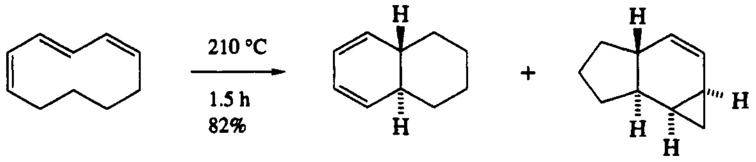

**(133)** **(19)** ~1:1 **(134)**

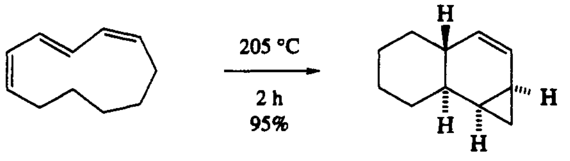

**(135)** **(136)**

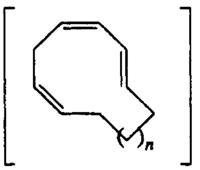

**(137)**

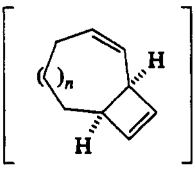

**(138)**

All-(*Z*) cyclononatetraene (**139**) has been shown[10,85,86] to follow the WH rules for its facile thermal rearrangement to *cis*-8,9-dihydroindene (**142**). For this process at 18–35 °C the activation parameters were determined to be $\Delta H^{\ddagger} = 19.8$ kcal mol$^{-1}$ and $\Delta S^{\ddagger} = -10.4$ cal mol$^{-1}$ K$^{-1}$.[85] Low-temperature photolysis of (**139**) followed by warming to 50 °C provided *trans*-8,9-dihydroindene (**141**), probably *via* an initial photochemical isomerization of (**139**) to the (*E,Z,Z,Z*)-tetraene (**140**), followed by ring closure.[86]

The annulenes from [10]annulene to [16]annulene react quite selectively by 6e⁻ disrotatory processes.[87] Thus the low-temperature photochemical generation[88,89] of cyclodecapentaene (**143**) from *trans*-9,10-dihydronaphthalene (**144**) or from (**145**) was followed by its thermal isomerization to *cis*-9,10-dihydronaphthalene (**146**). The (*E,Z,Z,Z,Z*)-cyclodecapentaene (**147**) has been postulated as inter-

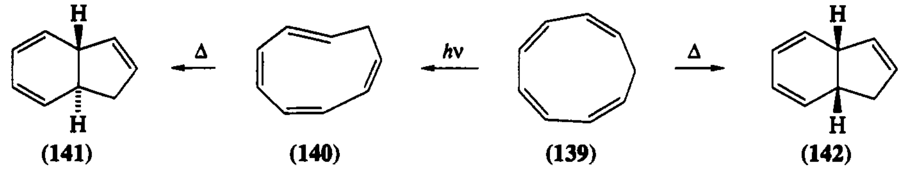

mediate in the interconversion of *cis*- (**146**) and *trans*-9,10-dihydronaphthalene (**144**). Similar low-temperature $6e^-$ electrocyclizations at or below 25 °C characterize the behavior of [12]annulene (**148**)[90a,b] and [16]annulene (**149**).[90c,d]

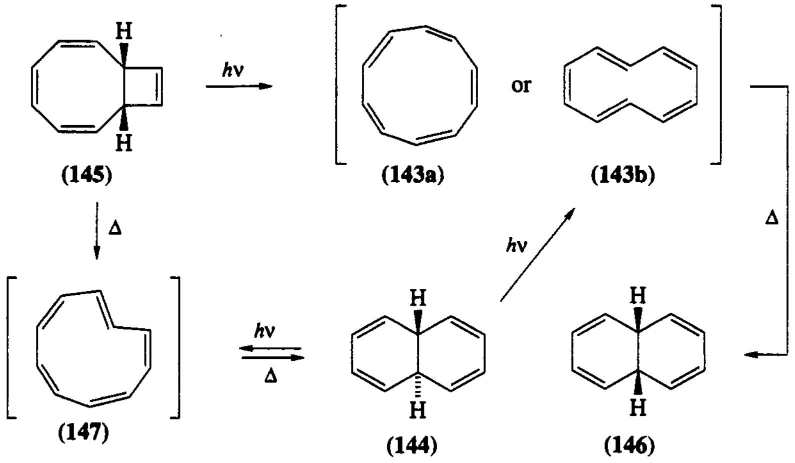

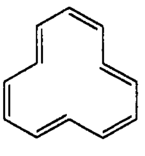

(**148**)

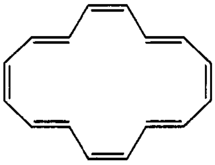

(**149**)

The triplet-sensitized photochemistry of medium-ring cyclic trienes has been investigated[91] in order to evaluate the role of the ground state conformation on triplet energy transfer. Sensitized irradiation of (*Z,E,Z*)-1,3,5-cyclodecatriene (**133**) at −70 °C resulted in a selective (*Z*)–(*E*) isomerization of the central double bond to give (**150**). Upon warming to room temperature, the hexalin (**21**) was formed, presumably *via* thermal electrocyclization of the (*E,Z,E*)-triene isomer (**20**), itself formed by sensitized two-bond isomerization of (**150**).[92] The higher homolog, (*Z,E,Z*)-1,3,5-cycloundecatriene (**135**), follows the same pathway, although the products are less stable and other thermal processes compete. The primary photoproduct at −70 °C is the (*Z,Z,Z*)-triene (**151**), which suffers a 1,7-H shift to the (*E,Z,Z*)-triene (**152**). Upon prolonged irradiation the *cis*-bicyclo[5.4.0]undeca-8,10-diene (**153**) is also formed. The triplet photochemistry of the (*E,Z,Z*)-triene (**152**) affords at room temperature a photoequilibrium mixture of the starting triene (~30%) and the bicyclic diene (**153**; ~70%). At lower temperature (−70 °C), besides starting (**152**; 80%) and (**153**; 5%), *trans*-bicyclo[7.2.0]undeca-2,10-diene (**154**; 15%) was also detected. The formation of the latter can be considered to involve the thermal electrocyclization of the (*E,E,Z*)-triene isomer (**155**), which in turn can be envisaged to be in photoequilibrium with the corresponding (*E,Z,E*)-triene isomer (**156**) *via* (**152**).[91]

### *(iv) Type IV: Ortho-condensed [1,6]-Annulated Systems*

This type of electrocyclization is illustrated by the formation of (**35**) and the related formation of (**46**) and (**47**) (see also Section 6.2.3) discussed earlier. Another example is the thermal conversion of trienone (**157**) to the ketone (**158**).[93] A similar transformation of a related triene intermediate has been postulated to account for the formation of (**162**) from (**161**) by pyrolysis of pyrethrin-I (**159**), which initially produces (**160**).[94]

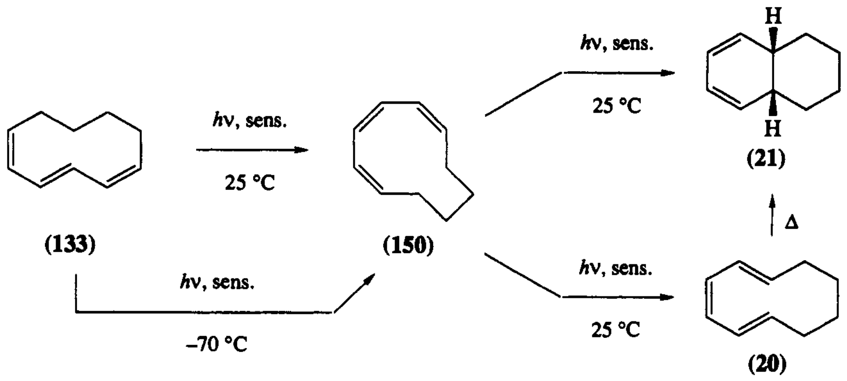
hν, sens.
25 °C
hν, sens.
-70 °C
hν, sens.
25 °C
hν, sens.
25 °C
Δ
H
H
(133)
(150)
(21)
(20)

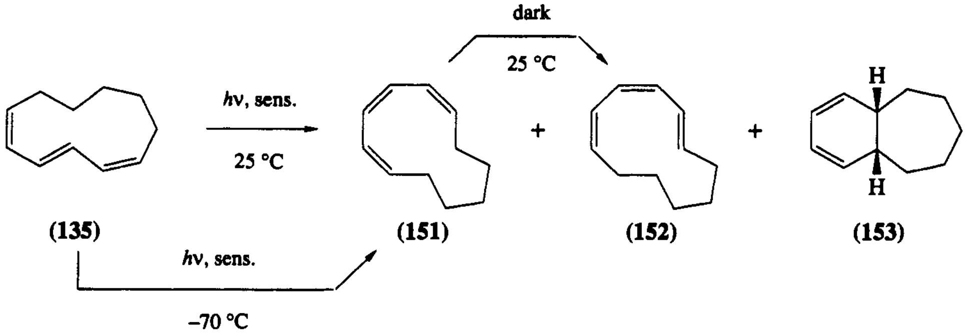
dark
25 °C
hν, sens.
25 °C
hν, sens.
-70 °C
+
+
H
H
(135)
(151)
(152)
(153)

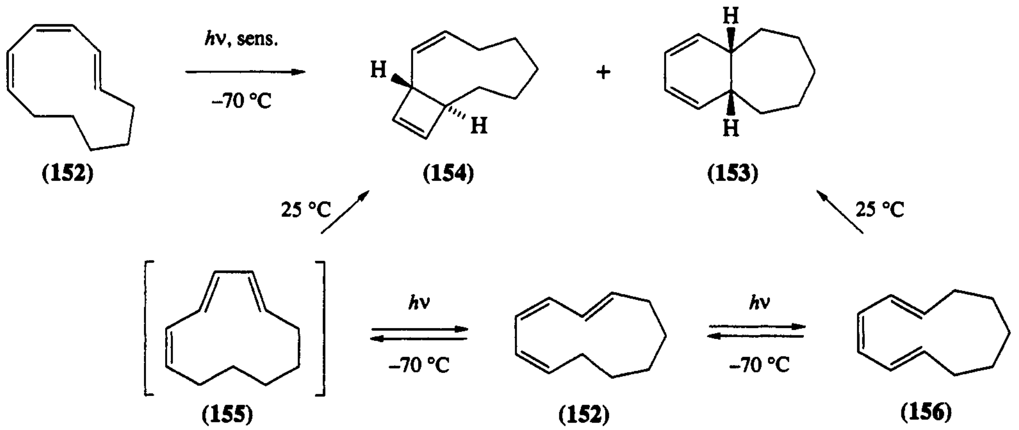
hν, sens.
-70 °C
H
H
+
H
H
(152)
(154)
(153)
25 °C
25 °C
hν
-70 °C
hν
-70 °C
(155)
(152)
(156)

The synthesis of 7,8-dihydroisoquinolines (**166**) can be efficiently achieved by FVP techniques. The reaction also provides an entry into the dihydroquinoline (**168**) and 1,2-dihydronaphthalene skeleton (**170**) by FVP of (**167**) and (**169**), respectively. Note that the method involves initial (*E*) to (*Z*) isomerization, electrocyclization and then a 1,5-H shift.[95]

Using the aforementioned cyclization of 1-aminohexatrienes, *cf.* (**68**) to (**70**) and (**79**) to (**80**), several aromatic compounds have been synthesized upon elimination of a dialkylamine from a dihydroaromatic precursor formed by the 6e$^-$ electrocyclization process. As an example, dihydrophenanthrene (**175**) can be synthesized in two different ways depending on the choice of the allyl anion synthon (**171** or **173**) or

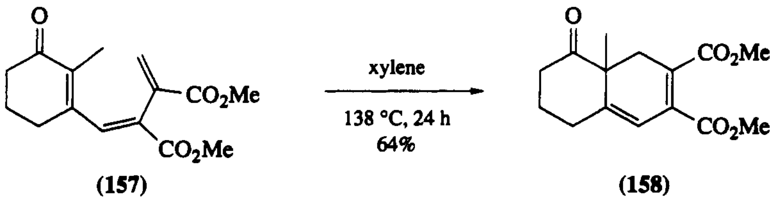
O
CO2Me
CO2Me
xylene
138 °C, 24 h
64%
O
CO2Me
CO2Me
(157)
(158)

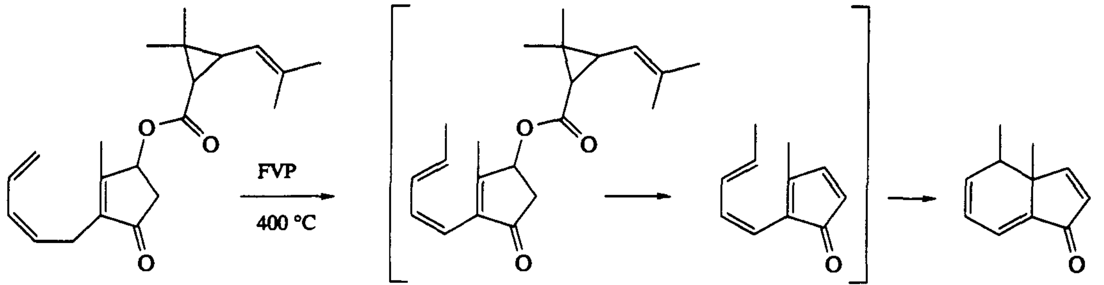

(159) (160) (161) (162)

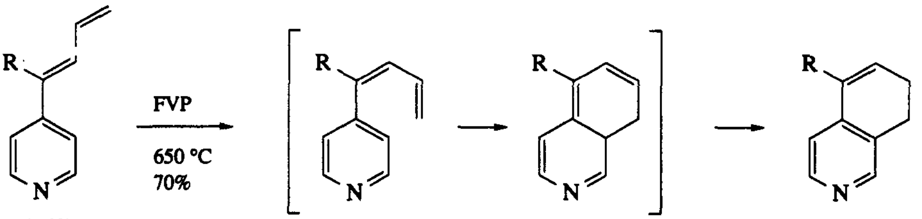
R
FVP
650 °C
70%
N

(163) (164) (165) (166)

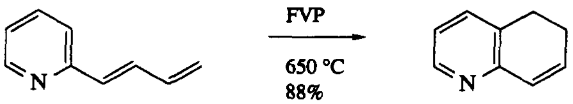
FVP
650 °C
88%
N

(167) (168)

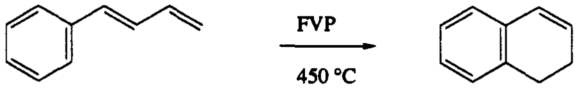

(169) (170)

the corresponding allyl cation synthon (**172** or **174**, respectively). The syntheses of 5-nitrotetralin (**177**), tetralone (**179**) and xanthone (**181**) further illustrate this versatile approach.[56]

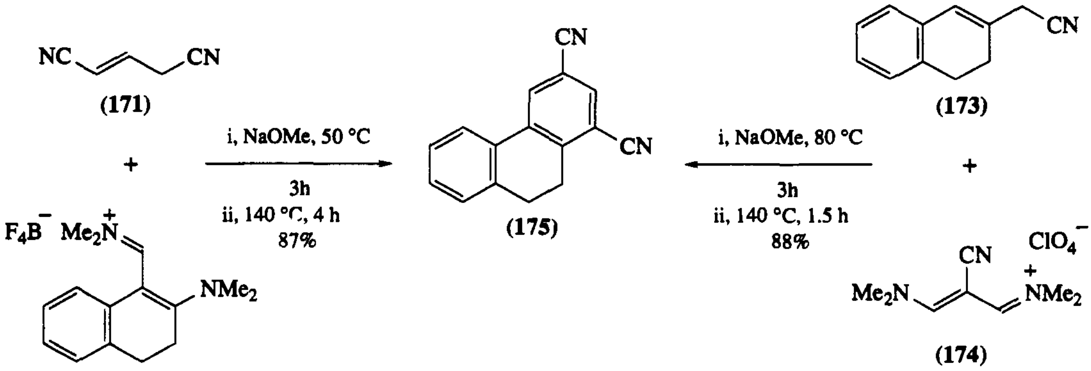
NC
CN
+
$F_4B^-$ $Me_2\overset{+}{N}$
NMe$_2$
i, NaOMe, 50 °C
3h
ii, 140 °C, 4 h
87%
CN
CN
CN
i, NaOMe, 80 °C
3h
ii, 140 °C, 1.5 h
88%
CN
+
CN
$ClO_4^-$
+
Me$_2$N
NMe$_2$

(171) (172) (175) (173) (174)

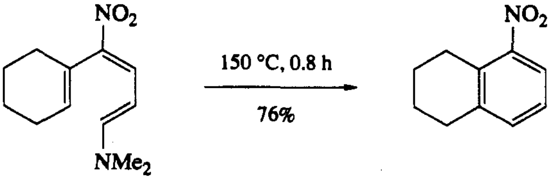
NO$_2$
NMe$_2$
150 °C, 0.8 h
76%
NO$_2$

(176) (177)

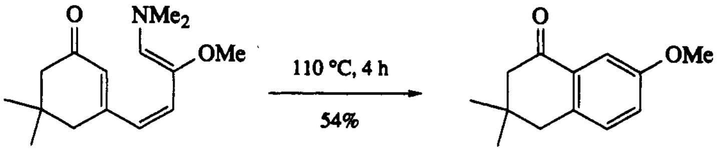

**(178)** **(179)**

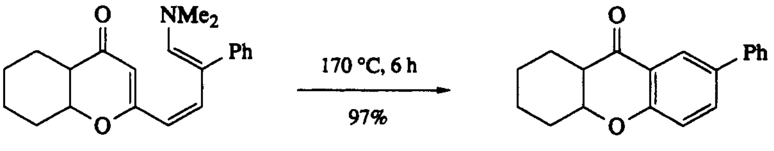

**(180)** **(181)**

In this benzannulation approach, the disruption of aromaticity upon cyclization requires higher activation energies compared with the open-chain aminohexatrienes. Another potential problem is associated with the regioselectivity of the cyclization. Although the cyano group (Y = CN) strongly favors the naphthalene derivative of (**184**) with the R group at C-5, a more sterically demanding R′ group can reverse the regioselectivity. When this problem is not present, efficient syntheses of aromatic compounds are readily achieved and a variety of complex aromatic arrays (naphthalenes, phenanthrenes, chrysenes, triphenylenes, benzo[*c*]phenanthrenes, pyrenes, *etc*.) can be synthesized.

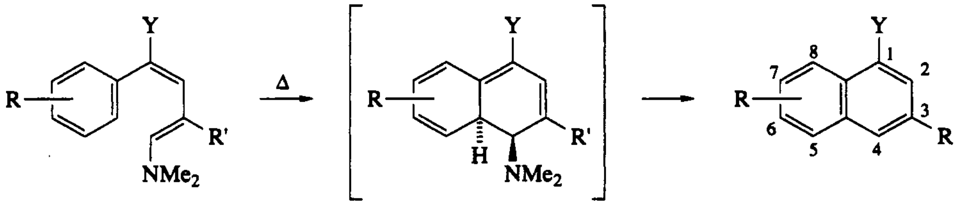

**(182)** **(183)** **(184)**

This electrocyclization leading to a 1,6-fused cyclohexadiene also takes place with polyenes. A photochemical example from the vitamin A field is exemplified by the conrotatory photocyclization of the (7*Z*)-isomer (**186**) of retinal (**185**) to the bicyclic derivative (**187**).[96] The photocyclization procedure has also been used in the aromatic series.[97,98] Thus the photocyclization–oxidation reaction of 1-phenyl-4-(2′-thienyl)-1,3-butadiene (**188**) gave 4-phenylbenzo[*b*]thiophene (**189**). Similarly, the 3′-thienyl analogue (**190**) afforded 7-phenylbenzo[*b*]thiophene (**191**), the reaction exhibiting high selectivity for cyclization to the logically more reactive thiophene nucleus.[97b]

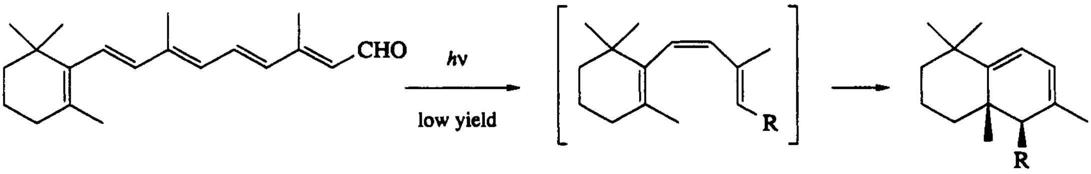

**(185)** **(186)** **(187)**

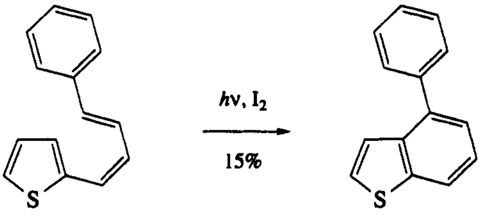

**(188)** **(189)**

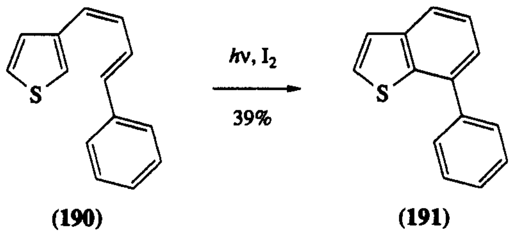

*(v) Types V–IX: Bridged Systems*

Examples in this series, whose cyclohexadiene units are all formally related by oxidation to *meta* (types V, VI and IX) and *para* (types VII and VIII) bridged cyclophanes of the kinds (**192**) and (**193**), respectively, appear not to exist in the literature (or they are at least rare and have escaped the attention of the authors of this review). Cyclophanes appear in standard textbooks[99] and there is a recent example of a 2,5-bridged hexa-1,3,5-triene, namely (**194**),[100] related by electrocyclization to a type VII 1,4-bridged cyclohexadiene. It is interesting that (**194**) is representative of a doubly orthogonal conformer of hexa-1,3,5-triene. However, the electrocyclization of hexatrienes to bridged 1,3-cyclohexadienes appears not to have been previously investigated.

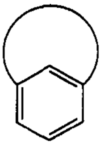
(**192**)

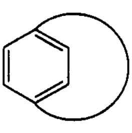
(**193**)

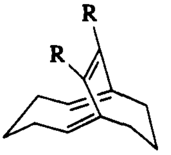

(**194a**) R = Me
(**194b**) R = H

### 6.2.2.2.2 Bis-annulated trienes

With a discussion of the 6e⁻ electrocyclic reactions of acyclic (Section 6.2.2.1) and mono-annulated hexa-1,3,5-trienes (Section 6.2.2.2.1) completed, it may be apparent to the reader that the topic of bis-annulated systems (this section) and higher-order annulated systems (Section 6.2.2.2.3) may be considered fairly direct extensions of the lower-order annulated systems. Accordingly, only a selection of the major types of bis- and higher-order annulated systems (presented in the order, types XI, XV and XIII and then higher-order annulated systems) will be presented.

*(i) Type XI: [1,2:4,5] Bis-annulated Cyclohexadienes*

This approach to cyclohexadienes can be considered an extension of that described for the precursor to type I cyclohexadiene in which the vinyl group is part of a cyclic structure. An example is the low-temperature photochemical generation of the bis-exomethylene compound (**196**) from the benzocyclobutene (**195**), which was followed by an electrocyclic reaction to give compound (**197**).[101] Thermolysis of (**198**) also leads to an assumed bis-exo-methylene intermediate (**199**), which electrocyclizes with involvement of the pyridinium ring to afford the alkaloid ellipticene (**200**) after dehydrogenation.[102]

Extensive investigations of the thermal and photochemical reactions of *trans*-2-benzylidene-1-(diphenylmethylene)indane (**201**) and derivatives[103] have been carried out. It has been shown that thermolysis of (**201**) (200 °C) yields the benzofluorene (**203**) in near quantitative yield. Thermal disrotatory closure of (**201**) to (**202**) followed by a 1,5-H shift would account for the *cis* stereochemistry of the product

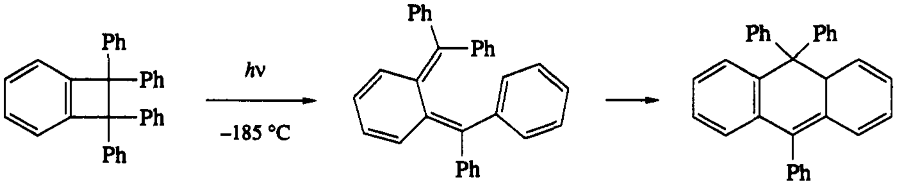

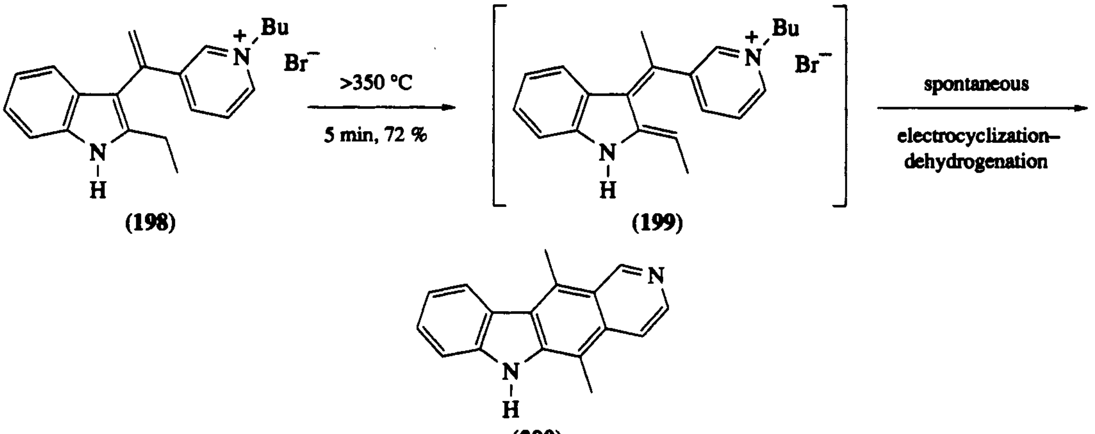
>350 °C
5 min, 72 %
spontaneous
electrocyclization–dehydrogenation
Bu
Br⁻
N
H

**(198)** **(199)** **(200)**

**(203)**. By contrast, photochemical irradiation of **(201)** at 366 nm affords **(205)**, the stereoisomer of **(203)**. It is proposed that **(201)** undergoes photochemically induced conrotatory ring closure to **(204)** followed by its thermal 1,5-H shift to give the observed **(205)**.

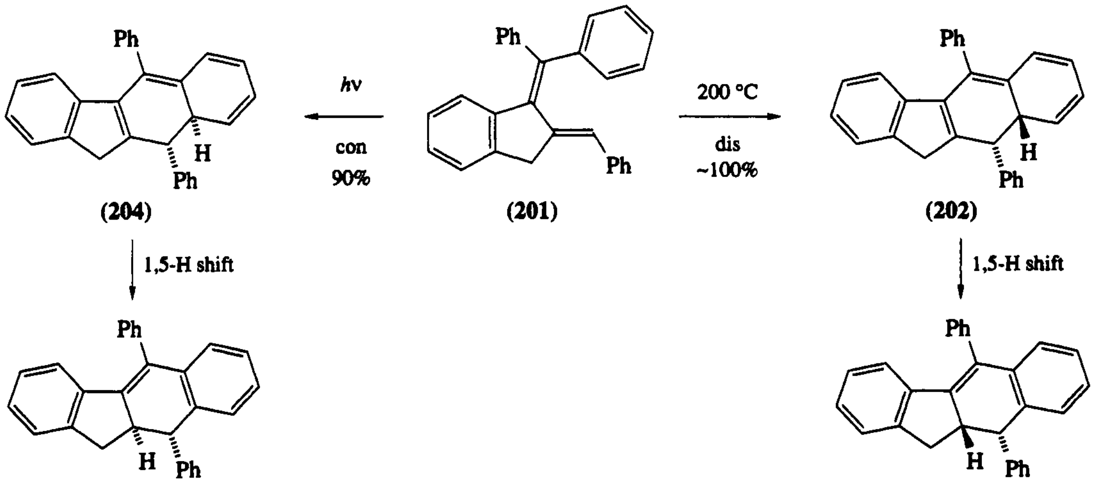
Ph
H
hν
con
90%
200 °C
dis
~100%
1,5-H shift
1,5-H shift

**(204)** **(201)** **(202)** **(205)** **(203)**

Similar results were obtained for the so called 'fulgides' (bis-methylene succinic anhydrides, *e.g.* **206** and **207**).[104] The related furyl analog **(208)** *via* **(209)** experiences photochemical (313–366 nm) ring closure to the deep red-colored cyclohexadiene **(210)** in which the competing 1,5-H shift cannot take place.[105] Cycloreversion occurs on irradiation with white light, which confers photochromic behavior to compounds like **(206)**–**(209)**. The high yield of photocoloration, the linearity of response of the fulgide **(209)** to irradiation and the ease of directly determining the concentration of **(210)** make this system a convenient actinometer.[105]

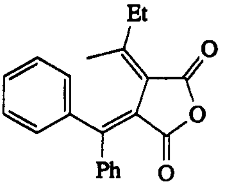

**(206)**

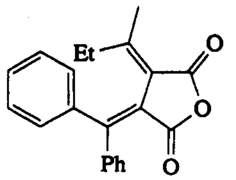

**(207)**

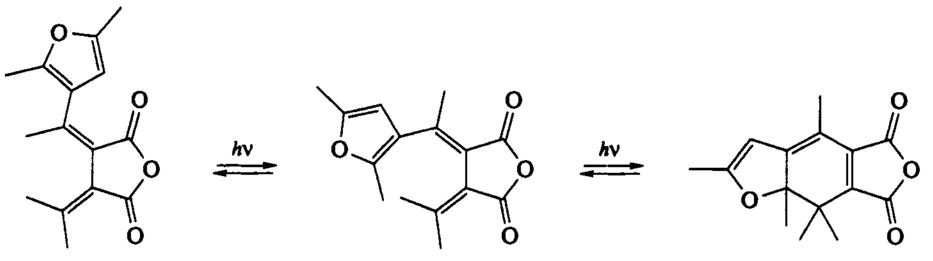

**(208)** **(209)** **(210)**

### *(ii) Type XV: [1,6:4,5] Bis-annulated Cyclohexadienes*

The photocyclization of stilbenes (**211**) (including its *in situ* oxidation) to phenanthrenes (**213**) and that of conjugated arylalkenes to polycyclic aromatics constitute one of the most studied and widely used applications of organic photochemistry.[4,106] Its potential synthetic utility is amplified by the existence of a number of natural products (mainly alkaloids)[107] that contain a phenanthrene subunit in their structure. In view of the plethora of examples contained in several excellent reviews,[4,106] only selected examples will be presented here with focus on the selectivity of the process.

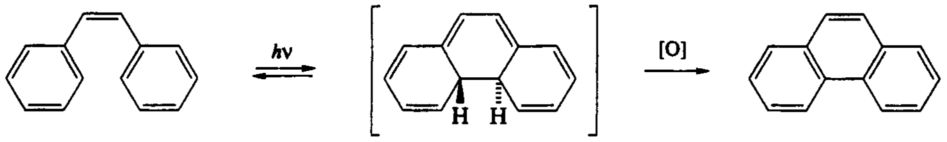

**(211)** **(212)** **(213)**

The initial photochemical step, (**211**) to (**212**), can be most simply viewed as a perturbed 6e$^-$ electrocyclic process, suggesting a *trans* configuration *via* conrotation for the dihydrophenanthrene intermediate (**212**). In support of this hypothesis, the stabilization of (**216**) by tautomerism to (**217**) in the photolysis of diethylstilbestrol (**214**),[108a] followed by ozonolysis, afforded only the racemic form of 1,2,3,4-butanetetracarboxylic acid (**218**).[108b] The majority of dihydrophenanthrenes, however, are thermally unstable and undergo conversion to phenanthrenes (under oxidative or non-oxidative conditions) or 1,*j*-H shifts to isomeric 9,10-dihydrophenanthrenes.[109]

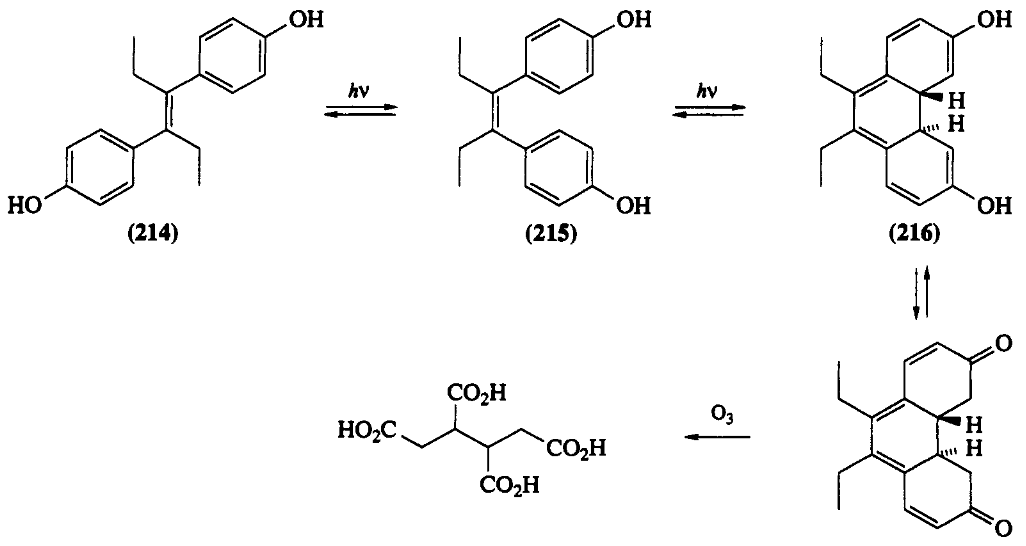

**(214)** **(215)** **(216)**

**(218)** **(217)**

The dehydrogenation step in air-saturated solutions is thought to proceed by a radical chain mechanism, but for preparative purposes it is advantageous to use a small amount of iodine. Other oxidizing agents which have been used include selenium and thiyl radicals and π-acceptors such as TCNE, TCNQ, chloranil and bromanil.[110]

When leaving groups are placed at an *ortho* position as in (**219**), and oxidant is excluded from the reaction medium, irradiation leads to a dihydrophenanthrene of the type (**220**) followed by a highly exothermic elimination reaction to give phenanthrene (**213**). The alternative pathway to (**222**) is interrupted at the dihydrophenanthrene stage (**221**) because of the absence of oxidant. As an example, an efficient synthesis[111] of aporphinoid alkaloid (**225**) is based on the photocyclization of *o*-bromostilbene derivative (**223**) *via* *E*2 elimination of HBr with $KOBu^t$ or, alternatively, by photolysis of the C—Br bond assisted by intramolecular radical complexation.[112] It should be noted that (**224**) is a tris-annulated type of cyclohexadiene which is not explicitly categorized in Figure 1.

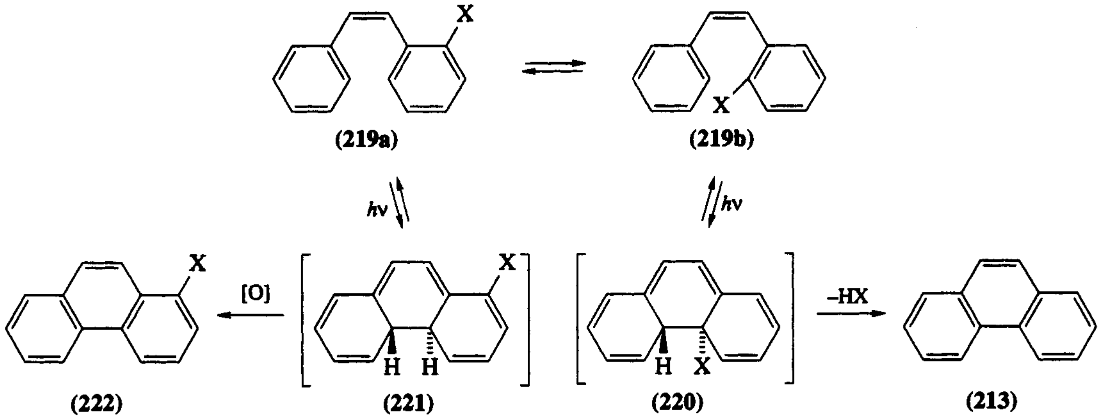

(**219a**) (**219b**)

(**222**) (**221**) (**220**) (**213**)

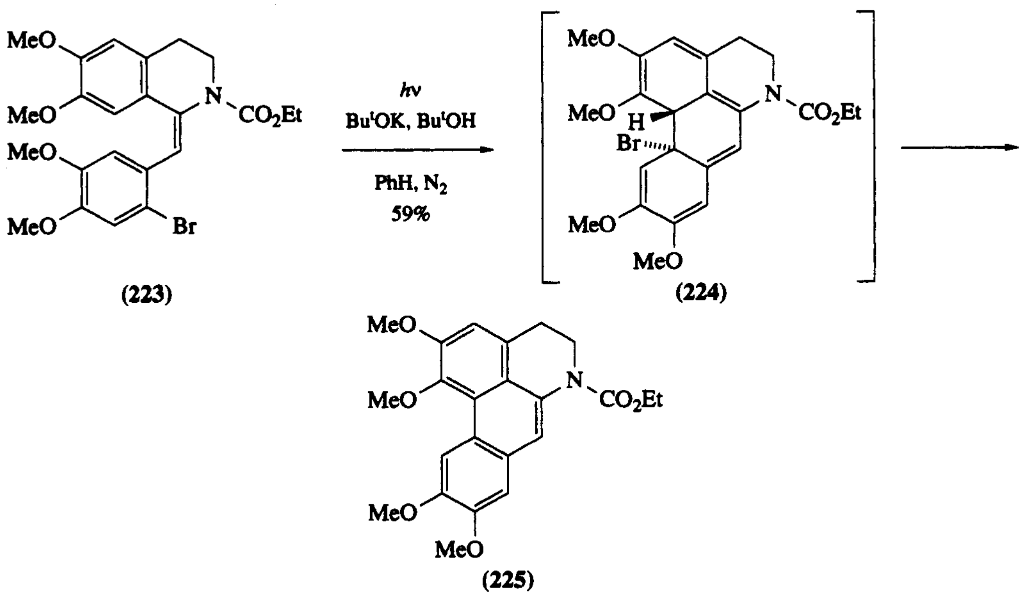

(**223**) (**224**)

(**225**)

The effect of substituents on the regioselectivity of the cyclization has been studied in *m*- (**226**) and *o*-substituted stilbenes (**219**) [the *p*-substituted (**229**) produce 3- or 6-substituted phenanthrenes (**230**)].[4] Generally, *m*-substituted stilbenes afford equal amounts of the 2- (**227**) and 4- (**228**) substituted phenanthrenes, in spite of the greater steric congestion in the latter. This has been rationalized in terms of the development of an early transition state for the photoexcitation of a mixture of ground-state conformers (**226a**) and (**226b**) before steric factors in the dihydrophenanthrene intermediate become significant. Selectivity in this series has been ascribed to several factors, such as selective destruction of the 4-substituted phenanthrenes during extended irradiation,[113] steric hindrance in polysubstituted cases, inefficient trapping of one of the dihydrophenanthrene intermediates, and finally, the influence of *m*-cyano and *m*-ethoxycarbonyl substituents, which afford, preferentially, 2-substituted phenanthrenes.[114] With respect to the effect of the *o*-substituents in (**219**), the different selectivity under oxidative (**222**) and non-oxidative (**213**) conditions has already been mentioned, wherein the latter becomes the predominant product when oxidant is excluded from the reaction mixture. A widely used approach to control selectivity uses an *ortho* substituent as in (**231**) either to direct the cyclization of stilbenes to 2-substituted phenanthrenes (**232**) or to block this position to give the alternative phenanthrene (**233**). Molecular orbital theoretical analyses have been developed in order to rationalize the selectivities observed for stilbene cyclizations.[106a,115]

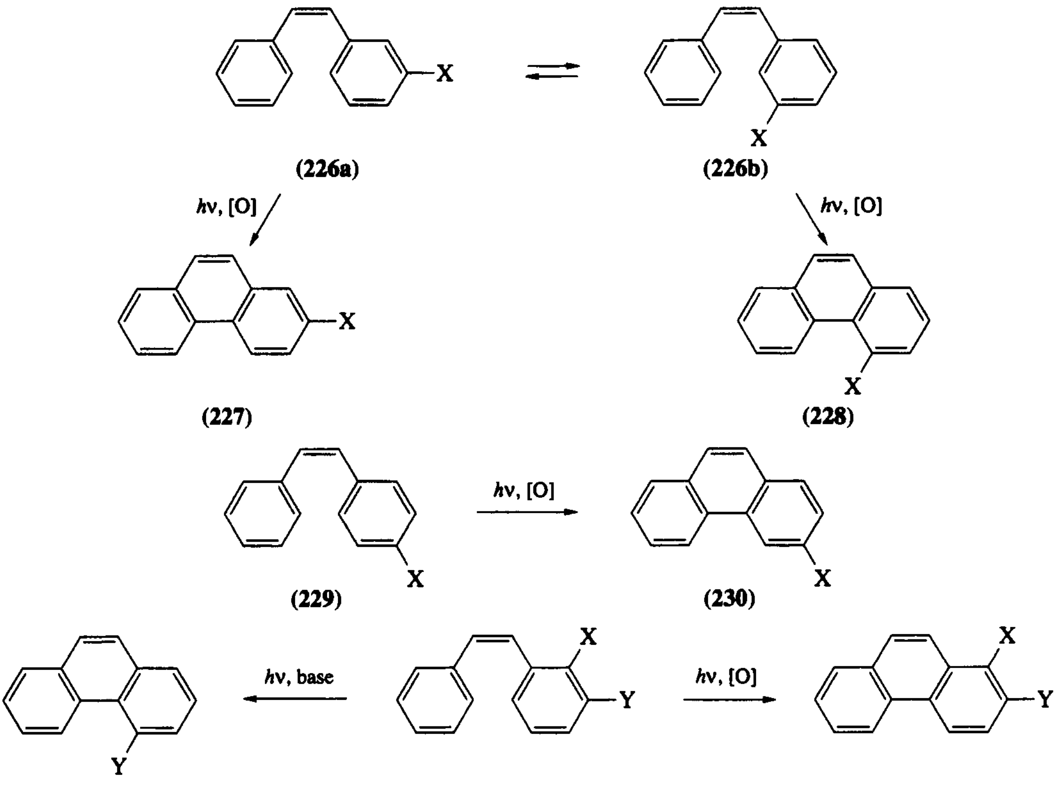

(**226a**) (**226b**)

(**227**) (**228**)

(**229**) (**230**)

(**233**) (**231**) (**232**)

This type of cyclization has recently been used in the carbocyclic field to synthesize the tetracyclic glycol (**234**), an advanced intermediate in the synthesis of the antimicrobial and amoebicidal agent ikarugamycin.[116] Thus photocyclization of a 2:1 mixture of trienes (**235**) and (**236**) led to a 4:1 mixture of the two possible conrotatory closure products (**237**) and (**238**), which likely reflect the conformational bias in the ground state of the (*Z*)-triene (**236a** and **236b**, respectively).[36]

### *(iii) Type XIII: [1,6:2,3] Bis-annulated Cyclohexadienes*

Only a few cases of thermal electrocyclizations of [1,2:3,4] bis-annulated trienes have been described. That the central double bond is part of a ring system eliminates the possibility of secondary thermal processes that were operating in the precursors to the simpler type IV cyclohexadienes. For example, the cyclization of diketone (**239**) to (**240**) takes place smoothly without interference from other thermal processes.[34]

A new entry into the aromatic steroid nucleus is based on this approach to construct the c-ring of cyclohexadiene (**242**) by thermolysis (xylene, 140 °C, 34 h) of the triene (**241**). Photolysis is an alternative, but the yields were lower. A phenyl group can be used as a component of the triene system, although more drastic conditions (180 °C, 4 days or FVP, 730 °C, 0.1 mmHg) are required to disrupt the aromaticity of its nucleus as in compound (**243**), which gives as a final product 5,6,11,12-tetrahydrochrysene (**245**).[117]

The thermolysis of vinylindoles (**246**) to carbazoles (**247**) in the presence of 5% Pd/C combines electrocyclic ring closure with rearomatization. Depending on the conditions, thermolysis of vinylindole (**246**) gives a mixture of benzocarbazoles (**247a**; 22%) and (**247b**; 17%) (xylene, 150 °C), (**247a**; 23%) and (**248b**; 16%) (1,2-dichlorobenzene, 180 °C), or (**247a**; 20%) and (**248a**; 29%) (decalin, 210 °C).[118]

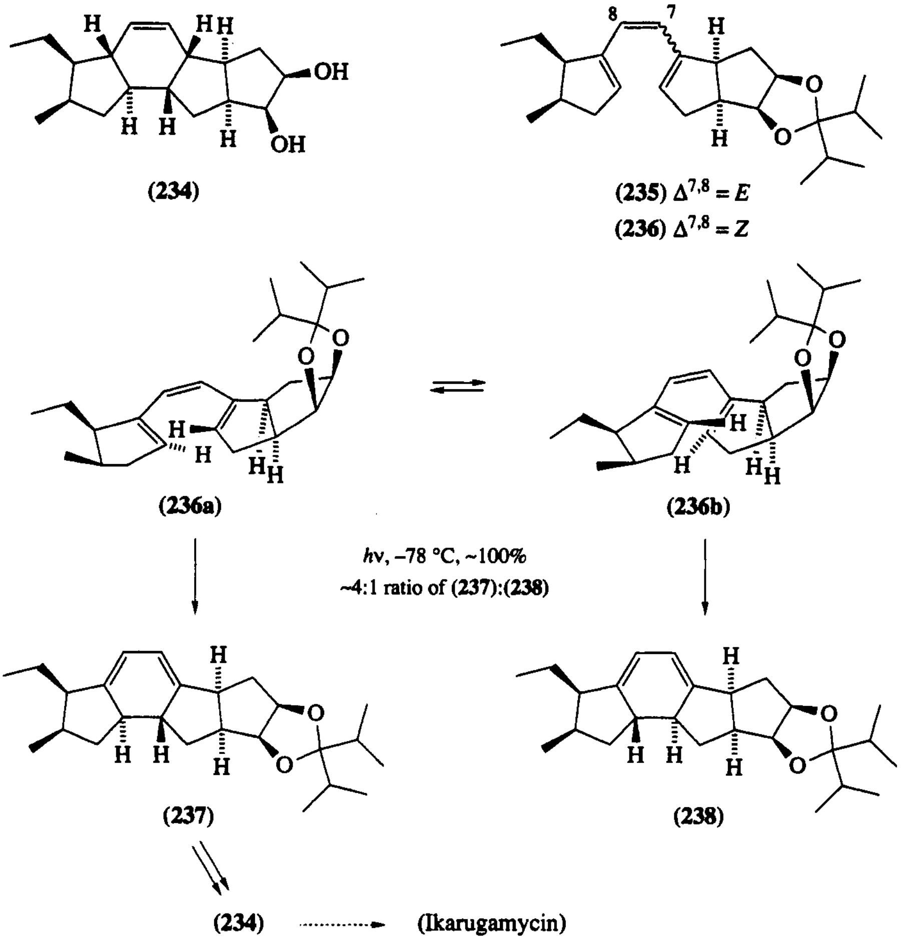
(234)
(235) $\Delta^{7,8} = E$
(236) $\Delta^{7,8} = Z$
(236a)
(236b)
$h\nu$, -78 °C, ~100%
~4:1 ratio of (237):(238)
(237)
(238)
(234)
(Ikarugamycin)

By contrast to the thermal process, the photochemistry of 2-vinylbiphenyl (**249**) and 4-vinylphenanthrene (**250**) has been widely used in connection with syntheses of polycyclic aromatic compounds, complementing the most commonly used stilbene to phenanthrene transformation.[4,106d] For example, the product obtained from the conrotatory photocyclization of 2-(α-styryl)biphenyl (**252**) can be trapped by an oxidant to give the phenanthrene (**254**) or suffers a 1,5-H shift to give the dihydrophenanthrene

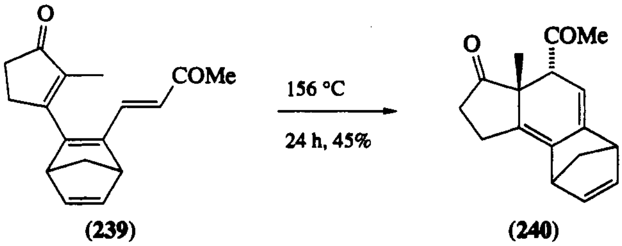
156 °C
24 h, 45%
(239)
(240)

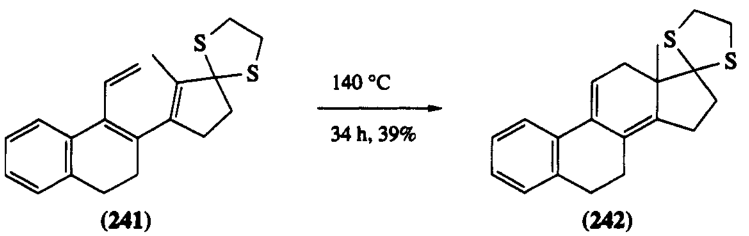
140 °C
34 h, 39%
(241)
(242)

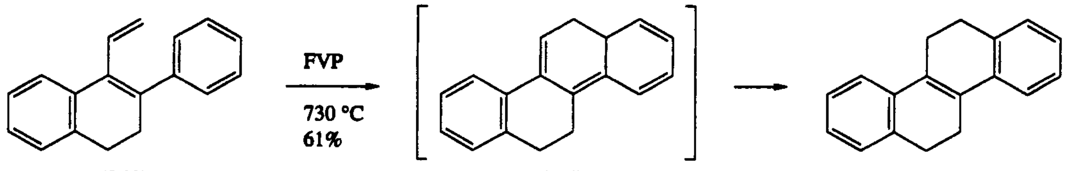

(243) (244) (245)

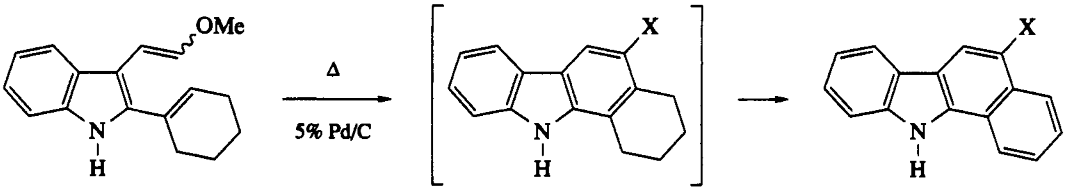
OMe
N
H
Δ
5% Pd/C
X
N
H
X
N
H

(246) (247a) X = OMe (247b) X = H (248a) X = OMe (248b) X = H

(255).[119] Similarly, the photochemical opening of cannabinol (**256**) to (**257**) was followed by ring closure and dehydration to the hydroxyphenanthrene (**258**), elimination of $H_2O$ being the internal trap of the initial cyclization product (**257**).[120] Note that the initial ring opening of (**256**) is an example of a photoinduced hetero electrocyclization reaction (Section 6.2.4.2).

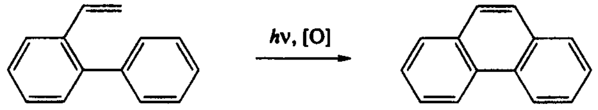

(249) (213)

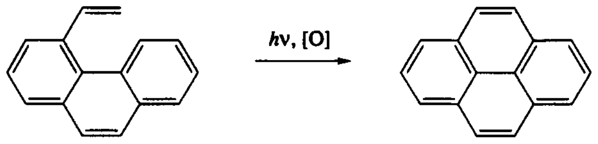

(250) (251)

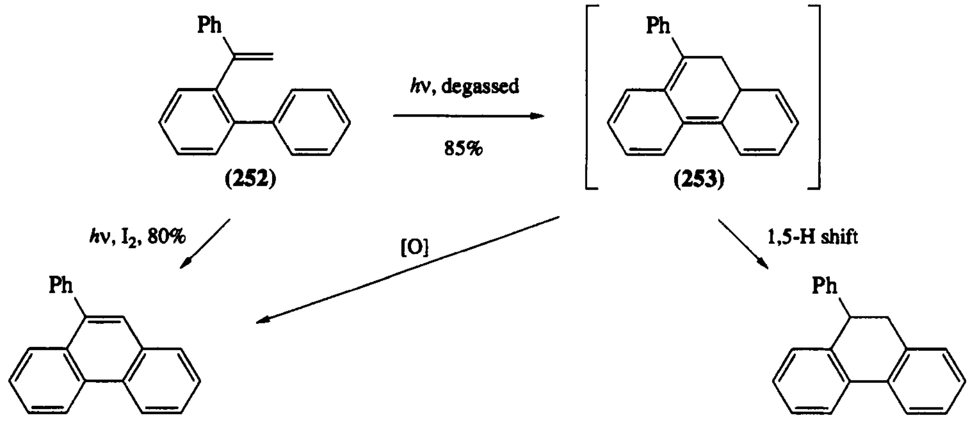
Ph
*h*ν, degassed
85%
Ph
*h*ν, $I_2$, 80%
[O]
1,5-H shift
Ph
Ph

(252) (253) (254) (255)

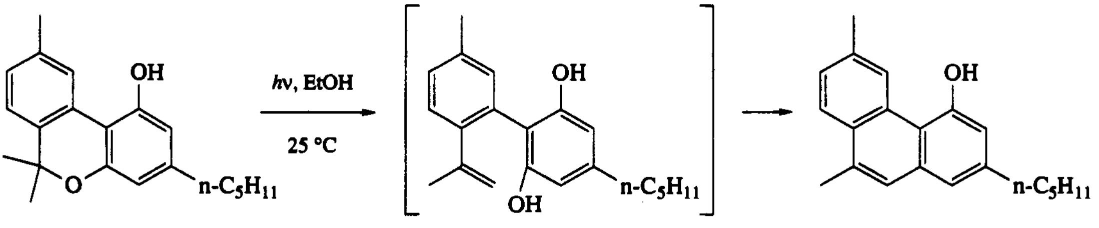
OH
O
n-$C_5H_{11}$
*h*ν, EtOH
25 °C
OH
OH
n-$C_5H_{11}$
OH
n-$C_5H_{11}$

(256) (257) (258)

2,2′-Divinylbiphenyl derivatives upon irradiation exhibit a competition between electrocyclic ring closure and [2 + 2] photocycloaddition, the nature of the resulting products being dependent on the experimental conditions and the substituents attached to the double bond. The simple divinylbiphenyl (**259**) produces a mixture of the singly and doubly electrocyclized products (**260**) and (**261**), respectively, the latter being obtained quantitatively upon prolonged irradiation. When a stilbene moiety is present in the system as in (**262**), the [2 + 2] intramolecular cycloaddition to (**264**) (after fast *E–Z* equilibration) is the main reaction taking place at short irradiation times. On further irradiation, (**264**) is quantitatively converted into tetrahydropyrene (**265**).[121]

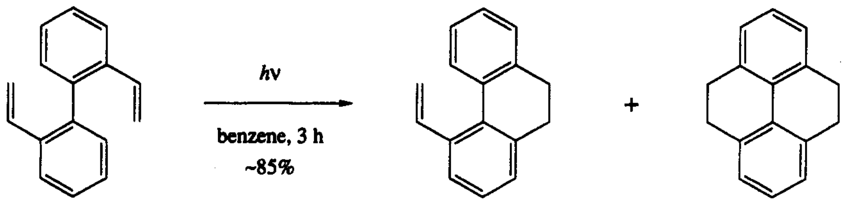

(**259**) (**260**) ~3:7 (**261**)

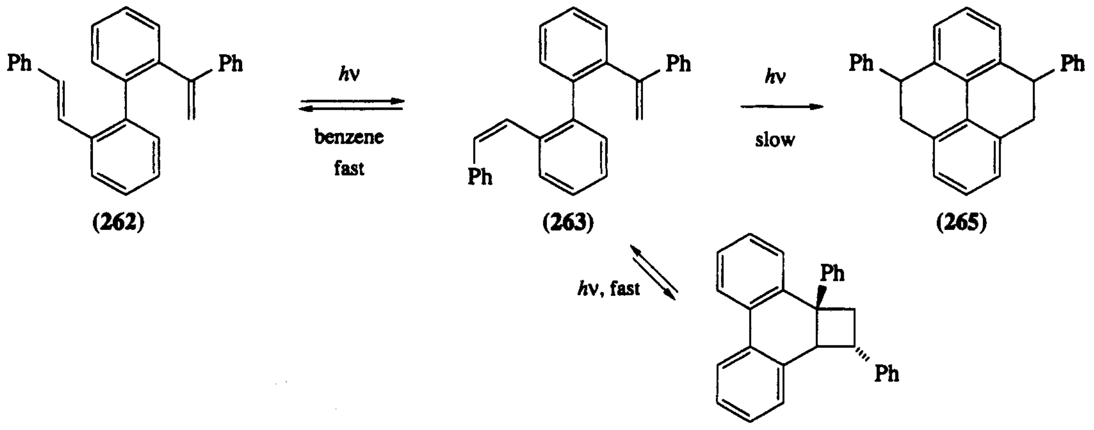

(**262**) (**263**) (**265**)

(**264**)

The ring-bearing moiety of the hexatriene can also be fused to a heterocycle. In the presence of an oxidant ($I_2$), the photolysis of a variety of 4-phenyl-3-vinylquinolones such as (**266**) yields benzo[*k*]phenanthridones (*e.g.* **267**) in good to excellent yields.[122] Similarly, photolysis of pyrroles (**268**) followed by treatment with DDQ gave fused indoles (**269**) (which contain a fused benzene, furan or thiophene ring).[62]

### *6.2.2.2.3 Higher-order annulated systems*

The known examples of the synthesis of higher-order annulated systems (exemplified by types XVI–XVII in Figure 2) involve photochemical cyclization followed by oxidation of arene analogs of stilbenes.

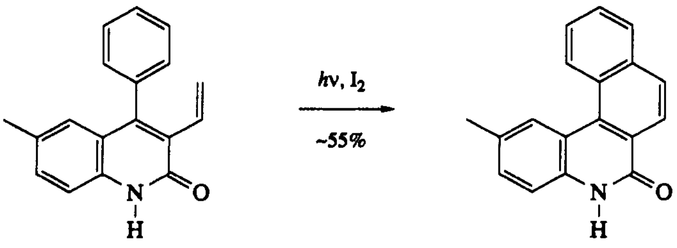

(**266**) (**267**)

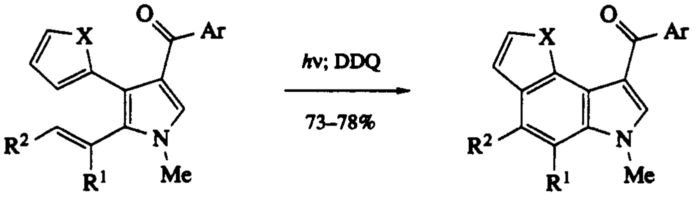

**(268)** X = CH=CH, O, S **(269)**

For example, the reported transformation of (**270**) to (**272**) is an extension of the transformation of (**211**) to (**213**) discussed earlier. As oxidant, $I_2$ in high concentrations is recommended due to the high propensity of the dihydrotriphenylene (**271**) to undergo ring opening (three aromatic rings would be formed to give starting material **270**).[123] An aromatic solvent is also required to transfer energy to the reactant in its singlet state, thus avoiding the dissipation of energy due to the light absorption of the product triphenylene (**272**). Many other examples are known, making this method an excellent choice for the preparation of polycyclic aromatic compounds.[4,106b,123]

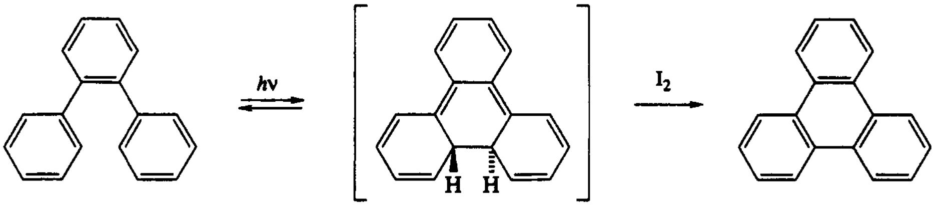

**(270)** **(271)** **(272)**

The polycyclic compound (**274**) can be efficiently obtained by photochemical irradiation of the 4-styrylphenanthrene derivative (**273**), with isolation of a dihydro intermediate.[124] Of course, only two of the three ring fused double bonds in this example are aromatic. The transformation of (**268**) to (**269**) presented earlier, wherein the $R^1$ and $R^2$ groups are part of a cycloalkenyl ring, represents another example of this kind.[62]

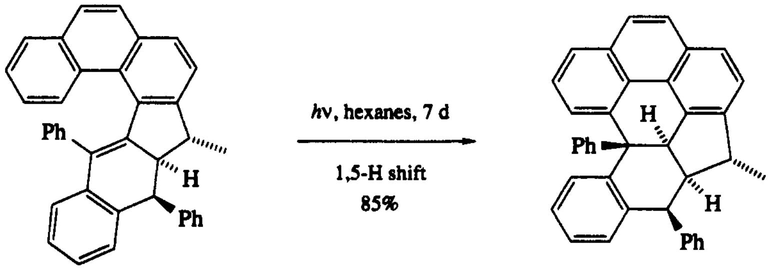

**(273)** **(274)**

Finally, the dianthrones and other doubly bridged tetraphenylethylenes can also be considered part of this group.[125] For example, dianthrone (**275**) upon photolysis leads to the presumed dihydro intermediate (**276**), which by two successive enolizations gives (**277**). Furthermore, a hydrogen transfer reaction between (**277**) and the dianthrone (**275**) gives helianthrone (**278**) and dianthranol (**279**). On extended irradiation, helianthrone (**278**) further cyclizes to afford mesonaphthodianthrone (**280**) and another molecule of (**279**) (wherein **275** can be viewed as oxidant to afford **279**).

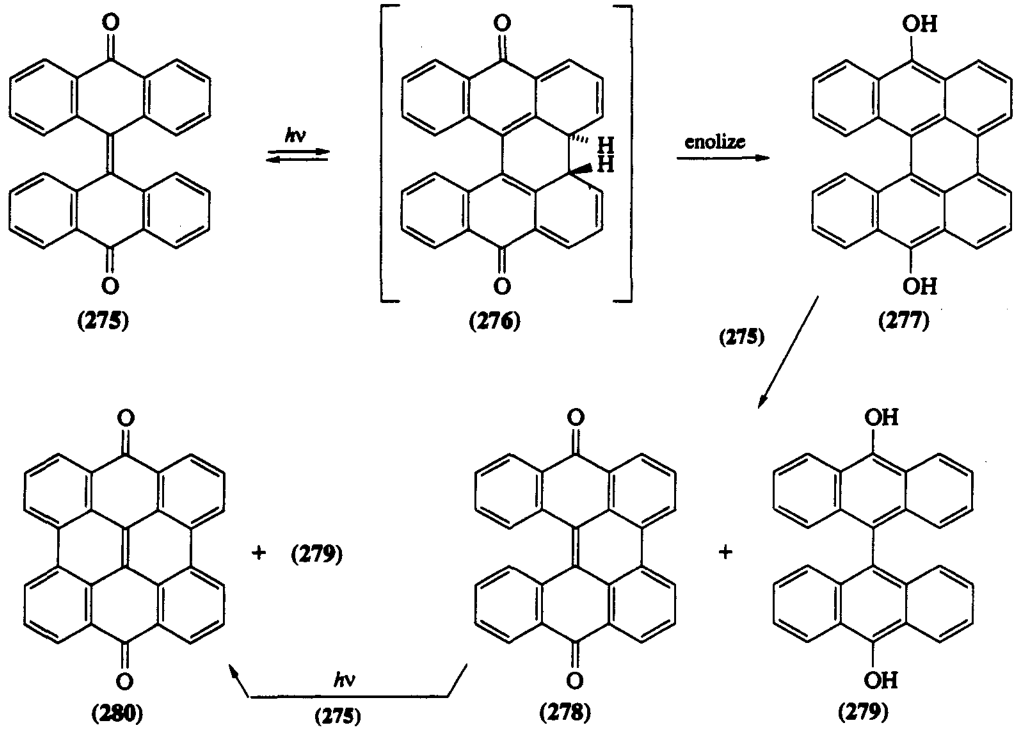

## 6.2.3 ELECTROCYCLIZATION OF *sp*-CARBON CONTAINING SYSTEMS

### 6.2.3.1 Ketenes

In 1968, Griffiths and Hart established that although dienylketene (**282**) (generated as the only photochemical product from cyclohexadienone **281**) cyclizes thermally to (**281**), other thermal cyclizations compete, such as the formation of the bicyclo[3.1.0]hexenone (**283**) or solvent (amines or alcohols) addition product (**284**).[126] The thermal formation of bicyclo[3.1.0]hexenones (**283**) from ketenes (**282**) can be photochemically reversed. Thus 2,4-cyclohexadienones (**287**) can be obtained from 2,5-cyclohexadienones (**285**).[127,128] The stereospecificity of the thermal ring opening of the bicyclo[3.1.0]hexenones to dienylketenes has been established.[128]

Studies of the low-temperature photochemistry of umbellone (**288**) established a dual pathway for its conversion to thymol (**291**).[129] Besides the opening of (**288**) to ketene (**289**), its direct conversion to the cyclohexadienone (**290**) was also postulated. However, this reaction depends on the substitution pattern, and in the case of lumisantonin (**292**) only traces of cyclohexenone (**294**) were detected in the photolysis

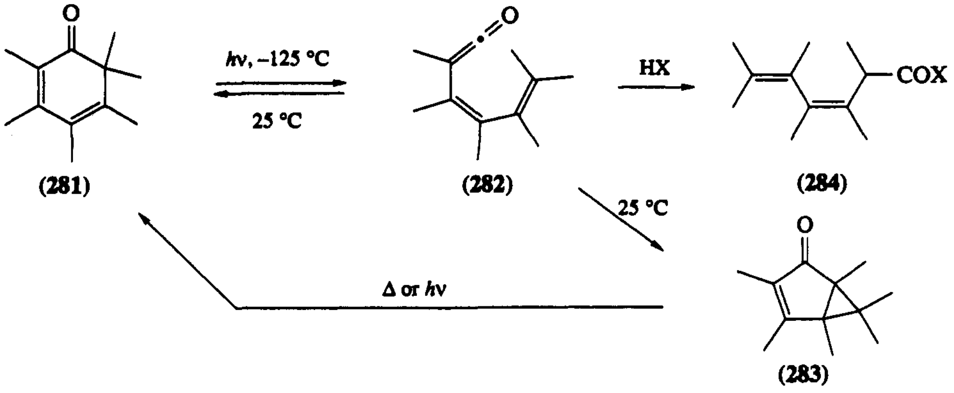

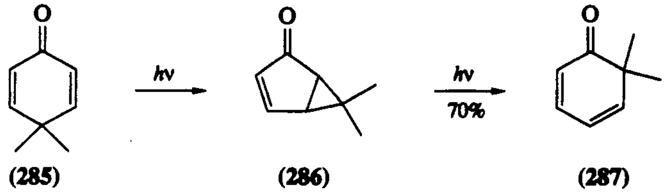

hν
hν
70%
(285)
(286)
(287)

mixture.[129] Most recently, the chemistry of dienylketenes has been reviewed[130a] and efforts have been directed towards substituent control of stereochemistry of the dienylketene to cyclohexadienone cyclization and synthesis applications in the diterpenoid area.[130b–d]

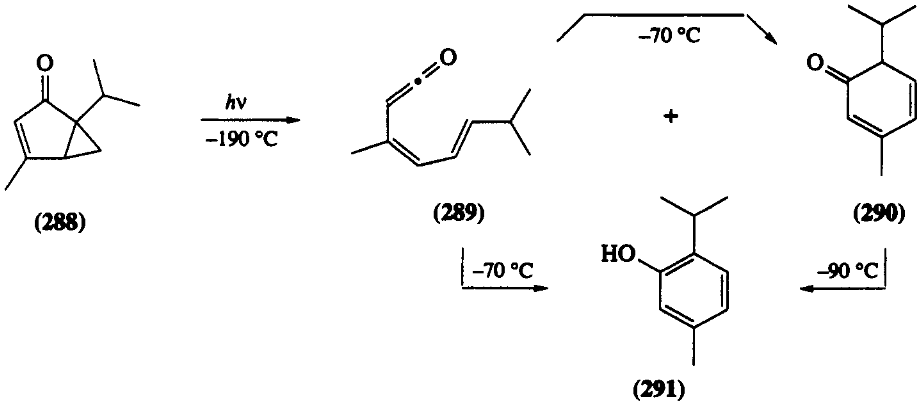

hν
-190 °C
-70 °C
+
-70 °C
-90 °C
HO
(288)
(289)
(290)
(291)

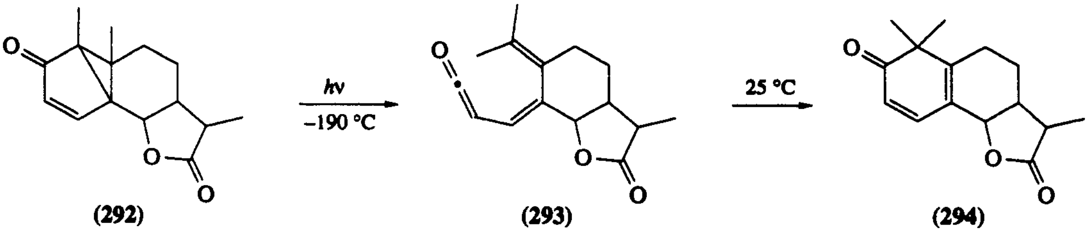

hν
-190 °C
25 °C
(292)
(293)
(294)

The competition of nucleophilic attack by solvent at the ketene *sp* center has been shown to be useful for obtaining aza analogues of dienylketenes, namely dienylketenimines (**297**) from ketene intermediates generated from (**295**). Upon dehydration, the addition product (**296**) afforded directly the *N*-alkylated cyclohexadienimines (**298**) in good yield. The expected dienylketenimines (**297**) were not isolated. Regeneration of spectroscopically detectable (**297**) can be achieved by photochemical irradiation of (**298**), its stability above 0 °C being solvent dependent.[131]

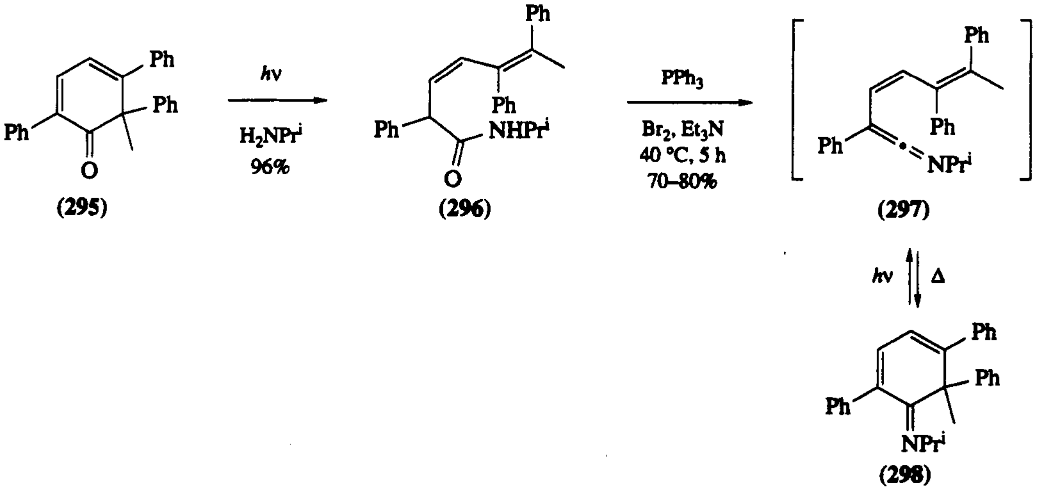

hν
$H_2NPr^i$
96%
$PPh_3$
$Br_2$, $Et_3N$
40 °C, 5 h
70–80%
hν
Δ
(295)
(296)
(297)
(298)

Another method to generate the dienylketene functionality is by thermal ring opening of arylcyclobutenones.[132] Thus the naphthol (**301**) was one of the products resulting from the condensation of diphenylketene and ethoxyacetylene[132a] and its formation likely involves opening of cyclobutenone (**299**) to the ketene (**300**) and electrocyclic closure of the latter. Similar results were obtained upon heating cyclobutenones (**302**)[132b] and (**303**),[132c] although the ability of the latter to ring open to two stereoisomeric dienylketenes led to additional products besides the naphthol.

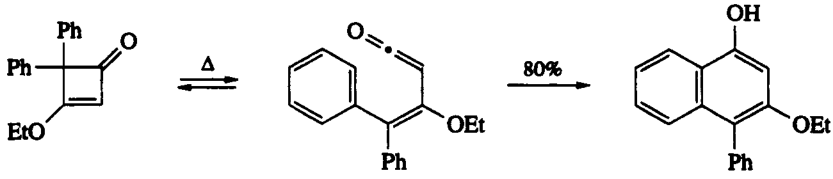

(**299**) (**300**) (**301**)

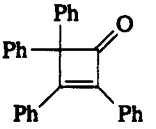

(**302**)

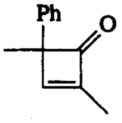

(**303**)

Naphthols are also obtained from arylmethyleneketenes generated by FVP of derivatives of Meldrum's acid (**304**).[133] The initial formation of 2-methylbenzylideneketene (**305**) can be envisaged, followed by a 1,5-H shift leading to the *o*-quinonoid ketene (**306**). Thermal cyclization to (**306**) and tautomerization provides a rationale for formation of 2-naphthol (**308**).[133a] This represents a transformation of *o*-tolualdehydes (starting materials for the preparation of **304**) to 2-naphthols. The related five-membered ring heterocyclic aldehydes with adjacent methyl substituents also experience the same thermal transformation, thus allowing the preparation of hydroxy derivatives of benzothiophene, benzofuran, dibenzofuran, indole and carbazole in good yields.[133b]

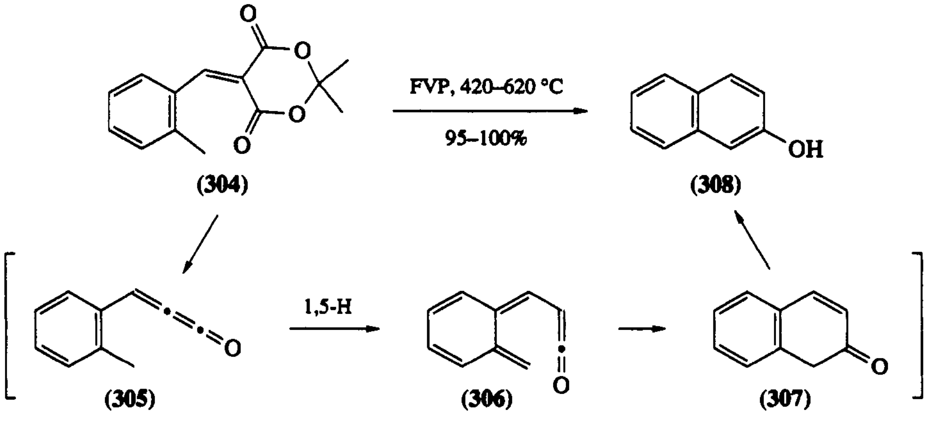

Phenols (**311**) are also the final products from the thermolysis (>140 °C) of aminocyclobutenones (**309**), generated by rearrangement of aminobicyclo[2.2.0]hexenones (addition products of ynamines and cyclobutenones) *via* ketene intermediate (**310**).[134] A related transformation (starting from ketenophilic acetylene derivatives and vinylketenes, leading after rearrangement to vinylcyclobutenone derivatives **312** and **315**) has been applied to the regiocontrolled synthesis of differentially protected resorcinol derivatives (**313**) and (**316**), respectively.[135] Demethylation of (**313**) and (**316**) provided the antifungal antibiotics DB-2073 (**314**) and grifolin (**317**), respectively.[135a] The hexasubstituted aromatic ring of mycophenolic acid (**325**) has also been synthesized using the same key strategy, combined with the regioselective bromination of the resulting phenol (**321**) at the C-6 aromatic position. Thus the cascade of electrocyclic reactions following thermolysis of a mixture of alkynyl ether (**318**) and cyclobutenone (**319**) provided the pentasubstituted resorcinol derivative (**321**), which was brominated to (**322**) and then transformed to the carboxylic acid (**323**). The phthalide (**324**) obtained upon heating (**323**) with catalytic HCl in MeOH was oxidized to mycophenolic acid (**325**).[135b]

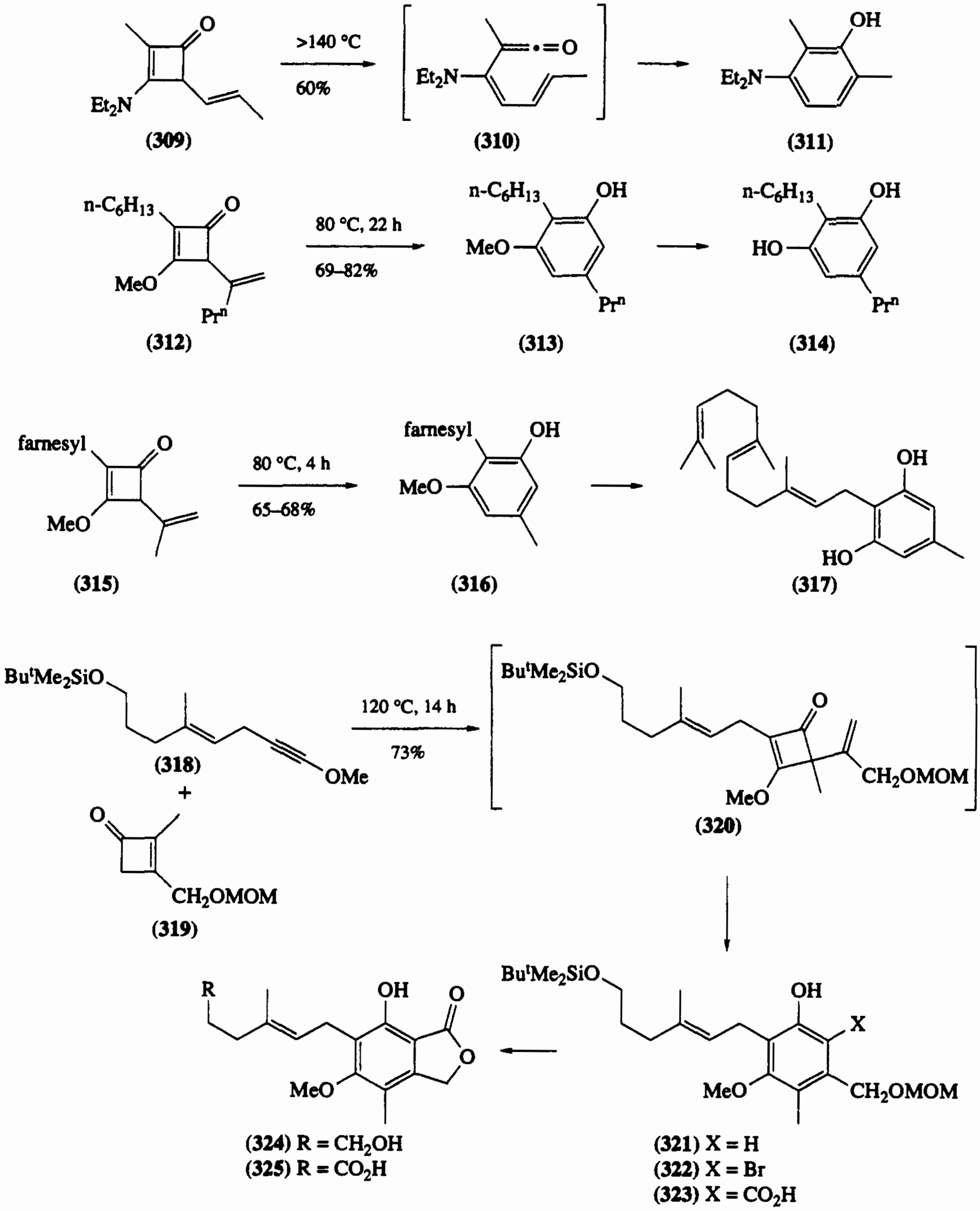
>140 °C
60%
Et2N
O
(309)
(310)
OH
(311)
n-C6H13
MeO
80 °C, 22 h
69–82%
Pr^n
(312)
(313)
HO
(314)
farnesyl
80 °C, 4 h
65–68%
(315)
(316)
(317)
Bu^tMe2SiO
OMe
120 °C, 14 h
73%
(318)
+
CH2OMOM
(319)
(320)
R
(324) R = CH2OH
(325) R = CO2H
X
(321) X = H
(322) X = Br
(323) X = CO2H

With related 4-vinyl- or 4-alkynyl-cyclobutenones (**326**) carrying a hydroxy group at the C-4 position, a similar sequence provides highly substituted quinones (**328**) or (**330**).[136] Extension of this approach to 4-aryl (or heteroaryl) cyclobutenones provides a general synthesis of highly substituted quinones of general structures (**332**) and (**334**).[136b–g] The transformation of (**336**) to (**338**) is representative of the methodology. Interestingly, the lithium reagent (**336**) adds selectively to the unsymmetrically substituted benzocyclobutenedione (**335**). This was followed by an outward rotation[15b] of the hydroxy group in the electrocyclic ring cleavage of the adduct (**337**) to give, after appropriate functional group transformation, the quinone (**338**) as a 13:1 mixture of regioisomers.[136b] A diradical mechanism has been proposed for the rearrangement of alkynylcyclobutenones.[136f,g]

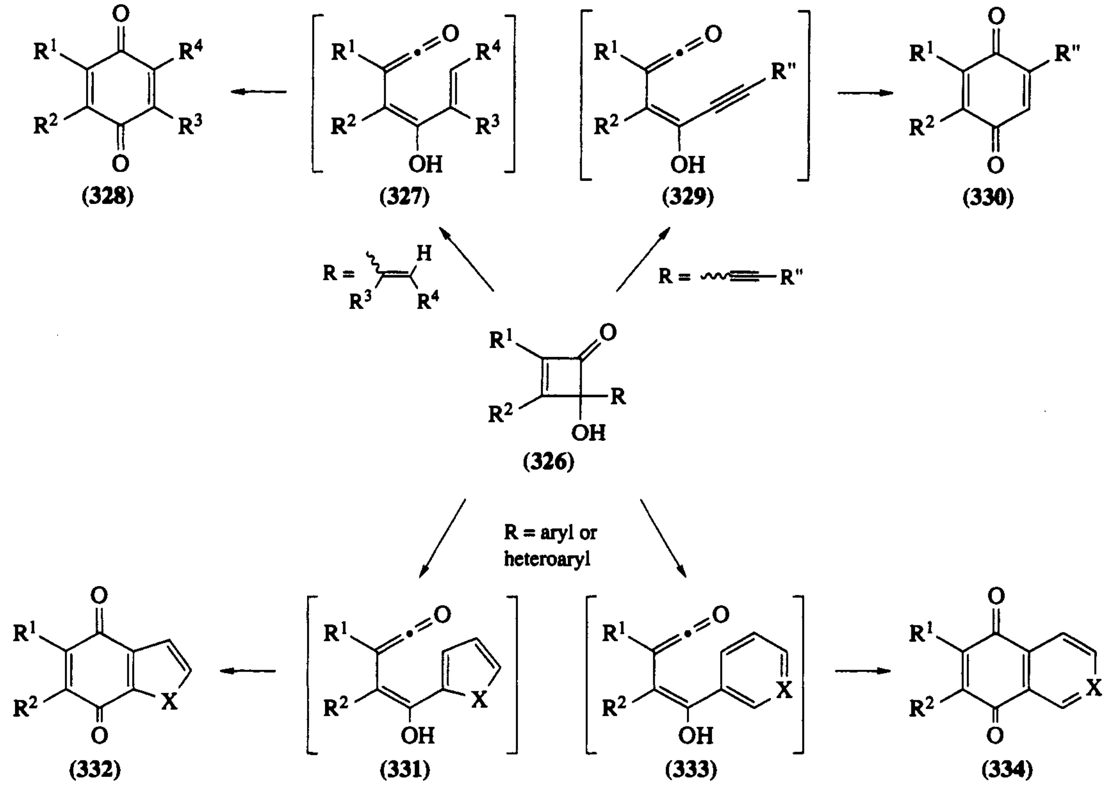
(328)
(327)
(329)
(330)
R =
R = R"
(326)
R = aryl or heteroaryl
(332)
(331)
(333)
(334)

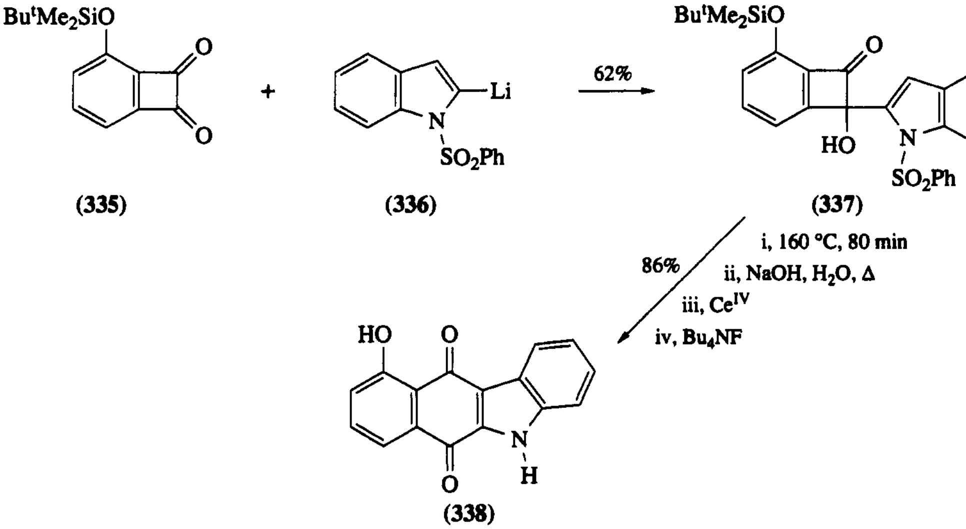
(335)
+
(336)
62%
(337)
86%
i, 160 °C, 80 min
ii, NaOH, H2O, Δ
iii, Ce^IV
iv, Bu4NF
(338)

### 6.2.3.2 Allenes

The participation of an allenic *sp* center in an electrocyclic reaction was earlier demonstrated in the pyrolysis (490 °C) of the pentadienylallene (**339**) to give *o*-xylene (**342**) together with alkyne (**343**).[137] The high temperature required is primarily necessary to effect isomerization of the double bond to the (*Z*) configuration as in (**340**), because both the 6e$^-$ electrocyclization of (**340**) to (**341**) as well as the aromatization of the latter to (**342**) possess lower activation barriers. That the 6e$^-$ electrocyclization of dienylallenes possesses a low activation barrier is evidenced by the formation of (**346**), presumably *via* dienylallene (**345**) from benzoate (**344**) by an $S_N2'$ reaction of the latter with a higher-order cuprate.[138a]

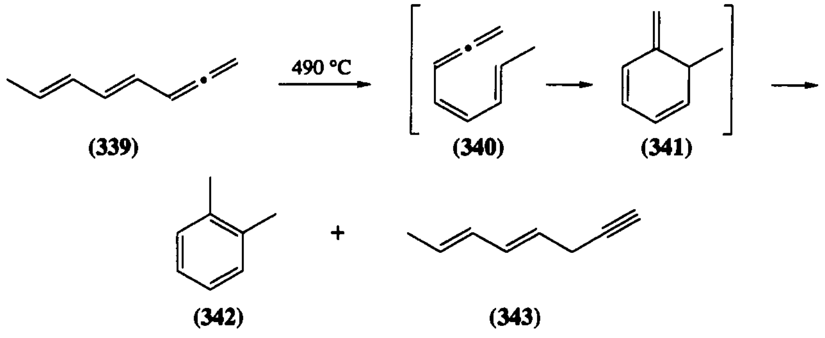

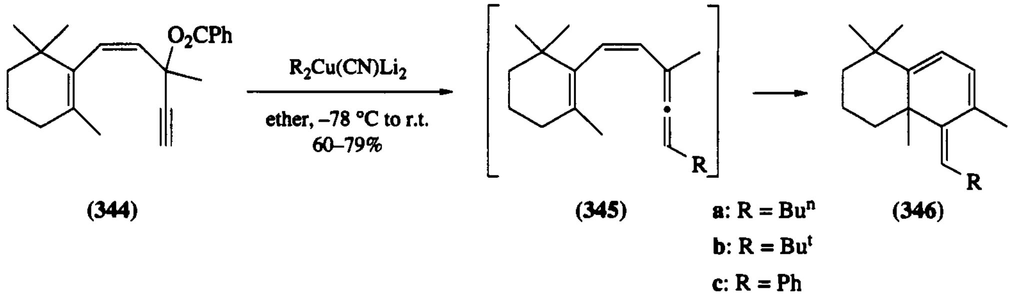

When the allenyldiene sulfoxide (**348**) was generated by treatment of the propargylic alcohol (**347a**) with phenylsulfenyl chloride, the allene spontaneously electrocyclized to the drimatriene sulfoxide (**349**). Related transformations were presented earlier in this chapter (*cf.* **44** to **46** and **47**).[35a] This multistep one-pot process is believed to occur by initial formation of the sulfenate ester (**347b**) which undergoes a 2,3-sigmatropic shift to give (**348**) in a completely stereoselective manner with respect to the allene configuration. This is followed by a completely stereoselective 6e⁻ electrocyclization in only one of the allowed disrotatory modes to afford (**349**). This stereomechanistic conjecture is firmly supported by the finding that optically enriched (*R*)-(**350**) afforded (**353**) in excellent yield with the (expected) stereochemistry and stereochemical purity. The absolute configuration of (**353**) at its bridgehead center was established by its transformation to (**354**), the antipode of which is known.[138b]

### 6.2.3.3 Alkynes

There are two obvious difficulties concerning the feasibility of effecting pericyclic reactions of alkynes.[139] The first concerns the geometry of the mandatory cyclic transition state. The second concerns the stability of the resulting products. While the geometry of an $sp^2$ center is well suited for attaining the cyclic array of the bent molecular framework, the presence of an alkynic center with bond angles of 180° demands a colinearity of three contiguous bonds. As a consequence, the transition state geometry requires considerable bond deformation. For the 6e⁻ electrocyclization process, the resulting product is a 1,2,4-cyclohexatriene. The less-unsaturated 1,2-cyclohexadiene is already known to be a species with a

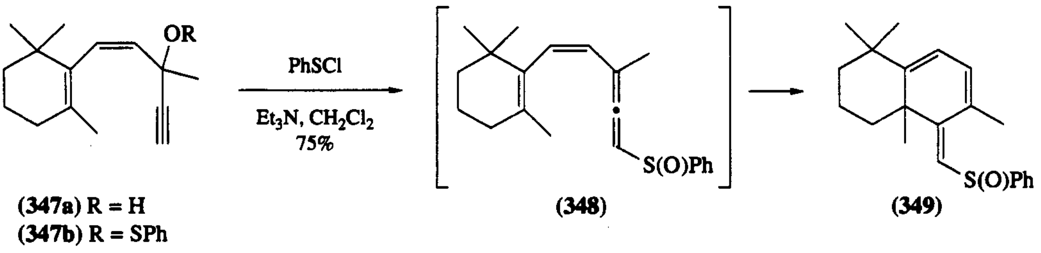

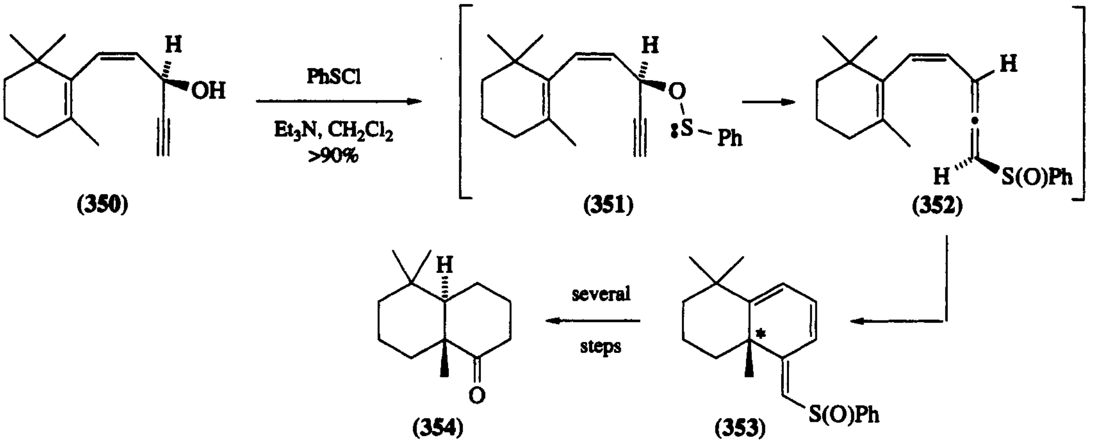

high degree of deformation and reactivity.[140] For the prototypical example in this series, namely (**356**) to (**357**), doubts about the mechanism of the conversion of (*Z*)-(**356**) and (*E*)-(**355**) to benzene (**358**) still remain.[141] Although the base-catalyzed thermal isomerization of 1,6-heptadiyne (**359**) to toluene (**361**) (and *trans*-dienyne **360**) is presumed to occur *via* (*Z*)-dienyne (**362**), the pericyclic nature of this process is uncertain[142a] (*cf.* the recent studies of neocarzinostatin[142b–m]).

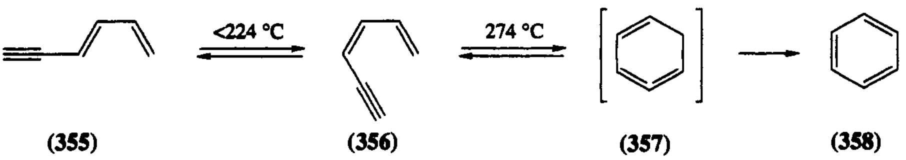

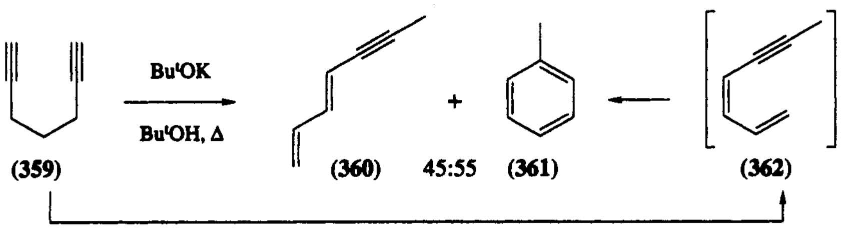

When both termini of the triene are alkynic units,[143] the reaction takes place *via* a diradical intermediate.[144] Heating of (*Z*)-1,6-dideuteriohex-3-ene-1,5-diyne (**363**) at 300 °C caused rapid scrambling of the deuterium label to give exclusively a mixture of (**363**) and the 3,4-dideuterio isomer (**365**). Also, when heated in different solvents, products of typical radical reactions were observed. These data together with detailed kinetic analysis and spectroscopic studies have led to the hypothesis of the intermediacy of the 1,4-dehydrobenzene diradical (**364**) (*p*-benzyne) in the process.[144]

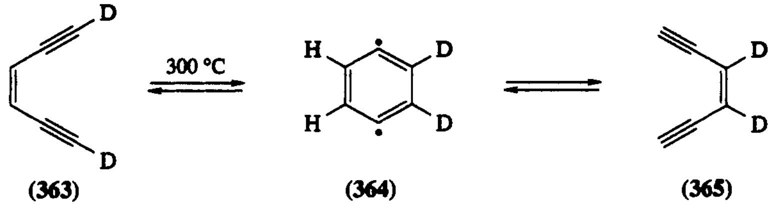

Intense synthetic and mechanistic efforts in this area are currently in progress[145] (see also the studies of neocarzinostatin[142b–m] and dynemicin A[145v–aa]) as a consequence of the isolation and structural elucidation of two potent antitumor agents, esperamicin and calichemicin, both with general structure (**366**). Both compounds in their aglycone component possess an enediyne bridge, which has been hypothesized to be involved in the DNA-damaging action through its isomerization to a diradical (**368**) after thiol conjugate addition (following nucleophilic attack on the central sulfur atom) to the α,β-unsaturated carbonyl group. The co-occurrence of (**369**) from the same microorganism further supports the mode of action of this antitumor agent.[145] An important question is whether the process (**367**) to (**368**) (or for that matter, the transformation of **356** to **357** or **363** to **364**) should even be considered a classical concerted pericyclic process.

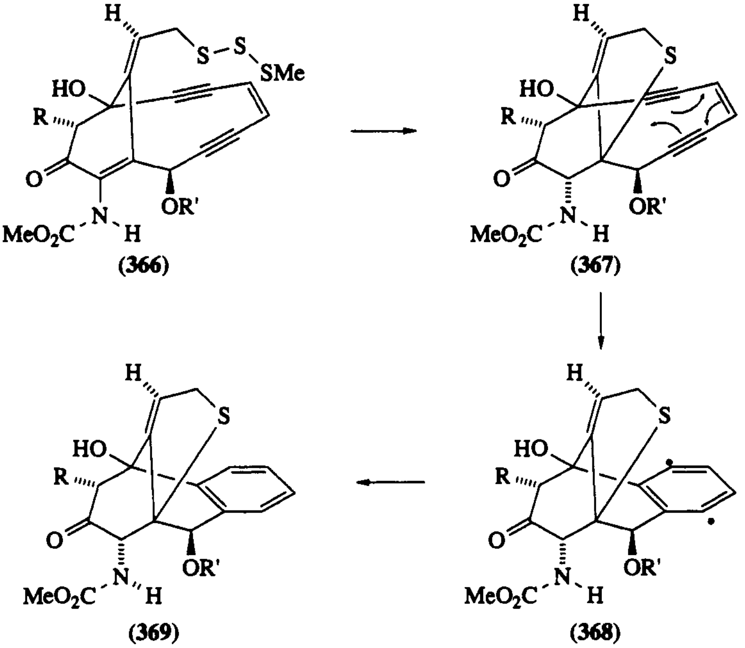

(**366**) (**367**) (**368**) (**369**)

## 6.2.4 MISCELLANEOUS RELATED TOPICS

### 6.2.4.1 Retro Electrocyclizations: Triene Syntheses

The discussion presented earlier (Section 6.2.2.1) revealed that ring opening of a 1,3-cyclohexadiene to a 1,3,5-hexatriene is kinetically sluggish (*e.g.* the automerization of **62**) and thermodynamically disfavored unless other factors such as ring strain intervene (*e.g.* **101**, **102** and related derivatives). The literature on thermal cycloreversions in triene syntheses is sparse, although there are some reports of the involvement of this step as part of a cascade of rearrangements of certain 1,3-cyclohexadienes. For example, a $6e^-$ electrocyclic ring opening has been postulated to take part in the formation of the dihydrosemibullvalene system (**373**).[146] The thermal decarbonylation (~210 °C) of the tetracyclone adduct (**370**) could be viewed as being followed by thermal $6e^-$ electrocyclic ring opening to (**372**) and then intramolecular cycloaddition to afford (**373**). Of course, the transformation of (**371**) to the putative (**372**) is completely analogous to the transformation (**121**) to (**120**) discussed earlier.

By contrast, the retro electrocyclization by photochemical irradiation is well known. For example, the photochemical transformation ($6e^-$ conrotatory ring opening) of provitamin D (**5**) to previtamin D (**3**) and then thermal isomerization (1,7-H shift) of the latter is a well-established sequence leading to vitamin D (**4**). It is a sequence[8] involved in vitamin D biosynthesis and in the laboratory synthesis of vitamin D. Moreover, the process is used commercially.

At low photochemical conversions the reversible transformation to the (*Z*)-hexatriene may dominate. However, the composition of the photostationary state depends upon the substitution pattern of the cyclohexadiene which controls the preferred conformation. It is believed that a planar 1,3-cyclohexadiene produces preferentially a bicyclo[2.2.0]hex-2-ene, *e.g.* molecules of the type (**374**), while dienes with skewed structures form hexatrienes.[37] Another factor that changes dramatically the composition of the photolysis mixture is the wavelength of irradiation.[44a] At 254 nm the photostationary state mixture of *cis*-bicyclo[4.3.0]nona-2,4-diene (**58**) and (*E*,*Z*,*Z*)-1,3,5-cyclononatriene (**59**) is 40% and 60%, respectively. At 300 nm, irreversible formation of tricyclo[4.3.0.$0^{2,5}$]non-3-ene (**374**) becomes the preferred pathway. The ratio of extinction coefficients of (**58**) and (**59**) at the wavelength used would explain the shift in the photoequilibrium mixture.[44a]

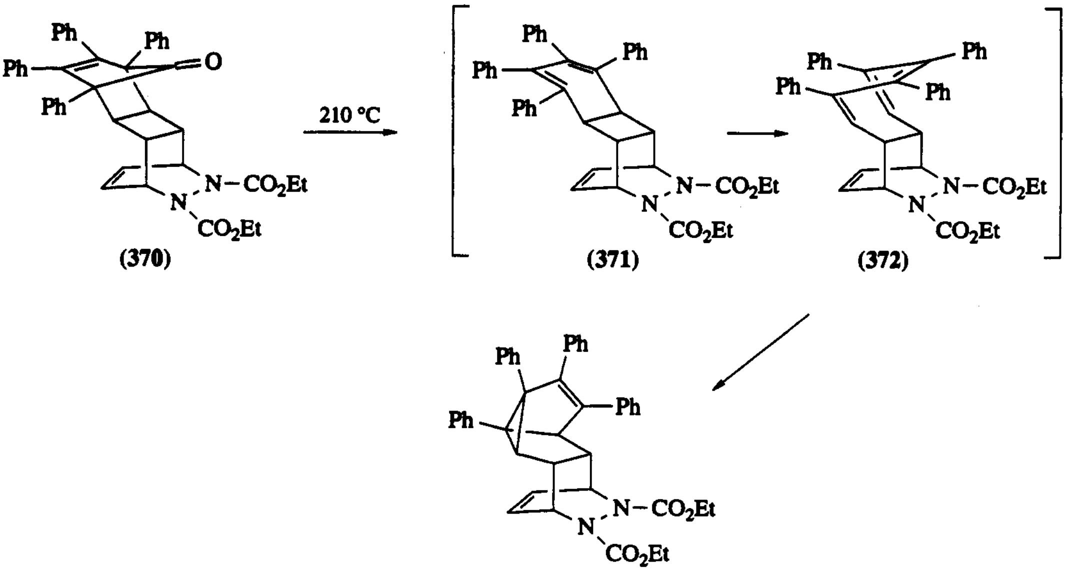

**(370)** **(371)** **(372)** **(373)**

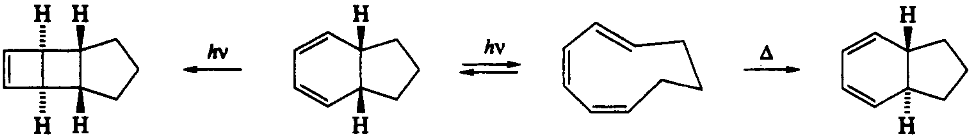

**(374)** **(58)** 40:60 **(59)** **(132)**

An example of a synthetic application in the natural products field concerns the ring opening of diene (**375**) to a *ca.* 1:1 mixture of starting material and triene (**376**), which upon hydrogenation yields dihydrocostunolide (**377**).[147] A synthesis of tetravinylethylene (**379**) was achieved by photoinduced (–78 °C) equilibration of tetraene (**378**) (containing ~4:1 of cyclic to acyclic form).[148]

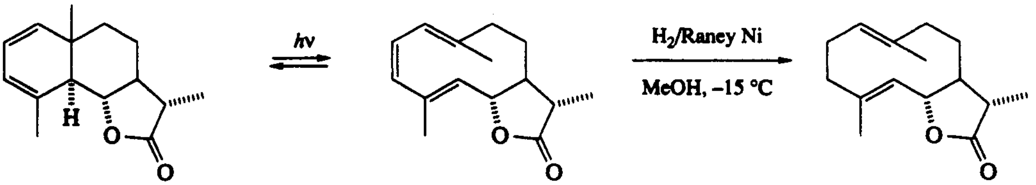

**(375)** 50–55:45–50 **(376)** **(377)**

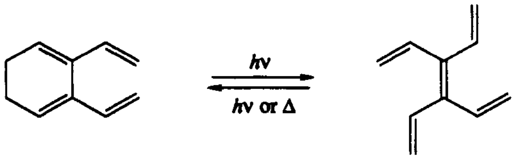

**(378)** **(379)**

A study of the photochemical isomerization of α-phellandrene (**380**)[149] provided a basis for the formulation of the 'accordancy principle' (Section 6.2.2.1). This states that the sense of the photochemically allowed conrotatory ring opening of a 1,3-cyclohexadiene is a function of the chirality of the diene. In the case of α-phellandrene (**380**), the conformer with a pseudoaxial isopropyl group (**380a**) is photoisomerized to the (*Z,Z*)-triene (**381**), while the conformer with a pseudoequatorial isopropyl group (**380b**) is converted to the (*E,Z*)-triene (**382**). Particularly noteworthy was the observed increase in the relative amount of (**382**) with a decrease in temperature, which was attributed to an increase in population of the more stable conformer (**380b**). Prolonged irradiation gave a mixture of isomeric trienes as well as tricyclic compounds.

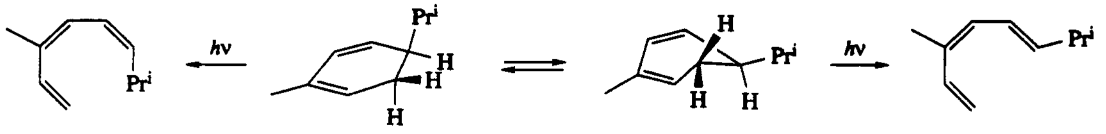

**(381)** **(380a)** **(380b)** **(382)**

The stereospecific conrotatory nature of the photochemically induced ring opening of 1,3-cyclohexadienes has been established.[45b] Thus photochemical ring opening of *cis*-5,6-dimethyl-1,4-diphenyl-1,3-cyclohexadiene (**383**) gave the (*E,Z,Z*)-hexatriene (**384**). Of the two possible products of conrotatory ring opening of the *trans* isomer (**385**) (namely **386** and **387**), the latter was considered to be produced because it underwent a thermally induced 1,7-H shift (also obtained from **384** in the same manner) to the triene (**388**). Similar results have been obtained for the hexalin series.[43,44a]

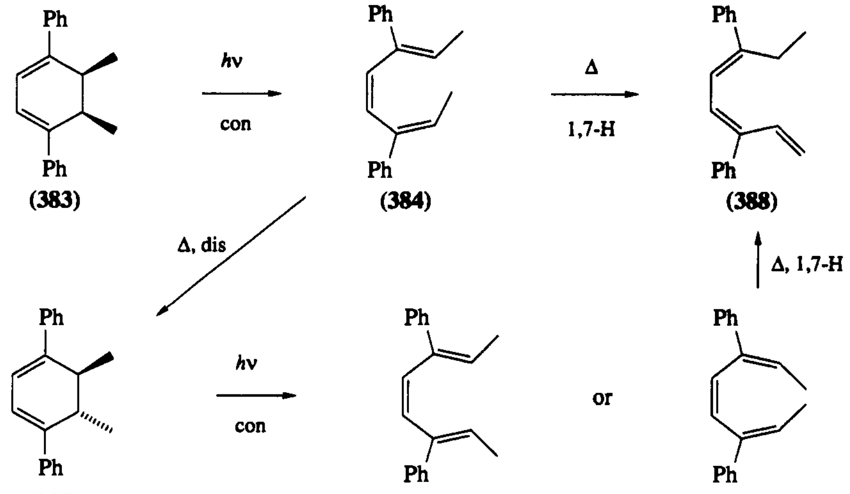

**(383)** **(384)** **(388)** **(385)** **(386)** **(387)**

The role of the ground-state conformations has also been investigated in 9,10-dimethylhexalins and related steroids.[82] The *trans*-hexalin (**389**) gave selectively (*E,Z,E*)-triene (**390**), while *cis*-hexalin (**391**) provided the (*Z,Z,E*)-isomer (**392**) as initial product, in agreement with the conrotatory nature of the reaction. The opposite mode of conrotation for (**389**) resulting in (*Z,Z,Z*)-triene (**393**) was not observed and has been ascribed to a disruption of conjugation by passing through a state where the developing *p*-orbitals would be orthogonal to the diene. Similar results were obtained for related steroids[82] and bicyclo[4.*n*.0]dienes (**21**), (**58**) and (**153**) described earlier.[44]

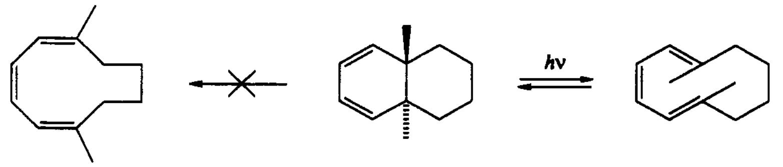

**(393)** **(389)** 46:54 **(390)**

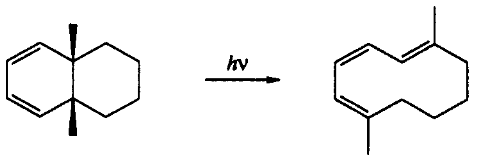

**(391)** **(392)**

Although not isolated, a trienyl-lactone intermediate (**397**) has been assumed to be responsible for the formation of *trans*-1,2-dihydrophthalide (**396**) (together with tricyclic compound **395**) in the photolysis of *cis*-1,2-dihydrophthalide (394). The isolation of intermediate (398) with (*Z,Z,Z*) stereochemistry (resulting from a photochemical double bond isomerization of the putative (397) provides some support for the suggested pathway.[150]

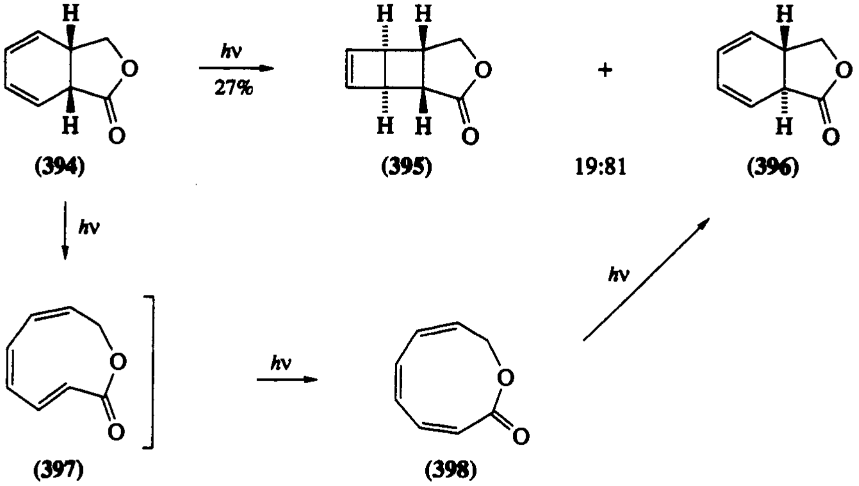

Finally, although sensitized irradiation of cyclohexadienes usually gives dimers, cyclohexadiene (399) gave trienes (401) in a ~1:1 ratio. The products of initial electrocyclic ring opening to the (*E,Z,Z*)-hexatrienes (400) are considered to undergo a 1,5-H shift (including geometric isomerization) to afford the observed isomeric trienes (401).[151]

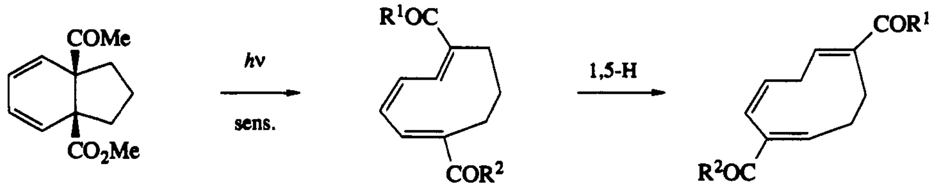

(399) (400) (401)

a: $R^1$ = Me, $R^2$ = OMe

b: $R^1$ = OMe, $R^2$ = Me

### 6.2.4.2 Heterocyclic Applications

As indicated in the Introduction, only a brief survey of hetero electrocyclizations will be presented here. The reader should refer to Marvell's excellent treatise[3a] or other sources[152] for leading references. However, there are several unique features of the heterocyclization process that are worth considering in this limited survey. In particular, when the heteroatom is placed at the end of the triene system, cyclizations often prove to be exceedingly facile. To focus on this feature of the reaction substrate, the following discussion will be restricted to electrocyclizations in which the heteroatom (oxygen and nitrogen since they are the most common) is located at the end of the triene.

The replacement of a carbon atom in (402a) by a heteroatom such as oxygen or nitrogen (402b,c) leads normally to an increase of the reaction rate of the electrocyclization.[3a] Steric effects probably play a major role in the observed rate enhancement although stereoelectronic and polar factors may also be important factors. Regarding steric effects, when the terminal $sp^2$ carbon is replaced by a heteroatom, one (nitrogen) or both (oxygen) of the terminal hydrogen atoms is replaced by a 'smaller' heteroatom lone pair. In point of fact, replacement of the two inside hydrogen atoms by deuterium in the parent system (1) as in (404a) reveals a slight acceleration in rate.[14] Thus cyclization of (404b) exhibits the expected normal secondary kinetic isotope effect for $sp^2$ to $sp^3$ rehybridization upon thermal disrotatory cyclization. In the case of (404a), disrotatory electrocyclization occurs with an inverse secondary kinetic isotope effect, wherein the steric isotope effect overrides the small, normal ($sp^2$ to $sp^3$ rehybridization) isotope effect.[14] The exceptionally rapid cyclization of dienylallenes (45) to (46) plus (47), (345) to (346), (348) to (349) and (352) to (353) is also probably due to the attenuation of steric factors (one of the terminal $sp^2$ carbon as in 402a is replaced by the $sp$ carbon of the allene).[35a,138] The stereoelectronic factor refers to the direct participation of the heteroatom lone pair in the cyclization. These types of transformations in which bonding and non-bonding atomic orbitals interchange roles have been defined as 'pseudopericyclic reactions'.[153]

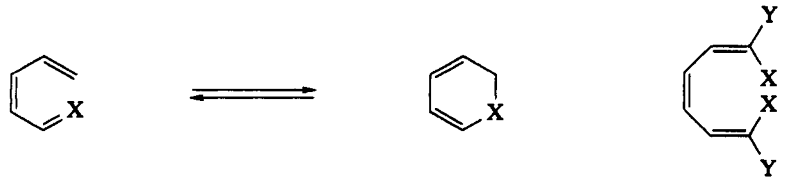

**(402)** a: X = $CR_2$; b: X = O; c: X = NR **(403)**

**(404a)** X = D, Y = H
**(404b)** X = H, Y = D

An early example of the reversible interconversion of dienones to α-pyrans was first observed for the α-pyran (**407**) obtained upon irradiation of β-ionone (**405**).[3a,154] In certain systems this reversibility is responsible for the (*Z*)–(*E*) isomerization of the terminal double bond of α,β-(*Z*)-isomers of 2,4-dienals and 2,4-dienones.[155]

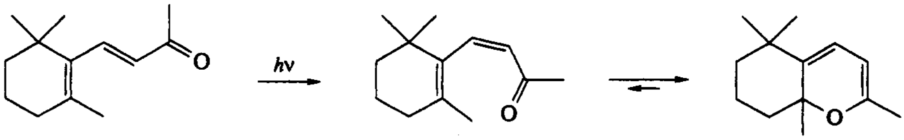

**(405)** **(406)** **(407)**

Conversion of (**408**) to chromone (**409**) is photochemically reversible and thus the system is photochromic.[156] Recently,[157] electrocyclic ring opening of benzocyclobutenes in tandem with a hetero electrocyclic ring closure is reported to provide a new route to isochromanones. Thus benzocyclobutene (**410**) upon thermolysis experiences ring opening to the *o*-quinodimethane (**411**) followed by electrocyclic ring closure and then ketonization to afford the isochromanone (**413**). The scheme can be further combined in tandem with other pericyclic processes (*e.g.* 3,3-sigmatropic reactions), providing a new methodology for the synthesis of natural products.[157c,d]

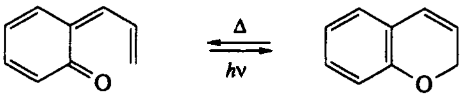

**(408)** **(409)**

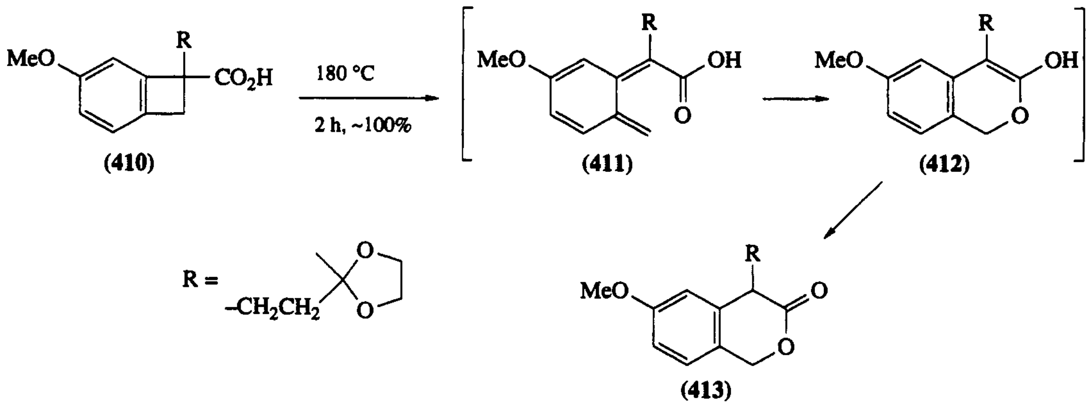

**(410)** **(411)** **(412)**

**(413)**

The electrocyclic ring closure of 1-azatrienes to 1,2-dihydropyridines is a favorable process.[3a] The possibility of stereoisomerism at the nitrogen atom in certain derivatives (oximes and their benzoates) provides an important argument in favor of the steric and/or stereoelectronic factors discussed above for the observed rapid rate of cyclization. While the (*E,Z,E*)-isomer (**414**) yielded cyclic products derived from (**415**) at 50 °C, the (*Z,Z,E*)-isomer (**416**) required 150 °C to afford the same product.[158]

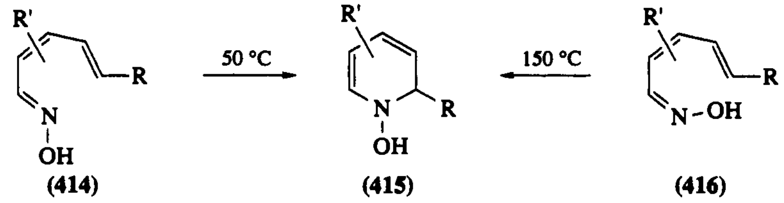
R'
R
N
OH
50 °C
R'
N
R
OH
150 °C
R'
R
N-OH
(414)
(415)
(416)

Recent examples of the hetero cyclization process include the conversion of azadiene (**417**) to dihydropyridine (**419**)[159a] and the Schiff base of 13-*t*-butyl-13-*cis*-retinal (**420**) into the dihydropyridine (**421**).[159b,c]

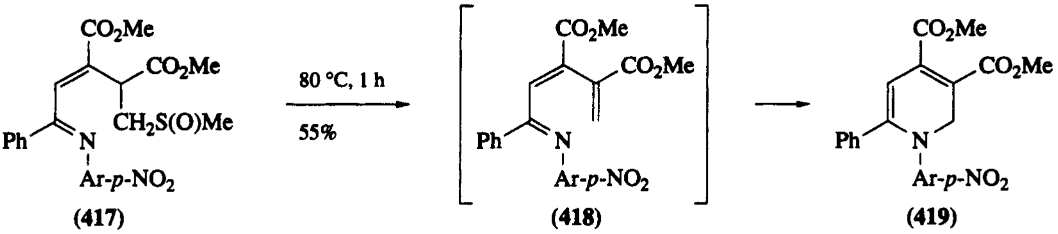
CO2Me
CO2Me
CH2S(O)Me
Ph
N
Ar-p-NO2
(417)
80 °C, 1 h
55%
CO2Me
CO2Me
Ph
N
Ar-p-NO2
(418)
CO2Me
CO2Me
Ph
N
Ar-p-NO2
(419)

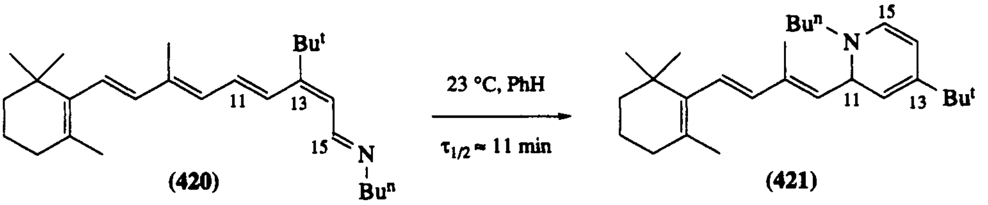
Bu^t
11
13
15
N
Bu^n
(420)
23 °C, PhH
τ1/2 ≈ 11 min
Bu^n
15
N
11
13
Bu^t
(421)

Other related reactions have led to complex aromatic systems, including pyridines or fused analogues (quinolines). Thus the transformation of (**422**),[160] (**424**),[161] and (**427**)[162] to (**423**), (**426**) and (**429**) exemplify the utility of the method.

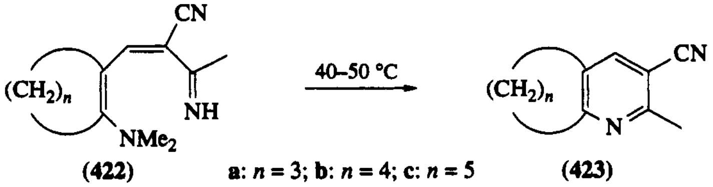
CN
(CH2)n
NH
NMe2
(422)
40–50 °C
a: n = 3; b: n = 4; c: n = 5
CN
(CH2)n
N
(423)

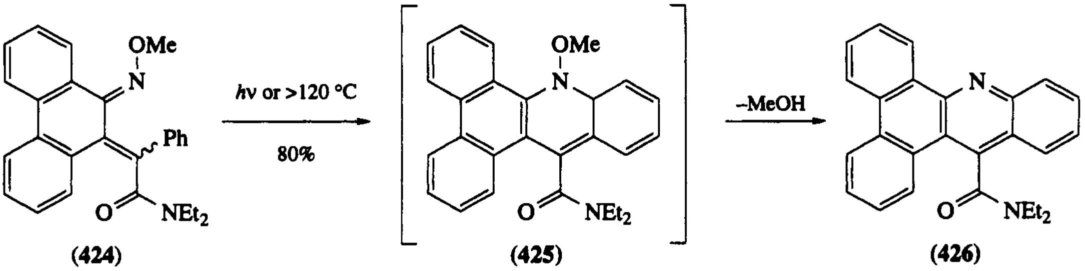
OMe
N
Ph
O
NEt2
(424)
hν or >120 °C
80%
OMe
N
O
NEt2
(425)
-MeOH
N
O
NEt2
(426)

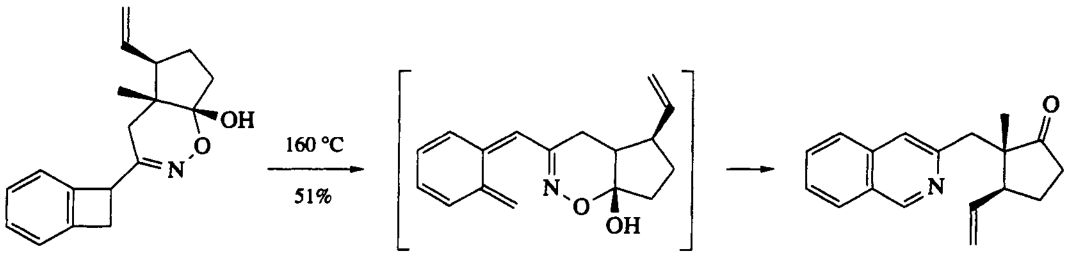

(427) (428) (429)

### 6.2.4.3 Higher-order Electrocyclic Processes

This final section will consist of a brief survey of the electrocyclization of systems with more than 6 electrons, which are not explicitly treated in this series with special emphasis on 8-electron systems. The excellent book published in 1980 by Marvell[3a] is therefore an obligatory reference here.

There are abundant examples in the literature which reveal that the thermal electrocyclization of 8e⁻ systems to form eight-membered rings proceeds with lower activation energies than for the lower vinylog, (*Z*)-hexatrienes. The helical geometry of the transition state leads to less steric congestion about the reacting termini of the octatetraene and this likely accounts for the facility of the thermal 8e⁻ conrotatory process. Minor structural differences can induce cycloreversion of the process.[3a]

The predicted[1] conrotatory nature of this electrocyclization has been definitively established.[163] The conrotatory mode was found to operate in the individual thermal electrocyclization of the stereoisomeric decatetraenes (**430**), (**431**) and (**432**). The former pair (**430** and **431**) afforded the *trans*-cyclooctatriene (**433**), while the latter (**432**) led to the *cis*-cyclooctatriene (**434**). Both cyclooctatrienes (**433**) and (**434**) were observed to be in equilibrium with the corresponding 6e⁻ electrocyclized derivatives (**435**) and (**436**), respectively.

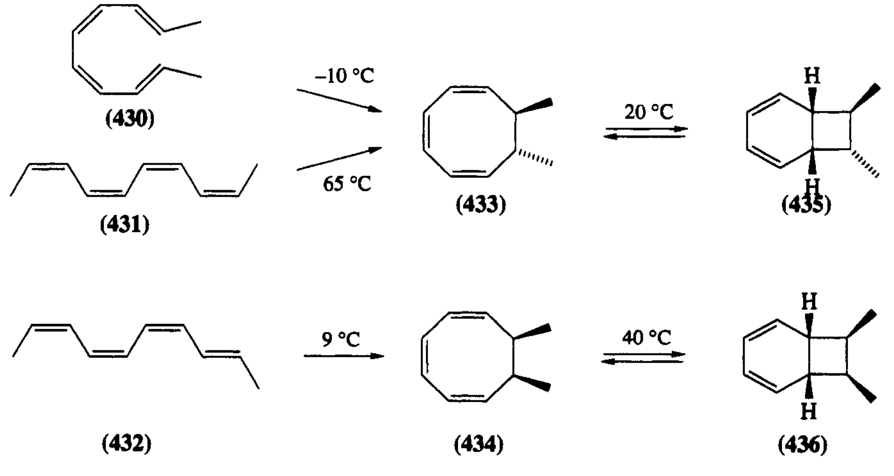

(430) (431) (433) (435) (432) (434) (436)

An elegant exploitation of the general understanding of pericyclic processes is reflected in the synthesis of the endiandric acids A–G, which was accomplished both in a stepwise and in a one-pot 'cascade' form.[164] In the latter case, generation (by catalytic hydrogenation) of the suitable polyunsaturated methyl ester progenitor (**437**) afforded the endiandric acids D and E methyl esters (**445**) and (**446**) at room temperature. The cyclooctatrienes (**441**) and (**442**), resulting from the initial 8e⁻ conrotatory process, could not be isolated and were found to cyclize to (**445**) and (**446**) resulting from a further 6e⁻ electrocyclization. Brief heating of the mixture at 100 °C afforded the endiandric acid A methyl ester (**449**), presumably the intramolecular Diels–Alder adduct of (**446**). The overall process represents the stereospecific formation of four new rings and eight chiral centers in a single operation from an achiral open-chain precursor. Similar experiments on the tetraene (**439**) gave, upon heating, a 4.5:1 mixture of endiandric acids F and G methyl esters, (**447**) and (**448**). Brief thermolysis of the mixture at 100 °C led to the isolation of endiandric acids B and C methyl esters (**450**) and (**451**) whose formation can be viewed as following a similar sequence as described before. In this case the process encompasses the transformation of an achiral precursor into two different skeletal arrangements with the concomitant formation of four cycles and eight asymmetric centers. The powerful predictive value of the WH rules serves in this case to resolve the seemingly anomalous finding of racemic natural products with eight asymmetric centers and points to the possibility of biogenesis without enzymatic intervention.[164]

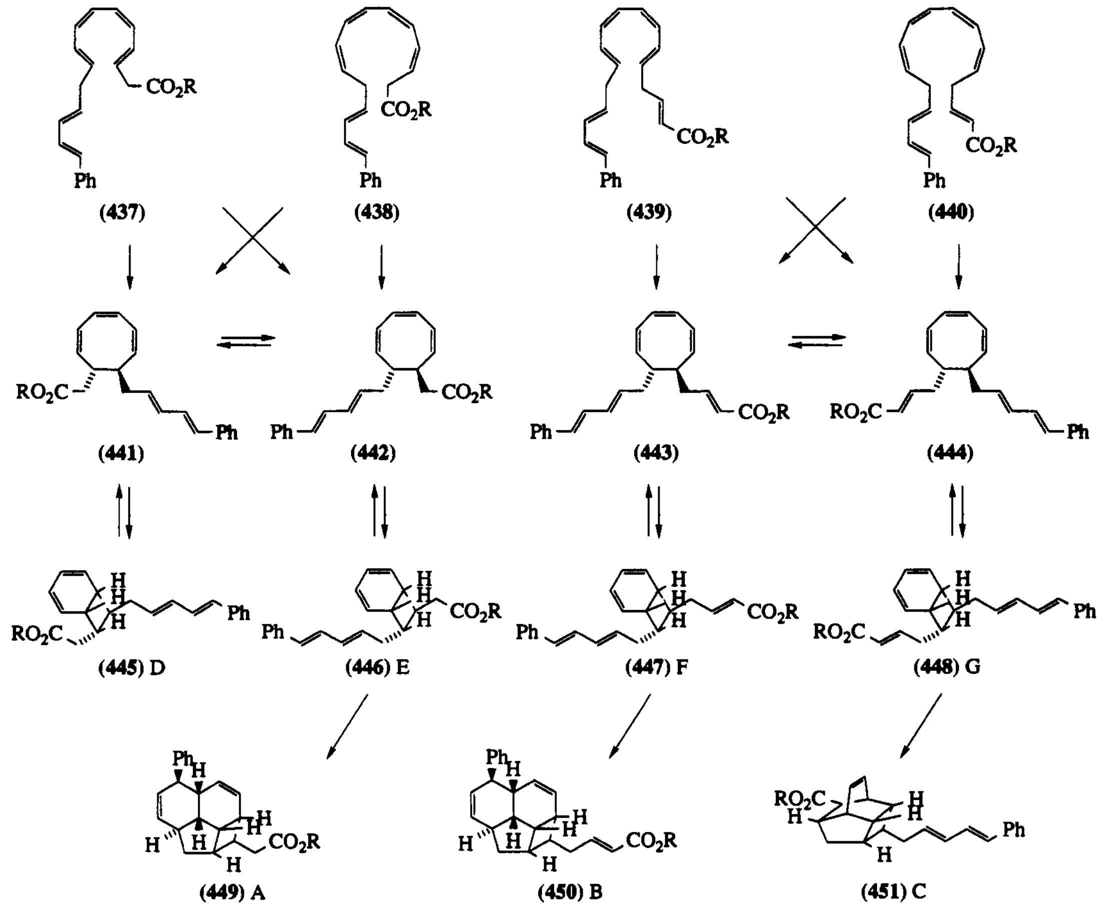

The stereochemistry of a thermally induced 10e$^-$ electrocyclization (predicted to be disrotatory) has not been firmly established and the main synthetic application is found in the formation of azulenes and ring-fused azulenes as in the transformation (**452**) to (**453**).[165] Thermolysis of (**454**) with spontaneous elimination of dimethylamine from intermediate (**455**) afforded the fused azulene structure (**456**).[56] The chemistry of even higher order (12e$^-$ to 20e$^-$) pericyclic processes has been recently reviewed.[166] An example of an unusual sequence of pericyclic processes is the transformation of heptahendecafulvadiene (**457**) to the pentacyclic hydrocarbons (**462**) and (**463**) in a 2:1 ratio. The pathway for this transformation can be viewed as an initial conrotatory 20e$^-$ electrocyclization followed by a cascade of 10e$^-$ and 6e$^-$ pericyclic processes.[167]

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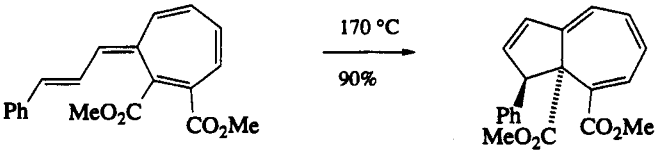

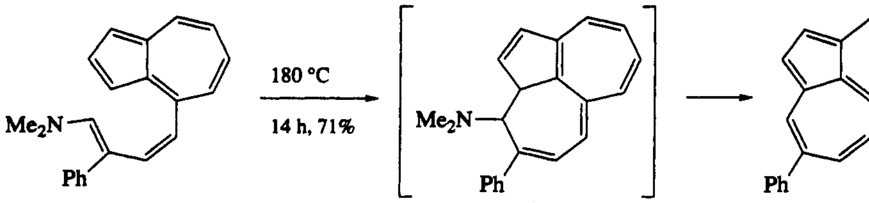

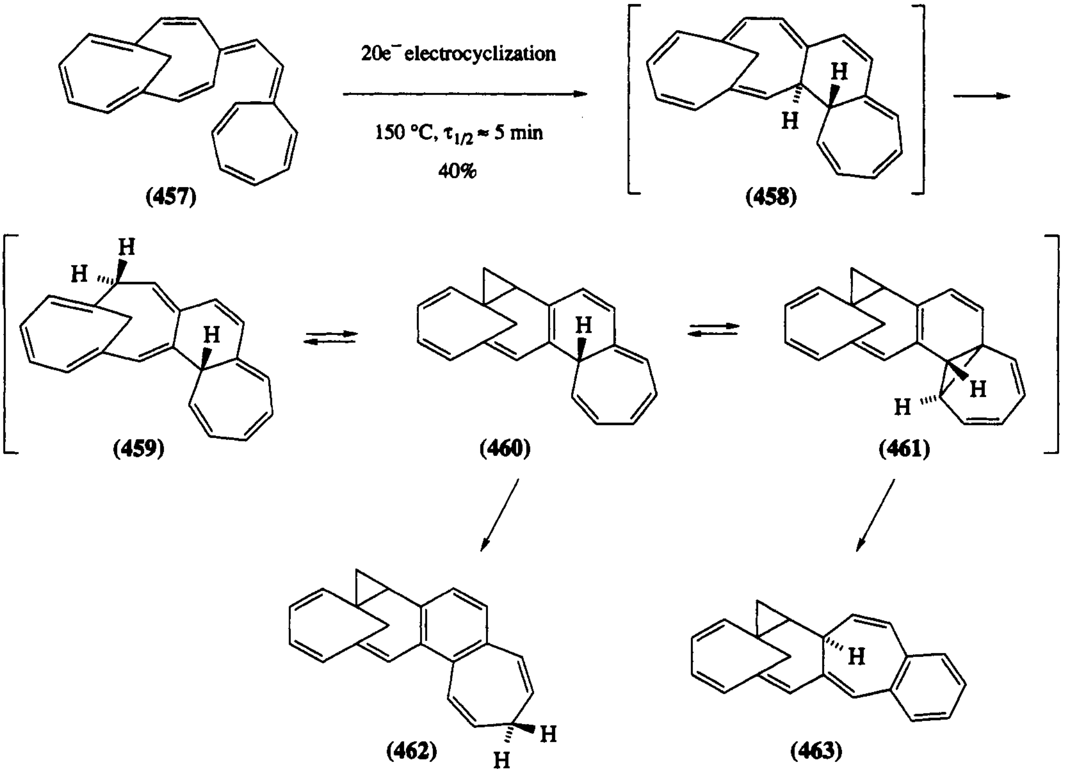

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# 6.3

# Nazarov and Related Cationic Cyclizations

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## 6.3.1 INTRODUCTION

### 6.3.1.1 Historical Background

During the 1940s and 1950s Nazarov and his coworkers extensively studied the formation of allyl vinyl ketones by hydration of dienynes and their subsequent acid-catalyzed closure to 2-cyclopentenones (Scheme 1).[1–38] The reaction was notable as one of the first general methods for the selective construction of isolated and, more importantly, ring-fused cyclopentenones. In many instances the dienynes could be transformed directly to cyclopentenones without isolation of intermediates.

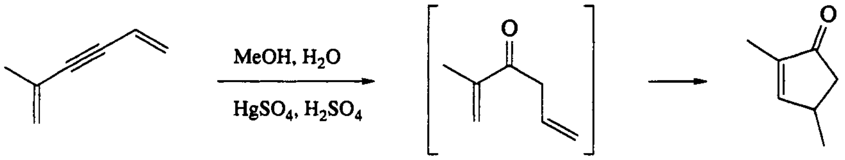

Scheme 1

The acid-catalyzed hydration cyclization of dienynes predates Nazarov. It was first reported and thoroughly examined by Marvel between 1933 and 1939.[39–45] While Marvel correctly proposed the intermediacy of allyl vinyl ketones, he formulated the cyclization products as 3-cyclohexen-1-ones. The structural assignment of many of these products was subsequently challenged.[46,47]

Ironically, until 1953, Nazarov incorrectly described the mechanism of the general transformation which now bears his name. In 1952, Braude and Coles[48] were the first to suggest the intermediacy of carbocations and demonstrated that the formation of 2-cyclopentenones actually proceeds *via* the α,α′-divinyl ketones (equation 1). This fact together with further mechanistic clarification, has led to the specific definition of the Nazarov cyclization as the acid-catalyzed closure of divinyl ketones to 2-cyclopentenones. This process was already documented in 1903 by Vorländer[49] who isolated a ketol of unknown structure by treatment of dibenzylideneacetone with concentrated sulfuric acid and acetic acid followed by mild alkaline hydrolysis (equation 2). The correct structure of Vorländer's ketol, finally proposed in 1955,[50] arises from Nazarov cyclization followed by oxidation and isomerization. Other examples of acid-catalyzed cyclizations of divinyl ketones exist in the early literature.[51,52]

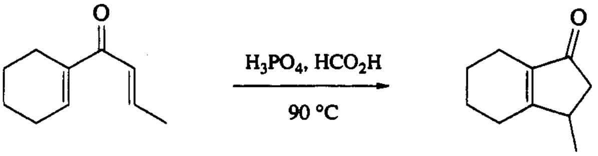

(1)

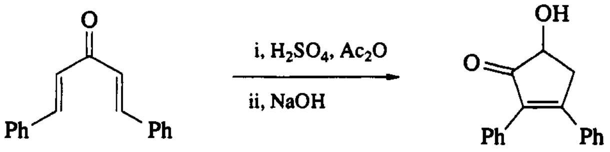

(2)

Shoppee[53] has clarified an early report by Japp and Maitland[54] on the formation of a cyclopentenone by treatment of either divinyl ketone or tetrahydropyrone with ethanolic hydrochloric acid (Scheme 2). This case illustrates a broader definition of the Nazarov cyclization that includes a wide variety of precursors.

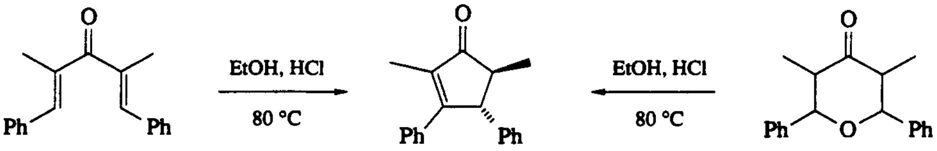

Scheme 2

Most of the variants of the Nazarov cyclization are operational equivalents in that they involve starting materials which are transformed into divinyl ketones under conditions which also induce subsequent closure to 2-cyclopentenones. Thus, the identification of divinyl ketones as key intermediates by Braude and Coles was critical in several ways for the development of the Nazarov cyclization in suggesting the use of precursors other than dienynes. A case in point is the 1953 report by Raphael[55] on the use of a propargyl amine as the divinyl ketone precursor (Scheme 3). A second important, although somewhat later advance was the recognition that Lewis acids can effectively induce the cyclization of divinyl ketones, an improvement over the classical reagent, 90% phosphoric acid.

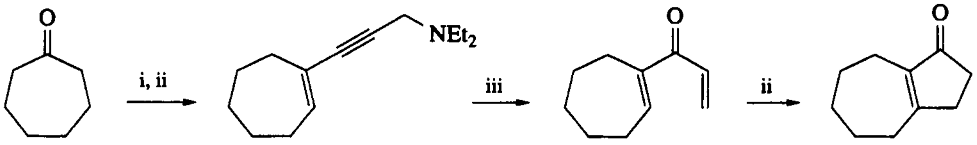

i, Li–C≡CCH$_2$NEt$_2$; ii, H$_3$PO$_4$, HCO$_2$H; iii, Hg(OAc)$_2$, H$_2$SO$_4$

Scheme 3

A third and critical advance in the development of the Nazarov cyclization was the demonstration that it belongs to the general class of cationic electrocyclic reactions (Scheme 4). This broadened its definition to include reactions which involve pentadienylic cations or equivalents and thus expanded the range of precursors for cyclopentenones. Further, the stereochemical features of electrocyclization enhanced the utility of the reaction and, in addition, stimulated the development of a photochemical variant.

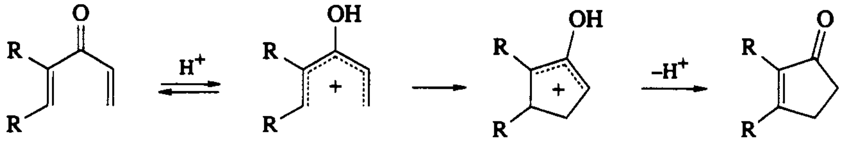

Scheme 4

### 6.3.1.2 Organization and Scope

It is the structural variety of the precursors which lends versatility to the Nazarov cyclization and which also serves as the organizational framework for this chapter. To facilitate presentation the reaction is divided into five categories: (i) (Lewis) acid-promoted and photochemical cyclization of divinyl and allyl vinyl ketones; (ii) silicon- and tin-directed Nazarov cyclizations of divinyl ketones; (iii) *in situ* generation/cyclization of divinyl ketones; (iv) solvolysis to produce divinyl ketone equivalents; (v) coupling reactions to form and cyclize divinyl ketones. The logic of this sequence follows from the order of decreasing structural similarity of the precursors to divinyl ketones. The last three subgroups encompass considerable structural diversity which will be discussed in each section.

The coverage is intended to be comprehensive in the presentation of structural variation in precursors. Within each category the issues of scope, limitations and, where appropriate, stereochemistry will be addressed with representative examples. The Nazarov cyclization was most recently reviewed in 1983.[56] Prior to that the reaction had been reviewed in the context of pentannulation.[57,58] The related electrocyclic closure of the less oxidized pentadienylic cations is discussed where mechanistically relevant. Extensive discussion of the chemistry of these species is available.[59]

## 6.3.2 MECHANISM AND STEREOCHEMISTRY

### 6.3.2.1 Mechanism and Stereospecificity

The first modern thinking about the mechanism of the Nazarov cyclization is due to Braude and Coles,[48] who suggested the intermediacy of a β-keto carbocation from either divinyl or allyl vinyl ketones. The ring is formed by intramolecular attack on the enone with concomitant generation of an α-keto carbocation. Loss of a β-proton from this intermediate affords the product. Nazarov[32,35,36] himself provided support for this proposal by demonstrating the incorporation of deuterium from $D_3PO_4$ in different positions from divinyl or allyl vinyl ketones.

It is now well established that the Nazarov cyclization is a pericyclic reaction belonging to the class of electrocyclizations. As with all pericyclic reactions, mechanism and stereochemistry are inexorably coupled and any discussion of one feature must invoke the other. In this section the stereospecific[60] aspects of the Nazarov cyclization are discussed, the stereoselective[60] aspects of the reaction are dealt with individually in each of the following sections.

The Nazarov cyclization is an example of a 4π-electrocyclic closure of a pentadienylic cation. The evidence in support of this idea is primarily stereochemical. The basic tenets of the theory of electrocyclic reactions[61] make very clear predictions about the relative configuration of the substituents on the newly formed bond of the five-membered ring. Because the formation of a cyclopentenone often destroys one of the newly created centers, special substrates must be constructed to allow this relationship to be preserved. Prior to the enunciation of the theory of conservation of orbital symmetry, Deno[62] and Sorensen[63–66] had observed the facile thermal cyclization of pentadienylic cations and subsequent rearrangements of the resulting cyclopentenyl cations. Unfortunately, these secondary rearrangements thwarted early attempts to verify the stereochemical predictions of orbital symmetry control. Subsequent studies with the pentamethyl derivative were successful.[67,68] The most convincing evidence for a pericyclic mechanism came from Woodward, Lehr and Kurland,[69] who documented the complementary rotatory pathways for the thermal (conrotatory) and photochemical (disrotatory) cyclizations, precisely as predicted by the conservation of orbital symmetry (Scheme 5).

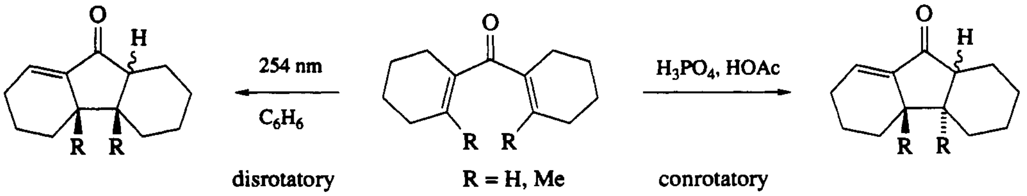

**Scheme 5**

Additional confirmation came from Shoppee who reinvestigated Vorländer's very early work on the thermal cyclization of dibenzylideneacetone[70] and dibenzylidene-3-pentanone[53] in the presence of acid. Careful experimentation revealed the conrotatory electrocyclic pathway for both of these substrates (Scheme 6).

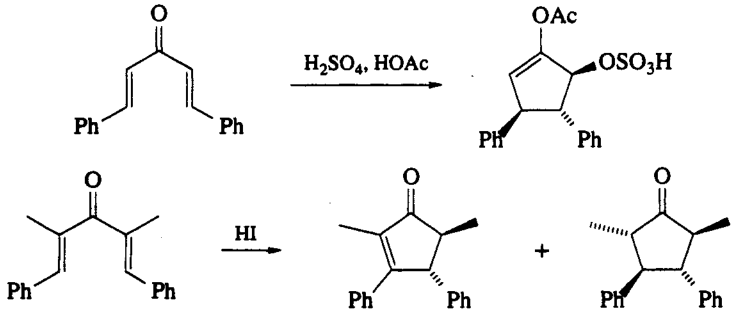

**Scheme 6**

The Woodward–Hoffman rules also predict that in a given cyclization mode a permutation of alkene geometry must be reflected in the configuration of the products. This test is precluded under the normal reaction conditions (acid, light) which would isomerize the dienone double bonds. However, Corey recently reported the formation of a *cis*-disubstituted cyclopentenone from a (*Z,E*)-precursor, derived from an allene oxide, which cyclizes *via* the 2-oxido pentadienylic cation (Section 6.3.8).[71]

The predicted photochemical disrotatory closure of protonated divinyl ketones has been documented in several laboratories, most notably by Nozaki,[72] Noyori,[73] and Cerfontain[74] (equation 3). The stereochemical outcome in these reactions was discernible due to secondary processes which preserved the sense of electrocyclization.

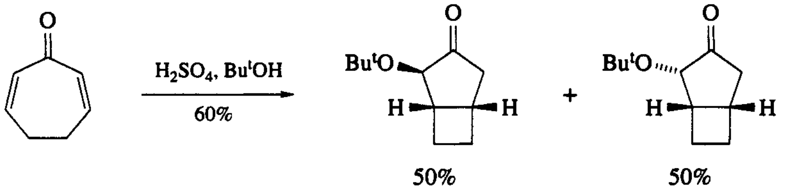

(3)

The cationic electrocyclization mechanism also allows predictions of substituent effects. In the rate-determining electrocyclization event, the distribution of positive charge changes as indicated by the asterisks in equation (4). Thus, the effect of substituents which stabilize positive charge should be to either accelerate (α-position) or decelerate (β-position) depending upon location. Further, α-substitution should be greater in magnitude since the charge is less delocalized.

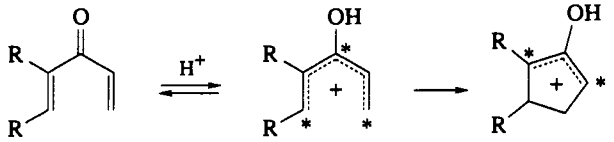

(4)

### 6.3.2.2 Relative Stereogenesis

Beyond the disrotatory or conrotatory stereochemical imperative which must accompany all Nazarov cyclizations there exists a secondary stereochemical feature. This feature arises because of the duality of allowed electrocyclization pathways. When the divinyl ketone is chiral the two pathways lead to diastereomers. The nature of the relationship between the newly created centers and preexisting centers depends upon the location of the cyclopentenone double bond. The placement of this double bond is established after the electrocyclization by proton loss from the cyclopentenyl cation (equation 5). Loss of $H^a$, $H^b$ or $H^c$ in this instance generates three tautomeric products. The lack of control in this event is a drawback of the classical cyclization. Normally, the double bond occupies the most substituted position corresponding to a Saytzeff process. The issue of stereoselection with chiral divinyl ketones is illustrated in Scheme 7. The sense of rotation is defined by clockwise (*R*) or counterclockwise (*S*) viewing down the C—O bond. Thus, depending on the placement of the double bond, the newly created center may be proximal or distal to the preexisting center. If $R^1$ = H the double bond must reside in a less substituted environment to establish stereoselectivity.

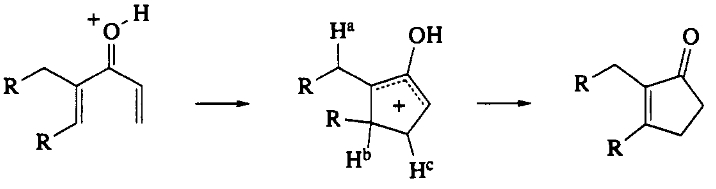

(5)

## 6.3.3 CYCLIZATION OF DIVINYL AND ALLYL VINYL KETONES

The original substrates studied by Nazarov were allyl vinyl ketones. These materials could be obtained easily by mercury(II) ion assisted hydrolysis of dienynes, themselves available from dehydration of vinyl

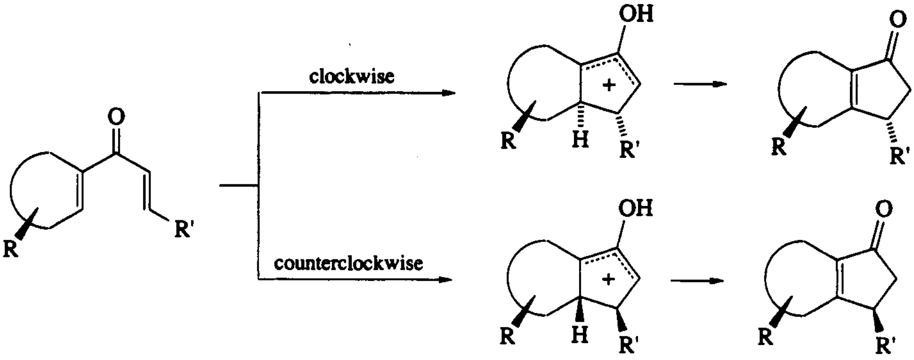

Scheme 7

acetylide adducts of ketones (Scheme 8). This approach allows incorporation of many substitution patterns.

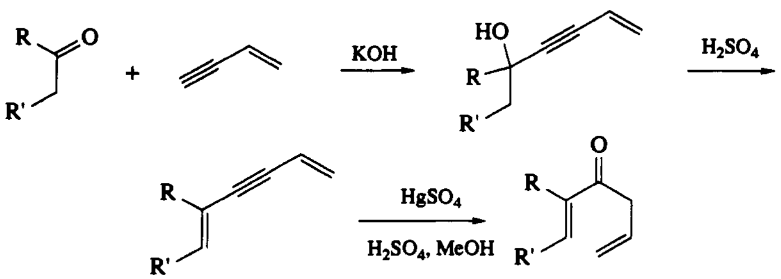

Scheme 8

Following the suggestion of Braude and Coles,[48] Nazarov established the role of the tautomeric divinyl ketones as the true precursors of cyclization. By conducting the cyclization of the allyl vinyl ketone (**1**) in $D_3PO_4$ it was established that one deuterium is introduced into the cyclic product (**2**; Scheme 9).[35] Direct cyclization of the divinyl ketone (**3**) with $D_3PO_4$ gave identical results.[36]

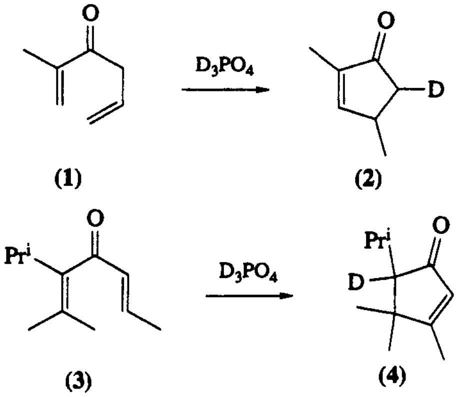

Scheme 9

Thus, in the following section the two different precursors are considered as equivalent and the organization follows structural patterns. In many other variants of the Nazarov cyclization, divinyl ketones are implicit intermediates formed from other precursors. In this section only those cases where a divinyl or allyl vinyl ketone was directly cyclized will be discussed.

### 6.3.3.1 Acyclic Precursors

The Nazarov cyclization is well suited for the construction of simple cyclopentenones adorned with various substitution patterns. A collection of representative structures prepared from either allyl vinyl or divinyl ketones is shown in Scheme 10. Many different alkyl groups are compatible with the substitution patterns. Aromatic substituents, especially at the α-position, have a beneficial effect on the reaction rate and yield. In all of those cases where a choice is possible, the double bond resides in the thermodynamically most stable position.

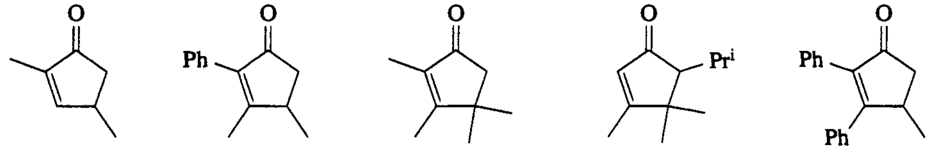

75% (ref. 20) 95% (ref. 17) 60% (ref. 18) 81% (ref. 27) 95% (ref. 30)

Scheme 10

### 6.3.3.2 Monocyclic Precursors

A useful feature of the Nazarov cyclization is the construction of fused bicyclic systems by annulation of a five-membered ring.[57] This requires one of the vinyl groups to be embedded in a ring. These precursors can be formed easily by vinyl alkyne addition to cyclic ketones followed by dehydration and hydrolysis. This procedure works well for symmetrical ketones but it gives regioisomers from unsymmetrical ketones such as 1- or 2-octalone.[11,22] A superior method, reported by Paquette,[75,76] involves the acylation of cycloalkenylsilanes to provide divinyl ketones (equation 6). The advantages of this protocol are discussed in Section 6.3.7.4.3.

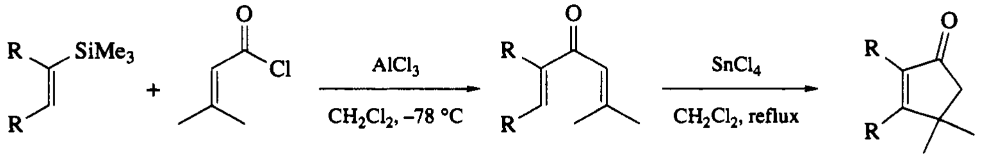

(6)

The preexisting ring may vary in size from 5 up to 12 members. In general the annulation yields are lowest with five-membered rings. A representative sampling of structural types is collected in Scheme 11. The stability of esters under the cyclization conditions is noteworthy.[79]

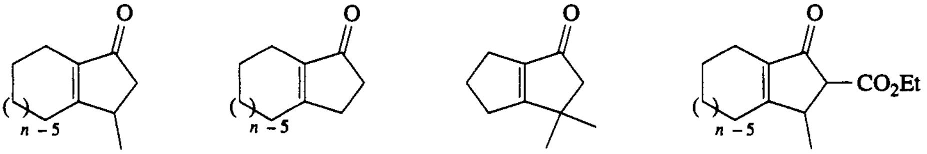

$n = 5$, 32% (ref. 75)
$n = 6$, 70% (ref. 7)
$n = 7$, 75% (ref. 77)
$n = 12$, 66% (ref. 75)

$n = 6$, 50% (ref. 48)
$n = 7$, 60% (ref. 77)

62% (ref. 78)

$n = 5$, 30% (ref. 79)
$n = 6$, 48% (ref. 79)
$n = 7$, 35% (ref. 79)

Scheme 11

The intervention of secondary cationic processes has been demonstrated in these systems by Ohloff (equation 7).[80] While cyclization of (**5**) proceeds normally, to (**6**), with $H_3PO_4$, *p*-toluenesulfonic acid gives products of Wagner–Meerwein rearrangement (**7**) or intramolecular acylation (**8**).

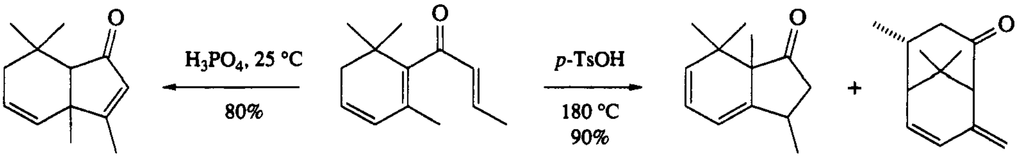

(**6**) (**5**) (**7**) (**8**)

(7)

The monocyclic substrates are well suited for discussion of relative stereocontrol. In a recently reported study employing *cis*- and *trans*-disubstituted substrates (**9**) and (**10**), high stereoselectivity could be obtained when gallium trichloride was used as the Lewis acid (Scheme 12).[81] In these reactions new stereocenters can be created at C(3) and C(3a). In the *cis* series both tautomeric products were formed as single stereoisomers while the *trans* series (**10**) produced a mixture of the tetrasubstituted isomers. A *post facto* epimerization was suggested as the cause for the lower selectivity. Discussion of the rotational sense is not warranted here as the configurations of the newly created centers were not rigorously established.

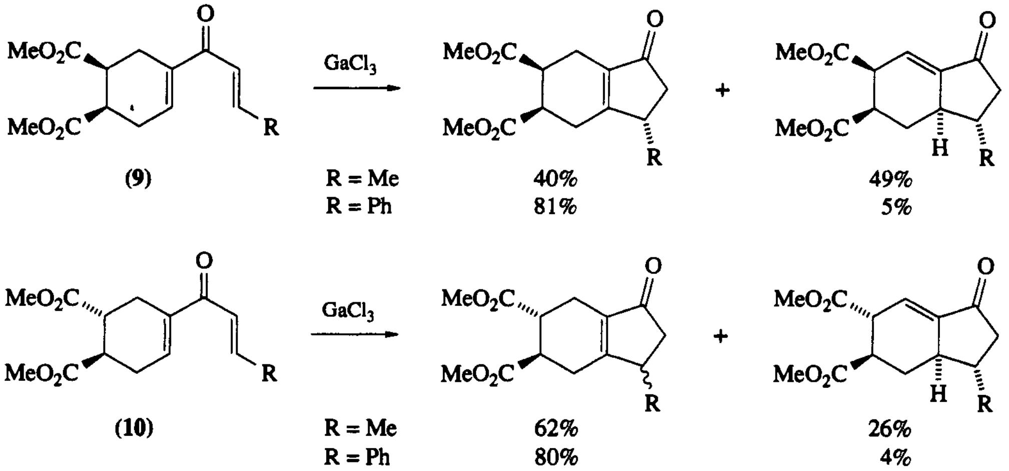

**Scheme 12**

### 6.3.3.3 Biscyclic Precursors

When both vinyl groups of a divinyl ketone are embedded in rings, a linearly fused tricyclic array results from cyclization. Five-,[82] six-[83] and seven-membered[83] rings have been employed in various combinations. In general, the product double bond occupies a ring fusion position. Structures of representative products are collected in Scheme 13. In the classic Woodward–Lehr cyclization (equation 8), the reaction conditions could be modified to allow formation of a significant quantity of the trisubstituted alkene thus permitting the establishment of a conrotatory pathway in the ground state.[69,84] The related substrate bearing two β-methyl groups gave rise to a single trisubstituted ketone possessing the *anti* arrangement of methyl groups.[85] Harding has made good use of the vicinal relationship of these quaternary centers in a synthesis of (±)-trichodiene (equation 9).[86]

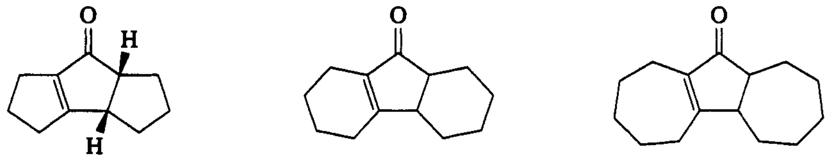

62% (ref. 82) 29% (ref. 48) 50% (ref. 83)

**Scheme 13**

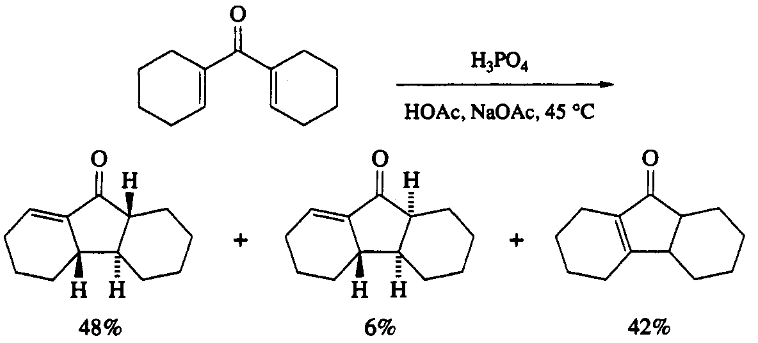

(8)

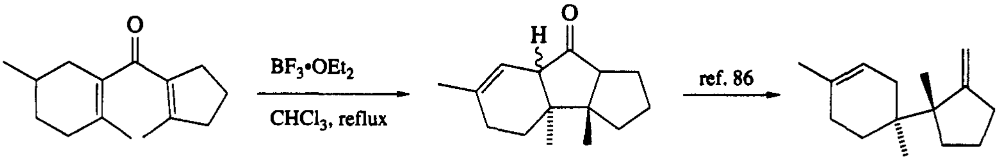

(9)

Mehta has examined relative stereocontrol in an approach to the carbocyclic nucleus of ophiobolins.[87] Cyclization of the triquinane (**11**) gave two products, (**12**) and (**13**), in a 4:1 ratio (Scheme 14). These products arise from opposite rotatory pathways as shown. Surprisingly, the major product arises from conrotation to the concave face of the diquinane unit. Finally, Nazarov has provided an interesting example of both fused and spiro mode annulations in equation (10).[26]

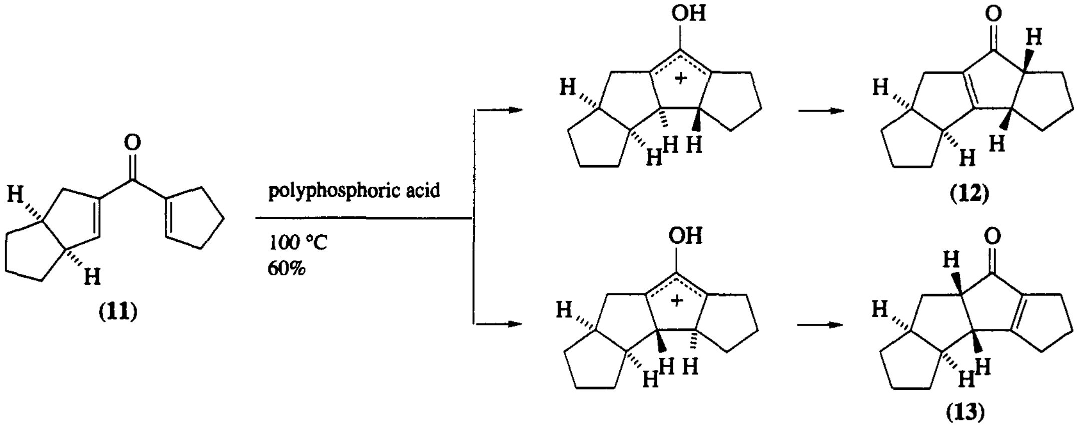

Scheme 14

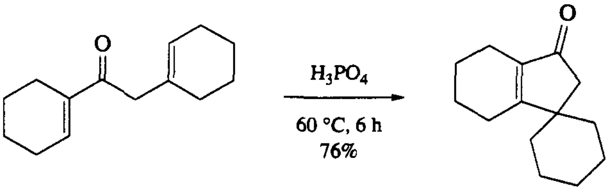

(10)

## 6.3.3.4 Aromatic Precursors

Under sufficiently vigorous conditions a benzene ring can be induced to participate in the Nazarov cyclization with both six-[88] and seven-membered[77] rings (equation 11).

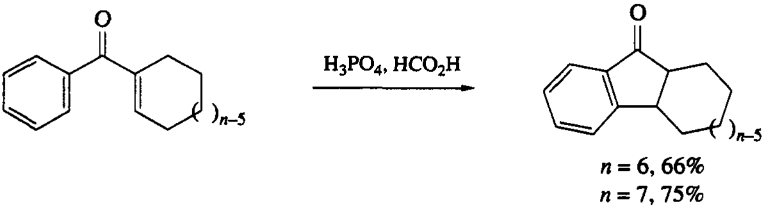

(11)

## 6.3.3.5 Anomalous Cyclizations

Considering the manifold reaction pathways available for carbocations it is not surprising that unexpected products have been isolated. Capture of the intermediate cyclopentenyl cation by nucleophiles was first shown by Shoppee (Scheme 6).[70] This pathway can become dominant, resulting in a transposition of the enone moiety by tautomerization and dehydration.

The 'abnormal' Nazarov cyclization reported by Hiyama[89,90] leads to transposed cyclopentenones by incorporating carboxylic acids as nucleophiles in the reaction medium. Both acyclic and monocyclic divinyl ketones can be employed, as shown in Scheme 15. Dioxolane acetals have also been used successfully in place of the carbonyl group.

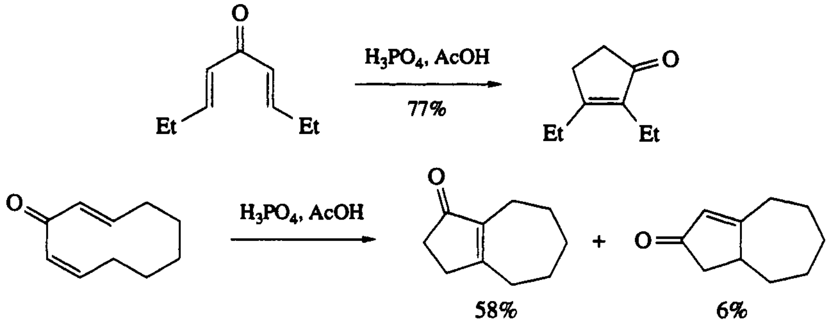

**Scheme 15**

Although only cross-conjugated divinyl ketones have been considered thus far, in principle conjugated dienones can also undergo the 4π-electrocyclization *via* the 1-oxypentadienylic cation. This pathway was found to dominate in a series of monocyclic dienyl vinyl ketones (**14**) examined by Denmark (equation 12).[91] The angularly substituted indanones (**15**) arise from cyclization of the dienyl ketone followed by a rapid Wagner–Meerwein shift (equation 13). The substituent effects on the migrating double bond are consistent with this mechanism.[91]

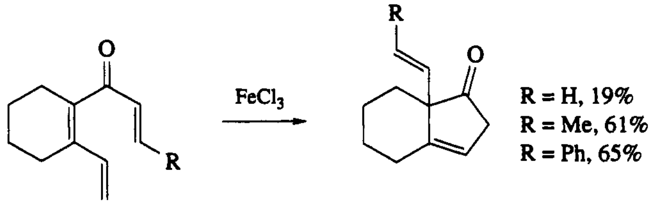

R = H, 19%
R = Me, 61%
R = Ph, 65%

(**14**) (**15**) (12)

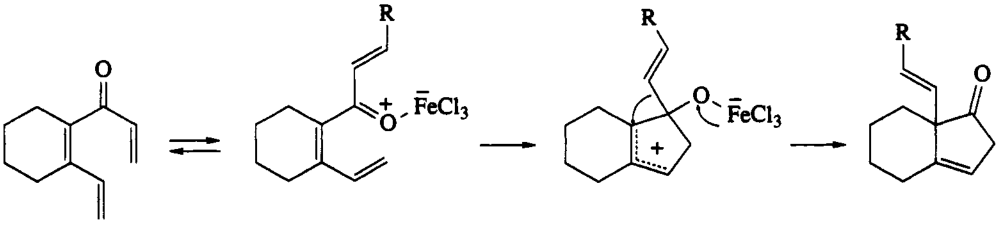

(13)

### 6.3.3.6 Photochemical Cyclizations

The theory of electrocyclic reactions predicts a disrotatory closure of 4π-systems in the excited state.[61] This prediction was verified in fact by Lehr[84] using the same biscyclohexenyl ketone (equation 14). The cyclization proceeded at various wavelengths in pentane as well as in benzene. The reaction could not be inhibited by naphthalene or piperylene. Sensitization with acetophenone did not accelerate the reaction. Finally, no deuterium was incorporated when $d_6$-benzene was used as solvent. β-Damascone undergoes an apparent disrotatory closure with capture of the zwitterionic intermediate by solvent (equation 15).[74]

The photocyclization of cyclic, cross-conjugated divinyl ketones has been investigated in various ring sizes. The simplest members of this group, 4,4-disubstituted-2,5-cyclohexadienones have been extensively studied,[92] but the subsequent skeletal reorganizations place these reactions beyond the scope of this chapter. The homologous cycloheptadienones give different products depending on reaction conditions (equation 16). The expected disrotatory closure occurs in acetic acid,[72] while a more complex series of

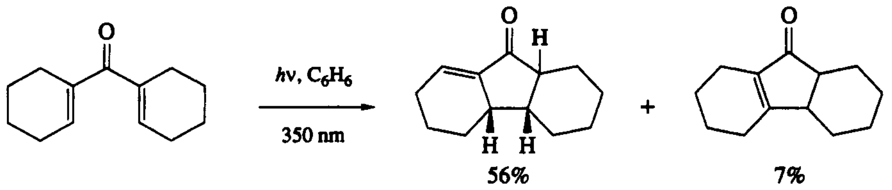

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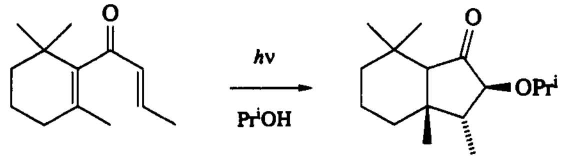

(15)

electrocyclizations and openings occurs in $FSO_3H$.[73] Noyori has further shown that medium ring divinyl ketones give the expected disrotatory closure upon irradiation in 97% $H_2SO_4$ (equation 17).[73]

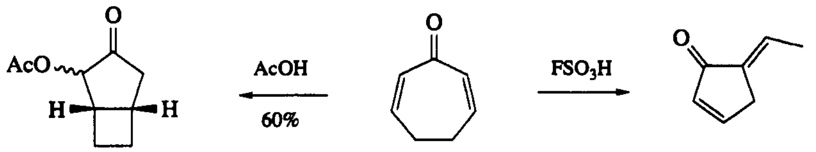

(16)

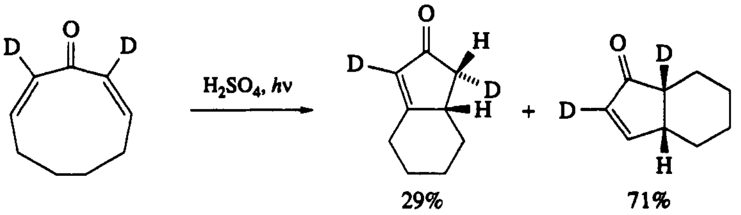

(17)

## 6.3.4 SILICON-DIRECTED NAZAROV CYCLIZATIONS OF DIVINYL KETONES (SDNC)

The recognition that the Nazarov cyclization is a cationic electrocyclization provided a better understanding of the controlling features of the reaction and a rationale for explaining its deficiencies. Among the latter, the most serious are: secondary cationic rearrangements[80] and unselective placement of the cyclopentenone double bond. These problems identify the cyclopentenylic cation (Scheme 4) as the offending intermediate from which these problems arise. By strategic placement of an efficient phantom electrofuge, the collapse of the intermediate cation is accelerated and directed in a preordained sense. By virtue of the β-cation-stabilizing properties of organosilicon groups[93] (the β-effect[94]), these substituents have proven extremely effective in the Nazarov cyclization. Equation (18) illustrates the principle. The β-silyl group acts as a 'spectator' until the crucial electrocyclization at which point it is stereoelectronically aligned[93] to direct collapse of the cation. Two important consequences of the directed collapse as shown are: (i) the placement of the double bond in the thermodynamically less stable position; and (ii) the creation of ring fusion stereocenters which allows the electrocyclic nature of the reaction to be expressed in relative stereogenesis.

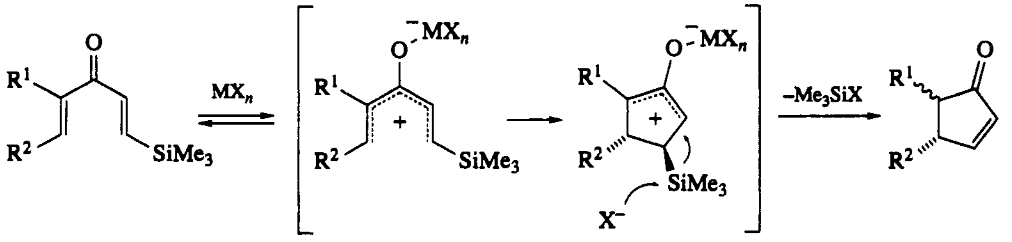

(18)

The TMS group has been most often employed. In certain circumstances larger alkyl and aryl groups attached to silicon have also been used successfully.[95] With (*Z*)-β-silyl divinyl ketones, Chenard[96] claims that the *t*-butyldimethylsilyl and, in some cases, the triethylsilyl group remain after cyclization (equation 19). That this feature is most likely due to a change in the alkene geometry and not the bulk of the silyl group is shown by the highly silicon-directed transformation of the (*E*)-isomer.[97]

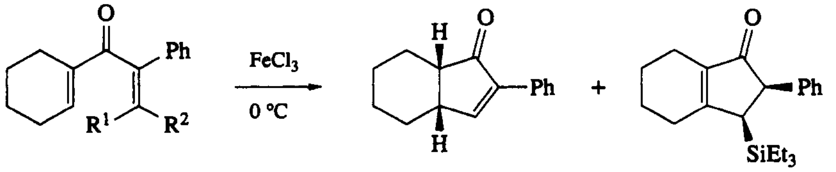

(19)

| | | |
|---|---|---|
| (*Z*): $R^1 = SiEt_3$; $R^2 = H$ | 18% | 24% |
| (*E*): $R^1 = H$; $R^2 = SiEt_3$ | 85% | 0% |

The construction of β-silyl divinyl ketones in many different structural settings has been well developed. The four principal connections outlined in Scheme 16 are as follows: path a,[98] vinyl organometallic addition to 3-trimethylsilyl-2-propenal;[99] path b,[98] 3-trialkylsilylvinyl organometallic[100,101] addition to enals; path c,[102] palladium-catalyzed carbonylation/coupling of 2-trimethylsilylvinyltrimethylstannane;[103] and path d,[104] acylation of a β-silyl copper reagent.[105]

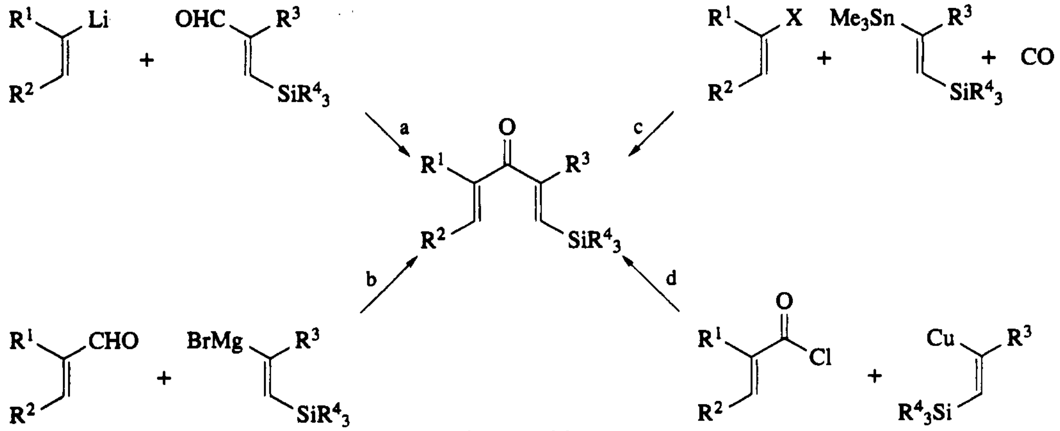

**Scheme 16**

In their initial studies on the SDNC, Denmark and Jones[98,106] demonstrated a Lewis acid dependence, with anhydrous $FeCl_3$ providing optimal results. Subsequently $BF_3{\cdot}OEt_2$ and $ZrCl_4$ have been used successfully where the oxidizing properties of $FeCl_3$ proved deleterious. The SDNC's proceed under much milder conditions than the classical variant. Only with highly substituted substrates or in certain annulations are temperatures above the ambient necessary.

### 6.3.4.1 Acyclic Precursors

Due to their ready isomerization simple cyclopentenones present a particular challenge in the Nazarov cyclization. In all of the cases studied in α- and β-monosubstituted and α,β-disubstituted systems the cyclopentenone product contained the double bond in the less substituted position, as required by loss of the silicon electrofuge (Scheme 17).[98,104] The relative configuration of substituents in disubstituted cases is controlled by kinetic protonation and weakly favors the *cis* isomers. Substituent effects in rate were particularly noted in these cases where substitution with α- and β-alkyl groups greatly accelerated and decelerated the reactions, respectively.

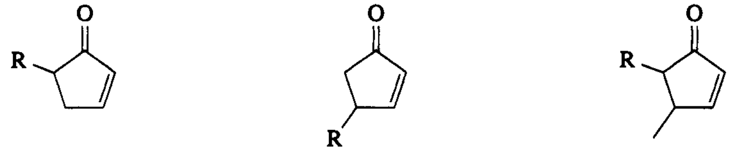

R = Et, 51%
R = Bu$^t$, 97%

R = Me, 54%
R = Ph, 27%

R = Me, 95%, *cis*:*trans* = 59/41
R = Et, 70%, *cis*:*trans* = 43/57

**Scheme 17**

### 6.3.4.2 Monocyclic Precursors (Achiral)

The SDNC is also very useful in the annulation mode with one endocyclic double bond. Various ring sizes, heterocycles and substituent patterns have been examined.[98] In the homologous series of cycloalkenyl groups the rate increases $5 < 6 < 7 \approx 8 \approx 12$ (Scheme 18). The ring fusion stereochemistry is established by kinetic protonation of the cross-conjugated iron enolate. This tends to favor the *cis* ring fusion. The accelerating effect of α-substitution is seen in the low temperature, high yielding cyclizations to form 2-substituted enones. Oxygen- and nitrogen-containing heterocycles also participate successfully.[104] Ring unsaturation is compatible with the reaction and shows the expected rate effects.[104]

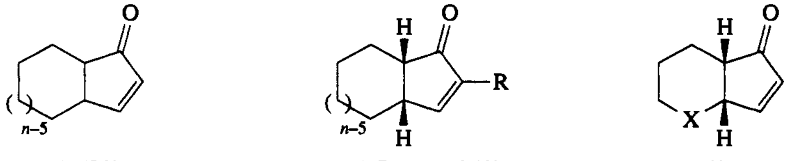

*n* = 5, 52%
*n* = 6, 84%
*n* = 7, 74%
*n* = 12, 78%

*n* = 5; R = Ph; 86%
*n* = 6; R = allyl; 76%

X = O, 60%
X = NCO$_2$Me, 76%

**Scheme 18**

### 6.3.4.3 Monocyclic Precursors (Chiral)

The stereochemical course of SDNC with ring-substituted monocyclic precursors has been studied in detail. The choice between the two allowed conrotations is influenced by: (i) ring size; (ii) substituent location; (iii) substituent size; and (iv) silyl group size.

In the cyclopentenyl series the relative stereoselection is variable.[95] With a simple methyl substituent vicinal to the newly forming bond the selectivity is poor. This may be remedied with bulkier silyl groups (Scheme 19) but in unacceptable yields. In the synthesis of (±)-$\Delta^{9(12)}$-capnellene, Stille[107] reports the formation of a single *cis*,*anti*,*cis*-triquinane (**16**) in the final SDNC. By contrast in an approach to hirsutene, the SDNC produced triquinane (**17**) as a 2.7:1 mixture favoring the desired *cis*,*anti*,*cis* isomer.[108]

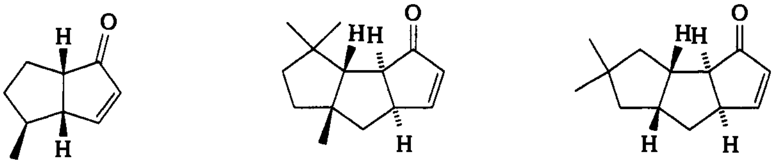

Me$_3$Si: 54/46, 50%
Pr$^i_3$Si: 79/21, 13%

(**16**)

(**17**)

**Scheme 19**

The cyclohexenyl system shows generally higher levels of selectivity. Substitution at the enone γ-carbon (**18**) has the strongest effect. The selectivity is sensitive to the size of the substituent as well as the size of the silyl groups. In all cases the major isomer contains a *trans* relationship between the hydrogens at the ring fusion and substitution position (Table 1).[109] Larger silyl groups (Pr$^i_3$Si) also enhanced the selectivity even in the simplest case of a methyl substituent. Substitution at other positions in the ring (**20**) and (**21**) led to less selective (*ca.* 3:1) cyclizations again favoring the *cis*,*trans* isomer for all positions

(Scheme 20). Finally, the tricyclic system (**22**) was formed selectively with the *cis,trans* isomer again preferred.[104]

**Table 1**

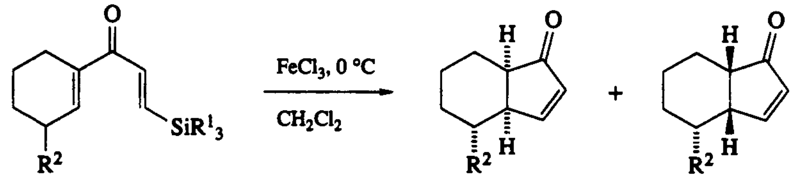
O
SiR$^1_3$
R$^2$
FeCl$_3$, 0 °C
CH$_2$Cl$_2$
H
O
H
R$^2$
+
H
O
H
R$^2$

(**18**) *cis,trans*-(**19**) *cis,cis*-(**19**)

| $R^1$ | $R^2$ | *Cis,trans-(19) (%)* | *Cis,cis-(19) (%)* | *Yield (%)* |
|---|---|---|---|---|
| Me | Me | 78 | 22 | 99 |
| Me | Vinyl | 70 | 30 | 66 |
| Me | Ph | 94 | 6 | 76 |
| Me | Bu$^t$ | 94 | 6 | 63 |
| Me | OBn | 90 | 10 | 76 |
| Pr$^i$ | Me | 91 | 9 | 70 |

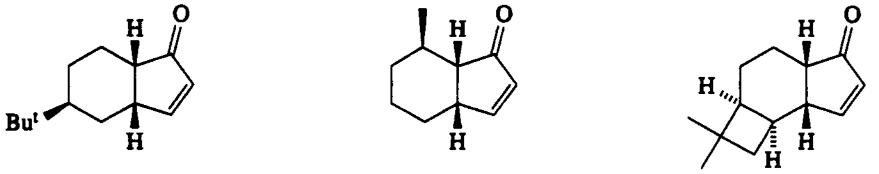
H
O
Bu$^t$
H
H
O
H
H
O
H
H
H
H

(**20**) 76/24, 82% (ref. 109) (**21**) 72/28, 85% (ref. 109) (**22**) 87/13, 70% (ref. 104)

**Scheme 20**

These trends are explained by analysis of the structures of the reactive conformations of the enones and the structures of the cyclopentenylic cations. Considering the $\gamma$-substituted series (**18**) the reactive half-chair conformation (**23**) places the substituent in an equatorial position (Scheme 21). In the cations resulting from conrotation (**24** and **25**) all atoms in the five-membered ring must lie in a plane, thus precluding an equatorial hydrogen. Thus the two conrotations, clockwise to (**24**) and counterclockwise to (**25**), lead directly to chair or boat conformations of the six-membered rings, respectively. The size of the substituent then plays two roles: first to fix the ring conformation and second to enhance opposite face approach.

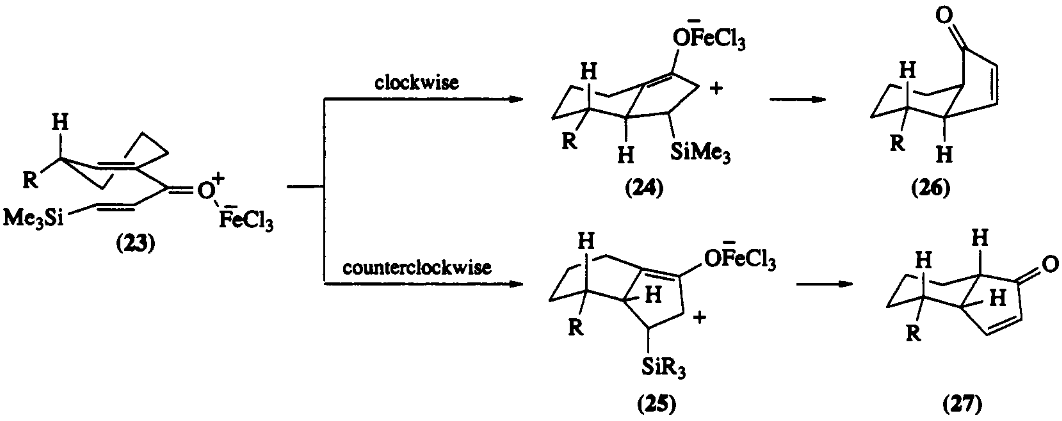
H
R
Me$_3$Si
O$^+$
$\bar{F}$eCl$_3$
(23)
clockwise
counterclockwise
$\bar{O}$FeCl$_3$
H
+
R
H
SiMe$_3$
(24)
O
H
R
H
(26)
H
$\bar{O}$FeCl$_3$
H
+
R
SiR$_3$
(25)
H
H
O
H
R
(27)

**Scheme 21**

These studies have been extended to include cycloheptenyl and cyclooctenyl systems using the benzyloxymethyl substituent. In these cases the analysis is complicated by the appearance of the *trans* ring fusion family of isomers. The results of extensive chemical correlation and molecular mechanics studies (Scheme 22)[97] show that the sense of relative stereogenesis changes (*cis* family) with remarkable degrees of selectivity (92:8 and 93:7). This switch is explained by a similar conformational analysis.

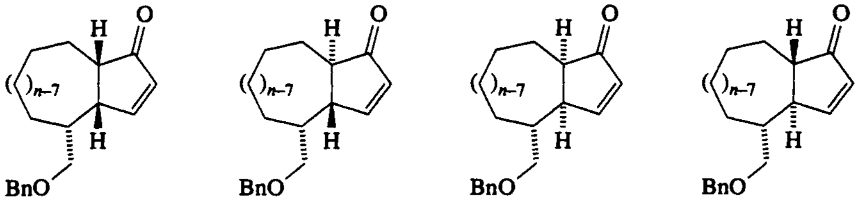

| | *cis,cis* (%) | *trans,cis* (%) | *cis,trans* (%) | *trans,trans* (%) | *Yield* (%) |
|---|---|---|---|---|---|
| *n* = 7 | 78 | 14 | 5 | 3 | 84 |
| *n* = 8 | 90 | 3 | 4 | 3 | 78 |

**Scheme 22**

### 6.3.4.4 Biscyclic Precursors

The formation of linearly fused tricycles serves to illustrate a variant of the SDNC. In these systems (**28**) the double bond must be directed away from both ring fusions. This was accomplished by placing the silyl group at a ring position again poised to direct the collapse of the intermediate cation (**29**; equation 20).

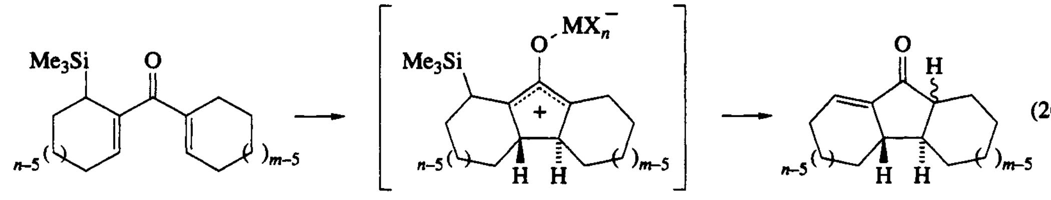

(**28**) (**29**) (**30**)

a: *n* = *m* = 6; 79%, *trans*
b: *n* = 6; *m* = 5; 88%, *cis*
c : *n* = *m* = 5; 77%, *cis*

These cyclizations occur much faster than the original SDNC since the electron-donating silyl group is in continuous overlap throughout the cyclization. The yields are generally good and the ring fusion stereochemistry well controlled.[110]

Since these substrates are chiral there exists the possibility of relative stereogenesis. However, since the original silicon-bearing stereocenter is destroyed in the process, the products of opposite conrotations are enantiomers. Thus, an optically active sample of (**28a**; 88% *ee*) was cyclized and provided (**30a**) with the same enantiomeric excess. This near perfect stereochemical coupling proceeds in the expected *anti* sense, as shown in equation (21).[111]

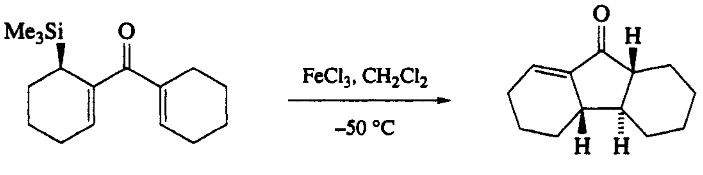

(**28a**) 88% *ee* (**30a**) 88% *ee*

### 6.3.4.5 Tin-directed Nazarov Cyclizations (TDNC)

Extension of the SDNC concept to include tin has been reported.[112] The cyclizations of various acyclic precursors proceeded under mild conditions in fair to excellent yields. As expected the less substituted cyclopentenone is formed in each case. This variant offers a different construction of the divinyl ketone by an aldol condensation (equation 22).

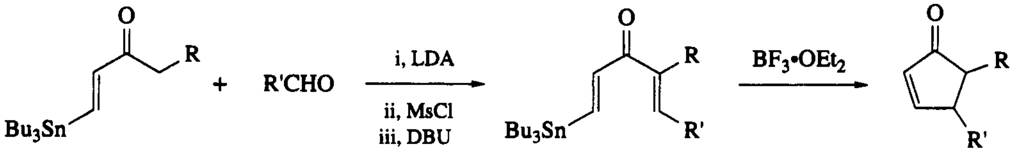

(22)

R = H; R' = Ph; 44%

R = Bu$^n$; R' = Me; 93%, 1.7:1

R = Bu$^n$; R' = styryl; 83%, 1.5:1

## 6.3.5 CYCLIZATION OF DIVINYL KETONES FROM *IN SITU* GENERATION

Access to the necessary divinyl ketones has been approached from many different directions. In this section those precursors which contain the carbon skeleton of the divinyl ketone will be discussed.

### 6.3.5.1 Cyclization of Divinyl Ketones from β′-Substituted Enones

The facile elimination of β-heterosubstituents in ketones allows for the ready construction of α,β-enones. Three different heteroatoms have been employed, chlorine, nitrogen and oxygen. The β′-chloro enones (products of Friedel–Crafts acylation) suffer Nazarov cyclization under standard conditions.[113,114] Jacquier has prepared a series of β′-amino enones (31) from Mannich condensations.[115] These substrates undergo cyclization in modest yields under standard conditions (equation 23). Takeda has found that the readily available[116] tetrahydro-4-pyranones (32) produce 2-cyclopentenone-4-carboxylates upon treatment with TMS-I (equation 24).[117] It is noteworthy that the putative α-carboalkoxy divinyl ketones have been independently cyclized by Marino using TMS-I.[79]

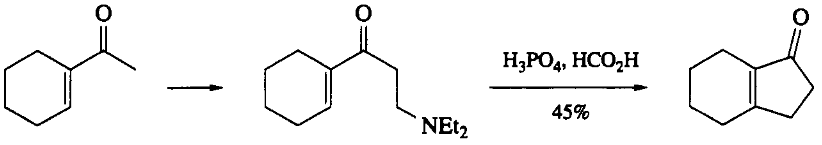

(31)

(23)

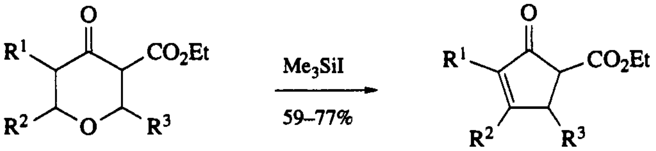

(32)

(24)

### 6.3.5.2 Cyclization of Divinyl Ketones from α′-Hydroxy Enones

Addition of acyl anion equivalents (propenal d$^1$ reagents) to ketones provides general access to α′-hydroxy enones. In an application of this method to pentannulation, the trimethylsilyl- or ethoxyethyl-protected cyanohydrins of α,β-enals were used.[118] The derived tertiary acetates undergo elimination (*p*-TsOH/benzene) to the divinyl ketones which cyclize in the acidic reaction medium (equation 25).[118] In some cases the α′-hydroxy or α′-silyloxy enones underwent cyclization but in much lower yields. Substitution in the ring and on the double bonds is compatible.

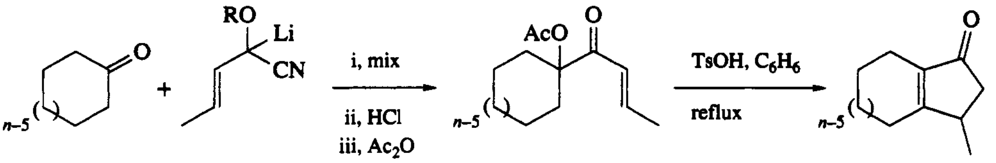

(25)

$n = 6$, 53%
$n = 7$, 60%
$n = 12$, 91%

### 6.3.5.3 Cyclization of Divinyl Ketones from Dienynes

The use of these precursors is due almost entirely to Nazarov[4,6,9,10,13–15,19,22–25,31] in work prior to 1950. The construction of dienynes from condensation of ketones and vinylalkynes followed by dehydration (Scheme 8) provides access to a broad range of structural types. Generally the dehydration occurs in a Saytzeff sense with unsymmetrical ketones.[119] The reagents most commonly used are phosphoric acid (occasionally with added formic acid) or concentrated hydrochloric acid. The conditions are rather harsh (50–80 °C) to accomplish both hydration of the alkyne and cyclization.

#### *6.3.5.3.1 Acyclic precursors*

The great majority of substrates employed are derived from vinylacetylene itself thereby providing 4-methyl-2-cyclopentenones, the 1- and 2-substituents arising from the ketone (equation 26). With α-branched ketones, 4,4-disubstituted-3-methylcyclopentenones are formed.[24,25]

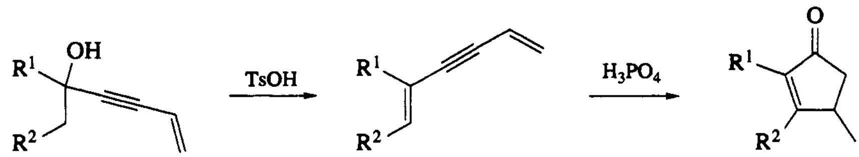

(26)

(33) (34)

$R^1 = R^2 = Me$; 71%
$R^1 = Ph$; $R^2 = Me$; 70%
$R^1 = Bu^t$; $R^2 = H$; 49%

#### *6.3.5.3.2 Monocyclic precursors*

The dienynes (34) derived from cyclic ketones also undergo cyclization to accomplish a cyclopentenone annulation.[8,11,13,14,22,26,31,120] Scheme 23 contains representative structures. The cyclododecyl system was derived from a silyldienyne prepared by a novel condensation route shown in equation (27).[120]

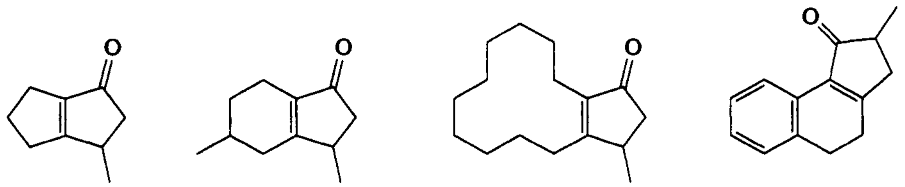

31% (ref. 8) 70% (ref. 13) 64% (ref. 120) 48% (ref. 22)

Scheme 23

### 6.3.5.4 Cyclization of Divinyl Ketones from Alkynic Alcohols

Moving one step further back in the synthetic sequence towards cyclopentenones identifies the alkynic alcohols as viable precursors. Since the subsequent dehydration–hydration–cyclization steps are all acid-

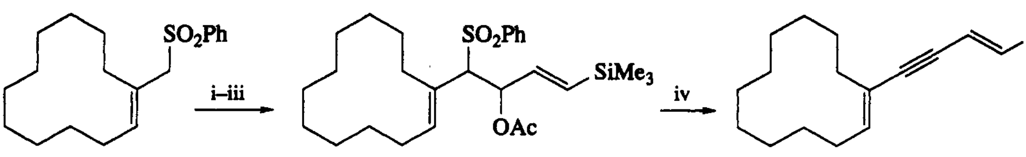

(27)

i, Bu$^n$Li; ii, 3-trimethylsilyl-2-propenal; iii, $Ac_2O$, Py; iv, KOBu$^t$

catalyzed processes, suitable conditions are easily identified. An alternative pathway may involve direct formation of an allyl vinyl ketone by Rupe rearrangement.[121] This approach has been applied exclusively to monocyclic substrates. The variation in precursor structure derives from the functionality present on the alkynic unit.

### *6.3.5.4.1 Enynol precursors*

Treatment of the vinylacetylene–ketone addition products (**33**; equation 26) with hot phosphoric acid or methanolic sulfuric acid induces the cascade to the ring fused systems.[11,25,31,122] With unsymmetrical ketones a mixture of regioisomers results.[34]

A interesting variation on this theme employing the isomeric enynol acetates (Scheme 24) has been developed by Rautenstrauch.[123] The cyclizations are induced by a Pd$^{II}$ catalyst in warm acetonitrile. The proposed mechanism is intriguing. Reaction is initiated by an anchimerically assisted palladation to (**35**) followed by opening the dioxolenium ion to a pentadienylic cation (**36**). The closure of (**36**) is analogous to the silicon-directed Nazarov cyclization in the ejection of the Pd$^{II}$ electrofuge from (**37**). Both secondary and tertiary acetates can be employed as well as both acyclic and monocyclic systems.

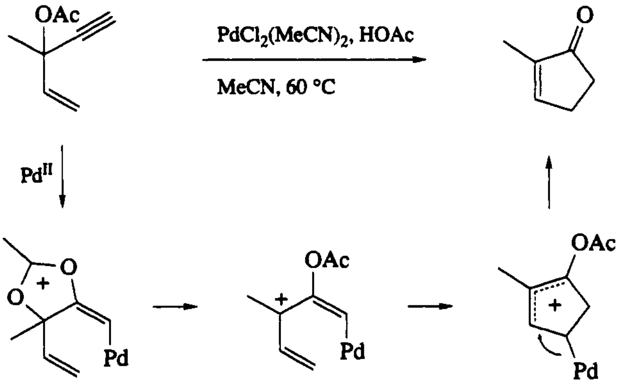

(**35**) (**36**) (**37**)

**Scheme 24**

### *6.3.5.4.2 Ynediol precursors*

For many years the preferred method for cyclopentannulation involved the acid-catalyzed transformation of ynediols (**38**) derived from addition of propargylic alcohol derivatives to ketones (equation 28). This strategy likely involves Rupe rearrangement to the β′-hydroxy enone followed by facile β-elimination to the requisite divinyl ketone. The conditions employed for this variant are generally milder, rarely requiring elevated temperatures. For acid catalysts, methanolic sulfuric acid, phosphoric acid and formic acid are generally employed. Eaton[124,125] has recommended the $P_2O_5$–$MeSO_3H$ system for this transformation, which has been used successfully by others.[126,127] A representative sampling of structures obtained from the many examples of this reaction is collected in Scheme 25. Acyclic and monocyclic precursors of five-,[129] six-,[126,128,130–132] seven-,[128] eight-[128] and twelve-membered rings[128,133–135] have been employed. Eaton[124] and McKervey[127] have reported double annulation of symmetrical tetraols in their approaches to dodecahedrane. The hexaquinacene in Scheme 25 was prepared by two sequential double annulations.[127]

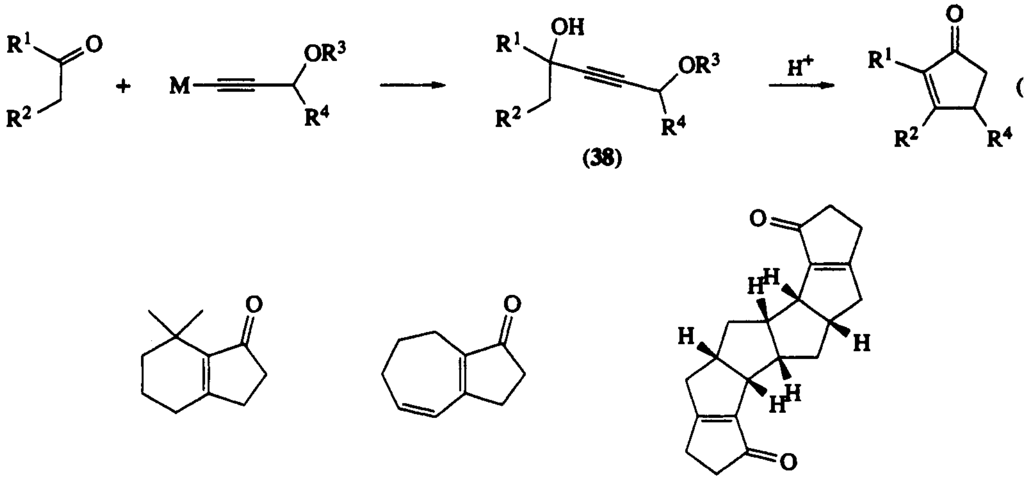

(28)

53% (ref. 126) 49% (ref. 128) 45% (ref. 127)

**Scheme 25**

The issue of relative stereogenesis has been studied in the context of this variant by Hiyama.[128] The preferred mode of electrocyclization is independent of substitution position but sensitive to the nature of the substituent. Thus conrotation produces the *trans* isomer of 1,2-disubstituted systems (**39**) and the *cis* isomer of 1,3-disubstituted systems (**40**) albeit with lesser selectivity (Scheme 26). The divergence of the stereochemical outcome here from that described in the SDNC (Section 6.3.4.3) arises from the consequences of the β-methyl group on ring conformation and avoidance of eclipsing interactions.

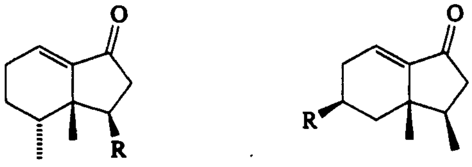

(**39**)

R = H, 60%
R = Me, 67%

(**40**)

R = $Pr^i$, 64%, *cis/trans* = 83/17
R = $CO_2Me$, 60%, *cis/trans* = 60/40

**Scheme 26**

The first example of this general process is due to Raphael[55] who, inspired by the mechanistic thinking of Braude,[48] suggested that alkynic amino alcohols (**41**) should serve to produce the desired divinyl ketone intermediates (equation 29). The reaction was found suitable for five-, six- and seven-membered ring monocyclic precursors, but the yields were low.

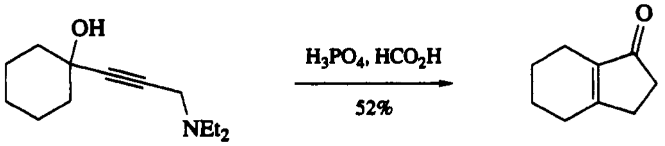

(**41**)

(29)

A higher oxidation state product is obtained by the analogous cyclization of propargylic acetals.[136] Unfortunately, the location of the additional unsaturation cannot be controlled.

#### 6.3.5.5 Cyclization of Divinyl Ketones from α-Vinylcyclobutanones

In 1983 Dreiding reported a general synthesis of α-vinylcyclobutanones (**42**) by the direct cycloaddition of vinylketenes and simple alkenes.[137] These strained compounds are prone to various rearrangement reactions. In the β,β-disubstituted series, treatment with catalytic amounts $BF_3{\bullet}OEt_2$ or $MeSO_3H$ results in the formation of divinyl ketones. If a full equivalent of $MeSO_3H$ is used the major product is the cyclopentenone arising from Nazarov cyclization (equation 30). The reaction is very sensitive to substitution pattern as four different classes of products arising from different pathways have been identified.[138,139]

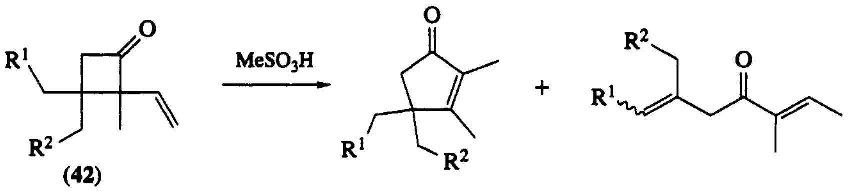

(**42**) (30)

| | | |
|---|---|---|
| $R^1 = Pr^n$; $R^2 = H$ | 65% | 11% |
| $R^1 = R^2 = CH_2$ | 71% | 3% |

### 6.3.6 CYCLIZATION OF DIVINYL KETONE EQUIVALENTS FROM SOLVOLYSIS

A variety of different precursors have been shown to rearrange to divinyl ketones or equivalent species under highly ionizing acidic conditions. Equivalents of both cross-conjugated and linear dienones have been generated and cyclize to cyclopentenones *in situ*. The structural diversity of substrates in this class is remarkable and testifies to the utility of these ring-forming reactions which are unified by the propensity for cationic electrocyclization.

#### 6.3.6.1 Solvolysis of Geminal Dichlorides

##### *6.3.6.1.1 Dichlorocyclopropylcarbinols*

The development of phase transfer catalysis greatly improved the generation of dichlorocarbene and increased the availability of dichlorocyclopropanes for synthesis.[140] Dichlorocyclopropanation of trisubstituted allylic alcohols proceeds cleanly. Heating the dichlorocyclopropylcarbinols (**43**) in 47% hydrobromic acid at 100 °C produces cyclopentenones in good yields (Scheme 27).[141,142] The reaction is proposed to proceed by cyclopropylcarbinyl cation ring opening to the divinyl geminal dichloride (**44**). Chloride ionization to the pentadienylic cation (**46**) initiates the electrocyclization to a chlorocyclopentadiene (**47**) which hydrolyzes to a cyclopentenone *in situ*.

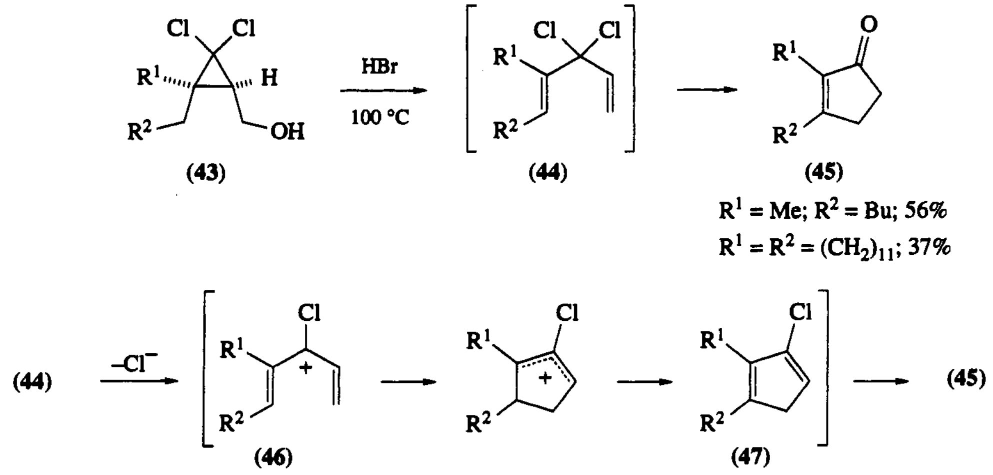

(**43**) (**44**) (**45**)

$R^1 = Me$; $R^2 = Bu$; 56%
$R^1 = R^2 = (CH_2)_{11}$; 37%

(**44**) (**46**) (**47**) (**45**)

Scheme 27

#### 6.3.6.1.2 Geminal dichloro homoallylic alcohols

As a test of the intermediacy of the divinyl dichloride (**44**) in the solvolysis of dichlorocyclopropylcarbinols, Hiyama[143] prepared the homoallylic alcohols (**48**) by addition of 1,1-dichloroallyllithium to cyclic ketones. Treatment of (**48**) with trifluoroacetic acid produced the cyclopentenones in very good yield (equation 31).[143] This reaction presumably proceeds by dehydration to the divinyl dichloride followed by a similar ionization–cyclization sequence. Interestingly the regioisomeric dichloride also underwent closure to a cyclopentenone.[142]

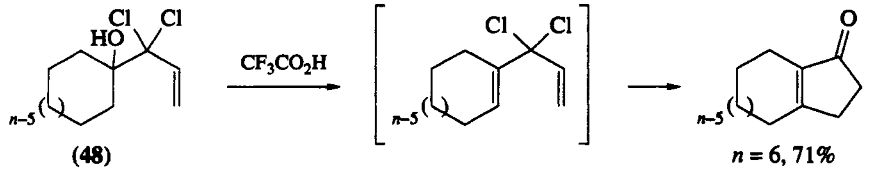

(**48**)

$n$ = 6, 71%
$n$ = 7, 87%
$n$ = 12, 90%

(31)

In a related study Gaioni[144] generated the divinyl dichloride by cheletropic extrusion of sulfur dioxide from the dichlorocarbene/3-sulfolene adduct (**49**). Under the reaction conditions the divinyl dichloride solvolyzes to the cyclopentenone as outlined previously (equation 32).

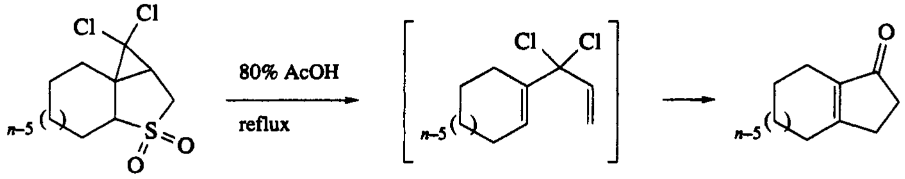

(**49**)

$n$ = 6, 26%
$n$ = 7, 80%
$n$ = 10, 60%

(32)

### 6.3.6.2 Solvolysis of 2-Furylcarbinols

The acid-catalyzed rearrangement of 2-furylcarbinols to 4-hydroxy-2-cyclopentenones was first described by Piancatelli[145] and subsequently investigated by him in detail.[146–152] The precursors are readily available from either Grignard synthesis with furfural or addition of 2-furyllithium to aldehydes. The facility of rearrangement is dependent upon ring substitution and differing reagents are recommended.

For bromo or unsubstituted furans, sulfuric acid is used, while for alkyl-substituted furans, zinc dichloride is most effective. The mechanism for this conversion is depicted in Scheme 28. Acid-catalyzed rearrangement of (**50**) to (**52**) provides access to the open oxocarbenium ion (**53**). This cation is seen as a 1-hydroxypentadienylic cation. Conrotatory closure of (**53**) generates a 1-hydroxycyclopentenylic cation (**54**) which is deprotonated to form the final product. A key feature of this reaction is the creation of the *cis* double bond in (**53**) from the opening of (**52**). The thermodynamically more stable *trans* isomers cannot cyclize. A representative assortment of structures prepared by this route is found in Scheme 29. The furyl carbinyl substituent ($R^2$) becomes the 5-substituent in the product. Substituents on furan positions 3,4 and 5 reside on cyclopentenone positions 2,3 and 4, respectively. The 4-hydroxy group and the 5-substituent are always *trans* in the product. Assuming the reactions are under kinetic control, this is a reflection of the preferred configuration of the 1-hydroxypentadienyl cation (**53**). Extension of this reaction to furfurylidenecarbinols in an approach to prostanoids was only moderately successful as other electrocyclic processes involving the furan ring intervened.[151]

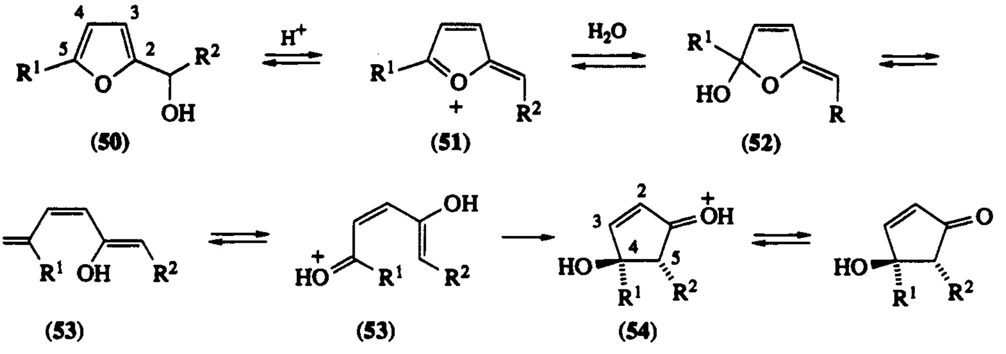

Scheme 28

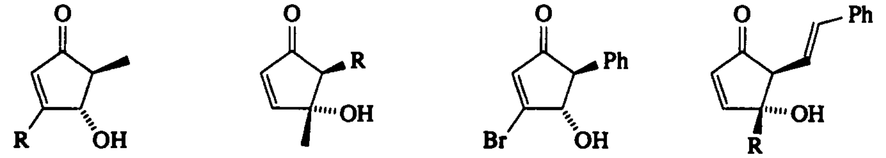

R = H, 30% (ref. 145)
R = Br, 81% (ref. 150)

R = $\mathrm{Bu^n}$, 18% (ref. 148)
R = Ph, 70% (ref. 148)

85% (ref. 150)

R = H, 65% (ref. 151)
R = Me, 30% (ref. 151)

Scheme 29

### 6.3.6.3 Solvolysis of Vinylallenes and Derivatives

#### *6.3.6.3.1 Epoxidation of vinylallenes*

Treatment of vinylallenes (**55**) bearing no allylic substituents with peracids results in epoxidation of the vinyl group. However, if the allene is substituted, the major product is a cyclopentenone (**57**; equation 33).[153,154] The mechanistic details of this transformation are still obscure. It is well known that allenes generally react with epoxidizing agents at the more substituted double bond.[155] In this case, however, it is difficult to distinguish the two possible pathways since the regioisomeric epoxides (**58**) and (**59**) can lead to the same zwitterionic intermediate (**60**) or cyclopropanone (**61**; Scheme 30). A concerted pericyclic process directly converting (**59**) to (**57**) was also put forward in the original work. Experimental support for the concerted pathway was forthcoming in the transformation of optically active (*R*)-allene (**62**) to optically active (*S*)-2,5-dimethyl-2-cyclopentenone (**63**; 15% *ee*; equation 34).[156] Unfortunately the enantiomeric purity of (**62**) was not determined. Nevertheless, this is not consistent with the intermediacy of achiral intermediates such as zwitterion (**60**), but rather with a thermally allowed [$_\pi 2_s + {}_\sigma 2_a + {}_\pi 2_a$] process. Goré has also described a photooxygenation procedure to achieve the same net transformation.[157] A collection of representative structures prepared by this method is found in (Scheme 31).[153,158–162] Both simple and fused cyclopentenones are available in modest yield. The precursor vinylallenes are obtained in various substitution patterns by hydrolysis of vinyl allenic Grignard reagents[163] or $S_N2'$ substitution on propargylic sulfonate or halides.[164]

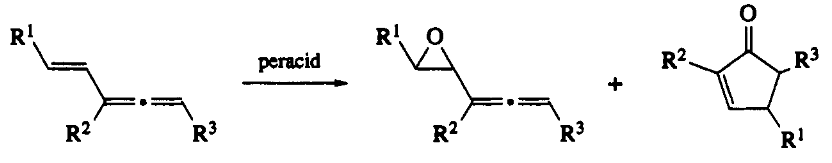

(33)

| (55) | (56) | (57) |
|---|---|---|
| $R^1 = \mathrm{Pr^n}$; $R^2 = R^3 = H$ | 55% | 0% |
| $R^1 = R^3 = H$; $R^2 = \mathrm{Pr^i}$ | 0% | 60% |
| $R^1 = R^2 = H$; $R^3 = \mathrm{Pr^n}$ | 3% | 57% |

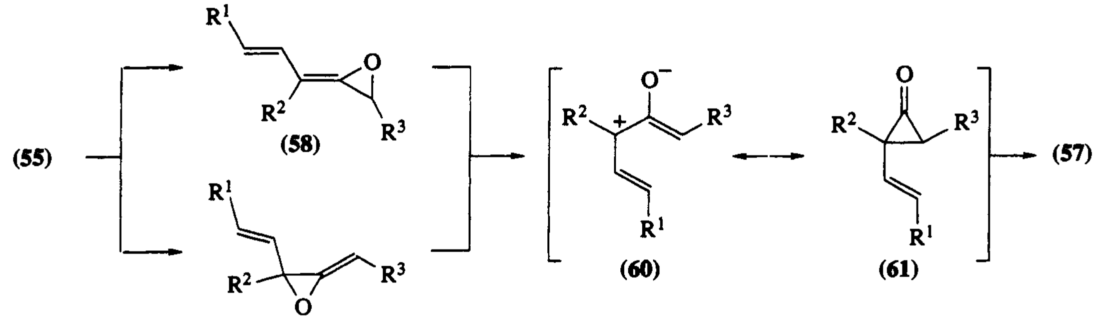
(55)
R1
R2
O
R3
(58)
R1
R2
R3
O
(59)
O−
R2
+
R3
R1
(60)
O
R2
R3
R1
(61)
(57)

**Scheme 30**

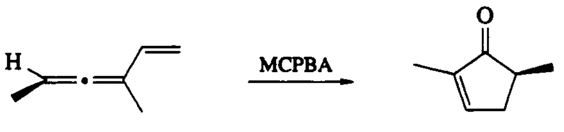

(*R*)-(62) (*S*)-(63)

(34)

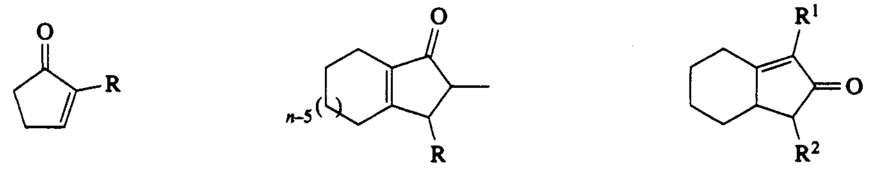
O
R
O
n-5
R
R1
O
R2

R = Me, 60% (ref. 153)
R = Bu$^n$, 60% (ref. 157)

R = Me; *n* = 6; 50% (ref. 158)
R = H; *n* = 12; 52% (ref. 161)

R$^1$ = R$^2$ = Me; 50% (ref. 158)
R$^1$ = n-$C_5H_{11}$; R$^2$ = H; 40% (ref. 157)

**Scheme 31**

### *6.3.6.3.2 Epoxidation of vinyl allenic alcohols*

Since epoxidation at the vinyl double bond is unproductive, it is desirable to direct reaction on the allene moiety. This can be accomplished by taking advantage of the hydroxy-directed epoxidation of allylic alcohols using the *t*-butyl hydroperoxide/vanadium(V) system.[165] The directing effects of both allylic and homoallylic type hydroxy groups have been examined at both positions of the vinylallene unit.[166–168] At the 1-position (**64**), primary, secondary and tertiary allylic alcohols are effective, while only primary homoallylic alcohols have been examined (equation 35). Presumably the directing effect of the hydroxy groups favors formation of the intermediate allene oxide (**65**). A sample of the compounds prepared by this route is shown in Scheme 32.[166]

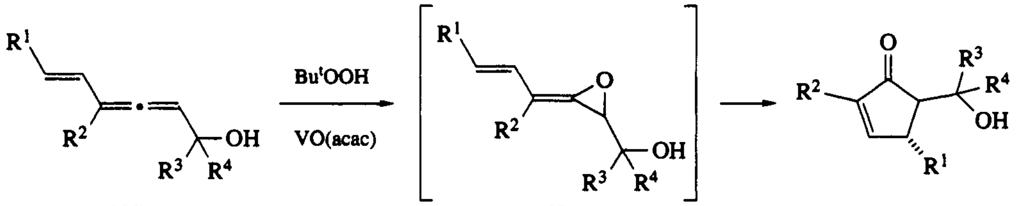
R1
R2
OH
R3
R4
Bu$^t$OOH
VO(acac)
R1
O
R2
OH
R3
R4
O
R2
R3
R4
OH
R1

(**64**) (**65**)

(35)

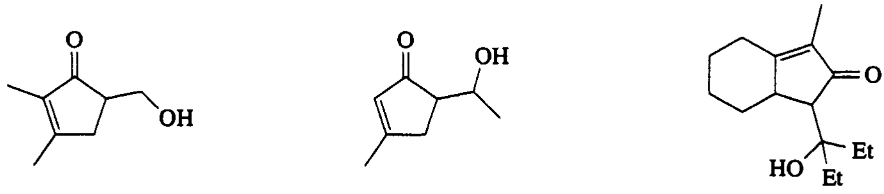
O
OH
O
OH
O
HO
Et
Et

50% 55% 45%

**Scheme 32**

Placement of the directing function at the 3-position (**66**) is also effective but regiochemistry of epoxidation is dependent upon the substitution of the hydroxy-bearing carbon. With secondary allylic alcohols the major product is the cyclopentenone with the allenyl epoxide as a minor by-product (equation 36). Tertiary alcohols give allenyl epoxides exclusively.[167]

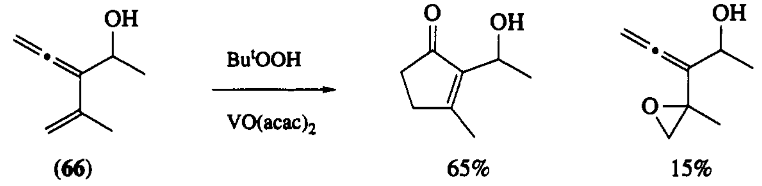

(36)

Homoallylic type alcohols (**67**), on the other hand, give predominantly cyclopentenones independent of substitution (equation 37). In the 3-hydroxyalkyl-substituted systems, presumably allene oxide (**68**) is the intermediate. Thus it would appear that the initial site of allene oxidation is not critical to the success of the reaction. Either precursor (**58**) or (**59**) is expected to give the observed stereochemical relationships of the newly formed stereocenters by the concerted mechanism.[169] Finally, Cha has noted that the two intermediates may lead to different stereochemical relationships by the zwitterionic mechanism.[168] This assumes a specific pathway for breakdown of (**58**) or (**59**). That stereochemical information is preserved in the reaction is shown by the selective transformations in equation (38).

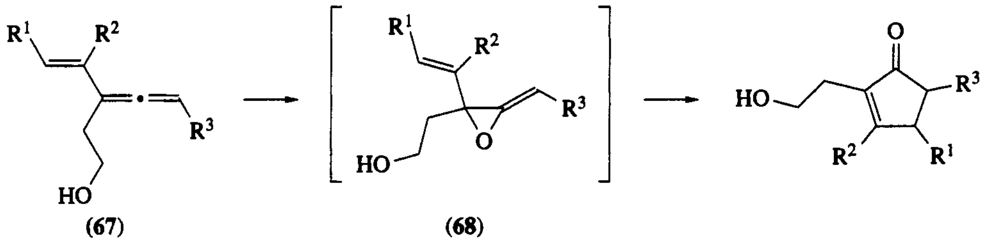

(37)

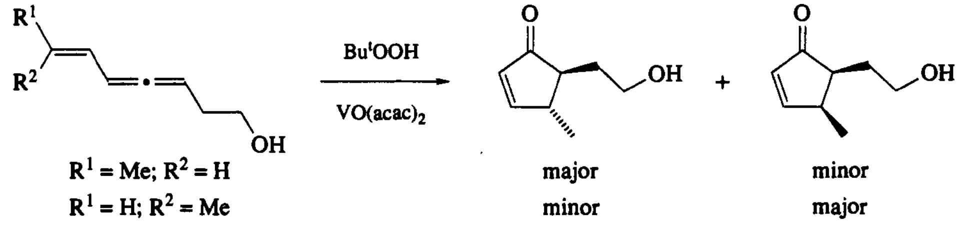

(38)

### 6.3.6.3.3 Solvometallation of vinylallenes

A similar electrophilic activation of the vinylallene to 2-cyclopentenone cyclization is possible using either mercury(II) acetate or thallium acetate.[170,171] Solvometallation of allenes is a well studied process[155] following expected Markovnikov attack at the central carbon by the metal salt. The yield of cyclopentenones was generally higher with acetoxymercuration (49–79%) compared to acetoxythallation (25–68%). Compounds of similar substitution pattern as were investigated with epoxidation (Scheme 31) were prepared. Mechanistically the reaction is remarkable for the facility of solvodemercuration (Scheme 33). Intermediates such as (**69**) or (**70**) lose elemental mercury spontaneously in the acetic acid medium to give the 2-cyclopentenones.

### 6.3.6.3.4 Solvolysis of alkoxyallenyl alcohols

A serendipitous discovery by Tius[172] has been developed into a useful α-methylenecyclopentene annulation procedure.[173,174] In an attempted synthesis of orthoquinones, Tius treated the allenyl alcohols (**71**), derived from addition of 1-lithio-1-methoxyallene to α-silyloxymethylene ketones, with $BF_3{\cdot}Et_2$. The product α-methylenecyclopentenones (**72**) were obtained in good yield (equation 39). The process can be

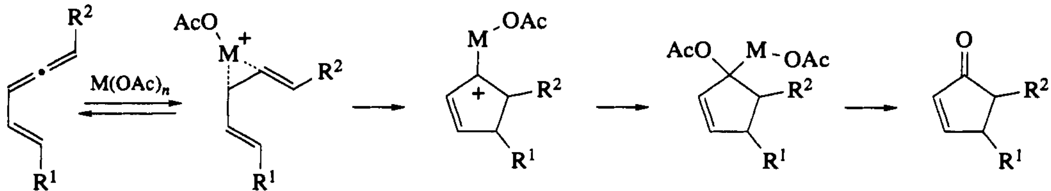

(69) (70)

Scheme 33

seen as a 1-oxypentadienyl cation cyclization (Section 6.3.6.2). This transformation has been generalized to incorporate functionalized α-methylene ketones. Scheme 34 contains a collection of the structures prepared by this route.[172] This method is extremely well suited for the synthesis of α-methylenecyclopentenone natural products.

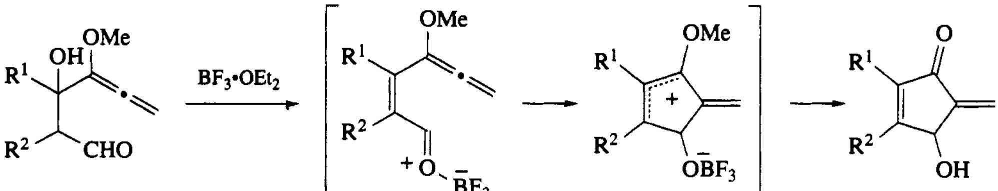

(71) (72) (39)

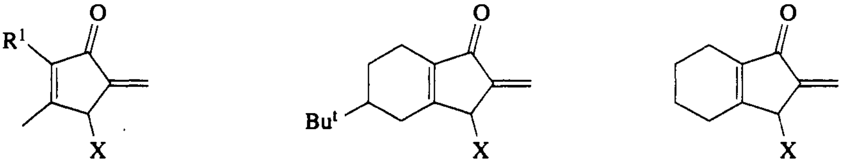

$R^1$ = Me; X = OH; 68%
$R^1$ = Et; X = OH; 72%

X = OH, 76%
X = H, 56%

X = Ph, 78%
X = SPh, 82%

Scheme 34

## 6.3.7 CYCLIZATION OF DIVINYL KETONES FROM *IN SITU* CONSTRUCTION

In all of the cases in the foregoing sections the substrates employed in the cyclization reactions contained all of the requisite carbon atoms to construct the ring. The subsequent transformations primarily involved functional group manipulations to produce the divinyl ketone or its equivalent for cationic cyclization. This final section includes those processes in which the divinyl ketone is constructed by a carbon–carbon bond forming reaction followed by cyclization under the reaction conditions. With one exception these carbon–carbon bond forming reactions involve an acyl derivative and an alkene or alkyne. The categorization is by acyl derivative.

### 6.3.7.1 Aliphatic Acid Halides

In 1974 Schegolev[175] reported the surprising isolation of 2-cyclopentenones from reaction of *in situ* generated acylium ions (**73**) and alkynes (equation 40). Evidence for the 1,5-hydride transfer to a vinyl cation (**74**) was secured from a study of cyclohexylacylium tetrafluoroborate with alkynes. Remarkably, in this system only products derived from fluoride capture of (**75**) were isolated.[176] The reaction was pursued by Jadhav[177] using propionyl chloride/silver tetrafluoroborate and long-chain internal alkynes. The yields were poor and regioselectivity ambiguous. While structurally similar to the Nazarov cyclization, these reactions are probably not mechanistically related.

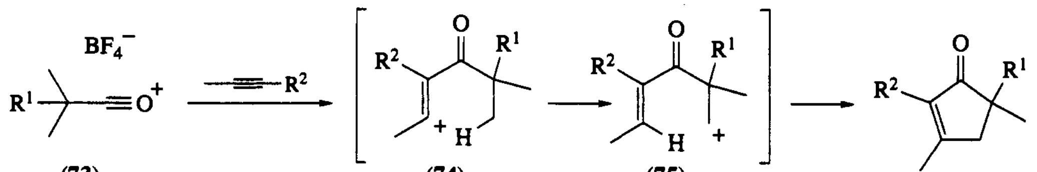

(73) (74) (75) (40)

### 6.3.7.2 Alkenic Acids

Unsaturated acylium ions generated from alkenic acids or anhydrides react with alkenes to produce cyclopentenones (equation 41).[88,178–181] With cycloheptene the major products arise from ring contraction. Again, it is unclear whether these reactions proceed *via* direct cyclization of (**76**) or a Nazarov cyclization.

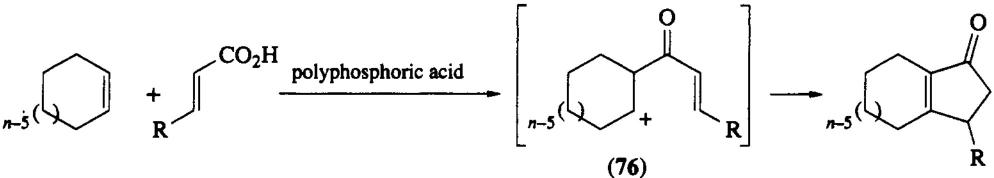

(76) (41)

R = Me; *n* = 6; 60%
R = Ph; *n* = 6; 26%
R = Me; *n* = 5; 22%

### 6.3.7.3 Alkenic Esters

These substrates, studied exclusively by Conia,[182] are a hybrid in that they contain all of the requisite carbon atoms for the ring but still require a coupling reaction. The action of hot polyphosphoric acid on alkenic esters (**77**) may begin by cracking the alkyl carbon–oxygen bond to produce an alkene and the parent acid. This new composition is in principle identical to the Dev mixture just described, and likely proceeds similarly by acylium ion generation and electrophilic attack on the *in situ* generated alkene (equation 42).

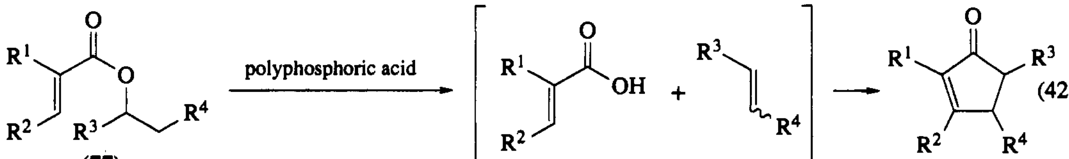

(77) (42)

Regiochemical ambiguities arise when $R^3$ and $R^4$ are similar groups. Another ambiguity arises due to the mobility of the cyclopentenone double bond. Thus, the same indenone (Scheme 35) is obtained by reaction of either isopropyl cyclohexenecarboxylate or cyclohexyl crotonate. The ease of preparation of the precursors allowed a broad survey of structural types. Scheme 35 contains representative structures of compounds prepared by this method.

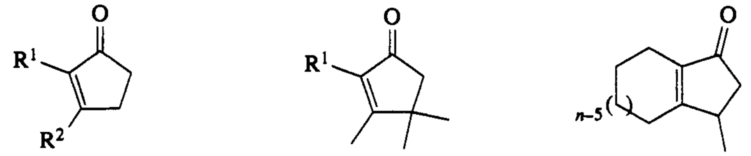

$R^1$ = H; $R^2$ = Me; 20%
$R^1$ = $R^2$ = Me; 20%

$R^1$ = H, 60%
$R^1$ = Me, 60%

*n* = 5, 20%
*n* = 6, 60%

Scheme 35

### 6.3.7.4 Alkenic Acid Chlorides and Bromides

Friedel–Crafts acylation of alkenes (Darzens–Nenitzescu reaction[183]) with unsaturated acylium ions generated from acid halides and Lewis acids constitutes a general synthesis of divinyl ketones.

#### *6.3.7.4.1 Alkenes*

As in the foregoing systems, a regiochemical ambiguity arises unless the alkene is either symmetrical or highly biased toward Markovnikov-type addition. Both acid chlorides and bromides can be employed. Aluminum trichloride is the preferred reagent.[113,184] Frequently the divinyl ketone or β′-chloro enone intermediates are isolable as by-products which can be subsequently cyclized. Representative structures are similar to those collected in Scheme 35.

#### *6.3.7.4.2 Alkynes*

A thorough and systematic study of the reaction between unsaturated acid chlorides and alkynes has been carried out by Martin.[185–188] The major cyclic products are 5-chloro-2-cyclopentenones (**78**) and 4-alkylidene-2-cyclopentenones (**79**; equation 43). Chlorinated divinyl ketones were also isolated. Nearly all substitution patterns have been investigated with regard to their effect on the distribution of cyclic and acyclic products. Obviously with acetylene only products of the type (**78**) are formed. The yields range from 30–70% with various alkyl groups $R^1$ and $R^2$. The use of terminal alkynes results in good regiocontrol, electrophilic attack always occurring in Markovnikov fashion. The alkylidenecyclopentenones (**79**) are generally the major products with highest overall yields for α,β-disubstituted acrylates. Internal alkynes have also been studied. In these reactions the 5-chloro-2-cyclopentenones (**78**) are the major products constituting 75–100% of the cyclic material in 30–60% overall yield. These systems present a stereochemical ambiguity in unsymmetrical alkynes where both possible regioisomers are formed. Representative structures prepared by this approach are found in Scheme 36.

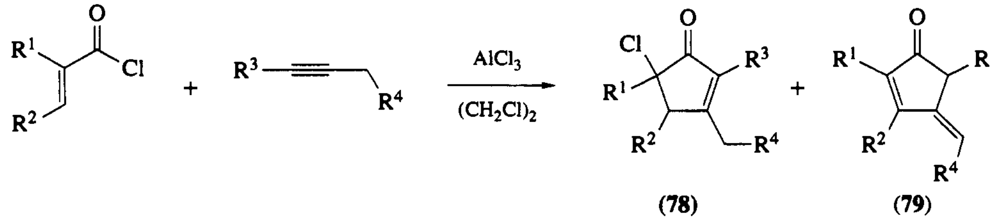

(43)

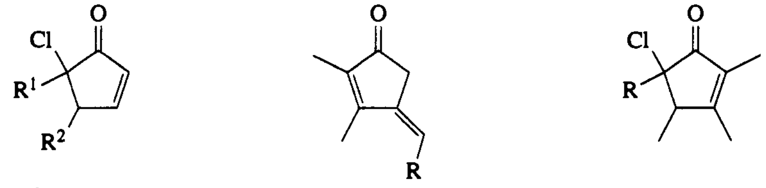

$R^1 = R^2 = H$; 40%
$R^1 = Me$; $R^2 = H$; 72%
$R^1 = H$; $R^2 = Me$; 60%

R = H, 40%
R = Me, 68%

R = H, 30%
R = Me, 40%

**Scheme 36**

#### *6.3.7.4.3 Trialkylsilylalkenes (vinylsilanes)*

A significant advance in the use of Friedel–Crafts acylation of alkenes to prepare divinyl ketones was the employment of vinylsilanes to control the site of electrophilic substitution.[189] Two groups have developed this approach to cyclopentenone annulation using slightly different strategies. In the method described by Magnus[190,191] the reagent vinyltrimethylsilane (**80**) is used primarily as an ethylene equivalent (equation 44). The construction of bicyclic systems followed readily as Nazarov cyclization proceeded under the reaction conditions. Tin(IV) chloride was found to be the most effective promoter of the overall transformation. As expected the position of the double bond is thermodynamically controlled.

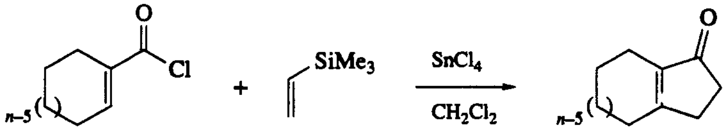

(80)

*n* = 5, 53%
*n* = 6, 46%
*n* = 7, 32%

(44)

Magnus has also made use of 1-phenylthio- and 2-phenylthio-vinylsilanes to introduce additional functionality in the cyclopentenone.[192–194] These reagents behave very differently. The 1-phenylthiovinylsilane (**81**) reacts with unsaturated acid chlorides in the presence of silver tetrafluoroborate to afford 3-phenylthio-2-cyclopentenone annulated products (**83**) in modest yields. It is suggested that a silicon-directed Nazarov cyclization of (**82**) intervenes to control the placement of the double bond (equation 45). No transformations of (**83**) were reported. The 2-phenylthiovinylsilane (**84**) also reacts with unsaturated acid chlorides (AlCl$_3$ catalyst) but to afford 5-phenylthio-2-cyclopentenone annulated products (**86**; equation 46). The surprising migration of the phenylthio group is seen to result from enolate capture of the electrofugal sulfenium ion expelled in the Nazarov cyclization.

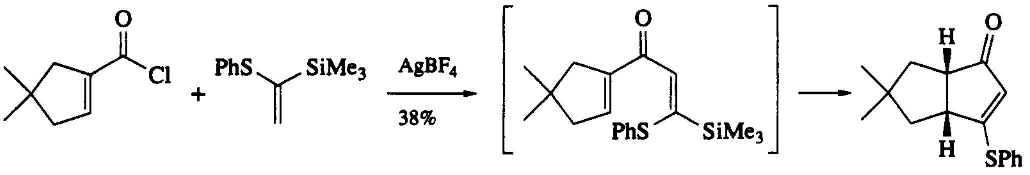

(81) (82) (83)

(45)

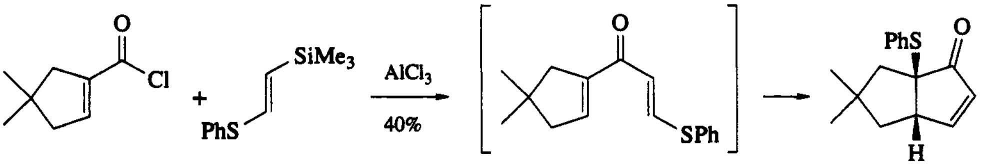

(84) (85) (86)

(46)

Vinyltrimethylsilane also reacts with substituted acryloyl chlorides to produce simple cyclopentenones in modest yield.[195] This reaction requires aluminum trichloride and 1,2-dichloroethane for optimal results.

A complementary approach, developed by Paquette,[75,76] uses substituted acryloyl chlorides as addends in reaction with structurally embellished vinylsilanes. A general route to the vinylsilanes (**87**) was found in the silylation of vinyllithiums generated by the Shapiro reaction.[196] The acylation with acryloyl chlorides takes place readily with aluminum trichloride to afford the divinyl ketones which are subsequently cyclized with tin tetrachloride. The Nazarov cyclization products were formed as a mixture of double bond isomers (equation 47). The best results were obtained with β,β-dimethylacryloyl chloride. Crotonyl chloride could be employed, but acryloyl chloride proved impractical. This method owes much of its utility to the regiocontrolled synthesis of the vinylsilanes, thereby clearly establishing the loci of cyclopentannulation.

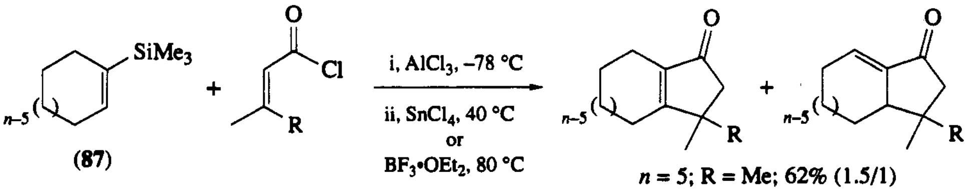

(87)

(47)

*n* = 5; R = Me; 62% (1.5/1)
*n* = 5; R = H; 58% (1/0)
*n* = 6; R = Me; 70% (1.5/1)
*n* = 6; R = H; 44% (1/0)
*n* = 7; R = Me; 57% (1/3.5)

## 6.3.8 APPLICATIONS IN SYNTHESIS

The Nazarov cyclization has been featured in a variety of synthetic endeavors involving both natural and unnatural[124,125] products. In the area of polyquinane natural products (±)-hirsutene (**88**),[194] (±)-modhephene (**89**),[197,198] (±)-silphinene (**90**),[129] (±)-$\Delta^{9(12)}$-capnellene (**91**)[107] and (±)-cedrene,[199] have all been prepared (Scheme 37). The synthesis of (**91**) is noteworthy in the iterative use of the silicon-directed Nazarov cyclization. The divinyl ketones were constructed by the carbonylation–coupling of enol triflates (**92**) and (**95**) with the β-silylvinylstannane (Scheme 38). The diquinane (**94**), obtained from Nazarov cyclization of (**93**), was transformed into enol triflate (**95**) which was coupled with the β-silylvinylstannane as before. Silicon-directed Nazarov cyclization of (**96**) was highly diastereoselective to provide the *cis,anti,cis* isomer of (**16**). The synthesis was completed by routine manipulations.

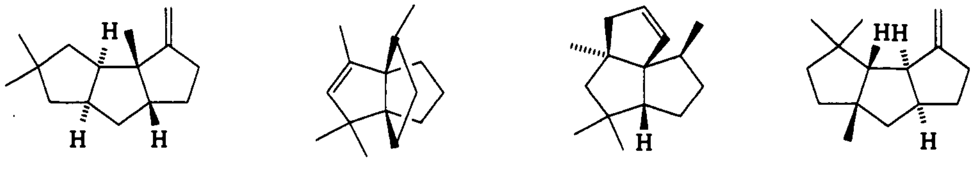

(**88**) (**89**) (**90**) (**91**)

Scheme 37

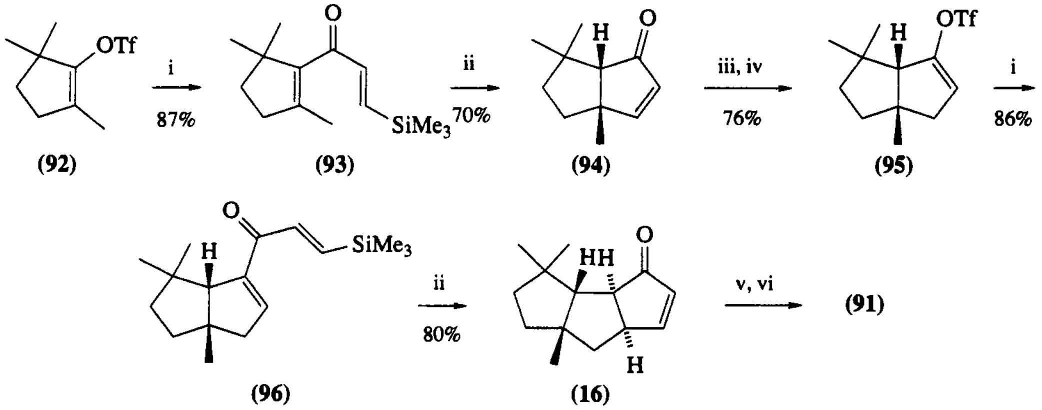

i, 3-trimethylsilylvinyltrimethylstannane, $Pd(Ph_3P)_4$, CO; ii, $BF_3 \cdot OEt_2$; iii, $LiBu^s{}_3BH$; iv, $Tf_2O$; v, $H_2$; vi, $Ph_3P=CH_2$

Scheme 38

The acetylene-based route (Raphael–Nazarov cyclization) has been used successfully to construct the five-membered rings in (±)-strigol[126] and (±)-norsterepolide.[131] This variant has also been used to perform a cyclopentenone annulation towards the construction of other sized rings in (±)-nookatone (**97**),[128] (±)-muscone (**98**)[133,184] and (±)-muscopyridine (**99**)[128] (Scheme 39). In the nookatone synthesis, the Nazarov cyclization served to set the stereochemical relationship between the isopropyl group and the ring fusion. A carbenoid ring expansion completed the synthesis. Since cyclododecanone is inexpensive, three-carbon ring expansion methods have been developed for the synthesis of (±)-muscone and (±)-muscopyridine.

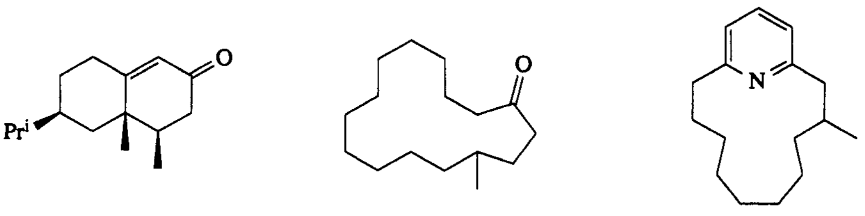

(**97**) (**98**) (**99**)

Scheme 39

For the construction of simple cyclopentanoid natural products, the Nazarov cyclization has been employed in the synthesis of *cis*-jasmone[141] and prostaglandin analogs[148,149,177] and (±)-vallerenal.[162] Tius has made good use of his cationic α-methylenecyclopentene forming process in the synthesis of the related natural products (±)-methylenomycin B, (±)-deepoxy-2,3-didehydromethylenomycin A **(100)**[173] and (±)-xanthocin.[174] The facile construction of **(100)** illustrates the utility of the method (Scheme 40). Addition of 1-lithioallenylmethoxymethyl ether to enone **(101)** produced the allenyl alcohol **(102)**. Cationic cyclization of **(102)** was induced by treatment with trifluoroacetic anhydride to afford the α-methylenecyclopentenone **(103)** in 65% yield. Photooxidative removal of the isoxazole[200] revealed the carboxy group and completed the synthesis.

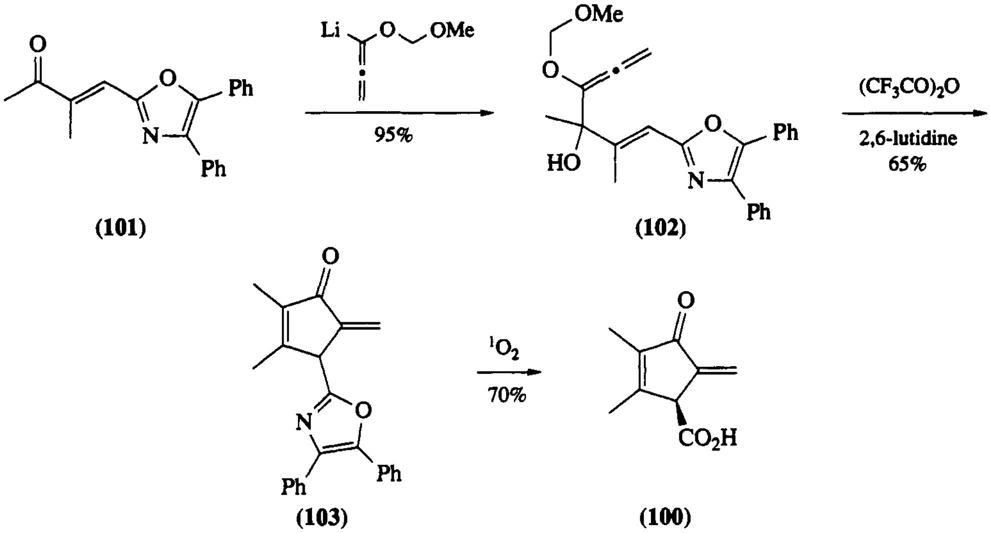

Scheme 40

The Nazarov cyclization has also been used industrially. In the Merck synthesis of (+)-indacrinone the indanone unit is formed by an aromatic Nazarov cyclization.[201]

Finally, there has been speculation and recent experimental support for the involvement of a Nazarov-type cyclization in the biosynthesis of *cis*-jasmonic acid[202,203] and marine-derived prostanoids.[204] Radio-label tracer studies have demonstrated the intermediacy of 8-HPETE **(104)** in the biosynthesis of prostanoid intermediate preclavulone A **(107)**.[204] This remarkable conversion was proposed to proceed by formation of allene oxide **(105)** followed by isomerization to **(107)** *via* the 2-oxidocyclopentadienyl cation **(106**; Scheme 41). To demonstrate the chemical feasibility of this proposal, Corey reported the transformation of epoxysilane **(108)** to, *inter alia*, the cyclopentenone **(111**; Scheme 42).[71] The reaction is presumed to involve formation of the allene oxide **(109)**[205] followed by isomerization to the 2-oxidopentadienylic cation **(110)**. Conrotatory closure of **(110)** is expected to produce the *cis* isomer of **(111)** as observed.

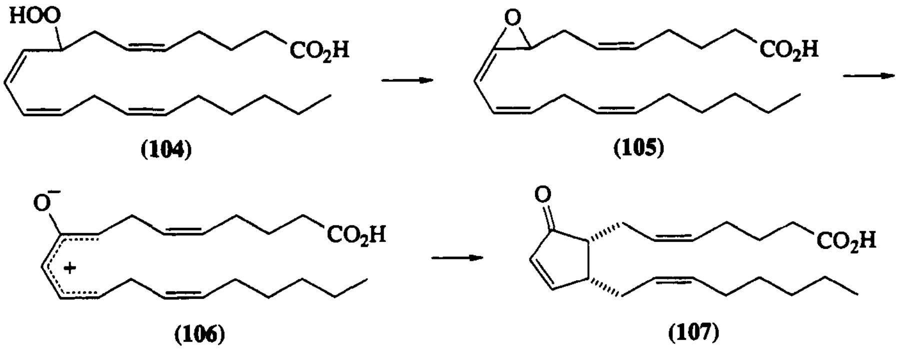

Scheme 41

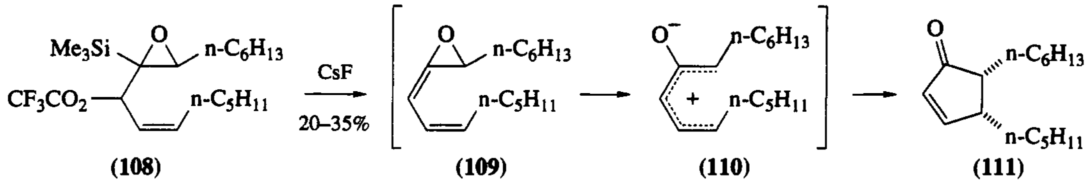

**Scheme 42**

Strong experimental support for the biochemical pathway is provided by the isolation and characterization of the allene oxide (**105**) by Brash.[206] Further, solvolysis of (**105**) produced (**107**) along with α-ketols.[207,208] The biochemical mechanism for formation of an allene oxide from 8-HPETE remains to be clarified.

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# 7.1

# Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements

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## 7.1.1 INTRODUCTION

The Cope rearrangement,[1] discovered in 1940 by Arthur C. Cope early in his outstanding career, comprises the thermal rearrangement of 1,5-dienes to isomeric 1,5-dienes (equation 1). Today it is recognized as the prototype all-carbon member of a large family of related rearrangements which include the Claisen, aza-, thia- and phospho-Claisen rearrangements, rearrangements of allylic esters, and a number of other variations collectively classified as 3,3-sigmatropic rearrangements.

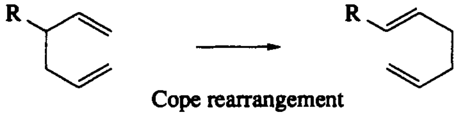

(1)

The special value of the Cope rearrangement in modern organic synthesis is due to the following characteristics, which provide a remarkable degree of specificity.

(i) The parent Cope rearrangement is effected thermally, without any requirement for acid or base catalysis, and can thus accommodate a wide variety of functional groups.

(ii) In creating a new C—C single bond at the expense of an existing bond in the substrate, the rearrangement generates 1,5-dienes in which the location of the new single bond and two double bonds is fixed unambiguously and predictably. The Cope rearrangement produces not only acyclic dienes but also cyclic dienes in rings of seven or more members, and is one of the most powerful methods of synthesis of medium rings.

(iii) Due to the highly ordered cyclic transition state the reaction is extremely stereospecific with respect both to the formation of unsymmetrical double bonds and to the creation of stereogenic centers. The substrate may have as many as four elements of stereochemistry in the six-carbon framework (two unsymmetrical double bonds and two asymmetric centers at the saturated carbons), and these are translated to four new elements, usually with near quantitative asymmetric transmission.[2]

(iv) The development of the oxy-Cope and anionic oxy-Cope reactions has greatly extended the utility of the Cope rearrangement by allowing easier access to diene substrates, lowering the temperature required for rearrangement, and producing carbonyl products irreversibly.

### 7.1.1.1 Oxy-Cope Rearrangement

Infrequent synthetic application of the Cope rearrangement was made in the first two decades following its discovery, probably for obvious reasons: the general methods available for the preparation of the 1,5-diene substrates could often be applied just as easily to the direct synthesis of the Cope product, making the rearrangement superfluous. This situation changed drastically with the discovery of the oxy-Cope rearrangement in 1964. Berson and Jones[3] pointed out that substitution of a hydroxy group at carbons C-3 or C-4 of a 1,5-diene resulted, after rearrangement, in an enol whose tautomerization led irreversibly to a δ,ε-unsaturated carbonyl compound (equation 2). Examples of oxy-Cope rearrangement are shown in equations (3)–(5). As these equations illustrate, several advantages accrue from carrying out the rearrangement as the oxy-Cope variation: (i) the Cope substrate is easily prepared by Grignard-type addition, either of a vinyl organometallic reagent to a β,γ-unsaturated carbonyl compound or of an allylic reagent to an α,β-unsaturated carbonyl compound; (ii) the oxy-Cope rearrangement is irreversible; (iii) the product of oxy-Cope rearrangement has two different functional groups, easily manipulated for further synthetic purposes.

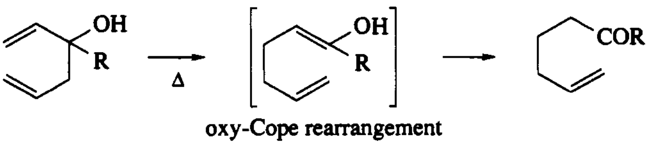

(2)

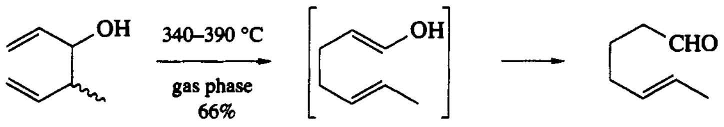

(ref.4) (3)

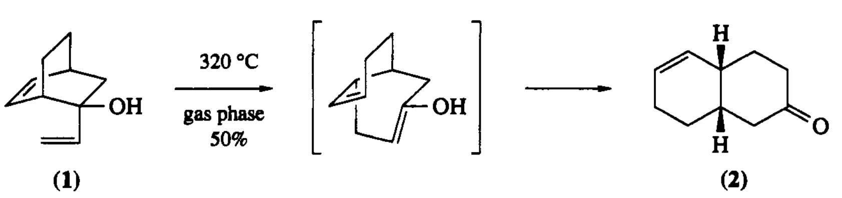

(ref.3) (4)

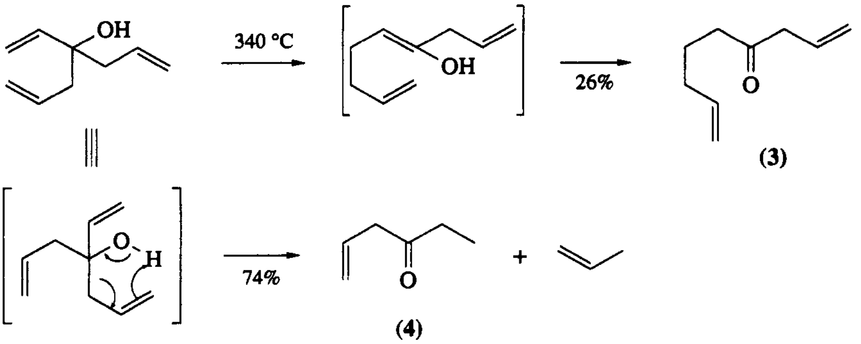

(ref.5) (5)

The principal drawback of the oxy-Cope rearrangement is the competing fragmentation of the substrate *via* a thermal retro-ene reaction, as seen in equation (5), where the Cope product (**3**) is overshadowed by the retro-ene product (**4**), an almost inevitable competitor whenever geometrically possible. In simple substrates fragmentation is frequently the major thermal pathway. One logical solution to this problem is to protect the hydroxy group as an ether or ester. Examples of the oxy-Cope rearrangement of methyl ethers and esters are shown in equations (6)[6] and (7),[7] which illustrate the good yields possible with protected alcohols.

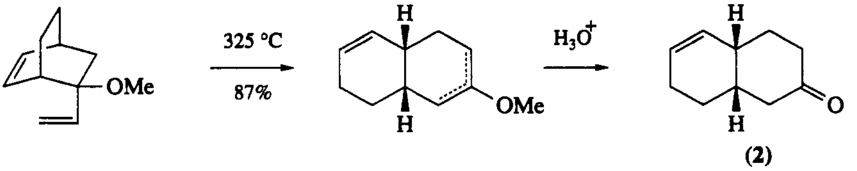

(6)

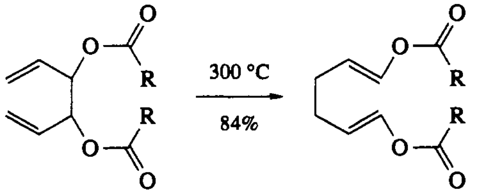

R = CHMe$_2$

(7)

It has also been observed that higher yields of oxy-Cope products are often obtained when *N*-methylpyrrolidone is added to the solvent,[8] probably interfering with inter- or intra-molecular hydrogen bonding.

The oxygen substituent has another important effect on the oxy-Cope process: Berson and Walsh[9] have shown that, at least in bridged bicyclic substrates of type (**5**), the hydroxy group lowers the bond dissociation energy by 24 kcal mol$^{-1}$ (1 cal = 4.18 J). This is sufficient to change the mechanism from a concerted one to a stepwise diradical process, which in turn may lead to significant amounts of 1,3-rearrangement as well as 3,3-rearrangement (equation 8).[9]

Thies[10] has shown that the 1,3-oxy-Cope rearrangement can be used to advantage as a two-carbon ring expansion method (equation 9).[10] Addition of vinyllithium to a cyclic β,γ-unsaturated ketone (**6**), followed by pyrolysis of the TMS ether (**7**) of the resulting alcohol, gives predominantly the 1,3-rearrangement product (**8**).

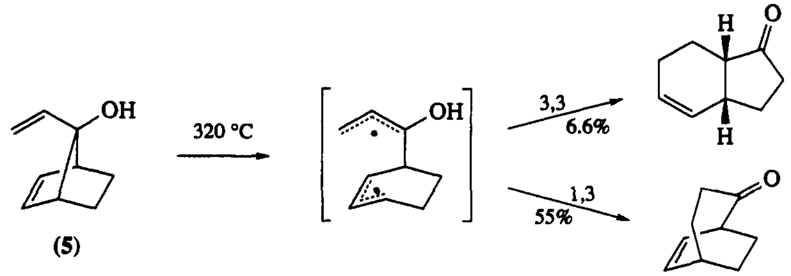
OH
320 °C
OH
3,3
6.6%
1,3
55%
H
O
H
O
(5)

(8)

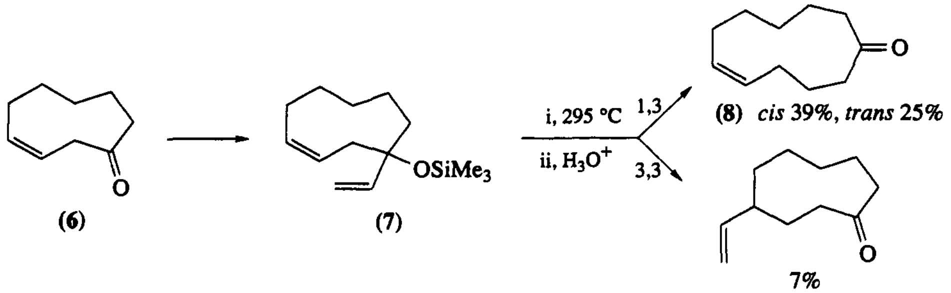
O
OSiMe3
i, 295 °C
ii, H3O+
1,3
3,3
O
(8) cis 39%, trans 25%
O
7%
(6)
(7)

(9)

### 7.1.1.2 Anionic Oxy-Cope Rearrangement

A major advance in synthetic applications of Cope rearrangements occurred in 1975, when Evans and Golob[11] reported their remarkable finding that rate enhancements of $10^{10}$–$10^{17}$ in oxy-Cope rearrangements can be achieved by using the 1,5-diene alkoxide as substrate. Sodium and, especially, potassium alkoxides were found most effective. Some examples of anionic oxy-Cope rearrangements are shown in equations (10)–(12), where the relatively mild reaction conditions required to induce rearrangement are indicated.

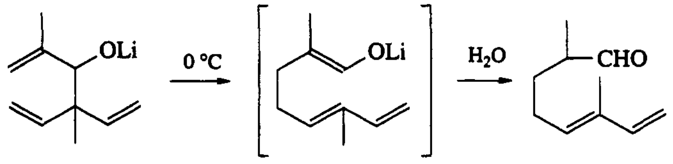
OLi
0 °C
OLi
H2O
CHO

(ref.12) (10)

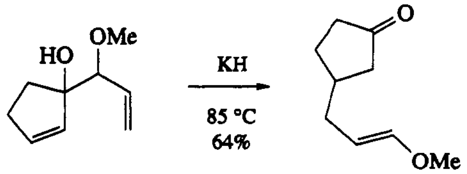
OMe
HO
KH
85 °C
64%
O
OMe

(ref.13) (11)

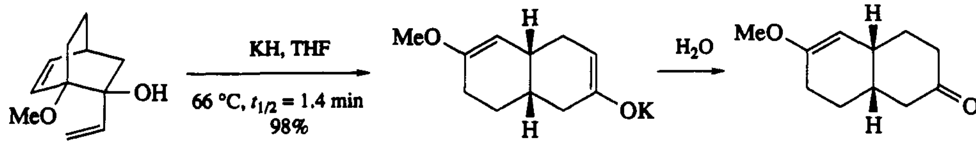
MeO
OH
KH, THF
66 °C, t1/2 = 1.4 min
98%
MeO
H
H
OK
H2O
MeO
H
H
O

(ref.11) (12)

A simplistic explanation of the rate acceleration provided by the alkoxide ion is that in the product, as an enolate, the negative charge is much more delocalized than in the alkoxide substrate. Theoretical calculations, however, show that the primary effect of the alkoxide is to weaken the carbon–carbon single bond,[14] rather than an effect on the transition state. The oxy-anion effect is seen in the gas phase as well as in solution.[15]

A simple model of substituent effects[16] predicts that both donor and acceptor groups substituted on the saturated carbons of a Cope substrate should increase the rate. Interesting examples have been published in which either an enolate ion (**9**)[17] or a carbocation (**10**)[18] in that position does indeed dramatically accelerate a Cope rearrangement.

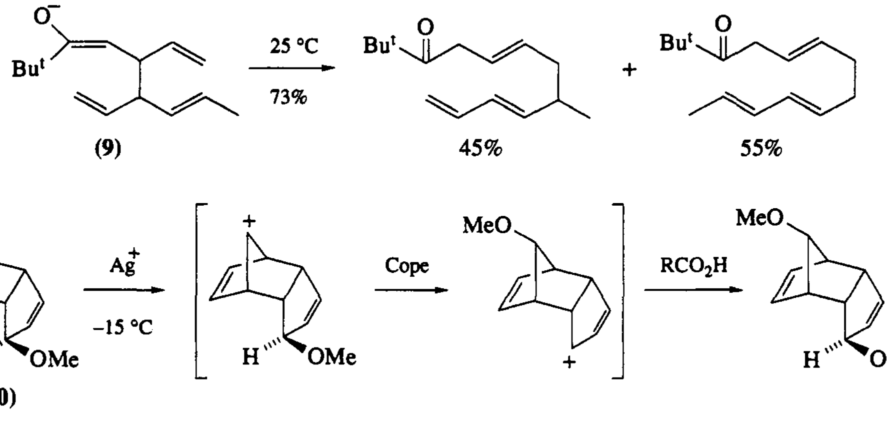

## 7.1.2 POSITION OF EQUILIBRIA IN COPE REARRANGEMENTS

Characteristic of all sigmatropic rearrangements, the Cope rearrangement is reversible; the starting and product 1,5-dienes exist at equilibrium at rearrangement temperature through a cyclic transition state. In the Claisen rearrangement the gain in energy which accompanies the conversion of a a vinyl ether double bond into a carbonyl double bond is usually sufficient to shift the equilibrium completely toward the carbonyl product, but the Cope rearrangement of the parent 1,5-hexadiene is degenerate, and so the position of equilibrium is determined by such other factors as the substitution pattern, conjugation, strain, or irreversible conversion of one diene to a more stable product. These factors are outlined below.

### 7.1.2.1 Alkyl Substitution

In the absence of conjugating substituents the equilibrium between isomeric 1,5-dienes will generally lie on the side of that with more-substituted double bonds, reflecting the relative stability ranking of tetra- > tri- > di- > mono-substituted alkenes. Some examples of this preference are given in Scheme 1. In each case the product contains a higher degree of alkyl substitution on the double bonds than does the starting 1,5-diene.

### 7.1.2.2 Conjugating Substituents

A second important factor is conjugation of one or both of the double bonds with π-substituents such as ketone, ester, cyano, or phenyl. Some examples are shown in Scheme 2. In each case the conjugated isomer heavily predominates at equilibrium.

The reactions in which Cope initially discovered this rearrangement exploit this factor and represent a strategy still useful in synthesis today, illustrated in Scheme 3. An α,β-unsaturated carbonyl compound (or cyanoacetic ester, *etc.*) is converted to the anion and alkylated with an allylic halide; alkylation of the ambident anion takes place next to the carbonyl group(s), creating a 1,5-diene. Heating then initiates the Cope rearrangement which brings the double bond back into conjugation. In equation (13) the condensation product of cyclohexanone with ethyl cyanoacetate is alkylated with allyl bromide to give the 1,5-diene (**13**); distillation at atmospheric pressure effects Cope rearrangement[28] to the conjugated isomer (**14**). Conia has used this technique extensively with α,β-unsaturated ketones. As seen in equation (14), alkylation of 2-benzyl-3-methylcyclohexenone with allyl bromide gives diene (**15**), which again rearranges[29] on heating to the isomeric conjugated ketone (**16**).

A recent variation of this strategy is due to Ziegler,[30] who used TMS ethers of cyanohydrins of α,β-unsaturated aldehydes as substrates. Alkylation with an allylic halide, such as crotyl bromide in equation (15), gave diene (**17**), which underwent Cope rearrangement on heating to afford the conjugated isomer (**18**). Work-up with KF in methanol afforded the ester (**19**) by way of an intermediate acyl cyanide.

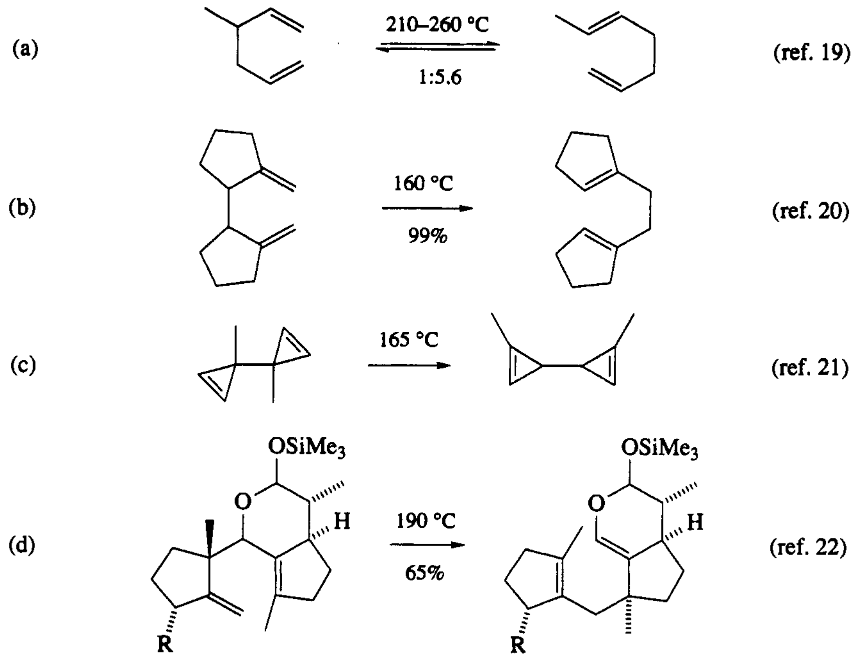

**Scheme 1** Cope equilibria in nonconjugated dienes

Equation (16) shows a practical application of this sequence to steroid synthesis; the ester (**20**) was converted by carbocation cyclization to estrone or 11-ketoprogesterone.

It should be noted that occasionally the preference for polyalkyl substitution of double bonds will outweigh conjugation with electron-withdrawing groups, and the Cope equilibrium then lies on the side of the nonconjugated isomer. In equation (17) the unconjugated ester (**21**) is favored by a 3:1 ratio,[23] and in equation (18) the conjugated sulfone (**22**) is converted in high yield to the unconjugated isomer.[31] In both cases the equilibrium position is apparently due to the greater degree of alkyl substitution in the nonconjugated isomers.

### 7.1.2.3 Aromatization of Cope Products

In some cases the driving force for Cope rearrangement may be the incorporation of one of the double bonds into an aromatic ring system. Equations (19) and (20) show two examples of generation of a five-membered aromatic nitrogen heterocycle by Cope rearrangement.[32] Indoline (**23**) rearranges readily to the indole isomer, while (**24**) rearranges, after tautomerization to the enamine (**25**), to the aromatic pyrazole (**26**).

Alternatively, a Cope product may be able to tautomerize to an aromatic ring, driving the equilibrium toward the aromatic product. A classic example is the second step in the '*para*' Claisen rearrangement of aryl allyl ethers. This step can be seen in isolated form in equation (21) in the rearrangement of 5-allyl-2,4-cyclohexadienones such as (**27**), which rearranges readily[33] to phenol (**28**). A useful modification of this principle is Evans' method[34] of introducing isoprenyl groups into quinones (equation 22). The dimethylallyl group in (**29**) is inserted by Grignard addition to a protected cyanohydrin of a naphthoquinone. Once the carbonyl group is released from the cyanohydrin TMS ether by treatment with silver fluoride, an oxy-Cope rearrangement occurs readily to give (**30**), and loss of methanol drives the equilibrium toward quinone (**31**).

Is the reverse possible, *i.e.* can a double bond of an aromatic ring participate in Cope rearrangement, destroying (at least temporarily) the aromaticity of the ring? In view of the close parallel between Cope and Claisen rearrangements, one might envision a Cope analog of the allyl aryl ether Claisen which would transfer an allyl group from a benzilic carbon to an *ortho* position on the ring (equation 23). Attempts to realize this possibility with simple benzenes have met with uniform failure, both in the parent case (R = H) or with conjugating substituents.[35] One of the few successful cases of aromatic double bond participation occurs with the thiophene (**32**) to give the rearranged isomer (**33**; equation 24);[36] the unprecedented cyclization to (**34**) which takes place at higher temperatures is also seen with naphthalene and

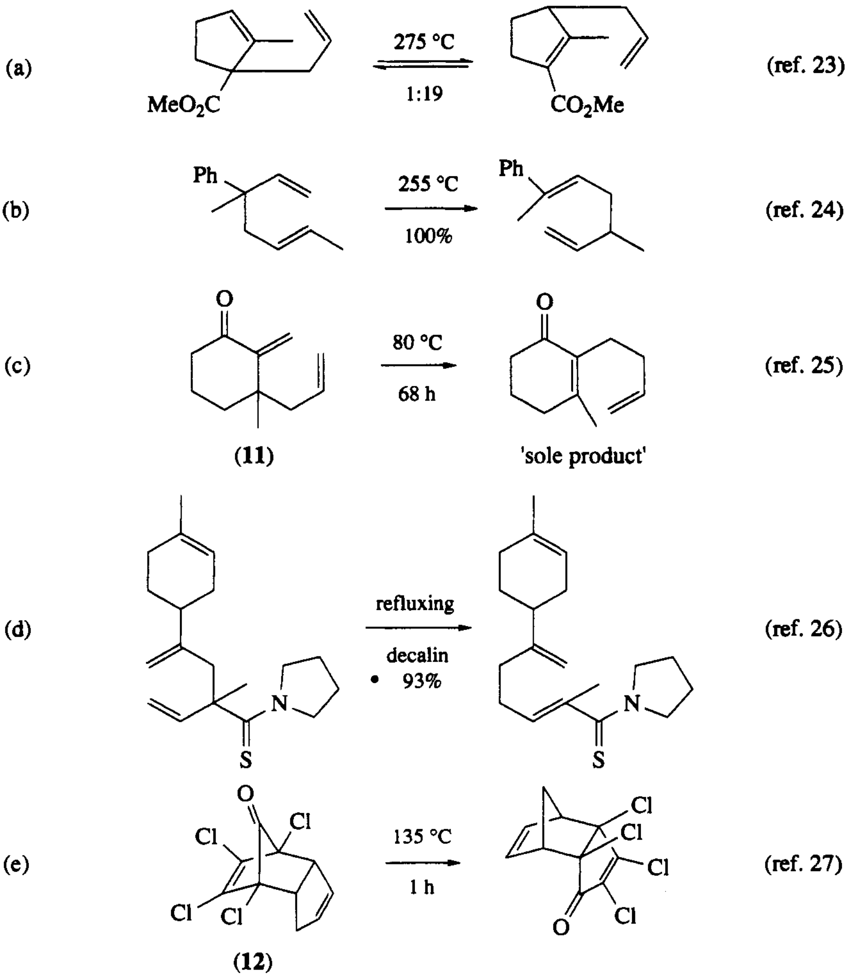

**Scheme 2** Effect of conjugation on Cope equilibria

phenanthrene analogs.[37] The only example of a benzene which undergoes Cope rearrangement is phenol (**35**), in which the cyclopropane ring lowers the otherwise high activation energy required for disruption of aromaticity, affording the benzocycloheptene (**36**; equation 25);[38] heteroaromatic analogs of (**35**) rearrange even more readily.[39]

Aromatic double bonds participate somewhat more easily in oxy-Cope rearrangements, where the driving force of tautomerization to a carbonyl compound helps to compensate for loss of aromaticity. Equation (26) shows one example,[40] in which 1,3- and 3,3-oxy-Cope products are formed from naphthalene (**37**). The best cases to date have been provided by Jung and coworkers in bicyclo[2.2.1]heptenols of type (**38**), which take advantage of relief of strain in the bridged ring system as well as the oxy-Cope effect to allow double bonds of furan and naphthalene to participate.[41] Cope rearrangement of (**38**) leads to the steroid skeleton (equation 27), and an imaginative route to coronafacic acid was realized from the benzofuran analog.

### 7.1.2.4 Ring Strain

A critical factor in the Cope equilibrium between a 1,2-divinylcycloalkane and cyclic diene partner is the strain associated with the particular ring sizes involved. *cis*-1,2-Divinylcyclopropanes and cyclobutanes are notorious for easy Cope rearrangements to less-strained seven- and eight-membered ring dienes, as shown in Scheme 4. *cis*-1,2-Divinylcyclopropane (**39**) undergoes a spontaneous Cope rearrangement below room temperature[42] to produce 1,4-cycloheptadiene (**40**), and *cis*-1,2-divinylcyclobutane (**41**) rearranges easily[43] to afford 1,5-cyclooctadiene (**42**). The relative strains in these two small rings are pitted against each other in the equilibrium between (**43**) and (**44**), and the equilibrium lies

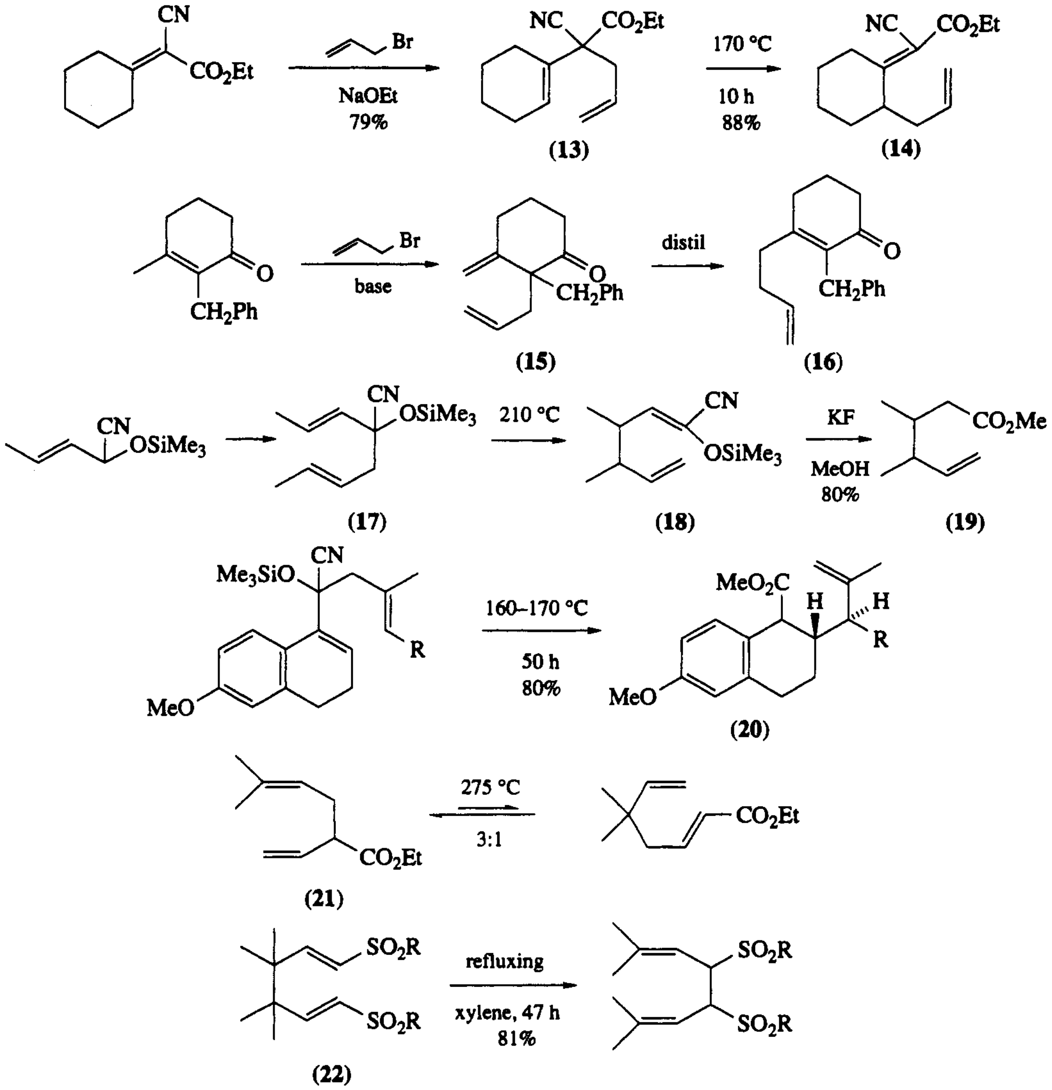

Br
NaOEt
79%
170 °C
10 h
88%
Br
base
distil
210 °C
KF
MeOH
80%
160–170 °C
50 h
80%
275 °C
3:1
refluxing
xylene, 47 h
81%

(13) (14) (13)

(15) (16) (14)

(17) (18) (19) (15)

(20) (16)

(21) (17)

(22) (18)

**Scheme 3** Exploiting conjugation in Cope equilibria

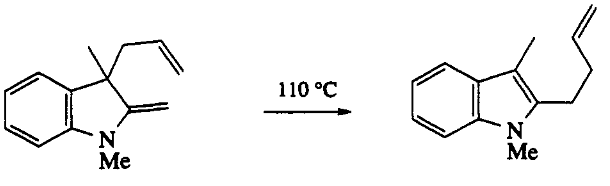

(23)

(19)

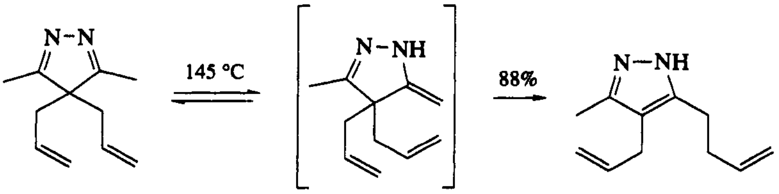

(24) (25) (26)

(20)

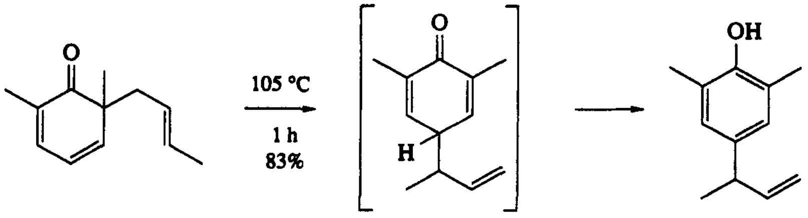
105 °C
1 h
83%
H
(27)
(28)

(21)

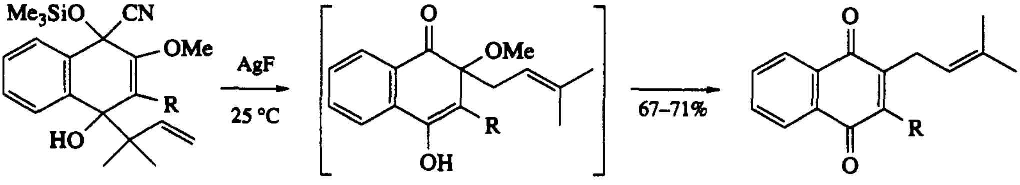
Me3SiO
CN
OMe
R
HO
AgF
25 °C
OMe
R
OH
67–71%
R
(29)
(30)
(31)

(22)

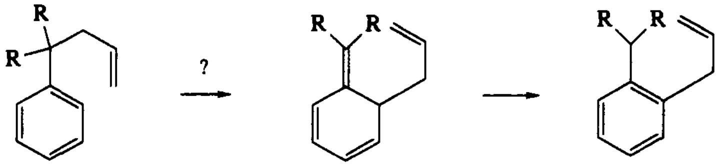

(23)

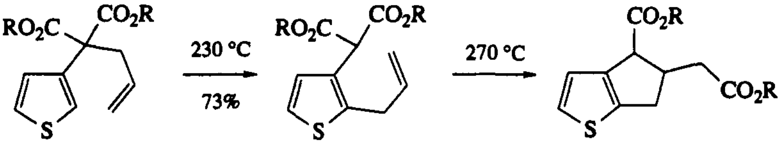
RO2C
CO2R
S
230 °C
73%
RO2C
CO2R
S
270 °C
CO2R
CO2R
S
(32)
(33)
(34)

(24)

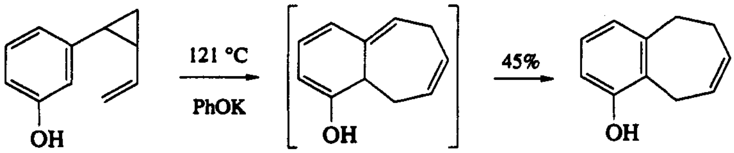
OH
121 °C
PhOK
OH
45%
OH
(35)
(36)

(25)

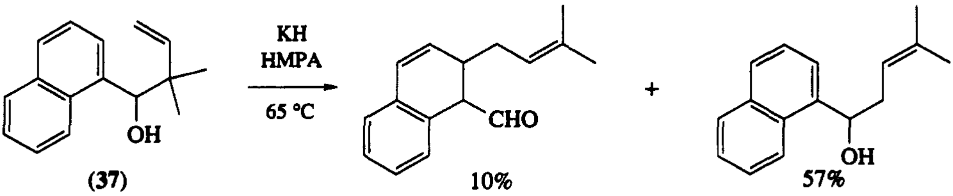
OH
KH
HMPA
65 °C
CHO
+
OH
(37)
10%
3,3-shift
57%
1,3-shift

(26)

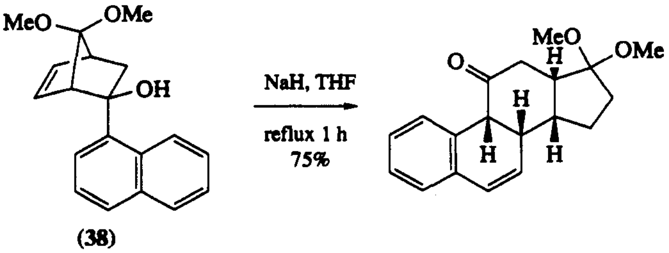
MeO
OMe
OH
NaH, THF
reflux 1 h
75%
MeO
H
OMe
O
H
H
H
(38)

(27)

completely on the side of the fused cyclobutane.[44] Cope rearrangement still occurs readily when the 1,2-divinylcyclopropane arrangement is built into bicyclic ring systems, as in diene (**45**), which rearranges[45] just above room temperature to the bicyclo[3.2.1]octadiene (**46**). Though not a 1,2-divinylcycloalkane, 2-vinylmethylenecyclopropane (**47**) also undergoes a low temperature Cope rearrangement to relieve the ring strain.[46]

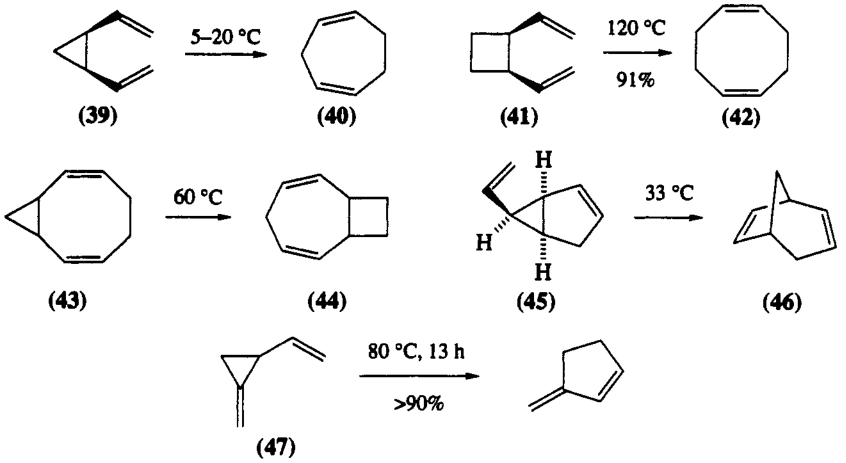

**Scheme 4** Cope equilibria in cyclopropanes and cyclobutanes

The position of equilibrium is totally reversed when one moves up to 1,2-divinylcyclopentanes and cyclohexanes (Scheme 5). Given relatively strain-free five- and six-membered rings *versus* considerable strain in the medium rings, the balance shifts in the opposite direction, and 1,5-cyclononadiene (**48**)[47] and cyclodecadiene (**50**)[48] rearrange completely to the divinylcycloalkanes (**49**) and (**51**). We will enlarge on the stereochemistry and synthetic applications of these rearrangements subsequently. The Cope rearrangement of the vinylbicyclo[2.2.2]octene (**52**) to diene (**53**) is an example of a 1,2-divinylcyclohexane whose rearrangement product is more stable,[49] but this is undoubtedly due primarily to the release of strain in the bicyclooctene. The rearrangement[50] of the methylenecyclooctene (**54**) to (**55**) is probably favored by the increased stability of a six- *versus* an eight-membered ring.

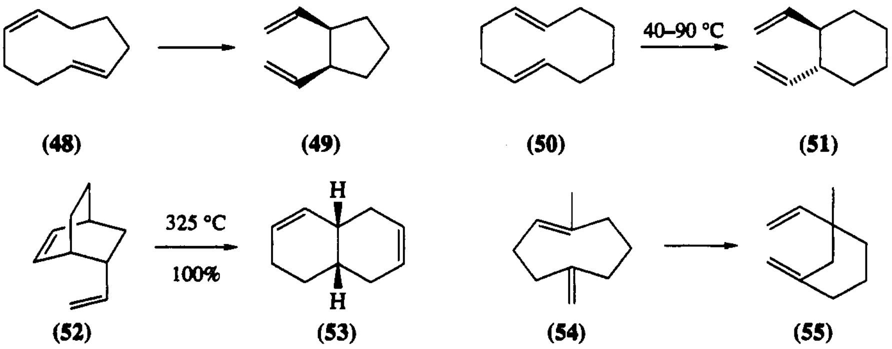

**Scheme 5** Cope equilibria in 1,2-divinyl-cyclopentanes and -cyclohexanes

### 7.1.2.5 Conformational Factors

In addition to the major factors discussed above, a number of Cope equilibria can be interpreted only in terms of more subtle conformational factors which favor one isomer. Consider the two hydroxydicyclopentadienes (**56**) and (**57**) in Scheme 6: at 140 °C each is in equilibrium with its Cope rearrangement product (**58**) or (**59**). For the *exo*-alcohol (**56**), the equilibrium ratio is 1:1, but in the *endo* isomer (**57**), where the hydroxy group suffers steric compression, the rearrangement product is favored by at least 4:1.[51] In the diphenylcyclopropene (**60**), conjugation would appear to favor the starting material, but the

1:1 ratio with its Cope product (61) at 140 °C may reflect the nonbonded interactions between the phenyl groups in the *cis*-stilbene starting material, relieved in the product.[52]

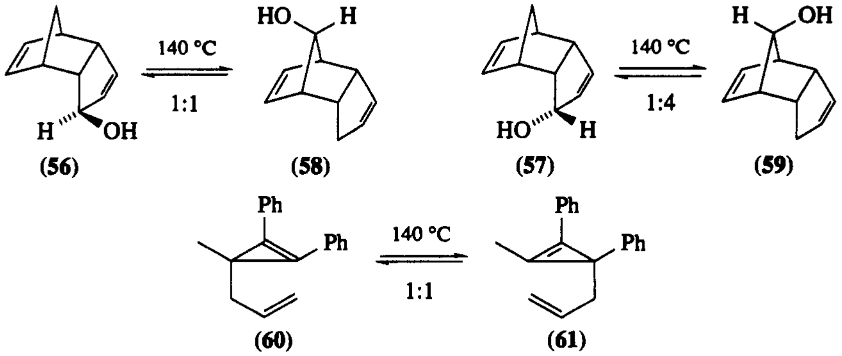
H
OH
140 °C
1:1
HO
H
(56)
(58)
140 °C
1:4
H
OH
HO
H
(57)
(59)
Ph
Ph
140 °C
1:1
Ph
Ph
(60)
(61)

Scheme 6 Conformational factors in Cope equilibria

### 7.1.2.6 Irreversibility of Oxy-Cope Rearrangements

As noted earlier, the generation in the oxy-Cope rearrangement of an enol which rapidly tautomerizes to a carbonyl compound effectively removes the Cope product from equilibrium and drives the rearrangement irreversibly; examples have been cited in equations (3)–(5), (10)–(12) and (26) and (27). Scheme 7 lists several additional examples which emphasize the ability of the oxy-Cope rearrangement

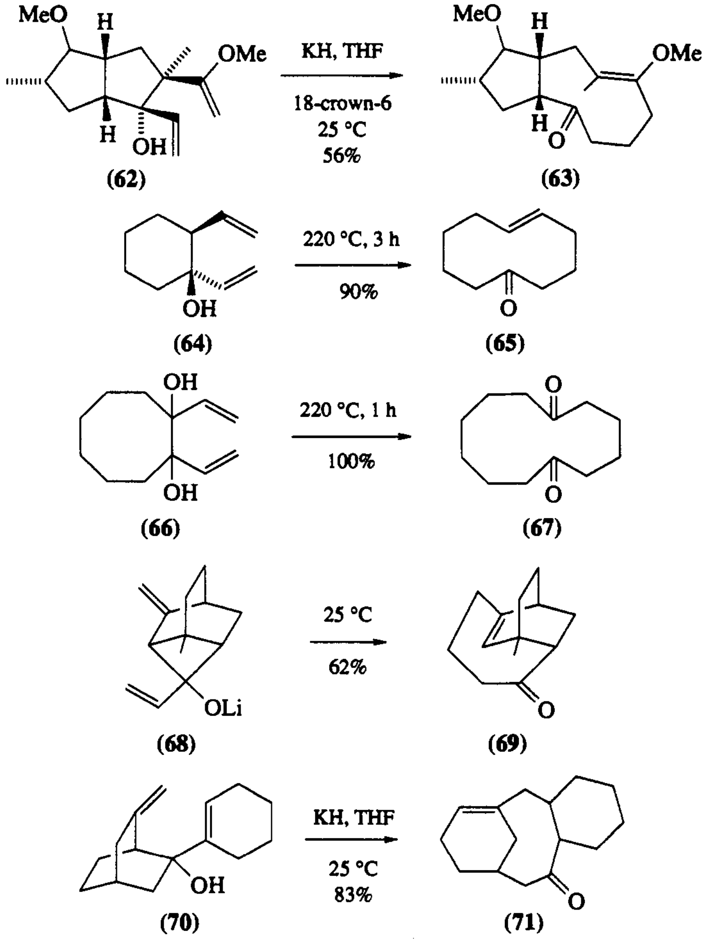
MeO
H
OMe
H
OH
(62)
KH, THF
18-crown-6
25 °C
56%
MeO
H
OMe
H
O
(63)
OH
(64)
220 °C, 3 h
90%
O
(65)
OH
OH
(66)
220 °C, 1 h
100%
O
O
(67)
OLi
(68)
25 °C
62%
O
(69)
OH
(70)
KH, THF
25 °C
83%
O
(71)

Scheme 7 Shift of unfavorable equilibria by oxy-Cope rearrangement to reverse the normal equilibrium or to produce strained products which would not have been possible by the normal Cope process.

1,2-Divinylcyclopentanes, as observed above, are usually the stable products of Cope equilibria, but the rearrangement of diene (**62**) is driven to the cyclononenone (**63**) by making it an irreversible oxy-Cope rearrangement.[53] Similarly 10-membered ring ketones, such as (**65**), can be prepared by oxy-Cope rearrangement of 1,2-divinylcyclohexanols (**64**),[54] and this versatile route to functionalized cyclodecanes has played an important role in the synthesis of germacrane sesquiterpenes. Rings containing 12 or more carbons can be synthesized in good yield by oxy-Cope rearrangement of 1,2-divinyl-1,2-cycloalkanediols, *e.g.* (**66**) to (**67**).[55] Considerably strained molecules such as the tricyclic ketones (**69**) and (**71**), both of which contain bridgehead double bonds, can be assembled in reasonable yields by oxy-Cope rearrangement of hydroxydiene precursors (**68**)[56] and (**70**);[57] the oxy-Cope reaction provides one of the attractive strategies which have been developed to construct the taxane skeleton in (**71**).

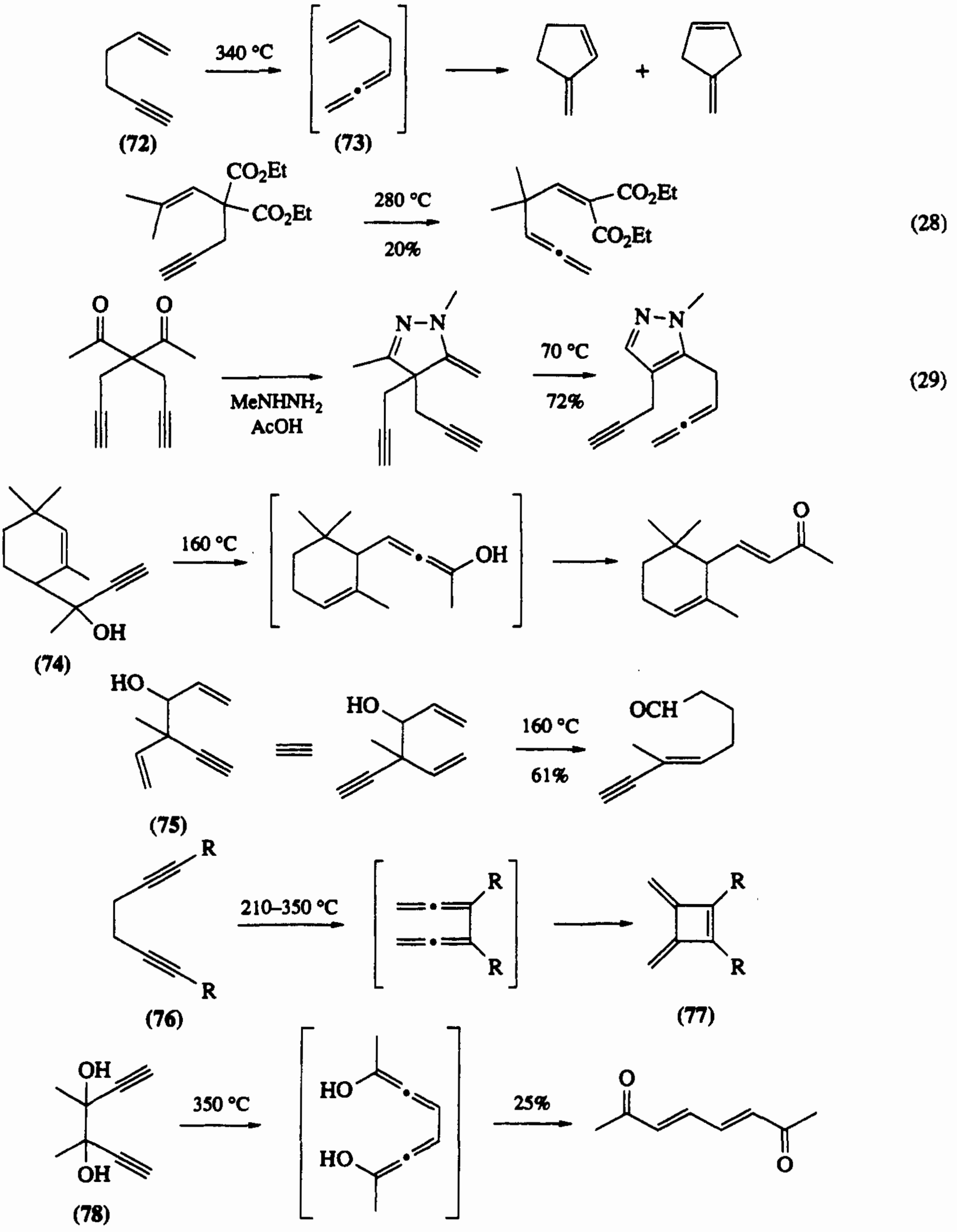
340 °C
(72)
(73)
+
CO2Et
CO2Et
280 °C
20%
CO2Et
CO2Et
(28)
O
O
MeNHNH2
AcOH
N–N
70 °C
72%
N–N
(29)
160 °C
OH
OH
O
(74)
HO
HO
160 °C
61%
OCH
(75)
R
210–350 °C
R
R
R
R
R
(76)
(77)
OH
OH
350 °C
HO
HO
25%
O
O
(78)

**Scheme 8** Cope rearrangement of 1,5-enynes and 1,5-diynes

## 7.1.3 PARTICIPATION OF ALKYNES AND ALLENES IN COPE REARRANGEMENT

### 7.1.3.1 Alkynes

While it may seem geometrically unlikely that a linear alkyne bond could fit into the constraints of a six-membered cyclic transition state, Cope rearrangement of 1,5-enynes and even 1,5-diynes works surprisingly well and provides a useful route to allenes. Examples are shown in Scheme 8. Simple cases such as the parent (**72**) do not provide a viable route to allenes because the products (**73**) cyclize at high temperatures,[58] but more highly substituted examples are synthetically useful, and those shown in equations (28)[59] and (29)[60] give isolable allenes. The oxy-Cope rearrangement of (**74**) leads to an allene enol which tautomerizes to an unsaturated ketone, providing a valuable intermediate in the β-ionone series.[61] The rearrangement of (**75**), designed to provide head-to-head competition between a vinyl *versus* an alkynyl group, shows that the normal unstrained Cope rearrangement of a 1,5-diene is preferred.[62]

Huntsman and Wristers have examined the Cope rearrangement of 1,5-diynes (**76**); these appear to rearrange normally to bisallenes, but the products undergo ready electrocyclization to bismethylenecyclobutenes (**77**) at the temperatures required for rearrangement.[63] Diynediol (**78**) undergoes oxy-Cope rearrangement to a linear dienedione, again by tautomerization of a bisenol.[64]

### 7.1.3.2 Allenes

One double bond of an allene unit participates readily in Cope rearrangements, leading to the useful result of placing a conjugated diene at that end of the product. Several examples are shown in Scheme 9. Bicyclic allene (**79**) is converted in high yield on heating to the hydroindane (**80**).[65] In an application of the oxy-Cope rearrangement to allenes, alcohol (**81**) is converted to diene (**82**), again in good yield.[66]

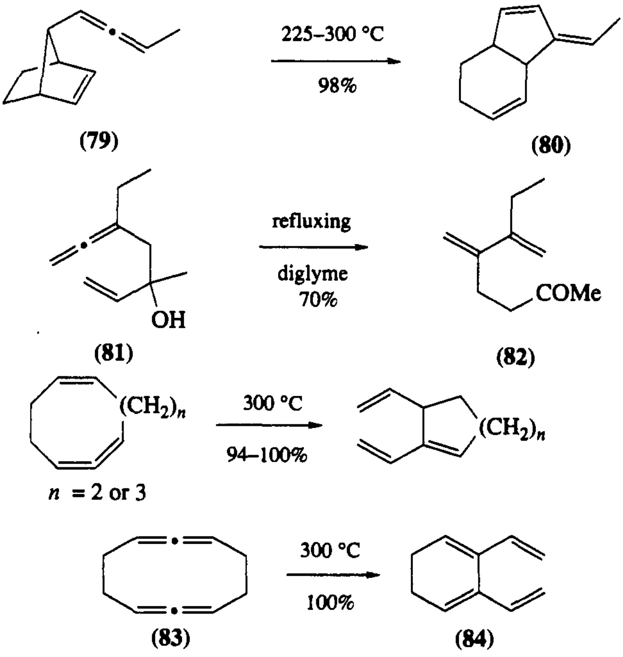

(30)

**Scheme 9** Cope rearrangement of allenes

When the allene and isolated double bond are both incorporated into a large ring, then Cope rearrangement affords 2,3-divinylcycloalkenes, as seen in equation (30).[67] The cyclic bisallene (**83**) affords 2,3-divinyl-1,3-cyclohexadiene (**84**), again in excellent yield.[67] These examples illustrate just how useful the allene variation of the Cope rearrangement is in the synthesis of interesting 1,3-dienes.

## 7.1.4 EXPERIMENTAL CONDITIONS; CATALYSIS

### 7.1.4.1 Experimental Conditions

The experimental simplicity of the Cope rearrangement is one of its most attractive features. As thermal reactions, the Cope and oxy-Cope rearrangements can be carried out in either of two basic ways.

(i) Heating the substrate neat or in a high boiling solvent (*e.g.* decalin, xylene, diphenyl ether) under reflux or in a sealed tube is the most common method. The rates of most Cope rearrangements show little response to solvent polarity, so that a variety of solvents are acceptable. Substrates of moderate molecular weight frequently undergo Cope rearrangement during distillation at atmospheric pressure.

(ii) Vapor-phase rearrangement in a flow apparatus is often used for volatile substrates; passing the vapors at low concentration through a heated tube with short contact time helps to minimize decomposition.

Descriptions of both techniques may be found in the 1975 *Organic Reactions* review[1] and in representative articles.[4]

Typical bases used to generate the alkoxide ion for the anionic oxy-Cope rearrangement include sodium and potassium hydrides and potassium hexamethyldisilazide. Preliminary treatment of commercial KH with iodine, to destroy the putative contaminants potassium and potassium superoxide, is reported[68] to result in reproducibly high yields of anionic oxy-Cope reactions with dienolates such as (**85**). Tetrahydrofuran is the common solvent, although higher boiling solvents (*e.g.* diglyme) may be necessary. Frequently the addition of a complexing agent for the potassium ion (*e.g.* 18-crown-6,[11] HMPT, or TMEDA[69]) is found advantageous.

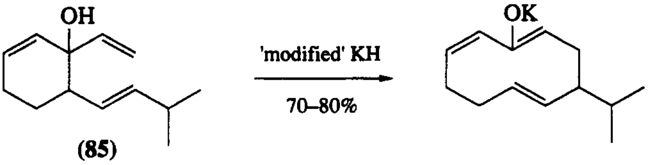

(**85**)

### 7.1.4.2 Catalysis

An experimental aspect of the Cope rearrangement particularly important in synthesis is the feature that it is frequently subject to catalysis. We have already seen that in the anionic oxy-Cope rearrangement enormous rate enhancements are realized by the incorporation of an alkoxide ion in the substrate. In many Cope rearrangements similar rate enhancements are achieved by the addition of catalysts, particularly acids and metals.[70]

#### *7.1.4.2.1 Acid catalysis*

A number of Cope rearrangements of acyl-substituted 1,5-dienes are markedly accelerated by protic or Lewis acids.

*(i) 2-Acyl-1,5-dienes*

An example of this category is ketone (**11**) in Scheme 2; thermal rearrangement requires several days at 80 °C, but equally good yields are obtained in 15 min at 25 °C if 1 equiv. of trifluoroacetic acid or boron trifluoride etherate is added.[25] A related case is enol ether (**86**), which rearranges to ketone (**87**) at room temperature in dilute acid.[25]

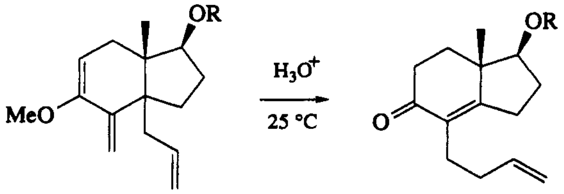

(**86**) (**87**)

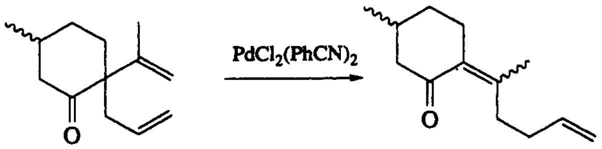
PdCl2(PhCN)2
O
O

(34)

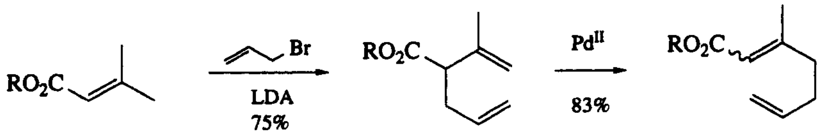
RO2C
Br
LDA
75%
RO2C
PdII
83%
RO2C

(35)

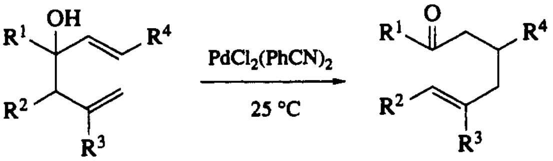
OH
R1
R4
R2
R3
PdCl2(PhCN)2
25 °C
O
R1
R4
R2
R3

(36)

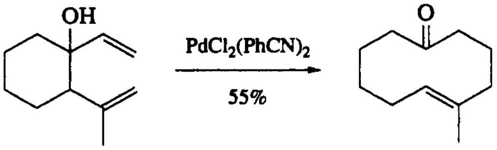
OH
PdCl2(PhCN)2
55%
O

(37)

example of 'cyclization-induced rearrangement catalysis', illustrated in equation (38). In this mechanism the metal coordinates with one of the double bonds, initiating a carbocation cyclization step which forms a transient cyclohexane ring intermediate. Upon loss of the metal, this opens to form the rearranged diene. Support for this mechanism is given by the observation that cyclohexenes are occasionally found as by-products of palladium-catalyzed Cope rearrangements, *e.g.* equation (39).

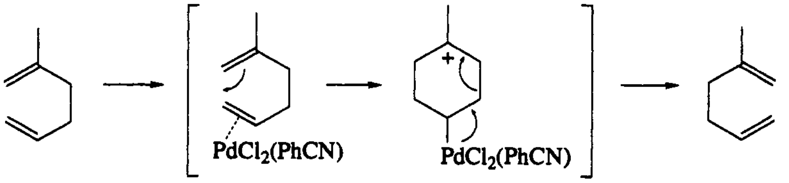
PdCl2(PhCN)
+
PdCl2(PhCN)

(38)

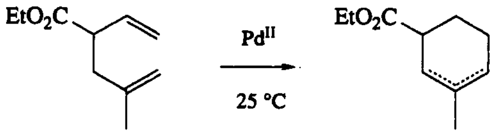
EtO2C
PdII
25 °C
EtO2C

(39)

An alternative view suggests that coordination of the Pd$^{II}$ catalyst with both double bonds of the 1,5-diene promotes dissociation into a bis($\eta^3$-allyl)palladium complex, followed by joining the allyl units together to form the isomeric 1,5-diene (equation 40).[80]

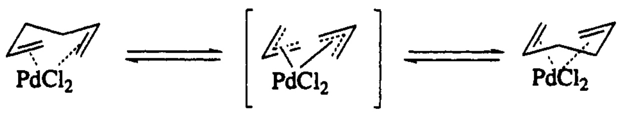
PdCl2
PdCl2
PdCl2

(40)

### *(ii) Other metal catalysts*

Scattered reports exist of catalysis of Cope rearrangements by metals other than palladium. Some amino-substituted 1,5-dienes exhibit weak catalysis by $Rh_2(CO)_4Cl_2$.[81] Gore and coworkers have studied the catalysis of oxy-Cope rearrangements by silver and mercury salts.[82] As shown in equation (41), stoichiometric quantities of mercury(II) trifluoroacetate effect oxy-Cope rearrangement to a mercuriated ketone, from which the mercury is removed by sodium borohydride reduction. The same overall result can be achieved by using a catalytic amount of mercury(II) ion in the presence of excess lithium trifluoroacetate. Silver triflate acts in a similar manner to catalyze the rearrangement of enynols, as illustrated in equation (42). Yields are variable with either silver or mercury(II) ion catalysis.

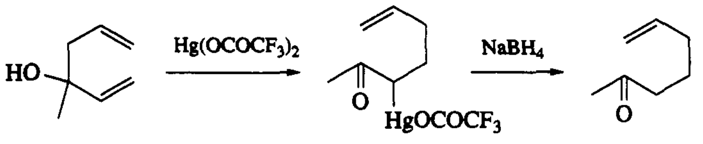
HO
Hg(OCOCF3)2
O
HgOCOCF3
NaBH4
O

(41)

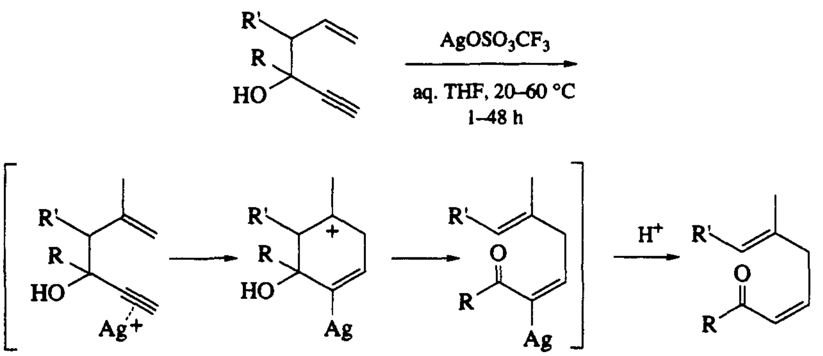
R'
R
HO
AgOSO3CF3
aq. THF, 20–60 °C
1–48 h
R'
R
HO
Ag+
R'
+
R
HO
Ag
R'
O
R
Ag
H+
R'
O
R

(42)

### *(iii) Photochemical initiation*

A handful of cases are known in which Cope rearrangement has been initiated by photolysis. Some of these are shown in Scheme 10. The examples reported to date are a fairly random collection and it is not

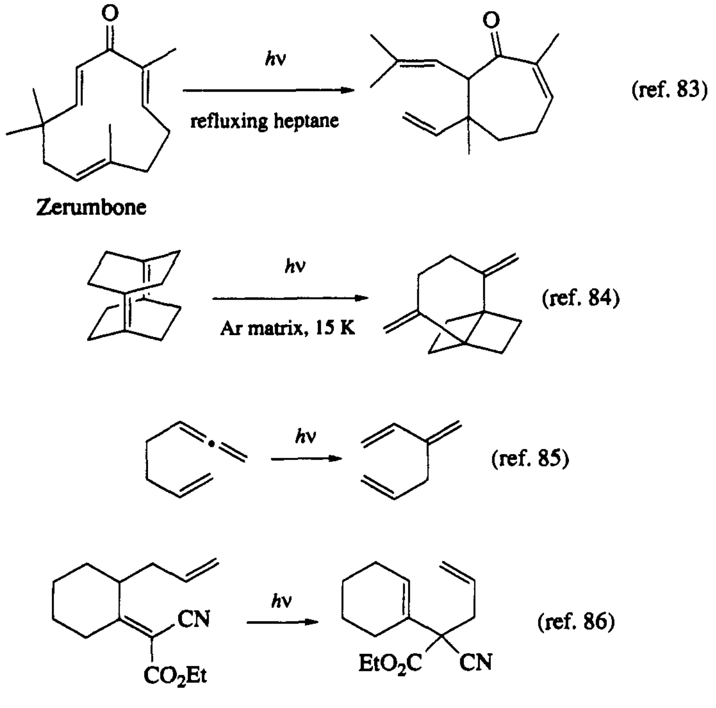
O
hν
refluxing heptane
O
(ref. 83)
Zerumbone
hν
Ar matrix, 15 K
(ref. 84)
hν
(ref. 85)
hν
CN
CO2Et
EtO2C
CN
(ref. 86)

(43)

**Scheme 10** Photochemical Cope rearrangement

#### *(ii) 1-Acyl-1,5-dienes*

The most commonly encountered examples of this type are the 4-allylcyclohexadienones and their derivatives, such as (**88**), which undergo room temperature Cope rearrangement, followed by aromatization, in the presence of acid.[71,72] It is interesting that the 3,3-Cope rearrangement competes with 1,2-migration (acid-catalyzed dienone–phenol rearrangement).

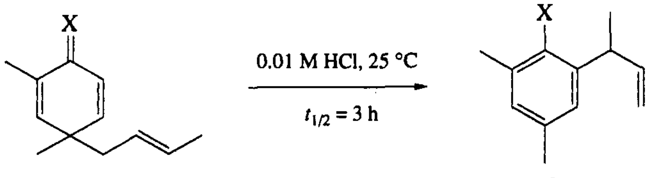

(**88a**) X = O
(**88b**) X = NNHTs

X = OH
X = NHNHTs

#### *(iii) 3-Acyl-1,5-dienes*

The best-known examples of this category are the tricyclic ketones illustrated by (**12**; Scheme 2), which again undergo room temperature Cope rearrangement in the presence of mineral or Lewis acids. The thermal rearrangement of (**12**) requires 1 h at 135 °C, but the rearrangement can be achieved in 3 min at 25 °C if a catalytic amount of sulfuric acid or aluminum chloride is added.[27]

Another example of a 3-acyl-1,5-diene is cyclohexadienone (**27**), which is converted to (**28**) at room temperature in a few minutes by 1% sulfuric acid.[71]

The origin of the catalytic effect of acids in these cases has not been proven definitively. All these reactions cited above could be considered examples of carbocation charge-accelerated rearrangements, seen earlier in substrate (**10**); coordination of the carbonyl group with a proton or Lewis acid creates a carbocation which weakens the nearby single bond in the 1,5-diene. Moreover, in classes (ii) and (iii), Cope rearrangement transforms the initial carbocation into a more stable cation, which would lower the activation energy. An alternative possibility for the 2-acyl-1,5-dienes is that the acid catalyst completely changes the mechanism from a concerted process to a two-step sequence, first a carbocation cyclization to form a new ring, followed by fragmentation. These possibilities remain to be sorted out.[70a]

As an example of what appears to be an acid-catalyzed Cope rearrangement in a simple diene lacking acyl substitution, (±)-3,4-diphenyl-1,5-hexadiene (**89**) rearranges in high yield on treatment with alumina at room temperature; a cyclization-induced rearrangement mechanism was suggested.[73] Catalysis of oxy-Cope rearrangement of (**90**) by weak acids, including ammonium salts and iodine, has been reported.[74]

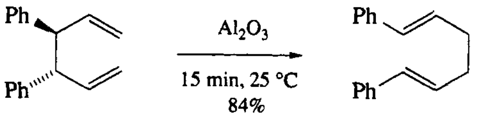

(**89**)

*(E,E)*

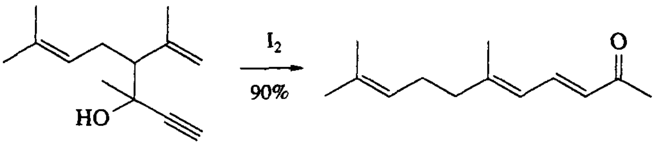

(**90**)

Pseudoionone

### *7.1.4.2.2 Metal catalysis*

While acid catalysis appears to be largely restricted to 1,5-dienes containing carbonyl substituents (or possibly other Lewis bases), several metal-containing catalysts have been shown to have a broader scope of application to a variety of 1,5-dienes.

#### *(i) Palladium*

In the initial discovery, made by Jonassen and coworkers in 1966, a stoichiometric amount of bis(benzonitrile)palladium dichloride was found to effect the rearrangement of (*E,Z*)-1,5-cyclodecadiene into *cis*-1,2-divinylcyclohexane (as its $PdCl_2$ complex) at room temperature (equation 31).[75] This was a striking contrast to the thermal process, which required a temperature of 150 °C. A series of substituted cyclodecadienes and, later, 1,2-divinylcyclobutanes was studied extensively by Heimbach and coworkers, again isolating the Cope products as palladium complexes.[76]

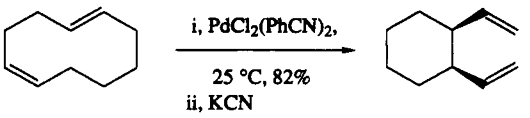

(31)

In a finding of greater practical significance, Overman and coworkers showed that the reactions could be carried out with catalytic amounts of the palladium(II) complex, and that the catalytic effect was broadly applicable to acyclic 1,5-dienes as well.[70b] In a typical example (equation 32), 2-methyl-3-phenyl-1,5-hexadiene rearranges in 1 h at room temperature in 87% yield in the presence of 0.06 equiv. of bis(benzonitrile)palladium dichloride, in contrast to the thermal rearrangement which has $t_{1/2}$ = 13 h at 177 °C. The catalyst thus provides an estimated rate acceleration of about $10^{10}$. The product is a 93:7 mixture of (*E*)- and (*Z*)-isomers, corresponding to the equilibrium ratio. Palladium acetate and tetrakis(triphenylphosphine) were ineffective as catalysts. One serious limitation is that the catalyzed reaction occurs only with those 1,5-dienes which possess an alkyl or aryl substituent at C-2 or C-5 (but not both).

The catalyzed rearrangements generally give stereochemical results analogous to the uncatalyzed, thermal reactions. For example, optically active (**91**) rearranges to a mixture of (*E*)- and (*Z*)-isomers of (**92**) with 96–97% *ee*, very similar to the results of thermal rearrangement.[77] The catalyzed rearrangement exhibits the same preference for the chair-like transition state conformation seen in the thermal reactions (see Section 7.1.7).

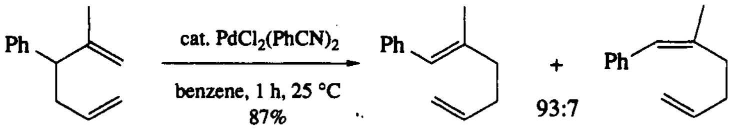

(32)

Pd$^{II}$ catalysis is also effective for dienes with electron-withdrawing groups at C-3, *e.g.* acid, ester, cyano, ketone, as seen in equations (33) and (34); it was shown that the catalyst equilibrates the geometric isomers around the conjugated double bond.[78] In equation (34) the catalyzed rearrangement occurs in good yield at room temperature, while the thermal rearrangement at 220–300 °C gave significant amounts of the β,γ-unsaturated isomer of the product along with ene cyclization products. The use of Pd$^{II}$ catalysis extends the application of the strategy seen earlier in equations (13) and (14); as illustrated in equation (35), alkylation of an α,β-unsaturated ester with an allyl halide gives a 1,5-diene, which can then be subjected to Cope rearrangement at room temperature.

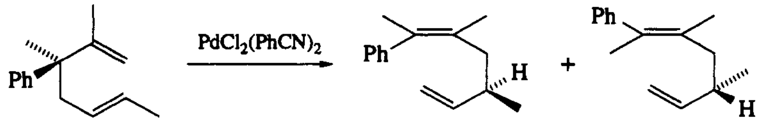

(3*R*,5*E*)-(**91**) (*Z*)-(**92**) 7:3 (*E*)-(**92**)

The same Pd$^{II}$ catalyst is also effective for oxy-Cope rearrangements (equation 36), provided that both R$^1$ and R$^3$ are alkyl groups.[79] An example of this application, shown in equation (37), is the catalyzed Cope rearrangement to a cyclodecenone.

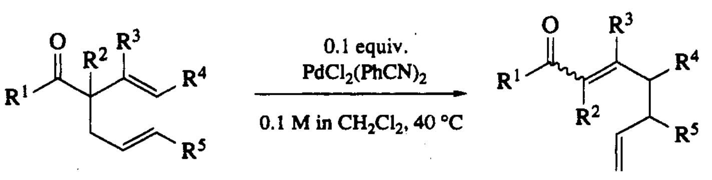

(33)

Several mechanisms have been proposed for palladium catalysis of Cope rearrangements.[70] Overman, who has examined metal ion catalysis of a number of 3,3-sigmatropic rearrangements, considers this an yet clear what factors facilitate the photochemical rearrangement, but it is interesting that at least in one case (equation 43) the normal equilibrium is reversed.

## 7.1.5 1,2-DIVINYLCYCLOALKANES

This section will focus on the use of the Cope rearrangement of 1,2-divinylcycloalkanes to synthesize carbocyclic rings of seven to ten members and even larger. As noted earlier in Section 7.1.2.4 and Schemes 4 and 5, the Cope equilibrium between divinylcycloalkanes and cyclic dienes is determined primarily by ring size; divinylcyclopropanes and cyclobutanes rearrange to cyclohepta- and cyclooctadienes, providing one of the best general routes to seven- and eight-membered rings. In 1,2-divinylcyclopentanes, cyclohexanes, and cycloheptanes, on the other hand, the equilibrium lies in the opposite direction, but use of the irreversible oxy-Cope reaction does permit the synthesis of 9-, 10- and 11-membered rings. Finally, when the vinyl groups are attached to medium rings of 8–12 members, the equilibrium shifts once again to favor the larger rings. We examine here each of the ring sizes in turn.

### 7.1.5.1 1,2-Divinylcyclopropanes

*cis*-1,2-Divinylcyclopropane (**39**) rearranges spontaneously below room temperature to 1,4-cycloheptadiene (**40**; Scheme 4) so readily that preparation of (**39**) by Hofmann degradation or other pyrolytic reactions[87] leads instead to (**40**), although (**39**) can be isolated[42] by conducting its synthesis by the Wittig reaction at –20 °C. The Cope rearrangement thus offers a straightforward route to simple cycloheptane natural products such as the dictyopterenes (equation 44)[88] and karahanaenone (equation 45).[89]

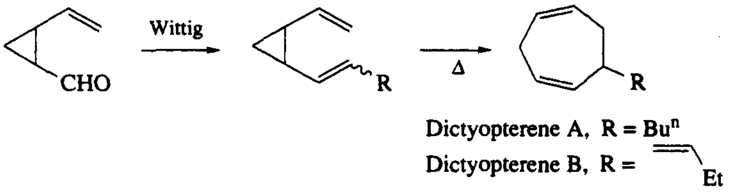

(44)

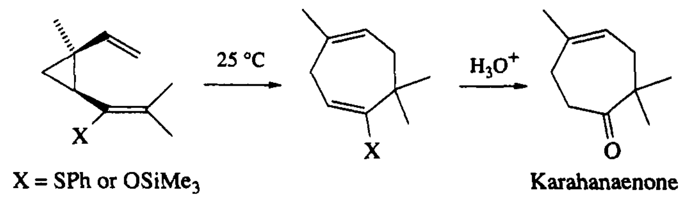

(45)

In order to use the divinylcyclopropane rearrangement for the construction of fused cycloheptanes, one of the double bonds must be incorporated in a separate, attached ring. Several practical methods have been developed to prepare the required substrates, as illustrated in Scheme 11.

(a) *Addition–elimination of vinylcyclopropyl organometallic reagents to β-substituted cycloalkenones.* Cyclopentenones and cyclohexenones with a leaving group at the β-carbon are easily prepared from the 1,3-diones, and undergo displacement when treated with organolithium or cuprate reagents derived from 2-vinyl-1-halocyclopropanes. Examples of this strategy are given in equations (46)–(48). In the simplest cases,[90] divinylcyclopropanes of type (**93**), prepared from enol ethers of cyclohexane-1,3-diones, rearrange on heating to bicyclic ketones of type (**94**). More highly substituted cyclopropanes have been prepared by cuprate displacement of 3-iodocyclohexenone (**95**), leading to alkylated bicyclo[5.4.0]undecanes (equations 47 and 48), including the sesquiterpene β-himachalene.[91]

(b) *Construction of cyclopropanes from sulfur ylides.* Sulfur ylides of type (**96**) are easily available by displacement of 3-chlorocyclopentenones by trimethyloxosulfonium ylide, and add to α,β-unsaturated aldehydes and ketones to furnish cyclopropanes (equation 49). Wittig reaction then gives the divinylcyclopropanes, which undergo Cope rearrangement on heating to afford hydroazulenes in good overall yields.[92]

Bridged cycloheptadienes are created when one of the vinyl double bonds is located in a ring fused to the cyclopropane, as seen in the conversion of (**45**) to (**46**); when both double bonds are in fused rings,

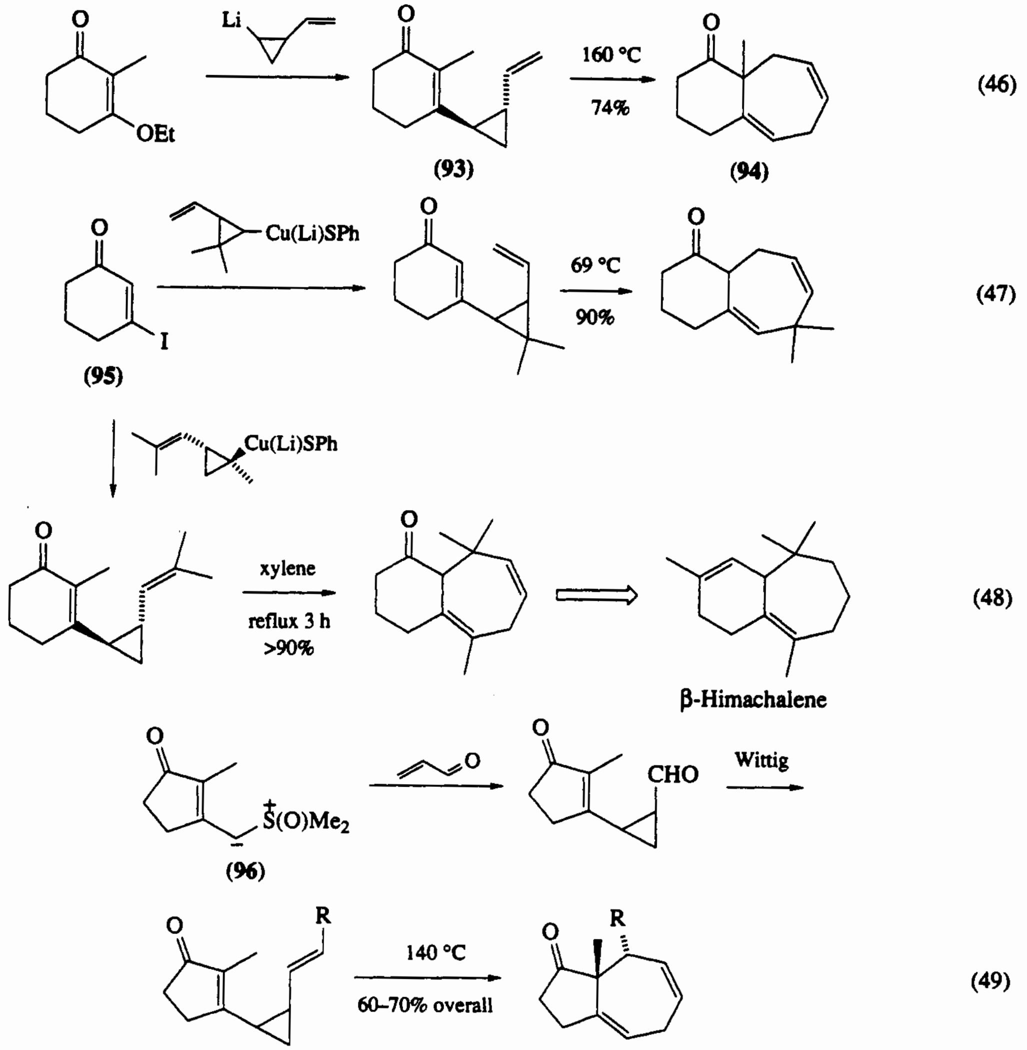

**Scheme 11** Fused cycloheptanes by Cope rearrangement

tricyclic skeletons result (equation 50).[93] Several general ways to prepare the necessary starting dienes are shown in Scheme 12.

(a) *Addition of vinylcarbenes to cyclic dienes.* In a noteworthy one-step synthesis developed by Davies,[94] vinylcarbenes are generated by rhodium-catalyzed decomposition of diazo esters in the presence of furan or cyclopentadiene; the initial cyclopropane adducts, derivatives of (**45**), are not isolated but rearrange to bicyclo[3.2.1]heptadienes (equation 51). An intramolecular version of this reaction is illustrated in equation (52).

(b) *Enol derivatives of 6-vinylbicyclo[3.1.0]hexan-2-ones.* Piers has shown that TMS enol ethers of the title ketones, as members of the (**45**) family, undergo Cope rearrangement leading, after hydrolysis of the enol ether, to bicyclooctenones.[95] A simple example is given in equation (53) and an application to the synthesis of quadrone is shown in equation (54).

*cis*-1,2-Divinylcyclopropanes are constrained to undergo Cope rearrangement through one of the boat conformations (**97**), since only *cis* double bonds are possible in 1,4-cycloheptadiene. *trans*-1,2-Divinylcyclopropanes (**98**) give the same products at higher temperatures, but only after isomerizing *via* a diradical intermediate to the *cis* isomers.[96] Consequently in the synthetic applications discussed above, either stereoisomer (or mixtures) can be used, the only difference being the temperature necessary to effect rearrangement. Terminal substituents on the double bonds retard the rate. Diene (**99**) rearranges to the *meso*-dimethylcycloheptadiene, but the *cis*-propenyl isomer (**100**) fails to undergo Cope rearrangement due to steric interactions between the methyls and the ring in the boat transition state.[97]

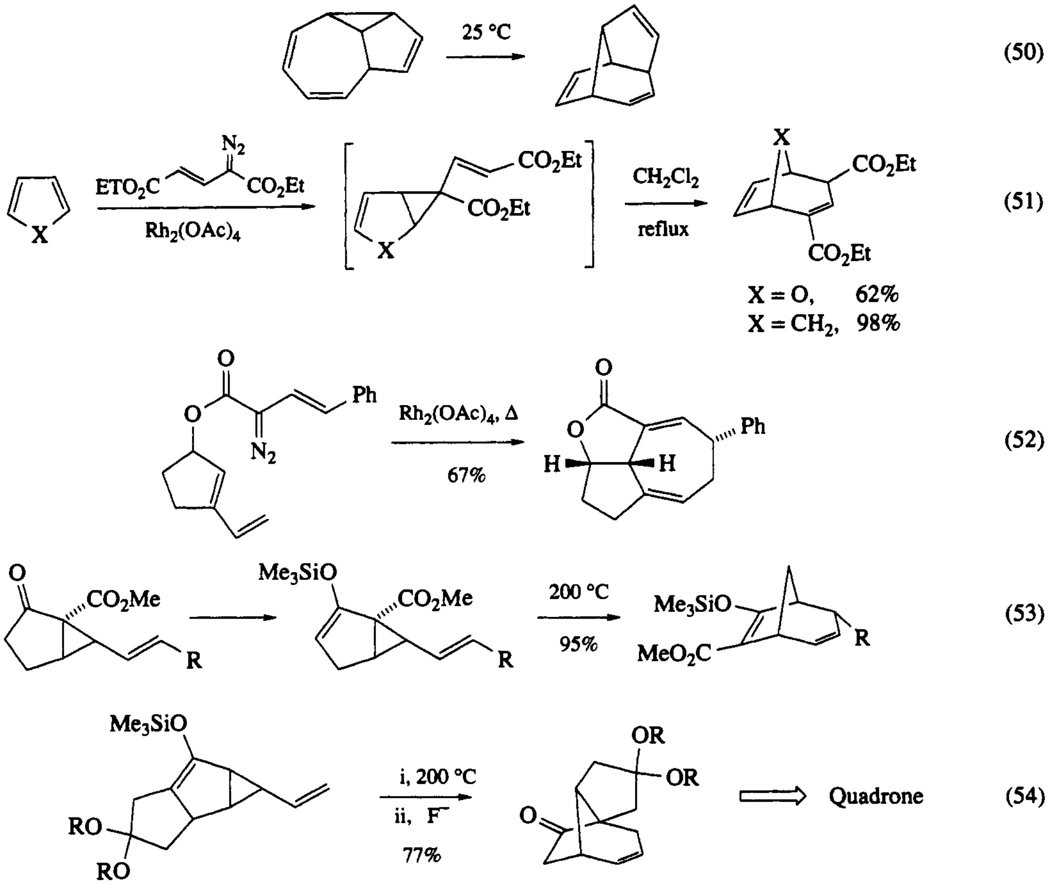
25 °C
(50)
N2
ETO2C
CO2Et
Rh2(OAc)4
X
CO2Et
CO2Et
CH2Cl2
reflux
X
CO2Et
CO2Et
X = O, 62%
X = CH2, 98%
(51)
O
O
Ph
N2
Rh2(OAc)4, Δ
67%
O
O
H
H
Ph
(52)
O
CO2Me
R
Me3SiO
CO2Me
R
200 °C
95%
Me3SiO
MeO2C
R
(53)
Me3SiO
RO
RO
i, 200 °C
ii, F⁻
77%
OR
OR
O
Quadrone
(54)

Scheme 12 Bridged cycloheptadienes by Cope rearrangement

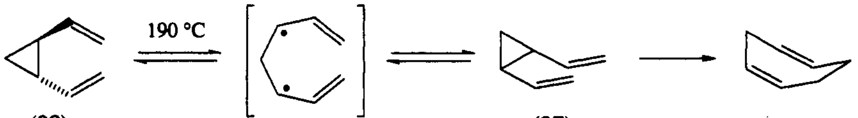

(98) (97)

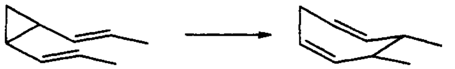

(99) *meso*

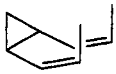

(100)

### 7.1.5.2 1,2-Divinylcyclobutanes

The Cope chemistry of this strained-ring substrate class parallels that of the divinylcyclopropanes, and is discussed in detail in Chapter 8.2, this volume. *cis*-1,2-Divinylcyclobutane (**41**) is stable at room temperature but rearranges at 120 °C to *cis,cis*-1,5-cyclooctadiene (equation 55).[43] *trans*-1,2-Divinylcyclobutane (**101**) requires higher temperatures since it must first equilibrate with (**41**) through a diradical intermediate, but the diradical here has other options, particularly closure to a vinylcyclohexene.[98] Substituents on the double bonds again retard the rate, and the two *cis*-methyls in (**102**) cause the transition state to choose a nonboat conformation.[99] Relief of ring strain is an obvious factor in the rearrangement of diene (**103**) to the bridgehead diene (**104**), which occurs at 60 °C.[100] Shea *et al.* have examined a series of Cope rearrangements of this type; when the small ring is a cyclopropane, the Cope rearrangement occurs spontaneously below −10 °C.

Oxy-Cope rearrangements are popular in the divinylcyclobutane series, because several good methods of preparation of 2-vinylcyclobutanones are available. A number of these ketones, such as (**105**), can be

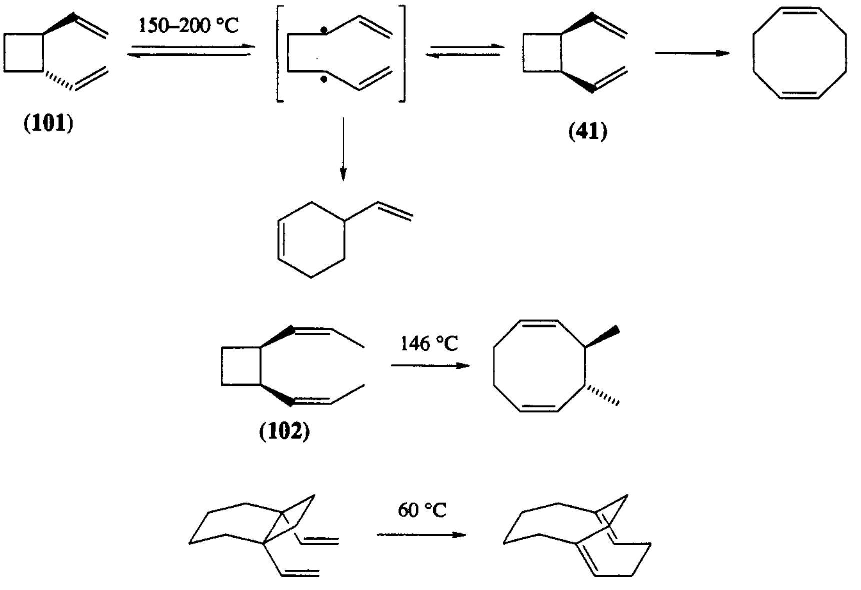

(101) (41) (55)

(102)

(103) (104)

prepared by ring expansion of cyclopropane intermediates.[101] Addition of a vinyl group to the ketone then affords the divinylcyclobutanol (**106**), ready for oxy-Cope rearrangement (equation 56; Scheme 13).[102] Equation (57) shows an example of this strategy in Gadwood's synthesis of poitediol; addition of lithium acetylide to cyclobutanone (**107**) occurs from the convex face, giving a *cis*-enyne which undergoes oxy-Cope rearrangement to the fused cyclooctadienone.[103]

Another common strategy for construction of fused cyclooctanones is to first build a fused cyclobutanone by [2 + 2] cycloaddition of a vinylketene to a cycloalkene. Equation (**58**) illustrates this approach with Paquette's synthesis of the tricyclic skeleton of the ophiobolins.[104] Cyclobutanone (**108**) is assembled by addition of a vinylketene to cyclopentadiene. Cyclopentenyllithium then adds to the less-hindered face of (**108**), and the lithium alkoxide undergoes a spontaneous anionic oxy-Cope rearrangement to afford the central cyclooctane ring.

In another approach to fused cyclooctanes, dienone (**109**) rearranges at 180 °C to bicyclic dienone (**110**). Adding fluoride ion in DMF allows the reaction to occur at –30 °C in doubled yield, apparently an 'enolate-assisted' Cope rearrangement. Since Majetich has shown that divinylcyclobutanes of type (**109**) are intermediates in some intramolecular allylsilane Michael additions, this finding permits the novel sequence of steps shown in equation (59) as a route to fused cyclooctanes.[105] Another variation to fused cyclooctanes uses the spiro substrate (**111**) in an anionic oxy-Cope rearrangement (equation 60).[102a]

Bridged cyclooctadienes result from Cope rearrangement of fused substrates, following the theme seen in Scheme 12. A general route to the requisite substrates is the [2 + 2] cycloaddition of vinylketenes to cyclic 1,3-dienes, illustrated in equations (61) and (62); the vinylketenes may be formed by dehydrohalogenation of unsaturated acid chlorides or by thermolysis of cyclobutenones.[106]

A final useful pattern incorporates one double bond into a spiro ring, leading *via* oxy-Cope rearrangement to bicyclic ring systems with bridgehead double bonds (equation 63).[107]

### 7.1.5.3 1,2-Divinylcyclopentanes

As noted in Section 7.1.2.4 the Cope equilibrium shifts when the ring size of a 1,2-divinylcycloalkane increases to 5–7, favoring the smaller ring. The equilibrium between *cis*-1,2-divinylcyclopentane (**49**) and (*Z*,*Z*)-1,5-cyclononadiene, reached at 220 °C from either component (equation 64), is 95:5 in favor of (**49**). This rearrangement must utilize a boat transition state, but (*E*,*Z*)-1,5-cyclononadiene, which also rearranges to (**49**), uses a chair transition state.[47] Rearrangements of substituted cyclononadienes have been little studied because of the inaccessibility of the substrates, but Paquette has examined oxy-Cope rearrangements of a series of cyclononatrienols,[108] two of which are shown in equations (65) and (66). In equation (66) the alcohol fails to undergo a thermal oxy-Cope, giving products of hydrogen shifts instead, but the room temperature anionic oxy-Cope works well, giving an aldehyde used as an intermediate in the synthesis of multifidene, an algae sperm attractant.

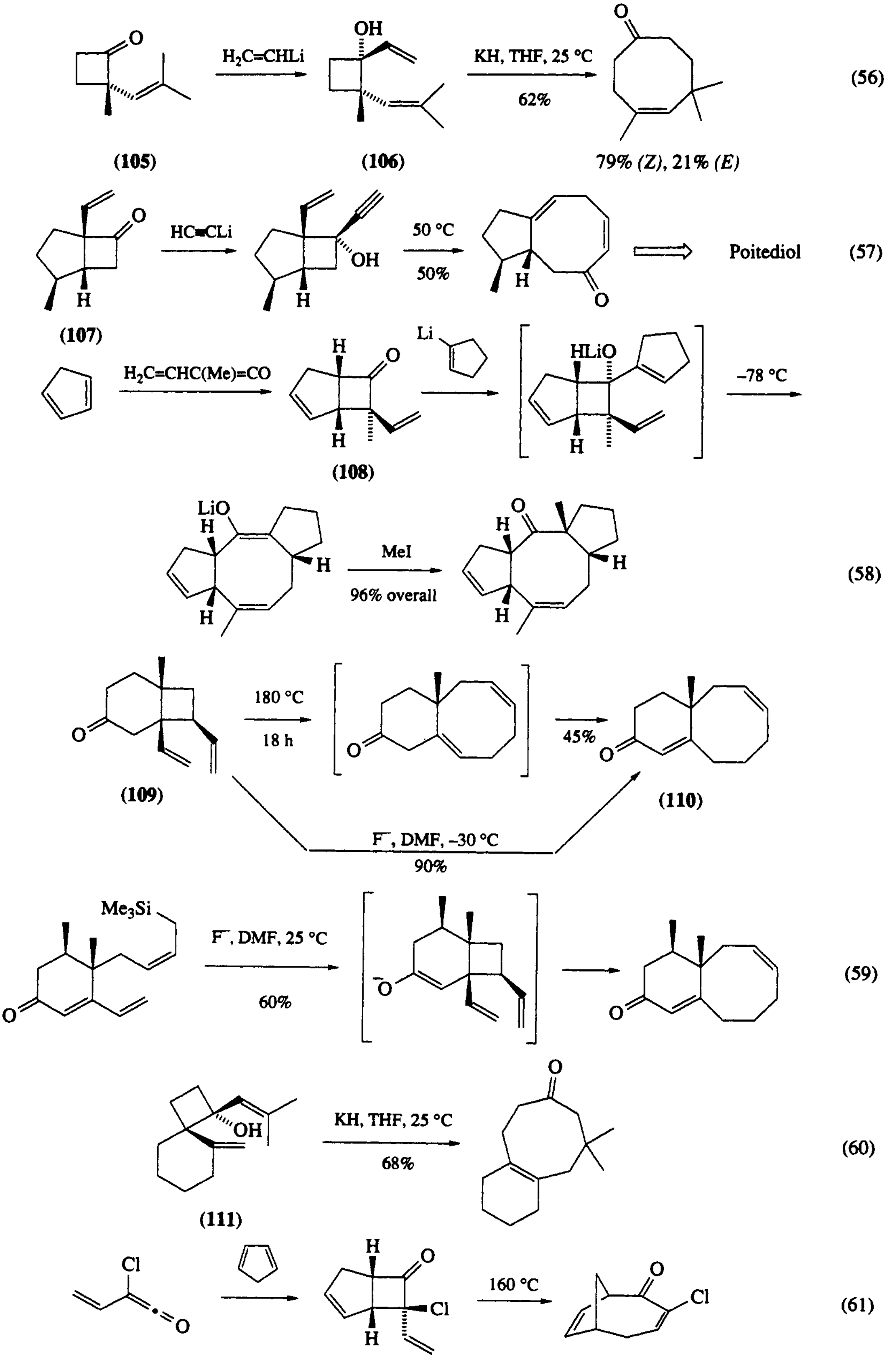

H₂C=CHLi
KH, THF, 25 °C
62%
(56)
(105)
(106)
79% (Z), 21% (E)
HC≡CLi
50 °C
50%
Poitediol
(57)
(107)
H₂C=CHC(Me)=CO
Li
HLiO
–78 °C
(108)
LiO
MeI
96% overall
(58)
180 °C
18 h
45%
(109)
(110)
F⁻, DMF, –30 °C
90%
Me₃Si
F⁻, DMF, 25 °C
60%
(59)
KH, THF, 25 °C
68%
(60)
(111)
160 °C
Cl
(61)

**Scheme 13** *(continued overleaf)*

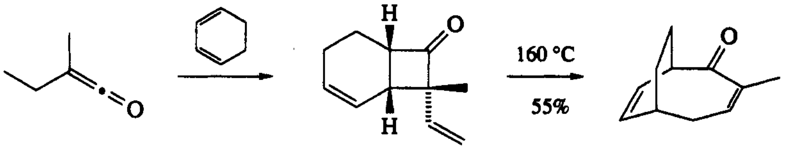
O
H
O
H
160 °C
55%
O

(62)

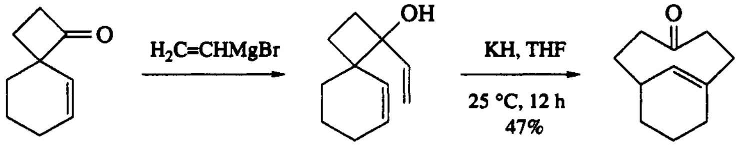
O
$H_2C$=CHMgBr
OH
KH, THF
25 °C, 12 h
47%
O

(63)

**Scheme 13** Cyclooctanones by oxy-Cope rearrangement

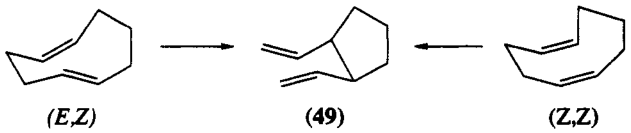

(64)

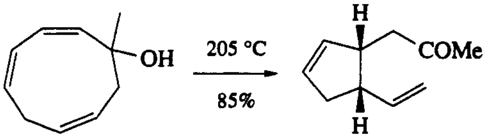
OH
205 °C
85%
H
COMe
H

(65)

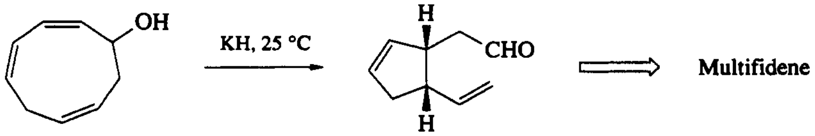
OH
KH, 25 °C
H
CHO
H
Multifidene

(66)

The normal equilibrium can be reversed, of course, by using the oxy-Cope rearrangement of a 1,2-divinylcyclopentanol; one example was shown in Scheme 7 (**62** → **63**) in which irreversible tautomerization of the enol gave a fused cyclononenone. Two additional examples are shown in equations (67)[107b] and (68), the latter a key step in a synthesis of phoracantholide.[109] The fused divinylcyclopentane shown in equation (69) undergoes anionic oxy-Cope rearrangement to a bridged cyclononenone.[110]

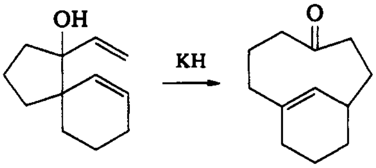

(67)

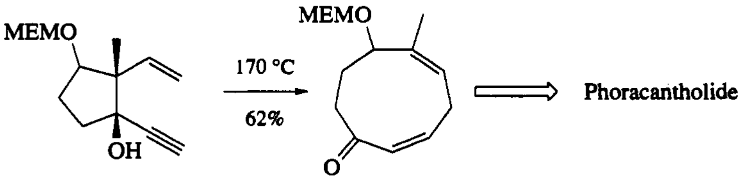
MEMO
OH
170 °C
62%
MEMO
O
Phoracantholide

(68)

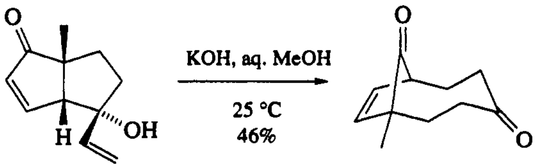
O
H
OH
KOH, aq. MeOH
25 °C
46%
O
O

(69)

### 7.1.5.4 1,2-Divinylcyclohexanes

The Cope equilibrium between 1,2-divinylcyclohexane (**51**) and 1,5-cyclodecadiene (**50**) lies completely on the side of the six-membered ring (Scheme 5); attempted preparation of (**50**) by Hofmann elimination[111] leads directly to (**51**; mostly *trans*), although the cyclodecadiene can be prepared at lower temperature. Optically active (**51**) racemizes at 200 °C through the Cope equilibrium[48] with (**50**), and optically active (**112**) racemizes on heating, by Cope rearrangement to its enantiomer.[112] The stereochemistry of these rearrangements is best accounted for by assuming that the transition state assumes a chair-like conformation; (*E,E*)-(**50**) rearranges to *trans*-(**51**), while (*E,Z*)-(**50**) affords *cis*-(**51**).[113]

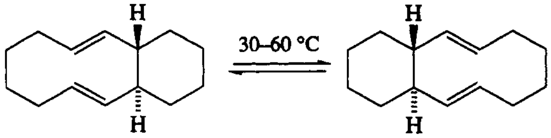

(–)-(**112**) (+)-(**112**)

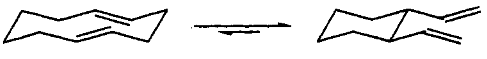

(*E,E*)-(**50**) *trans*-(**51**)

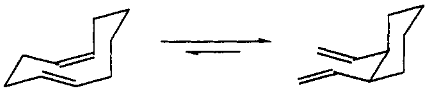

(*E,Z*)-(**50**) *cis*-(**51**)

This class of Cope rearrangement is commonly encountered among the germacrane sesquiterpenes, many of which contain a 1,5-cyclodecadiene skeleton. Examples are shown in Scheme 14. Distillation of germacrone (equation 70) effects Cope rearrangement to the divinylcyclohexane isomer pyrogermacrone.[114] Substituents on the cyclodecadiene ring affect the conformation chosen for rearrangement.[115] In hedycaryol for example, the hydroxyisopropyl group occupies an equatorial position in the preferred transition state conformation (**114**), leading to elemol of the configuration shown (equation 71).[116] Comparison of linderalactone and the related diol (**116**) in equations (72) and (73) is particularly instructive; the C—O bond of linderalactone must be axial, forcing the choice of chair conformation (**115**) for rearrangement, but in diol (**116**), the C—O bond is free to be equatorial in the alternate chair conformation (**117**), leading to the opposite configuration at the ring junction in the product.[115]

In highly substituted cyclodecadienes, Cope equilibria do not always lie totally on the side of the divinylcyclohexane. Linderalactone[117] and isolinderalactone, for example, exist in a 1:1 ratio at 160 °C (equation 72); the equilibrium has allowed a synthesis[118] of linderalactone through its isomer. Aldehyde (**118**) is converted in high yield to its cyclodecadiene isomer (**119**) by silica gel at room temperature, though curiously this Cope rearrangement cannot be effected by heating at 200 °C.[119] Pyrogermacrone is converted by fluoride ion at room temperature to the conjugated ketone (**113**; equation 70), apparently by catalyzing the equilibrium with germacrone and then the tautomerization to the more stable conjugated isomer.[105]

In this series, as well as the divinylcyclopentanes, the equilibria can be shifted completely in favor of the 10-membered ring by using the irreversible oxy-Cope rearrangement of 1,2-divinylcyclohexanols; the prototype (**64** → **65**) was shown in Scheme 7. This reaction type has found wide application in the synthesis of cyclodecane natural products, as illustrated in Scheme 15. In equation (74) the starting material was made beginning with (–)-carvone, leading after rearrangement to optically active germacranolides.[120] Equation (75) shows one of the first spectacular successes in this area, the oxy-Cope step in Still's total synthesis of periplanone B, the sex attractant of the American cockroach.[121] These examples illustrate the range of substituents which the low temperature, anionic oxy-Cope rearrangement can tolerate. The synthesis of eucannabinolide (equation 76)[122] is novel in incorporating one of the vinyl groups into a cyclobutene ring, and an even more strained cyclobutene transition state is involved in the rearrangement shown in equation (77).[123]

A final class of oxy-Cope rearrangements leading to cyclodecenones is represented by spirodienol (**120**), which rearranges to a bicyclic ketone (**121**) containing a bridgehead double bond.[107b] The related alkynic alcohols (**122**) behave similarly,[124] but when R is H the initial product undergoes an intramolecular Michael addition to afford (**123**).

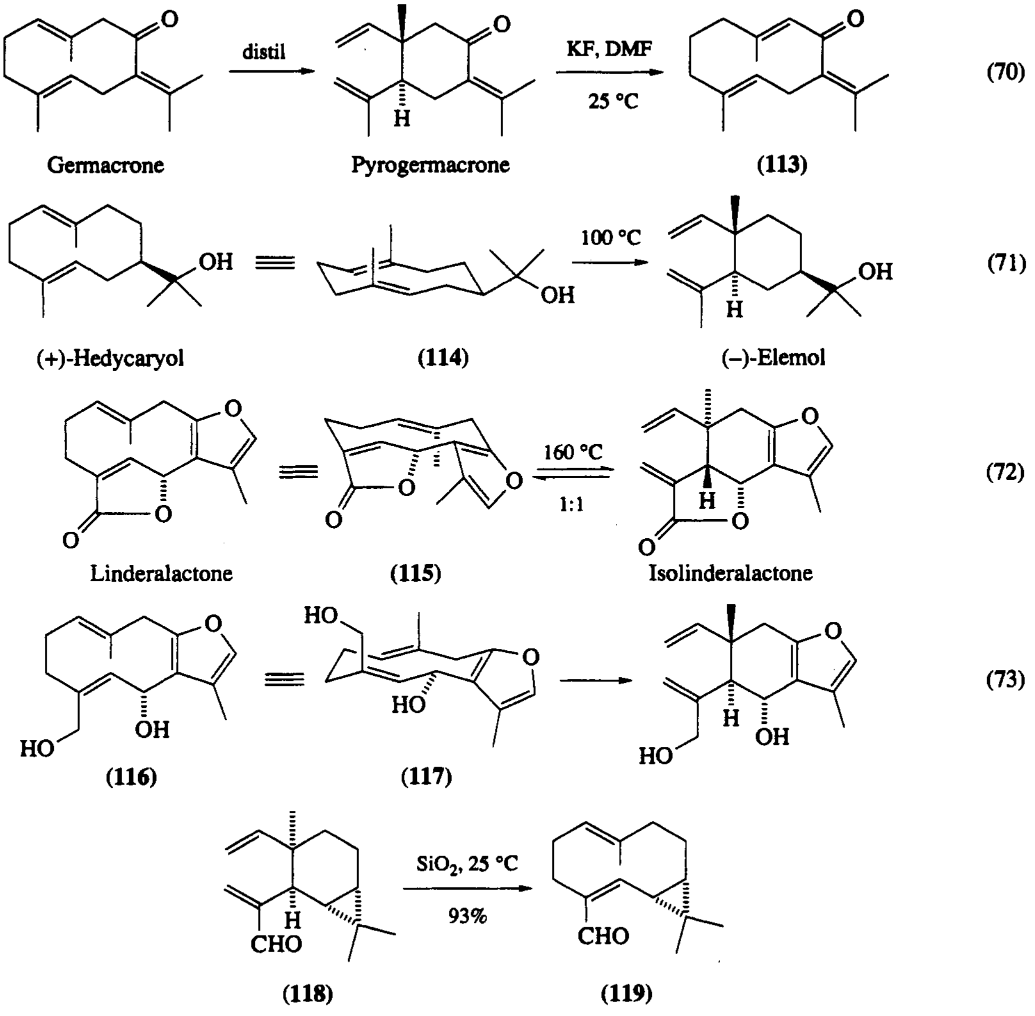

Scheme 14 Cope rearrangement of germacranes

A recent modification due to Sworin and Lin is to incorporate an additional functional group into the substrate so that the intermediate enol can cyclize by intramolecular $S_N2'$ or Michael reactions. As shown in equations (78) and (79), this provides a novel route to hydroazulenes.[125]

### 7.1.5.5 1,2-Divinylcycloheptanes

Very few Cope rearrangements of this type have been reported. The reaction shown in equation (80) implies that the divinylcycloheptane is favored in the equilibrium with a cycloundecadiene,[83] but more examples are needed before this generalization is secure.

At least one of the general protocols for effecting ring expansion by anionic oxy-Cope rearrangement has been applied to a cycloheptanone, and is shown in equation (81).[126] The 2-vinyl group is inserted by Grignard reaction with the 2-chloro ketone, and additional vinyl Grignard reagent yields the divinylcycloheptanol. Heating then effects oxy-Cope expansion to the 11-membered ketone.

### 7.1.5.6 1,2-Divinylcyclooctanes and Larger Rings

At this point the Cope equilibrium shifts direction again, and 1,2-divinylcyclooctanes and larger homologs rearrange in good yield to afford 12-membered and larger rings (Scheme 16). The strain present in medium rings (8–11 members) is clearly a determining factor in these equilibria. Equations (82)[127] and (83)[128] show simple examples of divinylcyclooctanes which rearrange to 12-membered rings.

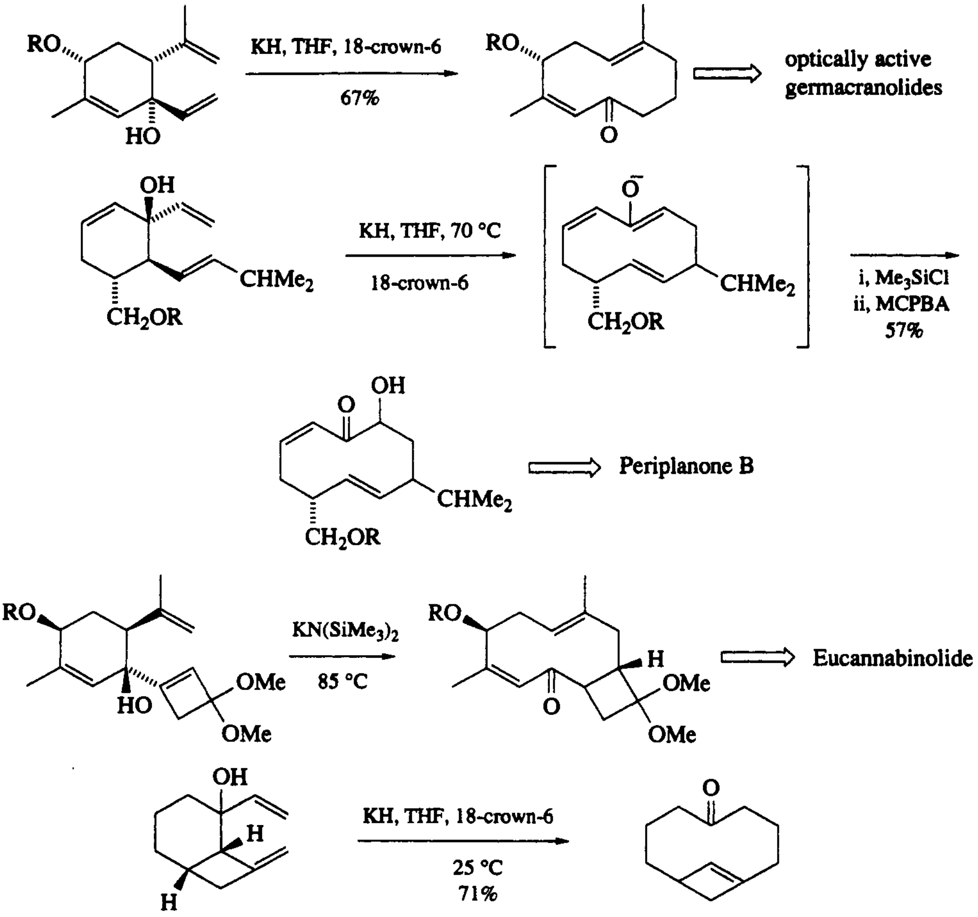
RO
HO
KH, THF, 18-crown-6
67%
RO
O
optically active germacranolides
OH
CHMe$_2$
CH$_2$OR
KH, THF, 70 °C
18-crown-6
O$^-$
CHMe$_2$
CH$_2$OR
i, Me$_3$SiCl
ii, MCPBA
57%
OH
O
CHMe$_2$
CH$_2$OR
Periplanone B
RO
HO
OMe
OMe
KN(SiMe$_3$)$_2$
85 °C
RO
H
OMe
O
OMe
Eucannabinolide
OH
H
H
KH, THF, 18-crown-6
25 °C
71%
O

(74)

(75)

(76)

(77)

**Scheme 15** Cyclodecenones by Cope rearrangement of 1,2-divinylcyclohexanols

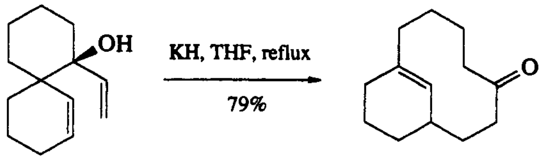
OH
KH, THF, reflux
79%
O

**(120)** **(121)**

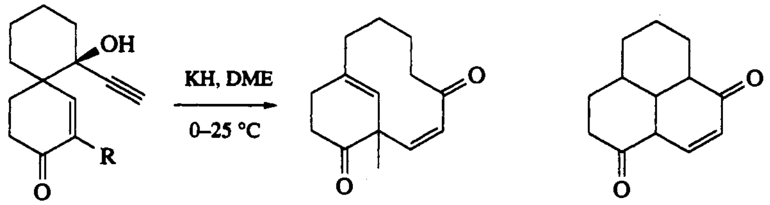
OH
R
O
KH, DME
0–25 °C
O
O
O
O

**(122)** R = Me, 67% **(123)** R = H, 55%

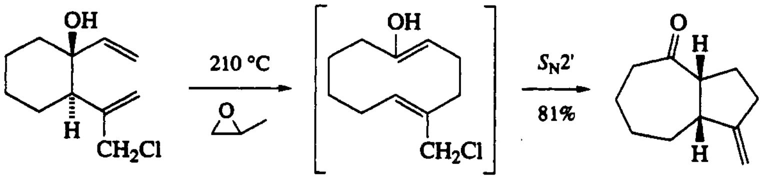
OH
H
CH$_2$Cl
210 °C
O
OH
CH$_2$Cl
$S_N2'$
81%
O
H
H

(78)

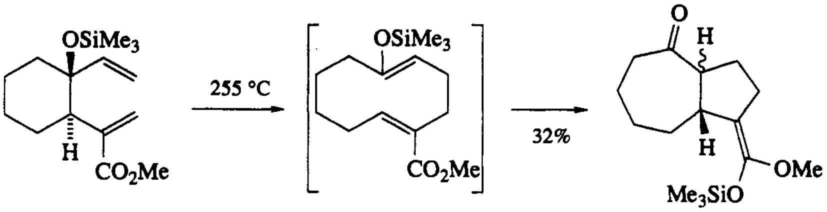

(79)

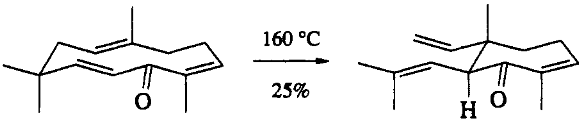

(80)

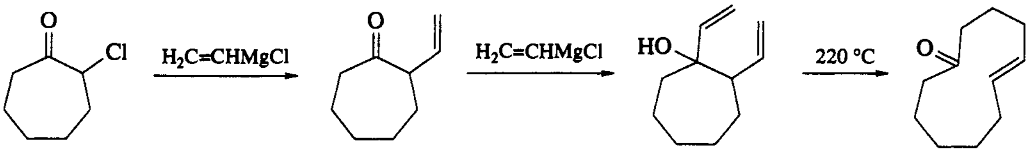

(81)

1,2,3,4-Tetravinylcyclobutane undergoes two consecutive Cope rearrangements, through a cyclooctane intermediate (equation 84), to a cyclododecatetraene.[129]

Larger rings participate easily in Cope rearrangements, and again the ring strain of a medium ring may help to induce rearrangement, as indicated by the mild conditions necessary for expansion of the divinylcycloundecane ring system in equation (85).[130] The four-carbon ring expansion which the Cope rearrangement allows offers the strategy of repetitive ring expansions leading to large rings. The most straightforward application is the oxy-Cope reaction, shown in equation (81) and again in equation (86)[126,128] for the cyclododecane substrate. A number of ways[128] have been published for introducing a 2-vinyl group into a cyclic ketone in addition to the method shown in equation (81); vinyl Grignard addition and oxy-Cope rearrangement then afford the enlarged ketone. Another practical repetitive strategy is shown in equation (87): two vinyl groups are inserted into a cyclic β-keto ester (**124**), and Cope rearrangement of the diene (**125**) affords a homologated β-keto ester which can be subjected to the same sequence.[131]

## 7.1.6 VINYLBICYCLOALKENES AND OTHER BRIDGED DIVINYLCYCLOALKANES

### 7.1.6.1 Vinylbicycloalkenes

The most popular Cope substrates of this class, represented by (**127**), can be considered relatives of 1,2-divinylcycloalkanes in which an additional carbon–carbon bond (as in **126**) generates a vinylbicycloalkene. Concerted Cope rearrangement of (**127**) is permitted as long as the vinyl group is *endo*, and leads to a fused bicyclic diene (**128**), necessarily *cis*. The ring systems most frequently employed have been bicyclo[2.2.1]heptenes ($x = y = 1$), leading to hydroindenes, and bicyclo[2.2.2]octenes ($x = 2, y = 1$), which afford *cis*-decalin skeletons. Examples of the former are shown in equation (88)[132] and the latter is illustrated in Scheme 5 (**52** → **53**).

The most common route to these substrates is a convergent one in which the vinyl moiety is joined by Grignard addition to the bicyclic ketone, giving an alcohol which serves directly in the oxy-Cope or anionic oxy-Cope rearrangement. Equation (89) exemplifies this strategy beginning with dehydrocamphor (**129**),[133] and equations (90)[134] and (91)[135] provide additional examples of construction of hydrindenones, as well as the example seen earlier in equation (27). Grignard addition can, of course, give a diastereomeric mixture of *endo*- and *exo*-alcohols, but fortunately the *endo* face of the ketone is usually more accessible and the major product is consequently that with the vinyl group *endo*. This simple two-step sequence is thus a powerful and versatile route to functionalized *cis*-hydrindanones; the rearrangement in equation (90) was used to synthesize dihydronepetalactone and, as illustrated in equation (91), an additional fused ring can be added if the vinyl group is incorporated into a ring.[135] Notice, in equation

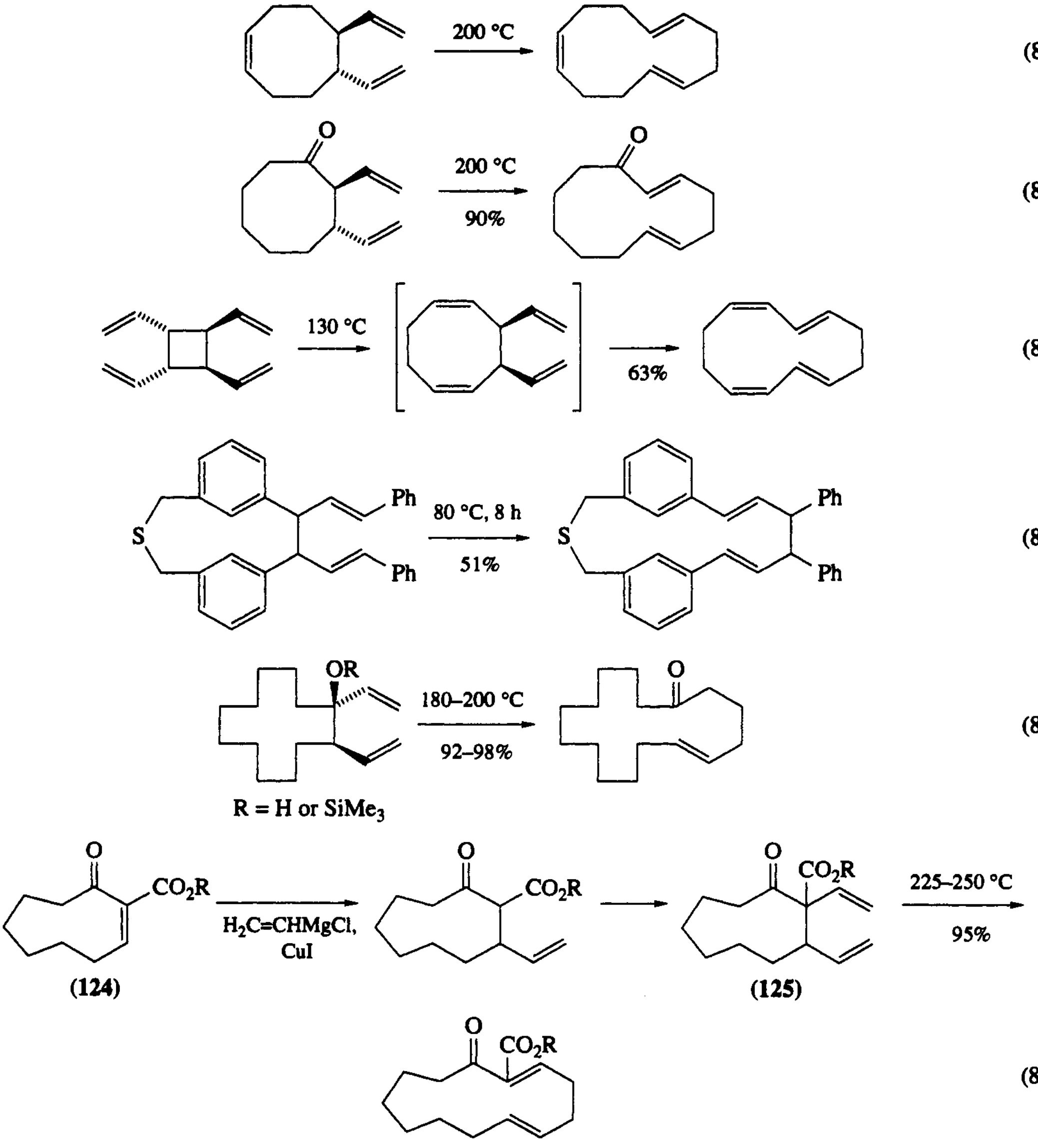
200 °C
200 °C
90%
130 °C
63%
Ph
Ph
80 °C, 8 h
51%
S
Ph
Ph
S
OR
180–200 °C
92–98%
O
R = H or SiMe$_3$
O
CO$_2$R
H$_2$C=CHMgCl, CuI
(124)
O
CO$_2$R
O
CO$_2$R
(125)
225–250 °C
95%
O
CO$_2$R

(82)

(83)

(84)

(85)

(86)

(87)

**Scheme 16** Cope rearrangements of 1,2-divinylcyclooctanes and larger rings

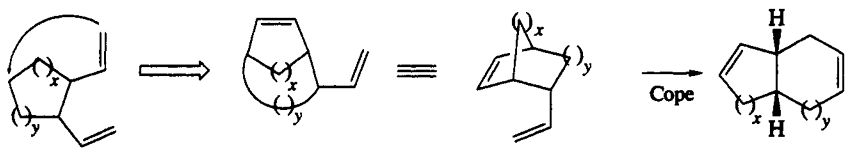
x
y
x
y
x
y
Cope
H
x
H
y

**(126)** **(127)** **(128)**

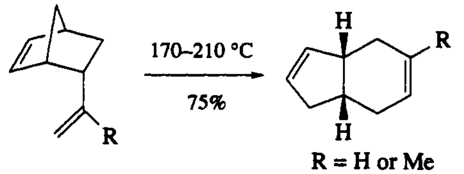
R
170–210 °C
75%
H
R
H
R = H or Me

(88)

(90), that a substituent at C-7 in the bicycloheptene becomes attached, in a predictable configuration, to the five-membered ring in the Cope product. Moreover, a *trans* substituent at the β-carbon of the vinyl group ends up in the six-membered ring in a predictable configuration, based on the fact that in the transition state (**130**) the group R prefers to lie oriented away from the rest of the molecule.

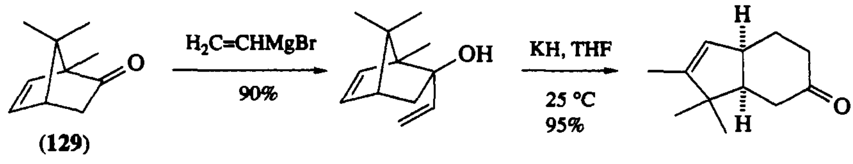
O
$H_2C{=}CHMgBr$
90%
OH
KH, THF
25 °C
95%
H
H
O

(**129**)

(89)

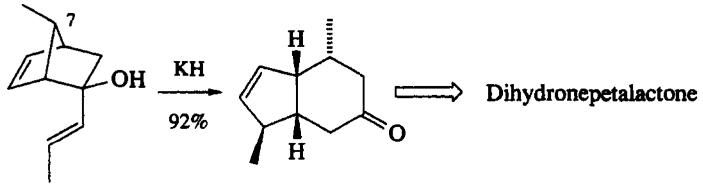
7
OH
KH
92%
H
H
O
Dihydronepetalactone

(90)

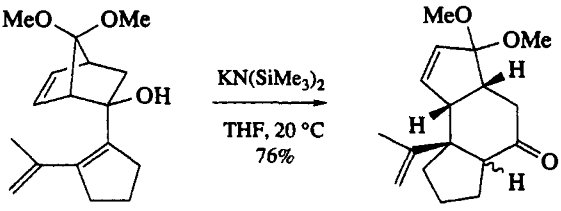
MeO
OMe
OH
$KN(SiMe_3)_2$
THF, 20 °C
76%
MeO
OMe
H
H
O
H

(91)

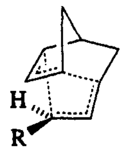

(**130**)

This strategy is equally powerful for the synthesis of *cis*-β-decalones from vinylbicyclo[2.2.2]octanols; examples were seen in equations (4), (6) and (12). Ketone (**2**), prepared in 98% yield by anionic oxy-Cope rearrangement, was the starting material for two syntheses of the alleged 'cannivonine',[136] and ketone (**131**; equation 92) was the key intermediate in Evans' synthesis of luciduline.[137] Propellane (**133**) is readily accessible[138] by oxy-Cope rearrangement of tricyclic alcohol (**132**; equation 93). The bicyclooctane skeleton may also incorporate heteroatoms, as in the aza derivative (**134**), which leads upon Cope rearrangement to a *cis*-hexahydroisoquinoline (**135**), an intermediate in Wender's elegant synthesis of reserpine (equation 94).[139] Again, if the vinyl group is contained in a ring, that ring becomes fused to the decalin skeleton, as in equation (95), showing Paquette's approach to a forskolin model.[140]

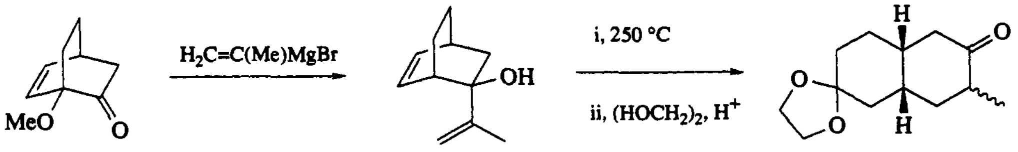
MeO
O
$H_2C{=}C(Me)MgBr$
OH
i, 250 °C
ii, $(HOCH_2)_2$, $H^+$
H
O
O
O
H

(**131**)

(92)

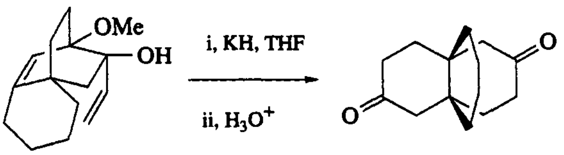
OMe
OH
i, KH, THF
ii, $H_3O^+$
O
O

(**132**) (**133**)

(93)

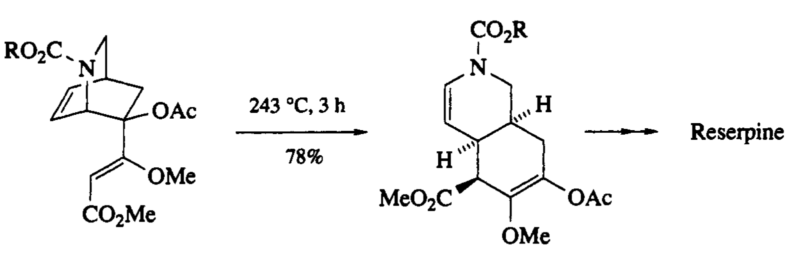

(134) (135)

(94)

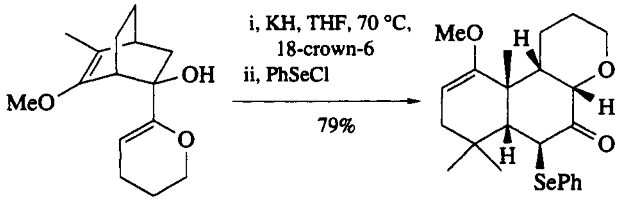

(95)

Still larger rings may be constructed by this general strategy; equation (96) shows the formation of a bicyclo[5.4.0]undecane by oxy-Cope rearrangement of a vinylbicyclo[3.2.2]nonane.[141]

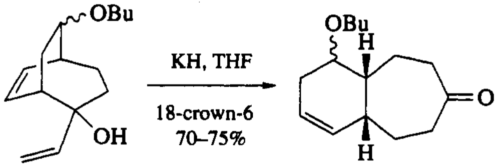

(96)

A related substrate group is the 7-vinylbicycloheptenes (**136**), which rearrange to tetrahydroindenes (**137**), double bond isomers of the products shown in equation (88); an example was encountered earlier in Scheme 9 (**79** → **80**). These, too, are usually performed as oxy-Cope reactions, but suffer from two problems in comparison with the oxy-Cope rearrangements of 2-vinylbicycloheptenols (equations 89–91): (i) addition of vinyl organometallic reagents to 7-ketobicycloheptenes is not very selective, and usually gives the *syn*-alcohol as the major product, not the *anti* isomer required for concerted Cope rearrangement[142]; (ii) as noted earlier for alcohol (**5**; equation 8), dienols of this type tend to give mostly 1,3-rearrangement products rather than 3,3-Cope rearrangements. This is also true for cyclic vinyl groups,[143] as shown in equation (97), which illustrates both of these problems. *anti*-Alcohol (**138**) is the minor product of addition, and it rearranges predominantly by a 1,3-pathway, giving only 14% of the Cope product (**139**). Somewhat unexpectedly, Paquette *et al.* have found that replacement of vinyl with dienyl groups markedly increases the extent of Cope rearrangement,[135] making this a practical route to tetrahydroindanones. Examples are seen in equations (98) and (99).

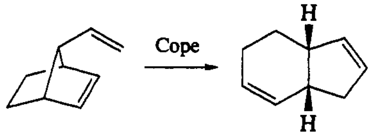

(136) (137)

### 7.1.6.2 2-*exo*-Methylene-6-vinylbicyclo[2.2.2]octanes

Another member of the divinylcycloalkane family is the title diene (**140**), which can be considered as a 1,2-divinylcyclohexane in which one vinyl group is connected to the ring by an additional carbon. Cope rearrangement of (**140**) is of synthetic interest in leading to a product (**141**) containing a bridgehead double bond. The few examples of this type realized so far all use the oxy-Cope rearrangement to ensure formation of the strained products. The simplest example is (**142**), which undergoes anionic oxy-Cope rearrangement in high yield to (**143**); Martin *et al.* have studied several examples of this type,[57] including the preparation of the taxane model (**71**; Scheme 7). More complex examples in which an additional ring

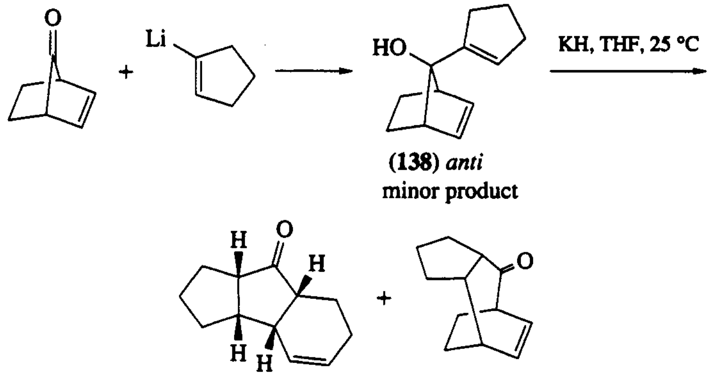

**(138)** *anti*
minor product

**(139)** 14%

42%

(97)

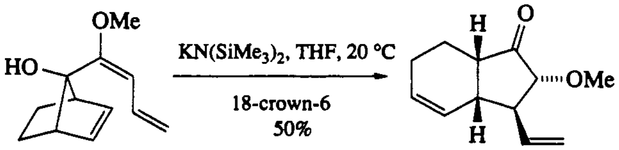
KN(SiMe$_3$)$_2$, THF, 20 °C
18-crown-6
50%

(98)

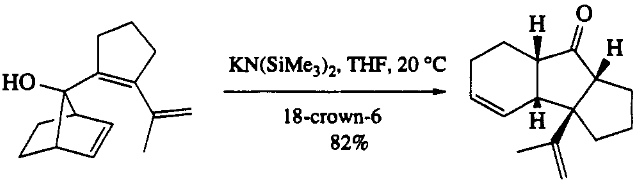
KN(SiMe$_3$)$_2$, THF, 20 °C
18-crown-6
82%

(99)

is present include the conversion of (**68**) to (**69**; Scheme 7) and the rearrangement of (**144**) to (**145**), the key step in Paquette's approach to cerorubenic acid acid-III.[144]

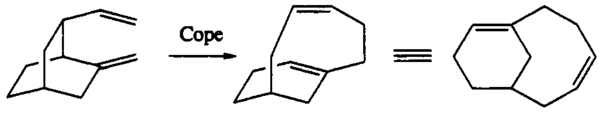

**(140)** **(141)**

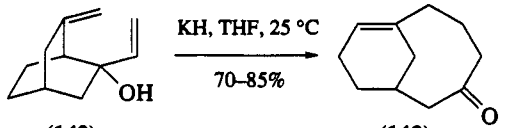
KH, THF, 25 °C
70–85%

**(142)** **(143)**

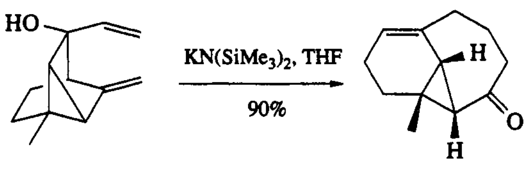
KN(SiMe$_3$)$_2$, THF
90%

**(144)** **(145)**

### 7.1.6.3 Bridged 1,5-Cyclooctadienes

A final variation of bridged divinylcycloalkanes is represented by (**146**), which can be thought of as a doubly bridged 1,2-divinylcyclooctane. Alternatively it can be considered as a bridged 1,5-cyclooctadiene which could participate in a Cope equilibrium[145] with the 1,2-divinylcyclobutane (**147**). A handful of rearrangements of this type are known, and in every case not only does the equilibrium lie totally on the side of the cyclobutane, but the rearrangement occurs under unusually mild conditions, sometimes at room temperature (equations 100 and 101).[146] Apparently the strain in the cyclobutane ring is more than compensated by relief of nonbonded interactions in the tricyclic starting materials.

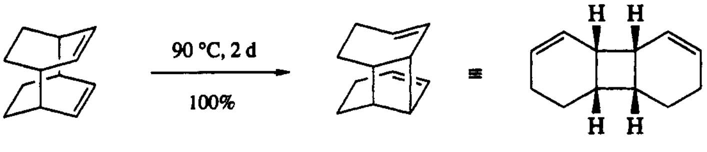

**(146)** **(147)**

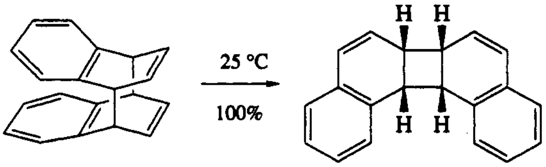

(100)

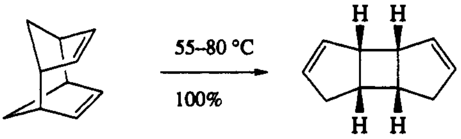

(101)

### 7.1.6.4 Double Diastereoselection with Chiral Vinyl Substituents

Previous examples in this section (especially equations 90 and 91, and 95–99) have made it clear that the use of substituted vinyl groups in oxy-Cope rearrangements of vinylbicycloalkenes leads to products with at least four stereogenic centers with essentially complete stereocontrol. If the vinyl moiety is not only cyclic but contains one or more chiral centers, then a large number of stereoisomeric products could result. In the search for control over the stereochemical outcome, Paquette *et al.* have investigated a series of chiral cyclopentene organometallic reagents (Scheme 17).[147]

Using the 7,7-disubstituted bicycloheptenone (±)-(**148**) reduces the number of possible stereoisomers, since organometallics add only from the *endo* face of the ketone. Still, when a chiral reagent such as (±)-(**149**) adds, two (±)-pairs (**150** and **151**) may result. The useful result is that one of these heavily predominates, in this case (**150**), by a ratio of 16:1. Related reagents (**152**)–(**155**) give diastereomeric ratios not as high, but in each case the diastereomeric products are easily separated by chromatography; the predominant sense of preference is the same in each case. Because the anionic oxy-Cope then proceeds with total stereospecificity, the Cope product from (**150**) contains six contiguous asymmetric centers fixed in a single relative configuration. This convergent sequence, joining a chiral ketone with a chiral vinylorganometallic reagent, followed by oxy-Cope rearrangement, not only regenerates a carbonyl group but creates six or more asymmetric centers with high specificity and control.[148] An example of its application is shown in equation (102): addition of the cerium reagent (**156**) to (**148**) gives alcohol (**157**) in a 12:1 diastereomeric ratio, and oxy-Cope rearrangement then provides the *as*-indacene subunit of ikarugamycin with its six asymmetric centers.[149]

When one of the initial reagents is optically active and the other is used in excess, then the diastereomeric preference results in kinetic resolution. An example[150] is the reaction of racemic (**149**; sixfold excess) with (–)-isopiperitenone (**158**), which gives (+)-(**159**) and (–)-(**160**) in a ratio of 4.8:1. After separation each of these undergoes anionic oxy-Cope rearrangement to the optically active cyclodecadienones (**161**) and (**162**). These incisive studies demonstrate that the oxy-Cope rearrangement can be used to rapidly assemble complex polycyclic skeletons with remarkable control over the creation of multiple chiral centers.

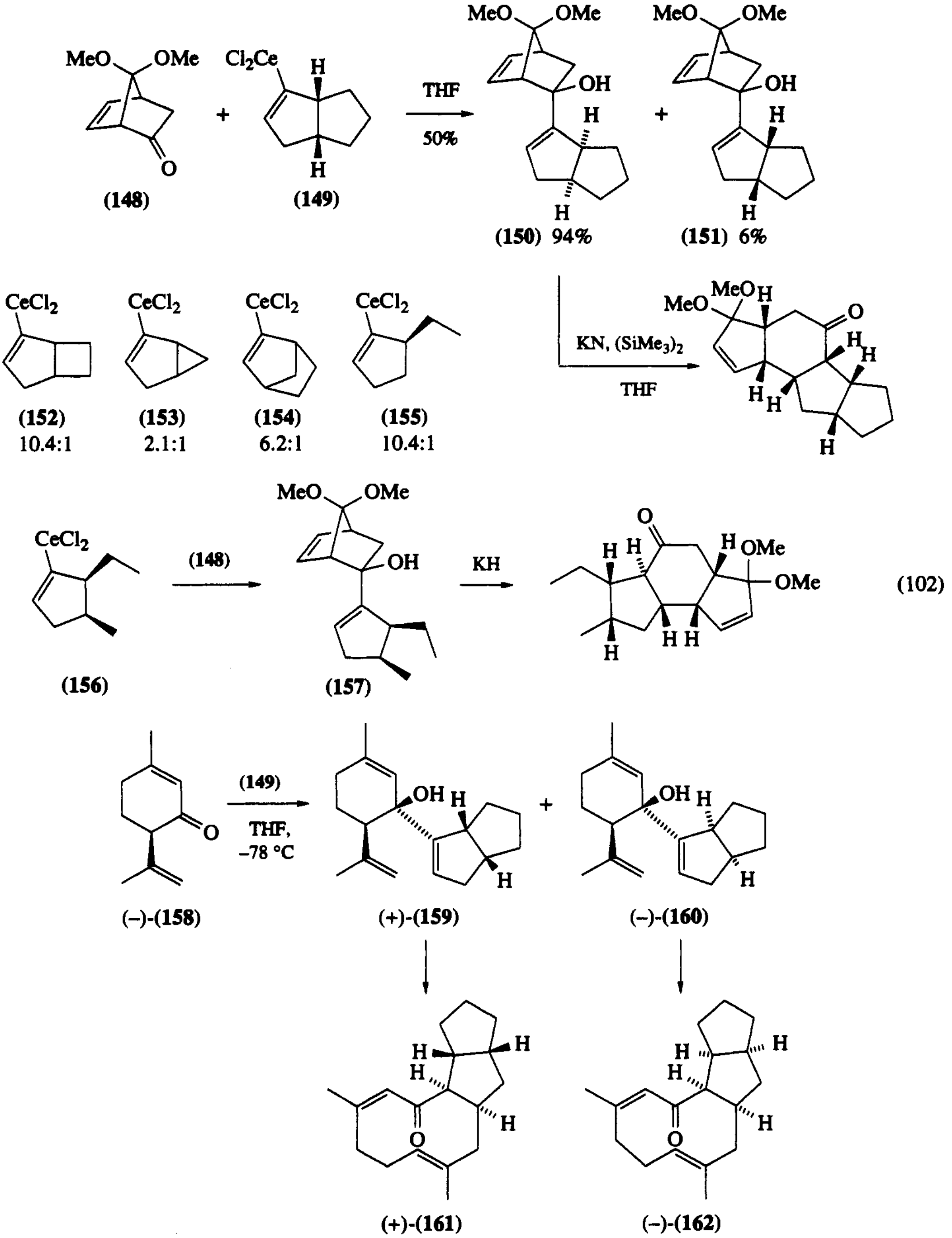
MeO
OMe
$Cl_2Ce$
(148)
(149)
THF
50%
OH
(150) 94%
(151) 6%
$CeCl_2$
(152)
10.4:1
(153)
2.1:1
(154)
6.2:1
(155)
10.4:1
KN, $(SiMe_3)_2$
THF
(156)
(148)
(157)
KH
(102)
(−)-(158)
(149)
THF,
-78 °C
(+)-(159)
(−)-(160)
(+)-(161)
(−)-(162)

**Scheme 17** Double diastereoselection with chiral vinyl organometallics

### 7.1.6.5 Tricyclic Skeletons

We close this section with a brief look at tricyclic skeletons formed by joining the vinyl group of a vinylbicycloalkane to the bicyclic ring system with additional carbons. Such skeletons are easily accessible through Diels–Alder reaction of cyclopentadienes with cyclic dienes or trienes. Cope rearrangements of dicyclopentadiene derivatives have the special property of regenerating the original ring system with shuffled carbons, as illustrated by rearrangement of (12) in Scheme 2. This reaction type was discovered by Woodward and Katz with the alcohols (56) and (57; Scheme 6), and a number of related examples are now known.[151]

When the vinyl group is situated in a ring larger than five, nondegenerate rearrangements of possibly more synthetic utility take place. The adduct (**163a**) of cyclopentadiene and *o*-benzoquinone, for example, rearranges to (**164a**) in refluxing benzene;[152] Cope rearrangement occurs so readily that frequently Diels–Alder adducts of cyclopentadienes are not isolated, as seen in equation (103) for the reaction with cyclohexadienones.[153]

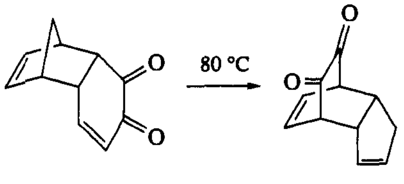

(**163a**) (**164a**)

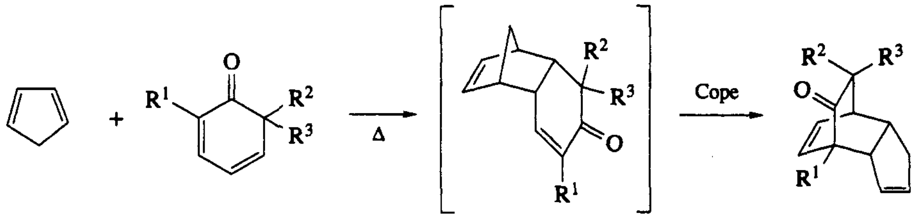

(103)

The facility of Cope rearrangement depends on the nature and length of the bridge connecting the vinyl group to the ring. Systems with bridges of three and four saturated carbons do not rearrange,[154] but unsaturated three-atom bridges still rearrange easily, as shown in equations (104)[155] and (105).[156]

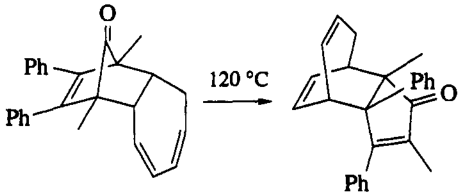

(104)

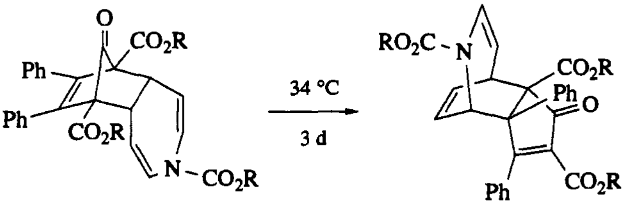

(105)

## 7.1.7 STEREOSPECIFICITY

The preceding discussion has demonstrated how the specificity inherent in the cyclic transition state may be used to fix structural elements in Cope products, establishing double bonds and other functional groups in definite relationships in a variety of acyclic and cyclic skeletons. This final section treats the remarkable consequences of cyclic transition states in stereochemical control, including alkene configuration and both relative and absolute configuration at stereogenic centers.[2]

### 7.1.7.1 Transition State Conformation

Restricting consideration to suprafacial–suprafacial geometries,[157] two limiting conformations are possible for the six-membered cyclic transition state, a four-center or 'chair' conformation with staggered allyl units which resembles chair cyclohexane, and a six-center or 'boat' conformation with eclipsed allyl fragments which approximates boat cyclohexane (Scheme 18). The classic experiments of Doering and Roth[160] first showed the preference for chair conformations in Cope rearrangements of acyclic 1,5-dienes. *meso*-3,4-Dimethyl-1,5-hexadiene rearranged to the (*E,Z*)-isomer of 2,6-octadiene, with only 0.3% of the (*E,E*) isomer (equation 106), while the racemic starting material afforded 90% of the (*E,E*)-octadiene and 10% of the (*Z,Z*)-isomer (equation 107). These results revealed a difference of at least 5.7 kcal mol$^{-1}$ in free energies of activation favoring chair conformations.

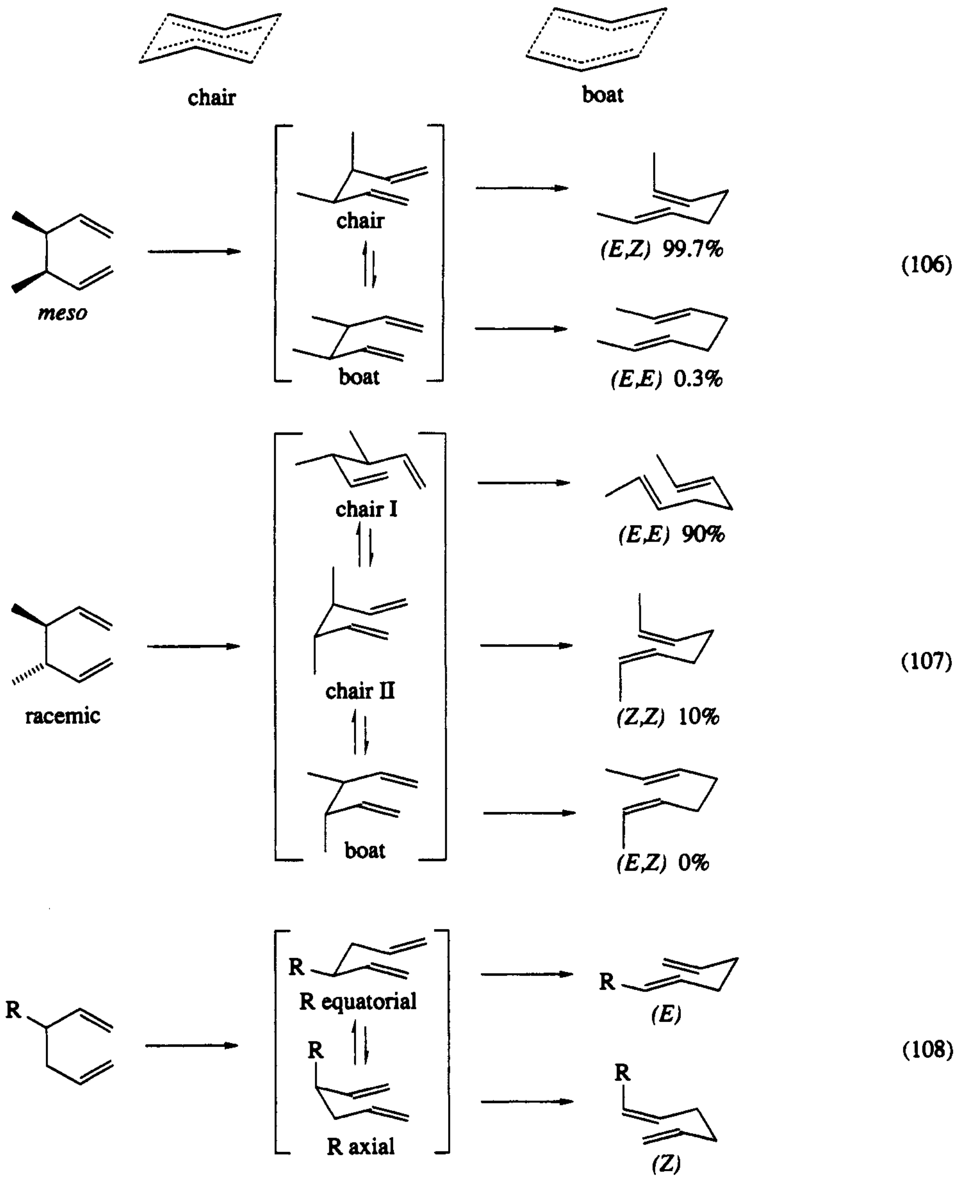

**Scheme 18** Cope transition state conformations

Several additional ingenious experiments devised to probe energy differences between chair and boat transition states have reached similar conclusions. In Scheme 1, equation (b), racemic 2,2′-bis(methylenecyclopentane), which must adopt a chair conformation for rearrangement, rearranges 18 000 times faster than its *meso* isomer, which must use a boat conformation.[20] Moreover, chair and boat transition states in equation (c), Scheme 1, would lead respectively to racemic and *meso* products; the observed product ratio of 130:1 gives an energy difference of 4.3 kcal mol$^{-1}$ favoring the chair conformation.[21]

Although most Cope rearrangements thus prefer chair transition states, the boat conformation is clearly energetically accessible and may be required by special structural features. In Scheme 1, equation (d), for example, the lactol ring forces the substrate to rearrange through a boat transition state.[22] 1,2-Divinylcyclopropanes and most 1,2-divinylcyclobutanes employ boat transition states, as noted in Section 7.1.5 since the vinyl groups are held nearly eclipsed, but increasing ring size allows greater flexibility. In 1,2-divinylcyclopentanes both chair and boat conformations are observed (equation 64), and the 1,2-divinylcyclohexane–1,5-cyclodecadiene equilibrium uses only chair conformations (*cf.* **50**). Vinylbicycloalkene rearrangements are forced into inflexible boat transition state conformations, imposing a fixed (and predictable) stereochemical relationship of chiral centers in the products, as seen earlier in equations (12), (27), (90), (94) and (95).

### 7.1.7.2 Double Bond Configuration

A corollary of the preference for chair conformations is the accompanying preference for substituents at $sp^3$ carbons to occupy equatorial, rather than axial, positions. This is shown clearly in the rearrangement in equation (107), which proceeds primarily through chair I conformation, with both methyls equatorial, rather than chair II, with the methyls axial. The immediate and important consequence, as emphasized in equation (108), is that transition states with equatorial substituents lead to (*E*)-double bonds, while axial substituents afford (*Z*)-double bonds, and that accordingly double bonds produced by Cope rearrangement are nearly always (*E*). Examples of this predominant formation of (*E*)-alkenes have been seen in equations (17), (36), (74)–(76), (81)–(87), and Scheme 1, equation (a), and with compounds (**85**) and (**89**). When two substituents are attached to the same carbon in the substrate, the larger, of course, prefers the equatorial position, still affording usually the (*E*)-alkene [*cf.* Scheme 2, equation (d)]. The relationship between 'size' of substituent and (*E*)/(*Z*) product ratios can be put on a quantitative basis: using experimental values of $\Delta G°$ for equatorial/axial preference of substituents in cyclohexanes allows the prediction of (*E*)/(*Z*) ratios in Cope products.[161] In the rearrangement of (**75**) two substituents (methyl and ethynyl) are of similar size and the product is a 55:45 (*Z*):(*E*) mixture.[62] In oxy-Cope rearrangements the equatorial/axial preference of the oxygen substituent often depends on solvent or charge; the rearrangement in equation (109)[162] affords (*E*)/(*Z*) mixtures when catalyzed by bases but nearly pure (*E*)-isomer when carried out in a nonpolar solvent.[162]

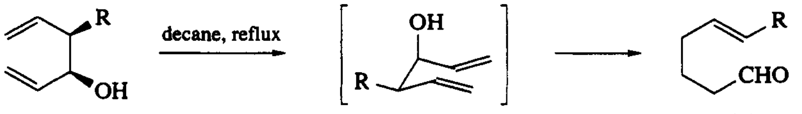

90–95% (*E*)

(109)

### 7.1.7.3 *Erythro–Threo* Ratios

When both vinyl groups contain β-substituents, two chiral centers are produced by Cope rearrangement. The asymmetry of two unsymmetrical double bonds is translated into a specific and predictable *erythro/threo* ratio by the cyclic transition state, as illustrated in equation (110). This *erythro/threo* specificity is nicely demonstrated in the experiments of Gajewski *et al.* (equation 111),[163] in which *threo*-(*Z*,*Z*)-4,5-dimethyloctadiene is cleanly equilibrated at 220 °C with the (*E*,*E*)-isomer. Another instructive study is that of Evans and Nelson,[13] who subjected all four racemates of alcohol (**163b**) to anionic oxy-Cope rearrangement; two are shown in equations (112) and (113). The *cis*- and *trans*-butenyl side chains lead to different stereoisomer mixtures, that in equation (112) giving a 96:4 ratio favoring one product, while in equation (113) the other predominates by 99:1. The specificity of these rearrangements was used to advantage in a stereospecific synthesis of (±)-juvabione. Another example of control of *erythro/threo* stereochemistry is seen in equation (16).

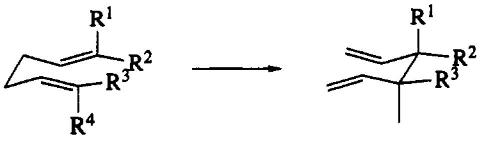

(110)

### 7.1.7.4 Transfer of Chirality

A final consequence of the chair transition state is its ability to effect a 'self-immolative' asymmetric synthesis, *i.e.* the transfer of chirality from a stereogenic center in the substrate to a new center in the

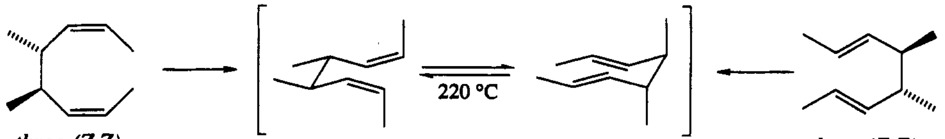

*threo-(Z,Z)* *threo-(E,E)* (111)

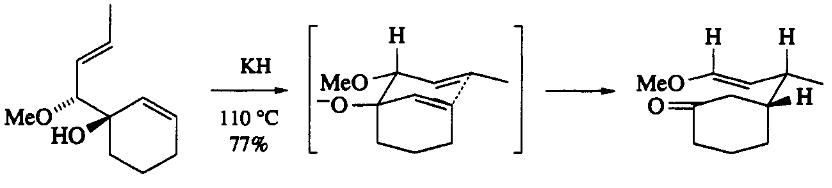

*trans*-(**163b**) (112)

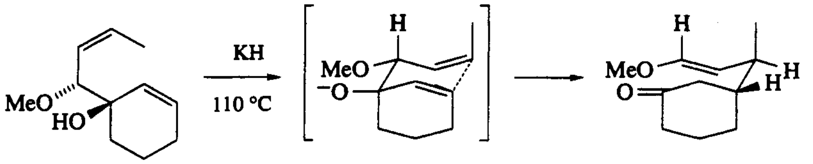

*cis*-(**163b**) (113)

product. This was first demonstrated by Hill and Gilman[24] in the investigation outlined in Scheme 19. Cope rearrangement of optically active (**164b**) led to two isomers of (**165**), resulting from the two chair transition states shown. The diastereomeric products had opposite configurations at both the double bond and asymmetric center, but most importantly, the degree of 'asymmetric transmission' was greater than 97%. Similar results were obtained with substrate (**166**), which gave the (*S*)-(*E*)- and (*R*)-(*Z*)-isomers of (**167**) in an 87:13 ratio, both formed with greater than 97% transfer of chirality. These results place an upper limit of 2–3% contribution from boat or any antara–antara transition states.[20] Another instructive example[164] is the Cope rearrangement of steroidal dienone (**168**); the chair transition state requires that an (*R*)-configuration be generated as the butenyl group migrates to C-4, but an (*S*)-configuration during migration to C-2.

The ability of the Cope rearrangement (as well as the Claisen and other sigmatropic rearrangements) to generate a new stereogenic center in a predictable configuration and with almost total stereospecificity is unique in organic synthesis in not requiring external chiral reagents, catalysts, or solvents; all the stereochemical information in the substrate is transferred to the product through a cyclic transition state which can usually be analyzed by the simple rules of cyclohexane conformational analysis. An elegant application is Koreeda's use of the anionic oxy-Cope rearrangement of (**171**) to create C-20 of the steroidal side chain in the correct (*R*)-configuration.[165] It is reassuring that the degree and direction of asymmetric induction in oxy-Cope and Pd-catalyzed Cope rearrangements[77] are essentially identical with those in simple thermal rearrangements.

## 7.1.8 CONCLUSIONS

Developments since 1940, when Cope first reported this striking rearrangement, have transformed it from a laboratory curiosity into a powerful synthetic method. Today's chemist can quickly assemble oxy-Cope substrates by Grignard additions and rearrange them at room temperature with base or metal catalysis. A wide range of ring sizes can be expanded or contracted by Cope rearrangements, and it has become one of the methods of choice for the preparation of medium rings. Equilibria can be controlled by choice of substituents and double bonds can be created in predictable configurations. The transfer of stereochemical information in a cyclic transition state allows stereogenic centers to be assembled in high optical purity. Finally, the emphasis in recent years on rearrangements of bridged bicyclic substrates has demonstrated that complex polycyclic molecules with six or more asymmetric centers can be constructed quickly and stereospecifically by rational design centered on Cope rearrangements.

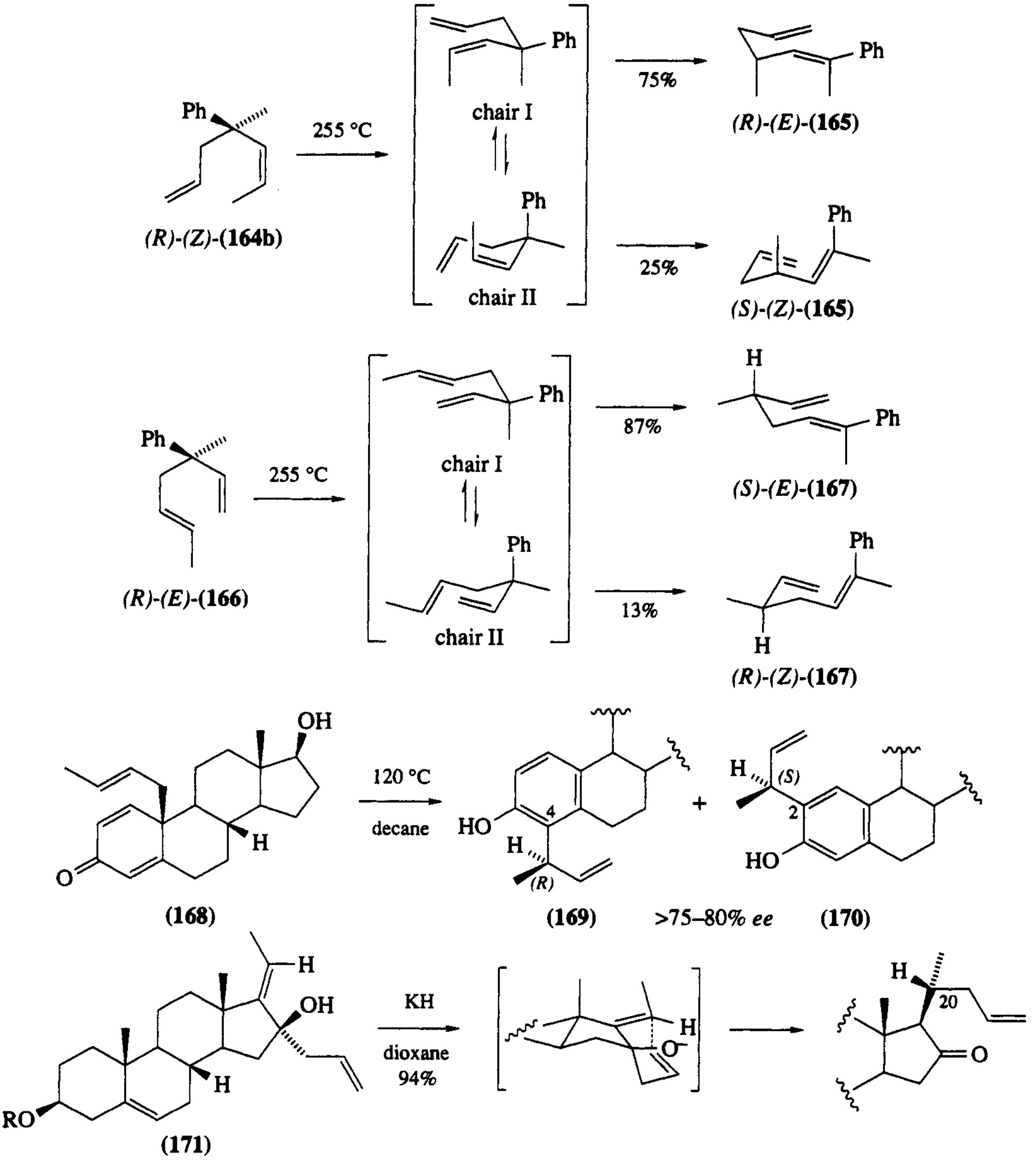
Ph
255 °C
(R)-(Z)-(164b)
Ph
chair I
Ph
chair II
75%
25%
Ph
(R)-(E)-(165)
Ph
(S)-(Z)-(165)
Ph
255 °C
(R)-(E)-(166)
Ph
chair I
Ph
chair II
87%
13%
H
Ph
(S)-(E)-(167)
Ph
H
(R)-(Z)-(167)
OH
H
O
(168)
120 °C
decane
HO
4
H
(R)
(169)
>75–80% ee
+
H
(S)
2
HO
(170)
H
OH
H
RO
(171)
KH
dioxane
94%
H
O⁻
H
20
O

**Scheme 19** Transfer of chirality in Cope rearrangements

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# 7.2

# Claisen Rearrangements

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## 7.2.1 INTRODUCTION

This article surveys variants of the Claisen rearrangement that are of general use in stereoselective organic synthesis. Recent results concerning the influence of steric and electronic parameters on transition state geometries are highlighted. The impact of the Claisen methodology in modern synthetic strategy and its application for the preparation of highly functionalized derivatives is exemplified.

Since its discovery in 1912,[1] the Claisen rearrangement of allyl vinyl ethers (**1** → **2**; equation 1) has become one of the most powerful tools for stereoselective carbon–carbon bond formation.[2] Much of its current popularity is due to the subsequent development of a series of new variants of this 3,3-sigmatropic rearrangement. In 1940, Carroll reported the base-catalyzed rearrangement of β-keto esters and allylic alcohols to alkenic ketones (**3** → **4** → **5**; equation 2).[3] Twenty years later, Saucy and Marbet demonstrated the acid-catalyzed reaction of tertiary propargylic alcohols with isopropenyl methyl ether to give β-ketoallenes in high yields (**6** → **7** → **8**; equation 3).[4] An application of this process for the preparation of geranylacetone led to a commercial synthesis of vitamin A.

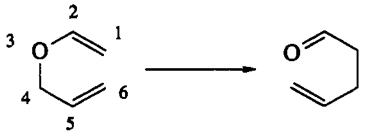

**(1)** **(2)**

Claisen (1)

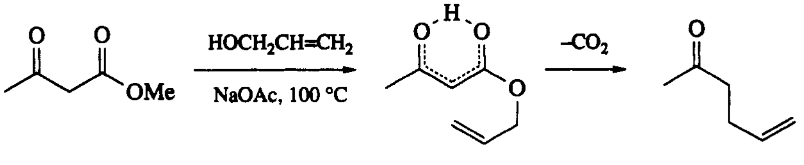

**(3)** **(4)** **(5)**

Carroll (2)

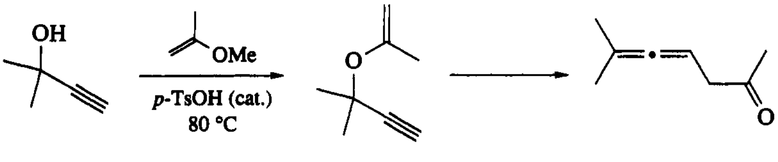

**(6)** **(7)** **(8)**

Saucy–Marbet (3)

Although the preparation of γ,δ-unsaturated carboxylic acids by the aliphatic Claisen rearrangement of magnesium enolates had been demonstrated as early as 1949,[5] a significant breakthrough was realized in 1964 by Eschenmoser and coworkers.[6] The exchange of amide acetals with allylic alcohols and subsequent *in situ* sigmatropic rearrangement greatly facilitated the stereoselective synthesis of γ,δ-unsaturated amides (**9** → **10** → 11; equation 4). The closely related acid-catalyzed exchange of orthoacetals with allylic alcohols, reported by Johnson and coworkers in 1970,[7] represents another important stage in the proliferation of the Claisen rearrangement in organic synthesis (**12** → **13** → **14**; equation 5). It is important to note that although both the Eschenmoser and the Johnson rearrangements are usually conducted at elevated temperatures, these conditions are required for the alcohol exchange reaction, and not for the actual rearrangement which can occur at significantly lower temperatures.[8]

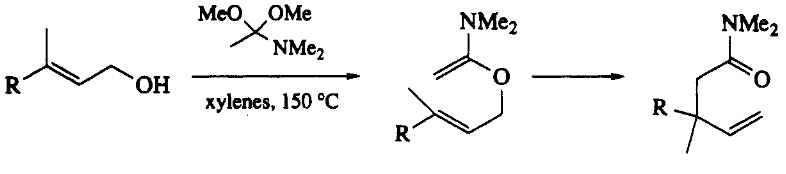

**(9)** **(10)** **(11)**

Eschenmoser (4)

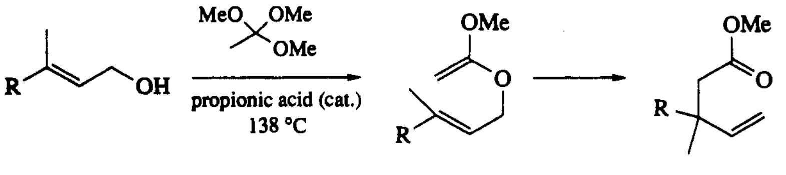

**(12)** **(13)** **(14)**

Johnson (5)

In 1972, a further brilliant improvement on the Claisen rearrangement was realized by Ireland and coworkers.[9] Ester enolization with lithium dialkylamide bases,[10] followed by silylation with TMS-Cl, generated reactive silyl ketene acetals at –78 °C or lower temperatures. Sigmatropic rearrangement to easily hydrolyzable γ,δ-unsaturated silyl esters occurred at ambient temperatures (**15** → **16** → **17**; equation 6). A particularly important aspect of this process is the simple control of enolate geometry that can be achieved by solvent selection.[11] The use of zinc enolates derived from α-halo esters in a Reformatsky–Claisen combination has also been briefly reported (**18** → **19** → **20**; equation 7).[12,13] However, the latter method has not been further developed, and in the past decade the Ireland silyl ester enolate sequence has proven to be perhaps the most general way to effect a stereocontrolled Claisen rearrangement.

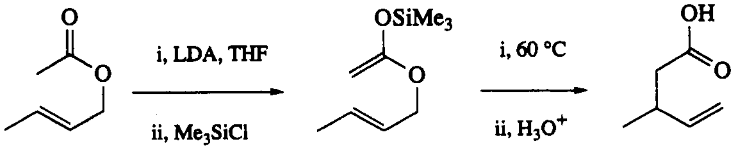

**(15)** **(16)** **(17)**

Ireland (6)

In 1978, Bellus and Malherbe reported a ketene version of the Claisen rearrangement. Treatment of allylic ethers with *in situ* prepared dichloroketene provided rearrangement products in good yield (**21** → **22** → **23**; equation 8).[14] This procedure works well also with allylic sulfides.[15,16] In 1982, finally, Denmark and Harmata demonstrated a first example of a carbanion-accelerated Claisen rearrangement (**24** → **25** → **26**; equation 9).[17] Related applications of the rate enhancement by formation of anionic species have been reported since,[18] and research in this area will undoubtedly provide further mechanistic insight into the 3,3-sigmatropic rearrangement and expand its synthetic scope even further.

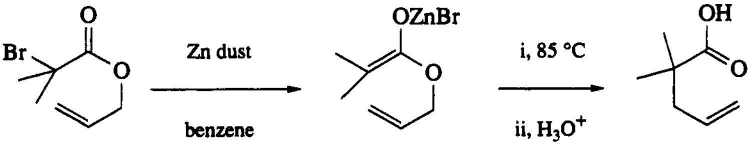

**(18)** **(19)** **(20)**

Reformatsky–Claisen (7)

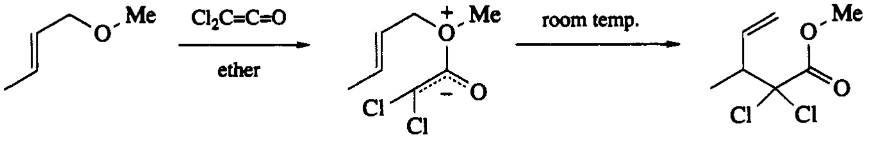

**(21)** **(22)** **(23)**

Ketene Claisen (8)

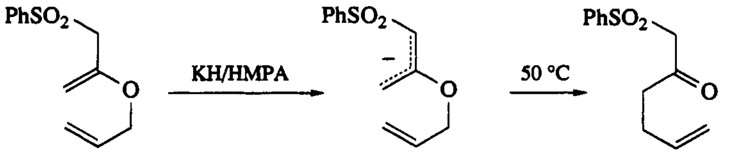

**(24)** **(25)** **(26)**

Carbanion-accelerated Claisen (9)

From 1964 to 1990, the discovery of highly versatile stereoselective variants supported a period of impressive growth in the number of synthetic efforts which employ a Claisen rearrangement for a key carbon–carbon bond forming process (Table 1). This increase in experimental applications was accompanied by a continuous interest in mechanistic analysis and theoretical understanding of the reaction.

In this review, the use of the Claisen rearrangement in stereoselective organic synthesis and mechanistic aspects of the reaction are highlighted. Due to the wealth of data, sections concerning the photo,[19] aza,[20] zwitterionic amino,[21] thia,[22] phospha[23] and metallo[24] as well as retro-Claisen[25] rearrangements had to be omitted. Polyhetero 3,3-sigmatropic shifts have also been excluded.[26] Consecutive processes involving Claisen rearrangements are covered in Chapter 7.3. The closely related 2,3-sigmatropic rearrangements are discussed in Chapter 4.6 of Volume 6 in this series. Literature examples were mostly taken from reports published between 1985 and 1990, in order to provide information complementary to previous[2] overviews.

**Table 1** Number of Publications with Reference to Claisen Rearrangements Between 1967 and 1990 (Source: Chemical Abstracts)

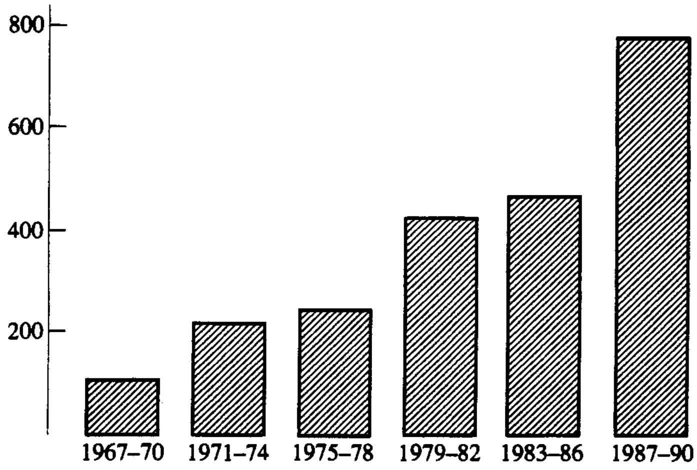

## 7.2.2 SYNTHETIC ASPECTS OF THE CLAISEN REARRANGEMENT

### 7.2.2.1 Definition

The Claisen rearrangement can formally be considered as the intramolecular *S*N′ addition of a carbonyl enol (X = O), thiocarbonyl enol (X = S) or enamine (X = N) to an allylic ether, sulfide or amine, respectively, forming a carbon–carbon σ-bond. The process involves concomitant π-bond migration and falls under the classification 3,3-sigmatropic shift.[27] It is usually referred to as concerted, although in fact a spectrum of mechanisms may be operative.[28] Other positions in (**27**) may be occupied by heteroatoms (hetero- and polyhetero-Claisen rearrangements) and the degree of unsaturation may be higher than depicted. In the aromatic Claisen rearrangement, carbons 1 and 2 are part of an aromatic system.

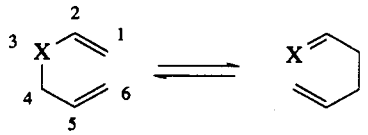

(**27**) (**28**)

X = O: Claisen rearrangement
X = S: thia-Claisen rearrangement
X = N: aza-Claisen rearrangement

### 7.2.2.2 Methods of Preparation of Allyl Vinyl Ethers

Allyl vinyl ethers are typically prepared by either mercury- or acid-catalyzed vinyl ether exchange with allylic alcohols or acid-catalyzed vinylation of allylic alcohols with acetals.[29] However, yields in these reactions are often low, and the use of mercury is not without concerns. Büchi and Vogel developed a mercury-free Claisen sequence, *via* reaction of sodium or lithium salts of primary and secondary allylic alcohols with the betaine (**29**) derived from ethyl propiolate and trimethylamine.[30] Heating of the product, (*E*)-3-(allyloxy)acrylic acid (**30**), leads to γ,δ-unsaturated aldehydes (**31**; Scheme 1). The scope of this reaction is limited to primary and secondary allylic alcohols. Tertiary allylic alcohols can be vinylated by a Michael-type addition to a vinyl sulfoxide, followed by elimination of PhSOH (Scheme 2).[31] This method is closely related to the earlier demonstrated intramolecular bromoetherification, followed by base-catalyzed elimination of HBr,[32] and the phenylselenenyl etherification/selenoxide elimination[33] reaction. Base-catalyzed intramolecular addition of allylic alcohols[34] or allyloxy radicals[35] to alkynes, or dehydration,[36] are alternative means for the construction of the vinyl ether functionality. Allyl vinyl ethers may also be generated from carbonyl precursors by Wittig-type alkenation reactions. Corey and Shulman made use of allyloxytrimethylphenylphosphonium ylides,[37] and Paquette and coworkers applied the Tebbe reagent for the preparation of allyl vinyl ether (**36**) from lactone (**35**) in the course of a synthesis of (±)-precapnelladiene (Scheme 3).[38] Interestingly, this ring expansion occurs only when the methyl group on the six-membered ring can assume an equatorial position in the chair-like transition state. Epimerization at the carbonyl α-position occurs due to enolate formation under the strongly basic thermolysis conditions.

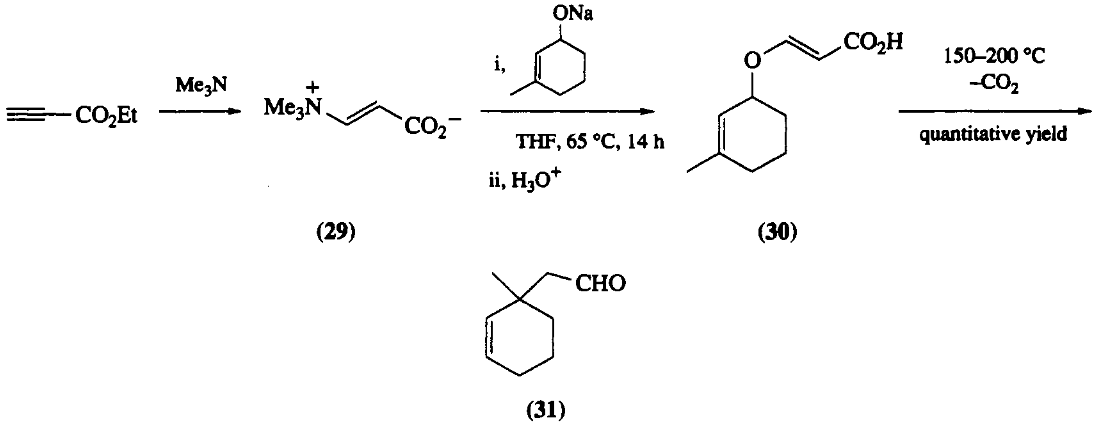
CO2Et
Me3N
Me3N+
CO2−
i, ONa
THF, 65 °C, 14 h
ii, H3O+
O
CO2H
150–200 °C
−CO2
quantitative yield
CHO
(29)
(30)
(31)

Scheme 1

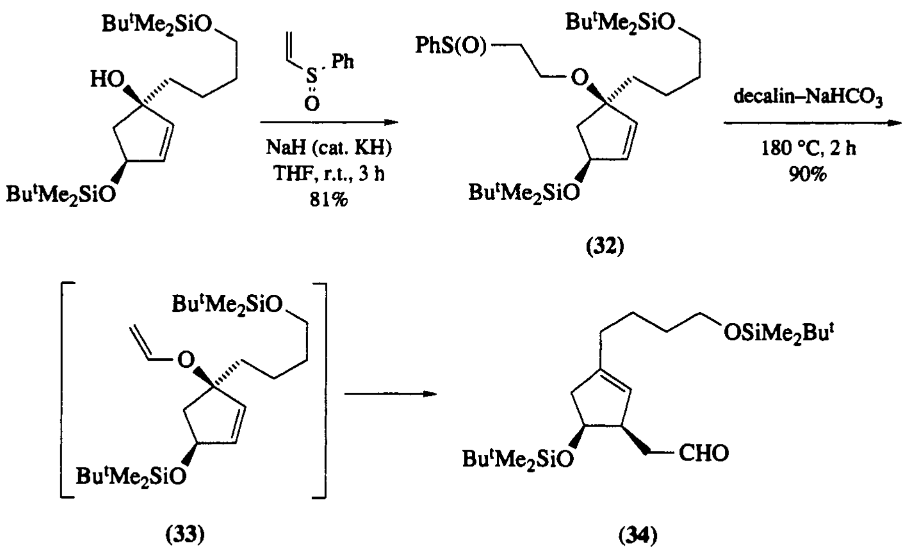
ButMe2SiO
HO
ButMe2SiO
S
Ph
O
NaH (cat. KH)
THF, r.t., 3 h
81%
PhS(O)
O
ButMe2SiO
ButMe2SiO
decalin–NaHCO3
180 °C, 2 h
90%
(32)
ButMe2SiO
O
ButMe2SiO
OSiMe2But
ButMe2SiO
CHO
(33)
(34)

Scheme 2

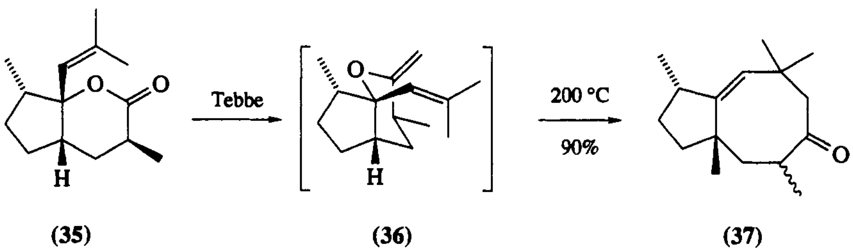
O
O
H
Tebbe
O
H
200 °C
90%
O
(35)
(36)
(37)

Scheme 3

Whereas Eschenmoser and Johnson variants of the Claisen rearrangement utilize an excess of amide acetal and orthoester precursors, respectively, for generation of the vinyl ether functionality, the Carroll and Ireland versions are especially useful because of the ease and economy in preparing the Claisen system, as will be seen in the following sections.

### 7.2.2.3 The Claisen Rearrangement of Allyl Vinyl Ethers

The uncatalyzed 'traditional' Claisen rearrangement of allyl vinyl ethers is still very much in use, especially for the preparation of quaternary centers of carbocyclic systems. The rearrangement is highly exothermic, but generally requires temperatures of 150–200 °C and is therefore limited to thermally stable compounds.

Recent representative examples of this procedure include an α-allylation of β-tetronic acids (Scheme 4),[39] the preparation of chiral 2,2-disubstituted cyclohexanones (**42**) in high enantiomeric excess *via* chirality transfer (Scheme 5),[40] and the rearrangement of intermediates for conformationally constrained peptide mimics (Scheme 6).[41] For their synthesis of neosporol, Ziegler and Nangia alkylated the potassium enolate (**46**) with mesylate (**47**) in HMPA.[42] The yield in the rearrangement of nitrile (**48**) was highly dependent upon the purity of the starting material. Trace impurities increased the amount of elimination product. In silylated glassware[43] and under high dilution conditions, a 16:1 mixture of diastereomeric ketones (**49**) and (**50**) was isolated (Scheme 7).

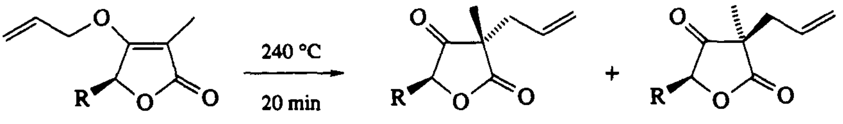

**(38)** **(39)** **(40)**

| | (39) | (40) |
|---|---|---|
| | *Isolated yield (%)* | |
| R = Me | 56 | 14 |
| R = Bn | 56 | 18 |
| R = Pr$^i$ | 58 | 7 |

Scheme 4

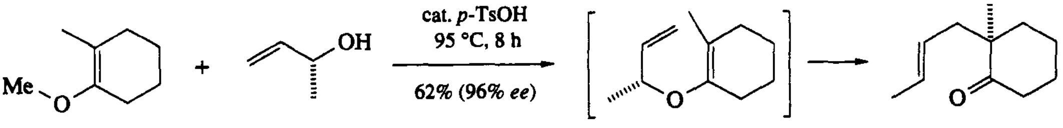

**(41)** **(42)**

Scheme 5

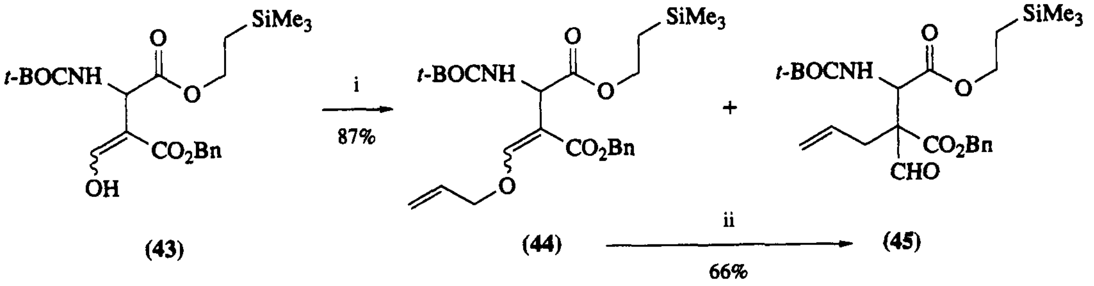

i, allyl iodide (1.2 equiv.), $Pr^i_2NEt$ (1.3 equiv.), acetone, 16 h; (**44**):(**45**) = 9:1; ii, decalin, reflux, 1 h

Scheme 6

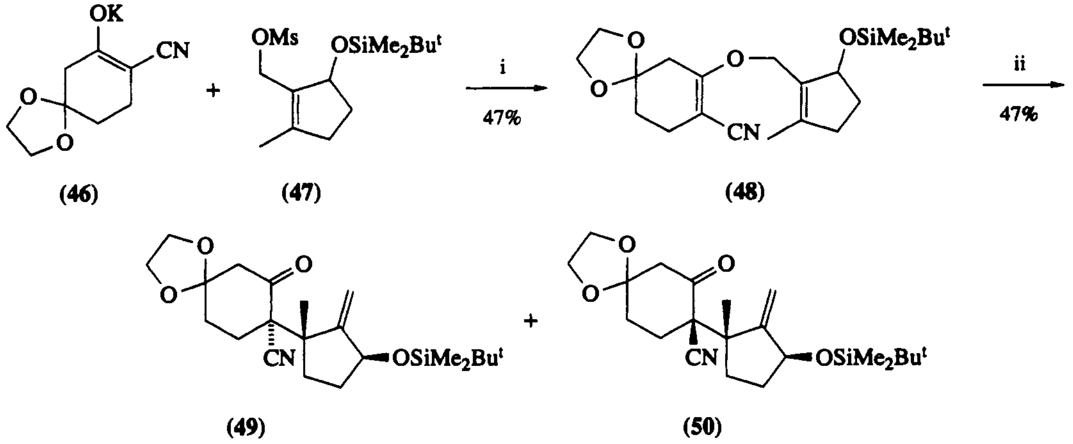

i, THF/HMPA, 0 °C, 18-crown-6, 2 h; ii, nonane, 151 °C, 4 h

Scheme 7

In a series of elegant studies, Paquette and coworkers demonstrated the potential of the Claisen rearrangement for the stereocontrolled total synthesis of natural products.[44] Dehydrative coupling[45] of (*Z*)-3-(trimethylsilyl)-2-propen-1-ol with cyclohexanone (**51**) under Kuwajima's conditions,[46] followed by rearrangement of enol ether (**52**) in decalin, led in excellent stereoselectivity (>99:1) to aldehyde (**53**; Scheme 8).[47] Concise construction of the eight-membered core of acetoxycrenulidine was achieved by intramolecular phenylseleno etherification of lactone (**54**), introduction of the exocyclic vinyl ether double bond by selenoxide elimination and subsequent Claisen rearrangement (Scheme 9, 66% from **54**).[48]

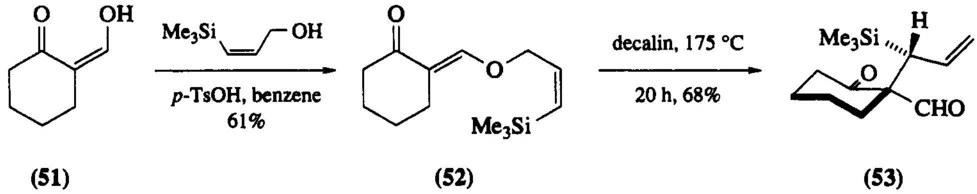

Scheme 8

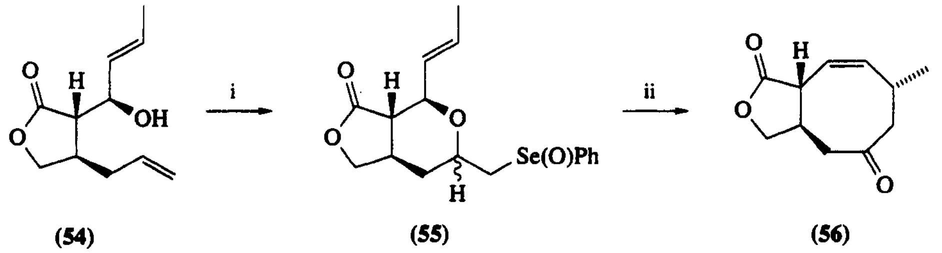

i, *N*-(phenylseleno)phthalimide, $CH_2Cl_2$; $NaIO_4$, $NaHCO_3$, MeOH, $H_2O$; ii, $Et_2NH$, mesitylene, Δ

Scheme 9

Mandai, Saito and coworkers recently described a new synthesis of isocarbacyclin, which features a crucial one-pot, three-step transformation: tandem tertiary allyl vinyl ether formation, Claisen rearrangement, and ene cyclization led from alcohol (**57**) directly to bicyclo[3.3.0]octane (**59**; Scheme 10).[49]

Clearly, due to improvements in the preparation of the allyl vinyl ether moiety, there is a trend even in the classical Claisen rearrangement to tackle more complex structural challenges successfully.

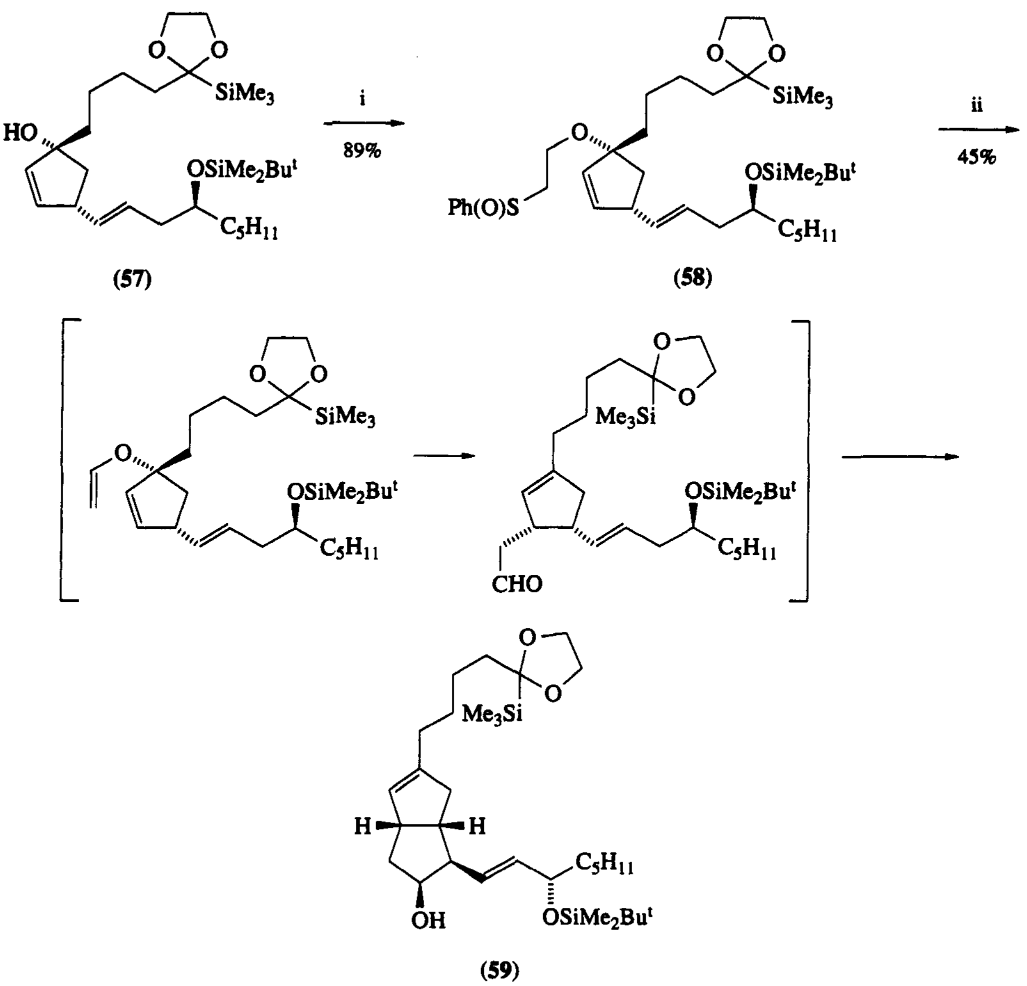

i, phenyl vinyl sulfoxide, NaH (1 equiv.)/KH (cat.), THF, r.t., 4 h; ii, $NaHCO_3$ (excess), decalin–α-pinane (2:1), 200 °C, 24 h

**Scheme 10**

### 7.2.2.4 The Aromatic Claisen Rearrangement

3,3-Sigmatropic rearrangement of an allyl aryl ether gives an *ortho*-dienone, which usually enolizes rapidly to the *ortho*-allylphenol (*ortho*-Claisen rearrangement, **60** → **62**, equation 10). If the *ortho* position is substituted, a second 3,3-sigmatropic shift followed by enolization yields a *para*-allylphenol (*para*-Claisen rearrangement, **60** → **64**, equation 10). In general, the *ortho*-Claisen product predominates, but sometimes some *para* product is obtained even if one or both *ortho* positions are unsubstituted.[50] No reaction occurs when all *ortho* and *para* positions are substituted. The rearrangement requires temperatures in the range of 150 to 225 °C and is usually regarded as concerted.[51] In the 'abnormal' Claisen rearrangement,[52] a subsequent homodienyl 1,5-sigmatropic H-shift leads to the formation of isomeric allyl phenols (**67**) and (**69**) (equation 11).[53] Recent applications of the aromatic Claisen rearrangement involve syntheses of flavenes,[54] dideoxydaunomycinone[55] and dihydrocoumarins.[56]

### 7.2.2.5 The Carroll Rearrangement

Among the most favorable features of the Carroll variant[3] of the Claisen rearrangement are the relative ease of preparation of the parent system by condensation of allylic alcohols with acetoacetic ester[57] or diketene and the defined configuration of the intermediately generated double bond. The Carroll rearrange-

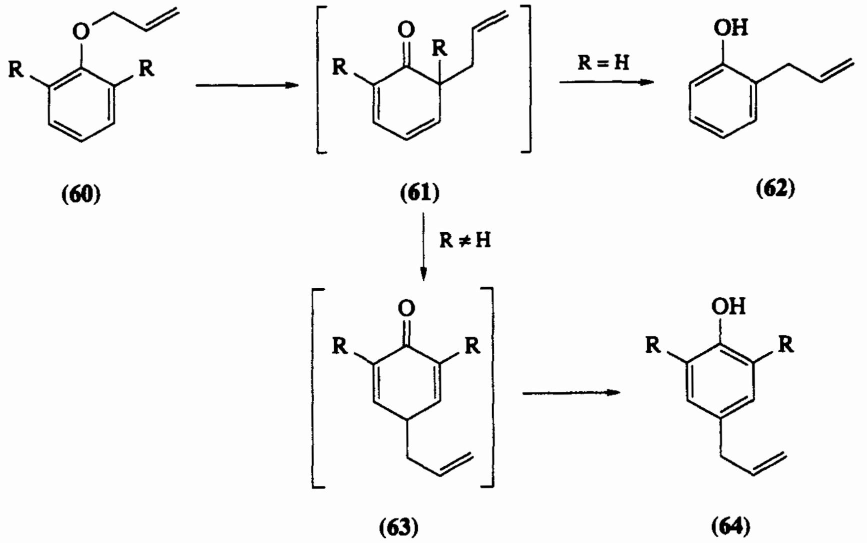

(10)

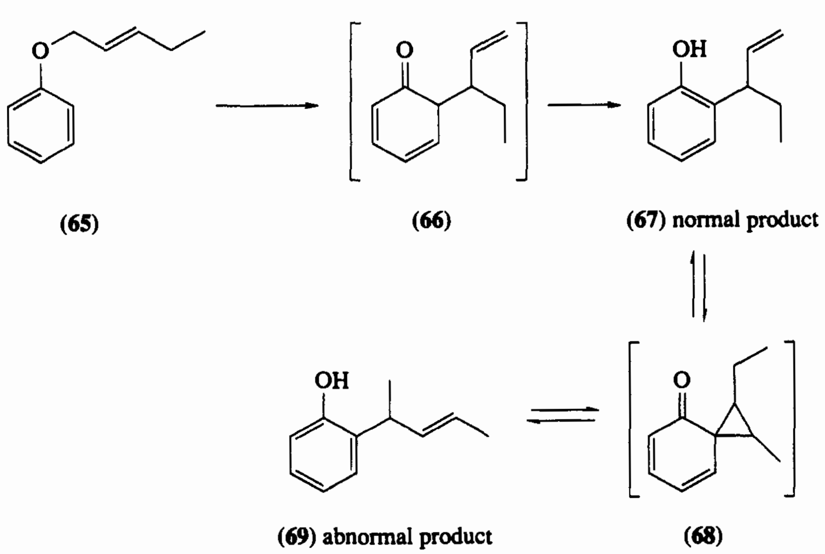

(11)

ment has been utilized on a commercial scale for the synthesis of geranyl acetone as well as β-ionone.[58,59]

An improved version of the Carroll reaction, the ester enolate Carroll rearrangement, was reported in 1984 by Wilson and Price.[60] Dianions of allylic acetoacetates, generated by treatment with 2 equiv. of LDA at −78 °C in THF, were rearranged at room temperature or 65 °C to yield β-keto acids in 40–80% yield (equation 12). In the course of a synthesis of the sesquiterpene isocomene, Snider and Beal used this method for the rearrangement of acetoacetate (**73**), prepared in 83% yield from reaction of cyclopentene (**72**) with diketene and a catalytic amount of DMAP (Scheme 11).[61] The (*E*)-isomer of ketone (**74**) is obtained stereospecifically, since there is a severe steric interaction between the methyl groups in the Carroll rearrangement transition state leading to the (*Z*)-isomer.

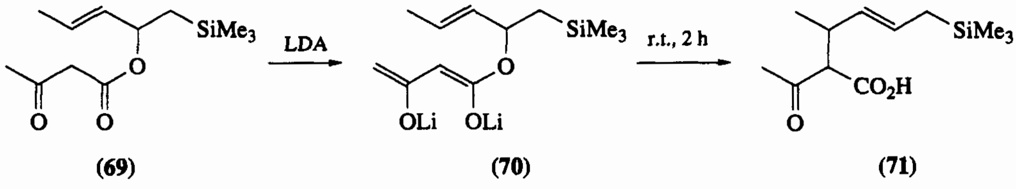

(12)

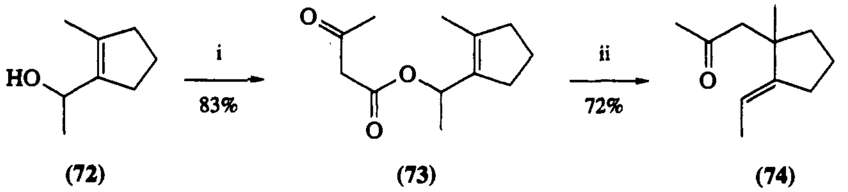

i, diketene, DMAP, ether, –25 °C to r.t.; ii, 2 equiv. LDA, THF, reflux and then $CCl_4$, reflux

**Scheme 11**

Another modification of the Carroll rearrangement was used by Gilbert and Kelly for the diastereoselective formation of contiguous quaternary centers.[62] Transformation of an allylic β-keto ester into a silylketene acetal is followed by a 3,3-sigmatropic rearrangement which generates the desired carbon–carbon bond in good yield and with excellent stereocontrol (Scheme 12). Ester (**79**) was thus isolated as a single isomer in 73% yield.

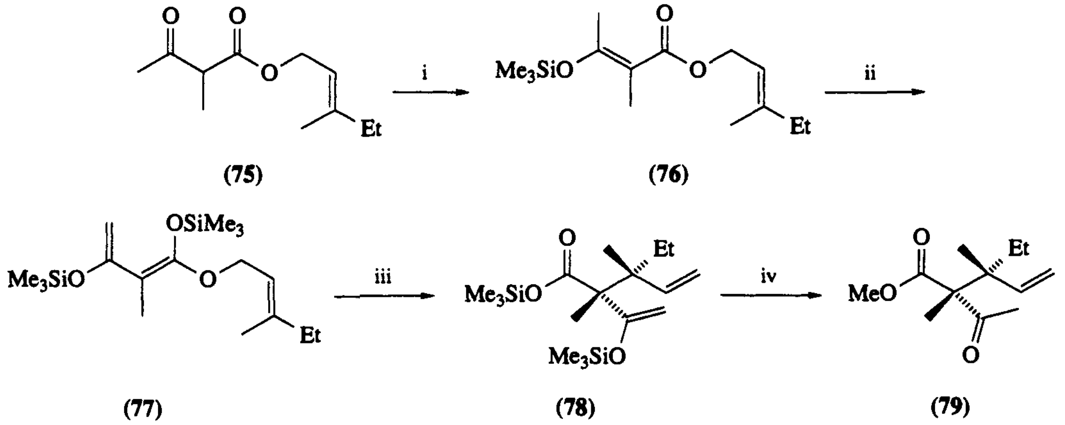

i, HMDS, imidazole, reflux; ii, LiTMP, TMEDA, THF, –50 °C; $Me_3SiCl$, $Et_3N$, HMPA, –78 °C, 4 h; iii, r.t., 3 h, then 40 °C, 12 h; iv, 1% HCl, MeOH, 0 °C, 15 min; $CH_2N_2$

**Scheme 12**

A Ciba-Geigy group used the Carroll reaction for the synthesis of hydroxyethylene dipeptide isosteres.[63] Alcohol (**80**) was converted with diethyl isopropylmalonate to the mixed malonic ester derivative (**81**) by $Ti(OEt)_4$ catalysis. Subsequent sigmatropic rearrangement of (**81**) was also effectively catalyzed by $Ti(OEt)_4$, thereby allowing a one-step conversion of the allylic alcohol (**80**) to ester (**82**) (Scheme 13).

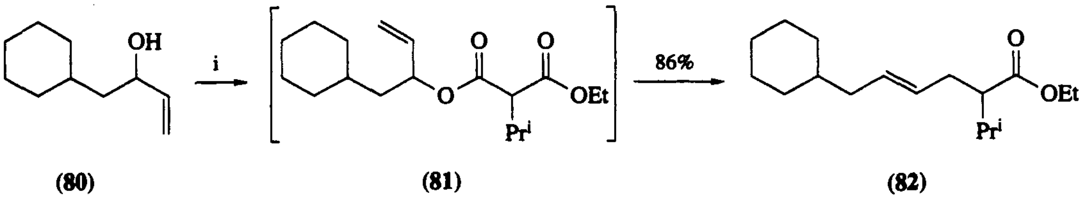

i, diethyl isopropylmalonate, $Ti(OEt)_4$, 160–190 °C

**Scheme 13**

### 7.2.2.6 The Eschenmoser Amide Acetal Rearrangement

The 3,3-sigmatropic shift of ketene *N,O*-acetals, first developed by Eschenmoser,[6,64] preceded studies of the ynamine-Claisen rearrangement,[65] where the reactive intermediate is formed at ambient temperature by treatment of the ynamine with an allylic alcohol. Sucrow and Richter have studied the stereochemistry of the rearrangement of the dimethyl acetal of *N*,*N*-dimethylpropionamide with (*E*)- and (*Z*)-crotyl alcohol.[66] Based on the assumption of a chair-like transition state,[67] the stereochemistry of the products can be explained by an axial orientation of the C(1)-methyl group of the ketene *N*,*O*-acetal (**83** and **88**; equation 13). (*Z*)-Ketene *N*,*O*-acetals (**83**) and (**88**) are predominant under thermodynamic reaction conditions. Using the ynamine method, Bartlett and Hahne succeeded in preparing the less stable kinetic diethylamide analogs of (*E*)-ketene *N*,*O*-acetals (**85**) and (**86**) at 140 °C, where rearrangement is competitive with isomerization.[68]

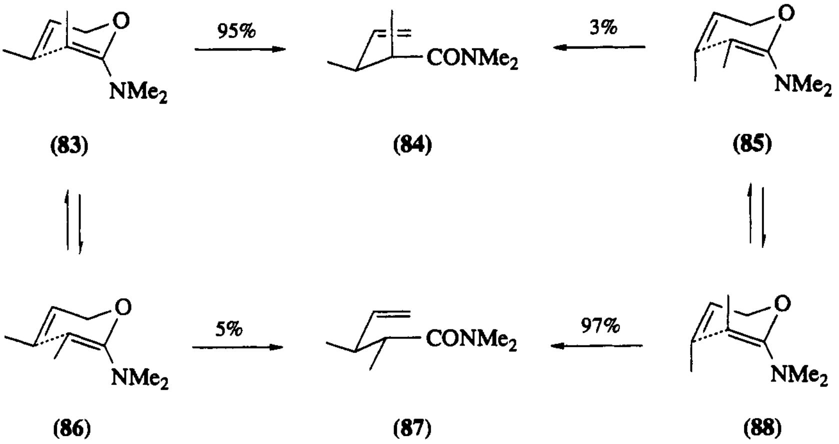

(13)

In a stereocontrolled route to thromboxane $B_2$, Corey and coworkers used the Eschenmoser rearrangement for the preparation of lactone (**91**; Scheme 14).[69] The product of the 3,3-sigmatropic shift, amide (**90**), is directly iodolactonized, thus avoiding often troublesome amide hydrolysis conditions. Another application involving a carbohydrate derivative was demonstrated by Fraser-Reid and coworkers (Scheme 15).[70] Reductive elimination of benzylidene (**92**), followed by *in situ* alkylation, Wittig reaction, DIBAL-H reduction and rearrangement, led to amide (**94**), which was transformed into the corresponding pyranoside diquinane by double radical cyclization.

*N*-Silylketene *N*,*O*-acetals can also be generated from allyl *N*-phenylimidates by deprotonation and subsequent *N*-silylation.[71] Predominant (*Z*)-configuration of the vinyl ether double bond in (**96**) leads, under the assumption of a chair transition state, with allylimidates (**95a–d**) preferentially to *anti*-products

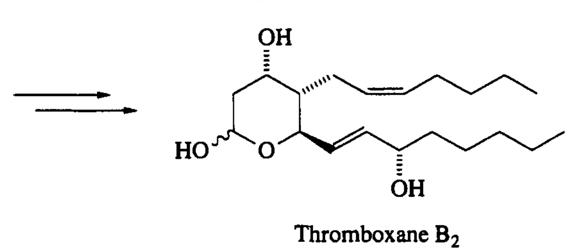

i, *N*,*N*-dimethylacetamide dimethyl acetal, diglyme, 25 to 160 °C; ii, $I_2$, THF/$H_2O$, 0 °C, then $Bu_3SnH$, $NaBH_4$, benzene

**Scheme 14**

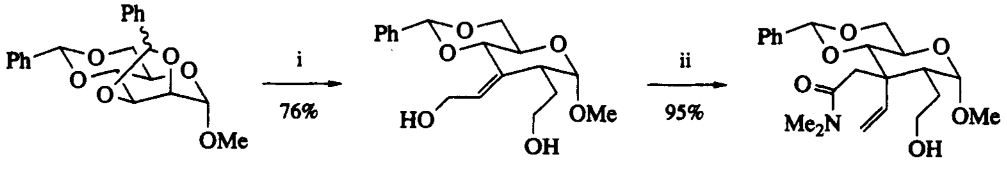

**(92)** **(93)** **(94)**

i, BuLi; $BrCH_2CO_2Et$; $Ph_3PCHCO_2Et$, THF; DIBAL-H, toluene; ii, *N*,*N*-dimethylacetamide dimethyl acetal, toluene, reflux, 4 Å MS; MeOH, $H_2O$, $Et_3N$

Scheme 15

**(97a–d)** (Scheme 16, Table 2). The sigmatropic rearrangement of (*E*)-configured allylic ester occurs smoothly at room temperature.[72] The striking drop in stereoselectivity observed for **(95e)** can be attributed to the partial formation of the (*E*)-configured enolate, probably due to energetically favorable chelate formation opposing energetically unfavorable $A^{1,3}$-strain[73] during the enolization process.

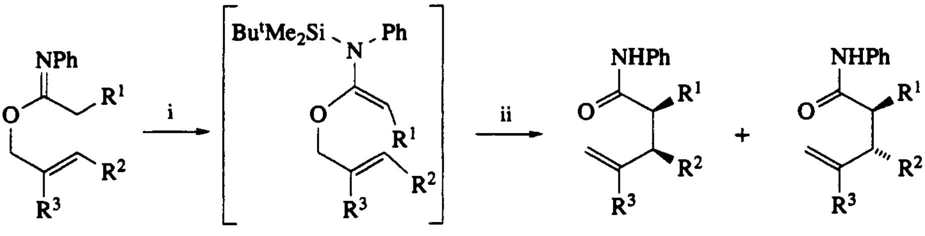

**(95)** **(96)** **(97)** **(98)**

i, LDEA, THF, 1 h, −78 °C; $Bu^tMe_2SiCl$, HMPA, 1 h, −20 °C; ii, 24 h, r.t.; $NH_4Cl$, $H_2O$

Scheme 16

**Table 2** Claisen Rearrangements of Allylimidates (95)[71]

| *Entry* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *Yield (%)* | *Ratio* *(97)* : | *(98)* |
|---|---|---|---|---|---|---|
| 1 | Me | Me | H | 67 | 90.7 | 9.3 |
| 2 | Me | *n*-Pr | H | 66 | 90.9 | 9.1 |
| 3 | Me | Me | Me | 59 | 98.1 | 1.9 |
| 4 | Me | Me | $SiMe_3$ | 64 | 99.2 | 0.8 |
| 5 | OMe | Me | H | 54 | 46.6 | 53.4 |

Complete chirality transfer in the formation of the quaternary center in acetal **(100)** was observed by Fujioka and coworkers in the synthesis of (*R*)-(+)-3′-methoxy-4′-*O*-methyljoubertiamine (Scheme 17).[74]

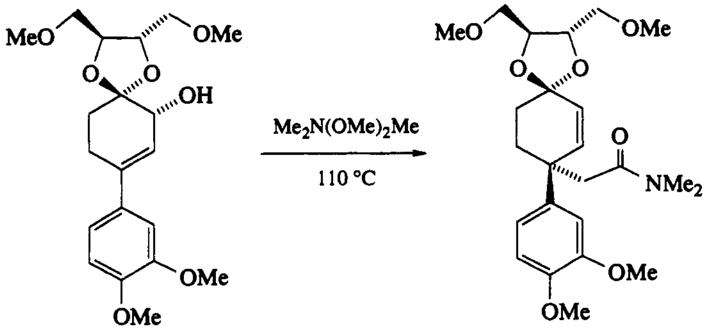

**(99)** **(100)**

Scheme 17

### 7.2.2.7 The Johnson Ortho Ester Rearrangement

Contrary to the Carroll and the Eschenmoser rearrangements, Johnson rearrangement[7] of propionic acid derivatives fails to give stereochemically defined ketene acetals.[75,76] This variant has therefore most successfully been applied to orthoacetates or ortho esters with fugitive groups in the α-position that are eliminated after the rearrangement step.[77] The stereoselectivity of the 3,3-sigmatropic shift itself, however, is excellent (generally >98%[7]). In an elegant synthesis of (+)-15(*S*)-prostaglandin $A_2$, Stork and Raucher used the Johnson rearrangement for a crucial transfer of chirality from alcohol (**101**) to ester (**103**) (Scheme 18a).[78] Due to expected formation of a mixture of (*Z*)- and (E)-ketene acetals, approximately a 1:1 mixture of epimers is formed (which in this particular synthesis is irrelevant because the center is equilibrated at the end).

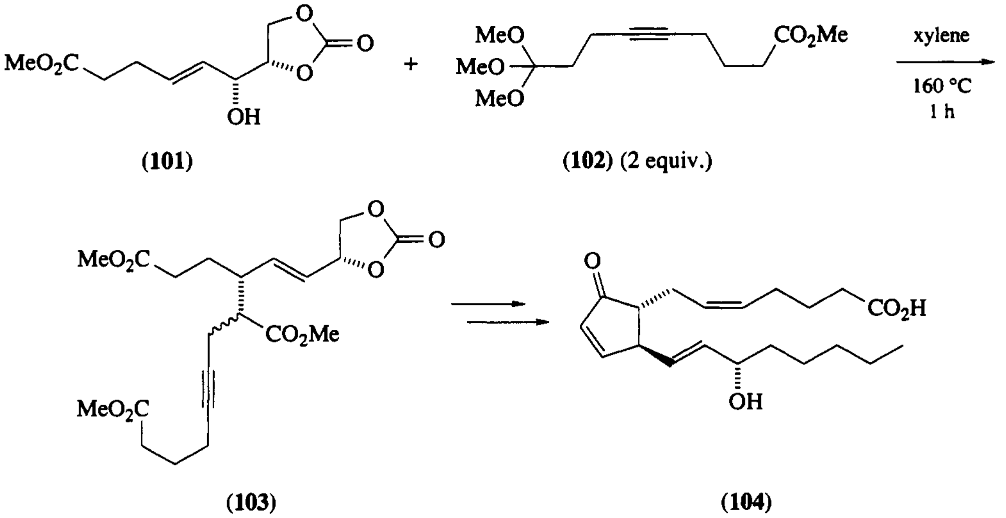

**(101)** + **(102)** (2 equiv.) → **(103)** → **(104)**

**Scheme 18a**

In an attempt to develop a synthetic strategy for 1,4- and 1,5-stereoselection by sequential aldol addition to α,β-unsaturated aldehydes followed by Claisen rearrangement, Heathcock and coworkers examined the Johnson–Faulkner rearrangement of aldol (**105**; Equation 14).[79] Although keto ester (**106**) was obtained in 40% yield, the major products seemed to derive from β-elimination.[80] In a somewhat related system, rearrangement of allylic alcohols (**108**) and (**109**), obtained by addition of isopropenylmagnesium bromide to aldehyde (**107**), yielded the same 1.5:1 mixture of ethyl esters (**110**) and (**111**) (Scheme 18b).[81] The desired isomer (**110**) was purified by HPLC and used in the total synthesis of the cyclodepsipeptide geodiamolide A. Suzuki, Kametani and coworkers applied the ortho ester rearrangement in their enantioselective synthesis of (–)-chokol A.[82] Allyl alcohol (**112**) was converted into the separable methyl esters (**113**) (51% yield) and (**114**) (19% yield), along with 5% recovered starting material (Scheme 19).

In the context of the synthesis of a precursor of 1α,25-dihydroxyvitamin $D_3$, Posner and Kinter treated allylic alcohol (**115**) with ethyl orthoacetate in a sealed tube.[83,84] The resultant γ,δ-unsaturated ester (**116**), formed in 85% yield, was sulfinated, oxidized and pyrolyzed to form the desired dienoate ester (**117**) in 35–40% overall yield (Scheme 20). This sequence was considerably improved by the use of sulfinylacetate (**118**). Johnson rearrangement and subsequent *in situ* sulfoxide pyrolytic 1,2-elimination gave ester (**117**) in a gratifying 89% yield as a 4:1 mixture of (*E*)/(*Z*) geometrical isomers.[85]

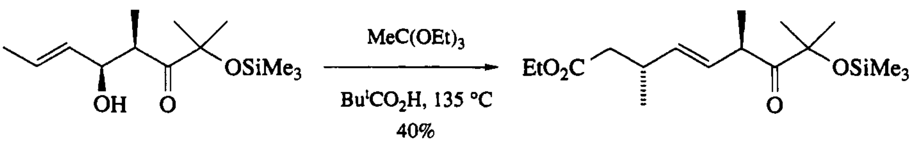

**(105)** → **(106)** (14)

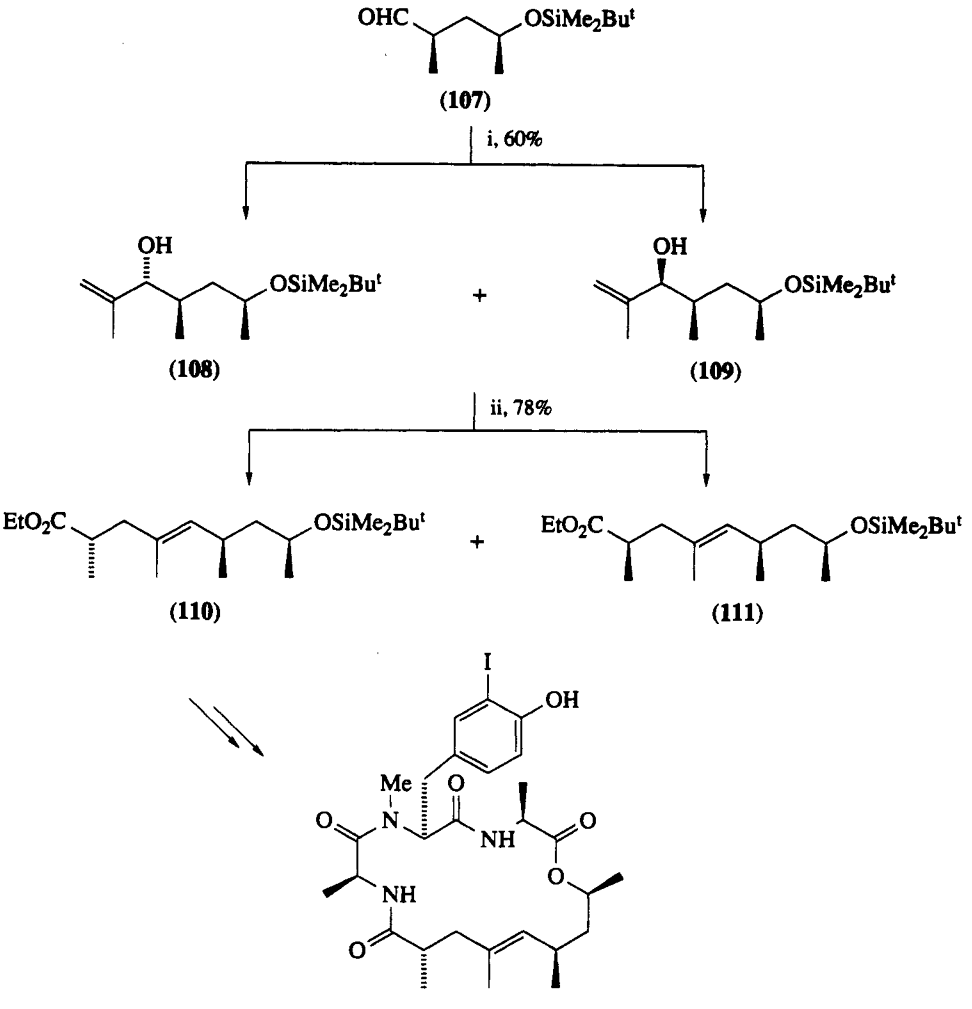
OHC
OSiMe$_2$Bu$^t$
(107)
i, 60%
OH
OSiMe$_2$Bu$^t$
(108)
+
OH
OSiMe$_2$Bu$^t$
(109)
ii, 78%
EtO$_2$C
OSiMe$_2$Bu$^t$
(110)
+
EtO$_2$C
OSiMe$_2$Bu$^t$
(111)
I
OH
Me
O
N
O
NH
O
O
NH
O

Geodiamolide A

i, $H_2C{=}C(Me)MgBr$, THF, reflux; ii, $MeCH_2C(OEt)_3$, $EtCO_2H$, 110 °C

**Scheme 18b**

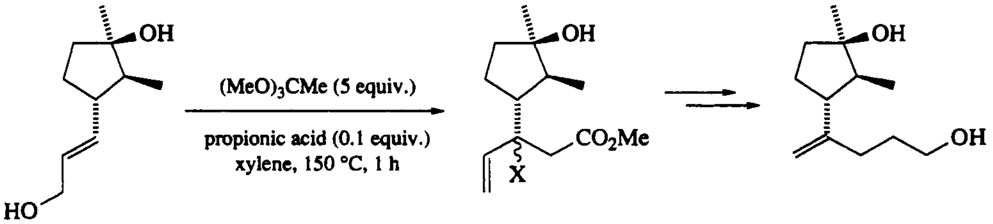
OH
HO
(MeO)$_3$CMe (5 equiv.)
propionic acid (0.1 equiv.)
xylene, 150 °C, 1 h
OH
CO$_2$Me
X
OH
OH

(112)

(113) X = β-H
(114) X = α-H

(–)-Chokol A

**Scheme 19**

### 7.2.2.8 The Ireland Silyl Ester Enolate Rearrangement

Since its introduction in 1972,[9] the Ireland silyl ester enolate variant of the Claisen rearrangement has become increasingly popular in organic synthesis. Areas of successful applications include the polyether

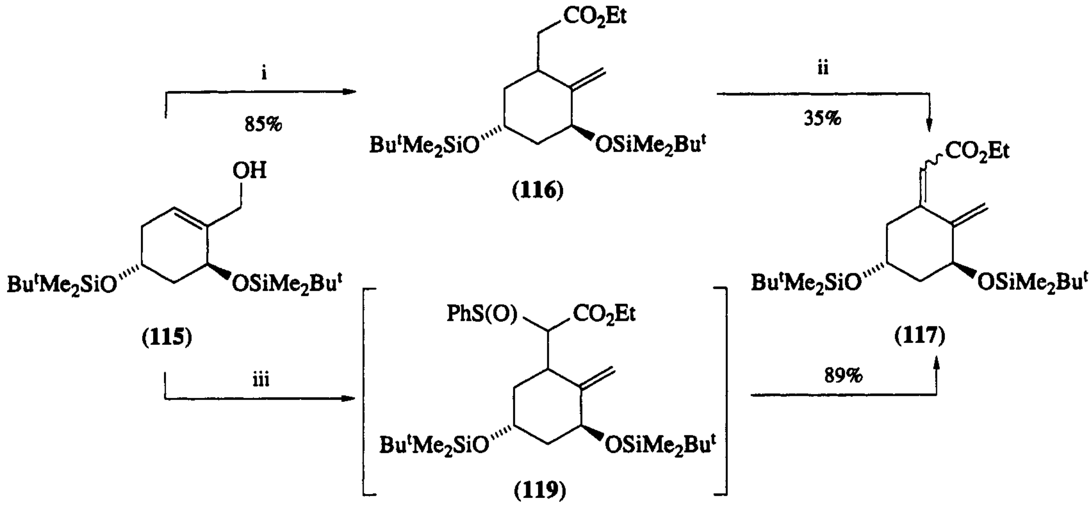

i, $MeC(OEt)_3$, $CH_2Cl_2$, acid (cat.), 150 °C, 2 h; ii, LDA, PhSSPh; MCPBA, 150 °C, 2 h;
iii, $PhS(O)CH_2C(OEt)_3$ **(118)**, trimethylbenzoic acid (cat.), $CH_2Cl_2$, 100 °C, 12 h

**Scheme 20**

antibiotics,[86] terpenes,[87] steroids,[88] iridoids,[89] tetronates,[90] amino acids,[91,92] *C*-glycosides,[93] carbocycles,[94] alkyl fluorides,[95] stannanes[96] and silanes.[97,98]

Several factors contribute to the versatility of the ester enolate Claisen rearrangement. Among these are the ability to use a stoichiometric combination of the alcohol and the acid components, the relatively low temperature[9c,99] of the pericyclic process that allows for the assembly of complex, highly functionalized structures, and the transformation of a carbon–oxygen into a carbon–carbon bond that lends itself easily to the assembly of contiguous quaternary centers.[100,101]

Another particularly important aspect of the Ireland rearrangement is that, through an efficient control of ketene acetal geometry, a highly reliable and predictable transfer of stereochemistry from starting material to product can be realized (Scheme 21).[9] Deprotonation of crotyl ester **(120)** with LDA[102] in THF leads, *via* the selective formation of the kinetically favored (*Z*)-ester enolate,[103,104] upon silylation to the (*E*)-silylketene acetal **(121)**.[105] After rearrangement at 65 °C and mild hydrolysis of the silyl ester, an 87:13 ratio of $\gamma,\delta$-unsaturated acids **(122)** and **(124)** is isolated in 79% yield. These two products can be obtained in a 19:81 ratio by using 23% HMPA/THF as a solvent system for the generation of the thermodynamically favored[106] (*Z*)-silylketene acetal **(123)** *via* the corresponding (*E*)-lithium enolate.[107]

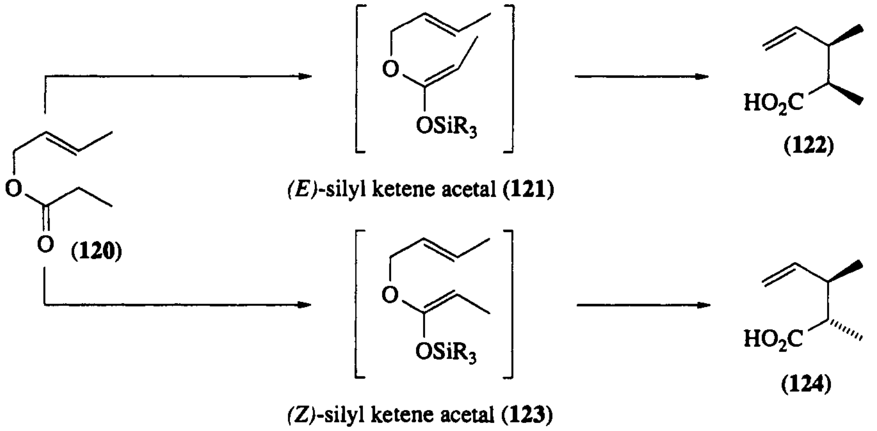
O
O
(120)
$OSiR_3$
(*E*)-silyl ketene acetal **(121)**
(*Z*)-silyl ketene acetal **(123)**
$HO_2C$
(122)
(124)

| *Conditions* | *Yield (%)* | *Ratio (122):(124)* |
|---|---|---|
| LDA, THF; $Me_3SiCl$; Δ; $NaOH/H_2O$ | 79 | 87:13 |
| LDA, THF/23% HMPA; $Me_3SiCl$; Δ; $NaOH/H_2O$ | 73 | 19:81 |

**Scheme 21**

The stereoselectivity of the formation of the (*E*)-lithium enolate and thus of the entire rearrangement can be significantly increased by a change in the reaction solvent from 23% HMPA/THF to 45% DMPU/THF (Scheme 22).[108,109]

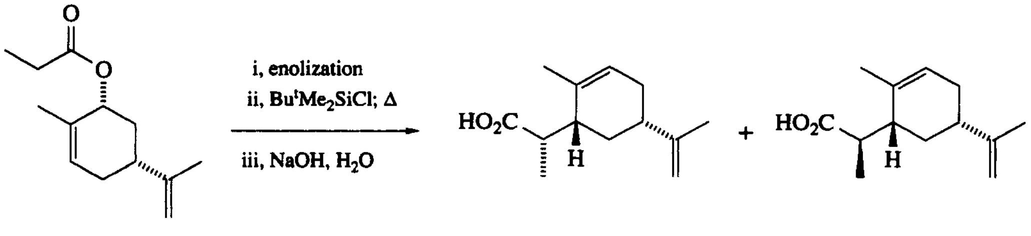

**(125)** **(126)** **(127)**

| *Enolization conditions* | *(126):(127)* | *Yield (%)* |
|---|---|---|
| LDA, 45% DMPU/THF | 98:2 | 60 |
| LDA, 23% HMPA/THF | 90:10 | 70 |
| LDA, THF | 25:75 | 56 |

**Scheme 22**

The preferred formation of the kinetically favored (*Z*)-silylketene acetal with amide bases in THF can be rationalized by a cyclic transition state model (**128**) that enables a close interaction between $Li^+$ cation, carbonyl oxygen and base (Scheme 23). The presence of additives such as HMPA or DMPU results in a greater degree of solvation of the lithium cation and a weakened $Li^+$–carbonyl oxygen interaction. Accordingly, the association between base and ester is diminished and the 1,3-diaxial strain in transition state (**129**) is reduced, whereas transition state (**128**) is still destabilized by $A^{1,3}$-strain.[110] In the presence of a slight excess of ester in the enolization mixture, a kinetic resolution process accounts for an additional increase in the ratio of the (*E*)- *vs.* the (*Z*)-lithium enolate (Table 3).[108]

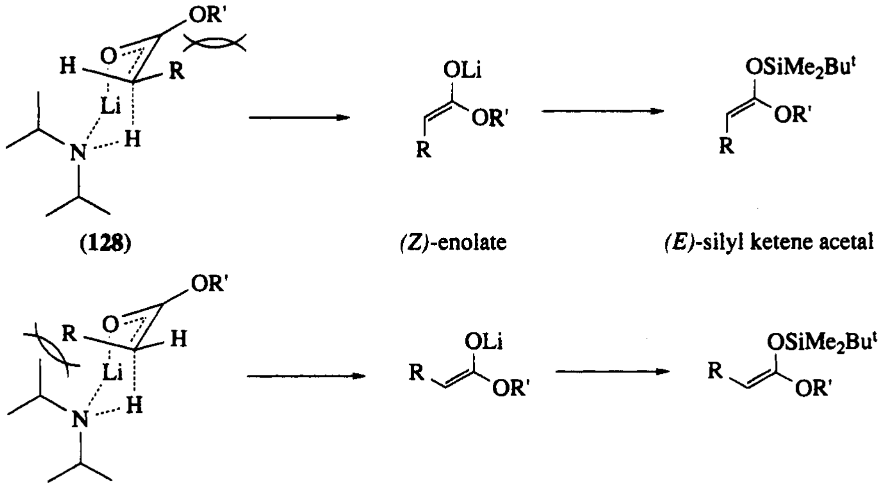

**(128)** (*Z*)-enolate (*E*)-silyl ketene acetal

**(129)** (*E*)-enolate (*Z*)-silyl ketene acetal

**Scheme 23**

It is important to note, however, that an observed erosion of diastereoselectivity in the Ireland silyl ester enolate rearrangement can be attributed either to the geometric integrity of the silylketene acetals or the selectivity of the chair-like *vs.* boat-like transition states, and interpretation and improvement of experimental stereoselectivities must take into account both of these factors.

As the ester enolate Claisen rearrangement allows for a stoichiometric combination of alcohol and acid components, it has been used for the formation of strategically important C—C bonds by esterification or lactonization and subsequent rearrangement, such as is elegantly demonstrated in the synthesis of the antibiotic chlorothricolide (Scheme 24).[111] Radical decomposition[112] of the selenoester of (**132**) leads to

**Table 3** Effect of Ester to Base Ratio on Stereoselectivity in Silylketene Acetal (SKA) Formation of Ethyl Propionate with LDA[108]

| *Entry* | *Solvent* | *Ester:base* | *(Z)-:(E)-SKA* | *Yield (%)* |
|---|---|---|---|---|
| 1 | THF | 1.4:1 | 1:1 | 5 |
| 2 | THF | 1 + 0.2:1[a] | 20:80 | 35 |
| 3 | THF | 1:1 | 6:94 | 90 |
| 4 | THF | 0.6:1 | 6:94 | 90 |
| 5 | THF/30% DMPU | 1.2:1 | ≥98:2 | 70 |
| 6 | THF/30% DMPU | 0.95:1 | 67:33 | 90 |
| 7 | THF/30% DMPU | 0.8:1 | 68:32 | 85 |
| 8 | THF/30% DMPU | 0.5:1 | 60:40 | 95 |
| 9 | THF/30% DMPU | 0.3:1 | 60:40 | 95 |
| 10 | THF/45% DMPU | 1.05:1 | ≥98:2 | 80 |
| 11 | THF/45% DMPU | 0.8:1 | 93:7 | 90 |
| 12 | THF/45% DMPU | 0.5:1 | 84:16 | 85 |
| 13 | THF/23% HMPA | 1.2:1 | 93:7 | 65 |
| 14 | THF/23% HMPA | 1:1 | 85:15 | 80 |
| 15 | THF/23% HMPA | 0.8:1 | 59:41 | 40 |
| 16 | THF/23% HMPA | 0.6:1 | 55:45 | 35 |
| 17 | THF/23% HMPA | 0.4:1 | 54:46 | 40 |

[a] 0.2 equiv. of the ester were added *after* addition of DMPU.

the decarbonylated product (**133**) in high yield. Interestingly, analogous reductive decarboxylation with open-chain precursors had led to cylopropanation or the formation of pentacycle (**134**) by radical cyclization.

In the total synthesis of the esterase inhibitor (±)-ebelactone A, Paterson and Hulme applied an aldol–Claisen strategy for a relay of 1,2-*syn* into 1,5-*syn* relative stereochemistry (Scheme 25).[79,113,114] The critical Ireland ester enolate rearrangement could be performed without protecting the $C_9$ ketone to give ester (**137**) in 74% overall yield.[115]

Danishefsky and coworkers have demonstrated the conversion of lactones to carbocycles by the 3,3-sigmatropic shift of silylketene acetals.[116,117] In the total synthesis of the *Fusarium* toxin equisetin, for example, keto lactone (**138**) was converted to its bissilyl derivative (**139**) by reaction with 2 equiv. of LDA and an excess of TMS-Cl.[118] *In situ* thermolysis of ketene acetal (**139**) led to a very smooth transformation into ester (**140**), which was carried on to equisetin (Scheme 26). This methodology was also applied by Schreiber and Smith in the preparation of the cyclohexyl moiety of the immunosuppressive agent FK-506.[119] Ireland–Claisen rearrangement of silylketene acetal (**142**), prepared by treatment with TBDMS-OTf and triethylamine at low temperature, provided, after hydrolysis of the silyl ester, the carboxylic acid (**143**) in 71% overall yield (Scheme 27). The strict translation of configuration *via* a boat-like transition state is typical for this permutation.

The Ireland ester enolate rearrangement of vinyl lactones can also be applied for the preparation of azacyclic systems. Silylketene acetal (**145**), again prepared by treatment of lactone (**144**) with a slight excess of TBDMS-OTf and triethylamine,[120] was easily converted to the substituted pipecolic acid (**146**) upon reflux in toluene (Scheme 28).[121] Claisen rearrangement mediated ring contraction of macrocyclic lactones was applied by Funk and coworkers for the preparation of the *in,out*-bicyclo[4.4.1]undecan-7-one core of the potent tumor promoter ingenol (Scheme 29).[122,123] The *in,out* bridged macrobicyclic lactone (**147**) does not suffer from the bending strain present in the smaller bicyclo[4.4.1]undecanone ring system and is therefore accessible without diversion to the *out,out* isomer. Addition of 4 equiv. of TIPS-OTf to a refluxing benzene solution of lactone (**147**) in the presence of 8 equiv. of triethylamine gave one major rearrangement product (**149**) in better than 15:1 selectivity and 77% yield. The stereochemical assignment of the two newly created stereogenic centers was verified by X-ray analysis of the bromolactone derivative.

Claisen ring contraction of lactones is amenable to the preparation of pyrrolidinecarboxylic acids, as demonstrated by Knight and coworkers in the enantiospecific total synthesis of (–)-α-kainic acid (Scheme 30).[124] Rearrangement of azalactone (**150**) proceeded smoothly only when the base (LDA) and the trapping agent (TBDMS-Cl) were premixed[125] at low temperature before addition of lactone (**150**). Silylketene acetal (**151**) underwent rearrangement at ambient temperature, and led, after hydrolysis of the silyl ester under mildly basic conditions, to the desired pyrrolidinedicarboxylic acid (**152**) in 55% overall yield. Previous studies have shown that such rearrangements proceed exclusively *via* a boat transition state when the lactone is 11-membered or smaller. An example of a tandem Brook[126]–Claisen rearrangement was recently reported by Kishi and coworkers in the total synthesis of ophiobolin C (Scheme

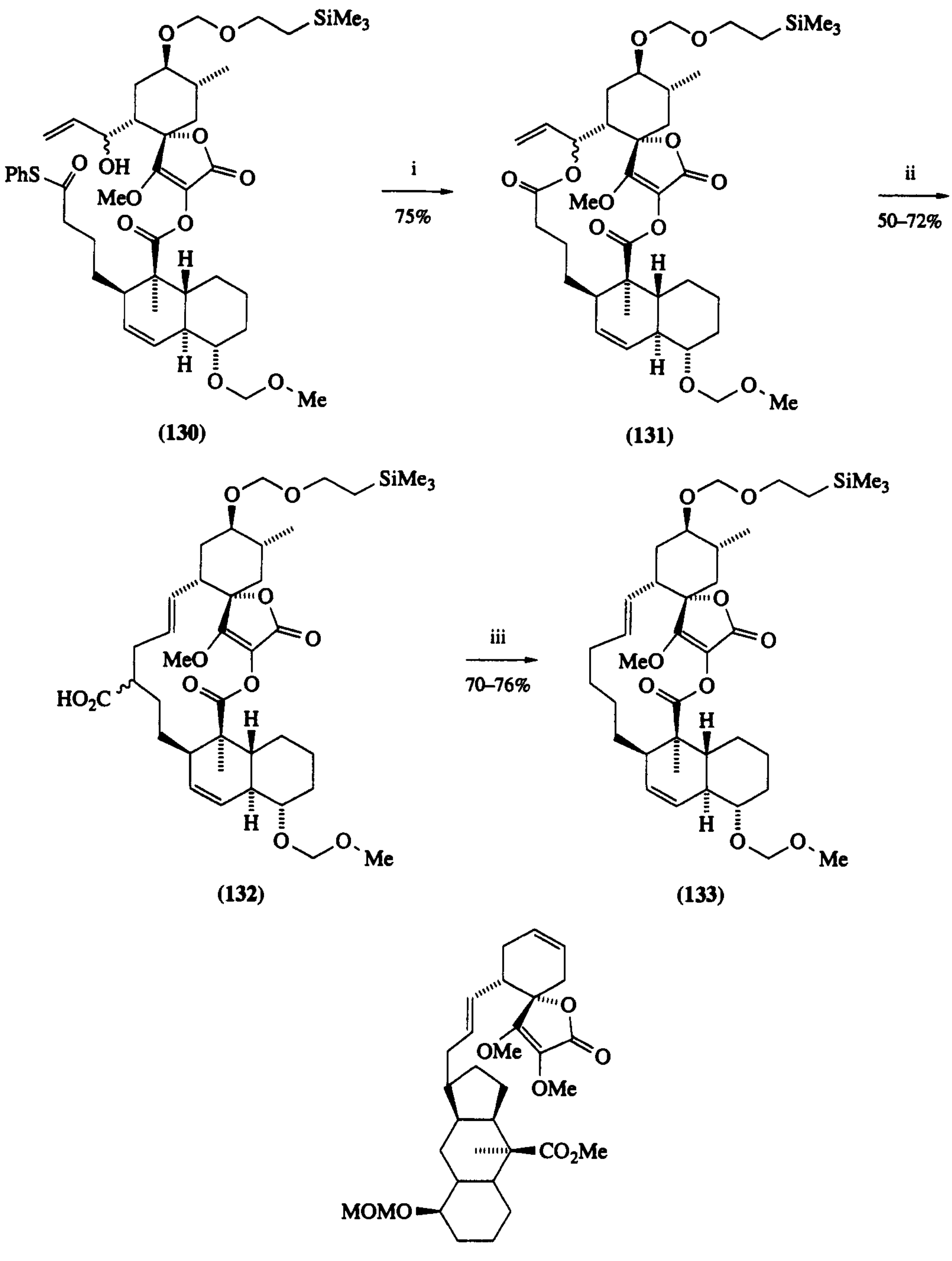

i, $Ag(O_2CCF_3)$, $Na_2HPO_4$, benzene, 82 °C; ii, KHMDS, THF, HMPA, −78 °C; HMPA, $Me_3SiCl$, $Et_3N$, THF; iii, $Cl_2POOPh$, $Et_3N$, THF, 0° C; PhSeH, $Et_3N$, THF, 0 °C; $Bu_3SnH$, AIBN, xylene, 130 °C

**Scheme 24**

31).[127] Silylketene acetal (**154**) was directly prepared from α-silyl ester (**153**) in xylene at 230 °C to give after acid hydrolysis the desired stereoisomer (**155**) in 72% overall yield with 6:1 stereoselectivity.[128,129]

Silylketene acetals are also obtained by TMS-Cl accelerated conjugate addition of cuprates.[130] The latter method suffers presently from low diastereoselectivities,[131] though it offers the attractive possibility of one-pot formation of two carbon–carbon bonds and three contiguous chiral centers (equation 15).

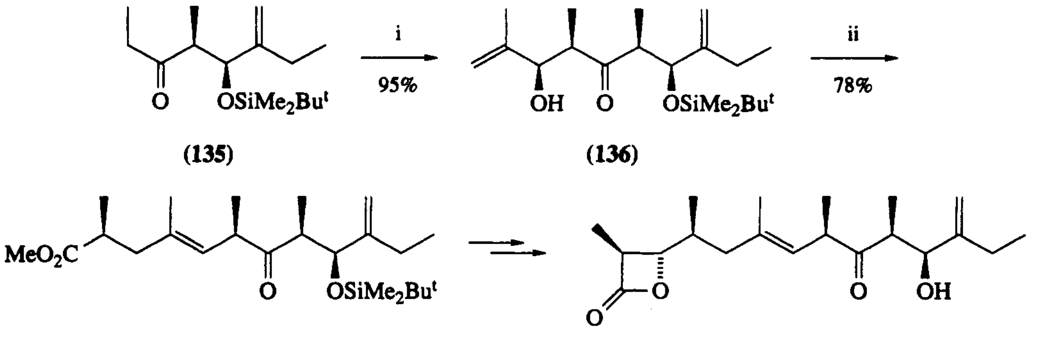
i
95%
ii
78%
O
OSiMe₂Buᵗ
OH
MeO₂C
O
OH

**(135)** **(136)**

**(137)** Ebelactone A

i, 9-BBNOTf, $Et_3N$, −78 °C, 3 h; $H_2C{=}C(Et)CHO$, −78 to 0 °C, 16 h; $H_2O_2$, MeOH–pH 7 buffer; ii, $(EtCO)_2O$, cat. DMAP, $Et_3N$, $CH_2Cl_2$, 0 to 20 °C, 2 h; $Me_3SiCl$, $Et_3N$, THF, LDA, −78 °C, 1 h; 20 °C, 1 h; 60 °C, 2 h; aq. 1% HCl; $CH_2N_2$, $Et_2O$, 0 °C

**Scheme 25**

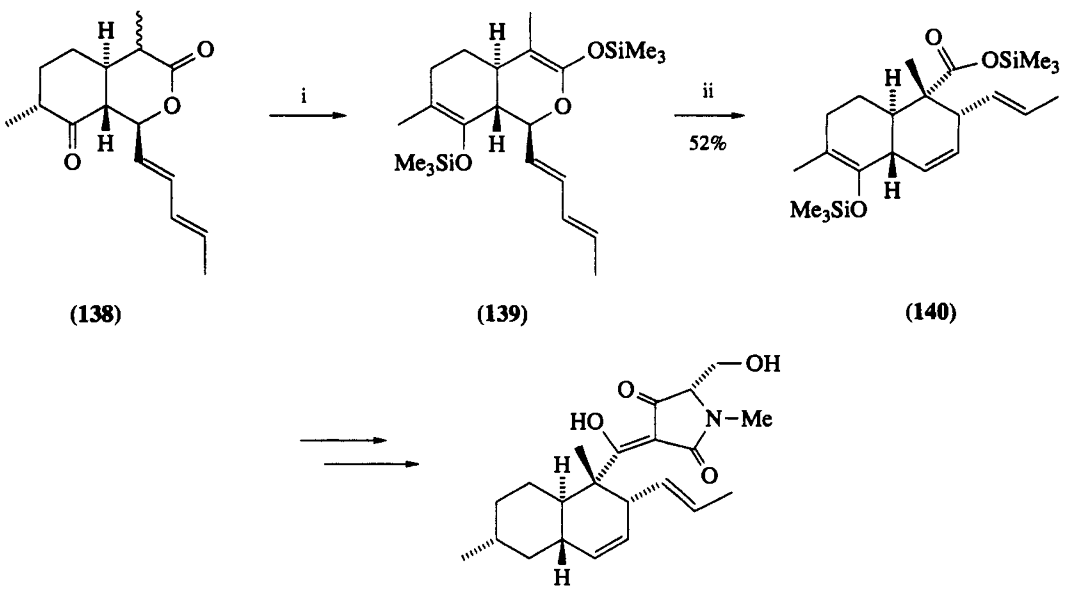
H
O
O
H
i
OSiMe₃
Me₃SiO
ii
52%
OSiMe₃
—OH
HO
N–Me
O

**(138)** **(139)** **(140)**

Equisetin

i, LDA, THF, $Me_3SiCl$, −78 °C, 30 min; ii, toluene, 105 °C, 10 h

**Scheme 26**

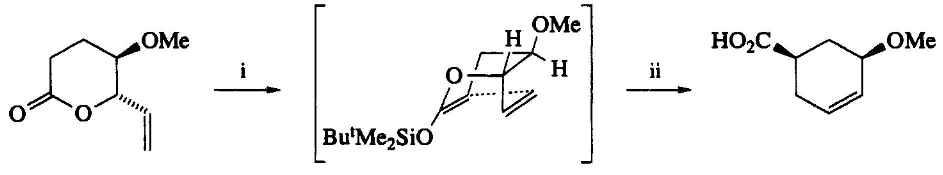
OMe
O
i
H
H
Buᵗ Me₂SiO
ii
HO₂C
OMe

**(141)** **(142)** **(143)**

i, $Bu^tMe_2SiOTf$, $Et_3N$, $CH_2Cl_2$, −78 to 0 °C; ii, toluene, 110 °C; THF, 1M HCl

**Scheme 27**

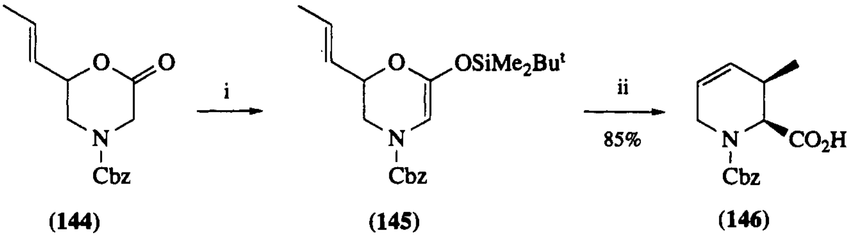
i
ii
85%
(144)
(145)
(146)

i, $Bu^tMe_2SiOTf$, $Et_3N$, $C_6D_6$; ii, toluene, reflux, 2 h; NaOH, $H_2O$, THF

**Scheme 28**

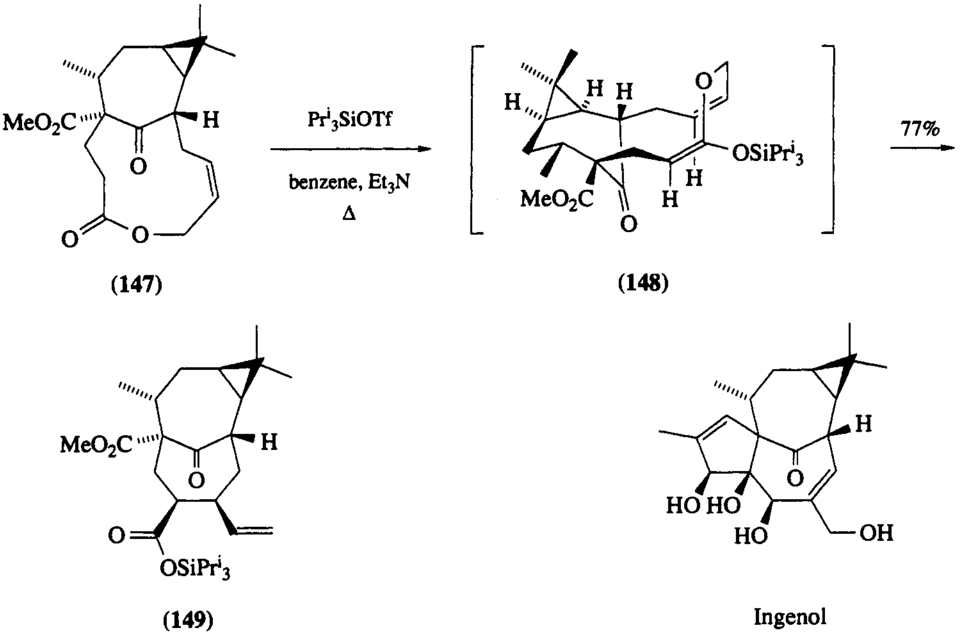
$Pr^i_3SiOTf$
benzene, $Et_3N$
Δ
77%
(147)
(148)
(149)
Ingenol

**Scheme 29**

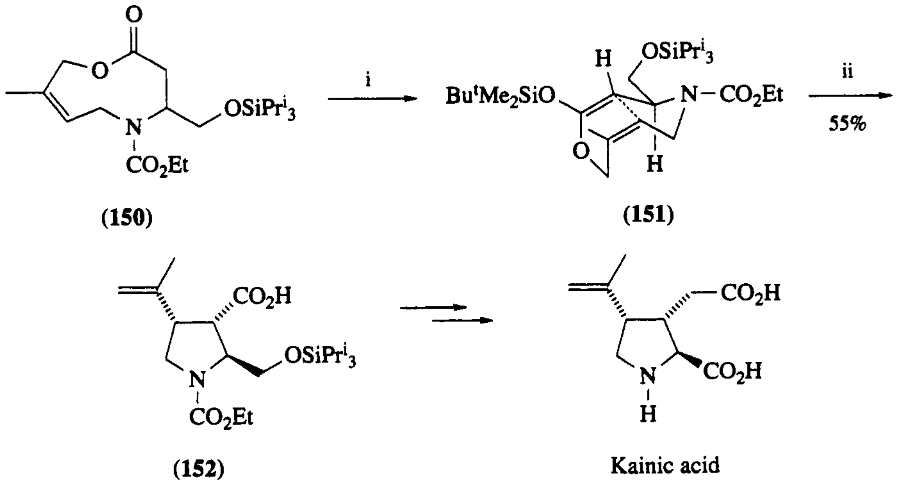
i
ii
55%
(150)
(151)
(152)
Kainic acid

i, LDA (2 equiv.), $Bu^tMe_2SiCl$ (2 equiv.), THF, −100 to 20 °C; ii, $K_2CO_3$, MeOH–$H_2O$, 20 °C, 2 h

**Scheme 30**

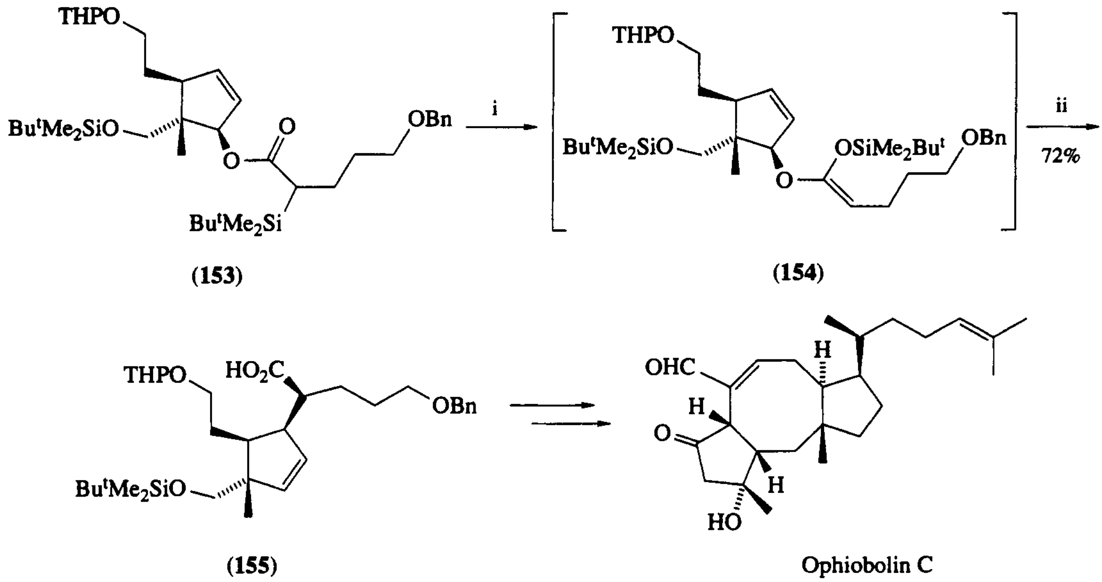

(153)

(154)

(155)

Ophiobolin C

i, xylene, 230 °C; ii, 1 M HCl–MeOH–Et$_2$O (1:1:1), r.t.

**Scheme 31**

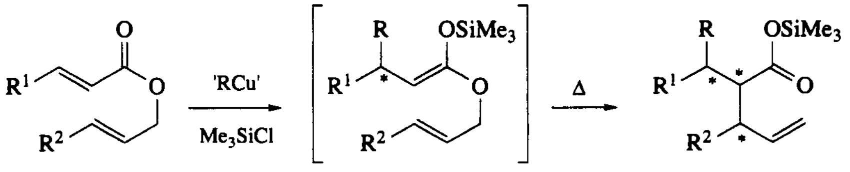

(15)

(156) (157) (158)

### 7.2.2.9 Charge-accelerated Claisen Rearrangements

Although versions of the ester enolate rearrangement of magnesium,[5] sodium,[132] and lithium[9] enolates as well as the anionic oxy-Cope shift[133] gave early testimony of the potential of charge-accelerated rearrangements,[134] the first example of a carbanion-accelerated Claisen rearrangement was only reported in 1982 by Denmark and Harmata.[17] Since then, however, many other charge-accelerated Claisen rearrangements have been reported.[135,136] In contrast to ethoxycarbonyl-, cyano-, and cyanohydrin-stabilizing groups, which did not promote rearrangement, the arylsulfonylmethylene substituent was shown to be well suited for this role based on ease of incorporation and accelerating potential.[137] Because of the ambident nature of the allyl anion (**159**), two regioisomers (**160**) and (**161**) can be formed in the rearrangement (equation 16). However, only path a in equation (16) is observed, a fact which was explained by the large difference in relative stability between β-ketosulfone anion (**160**) and ketone enolate (**161**). The rearrangement itself is highly stereoselective, providing a 95:5 mixture of *anti*- to *syn*-β-ketosulfone (**163**):(**164**) in 85% yield upon deprotonation of vinyl ether (**162**) with KH in DMSO in the presence of LiCl and subsequent rearrangement at 50 °C (Scheme 32). Mechanistically, this implies a high barrier to alkyl anion stereomutation relative to rearrangement. A chair-like transition state (**165**) accounts for the observed stereochemistry.[137] The limitations on this method are for the most part related to incompatibilities with the presence of anionic intermediates.

A high degree of asymmetric induction has been realized in the carbanion-accelerated Claisen rearrangement of phosphorus-stabilized anions.[138] Treatment of 1,3,2-oxazaphosphorinane (**166**) with freshly prepared lithium dimsylate[139] led to a 95:5 ratio of α-methyl ketones (**167**) and (**168**) (Scheme 33). Li$^+$ coordination combined with steric interactions provide the necessary control elements for stabilization of the highly organized allyl anion conformation (**169**).

α-Allyloxy ketones have also displayed remarkable rate accelerations. Ponaras compared the relative rates of rearrangement of cyclohexenone (**170**) and its derivatives.[140] In refluxing THF, ketone (**170**) af-

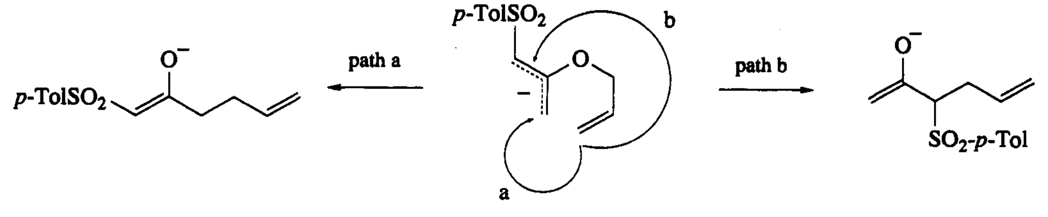

(16)

**(160)** **(159)** **(161)**

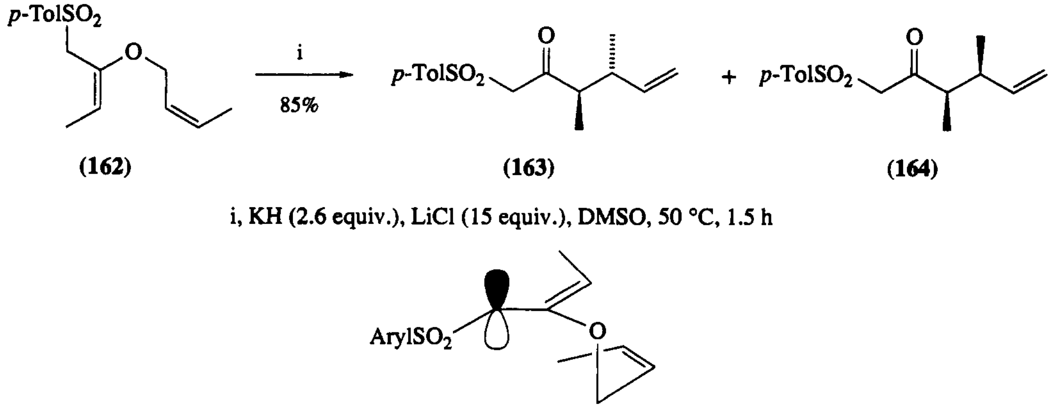

**(162)** **(163)** **(164)**

i, KH (2.6 equiv.), LiCl (15 equiv.), DMSO, 50 °C, 1.5 h

**(165)**

**Scheme 32**

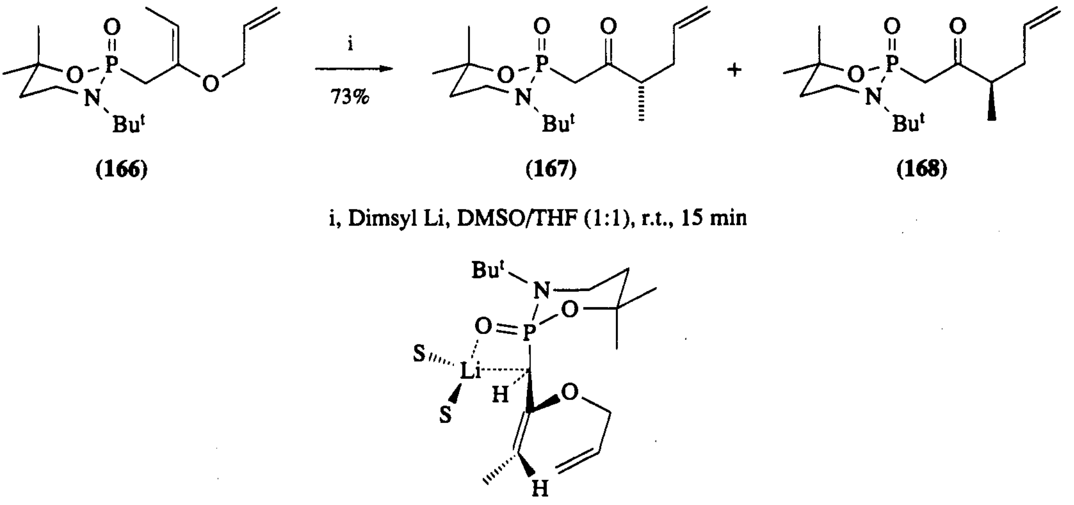

**(166)** **(167)** **(168)**

i, Dimsyl Li, DMSO/THF (1:1), r.t., 15 min

**(169)**

**Scheme 33**

fords diosphenol (**171**) with $t_{1/2}$ = 340 h, whereas acylhydrazone (**172**) and sodium salt (**173**) rearranged at $t_{1/2}$ = 22 h and $t_{1/2}$ = 1.5 h, respectively (Scheme 34).[141] This methodology can be applied for the formation of vicinal quaternary centers. In a related study, Koreeda and Luengo prepared copper enolate (**177**) by conjugate addition to 2-(allyloxy)-2-cyclohexenone (**176**).[18c] Warming of the reaction mixture to 0 °C resulted, within 15 min, in the smooth formation of the hydroxy ketone (**178**) in quantitative yield (Scheme 35). The silyl enol ether of (**177**), however, required a temperature as high as 63 °C to achieve a half-life of 1.6 h in its rearrangement. Koreeda and Luengo also measured rate acceleration as a function of the electron-donating ability of the MO group in enolate (**179**) (equation 17, Table 4).[18c] Rearrangement of the potassium enolate proceeded in toluene at –23 °C, whereas the sodium and lithium enolates required temperatures of 0 °C and 96.5 °C, respectively. Interestingly, with THF as a solvent the conditions required for the rearrangement were significantly milder. The rate enhancement was explained by a vinylogous weakening effect of the oxyanion on the O(3)—C(4) oxygen–carbon bond, similar to the effect encountered in the anionic oxy-Cope rearrangement.[142] In an application of this methodology, tricyclic ketone (**181**) was enolized with potassium *t*-butoxide and rearranged in THF with a half-life of *ca.* 2 min at 50 °C to afford α-hydroxy ketone (**183**) in 94% yield (Scheme 36).[143]

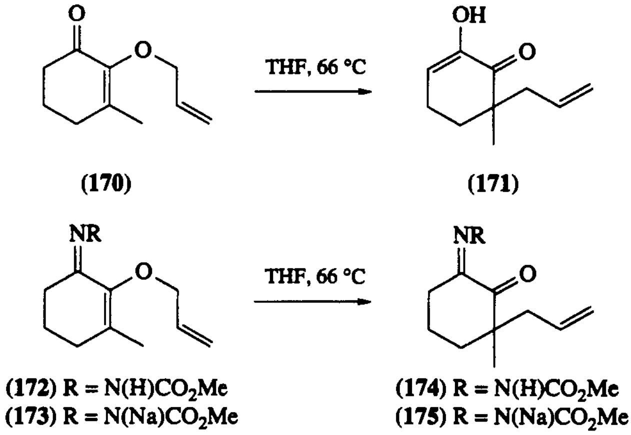

**(170)** **(171)**

**(172)** R = N(H)CO$_2$Me
**(173)** R = N(Na)CO$_2$Me

**(174)** R = N(H)CO$_2$Me
**(175)** R = N(Na)CO$_2$Me

**Scheme 34**

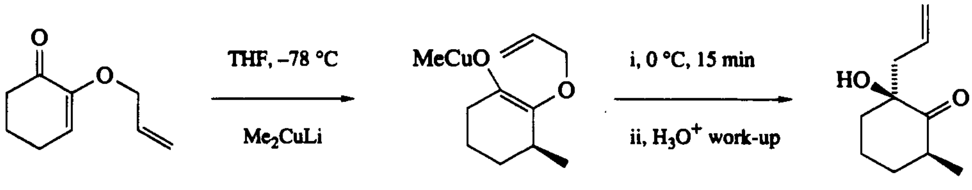

**(176)** **(177)** **(178)**

**Scheme 35**

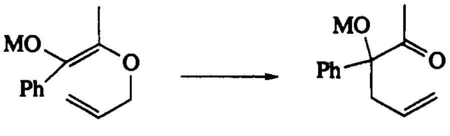

**(179)** **(180)** (17)

**Table 4** Results of Charge-accelerated Claisen Rearrangement of Enolates (179)[18c]

| *Entry* | *Solvent* | *Compound* (**179**) | *Temperature* (°C) | $t_{1/2}$ (*h*) |
|---|---|---|---|---|
| 1 | Toluene | M = K | –23 | 3.3 |
| 2 | Toluene | M = Na | 0 | 2.6 |
| 3 | Toluene | M = Li | 96.5 | 1.1 |
| 4 | Toluene | M = SiMe$_3$ | 71 | 0.5 |
| 5 | THF | M = K | –42 | 6.2 |
| 6 | THF | M = K | –23 | <0.1 |
| 7 | THF | M = Na | –23 | 2.4 |
| 8 | THF | M = Li | 67 | 1.3 |

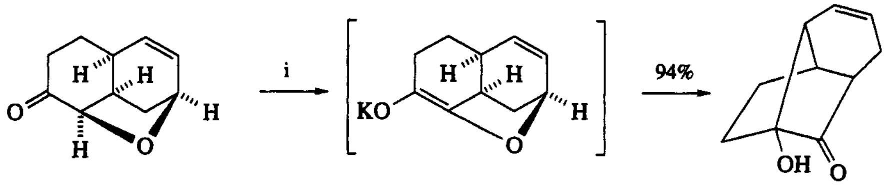

**(181)** **(182)** **(183)**

i, KOBu$^t$ (10 equiv.), THF, 50 °C

**Scheme 36**

### 7.2.2.10 Catalysis of Claisen Rearrangements

Catalysis of the Claisen rearrangement is as old as the rearrangement itself. In his original report,[1] Claisen mentioned the apparent rate-enhancing effect of ammonium chloride. Since then, modest to dramatic effects have been demonstrated for numerous Brønsted and Lewis acids, bases and transition metal complexes.[144] In an excellent comprehensive review, Lutz covered achievements in this field until 1984.[2f,145] In recent years, particular attention was given to increased stereocontrol, and aluminum catalysts emerged as especially useful reagents.[146,147,148] In many aspects, these systems can be considered as charge-accelerated 3,3-sigmatropic rearrangements.

An initial report by Oshima and coworkers stated that organoaluminum reagents promote the aliphatic Claisen rearrangement at room temperature under transfer of an alkyl or hydrogen residue to the aldehydic carbon.[149] Yamamoto and his group greatly expanded the scope of this process by the use of methylaluminum bisphenoxides. Rearrangement of optically active vinyl crotyl ether (**184**) with 2 equiv. of reagent (**185**) gave at –78 °C in 30 min an 84:16 ratio of the (*S*)-(*Z*)-aldehyde (**186**) and the (*R*)-(*E*)-aldehyde (**187**) in 74% yield with moderate transfer of the chirality (74–78% chiral transmission) (Scheme 37).[150] It is important to note that the thermal Claisen rearrangement of ethers such as (**184**) invariably results in highly (*E*)-selective product formation ($E/Z \approx 9{:}1$).[151] The alternative use of reagent (**188**) at –20 °C led to a 2:98 mixture of aldehydes (**186**) and (**187**) in 90% yield. The observed selectivities were explained by the two possible chair-like transition states (**189**) and (**190**) (equation 18). Conformation (**189**), highly unfavorable in the thermal Claisen rearrangement, would be favored over (**190**) in view of the severe 1,2-interaction between R and the exceptionally bulky organoaluminum reagent (**185**).[152] The origin of the exceedingly high (*E*)-selectivity with reagent (**188**) remained unclear. Yamamoto and coworkers subsequently applied this methodology to the highly regiospecific rearrangement of bisallyl vinyl ethers,[153] dienyl vinyl ethers, and the synthesis of the sex pheromone of the potato tuberworm moth.[154] Additionally, catalysis with chiral organoaluminum reagent (**192**) led to the successful asymmetric rearrangement of derivative (**191**; equation 19).[155,156] Acylsilane (**193**) was obtained in high optical purity (90% *ee*). This reaction sequence could also be applied to the corresponding trimethylgermyl derivatives.

In a series of recent reports, Paquette and coworkers examined the scope and stereochemistry of the alkylaluminum-catalyzed Claisen ring expansion reaction.[157] Treatment of vinyl ether (**195**), obtained from lactone (**194**) and Tebbe reagent, with DIBAL-H induced acceleration of the Claisen process and *in situ* ketone reduction to cyclooctanol (**196**; Scheme 38).[158] After 5 h at 25 °C, a 7:3 ratio of the α-carbinol (**196a**) and the reduction product (**197**) was isolated in 42% yield. In contrast, the use of $Bu^i{}_3Al$ led in high yield to a 5:1 mixture of carbinols (**196a**) and (**196b**), with no evidence for formation of (**197**). This process is completely (*Z*)-selective and provides the less strained *cis* double bond geometry. Due to steric constraints, rearrangement of endocyclic vinyl ether (**198**) has to proceed *via* boat-like transition state (**201**; Scheme 39). Tricycles (**199**) and (**200**) were isolated in 71% and 7% yields, respectively.[158]

### 7.2.2.11 Competitive Rearrangements

Typical side reactions that interfere in the aliphatic Claisen rearrangement are 2,3-sigmatropic shifts,[159] eliminations, and, especially in the Ireland variant, competitive Ferrier-type rearrangements,[160] ketene formation and *C*-silylation.[161] Usually, optimizing reaction parameters such as base, temperature, polarity of solvent and bulkiness of the silylating agents leads to a significant increase in the desired 3,3-sigmatropic pathway.[162,163]

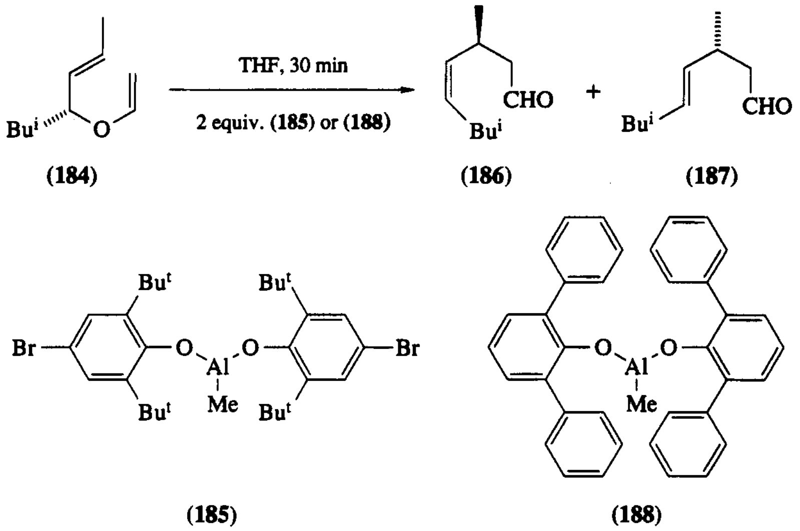
Bu$^i$
O
THF, 30 min
2 equiv. (185) or (188)
CHO
Bu$^i$
+
Bu$^i$
CHO
(184)
(186)
(187)
Bu$^t$
Bu$^t$
Br
O
Al
O
Br
Bu$^t$
Me
Bu$^t$
O
Al
O
Me
(185)
(188)

Scheme 37

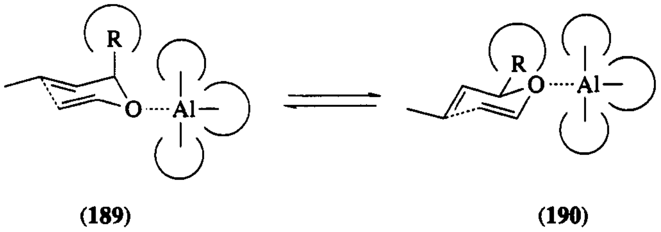
R
O
Al
R
O
Al
(189)
(190)

(18)

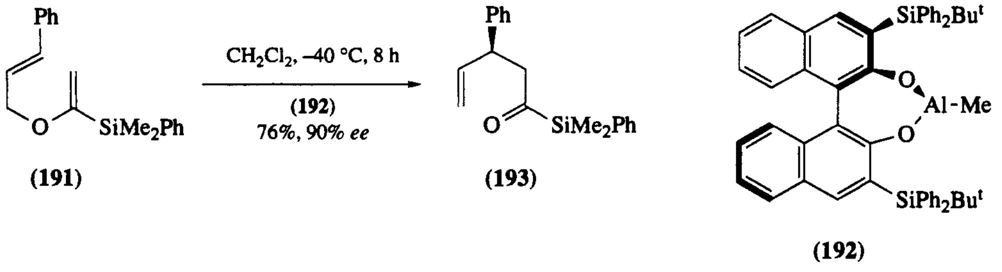
Ph
O
SiMe$_2$Ph
(191)
CH$_2$Cl$_2$, –40 °C, 8 h
(192)
76%, 90% ee
Ph
O
SiMe$_2$Ph
(193)
SiPh$_2$Bu$^t$
O
Al-Me
O
SiPh$_2$Bu$^t$
(192)

(19)

### 7.2.2.11.1 3,3 Claisen vs. 2,3 Wittig rearrangement

Generally, ester enolates of structure (**202**; R′ = M, R = Oalkyl) rearrange *via* a 3,3-shift,[164] whereas the corresponding amide enolates (**202**; R′ = M, R = N(alkyl)$_2$) and acid dianions (**202**; R′ = M, R = OM) prefer the 2,3-pathway (equation 20).[165] Both pathways have been observed with ketone enolates (**202**; R′ = M, R = alkyl). With substrate (**179**), Koreeda and Luengo observed only traces of Wittig rearrangement product (**205**), except for the lithium enolate, where (**205**) accounted for up to 20% of the reaction mixture (equation 21).[18c] Thomas and Dubini, however, reported predominant formation of 2,3 Wittig products (**207**) and (**209**) under base treatment of ketones (**206**) and (**208**) (equation 22).[166,167]

### 7.2.2.11.2 Regioselective rearrangement of divinylcarbinols

Several factors such as number and type of substituents contribute to the regioselectivity in the rearrangement of divinylcarbinols.[168,169] In a synthesis of the ring system of fastigilin-C, Tanis and coworkers succeeded in influencing the ratio of competitive Ireland–Claisen rearrangements through the cyclopentenyl or the furanyl double bond of substrate (**210**) by the nature of the alkyl groups on the silylating agent (Scheme 40).[170]

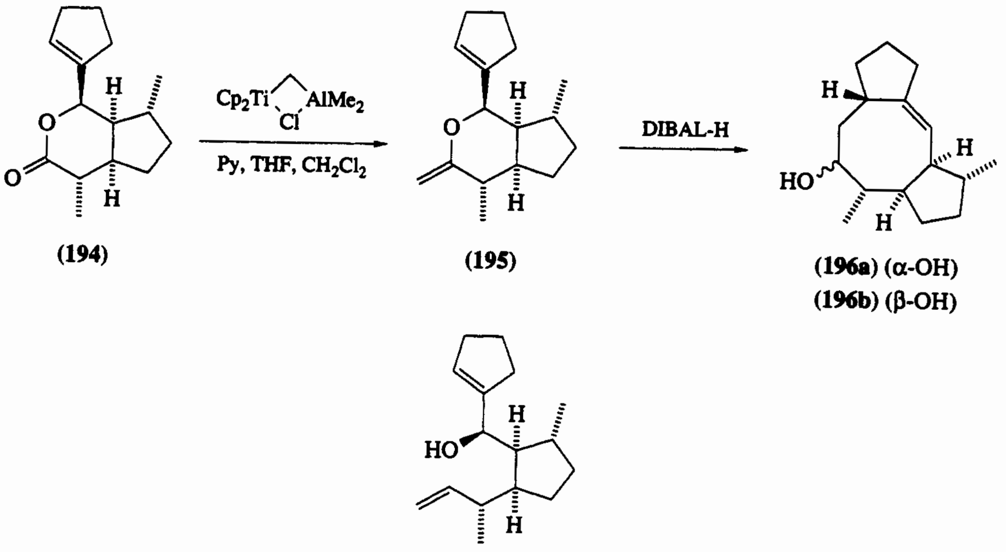
H
O
O
H
$Cp_2Ti$
Cl
$AlMe_2$
Py, THF, $CH_2Cl_2$
DIBAL-H
HO
H
H
HO

(194) (195) (196a) (α-OH) (196b) (β-OH)

(197)

Scheme 38

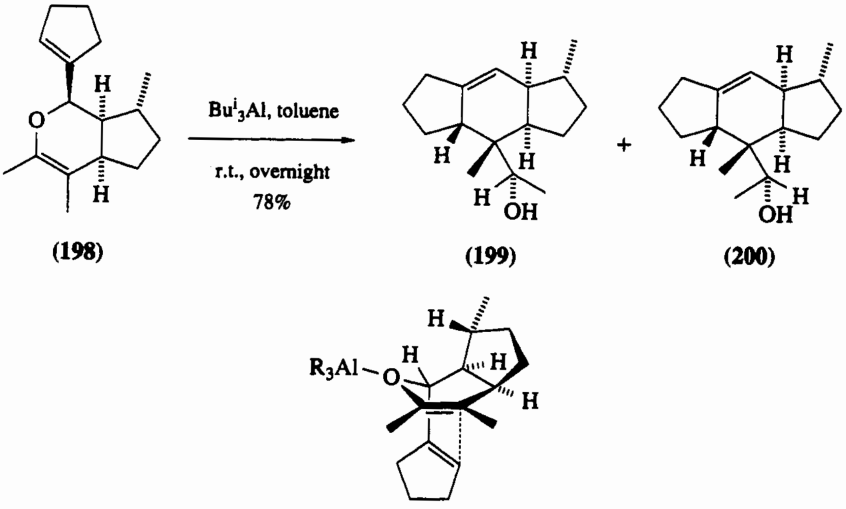
H
O
H
$Bu^i{}_3Al$, toluene
r.t., overnight
78%
H
OH
+
H
OH
$R_3Al$
O

(198) (199) (200)

(201)

Scheme 39

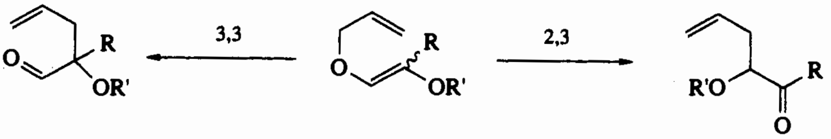
O
R
OR'
3,3
O
R
OR'
2,3
R'O
R
O

(203) (202) (204)

(20)

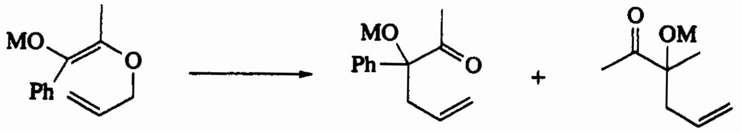
MO
O
Ph
MO
Ph
O
+
O
OM

(179) M = Li, Na, K, $SiMe_3$ (180) (205)

(21)

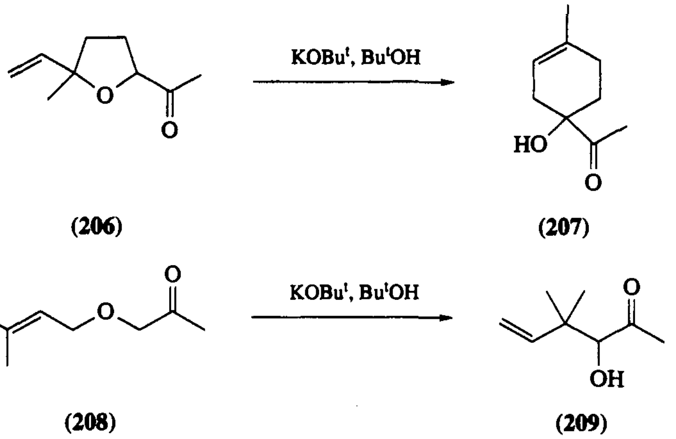

**(206)** **(207)** **(208)** **(209)** (22)

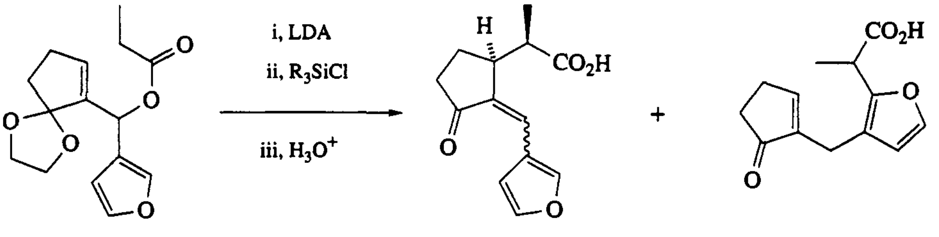

**(210)** **(211)** **(212)**

| *R$_3$SiCl* | *Yield (%)* | *Ratio (211):(212)* |
|---|---|---|
| Bu$^t$Me$_2$SiCl | 69 | 95:5 |
| Me$_3$SiCl | 79 | 75:25 |
| Pr$^i_3$SiCl | 73 | 20:80 |

**Scheme 40**

### *7.2.2.11.3 Elimination* vs. *rearrangement*

Elimination of the allylic ether moiety effectively competes in certain cases with the 3,3-sigmatopic shift.[171] A change in the variant of the Claisen rearrangement often leads to significant reduction of undesired elimination processes.[172]

A related problem is elimination in ester enolates with leaving groups in the β-position. Knight and coworkers observed virtually no α-allyl-β-amino acid product in the Ireland silyl ester enolate rearrangement of phthalate (**213**; Scheme 41).[91d] Rearrangement of the *N*-methoxycarbonyl analog (**214**), however, provided methyl ester (**215**) in a 79:21 mixture of stereoisomers after treatment with ethereal diazomethane.

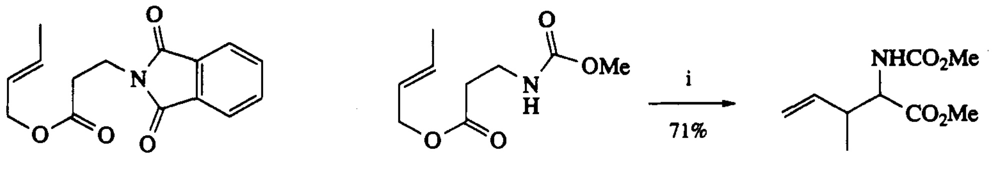

**(213)** **(214)** **(215)**

i, LDA, THF, –78 °C; Me$_3$SiCl; reflux, 4 h; hydrolysis; CH$_2$N$_2$

**Scheme 41**

Excellent experimental technique was required to effect formation of the monensin C/D ring system (**218**) *via* silyl ester enolate Claisen rearrangement of acid (**216**) and alcohol (**217**) (Scheme 42).[125a] Ester

**(221)** is extremely prone to fragmentation and furan formation (path a), β-elimination (path b) and Ferrier rearrangement (path c). Low temperature mixing of the furanoid acid chloride **(219)** and lithium alcoholate **(220)**, followed by ester enolization in a solution of premixed LDA and TMS-Cl at –100 °C provided the corresponding silylketene acetal. Warming to ambient temperature, followed by methyl ester formation, then led to tricycle **(218)** in an excellent 80% yield (isolated as a 1.5:1 mixture of diastereomers).

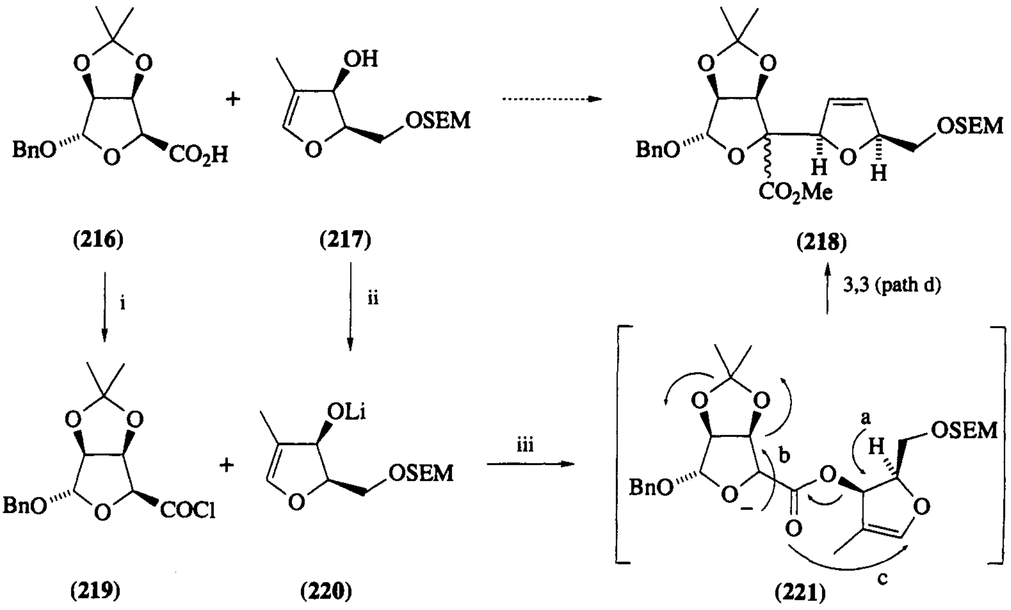

i, $(COCl)_2$, benzene, DMF (cat.); ii, $Bu^nLi$, DMAP, THF, –78 °C; iii, add **(219)** to **(220)**, –78 °C; add mixture to LDA, THF, $Me_3SiCl$, $Et_3N$, 10% HMPA/THF, –100 °C; r.t.; $H_3O^+$; $CH_2N_2$, ether

**Scheme 42**

### 7.2.2.12 Solvent Effects

Due to a relative insignificance of Coulomb interactions, pericyclic processes generally show little correlation between solvent polarity and reaction rates.[173] The discovery of White and Wolfarth that polar solvents increase the rate of the *ortho*-Claisen rearrangement similarly to electron-donating substituents was therefore of profound consequence.[174,175] Aliphatic Claisen rearrangement of allyl vinyl ethers also demonstrated a profound rate acceleration in polar solvents.[176] These results were interpreted in terms of a tight ion pair or dipolar transition state.[177,178] Grieco and coworkers determined first-order rate constants for the Claisen rearrangement of carboxylate **(222)** and methyl ester **(223)** (equation 23, Table 5).[179] In particular, they demonstrated that rearrangement of allyl vinyl ether **(226)** in water/methanol (2.5:1) containing 1 equiv. of sodium hydroxide smoothly occurs at 80 °C, affording an 85% isolated yield of aldehyde (**227**; equation 24).[180] Only after extensive experimentation had this transformation previously been achieved in 60% yield by McMurry and coworkers at 220 °C in a base-washed silylated glass tube containing toluene and sublimed sodium *t*-pentoxide, the major problem being vinyl ether elimination and cyclopentadiene formation.[181]

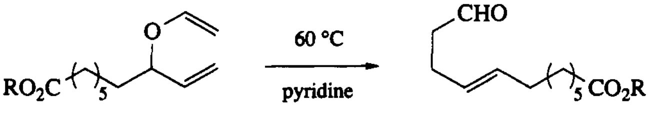

(23)

**(222)** R = Na
**(223)** R = Me

**(224)** R = Na
**(225)** R = Me

**Table 5** Rate Constants for the Aliphatic Claisen Rearrangement of Sodium Carboxylate (**222**) and Methyl Ester (**223**)[179]

| *Entry* | *Solvent* | $k \times 10^{-5}$ ($s^{-1}$) (**222**) | $k \times 10^{-5}$ ($s^{-1}$) (**223**) |
|---|---|---|---|
| 1 | $H_2O$ | 18 | |
| 2 | 75% $H_2O/CF_3CH_2OH$ | 6.9 | |
| 3 | $CF_3CH_2OH$ | 2.6 | 4.7 |
| 4 | 75% $H_2O$/MeOH | 11 | |
| 5 | 50% $H_2O$/MeOH | 4.6 | 3.6 |
| 6 | 25% $H_2O$/MeOH | 1.6 | 1.4 |
| 7 | MeOH | 0.79 | 0.72 |
| 8 | 75% $H_2O$/DMSO | 3.0 | |
| 9 | 25% $H_2O$/DMSO | 0.93 | 0.82 |
| 10 | EtOH | | 0.51 |
| 11 | $Me_2CHOH$ | | 0.42 |
| 12 | MeCN | | 0.25 |
| 13 | Acetone | | 0.18 |
| 14 | Benzene | | 0.17 |
| 15 | Cyclohexane | | 0.084 |

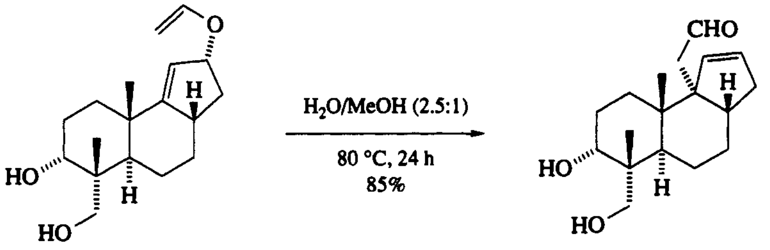

(**226**) (**227**)

(24)

### 7.2.3 ENZYMATIC CLAISEN REARRANGEMENTS

The 3,3-sigmatropic rearrangement of chorismate (**228**) to prephenate (**229**) in the shikimic acid pathway demonstrates the versatility of the Claisen rearrangement in a biochemical version (equation 25).[182] The enzyme chorismate mutase catalyzes this process by a factor of approximately 3 × $10^6$.[183] The entropy and the enthalpy for the uncatalyzed reaction are 20.71 kcal $mol^{-1}$ and −12.85 cal $mol^{-1}$ $K^{-1}$, respectively;[184] and it was shown that both uncatalyzed and enzymatic rearrangements proceed through a chair-like transition state (**230**), stabilized in polar media.[176,185,186] Bartlett and coworkers prepared transition state analog (**231**), which in fact proved to be a potent inhibitor of *E. coli* chorismate mutase-prephenate dehydrogenase.[187] Knowles and coworkers proposed a mechanism for the enzyme reaction that involves a heterolytic cleavage of the ether bond of chorismate by attack of an enzymic nucleophile in the rate-limiting step,[188] and Berchtold and coworkers established the structural requirements for enzyme catalysis in this process.[189]

Discussions concerning this intriguing biological Claisen rearrangement have been further enriched by the development of synthetic protein catalysts based on monoclonal antibodies.[190,191] The conjugate of transition state model (**232**) with carrier proteins keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA) was used for production of antibodies specific for (**232**).[192] The rate of the antibody-catalyzed rearrangement of chorismate to prephenate was subsequently compared with that of the uncatalyzed thermal rearrangement, affording a value of $k_{cat}/k_{un}$ of 1 × $10^4$ at 10 °C and pH 7.0.[190]

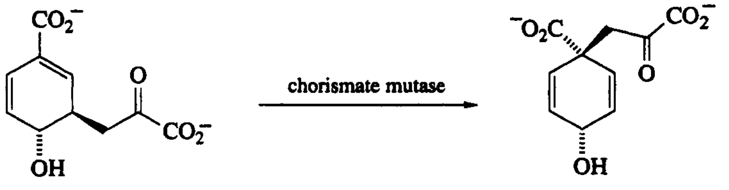

(**228**) (**229**)

(25)

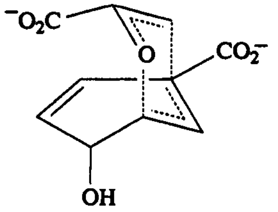

**(230)**

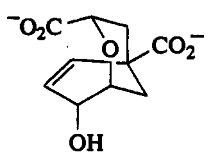

**(231)**

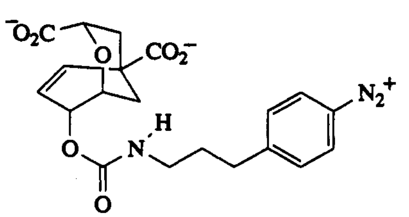

**(232)**

## 7.2.4 MECHANISTIC ASPECTS OF THE CLAISEN REARRANGEMENT

Claisen rearrangements are highly exothermic;[67,193,194] concerted but nonsynchronous[195] pericyclic reactions[196,197,198] with a characteristic negative entropy ($\Delta S^{\ddagger} = -10$ to $-15$ cal mol$^{-1}$ K$^{-1}$) and negative volume of activation.[199] Secondary deuterium kinetic isotope studies by Gajewski and coworkers indicate an early transition state,[200,201,202] where bond breaking is more advanced than bond making.[99,203] There is, however, still some disagreement as to which of the limiting alternatives to the aromatic transition state (**233**)[204] — oxaallyl radical–allyl radical pair (**234**), 2-oxacyclohexane-1,4-diyl (**235**) or dipole (**236**) — more accurately represents or contributes to the transition state structure (Figure 1).[176,205,206,207] Stabilization of the transition state ($TS^{\ddagger}$) by resonance interactions is therefore clearly an important factor.[207]

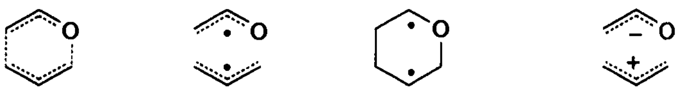

**(233)** **(234)** **(235)** **(236)**

**Figure 1**

### 7.2.4.1 Kinetics

The influence of donor and acceptor substituents on the rates of the Claisen and other sigmatropic rearrangements has been widely investigated.[208,209,210,211] A theoretical model by Carpenter and Burrows, based on Hückel molecular orbital (HMO) calculations, assesses the conjugative electron-withdrawing and -donating abilities of substituents. It predicts accelerating effects of donor substituents at C-1 and both donor and acceptor substituents at positions 2 and 4 of the Claisen system. Acceptor substituents at positions 1 and 6 and donor groups at positions 5 and 6 are predicted to decelerate the reaction.[212] Carpenter and Burrows synthesized the five isomeric cyano-substituted derivatives of the basic Claisen system and found the predictions of the HMO model fulfilled. Rate accelerations were observed with the C-2 ($k_{rel} = 111$), C-4 ($k_{rel} = 270$) and C-5 ($k_{rel} = 15.6$) substituted allyl vinyl ethers, while C-1 ($k_{rel} = 0.90$) and C-6 substitution ($k_{rel} = 0.11$) led to deceleration.[213] However, the HMO model did not remain without criticism.[214,215] In allyl vinyl ethers with a trifluoromethyl substituent at C-2 on the Claisen system, a rate enhancement by a factor 73 over the parent system was found. At C-4, the trifluoromethyl group did not bring about a significant rate effect, in contrast to the energetic benefit of 3.5 kcal mol$^{-1}$ with the cyano group at that position, suggesting that radical-stabilizing and not electron-withdrawing ability might be important in stabilizing the transition state.[216]

The accelerating effect of alkyl substituents on the Claisen rearrangement is well documented[9,217] but not as dramatic as the effect observed with electron-donating groups ($R_2N$—, EtO—, $R_3SiO$—) at C-2 of the allyl vinyl ether.[218] Accordingly, the ease of the Ireland Claisen reaction (the free energy of activation is reduced by roughly 9 kcal mol$^{-1}$ relative to allyl vinyl ether itself)[9] is mainly due to the stabilization of the $\pi$-bond of the oxaallyl species by the 2-(trialkyl)silyloxy substituent.[219] This results in a $TS^{\ddagger}$ structure with much more advanced O(3)—C(4) bond breaking than in the parent, unsubstituted rearrangement system.[99,176,203,206,207]

A C(6) donor substituent exerts a similar enhancing effect on the rate of the Claisen rearrangement, though somehow less pronounced than the rate-accelerating effect of the 2-silyloxy substituent (approx. 1.4 kcal mol$^{-1}$). As Curran and coworkers reported,[178,211] this vinylogous anomeric effect[220] of the C(6) donor substituent is especially effective in glycal systems. The energy of the $TS^{\ddagger}$ is decreased by assistance in the cleavage of the O(3)—C(4) bond, which results in an approximately tenfold acceleration of the rearrangement (Scheme 43). The combined accelerating effect of the 2- and 6-oxygen substituents most certainly leads to an increased dipolar character of the TS$^‡$ for the silyl ester enolate Claisen rearrangement,[221] with bond breaking substantially more advanced than bond formation (*cf.* structure **239**).

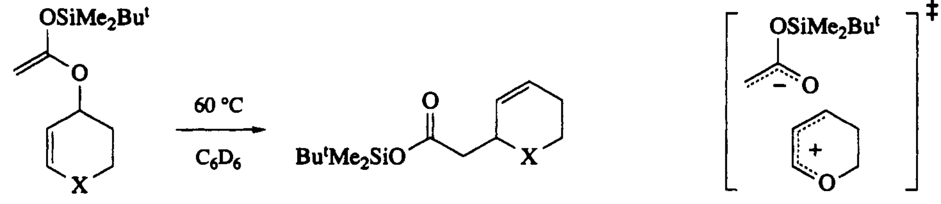

**(237)** **(238)** **(239)**

rates: X = O, 4.4 x $10^{-4}$ s$^{-1}$; X = CH$_2$, 4.9 x $10^{-5}$ s$^{-1}$

**Scheme 43**

Wilcox and Babston investigated the effect of alkyl substituents on the rate of the Ireland Claisen rearrangement of silylketene acetals (**240**)–(**242**) (R = H, Me, Et, Pr$^i$, neopentyl, CH$_2$SiMe$_3$; Figure 2).[222] Their data suggest the possibility of a '*syn*-diaxial' interaction in the order of 1.2 to 2.5 kcal mol$^{-1}$ ($\Delta\Delta G_Z^‡/E^‡$) in the transition state of the (*E*)-isomer (**242**), depending on the nature of the substituent R. Generally, steric bulk at C-5 was found to be rate accelerating, electron donation at this position, however, rate decelerating.

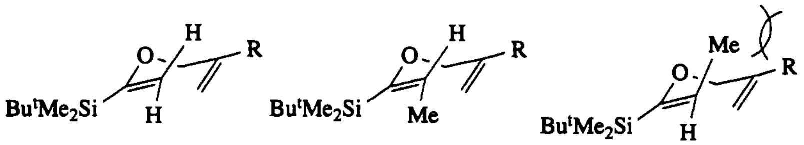

**(240)** **(241)** **(242)**

**Figure 2**

### 7.2.4.2 Transition State Structures

According to the Woodward–Hoffmann rules,[223] five concerted transition states are possible for the Claisen as well as the closely related Cope rearrangements: chair, boat, twist, cross and plane (Table 6).[224] Only the chair and boat TS$^‡$ have to be considered, as twist, cross and plane are antarafacial–antarafacial processes and require highly elevated temperatures.[199,225,226] For the correct prediction of product stereochemistry it is nevertheless crucial to know the preference for chair- or boat-like transition state in the actual 3,3-sigmatropic shift.

In acyclic systems, Claisen rearrangements show a well-established preference for chair-like transition states. With crotyl propenyl ether, the chair selectivity amounts to 97–98% at 142 °C, which corresponds to an approx. 3 kcal mol$^{-1}$ difference between the free energy of activation ($\Delta\Delta G^‡$) of chair and boat TS$^‡$ (equation 26).[67,227] The preference for a chair-like geometry in the TS$^‡$ is even more pronounced in the Cope rearrangement: 99.7% of the 3,4-dimethylhexa-1,5-diene rearranges at 225 °C *via* a chair-like TS$^‡$, corresponding to a $\Delta\Delta G^‡_{\text{chair-boat}}$ of −5.7 kcal mol$^{-1}$.[9a,228] The latter result closely parallels the difference in energy of the chair and boat conformations of cyclohexane (5–6 kcal mol$^{-1}$).[229]

In cyclic systems, however, conformational constraints can override the inherent preference for chair-like transition states in Cope[230] as well as Claisen[231] rearrangements and lead to a partial involvement if not a dominance of boat-like TS$^‡$ structures. In the Ireland rearrangement of lactones of type (**247**), for example, chair-like transition state (**249**) is accessible only when the diaxial bridging methylene chain becomes sufficient in length (*n* = 7, Scheme 44).[232] The preference of boat-like transition state (**250**) over (**251**) is due to a serious A$^{1,3}$-type interaction between the endocyclic oxygen atom and pseudoaxial substituent R in (**251**).

**Table 6** Transition State Models for 3,3-Sigmatropic Rearrangements[199]

| *Notation* | *Geometry* | *Symmetry* | *Type* |
|---|---|---|---|
| 3*s*,3*s* | 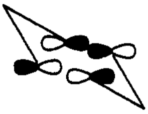 | $C_{2h}$ | Chair |
| 3*s*,3*s* | 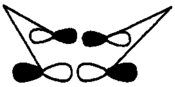 | $C_{2v}$ | Boat |
| 3*a*,3*a* | 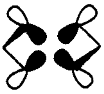 | $D_2$ | Twist |
| 3*a*,3*a* | 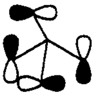 | $D_{2h}$ | Cross |
| 3*a*,3*a* | 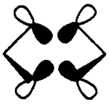 | $C_{2h}$ | Plane |

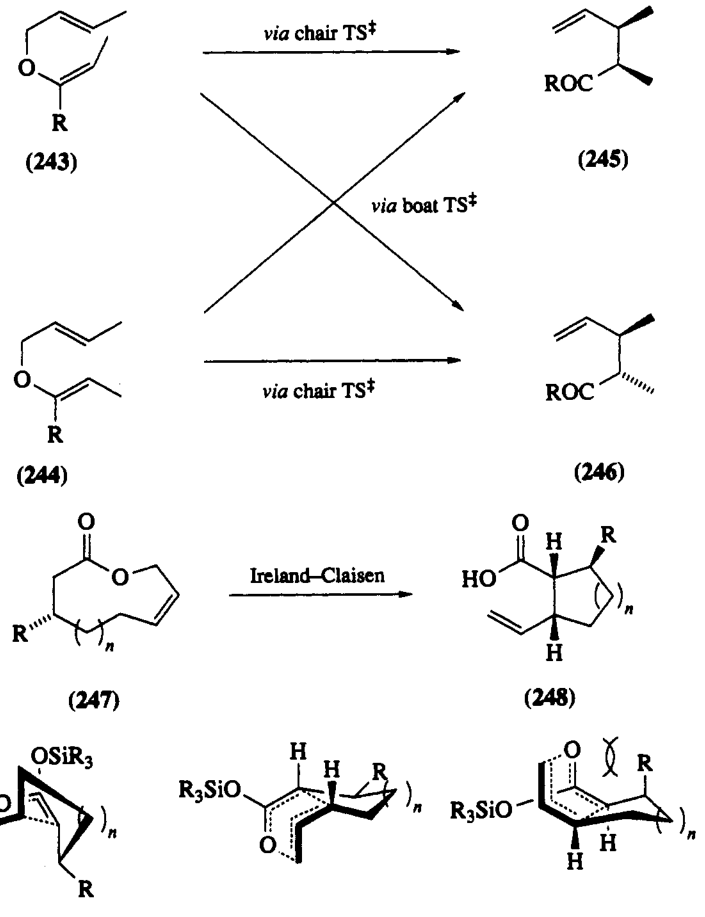

O
R
(243)
*via* chair TS‡
ROC
(245)
*via* boat TS‡
O
R
(244)
*via* chair TS‡
ROC
(246)
O
O
R
*n*
(247)
Ireland–Claisen
O
HO
H
R
*n*
H
(248)
OSiR$_3$
O
*n*
R
(249)
H
H
R
R$_3$SiO
O
*n*
(250)
O
R
R$_3$SiO
H
H
*n*
(251)

(26)

Scheme 44

In their syntheses in the vitamin D field, Lythgoe and coworkers demonstrated an impressive example of remote stereoselection in the Claisen rearrangement *via* differential transition state stabilization (Scheme 45).[233] Whereas (**252a**; $R^1$ = H, $R^2$ = Me) leads to a 70:30 mixture of diastereoisomers (**253**) and (**254**), respectively, with the chair-like transition state (**256**) providing the major isomer, its epimer (**252b**; $R^1$ = Me, $R^2$ = H) gives exclusively (**255**). Steric hindrance between the methyl group and the cyclohexane ring in (**256**) in this isomer overrides the chair–boat factor and leads to a clear preference for the boat-like transition state (**257**).

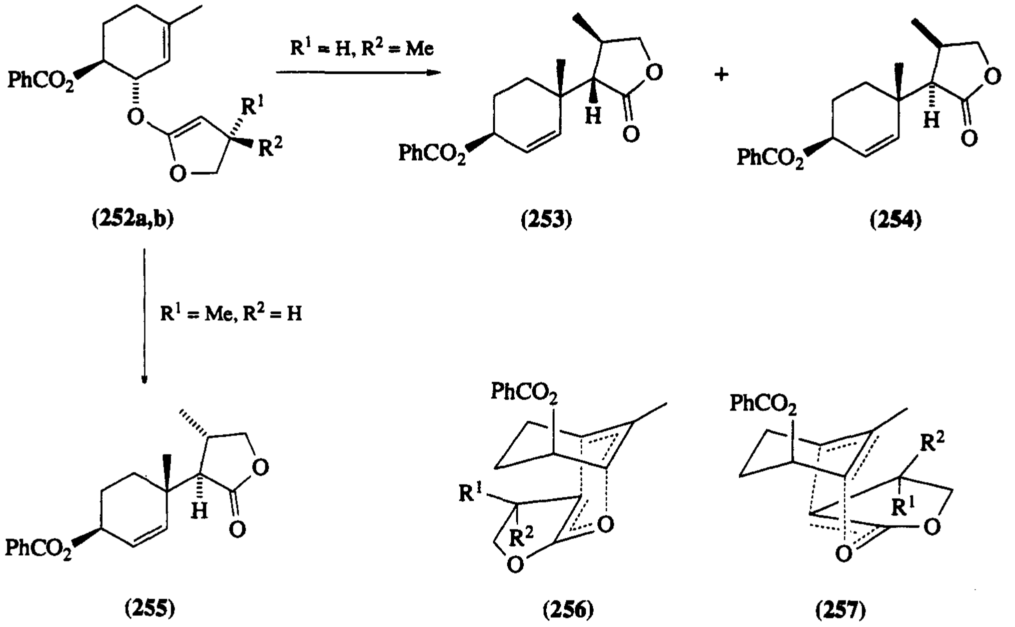

**Scheme 45**

The Ireland Claisen rearrangement of pyranoid glycals such as (**258**) generally occurs *via* a boat-like TS$^{\ddagger}$,[86a,86b,87c,90,93,234,235] presumably due to destabilizing steric interactions of the silyloxy substituent and the dihydropyran ring atoms in chair-like TS$^{\ddagger}$ (**260**) (Scheme 46).[9,37b,235] In furanoid glycal systems, the destabilizing interaction between the silyloxy substituent and the ring carbons in the chair-like TS$^{\ddagger}$ should be considerably diminished. However, there is still a strong preference for boat-like TS$^{\ddagger}$ geometries (Scheme 47). Additionally, the parent carbocyclic systems mostly demonstrate the usual chair selectivity in the 3,3-sigmatropic shift.[236,237] These striking results were explained by a stereoelectronic effect of the C(6) oxygen substituent on the relative stabilities of chair-like and boat-like TS$^{\ddagger}$ in the silyl ester enolate Claisen rearrangement.[238] A vinylogous anomeric effect of the C-6 oxygen leads to an increased relative stabilization of the more loosely organized[239] *endo*-type boat TS$^{\ddagger}$ in the order of 1 to 2 kcal mol$^{-1}$. This effect is especially pronounced in glycal systems and is apparently based on a more dipolar character of the boat-like TS$^{\ddagger}$ in these systems (**239**; Figure 3).[238] It was further demonstrated that the preferred transition state in the rearrangement of six- and five-membered carbocyclic systems such as (**266**) and (**267**) is highly dependent on steric factors, as the energy difference between chair- and boat-like TS$^{\ddagger}$ tends to be small.[238] With straight chain substrates, a significant contribution of the boat-like TS$^{\ddagger}$ to the rearrangement product mixture is only expected in bis-donor substituted allylic esters such as (**268**) (Figure 4).[238,240,241]

### 7.2.4.3 Elements of Stereocontrol

As pointed out earlier, the aliphatic Claisen rearrangement and its variants are powerful means to effect stereocontrolled C,C-bond formation. Highly ordered transition states effect a reliable transfer of stereochemistry from starting materials to products. Naturally, the geometry of the vinyl ether bond and the conformation of the transition state are crucial parameters in this process. The former issue is strongly dependent on the Claisen variant that is employed,[242] whereas the transition state geometry is controlled by both steric and electronic features of the Claisen system.[243] Additionally, the choice between diastereomeric transition states is often strongly influenced by stereogenic groups within, adjacent to, or even considerably removed from the allyl vinyl ether moiety.

### *7.2.4.3.1 Intrinsic transfer of stereochemistry*

Up to three chiral centers can directly be involved in the Claisen rearrangement (Equation 27). The configuration of the allylic chiral center at C-4 in (**269**) specifically relates to the configuration of the newly formed chiral centers in (**271**) and (**273**). Moreover, the ratio of diastereomeric transition states (**270**) and (**272**) greatly depends on the relative steric bulk of substituents $R^4$ and $R^{4'}$.[244] Thus, generally a highly selective course of the reaction *via* pathway A or pathway B can be predicted. It is important to note that the primary chiral center is destroyed in the rearrangement ('self-immolative' process[245]) and

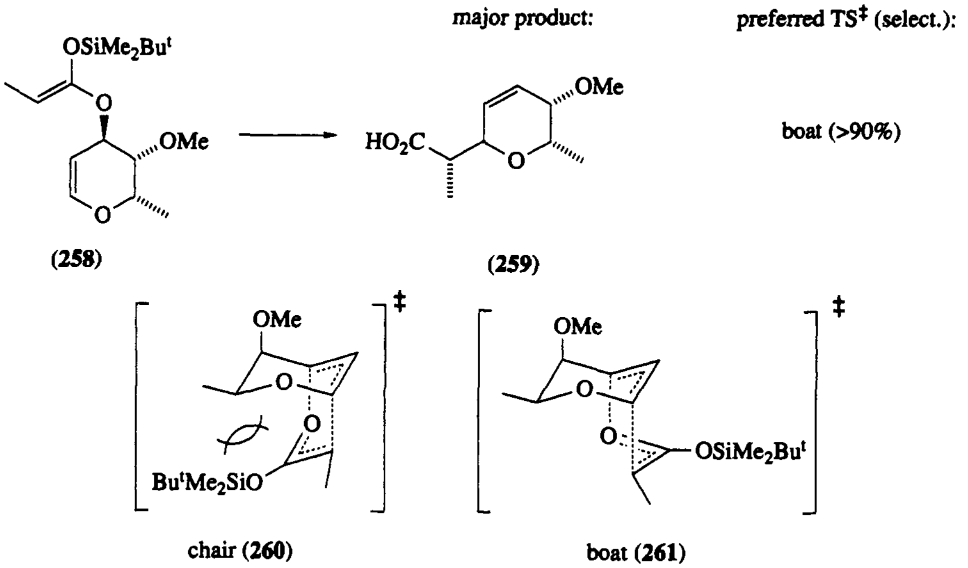
major product:
preferred TS‡ (select.):
OSiMe2But
O
OMe
O
HO2C
OMe
O
boat (>90%)
‡
OMe
O
O
ButMe2SiO
‡
OMe
O
O
OSiMe2But

(**258**) (**259**)

chair (**260**) boat (**261**)

**Scheme 46**

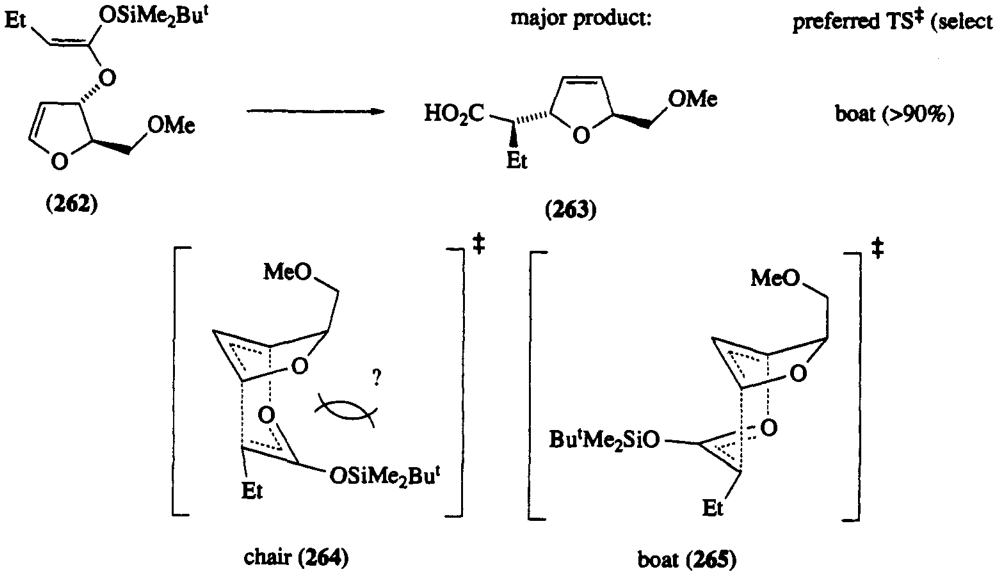
Et
OSiMe2But
O
OMe
O
major product:
HO2C
Et
O
OMe
preferred TS‡ (select.):
boat (>90%)
‡
MeO
O
?
O
Et
OSiMe2But
‡
MeO
O
ButMe2SiO
O
Et

(**262**) (**263**)

chair (**264**) boat (**265**)

**Scheme 47**

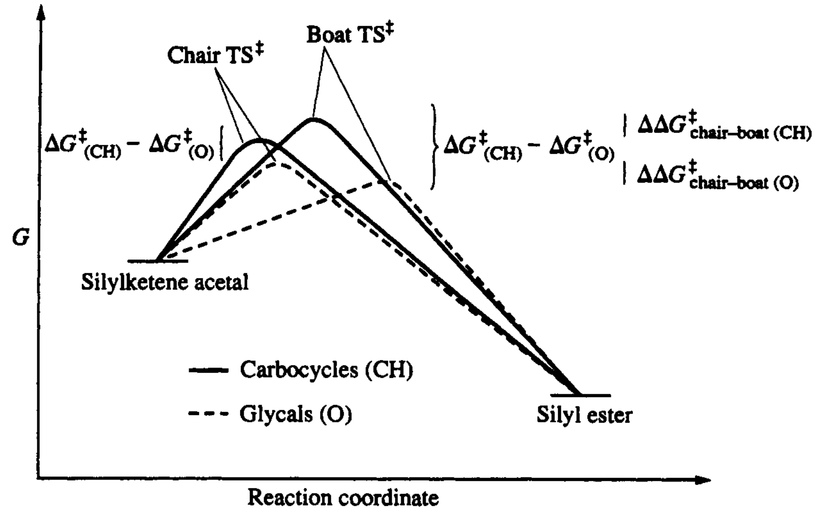

**Figure 3** Qualitive effect of C-6–carbon and C-6–oxygen substituents on the transition state energy of the ester enolate Claisen rearrangement

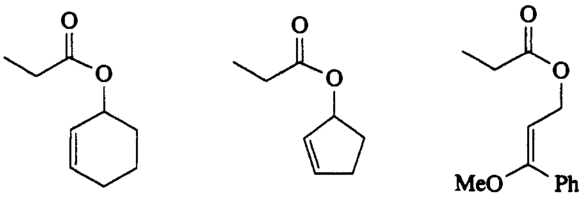

**(266)** **(267)** **(268)**

**Figure 4**

that a complementary set of products is obtained by a simple change in the geometry of the double bonds.

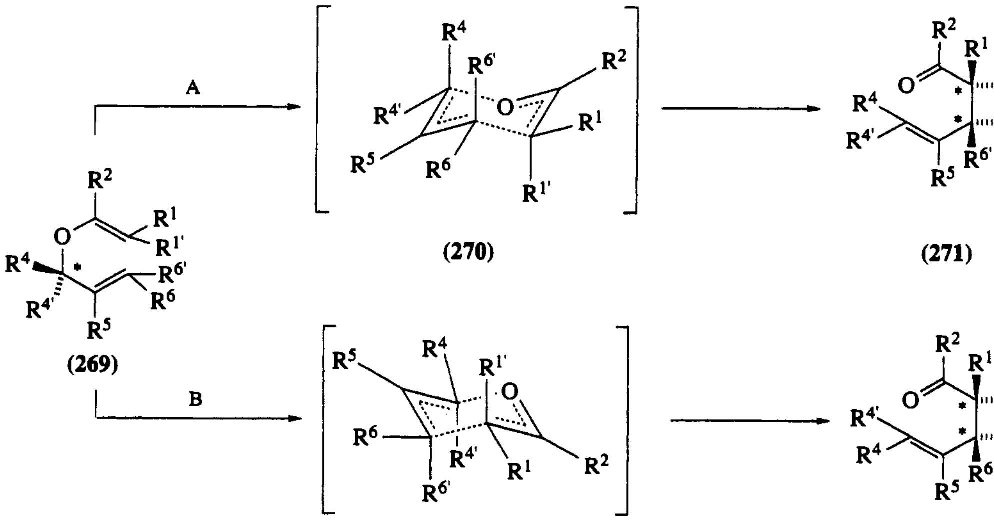

**(269)** **(270)** **(271)** **(272)** **(273)**

(27)

### *(i) Acyclic substrates*

Johnson rearrangement of allylic alcohols (**274**) and (**277**) led to the enantiomeric γ,δ-unsaturated esters (**276**) and (**279**), respectively (Scheme 48).[246] Both transition states (**275**) and (**278**) favor a pseudoequatorial position of the benzyloxymethylene substituent; the newly formed chiral center is obtained in very high optical purity through the chirality transfer process. As a consequence of this geometrical preference, secondary allylic alcohols invariably provide predominantly (*E*)-configured double bonds upon thermal Claisen rearrangement.[247,248] The (*E*)-selectivity usually increases with the steric bulk of the C-2 substituent, an effect which was rationalized by a pseudo-1,3-diaxial interaction in the transition state leading to the (*Z*)-alkene (**280**; Figure 5).[249]

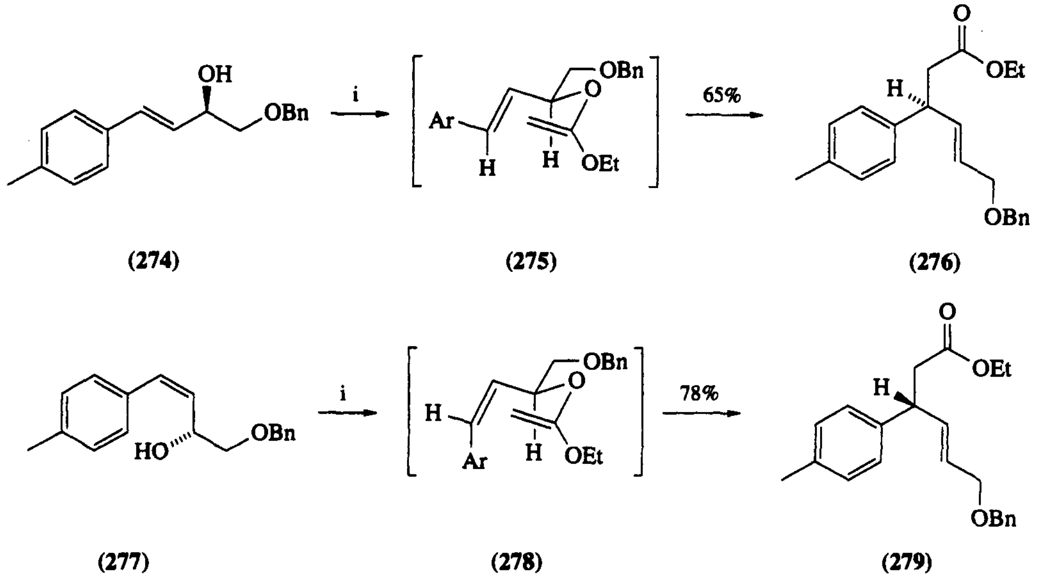

i, MeC(OEt)$_3$ (12 equiv.), pivalic acid (7 mol%), reflux 22 h

**Scheme 48**

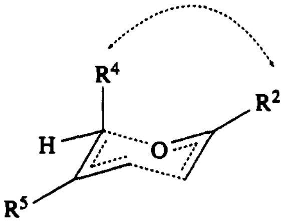

**(280)**

**Figure 5**

As expected, with tertiary allylic alcohol derivatives, the selectivity for the formation of the corresponding trisubstituted alkenes is significantly reduced.[29d,250] Eschenmoser rearrangement of alcohol (**281**), for example, led in 92% yield to a 7.1:1 ratio of (*E*)- to (*Z*)-amides (**282**) and (**283**) (Scheme 49).[251,252]

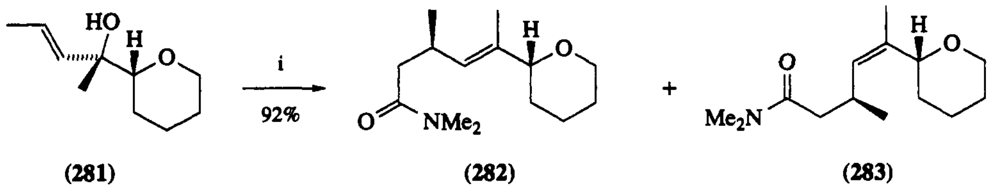

i, MeC(NMe$_2$)(OMe)$_2$, 120 °C

**Scheme 49**

### *(ii) Cyclic substrates*

In substrates where the allyl vinyl ether moiety is part of a cyclic system, steric and electronic constraints can profoundly affect transition state selection.[253] Ireland rearrangement of propionate (**125**), for example, leads in THF *via* the (*E*)-silylketene acetal to a 25:75 ratio of carboxylic acids (**126**) and (**127**) in 56% yield (Scheme 22).[238] Enolization in THF/45% DMPU generates the corresponding (*Z*)-silylketene acetal, which upon rearrangement and hydrolysis provides acid (**126**) in 60% yield as the only NMR detectable isomer. In THF/23% HMPA a 90:10 ratio of isomers is detected, in accord with the enolization stereoselectivity.[254] Consideration of the possible transition states for the 3,3-shift of propionate (**125**) leads to the conclusion that both the chair/chair- and the chair/boat-like transition states (**284**) and (**285**) shown in Scheme 50 are strongly destabilized due to the severe interaction between the axially oriented isopropenyl substituent and the vinyl ether portion. However, an alternative set of transition states, where the cyclohexene ring adopts a boat conformation, avoids these destabilizing interactions (**286** and **287**). With both the (*E*)-silylketene acetal ($R^1$ = H, $R^2$ = Me) and the (*Z*)-silylketene acetal ($R^1$ = Me, $R^2$ = H) geometry, boat/chair transition state (**286**) seems to be preferred over boat/boat transition state (**287**).[238]

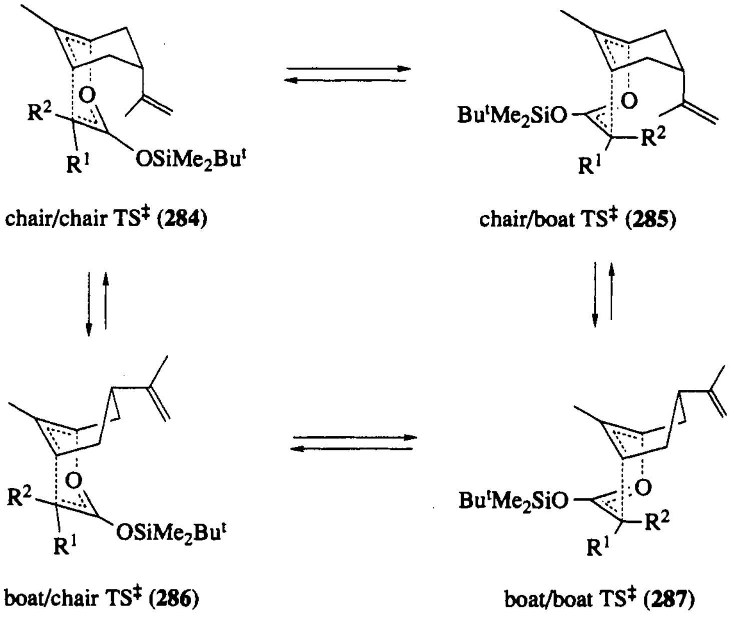

chair/chair TS‡ (**284**)

chair/boat TS‡ (**285**)

boat/chair TS‡ (**286**)

boat/boat TS‡ (**287**)

$R^1$, $R^2$ = H, Me

**Scheme 50**

Ireland rearrangement of the unsaturated macrolide (**288**) in THF/HMPA (3:1), followed by desilylation in aqueous hydrogen fluoride in acetonitrile, led in 70% yield to a 72:28 mixture of acids (**289**) and (**290**) (Scheme 51).[255] The intermediate silylketene acetal was found to be a single isomer, therefore both transition states (**291**) and (**292**) seem to participate in product formation (Figure 6).

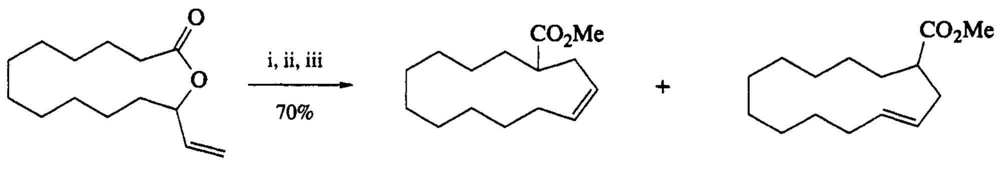

**(288)** **(289)** **(290)**

i, LDA (2 equiv.), THF/HMPA (3:1), –78 °C; Bu$^t$Me$_2$SiCl; ii, toluene, reflux, 8 h; iii, aqueous HF/pyridine; $CH_2N_2$, ether

**Scheme 51**

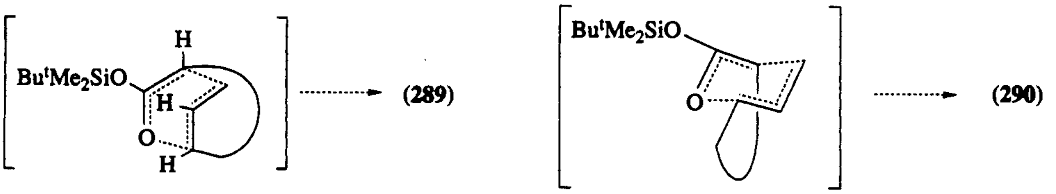

**(291)** **(292)**

**Figure 6**

### *7.2.4.3.2 Remote stereocontrol*

Besides the intrinsic stereochemistry that can be introduced into the Claisen system by an asymmetric carbon in the 4 position, remote centers of asymmetry can also lead to significant diastereocontrol in the rearrangement.

*(i) Acyclic substrates*

Ziegler and coworkers reported low diastereoselectivities in the Johnson rearrangement of an (*E*)-allyl alcohol positioned as a side chain of a trisubstituted cyclohexanone ketal derivative (equation 28).[256] Only a modest stereoselectivity was observed with the center of asymmetry in the vicinal position to the Claisen system, such as in the rearrangement of dioxolane derivative (**295**; Equation 29).[257,258] Ortho ester rearrangement of allylic alcohol (**297**), however, gave esters (**298**) and (**299**) in a ratio of 11.5:1 (Scheme 52).[259] Replacement of the bulky (t-butyldimethylsilyl)oxy group in (**297**) by a hydroxy group led to a drop in the observed diastereoselectivity of the rearrangement to 5.2:1. This indicates a possible destabilizing interaction of the ethoxy group and the ring substituent in transition state (**301**).

*(ii) Cyclic substrates*

Generally, Claisen rearrangement of ring-bearing substrates with remote asymmetric centers has led to higher stereoselectivities than in the acyclic series.[260] Kurth and coworkers used amino acid derived chiral auxiliaries such as (**302**) for the preparation of enantiomerically pure carboxylic acids.[261] The excellent facial selectivity in these systems was hampered, however, by poor chair *vs.* boat selectivities.

In the acid-catalyzed ortho ester Claisen rearrangement of allylic alcohol (**303**) with trimethyl orthobutyrate, diastereomers (**304**), (**305**) and (**306**) were isolated in a ratio of 63:30:7 (Scheme 53).[262] The 3,3-sigmatropic rearrangement occurred with a high degree of stereofacial selectivity from the β-face of the allylic alcohol (α:β > 13:1 for $H_a$).[263] In contrast, Claisen rearrangement of the enol ether (**307**) at 135–140 °C (PhH, sealed tube) provided the desired β-dicarbonyl compound (**308**) as a single diastereomer at

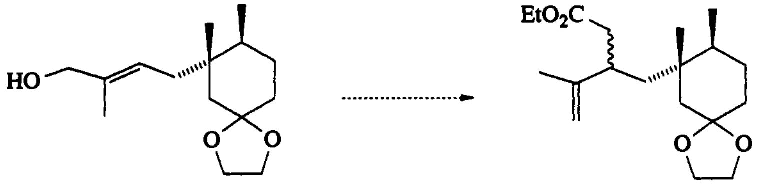

**(293)** **(294)** (28)

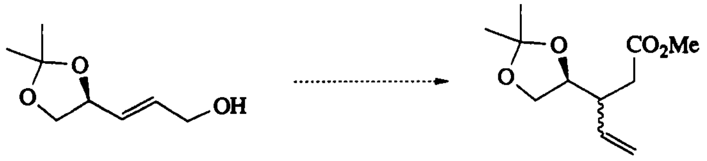

**(295)** **(296)** (29)

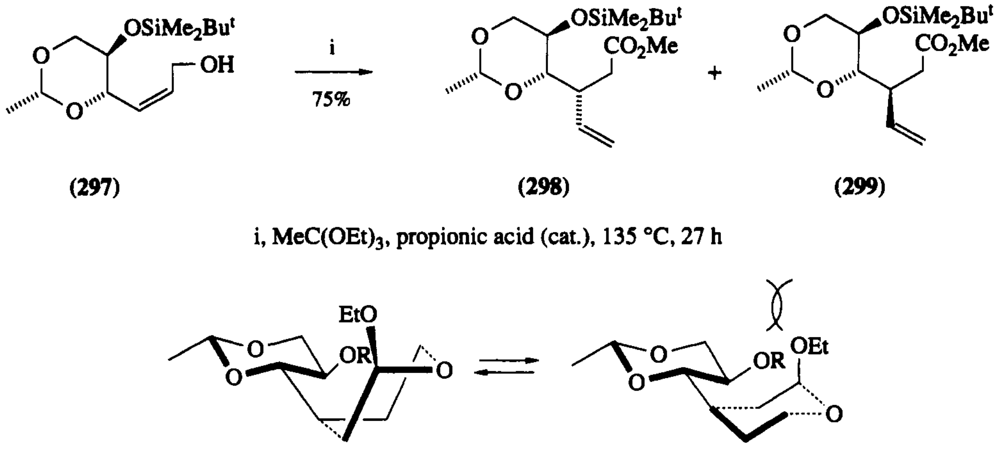
OSiMe$_2$Bu$^t$
OH
i
75%
CO$_2$Me
+
EtO
OR
O
OEt

**(297)** **(298)** **(299)**

i, MeC(OEt)$_3$, propionic acid (cat.), 135 °C, 27 h

**(300)** **(301)**

Scheme 52

C-15 in 55% yield (Scheme 53). In this case, the thermal Claisen rearrangement occurred stereospecifically from the α-face of the bicycle, presumably *via* chair transition state (**309**) (Scheme 54). Therefore it was concluded that the ortho ester rearrangement occurred predominantly *via* boat transition state (**310**), providing the first example of a difference in transition state geometry observed in Claisen variants with the same substrate.

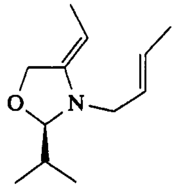

**(302)**

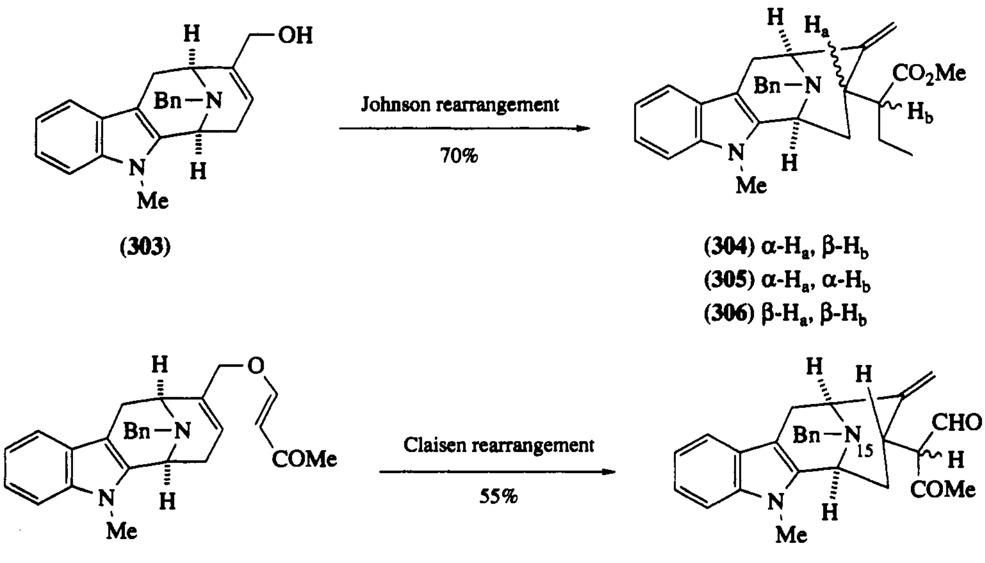
H
OH
Bn—N
N
H
Me
Johnson rearrangement
70%
H$_a$
CO$_2$Me
H$_b$
O
COMe
Claisen rearrangement
55%
CHO
15

**(303)**

**(304)** α-H$_a$, β-H$_b$
**(305)** α-H$_a$, α-H$_b$
**(306)** β-H$_a$, β-H$_b$

**(307)** **(308)**

Scheme 53

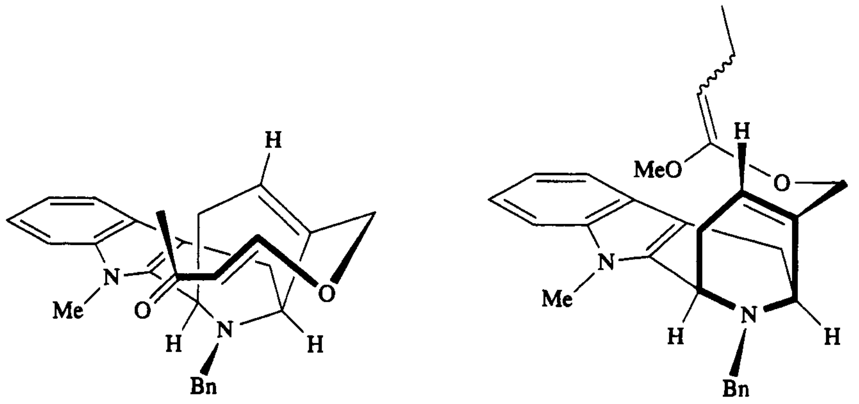

**(309)** **(310)**

Scheme 54

## 7.2.5 CONCLUSIONS

During the 1970s and the 1980s the Claisen rearrangement of allyl vinyl ethers has clearly become an extremely valuable tool in stereocontrolled organic synthesis. However, it still offers mechanistic challenges and synthetic opportunities attractive to the entire chemical community. Certainly, future research in areas such as the influence of substituents and catalysts on transition state structures of the Claisen rearrangement will have a significant impact in the general understanding of chemical reactivity and selectivity.

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# 7.3

# Consecutive Rearrangements

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## 7.3.1 INTRODUCTION

Sigmatropic rearrangements involve the allylic migration of σ-bonds that are in conjugation with the π-framework of the double bond. Not only do sigmatropic rearrangements provide for the formation of sigma bonds, but the migration of the double bond can establish new, reactive functionality that initiates subsequent rearrangements.

Consecutive rearrangements can be classified in three general categories: tandem, sequential and iterative. Tandem rearrangements require the reacting components of the rearrangement to be attached to one another prior to the initial rearrangement. Sequential rearrangements require chemical modification of the first rearrangement product prior to the second rearrangement. Iterative rearrangements are similar to sequential rearrangements except that the process may be conducted many times, and are often used for the synthesis of substances with repeating units.

The concept of consecutive reactions need not be limited strictly to sigmatropic reactions. However, only those reactions that involve a minimum of two sigmatropic rearrangements will be considered.

## 7.3.2 TANDEM AND SEQUENTIAL REARRANGEMENTS

### 7.3.2.1 [3,3]–[3,3] Rearrangements

#### *7.3.2.1.1 Claisen–Cope*

The first example of a tandem Claisen–Cope rearrangement was reported by Claisen in his final scientific paper.[1] Thermolysis of allyl aryl ether (**1**) provides phenol (**4**) in which the allyl residue has been incorporated into the propenyl side chain of (**1**; equation 1). The reaction proceeds through an initial Claisen rearrangement to afford transient 1,5-hexadiene (**2**) which undergoes a subsequent Cope rearrangement to provide unsaturated ketone (**5**). Rearomatization of (**5**) occurs, ostensibly catalyzed by the phenol, to afford irreversibly the observed product (**4**). Intermediate (**2**) may transfer the allyl group to both the *para* position (**3**) or to the methyl-bearing *ortho* position (**6**). Structure (**6**) may also be realized from allyl ether (**1**) by a direct Claisen rearrangement. The presence of 2- and 6-substituents prohibits premature tautomerization to an *o*-allylphenol.

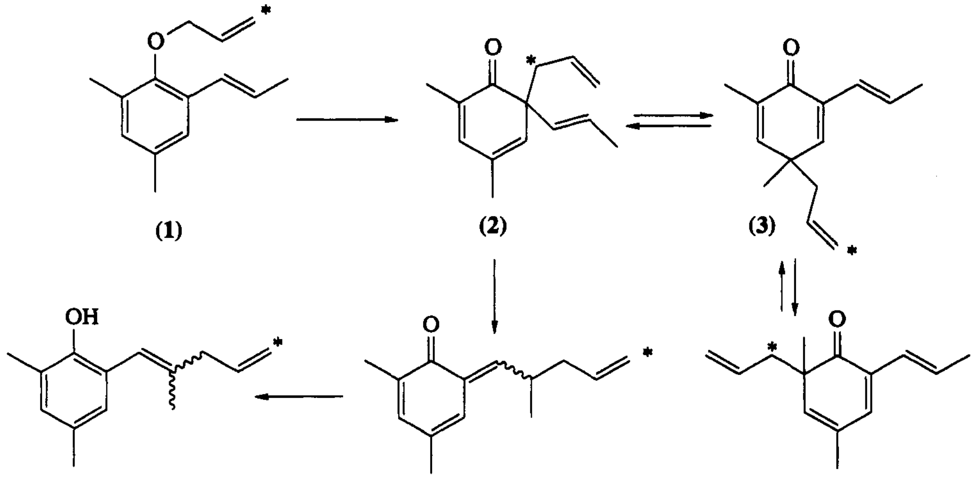

(**1**) (**2**) (**3**)

(**4**) (**5**) (**6**)

(1)

This reaction has been independently reinvestigated by Lauer[2] and Schmid.[3] Rearrangement of (**1**), bearing a $^{14}$C label at the distal carbon of the allylic moiety (starred), gives phenol (**4**) with 84% of the label at the terminal carbon of the side chain and 16% at the methylene group. This result demonstrates that the reaction proceeds principally through a double transposition of the allylic residue; the labeling pattern is maintained independent of the pathway to phenol (**4**).

The dienone (**8**; equation 2), prepared independently by allylation of sodium 2,6-dimethylphenolate, has been shown to undergo irreversible rearrangement to the *p*-allylphenol (**9**) and aryl allyl ether (**7**) ($k_2/k_{-1} = \sim 2.5$; 75–100 °C).[4] The rate constant $k_1$ for the forward reaction is negligible. In the aromatic Claisen–Cope sequence, the Claisen rearrangement is the slower step because the aromaticity of the ring must be overcome.

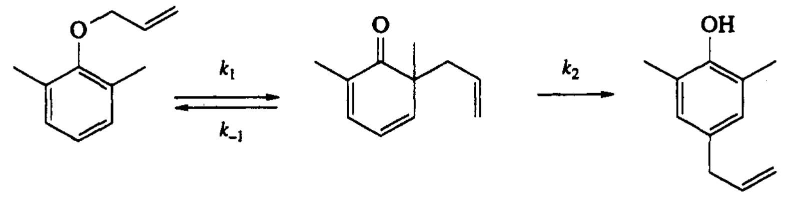

(**7**) (**8**) (**9**)

(2)

Although substituents at the 2- and 6-positions of the aromatic ring are generally employed to prohibit the formation of 2-substituted products, the tandem rearrangement has been observed in aryl vinyl ethers that are devoid of substituents at these positions. The rearrangement of aryl crotyl ether (**10**; equation 3) proceeds through intermediate (**11**), which can partition between 2-substituted phenol (**12**) and the Claisen–Cope product (**13**). The product distribution is solvent dependent; the prototropic isomerization of (**11**) to the *ortho*-substituted product (**12**) is facilitated by polar solvents (solvent, **12**/**13**): neat, 1/1; decalin, 1/1; *N*,*N*-diethylaniline, 4/1; benzonitrile, 8/1; *N*,*N*-dimethylformamide, 60/1.[5]

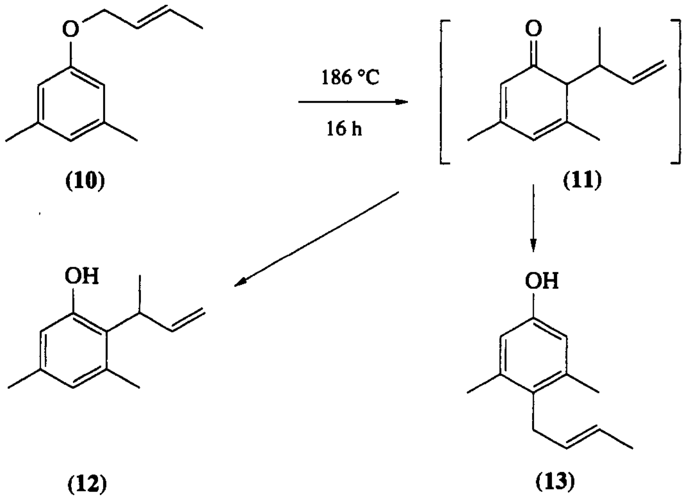

(3)

Steglich[6] has observed a tandem rearrangement in the transformation of aroyl phenylglycinates (**14**) to their respective oxazolinones (**16**; equation 4). The (*E*)-cinnamyl ester (**14a**) and the (*Z*)-cinnamyl ester (**14b**) provide the single (*E*)-alkene (**16a**). Both Claisen rearrangements (**15a** or **15b** giving **17a** or **17b**) are presumed to proceed through the more favorable chair-like transition state, while the aza-Cope rearrangement of the (*E*)-isomer (**17a**) (giving **16a**) occurs *via* the chair-like transition state and the (*E*)-isomer (**17b**) (giving **16b**) proceeds through the boat-like transition state.[7,8] In addition, the chiral (*E*)-ester (**14c**) (66% *ee*) undergoes tandem rearrangement with 100% chirality transfer *via* two chair-like transition states to afford oxazolinone (**16c**). The aza-Cope rearrangements are controlled by the allylic phenyl groups assuming an equatorial position in the transition state. Reductive removal of the heterocyclic ring of (**16c**) provides a route to chiral, nonracemic β,γ-unsaturated ketones.

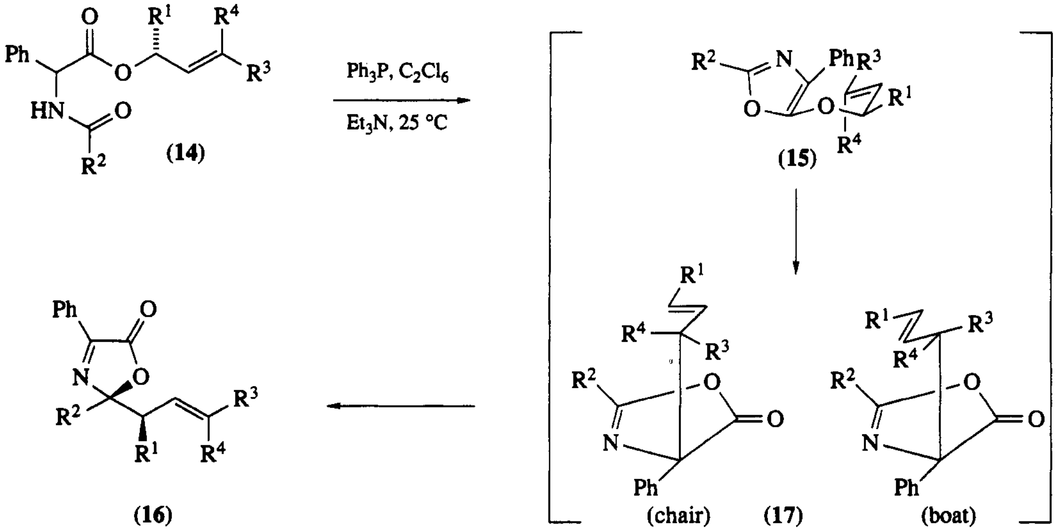

(4)

a: $R^1$ = H, $R^2$ = *p*-$ClC_6H_4$, $R^3$ = Ph, $R^4$ = H; b: $R^1$ = H, $R^2$ = *p*-$ClC_6H_4$, $R^3$ = H, $R^4$ = Ph;
c: $R^1$ = Me, $R^2$ = $R^3$ = Ph, $R^4$ = H

Tandem [3,3] rearrangements in the aromatic series may involve consecutive Claisen rearrangements. Thermolysis of ester (**18**; equation 5) is reported to give the benzopyran-2-one (**20**), whose structure is supported by an IR carbonyl frequency at 1690 cm$^{-1}$ (extended conjugation through the phenolic hydroxy) and a $^1$H NMR alkenic proton at δ7.67. The rearrangement of the initial Claisen product (**19**) to the (*E*)-cinnamate (**21**) is claimed to occur through transition state (**22**). Clearly, transition state (**22**) leads to (*Z*)-cinnamate (**23**; equation 6). Although stereochemical and mechanistic ambiguities remain, the tandem nature of the process is secure.[9]

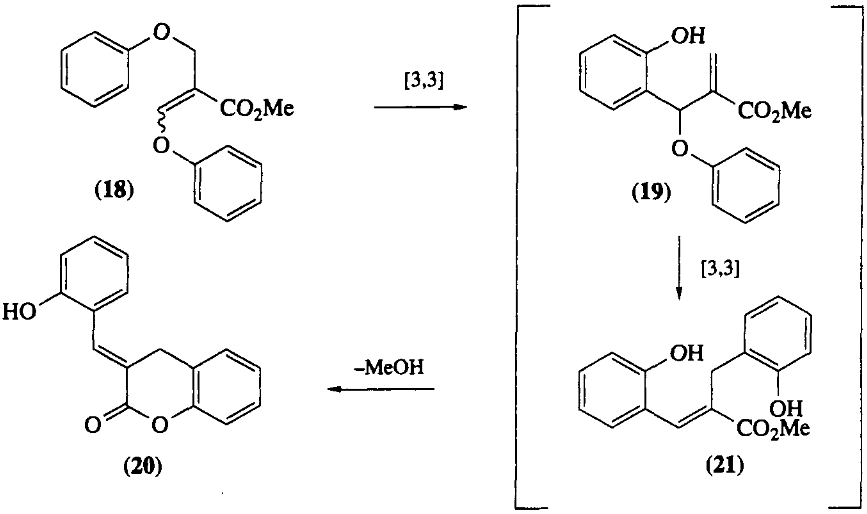

(**18**) (**19**) (**20**) (**21**)

(5)

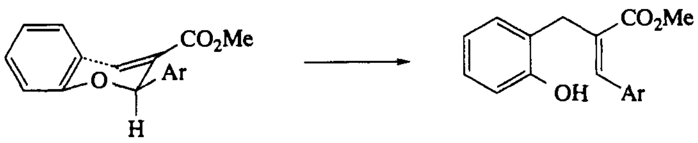

(**22**) (**23**)

(6)

The application of consecutive rearrangements to aliphatic systems has been exceptionally rewarding. A seminal contribution is provided by the work of Thomas, who has prepared β-sinesal (**26**; equation 7), a constituent of the essential oil of the Chinese orange, by the tandem Claisen–Cope rearrangement.[10]

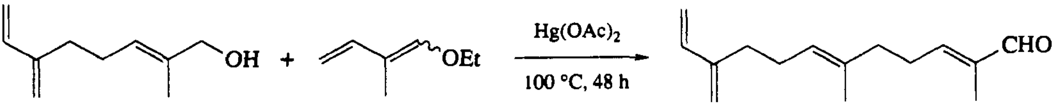

(7)

(**24**) (**25**) (**26**)

Mercury(II) acetate catalyzed exchange of allylic alcohol (**24**) with 1-ethoxy-2-methyl-1,3-butadiene (**25**) ostensibly forms the isomeric vinyl ethers (**28**) and (**32**) that do not interconvert rapidly under the reaction conditions (equation 8). Claisen rearrangement of the isomers affords the diastereomeric aldehydes (**29**) and (**33**). Although the chair-like transition state is generally preferred in Claisen rearrangements where the double bonds are not contained in rings, no stereochemical features are present in aldehydes (**29**) and (**33**) that will distinguish the chair-like from the boat-like transition state. Thus, diastereomer (**29**) is accessible from the (*E*)-vinyl ether *via* the chair-like transition state (**28**), or from the (*Z*)-vinyl ether *via* a boat-like transition state. Conversely, the (*E*)-vinyl ether rearranging through a boat-like transition state or the (*Z*)-vinyl ether rearranging through the chair-like transition state (**32**) gives diastereomer (**33**). The (6*E*)-double bond of β-sinesal must arise from Cope transition states (**30**) or (**34**) that bear the R substituent (R = $CH_2CH_2C(=CH_2)CH=CH_2$) in the equatorial position. Although no (2*Z*,6*E*)-isomer of β-sinesal (**26**) is detected as a product, the (2*Z*)-geometry has been observed in related rearrangements (*vide infra*) and presumably isomerizes to the more stable (2*E*)-geometry during the course of the reaction. The tandem Claisen–Cope rearrangement of equation (8) is the operational equivalent of the γ-alkylation of the anion of (*E*)-2-methyl-2-butenal, of which (**25**) is the dienol ether, with an activated form of the alcohol (**24**).

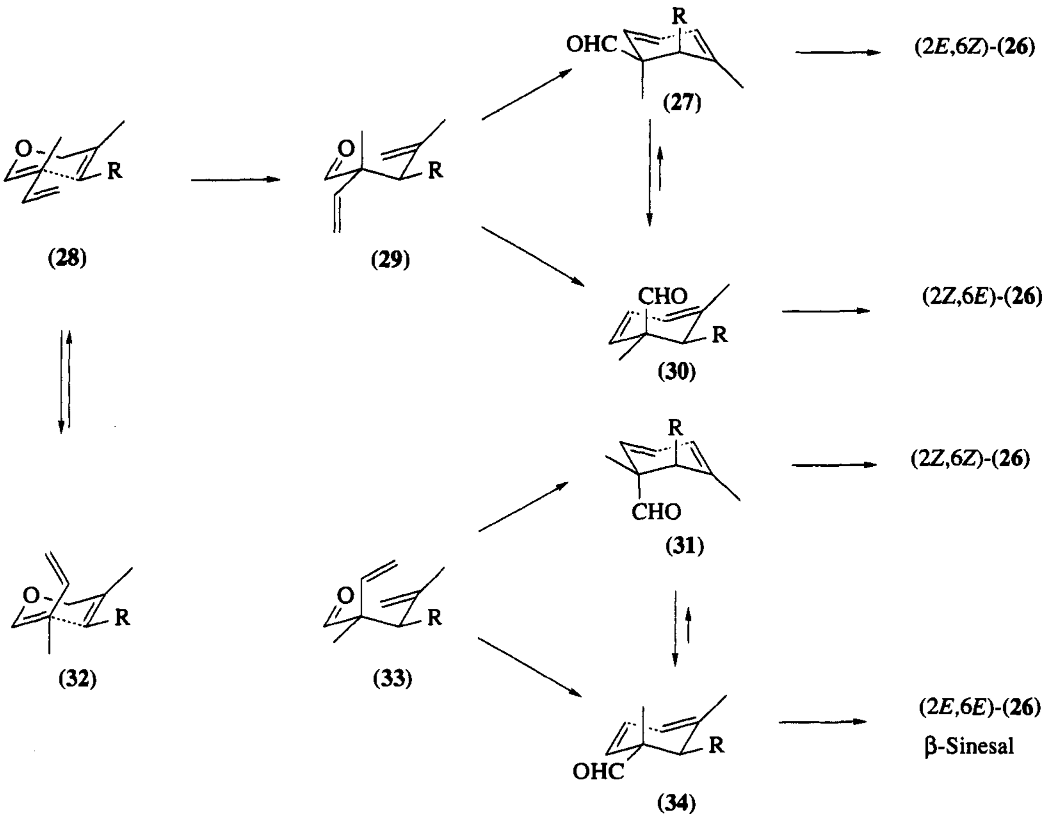

(8)

Because the Cope rearrangement is an equilibrium driven reaction, the application of the Claisen–Cope rearrangement to synthesis requires the target substrates to be more stable than their Cope precursors. Thus, in the instance of equation (8), the 1,5-hexadienes (**30**) and (**34**) bear a monosubstituted and a 1,1-disubstituted double bond, which are less stable than the trisubstituted double bonds of β-sinesal.

Thomas and Ozainne[11] have explored the tandem Claisen–Cope rearrangement on aromatic substrates. Treatment of 2-furfuryl alcohol with diene (**25**; equation 9) provides a 9:1 mixture of Claisen–Cope product (**39**) and furan (**37**), respectively. The minor component arises *via* the 'forbidden' [1,3] prototropic shift of the initial Claisen intermediate (**38**), thereby reestablishing the aromaticity of the furan ring.

When the reaction conditions that are successful with 2-furfuryl alcohol are applied to 3-furfuryl alcohol (**40**), only the product of alcohol exchange, diene (**41**), as a 1:1 mixture of isomers, is obtained (Scheme 1). Elevated temperature (350 °C) is required for the success of the rearrangement. Although the [1,3] prototropic rearrangement of intermediate (**43**) is not observed, the aldehyde (**42**) is produced as a minor component of the reaction mixture ostensibly arising *via* a homolytic scission–recombination of dienol ether (**41**). The products of [3,3] rearrangement are the unsaturated aldehydes (**45**) and (**44**), which are produced in an 85:15 ratio, respectively. Assuming that the chair-like transition state is operative, the (*E*)-isomer (**45**) is produced when the aldehyde group is equatorial (*cf.* transition state **50**), and the (*Z*)-isomer is formed when the aldehyde group is axial (*cf.* transition state **51**). The mixture of aldehydes is transformed in a two-step process into the natural product perillene (**46**).

The 85:15 mixture of alcohols (**47**) that serves as an intermediate in the synthesis of perillene can undergo a second Claisen–Cope rearrangement under moderate temperature conditions to afford an 80:20 mixture of the (*E*)-unsaturated aldehydes (**48**), torreyal and its (*Z*)-stereoisomer, respectively. Reduction of the aldehyde group of the mixture provides dendrolasin (**49**; Scheme 2). Both alcohols of the alcohol mixture (**47**) can channel through 1,5-hexadienes (**52**) and (**53**) after the initial Claisen rearrangement. The exclusive formation of the (6*E*)-double bond geometry is the result of the β-(α-furfuryl)ethyl chain occupying the equatorial position in the ensuing Cope rearrangement of (**52**) and (**53**). The iterative nature of the process permits the continuing interpolation of '(*E*)-isoprene' units into the growing chain.

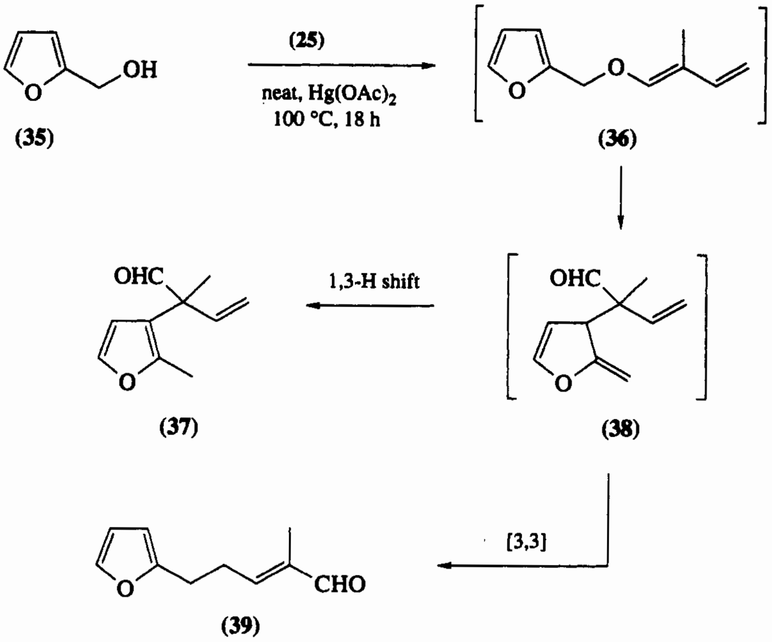
(25)
neat, Hg(OAc)$_2$
100 °C, 18 h
(35)
(36)
1,3-H shift
(37)
(38)
[3,3]
(39)

(9)

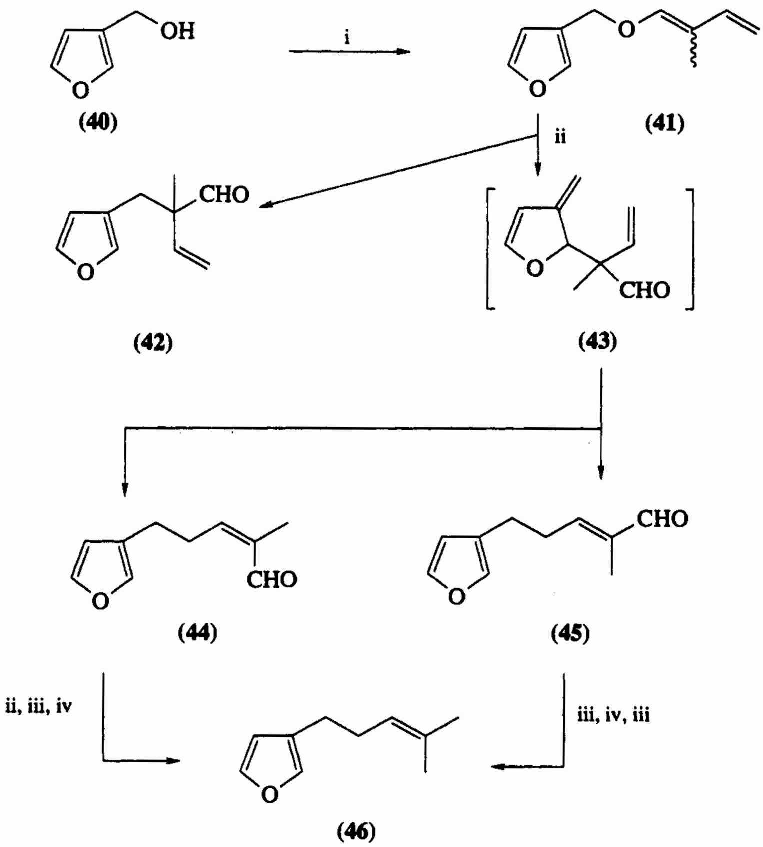
i
(40)
(41)
ii
(42)
(43)
(44)
(45)
ii, iii, iv
iii, iv, iii
(46)

i, **(25)**, Hg(OAc)$_2$, 100 °C, 15–24 h; ii, 350 °C; iii, LiAlH$_4$; iv, TsCl

**Scheme 1**

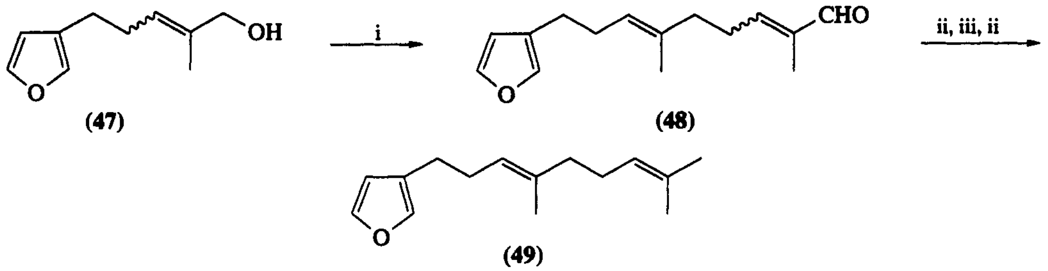

OH
i
CHO
ii, iii, ii
O
(47)
(48)
(49)

i, (**25**), Hg(OAc)$_2$, 100 °C, 18 h; ii, LiAlH$_4$; iii, TsCl

**Scheme 2**

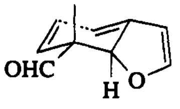

**(50)**

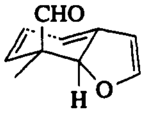

**(51)**

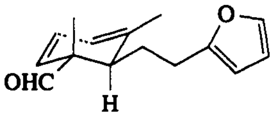

**(52)**

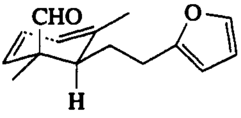

**(53)**

When the Claisen–Cope rearrangement is applied to (–)-*cis*-carveol (**54**; Scheme 3) at 100 °C, a dextrorotatory mixture of aldehydes (**55**) is isolated after the initial Claisen rearrangement, in addition to small amounts of the Claisen–Cope (*E*)-unsaturated aldehyde (**57**) ($[\alpha]_D = -5^\circ$) and its (*Z*)-isomer. Thermolysis of (**55**) at 150 °C gives aldehyde (**57**) ($[\alpha]_D = -8.4^\circ$) and at 400 °C the product displays no rotation. At elevated temperature the reaction presumably occurs *via* a diradical species as the rotation of *ent*-(**57**), prepared via (**56**) from (**54**), is $[\alpha]_D = +12^\circ$.[12]

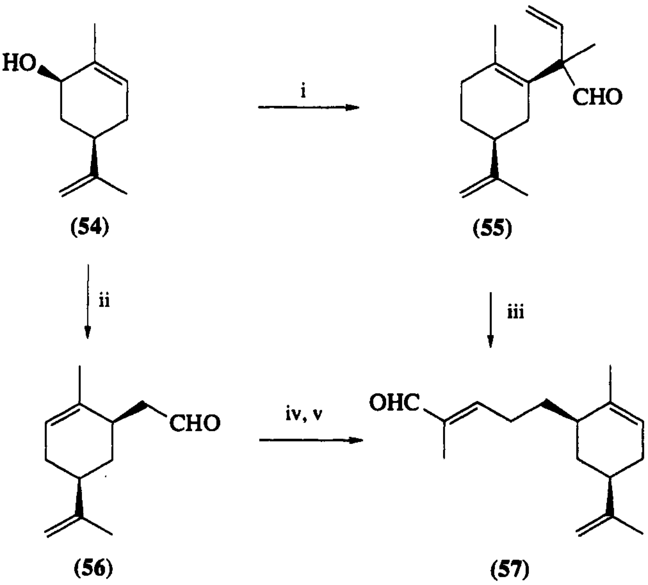

HO
i
CHO
(54)
(55)
ii
iii
CHO
iv, v
OHC
(56)
(57)

i, (**25**), Hg(OAc)$_2$, 100 °C, 17 h; ii, EtOCH=CH$_2$, 120 °C, 24 h; iii, 400 °C;
iv, MeCH=CHN(Li)Bu$^t$, Et$_2$O; v, H$_3$O$^+$

**Scheme 3**

The success of the Claisen–Cope rearrangement need not be limited to the production of aldehydes *via* enol ethers. Allylic alcohol (**58**) is successively transposed into a mixture of allylic isomers (**59**; Scheme 4), and is subjected to an orthoester Claisen rearrangement[13] at 150 °C to provide ester (**61**). The moderate temperature of the Claisen step permits the isolation of an intermediate (*cf.* Scheme 3) prior to the final Cope rearrangement (195 °C) to β,γ-unsaturated esters (**60**). The esters (**60**) are a 55:45 mixture of (*E*)- and (*Z*)-double bond isomers owing to the near equal steric bulk of the methyl and acetic acid residues in the transition state for the Cope rearrangement.[14]

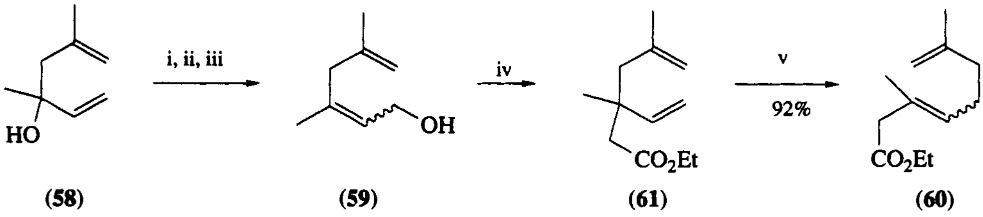

i, $PBr_3$, $Et_2O$; ii, NaOAc/DMF; iii, KOH/MeOH;
iv, $MeC(OEt)_3$, cat. 2,6-dimethylphenol, 150 °C, 3 h; v, 195 °C, 5.5 h

**Scheme 4**

Cookson[15] has studied substrates that can, in principle, effect a tandem Claisen–Cope–Cope rearrangement. By employing 1,1,3-trimethoxybutane as a surrogate for 1-methoxy-1,3-butadiene (equation 10), allylic alcohol (**62**) undergoes acid-catalyzed exchange to provide the transient β,γ-unsaturated aldehyde (**66**) which, lacking a substituent at the α-position, suffers a facile conjugation of the double bond that preempts the tandem process. This phenomenon has been also observed by Thomas.[10]

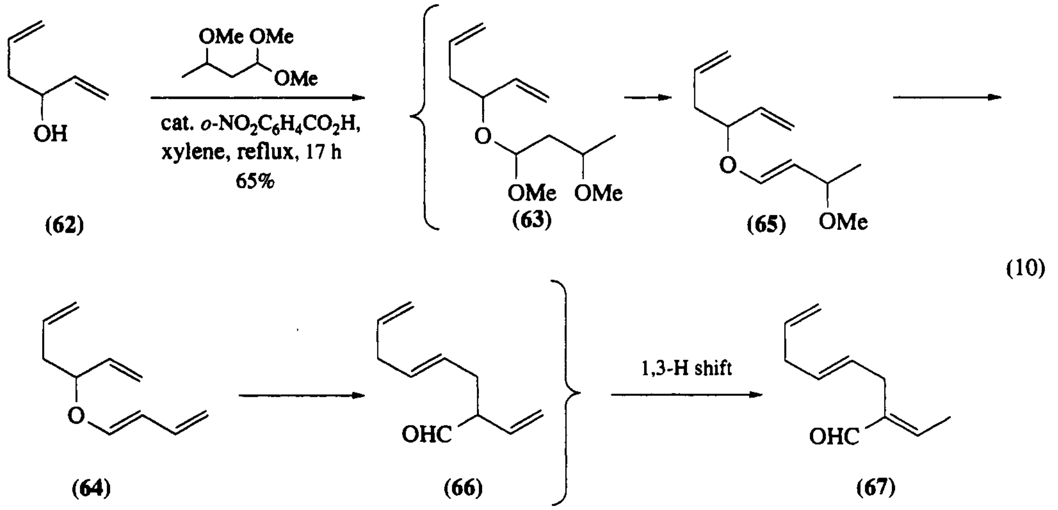

Alternatively, the acetal (**68**; Scheme 5), the analog of (**25**), provides aldehyde (**70**); in refluxing toluene the sequence stops after the Claisen rearrangement. When aldehyde (**70**) is heated at 190 °C, two successive Cope rearrangements occur; first, the α,β-unsaturated aldehyde (**72**) is formed, but not isolated, followed by rearrangement of the 1,5-hexadiene system of (**72**) to aldehyde (**73**). The initial Cope rearrangement, the product of which bears an aldehyde group on the 1,5-hexadiene framework, has a lower activation energy than the second rearrangement. When the reaction is run at 160 °C, aldehyde (**72**) can be isolated as an intermediate.

Reduction of aldehyde (**72**) to its alcohol (**74**; Scheme 6) followed by rearrangement with acetal (**68**) at 110 °C affords a 1:1 mixture (30% yield) of the initial Claisen rearrangement product (**76**) and the tandem Cope–Claisen product (**75**) that is formed from (**76**). These conditions illustrate the ease with which the Cope rearrangement can occur when a carbonyl function is present as a substituent. Once again, elevated temperature is required for the unsubstituted Cope transformation, (**75**) to (**77**). These operations provide another example of the iterative introduction of '(*E*)-isoprene' units into a growing chain.

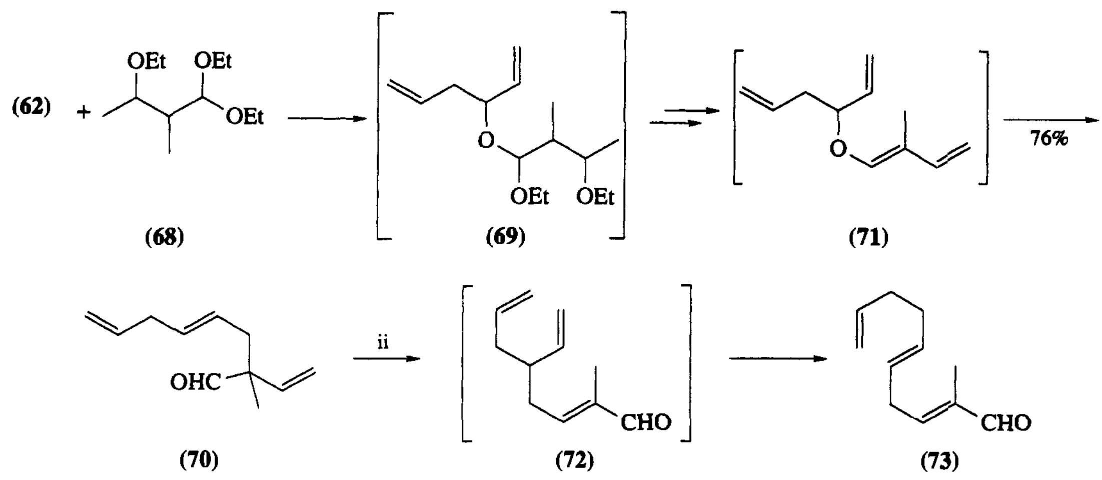

i, cat. $o$-$NO_2C_6H_4CO_2H$, toluene, 110 °C, 48 h; ii, decalin, 190 °C, 3 h

**Scheme 5**

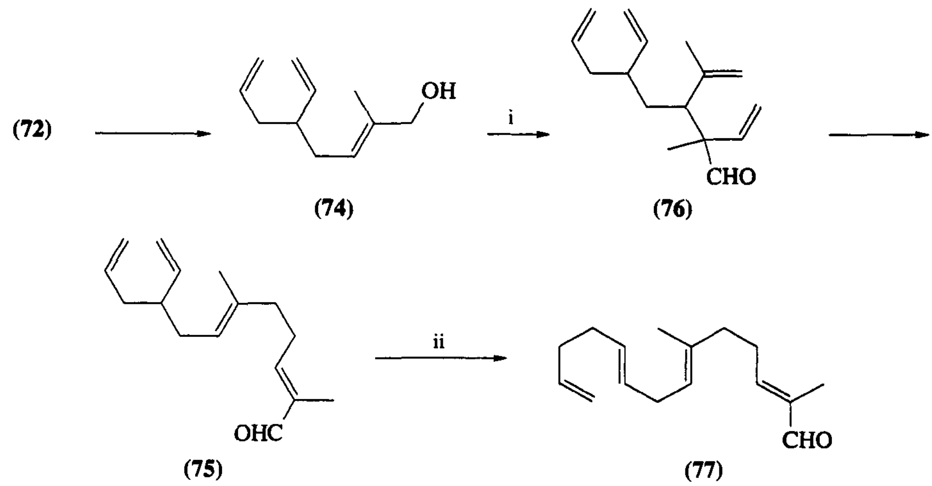

i, (**68**), cat. $o$-$NO_2C_6H_4CO_2H$, toluene, 110 °C, 48 h; ii, decalin, 190 °C, 24 h

**Scheme 6**

In the aborted Claisen–Cope rearrangement of equation (10), the presence of an additional substituent on the aldehyde α-carbon is required to prohibit enolization.[16] However, the absence of a substituent does not preclude a successful Claisen–Cope rearrangement if the conjugation step is reversible. Thus, exchange of β,β-dimethylallyl alcohol (**78**) with acetal (**79**) realizes aldehyde (**81**; equation 11) after the initial Claisen rearrangement; the Cope rearrangement product (**82**) is not observed. Alternatively, the β,γ-unsaturated aldehyde (**81**) undergoes reversible conjugation to (**83**) and deconjugation to the β,γ-unsaturated aldehyde (**85**), which rearranges irreversibly to a 70:30 mixture of (*E*)- and (*Z*)-aldehydes (**84**).

A Claisen–Cope rearrangement for the synthesis of 1,5-hexadienes is provided in Scheme 7.[17] The allyl vinyl ether (**88**), formed by acid-catalyzed exchange of alcohol (**78**) and 1,1-dimethoxyheptane (**86**), affords aldehyde (**87**). Conversion of the aldehyde to the diene (**89**) *via* a Wittig reaction and subsequent Cope rearrangement provides the more stable diene (**90**) that bears the (*E*)-double bond owing to the chain residing in an equatorial position in the transition state. This sequence requires an independent transformation before the second rearrangement and is, therefore, a sequential rearrangement. The process is formally a transmutation of the oxygen atom of the allyl vinyl ether (**88**) to the carbon in product diene (**90**).

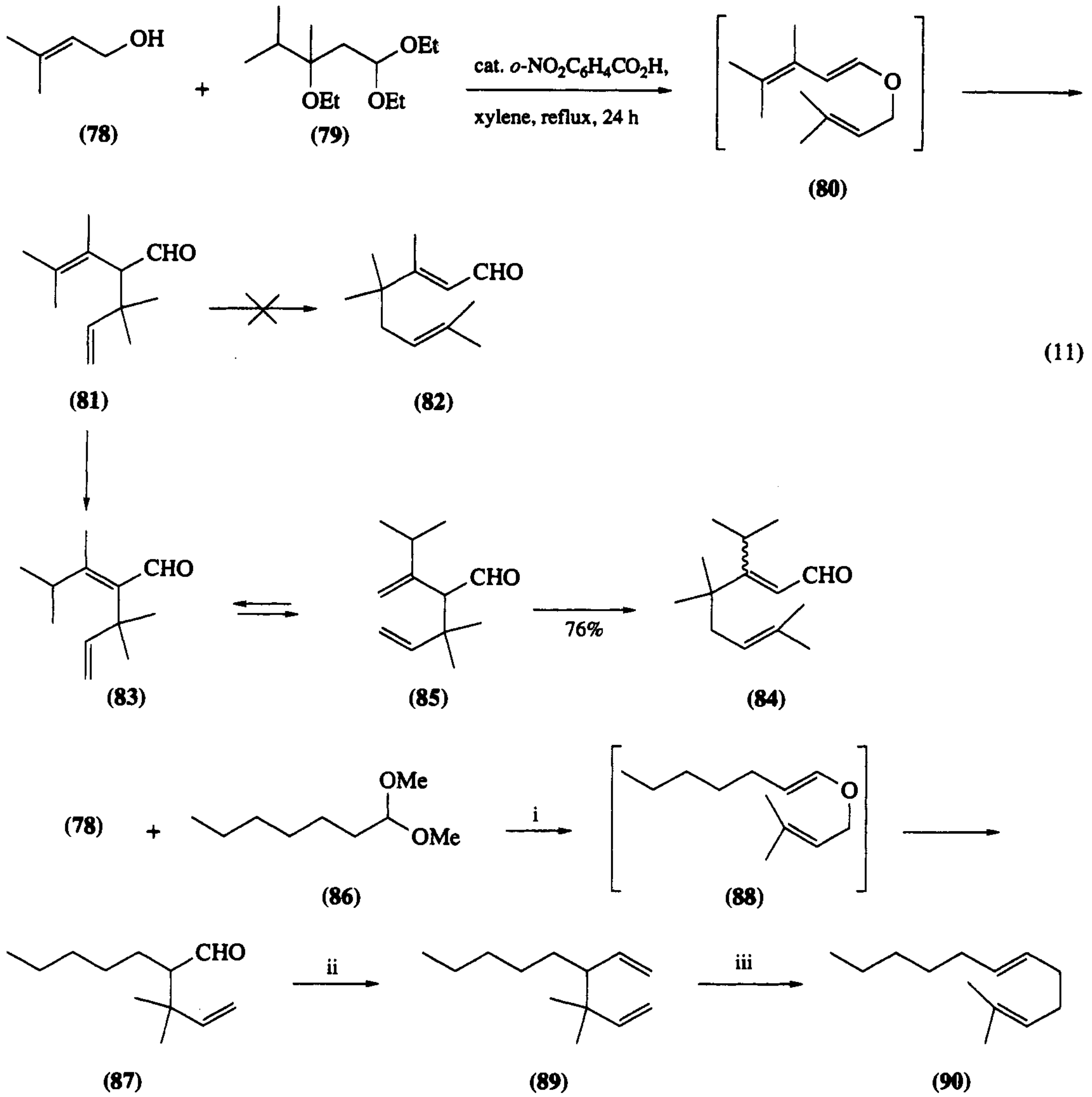

i, cat. $o$-$NO_2C_6H_4CO_2H$, mesitylene, 170 °C, 1 h; ii, $Ph_3PCH_2$, DMSO, 20 °C, 16 h; iii, DMSO, 190 °C

Scheme 7

### *7.3.2.1.2 Cope–Claisen*

One of the shortcomings of the tandem Claisen–Cope rearrangement is that the Cope rearrangement is equilibrium controlled. When the tandem reaction is practised in the reverse sense, any unfavorable Cope equilibria are driven to completion by an irreversible Claisen rearrangement. If the activation energy of the Claisen rearrangement is lower than that of the Cope rearrangement, which is generally the case, no intermediates will be isolated. Owing to the unfavorable Cope equilibrium of equation (12) (**91**/**92**, 4:1), ester (**92**) is an unsuitable precursor for the formation of allyl vinyl ether (**94**) and its eventual transformation to aldehyde (**95**). This difficulty is overcome by reduction of ester (**91**) to its alcohol and subsequent conversion of the resultant alcohol to vinyl ether (**93**). Thermolysis of (**93**; equation 13) provides the aldehyde (**95**) directly; allyl vinyl ether (**94**) is not observed.

The tandem Cope–Claisen rearrangement of triene (**96**; equation 14) creates a product with three new stereogenic centers. Only two of the four possible stereoisomers are formed, namely, aldehydes (**100**) and (**98**) in a 78:22 ratio. The factors that control the stereochemistry are the chair-like *versus* boat-like transition state of the Cope rearrangement (**96** giving **97**) and the formation of the carbon–carbon bond in

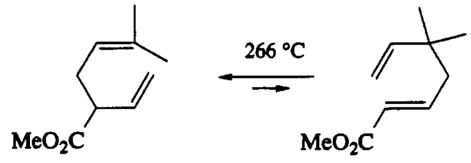

**(91)** **(92)**

(12)

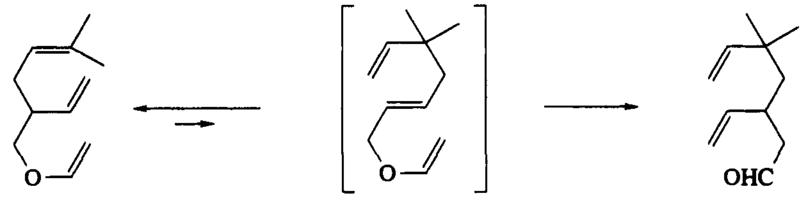

**(93)** **(94)** **(95)**

(13)

the Claisen step *cis* or *trans* to the ring substituent of **(97)**. The stereochemistry of the Cope rearrangement arises exclusively through the chair-like transition state, while the Claisen rearrangement proceeds preferentially *via* bond formation *trans* to the ring substituent. The major diastereomer **(100)** has been transformed into the pseudoguaianolide, aromatin.[18,19]

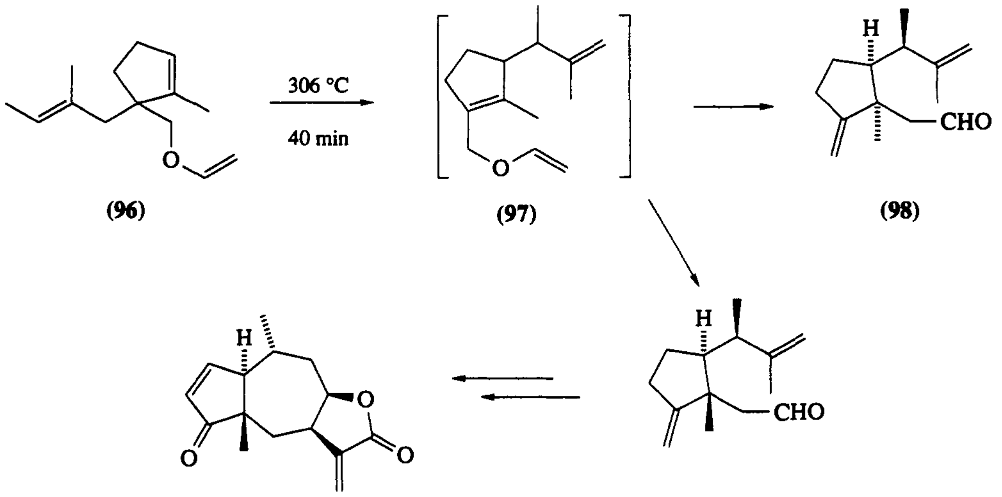

(14)

**(99)** **(100)**

The tandem Cope–Claisen rearrangement provides an excellent opportunity to transform *trans*-2,3-divinylcyclohexanes *via* the less stable (*E*,*E*)-1,5-cyclodecadienes to (*E*,*E*)-1,6-cyclodecadienes (equation 15). When the two *trans*-divinylcyclohexanes, **(101)** (TT) and **(102)** (CT), are independently thermolyzed at ~300 °C, the (*Z*,*Z*)-1,6-cyclodecadiene **(106)**, not the (*E*,*E*)-isomer **(103)**, is formed. In the transformation **(101)** to **(104a)** to **(103)**, the activation energy of the Claisen rearrangement is higher than that of the Cope rearrangement. At lower temperature (255 °C) interconversion of **(101)** and **(102)** occurs through the reversible Cope rearrangement. The interconversion is channeled through the crown conformations **(104a)** and **(104b)** of the intermediate (*E*,*E*)-1,5-cyclodecadiene. This process can be viewed as a stepwise 180° rotation of the ring double bonds passing through conformations **(104c)** and **(104d)** without entering the *cis* manifold. At the higher temperature this barrier is breached and the (*Z*,*Z*)-1,6-cyclodecadiene **(106)** is formed *via* the *cis*-1,2-divinylcyclohexanes **(105)** (TC) and **(107)** (CC). This view is supported by facile conversion of *cis*-1,2-divinylcyclohexane **(105)** (TC) to (*Z*,*Z*)-cyclodecadiene **(106)** at 255 °C, conditions that only interconvert **(101)** (TT) and **(102)** (TC). Reversible Cope isomerization of **(105)** (TC) to **(107)** (CC) occurs at 207 °C without Claisen rearrangement to **(106)**.

The success of this tandem Cope–Claisen rearrangement requires the lowering of the activation energy of the Claisen rearrangement below that of the Cope rearrangement. Recognizing that the Claisen rearrangement of *O*-silyl ketene acetals occurs more rapidly than vinyl ethers and that propionate- and isobu-

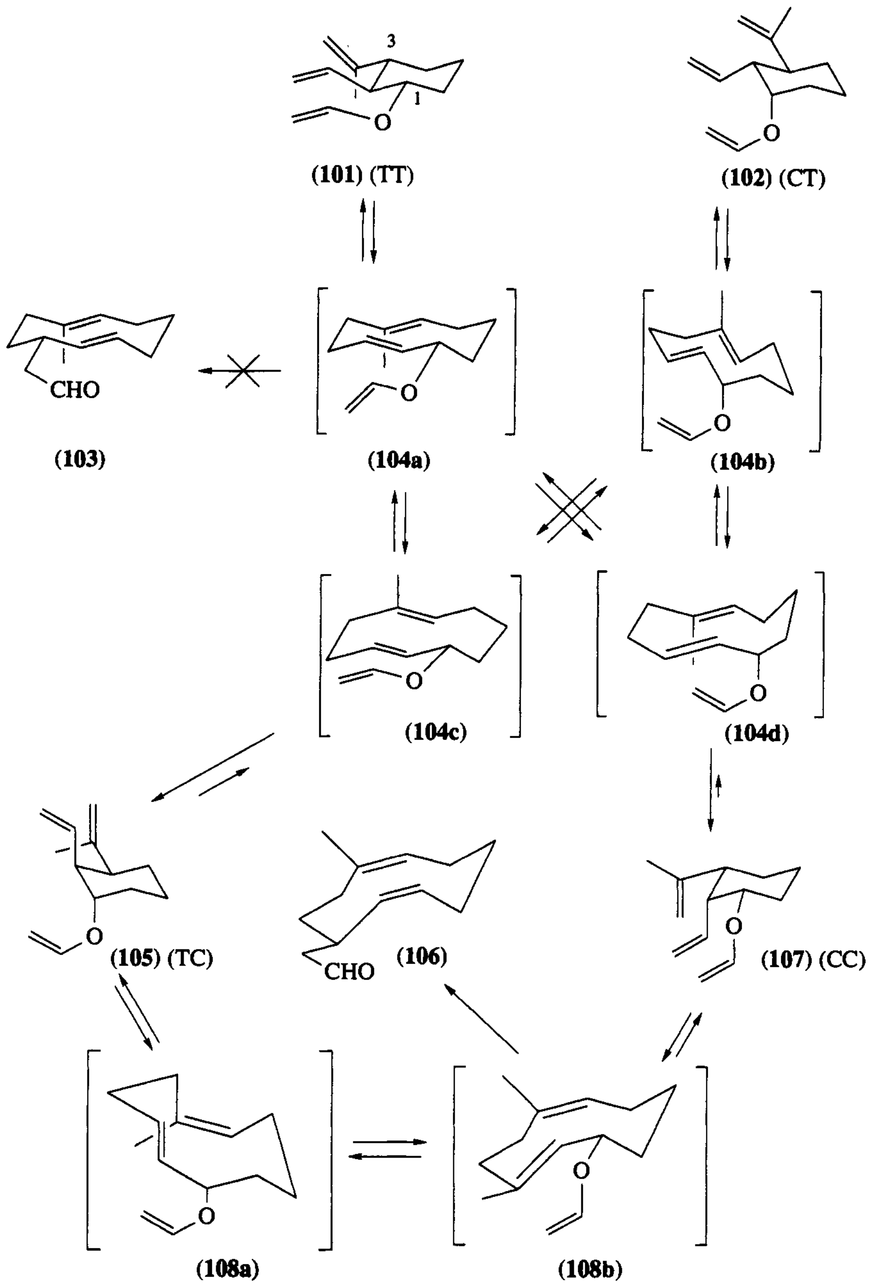

(15)

tyrate-derived *O*-silyl ketene acetals rearrange faster than those derived from acetate,[20] Raucher[21] has examined the reaction with the series of chiral 2,3-divinylcyclohexane *O*-*t*-butyldimethylsilyl ketene acetals (**109a**) to (**109c**) derived from (*S*)-(−)-carvone (equation 16). Thermolysis of (**109a**) at 205 °C effects equilibration with (**111a**) *via* the conformers (**110a**) and (**112a**) of the (*E*,*E*)-1,5-cyclodecadienes; in addition, the products of *O*- to *C*-silyl migration of (**110a**) and (**111a**) are also formed. The rearrangement of (**109b**) gives a mixture of three inseparable carboxylic acids; $^1$H NMR spectroscopy indicates the presence of an (*E*)-disubstituted double bond. Rearrangement of the isobutyrate-derived silyl ketene acetal (**109c**) provides the desired acid (**113d**) in 51% yield. The problem of *O*- to *C*-silyl migration is obviated by use of the triisopropylsilyl ester (TIPS), which permits the preparation of the ester (**113b**) in 30% yield. This substance has been transformed into the 10-membered ring lactone, (+)-dihydrocostunolide (**114**).[22]

The functionality and stereochemistry provided by aldehyde (**100**) have led to the use of the tandem Cope–Claisen rearrangement for the synthesis of estrone methyl ether (**117**)[23] and steroid synthons.[24] Thermolysis of triene (**115**; Scheme 8) provides aldehyde (**116**) as the major component of a 2/1 mixture;

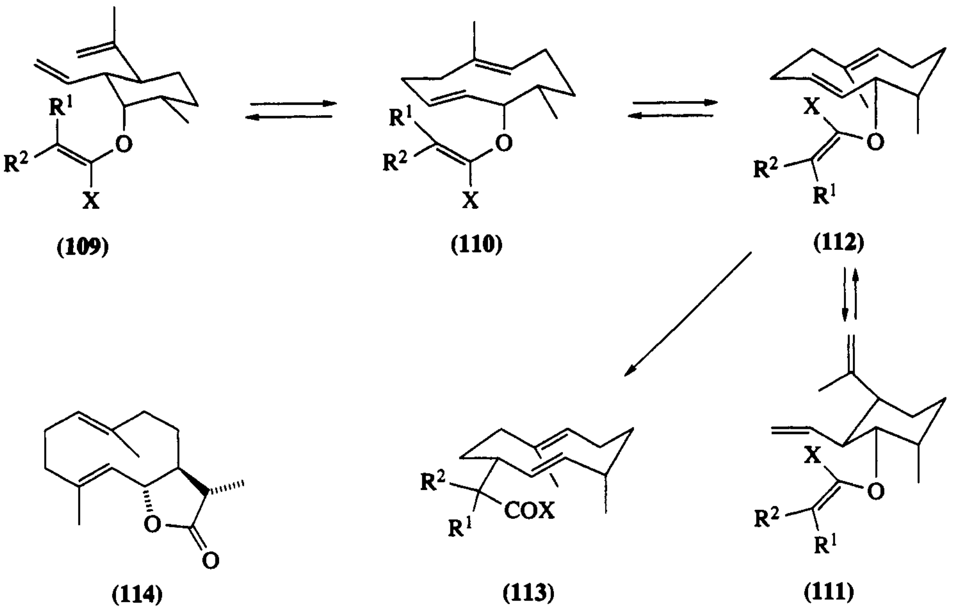
R1
R2
O
X
(109)
R1
R2
O
X
(110)
X
O
R2
R1
(112)
R2
R1
COX
(113)
O
O
(114)
X
O
R2
R1
(111)

(16)

a: $R^1$, $R^2$ = H, H; X = $OSiMe_2Bu^t$
b: $R^1$, $R^2$ = H, Me; X = $OSiMe_2Bu^t$
c: $R^1$, $R^2$ = Me, Me; X = $OSiMe_2Bu^t$
d: $R^1$, $R^2$ = Me; X = OH
e: $R^1$ = H, $R^2$ = Me; X = $OSiPr^i_3$
f: $R^1$ = H, $R^2$ = Me; X = OMe

the minor component is isomeric with (**116**) at the quaternary center. The stereochemistry of the C(8)–C(14) bond is the result of a chair-like transition state in the Cope rearrangement, a stereochemistry that is incorrect for construction of the steroid nucleus. This difficulty is corrected by ozonolysis of diene (**116**) and equilibration of the resultant tricarbonyl (**118**) to provide an intermediate that is amenable to reductive ring closure and subsequent transformation to (**117**).

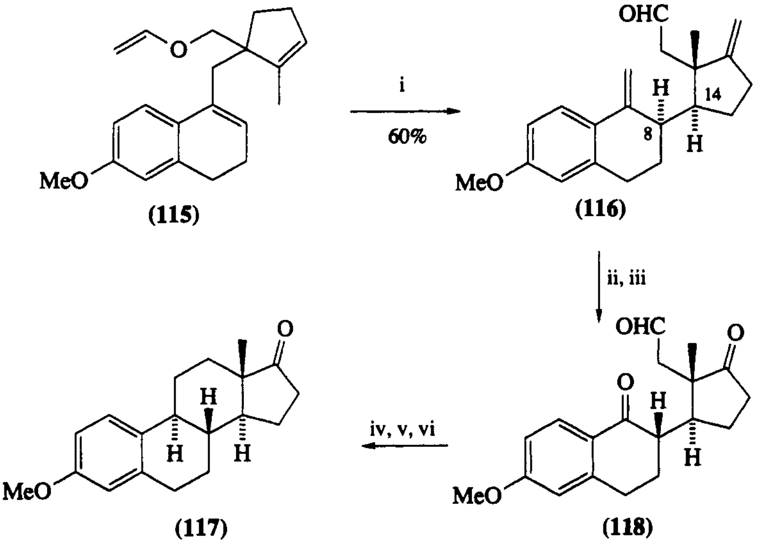
O
MeO
(115)
i
60%
OHC
H
14
8
H
MeO
(116)
ii, iii
OHC
O
O
H
H
MeO
(118)
iv, v, vi
O
H
H
H
MeO
(117)

i, 370 °C, 20 s; ii, $O_3$; iii, MeONa, MeOH; iv, $TiCl_3$, Zn/Ag, DME; v, K/$NH_3$; vi, $CrO_3$

**Scheme 8**

#### *7.3.2.1.3 Claisen–Claisen*

The use of two consecutive Claisen rearrangements has been accomplished in both the sequential and tandem modes. A noteworthy example of the former method has been applied creatively to syntheses in the vitamin D area by Lythgoe and his coworkers (Scheme 9).[25] (*R*)-Methyl orthodihydrocitronellate (**120**) is subjected to an orthoester Claisen rearrangement[13] with allylic alcohol (**119**) to produce esters (**121**). To avoid the formation of diastereomers, (**119**) must be used as the enantiomer shown, not as its racemate or other enantiomer. Although the stereochemistry at the stereogenic center bearing the ester group is not controlled, it is of no consequence in subsequent steps. Because benzoate (**121**) is allylic, its derived allylic alcohol is readily subjected to a second Claisen rearrangement *via* the Eschenmoser procedure[26] providing amide (**122**); subsequent Dieckmann cyclization affords the vitamin D synthon (**123**). The stereochemistry of each oxygen function in (**119**) dictates the eventual stereochemistry of each side chain introduced into (**122**).

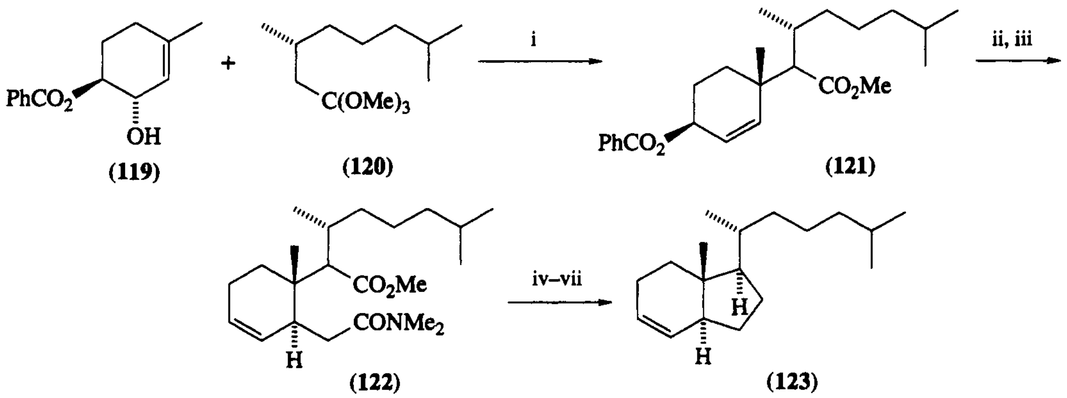

i, xylene, reflux, cat. $EtCO_2H$; ii, NaOH; iii, $MeC(OMe)_2NMe_2$, xylene, reflux; iv, KOH; v, $CH_2N_2$; vi, NaH, DMSO; vii, $H_3O^+$

**Scheme 9**

During preliminary studies on the synthesis of the pseudomonic acids, Curran[27] uncovered a rate enhancement attributable to the presence of the ring oxygen in the Claisen rearrangement of di-*t*-butyldimethylsilyl ketene acetal (**124**) to monoester (**125**). At 60 °C, the first Claisen rearrangement is an order of magnitude faster than the subsequent rearrangement of (**125**) to (**126**); however, the process can be accomplished effectively as a tandem rearrangement.

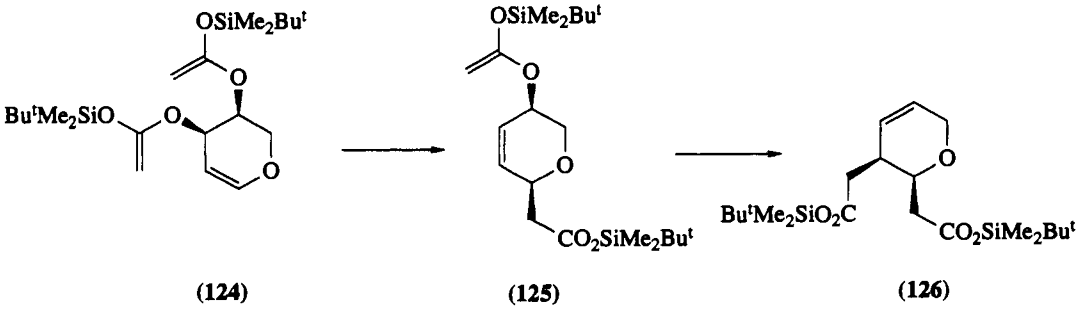

### 7.3.2.2 [2,3]–[3,3] Rearrangements

Nakai and his collaborators have explored in detail the stereochemistry of the [2,3] Wittig rearrangement of diallyl ethers and propargyl ethers and have applied the rearrangement in both the sequential and tandem modes with other sigmatropic rearrangements.[28] Preferential metalation of ether (**127**) at the methylene group of the allyl residue effects a [2,3] Wittig rearrangement to the versatile 1,5-hexadien-3-ol (**128**; equation 17), which is a 4:1 *threo*/*erythro* mixture.[29] The *threo*- and *erythro*-dienes (**128**) undergo oxy-Cope, anionic oxy-Cope,[30] or silyloxy-Cope rearrangement to afford aldehydes (**129**) with

67–95% (*E*)-alkene selectivity. The oxy-Cope is more (*E*)-alkene selective in nonpolar than in polar solvents, and reflects the high end of the selectivity range.

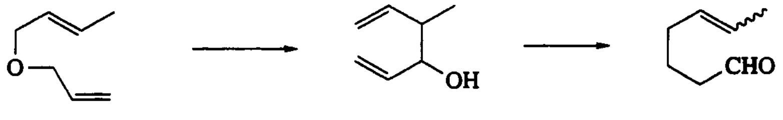

(17)

**(127)** **(128)** **(129)**

When converted to their (*E*)-2-butenyl ethers (**130**), dienols (**128**) serve as precursors for additional tandem processes. Thermolysis of the trienes (**130**) at 250 °C induces an initial oxy-Cope rearrangement to an allyl vinyl ether (**131**) that suffers irreversible Claisen rearrangement affording aldehyde (**132**; equation 18). While the diastereoselectivity of the reaction has not been determined, the geometry of the disubstituted double bond is exclusively of the (*E*)-configuration, a result that requires the secondary methyl group of triene (**130**) to be equatorial in the oxy-Cope transition state. Extended reaction time produces cyclopentanol (**133**), the product of an intramolecular oxy–ene reaction, at the expense of aldehyde (**132**). Trienes (**93**) and (**130**) differ in the relative positions of the oxygen and adjacent methylene group; accordingly, the products, (**95**) and (**132**), respectively, interchange the position of the aldehyde group and the proximate double bond.

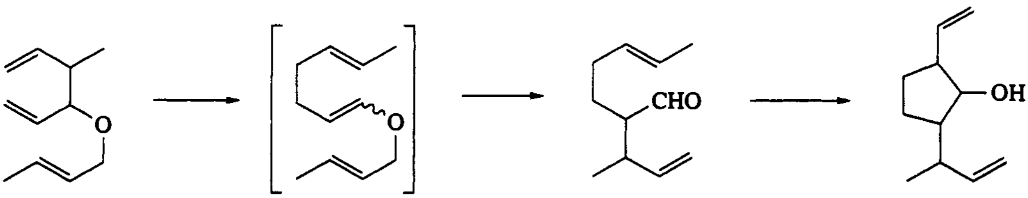

(18)

**(130)** **(131)** **(132)** **(133)**

Not only are the trienes (**130**) suitable for consecutive [3,3] sigmatropic rearrangements, but, as diallyl ethers, are candidates for an additional [2,3] Wittig rearrangement. Because the diallyl ethers (**130**) are prepared from diallyl ether (**127**), and metalation occurs preferentially at the methylene adjacent to the oxygen rather than the methine,[31] the methodology adumbrates the opportunity for iterative processes. This concept is practised, in part (equation 19), by the [2,3] Wittig rearrangement of diallyl ether (**134**) to trienols (**135**), which is followed by a tandem oxy-Cope/Cope rearrangement to aldehyde (**136**); the aldehydes are isolated as a 2/1 mixture of (*E*)- and (*Z*)-isomers, respectively.

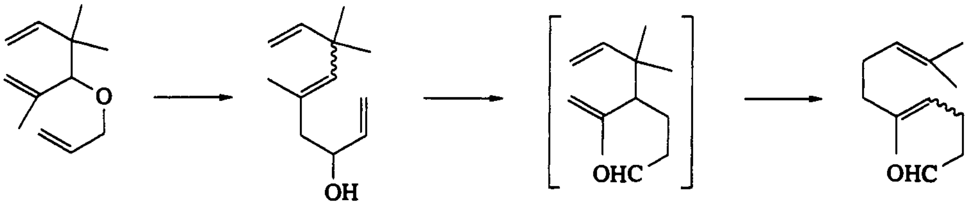

(19)

**(134)** **(135)** **(137)** **(136)**

### 7.3.2.3 Sulfur-based Rearrangements

The nucleophilicity of sulfur and its ability to stabilize α-carbanions provide sulfur compounds with unique opportunities for sigmatropic processes; consecutive rearrangements are no exception. The formation of salt (**140**) *via* $S_N2$ alkylation of (*E*)-2-butenyl bromide (**139**) followed by deprotonation leads to the intermediate allyl vinyl ether (**141**) which, under the conditions of the deprotonation, undergoes a thio-Claisen rearrangement to afford thioamide (**143**; Scheme 10).[32] Thermolysis of (**143**) at elevated temperature affords the Cope product (**142**) in addition to some of its deconjugated isomer. Several unique characteristics of the thio-Claisen sequence should be noted: first, the heteroatom–allyl bond is made in the alkylation step, this connection being not normally practised in the parent Claisen reaction;

and secondly, the direct α-alkylation of (**138**), or any of its congeners, would not be expected to give the $S_N2'$ butenyl unit of thioamide (**143**).

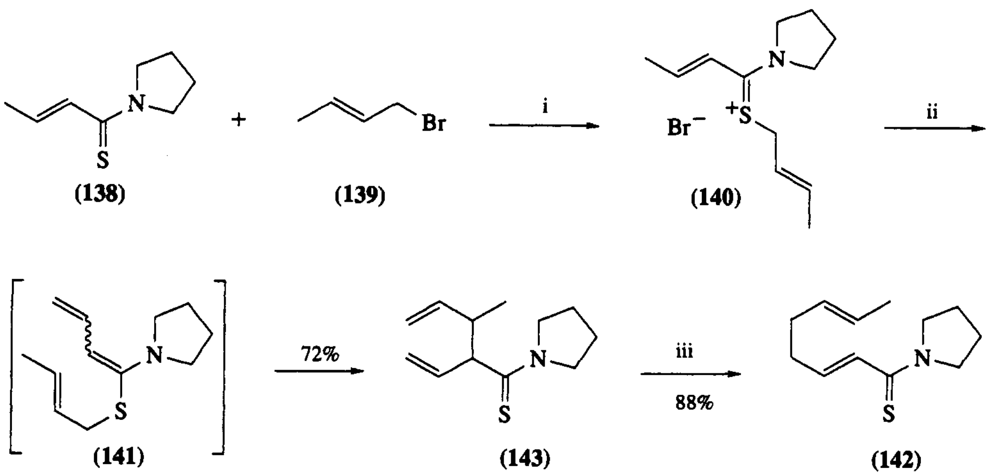

i, Bu$^t$OH, r.t.; ii, Bu$^t$OH, DBU, r.t.; iii, tetralin, reflux

Scheme 10

The ability of sulfur to stabilize carbanions is exemplified in the following cases. The pentadienyldithiocarbamate (**144**; Scheme 11) can be alkylated at the methylene group to afford the methylated product (**145**).[33] At 110 °C, the dithiocarbamate unit 'walks' its way to the other end of the pentadienyl chain *via* tandem [3,3] sigmatropic rearrangements. The formation of (**146**) is thermodynamically controlled as the more-substituted pentadienyl unit is formed. Dithiocarbamate (**146**) can be alkylated and eventually transformed into sulfur-free products; the sequence giving (**148**) from (**146**) is but one of these processes.

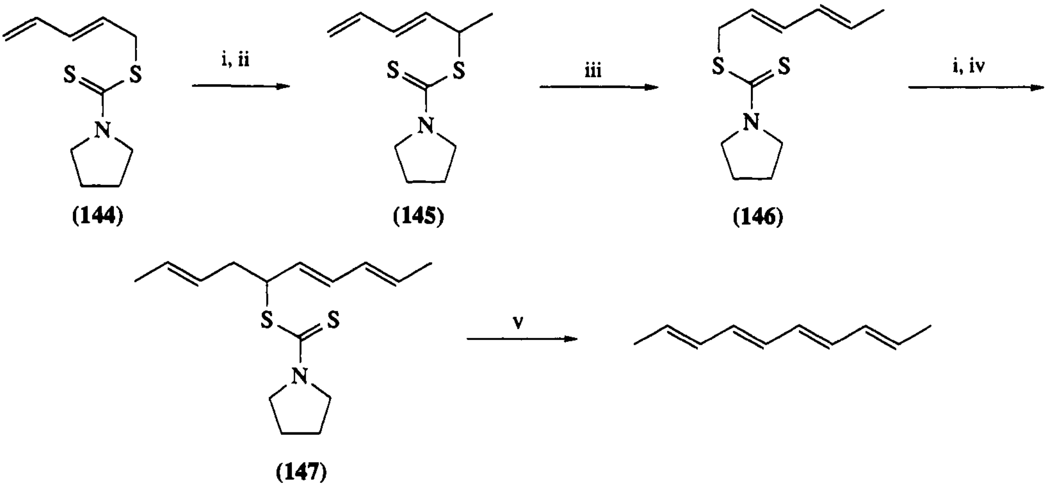

i, LDA, THF, –78 °C; ii, MeI; iii, toluene, reflux; iv, (**139**); v, MeI, LiF, $Li_2CO_3$, DMF

Scheme 11

A close relative of the previous tandem [3,3]–[3,3] sigmatropic rearrangement invokes its tandem [2,3]–[2,3] counterpart: the allylic sulfoxide–sulfenate rearrangement.[34] As a key step in the synthesis of 5-deoxyleukotriene D, Corey[35] applied the sequence of transformations illustrated in Scheme 12. The anion of allylic sulfoxide (**149**) undergoes 1,2-addition to methyl 5-formylpentanoate followed by low temperature benzoylation. Upon warming the reaction mixture to ambient temperature, a facile sulfoxide–sulfenate–sulfoxide rearrangement occurs that provides the thermodynamically more stable sulfoxide (**151**). By virtue of the Pummerer rearrangement, the dienyl sulfoxide unit of (**151**) is transformed into a 2,4-dienaldehyde, thereby allowing the dienyl sulfoxide (**149**) to function as an equivalent of the 4-formyl-(*E*,*E*)-1,3-butadienyl anion. In the examples of Schemes 11 and 12, the thermodynamically more stable (*E*,*E*)-diene is formed.

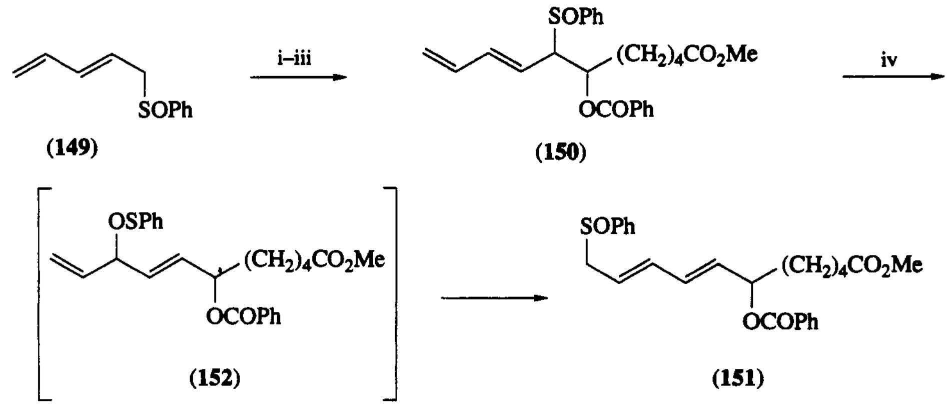

i, Bu$^n$Li, THF, –78 °C; ii, OHC(CH$_2$)$_4$CO$_2$Me; iii, PhCOCl, –40 °C; iv, 25 °C, 3 h

**Scheme 12**

## 7.3.3 ITERATIVE REARRANGEMENTS

### 7.3.3.1 Linear Processes

Faulkner and Petersen[36] have examined the effect of C(2)-substituents of ethyl vinyl ethers on the alkene geometry of the resultant Claisen product. The rearrangement of secondary allylic alcohol (**153**) as its vinyl ether provides a 90:10 ratio of (*E*/*Z*)-isomers (**154a**). The use of the Eschenmoser variant, *i.e.* dimethylacetamide dimethylacetal, affords a 99.4/0.6 ratio of the (*E*/*Z*)-amides (**154b**). Similarly, the application of 2-methoxypropene gives rise to the methyl ketone (**154c**) without any detectable (*Z*)-isomer. Based upon the assumption that the chair-like transition state is operative, transition state (**155**), having the ethyl substituent equatorial, encounters fewer pseudo-1,3-diaxial interactions than its counterpart (**156**). This effect is more pronounced when the R substituent is larger than hydrogen.

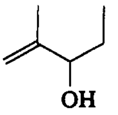

**(153)**

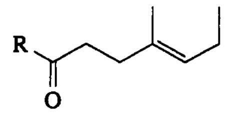

**(154)**
a: R = H
b: R = NMe$_2$
c: R = Me

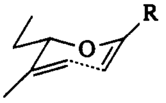

**(155)**

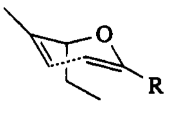

**(156)**

When 2-methoxy-3-methyl-1,3-butadiene and alcohol (**153**) are the reacting partners, the unsaturated ketone (**157**) results. In this instance, the R group is isopropenyl, and the stereochemistry of the isolated double bond is of the (*E*)-configuration. Reduction of the ketone (equation 20) provides a new secondary allylic alcohol (**158**) that can undergo iterative rearrangements. Each rearrangement introduces the equivalent of an isoprene unit in a head-to-tail fashion.

This strategy has been applied to the synthesis of the C$_{18}$ *Cecropia* juvenile hormone (JH) (**163**; Scheme 13) using the ketal (**160**) rather than an alkoxy butadiene.[37] Surprisingly, an α,β-unsaturated ester is obtained as an ~3:1 mixture from which the undesired (*E*)-isomer can be separated by fractional distillation. The iterated allylic alcohol (**163**) is transformed into its isomeric allylic alcohol which is subsequently reduced to an alkene and epoxidized to realize the target (**163**). The scheme also lends itself to

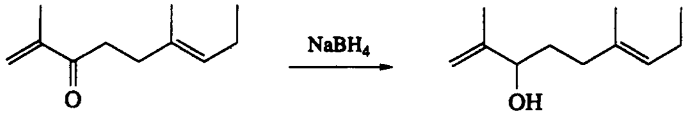

**(157)** **(158)** (20)

the synthesis of the enantiomers of JH by utilizing the enantiomers of 3-chloro-2,2-dimethoxy-3-methylpentane[38a] and 3-hydroxy-2,2-dimethoxy-3-methylpentane.[38b]

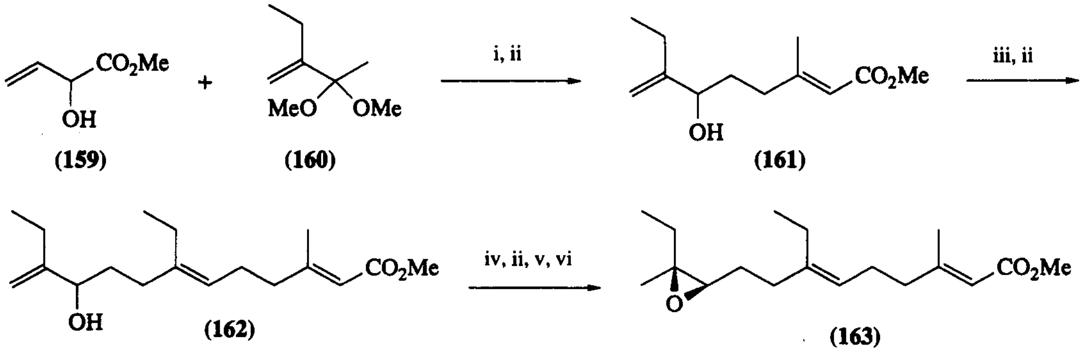

i, cat. 2,4-dinitrophenol, toluene, 110 °C; ii, $NaBH_4$; iii, cat. 2,4-dinitrophenol, toluene, 110 °C + **(160)**;
iv, $SOCl_2$; v, aq. NBS; vi, $K_2CO_3$

**Scheme 13**

Diol **(165)**[39] is an intermediate in the synthesis of the symmetrical triterpene, squalene **(167)**. Succindialdehyde serves as the central four carbons followed by bidirectional synthesis through diol **(164)**. The transformation of diol **(164)** into its higher homolog **(165)** requires several operations: (i) orthoacetate rearrangement[13] to a diester; (ii) reduction to a diol; (iii) oxidation to a dialdehyde; and (iv) addition of isopropenyllithium. A more convergent approach employs 3,3-dimethoxy-2-methylbut-1-ene in conjunction with diol **(164)**, a sequence that only requires reduction of the resultant isopropenyl ketone after rearrangement to realize diol **(165)**.[37]

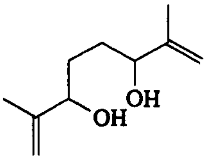

**(164)**

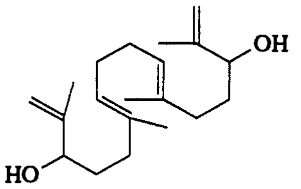

**(165)**

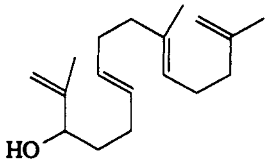

**(166)**

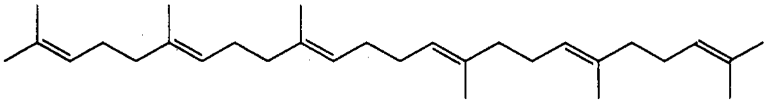

**(167)**

Allylic alcohol **(166)** is the product of 'right-to-left' linear iteration by this process. Not only is the trisubstituted alkene accessible with high stereochemical control, but also the (*E*)-disubstituted alkene is readily prepared. These linear polyenes play an important role in the biomimetic synthesis of steroids and higher terpenes.[40]

Vitamin E (α-tocopherol, **168**) bears two secondary methyl groups at the stereogenic centers in its side chain. An ingenious solution to the synthesis of this chain has been realized employing iterative Claisen rearrangements in a scheme that is enantioconvergent (Scheme 14).[41] Readily accessible 6-methyl-2-heptyn-4-ol, prepared by the addition of propynylmagnesium bromide to isovaleraldehyde, is resolved *via* the hemiphthalate α-methylbenzylamine salt to its (*R*)- and (*S*)-enantiomers, (**169**) and (**170**), respectively. Lindlar reduction of the (*R*)-enantiomer provides the (*R*)-(*Z*)-allylic alcohol (**171**), while dissolving metal reduction affords the (*S*)-(*E*)-enantiomer (**172**). Claisen rearrangement of either allylic alcohol, after exchange with ethyl vinyl ether, gives rise to (*S*)-(*E*)-unsaturated aldehyde (**173**). The rearrangement is also successful with the Eschenmoser,[26] Johnson[13] and Ireland[20] variants of the Claisen rearrangement.

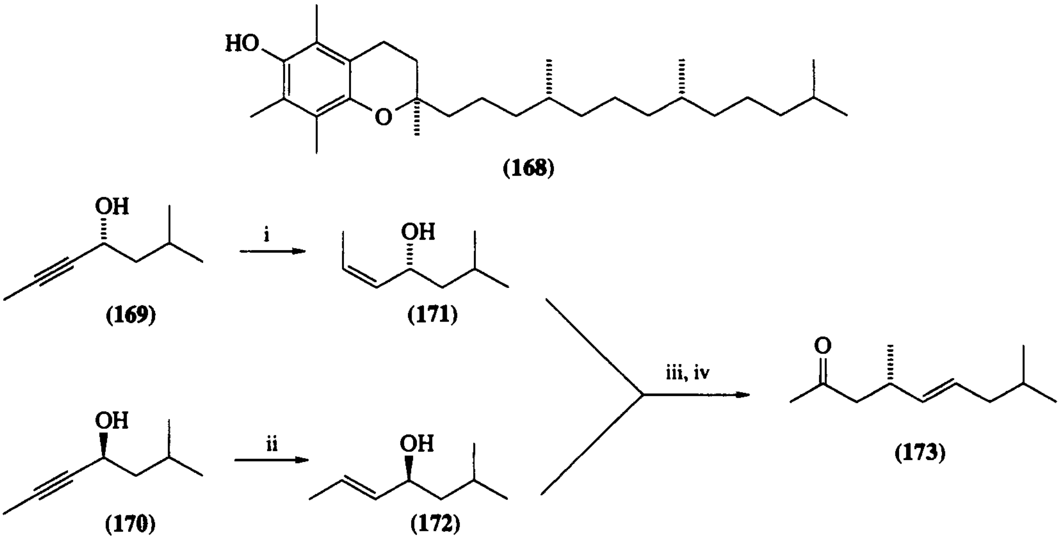

i, Lindlar cat., $H_2$; ii, Na/$NH_3$; iii, $EtOCH{=}CH_2$, $Hg(OAc)_2$; iv, PhH, reflux, 12 h

**Scheme 14**

Figure 1 illustrates the stereochemical control elements (*R*/*S*; *E*/*Z*) that are operative in this reaction. The *x*-axis (*R*,*S*) reflects the chair transition states for the enantiomers (**174**/*ent*-**174**; **175**/*ent*-**175**) of the vinyl ethers of the (*E*)- and (*Z*)-alcohols; the *y*-axis reflects the change of alkene geometry of a given absolute configuration. Passage from one quadrant to a contiguous one results in the opposite enantiomer of

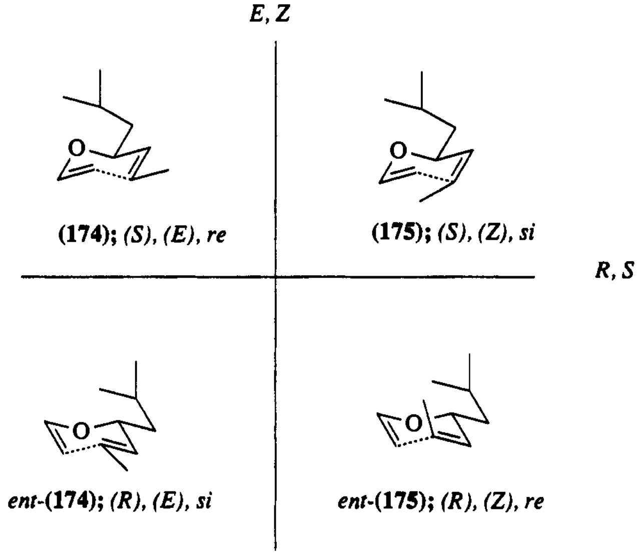

(**174**); *(S), (E), re*

(**175**); *(S), (Z), si*

*ent*-(**174**); *(R), (E), si*

*ent*-(**175**); *(R), (Z), re*

**Figure 1**

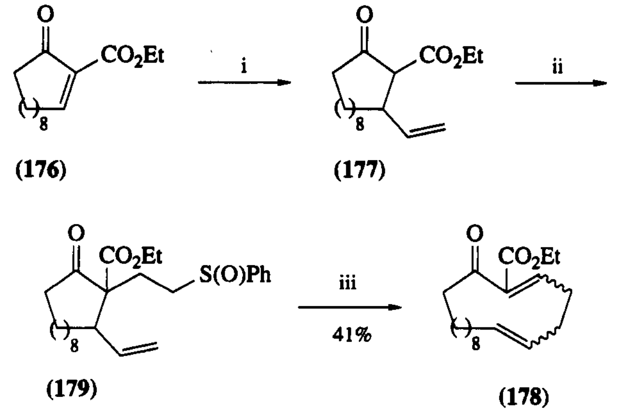

i, $H_2C$=CHMgCl, CuI; ii, NaH, $CH_2$=CHS(O)Ph; iii, 250 °C, $10^{-3}$ Torr

Scheme 15

the Claisen rearrangement product being formed; passage through two quadrants provides the same enantiomer. That is to say, change of an even number of control elements provides the same enantiomer; change of an odd number gives the opposite enantiomer. Thus, the quadrants corresponding to **(174)** and *ent*-**(175)** afford aldehyde **(173)**, while the quadrants corresponding to **(175)** and *ent*-**(174)** provide *ent*-**(173)**.

The second iteration is accomplished by the addition of propynylmagnesium bromide to aldehyde **(168)**; the 1:1 mixture of diastereomers is separated and treated as in Scheme 14.[42]

### 7.3.3.2 Ring-forming Processes

Iterative sigmatropic processes have been developed that achieve ring expansion or the formation of polycyclic structures. Schmid and coworkers[43] have investigated the iterative ring expansion shown in Scheme 15. The double bond of cycloalkylidene β-keto ester **(176)** is appended with a nucleophilic vinyl unit and an electrophilic vinyl group, the latter in the guise of phenyl vinyl sulfone. Thermolysis of **(179)** achieves elimination and Cope rearrangement, the two reactions constituting a tandem process, to afford the 16-membered cycloalkylidene β-keto ester **(178)**, the product of a four-atom ring expansion, as a mixture of geometric isomers. The product **(178)** of the rearrangement renews the functionality of **(176)**, and it is ready for a second ring expansion.

Vedejs[44] and Schmid[45] have independently developed an iterative ring expansion process that employs the [2,3] sigmatropic rearrangement of sulfur ylides (Scheme 16). Base-catalyzed rearrangement of the *trans*-substituted sulfonium salt **(181)** *via* the carbonyl-stabilized ylide gives rise to the (*Z*)-alkene **(183)** (67%) in addition to 5% of the more strained (*E*)-isomer. Wittig methylenation of **(183)** provides a new allylic sulfide **(182)**, which upon treatment with dimethyl diazomalonate in the presence of copper undergoes a second, three-atom ring expansion to malonate **(185)** which bears a new (*Z*)-alkene.

While the minor component, (*E*)-**(183)**, of the rearrangement of the *trans*-substituted sulfonium salt **(181)** may be rationalized by the chair-like transition state *trans*-(*E*)-**(186)**, the related transition state *trans*-(*Z*)-**(186)** does not account for the formation of the major product **(183)**, because the bond-forming carbon atoms are too remote from one another (equation 21). Alternatively, an isomerization of the *trans*-substituted sulfonium salt to its *cis* counterpart *via* several possible pathways[46] permits the formation of **(183)** *via* transition state *cis*-(*Z*)-**(186)**, or (*E*)-**(183)** through the twist transition state *cis*-(*E*)-**(186)**. While the formation of a *cis*-alkene is highly favored in the 8-membered ring, the 11-membered ring favors the formation of a *trans*-alkene.

The foregoing methods have been successfully applied to the synthesis of carbocyclic cytochalasans[47] and the macrolide methynolide (**191**; equation 22).[48] Iterative ring expansion of the five- and eight-membered ring sulfonium salts **(187)** and **(189)** leads to the 11-membered ring sulfur heterocycle **(190)**. Sulfonium salt **(189)** is a 1:1 mixture of stereoisomers that gives **(190)** with 16:1 selectivity in 76% yield.

Schmid[45] has successfully transformed the five-membered ring sulfonium salt **(192)** into the 17-membered ring sulfur thiacycle **(197)** in four iterations (Scheme 17). The products **(194)**, **(193)** and (*E*)-**(194)** are formed in a ratio of 67:27:6. The presence of tetrahydrothiophene **(193)** is the result of ylide formation at the more-substituted allylic site of salt **(192)** followed by [2,3] sigmatropic rearrangement. The

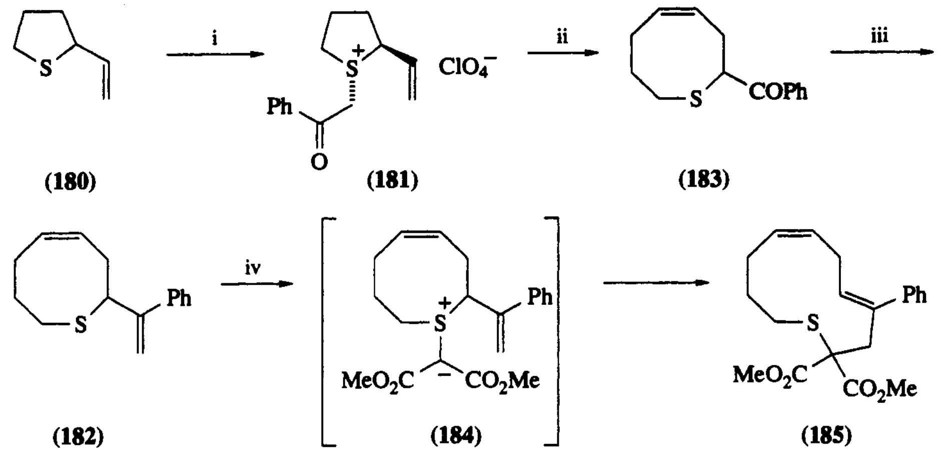
i
ii
iii
iv
S
Ph
O
ClO4⁻
COPh
MeO2C
CO2Me
(180)
(181)
(183)
(182)
(184)
(185)

i, PhCOCHN$_2$, 60% HClO$_4$, MeCN: ii, DBU, toluene, 90 °C;
iii, Ph$_3$PCH$_2$; iv, N$_2$C(CO$_2$Me)$_2$, copper bronze, 100 °C

**Scheme 16**

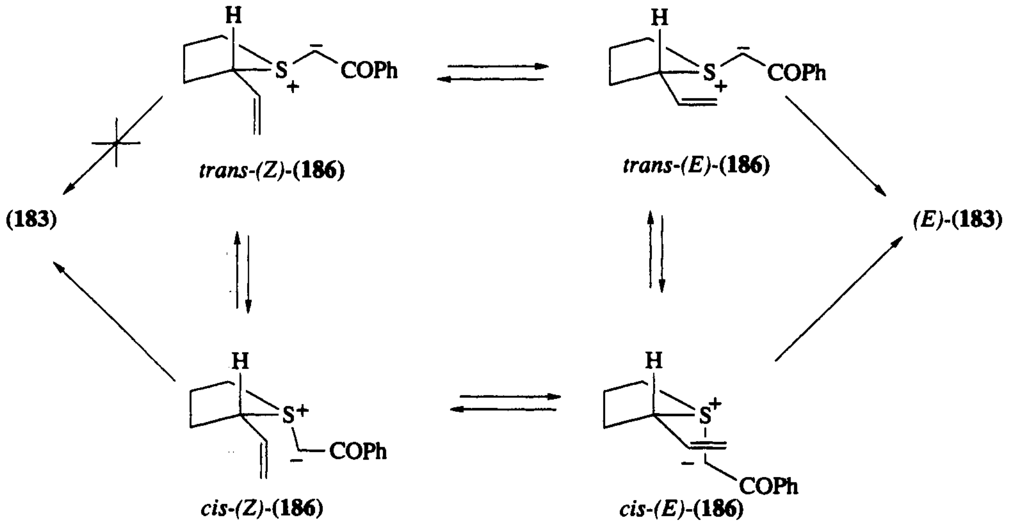
H
S
COPh
trans-(Z)-(186)
trans-(E)-(186)
(183)
(E)-(183)
cis-(Z)-(186)
cis-(E)-(186)

(21)

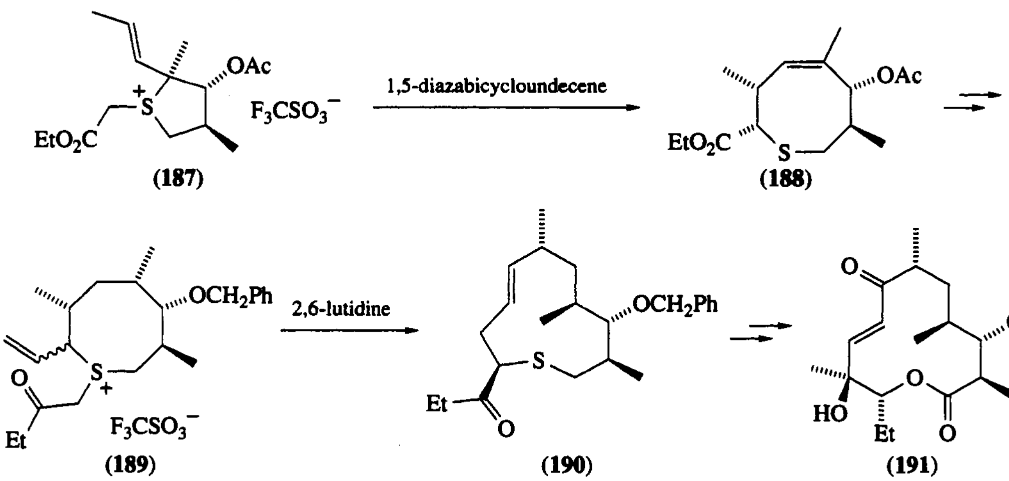
OAc
EtO2C
S
F3CSO3⁻
1,5-diazabicycloundecene
(187)
(188)
OCH2Ph
O
Et
2,6-lutidine
(189)
(190)
OH
HO
(191)

(22)

(*Z*)-thiacyclooctene (**194**) undergoes a successful [2,3] sigmatropic rearrangement to provide the 11-membered (*E*,*Z*)-triene (**196**) (76%) and triene (**195**) (11%), which arises from isomerization of the double bond of the vinyl group into conjugation with the sulfur atom in the intermediate sulfonium salt and subsequent thio-Claisen rearrangement. The third iteration to form the 14-membered ring (**198**) also introduces the alkene in the (*E*)-configuration; however, expansion to the 17-membered ring affords a 2:1 ratio of (*Z*,*E*,*E*,*Z*)-(**197**) and (*E*,*E*,*E*,*Z*)-(**197**), respectively. The rearrangements of Scheme 17 proceed in greater than 80% yield.

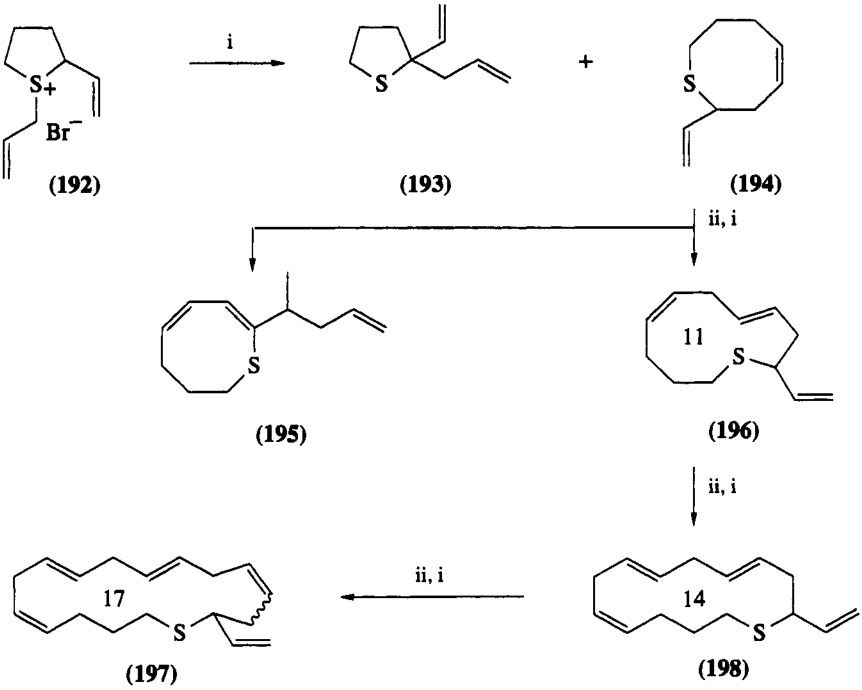

i, KOH, $H_2O$–pentane, 23 °C; ii, $H_2C{=}CHCH_2Br$, $F_3CCH_2OH$

**Scheme 17**

An iterative cyclopentannulation process invokes a series of Claisen rearrangements coupled with polyphosphoric acid mediated ring closures of the Claisen products (Scheme 18). The lithium aluminum hydride reduction of cyclopentenone (**204**) to the allylic alcohol gives the α-alcohol which requires inversion *via* the Mitsunobu procedure to achieve the desired β-configuration. As each successive ring is added, the alkyl chain is shortened by one carbon. Thus, structure (**208**) represents the extent to which annulation may be carried with a five-carbon chain; the numbers in the rings indicate the length of the carbon chain as each ring is formed. The possibility exists for alkylation of the cyclopentenone ring of (**208**) and continued annulation.

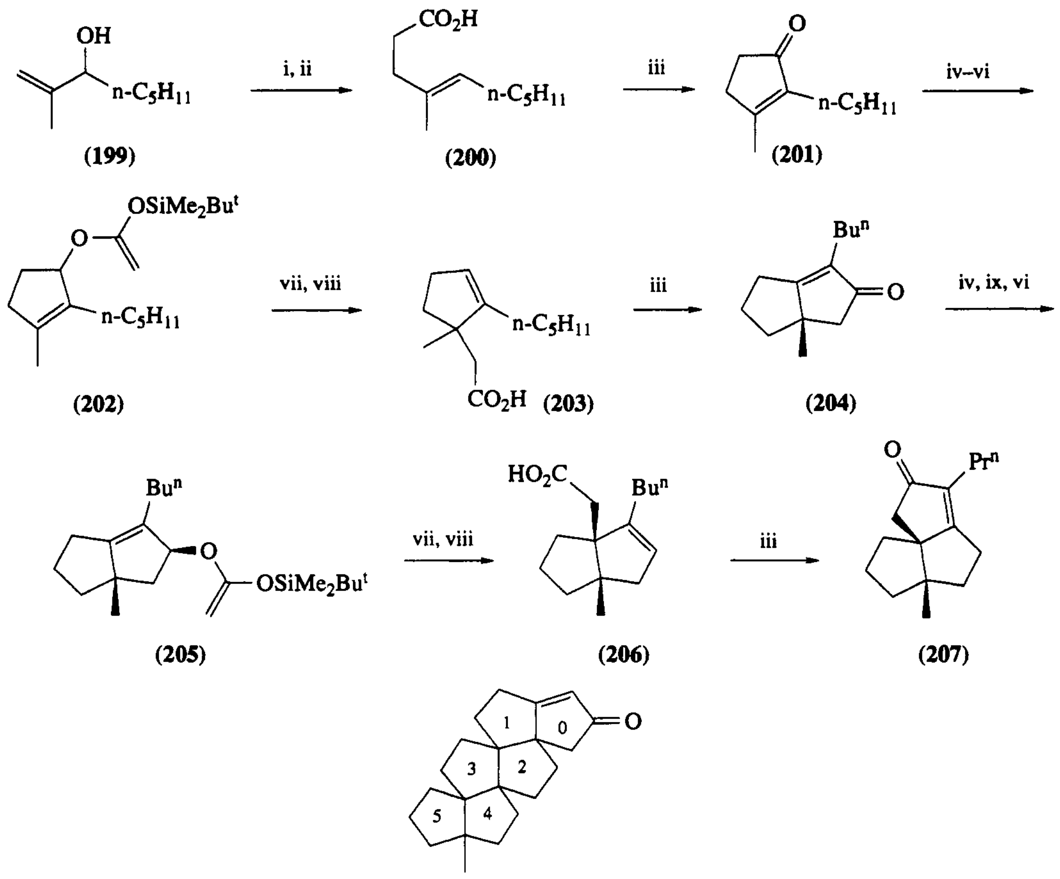

**(208)**

i, $MeC(OEt)_3$, $EtCO_2H$, 135 °C; ii, KOH, aq. MeOH, reflux; iii, PPA, 110 °C; iv, $LiAlH_4$; v, $Ac_2O$, Py, DMAP; vi, LICA, THF/HMPA, $Bu^tMe_2SiCl$, –78 °C; vii, 60 °C; viii, AcOH; ix, AcOH, DEAD, $Ph_3P$, $C_6H_6$

**Scheme 18**

## 7.3.4 REFERENCES

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# 8.1

# Rearrangements of Vinylcyclopropanes and Related Systems

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## 8.1.1 INTRODUCTION

Perhaps it is appropriate that this review be written some 100 years after the report of the first syntheses of cyclopropane derivatives by von Baeyer[1] and Perkin[2] and the formulation of the 'theory of ring strain' by von Baeyer.[1] The chemistry of small ring compounds has risen to prominence in the last 30 years. The popularity especially of the three-membered rings as intermediates in synthetic transformations has been due primarily to their latent energy content and to the almost endless number of chemical transformations in which these compounds and their derivatives can participate. New applications and novel permutations of the basic systems continue to appear at a fast pace. The fascinating chemistry associated with the strain of these intermediates continues to find wide applicability in the field of synthetic methodology and in the total synthesis of complex molecules.

The following discussion will highlight those transformations of vinylcyclopropanes and their derivatives that are selective with regard to regio- and stereo-chemistry. The discussion of such transformations is done from the position of a synthetic practitioner interested in their actual use. Omitted from this chapter are transformations likely to be covered in other parts of this volume (*e.g.* Cope rearrangements of divinylcyclopropanes). A guide to reviews dealing with the preparation of cyclopropane derivatives is provided. At the end of this chapter a survey of useful and general methodologies based on the title transformations is provided along with a tabular compilation of total syntheses featuring these rearrangements as key steps.

## 8.1.2 THEORETICAL AND MECHANISTIC CONSIDERATIONS OF THE VINYLCYCLOPROPANE SYSTEM

### 8.1.2.1 Bonding and Energetics of Cyclopropane Systems

The bonding in cyclopropane requires that the $sp^3$ hybrids be misaligned by approximately 22° from the imaginary line connecting the carbon atoms. The result is the so-called 'bent' bond having about 20% less orbital overlap than the corresponding bond in ethane. The Coulson–Moffitt[3] model (**1**) and the Walsh[4] model (**2**) use three $sp^3$-hybridized $CH_2$ groups and three $sp^2$-hybridized $CH_2$ groups, respectively. The overall hybridization of cyclopropane carbon–carbon bonds is thus $sp^{2.3}$; this greater $p$-character can be invoked in rationalizing the similarity of cyclopropane chemistry to that of alkenes. Because the bond angles are considerably less than the ideal 109.5°, cyclopropane suffers from significant angular (Baeyer) strain, as well as from torsional (Pitzer) strain from eclipsed carbon–hydrogen bonds.

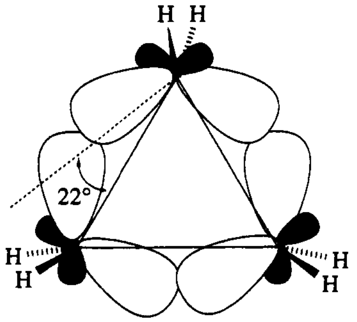

**(1)**

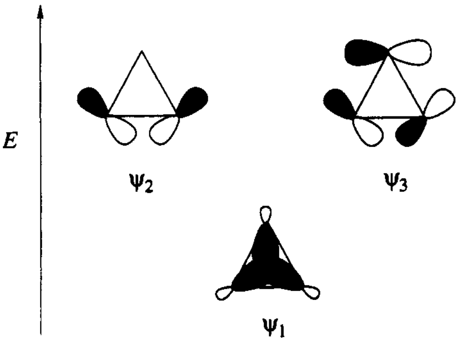

**(2)**

A unique treatment of cyclopropane has been advanced by Dewar,[5] who introduced the concept of $\sigma$-aromaticity, which explains some of the anomalous chemical and physical properties of cyclopropane. The notion of $\sigma$-conjugation implies that three $\sigma$-bonds form a cyclic system of six electrons; thus cyclopropane is aromatic by the $(4n + 2)$ rule. This explanation well accounts for the strain energy of cyclopropane. The actual value (27.5 kcal $mol^{-1}$)[6] is much lower than the predicted value of 104 kcal $mol^{-1}$ (1 cal = 4.2 J), calculated from the C—C—C bending force constants obtained spectroscopically.[5,7] A similar comparison for cyclobutane (antiaromatic by the above notion and the $4n$ rule) underestimated the strain energy.[5] $\sigma$-Aromaticity also accounts for such observations as $^1H$ NMR chemical shifts and the reactivity of cyclopropane toward electrophiles.

The cyclopropane ring is subject to a number of chemical transformations that are only possible because of its unique bonding and high energy content. It is the energy content (27.5 kcal $mol^{-1}$) that drives the diradical opening of cyclopropane, especially so if one (or both) of the resulting radicals becomes a part of a delocalized allylic system, as in the case of vinyl- or divinyl-cyclopropanes. Such resonance stabilization energy of an allylic radical system (12.6 kcal $mol^{-1}$)[8] can be used to explain the lower activation energy for reactions involving vinylcyclopropane (34–55 kcal $mol^{-1}$) compared with the activation energy for reaction resulting from diradical processes that involve only the cyclopropane ring (59–66 kcal $mol^{-1}$).[9–13]

The vinylcyclopropane unit contains the strain energy of the cyclopropane ring (27.5 kcal mol$^{-1}$), and it is this energy content that will be primarily responsible for its reactive options. Thermal ring fission can occur by any one of three mechanisms: [1,5] sigmatropic hydrogen shift, [$2\sigma_s + 2\pi_s$] concerted reorganization to cyclopentene, or a diradical fission followed by further reactions of the diradicals (recombination or hydrogen abstraction). This discussion has received considerable attention in both the mechanistic and the synthetic sense and has been the subject of several recent reviews.[9–21]

The bonding in vinylcyclopropane (**3**) is such that an *s-trans–gauche* conformational equilibrium exists to allow for maximum orbital overlap of the asymmetric component of cyclopropane orbitals with the $\pi$- or $\pi^*$-orbitals of the ethylene unit, as shown in (**3a**). From thermochemical studies it appears that conjugation of an alkene with cyclopropane stabilizes the system by 1.2 kcal mol$^{-1}$.[22,23] The conformational equilibrium for vinylcyclopropane was shown to consist of an *s-trans* minimum (**3b**) and two *gauche* conformers that are equal in energy and destabilized by 1.43 kcal mol$^{-1}$ with respect to the *s-trans* conformation. The barrier to interconversion has been determined to be 3.92 kcal mol$^{-1}$.[24]

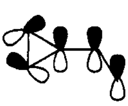

(**3a**)

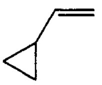

(**3**)

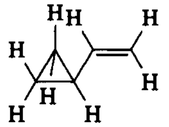

(**3b**)

The details of bonding and spectroscopic properties of cyclopropane derivatives have recently been reviewed.[13,23,25] In addition, the properties and energetics of cyclopropyl cations, anions, radicals, anion radicals and cation radicals have been amply reviewed, and comparisons have been made with their corresponding alkenic counterparts.[13,23,26]

### 8.1.2.2 Reactive Tendencies

To a synthetic chemist the analogy between cyclopropanes and alkenes is indeed an appropriate one. Virtually every reaction that an alkene undergoes has its counterpart in the repertoire of transformations possible with cyclopropanes. Thus conjugation of a cyclopropane to an alkene makes it possible to invoke a number of reaction modes and reactive intermediates that can be compared directly to their alkenic counterparts.

How a particular vinylcyclopropane will be electronically perturbed toward a specific mode of reactivity depends on the substitution of either the cyclopropane or the vinyl portion. All of the principal reactions of vinylcyclopropanes proceed *via* transition states that require stabilization by activating groups and/or release of the ring strain. To understand and to alter the reactive tendencies of substituted vinylcyclopropanes, we must understand the components of the possible transition state and the probable reactive intermediates involved. Table 1 shows the principal reaction pathways of the vinylcyclopropane system in the context of their intermediates, products, and alkenic equivalents.

The cyclopropylcarbinyl radical (**4**), the cyclopropylcarbinyl cation (**5**) and the cyclopropylcarbinyl anion (**6**) all dominate the expected reactivity of vinylcyclopropanes since one of these forms will be expected to be a major contributor to either a radical or a polar transition state. It is important to consider the various reactive subunits in some detail in order to understand the 'big picture' reactivity of a vinylcyclopropane system, especially as perturbed by additional substituents.

The dominant contributor to the reactivity of vinylcyclopropanes in any radical reaction is the form (**4a**), the cyclopropylcarbinyl radical system. The opening of a cyclopropylcarbinyl radical to a butenyl radical is among the fastest radical processes known, with a rate constant of $1.3 \times 10^8$ sec$^{-1}$.[27,28] The various stereoelectronic effects of this rearrangement have been reviewed.[29,30] The structure of (**4a**), deduced from its ESR spectrum[31,32] and in agreement with calculations (STO-36 basis set),[33] is in the bisected conformation shown, predicted to be 1.4 kcal mol$^{-1}$ more stable than its perpendicularly oriented counterpart. Above −100 °C only the butenyl radical (**4b**) can be detected. Substituent effects do not seem to operate here when the substituents are on the cyclopropane (*i.e.* product stabilization).[34] The cyclopropylcarbinyl cation and anion have structures similar to (**4a**), bisected conformations (**5**) and (**6**), respectively. A concise summary of solvolytic and mechanistic data for system (**5**) has recently appeared.[23] Reviews of cyclopropylcarbinyl anions and carbenes are also available.[12,13]

To understand how substituents, especially heteroatoms, will change the reactivity of these systems, the basic transformations shown in Table 1 should be kept in mind. The number of possibilities is limitless, especially upon the recognition that, depending on the substituents, any one of the above contribut-

**Table 1** Principal Reaction Modes of Vinylcyclopropanes

| *Reaction type* | *Reactive intermediate* | *Alkenic counterpart* | *Product(s)* |
|---|---|---|---|
| [1,*X*] Sigmatropic migration | 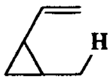<br>[1,5 shift] | 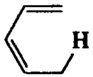 | 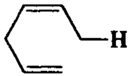 |
| Radical addition | 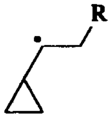<br>**(4)**<br>(cyclopropylcarbinyl radical)<br>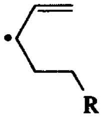 | 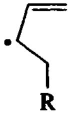 | 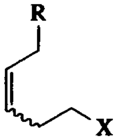<br>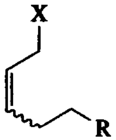 |
| Electrophilic addition | 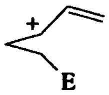<br>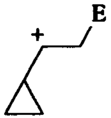<br>**(5)**<br>(cyclopropylcarbinyl cation) | 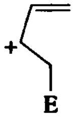 | 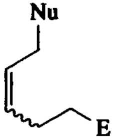<br>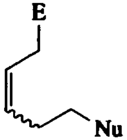 |
| Nucleophilic addition | 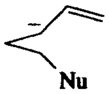<br>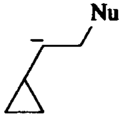<br>**(6)**<br>(cyclopropylcarbinyl anion) | 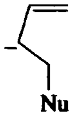 | 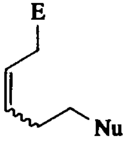<br>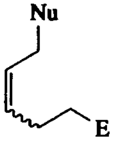 |
| Radical cleavage | 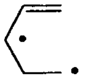 | 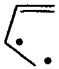 | 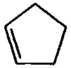<br>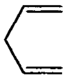<br>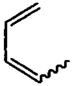 |

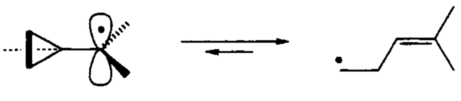

**(4a)** **(4b)**

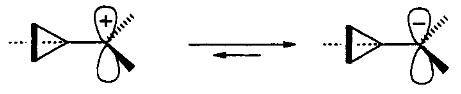

**(5)** **(6)**

ing structures (**4**), (**5**), or (**6**) can become operational on the mode of subsequent rearrangement of the vinylcyclopropane when such rearrangements occur from the homolytic or heterolytic manifolds. The question of concerted rearrangements, or the $[2\pi_s + 2\sigma_s]$ processes, is more difficult to address. Evidence exists on both sides of the argument with no clear-cut rules for or against a universally accepted mechanism. The next section will present the debate concerning this topic in more detail.

In terms of retrosynthetic or disconnective reasoning, cyclopropane is an ideal molecular building block. Because it can be expected to act as an alkene, all of the standard reactions can be performed with it. As it has an extra carbon, however, it serves as a marvelous 'synthetic wedge tool'[12] that can be used to either disrupt existing symmetry or consonance or to introduce it to the target. The concepts of synthetic consonance and dissonance formulated by Evans[35] or the 'cyclopropane trick' analogy of Seebach[36] are ideal in understanding the synthetic utility of cyclopropanes. Thus, for example, equilibrium addition of HBr across 1,3-butadiene yields 1-bromo-2-butene (**7**; equation 1), in which the halide enjoys an allylic relationship with the alkene. Similar addition to a vinylcyclopropane (equation 2) will, on the other hand, produce 1-bromo-3-pentene (**8**) where the same relationship is homoallylic. One can immediately see that the charge parity in the product alkenes has been inverted by the introduction of the odd carbon, and thus inverted reactivity of such alkenes can be expected in subsequent synthetic steps. This criterion is extremely important in synthetic schemes involving long range planning and placement of functional groups. This property of cyclopropane has been exploited in the pioneering efforts of Wenkert, who developed 1,4-dicarbonyl compound synthesis based on the ability of oxycyclopropylcarbinyl systems such as (**9**) to act as pseudo enols (equation 3).[20,37,38]

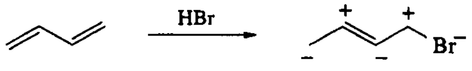

(**7**)

(1)

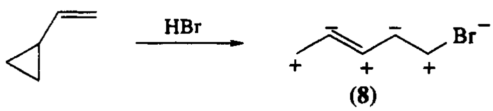

(**8**)

(2)

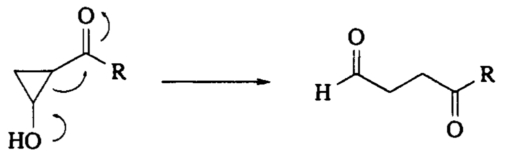

(**9**)

(3)

Finally the introduction of cyclopropane or vinylcyclopropane into organic compounds provides an opportunity to cross the odd/even manifolds in further synthetic steps aimed at the preparation of compounds of increased molecular complexity. Traditionally, any synthesis that involves intermediates with an odd number of atoms is more difficult because proper charge parity or consonance cannot be observed. A cyclopropane unit then functions as a topological operator in those cases where such crossover is desired.[39–41]

The most fascinating features of vinylcyclopropane reveal themselves upon the introduction of not only substituents but heteroatoms. The number of possible permutations of molecular connectivity in a system such as (**10**; Figure 1) is virtually limitless. (Consider the series of connectivity operations for a chemical system composed of an odd number of atoms with an external operator X (Figure 1). Whereas there is only one way to connect A and X, there are now six ways to connect X through the ring opening of the three-membered ring system (**i**) and 120 such different connections in the ring opening of the heterovinylcyclopropane (**ii**) and its interactions with X.[42]) The complexity of connectivities of (**10**) with an external operator X is related through the factorial (!) function and becomes even greater when the presence or the position of substituents in (**10**) or the complexity of X are added for consideration. The success in predicting the reactivity of a system such as (**10**) depends on the nature of component atoms, substituents, electronic perturbations, and the preference of some mechanistic pathways over others. To consider selective transformations of a system that has in excess of 120 possibilities may seem frivolous; fortunately there exists a number of simplifying parameters that provide for surprising selectivity as well as predictability of the rearrangements of any hetero-substituted system of type (**10**).

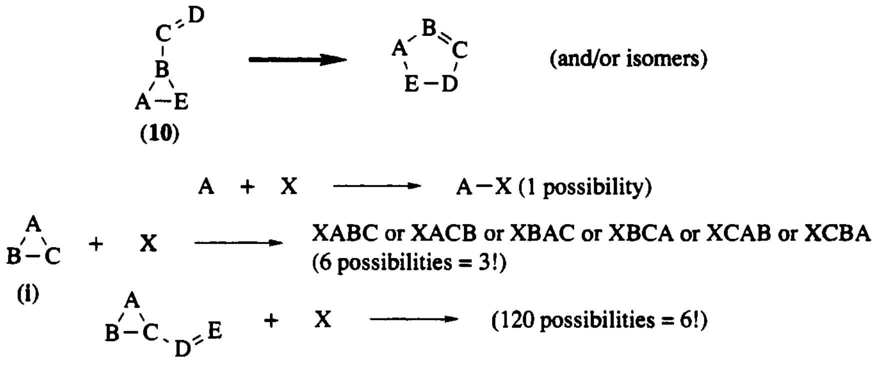

**Figure 1**

The substituent effects have been quantitatively addressed in the context of specific transformations, for example the vinylcyclopropane–cyclopentene rearrangement, and will be discussed in the appropriate sections. The donor/acceptor principles have been applied to thermal, heterolytic and transition metal catalyzed rearrangements and have been reviewed.[16,21] These principles take into account the possible intermediate structures listed in Table 1 and are used to explain the reactivity of a particular cyclopropane system. In the discussion that follows emphasis will be given to the processes that are uniformly selective with regard to regio-, stereo- and enantio-chemical integrity of the products.

### 8.1.2.3 Guide to Preparation

The inherent energy content of the cyclopropane ring demands that the method of introduction of a cyclopropyl subunit itself relies either on highly reactive intermediates or on irreversible or energetically, if not entropically, favored processes. Thus the synthesis of cyclopropane derivatives can be classified into three major categories: 1,3 bond forming sequences (equation 4);[43–45] carbene or carbenoid routes (equation 5);[46–50] and rearrangement pathways (equations 6 and 7).[51–54]

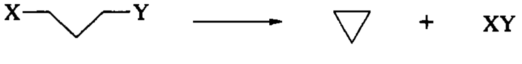

(4)

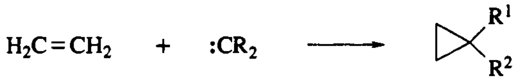

(5)

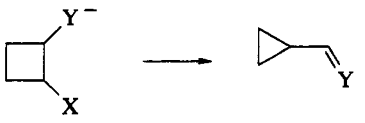

(6)

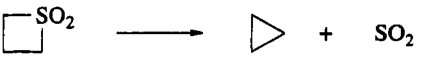

(7)

The procedures for the synthesis of cyclopropane derivatives, especially by the carbenoid route[43,45–49,55–57] or the ylide route (1,3-displacement),[19,20,45,58,59] have been amply reviewed. Equally well reviewed are the reactions of cyclopropanes and their use in synthetic methodology.[9,12,13,15–21,41] For the preparation of the more common cyclopropane derivatives, the use of suitably functionalized cyclopropyl building blocks that are commercially available would be recommended.

Vinylcyclopropanes are most easily prepared by one of the following methods: (i) cyclopropanation of conjugated dienes (inter- and intra-molecular) (equation 8);[41] (ii) permutations of the reactions of allylic ylides with Michael acceptors (equation 9);[19,20,45] (iii) ring opening of oxaspirocyclopentanes (equation 10);[19,20] (iv) additions of vinyl diazo compounds to alkenes (equation 11);[60] (v) indirect methods of formation, *e.g.* Wittig reaction of acylcyclopropanes and rearrangement pathways;[44,45] and (vi) in certain specific cases where the vinylcyclopropanes are immediately reacted further, by thermolysis of 1,4-dienes *via* [1,5] shift sigmatropic reactions.[41,61] The preparations of vinyloxiranes, vinylaziridines, cyclopropylcarbonyls and cyclopropylimines have been reviewed in different contexts (addition of ylides to carbonyl compounds, interaction of azides or diazo compounds with alkenes, *etc.*), but their preparations have not been summarized under a common heading. However, any reference dealing with the use of these compounds will provide a guide to one or more methods of their synthesis.

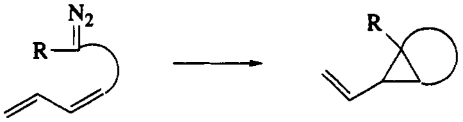

(8)

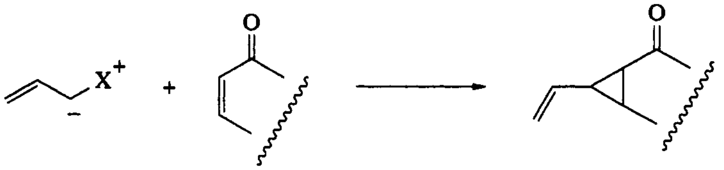

(9)

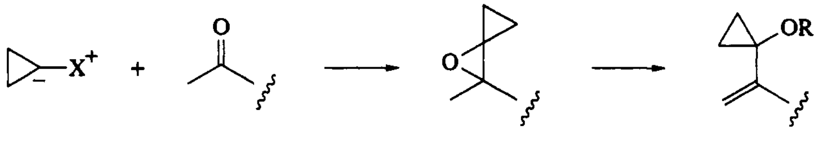

(10)

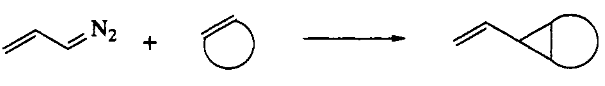

(11)

## 8.1.3 REARRANGEMENTS OF VINYLCYCLOPROPANES

The vinylcyclopropane system is subject to a wide variety of transformations ranging from thermolysis and photolysis to nucleophilic and electrophilic ring opening and transition metal catalysis. A common trait in all such transformations is the release of the ring strain and further reaction of the intermediates thus generated. Until recently the most commonly recognized transformations of vinylcyclopropanes were those resulting from thermally induced bond reorganizations. There are two major pathways available to vinylcyclopropanes on thermolysis: rearrangement to cyclopentene and ring opening to alkenes or dienes. The ability to predict which of these transformations is the most likely depends to a great extent on the substituents and on the precise conformational definitions and the orientation of the $\pi$-system of the vinyl group to the cyclopropane. As will be seen in further discussion, some element of control is available. The thermal cleavage of vinylcyclopropane can in principle provide any of the products depicted in Scheme 1. The analysis of the mechanistic pathways has been reviewed, but a great deal of uncertainty exists regarding the precise distinction between radical, zwitterionic or the concerted nature of these processes.[62]

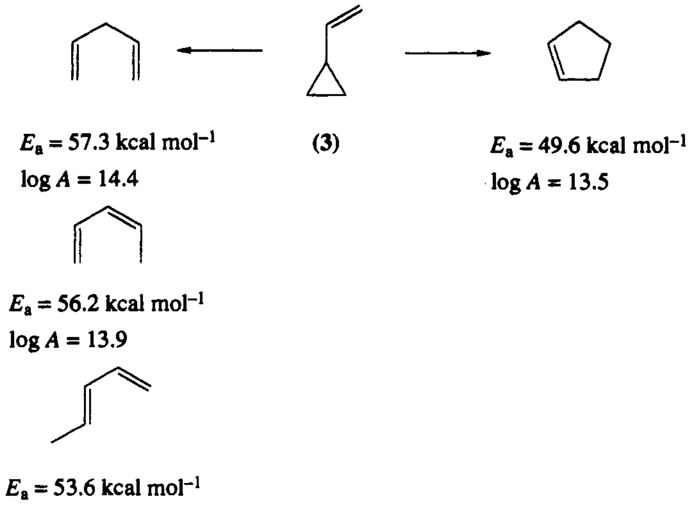
$E_a$ = 57.3 kcal mol$^{-1}$
log $A$ = 14.4
(3)
$E_a$ = 49.6 kcal mol$^{-1}$
log $A$ = 13.5
$E_a$ = 56.2 kcal mol$^{-1}$
log $A$ = 13.9
$E_a$ = 53.6 kcal mol$^{-1}$
log $A$ = 13.0

**Scheme 1**

### 8.1.3.1 [1,5] Shift Pathways

Under some circumstances the [1,5] sigmatropic shift of hydrogen from an alkyl group oriented *cis* to the vinyl group is the lowest energy pathway available to a vinylcyclopropane.[10,11,61] The classic experiments that led to the understanding of this process were performed by Winstein[63] and Frey.[61,64,65] The rearrangement of vinylcyclopropane (**11**) proceeded at 260 °C to furnish only the *cis*-alkene (**12**; equation 12).[64] This rearrangement usually proceeds with an activation energy of 30–35 kcal mol$^{-1}$,[9–11] and is thought to involve a chair-like (**13**) rather than a boat-like (**14**) transition state. Most of these rearrangements are stereospecific, yielding only the *cis*-alkene.

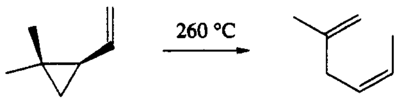

**(11)** **(12)** (12)

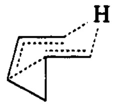

chair: 4.5 kcal mol$^{-1}$ more stable[65, 68]

**(13)**

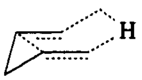

boat

**(14)**

The transformation has been shown to be reversible by careful study of the temperature profiles of flash vacuum pyrolysis of either *cis*-methylvinylcyclopropane (**15**) or diene (**16**; equation 13).[66] Only above 400 °C did the vinylcyclopropane show the expected tendency toward diradical cleavage, a process that requires a substantially higher activation energy (15–20 kcal mol$^{-1}$ higher) than the concerted [1,5] shift. This rearrangement also occurs stereospecifically in endocyclic vinylcyclopropanes such as (**17**; equation 14).[67] The migration of the hydrogen atom is governed by the principles of sigmatropic rearrangements, *i.e.* the pathway of the hydrogen atom is suprafacial.[68] The effect of substituents and their stereochemistry in this rearrangement was investigated.[69]

The fact that suitably sterically biased *cis*-alkylvinylcyclopropanes participate in these types of reactions attests to the ability of the cyclopropane ring to transfer conjugative properties and to act as a pseudo ene unit. Competing pathways of higher order may become dominant in those cases where the transition state is stabilized by extended conjugation, as in the case of (**18**) and its predominant [1,7] hydrogen shift (Scheme 2).[70]

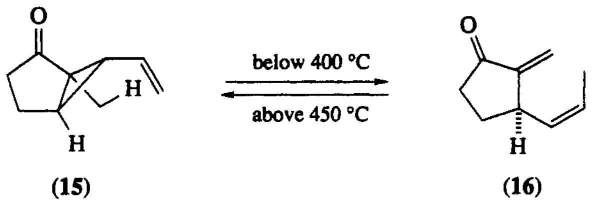

(13)

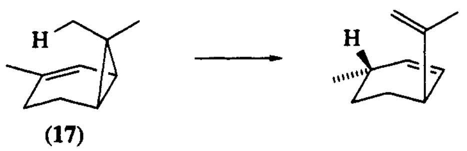

(14)

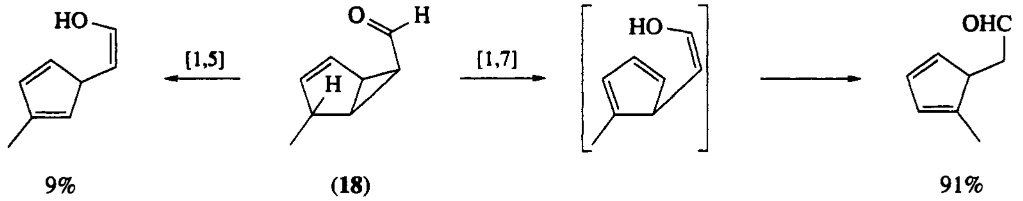

**Scheme 2**

Oxygen, nitrogen and carbon atoms can equally well participate in the 'vinyl' system. Table 2 provides a survey of some synthetically useful rearrangements of this type. In all cases the formation of the alkene is regioselective and in most cases it is stereospecific as well, according to the principles outlined above. The distinction between boat and chair transition states depends on the precise conformation of the reacting system, and this factor can be somewhat manipulated experimentally.

The synthetic utility of this process can be seen by evaluating the examples in Table 2. For example, because the cyclopropane serves as a pseudo alkene and because the [1,5] shift requires a six-membered transition state, it relates conceptually to the Cope and Claisen rearrangements. The $\gamma,\delta$-unsaturated carbonyl compounds in Table 2 are those that would otherwise be obtained *via* Claisen or orthoester Claisen rearrangements, which are normally effected under strongly acidic or strongly basic conditions (Scheme 3).

For compounds of small molecular weight, the [1,5] shift pathway may therefore be superior in the ease of preparation, simplicity and cost. In those instances where 1,4-dienes are easily constructed with the alkene predisposed *cis*, the resulting conversion to vinylcyclopropanes may in fact be superior to the use of carbenoid-based reagents in those instances where the resulting vinylcyclopropanes need not be isolated (Scheme 4). The retro-ene reaction of 1,4-dienes requires temperatures which induce immediate further reactive options in the vinylcyclopropane as soon as it is generated.[66]

Two examples that show selectivity in synthetic applications are the synthesis of cycloheptanone (**19**),[75] which involves ring expansion *via* a [1,5] hydrogen shift, and the synthesis of sarkomycin (**20**; Scheme 5).[66,76] In both of these protocols, the intermediate cyclopropyl ketone or vinylcyclopropane system could be rearranged to dihydrofurans or cyclopentenes respectively by the appropriate adjustments in the experimental conditions.[9,41]

### 8.1.3.2 Vinylcyclopropane–Cyclopentene Rearrangement

The thermal rearrangement of vinylcyclopropanes to cyclopentenes is probably the most recognized mode of reactivity of the vinylcyclopropyl system and one that has received the most attention. Discovered by Neureiter in 1959,[77] it was scrutinized in detail during the 1960s. The fundamental issue at that time revolved around the concerted $[2\pi_s + 2\sigma_s]$ *versus* diradical nature of the rearrangement. No resolution of this question materialized as both mechanisms were invoked to explain specific cases.[9–13] The experimental evidence in the majority of cases studied, however, supports a diradical-type cleavage of the vinylcyclopropane system and a reclosure of the allylic diradical with an average activation energy of about 45 kcal mol$^{-1}$, or approximately 15 kcal mol$^{-1}$ higher than the competing [1,5] shift pathway discussed in the previous section. What is puzzling is the apparent stereospecificity of the rearrangement of optically pure vinylcyclopropanes such as (**21**; equation 15).[78] The presence of 'forbidden' products, (–)-(**23**) and (+)-(**23**), would suggest a biradical mechanism, but the high degree of retention of optical purity

**Table 2** Thermal Rearrangements of *cis*-Alkylvinylcyclopropanes

| *Cyclopropane* | *Temperature* (°C) | *Alkene* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| 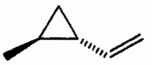 | 300 | 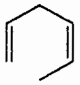 | — | 65, 71 |
| 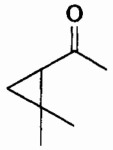 | 150 | 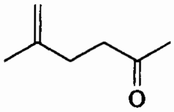 | 89.4 | 72 |
| 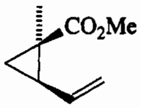 | 280 | 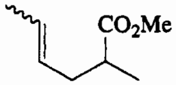 | 82.5 *(trans)*<br>17.5 *(cis)* | 72 |
| 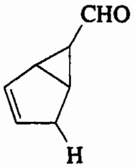 | 120 | 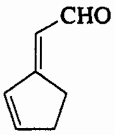 | — | 70, 73, 74 |
| 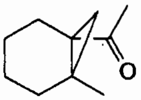 | 200 | 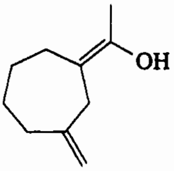 | 80 | 75 |
| 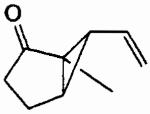 | 360 | 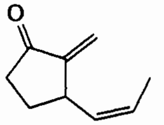 | 80 | 66 |

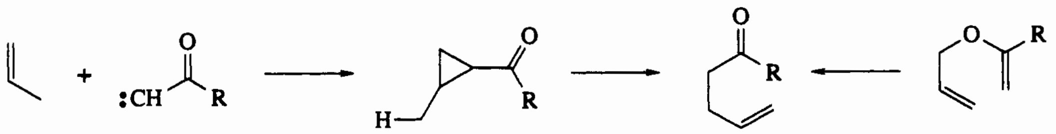

**Scheme 3**

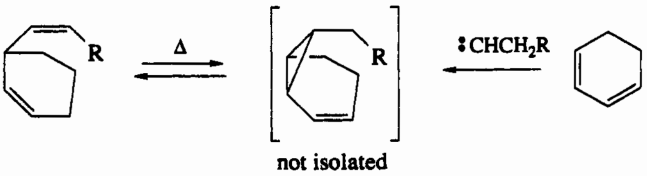

**Scheme 4**

(80.1 ± 0.4% at 60 °C, 68.8 ± 0.5% at 120 °C) would rule out any freely rotating diradical species.[62,78] This observation implies that if the regiochemistry of the rearrangement is controlled, the stereo- and enantio-chemical consequences will follow.

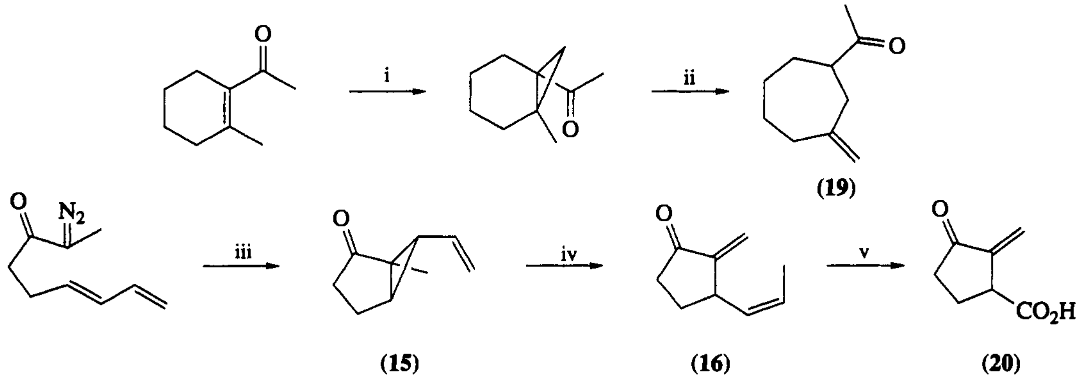

i, $LiAlH_4$; Simmons–Smith cyclopropanation, Collins oxidation; ii, 200 °C, 2 h; iii, $Cu(acac)_2$, PhH, Δ; iv, 450 °C, Pyrex; v, $O_3$, $CH_2Cl_2$, $Me_2S$; Jones oxidation

**Scheme 5**

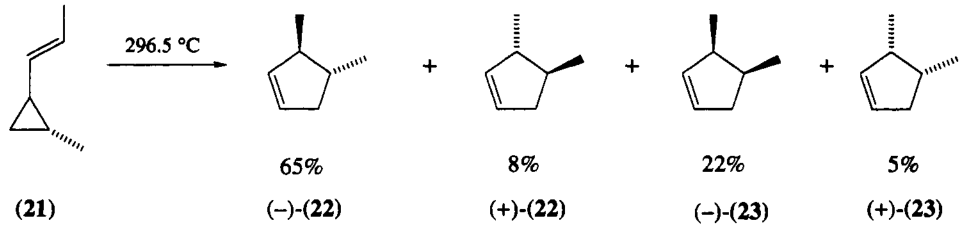

(15)

The molecular topology of this rearrangement is fascinating in its potentially limitless permutations. As indicated in Section 8.1.2.2, any one of the five atoms in the vinylcyclopropyl system may be replaced with almost any other atom (C, Si, P, N, O, S, *etc.*) and the overall reorganization to an unsaturated five-membered ring system remains operational. Thus cyclopropyl aldehydes, imines, ketones and esters yield the corresponding heteroatom analogs of cyclopentene, as do vinyloxiranes, vinylaziridines and vinylthiiranes. When electronegative elements are contained within the vinylcyclopropane framework, the mechanism may change from a diradical to a dipolar one.

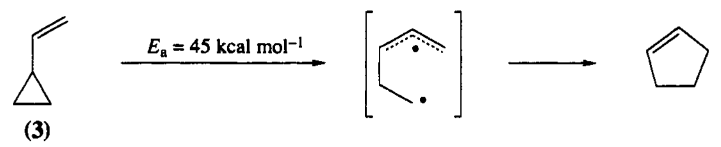

(16)

In the parent system (3), only one bond is activated toward a cleavage that produces an allylic radical (equation 16). In more-substituted cases, however, different degrees of activation may exist, and these will control the rate as well as the regiochemistry of the rearrangement. Some rather drastic differences in the conditions and the rate of the rearrangement can be seen in Table 3.

In general, increased carbon substitution, extended conjugation, or the presence of heteroatoms lowers the activation energy for the reorganization to cyclopentene. In some cases changes in carbon substitution cause the reaction pathway to deviate from the cyclopentene rearrangement entirely. Thus, in the rearrangement of keto vinylcyclopropanes of type (**24**; equation 17), only bond **a** is activated toward radical scission as a result of the electron-withdrawing effect of the carbonyl group.[41,97] No products that would result from scission of bonds **b** or **c** are observed until a higher order of substitution exists at the β-carbon, as in the case of (**26**), where the competition between the tertiary (bond **c**) and the secondary α-keto radical (bond **b**) clearly favored product (**27**) in several instances (equation 18).[98] Once the α-position was substituted, as in (**28**), the normal cyclopentene rearrangement took place (equation 19), indicating that a tertiary α-keto radical is favored over a tertiary radical.[41,99]

Activation by electron-donating heteroatoms accomplishes similar regioselective ring cleavage. It has been shown during the era of mechanistic investigations that heteroatom substitution of the cyclopropane moiety lowers significantly the activation energy of rearrangement, whereas similar substitution on the alkenic unit has little effect.[9] Several examples of this principle are shown in Table 3. In all of the cases,

**Table 3** Substituent Effects in the Vinylcyclopropane–Cyclopentene Rearrangement

| *Vinylcyclopropane* | *Cyclopentene* | $E_a$ (kcal mol$^{-1}$) | *Ref.* |
|---|---|---|---|
| 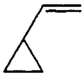 | 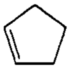 | 49.7 | 79–81 |
| 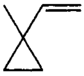 | 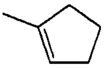 | 49.4 | 82, 83 |
| 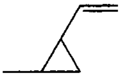 | 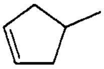 | 48.7 | 65, 83 |
| 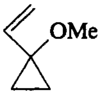 | 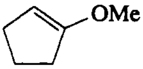 | 44.7 | 20, 84 |
| 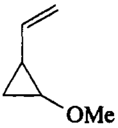 | 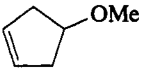 | 38.7 | 20, 84 |
| 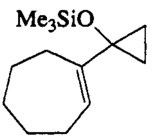 | 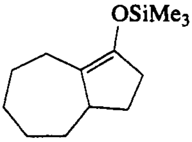 | 42 | 85 |
| 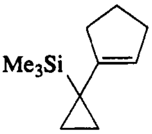 | 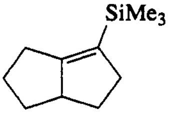 | — | 81 |
| 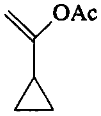 | 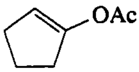 | — | 86 |
| 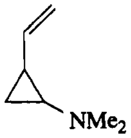 | 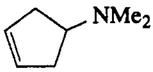 | 31.2 | 87 |
| 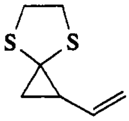 | 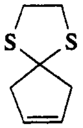 | — | 88 |
| 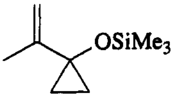 | 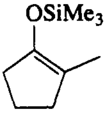 | — | 89 |
| 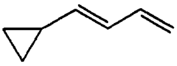 | 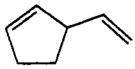 | 44.5 | 11 |

**Table 3** *(continued)*

| *Vinylcyclopropane* | *Cyclopentene* | $E_a$ (kcal mol$^{-1}$) | *Ref.* |
|---|---|---|---|
| 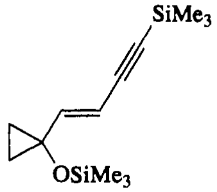 | 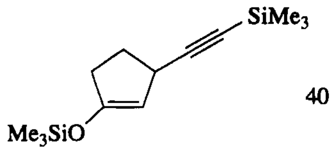 | 40.5 | 90 |
| 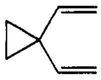 | 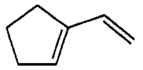 | 39.6 | 91 |
| 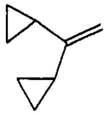 | 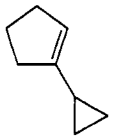 | 51.1 | 92 |
| 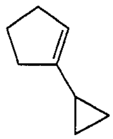 | 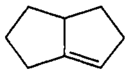 | 51.3 | 92 |
| 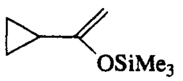 | 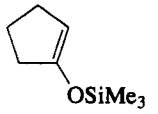 | 51.3 | 15, 83, 93 |
| 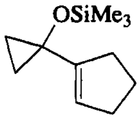 | 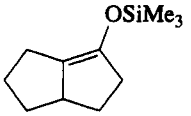 | 44.3 | 83 |
| 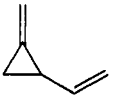 | 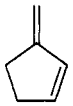 | 25.8 | 94 |
| 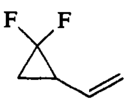 | 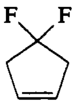<br>a | 41.5 | |
| | 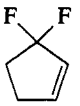<br>b<br>a:b = 4:96 | 37.9 | 95, 96 |

the cleavage of the cyclopropane ring occurs regioselectively in such a way as to provide a diradical that is contained in an allylic system on one side and α to the heteroatom on the other, or both, as shown in equations (20) and (20a). When directly attached to the cyclopropane, oxygen, sulfur and nitrogen all exhibit the accelerating effect, whereas silicon retards the rearrangement.[15,81] Fluorine has been shown to destabilize vinylcyclopropanes by 12–14 kcal mol$^{-1}$.[95,96]

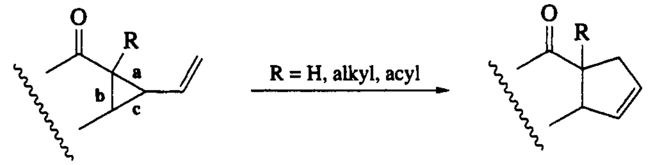
O
R
a
b
c
R = H, alkyl, acyl
O
R

**(24)** **(25)** (17)

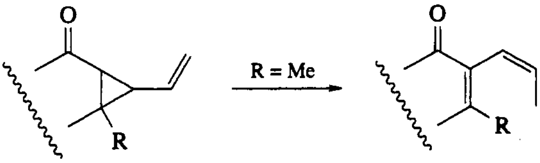

**(26)** **(27)** (18)

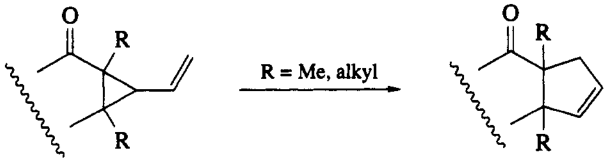
O
R
R
R = Me, alkyl
O
R
R

**(28)** **(29)** (19)

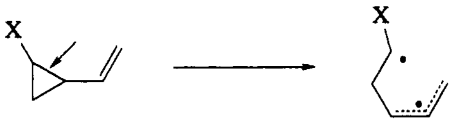

(20)

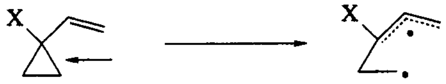

(20a)

The following examples further illustrate the selectivity that can emerge from this analysis (Scheme 6). Divinylcyclopropane (**30**) underwent exclusively the cleavage of the siloxy-substituted ring[83] with activation enhancement of *ca.* 5 kcal mol$^{-1}$, whereas the silyl-substituted counterpart (**31**) preferred the cleavage of the carbon-substituted ring due to the decelerating effect of silicon.[81]

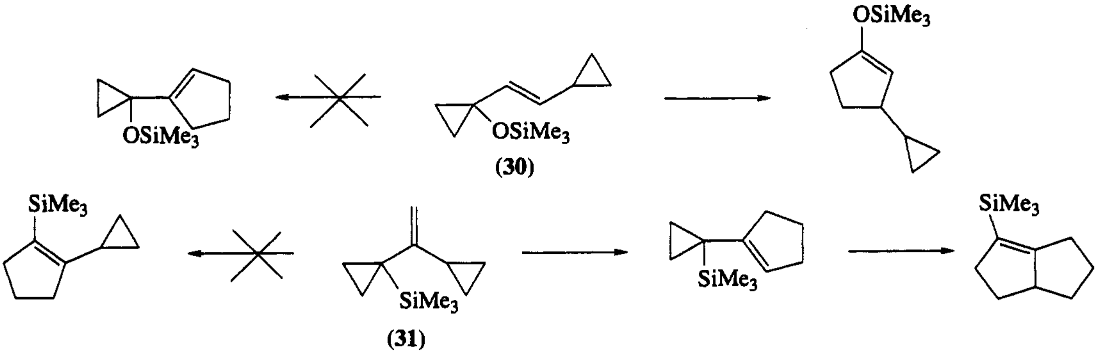
OSiMe3
OSiMe3
(30)
OSiMe3
SiMe3
SiMe3
(31)
SiMe3
SiMe3

**Scheme 6**

Examples of rearrangements where odd electron species may be intermediates include the concerted (and stereospecific) rearrangements of alkoxides such as (**33**), generated from β-chloro esters (**32**) with *n*-butyllithium at low temperature[100] and the cation radical accelerated rearrangement of (**35**; Scheme 7).[101] The exact mechanism of either of these transformations is not known. A concerted ring closure of an anion radical (**37**) was proposed in the former case, whereas either a stepwise isomerization of a trimethylene cation radical (**38**) or a concerted rearrangement involving an odd electron pericyclic transition state was invoked for the latter. The rate enhancement in the rearrangements of vinylcyclopropanes such as (**35**) has been estimated to be $>10^9$ as compared to the thermal reorganization that occurred only above 200 °C.[101] It should be noted that odd electron species do not subscribe to the normal rules concerning symmetry forbidden reactions and that ample precedent is available concerning accelerating effects in such reactions by creating odd electron intermediates.[102]

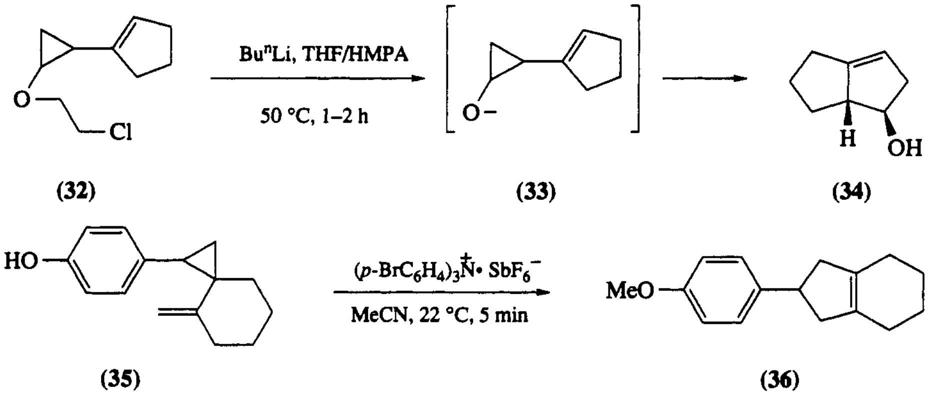

Scheme 7

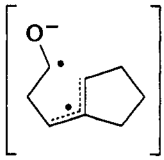

(**37**)

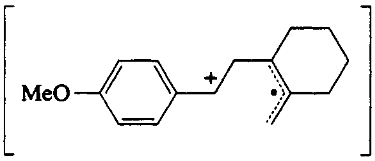

(**38**)

A similar acceleration has most recently been observed in the rearrangement of vinylcyclopropanes of type (**39**; Scheme 8).[103] This fluoride-mediated vinylcyclopropane–cyclopentene isomerization proceeds at −78 °C to give (**40**) in 85% yield; this is to date the mildest condition available. Two possible intermediates, the enolate anion (**39a**) or the diradical anion (**39b**), may be responsible for such acceleration in analogy to the enolate anion accelerated divinylcyclobutane rearrangement recently reported.[104] The mechanism of this transformation is unclear but may involve anion acceleration similar to that observed in the rearrangement of sulfonyl anions derived from (**42**; Scheme 8).[105] By comparison the thermolysis of (**39**) produced exclusively the *endo* isomer of (**41**) at 580 °C.[103]

Most recently, a vinylcyclopropane rearrangement that appears to involve anion acceleration was reported to take place during an interesting [4 + 2 − 1] annulation, depicted in Scheme 9. Following the [4 + 2] cyclization of the thiocarbonyl compound, the [2,3] sigmatropic ring opening of the anion generates a thioenolate anion-terminated vinylcyclopropane, which rearranges at low temperature and is trapped with an alkylating agent. The stereoselectivity of this ring closure was reported to favor *syn* substitution by 13:1.[106] This process is similar in concept to the rearrangement of vinylcyclopropane (**39**).

Photochemical rearrangements of vinylcyclopropanes have been reported under both direct and sensitized conditions; the field has been reviewed on several occasions.[9,12,14] In 1962 the investigation of the addition of photochemically generated methylene diradical to butadiene led to speculations regarding the possibility of direct 1,4-addition of a carbene to a diene.[107] Such direct additions, however, have been found operating only in the cases of sterically constricted dienes such as (**43**) or (**44**).[108] A photochemical vinylcyclopropane–cyclopentene rearrangement taking place during the reaction can account for the observed products. The sensitized conditions generate triplet species with $E_T = 80$ kcal mol$^{-1}$, far above the activation barrier for the vinylcyclopropane cleavage, and thus promote other, competing pathways. Both diradical and zwitterionic species (and sometimes carbenes) have been proposed as intermediates in

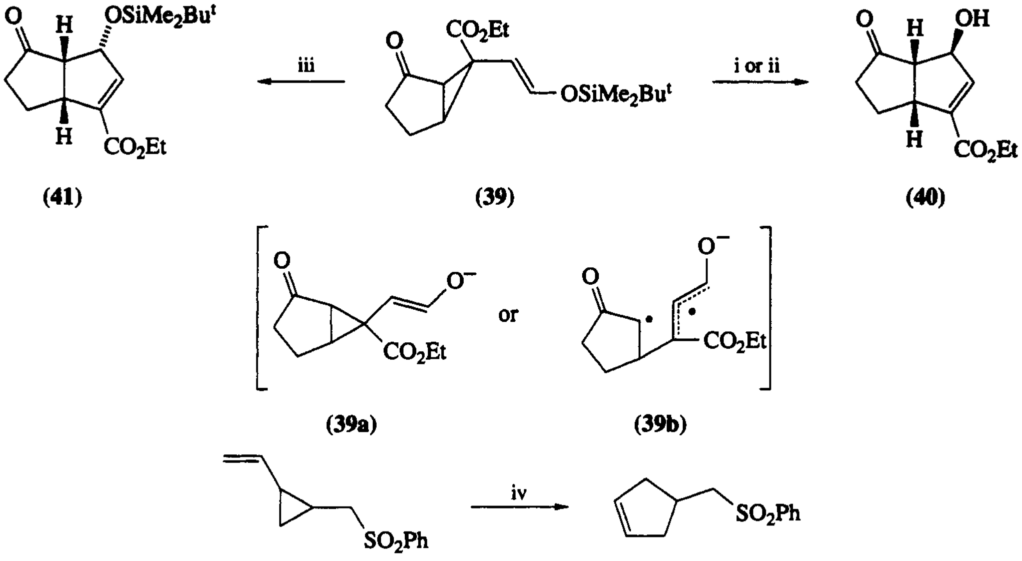

**(41)** **(39)** **(40)**

**(39a)** **(39b)**

**(42)** 97%

i, KF, 18-crown-6, THF, –78 °C; ii, $Bu^n_4NF$, $H_2O$, THF, –10 °C; iii, 580 °C, $PbCO_3$/Vycor; iv, $Bu^nLi$, THF, HMPA, –78 to –30 °C

**Scheme 8**

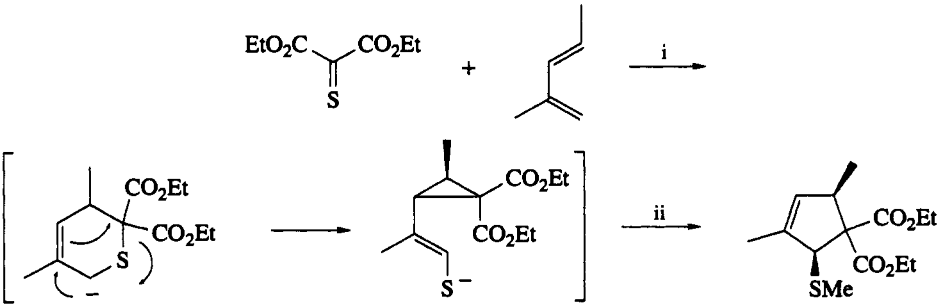

i, $LiNPr^i_2$ or $KN(Me_3Si)_2$, THF, –78 °C; ii, MeI

**Scheme 9**

transformations of this type.[109] The example in Scheme 10 illustrates such intermediates.[109] Photolytic rearrangements of vinylcyclopropenes such as **(45)** lead to cyclopentadienes *via* diradical recombination, bicyclo[2.1.0]pentane diradicals or carbene intermediates (equation 21).[110]

Rearrangements of endocyclic vinylcyclopropanes under direct irradiation lead to useful yields of ring-contracted products as the examples in Table 4 illustrate. Some regioselectivity is observed in the rearrangements of unsymmetrical vinylcyclopropenes, which lead to cyclopentadienes **(46)** and **(47)** (equation 22).[114] A similar rearrangement of a cyclopropene ester, where the carbonyl serves as a vinyl equivalent, produced furan **(48)** with similar regioselectivity (equation 23).[115] For additional examples of vinylcyclopropene rearrangements consult Section 8.1.7.

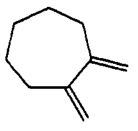

**(43)**

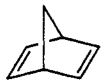

**(44)**

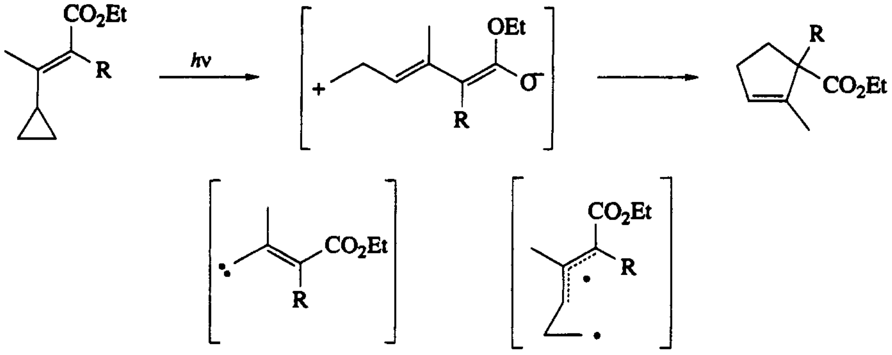
CO2Et
R
hv
OEt
+
O⁻
R
R
CO2Et
CO2Et
R
CO2Et
R

**Scheme 10**

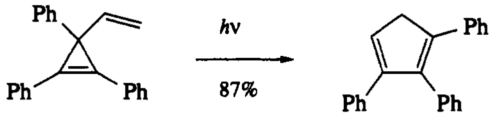
Ph
Ph
Ph
hv
87%
Ph
Ph
Ph

**(45)**

(21)

**Table 4** Photochemical Vinylcyclopropane–Cyclopentene Rearrangements

| *Vinylcyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 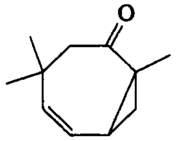 | *h*v, MeOH | 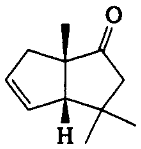 | 56 | 111 |
| 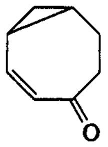 | *h*v, acetone | 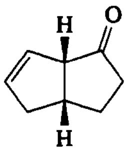 | 82 | 112 |
| 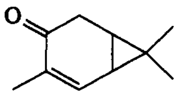 | *h*v, TFA | 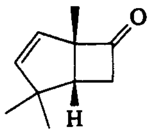 | — | 113 |
| 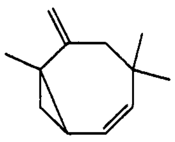 | *h*v, MeOH | 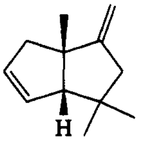 | 56 | 112 |

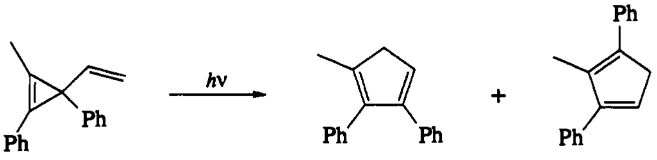
Ph
Ph
hv
Ph
Ph
+
Ph
Ph

**(46)** 2.5:1 **(47)**

(22)

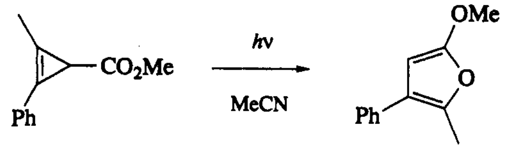

**(48)**

(23)

The photochemical transformations of vinylcyclopropanes are of mechanistic interest, but because of the high energy of the reaction intermediates, especially in the triplet manifold, practical applications are scarce. The regio- and stereo-selective aspects are, however, similar to those of the thermal processes. Additional methods that provide for the cyclopentene rearrangement involve the degenerate photochemical rearrangements observed by Wender during meta-photocycloaddition of arenes and alkenes and utilized extensively in the synthesis of triquinane sesquiterpenes.[41,116,117] (See Section 8.1.9 or ref. 41 for a recent summary.)

Transition metal catalyzed rearrangements have received considerable attention because of the mild conditions required for these rearrangements. The interaction of the vinylcyclopropanes with metal catalysts is accompanied by ligand insertion in most cases. This topic has recently been reviewed.[118] Rhodium-catalyzed rearrangements of vinylcyclopropanes (**49**) have been studied (Scheme 11),[119,120] and found to yield diquinanes (**50**) in an apparent $[2\pi_s + 2\pi_a]/[2\pi_s + 2\sigma_a]$ process.[119] It appears that the presence of an additional ligand in vinylcyclopropane (**49**) is necessary for the rearrangement.[119,121,122] In contrast, both isomers of vinylcyclopropane (**51**) give diene (**52**) in a process involving stereospecific β-hydride elimination (equation 24). No cyclopentene formation was observed. In one case, a carbonyl was thought to assume the function of an additional alkenic ligand. Vinylcyclopropane (**53**) gave exclusively triquinane (**54**; equation 25), whereas the pyrolytic conditions led to a mixture of *cis-anti-cis* and *cis-syn-cis* isomers in a 6:1 ratio.[122] Few examples exist where simple vinylcyclopropanes (without the additional ligand) rearrange to cyclopentenes; rather they rearrange to dienes. In the case of divinylcyclopropylethylene (**55**) it can be argued that the nonparticipating cyclopropane serves the function of this additional ligand (equation 26).[121]

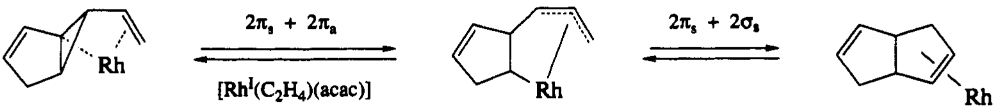

**(49)** **(50)**

**Scheme 11**

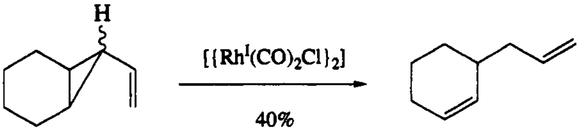

**(51)** **(52)**

(24)

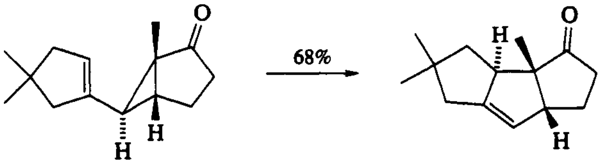

**(53)** **(54)**

(25)

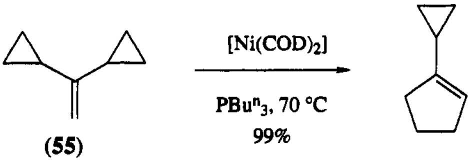

**(55)**

(26)

The presence of additional unsaturation in vinylcyclopropane (**56**) was invoked as an explanation for its facile nickel(0)-catalyzed rearrangement to vinylcyclopentene (**57**) in excellent yield (Scheme 12).[121] The geometry of the diene in (**56**) turned out not to be important as the ring opening led to the equilibration of (*E*)- and (*Z*)-isomers prior to the final closure. The reaction was therefore stereoselective, but cyclopentene (**57**) suffered, in some cases, isomerization to (**58**) under the reaction conditions.[121]

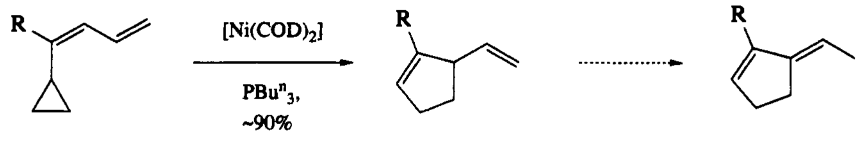
R
[Ni(COD)2]
PBun3,
~90%
R
R

(**56**) (**57**) (**58**)

R = Me, alkyl, Ph

**Scheme 12**

The copper-catalyzed rearrangement of vinylcyclopropane (**59**) was thought to involve the π-allyl systems (**60a**) and (**60b**) (Scheme 13). The regioselectivity of this rearrangement was only two-fold; however, both enol ethers (**61**) and (**62**) can be hydrolyzed to the 1,4-dicarbonyl system (**63**). Platinum- and rhodium-catalyzed decomposition of (**59**) yielded dienes.[123]

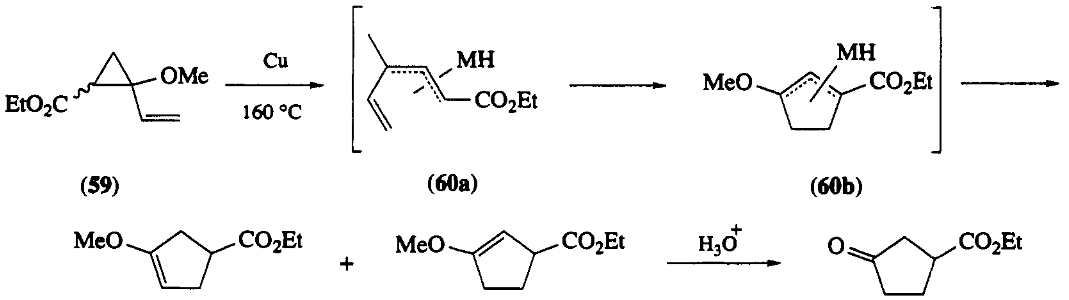
OMe
EtO2C
Cu
160 °C
MH
CO2Et
MH
MeO
CO2Et
(59)
(60a)
(60b)
MeO
CO2Et
+
MeO
CO2Et
H3O+
O
CO2Et

(**61**) 2:1 (**62**) (**63**)

**Scheme 13**

Palladium-catalyzed rearrangements of dienylcyclopropanes have also been reported. Vinylcyclopropane (**64**) gave cyclopentene (**65**) without regard to the (*E*)/(*Z*) composition of the diene (equation 27).[124] Similar results with respect to (*E*) and (*Z*) mixtures were also observed in the more-substituted case of (**66**) with moderate stereoselectivities (3:1) observed upon reclosure (equation 28). It has been suggested that the palladium-catalyzed rearrangement is in fact a nucleophilic-like opening followed by reclosure. Such transformations are discussed in Section 8.1.3.4 in the context of the stepwise opening of activated vinylcyclopropanes with iodide and other nucleophiles.

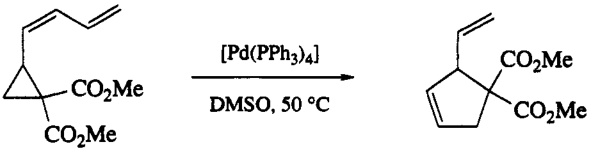
CO2Me
CO2Me
[Pd(PPh3)4]
DMSO, 50 °C
CO2Me
CO2Me

(**64**) (**65**) (27)

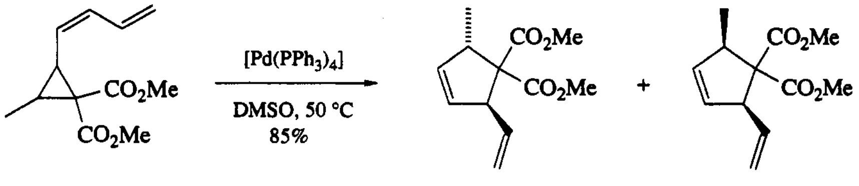
CO2Me
CO2Me
[Pd(PPh3)4]
DMSO, 50 °C
85%
CO2Me
CO2Me
+
CO2Me
CO2Me

(**66**) (**67**) 3:1 (28)

In summary, the regio- and stereo-chemical course of the vinylcyclopropane–cyclopentene rearrangement can be predicted by analyzing the donor/acceptor qualities of the substituents and by considering the nature of the intermediates in the incipient ring closures. It can be concluded that, based on the discussion above, only one bond in a vinylcyclopropane system will be predominantly activated toward regioselective cleavage. The stereochemical outcome will then be governed by the energetics of the corresponding substituted cyclopentene, which is formed from a cisoid conformation of a biradical such as (**68**; equation 29). It should be noted that, if such a conformation cannot be reached for steric reasons (the size of $R_2$ >> $R_3$, for example), then processes other than cyclopentene formation will predominate.[125] In functionalized cyclopentenes the stereoselectivity would be expected to be dominated by the *endo* effect, which governs the radical closures.[41,126,127] In fused systems, either the kinetic *endo* effect or the relative energetics of *cis versus trans* fusion will determine the stereochemistry at the ring junction. In the field of polycyclopentenoids, for example, this issue is relatively unimportant as all ring junctions prefer to be in the thermodynamically more stable *cis* form.

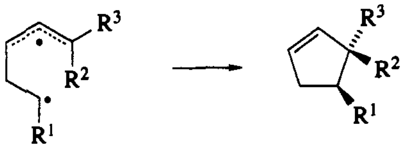

**(68)** **(69)**

(29)

The stereochemistry of those rearrangements involving concerted processes can be rationalized with the results of Baldwin's experiment[78] for those vinylcyclopropanes that contain no resident chirality other than at the centers that become diradicals. Rearrangements of optically active vinylcyclopropanes that contain set chirality at centers remote to the rearrangement site, such as vinylcyclopropanes (**70**; equation 30) and (**72**; equation 31), lead to the retention of 100% optical purity in the products.[128,129] Although the enantioselective preparation of cyclopentenes by this method is not routine, save isolated examples,[41] it should be expected that in optically pure vinylcyclopropanes of type (**74**; equation 32), the rearrangement would proceed with complete retention of optical configuration since center **b** is not involved in the rearrangement. The increased use of such processes awaits the development of a suitable methodology for the generation of optically pure vinylcyclopropanes.

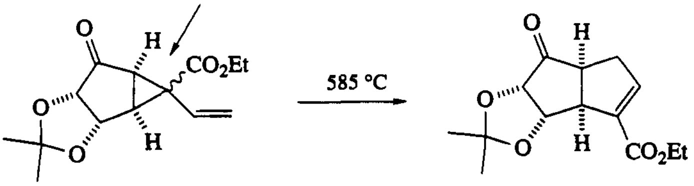

**(70)** **(71)**

(30)

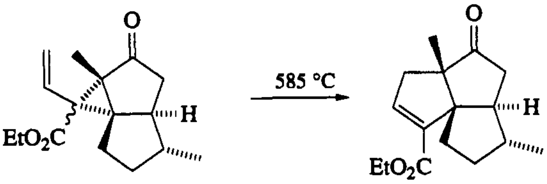

**(72)** **(73)**

(31)

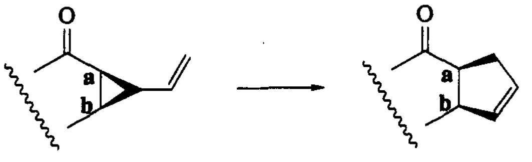

**(74)**

(32)

A summary of the synthetic methods based on the vinylcyclopropane rearrangements appears in Section 8.1.8. The listing of total syntheses featuring this rearrangement and its heteroatom variants is compiled in Section 8.1.9.

### 8.1.3.3 Ring Expansions of Oxyvinylcyclopropanes

Vinylcyclopropanes substituted with oxygen (or sulfur or selenium) are susceptible to ring expansion to the corresponding cyclobutanone derivative in addition to the expected cyclopentene rearrangement (Scheme 14). The oxycyclopropane can be viewed as a pseudo enol in those interactions with electrophiles that would involve the vinyl group. The resulting cyclopropylcarbinyl system (**75**) will interact with nucleophiles either directly (path a) or through ring opening (path b; Scheme 15). The participation of either bond **a** or **b** in this opening will depend on the precise conformation of (**75**), which is in turn dependent on the nature of the cation and its solvation, as well as on the tendency of the cyclopropylcarbinyl cation (**75a**) to unravel. When proper orbital overlap exists, one of these bonds will participate in opening the cyclopropane to yield (**77**) or it will act as an internal nucleophile in its migration (and concomitant ring expansion to **78**). This latter process has been developed and extensively utilized by Trost in spirocyclobutanone annulation.[19,20] A less common reaction of oxyvinylcyclopropanes would involve normal electrophilic opening of the oxycyclopropane, as, for example, that occurring in the generation of the β-stannyl enone (equation 33).[15]

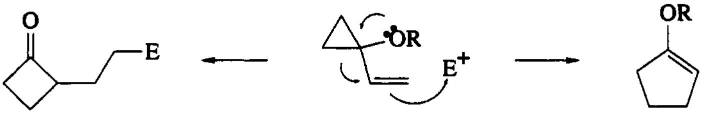

Scheme 14

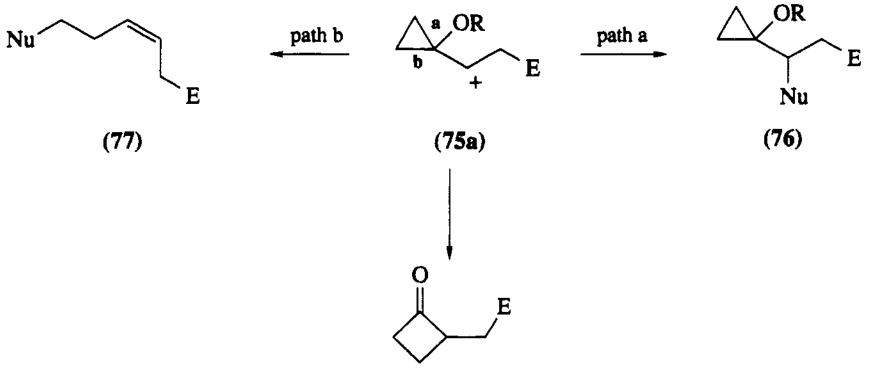

(**77**) (**75a**) (**76**)

(**78**)

Scheme 15

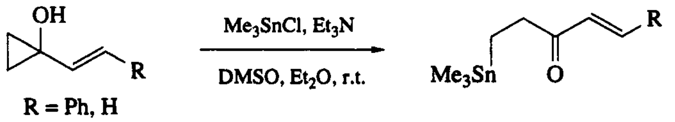

(33)

The ylide-based methodology of oxaspirocyclopentanes in synthesis provided the elements of control shown in Scheme 14. The oxaspirocyclopentane system (**79**), prepared from the corresponding cyclopropyl and carbonyl compounds, can be eliminated by a variety of methods to vinylcyclopropane (**80**), which can be used in cyclopentene annulation or be rearranged to spirocyclobutanone (**81**; Scheme 16).[20] When treated with acid, vinylcyclopropane (**80**) generates cations of type (**75b**), which collapse to cyclobutanones whose stereochemistry depends on the precise conditions and the solvating properties of the acid used. For example, treatment of epoxide (**82**) with protic acids resulted in approximately 80:20 selectivity in the formation of (**84a**; Scheme 17).[130] When the equilibrium of (**83a**) and (**83b**) was retarded by the use of counterions that accelerated the migration by rendering the oxygen more electron releasing (and also prevented the rotation leading to the more stable conformer **83b**), only (**84a**) was observed. The rearrangement occurs with inversion of configuration at the migrating center; this would be consistent with a thermally allowed [2*a* + 2*a* + 2*s*] concerted process, which has been invoked to explain the formation of cyclobutanones during pyrolysis of vinylcyclopropanols such as (**86**; equation 34).[15,20] The stereochemistry of this rearrangement has been shown to involve the intramolecular *cis* addition of H (or D) to the double bond *via* the transition state (**87**), which is not consistent with a concerted process.[131,132]

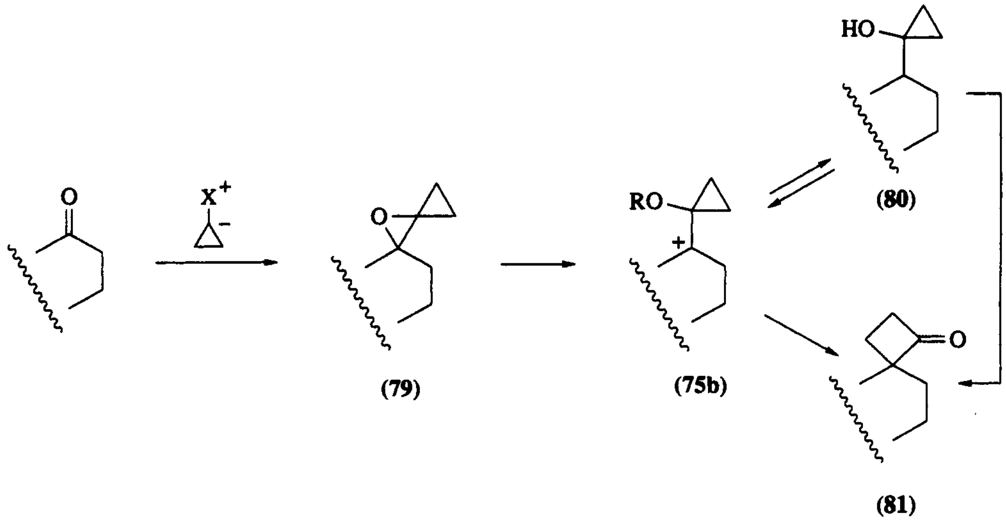
O
X+
O
RO
+
HO
(79)
(75b)
(80)
(81)
O

Scheme 16

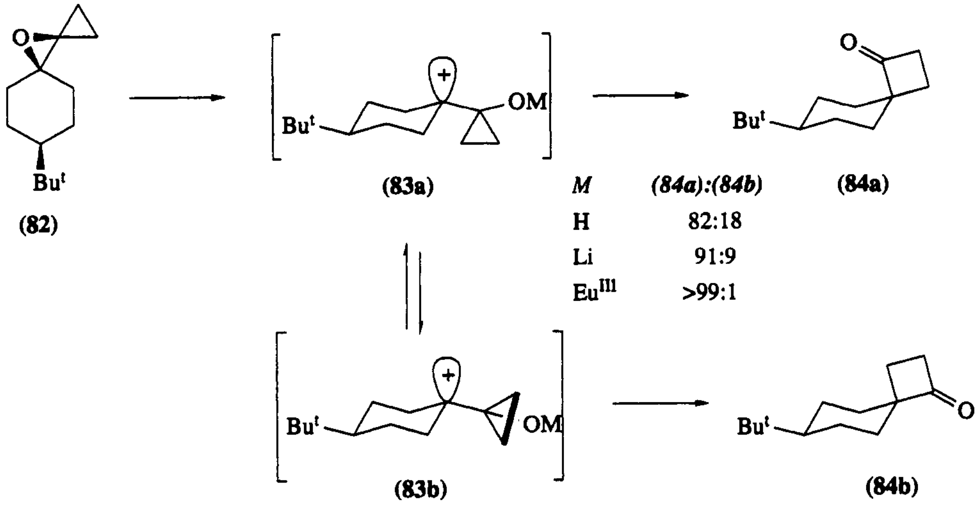
O
Bu^t
(82)
Bu^t
OM
(83a)
O
Bu^t
(84a)
Bu^t
OM
(83b)
Bu^t
O
(84b)

| *M* | *(84a):(84b)* |
|---|---|
| H | 82:18 |
| Li | 91:9 |
| Eu$^{III}$ | >99:1 |

Scheme 17

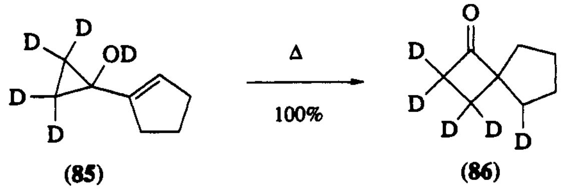
D
D
OD
D
D
Δ
100%
O
D
D
D
D
D
(85)
(86)

(34)

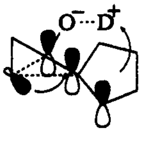

(87)

Finally the stereochemistry of cyclobutanone is subject to complete control by adjusting the experimental conditions of the reaction, which can lead to either a single or a double inversion at the migrating center. Thus $LiBF_4$-catalyzed opening of epoxide (**88**) leads (through inversion) to cyclobutanone (**89**), whereas phenyl selenide opening (inversion) followed by oxidation to a selenoxide leaving group leads, through a second inversion, to the diastereomer (**91**) (Scheme 18).[20,133] Table 5 illustrates the utility of cyclobutanone annulation in the preparation of spirocyclic ketones from oxygen- and sulfur-substituted vinylcyclopropanes.

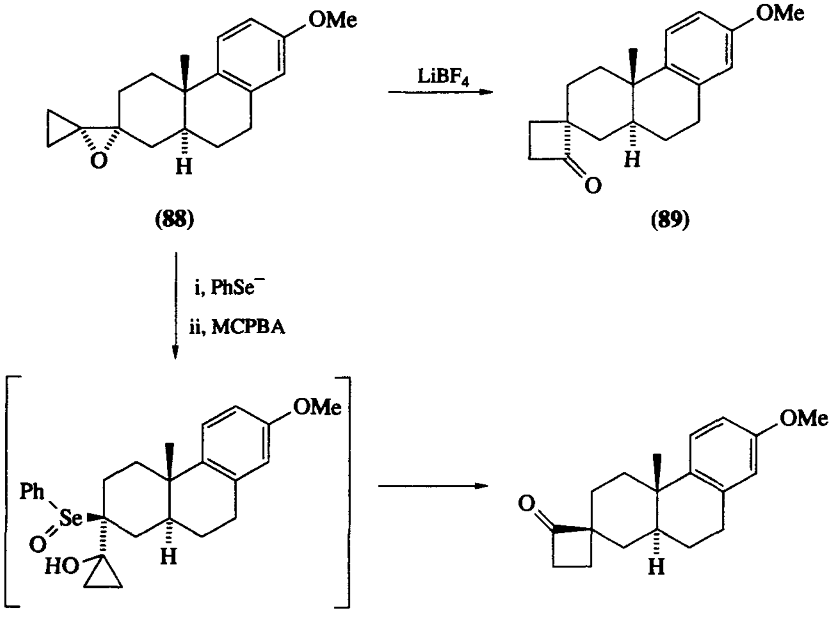

**Scheme 18**

Vinylogous modes of this rearrangement are also possible. Complex systems can be attained by utilizing a built-in electrophile in an intramolecular ring expansion/alkylation, as shown in equation (35). This kind of cyclization is applicable to seven- and eight-membered carbocyclic ring synthesis and proceeds with approximately 12:1 stereoselectivity, which is due to the more stable, parallel conformation depicted in equation (35).[140]

Thus by recognition of the reactive options of the basic system (**75**) and the possibilities involving either further conjugation of functional groups or substitution possibilities, virtually limitless methodology is available. Recent reviews of this topic[15,20] point out the vast number of ring systems and substitution patterns available.

### 8.1.3.4 Reactions with Nucleophiles (Normal and Vinylogous Modes)

When a vinylcyclopropane is substituted with an electron-withdrawing group, donor/acceptor symmetry causes the electrons to flow in one particular direction. Such a system, for example (**92**), is susceptible to nucleophilic opening by either external agents ($Nu^-$) or by causing additional electrons to flow from heteroatom X to the cyclopropane weakened by electron withdrawal. The latter process usually takes place under acid catalysis and after substantial development of carbonium ion character at the site of the heteroatom. As the agency of a heteroatom lone pair can be considered in the same light as an external nucleophilic attack, this process will also be mentioned briefly in this section. Control of regiochemistry among the four possible modes of opening is available by careful consideration of stereoelectronic effects and choice of experimental conditions.

The opening of activated cyclopropanes with nitrogen nucleophiles has been widely applied to the synthesis of pyrrolizidine and pyrroline alkaloids by Danishefsky; this subject has been reviewed.[12,141] A number of pyrroline annulations have been based on this principle, illustrated in equation (35a).[12,141–143] Similar opening can be accomplished with halides, cuprates, and sulfur or selenium nucleophiles.[12,16,21]

Table 5 Cyclobutanone Synthesis

| *Vinylcyclopropanol or oxaspirocyclopentene equivalent* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 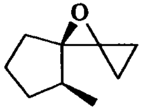 | LiBF$_4$, PhH, r.t. to reflux | 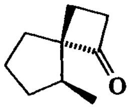<br>(96:4) | 61 | 133 |
| 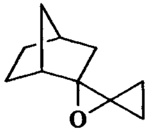 | LiBF$_4$, PhH, r.t. to reflux | 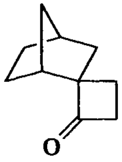<br>(91:9) | 92 | 130 |
| 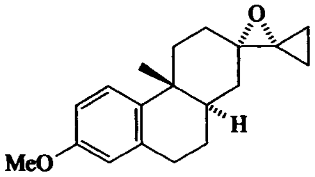 | LiBF$_4$, PhH, r.t. to reflux | 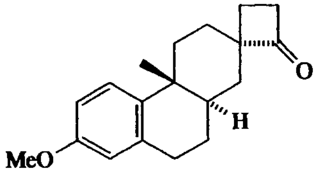 | 70–75 | 134 |
| 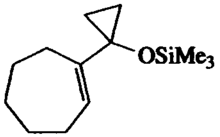 | 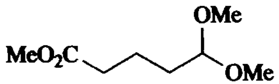<br>Me$_3$SiOSO$_2$CF$_3$ (cat.) | 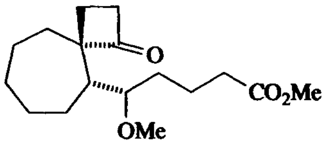 | 95 | 135 |
| 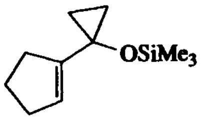 | dioxane, Br$_2$ | 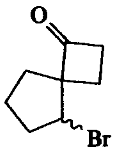 | 84 | 136 |

Table 5 *(continued)*

| *Vinylcyclopropanol or oxaspirocyclopentene equivalent* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 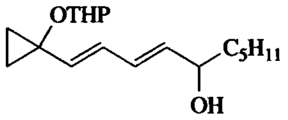 OTHP<br>$C_5H_{11}$<br>OH | PPTS, EtOH 95% | 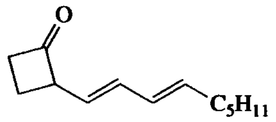 | 83 | 137 |
| 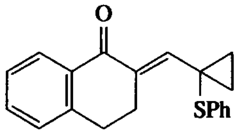 | 50% aq. TFA | 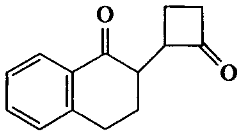 | 95 | 138 |
| 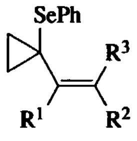 SePh<br>$R^3$<br>$R^1$<br>$R^2$<br>$R^1$, $R^2$, $R^3$ = H, alkyl | TsOH, $H_2O$, PhH, Δ | 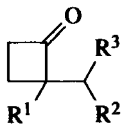 | 63–90 | 17, 139 |

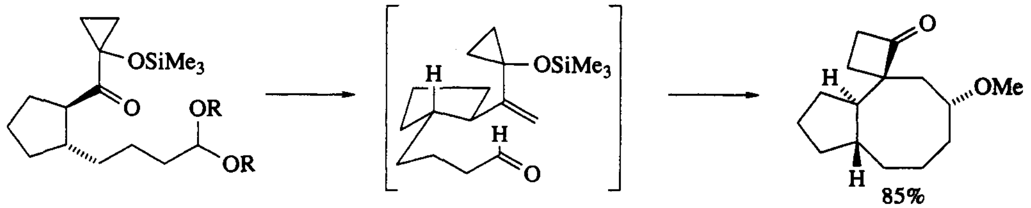
OSiMe3
O
OR
OR
H
OSiMe3
H
O
O
H
OMe
H

85%
11.5:1:1
mixture of diastereoisomers

(35)

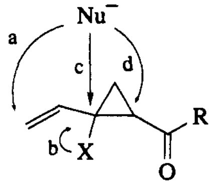

**(92)**

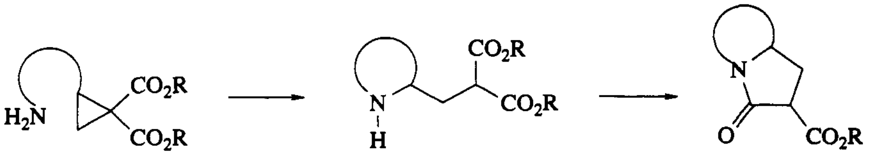
H2N
CO2R
CO2R
N
H
CO2R
CO2R
N
O
CO2R

(35a)

With vinylcyclopropanes such ring opening can still occur without the participation of the alkene and with inversion of configuration at the reacting center. The opening of cyclopropyl keto ester (**93**) has been used in an approach to prostanoids (equation 36),[144,145] whereas the opening of tricyclic systems (**95**)[146] and (**97**)[147] served in the synthesis of vernolepin and vernomenin (equations 37 and 38). Similarly, vinylcyclopropane (**99**) reacted with $Me_2CuLi$ to give stereoselectively propellane (**100**) in an approach to modhephene (equation 39).[148]

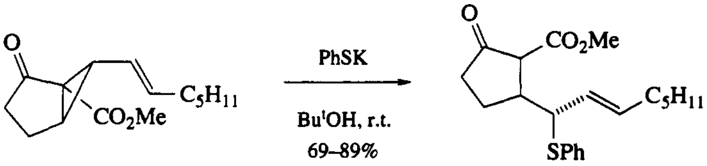
O
C5H11
CO2Me
PhSK
BuᵗOH, r.t.
69–89%
O
CO2Me
C5H11
SPh

**(93)** **(94)**

(36)

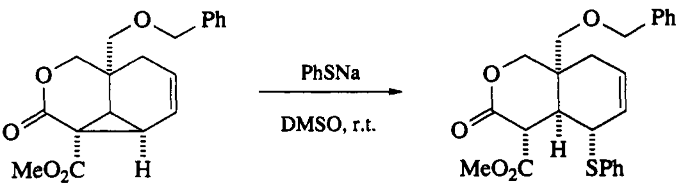
O
Ph
O
O
MeO2C
H
PhSNa
DMSO, r.t.
O
Ph
O
O
H
MeO2C
SPh

**(95)** **(96)**

(37)

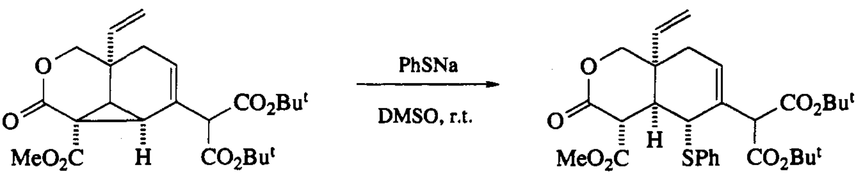
O
O
CO2Buᵗ
MeO2C
H
CO2Buᵗ
PhSNa
DMSO, r.t.
O
O
CO2Buᵗ
H
MeO2C
SPh
CO2Buᵗ

**(97)** **(98)**

(38)

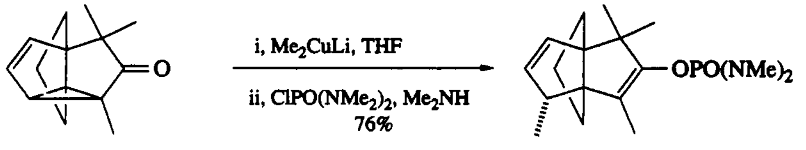

(39)

**(99)** **(100)**

The vinylogous mode of opening depends to a great extent on the conformation of the vinylcyclopropane. Of the two conformations (**101a**) and (**101b**), the *s-trans* or antiperiplanar arrangement in (**101b**) is preferred (1.17 kcal mol$^{-1}$) and cannot be reached in a cyclic or conformationally rigid system.[149] Vinylcyclopropanes such as (**102**) react with enamines in refluxing *p*-cymene to furnish, after hydrolysis, ketones (**103**) through the vinylogous mode of opening (equation 40).[150]

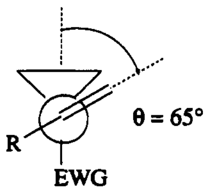

**(101a)** Synclinal *(gauche)*

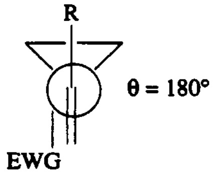

**(101b)** Antiperiplanar

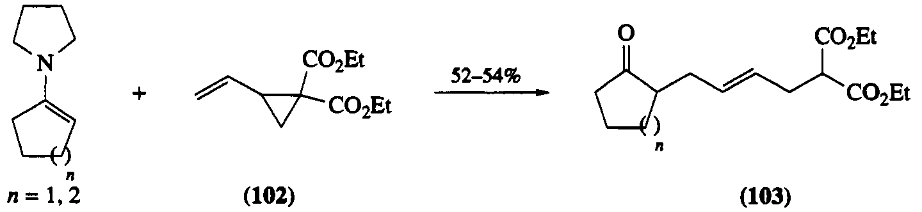

(40)

**(102)** **(103)**

The opening of cyclopropyl ketones, investigated by Miller,[151] has been adapted to vinylogous opening of vinylcyclopropanes in the development of a milder procedure for cyclopentene annulation.[152] In the presence of Lewis acids, the (*E*):(*Z*) selectivity in the formation of allylic iodides (**105**) was 80:20, whereas only marginal selectivity (60:40) was observed with TMSI alone (Scheme 19).[128,152] Similar results were also obtained with tosyl iodide[153] and, under some circumstances, with LiI at higher temperatures.[154] A recent review summarizes the reactivity and the synthetic utility of vinylogous modes of opening as well as the preparation of activated donor/acceptor-functionalized vinylcyclopropanes and their behavior in nucleophilic and electrophilic addition reactions.[45]

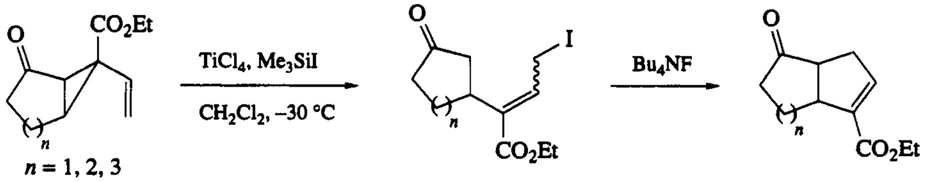

**(104)** **(105)** **(106)**

**Scheme 19**

Donor- or acceptor-substituted vinylcyclopropanes such as (**107**) afford products of vinylogous opening (**108**) with a wide variety of nucleophiles (equation 41).[16] The palladium(0)-catalyzed ring opening of vinyl- or dienyl-cyclopropanes such as (**64**) and (**111**) is thought to involve a nucleophilic attack to form zwitterion (**109**), which collapses to a vinylcyclopentene (and not cycloheptadiene) through the preferred W-conformation (**110**; Scheme 20).[45,122] The mechanism of these openings has been studied.[155,156]

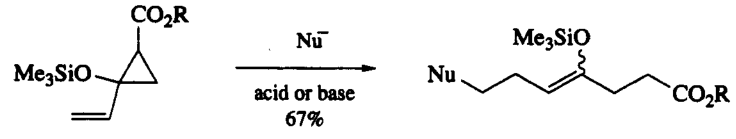
$CO_2R$
$Me_3SiO$
$Nu^-$
acid or base
67%
$Me_3SiO$
Nu
$CO_2R$

(41)

**(107)** **(108)**

$Nu^- = MeNO_2, MeOH, PhSH, Et_2NH, PhSO_2H, HF$

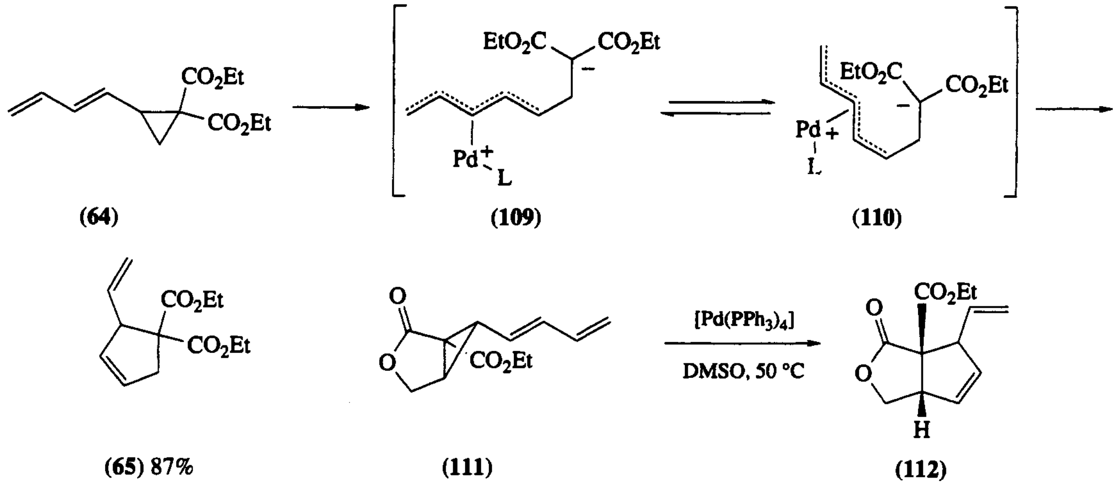
$CO_2Et$
$CO_2Et$
**(64)**
$EtO_2C$
$CO_2Et$
$Pd^+$
L
**(109)**
$EtO_2C$
$CO_2Et$
Pd+
L
**(110)**
$CO_2Et$
$CO_2Et$
**(65)** 87%
O
O
$CO_2Et$
**(111)**
$[Pd(PPh_3)_4]$
DMSO, 50 °C
$CO_2Et$
O
O
H
**(112)**

**Scheme 20**

Addition of carbon nucleophiles to doubly activated vinylcyclopropanes has also been reported. Increasing the vinylcyclopropane ratio to two equivalents led to the isolation of doubly alkylated product (**116**) selectively (equation 42).[157,158] All of the reactions discussed in this section, as well as their various permutations, have been the subject of an excellent review.[45]

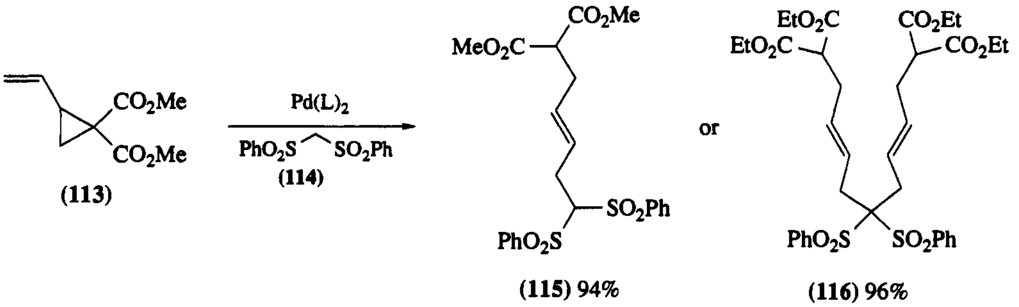
$CO_2Me$
$CO_2Me$
**(113)**
$Pd(L)_2$
$PhO_2S$
$SO_2Ph$
**(114)**
$CO_2Me$
$MeO_2C$
$SO_2Ph$
$PhO_2S$
**(115)** 94%
or
$EtO_2C$
$EtO_2C$
$CO_2Et$
$CO_2Et$
$PhO_2S$
$SO_2Ph$
**(116)** 96%

(42)

### 8.1.3.5 Radical Reactions or Cycloadditions

Addition of free radical species to vinylcyclopropane results either in the abstraction of hydrogen from the cyclopropane or ring opening through the agency of the cyclopropylcarbinyl radical generated upon the initial addition.[12] The latter process has found some synthetic applications, for example, in the ring opening of triquinane (**117**) with benzenethiol (equation 43).[124]

Alkylboranes undergo free radical 1,6-addition to keto vinylcyclopropanes, as shown in Scheme 21. The mechanism postulated involves the generation and ring opening of cyclopropylcarbinyl radical (**119**).[159] Free radical polymerization of substituted vinylcyclopropanes through both 1,2- and 1,5-type additions has also been reported.[160] A recent application of these types of procedures to synthetic methodology has been demonstrated in the cyclopentane annulation depicted in equation (44). The stereo- and regio-selectivity in the formation of cyclopentanes (**120**) is acceptable. (*Syn* orientation of the alkenic substituent with the vinyl group was observed, and there was about a 3:1 preference for *cis* substitu-

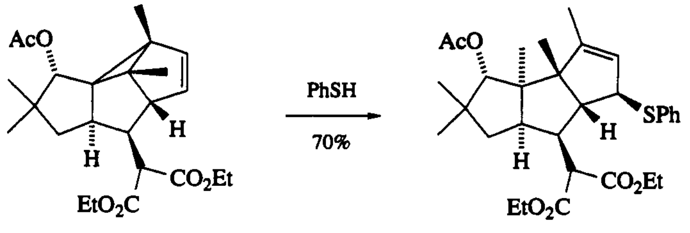
AcO
H
H
CO2Et
EtO2C
PhSH
70%
AcO
SPh
H
H
CO2Et
EtO2C

**(117)** **(118)** (43)

tion.)[161] Similar technology was applied to the preparation of tetrahydrofurans from vinyloxiranes (see Section 8.1.4.1).[162] Vinylcyclopropanes such as (**121**) also undergo radical addition with PhSH or Bu3SnH to afford functionalized enol ethers (**122**), which are hydrolyzed to ketones, thus eliminating the stereochemical problems of alkene geometry (Scheme 22).[16]

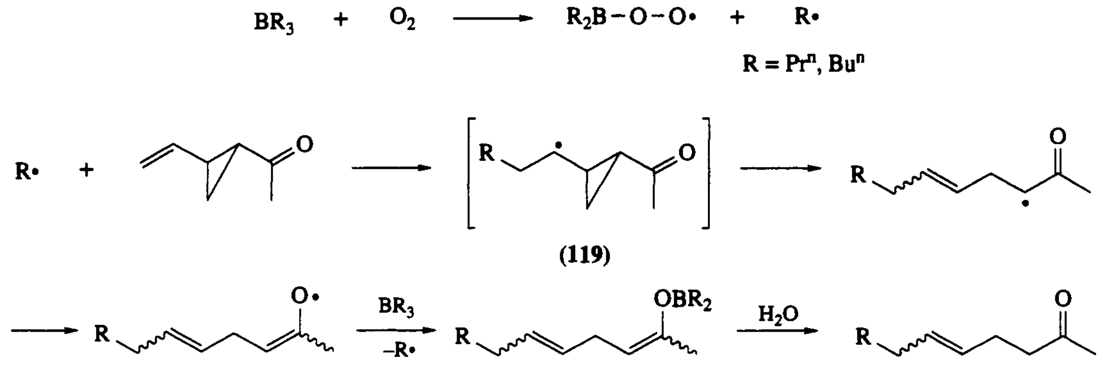
BR3 + O2 → R2B–O–O• + R•
R = Prn, Bun
R• +
O
R
O
R
O
(119)
O•
R
BR3
–R•
R
OBR2
H2O
R
O

Scheme 21

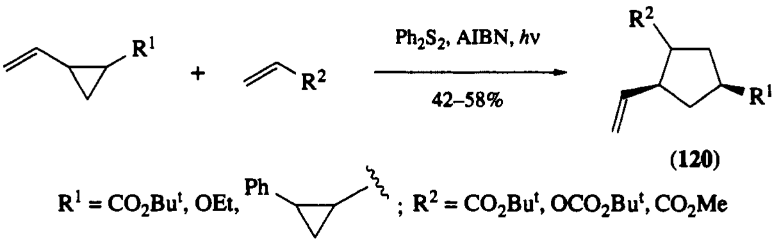
R1
+
R2
Ph2S2, AIBN, hν
42–58%
R2
R1
R1 = CO2But, OEt,
Ph
; R2 = CO2But, OCO2But, CO2Me

(44)

**(120)**

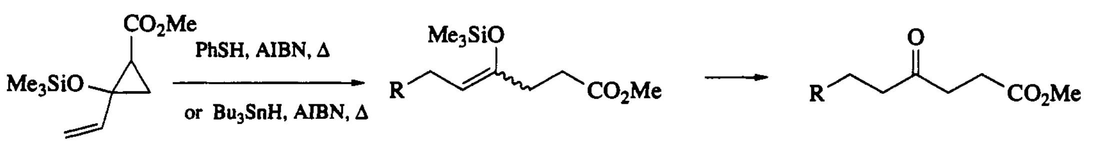
CO2Me
Me3SiO
PhSH, AIBN, Δ
or Bu3SnH, AIBN, Δ
Me3SiO
R
CO2Me
O
R
CO2Me

**(121)** **(122)** R = SPh, 30%; SnBu3, 85% **(123)**

Scheme 22

Cycloadditions of vinylcyclopropanes have also been studied.[163] For example, vinylcyclopropane (**124**) gave the Diels–Alder adduct (**125**), presumably as a single (*endo*) stereoisomer (Scheme 23). On the other hand, the reaction of (**124**) with tetracyanoethylene took a different course, resulting in the formation of cyclopentene (**126**). A possible mechanism involves the transformation shown in Scheme 24. It should be noted that the norphenyl derivative of (**124**) gave the corresponding cyclopropylcyclobutane supporting the intermediacy of the proposed zwitterion (**127**). A tin-promoted free radical opening of dienylcyclopropanes has recently been reported, but unfortunately the stereoselectivity of the radical closure was modest (Scheme 25).[164]

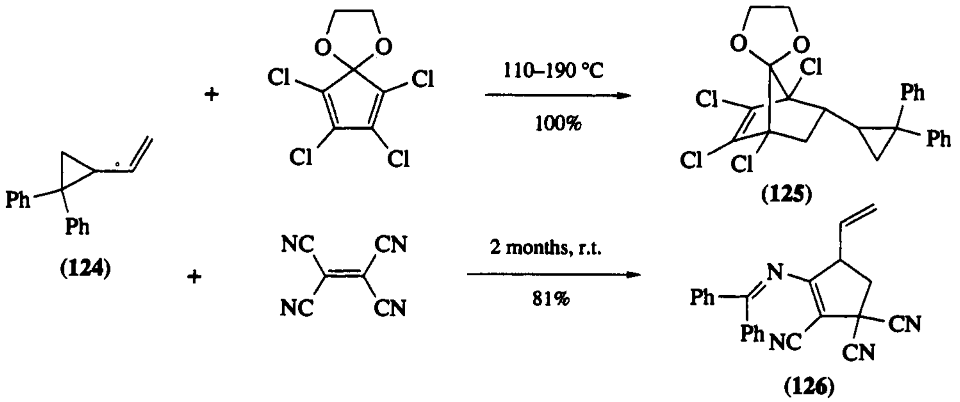

**Scheme 23**

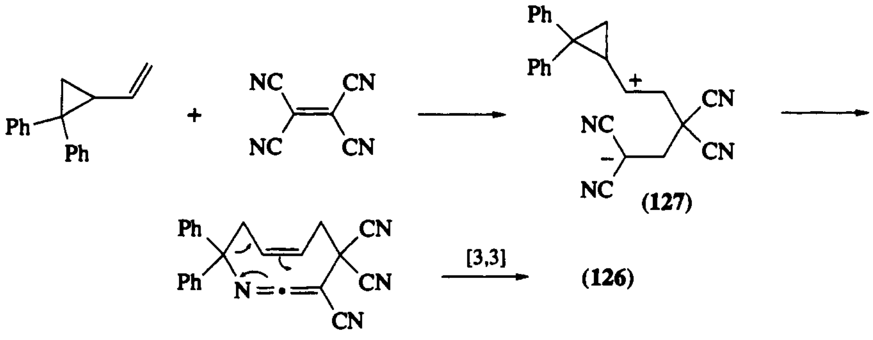

**Scheme 24**

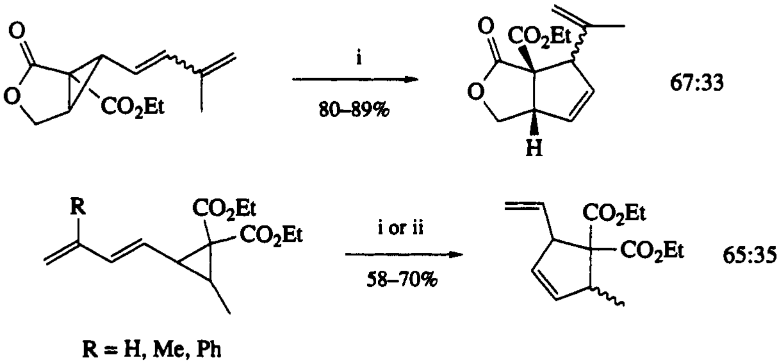

i, $Ph_3SnH$ or PhSH, AIBN, 80 °C; ii, $Ph_3GeH$ or $Bu^n{}_3SnH$, AIBN, 80 °C

**Scheme 25**

## 8.1.4 REARRANGEMENTS OF VINYLOXIRANES

Rearrangements of vinyloxiranes proceed by analogy with the corresponding vinylcyclopropane reorganization with two notable exceptions: first, they generally require lower activation energy and therefore take place under milder conditions, and, second, most of the thermal rearrangements proceed through zwitterionic or ylide-like intermediates, which are uncommon in carbocyclic cases. The nucleophilic opening of systems such as (**128**) is more complex because of the coordinative abilities of oxygen and the increased number of nucleophilic interactions that are possible (Scheme 26). Nevertheless, some parallel behavior and predictability in vinyloxirane rearrangements are available.

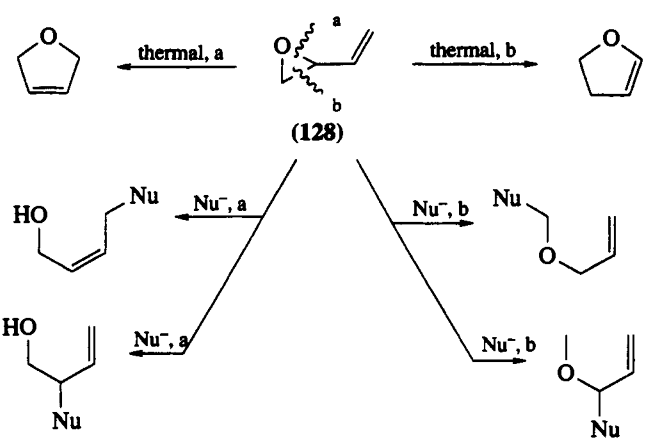

**Scheme 26**

### 8.1.4.1 Thermal Isomerization

The study of benzene oxide–oxepin tautomerism, reviewed in the late 1960s, revealed a competing pathway in the rearrangements of *trans*-divinyloxiranes of type (**129**; Scheme 27).[165,166] The corresponding *cis* isomer gave only oxepin (**131**), whereas the *trans* isomer gave a 7:3 mixture of dihydrofuran (**132**) and oxepin (**131**). The activation parameters implied that the intermediate was biradical (**130**) (*cis*-oxide: $\Delta H^{\ddagger} = 24.6$ kcal mol$^{-1}$, $\Delta S^{\ddagger} = -11.3$ cal deg$^{-1}$ mol$^{-1}$; *trans*-oxide: $\Delta H^{\ddagger} = 36$ kcal mol$^{-1}$, $\Delta S^{\ddagger} = -0.4$ cal deg$^{-1}$ mol$^{-1}$).[165] These values indicate processes far lower in energy than those operating in the vinylcyclopropane rearrangement, while their difference (11 kcal mol$^{-1}$) led to the conclusion that the rearrangement was concerted for the *syn* isomer and biradical for the *trans* compound.

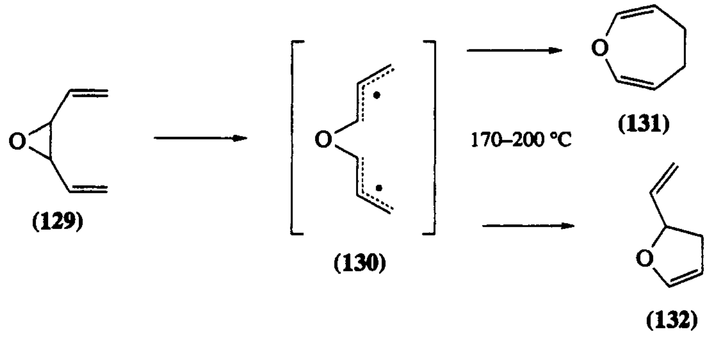

**Scheme 27**

The mechanism has since been studied on a number of occasions, and it is generally agreed that concerted, electrocyclic closures of ylides are operating in the formation of either oxepins or vinylfurans.[167,168–171] The rate of racemization of optically pure vinyloxiranes has been shown to be six times faster than the isomerization to the dihydrofuran.[167] Alternatively, cleavage of a vinyloxirane to a carbon–oxygen diradical pair or to a carbene–carbonyl pair has been considered for processes that do *not* usually lead to the formation of dihydrofuran[167,169,172] (though there is a notable exception[172]). Corresponding [1,5] shift pathways are also known for those oxiranes that contain a *cis*-oriented alkyl group with at least one hydrogen.[169]

The regio- and stereo-selectivity of this rearrangement has been addressed and found to be excellent.[168] Thus either isomer of vinyloxirane (**133**) yielded dihydrofuran (**134**) stereoselectivity, whereas the rearrangements of vinyloxiranes (**135**) led to a mixture of *cis* and *trans* isomers (Scheme 28). (*Cis*/*trans* isomerization was also accomplished photochemically.)[173] The results were rationalized by involving ylides of type (**137**) and their allowed $[2\pi_s + 2\sigma_a]$ or $[2\pi_a + 2\sigma_s]$ closures for the former case and biradicals for the latter, although the epimerization may have taken place after the rearrangement because of the presence of an acidic proton.[168]

A number of substituents can be placed on the periphery of the vinyloxirane system. For example, extensively studied were alkynyl- and dienyl-oxiranes of the general structures represented by (**138a**) to

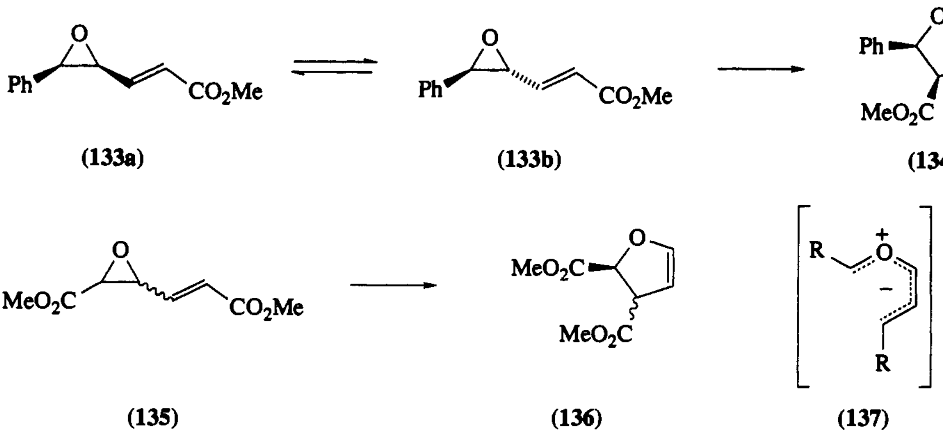

Scheme 28

**(138d)**. Their isomerization to various oxidation states of oxepins competed in some cases with the formation of the corresponding vinylfurans.[168,169,171,174,175]

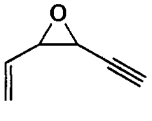
**(138a)**

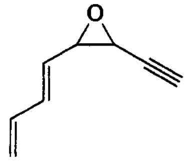
**(138b)**

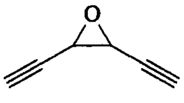
**(138c)**

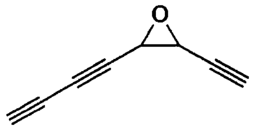
**(138d)**

The control of furan *versus* oxepin manifolds has been addressed recently. Vinyloxiranes of type **(139)** yielded oxepins **(140)** at lower temperatures, whereas higher temperatures gave dihydrofurans **(141**; Scheme 29),[176] indicating that the Cope-type rearrangement of *cis*-divinyloxirane may be controlled by precisely defining the temperature profile of the flash vacuum pyrolysis.[176,177]

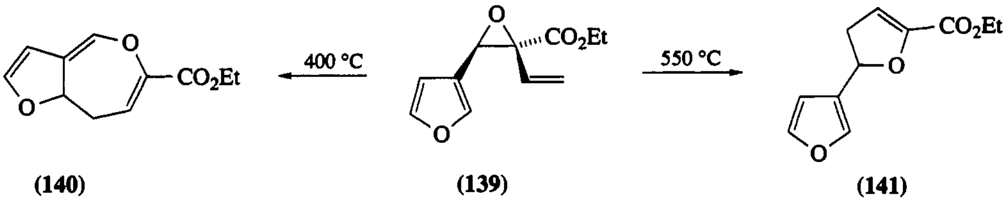

Scheme 29

A [2 + 3] dihydrofuran annulation methodology was recently developed based on this rearrangement. Divinyloxiranes **(142)** were generated by the stereospecific addition of the lithium dienolate of ethyl α-bromocrotonate to aldehydes, and the subsequent pyrolysis to dihydrofurans **(143**; Scheme 30) occurred in excellent isolated yields (except for R = Bu$^n$, Pr$^i$).[176]

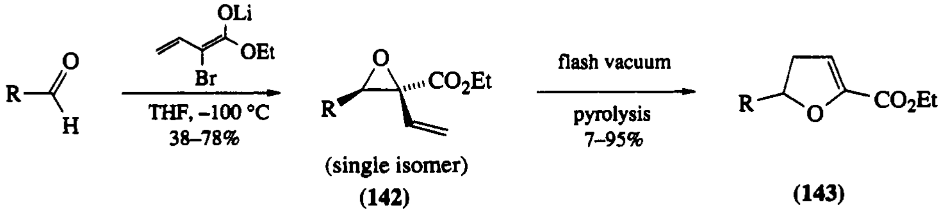

R = Bu$^n$, Pr$^i$, Ph, $CH_2$=CH, 2-furyl, 3-furyl

Scheme 30

Radical addition of alkenes to vinyloxiranes to yield tetrahydrofurans was reported in analogy to the similar reaction of vinylcyclopropanes (equation 45),[161] with the same regio- and stereo-selectivity (with a predominance of *syn* isomers having the regiochemistry indicated in **144**).[162] Radical polymerization of vinyloxiranes has also been reported.[178] The rearrangements of vinylthiiranes proceed in a similar fashion to those of vinyloxiranes. The general field of thermal rearrangements of three-membered heterocycles containing oxygen, sulfur or nitrogen has recently been reviewed.[179] A vast majority of the literature on the rearrangements of vinyloxirane systems deals with those cases where Cope-like rearrangements of the divinyloxiranes are possible. The expansions of such systems to oxepins and further rearrangements and transmutations of, for example, vinylalkynyloxiranes to vinylcyclopropyl aldehydes have also been studied and reviewed.[175,177,179] Some of the reactivity patterns of vinyloxiranes and their derivatives are shown in Table 6.

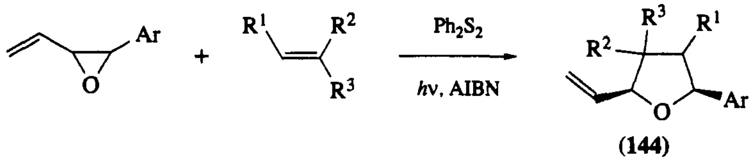

**(144)**

(45)

### 8.1.4.2 Nucleophilic Opening

Vinyloxiranes react with nucleophiles in three regiochemically distinct ways: with α, β and vinylogous modes of opening. The subject has been of considerable interest in the context of acyclic stereoselection and generation of allylic alcohols in an iterative fashion.

Cyclic vinyloxiranes react with organocuprates with inversion of configuration (*anti*) and in a vinylogous mode (equation 46), not by the expected $S_N2$ reaction that simple oxiranes are known to undergo. This subject has recently been summarized.[185]

The conformation of vinyloxirane is restricted in such cases, whereas the acyclic vinyloxiranes, like vinylcyclopropanes, enjoy a conformational equilibrium, which determines the (*E*):(*Z*) ratio of the allylic alcohols that result from interactions with nucleophiles. For example, vinyloxirane (**145**) gave a 4:1 (*E*):(*Z*) ratio of allylic alcohols (**146**; equation 47) with $Ph_2Cu(CN)Li_2$, but a 7:2 ratio when $(2\text{-}C_5H_5NCH_2)_2Cu(CN)Li_2$ was used (Scheme 31).[186]

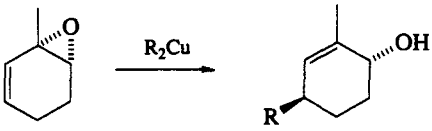

(46)

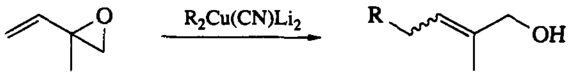

**(145)** **(146)**

(47)

R = Ph (*E*):(*Z*) = 3.4:1

R =

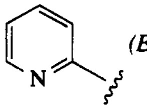

(*E*):(*Z*) = 7:2

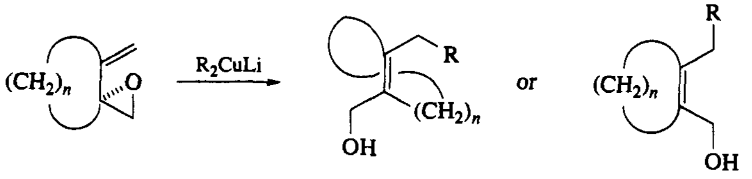

(48)

| *n* | *ee* (%) | *trans*:*cis* |
|---|---|---|
| 10, 12 | 82–92 | 99:1 |
| 14 | racemization | 89:11 |

Table 6 Rearrangements of Vinyloxiranes and Related Compounds

| *Vinyloxirane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 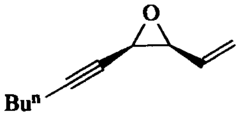 | 335 °C, gas phase | 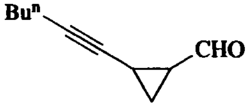 | 83 | 175 |
| 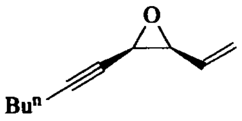 | 150 °C, $CCl_4$, sealed tube | 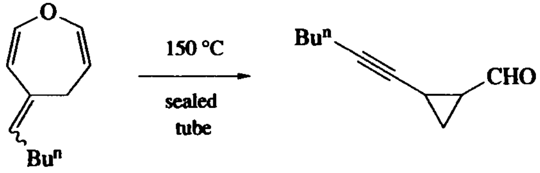  O<br>Bu<sup>n</sup><br>150 °C<br>sealed tube<br>Bu<sup>n</sup><br>CHO | 90 | 175 |
| 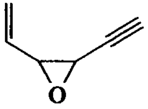 | 405 °C | 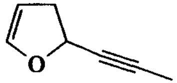 | 87 | 180 |
| 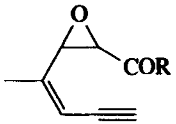 | 350 °C | 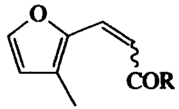 *(E)*:*(Z)* = 11:1 | 70–80 | 172 |
| 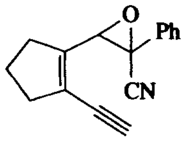 | 170 °C | 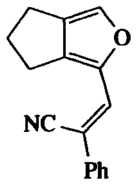 *(Z)*:*(E)* = 9:1 | 85 | 170 |

Table 6 *(continued)*

| *Vinyloxirane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 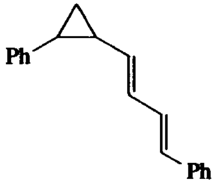 | 170 °C | 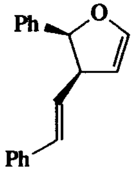 | 100 | 181 |
| 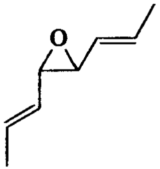 | 210–250 °C | 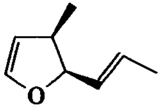 | 70–80 | 182 |
| 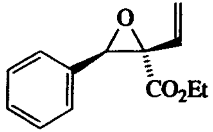 | 500 °C, 0.02 mmHg | 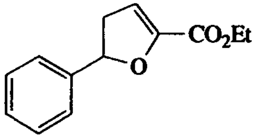 | 95 | 176 |
| 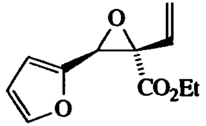 | 500 °C, 0.02 mmHg | 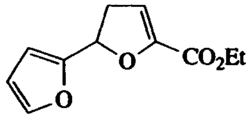 | 69 | 176 |
| 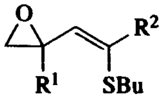 | $HgSO_4$, $H_2O$ | 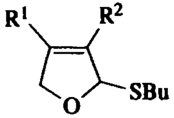 | — | 183 |
| 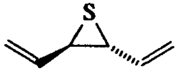 | 340–360 °C | 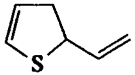 | — | 184 |

Stereoselective $S_N2'$ addition of cuprates has been documented for vinyloxiranes such as **(147a)** and **(147b)**. The pairs **(148)** and **(149)** are enantiomeric, so this selectivity also reflects a controlled access to all four enantiomers of these alcohols. The normal $S_N2$ opening or elimination pathways were suppressed in these systems.[185] The selectivity increased with (*Z*)-isomers in all cases studied. The stereochemistry of the cuprate additions to optically pure macrocyclic (and exocyclic) vinyloxiranes has also been investigated (equation 48).[187]

Palladium-catalyzed nucleophilic opening of vinyloxiranes received much attention and led to the development of a methodology for *cis*-hydroxylation, as shown in Scheme 32. In this procedure the normally expected distal approach of the oxygen nucleophile is suppressed by intramolecular trapping with carbonate.[188]

Carbon as well as amine nucleophiles add to vinyloxiranes in a vinylogous sense with palladium(0) catalysis. In all such cases the initial nucleophilic attack on the vinyloxirane probably proceeds as depicted in Scheme 25, and its success would be governed by the usual steric effects. Some useful examples are shown in Table 7.

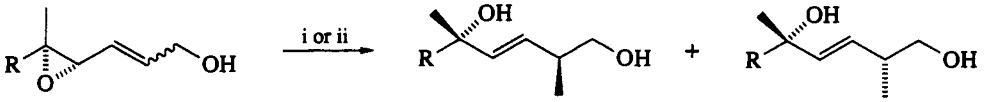

**(147a)** **(148a)** **(148b)**

| *(147a)* | *(148a)*:*(148b)* | *Yield* (%) |
|---|---|---|
| *(E)* | 84:16 | 81 |
| *(Z)* | 1:99 | 88 |

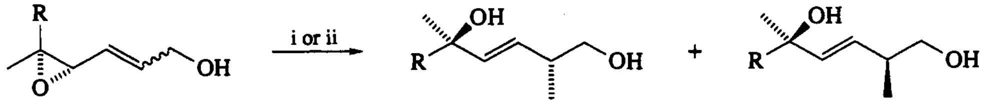

**(147b)** **(149a)** **(149b)**

| *(147b)* | *(149a)*:*(149b)* | *Yield* (%) |
|---|---|---|
| *(E)* | 14:86 | 95 |
| *(Z)* | 97:3 | 95 |

R = H, $SiMe_2Bu^t$, 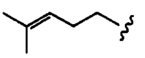

i, $LiMe_2Cu$, $THF/Et_2O$ (4:1), 0 °C; ii, LiMeCuCN, $Et_2O$, 0 °C

Scheme 31

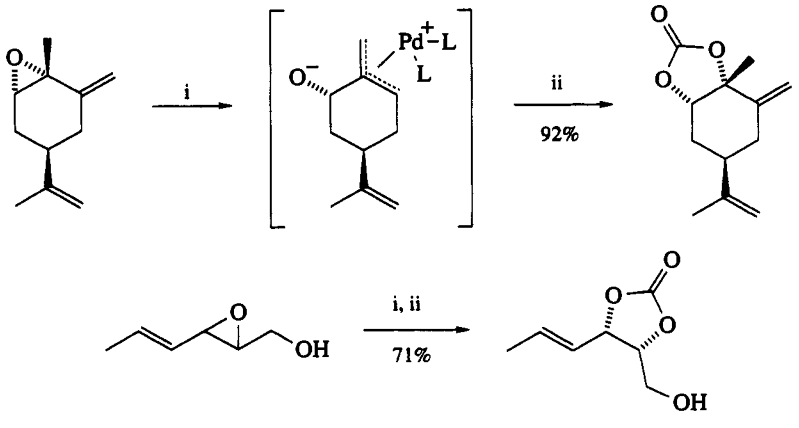

i, $[Pd\{P(OPr^i)_3\}_4]$, 30 min, THF, r.t; ii, $CO_2$

Scheme 32

**Table 7** Addition of Nucleophiles to Vinyloxiranes

| *Vinyloxirane* | *Nucleophile* | *Catalyst* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 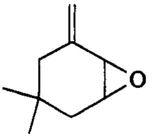 | 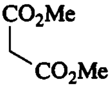 | [Pd(PPh$_3$)$_4$] | 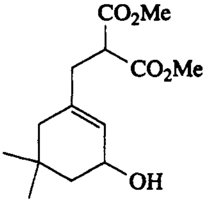 | 85 | 189 |
| 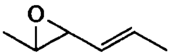 | 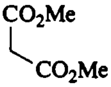 | [Pd(PPh$_3$)$_4$] | 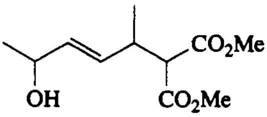 | 76 | 189 |
| 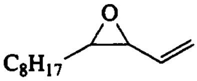 | 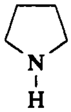 | [Pd(PPh$_3$)$_4$] | 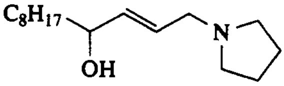 | 92 | 190 |
| 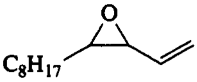 | 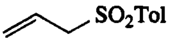 | [Pd$_3$(TBAA)$_3$] | 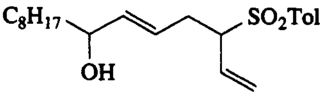 | 64 | 190 |
| 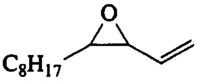 | 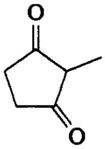 | [Pd(PPh$_3$)$_4$] | 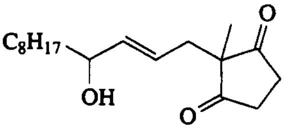<br>*(E)*:*(Z)* = 98:2 | 91 | 190 |
| 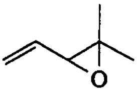 | 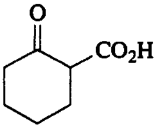 | [Pd(PPh$_3$)$_4$] | 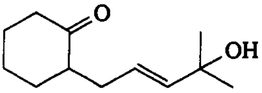 | 54 | 191 |
| 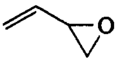 | 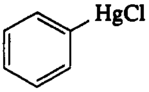 | Li$_2$PdCl$_4$ | 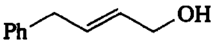 | 76 | 192 |
| 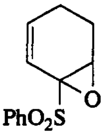 | 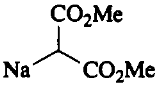 | (no catalyst) | 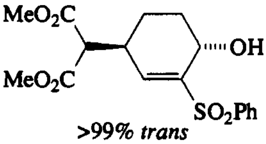<br>>99% *trans* | 89 | 193 |
| 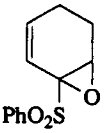 | 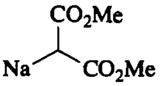 | Pd(DBA)$_2$ | 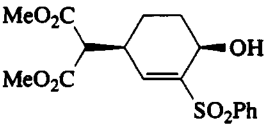 | 85 | 193 |

**Table 7** *(continued)*

| *Vinyloxirane* | *Nucleophile* | *Catalyst* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 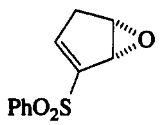 | $Me_2CuLi$ | $Me_3Al$ | 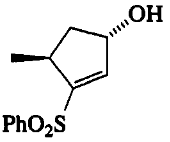<br>*trans*:*cis* = 92:8 | 80 | 194 |
| 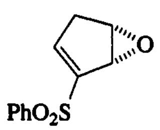 | MeLi | $LiClO_4$ | 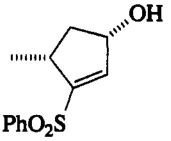<br>*cis*:*trans* = 95:5 | 81 | 194 |

For the sake of comparison, the regio- and stereo-selectivity of some nucleophilic openings of vinyloxiranes with organometallic reagents derived from copper, lithium, sodium and other metals indicate the control available under some conditions. Complete control of diastereoselectivity in the opening of cyclic vinyloxiranes is available, for example by utilizing palladium(0)-catalyzed conditions in the reaction of the sodium salt of dimethyl malonate with cyclic vinyloxiranes.[193,194] Increased substitution on the vinyl portion of the vinyloxirane leads to isomerization with opening, as in the case of the disubstituted vinyloxirane (**150**; equation 49).[191]

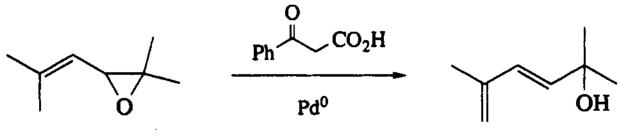

**(150)**

(49)

Other nucleophilic reagents effect the opening of vinyloxiranes in a similar fashion. Sodium phenoxide reacts with vinyloxiranes as illustrated in Scheme 33, with some control of regiochemistry.[195] Vinylaluminum reagents give $S_N2'$ products exclusively,[196] whereas alkynides of titanium open epoxides such as (**151**) regioselectively by an $S_N2$ process.[197] Vinyloxiranes react with allylstannanes in the presence of Lewis acids with excellent regioselectivity, as shown in Scheme 34. Similar selectivity for the internal substitution was observed for allylsilanes.[198] In contrast, Grignard or cuprate reagents favor the $S_N2'$ opening leading to (**153b**) in 70:30 and 80:20 ratios, respectively. Rhodium(I)-catalyzed rearrangements of vinyloxiranes yield α,β-unsaturated aldehydes and ketones.[199]

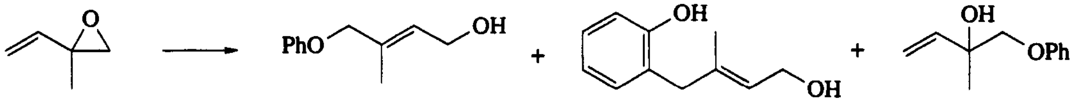

**(151)** **(152a)** **(152b)** **(152c)**

| *Conditions* | *(152a) (%)* | *(152b) (%)* | *(152c) (%)* | *% yield* |
|---|---|---|---|---|
| PhONa, DMSO | – | – | 100 | 61 |
| PhONa, $Et_2O$ | 6 | 45 | 49 | 43 |
| PhONa, $CF_3CH_2OH$ | 4 | 76 | 20 | 53 |

**Scheme 33**

Cyclic vinyloxiranes were opened with *t*-butyldimethylsilyl cyanide to yield isonitriles, as shown in equation (50).[200] The opening of vinyloxiranes like (**142**) with TMS-I, TMS-I/$TiCl_4$ and $SmI_2$ was attempted in an effort to provide a topographical option for the [2 + 3] dihydrofuran annulation. While the 2,5-substitution pattern inherent in (**143**) is furnished through thermolytic rearrangements, the 2,3-isomer would result from an $S_N2'$ opening of (**142**) to allylic iodide (**154**), which would cyclize to 2,3-functionalized dihydrofuran (**155**; Scheme 35).[128] Only marginal results were obtained under conditions adapted from similar opening of vinylcyclopropanes with trimethylsilyl iodide and titanium tetrachloride.[128] However, $SmI_2$ opening consistently gave the regioisomer (**156**),[201] albeit in poor yields perhaps because of the reducing properties of this reagent.[202]

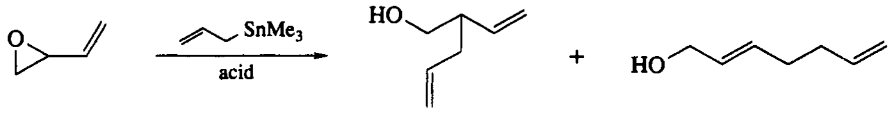

**(153a)** **(153b)**

| *Acid* | *(153a)* (%) | *(153b)* (%) |
|---|---|---|
| $BF_3$ | 91 | 0 |
| $AlCl_3$ | 52 | 0 |
| $TiCl_4$ | 14 | 0 |

**Scheme 34**

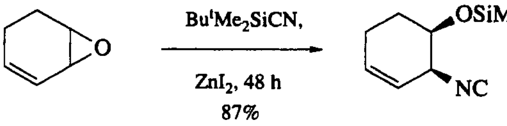

(50)

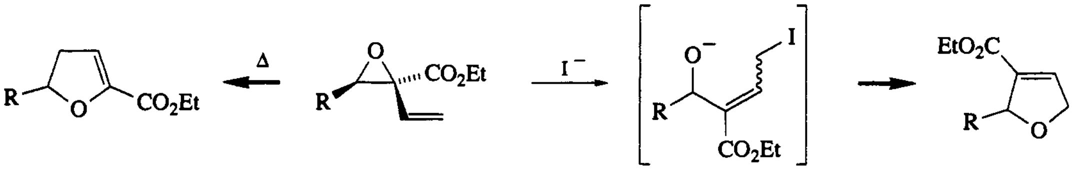

**(143)** **(142)** **(154)** **(155)**

**Scheme 35**

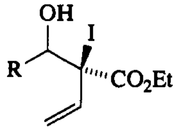

**(156)**

## 8.1.5 REARRANGEMENTS OF VINYLAZIRIDINES

Like vinyloxiranes, vinylaziridines are subject to a number of rearrangements that parallel the pathways available to vinylcyclopropanes. Unlike vinyloxiranes, however, vinylaziridines undergo extremely well controlled nucleophilic opening to furnish pyrrolines under nonthermolytic conditions. They are easily prepared from alkenes and azides *via* triazolines.[203] Because of the valency of nitrogen there are two topographical isomers possible (**157** or **159**), each leading to a different tautomer of pyrroline (**158** or **160**), and an additional isomer, 3-pyrroline (**161**), available through cleavage of bond **a** in (**159**; Scheme 36). This remarkable property of vinylaziridines translates into selective preparation of all possible isomers of pyrroline, 1-, 2- and 3-pyrroline, by careful 'tuning' of the reactivity of (**157**) and (**159**) through substituent effects and the knowledge of probable reaction intermediates. Much of the thermal and photochemical behavior of vinylaziridines may be rationalized through either diradical or zwitterionic (azomethine ylide) intermediates. This subject has been thoroughly summarized.[41,179,204]

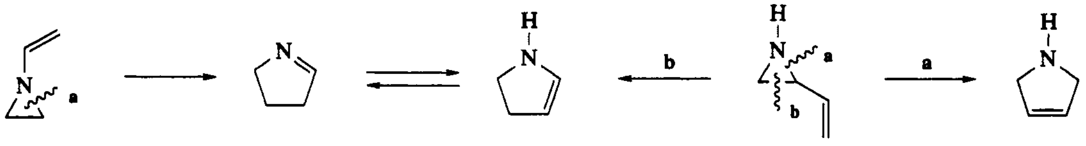

**(157)** **(158)** **(160)** **(159)** **(161)**

**Scheme 36**

Vinylaziridines such as (**162**) have been rearranged thermally to 3-pyrrolines (equation 51),[205,206] presumably through one of the species (**164**). Substituents play an important role in the likelihood of these intermediates.[207] The energy of activation for carbon–nitrogen bond cleavage has been estimated to be 12–14 kcal mol$^{-1}$ (compared with 27 kcal mol$^{-1}$ for cyclopropane).[208] Vinylaziridines of type (**165**; R = alkyl) furnish 1-pyrrolines (**166**) or, if X is another heteroatom, the corresponding heterocyclopentenes (equation 52; Section 8.1.7).[206,209]

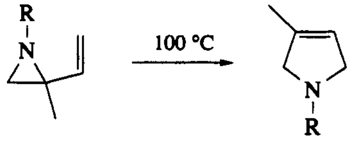

(**162**) (**163**) (51)

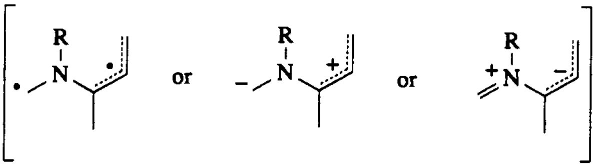

(**164**)

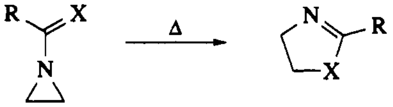

(**165**) (**166**) X = $CR_2$, O, S, NR (52)

The competing reaction involves the formation of imines (presumably *via* diradicals and hydrogen migration), as proposed by Logothetis to account for the formation of imines in the thermolysis of aziridines.[210] Imine formation is sometimes observed as a competing pathway in the thermolysis of *N*-substituted vinylaziridines,[211] and can also be rationalized by a process analogous to a [1,5] homodienyl shift.[179,212,213] In cyclic systems having proper stereochemistry (*endo*) this process may predominate, as evidenced by the isolation of only the (*E*)-alkene (**168**; R = $CO_2Et$; Scheme 37).[212,213]

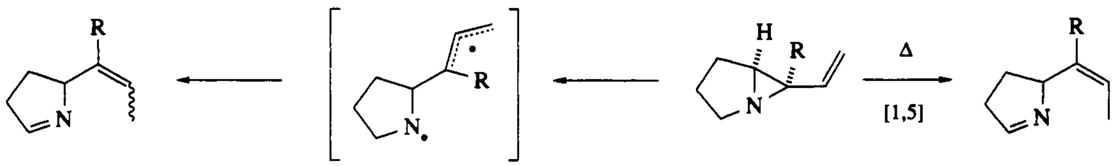

(**168**) (**167**) R = H, $CO_2Et$ (**168**)

Scheme 37

Reaction of vinylaziridines (**169**) with NaI in refluxing acetone led to 3-pyrrolines (**171**; Scheme 38).[214,215] When the *N*-substituent contains an additional alkene as in the case of (**169a**), the possibility of an intervening Cope-like rearrangement will complicate pyrroline formation. The selectivity between these two pathways usually depends on the stereochemistry of the vinylaziridine and the temperature of the rearrangement. (Higher temperatures favor the pyrroline formation as the Cope rearrangement is frequently reversible.) No *cis*/*trans* isomerization was observed in the case of (**169a**).[216] The divinylaziridine rearrangement as well as the [1,5] shift pathways of vinylaziridines can be controlled according to the principles found valid with vinylcyclopropanes or vinyloxiranes. Some aspects of the rearrangements of vinylaziridines have been reviewed.[179,180]

Photochemical rearrangements have also been reported, as shown in equation (53).[217,218] Transition metal catalyzed rearrangement [palladium(0)] of a dienylaziridine has been reported in one case,[219] and a radical opening of a dienylaziridine led to pyrroline formation under the conditions of radical initiation with AIBN/$Ph_3SnH$ (equation 54).[164] For those vinylaziridines that contain additional unsaturation, the corresponding aza equivalent of a divinylcyclopropane Cope rearrangement is the usual pathway.[220] The subject of heterodivinylcyclopropane Cope rearrangement is covered in detail elsewhere.[177] The pyrroline–azepine pathways are usually controllable by determining temperature profiles for the reactions. Higher temperatures favor pyrroline formation.

Compared to vinylcyclopropanes, vinylaziridines have not enjoyed wide applicability in synthetic schemes or annulation prior to the discovery and development of [4 + 1] pyrroline annulation (Scheme 39).[41,212,213,221–223] Activation of the dienes with electron-withdrawing groups proved necessary for the formation of vinylaziridines (**173**) and (**176**) (through intermediate triazolines and their thermal decomposition).[223] Noteworthy is the selectivity in bond activation in (**173**) and (**176**). Whereas thermolysis of (**173**) leads to pyrrolizidine (**178**),[212,213,223] through the probable agency of azomethine ylide (**179**), the nucleophilic opening leads exclusively to (**174**) through intermediate allylic iodides (**180**), which are produced as mixtures of (*E*)- and (*Z*)-isomers but are converted to (**174**) through equilibration and recycling of the (*Z*)-isomer (Scheme 40).[221]

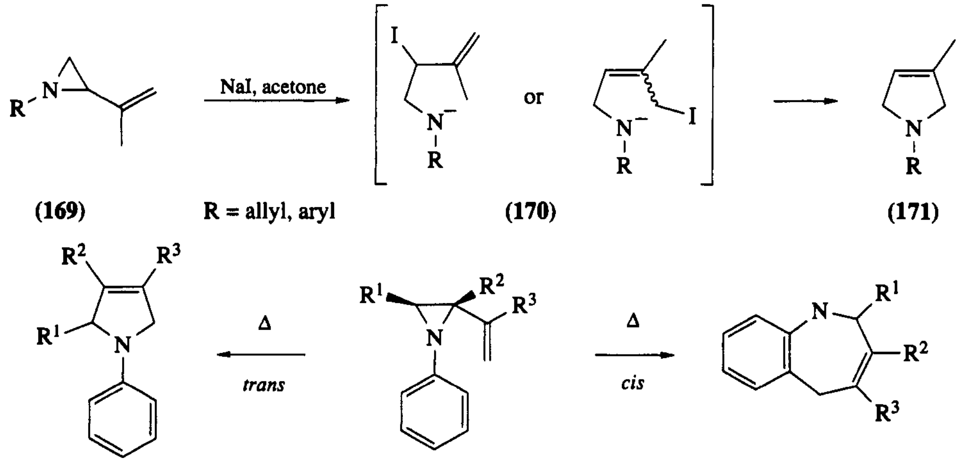

(**169**) R = allyl, aryl (**170**) (**171**)

(**169a**)

**Scheme 38**

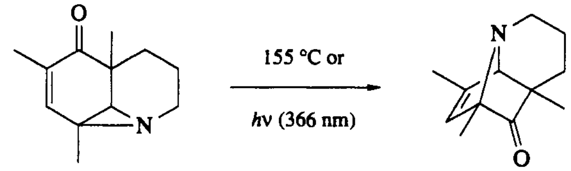

(53)

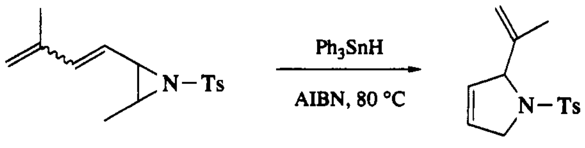

(54)

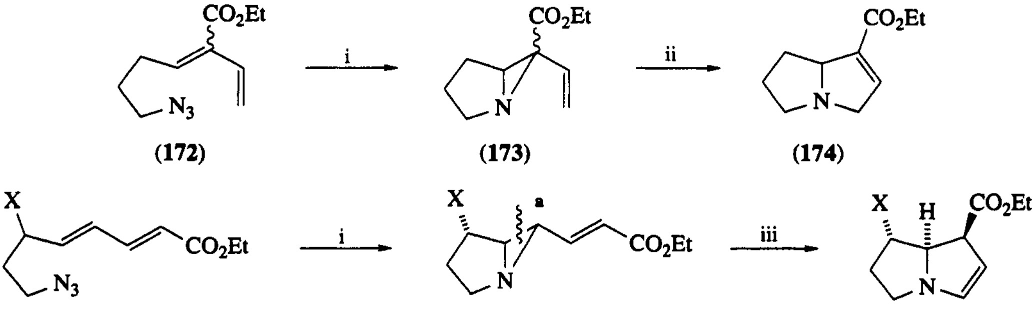

(**172**) (**173**) (**174**)

(**175**) X = H, OR (**176**) (**177**)

i, toluene, Δ; ii, $Me_3SiI$, $CH_2Cl_2$, –50 °C; iii, 485 °C

**Scheme 39**

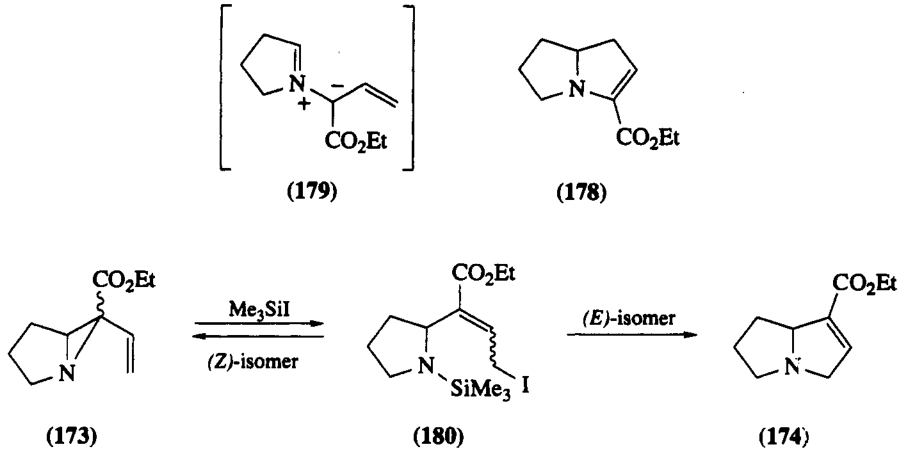

**(179)** **(178)**

**(173)** **(180)** **(174)**

**Scheme 40**

When oxygenated diene (**175**; X = OR) was utilized, a single isomer of pyrrolizidine (**177**) was formed on thermolysis.[222] (The stereochemistry of the carboxylate was rationalized by the *endo* effect.) Thus a highly selective procedure for the exhaustive synthesis of pyrrolizidine alkaloids was developed (see Sections 8.1.8 and 8.1.9).[41]

Azides (**175**; X = OH) were resolved through microbial reduction of β-keto esters (**181**) with baker's yeast and provided the azido dienes (**182**) and (**183**) in about 70% *ee* in an approach to enantiocontrolled synthesis of pyrrolizidines (equation 55).[224] In this series extensive racemization took place prior to or during the vinylaziridine formation. A conversion of chlorobenzenediol (**184**) to lactone (**185**) and elaboration of this material to either enantiomer of trihydroxyheliotridane (**187**) constituted a fully enantiocontrolled approach to both enantiomeric series of highly oxygenated pyrrolizidine alkaloids (Scheme 41).[225]

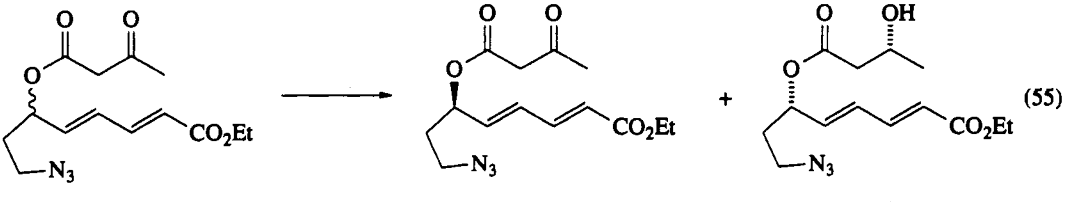

(55)

**(181)** **(182)** **(183)**

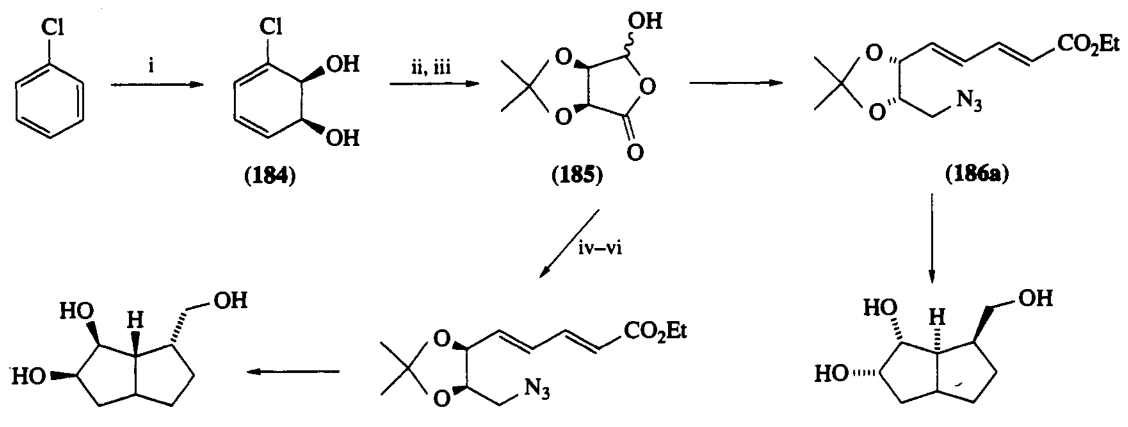

**(184)** **(185)** **(186a)**

**(187b)** **(186b)** **(187a)**

i, *Pseudomonas putida* 39D; ii, dimethoxypropane, HCl; iii, $O_3$, $Me_2S$; iv, $Ph_3PCH_2CHCHCO_2Et$, $Br^-$;

v, $BH_3$, THF; vi, MsCl, $Et_3N$, then $NaN_3$

**Scheme 41**

Recently, compounds of type (**188**; Scheme 42) have been found to yield pyrrolines (**190**) through the vinylaziridine–pyrroline rearrangement of (**189**) (not isolated) in refluxing $CHCl_3$ or THF, albeit in moderate yields (31–62%).[226] The heteroatom substitution apparently accelerates the rearrangement.

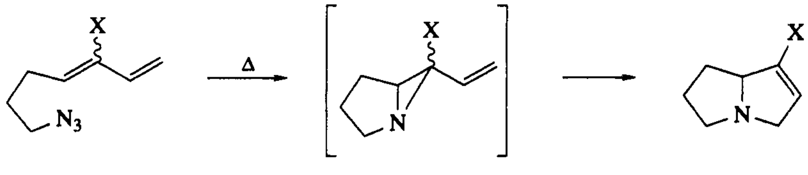

**(188)** **(189)** **(190)**

X = SPh, $OSiMe_2Bu^t$, $O(CH_2)_2OEt$

**Scheme 42**

## 8.1.6 CYCLOPROPYL-CARBONYLS AND -IMINES

When the vinylcyclopropane system contains a heteroatom within the alkene portion, it is highly susceptible to rearrangements governed by donor–acceptor principles. Under appropriate conditions the ring closure of systems such as (**191**), in addition to the normal diradical pathways, can occur by two additional mechanisms: unravelling of a cyclopropylcarbinyl cation system (path a) or the action of a lone pair of an additional donor atom (or a full anion) resembling the unravelling of a cyclopropylcarbinyl anion (path b; Scheme 43). Ideally, both processes can reinforce one another to lead to a facile rearrangement of systems such as (**192**) to the corresponding 1,4-dicarbonyl compounds, reported as early as 1938 (Scheme 44).[227] Recognition that the cyclopropylcarbinyl cation unravels to provide additional unsaturation led to the methodology of acid- or base-catalyzed unravelling of systems of type (**192a**) to corresponding β,γ-unsaturated carbonyls (equation 56).[228]

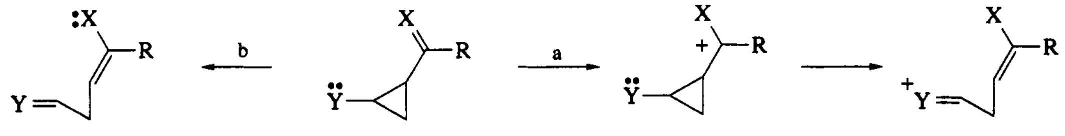

(**191**)

X = O, NR; R = alkyl, aryl, OR

**Scheme 43**

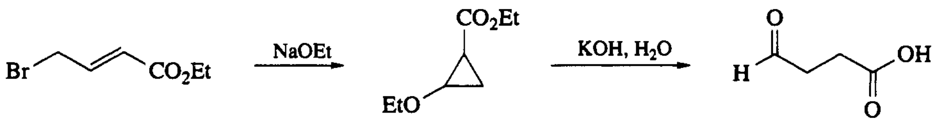

(**192**)

**Scheme 44**

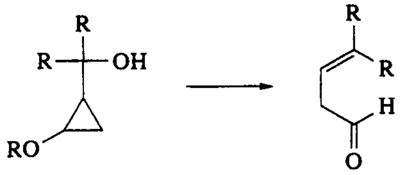

(**192a**) (56)

The above processes constitute the foundation on which Wenkert developed a general synthetic methodology applicable to terpenoid and alkaloid syntheses.[37,38] In some instances, the carbonyl can be viewed as a vinyl moiety participating in the overall heterovinylcyclopropane–cyclopentene rearrangement, as shown in Scheme 45, even though the mechanism involves the cyclopropylcarbinyl rearrangement. Some applications of this reaction are shown in Table 8.

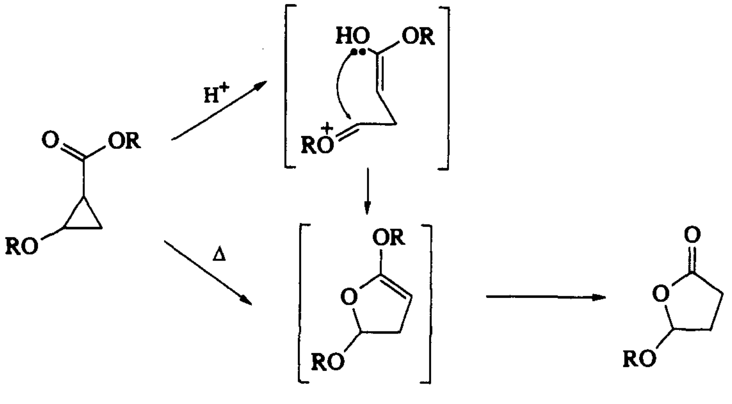

**Scheme 45**

**Table 8** Synthesis of Dihydrofurans

| *Cyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 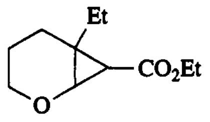 | $H^+$ | 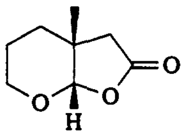 | 93 | 229 |
| 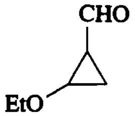 | $H^+$ | 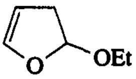 | 70–74 | 230, 231 |
| 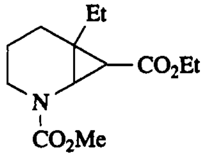 | $H^+$ or $OH^-$ | 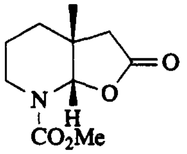 | 88 | 232 |
| 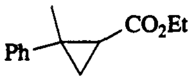 | HCl, Δ | 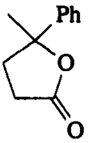 | 80 | 233 |

Alumina-catalyzed conversion of either isomer of (**193**) to dihydrofuran (**194**) was reported as an alternative to acid-catalyzed conditions (equation 57).[234] A methodology of α-methylene lactone synthesis relies on the solvolysis of cyclopropyl esters of type (**195**) to give α-methylene lactone (**196**) with $Li_2CO_3$ in dioxane (equation 58). The formation of the undesired diene (**197**) was diminished by the use of $AgClO_4$.[235]

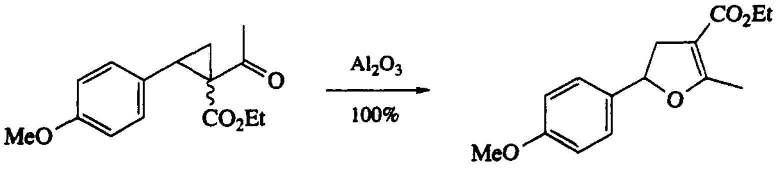

(**193**) (**194**) (57)

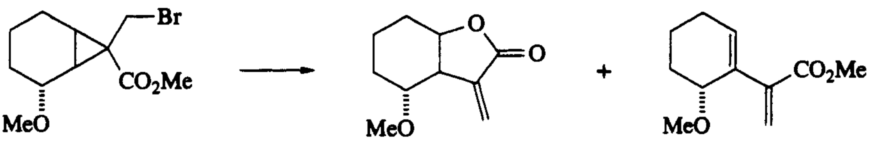
Br
CO2Me
MeO
O
O
MeO
+
CO2Me
MeO

(58)

**(195)** **(196)** 85% **(197)** 15%

Vinylcyclopropanes containing carboxylates react selectively through the agency of the carbonyl group in acid-catalyzed rearrangements, as shown in equation (59).[236] It is noteworthy that neither of the two alternative pathways, the divinylcyclopropane Cope rearrangement of (**198**) or cyclopentene rearrangement(s), takes place. Further examples of carboxylate over vinyl selectivity are seen in the rearrangements of cyclopropanes (**199**) and (**200**) to the corresponding tetrahydrofuranones (Scheme 46).[237]

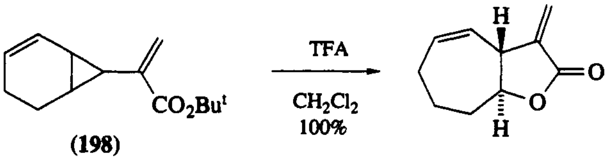
CO2Bu^t
TFA
CH2Cl2
100%
H
O
O
H

(59)

**(198)**

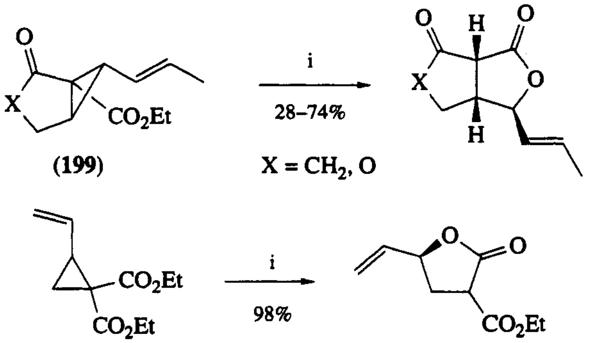
O
X
CO2Et
i
28–74%
X = CH2, O
O
H
O
X
O
H
CO2Et
CO2Et
i
98%
O
O
CO2Et

**(199)**

**(200)**

i, $(Me_3SiO)_2SO_2$, $Cl(CH_2)_2Cl$, reflux, 1 h

**Scheme 46**

Donor–acceptor-substituted heterovinylcyclopropanes also react by addition or trapping of any intermediates generated during these rearrangements, as the example in Scheme 47 indicates.[238] Further examples of the ring-opening modes and subsequent functionalizations have been exhaustively reviewed.[16,21,45] The examples in Table 9 show the additional modes of reactivity of carbonylcyclopropanes: reduction of cyclopropane, nucleophilic and electrophilic ring opening and thermal reactions. Recent reviews can be consulted for further examples.[12,16,21,251]

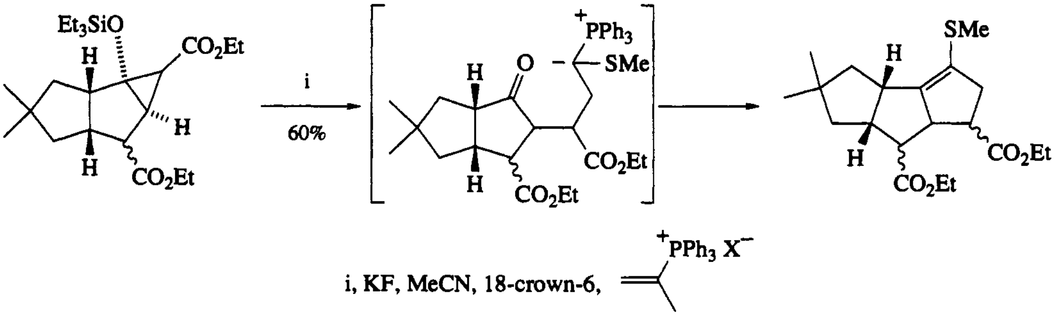
Et3SiO
H
CO2Et
H
H
CO2Et
i
60%
+PPh3
H
O
SMe
CO2Et
H
CO2Et
SMe
H
H
CO2Et
CO2Et
i, KF, MeCN, 18-crown-6,
+PPh3 X−

**Scheme 47**

**Table 9** Some Reactions of Carbonyl Cyclopropanes

| *Cyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 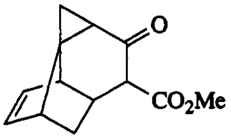 | $H_2$, Pd/C, MeOH | 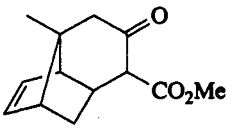 | 95 | 239 |
| 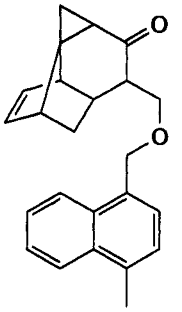 | $CrSO_4$, Zn, DMF/$H_2O$ (2:1) | 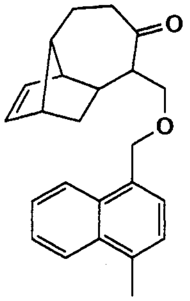 | 84 | 239 |
| 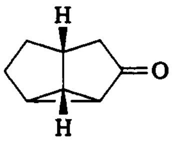 | $Bu^tMe_2SiI$ | 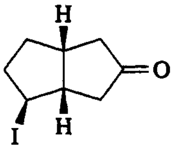 + 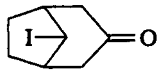<br>5:1 | 84 | 240 |
| 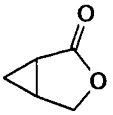 | PhSeNa, DMF, 120 °C | 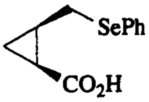 | 81 | 241 |
| 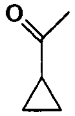 | PhSeLi | 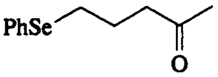 | 90 | 242 |
| 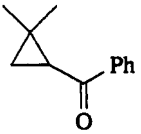 | i, $Me_3SiI$, $CCl_4$; ii, $H_2O$ | 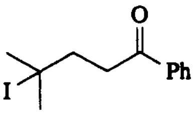 | 98 | 243 |
| 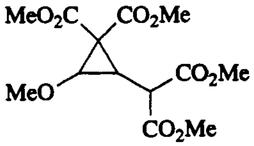 | DMSO, 25 °C | 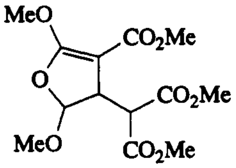 | — | 244 |
| 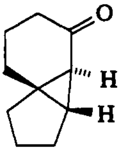 | conc. HCl, $Et_2O$ | 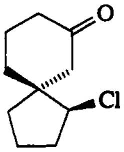 | 72 | 245 |

**Table 9** *(continued)*

| *Cyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 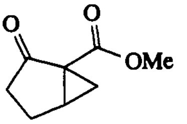 | RSH (R = Ph, Bn, n-hexyl) | 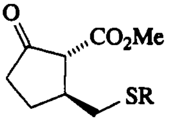 | 61–93 | 246 |
| 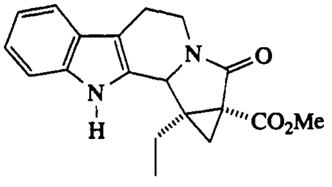 | TFA, $CH_2Cl_2$, r.t. | 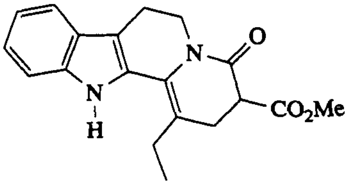 | 80 | 247 |
| 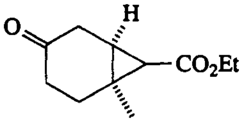 | NaOAc (catalyst), EtOH | 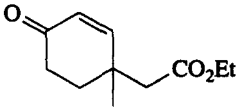 | 87 | 248 |
| 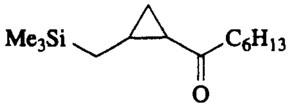 | $BF_3$, AcOH, $CH_2Cl_2$, 0 °C | 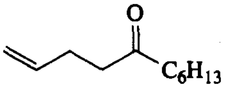 | — | 249 |
| 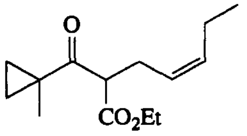 | 515 °C, 1–3 torr, glass wool | 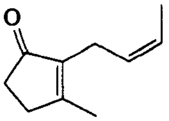 | — | 250 |
| 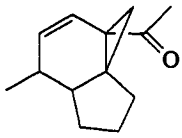 | 175 °C | 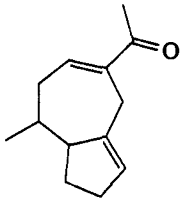 | 70 | 75 |
| 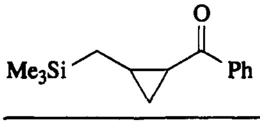 | $BF_3$•$OEt_2$, AcOH | 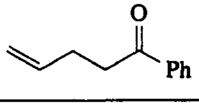 | 81 | 249 |

Rearrangements of cyclopropylimines have been studied in the context of the effects of heteroatom substitution on rearrangements of cyclopropanes quite recently, even though the cyclopropylimine–pyrroline rearrangement (the Cloke rearrangement) has been known since 1929, long before the discovery of the parent vinylcyclopropane system.[252] Dicyclopropylimine (**201**) rearranged to pyrroline (**202**), not to 2-pyrroline (**203**), the product expected from the accelerating effect of the amino substituent (Scheme 48). Further reaction and hydrolysis led to pyrrolizidone (**205**).[253] The effects of substituents (N, S) were investigated on substrates shown in equation (60).[253] Sulfur and nitrogen did not exert an effect of the magnitude expected from similar studies on vinylcyclopropanes, and this may be attributed to the mechanistic duality of this rearrangement, which may involve nucleophilic opening followed by alkylation. The observed preference for the rearrangement of the less-substituted cyclopropane may have its roots in steric effects and the preference for the nucleophilic attack at the less-substituted site. A different result was obtained by Stevens.[254,255] The piperido-substituted cyclopropane in (**206**) rearranged on thermolysis in the presence of an acid with a non-nucleophilic counterion and gave pyrrole **(207)** upon further, acid-catalyzed elimination (equation 61).[254,255]

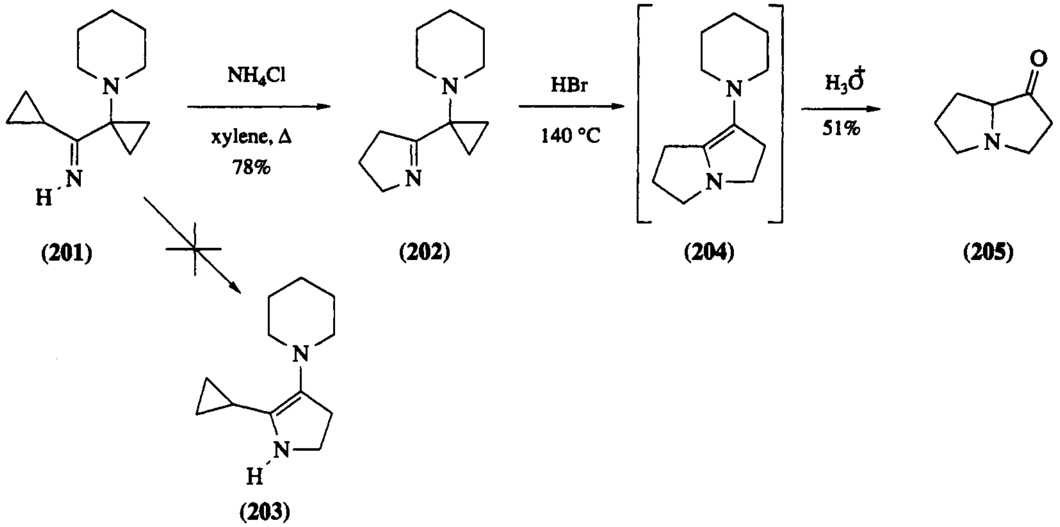
NH$_4$Cl
xylene, Δ
78%
HBr
140 °C
H$_3$O$^+$
51%
(201)
(202)
(204)
(205)
(203)

**Scheme 48**

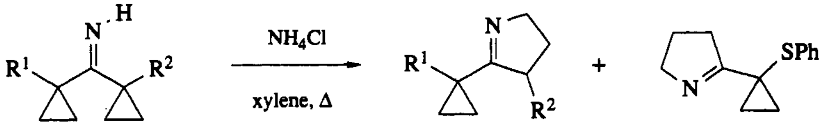
NH$_4$Cl
xylene, Δ
R$^1$
R$^2$
SPh

(60)

| | | | |
|---|---|---|---|
| **(206a)** | $R^1$ = piperidinyl, $R^2$ = H | 78% | – |
| **(206b)** | $R^1$ = piperidinyl, $R^2$ = SH | 69% | – |
| **(206c)** | $R^1$ = H, $R^2$ = SPh | 28% | 22% |

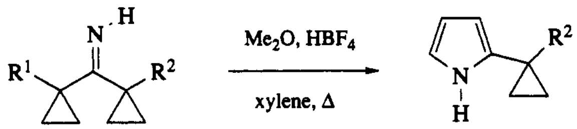
Me$_2$O, HBF$_4$
xylene, Δ
R$^1$
R$^2$

(61)

$R^1$ = piperidinyl **(207)**

| | | |
|---|---|---|
| **(206a)** | $R^2$ = H | 32% |
| **(206b)** | $R^2$ = SPh | 42% |

Cyclopropylimines are usually generated by reduction of nitriles or condensation of carbonyl compounds with amines.[255,256] An alternative to this process involves the generation of cyclopropylimmonium salts such as **(209)** at room temperature from cyanohydrin equivalent (**208**; Scheme 49).[257]

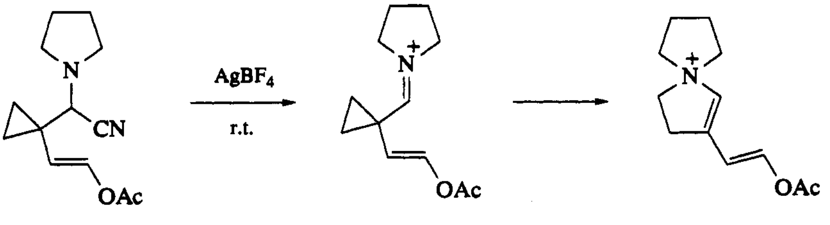
AgBF$_4$
r.t.
(208)
(209)

**Scheme 49**

The rearrangement proceeds thermally, under acid catalysis by HBr, $NH_4Cl$, or *via* nucleophilic opening and reclosure as in the case of vinylaziridines. Some examples of these processes are shown in Table 10. Sulfur substitution has been found effective in accelerating the rearrangement as well as serving as a site of further functionalization. This feature has been especially exhibited in the synthesis of pyrrolizidine and *Amaryllidaceae* alkaloids.[255,256] Section 8.1.9 gives a list of applications.

**Table 10** Cyclopropylimine Rearrangement

| *Cyclopropylimine* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 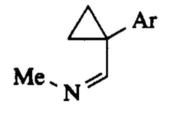 <br>Ar = $p$-MeOC$_6$H$_4$ | $NH_4Cl$, 130 °C | 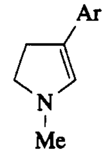 | 100 | 258, 259 |
| 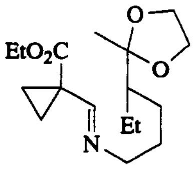 | $NH_4Cl$, Δ | 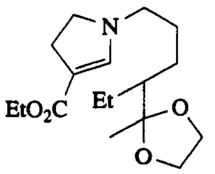 | 80 | 260 |
| 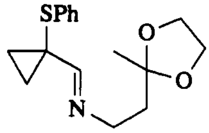 | $NH_4Cl$, Δ | 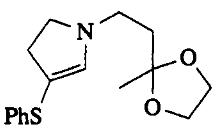 | 88 | 261 |

## 8.1.7 MISCELLANEOUS SYSTEMS

It would be difficult to list all of the cases involving the various combinations of heteroatom substitution in a vinylcyclopropane system. It has been recognized that virtually any heteroatom or any degree of unsaturation can be incorporated into the parent vinylcyclopropane system for almost limitless variability in the type of products that can be expected upon its rearrangements.[42,262] The general transformations depicted in equation (62) have been summarized and reviewed[18,179,263–266] in the context of the synthesis of five-membered heterocycles. Vinylcyclopropenes, methylenevinylcyclopropanes and cyclopropylalkynes all undergo the requisite rearrangements to five-membered rings.[9] The products are the corresponding cyclopentadienes or methylenecyclopentenes and their heteroatom analogs. These topics have been reviewed.[9,13,18,266] The mechanism of these transformations ranges from diradical scission to carbene generation and rearrangement.[18,266,267] Some of the representative transformations are shown in Table 11.

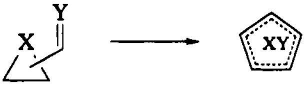

(62)

General discussions and reviews of rearrangements of heterovinylcyclopropane systems with one heteroatom[264] and two or more heteroatoms[263,264,274] not discussed in the previous section are available. Their rearrangements are governed by principles discussed previously, *i.e.* most stable diradical or ylide intermediate or the least-hindered site for nucleophilic attack in the case of nucleophilic openings. The electronegativity of the heteroatom and the conditions of rearrangement determine the regiochemistry of bond cleavage. With systems containing additional unsaturation, the divinylcyclopropane Cope rearrangement remains a viable option.[177] Table 12 lists the rearrangements of various nitrogen-, oxygen-, and sulfur-containing systems. Syntheses of pyrroles,[286] furans[287,288] and thiophenes[289] by the rearrangement of appropriate heterocyclopropanes have been summarized.

**Table 11** Rearrangements of Cyclopropenes, Cyclopropylalkynes and Methylenecyclopropanes

| *Cyclopropane* | *Conditions* | *Product(s)* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 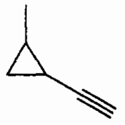 | 530 °C | 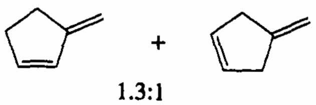 1.3:1 | 67 | 268 |
| 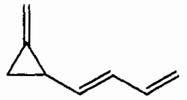 | 56 °C | 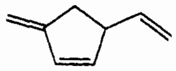 | — | 269 |
| 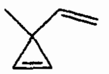 | [Pd(DBA)$_2$], 35 °C, 2 h | 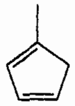 | 61 | 18 |
| 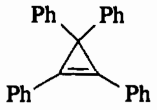 | AgClO$_4$, PhH, r.t. | 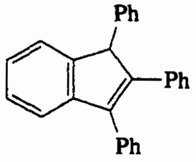 | 100 | 270 |
| 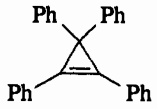 | 200 °C | 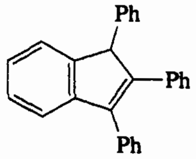 | 100 | 271 |
| 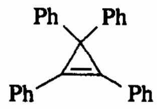 | *h*ν | 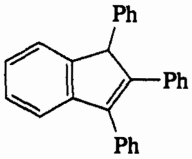 | 46 | 267 |
| 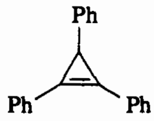 | [(C$_2$H$_4$)PtCl$_2$], CHCl$_3$<br>r.t., 13 h | 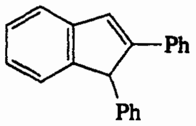 | — | 272 |
| 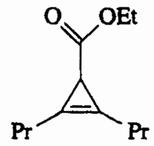 | Cu$^I$, 100 °C | 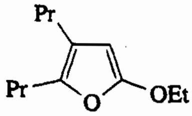 | 80 | 273 |

The selectivity between five- and seven-membered ring expansions is usually controlled by the parameters discussed for carbocyclic cases; that is, higher temperatures will favor five-membered rings, whereas the Cope-like rearrangements will be reversible at lower temperatures. A regioselectivity between thermal or photochemical rearrangements and metal-mediated rearrangements is illustrated by the examples involving azirines in equation (63)[290] and Scheme 50.[291] In the rearrangements of azirines the stereochemistry of the alkene determines the regiochemistry of the rearrangement and therefore the pathway (formation of five- *versus* seven-membered rings) to products, as shown in equations (64) and (65).[292] No *cis*/*trans* isomerization was observed, in direct analogy to a similar rearrangement of divinylaziridines of type (**169a**) in Section 8.1.5.[216]

**Table 12** Rearrangements of Miscellaneous Systems

| *Cyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 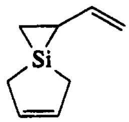 | $h\nu$, 254 nm, 310 °C | 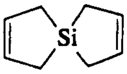 | 32 | 275 |
| 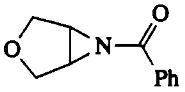 | 235–250 °C | 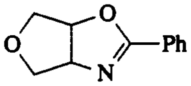 | 33 | 276 |
| 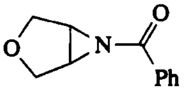 | NaI, MeCN, r.t. | 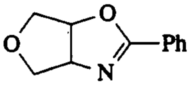 | 79 | 276 |
| 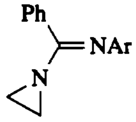<br>Ar = $p$-$O_2NC_6H_4$ | I$^-$ or SCN$^-$ | 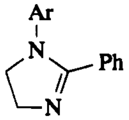 | 90 | 277 |
| 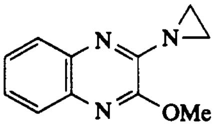 | NaI, acetone, Δ | 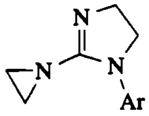 | 78 | 278 |
| 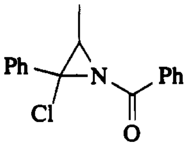 | acetone, 5 °C | 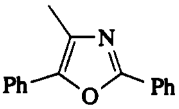 | 75 | 279, 280 |
| 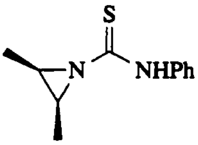 | TsOH, PhH | 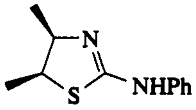 | 84 | 281 |
| 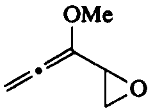 | KOBu$^t$, DMSO, r.t. | 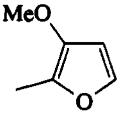 | 75 | 282 |
| 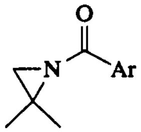<br>Ar = $p$-$O_2NC_6H_4$ | NaI, acetone, Δ | 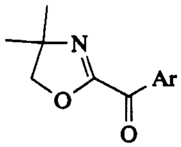 | 93 | 283 |
| 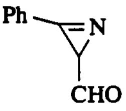 | 200 °C | 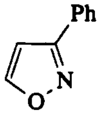 | 80 | 284 |

**Table 12** *(continued)*

| *Cyclopropane* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 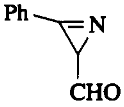 | *h*ν | 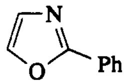 | — | 284 |
| 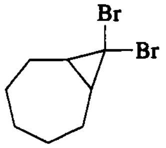 | MeLi | 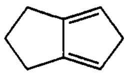 | 94 | 285 |

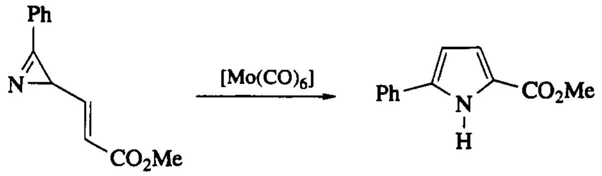

(63)

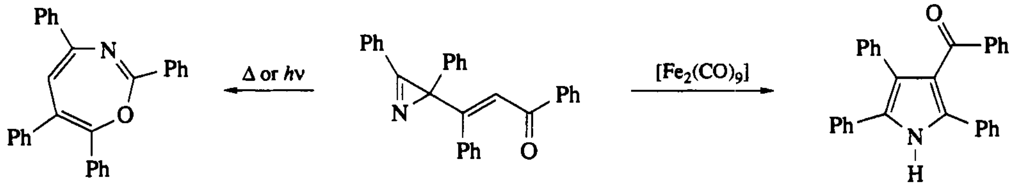

**Scheme 50**

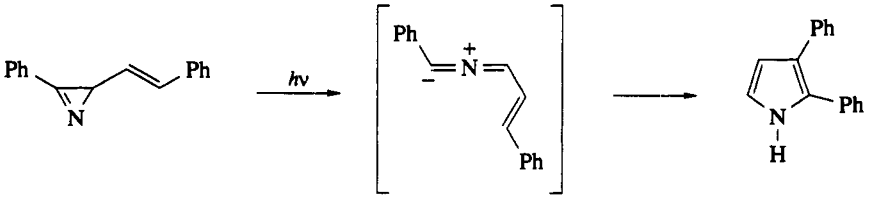

(64)

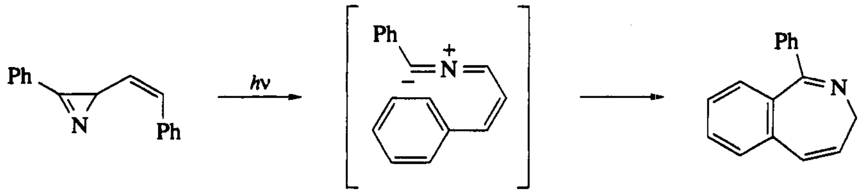

(65)

Other systems that undergo this rearrangement are dibromovinylcyclopropanes (through cyclopropylcarbene) equation (66),[293] and silavinylcyclopropanes in those cases where they can be isolated, as 1,4-addition is the normal mode of addition of silalenes to conjugated dienes (equation 67).[294]

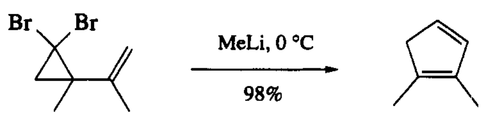

(66)

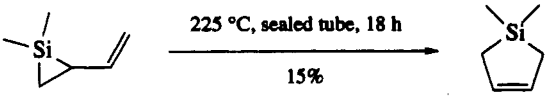

(67)

## 8.1.8 SURVEY OF GENERAL METHODOLOGIES

The chemistry discussed in this chapter has been exploited in several important general methods of synthesis. These are summarized in this section with leading references provided. Additional aspects of the rearrangements can be appreciated by analysis of the heterodivinylcyclopropane systems that are reviewed elsewhere.[177] The following survey provides a schematic review of the general methods of synthesis that have surfaced over the years and that are based on the rearrangements of vinylcyclopropanes and their analogs.

Trost developed a general method of synthesis of vinylcyclopropanes (and their sulfur and oxygen analogs) through the application of ylide addition to carbonyl compounds. Three major methods involve the cyclopentene annulation, cyclobutanone synthesis, and ring expansion with concomitant alkylation (Scheme 51).[20]

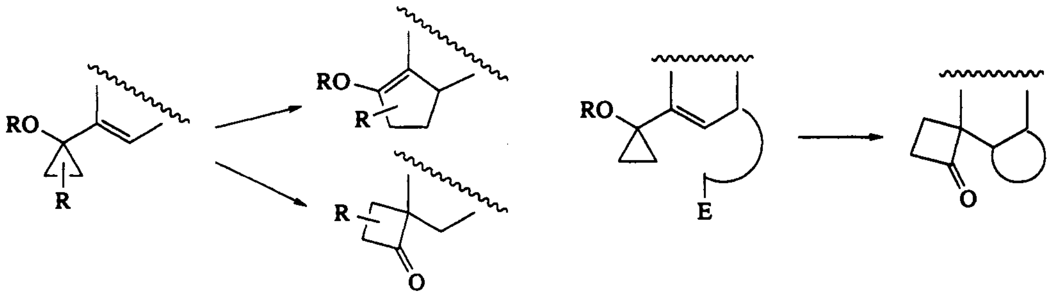

Scheme 51

Hudlicky developed a general method of triquinane synthesis based on a cyclopropanation–rearrangement sequence of dienic diazo ketones (Scheme 52). Topological selectivity of linear *versus* angular triquinane synthesis has been achieved.[41]

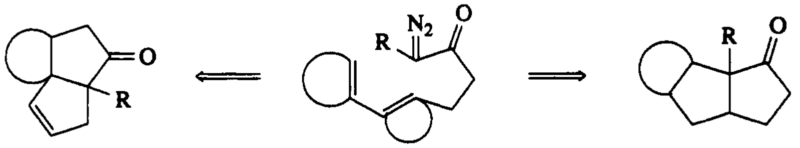

Scheme 52

Extension of this methodology to nitrogenous compounds (Scheme 53) has been implemented *via* azide cycloadditions to dienes as a facile means of synthesis of functionalized pyrrolizidines.[41,223] Recently a [2 + 3] methodology was developed (Scheme 54) that promises to have wide applicability in the synthesis of cyclopentanoids, bridged systems and dihydrofurans.[41]

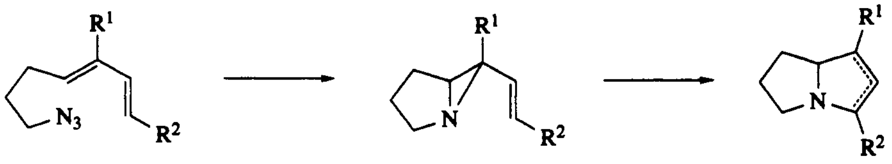

Scheme 53

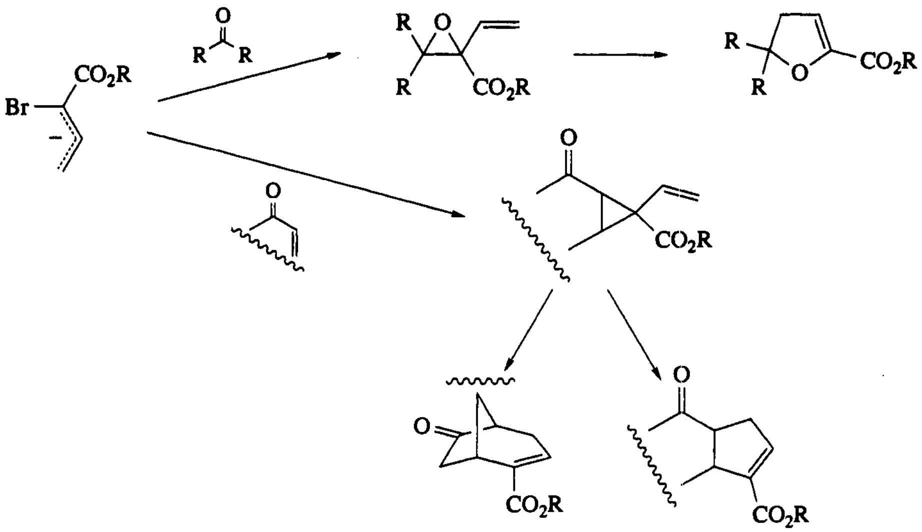

Scheme 54

The cyclopropylimine–pyrroline rearrangement (equation 68) has been exploited by Stevens in alkaloid syntheses.[255,256] Wenkert's cyclopropylcarbinyl rearrangement (equation 69) served extremely well in the design of 1,4-dicarbonyl synthons or β,γ-unsaturated carbonyl compounds which then were expressed in numerous syntheses of terpenoid and alkaloid natural products.[37,38] Donor–acceptor concepts continue to be expressed in the applicability of these rearrangements to organic synthesis.[16,21]

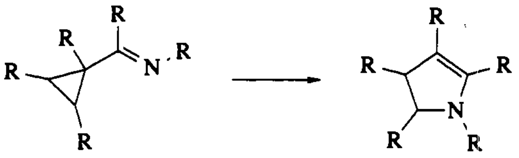

(68)

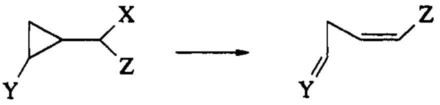

(69)

X = OR; Y = R$\bar{C}$H, O, NR; Z = H, R, OR

## 8.1.9 SURVEY OF TOTAL SYNTHESES

In this section those rearrangements of vinylcyclopropanes and their analogs that have been used in the synthesis of natural products are featured. The chronological listing of the syntheses provides an additional guide and cross-reference to specific literature dealing with the methodology discussed in this chapter. The presentation of the key steps in the context of the overall targets highlights the variety of structural types accessible *via* the rearrangements. The tabular survey is divided into three sections: Table 13 lists the cases of vinylcyclopropane–cyclopentene rearrangements; Table 14 compiles the rearrangements of vinylaziridines and cyclopropylimines to pyrrolines; and Table 15 shows transformations of vinyloxiranes or cyclopropylcarbonyls to dihydrofuran synthons.

**Table 13** Vinylcyclopropane–Cyclopentene Rearrangement

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Trost (1974) | 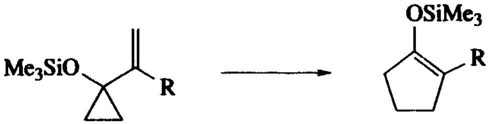<br>R = (CH$_2$)$_6$CO$_2$Bu$^t$ | 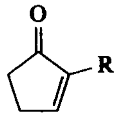<br>Prostaglandin intermediate | 295 |
| Trost (1979) | 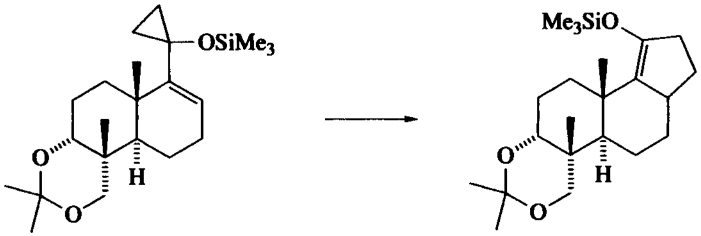 | 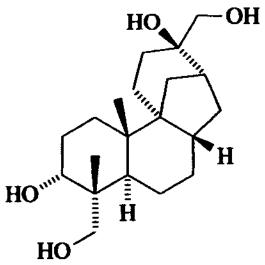<br>Aphidicolin | 296 |
| Piers (1979) | 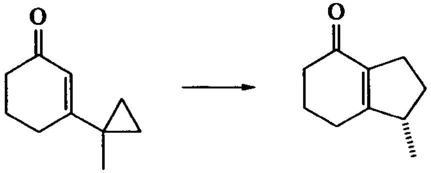 | 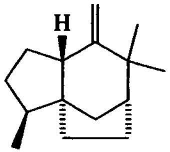<br>Zizaene | 297 |

**Table 13** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Hudlicky (1980) | 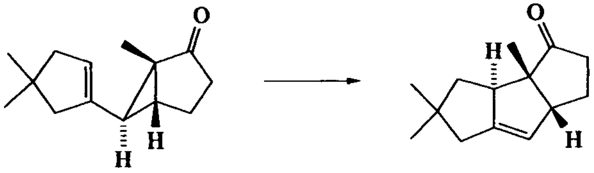 | 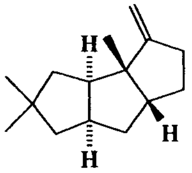<br>Hirsutene | 298 |
| Salaun (1981) | 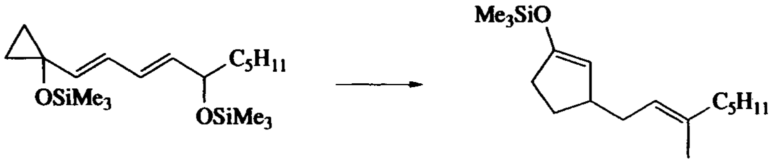 | 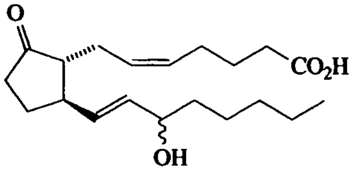<br>11-Deoxyprostaglandin $E_2$ | 90 |
| Paquette (1982, 1984) | 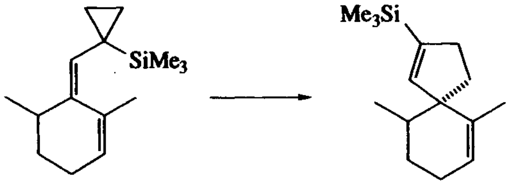<br>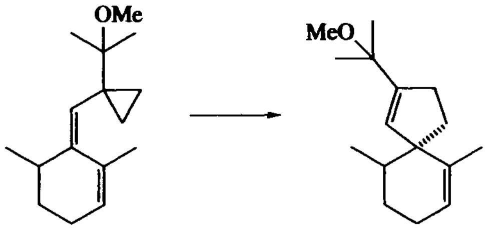 | 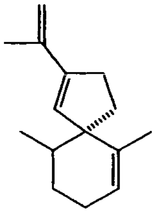<br>α-Vetispirene | 299, 300 |

**Table 13** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Piers (1983) | 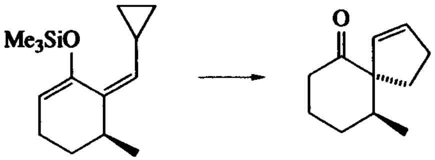 | 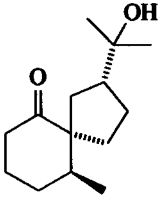 <br>Hinesol | 301 |
| | | 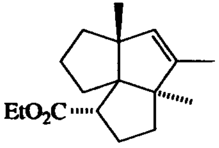 <br>Isocomenic acid (1983) | 302 |
| Hudlicky (1983) | 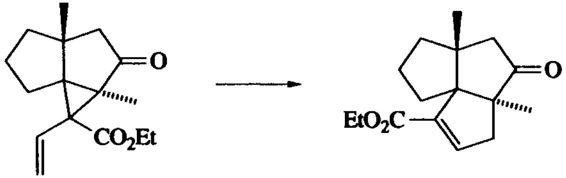 O<br>CO$_2$Et<br>EtO$_2$C<br>O | 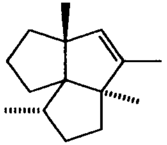<br>Isocumene | 303 |
| | | 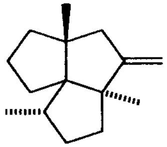<br>β-Isocomene (1984) | 303 |
| Salaun (1983) | 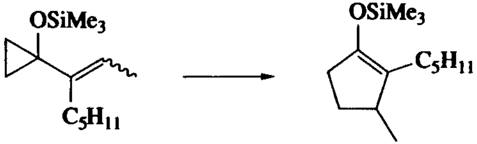 OSiMe$_3$<br>C$_5$H$_{11}$<br>OSiMe$_3$<br>C$_5$H$_{11}$ | 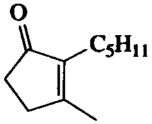 <br>Dihydrojasmone (and jasmone) | 304 |

**Table 13** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Wender (1983) | 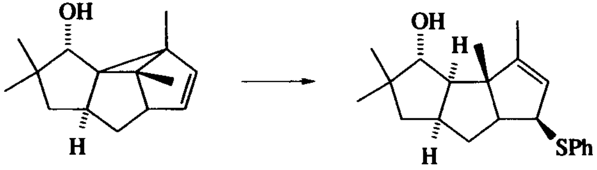 | 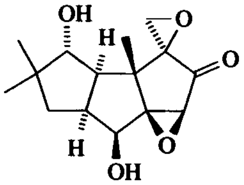 Coriolin | 117 |
| Salaun (1984) | 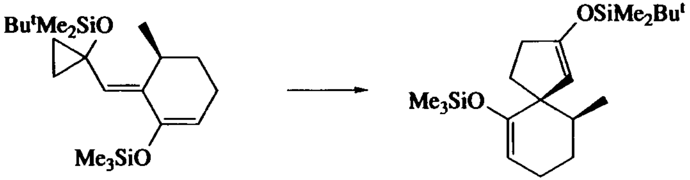 | 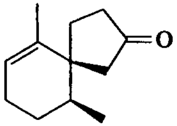 Spirovetivane | 305 |
| Wender (1985) | 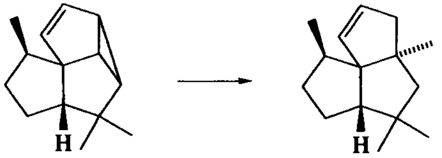 | 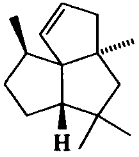 Silphinine | 306 |
| Salaun (1985) | 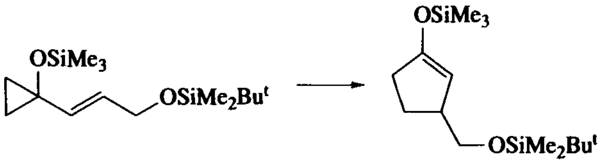 | 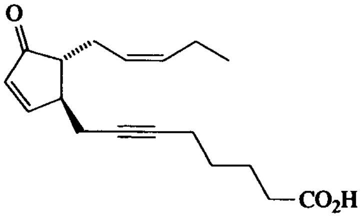 Dicranenone | 307 |

Table 13 *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Corey (1985) | 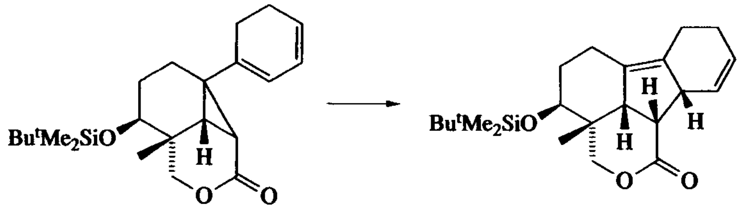 | 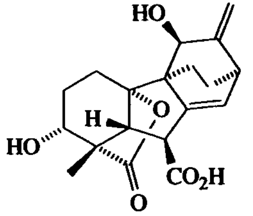<br>Antheridiogen-An | 308 |
| Hudlicky (1986) | 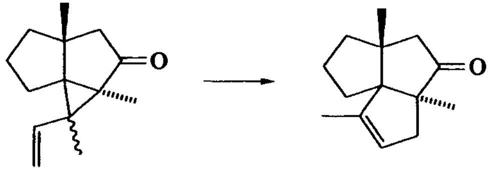 | 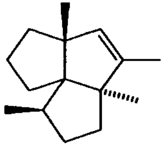<br>Epiisocomene | 309 |
| Hudlicky (1987) | 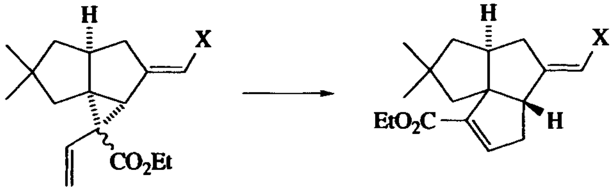 | 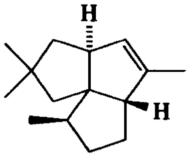<br>Pentalenene | 310, 311 |
| Hudlicky (1987) | 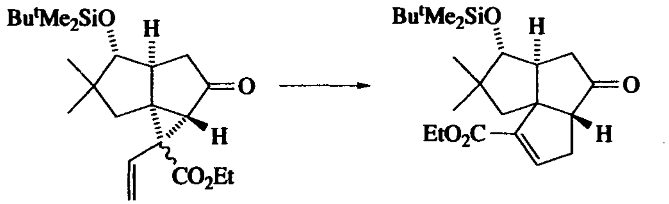 | 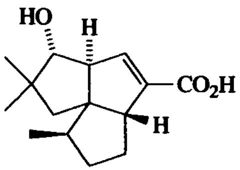<br>Pentalenic Acid | 311 |

Table 13 *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Hudlicky (1988) | 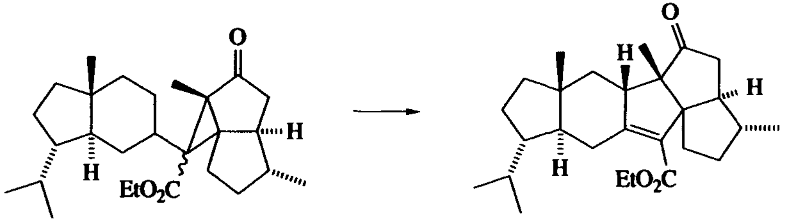 O<br>H<br>EtO2C<br>H<br>O<br>H<br>H<br>H<br>EtO2C | 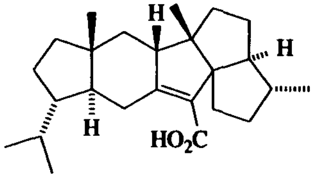 <br>Retigeranic acid | 99, 128 |
| Hudlicky (1989) | 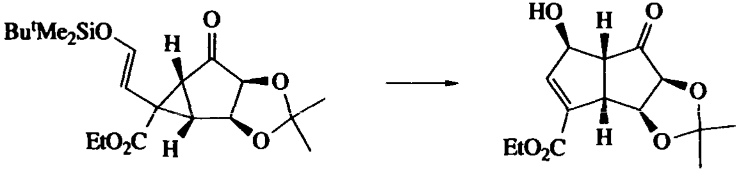 Bu<sup>t</sup>Me2SiO<br>H<br>O<br>O<br>O<br>EtO2C<br>H<br>HO<br>H<br>O<br>O<br>O<br>EtO2C<br>H | 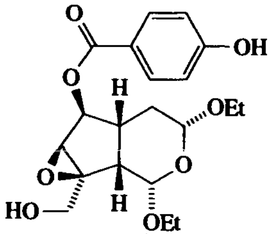 O<br>OH<br>O<br>H<br>OEt<br>O<br>O<br>HO<br>H<br>OEt<br>Specionin | 103, 128, 312 |

**Table 14** Cyclopropylimine– and Vinylaziridine–Pyrroline Rearrangements

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Stevens (1967) | 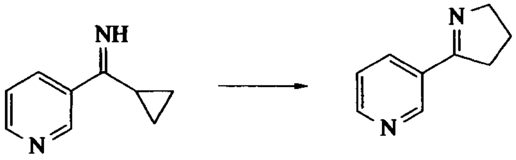 | 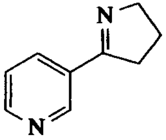<br>Mysomine | 313, 314 |
| Stevens (1967) | 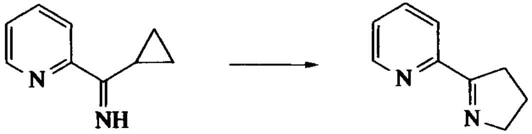 | 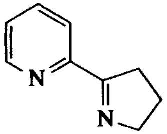<br>Apoferrosamine | 313, 314 |
| Stevens (1968)<br>Keely (1968) | 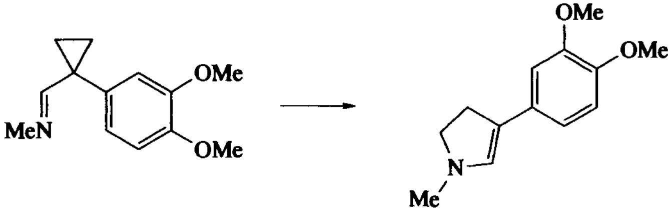 | 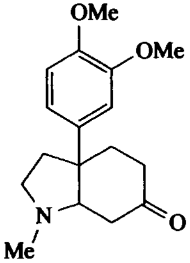<br>Mesembrine | 315–318 |
| Breuer (1969) | 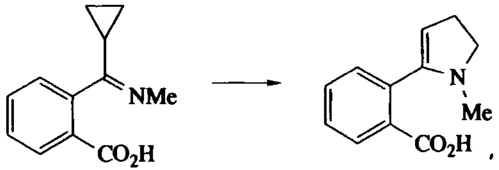 | 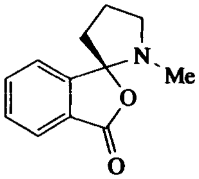<br>Shihunine | 319 |

**Table 14** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Stevens (1971) | 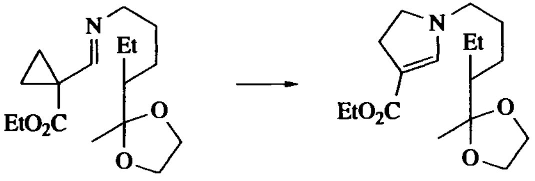 | 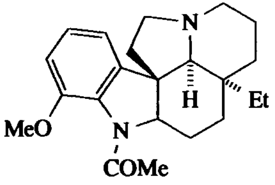<br>Aspidospermine | 260 |
| Stevens (1972) | 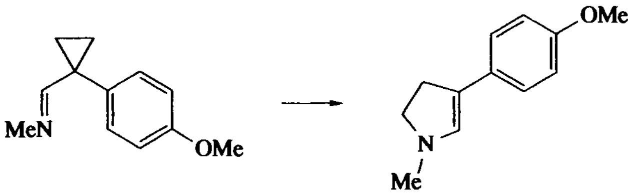 | 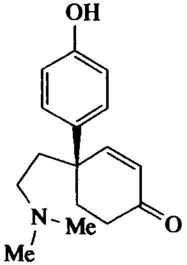<br>Joubertiamine | 258 |
| Stevens (1972) | 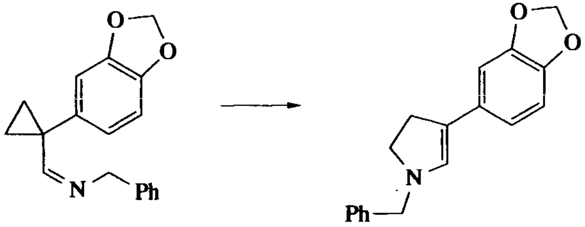 | 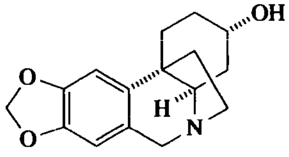<br>Elwesine | 320 |
| Comes (1973) | 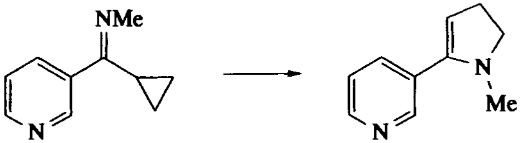 | 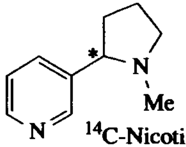<br>$^{14}$C-Nicotine | 321 |

**Table 14** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Stevens (1975) | 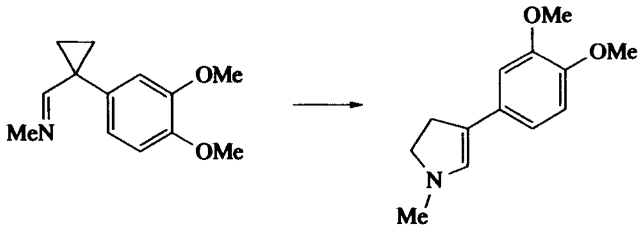 | 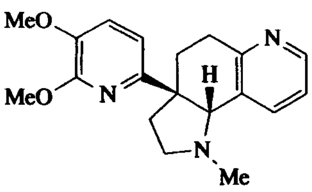<br>Sceletium alkaloid A-4 | 317 |
| Stevens (1976) | 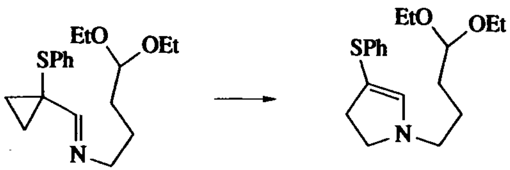 | 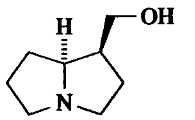<br>Isoretronecanol | 261 |
| Stevens (1976) | 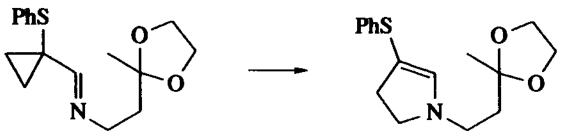 | 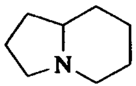<br>δ-Coniceine | 261 |
| Stevens (1977) | 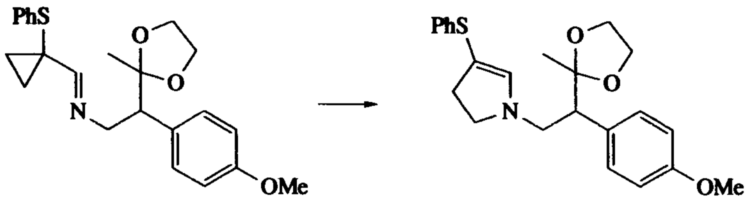 | 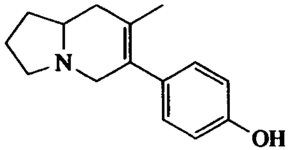<br>Ipalbidine | 322 |

**Table 14** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Stevens (1977) | 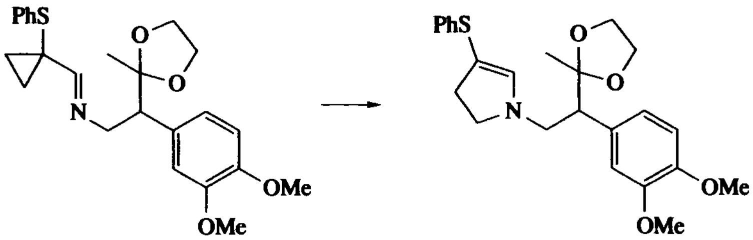 | 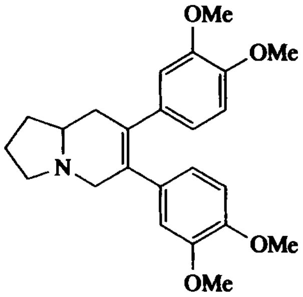<br>Septicine | 322 |
| Hudlicky (1984, 1985 1986, 1987) | 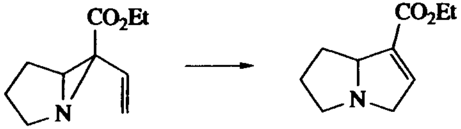 | 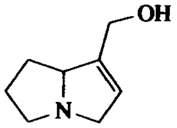<br>Supinidine | 212, 221 |
| Pearson (1985) | | | 213 |
| Hudlicky (1986) | 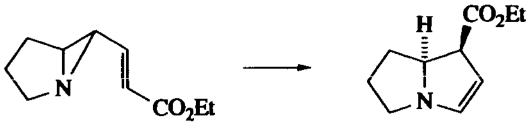 | 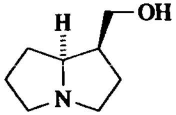<br>Isoretronecanol<br>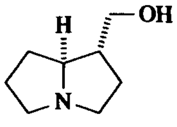<br>Tracelanthamidine | 221, 223 |

**Table 14** *(continued)*

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Maruyama (1987) | 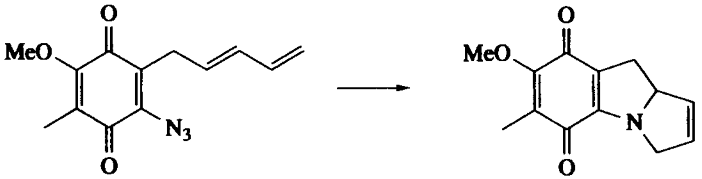 | 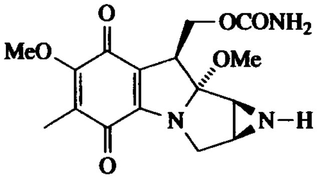<br>Mitomycin A | 323 |
| Hudlicky (1988) | 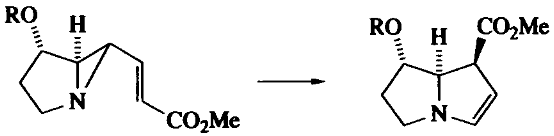 | 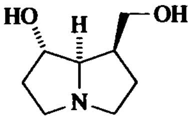<br>Dihydroxyheliotridane<br>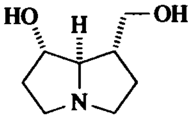<br>Hastanecine | 222, 251 |
| Hudlicky (1989) | 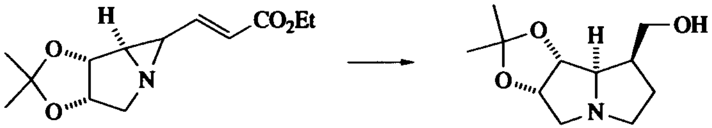 | 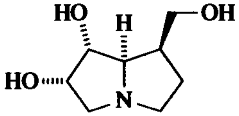<br>Trihydroxyheliotridane | 225, 251 |

**Table 15** Vinyloxirane and Cyclopropyl–Carbonyl–Dihydrofuran Rearrangements

| *Author (year)* | *Key transformation* | *Target* | *Ref.* |
|---|---|---|---|
| Wenkert (1978) | 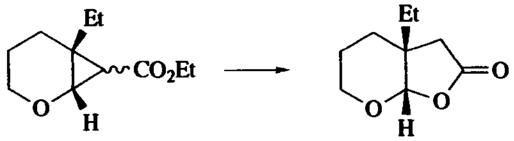<br>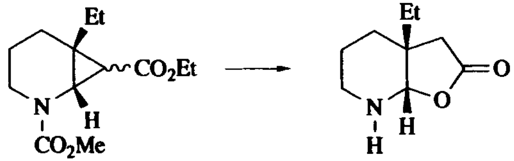 | 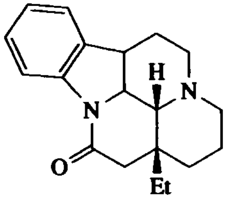<br>Eburnamonine | 223 |
| Wenkert (1988) | 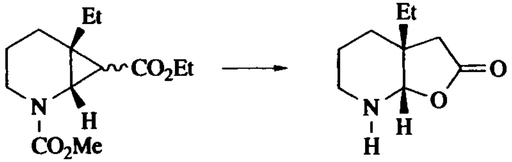 | 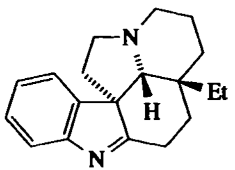<br>Dehydroaspidospermidine<br>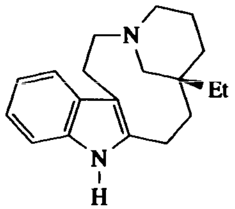<br>Quebrachamine | 324 |
| Hudlicky (1989) | 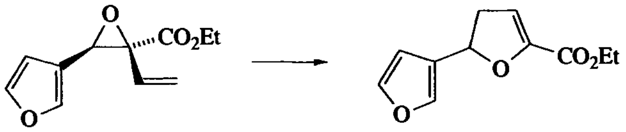 | 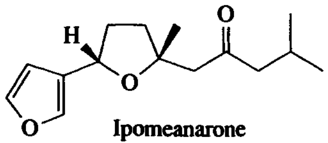<br>Ipomeanarone | 176 |

## 8.1.10 CONCLUSION

The chemistry associated with the vinylcyclopropane system and its heteroatom analogs has indeed provided for an incredible variety of transformations. In this chapter an attempt at a survey and a classification has been made in order to place all of the mechanistic pathways over a common denominator. Until now each system has been dealt with separately in the literature except for the vinylcyclopropane–cyclopentene rearrangement, which has been reviewed in the same light as a name reaction. Upon reading this chapter it will become obvious that the immense amount of chemistry done to date bodes well for even better powers of predictability and increased utility of those transformations yet to be applied in organic synthesis. Further development of general synthetic strategies and their application in systematic preparation of complex molecules, as well as the basic understanding of mechanistic details, will indeed continue to be expressed especially in the systematic design of five-membered carbo- and hetero-cyclic compounds. The vinylcyclopropane–cyclopentene rearrangement and all of its variants therefore serve the same function in the domain of five-membered ring compounds as the Diels–Alder reaction occupies in the field of cyclohexane synthesis. It is hoped that through the summary and classification of the chemistry associated with the title systems this comparison has been amply demonstrated.

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# 8.2

# Rearrangements of Divinylcyclopropanes

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## 8.2.1 INTRODUCTION

The facile thermal $\sigma^2s + \pi^2s + \pi^2s$ (Cope) rearrangement of *cis*-1,2-divinylcyclopropane (**1**) to 1,4-cycloheptadiene (**2**) was first reported in 1960 by Vogel.[1] In his experiments, Vogel did not isolate (**1**), since, under the conditions of its formation (*e.g.* thermolysis of **3** at 80 °C), (**1**) rearranges rapidly to (**2**). Indeed, it was not until more than a decade later that (**1**) was isolated and shown to rearrange to (**2**) with half-lives of approximately 90 s and 25 min at 35 °C[2] and 11 °C,[2,3] respectively.

Not unexpectedly, *trans*-1,2-divinylcyclopropane (**4**) is much more stable than the *cis* isomer (**1**) and is a readily isolable compound. Nevertheless, at elevated temperatures, *e.g.* 190 °C, (**4**) undergoes smooth bond reorganization to provide 1,4-cycloheptadiene (**2**) in essentially quantitative yield.[1a,1c] Thus, at the time that the Cope rearrangement of 1,2-divinylcyclopropane systems was discovered,[1] it was already clear that both *cis* and *trans* isomers could, in principle, serve as suitable substrates for the reaction. As it turns out, this is an important reaction characteristic, since, in most (but not all) cases, it makes unnecessary the stereoselective preparation of either the *cis* or *trans* starting material.

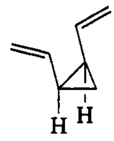

**(1)**

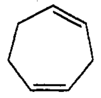

**(2)**

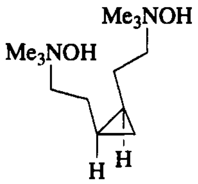

**(3)**

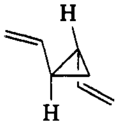

**(4)**

Since 1960, the thermolysis of 1,2-divinylcyclopropanes has been studied quite extensively from a mechanistic point of view. However, particularly since 1975, synthetic applications of the rearrangement reaction have been explored and these studies have shown that the reaction provides a versatile, effective method for the construction of functionalized mono-, bi- and tri-cyclic substances.[4] In this chapter the mechanistic features of the rearrangement will be outlined briefly. The major portion of the discussion will deal with synthetic aspects of this interesting process.

## 8.2.2 MECHANISTIC CONSIDERATIONS

### 8.2.2.1 Rearrangement Pathways

It appears to be well accepted that the thermal rearrangement of *cis*-1,2-divinylcyclopropane (**1**) proceeds in a concerted fashion *via* a boat-like transition state, in which the vinyl groups lie over the three-membered ring.[5–7] Thus, conformational orientation of (**1**) as shown in (**1b**; equation 1), followed by bond reorganization by way of a transition state represented by (**A**), provides 1,4-cycloheptadiene (**2**), in which both double bonds have *cis* stereochemistry. Concerted rearrangement of (**1**) *via* a chair-like transition state derived directly from conformation (**1a**) would lead to the highly strained *trans,trans*-1,4-cycloheptadiene and it is clear that such a pathway would be of a much higher energy than that involved in the conversion of (**1b**), *via* (**A**), into (**2**).

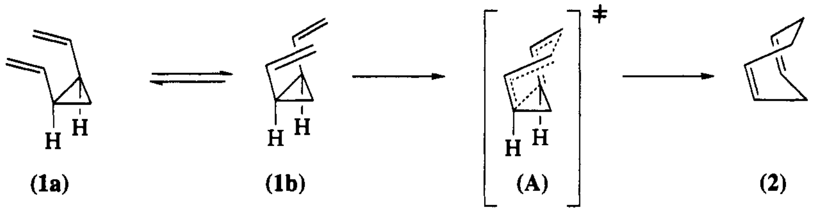

(1)

The thermolytic transformation of *trans*-1,2-divinylcyclopropane (**4**) into 1,4-cycloheptadiene (**2**) probably proceeds *via* the pathway shown in equation (2). Homolytic cleavage of the cyclopropane ring of (**4**) provides the resonance stabilized diradical (**5**), which, in addition to reverting to (**4**), can undergo bond rotation and subsequent ring closure to give *cis*-1,2-divinylcyclopropane (**1**). The latter substance then rearranges, by way of conformation (**1b**), into (**2**).

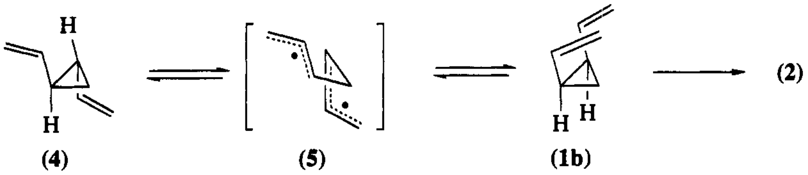

(2)

The energy of activation $E_a$ for the overall conversion of (**4**) into (**2**) has been reported[7,8] to be in the range 32.1–34.3 kcal mol$^{-1}$ (1 kcal ≈ 4.2 kJ). In comparison, the data reported by Brown *et al.*[2] and Schneider and Rau[9] show that $E_a$ for the rearrangement of (**1**) to (**2**) is about 19–20 kcal mol$^{-1}$. Thus, for the conversion of (**4**) into (**2**), the rate-determining step is the isomerization of (**4**) into (**1**), presumably *via* the diradical (**5**). This characteristic is common to most of the known rearrangements of 1,2-divinylcyclopropane systems. That is, for a given pair of isomers, *trans* to *cis* isomerization is generally slower than Cope rearrangement of the *cis* isomer. However, it must be noted that there are exceptions to this generalization, since thermolysis of certain substituted *cis*-1,2-divinylcyclopropanes results only in *cis–trans* isomerization and not in sigmatropic rearrangement (*vide infra*).

### 8.2.2.2 Substituent Effects

Substituents attached to the terminal carbons of the vinyl groups can have a profound effect on the rate of Cope rearrangement of *cis*-1,2-divinylcyclopropane systems. For example, Table 1 compares the relative rate of the sigmatropic rearrangement of the parent substance (**1**) with those of the simply substituted substrates (**6**)–(**8**).[9] It can be seen that, although the rate-depressing effects of methyl substituents situated *trans* on the vinyl groups (substrates **6** and **7**) are relatively minor, the effect of a *cis* substituent (substrate **8**) is dramatic. On the basis of the rate data, the destabilizing free energies of activation ($\Delta\Delta G$‡) associated with the steric interactions in transition states (**B**)–(**D**) (Table 1) were calculated.[9] The values (Table 1) show that the methyl–ring interaction in transition state (**D**) produces by far the largest steric effect. Indeed, Schneider and Rau[9] showed that the *cis,cis,cis* substrate (**11**) undergoes reversible *cis–trans* isomerization, (**11**) to (**12**), much faster than it undergoes Cope rearrangement to (**10**; Scheme 1). In a related study, Baldwin and Ullenius[10] reported that, at 165 °C, the (**11**):(**12**) ratio at equilibrium is about 1:4. Furthermore, heating (**12**) at 178 °C for 4.2 h or 75 h gives, in addition to an equilibrium mixture of (**11**) and (**12**), minor (4%) or significant (35%) amounts of the Cope rearrangement product (**10**). Thus, although the sigmatropic bond reorganization of (**11**) is not precluded, the steric interactions present in the transition state (**E**; Scheme 1) make this a higher energy pathway than the isomerization of (**11**) to (**12**).

Other studies have also qualitatively demonstrated the effect of substitution patterns on the ease of *cis*-divinylcyclopropane rearrangements. For example, at temperatures in the range 0–20 °C, the substrates (**13**)–(**15**) are readily transformed into the cycloheptadienes (**16**)–(**18**), respectively (Scheme 2).[11-13] The rearrangement of (**15**) to (**18**) occurs with a half-life of approximately 50 min at 15 °C,[13] and is thus marginally slower than the thermal conversion of the parent *cis*-1,2-divinylcyclopropane (**1**) into 1,4-cycloheptadiene (**2**).[2,3] On the other hand, complete transformation of (**19**) into (**16**) requires heating at 75 °C for 5 h (Scheme 2),[11] again demonstrating the notable rate-retarding effect of a *cis* substituent.

The highly substituted *cis*-divinylcyclopropanes (**20**) and (**21**) do not undergo sigmatropic rearrangement at all.[14] Apparently, the highly sterically congested nature of the transition states (**F**) precludes this possibility. Thermolysis of (**20**) and (**21**) at 170–180 °C produces only equilibrium mixtures of these substances and the corresponding *trans* isomers (**22**) and (**23**), respectively (Scheme 3).[14]

## 8.2.3 MONOCYCLIC DIVINYLCYCLOPROPANES

### 8.2.3.1 Stereospecificity

Rearrangement of (**7**) at –10 to 30 °C (Table 1, *vide supra*) provides quantitatively *cis*-6,7-dimethyl-1,4-cycloheptadiene (**10**).[9] Furthermore, prolonged heating of (**11**) at 178 °C produces, in addition to the *trans* isomer (**12**), the same sigmatropic rearrangement product (**10**; Scheme 1).[10] Other studies have shown that thermolyses (178 °C, 4.2 h) of substrates (**24**) and (**25**) give, in quantitative yields, the epimeric cycloheptadienes (**10**) and (**27**), respectively.[10] Presumably, these transformations proceed by way of the corresponding *cis*-1,2-di(1-propenyl)cyclopropanes (**7**) and (**26**).[10]

Collectively, the results summarized above show that, with respect to the stereochemistry of appropriately substituted vinyl groups, the (reversible) *trans* to *cis* isomerization (*e.g.* **12** $\rightleftharpoons$ **11**; **24** $\rightleftharpoons$ **7**; **25** $\rightleftharpoons$ **26**) and the sigmatropic rearrangement of the *cis*-1,2-divinylcyclopropane systems (*e.g.* **7** or **11** → **10**; **26** → **27**) are completely stereospecific. In connection with carrying out stereoselective syntheses, the importance of this reaction characteristic is obvious. Indeed, the stereospecific nature of the Cope rearrangement of 1,2-divinylcyclopropanes has been demonstrated with substrates that are structurally more complex than those discussed above. Specific examples will be presented later in this chapter.

### 8.2.3.2 Enantiospecificity

Relatively little work has been done in this area. In studies related to the total synthesis of the marine natural product (*R*)-(–)-dictyopterene C′ (**30**), Jaenicke and coworkers[15] have shown that the enantio-

**Table 1** Cope Rearrangement of some *cis*-1,2-Divinylcyclopropane Systems[9]

| *Substrate* | *Transition state* | *Steric interaction(s) (destabilizing free energy)*[a] | *Product* | $k_{rel}$ *(40 °C)*[b] |
|---|---|---|---|---|
| 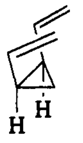 **(1)** | 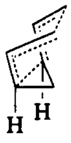 **(A)** | — | 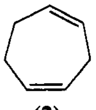 **(2)** | 5800 |
| 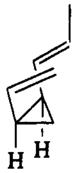 **(6)** | 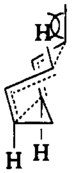 **(B)** | Me–H (0.84) | 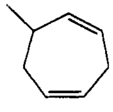 **(9)** | 1500 |
| 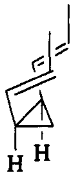 **(7)** | 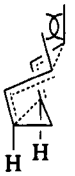 **(C)** | Me–Me (1.03) | 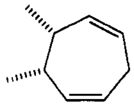 **(10)** | 1100 |
| 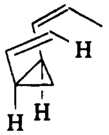 **(8)** | 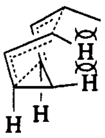 **(D)** | Me–H (0.84)<br>Me–Ring (4.55) | 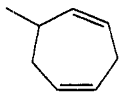 **(9)** | 1 |

[a] ΔΔG†, in kcal $mol^{-1}$, calculated at 40 °C. [b] By extrapolation of the fast (**1**, **6** and **7**) and slow (**8**) runs. Rate constants were determined as averages of 5 runs at 6 to 8 temperatures over a range of a least 40 °C: (**1**), –20 to 20 °C; (**6**), –10 to 30 °C; (**7**), –10 to 30 °C; (**8**), 50 to 98 °C.

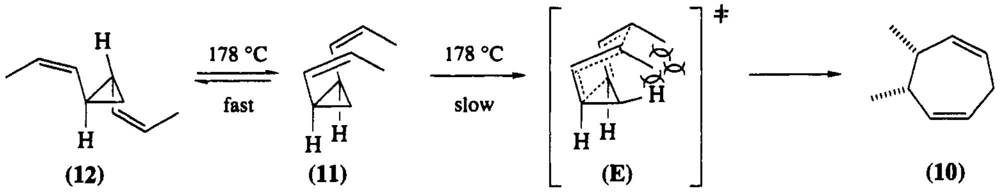

**Scheme 1**

merically pure substrates (**28**) and (**29**) rearrange cleanly to the corresponding enantiomerically pure products (**30**) and (**31**), respectively (Scheme 4). Non-natural (*S*)-(+)-dictyopterene C′ (**31**) is also obtained by rearrangement of (1*R*,2*S*)-1-[(*E*)-1-hexenyl]-2-vinylcyclopropane (Scheme 4).[16] These results show, not unexpectedly, that the Cope rearrangements of rather simply substituted *cis*-divinylcyclopropanes are enantiospecific.

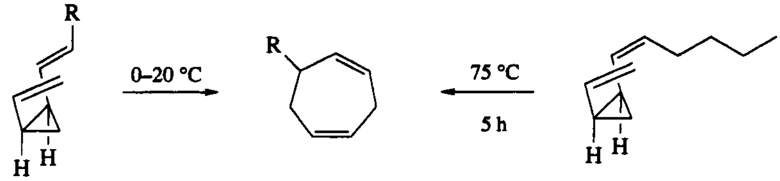

**(13)** R = Bu$^n$
**(14)** R = (*E*)-1-butenyl
**(15)** R = (*Z*)-1-butenyl

**(16)** R = Bu$^n$
**(17)** R = (*E*)-1-butenyl
**(18)** R = (*Z*)-1-butenyl

**(19)**

**Scheme 2**

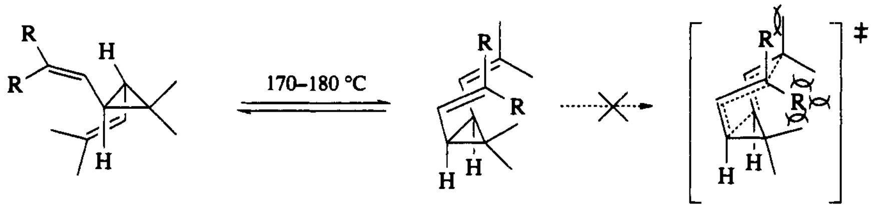

**(22)** R = H (75%)
**(23)** R = Me (72%)

**(20)** R = H (25%)
**(21)** R = Me (28%)

**(F)** R = H or Me

**Scheme 3**

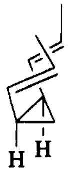

**(7)**

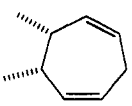

**(10)**

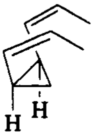

**(11)**

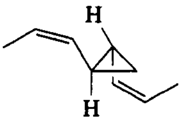

**(12)**

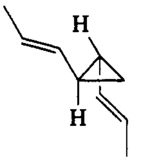

**(24)**

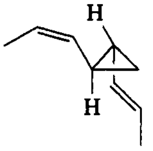

**(25)**

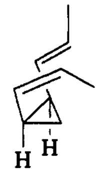

**(26)**

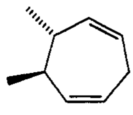

**(27)**

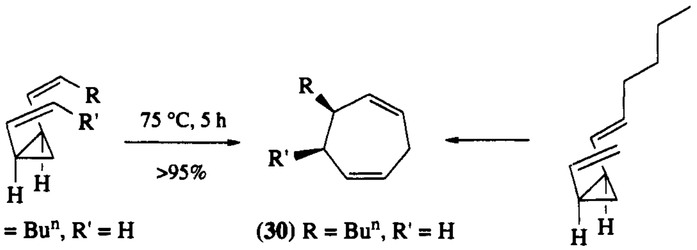

**(28)** R = Bu$^n$, R' = H
**(29)** R = H, R' = Bu$^n$

**(30)** R = Bu$^n$, R' = H
**(31)** R = H, R' = Bu$^n$

**Scheme 4**

With monocyclic *trans*-1,2-divinylcyclopropanes, chirality transfer is, apparently, poor. Thermolysis of (+)-dictyopterene A (**33**) at 165 °C for 48 h and of (–)-dictyopterene B (**34**) at 103–108 °C for 40 h gives, in each case, a mixture of the two enantiomeric Cope rearrangement products, (**30**), (**31**) and (**37**), (**40**), respectively (Scheme 5).[17] Although the uncertainty associated with the optical purities and (or) rotations of the various substances involved[15,17] made a quantitative determination of the product ratios difficult, it is evident from the results that enantiomers (**31**) and (**37**) predominated marginally over (**30**) and (**40**), respectively. This observation has been rationalized[18] by postulating that, in the intermediate diradical (**35**), the allyl system rotates more rapidly, to give (**36**), than the more bulky heptenyl or heptadienyl groups, to produce (**38**). Ring closure of (**36**) and (**38**), followed by bond reorganization of the (enantiomeric) *cis*-divinylcyclopropanes (**32**) and (**39**), produces the final products.

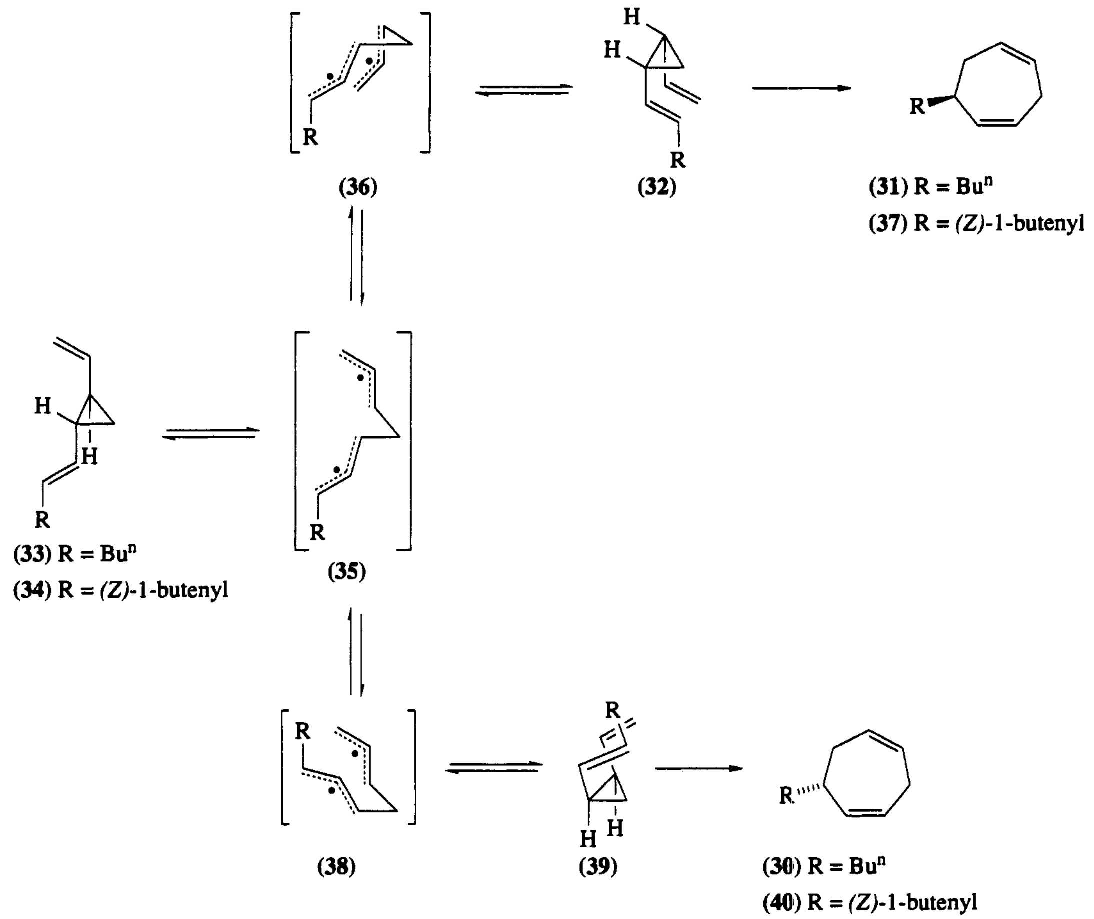

**Scheme 5**

Although further work in this area is desirable, it appears that in the Cope rearrangement of simple *trans*-divinylcyclopropanes, such as (**33**) and (**34**), enantioselectivity is poor.

### 8.2.3.3 Synthesis of Functionalized Cycloheptanes

The use of the Cope rearrangement of 1,2-divinylcyclopropanes for the synthesis of functionalized seven-membered rings has been illustrated in a number of studies. For example, thermolysis of (**41**) (mixture of *cis* and *trans* isomers), followed by cleavage of the enol silyl ether function in the resultant product (**42**), provides the natural product karahanaenone (**43**; Scheme 6).[19] In this case, as in many others, the fact that (**41**) was not stereochemically homogeneous was of no consequence, since both isomers of (**41**) cleanly afford the same rearrangement product. Similarly, sigmatropic rearrangement of the isomers (**44**) and (**45**) and subsequent hydrolysis of the resultant vinyl sulfide (**46**) also produces karahanaenone (**43**).[20] The efficient conversion of substrate (**47**) into the keto ester (**50**) *via* a route in which the Cope rearrangement of (**48**) played a key role has been reported.[21]

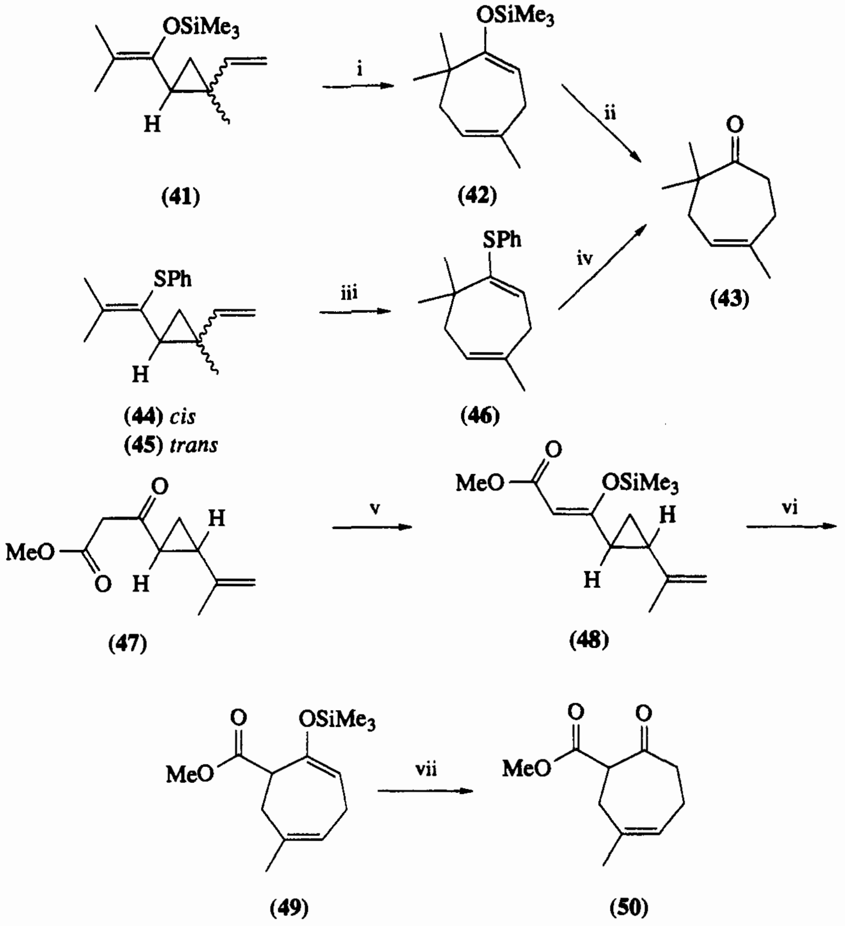

i, 165–175 °C, PhH; ii, Bu$^n$Li, THF; iii, *cis*, 25 °C; *trans*, 160 °C (70%); iv, $HgCl_2$, $H_2O$–MeCN (45%);
v, $Me_3SiCl$, $Et_3N$, $Et_2O$ (100%); vi, 210 °C, PhH (96%); vii, KF, MeOH (95%)

**Scheme 6**

In an investigation related to the synthesis of substituted 4-cyclohepten-1-ones,[22] the stereochemically homogeneous *cis*-2-vinylcyclopropyl ketones (**51a–51d**) were converted cleanly to the enol silyl ethers (**52**; Scheme 7). Thermolysis of the latter substances, followed by acid hydrolysis of the resultant products (**53**), gives excellent yields of the ketones (**54a–54d**). Interestingly, however, kinetic deprotonation of each of the *cis*-ketones (**51e–51h**) is not chemoselective. Treatment of these substrates with LDA–TBDMS-Cl provides mixtures of the enol silyl ethers (**55**) and (**56**), in ratios varying from 4:1 (substrate **51g**) to 1:9 (substrate **51f**). Fortunately, the *trans*-ketones (**57e–57h**) give synthetically more satisfactory results, since these substances can be converted chemoselectively into the *trans*-divinylcyclopropanes (**58**). As expected, Cope rearrangements of compounds (**58**) require temperatures considerably higher than those employed for the conversion of (**52**) into (**53**). However, the reactions are clean and the products (**59**), obtained in good to excellent yields, are readily hydrolyzed to the ketones (**54e–54h**).

In a recent study of the chemistry of the cyclopropenone acetal (**60**), the very interesting transformation shown in equation (3) was achieved.[23] Although this conversion was the only reported example of this novel process, it seems likely that the use of other functionalized and (or) stereochemically modified reagents would provide efficient syntheses of a wide variety of interestingly substituted seven-membered rings.

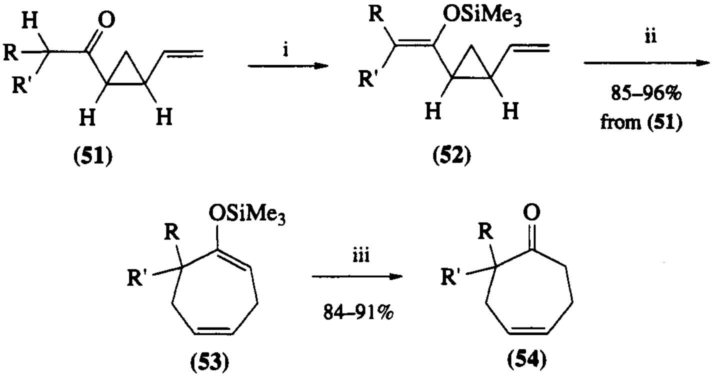
(51)
i
(52)
ii
85–96%
from (51)
(53)
iii
84–91%
(54)

**a**: R = Bu$^n$, R' = H; **b**: R = Ph, R' = H; **c**: R, R' = $(CH_2)_3$; **d**: R, R' = $(CH_2)_4$

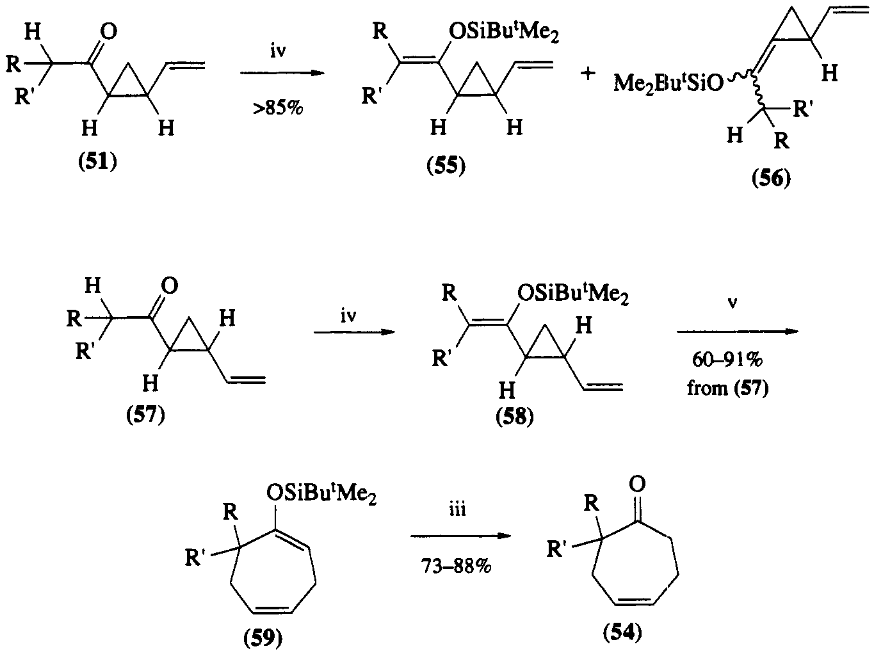
(51)
iv
>85%
(55)
+
(56)
(57)
iv
(58)
v
60–91%
from (57)
(59)
iii
73–88%
(54)

**e**: R, R' = $(CH_2)_5$; **f**: R, R' = $CH_2CMe_2(CH_2)_3$; **g**: R, R' = $(CH_2)_6$; **h**: R = Bu$^t$, R' = H

i, LDA, THF; $Me_3SiCl$, $Et_3N$; ii, 100–110 °C, 30 min; iii, HCl, $H_2O$, MeOH; iv, LDA, THF; $Bu^tMe_2SiCl$, HMPA; v, 230 °C, 30–60 min

Scheme 7

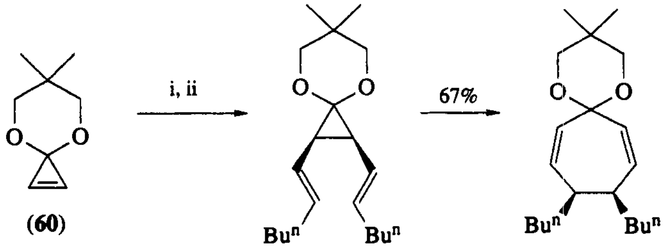

(3)

i, $(Bu^n)_2CuLi$, THF–$Et_2O$, −70 °C; ii, Bu$^n$ I, $(Ph_3P)_4Pd$, −70 °C to r.t.

## 8.2.4 β-(2-VINYLCYCLOPROPYL)-α,β-UNSATURATED KETONES

### 8.2.4.1 Synthesis of Functionalized Bicyclo[5.*n*.0]alkanes and Related Substances

The Cope rearrangement of 1,2-divinylcyclopropane systems in which one of the vinyl groups is part of an α,β-unsaturated ketone moiety has found considerable use in synthesis. A significant number of substrates have been prepared and subjected to thermal rearrangement and some of the products have been employed effectively for natural product syntheses.

The reaction of 2-vinylcyclopropyllithium reagents with β-alkoxy enones has served well as a method for preparing β-(2-vinylcyclopropyl) enones.[19,24] For example, treatment of **(61)** with a mixture of *cis*- and *trans*-2-vinylcyclopropyllithium, followed by mild acid hydrolysis of the resultant products, provides the epimeric divinylcyclopropanes **(62)** and **(63)** (Scheme 8).[19] Although **(62)** rearranges slowly at room temperature, the *trans* substrate **(63)** requires, as expected, elevated temperatures for rearrangement. Indeed, heating of the mixture of **(62)** and **(63)** at 170–180 °C provides **(64)** cleanly and efficiently.[19] Thus, not unexpectedly, the stereoselective preparation of the requisite divinylcyclopropane substrates is unnecessary, since both **(62)** and **(63)** are readily converted into the same product **(64)**. In similar fashion, the enones **(66)**–**(68)** are smoothly transformed into the rearrangement products **(65)**, **(71)** and **(72)**, respectively.[19] Under the rearrangement reaction conditions, the primary products **(69)** and **(70)**, derived from **(67)** and **(68)**, undergo isomerization to the more stable enones **(71)** and **(72)**, respectively.

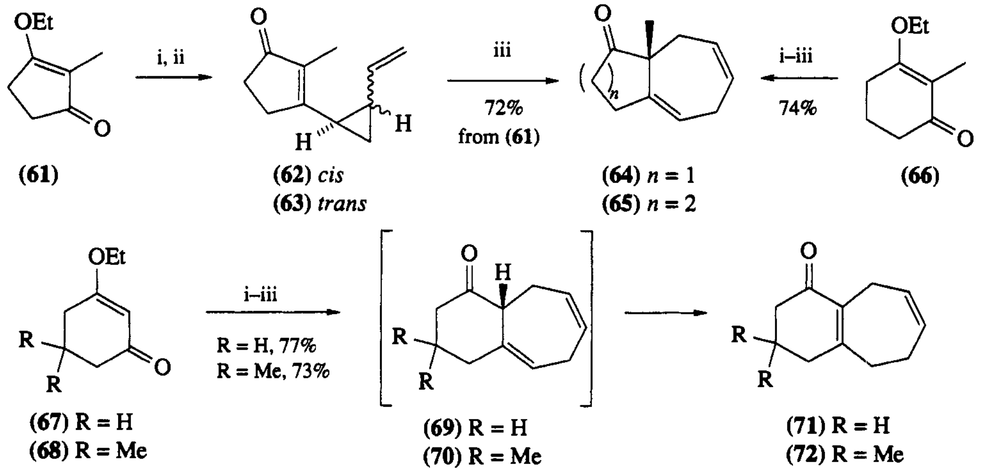

i, 7:3 mixture of *cis*- and *trans*-2-vinylcyclopropyllithium, $Et_2O$; ii, HCl, $H_2O$; iii, 170–180 °C, PhH

**Scheme 8**

Chemoselective Wittig reactions on keto aldehydes, such as **(73)** and **(74)**, also provide substrates suitable for sigmatropic rearrangement.[25,26] For example, treatment of **(74)** (mixture of epimers) with $Ph_3P{=}CHCO_2Et$ provides the *trans*-divinylcyclopropane (**75**; 86%) and the keto ester (**77**; 8%), the latter being derived from room temperature Cope rearrangement of the initially formed intermediate (**76**; Scheme 9).[26] Thermolysis of **(75)** produces **(77)** quantitatively. The efficient conversions of **(75)** and **(76)** into the stereochemically homogeneous keto ester **(77)** again illustrates the highly stereoselective nature of the sigmatropic rearrangement of *cis*- and *trans*-1,2-divinylcyclopropane systems.

The reaction of cyclopropylcuprate reagents with β-iodo enones has proven to be a useful method for preparing β-(2-vinylcyclopropyl) enones. For example, reaction of **(78)** with the cuprate reagent **(79)** (7:3 mixture of *cis* and *trans* isomers, readily prepared from the corresponding mixture of 1-bromo-2-vinylcyclopropanes), followed by thermal rearrangement of the resultant product **(80)**, gives the ketone (**81**; Scheme 10).[27] Similarly, the substrates **(82)**–**(84)** are smoothly transformed into the bicyclic ketones **(71)**, **(64)** and **(65)**, while subjection of the (*E*)-2-(iodomethylene)cycloalkanones **(85)** and **(86)** to the same reaction sequence affords the corresponding spirodienones **(87)** and **(88)**. Since the iodo enones are readily prepared from 1,3-dicarbonyl compounds[28] and the cuprate reagent **(79)** is obtained *via* a separate synthetic route, the overall annulation sequences are convergent, short, and efficient.

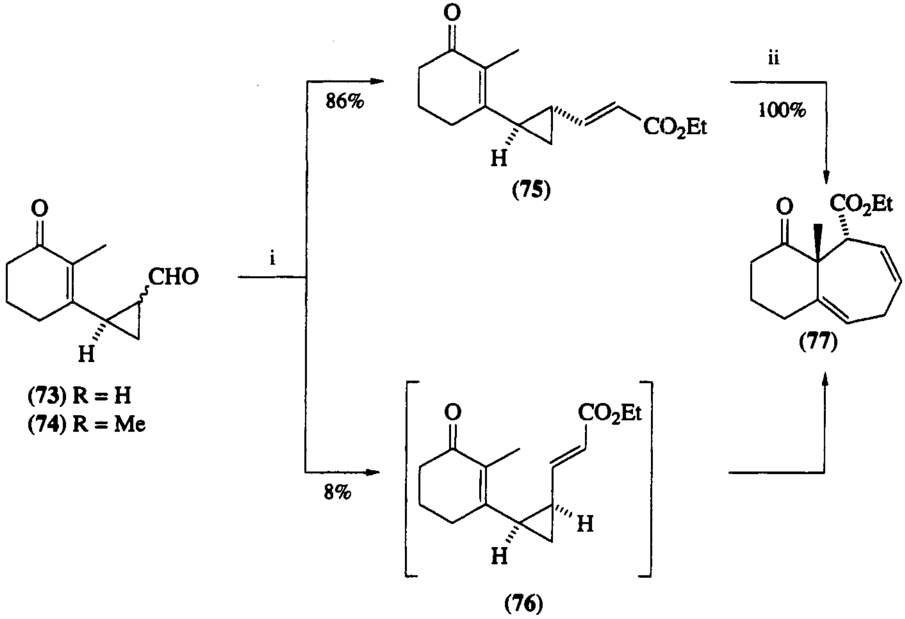
O
CHO
H
(73) R = H
(74) R = Me
i
86%
8%
O
CO2Et
H
(75)
ii
100%
O
CO2Et
(77)
O
CO2Et
H
H
(76)

i, $Ph_3P{=}CHCO_2Et$, THF, 20 °C; ii, 140 °C, xylene, 6 h

**Scheme 9**

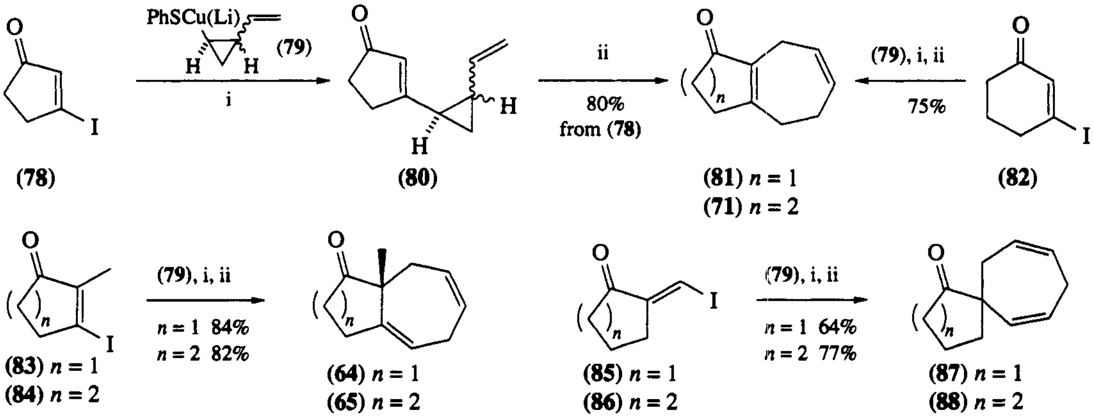
O
I
(78)
PhSCu(Li)
H
H
(79)
i
O
H
H
(80)
ii
80%
from (78)
O
n
(81) n = 1
(71) n = 2
(79), i, ii
75%
O
I
(82)
O
n
I
(83) n = 1
(84) n = 2
(79), i, ii
n = 1 84%
n = 2 82%
O
n
(64) n = 1
(65) n = 2
O
n
I
(85) n = 1
(86) n = 2
(79), i, ii
n = 1 64%
n = 2 77%
O
n
(87) n = 1
(88) n = 2

i, THF, –78 °C, 1 h; –20 °C, 1 h; 0 °C, 1–2 h; ii, neat, 180 °C, 30–45 min

**Scheme 10**

Cuprate methodology can also be used to prepare more highly substituted substrates. Thus, treatment of the 3-iodo-2-cyclohexen-1-ones (**82**) and (**84**) with the epimeric, stereochemically homogeneous cuprates (**89**) and (**90**) produces the divinylcyclopropanes (**91**)–(**94**) in excellent yields (equation (4)).[27]

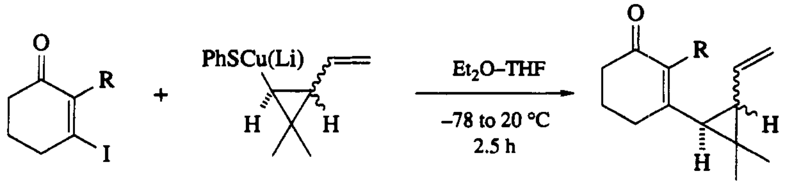
O
R
I
+
PhSCu(Li)
H
H
Et2O-THF
-78 to 20 °C
2.5 h
O
R
H
H

(4)

(**82**) R = H
(**84**) R = Me

(**89**) *cis*
(**90**) *trans*

(**91**) R = H, *cis* (88%)
(**92**) R = Me, *cis* (76%)
(**93**) R = H, *trans* (95%)
(**94**) R = Me, *trans* (82%)

Rearrangement of the epimers (**91**) and (**93**) is, in each case, unexceptional (Scheme 11).[27] Thermolysis of (**91**) in hexane provides the dienone (**95**), while heating either (**91**) or (**95**) at 110 °C (neat) affords the conjugated ketone (**96**). Although, as expected, rearrangement of (**93**) requires much higher temperatures, the same product (**96**) is formed in good yield. Presumably, this conversion proceeds by way of the stabilized diradical (**97**) and the *cis*-divinylcyclopropane (**91**).

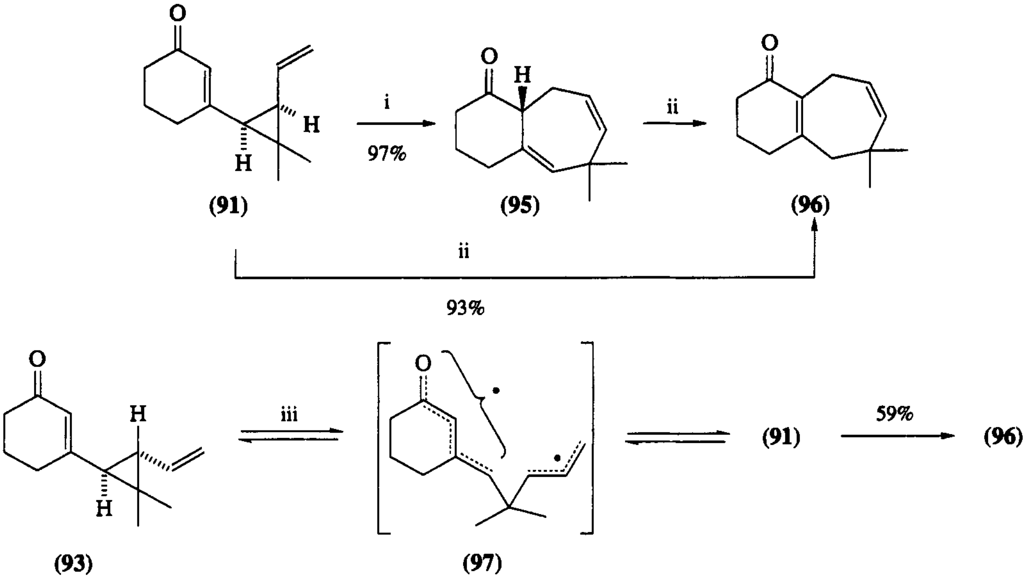

i, hexane, reflux, 4 h; ii, neat, 110 °C, 10 min; iii, *o*-dichlorobenzene, 220 °C, 14 h

**Scheme 11**

The *cis* substrate (**92**) represents an interesting case. Thermolysis of this material under a variety of conditions produces mixtures of (**94**) and (**98**), in which the latter substance nearly invariably predominates (Scheme 12).[27] For example, heating of (**92**) in collidine at 140–150 °C gives (**94**) and (**98**) in a ratio of about 1:2. Under these and other thermolysis conditions, the *trans*-divinylcyclopropane (**94**) is stable.

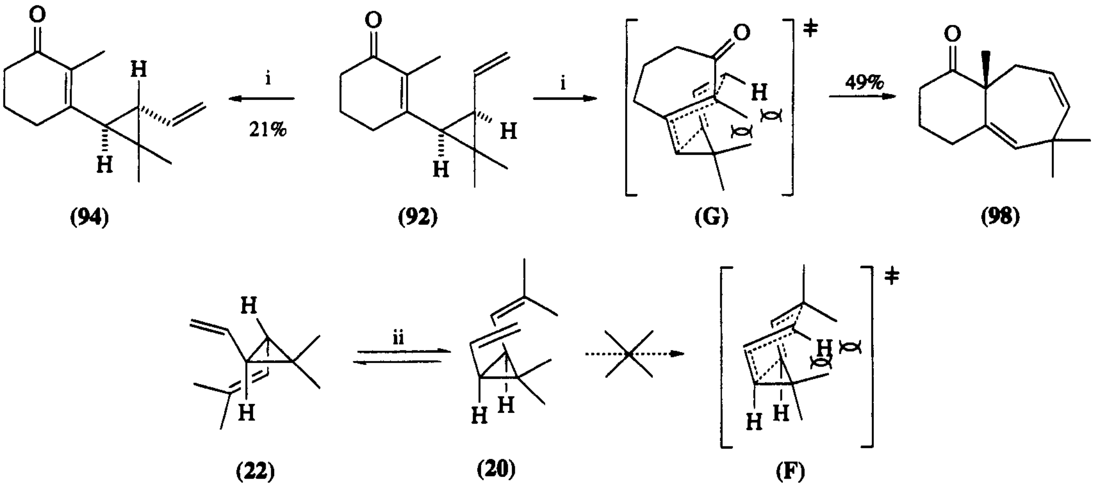

i, collidine, 140–150 °C, 43.5 h; ii, 180 °C, 3 h

**Scheme 12**

As mentioned previously, thermolysis of (**20**) at 180 °C does not result in Cope rearrangement but provides an equilibrium mixture of (**20**) and its epimer (**22**).[14] Interestingly, in terms of steric congestion, the transition states for Cope rearrangement of (**20**) and (**92**), (**F**) and (**G**), respectively, are similar (Scheme 12). Therefore, it is noteworthy that (**92**) does undergo sigmatropic rearrangement (albeit in competition with isomerization to **94**), while (**20**) does not. In (**92**), of course, one of the substituted vinyl groups is part of an α,β-unsaturated ketone function and, apparently, this structural feature lowers the activation energy of the Cope rearrangement process.

The *trans* substrate (**94**) is quite resistant to thermal rearrangement. However, thermolysis of this substance at 220 °C (Scheme 13)[27] provides the Cope rearrangement product (**98**) and the trienone (**99**), in a ratio of 1:4. Product (**99**) results from a [1,5] sigmatropic hydrogen migration, presumably *via* a transition state that can be represented by (**H**).[6,29] Interestingly, in the thermolysis of (**94**), the latter process is energetically more favorable than the alternative Cope rearrangement pathway.

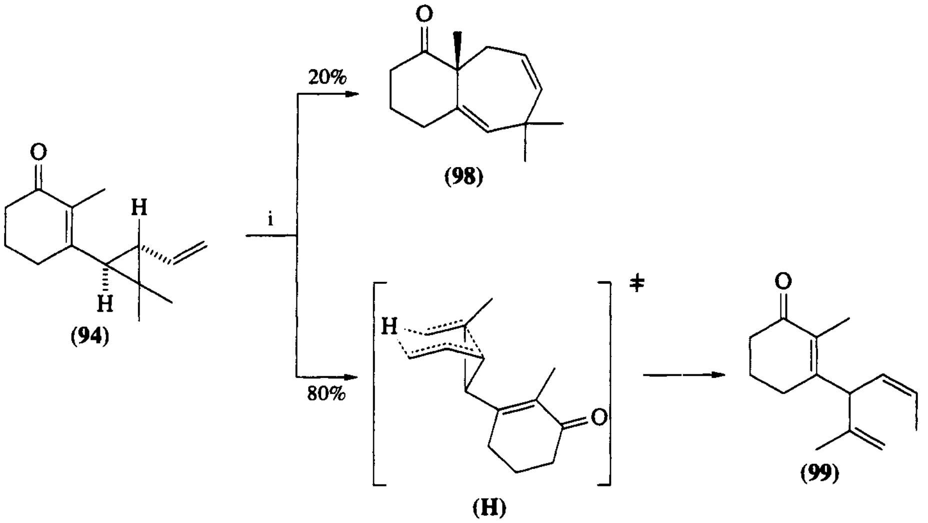

i, *o*-dichlorobenzene, 220 °C, 16 h

**Scheme 13**

From a synthetic viewpoint, a comparison of the thermolyses of the epimers (**92**) and (**94**) (Schemes 12 and 13) illustrates the point, previously mentioned, that, in certain cases in which alternative modes of rearrangement are possible, the stereoselective formation of the *cis*-divinylcyclopropane substrate is important. Thus, while thermal rearrangement of the *cis* substrate (**92**) provides the Cope rearrangement product (**98**) in reasonable yield, thermolysis of the *trans* isomer (**94**) does not.

### 8.2.4.2 Natural Product Syntheses

Naturally occurring compounds that possess as part of their structures bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane skeletons are very common in the terpenoid family of natural products. Since both of these carbon frameworks are readily prepared by sigmatropic rearrangement of β-(2-vinylcyclopropyl) enones, it is not surprising that this method has been applied to the total synthesis of terpenoids.

Wender *et al.* have reported interesting syntheses of the pseudoguaiane sesquiterpenoids (±)-damsinic acid (**104**) and (±)-confertin (**105**) (Scheme 14).[30] Using methodology similar to that described earlier (see Scheme 8) the enone (**61**) is converted into a 1:4 mixture of the epimeric divinylcyclopropanes (**100**) and (**101**), respectively. Interestingly, thermolysis of this mixture at temperatures ≥ 140 °C gives a mixture of the desired dienone (**102**) and the trienone (**103**), also in a ratio of 1:4, respectively. Clearly, while the *cis* substrate (**100**) is readily transformed into (**102**), the thermal isomerization of the *trans* isomer (**101**) into (**100**) is precluded by the more facile rearrangement of (**101**) to (**103**) *via* a [1,5] sigmatropic hydrogen shift.[6,29] Thus, it appeared initially that an efficient preparation of (**102**) would require the stereoselective preparation of the *cis* substrate (**100**).

Not unexpectedly, it is found that, although the *cis* substrate (**100**) rearranges readily at 98 °C, the *trans* isomer (**101**) is stable under these conditions. More important, however, was the finding that the two isomers (**100**) and (**101**) can be equilibrated by photolysis. Consequently, the problem of preparing

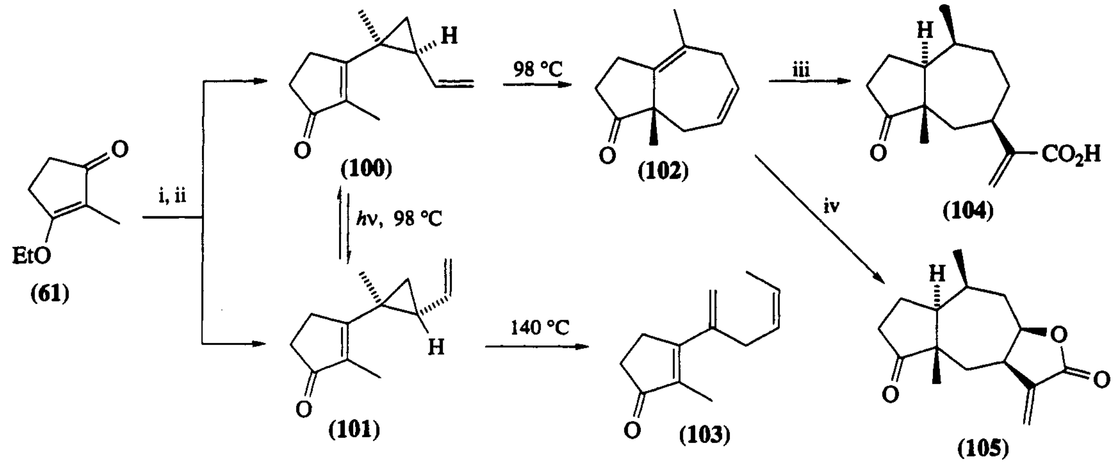

i, 1:4 mixture of *cis-* and *trans*-1-methyl-2-vinylcyclopropyllithium; ii, $H_3O^+$; iii, 9 steps; iv, 10 steps

Scheme 14

(**100**) stereoselectively was elegantly circumvented by subjecting the mixture of (**100**) and (**101**) to simultaneous irradiation (>290 nm) and thermolysis (98 °C). In this manner, both (**100**) and (**101**) are converted into (**102**) and the latter material is obtained in excellent yield (80–90%). The dienone (**102**) serves as a useful intermediate for the synthesis of (±)-damsinic acid (**104**) and (±)-confertin (**105**).[30]

The bicyclo[5.4.0]undecane sesquiterpenoid (±)-β-himachalene (**109**) was prepared *via* a route in which thermolysis of a β-(2-vinylcyclopropyl) enone played a key role (Scheme 15).[31] Reaction of the β-iodo enone (**82**) with the stereochemically homogeneous cyclopropylcuprate (**106**) provides the functionalized *trans*-divinylcyclopropane (**107**). Thermolysis of (**107**) gives exclusively the Cope rearrangement product (**108**), which is converted into (±)-β-himachalene (**109**). Notably, in contrast to structurally related systems (*vide supra*), the β,γ-unsaturated ketone function in (**108**) shows no inclination to rearrange to the corresponding α,β-unsaturated (conjugated) ketone.

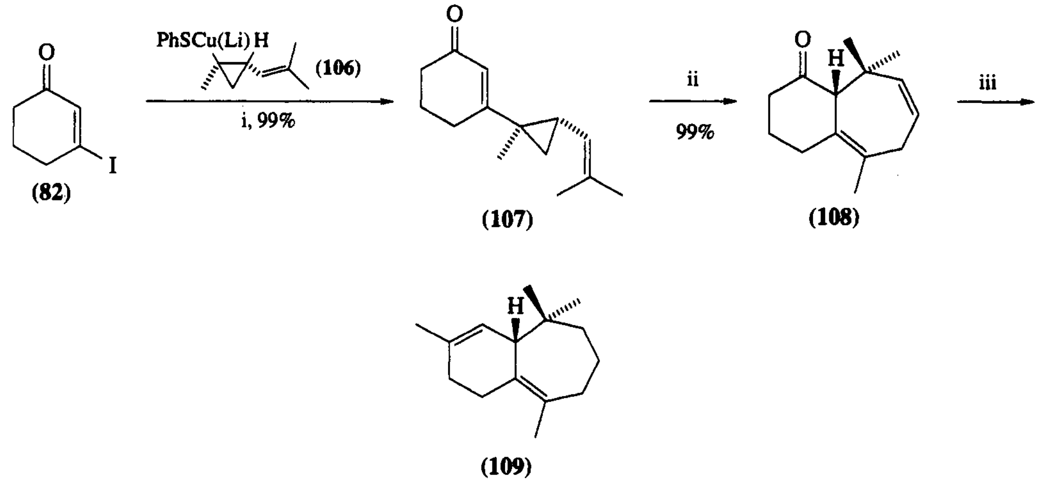

i, THF–$Et_2O$, –78 °C, 10 min; –20 °C, 15 min; r.t., 2 h; ii, xylene, reflux, 3 h; iii, 4 steps

Scheme 15

It is interesting to compare the thermal behavior of compounds (**101**; Scheme 14) and (**107**; Scheme 15). Although, in each case, the substrate reacts chemoselectively, (**101**) undergoes solely [1,5] sigmatropic hydrogen migration to give (**103**), while thermolysis of (**107**) proceeds exclusively by way of Cope rearrangement to provide (**108**). This remarkable difference between structurally rather similar substrates may be rationalized as follows. The rate-limiting steps of the Cope rearrangement of **(101)** and **(107)** would be (are) the isomerization of these substances into the corresponding *cis* isomers, presumably *via* the diradicals **(110)** and **(111)**, respectively. Due to the difference in substitution patterns (methyl groups), it seems likely that **(111)** would be more stable than **(110)**. Therefore, assuming little energy difference between **(101)** and **(107)**, one might expect that the energy of activation for the Cope rearrangement process involving **(107)** would be marginally lower than that involving **(101)**. More importantly, however, the (supposed) transition state for [1,5] sigmatropic hydrogen migration[6,29] in substrate **(107)** would be destabilized by a notable steric interaction, as shown in **(J)**. The corresponding transition state **(I)** derived from **(101)** is devoid of any major steric repulsions and, therefore, one would expect that the energy barrier for **(101)** → **(I)** would be considerably lower than that for **(107)** → **(J)**. Energetically, the two effects outlined above reinforce each other and, therefore, it is possible to rationalize, at least qualitatively, why the thermal rearrangements of **(101)** and **(107)** proceed *via* distinctly different pathways.

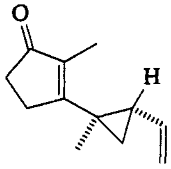

**(101)**

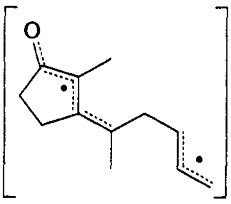

**(110)**

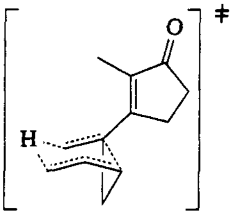

**(I)**

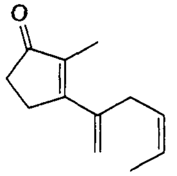

**(103)**

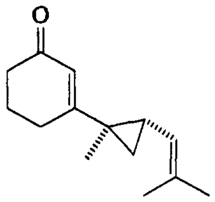

**(107)**

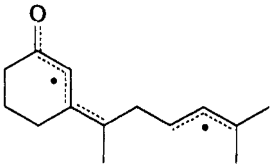

**(111)**

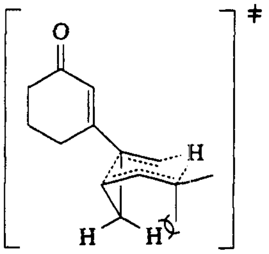

**(J)**

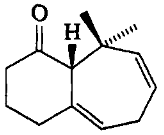

**(108)**

In connection with developing a synthetic approach to tigliane-, daphnane- and ingenane-type diterpenoids, Wender *et al.* have reported the reaction sequence shown in Scheme 16.[32] Interestingly, the functionalized *cis*-divinylcyclopropane **(112)** rearranges readily at room temperature, thus providing, in highly stereoselective fashion, the structurally rather complex product **(113)** from relatively simple starting materials.

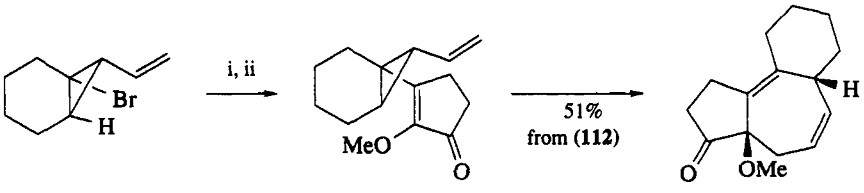

**(112)** **(113)**

i, Bu$^t$Li, Et$_2$O; 2,3-dimethoxy-2-cyclopenten-1-one; ii, H$_3$O$^+$, r.t.

**Scheme 16**

### 8.2.5 6-(1-ALKENYL)BICYCLO[3.1.0]HEX-2-ENES

### 8.2.5.1 Background

The Cope rearrangement of 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene **(114)** to bicyclo[3.2.1]octa-2,6-diene **(115)**[33] has been shown[34] to take place with a half-life of approximately 1 d at 25 °C ($E_a$ = 22.9 kcal mol$^{-1}$) (Scheme 17). As expected, the *exo* isomer (**116**), although stable at ambient temperatures, rearranges at elevated temperatures (*e.g.* 195 °C)[35] to provide the bicyclic diene (**115**) cleanly and efficiently. By means of an elegant study using optically active substrates, Baldwin and Gilbert[35] have shown that rearrangement of (**116**) to (**115**) proceeds entirely *via* a one-center epimerization at C-6 and not by way of inversion at both bridgehead carbons. Thus, thermolyses of optically active (**114**) and (**116**) (identical optical purities, absolute configurations as shown in Scheme 17) at 60 °C and 195 °C, respectively, give the same product (**115**). Importantly, the two samples of the latter substance exhibit essentially identical optical rotations. Presumably, the conversion of (**116**) into (**115**) involves the intermediacy of the diradical (**117**). The latter species, upon suitable bond rotation and ring closure, would give (**114**), which would rapidly rearrange to (**115**).

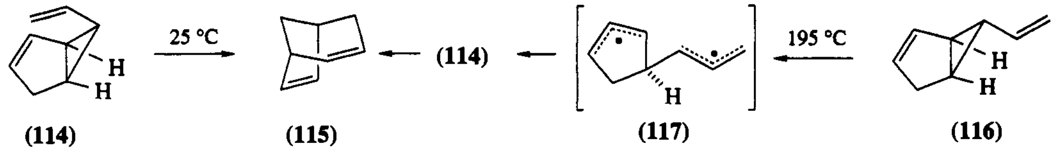

**Scheme 17**

The Cope rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes would appear to be a (potentially) excellent method for the preparation of functionalized, substituted bicyclo[3.2.1]octanes. Therefore, particularly since the latter carbon skeleton is a common structural feature of many terpenoid natural products, it is surprising that during the period 1965–1980 this type of transformation received relatively little attention from the community of synthetic organic chemists. The 1980s, however, have seen considerable activity in this area and the results of some of this work is summarized in the next two subsections of this chapter.

### 8.2.5.2 Synthesis of Substituted Bicyclo[3.2.1]octa-2,6-dienes

The readily available aldehyde (**118**) has served as a suitable precursor for a number of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes. For example, treatment of (**118**) with $Ph_3P{=}CHCO_2Me$ gives a mixture of the bicyclic diene esters (**121**)–(**123**) (Scheme 18).[36] In view of the stereospecific nature of the Cope rearrangement process (*vide supra*), it is highly likely that (**121**) and (**122**) are derived by bond reorganization of the initially formed Wittig products (**119**) and (**120**), respectively. The ratio of (**121**):(**122**) is, therefore, a reflection of the (expected) fact that the Wittig reaction produces primarily the *trans*-α,β-unsaturated ester (**119**). The diene ester (**123**) is, presumably, formed by partial isomerization of (**121**) and (or) (**122**).

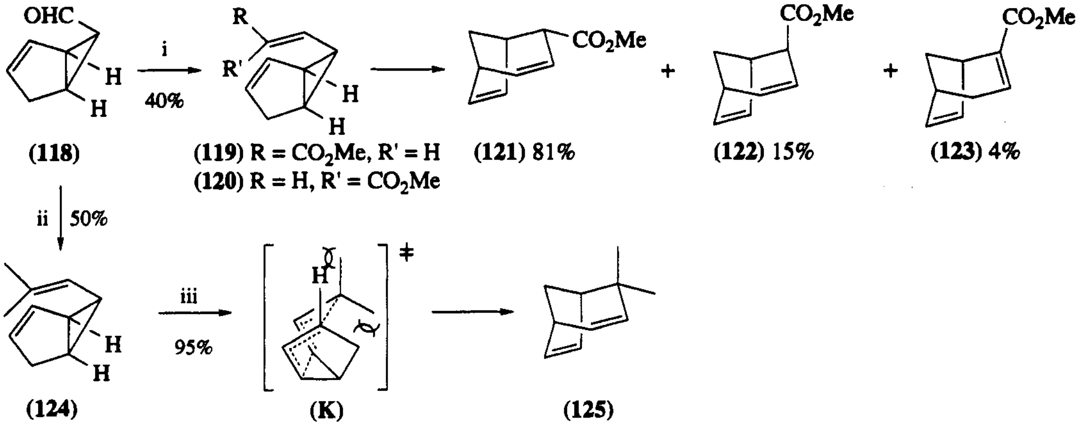

i, $Ph_3P{=}CHCO_2Me$, PhH, reflux, 18 h; ii, $Ph_3P{=}CMe_2$, THF, reflux, 1 h; iii, 350 °C, 15 Torr (1995 Pa)

**Scheme 18**

Substitution of the 6-*endo*-(1-alkenyl) moiety with alkyl groups notably retards the rate of rearrangement. For example, in contrast to the 'parent' substrate (**114**), the diene (**124**) (readily obtained from the aldehyde **118**) is stable under the conditions of its preparation and, at room temperature, can be stored without change for months (Scheme 18).[37] Presumably, steric crowding in the transition state (**K**) for the Cope rearrangement is primarily responsible for this stability. Nevertheless, flash vacuum thermolysis of (**124**) provides (**125**) quantitatively.[37]

Reaction of the ether aldehyde (**126**) with $Ph_3P{=}CH_2$ provides the diene (**128**; Scheme 19).[38] Furthermore, subjection of (**126**) to a Knoevenagel condensation using malonic acid gives a mixture of the acids (**131**)–(**133**). These conversions demonstrate the feasibility of effecting stereoselective functionalization at C-8 of bicyclo[3.2.1]octa-2,6-diene systems (*e.g.* **128**, **131** and **132**) by starting with the corresponding C(4)-substituted 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes (*e.g.* **127**, **129** and **130**). It is also pertinent to mention explicitly the formation of the acid (**132**). The transition state for the Cope rearrangement of (**130**), the presumed precursor of (**132**), is destabilized by a severe steric interaction between a $CO_2H$ group and the *endo*-Bu$^t$O function (see **L**, R = H, R′ = $CO_2H$). Consequently, if this conversion is indeed a 'normal' Cope rearrangement, the facility with which it proceeds is surprising.

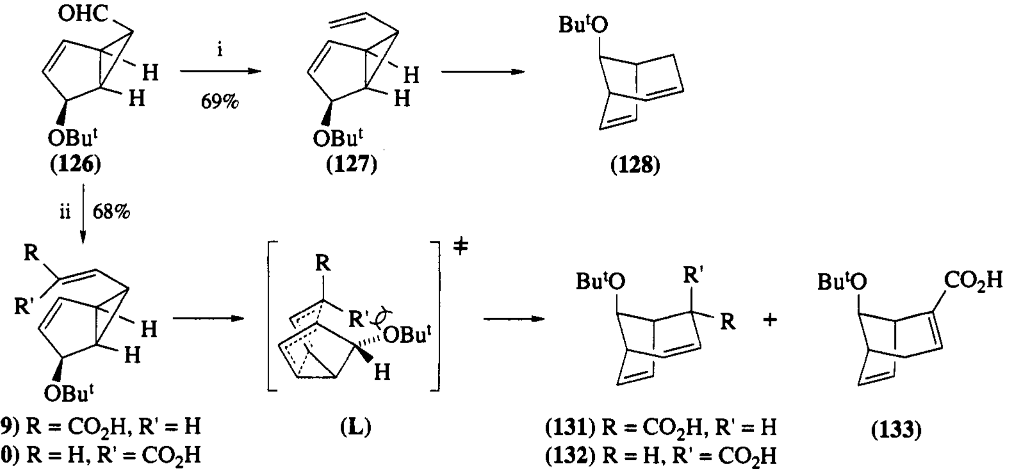

i, $Ph_3P{=}CH_2$, THF, reflux, 3 h; ii, $CH_2(CO_2H)_2$, piperidine, pyridine, 100 °C, 2 h

Scheme 19

Interesting recent studies have shown that bicyclo[3.1.0]hex-2-enes suitable for Cope rearrangement may be prepared directly from cyclopentadiene.[39,40] For example, carbenoid addition of the diazo diester (**134a**) to cyclopentadiene, followed by distillation of the product, gives the bicyclic diene (**136a**) in 98% yield (Scheme 20).[39] When the alkoxy-substituted diazo esters (**134b**–**134e**) are employed, the *endo*-divinylcyclopropanes (**135b**–**135e**) can be isolated in excellent yields and are found to be stable for days at room temperature. However, in refluxing toluene, these substances rearrange cleanly to the stereochemically homogeneous alkoxy diesters (**136b**–**136e**). The remarkable feature of these transformations is the highly stereoselective nature of the carbenoid addition reactions, which provide only the *endo*-divinylcyclopropanes (**135**). Also, as expected, the Cope rearrangements of (**135b**–**135e**) are completely stereoselective, with the *cis*-R and *trans*-$CO_2Et$ substituents on the 6-(1-alkenyl) group of (**135**) ending up *exo* and *endo*, respectively, in the diene products (**136**).

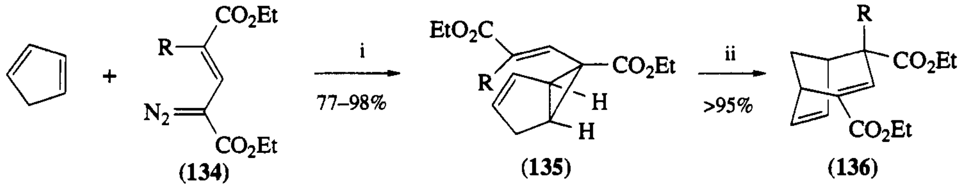

**a**, R = H; **b**, R = OMe; **c**, R = OEt; **d**, R = OPr$^i$; **e**, R = OBu$^t$

i, $Rh_2(OAc)_4$; ii, distillation (**135a**) or PhMe, reflux, 12 h (**135b**–**e**)

Scheme 20

Recent investigations have demonstrated that 6-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones are excellent precursors of Cope rearrangement substrates. The efficacy of this methodology may be illustrated initially by the synthesis of the diastereomeric ketones (**141**) and (**146**; Scheme 21).[41] Carbenoid cyclization of the diazo compounds (**137**) and (**142**) provides the bicyclic ketones (**138**) and (**143**). Since ring closures of this type are well known to be stereospecific with respect to the stereochemistry of the double bond involved, only the expected 6-*exo* substituted products are formed. Thermolytic sigmatropic rearrangement of the enol silyl ethers (**139**) and (**144**) (readily derived from **138** and **143**) proceeds in stereospecific fashion to afford the bicyclic dienes (**140**) and (**145**). The latter substances are readily converted into the epimeric keto alkenes (**141**) and (**146**). These syntheses illustrate clearly the stereochemical control that can be achieved *via* Cope rearrangement of bicyclo[3.1.0]hex-2-ene substrates possessing geometrically isomeric 6-(1-alkenyl) groups.

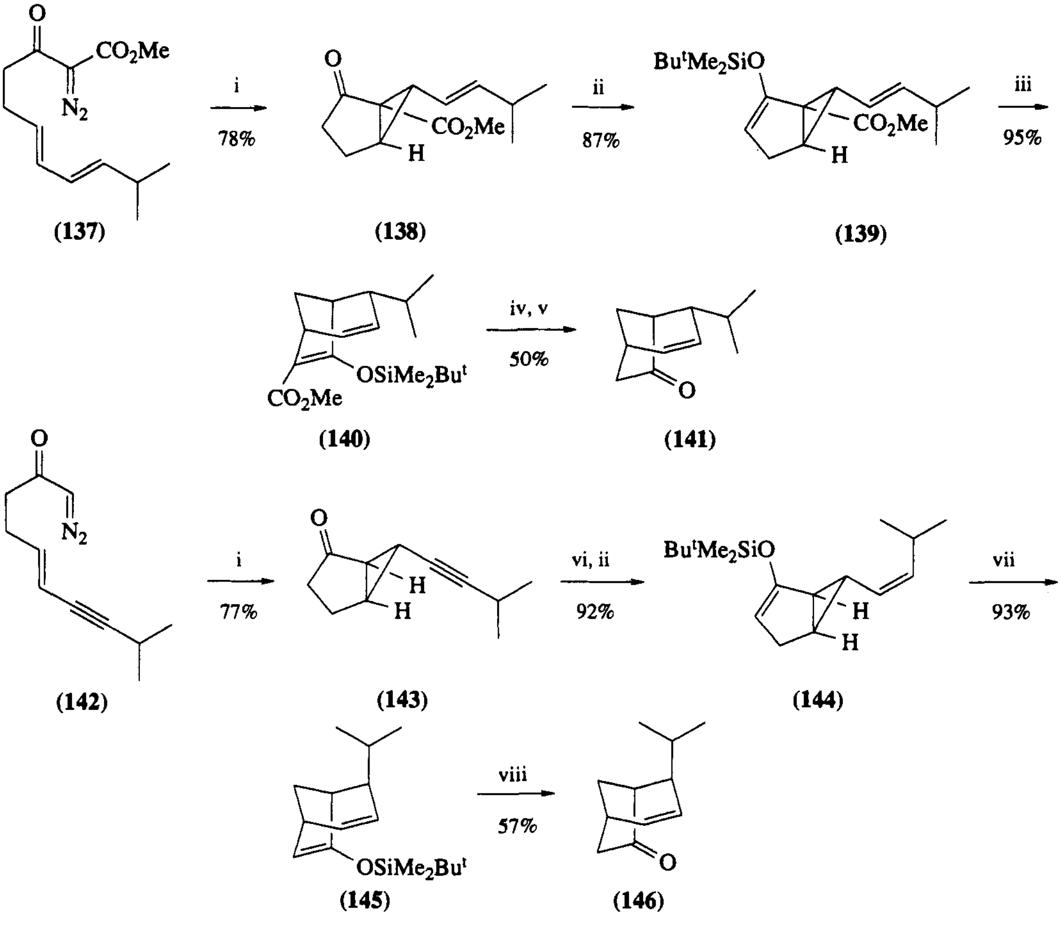

i, $Cu(acac)_2$, PhH, reflux; ii, LDA, THF, –78 °C; $Bu^tMe_2SiCl$, HMPA, –78 °C to r.t.; iii, 200 °C, 2 h, PhH (sealed tube); iv, $Bu^n{}_4NF$, THF; v, HCl, $H_2O$, THF, reflux; vi, $H_2$, $Pd/CaCO_3$, quinoline, pentane; vii, 240 °C, 4.5 h, PhH, (sealed tube); viii, HCl, $H_2O$, THF, r.t.

Scheme 21

Thermolysis of the enol silyl ethers (**147a–147c**) (readily prepared *via* the methods outlined in Scheme 21, see **137** → **139**) provides high yields of the bicyclic dienes (**148a–148c**), as shown in equation (5).[41] Furthermore, the keto ester (**149**), when subjected to the reaction conditions shown in equation (6), is smoothly converted into the diene ester (**151**), presumably *via* the *cis*-divinylcyclopropane (**150**).[42]

The conversions summarized in Scheme 21 and equations (5) and (6) show clearly the synthetic versatility of using bicyclo[3.1.0]hexan-2-ones as precursors of divinylcyclopropanes. Indeed, bicyclo[3.2.1]octa-2,6-dienes possessing alkyl substituents at either bridgehead position (**148a**,**148c**) or at C-4 with *endo* (**141**,**148b**) or *exo* orientation (**146**) are readily prepared. Furthermore, the rearrangement

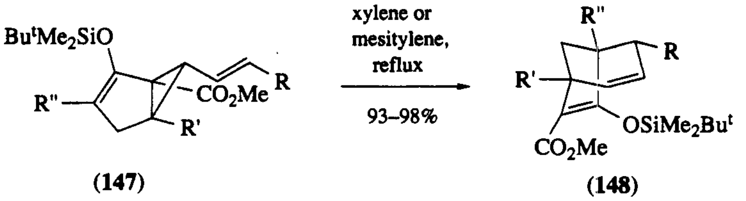
Bu$^t$Me$_2$SiO
R''
CO$_2$Me
R
R'
xylene or mesitylene, reflux
93–98%
R''
R
R'
OSiMe$_2$Bu$^t$
CO$_2$Me

(147) (148) (5)

**a**, R = R'' = H, R' = Me; **b**, R = R' = Me, R'' = H; **c**, R = R' = H, R'' = Me

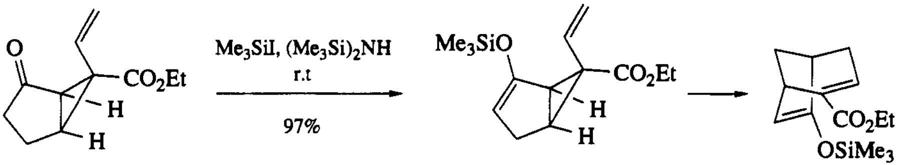
O
CO$_2$Et
H
H
Me$_3$SiI, (Me$_3$Si)$_2$NH
r.t
97%
Me$_3$SiO
CO$_2$Et
H
H
CO$_2$Et
OSiMe$_3$

(149) (150) (151) (6)

products contain, on the three carbon and two carbon bridges of the bicyclic system, functional groups that are readily amenable to further synthetic manipulations.

Bicyclo[3.1.0]hexan-2-ones are also suitable precursors for the synthesis of C(8)-functionalized bicyclo[3.2.1]octa-2,6-dienes. For example, the bicyclic enone (**153**), readily prepared from the ketone (**152**), contains a *trans*-divinylcyclopropane system in which one of the 'vinyl' groups consists of the enone carbon–carbon double bond. Indeed, thermolysis of (**153**) provides the Cope rearrangement product (**154**), which possesses at C-8 a synthetically versatile carbonyl group (Scheme 22).[41] Alternatively, copper(I)-catalyzed conjugate addition of vinylmagnesium bromide to the enone (**153**) provides a single product (**155**). The stereoselectivity of this process may be attributed to steric factors, with the reagent approaching the enone system from the less-hindered convex face. Thermolytic sigmatropic rearrangement of the enol silyl ether (**156**), readily obtained from (**155**), provides the triene (**157**), which can be hydrolyzed to the keto diene (**158**).[41] Thus, bicyclo[3.2.1]octane systems possessing at C-8 a useful functional group (*e.g.* **154**) or an *exo* substituent (*e.g.* **157** and **158**) are readily prepared.

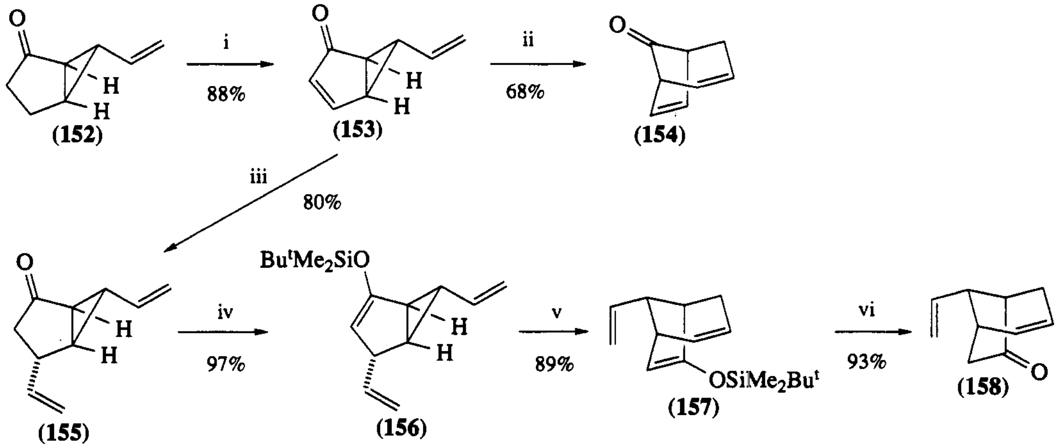
O
H
H
(152)
i
88%
O
H
H
(153)
ii
68%
O
(154)
iii
80%
O
H
H
(155)
iv
97%
Bu$^t$Me$_2$SiO
H
H
(156)
v
89%
OSiMe$_2$Bu$^t$
(157)
vi
93%
(158)
O

i, LDA, THF, –78 °C; PhSeCl, –78 to 0 °C; HOAc, $H_2O$, $H_2O_2$, 0 °C; ii, 160 °C, 4 h, PhH (sealed tube); iii, $H_2C{=}CHMgBr$, CuBr•$Me_2S$, THF, –30 to 0 °C; iv, LDA, THF, –78 °C; Bu$^t$Me$_2$SiCl, HMPA, –78 °C to r.t.; v, 200 °C, 5 h, PhH (sealed tube); vi, HCl, $H_2O$, THF, r.t.

**Scheme 22**

### 8.2.5.3 Natural Product Syntheses

On the basis of the work summarized above, it would appear that the Cope rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes should be usefully applicable to the synthesis of natural products that possess, as part of their structures, the bicyclo[3.2.1]octane carbon skeleton. Recent work in this area, involving total syntheses of the sesquiterpenoids (±)-sinularene, (±)-prezizanol and (±)-prezizaene, is discussed below.

The key intermediate for the synthesis of (±)-sinularene (**159**),[43] a structurally unusual marine natural product, was the bicyclic divinylcyclopropane (**160**). Successful Cope rearrangement of this substance would be expected to proceed *via* the *endo* isomer (**161**) to produce the bicyclo[3.2.1]octa-2,6-diene (**162**), possessing the correct stereochemistry at C-4 (*exo*-isopropyl group) and functionality (*exo*-vinyl group at C-8, enol ether associated with C-6 and C-7) that would allow the straightforward preparation of the tricyclic ring system of (±)-(**159**).

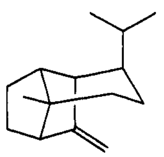

**(159)**

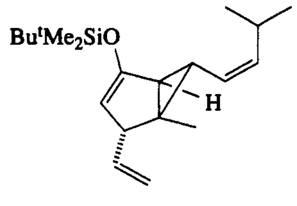

**(160)**

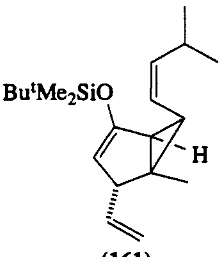

**(161)**

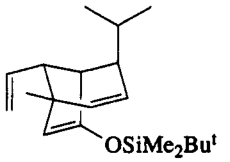

**(162)**

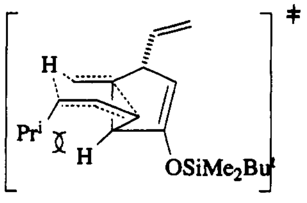

**(M)**

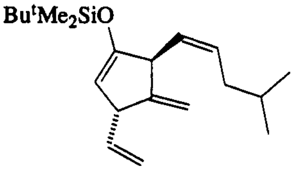

**(163)**

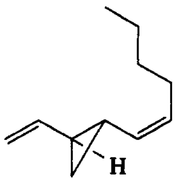

**(164)**

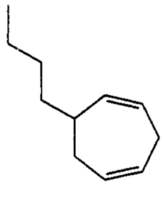

**(16)**

In theory, thermolysis of (**160**) could also result in a [1,5] sigmatropic hydrogen migration,[6,29] involving the C-5 methyl group, to produce the unusually substituted cyclopentene (**163**). However, the expected transition state for this process[6,29] would be destabilized by a severe steric repulsion, as shown in (**M**), and, therefore, the energy of activation ($E_a$) for (**160**) → (**163**) would probably be considerably higher than 31.2 kcal mol$^{-1}$, the value associated with the conversion of the 'parent' *cis*-1-methyl-2-vinylcyclopropane into *cis*-1,4-hexadiene.[44] On the other hand, lack of appropriate literature data makes it difficult to predict the value of $E_a$ associated with the isomerization of (**160**) to (**161**), the rate-determining step for the conversion (**160**) → (**162**). Nevertheless, since the energy of activation for the transformation of (**164**, racemate) into (**16**) has been shown[8] to be 32.8 ± 0.8 kcal mol$^{-1}$, one might expect $E_a$ for (**160**) → (**161**) to be in the range 31–33 kcal mol$^{-1}$. Consequently, of the two alternative rearrangement pathways (**160** → **162** or **163**), it appeared that the Cope rearrangement would be energetically favored. This expectation turned out to be correct.

The stereochemically controlled synthesis of the key substrate (**160**) is outlined in Scheme 23.[43] A stereoselective ortho ester based Claisen rearrangement is employed to convert the alcohol (**165**) into the ester (**166**), which is transformed *via* a standard sequence of reactions into the bicyclic ketone (**167**). Chemo- and stereo-selective hydrogenation of the latter material provides the bicyclo[3.1.0]hexan-2-one (**168**), possessing the required (*Z*)-3-methyl-1-butenyl group at C-6. To set the stage for introduction of the necessary C-4 vinyl group, the ketone (**168**) is converted into the enone (**169**) by Pd(OAc)$_2$ oxidation of the corresponding enol trimethylsilyl ether. Treatment of (**169**) with lithium divinylcuprate gives a mixture of (**170**) and the corresponding C-4 epimer, in a ratio of about 9:1, respectively. Although this conjugate addition was not entirely stereoselective, the major product, resulting from approach of the cuprate reagent to the less-hindered side of the enone (**169**), possesses the required *exo* stereochemistry at C-4.

Routine conversion of the ketone (**170**) into the enol silyl ether (**160**) set the stage for investigating the key Cope rearrangement reaction. In the event, thermolysis of (**160**) provides a single product (**162**) in high yield. This result not only confirmed the expectation that the Cope rearrangement of (**160**) would be energetically favored over the alternative [1,5] sigmatropic hydrogen migration, but also demonstrated the efficacy of the Cope process for the stereoselective synthesis of a highly functionalized bicyclo[3.2.1]octa-2,6-diene. The diene (**162**) was readily converted into (±)-sinularene (**159**).[43]

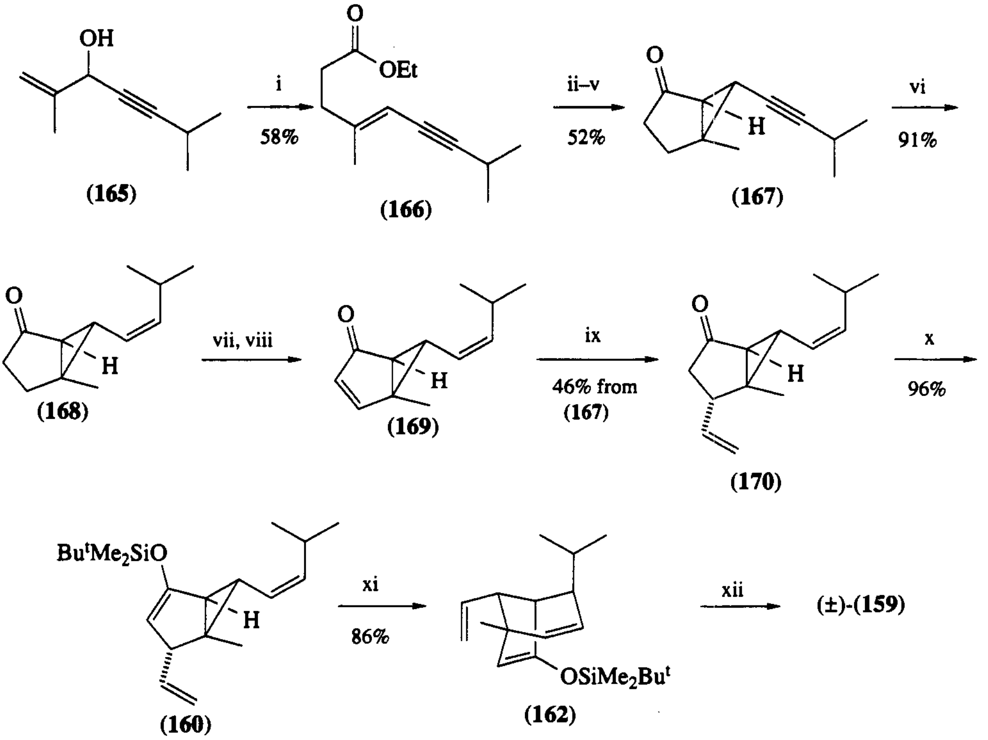

i, $(EtO)_3CMe$, $EtCO_2H$, 130 °C, 20 h; ii, KOH, $H_2O$–MeOH; iii, $(COCl)_2$, PhH, reflux; iv, $CH_2N_2$, $Et_2O$; v, $Cu(acac)_2$, PhH, reflux; vi, $H_2$, $Pd/CaCO_3$, n-$C_5H_{12}$; vii, $Me_3SiI$, $Et_3N$, $CH_2Cl_2$, −78 °C; viii, $Pd(OAc)_2$, MeCN, r.t.; ix, $(CH_2{=}CH)_2CuLi$, $Et_2O$, −30 °C to r.t.; x, LDA, THF, −78 °C; Bu$^t$Me$_2$SiCl, THF–HMPA, −78 °C to r.t.; xi, 220 °C, 4.5 h, PhH (sealed tube); xii, 4 steps

**Scheme 23**

The key step of the total syntheses of (±)-prezizanol (**171**) and (±)-prezizaene (**172**) was initially envisaged to be the Cope rearrangement of the 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene (**173**).[45] The stereoselective synthesis of this material was readily achieved,[45] but, unfortunately, thermolysis of (**173**) in benzene at temperatures in the range 155–220 °C produces a plethora of products from which the desired material (**175**) can be isolated in only poor yields (25% at best).[45,46] In contrast, thermolysis (PhH, 190 °C, 9 h) of substrate (**176**) proceeds cleanly to give (**177**).[45] Therefore, it is evident that the unsatisfactory nature of the rearrangement of (**173**) is due to the presence of the β,γ-unsaturated ester function, which, perhaps not surprisingly, is unstable at the high temperatures necessary to effect isomerization of (**173**) into the *endo* isomer (**174**). Therefore, since the [3,3] sigmatropic rearrangement of (**174**) would be expected to occur at relatively low temperatures, it appeared that the efficient production of (**175**) would have to involve the intermediacy of (**174**) rather than (**173**).

The stereoselective preparation of the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene (**174**) was achieved *via* the route summarized in Scheme 24.[46] Slow addition of a THF solution of the dichlorocyclopropane

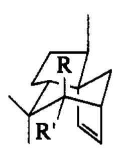

(**171**) R = Me, R' = OH
(**172**) R, R' = $CH_2$

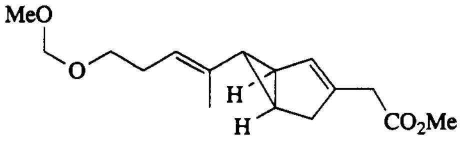

(**173**)

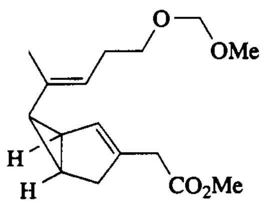

(**174**)

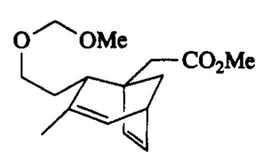

(175)

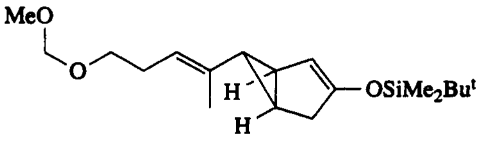

(176)

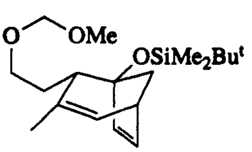

(177)

(**178**) to an excess of *t*-butyllithium at −107 °C, followed by protonation of the resultant intermediate, gives a mixture of (**179**) and the corresponding *exo*-chloride (4:1, respectively), from which (**179**) is obtained in 55% yield by chromatography. Treatment of (**179**) with lithium 4,4′-di-*t*-butylbiphenylide, conversion of the resultant cyclopropyllithium reagent into the corresponding organozinc chloride and palladium(0)-catalyzed coupling of the latter species with (*E*)-2-iodo-5-methoxymethoxy-2-pentene affords the bicyclic alkene (**180**). A standard sequence of reactions transforms the latter material into the α,β-unsaturated ester (**181**), which, upon deconjugation *via* the corresponding enolate anion, is converted into the key intermediate (**174**). At room temperature, the *cis*-divinylcyclopropane (**174**) rearranges slowly to (**175**) and, upon distillation at 110 °C under reduced pressure, is converted into (**175**) in essentially quantitative yield. Thus, a comparison of the thermolytic behavior of the epimers (**173**) and (**174**) shows clearly that, for the preparation of the bicyclic diene (**175**) *via* a Cope rearrangement process, the *endo* isomer (**174**) is a much more effective precursor than the *exo* isomer (**173**). Compound (**175**) serves as a suitable intermediate for the total synthesis of (±)-prezizanol (**171**), which, upon dehydration, gives (±)-prezizaene (**172**).[46]

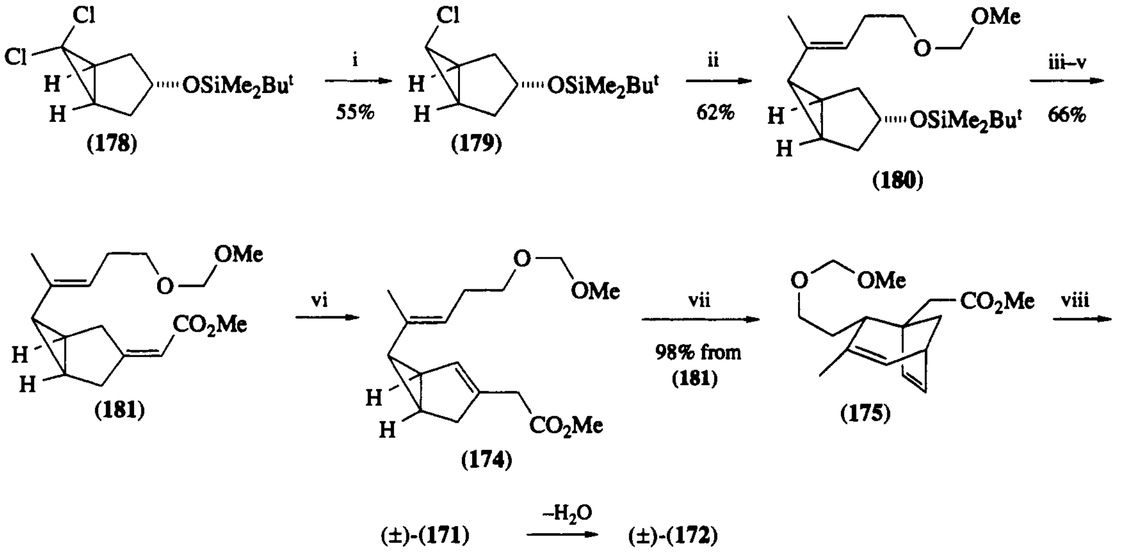

i, Bu$^t$Li, THF–Et$_2$O–pentane, −107 °C; AcOH, Et$_2$O, −107 °C; ii, (4,4′-di-*t*-butylbiphenyl)$^-$ Li$^+$, THF, −78 °C; ZnCl$_2$, THF, −78 to 0 °C; (Ph$_3$P)$_4$Pd, (*E*)-2-iodo-5-methoxymethoxy-2-pentene, THF, reflux, 1 h; iii, TBAF, THF; iv, PCC, NaOAc, CH$_2$Cl$_2$; v, [(MeO)$_2$POCHCO$_2$Me]Li, THF; vi, LDA, THF, −78 °C; HOAc, Et$_2$O, −78 °C; vii, 110 °C, 0.1 Torr (13.3 Pa); viii, 11 steps

Scheme 24

### 8.2.6 7-(1-ALKENYL)BICYCLO[4.1.0]HEPT-2-ENES

Although relatively little work has been done in this area, Schneider and Csacsko[47] have shown that 7-*endo*-vinylbicyclo[4.1.0]hept-2-ene (**182**) rearranges to bicyclo[3.2.2]nona-2,6-diene (**183**) under conditions (≤ 25 °C) similar to those required for bond reorganization of *cis*-1,2-divinylcyclopropane or

6-*endo*-vinylbicyclo[3.1.0]hex-2-ene. Furthermore, the corresponding *exo* isomer (**184**), upon thermolysis at 160 °C, also provides the bicyclic diene (**183**) in essentially quantitative yield (Scheme 25).[47]

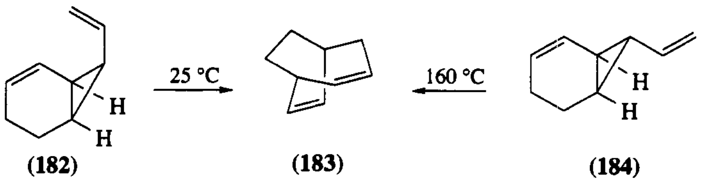

(**182**) (**183**) (**184**)

**Scheme 25**

Thermolysis of the enone (**185**) produces the tricyclic ketone (**188**) in high yield (Scheme 26).[48] Supposedly, this transformation involves initial isomerization, *via* a diradical intermediate, of (**185**) into the *endo* isomer (**186**). Cope rearrangement of the latter substance gives the β,γ-unsaturated ketone (**187**), which, under the reaction conditions, isomerizes to the more stable conjugated isomer (**188**).

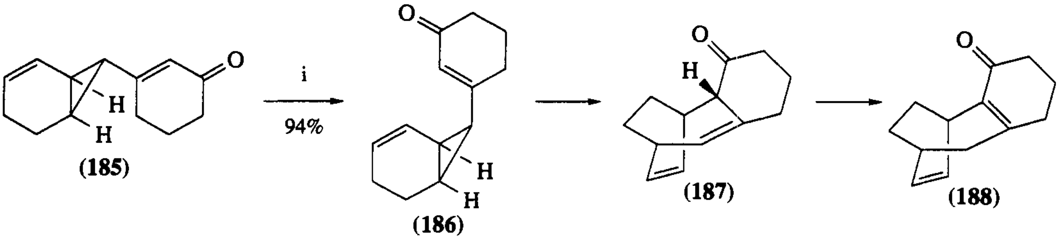

(**185**) (**186**) (**187**) (**188**)

i, *o*-dichlorobenzene, reflux, 40 h

**Scheme 26**

The synthesis of bicyclo[3.2.2]non-6-en-3-one (**192**) and the spiro-substituted derivatives (**195**) can be achieved *via* similar methodology. Thus, thermolysis of the enol silyl ether (**190**), which is readily derived from the ketone (**189**), gives the bicyclic substance (**191**). Mild acid hydrolysis of (**191**) affords (**192**; Scheme 27).[49] In a similar fashion the *exo*-ketones (**193**) have been converted, *via* the enol silyl ethers (**194**), into the tricyclic keto alkenes (**195**).[49]

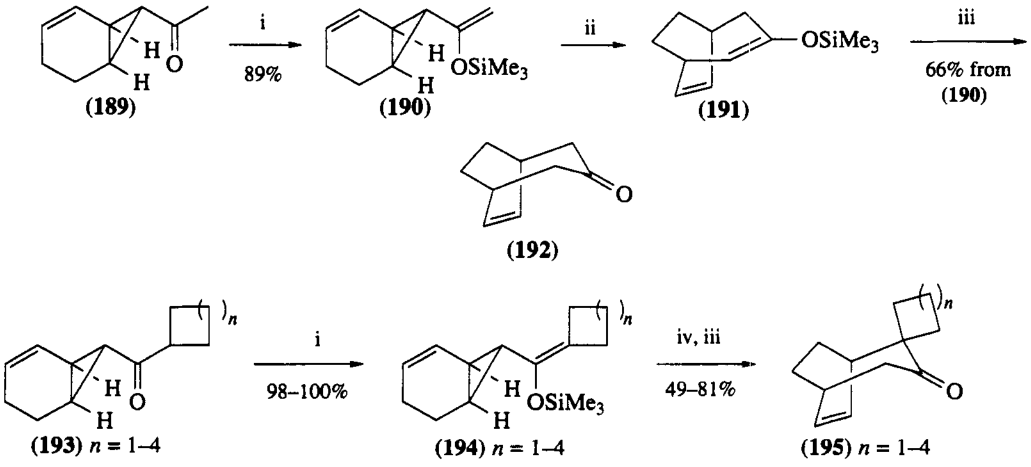

(**189**) (**190**) (**191**)

(**192**)

(**193**) $n$ = 1–4 (**194**) $n$ = 1–4 (**195**) $n$ = 1–4

i, LDA, THF, –78 to 0 °C; Me$_3$SiCl, –78 °C to r.t.; ii, 240 °C, neat, 6 h; iii, HCl, H$_2$O, THF; iv, 240 °C, neat, 12 h

**Scheme 27**

Although small in number, the investigations summarized above show that the Cope rearrangement of 7-(1-alkenyl)bicyclo[4.1.0]hept-2-enes is an effective method for the synthesis of usefully functionalized bicyclo[3.2.2]nona-2,6-dienes.

## 8.2.7 TRICYCLIC 1,2-DIVINYLCYCLOPROPANE SYSTEMS

### 8.2.7.1 Synthesis of Tricyclic Substances Containing the Bicyclo[3.2.1]octane Carbon Skeleton

Recent studies, directed primarily toward the development of synthetic approaches to tricyclic and tetracyclic natural products, have demonstrated the viability of Cope rearrangements of substrates possessing a 1,2-divinylcyclopropane moiety as part of a tricyclic ring system. In these investigations, as in related studies described earlier (*vide supra*), one of the 'vinyl' groups is introduced by conversion of a ketone function into an enol silyl ether. For example, transformation of the tricyclic ketone (**196**) into the *trans*-divinylcyclopropane (**197**), followed by thermolysis of the latter substance, affords the tricyclic diene (**198**) cleanly and efficiently (Scheme 28).[50] Cleavage of the enol silyl ether function of (**198**) provides the ketone (**199**). In a similar fashion, the ketone (**200**), an isomer of (**196**), is transformed smoothly into the bridged tricyclic ketone (**203**) *via* the isolable intermediates (**201**) and (**202**) (Scheme 28).[51] It is worthwhile to note explicitly that, although the products (**199**) and (**203**) possess the same carbon skeleton, the functional groups are located at different positions.

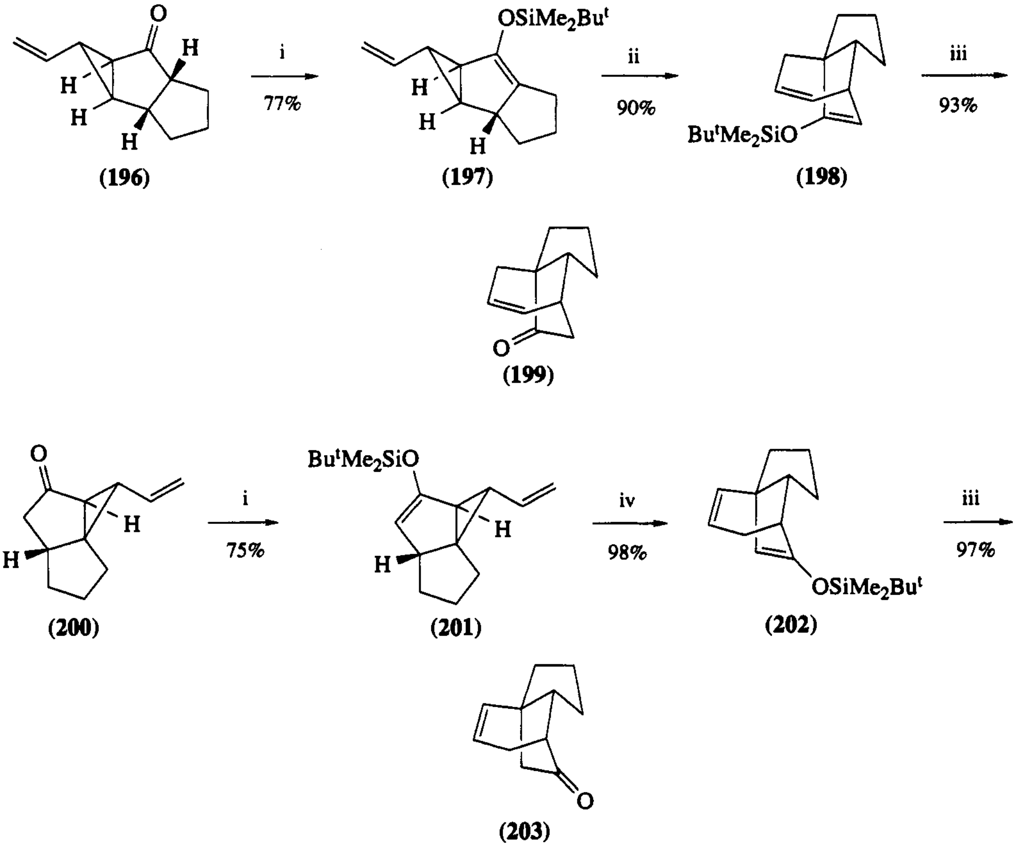

i, LDA, THF, –78 °C; Bu$^t$Me$_2$SiCl, THF–HMPA, –78 °C to r.t.; ii, 155 °C, 5 h, PhH (sealed tube); iii, TBAF, THF, –78 °C; iv, 170 °C, 5 h, PhH (sealed tube)

**Scheme 28**

Hudlicky and coworkers[42,52] have reported recently the Cope rearrangement of similar, but more highly functionalized substrates. For example, the keto esters (**204**) and (**205**) are readily converted into the corresponding enol ethers (**206**) and (**207**) (Scheme 29).[42,52] Thermolysis of the latter substances at high temperatures, followed by acid hydrolysis of the enol ether functions in the resultant products, affords primarily the products (**208**) and (**209**) derived from Cope rearrangements, accompanied by lesser amounts of the angularly fused triquinanes (**210**) and (**211**), respectively. Interestingly, when the substrates (**212**) and (**213**), containing *endo*-vinyl substituents, are treated with TMS-I in the presence of (TMS)2NH, the tricyclic substances (**216**) and (**217**) are obtained directly (Scheme 29).[42,52] Not unexpectedly, the intermediate *cis*-divinylcyclopropanes (**214**) and (**215**) undergo sigmatropic rearrangement at relatively low temperatures.

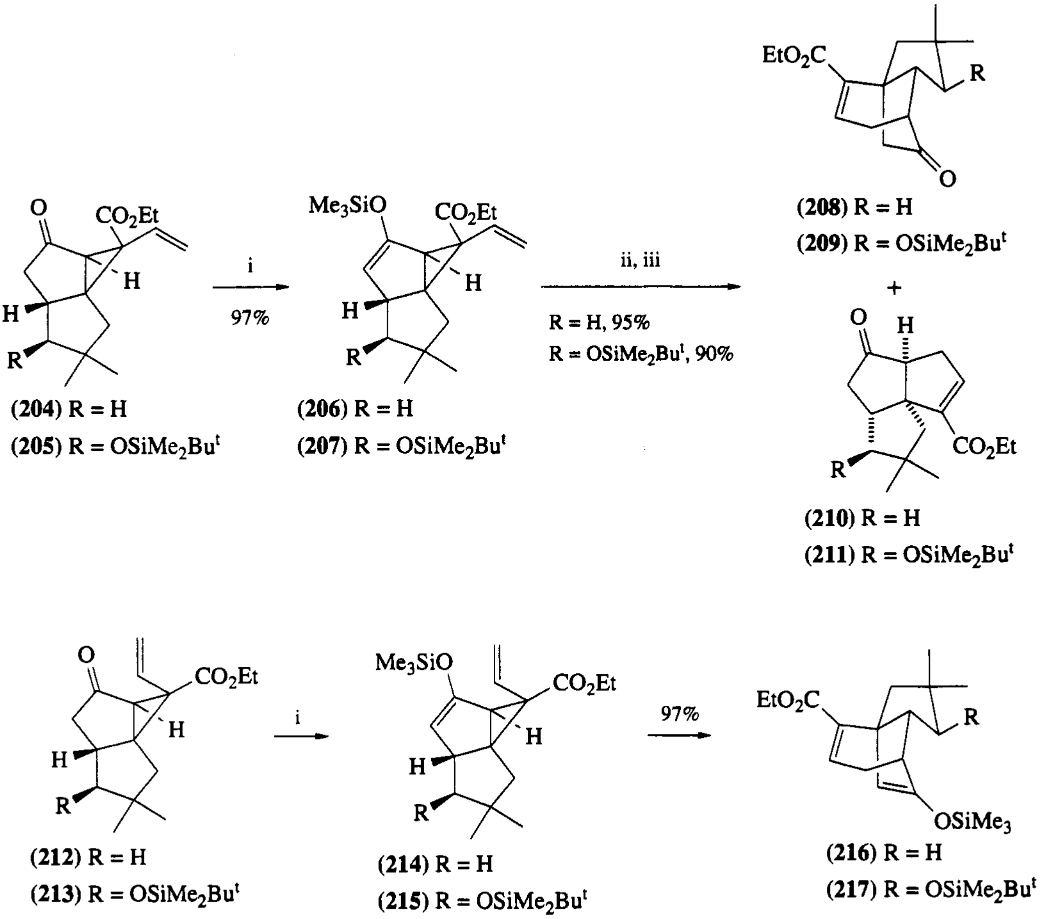

i, $Me_3SiI$, $(Me_3Si)_2NH$, pentane, −20 °C; ii, 585 °C, $PbCO_3$-conditioned Vycor tube; iii, HCl, $H_2O$, $CH_2Cl_2$

**Scheme 29**

### 8.2.7.2 Natural Product Synthesis

The cytotoxic sesquiterpenoid (−)-quadrone, isolated from the fungus *Aspergillus terreus*, possesses the constitution and absolute stereochemistry shown in (**218**). The tricyclic carbon skeleton of this interesting natural product is the same as that found in compound (**198**), which, as described above (Scheme 28), is readily prepared by thermolysis of the tricyclic diene (**197**).[50] Thus, it appeared that the Cope rearrangement of a suitably substituted and functionalized derivative of (**197**) might serve effectively as a key intermediate in a total synthesis of (±)-quadrone (**218**); that is, successful Cope rearrangement of a substrate, such as (**219**), would provide, stereoselectively, the tricyclic substance (**220**). Presumably, the intermediate (**220**) could then be converted into the keto aldehyde (**221**), which had already been transformed into (±)-quadrone (**218**).[53]

Treatment of the ketone (**222**) as shown in Scheme 30[51] gives a mixture of products from which the required divinylcyclopropane (**219**) may be isolated (chromatography) in 47% yield. Unfortunately, sub-

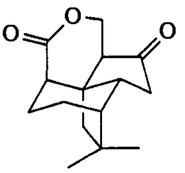

**(218)**

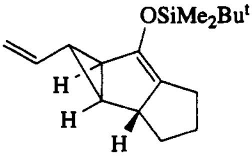
OSiMe$_2$Bu$^t$
H
H
H

**(197)**

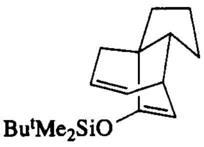

**(198)**

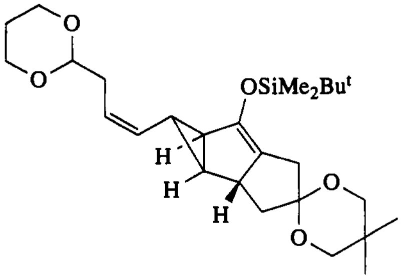
OSiMe$_2$Bu$^t$
H
H
H

**(219)**

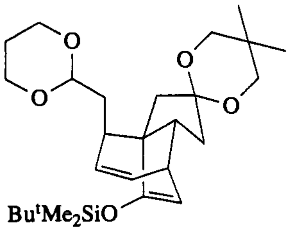

**(220)**

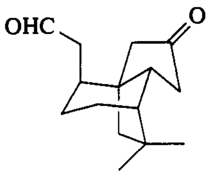

**(221)**

strate (**219**) does not undergo Cope rearrangement. Thermolysis of this material provides a mixture of products that does not contain any of the diene (**220**).[51]

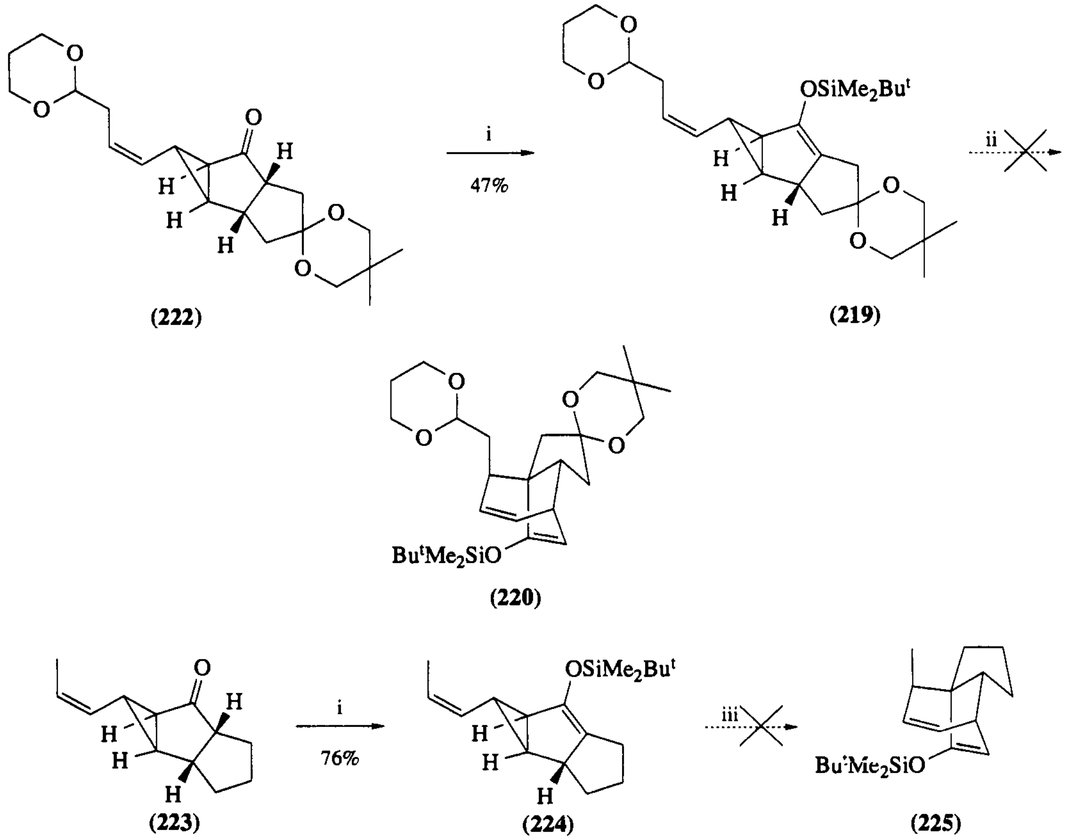
H
H
H
H
i
47%
OSiMe$_2$Bu$^t$
H
H
H
ii
(222)
(219)
Bu$^t$Me$_2$SiO
(220)
H
H
H
H
i
76%
OSiMe$_2$Bu$^t$
H
H
H
iii
Bu$^t$Me$_2$SiO
(223)
(224)
(225)

i, LDA, THF, –78 °C; Bu$^t$Me$_2$SiOSO$_2$CF$_3$, THF–HMPA, –78 °C to r.t.; ii, 170 °C, 5 h, PhH (sealed tube); iii, 170–175 °C, 4 h, PhH (sealed tube)

**Scheme 30**

In an effort to probe the reason(s) underlying the failure of the attempted thermolytic conversion of (**219**) into (**220**), the structurally simpler substrate (**224**) was prepared from the ketone (**223**; Scheme 30).[51] Interestingly, thermolysis of (**224**) also provides a mixture of products, a careful spectral examination of which shows clearly that the Cope rearrangement product (**225**) is not present. A comparison of this result with that obtained from thermolysis of (**197**), which proceeds smoothly to give (**198**) in 93% yield, shows once again that *cis* substituents on the 'vinyl' groups can have a profound effect on the efficacy of the Cope rearrangement of 1,2-divinylcyclopropane systems. Furthermore, since one would expect isomerization of (**224**) to the corresponding *endo* isomer (**226**) to be a facile process (Scheme 31), the failure of the conversion (**224**) → (**225**) must be related to the second step, involving sigmatropic rearrangement of (**226**) to (**225**). Indeed, an examination of molecular models indicates that, due to the inflexible nature of the tricyclic ring system of (**226**), the (proposed) transition state for the conversion (**226**) → (**225**) possesses a severe steric interaction between the angular proton and the methyl group of the *cis*-1-propenyl moiety (see **N**; Scheme 31). Apparently, due primarily to this destabilizing feature, the transition state (**N**) is disfavored relative to those related to other modes of bond reorganization and, therefore, none of the Cope rearrangement product (**225**) is produced. A similar line of reasoning may be invoked to rationalize the failure of (**219**) to undergo sigmatropic rearrangement to (**220**).

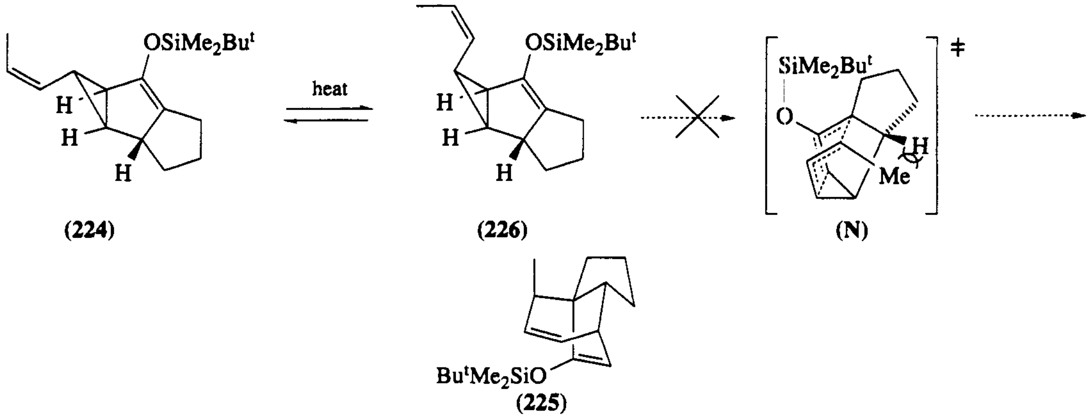

Scheme 31

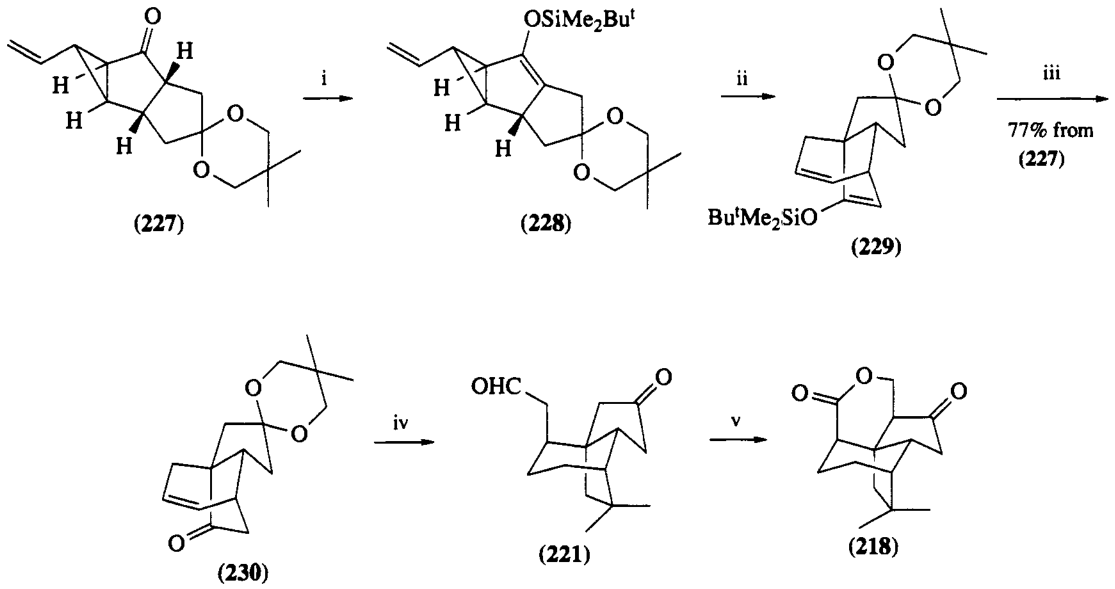

i, LDA, THF, –78 °C; $\mathrm{Bu^tMe_2SiOSO_2CF_3}$, THF–HMPA, –78 °C to r.t.; ii, 170-175 °C, 5 h, PhH (sealed tube); iii, TBAF, THF, –78 °C; iv, 10 steps; v, see ref. 53

Scheme 32

A successful formal total synthesis of (±)-quadrone (**218**) *via* a route in which a divinylcyclopropane rearrangement played a key role was achieved by employing the substrate (**228**; Scheme 32).[54] This material is readily prepared from the ketone (**227**) and, in contrast to compounds (**219**) and (**224**), undergoes smooth Cope rearrangement to the tricyclic diene acetal (**229**), which is easily transformed into the keto acetal (**230**). A rather lengthy sequence of reactions effects conversion of (**230**) into the keto aldehyde (**221**), which, as mentioned previously, has served as an intermediate in a total synthesis of (±)-quadrone (**218**).[53]

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# 8.3
# Charge-accelerated Rearrangements

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## 8.3.1 CHARGE-ACCELERATED REARRANGEMENTS: BACKGROUND

### 8.3.1.1 Introduction

The strain intrinsic to small-ring compounds creates a potential for facile rearrangement which is not present in more conventional molecules. This characteristic of three- and four-membered rings has been extensively exploited in synthesis, particularly in such well-established ring expansion strategies as the vinylcyclopropane and divinylcyclobutane rearrangements. Although these reactions have proven utility as synthetic methods, they often suffer from serious limitations. Many of these rearrangements only proceed under relatively harsh reaction conditions (*e.g.* at high temperatures), and frequently require the application of special techniques such as flash vacuum pyrolysis. Side reactions complicate the course of some small-ring rearrangements, compromising the efficiency of the reactions, and leading to mixtures of isomeric products which can be difficult to separate. Often these rearrangements also proceed with disappointingly low stereoselectivity.

It is now established that many of these limitations can be overcome by exploiting the accelerated rearrangements of small-ring compounds bearing charged substituents. The subject of this chapter is an overview of the progress recorded in this area to date. To place this chemistry in proper perspective, this background section summarizes the general features of charge-accelerated pericyclic reactions which have emerged during the past 20 years from studies of compounds which do not incorporate small rings. It should be noted that this subject is treated in greater detail in the chapters specifically concerned with sigmatropic processes (Chapters 7.1–7.3, this volume).

### 8.3.1.2 Azaanion- and Oxyanion-accelerated Rearrangements

The thermal rearrangement of 3-hydroxy-substituted 1,5-hexadiene derivatives (the 'oxy-Cope' rearrangement) is regarded as a useful synthetic route to δ,ε-unsaturated carbonyl compounds.[1] This 3,3-sigmatropic process is generally carried out at 200–400 °C, and is frequently accompanied by side reactions such as fragmentation initiated by 1,5-hydrogen shifts. In 1975, Evans and Golob[2] reported the remarkable observation that the potassium salts derived from 3-hydroxy-1,5-hexadienes undergo dramatically accelerated oxy-Cope rearrangement, in some cases exhibiting rate enhancements of $10^{17}$ compared to the corresponding alcohols. For example, the half-life for the rearrangement of (**1**; equation 1) at 66 °C was calculated to be only 1.4 min. The isomeric alkoxide (**3**), however, remained unchanged even after heating for 24 h. This and later observations by Evans and coworkers provided strong evidence that these rearrangements follow concerted pathways.[3,4] Since its discovery in 1975, the anionic variant of the oxy-Cope rearrangement has been widely exploited, particularly in the area of natural product synthesis.[5,6]

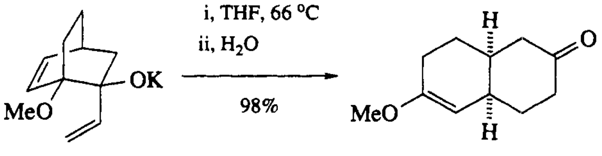

(1)

(**1**) (**2**)

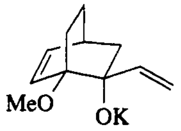

(**3**)

Providing a rationale for the extraordinary rate acceleration observed in these reactions has been the aim of several theoretical and mechanistic studies. For example, Evans has shown from estimates of bond dissociation energies[7] as well as by *ab initio* calculations[8] that the effect of an oxyanion substituent is to weaken the adjacent carbon–carbon bond, thus facilitating the dissociation of this bond which is undergoing cleavage in the transition state for rearrangement. The experiments of Evans and coworkers stimulated Carpenter to develop a simple but operationally useful model for predicting the effect of substituents on a wide variety of pericyclic reactions.[9] According to this model, the activation energy for rearrangement of the anionic species is reduced because of the increased charge delocalization possible in the pericyclic transition state which, by definition, involves a completely conjugated array of orbitals. This stabilizing interaction is not present in the reactant, and consequently the net result is a reduction in $\Delta^{\ddagger}$. Carpenter's model predicts that this stabilizing effect should be observed for 'anionic, radical, or cationic substituents, provided that the skeletal atoms form an even-membered, uncharged ring in the transition state'.[10]

The ability of charged substituents to accelerate the 3,3-sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) has also been documented. The effect of oxyanion substituents on the rate and course of aliphatic Claisen rearrangements has been the subject of particular attention.[5,11] In 1972, Ireland and Mueller reported that the lithium enolate derivatives of allyl esters undergo rapid and effi-

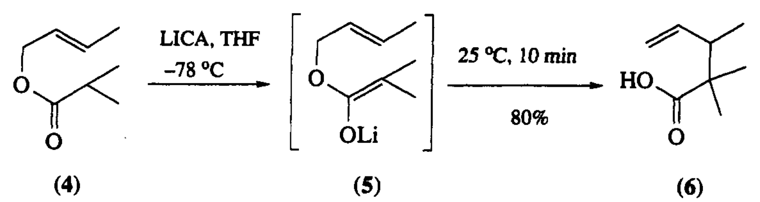

(2)

cient rearrangement at ambient temperature (*e.g.* equation 2).[12–14] By contrast, the thermal aliphatic Claisen rearrangement of allyl vinyl ethers generally requires temperatures in excess of 150 °C.

Oxyanion substituents at the terminal vinyl carbon of allyl vinyl ethers can also impart a considerable rate acceleration to the Claisen rearrangement. For example, enolate derivatives of α-allyloxy ketones rearrange to α-hydroxy-γ,δ-unsaturated ketones at temperatures as low as −42 °C; this reaction has been employed in an elegant tandem conjugate addition–Claisen rearrangement strategy (equation 3).[15] In some cases, however, the reactions of enolates derived from α-allyloxy carbonyl compounds have been found to follow alternative 2,3-sigmatropic (Wittig-type) rearrangement pathways.[16]

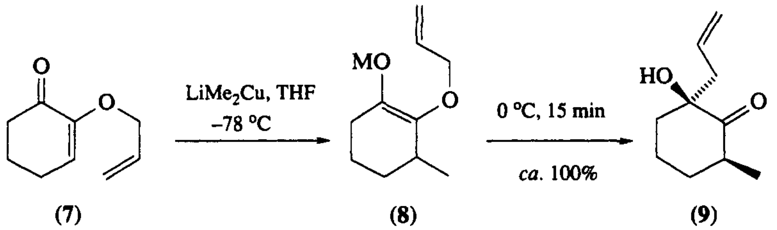

(3)

The familiar Cope and Claisen rearrangements are classified as 3,3-sigmatropic rearrangements; by comparison, thermal 1,3-sigmatropic migrations of carbon atoms (equation 4) have received relatively little attention. Carpenter's model[9] predicts that an oxyanion substituent positioned at either terminus of the migrating σ-bond should facilitate these rearrangements, and in fact, recent studies have demonstrated that 1,3-sigmatropic shifts of alkali metal salts of both allylic (equation 5) and homoallylic (equation 6) alcohols can exhibit dramatic rate accelerations.

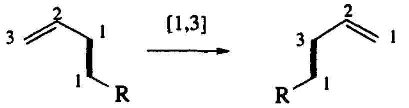

(4)

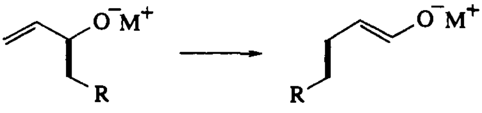

(5)

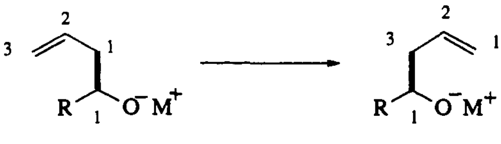

(6)

Early examples of accelerated 1,3-sigmatropic rearrangements involving allylic alcohol derivatives were reported by Thies and Seitz.[17] Thies and coworkers had previously employed thermal rearrangements of medium-ring 1-trimethylsilyloxy-1-vinyl-3-cycloalkene derivatives as a useful method for two-carbon ring expansion. These reactions require relatively high temperatures (280–350 °C), however, and in some cases, *e.g.* (**10**) → (**12**), proceed in rather poor yield (Scheme 1). Thies and Seitz found that the ring expansion of the corresponding potassium alkoxides in highly dissociating media such as HMPA occurs rapidly at room temperature, and is often considerably cleaner than the analogous thermal rearrangements. This two-carbon ring expansion strategy has also been successfully applied to several medium-ring 1-vinyl-3-cycloalkenols (equation 7), although in some cases oxy-Cope rearrangement, *e.g.* (**13**) → (**16**), is observed as a competing process. In the case of larger ring systems, *e.g.* cyclotridecenol, 3,3-sigmatropic rearrangement in fact becomes the predominant mode of reaction.

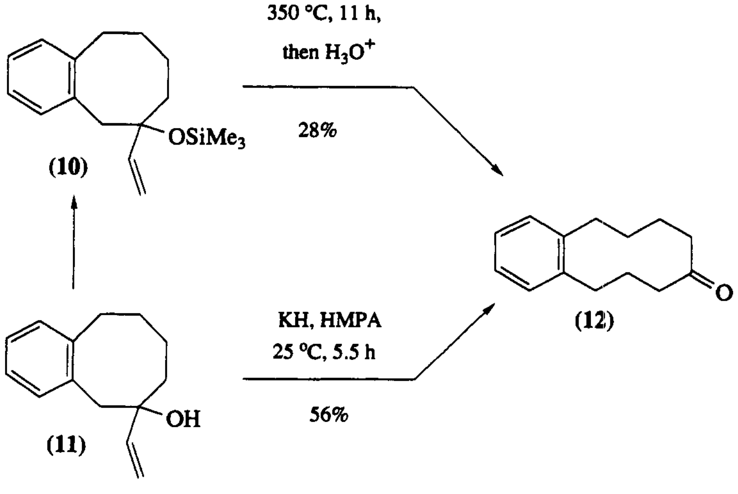

**Scheme 1**

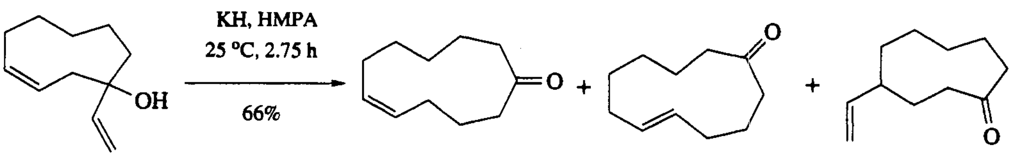

(7)

**(13)** **(14)** 54% **(15)** 35% **(16)** 11%

A noteworthy feature of these 1,3-rearrangements is the requirement that the migrating carbon be activated by a vinyl or aryl π-bond; that is, in equation (5), R must be a vinyl or aryl group. Saturated 1-vinylcycloalkanols such as (**17**) show no tendency to rearrange when treated with KH in HMPA at room temperature.[17b] These results are consistent with a concerted 1,3-shift mechanism, but also raise the possibility that these reactions can follow a stepwise pathway involving fragmentation to an allylic (or benzylic) carbanion, followed by intramolecular Michael addition. Related 1,3-rearrangements in which the migrating carbon is even more activated (*e.g.* as a dithiane derivative) appear to proceed *via* such retro-aldol/conjugate addition mechanisms.[18]

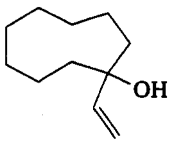

**(17)**

Zoeckler and Carpenter have also studied oxyanion-accelerated 1,3-sigmatropic rearrangements of allylic alcohols, focusing particular attention on the stereochemical course of the reaction.[10] An interesting feature of Carpenter's model for accelerated pericyclic reactions is that it predicts that charged substituents should accelerate orbital symmetry forbidden[19] pathways more than the corresponding allowed ones. This principle is a consequence of the ability of charged substituents to more effectively stabilize antiaromatic forbidden transition states by interacting with the low-lying LUMO or high-lying HOMOs which they possess. In accord with these predictions, the 1,3-sigmatropic rearrangement of (**18**; equation 8) was found to proceed predominantly (≥65%) by the suprafacial-retention pathway to afford (**19**), even

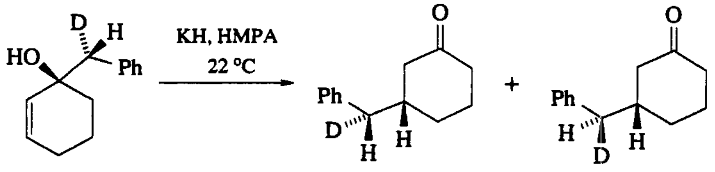

(8)

**(18)** **(19)** **(20)**

though the Woodward–Hoffmann rules suggest that inversion of configuration at the migrating carbon should be favored.

Several examples of anion-accelerated 1,3-sigmatropic rearrangements involving homoallylic alcohols (equation 6) have also been reported. In fact, reactions of this type involving lithium, magnesium, and zinc alkoxides have been known for many years.[20] However, whereas the rearrangements of magnesium and zinc salts of alcohols such as (**21**; equation 9) require several days of heating at 65 °C, the reactions of the corresponding potassium salts are complete within minutes at 0 °C.[21] The sodium salt of 7-norbornadienol (**23**) is subject to a similar 1,3-sigmatropic shift which takes place at room temperature. In this reaction the norcaradiene derivative which is generated then undergoes a further disrotatory 6π-electrocyclic rearrangement to eventually furnish methyl tropyl ether (equation 10).[22] Krow and Reilly have reported a very similar 1,3-shift, accelerated by an azaanion substituent (equation 11).[23] Deuterium-labeling studies indicated that this rearrangement occurs *via* suprafacial migration with predominant retention of configuration at the migrating carbon, an outcome which is in accord with Carpenter's model.

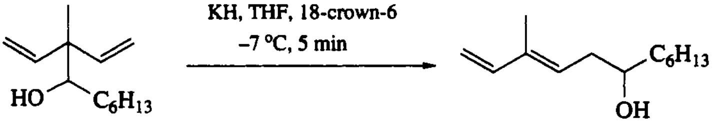

(**21**) (**22**) (9)

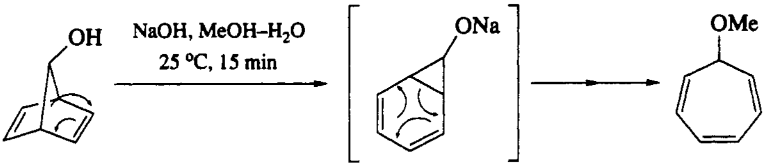

(**23**) (**24**) (**25**) (10)

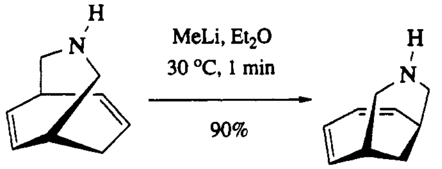

(**26**) (**27**) (11)

The ability of an oxyanion substituent to facilitate 1,5-hydrogen sigmatropy was demonstrated by Paquette *et al.* in 1980. For example, rearrangement of the potassium salt of 2,4-cycloheptadienol occurs more than $10^5$ times faster than the rearrangement of the corresponding alcohol (equation 12).[24] Accelerated 1,5-shifts of alkyl, vinyl, aryl and cyclopropyl groups in cyclopentadiene derivatives (*e.g.* equation 13) have also been reported.[25]

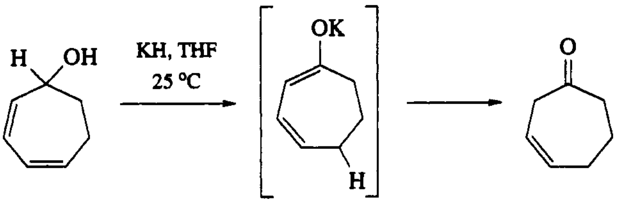

(**28**) (**29**) (**30**) (12)

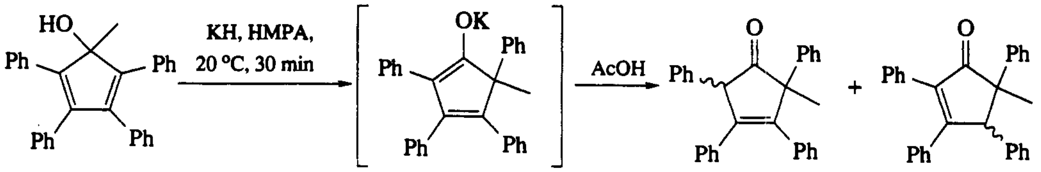

(31) (32) (33) 76% (34) 24% (13)

### 8.3.1.3 Carbanion-accelerated Rearrangements

The ability of certain carbanion substituents to accelerate the aliphatic Claisen rearrangement has been documented in several laboratories. These reactions bear close analogy to the Ireland ester enolate rearrangement and related oxyanion-accelerated processes discussed in the previous section. Denmark reported the first examples of the carbanion-accelerated Claisen rearrangement in 1982.[26] Subsequent studies have established that this reaction has broad scope and provides a valuable synthetic route to $\gamma,\delta$-unsaturated ketones.[27] Arylsulfonyl-stabilized carbanions appear to be particularly effective in promoting these reactions. Analogous carbanions stabilized by other sulfur-based functional groups tend to decompose *via* elimination pathways, and nitrile and ester derivatives also fail to undergo rearrangement, presumably due to the extensive delocalization of charge in these anions.

The arylsulfonyl carbanion accelerated Claisen rearrangement is completely regioselective and has also been found to be highly diastereoselective (Scheme 2).[27a] The stereochemical course of the reaction conforms to the familiar chair-like transition state model usually invoked for the classic thermal process. Recently, high degrees of asymmetric induction have been observed in the rearrangements of chiral cyclic phosphoramidate stabilized carbanion derivatives.[27c]

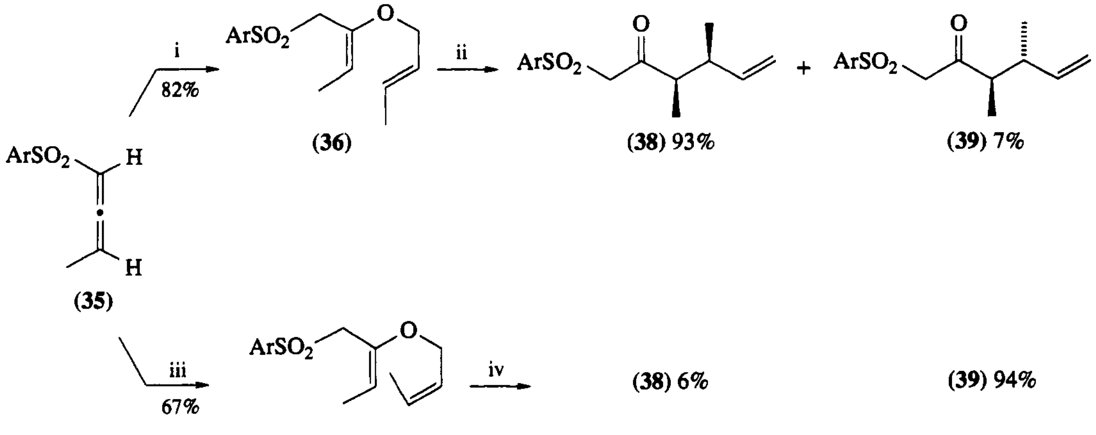

(36) (38) 93% (39) 7%

(35)

(38) 6% (39) 94%

(37)

i, (*E*)-$HOCH_2CH{=}CHMe$, NaH, THF; ii, $KCH_2SOMe$, DMSO, 20 °C, 4 h;
iii, (*Z*)-$HOCH_2CH{=}CHMe$, NaH, THF; iv, $LiCH_2SOMe$, DMSO, 50 °C, 1.5 h

Scheme 2

Other carbanionic substituents are equally effective in promoting unusually facile rearrangements of allyl vinyl ethers. Ponaras has reported that the rearrangement of the hydrazone sodium salt (**41**; equation 14) occurs with $t_{1/2}$ = 15 h at 66 °C; note that this reaction creates a sterically congested product with two adjacent quaternary centers.[28] Büchi and Vogel have described Claisen rearrangements accelerated by carboxylic acid dianions (equation 15).[29] No rearrangement was observed at 120 °C with the corresponding simple carboxylate salt.

Blechert has developed an interesting synthesis of 2-substituted indoles which involves the conjugate addition of *N*-phenylhydroxylamine salts (or *N*-phenylnitrones) to electron-deficient allenes, followed by carbanion-accelerated hetero-Cope rearrangement of the Michael adduct.[30] For example, addition of the hydroxylamine salt (**46**) to the allenyl sulfone (**47**) produces the anion (**48**), which undergoes rapid 3,3-sigmatropic rearrangement to afford the $\beta$-keto sulfone (**49**). Cyclization to the indole proceeds smoothly upon exposure to formic acid (Scheme 3).

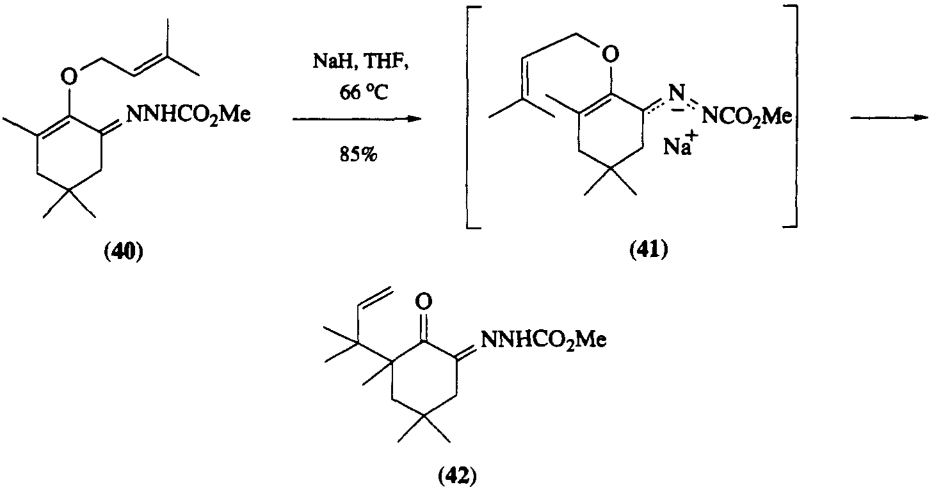
NNHCO2Me
NaH, THF, 66 °C
85%
O
N
NCO2Me
Na+
(40)
(41)
(42)

(14)

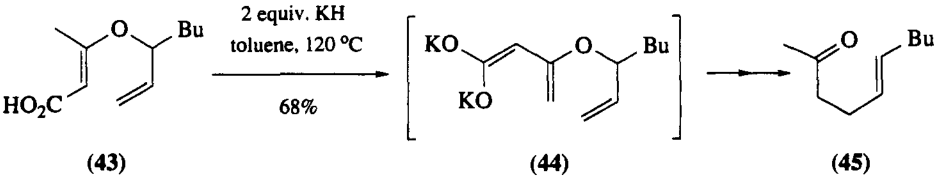
Bu
HO2C
2 equiv. KH toluene, 120 °C
68%
KO
KO
O
(43)
(44)
(45)

(15)

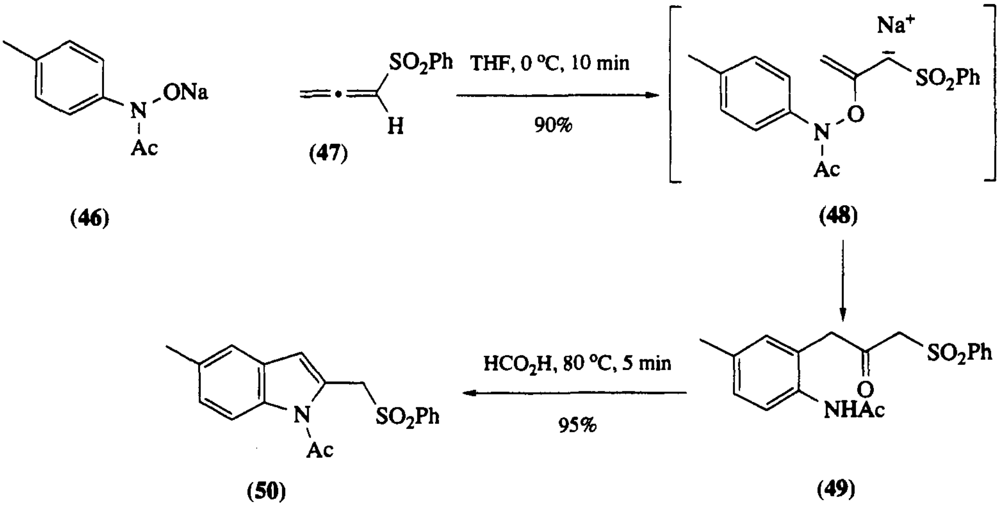
ONa
N
Ac
SO2Ph
H
THF, 0 °C, 10 min
90%
Na+
HCO2H, 80 °C, 5 min
95%
O
NHAc
(46)
(47)
(48)
(49)
(50)

Scheme 3

Wender and coworkers reported the first example of an enolate-accelerated Cope rearrangement in 1985.[31] Exposure of the trienone (**51**; Scheme 4) to potassium hydride in THF at room temperature for 17 h led to the formation of a 1.2:1 mixture of (**55**) and (**54**); each rearranged trienone was produced as a mixture of alkene isomers. The facility with which the rearrangement of the ketone enolates takes place is underscored by the observation that the corresponding silyl enol ethers remain unchanged under identical conditions, and require temperatures in excess of 100 °C for efficient rearrangement.

Finally, no examples of carbanion-accelerated 1,3-sigmatropic rearrangements appear to have been observed to date, although Okamura and coworkers have reported a transformation which may involve a sulfinyl carbanion accelerated 1,5-hydrogen shift.[32]

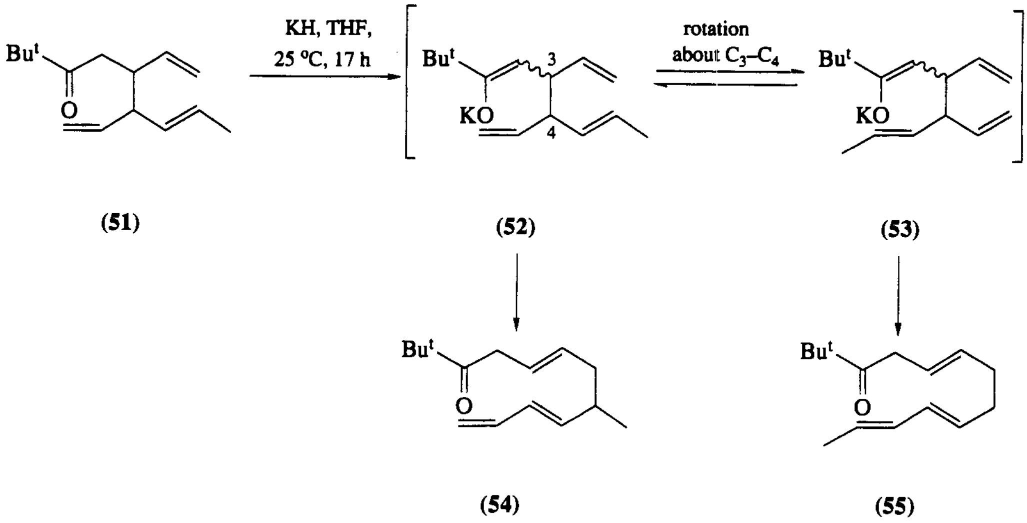

Scheme 4

## 8.3.2 CHARGE-ACCELERATED REARRANGEMENTS OF CYCLOPROPANES

### 8.3.2.1 Introduction

The rearrangement of a cyclopropane ring is the pivotal step in a large number of important synthetic strategies.[33] Cyclopropane ring expansion and ring fission reactions have been effected using a very wide range of reaction conditions. Thus, rearrangements have been induced by both thermal and photochemical activation of cyclopropane derivatives, by treatment with nucleophilic, electrophilic, and radical species, and also with the aid of various main-group and transition metal reagents. Many of these rearrangements involve charged cyclopropane derivatives as either starting materials or reactive intermediates. The subject of this chapter is charge-accelerated small-ring rearrangements; this area is defined as including only those reactions which, although accelerated by charged substituents, nonetheless can also take place in the absence of such substituents. Among cyclopropane rearrangements, the most important process of this type is the vinylcyclopropane to cyclopentene rearrangement.

The vinylcyclopropane (VCP) rearrangement is the subject of several excellent reviews,[34] including Chapter 8.1, this volume. As detailed in these references, the VCP rearrangement has seen extensive application as a strategy for the synthesis of a variety of substituted and functionalized five-membered carbocycles. In spite of these successful applications, several features of the conventional, thermal process compromise its utility as a general synthetic method. As will be seen in the next section, these limitations can to a large extent be overcome through recourse to charge-accelerated variants of the reaction. The most serious limitations associated with the thermal version of the VCP rearrangement include those mentioned below.

(i) *Extreme reaction conditions.* The vinylcyclopropane to cyclopentene rearrangement proceeds with activation energies in the range of 30 to 65 kcal $\mathrm{mol}^{-1}$ (1 cal = 4.18 J).[34b] Consequently, high temperatures (frequently over 500 °C) are required to effect the reaction, particularly in sterically congested systems. In some cases these harsh conditions are not compatible with highly functionalized synthetic intermediates.

(ii) *Limited scope.* Synthetically significant substrates sometimes resist rearrangement within the range of reasonable reaction temperatures. For example, while the rearrangement of (**56**; equation 16) proceeds smoothly at 332 °C, the isomeric vinylcyclopropane (**58**; in which the requisite rearrangement conformation is sterically disfavored) is totally inert under these conditions, and at higher temperatures undergoes polymerization.[35]

(iii) *Side reactions.* The intervention of side reactions further limits the scope of the thermal vinylcyclopropane rearrangement. In particular, cyclopropanes with *syn*-vinyl and α-CH-bearing groups are subject to homo 1,5-hydrogen shifts leading to 1,4-dienes, and rarely undergo satisfactory vinylcyclopropane rearrangement. The activation energy for this concerted retro-ene process is typically 31 to 33 kcal $\mathrm{mol}^{-1}$, significantly lower than the energy usually required for the VCP rearrangement.

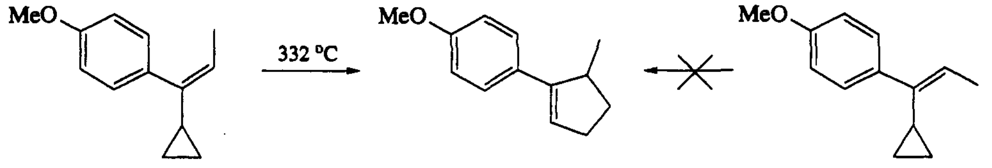

(16)

**(56)** **(57)** **(58)**

Even in vinylcyclopropane derivatives in which the vinyl group is *anti* to the CH group, thermolysis often leads to 1,4-dienes as a result of isomerization to the *syn* isomer, followed by 1,5-shift (*e.g.* equation 17).[36]

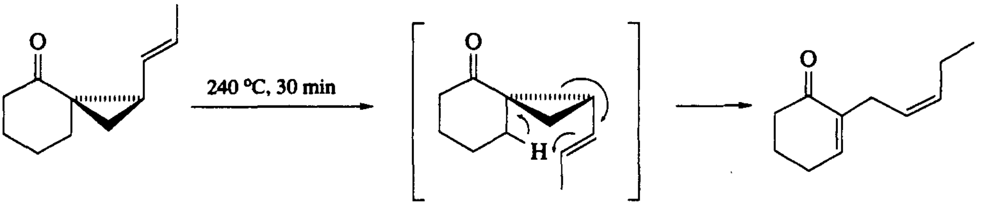

(17)

**(59)** **(60)** **(61)**

(iv) *Stereochemical ambiguities.* As illustrated with equation (18), the thermal VCP rearrangement generally proceeds with modest stereoselectivity.[37] A problem in some cases is that at the high reaction temperatures diastereomerization of the initial cyclopropane occurs more rapidly than rearrangement. Note that in the reaction depicted in equation (18) the major product formed is in fact the diene (**67**), the result of homo 1,5-sigmatropic hydrogen shift (1,4-diene:total cyclopentenes = 13:1).

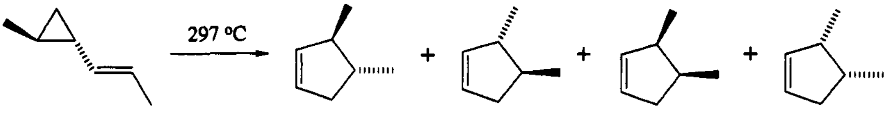

(18)

**(62)** **(63)** 65% **(64)** 8% **(65)** 22% **(66)** 5%

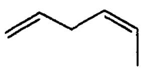

**(67)**

### 8.3.2.2 Oxyanion-accelerated Vinylcyclopropane Rearrangements

The first example of a charge-accelerated vinylcyclopropane rearrangement was reported by Danheiser *et al.* in 1980.[38] Cleavage of the diastereomeric 2-chloroethoxy ethers (**68**; equation 19) with *n*-butyllithium[39] at 0 °C generated the vinylcyclopropanol lithium salts (**69**), which rearranged smoothly to the cyclopentenol (**70**) upon warming to room temperature. The facility of this oxyanion-accelerated process stands in dramatic contrast to the high temperatures required to effect conventional thermal vinylcyclopropane rearrangements. Although electron-donating substituents had previously been shown to increase the rate of the VCP rearrangement, even these systems require temperatures in excess of 200 °C for efficient reaction. For example, the activation energies for the rearrangement of 1-methoxy-2-vinylcyclopropane and 1-dimethylamino-2-vinylcyclopropane have been determined to be 39 and 31 kcal $mol^{-1}$, respectively.[40]

As outlined in Scheme 5, tertiary cyclopropanol salts are also subject to the oxyanion-accelerated VCP rearrangement. In this sequence the requisite vinylcyclopropanol salts are conveniently prepared from readily available 1,1-dibromocyclopropanes by sequential halogen–metal exchanges, followed first by alkylation,[41] and then by oxygenation.[42] Products resulting from alternative 1,5-hydrogen shift (retro-ene) pathways were not detected in these reactions.

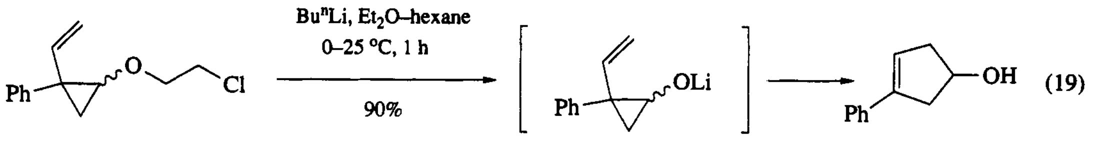

**(68)** **(69)** **(70)** (19)

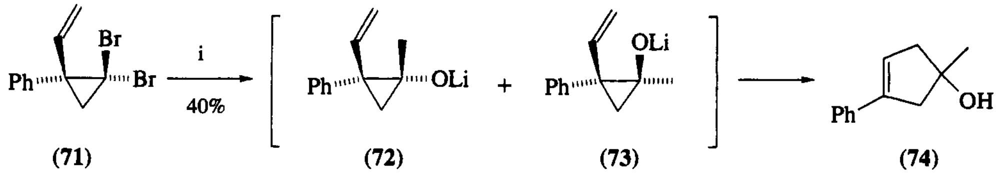

**(71)** **(72)** **(73)** **(74)**

i, 1 equiv. Bu$^n$Li, −100 °C, then 1 equiv. MeI, then 2 equiv. Bu$^t$Li (−78 °C), then bubble in $O_2$, warm to 25 °C

**Scheme 5**

Further studies on the scope and stereochemical course of the oxyanion-accelerated vinylcyclopropane rearrangement were reported in 1981.[43] This paper introduced a general [4 + 1] annulation strategy for the synthesis of cyclopentene derivatives in which the anion-accelerated VCP rearrangement functions as the key step. In this report, the accelerated version of the vinylcyclopropane rearrangement was also shown to proceed with remarkably high stereoselectivity, in further contrast to the thermal process.

For the purposes of synthetic planning, the overall transformation may be viewed as the suprafacial *exo* cycloaddition of hydroxycarbene across the termini of a conjugated diene (equation 20). Operationally, the annulation is accomplished in two steps. The first step involves the stereospecific *syn* addition of 2-(chloroethoxy)carbene[44] to the 1,3-diene to produce a mixture of vinylcyclopropanes **(76)** and **(77)**. Exposure of these isomeric ethers to *n*-butyllithium in a mixture of THF, hexane, and HMPA at 0 to 50 °C then effects ether cleavage[39] and rearrangement of the resulting lithium salts in a single step. The intermediate *syn*- and *anti*-2-vinylcyclopropanol salts rearrange by topologically different pathways to afford, in most cases, a single cyclopentenol.

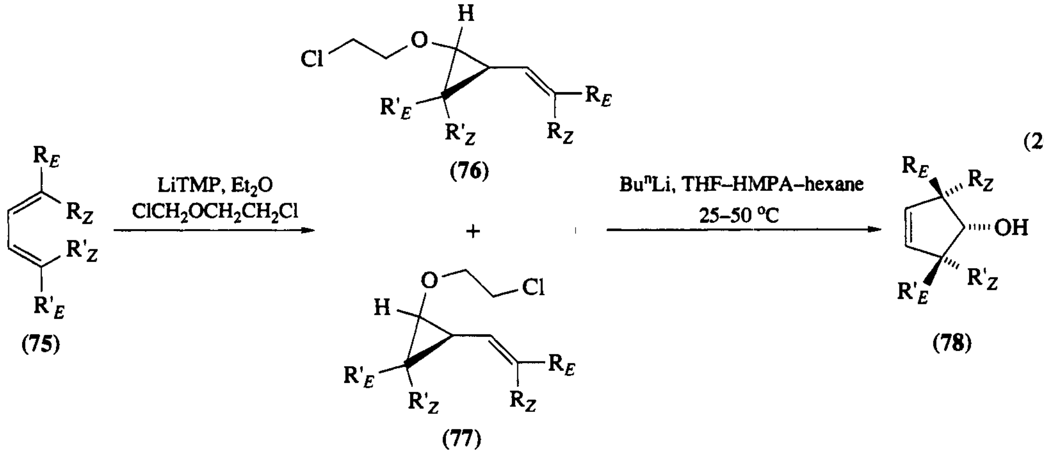

**(75)** **(76)** **(77)** **(78)** (20)

Application of the [4 + 1] strategy to (*E*)- and (*Z*)-6-phenyl-1,3-hexadiene illustrates the stereochemical course of the annulation (Scheme 6). Addition of 2-(chloroethoxy)carbene in each case occurs exclusively at the less-substituted double bond to afford a mixture of *syn*- and *anti*-2-vinylcyclopropyl ethers. Rearrangement of the corresponding lithium salts then furnishes **(82)** [99:1 mixture of **(82)** and **(83)** from the (*E*)-diene **(79)**] and **(83)** [exclusive product from the (*Z*)-diene **(84)**] in accord with the paradigm expressed in equation (20). Separate rearrangement of pure **(80)** and **(81)** revealed that the trace of *cis*-substituted cyclopentenol produced from the (*E*)-diene originates entirely in the rearrangement of the *syn* isomer **(81)**. In addition, the stereochemical integrity of the lithium salts derived from **(82)** and **(83)** upon prolonged heating suggests that these cyclopentenols are the kinetic products of rearrangement.

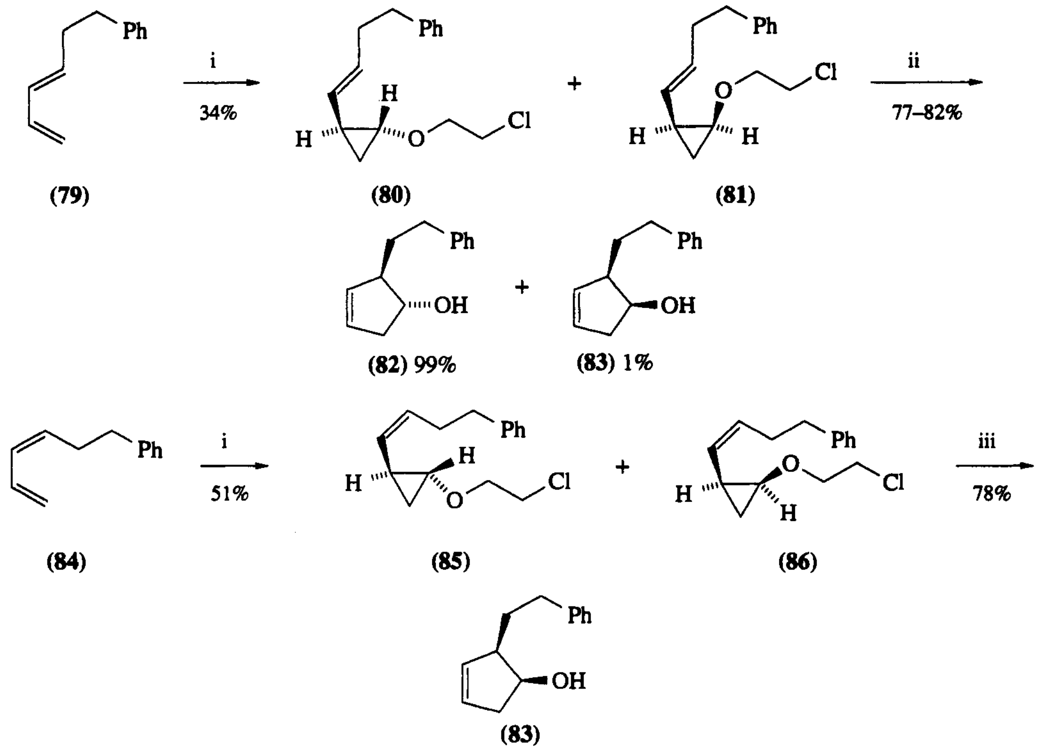

i, LiTMP, $Et_2O$, $ClCH_2OCH_2CH_2Cl$; ii, $Bu^nLi$, THF–HMPA–hexane, 25 °C, 1 h;
iii, $Bu^nLi$, THF–HMPA–hexane, 50 °C, 1 h

**Scheme 6**

A variety of other conjugated dienes participate in the [4 + 1] annulation with stereochemistry in accord with the predictions of equation (20). The 1-vinylcycloalkenes (**87**)–(**89**) can be viewed as (*E*)-substituted dienes, and are thus expected to yield the *exo*-alcohols (**90**)–(**92**). In each of these cases carbene addition generates a mixture of four intermediate 2-vinylcyclopropyl ethers, each of which then rearranges to produce exclusively the predicted stereoisomer. Application of the annulation to the endocyclic (*Z*,*Z*)-dienes (**93**) and (**94**) also generates in each case a single bicyclo[*n*.2.1]alkenol, and the (*E*,*E*)-diene (**97**) similarly reacts to afford exclusively the cyclopentenol (**98**; Scheme 7).

In contrast to the very high stereoselectivities observed for the reactions discussed above, the mixture of vinylcyclopropanol salts obtained from (*E*,*Z*)-2,4-hexadiene (**99**) rearranges to the predicted cyclopentenol (**102**) with a preference of only 4:1. Separate rearrangement of the vinylcyclopropyl ethers (**100**) and (**101**; Scheme 8) suggests that the paradigm expressed in equation (20) cannot be applied to systems incorporating C-3 substituents *syn* to the vinyl group on the cyclopropane ring. Note, however, that the desired VCP rearrangement does occur smoothly in this system, and no retro-ene cleavage of the cyclopropane ring was observed to take place as in the case of analogous thermal reactions.

The stereochemical course of the oxyanion-accelerated vinylcyclopropane rearrangement can be explained on the basis of several alternative mechanisms.

(i) *Concerted 1,3-sigmatropic shift mechanism.* Four stereochemically distinct pathways can be distinguished for a concerted 1,3-sigmatropic shift: suprafacial migration across the π-system with either inversion (*si* pathway) or retention (*sr*) at the migrating center, and antarafacial rearrangement with either inversion (*ai*) or retention (*ar*) at the migrating center. Three effects have been suggested to contribute to determining the relative energies for these alternative pathways: (a) conservation of orbital symmetry (Woodward and Hoffmann)[19] predicts that the transition states for the *si* and *ar* pathways should be of lower energy than those for the *sr* and *ai* modes of reaction; (b) the Berson–Salem subjacent orbital effect[45] predicts stabilization of the transition states for the orbital symmetry disfavored *sr* and *ai* pathways due to interaction of the π-orbital of the migrating carbon and the subjacent HOMO bonding orbital of the allylic system; (c) as discussed earlier, Carpenter predicts that a charged substituent should stabilize the orbital symmetry disfavored pathway in a sigmatropic rearrangement more than it stabilizes the symmetry favored one.[10,46]

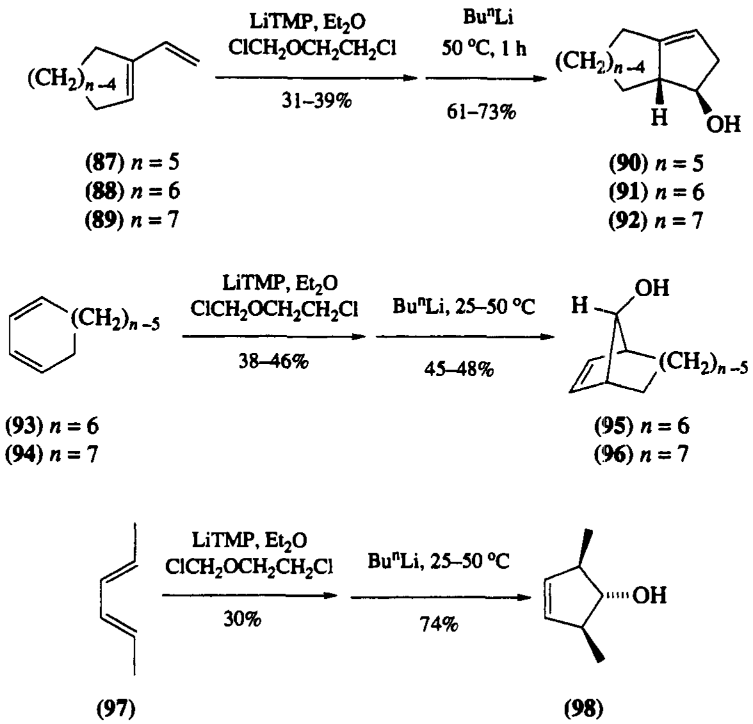
(CH2)n-4
LiTMP, Et2O
ClCH2OCH2CH2Cl
31–39%
BunLi
50 °C, 1 h
61–73%
(CH2)n-4
H
OH
(87) n = 5
(88) n = 6
(89) n = 7
(90) n = 5
(91) n = 6
(92) n = 7
(CH2)n-5
LiTMP, Et2O
ClCH2OCH2CH2Cl
38–46%
BunLi, 25–50 °C
45–48%
H
OH
(CH2)n-5
(93) n = 6
(94) n = 7
(95) n = 6
(96) n = 7
LiTMP, Et2O
ClCH2OCH2CH2Cl
30%
BunLi, 25–50 °C
74%
OH
(97)
(98)

Scheme 7

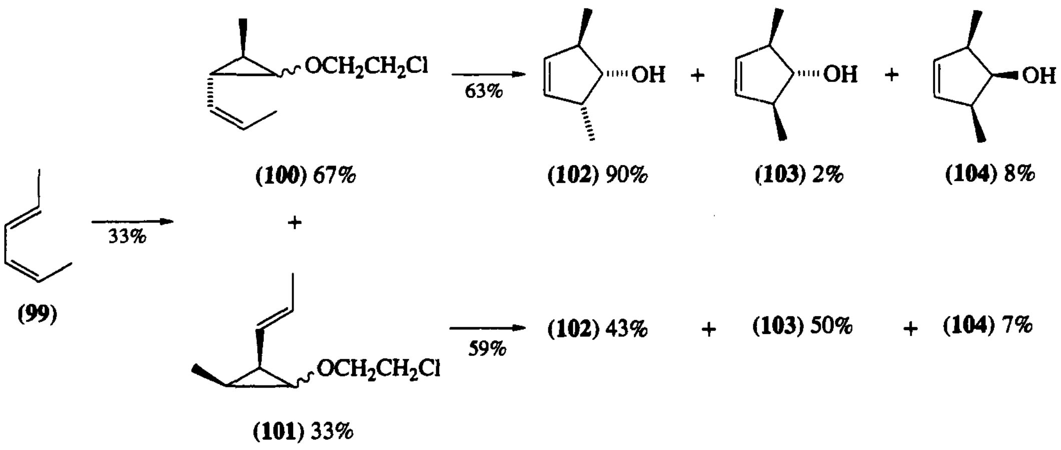
OCH2CH2Cl
63%
OH
OH
OH
(100) 67%
(102) 90%
(103) 2%
(104) 8%
33%
+
(99)
(102) 43%
(103) 50%
(104) 7%
59%
OCH2CH2Cl
(101) 33%

Scheme 8

Scheme 9 shows the possible rearrangement products from suprafacial 1,3-sigmatropic migration of the isomeric vinylcyclopropanol salts (**105**) and (**106**). The '*exo* suprafacial' annulation product generally observed (equation 20) corresponds to cyclopentenol (**107**) in this scheme. Conservation of orbital symmetry requires that the *si* pathway should be favored for the isomer (**105**) in which the oxyanion substituent is *anti* to the vinyl group on the cyclopropane ring. However, migration with inversion at C-1 is sterically disfavored for the isomeric salt (**106**) in which the vinyl and oxyanion substituents are oriented *syn* on the cyclopropane ring; the clockwise somersaulting action required at the migrating atom would force the solvated lithium alkoxide into the allylic framework in this transition state. This isomer consequently rearranges *via* the subjacent orbital stabilized *sr* pathway. Thus, both (**105**) and (**106**) are expected to rearrange *via* topologically different concerted pathways to afford the same cyclopentenol (**107**).

(ii) *Stepwise mechanisms.* These can also be proposed to account for the oxyanion-accelerated vinylcyclopropane rearrangement (Scheme 10). However, these stepwise pathways involving diradical and allylic anion aldehydes are only compatible with the observed stereochemical results provided that cyclization of the intermediates occurs faster than conformational interconversions. The observation that the

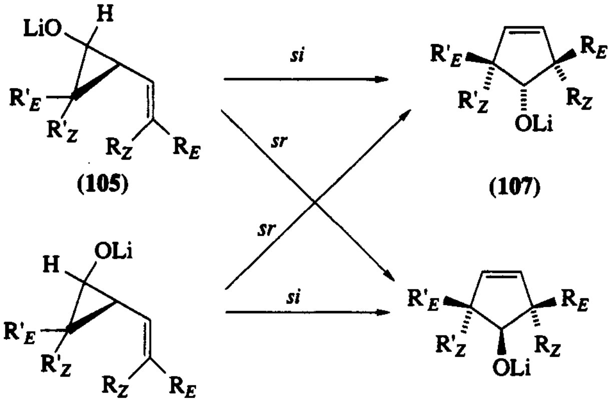

**Scheme 9**

rearrangements of (**101**) and the vinylcyclopropanes derived from (**97**) result in different product distributions, excludes mechanisms involving freely rotating acyclic intermediates, since in that case both reactions would proceed through a common intermediate and therefore yield the same results.

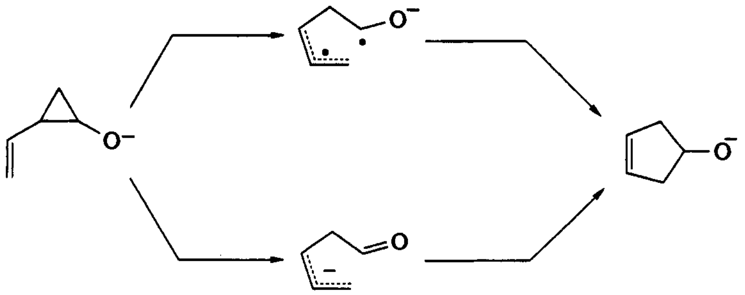

**Scheme 10**

Several unsuccessful oxyanion-accelerated vinylcyclopropane rearrangements have also been noted. For example, the lithium alkoxides derived from the highly substituted 2-vinylcyclopropyl ethers (**109**) failed to undergo rearrangement even after prolonged heating at 66 °C. Treatment of (**110**; derived from 2-ethoxybutadiene) with *n*-butyllithium resulted in the formation of complex mixtures in which no cyclopentenol could be detected. Fragmentation of the oxyanion intermediate apparently occurs more rapidly than 1,3-sigmatropic rearrangement in this system. Finally, several reports have appeared indicating that the alkali metal salts of 1-vinylcyclopropanols are not subject to accelerated vinylcyclopropane rearrangement.[47,48] For example, thermolysis of (**111**) in toluene gave the fragmentation product (**112**) with no evidence of VCP rearrangement.[48]

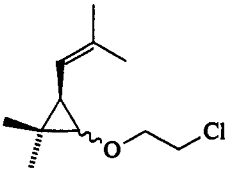

**(109)**

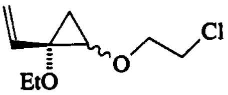

**(110)**

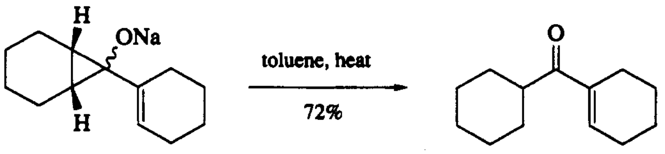

**(111)** **(112)** (21)

### 8.3.2.3 Carbanion-accelerated Vinylcyclopropane Rearrangements

The ability of carbanionic substituents to accelerate the vinylcyclopropane rearrangement was reported by Danheiser and coworkers in 1985.[49] α-Sulfonyl carbanions proved to be the most effective activating groups for these reactions. For example, exposure of (**113**; equation 22) to 1.2 equiv. of *n*-butyllithium in 5:1 THF–HMPA at –78 °C generated the corresponding lithium derivative, which rearranged smoothly upon warming to –30 °C to afford the cyclopentene (**114**) in 97% yield. The carbanion-accelerated vinylcyclopropane rearrangement thus occurs with even greater facility than the oxyanion-accelerated version of the reaction.

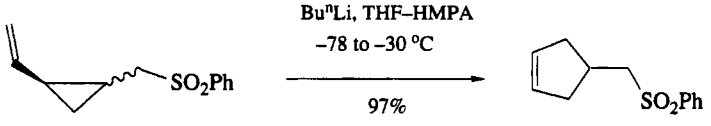

(**113**) (**114**) (22)

The use of HMPA as cosolvent is crucial to the success of these reactions; in its absence no rearrangement was observed to occur, even after warming to higher temperatures. Interestingly, if the lithium derivative of (**113**) is quenched at –78 °C with methanol, then the (vinylcyclopropyl)methyl sulfone is recovered, but the ratio of *syn* and *anti* diastereomers is significantly different from that in the starting material (an increase in the amount of the *anti* isomer is observed). Also noteworthy is the observation that the rearrangement of the corresponding potassium derivative is complicated by the formation of acyclic by-products such as (**115**). These results suggest the possibility that heterolytic cleavage of the metallated (vinylcyclopropyl)methyl sulfones is occurring in these reactions, and that the accelerated VCP rearrangement may proceed *via* a stepwise fragmentation–conjugate addition pathway.

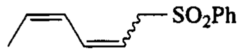

(**115**)

From the perspective of synthetic analysis, the anion-accelerated vinylcyclopropane rearrangement provides a method, analogous to the Diels–Alder reaction, for the conversion of conjugated dienes to cyclopentene derivatives. As outlined in the previous section, the oxyanion-accelerated version of the reaction serves as the key step in a process which results in the effective 1,4-addition of hydroxycarbene about the termini of a 1,3-diene (Scheme 11). The carbanion-accelerated vinylcyclopropane rearrangement comprises the pivotal step in a second-generation version of this [4 + 1] annulation strategy, which extends the method to include the synthesis of cyclopentene derivatives bearing a variety of functionalized substituents in place of the hydroxy group on the new five-membered ring.

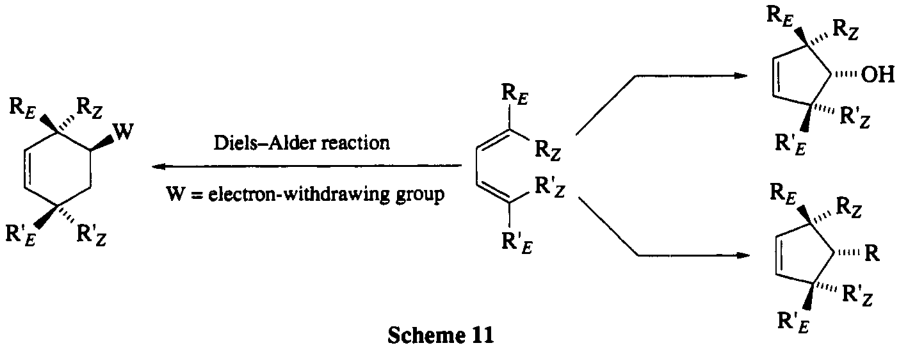

Scheme 11

A typical annulation sequence (utilizing 1,3-cyclohexadiene as the diene component) is outlined in Scheme 12. Addition of monobromocarbene (generated from $CH_2Br_2$ and NaHMDS by the method of Martel)[50] furnished the isomeric bromocyclopropanes (**117**) and (**118**). Phenylthiomethylation was then achieved by coupling the Grignard derivatives with iodomethyl phenyl sulfide in the presence of 0.05 equiv. of $Li_2CuCl_4$[51] in THF–$Et_2O$ at –30 to 25 °C. Next, chemoselective oxidation of the resulting sulfides was accomplished using $MoO_5{\cdot}HMPA{\cdot}H_2O$,[52] or alternatively, with MCPBA or potassium hydrogen persulfate ('oxone').[53] Exposure of the resulting pair of sulfones (**119**) and (**120**) to 1.2 equiv. of

$Bu^nLi$ in THF–HMPA at –78 °C, followed by warming to room temperature, then furnished the expected norbornene (**121**) as a single stereoisomer in 87% yield.

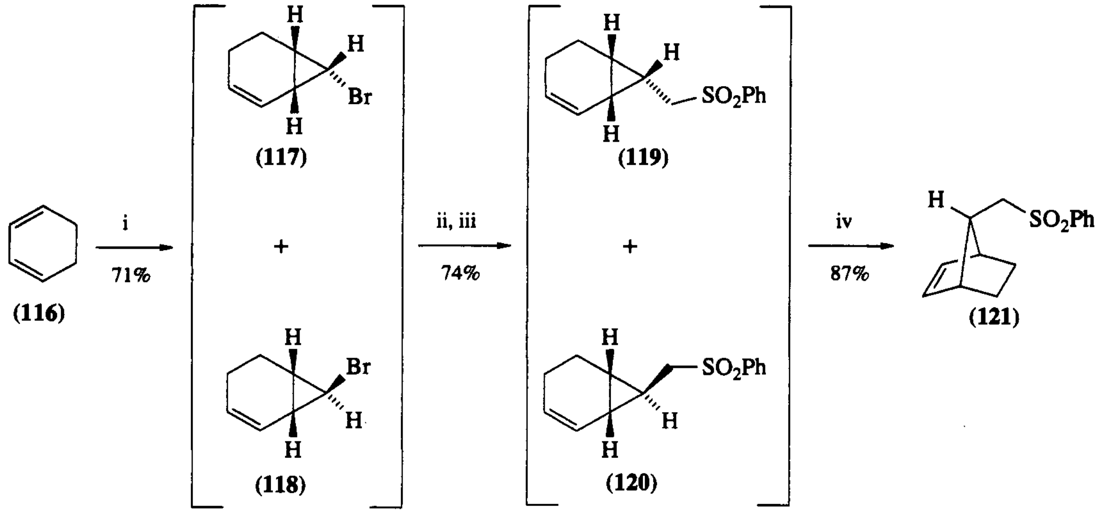

i, NaHMDS, $CH_2Br_2$, pentane; ii, $Bu^tLi$, $MgBr_2$, $PhSCH_2I$, cat. $Li_2CuCl_4$, THF–$Et_2O$;
iii, $MoO_5$–HMPA–$H_2O$, $CH_2Cl_2$; iv, $Bu^nLi$, THF–HMPA, –78 to 25 °C

Scheme 12

As illustrated with the above example, a notable feature of this annulation method is its stereoselectivity. As in the earlier version of the method, the overall annulation process can be viewed as accomplishing the effective suprafacial *exo* cycloaddition of a substituted carbene to the conjugated diene (Scheme 11). However, the generality of this stereochemical control does not appear to be as impressive as in the previous oxyanion-based strategy. Thus, whereas rearrangement of the (vinylcyclopropyl)methyl sulfones derived from (*E*)-1,3-pentadiene affords almost exclusively the predicted *trans*-substituted cyclopentene, annulation employing (*Z*)-1,3-pentadiene produces a mixture of cyclopentenes in which the expected *cis*-substituted isomer is the minor product (Scheme 13).

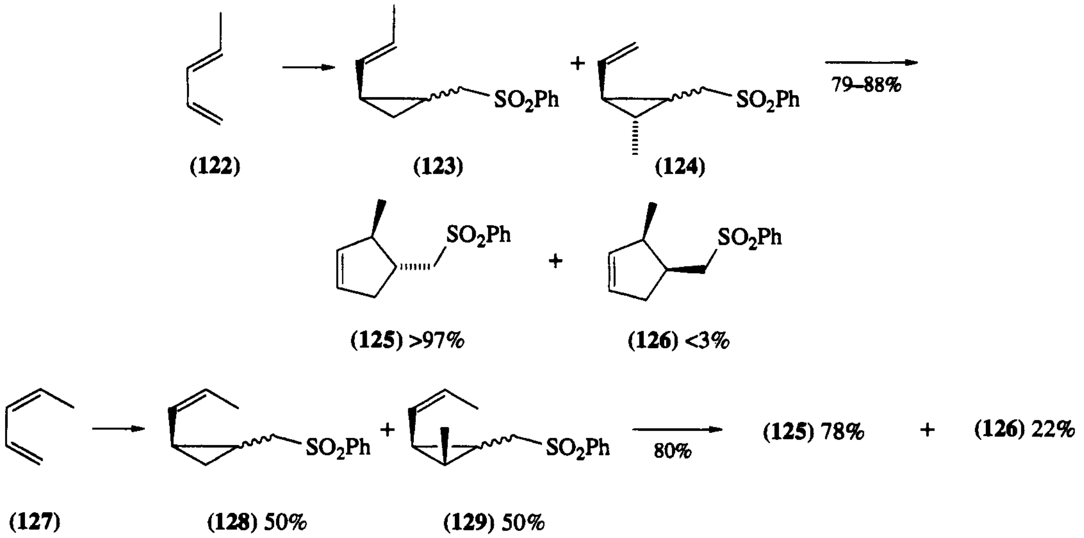

Scheme 13

The synthetic utility of this annulation methodology is significantly enhanced by the fact that the cyclopentenylmethyl sulfone anions generated in the rearrangement step can be trapped *in situ* with a variety of organic electrophiles, and that desulfonylation can then be conveniently achieved in the same flask under mild conditions. The transformations outlined in Scheme 14 illustrate this strategy. Thus, rearrangement of the lithium derivatives of (**131**) and (**132**) occurs upon warming from –78 to –20 °C; addition of excess *t*-butanol and lithium metal then effects reductive desulfonylation to afford (**133**) in good overall yield. Alternatively, the rearranged cyclopentenylmethyl sulfone anion can also be alkylated prior to reduction, as illustrated in the transformation of (**134**) to (**135**).

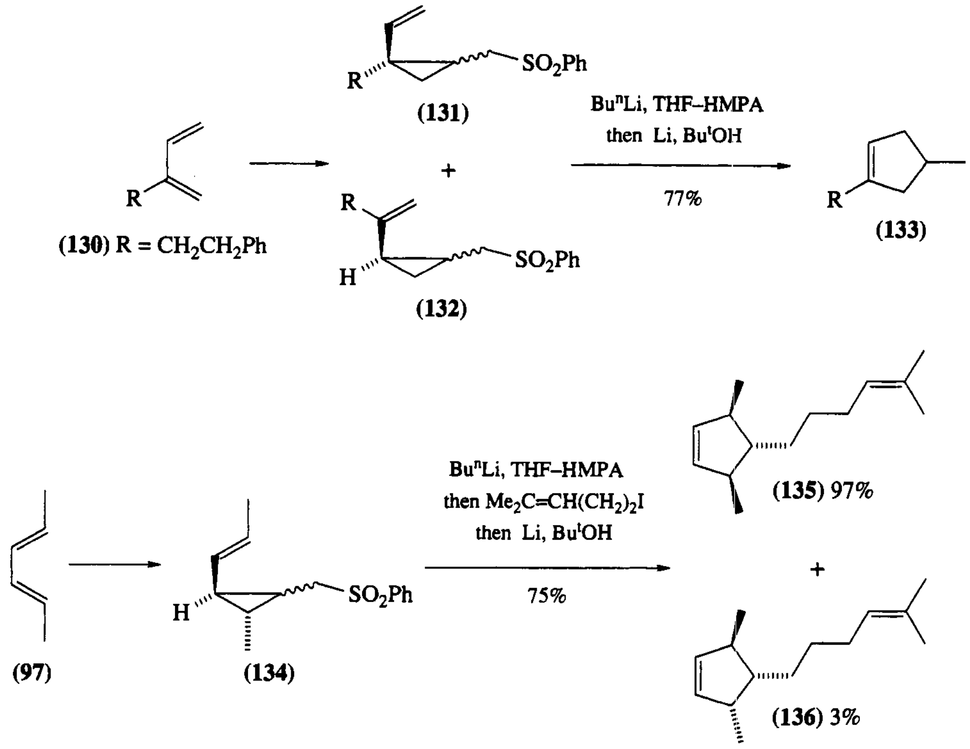

**Scheme 14**

Cyclopentene derivatives with unsaturated appendages are also available *via* this general annulation strategy; representative examples are presented in Scheme 15. In these several transformations desulfonylation is achieved using base-induced β-elimination, *via* the fluoride-promoted elimination of β-silyl sulfones,[54] and by means of Brook rearrangement chemistry according to the method of Reich.[55] In summary, a wide variety of complex functionalized cyclopentenes are available using this versatile [4 + 1] annulation method. The sulfonyl group serves a dual role in this strategy as a carbanion-stabilizing group: first to accelerate the vinylcyclopropane rearrangement, and then to facilitate the functionalization of the resulting cyclopentene derivative.

### 8.3.2.4 Carbocation-accelerated Vinylcyclopropane Rearrangements

Several vinylcyclopropane to cyclopentene rearrangements have been reported in which a cationic substituent appears to facilitate the reaction. For example, exposure of (**150**; equation 23) to excess diethylaluminum chloride at 0 °C for 12 min furnished (**151**), which served as a key intermediate in Corey and Myers' synthesis of the plant hormone antheridogen-An.[56] Attempts to effect this transformation thermally were unsuccessful. In a similar fashion, treatment of (**152**; equation 24) with boron tribromide induced VCP rearrangement of this compound at room temperature, probably *via* initial cleavage to the allylic carbocation (**153**).[57] The reaction of the analogous vinylcyclopropane lacking a phenyl group failed to go to completion under these conditions.

Dinnocenzo and Conlon have described the remarkable effect of one-electron oxidation on the rate of certain vinylcyclopropane rearrangements.[58] Exposure of several 1-*p*-anisyl-2-vinylcyclopropane derivatives to a catalytic amount of tris(4-bromophenyl)aminium hexafluoroantimonate in acetonitrile at room temperature was found to induce ring expansion to form cyclopentenes (equation 25); temperatures in excess of 200 °C are required for the conventional thermal rearrangement of these systems. At this time it is uncertain whether these reactions follow concerted mechanisms, or are stepwise processes involving trimethylene cation radical intermediates.

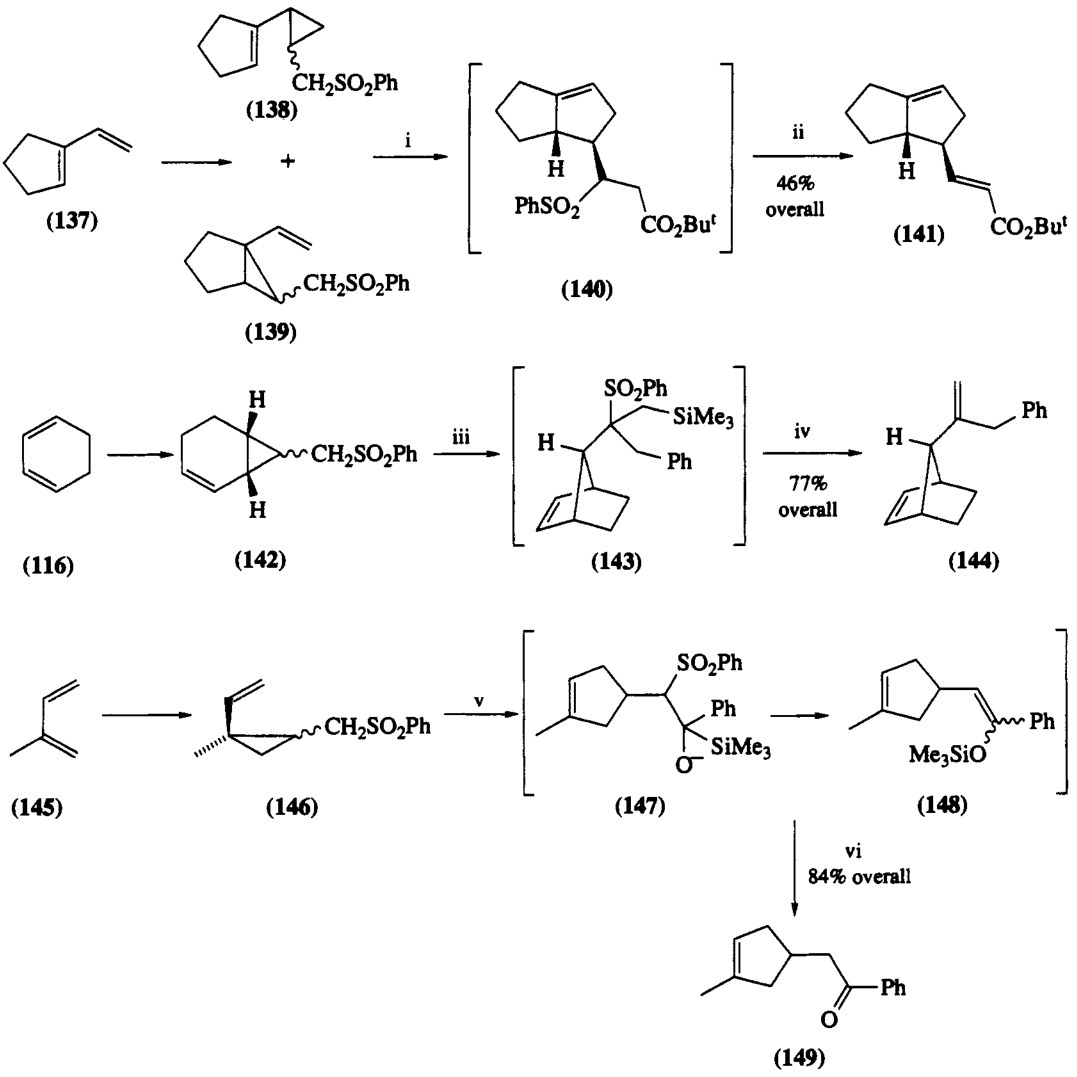
CH2SO2Ph
(138)
(137)
+
i
CH2SO2Ph
(139)
H
PhSO2
CO2Bu^t
(140)
ii
46%
overall
H
(141)
CO2Bu^t
(116)
H
CH2SO2Ph
H
(142)
iii
SO2Ph
SiMe3
H
Ph
(143)
iv
77%
overall
H
Ph
(144)
(145)
CH2SO2Ph
(146)
v
SO2Ph
Ph
O⁻
SiMe3
(147)
Me3SiO
Ph
(148)
vi
84% overall
Ph
O
(149)

i, $Bu^nLi$, THF–HMPA, –78 to 25 °C, then add $BrCH_2CO_2Bu^t$, –78 to 25 °C; ii, DBU, –78 to 25 °C; iii, $Bu^nLi$, –78 to 25 °C, then add sequentially $Me_3SiCH_2I$, $Bu^nLi$, and $PhCH_2Br$, –78 to 25 °C; iv, $Bu^n{}_4NF$; v, $Bu^nLi$, –78 to 25 °C, then add $PhCOSiMe_3$, LiBr; vi, KF, $H_2O$

**Scheme 15**

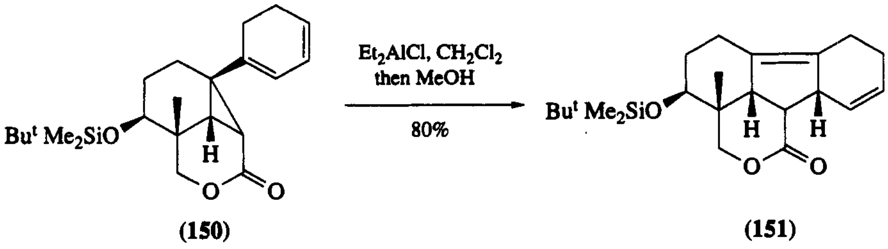
Bu^t Me2SiO
H
O
O
(150)
Et2AlCl, CH2Cl2
then MeOH
80%
Bu^t Me2SiO
H
H
O
O
(151)

(23)

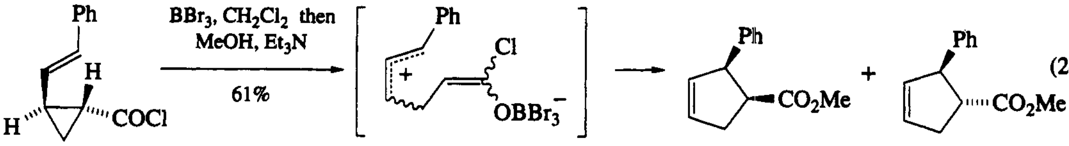

**(152)** **(153)** **(154)** 86% **(155)** 14% (24)

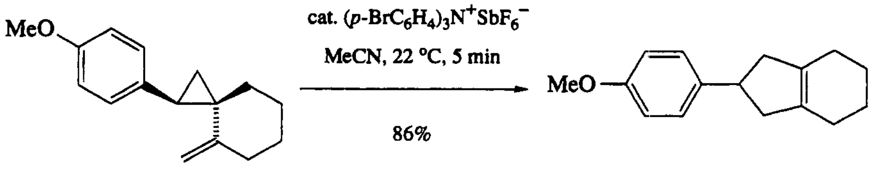

**(156)** **(157)** (25)

## 8.3.3 CHARGE-ACCELERATED REARRANGEMENTS OF CYCLOBUTANES

### 8.3.3.1 Vinylcyclobutane Rearrangements

#### *8.3.3.1.1 Introduction*

In the three decades since its discovery,[59] the vinylcyclobutane to cyclohexene rearrangement has been the subject of numerous mechanistic studies,[60] including Berson's elegant investigation of the stereochemical course of 1,3-sigmatropic rearrangements.[45c,61] In this classic study, Berson and Nelson demonstrated that the (necessarily) suprafacial rearrangement of the bicyclo[3.2.0]heptene (**158**; equation 26) occurs with inversion of configuration at the migrating carbon, in full accord with the predictions of orbital symmetry. However, in spite of this attention, to date the vinylcyclobutane (VCB) rearrangement has seen limited application as a practical method for the synthesis of cyclohexene derivatives. High temperatures are generally required to effect the rearrangement, and the scope of the reaction is further limited by the intervention of side reactions such as fragmentation, as illustrated in equation (27).[62]

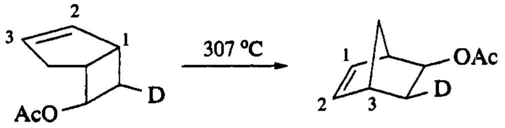

**(158)** **(159)** (26)

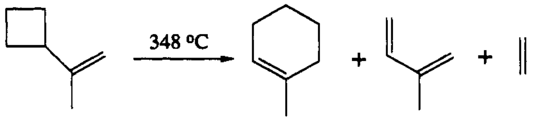

(27)

#### *8.3.3.1.2 Oxyanion-accelerated rearrangement of 2-vinylcyclobutanol derivatives*

The first example of an oxyanion-accelerated vinylcyclobutane rearrangement was reported by Wilson and Mao in 1978.[63] Exposure of *exo*-bicyclo[3.2.0]hept-2-en-7-ol (**160**) to excess potassium hydride in THF at room temperature for 3 h afforded a mixture (8:1) of *exo*- and *endo*-norbornenol in addition to unrearranged starting material (Scheme 16). Although the *endo*-bicycloheptenol (**163**) was stable under these conditions, 1,3-rearrangement did occur upon heating or in the presence of added 18-crown-6. Once again the major norbornenol produced was the *exo* isomer (**161**). These stereochemical results were interpreted as being consistent with a concerted mechanism, in which the *exo* isomer (**160**) rearranges *via* a suprafacial inversion (*si*) pathway as in the thermal 1,3-sigmatropic shifts (equation 26) studied earlier by Berson. The *endo* isomer (**163**), however, rearranges *via* the alternate *sr* pathway; in this case Wilson suggests that the transition state for orbital symmetry favored *si* migration is destabilized by steric interactions similar to those discussed earlier (Section 8.3.2.2) in the context of the oxyanion-accelerated VCP rearrangement. Wilson and Mao noted further that, since the thermodynamic ratio of (**161**) to (**162**) is approximately 6:1, it is also possible that a stepwise mechanism may be operating in these reactions.

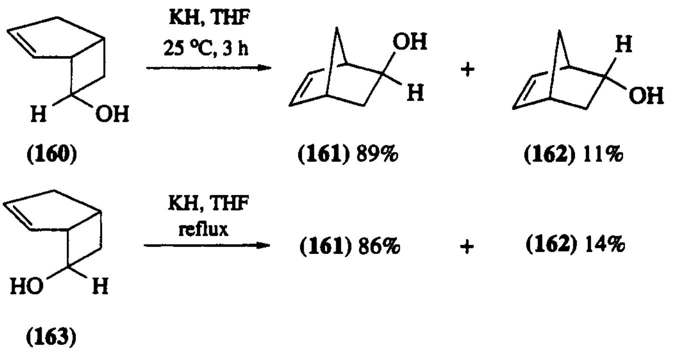
KH, THF
25 °C, 3 h
OH
H
+
H
OH
H
OH
(160)
(161) 89%
(162) 11%
KH, THF
reflux
(161) 86%
+
(162) 14%
HO
H
(163)

Scheme 16

Further studies defining the scope and stereochemical course of the oxyanion-accelerated vinylcyclobutane rearrangement were subsequently carried out in the laboratories of Danheiser[64] and Cohen.[65] Potassium, sodium[66] and even lithium alkoxides have been employed as the activating substituent in these reactions. For example, Danheiser has described a ring expansion strategy which involves the addition of lithium tri-*s*-butylborohydride or an alkyllithium reagent to a 2-vinylcyclobutanone derivative. The resultant cyclobutanol lithium salt rearranges at room temperature to afford the expected cyclohexenol, generally in good yield, as illustrated in Scheme 17. In contrast to these results, the lithium alkoxides produced by reduction of the isobutenyl derivative (**167**) resisted rearrangement even at 70 °C in the presence of HMPA. However, it was found that VCB rearrangement can be achieved in this and other difficult cases by means of the corresponding potassium salts, which are conveniently generated *in situ* from 2-vinylcyclobutanones under the conditions described in equation (28).

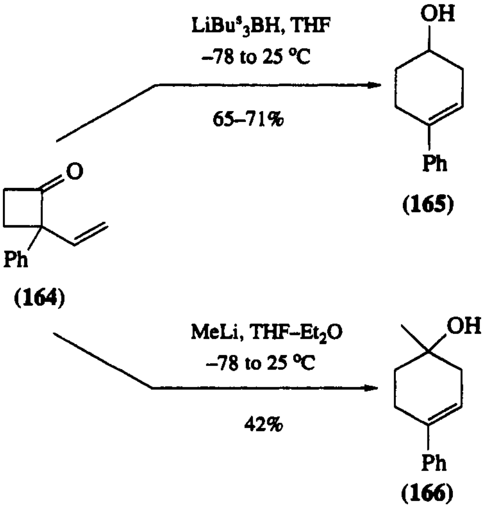
LiBu$^s_3$BH, THF
−78 to 25 °C
65–71%
OH
Ph
(165)
O
Ph
(164)
MeLi, THF–Et$_2$O
−78 to 25 °C
42%
OH
Ph
(166)

Scheme 17

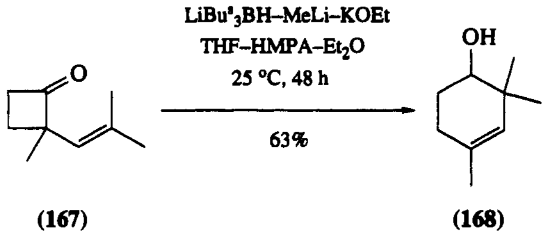
LiBu$^s_3$BH–MeLi–KOEt
THF–HMPA–Et$_2$O
25 °C, 48 h
63%
O
OH
(167)
(168)

(28)

Certain arylcyclobutane derivatives also appear to be subject to oxyanion-accelerated 1,3-sigmatropic rearrangement. Cohen and coworkers found that exposure of the diastereomeric 2-(2-furyl)cyclobutanols (**169**; Scheme 18) to potassium hydride in THF at room temperature results in rearrangement to the tetrahydrobenzofuran (**171**), albeit in modest yield.[65a] However, under the same conditions the tertiary alcohol (**170**) suffers fragmentation to ketone (**172**), presumably *via* heterolytic cleavage of the alkoxide followed by proton transfer. Similar findings have been reported by Snider and Niwa; these workers also examined the chemistry of the phenylcyclobutanol derivative (**173**).[67] Treatment of this secondary alcohol with potassium hydride in THF led to fragmentation, with no evidence for 1,3-sigmatropic rearrangement being obtained (equation 29).

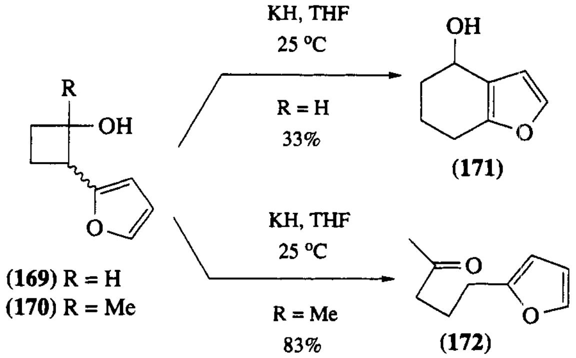

**Scheme 18**

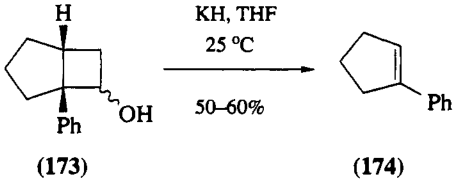

(29)

The oxyanion-accelerated vinylcyclobutane rearrangement is in many cases a highly stereoselective process, although the mechanistic basis of this stereoselectivity is not completely understood. Complicating the problem is the fact that epimerization of the intermediate vinylcyclobutanol salt takes place, at least in some cases, faster than 1,3-rearrangement.[65] Some generalizations with predictive value can be made, however. As in the case of the vinylcyclopropanes discussed in Section 8.3.2.2, systems in which the hydroxy group is *anti* to the vinyl substituent appear to rearrange preferentially by suprafacial inversion pathways. On the other hand, the overall stereochemical course of the reactions of the corresponding cyclobutanes with *syn* hydroxy and vinyl groups appears to be suprafacial retention. It should be noted, however, that these generalizations only appear to be applicable to reactions carried out in highly dissociating media.

The transformations of the epimeric vinylcyclobutanols (**175**) and (**178**), studied by both Danheiser[64] and Cohen,[65] are representative (Scheme 19). In this case, both the *syn*- and *anti*-vinylcyclobutanol potassium salts rearrange to form mainly the *exo*-alcohol (**177**), provided that the reaction is carried out in the presence of HMPA[64] or 18-crown-6.[65] However, note that exposure of the *syn*-2-vinylcyclobutanol (**178**) to potassium hydride in THF at room temperature for 4 d led to its epimerization to the more stable *anti* isomer (**175**); very little rearrangement took place under these conditions. Interestingly, in the absence of complexing agents the rearrangement of (**175**) (which proceeds only upon heating) affords a mixture of products in which the *endo* isomer (**176**) predominates. Cohen has suggested that the chelated species (**179**) may be involved as an intermediate leading to the *endo*-alcohol in the case of the reaction carried out in THF alone.

The transformations summarized in Scheme 20 provide further insight into the stereochemical course of the oxyanion-accelerated VCB rearrangement. 1,3-Migration of the '*anti*-type' vinylcyclobutanol salt (**181**) leads to the *exo*-alcohol (**182**) *via* rearrangement with inversion at the migrating carbon, while rearrangement of the *syn* isomer (**185**) takes place predominantly with retention of configuration to afford (**183**). Although these results are in accord with the stereochemical predictions for concerted 1,3-sigma-

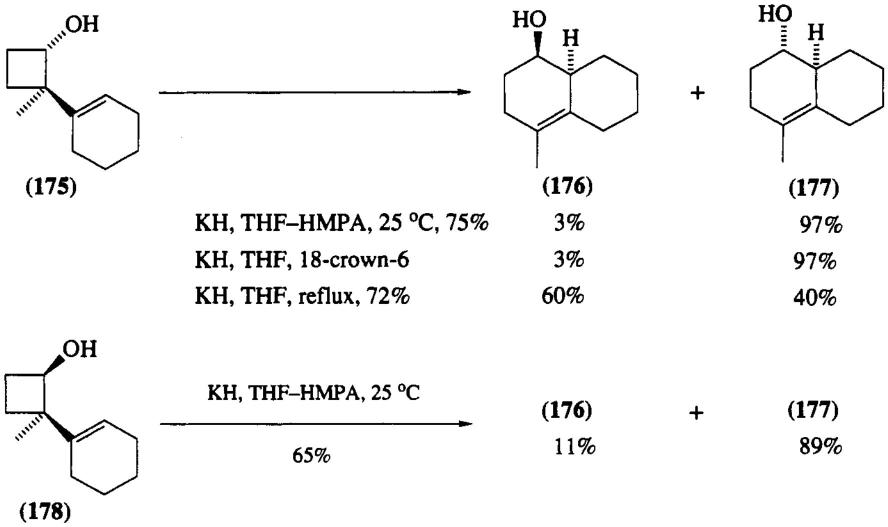
OH
(175)
HO
H
(176)
+
HO
H
(177)
KH, THF–HMPA, 25 °C, 75% 3% 97%
KH, THF, 18-crown-6 3% 97%
KH, THF, reflux, 72% 60% 40%
OH
(178)
KH, THF–HMPA, 25 °C
65%
(176) 11%
+
(177) 89%

Scheme 19

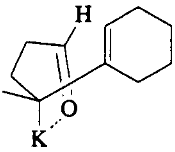

**(179)**

tropic rearrangements, it is likely that in most if not all cases the accelerated VCB rearrangement follows a stepwise pathway involving allylmetal aldehyde intermediates.

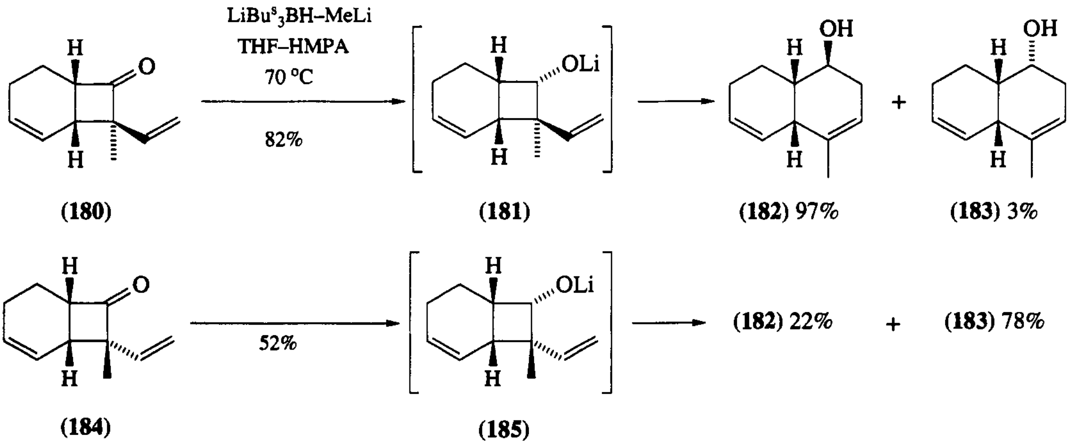
H
O
H
(180)
LiBu$^s{}_3$BH–MeLi
THF–HMPA
70 °C
82%
H
OLi
H
(181)
H
OH
H
(182) 97%
+
H
OH
H
(183) 3%
H
O
H
(184)
52%
H
OLi
H
(185)
(182) 22%
+
(183) 78%

Scheme 20

The accelerated vinylcyclobutane rearrangement functions as the key step in several useful strategies for the assembly of functionalized six-membered carbocycles. As outlined in Scheme 21, these strategies are conveniently classified according to the approach used to synthesize the pivotal vinylcyclobutanol intermediate.

Bauld and coworkers have examined the cation radical cycloadditions of 1,3-dienes with electron-rich alkenes and found that, under photosensitized electron-transfer conditions, [2 + 2] cycloaddition is in many cases favored over Diels–Alder addition. Thus, as illustrated in equation (30), 1,1′-dicyclopentenyl (**186**) reacts with β-chloroethyl vinyl ether under electron transfer conditions to afford the cyclobutane adduct (**187**), which was cleaved to the cyclobutanol (**188**) in 70% yield upon treatment with *n*-butyllithium. Oxyanion-accelerated VCB rearrangement then provided (**189**) as a mixture of diastereomers in

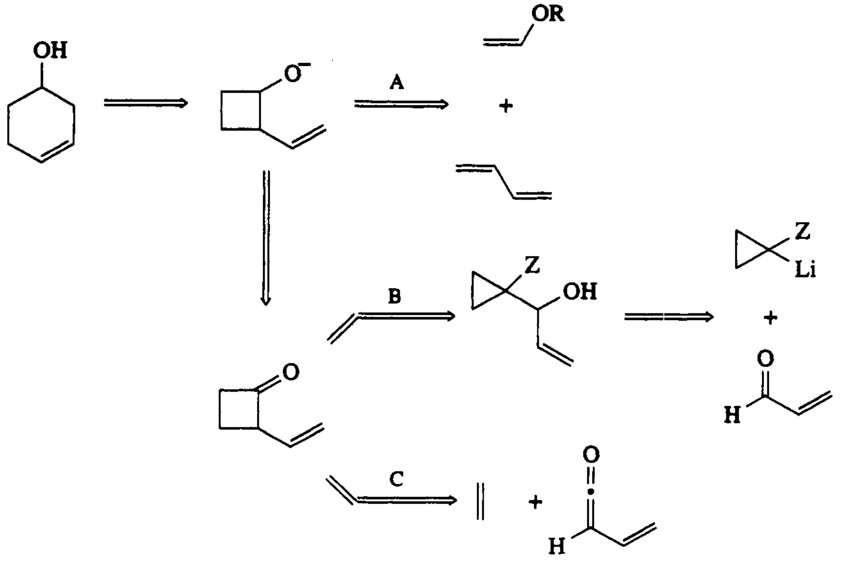

Scheme 21

60% yield.[68,69] This transformation represents the only example of the implementation of strategy A (Scheme 21) which has been reported to date.

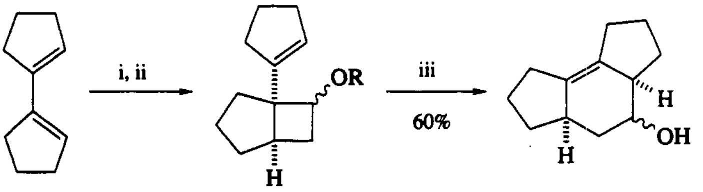

(30)

**(186)** **(187)** R = $CH_2CH_2Cl$ **(188)** R = H **(189)**

i, $H_2C{=}CHOCH_2CH_2Cl$, *hv*, 1,4-dicyanobenzene, $CH_2Cl_2$; ii, $Bu^nLi$, $Et_2O$–HMPA; iii, KH, THF, reflux

Thus far, the most widely employed route to 2-vinylcyclobutanones has involved the addition of the 1-lithio derivative of thiophenyl- or methoxy-cyclopropane to an α,β-unsaturated carbonyl compound, followed by acid-promoted ring expansion of the resulting cyclopropylcarbinol (strategy B in Scheme 21).[70] In conjunction with the oxyanion-accelerated VCB rearrangement, this approach provides a useful three-step [3 + 3] annulation route to 3-cyclohexenol derivatives (equation 31).[64,65] Scheme 22 outlines the application of this strategy to the synthesis of the eudesmane sesquiterpene (–)-β-selinene.[65a] Addition of 1-lithio-1-methoxycyclopropane to (–)-perillaldehyde and subsequent acid-catalyzed rearrangement[70c] furnished the cyclobutanone (**191**) in 67% overall yield. Reduction with lithium aluminum hydride then produced (**192**) as an 82:18 mixture of *cis* and *trans* isomers. Exposure of this mixture of vinylcyclobutanols to excess potassium hydride in THF at reflux next induced 1,3-rearrangement to afford (**193**), which without purification was oxidized and isomerized to the conjugated enone (**194**) in 65% overall yield. Conjugate addition of $MeCuBF_3$ and Wittig methylenation completed the synthesis of (–)-β-selinene.

Strategy C in Scheme 21 employs the [2 + 2] cycloaddition of vinylketenes and 1,3-dienes to generate the requisite 2-vinylcyclobutanone intermediates for oxyanion-accelerated VCB rearrangement. The sequence presented in Scheme 23 illustrates this two-step [4 + 2] annulation strategy, the overall result of

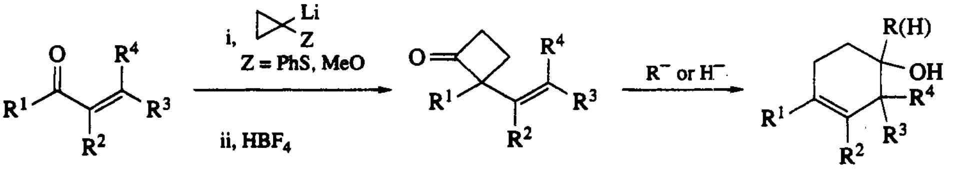

(31)

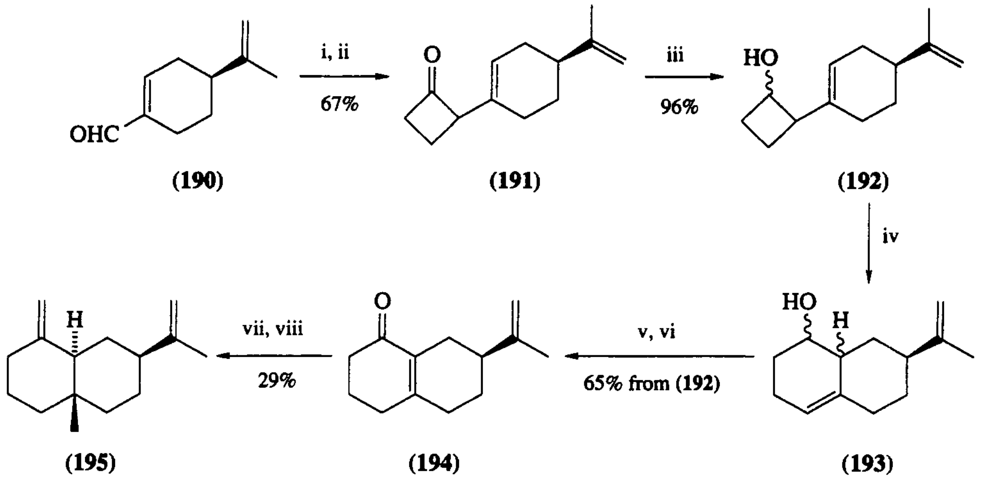

i, 1-lithio-1-methoxycyclopropane, THF; ii, 48% $HBF_4$, THF; iii, $LiAlH_4$, $Et_2O$; iv, KH, THF, reflux, 1 h; v, Jones oxidation; vi, $Al_2O_3$ chromatography; vii, $MeCuBF_3$, $Et_2O$; viii, $Ph_3P{=}CH_2$, DMSO

**Scheme 22**

which is a suprafacial addition with respect to the two-carbon (alkene) component.[64] The vinylketenes required for the [2 + 2] cycloaddition step are conveniently generated *via* the 1,4-dehydrohalogenation of α,β-unsaturated acid chlorides. It should be noted, however, that the scope of this reaction is limited to the more ketenophilic alkenes; simple alkenes such as 1-hexene react slowly with vinylketenes at 90 °C to produce the desired 2-vinylcyclobutanones in relatively low yield. On the other hand, the intramolecular addition of unactivated alkenes to ketenes is a more efficient process, and Snider and coworkers have recently employed this strategy to prepare the tetracyclic vinylcyclobutanone derivative (**202**; Scheme 24).[71] Reduction of this ketone with sodium borohydride furnished the cyclobutanols (**203**) as a 19:1 mixture of diastereomers, which were then converted to the corresponding potassium salts in the usual fashion by treatment with excess potassium hydride. The oxyanion-accelerated VCB rearrangement proceeded smoothly in this case at only 0 °C, and produced the tetracyclic steroid model compound (**204**) in 90% yield. The stereochemistry of the two isomers (78:22) which were obtained could not be determined from the data available.

In summary then, the oxyanion-accelerated rearrangement of 2-vinylcyclobutanol derivatives is now established as an attractive method for achieving two-carbon ring expansion under relatively mild conditions. In conjunction with the efficient synthetic routes to vinylcyclobutanones outlined in Scheme 21, this version of the VCB rearrangement provides several strategically novel annulation methods for the construction of six-membered carbocycles.[72]

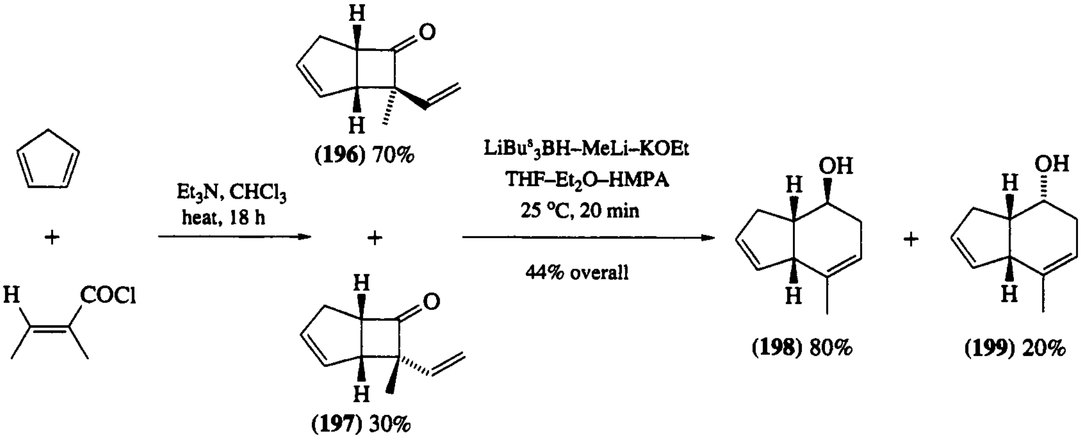

**Scheme 23**

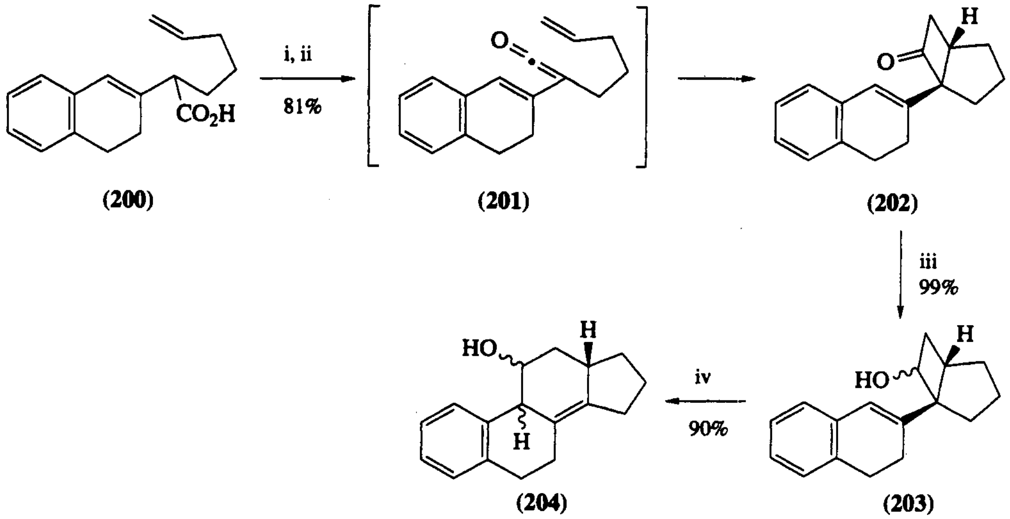

i, $(COCl)_2$, benzene, 55 °C; ii, $Et_3N$, toluene, reflux; iii, $NaBH_4$, MeOH, 25 °C; iv, KH, THF, 0 °C, 2 h

**Scheme 24**

### *8.3.3.1.3 Oxyanion-accelerated rearrangement of 1-vinylcyclobutanol derivatives*

The substitution of an oxyanion substituent at carbon-1 of a vinylcyclobutane ring has been shown to facilitate the 1,3-rearrangement of this system, leading to a cyclohexanone enolate. These ring expansions appear to follow stepwise reaction pathways involving initial heterolytic cleavage to form an anionic α,β-unsaturated ketone intermediate, which then cyclizes *via* internal Michael addition to generate the six-membered ring. Only 1-vinylcyclobutanol derivatives that bear an anion-stabilizing group at carbon-2 are subject to the reaction. The transformation outlined in equation (32) is representative.[67] Addition of vinyllithium to 1-phenylbicyclo[3.2.0]hept-7-one produced the requisite vinylcyclobutanol (**205**) as a single diastereomer (stereochemistry not assigned) in 51% yield. At –40 °C the potassium salt of this cyclobutanol rearranged to the enolate derivative of (**207**), presumably *via* initial heterolytic cleavage to the benzylic carbanion (**206**). This intermediate was also observed to undergo further fragmentation (eliminating the enolate derivative of methyl vinyl ketone), and 1-phenylcyclopentene was isolated as a by-product of the ring expansion in 15% yield.

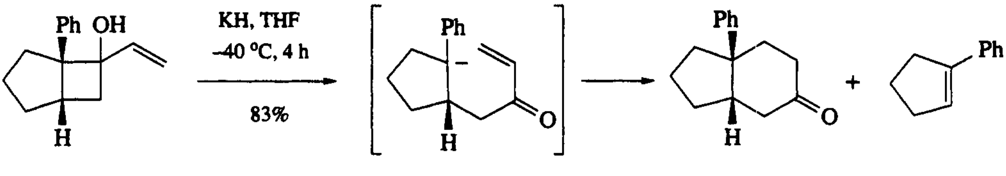

(32)

Similar 1,3-rearrangements involving more highly functionalized 2-aryl-1-vinylcyclobutanol derivatives have been studied by Sano and coworkers;[73] Scheme 25 outlines the application of this process in an interesting synthetic approach to the erythrina alkaloids.[73c] [2 + 2] Photocycloaddition of 1-methoxy-3-trimethylsiloxybutadiene to (**208**) provided the requisite vinylcyclobutanol silyl ether (**209**) in 72% yield. Exposure of (**209**) to TBAF at –30 °C for several minutes then induced ether cleavage and 1,3-rearrangement of the resulting salt to afford the enolate (**210**), which upon elimination of methoxide provided the desired enone (**211**) in 82% overall yield. By contrast, the thermal VCB rearrangement of (**209**) required heating above 110 °C, and produced (**211**) (after enol ether hydrolysis) in only 38% yield.[74]

1-Vinylbenzocyclobutanol salts also undergo stepwise anion-accelerated 1,3-rearrangements to form six-membered rings. For example, Caubere has used the 'arynic condensation' of ketone enolates with benzyne to generate benzocyclobutanol salts such as (**212**; equation 33) which rearrange at 45 °C to form α-tetralones.[75] Swenton has employed related rearrangements in his elegant annulation approaches to the anthracyclinone and tetracycline antibiotics.[76] For example, addition of (**215**; from the corresponding

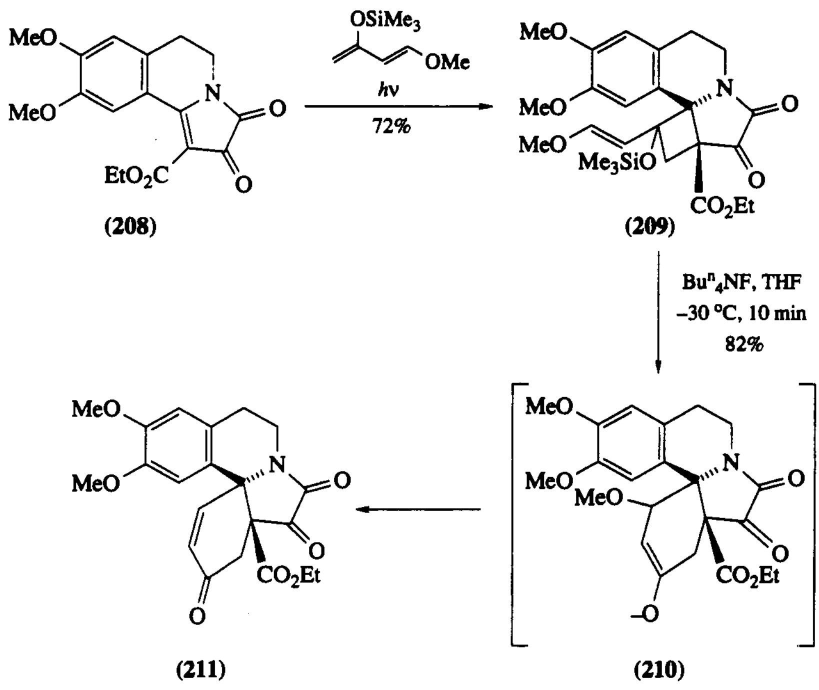

(208) (209) (210) (211)

Scheme 25

bromide using 2 equiv. of *n*-butyllithium) to benzocyclobutenedione monoketal (**214**) furnished the vinylcyclobutane (**216**), which rearranged at 50 °C to produce the tetracyclic quinone (**218**) in 55–65% overall yield after ketal hydrolysis (Scheme 26). This annulation product served as an intermediate for the synthesis of the antitumor antibiotic 4-demethoxydaunomycinone.

In the reactions discussed above an aromatic ring stabilizes the negative charge which develops at the C-2 position of the original cyclobutane ring. Cohen has demonstrated the ability of certain sulfur substituents to function in a similar capacity.[77] For example, ring expansion of the potassium salt derived from (**220**) proceeded smoothly in THF–HMPA upon warming from –11 °C to room temperature to afford 4-thiophenylcyclohexanone in 60% yield (equation 34).

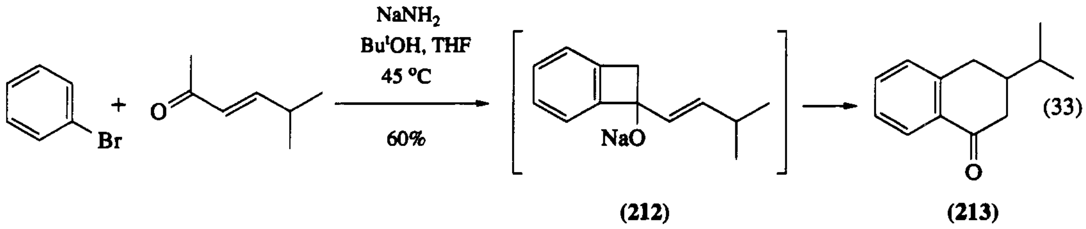

(212) (213) (33)

### 8.3.3.1.4 Azaanion-accelerated vinylcyclobutane rearrangements

Bauld and coworkers have developed a strategy for the effective [4 + 2] cycloaddition of a vinylamine to a conjugated diene which features an azaanion-accelerated vinylcyclobutane rearrangement as a key step.[69,78] Equation (35) illustrates this interesting approach to 3-cyclohexenylamine derivatives. Under photosensitized electron transfer conditions, the cation radical [2 + 2] cycloaddition of *N*-methyl-*N*-vinylacetamide takes place smoothly with a wide range of conjugated dienes. No [4 + 2] adducts are detected in these reactions, even with *s-cis*-dienes such as 1,3-cyclohexadiene. Base-promoted hydrolysis then furnishes cyclobutylamines such as (**222**; 3.2:1 mixture of *anti* and *syn* isomers), which rearrange to the desired cyclohexenes upon heating in THF in the presence of excess potassium hydride.

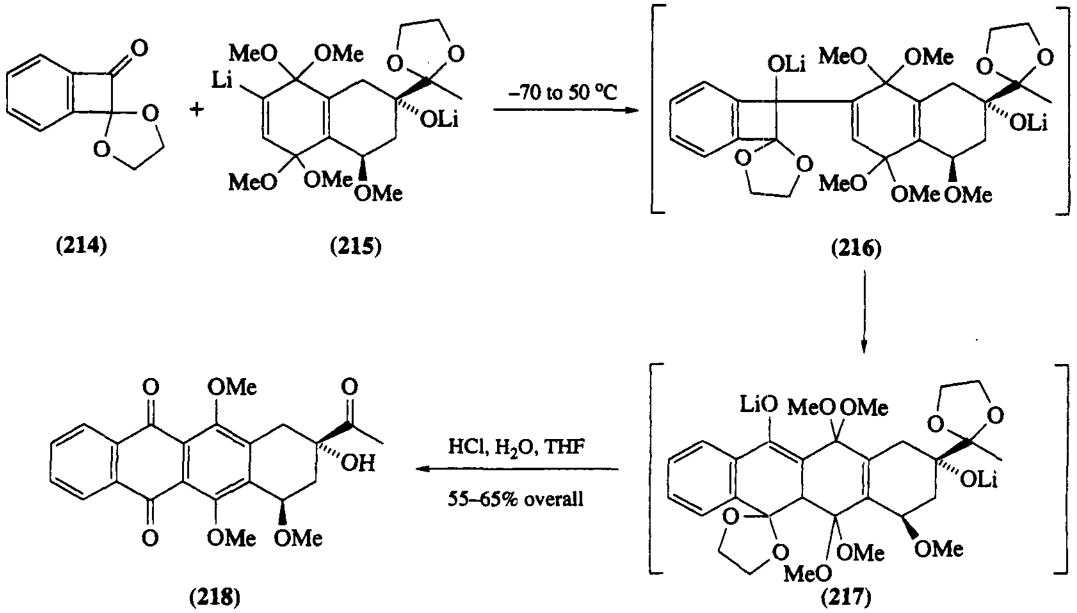

**Scheme 26**

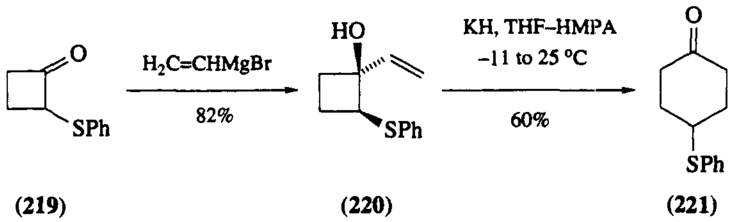

(34)

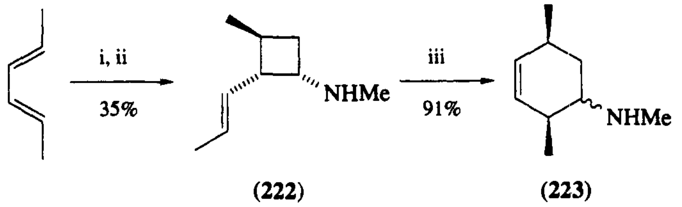

(35)

i, *N*-methyl-*N*-vinylacetamide, 1,4-dicyanobenzene, *h*v, MeCN, 72 h;
ii, KOH, NH$_2$NH$_2$, HOCH$_2$CH$_2$OH, 110 °C; iii, KH, THF, reflux, 1 h

## 8.3.3.2 Divinylcyclobutane Rearrangements

### *8.3.3.2.1 Introduction*

The isolation of a variety of biologically important natural products with structures incorporating eight-membered rings has led to increased interest in the search for new methodology for the synthesis of cyclooctane derivatives. Traditionally, the most popular synthetic routes to cyclooctanes have involved one- and two-carbon ring expansions and the cleavage (or fragmentation) of bi- and poly-cyclic systems already incorporating eight-membered rings.[79] Methods based on the cyclization of acyclic precursors have also been explored, but usually are only marginally successful due to unfavorable enthalpic and entropic factors. Recently, the 3,3-sigmatropic rearrangement of 1,2-divinylcyclobutane derivatives has emerged as an attractive and generally successful strategy for the preparation of cyclooctane derivatives. Charge-accelerated versions of the reaction proceed under unusually mild conditions and have further expanded the scope and synthetic utility of this strategy. This section reviews the general features of the divinylcyclobutane (DVCB) rearrangement, which is also discussed in detail in Chapter 7.1, this volume.

The thermal DVCB rearrangement was first reported by Vogel in 1958.[80] Subsequent extensive physical organic studies by Berson and other workers elucidated the important mechanistic features of the reaction.[81] Driven by the release of cyclobutane ring strain, this Cope rearrangement often proceeds at significantly lower temperatures (generally in the range 60–140 °C) than analogous reactions involving acyclic 1,5-dienes. As illustrated in equation (36), *cis*-divinylcyclobutanes rearrange *via* boat-like transition states to afford *cis,cis*-1,5-cyclooctadienes.[81e] In these systems the chair-like geometry normally favored for the acyclic Cope rearrangement is difficult to achieve, and in any event would lead to the formation of severely strained *cis,trans*-cyclooctadienes. The analogous rearrangements of *trans*-divinylcyclobutane derivatives are generally carried out at somewhat higher temperatures (140–210 °C), and often produce complex mixtures of several products (*e.g.* Scheme 27).[81e] In this example the major reaction pathway followed is 1,3-sigmatropic rearrangement leading to the cyclohexenes (**229**) and (**230**); [2 + 2] cycloreversion (producing *trans*-piperylene) is also observed as a side reaction. Interestingly, the Cope rearrangement of the *trans*-divinylcyclobutane produces the same cyclooctadiene (**226**) formed in the reaction of the *cis*-divinylcyclobutane (**224**). The rearrangement of the *trans* compound is believed to take place by an indirect mechanism involving initial epimerization to (**224**), followed by sigmatropic rearrangement.

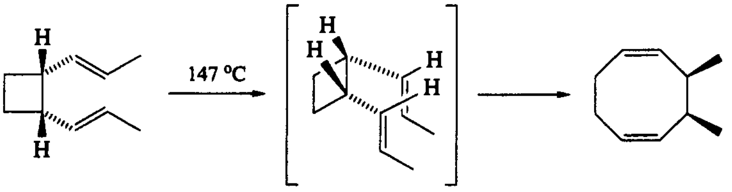

(36)

(**224**) (**225**) (**226**)

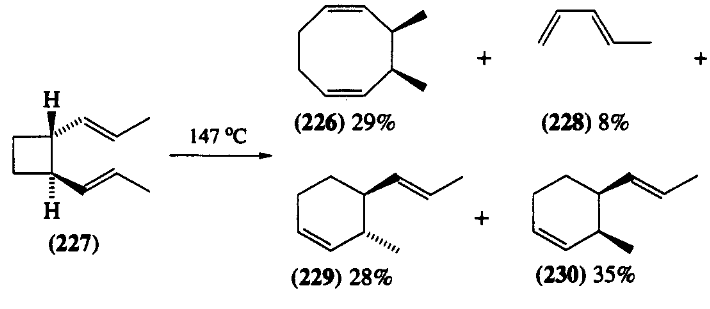

**Scheme 27**

The application of the divinylcyclobutane rearrangement to the synthesis of functionalized cyclooctane derivatives began to receive serious attention in the early 1980s. The general synthetic strategies which have emerged from these studies are conveniently classified according to the method used to prepare the key 1,2-divinylcyclobutane intermediates. The most important strategies devised to date are based on: (i) the thermal [2 + 2] cycloaddition of vinylketenes with 1,3-dienes; (ii) photochemical [2 + 2] diene–diene cycloadditions; and (iii) the addition of vinyl organometallic compounds to 2-vinylcyclobutanones, which are themselves generally prepared *via* the acid-promoted rearrangement of cyclopropylcarbinols as discussed in Section 8.3.3.1.2.

The first approach, based on thermal vinylketene–diene cycloadditions, was independently developed in three laboratories and first reported in 1982.[82–84] The overall transformation constitutes a powerful [4 + 4] annulation strategy for the synthesis of eight-membered carbocycles (Scheme 28). Several options are available for the generation of the requisite vinylketene intermediates. One approach, employed by Danheiser and coworkers,[82] involves the 4π-electrocyclic ring opening of cyclobutenones and is illustrated in equation (37). Thermolysis of the cyclobutenone (**231**) in benzene at 120 °C produces isopropenylmethylketene, which combines with 1,3-cyclohexadiene in a regiospecific [2 + 2] cycloaddition. At the elevated reaction temperature the resulting 2,3-divinylcyclobutanone then undergoes 3,3-sigmatropic rearrangement to afford the eight-membered ring annulation product. The overall transformation thus involves a cascade of three pericyclic reactions, each step representing a different major class of pericyclic process.

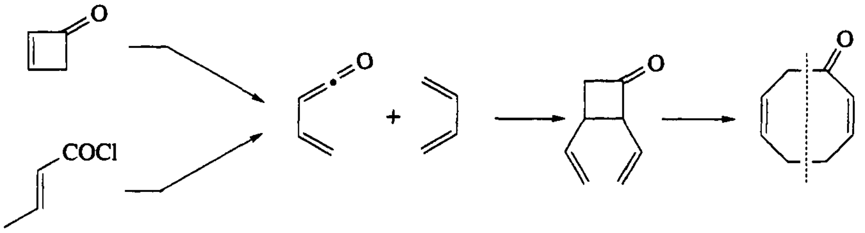

Scheme 28

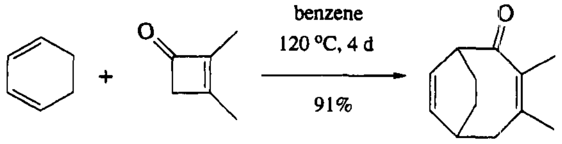

**(116)** **(231)** **(232)** (37)

A related [4 + 4] annulation strategy relies on the base-promoted 1,4-dehydrochlorination of α,β-unsaturated acid chlorides;[82,83] the transformation outlined in Scheme 29 (reported by Dreiding and coworkers)[83] illustrates this approach. In some cases it is possible to effect all three steps — ketene generation, [2 + 2] cycloaddition, and Cope rearrangement — in a single synthetic operation.[82]

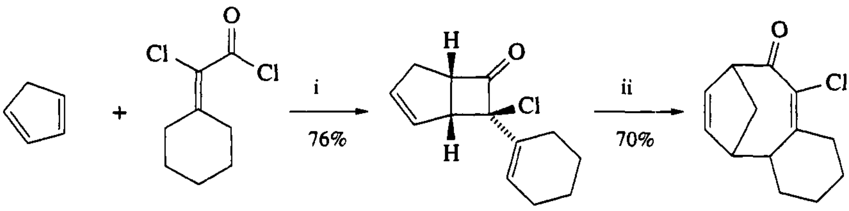

**(233)** **(234)** **(235)** **(236)**

i, $Et_3N$, $CHCl_3$, 25 °C, 15 h; ii, xylene, 145 °C, 4 h

Scheme 29

In principle, the photoinduced diene–diene [2 + 2] cycloaddition reaction should provide a particularly expeditious route to 1,2-divinylcyclobutanes. Unfortunately, these diene–diene cycloadditions generally produce complex mixtures of regio- and stereo-isomeric dimers and have little practical value in synthesis. Recently, Wender and Correia demonstrated that the intramolecular variant of the reaction circumvents these selectivity problems and provides an efficient route to substrates for DVCB rearrangements.[85] The transformations outlined in Scheme 30 illustrate this approach. Irradiation of tetraene (**237**) furnished the *cis*- and *trans*-divinylcyclobutanes (**238**) and (**239**) as a 1:1 mixture in 80% yield. Thermolysis of *cis* isomer (**238**) in benzene at 130 °C then afforded the desired cyclooctadiene in nearly quantitative yield. More vigorous conditions (200 °C) were required for rearrangement of the *trans*-divinylcyclobutane, and in this case the product of 1,3-rearrangement (**241**; mixture of 4 isomers) was formed along with the desired Cope rearrangement product.

Finally, a third synthetic approach to 1,2-divinylcyclobutanes employs the addition of vinylmetal reagents to 2-vinylcyclobutanones which are available using the methods discussed earlier in Section 8.3.1.2. A novel variant of this strategy was exploited by Gadwood and his coworkers in their total synthesis of the cyclooctanoid sesquiterpene poitediol (**247**).[86] As outlined in Scheme 31, the key step in this synthesis involved the addition of lithium acetylide to (**244**) and oxy-Cope rearrangement of the resulting alkynylvinylcyclobutanol at 50 °C to afford the bicyclo[6.3.0]undecadienone (**246**) in 50% overall yield. The initial product of this remarkably facile 3,3-sigmatropic rearrangement is a high-energy 1,2,5-cyclooctatrienol derivative; rapid enol–ketone tautomerization produces the final cyclooctadienone product.

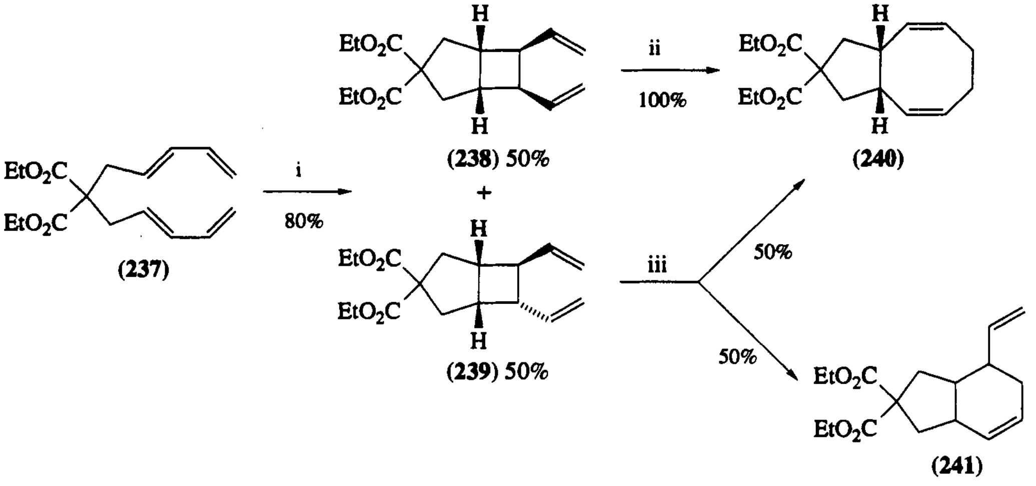

i, $h\nu$, hexane, $Ph_2CO$ (sensitizer); ii, benzene, 130 °C, 4 h; iii, benzene, 200 °C, 24 h

**Scheme 30**

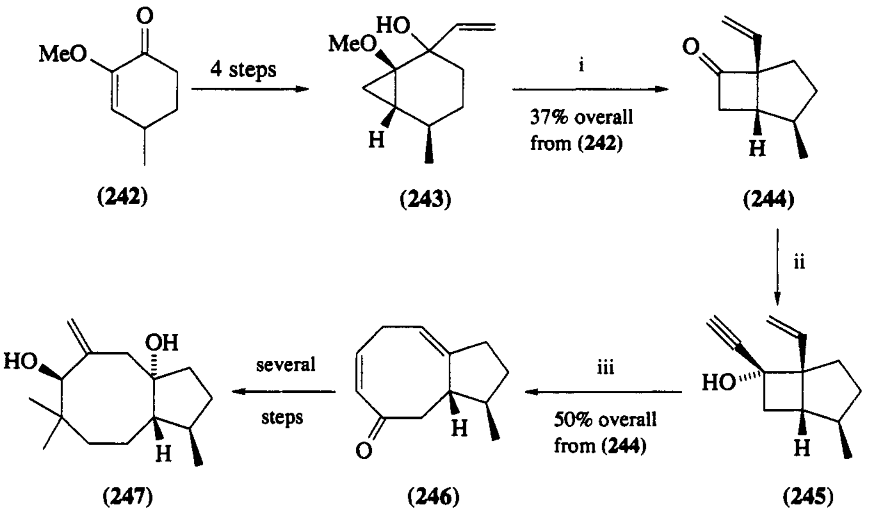

i, $BF_3$–$Et_2O$, $Et_2O$, 0 °C, 10 min; ii, LiC≡CH, THF, –30 °C; iii, THF, 50 °C, 3 h

**Scheme 31**

### *8.3.3.2.2 Anion-accelerated divinylcyclobutane rearrangements*

In principle, the oxyanion-accelerated version of the divinylcyclobutane rearrangement might offer several advantages over the thermal reaction discussed in the preceding section. Particularly attractive is the prospect of achieving the ring expansion of both *cis*- and *trans*-divinylcyclobutane derivatives under relatively mild conditions without the intervention of troublesome side reactions. In fact, these hopes have to a large extent been realized, and the anion-accelerated DVCB rearrangement constitutes a key step in several useful strategies for the synthesis of substituted cyclooctanes.

The first examples of the oxyanion-accelerated DVCB rearrangement were observed in the laboratories of Kahn,[87] Levine[88] and Gadwood.[89] Particularly noteworthy are the studies of Gadwood and Lett, who reported their systematic investigation of the scope and stereochemical course of the reaction in 1982.[89] As illustrated with the example in Scheme 32, Gadwood and Lett elected to assemble all of their rearrangement substrates *via* the addition of alkenylmetal compounds to 2-vinylcyclobutanones; the latter were conveniently prepared from α,β-enones according to the method of Trost.[70] Exposure of the *trans*-divinylcyclobutanol (**249**) to potassium hydride in THF at room temperature led to its rapid rearrangement to a mixture of *cis*- and *trans*-cyclooctenones. Presumably this Cope rearrangement proceeds *via* the initial isomerization of (**249**) to the corresponding *cis*-divinylcyclobutanol salt. The success of this reaction stands in contrast to the results of the thermal rearrangement of related *trans*-divinylcyclobutanes, which as discussed in the preceding section, generally afford significant quantities of 1,3-sigmatropic rearrangement products in addition to the desired cyclooctadienes. Another interesting feature of the oxyanion-accelerated rearrangement of (**249**) is the appearance of the *trans*-cyclooctenone (**251**) as a minor product of the reaction. This isomer is presumably formed *via* the chair-like conformation (**254**); steric interactions between the *endo* terminal methyl groups and the cyclobutane ring protons appear to destabilize the normally favored boat-like transition state conformation (**252**). Related oxyanion-accelerated DVCB rearrangements favoring the formation of (*E*)-cyclooctenones have been reported by Frei and coworkers.[90]

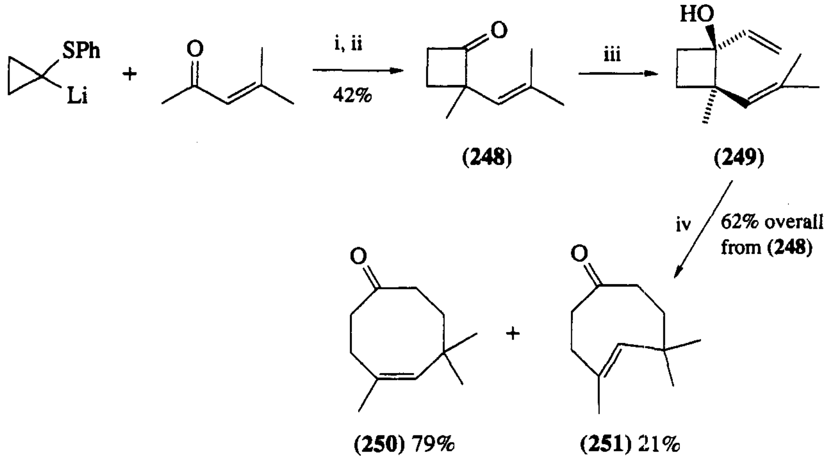

i, THF, 0 °C; ii, *p*-TsOH, benzene, reflux, 1.5 h; iii, $H_2C{=}CHLi$, $Et_2O$, −78 °C; iv, KH, THF, 25 °C, 45 min

**Scheme 32**

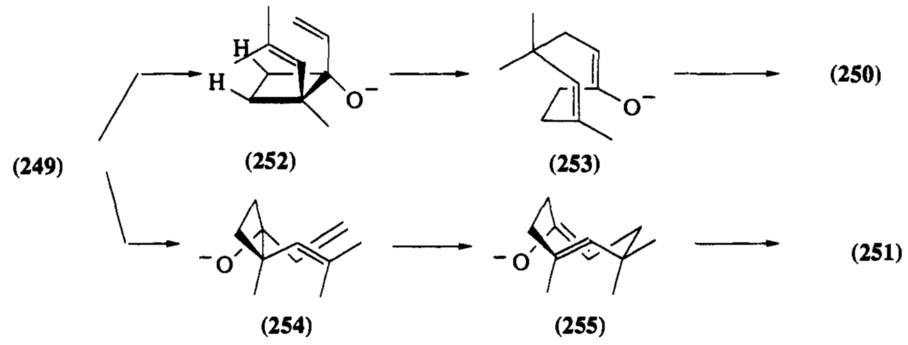

**Scheme 33**

Gadwood and Lett also described the rearrangement of several divinylcyclobutanols derived from the spirononenone (**256**); similar reactions had been studied earlier by Kahn[87] and by Levine.[88] The potassium salts obtained from both the *cis*- and *trans*-divinylcyclobutanols (**257**) and (**258**) rearranged smoothly at room temperature to produce the interesting bridgehead alkene containing bicyclo[5.3.1]undecenone (**259**) in excellent yield (Scheme 34). Once again, cyclohexene by-products resulting from alternative 1,3-sigmatropic rearrangement pathways were not detected in this reaction.

The chemistry of the divinylcyclobutanols derived from 5-methylenespiro[3.5]nonanone (**260**) proved to be more complicated than the reactions described above. As expected, the oxyanion-accelerated 3,3-sigmatropic rearrangement of the *cis* isomer (**261**) was extremely facile as a consequence of the rigid *s-cis* orientation of the exocyclic methylene group (Scheme 35). The rearrangement of the *trans* isomer, however, produced none of the desired Cope product; instead this cyclobutanol salt underwent exclusive 1,3-rearrangement to afford the cyclohexenol derivative (**264**). It is uncertain whether this transformation

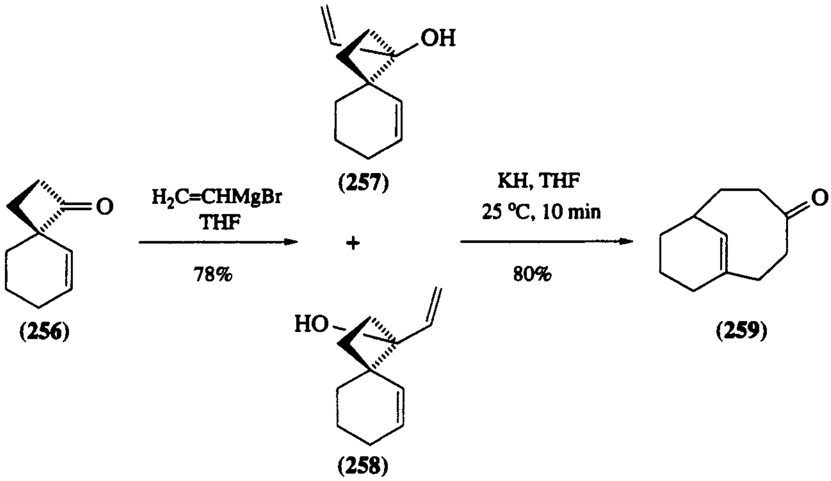

Scheme 34

proceeds *via* a concerted mechanism or involves a stepwise pathway initiated by heterolytic cleavage to an allylmetal ketone intermediate.

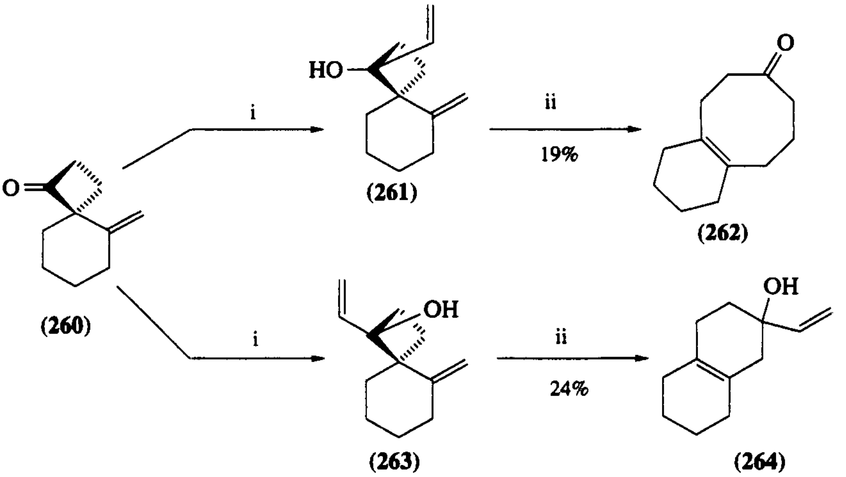

i, $H_2C$=CHLi, $Et_2O$, –78 °C, 15 min, then quench at –78 °C with AcOH; ii, KH, THF, 25 °C, 30 min

Scheme 35

A second attractive strategy for the synthesis of eight-membered carbocycles utilizes the [2 + 2] cycloaddition of vinylketenes in conjunction with the oxyanion-accelerated DVCB rearrangement. Paquette and coworkers have examined the application of this strategy to the synthesis of the dicyclopenta[*a,d*]cyclooctane ring system which is incorporated in the structures of the ophiobolane and related sesterterpenes.[91] As discussed earlier (see Scheme 23), the addition of methylvinylketene to cyclopentadiene provides a 70:30 mixture of diastereomeric cycloadducts; separation of these isomeric vinylbicycloheptenones can be accomplished by means of high-pressure liquid chromatography. Addition of cyclopentenyllithium to the *exo*-vinyl isomer (**196**) at –78 °C then produces the cyclobutanol salt (**265**), which undergoes spontaneous Cope rearrangement at this temperature to furnish the enolate (**266**). Alkylation with methyl iodide then affords the desired tricyclic product (**267**) in 96% overall yield (Scheme 36).

Intramolecular vinylketene cycloadditions have also found use as an efficient method for the preparation of divinylcyclobutanols suitable for accelerated oxy-Cope rearrangement. A typical reaction sequence is outlined in Scheme 37.[92] In this case the cyclobutanol salt produced by addition of vinyllithium to (**270**) at –78 °C was observed to undergo 3,3-sigmatropic rearrangement simply upon warming to room temperature; the tricyclic enone (**272**) incorporating a *trans*-cyclooctene ring was thus formed in 62% overall yield from (**270**).

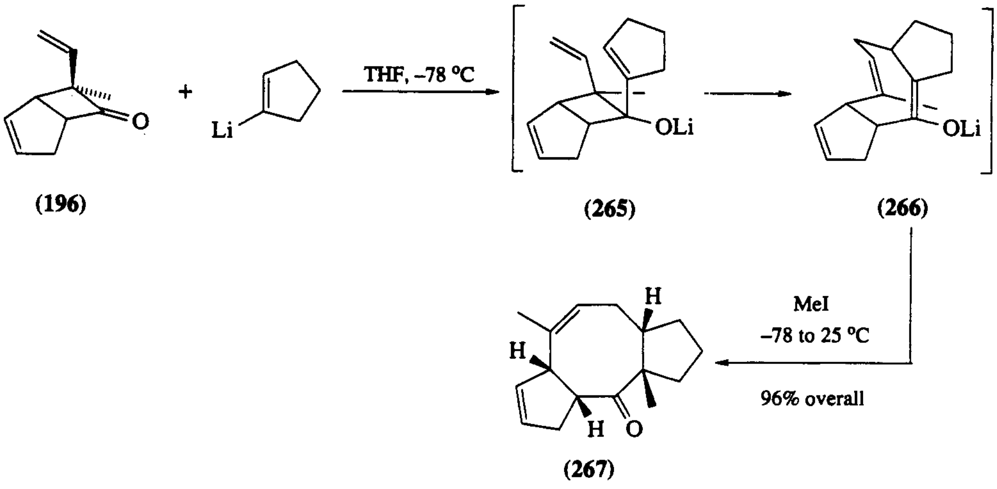

**Scheme 36**

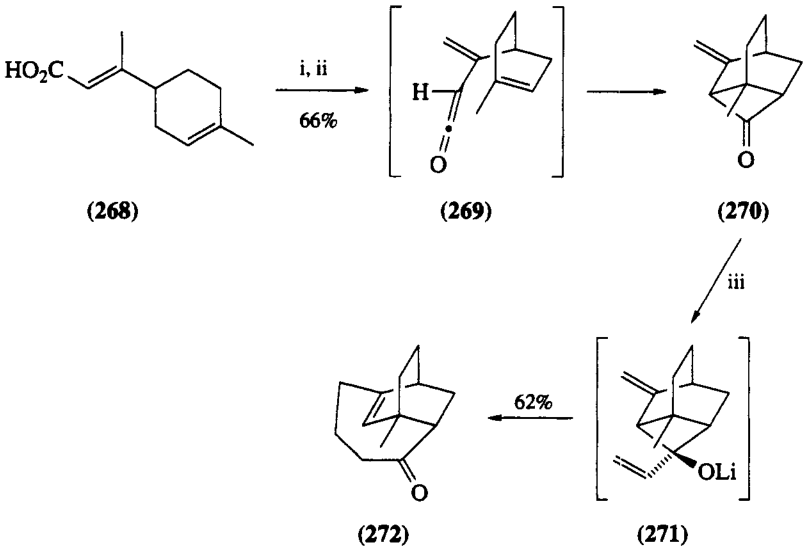

i, $(COCl)_2$, benzene, 25 to 55 °C; ii, $Et_3N$, toluene, reflux, 3 h; iii, $H_2C{=}CHLi$, THF, –78 to 25 °C

**Scheme 37**

Finally, a recent study by Majetich and Hull has demonstrated the feasibility of the carbanion-accelerated divinylcyclobutane rearrangement.[93] Whereas the thermal rearrangement of the divinylcyclobutane (**273**; Scheme 38) required extended heating at 180 °C and proceeded in modest yield, the corresponding enolate was shown to rearrange smoothly at –35 °C in 90% yield. As illustrated in Scheme 39, the enolate-accelerated DVCB rearrangement can be employed in tandem with the intramolecular fluoride-promoted Michael addition of allylsilanes to provide an attractive route to a variety of fused bicyclic cyclooctane derivatives.

### 8.3.3.3 Cyclobutene Rearrangements

#### *8.3.3.3.1 Introduction*

The electrocyclic ring opening of cyclobutenes has found considerable use as a method for the synthesis of 1,3-dienes. The reaction has recently been reviewed by Marvell[94] and is also the subject of

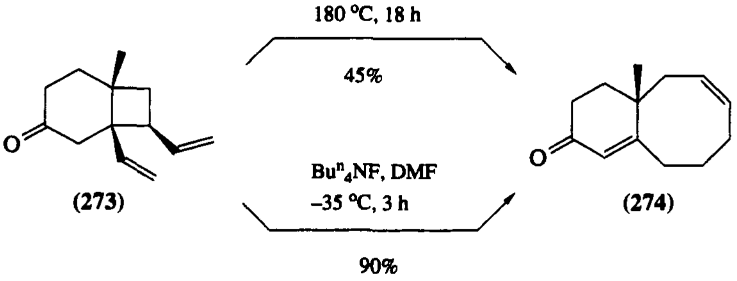

**Scheme 38**

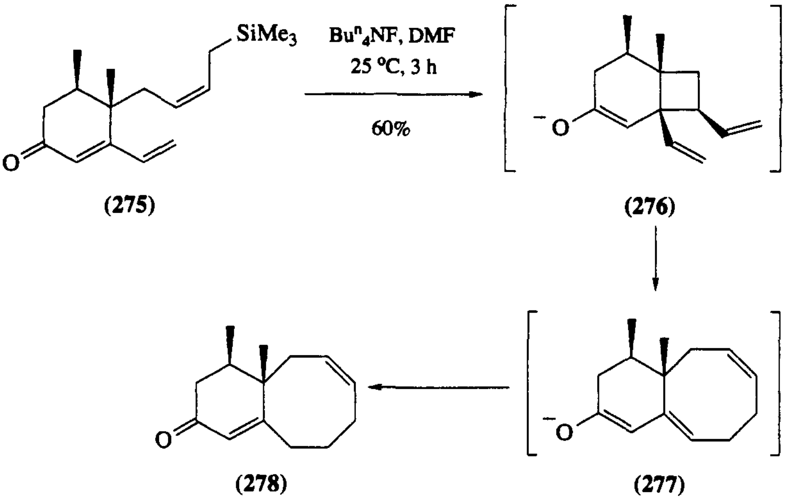

**Scheme 39**

Chapter 6.1, this volume. Several important synthetic strategies feature the electrocyclic cleavage of a cyclobutene derivative as a key step. Particularly noteworthy in this regard is the thermolysis of benzocyclobutenes, which serves as a convenient method for the generation of *o*-quinodimethanes. These highly reactive conjugated dienes readily participate in both inter- and intra-molecular Diels–Alder reactions, and the tandem electrocyclic cleavage–cycloaddition strategy provides a powerful method for the preparation of a wide range of complex six-membered ring-containing compounds. The application of this strategy in elegant total syntheses of a variety of steroids, alkaloids and lignan antitumor agents is well documented.[95]

Cyclobutene thermolyses are typically performed at temperatures ranging from 80 to 200 °C. Carpenter's model (see Section 8.3.1.2)[9] suggests that electron-donor substituents at C-3 of the four-membered ring should enhance the rate of electrocyclic ring cleavage. This prediction has received experimental verification; for example, the activation energy for the ring opening of 3-ethoxycyclobutene was determined to be 9 kcal mol$^{-1}$ lower than that required for the parent system.[96] A particularly interesting recent development is the finding that these conrotatory electrocyclic processes occur with a strong preference for the 'outward' rotation of C-3 donor substituents, as illustrated with the transformation outlined in equation (38).[97]

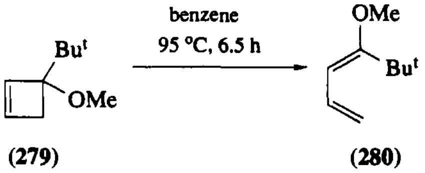

(38)

### *8.3.3.3.2 Anion-accelerated electrocyclic cleavage of cyclobutenes*

The ability of both oxyanionic and carbanionic substituents to facilitate the electrocyclic ring opening of cyclobutenes has now been documented.[98] For example, the oxyanion-accelerated electrocyclic cleavage of benzocyclobutenes has been examined by Choy and Yang;[99] some of their results are summarized in Scheme 40. Addition of 1.1 equiv. of *n*-butyllithium to the benzocyclobutenol (**281**) in THF at –78 °C and subsequent warming to –25 °C led to the formation of a burgundy red solution believed to contain the oxyanion-substituted *o*-quinodimethane (**285**). Efficient Diels–Alder cycloadditions were observed to take place when the electrocyclic cleavage reaction was carried out in the presence of electron-deficient dienophiles such as dimethyl fumarate and γ-crotonolactone (Scheme 40). These cycloadditions proceed under considerably milder conditions than the analogous thermal reactions, and in many cases exhibit increased selectivity for the formation of the *endo* Diels–Alder adducts.

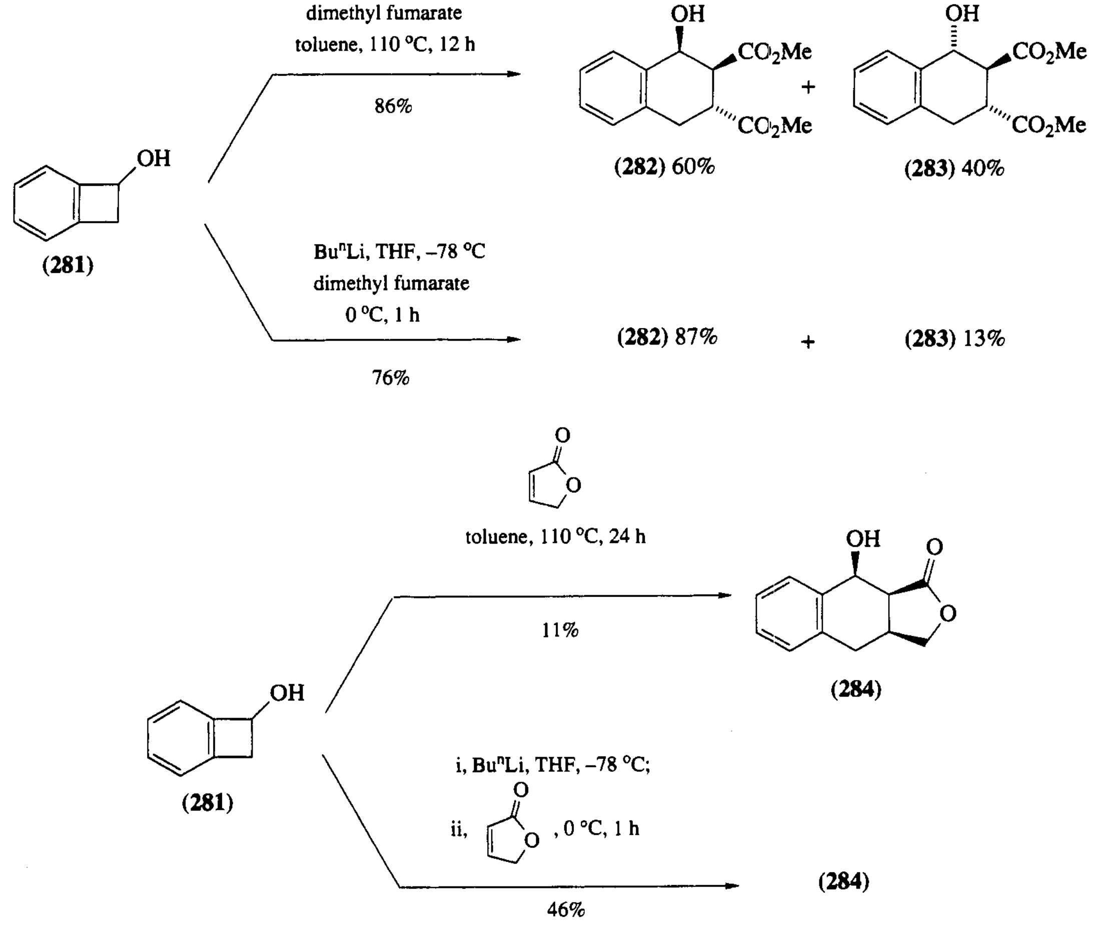
dimethyl fumarate
toluene, 110 °C, 12 h
86%
OH
CO2Me
+
CO2Me
OH
CO2Me
CO2Me
OH
(281)
(282) 60%
(283) 40%
BunLi, THF, –78 °C
dimethyl fumarate
0 °C, 1 h
76%
(282) 87%
+
(283) 13%
O
O
toluene, 110 °C, 24 h
11%
OH
O
O
(284)
OH
(281)
i, BunLi, THF, –78 °C;
ii,
O
O
, 0 °C, 1 h
46%
(284)

**Scheme 40**

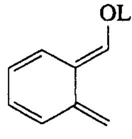

**(285)**

Kametani and his group have described several examples of carbanion-accelerated cyclobutene ring openings.[100] As outlined in Scheme 41, cyclobutenes substituted with arylsulfonyl-, arylsulfinyl- and diphenylphosphinoyl-stabilized carbanions all undergo extraordinarily facile electrocyclic cleavage at temperatures below –20 °C. It is unclear whether these reactions follow concerted mechanisms or involve heterolytic cleavage of the cyclobutene ring. The formation of the peculiar rearranged products such as

**(290)** in reactions in the sulfoxide series has been explained on the basis of a mechanism involving sequential 2,3-sigmatropic rearrangements (equation 39).

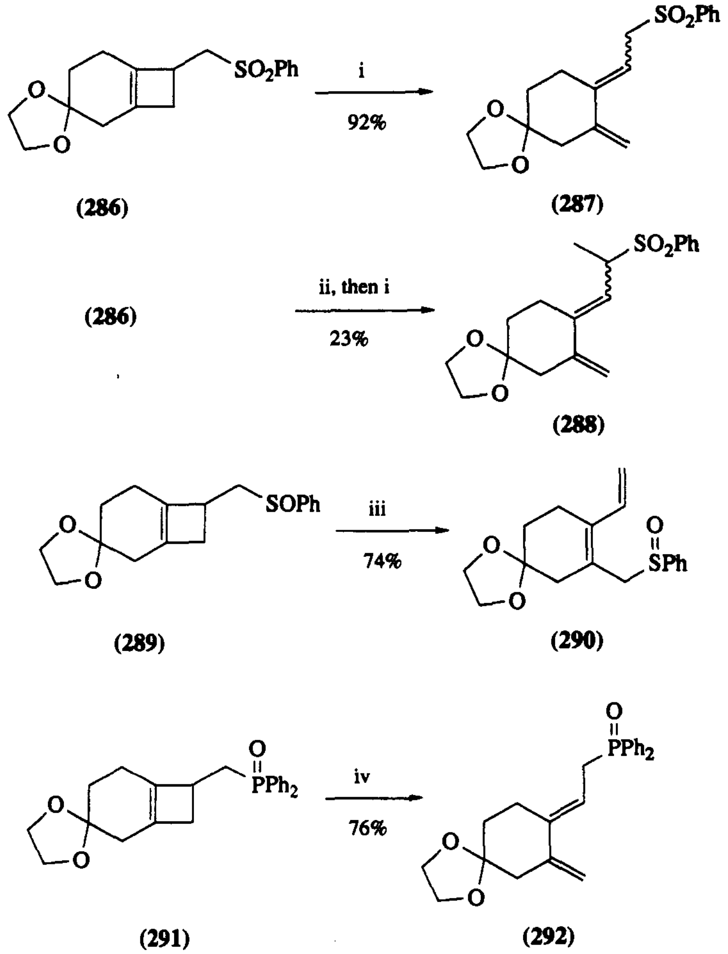
SO$_2$Ph
i
92%
(286)
(287)
ii, then i
23%
(288)
SOPh
iii
74%
SPh
(289)
(290)
PPh$_2$
iv
76%
(291)
(292)

i, 1.2 equiv. Bu$^n$Li, THF, –78 to –30 °C, 10 min; ii, 1.2 equiv. Bu$^n$Li, THF, then 1.2 eqiuv. MeI, –78 °C; iii, LDA, THF, –78 °C to –30 °C; iv, 7 equiv. LDA, THF, –20 °C, 16 h

**Scheme 41**

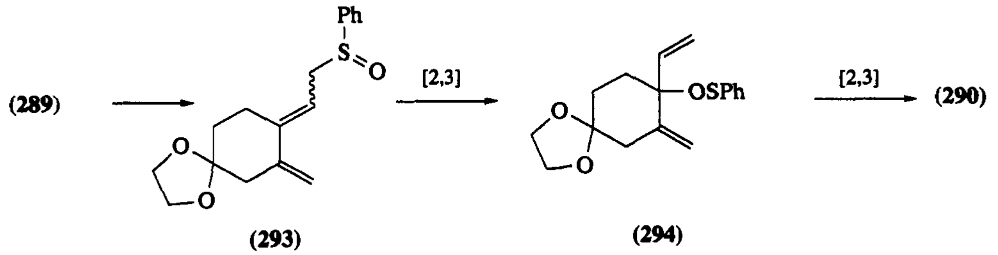
(289)
Ph
S
O
[2,3]
OSPh
[2,3]
(290)
(293)
(294)

(39)

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# 9.1
# The Pauson–Khand Reaction

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## 9.1.1 GENERAL CONSIDERATIONS

### 9.1.1.1 Introduction

Although the *a priori* development of multicomponent cycloaddition reactions involving selective incorporation of three or more different molecules may seem to be a daunting task, numerous such reactions exist.[1] Indeed, study of the chemistry of transition metals in the presence of organic π-systems over the past four decades has led to the serendipitous discovery of a marvelous array of multicomponent processes. More recently, as a fuller understanding of mechanisms of transition metal reactions has evolved, the intentional development of still more remarkably powerful reactions has taken place.[2] Among the several systems that have been found to be suitable for the cocycloaddition of alkynes, alkenes and carbon monoxide,[3–5] the most extensively studied is the one first reported in detail by Khand and Pauson in 1973,[6] a cyclopentenone synthesis from the three components and $Co_2(CO)_8$, a formal [2 + 2 + 1] cycloaddition (equation 1). This reaction was discovered in the course of a study aimed principally at the preparation and characterization of various alkene and alkyne complexes derived from $Co_2(CO)_8$. During the subsequent half-dozen years or so the Pauson group was virtually alone in pursuing the development of this reaction, carrying out a number of extensive series of studies of remarkable breadth and depth. The Pauson–Khand reaction has now taken a place amidst the more conventional methodological approaches to the challenging cyclopentenone ring system, is a focus of study by a number of research groups and has been used in synthetic applications by many more.

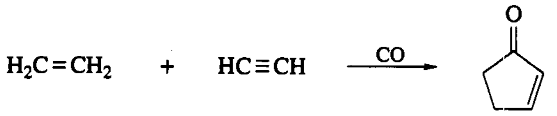

(1)

The reaction is carried out in one of two principal ways. In the more common stoichiometric method, the alkyne is allowed to react with $Co_2(CO)_8$ at room temperature over the course of several hours in hydrocarbon or ethereal solvent to generate the thermally stable, readily characterized complex $Co_2(CO)_6{\cdot}RC{\equiv}CR'$.[7] This in turn reacts under moderate heating with a wide variety of alkenes to generate cyclopentenones, giving typical yields in the 30–60% range (equations 2 and 3).[8,9] The reaction is normally carried out under an atmosphere of either nitrogen or carbon monoxide; if the alkyne in $Co_2(CO)_6{\cdot}RC{\equiv}CR'$ is a gas, it is typically incorporated into the atmosphere above the reaction mixture as well. Depending on the reactivity of the substrate, reaction times range from hours to days at temperatures between 70 and 110 °C for all but the most unreactive alkenes. The use of pressure above 1 atm is usually unnecessary, although improvements in yields have occasionally been noted when the reaction is carried out in a sealed tube.

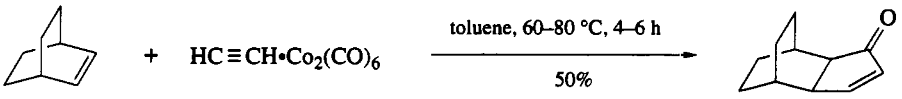

(2)

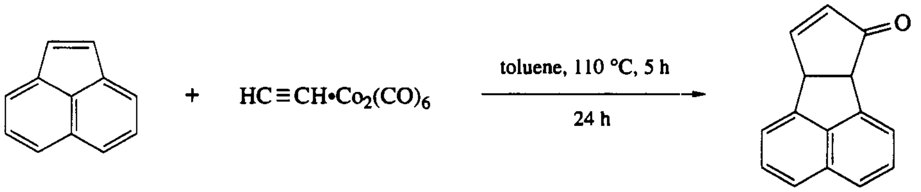

(3)

When the reaction involves a gaseous alkyne, it is often both feasible and advantageous to carry it out in a catalytic fashion by stirring a mixture of alkene and *ca.* 10 mol % $Co_2(CO)_8$ in an inert solvent under a 1:1 alkyne/carbon monoxide atmosphere. Provided that potential side reactions involving the alkene and $Co_2(CO)_8$ do not compete, the continuous supply of excess alkyne allows trapping and recycling of reactive cobalt-containing fragments to occur, while also compensating for independent side reactions that consume the alkyne, such as trimerization to benzene derivatives. The result is substantially improved yields in the most favorable cases (equation 4).[10]

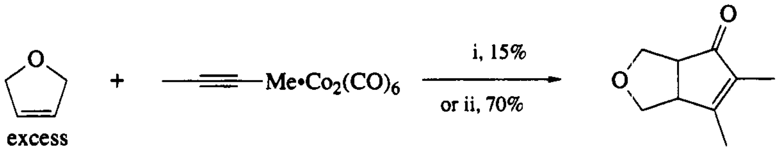

(4)

i, toluene, 110 °C, 8 h, $N_2$; ii, isooctane, 85 °C, 8 d, 1:1 CO/2-butyne

### 9.1.1.2 Scope of the Reaction

The scope of the Pauson–Khand reaction with respect to substrate structure is considerable. Virtually all alkynes that have been tried participate, except derivatives of propynoic acid. Most satisfactory are acetylene itself and simple terminal alkynes, including arylalkynes. Internal alkynes give consistently lower yields of cyclopentenones. The scope of the reaction with respect to the alkene is typically somewhat more limited. Strained cyclic alkenes are the best substrates, typically reacting at 60–80 °C over a period of several hours. Steric hindrance around the double bond exerts a significant deleterious effect on the cycloaddition. In particular, tri- and tetra-substituted double bonds, and double bonds containing large allylic substituents, even when contained in a strained ring, frequently give cyclopentenones only in low yields, if at all. This is apparently due to a reduction in the ability of the alkene to compete with additional molecules of alkyne for reaction with the initially formed $Co_2(CO)_6{\cdot}RC{\equiv}CR'$ complex. As a result, reactions such as alkyne trimerization, and multicomponent cycloadditions involving only alkyne and carbon monoxide, normally only minor side reactions, become the principal processes taking place, leading to a variety of products (equation 5).[11] Simple acyclic alkenes and unstrained cyclic alkenes are also generally poor substrates, rarely giving cyclopentenones in yields better than 40%. Several techniques for improving yields of cyclopentenones in these less favorable situations have been employed, and these will be described in the appropriate sections.

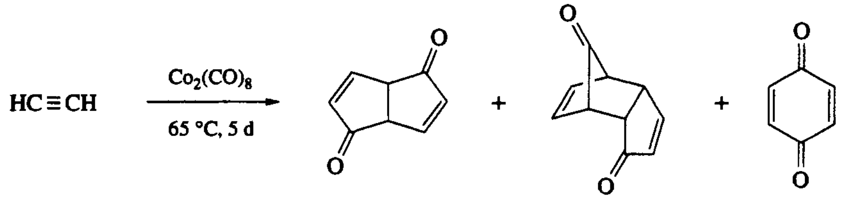

(5)

| | | | |
|---|---|---|---|
| benzene: | 9% | 3% | trace |
| DME: | 1% | 10% | 1% |

As examples that follow will reveal, the Pauson–Khand reaction possesses substantial functional group tolerance. It is completely compatible with a wide range of functionality including ethers, alcohols, tertiary amines, sulfides, ketones, ketals, esters, tertiary amides, and aromatic rings including benzene, furan and thiophene. Partial tolerance of the following groups has also been observed: alkyl and aryl halides, vinyl ethers and esters, and less reactive alkenes and alkynes in the presence of more reactive unsaturation.[12] Cyclopentenone formation generally appears not to be adversely affected by conjugation of either substrate π-system with another carbon–carbon π-bond. However, a few examples of reduced or anomalous reactivity have been reported in substrates bearing other allylic or propargylic functionality. Most noticeably, alkenes conjugated with electron-withdrawing substituents react very differently. Formal addition of a vinylic C—H bond across the triple bond of the alkyne results in the formation of 1,3-dienes (equation 6).[13] A possible mechanistic relationship between this process and the formation of cyclopentenones will be presented in the section that follows.

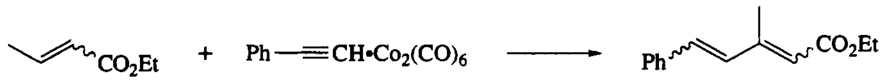

(6)

Excellent background material on the Pauson–Khand reaction is available in reviews published by Pauson in 1977, 1985 and 1988.[14–16]

## 9.1.2 MECHANISM: REGIO- AND DIASTEREO-SELECTIVITY

Direct studies of the mechanism of the Pauson–Khand reaction have been limited to the observations made very early on by the Pauson group indicating the unambiguous intermediacy of the $Co_2(CO)_6$·RC≡CR′ complex in the process. Although alkene complexes derived from $Co_2(CO)_8$ are well known, if limited in number, they have been shown not to give rise to cyclopentenones upon treatment with alkynes.[6] Attempts to observe intermediates spectroscopically beyond the alkyne complexation stage have been unsuccessful; invariably the only species detected during the course of the reaction are the final products themselves. It is most reasonable to assume that, whatever the mechanistic sequence that follows alkyne complexation, the rate-determining step occurs early in the sequence, precluding the build-up of any subsequent intermediates to observable levels.

Nevertheless, although direct mechanistic evidence beyond the alkyne complexation stage is lacking, a hypothesis has been inferred from observations of regio- and stereo-chemistry in a large number of examples of Pauson–Khand cycloaddition.[17] This is illustrated using the reaction between the $Co_2(CO)_6$·propyne complex and 1-methoxybicyclo[3.2.0]hepta-3,6-diene, reported by Pauson and coworkers in 1977 (Scheme 1).[18] In common with the majority of transition metal mediated organic cycloaddition reactions known at the present time, the principal controlling interactions appear to be steric in nature. Complexation of the alkene to cobalt *via* a standard dissociative mechanism initiates the sequence. With bicyclic alkene substrates such as the one shown, the less hindered *exo* face of the π-bond preferentially complexes to the metal. This process is almost certainly reversible. The step that follows, insertion of the complexed face of the alkene π-bond into one of the formal cobalt–carbon bonds of the alkyne complex, is thought to be both the rate- and product-determining step. Both regio- and stereochemistry are kinetically controlled, chiefly by steric interactions in this irreversible insertion process. In the example shown, the diastereofacial selectivity upon alkene complexation is preserved upon insertion, a stereospecific process that leads exclusively to a *cis-exo* ring fusion. This result is nearly universally observed with bicyclic alkenes, including those employed in the first reported examples of the reaction: norbornene, norbornadiene and several of their derivatives.[6]

During the insertion into the cobalt–carbon bond, regiochemistry with respect to both alkyne and alkene is determined. The incipient carbon–carbon bond is most susceptible to steric crowding; for example, a 1,3-pseudodiaxial interaction (A in Scheme 1) develops between the substituent on the alkyne carbon and any allylic group on the alkene. As a result, if the alkyne is unsymmetrical, insertion and carbon–carbon bond formation proceed exclusively at the alkyne carbon possessing the smaller substituent (*i.e.* H in a terminal alkyne, leading eventually to a 2-substituted enone). With steric hindrance at the alkyne carbon thus removed, a second 1,3-pseudodiaxial interaction comes into play, capable of exerting regiocontrol of an alkene unsymmetrically substituted at the allylic positions. This interaction (B in Scheme 1) involves an allylic substituent with the $Co(CO)_3$ moiety. In order to minimize this interaction, the alkene carbon bearing the larger allylic substituent inserts away from the cobalt, thus forming the new carbon–carbon bond with the alkyne carbon. Subsequent CO insertion, reductive elimination of one cobalt, and decomplexation of the other give the final product.

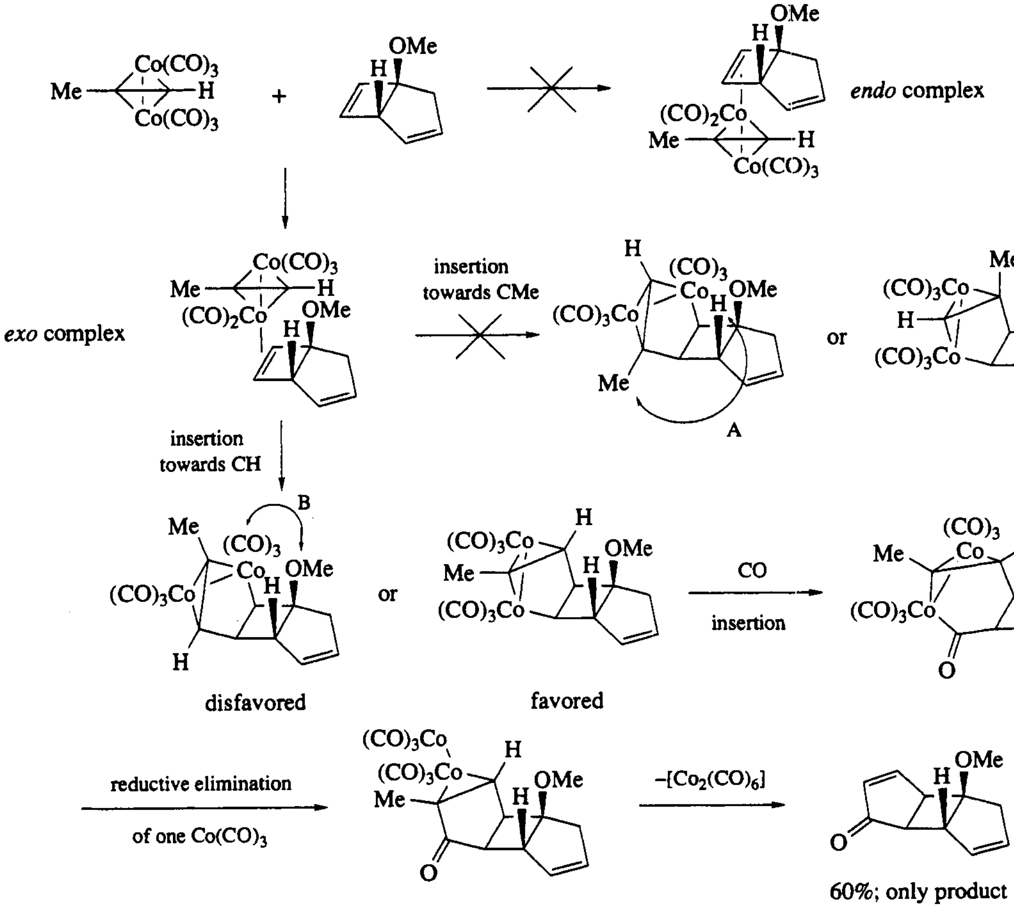

Scheme 1

Briefly summarized, the less-hindered face of the alkene inserts into the less-hindered formal cobalt–carbon bond of the starting complex, with the orientation of alkene insertion placing the larger allylic substituent away from cobalt. The overall result is: (i) *cis-exo* ring fusion stereochemistry; (ii) alkyne regiochemistry placing the larger alkyne substituent α to the new ketone carbonyl and (iii) alkene regiochemistry placing the larger allylic substituent *anti* to the new ketone carbonyl. The first two preferences are strong ones; indeed, no exceptions to the second are known. As to the third, it should be pointed out that the bicyclo[3.2.0]hept-6-ene system is an unusually regioselective substrate. Indeed, the steric sensitivity of this system is strikingly illustrated in the total reversal of regiochemistry upon replacement of a ring fusion hydrogen with methyl, which is effectively larger than methoxy (equation 7).[19]

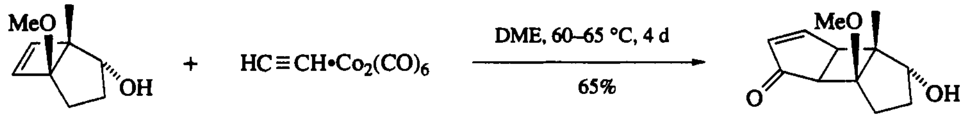

(7)

In general, however, the issue of alkene regiochemistry is still incompletely resolved, as it is dependent on both the nature of the alkene as well as the alkyne. Thus, while the systems depicted in Scheme 1 and equation (7) are totally regioselective, most other types of bicyclic alkenes give mixtures of regioisomers, although the isomer predicted on the basis of the analysis above always predominates. Furthermore, regiocontrol with simpler alkenes is more difficult to predict. Simpler terminal alkenes themselves display little or no regioselectivity upon reaction with acetylene or terminal alkynes, although incorporation of the alkyne remains totally regioselective (equation 8).[20,21] In addition, alkyne regiocontrol remains high even in reactions with ethylene itself, even though some of the steric interactions alluded to earlier are obviously absent (equations 9 and 10).[16] Krafft has suggested that steric effects may play a controlling role prior to insertion, by favoring specific configurational and conformational isomers of the alkene complex for subsequent reaction. Thus of the three possible configurational isomers at pseudooctahedral cobalt, the one most likely to lead to insertion contains the alkene complexed *trans* to the bond between cobalt and the substituted alkyne carbon, avoiding a steric interaction with the latter. Insertion can therefore only occur into the other cobalt–carbon bond, fixing the alkyne regiochemistry (Scheme 2, R′ = H). With most terminal alkenes, there will be little preference between the two possible reactive conformations about the cobalt–alkene bond, resulting in no regioselectivity in alkene incorporation (*cf.* equation 8). However, if the R′ group on the alkene is sufficiently large, conformation (**2**) is preferred (Scheme 2), placing the large group *anti* to the cobalt–carbon bond. This results in a preference for the 5-substituted cyclopentenone, as has been observed by Pauson in the case of 3,3-dimethyl-1-butene (*t*-butylethylene; equation 11).[16]

Strong support for this picture has been provided by Krafft in the observation of greatly increased alkene regioselectivity in Pauson–Khand cycloadditions with internal alkynes (equation 12).[21] As above, the site of coordination of the alkene determines alkyne regioselectivity, while the conformation of the coordinated alkene prior to insertion determines alkene regioselectivity. The presence of groups larger than hydrogen on both alkyne carbons introduces unavoidable steric interactions biasing the system towards alkene insertion from a conformation similar to conformation (**2**) in Scheme 2. This more detailed analysis has only been applied to terminal alkenes, in which steric differentiation between the alkene carbons is large. Comparable application to bicyclic systems such as those discussed earlier (*i.e. cis*-disubstituted alkenes) will be more complicated. Steric differentiation is much smaller, and, in addition, it will

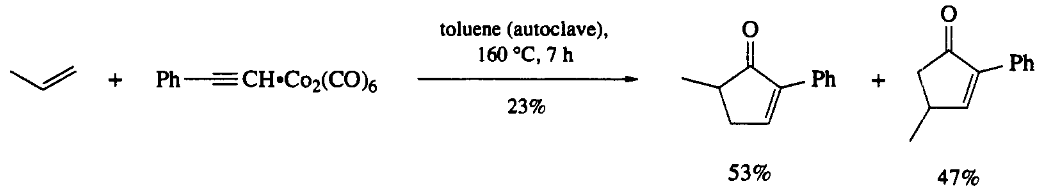

(8)

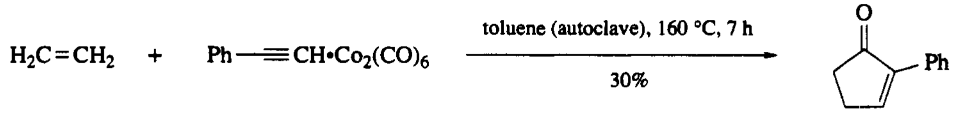

(9)

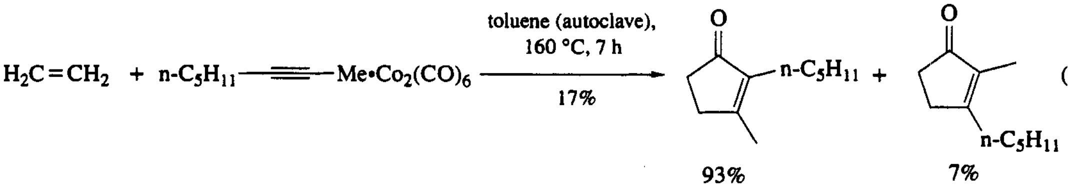

(10)

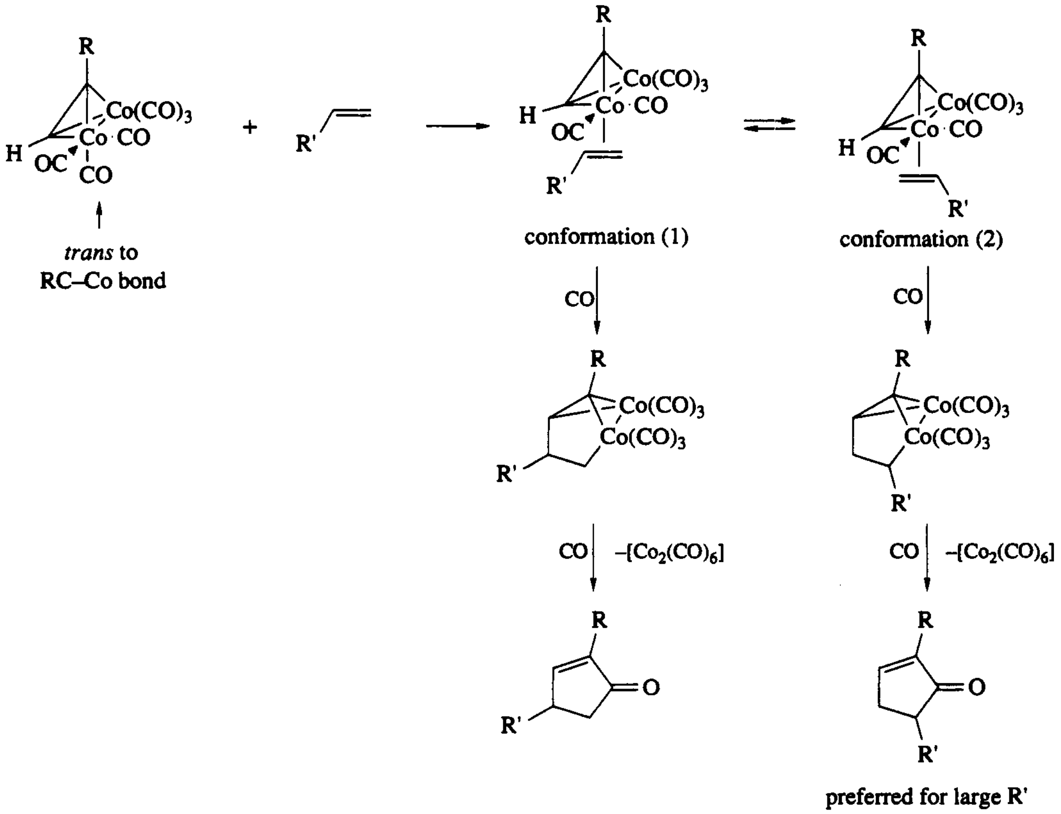
*trans* to
RC–Co bond
conformation (1)
conformation (2)
CO
–[Co$_2$(CO)$_6$]
preferred for large R'

**Scheme 2**

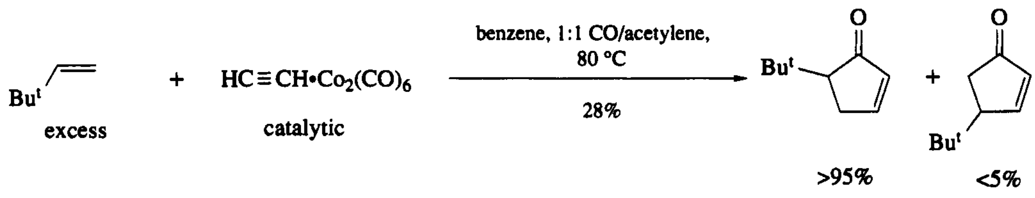
excess
catalytic
benzene, 1:1 CO/acetylene, 80 °C
28%
>95%
<5%

(11)

be necessary to consider the effects on regiochemistry of the chirality of both the allylically substituted alkene as well as the alkene–alkyne–cobalt complex, in which the cobalt becomes a stereocenter, thus introducing an additional diastereoselection problem in the formation of the complex itself. At present, the simpler analysis based upon pseudoaxial interactions will have to suffice.

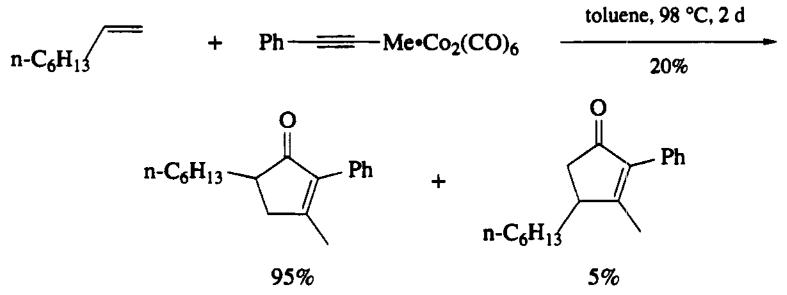
toluene, 98 °C, 2 d
20%
95%
5%

(12)

Electronic effects on alkene regioselectivity in the Pauson–Khand reaction have also been observed. The regioselectivity observed in cycloadditions of norbornen-2-ones has been interpreted as arising from an electronic preference for attachment of the $\delta^+$ C-5 of the alkene to an alkyne carbon rather than cobalt in the bond-forming insertion step (equation 13). In these systems electronic and steric effects have been separated by carrying out identical reactions with the corresponding norbornen-2-ols, in which the alkene-polarizing homoconjugation interaction has been removed. The observation of *ca.* 1:1 product ratios from the latter (equation 14) supports the interpretation given above, and is consistent with earlier results from the Pauson group involving reactions of styrene derivatives (see Section 9.1.3.1).[22]

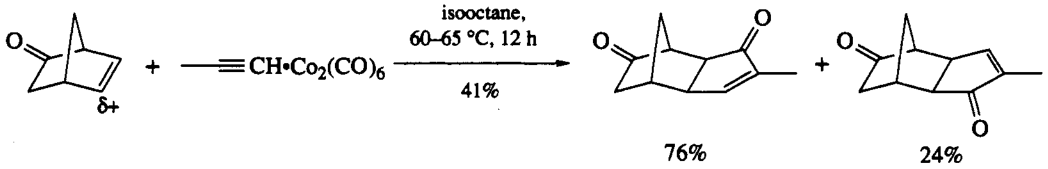

(13)

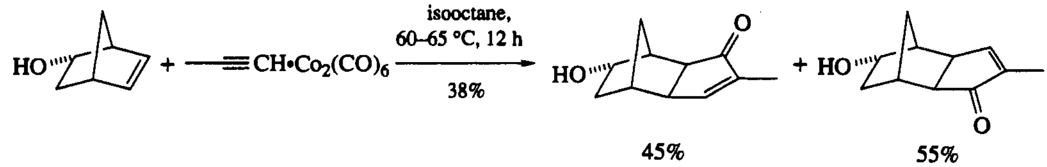

(14)

As already mentioned, alkenes attached to electron-withdrawing groups react anomalously, giving 1,3-dienes (equation 6).[13] The reaction is completely regioselective, with the new carbon–carbon bond forming between the less-hindered alkyne carbon and the less-hindered alkene carbon, which also happens to be the $\delta^+$ polarized alkene carbon. It is therefore reasonable to assume that complexation of the alkene and subsequent insertion still occur as illustrated in Scheme 1, and are controlled by the same steric and electronic factors. The electron-withdrawing group in every example of this reaction is π-conjugating. This probably renders a β-hydrogen elimination/reductive elimination sequence competitive with CO insertion, by providing a driving force for regeneration of the alkene (Scheme 3).

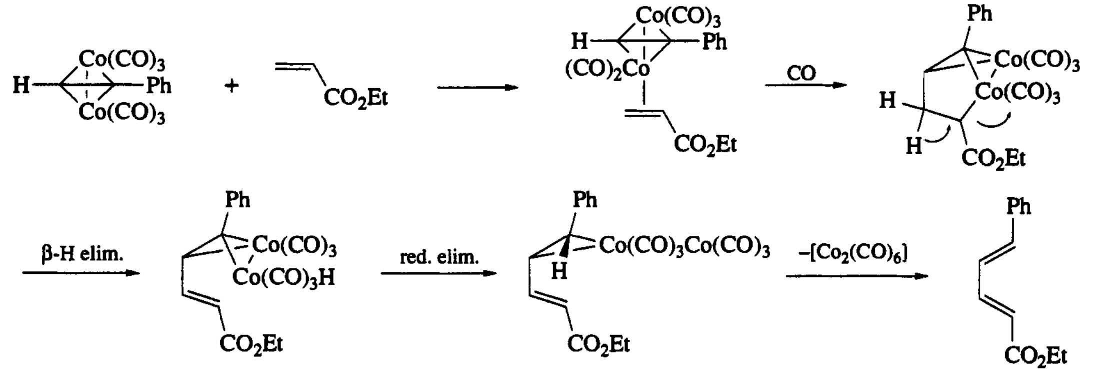

**Scheme 3**

## 9.1.3 INTERMOLECULAR PAUSON–KHAND REACTION

### 9.1.3.1 Reactions involving Acyclic Alkenes: Chemo-, Regio- and Diastereo-selectivity

Application of the Pauson–Khand reaction to simple acylic alkenes has been limited by both low reactivity and lack of regiocontrol in incorporation of the alkene. Among simple alkenes, ethylene provides the most consistently useful results. Yields with terminal alkynes range from 30–60% (equations 9,15 and 16);[23,24] internal alkynes have also been used with some success (equation 10).[16] Forcing conditions (toluene, 130–160 °C, 60–80 atm, autoclave) are usually required for best results, although it has been recently demonstrated that the reaction proceeds, albeit slowly, at reduced pressures and temperatures (equation 17).[16,25]

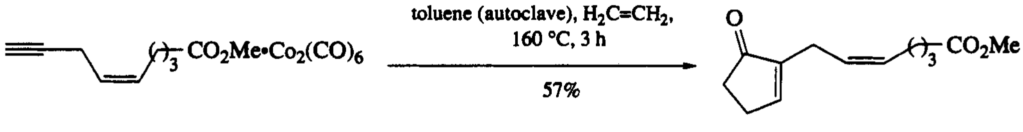

(15)

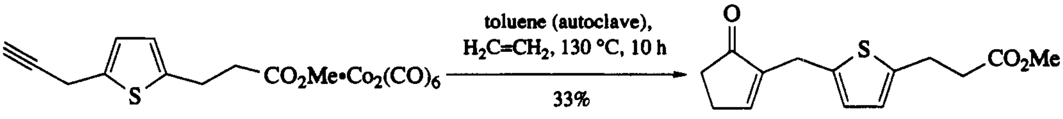
CO2Me•Co2(CO)6
toluene (autoclave), H2C=CH2, 130 °C, 10 h
33%
O
S
CO2Me

(16)

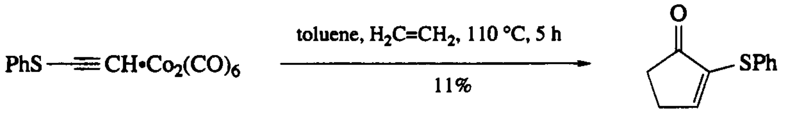
PhS—≡CH•Co2(CO)6
toluene, H2C=CH2, 110 °C, 5 h
11%
O
SPh

(17)

As already mentioned, terminal alkenes usually give modest yields but no regioselectivity in reaction with terminal alkynes. Isolated examples of regiocontrol have been reported in the case of allyl ethers (equation 18);[16,26] note that the R = Me situation is consistent with Krafft's results (equation 12).[21] In the case of R = H, a remarkable and unexplained effect is observed in which the regioselectivity is totally lost when reaction is carried out in a nonaromatic solvent. On the other hand, of considerable potential is another recent observation by Krafft that alkenes containing groups capable of acting as soft ligands at a homoallylic position give both enhanced yields and regioselectivities. This is thought to result from coordination of the heteroatom to cobalt prior to insertion, thereby fixing the conformation of the alkene to favor the 5-substituted product (Scheme 4).[27] Reduced but still usable (*ca.* 3:1) selectivity is observed when the heteroatom is one carbon further removed from the double bond. For optimal yields in these situations it is necessary to exclude carbon monoxide from the atmosphere above the reaction.

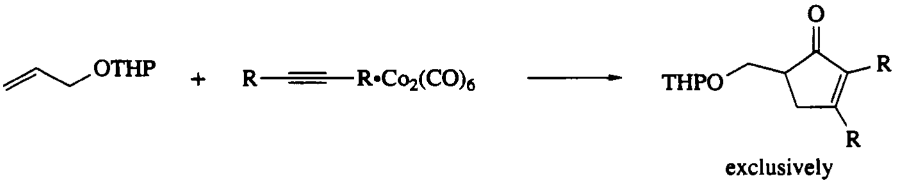
OTHP
+
R—≡—R•Co2(CO)6
THPO
O
R
R
exclusively

(18)

R = H: benzene, 80 °C, 8 h, 48%; R = Me: toluene, 110 °C, 8 h, 32%

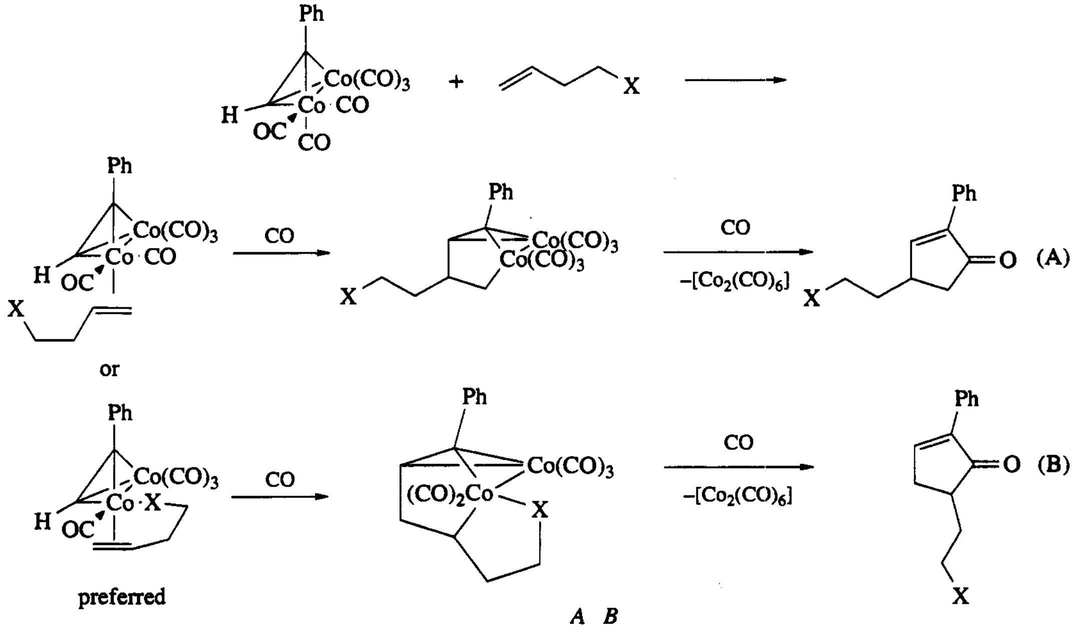
Ph
Co(CO)3
Co CO
H
OC
CO
+
X
CO
Co(CO)3
Co(CO)3
X
CO
-[Co2(CO)6]
O
(A)
or
preferred
Co·X
(CO)2Co
(B)

| | *A* | *B* |
|---|---|---|
| R = NMe$_2$: 72% | 1 | : 5 |
| R = SMe: 61% | 1 | : ≥20 |

**Scheme 4**

Conjugated acyclic dienes (in contrast to cyclic dienes, Section 9.1.3.2), like alkenes conjugated to electron-withdrawing groups, give only linear oligomerization, resulting in acyclic polyene products.[14]

Styrene derivatives have been extensively studied and are intermediate, giving both dienes and 5-arylcyclopentenones, both with complete regioselectivity, consistent with expectations. Attempts to explain and control chemoselectivity in such systems have been made in several studies by the Pauson group. Initial notions that chemoselectivity might be related to electron-withdrawing capability of the aryl substituent have not been supported by the evidence. For a variety of styrene derivatives containing *para* substitution the product ratio of cyclopentenone to linear diene varies in no readily interpretable way with the nature of the substituent, nor does complexation of the strongly electron-withdrawing $Cr(CO)_3$ unit to the arene have a consistent effect (equation 19).[20,28,29] Fragmentary data indicate that alkyl alkynes give more cyclopentenone and less diene than do aryl alkynes in reactions with styrenes. Allylarenes (3-arylpropenes) also give 5-substituted cyclopentenones with complete regioselectivity, for no obvious reason (equation 20).

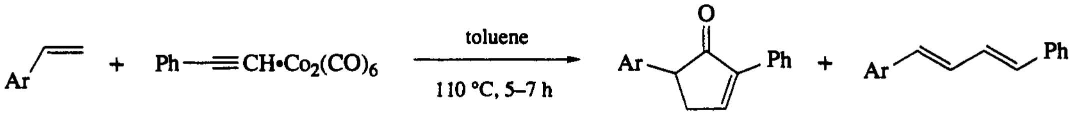

(19)

| | | | |
|---|---|---|---|
| Ar = Ph: | 31% | 77% | 23% |
| Ar = Ph•$Cr(CO)_3$: | 69% | 54% | 46% |
| Ar = *p*-Tol: | 39% | 33% | 67% |
| Ar = *p*-Tol•$Cr(CO)_3$: | 68% | 57% | 43% |
| Ar = *p*-$ClC_6H_4$: | 29% | 55% | 45% |
| Ar = *p*-$ClC_6H_4$•$Cr(CO)_3$: | 29% | 0% | 100% |

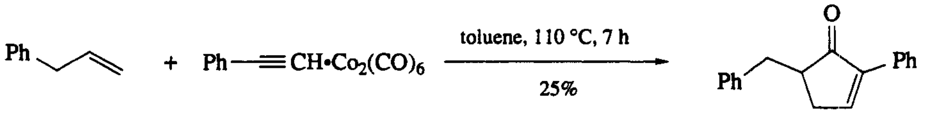

(20)

Considerably less work has been carried out with more heavily substituted acyclic alkenes; for all practical purposes these cannot at present be considered useful substrates. A significant exception exists in the reactivity of the homoallylically derivatized systems of Krafft; again, greatly improved yields are observed along with impressive regioselectivity but no diastereoselectivity (equations 21 and 22). It is not known at what stage stereochemistry at the saturated α-carbon is lost.[27]

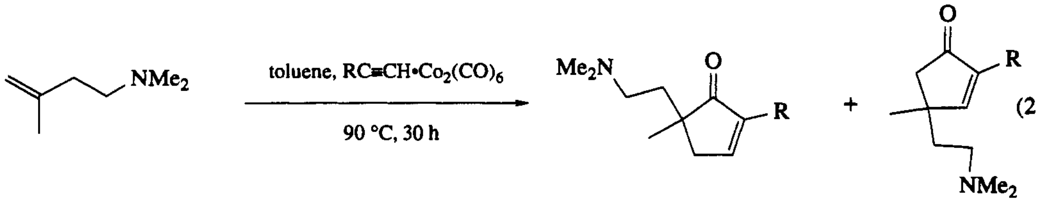

(21)

| | | |
|---|---|---|
| R = Ph: 77% | 95% | 5% |
| R = Bu: 60% | 94% | 6% |

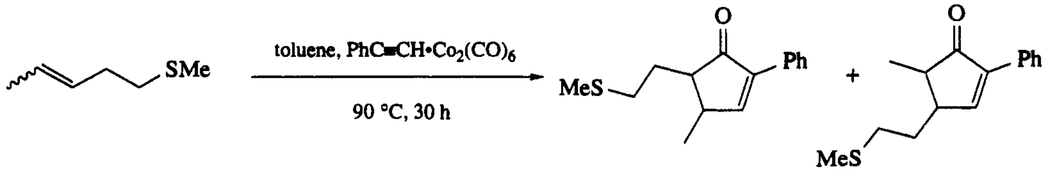

(22)

| | | |
|---|---|---|
| (*E*)-alkene: 40% | 87% (*trans*/*cis* = 12:1) | 13% |
| (*Z*)-alkene: 73% | ≥97% (*trans*/*cis* = 19:1) | ≤3% |

Limited work has revealed that vinyl and allyl halides cyclize only in low yield, and the products suffer halogen loss in the process.[20] Also, unlike allyl ethers, vinyl ethers and esters are only marginally suitable substrates for Pauson–Khand cycloaddition (equation 23).[30] Part of the difficulty lies in the sensitivity of both the substrates and the products to decomposition under the reaction conditions.

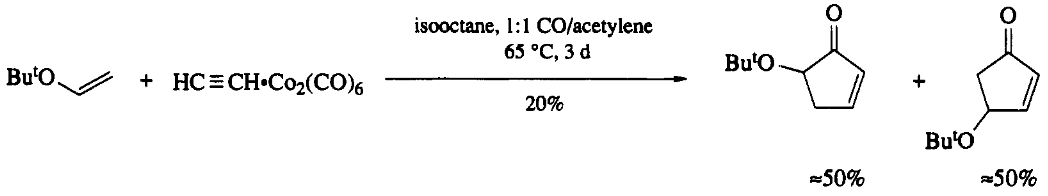

(23)

### 9.1.3.2 Reactions involving Monocyclic and Fused Bicyclic Alkenes: Chemo- and Regio-selectivity

The first alkenes studied as substrates for Pauson–Khand cycloaddition were strained bicyclics containing the double bond in four- or five-membered rings. Simple cyclobutenes do not appear to have been examined as substrates, but bicyclo[3.2.0]hept-6-enes have been used with considerable success. Pauson found the parent system to be generally reactive towards both terminal and internal alkynes, forming the expected *cis,anti,cis*-tricyclo[5.3.0.0$^{2,6}$]dec-4-en-3-ones *via exo* face selective cycloaddition (equation 24). As mentioned earlier, total regioselectivity was obtained in the case of substrates with ring fusion (*i.e.* allylic) substitution, with the larger allylic group ending up *anti* to the newly introduced cyclopentenone carbonyl (Scheme 1; equations 7, 25 and 26).[18,19]

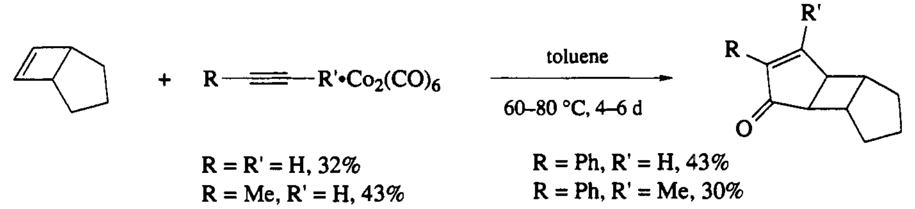

(24)

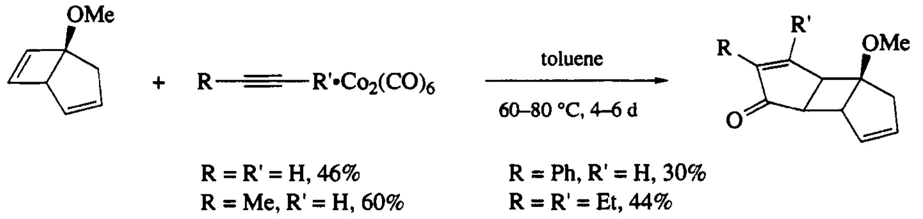

(25)

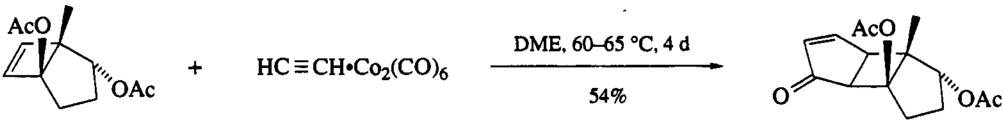

(26)

Although unstrained cyclic alkenes are generally less reactive than strained systems, cyclopentene and dihydrofuran are important exceptions. Required reaction temperatures are higher in some cases (120–160 °C), but no other special conditions are necessary and yields are frequently excellent. Cyclopentene itself reacts with terminal alkenes to give 30–60% yields of cyclopentenones (equation 27).[20,24] This reaction has seen extensive and imaginative development by de Meijere in the use of cyclopropylacetylenes as cycloaddition partners (see Section 9.1.3.4). Moreover, 1-methylcyclopentene, which reacts with acetylene to give <20% yields of cyclopentenones under normal conditions, becomes an excellent substrate when the catalytic modification of the cycloaddition procedure is used (equation 28).[16,25b] The remarkable regioselectivity may be due to a combination of (admittedly small) 1,3-pseudodiaxial interactions and electronic effects (*cf.* Scheme 1 and equation 13); recall that the Krafft conformational analysis involves interactions of internal alkynes only.

In contrast to acyclic dienes, cyclopentadienes and fulvenes react chemoselectively with alkynes to give cyclopentenones, the former in excellent yield but somewhat reduced regioselectivity, the latter less efficiently, although only one regioisomer is obtained (equations 29 and 30). Note that the favored posi-

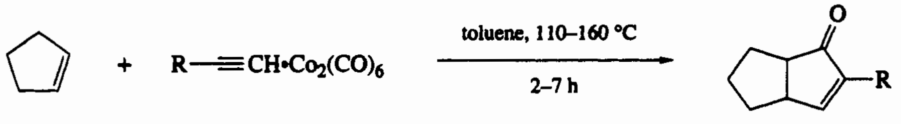

(27)

R = Ph, 47%; R = SPh, 53%; R = $(CH_2)_6CO_2Me$, 33%

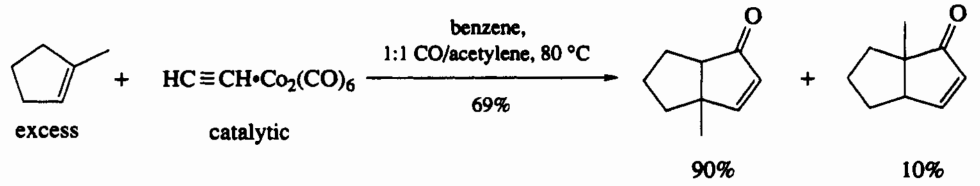

(28)

tion of conjugated unsaturation is the 5-position of the product, as was the case with styrene derivatives. Indene derivatives behave similarly. The fact that dienes are observed only as very minor products, if at all, reflects the clear superiority of the cyclopentene system over simple alkenes in Pauson–Khand annulation (equation 31). The same is true for acenaphthalene (equation 3), which also reacts with propyne and phenylacetylene to give exclusively cyclopentenones.[9]

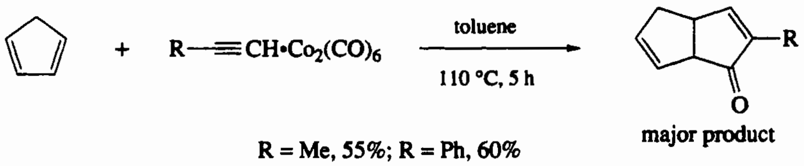

(29)

R = Me, 55%; R = Ph, 60%

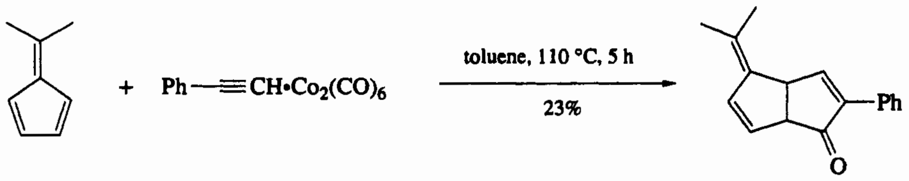

(30)

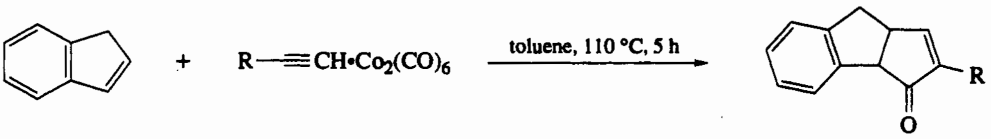

(31)

R = H, 31%; R = Me, 41%; R = Ph, 52% (+ 4% diene)

Other ring-fused cyclopentenes have been studied by both Pauson and Serratosa. Pauson's studies show the expected chemoselectivity when a cyclopentene is present together with a more reactive alkene moiety. In the system shown (equation 32), the cyclopentene is in fact totally inert under conditions required for the norbornene double bond to react.[12] Pentalene-derived substrates present an interesting variation on the basic theme. Serratosa's group has found an unexpected alkene isomerization to precede cycloaddition in the bicyclo[3.3.0]oct-2-ene system. Thermodynamics favors the double bond between C-2 and C-3; however, the double bond at C-1 is more reactive in spite of its increased steric hindrance. Under a variety of conditions, contrathermodynamic double bond isomerization is observed, and only products resulting from reaction of the double bond towards the ring fusion are observed (equation 33).[31] Note the regioselectivity, which is in the same direction as that observed for another trisubstituted alkene, 1-methylcyclopentene (equation 28). It is presumed that a standard hydrogen transfer mechanism involving π-allyl complexes mediates this process; certainly the presence of a tertiary allylic C—H bond in the starting alkene renders this feasible. Cyclopentenone yields in this system increase with temperature, but so do the yields of side products, including the corresponding cyclopentanones and products in which hydrogenolysis of the silyl ether has taken place. These reductions are further evidence for the intermediacy of metal hydrides, such as the ones that would mediate the aforementioned alkene isomerization. The 2-methyl-substituted analog has been found to undergo similar reaction by Pauson: isomerization of the alkene again precedes cycloaddition (equation 34). Although the yield is low, the reaction is noteworthy as the only case in which a tetrasubstituted alkene gives an isolable enone product from a Pauson–Khand reaction. The lack of regioselectivity in the more symmetrical system is expected.[16,25b]

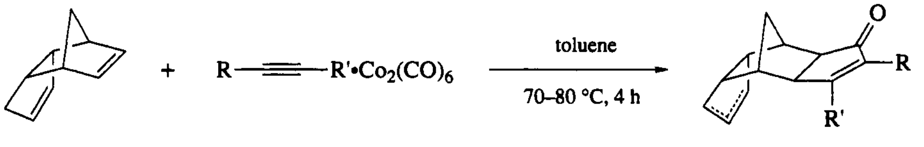
R———R'•Co$_2$(CO)$_6$
toluene
70–80 °C, 4 h
O
R
R'

(32)

R = R' = H, 74%
R = Me, R' = H, 51%

R = Ph, R' = H, 57%
R = Ph, R' = Me, 32%

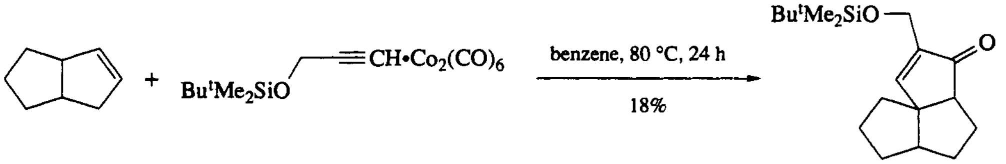
≡CH•Co$_2$(CO)$_6$
Bu$^t$Me$_2$SiO
benzene, 80 °C, 24 h
18%
Bu$^t$Me$_2$SiO
O

(33)

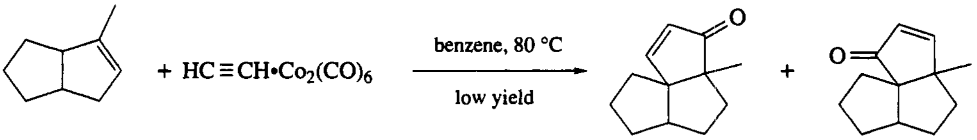
+ HC≡CH•Co$_2$(CO)$_6$
benzene, 80 °C
low yield
O
O

(34)

Regarding five-membered rings involving heteroatoms, 1-acetoxycyclopentene gives a single isolated product, although the conditions are such that the other regioisomer may not have survived (equation 35). Another case of alkene isomerization is presented in equation (36). Reaction from exclusively the internal double bond isomer again gives a single regioisomer; it is not known whether this results from the same factors controlling the reactions of other trisubstituted alkenes, or if this is another artifact arising from further chemistry under cycloaddition conditions.[16,25b]

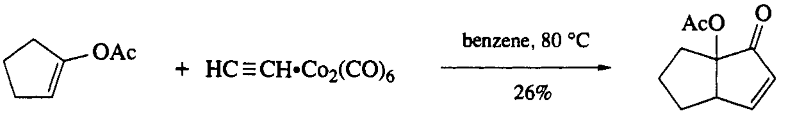
OAc
+ HC≡CH•Co$_2$(CO)$_6$
benzene, 80 °C
26%
AcO
O

(35)

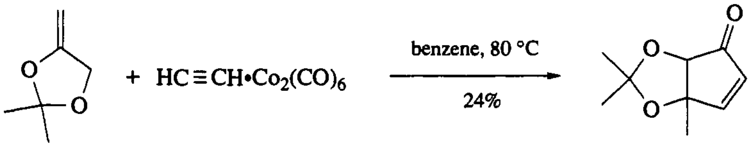
O
O
+ HC≡CH•Co$_2$(CO)$_6$
benzene, 80 °C
24%
O
O
O

(36)

Dihydrofurans have seen considerable use as substrates in the Pauson–Khand reaction. The parent compound reacts in excellent yield with acetylene, terminal and internal alkynes. Yields in this system respond very well to the use of catalytic reaction conditions (equation 4). Another unusual experimental modification has also been found by Pauson to be useful in this system: addition of tri-*n*-butylphosphine oxide nearly doubles the product yield in certain cases (equation 37). The role of the added substance is unclear. Addition of phosphine oxide does not always improve reaction efficiency; at this time there are no guidelines to indicate when its use might be beneficial. Substituted dihydrofurans give somewhat lower but still acceptable yields; the poor regioselectivity in unsymmetrical cases is the more significant difficulty with these substrates (equation 38).[14,25a,32]

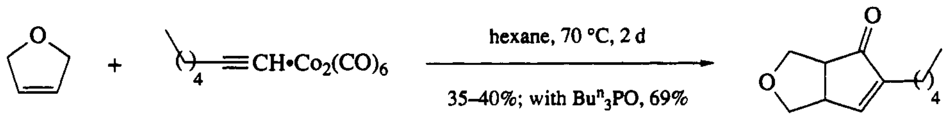
O
+
4
≡CH•Co$_2$(CO)$_6$
hexane, 70 °C, 2 d
35–40%; with Bu$^n{}_3$PO, 69%
O
O
4

(37)

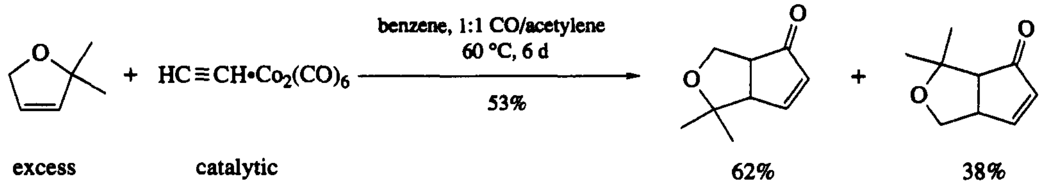

(38)

Alkenes in larger rings show acceptable reactivity in some cases but not others. For example, cycloheptene and cyclooctene give moderate yields of cyclopentenones upon reaction with phenylacetylene (equation 39), but none of the simple cycloalkenes reacts well with alkyl alkynes and cyclohexene itself is a very poor substrate.[20] Attachment of a 2-dimethylaminoethyl chain onto cyclohexene (*i.e.* homoallylic nitrogen) introduces useful reactivity (equation 40).[27] Dihydronaphthalene is also a usable substrate, perhaps due to reduced steric hindrance in the flattened ring. It displays the expected regioselectivity for a styrene analog (equation 41).[28] Cyclohexadienes do not give cyclopentenones directly under Pauson–Khand conditions. Instead, an apparently catalyzed Diels–Alder reaction takes place with the alkyne first, giving a bicyclo[2.2.2]octa-1,4-diene; this then participates in Pauson–Khand cycloaddition with additional alkyne (equation 42; Section 9.1.3.3). The product thus contains two molecules of starting alkyne, one of alkene and one of CO.[8]

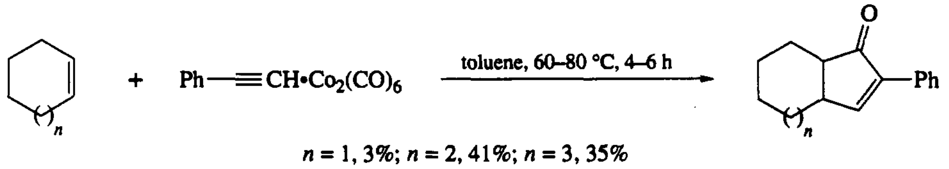

(39)

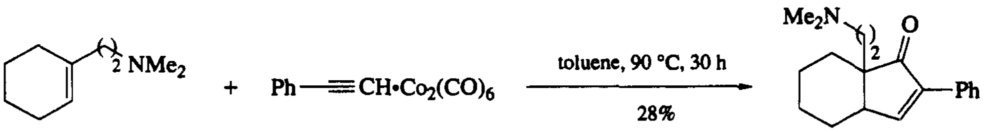

(40)

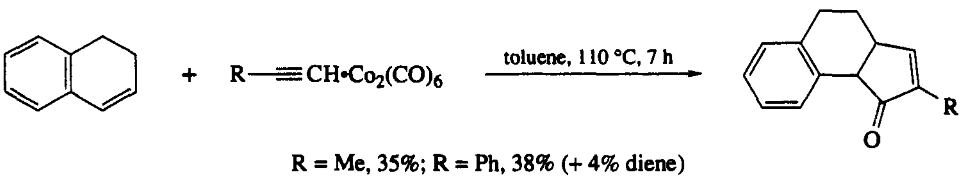

(41)

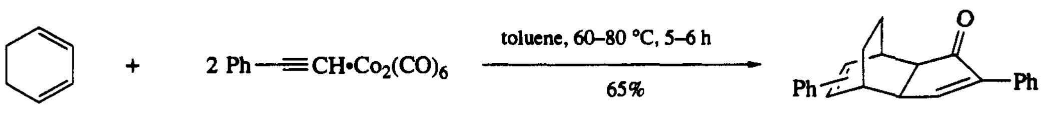

(42)

### 9.1.3.3 Reactions involving Bridged Bicyclic Alkenes: Regio- and Diastereo-selectivity

Five-membered ring alkenes contained in bridged bicyclic or polycyclic systems are by far the most extensively studied substrates for intermolecular Pauson–Khand reaction. Comprehensive surveys carried out by the Pauson group identified many of the key features of the process in these substrates.[6,12] Norbornene is nearly ideal, displaying such a wide scope of reactivity towards alkynes that it is usable as a test of the suitability of an alkyne as a Pauson–Khand substrate (equation 43).[15,24,33] Yields of cyclopentenones, all of which are formed with complete regioselectivity and *exo*-diastereofacial stereoselectivity, range for internal alkynes typically between 20 and 40%, and for terminal alkynes from 30 to >70% using catalytic conditions. Monoaryl substitution on the double bond is tolerated to a certain extent as well (equation 44). Reactivity of norbornenones and norbornenols has been discussed (equations 13 and 14).[22]

Both double bonds in norbornadiene are similarly reactive, so yields of tricyclic enones are limited by continued reaction of the initial product.[6,12,24] Use of a large excess of the diene is a partial remedy. This

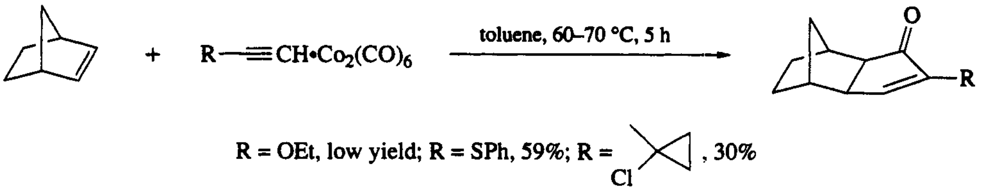
+
R—≡CH•Co₂(CO)₆
toluene, 60–70 °C, 5 h
O
R
R = OEt, low yield; R = SPh, 59%; R =
Cl
, 30%

(43)

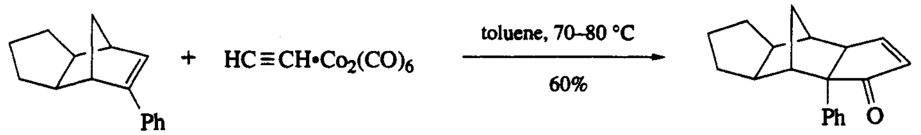
Ph
+ HC≡CH•Co₂(CO)₆
toluene, 70–80 °C
60%
Ph O

(44)

substrate is unique in affording small amounts of *endo*-fused products in some cases, probably as a result of reduced steric differentiation between the faces of the double bond (equation 45).[34] When cycloaddition is permitted to proceed at the second double bond, the result is low yield but regioselective formation of *anti*-diketones (equation 46). Chemoselectivity in systems containing less strained double bonds has been mentioned (equation 32);[12] this is also observed in systems with less electron rich double bonds (equation 47). Among heterocyclic analogs, 2,3-diaza-5-norbornene shows Pauson–Khand reactivity, but 7-oxanorbornadiene deoxygenates to an aromatic system.[14,15]

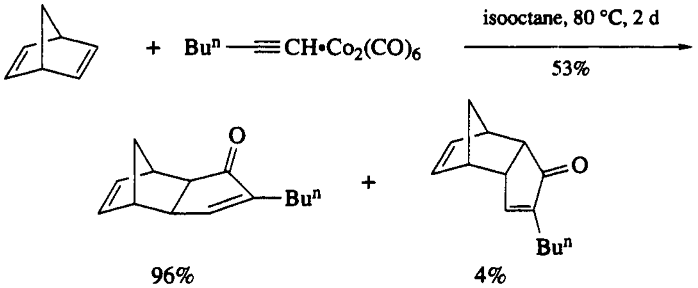
+ Buⁿ—≡CH•Co₂(CO)₆
isooctane, 80 °C, 2 d
53%
O
Buⁿ
+
O
Buⁿ
96%
4%

(45)

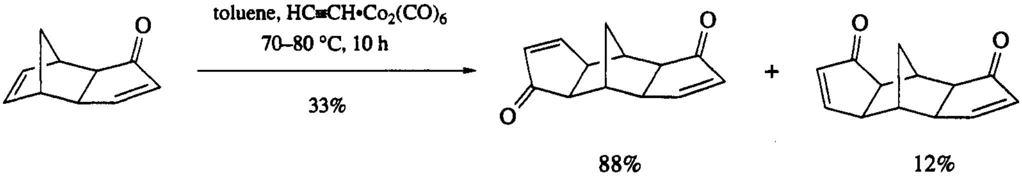
O
toluene, HC≡CH•Co₂(CO)₆
70–80 °C, 10 h
33%
O
O
+
O
O
88%
12%

(46)

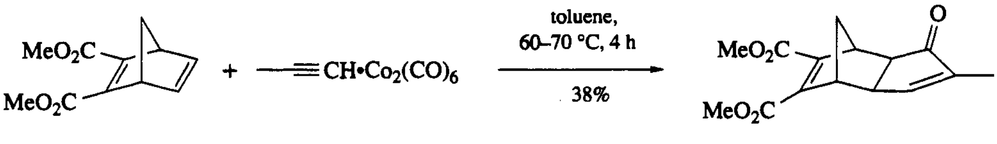
MeO₂C
MeO₂C
+ —≡CH•Co₂(CO)₆
toluene,
60–70 °C, 4 h
38%
O
MeO₂C
MeO₂C

(47)

As bridged dihydrofuran analogs, 8-oxabicyclo[3.2.1]oct-6-enes are also useful substrates. Only low to moderate regioselectivity is observed in the cycloaddition of bridgehead substituted examples of these compounds (equation 48). In this system Pauson–Khand reactivity is eliminated by either further substitution on the double bond or even a bulky bridgehead substituent.[17] The analog containing an amide nitrogen in place of the oxygen bridge has also been cyclized successfully (equation 49).[35]

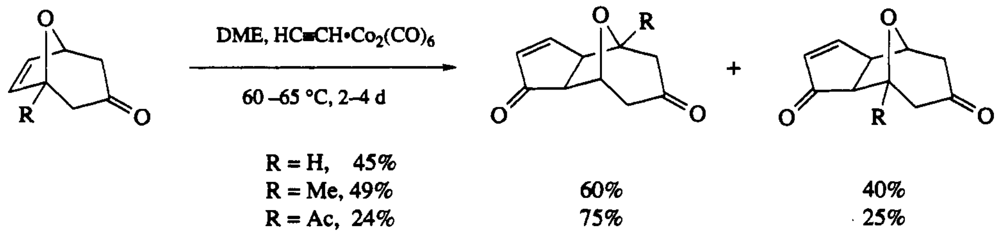
O
R
O
DME, HC≡CH•Co₂(CO)₆
60–65 °C, 2–4 d
O R
O
O
+
O
O
R
O
R = H, 45%
R = Me, 49%
R = Ac, 24%
60%
75%
40%
25%

(48)

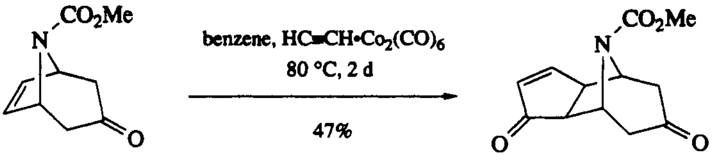
CO2Me
N
O
benzene, HC≡CH•Co2(CO)6
80 °C, 2 d
47%
CO2Me
N
O
O

(49)

Bicyclo[2.2.2]octenes are good to excellent substrates, quite comparable to norbornene-based systems (equation 50).[8]

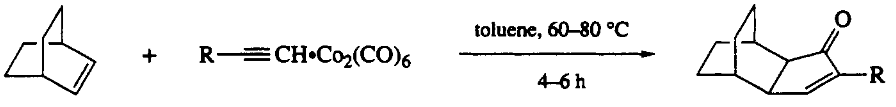
+
R—≡CH•Co2(CO)6
toluene, 60–80 °C
4–6 h
O
R

(50)

R = H, 50%; R = Me, 19%; R = Ph, 34%

### 9.1.3.4 Synthetic Applications

Numerous synthetic applications of the intermolecular Pauson–Khand reaction have been reported. Pauson has reported a number of very direct applications of cycloadditions of ethylene in the synthesis of prostanoids and jasmone analogs (*e.g.* equations 15 and 16).[23,24,36a] This is a reliable entry to 2-substituted cyclopentenones. The suitability of cyclopentene and dihydrofuran as substrates has permitted the extension of this work to the preparation of still further varieties of prostaglandin analogs (*e.g.* equations 27 and 51).[36b] Simple 4,5-disubstituted 2-cyclopentenones are not as directly accessible, but may be prepared from the cycloaddition products of norbornadiene (equation 45). A sequence of conjugate addition followed by retro-Diels–Alder reaction affords the product (Scheme 5).[34] Dihydrofuran cycloadditions have been used by Billington in the syntheses of the antibiotic methylenomycin B (Scheme 6),[26] as well as cyclomethylenomycin A (synthetic precursor to the antibiotic methylenomycin A), cyclosarkomycin (precursor to the antitumor agent sarkomycin)[10] and the iridoid Japanese hop ether.[32]

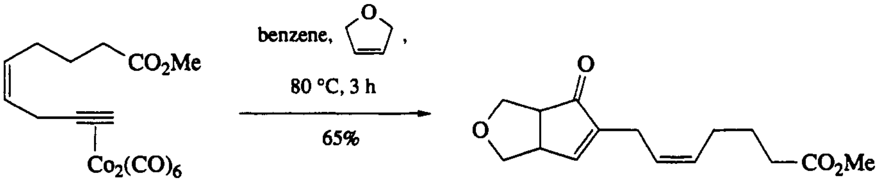
CO2Me
Co2(CO)6
benzene,
O
80 °C, 3 h
65%
O
O
CO2Me

(51)

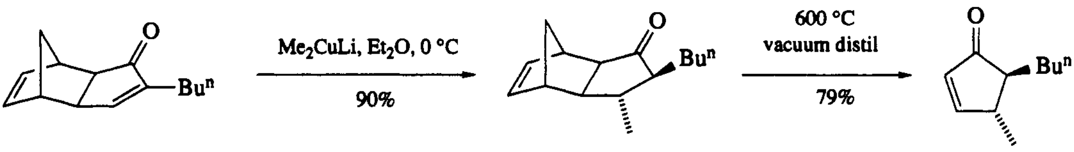
O
Bun
Me2CuLi, Et2O, 0 °C
90%
O
Bun
600 °C
vacuum distil
79%
O
Bun

(from equation 45)

Scheme 5

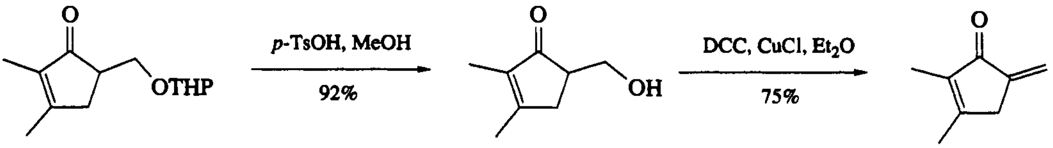
O
OTHP
p-TsOH, MeOH
92%
O
OH
DCC, CuCl, Et2O
75%
O

(from equation 18)

Scheme 6

Variations on the hydrazulene skeleton have been approached *via* the Pauson–Khand reaction, several with high regio- and diastereo-selectivity. Pauson's cycloadditions of cycloheptene provided the first entries but were limited in scope and efficiency (equation 39).[20] Several synthetic equivalents of cycloheptenes displaying greater reactivity include 8-oxa- and 8-aza-bicyclo[3.2.1]oct-6-enes (equations 48 and

49),[17] and bicyclo[3.2.0]hept-6-enes (equation 7). Two syntheses of the sesquiterpene furanether B have been completed, based on cycloaddition reactions in the 8-oxa series (Scheme 7).[37] The bicyclo[3.2.0]heptenes provide especially versatile access to systems transformable into both the guaianolide and pseudoguaianolide natural product structural types (Scheme 8).[19]

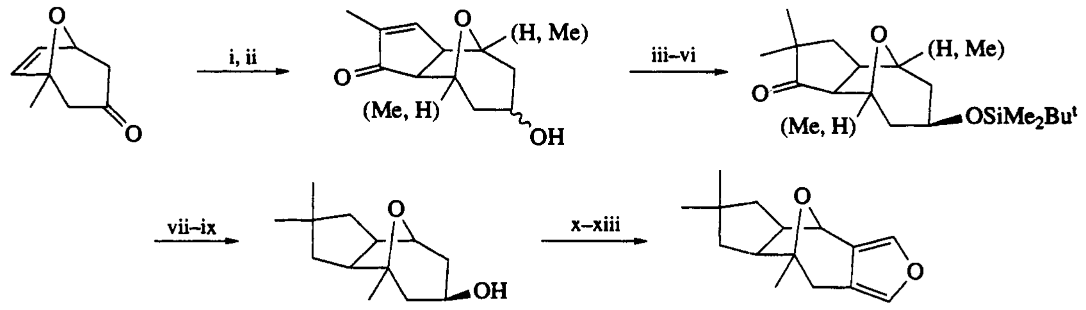

i, LiAlH$_4$, Et$_2$O (96%); ii, MeC≡CH•Co$_2$(CO)$_6$, benzene, 65–70 °C, 2 d (75%); iii, separate; iv, Bu$^t$Me$_2$SiCl, imidazole, DMF (98%); v, H$_2$, 5% Pd/C, EtOAc, MeOH (100%); vi, MeI, KOBu$^t$, Bu$^t$OH, benzene (100%); vii, LiAlH$_4$, Et$_2$O (100%); viii, NaH, then CS$_2$, then MeI, THF (100%); ix, Bu$^n_3$SnH, AIBN, toluene, 110 °C (50%); x, PCC, CH$_2$Cl$_2$; xi, EtOCHO, NaOMe, benzene (≈50%); xii, Bu$^n$SH, *p*-TsOH, benzene, 80 °C (100%); xiii, Me$_3$S$^+$MeSO$_4^-$, CH$_2$Cl$_2$, NaOH, H$_2$O, then HCl, THF (46%)

**Scheme 7**

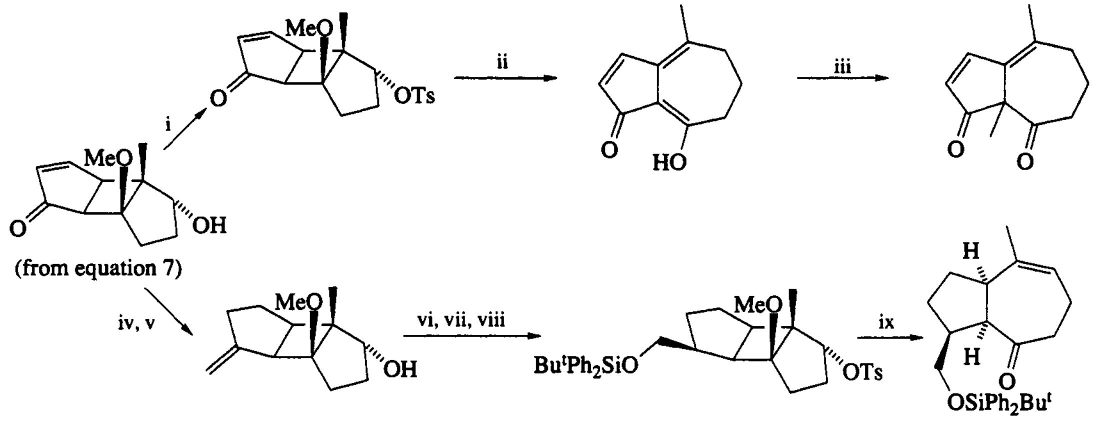

i, *p*-TsCl, pyridine, 0 °C (≈100%); ii, NaHCO$_3$, CaCO$_3$, pyridine, MeOH, H$_2$O, 65 °C (90%); iii, MeI, K$_2$CO$_3$, acetone, 55 °C (82%); iv, H$_2$, 5% Pd/C, MeOH (98%); v, Ph$_3$P=CH$_2$, Ph$_3$PMe$^+$ Br$^-$, DMSO, 60 °C (88%); vi, BH$_3$•SMe$_2$, THF, then NaOH, H$_2$O$_2$, 60 °C (90%); vii, Bu$^t$Ph$_2$SiCl, Et$_3$N, DMAP (76%); viii, *p*-TsCl, pyridine, 0 °C (94%); ix, NaHCO$_3$, CaCO$_3$, pyridine, MeOH, H$_2$O, 65 °C (72%)

**Scheme 8**

In a novel combination of Pauson–Khand cycloaddition with vinylcyclopropane chemistry, de Meijere has described an entry to linearly fused triquinanes beginning with cyclopropylalkynes. Cyclopentenone formation has been carried out with a variety of substitution patterns on the cyclopropane, and moderate yields achieved with both norbornene and cyclopentene as substrates. Thermal vinylcyclopropane–cyclopentene rearrangement of the cycloaddition products leads to the final tricyclic system (Scheme 9).[33,38]

Serratosa's entry into the angularly fused triquinanes, mentioned earlier (equation 33), succeeds for terminal but not internal propargyl ethers. The *in situ* alkene isomerization that precedes cycloaddition renders synthesis of the bicyclo[3.3.0]oct-1-ene isomer unnecessary, making this a most direct synthetic process in spite of the modest yields.[31]

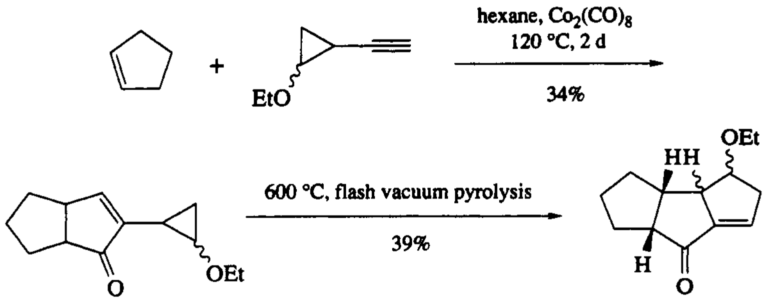

**Scheme 9**

## 9.1.4 INTRAMOLECULAR PAUSON–KHAND REACTION: DIASTEREOSELECTIVITY

### 9.1.4.1 Reactions involving Acyclic All-carbon Enynes

Enynes in which three or four atoms separate the double and triple bonds cyclize upon complexation to $Co_2(CO)_8$ and subsequent heating to give bicyclic enones (equation 52). With the exception of slightly elevated temperatures the conditions required are no different than those of the stoichiometric procedure described earlier for reactive substrates in intermolecular Pauson–Khand reactions. The intramolecular cycloaddition cannot in general be carried out under catalytic conditions. Hex-1-en-5-yne, which would give a four-membered ring upon intramolecular cycloaddition, instead undergoes alkyne trimerization exclusively.[39] The most extensively studied systems are those derived from hept-1-en-6-yne, as the products, bicyclo[3.3.0]oct-1-en-3-ones, are useful in the synthesis of numerous cyclopentane-based polycyclics.

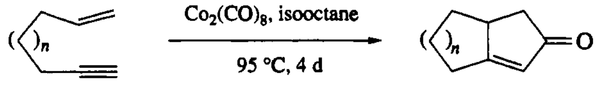

(52)

$n = 1$, 31%; $n = 2$, 35–40%

Considerable information on the effects of substitution on these reactions has been collected from the work of Magnus, Hua and Serratosa. Magnus carried out the first systematic examinations of the factors that contribute to diastereoselectivity in these reactions, and all three workers have compiled results bearing on the effects of substitution on yields and reaction rates. Toleration and effect of substitution in these cyclizations is a function of position. Indeed, the detailed effects of substitution on Pauson–Khand reactivity have been readily accommodated by a mechanism that is in all important aspects identical to that previously described.[40] As alkene insertion takes place into a cobalt–carbon bond of the enyne–hexacarbonyldicobalt complex, pseudodiaxial interactions develop between any substituent on the terminus of the alkyne (C-7) and those substituents at the allylic (C-3) and propargylic (C-5) positions of the original enyne that are positioned to end up on the *endo* face of the product. Thus the insertion is preferentially directed to place the larger of these substituents in *exo* orientations. The larger these substituents are, the greater the diastereoselectivity obtained (Schemes 10 and 11). It should be noted that later work of Serratosa suggests the operation of an additional process that may contribute to diastereoselectivity in the case of labile propargyl substituents (see Section 9.1.4.3).

Unprotected alcohols occasionally interfere with the intramolecular reaction. Although the *t*-butyldimethylsilyl protecting group has been most frequently used in these situations, it too is occasionally unsuitable, in which case the methoxymethyl (MOM) group is preferred.

Comparison of equation (52) with Schemes 10 and 11 suggests that substitution at C-4 confers substantial benefit in terms of both yield and reaction time. This is most likely a result of a *gem*-dialkyl effect in which conformations placing the alkene and complexed-alkyne ends of the system in close proximity are rendered enthalpically more favorable by increasing substitution on the intervening atoms. The reduced contribution of $\Delta H^{\ddagger}$ to $\Delta G^{\ddagger}$ associated with alkene complexation allows it to better compete with intermolecular side reactions (*i.e.* trimerization of the otherwise more reactive alkyne moieties). Hua has made similar observations in simpler systems (equation 53).[41] No stereocontrol at C-4 is available, however, the position being too remote from the reaction centers (equation 54).[42]

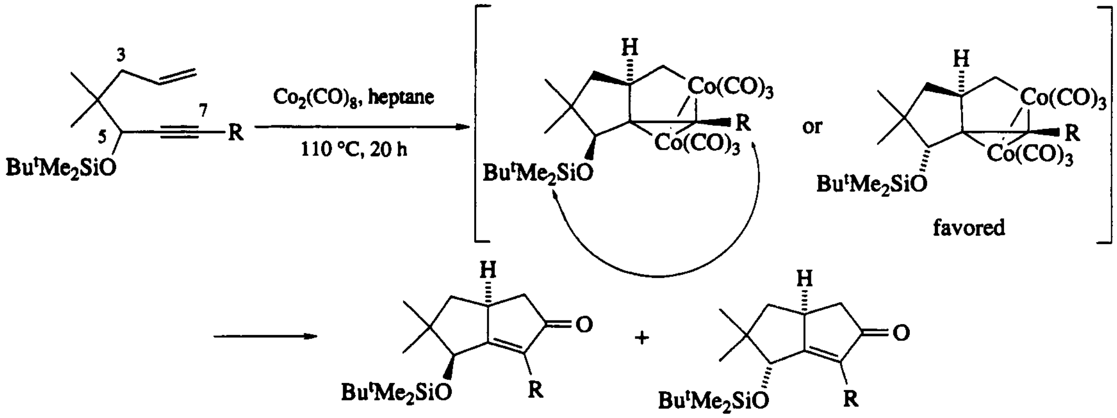

| | | |
|---|---|---|
| R = Me, 65% | 23% | 77% |
| R = $Me_3Si$, 79% | 4% | 96% |

**Scheme 10**

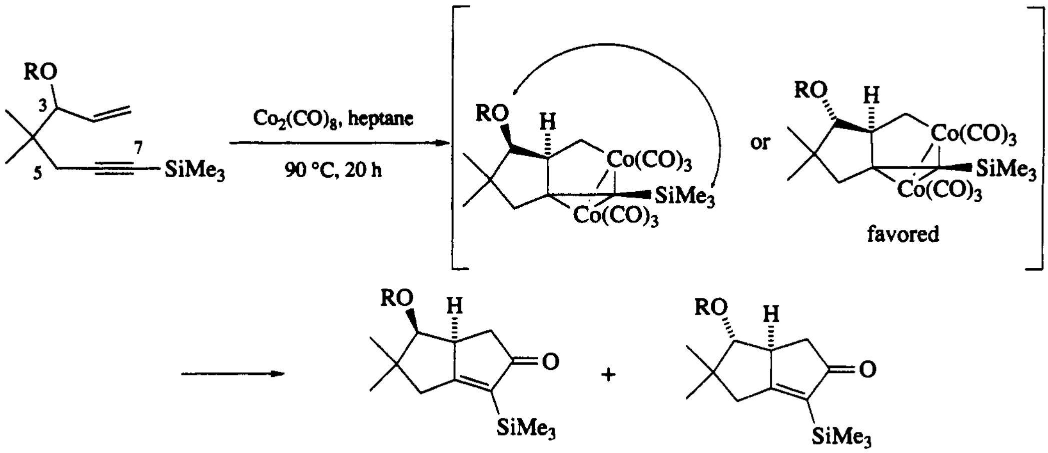

| | | |
|---|---|---|
| R = H, 25% | 28% | 72% |
| R = MOM, 68% | 0% | 100% |

**Scheme 11**

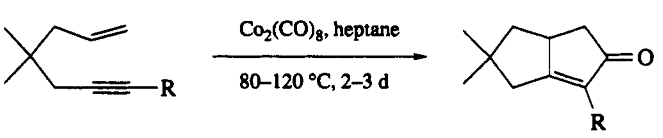

(53)

R = H, 58%; R = $CH_2OSiMe_2Bu^t$, 65%

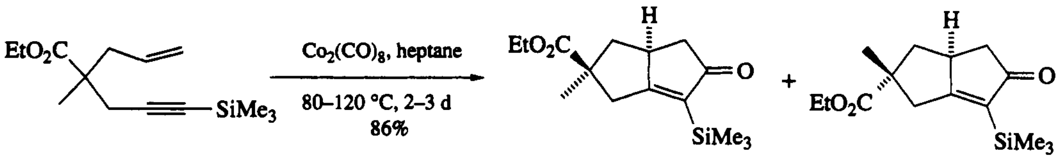

(54)

45% 55%

Recent work of Serratosa has identified limitations in substitution tolerance when substituents are lacking at C-4.[43] The formation of even modest yields of cycloaddition products require more forcing conditions, and double bond reduction becomes a significant process. Surprisingly, *gem*-dimethyl groups at C-1 are accommodated (equation 55). Without the *gem*-dialkyl assistance from groups at C-4, however, propargyl (C-5) substitution now becomes a liability, especially in conjunction with substitution at the alkyne terminus (equation 56). Diastereoselectivity was not determined in these low yield reactions, although mixtures of stereoisomers were obtained in each case.

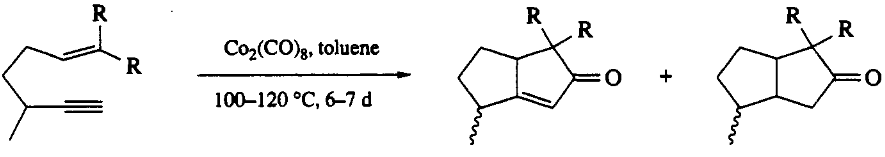
R
R
$Co_2(CO)_8$, toluene
100–120 °C, 6–7 d
R
R
O
+
R
R
O

(55)

| | | |
|---|---|---|
| R = H, 30% | 83% | 17% |
| R = Me, 23% | 87% | 13% |

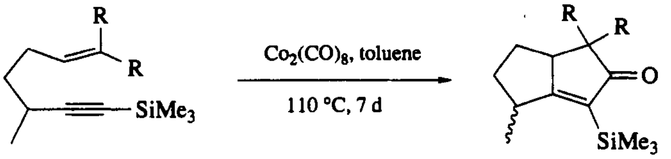
R
R
SiMe3
$Co_2(CO)_8$, toluene
110 °C, 7 d
R
R
O
SiMe3

(56)

R = H, 15%; R = Me, 0%

### 9.1.4.2 Reactions involving Acyclic Heteroatom-containing Enynes

The ready access of allyl propargyl ethers from $Co_2(CO)_6$-complexed propargyl cations, whose chemistry has been extensively developed by Nicholas,[44] has made them the most frequently studied heteroatom-containing substrates for intramolecular Pauson–Khand cycloaddition. Initial work by Billington established the feasibility of these systems as cycloaddition substrates, albeit in only moderate yields (equation 57).[45] The collaboration of Smit and Caple has also combined even more extensively developed versions of Nicholas chemistry with Pauson–Khand cycloaddition to access novel heteropolycyclics (Scheme 12).[46] Schreiber has demonstrated still another direction of development of Nicholas chemistry. Incorporation of an alkyne in a medium-sized ring is achieved by exploiting the 'bending' of the triple bond by cobalt complexation in the course of alkylative ring formation *via* the stabilized propargyl cation complex. The resulting system is then capable of inter- as well as intra-molecular Pauson–Khand cycloaddition (Scheme 13).[47]

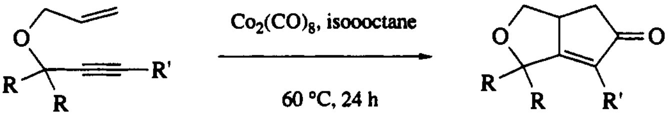
O
R'
R
R
$Co_2(CO)_8$, isooctane
60 °C, 24 h
O
O
R
R
R'

(57)

R = R' = H, 14%; R = Me, R' = H, 29%; R = H, R' = Me, 41%

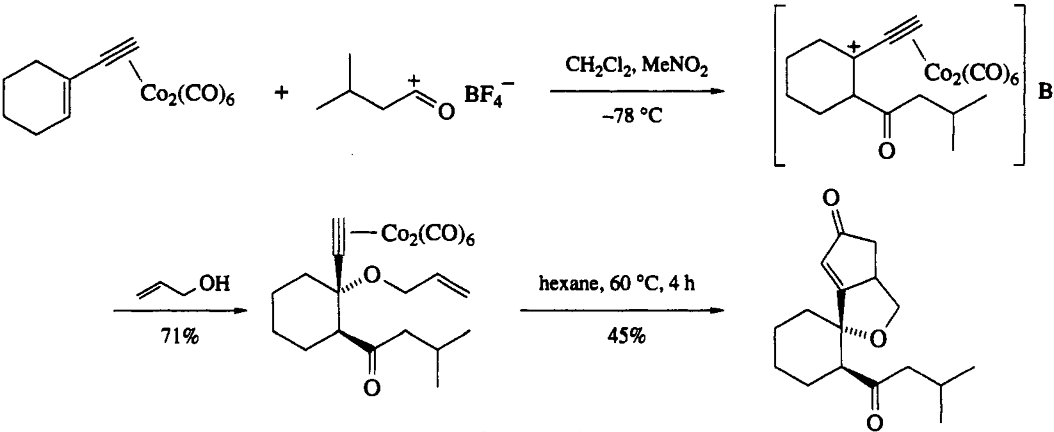
$Co_2(CO)_6$
+
+
O
$BF_4^-$
$CH_2Cl_2$, $MeNO_2$
–78 °C
+
$Co_2(CO)_6$
O
$BF_4^-$
OH
71%
$Co_2(CO)_6$
O
O
hexane, 60 °C, 4 h
45%
O
O
O

Scheme 12

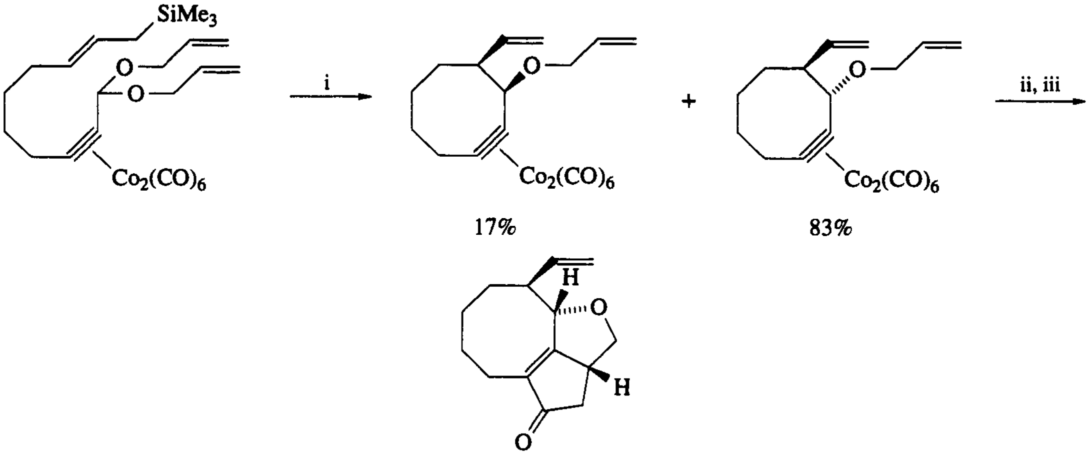

i, $BF_3 \cdot Et_2O$, $CH_2Cl_2$, –78 °C to 25 °C; ii, separate and purify *trans* isomer; iii, CO, PhH, 60 °C, 4 h (85%)

**Scheme 13**

In the course of work in the Smit and Caple groups the remarkable discovery was made that adsorption of the cobalt-complexed enyne ether onto silica gel enormously facilitates intramolecular Pauson–Khand cycloaddition. Reactions that in solution require 24 h heating at temperatures ranging from 60 to ≥100 °C may be carried to completion in under 2 h by gentle heating of the dry silica gel adsorbate under oxygen or air (equation 58).[48] Apparently adsorption to silica favors reactive conformations in a manner similar to that of bulky substitution, facilitating cycloaddition by means of a novel variant of the *gem*-dialkyl effect. As the examples show, the process is remarkably tolerant of substitution throughout the molecule, although bulky groups on the alkyne terminus do not appear to have been examined. Stereochemical aspects of the process are not clear from the published examples, although reasonable expectations would parallel the findings of Magnus in the all-carbon systems described previously: a tendency for substituents in allyl or propargyl positions to end up *exo* relative to the newly formed ring fusion. The technique is also applicable to ordinary enynes containing polar substituents and enynes containing heteroatoms other than oxygen (equations 59 and 60). Indeed, it is now known that heteroatoms, while helpful, are not necessary: even simple intermolecular cycloadditions of hydrocarbon substrates have been found to benefit from adsorption on various dry supports. Sonication also provides some acceleration, allowing reactions to be carried out at still lower temperatures (*e.g.* ≤45 °C).[25a,49]

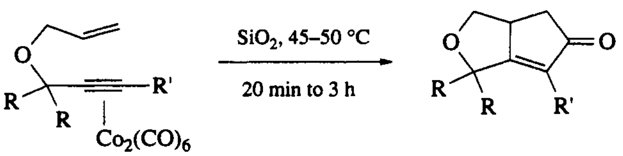

(58)

R = R' = H, 58%; R = Me, R' = H, 75%; R = H, R' = Me, 60%

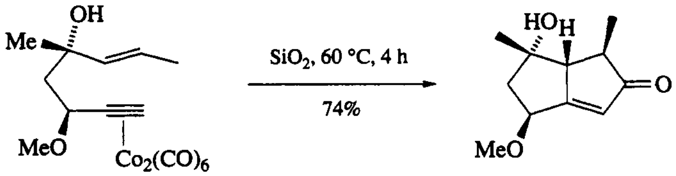

(59)

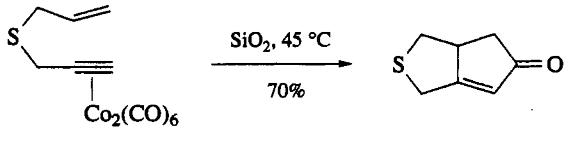

(60)

In the 'dry' Pauson–Khand reaction system oxygen is necessary in order to prevent hydrogenolysis of the allylic carbon–oxygen bond in the product. This process is presumably effected by hydridocobalt species whose formation is facilitated by adsorption, although the details are not known. The oxygen may serve simply to scavenge adsorbed cobalt hydride species. In any event, Smit has demonstrated that the hydrogenolysis process may be selectively promoted if desired by carrying out the reaction under 'dry' conditions on alumina under an argon atmosphere. This results in 3-alkyl-4-(hydroxyalkyl)cyclopentenones directly, in yields consistently in the 70% range (equation 61).[50]

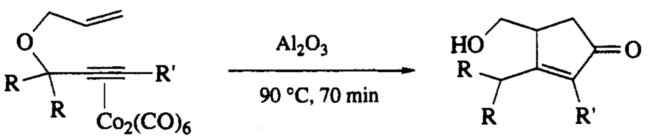

(61)

R = R' = H, 70%; R = Me, R' = H, 69%; R = H, R' = Me, 73%

### 9.1.4.3 Reactions involving Cyclic Enynes

As might be expected from comparable intermolecular situations, incorporation of the alkene partner in a ring of appropriate size is compatible with intramolecular Pauson–Khand reaction. However, steric and functional group considerations are essential in order to achieve acceptable results. To date work in this area has been limited to cyclopentenes containing pendant alkynes. A variety of 1-(4-pentynyl)cyclopentenes and 3-(3-butynyl)cyclopentenes have been examined by both ourselves and the Serratosa group, and a reasonably useful framework for determining the applicability of the reaction has emerged. Pauson–Khand cycloaddition of 1-(4-pentynyl)cyclopentene itself gives rise to the angularly fused triquinane (tricyclo[6.3.0.0.$^{1,5}$]undecane) ring system, the basis of a number of compounds of recent synthetic interest (see Section 9.1.4.4). This substrate, containing a trisubstituted alkene partner, is in fact already at the substitution limit for useful reactivity: its derivative containing additional methyl substitution and therefore a tetrasubstituted double bond gives only trace amounts of enone product (equation 62).[51]

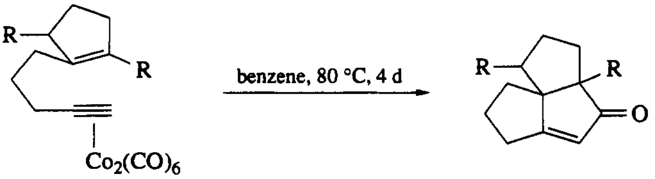

(62)

R = H, 35%; R = Me, ≈0%

The reaction has been shown to benefit from *gem*-dialkyl acceleration and to exhibit useful diastereoselectivity in the cycloaddition of an appropriately substituted analog (Scheme 14).[52] In this case the twist about the newly formed spiro center generates a 1,3-pseudodiaxial interaction between the propargyl methylene and the *endo* group at the C-5 allylic position on the cyclopentene ring, thus favoring the formation of the *exo*-methyl stereoisomer. This stereocontrol is compromised by additional substitution. The (*RS*)/(*SR*) diastereomer of an alkoxy-substituted analog gives a mixture of *endo*- and *exo*-methyl-substituted enones in which the latter no longer predominates (Scheme 15). The cause of this effect is not clear, although the alkoxy-substituted products are unstable under the reaction conditions and the observed ratio is likely not to be the kinetic one. The situation with the (*RR*)/(*SS*) diastereomer is more straightforward: the *endo*-methyl product forms exclusively. In this situation the *exo* isomer experiences a 1,3-interaction between the methyl and the methoxymethyl group that is far more severe than the *endo*-methyl–propargyl methylene interaction that controls its deoxygenated analog. In these latter systems it was found that protection of the allylic hydroxy group was essential for Pauson–Khand reactivity to be observed.

Trimethylsilyl substitution at the alkyne terminus totally eliminates cycloaddition reactivity in these systems.[53] Examination of possible structures of Pauson–Khand intermediates reveals steric interactions involving this silyl group occurring at both the alkene complexation and insertion stages. The analysis in Scheme 16 shows four possible complexation modes of the alkene. Complexation *cis* to the second cobalt appears to be disfavored by steric interactions involving the ligands on this cobalt with allylic groups (Scheme 16, structures **3** and **4**). The alternative, complexation *trans* to the second cobalt, can occur from either pseudoboat (Scheme 16, structure **5**) or pseudochair (Scheme 16, structure **6**) conformations of the side chain, and involves opposite faces of the alkene. The latter conformation, which also experiences less steric congestion involving allylic groups with the alkyne terminus, is probably the one favored in

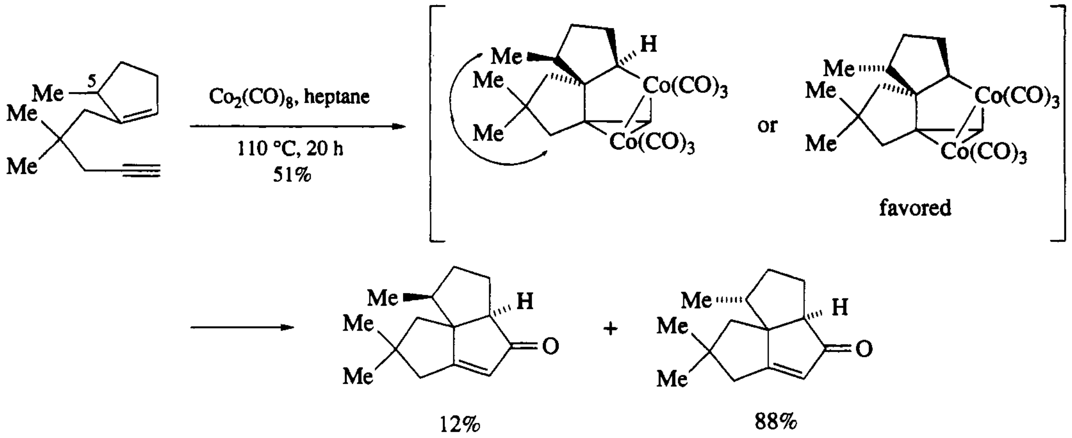

Me
Me
5
Me
Co2(CO)8, heptane
110 °C, 20 h
51%
Me
Me
Me
H
Co(CO)3
Co(CO)3
or
Me
Me
Me
Co(CO)3
Co(CO)3
favored
Me
Me
Me
H
O
+
Me
Me
Me
H
O
12%
88%

**Scheme 14**

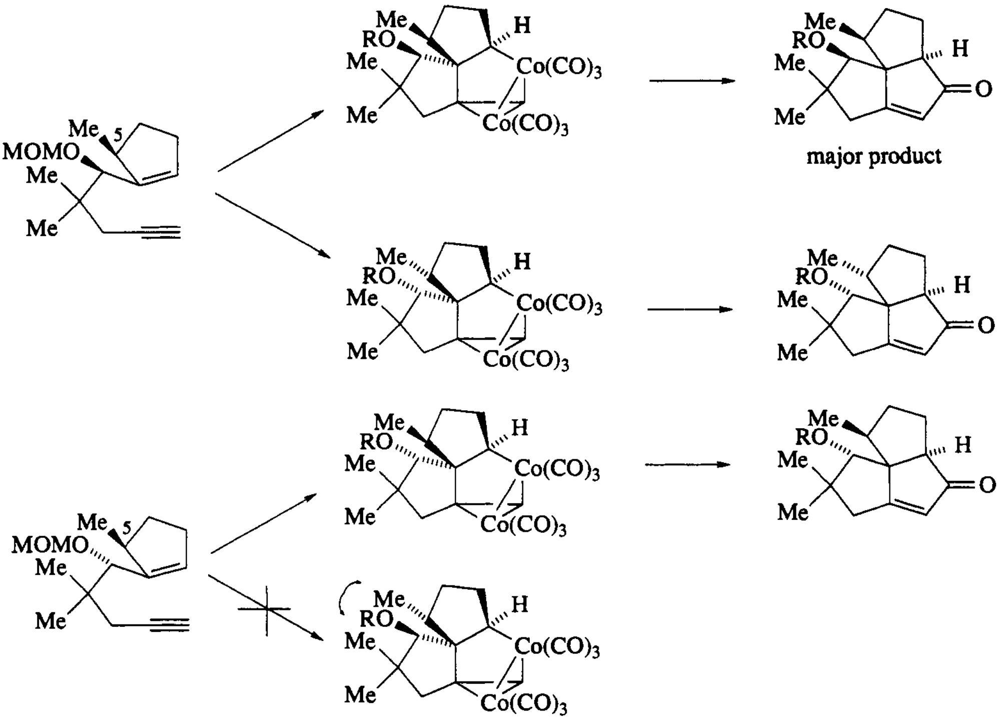

Me
MOMO
Me
5
Me
Me
RO
Me
Me
H
Co(CO)3
Co(CO)3
Me
RO
Me
Me
H
O
major product
Me
RO
Me
Me
H
Co(CO)3
Co(CO)3
Me
RO
Me
Me
H
O
Me
MOMO
Me
5
Me
Me
RO
Me
Me
H
Co(CO)3
Co(CO)3
Me
RO
Me
Me
H
O
Me
RO
Me
Me
H
Co(CO)3
Co(CO)3

Reagent: $Co_2(CO)_8$, benzene, 80 °C, 18–22 h, 30%

**Scheme 15**

the observed cycloaddition when R = H. The structure, (**8**), shown at the bottom of the scheme, with R *cis* to the newly formed ring fusion and *trans* to the cyclopentene ring originally present, is the likely intermediate (compare Schemes 10, 11, 14 and 15). Evidently, even the relatively unimportant-looking steric interaction leading to this intermediate is sufficient to eliminate useful reactivity when R = TMS. In any event this establishes that practical intramolecular reactivity of trisubstituted alkenes is limited to terminal alkynes and, further, suggests that a similar restriction might also apply to simple acyclic hept-1-en-6-ynes containing an additional substituent at C-2. Such situations do not appear to have been examined as yet.

Similar intramolecular cycloadditions of cyclic alkenes containing alkynyl substitution have been explored by Serratosa in the 3-(3-butynyl)cyclopentene series. The product in this case is a triquinacene derivative, a tricyclo[5.2.1.$0^{4,10}$]decane. Since the targets in Serratosa's studies required functionalization of all three five-membered rings, all cycloaddition substrates utilized contained varying degrees of sub-

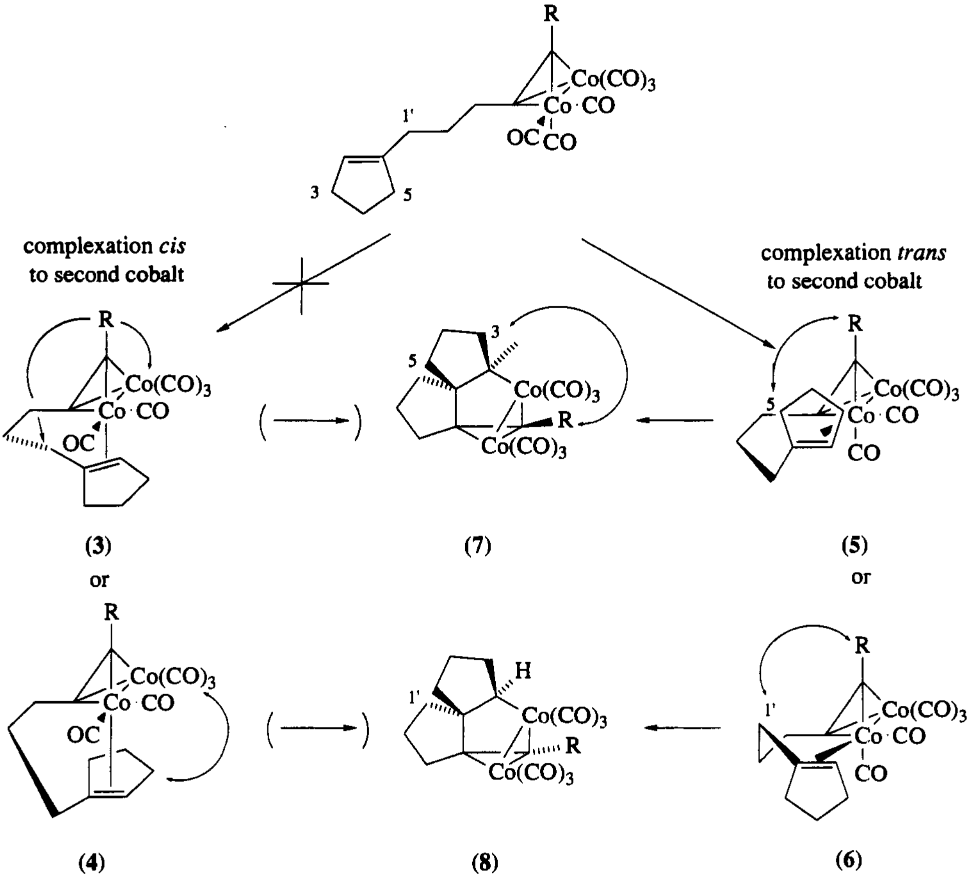
R
1'
3
5
complexation *cis* to second cobalt
complexation *trans* to second cobalt
(3)
or
(4)
(7)
(8)
(5)
or
(6)

Scheme 16

stitution. In this class of substrate the alkene is effectively *cis*-1,2-disubstituted, and therefore it may complex to a cobalt in an orientation that avoids steric interaction with a substituent on the alkyne terminus. Substrates in which the alkyne is not terminally substituted undergo cycloaddition in variable yields.[54] The reaction also tolerates unsubstituted hydroxy functionality when carried out under 'dry' (Smit–Caple) conditions (Scheme 17).

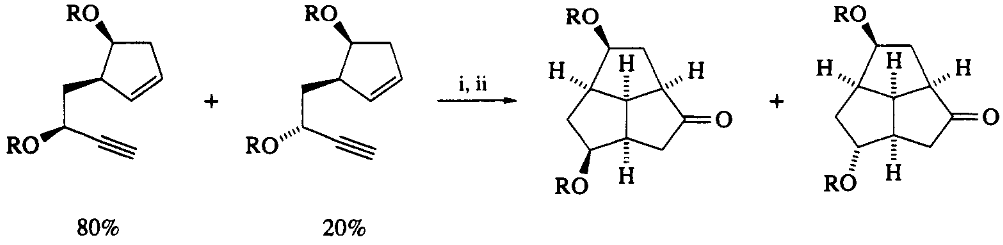

| *R* | *Total yield* | | |
|---|---|---|---|
| Bn | 60% | 70% | 30% |
| $Bu^tMe_2Si$ | various | 78% | 22% |
| H | 16% | – | – |

R = Bn: i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h; ii, $H_2$, 10% Pd/C, EtOH, $Et_3N$

R = $Bu^tMe_2Si$: i, $Co_2(CO)_8$, isooctane, 160 °C, 3 d; ii, $H_2$, 10% Pd/C, EtOH, $Et_3N$

R = H: i, $Co_2(CO)_8$, benzene, then $SiO_2$, remove solvent, 120 °C, 2 h; ii, $H_2$, 10% Pd/C, EtOH

Scheme 17

That the apparent changes in diastereomer ratio between reactants and products shown in the above examples were significant was confirmed by the results of cycloadditions of silyl-substituted alkyne analogs. In these cases only a single product, with the opposite stereochemistry to the dominant isomer in the examples above, is formed (equation 63). This result plus the high chemical yield require that a mechanism for isomerization be operative. Serratosa and coworkers proposed that the diastereomer that would lead to the unobserved *endo*-5-alkoxy isomer is rendered completely unreactive towards cycloaddition by steric interference from the silyl group. Instead, ionization of the propargylic leaving group, facilitated by the strong stabilization imparted to the propargylic cation by complexation to cobalt, allows the center to isomerize to the diastereomeric precursor to the 5-*exo* product, which then forms readily.[55] This result is of interest in the context of Magnus' earlier results (*e.g.* Scheme 10). In those systems the substrate contains only a single stereocenter and is racemic. Its isomerization merely interconverts enantiomers and therefore is an 'invisible' process. However, substrates with a second stereocenter (*e.g.* equation 59) may be worth reexamination for effects of this isomerization, and future applications of this chemistry that aim towards the preparation of optically active enones from optically pure substrates will face obvious difficulties if isomerization at a labile propargyl stereocenter cannot be prevented.

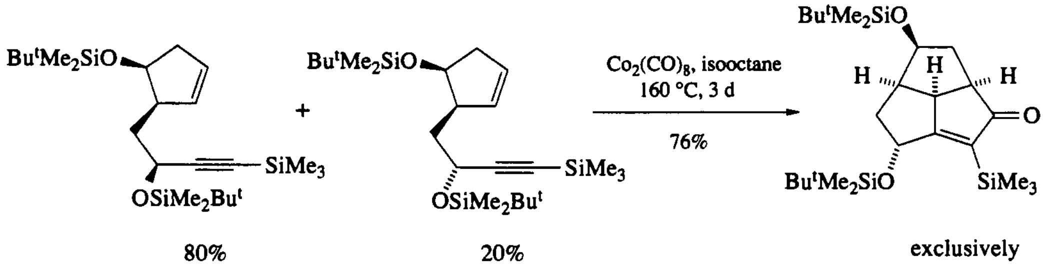

(63)

### 9.1.4.4 Synthetic Applications

Magnus was the first to develop extensive synthetic applications of the Pauson–Khand preparation of the bicyclo[3.3.0]oct-1-en-3-one system. His efforts amply demonstrate the degree to which the high level of functionality in the Pauson–Khand products can be directly utilized in building more complex structures. A formal synthesis of the antitumor sesquiterpene coriolin illustrates a very efficient sequence for construction of the third ring in the linearly fused triquinane series in the presence of considerable functionality (Schemes 10 and 18).[40a] A synthesis of the related triquinane hirsutic acid utilizes the observation that the proper stereochemical relationship between the substituents at C-7 and the ring-fusion carbon (C-5) of the bicyclo[3.3.0]oct-1-en-3-one system, while not controllable in the cycloaddition reaction itself, may be readily established by acid- or base-catalyzed equilibration (equation 54 and Scheme 19).[42]

In a short and completely diastereoselective synthesis of the unusual tetracyclic natural product quadrone, Magnus was able to minimize an interfering hydrogenolysis problem involving the propargylic ether by the addition of a hindered pyridine base, which presumably scavenges highly acidic cobalt hydride species (equation 64). In contrast, addition of a phosphine oxide only exacerbated the problem.[56] Note that the three syntheses just described illustrate diastereocontrol strategies for every position around the bicyclic enone system with the exception of the saturated α-carbon (C-4). Both Magnus and Mulzer have described stereoselective synthesis of optically active carbocycline analogs.[57,58] Magnus derived

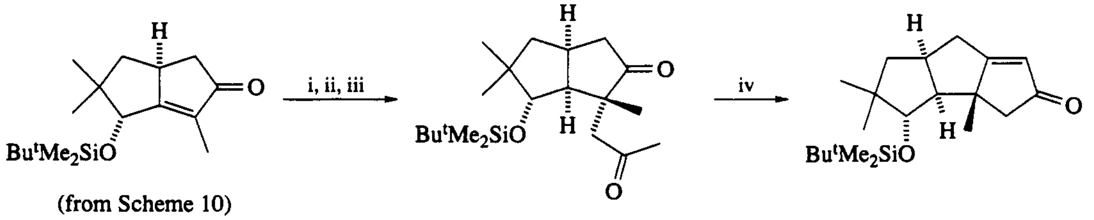

i, $H_2$, 10% Pd/C, EtOH (92%); ii, NaH, allyl bromide, DME (79%);
iii, $O_2$, $PdCl_2$, CuCl, DMF (64%); iv, Bu$^t$OK, Bu$^t$OH (74%)

Scheme 18

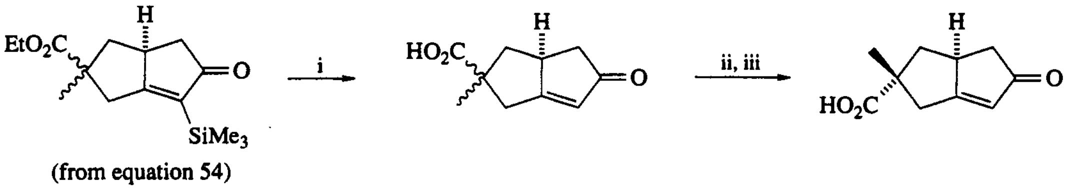
H
EtO2C
O
SiMe3
(from equation 54)
i
H
HO2C
O
ii, iii
H
HO2C
O

i, $MeSO_3H$, 75 °C, 135 min (96%); ii, *p*-TsOH, benzene, 80 °C, 4 h (100%); iii, separate and recycle undesired isomer three times (90% yield of isomer shown)

**Scheme 19**

enyne stereochemistry from D-(+)-ribonolactone, but Pauson–Khand reaction on a *trans*-disubstituted γ-butyrolactone was thwarted by excessive strain. Instead, a seven-membered ring ketal analog was used successfully (equation 65). Mulzer's stereochemistry was derived from derivatives of (+)- or (–)-glyceraldehyde.

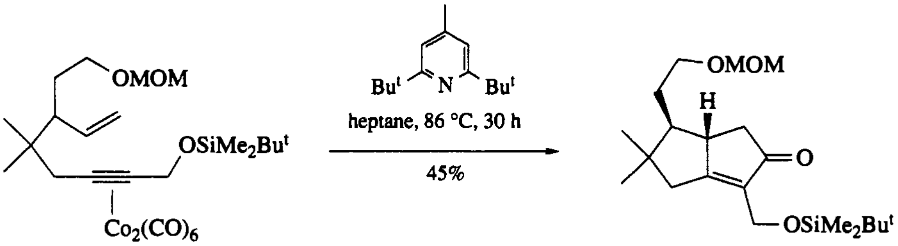
OMOM
OSiMe2Bu^t
Co2(CO)6
Bu^t
N
Bu^t
heptane, 86 °C, 30 h
45%
OMOM
H
O
OSiMe2Bu^t

(64)

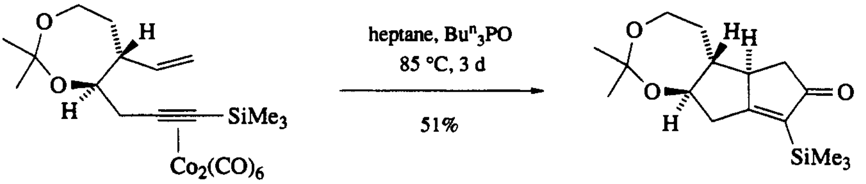
O
H
O
H
SiMe3
Co2(CO)6
heptane, Bu^n3PO
85 °C, 3 d
51%
O
HH
O
O
H
SiMe3

(65)

Hua has used the products of Pauson–Khand cycloadditions for syntheses of optically active pentalenene and racemic pentalenolactone E methyl ester. The racemic ketone in the first case was converted to the necessary optically active intermediate by kinetic resolution *via* 1,4-addition of an optically active allyl sulfoxide anion. These represented the first synthesis of natural products containing the angularly fused triquinane skeleton from bicyclic Pauson–Khand products (equation 53 and Scheme 20).[41]

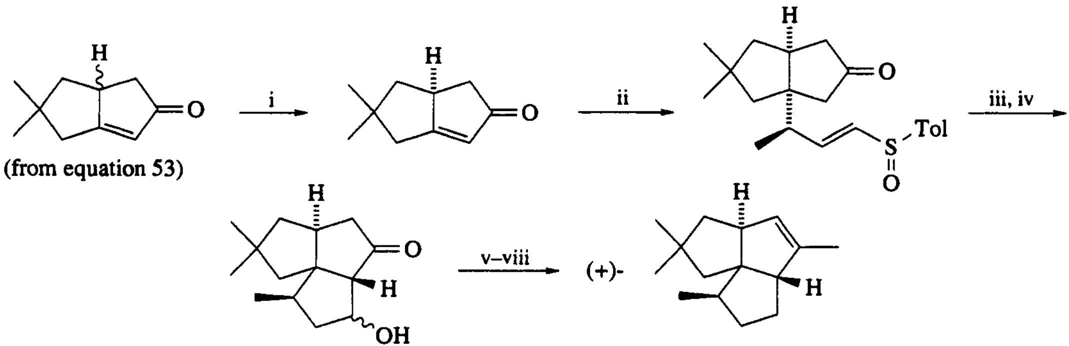
H
O
(from equation 53)
i
H
O
ii
H
O
S
Tol
O
iii, iv
H
O
H
OH
v–viii
(+)-
H
H

Pentalenene

i, 0.5 equiv. (*S*)-*trans*-*p*-$MeC_6H_4S(O)CH{=}CHCH_2Li$, THF, –78 °C, 30 min (45%); ii, 2.0 equiv. racemic *trans*-*p*-$MeC_6H_4S(O)CH{=}CHCH(Me)Li$, THF, –78 °C, 45 min (91%); iii, Zn, AcOH (95%); iv, $HCO_2H$, $CF_3CO_2H$, 60 °C, 24 h, then $K_2CO_3$, MeOH (64%); v, MeMgBr, $Et_2O$, 0 °C (70%); vi, $(Me_2N)_2POCl$, $Et_3N$, DMAP, toluene, 60 °C, 10 h (96%); vii, Li, $Bu^tOH$, $EtNH_2$, THF, 0 °C, 30 min (97%); viii, $BF_3$, $Et_2O$, $CH_2Cl_2$ (99%)

**Scheme 20**

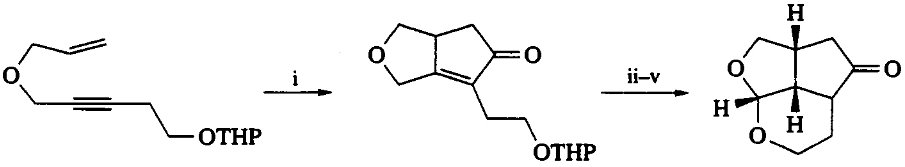

i, isooctane, 60 °C, 24 h (41%); ii, $H_2$, Raney Ni, EtOH; iii, *p*-TsOH, MeOH; iv, $NaNO_2$, $H_2SO_4$, $H_2O$, –10 °C, 1 h; v, *hν*, benzene, 0 °C, 15 h

**Scheme 21**

A formal synthesis of the natural product aucubigenone by Billington has made use of a very direct route involving Pauson–Khand cycloaddition of an allyl propargyl ether (Scheme 21).[45]

Since our direct route to angularly fused triquinanes from cycloaddition of 1-(4-pentynyl)cyclopentenes is limited to trisubstituted alkenes and simple terminal alkynes, bisnorisocomene, but not isocomene itself, could be prepared (Scheme 22).[51,53] However, this limitation is not a factor for most other compounds in this class of natural products, and the steric interactions described earlier worked to our advantage in a diastereocontrolled synthesis of pentalenene (see structure, Scheme 20). The natural product was obtained by subjecting the product of Scheme 14 to the sequence i, Li, $NH_3$, MeOH; ii, MeLi, $Et_2O$; iii, *p*-TsOH, benzene, reflux.[52]

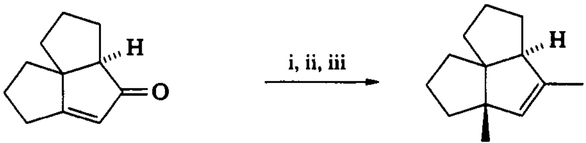

(from equation 62)

i, $Me_2CuLi$, $Et_2O$, 0–25 °C, 2 h (89%); ii, MeLi, $Et_2O$, THF, –78 °C, 150 min (91%); iii, $SOCl_2$, pyridine, THF, –45 to 25 °C, 15 min (66%)

**Scheme 22**

Serratosa has critically evaluated the various entries to the triquinacene system available *via* Pauson–Khand chemistry, concluding that a route involving cycloaddition of the dibenzylated enyne substrate (Schemes 17 and 23) is operationally the simplest for preparation of multigram quantities of tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-trione. This in turn is a key intermediate for the study of synthetic entries to dodecahedrane and its derivatives. An optically active version of this synthesis has been developed as well.[54c,d]

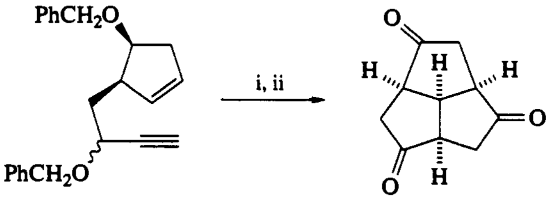

(from Scheme 17)

i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h (60–70%); ii, $H_2$, 10% Pd/C, EtOH, then PCC, Celite (63%)

**Scheme 23**

Finally, there have been a number of additional recent methodological advances.[59]

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# 9.2
# Metal–Carbene Cycloadditions

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## 9.2.1 INTRODUCTION

The chemistry of transition metal carbene complexes has been examined with an eye to applications in organic synthesis ever since their discovery by Fischer in 1964, and the growth in the number of useful applications has been exponential with time.[1–3] There are two types of transition metal carbene complexes; those which have electrophilic carbene carbons and which are typified by the pentacarbonylchromium complex (**1**), and those which have nucleophilic carbene carbons and which are typified by the biscyclopentadienyltitanium complex (**2**). Complexes (**1**) and (**2**) are often referred to as 'carbene' and 'alkylidene' complexes, respectively. This review will be limited to the chemistry of electrophilic carbene complexes of the Fischer type. The chemistry of the nucleophilic alkylidene complexes will be covered in Chapter 9.3, this volume.[4]

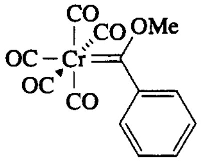

**(1a)**
A Fischer carbene complex

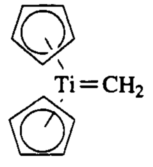

**(2)**
An alkylidene complex

An overview of the chemistry of the electrophilic transition metal carbene complexes will be presented, which will focus on those reactions that have established potential in organic synthesis, and on actual applications in the synthesis of organic molecules. Emphasis will be given to chemistry that has not been reviewed[1-3] and includes the literature up to the end of 1988 with a few citations from 1989. The chemo-, regio- and stereo-selectivity of the reactions of carbene complexes will be emphasized, and in Section 9.2.2 special focus will be made on the comparisons between carbene complexes and their organic analogs. The organization of this material begins with the separation of the reactions of carbene complexes into two groups: (i) those that occur at a substituent of the carbene carbon and in which the metal–carbene bond remains intact (Section 9.2.2); and (ii) those that occur at the metal center and which involve the metal–carbene bond (Section 9.2.3). Most of the reactions in this chapter involve the combining of C—C π-bonds and thus fall under the subject heading of this volume. Also included, however, are several ionic reactions of carbene complexes (Sections 9.2.2.5, 9.2.2.6 and 9.2.2.7), which are not covered in any other chapter in this work. The coverage of cyclopropanation reactions of carbene complexes will be only be briefly included for completeness, and a more extensive treatment can be found in Volume 4, Chapter 4.6.

The various methods for the preparation of carbene complexes will not be presented here, as they have been extensively reviewed elsewhere.[1a,2] The syntheses of the carbene complexes from the noncarbene complex precursors presented in this review have almost all been by Fischer's original procedure (equation 1), involving the addition of an organolithium to a metal carbonyl, followed by alkylation of the resulting metal acylate. Grignard reagents are not as useful as organolithiums, and there is essentially no limit to the nature of the organolithium that may be employed. The yields of carbene complexes by the Fischer method are good to excellent and can often be prepared on an open-ended scale since most common complexes are solids and purification can be accomplished by crystallization. Most transition metal carbene complexes can be handled in the presence of air and thus alternatively can be purified on silica gel in the presence of air without noticeable losses. The sensitivity of these complexes to air increases with temperature, and for reactions carried out above room temperature, an inert atmosphere is normally employed. Finally, the cost of Group 6 metal carbonyls at 20–50 cents mmol$^{-1}$ makes them no more expensive to use in stoichiometric reactions than the typical organic reagent.

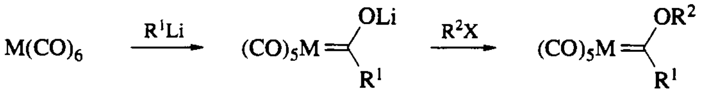

(3) M = Cr, Mo, W (4) (5) (1)

As the chemistry of Fischer carbene complexes has developed, the synthesis of new complexes by elaboration of existing complexes has naturally become increasingly important. The reactions that have become important in this regard are largely those that are discussed in Section 9.2.2. Two methods for the preparation of Fischer carbene complexes from noncarbene complex precursors, that were introduced early on but have recently been more fully developed, are mentioned here because they may find increasing utility.[5-9] The first involves preparation from Group 6 metal pentacarbonyl dianions and has been used for the preparation of carbene complexes from amides[5] and acid halides.[6] The optimal procedure in the case of amides is illustrated in Scheme 1, and is generally useful for the preparation of amino carbene complexes in very good yields.[5] This method has the advantage that amino complexes can be prepared without the intermediacy of the alkoxy complex that must of necessity be produced by the Fischer procedure. The second method involves the rearrangement of a metal–alkyne complex to a metal–alkylidene complex, which is then trapped by an alcohol. This reaction has been optimized in specific systems,[7,8] but has yet to be optimized in the more general case that is included in Scheme 1.[9] This method has the advantage that highly reactive anionic reagents need not be employed, and that the alkoxy substituent R$^1$

need not be limited to one that is derived from a reactive carbon electrophile as is necessary by the Fischer procedure.

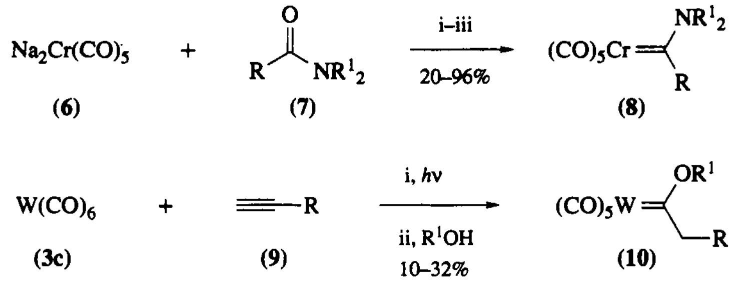
Na2Cr(CO)5
+
(6)
R
NR12
(7)
i–iii
20–96%
(CO)5Cr
NR12
R
(8)
W(CO)6
+
(3c)
R
(9)
i, hν
ii, R1OH
10–32%
(CO)5W
OR1
R
(10)

i, THF, –78 to 0 °C; ii, 3 equiv. $Me_3SiCl$, –78 °C; iii, $Al_2O_3$, –78 to 25 °C

Scheme 1

## 9.2.2 REACTIONS ON THE CARBENE LIGAND: THE METAL AS REACTIVITY AND SELECTIVITY AUXILIARY

### 9.2.2.1 [2 + 2] Cycloadditions

The first examples of a [2 + 2] cycloaddition at an unsaturated substituent on a carbene ligand have been recently reported.[10] In the example shown in Scheme 2 it can be seen that the cycloadditions can occur very rapidly between enol ethers and alkynic carbene complexes. Alkynic carbene complexes can serve as surrogates for alkynic esters since the cycloadducts can be very efficiently oxidized to their corresponding esters. While the [2 + 2] cycloaddition of methyl tetrolate and dihydropyran is unknown, a comparison can be made between the alkynic carbene complex (**12b**), which reacts at room temperature, and the doubly activated alkynic ester (**15**), which will only react at 180 °C with the same substrate.

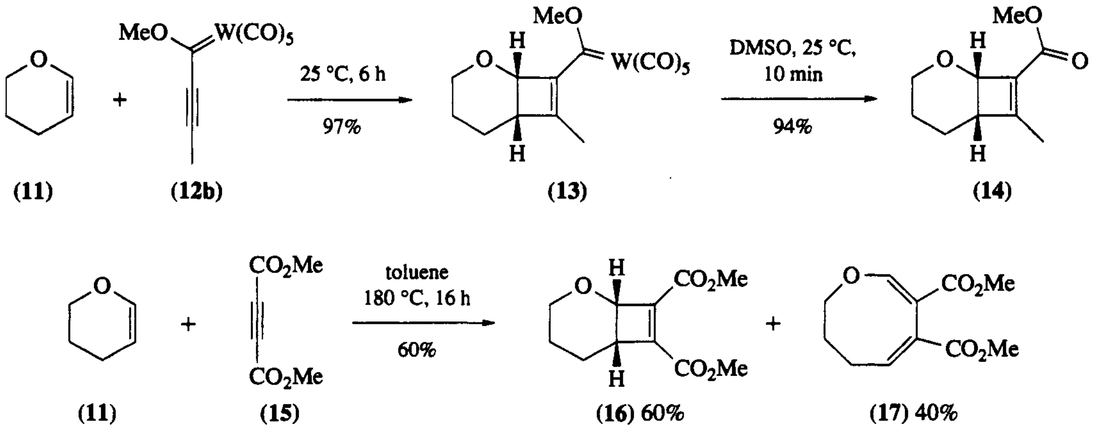
(11)
MeO
W(CO)5
(12b)
25 °C, 6 h
97%
MeO
H
W(CO)5
H
(13)
DMSO, 25 °C, 10 min
94%
MeO
H
O
H
(14)
(11)
CO2Me
CO2Me
(15)
toluene
180 °C, 16 h
60%
H
CO2Me
H
CO2Me
(16) 60%
CO2Me
CO2Me
(17) 40%

Scheme 2

The [2 + 2] cycloaddition of the propynyl tungsten complex (**12b**) has been found to be stereospecific with the *cis* and *trans* isomers of ethyl propenyl ether.[11] The reaction with *cis*-propenyl ethyl ether gave rise to the cyclobutenyl complex (**18**), in addition to a minor amount of the ring-opened dienyl carbene complex (**19**). The stereochemistry about the double bonds in the dienyl complex (**19**) revealed that it was derived from a thermal electrocyclic conrotatory ring opening of the *cis*-cyclobutenyl carbene complex (**18**) and thus the stereochemistry is completely retained in this cycloaddition. In support of this analysis it was found that cyclobutenyl complex (**18**) could be thermally opened to the dienyl complex by heating in an inert solvent at 50 °C. In the cycloaddition of the propynyl complex (**12**) with *trans*-

propenyl ethyl ether the expected cyclobutenyl complex (**20**) was not observed, and the only product that was isolated from this reaction was the (*Z*,*E*)-dienyl carbene complex (**21**). Again this stereochemistry about the diene is that expected from the ring opening of the cyclobutenyl complex that would result from the [2 + 2] cycloaddition occurring with retention of configuration about the propenyl ethyl ether. It is not unreasonable that ring opening of the *cis*-cyclobutenyl complex (**18**) should be more sluggish than for the *trans* complex (**20**), since a conrotatory opening requires that one of the substituents in (**18**) rotates inward. If there is a stepwise mechanism for this cycloaddition, then in this case the second step occurs faster than bond rotation. The reason for low mass balance for the *trans*-propenyl ether reaction has not been determined. The [2 + 2] cycloaddition of alkynyl carbene complexes with enol ethers could prove useful in the preparation of 2-substituted dienyl carbene complexes, which would be difficult to prepare with the Fischer procedure.

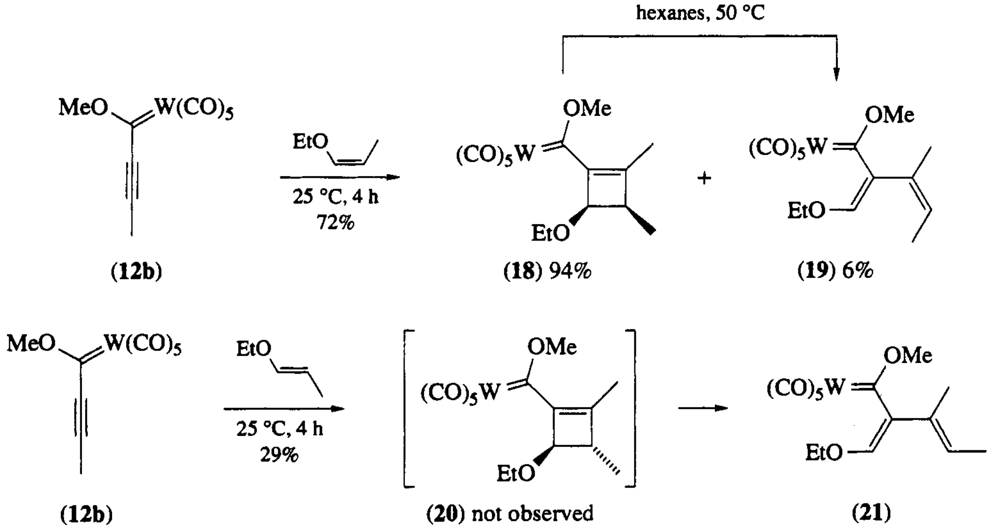

**Scheme 3**

The only other examples of [2 + 2] cycloadditions come not from carbene complexes, but from vinylidene complexes.[12,13] The [2 + 2] cycloadditions of imines with vinylidene complexes was developed by Barrett and represent the first synthetic applications with this class of organometallic compounds.[14] The reaction of the vinylidene complex (**22**) with *N*-methyl benzaldehyde imine gives the cationic cyclic carbene complex (**23**) in 46% yield. The expected azacyclobutene–iron complex (**30**) was not observed and apparently very quickly reacts with a second equivalent of the imine. The β-lactam (**24**) could be obtained in good yield upon oxidation of the carbene complex (**23**) with iodosylbenzene. The same β-lactam could be obtained in a slightly different manner from the chromium metal acylate (**25**). Sequential treatment of this salt with tosyl chloride and then the same imine produced the carbene complex (**26**), which was oxidized in 97% yield to (**24**). There are two possible pathways for the sequence of events in the chromium case. Deprotonation of the product from the tosylation of (**25**) would give the anionic carbene complex (**28**), which can undergo β-elimination to the vinylidene complex (**27**) or condense with the imine followed by subsequent ring closure to give the cyclic carbene complex (**29**). Preliminary experiments indicate that the latter is most likely. In either event, the chromium complex (**29**), like the iron analog (**30**), is apparently not stable with respect to reaction with a second equivalent of imine.

The incorporation of the second equivalent of imine can be prevented in these reactions if a vinylidene complex, such as (**31**), is employed which is β,β-disubstituted. Under the optimized conditions indicated, the reaction of (**31**) with *N*-methyl benzaldehyde imine will provide the cycloadduct (**32**) in quite good yield. A rather unorthodox oxidation procedure ($Bu_4NNO_2$, 6.5 kbar; 1 bar = $10^5$ Pa) is required for the effective cleavage of the cationic complex (**32**) to the β-lactam (**33**). This reaction was shown to involve a two-step process, since the salt (**37**) could be isolated in 80% yield by column chromatography if the reaction was stopped shortly after the reaction mixture was brought to room temperature. The reaction with the cyclic thioimidate (**34**) indicates that vinylidene complexes can be useful in the synthesis of functionalized β-lactams in good yields with high stereoselectivity.

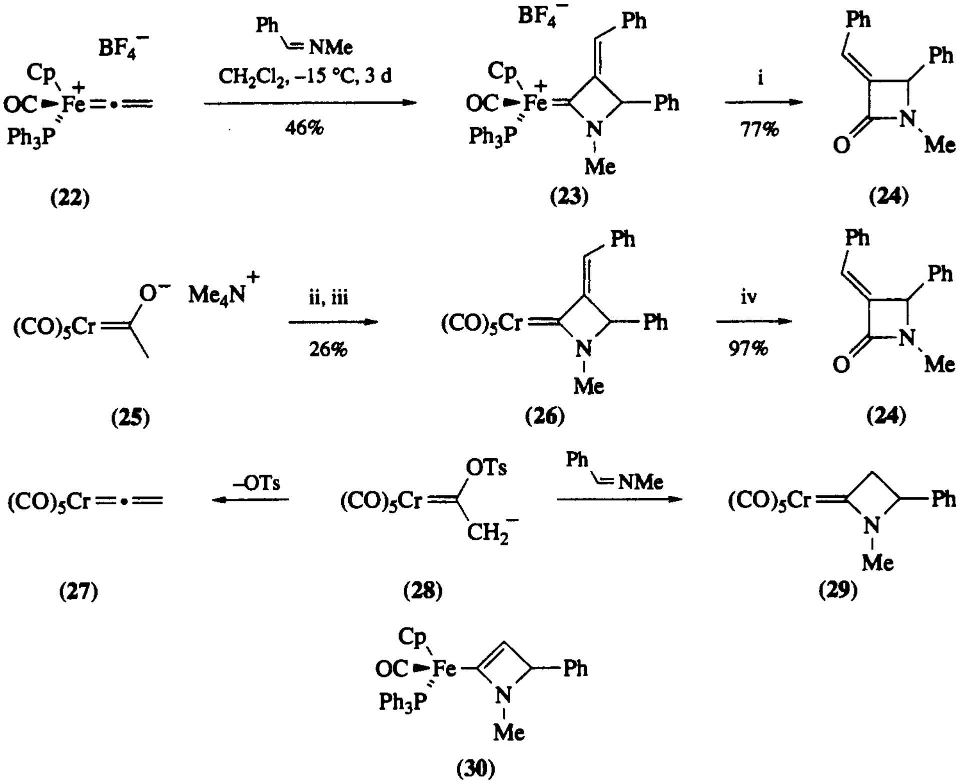
BF4⁻
Cp
OC
Fe
Ph3P
+
(22)
Ph
NMe
CH2Cl2, −15 °C, 3 d
46%
(23)
i
77%
(24)
O⁻ Me4N⁺
(CO)5Cr
(25)
ii, iii
26%
(26)
iv
97%
(24)
(CO)5Cr
(27)
−OTs
OTs
CH2⁻
(28)
Ph
NMe
(29)
(30)
Me
N
O

i, PhIO, $CH_2Cl_2$, 25 °C, 2 d; ii, TsCl, $CH_2Cl_2$, 25 °C, 10 min; iii, PhCH=NMe, 25 °C, 8 h;
iv, PhIO, $CH_2Cl_2$, 25 °C, 4 d

**Scheme 4**

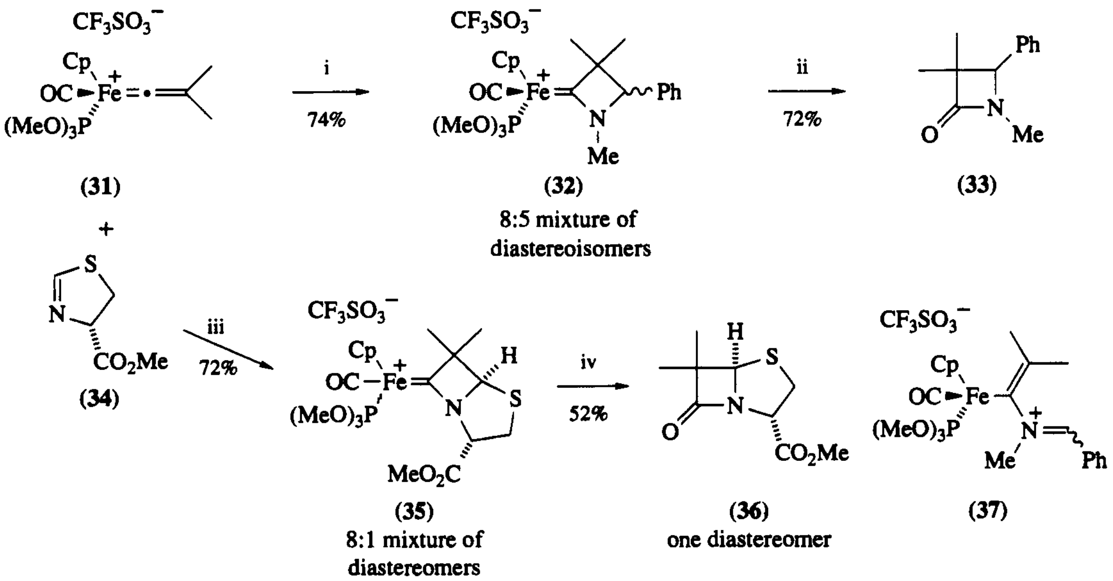
CF3SO3⁻
Cp
OC
Fe
(MeO)3P
+
(31)
i
74%
(32)
8:5 mixture of diastereoisomers
ii
72%
Ph
N
Me
O
(33)
+
S
N
CO2Me
(34)
iii
72%
H
S
MeO2C
(35)
8:1 mixture of diastereomers
iv
52%
(36)
one diastereomer
(37)

i, PhCH=NMe, $ClCH_2CH_2Cl$, Amberlyst A21 resin, 25 °C, 1 h, reflux 2 h;
ii, $Bu_4NNO_2$, $CH_2Cl_2$, 6.5 kbar, 60 h; iii, (34), conditions in i; iv, PhIO, EtOH, 25 °C, 4 d

**Scheme 5**

### 9.2.2.2 [3 + 2] Cycloadditions

The only examples of [3 + 2] cycloadditions of carbene complexes are of diazoalkanes with alkynyl complexes.[15,16] The reactions of the chromium and tungsten propynyl complexes, (**12a**) and (**12b**), with trimethylsilyldiazomethane give high yields of the pyrazole carbene complexes (**38**).[15] The reaction of alkynyl complexes with diazomethane was first reported by Fischer, but with diazomethane the pyrazole complex (**38**) was not isolated. The carbene ligand was cleaved to give a nonorganometallic product with the less sterically hindered diazoalkane.[16] The pyrazole complexes of the type (**38**) can be isolated from the reaction with diazomethane if conditions are carefully controlled but the yields are low, since carbene ligand cleavage can not be completely suppressed. The cycloaddition of a number of alkynyl carbene complexes with trimethylsilyldiazomethane and 3-diazopropene give good to excellent yields of pyrazole complexes. Of particular advantage in these cycloadditions is the regioselectivity. The reaction of methyl tetrolate (**41**) with trimethylsilyldiazomethane gives approximately a 2:1 mixture of the two possible cycloadducts, whereas both the chromium and tungsten complexes, (**12a**) and (**12b**), give a greater than 300:1 selectivity for the cycloadduct (**38**). It was demonstrated that the pyrazole carbene complex (**38**) can be oxidized in high yield to the ester (**39**). From the point of view of regioselectivity and the relative rates of the reactions, alkynyl carbene complexes should prove to be useful as synthons for alkynyl esters in [3 + 2] cycloadditions. The reactions of other carbene complexes and other 1,3-dipoles have yet to be investigated.

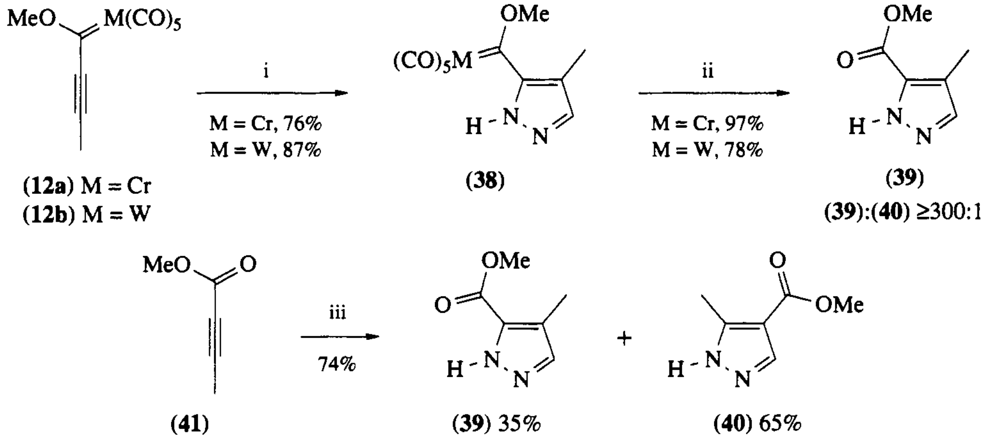

i, $Me_3SiCHN_2$, hexane, 25 °C, 2–4 h; ii, $Ce(NH_3)_6(NO_3)_2$, $Et_2O$, 25 °C, 30 min;
iii, $Me_3SiCHN_2$, hexane, 69 °C, 5 d

**Scheme 6**

### 9.2.2.3 [4 + 2] Cycloadditions

The most thoroughly studied pericyclic reaction of carbene complexes is the Diels–Alder reaction of α,β-unsaturated complexes. The first examples were published in 1983 and since that time a number of other reports have appeared which together demonstrate that this reaction is a useful tool for the preparation of highly functionalized carbene complexes and should have significant utility in organic synthesis.[17–29] In the first study a comparison was made between the Diels–Alder reactions of the vinyl carbene complexes (**42**) and methyl acrylate with several 1,3-dienes.[17] The reaction of the vinyl chromium carbene complex (**42a**) with isoprene occurs at room temperature in three hours, whereas its ester analog, methyl acrylate (**45**), has been reported to react in seven months at this temperature. The rate enhancement for the reaction of the carbene complex (**42a**) over methyl acrylate is $2 \times 10^4$ and associated with this rate enhancement is a significant increase in the regioselectivity. These enhanced rates and regioselectivities are comparable to those observed for the aluminum trichloride mediated Diels–Alder reaction of methyl acrylate and isoprene. Since carbene complexes can be easily oxidized to esters, this initial report pointed to the potential that vinyl carbene complexes could have as synthons for esters in the Diels–Alder reaction.

The earliest studies examining the stereoselectivity of these reactions involved cyclopentadiene[17,18,20] and among the examples in the literature is the reaction of the isopropenyl chromium complex (**48a**).[18] The reaction is rapid and gives the *endo* and *exo* adducts (**49**) and (**51**), as well as the chelated complex

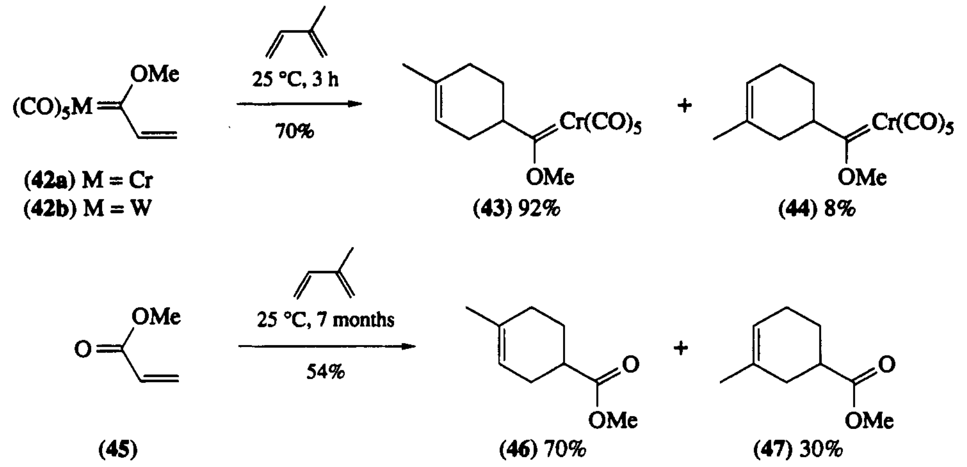

OMe
(CO)5M
25 °C, 3 h
70%
Cr(CO)5
OMe
+
Cr(CO)5
OMe
(42a) M = Cr
(42b) M = W
(43) 92%
(44) 8%
OMe
O
25 °C, 7 months
54%
O
OMe
+
O
OMe
(45)
(46) 70%
(47) 30%

Scheme 7

(**50**) derived from the *endo* adduct. The assignment of stereochemistry was made on the basis of the observation that the *endo* adduct (**49**) could be converted upon heating to the chelated complex (**50**), which in turn was characterized by X-ray diffraction. The stereoselectivity of this reaction thus is in favor of the *endo* adduct, but only by a small amount (60:40).[19] The reaction of methyl methacrylate with cyclopentadiene is also not stereoselective and in fact gives a small preference for the *exo* adduct. The Lewis acid mediated reaction of methyl methacrylate with cyclopentadiene, interestingly, also gives a 60:40 mixture of *endo* to *exo*.

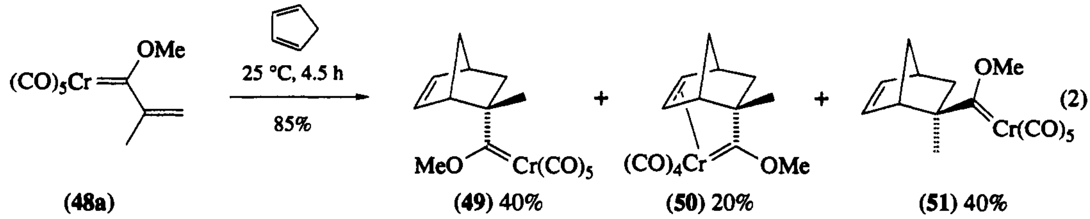

OMe
(CO)5Cr
25 °C, 4.5 h
85%
MeO
Cr(CO)5
+
(CO)4Cr
OMe
+
OMe
Cr(CO)5
(2)
(48a)
(49) 40%
(50) 20%
(51) 40%

The stereospecificity of the reactions of the *trans*- and *cis*-propenyl complexes (**52b**) and (**55**) with cyclopentadiene has been investigated.[20] The *trans*-propenyl complex (**52b**) affords the *endo* and *exo* adducts as a 90:10 mixture, in which the *trans* stereochemistry present in the carbene complex is completely retained in both cycloadducts. As a point of comparison, the reaction of *trans*-methyl crotonate with cyclopentadiene gives a 54:46 *endo*:*exo* ratio in the thermal reaction and a 93:7 ratio in the aluminum chloride mediated reaction. The stereospecificity of these reactions was established when it was found that the *cis*-propenyl carbene complex (**55**) was found to give the *cis*-derived *endo* and *exo* adducts (**56**) and (**57**) in an 84:16 ratio. Thus, no evidence for stereochemical crossover could be found in the reactions of (**52b**) or (**55**) in their reactions with cyclopentadiene.

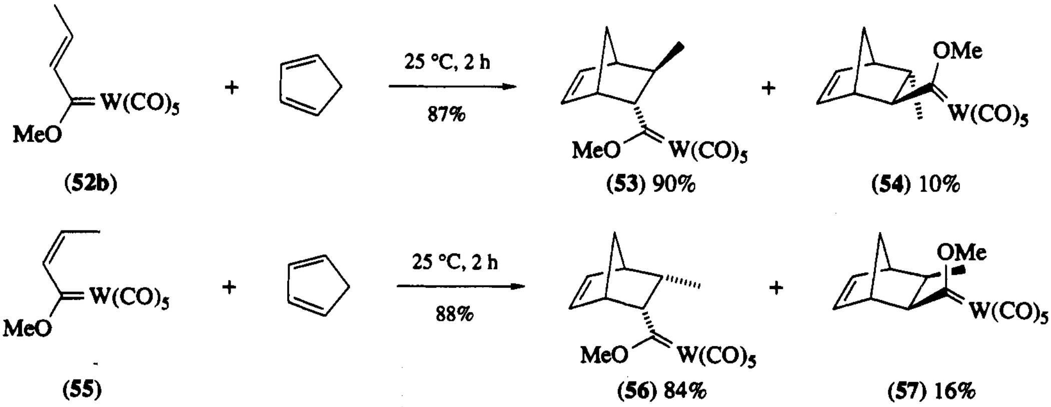

W(CO)5
MeO
+
25 °C, 2 h
87%
MeO
W(CO)5
+
OMe
W(CO)5
(52b)
(53) 90%
(54) 10%
W(CO)5
MeO
+
25 °C, 2 h
88%
MeO
W(CO)5
+
OMe
W(CO)5
(55)
(56) 84%
(57) 16%

Scheme 8

The reaction of the unsubstituted vinyl tungsten complex (**42b**) was found to be completely *exo* selective in its cycloaddition with the diene (**58**).[21] The reaction of this same diene with methyl acrylate also occurred with exclusive *exo* addition giving the adduct (**60**), but at a significantly lower rate. The stereochemistry of the carbene complex cycloadduct (**59**) was confirmed by oxidation with DMSO, which gave the ester (**60**) which was identical with the adduct obtained from the reaction of diene (**58**) with methyl acrylate. It was interesting to observe that, despite the much greater reactivity of the carbene complex (**42b**) compared to methyl acrylate, the *exo* adduct was the only isomer isolated in each reaction. This is especially interesting in light of the increased *endo* selectivities observed for the carbene complexes over their ester analogs in cycloaddition with the parent cyclopentadiene.

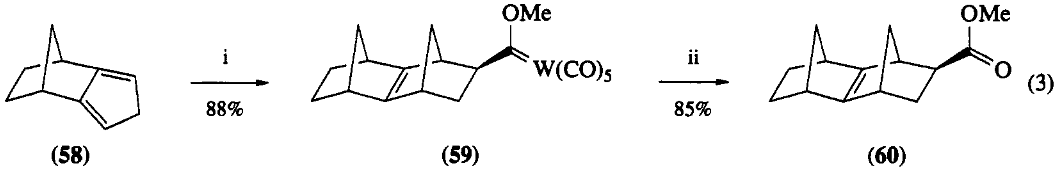

i, (**42b**) M = W, PhH, 20 °C, 15 min; ii, DMSO, 25 °C, 58 h

In the Diels–Alder reaction, the typical dienophile will display lower stereoselectivity with acyclic dienes than with cyclic dienes. This is the case for the reactions of both methyl crotonate and the propenyl tungsten complex (**52b**) with Danishefsky's diene (Scheme 9).[20] Carbene complex (**52b**) gives a 58:42 selectivity in favor of the *exo* adduct (**66**), while methyl crotonate gives a similar selectivity of 66:34 in favor of the *exo* adduct (**63**) (**64** and **65** are both derived from elimination of methanol from the *endo* adduct). This example reveals that the Diels–Alder reactions of carbene complexes are viable with functionalized and highly electron rich dienes. Furthermore, although the reaction of the carbene complex (**52b**) with Danishefsky's diene is not stereoselective, it does occur with a much greater rate and efficiency than that for the organic ester for which it can serve as synthon.

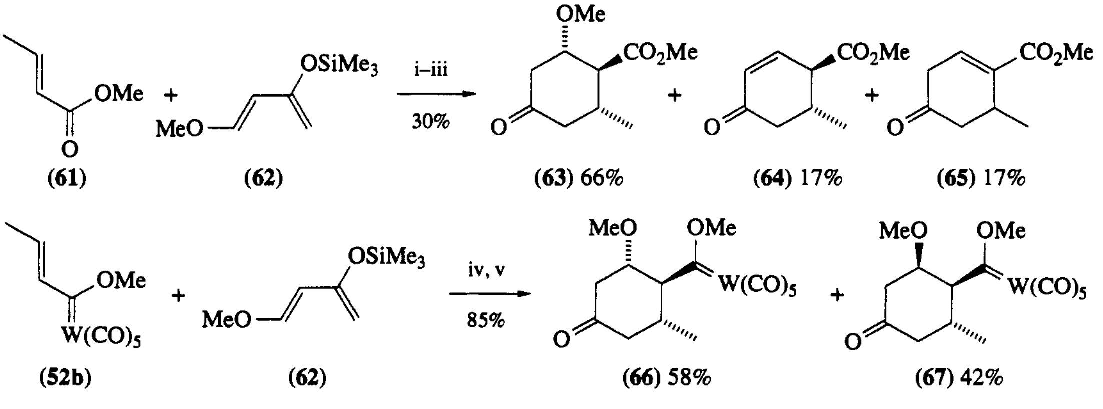

i, toluene, 110 °C, 2 d; ii, 0.005 M HCl, THF, 25 °C, 1 h; iii, silica gel; iv, 25 °C, 2 min;
v, silica gel, ether/hexane/$CH_2Cl_2$, 25 °C, 3.5 h

**Scheme 9**

The reaction of the propenyl tungsten complex (**52b**) with the trisubstituted *trans,trans*-diene (**68**) occurs with retention of the stereochemistry of both the diene and the dienophile.[20] In this reaction the facial selection at the 1,3-diene favors the formation of the *exo* adduct (**69**) by a factor of 4:1. The reaction of the relatively unhindered tungsten complex (**52b**) gives high yields of Diels–Alder adducts with both of the electron rich dienes (**68**) and (**62**; Scheme 9) with no cyclopropane side products, which is to be contrasted with more highly substituted alkenyl chromium carbene complexes (Section 9.2.3.1.1).[22,23]

The [4 + 2] cycloadditions of alkynyl carbene complexes with 1,3-dienes have also been examined and, as illustrated by the examples in Scheme 10, they occur with the same increased rates that are observed for alkenyl complexes over their organic ester analogs.[24–26] The reaction of the propynyl chromium complex with cyclopentadiene occurs in 2 h at room temperature to give the cycloadduct (**71**) in 85% yield after purification by silica gel chromatography.[24] On the other hand, the reaction of methyl tetrolate only gives a low yield of the cycloadduct (**72**) under relatively forcing conditions. A good yield

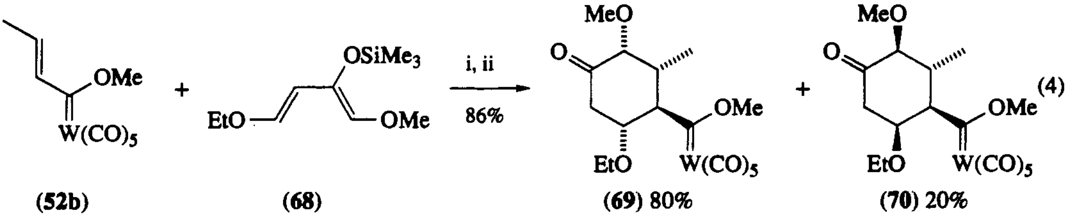

i, PhH, 25 °C, 68 h; ii, silica gel, hexane/ether, 25 °C, 2.5 h

of the analogous cycloadduct can be obtained with the more reactive tetrolyl chloride; however, the reaction is significantly slower than the reaction of the carbene complex (**12a**) and the cycloadduct is not stable to chromatography. There is clearly potential for alkynyl carbene complexes to serve as synthons for alkynyl esters in the Diels–Alder reaction. Additionally, as will be seen in Section 9.2.3.2.4, the cycloadducts from alkynyl carbene complexes and 1,3-dienes can be employed in various annulation reactions.

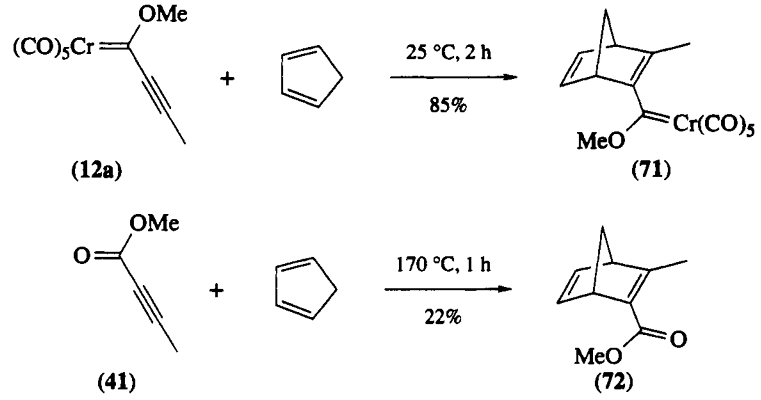

**Scheme 10**

There are only two reports in the literature concerning the Diels–Alder reactions of carbene complexes where the diene is part of the carbene complex.[10,27] The example in equation (5) illustrates the utility of the [2 + 2] cycloadditions discussed in Section 9.2.2.1. The [2 + 2] cycloaddition of the propynyl tungsten complex (**12b**) and ethyl vinyl ether proceeds at room temperature; however, the subsequent electrocyclic ring opening of the resulting cyclobutenyl carbene complexes occurs at a similar rate, and the initial cycloadduct is isolated in only a low yield (6%).[10] The major product is the dienyl carbene complex (**74a**), which can be obtained in 40% yield, and this will react with a number of reactive dienophiles in Diels–Alder reactions. In the case of propargyl aldehyde, the initial cycloadduct eliminated ethanol and gave the aryl carbene complex (**74b**). Such an aryl complex bearing an aldehyde group would be rather difficult to prepare by the standard procedures. It is apparent that the ethoxy group in (**74b**), and not the electron-withdrawing carbene complex functionality, is controlling the regiochemistry. A possible explanation involves the preference for a conformer about the carbene-carbon to the carbon of the 2-position of the diene in which the electronic influence of the carbene complex functionality is not felt in the diene.

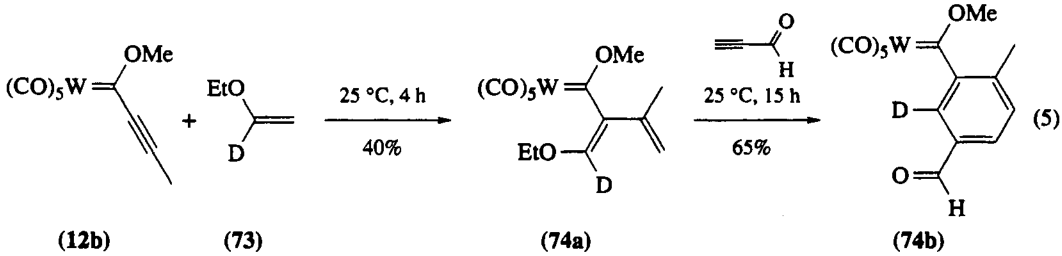

Both of the examples of intramolecular Diels–Alder reactions of carbene complexes involve the 1,3-diene tethered through the heteroatom ancilliary substituent of the carbene carbon.[25,28] The example shown in Scheme 11 is the only example of a Diels–Alder reaction of an amino carbene complex.[28] Alkenylamino and alkynylamino complexes are inert to reaction under intermolecular conditions with very reactive dienophiles, such as cyclopentadiene and Danishefsky's diene.[28,29] The aminolysis of the methoxy complex (**48b**) with the amine (**75**) represents the most common method for the preparation of amino carbene complexes.[1,2] It is typical that two isomeric amino carbene complexes are obtained by this procedure, and, as is the case for the complexes (**76**) and (**77**), it is also typical that these isomers about the carbene–nitrogen bond are not interconvertable, even at elevated temperatures. The (*E*)-isomer (**76**) was separated and was found to undergo an intramolecular Diels–Alder reaction at 80 °C to give the interesting tricyclic carbene complex (**78**).

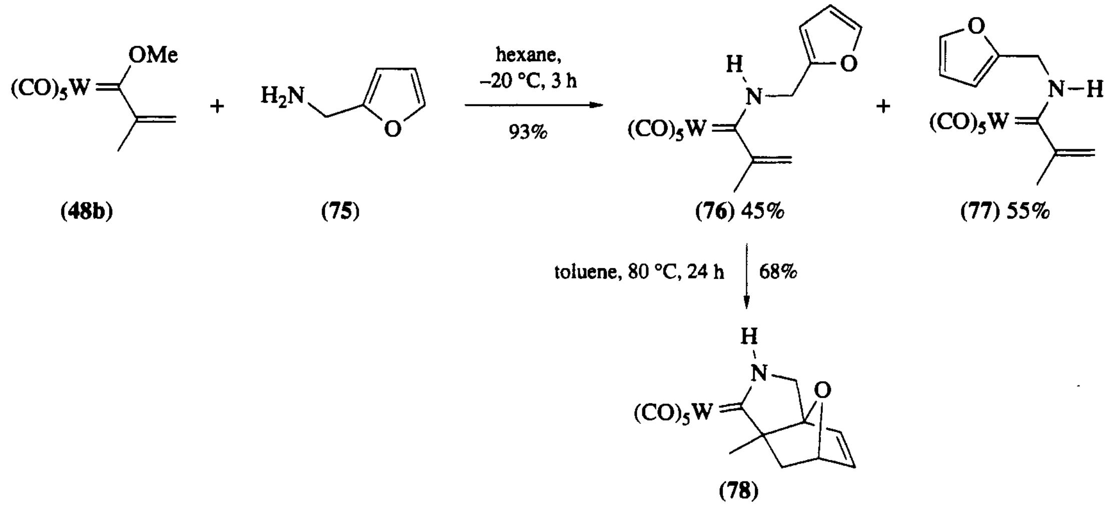

**(48b)** **(75)** **(76)** 45% **(77)** 55% **(78)**

**Scheme 11**

The final example is illustrative of another advantage that the Diels–Alder reactions of carbene complexes can offer. The Diels–Alder reaction of the α-silapyran (**79**) with methyl acrylate requires heating to 120 °C before a reaction ensues.[17,20] The expected cycloadduct (**80**) was not observed and it is likely that this is due to a subsequent retro-Diels–Alder reaction involving extrusion of a silicon–oxygen double bond. This thermal limitation to this reaction can not be overcome by the typical approach to this kind of problem in conventional Diels–Alder technologies, that is the use of Lewis acids. The silapyran (**79**) is relatively sensitive and all attempts to effect its reaction with standard Lewis acids ($AlCl_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$) failed. Alkenyl carbene complexes, such as (**42b**), are relatively tolerant of sensitive organic functionalities and, at least in this case, tolerant of pathways that would be competitive to the Diels–Alder reaction, which then occurs at room temperature to give clean formation of the cycloadduct (**81**).

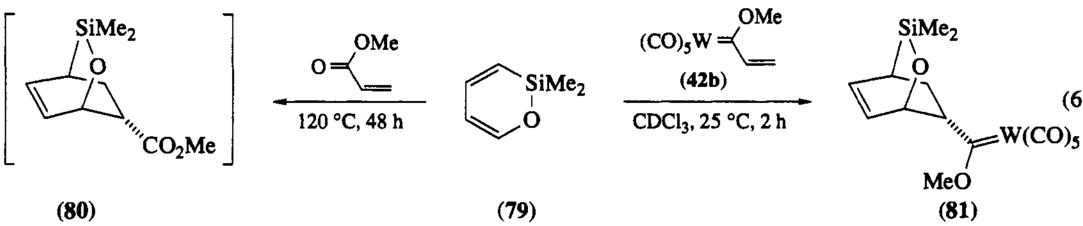

(6)

**(80)**
not observed

**(79)**

**(81)**

The Diels–Alder reactions have been examined for a number of alkenyl and alkynyl complexes with a dozen or so different dienes and the general observation is that they occur with rates, regio- and stereoselectivities that are normally only associated with the Lewis acid mediated reactions of their corresponding organic esters. The Diels–Alder reaction of carbene complexes has been introduced more recently than other reactions of carbene complexes that have found applications in syntheses of various organic targets. Although the Diels–Alder reaction of carbene complexes has yet to be employed in natural product synthesis, the special advantages that they offer suggests that this situation may change.

### 9.2.2.4 Ene Reactions and Sigmatropic Rearrangements

Very few pericyclic reactions of carbene complexes have been studied that are not in the cycloaddition class. The two examples that are known involve ene reactions and Claisen rearrangements. Both of these reactions have been recently studied and thus future developments in this area are anticipated. Ene reactions have been observed in the the reactions of alkynyl carbene complexes and enol ethers, where a competition can exist with [2 + 2] cycloadditions.[11] Ene products are the major components from the reaction of silyl enol ethers and [2 + 2] cycloadducts are normally the exclusive products with alkyl enol ethers (Section 9.2.2.1). As indicated in equation (7), methyl cyclohexenyl ether gives the [2 + 2] adduct (**84a**) as the major product along with a minor amount of the ene product (**83a**). The *t*-butyldimethylsilyl enol ether of cyclohexanone gives the ene product 9:1 over the [2 + 2] cycloadduct. The reason for this effect of silicon is not known at this time but if the reaction is stepwise, this result is one that would be expected on the basis of the silicon-stabilizing effect on the β-oxonium ion.

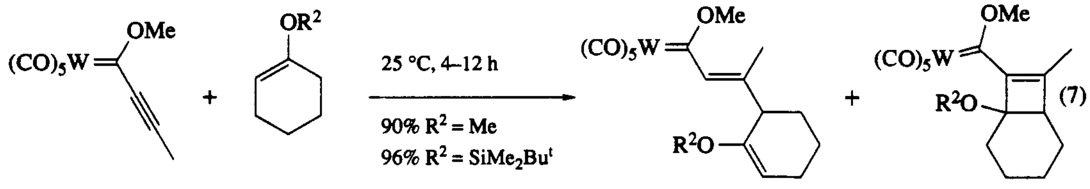

**(12b)** **(82a)** $R^2 = Me$ **(83a)** 23% **(84a)** 77%

**(82b)** $R^2 = SiMe_2Bu^t$ **(83b)** 90% **(84b)** 10%

Cationic iron–carbene complexes were used as precursors in the Claisen rearrangement of the iron-substituted allyl vinyl ethers (**86**).[30] The carbene complexes were generated *in situ* from the corresponding iron–acyl complexes by deoxygenation to cationic vinylidene complexes, which were trapped by an allyl alcohol. The cationic iron–carbene complexes were not isolated, but were deprotonated directly to give the allyl vinyl ether complexes (**86**). The Claisen rearrangement of these complexes occurred in refluxing benzene to give the iron–acyl complexes (**87**). The yields were only modest, but they were determined for the overall process involving four steps from the iron–acyl complexes that were the precursors to the carbene complexes (**85**). These Claisen rearrangements were found not to proceed with useful stereoselectivities. The complex (**87b**) was obtained as a complex mixture of diastereomers. These first examples of ene reactions and Claisen rearrangements of carbene complexes should stimulate further study of pericyclic reactions of the noncycloaddition type.

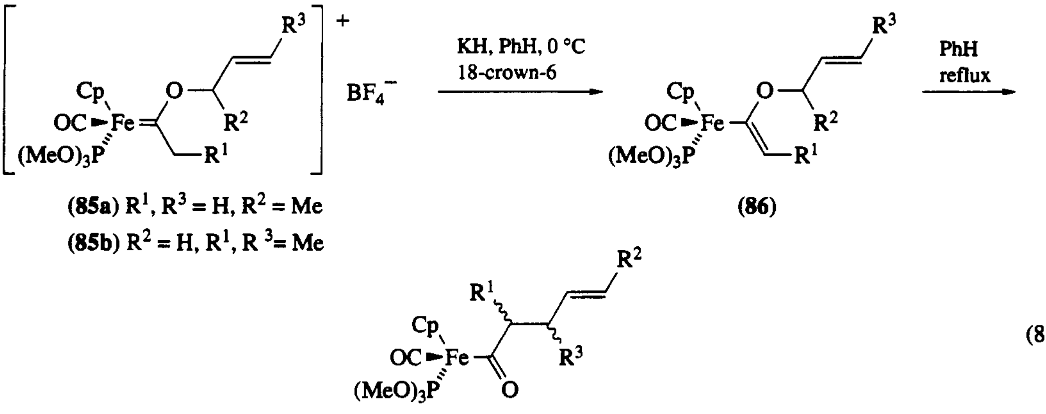

**(85a)** $R^1, R^3 = H, R^2 = Me$

**(85b)** $R^2 = H, R^1, R^3 = Me$

**(86)**

**(87a)**[a] 60%

**(87b)**[a,b] 34%

[a]Yield from the iron acyl precursor of (**85**). [b]Complex mixture of diastereomers.

### 9.2.2.5 Coupling of Anions of the Carbene Ligand with C—X σ-Bonds

The alkylation of carbene complexes is one of the potentially most useful methods for the preparation of highly substituted and/or highly functionalized carbene complexes *via* the elaboration of more simple and readily available carbene complexes. The high acidity of protons on a carbon α to the carbene was first recognized by Kreiter in 1968.[31] In the years to follow, it was the work of Casey that revealed the scope of the reactions of anions generated from alkyl carbene complexes with electrophiles.[33,34] The p$K_a$ of the methyl complex (**88a**)[33,34] was found to be nearly equal to that of *p*-cyanophenol (p$K_a \approx 8$) and it thus might be expected that the conjugate base (**89**) is a relatively stable and unreactive anion. The alkylation of the anion (**89**) with methyl iodide is successful but is not synthetically useful, due to the low yield.[33] Alkylation of (**89**) with other simple alkyl halides has not been reported. The reactions of the 'enolates' of carbene complexes with epoxides is one that has found use in the preparation of substituted 2-oxacyclopentylidene complexes of the type (**93**).[35] These complexes can be oxidatively cleaved to γ-butyrolactones and have been employed in the synthesis of α-methylene-γ-butyrolactones.[36] The anions generated from the cyclic carbene complexes (**93**) are more reactive towards alkylating reagents than noncyclic alkyl complexes and this may be for stereoelectronic reasons. In the stoichiometric additions of carbene enolates to enones, the cyclic complex (**93a**) gives a 41% yield of the adduct (**96**), whereas the methyl complex (**88a**) is alkylated in only 22% yield.[37] It is interesting that, in the presence of a catalytic amount of base, the reaction of (**93a**) with methyl vinyl ketone gives the bis adduct (**97**). As indicated by the reaction of 3-penten-2-one, the complex (**93a**) can be alkylated in good yield by a number of substituted enones. The efficiency of these alkylations is greatly increased with more active alkylating agents, but as illustrated for complex (**88a**) and methyl bromoacetate, dialkylation is usually a serious side reaction.[38]

The cyclic carbene complex (**93a**) can be alkylated in good yield with allyl bromide, but again, significant dialkylation was reported.[39] The tungsten complex, however, was reported to be alkylated with allyl bromide in good yield, and no dialkylation product was reported.[40] The alkylation product (**104**) was used to prepare the complex (**105**) *via* a metathesis reaction with $WOCl_4$, and it was surprising to find that this could be carried out to any extent without affecting the tungsten–carbene bond. The dialkyation problem can often be avoided for chromium complexes using inverse addition of the reagents. The methyl chromium complex (**88a**) can be monoalkylated in good yield (72%) with allyl bromide if anion (**89**) is added to a solution of allyl bromide.[41] The alkyations of alkyl(alkoxy) pentacarbonyl carbene complexes are not useful with simple alkyl halides and this is illustrated in the fact that even the more reactive anion derived from complex (**93a**) can only be alkylated with ethyl bromide in 20% yield.[42]

The anions generated from tetracarbonyl(phosphine) carbene complexes are more reactive in their reactions with organic electrophiles.[43] This is consistent with the observation that the p$K_a$ of the methyl pentacarbonyl complex (**88a**) is increased by six orders of magnitude when one of the carbon monoxide ligands is replaced with tributylphosphine. The anion generated from (**106**) will give good yields of alkylated products with simple alkyl halides such as ethyl bromide; however, dialkylation is still a serious side reaction. It has been reported that both pentacarbonyl and tetracarbonyl(phosphine) complexes can be efficiently monoalkylated with alkyl triflates (primary and secondary). The anion (**89**) for example, can be monoalkyated with the 3-butenyl triflate in 80% yield.[43]

The anions generated from alkylamino carbene complexes can be alkylated in high yields with simple alkyl halides without any detectable amount of dialkylation.[44] This is illustrated for the methyl pyrrolidine complex (**109**), which can be alkylated cleanly with ethyl bromide to give the monoalkylated product (**110**) in 87% yield. The methyl pyrrolidine complex (**109**) can be prepared in nearly quantitative yield quite simply by treating an ether solution of the methyl methoxy complex (**88a**) with pyrrolidine at room temperature for a few minutes. A few examples of diastereoselective alkylations are known. The *O*-alkylimidate carbene complex (**112**) can be alkylated with methyl triflate to give a 93:7 mixture of (**113**) and (**114**), which are diastereomers as a result of the chiral axis about the aza–allenyl linkage.[45] Other examples of diastereoselective alkylations will be presented in Section 9.2.2.7.

### 9.2.2.6 Coupling of Anions of the Carbene Ligand with C—X π-Bonds

The condensation of the anions generated from alkyl alkoxy pentacarbonyl carbene complexes with carbonyl compounds occurs with the formation of α,β-unsaturated carbene complexes of the type (**117**). This reaction was first explored by Casey and it was found that this reaction was limited to nonenolizable aldehydes.[32] The reaction of the anion (**89**) with benzaldehyde gave the styryl complex (**117**) in 48% yield, and with pivaldehyde the corresponding unsaturated carbene complex was obtained in 26% yield. No reaction was observed with several ketones, including acetone, acetophenone, benzophenone and cyclopentanone.[46] Reactions with enolizable aldehydes, including butanal, diphenylacetaldehye and acetaldehyde, also failed.[46] Recently a modification of this reaction was reported that does not require the stoichiometric generation of the anion (**89**).[47] The complex (**88c**) was observed to give the unsaturated

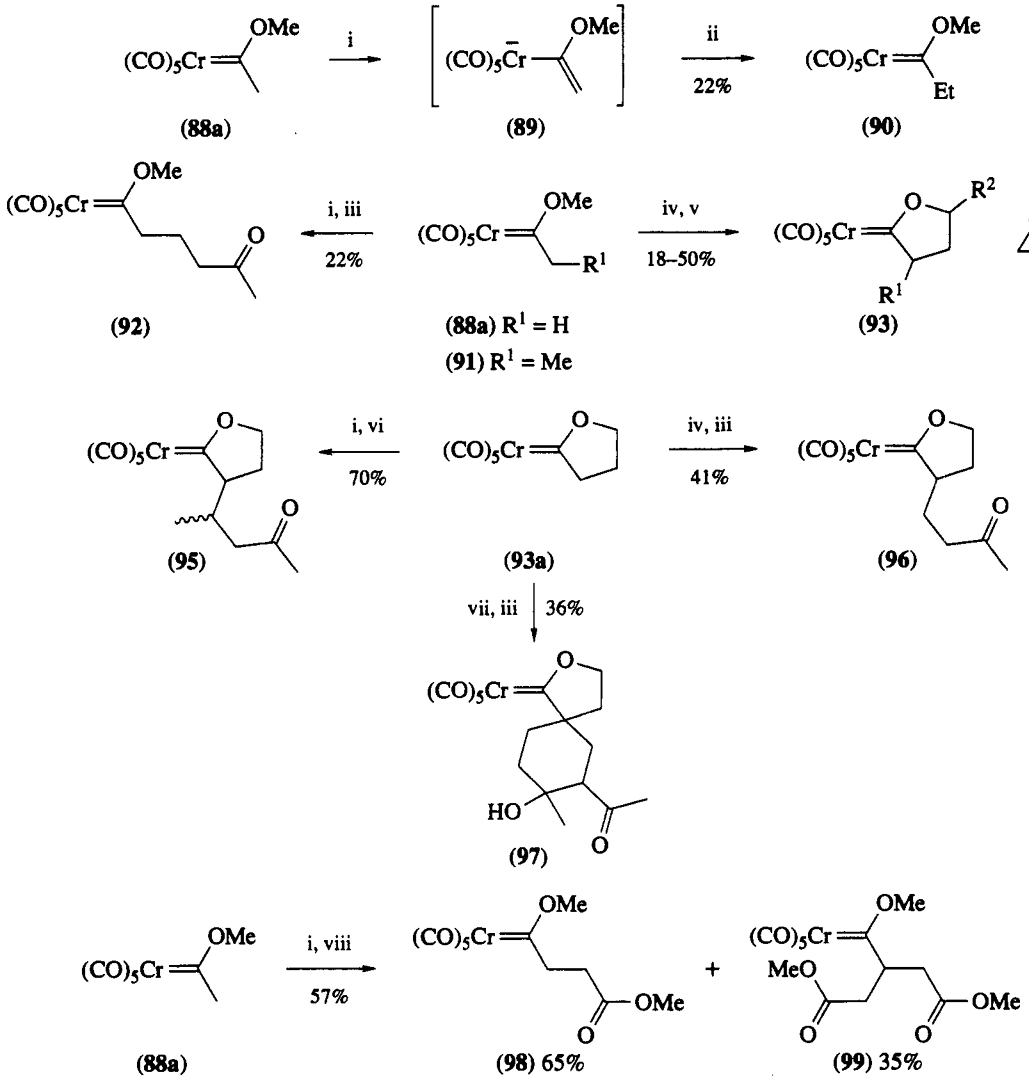

i, $Bu^nLi$ (1.0 equiv.), THF, –78 °C; ii, MeI (1.0 equiv.), –78 to 0 °C, 30 min;
iii, methyl vinyl ketone (1.5 equiv.), 0 °C, 2 h; iv, $Bu^nLi$ (1.0 equiv.), THF, –78 to 0 °C;
v, (**94**) (1.5 equiv.), 0 °C, 0.5–2 h; vi, *trans*-3-penten-2-one, 25 °C, 2 h;
vii, $Bu^nLi$ (0.1 equiv.), THF, –78 °C; viii, methyl bromoacetate (1.0 equiv.), 0 °C, 1 h

**Scheme 12**

complexes (**117**) with the aldehyde (**115**) in the presence of triethylamine and trimethylsilyl chloride. The reaction was reported only for nonenolizable aldehydes. The aldol adducts are not isolable from these reactions and, apparently, the initial adduct (**116**) undergoes proton transfer from the more acidic methylene group α to the carbene carbon, and the resulting anion suffers rapid β-elmination of the hydroxy group.

The isolation of the initial aldol products from the condensation of the 'enolates' of carbene complexes and carbonyl compounds is possible if the carbonyl compound is pretreated with a Lewis acid.[48] As indicated in equation (9), the scope of the aldol reaction can also be extended to ketones and enolizable aldehydes by this procedure. The condensations with ketones were most successful when boron trifluoride etherate was employed, and for aldehydes, the Lewis acid of choice is titanium tetrachloride. The carbonyl compound is pretreated with a stoichiometric amount of the Lewis acid and to this is added a solution of the anion generated from the carbene complex. An excess of the carbonyl–Lewis acid complex (2–10 equiv.) is employed; however, above 2 equiv. only small improvements in the overall yield are realized.

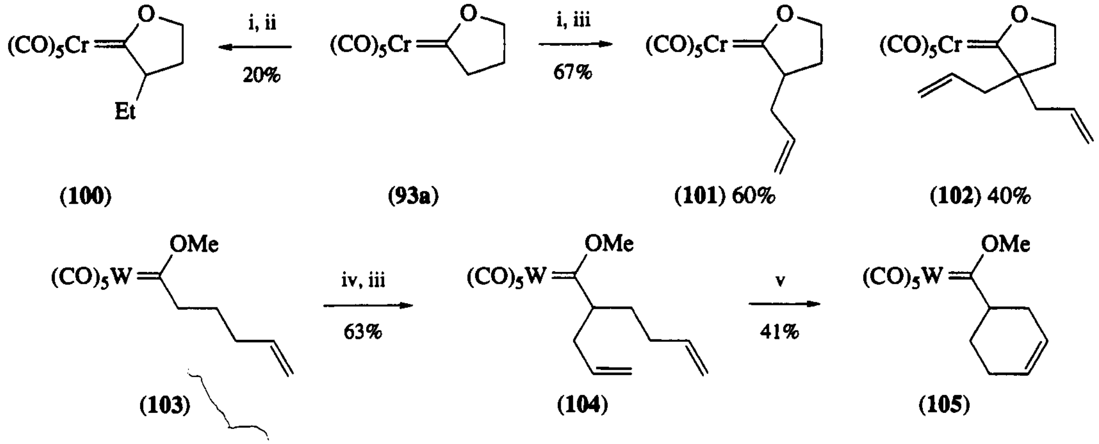
i, ii
20%
i, iii
67%
iv, iii
63%
v
41%
(100)
(93a)
(101) 60%
(102) 40%
(103)
(104)
(105)

i, Bu$^n$Li (1.0 equiv.), THF, –78 °C; ii, EtBr (1.3 equiv.) 67 °C, 45 min;
iii, allyl bromide (1.0 equiv.), 0 °C, 12 h; iv, Bu$^n$Li (1.0 equiv.), THF, –60 °C;
v, WOCl$_4$ (1 equiv.), Ph$_2$SiH$_2$ (2 equiv.), hexane, 60 °C, 2 h

**Scheme 13**

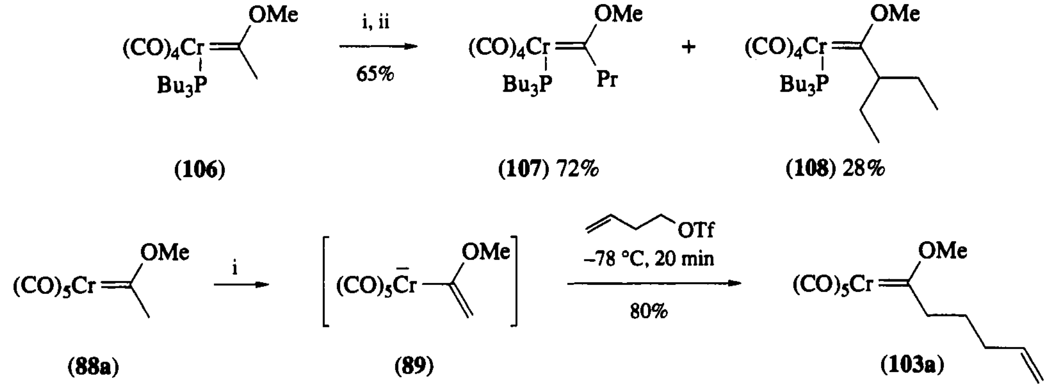
i, ii
65%
(106)
(107) 72%
(108) 28%
i
–78 °C, 20 min
80%
(88a)
(89)
(103a)

i, Bu$^n$Li (1.0 equiv.), THF, –78 °C; ii, EtBr (3 equiv.), 22 °C, 10 h

**Scheme 14**

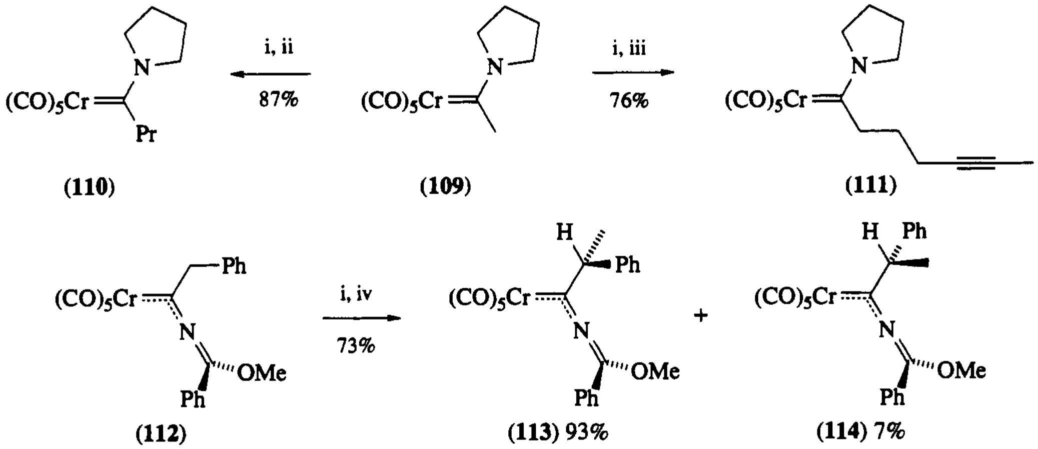
i, ii
87%
i, iii
76%
(110)
(109)
(111)
i, iv
73%
(112)
(113) 93%
(114) 7%

i, Bu$^n$Li (1.0 equiv.), THF, –78 °C; ii, EtBr (2.0 equiv.), 0 °C, 40 min;
iii, 1-iodo-3-pentyne (2.0 equiv.), 0 °C, 1 h; iv, methyl triflate, 0 °C, 40 min

**Scheme 15**

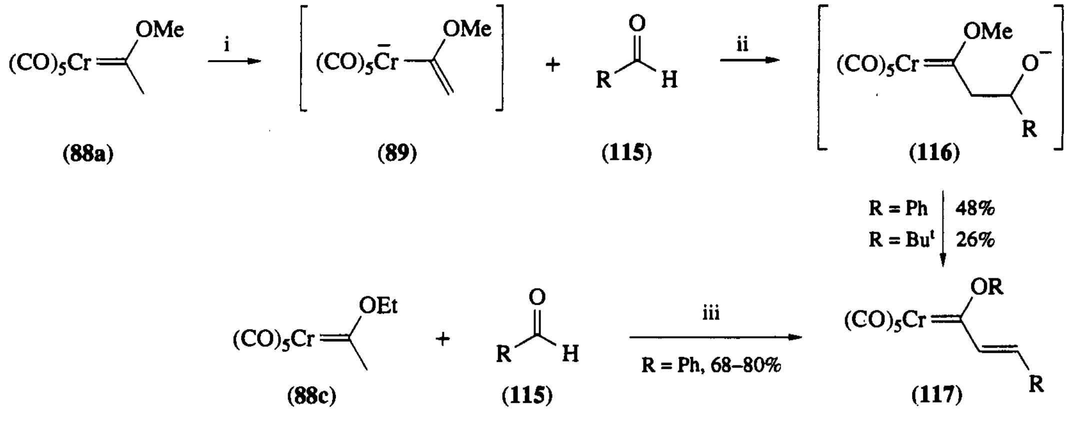

i, Bu$^n$Li, Et$_2$O, –78 °C; ii, –78 to 25 °C, 2 h;
iii, (**115**) (1.0 equiv.), Et$_3$N (4 equiv.), Me$_3$SiCl (3.0 equiv.) 25 °C, 1–14 d

**Scheme 16**

The aldol adduct (**120**) is obtained in 59% yield with 2 equiv. of the carbonyl–Lewis acid complex and in 67% with 10 equiv.

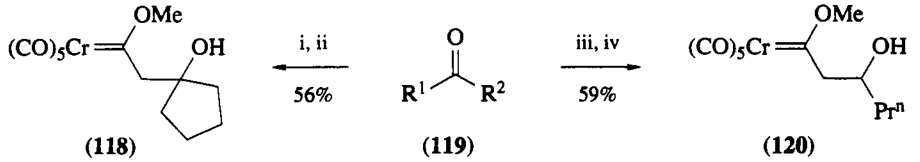

(9)

i, BF$_3$•Et$_2$O (1.0 equiv.), Et$_2$O, 0 °C; ii, (**89**) (0.1 equiv.), 0–25 °C, 20–30 min;
iii, TiCl$_4$ (1.0 equiv.), CH$_2$Cl$_2$, –78 °C; iv, (**89**) (0.5 equiv.), –78 °C, 1 h

The condensation of the α-anions of carbene complexes with acid halides cannot be stopped at the monoacylated product.[49] The reaction of the anion generated from the tungsten complex (**88b**) with acetyl chloride gives a 2:1 mixture of the enol acetate complexes (**121**) and (**122**) along with recovered (**88b**). The initially formed β-keto carbene complex (**124**) was not isolated, and apparently acetyl chloride more rapidly *O*-acylates (**124**) than *C*-acylates the enolate of (**88b**); the reason for this may be due to rapid proton transfer from (**124**) to the anion of (**88b**). The related complexes of the type (**123**) can be prepared in high yield from the reaction of the anion of (**88a**) with electrophiles generated from the treatment of orthoesters with Lewis acids.[48] This type of product can also be obtained from acetals that have been pretreated with Lewis acids[48] and from alkyl enol ethers in the presence of trifluoroacetic acid.[50] The reaction of carbene complexes with *N,N*-dimethylformamide dialkyl acetals has recently been reported to give β-aminoalkenyl complexes of the type (**126**).[51] Complexes of the type (**126**) can only be prepared from the methyl complex (**88a**), and unexplainedly, the ethyl complex (**91a**) gives the dimethoxy complex (**125**).

The stereochemistry of the aldol reaction has been examined with regard to simple diastereoselective induction.[48] The anion generated from the ethyl carbene complex (**91a**) was added to a solution of benzaldehyde that had been pretreated with titanium tetrachloride and the resulting aldol adduct was obtained as an 86:14 mixture of diastereomers in favor of the *u*-isomer. This example demonstrates that carbene complexes could have value as synthons for esters in the aldol reaction since the corresponding aldol reaction of methyl propionate with benzaldehyde is nonselective and gives a 62:38 mixture (in favor of the *l*-isomer) of the β-hydroxy esters (**128**). That carbene complexes could be synthons for esters was established by the fact that the purified *u*-isomer of the carbene complex (**127**) could be oxidized in 73% yield to the ester (**128**), in which the stereochemistry was completely retained (>99.4% diastereomeric purity).[48] That the stereochemistry could have been lost during this oxidation was of some prior concern given the high acidity of carbene complexes. The origin of the stereoselectivity in the reaction in equation (10) is not known, since the stereochemistry of the 'enolate' generated from (**91a**) is not known under the reaction conditions.

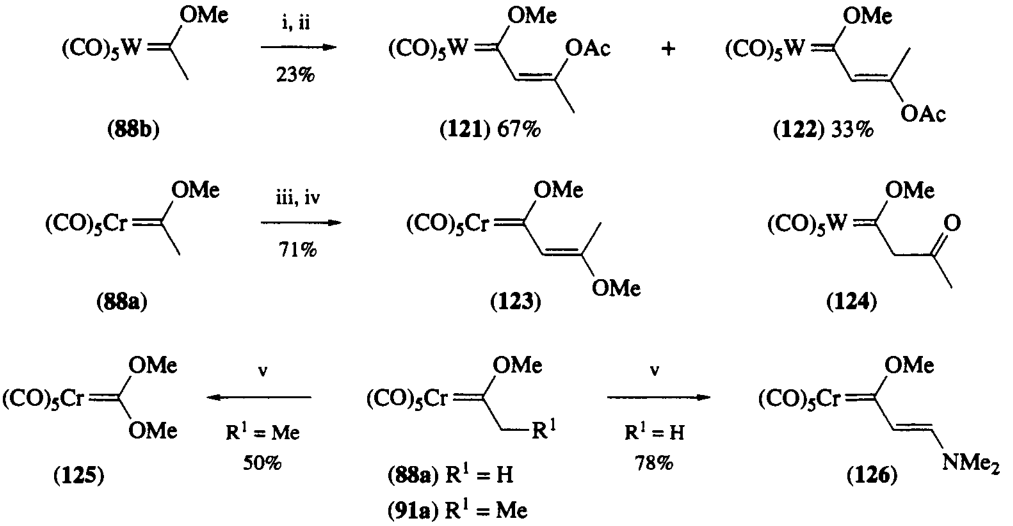

i, $Bu^nLi$, THF, –20 °C; ii, AcCl (2.2 equiv), 5 min; iii, $Bu^nLi$, $Et_2O$, –78 °C;
iv, addition to a $CH_2Cl_2$ solution of $MeC(OMe)_3–TiCl_4$ complex (10 equiv.), –78 to 0 °C;
v, $(MeO)_2CHNMe_2$ (1.0 equiv.), DMF, 20 °C, 30 min

Scheme 17

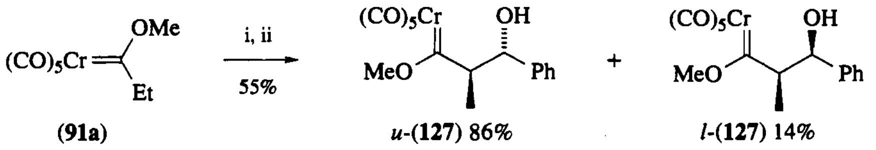

(10)

i, $Bu^nLi$, $Et_2O$, –78 °C;
ii, addition to a $CH_2Cl_2$ solution of benzaldehyde–$TiCl_4$ complex (2.0 equiv.), –78 °C, 1 h

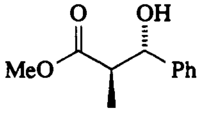

*u*-(**128**)

The aldol reactions of amino carbene complexes are superior to the aldol reactions of alkoxy carbene complexes in several respects.[52] First, the condensations of the anions generated from alkyl amino carbene complexes can be carried out with both aldehydes and ketones without the need to precoordinate the carbonyl compound with a Lewis acid. Second, high yields of the aldol adducts can be obtained even with stoichiometric amounts of the carbonyl compound. Third, as illustrated in Scheme 18, it has been found that aldol reactions of amino carbene complexes display much higher diastereofacial selective addition to chiral aldehydes than do alkoxy complexes. The anion of the methyl pyrrolidine complex (**109**) will add to 2-phenylpropanal to give the Cram product *l*-(**113**) with greater than 97:3 stereoselectivity. This is the highest facial selection ever observed for the addition of an enolate of a carbonyl compound to this aldehyde. Employing the carbonylative demetallation procedure developed by Hegedus (Section 9.2.2.8),[53] the aldol adduct *l*-(**115**) can be converted to the 2-amino-γ-butyrolactone (**117**) with reasonable stereoselectivity. These results should prompt further examination of the utility of carbene complexes in stereoselective aldol reactions.

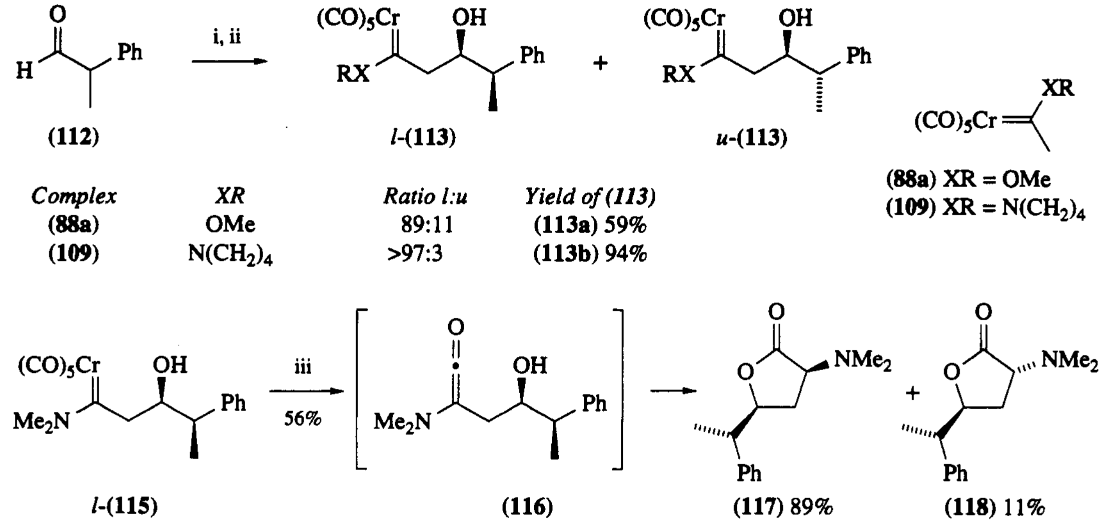

| Complex | XR | Ratio l:u | Yield of (113) |
|---|---|---|---|
| **(88a)** | OMe | 89:11 | **(113a)** 59% |
| **(109)** | N(CH$_2$)$_4$ | >97:3 | **(113b)** 94% |

i, for **(88a)** the anion of **(88a)** is added to a $CH_2Cl_2$ solution of a $TiCl_4$ complex with **(112)** (2.0 equiv.), −78 °C, 1 h; ii, for **(109)**, **(112)** (2.0 equiv.) is added to a THF solution of the anion of **(109)**, −78 °C, 10 min; iii, MeCN, *h*ν, 4 h

**Scheme 18**

### 9.2.2.7 Michael Additions to α,β-Unsaturated Carbene Complexes

Conjugate additions to α,β-unsaturated carbene complexes have not been extensively studied; however, from the few reports that have appeared in the literature one can get a brief sense of the scope, limitations and special features of these reactions that may ultimately find application in synthetic organic chemistry. One of the earliest examples involves the addition of amines to alkynyl carbene complexes.[54] The example in Scheme 19 is particularly interesting because complete control between 1,4- *versus* 1,2-addition can be exercised simply by proper choice of reaction temperature. The complex **(119)** suffers exclusive 1,2-addition with dimethylamine at −90 °C and exclusive 1,4-addition at −20 °C. The 1,2-adduct **(120)** will further react with dimethylamine, but the 1,4-adduct **(122)** will not. This example demonstrates the importance of being attentive to reaction conditions when preparing amino carbene complexes, such as the alkynyl complex **(120)**, or the alkenyl complex **(76)** in Scheme 11.

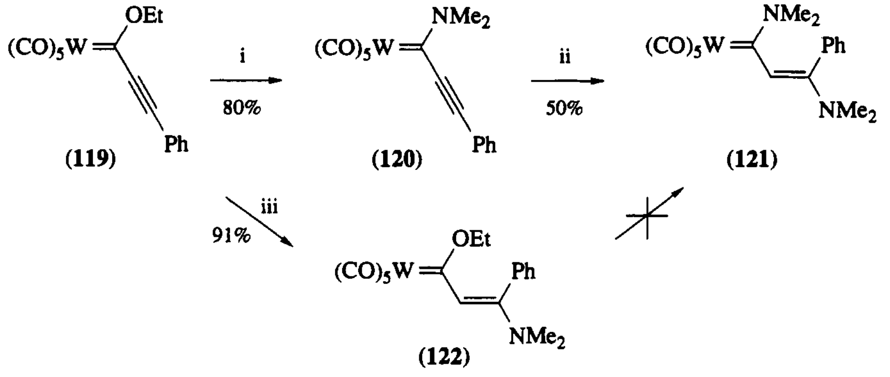

i, $HNMe_2$ (8 equiv.), $Et_2O$, −80 °C, 1 h; ii, $HNMe_2$ (8 equiv.), $Et_2O$, 20 °C, 1 h; iii, $HNMe_2$ (10 equiv.), $Et_2O$, −20 °C, 1 h

**Scheme 19**

One of the first studies directed to carbon–carbon bond formation *via* Michael addition to α,β-unsaturated carbene complexes involved the examination of the traditional reagent for this purpose in organic systems. The reactions of the styryl complex **(123)** with phenyllithium and diphenyl cuprate were compared as indicated in Scheme 20, but neither were particularly efficient.[55] As would be the case in organic systems, the cuprate gave higher proportions of 1,4-addition than the organolithium reagent. In addition to the expected 1,4-adduct (**124**), two nonorganometallic products were also formed. The enol ether (**125**) most likely results from γ-protonation of the initial 1,2-adduct (**128**). The enol ether (**126**) is likely a 1,4-addition derived product resulting from the protonation of 'enolate' (**127**) on the metal rather than on carbon, and subsequent reductive elimination from the resulting metal hydride intermediate.

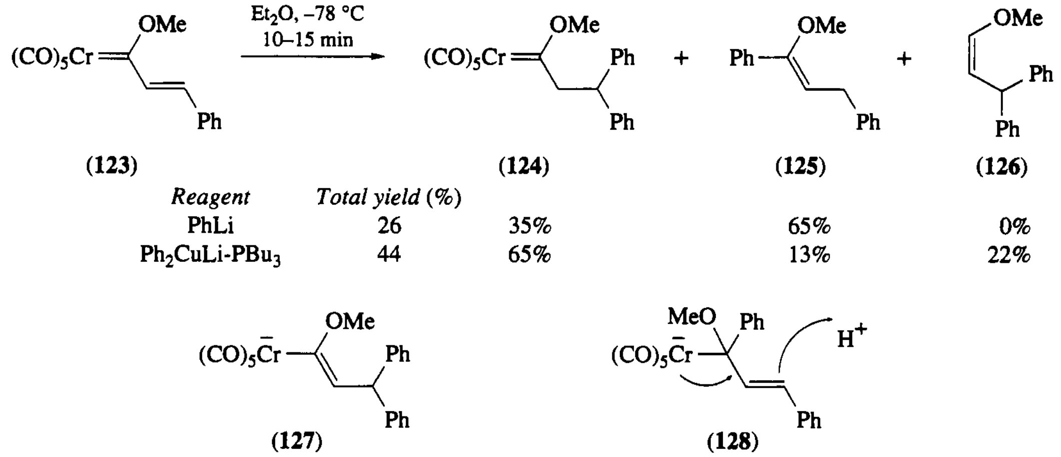

(**123**) (**124**) (**125**) (**126**)

| *Reagent* | *Total yield* (%) | (**124**) | (**125**) | (**126**) |
|---|---|---|---|---|
| PhLi | 26 | 35% | 65% | 0% |
| $Ph_2CuLi\text{-}PBu_3$ | 44 | 65% | 13% | 22% |

(**127**) (**128**)

**Scheme 20**

Greater success in Michael additions with carbon nucleophiles was achieved with ketone enolates.[56] The enolate of isobutyrophenone will undergo 1,4-addition to the isobutenyl carbene complex (**131**) in 71% yield and the enolate of cyclopentanone will react with the same carbene complex to give the Michael adduct (**133**) in 82% yield. Cleavage of the carbene ligand in (**133**) with diazomethane generates the homologated enol ether (**134**), which upon purification on silica gel gives rise to the diketone (**138**) and the aldol closed product (**137**) in a total of 65% yield. Alternatively, base-induced cleavage of the metal from the Michael adduct (**133**) with pyridine gives the (*Z*)-enol ether (**136**) in 82% yield. Hydrol-

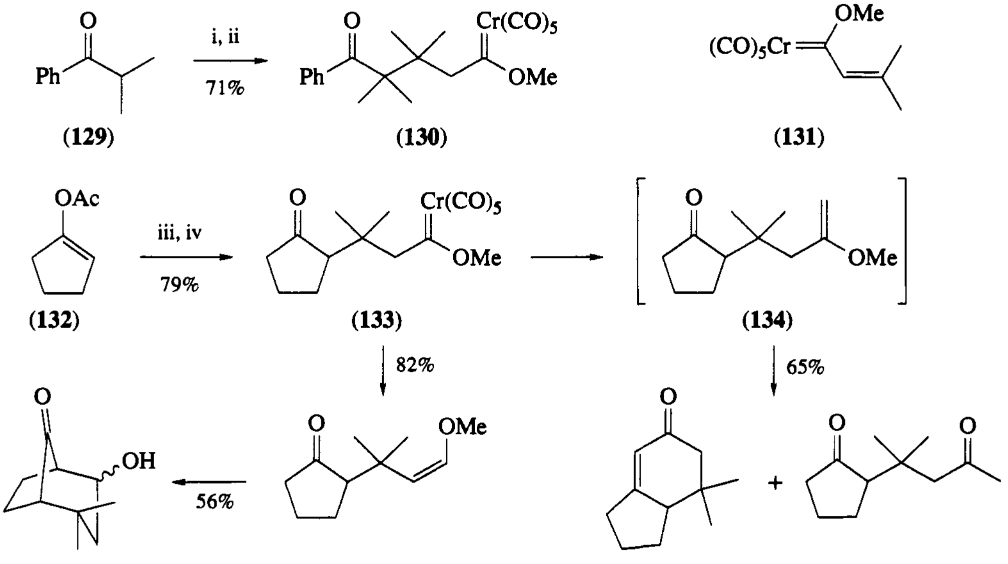

(**129**) (**130**) (**131**)

(**132**) (**133**) (**134**)

(**135**) (**136**) (**137**) 34% (**138**) 66%

i, KOBu$^t$ (1.0 equiv.), THF, 0 °C, 15 min; ii, addition to (**131**) (1.0 equiv.), THF, –78 °C, 40 min; iii, MeLi, THF, 15 min, –78 °C; iv, addition to (**131**), (0.88 equiv.), –78 °C, 5 min; v, $CH_2N_2$ (excess), PhH, 25 °C, 30 min; vi, silica gel; vii, pyridine (12 equiv.), heptane, 100 °C, 14 h; viii, 2M HCl

**Scheme 21**

ysis of **(136)** gives the intramolecular aldol product as a mixture of diastereomers. In addition to the high efficiency of the Michael addition of ketone enolates to α,β-unsaturated carbene complexes is the degree of steric congestion tolerated by these condensations as illustrated in the formation of **(130)**. The addition of an enolate to an α,β-unsaturated carbonyl compound with the generation of two adjacent quaternary centers has not been accomplished in the all-carbon case.

In line with the observed greater propensity of softer nucleophiles to Michael add to α,β-unsaturated carbene complexes, the 'enolates' of carbene complexes undergo very facile conjugate additions to α,β-unsaturated carbene complexes. This type of reaction was observed early on,[36] but a recent report more clearly defines its potential. Two of the twelve examples from the work of Macomber are included in Scheme 22.[57] The condensation of the 'enolate' of the ethyl complex **(139)** with the isopropenyl complex **(141)** occurs in a highly stereoselective fashion to give only the *meso* adduct **(140)** in 58% yield. The formation of the adduct **(143)** illustrates that the Michael addition can be coupled with alkyation of the enolate resulting from the conjugate addition. The alkylation step with allyl bromide in the formation of **(143)** occurs stereoselectively with approach of the alkylating agent from the least-hindered side of the enolate. The adducts in these reactions are bis-carbene complexes and a unique opportunity provided by these complexes is an approach to five-membered ring synthesis. Thermolysis of adduct **(145)** gives the 1,2-dimethoxycyclopentene **(146)** in 90% yield. The parent 1,2-dimethoxycyclopentene is apparently an unknown compound and the Michael additions of carbene complexes clearly provides a facile entry to functionalized systems of this class. The dimerization of carbene complexes to give alkenes has long been known for intermolecular reactions,[1,2] but they occur with lower yields than that observed from the thermolysis of **(145)**, which is the first example of an intramolecular dimerization.

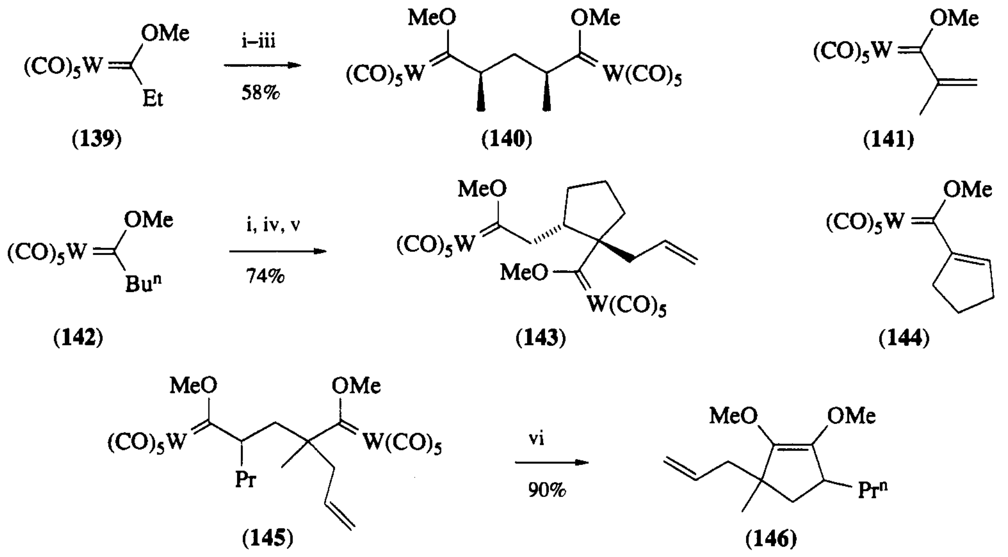

i, Bu$^n$Li, THF, –78 °C; ii, **(141)** (1.0 equiv.), –78 °C, 1 h; iii, $Me_3SiCl$ (1.0 equiv.), –78 to 25 °C; iv, **(144)** (1.0 equiv.), –78 °C, 1 h; v, allyl bromide (1.0 equiv.), –78 to 25 °C; vi, PhH, 75 °C, 3 h

**Scheme 22**

### 9.2.2.8 Nucleophilic Substitutions at and Cleavage of the Carbene Ligand

There is a very large number of reactions of carbene complexes that result in cleavage of the carbene ligand from the metal. These reactions are too numerous to include in this review and have been thoroughly treated in other reviews on the chemistry of carbene complexes.[1,2] Nucleophilic substitution reactions are an important class of reactions for the preparation of carbene complexes. This general reaction is indicated in equation (11) by the transformation of **(147)** to **(149)** and is most important for heteroatom nucleophiles, most typical being nitrogen, sulfur and oxygen. Examples of substitution of an alkoxy group for an amino group can be found in Schemes 11 and 19. Other nucleophiles of synthetic importance in substitution reactions include hydride and aryllithiums.

In most reactions involving addition of a reagent to the carbene carbon the outcome is liberation of the carbene ligand in the general process indicated by **(147)** to **(148)** in equation (11). Reactions of this type

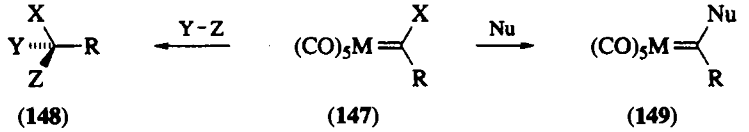

(11)

are of course of key importance in the use of carbene complexes as surrogates for organic functional groups in the reactions described in this section (Section 9.2.2), where the advantages of the metal as reactivity and selectivity auxilliary can be exploited. Examples of this type will not be included here, but can be found in the oxidative cleavages in Schemes 2, 4–6 and equation (3), in the diazomethane cleavage in Scheme 21, and in the pyridine cleavage in Scheme 21. Depending on the nature of the cleavage reaction, carbene complexes not only can serve as synthons for organic esters (their closest organic analogs), but also for a variety of other organic functional groups, including ketones, aldehydes, enol ethers, alkyl ethers, allenes and 1,3-dienes.[1,2,58]

One new method that has been reported recently will be mentioned since it has significant potential in organic synthesis. Hegedus has reported that the carbene ligand can be carbonylatively liberated upon photolysis with UV radiation.[53] Irradiation of the methoxy complex (**1a**) in the presence of methanol generated the α-methoxy ester (**152**) in 69% yield. With the development of this new method for ligand liberation, carbene complexes can serve as alkoxy- and amino-ketene synthons. This reaction most likely involves the generation of either a free or coordinated ketene and, as illustrated in the photolysis of the optically active complex (**150**), the ketene intermediate can also be trapped in an intramolecular fashion. Significant asymmetric induction in this intramolecular trapping was observed since the lactone (**154**) was produced 9:1 over its diastereomer (**155**). Since lactones of the type (**154**) can be cleaved to amino acids, this should have potential in the synthesis of optically active α-amino acids. An additional example of the utility of this method for removing the metal can be found in Scheme 18.

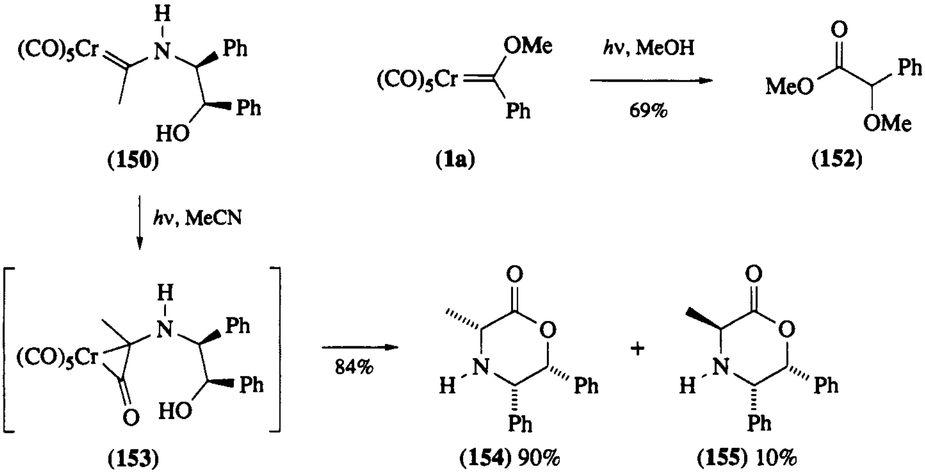

Scheme 23

## 9.2.3 REACTIONS AT THE METAL CENTER: CYCLOADDITIONS IN THE COORDINATION SPHERE

### 9.2.3.1 Coupling of the Carbene Ligand with Alkenes and 1,3-Dienes

#### *9.2.3.1.1 Three-membered rings* via *[2 + 1] cycloadditions: cyclopropanes*

One of the first reactions of carbene complexes to be investigated after their discovery was the cyclopropanation of alkenes. This reaction has been extensively studied and will only be briefly surveyed here. Two excellent reviews of this subject have appeared,[59,60] and the cyclopropanation of alkenes with carbene complexes is covered in Volume 4, Chapter 4.8 of this work. The investigation of this reaction has been driven not only by potential synthetic applications, but also due to the relationship of this reaction to alkene metathesis. The first examples, reported by Fischer and Dötz, showed that good to moderate yields of cyclopropanes could be obtained from the reaction of aryl carbene complexes with both electon-rich[61] and electron-deficient alkenes.[62] In the case of the former, good yields of cyclopropanes could be obtained only if the reaction was carried out under pressure of carbon monoxide. The reactions were not particularly stereoselective as illustrated by the formation of **(157)** and **(158)** in a 3:1 ratio under 100 atm (1 atm = 101 kPa) of carbon monoxide in a total of 61% yield. Recently, it has been reported that higher yields and stereoselectivities could be achieved with silyl enol ethers.[63] An unactivated alkene such as tetramethylethylene could not be cyclopropanated even under forcing conditions.[64] The fact that good yields of cyclopropanes could be obtained with both electron-rich and electron-deficient alkenes, but not simple alkenes, suggests that the two reactions in Scheme 24 operate with different mechanisms.

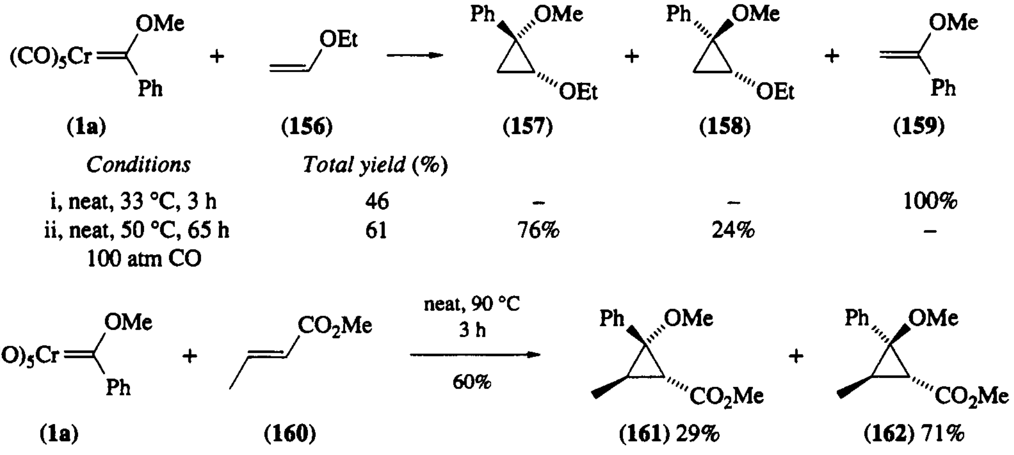

**(1a)** **(156)** **(157)** **(158)** **(159)**

| *Conditions* | *Total yield (%)* | (157) | (158) | (159) |
|---|---|---|---|---|
| i, neat, 33 °C, 3 h | 46 | – | – | 100% |
| ii, neat, 50 °C, 65 h<br>100 atm CO | 61 | 76% | 24% | – |

**(1a)** **(160)** **(161)** 29% **(162)** 71%

**Scheme 24**

Unactivated alkenes can be cyclopropanated if more electrophilic carbene complexes are employed or if the cyclopropanation is carried out in an intramolecular fashion. As an example of the former approach, Casey prepared the highly reactive benzylidene complex **(164)** *in situ* and found that it will efficiently cyclopropanate most unactivated alkenes. This is illustrated in Scheme 25 by its reaction with 1-methylcyclopentene.[65] It has since been found that the complex **(164)** could be isolated and can be

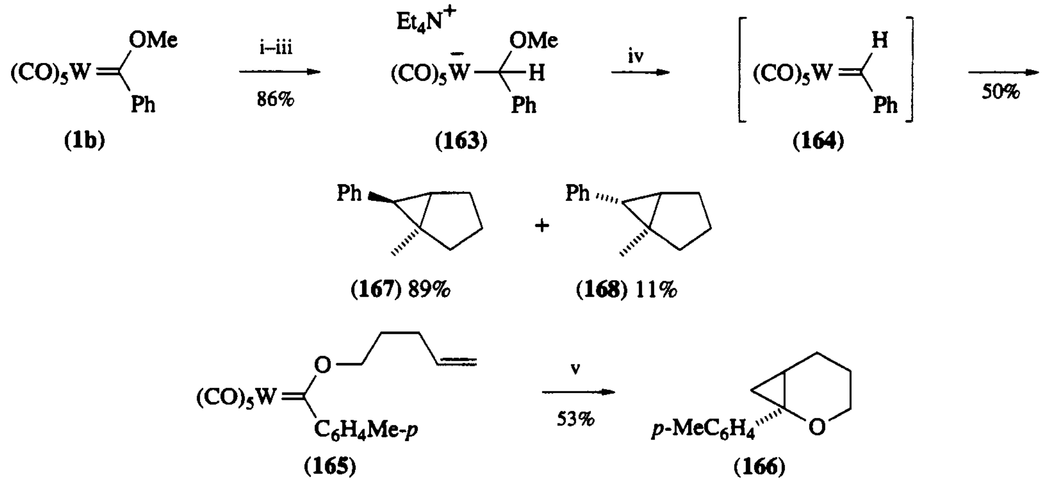

**(1b)** **(163)** **(164)** **(167)** 89% **(168)** 11% **(165)** **(166)**

i, HB(OPrⁱ)₃, THF, (1.5–2.2 equiv.), 0 °C; ii, 1 M NaOH; iii, Et₄NBr (3 equiv.); iv, 1-methylcyclopentene (excess), $CF_3CO_2H$ (3 equiv.), $CH_2Cl_2$, –78 °C, 40 min, –78 to 25 °C; v, PhH, 70 °C, 13 h

**Scheme 25**

handled in the solid form.[66] A number of intramolecular cyclopropanations related to the example shown in Scheme 25 have been examined, mainly as a probe for mechanistic issues, nonetheless, given the ease of preparation of compounds of the type (**165**) this could be a useful synthetic method.[67–69]

Efficient cyclopropanations of unactivated alkenes can also be achieved with cationic cyclopentadienyliron–carbene complexes and this area has been developed by Brookhart,[70] Casey[71] and Helquist.[72] Alkylation of the α-thioalkyl iron complex (**169**) generates the cationic carbene complex (**170**), which is not observed, but presumably very rapidly cyclopropanates the unactivated alkene to give the tricyclic compound (**171**) as a single diastereomer.[73] Optically active cyclopropanes can be obtained by asymmetric induction from the iron center by employing carbene complex precursors of the type (**172**), in which the iron center was resolved with the aid of a chiral phosphine ligand in place of one of the two carbon monoxide ligands.[74] The carbene complex (**173**) was generated in the presence of styrene and very rapidly led to the formation of the cyclopropanes (**174**) and (**175**). This reaction was not particularly selective with regard to the formation of diastereomers, but each was formed with reasonably high optical purity.

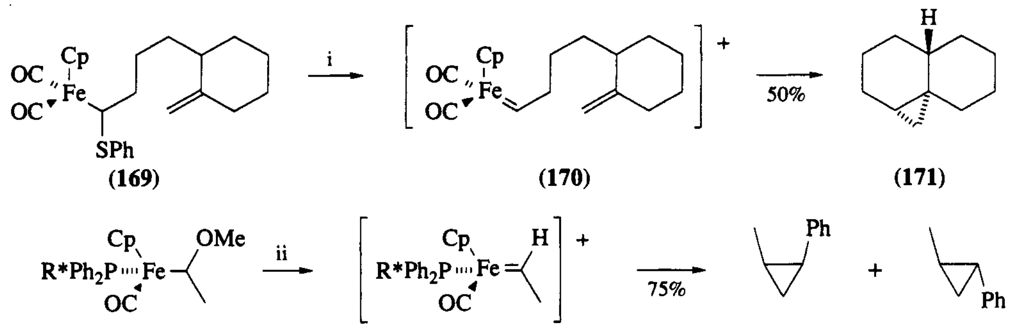

(**169**) (**170**) (**171**)

(**172**) 98% *ee*
R* = (*S*)-2-methylbutyl

(**173**)

(**174**) 22%
84% *ee*

(**175**) 78%
88% *ee*

i, $(MeO)_3CBF_4$ (1.25 equiv.), $CH_2Cl_2$, 25 °C, 12 h;
ii, styrene (8 equiv.), $Me_3SiOTf$ (1 equiv.), $Et_3N$ (0.05 equiv.), $CH_2Cl_2$, –78 to 25 °C

**Scheme 26**

In a recent development, it has been found that the cyclopropanations of electron-deficient alkenes with heteroatom-stabilized complexes, such as (**1a**), need not be carried out with the alkene as solvent (as are the reactions in Scheme 24), but in fact better yields are obtained if the reaction is performed stoichiometrically in cyclohexane.[75,76] A variety of different electron-deficient alkenes were examined including the dienyl ester (**176**) which gave a 4:1 mixture of diastereomers in 70% total yield. This report should stimulate a reconsideration of the potential of these reactions for synthetic organic applications.

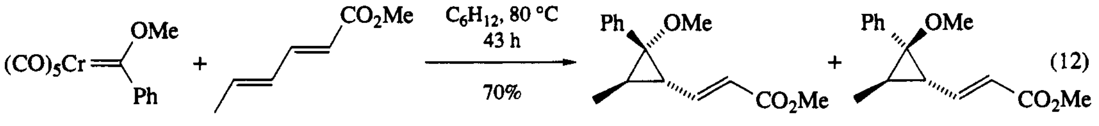

(**1a**) (**176**) 1 equiv. (**177**) 80% (**178**) 20%

The cyclopropanation reaction has been extended to electron-rich dienes with the recent report of the reactions shown in Scheme 27.[22] The carbene complex in this reaction was the cyclohexenyl chromium complex (**179a**) and the resulting products from its reaction with the diene (**180**) were found to be the *trans*-divinylcyclopropane (**181**) and the seven-membered dienol ether (**183**). The latter presumably results from the Cope rearrangement of the initially formed *cis*-divinylcyclopropane (**182**) and the stereoselectivity of the cyclopropanation is 1.7:1.0. The *trans*-divinylcyclopropane (**181**) can thermally be converted to the same diastereomer (**183**) and thus this tandem cyclopropanation–Cope sequence should have potential for the construction of highly functionalized seven-membered rings. Although the reasons for it are unknown at this time, it was observed that the analogous reaction of the tungsten complex (**179b**) did not give cyclopropanation products, but rather the Diels–Alder adduct (**184**).

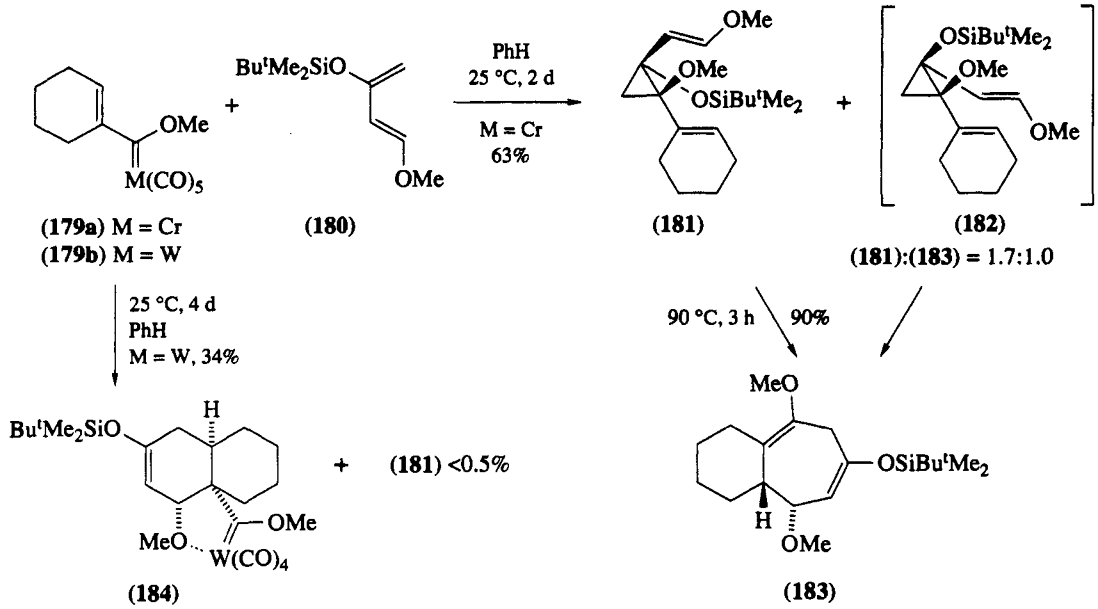
OMe
M(CO)5
(179a) M = Cr
(179b) M = W
+
Bu^tMe2SiO
OMe
(180)
PhH
25 °C, 2 d
M = Cr
63%
OMe
OMe
OSiBu^tMe2
(181)
+
OSiBu^tMe2
OMe
OMe
(182)
(181):(183) = 1.7:1.0
25 °C, 4 d
PhH
M = W, 34%
90 °C, 3 h
90%
Bu^tMe2SiO
H
MeO
OMe
W(CO)4
(184)
+ (181) <0.5%
MeO
OSiBu^tMe2
H
OMe
(183)

Scheme 27

### 9.2.3.1.2 *Four-membered rings* via *[2 + 1 + 1] cycloadditions: cyclobutanones*

In a recent publication in 1989, Sierra and Hegedus reported that cyclobutanones can be obtained from the photolysis of Fischer carbene complexes in the presence of alkenes.[77] The cyclobutanones are produced as a single diastereomer and a single regioisomer in high yields. A few of the examples from this report are presented in Scheme 28. Electron-rich alkenes give high yields of cyclobutanones as a single regioisomer, unactivated alkenes also work well and react with retention of stereochemistry, as illustrated in the case of *cis*-2-butene. The yield with styrene falls off, and electron-deficient alkenes such as methyl acrylate and acrylonitrile fail. The intramolecular reaction of the carbene complex (**186**) is most successful if the reaction is carried out under an atmosphere of carbon monoxide. The first step of this reaction is thought to involve a photo-induced insertion of carbon monoxide to give the ketene complex (**188**). It is suspected that the cyclobutanones are a result of the reaction of the ketene complex (**188**) with the alkenes rather than the result of a [2 + 2] cycloaddition of the alkene with a metal-free ketene, but at this time this issue cannot be resolved. This method for the generation of cyclobutanones is clearly superior in terms of yields and reaction conditions to the traditional [2 + 2] cycloaddition of alkenes and alkoxyketenes generated from acid halides.

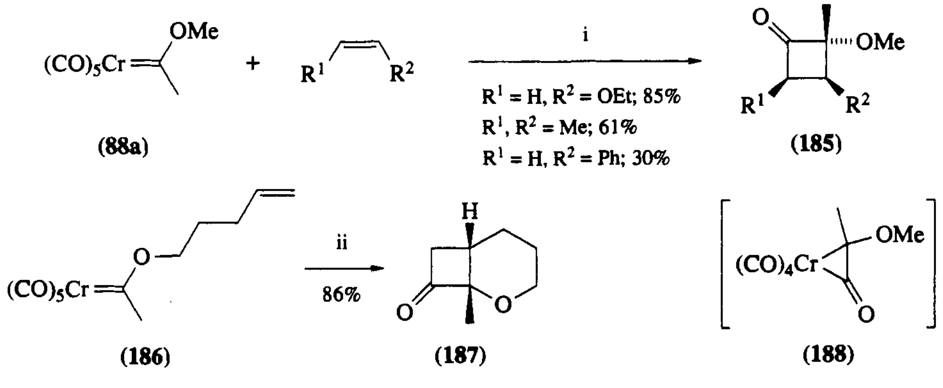
OMe
(CO)5Cr
(88a)
+
R1
R2
i
R1 = H, R2 = OEt; 85%
R1, R2 = Me; 61%
R1 = H, R2 = Ph; 30%
O
OMe
R1
R2
(185)
O
(CO)5Cr
(186)
ii
86%
H
O
O
(187)
OMe
(CO)4Cr
O
(188)

i, *h*v, MeCN, 15 h, 25 °C; ii, same as i except the reaction was carried out under CO

Scheme 28

### 9.2.3.1.3 Coupling leading to acyclic products

The reaction of carbene complexes with alkenes generally leads to cyclopropane formation or to metathesis; however, in the reactions of the iron carbene complexes (**189**) with alkenes a new mode of reactivity was uncovered.[78] The reactions of (**189**) with a variety of alkenes lead to the acyclic coupling products (**190**) and (**191**). These products are thought to arise from a β-hydride elimination in the ferracyclobutane intermediate (**192**) and a subsequent reductive elimination from the allyl complex (**193**), which can occur in either of two directions to give (**190**) or (**191**). The regiochemistry of the incorporation of the alkene into the ferracyclobutane is independent of the nature of the alkene. The regioselectivity in the formation of (**192**) is consistent with a steric consideration or with a two-step mechanism involving a diradical intermediate, but not a two-step mechanism involving a zwitterionic intermediate. The present view is that steric effects lead to the stereoselective formation of (**192**), since an alkene with a cyclopropyl substituent is converted to the coupling products (**190**) with the cyclopropyl ring intact.

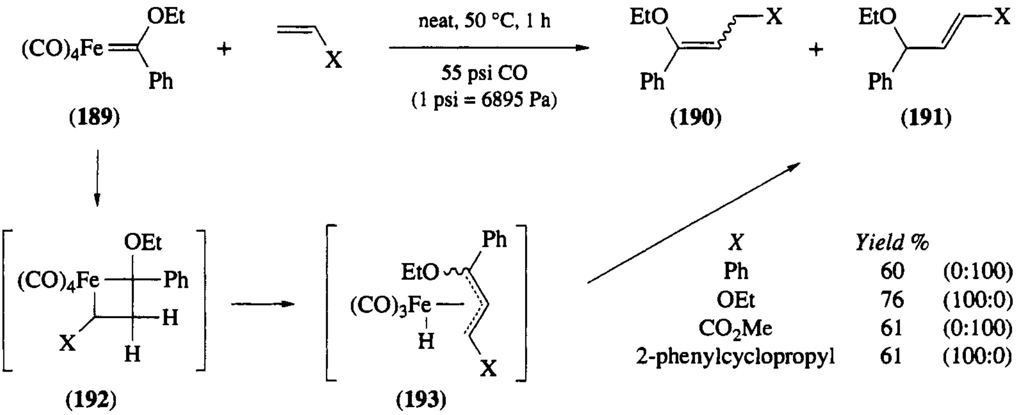

| *X* | *Yield %* | |
|---|---|---|
| Ph | 60 | (0:100) |
| OEt | 76 | (100:0) |
| $CO_2Me$ | 61 | (0:100) |
| 2-phenylcyclopropyl | 61 | (100:0) |

**Scheme 29**

A similar type of reaction has been observed in the reactions of iron–carbene complexes with 1,3-dienes.[79] In this case the direction of reductive elimination in the metal hydride intermediate corresponding to (**193**) is constrained to that which generates a conjugated 1,3-diene; however, two isomeric products are also obtained from this reaction which are epimers about the face of the diene to which the iron tricarbonyl group is attached. This reaction produces highly functionalized 1,3-dienyl complexes of iron in high yield under relatively mild conditions and will likely play a role in the development of the

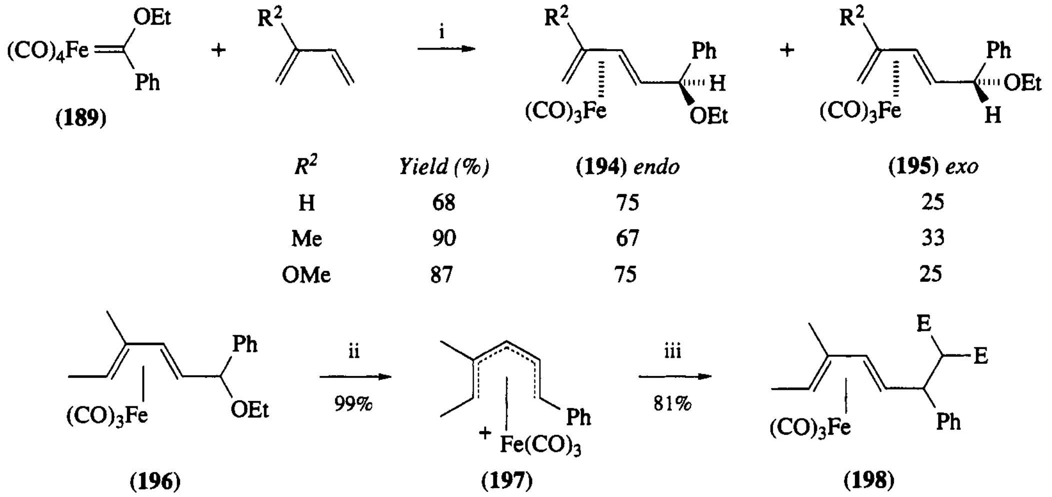

| $R^2$ | *Yield (%)* | (**194**) *endo* | (**195**) *exo* |
|---|---|---|---|
| H | 68 | 75 | 25 |
| Me | 90 | 67 | 33 |
| OMe | 87 | 75 | 25 |

i, hexane, 25 °C, 0.5–10 h; ii, $HClO_4$, $Ac_2O$, 0 °C; iii, diethyl sodiomalonate, 25 °C

**Scheme 30**

chemistry of 1,3-dienyl complexes of iron. This is illustrated in Scheme 30 with the generation of the cationic $\eta^5$-dienyl complex (**197**) by the treatment of (**196**) with acid. Although the chemistry of cyclic $\eta^5$-dienyl complexes of iron has been explored by a number of groups for two decades, the chemistry of acyclic complexes of the type (**197**) is essentially undeveloped. In one of the few examples of nucleophilic addition to such complexes, the 1,3-dienyl complex (**198**) can be obtained in 81% yield from the addition of diethyl sodiomalonate to (**197**).

### 9.2.3.2 Coupling of the Carbene Ligand with Alkynes

#### *9.2.3.2.1 Three-membered rings* via *[2 + 1] cycloadditions: cyclopropenes*

The reaction of alkenes with Fischer carbene complexes most typically leads to cyclopropane products; however, the formation of a three-membered ring product from a reaction with an alkyne has been observed on only one occasion.[80] The reaction of the cationic iron–carbene complex (**199**) with 2-butyne presumably leads to the formation of the cyclopropene (**200**), which was unstable with respect to hydride abstraction by the starting carbene complex and the ultimate product isolated from this reaction was the cyclopropenium salt (**201**) and the benzyl–iron complex (**202**). Cyclopropene products have never been observed from Group 6 carbene complexes despite the extensive investigations of these complexes with alkynes that have been carried out since the mid 1970s.

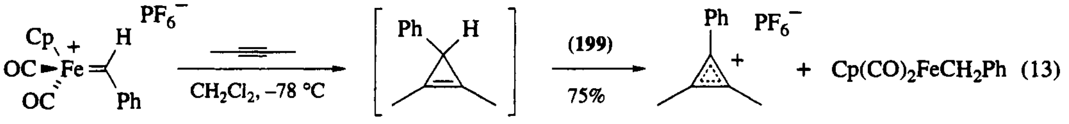

(**199**) (**200**) (**201**) (**202**)

#### *9.2.3.2.2 Four-membered rings* via *[2 + 1 + 1] cycloadditions: cyclobutenones*

The reactions of Group 6 carbene complexes with alkynes has been studied extensively since the mid 1970s, and normally these reactions produce six-membered ring products, but in a dozen or so instances cyclobutenone products have been observed.[81,82] In most cases cyclobutenones were minor products from these reactions, but in a few cases where circumstances were favorable they were the major products of the reaction. Cyclobutenone formation is the result of the assembly of the pieces indicated diagramatically in (**205**). A mechanistic discussion of their formation will be deferred until Section 9.2.3.2.4 The first report of a cyclobutenone was by Dötz who found that the reaction of the methyl complex (**88a**) with diphenylacetylene produced cyclobutenone (**203**) as an aryl chromium tricarbonyl complex (coordinated to one of the phenyl groups) in 27% yield.[83] It was later found that the yield of (**203**) (as the metal-free cyclobutenone) could be increased to 70% if the reaction was carried out in the presence of 1 equiv. of triphenylphosphine.[84] This reaction is not general, as it was found that cyclobutenones are not produced in this reaction with terminal alkynes or with internal alkynes, such as 3-hexyne, that are not as sterically encumbered as diphenylacetylene.[84] That sterically bulky substituents on the alkyne favor cyclobutenone formation can be seen in the example from the work of Yamashita of the reaction of complex (**1a**) with ethyl *t*-butylpropynate, which gives (**204**) in 93% yield, whereas the same reaction with ethyl phenylpropynate does not give any cyclobutenone.[85]

The formation of cyclobutenones is also affected by solvent and internal chelating groups, as indicated by the reactions in equation (14).[86,87] As indicated by the first two reactions, cyclobutenone formation is favored in the more polar solvent. The third and fourth reactions indicate that cyclobutenone formation is also favored by the presence of an oxygen substituent that can chelate to the metal center during the reaction. These observations, however, are not general. For example, the quinone products (to be discussed in Section 9.2.3.2.4i) are formed in high yield from the reaction of complexes of the type (**206**, R = H and R = OMe) with terminal alkynes in both THF and acetonitrile. Although dependence of cyclobutenone formation on chelation in complexes of the type (**206**) is consistent with the observed effect of triphenylphosphine on the reaction of complex (**1a**), the reaction of the (**206**, R = H) is unaffected by the presence of triphenylphosphine. At this point in time, the reactions of carbene complexes with alkynes cannot be employed as a general approach to the synthesis of cyclobutenones.

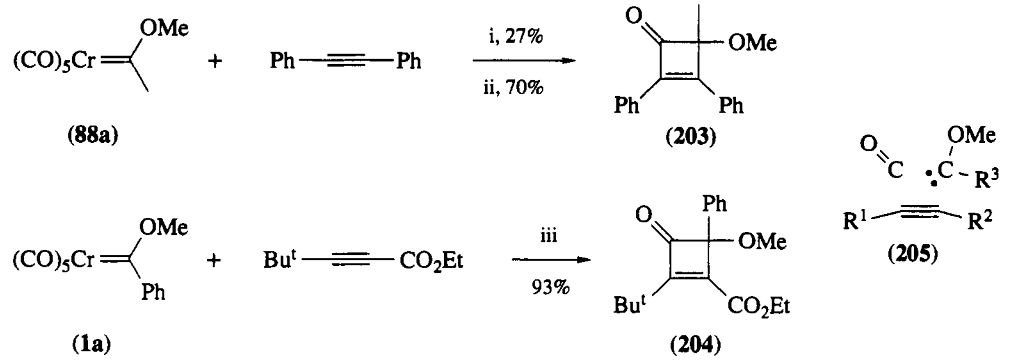

i, $Bu^n{}_2O$, 70 °C, 1 h; ii, THF, 1 equiv. $Ph_3P$, 80 °C, 24 h; iii, THF, 65 °C, 6 h

Scheme 31

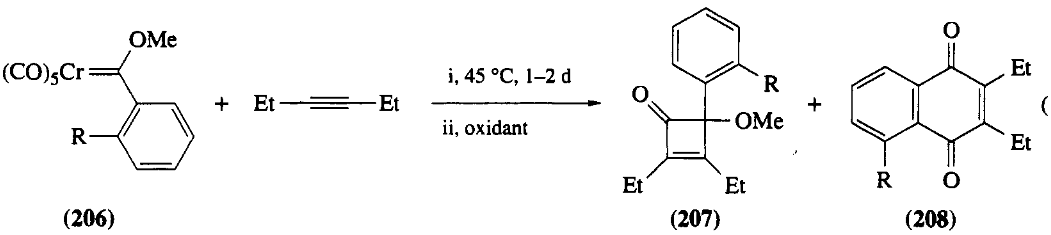

(14)

| R | Solvent | Oxidant | (207) Yield (%) | (208) Yield (%) |
|---|---|---|---|---|
| H | THF | $Ce^{IV}$ | <2 | 88 |
| H | MeCN | $Fe^{III}$ | 23 | 38 |
| *o*-OMe | MeCN | air | 43 | <2 |
| *o*-$OBu^t$ | MeCN | $Fe^{III}$ | 23 | 24 |

### 9.2.3.2.3 Five-membered rings

#### (i) [3 + 2] Cycloadditions—cyclopentadienes and indenes

In almost all situations the reactions of Fischer carbene complexes of chromium with alkynes lead to the formation of six-membered ring products, but on several occasions five-membered ring annulated products have been observed as minor products or as major products if the formation of six-membered rings is blocked.[81] In an early report by Dötz, the reaction of the 2,6-dimethylphenyl complex (**209**) was observed to react with diphenylacetylene to give the complexed and uncomplexed indenes (**210**) and (**211**).[88] This reaction is not general; if one or two of the methyl groups are removed from complex (**209**) only six-membered ring products are observed and these reactions will be discussed in Section 9.2.3.2.4i. These annulations occur with cyclization to the aryl substituent of the carbene carbon, the overall transformation is represented by the assembly of the pieces indicated diagramatically by structure (**213**), and a mechanistic consideration of this reaction will be presented in Section 9.2.3.2.4.

While unsubstituted aryl complexes of chromium react with alkynes to give six-membered ring products, the tungsten carbene complex (**1b**) was reported to react with diphenylacetylene to give the indene (**212**) in 90% yield.[89] This reaction with tungsten complexes was reported to fail with terminal alkynes and sterically less encumbered disubstituted alkynes. This was attributed to competing polymerization of the alkyne, although this can be offset in many cases if the reactions are carried out at low concentrations.[90] It was reported that five-membered annulation is favored by polar coordinating solvents,[86,87] and Yamashita found that carbene complexes bearing an amino ancilliary substituent, such as (**214**), undergo reactions with alkynes in DMF to exclusively give five-membered ring annulated products.[91] This reaction is general for aryl complexes with both disubstituted and terminal alkynes; (**216**) is obtained from the reaction of (**214**) and 1-hexyne in 95% yield.

The five-membered annulation of amino complexes appears not to be general for alkenyl complexes. The reaction of the morpholino complex analogous to (**217**) with 3-hexyne in DMF gives a low yield

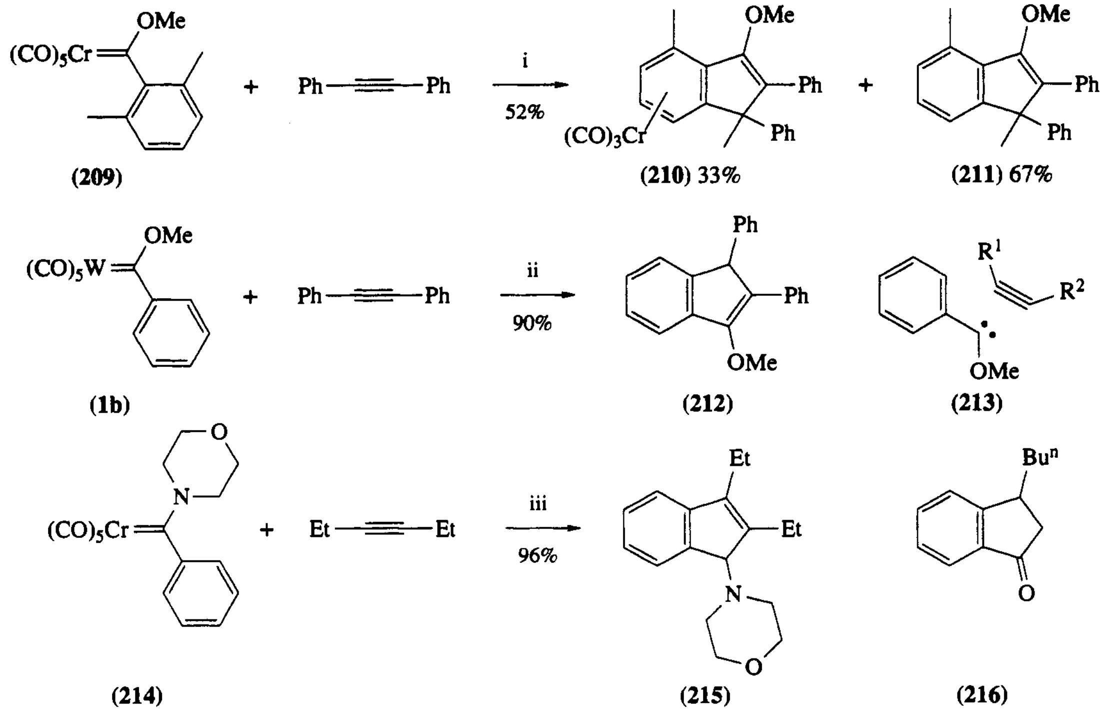

i, *n*-butyl ether, 100 °C, 2 h; ii, toluene, 100 °C, 3 h; iii, DMF, 125 °C, 5 h

**Scheme 32**

(<10%) of a mixture of compounds that has not yet been identified.[90] The reactions comparing the three Group 6 metals indicated in equation (15) include the first examples of the annulation of a molybdenum–carbene complex.[90] In contrast to the aryl tungsten complex (**1b**), the alkenyl tungsten complex (**219**) (as well as the chromium complex **217**) gives only the six-membered ring annulated product (**220**) with 3-hexyne. The molybdenum complex (**218**), however, gives the five-membered ring annulated product (**221**) as the major product of the reaction. The enone (**221**) is the result of the acid hydrolysis of the primary product of the reaction, which is presumably the cyclopentadiene (**222**) or isomers thereof. This is the first example of the formation of a five-membered ring annulated product from the reaction of an alkenyl carbene complex and should stimulate further investigations of the chemistry of molybdenum–carbene complexes.

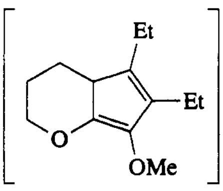

**(222)**

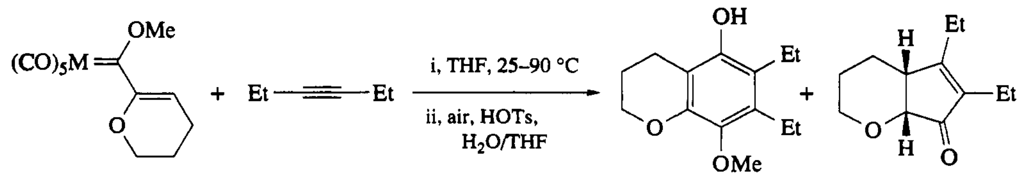

(15)

| *Complex* | *M* | *Yield* (%) | **(220)** | **(221)** |
|---|---|---|---|---|
| **(217)** | Cr | 73 | >99% | <1% |
| **(218)** | Mo | 67 | 12% | 88% |
| **(219)** | W | 77 | >98% | <2% |

### *(ii) [2 + 2 + 1] Cycloadditions: furans*

As is the case with cyclobutenones and five-membered annulation products, furans are usually only observed as minor products in the reaction of chromium–carbene complexes and alkynes, and have only been observed in a few instances.[81] One exception is the reaction of the ferrocenyl carbene complex (**223**) with diphenylacetylene for which the furan (**224**) was reported as the only product.[92] The reactions of carbene complexes of other metals with alkynes have been more recently found to display higher selectivity for the formation of furan products. Iron amino carbene complexes of the type (**225**) will react with a variety of alkynes to give furans as either the major or exclusive product.[93] The reaction of (**225**) with methyl tetrolate gives exclusively the aminofuran (**226**) as a single regioisomer. Other alkynes give varying amounts of pyrone and two-alkyne annulation products along with the furans. Cobalt–carbene complexes of the type (**227**) give exclusively furan products with all of the alkynes that were examined.[94] The furan nucleus is constructed from the pieces indicated diagramatically in (**229**) and the mechanism will be briefly presented in Section 9.2.3.2.4i. The connectivity indicated in the assembly (**229**) was determined by two labeling experiments, and the reader is referred to the original report for a discussion of these experiments.[82]

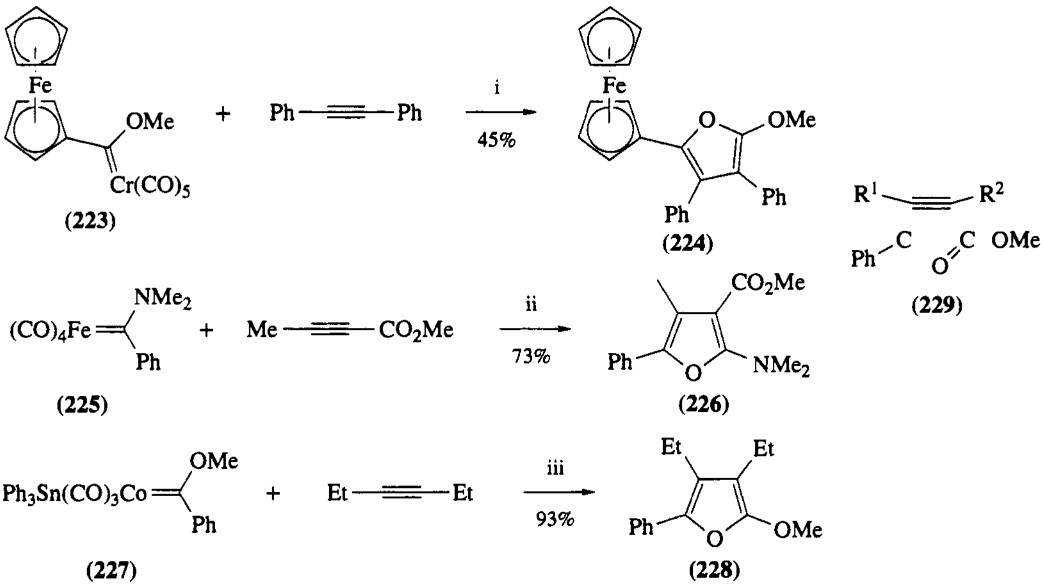

Fe
OMe
Cr(CO)5
(223)
+
Ph—≡—Ph
i
45%
Fe
O
OMe
Ph
Ph
(224)
R1—≡—R2
Ph C C OMe
O
(229)
NMe2
(CO)4Fe
Ph
(225)
+
Me—≡—CO2Me
ii
73%
CO2Me
Ph
O
NMe2
(226)
OMe
Ph3Sn(CO)3Co
Ph
(227)
+
Et—≡—Et
iii
93%
Et
Et
Ph
O
OMe
(228)

i, $Bu^n{}_2O$, 80 °C, 4 h; ii, $ClCH_2CH_2Cl$, 60 °C, 1 h; iii, PhH, 50 °C, 6 h

**Scheme 33**

The high selectivity of the reaction of cobalt–carbene complexes with alkynes for furan products was taken advantage of in the synthesis of bovolide, a natural flavor constituent of butter.[94] The carbene complex (**230**) was prepared in two steps from *n*-pentanal and was treated with 3 equiv. of 2-butyne. The crude reaction mixture, which presumably contained the furan (**231**), was treated directly with 3 equiv. of trimethylsilyl iodide to give bovolide in ~ 50% yield from carbene complex (**230**).

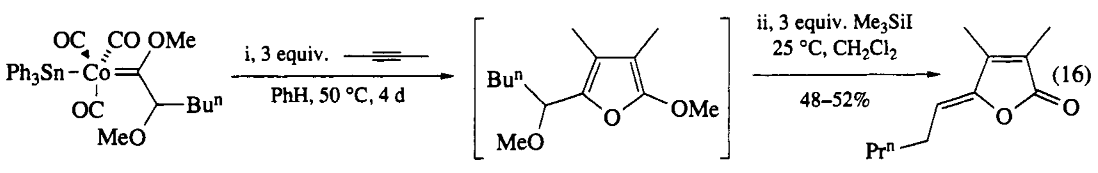

OC
CO
OMe
Ph3Sn–Co
OC
Bun
MeO
i, 3 equiv. —≡—
PhH, 50 °C, 4 d
Bun
MeO
O
OMe
ii, 3 equiv. Me3SiI
25 °C, CH2Cl2
48–52%
Prn
O
O
(16)

**(230)** **(231)** **(232)** Bovolide

### *9.2.3.2.4 Six-membered rings*

#### *(i) [3 + 2 + 1] Cycloadditions; benzannulation and cyclohexadienone annulation*

With the possible exception of the cyclopropanation of alkenes, the most thoroughly examined reaction of Fischer carbene complexes is that with alkynes.[1–3] The reactions in this class that have been of most interest to date are those that lead to six-membered ring 4-alkoxyphenols of the general type (**234**). This reaction is a benzannulation, in which the newly formed benzene ring is generated in the coordination sphere of the metal under neutral conditions at near ambient temperatures from the pieces indicated diagramatically in (**235**). This benzannulation reaction produces new benzene rings that have a 1,4-dioxygen substitution pattern and it is for perhaps this reason that it is the most extensively applied reaction of carbene complexes in organic synthesis.

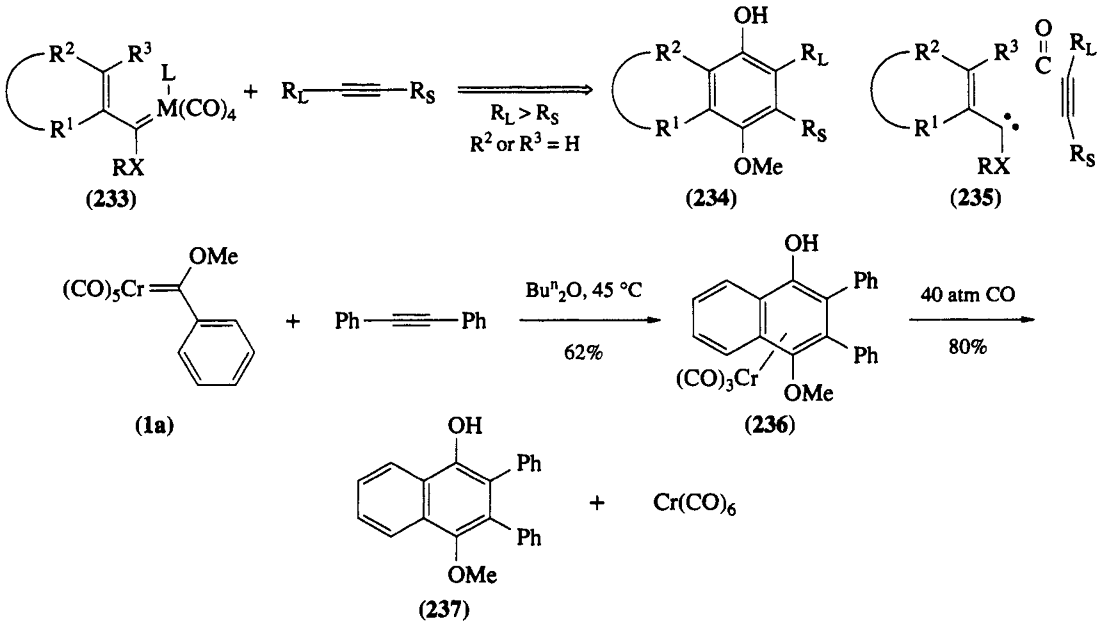

**Scheme 34**

A comprehensive treatment of the benzannulation of Fischer carbene complexes with alkynes is not possible in this review, and thus instead the material presented here will hopefully serve to give the reader an overview of its scope and limitations. The first report of this reaction was in 1975 by Dötz in which he describes the formation of the naphthol chromium tricarbonyl complex (**236**) from the reaction of the phenyl chromium complex (**1a**) with diphenylacetylene.[95] In the intervening years over 100 papers have been published describing various aspects of this reaction.[1–3] The reaction of the generic carbene complex (**233**; Scheme 34) with alkynes will serve to focus the organization of the scope and limitations of the benzannulation reaction. The issues to be considered are: (i) the regioselectivity with unsymmetrical alkynes; (ii) possible mechanisms; (iii) applications in natural product syntheses; (iv) the effect of substitution on the aryl or alkenyl substituent of the carbene carbon; (v) functionality on the alkyne; (vi) effects of the solvent and the concentration of the alkyne; (vii) tandem applications with other reactions of carbene complexes; (viii) reactions where aromatization is blocked (cyclohexadienone annulation); (ix) annulation of aryl *versus* alkenyl carbene complexes; (x) the effect of the ligands L on the metal; (xi) the effect of the ancilliary substituent RX; and (xii) reactions with —C≡X functionality.

*(a) Regiochemistry of alkyne incorporation.* All of the studies in the literature suggest that the regioselectivity of the incorporation of an unsymmetrical alkyne is determined by the steric differences of the alkyne substituents and not by their electronic differences.[3,96] The regioselectivity with unsymmetrical disubstituted alkynes is low for alkenyl complexes as well as for aryl complexes, as indicated by the the reaction of complex (**1a**) with 2-pentyne.[97] The major isomer is always that in which the sterically larger group is incorporated adjacent to the phenol functionality. This lack of regiocontrol for unsymmetrical disubstituted alkynes can be overcome in intramolecular annulations in which the alkyne is tethered to

the ancillary substituent RX (**233**; Scheme 34) and in this manner regioselective syntheses of deoxyfrenolicin (**263**),[98,115] nanaomycin (**264**),[98,115] angelicin (**271**)[99] and sphondin (**272**)[99] were possible (Scheme 37). The benzannulations of both aryl and alkenyl complexes are highly regioselective with terminal alkynes and in the case of the reaction of (**241**) with 1-pentyne this was greater than 250:1.[3]

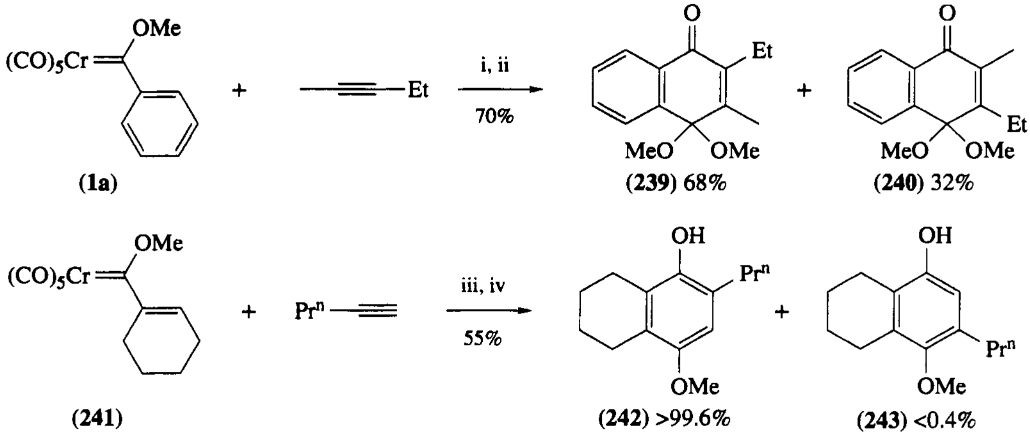

i, $Bu^n{}_2O$, 45 °C, 24 h; ii, $Ce(NO_3)_6(NH_4)_2$, methanol, 25 °C, 30 min;
iii, THF, 45 °C, 24 h; iv, $FeCl_3$–DMF, THF, 25 °C, 30 min

**Scheme 35**

*(b) Mechanistic considerations.* A consideration of all of the mechanistic possibilities for all of the nine known structural types[81] from the reactions of Fischer carbene complexes with alkynes is not possible in this review.[1d,3,82,87,100] The mechanistic possibilities presented in Scheme 36 are for the formation of the five-membered ring annulated product (**250**),[101] the benzannulated product (**253**), the two-alkyne-annulated product (**258**)[102] and polyalkyne.[103] With regard to the mechanism for the formation of the six-membered benzannulated product (**253**) there are two mechanisms that have been proposed, neither of which can be ruled out on the basis of existing data. The kinetics of the reaction suggest that the first step is the dissociation of a carbon monoxide ligand to generate the unsaturated intermediate (**245**).[100a] This step is thought to be the rate-limiting step in most situations and all subsequent steps are then fast, which is consistent with the fact that none of the intermediates indicated in Scheme 36 have been isolated from these reactions where M is chromium. The vinyl ketene complex (**255**) has been isolated when M is cobalt[94] and vinyl ketenes have been trapped[81] or isolated where the metal is displaced from the vinyl ketene functionality.[81]

The second step is proposed to involve the addition of the alkyne to give the alkyne complex (**246**). The next step involves carbon–carbon bond formation between the carbene carbon and one of the alkyne carbons and it is this step which may determine the regioselectivity of the reaction. The regioselectivity can be accounted for by a consideration of the most stable conformer of the alkyne complex (**246**) on the basis of steric interactions; this should be that which has the smallest substituent adjacent to the carbene ligand and the largest substituent adjacent to the *trans* carbon monoxide ligand. Electrocyclic ring opening of (**247**) would generate the vinyl carbene complex intermediate (**248**), which is the branch point between the two mechanisms that have been proposed for the formation of the benzannulated product (**253**).[1d,100]

The mechanism proposed by Dötz involves the insertion of a carbon monoxide into the vinyl carbene complex intermediate with the formation of the vinyl ketene complex (**255**).[100a] Electrocyclic ring closure of (**255**) leads to the cyclohexadienone complex (**252**), which is related to the final benzannulation product by a tautomerization when R is hydrogen. The mechanism proposed by Casey differs from that of Dötz in that the order of the steps involving carbon monoxide insertion and cyclization to the aryl or alkenyl substituent is reversed.[1d] Specifically, the vinyl carbene complex intermediate (**248**) first undergoes cyclization to the metallacyclohexadiene (**249**), followed by carbon monoxide insertion to give the intermediate (**251**), and finally reductive elimination to give cyclohexadienone intermediate (**252**). At this time the circumstantial evidence favors the intermediacy of vinyl ketene intermediates since they can be trapped from these reactions[81] and isolated where the metal is dispaced from the vinyl ketene functionality;[81] however, there is not any evidence which can rule out the alternative mechanism.

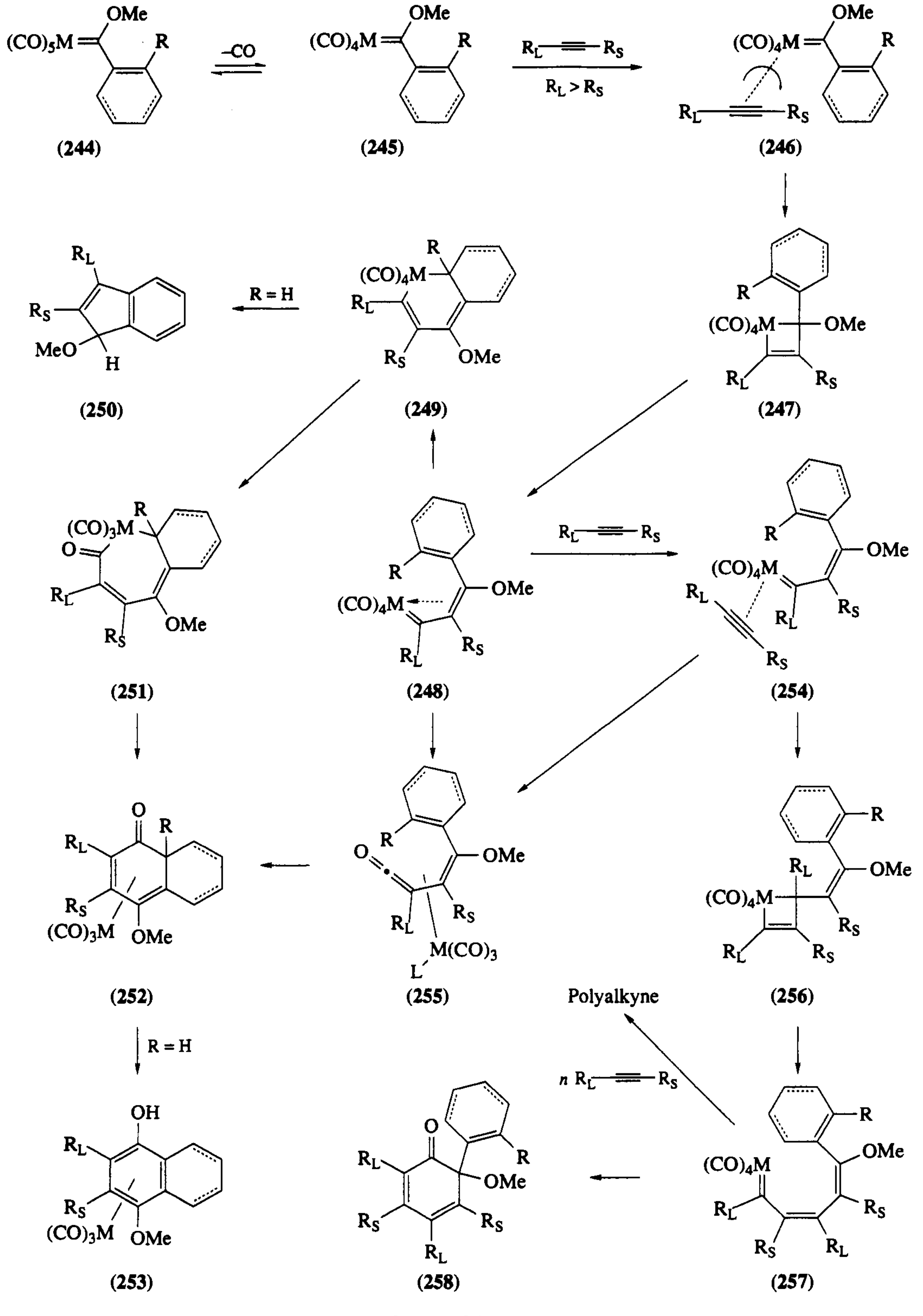

(244)
(245)
(246)
(247)
(248)
(249)
(250)
(251)
(252)
(253)
(254)
(255)
(256)
(257)
(258)
–CO
R_L≡R_S
R_L > R_S
R = H
R = H
n R_L≡R_S
Polyalkyne
(CO)5M
(CO)4M
(CO)3M
M(CO)3
OMe
MeO
OH
R
R_L
R_S
L

**Scheme 36**

*(c) Applications in natural product synthesis.* The applications of the benzannulation of Fischer carbene complexes to natural product synthesis is too extensive to review comprehensively here. Those targets which have been realized in either formal or total synthesis are listed in Scheme 37 and they include the total syntheses of vitamins $K_{1(20)}$, $K_{2(5)}$, $K_{2(10)}$ and $K_{2(15)}$,[104] the total synthesis of vitamin E,[105] the

total syntheses of deoxyfrenolicin and nanaomycin,[98] the total synthesis of 7-ethoxyprecocene,[106] the total synthesis of khellin,[107] the total syntheses of angelicin, sphondin, heratomin and thiosphondin,[99] and formal syntheses of 4-demethoxydaunomycinone, daunomycinone and 11-deoxydaunomycinone.[3,108,109]

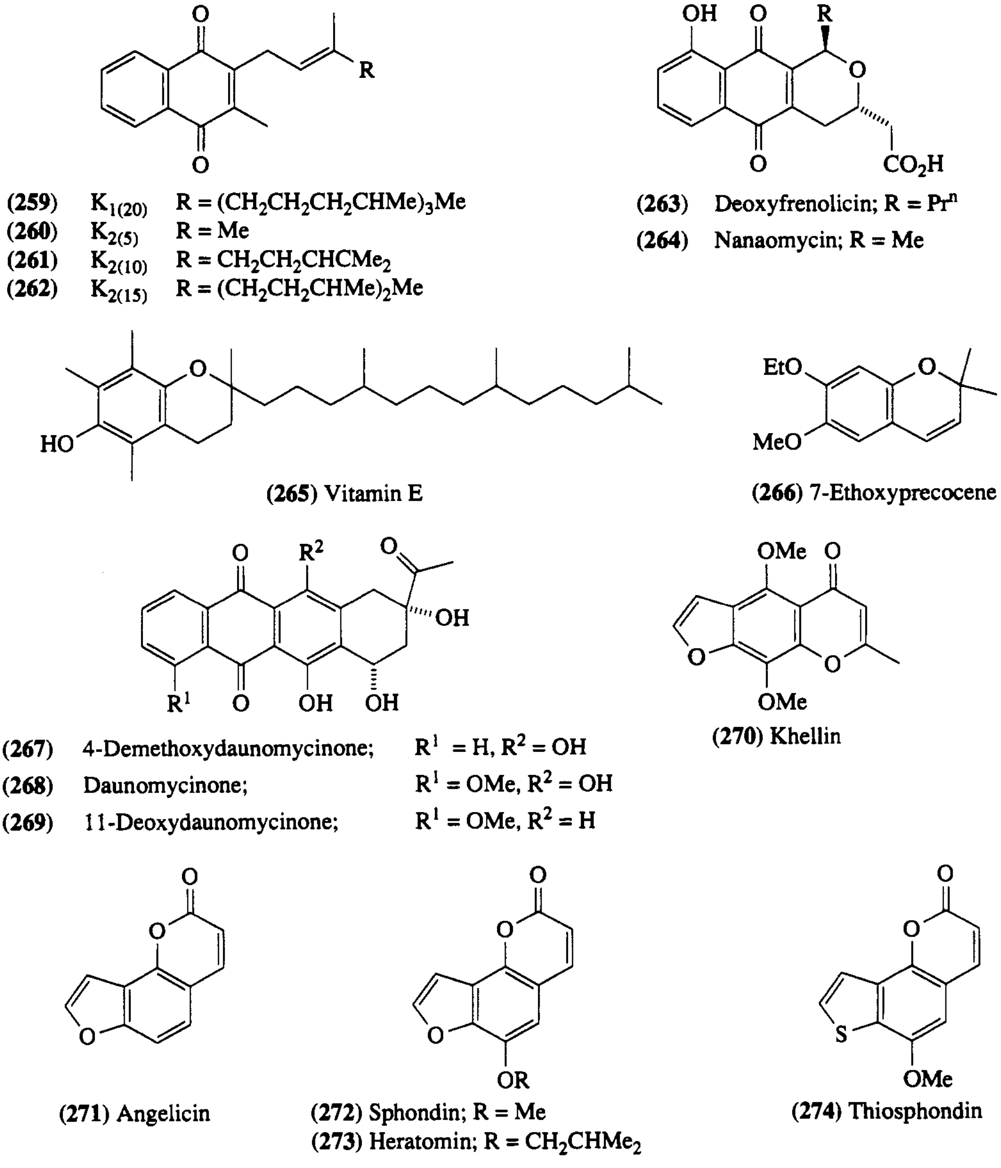

**(259)** $K_{1(20)}$ R = $(CH_2CH_2CH_2CHMe)_3Me$
**(260)** $K_{2(5)}$ R = Me
**(261)** $K_{2(10)}$ R = $CH_2CH_2CHCMe_2$
**(262)** $K_{2(15)}$ R = $(CH_2CH_2CHMe)_2Me$

**(263)** Deoxyfrenolicin; R = $\mathrm{Pr^n}$
**(264)** Nanaomycin; R = Me

**(265)** Vitamin E

**(266)** 7-Ethoxyprecocene

**(267)** 4-Demethoxydaunomycinone; $R^1$ = H, $R^2$ = OH
**(268)** Daunomycinone; $R^1$ = OMe, $R^2$ = OH
**(269)** 11-Deoxydaunomycinone; $R^1$ = OMe, $R^2$ = H

**(270)** Khellin

**(271)** Angelicin

**(272)** Sphondin; R = Me
**(273)** Heratomin; R = $CH_2CHMe_2$

**(274)** Thiosphondin

**Scheme 37**

The two syntheses of 11-deoxydaunomycinone are summarized in Schemes 38 and 39 as they are illustrative of the viability of carbene complexes as intermediates in organic synthesis. The synthesis by Dötz and Popall begins with the chelated *o*-methoxyphenyl carbene complex (**275**)[124,127] and the alkyne (**276**).[109d,e] A single regioisomer of the phenol (**277**) was obtained in 76% yield in the benzannulation. After protection of the phenol and carbon homologation of the ketone to the acid, an intramolecular Friedel–Crafts reaction gave the tetracyclic dione (**279**) in 45% overall yield from (**277**). This represents a formal synthesis of 11-deoxydaunomycinone (**269**) since it has been reported that (**279**) can be converted to (**269**) by the procedures of Sih[110] and Johnson.[111]

The synthesis of 11-deoxydaunomycinone by Wulff and Xu is presented in Scheme 39 and involves the benzannulation of the non-chelated *o*-methoxyphenyl complex (**280**) with the alkyne (**281**).[108c] The utilization of a *t*-butyl ester in the alkyne (**281**) makes possible a one-pot construction of the tetracyclic dione (**282**) *via* a tandem benzannulation–Friedel–Crafts cyclization. After the reaction between the

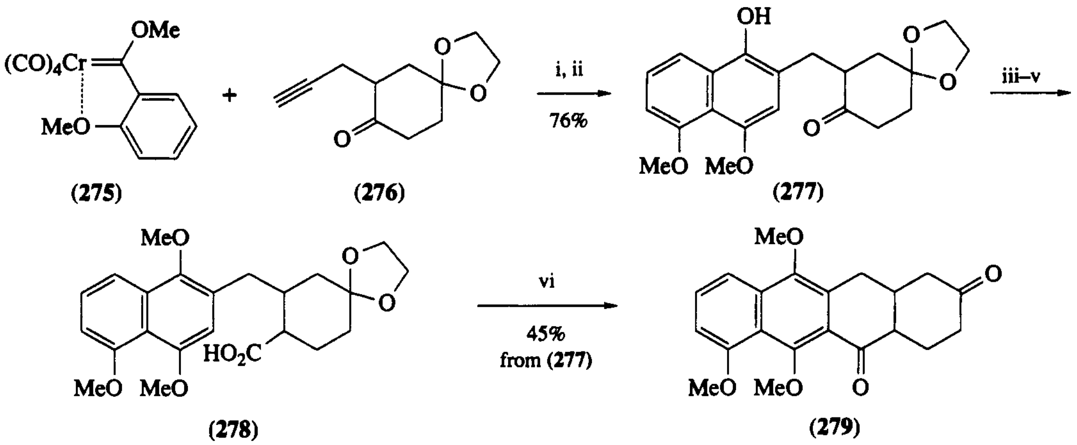

i, Bu$^t$OMe, 40 °C, 1 h; ii, $CH_2Cl_2$, 75 bar CO (1 bar = 100 kPa), 70 °C, 72 h; iii, $CH_2N_2$ (excess); iv, $TosCH_2NC$, KOBu$^t$, THF, −10 °C; v, HOAc; vi, TFA, TFAA, 0 °C

**Scheme 38**

complex (**280**) and alkyne (**281**) is complete, the reaction is opened to air for 10 min to allow for the oxidative removal of the chromium tricarbonyl group, and then is diluted with trifluoroacetic anhydride containing a small of amount of sodium acetate to protect the phenol. After 10 min, the mixture is again diluted with trifluoroacetic acid to effect cleavage of the *t*-butyl ester and the Friedel–Crafts cyclization which yields, after base work-up to deprotect the phenol, the tetracyclic dione (**282**) in 56% yield. If (**282**) is not purified, but oxidized directly, the anthracyclinone (**283**) can be obtained to 61% overall yield from alkyne (**281**). A slightly higher overall yield of (**283**) can be obtained if the reaction is carried out with the alkyne (**284**) containing a methyl ester (since **281** is prepared from **284**); however, the convenience of a one-pot reaction is lost since it is not possible to cleave the methyl ester and simultaneously effect the Friedel–Crafts closure. No difference in the yield for the benzannulation step was noted between the reactions of (**284**) and either (**280**) or (**275**).

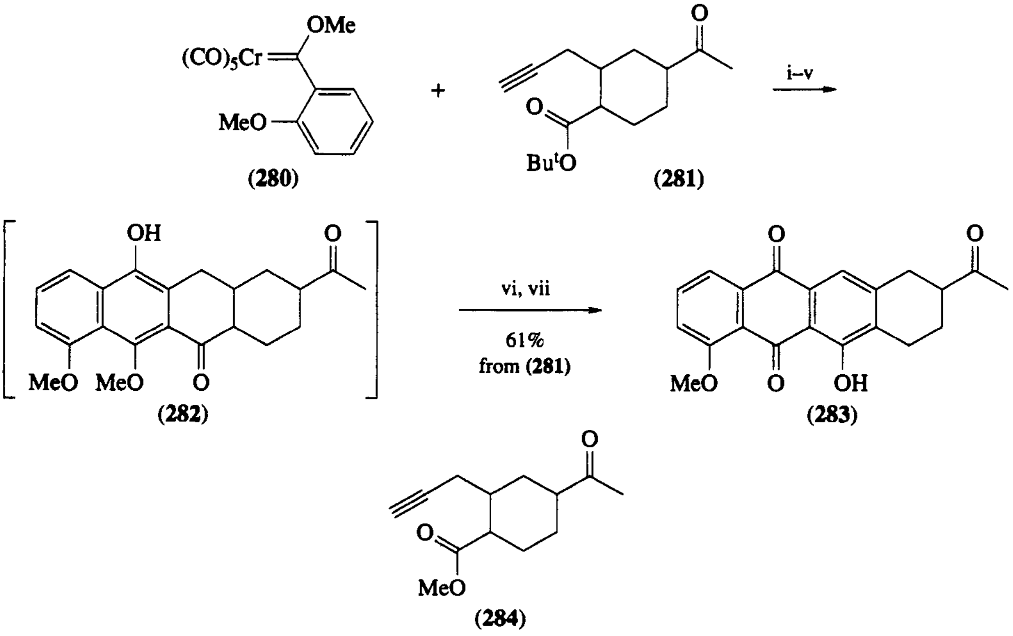

i, PhH, 75 °C, 12 h; ii, air, 10 min, 25 °C; iii, $(CF_3CO)_2O$, NaOAc, 10 min; iv, $CF_3CO_2H$, 1.5 h, 25 °C; v, aq. NaOH; vi, AgO, $HNO_3$, acetone, 25 °C; vii, $O_2$, DMF, 100 °C, 3 h

**Scheme 39**

An appreciation of the value of carbene complexes in anthracycline synthesis can be obtained by comparing the two syntheses of 11-deoxydaunomycinone shown in Scheme 38 and 39 with the 20 other syntheses that do not involve transition metal reagents.[112–114] The overall yields for the 22 reported syntheses of 11-deoxydaunomycinone range from 0.05% to 9.7%. The overall yield for the synthesis of (**269**) according to Scheme 38 can be calculated to be 2.8% starting from cyclohexan-1,4-dione monoethylene acetal and including the five steps by Sih[110] and three steps by Johnson.[111] The overall yield for the synthesis of (**269**) according to Scheme 39 can be calculated to be 8.5% starting from methyl vinyl ketone and, including four steps by Johnson.[111] By this criteria, the synthesis in Scheme 39 ranks second out of 22 and clearly demonstrates the efficacy of carbene complexes as intermediates in organic synthesis.

*(d) Functionality on the aryl and alkenyl substituent.* Although not yet completely defined, the range of functionality on the aryl complex (**1a**) and the alkenyl complex (**233**; Scheme 34) that can be tolerated in the benzannulation reaction is beginning to be established. Benzannulations of aryl complexes of the type (**1a**) have been examined and found to be successful with *o*-methoxy,[87,96a,98,108c,d,109c,d,e] *m*-methoxy,[96a] *p*-methoxy,[87] *o*-*t*-butoxy,[87] *m*-methyl,[96a] *p*-methyl,[82,121,125] *m*-trifluoromethyl,[96a] *p*-trifluoromethyl[121] and *p*-chromium carbene complex[131] substituents. The annulations of diaryl complexes have been examined but the yields are not generally useful.[120] The annulations of naphthyl complexes have been examined[121,125] and have been employed in the synthesis of daunomycinone and 4-demethoxydaunomycinone.[109] The annulations of a number of heteroaryl complexes have been reported by Dötz, Yamashita and Wulff. These include complexes derived from furans,[128] thiophenes,[99,121,132] pyrroles,[118,119] pyrazoles[15] and indoles[117] and an example of the annulation of the latter is shown in Scheme 40. The annulation of the furyl complex (**285**) indicated in Scheme 40 was employed in the synthesis of khellin.[107]

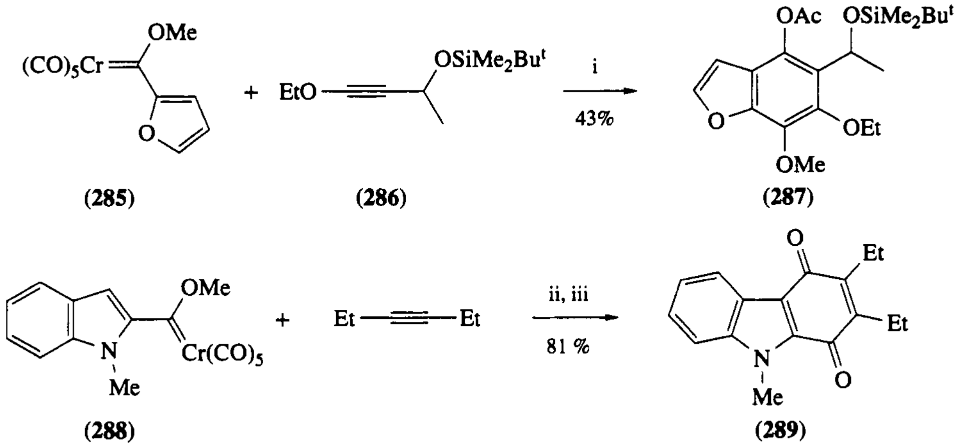

i, THF, Ac$_2$O, NEt$_3$, 65 °C, 10 h; ii, THF, 50 °C, 24 h; iii, Ce(NO$_3$)$_6$(NH$_4$)$_2$, 25 °C, 30 min

**Scheme 40**

The annulations of alkenyl complexes of the type (**233**; Scheme 34) have been examined mainly with alkyl substituents and in a few cases with oxygen[87,106,126] and silicon[108b,c] substituents in a variety of cyclic and noncyclic systems.[129] It is notable that the benzannulations of the parent vinyl complex of (**233**) (**42a**; Scheme 7) fail, which is apparently due to competing polymerization of (**42a**).[106] Annulations of complexes of the type (**233**) are successful if at least one of the three substituents is nonhydrogen. Benzannulations of alkenyl complexes have been employed in the synthesis of 7-ethoxyprecocene,[106] vitamin E[105,123] and daunomycinone.[108a–c]

*(e) Functionality on the alkyne.* Considerable progress has been made towards identifying the scope and nature of the functionality that can be present on the alkyne and tolerate the benzannulation reaction. The benzannulation reaction can give good yields with silyl groups[134] directly substituted on the alkyne carbon and gives lower yields with oxygen[135] and carbonyl groups[136] directly attached to the alkyne carbon. The reaction can give good to excellent yields with functionalized arylalkynes[96b,100a] and alkylalkynes bearing esters,[137] alkenes,[122,138] amides,[139] α-ethers,[140] lactones,[108a–c] sulfides,[99,130] enol

ethers,[106,108c] tosylates,[117] ketones,[108d,109c–e] nitriles[108c] and acetal groups[96c,107,109c,d] on the alkyl chain. Alkylalkynes bearing remote alcohol groups do give benzannulated products, but usually in competition with ketene trapping products.[82,125]

The benzannulation reaction has the advantage that a great range of functionality can be tolerated by the reaction. One major limitation involves alkynes with leaving groups alpha to the alkyne function (α-ethers[140]), where a competing pathway is *o*-quinone methide formation.[119] The competing pathway can often be overcome by carrying out the benzannulation reaction in the presence of triethylamine and acetic anhydride, such that the phenol functionality of the benzannulated product is trapped *in situ*.[118] Another major limitation involves the presence of carbonyl groups conjugated with the alkyne.[136] Benzannulation products can often be obtained from reactions of alkynes of this type, but the yields are usually reduced. The example in equation (17) is presented since the reactions of conjugated and nonconjugated esters have been carried out on the same complex. The reaction of (**285**) with methyl-4-pentynoate gives the phenol (**291**) in 55% yield and has been employed in the synthesis of sphondin and angelicin.[99] The reaction of the same complex with methyl propiolate only gives the annulated product (**292**) in 21% yield.[107]

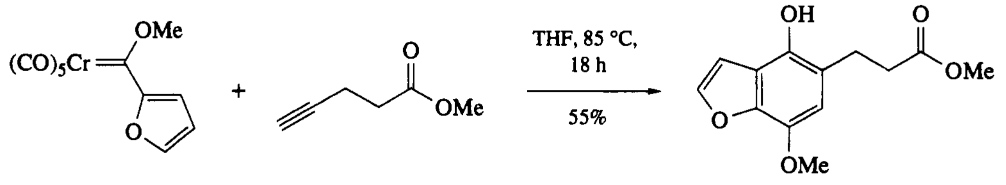

(**285**) (**290**) (**291**) (17)

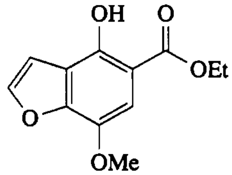

(**292**) 21%

(*f*) *Effects of the solvent and the concentration of the alkyne*. The role of the solvent can be extremely important in determining the product distribution from the reaction of Fischer carbene complexes with alkynes. Early on it was thought that the reaction displayed its highest selectivity for benzannulated products in more polar solvents,[141] but subsequent studies have shown that it is highest in nonpolar solvents.[87] This is illustrated by the reaction in equation (18) for the reaction of the complex (**280**) with 3-hexyne in hexane and THF (see also equation 14 and Scheme 32).[87] The product distribution has also been found to depend in some cases on the concentration of the alkyne, as is illustrated for the reaction of (**280**) with 3-hexyne, where at 0.01 M in alkyne (0.005 M in **280**) the five-membered ring annulated products are the major products. An explanation for this phenomenon, termed the allochemical effect, is illustrated in Scheme 36 and has been proposed to be due to an increased rate of CO insertion as a result of the coordinated alkyne in intermediate (**254**).[87,90]

(*g*) *Tandem Diels–Alder–benzannulation*. The potential of the benzannulation reaction in organic synthesis can be enhanced when it is coupled with other reactions of carbene complexes and the tandem Diels–Alder–benzannulation sequence is particularly attractive in this regard.[3,15,24] The Diels–Alder reaction of the alkynyl carbene complex (**296**) with 2,3-dimethylbutadiene gives the alkenyl complex (**297**) in 89% yield after chromatography.[24] The benzannulation of (**297**) with 1-pentyne gives the trimethylsilyl-protected phenol–metal complex (**298**) in essentially quantitative yield. This tandem cycloaddition–annulation sequence can also be carried out concurrently. In the presence of both the diene and the alkyne, the carbene complex (**296**) chemoselectively reacts with the diene and the *in situ* generated Diels–Alder adduct (**297**) chemoselectively reacts with the alkyne. The tandem Diels–Alder–benzannulation sequence has been used in the preparation of an intermediate employed in the synthesis of daunomycinone (**268**; Scheme 37).[24]

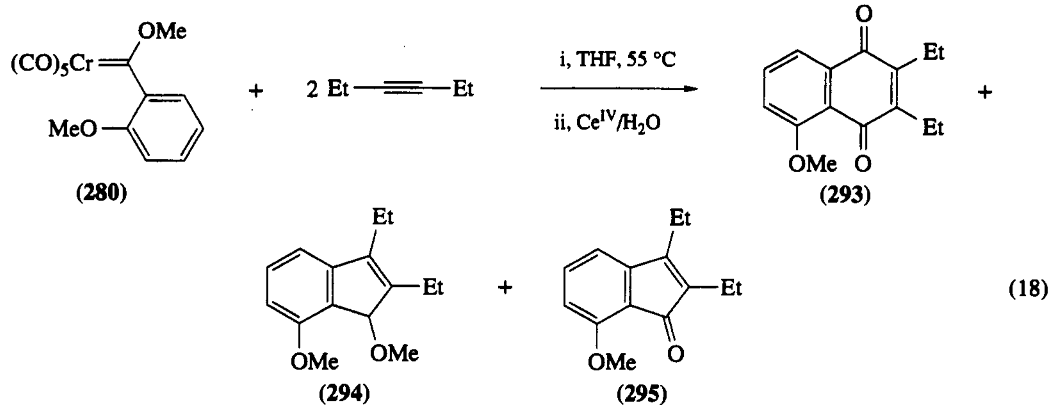

(18)

| *Solvent* | *[Alkyne]* | *Yield (%)* | *(293)* | *(294) + (295)* |
|---|---|---|---|---|
| hexane | 0.3 | 83 | 100% | not determined |
| THF | 1.0 | 84 | 73% | 27% |
| THF | 0.01 | 80 | 6% | 94% |

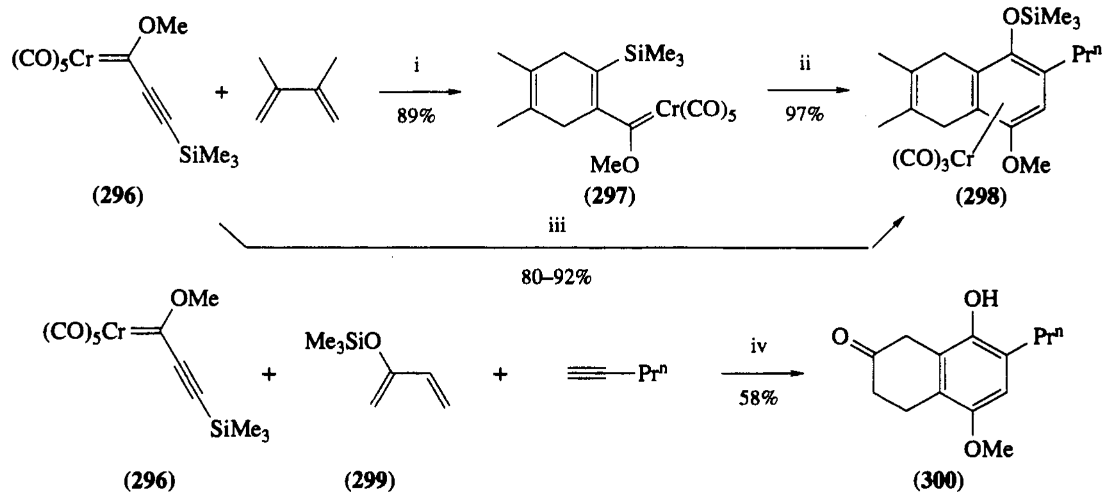

i, neat, 50 °C, 4 h; ii, 1-pentyne (1.5 equiv.), THF, 45 °C, 24 h; iii, 2,3-dimethyl-1,3-butadiene (excess), 1-pentyne (2 equiv.), THF, 50 °C, 60 h; iv, a) THF, 50 °C, 36 h; b) silica gel, air

**Scheme 41**

*(h) Benzannulation where aromatization is blocked: cyclohexadienone annulation.* Alkenyl carbene complexes in which the β-vinyl carbon is disubstituted produce cyclohexadienone products from reactions with alkynes.[142] In the case of the complex (**301**) which contains a chiral center there is significant asymmetric induction in the selective formation of the *trans*-decaladienone (**302**), which was greater than 90% for alkynes that were examined.[116] The formation of cyclohexadienone products occurs because the final step of the mechanism is thwarted: tautomerization of (**252**) in Scheme 36 is prevented when R is a group of low migratory ability. An additional example of the cyclohexadienone annulation is included in Scheme 42, which was recently reported as a potential new route for the synthesis of the *Aspidosperma* alkaloids.[117]

*(i) Benzannulation of aryl* versus *alkenyl complexes.* The reactions of alkynes with aryl (**1a**) or alkenyl complexes (**233**; Scheme 34) generally produce good to excellent yields of benzannulated products. There appears to be no significant difference in the type of functional groups they can tolerate. The annulations of alkenyl complexes seem to be less sensitive to the nature of the solvent.[87] With the excep-

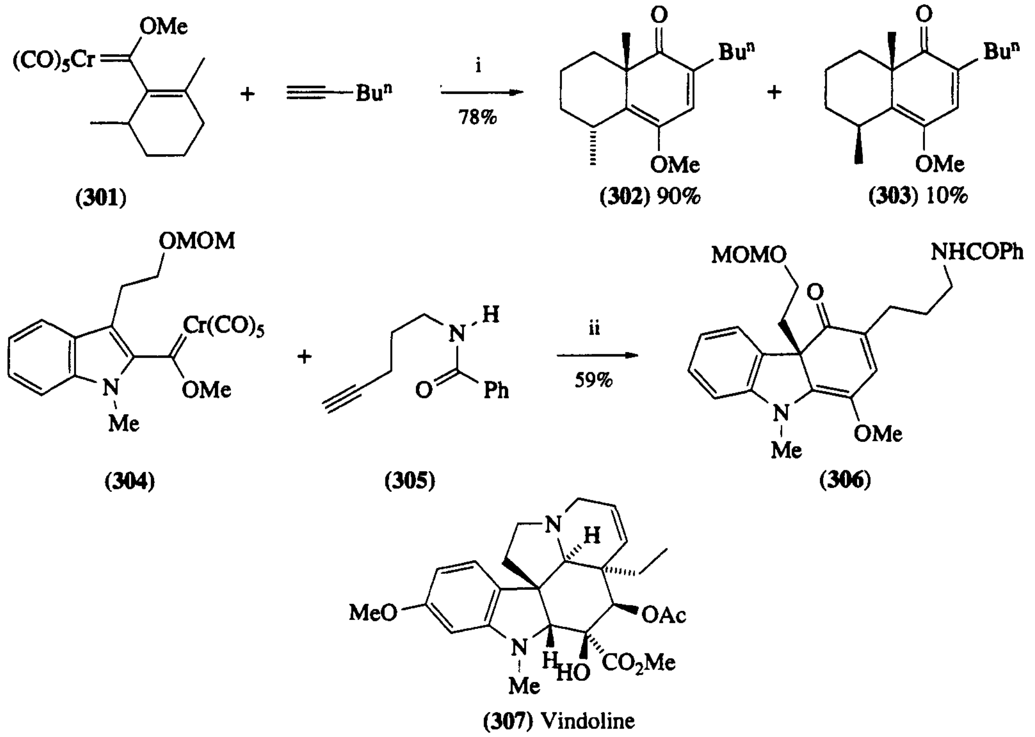

i, THF, 45 °C, 24 h; ii, PhH, 50 °C, 17 h

**Scheme 42**

tion of the molybdenum complex[90] shown in equation (15) the formation of five-membered ring products and cyclobutenones has not been observed from the reaction of an alkyne and an alkenyl carbene complex. The cyclohexadienone annulation is also useful mainly for alkenyl complexes, the reactions of *ortho*-blocked aryl complexes generally give five-membered ring annulated products (Scheme 32), with the only known exception being the reactions of *ortho*-blocked indole carbene complexes (Scheme 42).[117]

*(j) The effect of the ligand complement on the metal.* Only two reports have appeared which describe the benzannulation of carbene complexes of the type (**233**) (alkenyl or aryl), in which the ligand complement is not pentacarbonyl.[43,120] In both reports it was observed that if one of the carbon monoxides is replaced by a phosphine that the reaction gives the same products but generally in lower yields. Further investigations are warranted in this area.

*(k) The effect of the ancilliary substituent RX.* Up to now, the benzannulation reaction has been almost exclusively limited to alkoxy functional groups as the ancilliary substituent RX in (**233**; Scheme 34) for both alkenyl and aryl complexes. As indicated in Section 9.2.3.2.3i nitrogen substituents lead to five-membered ring annulation products,[87,91,133] and six-membered ring benzannulation products (Scheme 32) have yet to observed from the reaction of amino complexes. Only one example of the benzannulation of a complex bearing a thiol group has been reported, and although it gave the six-membered ring benzannulated product, the yield was lower than for its methoxy analog.[3] Control of the group RX has the potential to allow for further fine tuning of the benzannulation reaction.

*(l) Reactions with other carbon triple bonded functional groups.* The substitution of nitrile for alkynes does not lead to pyridines or quinolines in the benzannulation reaction.[143,144] Instead noncyclic products are obtained that are the result of insertion of the carbon–nitrogen triple bond into the metal–carbene bond. On the other hand, in a very recent report it was found that $\lambda^3$-phosphaalkynes will undergo the benzannulation reaction to produce phosphaarene chromium tricarbonyl complexes.[145]

### (ii) [2 + 2 + 1 + 1] Cycloadditions: two-alkyne annulations and pyrone formation

The reactions of Fischer carbene complexes with alkynes can under certain conditions lead to products that result from the incorporation of two alkynes, the carbene ligand and a carbon monoxide. In intermolecular reactions, this is most commonly observed for acetylene itself or for sterically unhindered alkynes.[3,102] As can be anticipated by the mechanism in Scheme 36, two-alkyne incorporated products of the type (**258**) are also favored for high alkyne concentration. Synthetically, the two-alkyne reactions are most useful in intramolecular reactions, two of which have been reported and are exemplified by the reactions in Scheme 43. The typical product from the reaction of a Fischer carbene complex with a diyne, such as (**308**), is a bicyclic phenol of the type (**309**).[3,43,102] These products are apparently the result of the assembly of pieces indicated by (**311**). Under some conditions, dienones of the type (**310**) and (**314**) can be isolated, and it is thought they are the immediate precursors of the phenol products *via* an *in situ* reduction by a chromium(0) species. This reaction is completely regioselective with diyne (**308**) and the phenol (**309**) results from incorporation of the terminal alkyne of (**308**) before the disubstituted alkyne.[102] Phenols of the type (**309**) have also been observed from the reaction of diynes with carbyne complexes.[146a]

A less efficient mode of the two-alkyne annulation is the intra-intermolecular reaction of an alkyne-containing carbene complex of the type (**312**) with a second alkyne.[146b] Under optimal conditions, these reactions will lead to moderate yields of bicyclic phenols of the type (**313**), which result from the assembly of pieces indicated by (**315**). The precursor dienones (**314**) can be isolated as minor products from these reactions.[147] Applications of the two-alkyne annulations in organic synthesis have not yet been reported.

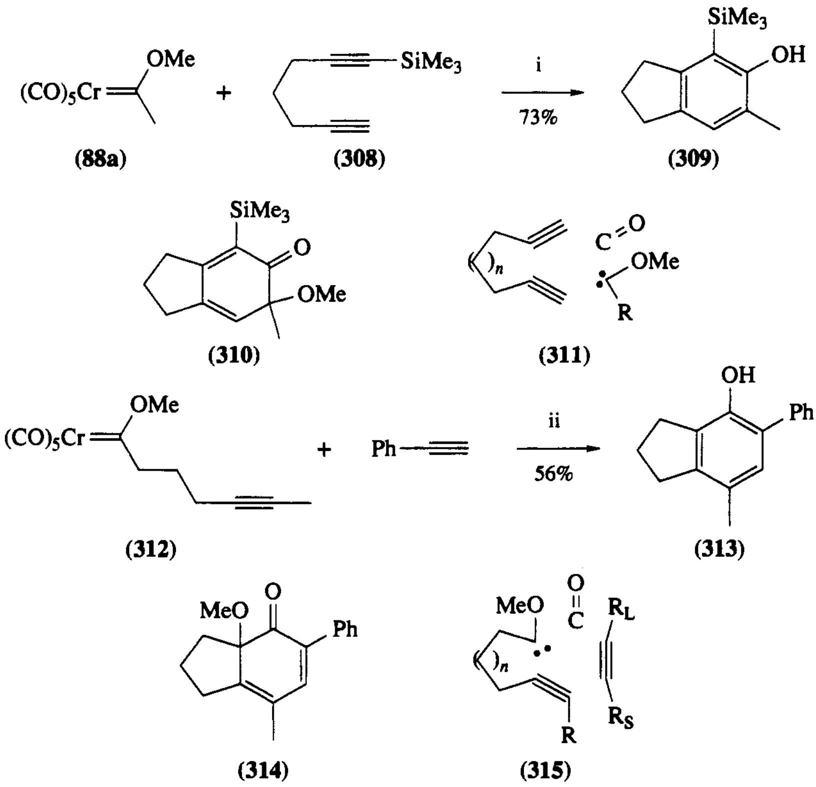

i, THF, 70 °C, 6 h; ii, MeCN, 50 °C, 36 h

**Scheme 43**

Alkoxy iron complexes of the type (**316**) will also react with alkynes to give six-membered ring products that, like the two-alkyne annulation, are formally the result of a [2 + 2 + 1 + 1] cycloaddition. The formation of these pyrone complexes (**317**) have only been reported from the reactions of alkynes with iron–carbene complexes.[93,148] These pyrones are also the only product from the reaction of an alkyne with any carbene complex which incorporates one alkyne, two carbon monoxides and the carbene ligand.

Pyrone formation by this reaction appears to be general (eight examples) and quite efficient (33–93%) and for a discussion of mechanistic possibilities the reader is referred to the primary literature.[148] With terminal alkynes, pyrone formation occurs with the same regioselectivity as is observed in the benzannulation reaction of chromium complexes ($R^1$ = Ph, $R^2$ = H).

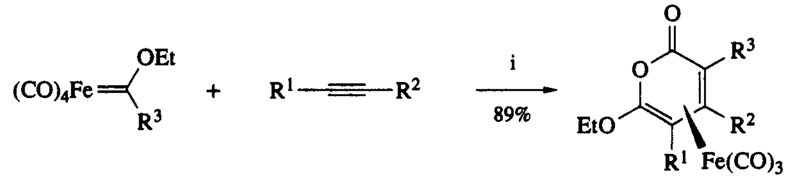

(19)

**(316)** $R^3$ = Ph, $R^1$ = $R^2$ = Me **(317)**

i, $CH_2Cl_2$, 70 °C, 1 h, 55 psi carbon monoxide

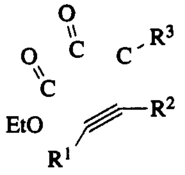

**(318)**

### 9.2.3.2.5 *Coupling leading to acyclic products*

The reaction of alkyl-substituted tungsten–carbene complexes of the type (**88b**) have been reported by Macomber to react with alkynes to give dienes of the type (**319**).[149] One mechanism that has been proposed to account for this product is a β-hydride elimination from the metallacyclobutene intermediate (**320**) and subsequent reductive elimination in the metal hydride species (**321**). An additional example of this type of reaction has been reported by Rudler, also for an alkyl tungsten carbene complex.[150] Chromium complexes have not been observed to give diene products of this type; the reaction of the analogous chromium complex (**88a**) with diphenylacetylene gives a cyclobutenone as the only reported product (see Scheme 31).[83] Acyclic products are observed for both tungsten and chromium complexes in their reactions with ynamines. These reactions produce amino-stablized carbene complexes that are the result of the formal insertion of the ynamine into the metal–carbene bond.[151–153]

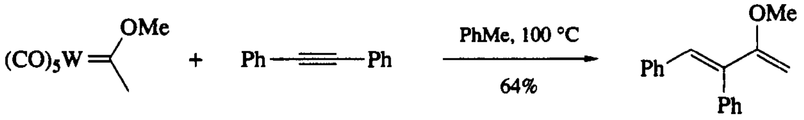

(20)

**(88b)** **(319)**

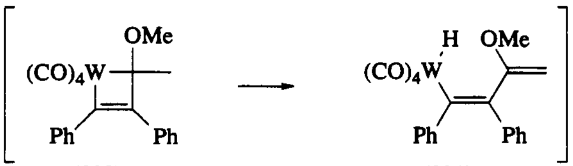

**(320)** **(321)**

### 9.2.3.2.6 *Coupling leading to intercepted products*

The two-alkyne annuation reactions shown in Scheme 43 are actually reactions of this class since mechanistically they can be viewed as the interception of vinyl carbene complex intermediate (**248**) in Scheme 36 by an alkyne. In addition to alkynes, intermediates from the reactions of Fischer complexes and alkynes have also been intercepted with alcohols and amines.[154,155] In all of the known examples these trapping reactions produce β,γ-unsaturated esters and amides that apparently result from the trapping of vinyl ketene complexed intermediates of the type (**255**; Scheme 36) by alcohols or amines.

The first examples of the interception of intermediates from these reactions by alkenes were reported in 1985 by Wulff,[156] Katz[157] and Rudler.[158] Wulff reported that enynes of the type (**322**) would react with Fischer carbene complexes to give bicycloheptanones of the type (**323**) and (**324**). In contrast to these results, Hoye has recently observed that enynes derived from dimethyl malonate will react with the same carbene complex to give bicyclohexane products of the type (**326**) and (**327**).[160] It is possible that the difference between these two observations can be accounted for on the basis of the Thorpe–Ingold effect on the two possible pathways for the vinyl carbene complexed intermediate (**329**). When the substituents R in (**329**) are not hydrogen, the intramolecular formation of the metallacyclobutane (**330**) would be favored relative to the CO insertion that generates the vinyl ketene complex (**328**). Reductive elimination from (**330**) would give the bicyclohexane products, and an intramolecular [2 + 2] cycloaddition of the alkene and the ketene in (**328**) would lead to the bicycloheptanone products. Another possible outcome for the metallacyclobutane intermediate (**330**) is a metathesis reaction leading to cycloalkene products and these have been observed.[157,160] The Thorpe–Ingold effect does not account for the formation of cyclopropane products from the double intramolecular reaction of the complex (**331**), which gives the tricyclic product (**332**) in high yield.[160] Much yet needs to be learned before the outcome of reactions of this type can be predicted.

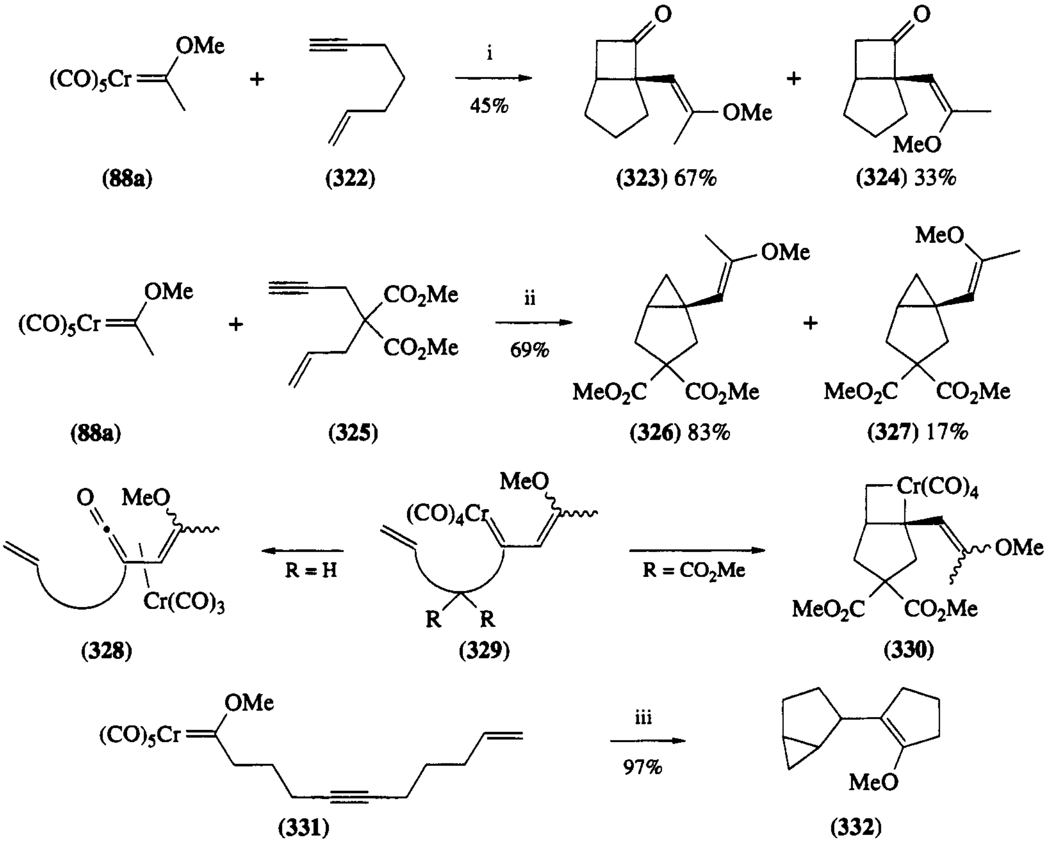

i, MeCN, 70 °C, 3 h; ii, PhH, 80 °C, 2 h; iii, PhH, 80 °C, 5 h

**Scheme 44**

In a variation of the reactions in Scheme 44, Rudler has reported that the alkene which intercepts the vinyl carbene complex leading to cyclopropane products can be tethered onto the starting carbene complex.[158] This was extensively studied for the reaction of the carbene complex (**334**) with a number of alkynes leading to bicycloheptanones of the type (**336**).[150] This reaction is quite general (14 examples, 44–95%) and is regioselective with terminal alkynes, *i.e.* it occurs in the same sense that has been observed for the benzannulation reaction (R′ = H in **336**). Acetylene fails and cyclooctyne gives a reduced yield (31%) of (**336**). The intermediate (**335**) was not observed in these reactions and apparently suffers hydrolysis upon purification on silica gel. The interesting tricyclic product (**338**) can be obtained from the reaction of the cyclopentenyl complex (**337**) with 3-hexyne. Products similar to (**336**) can be obtained from the reactions of amino complexes in which the alkene is tethered through the nitrogen.[159]

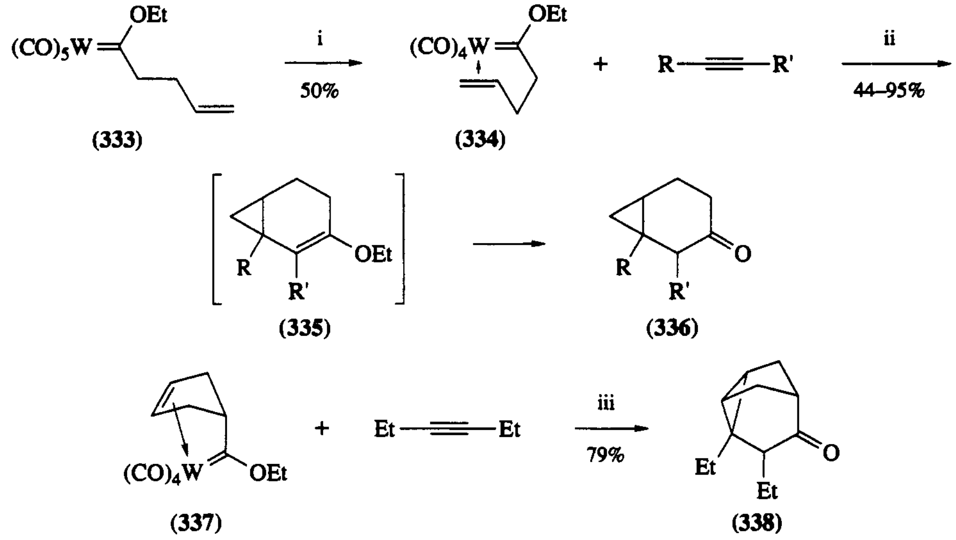

i, PhH, 78 °C, 12 h; ii, $CH_2Cl_2$, 10 °C, 12 h; iii, hexane, 25 °C, 48 h

**Scheme 45**

Recently, two groups have reported reactions of Fischer carbene complexes with alkynes, in which intermediates have been intercepted by ring-opening reactions. The tetrahydropyridine carbene complex (**339**) was found to react with diphenylacetylene to give the two fused azabicyclics (**340**) and (**341**) in a total of 50% yield.[161,167] These products are proposed to both have a common mechanistic origin in the zwitterionic intermediate (**342**), which is a tautomeric form of the vinyl carbene complexed intermediate (**248**) in Scheme 36. Each product arises from a ring opening of the tetrahydropyridine ring at the allylic carbon–nitrogen bond of the ammonium ion in (**342**), and are differentiated by whether the chromium migrates to the $\alpha$- or $\gamma$-carbon. The generality of this reaction has not been established with other alkynes; however, it has been shown to occur with diphenylacetylene with cyclic amino carbene complexes of other ring sizes (three and five). Analogous products are obtained from the reaction of a dihydropyrrole complex; however, with saturated tetrahydropyrrole complexes, ring opening cannot occur in the same manner and leads to a different ring system.[162] Ring opening also occurs with aziridine complexes, but the products isolated from these reactions differ in that they have 2 equiv. of the alkyne incorporated.[162,163]

Reaction intermediates can also be intercepted by the ring opening of carbocyclic substituents attached to the carbene carbon as illustrated by the reaction reported by Herndon involving the cyclopropyl carbene complex (**347**).[164] Depending on the nature of the alkyne, this reaction can produce varying amounts of the three isomeric cyclopentenones (**348**)–(**350**). The data given in Scheme 47 refer to the reaction with diphenylacetylene, but the reaction is general for a number of alkynes (nine examples, 0–85%). The regioselectivity was examined for terminal alkynes; it is the same as observed for the benzannulation reaction and the products from these reactions have the terminal alkynic hydrogen incorporated at $R^2$. The ring opening is proposed to occur at the intermediate (**351**), which is an $\eta^2$-tautomer of the vinylketene intermediate (**255**) in Scheme 36. The ultimate intermediate proposed for this reaction is the cyclopentadienone complex (**354**), which must add the elements of dihydrogen to produce the final products. This is consistent with the observation that yields are higher when the reaction is carried out in the presence of reducing agents. The reactions in Scheme 46 and 47 have opened several interesting mechanistic issues and some novel synthetic possibilities.

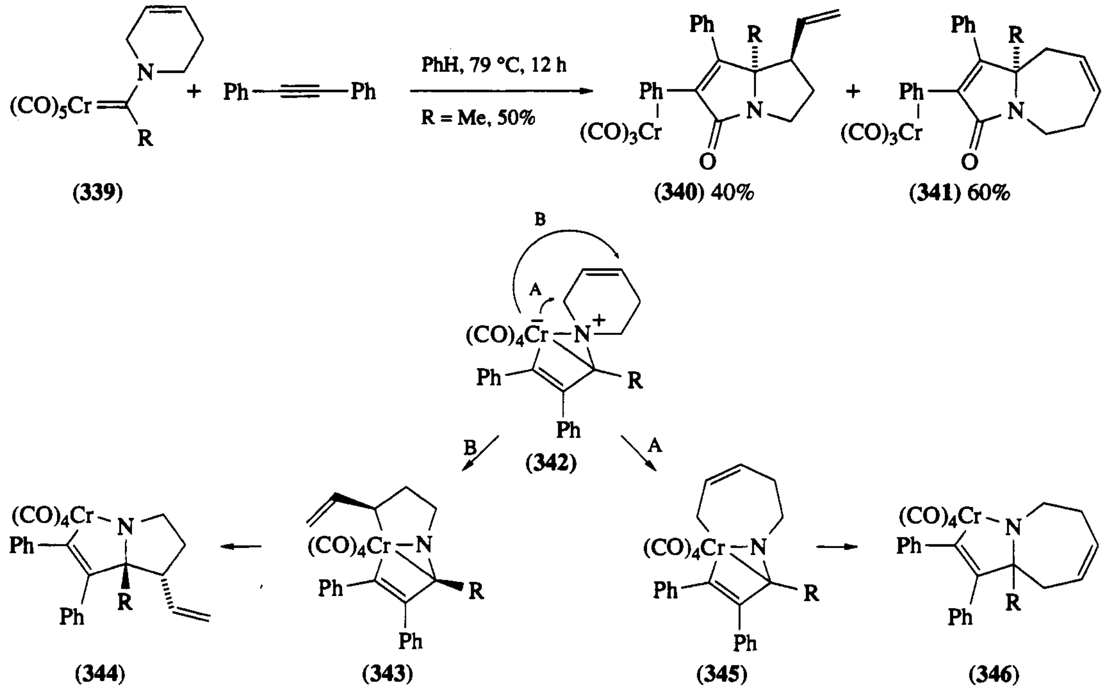
PhH, 79 °C, 12 h
R = Me, 50%
(339)
(340) 40%
(341) 60%
(342)
(343)
(344)
(345)
(346)
A
B

Scheme 46

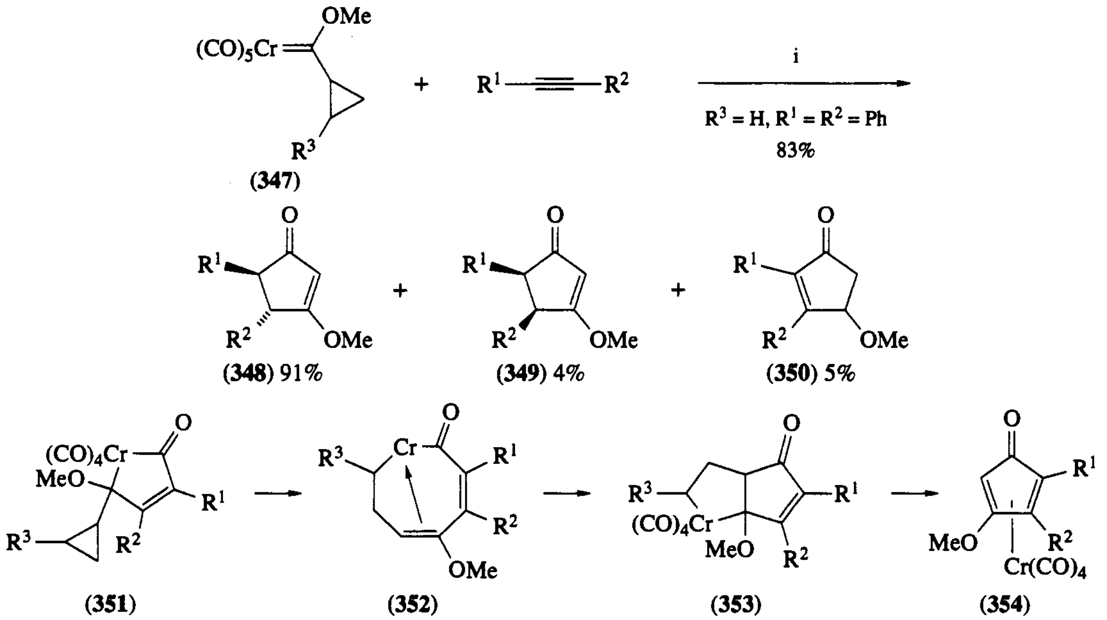
i
R³ = H, R¹ = R² = Ph
83%
(347)
(348) 91%
(349) 4%
(350) 5%
(351)
(352)
(353)
(354)

i, 1% aqueous dioxane, 101 °C, 4–6 h

Scheme 47

## 9.2.3.3 Coupling of the Carbene Ligand with Cumulenes and C—X π-Bonds

### *9.2.3.3.1 Allenes*

The first reaction of a Fischer carbene complex with an allene was reported by Aumann in 1987.[165] The initial event in this reaction was presumably the formation of the methylene metallacyclobutane intermediate (**356**). This intermediate could have undergone reductive elimination to give a methylenecyclopropane, but apparently preferred to rearrange to the trimethylenemethane complexes (**357**) and (**358**). Also formed in this reaction is the bismethylenecyclopentane (**359**), which was shown either by prolonged reaction times or separate experiments to arise *via* [3 + 2] cycloaddition of a molecule of the allene with the trimethylenemethane complexes (**357**) and (**358**). Trimethylenemethane complexes of iron can be obtained in a similar manner from the reaction of iron–carbene complexes with allenes and have the advantage that they can be prepared cleanly since subsequent [3 + 2] cycloaddition of the allene with the products is not observed.[166] The [3 + 2] cycloadditions of the isolated iron trimethylenemethane complexes prepared in this manner have not yet been examined. Although this reaction has not yet been extended to other allenes or carbene complexes other than aryl, this initial observation is particularly exciting given the established synthetic utility of transition metal trimethylenemethane complexes and the uniquely functionalized trimethylene complexes that are accessible from the reaction of Fischer carbene complexes with allenes.

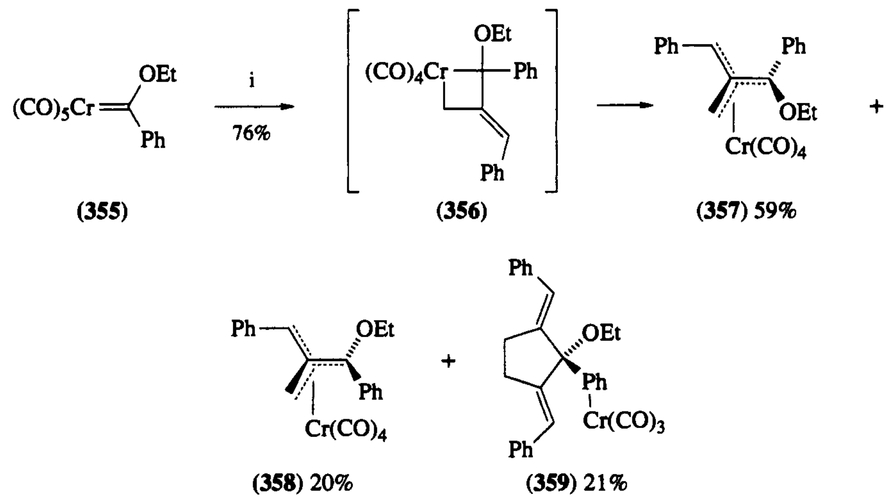

(21)

### *9.2.3.3.2 Imines*

The synthetic applications of photo-induced reactions of Fischer carbene complexes have been developed in the laboratories of Hegedus over several years.[167–172] The development of this chemistry as a method for cyclobutanone synthesis was discussed in Section 9.2.3.1.2. The area that has been most thoroughly developed at this time is the synthesis of β-lactams from the photo-induced reactions of carbene complexes and imines. As indicated in Scheme 48 this reaction is general for a number of substrates and gives β-lactams in fair to high yields with complete stereoselectivity.[168] This chemistry was first developed with alkoxy-substituted complexes for the complexes for the synthesis of 6- and 7-alkoxy analogs of β-lactam antibiotics.[167–169] The exposure of the complex (**88a**) to sunlight in the presence of the homochiral thiazoline ester (**34**) gave the penicillin analog (**364**) as a single diastereomer in 42% yield.[168] In a similar manner, the photolysis of (**88a**) in the presence of the thiazine (**363**) gave the cephalosporin analog (**365**) in 52% yield as a single diastereomer.[169] The preparation of oxapenam and oxacepham analogs failed with chromium carbene complexes; however, this was successful with molybdenum complexes.[169] Photolysis of the complex (**88c**) with the oxazine (**366**) gave the oxacepham analog (**367**) in 41% yield. The reaction of the complex (**88c**) with the oxazoline (**368**) gave the corresponding oxapenam analog in 14% yield.

In penicillins of the type (**370**) the position α to the carbonyl in the four-membered ring bears a hydrogen and a nitrogen substituent. This requires that unsubstituted amino carbene complexes of the type (**369**) be readily available and was the driving force for the development of the procedure for the prep-

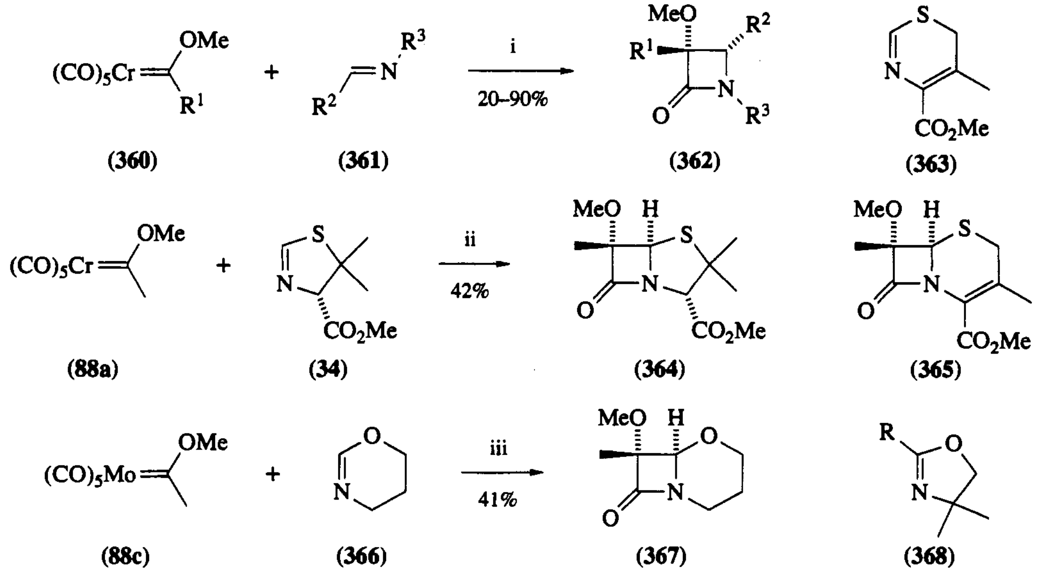

i, $Et_2O$, sunlight, 2–4 h, or $Et_2O$, vitalite fluorescent tubes, 10–20 h; ii, $CH_2Cl_2$, sunlight, 2 d; iii, THF, 0 °C, rayonet reactor with 3000 Å and 5000 Å lamps, 48 h

Scheme 48

aration of carbene complexes that is illustrated in Scheme 1. As it turned out, the amino complex (**369**) is more versatile in the synthesis of β-lactams than alkoxy complexes. The reaction of (**369**) with (**34**) in the presence of light allowed for the preparation of the penicillin analog (**370**) in 93% yield as a single diastereomer.[170] The reaction of (**369**) with the thiazine (**371**) proceeded in 77% yield and subsequent dehydration produced a cephalosporin analog. Unlike the alkoxy chromium complex (**88a**), the amino chromium complex (**369**) would react with oxazines and oxazolines to produce oxacephams and oxapenams.

The reactions of both alkoxy and amino complexes are highly stereoselective and give the unnatural epimer at the C-6 position in the penicillin analogs, but methods are known for inversion at this center. The mechanism of these reactions is thought to involve the intermediacy of a metal–ketene complex whose formation is photo-induced.[171,172] Early indications that this was the case came when it was found these reactions fail to give cyclic products of any kind under thermal conditions. More recently, vinylketene complexes have been trapped from these reactions.[171] With the recent realization that metal–ketene intermediates are likely to be involved in these reactions further development of the photo-induced reactions of Fischer carbene complexes can be anticipated.

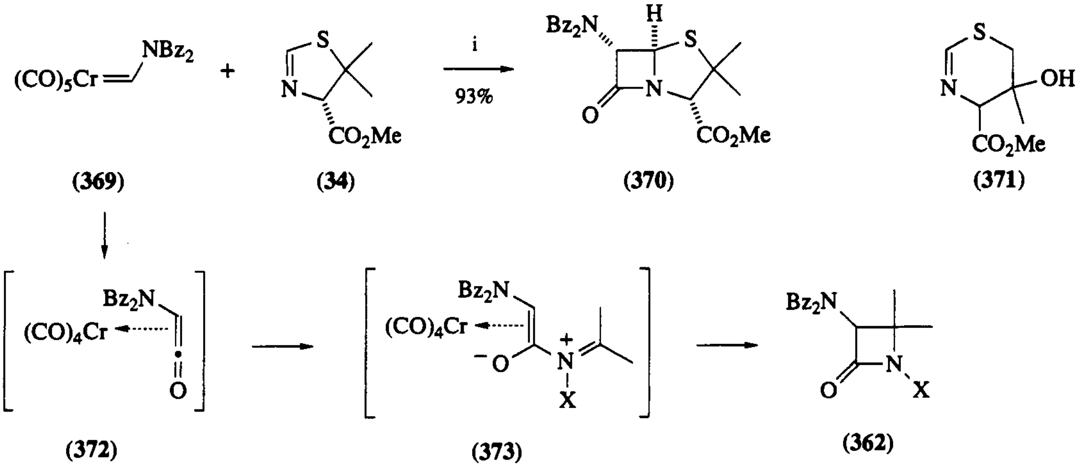

i, MeCN, 0 °C, 450 W lamp, 9 h

Scheme 49

### *9.2.3.3.3 Isonitriles*

The chemistry associated with the reaction of Fischer carbene complexes with isonitriles has been investigated over the last 20 year period, mainly by Aumann. It is not possible to cover this material comprehensively in this review, however, and an excellent overview of this area has appeared in the literature.[173] All of the chemistry reported to date actually involves reactions of the ketenimine complex (**376**), which is generated by the coupling of the carbene ligand and an isonitrile. If the reaction of the carbene complex and an isonitrile is carried out in a coordinating solvent, such as acetonitrile, the free ketenimine (**377**) can be isolated. In the case of Group 6 metals, the ketenimine in complexes of the type (**376**) are bound through the nitrogen.[174] The electrophilicity of ketenimines is reversed when coordinated to a metal. Free ketenimines suffer nucleophilic attack at the central carbon, whereas the ketenimine complexes (**376**) add nucleophiles at the terminal carbon and, thereby, provide for an alternative preparation of amino carbene complexes.[175] Ketenimine complexes also will undergo head to head dimerization at the carbon–carbon bond.[176]

Ketenimine complexes can serve as three-atom components in [3 + 2] cycloadditions. The reaction of the tungsten complex (**378**) with cyclohexyl isonitrile and phenyl isocyanate produces the heterocyclic carbene complex (**379**), which is the result of the *in situ* trapping of a ketenimine complex with the isocyanate.[177] Complexes of the type (**379**) can be oxidatively cleaved to give the previously inaccessible 5-ethoxyhydantoins. [3 + 2] Cycloadditions of this type have also been carried out with aldehydes.[177]

In the presence of 2 equiv. of isonitrile, [3 + 1] cycloadditions can be effected leading to the formation of the cyclic amino carbene complex (**381**), which can be cleaved in high yield to the β-lactam (**382**). This reaction gives highest yields with iron–carbene complexes,[175] although for manganese complexes the initial ketenimine complex (**376**) reacts sluggishly with the second equivalent of isonitrile making it possible to sequentially incorporate two different isonitriles.[178]

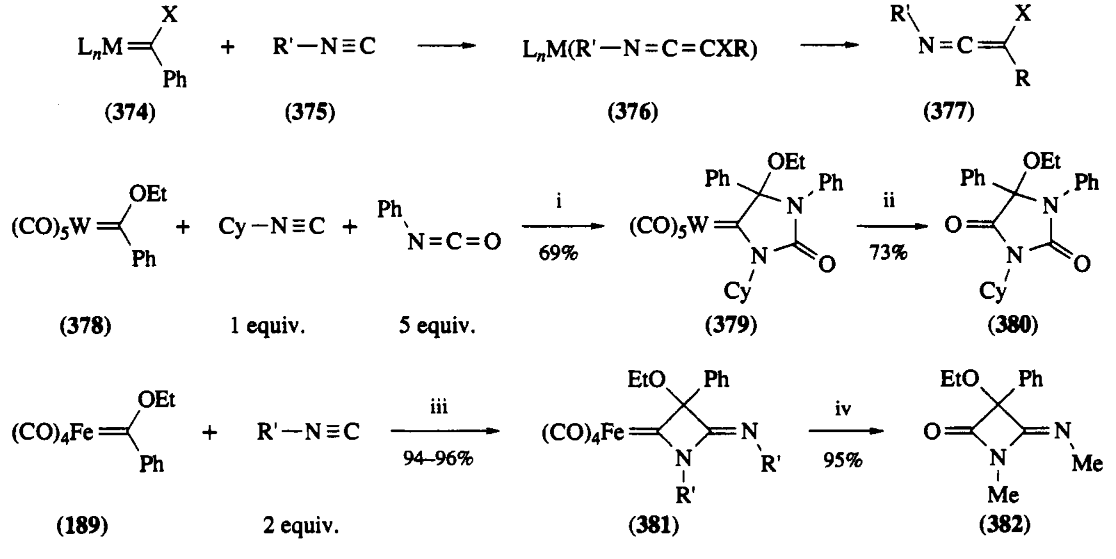

i, $Et_2O$, 25 °C, 24 h; ii, $KMnO_4$, $Fe(NO_3)_3$, acetone/water; iii, pentane, 20 °C, 1 h; iv, $KMnO_4$, benzene/water, 25 °C

**Scheme 50**

The reactions of alkenyl carbene complexes with isonitriles can produce a variety of products whose distribution is sensitive to the nature of the isonitrile. Reacting 3 equiv. of aryl isonitrile with the alkenyl complex (**383**) produces the dihydro-γ-carbolinone (**385**).[174] The ketenimine in (**384**) is liberated with a second equivalent of the isonitrile, and the the third equivalent undergoes a formal [4 + 2] cycloaddition with the free ketenimine. With sterically encumbered isonitriles, the ketenimine is more rapidly liberated from the metal by a second isonitrile and 2 equiv. are required to drive the reaction to completion. Free ketenimines that are generated in this manner can be trapped *via* their [4 + 2] cycloadditions with maleic anhydride.[179] Primary and secondary alkyl isonitriles will react with alkenyl carbene complexes to give cycloadducts that can be converted to pyrroles[179] or products that contain five-membered ring carbocycles.[179,180]

The chemistry associated with the reactions of isonitriles and carbene complexes is extraordinarily rich and should find applications in organic synthesis.

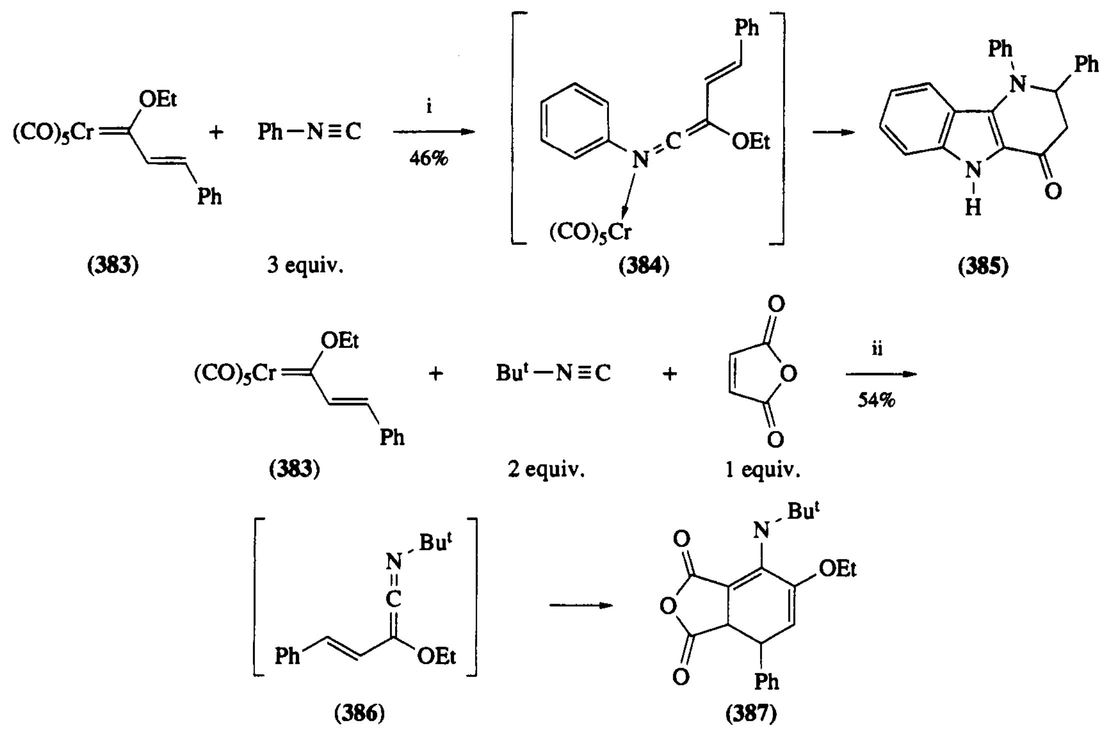

i, pentane, 20 °C, 2 h; ii, toluene, 80 °C, 4 h

**Scheme 51**

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# 9.3

# Alkene Metathesis and Related Reactions

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## 9.3.1 INTRODUCTION

The alkene metathesis reaction between carbon–carbon double bonds is now a well-established synthetic method in industrial operations and in the laboratory.[1] Recently it has been recognized that a closely related, transition metal catalyzed reaction takes place between a carbon–carbon double bond and a carbon–oxygen double bond.[2] This latter process, which can be considered as a Wittig analog, shows promise of becoming an important tool of synthesis strategy.[3]

## 9.3.2 REACTIONS BETWEEN CARBON–CARBON DOUBLE BONDS

The alkene metathesis reaction represents a unique carbon skeleton rearrangement in organic chemistry. This reaction, which grew out of the studies of catalysts related to alkene polymerization, results in the cleavage of the carbon–carbon double bond of an alkene and the redistribution of the resulting alkylidene fragments (equation 1).[1] The same reaction carried out with cyclic alkenes generally results in the formation of polymers (equation 2).

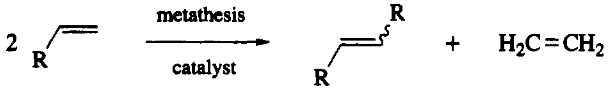

(1)

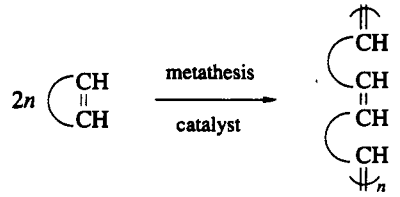

(2)

Although there was considerable controversy over the mechanism of this unique reaction, it is now generally accepted that the reaction proceeds through a series of metallacycle and carbene complexes as shown in equation (3).[4] Although the relative stabilities of the carbenes and metallacycles can change with reaction conditions, catalyst composition and alkene substitution, the fundamental mechanism appears to be the same for all catalysts.[5]

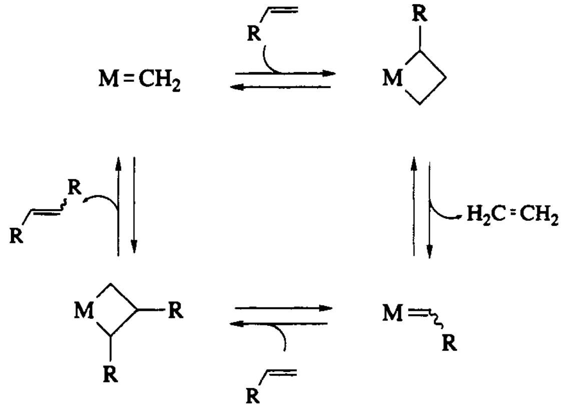

(3)

The original catalysts reported for the metathesis of acyclic alkenes were related to alkene polymerization systems. Banks and Bailey reported in 1964 that the heterogeneous cobalt molybdate complexes would promote the metathesis reaction.[6] Since that time a wide variety of catalysts that use Mo, W and Re as the active metal in combination with a variety of supports, promoters and activation conditions have been reported.[1] These heterogeneous catalysts are the systems of choice for most industrial fine chemical applications.

Eleuterio had described the formation of polymers by the ring opening of cyclic alkenes as early as 1957.[7] It is now well understood that the cyclic and acyclic alkene metathesis reactions, although they lead to very different type products, are the same fundamental reaction.[8] For polymerizations and other applications, a series of nonsupported catalysts have been generated. These catalysts usually result from mixing a tungsten or molybdenum halide with an alkylaluminum. Although the resulting mixture contains a low concentration of the active species, these systems can be extremely active at room temperature. For example, a room temperature catalyst mixture of $WCl_6$/EtOH/$Et_2AlCl$ will convert $10^4$ moles of 2-pentene per mole of tungsten in 3 min with 99.6% selectivity to 2-butene and 3-hexene. Due to the strong Lewis acidity of these systems, only a few functionalized alkenes can be successfully metathesized using these Zeigler type catalysts.[8b] In all of these systems the generation of the initial carbene complex is inefficient and appears to be the rate-limiting reaction.

Recently, highly efficient catalysts have been developed that are one component systems and contain a preformed alkylidene or metallacycle as the catalyst initiator.[2c,9–11] Some of these complexes have shown excellent utility in the synthesis of organic molecules and will be the major topic of the last part of this chapter.[2,12] These complexes will not only change many of the approaches in simple alkene metathesis but will also have a major influence on the future applications in organic and polymer synthesis.

### 9.3.2.1 Industrial Applications

The simplest example of alkene metathesis, the disproportionation of propylene to ethylene and 2-butene, was the first commercial application of this reaction. Changes in the relative economic value of the three alkenes resulted in the early closing of this facility.[13] The general process, called the Phillips Triolefin Process, is now used to produce neohexene from ethylene and the dimer of isobutylene (equation 4).

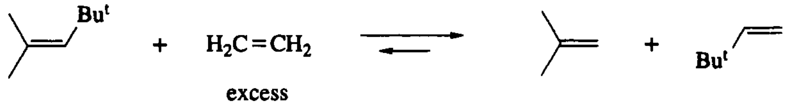
Bu$^t$
+
$H_2C=CH_2$
excess
+
Bu$^t$

(4)

The largest commercial application of metathesis is as a major step in the Shell Higher Olefin Process (SHOP).[14] In this process, ethylene is oligomerized to prepare $C_{10}$ to $C_{20}$ alkenes to be used in the production of fatty acid alcohols. The nickel-catalyzed oligomerization process gives a broad distribution of α-alkenes. Those that are of higher and lower molecular weight than desired are separated and isomerized to internal alkenes. This mix of high and low molecular weight internal alkenes is metathesized to a new broad distribution of alkenes. The desired molecular weight materials are removed and the remainder is again recycled. By this process most of the ethylene can be redistributed to the desired molecular weight range (equation 5).

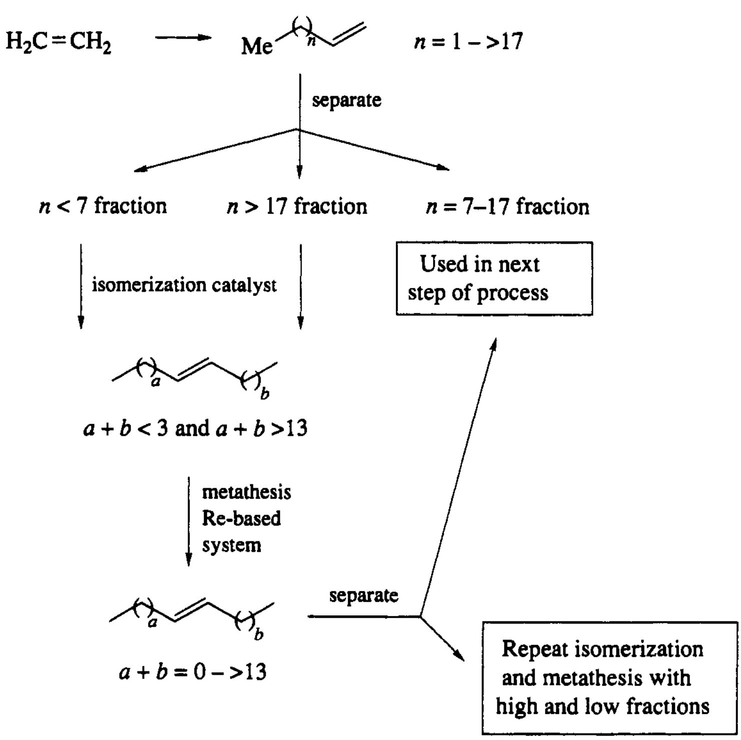
$H_2C=CH_2$
Me
n
$n = 1 - >17$
separate
$n < 7$ fraction
$n > 17$ fraction
$n = 7–17$ fraction
isomerization catalyst
Used in next step of process
a
b
$a + b < 3$ and $a + b > 13$
metathesis Re-based system
a
b
$a + b = 0 - >13$
separate
Repeat isomerization and metathesis with high and low fractions

(5)

Cross metathesis of ethylene with internal alkenes provides a facile route to terminal alkenes. A number of processes have been described that use this transformation; however, the only products, besides neohexene,[13] that appear to be important are the α,ω-dienes that result from metathesis of cyclic alkenes with an excess of ethylene.[15] This family of compounds should find a wide variety of applications.

### 9.3.2.2 Fine Chemical Synthesis

Applications of metathesis to the synthesis of more complex organic molecules has been limited by the lack of tolerance of the catalyst systems for functional groups. Many of the new catalyst systems that are being developed appear to be less sensitive to basic functional groups.[11,16] It is anticipated that there will be numerous advances in this area over the next few years as better and more easily synthesized catalysts become available.

### 9.3.2.3 Pheromone Synthesis

Since a number of insect pheromones are nonfunctionalized alkenes, they are potential target molecules for synthesis from petrochemicals by the metathesis reaction. Cross metathesis between unsymmetrical internal alkenes can lead to a complex mixture of products; however, in some cases, this reaction provides the easiest method for production of such alkenes. For example, the pheromone for *Musca domestica*, tricosene, has been prepared from 2-hexadecene and 9-octadecene (equation 6).[17] Both of these alkenes are readily available.

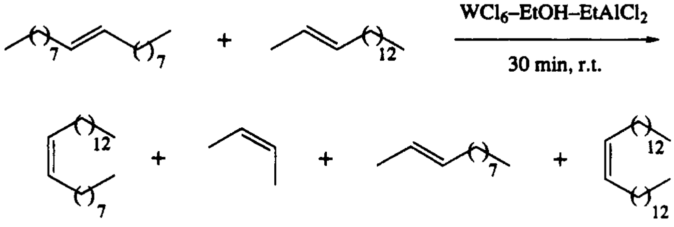

9-Tricosene,
9% isolated

other cross products

(6)

A few of the heterogeneous catalysts will catalyze a number of turnovers of nonconjugated unsaturated esters.[8b] The catalysts (**1** and **2**) appear to be of too low efficiency to be used commercially.

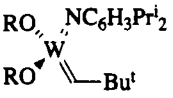

(**1**)

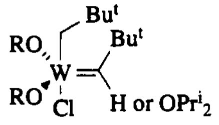

(**2**)

As will be seen later in this chapter, many early transition metal alkylidenes and metallacycles of the type required for metathesis (examples containing Ti, Ta, W and Mo as transition element) will undergo reactions with many organic functional groups. Although it was believed that this reactivity would limit the application of metathesis to nonfunctionalized alkenes, recent advances in the synthesis of one component catalysts of tungsten and molybdenum and the development of catalysts based on the later transition metals Re and Ru, suggest that catalysts can be prepared that are much less sensitive to basic functionalities. The key to functional group tolerance is to develop complexes that will react with alkenes in competition with heteroatom functionality. The tungsten catalysts prepared by the group of Schrock[11] and of Basset[9] will catalyze the metathesis of methyl oleate to the corresponding diester (equation 7).

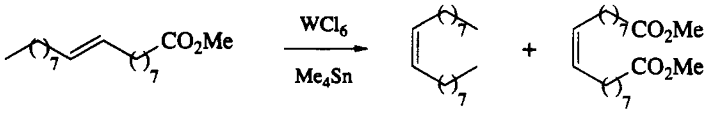

(7)

Related molybdenum catalysts appear to show even more functional group tolerance. To date, the major test of functional group compatibility has been in the synthesis of polymers; however, it is anticipated that this activity will persist into acyclic metathesis. Later transition metals are active in the metathesis polymerization of highly functionalized cyclic alkenes. These catalyst systems, which appear to tolerate almost all functional groups, show very low activity for acyclic alkene metathesis.[18] If these systems can be activated, the problems associated with the use of alkene metathesis in the synthesis of multifunctional organics will be solved.

### 9.3.2.4 Synthesis of Macrocycles

Two approaches to the formation of large rings by metathesis have been attempted. The first approach is demonstrated by the synthesis of 9-octadecen-18-olide by Tsuji[19] by the closure of an α,ω-diene (equation 8). Although the yield in this reaction is low (18%), the result demonstrates the potential of this approach, especially in view of the functional group tolerant catalysts that are now available.

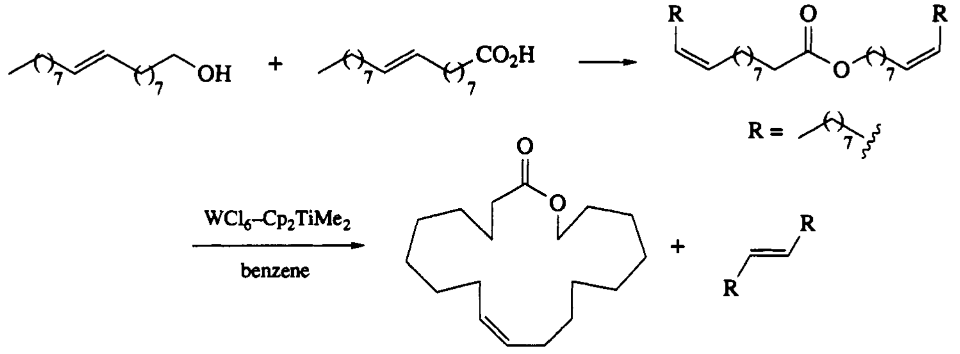

(8)

18% yield
9-Octadecen-18-olide

The second approach, which involves the dimerization of cyclic alkenes to larger cyclic dienes, appears to be successful for certain ring sizes. For example, cyclooctene can be dimerized to 1,9-cyclohexadecadiene in 34% yield and cycloheptene is dimerized in an 80% yield to 1,8-cyclotetradecadiene.[20] A careful consideration of the mechanism of this transformation is important in understanding the experimental conditions required to obtain dimers instead of the thermodynamically favored ring-opened polymer. Each step in the reaction is reversible and the rate of chain growth is related to the rate of the forward bimolecular reaction between the growing polymer chain and more monomer, $k_p$, and the unimolecular back-biting reaction with a double bond in the tail of the polymer, $k_{bb}$. If reaction takes place with the last double bond formed, starting material is produced. However, if a double bond further down the chain reacts, a larger cycle is formed (equation 9).

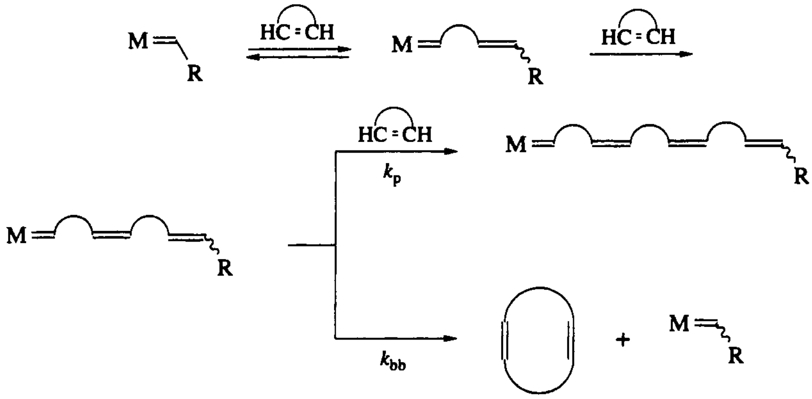

(9)

Consequently, in order to optimize the yield of the dimer resulting from a unimolecular reaction, the concentration of the starting material in contact with the catalyst must remain low. Also, since the product dimer can also react with the catalyst to produce larger rings, it must be removed from the reaction as it is formed. Both of these requirements are accomplished by using a soxhlet extractor as the reactor. A heterogeneous catalyst is used to facilitate the separation of the products from the catalyst. The catalyst ($Re_2O_7/Al_2O_3$) is maintained in the cup of the apparatus and the reactant is circulated over the catalyst by heating the reactant in a lower boiling solvent such as pentane or hexane. In this way only a low concentration of the reactant is in contact with the catalyst at any time, and the products are rapidly removed from the catalyst. Since the products are much higher boiling than the reactants, only small amounts of the products are recycled (equation 10). In both cases, the thermodynamic mixture of stereoisomers is formed. The high yield of the dimer from cycloheptene is attributed to the exceptional conformational stability of the *trans,trans*-1,8-cyclotetradecadiene.

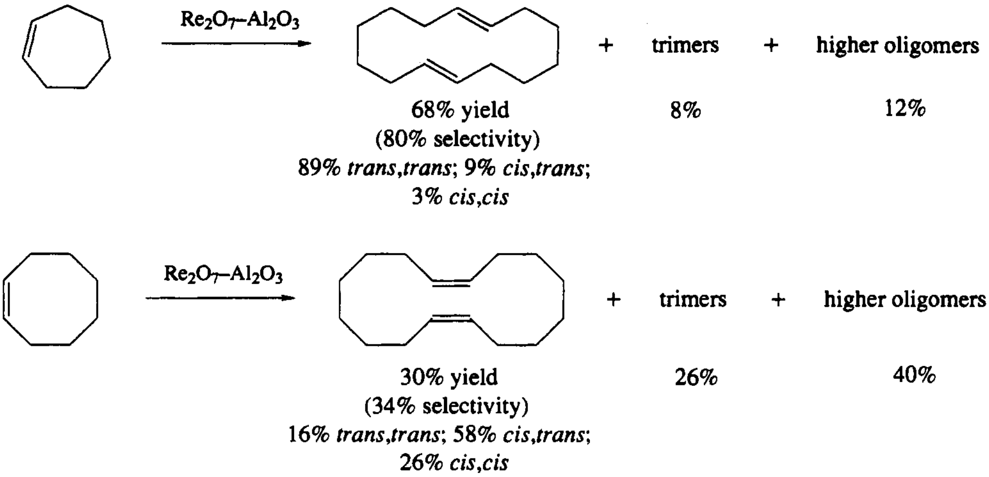

68% yield (80% selectivity) 89% *trans,trans*; 9% *cis,trans*; 3% *cis,cis* — trimers 8% — higher oligomers 12%

(10)

30% yield (34% selectivity) 16% *trans,trans*; 58% *cis,trans*; 26% *cis,cis* — trimers 26% — higher oligomers 40%

### 9.3.2.5 Polymer Applications

The developments of the metathesis reaction for polymer synthesis have paralleled the opportunities in acyclic chemistry. Acyclic and cyclic metathesis were discovered independently and only later were recognized as the same reaction. Most of the work in the area of ring-opening metathesis polymerization (ROMP) is outside the scope of this article, and only those areas where the results suggest possibilities in organic synthesis will be discussed in detail.

As discussed above in the mechanism of the alkene dimerization reaction, the polymerization of simple alkenes proceeds by the basic metathesis mechanism. Since polymers that are prepared from complex monomers require homogeneous catalysts, much of the early 'organometallic' catalyst development has had polymer synthesis as the driving force. Recently, developments in the synthesis of organometallic complexes that serve as well-defined catalysts for metathesis have opened many opportunities in the area of polymer synthesis.[21]

The speed and efficiency of chain growth relative to termination of the metathesis catalysts provides high molecular weight polymers. Different catalyst mixtures produce different double bond geometries and tacticities.[22] These factors have been studied in detail since one of the first promising polymers produced by ROMP was polypentenamer. The all-*trans* isomer is an elastomer and was studied as an excellent material for tire manufacture, while the *cis* isomer is a nonelastomeric solid (equation 11).[23]

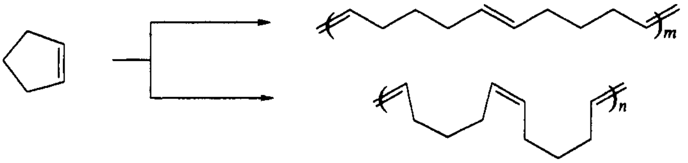

(11)

To date, low volumes of materials have been produced commercially from norbornene and cyclooctene.[24] Numerous products are expected to result from the material produced by the ROMP of dicyclopentadiene in a RIM (reaction injection molding) process. In a RIM process, two streams of a monomer are mixed in the mold where it is polymerized to the final part.[25] In this case, one of the monomer streams contains a tungsten complex while the second contains an alkyl aluminum activator. When the two streams of dicyclopentadiene are mixed, the metathesis catalyst is formed and the monomer is ROMP polymerized (equation 12).

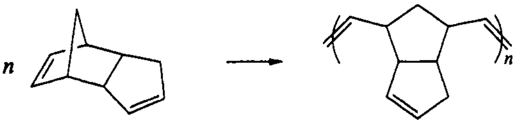

(12)

Recent advances in ROMP chemistry have resulted from the finding that the isolated organometallic carbene and metallacycle complexes give living polymers. These systems continue to add monomers to the end of the growing chain without chain transfer or termination. From a polymer synthesis viewpoint, this result opens the way for the synthesis of monodispersed polymers, block copolymers and a variety of materials with tailored properties. For example, the metallacycle formed from norbornene and the Tebbe reagent[2c] can be isolated and characterized. When this metallacycle is heated with more norbornene, polynorbornene is produced.[26] If the reaction is cooled to room temperature, the reaction stops and a polymer can be isolated that contains a metallacycle at the end. When this metallacycle is heated with a carbonyl compound, the intermediate alkylidene undergoes a Wittig type reaction, of the type that will be discussed later, to give a high yield of an end-capped polymer (equation 13).[27]

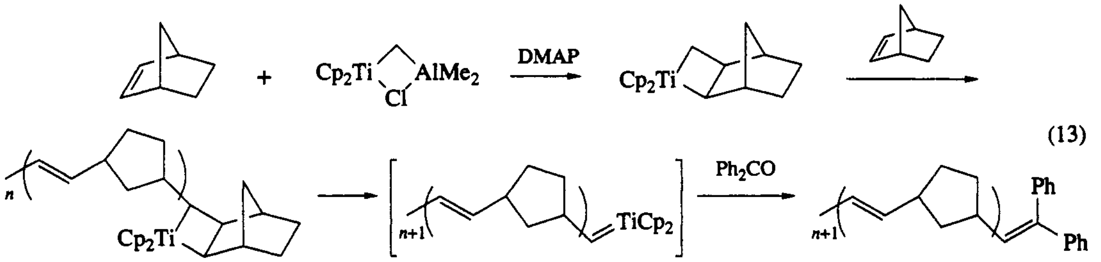

(13)

If this reaction is carried out as an intramolecular reaction, interesting ring systems are produced. This reaction was used to produce a precursor to capnellene[28] and involves all the same reactions as used in the polymer synthesis (equation 14).

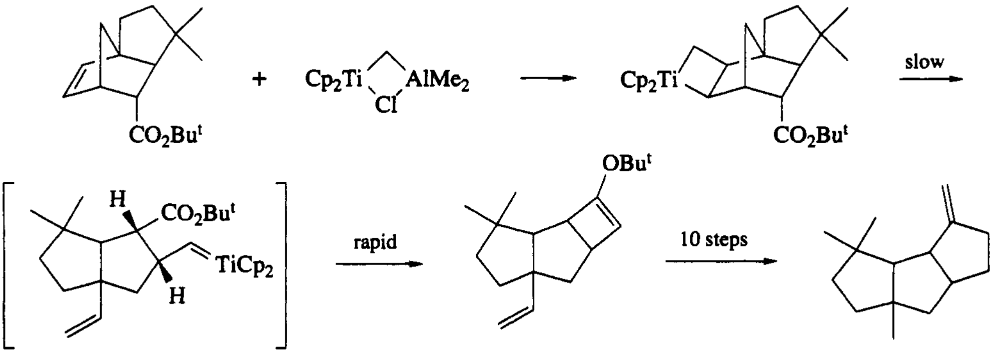

(14)

$\Delta^{9,12}$-Capnellene

With the availability of the newer catalysts discussed above that are more tolerant of functionality, it is anticipated that a wide variety of synthetically useful carbon skeleton rearrangements can be carried out. For example, the molybdenum catalyst shown in equation (15) gives a high molecular weight, living polymer with *endo,endo*-5,6-dicarbomethoxynorbornene. This result demonstrates that the rate of reaction of the growing alkylidene with the alkene double bond is much faster than the competing 'Wittig' reaction of the alkylidene with the carbonyl functionality.[16]

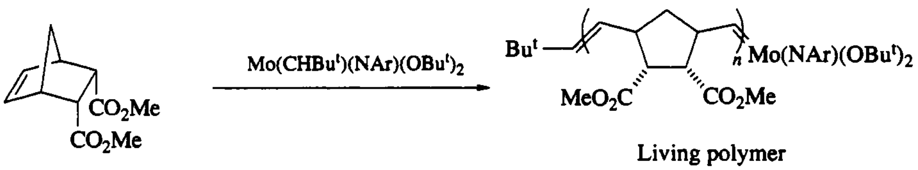

(15)

Living polymer

Another area of ROMP in the early stages of development is the polymerization of highly functionalized monomers in protic and aqueous solutions. These catalysts appear to tolerate most organic functional groups and will polymerize highly functionalized monomers (equation 16).[18] The development of the organometallic chemistry of these catalysts will open a variety of new applications of metathesis in organic synthesis.

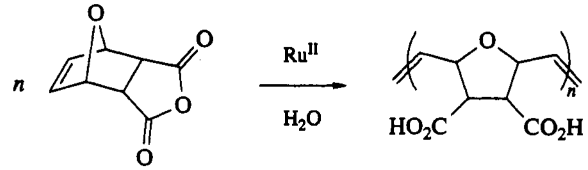

(16)

## 9.3.3 REACTIONS BETWEEN CARBON–CARBON AND CARBON–OXYGEN DOUBLE BONDS

Alkene metathesis catalysis involves intermediates in which a transition metal is multiply bonded to carbon. These species are often referred to as nucleophilic carbenes when the carbon atom is negatively polarized. A more functional description is to name these compounds as alkylidene complexes, since they react to transfer an alkylidene moiety from a transition metal to a substrate carbon atom.[2d] Previous sections of this chapter have focused on a common example of this chemistry; the process of metathesis that involves transition metal mediated interaction of carbon–carbon multiple bonds.

In this section we will consider the interactions between transition metal complexes and carbon–oxygen double bonds, *i.e.* carbonyl groups. The transition metal functions as a reagent to deliver an alkylidene fragment and replace the oxygen atom. The process is analogous to a Wittig reaction (equation 17).[29]

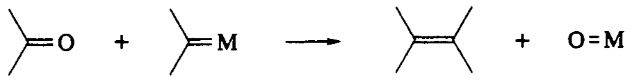

(17)

M = metal

Compounds of the early transition metals have been found to function in this way. Titanium, zirconium, tantalum and tungsten are among the most prominent metals in these complexes. The complexes of titanium form the basis for most of the reagents currently reported in synthesis applications.

### 9.3.3.1 Titanium Based Reagents

The titanium–aluminum methylidene (3), commonly known as the Tebbe reagent,[2c] was the first well-characterized compound in this series. The Tebbe reagent (3) and related metallacycles (4) have been used principally as methylidene sources toward carbonyl groups. Both are believed to provide the titanium methylidene (5).[2c,3]

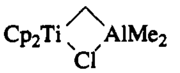

(3)

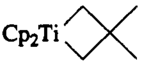

(4)

$Cp_2Ti=CH_2$

(5)

In the case of the Tebbe reagent, the titanium methylidene is presumably released by some Lewis base. That base is often the heteroatom of the substrate. A Lewis base such as tetrahydrofuran or pyridine may be added to the reaction and usually enhances reactivity relative to reaction with the substrate alone.[2a,b]

The metallacycles (4) generate the requisite titanium methylidene thermally. Consistent with this is the observation that reaction with a carbonyl compound is first order in the metallacycle and zero order in the carbonyl compound.[30] Metallacycle stability depends on the alkene moiety that has replaced the aluminum–chlorine portion of (3) and thus could provide a series of reagents whose reactivity is temperature dependent.[31]

The titanium methylidene interacts with the carbonyl carbon–oxygen double bond in a sequence that is believed to resemble the metathesis process. With the metallacycle (4), a titanium oxametallacycle is believed to be formed, which then decomposes to generate the new carbon–carbon double bond and a titanium–oxygen product.[3] The driving force for the reaction has been attributed to the oxophilicity of titanium (equation 18).[32]

Reaction of the titanium–aluminum reagent (3) is more complex. If no additional Lewis base is employed, the carbonyl compound takes that function. Interaction with the aluminum atom is required to

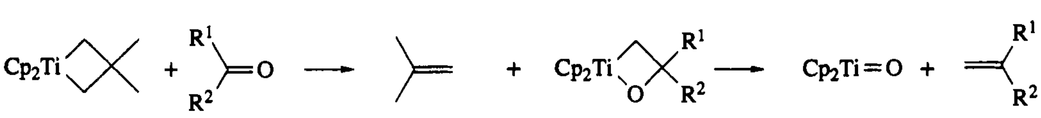

(18)

'release' the methylidene. Kinetic studies of the reaction with esters indicate a second-order process, first-order in the reagent and first-order in the ester.[33] The large negative entropy for this process suggests that an intermediate forms, possibly a six-membered ring metallacycle, which then leads to the observed product. In contrast to the related reaction with the metallacycle, the major titanium-containing product is Cp2TiClMe while the oxygen of the original carbonyl group is found in a methylaluminoxy polymer (equation 19).

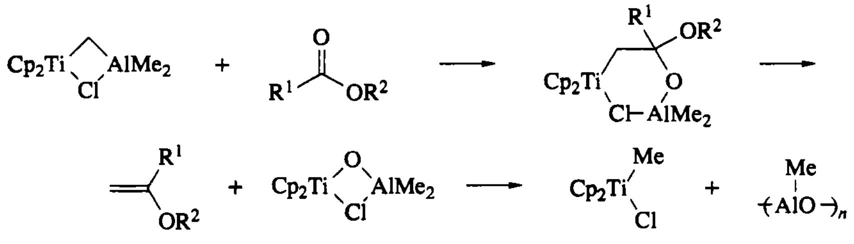

(19)

The Tebbe reagent and its metallacycle analogs have proven particularly valuable for the formation of enol ethers from esters.[2a,b,3,34] This methylenation of an ester carbonyl is not normally accomplished using the classical Wittig phosphoranes.[29,35] The same methylenation process takes place with lactones.[2a,b,3,36] In fact, the sequence has been used to methylenate a lactone, and the methylidene product then allowed to undergo an electrocyclic reaction (equation 20).[37] Similarly, the carbonyl group of sugar lactones reacts with the reagent (equation 21).[38]

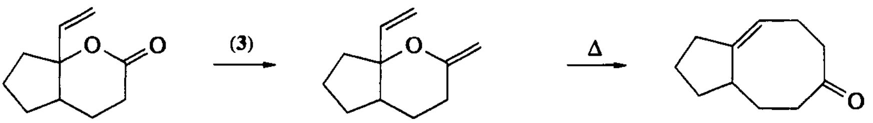

(20)

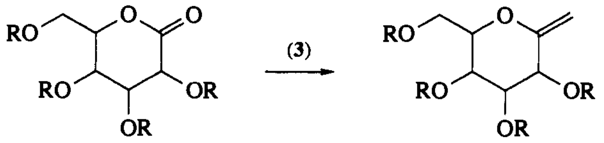

(21)

The Tebbe and metallacycle reagents are also effective at ketone and aldehyde methylenation.[2b,c,39] In this reaction, they are similar to the Wittig reagent, methylenetriphenylphosphorane. A comparison of the effectiveness of the Tebbe reagent and the Wittig reagent indicates that the Tebbe reagent is comparable to or better than the Wittig reagent for the methylenation of ketones. The value of the Tebbe reagent for methylenation is particularly obvious when the carbonyl substrate is hindered (equation 22).[40]

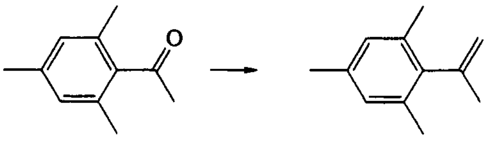

(22)

Tebbe reagent, 77%; Wittig reagent, 4%

Stereochemistry is retained in substrates containing carbon–carbon double bonds.[2a] Furthermore, the absence of a basic medium provides a process in which epimerization of a chiral center is not a problem.[3,41] The method also accomplishes methylenation of enolizable ketones,[42] a process not very successful with the Wittig reagent.

In some cases, there appears to be competition between reaction of (**3**) with the carbonyl and with the terminal alkene product. In the latter case a metallacycle is believed to be formed, which, on protonolysis, leads to the product of *gem*-dimethylation of the original carbonyl.[2b,3] This transformation has only been observed with unhindered aldehydes and ketones, but does, in itself, provide a rather useful synthetic sequence (equation 23).

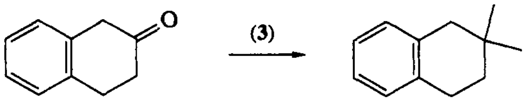

(23)

Amides are converted to enamines by reaction with the Tebbe reagent (equation 24),[2b] whereas acyl halides lead to enolates (equation 25).[43] Anhydrides lead to a combination of enolate formation, methylenation and enolization.[44]

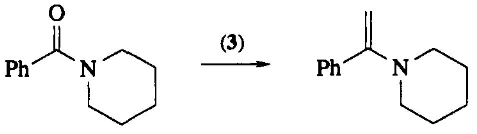

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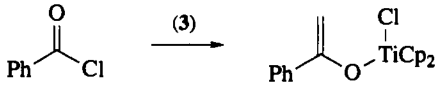

(25)

The Tebbe reagent is a methylidene transfer reagent. Attempts to prepare the homologous titanium–aluminum reagents, *i.e.* ethylidene, *etc.*, have failed, presumably because β-hydride abstraction destroys the complex.[45] However, some success at homologous alkylidene transfer has been attained through hydroalumination of an alkenyltitanium complex. A spectroscopically identified intermediate is formed which then alkylidenates a ketone carbonyl.[46] This, along with other titanium–aluminum reagent mixtures, suggests the possibility of alkenylation,[47] though none of these potential methods have been used in synthesis.

A rather novel approach makes use of the reaction between the titanium metallacycle (**4**) and one double bond of an allene to produce a new metallacycle. That new metallacycle then transfers the allene to a carbonyl compound (equation 26).[48]

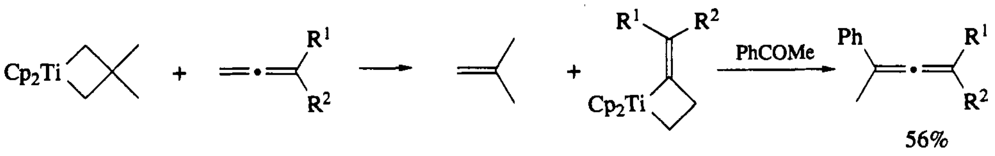

(26)

The synthesis of capnellene discussed earlier is an interesting example in which (**3**) was used to generate a new titanium alkylidene which then underwent an intramolecular reaction with an ester carbonyl. The process effectively involved carbonyl alkylidenation by a substituted titanium alkylidene (equation 14). In this case steric factors apparently account for the desired reaction selectivity.[28]

The Tebbe reagent can be isolated before use or prepared as an *in situ* mixture.[49] Other *in situ* reaction mixtures which mimic many of the synthetic results of the Tebbe reagent have been introduced. For example, a mixture of $TiCl_4$, Zn and $CH_2Br_2$ provides a reagent that methylenates ketones,[50] including those that are commonly enolized under the conditions of the Wittig reaction.[51] The procedure was used for the methylenation of gibberellins and their analogs (equation 27)[52] and has also been used with other natural products (equation 28).[53]

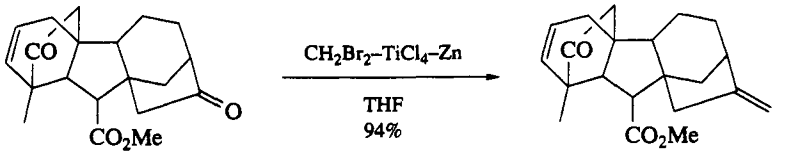

(27)

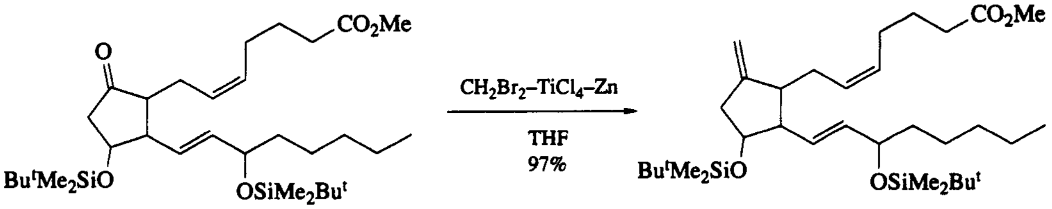

(28)

Dideuteriomethylenation has been accomplished by utilizing $CD_2Br_2$,[52,54] and $^{13}C$ has been introduced using $^{13}CH_2Br_2$.[55] The method has been developed as an organic synthesis procedure[50a] and is currently the most widely used of the titanium based methylenating reagents.

The compositions of these types of reagents are not yet understood, though it has been suggested that the active agent may be a *gem*-dimetallic methylene reagent rather than a carbenoid. For example, the reaction of $CH_2(ZnI)_2$ with $Cp_2TiCl_2$ in THF gives a reagent which methylenates ketones and whose NMR spectral data suggest $Cp_2TiCH_2{\cdot}ZnX_2{\cdot}(THF)$.[56] A reagent containing titanium and magnesium has also been reported to methylenate ketones.[57]

The reagent formed with $TiCl_4$ is reported to give good yields with ketones, though pinacol-type products often result when the carbonyl compound is an aldehyde. However, the use of $Ti(OPr^i)_4$ is reported to be selective for methylenation of aldehydes.[58]

All of the dihaloalkane-based reagent mixtures discussed above have only been reported to be effective for alkylidenation of ketones and in some cases aldehydes. Modification of the $TiCl_4$/Zn dibromoalkane reagent by adding *N,N,N′N′*-tetramethylethylenediamine (TMEDA) is reported to alkylidenate esters,[59] a reaction similar to that of the Tebbe reagent and its metallacycle analogs. The reagent mixtures derived from $TiCl_4$ and Zn have recently been reported to accomplish $C_2$ and higher alkylidenation by using dihaloalkanes (equation 29).[60]

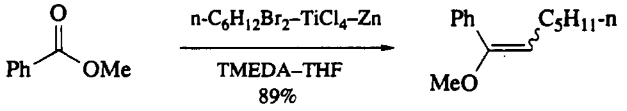

(29)

## 9.3.3.2 Other Transition Metal Based Reagents

Compounds of tantalum and niobium were among the earliest reagents investigated for alkylidene transfer to carbonyl.[2d,61] Ketones, aldehydes, esters and amides were found to react with a neopentylidene reagent. Note that there are no β-hydrogen atoms in this reagent, so that the instability associated with most nonmethylene examples is not present (equation 30). Interestingly, the tantalum analog of the Tebbe reagent ($Cp_2Ta{=}CH_2$) is not an effective methylenation reagent for ketones.[61]

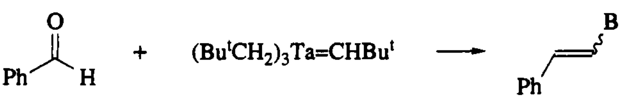

(30)

Zirconium–aluminum analogs of the Tebbe reagent have been reported to react with carbonyl compounds slowly, in low yield[62] or not at all.[63] However, zirconium alkylidenes which are stabilized by a phosphorus rather than an aluminum ligand do transfer their alkylidene moiety to carbonyl.[64] These results provide some of the few examples of long chain alkylidene transfer to carbonyl from an organometallic reagent (equation 31).

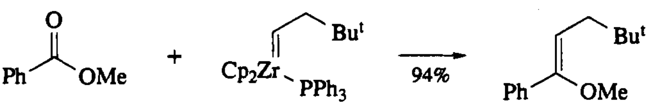

(31)

Tungsten alkylidenes have also been shown to accomplish carbonyl alkylidenation.[65] Aldehydes, ketones, esters and amides have been used as the carbonyl moiety. These reactions involve metallacycle intermediates and appear to parallel much of the metathesis chemistry (equation 32).

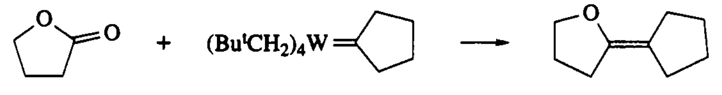

(32)

A series of molybdenum alkylidene complexes react with aldehydes, and in some cases ketones, to give the product of methylenation (equation 33).[66] Some of the examples appear to involve an alkylidene, while others may follow an addition–elimination route typical of the Peterson alkenations.[67] Probably the most interesting aspect of this work is the observation that some of the methylenation reactions can be carried out in aqueous or ethanolic media (equation 33).[66]

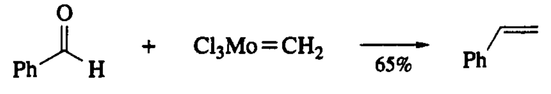

(33)

A metallacycle in which uranium, silicon and nitrogen atoms connect to the methylene group has been shown to methylenate a variety of aldehydes and ketones, including some carbonyl compounds which do not react well in the Wittig process (equation 34).[68] This material exemplifies the complexity and sophistication that is being used to develop reagent and catalyst systems.

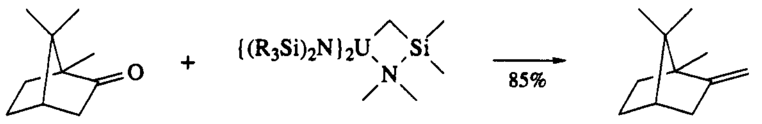

(34)

## 9.3.4 CONCLUSIONS

The metathesis reaction between carbon–carbon double bonds (alkene metathesis) is well established in commercial scale synthesis. It is a key component of some polymerization processes and is the route to nonfunctionalized alkenes which find applications in fine chemical synthesis. The development of well-defined, functional group tolerant catalysts will lead to a much greater role for alkene metathesis in synthesis.

The related reaction between carbon–carbon and carbon–oxygen double bonds is just beginning to be developed. This Wittig analog provides new routes for carbonyl alkylidenation of aldehydes, ketones and members of the carboxylic acid family.

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# 9.4

# [2 + 2 + 2] Cycloadditions

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## 9.4.1 INTRODUCTION

This section will address transition metal mediated cycloaddition processes that fall into the [2 + 2 + 2] category: reactions involving three components, each of which formally contributes two electrons towards the final product of cycloaddition. Since the designation (in square brackets) refers to the electrons and not the atoms contributed by each cycloaddition component, reactions involving cycloaddition participants such as CO, isonitriles and heteroatoms are included. Products formed will include four-membered rings from 2 + 1 + 1 cycloaddition (atom, not electron designation), five-membered rings from 2 + 2 + 1 cycloaddition, and, of course, six-membered rings from 2 + 2 + 2 processes. Several reactions which fall into the formal [2 + 2 + 2] category are covered elsewhere: the Pauson–Khand (2 + 2 + 1) reaction (Volume 5, Chapter 9.1), 2 + 1 + 1 and 2 + 2 + 1 cycloadditions of metal carbenes (Volume 5, Chapter 9.2), and zirconium-promoted 2 + 2 + 1 bicyclization of enynes (Volume 5, Chapter 9.5).

Mechanistically, the term cycloaddition applies in only a formal sense to most of the reactions in the section; virtually none of these reactions involves true single-step cycloaddition of all three components that appear in the final product. More typically, cycloaddition involving a transition metal fragment and one or two other components leads to a metallacyclic intermediate whose reaction with the remaining component(s) ultimately gives rise to the final organic ring system.[1] As organic synthesis is the focus of these volumes, this section will not cover cycloaddition reactions that give rise to metal-containing species from which the metal-free organic product cannot readily be liberated.

## 9.4.2 SYNTHESIS OF FOUR- AND FIVE-MEMBERED CARBOCYCLIC RINGS

### 9.4.2.1 Cyclobutenediones and Related Compounds

A number of $Ni^0$ complexes with donor ligands react with unsaturated substrates to give five-membered ring nickelacycles. Upon reaction of either phenyl- or diphenyl-acetylene with $(bipy)Ni(CO)_2$ (bipy = 2,2′-bipyridyl) under carbon monoxide a nickelacyclopentenedione complex forms in high yield. Further reaction with either higher pressures of CO or with maleic anhydride induces reductive elimination, liberating a cyclobutenedione, formally the product of a six-electron 2 + 1 + 1 cycloaddition (Scheme 1). Complex formation also occurs from alkylacetylenes, but subsequent reductive elimination does not, restricting the utility of this chemistry.[2] Similar chemistry had earlier been found in the reactions of $Ni(CNAr)_4$ with diarylalkynes, from which varying yields of diiminocyclobutenes could be isolated.[3]

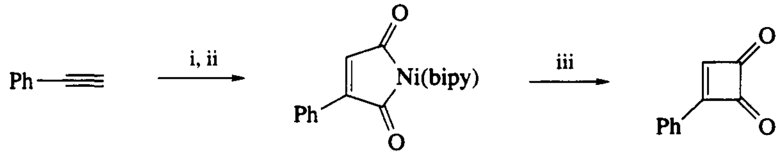

i, $(bipy)Ni(CO)_2$, THF, 24 h; ii, CO, 80 °C, 64% overall; iii, 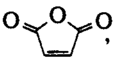, 6 h, 80%

Scheme 1

### 9.4.2.2 Cyclopentanones: Regio- and Diastereo-selectivity

A number of cycloaddition reactions of alkenes with transition metals are known to produce metallacyclopentanes, which in turn may yield cyclopentanones upon treatment with carbon monoxide, the net result being that of a formal 2 + 2 + 1 cycloaddition process. The most general involves the use of any of the iron carbonyls to generate polycyclic ketones directly from strained alkenes, generally compounds related to norbornadiene.[4,5] The reaction may be carried out thermally or photochemically, usually with less than a full equivalent of iron carbonyl. The metallacyclic intermediate is not observed, but proceeds directly to product. Yields are lower with most norbornene derivatives. The reaction is normally completely diastereoselective, generating *exo,trans,exo*-fused cyclopentanone rings, and it proceeds with complete regioselectivity from homoconjugated substrates (equations 1 and 2).[6] The stereochemical course of the reaction may be altered dramatically by remote groups capable of metal coordination (equation 3).[7] A few mixed cycloadditions are known.[8]

Among simpler cyclic alkenes, cyclobutenes are reported to undergo similar transformations.[9] Cyclopentenes and cyclohexenes react only under extreme conditions, giving very low yields.[10]

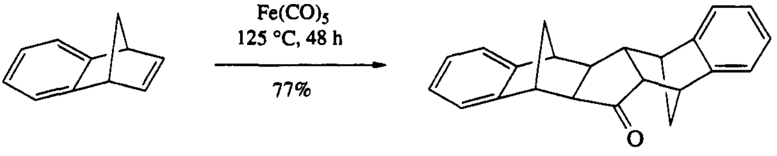

(1)

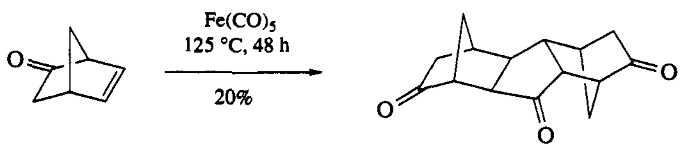

(2)

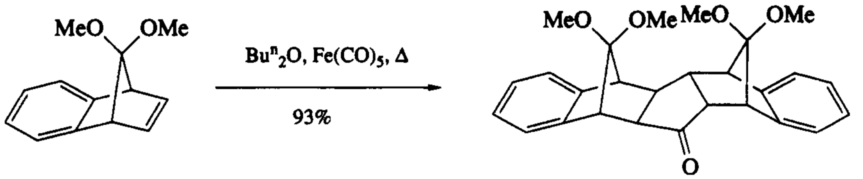
MeO OMe
Bu^n2O, Fe(CO)5, Δ
93%
MeO OMe MeO OMe
O

(3)

In general, acyclic alkenes do not give cyclopentanones upon reaction with low-valent metals and CO. Although a large number of metallacyclopentanes are known, many of which give cyclopentanones upon carbonylation, most are not readily formed from the corresponding alkenes and must be prepared in other ways.[11-14] Noteworthy exceptions include the completely regioselective reaction of methyl acrylate with iron carbonyl[15] and an intramolecular variant using α,ω-dienes with $Ni^0$ (Scheme 2). The latter reaction is completely diastereoselective to give the *trans*-fused bicyclic from the 1,7-diene; reaction of 1,6-heptadiene to give bicyclo[3.3.0]octan-3-one is however a much lower yield process (25%) exhibiting only 3:1 *trans*/*cis* diastereoselectivity.[16]

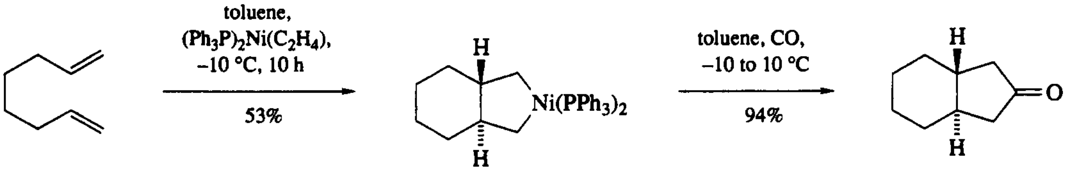
toluene,
(Ph3P)2Ni(C2H4),
-10 °C, 10 h
53%
H
Ni(PPh3)2
H
toluene, CO,
-10 to 10 °C
94%
H
O
H

Scheme 2

### 9.4.2.3 Cyclopentenones and Related Compounds: Chemo-, Regio- and Diastereo-selectivity

Although the Pauson–Khand reaction (Volume 5, Chapter 9.1) and the Negishi bicyclization (Volume 5, Chapter 9.5) are the two most thoroughly studied cyclopentenone syntheses using transition metals, several additional methods exist. Metallacycles derived regioselectively from alkynes, alkenes containing ester groups, and the CpCo fragment (Cp = $\eta^5$-$C_5H_5$) react with carbon monoxide to give cyclopentenones, and with isonitriles to give the corresponding enamines (*i.e.* 1-amino-1,3-cyclopentadienes) (Scheme 3).[17] As the Pauson–Khand reaction is ill-suited for substrates bearing electron-withdrawing groups, this method is complementary in scope.

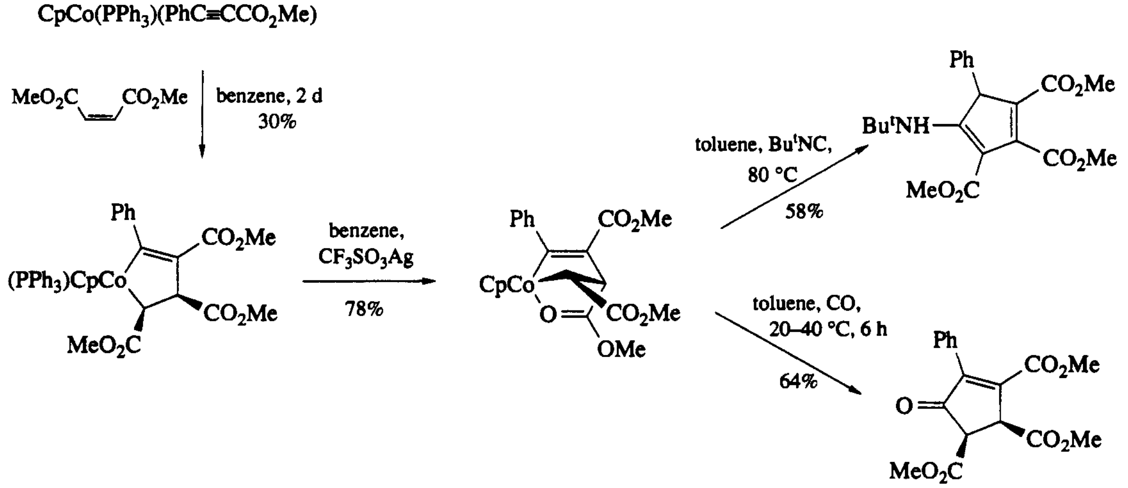
CpCo(PPh3)(PhC≡CCO2Me)
MeO2C CO2Me
benzene, 2 d
30%
Ph
CO2Me
(PPh3)CpCo
CO2Me
MeO2C
benzene,
CF3SO3Ag
78%
Ph CO2Me
CpCo
O CO2Me
OMe
toluene, Bu^tNC,
80 °C
58%
Ph
CO2Me
Bu^tNH
CO2Me
MeO2C
toluene, CO,
20–40 °C, 6 h
64%
Ph
CO2Me
O
CO2Me
MeO2C

Scheme 3

A cycloaddition of alkynes, *allenes* and CO under conditions that generate the $Fe(CO)_4$ fragment gives rise completely regioselectively to 4-methylenecyclopentenones (equation 4). Terminal alkynes are incorporated with the substituent largely or totally in the 2-position of the product, and the substituent in unsymmetrical allenes ends up preferentially on the exocyclic carbon rather than at position 5. Although the (*Z*) diastereoisomer of the exocyclic double bond appears to be the kinetic product, isomerism readily occurs thermally in the presence of the metal carbonyl.[18]

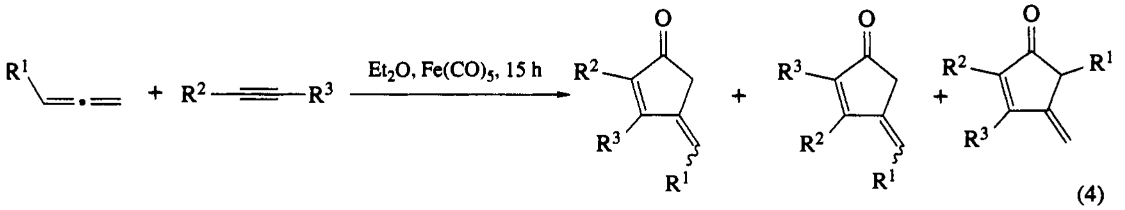

(4)

| *R$^1$* | *R$^2$* | *R$^3$* | | | | |
|---|---|---|---|---|---|---|
| H | Ph | H | 15% | 75% | 25% | - |
| Ph | H | H | 48% | 100% | | 0% |
| Ph | Ph | H | 18% | 100% | 0% | 0% |
| PhCH$_2$ | Ph | Ph | 25% | 80% | | 20% |

An intramolecular reaction of 1,5- and 1,6-enynes with isonitriles takes place in the presence of Ni(COD)$_2$ (COD = 1,5-cyclooctadiene) and phosphines, giving bicyclic cyclopentenone imines (equation 5).[19] Stereochemical characteristics in substituted systems appear to parallel those in the intramolecular Pauson–Khand: enynes with substituents in propargylic positions cyclize preferentially to products in which those substituents occupy *exo* positions relative to the newly created ring fusion. It is likely that these reactions proceed *via* similar mechanisms involving insertion into bonds of metallacycles, although the order of incorporation of the three two-electron systems into the precursor to the final product is open to question in the nickel system.

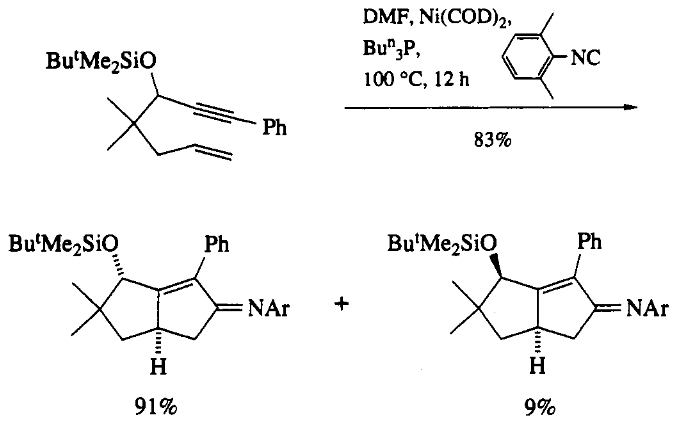

(5)

In a mechanistically quite different process Ni(CO)$_4$ is the catalyst precursor and the double bond of an allylic halide serves as the alkene component in another cyclopentenone synthesis. Sequential insertion of the alkyne and CO into an initially formed allyl–Ni complex leads to the primary cyclization product, a (2-oxo-3-cyclopenten-1-yl)methylnickel complex (Scheme 4). The final product of the sequence depends on which of several possible reactions of the latter take place. Important features of this reaction have been described in several reviews.[20–22]

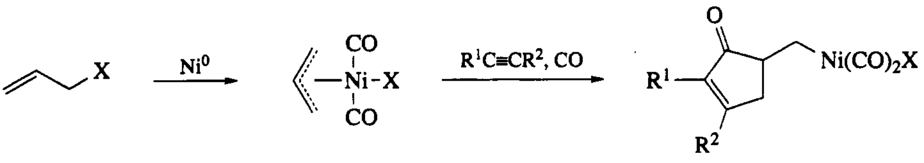

**Scheme 4**

A variety of alkynes follow this reaction sequence in reactions with allyl and crotyl chlorides, as well as with methyl 4-bromocrotonate. All examples proceed with total regioselectivity with respect to carbon–carbon bond formation between unsubstituted carbon atoms of unsymmetrical alkynes and allyl derivatives. The final products are derived from further insertions of CO and alkyne, followed either by protonolysis to give an enone side chain, or another CO insertion and cyclization to a lactone (equation 6).[23] Chemoselectivity is to some extent possible by control of reaction conditions. Methallyl halides are anomalous in giving rise to six- instead of five-membered ring products.[24]

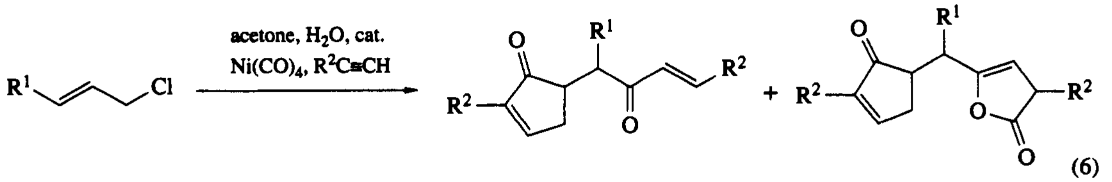

(6)

| $R^1$ | $R^2$ | | | |
|---|---|---|---|---|
| H or Me | H | | 0% | major product |
| H | Me | 84% | 33% | 67% |
| H or Me | Ph | 68–71% | 94–100% | 0–6% |

### 9.4.2.4 Cyclopentadienones and Related Compounds: Chemo- and Regio-selectivity

In 1953 Reppe reported the isolation of 1-indanone, the product of decarbonylation of the Diels–Alder dimer of cyclopentadienone, from the reaction of acetylene with $Ni(CO)_4$.[25] A wide variety of metal-based systems have been found to be capable of such chemistry, and both indanone and cyclopentadienone dimer are occasionally encountered as byproducts of reactions involving acetylene and metal carbonyl systems.[26] The interaction of a variety of transition metal fragments with alkynes has also long been known to give rise to cyclopentadienones in the form of metal-bound complexes.[27] Reactions of the iron carbonyls with alkynes are typical, producing varying yields of cyclopentadienone–$Fe(CO)_3$ complexes under thermal conditions. Examples include $Fe(CO)_3$-complexed tetrakis(dimethylamino)cyclopentadienone, which is obtained in moderate yields from $Fe(CO)_5$ in refluxing octane,[28] and the tetracyclopropyl[29] and tetraisopropyl[30] analogs, which are accessible in somewhat lower yields, from $Fe_3(CO)_{12}$ at 175–180 °C (equation 7). Treatment of the latter two complexes with trimethylamine oxide enables isolation of the metal-free dienones and is the most reliable general method for liberation of stable cyclopentadienones from complexation with metal carbonyl fragments.

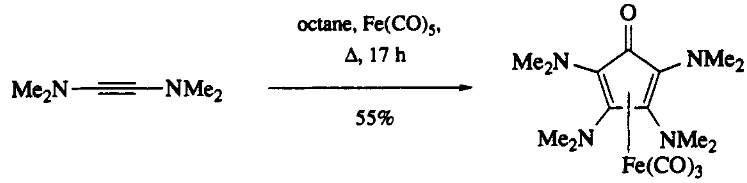

(7)

Stable, isolable metallacycles are also obtained from reaction of complexes that serve as sources of the CpCo fragment (*e.g.* $CpCo(PPh_3)_2$) and alkynes. Upon carbonylation these typically give high yields of cobalt-complexed cyclopentadienones.[31,32] Direct reaction of $CpCo(CO)_2$ with alkynes is similarly useful. The cycloaddition of di(*t*-butoxy)acetylene upon photolysis with $CpCo(CO)_2$ is an example (Scheme 5). In all these systems the final complexes lack coordinated CO, and therefore amine oxides are not suitable reagents for liberating the stable cyclopentadienones. Tetra(*t*-butoxy)cyclopentadienone is accessible on a preparative scale *via* controlled electrochemical oxidation.[33] Other oxidants such as $Cr^{VI}$ have been used as well in other systems.

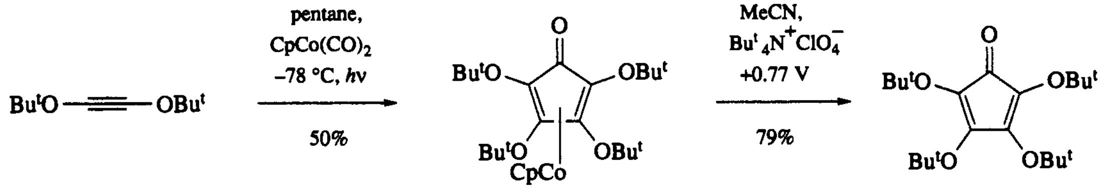

Scheme 5

Unsymmetrically substituted alkynes display a significant degree of regioselectivity in these reactions, usually in favor of products with the larger substituents in positions 2 and 5, with lesser amounts of 2,4-disubstituted products.[34] Isolated examples are known where the latter, unsymmetrical products predominate, usually as a result of extreme steric interactions that would be generated around the metal upon coupling the less-hindered ends of the two alkynes (equation 8).[35,36]

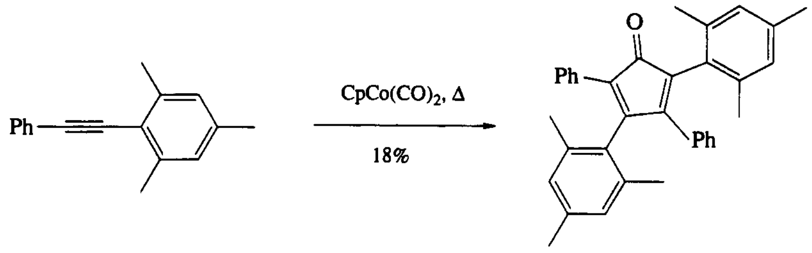

(8)

A number of examples exist involving reactions of $CpCo(CO)_2$ and silylated alkynes. Cycloaddition of $Me_3SiC{\equiv}CH$ gives a 3:1 mixture of 2,5- and 2,4-bis(trimethylsilyl)cyclopentadienone complexes. The use instead of $[C_5Me_5]Co(CO)_2$ reverses the regioselectivity to 1:3.7, presumably due to the increased steric crowding about cobalt (equation 9).[37] This effect has yet to be exploited in synthesis.

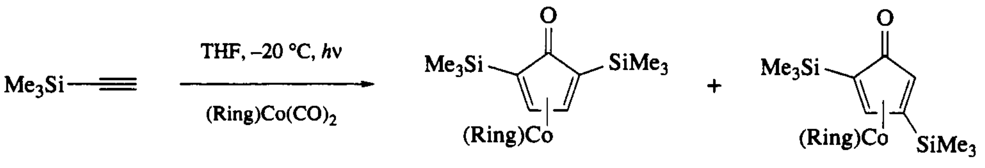

(9)

| *Ring* | | |
|---|---|---|
| Cp | 75% | 25% |
| $C_5Me_5$ | 21% | 79% |

In this general area quite efficient intramolecular examples have been described as well (Scheme 6). A thorough examination of the intermediates and likely mechanisms associated with this system has been published.[38] In particular, it has been found that the type of metallacycle formed depends on the length of the chain separating the two alkyne units in the diyne. Efficient intramolecular cycloaddition to a bicyclic metallacycle occurs only from 1,6- and 1,7-diynes. The poor results on attempted cyclization of 1,5-diynes to give highly strained bicyclo[3.2.0]hepta-1,4-dien-3-ones result from resistance towards closure of the strained four-membered ring upon metallacycle formation.[39]

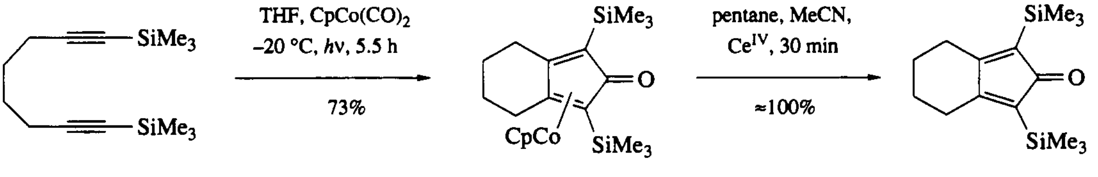

**Scheme 6**

The use of complexes in which unsymmetrical disubstitution is present on the Cp ring leads to diastereoselection in the cycloaddition process, leading to chiral cyclopentadienone complexes.[40] In the course of subsequent transformations stereochemical information has been shown to be transferable to the complexed cyclopentadienone ring (Scheme 7).[41]

Although catalytic preparations of cyclopentadienones with other metal systems are known, chemoselectivity is often a problem. For example, the reactions of 2-butyne, 3-hexyne and diphenylacetylene with $[(CO)_2RhCl]_2$ at 80 °C give mixtures of hexasubstituted benzenes, metal-complexed, tetrasubstituted cyclopentadienones and quinones.[42] An exception is the preparation of the stable tetrakis(trifluoromethyl)cyclopentadienone from the alkyne;[43] the unusual electronic properties of the product make this result lack generality.

Also lacking generality due to chemoselectivity problems are attempts at achieving intramolecular cycloadditions from α,ω-diynes in the presence of iron carbonyls.[44,45] An efficient two-stage intramolecu-

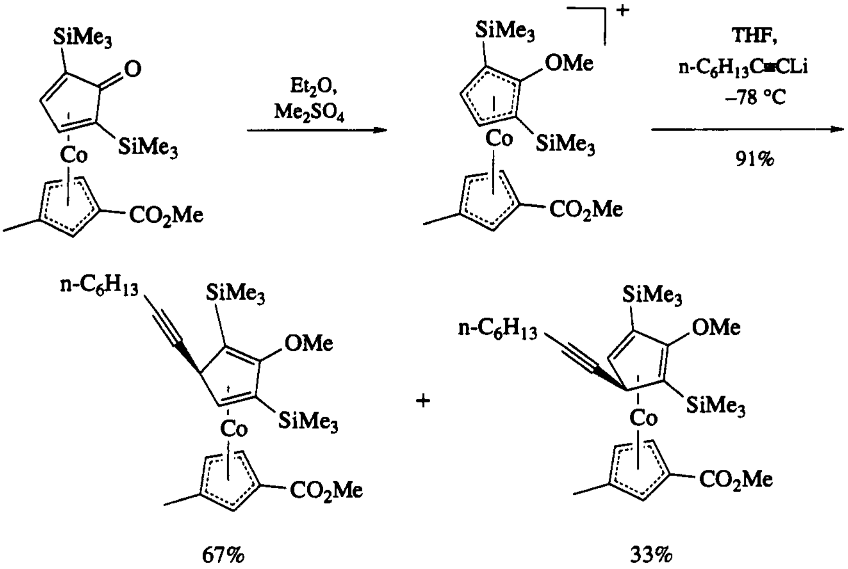
SiMe3
O
Co
SiMe3
CO2Me
Et2O, Me2SO4
SiMe3
OMe
Co
SiMe3
CO2Me
+
THF, n-C6H13C≡CLi
-78 °C
91%
n-C6H13
SiMe3
OMe
Co
SiMe3
CO2Me
+
n-C6H13
SiMe3
OMe
Co
SiMe3
CO2Me
67%
33%

**Scheme 7**

lar process starting with a variety of α,ω-diphenyldiynes and a rhodium-based reagent is known, however. Reaction with tris(triphenylphosphine)rhodium(I) chloride gives excellent yields of the corresponding rhodacyclopentadienes, which give the dienones upon carbonylation (Scheme 8). In addition, the corresponding imines are formed upon reaction with isonitriles.[46]

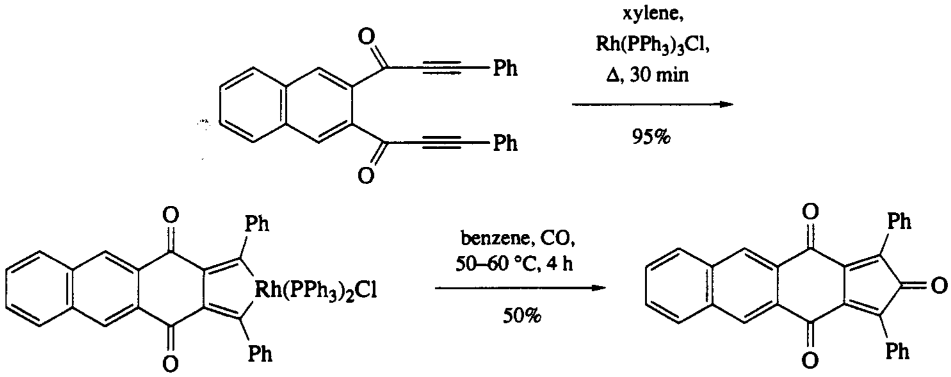
O
Ph
Ph
O
xylene, Rh(PPh3)3Cl, Δ, 30 min
95%
O
Ph
Rh(PPh3)2Cl
Ph
O
benzene, CO, 50–60 °C, 4 h
50%
O
Ph
O
Ph
O

**Scheme 8**

A catalytic, completely regioselective conversion of 4,4-dimethyl-2-pentyne (methyl-*t*-butylacetylene) to 2,5-di(*t*-butyl)-3,4-dimethylcyclopentadienone is mediated by $(PhCN)_2PdCl_2$.[47] Other examples exist for early[48] as well as late transition metals, and an isonitrile has been used as a CO equivalent in one $Ni^0$-based system as well.[49] Finally, a heterogeneous catalytic intramolecular cycloaddition of diynes has been developed, leading to cyclopentadienones which either dimerize (Diels–Alder) or in certain cases may be trapped by nucleophiles (equation 10).[50]

Using $Ni(CO)_4$ as both reducing agent and cycloaddition mediator, *o*-diiodobenzene may be induced to serve as a benzyne equivalent in a cycloaddition with alkynes leading to indenones. Yields are consistently good and regioselectivity with terminal alkynes for the 2-substituted product excellent (equation 11).[51,52]

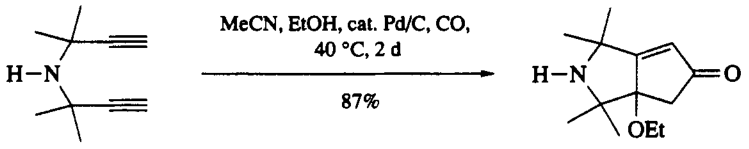
H–N
MeCN, EtOH, cat. Pd/C, CO, 40 °C, 2 d
87%
H–N
O
OEt

(10)

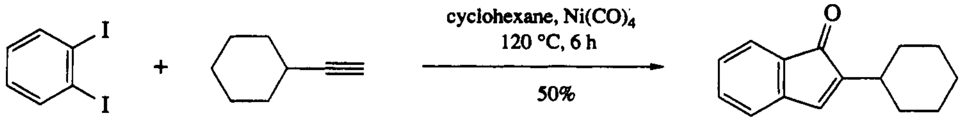

(11)

## 9.4.3 SYNTHESIS OF FIVE-MEMBERED HETEROCYCLIC RINGS

### 9.4.3.1 Furans

Oxidation of rhodacyclopentadienes, prepared from diynes as shown in Scheme 8, with either atmospheric oxygen or with peroxides gives furans in modest yields (Scheme 9).[46]

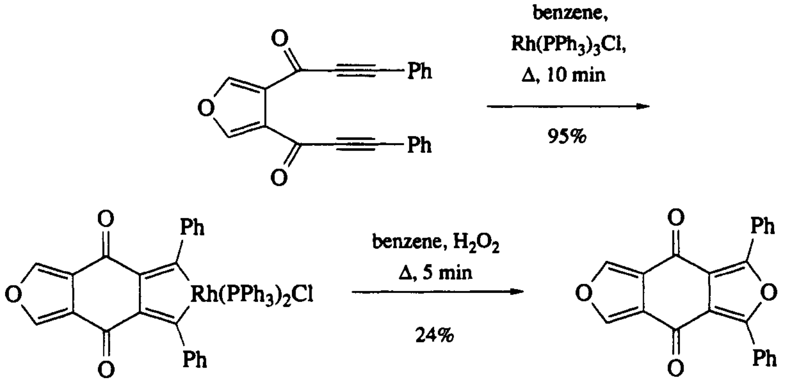

Scheme 9

In an isolated intermolecular example air oxidation of the polymeric metallacycle derived from dimethyl acetylenedicarboxylate and a source of $Pd^0$ gives a 45% yield of the corresponding furan tetraester.[53]

### 9.4.3.2 Furanones: Regioselectivity

The synthesis of furanones (γ-lactones) from alkynes and carbon monoxide consititutes a unique variation of the [2 + 2 + 2] pattern. The ring incorporates both carbons from the C≡C, the carbon from one CO, and both carbon and oxygen from the other CO. The process is therefore a 2 + 2 + 1 cycloaddition of the form $[2\pi_{C\equiv C} + 2\pi_{C=O} + 2n_{CO}]$. The formal result of such a cycloaddition is a carbene at position 4, the carbon atom of the $\pi_{CO}$ participant (equation 12).

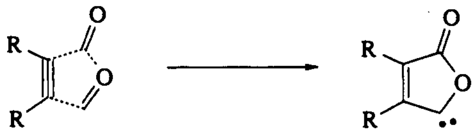

(12)

In one common mechanistic version of the reaction one of the molecules of CO is incorporated as a metal acyl. Insertions of alkyne and CO lead to a 4-keto-2-alkenoyl metal derivative. Cyclization *via* insertion of the 4-keto group into the acyl–metal bond generates a 4-metallalactone complex containing both the metal and the R group originally present in the starting acyl RCOM attached to C-4 of the new ring (the 'carbenoid' carbon mentioned above) (Scheme 10). Regioselectivity with regard to alkyne insertion is normally controlled sterically, with the first new carbon–carbon bond forming between the acyl carbonyl and the less sterically hindered alkyne carbon. This places the larger alkyne substituent closer to the lactone carbonyl group. Model studies have confirmed the feasibility of mechanistic variations such as $\eta^3$ (allyl) complexation to the metal.[54]

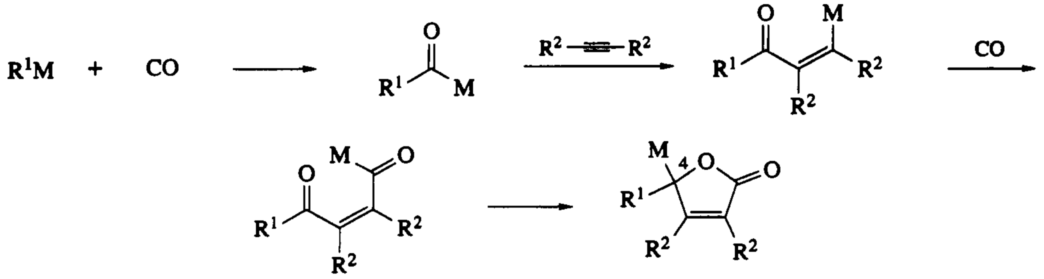

Scheme 10

Unsaturated lactones lacking substitution at C-4 are the simplest ones available *via* this general type of cycloaddition. Several syntheses of these lactones are of practical value, including two Pd-based methods.[55] However, the considerable utility of metal carbonyl anions in lactone synthesis is illustrated by a rhodium carbonyl anion catalyst system which gives very high yields upon reaction with a variety of internal alkynes under weakly basic aqueous conditions, essentially water–gas shift conditions. These conditions were established to maximize chemoselectivity with respect to other possible alkyne carbonylation products. Regioselectivity is modest in this process, but was not examined systematically (equation 13).[56]

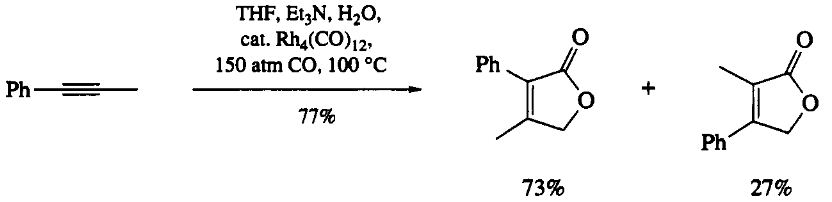

(13)

Addition of an alkene insertion step to the sequence above prior to reductive elimination of the final product gives an alkene-derived R group. Although for reliable results the reaction is restricted to ethylene, giving an ethyl substituent at C-4, yields and alkyne regioselectivity are reasonable (equation 14).[57]

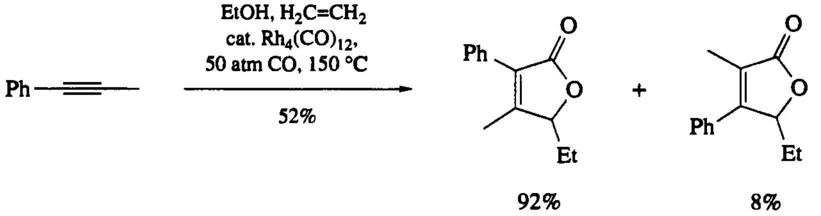

(14)

In still another variation on the above Rh-catalyzed system, lactones with 4-alkoxy substitution are obtained from internal alkynes by omitting the alkene and introducing one of several oxygen bases (equation 15).[58] As before the reaction is characterized by good yields and modest regioselectivity. The mechanism involved here is not well understood.

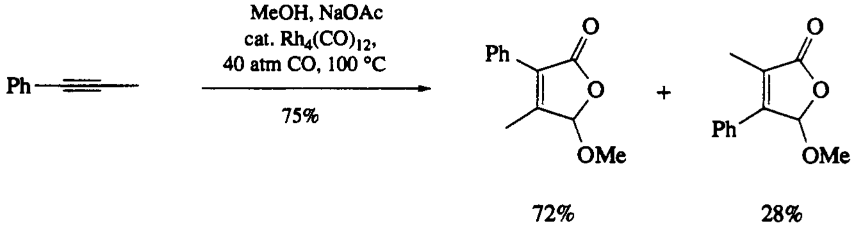

(15)

Several first-row metals display varying utility in stoichiometric lactone syntheses. The general mechanism described above is followed in a reaction sequence that begins with acyl complexes derived from reaction of $^{-}Co(CO)_4$ with MeI and CO. Under phase transfer conditions these react with alkynes to give

4-keto-2-alkenoylcobalt intermediates. These in turn react with hydroxide to give an unsaturated keto acid, which cyclizes spontaneously to a γ-hydroxylactone (equation 16).[59] The reaction is general for terminal alkynes and displays total regioselectivity. Saturated 2,4-disubstituted-γ-butyrolactones are formed in a similar process that uses manganese carbonyl anions instead of cobalt.[60]

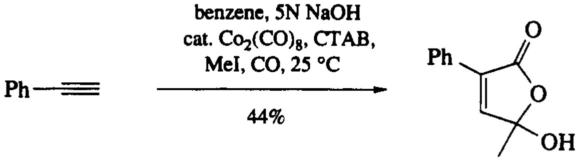

(16)

When the acylcobalt species is derived from a compound containing halogen on an activated carbon (*e.g.* an α-halo ester or nitrile) an elimination may occur to introduce an exocyclic double bond in the final product. This sequence, leading to lactones of pentadienoic acids, is general for both terminal and internal alkynes in the presence of amine bases (equation 17).[61]

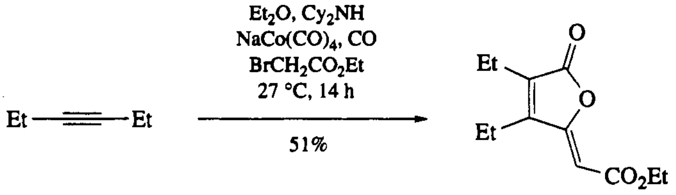

(17)

Acyl halides and alkynes also give lactones upon reaction with $Ni(CO)_4$ in an aqueous acetone medium. The result in this system is typically a β,γ-unsaturated lactone, formed together with some product derived from condensation with molecules of solvent (equation 18).[62] Lactones are also formed in low yield as byproducts from the reactions of acylnickel carbonyl anions (derived from addition of RLi to $Ni(CO)_4$) with terminal alkynes at −30 °C.[63] A single example of γ-aminolactone formation is reported from 2-butyne, CO and diethylamine, catalyzed by $(Et_2NH)_2NiBr_2$.[64]

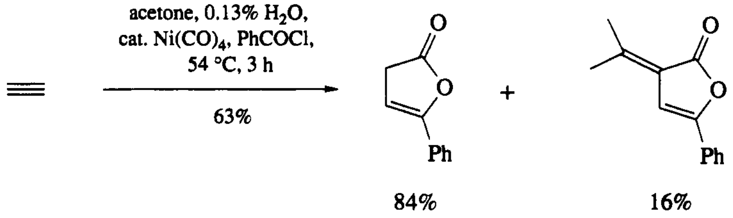

(18)

Of more specialized interest is the reaction of alkynes with $Co_2(CO)_8$ in polar solvents under conditions of elevated temperature and CO pressure. The major products are the (*E*) and (*Z*) isomers of so-called bifurandiones, the products of formal (but not actual) carbene dimerization.[65] An intermediate, a complex of this lactone-derived carbene bridging a $Co_2(CO)_7$ moiety, may be isolated from reactions of alkyl-, aryl- or dialkyl-acetylenes with $Co_2(CO)_8$. Its formation is completely regioselective even for ethyl *vs.* methyl, placing the larger group α to the lactone carbonyl.[66,67] In the subsequent formation of the bifurandione itself regioselectivity in alkyne incorporation into the second ring is incomplete and in the *opposite direction*, an observation which remains unexplained (Scheme 11).[68–70]

### 9.4.3.3 Furandiones

Formal $[2\pi_{C=C} + 2\pi_{CO_2} + 2n_{CO}]$ and $[2\pi_{C\equiv C} + 2\pi_{CO_2} + 2n_{CO}]$ cycloadditions give rise to 2,5-furandiones (succinic and maleic anhydrides). Thus the complex $(CDT)Ni^0$ (CDT = 1,5,9-cyclododecatriene) reacts with either alkenes or alkynes and $CO_2$ in the presence of diamines or diphosphines to give 5-nickelafuranones. Upon exposure to CO these give the corresponding anhydrides (Scheme 12).[71] Ethylene, acetylene and 2-butyne have been carried through this sequence.

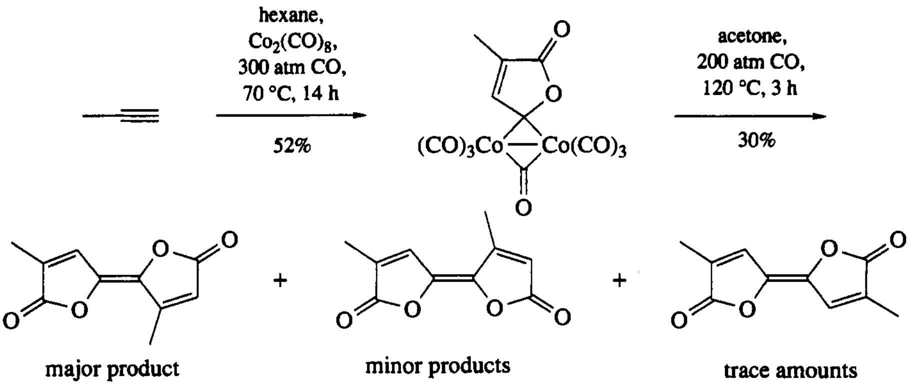
hexane,
Co2(CO)8,
300 atm CO,
70 °C, 14 h
52%
(CO)3Co
Co(CO)3
acetone,
200 atm CO,
120 °C, 3 h
30%
major product
minor products
trace amounts

Scheme 11

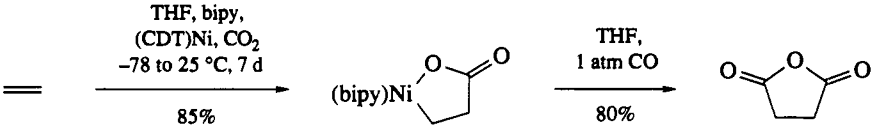
THF, bipy,
(CDT)Ni, CO2
-78 to 25 °C, 7 d
85%
(bipy)Ni
THF,
1 atm CO
80%

Scheme 12

### 9.4.3.4 Thiophenes, Selenophenes and Similar Heterocycles: Regioselectivity

In contrast to the limited number of approaches to furans, several metallacyclopentadienes derived from reactions of alkynes with appropriate metal complexes may be used as precursors to other five-membered ring heteroaromatics. As was the case with furans, rhodacyclopentadienes are usable for conversion to thiophenes and selenophenes, although yields are typically low.[46,72] Iron-containing metallacycles may also be employed as precursors to thiophenes, however, and some of the yields obtained in reactions with $S_8$ are quite good (Scheme 13).[73] Greater flexibility is obtained using a cobalt-based process which allows the sequential incorporation of two different alkynes, followed by a heteroatom, into a heterocyclic product.[74] Typically reaction of $CpCo(PPh_3)_2$ at room temperature with first one and then a second alkyne proceeds in good yield to the cobaltacycle with good to excellent regioselectivity in most cases, forming the new carbon–carbon bond between the least sterically hindered alkyne carbons. Reaction with elemental sulfur or selenium gives rise to the final heterocycle (Scheme 14).

In one case, formation of the thiophene from sulfur and dimethyl acetylenedicarboxylate, a viable catalytic procedure was optimized (75% yield) by using CpCo(COD) and elemental selenium, which promotes thiophene formation in refluxing toluene. The role of the Se is not known, and the implications of these results have not been explored.[75]

A wide variety of main group heteroatom-containing ring systems are formed by the reaction of appropriate reagents with metallacycles derived from cycloaddition of '$Cp_2Zr^{II}$' with alkynes, diynes, dienes, enynes or alkynenitriles. This is an exceptionally general process of considerable potential, especially for the synthesis of less-common types of heterocycles (Schemes 15 and 16).[76]

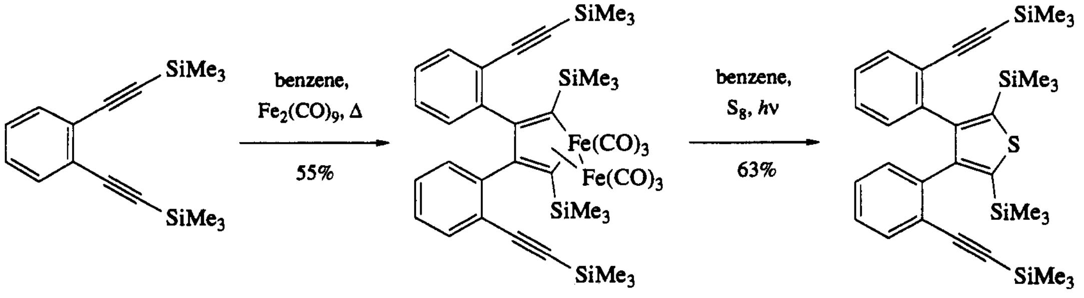
SiMe3
SiMe3
benzene,
Fe2(CO)9, Δ
55%
SiMe3
SiMe3
Fe(CO)3
Fe(CO)3
SiMe3
SiMe3
benzene,
S8, hν
63%
SiMe3
SiMe3
S
SiMe3
SiMe3

Scheme 13

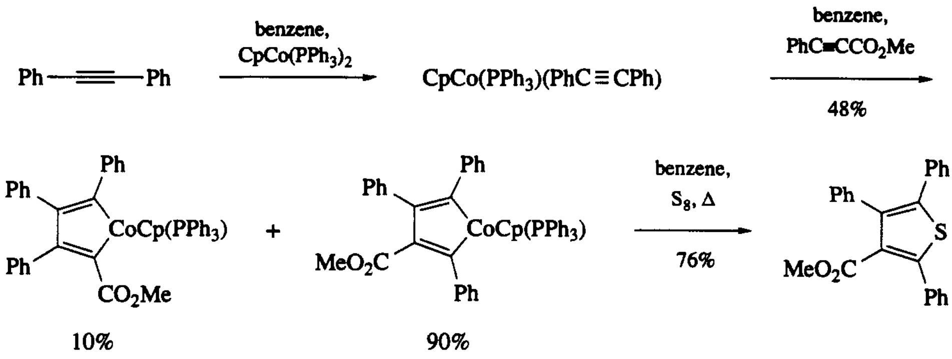
Ph
Ph
benzene,
CpCo(PPh3)2
CpCo(PPh3)(PhC≡CPh)
benzene,
PhC≡CCO2Me
48%
Ph
Ph
CoCp(PPh3)
Ph
CO2Me
10%
+
Ph
Ph
CoCp(PPh3)
MeO2C
Ph
90%
benzene,
S8, Δ
76%
Ph
Ph
S
MeO2C
Ph

**Scheme 14**

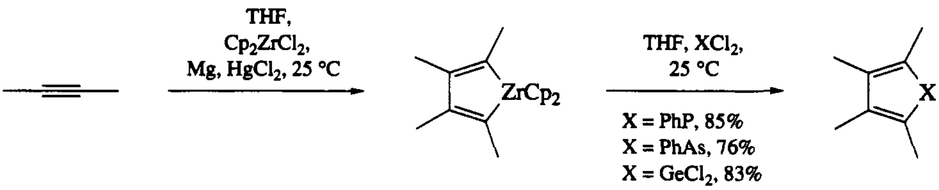
THF,
Cp2ZrCl2,
Mg, HgCl2, 25 °C
ZrCp2
THF, XCl2,
25 °C
X = PhP, 85%
X = PhAs, 76%
X = GeCl2, 83%
X

**Scheme 15**

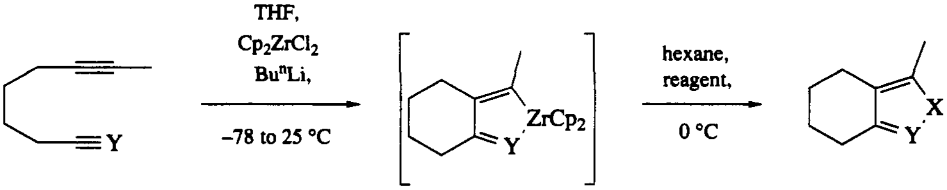
Y
THF,
Cp2ZrCl2
BunLi,
–78 to 25 °C
ZrCp2
Y
hexane,
reagent,
0 °C
X
Y

| *Y* | *Reagent* | *Yield (%)* | *X* |
|---|---|---|---|
| CH | $S_2Cl_2$ | 55 | S |
| CH | $Se_2Cl_2$ | 53 | Se |
| CH | $Me_2SnBr_2$ | 82 | $SnMe_2$ |
| N | $S_2Cl_2$ | 65 | S |

**Scheme 16**

### 9.4.3.5 Pyrroles and Related Compounds

Both the rhodium- and cobalt-containing metallacycles described in the previous section react with nitrosobenzene to give low yields of *N*-phenylpyrroles (Scheme 17).[46,72,74]

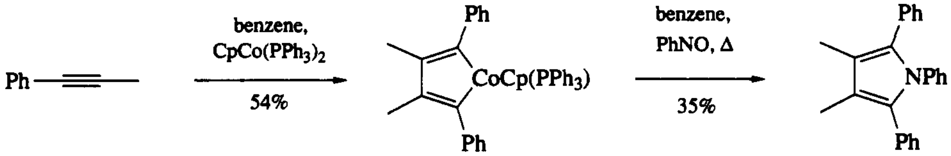
Ph
benzene,
CpCo(PPh3)2
54%
Ph
CoCp(PPh3)
Ph
benzene,
PhNO, Δ
35%
Ph
NPh
Ph

**Scheme 17**

Succinimides and maleimides are accessible *via* processes analogous to those described for the corresponding anhydrides (see Section 9.4.3.3). Reactions of $(COD)_2Ni^0$ with either alkenes or alkynes and isocyanates (*i.e.* heterocumulene analogs of $CO_2$) give azametallacycles that upon carbonylation yield cyclic imides. With alkenes high yields of metallacycles are formed from both simple isocyanates as well as α,ω-diisocyanates. Carbonylation yields are variable, however (Scheme 18). Alkynes give lower metallacycle yields but high yields of the final imide (Scheme 19).[77]

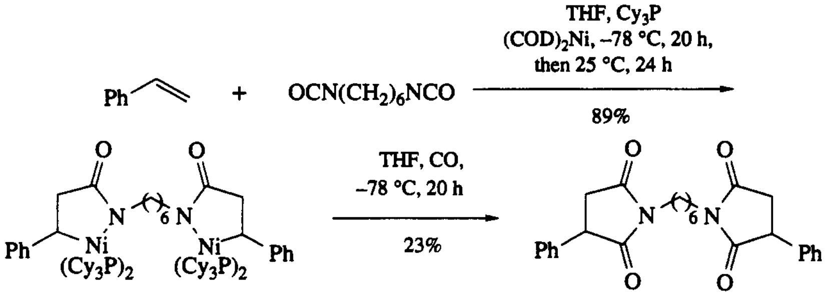
THF, Cy3P
(COD)2Ni, –78 °C, 20 h,
then 25 °C, 24 h
89%
OCN(CH2)6NCO
THF, CO,
–78 °C, 20 h
23%
Ph
Ni
(Cy3P)2
6
O
N

**Scheme 18**

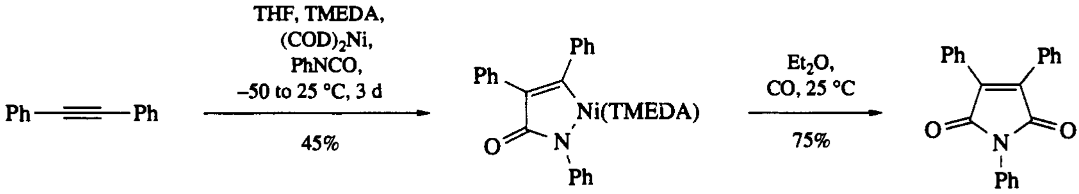
THF, TMEDA,
(COD)2Ni,
PhNCO,
–50 to 25 °C, 3 d
45%
Ph
Ni(TMEDA)
Et2O,
CO, 25 °C
75%
O
N

**Scheme 19**

Allenes may take the place of alkenes in this process, leading to *exo*-methylenesuccinimides as products. With unsymmetrically substituted allenes, the less-substituted double bond is chemoselectively incorporated into the heterocyclic ring.[78] The alkene may also be replaced by an aldehyde in this cycloaddition, leading to 1,3-oxazole-2,4-diones (Scheme 20).[79]

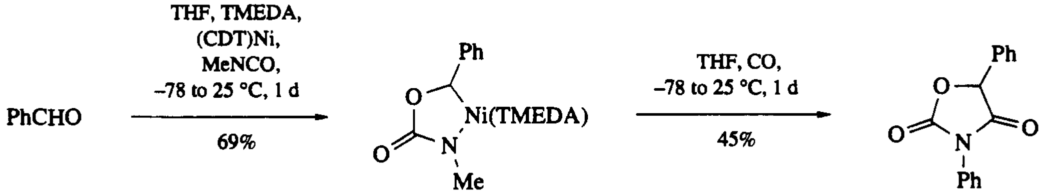
THF, TMEDA,
(CDT)Ni,
MeNCO,
–78 to 25 °C, 1 d
69%
PhCHO
Ph
O
Ni(TMEDA)
N
Me
THF, CO,
–78 to 25 °C, 1 d
45%
Ph

**Scheme 20**

## 9.4.4 SYNTHESIS OF SIX-MEMBERED CARBOCYCLIC RINGS

### 9.4.4.1 Cyclohexanes and Cyclohexenes: Regioselectivity

There are few cycloadditions involving either three alkenes, to produce cyclohexanes, or two alkenes and an alkyne, to produce cyclohexenes.[80] The appropriate metallacyclic precursors containing the CpCo fragment have in fact been prepared and examined for reactivity. Both cobaltacycloheptanes and cobaltacycloheptenes undergo β-hydride elimination, producing 1-heptenes and 1,6-heptadienes respectively, in preference to reductive elimination of the metal and coupling to produce cyclic products.[81]

Nonetheless, there are a small number of systems that do mediate such [2 + 2 + 2] cycloadditions. With allenes as the 'alkene', cycloaddition with both acetylene and terminal alkynes proceeds regioselectively to give 3,5-dimethylenecyclohexenes using $\mathrm{Ni^{II}}$ catalysts, and mostly 3,6-dimethylenecyclohexenes using $\mathrm{Ni^{0}}$ catalyst precursors (equation 19).[82] Norbornadiene undergoes so-called 'homo-Diels–Alder' cycloaddition with both alkenes and alkynes in the presence of nickel catalysts.[83] Further elaboration of this chemistry with alkynes but not alkenes has been described using a Co/Al catalyst system (equation 20).[84] Attempts to produce cyclohexenes *via* all-intramolecular [2 + 2 + 2] cycloaddition of 1,13-dien-7-ynes or 1,11-dien-6-ynes have been unsuccessful.[85]

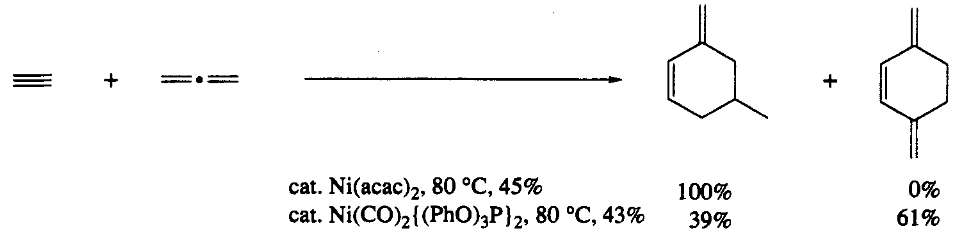
cat. Ni(acac)$_2$, 80 °C, 45%
cat. Ni(CO)$_2${(PhO)$_3$P}$_2$, 80 °C, 43%
100%
39%
0%
61%

(19)

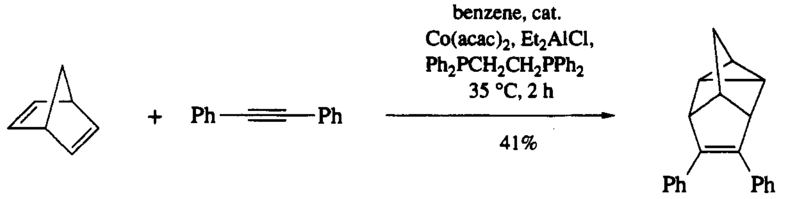

(20)

### 9.4.4.2 Cyclohexadienes: Regio- and Diastereo-selectivity

The synthesis of the 1,3-cyclohexadiene system using transition metals has generally involved reaction of the intermediate metallacyclopentadiene derived from two alkynes and a metal fragment with an alkene. Many systems have been developed for this process, although sensitivity of the product diene towards aromatization or other subsequent reactions is an occasional problem.[86] The alternative insertion sequence, involving a metallacyclopentene derived from one alkyne and one alkene, is generally unsuitable as reactions of such species with alkynes usually give linear products. Thus the cobaltacyclopentadiene derived from diphenylacetylene reacts *stoichiometrically* with methacrylonitrile to give both cyclohexadiene and pyridine products (equation 21) (see Section 9.4.5.1). However, reaction of diphenylacetylene with methacrylonitrile in the presence of catalytic amounts of the monoalkyne complex CpCo(PPh$_3$)(PhC≡CPh) leads only to acyclic products. Thus the alkene and not the alkyne preferentially complexes to the metal, and the cobaltacyclopentene, once formed, reacts with additional alkene to form linear products instead of undergoing cycloaddition with the alkyne.[87] Only occasionally does the alkyne compete sufficiently well for complexation to the metal to prevent metallacyclopentene formation, in which case catalytic cycloaddition is possible.[74] Thus under most circumstances cyclohexadiene formation requires that the metallacyclopentadiene be preformed, and then reacted stoichiometrically with alkene. Incorporation of the alkene is highly diastereoselective with retention of stereochemistry. Typically the product is isolated as a diene–metal complex from which the metal is removed by oxidation (Scheme 21).[88]

Although cobaltacyclopentene complexes react preferentially with alkenes, they can be preformed and reacted with alkynes, providing an alternative stoichiometric permutation for 1,3-cyclohexadiene synthesis (Scheme 22).[89]

Regioselectivity in metallacyclopentadiene formation has been considered in earlier sections (Sections 9.4.2.4 and 9.4.3). As the examples show, mixtures are typically formed containing isomers in which the larger alkyne substituents are either in positions 2 and 4 or positions 2 and 5, resulting in cyclohexadienes with the large groups in either a 1,3- or a 1,4-disposition. Total regioselectivity (larger group at C-2 or C-5 in the metallacycle) may be achieved with alkynes containing attached groups sufficiently different in size, *e.g.* Ph or CO$_2$Me *vs.* Me, or anything *vs.* H. Systematic examination of alkene regioselectivity has not been done. Exceptional 1,3-selectivity is found in the Ni$^0$-catalyzed cocycloaddition of phenylacetylene with *N*-methylmaleimide (equation 22).[90]

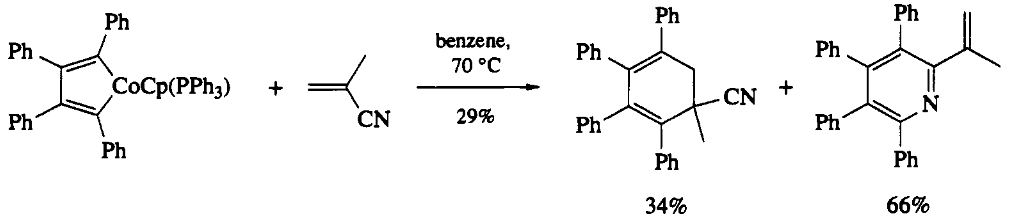

(21)

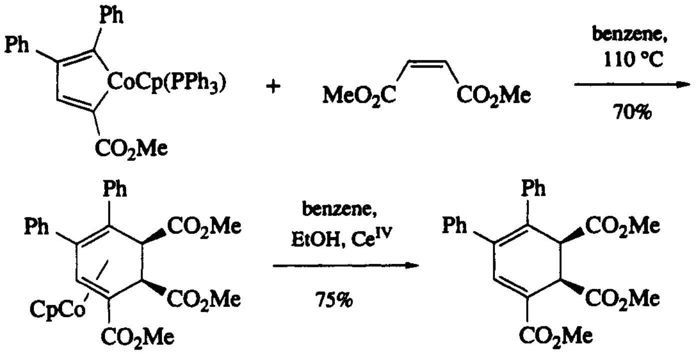
benzene,
110 °C
70%
benzene,
EtOH, Ce^IV
75%
CoCp(PPh3)
CpCo
Ph
CO2Me
MeO2C

**Scheme 21**

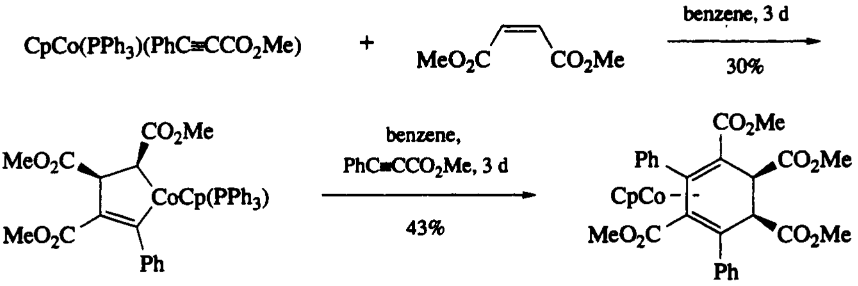
CpCo(PPh3)(PhC≡CCO2Me)
benzene, 3 d
30%
benzene,
PhC≡CCO2Me, 3 d
43%
CoCp(PPh3)
CpCo
Ph
CO2Me
MeO2C

**Scheme 22**

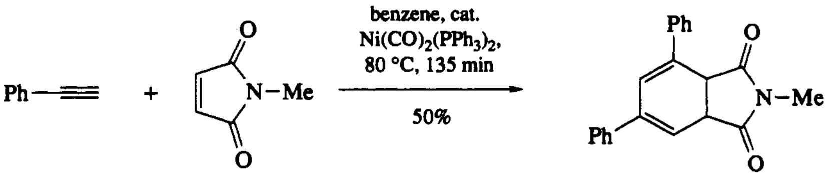
benzene, cat.
Ni(CO)2(PPh3)2,
80 °C, 135 min
50%
N–Me
Ph
O

(22)

Partially intramolecular versions of this process, *e.g.* cycloadditions of α,ω-enynes with alkynes, give only low yields of ring-fused 1,3-cyclohexadienes, even when hindered alkynes incapable of cyclotrimerization side reactions (*e.g.* $Me_3SiC{\equiv}CSiMe_3$) are used (see Section 9.4.4.3).[91] However, when the alkene portion of the enyne is part of a heteroaromatic ring such as a pyrrole, an indole or an imidazole, cycloaddition has been found to proceed smoothly, allowing access to remarkably complex heteropolycyclic products.[92–94] Regioselectivity with regard to incorporation of the alkyne is variable, but tends to favor large alkyne substituents at C-1 of the cyclohexadiene ring (equation 23). Although either $CpCo(CO)_2$ or $CpCo(CH_2{=}CH_2)_2$ may be used as the CpCo source in these reactions, the latter gives rise to higher regioselectivities with unsymmetrical alkynes.

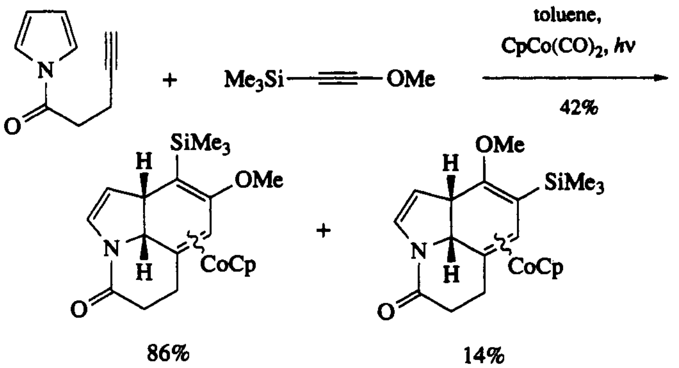
Me3Si———OMe
toluene,
CpCo(CO)2, hν
42%
SiMe3
OMe
H
N
O
CoCp
86%
14%

(23)

Upon extended heating with stoichiometric $CpCo(CO)_2$ all-intramolecular cycloadditions of 1-ene-6,12-diynes to form cobalt-complexed cyclohexadienes take place in good yields (Scheme 23).[95,96] High diastereoselectivity in the formation of the complex is sometimes observed in these processes, as is considerable tolerance for steric hindrance.[97,98]

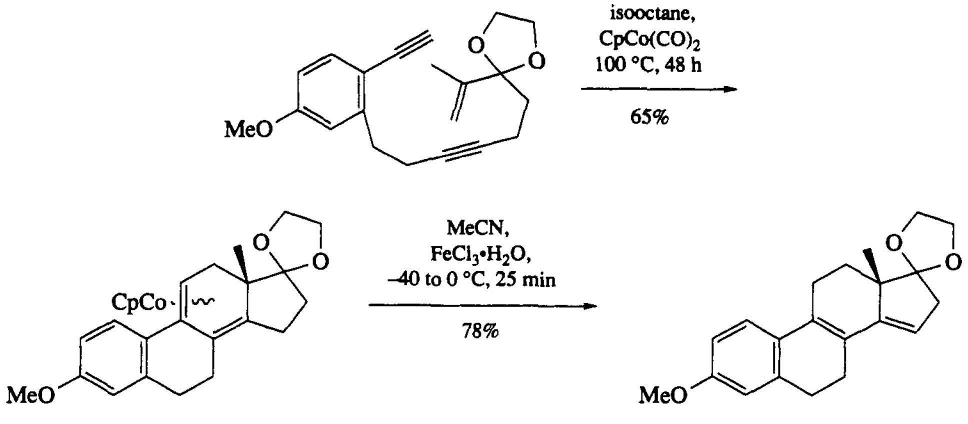

Scheme 23

Complementary cycloadditions of 7-ene-1,13-diynes proceed with similar success, and are noteworthy in their ability to incorporate tetrasubstituted alkenes with total diastereoselectivity (equation 24).[99,100] Incorporation of the alkene into a heteroaromatic ring is compatible with all-intramolecular cycloadditions of this type as well (equation 25).[93]

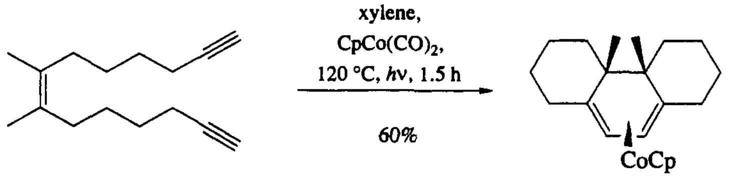

(24)

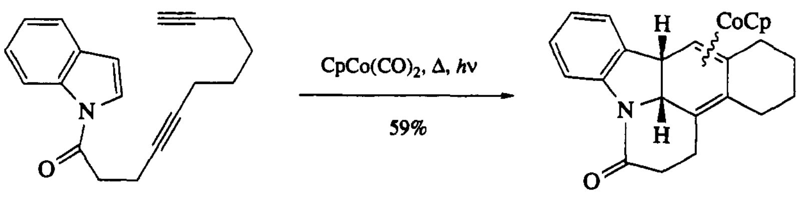

(25)

### 9.4.4.3 Benzenes: Chemo- and Regio-selectivity

The cyclotrimerization of alkynes to give benzene derivatives is perhaps the most general reaction of these compounds in the presence of transition metal complexes. Practically any mono- or di-substituted alkyne, in addition to acetylene itself, may be cyclotrimerized. In addition, cocycloadditions involving more than one different alkyne are possible with some degree of selectivity, and intramolecular versions of the reaction have seen sophisticated development.

A wide variety of homogeneous and heterogeneous catalysts are available for alkyne cyclotrimerization. As a result, numerous mechanistic pathways have been established for the different versions of this process, each characteristic of the metals involved in the system.[101] The most common involves the intermediacy of metallacyclopentadienes, derived as already shown from any number of metal fragments and two alkynes. Upon opening a vacant coordination site, these systems may readily complex a third alkyne, which may insert to give a transient metallacycloheptatriene from which the benzene product is ultimately released *via* reductive elimination of the metal (Scheme 24).[102]

The major regiochemical consequence of this mechanism is that trimerization of unsymmetrically substituted alkynes gives rise mostly to benzenes in which the most sterically demanding substituents occupy positions 1, 2 and 4 around the ring. To a lesser extent products with the 1,3,5-substitution pattern

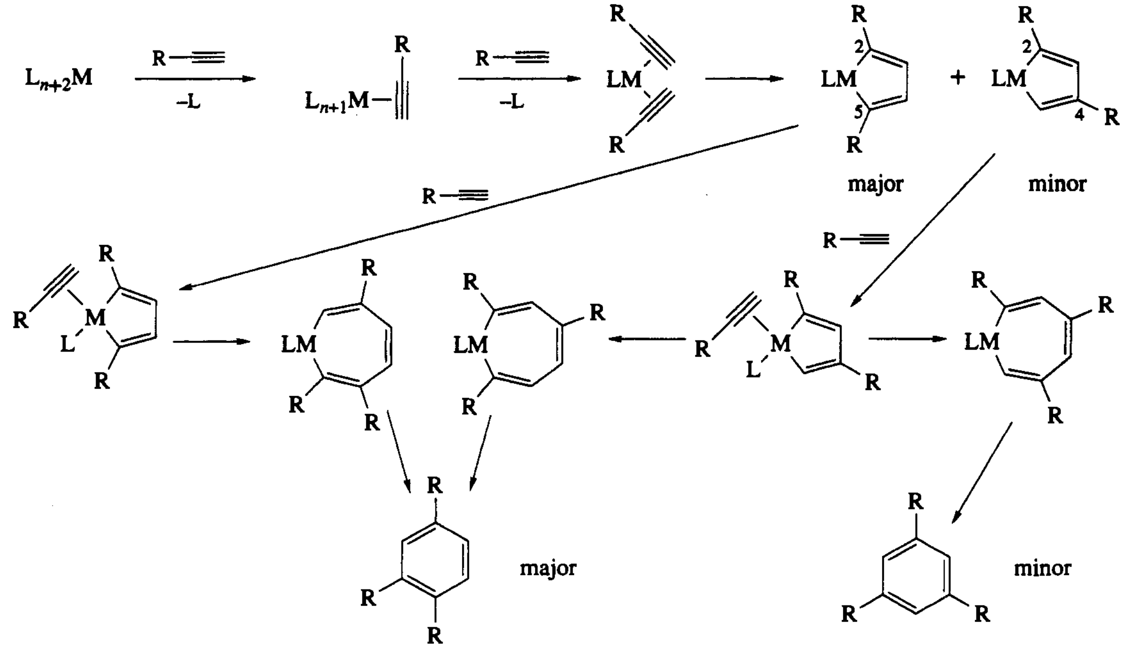

Scheme 24

are also obtained. In the sequence regioselection can be seen to occur at two stages: in the formation of the metallacyclopentadiene, and in the subsequent insertion of the third alkyne. The preference for formation of the metallacyclopentadiene with the larger substituents at positions 2 and 5 has been noted, and must lead exclusively to the 1,2,4-substitution pattern, irrespective of the sense of the final insertion.[103] The formation of products with a 1,3,5-pattern requires the intermediacy of a metallacycle with a 2,4-disubstitution pattern. Even so, the latter can still give rise to 1,2,4-products as well (illustrated for terminal alkynes in Scheme 24). Although examples of reactions showing quite high levels of regioselectivity towards either 1,2,4- or 1,3,5-trisubstituted benzenes are well-known, few of these systems have been studied to the extent that rational control of regioselectivity is possible.

Supporting evidence for the above mechanistic patterns in the majority of metal systems was first established in elegant isotopic labeling studies, which showed clearly that no intermediate with the symmetry of a cyclobutadiene was involved.[104] In one system, the reaction of a cobaltacyclopentadiene with $MeO_2CC{\equiv}CCO_2Me$, benzene formation does not involve direct complexation of the third alkyne to the metal. It has therefore been suggested that the conventional insertion process has been here replaced by a direct Diels–Alder reaction with the metallacycle, perhaps as a result of electronic factors (Scheme 25).[105]

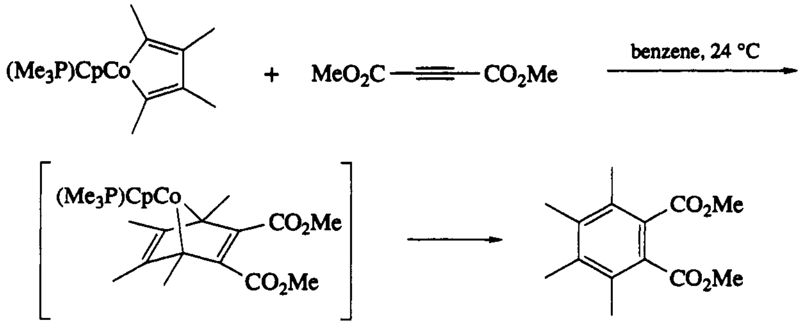

Scheme 25

The general mechanistic picture presented above applies to a number of synthetically useful systems including the first to be discovered, in which trimerization of acetylene to benzene, and propargyl alcohol to a 1:1 mixture of 1,2,4- and 1,3,5-trisubstituted benzene derivatives was catalyzed by $(Ph_3P)_2Ni(CO)_2$.[80] Phosphine nickel carbonyls are usually much more highly regioselective for 1,2,4-

products, although their reactivity in simple trimerizations is mostly limited to terminal alkynes, preferably with carbonyl substitutents (equation 26).[106]

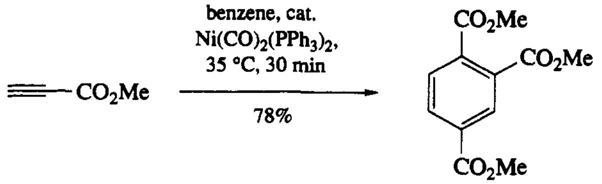

(26)

Another system that appears to follow the same pattern utilizes $(\eta^5\text{-indenyl})\mathrm{Rh(C_2H_4)_2}$, which is remarkably effective for the regioselective trimerization of 3,3-dimethyl-1-butyne (*t*-butylacetylene), giving rise to 1,2,4-tri(*t*-butyl)benzene in 76% yield, and only 8% of the 1,3,5-isomer.[107] On the other hand, unusually high 1,3,5-regioselectivity has been observed from certain $\mathrm{Ni^{II}}$-based catalysts: $\mathrm{(Bu_3P)NiBr_2}$, which converts (*S*)-3-methyl-1-butyn-3-ol exclusively into the corresponding 1,3,5-trisubstituted benzene derivative in moderate yield,[108] and $[(\eta^3\text{-allyl})\mathrm{NiCl}]_2$, which gives 1,3,5-trisubstituted benzenes from terminal alkynes in excellent yields with very good selectivity (equation 27).[109]

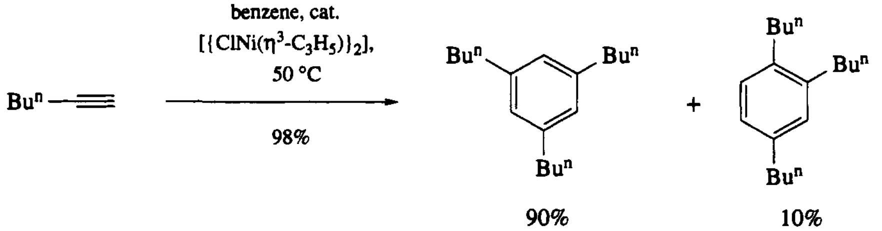

(27)

Chemoselective cocycloaddition of two molecules of a terminal alkyne together with one molecule of an internal alkyne into a benzene product is possible due to the relative unreactivity of phosphine nickel carbonyls towards simple trimerization of the internal alkyne itself (equation 28).[106,110] Careful control of reaction conditions has also permitted selective intermolecular cocycloaddition in the presence of cobalt catalysts as well; for example, diphenylacetylene and 3-hexyne give rise to a 57% yield of 1,2,3,4-tetraphenyl-5,6-diethylbenzene.[111]

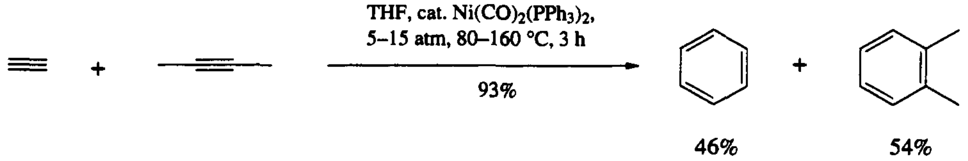

(28)

The feasibility of carrying out chemoselective cocycloadditions by reacting a preformed metallacyclopentadiene and an alkyne has been explored. Despite some success in the area (*e.g.* equation 29),[53,74] chemoselectivity is generally compromized by the fact that the metal fragments liberated after one cocycloaddition cycle are catalytically active in promoting simple cyclotrimerization of the added alkyne.[102]

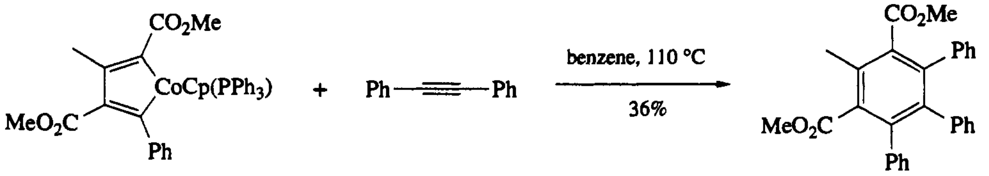

(29)

A number of other mechanistic sequences are thought to occur in alkyne trimerizations mediated by other metal systems. Catalysts derived from $\mathrm{Co_2(CO)_8}$ follow a characteristic sequence of steps that involves exclusively dinuclear complexes (Scheme 26). The nature of the final '$\mathrm{(alkyne)_3Co_2(CO)_4}$' intermediate, a so-called 'flyover' complex, is supported by both X-ray crystal structure data as well as its involvement in forming other products besides benzenes.[26,32] These dinuclear cobalt systems are noteworthy due to their wide scope of reactivity as well as their ability to trimerize alkynes in high yield with high 1,2,4-selectivity (equation 30).[111]

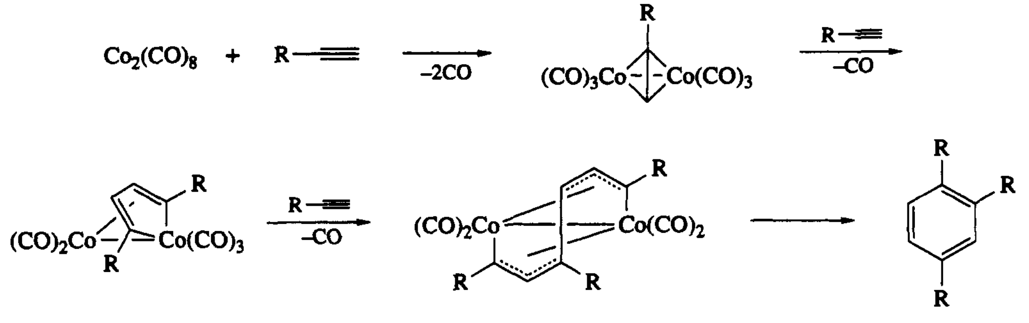
Co2(CO)8
+
R
-2CO
(CO)3Co
Co(CO)3
R
-CO
(CO)2Co
Co(CO)3
R
-CO
(CO)2Co
Co(CO)2
R

**Scheme 26**

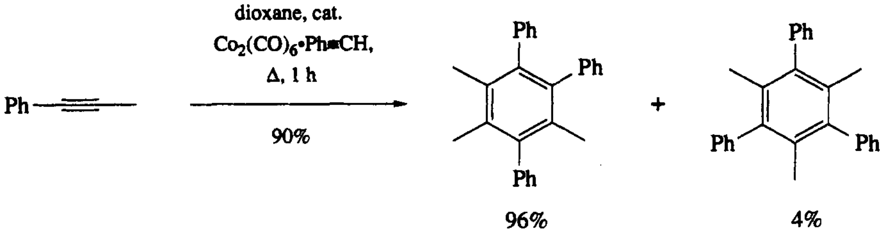
Ph
dioxane, cat.
Co2(CO)6•Ph≡CH,
Δ, 1 h
90%
Ph
+
96%
4%

(30)

A characteristically different mechanism appears to operate in alkyne trimerization systems based on $PdCl_2$.[112] Cationic metal complexes are involved in which initial halide transfer to an alkyne carbon is followed by sequential linear insertion of two more alkyne moieties. Metallacyclopentadiene intermediates are not involved in this sequence. Unique to this mechanism is the subsequent ring-closure to a *cyclopentadienylmethyl* metal derivative, which, *via* halide transfer back to the metal, eventually leads to benzene *via* a bicyclo[3.1.0] system (Scheme 27). Support for this mechanism comes in part from the isolation of methylcyclopentadienyl-derived structures in several cases, including pentalene derivatives from further alkyne insertion followed by a second ring-closure.[113]

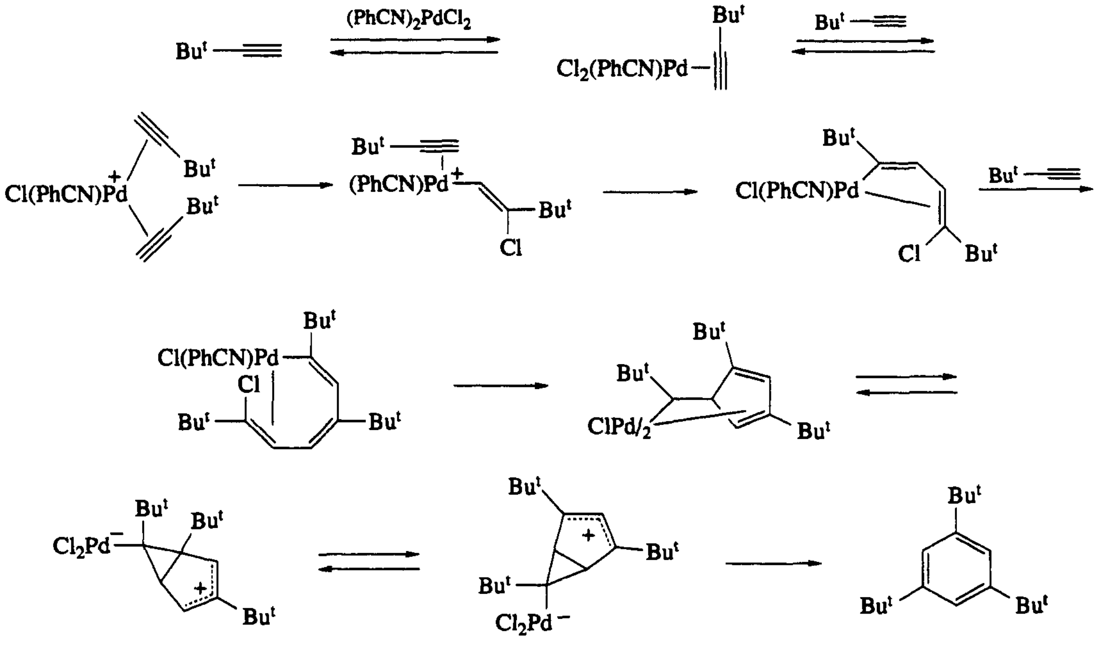
Bu^t
(PhCN)2PdCl2
Cl2(PhCN)Pd
Cl(PhCN)Pd
(PhCN)Pd
Cl
ClPd/2
Cl2Pd

**Scheme 27**

Regiocontrol in the insertion sequence appears to be steric in origin, with large groups directed away from the bulky metal. A tail-to-tail linkage sequence followed by rearrangement leads to 1,3,5-tris(*t*-butyl)benzene as the sole benzenoid product from trimerization of *t*-butylacetylene in the presence of $PdCl_2$.

The dual characteristics of sequential insertion and lack of metallacyclopentadiene formation appear to apply to other high-valent metal halide catalysts as well, *e.g.* $NbCl_5$. Regioselectivity varies from one system to the next, however. The related Ziegler-type catalysts typically give 1,3,5-systems in comparable or greater amounts relative to their 1,2,4-isomers.[114] For example, $TiCl_4/AlEt_2Cl$ converts phenylacetylene in high yield into a mixture of 1,3,5- and 1,2,4-triphenylbenzenes, with 80:20 regioselectivity.[115] These systems display extraordinary reactivity; for example, the trimerization of ω-chloro-1-alkynes is complete in 5 min at 0 °C in the presence of $TiCl_4/AlBu^i_3$.[116] A mechanistic study dealing with Ziegler-type catalysts confirmed the lack of involvement of metallacyclopentadienes and concluded that benzene formation involved a template-type concerted cycloaddition, although the sequential insertion mechanism outlined above appears equally consistent with the results.[117] Catalysis of alkyne trimerization by $AlCl_3$ is a mechanistically distinct process which does involve a complexed cyclobutadiene.

High yields of benzenes are formed from internal alkynes (and a few select terminal alkynes) upon heating in the presence of a soluble catalyst generated by combining $Me_3SiCl$ and Pd/C. Although neither the mechanism nor the structure of any active intermediate is known, the procedure is so simple operationally as to be the method of choice for symmetrical systems (equation 31).[118] Regioselectivity is mixed in the few instances reported; it is impossible at this time to draw conclusions as to possible similarities with $PdCl_2$ systems.

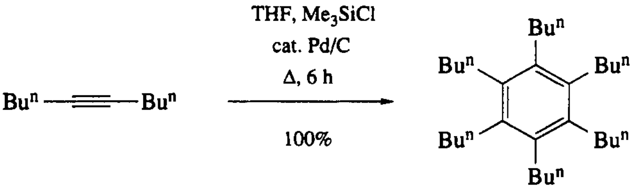

(31)

A commercially available heterogeneous catalyst derived from coating $K_2CrO_4$ on a silica/alumina support is capable of trimerizing alkynes in good yields under very mild conditions.[119] This system has been found to be quite useful in the syntheses of $^{11}C$-radiolabeled benzenes from the corresponding alkynes. Regioselectivity with unsymmetrical alkynes is moderate and favors 1,2,4-isomers. For example, propyne is trimerized to give a 4:1 ratio of 1,2,4- and 1,3,5-trimethylbenzenes.[120] The mechanism proposed invokes a unique concerted cycloaddition route to a surface-bound metallacycloheptatriene (Scheme 28). Chemoselective cotrimerizations have also been demonstrated with this catalyst.

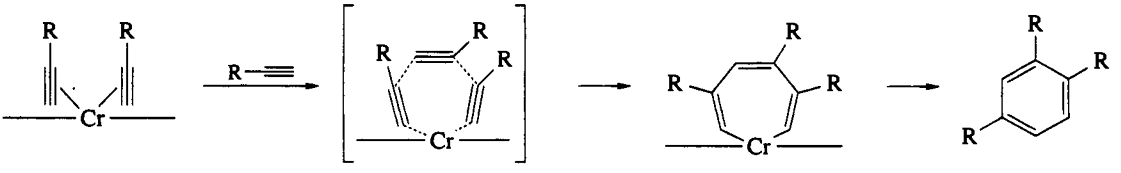

Scheme 28

Without question, the metal-promoted cycloaddition of three alkynes to produce benzenes is the most extensively studied organometallic cycloaddition in intramolecular versions. Early work indicated the utility of $Ni^0$ systems (*e.g.* $Ni(CO)_2(PPh_3)_2$), Ziegler catalysts and rhodacyclopentadienes in the partially intramolecular cocycloaddition of α,ω-diynes with additional alkynes.[46,121-123] Ziegler catalysts were noteworthy in giving rise to products containing the benzocyclobutene moiety from reactions of 1,5-hexadiyne, while the Rh systems showed considerable utility in the preparation of anthraquinone derivatives from appropriate diyne precursors (Scheme 29).

As is the case with totally intermolecular cocycloadditions, chemoselectivity is a potential problem in partially intramolecular systems where the desired process, combination of a diyne with a monoyne, may face competition from cycloadditions involving either exclusively the diyne or exclusively the monoyne. In practice chemoselectivity is readily achieved. Phosphite complexes of $Ni^0$ chemoselectively catalyze rapid and efficient cycloaddition of alkynes to heteroatom-containing diynes in good yields (equation

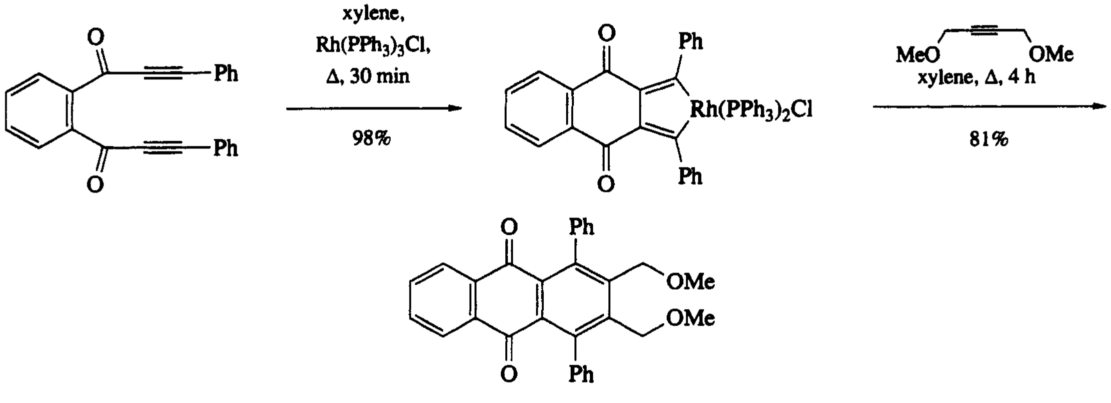

Scheme 29

32).[124] Wilkinson's catalyst ($RhCl(PPh_3)_3$) is similarly effective, and both systems show considerable functional group tolerance (equation 33).[125]

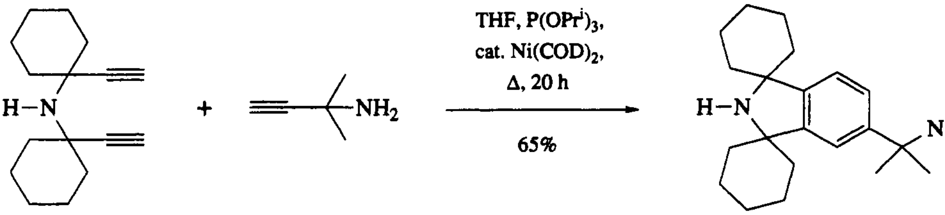

(32)

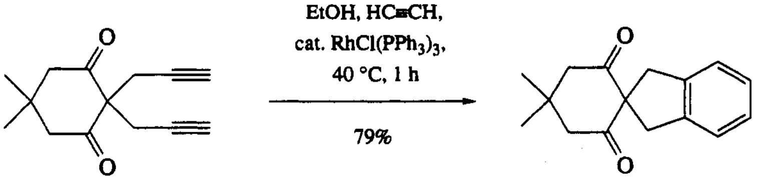

(33)

The most extensively studied system for partially intramolecular cycloadditions is also the one with the widest demonstrated scope, a system in which any one of several $CpCoL_2$ species acts as a catalyst precursor.[126] The CpCoL fragments actually involved in catalysis are extremely reactive, being relatively unhindered sterically. The principal factor determining the conditions necessary for cycloaddition to occur is the ease of inducing the $CpCoL_2 \rightarrow CpCoL$ transformation to take place. Although the earliest work, in which L = CO, required temperatures approaching 200 °C, these methods have been superseded by either combined thermal/photochemical conditions for dissociation of CO from $CpCo(CO)_2$, or the use of more labile precursors, in which L = $PPh_3$ or $CH_2{=}CH_2$. Instances in which catalytic activity is exhibited at –78 °C are known for the latter system. Careful selection of substrate characteristics is necessary for control of chemoselectivity in such highly reactive systems. Reactivity towards simple $\alpha,\omega$-diynes is very similar to that found from Ziegler systems: trimerization to give alkanes $\alpha,\omega$-substituted with annulated benzenes occurs and, again, benzocyclobutene derivatives are accessible (equation 34; $n$ = 0). Benzocyclobutene formation follows a slightly different mechanistic pathway than formation of benzocyclopentenes and benzocyclohexenes. In the latter two cases an intramolecular first step forms a bicyclic metallacycle, which goes on to react with the additional alkyne. This pathway is unavailable for 1,5-hexadiynes due to strain in closing the metallabicyclo[3.2.0]heptadiene. Instead, the first step is *intermolecular*, combining one end of the diyne with the additional alkyne. Only then does reaction at the free end of the diyne occur. As a result, four-membered ring formation is delayed to a later stage in the sequence, where it is fused to a larger ring.[38]

Chemoselectivity in cocycloadditions is typically poor unless the additional alkyne is resistant to simple cyclotrimerization. Examples of alkynes which satisfactorily fulfill this requirement include $Me_3SiC{\equiv}CSiMe_3$, $Me_3SiC{\equiv}COMe$ and $Me_3SnC{\equiv}CSnMe_3$. In the case of the unsymmetrical alkyne,

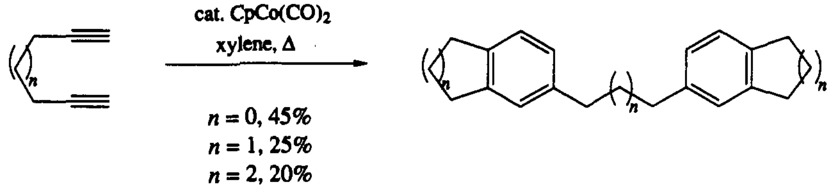
cat. CpCo(CO)2
xylene, Δ
n = 0, 45%
n = 1, 25%
n = 2, 20%
n
n
n

(34)

cycloaddition typically proceeds with total or near-total regioselectivity, as is illustrated in syntheses of tetracyclic isoquinolinoid alkaloids in the protoberberine series. Regiocontrol arises from the steric preference for forming bonds between the least sterically hindered carbons, with the relatively unhindered metal atom becoming linked to the more hindered end of the inserting alkyne (Scheme 30).[127]

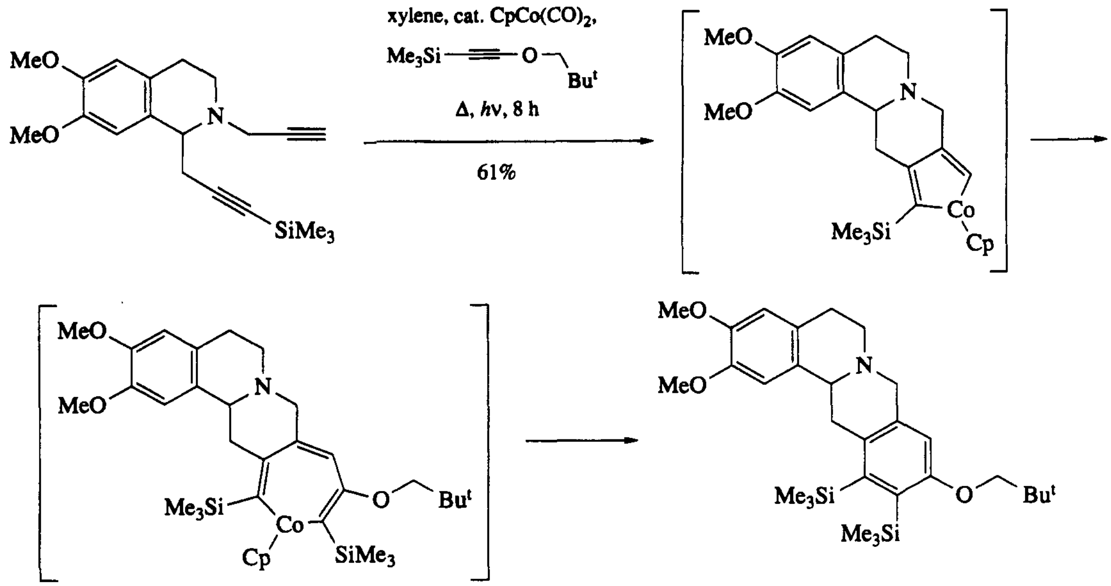
MeO
MeO
N
SiMe3
xylene, cat. CpCo(CO)2,
Me3Si—≡—O—\ Bu^t
Δ, hv, 8 h
61%
MeO
MeO
N
Me3Si
Co
Cp
MeO
MeO
N
Me3Si
Co
Cp
O
Bu^t
SiMe3
MeO
MeO
N
Me3Si
Me3Si
O
Bu^t

Scheme 30

The utility of this chemistry in synthesis is considerably enhanced by the versatility of the arylsilane and stannane functionalities in further transformations such as electrophilic substitution and migration reactions (Scheme 31).

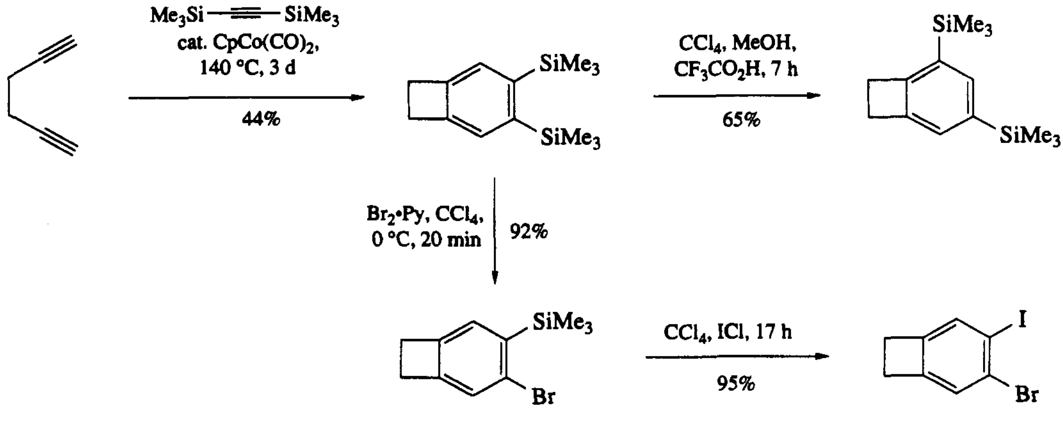
Me3Si—≡—SiMe3
cat. CpCo(CO)2,
140 °C, 3 d
44%
SiMe3
SiMe3
CCl4, MeOH,
CF3CO2H, 7 h
65%
SiMe3
SiMe3
Br2•Py, CCl4,
0 °C, 20 min
92%
SiMe3
Br
CCl4, ICl, 17 h
95%
I
Br

Scheme 31

The availability of benzocyclobutenes from cocycloadditions of 1,5-hexadiynes and hindered alkynes has been elaborated into an iterative synthesis of a variety of novel polycyclic biphenylene derivatives.

Repetitive annulations have been achieved by a cycloaddition/refunctionalization/coupling sequence: cycloaddition of an *o*-di(ethynyl)arene to $Me_3SiC{\equiv}CSiMe_3$ gives an *o*-bis(trimethylsilyl)arene, which represents the product of formal 'cyclobutabenzannulation' on the original arene. Electrophilic iodination of the silyl groups generates a new *o*-diiodoarene, suitable for another cycle. As the polycyclic becomes more extended, the sensitivity of the system to electrophilic conditions increases. To compensate, $Me_3SnC{\equiv}CSnMe_3$ is used in later cycles in order to exploit the higher reactivity of arylstannanes towards electrophilic substitution under mild conditions (Scheme 32).[128] Similar methodology has provided routes to both linear and nonlinear polycyclics and heterocyclics of theoretical and synthetic interest.[129–131]

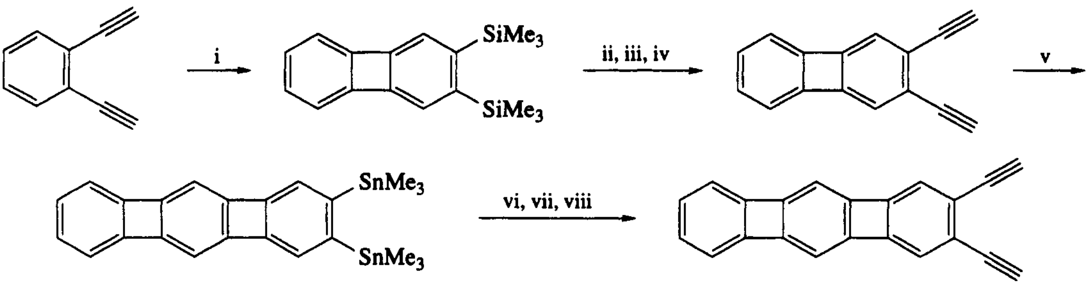

i, $Me_3SiC{\equiv}CSiMe_3$, cat. $CpCo(CO)_2$, Δ, *hν*, 10 h, 96%; ii, ICl, $CCl_4$, 0–20 °C, 1 h, 63%; iii, $Me_3SiC{\equiv}CH$, piperidine, cat. $PdCl_2(PhCN)_2$, CuI, 20–85 °C, 2 h, 75%; iv, KOH, MeOH, $Et_2O$, 10 min, 100%; v, $Me_3SnC{\equiv}CSnMe_3$, xylenes, cat. $CpCo(CO)_2$, Δ, *hν*, 3.5 h, 20%; vi, $I_2$, $CHCl_3$, 1 h, 80%; vii, $Me_3SiC{\equiv}CH$, $Et_3N$, cat. $PdCl_2(PhCN)_2$, 23 °C, 20 h, 75%; viii, KOH, MeOH, 1 h, 95%

**Scheme 32**

Further synthetic utility is derived from the reactivity of benzocyclobutenes towards thermal electrocyclic ring opening, producing highly reactive *o*-quinodimethanes (*o*-xylylenes). In suitably designed systems, efficient intramolecular Diels–Alder cycloaddition can follow ring-opening, leading to products of substantial complexity in a single experimental operation.[132,133] The landmark synthesis of A-ring aromatic steroids in general and estrone in particular by Vollhardt represents the epitome of development of the general sequence, which has also made accessible several other types of polycyclics and heteropolycyclics (Scheme 33).[134,135]

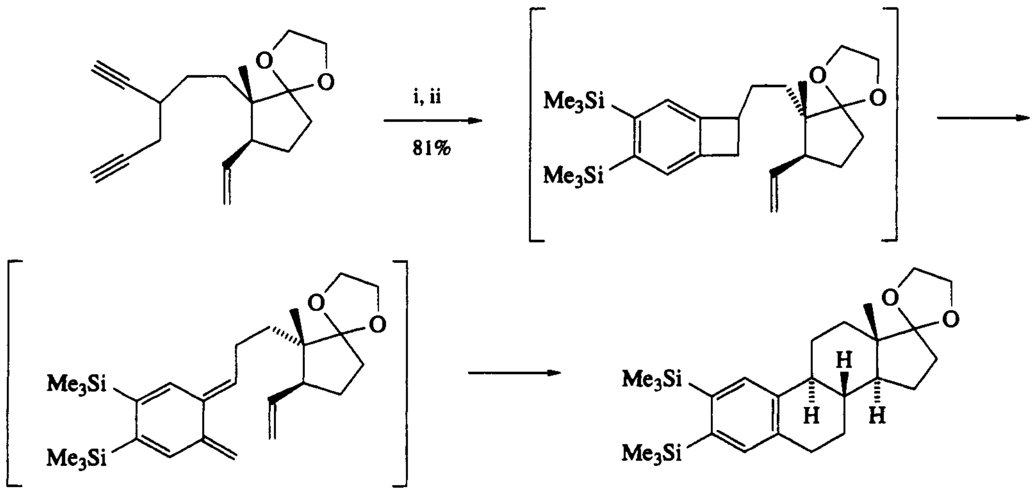

i, $Me_3SiC{\equiv}CSiMe_3$, cat. $CpCo(CO)_2$, Δ, 41 h; ii, decane, 180 °C, 20 h

**Scheme 33**

Finally, a spectacular example involving the totally intramolecular cyclization of an enetriyne has been demonstrated in an approach to a novel B-ring aromatic steriod (Scheme 34).[136]

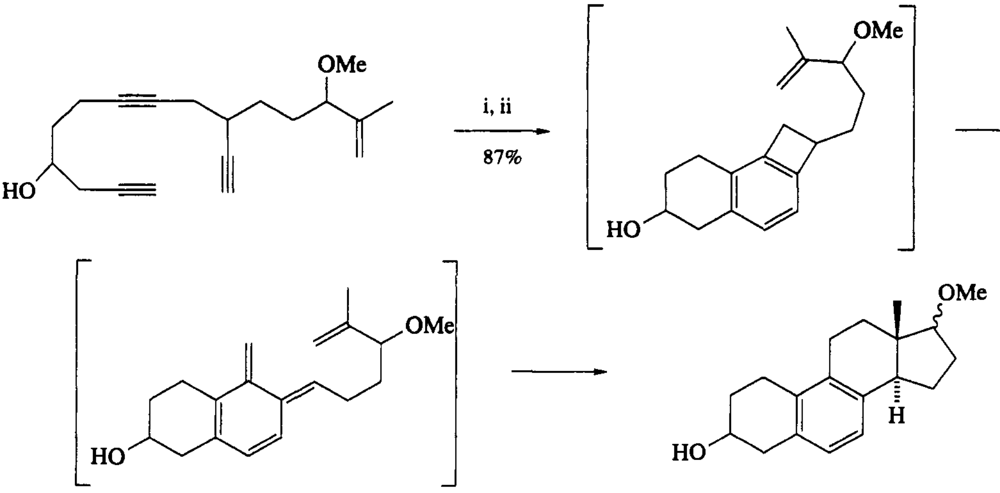

i, xylene, cat. $CpCo(CO)_2$, Δ, *h*ν, 1 h; ii, decane, Δ, 20 h

**Scheme 34**

## 9.4.5 SYNTHESIS OF SIX-MEMBERED HETEROCYCLIC RINGS

### 9.4.5.1 Pyridines: Chemo- and Regio-selectivity

The synthesis of the pyridine ring system by incorporation of a nitrile in a cocycloaddition reaction with two alkynes is closely related to the synthesis of benzenes. The same catalysts are generally active in both processes. Questions concerning chemoselectivity and regioselectivity considered in the section on benzenes apply here as well, but in the case of pyridine synthesis the critical chemoselection is the competition between pyridine formation and benzene formation: *i.e.* the ability of the nitrile to successfully compete for incorporation into a cycloaddition process. As virtually all the early examples of this process involved cobalt-based systems, much of the mechanistic work developed in connection with alkyne trimerization can be applied to pyridine synthesis. It is generally accepted that the same metallacyclopentadiene intermediates involved in alkyne trimerizations form on the pathway to pyridines as well. This is supported by kinetic data that indicate that rates of pyridine formation are independent of nitrile concentration. As cobalt in the CpCo fragment is initially in the +1 oxidation state, the preference for π-complexation to moderately π-acidic alkynes in preference to σ-donor nitriles is reasonable. Once ring-formation to the cobaltacyclopentadiene has taken place, however, complexation preferences at the now oxidized (+3) metal center are reversed. There should be a natural chemoselectivity preference for nitrile complexation, and, consequently, pyridine formation, and this expectation is generally realized. The sense of insertion of the nitrile is such that the nitrogen remains bound to the metal, and a new carbon–carbon bond is formed (see equation 39, below).

Early attempts at direct reaction of nitriles with cobaltacyclopentadiene complexes gave modest yields of pyridines, but, more importantly, demonstrated that the reaction was catalytic. With $CpCo(PPh_3)$(alkyne) as catalyst precursor, reaction occurs even at room temperature with a variety of nitriles.[137,138] Through a painstaking series of studies Bönnemann demonstrated practical improvements in convenience and overall yield through the use of more labile CpCoL sources, while maximizing chemoselectivity by maintaining an excess of nitrile and adding the alkyne in portions. In this way excellent yields of 2-alkyl- and 2-aryl-pyridines are synthesized from acetylene and nitriles, using either CpCo(COD) as catalyst, or any of a variety of soluble $Co^I$ species capable of generating catalytic fragments *in situ*.[139,140] Pyridine itself is also accessible from acetylene and hydrogen cyanide.[141] Yields of pyridines equal to or greater than 90% are commonplace using this methodology, the reaction requiring only 2–3 h at 120–130 °C, and exhibiting catalytic turnover numbers of several hundred (equation 35).[142] Applications of this methodology in the preparation of pyridines containing chiral substituents at C-2 exist (equation 36).[143,144] A significant extension of this reaction makes use of the fact that arylnitriles, and pyridylnitriles in general, may be employed in further cycloaddition processes. Thus conversion of the product of equation (36) into a new 2-cyanopyridine allows access *via* a second cycloaddition with acetylene to a new optically active *bi*pyridine, of potential value as a ligand for transition metal systems involved in asymmetric synthesis (equation 37).[145,146]

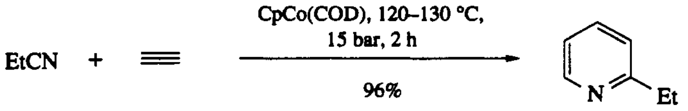

(35)

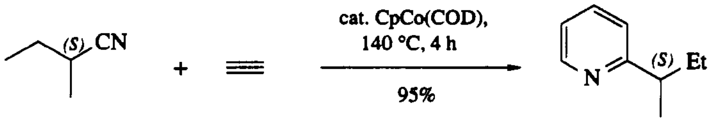

(36)

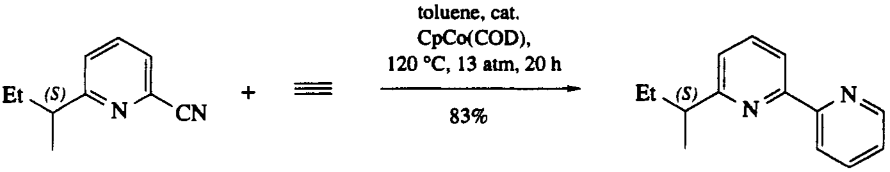

(37)

Substituted alkynes react readily with nitriles in the presence of these catalysts to generate substituted pyridines. Symmetrically disubstituted internal alkynes give rise to excellent yields of pentasubstituted pyridines (equation 38). In the case of monosubstituted and unsymmetrically disubstituted alkynes regioselectivity becomes an important issue, and one which is not generally amenable to good control from a synthetic point of view. Although pyridines are formed in good (*ca.* 65%) yields from nitriles and monoalkyl- or aryl-alkynes, regioselectivity is only modest in most cases: both 2,4,6- and 2,3,6-trisubstituted pyridines form in substantial amounts.[103] Ratios of *ca.* 2:1 in favor of the 2,4,6-trisubstituted pyridine are typical (equation 39).[147] The 2,4- and 2,5-disubstituted cobaltacyclopentadiene intermediates must therefore both participate in these processes, with the *former* being the predominant reactive species, in contrast to the situation encountered in the trimerization of alkynes. Insertion of the nitrile is regioselective for bond formation with the less sterically hindered carbon attached to the metal.[148] Not surprisingly, the lack of overall regiocontrol renders attempts at cocycloaddition using a nitrile and two different alkynes essentially worthless as a synthetic technique.[139]

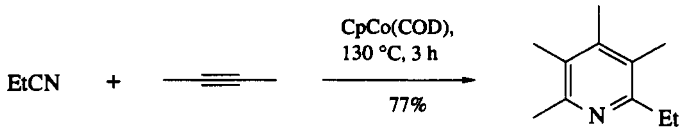

(38)

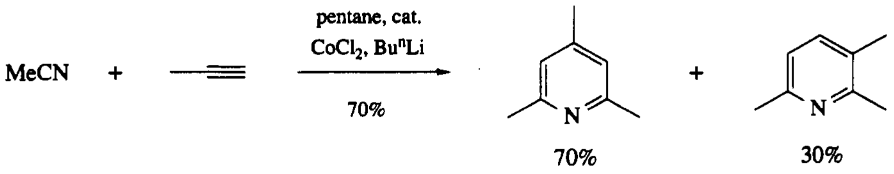

(39)

The properties of the $Co^{I}$-based catalysts are a sensitive function of ligand structure. Both reactivity and regioselectivity have been studied in an extensive series of systems containing a variety of substituted cyclopentadienyl and other related ligands. The ease of dissociation of the two-electron ligands determines the ease with which the active 16-electron catalytic species may be generated. Thus $CpCo(CH_2{=}CH_2)_2$ is capable of initiating cycloaddition at room temperature, while CpCo(COD) is inactive below *ca.* 125 °C. Since reasonable turnover rates still require elevated temperatures, this distinction is not a particularly important one in practice.

For a series of complexes containing the same dissociating ligand(s), the electron density at the metal is the most important remaining factor, and is of considerable practical importance. Electron-poor metal centers such as that in $(C_5H_4COMe)Co(COD)$ exhibit the highest reactivity but the lowest regioselectivity (*ca.* 1.5:1). In contrast, the electron-rich metal in $(C_5Me_5)Co(COD)$ is much more selective, giving better than a 3.5:1 ratio of 2,4,6- to 2,3,6-trisubstituted products, but exhibits greatly reduced reactivity and gives chemical yields that are too low to be preparatively useful. It is reasonable to assume that complexation of the nitrile to the intermediate metallacycle is facilitated by electron deficiency at the metal center, while regioselectivity in favor of the 2,4-disubstituted metallacycle benefits most from extreme steric crowding. A reasonable compromise is found in the 1,2-bis(trimethylsilyl)cyclopentadienylcobalt system, which gives regioselectivity approaching that in the $C_5Me_5$ system, but preserves both reactivity and excellent pyridine *vs.* benzene chemoselectivity.[149,150] Vapor-deposited Co atoms are also effective catalysts for pyridine formation, like $CpCo(CH_2{=}CH_2)_2$ showing activity even at room temperature, but giving optimal results at 120 °C: 80% yields, 7:1 chemoselectivity and *ca.* 2:1 2,4,6-regioselectivity.[151] Similar results are obtained with both soluble and polymer-bound $Rh^I$-based catalyst systems. With these regioselectivity in reactions of nitriles with terminal alkynes varies over a wider range than is found with Co; the $(C_5Me_5)Rh$ system in particular gives better than a 4:1 preference for 2,4,6-trisubstituted products, and exhibits higher reactivity than its Co counterpart. However, yields and chemoselectivities are generally lower than with Co-based catalysts, especially in the more regioselective systems.[152]

Although extensive work with heteroatom-containing nitrile analogs has not been done, successful cycloadditions along these lines include the synthesis of 2-aminopyridine from cyanamide,[140] and syntheses of 2-alkylthiopyridines from alkyl thiocyanates.[153] However, nitriles containing strongly electron-withdrawing substituents are poor substrates.[140]

Partially intramolecular cycloadditions of nitriles with α,ω-diynes have proven to be excellent means by which di- and poly-cyclic pyridine derivatives may be prepared. Nitrile insertion is highly regioselective, as expected from the results of intermolecular analogs (equation 40).[154] Heteroatom-bridged diynes have been used equally successfully: dipropargyl ethers, in synthetic approaches to pyridoxine, and dipropargylamines, in chemoselectivity studies where $Co^I$-based catalysts were found to be most pyridine-selective, although a $CoCl_2$/Mn-derived catalyst is also useful in certain cases (equation 41).[155–157] A novel form of intra- *vs.* inter-molecular chemoselectivity has been uncovered in cycloadditions of α,ω-diynes catalyzed by Co atoms from vapor deposition: deposition in toluene gives predominantly the expected partially intramolecular cycloaddition of 1,7-octadiyne to the corresponding bicyclic pyridine. In contrast, deposition in mesitylene gives largely *inter*molecular cycloaddition involving only one triple bond from each diyne, forming mostly di(5-hexynyl)methylpyridines as products (equation 42).[158]

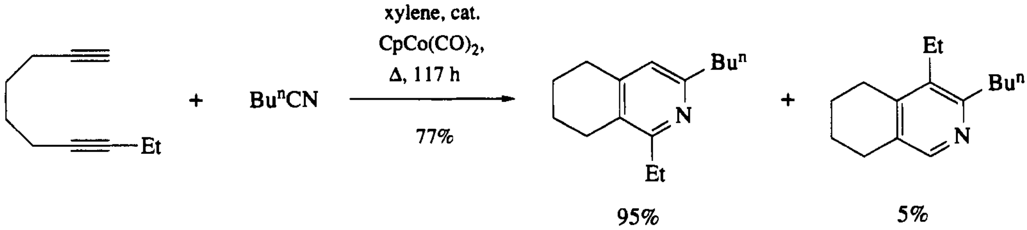

(40)

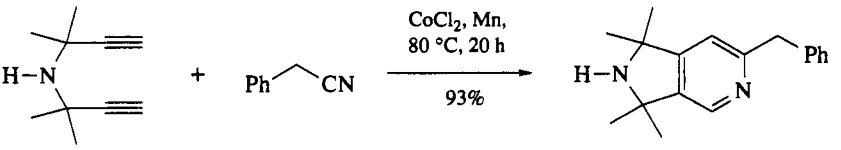

(41)

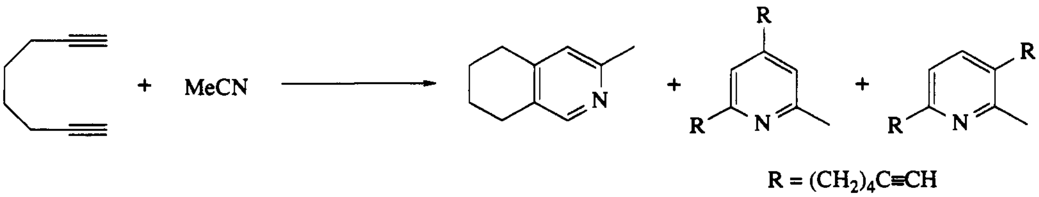

(42)

| | | | |
|---|---|---|---|
| Co, toluene, 25 °C, 73% | 86% | 12% | 2% |
| Co, mesitylene, 25 °C, 66% | 45% | 44% | 11% |

The cocycloaddition of α,ω-cyanoalkynes with alkynes is another efficient entry to bicyclic pyridines. In this process an intermediate metallacyclopentadiene is formed intermolecularly from the cyanoalkyne and the alkyne. The larger alkyne substitutent ends up nearer the metal with very high regioselectivity except in the case of 2-hexyne, where selectivity is reduced to about 3:2 (equation 43).[159]

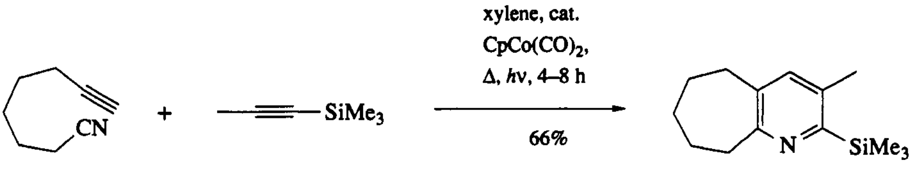

(43)

Intramolecular cycloaddition does not occur with α,ω-dinitriles; each cyano group instead undergoes independent cocycloaddition with two molecules of alkyne to afford high yields of di(2-pyridyl)alkanes. The reaction may also be controlled to give high yields of 2-(ω-cyanoalkyl)pyridines.[151]

### 9.4.5.2 Pyridones and Related Compounds: Chemo- and Regio-selectivity

Pyridones are accessible from formal [2 + 2 + 2] cycloaddition of two alkynes and an organic isocyanate. Two quite distinct catalyst systems have been developed for this reaction, with significant differences between them in mechanism and mechanistic implications on selectivity.

The first system to be developed utilizes CpCoL fragments in a catalytic cycle that proceeds through the usual cobaltacyclopentadiene intermediate. Indeed, preformed cobaltacyclopentadienes are effective catalyst precursors for this reaction; cobaltocene has also been used. As was the case in trimerization reactions of unsymmetrical alkynes, a preference is found for product formation through the metallacycle with larger groups at positions 2 and 5. When the metallacycle is unsymmetrical, total regioselectivity is observed in the subsequent insertion of the isocyanate, with the carbon of the latter bonding exclusively to the less-hindered end of the cobaltacyclopentadiene system. The result is primarily the formation of the pyridone ring system with the larger alkyne substituents at positions 3 and 6, from the 2,5-metallacycle, with lesser amounts of the isomer with large groups at positions 4 and 6, from the 2,4-metallacycle (equation 44).[160] Stoichiometric reactions between preformed cobaltacyclopentadienes and isocyanates are high yield, completely regioselective processes, consistent with this mechanism.[161] Another catalyst precursor, $CpCo(C_2H_4)_2$, is useful for terminal alkynes, and is especially regioselective for 3,6-disubstituted pyridones when an aryl substituent is present in either substrate, although chemoselectivity relative to benzene formation is not so good (equation 45).[162]

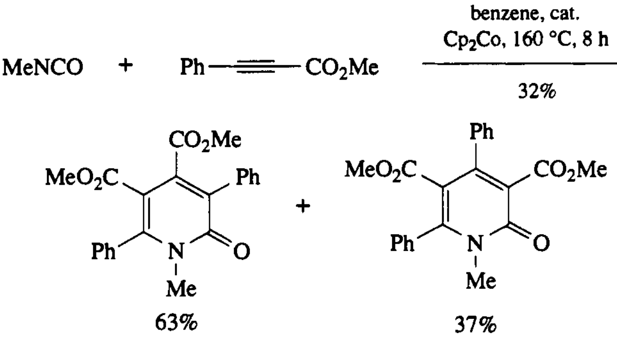

(44)

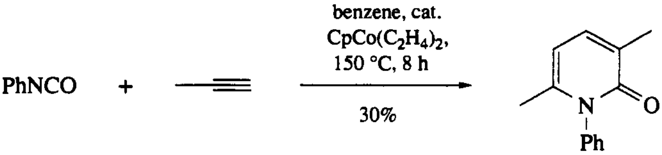

(45)

A $Ni^0$-based system related to those already described in connection with syntheses of both cyclobutenediones and several five-membered heterocycles (Sections 9.4.2.1, 9.4.3.3 and 9.4.3.5) is also capable of catalyzing pyridone synthesis from isocyanates and alkynes. However, the structures found for the isolable metallacyclic intermediates in this system imply a completely different insertion sequence: isocyanate first, followed by the two alkynes (Scheme 35). As a consequence, the regiochemistry found in the products of reaction of unsymmetrical alkynes is the reverse of that typical of $Co^I$: larger substituents end up at positions 4 and 6. Thus, starting with the carbonyl carbon of the isocyanate, each carbon–carbon bond forming event is strongly regioselective for the less-hindered alkyne carbon (equation 46). The yield shown is typical for reactions with internal alkynes; terminal alkynes give much poorer results.[163] An Rh-based system is also regioselective for the same substitution pattern, but chemoselectivity with regard to competing alkyne trimerization is poor.[164]

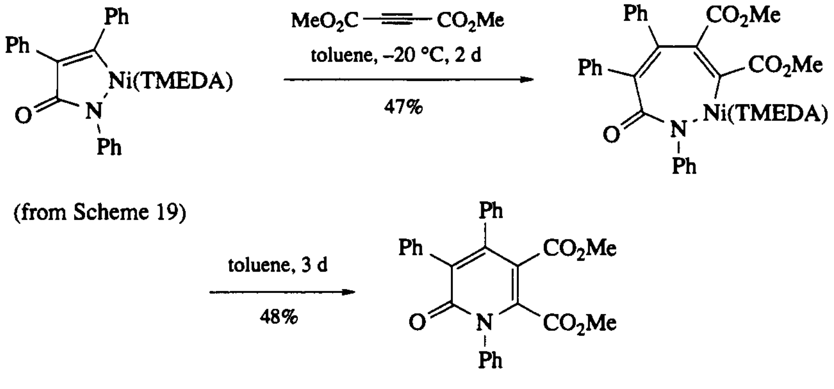
Ph
Ph
Ni(TMEDA)
O
N
Ph
$MeO_2C$—≡—$CO_2Me$
toluene, –20 °C, 2 d
47%
Ph
$CO_2Me$
Ph
$CO_2Me$
Ni(TMEDA)
O
N
Ph
toluene, 3 d
48%
Ph
Ph
$CO_2Me$
O
N
$CO_2Me$
Ph
(from Scheme 19)

**Scheme 35**

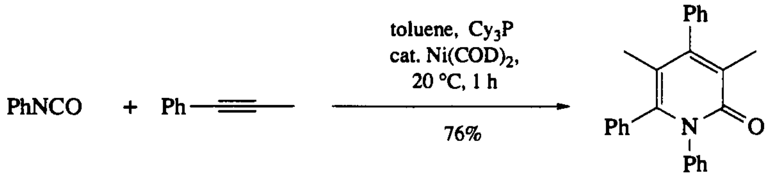
PhNCO
+
Ph—≡—
toluene, $Cy_3P$
cat. $Ni(COD)_2$,
20 °C, 1 h
76%
Ph
Ph
N
O
Ph
(46)

Among partially intramolecular versions of this cocycloaddition, α,ω-diynes have been found to cycloadd only with low efficiency to isocyanates in the presence of CpCo precursors. In contrast, ω-isocyanatoalkynes react smoothly with silylated alkynes in the presence of $CpCo(CO)_2$, giving high yields of products formed with excellent chemoselectivity and modest to excellent regioselectivity (equation 47). The regioselectivity is most likely controlled in a manner similar to that in equation (43).[165]

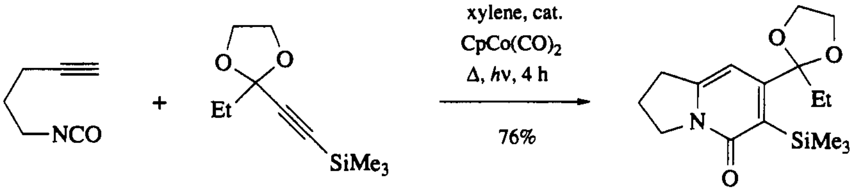
NCO
+
O
O
Et
$SiMe_3$
xylene, cat.
$CpCo(CO)_2$
Δ, hν, 4 h
76%
O
O
Et
N
$SiMe_3$
O
(47)

Replacement of organic isocyanates by carbodiimides in cycloadditions with alkynes results in a synthetic entry into the closely related 2-iminopyridine series of heterocycles. Both $Co^I$ and $Ni^0$ catalysts have been used for such cycloadditions. Remarkably, however, in each catalyst system the regioselectivity is reversed as compared with the otherwise analogous isocyanate cycloaddition. Either catalytic $Ni^0$ or a preformed $Ni^0$ complex of the carbodiimide reacts to produce excellent yields of cocycloaddition products from internal alkynes, with larger substituent groups ending up at positions 3 and 6 (equation 48, *cf.* equation 46).[166]

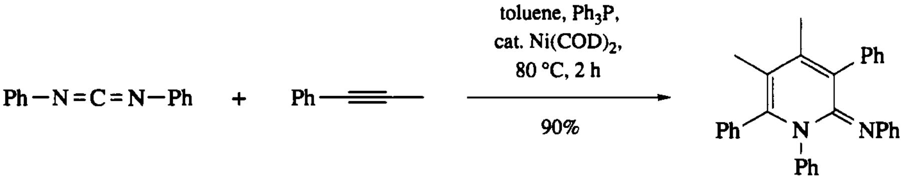
Ph—N=C=N—Ph
+
Ph—≡—
toluene, $Ph_3P$,
cat. $Ni(COD)_2$,
80 °C, 2 h
90%
Ph
Ph
N
NPh
Ph
(48)

Similarly, although the yields are lower, the $Co^I$ catalysts also show generally reversed regioselectivity in reactions with carbodiimides as compared with isocyanates.[160,162] In fact, the 4,6-disubstituted product is formed with complete regioselectivity in reactions of di(*p*-tolyl)carbodiimide with terminal alkynes, although dialkylcarbodiimides are rather unselective; internal alkynes give mixtures as well (equation 49). Chemoselectivity with respect to benzene formation is moderate in these systems.

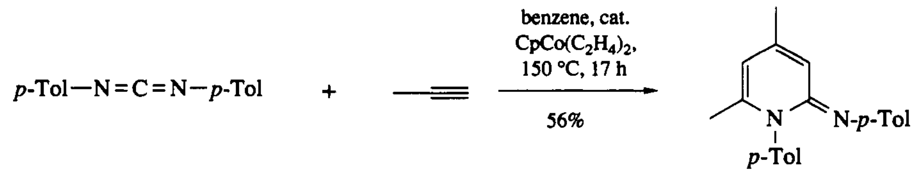
p-Tol—N=C=N—p-Tol
+
benzene, cat.
$CpCo(C_2H_4)_2$,
150 °C, 17 h
56%
N
N-p-Tol
p-Tol

(49)

### 9.4.5.3 Pyrones and Similar Heterocycles: Chemo- and Regio-selectivity

In a reaction completely analogous to the pyridone synthesis in Scheme 35, 5-nickelafuranones formed from $Ni^0$, an alkyne and carbon dioxide (see Section 9.4.3.3) react with additional alkyne to give 2-pyrones (Scheme 36).[71,167] Under catalytic conditions this becomes a viable synthesis of the heterocycle beginning with internal alkynes, especially when the solvent system and ligand environment of the metal are properly optimized (equation 50).[168] Regioselectivity with unsymmetrical systems is similar to that shown in equation (46): large groups at positions 4 and 6, as a result of carbon–carbon bond forming steps that involve the less-hindered carbon of each inserting alkyne. Unfortunately neither terminal alkynes nor alkynes with aryl substituents are useful substrates.[169]

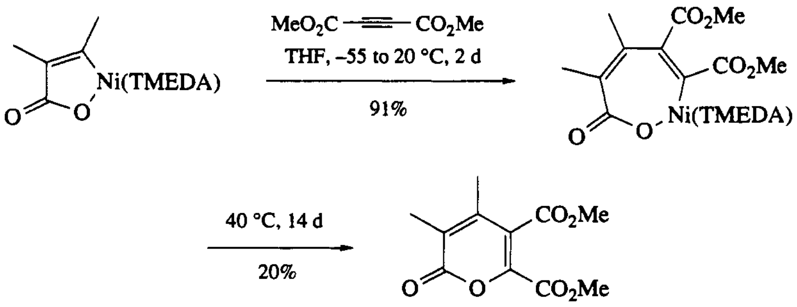
Ni(TMEDA)
O
O
$MeO_2C$—≡—$CO_2Me$
THF, –55 to 20 °C, 2 d
91%
$CO_2Me$
$CO_2Me$
Ni(TMEDA)
O
O
40 °C, 14 d
20%
$CO_2Me$
$CO_2Me$
O
O

**Scheme 36**

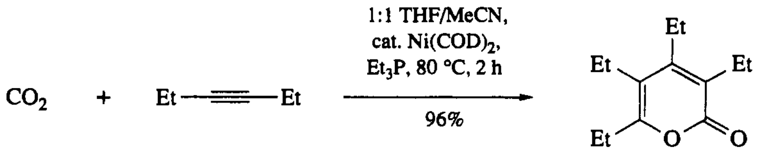
$CO_2$
+
Et—≡—Et
1:1 THF/MeCN,
cat. $Ni(COD)_2$,
$Et_3P$, 80 °C, 2 h
96%
Et
Et
Et
Et
O
O

(50)

An intramolecular version of this process has been described, leading to bicyclic 2-pyrones. Diynes in which both alkyne functions are internal and are linked by three-, four- or five-atom chains cycloadd to carbon dioxide in the presence of catalytic $Ni^0$ and various trialkylphosphines (equation 51). Terminal diynes require stoichiometric metal and give lower yields, however. Extensive studies of ligand effects on yield and chemoselectivity have established a broad scope for the process and pointed out important practical differences between it and the intermolecular reactions described above.[170]

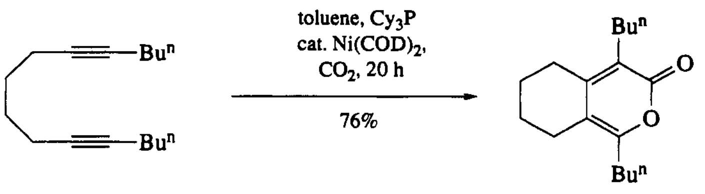
—$Bu^n$
—$Bu^n$
toluene, $Cy_3P$
cat. $Ni(COD)_2$,
$CO_2$, 20 h
76%
$Bu^n$
O
O
$Bu^n$

(51)

A novel cycloaddition of diynes with aldehydes is catalyzed by the same metal system, giving rise to bicyclic α-pyrans after 1,5-hydrogen shifts. Yields of these sensitive compounds are remarkably high (equation 52).[171]

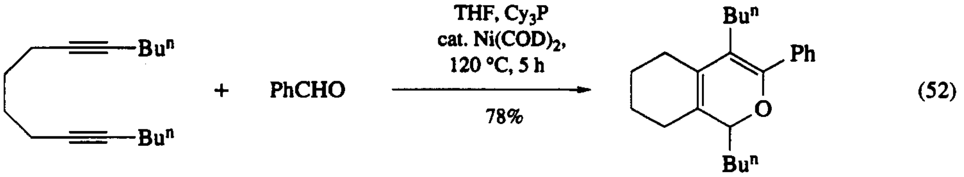

### 9.4.5.4 Other Heterocycles

Cobaltacyclopentadienes react with $CS_2$ to form thiopyran-2-thiones, and with methyl isothiocyanate to form pyridine-2-thiones, respectively, in two little-explored analogs of the processes described above.[137,172]

Multiple insertion reactions of isocyanates have been observed in the presence of $Ni^0$ catalysts. Pyrimidinediones are obtained in low yield from reaction of diphenylacetylene with excess alkyl isocyanates in the presence of Ni(COD).[163a] Similarly, alkyl and aryl isocyanates undergo simple cyclotrimerization to form symmetrical triazinetriones in the presence of both low-valent Ni and Ti catalysts.[173]

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# 9.5
# Zirconium-promoted Bicyclization of Enynes

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## 9.5.1 INTRODUCTION

Carbometallation,[1,2] as represented by equations (1a) and (1b), is one of only several fundamentally different types of transformations permitting carbon–carbon bond formation that organotransition metals undergo.[3] It is, in fact, a ubiquitous process observable with a wide variety of organotransition metals, one of the most representative examples being the Ziegler–Natta polymerization.[4]

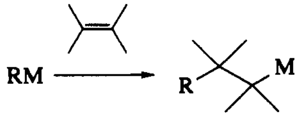

(1a)

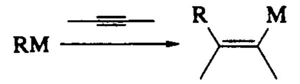

(1b)

Until recently, most of the organic compounds prepared *via* carbometallation had been relatively simple and highly symmetrical cyclic or polymeric compounds.[5] More recently, however, intensive efforts have been made to utilize carbometallation reactions in the synthesis of complex molecules. In particular, the fact that two new bonds, *i.e.* one carbon–carbon and one carbon–metal, are formed in carbometallation has led to the development of a number of cyclization methodologies.[6] Furthermore, carbometallation can, in principle, be observed with metal–carbene and metal–carbyne complexes as well as with metallacyclopropanes and metallacyclopropenes (Schemes 1 and 2).

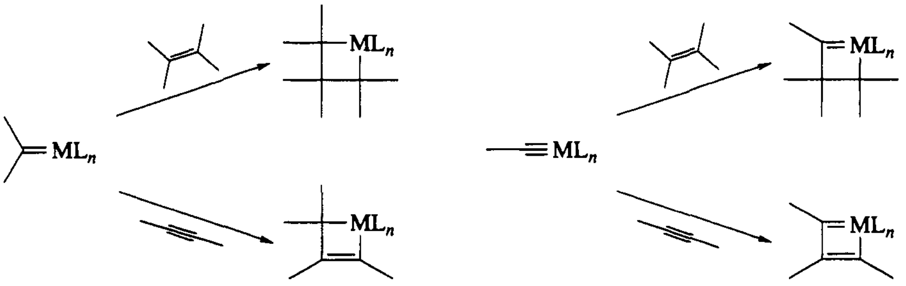

**Scheme 1**

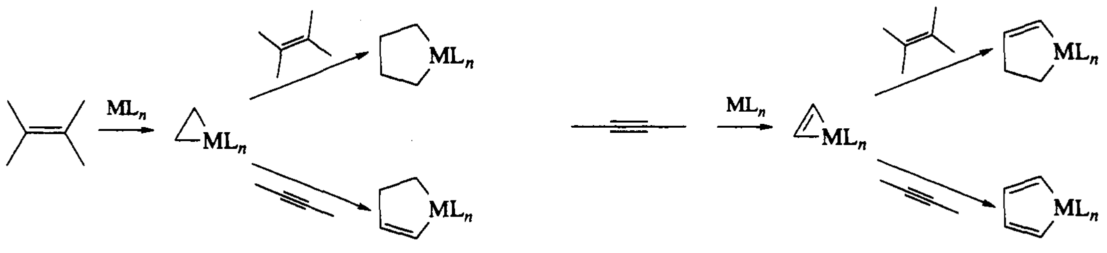

**Scheme 2**

This chapter summarizes cyclization reactions of alkynes and alkenes promoted by Zr and other Group IV metals that are thought to proceed *via* transformations shown in Scheme 2. It is clear from Scheme 2 that the formation of five-membered metallacycles can be complicated by at least two potential problems, one dealing with pairing alkynes and alkenes, pair selectivity hereafter, and the other dealing with the regiochemistry of alkynes and alkenes. These difficulties can be substantially alleviated by linking the two unsaturated units. Of particular interest is the bicyclization reaction of enynes (equation 2), since the desired products, *i.e.* metallacyclopentene derivatives, would readily allow further regioselective transformations. Also attractive are the related reactions of diynes that can give exocyclic conjugated dienes of defined stereochemistry suitable for use in the Diels–Alder reaction (equation 3) and those of dienes (equation 4).

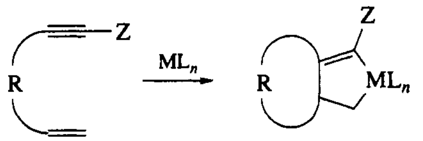

(2)

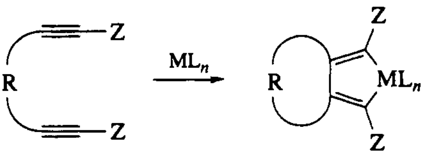

(3)

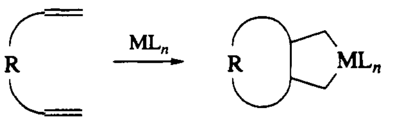

(4)

Consideration of molecular orbital interactions suggests that it would be ideal to use a transition metal complex having at least two empty and one filled nonbonding metal valence shell orbital, *i.e.* a ≤14-electron species, for observing facile bicyclization reactions shown in equations (2)–(4). This is based on assumptions that effective π-complexation of an alkyne or an alkene with a metal complex requires the simultaneous availability of one empty and one filled nonbonding metal orbital[7] and that carbometallation is greatly facilitated by the availability of an empty orbital.[1] These points are illustrated for the case of enyne bicyclization in equation (5).

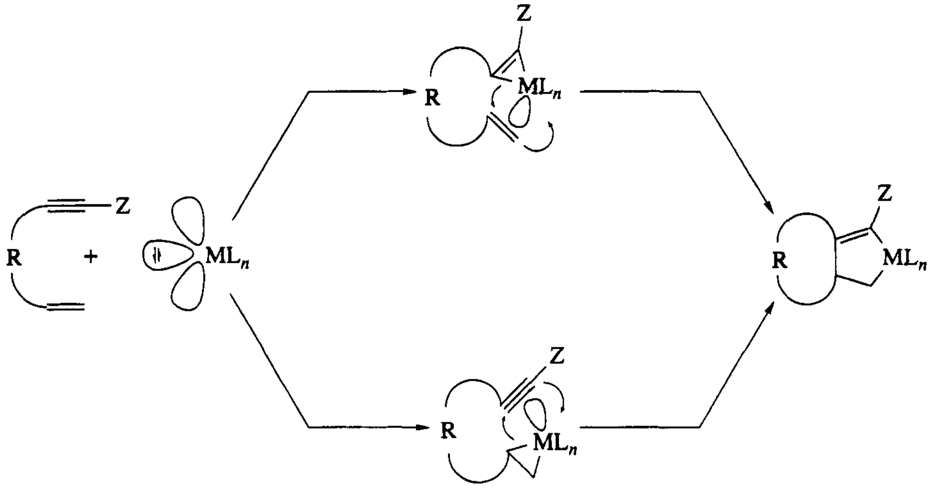

(5)

## 9.5.2 ENYNE BICYCLIZATION

Prior to the development of enyne bicyclization reactions promoted by Zr and other Group IV metals, the Co-catalyzed enyne bicyclization–carbonylation reaction (the Pauson–Khand reaction[8]) was known. This reaction is discussed in Volume 5, Chapter 9.1. In the Pauson–Khand reaction, the overall transformation is the conversion of enynes into bicyclic enones, and the organometallic bicyclic intermediates are usually neither readily available nor isolated. The use of $Co_2(CO)_8$, an 18-electron species, necessitates relatively high reaction temperatures. These and other limitations suggested the desirability of developing alternative enyne bicyclization reactions.

### 9.5.2.1 Zirconium-promoted Bicyclization and Reactions of Zirconabicycles

It was reported earlier that treatment of 2 equiv. of an alkyne with '$ZrCp_2$', generated by reduction of $Cl_2ZrCp_2$ by various methods, produced the corresponding zirconacyclopentadienes.[9,10] Using Farona's procedure,[10] consisting of treatment of $Cl_2ZrCp_2$ with Mg (10 equiv.) and $HgCl_2$ (1 equiv.), 7-(trimethylsilyl)-1-hepten-6-yne (**1a**) can be converted into (**2a**) in 90% yield (equation 6).[11] The product shows two distinct singlets for the two Cp protons at $\delta$ 5.78 and 5.82 p.p.m. in toluene-$d_8$. Carbonylation of (**2a**) with 1.1 atm of CO at 0 °C for 2 h gives the corresponding bicyclic enone (**3a**) in 55–75% isolated yield based on (**1a**). Protonolysis of (**2a**) with 3 M HCl provides (**4a**) in 90% yield, while its iodinolysis affords (**5a**) in 75% yield. The stereochemistry of (**4a**) has been clearly established by comparing its spectral data with those of an authentic sample prepared by an independent method.[12] Similarly, 8-(trimethylsilyl)-1-octen-7-yne (**1b**) can be converted into (**2b**), (**3b**), (**4b**) and (**5b**) in 90, 60, 87 and 76% yields, respectively. Treatment of (**5b**) with 1 equiv. of Bu$^n$Li in ether at –78 °C[13] cleanly gives (**6**) in 70% yield (equation 7).

Although Farona's procedure is satisfactory in the cases shown above, the use of a large excess of Mg and $HgCl_2$ is not synthetically attractive. In the search for an alternative procedure for generating '$ZrCp_2$', treatment of $Cl_2ZrCp_2$ with 2 equiv. of an alkyllithium, especially Bu$^n$Li, or an alkylmagnesium halide has been shown to serve as a more convenient and satisfactory procedure.[14] The bicyclization–carbonylation of (**1a**) run in THF, ether, benzene, toluene and hexane gives (**3a**) in 73, 62, 77, 74 and 66% yields by GLC, respectively.[15] Thus, the yields are quite insensitive to the solvents.

The results of the enyne bicyclization–carbonylation summarized in Table 1 and those of less successful experiments not included in Table 1, indicate the following. First, the Zr-promoted bicyclization reaction to produce zirconabicycles generally proceeds in $\geq$80% yields. Secondly, terminal alkynes have failed to undergo this reaction for reasons as yet unclear. The relatively high acidity of terminal alkynes appears to be responsible for the failure. On the other hand, various carbon groups, such as Me, Pr$^n$, $(CH_2)_2CH{=}CH_2$, $CH_2SiMe_3$, aryl, and alkenyl, as well as silyl and stannyl groups, can serve as satisfac-

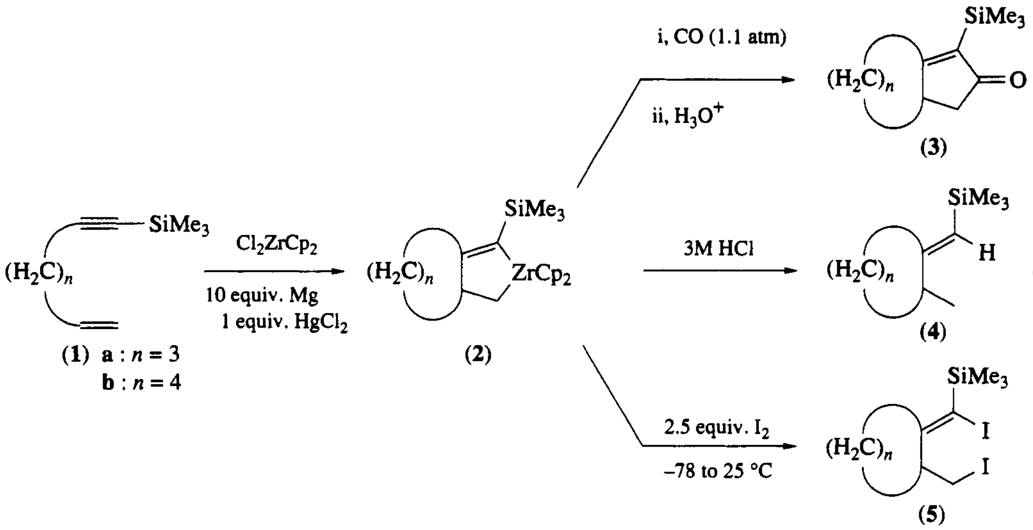

(6)

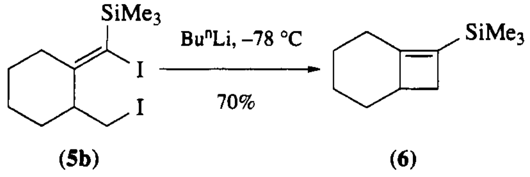

(7)

tory substituents.[16,17] Thirdly, both five- and six-membered rings can be fused to the zirconacyclopentene or cyclopentenone moiety, although only a few examples of six-membered ring fusion have so far been obtained. Fourthly, a wide variety of carbon and heteroatom substituents can be accommodated, as judged by the examples given in equations (8) and (9).

The required highly carbon-substituted enynes, such as (7) and (8), are conveniently prepared by the Sakurai–Hosomi allylsilane conjugate addition,[18] followed by conversion of methyl ketones into silylated alkynes,[19] as shown in equation (10).[11]

Even oxygenated enynes, such as **(11)** and **(12)**, react satisfactorily (equations 11–13).[20]

Fifthly, the bicyclization reaction of nitrogen-containing enynes, *i.e.* **(16)**–**(18)**, not only proceeds satisfactorily but also reveals an intriguing and beneficial heteroatom effect.

The smooth cyclization of **(16)** to produce (**19**; equation 14) is somewhat surprising in the light of many unsuccessful attempts to effect a similar cyclization reaction of (**20**; equation 15).[16] The reactions of **(17)** and **(18)** are strictly stereospecific (equation 16).[16]

### 9.5.2.2 Synthetic Applications of the Zirconium-promoted Bicyclization of Enynes

It is clear from the results presented above that the Zr-promoted bicyclization of enynes is applicable to the synthesis of a wide variety of monocyclic, bicyclic and polycyclic compounds, including terpenoids. At present, however, the number of such applications is still very small.

The stereodefined dienynes represented by **(22)** can now be readily prepared *via* either allylalumination[21] of 1,4-diynes, as in the synthesis of **(22a)** shown in equation (17),[15] or Cu-catalyzed allylmagnesiation of propargyl alcohols,[22] as shown in equation (18).[17]

After conversion of **(22)** into the corresponding $Me_3Sn$ derivatives **(23)**, the Zr-promoted bicyclization–carbonylation–iodinolysis of **(23)** gives **(24)** in good yields, as shown in equation (19).[23]

The formation of **(24)** is >98% stereoselective. Efforts are currently being made to apply this methodology to the synthesis of carbacyclin **(25)**.[24] A model study indicates that the Pd-catalyzed cross-coupling reaction of alkenylzinc derivatives[25] is a promising method for the attachment of the so-called prostanoid ω-side chain, as shown in equation (20).

Another promising application is to use the Zr-promoted bicyclization of enynes for controlling the stereochemistry of aliphatic carbon centers, as exemplified by the synthesis of a key intermediate **(26)**[20] for invictolide **(27)** shown in Scheme 3.

**Table 1** Zirconocene-promoted Bicyclization–Carbonylation of Enynes[a]

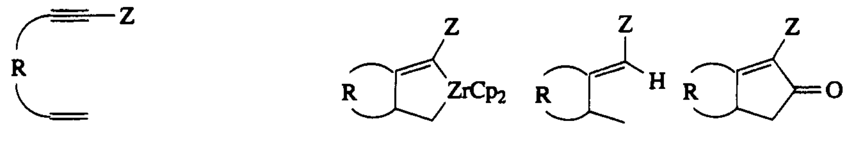
Z
R
Z
R
ZrCp2
Z
R
H
Z
R
O

| *R* | *Z* | *Procedure*[b] | *Yield*[c] *(%)* | *Yield*[d] *(%)* | *Yield*[e] *(%)* | *Ref.* |
|---|---|---|---|---|---|---|
| $(CH_2)_3$ | TMS | A | 95 | 75 | 65 | 11, 15 |
| $(CH_2)_4$ | TMS | B | 90 | 87 | 60 | 11, 15 |
| $(CH_2)_3$ | $SnMe_3$ | A[f] | 92 | 60 | 63 | 15, 16 |
| $(CH_2)_3$ | Me | A | 95 | 65 | 65 | 15, 16 |
| $(CH_2)_3$ | $(CH_2)_2CH{=}CH_2$ | A | 80 | 55 | — | 15, 16 |
| $(CH_2)_3$ | $CH_2TMS$ | A[f] | 90 | — | 55 | 15 |
| $(CH_2)_3$ | Ph | A[f] | 90 | 70 | 55 | 15, 16 |
| $(CH_2)_3$ | CH=CHHex-(*E*) | A | 80 | 75 | 50 | 15, 16 |
| $(CH_2)_3$ | [g] | A | — | 80 | — | 15, 16 |
| $(CH_2)_2CMe_2$ | TMS | B | — | — | 50 | 11, 15 |
| $CH_2CMe_2CH_2$ | TMS | B | — | — | 60 | 11, 15 |
| (*E*)-$MeCH{=}C(CH_2)_2$ | TMS | B | — | — | 55 | 11, 15 |
| (*E*)-$Bu^nCH{=}C(CH_2)_2$ | TMS | A | 95 | — | 70 | 17 |
| (*E*)-$Bu^n(Me)C{=}C(CH_2)_2$ | TMS | A | 92 | — | 73 | 17 |
| (*Z*)-$Bu^n(Me)C{=}C(CH_2)_2$ | TMS | A | 93 | — | 65 | 17 |
| $PhCH_2N(CH_2)_2$ | TMS | A | 85 | — | 66 | 15, 16 |
| **(16)** |  | A | 95 | 72 | 77 | 15, 16 |
| **(17)** |  | A | 92 | 62 | — | 15, 16 |
| **(18)** |  | A | 86 | — | — | 15, 16 |
| [h] | $Pr^n$ | A | — | 94[i] | — | 20 |
| **(12a)** |  | B | — | 70[j] | — | 20 |
| **(12b)** |  | B | — | [k] | — | 20 |

[a] Unless otherwise mentioned, the reaction is run in THF. [b] A = $Cl_2ZrCp_2 + 2Bu^nLi$; B = $Cl_2ZrCp_2 + Mg + HgCl_2$. [c] By $^1H$ NMR. [d] Isolated. [e] Isolated. [f] Benzene used as solvent. [g] Z = $CH{=}CHCH(OSiMe_2Bu^t)n\text{-}C_5H_{11}$. [h] R = $(CH_2)_2CH(OSiMe_2Bu^t)$. [i] A 2.5:1 mixture of (**13a**) and (**13b**). [j] A 62:8 mixture of (**14a**) and (**14b**). [k] This product is obtained as a by-product arising from (**12b**) in the reaction of a 74:26 mixture of (**12a**) and (**12b**).

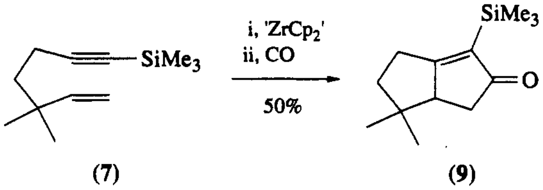
SiMe3
i, 'ZrCp2'
ii, CO
50%
SiMe3
O
(7)
(9)

(8)

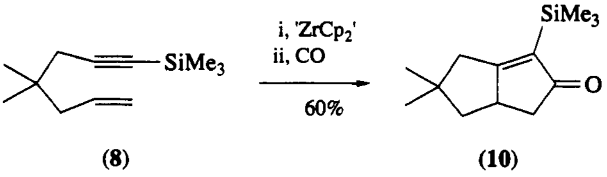
SiMe3
i, 'ZrCp2'
ii, CO
60%
SiMe3
O
(8)
(10)

(9)

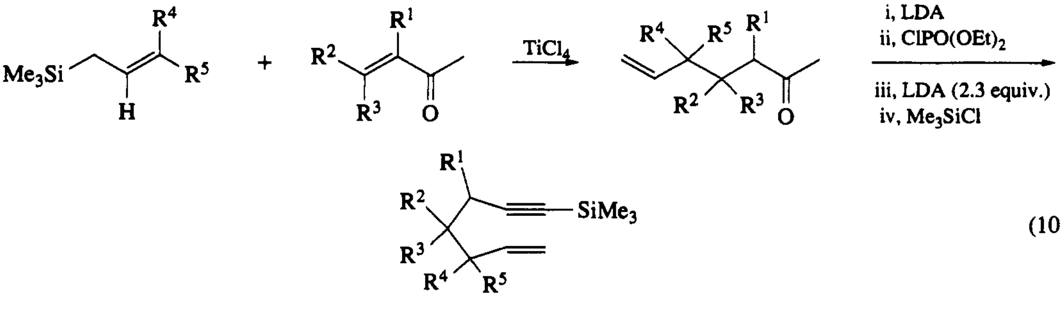
R4
Me3Si
R5
H
+
R1
R2
R3
O
TiCl4
R4
R5
R1
R2
R3
O
i, LDA
ii, ClPO(OEt)2
iii, LDA (2.3 equiv.)
iv, Me3SiCl
R1
R2
SiMe3
R3
R4
R5

(10)

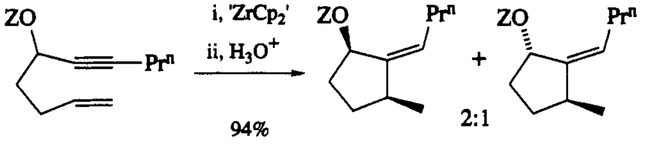
ZO
Pr$^n$
i, 'ZrCp$_2$'
ii, H$_3$O$^+$
94%
ZO
Pr$^n$
+
2:1
ZO
Pr$^n$

(11)

**(11)** Z = SiMe$_2$Bu$^t$ **(13a)** **(13b)**

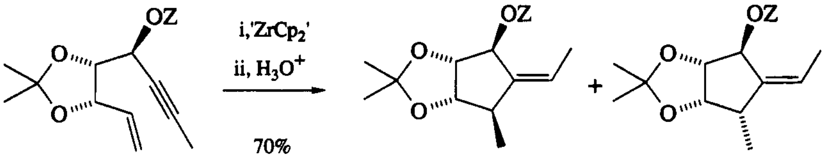
OZ
O
O
i,'ZrCp$_2$'
ii, H$_3$O$^+$
70%
OZ
O
O
+
OZ
O
O

(12)

**(12a)** **(14a)** 62:8 **(14b)**

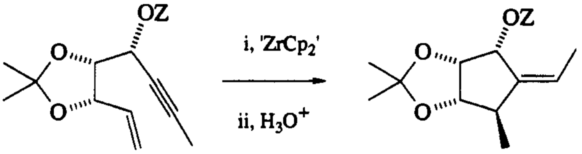
OZ
O
O
i, 'ZrCp$_2$'
ii, H$_3$O$^+$
OZ
O
O

(13)

**(12b)** **(15)** Z = SiMe$_2$Bu$^t$

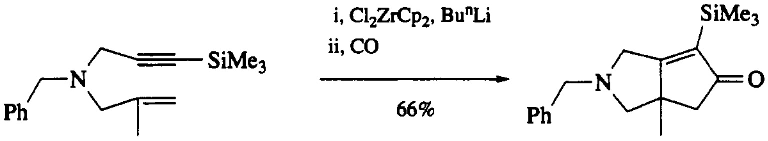
SiMe$_3$
N
Ph
i, Cl$_2$ZrCp$_2$, Bu$^n$Li
ii, CO
66%
SiMe$_3$
N
O
Ph

(14)

**(16)** **(19)**

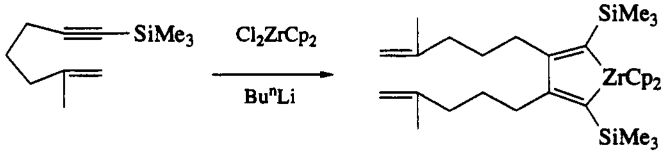
SiMe$_3$
Cl$_2$ZrCp$_2$
Bu$^n$Li
SiMe$_3$
ZrCp$_2$
SiMe$_3$

(15)

**(20)** **(21)**

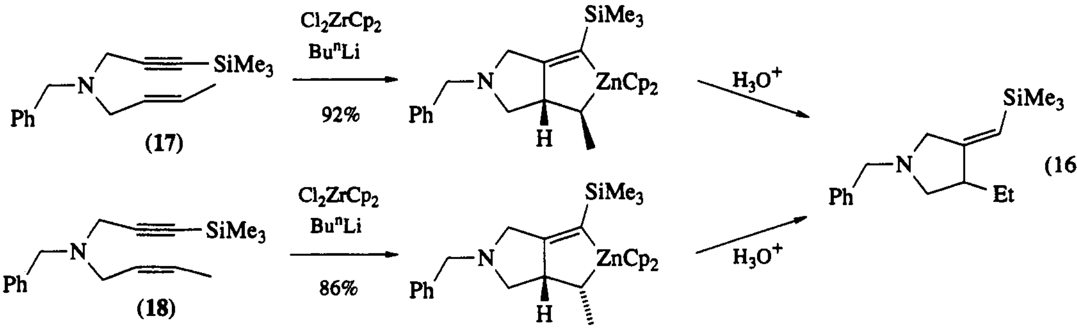
N
SiMe$_3$
Ph
Cl$_2$ZrCp$_2$
Bu$^n$Li
92%
SiMe$_3$
N
ZnCp$_2$
Ph
H
H$_3$O$^+$
SiMe$_3$
N
Ph
Et
N
SiMe$_3$
Ph
Cl$_2$ZrCp$_2$
Bu$^n$Li
86%
SiMe$_3$
N
ZnCp$_2$
Ph
H
H$_3$O$^+$

(16)

**(17)** **(18)**

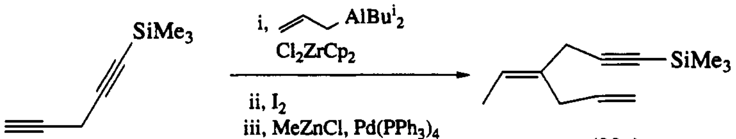
SiMe$_3$
i, AlBu$^i_2$
Cl$_2$ZrCp$_2$
ii, I$_2$
iii, MeZnCl, Pd(PPh$_3$)$_4$
SiMe$_3$

(17)

**(22a)**

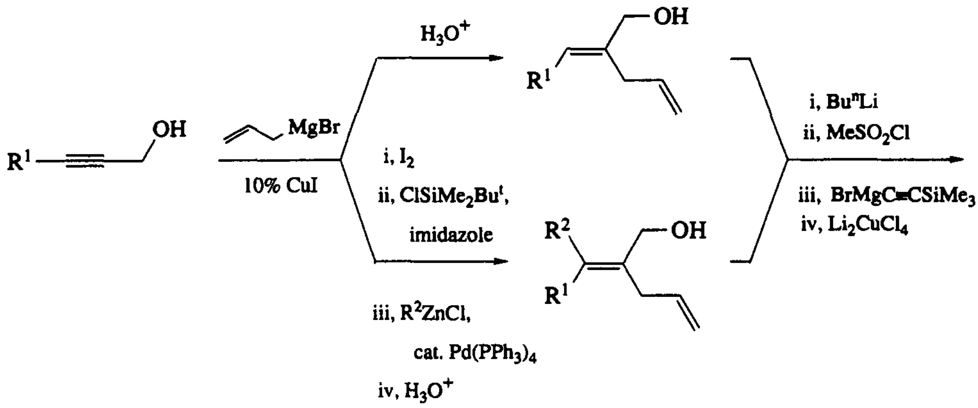
R¹ OH
MgBr
10% CuI
H3O+
R¹ OH
i, I2
ii, ClSiMe2Bu^t,
imidazole
iii, R²ZnCl,
cat. Pd(PPh3)4
iv, H3O+
R² R¹ OH
i, BuⁿLi
ii, MeSO2Cl
iii, BrMgC≡CSiMe3
iv, Li2CuCl4

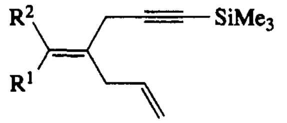

**(22)**

**(22b)** $R^1 = Bu^n$, $R^2 = H$
**(22c)** $R^1 = Bu^n$, $R^2 = Me$
**(22d)** $R^1 = Me$, $R^2 = Bu^n$

(18)

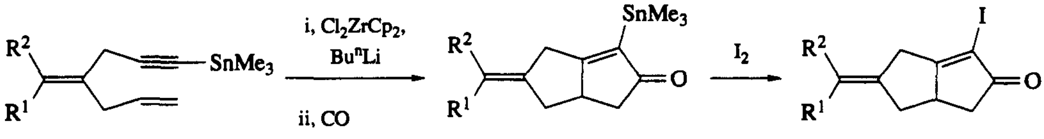
R² R¹ SnMe3
i, Cl2ZrCp2, BuⁿLi
ii, CO
R² R¹ SnMe3 O
I2
R² R¹ I O

(19)

**(23)** **(24)**

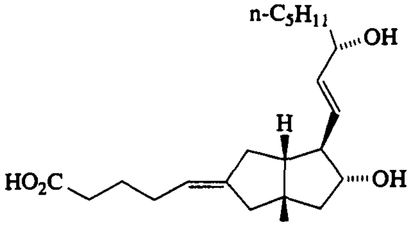
n-C5H11
OH
H
HO2C
OH
H

**(25)**

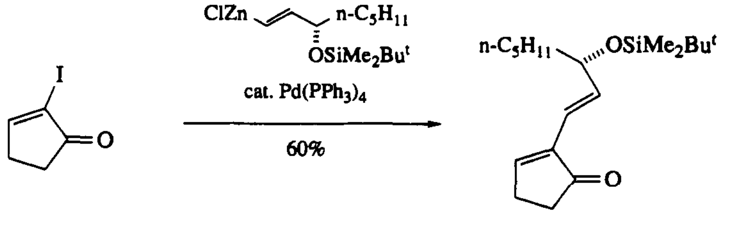
I
O
ClZn n-C5H11
OSiMe2Bu^t
cat. Pd(PPh3)4
60%
n-C5H11 OSiMe2Bu^t
O

(20)

Although the product yields are very modest (40–50%), conversion of zirconacyclopentenes into the corresponding S-, Se- and Sn-containing cyclopentene derivatives has also been reported (equations 21 and 22).[20]

### 9.5.2.3 Bicyclization Promoted by Other Group IV Metals

Although the number of examples of the Ti-promoted bicyclization of enynes is very limited, the reaction appears to proceed satisfactorily in some favorable cases, as shown in equations (23) and (24).[20] The presumed titanacyclic intermediates do not appear to have been characterized.

In more demanding cases, however, the Ti-promoted bicyclization reaction appears to be far inferior to the Zr-promoted reaction. For example, the reported yields of **(28)** for the Ti- and Zr-promoted reactions

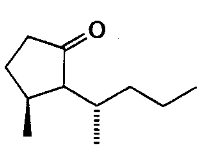

**(26)**

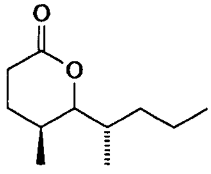

**(27)**

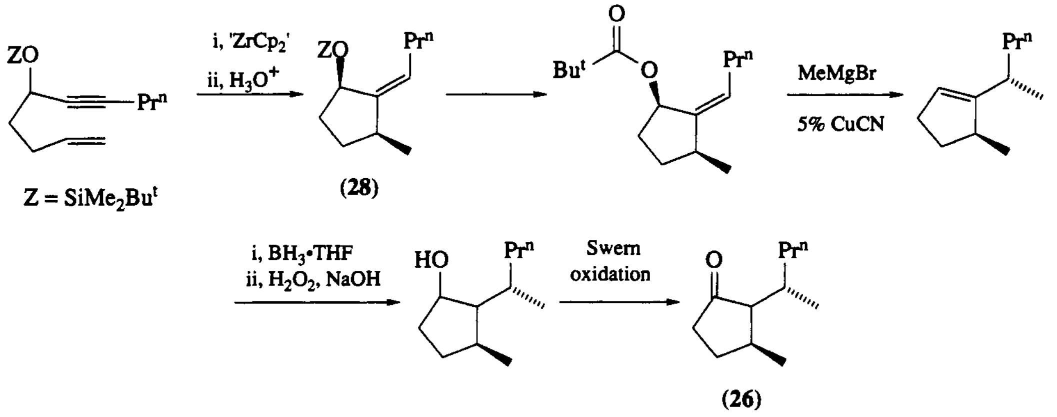
ZO
Pr$^n$
Z = SiMe$_2$Bu$^t$
i, 'ZrCp$_2$'
ii, H$_3$O$^+$
ZO
Pr$^n$
(28)
O
Bu$^t$
O
Pr$^n$
MeMgBr
5% CuCN
Pr$^n$
i, BH$_3$•THF
ii, H$_2$O$_2$, NaOH
HO
Pr$^n$
Swern oxidation
O
Pr$^n$
(26)

**Scheme 3**

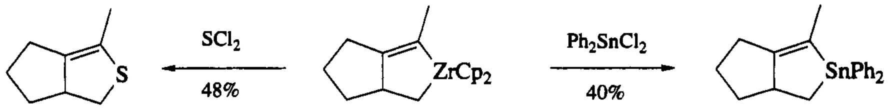
S
SCl$_2$
48%
ZrCp$_2$
Ph$_2$SnCl$_2$
40%
SnPh$_2$

(21)

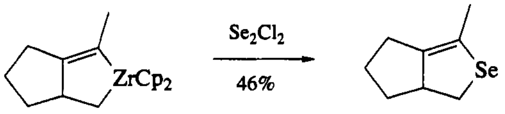
ZrCp$_2$
Se$_2$Cl$_2$
46%
Se

(22)

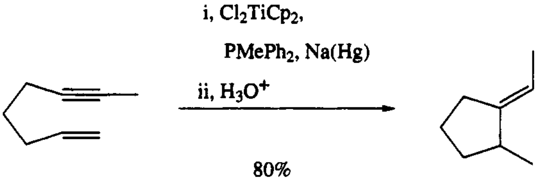
i, Cl$_2$TiCp$_2$,
PMePh$_2$, Na(Hg)
ii, H$_3$O$^+$
80%

(23)

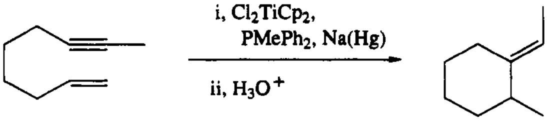
i, Cl$_2$TiCp$_2$,
PMePh$_2$, Na(Hg)
ii, H$_3$O$^+$

(24)

are 33 and 94%, respectively.[20] Furthermore, the use of a phosphine as a stabilizer appears to be essential for the Ti-promoted reaction,[15] thereby offsetting any economical advantage Ti might offer.

Treatment of $Cl_2HfCp_2$ with 2 equiv. of Bu$^n$Li gives Bu$^n_2$HfCp$_2$ as a discrete product that is stable at 25 °C.[15] Its reaction with 7-(trimethylsilyl)-1,6-heptenyne (**1a**) is much slower than that of '$ZrCp_2$' but proceeds smoothly at 100 °C for 5 h to give the expected hafnabicycle (**29**) in 90% yield. Its carbonylation with 3 atm of CO at 25 °C for 2 h gives (**3a**) in 80% GLC yield based on (**1a**; equation 25).[15]

Although no advantage to the use of relatively expensive Hf has been noted so far, the higher stability of organohafnium intermediates relative to the corresponding Zr compounds promises to provide some significant synthetic advantages.

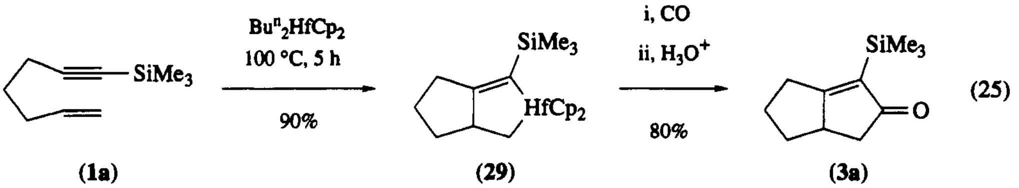

(25)

## 9.5.3 DIYNE BICYCLIZATION

Bicyclization of linear diynes (**30**) to produce bicyclic metallacyclopentadienes (**31**) followed by their conversion into *trans,trans*-1,2-bis(alkylidene)cycloalkanes (**32**) is a highly attractive synthetic operation primarily because (**32**) can now serve as the diene component in the Diels–Alder reaction (equation 26).

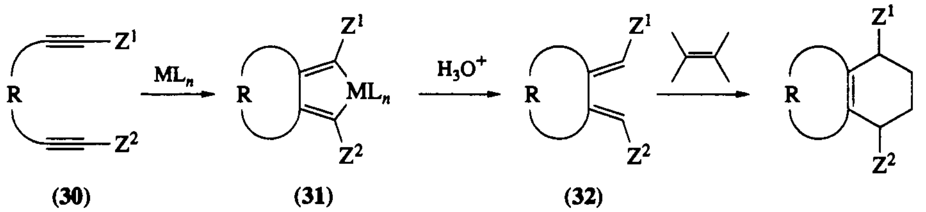

(26)

The first generally applicable procedure for the conversion of (**30**) into (**32**) was developed with $Cl_2TiCp_2$,[26,27] as shown in equation (27).

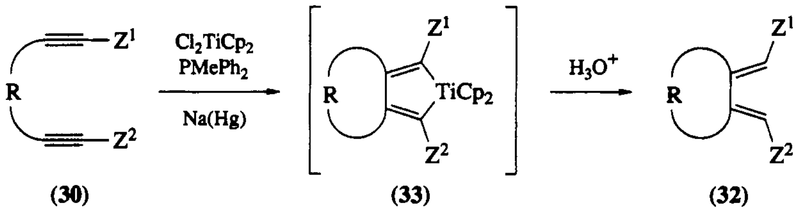

(27)

The titanabicycles (**33**) do not appear to have been fully characterized as such. Subsequently the corresponding Zr reaction was reported as an alternative procedure (equation 28).[14,15,27]

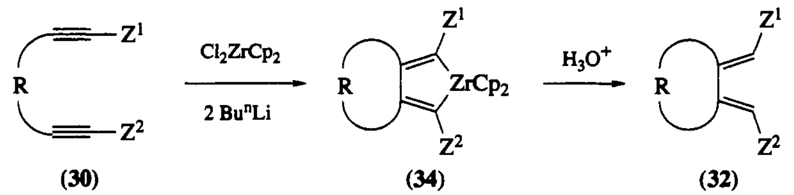

(28)

In this case, some of the zirconabicycles (**34**) have been fully characterized. No attempts as yet appear to have been made to use Hf in the conversion of (**30**) into (**32**).

The experimental results summarized in Table 2 may permit the following generalizations. First, although both Ti and Zr are satisfactory in many cases, the Ti procedure is far more sensitive to steric and ring strains than the Zr procedure. Thus, the presence of one or more Pr$^i$, Bu$^t$, TMS and other sterically demanding groups causes a major decrease in product yield in the Ti reaction. Furthermore, the applicability of the Ti procedure is practically limited to the preparation of only five- and six-membered rings, while the Zr procedure can be used to synthesize four- to seven-membered rings. It is reasonable to state that the Zr procedure is, in general, either comparable or superior to the Ti procedure. So far, the superiority of the Ti procedure has been observed only in the reaction of 1,8-diethoxy-1,7-octadiyne.

The Diels–Alder reaction of the conjugated dienes (**32**) is well established. The following reaction sequence illustrates the potential synthetic utility of a combination of the bicyclization and the Diels–Alder reaction (equation 29).[27]

**Table 2** Ti- or Zr-promoted Bicyclization–Protonolysis of Diynes

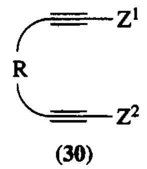

**(30)**

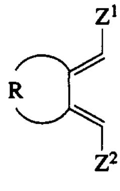

**(32)**

| *R* | *Z*$^1$ | *Z*$^2$ | *Yield Using Ti (%)*[a] | *Yield Using Zr (%)*[b] | *Ref.* |
|---|---|---|---|---|---|
| $(CH_2)_2$ | Me | Me | 0 | 89 | 27 |
| $(CH_2)_2$ | Me | $Bu^n$ | — | 67 (76) | 14 |
| $(CH_2)_3$ | Me | Me | 78 | 70 | 27 |
| $(CH_2)_3$ | Et | Et |  | 80 (85) | 14 |
| [c] | Me | Me | 19 | 82 | 27 |
| $H_2COCH_2$ | Me | Me | 72 | — | 27 |
| $H_2COCH_2$ | [d] | [d] | 67 | 55 | 27 |
| [e] | Me | $(CH_2)_2NH_2$ | — | 41 | 27 |
| $(CH_2)_4$ | Me | Me | 89 | 70, 55 (84) | 14, 27 |
| $(CH_2)_4$ | Et | Et | 83 | 77 | 27 |
| $(CH_2)_4$ | $Pr^i$ | $Pr^i$ | 16 | 67 | 27 |
| $(CH_2)_4$ | $Bu^t$ | $Bu^t$ | 0 | 65 | 27 |
| $(CH_2)_4$ | Me | $Pr^i$ | 56 | 69 | 27 |
| $(CH_2)_4$ | Me | $Bu^t$ | 31 | 49 | 27 |
| $(CH_2)_4$ | Me | $(CH_2)_2OH$ | 79 | 63 | 27 |
| $(CH_2)_4$ | TMS | TMS | 0 | 89 (97) | 14, 27 |
| $(CH_2)_4$ | OEt | OEt | 63 | <16 | 27 |
| [f] | Me | Me | — | 60 | 27 |
| $(CH_2)_5$ | Me | Me | 24 | 45, 40 (60) | 14, 27 |
| $(CH_2)_6$ | Me | Me | 0 | <2 | 27 |

[a] Isolated. [b] Isolated. The numbers in parentheses are GLC yields. [c] R = $CH_2CH_2CH(OSiMe_2Bu^t)$. [d] $Z^1 = Z^2$ = 1,3-benzodioxol-5-yl. [e] R = $CH_2CH_2CH(OTMS)$. [f] R = 1,2-$(CH_2)_2C_6H_4$.

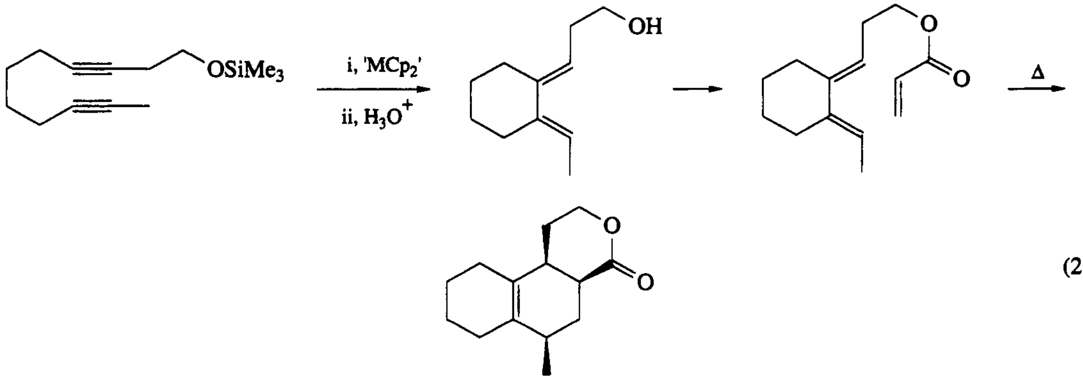

(29)

## 9.5.4 DIENE BICYCLIZATION

The double bonds in dienes can be isolated, conjugated, or cumulated. The reaction of conjugated dienes with '$ZrCp_2$' can give 1-zircona-3-cyclopentenes. This aspect of organozirconium compounds has been extensively studied and reviewed.[28–30] In fact, the conjugated diene–'$ZrCp_2$' reaction does not lead to the formation of bicyclic structures (equation 30). It instead gives monocyclic allylic zirconium derivatives exhibiting characteristics very different to those discussed above. For these reasons, the chemistry of the conjugated diene–'$ZrCp_2$' reaction is excluded from this review. Little or nothing is known about the cumulated diene–'$ZrCp_2$' reaction. The relatively high acidity of cumulenes may cause a difficulty similar to that observed with terminal alkynes.

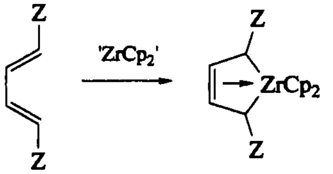

(30)

The reaction of 1,7-octadiene with $Cp_2Zr$–phosphine complexes generated by treatment of $Cp_2Zr(R)H$ with 2 equiv. of phosphine was briefly reported to give a 90% yield of the expected zirconabicycle (**35**; equation 31) as a 1:1 stereoisomeric mixture.[31] The nonstereoselectivity is rather disappointing, but this aspect may need to be reexamined in the light of more recent results in this area. No paper on the corresponding Hf reaction appears to have been published.

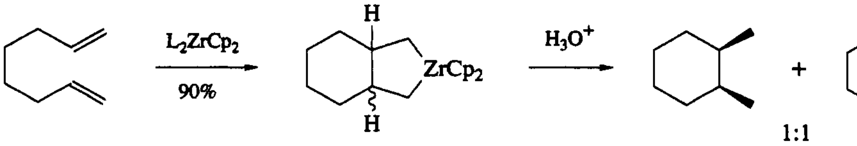

(**35**)

(31)

Earlier, the corresponding reaction of '$TiCp_2$' was investigated under carbonylation conditions.[32] Although bicyclization may have occurred, the yield of 2-perhydroindanone was reported to be only 2% (equation 32). On the other hand, the reaction of $Cl_2TiCp_2$ with 1,2-bis(lithiomethyl)cyclohexane gave, after carbonylation, a 20% yield of the expected 2-perhydroindanone (equation 33).[32]

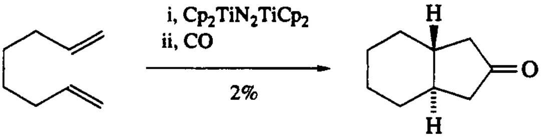

(32)

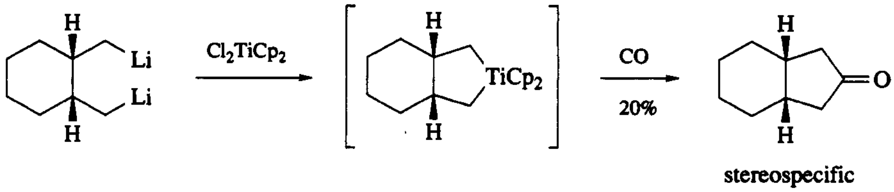

(33)

## 9.5.5 FORMATION AND REACTIONS OF THREE-MEMBERED AND FIVE-MEMBERED ZIRCONACYCLES

It has so far been assumed that treatment of $Cl_2ZrCp$ with reducing agents, such as Mg and $HgCl_2$ or $Bu^nLi$, produces species that effectively act as $ZrCp_2$, *i.e.* '$ZrCp_2$'. Another key assumption has been that '$ZrCp_2$' interacts with alkynes and alkenes to produce zirconacyclopropenes and zirconacyclopropanes respectively, which then undergo cyclic carbometallation to afford five-membered zirconacycles. As such, these were only working hypotheses without sufficient experimental support. A few important aspects to be clarified are as follows. First, can three-membered zirconacycles actually be formed? Secondly, if they are indeed formed, how are they formed? Thirdly, can they serve as intermediates for five-membered zirconacycles? And how? Because of the current synthetic significance of organozirconium compounds in this area, this section deals mainly with zirconacycles.

### 9.5.5.1 Formation of Zirconacyclopropenes and Zirconacyclopropanes

At the outset of the subsection, it should be emphasized that distinction between metallacyclopropenes and $\eta^2$-alkyne–metal complexes or that between metallacyclopropanes and $\eta^2$-alkene–metal complexes is largely a matter of semantics or convenience. Most or perhaps all of these species should probably be viewed as hybrids of three-membered metallacycles and $\pi$-complexes.

Prior to the development of the cyclization reactions discussed earlier, some three-membered metallacycles containing Group IV metals were known. In 1968, the thermal reaction of $Ph_2TiCp_2$ with $PhC{\equiv}CPh$ producing (**36**; equation 34) was reported.[33] One of the presumed intermediates was (**37**). No experimental support was presented, and the mechanistic interpretation was probably erroneous in the light of what is now known. The same compound was later prepared by another method, and benzyne–titanocene complex (**38**; equation 35) was suggested as an intermediate.[34]

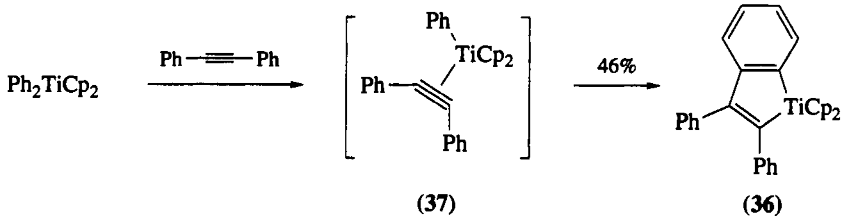
Ph₂TiCp₂
Ph—≡—Ph
Ph
TiCp₂
Ph
Ph
46%
Ph
TiCp₂
Ph
(37)
(36)

(34)

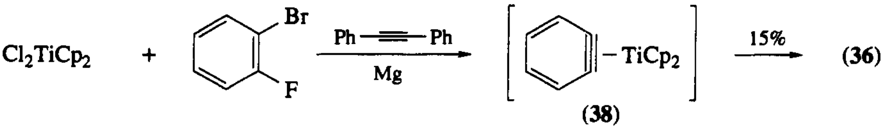
Cl₂TiCp₂
+
Br
F
Ph—≡—Ph
Mg
–TiCp₂
(38)
15%
(36)

(35)

In an analogous manner, either thermolysis at 70 °C or photolysis of $Ph_2ZrCp_2$ was thought to generate benzyne–zirconocene (**39**; equation 36), but no direct evidence was provided.[35]

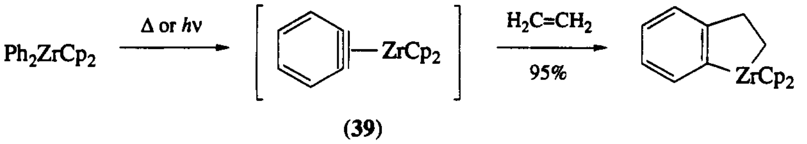
Ph₂ZrCp₂
Δ or hν
—ZrCp₂
(39)
H₂C=CH₂
95%
ZrCp₂

(36)

Probably the first metallacyclopropene containing a Group IV metal that has been isolated and characterized is a diphenylacetylene–titanocene complex (**40**) prepared by the reaction of $(OC)_2TiCp_2$ with diphenylacetylene, as in equation (37).[36] Its structure was established primarily by X-ray crystallography.

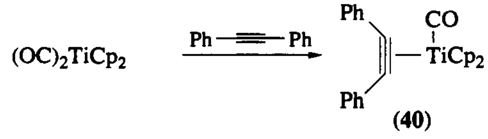
(OC)₂TiCp₂
Ph—≡—Ph
Ph
CO
—TiCp₂
Ph
(40)

(37)

In 1983, $(\eta^5\text{-}C_5Me_5)_2Ti(\eta^2\text{-}CH_2{=}CH_2)$ (**41**; equation 38) was prepared as the first example of metallacyclopropanes containing a Group IV metal, and its structure was established by X-ray analysis and other spectroscopic means.[37]

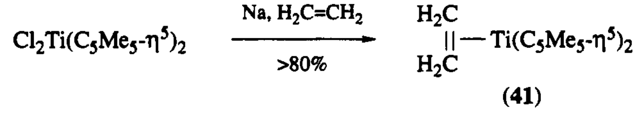
Cl₂Ti(C₅Me₅-η⁵)₂
Na, H₂C=CH₂
>80%
H₂C
H₂C
—Ti(C₅Me₅-η⁵)₂
(41)

$$Cl_2Ti(C_5Me_5\text{-}\eta^5)_2 \xrightarrow[>80\%]{Na,\ H_2C=CH_2} \begin{matrix} H_2C \\ \| \\ H_2C \end{matrix} \!\!-Ti(C_5Me_5\text{-}\eta^5)_2 \quad (38)$$

Somewhat surprisingly, no report on the preparation of zirconacyclopropenes or zirconacyclopropanes as discrete, characterizable species and/or their full spectroscopic characterization was available until a few years ago. Probably, stilbene–zirconocene (**42**; equation 39) is the first example of such compounds spectroscopically characterized.[14]

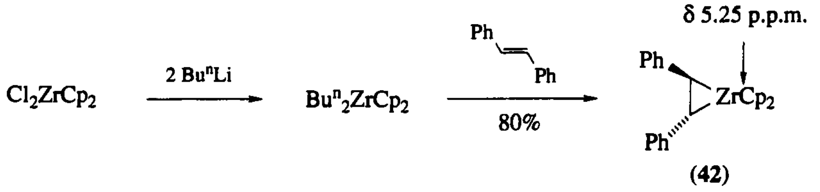
Cl₂ZrCp₂
2 BuⁿLi
Buⁿ₂ZrCp₂
Ph
Ph
80%
δ 5.25 p.p.m.
Ph
ZrCp₂
Ph
(42)

(39)

The compound (**42**) gives, on treatment with 3 M HCl, bibenzyl and stilbene in 79 and 7% yields, respectively, and reacts with $PMe_3$ to give a 1:1 complex (**43**; equation 40).[38]

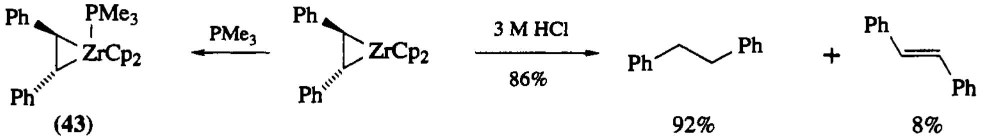

(**43**)

(40)

Since 1986, the following zirconacyclopropenes as well as one zirconacyclopropane, *i.e.* (**43**),[38] have been characterized by X-ray and other spectroscopic means. The compound (**44**)[39] represents a benzyne–zirconocene complex, and (**45**)[40] is an example of a cycloalkyne–zirconocene complex. Although these compounds are interesting and significant in their own right, they do not provide support for the formation of zirconacyclopropenes from alkynes and '$ZrCp_2$', because the alkyne components are generated *in situ* and have probably never been free.

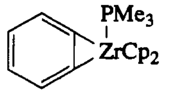

(**44**)

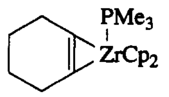

(**45**)

The first isolated and fully characterized zirconacyclopropene prepared by the reaction of free alkyne and '$ZrCp_2$' is (**46**; equation 41; Figure 1).[41] Independently and simultaneously, another X-ray structure of an acyclic alkyne–zirconocene (**47**) prepared as shown in equation (42) was also published.[42] The first X-ray structure of a zirconacyclopropane derivative is shown in Figure 2.[38]

It has now been established that both zirconacyclopropenes and zirconacyclopropanes can be prepared as discrete and fully characterizable species. More relevant to the present discussion is that these species can be generated by the reaction of free alkynes or alkenes with '$ZrCp_2$', as shown in equations (39) and (41). Another useful piece of information is that the formation of (**46**) from diphenylacetylene according to equation (41) is about 150 times as fast as that of (**43**) from (*E*)-stilbene under the same conditions, indicating that, in comparable situations, alkynes are far more reactive than alkenes towards '$ZrCp_2$'. Little definitive information is currently available on the formation of related three-membered hafnacycles.

The second question to be answered is how three-membered zirconacycles are formed. This will no doubt depend on the starting compounds, the reagents and the reaction conditions. A reasonably clear mechanistic scheme has emerged for the reactions of '$ZrCp_2$' derived from $Cl_2ZrCp_2$ and $Bu^nLi$.[14,15] Treatment of $Cl_2ZrCp_2$ with 2 equiv. of $Bu^nLi$ at −78 °C gives $Bu^n{}_2ZrCp_2$ in nearly quantitative yield. Although the compound is too unstable to fully identify as such, it has been characterized by NMR. Its treatment with 2 equiv. of iodine gives $Bu^nI$ in excellent yield. Furthermore, the corresponding reaction of $Cl_2HfCp_2$ gives $Bu^n{}_2HfCp_2$, which is stable at 25 °C and readily characterizable. Treatment of $Bu^n{}_2ZrCp_2$ with 2 equiv. of $PMe_3$ gives a relatively stable complex, which was initially and erroneously identified as $Cp_2Zr(PMe_3)_2$ on the basis of a triplet-like $^1H$ NMR signal for the Cp group.[14] The original simplistic view was as shown in equation (43).

An alternate structure (**48**) was suggested.[42] Reexamination has established that it is a *ca.* 90:10 mixture of (**49**) and (**48**).[15] It now is likely that '$ZrCp_2$' generated *in situ* from $Cl_2ZrCp_2$ and $2Bu^nLi$ is (**50**). It is also likely that (**50**) is formed directly from $Bu^n{}_2ZrCp_2$, as shown in equation (44).

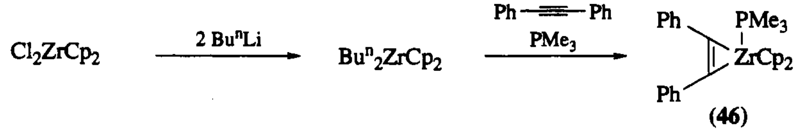

(**46**)

(41)

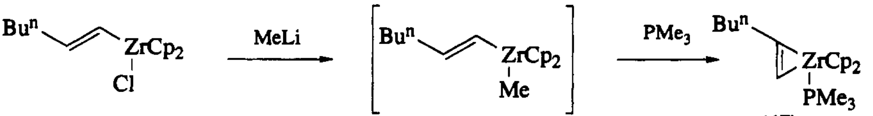

(**47**)

(42)

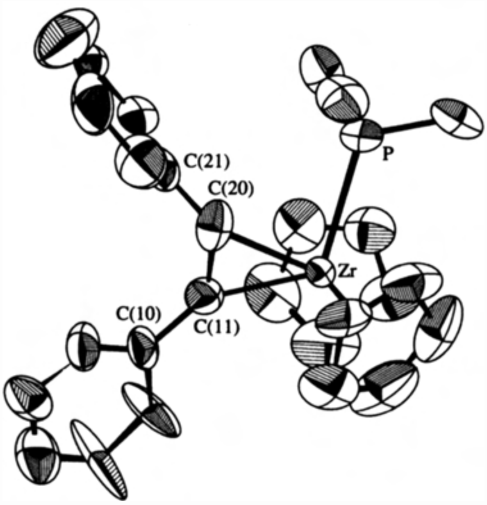

**Figure 1** Molecular structure and atom labeling scheme for $Cp_2Zr(PhC{\equiv}CPh)(PMe_3)$ (**46**). Selected bond lengths and angles are as follows: Zr—C(10) = 2.20(4) (Å); Zr—C(20) = 2.25(4); Zr—P = 2.70(1); C(10)—C(20) = 1.36(6); C(10)—Zr—C(20) = 36(1)°; Zr—C(10)—C(20) = 74(2); Zr—C(20)—C(10) = 70(2); C(11)—C(10)—C(20) = 134(4); C(10)—C(20)—C(21) = 133(4)

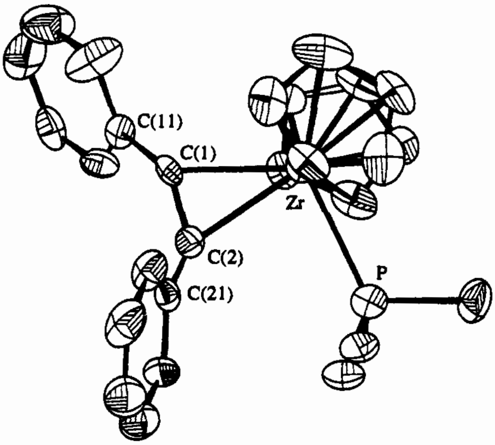

**Figure 2** Molecular structure and atom labeling scheme for $Cp_2Zr(PhCH{=}CHPh)(PMe_3)$(**43**). Selected bond lengths (Å) and angles are as follows: Zr—P = 2.715(5); Zr—Cl = 2.361(15); Zr—C(2) = 2.426(15); C(1)—C(2) = 1.376(21); C(1)—C(11) = 1.509(22); C(2)—C(21) = 1.495(22); C(1)—Zr—C(2) = 33.4(5)°; C(11)—C(1)—C(2) = 127.2(14); C(21)—C(2)—C(1) = 122.8(14); P—Zr—C(2) = 75.9(9); Zr—C(2)—C(1) = 70.7(9); P—Zr—C(1) = 114.5(4); P—Zr—C(2) = 81.3(4); Zr—C(1)—C(11) = 123.5(1); Zr—C(2)—C(21) = 125.2(10)

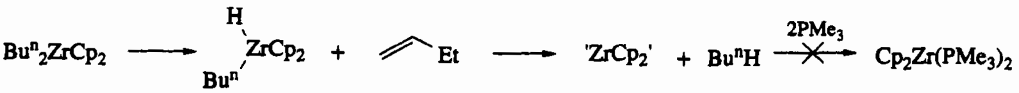

$$Bu^n{}_2ZrCp_2 \longrightarrow H(Bu^n)ZrCp_2 + \text{CH}_2{=}\text{CHEt} \longrightarrow \text{'}ZrCp_2\text{'} + Bu^nH \xrightarrow[\times]{2PMe_3} Cp_2Zr(PMe_3)_2 \qquad (43)$$

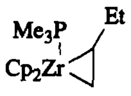

**(48)**

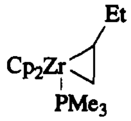

**(49)**

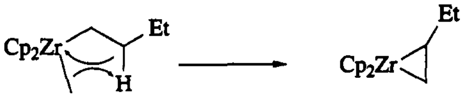

**(50)**

(44)

Further investigation of alkene ligand exchange processes has revealed a novel semiassociative–semidissociative mechanism for alkene ligand exchange shown in Scheme 4. The salient feature of the mechanism is that, in an associative process, an alkene ligand partially dissociates to generate a dipolar species in which C and Zr are positively and negatively polarized, respectively.[43]

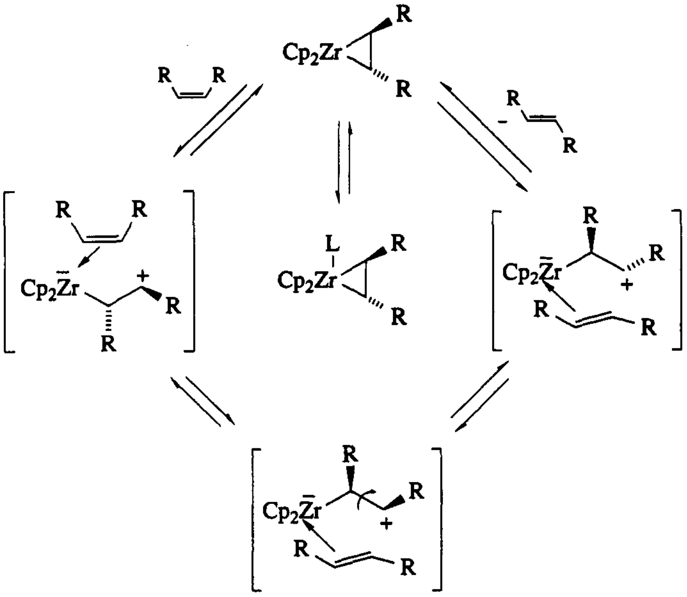

**Scheme 4**

The conclusions summarized in Scheme 4 are based on the following. First, the reaction of $Bu^n{}_2ZrCp_2$ with either (*E*)- or (*Z*)-stilbene gives exclusively the (*E*)-stilbene–zirconocene complex (**42**). (*Z*)-Stilbene is isomerized to the (*E*)-isomer under the catalytic influence of '$ZrCp_2$'. Secondly, whereas the complexation and/or isomerization processes are retarded by electron-donating phosphines, an electron-donating substituent, *e.g.* Me, in the *para* position of stilbene accelerates these processes, the ρ value being *ca.* –2.9. Thirdly, the proposed mechanism is in accord with simple molecular orbital considerations. Although yet to be further clarified, the reaction of an alkyne with (**50**), a formal $d^0$, 16-electron species, probably proceeds in a similar manner (equation 45).

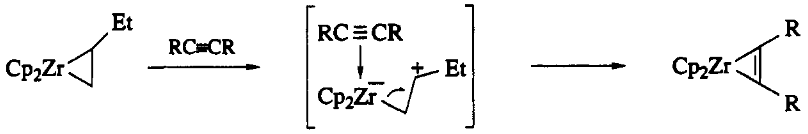

(45)

### 9.5.5.2 Formation of Zirconacyclopentadienes, Zirconacyclopentenes and Zirconacyclopentanes *via* Three-membered Zirconacycles

Earlier studies of the preparation of five-membered zirconacycles either do not discuss the intermediacy of three-membered zirconacycles or merely suggest their intermediacy. Such studies include those on the formation of zirconacyclopentadienes,[9,10,14,26,27] zirconacyclopentenes,[11,16,20,44–46] and zirconacyclopentanes.[31,35]

The recent availability of well-defined zirconacyclopropenes[39–42] and zirconacyclopropanes[14,15,38,43] has permitted investigation of their conversion into five-membered zirconacycles. In general, zirconacyclopropenes readily undergo coupling with alkynes, alkenes, nitriles, aldehydes and ketones to produce the corresponding five-membered zirconacycles. Some representative results involving zirconacyclopropenes corresponding to acyclic alkynes,[41,42] cyclic alkynes[40] and benzynes[39] are shown in Schemes 5–9. These results show some remarkable pair selectivity and regioselectivity.

The precise mechanisms of the conversion of zirconacyclopropenes into five-membered zirconacycles are still unclear. For the reactions of alkynes and alkenes, a concerted carbometallation mechanism earlier proposed[1] appears to be plausible, but remains only a reasonable working hypothesis. One useful piece of information is that the reaction of an *in situ* generated benzyne–zirconocene complex with stilbene is stereospecific, as shown in equation (46),[45] suggesting that, in contrast to the formation of some three-membered zirconacycles, this and other related reactions may be concerted.

With the information available at present, the following mechanistic scheme may be proposed for the bicyclization of (**1a**) with ‘ZrCp$_2$’ generated *in situ* by treating Cl$_2$ZrCp$_2$ with Bu$^n$Li. The reaction of Cl$_2$ZrCp$_2$ with 2 equiv. of Bu$^n$Li initially produces at –78 °C Bu$^n{}_2$ZrCp$_2$ which, in the presence of (**1a**), decomposes to generate 1-butene–zirconocene (**50**) as ‘ZrCp$_2$’. Interaction of (**50**) with (**1a**) initially produces, most likely *via* a semiassociative–semidissociative mechanism (Scheme 4), an intermediate repre-

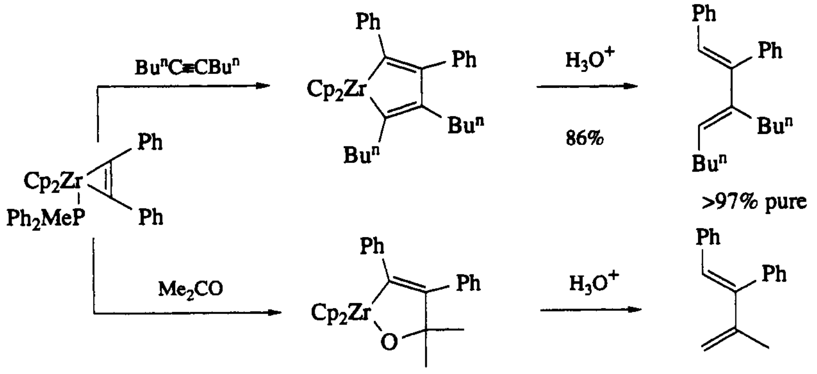

**Scheme 5**

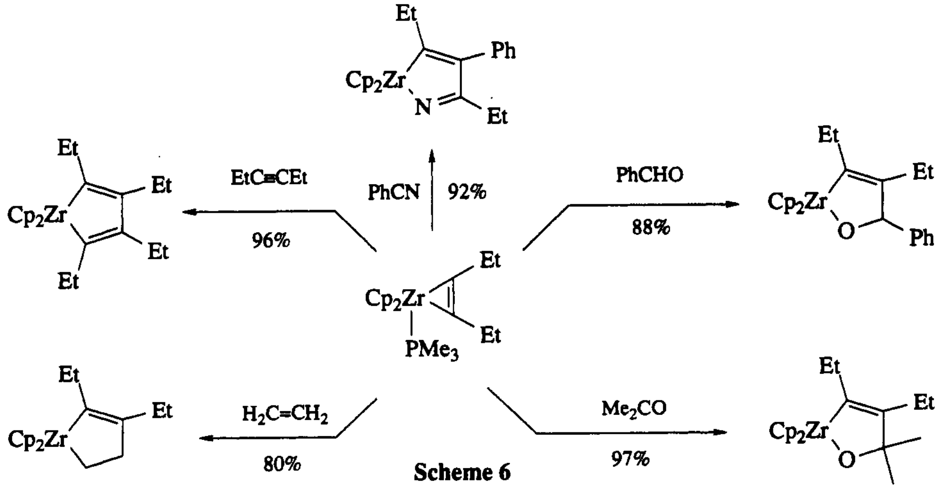

**Scheme 6**

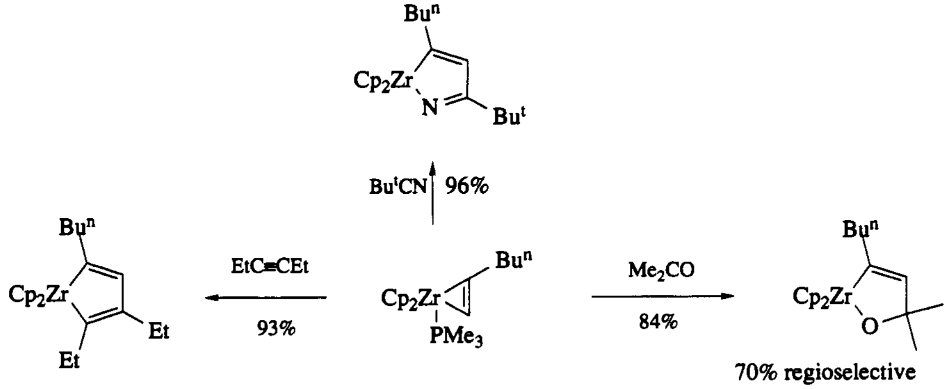
Bu^n
Cp2Zr
N
Bu^t
Bu^tCN
96%
EtC≡CEt
93%
Me2CO
84%
PMe3
Et
O
70% regioselective

**Scheme 7**

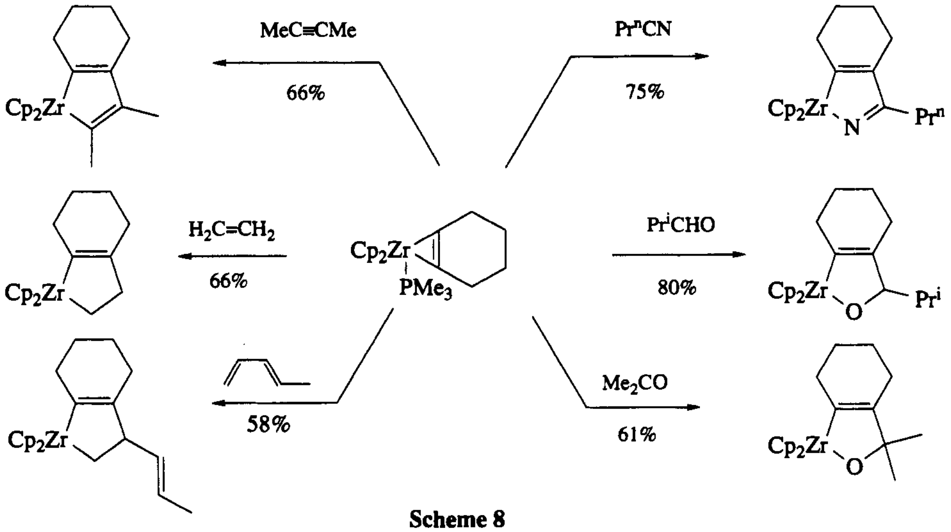
MeC≡CMe
66%
Pr^nCN
75%
Cp2Zr
N
Pr^n
H2C=CH2
66%
PMe3
Pr^iCHO
80%
O
Pr^i
58%
Me2CO
61%

**Scheme 8**

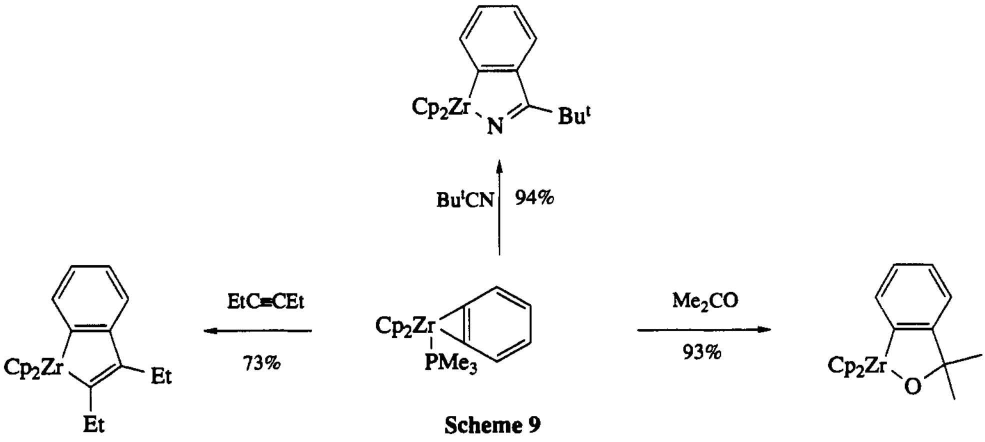
Cp2Zr
N
Bu^t
Bu^tCN
94%
EtC≡CEt
73%
Me2CO
93%
PMe3
Et
O

**Scheme 9**

sented by (**51**), which then undergoes concerted intramolecular carbozirconation to give (**2a**), as depicted in equation (47).

Formation of (**51**) rather than the zirconacyclopropane derivative (**52**) is reasonable in the light of the considerably higher reactivity of alkynes relative to alkenes. Furthermore, the following intriguing results not only reveal some remarkable reactivity of five-membered zirconacycles but also support the intermediacy of (**51**) rather than (**52**; equation 48).[15]

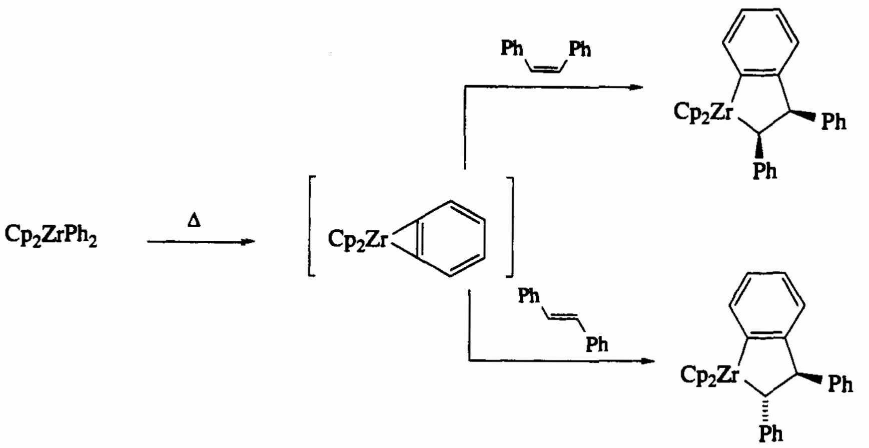
Cp2ZrPh2
Δ
Cp2Zr
Ph Ph
Cp2Zr
Ph
Ph
Ph
Ph
Cp2Zr
Ph
Ph

(46)

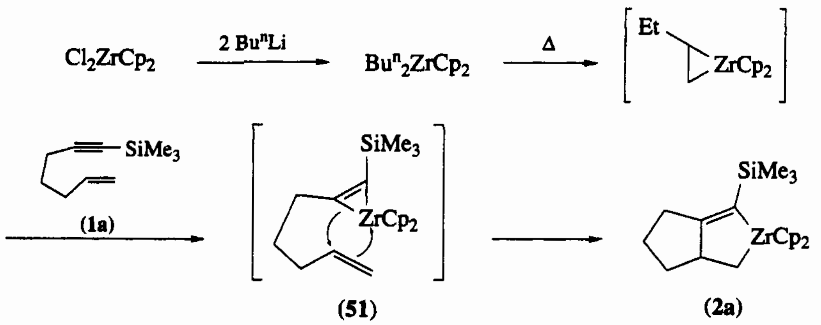
Cl2ZrCp2
2 BunLi
Bun2ZrCp2
Δ
Et
ZrCp2
SiMe3
(1a)
SiMe3
ZrCp2
(51)
SiMe3
ZrCp2
(2a)

(47)

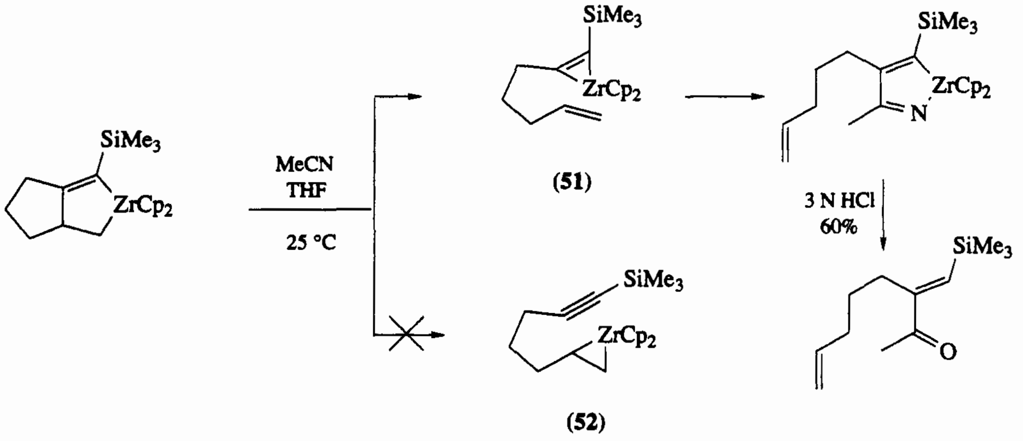
SiMe3
ZrCp2
MeCN
THF
25 °C
SiMe3
ZrCp2
(51)
SiMe3
ZrCp2
N
3 N HCl
60%
SiMe3
O
SiMe3
ZrCp2
(52)

(48)

The reactions of zirconacyclopropanes with alkenes and alkynes are somewhat more capricious and unpredictable than those of zirconacyclopropenes. Zirconacyclopropanes display both σ- and π-reactivities even toward compounds of the same class. For example, the reaction of 1-butene–zirconocene (**50**) with stilbene gives stilbene–zirconocene (**42**) *via* alkene displacement (π-reactivity), as shown in equation (39). On the other hand, the corresponding reaction with styrene gives exclusively a zirconacyclopentane derivative (**53**), displaying a high pair selectivity and a high and intriguing regioselectivity, as shown in Scheme 10.[47] Protonolysis, deuterolysis and iodinolysis cleanly give the expected products in good yields, and carbonylation provides (**54**) in 70% yield, after oxidation of the corresponding cyclopentanol formed as a minor by-product of (**54**).[47] The isolated product (**54**) is a 5:1 mixture of two possible diastereomers. Since (**54**) is readily epimerizable, this ratio may not represent the stereoselectivity of the cyclization step. Regardless of the precise stereochemistry of the reaction, the pair-selective and regioselective alkyl–alkene coupling and carbonylation reactions can provide potentially attractive synthetic tools.

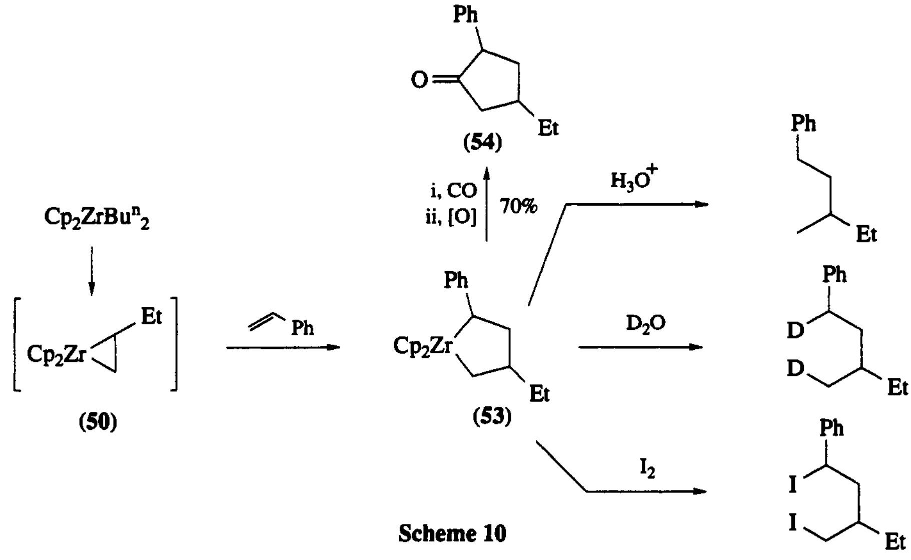

Ph
O
(54)
Et
i, CO
ii, [O]
70%
$H_3O^+$
Ph
Et
$Cp_2ZrBu^n_2$
Ph
Et
$Cp_2Zr$
Ph
$Cp_2Zr$
$D_2O$
D
D
Et
(50)
Et
(53)
Ph
$I_2$
I
I
Et

**Scheme 10**

Interestingly, the reaction of $Cp_2ZrBu^n_2$ with 1-butene cleanly and selectively gives (**55**).[47] At present, the difference in regiochemistry between Scheme 10 and equation (49) cannot readily be explained. Presumably, placement of alkyl substituents in the 3- and 4-positions of the zirconacyclopentane ring is favored by steric factors, whereas additional electronic factors, such as formation of the benzyl cation rather than alkyl cations, may favor placement of aryl substituents in the 2- or 5-position. This point, however, needs to be further investigated. Unfortunately, the reaction of (**50**) with other terminal alkenes containing alkyl substituents is not pair selective, giving essentially statistical mixtures of three cyclic products, even though the reaction is highly regioselective and apparently stereoselective, favoring the *trans* relationship between the two substituents (equation 50).[47] These results suggest that the formation of zirconacyclopentanes from zirconacyclopropanes is readily reversible (equation 51), as in the cases of zirconacyclopentenes shown in equation (48).

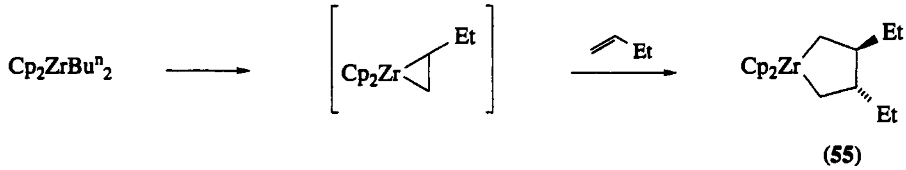

$Cp_2ZrBu^n_2$
Et
$Cp_2Zr$
Et
$Cp_2Zr$
Et
Et
(55)

(49)

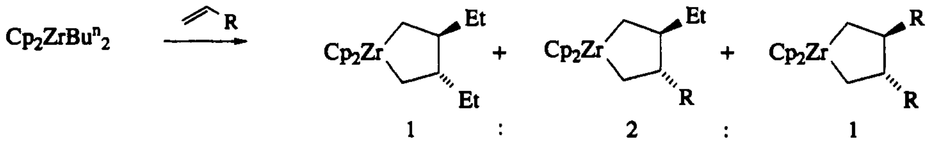

$Cp_2ZrBu^n_2$
R
$Cp_2Zr$
Et
Et
+
$Cp_2Zr$
Et
R
+
$Cp_2Zr$
R
R
1 : 2 : 1

(50)

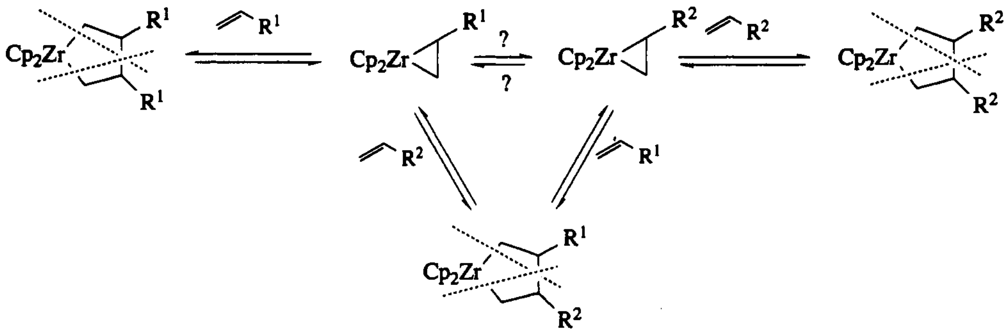

$Cp_2Zr$
$R^1$
$R^1$
$R^1$
$Cp_2Zr$
$R^1$
?
?
$Cp_2Zr$
$R^2$
$R^2$
$Cp_2Zr$
$R^2$
$R^2$
$R^2$
$R^1$
$Cp_2Zr$
$R^1$
$R^2$

(51)

The reaction of $Cp_2ZrBu^n_2$ with conjugated dienes produces previously reported zirconacycles[28–30] of the type represented by (**57**; equation 52). A wide variety of substituents can, in principle, be readily incorporated in $Cp_2ZrR_2$, and a wide variety of conjugated dienes appear to participate in the reaction. Consequently, this provides a convenient alternative to the previously developed procedures.[28–30]

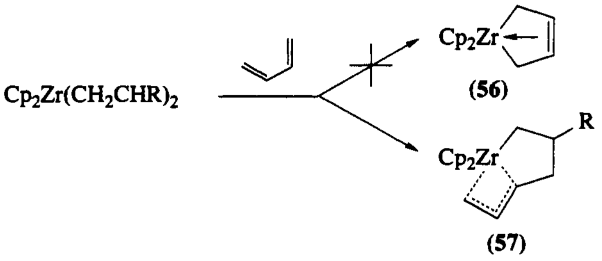

(52)

One application of the reaction shown in equation (52) is the conversion of cyclic, conjugated dienes into exocyclic alkenes. Although the stereochemistry of the reaction needs to be established, the cyclization–protonolysis sequence may provide a convenient route to stereodefined exocyclic alkenes, as suggested by the examples given in equations (53) and (54).[48] These reactions are all at least 90–95% regioselective, as judged by $^{13}C$ NMR.

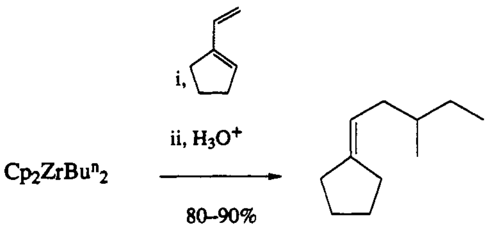

(53)

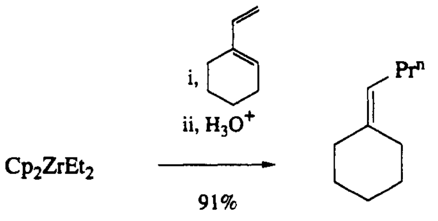

(54)

## 9.5.6 CONCLUSION

The results presented above indicate that the Zr-promoted bicyclization reactions of enynes and diynes constitute novel and attractive synthetic methods. The corresponding reaction of dienes remains to be developed. Somewhat unexpectedly, the reactions of monoalkynes and monoalkenes can, in many cases, be highly pair selective and regioselective. Many aspects of these reactions also need to be further developed. Besides being attractive from the viewpoint of organic synthesis, the chemistry of '$ZrCp_2$' provides a number of novel structural and mechanistic features that broaden the horizon of organometallic chemistry.

Many unaccomplished and yet highly necessary tasks remain. The scope and limitations as well as mechanistic details of most of the reactions discussed above need to be further delineated. More extensive and challenging applications of the newly developed reactions to the synthesis of natural products and other complex organic molecules must also be carried out. In addition, other less routine but highly desirable aspects should also be explored. These include asymmetric cyclization and catalytic procedures for cyclization–carbonylation.

In general, the corresponding organotitanium reactions appear to be more prone to steric hindrance and other strain factors. In principle, this may be overcome by various approaches, such as stabilization by suitable ligands. Nonetheless, it appears at present that, on balance, advantages of using the Ti reactions may be observed only in a limited number of cases. On the other hand, organohafnium compounds appear to be generally more stable or less reactive than the corresponding organozirconium compounds, even though they appear to participate in most of the corresponding reactions. This and the higher cost of Hf relative to that of Zr makes Hf less attractive than Zr. However, the greater thermal stability of organohafnium compounds may prove to be advantageous in some cases where the instability of organozirconium compounds may be the cause for difficulties.

As is clear from the introductory discussion, most, if not all, of the *d*-block transition metals are expected to participate in reactions that are related to those discussed here. In addition to the Co-based methodology[8] mentioned earlier, some related reactions of Pd and Ni[49–56] are known. Also related are the cyclization reactions of metal–carbene complexes containing Cr, Mo, W and other transition metals with alkynes and alkenes[57] and a recently reported Nb- or Ta-promoted diyne–alkyne cyclization reaction,[58] which appears to be closely related to a number of previously developed alkyne cyclotrimerization reactions, such as those catalyzed by Co.[59] Investigations of reactions involving other transition metals may prove to be important especially from the viewpoint of developing asymmetric and catalytic procedures.

The author wishes to thank his coworkers whose names appear in the references section, especially S. J. Holmes, F. E. Cederbaum, D. S. Swanson, T. Takahashi, and C. J. Rousset.

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# 9.6

# Metal-catalyzed Cycloaddition of Small Ring Compounds

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## 9.6.1 INTRODUCTION

Highly strained carbon–carbon double bonds and even carbon–carbon σ-bonds of small ring compounds interact readily with transition metal complexes. Such perturbation activates them to enter into intra- and inter-molecular cycloadditions with cleavage of carbon–carbon σ-bonds.[1]

## 9.6.2 TRANSITION METAL CATALYZED REACTIONS OF BICYCLO[1.1.0]BUTANES: SYNTHESIS OF ALLYLCYCLOPROPANES

Bicyclo[1.1.0]butanes (**1**; equation 1),[2] the smallest bicyclic hydrocarbons, are highly strained but stable at ambient temperature. Under the influence of a catalytic amount of a nickel(0) complex, however, they undergo cleavage of the central bond and one of the four peripheral bonds and enter into cycloaddition reactions with electron deficient alkenes to afford allylcyclopropane derivatives. Reaction of bicyclo[1.1.0]butane (**1a**) and methyl acrylate catalyzed by [Ni(AN)$_2$] (AN = acrylonitrile) affords methyl 2-allylcyclopropanecarboxylates (**2a**) in quantitative yield (*cis*:*trans* = 65:35).[3] Similarly, allylcyclopropanes are obtained in good yields by use of (**1b**), 1-methoxycarbonylbicyclo[1.1.0]butane, 1-cyanobicyclo[1.1.0]butane, *etc.*[3a] The reactions of (**1a**) with 2,3-*cis*-dideuterated methyl acrylate and with dimethyl fumarate and dimethyl maleate indicate that the overall process proceeds with excellent stereospecificity and with retention of configuration in the alkenic reaction partner (equation 2).

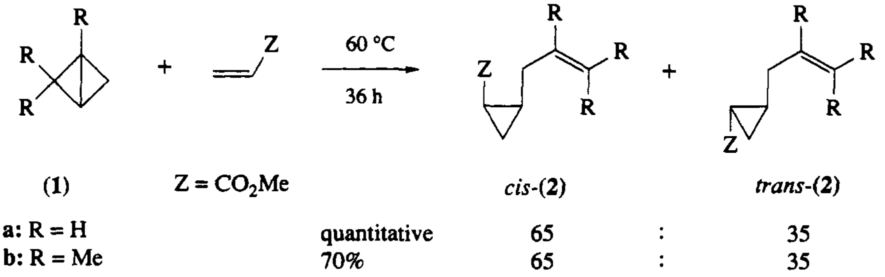

(1)

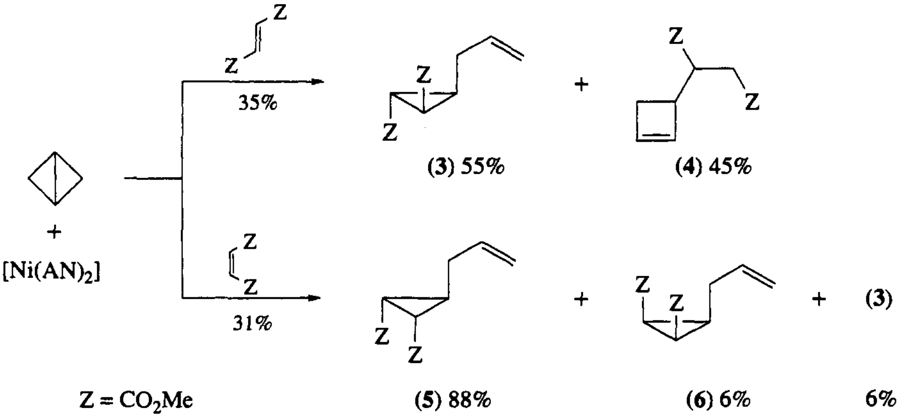

(2)

This coupling reaction can be formally viewed as a metal-assisted intramolecular retrocarbene addition of bicyclobutanes, followed by intermolecular cycloaddition of the resulting allylcarbene–nickel complexes to alkenes.

Methoxycarbonylcyclopropane derivatives are also obtained in 38% yield (*cis*:*trans* = 30:8) by the reaction of 1-methylbicyclo[1.1.0]butane with methyl acrylate in the presence of a catalytic amount of [{RhCl(norbornadiene)}$_2$], in addition to 2-methyl-1,3-butadiene (37%) and 2,7-dimethyl-1,4,7-octatriene (25%).[4]

## 9.6.3 TRANSITION METAL CATALYZED REACTIONS OF BICYCLO[2.1.0]PENTANES: SYNTHESIS OF BICYCLO[2.2.1]HEPTANES

Bicyclo[2.1.0]pentane (**7**; equation 3) readily undergoes a cycloaddition across carbon–carbon double bonds in the presence of nickel(0) complexes.[5] The mode is formally analyzed as a thermally forbidden [2 + 2] process[6] and is in striking contrast to that of the lower homolog, bicyclo[1.1.0]butane, which suffers cleavage of two σ-bonds and affords formal allylcarbene addition products.[7] When a solution of bicyclo[2.1.0]pentane (**7**) and [Ni(AN)$_2$] in excess methyl acrylate is heated at 40 °C for 36 h under a nitrogen atmosphere, the stereoisomeric cycloadducts *exo*- and *endo*-2-methoxycarbonylbicyclo[2.2.1]heptane (**8a**) and (**9a**) (50:50 ratio) are produced in 66% combined yield, in addition to the monocyclic product methyl 3-(cyclopent-2-enyl)propionate (**10a**; 22%). Reaction of (**7**) with acrylonitrile affords the corresponding adducts (**8b**), (**9b**) and (**10b**).

In contrast to the purely thermal cycloaddition which occurs in a nonstereospecific manner with respect to alkenes in low yield, nickel(0) catalysis results in a highly stereospecific cycloaddition, as demonstrated by the reactions between (**11**; equation 4) and dimethyl fumarate or dimethyl maleate.

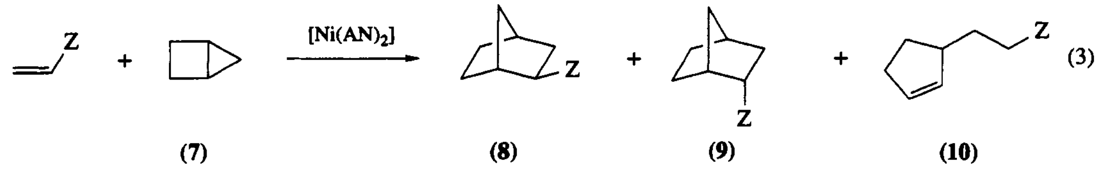

| | | | | |
|---|---|---|---|---|
| **a**: Z = $CO_2Me$ | 40 °C/36 h | 66% | 50:50 | 22% |
| **b**: Z = CN | 70 °C/36 h | 75% | 62:38 | 16% |

Interestingly, the purely thermal cycloaddition occurs with inversion of the configurations at C-1 and C-4 of (**11**), while the nickel(0)-catalyzed reaction proceeds with retention of configuration at these carbons.

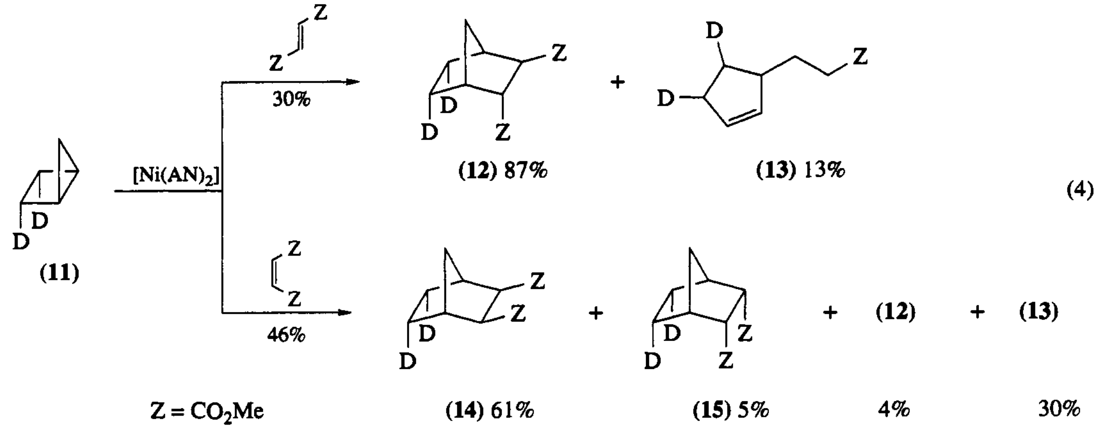

## 9.6.4 TRANSITION METAL CATALYZED REACTIONS OF OTHER STRAINED POLYCYCLIC HYDROCARBONS

Quadricyclane (**16**; equation 5) reacts with electron deficient alkenes in the presence of [Ni(acrylonitrile)$_2$] to afford the cycloadducts (**17a**) and (**17b**) in moderate yields, along with some norbornadiene.[8] This catalytic cycloaddition proceeds in a highly stereospecific manner with retention of alkene configuration. The same compounds are obtained using norbornadiene in place of (**16**) under similar catalytic conditions. In the absence of transition metals, though under rather forcing conditions, quadricyclane (**16**) reacts with electron deficient alkenes in a concerted [2 + 2 + 2] manner to give tricyclo[4.2.1.0$^{2,5}$]non-7-enes.[9]

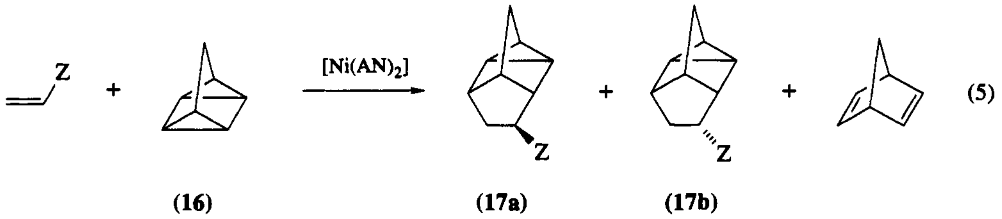

| | | | |
|---|---|---|---|
| Z = CN | 20 °C/48 h | 50% 49:51 | 30% |
| $CO_2Me$ | | 58% 40:60 | – |

*exo*-Tricyclo[3.2.1.0$^{2,4}$]oct-6-ene (**18**; equation 6) as either neat liquid or solution in $CDCl_3$, is converted quantitatively into tetracyclo[3.3.0.0$^{2,8}$.0$^{4,6}$]octane (**19**) in the presence of 10 mol % of [{$RhCl(CO)_2$}$_2$] at room temperature.[10] This reaction is also promoted by [$RhCl(PPh_3)_3$] at elevated temperature. In the latter reaction, a metallacyclic intermediate has been proposed.[11] Failure of the *endo* isomer (**20**) to undergo a similar reaction shows that the *exo* arrangement of the fused cyclopropane ring in (**18**) is prerequisite for the occurrence of the valence isomerization. Tetracyclo[4.3.0.0$^{2,4}$.0$^{3,7}$]non-8-ene (**21**), a compound closely related to (**18**), is not converted to (**22**) in the presence of [{$RhCl(CO)_2$}$_2$] at room temperature for two days or with [$RhCl(PPh_3)_3$] at 170 °C for three days.[12]

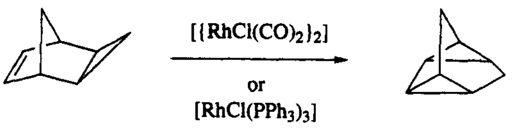

**(18)** **(19)** (6)

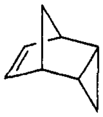

**(20)**

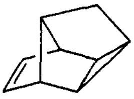

**(21)**

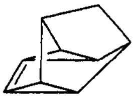

**(22)**

Rhodium(I) complexes are efficient catalysts for the valence isomerizations of cubane (**23a**; equation 7) and its derivatives to the corresponding *syn*-tricyclo[4.2.0.0$^{2,5}$]octa-3,7-dienes. When a stoichiometric amount of [{RhCl(CO)$_2$}$_2$] is added to a chloroform solution of cubane, the organorhodium compound (**24**) is obtained in about 90% yield. Treatment of (**24**) with a stoichiometric amount of triphenylphosphine gives, in about 90% yield, the polycyclic ketone (**25**) together with a small amount (5–10%) of cyclooctatetraene.[13] A similar reaction is also reported for the methoxycarbonyl derivative (**23b**).

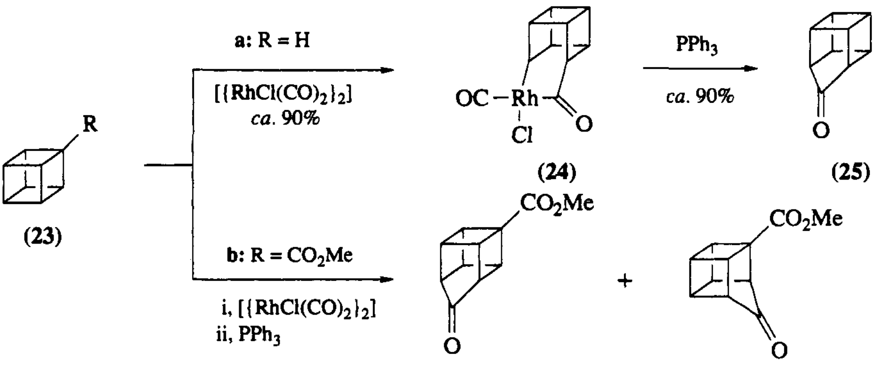

**(23)** **(24)** **(25)** (7)

## 9.6.5 TRANSITION METAL CATALYZED REACTIONS OF METHYLENECYCLOPROPANES: SYNTHESIS OF METHYLENECYCLOPENTANES

Although methylenecyclopropanes[14] are highly strained molecules, they are stable at ambient temperature. At elevated temperature they undergo [2 + 2]-type reaction with alkenes[15] such as butadiene and maleic anhydride and [3 + 2] reaction with tetracyanoethylene.[16] The latter reaction involves a trimethylenemethane diradical intermediate. For catalytic transformations of methylenecyclopropanes, nickel(0) and palladium(0) complexes have been used successfully.

In the presence of [Ni(COD)$_2$], methylenecyclopropane (**26**; equation 8) cyclodimerizes at temperatures as low as –15 °C to give (**27**), (**28**) and small amounts of higher oligomers.[17] When [Ni(COD)$_2$] is used as a catalyst with electron deficient alkenes (*e.g.* dialkyl fumarate or maleic anhydride) as additives, cyclopentane derivative (**27**) is obtained as a major product (60–65% yield), along with (**28**) (1–4%), 1,3-dimethylenecyclohexane (1–12%) and oligomers (<25%).[18] Reaction of (**26**) using nickel(0) compounds, modified by trialkylphosphines, as catalysts gives a complex mixture which consists of open chain and cyclic $C_{12}H_{18}$ hydrocarbons in up to 95% combined yield.[19] Palladium(0) complexes prepared *in situ* from triisopropylphosphine and [Pd(DBA)$_2$], or from triisopropylphosphine, diethylaluminum ethoxide and [Pd(acac)$_2$], catalyze the dimerization of (**26**) to (**27**) in high yield and with high selectivity.[20]

Synthetically useful [3 + 2] cycloadditions of (**26**) and alkenes to give methylenecyclopentanes have been attained in the presence of a catalytic amount of nickel(0) or palladium(0) complexes.

[Pd(DBA)$_2$]/PPr$^i_3$ (equation 9) catalyzes the cycloaddition of (**26**) with strained alkenes to give the corresponding methylenecyclopentanes.[20] The codimer, methylenecyclopentane, is also obtained in 20% yield from the reaction of (**26**) with ethylene, along with (**27**) in 64% yield, in the presence of [Pd(acac)$_2$]/PPr$^i_3$/Et$_2$AlOEt.

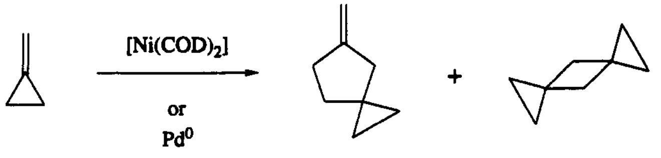
[Ni(COD)$_2$]
or
Pd$^0$
+

**(26)** **(27)** **(28)**

(8)

| | |
|---|---|
| [Ni(COD)$_2$] | 50%; **(27)**:**(28)** = 80:20 |
| [Ni(COD)$_2$]/dibutyl fumarate | 68%; **(27)**:**(28)** = 94:6 |
| [Ni(COD)$_2$]/maleic anhydride | 67%; **(27)**:**(28)** = 98:2 |
| [Pd(DBA)$_2$]/PPr$^i_3$ | 100%; selectivity of **(27)** = 91% |
| [Pd(acac)$_2$]/PPr$^i_3$/Et$_2$AlOEt | 100%; selectivity of **(27)** = 94% |
| [Pd(PPh$_3$)$_4$] | 4%; selectivity of **(27)** =100% |

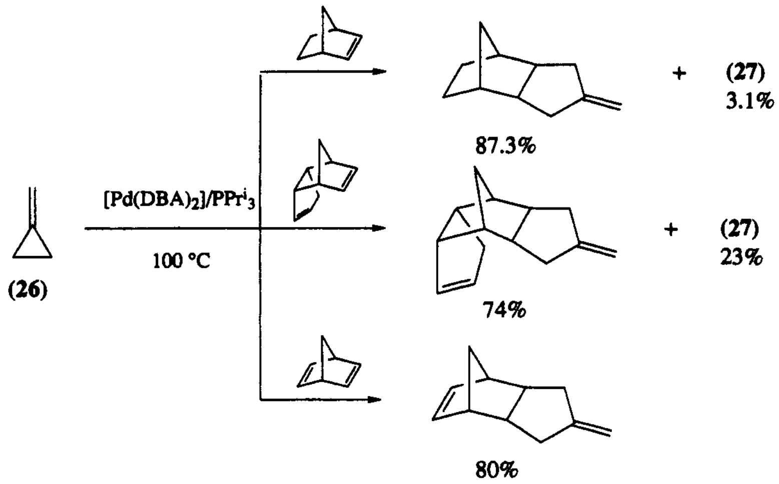
[Pd(DBA)$_2$]/PPr$^i_3$
100 °C
(26)
+ (27)
3.1%
87.3%
+ (27)
23%
74%
80%

(9)

When isopropylidenecyclopropane (**29a**; equation 10) or diphenylmethylenecyclopropane (**29b**) is used, the codimerizations with alkenes such as ethylene, styrene or norbornene giving alkylidenecyclopentanes are achieved under mild conditions in more than 75% yields.[21]

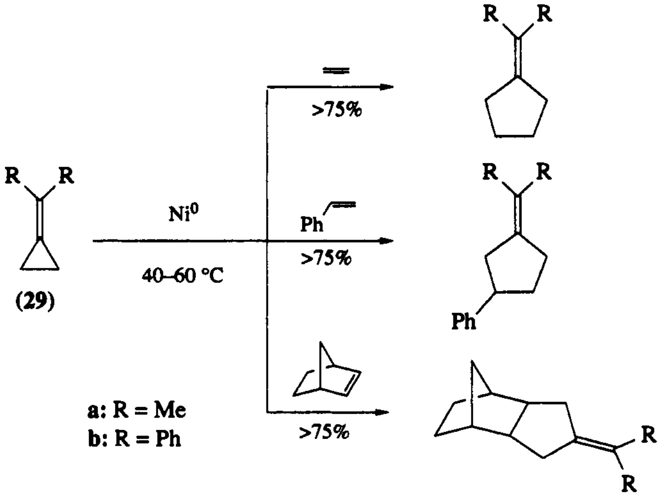
R
R
Ni$^0$
40–60 °C
(29)
a: R = Me
b: R = Ph
>75%
Ph
>75%
>75%
Ph

(10)

(Diphenylmethylene)cyclopentane derivatives (**30**; equation 11) are also obtained by the reaction of (**29b**) with simple alkenes in the presence of [PdCp($\eta^3$-allyl)] and triisopropylphosphine.[22]

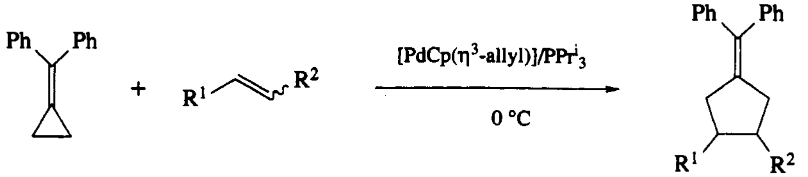

(29b) (30) (11)

| $R^1$ | $R^2$ | Yield (%) | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|---|---|
| H | H | 83 | H | Ph | 88 |
| H | Me | 83 | H | $CH{=}CH_2$ | 48 |
| H | Et | 86 | $-CH_2CH_2-$ | | 61 |

1-Methylene-2-vinylcyclopropane is cyclodimerized by palladium(0)/$PPr^i_3$ systems to give carbocycles such as 5-methylene-3-vinylallylidenecyclohexane (41%) and 3-methyleneallylidenecyclooct-5-ene (13%). Codimerization of 1-methylene-2-vinylcyclopropane with norbornene is also catalyzed by $[Pd(DBA)_2]/PPr^i_3$ to afford 4-allylidenetricyclo[5.2.1.$0^{2,6}$]decane (55%) and 4-methylene-3-vinyltricyclo[5.2.1.$0^{2,6}$]decane (17%).[23]

Compound (**26**) reacts with methyl acrylate in the presence of nickel(0) complexes (*e.g.* $[Ni(acrylonitrile)_2]$,[24] $[Ni(COD)_2]$[25]) under mild conditions to give 3-methoxycarbonylmethylenecyclopentane (**31**; equation 12) in high yields (>82%). Use of methyl vinyl ketone or acrylonitrile as the substrate also gives rise to the corresponding methylenecyclopentane.[24a] Cycloadditions of 2-methyl- or 2,2-dimethyl-methylenecyclopropanes with $CH_2{=}CHZ$ (Z = electron-withdrawing group) give 4-substituted 2-methyl- or 2,2-dimethyl-methylenecyclopentanes (30–60%), while 2,2,3,3-tetramethylmethylenecyclopropane gives no cycloadducts on reaction with electron deficient alkenes.[22]

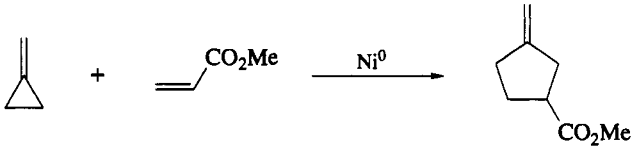

(26) (31) >82% (12)

The complexes $[Ni(acrylonitrile)_2]$[24b] and $[Ni(COD)_2]$[25] catalyze [3 + 2] cycloadditions of (**26**) with electron deficient 1,2-disubstituted alkenes to afford 2,3- or 3,4-disubstituted methylenecyclopentanes such as (**32**) and (**33**). Similar reactions have been reported by use of tertiary phosphine complexes of nickel(0)[26] and palladium(0)[27] (equation 13 and Table 1). The reaction proceeds regioselectively to give (**32**) or (**33**) depending on both the alkene structure and catalytic system. Reactions catalyzed by phosphine–palladium(0) complexes afford only products of the type (**32**), *via* selective cleavage of the C(2)—C(3) bond of (**26**).

Cycloadditions of isopropylidenecyclopropane (**29a**) or diphenylmethylenecyclopropane (**29b**) with electron deficient alkenes are catalyzed by $[Ni(acrylonitrile)_2]$[24a] or triarylphosphite–nickel(0) compounds (Table 2)[28] to give alkylidenecyclopentane derivatives (**34**) and (**35**) in high yields (equation 14).

2-(Trimethylsilyl)methylenecyclopropane (**36**; equation 15) is usable instead of methylenecyclopropane in reactions with electron deficient alkenes involving $[PdCp(\eta^3\text{-allyl})]/PPr^i_3$, giving silylated methylenecyclopentanes (**37**) and (**38**) in good yields and with better selectivities than those obtained from unsubstituted methylenecyclopropane (**26**). The trimethylsilyl group can be easily removed by protonolysis with trifluoroacetic acid.[29]

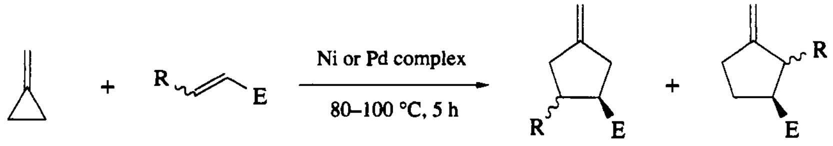

(26) (32) (33) (13)

**Table 1** Reactions of Methylenecyclopropane and Electron Deficient Alkenes in the Presence of Nickel(0) or Palladium Complexes

| *R* | *E* | *Catalyst*$^a$ | *Yield (%)* | *Composition (%)* *Cis-(32)* | *Trans-(32)* | *Cis-(33)* | *Trans-(33)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| H | $CO_2Me$ | A | 55 | | | | | 26 |
| H | $CO_2Me$ | B | 92 | | | | | 25 |
| H | $CO_2Me$ | C | 87.5 | | | | | 27b |
| Me | $CO_2Me$ (*E*) | A | 55 | | | 22 | 78 | 26 |
| Me | $CO_2Me$ (*E*) | B | 43 | | | 0 | 100 | 25 |
| Pr | $CO_2Me$ (*E*) | A | 50 | | | 27 | 73 | 26 |
| $(CH_2)CO_2Me$ | $CO_2Me$ (*E*) | A | 49 | | | 28 | 72 | 26 |
| $CO_2Et$ | $CO_2Et$ (*Z*) | A | 42 | 25 | 75 | | | 26 |
| $CO_2Et$ | $CO_2Et$ (*Z*) | D | 78.2 | 23 | 77 | | | 27b |
| $CO_2Me$ | $CO_2Me$ (*Z*) | B | 78 | | | 90 | 10 | 25 |
| $CO_2Et$ | $CO_2Et$ (*E*) | A | 72 | 4 | 96 | | | 26 |
| $CO_2Et$ | $CO_2Et$ (*E*) | C | 89.2 | 4 | 96 | | | 27b |
| $CO_2Et$ | $CO_2Et$ (*E*) | E | 79.0 | 4 | 96 | | | 27b |
| Me | CHO (*E*) | A | 54 | | | 9 | 91 | 26 |
| 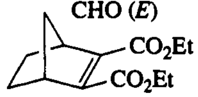 | | A | 62 | 100 | | | | 26 |

$^a$A, $[Ni(COD)_2]/PPh_3$; B, $[Ni(COD)_2]$; C, $[PdCp(\eta^3\text{-allyl})]/PPr^i_3$; D, $[PdCp(\eta^3\text{-allyl})]/P(OEt)_3$; E, $[Pd(DBA)_2]/PPr^i_3$.

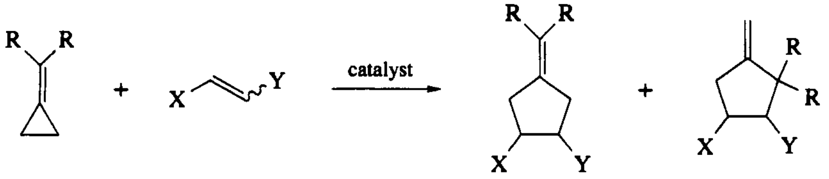

(29) (34) (35) (14)

a: R = Me
b: R = Ph

catalyst A, $[Ni(COT)_2]/P(OAr)_3$
catalyst B, $[Ni(COD)_2]/P(OAr)_3$

**Table 2** Reactions of Alkylidenecyclopropanes with Electron Deficient Alkenes in the Presence of Nickel(0) Complexes[28]

| *(29)* | *R* | *X* | *Y* | *Catalyst*$^a$ | *Temp (°C)* | *Time(h)* | *Yield (%)* *(34)* | *(35) (X, Y)* |
|---|---|---|---|---|---|---|---|---|
| b | Ph | H | $CO_2Me$ | A | 50 | 8 | 79 | |
| a | Me | H | $CO_2Me$ | B | 100 | 5 | 81 | 14 ($CO_2Me$, H) |
| b | Ph | Me | $CO_2Me$ (*E*) | B | 120 | 5 | 75 (*trans*) | |
| a | Me | Me | $CO_2Me$ (*E*) | B | 110 | 5 | 14 (*trans*) | 46 (*trans*)<br>(Me, $CO_2Me$) |
| b | Ph | $CO_2Et$ | $CO_2Et$ (*E*) | B | 100 | 3 | 98 (*trans*) | |
| a | Me | $CO_2Et$ | $CO_2Et$ (*E*) | B | 120 | 5 | 56 (*trans*) | 34 (*trans*) |
| b | Ph | $CO_2Et$ | $CO_2Et$ (*Z*) | B | 120 | 5 | 28 (*cis*)<br>69 (*trans*) | |
| a | Me | $CO_2Et$ | $CO_2Et$ (*Z*) | B | 130 | 10 | 57 (*trans*) | 23 (*trans*) |
| b | Ph | H | CN | A | 120 | 5 | 82 | |
| a | Me | H | CN | A | 120 | 5 | 47 | 4 (H,CN) |

$^a$A, $[Ni(COT)_2]/P(OAr)_3$; B, $[Ni(COD)_2]/P(OAr)_3$.

The nickel(0)-catalyzed codimerizations of methylenecyclopropane (**26**) or 2,2-dimethylmethylenecyclopropane with the chiral derivatives of acrylic acid lead to optically active 3-methylenecyclopentanecarboxylic esters or amides (**39**; equation 16) in good yields (Table 3). When (–)-camphorsultam acrylate is used, 3-methylenecyclopentanecarboxylic amides are obtained in up to 98% *de*.[30]

The seven-membered ring product (**49**; equation 17) is obtained as a mixture of the *trans* and *cis* isomers (82:18) in 67% yield from the reaction of (**26**) with dimethyl muconate (**48**) in the presence of a

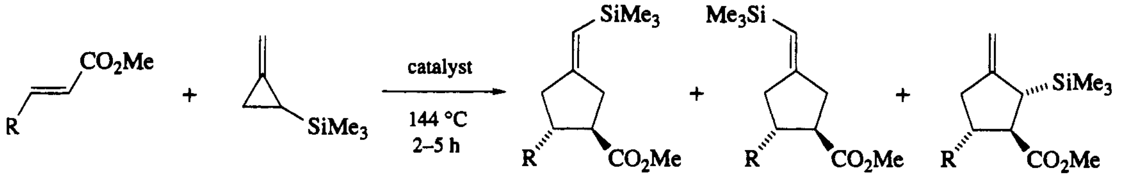

**(36)** (*Z*)-**(37)** (*E*)-**(37)** **(38)**

catalyst: [PdCp($\eta^3$-allyl)]/PPr$^i_3$ (15)

| | | | | | | |
|---|---|---|---|---|---|---|
| R = H | 78% | 53 | : | 47 | : | 0 |
| R = Me | 79% | 57 | : | 43 | : | 0 |
| R = $CO_2Me$ | 87% | 0 | : | 90 | : | 10 |

palladium(0) catalyst.[13] On the other hand, methyl 2,4-pentadienoate reacts with (**26**) only at the terminal C=C bond, giving methyl 3-(3-methylenecyclopentyl)prop-2-enoate in poor yield (25%).[31]

Bicyclic ketones are prepared by cycloadditions of methylenecyclopropanes with cyclic α,β-unsaturated carbonyl compounds. *cis*-Bicyclo[3.3.0]octan-2-ones (**50**), (**51**) and (**52**) are obtained in good yields by phosphine–nickel(0)-catalyzed cross coupling reactions of 2-cyclopentenone with methylenecyclopropanes in the presence of 0.1–1 equiv. of triethylborane as a Lewis acid (equations 18 and 19 and Table 4).[32]

(Diphenylmethylene)cyclopropane (**29b**) reacts with α,β-unsaturated cyclic ketones in the presence of [PdCp($\eta^3$-allyl)] and triisopropylphosphine to afford compounds (**53**) in moderate to high yields (equation 20).[22]

When 2-(trimethylsilyl)methylenecyclopropane (**36**; equation 21) is allowed to react with cyclic unsaturated ketones in the presence of [PdCp($\eta^3$-allyl)]/PPr$^i_3$, silylated methylenecyclopentanes (**54**) and (**55**) are produced in good yields and with better selectivities than those obtained from unsubstituted methylenecyclopropane. The trimethylsilyl group can easily be removed.[29]

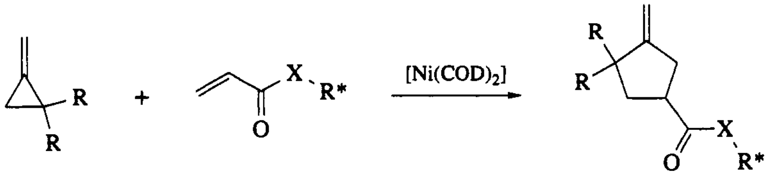

**(39)** (16)

R*—X—:

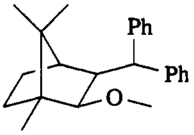

(1*R*,2*R*,3*S*)-(**40**)

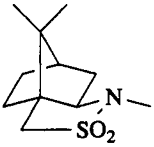

(7*S*)-(**41**)

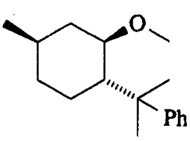

(1*R*,2*S*,5*R*)-(**42**)

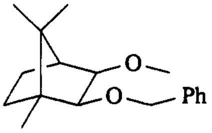

(1*R*,2*S*,3*R*)-(**43**)

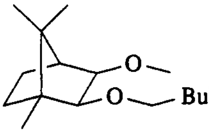

(1*R*,2*S*,3*R*)-(**44**)

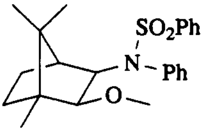

(1*R*,2*S*,3*R*)-(**45**)

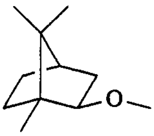

(1*R*,2*R*,4*R*)-(**46**)

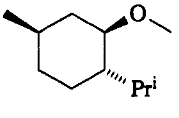

(1*R*,2*S*,5*R*)-(**47**)

**Table 3** Cycloadditions of Methylenecyclopropanes with Chiral Acrylic Acid Derivatives, Catalyzed by $[Ni(COD)_2]$[30]

| *R* | *R*—X—* | *Temperature (°C)* | *Time (h)* | *Yield (%)* | *De (%)* | *Configuration at C-1* |
|---|---|---|---|---|---|---|
| H | **(40)** | –20 | 24 | 93 | 80 | (*S*) |
| Me | **(40)** | 20 | 20 | 63 | 25 | — |
| H | **(41)** | 20 | 16 | 79 | 83 | (*S*) |
| H | **(41)** | 0 | 20 | 80 | 86 | (*S*) |
| H | **(41)** | –20 | 16 | 72 | 91 | (*S*) |
| H | **(41)** | –35 | 24 | 76 | 86 | (*S*) |
| Me | **(41)** | 0 | 20 | 86 | 98 | (*S*) |
| H | **(42)** | –20 | 24 | 59 | 78 | (*R*) |
| Me | **(42)** | 20 | 14 | 55 | 55 | — |
| H | **(43)** | –20 | 72 | 85 | 30 | — |
| H | **(44)** | 20 | 72 | 47 | 46 | — |
| H | **(45)** | –20 | 72 | 38 | 68 | (*S*) |
| H | **(46)** | 25 | 7 | 92 | 3 | — |
| H | **(47)** | –20 | 72 | 78 | 26 | — |

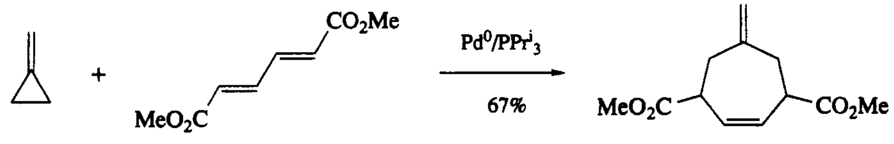
+
$CO_2Me$
$MeO_2C$
$Pd^0/PPr^i_3$
67%
$MeO_2C$
$CO_2Me$

**(26)** **(48)** **(49)**

(17)

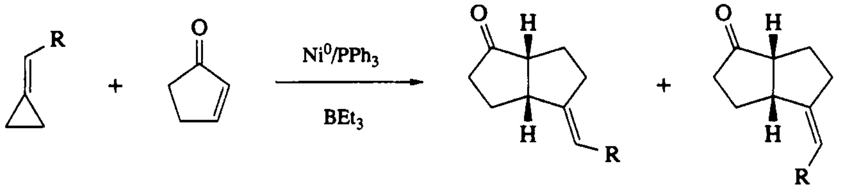
R
+
O
$Ni^0/PPh_3$
$BEt_3$
O
H
H
R
+
O
H
H
R

*(E)*-**(50)** *(Z)*-**(50)**

(18)

| *R* | *Yield (%)* | | | |
|---|---|---|---|---|
| H | 50 | | | |
| n-$C_5H_{11}$ | 68 | 85 | : | 15 |
| Ph | 72 | 100 | : | 0 |

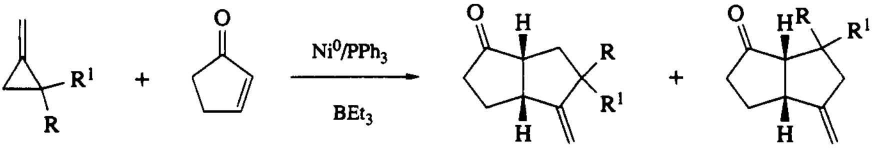
$R^1$
R
+
O
$Ni^0/PPh_3$
$BEt_3$
O
H
R
$R^1$
H
+
O
H
R
$R^1$
H

**(51)** **(52)**

(19)

**Table 4** Cycloadditions of Methylenecyclopropanes with 2-Cyclopentenone, Catalyzed by a $PPh_3$–$Ni^0$–$BEt_3$ System[32]

| *R* | *R*$^1$ | *Yield (%)* | *Isomer ratio* | | | |
|---|---|---|---|---|---|---|
| | | | *Endo-*(**51**) | *Exo-*(**51**) | *Endo-*(**52**) | *Exo-*(**52**) |
| Me | H | 73 | 63 | 37 | | |
| Ph | H | 75 | | | 61 | 39 |
| $SiMe_3$ | H | 50 | 68 | 32 | | |
| Me | Me | 37 | | | | |

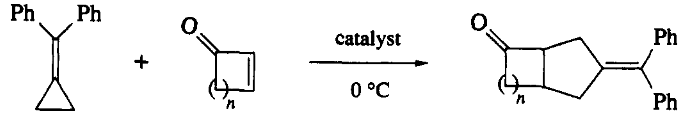

**(29b)** **(53)** (20)

catalyst $[PdCp(\eta^3\text{-allyl})]/PPr^i_3$

$n$ = 2, 97%
$n$ = 3, 76% *cis:trans* = 74:26
$n$ = 4, 80% *cis:trans* = 16:84

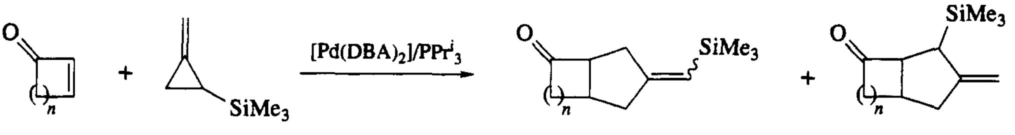

**(36)** **(54)** **(55)** (21)

| | | | | | |
|---|---|---|---|---|---|
| $n = 2$ | 144 °C | 5 h | 81% | 72% (*cis, (Z):(E)* = 5:2) | 28% |
| $n = 3$ | 110 °C | 15 h | 31% | 68% ( 4 isomers) | 32% |
| $n = 4$ | 144 °C | 5 h | 71% | 72% (*trans, (Z):(E)* = 5:3) | 28% |

Nickel(0)-catalyzed [3 + 2] cycloadditions of methylenecyclopropanes with *N*-substituted maleimides (**56**; equation 22) lead almost exclusively to 5-alkylidenehexahydro-1*H*-cyclopenta[*c*]pyrrolo-1,3-diones (**57**) and (**58**; equation 23). A similar reaction occurs in the presence of a palladium(0) catalyst, but with lower selectivity. Unsubstituted maleimide and maleic anhydride do not undergo this cycloaddition. Ozonolysis of (**57**) and (**58**) into the corresponding ketone derivatives (62–78% yield) followed by reduction of both carbonyl groups gives 1*H*-cyclopenta[*c*]pyrroles, which are of interest with regard to their pharmacological activity (98% yield).[33]

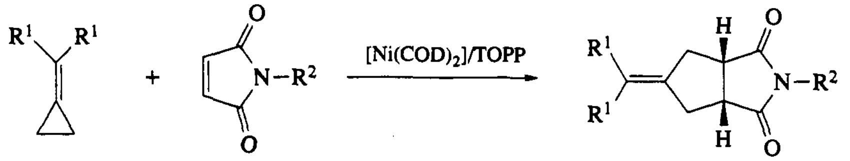

**(56)** **(57)** (22)

| *R¹* | *R²* | *Catalyst ratio* | *Conditions* | *Yield (%)* |
|---|---|---|---|---|
| H | Ph | $[Ni(COD)_2]/TOPP$ = 1:1 | 70 °C/20 h | 12 |
| Me | Ph | $[Ni(COD)_2]/TOPP$ = 1:1.5 | 120 °C/5 h | 90 |
| Me | Ph | $[Ni(COD)_2]/TOPP$ = 1:4 | 120 °C/14 h | 84 (isolated) |
| Me | Me | $[Ni(COD)_2]/TOPP$ = 1:4.5 | 120 °C/10 h | 93 |
| Ph | Ph | $[Ni(COD)_2]/TOPP$ = 1:2 | 120 °C/2 h | 83 (isolated) |

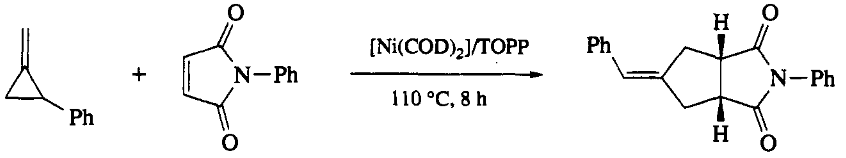

**(58)** 82% (23)

Additions of methylenecyclopropanes to alkynes (**59**; equation 24) give 4-methylene-1-cyclopentenes (**60**), (**61**) and (**62**) in the presence of phosphite-coordinated nickel(0) catalysts (Table 5). Alkynylsilanes are particularly suitable for these codimerizations. In the reactions with 1-alkynes or dialkylalkynes, oligomerization of the alkynes cannot be avoided. When alkynes with electron-attracting substituents are used, cyclotrimerization is so rapid that cross addition no longer occurs.[34]

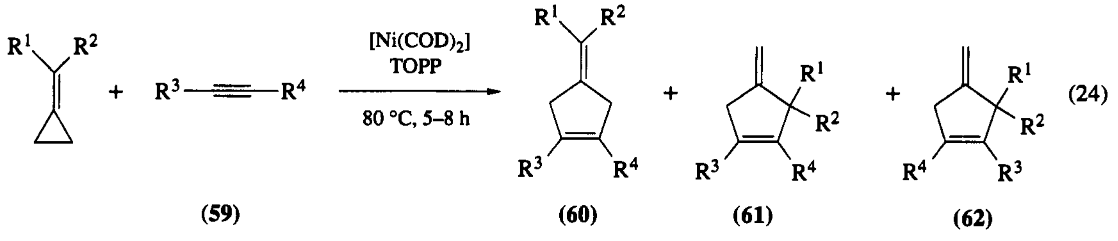

**(59)** **(60)** **(61)** **(62)**

TOPP = $P(OC_6H_4Ph\text{-}o)_3$

Table 5 Cycloadditions of Methylenecyclopropanes with Alkynes, Catalyzed by TOPP–[Ni(COD)$_2$][34]

| *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *Yield (%)* | *Composition (%)* (60) | (61) | (62) |
|---|---|---|---|---|---|---|---|
| H | Ph | $SiMe_3$ | $SiMe_3$ | 41 | | 100 | |
| Me | Me | $SiMe_3$ | $SiMe_3$ | 50 | | 100 | |
| Ph | Ph | $SiMe_3$ | $SiMe_3$ | 71 | 48 | 52 | |
| H | n-$C_5H_{11}$ | Me | $SiMe_3$ | 82 | 12 | 63 | 25 |
| Me | Me | Et | $SiMe_3$ | 88 | | 85 | 15 |
| Ph | Ph | Et | $SiMe_3$ | 92 | 60 | 24 | 16 |
| H | H | $CH_2OSiMe_3$ | $SiMe_3$ | 59 | | | |
| Me | Me | $CH_2OSiMe_3$ | $SiMe_3$ | 82 | 6 | 60 | 34 |
| Ph | Ph | $CH_2OSiMe_3$ | $SiMe_3$ | 90 | 53 | 2 | 45 |
| H | H | $CO_2Me$ | $SiMe_3$ | 72 | | | |
| H | n-$C_5H_{11}$ | $CO_2Me$ | $SiMe_3$ | 65 | 25 | 22 | 53 |
| Me | Me | $CO_2Me$ | $SiMe_3$ | 64 | 41 | 21 | 38 |
| Ph | Ph | $CO_2Me$ | $SiMe_3$ | 63 | 100 | | |
| Me | Me | Me | Me | 66 | 6 | 94 | |
| Ph | Ph | Me | Me | 95 | 6 | 94 | |
| Ph | Ph | $CH_2OSiMe_3$ | $CH_2OSiMe_3$ | 86 | 57 | 43 | |

In the co-oligomerization of methylenecyclopropane (**26**) with allene (**63**; equation 25) on a palladium(0) catalyst, prepared *in situ* from [Pd(acac)$_2$], triisopropylphosphine and diethylaluminum ethoxide, or from [Pd(DBA)$_2$] and triisopropylphosphine, cyclic hydrocarbons such as 2-methylenespiro[2.4]heptane (**27**), 1,3-dimethylenecyclopentane (**64**) and 1,3,5-trimethylenecycloheptane (**65**) are formed.[35]

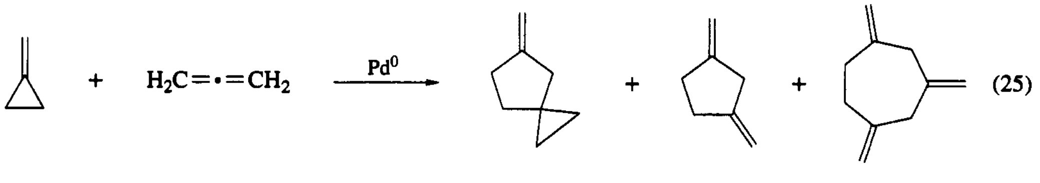

| (26) (63) | (27) | (64) | (65) |
|---|---|---|---|
| [Pd(acac)$_2$]/PPr$^i_3$/Et$_2$AlOEt | 23% | 40% | 10% |
| [Pd(DBA)$_2$]/PPr$^i_3$ | 38% | 14% | 25% |

[Pd(PPh$_3$)$_4$]- or (PhO)$_3$P/[Ni(COD)$_2$]-catalyzed [3 + 2] cycloadditions of methylenecyclopropanes with ketenimines (**66**) lead selectively to pyrroles (**67**; equation 26), (**68**) and (**69** (equation 27), or α-methylene-Δ$^3$-pyrrolines (**70**; equation 28) depending on the substituents of the imino group and the methylenecyclopropanes. Diphenylketene-*N*-methylimine reacts with (**26**) to give 1-methylimino-3-methyl-5,5-diphenylcyclopent-2-ene in 38% yield.[36]

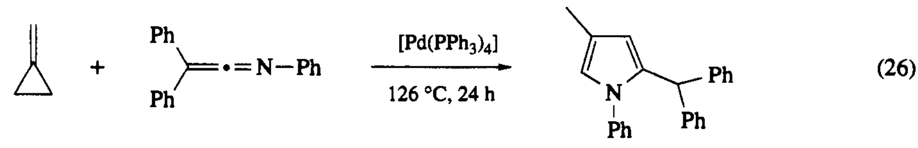

**(26)** **(66)** **(67)** 96%

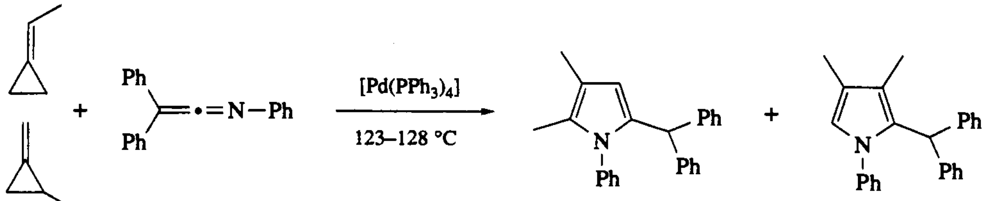

(27)

**(66)** **(68)** 44–46% **(69)** 31%

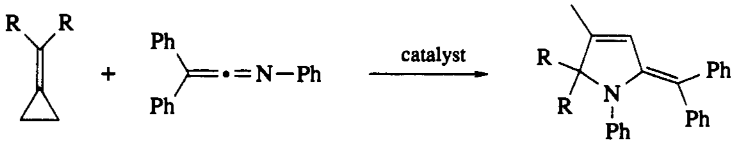

(28)

**(66)** **(70)**

| | | | |
|---|---|---|---|
| R = Me | $[Pd(PPh_3)_4]$ | 123 °C/30 h | 93% |
| | $[Ni(COD)_2]$/TOPP | 70 °C/7 h | 93% |
| R–R = $-(CH_2)_5-$ | $[Pd(PPh_3)_4]$ | 127 °C/30 h | 91% |
| | $[Ni(COD)_2]$/TOPP | 70 °C/5 h | 94% |

Palladium(0)–phosphine complexes catalyze the reaction of methylenecyclopropanes and $CO_2$ with opening of the three-membered ring to give γ-lactones.[37] When isopropylidenecyclopropane is treated in benzene with $CO_2$ (40 atm) at 126 °C for 20 h in the presence of a catalytic amount of $[Pd(DBA)_2]/PPh_3$, lactone (**71**; equation 29) is formed in 69% yield accompanied by 3,4,4-trimethyl-2-buten-4-olide (**72**) in 8% yield. Cyclopropylidenecyclohexane and butylidenecyclopropane also react with $CO_2$ to give the corresponding lactones and butenolides in moderate yields. With methylenecyclopropane (**26**) as substrate, further alkylation of 3-methyl-2-buten-4-olide proceeds under the same catalytic conditions to give cotrimer, cotetramer, copentamer, *etc.*, while 2,2-dimethylmethylenecyclopropane and *cis*-2,3-dimethylmethylenecyclopropane do not react under similar conditions.

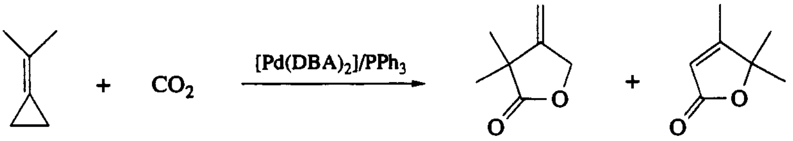

(29)

**(71)** **(72)**

Lactone (**71**; equation 30) undergoes cycloaddition to aromatic and aliphatic aldehydes in the presence of a catalytic amount of a palladium(0) complex to give 3-methylenetetrahydrofuran derivatives (**73**) with the liberation of carbon dioxide. α,β-Unsaturated carbonyl compounds also react with (**71**) to give (**35**) (equation 31 and Table 6).[38]

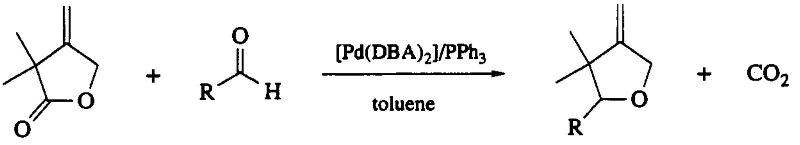

(30)

**(71)** **(73)**

| *R* | *Conversion (%)* | *Yield (%)* |
|---|---|---|
| Ph | 100 | 100 |
| 1-Np | 72 | 69 |
| CH=CHPh | 25 | 16 |
| 1-furyl | 69 | 67 |

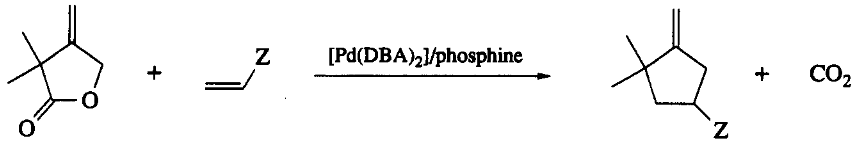

**(71)** Z = electron-withdrawing group **(35)**

(31)

**Table 6** Reaction of **(71)** with α,β-Unsaturated Carbonyl Compounds Catalyzed by Phosphine–[Pd(DBA)$_2$][38]

| *Substrate* | *Phosphine* | *Product* | *Yield (%)* |
|---|---|---|---|
| 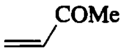 | DPPE | 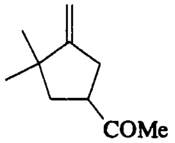 | 25 |
| 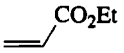 | $PPh_3$ | 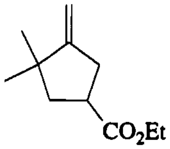 | 38 |
| 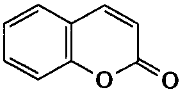 | $PPh_3$<br>DPPE | 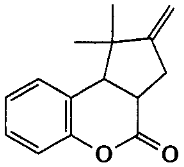 | 66<br>92 |

## 9.6.6 TRANSITION METAL CATALYZED REACTIONS OF CYCLOPROPENES: SYNTHESIS OF VINYLCYCLOPROPANES

Cyclopropenes are highly strained and thus very reactive molecules. Cyclopropene itself tends to polymerize even below 0 °C and 1-methylcyclopropene dimerizes within minutes at room temperature *via* an ene reaction. In contrast, 3,3-dimethylcyclopropene does not undergo an ene reaction even at 100 °C, but it readily oligomerizes under the influence of nickel(0)[39] or cyclodimerizes to 3,3,6,6-tetramethyltricyclo[3.1.0.$0^{2,4}$]hexane (80% yield) in the presence of palladium(0).[40] 1,2-Diphenylcyclopropene is converted to 1,2,4,5-tetraphenylcyclohexa-1,4-diene in the presence of palladium(0) in high yield (equation 32).[14]

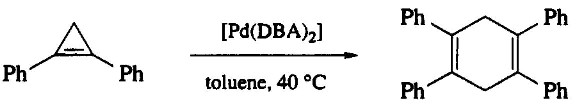

95%

(32)

When electron deficient alkenes are added to cyclopropene derivatives (**74**; equation 33) and (**77**; equation 34) in the presence of [Ni(COD)$_2$], vinylcyclopropanes are formed in good yields.[41] For example, dialkyl fumarate or maleate reacts with 3,3-dimethylcyclopropene in the presence of [Ni(COD)$_2$] to give 2,3-bis(alkoxycarbonyl)-1-(2-methyl-1-propenyl)cyclopropanes (**75**), (**76**), (**78**) and (**79**), in which alkene stereochemistry is chiefly retained, in 50–73% yields. Reaction of methyl acrylate with 3,3-dimethylcyclopropene results in the formation of several products, while reaction of methyl acrylate with 3,3-diphenylcyclopropene gives vinylcyclopropane derivatives (**80**; equation 35) in 85% yield. Under similar conditions, methyl crotonate reacts with (**74a**) to give (**82**) in low yield (equation 36).[41] Catalysis with nickel(0)/$PR_3$,[42] [Ni(CO)$_4$],[43] [Pd(DBA)$_2$][44] or [Pd(DBA)$_2$]/$PPr^i_3$[31] gives mainly homooligomers and mixed oligomers with a small amount of 1:1 cycloadducts. In these cycloaddition reactions, vinylcarbene–metal complexes are formed at first by the reaction of cyclopropene with low valent metals. The carbene complexes then react with alkenes to give vinylcyclopropane derivatives.

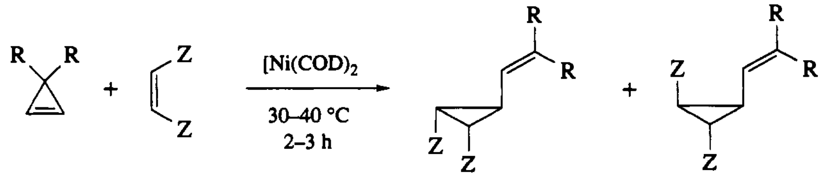
R
R
Z
Z
[Ni(COD)$_2$
30–40 °C
2–3 h
R
R
Z
Z
R
R
Z
Z

(33)

**(74)** Z = $CO_2Me$ **(75)** **(76)**

| | | | (75) | | (76) |
|---|---|---|---|---|---|
| **a**: | R = Me | 60% | 97 | : | 3 |
| **b**: | R = Ph | 65% | 79 | : | 21 |

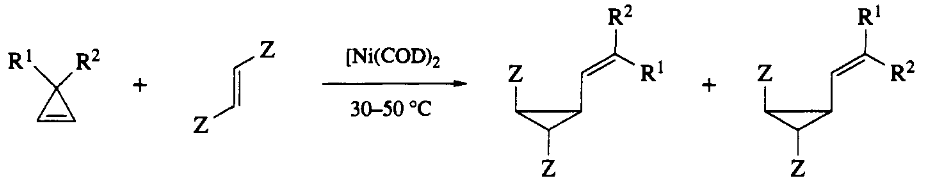
$R^1$
$R^2$
Z
Z
[Ni(COD)$_2$
30–50 °C
$R^2$
$R^1$
Z
Z
$R^1$
$R^2$
Z
Z

(34)

**(77)** Z = $CO_2R^3$ **(78)** **(79)**

$R^1 = R^2 = R^3 = Me$ 50%

$R^1 = R^2 = Me$, $R^3 = Et$ 73%

$R^1 = Me$, $R^2 = Ph$, $R^3 = Et$ 84% *(E)*:*(Z)* = 89.5:10.5

$R^1 = R^2 = Ph$, $R^3 = Et$ 87%

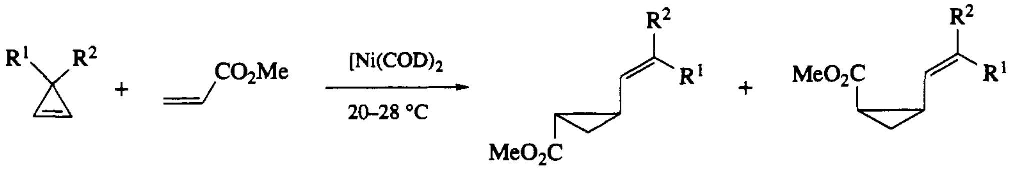
$R^1$
$R^2$
$CO_2Me$
[Ni(COD)$_2$
20–28 °C
$R^2$
$R^1$
$MeO_2C$
$R^2$
$MeO_2C$
$R^1$

(35)

**(77)** *trans*-**(80)** *cis*-**(80)**

| | | *trans*-(80) | | *cis*-(80) |
|---|---|---|---|---|
| $R^1 = R^2 = Me$ | 39% | 51 | : | 49 |
| $R^1 = Me$, $R^2 = Ph$ | 51% | 64 *(E)*:*(Z)* = 51:49 | : | 36 *(E)*:*(Z)* = 92:8 |
| $R^1 = R^2 = Ph$ | 85% | 86 | : | 14 |

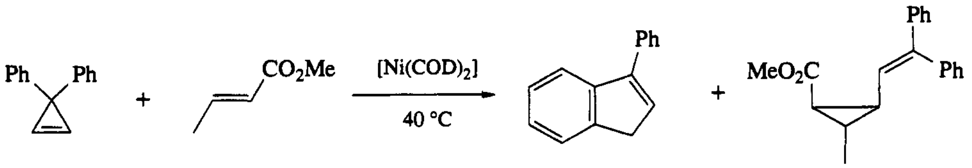
Ph
Ph
$CO_2Me$
[Ni(COD)$_2$]
40 °C
Ph
$MeO_2C$
Ph
Ph

(36)

**(74a)** **(81)** 26% **(82)** 16%

Vinylcarbene is also regarded as an intermediate in the catalytic isomerization of cyclopropene in the presence of $[CuCl\{P(OPh)_3\}]$.[45] 3-Methyl-3-cyclopropylcyclopropene (**83a**) and 3,3-dicyclopropylcyclopropene (**83b**) react with cyclopentene derivatives under the influence of $CuCl/P(OPh)_3$ to yield *endo*-vinylcyclopropane derivatives (**84**; equation 37) in 55–72% yields. 3-Methoxycarbonyl-1-propylcyclopropene also reacts with norbornadiene in the presence of CuCl to give the corresponding vinylcarbene adducts in 60% yield.

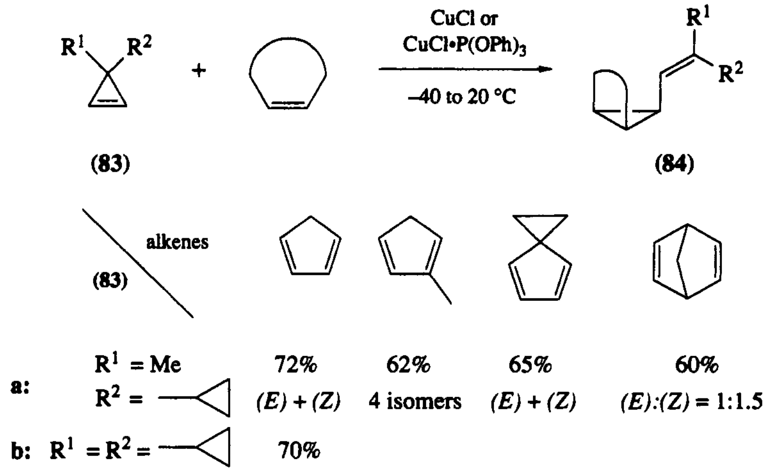
R¹
R²
+
CuCl or
CuCl•P(OPh)₃
–40 to 20 °C
R¹
R²
(83)
(84)
alkenes
(83)
a:
R¹ = Me
R² =
b: R¹ = R² =
72%
(E) + (Z)
70%
62%
4 isomers
65%
(E) + (Z)
60%
(E):(Z) = 1:1.5

(37)

In the presence of [Ni(COD)₂], 3,3-dimethoxycyclopropene (**85**; equation 38) reacts with methylacrylate, dimethyl fumarate and dimethyl maleate to give the corresponding vinylcyclopropanes (**86**) and (**87**), respectively.[46]

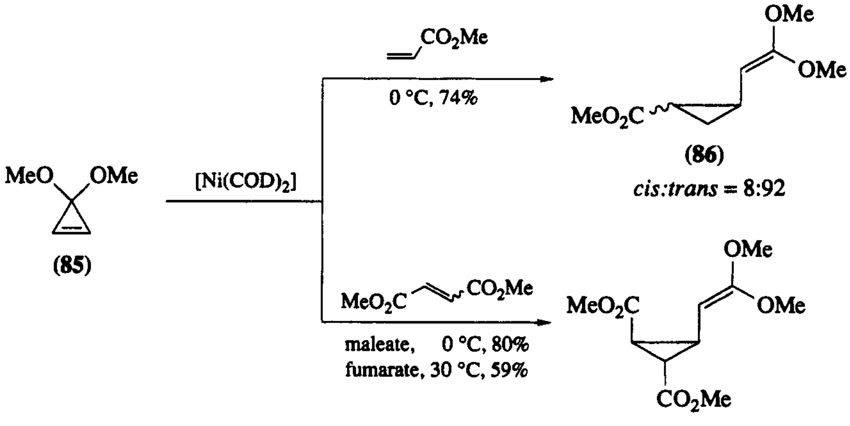
MeO
OMe
[Ni(COD)₂]
CO₂Me
0 °C, 74%
OMe
OMe
MeO₂C
cis:trans = 8:92
MeO₂C
CO₂Me
maleate, 0 °C, 80%
fumarate, 30 °C, 59%
OMe
MeO₂C
OMe
CO₂Me

**(85)**

**(86)**

**(87)**

(38)

Benzocyclopropene (**88**) and naphtho[*b*]cyclopropene react with various alkenic substrates to give cycloaddition products in the presence of silver ion.[47] Reaction of (**88**; equation 39) with butadiene assisted by 1 mol % of $AgBF_4$ in benzene (0 °C, 30 min) gives (**89**) and (**90**). Dimethylallene (**91**; equation 40) and oct-4-yne (**95**; equation 41) also react readily with (**88**) in the presence of silver ion to give the corresponding cycloaddition products (**92**), (**93**) and (**96**), together with acyclic products (**94**) and (**97**).

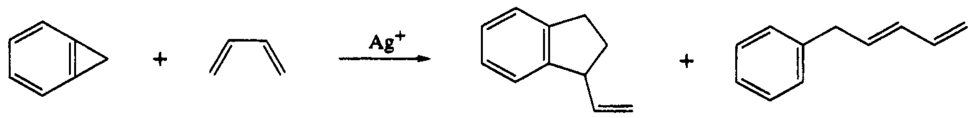

(39)

**(88)** **(89)** 64% **(90)** 26%

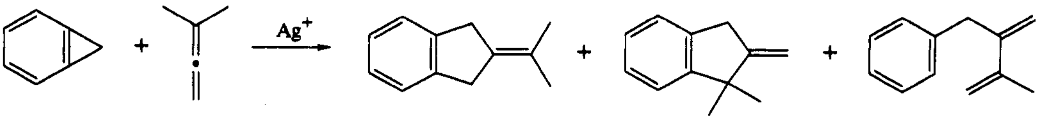

(40)

**(91)** **(92)** 39% **(93)** 19% **(94)** 19%

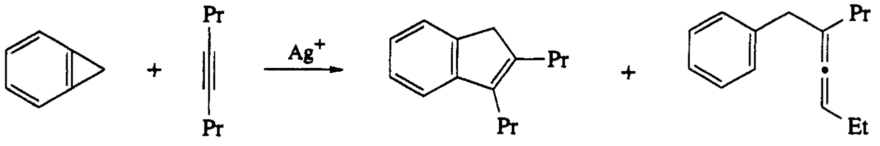

(95) (96) 25% (97) 14%

(41)

## 9.6.7 TRANSITION METAL CATALYZED REACTIONS OF VINYLCYCLOPROPANES: SYNTHESIS OF CYCLOPENTANE DERIVATIVES

Vinylcyclopentane derivatives (**99**) are prepared from the palladium(0)-catalyzed cycloaddition reaction of vinylcyclopropane (**98**), bearing two electron-withdrawing groups, with electron deficient alkenes (equation 42 and Table 7).[48] The reaction can be formally envisaged as a 1,3-dipolar cycloaddition.

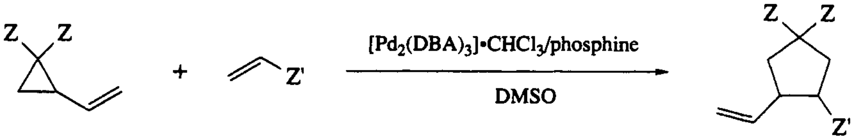

(42)

(**98**)

Z, Z' = electron withdrawing group

(**99**)

## 9.6.8 TRANSITION METAL CATALYZED REACTIONS OF CYCLOPROPANONES AND RELATED COMPOUNDS

Heterocyclic spirans are prepared by [Ni(CO)$_4$]-promoted tandem cycloaddition of diphenylcyclopropanone (**100**) to isothiocyanates (**101**; equation 43) or to carbon disulfide (**105**; equation 44). When an equimolar mixture of (**100**), (**101**) and [Ni(CO)$_4$] is allowed to react in DMF at 65–70 °C, two heterocyclic spirans, pyrrolin-2-one-5-spiro-5′-thiolen-4′-one (**102**), and (**103**), are formed in addition to the pyrroline derivative (**104**). Similarly, carbon disulfide (**105**), reacts with (**100**) to give thiolen-2-one-5-spiro-5′-thiolen-4′-one (**106**) along with a small amount of 1:1 cycloadduct (**107**).[49]

1-Ethoxy-1-trimethylsiloxycyclopropane (**108**; equation 45) is a stable and distillable liquid and is available in good yield by reductive silylation of ethyl 3-chloropropanoate.[50] Compound (**108**) smoothly reacts below 0 °C with aliphatic aldehydes in the presence of a slight excess of TiCl$_4$ giving γ-lactones (**109**) in high yield, while reaction with aromatic aldehydes gives linear adducts.[51] The reaction of 1-isopropoxy-1-siloxycyclopropane (**110**; equation 46) with TiCl$_4$ gives crystalline 3-trichlorotitanium propionate (**111**) in 82% yield. When complex (**111**) is treated with half an equivalent of a tetraalkoxytitanium complex and then with ketones, γ-lactones (**112**) are obtained in high yields.[52]

The addition of a carbonyl compound to methyl 2-siloxycyclopropanecarboxylate (**113**; equation 47) in the presence of a stoichiometric amount of TiCl$_4$ affords a mixture of hydroxyalkylation products (**114**) and (**115**), which are versatile starting materials for highly substituted tetrahydrofurans, dihydrofurans, and γ-butyrolactones.[53]

## 9.6.9 TRANSITION METAL CATALYZED REACTION OF CYCLOPROPENONES

Tetrasubstituted 1,4-benzoquinones (**117**) are formed by the [Ni(COD)$_2$]-catalyzed dimerization of 2,3-disubstituted cyclopropenones (**116**; equation 48) (R = Ph, 51%; R = Pr, 43%; R—R = —(CH$_2$)$_5$—, 18% yield).[54]

Reactions of diphenylcyclopropenone with ketenes (**118**; equation 49) in the presence of a catalytic amount of [Ni(CO)$_4$] afford 1:1 cycloadducts, cyclopentene-1,2-diones (**119**) and -1,3-diones (**120**), in more than 80% yields. The yields of the products are significantly affected by variation of the solvent used in the reaction, and DMF is the solvent of choice.[55]

**Table 7** Reactions of Vinylcyclopropanes and α,β-Unsaturated Carbonyl Compounds Catalyzed by Palladium(0) Complexes [48]

| *Substrates* [a] | | *Phosphine* | *Temperature* (°C) | *Time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|---|---|---|
| 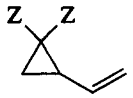 | 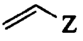 | DPPE | 80 | 2 | 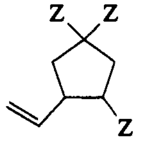 | 84 |
| 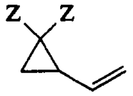 | 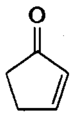 | $PBu^n_3$ | 30 | 1 | 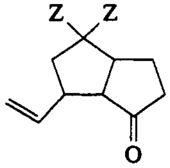 | 87 |
| 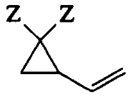 | 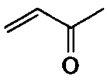 | $PBu^n_3$ | 30 | 1 | 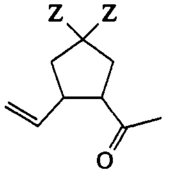 | 66 |
| 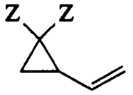 | 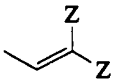 | $PBu^n_3$ | 30 | 3 | 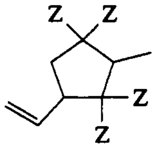 | 89 |
| 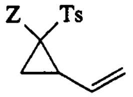 | 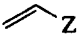 | $PBu^n_3$ | 30 | 3 | 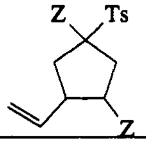 | 77 |

[a] Z = $CO_2Me$.

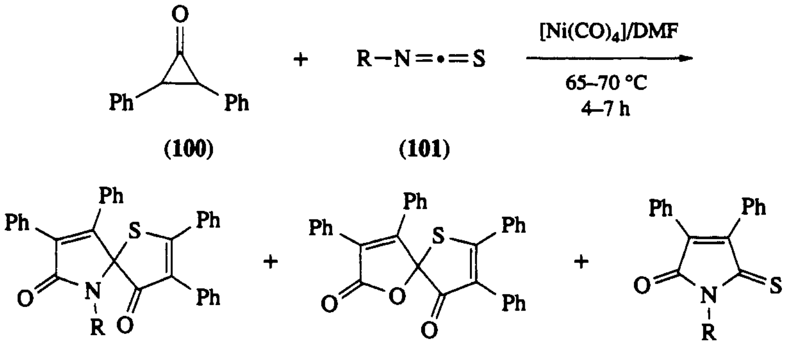

(100) (101)

(102) (103) (104) (43)

| | (102) | (103) | (104) |
|---|---|---|---|
| R = Ph | 30% | 17% | 6% |
| R = COPh | 50% | – | – |

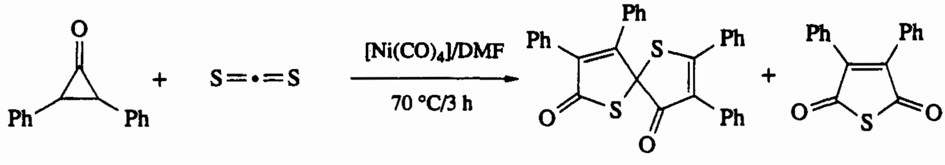

**(100)** **(105)** **(106)** 41% **(107)** 3% (44)

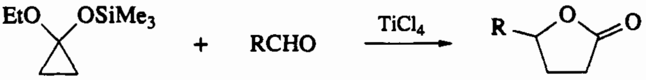

**(108)** **(109)** (45)

$R = Pr$ 77%
$R = C_8H_{17}$ 81%

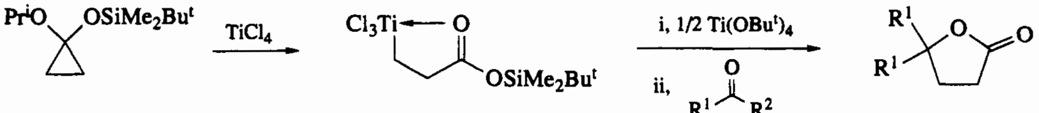

**(110)** **(111)** **(112)** (46)

| | | | |
|---|---|---|---|
| $R^1 = Me, R^2 = Ph$ | 20 °C | 1 h | 93% |
| $R^1\text{–}R^2 = \text{–}(CH_2)_5\text{–}$ | 20 °C | 18 h | 84% |

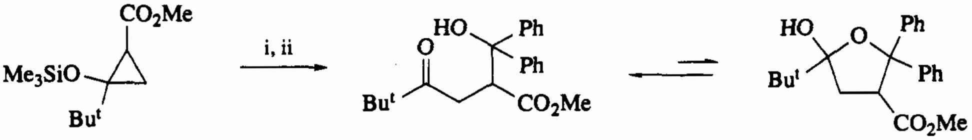

**(113)** **(114)** **(115)** (47)

i, $Ph_2C{=}O$, $TiCl_4$, –78 to 20 °C, $CH_2Cl_2$; ii, $H_2O$, 95% yield

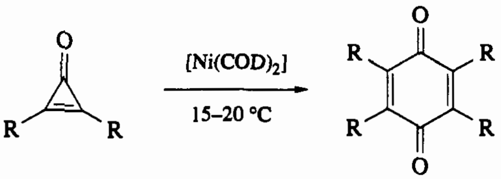

**(116)** **(117)** (48)

## 9.6.10 TRANSITION METAL CATALYZED REACTIONS OF CYCLOBUTENEDIONES: SYNTHESIS OF QUINONES

Benzocyclobutenedione (**121**) and cyclobutenedione (**125**) react with the low valent cobalt complex $[CoCl(PPh_3)_3]$ to form phthaloylcobalt (**122**; equation 50) and maleoylcobalt complexes, respectively. Subsequent treatment of (**122**) ($L = PPh_3$) with one equivalent of dimethylglyoxime (DMG) in pyridine provides a route to the dimethylglyoxime variant (**123**) in high yields. From the phthaloylcobalt complex (**123**), naphthoquinones (**124**) are prepared in high yield simply by heating (**123**) to 80 °C in the presence of an alkyne and a mild Lewis acid such as $CoCl_2{\cdot}6H_2O$. Similarly, benzoquinones (**126**; equation 51) are obtained from (**125**). Effective reaction rates were only achieved at room temperature in the presence of a strong Lewis acid such as $SnCl_4$ or $Zn(OSO_2CF_3)_2$.[56] Complex (**122**) also reacts directly with alkynes on treatment with $AgBF_4$ in MeCN, but more forcing conditions (110 °C, 20–40 h) are necessary for reasonable reaction rates compared to that of the reaction of (**123**). Iron compounds can also be used for this transformation and the phthaloyltetracarbonyliron complex produces naphthoquinones simply on

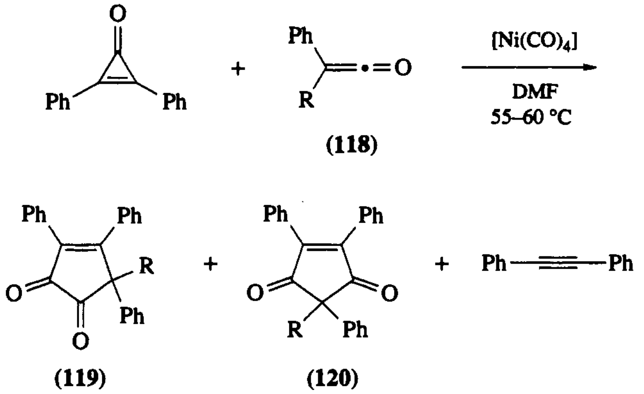

(118) (119) (120)

(49)

| *R* | *Solvent* | | *Yield (%)* | |
|---|---|---|---|---|
| Ph | DMF | 85.9 | trace | 4.8 |
| Ph | THF | 11.0 | 8.5% | 24.1 |
| Et | DMF | 85.3 | trace | 5.8 |

heating in MeCN in the presence of alkynes (100 °C, 6 h). Similar or even better results are obtained by using iron complexes instead of cobalt compounds. Sterically demanding alkynes, however, give significantly higher yields of the naphthoquinone products using cobalt instead of iron.

Nanaomycin A (**128**), an antibiotic pyranonaphthoquinone, has been synthesized *via* this route starting from (**127**).[57] This method has also been applied to the synthesis of royleanone (**129**), an abietanoid diterpene quinone possessing antitumor cytotoxicity, in which the highly substituted quinone skeleton has been efficiently constructed by using the maleoylcobalt complex.[58]

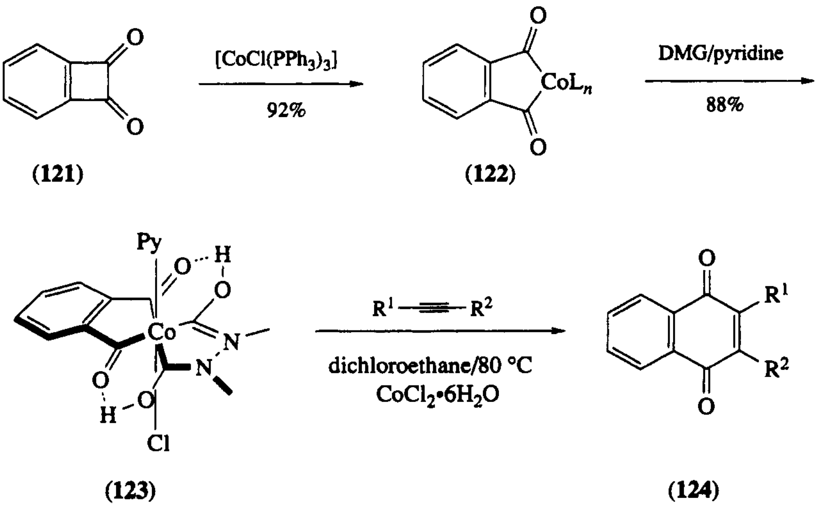

(121) (122) (123) (124)

(50)

| *R¹* | *R²* | *Yield (%)* | *R¹* | *R²* | *Yield (%)* |
|---|---|---|---|---|---|
| Bu | H | 87 | Et | OEt | 85 |
| Me | $CO_2Et$ | 99 | Me | $CH_2CH{=}CMe_2$ | 94 |

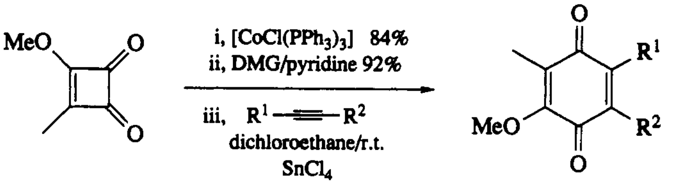

(51)

(125) (126)

| $R^1$ | $R^2$ | *Yield* (%) | *Regioisomer ratio* |
|---|---|---|---|
| Bu | H | 65 | 10:1 |
| Me | $CO_2Me$ | 62 | 20:1 |
| $CH_2SiMe_2Bu^t$ | Me | 51 | 20:1 |
| $(CH_2)_2N(CH_2Ph)(COCO_2Et)$ | H | 65 | 7:1 |

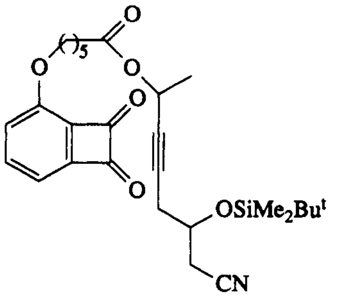

**(127)**

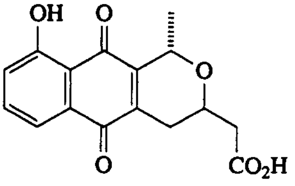

**(128)** Nanaomycin A

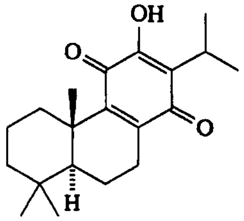

**(129)** Royleanone

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This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

Abbott, D. E., $6^{12,12c}$, $10^{40}$, $573^{53,54}$

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# COMPREHENSIVE ORGANIC SYNTHESIS

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## Volume 6

## HETEROATOM MANIPULATION

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C $\pi$-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N'*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Synthesis of Alcohols and Ethers

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## 1.1.1 INTRODUCTION

Alcohols can be obtained from many other classes of compounds such as alkyl halides, amines, alkenes, epoxides and carbonyl compounds. The addition of nucleophiles to carbonyl compounds is a versatile and convenient method for the the preparation of alcohols. Regioselective oxirane ring opening of epoxides by nucleophiles is another important route for the synthesis of alcohols. However, stereospecific oxirane ring formation is prerequisite to the use of epoxides in organic synthesis. The chemistry of epoxides has been extensively studied in this decade and the development of the diastereoselective oxidations of alkenic alcohols makes epoxy alcohols with definite configurations readily available. Recently developed asymmetric epoxidation of prochiral allylic alcohols allows the enantioselective synthesis of 2,3-epoxy alcohols.

For reason of space, emphasis will be placed on the reaction of functionalized epoxides with carbon nucleophiles. However, isomerization of epoxides and intramolecular oxirane ring opening leading to cyclic compounds could not be included. In order to avoid overlap with other articles in this series, reductive cleavage of epoxides is not discussed. Some 1,2-rearrangement reactions leading to alcohols are described because the reactions are apparently useful for the preparation of alcohols with high stereoselectivity. Substitution at the carbon atom adjacent to oxygen, which is an important method for the conversion of ethers, could not be considered. The conventional but still important classes of displacement reactions such as those involving alkyl halides or amines are discussed briefly. Readers are referred to excellent reviews and monographs.[1-3]

## 1.1.2 PREPARATION OF ALCOHOLS

### 1.1.2.1 Substitution of Alkyl Halides

Although the hydrolysis of alkyl halides to alcohols has been extensively investigated,[1] an alternative two-step sequence involving substitution with carboxylate ion is more practical for the preparation of alcohols.[4] Activation of the carboxylate anion prepared by the reaction of the acid with a base can be achieved:[5] (i) by use of a polar aprotic solvent; and (ii) by use of aprotic apolar solvents under phase transfer catalysis, polymer conditions, or with crown ethers.

The second-order alkylation rates of carboxylate salts are influenced by the nature of the cation, solvent and the alkyl halides. In general, carboxylate anions with soft (large) counterions are more reactive than those with hard counterions because of higher charge separation in the former.[6] Thus, the anticipated order of increasing reactivity $Li^+(1) < Na^+(1.1) < K^+(1.5) < Cs^+(2)$ was observed in the reaction of 2-methyl-2-propylpentanoate with 1-iodopentane at 60 °C in HMPA–EtOH (1:1 v/v).[6]

Rapid and nearly complete alkylation of carboxylate salts with reactive organic halides has been demonstrated in nonpolar and polar solvents. With less reactive alkyl halides, the use of dipolar aprotic solvents for alkylation has been marginally successful.[6] The rate of alkylation of potassium 2-methyl-2-propylpentanoate with 1-chlorohexane in four dipolar aprotic solvents at 60 °C decreased in the order HMPA > *N*-methylpyrrolidone > DMSO > DMF.[6]

The order of reactivity of the halogen in simple alkyl halides in $S_N2$ reactions is I > Br > Cl. The relative rates of the alkylation of potassium 2-methyl-2-propylpentanoate with 1-iodopentane, 1-bromopentane and 1-chlorohexane in HMPA at 60 °C are reported to be 587, 35 and 1.[6]

Elucidation of rates with variation in cation, solvent and halide ion indicates that the combination of alkyl iodides and cesium salts in HMPA offers the optimum alkylation conditions for preparative use.[6] The reactions of cesium carboxylates with alkyl halides and sulfonates will be discussed in Section 1.1.2.5 in connection with inversion processes.

One of the crucial side reactions in the displacement reactions of alkyl halides is elimination, which can generally be neglected in the reaction of primary alkyl halides. On the other hand, a considerable amount of alkene invariably forms in the reaction of secondary alkyl halides. This undesirable side reaction can be minimized by the use of cesium carboxylates.[7]

The reaction of potassium carboxylates with alkyl halides without the use of a solvent in the presence of catalytic amounts of a tetraalkylammonium salt proceeds smoothly to give the corresponding esters in good to excellent yields, except for cyclohexyl bromide where elimination mainly takes place.[5] Alkylation of *o*- and *p*-hydroxybenzoic acid selectively takes place at the $CO_2K$ group.[5a]

A more direct procedure for the displacement step is the use of a very powerful nucleophilic superoxide radical ion where an alkyl halide or sulfonate is directly converted into the corresponding alcohol (Scheme 1).[8] Elimination is an important side reaction in certain cases.[8a]

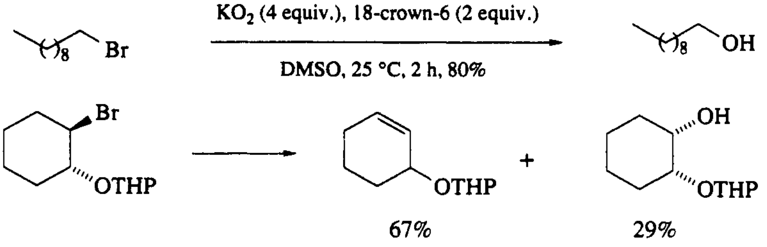

Scheme 1

On treatment with suitable oxidizing agents, alkyl iodides are transformed into products of either elimination or nucleophilic substitution, depending on the initial structure and the reaction conditions.[9] Effective oxidants include $Cl_2$, $Br_2$, $HNO_3$, $N_2O_5$, $AcONO_2$, $NOBF_4$, $NO_2BF_4$, $K_2Cr_2O_7$, $KMnO_4$, $Cl_2O_7$, $ClOClO_3$, $Cl_2O$, $(FSO_2O)_2$, $I(CO_2CF_3)_3$, $PhI(CO_2CF_3)_2$ and MCPBA (Scheme 2). The intermediacy of hypervalent organoiodides has been proposed; groups containing hypervalent iodine are good leaving groups. For example, otherwise unreactive 1-iodonorbornane can be converted into the corresponding bromide.[9]

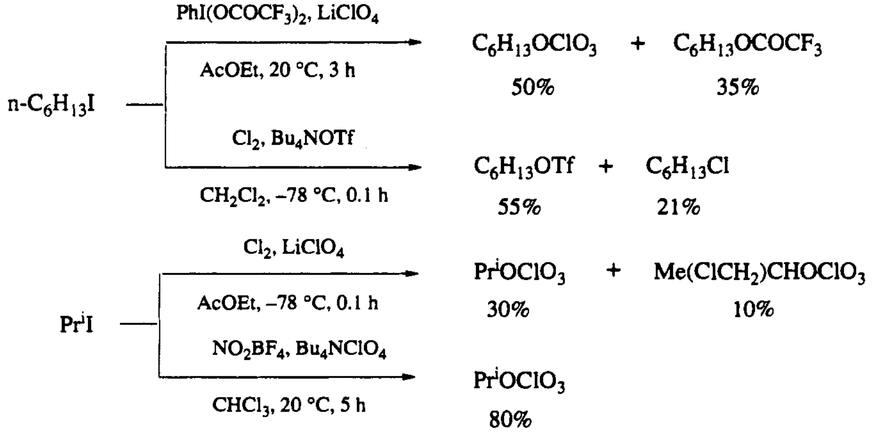
n-C6H13I
PhI(OCOCF3)2, LiClO4
AcOEt, 20 °C, 3 h
C6H13OClO3 + C6H13OCOCF3
50%
35%
Cl2, Bu4NOTf
CH2Cl2, -78 °C, 0.1 h
C6H13OTf + C6H13Cl
55%
21%
PriI
Cl2, LiClO4
AcOEt, -78 °C, 0.1 h
PriOClO3 + Me(ClCH2)CHOClO3
30%
10%
NO2BF4, Bu4NClO4
CHCl3, 20 °C, 5 h
PriOClO3
80%

**Scheme 2**

Allylic iodides with excess amounts of peroxy acids in a two-phase system in the presence of an inorganic base give the corresponding rearranged allylic alcohols in good yields (Scheme 3).[10] It has been demonstrated that the reaction proceeds under milder conditions than the Mislow–Evans reaction.[10]

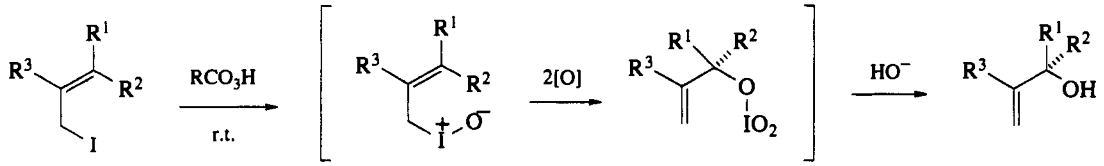
R1
R3
R2
I
RCO3H
r.t.
R1
R3
R2
I
O−
2[O]
R1
R2
R3
O
IO2
HO−
R1
R2
R3
OH

**Scheme 3**

Bis(tributyltin) oxide acts as a mild and neutral oxygen transfer agent in converting primary alkyl iodides and bromides into alcohols in the presence of silver salts in DMF (Scheme 4).[11]

$$\mathrm{RX} + (\mathrm{Bu_3Sn})_2\mathrm{O} \xrightarrow[\mathrm{DMF}]{\mathrm{AgOTf\ or\ AgNO_3}} \mathrm{ROSnBu_3} \xrightarrow[(\mathrm{H_2O})]{\text{work-up}} \mathrm{ROH}$$

**Scheme 4**

### 1.1.2.2 Deamination of Amines *via* Diazonium Salts

Treatment of a primary aliphatic amine with nitrous acid or its equivalent produces a diazonium ion which results in the formation of a variety of products through solvent displacement, elimination and solvolysis with 1,2-shift and concurrent elimination of nitrogen.[12] The stereochemistry of the deamination–substitution reaction of various secondary amines was investigated as early as 1950, when an $S_N1$-type displacement was suggested.[13] Thus, the process can hardly be utilized for the preparation of alcohols except in cases where additional factors controlling the reaction course exist. Deamination–substitution of α-amino acids can be utilized for the preparation of chiral alcohols.

The reaction of optically active α-amino acids with nitrous acid or nitrosyl chloride gives α-hydroxy or α-halo acids with retention of configuration due to the neighboring carboxylate participation.[14–17] Examination of the reaction of phenylalanine and its *para*-substituted derivatives revealed that the product distribution and outcome of the stereochemistry depend on both the solvent used and the substituent on the aromatic ring. The results may be rationalized by assuming the intermediacy of an unstable lactone (**1**). When a solvent of high nucleophilicity is used, it attacks the α-carbon of (**1**) from the backside of the oxygen to give the corresponding substituted product with net retention of configuration. When the reaction is carried out in a solvent of low nucleophilicity, the aryl group migration takes place prior to intermolecular displacement to afford the migration product (Scheme 5).[18]

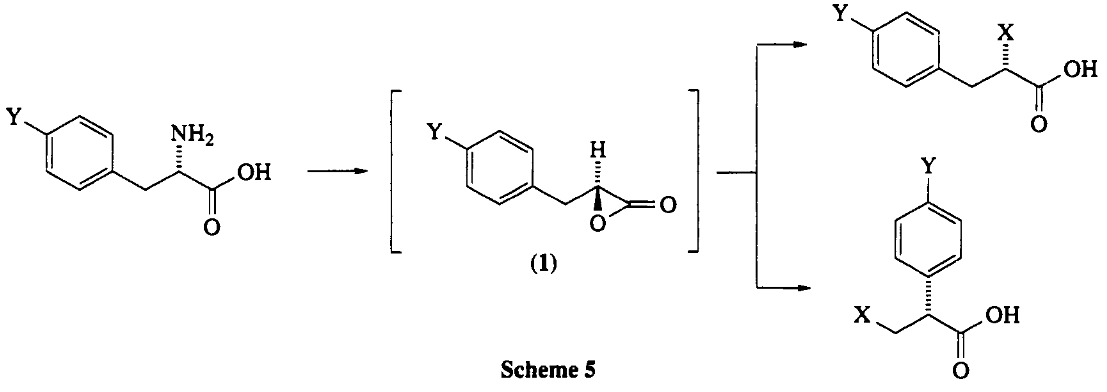

**Scheme 5**

Contrary to the case of free α-amino acids, deamination–substitution of esters of α-amino acids generally proceeds with racemization with excess inversion about the α-carbon atom.[13,18] However, reaction of the ethyl ester of phenylalanine and its derivatives with sodium nitrite in trifluoroacetic acid affords substitution products with retention of configuration and migration products with inversion of configuration. This result may be explained by assuming initial formation of the phenonium intermediate (**2**; Scheme 6).[18]

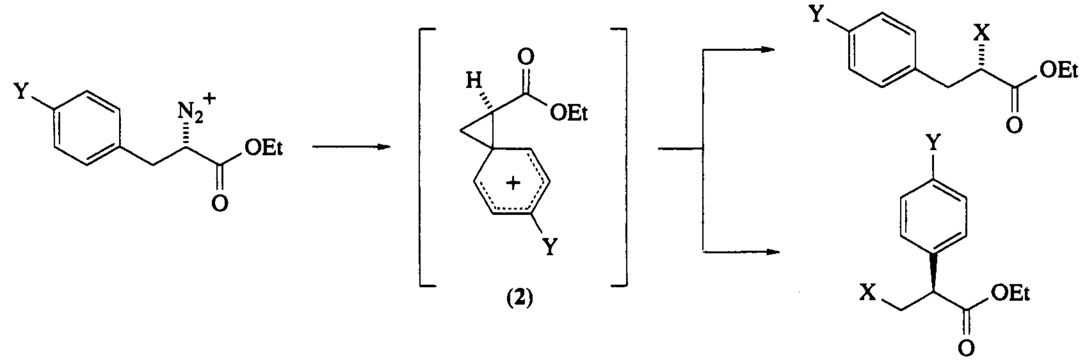

**Scheme 6**

### 1.1.2.3 Oxirane Ring Opening by Carbon Nucleophiles

#### *1.1.2.3.1 Reaction of epoxides with organometallic reagents*

The reaction of epoxides with carbon nucleophiles generates new carbon–carbon σ-bonds, and this reaction can be utilized as a versatile procedure for the preparation of a variety of alcohols, provided that the ring opening takes place in a regioselective manner. This section deals with the reactions of organometallic reagents with 2,3-epoxy alcohols and conjugated epoxides, *i.e.* where the oxirane ring is directly bonded to a π-electron system. The behavior of conjugated epoxides toward nucleophiles can be rationalized in terms of the principle of 'hard and soft acids and bases (HSAB)'.[19]

The reactions of epoxides with organometallic reagents are sometimes curtailed owing to competing reactions arising from the Lewis acidity or basicity of the organometallics used.[20] The hardness of the organometallic reagent (RLi > RMgX > RCu or $R_2CuLi$) is directly related to the metal atom.[21] Of carbon nucleophiles, organocuprates are the reagents of choice, while Grignard reagents sometimes result in concomitant formation of side products arising from the substitution by halide ion.[19a,20] Higher order mixed organocuprates of the general formula $R_2Cu(CN)Li_2$ are superior to $R_2CuLi$.[22] The cyanocopper reagents are considered to be softer than the cuprate and simple copper reagents.[19c] The reactions using organoaluminum reagents are interesting alternatives to those using organocopper reagents where complementary regioselectivity is generally observed.[23] It is noteworthy that the addition of $BF_3{\cdot}Et_2O$ causes enhancement of reactivity.[23e]

### *1.1.2.3.2 2,3-Epoxy alcohols*

The partial structural unit with definite configuration at three consecutive chiral centers, (**3**), (**4**), (**5**) or (**6**), is often found in natural products (Scheme 7).

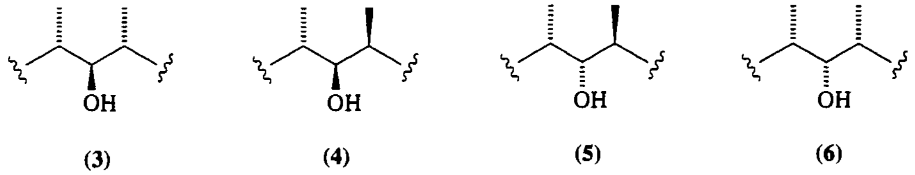

Scheme 7

Kishi and coworkers have studied the ring opening of 2,3-epoxy alcohols having different stereochemistry.[24] (*Z*)-Epoxy alcohol (**7**) reacted with $Me_2CuLi$ to give exclusively (**8**). Alternatively, the reaction of (**7**) with vinylcuprate followed by deoxygenation afforded (**9**). The reaction of (**10**) with $Me_2CuLi$ gave (**11**; Scheme 8).[24]

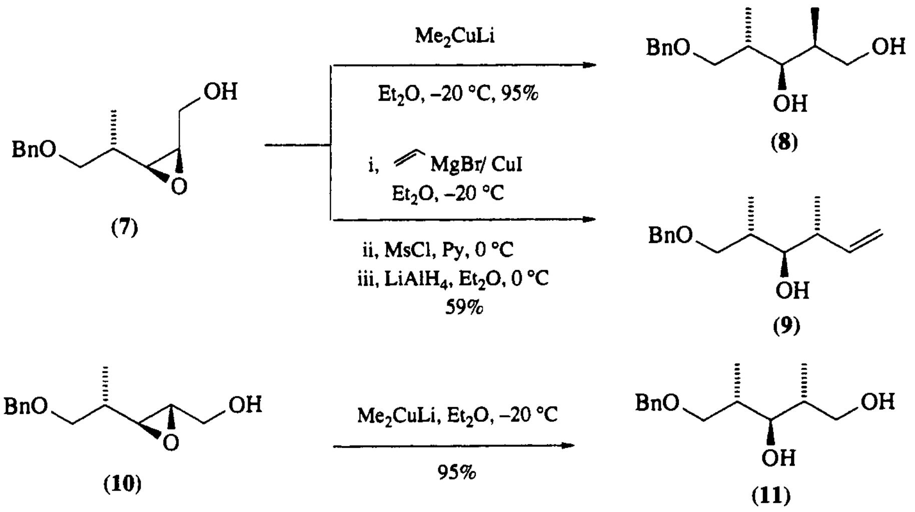

Scheme 8

The reaction of (**12**) with $Me_2CuLi$ also takes place at C-2 to give (**13**) without contamination of the regioisomeric 1,2-diol.[25] In the reaction of tritylated 3,4-epoxy alcohol (**14**; Scheme 9) with homoallylcuprate (**15**), addition of $BF_3{\cdot}Et_2O$ was required for the initiation of the reaction producing (**16**) along with a small amount of (**17**).[26]

The reaction of (*E*)-(**18**) with $Me_2CuCNLi_2$ shows a moderate level of regioselectivity, giving a 6:1 ratio of 1,3-diol (**19a**) and regioisomeric 1,2-diol (**20**).[27a] The corresponding (*Z*)-epoxide (*Z*)-(**18**) reacts with $Me_2CuLi$ to give the 1,3-diol (**19b**) as the sole product.[27b] The reaction of the less-hindered epoxide (**21**) or (**22**) with $Me_2CuLi$ does not show any regioselectivity, affording a mixture of isomeric diols in a ratio of 1:1 (Scheme 10).[24a,27c] These results suggest that the regiochemical preference observed in the reactions of epoxy alcohols appears to be steric in origin.[27d]

On the other hand, the reaction of (**23a**) with $Me_2CuLi$ yields a 55:45 mixture of 1,2- and 1,3-diols. The reaction of the TBDMS derivative (**23b**) with $Me_2CuLi$ under identical conditions results in the formation of (**24**) with about 20:1 regioselectivity. In this case, the regioselectivity observed has been attributed to complexation of the nucleophile with the substrate.[28]

C-3 selectivity has been attained by the use of 2,3-epoxy alcohols having a bulky protective group. Thus, (**25**) reacts with alkenylmagnesium bromide (**26**) in the presence of a catalytic amount of CuI to

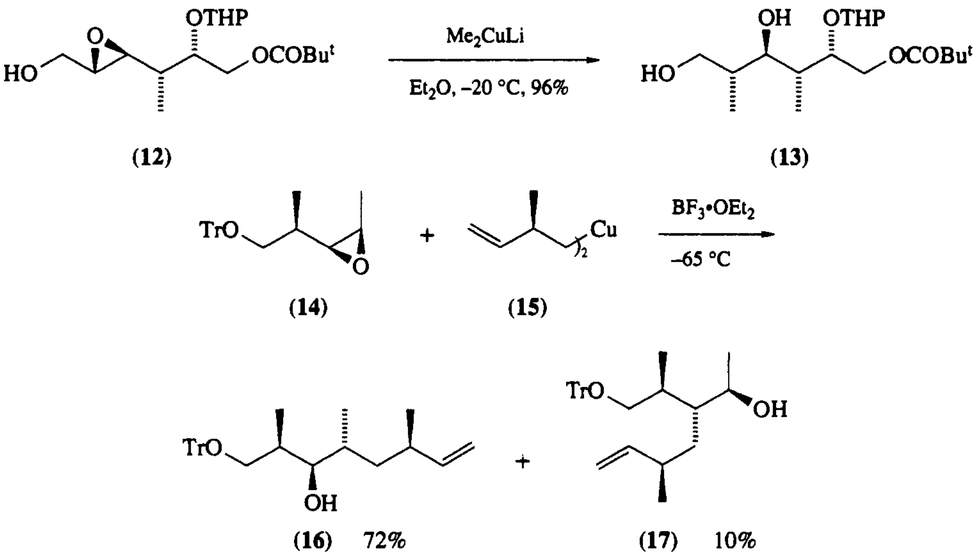
OTHP
O
HO
OCOBu$^t$
Me$_2$CuLi
Et$_2$O, -20 °C, 96%
OH
OTHP
HO
OCOBu$^t$
(12)
(13)
TrO
O
+
Cu
2
BF$_3$•OEt$_2$
-65 °C
(14)
(15)
TrO
OH
+
TrO
OH
(16) 72%
(17) 10%

Scheme 9

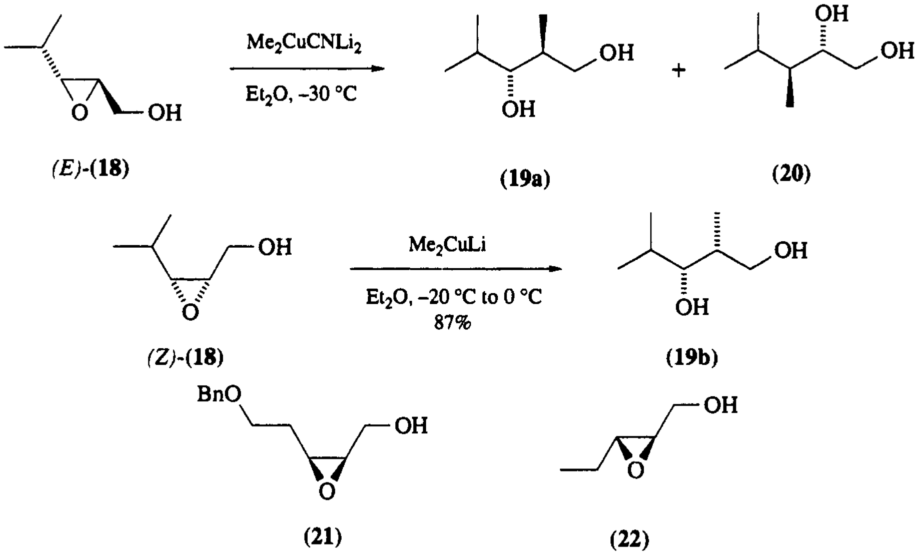
O
OH
Me$_2$CuCNLi$_2$
Et$_2$O, -30 °C
OH
OH
+
OH
OH
(E)-(18)
(19a)
(20)
OH
O
Me$_2$CuLi
Et$_2$O, -20 °C to 0 °C
87%
OH
OH
(Z)-(18)
(19b)
BnO
OH
O
OH
O
(21)
(22)

Scheme 10

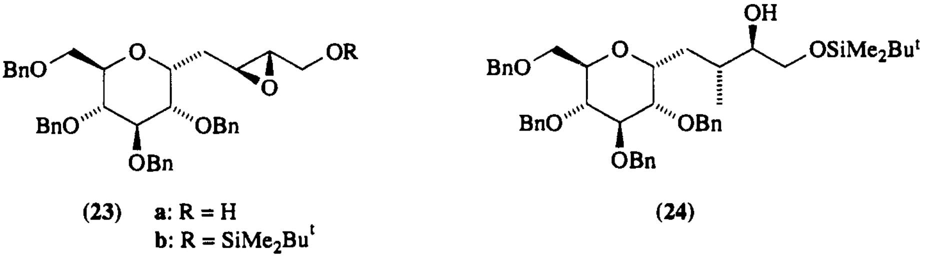
BnO
O
OR
O
BnO
OBn
OBn
OH
BnO
O
OSiMe$_2$Bu$^t$
BnO
OBn
OBn
(23) a: R = H
b: R = SiMe$_2$Bu$^t$
(24)

Scheme 11

give (**27**) as the sole product.[29a] Contrary to the case of (**25**), the reaction of (**28**) with a variety of organocuprates gives (**29**) and (**30**) in ratios ranging from 1:1 to 1.5:1, favoring the 1,3-diol derivative (**29**). However, when the reaction was carried out with 2 equiv. each of Me$_2$CuLi and BF$_3$·Et$_2$O, (**29**) and (**30**) were formed in a ratio of 15:85 (Scheme 12).[29b]

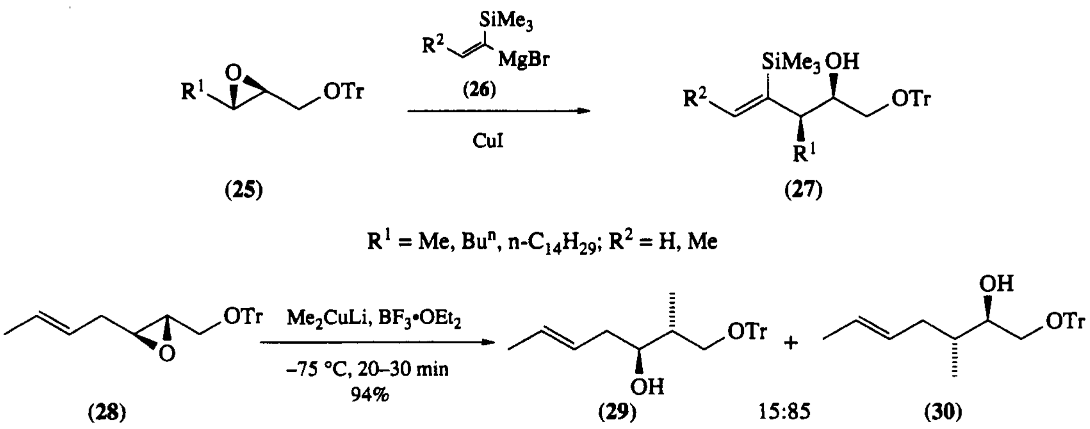

**Scheme 12**

C-3 attack predominantly takes place in the reaction of 2,3-epoxy alcohols with organoaluminum compounds such as Me$_3$Al, PhC≡CAlEt$_2$, Me$_3$SiC≡CAlEt$_2$, Bu$^i_2$AlH and Bu$^i_3$Al.[30] The yield and stereochemical outcome depend on the substrates and organoaluminum reagents used.[30c]

The following examples illustrate the complementary regioselectivities exhibited in the reactions using Me$_2$CuLi and Me$_3$Al (Scheme 13).[30a,30b] One problem which remains to be solved, however, is the proclivity of alkylaluminum reagents such as Et$_3$Al to serve as hydride donors.[30a]

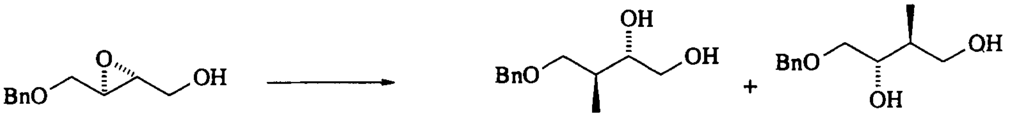

| *Conditions* | *Ratio* |
|---|---|
| Me$_2$CuLi, Et$_2$O, −20 °C | 1:6 |
| Me$_3$Al, CH$_2$Cl$_2$, 0–23 °C | 5:1 |

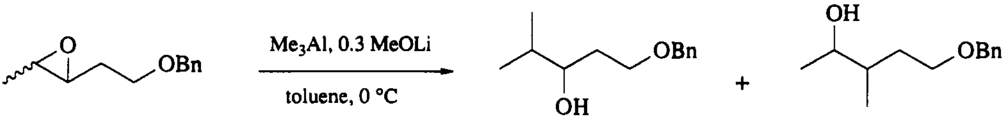

| *Reagents* | *Yield (%)* | *Ratio* |
|---|---|---|
| (*Z*)-epoxide | 87 | 95:5 |
| (*E*)-epoxide | 85 | 99:1 |

**Scheme 13**

Epoxide (**31**) reacts with 2 equiv. of lithium acetylide–ethylenediamine complex at the C-3 position.[31] Terminal epoxide (**32**) reacts smoothly with the lithium alkynide (**33**) to give a 1,2-diol in good yield.[32] Alkynylboranes (**34**) have been demonstrated to be useful for alkynylation of epoxides (Scheme 14).[33]

The reactions of 2,3-epoxy alcohols with organometallic reagents are influenced by various factors which include not only the solvent and the structure of the reactants but also the gegen cation of the oxyanion of the epoxy alcohol. Sulfone-stabilized allyllithium (**35b**) reacts sluggishly with lithium alkoxide (**36a**) in THF–HMPA to give the coupled product (**37a**) in 9% yield with 90% recovery of (**35a**). Under identical conditions, however, the magnesium epoxide (**36b**) gave (**37a**) in 70% yield as an 8:1 mixture of diastereomers. In contrast, (**36a**) reacts negligibly with (**35b**) in THF. Furthermore, the TMS ether (**36c**) and the ethoxyethyl (EE) ether (**36d**) give no coupling product at all with (**35b**). Although the thiophenyl-stabilized allyllithium (**35c**) is more reactive than (**35b**), the corresponding coupling product (**37b**) is obtained as a 1:1 mixture of diastereomers (Scheme 15).[34]

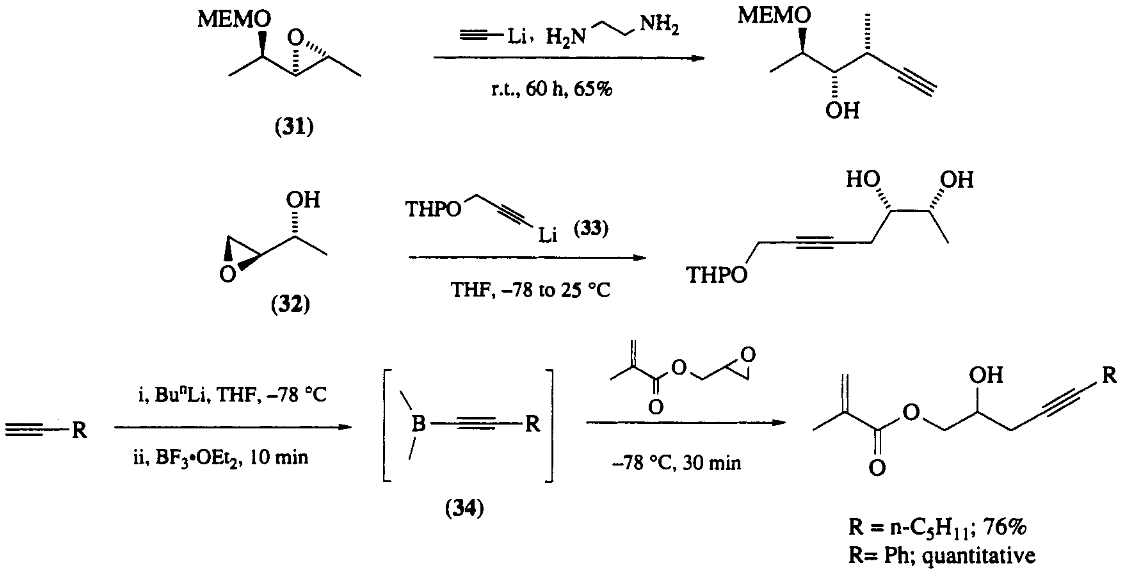
MEMO
(31)
≡—Li, $H_2N$⁀⁀$NH_2$
r.t., 60 h, 65%
MEMO
OH
OH
O
(32)
THPO
Li (33)
THF, −78 to 25 °C
HO
OH
THPO
≡—R
i, $Bu^nLi$, THF, −78 °C
ii, $BF_3•OEt_2$, 10 min
B—≡—R
(34)
O
O
−78 °C, 30 min
OH
R
O
O
R = n-$C_5H_{11}$; 76%
R= Ph; quantitative

**Scheme 14**

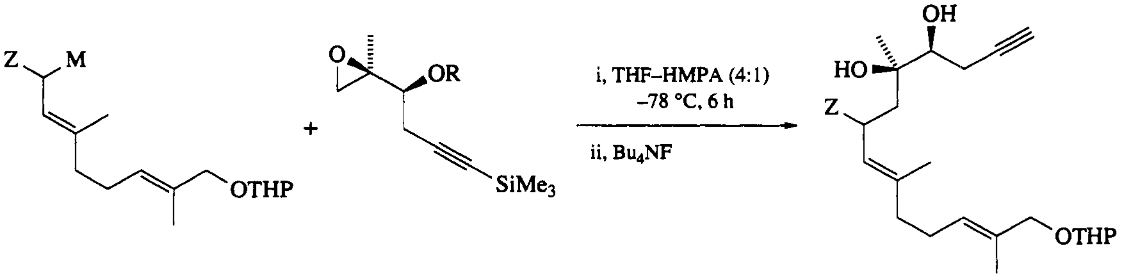
Z
M
OTHP
+
O
OR
$SiMe_3$
i, THF–HMPA (4:1)
−78 °C, 6 h
ii, $Bu_4NF$
OH
HO
Z
OTHP

(35) a: Z = $SO_2Ph$; M = H
b: Z = $SO_2Ph$; M = Li
c: Z = SPh; M = Li

(36) a: R = Li
b: R = MgBr
c: R = $SiMe_3$
d: R = CH(Me)OEt

(37) a: Z = $SO_2Ph$
b: Z = SPh

**Scheme 15**

The reaction of (*Z*)-3-hydroxycyclohexene oxide (**38a**) with $Me_2CuLi$ gave 1,2-diol (**39a**) in preference to 1,3-diol (**40a**), while the (*E*)-isomer (**41a**) showed the reversed regioselectivity. The corresponding methyl ethers (**38b**) and (**41b**) showed even lower regioselectivity than the unprotected substrates.[35a] These results suggest that the regioselectivity is controlled by various factors, including conformational effects.

Danishefsky and coworkers have studied the ring opening reactions of a series of (*Z*)- and (*E*)-epoxides, (**38a**), (**38c**), (**41a**) and (**41c**), with $^-CH_2CO_2^-$ and with $Et_2AlC{\equiv}COEt$ and have demonstrated that the reaction course in the alane opening depends largely on the stereochemical relationship between the oxy function and the epoxide, and only to an insignificant extent on whether the oxygen is initially in the form of a hydroxy group or a trimethylsilyl ether. On the other hand, in the dianion case, the nature of the oxygen, rather than its stereochemical relationship with the epoxide, is decisive for the regioselectivity of the ring opening.[35b]

Regioselectivity is markedly enhanced in conformationally more biased systems such as carbohydrates and fused bicyclic compounds. Some examples are shown in Scheme 17.[36–38]

In view of the large number of naturally occurring polyols having definite configuration, a variety of methodologies to construct such systems by utilizing the reactivity of epoxides have been reported.[39]

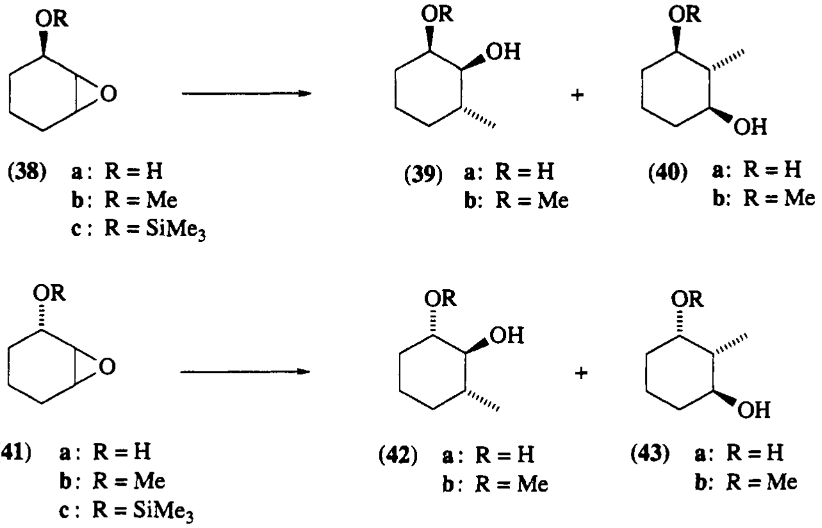

(38) a: R = H
b: R = Me
c: R = SiMe$_3$

(39) a: R = H
b: R = Me

(40) a: R = H
b: R = Me

(41) a: R = H
b: R = Me
c: R = SiMe$_3$

(42) a: R = H
b: R = Me

(43) a: R = H
b: R = Me

Scheme 16

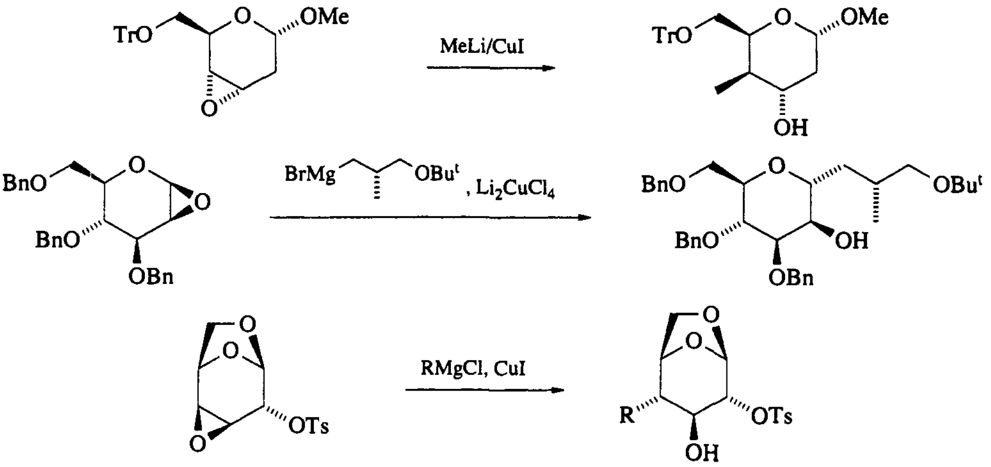

Scheme 17

### 1.1.2.3.3 Vinyl epoxides

The reaction of 3,4-epoxy-1-butene (**44**) with Grignard reagents affords a mixture of products resulting from direct attack on the oxirane ring ($S_N2$) and on the double bond ($S_N2'$). The product distribution depends on the nature of the Grignard reagents. Alkyllithiums are favored for the direct attack on the oxirane carbon (C-3 attack), while lithium dialkylcuprates give the $S_N2'$ displacement products (C-1 attack) with high regioselectivity (Scheme 18, Table 1).[20b,22,40]

The regioselectivity of the reaction of organo-yttrium and -lanthanoid reagents with (**44**) is complementary (C-3 attack) to that obtained with organocuprates (Table 1).[40b]

In contrast to the reactions of acyclic substrates, 3,4-epoxycyclohexene (**48**) reacts with Me$_2$CuLi to give both $S_N2$ and $S_N2'$ displacement products (**49**) and (**50**).[41] By the use of MeCuCNLi, however, (**48**) gives (**49**) in 95% yield (100% *trans*).[42a] The resulting product of general formula (**51**) can be converted into an epoxy enol ether (**52**) which again undergoes anti-$S_N2'$ reaction with MeCuCNLi to produce (**53**) in essentially quantitative yield (Scheme 19).[42b,43]

The reaction has been extended to 1,4-chirality transfer. For instance, epoxide (**54**) reacts with lithium isohexylcyanocuprate to afford isomerically pure (**55**; Scheme 20).[42c] This strategy has been applied to the total synthesis of prostaglandins.[42d]

In general, $S_N2'$ displacement on cyclic vinyl epoxides by organocopper reagents has been found to proceed with inversion (*anti* pathway). However, acyclic vinyl epoxides can react *via* either *s-cis* or

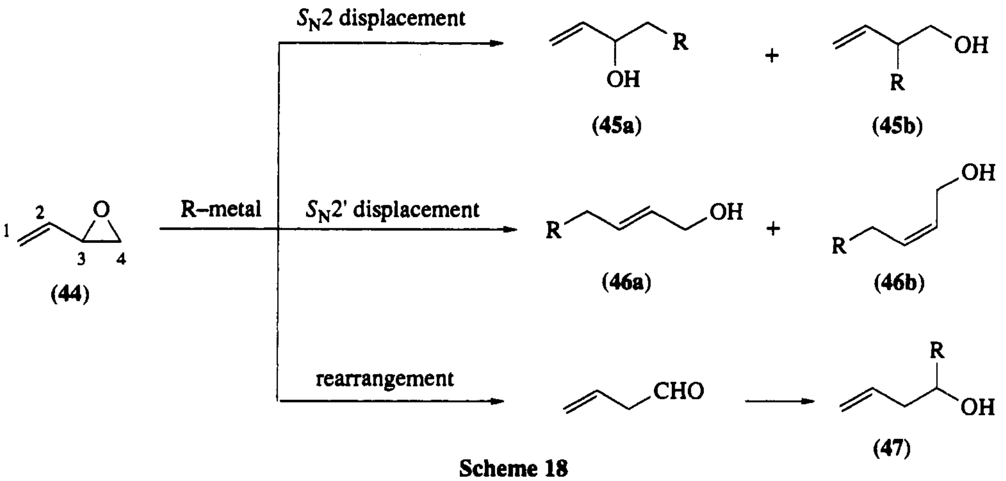
$S_N2$ displacement
R–metal
$S_N2'$ displacement
rearrangement
1
2
3
4
O
(44)
(45a)
(45b)
(46a)
(46b)
(47)
R
OH
CHO
+

Scheme 18

Table 1 Reaction of (44) with Organometallics (Scheme 18)

| *R–metal* | *Yield (%)* | *Product distribution* (*45a*) | (*45b*) | (*46*) | (*46a:46b*) | (*47*) | *Ref.* |
|---|---|---|---|---|---|---|---|
| MeMgBr | | 1 | 36 | 44 | (3.1:1) | 19 | 20b |
| $Me_2Mg$ | | 1 | 81 | 16 | (4.7:1) | 2 | 20b |
| MeLi | | 17 | 63 | 20 | (1.1:1) | | 20b |
| $Me_2CuLi$ | | | 6 | 94 | (3.8:1) | | 20b |
| $Ph_2CuCNLi_2$ | 96 | | | 100 | (4:1)[a] | | 22 |
| $Me_3Al$ | 54 | <1 | 85 | 13 | (6:1) | | 40b |
| MeLi/Sm[N(TMS)$_2$]$_3$ | 85 | 2 | 95 | <2 | (1:1) | | 40b |
| MeLi/Y[N(TMS)$_2$]$_3$ | 80 | <1 | 96 | <3 | (1:1) | | 40b |

[a] 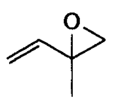 was used.

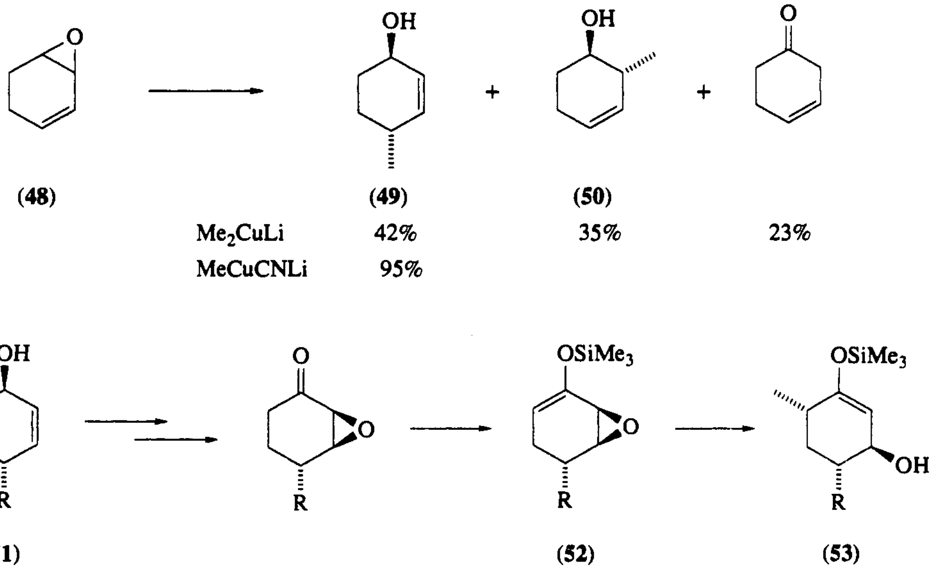
(48)
(49)
(50)
(51)
(52)
(53)
O
OH
$Me_2CuLi$
42%
35%
23%
MeCuCNLi
95%
R
$OSiMe_3$
+

Scheme 19

*s- trans* conformers and thus yield mixtures of (*E*)- and (*Z*)-products of $S_N2'$ reaction.[44] Marshall and coworkers have studied the reactions of (*E*)- and (*Z*)-vinyl epoxides, (*E*)-(**56**) and (*Z*)-(**56**), with methylcuprates where not only $S_N2'$ displacement products (*E*)-(**57**) and (*Z*)-(**57**) but also $S_N2$ displacement

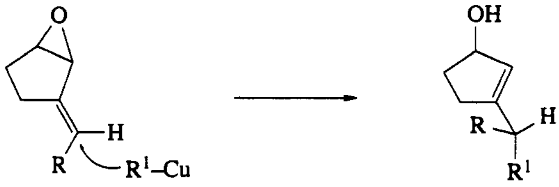

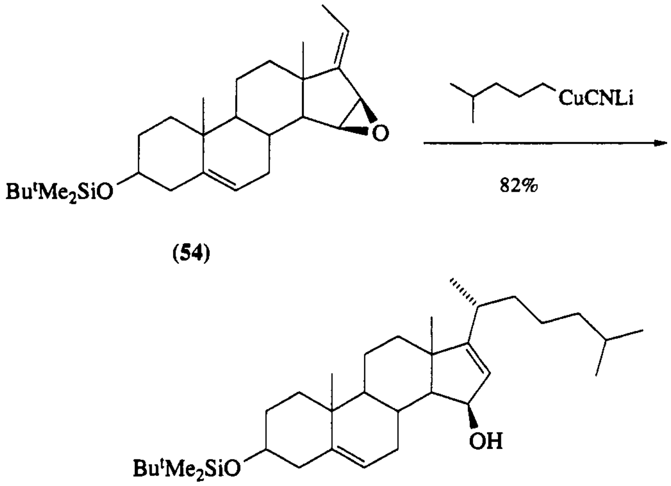

**(54)**

**(55)**

**Scheme 20**

products (*E*)-(**58**) and (*Z*)-(**58**) are formed, and diene (**59**) as well (Scheme 21, Table 2).[44] The more-substituted systems, (*E*)- and (*Z*)-(**60**), and (*E*)- and (*Z*)-(**61**), yield only $S_N2'$ displacement products. In all the cases examined ($Me_2CuLi$, $THF/Et_2O$ 4:1, 0 °C and MeCuCNLi, $Et_2O$, 0 °C), *anti* attack is more favorable than *syn* attack.[44]

On treatment with a palladium(0) catalyst, vinyl epoxides undergo facile unimolecular rearrangement to give dienols or enones depending on the substitution pattern of the substrate.[45] In the presence of an active methylene compound in the reaction system, however, a single alkylation product is formed.[46] Cyclic and acyclic vinyl epoxides participate equally well. The reaction proceeds with clean alkylation from the same face as the oxygen of the epoxide, and proceeds with allyl inversion (Scheme 22).[46]

### *1.1.2.3.4 2,3-Epoxy acids*

The reactions of organometallics with 3-substituted glycidic esters proceed through C-2 or C-3 attack depending on the nature of the reagent. With organocuprates, preferential C-2 attack generally takes place.[47] Thus, the ring opening reactions of methyl 2,3-epoxycarboxylates (**62a**) to (**62d**) with organocuprates proceed with perfect regio- and stereo-control to give the corresponding 3-hydroxycarboxylates (**63**) in around 60% isolated yields with >99% inversion at C-2.[48] However, 2,3-epoxy esters having α-branched substituents at the C-3 position (**62e**, **62f**) are inert and are recovered unchanged (Scheme 23).[48]

On the other hand, terminal epoxy esters react with cuprates $R_2CuM$ (M = Li, Mg) at the C-3 position to afford exclusively 2-hydroxy esters (Scheme 23).[47a]

C-3 attack on nonterminal 2,3-epoxy esters takes place when organoaluminum reagents are used instead of cuprates (Scheme 24).[49]

The reactions of (*E*)-2,3-epoxy acids (*E*)-(**64**) with organocopper reagents afford the products of attack at C-2 (**65**) in preference to those at C-3 (**66**), while (*Z*)-isomer (*Z*)-(**64**) undergoes C-3 attack to give (**68**) as the main products (Scheme 25).[50]

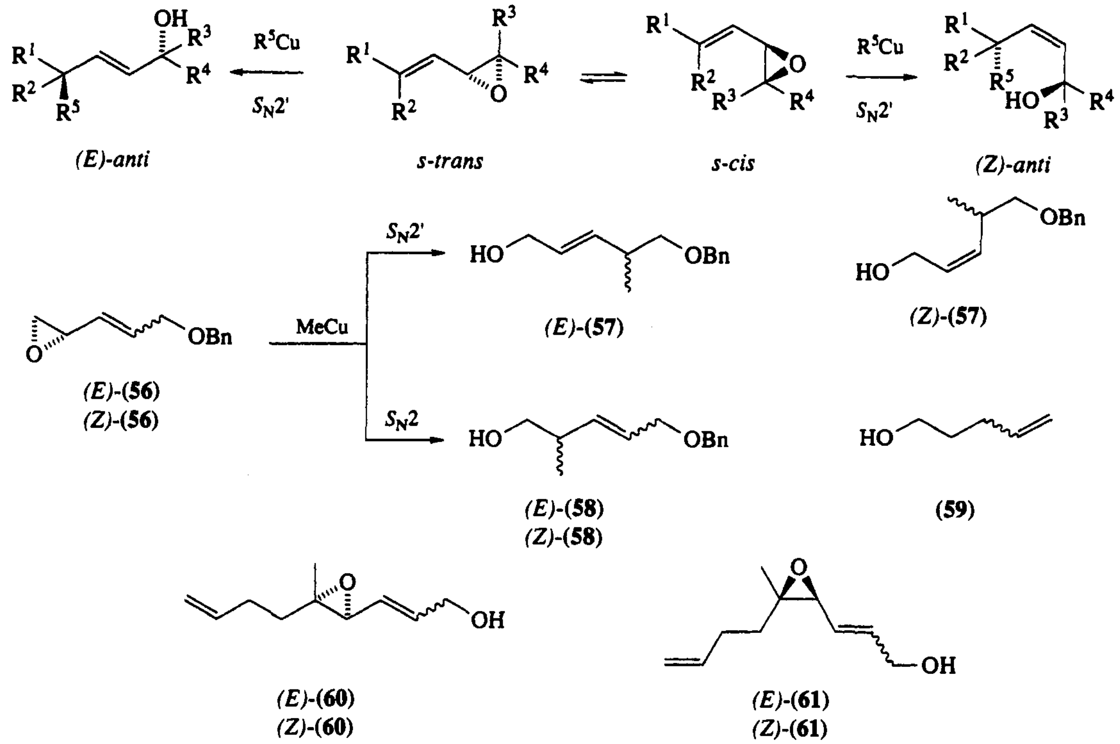
OH
R1
R2
R3
R4
R5
R5Cu
SN2'
(E)-anti
s-trans
s-cis
(Z)-anti
O
OBn
MeCu
SN2'
SN2
HO
(E)-(56)
(Z)-(56)
(E)-(57)
(Z)-(57)
(E)-(58)
(Z)-(58)
(59)
OH
(E)-(60)
(Z)-(60)
(E)-(61)
(Z)-(61)

**Scheme 21**

**Table 2** Cuprate Addition to (*E*)-(**56**) and (*Z*)-(**56**) (Scheme 21)[44]

| *Substrate* | *Method*[a] | *Yield* (%) | $S_N2'$ (*E*)-(57) | $S_N2'$ (*Z*)-(57) | $S_N2$ (*E*)-(58) | $S_N2$ (*Z*)-(58) | (59) | $S_N2'/S_N2$ |
|---|---|---|---|---|---|---|---|---|
| (*E*)-(**56**) | A | 87 | 69.5 | 7.3 | 11.8 | 0 | 11.4 | 5.6 |
| (*Z*)-(**56**) | A | 83 | 81.0 | 0 | 2.9 | 6.1 | 10.0 | 9.0 |
| (*E*)-(**56**) | B | 76 | 28.2 | 60.6 | 12.2 | 0 | 0 | 7.9 |
| (*Z*)-(**56**) | B | 78 | 82.2 | 0 | 0 | 11.8 | 6.0 | 7.0 |

[a] A: MeCuCNLi, $Et_2O$, 0 °C. B: MeLi, CuI, $BF_3 \cdot Et_2O$, THF/$Et_2O$ (5:1), −78 to 25 °C.

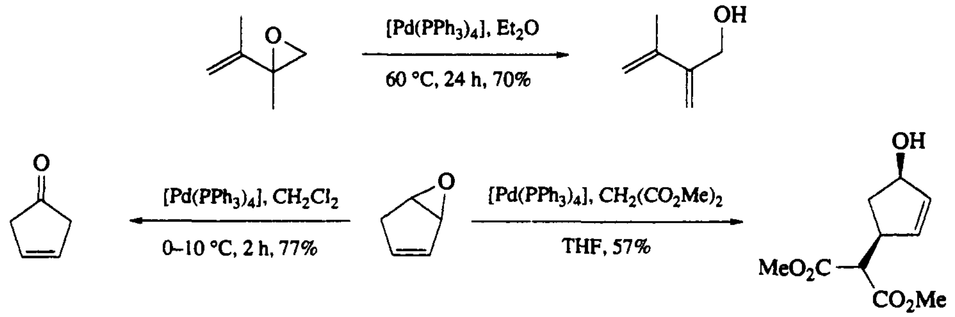
O
[Pd(PPh3)4], Et2O
60 °C, 24 h, 70%
OH
O
[Pd(PPh3)4], CH2Cl2
0–10 °C, 2 h, 77%
O
[Pd(PPh3)4], CH2(CO2Me)2
THF, 57%
OH
MeO2C
CO2Me

**Scheme 22**

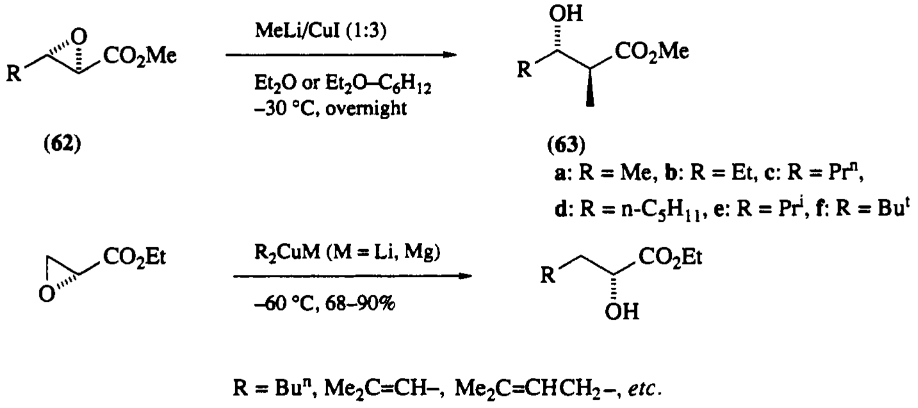
(62)
MeLi/CuI (1:3)
$Et_2O$ or $Et_2O–C_6H_{12}$
–30 °C, overnight
(63)
a: R = Me, b: R = Et, c: R = $Pr^n$,
d: R = n-$C_5H_{11}$, e: R = $Pr^i$, f: R = $Bu^t$
$R_2CuM$ (M = Li, Mg)
–60 °C, 68–90%
R = $Bu^n$, $Me_2C$=CH–, $Me_2C$=CH$CH_2$–, etc.

Scheme 23

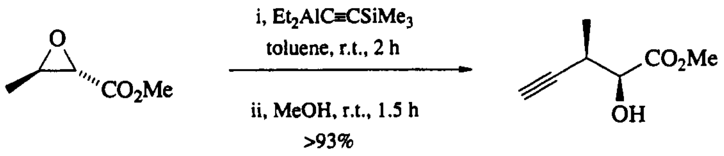
i, $Et_2AlC≡CSiMe_3$
toluene, r.t., 2 h
ii, MeOH, r.t., 1.5 h
>93%

Scheme 24

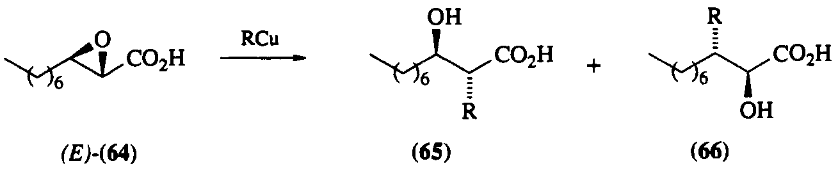
RCu
(E)-(64)
(65)
(66)

| *Reagent* | *Yield (%)* | *Ratio (65):(66)* |
|---|---|---|
| $Me_2CuLi$ | 91 | 8:1 |
| $Bu^n{}_2CuLi$ | 93 | 12:1 |
| $Bu^n{}_2CuCNLi_2$ | 87 | 8:1 |
| $Ph_2CuCNLi_2$ | 81 | 6:1 |

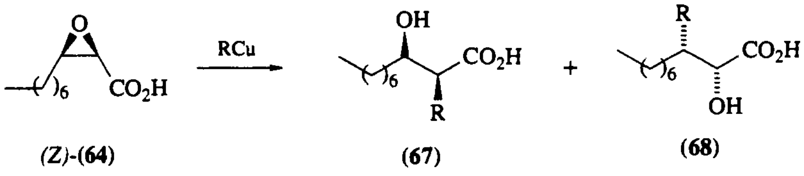
RCu
(Z)-(64)
(67)
(68)

| *Reagent* | *Yield (%)* | *Ratio (67):(68)* |
|---|---|---|
| $Me_2CuLi$ | 84 | 1:17 |
| $Bu^n{}_2CuLi$ | 88 | 1:11 |
| $Bu^n{}_2CuCNLi_2$ | 89 | 1:16 |
| $Ph_2CuCNLi_2$ | 82 | 1:7 |

Scheme 25

### 1.1.2.4 Rearrangement Reactions Leading to Alcohols

#### *1.1.2.4.1 Sigmatropic rearrangement*

[2,3] Sigmatropic rearrangements such as the Wittig rearrangement and the rearrangements of sulfoxides and selenoxides are considered as intramolecular $S_N2'$ reactions producing unsaturated alcohols and have long received widespread interest because of their synthetic importance. The reactions involving 1,2-shift can, in a sense, also be considered as intramolecular displacements and generally take place with high stereospecificity with respect to the migrating group and the migration terminus. This section briefly deals with some 1,2-rearrangement processes which can be utilized in the preparation of chiral alcohols. Since [2,3] sigmatropic rearrangements and organoboron chemistry have been surveyed in excellent review articles and monographs,[51] these subjects are not covered in this section.

#### *1.1.2.4.2 Epoxy silyl ether rearrangement*

The Lewis acid mediated rearrangement of epoxy silyl ether (**69**) affords the corresponding β-hydroxycarbonyl compound (**70**; Scheme 26).[52]

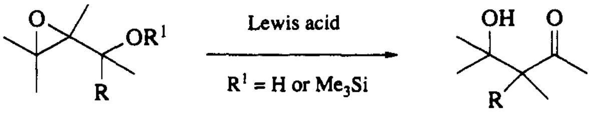

**(69)** **(70)**

**Scheme 26**

In the reaction of α,α,β-trialkyl derivative (**71a**), facile migration of the alkyl group is observed, whereas the aryl group migrates preferentially from the alkyl aryl derivative (**71b**; Scheme 27, Table 3).[52]

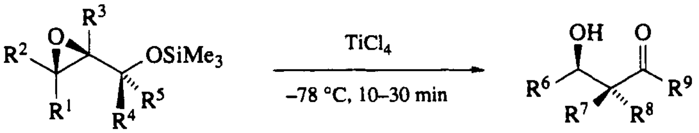

**(71a)–(71g)** **(72)–(77)**

**Scheme 27**

In the case of β-monosubstituted derivatives (**71c**) to (**71g**), only aryl and alkenyl groups participate in the selective 1,2-rearrangement, reflecting the low migratory aptitude of the alkyl group. The rearrangement is highly stereoselective with respect to the geometry of the epoxide moiety but not to the configuration of the alkoxy α-carbon. Thus, both *erythro–trans* isomer (**71c**) and *threo–trans* isomer (**71d**) give the same *threo*-aldol (**74**) as the sole isolable product, while *threo–cis* isomer (**71e**) exclusively gives *erythro*-aldol (**75**). Epoxides (**71f**) and (**71g**) give (**76**) and (**77**), respectively.[52] These results can be interpreted as the rigorous *anti* migration of the phenyl and alkenyl groups with complete retention of the alkene geometry.[52,53]

Concerning Lewis acids, a catalytic amount of $Me_3SiI$ or $Me_3SiOTf$, as well as a stoichiometric amount of $TiClO_4$ or $BF_3{\cdot}Et_2O$, is effective. The favorable choice of Lewis acids with respect to the substitution pattern of the substrates has been reported.[54] This methodology has been successfully utilized in the total synthesis of natural products which include avenaciolide and mycinolide IV.[54,55]

#### *1.1.2.4.3 Criegee rearrangement*

The acylations of α-alkoxy hydroperoxides such as (**79**) furnish peroxy esters that are related to the intermediate produced in the Baeyer–Villiger reaction.[56–58] The peroxy ester undergoes the Criegee rearrangement to a dioxonium ion which in turn is converted into an ester. Thus, ozonolysis of (+)-(*E*)-dihydrocarvone (**78**) affords a 1:1 mixture of diastereomers (**79**). Acetylation and rearrangement

**Table 3** Rearrangement of (71) (Scheme 27)[52]

| *(71)* | | | | *Substrate* | | *Product number* | | | *Product* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *R*$^5$ | | *R*$^6$ | *R*$^7$ | *R*$^8$ | *R*$^9$ | *Yield (%)* |
| **a** | H | H | Me | Me | Me | (72) | H | Me | Me | Me | 48 |
| **b** | H | H | Me | Ph | Me | (73) | H | Me | Ph | Me | 75 |
| **c** | H | Me | H | Ph | Me | (74) | Me | H | Ph | Me | 95 |
| **d** | H | Me | H | Me | Ph | (74) | | | | | 79 |
| **e** | Me | H | H | Me | Ph | (75) | Me | Ph | H | Me | 81 |
| **f** | H | Pr | H | $CH_2CH_2Ph$, $CH_2{=}CTMS$ | | (76) | Pr | H | $CH_2{=}CTMS$ | $CH_2CH_2Ph$ | 98 |
| **g** | Pr | H | H | $CH_2CH_2Ph$, $CH_2{=}CTMS$ | | (77) | Pr | $CH_2{=}CTMS$ | H | $CH_2CH_2Ph$ | 75 |

provides (**81a**) and (**81b**) in 60% and 20% yields, respectively, after aqueous work-up.[56] The intermediate peroxy acetate (**80**) can be isolated (84% yield) and purified (Scheme 28).[56] Similarly, lactone (**82**) is successfully converted into (**84**), which is differentially functionalized at the termini of the growing chain, *i.e.* primary hydroxy group and double bond.[58]

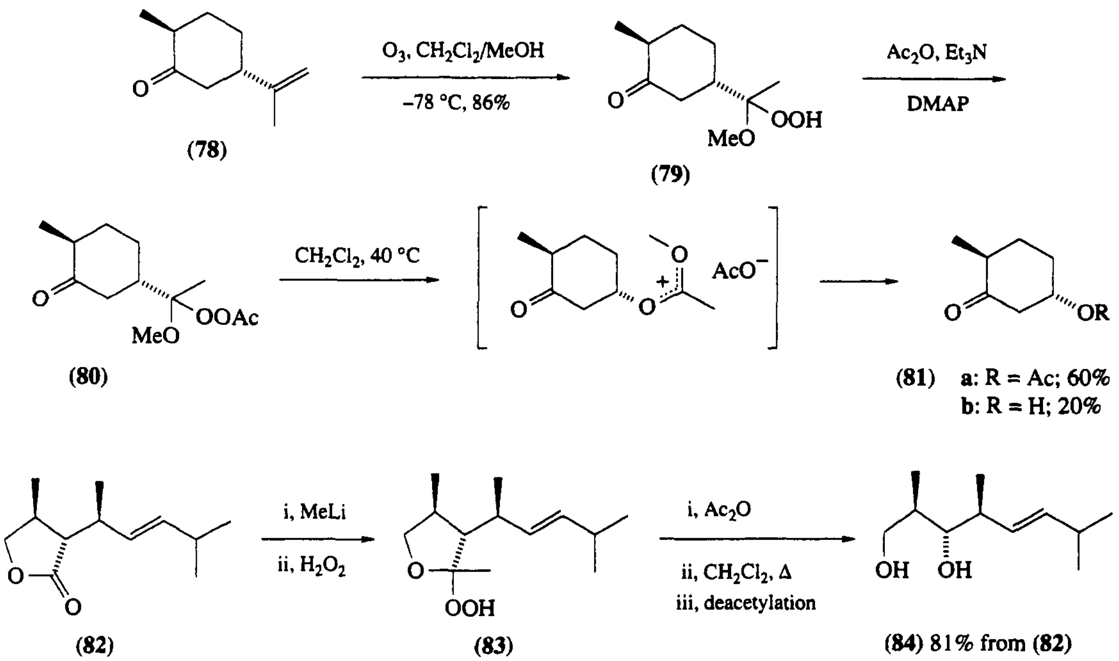
(78)
O₃, CH₂Cl₂/MeOH
–78 °C, 86%
OOH
MeO
(79)
Ac₂O, Et₃N
DMAP
OOAc
MeO
(80)
CH₂Cl₂, 40 °C
AcO⁻
OR
(81) a: R = Ac; 60%
b: R = H; 20%
(82)
i, MeLi
ii, H₂O₂
OOH
(83)
i, Ac₂O
ii, CH₂Cl₂, Δ
iii, deacetylation
OH OH
(84) 81% from (82)

**Scheme 28**

### *1.1.2.4.4 Oxidative cleavage of silicon–carbon bonds leading to alcohols*

Certain functionalized silyl groups bonded to $sp^3$- or $sp^2$-carbon atoms (**85**) are readily converted into hydroxy groups on treatment with peroxy acids or $H_2O_2$ (Scheme 29).[59–61]

$$\underset{(\mathbf{85})}{R_nSiF_{4-n}} \quad + \quad \text{MCPBA} \longrightarrow n\text{ROH}$$

**Scheme 29**

The oxidative cleavage reactions are considered to proceed through the intramolecular migration of the organic group to the oxygen in extracoordinate silicon intermediates (Scheme 30).[59] Typical oxidation conditions and silyl groups amenable to conversion to OH groups are summarized in the literature.[59]

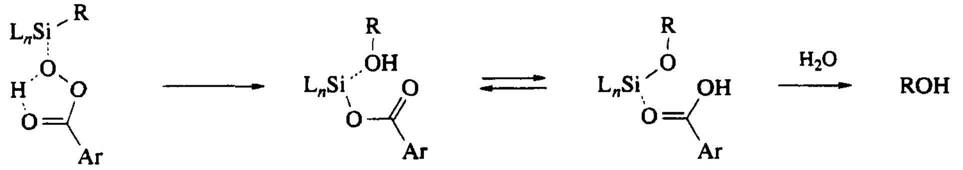
LₙSi
R
H
O
Ar
OH
H₂O
ROH

L = F, R, and/or donor solvent

**Scheme 30**

The rearrangement regularly takes place with retention of configuration at the carbon atom to which the silyl group is attached, and it is compatible with ketone and ester groups. In the case of β-hydroxysilanes, no Peterson-type elimination occurs. Some representative reactions are shown in Scheme 31.

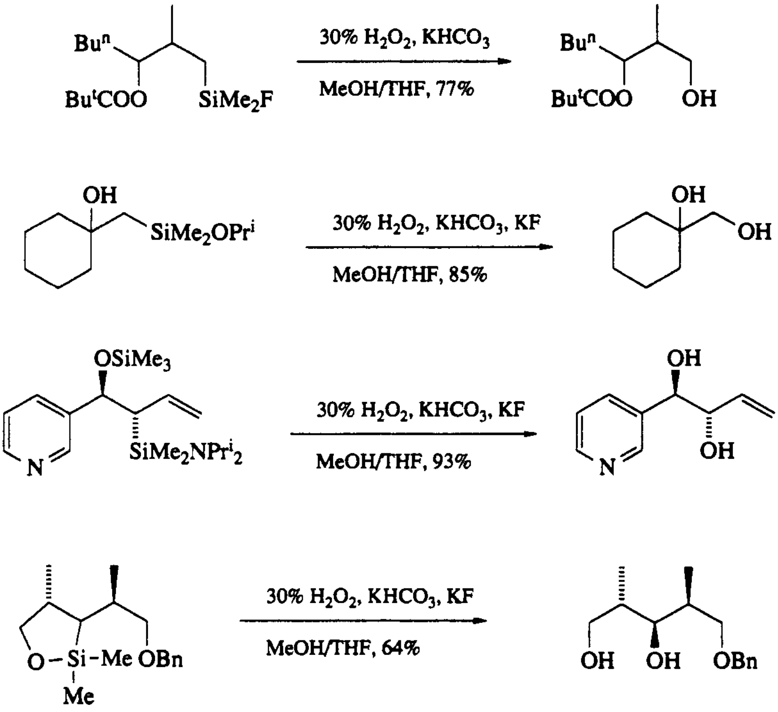
Bu^n
Bu^tCOO
SiMe₂F
30% H₂O₂, KHCO₃
MeOH/THF, 77%
OH
SiMe₂OPr^i
30% H₂O₂, KHCO₃, KF
MeOH/THF, 85%
OSiMe₃
N
SiMe₂NPr^i₂
MeOH/THF, 93%
O
Si
Me
OBn
MeOH/THF, 64%

Scheme 31

When organosilicon compounds of general formula $PhMe_2Si—R$, $(CH_2{=}CHCH_2)Me_2Si—R$ and $(RMe_2Si)_2O$ are used, the Ph—Si, $CH_2$—Si or SiO—Si bond must first be cleaved by fluoride ion to give fluorosilanes which subsequently react with peroxy acids or $H_2O_2$. Recently, the use of $Br_2$–AcOOH or $Hg(OAc)_2$–AcOOH systems has been reported to be effective for the conversion of $PhMe_2Si—R$ into the corresponding alcohols, allowing the two-step sequence to be carried out in one operation (Scheme 32).[62a] The $PhMe_2Si$ group has recently been demonstrated to be superior to the $(Pr^iO)Me_2Si$ group in carbohydrate chemistry.[62b]

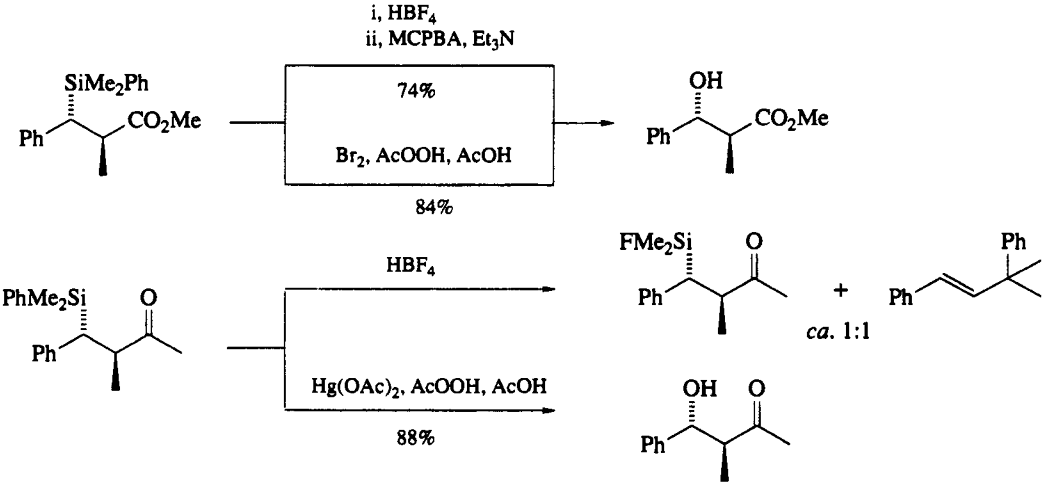
i, HBF₄
ii, MCPBA, Et₃N
74%
Br₂, AcOOH, AcOH
84%
SiMe₂Ph
Ph
CO₂Me
OH
PhMe₂Si
O
HBF₄
Hg(OAc)₂, AcOOH, AcOH
88%
FMe₂Si
+
ca. 1:1

Scheme 32

A one-pot synthesis of anti-Markovnikoff alcohols from terminal alkenes has been achieved by hydrosilylation (catalyst: $H_2PtCl_4$, $[RhCl(PPh_3)_3]$) with alkoxysilanes and subsequent oxidation.[59,63] Although hydrosilylation of internal alkenes is difficult, intramolecular hydrosilylation of allylic and homoallylic alcohols proceeds smoothly with high regio- and stereo-selectivities.[63] In view of the high regioselectivity and the wide range of functional group compatibility, the present method may be a useful alternative to the hydroboration–oxidation process. It is noteworthy that the 1,3-diols formed by intramolecular hydrosilylation–oxidation of allylic and homoallylic alcohols have structures which are complementary to those obtained by the intermolecular hydroboration–oxidation reaction (Scheme 33).[59a,63a] Approaches to construct 1,3-diol skeletons have been demonstrated.[59,63]

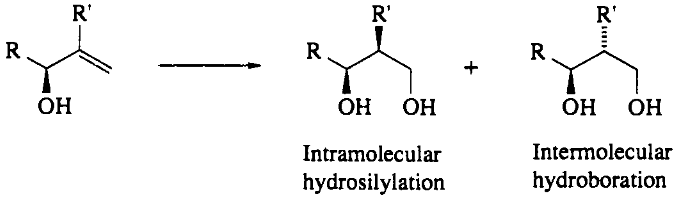

Scheme 33

## 1.1.2.5 Inversion of Alcohols

### 1.1.2.5.1 *Activation of hydroxy groups*

Alcohols are available in a variety of cyclic and acyclic forms, and, as such, have been utilized as versatile starting materials for the construction of carbon compounds including natural products with many centers of chirality. In order to functionalize and manipulate the hydroxy group in alcohols by a displacement process, activation of the hydroxy group is an important step which involves: (i) activation of the O—H bond to enhance the nucleophilicity of the oxygen; or (ii) activation of the R—O bond to convert the alcohol into a reactive alkylating reagent.

Conversion of alcohols into metal alkoxides is a common procedure for the enhancement of nucleophilicity in which the nature of the metal cation affects strongly the reactivity of the alkoxide.[64] Noyori and coworkers have demonstrated that metals having greater affinity to oxygen than to nitrogen allow selective activation of the hydroxy group of $NH_2$-unblocked nucleosides.[65] Thus, lithium alkoxytriaryloxyaluminates $LiAl(OAr)_3$—OR (R = nucleoside residues) react with diaryl phosphorochloridates to give the corresponding nucleotides in 69–88% yields with little (<1%) or no formation of *N*-phosphorylated products (Scheme 34).

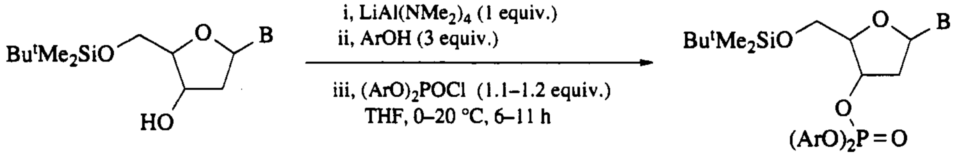

Scheme 34

Trialkyltin alkoxides (**86**) and dialkylstannylene[5] (**87**) have recently attracted attention because a tin atom attached to an oxygen atom enhances the nucleophilicity of the latter without increasing its basicity.[64] The synthetic applications of tin alkoxides manifest most remarkably in the case of polyols. For example, 1,2,6-hexanetriol was first stannylated with 1 equiv. of $(Bu_3Sn)_2O$, followed by treatment with benzoyl chloride giving (**88**) in 67% yield. Intermediacy of the tributyltin ether (**89**) was proposed for the regioselective benzoylation (Scheme 35).[66a]

Benzoylation of 1,2-diol (**90**) by the conventional method (BzCl, Py) and subsequent silylation affords primary ester (**92**) in preference to the secondary ester (**93**) in a ratio of 96:4 (81% yield). A dramatic reversal of chemoselectivity is observed when (**90**) is first converted into dioxastannolane (**91**) followed by treatment with benzoyl chloride and work-up, giving (**92**) and (**93**) in a ratio of 5:95 (Scheme 36).[66b]

Another type of activation of the hydroxy group of alcohols involves the introduction of functional groups in order to facilitate the carbon–oxygen bond cleavage in the subsequent nucleophilic displacement reactions, *i.e.* conversion of an alcohol into a reactive alkylating reagent.

Sulfonation of alcohols is a most common approach to this end. The reactivity of sulfonates is strongly influenced by the solvent used. The kinetic study of the nucleophilic substitution of a series of *n*-octyl derivatives $C_8H_{17}X$ (X = Cl, Br, I, OTs and OMs) with $N_3^-$ in different solvents (MeOH, DMSO, PhCl and cyclohexane) reveals the following nucleofugacity scales: OTs > I > OMs ≥ Br >> in MeOH; I > Br

$R_3SnOR'$

**(86)**

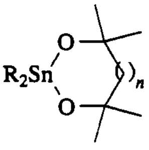

**(87)**

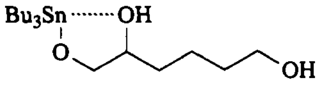
Bu₃Sn
OH
O
OH

**(89)**

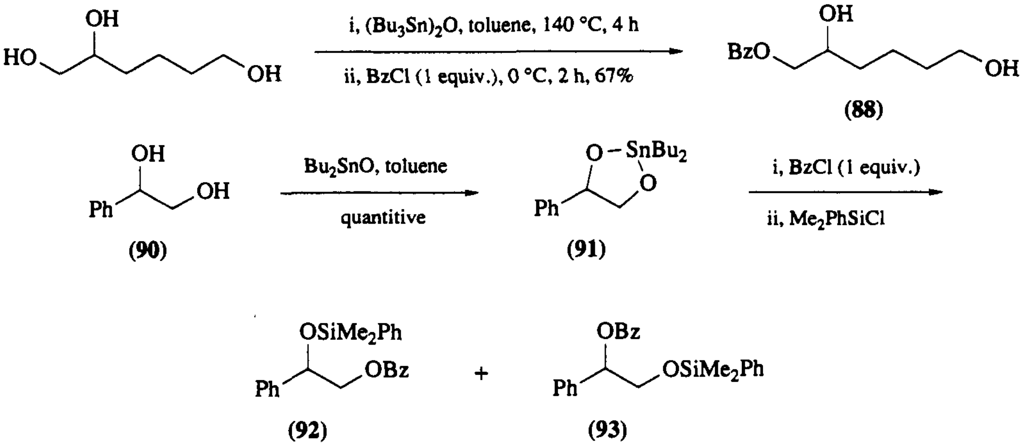
HO
OH
OH
i, (Bu₃Sn)₂O, toluene, 140 °C, 4 h
ii, BzCl (1 equiv.), 0 °C, 2 h, 67%
BzO
OH
OH
(88)
Ph
OH
OH
(90)
Bu₂SnO, toluene
quantitive
O – SnBu₂
O
Ph
(91)
i, BzCl (1 equiv.)
ii, Me₂PhSiCl
OSiMe₂Ph
OBz
Ph
(92)
+
OBz
OSiMe₂Ph
Ph
(93)

Scheme 35

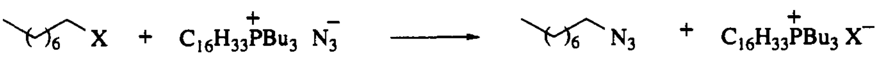
6
X
+
C₁₆H₃₃P⁺Bu₃ N₃⁻
6
N₃
+
C₁₆H₃₃P⁺Bu₃ X⁻

X = TsO, MsO, I, Br, Cl

Scheme 36

> OTs > OMs > Cl in DMSO; I > OTs ~Br > OMs >> Cl in PhCl; and OTs > OMs > I > Br > Cl in cyclohexane (Scheme 36).[67]

Triflates are more reactive than mesylates and tosylates.[68] Triflates are generally prepared by the reaction of alcohols with triflic anhydride in the presence of pyridine at low temperature. In the case where concomitant pyridinium salt formation lowers the yield of the desired triflate, more-hindered bases such as (**94**) have been used (Scheme 37).[69]

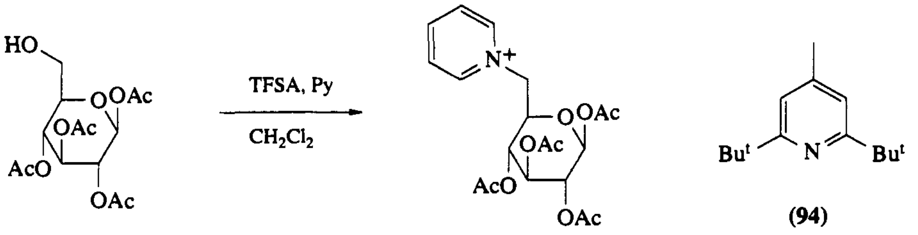
HO
OOAc
OAc
AcO
OAc
TFSA, Py
CH₂Cl₂
N+
OOAc
OAc
AcO
OAc
Buᵗ
N
Buᵗ
(94)

Scheme 37

Nucleophilic openings of cyclic sulfonates which are less hindered, or activated by an adjacent carbonyl group, occur at room temperature in usually less than 30 min. In these reactions, DMF is the solvent of choice. Selective hydrolytic removal of the sulfate group can be achieved under controlled conditions (Scheme 38).[70]

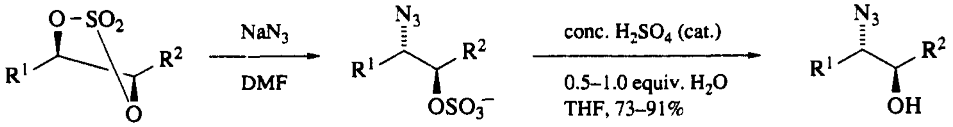
O – SO₂
R¹
R²
O
NaN₃
DMF
N₃
R¹
R²
OSO₃⁻
conc. H₂SO₄ (cat.)
0.5–1.0 equiv. H₂O
THF, 73–91%
N₃
R¹
R²
OH

Scheme 38

Introduction of partial structure (**95**) or (**96**) into the hydroxy group of an alcohol is also effective for activating the carbon–oxygen bond. Typical reactive imino and imidium ethers are shown in Scheme 39.[71-75]

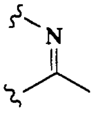

(**95**)

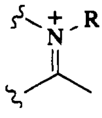

(**96**)

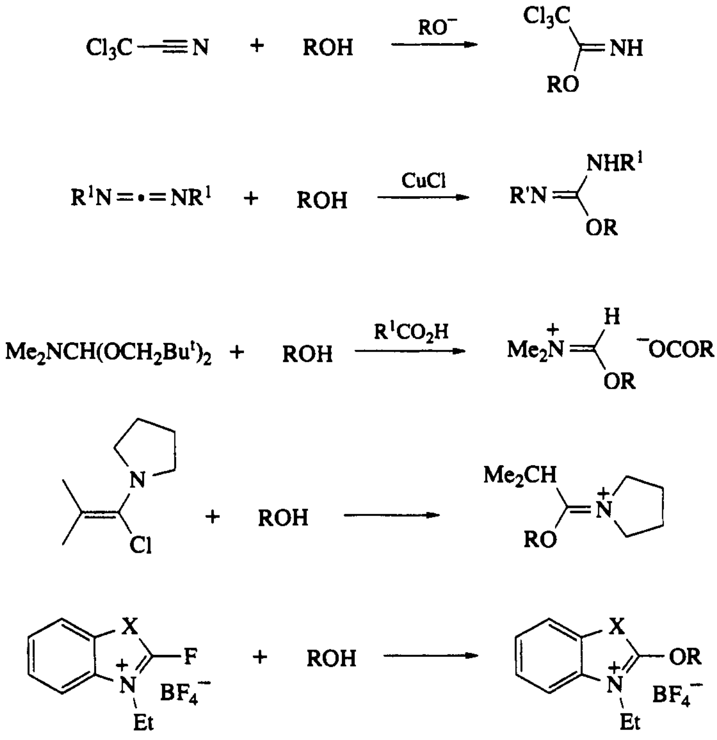

**Scheme 39**

Alkoxyphosphonium salts (**99**), formed by the reaction of trivalent phosphorus compounds with oxidizing electrophiles (**97**) in the presence of alcohols, have been recognized as versatile and reactive alkylating reagents. Although the mechanism has not yet been fully elucidated, the reaction might involve initial formation of (**98**). Compound (**98**) in turn reacts with an alcohol to give (**99**) which can undergo nucleophilic substitution either with its own counteranion (path a or b) or with other nucleophiles present in the reaction system (path c in Scheme 40). Thus, in order to facilitate the alkylation of external nucleophiles (path c), the choice of (**97**) is crucial for the success of the conversion. The reaction generally proceeds under mild conditions and possesses some valuable features such as regioselectivity; no allylic rearrangement; and inversion of configuration at the secondary carbinol centers. Comprehensive review articles on this process have been published.[76]

π-Allylpalladium complexes formed by the reaction of allyl acetates with palladium(0) compounds react with nucleophiles yielding the allylic alkylation products. In this catalytic process, the allylic position of the allyl alcohols is activated by acetylation.[77] The displacement reactions of sulfonates or alkoxyphosphonium salts generally take place with inversion of configuration. In contrast, the palladium-assisted alkylation proceeds with net retention of configuration (Scheme 41).[77]

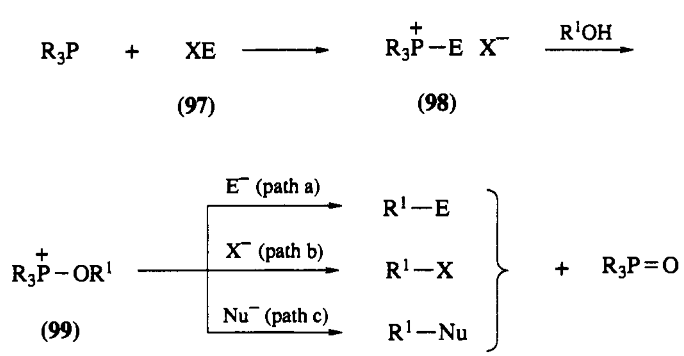
$R_3P$ + XE → $R_3\overset{+}{P}-E\ X^-$ $\xrightarrow{R^1OH}$
(97)
(98)
$R_3\overset{+}{P}-OR^1$
(99)
$E^-$ (path a)
$X^-$ (path b)
$Nu^-$ (path c)
$R^1-E$
$R^1-X$
$R^1-Nu$
+ $R_3P=O$

Scheme 40

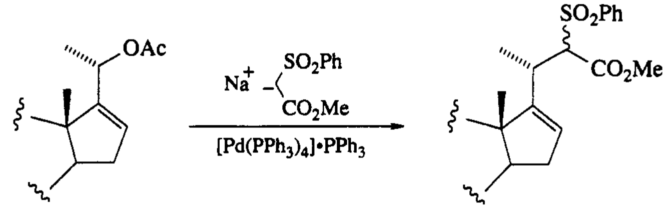
OAc
$Na^+$ $SO_2Ph$ $CO_2Me$
$[Pd(PPh_3)_4]$•$PPh_3$
$SO_2Ph$
$CO_2Me$

Scheme 41

### *1.1.2.5.2 Inversion of alcohols*

Although many useful methods to produce chiral alcohols have recently been developed, there is still need of a convenient procedure to invert the configurations of secondary carbinol centers. In principle, the inversion of configuration could be accomplished by initial activation of the R—OH bond of an alcohol and subsequent $S_N2$ displacement using oxyanions. The reaction sequences that can be used in the inversion of configuration are summarized in Scheme 42.

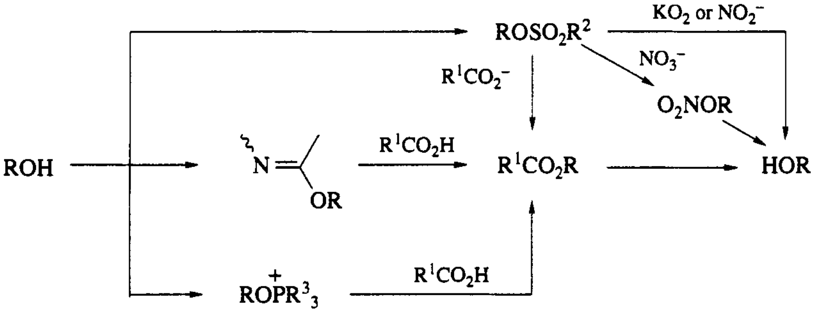
ROH
$ROSO_2R^2$
$KO_2$ or $NO_2^-$
$NO_3^-$
$O_2NOR$
$R^1CO_2^-$
$R^1CO_2H$
$R^1CO_2R$
HOR
N
OR
$RO\overset{+}{P}R^3_3$
$R^1CO_2H$

Scheme 42

The reactions of alkyl sulfonates with sodium, potassium or tetraalkylammonium carboxylates generally proceed with inversion of configuration. In the case of *s*-alkyl sulfonates, however, a varied amount of elimination products is invariably formed.[78] Of all metal carboxylates, cesium salts (Scheme 43) have proved vastly superior with respect to reactivity and the suppression of undesirable side reactions.[79]

The addition of 18-crown-6 to the reaction system is effective for suppression of the elimination reaction. Thus, the mesylate of (**100**; Scheme 43) reacts with AcOCs in the presence of 18-crown-6 (0.5 equiv.) in benzene (reflux, 1 h) to afford the inverted acetate (**101**) in 70% yield along with a small amount of elimination product (<5%). Without the crown ether, the elimination product is predominantly formed.[79e]

Nitrate ion can be another effective nucleophile for inversion. It has been demonstrated that, due to the low basicity of the nucleophile, the competing elimination reaction is almost completely suppressed and the resulting nitro esters can be readily converted into alcohols by reductive processes.[80] One serious

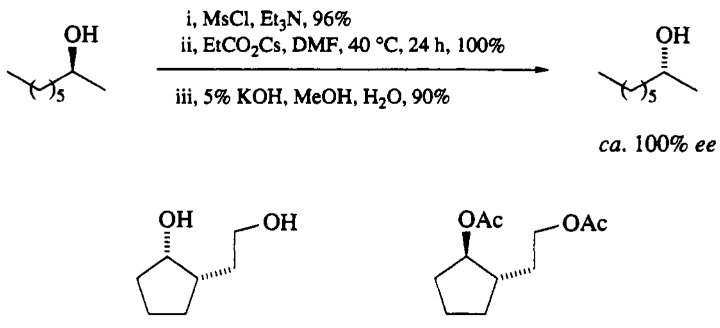
OH
i, MsCl, Et3N, 96%
ii, EtCO2Cs, DMF, 40 °C, 24 h, 100%
iii, 5% KOH, MeOH, H2O, 90%
OH
ca. 100% ee
OH
OH
OAc
OAc

**(100)** **(101)**

**Scheme 43**

drawback of the procedure is that racemization takes place to some extent under the reaction conditions. However, the racemization can be circumvented by the use of more efficient leaving groups such as the pyridylsulfonyloxy group.[80]

The reactions of alkyl sulfonates with superoxide ion and with nitrite ion directly afford the corresponding inverted alcohols.[8,81] Although displacement by superoxide ion has been successfully utilized in prostaglandin chemistry, elimination again takes place to some extent, depending on the structures of the substrates. In the reaction with nitrite ion, ketone and nitroalkane are also formed. The inversion of cyclopentanol derivatives *via* tosylates has been studied by the use of various methods involving displacement by benzoate, nitrite ion and superoxide ion as well as the diethyl azodicarboxylate (DEAD)–$Ph_3P$ procedure, where varied amounts of elimination products are invariably formed.[81a]

Imino ethers and 2-alkoxybenzthiazolium salts prepared from chiral alcohols react with carboxylic acids to give the esters of the corresponding inverted alcohols (Scheme 39).[71c,72d,73,75a] The reaction of a chiral alcohol with a carboxylic acid, DEAD and $Ph_3P$ affords the ester of the inverted alcohol (Scheme 44).[82] Diisopropyl or dimethyl azodicarboxylate can be used instead of DEAD. Little difference between these reagents has been reported.[83]

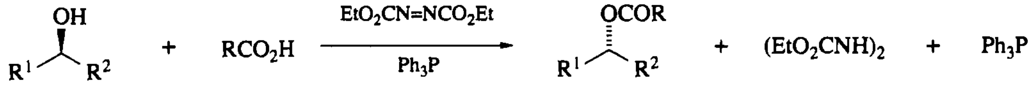

**Scheme 44**

Although the DEAD–$Ph_3P$ procedure has been utilized in the inversion of a variety of alcohols, sterically crowded hydroxy groups do not enter into the reaction. In such cases, the sulfonate route can be used. For example, the coupling of free acid (**102a**) with alcohol (**103a**) by the use of DEAD and $Ph_3P$ affords the desired inverted ester (**104a**) in <30% yield, while mesylate (**103b**) reacts with potassium carboxylate (**102b**) (DMF, 75 °C, 18 h) to give (**104b**) in 86% yield (Scheme 45).[84]

The reagent formed by combining $Ph_3P$ with benzoyl peroxide (BPO) reacts with alcohols to give benzoates in moderate to good yields. The reaction proceeds with essentially complete inversion of the configuration at the secondary carbinol stereocenters. It is noteworthy that 1,2-diols are benzoylated at the secondary hydroxy group in preference to the primary one (Scheme 46).[85] The product ratio is practically the same as that obtained by the DEAD–$Ph_3P$ procedure.[86] Therefore, as far as benzoylation is concerned, the BPO–$Ph_3P$ procedure seems attractive because the removal of hydrazine dicarboxylate from the desired product is sometimes troublesome in the DEAD–$Ph_3P$ procedure.

## 1.1.3 PREPARATION OF ETHERS

### 1.1.3.1 Cyclic and Acyclic Ethers

Acyclic and cyclic ethers are synthesized by the reaction of activated alcohols with alkoxide or aryl oxide anions. Alkyl halides and epoxides can also be utilized as versatile electrophiles for the preparation

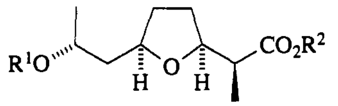

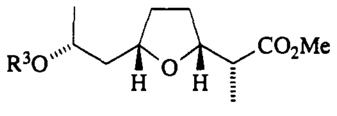

**(102a)** $R^1 = SiMe_2Bu^t$
$R^2 = H$
**(102b)** $R^1 = H$
$R^2 = K$

**(103a)** $R^3 = H$
**(103b)** $R^3 = Ms$

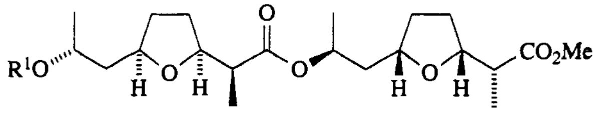

**(104a)** $R^1 = SiMe_2Bu^t$
**(104b)** $R^2 = H$

**Scheme 45**

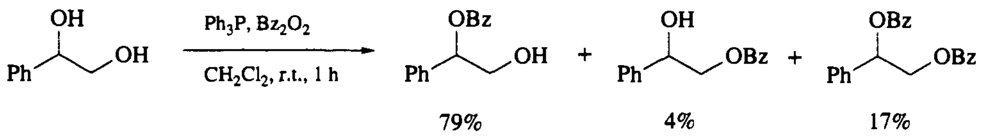

**Scheme 46**

of ethers. Since comprehensive reviews of the preparation of ethers have been published,[2,87] only a limited number of examples will be described in this section.

Of the activated alcohols described in Section 1.1.2.5.1, alkyl sulfonates are convenient alkylating reagents because they can be readily prepared and handled. The correct choice of sulfate–alcoholate combination is often crucial for successful ether synthesis. Thus, for the preparation of cholesteryl ethers from the tosyl derivative of cholesterol and alkoxides, the reaction must be carried out at 110 °C for 2.5 h in a sealed tube. Alternatively, the sodium salt of cholesterol can be reacted with an alkyl mesylate at 80 °C for 1 h in DMF to give the corresponding ether in 62–68% yield.[88]

Benzyl, 4-methoxybenzyl and triarylmethyl groups are used in the protection of the hydroxy groups. Compared to typical benzylation conditions (BnBr, NaH in DMF), benzylation by triflate proceeds under milder conditions without affecting alkali labile groups. Treatment of carbohydrates (**105**), (**106**) and (**107**) with benzyl triflate, generated from benzyl alcohol and triflic anhydride in 2,6-di-*t*-butylpyridine at –70 °C, gives the corresponding benzylated derivatives in 93%, 89% and 60% yields, respectively. Similarly, the methyl ethers are prepared using methyl triflate, but the reaction requires heat and longer reaction time.[69a,89] Benzylation of (**108**) is successfully carried out with preformed benzyl triflate to afford (**109**) in 96% yield without epoxide formation. By the reaction with $K_2CO_3$, (**108**) gives epoxide (**110**).[90] Triflate (**111**) reacts with various nucleophiles ($BzO^-$, $N_3^-$, $RS^-$) to give the corresponding mannopyranosides (**113**) in 82–89% yields. On the other hand, the reaction of (**111**) with NaOMe exclusively gives anhydromannopyranoside (**112**; Scheme 47).[91]

Benzyl trichloroacetimidate (**114a**) reacts with alcohols in the presence of TFA to afford benzyl ethers.[92] 4-Methoxybenzyl trichloroacetimidate (**114b**), which is much more reactive than (**114a**) and very sensitive to strong acids, reacts smoothly with various kinds of alcohol to give the corresponding methoxybenzyl ether. The catalyst used is CSA (10 mol%), PPTS (10 mol%), $TrClO_4$ (3 mol%) or TFA (0.3 mol%). Under these conditions, alcohols having either acid or base labile groups, such as (**115**) and (**116**), are successfully protected (Scheme 48).[93]

Selective protection of the primary hydroxy group in polyols by the trityl group can generally be accomplished by the reaction with trityl chloride in pyridine. The use of DMAP (0.04 equiv.) and $Et_3N$ (1.5 equiv.) facilitates the reaction.[94] Selective phenylation of one hydroxy group of diols can be carried out by the reaction with triphenylbismuth diacetate. While regioselectivity for primary–secondary vicinal diols is poor, only secondary alcoholic functions are converted to the phenyl ether in secondary–tertiary vicinal diols. Although phenylation of glycols occurs smoothly, monohydroxy alcohols are left essentially intact.[95]

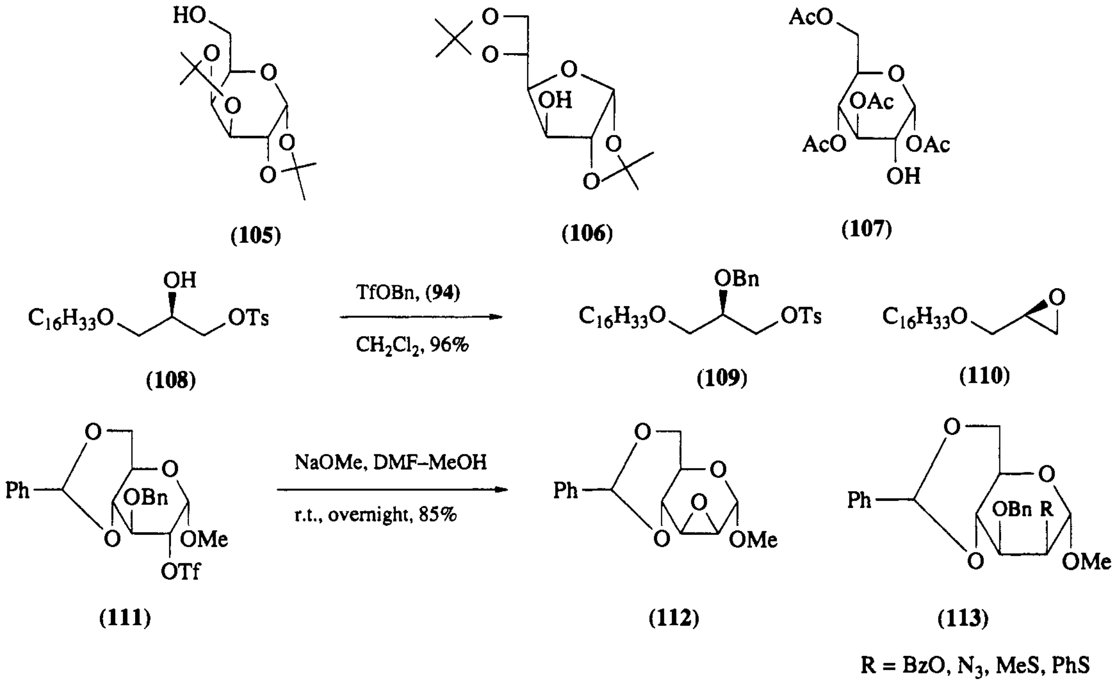
(105)
(106)
(107)
(108)
TfOBn, (94)
CH2Cl2, 96%
(109)
(110)
(111)
NaOMe, DMF-MeOH
r.t., overnight, 85%
(112)
(113)
R = BzO, N3, MeS, PhS

Scheme 47

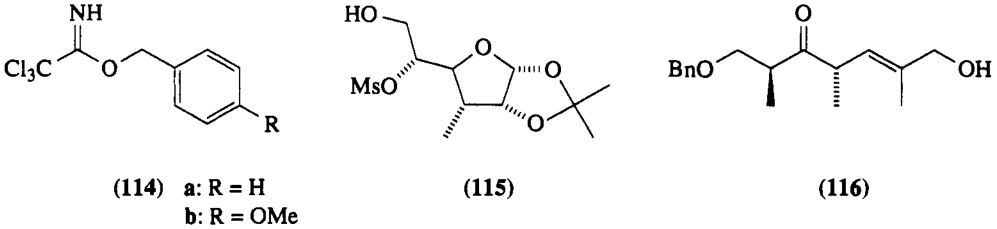
(114) a: R = H
b: R = OMe
(115)
(116)

Scheme 48

In view of the fact that many complex dihydro- and tetrahydro-furans possess valued biological properties, a variety of procedures for the construction of such systems has been reported.[2f] The reactivity pattern of the cyclic ether formation with respect to ring size has been briefly discussed.[3i,96]

Of the alkylation systems described in Section 1.1.2.5.1, the DEAD–$Ph_3P$ procedure cannot be used in the preparation of acyclic dialkyl ethers, but alkyl aryl ethers and cyclic ethers have been synthesized. The $Ph_3P$–$CCl_4$ system is also effective for the cyclodehydration of 1,4- and 1,2-diols to tetrahydrofurans and epoxides, respectively.[97]

In the presence of a palladium(0) catalyst, allyl acetates having hydroxy functions afford cyclic ethers. Thus, exposure of (**117a**)–(**117c**), 1:1 diastereomeric mixtures, to $[(DBA)_3Pd_2]/CHCl_3$–$Ph_3P$ at room temperature gives rise to the same cyclic ether (**118**) in 92–96% yields as a 9:1 isomeric mixture. No cyclization products derived from the secondary alcohol serving as the nucleophile are detected (Scheme 49). By this procedure, five- to seven-membered cyclic ethers have been prepared.[98]

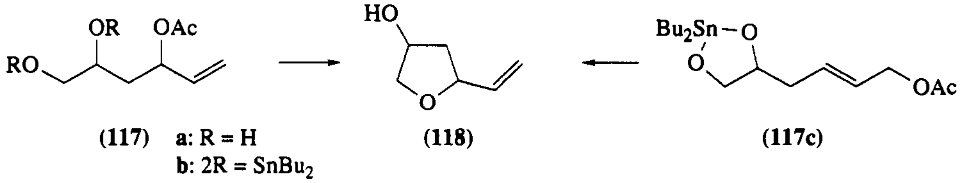
(117) a: R = H
b: 2R = SnBu2
(118)
(117c)

Scheme 49

The acid-catalyzed cyclodehydration of (±)- and meso-2,5-hexanediol has been shown to proceed with inversion of configuration in most cases, affording *cis*- and *trans*-2,5-dimethyltetrahydrofuran, respectively. However, various extents of racemization are observed in the actions of certain Lewis acids and $H_2SO_4$.[99] The stereospecific cyclization of diols to tetrahydrofurans occurs if phenylthio participation is involved. The reactions of 2-phenylthio-1,4-diols such as (**118**) with dimethyl sulfate afford (**119**) with net retention of configuration, whereas acid-catalyzed cyclizations of 4-phenylthio-1,3-diols such as (**120**) take place with PhS migration and hence inversion at both the migration origin and terminus (Scheme 50).[100]

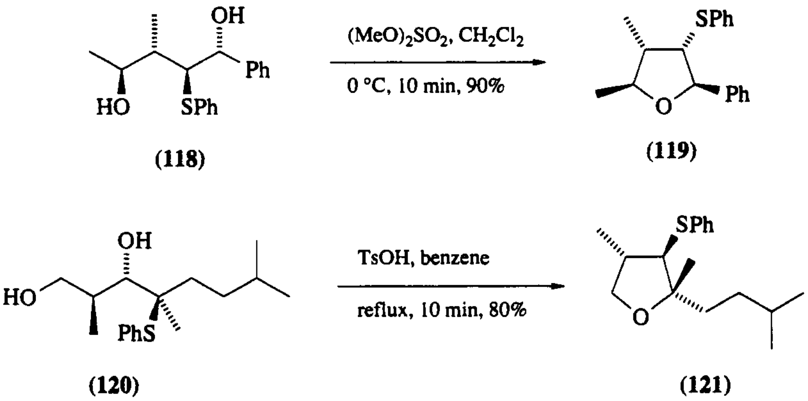

(**118**) (**119**) (**120**) (**121**)

**Scheme 50**

A transition metal catalyzed synthesis of ethers by carbene insertion into the O—H bond has been reported. Not only saturated but also unsaturated alcohols can be utilized in this catalytic process.[101]

Intermolecular and intramolecular oxirane ring opening reactions by alkoxides and phenoxides also provide efficient and stereospecific preparations of acyclic and cyclic ethers. The procedures have been surveyed in detail.[3]

### 1.1.3.2 Epoxides

Perhaps the most widely used procedure for epoxide synthesis is peroxide or peroxy acid oxidation of alkenes, which is discussed in Volume 7, Chapters 3.1 and 3.2.

Another important method involves intramolecular $S_N2$ displacement of an alcohol with an appropriate leaving group in the β-position (**122**; Scheme 51). In this approach, the preparation of β-functionalized alcohols having definite configuration at both the α- and β-carbon atoms is prerequisite. The most promising strategy to achieve the correct construction and configuration of the intermediates is the transformation of natural products by stereochemically unambiguous processes. For details on this approach, the reader is referred to an excellent review.[102]

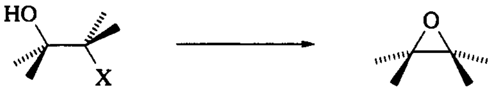

(**122**)

$X = \text{halogen}, RSO_3, R_2\overset{+}{S}, R_3\overset{+}{P}O$, *etc.*

**Scheme 51**

Stereoselective preparation of precursors to epoxides can also be achieved by the aid of the structure of the substrates, especially in the cyclic systems. Scheme 52 illustrates the stereochemical outcome of epoxide formation *via* the bromohydrin route and the peroxy acid oxidation procedure.[103]

Intramolecular participation of an appropriately placed nucleophile promises to be a useful strategy for the stereocontrolled synthesis of acyclic systems. Thus, halocyclization of unsaturated carboxylic acids, alcohols and functionalized alcohols (**123**) can be effected by a variety of electrophilic halogenating

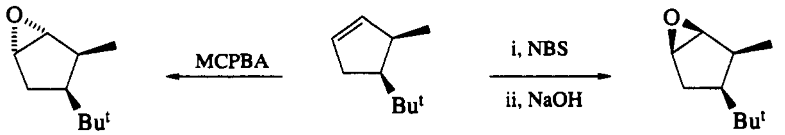
MCPBA
i, NBS
ii, NaOH
Bu^t
Bu^t
Bu^t

Scheme 52

agents affording stereochemically biased halomethyl heterocycles. Lactones, cyclic carbonates and cyclic phosphates thus formed are in turn converted into epoxides *via* halohydrins (Scheme 53).[104]

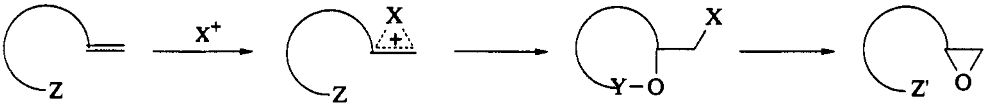

**(123)** $Z = CO_2R, OC(O)OR, OP(O)(OR)_2$, *etc.*

Scheme 53

Treatment of homoallylic phosphates with $I_2$ results in the formation of thermodynamically more stable cyclic phosphates which are converted into *erythro*-epoxides with high stereoselectivity (Scheme 54).[105] The procedure (phosphate extension) allows otherwise difficult stereoselective conversion of homoallylic alcohols into 3,4-epoxy alcohols.

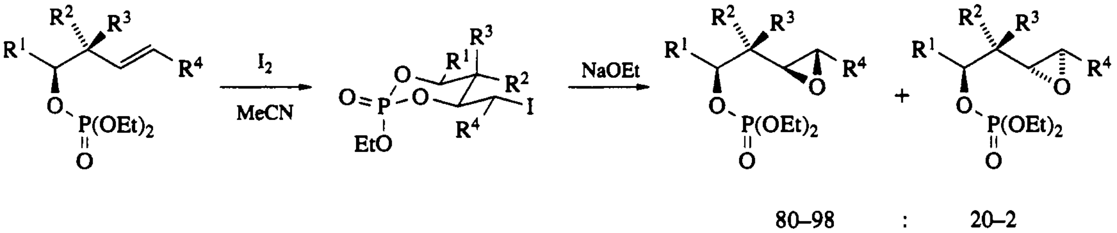
R1
R2
R3
R4
O
P(OEt)2
O
I2
MeCN
R3
R1
R2
O
O=P-O
EtO
R4
I
NaOEt
R1
R2
R3
R4
O
P(OEt)2
O
O
+
R1
R2
R3
R4
O
P(OEt)2
O
O
80–98 : 20–2

Scheme 54

Iodolactonization and iodocarbonylation can also be utilized for the stereoselective epoxidation of alkenic esters and alcohols (Scheme 55).[106,107]

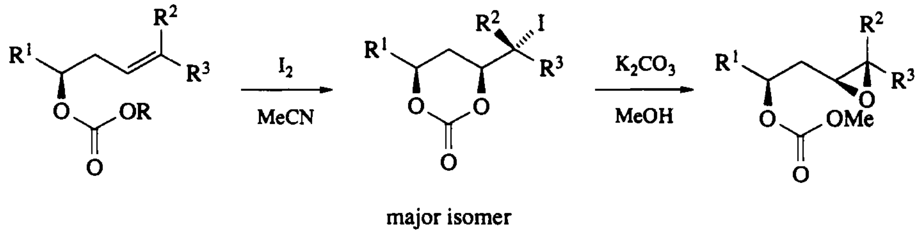
R1
R2
R3
O
OR
O
I2
MeCN
R1
R2
I
R3
O
O
O
major isomer
K2CO3
MeOH
R1
R2
R3
O
O
OMe
O

Scheme 55

Tin(II) triflate mediated cross aldol reactions between α-bromo ketone (**124**; Scheme 56) and aldehydes afford *syn*-α-bromo-β-hydroxy ketones (**125**) with high stereoselectivity. The resulting halohydrins are converted to the corresponding (*Z*)-2,3-epoxy ketones (**126**).[108] Chiral aldehyde (**127**) reacts with lithium alkynide (**128**) followed by mesylation and base treatment to give chirally pure (*E*)-epoxide (**129**). The initially formed alkoxide anion should be trapped *in situ* by mesylation, otherwise partial racemization takes place owing to benzoate scrambling (Scheme 56).[109]

Epoxides can also be prepared from a variety of β-functionalized alcohols such as β-hydroxy sulfoxides,[110] β-hydroxysulfonium salts,[111] β-hydroxy selenides[112] and vicinal diols. In the use of unsymmetri-

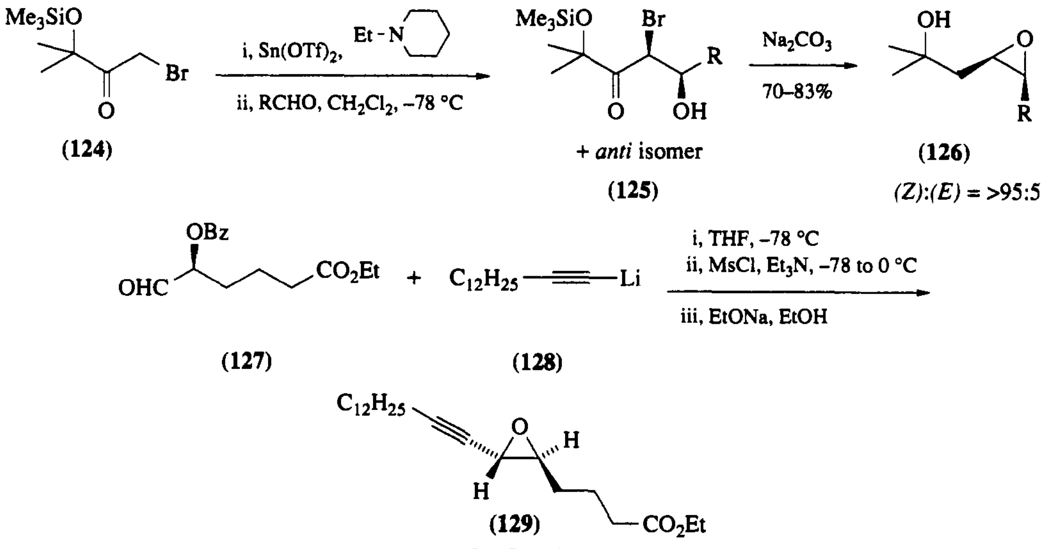
Me3SiO
Br
O
(124)
i, Sn(OTf)2, Et-N
ii, RCHO, CH2Cl2, -78 °C
Me3SiO
Br
R
O
OH
+ *anti* isomer
(125)
Na2CO3
70–83%
OH
O
R
(126)
*(Z)*:*(E)* = >95:5
OBz
OHC
CO2Et
+
C12H25
Li
i, THF, -78 °C
ii, MsCl, Et3N, -78 to 0 °C
iii, EtONa, EtOH
(127)
(128)
C12H25
O
H
H
(129)
CO2Et
*(E)*:*(Z)* = 4:1

**Scheme 56**

cal vicinal diols, regioselective activation of one hydroxy group of the two is prerequisite.[87] Scheme 57 illustrates some examples of the preparation of epoxides from vicinal diols.[113–119]

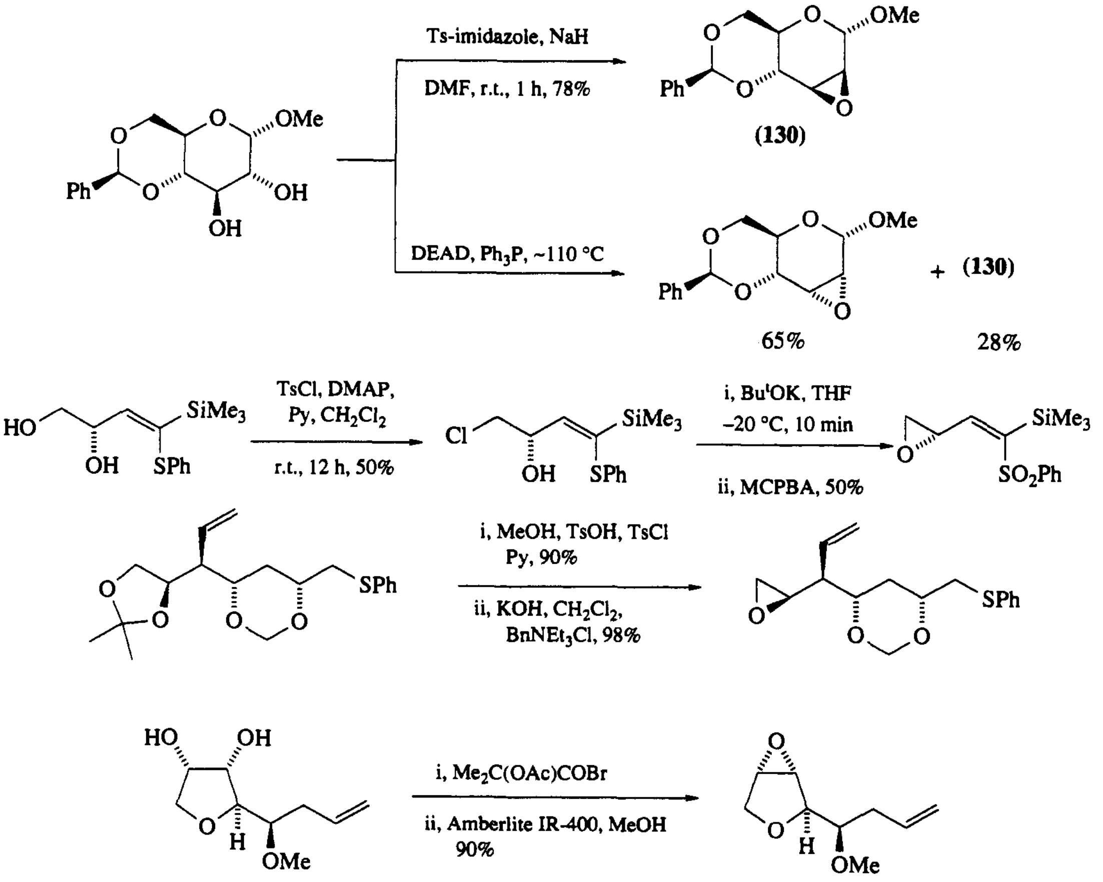
O
O
OMe
Ph
O
OH
OH
Ts-imidazole, NaH
DMF, r.t., 1 h, 78%
(130)
DEAD, Ph3P, ~110 °C
+ (130)
65%
28%
HO
SiMe3
OH
SPh
TsCl, DMAP,
Py, CH2Cl2
r.t., 12 h, 50%
Cl
SiMe3
OH
SPh
i, Bu^tOK, THF
-20 °C, 10 min
ii, MCPBA, 50%
O
SiMe3
SO2Ph
SPh
i, MeOH, TsOH, TsCl
Py, 90%
ii, KOH, CH2Cl2,
BnNEt3Cl, 98%
SPh
HO
OH
O
H
OMe
i, Me2C(OAc)COBr
ii, Amberlite IR-400, MeOH
90%
O
O
H
OMe

**Scheme 57**

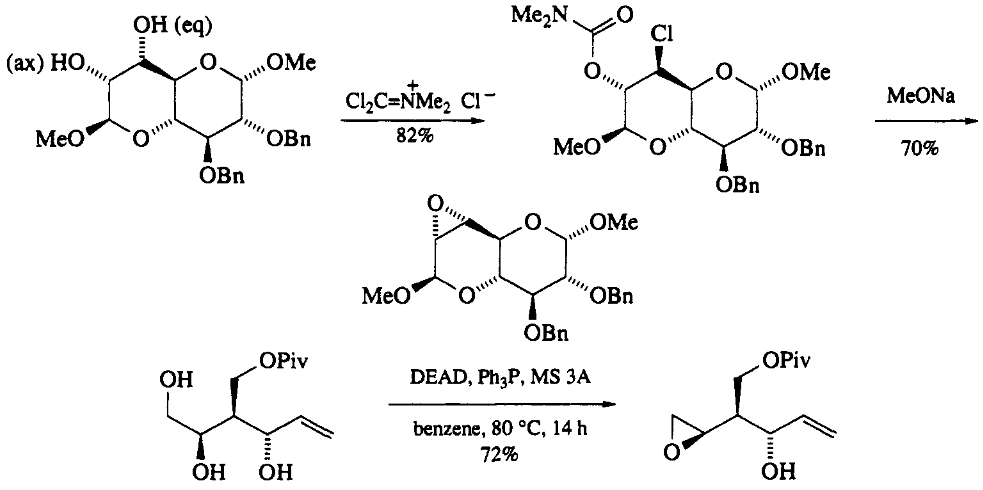

**Scheme 57 *(continued)***

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# 1.2
# Synthesis of Glycosides

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## 1.2.1 INTRODUCTION

Glycoside synthesis is a very common reaction in nature, providing a great variety of compounds, for instance oligosaccharides as such, or glycoconjugates with lipids (glycolipids), proteins (glycoproteins) and many other naturally occurring substances. However, the important biological implications of the attachment of sugar moieties to an aglycon are only now becoming more and more obvious, creating a growing interest in this field. For instance, the presence of complex carbohydrate structures as integral constituents of membranes and cell walls has led to manifold activities in recent research.[1–7] An especially important role amongst these glycoconjugates seems to be played by the glycosphingolipids,[1–3] the glycophospholipids[1] and the glycoproteins.[1–6] Their manifold functions are based on a great structural diversity of the oligosaccharide portion, which is inherent to the variability in glycoside bond formation.[1,4] This point was recently impressively illustrated,[1] rendering oligosaccharides ideal as carriers of biological information and specificity.

This knowledge is based on an enormous extension and improvement of the methodologies for structure determination[8] and for chemical synthesis,[1,2,5,6,9–12] as will be outlined below. The synthesis of glycosides, oligosaccharides and glycoconjugates is characterized by a much larger number of possibilities for coupling than that of other biopolymers, such as peptides or proteins and ribo- or deoxyribo-nucleotides.[1] In contrast to peptides and nucleotides, in which the informational content is determined solely by the number and sequence of different monomer units, the informational content of oligosaccharides is fixed additionally by the site of coupling, the configuration of the glycosidic linkage (α or β) and the occurrence of branching. Thus, oligomers made up of carbohydrates can carry considerably more information per atomic unit than proteins and nucleotides.[1]

The structural variety complicates the synthesis of glycosides and even more so of complex oligosaccharide structures. It has only recently been possible to develop methods for the synthesis of complex oligosaccharides and glycoconjugates. The results obtained in glycoside and saccharide synthesis will be summarized as outlined in Scheme 1 (paths A–D). (a) The Fischer–Helferich method, describing the direct acid-catalyzed acetalization procedures, where direct substitution of the anomeric hydroxy group takes place. (b) The Koenigs–Knorr method and its variants. In the classical Koenigs–Knorr method, and the subsequently developed efficient variants, the generation of glycosyl donor properties is achieved through exchange of the anomeric hydroxy group for a halide leaving group (halide = bromide, chloride and recently fluoride, with some special properties) and reaction of the glycosyl halides in the presence of heavy metal salts. This general principle also includes the use of thioglycosides and 1,2-epoxides as glycosyl donors. (c) The trichloroacetimidate method and other anomeric oxygen activations. The direct base-catalyzed activation of the anomeric oxygen with trichloroacetonitrile (and related compounds; see Section 1.2.4.2) yields *O*-glycosyltrichloroacetimidates, which exert very high glycosyl donor properties under mild acid catalysis. Related approaches *via* sulfonate, phosphate, acetate and orthoester formation respectively are included. (d) The anomeric *O*-alkylation method. The direct anomeric *O*-alkylation of pyranoses and furanoses is a completely different substitution process, requiring 1 equiv. of base for the removal of the anomeric hydroxy group proton.

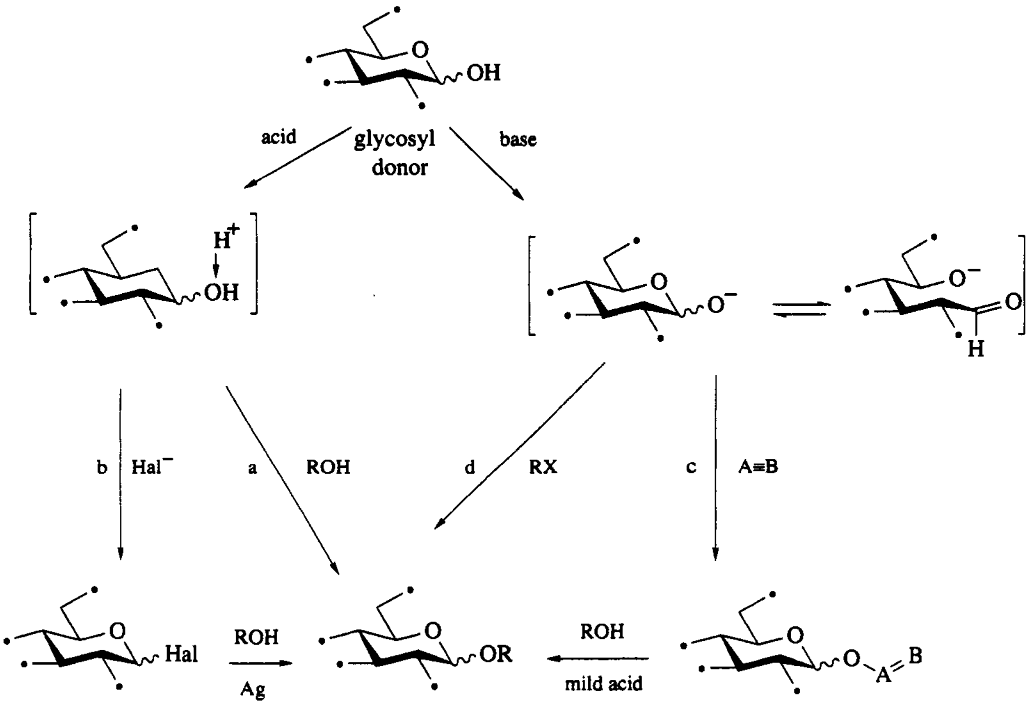

(a) Fischer–Helferich (acid activation); (b) Koenigs–Knorr (Br, Cl, (I) activation, F activation and RS activation); (c) trichloroacetimidate ($OC(NH)CCl_3$ activation and OAc, $OSO_2R$, $OPO_3R_2$ activation); (d) anomeric *O*-alkylation (base activation)

**Scheme 1** Synthesis of glycosides and saccharides

Other methods have gained practically no importance. Special problems in the application of methods (a)–(d) to 2-deoxyglycoside synthesis will be reported in Section 1.2.7.

## 1.2.2 THE FISCHER–HELFERICH METHOD

In a glycoside synthesis, a polyfunctional sugar component must be linked to an acceptor (which is another sugar component in saccharide synthesis). Regioselectivity is generally achieved when the glycosylating component (*i.e.* the glycosyl donor) possesses selectively protected hydroxy groups and an activating group at the anomeric C-atom, and when the component with the acceptor group (*i.e.* the glycosyl acceptor, for instance O-, N-, S- or C-nucleophiles) possesses protective groups at all other acceptor functions (Scheme 1). Thus, complicated protection strategies (Volume 6, Chapter 3.1) and suitable procedures for activation at the anomeric C-atom are required. In addition, the coupling step must occur diastereoselectively with respect to formation of an α- or β-linkage.

In the classical Fischer–Helferich method *O*-glycosides are obtained from hemiacetals and alcohols in an acid-catalyzed reaction as a variant of the common acetal formation (Scheme 1).[9] This reaction is reversible; it is therefore not applicable to the synthesis of compounds with more than one glycoside bond (*i.e.* to the synthesis of oligosaccharides and glycoconjugates) because other glycosidic bonds will be affected. In addition, the diastereocontrol at the anomeric position is based on thermodynamic energy differences between the corresponding α- and β-anomers. The axial position for the anomeric OR group is disfavored by steric arguments (unfavorable 1,3-diaxial interactions) and favored by the anomeric effect (favorable stereoelectronic interactions between the ring oxygen and the anomeric carbon–oxygen bond).[13] These two opposing effects often have similar magnitudes, therefore usually an anomeric mixture of products is obtained, or, due to a slight preponderance of the anomeric effect, more of the α-anomer is formed.

The merits of the Fischer–Helferich method today are mainly in its use for the synthesis of simple glycosides required as starting materials in oligosaccharide synthesis and as chiral synthons.[14] The strategy for sugar protection usually starts with the formation of a methyl, benzyl or allyl glycoside directly from the unprotected sugar, followed by selective introduction of additional protective groups (benzylidene, isopropylidene, benzyl, silylacetyl, benzoyl, *etc.*). Due to ring–chain tautomerism (Scheme 2), with excess alcohol and acid as catalyst, α- and β-furanosides and α- and β-pyranosides can be obtained, leaving three hydroxy groups unprotected in the case of pentoses and four in the case of hexoses. The result is dependent on the individual sugar and the reaction conditions. Due to the ring strain, other glycoside ring sizes are not commonly found and furthermore the open chain *O,O*-acetal is not formed *via* this route. Furanose formation is usually faster than pyranose formation, a phenomenon also typical for other saturated ring closure reactions.[15] However, the occurrence of several acid-catalyzed equilibration reactions (as indicated in Scheme 2) with different kinetics makes product control difficult. Therefore the

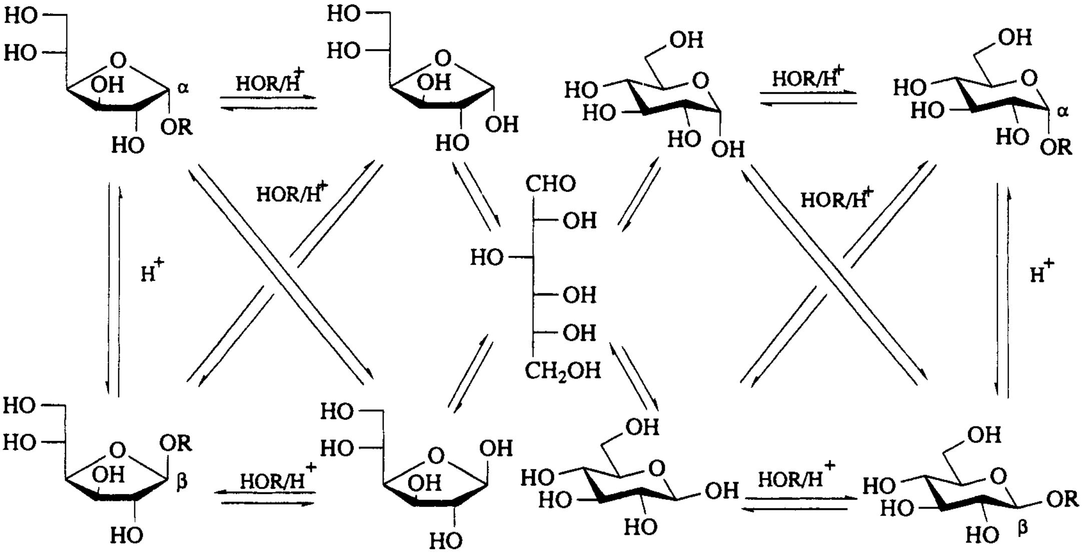

Scheme 2

search for procedures resulting in the convenient isolation of one product has gained tremendous importance. Some typical examples are given in Table 1.[16–31]

**Table 1** Acid-catalyzed Formation of 1-*O*-Protected Sugars Commonly Used in Sugar Transformations[a]

| *Starting material* | | *1-O-Protected sugars* | |
|---|---|---|---|
| Glc | 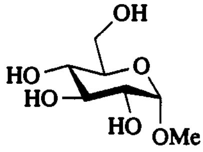<br>(ref. 16) | 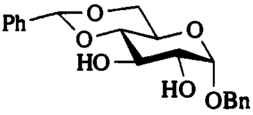<br>(ref. 17) | 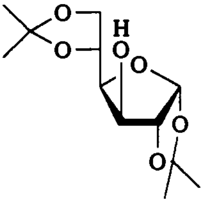 |
| Gal | 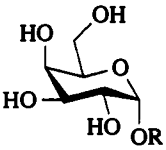<br>R = Me (ref. 19)<br>R = Allyl (ref. 20) | 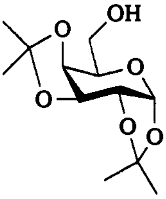<br>(ref. 21) | |
| Man | 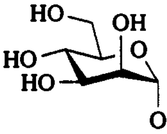<br>R = Me (ref. 22)<br>R = Bn (ref. 23) | 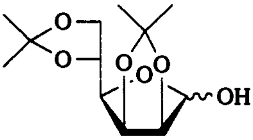<br>(ref. 18) | |
| GlcNAc | 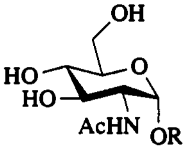 | R = Allyl (ref. 20)<br>R = Bn (ref. 24) | |
| Ara | 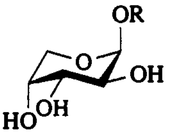<br>R = Me (ref. 25)<br>R = Bn (ref. 26) | 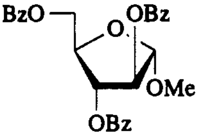<br>(ref. 27) | 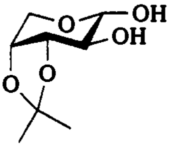<br>(ref. 28) |
| Rib | 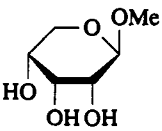<br>(ref. 29) | 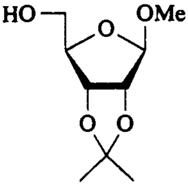<br>(ref. 30) | 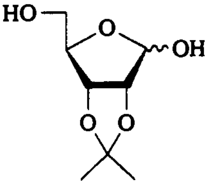<br>(ref. 31) |

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[a] References for the syntheses are given in brackets.

The combination of this simple acid-catalyzed glycoside synthesis with additional acetal formations in the presence of a ketone (mainly acetone and cyclohexanone) furthers the versatility of this method. Thus, from *O*-unprotected hexoses and pentoses respectively, in convenient acid-catalyzed procedures compounds with only one or two *O*-unprotected hydroxy groups are directly accessible, providing convenient functional group control in subsequent reactions (Table 1; in some cases even the sugar aldehyde group is left unprotected). Most of these compounds are now commercially available. They are extensively used as starting materials in research laboratories and even in technical processes. For instance, diacetone sorbose (obtained from acetone and L-sorbose under acidic conditions) is an intermediate in the commercial vitamin C synthesis[32] and D-arabinose derivatives could become starting materials for a short (+)-biotin synthesis.[33,34]

However, another application of the Fischer–Helferich method clearly exhibits its limitations. Long chain alkyl glycosides have gained interest as nonionic surfactants.[35] Their technical synthesis is based on acid catalysis of the reaction between glucose and alcohol. Due to the inherent solubility problems, typical drawbacks of the Fischer–Helferich method are encountered: the technical product consists of a mixture of different anomers and, due to the fact that excess alcohol cannot be used for solubilization of the reaction mixture, reaction of glucose with itself is also found.

Due to the drawbacks of the Fischer–Helferich method it was early recognized that other approaches to glycoside and saccharide synthesis had to be introduced.

## 1.2.3 THE KOENIGS–KNORR METHOD AND ITS VARIANTS: ACTIVATION THROUGH ANOMERIC OXYGEN EXCHANGE REACTIONS

### 1.2.3.1 General Aspects of Glycoside Bond Formation

A versatile and generally applicable method for a diastereocontrolled glycoside and saccharide synthesis seems to necessitate a two-step procedure with the following requirements.[1]

The first step, activation of the anomeric center generating the glycosyl donor, requires: (i) convenient formation of a sterically uniform glycosyl donor; (ii) adoption, according to choice, of either α- or β-configuration; and (iii) thermal stability of the glycosyl donor at least to room temperature; eventually chromatographic purification should be possible.

The second step, the glycosyl transfer to the acceptor providing the glycoside, the oligosaccharide or the glycoconjugate, requires: (i) catalysis of the glycosyl transfer by simple means; (ii) irreversibility of the reaction; (iii) that the configuration of other glycosidic bonds is not affected in the process; (iv) high chemical yield; and (v) high α- or β-selectivity *via* diastereocontrolled inversion or retention of configuration at the anomeric center (usually attained in a kinetically controlled reaction).

### 1.2.3.2 The Koenigs–Knorr Method: Bromide and Chloride as Leaving Groups

In the classical Koenigs–Knorr method, dating from 1901,[36] and the subsequently developed efficient variants, the activation step is achieved through the formation of glycosyl halides (halogen = bromine and chlorine) and their reaction in the second step, the glycosyl transfer step, in the presence of heavy metal salts (preferentially silver and mercury salts). This method has been critically reviewed,[1,5] giving the following general picture.

#### *1.2.3.2.1 Glycosyl halide formation*

The exchange of the anomeric hydroxy group for bromine or chlorine, carried out with typical halogenating agents (and all other hydroxy groups *O*-protected), leads mainly to the product with the halogen atom in an axial position. Because the subsequent discussion is mainly restricted to the important sugars D-glycopyranose (Glc), 2-acetamino-2-deoxy-D-glucopyranose (GlcNAc), D-galactopyranose (Gal), 2-acetamino-2-deoxy-D-galactopyranose (GalNAc) and D-mannopyranose (Man), which prefer the $^1C_4$ conformation, axial orientation at the anomeric position corresponds with the α-anomer and equatorial orientation with the β-anomer, respectively.

### *1.2.3.2.2 Glycosyl halide stability and reactivity*

The stability and reactivity of the glycosyl halides is greatly dependent on the halogen, the sugar and the protective groups. The thermal stability increases from bromide to chloride and by substituting electron-donating protective groups for electron-withdrawing protective groups. Dramatic changes in stability are observed; thus the well-known acetobromoglucose (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide) can be readily prepared and stored at 0 °C, whereas the frequently used 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide is thermally unstable as low as –78 °C (glycosyl iodides are usually too unstable). Therefore, many glycosyl halides are prepared *in situ* and used without further purification, thus necessitating the use of compounds which are frequently sterically nonhomogeneous and sometimes even impure. In addition, the glycosyl halides are highly sensitive to hydrolysis.

The reactivity of the glycosyl halides increases in reverse order compared with stability; protective groups at different positions exert 'remote electronic effects'. The influence of these groups does not depend only on the distance to the anomeric carbon atom;[37] thus electron-withdrawing *O*-protective groups at C-4 lower the C-1 reactivity quite strongly due to through-bond interactions.

### *1.2.3.2.3 α/β-Selectivity in glycoside synthesis*

A stereocontrolled nucleophilic substitution of the glycosyl halogen by an $S_N2$ mechanism would provide the β-glycosides from the generally readily available α-glycosyl halides. Thus the only existing problem would be the generation of the thermodynamically less stable β-halogenoses. However, the situation is much more complicated, because most glycosyl acceptors are not reactive enough for a simple base-catalyzed nucleophilic substitution at the anomeric center. Therefore, the reactivity of the glycosyl halide itself has to be adjusted to the special synthetic problem by varying the halide and the protective group pattern, and, above all, by selecting a proper halophilic 'catalyst' (required in equimolar amounts) as a coactivator. In addition, appropriate solvents and temperatures have to be chosen in relation to the glycosyl acceptor reactivity (which can also be varied by varying the protective group pattern). The fact that glycosyl halides will eventually exhibit the features of α-halogen ethers implies that at least the reactive representatives will favor $S_N1$-type mechanisms which are not stereoelectronically controlled. Therefore all the other factors mentioned above will play important roles in diastereoselection.

Due to the general structure of hexoses (and pentoses) and due to the importance of the hydroxy group next to the anomeric position, four different structural situations are generally differentiated (Scheme 3). The ease of formation of these different anomeric linkages is mainly dependent on the strength of the anomeric effect, which is comparatively stronger in the α-*manno*-type than in the α-*gluco*- (and the α-*galacto*-) type sugars, and possible neighboring group participation of protective groups at the functional group at C-2. Thus the readily available α-glucosyl halide (**1**; Scheme 4), presumably *via* a tight (or a solvent-separated) ion pair (**2**), or the β-glucosyl halide (**4**), collapses to a dioxolanium intermediate (**5**), which is attacked by the glycosyl acceptor almost exclusively from the β-face, cleanly providing β-glucopyranosides (**6**). In the reaction course conformational changes to half-chair forms are required for oxygen lone pair orbital overlap with the C-1 carbonium ion. Due to the intramolecularity of formation of (**5**), bimolecular attack at (**2**) from the α-face, providing α-glucopyranosides (**3**), can be obtained only with difficulty, usually necessitating thermodynamic control. Obviously orthoester (**7**) formation is a competing side reaction, which can be reversed by acid treatment. Therefore orthoesters (**7**) can also be successfully applied to β-glucopyranoside (**6**) synthesis (see Section 1.2.4.1)

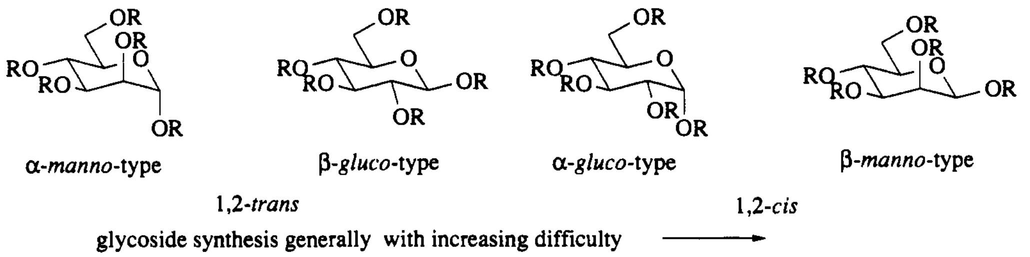

Typical examples – *gluco*-type: D-Glc, D-GlcNAc, D-GlcA, MurAc, D-Gal, D-GalNAc, L-Fuc;
*manno*-type: D-Man, L-Rha

**Scheme 3**

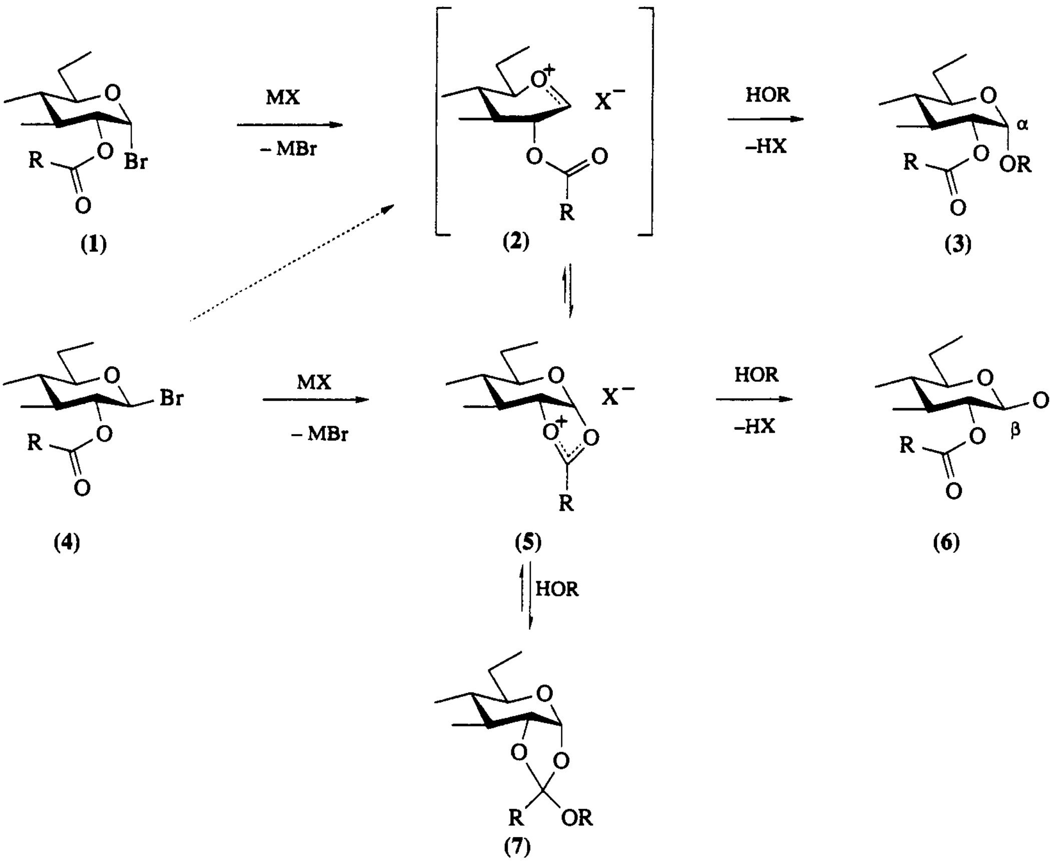

**Scheme 4**

These considerations explain the experimentally found ease of formation of α-*manno*-type structures (Scheme 3) because they are favored by the anomeric effect and by neighboring group participation (Scheme 3). β-*Gluco*-type structures are also readily accessible when neighboring group participation is applicable. However, the formation of α-*gluco*-type structures depends strongly on thermodynamic control (or $S_N2$-type reactions) without recurrence to neighboring group participation. Obviously, the formation of β-*manno*-type structures is supported neither by the thermodynamic anomeric effect nor by neighboring group participation. It is strictly dependent on an $S_N2$-type reaction starting from the readily accessible α-*mannosyl*-type halides. Therefore this structural type is most difficult to prepare.

### *1.2.3.2.4 Other variables in glycoside bond formation*

The above conclusions concerning the stability and reactivity of glycosyl halides and their diastereocontrol in substitution reactions with glycosyl acceptors have to be complemented by the other variables in glycoside bond formation.

*(i) The catalyst*

As catalysts (or coactivators, required in at least equivalent amounts), various silver or mercury salts are applied. Mercury-containing components, especially $Hg(CN)_2$ in nitromethane as solvent or cosolvent, were introduced by Helferich and coworkers,[38] and are therefore often referred to as 'Helferich conditions'. Important aspects are differences in reactivity and the generation of equivalent amounts of acid and/or water in the course of glycoside bond formation. For the most common catalysts the following order of reactivity has been generally confirmed: $AgOTf/Ag_2CO_3 > AgClO_4/Ag_2CO_3 > Hg(CN)_2/HgBr_2 > Hg(CN)_2$.[5] The formation of acid can be circumvented by the addition of $Ag_2CO_3$ in combination with catalytic amounts of AgOTf or $AgClO_4$ and the use of a base, for instance collidine. Water is commonly removed with Drierite or molecular sieves (3Å and 4Å).

*(ii) The solvent*

Solvents which are poor donors are commonly used in glycoside synthesis, for instance dichloromethane, cyclohexane or petroleum ether. These solvents favor *S*N2-type reactions. Solvents which are better donors, for instance ethers (diethyl ether, THF, *etc.*), acetonitrile, pyridine, nitromethane *etc.*, each result in a typical change in the reaction course due to their different participation in the stabilization of the reaction intermediates. With ethers, acetonitrile and pyridine participation leads to onium-type intermediates (Scheme 5; **8** and **9**), which eventually provide, *via* fast equilibration, mainly the β-anomer (**8**), due to their higher thermodynamic stability, based on the 'inverse anomeric effect'.[13,39] Thus α-product formation is often favored in these solvents (see Section 1.2.3.2.5). Solvents with even higher dielectric constants commonly result in lower diastereocontrol in glycoside synthesis.

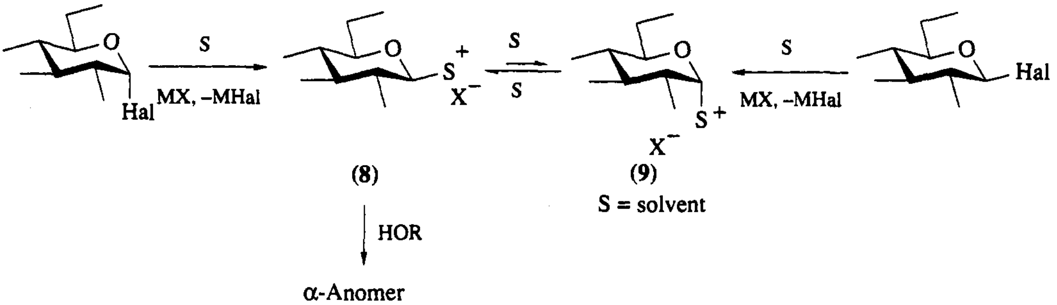

**Scheme 5**

Recently, *in situ* generation of onium-type intermediates from pentenyl glycosides was suggested by Fraser-Reid and coworkers[40] for glycoside synthesis. Thus far the α,β-selectivities in this process have mainly been found to be low.

*(iii) The temperature*

Due to the low thermal stability of many glycosyl halides reaction temperatures above room temperature are usually not applied. The general tendency to favor the stereoelectronically controlled *S*N2-type reaction is reason to use reaction temperatures as low as possible. However, solubility and reactivity are commonly the decisive factors for reaction temperature selection.

*(iv) The acceptor*

The acceptor reactivity exhibits big differences, which are due to steric, stereoelectronic (*e.g.* anomeric configuration) and inductive (*e.g.* electronic character of protective groups effects), with the steric effect usually predominating. When all groups are equatorial (for instance *gluco*-type in $^{1}C_4$-conformation) the following reactivity order is observed: 6-OH > 3-OH > 2-OH > 4-OH.[5] Axial hydroxy groups are usually less reactive than equatorial hydroxy groups (3-OH *versus* 4-OH in galactopyranose). These observations were successfully applied in regioselective saccharide syntheses with partially *O*-protected glycosyl acceptors (see Section 1.2.3.2.5).

### *1.2.3.2.5 Examples*

Prominent oligosaccharide structures found in glycoconjugates include blood group antigenic determinants, the carbohydrate–peptide connections of *O*- and *N*-glycoproteins, the carbohydrate–ceramide connections of glucosphingolipids, fundamental structures of *O*- and *N*-glycoproteins and of glycosphingolipids, and oligosaccharide units of lipopolysaccharides;[1–7] these have attracted the interest of synthetic chemists. The versatility of the Koenigs–Knorr method has been demonstrated in this area in the last 20 years.[5]

The ease of α-*manno*-type connection starting from 2-*O*-acetyl-α-mannopyranosyl bromides (**10**) and (**11**) is exhibited in the synthesis of fragments (**14**) of the *N*-glycosidically linked carbohydrate portion (**13**) in glycoproteins (Scheme 6).[41] However, other important aspects of efficient oligosaccharide syntheses are also exhibited in this example: these are partial *O*-protection for starting material synthesis with the help of regioselective stannylation and subsequent benzylation, regioselective mannosylation and block synthesis for the attachment of the lactosaminyl residue. The required lactosaminyl donor (**12**) is obtained from lactal *via* azidonitration by the cerium ammonium nitrate route introduced by Lemieux and coworkers.[42]

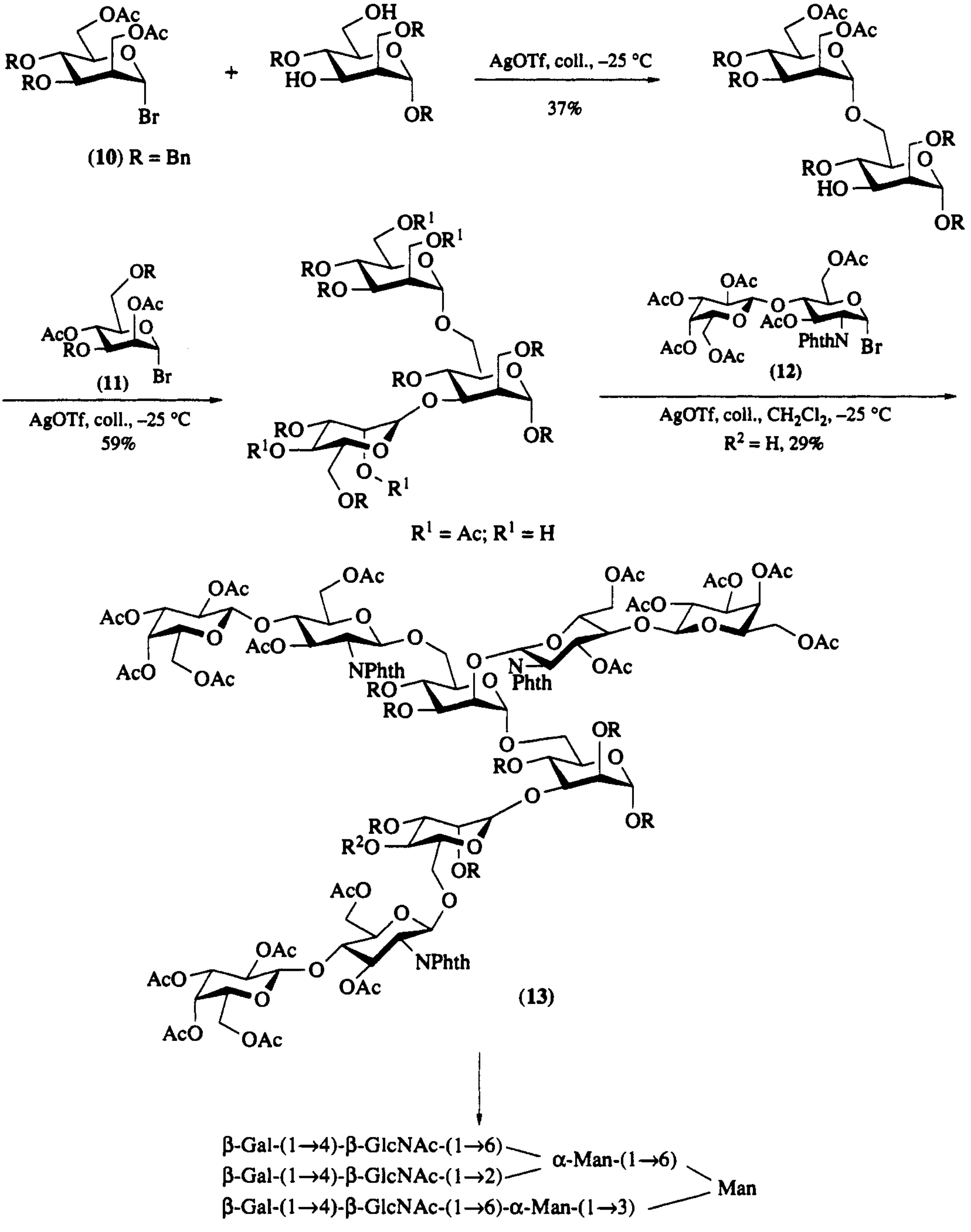
(10) R = Bn
AgOTf, coll., –25 °C
37%
(11)
AgOTf, coll., –25 °C
59%
R¹ = Ac; R¹ = H
(12)
AgOTf, coll., CH₂Cl₂, –25 °C
R² = H, 29%
(13)
β-Gal-(1→4)-β-GlcNAc-(1→6)
β-Gal-(1→4)-β-GlcNAc-(1→2)
α-Man-(1→6)
β-Gal-(1→4)-β-GlcNAc-(1→6)-α-Man-(1→3)
Man
(14)

**Scheme 6**

The α-Rhamnopyranosyl connection often met in repeating units of lipopolysaccharides is obtained by analogous procedures.[5,43]

β-Glucopyranosyl and β-D-galactopyranosyl connection (β-*gluco*-type) can be readily attained if the reactivity of 2-*O*-acyl-protected donors is sufficient for the acceptor reactivity. Scheme 7[44] demonstrates this difference clearly. The galactosyl donor (**16**) reacts with the acceptor (**15**) cleanly to give the β-disaccharide (**18**). However, under the same conditions compound (**17**) with R = acetyl gives practically no product, and compound (**17**) with R = benzyl is still much less reactive than compound (**15**), although the corresponding β-disaccharide (**19**) is obtained in good yield after longer reaction time.

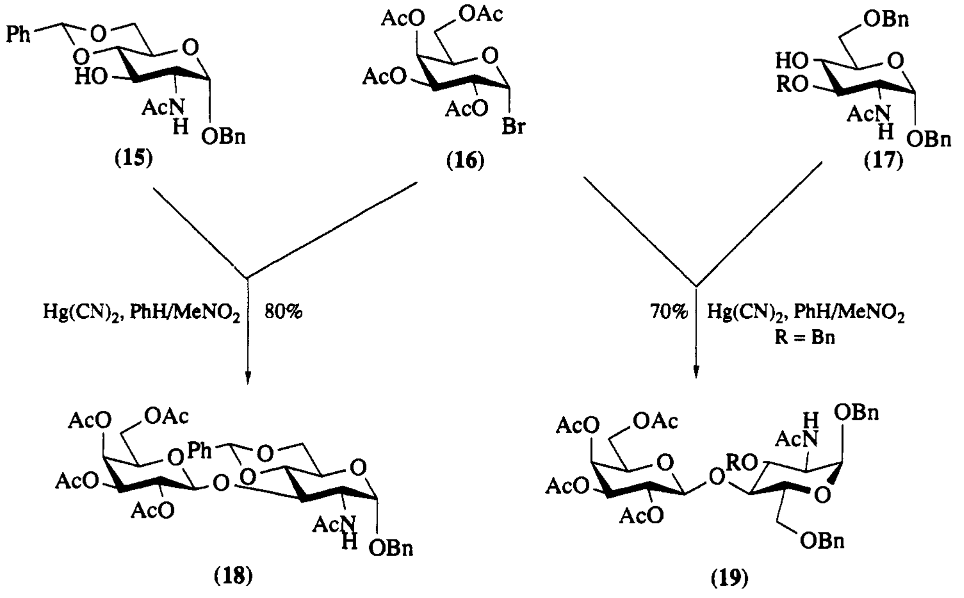

**Scheme 7**

Neighboring group participation for β-glucosamine and β-galactosamine connection is best achieved with the 2-deoxy-2-phthalimido group. Because of the excellent leaving group properties of the generated oxazolinium intermediate, high yields and high β-selectivities are usually observed (Scheme 6).[41] The required removal of the phthalimido group (with hydrazine) for the subsequent *N*-acetylation (to provide the acetamino compounds found in natural products) has already inspired work using the 2-acetamino group as a neighboring group in β-selective glycoside syntheses. However, due to the presence of an NH group, stable oxazolines are obtained from the corresponding glycosyl halides. Under strong acidic catalysis (attack of the acid at the oxazoline nitrogen) these intermediates exert glycosyl donor properties with reactive acceptors possessing the required acid stability.[5]

The investigation of 2-azido-2-deoxy sugars in glycoside synthesis has demonstrated that this group is largely a nonparticipating group. It was therefore mainly applied to corresponding α-*gluco*-type syntheses.[5]

The frequent occurrence of the α-D-galactopyranosyl, 2-acetamino-2-deoxy-α-D-galactopyranosyl, α-L-fucopyranosyl and α-D-glycopyranosyl connections in glycosides and saccharides has intensified the search for appropriate variations of the Koenigs–Knorr method. Obviously, nonparticipating groups (*e.g.* 2-*O*-benzyl, 2-azido-2-deoxy, *etc.*) and β-glycosyl halides were best applied to promote an $S_N2$-type reaction. The viability of this approach is demonstrated in Scheme 8,[45] where, with the help of electron-withdrawing *O*-protection in the donor (**20**) and the acceptor (**21**), the cellobiose derivative (**22**) is obtained. The decreased reactivity had to be overcome by the use of strong silver catalysts.

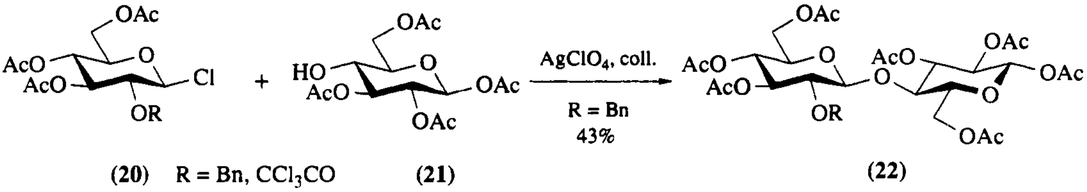

**Scheme 8**

All this points to finding a means for the generation of the less stable β-glycosyl halides. This problem was solved by Lemieux and coworkers[46] with the help of the '*in situ* anomerization' of α-halogenoses with halide ions. Thus the β-halogenoses which are obtained are higher in ground state energy and more reactive towards glycosyl acceptors than α-halogenoses, preferentially affording, *via* an $S_N2$-type reaction, the α-glycosides. This is qualitatively demonstrated in Scheme 9. For the transition state geometries, half-chair-like geometries are suggested. Lemieux and coworkers[47] applied tetraalkylammonium halides for catalysis of this reaction, which turned out to be efficient only for reactive glycosyl donors. Later it was found by Paulsen and coworkers[48] that other soluble catalysts ($Hg(CN)_2$, $HgBr_2$, $AgClO_4$, AgOTf) are more efficient, providing α-glycosides using less reactive glycosyl donors under mild conditions. For instance, the important A, B and H blood group antigenic determinants were obtained with the help of this method (Scheme 10).[49,50] The synthesis of the H and B (type 2) determinants is exhibited starting from the lactosamine acceptor (**23**), which is first connected with the fucosyl donor (**24**), providing trisaccharide (**25**), and then with the galactosyl donor (**26**) to yield the tetrasaccharide (**27**). Subsequent deprotection of saccharides (**25**) and (**27**) provided the desired blood group determinants. In this α-glycosylation procedure, intermediates with the counterions of the catalysts or complexes with the complete catalyst are presumably generated[5] which correspond to β-halogenoses in their reaction behavior. This relates this process to the influence of participating solvents, which exert a similar effect. This could be successfully demonstrated in α-D-glucopyranuronic acid synthesis (Scheme 11).[51] Acetonitrile proved to be particularly suitable; with the glycosyl donor (**28**) excellent yields of α-glycosides (**29**) were obtained with various acceptors. Nitrilium–nitrile association, as shown in structures (**30**), presumably hinders attack by the acceptor at the nitrilium carbon.

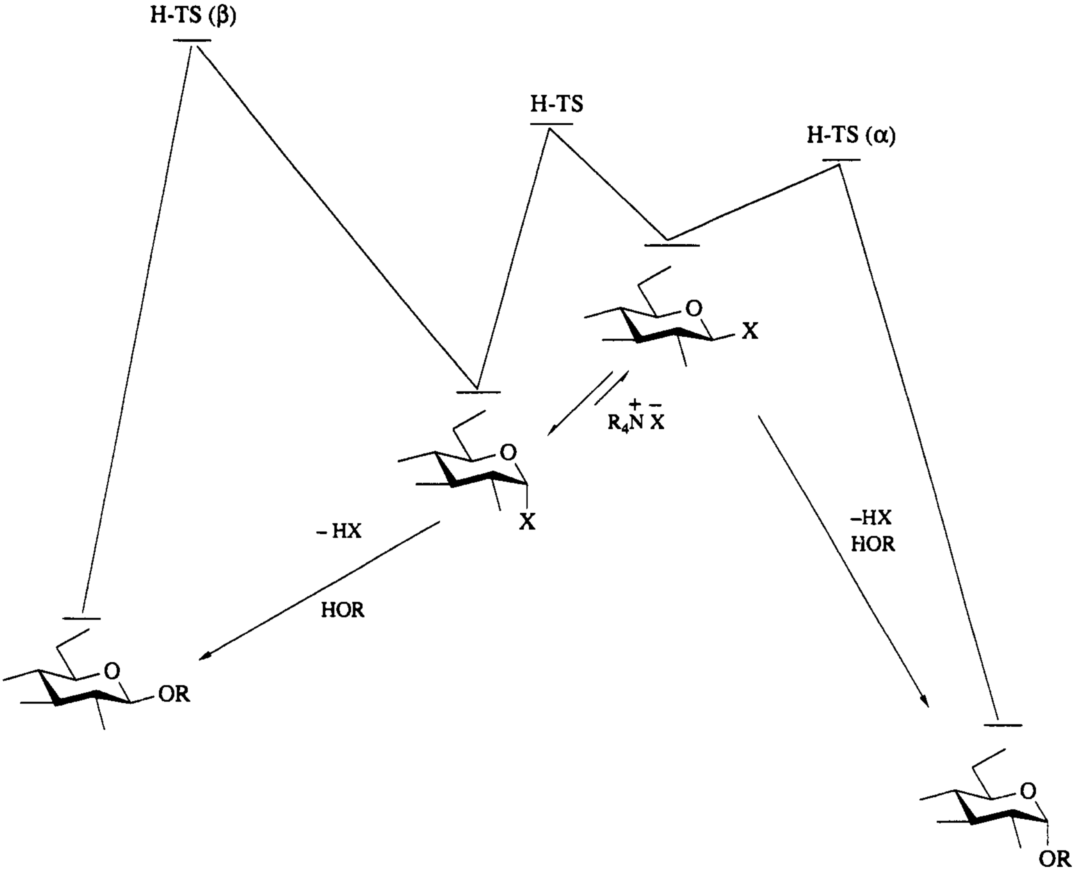

H-TS = half-chair transition state

**Scheme 9** *In situ* anomerization procedure

β-*Manno*-type connection became important because this glycoside bond was found in the branching position of *N*-glycoproteins. Previous investigations with α-mannosyl bromide and reactive acceptors in the presence of insoluble silver oxide[52] inspired Paulsen and coworkers[53] to develop an insoluble heterogeneous silver silicate catalyst system, which proved to be very successful in β-mannopyranoside formation. Later silver zeolite was introduced by Garegg and coworkers[54] for the same purpose. A key synthesis was the β-mannopyranosyl connection to the 4-O of *N*-acetylglycosamine found in *N*-glycoproteins. An example of these investigations is exhibited in Scheme 12.[55] The mannosyl donor (**31**), with a nonparticipating 2-O protective group, reacts in good β-selectivity with the 1,6-anhydro-2-azidoglu-

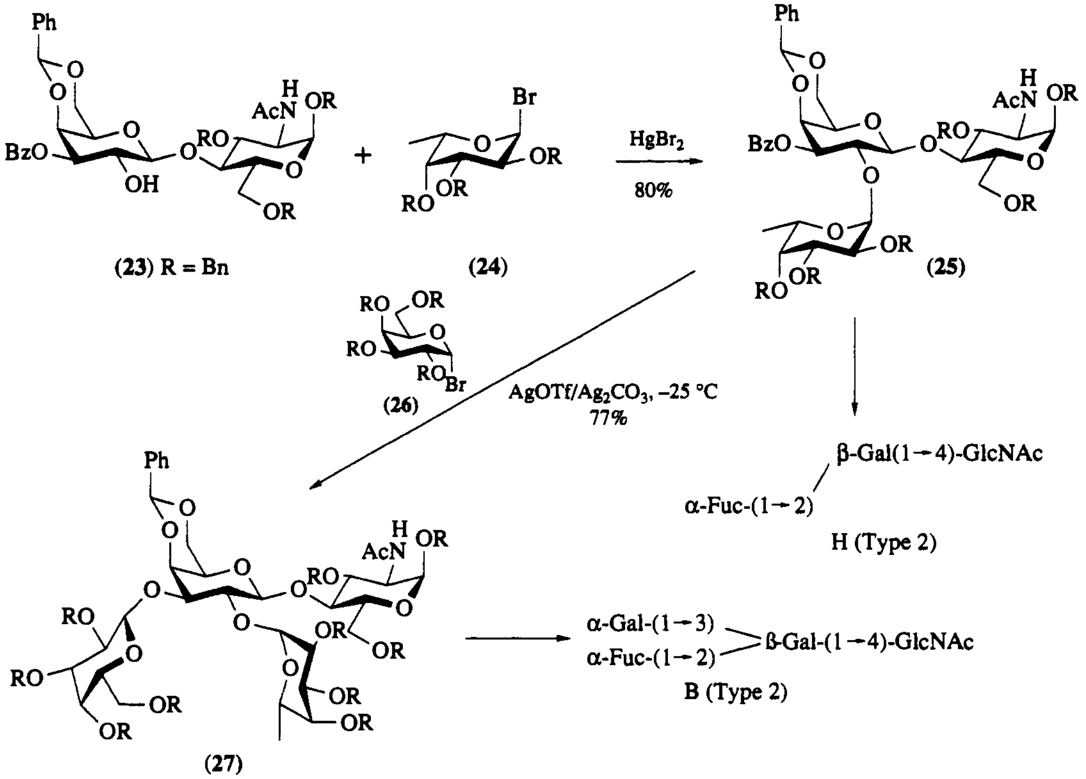
(23) R = Bn
(24)
HgBr2
80%
(25)
(26)
AgOTf/Ag2CO3, -25 °C
77%
β-Gal(1→4)-GlcNAc
α-Fuc-(1→2)
H (Type 2)
(27)
α-Gal-(1→3)
α-Fuc-(1→2)
ß-Gal-(1→4)-GlcNAc
B (Type 2)

Scheme 10

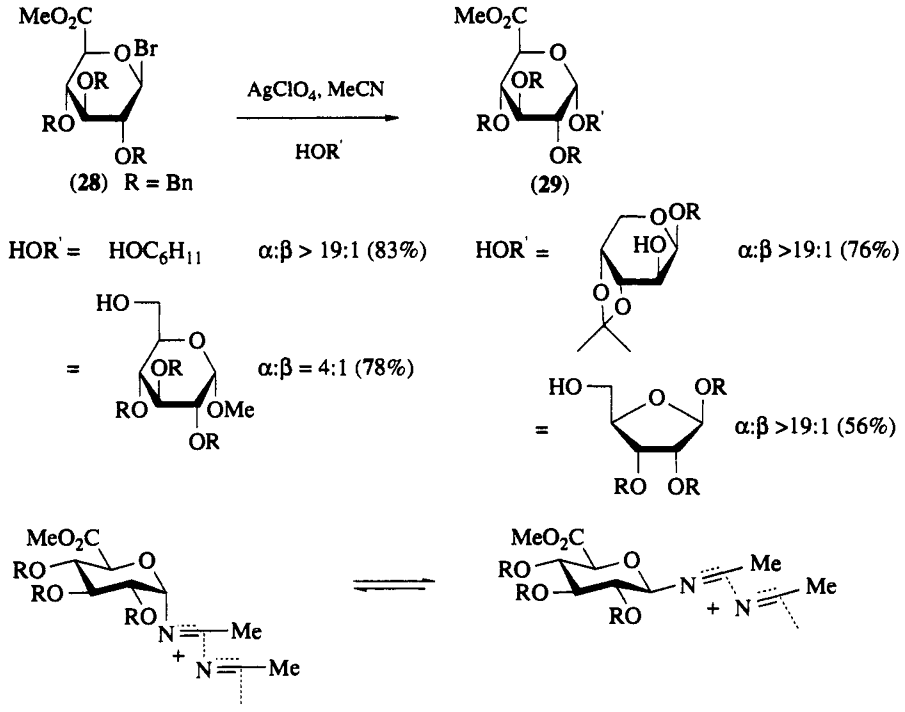
(28) R = Bn
AgClO4, MeCN
HOR'
(29)
HOR' = HOC6H11 α:β > 19:1 (83%)
HOR' =
α:β >19:1 (76%)
=
α:β = 4:1 (78%)
=
α:β >19:1 (56%)
α-(30)
β-(30)

Scheme 11

cose acceptor (**32**), which is more reactive than a corresponding $^1C_4$-conformer, to give the desired disaccharide (**33**). Subsequent α-selective dimannosylation with (**34**), which has a participating group in the

2-*O*-position, provides the branched tetrasaccharide (**35**) in high yield. Further processing furnishes the unprotected tetrasaccharide (**36**).

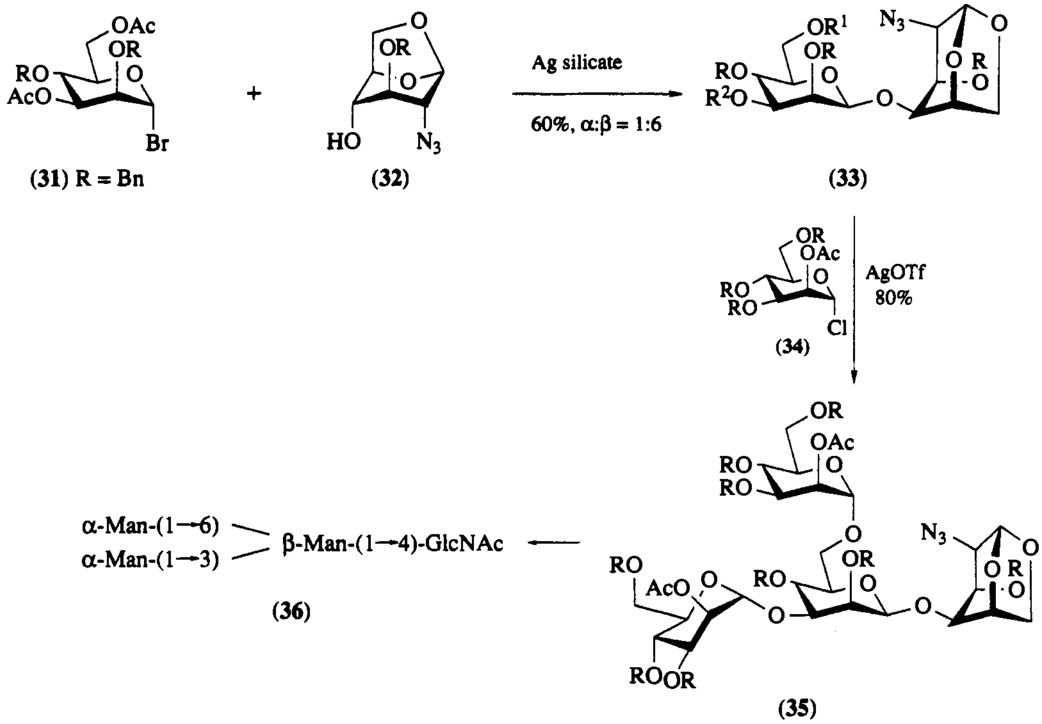

**Scheme 12**

β-Rhamnopyranoside structures, found in repeating units of the lipopolysaccharides of bacteria, have been also obtained with the help of these procedures.

### *1.2.3.2.6 Summary*

In conclusion, the results with the Koenigs–Knorr method can be summarized as follows.

Firstly, the reactivity of the glycosyl donor can be varied over wide ranges by the choice of the halogen, the protecting group pattern, the catalyst, the solvent and the temperature. In this way the glycosyl donor reactivity can be adjusted to the glycosyl acceptor reactivity (which can also be varied).

Secondly, diastereoselectivity in the glycoside formation is attained by: (i) participation of neighboring groups for β-glycosides of glucose, glucosamine, galactose and galactosamine and for α-glycosides of mannose, fucose and rhamnose; (ii) *in situ* anomerization of the α-glycosyl halide to the more reactive β-glycosyl halide, which reacts preferentially to give the more stable α-glycosides of glucose, glucosamine, galactose and galactosamine (*i.e.* exploitation of the thermodynamic anomeric effect); and (iii) heterogeneous catalysis, which gives good results in the difficult formation of the β-mannose and β-rhamnose linkage.

The application of these observations has also led to many excellent results in *N*-glycoside synthesis. (The discussion of the special aspects of *N*- and *C*-glycoside synthesis is beyond the scope of this chapter.) However, severe, partly inherent disadvantages of the Koenigs–Knorr method could not be overcome. These include the low thermal stability and the sensitivity to hydrolysis of many glycosyl halides, and the use of at least equimolar amounts of heavy metal salts as 'catalysts', which are partly toxic or even explosive, to mention only a few aspects. This had led to an increased search for improved methods applicable also to large scale preparations.

### 1.2.3.3 Fluoride as Leaving Group

For the generation of glycosyl donor properties, other anomeric oxygen exchange reactions have been investigated. Closely related to the Koenigs–Knorr method, where bromide and chloride are the leaving groups, fluorine has been introduced as a leaving group by Micheel and coworkers (Scheme 1)[56] and has recently been investigated for glycoside synthesis.[1,5,6,12] The higher thermal stability and the higher stability towards many reagents is due to the higher strength of the carbon–fluorine bond as compared to the other carbon–halogen bonds. This enabled even base-catalyzed modifications of unprotected hydroxy groups in the presence of an anomeric fluorine atom.[57] For instance, successful *O*-benzylation of *O*-unprotected α-D-glucopyranosyl fluoride was recently described, exhibiting possible advantages in terms of the strategy of glycoconjugate synthesis.[57] However, the higher strength of the carbon–fluorine bond may concomitantly lower the glycosyl donor properties of glycosyl fluorides. Therefore, specifically fluorophilic promoters were searched for. The $SnCl_2/AgClO_4$ system was introduced by Mukaiyama and coworkers[58] and applied by several groups[59] to glycoside syntheses, resulting in good yields and reasonable α-selectivity with nonparticipating 2-*O*-protective groups. In addition, several methods for the synthesis of glycosyl fluorides were recently reported.[59,60]

Because of the complexity of the $SnCl_2/AgClO_4$ catalyst system several other fluorophilic Lewis acids were investigated as catalysts in this reaction, for instance $SiF_4$,[61] $SnF_4$,[62] $TiF_4$,[62] $BF_3{\cdot}OEt_2$[63] and TMSOTf.[61] Thus with relatively reactive acceptors good glycoside yields were usually obtained; however, good diastereoselectivities were generally only observed for reactions with 2-*O*-participating groups. In cases with nonparticipating groups, the α:β ratio of the products depends on the solvent used rather than on the stereochemistry of the glycosyl fluoride, disproving a direct $S_N2$ reaction course as expected due to the special character of the carbon–fluorine bond. Even a retentive glycoside formation mechanism has been discussed for the $TiF_4$ catalyst.[62,64]

Relatively few applications of glycosyl fluorides in complex oligosaccharide syntheses have been reported thus far.[65] Therefore a general statement of the importance of glycosyl fluorides as glycosyl donors is not possible. Up to now the value of glycosyl fluorides seems to be limited. Glycosyl fluorides have also proved useful in the synthesis of *C*-glycosides.[63a,66]

### 1.2.3.4 Sulfur as Leaving Group

Recently thioglycosides, where the anomeric oxygen is replaced by an alkyl- or aryl-thio group, have attracted considerable attention as glycosyl donors (Scheme 1).[67] As with the glycosyl fluorides, thioglycosides offer efficient temporary protection of the anomeric center, and, in addition, several sulfur-specific activation reactions for generating glycosyl donor properties exist. Particularly obvious is the selective activation of thioglycosides by thiophilic metal salts. These include mercury(II) salts ($HgSO_4$,[68] $HgCl_2$,[69] PhHgOTf,[70] $Hg(OBz)_2$,[71] $Hg(NO_3)_2$[72]), copper(II) triflate[73] and lead(II) perchlorate.[74,75] However, besides the disadvantageous use of heavy metal salts, the activation itself was too weak to be of general applicability to glycoconjugate synthesis. The problem was partly circumvented by using heterocyclic thioglycosides.[75,76] For instance, Mukaiyama and coworkers[73] used benzothiazolyl thioglucoside (**37**; Scheme 13) in the presence of $Cu(OTf)_2$ as catalyst. Hanessian and coworkers[72] studied the reaction of the *O*-unprotected glucosyl thio heterocycles (**38**) and (**39**) with reactive glycosyl acceptors, employing $Hg(NO_3)_2$ as the catalyst and acetonitrile as the solvent. They obtained *O*-glycosides and the disaccharide Glc(1 → 6)Gal in good yields, but with only modest α/β selectivities. Comparative studies on the effect of proton activation with phenyl thioglucoside (**38**; X = Y = CH) and pyridyl thioglucoside (**38**; X = N, Y = CH), demonstrated the dramatic effect of the heteroatom (termed 'remote activation') as a basic anchor for the proton, resulting in a better leaving group due to the electron-withdrawing character. Not surprisingly, this kind of approach to glycoside synthesis has been successfully applied to the more reactive 2-deoxyglycosyl donors (see Section 1.2.7), for instance in the synthesis of erythromycin,[74] avermectin[75] and digitoxin.[69]

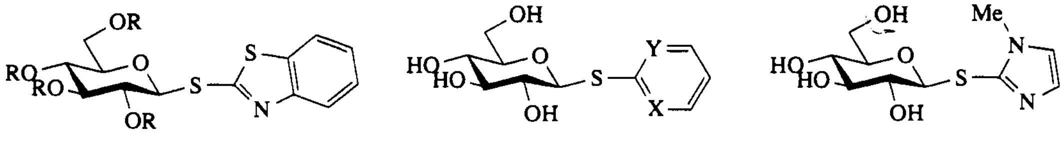

(**37**) R = Bn (**38**) (**39**)

X = N, Y = CH; X = Y = N; X = Y = CH

Scheme 13

Besides metal salts (and protons), bromonium and chloronium ions are also highly thiophilic. Recent work has demonstrated that, in a two-step process, thioglycosides can first be transformed with bromine and chlorine into the corresponding glycosyl halides (providing the thermodynamically more stable α-halides), thus subsequently enabling the application of the Koenigs–Knorr method.[67,77] If the counterion of the halonium is a poor nucleophile (for instance in *N*-bromosuccinimide), then direct reaction with alcohols as competing *O*-nucleophiles should be preferred. This has been confirmed[72] and, starting from phenyl thioglycosides, a wide scope for this reaction observed;[76] however, low α,β-selectivities were frequently obtained.

Sulfonium, ammonium and phosphonium groups are suitable as leaving groups for nucleophilic displacement reactions at the anomeric center. Schuerch and coworkers[78] have studied these groups and found the following order of reactivity: sulfonium > ammonium > phosphonium compounds, putting the interest mainly on thioglycosides. Thus Lönn reported good glycosidation results for sulfonium leaving groups obtained from alkylthioglycosides and methyl triflate.[79,80] One example is exhibited in Scheme 14.[79] Starting from thioglycoside (**40**) and the mannose acceptor (**41**), owing to phthalimido group control the β-connected tetrasaccharide (**42**) was obtained in good yield. The corresponding unprotected compound (**44**) has been found as a constituent of glycoproteins in the urine of patients suffering from fucosidosis.[80] 1,2-Elimination in this glycosidation procedure, previously reported by Kronzer and Schuerch,[78] was also observed as a competing reaction leading to the glycal derivative (**43**). The low α/β-selectivity observed for nonparticipating 2-*O*-protective groups, the health hazard of methyl triflate and the formation of methylation products in other side reactions are additional disadvantages of this methodology.[79] However, dimethyl(methylthio)sulfonium triflate (DMTST), recently introduced by Fügedi and Garegg,[81] is highly thiophilic and gives rise to faster glycosylations than does methyl triflate. Glycosyl donors with neighboring group partication during reaction generate 1,2-*trans*-linked glycosides (α-*manno*-type, β-*gluco*-type) in excellent yields and virtually complete stereospecificity. However, with nonparticipating groups the α/β-selectivity is usually low.[79] Recent application for generating the α-

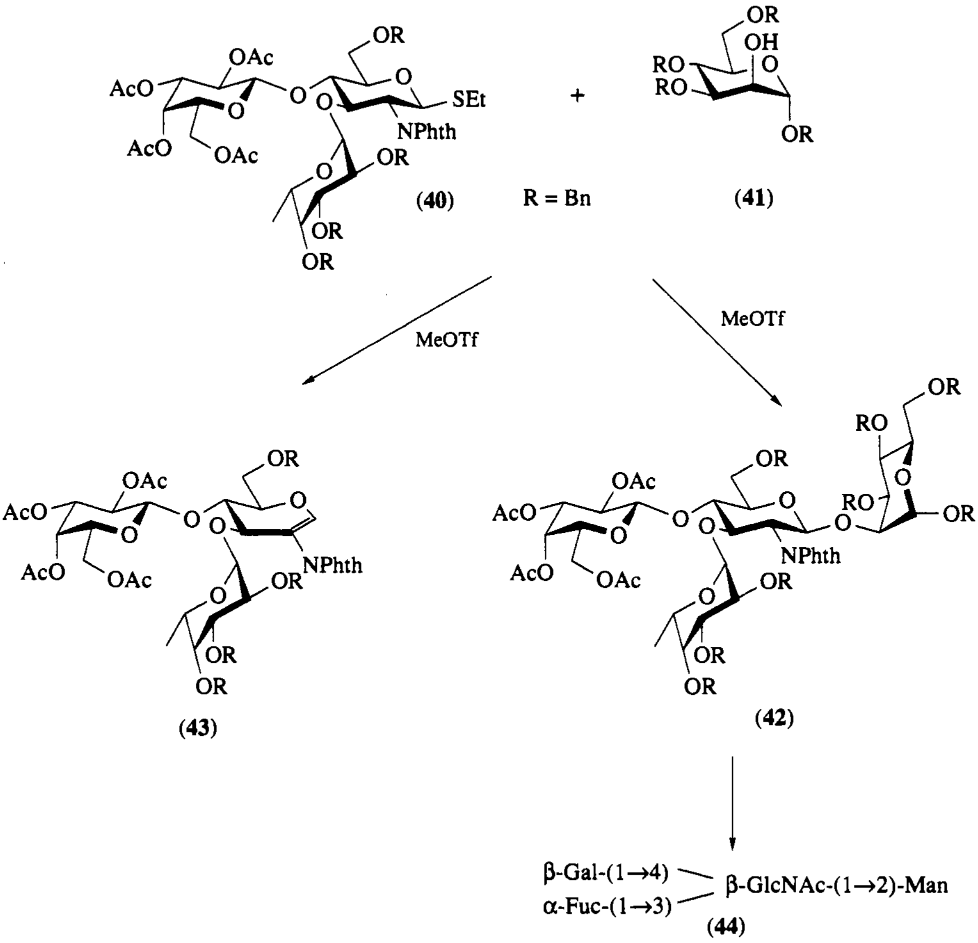

Scheme 14

*gluco*-type linkage found in *O*-glycoproteins of the mucin-type core structures (**50** and **51**; Scheme 15) met with limited success.[82] The donor properties of compounds (**45**) and (**47**) towards serine derivative (**46**) were low with methyl triflate but excellent with DMTST, giving the saccharides (**48**) and (**49**). Good α-selectivity was only obtained for (**45**).

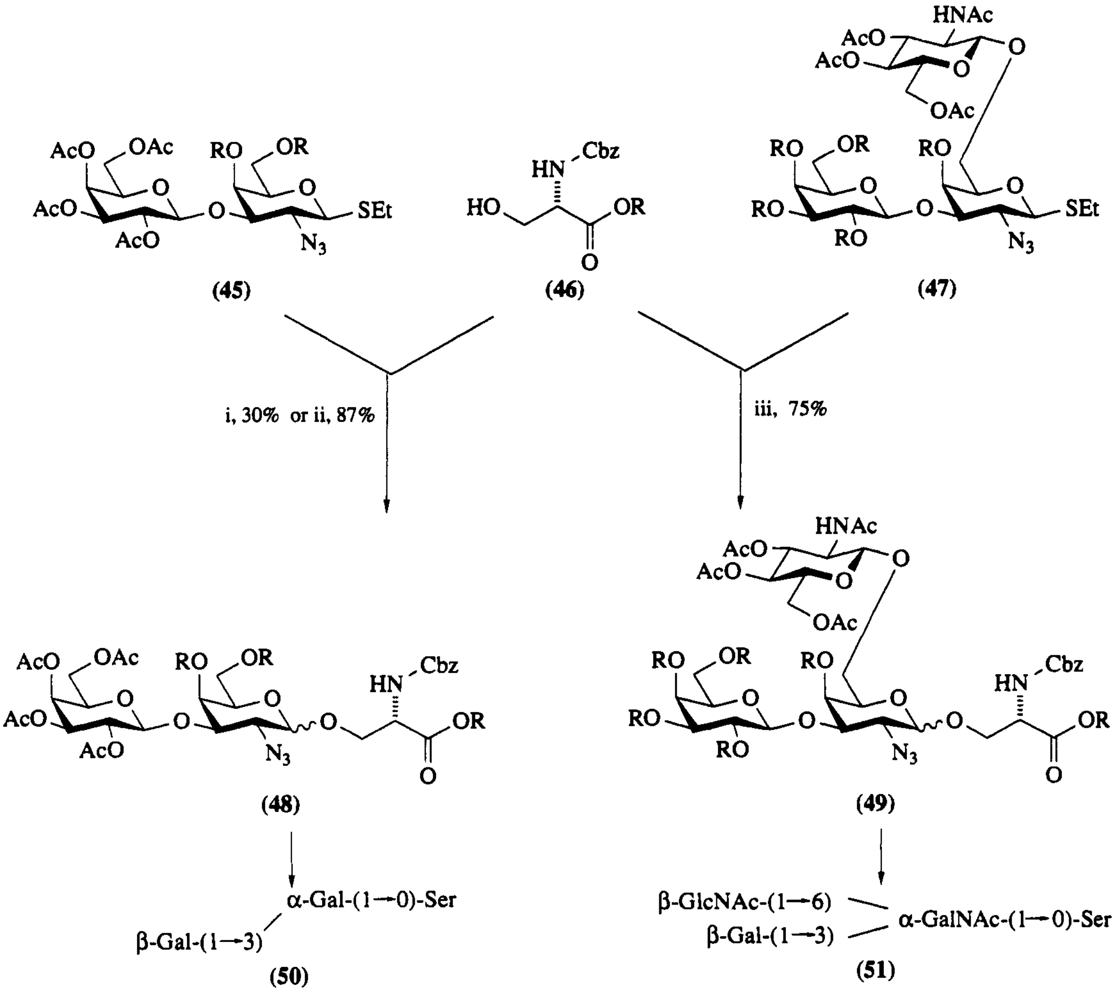

i, MeOTf, 8 d (α:β ≈ 4:1); ii, DMTST, 12 h (α:β ≈ 5:1); iii, DMTST, 1 h (α:β ≈ 1:2)

**Scheme 15**

Due to the interest in thioglycosides, the methods of their synthesis from glycosyl halides with thiolates or by *S*-alkylation of 1-thioaldoses[83] have been complemented by new methods.[76,84]

Glycosyl disulfides, sulfonic acids and sulfones have not exhibited interesting glycosyl donor properties.[85]

### 1.2.3.5 Anhydro Sugars as Glycosyl Donors

1,2-Anhydro sugars promise good glycosyl donor properties due to the ring strain in the alkoxy epoxide moiety. Brigl's anhydride was thus used for the synthesis of disaccharides,[86] iridoid glycosides[87] and aryl glycosides;[88] however, only modest results were obtained. Obviously, as stated earlier,[1] the possibilities of this reaction are not exhausted. Therefore renewed interest in this reaction seems promising.[89]

Other 1,*x*-anhydro sugars (*x* > 2), possessing lower ring strain, exhibit lower reactivity.[1]

## 1.2.4 THE TRICHLOROACETIMIDATE METHOD AND OTHER ANOMERIC OXYGEN ACTIVATION METHODS FOR GLYCOSIDE SYNTHESIS

### 1.2.4.1 Introduction and Earlier Examples of Oxygen Activation

The requirements for glycoside synthesis introduced in Section 1.2.3.1 are obviously not met by any of the methods described. However, it seems that the general strategy for glycoside synthesis is reasonable, namely: (i) that the first step should involve a sterically uniform activation of the anomeric center with formation of a stable glycosyl donor having either an α- or β-structure; and (ii) that the second step should involve a catalyzed, sterically uniform, irreversible glycosyl transfer to the acceptor, proceeding with either retention or inversion at the anomeric center in high chemical yield and without affecting other bonds.

Apart from the direct acid activation (Scheme 1, path a) or acid-supported anomeric oxygen exchange for a leaving group (Scheme 1, path b), base-catalyzed transformation of the anomeric oxygen into a good leaving group (Scheme 1, path c) should be possible. Therefore, it is not surprising that 1-*O*-toluenesulfonylation has been known for a long time.[90] However, these compounds were prepared by reaction of the corresponding α-glycosyl halides with silver toluenesulfonate, providing predominantly α-toluenesulfonates; their use in glycoside synthesis could not gain any general importance even though several variations were investigated; for instance, introduction of electron-withdrawing *O*-protection to increase the $S_N2$ character of glycoside synthesis[1] or the use of a better leaving group.[1] The amounts of reagent and the difficult stereocontrol of both intermediate and product prevented a broader application of glycosyl sulfonates. Apparently the route *via* glycosyl halides and their activation with silver triflate[91] (see Section 1.2.3.2), demonstrating the close relation of these methods, is considerably more efficient.

Glycosyl transfer in nature takes place *via* glycosyl pyrophosphate or phosphate derivatives of nucleosides.[92] Surprisingly, only a few nonenzymic investigations with glycosyl phosphates have appeared.[93] The imitation of specific enzymatic processes in the laboratory requires an arsenal of enzymes which is not as yet available. However, interesting investigations with glycosyl transferases and also with glycosyl hydrolases have been reported.[94]

Studies on 1-*O*-activation with the Mitsunobu reagent have not attained general importance.[1]

Activation of the anomeric oxygen by 1-*O*-acylation results in relatively low glycosyl donor properties. Therefore, either high temperatures in glycoside synthesis (carbonate activation[95]) or strong acidic catalysts are required. The acid lability of the sugar can be lowered by *O*- and *N*-acetylation, *O*-benzoylation and *N*-phthalimidoylation respectively, providing neighboring group active protective groups. This approach ultimately leads to the conditions of the Fischer–Helferich method (Scheme 1), which does not require a 1-*O*-activated intermediate but builds up the glycosyl donor potential solely by the action of strong acids. Thus the conversion of 1-*O*-acylated sugars into simple *O*-glycosides was successfully performed with the help of Lewis acids, for instance $ZnCl_2$, $SnCl_4$, $FeCl_3$, $BF_3{\cdot}OEt_2$ and $Ph_3CClO_4$.[1] In recent years the use of trimethylsilyl triflate as catalyst has afforded good results for *O*-[5,96] and *N*-glycoside[97] synthesis. The simplicity of the procedure offers valuable additions to glycoside and saccharide synthesis.

1-*O*-Silylation, for instance, providing 1-*O*-trimethylsilyl glycosides from 1-*O*-unprotected sugars in an anomerically pure form, has been shown by Tietze and coworkers to be useful in phenyl glycoside and 1,1′-diacetal (see Section 1.2.5) synthesis with *O*-silylated acceptors[98] and trimethylsilyl triflate as catalyst. The diastereoselectivity was dependent on *O*-protection.

The synthesis of orthoesters from 2-*O*-acylglycosyl halides and their mercury salt catalyzed rearrangement to glycosides and saccharides have been known for a long time.[5,9] The alkylating character, known for orthoesters especially under acidic conditions, generates the glycosyl donor properties. Thus, carboxylic acids furnish 1-*O*-acyl compounds.[99] The development of the orthoester method by Kochetkov and coworkers[100] has exhibited one major disadvantage, the formation of 2-*O*-unsubstituted sugars by a competing acid attack at the 2-*O*-atom. This side reaction could be overcome by formation of the acyloxonium intermediate and trapping it with cyanide or with an alkylthio group. Then *O*-trityl sugars as acceptors and trityl perchlorate or trityl tetrafluoroborate as coactivator result in good yields of 1,2-*trans*-linked disaccharides of glucose, galactose, mannose and rhamnose.[100]

### 1.2.4.2 The Trichloroacetimidate Method:[1,2] Derivation of New Principles for Glycoside Synthesis; Trichloroacetimidate Formation

The anomeric oxygen activations described above could not fulfill the requirements put forward. Either they failed to provide both activated intermediates or both anomeric glycosides were not obtained. Obviously, for a stereocontrolled activation of the anomeric oxygen, the anomerisation of the 1-OH, or the 1-O⁻, group in the presence of base has to be taken into account (Scheme 16). Thus, in a reversible activation process and with the help of kinetic and thermodynamic reaction control both activated anomers should eventually be obtainable.

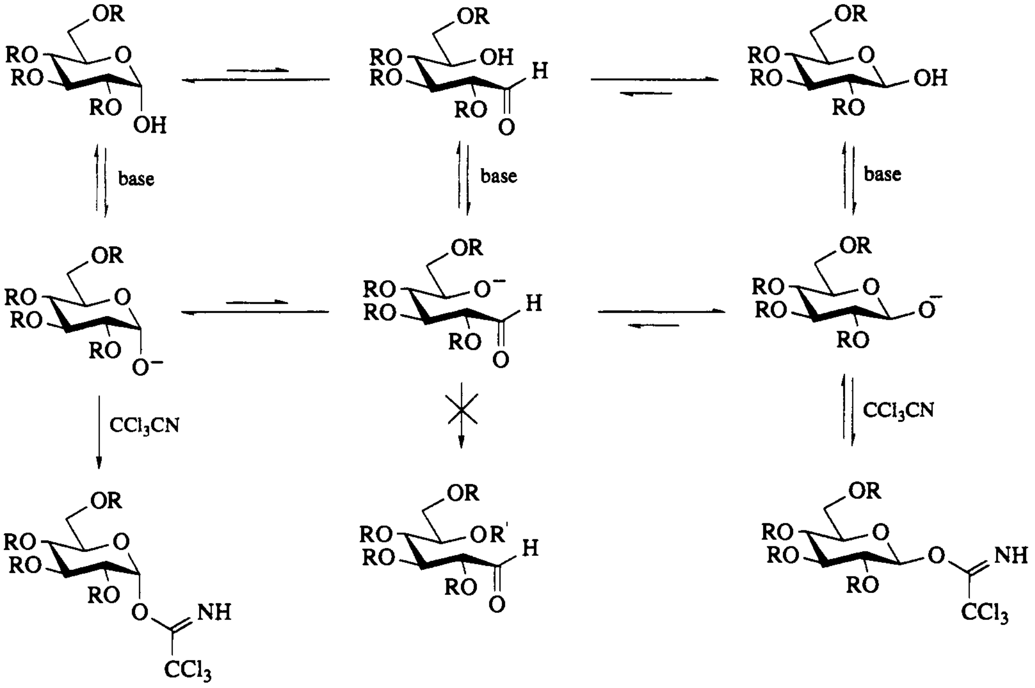

Scheme 16

These considerations suggested that pyranoses and furanoses should undergo base-catalyzed addition directly and in a stereocontrolled manner to suitable triple bond systems A≡B (or compounds containing cumulative double bond systems A=B=C, Scheme 1, path c). Only instability of aldehydic intermediates in basic media and insufficient or undifferentiated reactivities of the α- and β-alkoxides seemed to lower the expectations for a stereocontrolled anomeric *O*-activation.

The formation of stable *O*-activated intermediates can be promoted by independent catalysis of the activation and glycosylation steps. Thus, after basic activation and trapping of the *O*-activated intermediates (first step), mild acid treatment, leading to irreversible acetal formation (second step), remains as the simplest form of catalysis for the glycosylation. The stable intermediates thus obtained in the first step should, by appropriate choice of the centers A and B (or A, B and C), have good glycosyl donor properties in the presence of acid. The water liberated in the glycoside formation is transferred, in two separate steps, to the activating agent A≡B (or A=B=C), thus providing the driving force for the reaction. This concept should fulfill the requirements given above for a good glycoside or saccharide synthesis, as demonstrated by the trichloroacetimidate method.

Electron deficient nitriles such as trichloroacetonitrile (A≡B; A = N, B = $CCl_3$) are known to undergo direct and reversible base-catalyzed addition of alcohols to give *O*-alkyl trichloroacetimidates.[1] This imidate synthesis has the advantage that the free imidates can be isolated as stable adducts, which are less sensitive to hydrolysis than their salts.

A detailed study of trichloroacetonitrile addition to 2,3,4,6-tetra-*O*-benzyl-D-glucose showed[1,101] that from the 1-oxide the β-trichloroacetimidate is formed preferentially or even exclusively in a very rapid and reversible addition reaction (Scheme 16). However, this product anomerizes in a slow, base-catalyzed reaction (*via* retroreaction, 1-oxide anomerization and renewed addition) practically completely to the α-trichloroacetimidate, with the electron-withdrawing 1-substituent in an axial position as favored by the thermodynamically efficient anomeric effect.[101,102] Thus with different bases, for instance $K_2CO_3$ and

NaH, both anomers can be isolated in pure form and high yield *via* kinetic and thermodynamic reaction control. Both anomers are thermally stable and can be stored easily.

The higher nucleophilicity of the β-oxide can be attributed to a steric effect in combination with a kinetically effective stereoelectronic effect, resulting from repulsions of lone electron pairs or from dipole effects (Scheme 17).[101,102] This effect should be more pronounced in β-pyranosyl oxides than in β-pyranosides due to differences in oxygen lone pair orbitals. In addition, this kinetic anomeric effect should be particularly efficient in the β-mannopyranosyl oxide where the thermodynamic anomeric effect, favoring the α-anomer, is also stronger. This is confirmed in anomeric *O*-alkylation (see Section 1.2.5).

(a) Dipole–dipole interaction

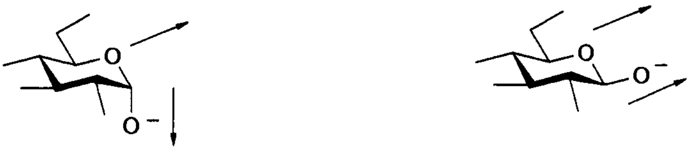

(b) Lone-pair–orbital interaction

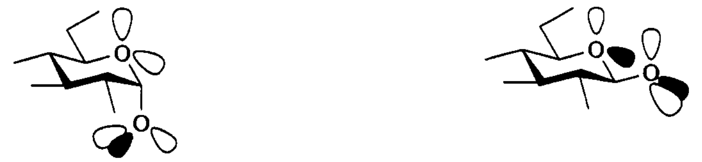

**Scheme 17** Enhanced nucleophilicity of β-oxides (kinetic anomeric effect)

The stereoselective anomeric *O*-activation of carbohydrates and their derivatives through the formation of *O*-glycosyl trichloroacetimidates is applicable to all important *O*-protected hexopyranoses (Glc, Gal, Man, Fuc, Rha, GlcN, GalN), hexofuranoses, pentopyranoses and pentofuranoses, as well as to glucuronic acid, galacturonic acid and muramic acid, commonly providing stable compounds in a stereocontrolled manner. Thus the requirement for the first step, generation of an appropriate glycosyl donor, is fulfilled.

### 1.2.4.3 The Trichloroacetimidate Method: Application to Glycoside and Saccharide Synthesis

Ultimately, the significance of the *O*-glycosyl trichloroacetimidates is derived solely from their glycosylation potential under acidic catalysis. This potential has indeed been confirmed in various laboratories.[1,10–12,82,103–110]

The direct glycosylation of Brønsted acids is a particularly advantageous property of these new glycosyl donors.[1] Carboxylic acids usually react with inversion of configuration at the anomeric center to give *O*-acyl compounds without addition of any catalyst. The uncatalyzed glycosyl transfer from *O*-glycosyl trichloroacetimidates to phosphoric acid mono- and di-esters opens a simple route to glycosyl phosphates and glycophospholipids,[111] which are of interest as intermediates in biological glycosyl transfer and as constituents of cell membranes. Thus, from trichloroacetimidate (**53**; Scheme 18) the glycosyl phosphate (**54**) was obtained[112] and transformed *via* (**56**) into (**55**), which is an important intermediate in plant sulfolipid formation.[113] The anomeric configuration of the phosphate products obtained is determined by the acidity of the phosphoric acids applied; weak acids provide the inversion products, stronger acids lead directly to the thermodynamically more stable anomer. Phosphonates and phosphinates can be obtained similarly.[114]

Alcohol components for reaction as glycosyl acceptors generally require the presence of an acidic catalyst.[1] Boron trifluoride etherate at −40 °C to room temperature in dichloromethane or dichloromethane/hexane as solvents has proved to be very suitable with regard to yield and diastereoselectivity. This is exemplified by many successful applications of this method, until now mainly to hexopyranoside synthesis.[1,2] With neighboring group participation of 2-*O*- or 2-*N*-protective groups the 1,2-*trans*-products were obtained; with the nonparticipating 2-*O*-benzyl protective group or with the 2-azido-2-deoxy group inversion of configuration at the anomeric center was found to be preferred. For 1,2-*cis*-products (α-hexopyranosides of Glc, Gal, GlcN, GalN, Man, Rha, Fuc) good results were obtained *via* inversion of

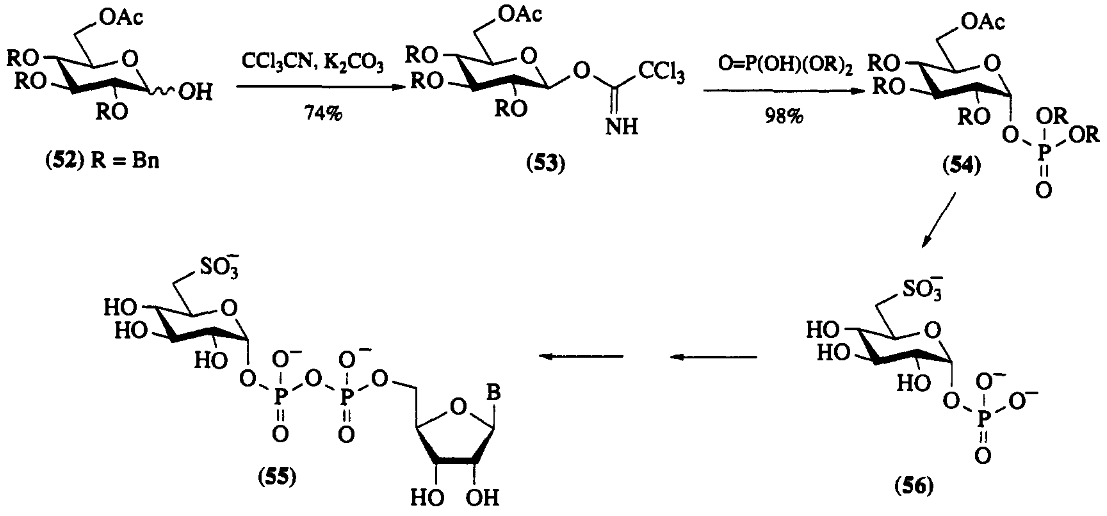

Scheme 18

configuration at the anomeric center or performing the reaction with diethyl ether as the solvent and trimethylsilyl triflate as the catalyst.[115]

Because of the great importance of glycoconjugates as cell wall constituents of bacteria and as cell membrane constituents of all vertebrates (essentially glycosphingolipids and glycoproteins), a few applications to their syntheses will be discussed.

Amongst cell wall constituents of bacteria the cell wall peptidoglycan (called murein) has become increasingly important.[116] This peptidoglycan chain has a β(1 → 4)-linked glycan chain consisting of alternating *N*-acetylglucosamine and *N*-acylmuramic acid units (Scheme 19), which are cross-linked by a peptide chain (*e.g.* by L-Ala-D-iso-Glu-*meso*-DAP-D-Ala and Gly). The resulting peptidoglycan network and fragments of it exhibit pronounced immunostimulatory and antitumor properties. Therefore, the

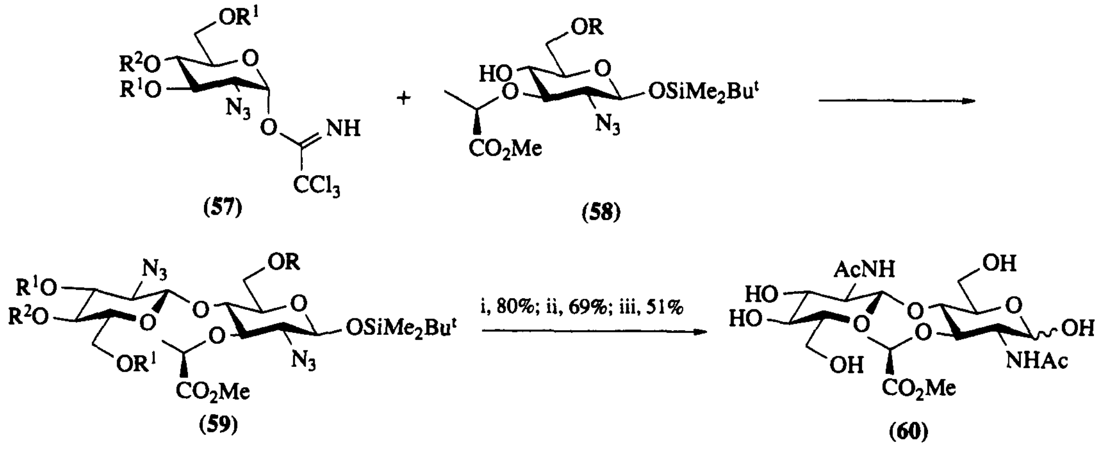

| *R^1* | *R^2* | *R* | *Catalyst* | β (%) | α (%) |
|---|---|---|---|---|---|
| Bn | Bn | $SiMe_2Bu^t$ | $BF_3{\cdot}OEt_2$ | low | low |
| Bn | Bn | $SiMe_2Bu^t$ | $Me_3SiOTf$ | 39(57) | 23(33) |
| Bn | Bn | Bz | $Me_3SiOTf$ | 8 | 16 |
| Bn | Bn | Bn | $BF_3{\cdot}OEt_2$ | 76 | – |
| Bn | Allyl | Bn | $BF_3{\cdot}OEt_2$ | 86 | – |

i, TBAF, $Ac_2O$, THF; ii, $NiCl_2$, $B(OH)_3$, $NaBH_4$, $Ac_2O$; iii, NaOMe, MeOH then Pd/C, MeOH, dioxane

Scheme 19

synthesis of partial structures is of interest. For the synthesis of the GlcNAc β(1 → 4) MurNAc disaccharide (Scheme 19),[117] based on the trichloroacetimidate method, the donor (**57**) and the acceptor (**58**) were treated with an acidic catalyst. However, as indicated in the table in Scheme 19, the result was very much dependent on the 6-*O*-protection of the acceptor (**58**). Bulky groups, *e.g.* *t*-butyldimethylsilyl (TBDMS), or electron-withdrawing groups, *e.g.* benzoyl (Bz), did not improve the known low reactivity of the 4-OH group in glucosamine and derivatives. However, when a benzyl (Bn) group was introduced for 6-*O*-protection, the trichloroacetimidate method afforded in excellent yields and complete β-selectivity the desired disaccharides (**59**). Application of standard deprotection procedures resulted in the GlcNAc β(1 → 4) MurNAc disaccharide (**60**), which had already been synthesized *via* the Koenigs–Knorr procedure.[118]

The glycosphingolipids, being membrane constituents, possess a lipophilic ceramide (*N*-acylated sphingosine) moiety, which is part of the outer plasma membrane bilayer. The hydrophilic oligosaccharide moiety is therefore located on the outer membrane surface (see Section 1.2.1). After several investigations it became obvious that the best method for the glycosylation of these compounds proved to be the trichloroacetimidate method, which afforded better yields in glycosphingolipid syntheses than syntheses applying the Koenigs–Knorr method and variations of it.[119] This ceramide glycosylation procedure (Scheme 20) was recently also successfully applied by Ogawa and coworkers, for instance, to the synthesis of the $G_{M3}$ ganglioside and other tumor-associated antigens.[108] However, the yields are still not satisfactory, even though an improvement could be obtained by a sugar 2-*O*-pivaloyl group.[120] Therefore, based on a new sphingosine synthesis,[121] a versatile azidosphingosine glycosylation method was introduced by us[2,122] which was high yielding even in a recently performed *lactoneo*tetraosyl ceramide

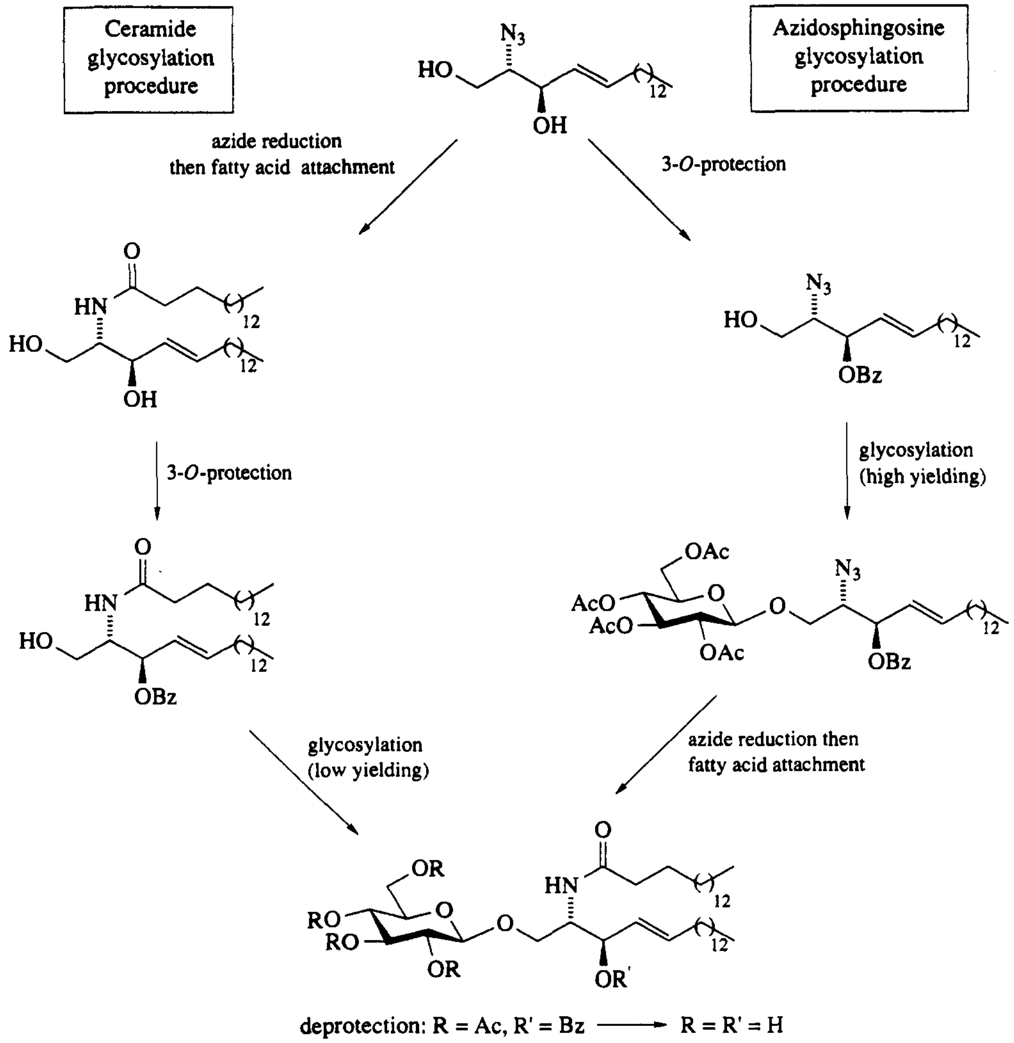

Ceramide glycosylation procedure
Azidosphingosine glycosylation procedure
N3
HO
OH
12
azide reduction then fatty acid attachment
3-O-protection
O
HN
HO
OH
12
12
N3
HO
OBz
12
3-O-protection
glycosylation (high yielding)
O
HN
HO
OBz
12
12
OAc
AcO
AcO
O
OAc
O
N3
OBz
12
glycosylation (low yielding)
azide reduction then fatty acid attachment
OR
RO
RO
O
OR
O
O
HN
OR'
12
12
deprotection: R = Ac, R' = Bz → R = R' = H

**Scheme 20** Glycosphingolipid synthesis

synthesis.[123] This is also exhibited in the synthesis of cerebrosides (**64**) and (**65**) from *Tetragonia tetragonoides* possessing antiulcerogenic activity (Scheme 21).[124] The glucosylation with the *O*-acetylated trichloroacetimidate (**61**) to yield the intermediates (**62**) and (**63**) was β-specific.

### 1.2.4.4 The Trichloroacetimidate Method: Conclusions

The requirements for new glycosylation methods, outlined at the beginning, are practically completely fulfilled by the trichloroacetimidate method. This is indicated by the many examples and can be summarized as follows.

Features of the activation of the anomeric center are: (i) convenient base-catalyzed trichloroacetimidate formation; (ii) controlled access to α- or β-compounds by choice of the base; and (iii) thermal stability of α- and β-trichloroacetimidates up to room temperature (if required, silica gel chromatography can be performed).

Features of the glycosyl transfer are: (i) catalysis by acids (mainly Lewis acids) under very mild conditions; (ii) irreversible reaction; (iii) that other glycosidic bonds are not affected; (iv) usually high chemical yield (reactivity corresponds to the halogenose/silver triflate system); and (v) that stereocontrol of glycoside bond formation is mainly good to excellent: (a) participating protective groups give 1,2-*trans*-glycopyranosides, yielding β-glycosides of Glc, GlcN, Gal, GalN, Mur, Xyl, 2-deoxy-Glc and α-glycosides of Man, Rha; and (b) with nonparticipating protective groups, $BF_3 \cdot OEt_2$ as catalyst favors inversion of anomer configuration, yielding β-glycosides of Glc, GlcN, Gal, GalN, Xyl, Mur and GlcA, while TMSOTF as catalyst favors the thermodynamically more stable anomer, yielding α-glycosides of Glc, GlcN, Gal, GalN, Man, Fuc and Mur.

Besides the oxygen nucleophiles discussed here, nitrogen,[125] carbon,[126] halogen,[1,2] sulfur[127] and phosphorus nucleophiles[128] have also been used successfully as glycosyl acceptors for this reaction, illustrating in terms of stability, reactivity and general applicability the outstanding glycosyl donor properties of *O*-glycosyl trichloroacetimidates, which resemble in various aspects the natural nucleoside diphosphate sugar derivatives. Thus, the base-catalyzed *O*-glycosyl trichloroacetimidate formation has become a very competitive alternative to glycosyl halide and glycosyl sulfide formation.

### 1.2.4.5 Related Methods

The β-glycosyl imidates prepared by Sinay and coworkers[129] from α-glycosyl halides and *N*-substituted amides (particularly *N*-methylacetamide) using 3 equiv. of silver oxide have proven to be relatively unreactive in acid-catalyzed glycosidations.[5] The reactions proceed with inversion of configuration to form α-glycosidic linkages.[130] Neighboring group active protecting groups such as 2-*O*-acetyl lead to orthoester formation and not directly to the glycoside or saccharide.[130] The laborious synthesis of these imidates and their comparatively low reactivity have led to only a few special applications.[1,5]

Reactions with the Vilsmeier–Haack reagent,[1] with 2-fluoro-1-methylpyridinium tosylate[131] and with 2-chloro-3,5-dinitropyridine[131] for anomeric *O*-activation were investigated. The last reagent provided a glycosyl transfer method which is most closely related to the trichloroacetimidate method. However, routes for the specific preparation of the corresponding intermediates with the β-configuration have not been developed, and hydroxy groups that are difficult to glycosidate have not been studied to date. The isourea group, generated by carbodiimide reactions,[132] requires drastic conditions for reactions with glycosyl acceptors, limiting their usefulness.

## 1.2.5 THE ANOMERIC *O*-ALKYLATION METHOD[1,2]

The direct anomeric *O*-alkylation of furanoses and pyranoses with simple alkylating agents, for instance excess methyl iodide and dimethyl sulfate, has long been known.[1] Depending on the reaction conditions, either α- or β-glycosides are formed. A case of trehalose formation can be interpreted similarly.[1] Surprisingly, no studies to use this simple method in more complex glycoside and saccharide syntheses have been reported previously. At first direct anomeric *O*-alkylation (Scheme 1, path d) seemed very unlikely to fulfill all the requirements for a glycoside and saccharide synthesis. When all the remaining hydroxy groups are blocked by protecting groups, the ring–chain tautomerism between the two anomeric forms and the open-chain form (Scheme 17) already give three possible sites for attack of the alkylating agent. Thus the yield, the regioselectivity and the stereoselectivity of the direct anomeric *O*-alkylation

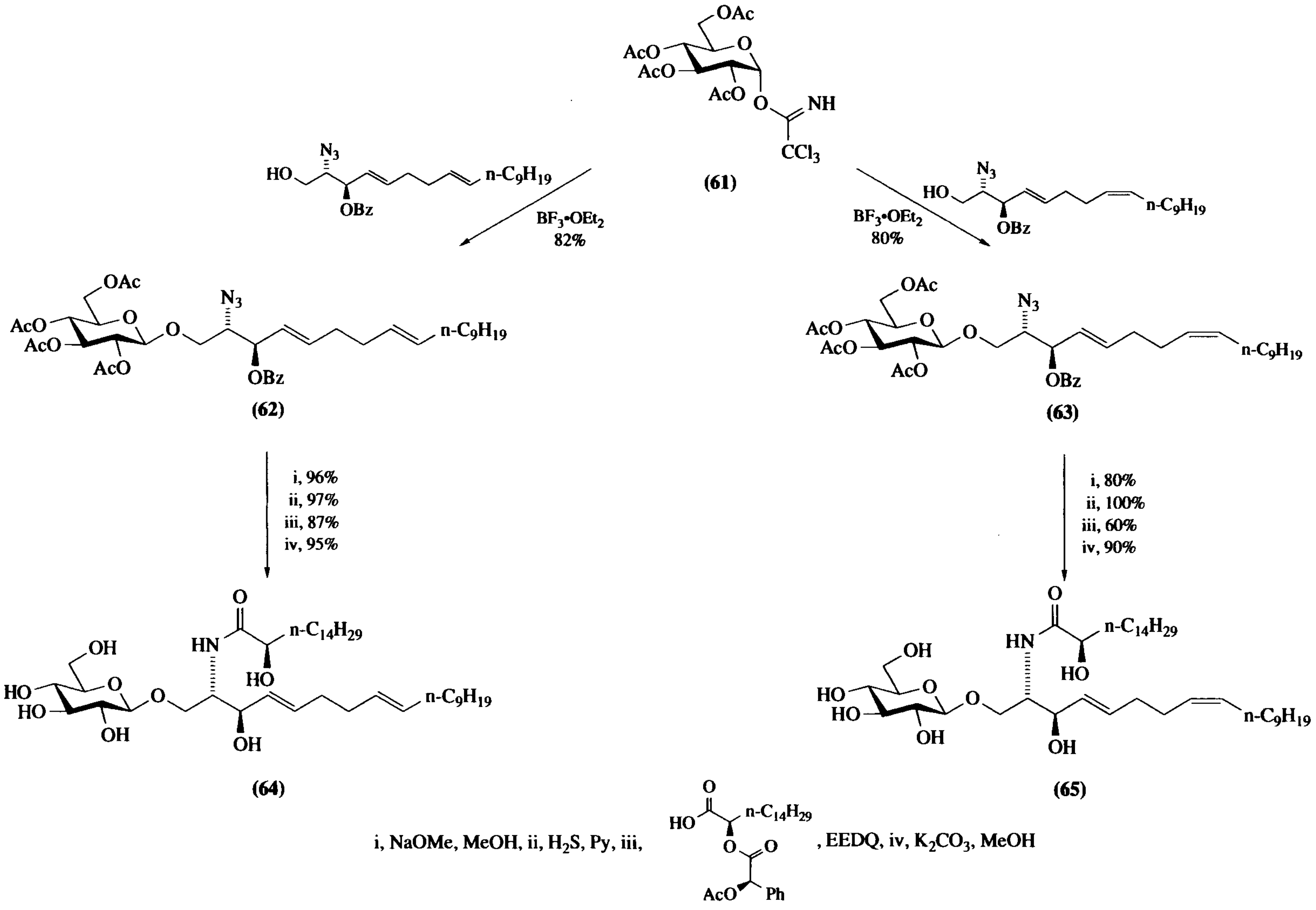
(61)
BF$_3$•OEt$_2$
82%
BF$_3$•OEt$_2$
80%
(62)
(63)
i, 96%
ii, 97%
iii, 87%
iv, 95%
i, 80%
ii, 100%
iii, 60%
iv, 90%
(64)
(65)

i, NaOMe, MeOH, ii, $H_2S$, Py, iii, , EEDQ, iv, $K_2CO_3$, MeOH

**Scheme 21**

are governed by at least the following factors: (i) the stability of the deprotonated species; (ii) the ring–chain tautomeric equilibrium and its dynamics; and (iii) the relative reactivities of the three *O*-deprotonated species. Due to the irreversibility of the *O*-alkylation reaction, a kinetically regio- and stereo-controlled reaction course is required for selective product formation.

The first experiments with iodides revealed that better alkylating agents are required. Excellent reactivity was found for triflates providing, for instance with 2,3-*O*-isopropylidene-D-ribose and derivatives, depending on the reaction conditions, very high yields of α- and β-disaccharides respectively.[133]

Even partial *O*-protection was compatible with this reaction. The stereocontrol was effected by intramolecular metal–ion complexation. This could be substantiated by investigations on D-mannofuranose (**66**; Scheme 22).[134] Structure β-(**66**) shows that the β-oxide has practically ideal crown ether geometry, which probably stabilizes the β-configuration in less solvating media but decreases the reactivity.[134] Good β-selectivity with especially reactive electrophiles is thus to be expected under kinetic control. Accordingly, with the triflates (**67**) the β-D-mannofuranosides β-(**68**) were obtained almost exclusively. Furthermore, the expected influence of the reactivity of the electrophile on the anomeric ratio could be confirmed. If the intramolecular complexation is responsible for the high β-selectivity, more strongly solvating conditions should promote the α-selectivity. This was confirmed by the addition of an equimolar amount of crown ether. The alkylating agents then gave exclusively the corresponding α-D-mannofuranosides α-(**68**). Added sodium iodide had a competitive effect. Thus, for the furanoses studied, the stereocontrol results primarily from steric and chelate effects.

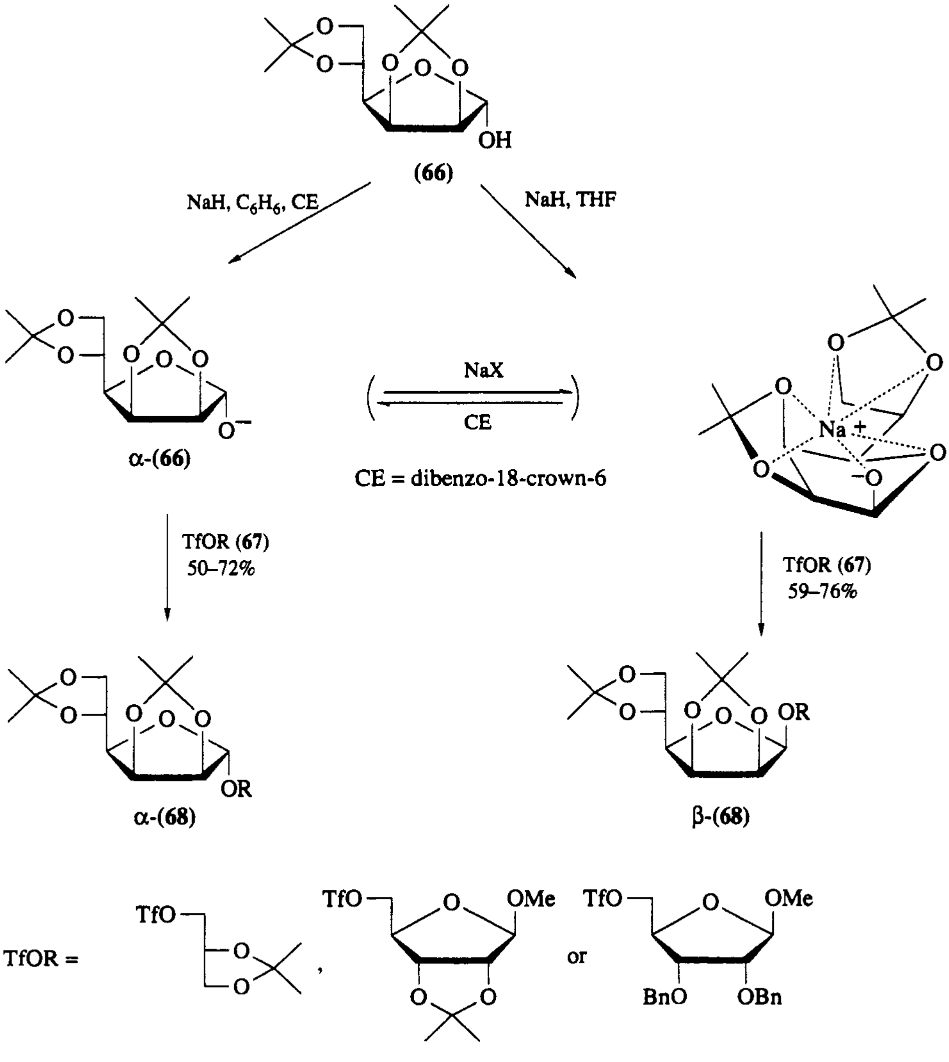

**Scheme 22**

2,3,4,6-Tetra-*O*-benzylglucose (Scheme 16) exists at room temperature in benzene or THF in an α:β anomeric ratio of ≈4:1.[135,136] This ratio is presumably not much changed on 1-*O*-deprotonation. However, when the acylation of the 1-*O*-lithiated species with decanoyl chloride is studied as a function of solvent and temperature, other relations are obtained (Figure 1).[135,138] Higher temperatures, especially in benzene, favor the β-product. Essentially the same result is obtained with the sodium salt and methyl triflate as alkylating agent.[138] The rate of α/β-anomerization and, due to the kinetic anomeric effect, the increased nucleophilicity of the β-oxide are responsible for this result. The addition of crown ether had no significant influence. Therefore, intramolecular complexation probably does not play a major role.[138]

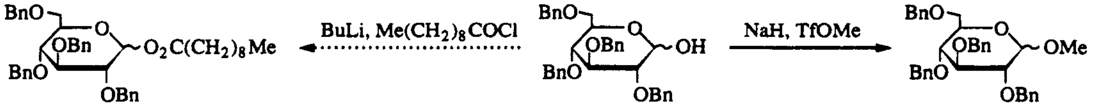

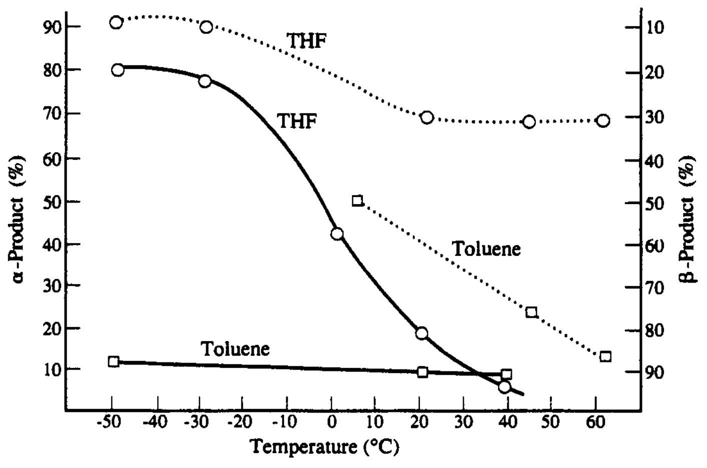

**Figure 1** Reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucose in the presence of base with *n*-decanoyl chloride[135] (········) and with methyl triflate[138] (———) as a function of temperature and solvent

Thus, for instance, 2,3,4,6-tetra-*O*-benzyl-D-glucose, 6-*O*-unprotected 2,3,4-tri-*O*-benzyl-D-glucose and 2,3,4-tri-*O*-benzyl-D-galactose, 2,3,4,6-tetra-*O*-benzyl-D-mannose and 2,3,4-tri-*O*-benzyl-D-xylose were selectively transformed into the corresponding β-D-pyranosides, providing the corresponding glycosides and disaccharides in high yields. With bulky groups in the 6-*O*-position even α-selectivity could be reached in some cases.[1,2,133,134,137–139] Thus, the direct anomeric *O*-alkylation of sugars by primary triflates has become one of the most simple methods for stereocontrolled glycoside and saccharide synthesis. 1,1′-Diacetal formation has also been suggested to follow this reaction course.[1] However, further experiments are required to extend this method to high yield reactions with secondary triflates.[1]

The hydrophilic part of lipopolysaccharides consists of a complex oligosaccharide which is linked *via* KDO (3-deoxy-D-manno-2-octulosonate; α(2 → 6′)-connection) to a β(1 → 6)-linked glucosamine disaccharide.[7] The application of the Koenigs–Knorr method to generate this type of α-glycoside bond with KDO-halogenoses as donors has mainly led to unsatisfactory results due to hydrogen halide elimination and β-glycoside formation.[140] (Similar problems are encountered with neuraminic acid.) Better results were recently reported for fluoride as the leaving group.[141]

Base-catalyzed anomeric *O*-activation of KDO seemed to cause serious problems due to ring–chain tautomerism and due to the presence of the additional carboxylate group. However, for the application of the anomeric *O*-alkylation procedure solutions to these problems could be found.[142] The 4,5:7,8-di-*O*-cyclohexylidene derivative (**69**; Scheme 23) prefers the boat conformation providing, with the carboxamide group and the oxygens of C-5 and C-8, a tetradentate chelate ligand for the complexation of metal ions (Scheme 24). This complexation, generating dianionic species, offers high nucleophilic reactivity and α-diastereoselectivity, providing, with the 6-*O*-triflate of glucose (**70**) and glucosamine derivative (**71**), the desired α(1 → 6)-connected disaccharides (**72**) and (**73**) in good yield; they were transformed into compounds (**74**) and (**75**), respectively.

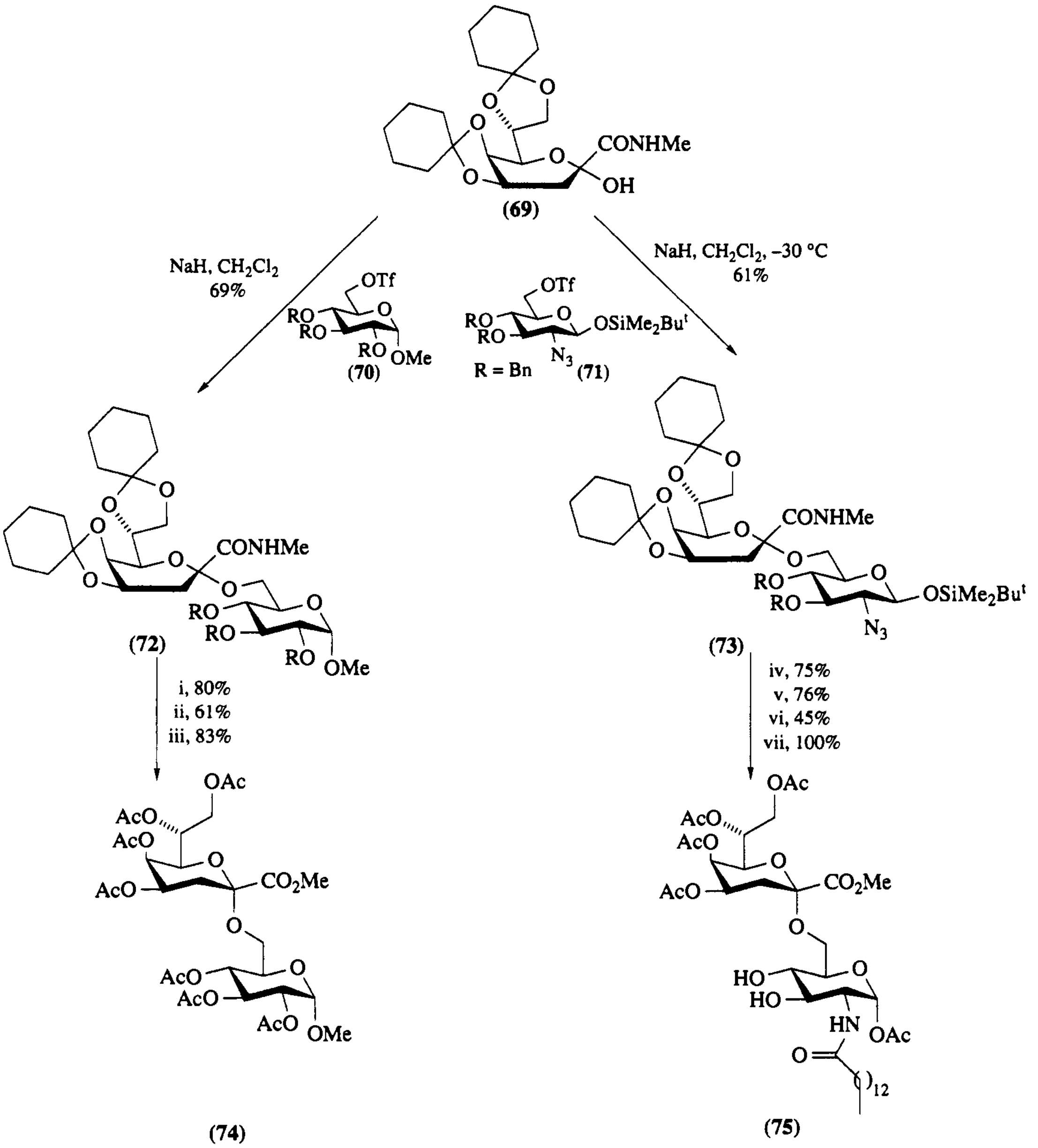

CONHMe
OH
(69)
NaH, $CH_2Cl_2$
69%
OTf
RO
RO
RO
OMe
(70)
OTf
RO
RO
OSiMe$_2$Bu$^t$
N$_3$
R = Bn
(71)
NaH, $CH_2Cl_2$, -30 °C
61%
CONHMe
(72)
i, 80%
ii, 61%
iii, 83%
(73)
iv, 75%
v, 76%
vi, 45%
vii, 100%
OAc
AcO
CO$_2$Me
OMe
HO
HN
OAc
)$_{12}$
(74)
(75)

i, Pd/C, $H_2$ then $Ac_2O$, Py; ii, $CF_3CO_2H$ then $Ac_2O$, Py; iii, $NaNO_2$,, HOAc, $Ac_2O$ then Δ; iv, $NaNO_2$ , HOAc, $Ac_2O$ then Δ; v, $H_2S$, Py then $Me(CH_2)_{12}COCl$; vi, $CF_3CO_2H$ then $Ac_2O$, Py; vii, Pd/C, $H_2$

**Scheme 23**

In conclusion, the direct anomeric *O*-alkylation is an especially simple procedure for glycoside and saccharide synthesis, giving generally high yields and excellent diastereoselectivities, depending on intramolecular complexation, rate of anomerization and varying nucleophilicities of the α- and β-anomeric oxides. The limitation to primary alkylating agents will hopefully be overcome by different reaction conditions.

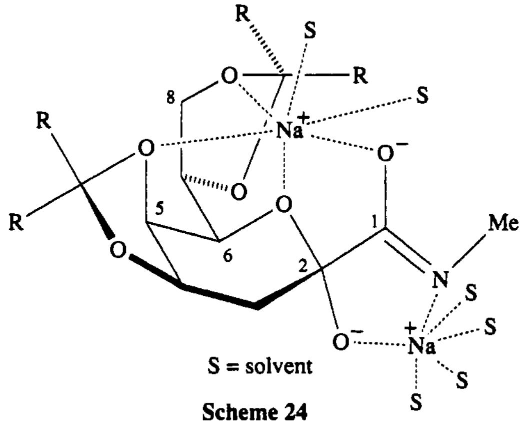

Scheme 24

## 1.2.6 SPECIAL METHODS

For acetal formation, besides the methods discussed thus far, further possibilities exist. For instance, oxidation/reduction methods could be envisaged. Thus, as described,[143] the acceptor can be oxidized to the acid. Anomeric *O*-acylation is a convenient process (see Section 1.2.4), requiring in the final step reduction of the acyloxy group to the alkoxy group, which could be performed in simple cases with borane. Similarly the donor could be oxidized to the lactone stage (and derivatives) and then acceptor addition and reduction would lead to the desired product. However, the efficiency of such methods has to be evaluated on the basis of the existing methodology.

## 1.2.7 GLYCOSIDES AND SACCHARIDES OF 2-DEOXY SUGARS

With 2-deoxy sugars, which lack an electron-withdrawing 2-substituent and also lack neighboring group participation, generally low stability of the glycosyl halides and low α/β-selectivity in glycoside and saccharide synthesis has been encountered. With modifications these statements are also true for KDO and neuraminic acid, which possess an electron-withdrawing caboxylate group at the anomeric position. (A detailed discussion of these two sugars met in glycoconjugates is beyond the scope of this chapter; for anomeric *O*-alkylation of KDO see Section 1.2.5.) Therefore a temporarily anchimerically assisting group was required in the 2-position, which is most readily introduced starting from glycals. This is demonstrated in Scheme 25 for a D-glucal derivative. $Y^+X^-$ addition can take place from the

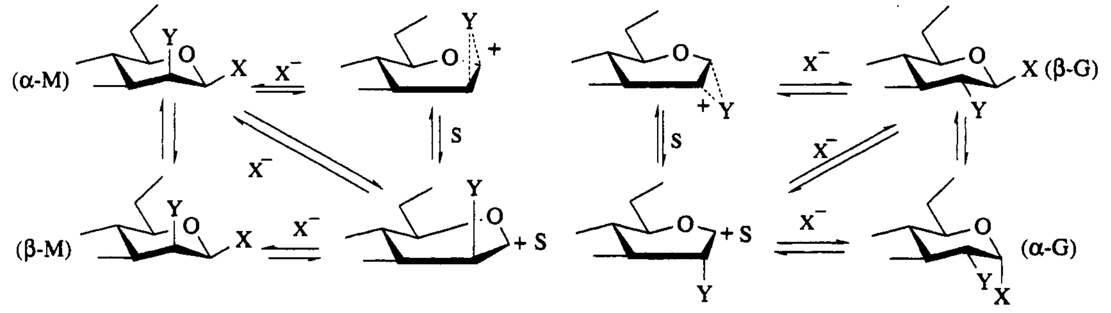

Y = anchimerically assisting, removable group; X = leaving group or HOR' (acceptor); S = solvent

Scheme 25

β-site ($Y^+$) giving α,β-D-*manno* (M) configuration or from the α-site ($Y^+$) giving α,β-D-*gluco* (G) configuration. Neighboring group participation of the 2-substituent, Y, favors α-glycoside formation from the *manno* isomers and β-glycoside formation from the *gluco* isomers.

Several YX additions have been investigated. Reaction with iodine, silver salts and base in the presence of the glycosyl acceptor gave mainly the α-isomer.[144] The same result was obtained for *N*-bromosuccinimide,[145] *N*-iodosuccinimide (NIS)[146] and phenylselenyl chloride[147] in acetonitrile in the presence of the glycosyl acceptor. From these methods the NIS method, introduced by Thiem and coworkers,[146] has gained relatively wide use. Phenylsulfenate ester addition[148] gave varying *manno*:*gluco* addition ratios, resulting, after removal of the temporary phenylthio group, in α:β glycoside ratios from 1:1 to 1:4.

The recent addition of benzenesulfenyl chloride[149] to 3,4,6-tri-*O*-benzyl-D-glucal (**76**) resulted in practically complete *gluco* formation, providing easy access to the corresponding α-trichloroacetimidate (**77**; Scheme 26),[149] which turned out to be an exceptionally reactive glycosyl donor, even though the com-

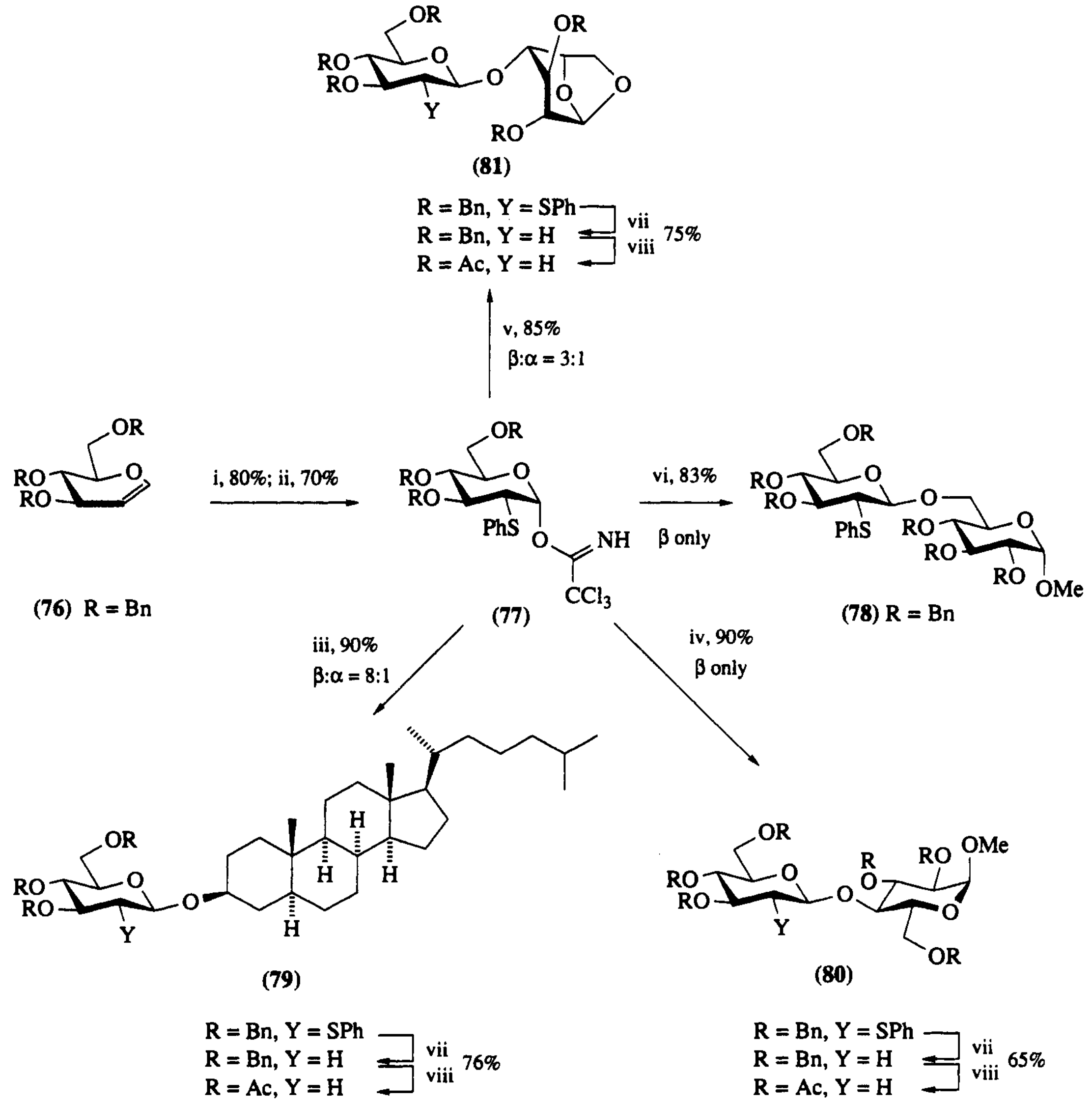
(81)
R = Bn, Y = SPh
R = Bn, Y = H
R = Ac, Y = H
vii
viii
75%
v, 85%
β:α = 3:1
(76) R = Bn
i, 80%; ii, 70%
(77)
PhS
NH
CCl3
vi, 83%
β only
(78) R = Bn
OMe
iii, 90%
β:α = 8:1
iv, 90%
β only
(79)
R = Bn, Y = SPh
R = Bn, Y = H
R = Ac, Y = H
vii
viii
76%
(80)
R = Bn, Y = SPh
R = Bn, Y = H
R = Ac, Y = H
vii
viii
65%

i, PhSCl, THF then $Na_2CO_3$, $H_2O$/THF, Δ, 2 h; ii, $CCl_3CN$, NaH; iii, HOR′, $BF_3{\bullet}OEt_2$, r.t.; iv, HOR′, $BF_3{\bullet}OEt_2$, 0 °C; v, HOR′, $BF_3{\bullet}OEt_2$, −95 °C; vi, HOR′, $BF_3{\bullet}OEt_2$, −40 °C; vii, Raney Ni, THF; viii, Pd/C, $H_2$, EtOAc then Py, $Ac_2O$

**Scheme 26**

pound is relatively stable. With various glycosyl acceptors the desired 2-deoxy-β-D-glucopyranosides (78–81) were obtained in high yields and with good β-selectivities at temperatures as low as –95 °C. Previous methods for 2-deoxy-β-glucopyranoside synthesis required the independent generation of 2-bromo-2-deoxy- or 2-deoxy-2-phenylthioglucopyranosyl halides.[150]

## ACKNOWLEDGEMENT

It is a great pleasure to acknowledge the contributions of my very capable collaborators, who developed some of the methods for glycoside synthesis described in this chapter. They are individually mentioned in the references. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Bundesministerium für Forschung und Technologie.

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# 1.3

# Synthesis of Amines and Ammonium Salts

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## 1.3.1 INTRODUCTION

This chapter covers only the reactions of nitrogen nucleophiles with substrates having appropriate leaving groups and with epoxides and aziridines.[1] The reactions of electrophiles with the anion on the carbon atom adjacent to the nitrogen atom, have recently attracted attention in connection with asymmetric synthesis of chiral amines.[2a–2c] To keep this chapter to a reasonable length, however, this subject is not described. For the same reason, rearrangement reactions leading to amines and their derivatives are not included.[2d,2e]

## 1.3.2 ALKYLATION OF AMINES AND AMINE SYNTHONS

### 1.3.2.1 Alkylation of Amines by Alkyl Halides

Alkylation of ammonia and another amine is, in principle, the most straightforward route to an amine. It is well known, however, that the value of this method in the laboratory is sometimes limited because of concomitant polyalkylation (Scheme 1).

For this reason, primary amines are generally prepared *via* azides or by the Gabriel synthesis and related procedures which will be described in Section 1.3.2.3. For the preparation of secondary amines, a

$$NH_3 + RX \longrightarrow RNH_2 + R_2NH + R_3N + R_4N^+X^-$$

**Scheme 1**

suitable excess of the amine component is generally used. Thus, the reaction of bromide (**1**) with an excess of 1,3- or 1,4-diamines (**2a**) and (**2b**) afforded the expected polyamine (**3a**) and (**3b**) (Scheme 2).[3]

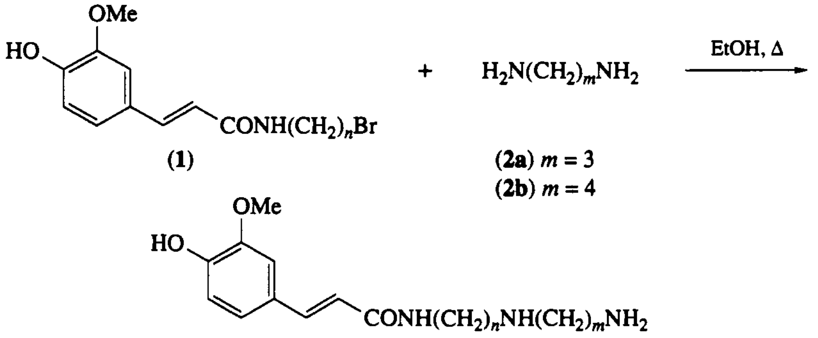

(**1**)

(**2a**) $m = 3$
(**2b**) $m = 4$

(**3a**) $n = 4$, $m = 3$; 68%
(**3b**) $n = 3$, $m = 4$; 49%

**Scheme 2**

Onaka and coworkers have reported highly selective *N*-monoalkylation of aniline and its derivatives over alkali cation exchanged X- and Y-type zeolites. The intrinsic pore structures of X and Y zeolites are assumed to be responsible for the high selectivity. Linde 3A zeolites cannot promote the alkylation of aniline because of their smaller pore structure (Scheme 3).[4a] Aniline derivatives having strong electron-withdrawing substituents, such as *p*-nitroaniline, which is otherwise hardly alkylated even in the presence of KOH, can be successfully alkylated in benzene.[4b,4c] Celite coated with KF is also effective for the alkylation of amines.[5,6]

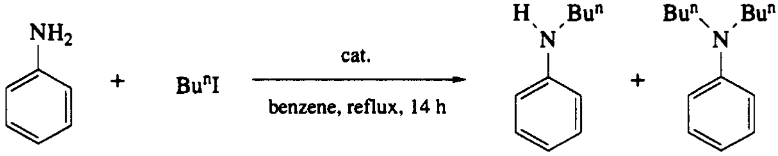

| cat., | | |
|---|---|---|
| KX | (64%) | 74:1 |
| KY | (67%) | 97:1 |
| NaY | (58%) | 120:1 |
| 3A | (0.8%) | – |

**Scheme 3**

The use of phase-transfer catalysts in the presence of inorganic bases accelerates the alkylation of aromatic amines.[7] High pressure conditions have been used in the arylation of amines. Thus, no reaction took place between *p*-nitrochlorobenzene and acyclic aliphatic amines, such as $Bu^nNH_2$, $Bu^iNH_2$, $Bu^sNH_2$, $Bu^tNH_2$ and $Bu_2NH$ at 80 °C under 1 atm, while the corresponding secondary and tertiary aromatic amines were obtained under high pressures of 6–12 kbar (1 kbar = $10^5$ kPa) in THF at 50 °C for 20 h (Scheme 4). Cyclic amines (morpholine, piperidine and pyrrolidine) showed extremely high reactivity to give the corresponding *N*-*p*-nitrophenyl derivatives in quantitative yields under 6.0 kbar.[8]

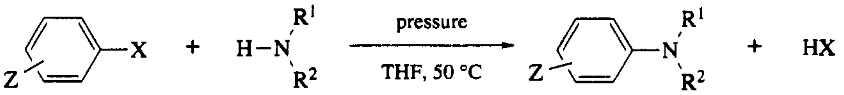

X = Cl, Br, I; Z = *p*-$NO_2$, *o*-$NO_2$, *m*-$NO_2$, *p*-CN, *p*-Ac

**Scheme 4**

The amination of the α-carbon atom of carboxylic acid derivatives has been extensively studied by Effenberger and coworkers.[9] Ethyl (*S*)-α-bromopropionate reacted with (*R*)-1-phenylethylamine to give (2*R*,1′*R*)- and (2*S*,1′*R*)-*N*-(1′-phenylethyl)alanine ethyl ester, *e.g.* (2*R*,1′*R*)-(**4**) and (2*S*,1′*R*)-(**4**). Prolonged reaction time afforded the products in higher yields with decreasing stereospecificity (Scheme 5).

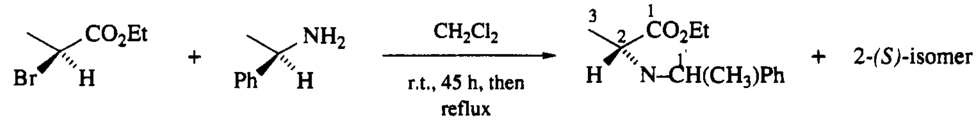

(2*R*,1′*R*)-(**4**) (2*S*,1′*R*)-(**4**)

| *Reflux* (h) (*Yield*, %) | (*2R,1′R*)-(*4*):(*2S,1′R*)-(*4*) |
|---|---|
| 48 (35) | 9:1 |
| 117 (60) | 7:1 |
| 248 (80) | 5:1 |

**Scheme 5**

α-Bromocarboxamide (**5a**) reacted with amines in the presence of NaH (method A) or phase-transfer catalysts (method B) to give α-aminocarboxamides (**6**). Sterically hindered amines, such as *t*-butylamine or diethylamine, can be successfully introduced. Nonionizable amide (**5b**) afforded only the corresponding acrylamide. In view of these results, zwitterions (**7a**) have been assumed as intermediates rather than aziridinones (**7b**; Scheme 6).[10]

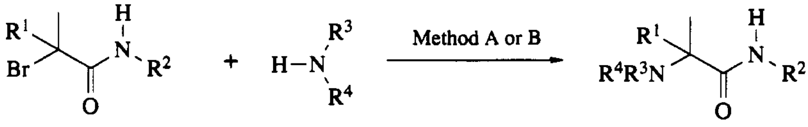

(**5a**) (**6**)

$R^1$ = Me, Et; $R^2$ = Bu$^t$, Bn, Ph

Method A: NaH, THF, 75 min, 66–88%

Method B: NaOH aq. (50%), $CH_2Cl_2$, Bu$^n{}_4$NBr, 4–10 h, 68–80%

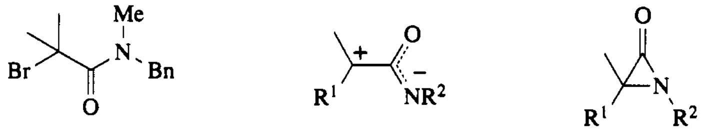

(**5b**) (**7a**) (**7b**)

**Scheme 6**

α-Bromocarboxyhydrazides (**8**) reacted with amines to give the corresponding α-aminocarboxyhydrazides (**9**), which were converted into free acids by alkaline hydrolysis (Scheme 7). Intermediacy of aziridinone (**10**) has been assumed.[11]

Various methods for the synthesis of allylamines have been reported.[12–15] Reaction of allylic bromide (**11**) with amines gave $S_N2$ and $S_N2'$ substitution products in the ratio $S_N2$:$S_N2'$ ranging from *ca.* 1:20 for the reaction with piperidine to 9:1 for the reaction with diisopropylamine (Scheme 8).[12] The product distribution changes with a slight change in the electron-withdrawing capacity of the arenesulfonyl group, as well as the structure of the amines.

Functionalized β-amino-α,β-unsaturated lactones,[13a] esters[13b] and nitriles[13b] can be prepared by nucleophilic vinylic substitution of halogen atoms by amines on the corresponding β-halo-α,β-unsaturated compounds (**12**), (**13**) and (**15**) (Scheme 9). 3-Bromo-2-butenoates (*E*)-(**13**) and (*Z*)-(**13**) reacted with secondary amines to give (*E*)-β-aminopropenoates (*E*)-(**14**) regardless of the initial stereochemistry, while the reaction with primary amines yielded a mixture of (*E*)- and (*Z*)-(**14**), when $R^1$ = H, with the latter predominant. In contrast, the substitution of (*E*)- and (*Z*)-nitriles, (*E*)-(**15**) and (*Z*)-(**15**), with second-

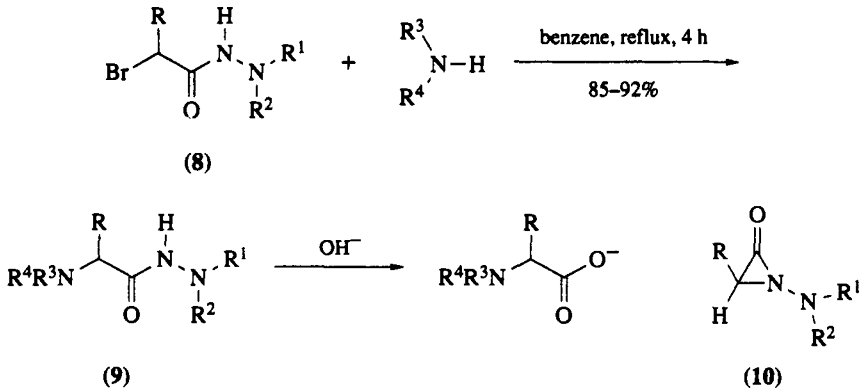
benzene, reflux, 4 h
85–92%
(8)
OH⁻
(9)
(10)

R = 4-$MeC_6H_4$, 4-$ClC_6H_4$, 3,4-$Cl_2C_6H_3$, Et; $R^2$ = $CO_2Me$, COMe, COPh;
$R^3R^4NH$ = $Et_2NH$, $PhNH_2$, $BnNH_2$, $Bu^tNH_2$

Scheme 7

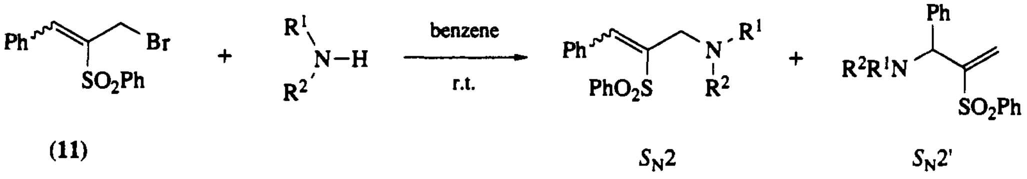
benzene
r.t.
(11)
$S_N2$
$S_N2'$

Scheme 8

ary amines proceeded with retention of original alkene configuration, whereas with primary amines (*E*)-isomers were formed as main products, *e.g.* (*E*):(*Z*) = 85:1 to 5:25. When the substitution was carried out with aziridine on the four substrates, (*E*)-(**13**), (*Z*)-(**13**), (*E*)-(**15**) and (*Z*)-(**15**), the reactions proceeded in every case with retention of configuration.[13b,c]

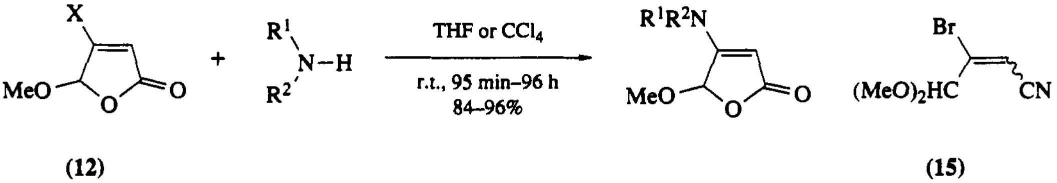
THF or $CCl_4$
r.t., 95 min–96 h
84–96%
(12)
(15)

X = Cl, Br; $R^1R^2NH$ = $BnNH_2$, $Et_2NH$, piperidine, pyrazolidine

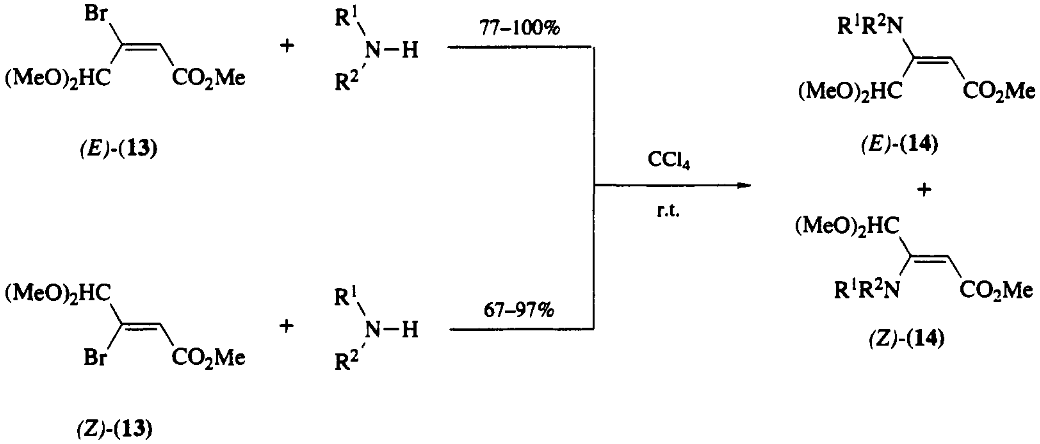
77–100%
67–97%
$CCl_4$
r.t.
(*E*)-(13)
(*Z*)-(13)
(*E*)-(14)
(*Z*)-(14)

$R^1R^2NH$ = $Et_2NH$, $BnNH_2$, pyrazolidine, perhydro-1,4-oxazine

Scheme 9

2-(Alkylthio)- and 2-(alkylsulfinyl)-1-alkenyl ketones (**16a**) and (**16b**) reacted with a variety of amines to give 2-amino-1-alkenyl ketones (**17a**) and (**17b**) (Scheme 10).[14]

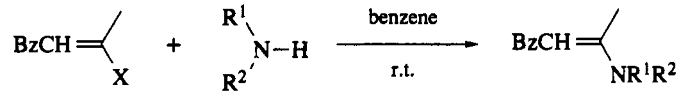
BzCH
X
R1
N–H
R2
benzene
r.t.
BzCH
NR1R2

(**16a**) X = SEt
(**16b**) X = S(O)Et

(**17a**) X = SEt
(**17b**) X = S(O)Et

| *R¹R²NH* | *(17a)* | *(17b)* |
|---|---|---|
| 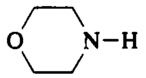 | r.t., 15 h, 85% | r.t., 3 h, 99% |
| (Me)$_2$NH | r.t., 15 h, 65% | r.t., 1 h, 95% |

**Scheme 10**

The Wittig–Horner type reaction of aliphatic ketones with dimethyl diazomethylphosphonate gave the diazoalkenes (**19**), which were trapped by amines thus affording enamines (**18**) of the next higher aldehydes (Scheme 11).[15] For the preparation of allylic amines, the reader is referred to a comprehensive review.[16]

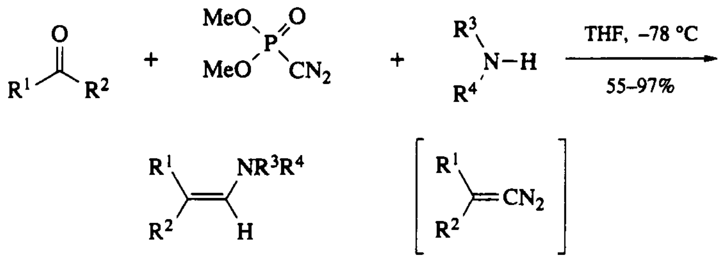
O
R1
R2
MeO
O
P
MeO
CN2
R3
N–H
R4
THF, -78 °C
55–97%
R1
NR3R4
R2
H
R1
CN2
R2

(**18**) (**19**)

**Scheme 11**

Intramolecular displacement of aliphatic amines having a suitable leaving group also affords cyclic amines. In order to avoid further alkylation, the amino function is protected by appropriate groups. The tosyl group has frequently been utilized to this end, where cyclization proceeds through an anionic displacement reaction.

The rate of cyclization varies with ring size. Kinetic studies of cyclization of a series of anions derived from *N*-tosyl-ω-bromoalkylamines, TsNH(CH$_2$)$_n$Br with $n$ = 2–6, in DMSO–H$_2$O (99:1) have revealed that the rates vary markedly with ring size in the order 5 > 3 > 6 > 7 > 4. First-order rate constants ($k_{intra}$) for cyclization have been translated into effective molarities (*EM*) with reference to the intermolecular alkylation ($k_{inter}$) of *N*-tosylbutylamine with butyl bromide (30-fold excess). The results are shown in Scheme 12.[17]

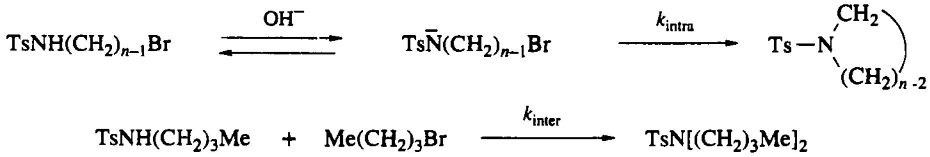
TsNH(CH2)n–1Br
OH−
TsN̄(CH2)n–1Br
kintra
Ts–N
CH2
(CH2)n-2
TsNH(CH2)3Me
+
Me(CH2)3Br
kinter
TsN[(CH2)3Me]2

| $n$ | *EM** (mol L$^{-1}$) | $n$ | *EM** (mol L$^{-1}$) |
|---|---|---|---|
| 3 | 1.92 x 10$^3$ | 6 | 2.82 x 10$^2$ |
| 4 | 0.59 | 7 | 1.36 |
| 5 | 1.38 x 10$^4$ | | |

* Calculated as $k_{intra}$ / $k_{inter}$

**Scheme 12**

In the preparation of cyclic amines, especially large-membered and strained ones, the use of cesium salts of tosylamides exhibits enhanced reactivity (Scheme 13).[18] The solvent also plays an important role. Macrocyclization can also be successfully carried out under high pressure conditions.[19]

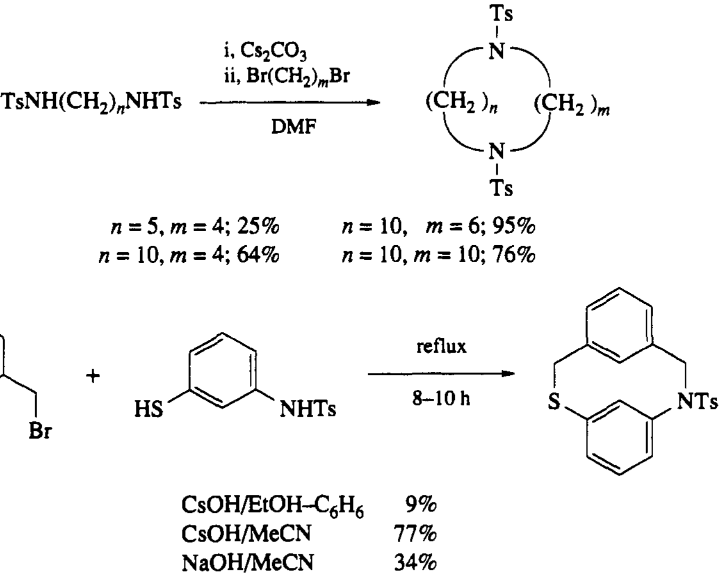
TsNH(CH2)nNHTs
i, Cs2CO3
ii, Br(CH2)mBr
DMF
Ts
N
(CH2)n
(CH2)m
N
Ts
n = 5, m = 4; 25%
n = 10, m = 4; 64%
n = 10, m = 6; 95%
n = 10, m = 10; 76%
Br
Br
+
HS
NHTs
reflux
8–10 h
S
NTs
CsOH/EtOH–C6H6 9%
CsOH/MeCN 77%
NaOH/MeCN 34%

**Scheme 13**

Dealkylation of tertiary amines and quaternary ammonium salts affords lower substituted amines. Reaction systems that can be utilized to cleave a C—N bond involve sodium amalgam (Emde degradation), $LiAlH_4$, $H_2$/Pd, sodium hydrogen telluride, cyanogen bromide (von Braun reaction) and acyl chlorides.[20] 1,1′-Binaphthyl substituted secondary and tertiary amines (**21**) and (**22**) were synthesized by double alkylation of primary or secondary amines with 2,2′-bis(bromomethyl)-1,1′-binaphthyl (**20**), followed by reduction (Scheme 14). Diaminated binaphthyls of type $(R'RNCH_2Ar)_2$ were never formed even when a very large excess of amine is present.[20a]

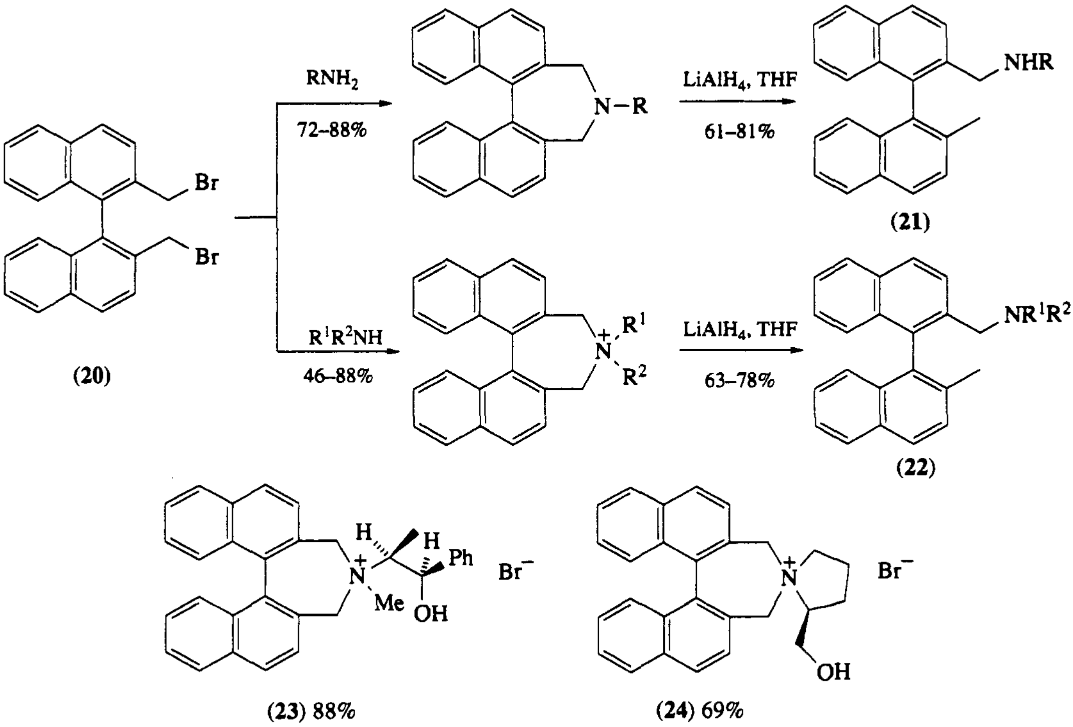
Br
Br
(20)
RNH2
72–88%
N–R
LiAlH4, THF
61–81%
NHR
(21)
R1R2NH
46–88%
+
N
R1
R2
LiAlH4, THF
63–78%
NR1R2
(22)
H
H
Ph
N
+
Me
OH
Br−
(23) 88%
N
+
OH
Br−
(24) 69%

**Scheme 14**

The reaction of amino alcohols, such as ephedrine or prolinol, with (**20**) took place at the nitrogen atom to give quaternary ammonium salts (**23**) and (**24**) (Scheme 14).[20a] The selective *N*-alkylation was again observed in the reaction of amino alcohol (**25**) with *N*-ethylchloroacetamide (2.05 equiv.) in MeCN in the presence of $Na_2CO_3$ under reflux. Subsequent reduction of the resulting diamide gave triamine (**26**; Scheme 15).[21a] Chlorohydrin (**27**) reacted with excess primary amines in the presence of $Na_2CO_3$ or $K_2CO_3$ to give secondary amines (**28**; Scheme 15).[21b] The chemoselectivity observed can be explained by higher nucleophilicity of the amino group than the hydroxy group; $Na_2CO_3$ as the base cannot remove the proton from the pendant hydroxy group.

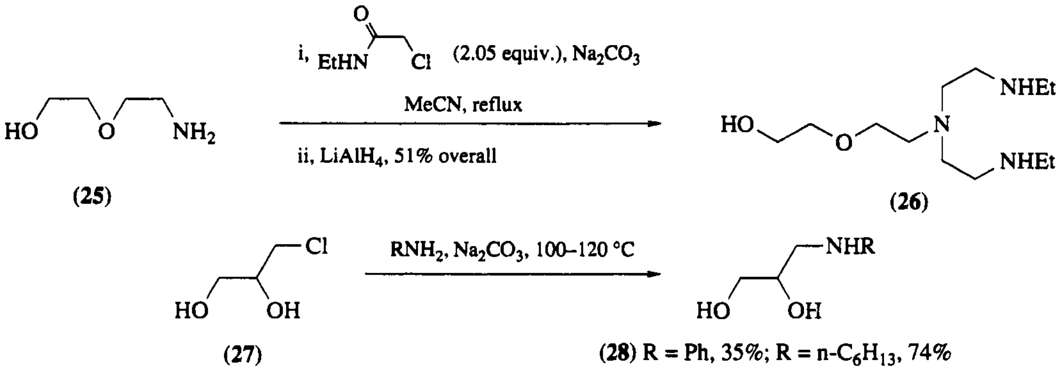
i, EtHN(C=O)CH2Cl (2.05 equiv.), Na2CO3
MeCN, reflux
ii, LiAlH4, 51% overall
(25)
(26)
RNH2, Na2CO3, 100–120 °C
(27)

(**28**) R = Ph, 35%; R = n-$C_6H_{13}$, 74%

**Scheme 15**

When the hydroxy group of amino alcohol was converted into alkoxide, alkylation took place at the oxyanion in preference to the nitrogen atom. Thus, the sodium alkoxide derivative of (**28**) reacted with polyethylene glycol ditosylate or dichloride (**29a–29c**) to give the corresponding aminomethyl crown ethers (**30**).[21b] Chiral amino alcohols (**31**) can be converted into amino ethers (**32**) *via* alkoxides.[22] In contrast, treatment of *N*-tosylamino alcohol (**33**) with NaH, followed by reaction with a fivefold excess of 1,2-dibromoethane afforded (**34**; Scheme 16).[23a]

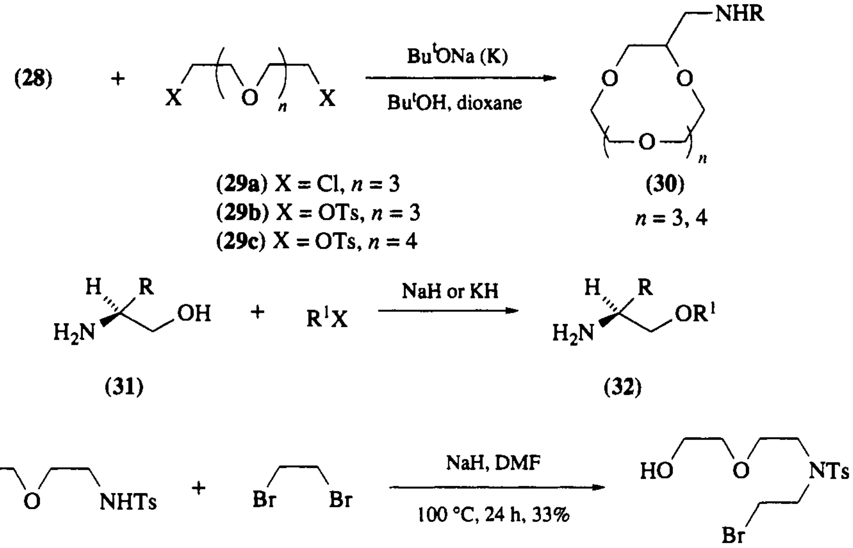
(28)
+
Bu$^t$ONa (K)
Bu$^t$OH, dioxane
(29a) X = Cl, n = 3
(29b) X = OTs, n = 3
(29c) X = OTs, n = 4
(30)
n = 3, 4
+
NaH or KH
(31)
(32)
+
NaH, DMF
100 °C, 24 h, 33%
(33)
fivefold excess
(34)

**Scheme 16**

Chemoselective *N*-ethylation of Boc-amino acids can be accomplished without racemization *via* the corresponding dianions. Thus, *N*-*t*-butoxycarbonylamino acid (**35**) was converted into dianion (**36**) by treatment with 2 equiv. of Bu$^t$Li, followed by the reaction with 1 equiv. of triethyloxonium tetrafluoroborate to give *N*-ethyl derivative (**37**) along with a trace of ethyl ester (**38**). On treatment with 2.2 equiv. of the triethyloxonium salt (**36**; R = Ph) gave (**38**; R = Ph) in 95% yield (Scheme 17).[23b]

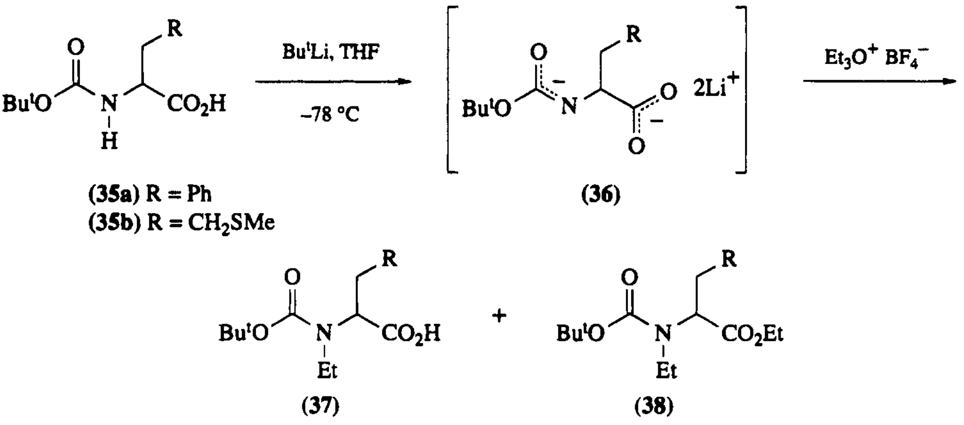

(35a) R = Ph
(35b) R = $CH_2SMe$

(36)

(37)

(38)

Scheme 17

### 1.3.2.2 Alkylation of Amines by Sulfonates and Other Activated Alcohols

Alcohols are readily available in a variety of cyclic and acyclic forms, chain lengths and sense of chirality. Therefore, alcohols have been utilized as versatile starting materials in organic synthesis. In order to prepare amines from alcohols by substitution reactions, the hydroxy group must be converted into a leaving group appropriate to subsequent displacement with nitrogen nucleophiles. Although halogenation is often utilized to this end, introduction of suitable activating groups may be more convenient for the conversion of an alcohol into an alkylating reagent. Of a variety of activated alcohols described in Section 1.2.5, sulfonates are most frequently utilized in the preparation of amines.

A systematic study of the substitution reactions of chiral ethyl propionate derivatives having a leaving group at the α-position (**39a**–**39e**) with amines reveals that nucleofugacity of the leaving group decreases in the order TfO >> Br > MsO > TsO > Cl and that decreasing reactivity causes increasing racemization and elimination as a consequence of the drastic conditions that are required (Scheme 18 and Table 1). As described in the previous section (Scheme 5), the reaction of (**39d**) with (*R*)-1-phenylethylamine accompanied considerable racemization.[9,24]

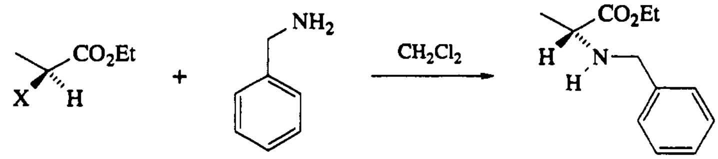

(39) a: X = OTf
b: X = OMs
c: X = OTs
d: X = Br
e: X = Cl

(40)

Scheme 18

Table 1 Reaction of (**39a**)–(**39e**) with Benzylamine under Reflux after 0 °C, 20 min and Room Temperature, 75 min (Scheme 18)[9]

| *(39)* | *Yield (%) of (40) after* | | | | |
|---|---|---|---|---|---|
| | *0.5[a] h* | *20 h* | *100 h* | *210 h* | *250 h* |
| **a** | 100 | | | | |
| **b** | | 10 | 30 | | 50 |
| **c** | | 10 | 20 | | 45 |
| **d** | | 35 | 70 | | |
| **e** | | | | trace | |

[a] At 0 °C.

The reaction of alcohol (**41**) with TFAA, followed by treatment with sodium azide, gave (**42**) in 75% overall yield. The *p*-toluenesulfonate or methanesulfonate of (**41**) has also been demonstrated to react with sodium azide affording (**42**) but in lower yield. Deprotection and subsequent reduction with hydrogen sulfide gave amine (**43**; Scheme 19).[25]

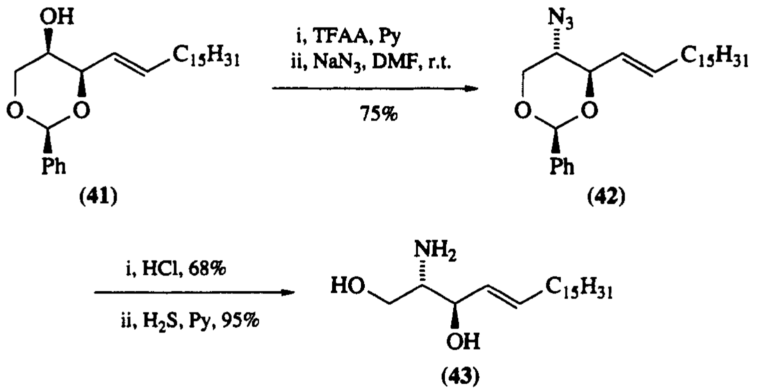
OH
$C_{15}H_{31}$
O
O
Ph
(41)
i, TFAA, Py
ii, $NaN_3$, DMF, r.t.
75%
$N_3$
$C_{15}H_{31}$
O
O
Ph
(42)
i, HCl, 68%
ii, $H_2S$, Py, 95%
$NH_2$
HO
$C_{15}H_{31}$
OH
(43)

**Scheme 19**

The displacement of sulfonates with amines or azide ion generally proceeds with inversion of the configuration at the secondary methanol center. As an alkylating reagent, sulfonates are, in general, superior to the corresponding halides. For instance, the alkylation of *p*-toluidine with 2-*t*-butyl-1,3-bis(tosyloxy)propane (**44a**) afforded azetidine (**45**) in 35% yield, while dichloride (**44b**) afforded a lower yield of (**45**) due mainly to competitive elimination (Scheme 20).[26] Dibromides (**46**) and (**47**) reacted with *p*-toluidine giving the corresponding azetidine in 75% and 14% yields, respectively. The reactions shown in Schemes 14 and 20 suggest that the yields of cyclic amines formed by the reaction of bifunctional alkylating reagents with amines are influenced not only by leaving group but also by substitution patterns of the substrates.

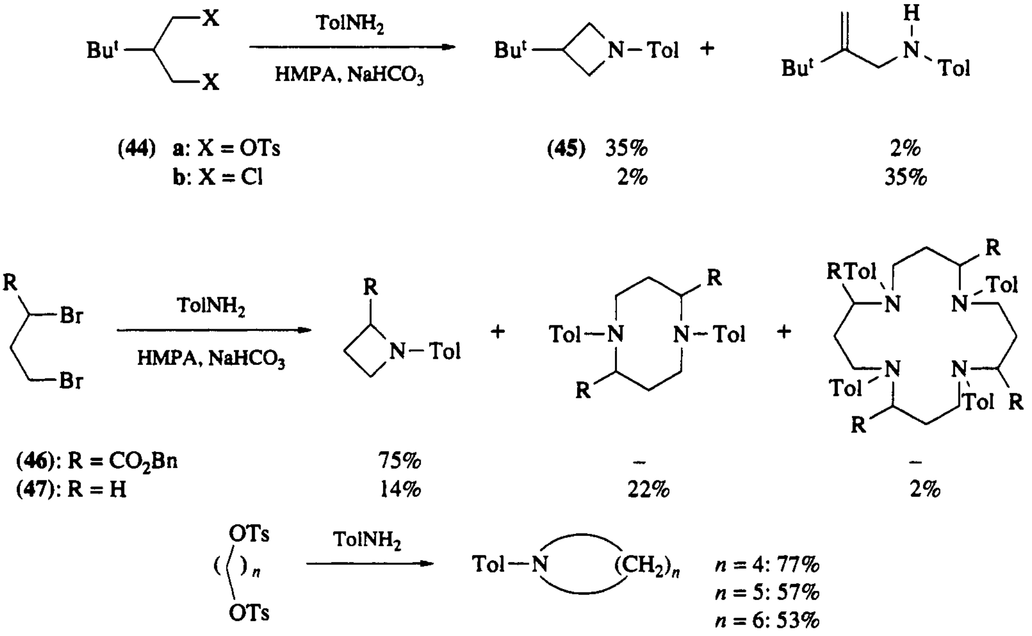
$Bu^t$
X
X
$TolNH_2$
HMPA, $NaHCO_3$
$Bu^t$
N–Tol
+
H
N
Tol
$Bu^t$
(44) a: X = OTs
b: X = Cl
(45) 35%
2%
2%
35%
R
Br
Br
$TolNH_2$
HMPA, $NaHCO_3$
R
N–Tol
+
R
Tol–N
N–Tol
R
+
R
RTol
N
Tol
N
N
Tol
N
Tol
R
R
(46): R = $CO_2Bn$
(47): R = H
75%
14%
–
22%
–
2%
OTs
$n$
OTs
$TolNH_2$
Tol–N
$(CH_2)_n$
$n$ = 4: 77%
$n$ = 5: 57%
$n$ = 6: 53%

**Scheme 20**

Hydrogenolysis of bromo azide (**48a**) gave bromoamine (**49a**). Cyclization of (**49a**), followed by protection, afforded bicycloamine (**50**) in 59% overall yield. By a similar procedure, tosyl azide (**48b**) afforded (**50**) in 64% overall yield (Scheme 21).[27]

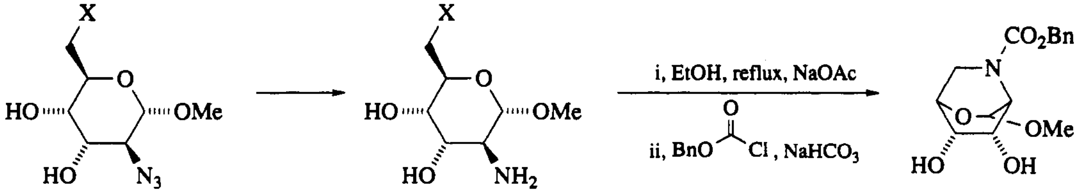

**(48a)** X = Br
**(48b)** X = OTs

**(49a)** X = Br
**(49b)** X = OTs

**(50)** 59% (from **48a**)
64% (from **48b**)

**Scheme 21**

Sulfonates do not necessarily show the same reaction pattern as halides. It has been reported that p-toluenesulfonate (**51a**) and methanesulfonate (**51b**) reacted with azide ion and cyanide ion to give (**52a**) and (**52b**), while iodide (**51c**) gave (**53a**) and (**53b**) (Scheme 22).[28]

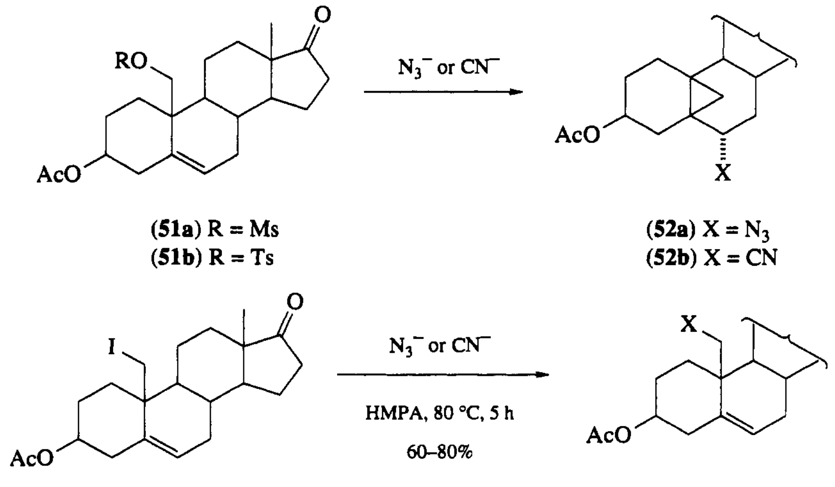

**(51a)** R = Ms
**(51b)** R = Ts

**(52a)** X = $N_3$
**(52b)** X = CN

**(51c)**

**(52a)** X = $N_3$
**(52b)** X = CN

**Scheme 22**

Monosulfonation of primary and secondary diols can generally be accomplished under controlled conditions.[29] The selective tosylation of diol (**54**), followed by reaction with trimethylamine in a sealed tube and ion exchange with Dowex-1(Cl$^-$) resin gave (+)-muscarine chloride (**55**; Scheme 23).[30] Intramolecular alkylation of cyclic amine (**56**) gave quaternary ammonium salt (**57**); subsequent hydrogenolysis of the benzyl group in (**57**) afforded (**58**; Scheme 23).[31]

Activated alcohols other than sulfonates can also be utilized in the alkylation of amines. For example, *O*-methyl-*N*,*N'*-dicyclohexylisourea reacted with 4-dimethylaminobutanoic acid to give ammonium salt (**59**; Scheme 24).[32,33] *O*-Alkylisourea can also be used in the alkylation of imides.[34a]

2-Oxazolines (**60**) reacted with secondary amines in the presence of a catalyst to give *N*-(2-aminoethyl)carboxamides (**61**), which were hydrolyzed to unsymmetrically substituted diaminoethanes (**62**). Although reaction conditions are drastic, the yields of products are high (Scheme 24).[34b]

Alkoxyphosphonium salts can also be utilized in the alkylation of amines,[35] where methods of generation of the phosphonium salts are crucial. The reaction of aminophosphonium reagent (**63**) with alkoxides in the presence of amines to be alkylated (80 °C, 1 h in DMF for secondary amines and in benzene for primary amines) afforded the corresponding higher substituted amines in good to excellent yield. Phosphonium amide (**64**) has been proposed as a key intermediate (Scheme 25).[36] Various amines and azides have been prepared by the use of alkoxy[tris(dimethylamino)]phosphonium salts (**65**).[35a]

Reagents formed by combining $Ph_3P$ with $CCl_4$ and with diethyl azodicarboxylate (DEAD) promote cyclization of amino alcohols to cyclic amines (Scheme 26).[37,38] Various 2-amino alcohols reacted with diethoxytriphenylphosphorane (**66**) to afford the corresponding aziridines in 85–90% yields. The reaction proceeds with retention of the configuration at the amino carbon (C-2) (Scheme 26).[39] In view of

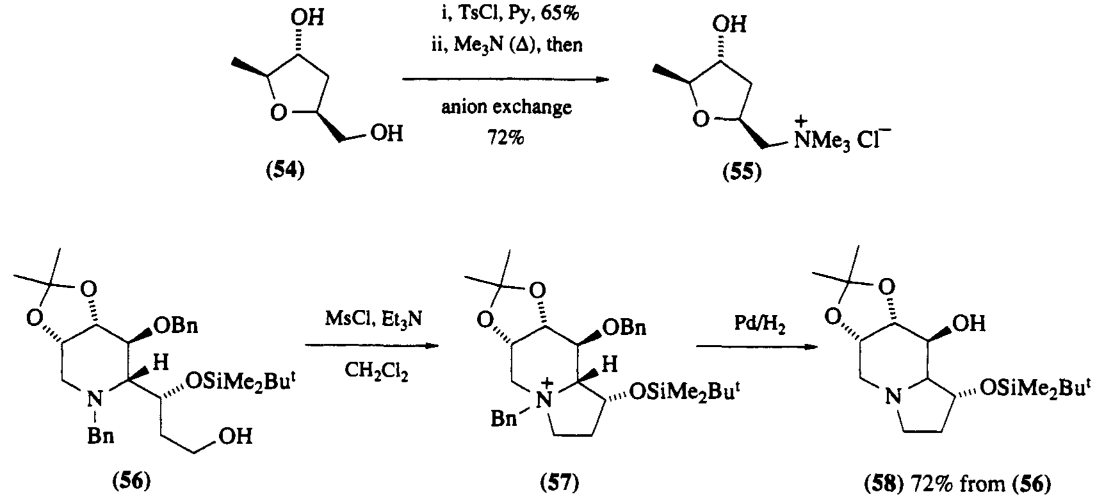

i, TsCl, Py, 65%
ii, $Me_3N$ (Δ), then
anion exchange
72%
(54)
(55)
$\overset{+}{N}Me_3$ $Cl^-$
MsCl, $Et_3N$
$CH_2Cl_2$
Pd/$H_2$
OBn
$OSiMe_2Bu^t$
Bn
(56)
(57)
(58) 72% from (56)

Scheme 23

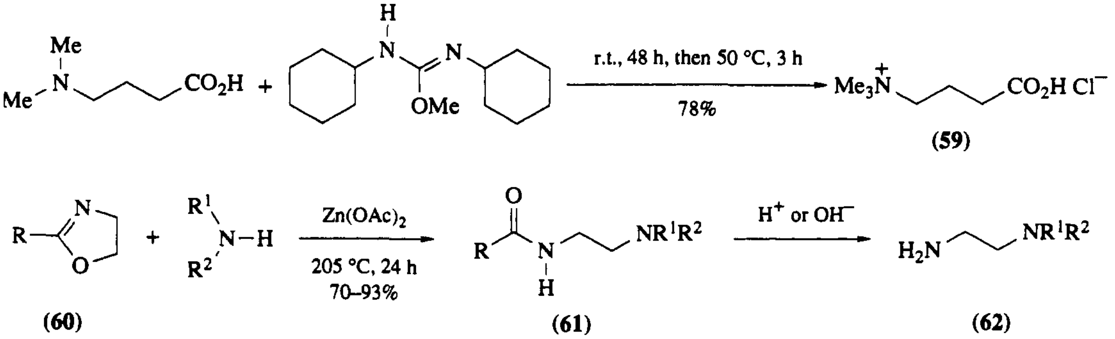

r.t., 48 h, then 50 °C, 3 h
78%
$Me_3\overset{+}{N}$ $CO_2H$ $Cl^-$
(59)
$Zn(OAc)_2$
205 °C, 24 h
70–93%
$H^+$ or $OH^-$
$NR^1R^2$
$H_2N$
(60)
(61)
(62)

R = Et, $C_{11}H_{23}$, $Bu^t$, Ph; $R^1R^2NH$ = $Et_2NH$, $Bu_2NH$, morpholine, piperidine

Scheme 24

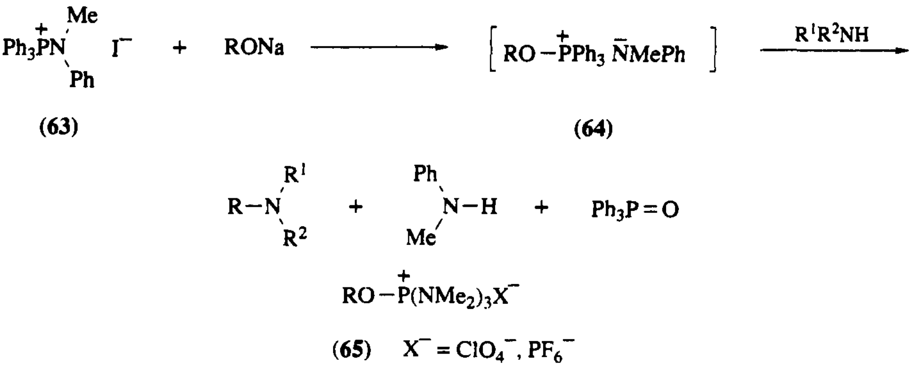

$Ph_3\overset{+}{P}N(Me)Ph$ $I^-$
RONa
$[RO-\overset{+}{P}Ph_3\ \overset{-}{N}MePh]$
$R^1R^2NH$
(63)
(64)
$Ph_3P=O$
$RO-\overset{+}{P}(NMe_2)_3X^-$
(65) $X^- = ClO_4^-$, $PF_6^-$

Scheme 25

the availability of the starting materials and the stereochemical outcome of the reaction, the procedure may be one of the most useful methods for the preparation of chiral aziridines.

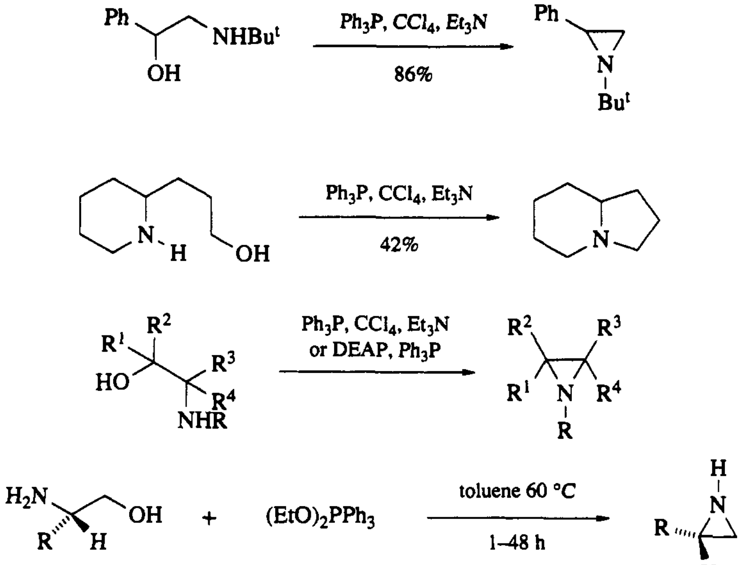

**(66)**

R = Bn, 85%; R = $Me_2CHCH_2$, 90%; R = $Me_2CH$, 90%

**Scheme 26**

## 1.3.2.3 Manipulation of Amino Group Equivalents

### *1.3.2.3.1 Alkylation of azide ion*

Azide anion, which is more nucleophilic than amines, reacts with alkyl halides and activated alcohols giving the corresponding alkyl azides. Phase-transfer conditions can also be utilized.[40] For details, readers are referred to a comprehensive review.[41] Alkyl azides thus formed can be readily transformed into primary amines by a variety of reagents or reaction systems which involve catalytic hydrogenation,[40–42] $LiAlH_4$,[43] $NaBH_4$ under phase-transfer conditions,[44a] $NaBH_4/THF/MeOH$,[44b] $Ph_3P$ or $(RO)_3P/H_2O$,[45] $H_2S/Py$,[46] $Pd–C/HCO_2NH_4/MeOH$,[47] NaTeH,[48] nickel boride[49] and $SnCl_2/MeOH$.[50]

The reduction system must be chosen by taking into account the substitution pattern of substrates. For example, azide (**67**) was converted into the amine (**68**) by treatment with $SnCl_2$ in MeOH (64% yield), whereas catalytic hydrogenation or $LiAlH_4$ reduction could not be used due to loss of the 5-bromo group.[51] Azide (**69**) was converted into piperidine (**70**) by the reaction with $Ph_3P$ in $CHCl_3/H_2O$ in 61% yield (Scheme 27).[52] The reaction of azides with $PPh_3$ gives iminophosphoranes (Staudinger reaction), hydrolysis of which affords primary amines. The procedure has an advantage because the initially formed iminophosphoranes can also be utilized as key intermediates for various nitrogen compounds, such as secondary amines, aziridines, amides, imines, nitro compounds and aminophosphonium salts.[53] Nickel boride generated *in situ* from $NaBH_4$ and nickel chloride does not reduce a ketone, ester, epoxide or a double bond.[49] Sodium hydrogen telluride is inert to unconjugated carbon–carbon double and triple bonds, unconjugated carbonyl, carboxyl, amide, ester, cyano and sulfone groups.[48]

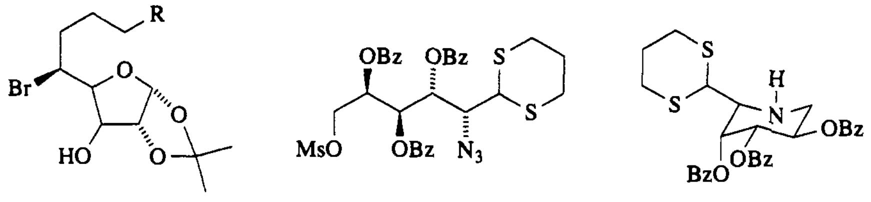

**(67)** R = $N_3$
**(68)** R = $NH_2$

**(69)**

**(70)**

**Scheme 27**

Benzyl 2-azido-3-(benzyloxy)propionate was converted into (±)-serine and its derivatives by variation of hydrogenation conditions (Scheme 28).[40]

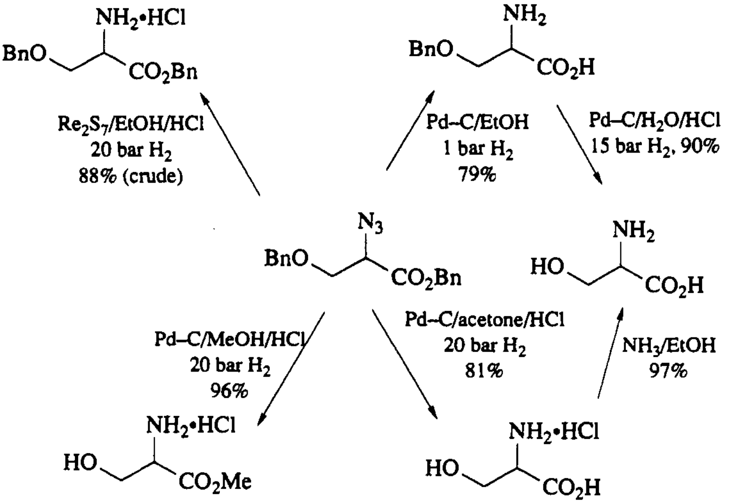
NH$_2$•HCl
BnO
CO$_2$Bn
Re$_2$S$_7$/EtOH/HCl
20 bar H$_2$
88% (crude)
NH$_2$
BnO
CO$_2$H
Pd–C/EtOH
1 bar H$_2$
79%
Pd–C/H$_2$O/HCl
15 bar H$_2$, 90%
N$_3$
BnO
CO$_2$Bn
NH$_2$
HO
CO$_2$H
Pd–C/MeOH/HCl
20 bar H$_2$
96%
Pd–C/acetone/HCl
20 bar H$_2$
81%
NH$_3$/EtOH
97%
NH$_2$•HCl
HO
CO$_2$Me
NH$_2$•HCl
HO
CO$_2$H

**Scheme 28**

One-pot procedures for conversion of an azide to an *N*-protected amine have been reported (Scheme 29).[54]

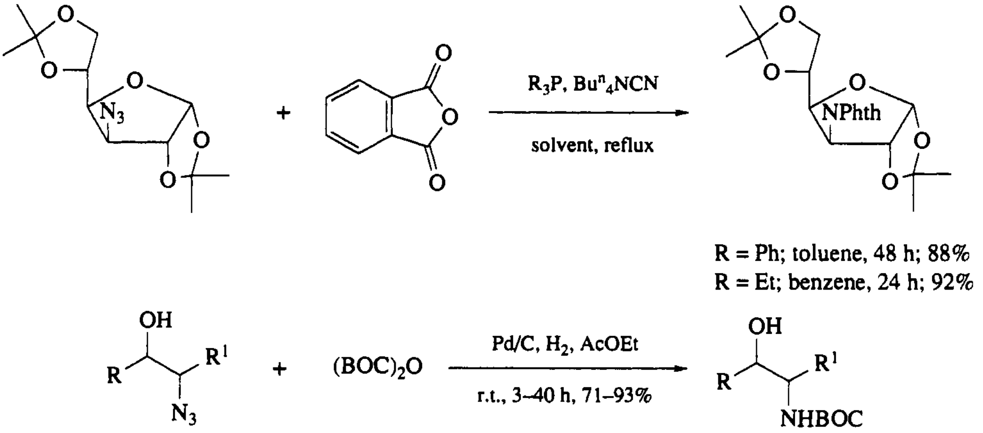
O
O
O
N$_3$
O
O
+
O
O
O
R$_3$P, Bu$^n_4$NCN
solvent, reflux
O
O
O
NPhth
O
O
R = Ph; toluene, 48 h; 88%
R = Et; benzene, 24 h; 92%
OH
R
R$^1$
N$_3$
+
(BOC)$_2$O
Pd/C, H$_2$, AcOEt
r.t., 3–40 h, 71–93%
OH
R
R$^1$
NHBOC

**Scheme 29**

Since the reaction of alkylating reagents with azide ion generally proceeds through an $S_N2$ process, inversion of the reaction center takes place. Thus, for the synthesis of amines with a definite configuration at the carbon atom to which the amino group is attached, the preparation of enantiometrically pure alkylating reagent is a prerequisite.

Chiral α-halo esters (**72a**) and (**72b**) and α-halo imide (**72c**) have been prepared in high diastereomeric purity by the use of Oppolzer's chiral auxiliary (**71a**) and (**71b**) and Evans' chiral auxiliary (**71c**), respectively. The reactions of (**72a**), (**72b**) and (**72c**) with azide ion proceeded with inversion of configuration (Scheme 30).[55,56] In the latter reaction, the use of NaN$_3$ (DMF or DMSO, 0 °C) has been reported to afford 2–5% epimerization.[56] The azides thus prepared were transformed into the corresponding amino acids with high chemical and optical yields.

Reaction of chiral boronates (**73**) with (dihalomethyl)lithium afforded (1*S*)-1-haloboronate (**74**), which was converted into (1*R*)-1-azidoboronate (**75**). Homologation of (**75**) with (dichloromethyl)lithium to 1-chloro-2-azidoboronate, oxidation to azido acid and catalytic hydrogenation afforded (–)-amino acids in 32–63% overall yields with 92–96% *ee* (Scheme 31).[57] The procedure has also been applied to the preparation of a chiral *vic*-amino alcohol.[58]

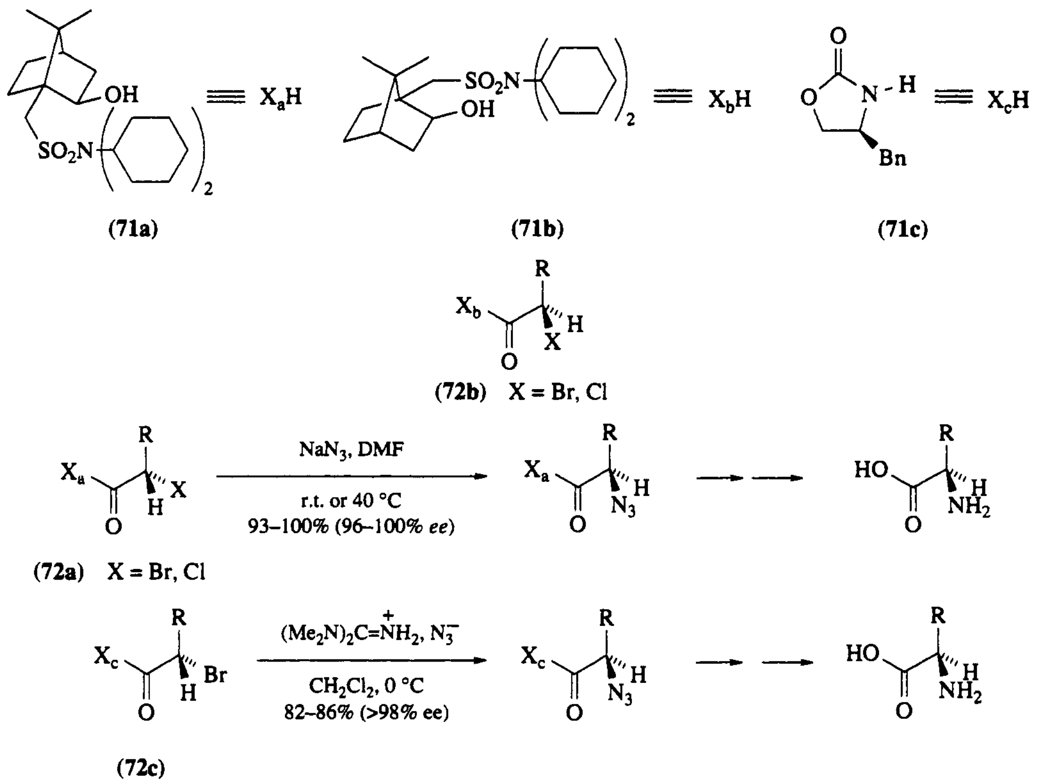
OH
SO2N
2
≡ XaH
(71a)
SO2N
OH
2
≡ XbH
(71b)
O
O
N - H
Bn
≡ XcH
(71c)
R
Xb
H
X
O
(72b) X = Br, Cl
R
Xa
X
H
O
NaN3, DMF
r.t. or 40 °C
93–100% (96–100% ee)
R
Xa
H
N3
O
R
HO
H
NH2
O
(72a) X = Br, Cl
R
Xc
Br
H
O
(Me2N)2C=NH2+, N3−
CH2Cl2, 0 °C
82–86% (>98% ee)
R
Xc
H
N3
O
R
HO
H
NH2
O
(72c)

Scheme 30

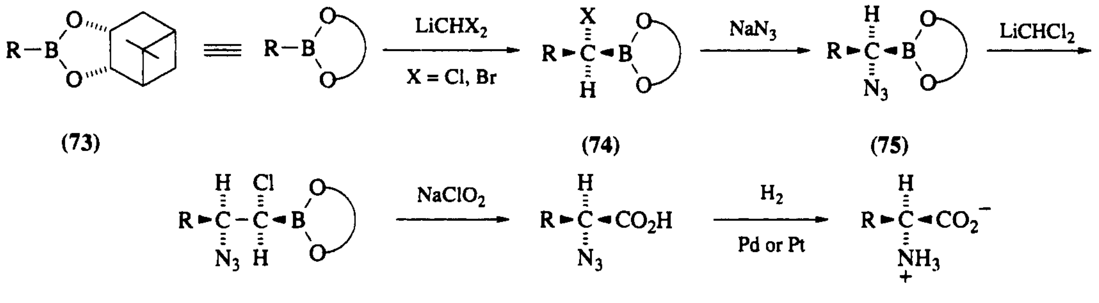
R–B
O
O
≡
R–B
O
O
(73)
LiCHX2
X = Cl, Br
X
R►C◄B
H
(74)
NaN3
H
R►C◄B
N3
(75)
LiCHCl2
H Cl
R►C–C◄B
N3 H
NaClO2
H
R►C◄CO2H
N3
H2
Pd or Pt
H
R►C◄CO2−
NH3
+

Scheme 31

Brown and coworkers have reported chiral organoboron reagent mediated asymmetric synthesis of primary amines of high optical purity (Scheme 32).[59] Stereospecific synthesis of secondary amines and *N*-substituted aziridines by the use of organoboron reagents has also been reported.[60]

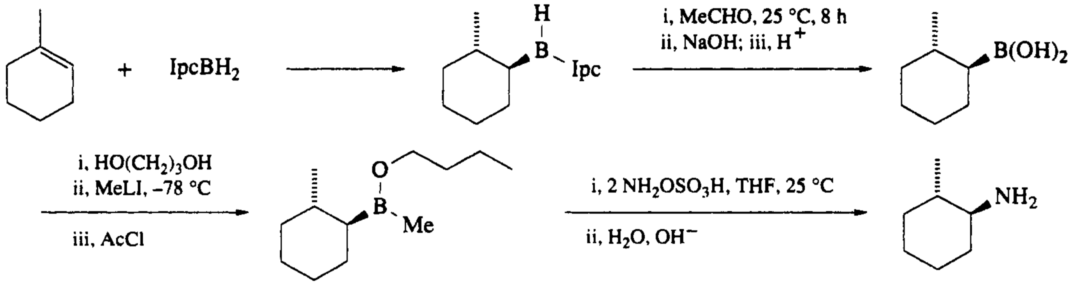
+ IpcBH2
H
B
Ipc
i, MeCHO, 25 °C, 8 h
ii, NaOH; iii, H+
B(OH)2
i, HO(CH2)3OH
ii, MeLI, -78 °C
iii, AcCl
O
B
Me
i, 2 NH2OSO3H, THF, 25 °C
ii, H2O, OH−
NH2
99% ee

Scheme 32

Alcohols were directly converted into azides by the reaction with $HN_3$, DEAD and triphenylphosphine.[61] Combination of this procedure with the Staudinger reaction makes it possible to convert alcohols into amines by a one-pot method (Scheme 33).[62]

$$\underset{\text{1 equiv.}}{ROH + HN_3} + \underset{\text{1.1equiv.}}{Pr^iO_2C-N=N-CO_2Pr^i} \xrightarrow[\text{r.t., 1 h, then 50 °C, 3 h}]{\text{PPh}_3\text{ (2.2 equiv.), THF}}$$

$$\left[R-N=PPh_3\right] \xrightarrow[\text{ii, 1 N HCl, 47–85\%}]{\text{i, H}_2\text{O, 50 °C, 3 h}} R\overset{+}{N}H_3\,Cl^-$$

**Scheme 33**

Regioselective substitution of a hydroxy group of di- and poly-ols by the azido group is an important step for the preparation of amino alcohols. Azidation of polyols *via* an alkoxyphosphonium salt generally takes place at the less-hindered site.[35,61] Nucleophilic opening of cyclic sulfates (**76a**) and (**76b**) with azide ion took place with high regioselectivity to give sulfates (**77a**) and (**77b**), which were converted into azido alcohol (**78a**) and (**78b**) under controlled conditions (Scheme 34).[63]

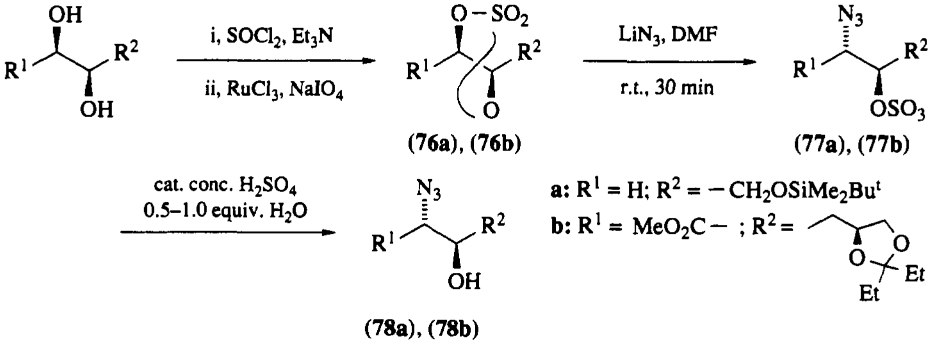

OH
R1
R2
OH
i, SOCl2, Et3N
ii, RuCl3, NaIO4
O–SO2
O
(76a), (76b)
LiN3, DMF
r.t., 30 min
N3
OSO3−
(77a), (77b)
cat. conc. H2SO4
0.5–1.0 equiv. H2O
N3
OH
(78a), (78b)
a: R1 = H; R2 = –CH2OSiMe2But
b: R1 = MeO2C– ; R2 =
O
O
Et
Et

**Scheme 34**

The reaction of tertiary alcohols or tertiary alkyl halides with trimethylsilyl azide in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$ for alcohols and $SnCl_4$ for halides) afforded tertiary alkyl azides (Scheme 35).[45c,64]

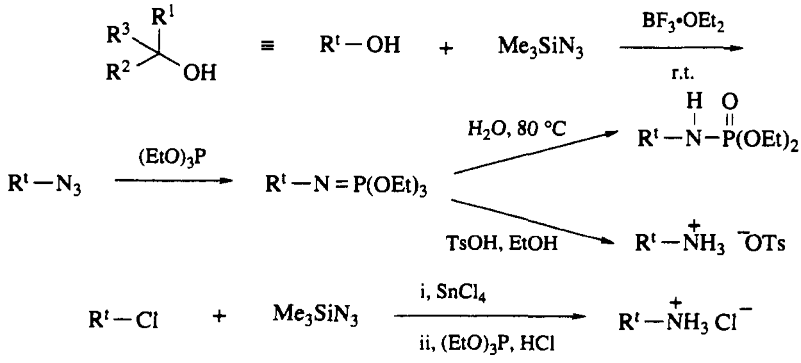

R1
R3
R2
OH
≡ Rt–OH + Me3SiN3
BF3•OEt2
r.t.
Rt–N3
(EtO)3P
Rt–N=P(OEt)3
H2O, 80 °C
Rt–N(H)–P(O)(OEt)2
TsOH, EtOH
Rt–NH3+ −OTs
Rt–Cl + Me3SiN3
i, SnCl4
ii, (EtO)3P, HCl
Rt–NH3+ Cl−

**Scheme 35**

### *1.3.2.3.2 Gabriel synthesis*

The Gabriel synthesis is a classical but still useful procedure for the preparation of primary amines. The method consists of alkylation of phthalimide anion with an appropriate alkylating reagent and subsequent removal of the phthaloyl group to generate primary amines (Scheme 36).[65]

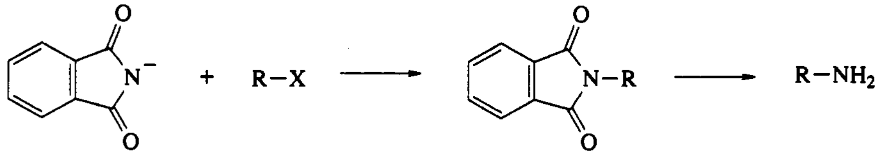

Scheme 36

Alkyl halides and alkyl sulfonates have been generally used as alkylating reagents. An example of the conversion of an alcohol into a primary amine by the Gabriel synthesis is shown in Scheme 37.[66]

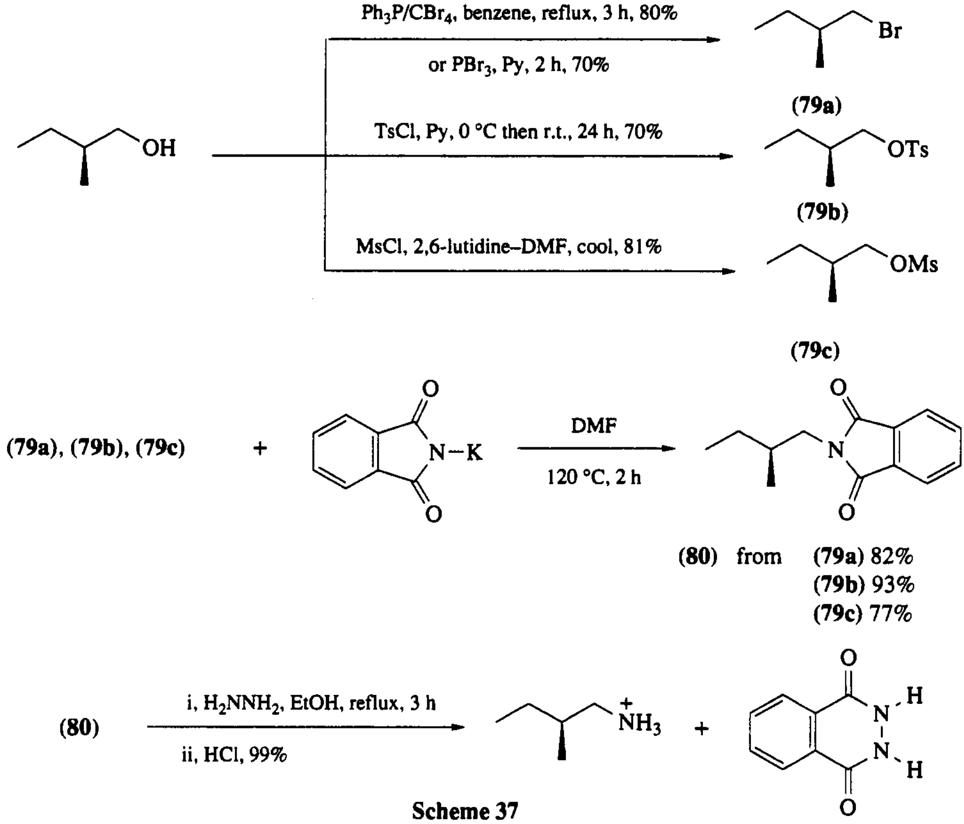

Scheme 37

Alkylation of phthalimide anion can be carried out under solid–liquid phase-transfer conditions, using phosphonium salts[67] or ammonium salts.[68] In the reaction systems using hexadecyltributylphosphonium bromide, alkyl bromides and alkyl methanesulfonate are more reactive than alkyl chlorides. Octyl iodide is less reactive than the corresponding bromide and chloride.[67] (*R*)-2-Octyl methanesulfonate was converted into (*S*)-2-octylamine with 92.5% inversion.[67] Kinetic resolution of racemic ethyl 2-bromopropionate by the use of a chiral quaternary ammonium salt catalyst has been reported.[68] Under liquid–liquid phase-transfer conditions, *N*-alkylation of phthalimide has been reported to give poor results.[68b]

In the presence of [2.2.2]cryptand, the reaction of potassium phthalimide with alkyl halides proceeded smoothly in THF or benzene even at room temperature to give the corresponding *N*-alkylphthalimides in good to excellent yields.[69]

The alkylation of phthalimide can also be accomplished with *O*-alkylisoureas and alkoxyphosphonium salts. Thus, the reaction of *O*-alkyl-*N*,*N*′-cyclohexylisourea with phthalimide afforded *N*-alkylphthalimides in 60–70% yields (DMF, 120 °C, 2–24 h). Starting from (*R*)-2-octylisourea, (*S*)-2-octylamine was obtained in 97.6% *ee*, indicating 98% inversion of the configuration took place.[34a]

The reactions involving alkoxyphosphonium salts are also effective for the *N*-alkylation of phthalimide with virtually complete inversion of the secondary methanol center.[35,61] Thus, the reaction of (*S*)-alcohol (**81**) with phthalimide, DEAD and triphenylphosphine afforded (**82**), which was subjected to a sequence of reactions to yield (2*R*,5*R*)-diamine (**83**) and the (2*R*,5*S*)-isomer in a ratio of 99.4:0.6.[70] The secondary methanol center of alcohol (**84**) was again inverted in the reaction with phthalimide, DEAD and triphenylphosphine giving (**85**).[71] In contrast, alcohol (**86**) afforded *syn*- and *anti*-phthalimide derivatives (**87**) and (**88**) in a ratio of 1:1 under similar conditions (Scheme 38).[72] This result would be explained by assuming intermediacy of a carbonium ion, which is stabilized by an adjacent *p*-methoxyphenyl group.

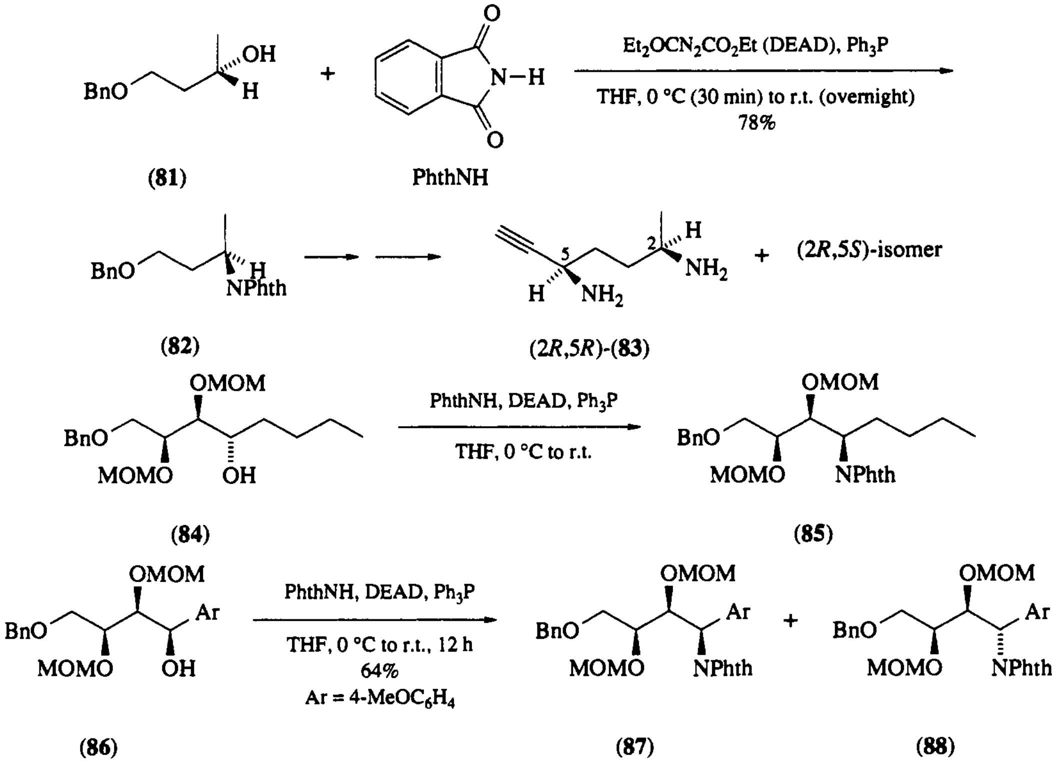
BnO
OH
H
+
N−H
O
O
$Et_2OCN_2CO_2Et$ (DEAD), $Ph_3P$
THF, 0 °C (30 min) to r.t. (overnight)
78%
(81)
PhthNH
BnO
H
NPhth
H
5
2
H
NH2
NH2
+ (2*R*,5*S*)-isomer
(82)
(2*R*,5*R*)-(83)
OMOM
BnO
MOMO
OH
PhthNH, DEAD, $Ph_3P$
THF, 0 °C to r.t.
OMOM
BnO
MOMO
NPhth
(84)
(85)
OMOM
Ar
BnO
MOMO
OH
PhthNH, DEAD, $Ph_3P$
THF, 0 °C to r.t., 12 h
64%
Ar = $4\text{-}MeOC_6H_4$
OMOM
Ar
BnO
MOMO
NPhth
+
OMOM
Ar
BnO
MOMO
NPhth
(86)
(87)
(88)

**Scheme 38**

Alkylthiophosphonium salts (**90**) prepared from thiol (**89**) can also be utilized as an alkylating reagent for phthalimide. The reaction proceeds with inversion of configuration at the reaction site (Scheme 39).[73]

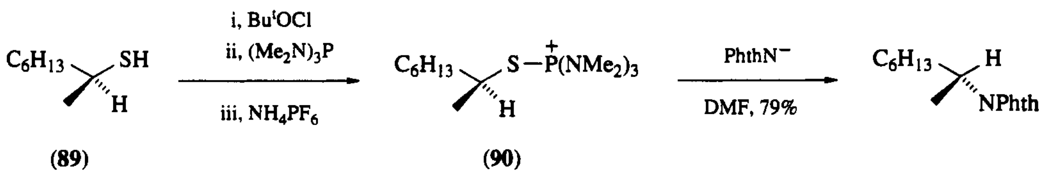
$C_6H_{13}$
SH
H
i, $Bu^tOCl$
ii, $(Me_2N)_3P$
iii, $NH_4PF_6$
$C_6H_{13}$
$S-\overset{+}{P}(NMe_2)_3$
H
$PhthN^-$
DMF, 79%
$C_6H_{13}$
H
NPhth
(89)
(90)

**Scheme 39**

### *1.3.2.3.3 Modified Gabriel synthesis*

Although alkylation of phthalimide can now be performed under mild conditions as described in the preceding section, the final deprotection step still requires somewhat drastic conditions, *e.g.* the use of strong acid or base, or, alternatively, hydrazinolysis, at elevated temperature, due to the inherent stability of the phthaloyl group.[65] This has prompted investigation of a number of alternatives to phthalimide which afford *N*-alkyl derivatives amenable to milder deprotection.

Methyl *t*-butyl iminodicarboxylate (**91**) and di-*t*-butyl iminodicarboxylate (**93**) have been used in a modified Gabriel synthesis.[74–76] Thus, the potassium salt of (**91**) reacted with alkyl halides to give the corresponding *N*-alkylated products (**92**) in 59–95% yields (in DMF or DMSO, 20–60 °C) except for alkylating reagents susceptible to base-catalyzed side reactions. Under basic conditions, (**92**) gave *N*-*t*-butoxycarbonylamines, whereas, with trifluoroacetic acid, *N*-methoxycarbonylamines were obtained (Scheme 40).[74]

The potassium salt of (**93**) reacted with allylic bromides (**94**) to afford protected amines (**95**). Hydrogenolysis of (**95a**), followed by successive treatment with HBr–AcOH and ion exchange resin gave amino alcohol (**96**). Treatment of (**95a**) with HBr–AcOH gave allylamine (**97**; Scheme 40).[76]

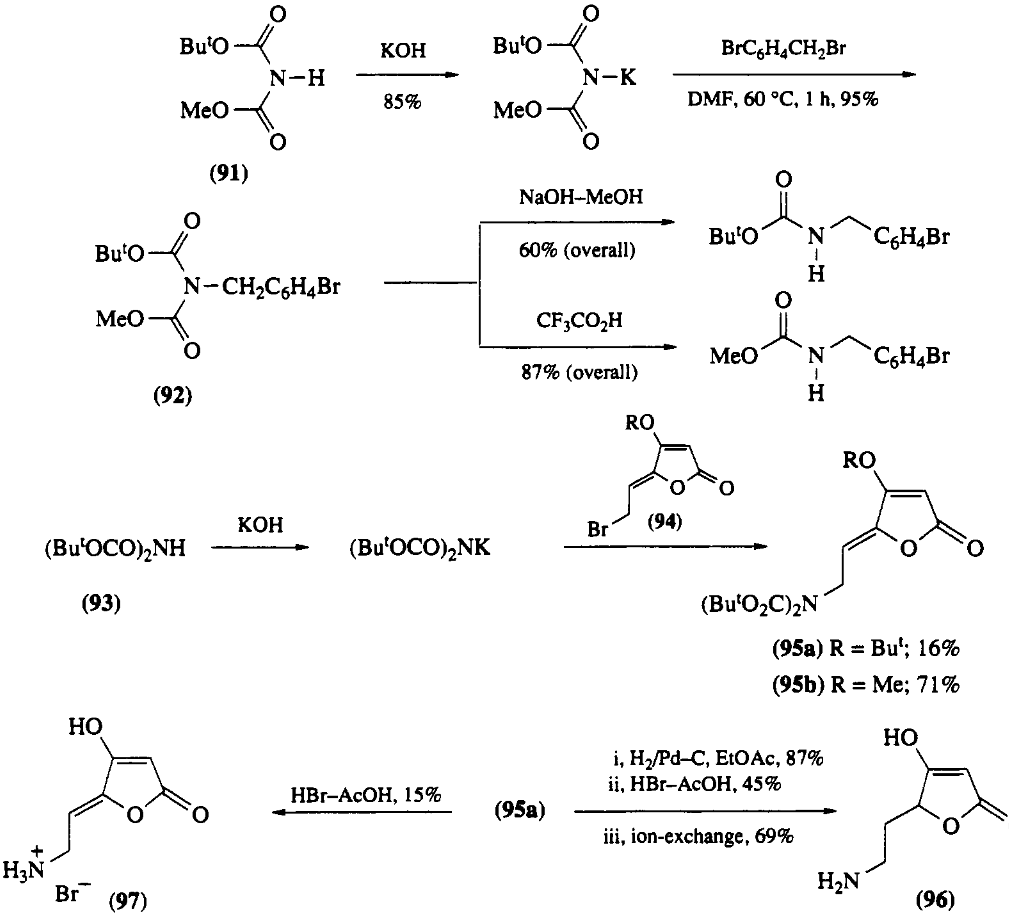
KOH
85%
BrC6H4CH2Br
DMF, 60 °C, 1 h, 95%
(91)
NaOH–MeOH
60% (overall)
CF3CO2H
87% (overall)
(92)
KOH
(93)
(94)
(95a) R = Bu^t; 16%
(95b) R = Me; 71%
HBr–AcOH, 15%
(95a)
i, H2/Pd–C, EtOAc, 87%
ii, HBr–AcOH, 45%
iii, ion-exchange, 69%
(97)
(96)

**Scheme 40**

The sodium salt of diethyl *N*-(*t*-butoxycarbonyl)phosphoramidate (**98**) reacted with alkyl halides in boiling benzene in the presence of tetrabutylammonium bromide to give the corresponding *N*-alkyl derivatives (**99**) in 71–95% yields for primary alkyl halides and 38–58% yields for secondary α-halo esters (in MeCN). The phosphoryl and *t*-butoxycarbonyl groups were removed by treatment overnight with benzene saturated with dry HCl (Scheme 41).[77a]

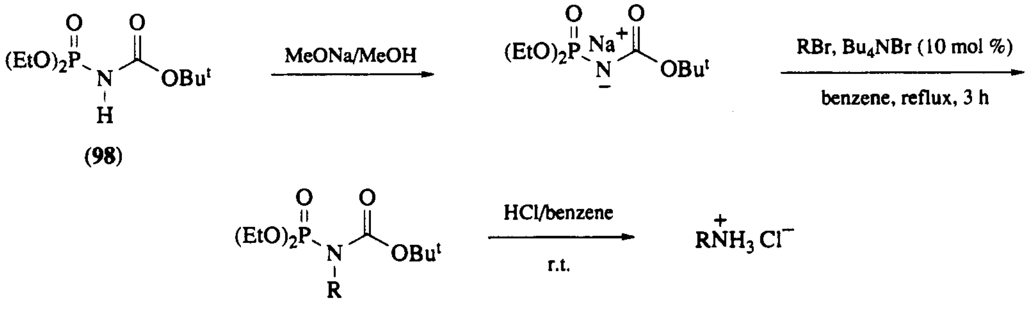
(98)
MeONa/MeOH
RBr, Bu4NBr (10 mol %)
benzene, reflux, 3 h
(99)
HCl/benzene
r.t.
RNH3 Cl−

**Scheme 41**

Alkylation of (**98**) can also be carried out by reaction with alcohols in the presence of DEAD and triphenylphosphine at room temperature. The yields of crude (**99**) were in the range 80–90% for primary alcohols and 70–75% for secondary alcohols with nearly complete inversion of the secondary methanol center.[77b]

Sulfonyl groups can also be utilized to reduce the basicity of amino functions. Inter- and intra-molecular cyclization using bifunctional tosylamides have been widely utilized in the preparation of macrocyclic polyamines (Scheme 13). Trifluoromethanesulfonamide and its derivatives can also be used in the preparation of primary and secondary amines.[78]

In contrast to the anion of diethyl phosphoramidate or trifluoromethanesulfonamide, which cannot be cleanly monoalkylated,[77,78] the anion of trifluoroacetamide (**100**) was monoalkylated by alkyl halides or alkyl methanesulfonate. The resulting *N*-alkylamides (**101**) were converted into primary amines by alkaline hydrolysis or reduction (NaBH4; Scheme 42). Various primary amines were prepared from (**100**) with primary alkyl iodides or methanesulfonate, benzyl and allyl halides, α-bromocarbonyl compounds and 2,4-dinitrochlorobenzene. However, competitive elimination is a serious side reaction for less reactive primary alkyl chlorides and secondary halides or methanesulfonate. The synthesis of secondary amines from (**100**) has also been reported.[79]

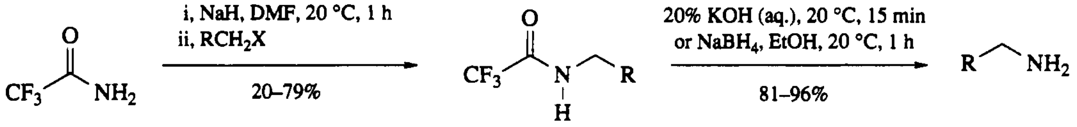

(**100**) (**101**)

**Scheme 42**

### 1.3.2.3.4 *Alkylation of amine synthons having a nitrogen–heteroatom bond*

One of the two hydrogen atoms of phosphoramidates can be temporarily blocked with a trimethylsilyl group. The sodium salt of diethyl *N*-(trimethylsilyl)phosphoramidate (**102**) reacted with alkyl bromides in benzene in the presence of 10 mol % of tetra-*n*-butylammonium bromide to afford, after desilylation, the corresponding *N*-alkyl derivatives (**103**) in 79–95% yields for primary alkyl halides. Secondary alkyl halides gave poor results (Scheme 43). The addition of the quaternary ammonium salt is essential to promote the alkylation reaction.[80] Hexamethyldisilazane and its cyclic analogs can also be utilized in the preparation of amines under moderate conditions (Scheme 43).[81,82]

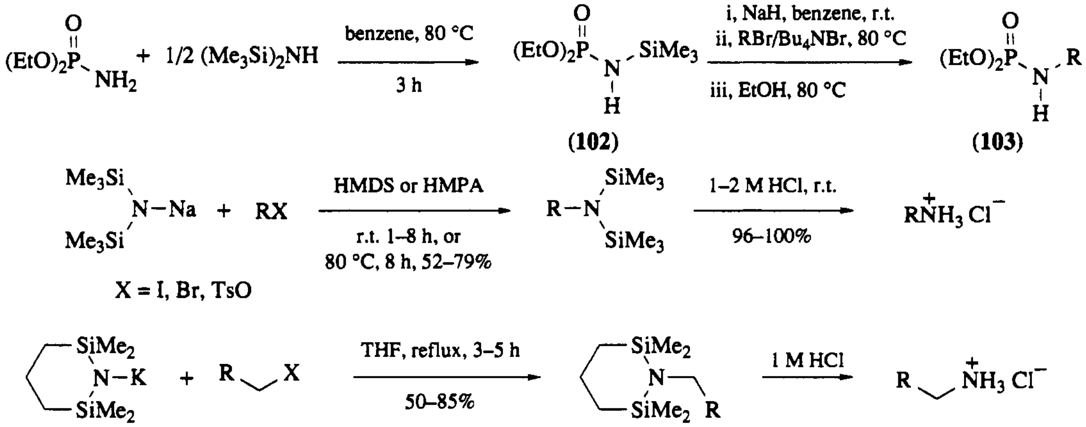

(**102**) (**103**)

**Scheme 43**

The utility of sulfenimides has been demonstrated.[83] The procedure has the particular advantage of using practically neutral conditions for the final deblocking step (Scheme 44).

*N*-Alkylation of benzylhydroxylamine by a primary alkyl bromide proceeded smoothly at room temperature. HMPA is the solvent of choice and addition of tetraethylammonium iodide facilitates the reaction. Dehydration of the resulting *N*-alkylhydroxylamines and subsequent acid hydrolysis gave the corresponding primary amines (Scheme 45).[84]

Alkylation of imino or amidine nitrogen and subsequent hydrolysis give rise to amines. For instance, alkylation of imine esters (**104a**) or amidine esters (**104b**) with dimethyl sulfate or methyl triflate, fol-

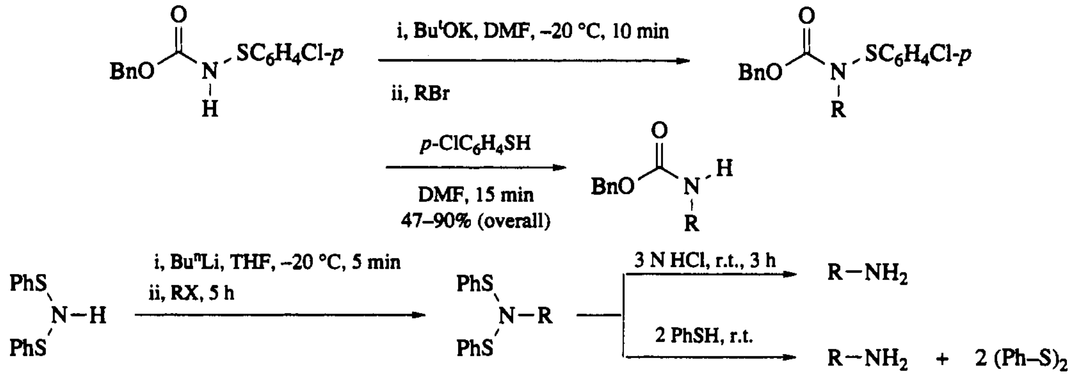

BnO
N
SC$_6$H$_4$Cl-*p*
H
i, Bu$^t$OK, DMF, –20 °C, 10 min
ii, RBr
R
*p*-ClC$_6$H$_4$SH
DMF, 15 min
47–90% (overall)
PhS
N–H
i, Bu$^n$Li, THF, –20 °C, 5 min
ii, RX, 5 h
N–R
3 N HCl, r.t., 3 h
R–NH$_2$
2 PhSH, r.t.
R–NH$_2$ + 2 (Ph–S)$_2$

**Scheme 44**

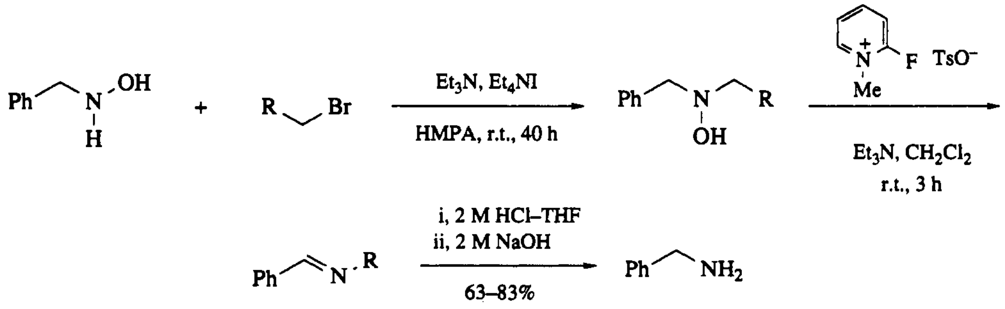

Ph
N
OH
H
R
Br
Et$_3$N, Et$_4$NI
HMPA, r.t., 40 h
F TsO$^-$
Me
Et$_3$N, CH$_2$Cl$_2$
r.t., 3 h
i, 2 M HCl–THF
ii, 2 M NaOH
63–83%
NH$_2$

**Scheme 45**

lowed by hydrolysis, afforded the corresponding *N*-methylamino acids with retention of optical activity (Scheme 46).[85]

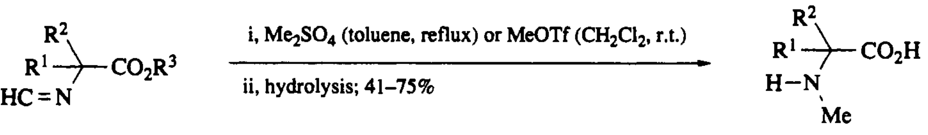

R$^2$
R$^1$
CO$_2$R$^3$
RHC=N
i, Me$_2$SO$_4$ (toluene, reflux) or MeOTf (CH$_2$Cl$_2$, r.t.)
ii, hydrolysis; 41–75%
CO$_2$H
H–N
Me

**(104a)** R = Ar
**(104b)** R = Me$_2$N

**Scheme 46**

The reaction of benzothiazolium iodide (**105**) with 2 mol of a primary aliphatic amine or 1 mol each of an aromatic amine and triethylamine gave benzothiazolimine (**106**). Methylation of (**106**) and subsequent treatment of the resulting amidinium salts (**107**) with butylamine afforded the corresponding *N*-methylamine (Scheme 47).[86]

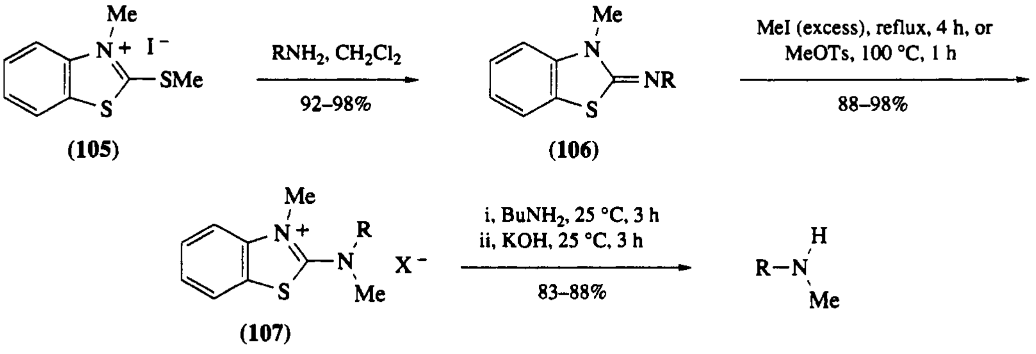

Me
N+ I$^-$
SMe
S
RNH$_2$, CH$_2$Cl$_2$
92–98%
NR
MeI (excess), reflux, 4 h, or
MeOTs, 100 °C, 1 h
88–98%
R
X$^-$
i, BuNH$_2$, 25 °C, 3 h
ii, KOH, 25 °C, 3 h
83–88%
H
R–N

**(105)** **(106)** **(107)**

**Scheme 47**

*N*-Alkylation of hexamethylenetetramine gave the corresponding quaternary ammonium salts, which were converted into primary amines without concomitant formation of secondary amines (Delépine reaction).[87]

### 1.3.3 REACTION OF π-ALLYL COMPLEXES WITH NITROGEN NUCLEOPHILES

Palladium-catalyzed nucleophilic substitution reactions of allylic substrates have become useful in organic synthesis.[88] As allylic substrates, allyl alcohols, halides, carboxylates, phosphates or vinyl epoxides can be utilized.

Although nucleophiles generally substitute allylic leaving groups with retention of configuration, the substitution of allylic carboxylates sometimes proceeds in a nonstereospecific manner due to palladium-catalyzed isomerization of the substrates (Scheme 48).[89]

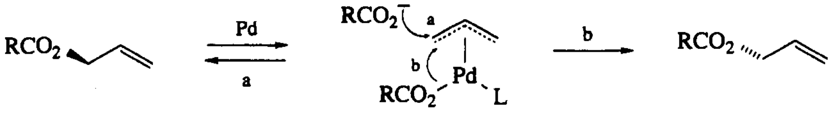

Scheme 48

This drawback has been overcome by the use of polymer-supported palladium catalysts.[90] Addition of LiCl also provides remarkably enhanced selectivity without affecting the reaction rate.[89] Thus, the reaction of *cis*-acetate (**108a**) reacted with diethylamine in the presence of $Pd(PPh_3)_4$ to give *cis*-amine (**109a**) in good yield, whereas *trans*-acetate (**108b**) afforded (**109a**) and *trans*-amine (**109b**) with the former predominant. However, the addition of LiCl in the reaction system resulted in the formation of (**109b**) as the main product (Scheme 49).[89] The observed effect of LiCl on the stereochemistry of the reaction has been attributed to the formation of intermediate (**110**), where chloride blocks the coordination of acetate (Scheme 49).[89]

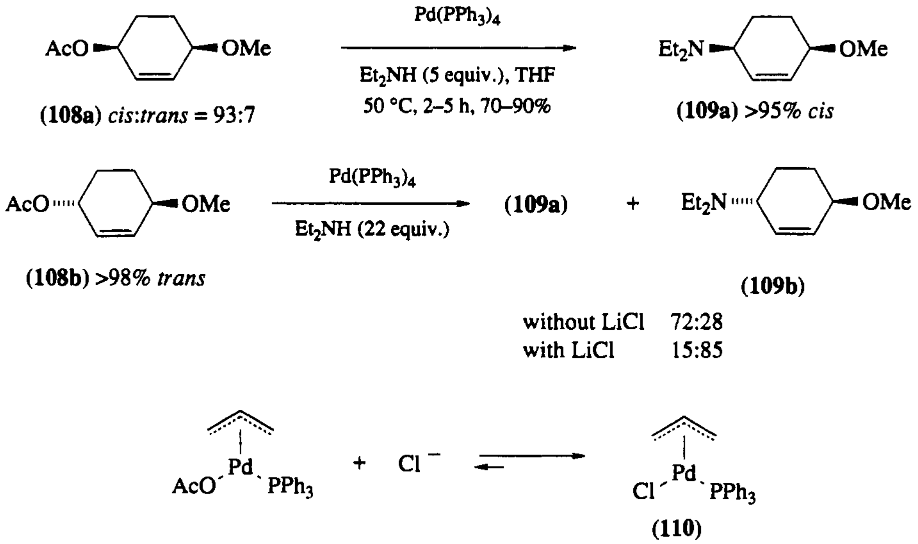

Scheme 49

The reaction of (*E*)-(*syn*)-2-acetoxy-5-chloro-3-hexene, *syn*-(**111**), with diethylamine in the presence of a palladium catalyst gave (*E*)-(*syn*)-2-acetoxy-5-(dimethylamino)-3-hexene, *syn*-(**112**). In contrast, the reaction of *syn*-(**111**) with diethylamine under $S_N2$ conditions afforded the *anti* isomer, (*anti*-(**112**); Scheme 50).[91]

The fugacity of the leaving groups at allylic positions is demonstrated to be in the order $—OPO(OEt)_2$ > —OAc > —OH and —Cl > —OAc > —OH.[92–94] Therefore, chemoselective stepwise substitution of differentially substituted bifunctional allylic substrates is possible as depicted in Scheme 51.[92,94] In the

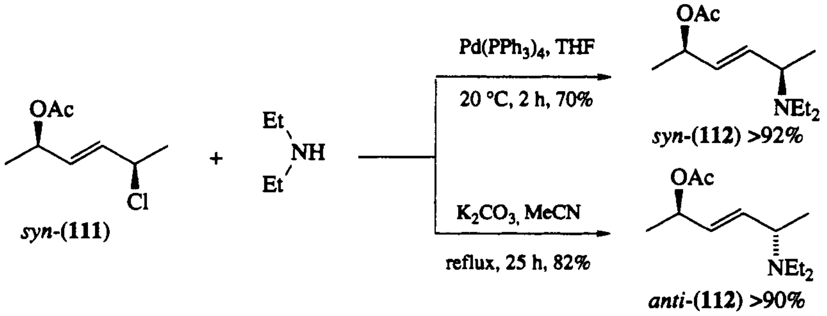
OAc
Cl
syn-(111)
Et
NH
Et
Pd(PPh3)4, THF
20 °C, 2 h, 70%
K2CO3, MeCN
reflux, 25 h, 82%
OAc
NEt2
syn-(112) >92%
OAc
NEt2
anti-(112) >90%

Scheme 50

transformation of acyclic allylic substrates, the resulting amines have, in general, the (*E*)-configuration irrespective of the original alkene geometry.[93,94]

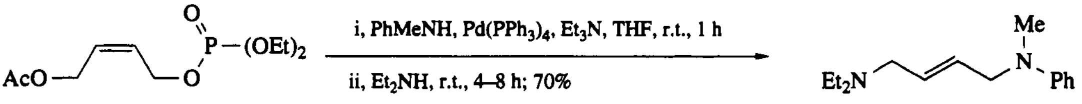
AcO
O
P—(OEt)2
O
i, PhMeNH, Pd(PPh3)4, Et3N, THF, r.t., 1 h
ii, Et2NH, r.t., 4–8 h; 70%
Me
N
Ph
Et2N

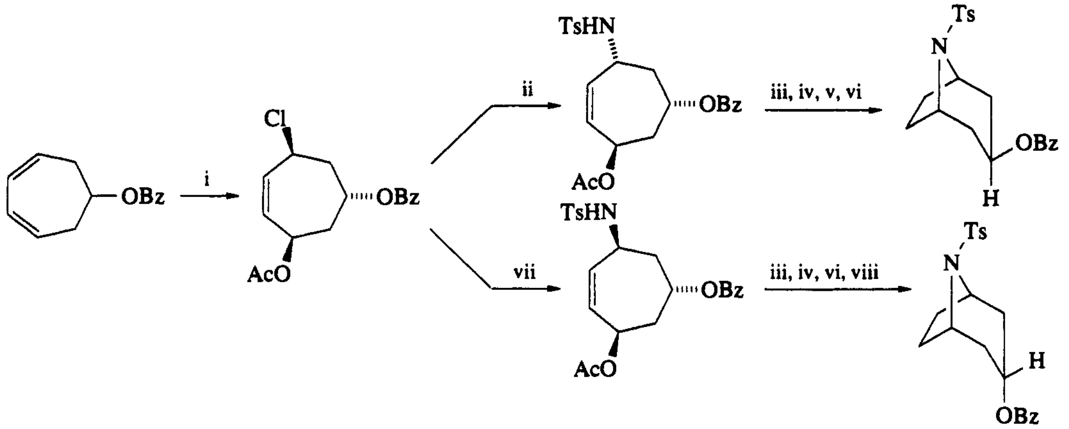
OBz
i
Cl
OBz
AcO
ii
vii
TsHN
OBz
AcO
TsHN
OBz
AcO
iii, iv, v, vi
iii, iv, vi, viii
Ts
N
OBz
H
Ts
N
H
OBz

i, Pd(OAc)$_2$, LiCl, LiOAc, *p*-benzoquinone, AcOH (77%); ii, NaNHTs, MeCN–DMSO, 80 °C, 3 h (77%); iii, $H_2$ (6 atm), RhCl(PPh$_3$)$_3$, EtOH, 20 °C, 15 h (98%, 95%); iv, NaOH, MeOH–$H_2O$ (98%, 95%); v, MsCl, Et$_3$N, THF (100%); vi, $K_2CO_3$, MeOH, 1 h, 20 °C (97%, 90%); vii, NaNHTs, Pd(PPh$_3$)$_4$, MeCN–DMSO, 20 °C, 12 h (64%); viii, DEAD, ZnCl$_2$, Bu$_3$P, 20 °C, 3 h (95%)

Scheme 51

Although a variety of primary and secondary amines can be utilized as nitrogen nucleophiles, amination of allylic substrates with ammonia has been reported to be unsuccessful. Therefore, bis(*p*-methoxyphenyl)methylamine,[95] sodium *p*-toluenesulfonamide[96] or sodium azide[97] have been utilized instead of ammonia. In the presence of a palladium catalyst, imides, such as phthalimide, react with allylic esters with the exception of geranyl and linalyl acetates. *O*-Geranyl- and *O*-linalyl-isourea derivatives, however, reacted with phthalimide giving the expected *N*-allylic phthalimides in 65% and 71% yields, respectively.[98]

The intermolecular reaction described above has been extended to intramolecular displacement leading to cyclic amines.[99] Reaction of allylic alcohols with morpholine in the presence of a nickel catalyst has also been reported.[100]

In the presence of a palladium catalyst, allyl epoxides (**113**) react with nitrogen nucleophiles at the alkenic carbon atom remote from the oxirane ring to give 1,4-adducts (**114**).[101] In the absence of a palladium catalyst, azide ion attacks the oxirane ring affording 1,2-adducts (**115**; Scheme 52 and Table 2).[101b] Vinyl epoxide (**116**) gave 1,2- and 1,4-azido alcohol in a ratio of 1:1.5 irrespective of the reaction system.[101b] Intramolecular cyclization of vinyl epoxide (**117**) in the presence of a palladium catalyst afforded isoquinuclidine (118; Scheme 52).[101c]

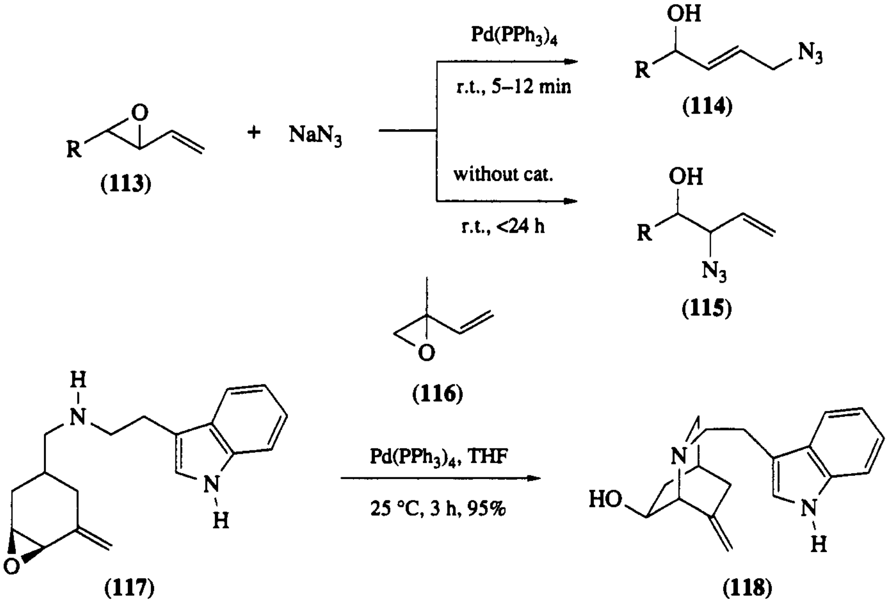
(113)
+ NaN₃
Pd(PPh₃)₄
r.t., 5–12 min
without cat.
r.t., <24 h
(114)
(115)
(116)
(117)
Pd(PPh₃)₄, THF
25 °C, 3 h, 95%
(118)

**Scheme 52**

**Table 2** Reaction of (**113**) with $NaN_3$ in the Presence and Absence of $Pd(PPh)_4$ (Scheme 52)[101b]

| *(113)* | *Yield (%) (syn:anti) with $Pd^0$ (114)* | *Yield[a] (%) (syn:anti) without cat. (115)* |
|---|---|---|
| R = 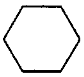 | 77 | NR |
| R = Ph | 81 | NR |
| R = 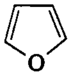 | 68 | 85 (1:1.5) |
| R = 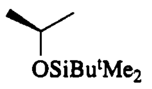 | 75 (1:1) | NR |
| 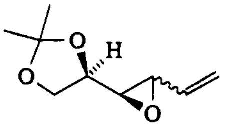<br>(2:1) | 75 (2:1) | 88 |
| 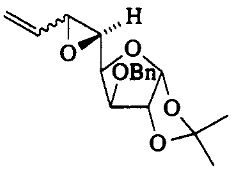<br>(9:1) | 82 (9:1) | NR |

[a] NR = not recorded.

The palladium-catalyzed reaction of 4-acyloxy-2-alkenoate (**119**) with various primary amines afforded the corresponding 4-amino-2-alkenoates (**120**). The reactivity of (**119**) strongly depends on the acyl groups at C-4 (Scheme 53).[102] 4,5-Epoxyhex-2-enoate (**121**) hardly reacted with diethylamine, ethyl carbamate and *N*-methylacetamide in the presence of a $Pd^0$ catalyst, whereas more acidic nitrogen nucleophiles, such as phthalimide, *p*-toluenesulfonamide and benzenesulfonamide, reacted with **(121)** to give γ-*N*-substituted products (**122**; Scheme 53).[103]

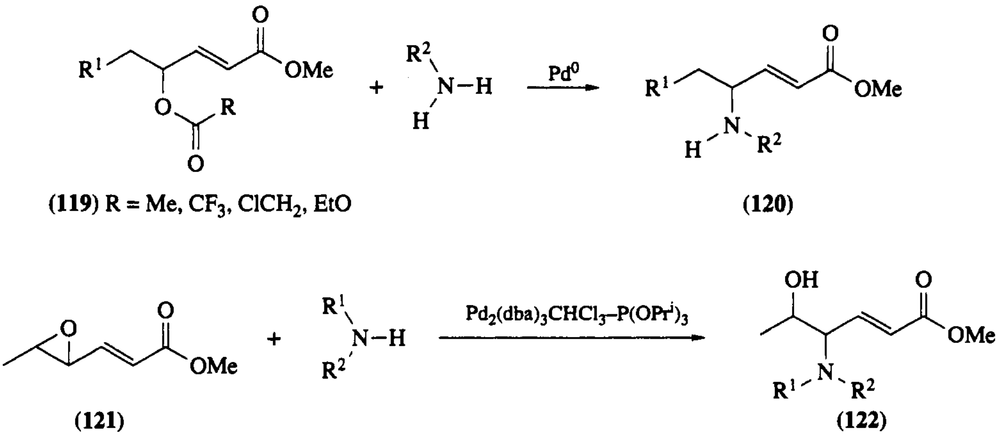

**(119)** R = Me, $CF_3$, $ClCH_2$, EtO

**(120)**

**(121)**

**(122)**

**Scheme 53**

Cyclization of 2-butene dicarbamate **(123)** in the presence of a palladium catalyst coordinated with chiral ligands **(124)** gave optically active 4-vinyl-2-oxazolidones **(125)**, which were hydrolyzed to optically active 2-amino-3-butenols (Scheme 54).[104]

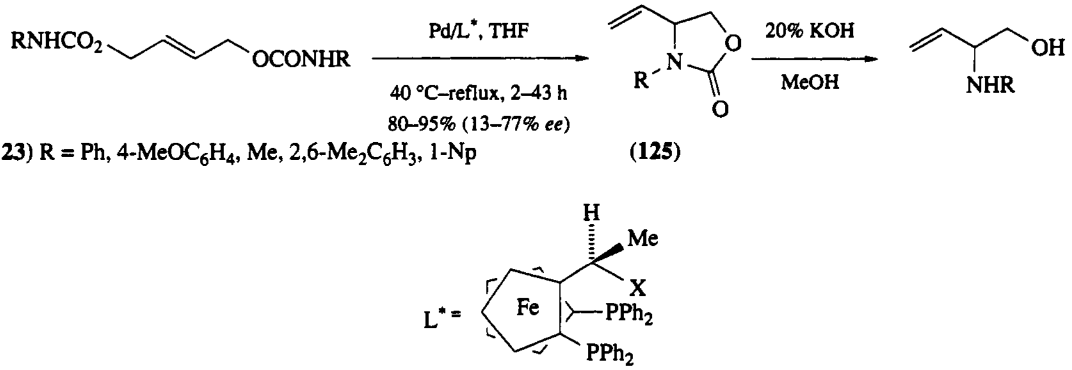

**(123)** R = Ph, $4\text{-}MeOC_6H_4$, Me, $2,6\text{-}Me_2C_6H_3$, 1-Np

**(125)**

**(124)** X = $NMeCH(CH_2OH)_2$, $NMeCH_2CH_2OH$, $NMe_2$, OH

**Scheme 54**

## 1.3.4 RING OPENING OF SMALL RING HETEROCYCLES BY NUCLEOPHILES

### 1.3.4.1 Epoxides

Reaction of epoxides with nitrogen nucleophiles affords a variety of β-hydroxyamines and their equivalents. Comprehensive review articles have been published.[105] In conjunction with the development of diastereoselective and enantioselective syntheses of epoxy alcohols, selective oxirane ring cleavage of 2,3-epoxy alcohols and carboxylates by nitrogen nucleophiles has become a versatile route to various amines and their equivalents. For details, the reader is referred to refs. 105c and 105d.

In the reaction with methyloxirane in $H_2O$ at 20 °C, the reactivity of the amines decreases in the order: piperazine > dimethylamine > pyrrolidine > piperidine > morpholine > diethylamine > di-*n*-butylamine > di-*n*-propylamine.[106] Under neutral or basic conditions, nucleophiles generally attack at the sterically less-hindered carbon atom of the oxirane ring.

The simplest method for the preparation of β-amino alcohols consists of heating an amine with an epoxide; limitations sometimes occur with poorly nucleophilic amines and with sensitive epoxides. Another limitation is that the first addition of an amine to an epoxide is often followed by one or more secondary additions (Scheme 55). Therefore, for a primary amine, an excess of the amine is used so that secondary reactions are reduced to a minimum. When a secondary amine is reacted with an epoxide, the product is a tertiary amine and the secondary reaction is insignificant.[106,107]

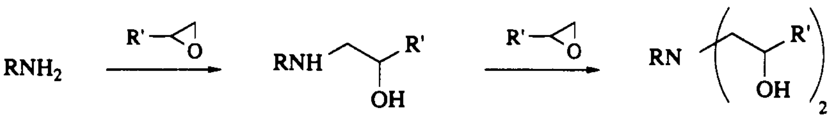

**Scheme 55**

In order to facilitate the reaction and to improve the regioselectivity of the oxirane ring opening, various procedures have been devised. Cation-exchange zeolites are efficient catalysts for the reaction of amines with epoxides.[108] The advantages of amine-doped alumina over the conventional homogeneous systems have been demonstrated.[109] Moderately acidic and basic zeolites show higher catalytic activity compared to strongly acidic or basic zeolites.[109,110]

Since enantiomerically pure 2,3-epoxy alcohols are readily available by the Sharpless epoxidation procedure,[105,111] the regioselective ring opening of 2,3-epoxy alcohols by nitrogen nucleophiles provides a convenient route to a variety of homochiral amines. A convenient procedure for the conversion of 2,3-epoxy alcohols to 1,2-epoxy-3-alkanols has been developed.[112]

1,2-Epoxy-3-alkanols (**126a**) and (**126b**) reacted with sodium azide to afford 1-azido-2,3-diols (**127a**) and (**127b**) in good yields (Scheme 56).[112]

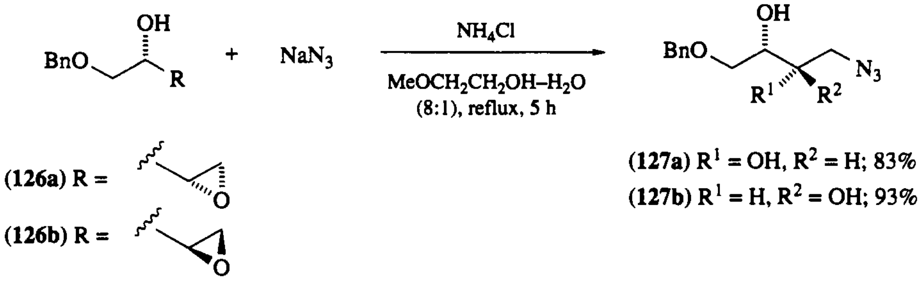

(**126a**) R =

(**126b**) R =

(**127a**) R$^1$ = OH, R$^2$ = H; 83%

(**127b**) R$^1$ = H, R$^2$ = OH; 93%

**Scheme 56**

Under basic conditions, 2,3-epoxy alcohols rearrange to 1,2-epoxy-3-alkanols (the Payne rearrangement), resulting in an equilibrium mixture. Therefore, the oxirane ring opening of 2,3-epoxy alcohols with amines under Payne rearrangement conditions ($H_2O$, base) generally affords three possible isomers with rather poor regioselectivity.[112] Studies on the reaction of a series of 2,3-epoxy alcohols of general formula (**128**) and related compounds with sodium azide under nonisomerized conditions ($NH_4Cl$, in 2-methoxyethanol/$H_2O$) have revealed that the ratio of C-3 to C-2 attack is in the range 4:1–C-2 only.[113] In view of the results obtained, it has been demonstrated that, in addition to steric effects, electronic effects can play an important role in regioselectivity of oxirane ring opening reactions.[113] The reaction of epoxy alcohol (**129**) with benzylamine or sodium azide occurred exclusively at the position remote from the free hydroxy group, giving aminodiol (**130**) or azidodiol (**131**) as the sole product (Scheme 57).[114]

The rate and regioselectivity (C-3 attack) of the oxirane ring opening of 2,3-epoxy alcohols by nucleophiles are markedly increased by the addition of $Ti(OPr^i)_4$. Thus, the reaction of 2,3-epoxyhexanol with excess diethylamine in the presence of $Ti(OPr^i)_4$, 1,2-diol (**132**) and 1,3-diol (**133**) were formed in 90% yield in a ratio of 20:1, while, in the absence of the alkoxide, (**132**) and (**133**) were obtained in 4% yields in a ratio of 3.7:1 (Scheme 58).[115]

Regioselective C-2 amination of 2,3-epoxy alcohols can be realized by intramolecular oxirane ring opening of the carbamates prepared by the reaction of the epoxy alcohols with isocyanates.[116,117] In some cases, however, acyl transfer is a serious side reaction (Scheme 59).[117]

In this connection, intramolecular Michael addition of *O*-carbamates to α,β-unsaturated esters (Scheme 60),[118] iodo cyclization of allylic and homoallylic trichloroacetamidates[119] or aminomercuration of alkenic carbamates[119] has been used for the preparation of amino alcohols.

Tetraphenylstibonium triflate ($Ph_4SbOTf$; **134**) has been reported to be an effective catalyst for oxirane ring opening. Thus, otherwise unreactive cyclohexene oxide reacted smoothly with diethylamine in the presence of (**134**) ($CH_2Cl_2$, 40 °C, 20 h) to give (*E*)-2-diethylaminocyclohexanol in 75% yield.[120]

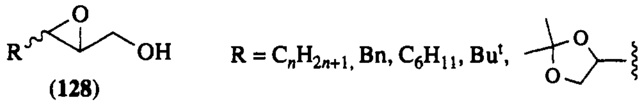

**(128)**

$R = C_nH_{2n+1}$, Bn, $C_6H_{11}$, $Bu^t$,

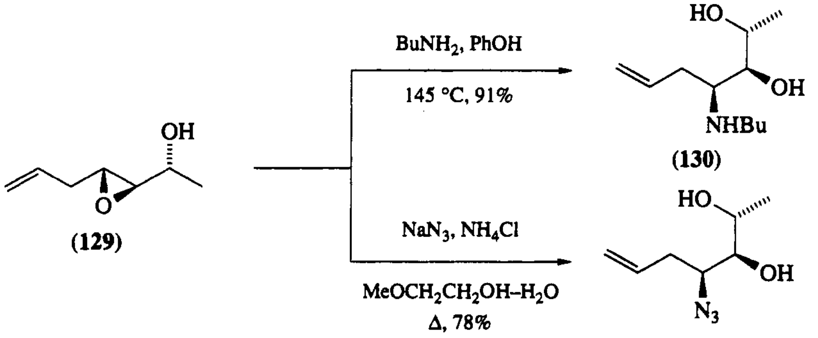
BuNH$_2$, PhOH
145 °C, 91%
NaN$_3$, NH$_4$Cl
MeOCH$_2$CH$_2$OH–H$_2$O
Δ, 78%
HO
OH
NHBu
N$_3$

**(129)** **(130)** **(131)**

Scheme 57

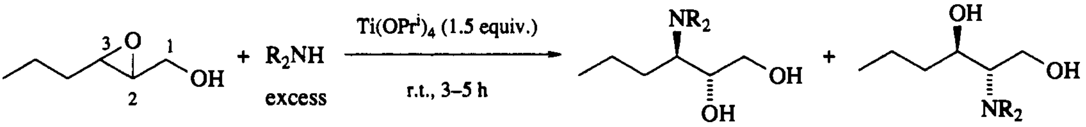
3
1
2
OH
+ R$_2$NH
excess
Ti(OPr$^i$)$_4$ (1.5 equiv.)
r.t., 3–5 h
NR$_2$
OH
+

**(132)** **(133)**

R = Et (90%) 20:1

R = $CH_2$=$CH_2CH_2$ (96%) 100:1

Scheme 58

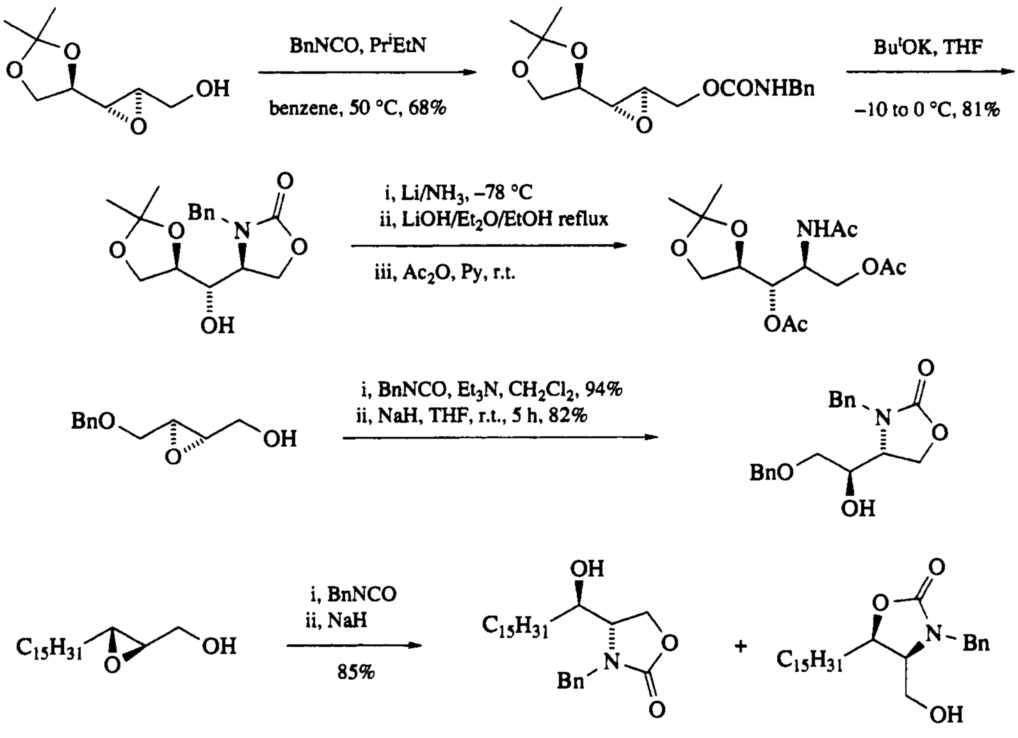
BnNCO, Pr$^i$EtN
benzene, 50 °C, 68%
OCONHBn
Bu$^t$OK, THF
−10 to 0 °C, 81%
i, Li/NH$_3$, −78 °C
ii, LiOH/Et$_2$O/EtOH reflux
iii, Ac$_2$O, Py, r.t.
NHAc
OAc
i, BnNCO, Et$_3$N, CH$_2$Cl$_2$, 94%
ii, NaH, THF, r.t., 5 h, 82%
BnO
Bn
i, BnNCO
ii, NaH
85%
C$_{15}$H$_{31}$

58:42

Scheme 59

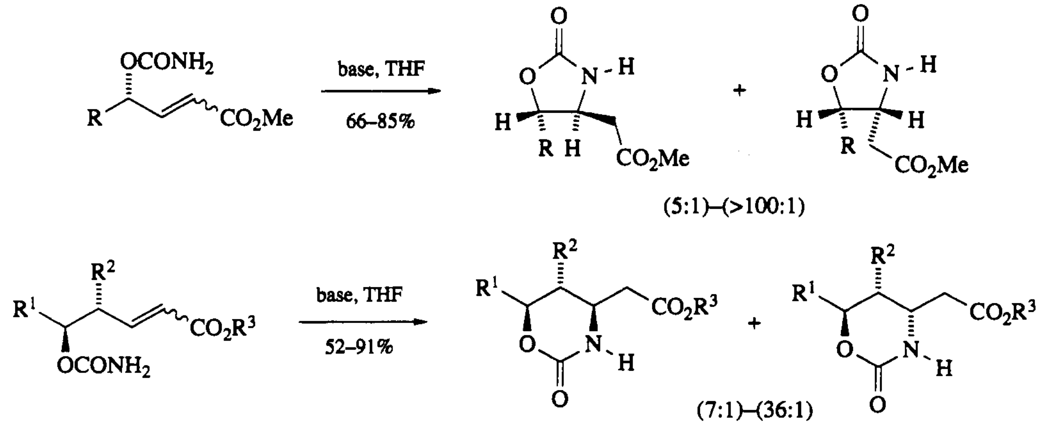

OCONH2
R
CO2Me
base, THF
66–85%
O
O
N-H
H
R H
CO2Me
+
O
O
N-H
H
H
R
CO2Me
(5:1)–(>100:1)
R2
R1
CO2R3
OCONH2
base, THF
52–91%
R2
R1
CO2R3
O
N
H
O
+
R2
R1
CO2R3
O
N
H
O
(7:1)–(36:1)

**Scheme 60**

Conversion of amines into metal amides is an alternative method to facilitate the oxirane ring opening. The metal amides used are, for example, diethylaluminum amides,[121a] trimethylsilylamides[121b] and halomagnesium amides.[121c]

α,β-Epoxy sulfoxides reacted with various amines to afford the corresponding α-amino ketones (Scheme 61).[122]

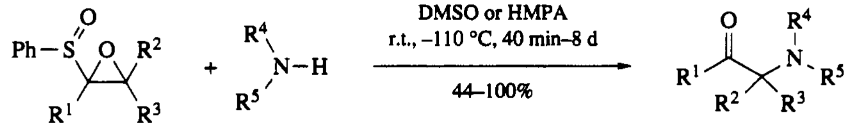

O
Ph–S
O
R2
R1
R3
+
R4
N–H
R5
DMSO or HMPA
r.t., –110 °C, 40 min–8 d
44–100%
O
R4
N
R5
R1
R2
R3

**Scheme 61**

Alkali metal azides react with epoxides in a appropriate solvent to give vicinal azidohydrins. Phase-transfer reagents may be used. The reactions usually require high temperatures and/or long reaction times.

Reaction of epoxide (**135**) with tetra-*n*-butylammonium azide in the presence of trimethylsilyl azide (TMSN$_3$) afforded a high yield of azidohydrin (**136**) along with *ortho*-acyl azide (**137**; Scheme 62).[123] It has been reported that omission of TMSN$_3$ in the reaction resulted in extensive acyl transfer. Lewis acid catalyzed oxirane ring opening (ZnCl$_2$/TMSN$_3$) of (**135**) gave (**137**).[123]

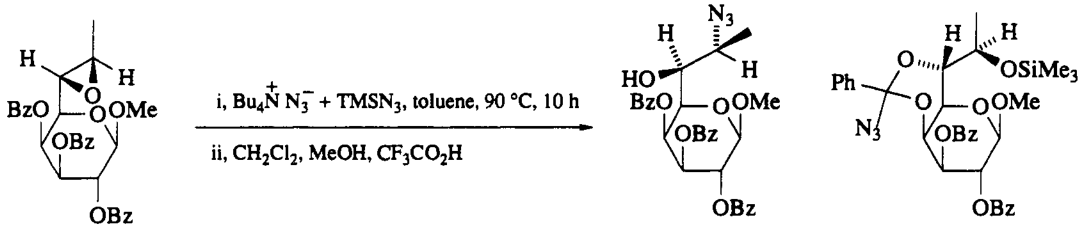

H
H
BzO
O
OMe
OBz
OBz
i, Bu4N N3 + TMSN3, toluene, 90 °C, 10 h
ii, CH2Cl2, MeOH, CF3CO2H
N3
H
H
HO
BzO
OMe
OBz
OBz
H
H
Ph
O
OSiMe3
O
OMe
N3
OBz
OBz

(**135**) (**136**) 78% (**137**) 14%

**Scheme 62**

TMSN$_3$ can also react with epoxides in the presence of an appropriate catalyst (Scheme 63), such as ZnCl$_2$,[124] Ti(OPr$^i$)$_4$,[115,125] VO(OPr$^i$)$_3$,[125a] CpVCl$_2$,[125a] Et$_2$AlF,[126] Al(OPr$^i$)$_3$[127] or BF$_3$·OEt$_2$.[128,129b]

When 2,3-anhydro-4-*O*-tosyl pyranoside (**138**) reacted with sodium azide, azide ion attacked first at C-4 and then oxirane ring opening took place, giving diazido derivatives (**139a**) and (**139b**).[129a] In contrast, in the reaction of (**138**) with TMSN$_3$ in the presence of BF$_3$·OEt$_2$, only oxirane ring cleavage occurred to give (**140a**) and (**140b**).[129b] Alternatively, 2,3-anhydrotriflate (**141**) reacted with sodium azide affording anhydroazide (**142**; Scheme 64).[129c]

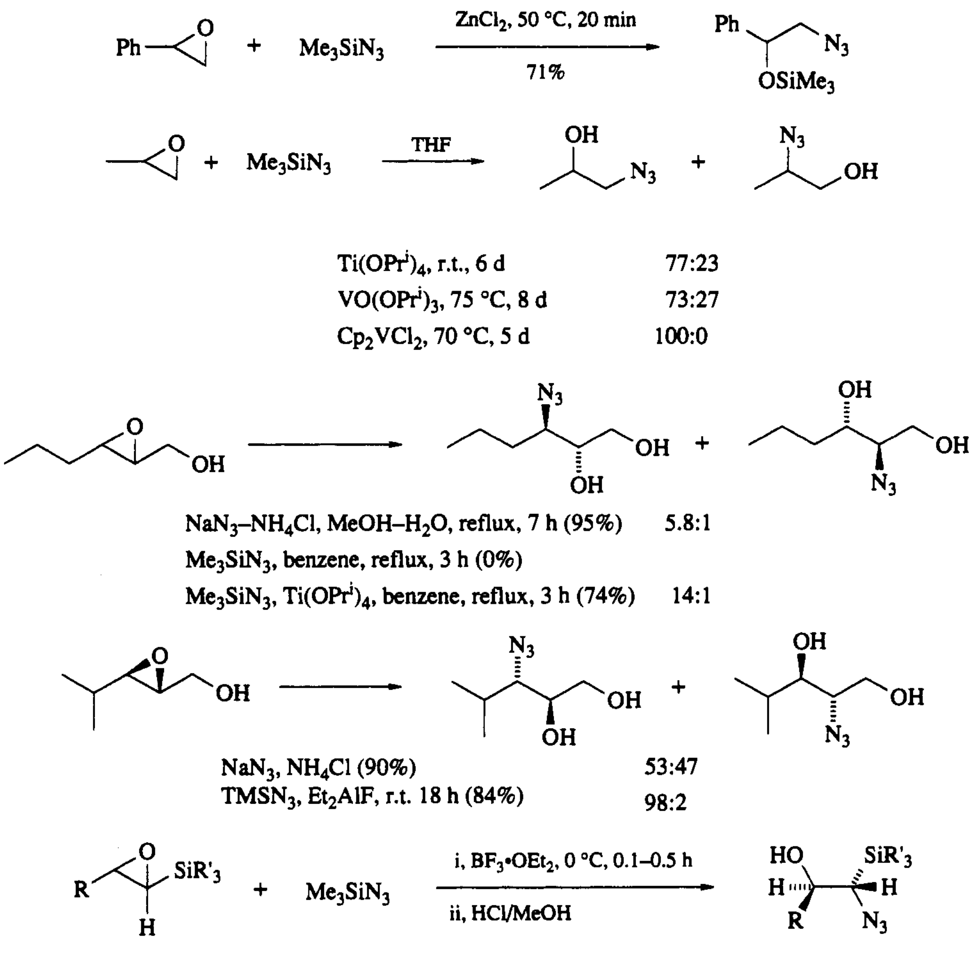
ZnCl2, 50 °C, 20 min
71%
THF
Ti(OPr^i)4, r.t., 6 d 77:23
VO(OPr^i)3, 75 °C, 8 d 73:27
Cp2VCl2, 70 °C, 5 d 100:0
NaN3–NH4Cl, MeOH–H2O, reflux, 7 h (95%) 5.8:1
Me3SiN3, benzene, reflux, 3 h (0%)
Me3SiN3, Ti(OPr^i)4, benzene, reflux, 3 h (74%) 14:1
NaN3, NH4Cl (90%) 53:47
TMSN3, Et2AlF, r.t. 18 h (84%) 98:2
i, BF3•OEt2, 0 °C, 0.1–0.5 h
ii, HCl/MeOH

R = H, R' = Me, 86%; R = 1-hydroxycyclohex-1-yl, R' = Et, 74%

**Scheme 63**

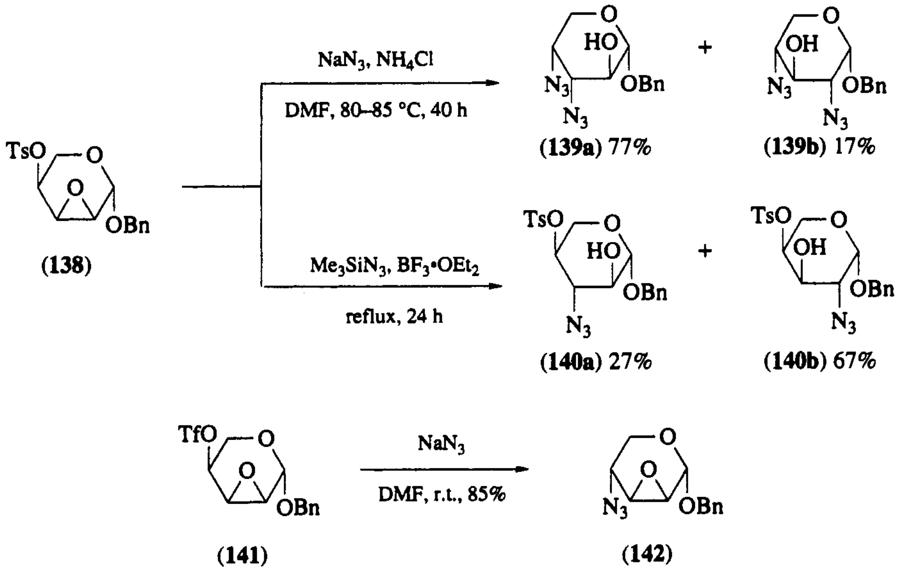
(138)
NaN3, NH4Cl
DMF, 80–85 °C, 40 h
(139a) 77%
(139b) 17%
Me3SiN3, BF3•OEt2
reflux, 24 h
(140a) 27%
(140b) 67%
(141)
NaN3
DMF, r.t., 85%
(142)

**Scheme 64**

As shown in Scheme 63, the regioselectivity of oxirane ring opening of 2,3-epoxy alcohols is increased in TMSN3–Lewis acid systems compared to conventional systems using sodium azide. It has been reported, however, that sodium azide supported on zeolite CaY facilitates the C-3 attack.[130]

A mild and highly stereoselective transformation of epoxides to azido alcohols by treatment with Et3Al–HN3 in toluene has been reported (Scheme 65).[131]

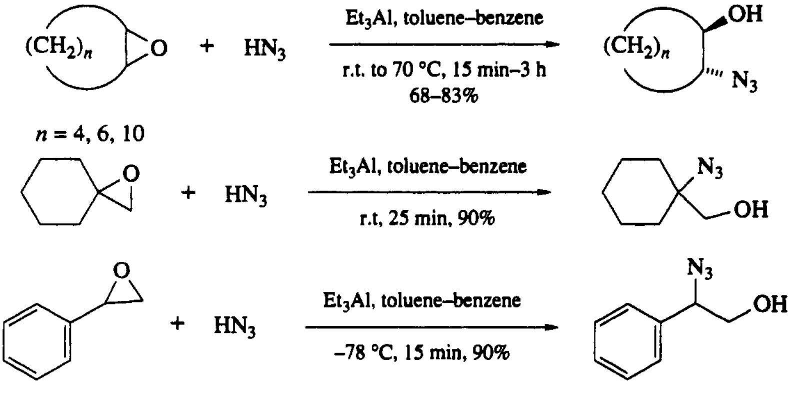
$(CH_2)_n$
O
+ $HN_3$
$Et_3Al$, toluene–benzene
r.t. to 70 °C, 15 min–3 h
68–83%
OH
$N_3$
$n$ = 4, 6, 10
r.t, 25 min, 90%
−78 °C, 15 min, 90%

Scheme 65

As described above, 1,2-azido alcohols can be stereospecifically prepared from epoxides. 1,2-Azido alcohols thus prepared reacted with triphenylphosphine or trialkyl phosphites to afford aziridines, where inversion of both centers of the original epoxides takes place (Scheme 66).[123,132] Intramolecular oxirane ring opening by nitrogen nucleophiles affords heterocyclic compounds.[133]

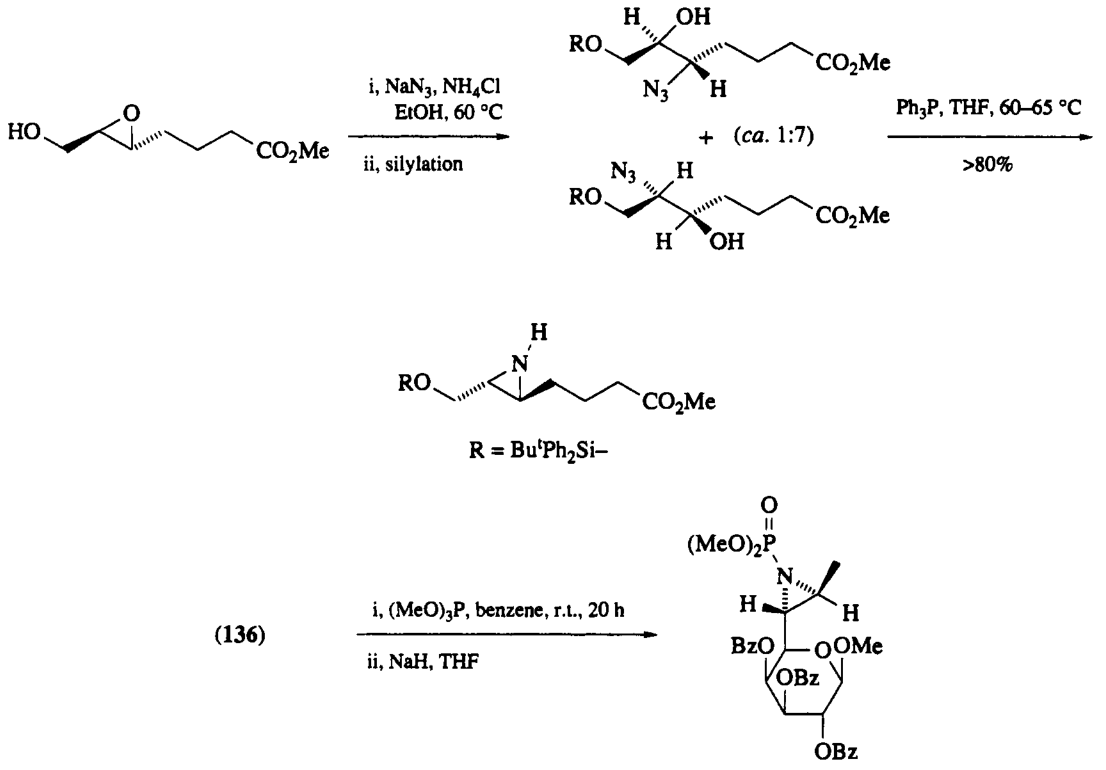
HO
O
$CO_2Me$
i, $NaN_3$, $NH_4Cl$
EtOH, 60 °C
ii, silylation
RO
H
OH
$N_3$
+ (*ca.* 1:7)
$Ph_3P$, THF, 60–65 °C
>80%
N
R = $Bu^tPh_2Si$–
(136)
i, $(MeO)_3P$, benzene, r.t., 20 h
ii, NaH, THF
O
$(MeO)_2P$
BzO
OMe
OBz

Scheme 66

### 1.3.4.2 Aziridines

Aziridines can be prepared by various methods which involve dehydration of β-amino alcohols and dehydrohalogenation of β-amino halides.[134] Therefore, the reactions of aziridines with oxygen nucleophiles[135] and halide ions[136] will not be described in this section. A short review article has been published.[137]

Aziridines may be classified into two groups.[138] 'Activated aziridines (**143a**)' contain substituents capable of stabilizing a negative charge developed in the transition state of nucleophilic ring opening. The activated aziridines undergo ring-opening reactions with nucleophiles in the absence of catalysts (Scheme 67),[138,139] while 'unactivated aziridines (**143b**)' generally require acidic catalysts to promote the reaction. Since aziridine activated by a carbonyl group is an ambident electrophile, nucleophiles can attack the carbonyl carbon (Scheme 67, path a) and the ring carbon (Scheme 67, path b).

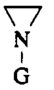

(**143a**) G = COR, $SO_2R$, $CO_2R$
(**143b**) G = H, alkyl, aryl

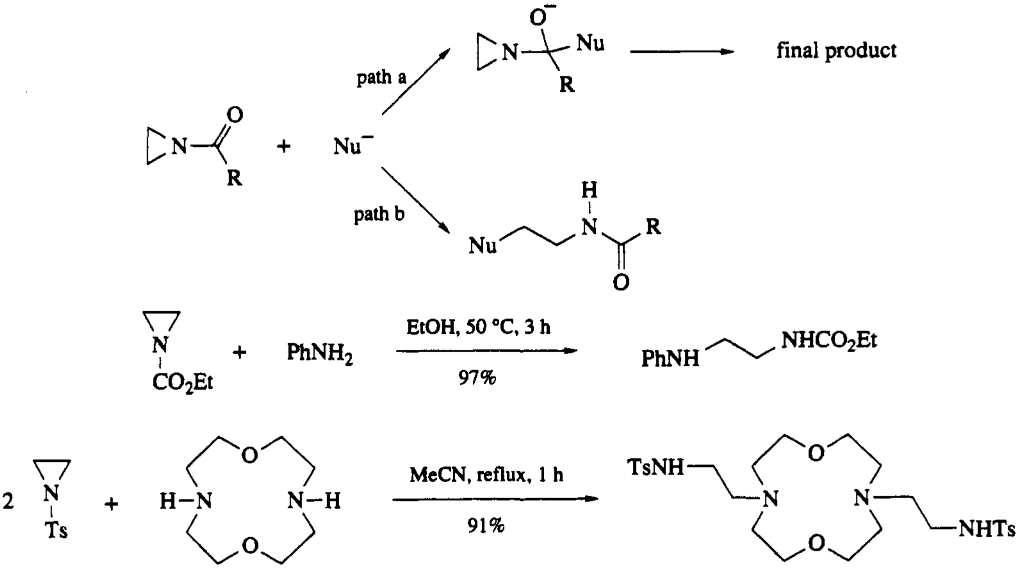

**Scheme 67**

Transformation of 1,3-diamino-2-propanol (**144**) into vicinal diamines has been reported.[140] Thus, the bis(benzyloxycarbonyl) derivative of (**144**) was mesylated to give (**145**), which was converted into 1-benzyloxycarbonylaziridine (**146**). Acetic acid and HCl reacted at the ring carbon of (**146**) affording 2,3-diamino-1-propanol (**147**) and 1-chloro-2,3-diaminopropane (**148**; Scheme 68). On the other hand, the reaction of (**146**) with Grignard reagents and sodio malonates resulted in the loss of the carbamate protecting group. In contrast, the sulfonamide derivative (**149**) could be converted into diamines (**151**) and (**152**) *via* 1-tosylaziridine (**150**; Scheme 68).

1-Ethoxycarbonylaziridine (**153**) has been reported to react with lithium amides affording carbonyl addition–elimination products (**154**; Scheme 69).[141] The reaction of (**153**) with trityllithium proceeded through path b in Scheme 67, while diphenylmethyllithium gave both 1-(diphenylacetyl)aziridine (path a; 33%) and *N*-(3-diphenylpropyl)carbamate (path b; 66%). Benzyllithium, *t*-butyllithium and lithium phenylacetylide afforded the corresponding symmetrical ketones (**155**).[141] 1-Acylaziridines (**156**) reacted with various organolithium and Grignard reagents to produce ketones (**157**) in high yields (Scheme 69).[142] 1-Tosylaziridine (**158**) reacted with 2-butynylmagnesiumm bromide to give ring-opened products (**159a** and **159b**; Scheme 69).[143]

The studies of the reaction of 1-substituted-2-phenylaziridines (**160a**), (**160b**) and (**160c**) with carbon nucleophiles have revealed that regioselectivity depends on the reagent used and reaction conditions. In general, methyl–metal reagents (MeMgBr, $Me_2CuLi$ and $MeCu{\cdot}BF_3$) tend to attack the C-2 of (**160**) to give (**161**; Scheme 70). 1-Tosylaziridine (**160b**) was found to be more reactive than (**160a**). MeLi caused decomposition of (**160b**) and displacement of the *N*-substituent of (**160a**). 1-Methylaziridine (**160c**) was decomposed by $Me_2CuLi$ or $MeCu{\cdot}BF_3$.[144]

In the reaction with carbon nucleophiles and with nitrogen nucleophiles, the reaction site on 1-substituted-2,2-dimethylaziridines (**163**) depends on the degree of leaving group activation. Thus, highly activated aziridine was attacked at C-3, while less activated aziridines were attacked at C-2 (Scheme 70).[145] The reaction of (**163**; G = Ts—, 2,5-$Cl_2C_6H_3SO_2$—, Bu$^t$C(O)—) with Grignard reagents (RMgX) is

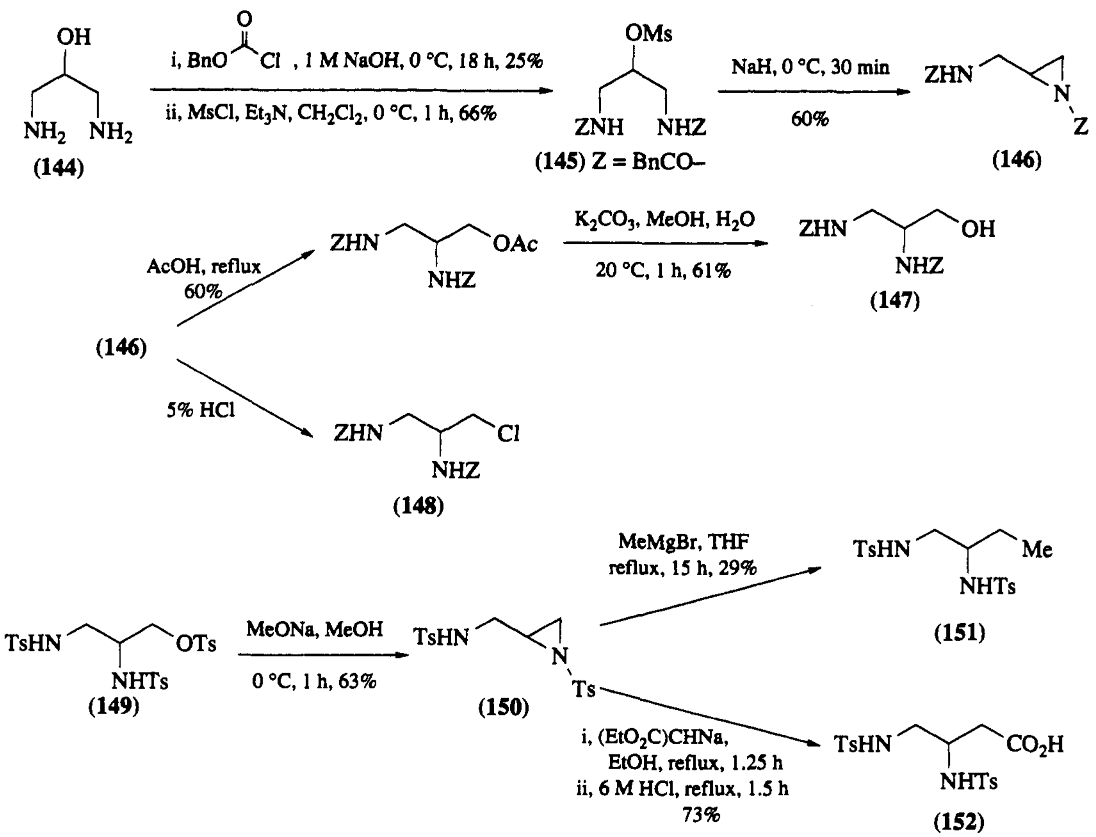
(144)
i, BnOCOCl, 1 M NaOH, 0 °C, 18 h, 25%
ii, MsCl, Et3N, CH2Cl2, 0 °C, 1 h, 66%
(145) Z = BnCO–
NaH, 0 °C, 30 min
60%
(146)
AcOH, reflux
60%
K2CO3, MeOH, H2O
20 °C, 1 h, 61%
(147)
5% HCl
(148)
(149)
MeONa, MeOH
0 °C, 1 h, 63%
(150)
MeMgBr, THF
reflux, 15 h, 29%
(151)
i, (EtO2C)CHNa,
EtOH, reflux, 1.25 h
ii, 6 M HCl, reflux, 1.5 h
73%
(152)

Scheme 68

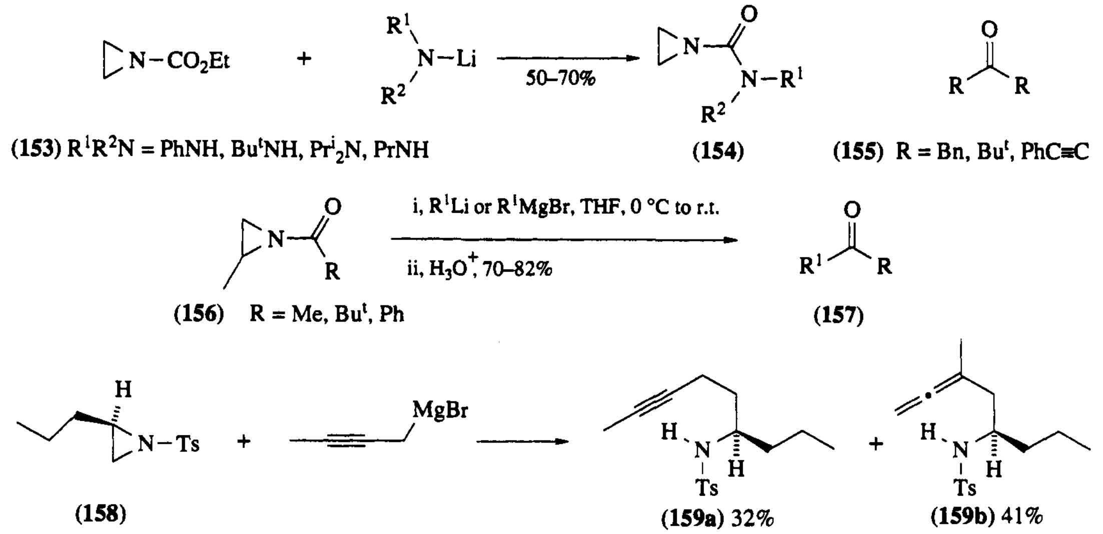
50–70%
(153) R¹R²N = PhNH, ButNH, Pri2N, PrNH
(154)
(155) R = Bn, But, PhC≡C
i, R¹Li or R¹MgBr, THF, 0 °C to r.t.
ii, H3O+, 70–82%
(156) R = Me, But, Ph
(157)
(158)
(159a) 32%
(159b) 41%

Scheme 69

more complicated; the product distribution depends on the activating group G, R, X and reaction conditions.[146]

Boron trifluoride etherate promotes the nucleophilic ring opening of unactivated aziridines with diorganocopperlithiums leading to both primary and secondary amines (Scheme 71).[147] Reaction of 1-benzyldiaziridine (**164a**) with $Me_2CuLi$ promoted by $BF_3 \cdot OEt_2$ afforded monobenzylamine (**165**) and piperidine derivative (**166**). When 1-benzyloxycarbonyl- or 1-tosyl-diaziridine (**164b**) and (**164c**) were allowed to react with $Me_2CuLi$ without Lewis acid catalysts, diamine (**167b**) or (**167c**) was obtained (Scheme 71).[132c]

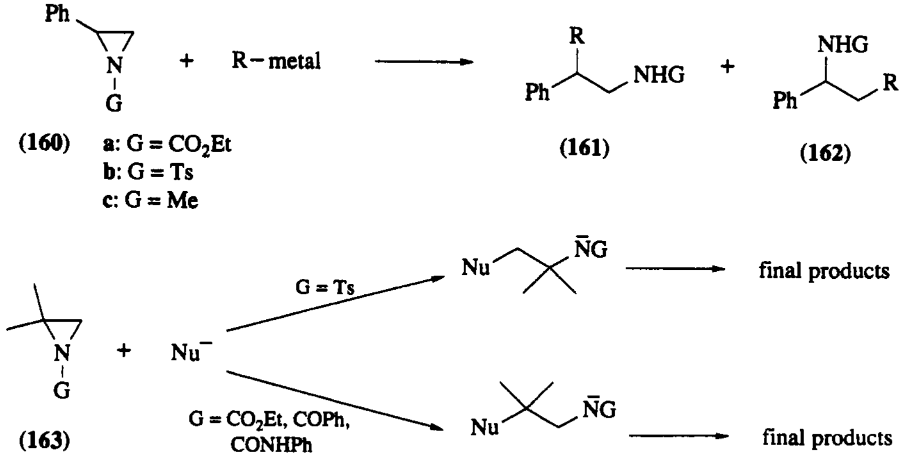
(160) a: G = CO2Et
b: G = Ts
c: G = Me
R-metal
(161)
(162)
(163)
Nu⁻
G = Ts
G = CO2Et, COPh, CONHPh
final products
final products

**Scheme 70**

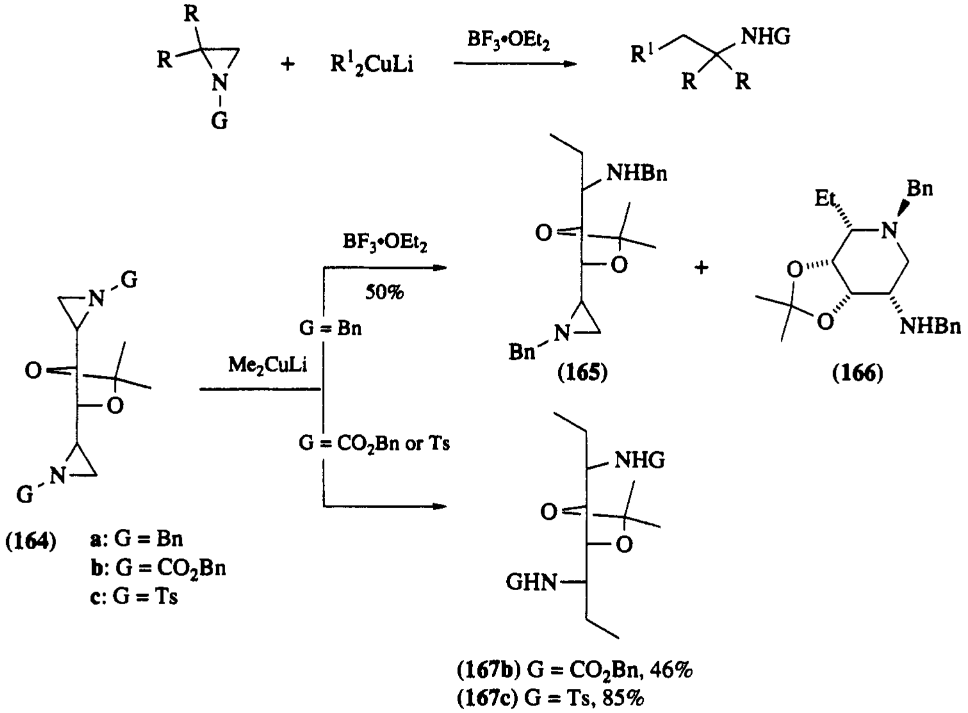
BF3•OEt2
R¹2CuLi
BF3•OEt2
50%
G = Bn
Me2CuLi
G = CO2Bn or Ts
(164) a: G = Bn
b: G = CO2Bn
c: G = Ts
(165)
(166)
(167b) G = CO2Bn, 46%
(167c) G = Ts, 85%

**Scheme 71**

Sodium enolates of ketones and disodium enediolates of substituted phenylacetic acids reacted with activated aziridines to afford γ-amido ketones and γ-amidobutyric acids, respectively (Scheme 72).[148]

Aziridine-2-carboxylic acid esters can be utilized as versatile precursors for amino acid derivatives.[149] Although the product distribution resulting from the reaction of activated aziridine-2-carboxylates with amines depends on the structure of the reactants, the reactions with alcohols or thiols in the presence of acidic catalysts generally gave the α-amino acid derivatives (Scheme 73).[149,150] On the other hand, free 3-methyl-2-aziridinecarboxylic acids (**168**) reacted with thiophenol, cysteine and glutathione to afford β-amino acid derivatives with sulfur substituents at the α-position as the main product (Scheme 73).[151]

The reaction of activated aziridine-2-carboxylic acid methyl esters (**169**) with ethoxycarbonylmethylenetriphenylphosphorane resulted in the formation of phosphorane (**170**) along with phosphorane (**171**) and aziridine (**172**), with the exception of (**169d**), where (**172d**) was obtained as the sole product (Scheme 74).[152] Phosphorane (**170b**) was converted into 4-methylene-(2*S*)-glutamic acid (**173**).[152]

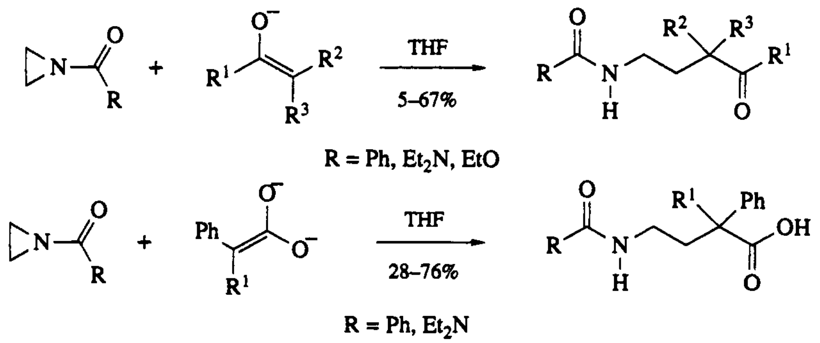
THF
5–67%
R = Ph, Et2N, EtO
THF
28–76%
R = Ph, Et2N

Scheme 72

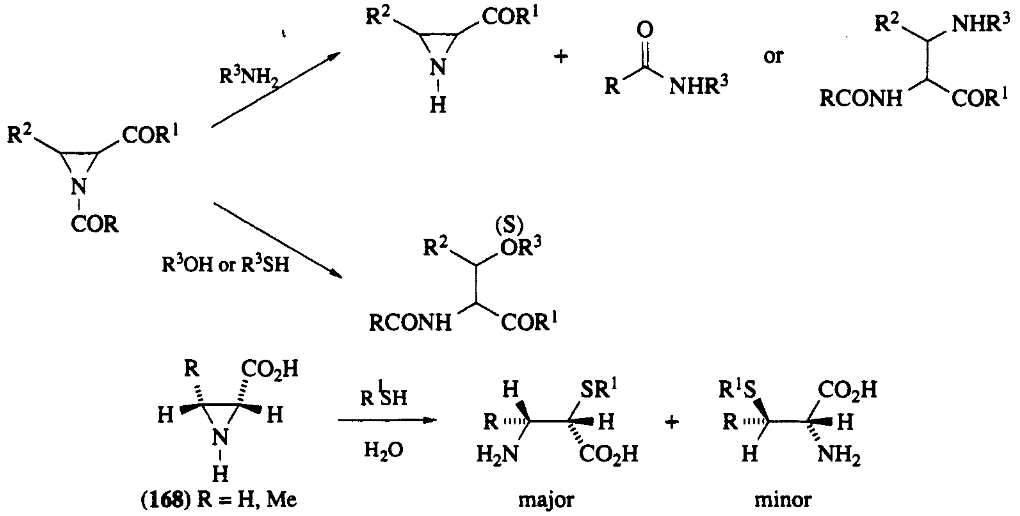
R3NH2
R3OH or R3SH
or
(S)
R1SH
H2O
(168) R = H, Me
major
minor

Scheme 73

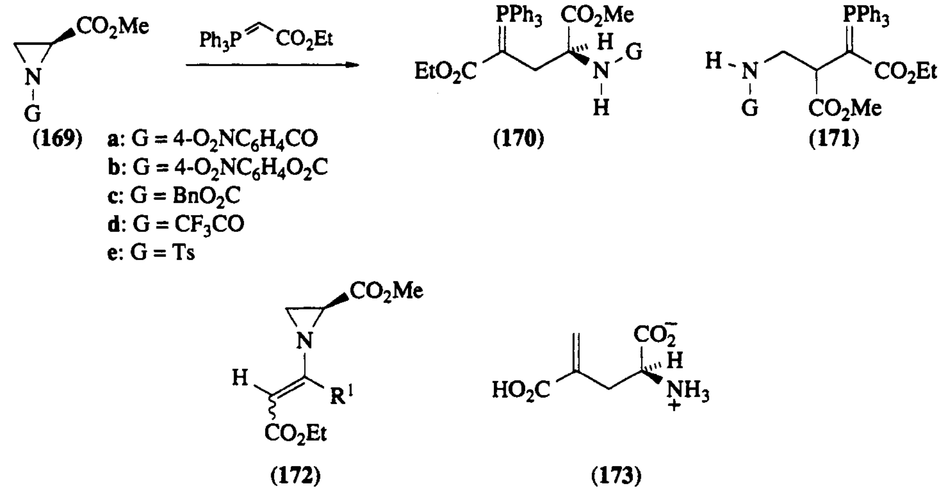
Ph3P CO2Et
(169) a: G = 4-O2NC6H4CO
b: G = 4-O2NC6H4O2C
c: G = BnO2C
d: G = CF3CO
e: G = Ts
(170)
(171)
(172)
(173)

Scheme 74

The reaction of (*Z*)- and (*E*)-1-arylsulfonylaziridines with dimethyloxosulfoniummethylide proceeded stereospecifically to yield (*E*)- and (*Z*)-azetidines, respectively (Scheme 75).[153]

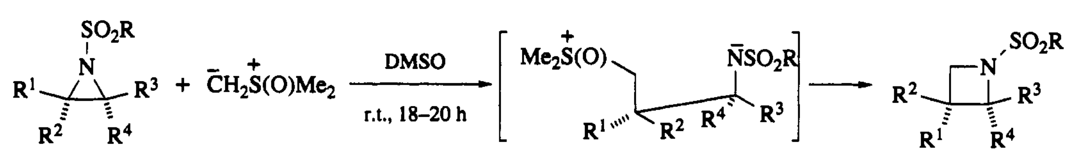

R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$

44–80%

**Scheme 75**

Thermal rearrangement of cyclic and acyclic 1-ethoxycarbonylaziridines (**174a**) and (**174b**) afforded allylic carbamates, which were hydrolyzed to primary allylic amines (Scheme 76).[154]

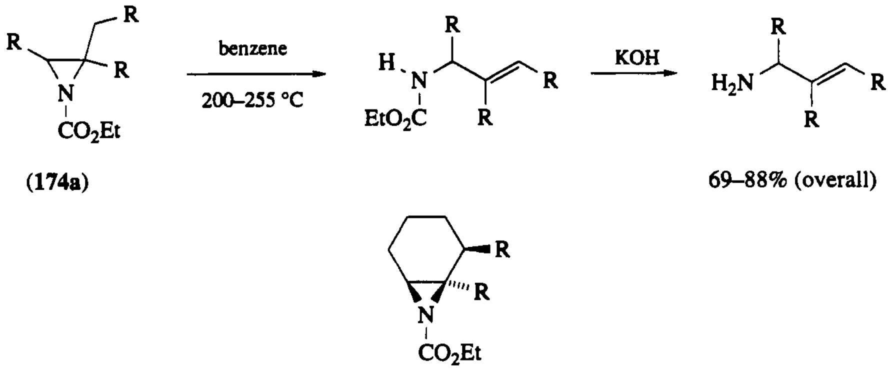

(**174a**)

69–88% (overall)

(**174b**)

**Scheme 76**

Reaction of 1-acylaziridines with LiAlH$_4$ resulted only in attack at the carbonyl site. In contrast, reduction of (**153**) with NaBH$_4$ in ethanol gave ethyl *N*-ethylcarbamate.[141] Reduction of chiral aziridines (**175**) with various metal hydrides reveals that Red-Al gave the best result (Scheme 77 and Table 3).[132c]

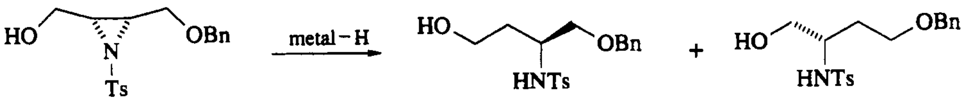

(**175**) (**176**) (**177**)

**Scheme 77**

**Table 3** Reduction of (**175**; Scheme 77)[132c]

| *Reagent and reaction conditions* | *Isolated yield* (%) | *Ratio* (*176*):(*177*) |
|---|---|---|
| Red-Al, THF, −78 °C | 86 | >100:1 |
| LAH, THF, −20 °C | 80 | >100:1 |
| DIBAL-H, THF, −78 °C → r.t. | 30[a] | >100:1 |
| DIBAL-H, C$_6$H$_6$, 0 °C → r.t. | 20[a] | 1:1 |
| NaBH$_4$/Ti(OPr$^i$)$_4$, C$_6$H$_6$, r.t. | No reaction | |

[a] Reaction incomplete.

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# 1.4

# Synthesis of Nitroso, Nitro and Related Compounds

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## 1.4.1 NITROSO COMPOUNDS

Some comprehensive reviews of the chemistry of *C*-nitroso compounds already exist.[1] Since the latest general review was published, no other relevant new findings on the formation of nitroso compounds by substitution processes have been reported. Reviews of special interest deal with the syntheses and properties of aliphatic fluoronitroso compounds,[2] nitrosoalkenes and nitrosoalkynes,[3] electrophilic *C*-nitroso compounds,[4] α-halonitroso compounds[5] and nitrosation mechanisms.[6]

Indirect replacement of the α-hydrogen atom of carboxylic esters by the nitroso group is remarkable.[7] This procedure uses ketene *O*-alkyl *O'*-silyl acetals (**1**), generated from carboxylic esters, which are treated with nitric oxide or isopentyl nitrite in the presence of titanium(IV) chloride. In the absence of an α-hydrogen α-nitroso esters (**2**) are obtained. α-Nitroso esters with an α-hydrogen undergo isomerization to oximes of α-keto esters (**3**; equation 1). Similarly, silyl enol ethers of aldehydes or ketones can be used instead of the carbonyl compound itself for nitrosation. Thus, treatment of enol ether (**4**) with nitrosyl chloride gives the α-nitroso aldehyde (**5**; equation 2),[8] which is quite stable at 0 °C, but dimerizes at room temperature.

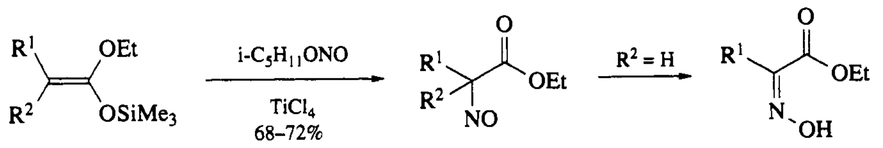

(1)

(**1**) $R^1$ = Me, Et, Ph; $R^2$ = Me, Ph (**2**) (**3**)

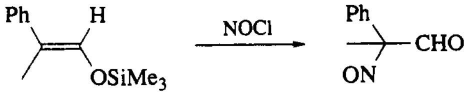

(2)

(**4**) (**5**)

## 1.4.2 NITRO COMPOUNDS

There are several general reviews of this area of chemistry.[9] This section covers mainly novel methods and improvements to established procedures for the preparation of nitro compounds which have been published within the last 10 years.

### 1.4.2.1 Aliphatic Nitro Compounds

### *1.4.2.1.1 Nitroalkanes*

Substitution of halogen by a nitro group is still one of the most important methods for the laboratory preparation of primary and secondary nitroalkanes. With sodium nitrite, solvents such as dimethylformamide and dimethyl sulfoxide are employed. For example, (*Z*)-1-nitrohex-3-ene (**7**) was prepared from (*Z*)-1-bromohex-3-ene (**6**; equation 3).[10] For the transformation of α-bromo esters into α-nitrocarboxylic esters the use of an anion-exchange resin in anhydrous benzene or ethanol has been recommended. With

(*R*)-ethyl 2-bromopropanoate (**8**) under these conditions the corresponding (*S*)-nitro ester (**9**) is formed with inversion of configuration (equation 4), but it racemizes during the reaction.[11] A short review of the preparation of chiral nitro compounds exists.[12]

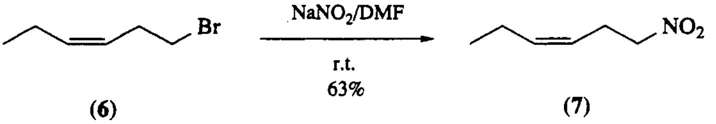

(3)

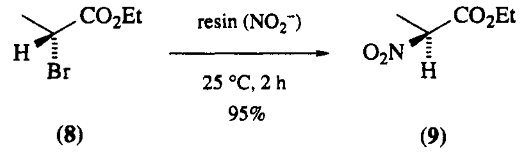

(4)

The condensation of dianions of ring-methoxylated phenylacetic acids like (**10**) with methyl nitrate provides a general, one-step procedure to the corresponding phenylnitromethane (**11**; equation 5).[13] Methods for the preparation of nitroacetic esters have been summarized.[14]

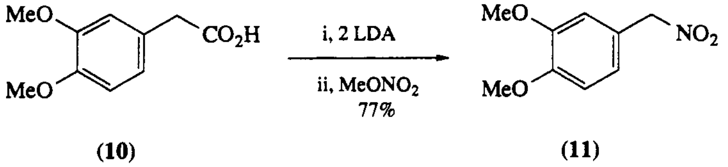

(5)

The alkyl nitrate nitration, a reaction of a nitrate ester in the presence of a base with active methylene compounds, enables the introduction of a nitro group at carbons in the α-position to the activating group. This reaction has been applied to a variety of active methylene compounds such as ketones, aliphatic carboxylic esters, amides, lactams, alkane sulfonate esters, activated toluenes and heterocyclic compounds.[15] The preparation of cyclic α-nitro ketones as well as the synthetic utility of these synthetic intermediates has been reviewed.[16] 2-Nitrocyclopentanone has been synthesized by three routes starting with cyclopentanone (**12**; Scheme 1).[17] Treatment of the potassium enolate of cyclopentanone with pentyl nitrate gives 2-nitrocyclopentanone (**13**) in 92% yield. An alternative route to 2-nitrocyclopentanone (**13**) in 87% yield is the nitration of 1-acetoxycyclopentene (**14**) with acetyl nitrate, generated *in situ* from nitric acid and acetic anhydride. Nitration of 1-trimethylsiloxycyclopentene (**15**) with nitronium tetrafluoroborate gives (**13**) in a yield of 41%. Enol ethers (**14**) and (**15**) can be obtained from cyclopentanone.

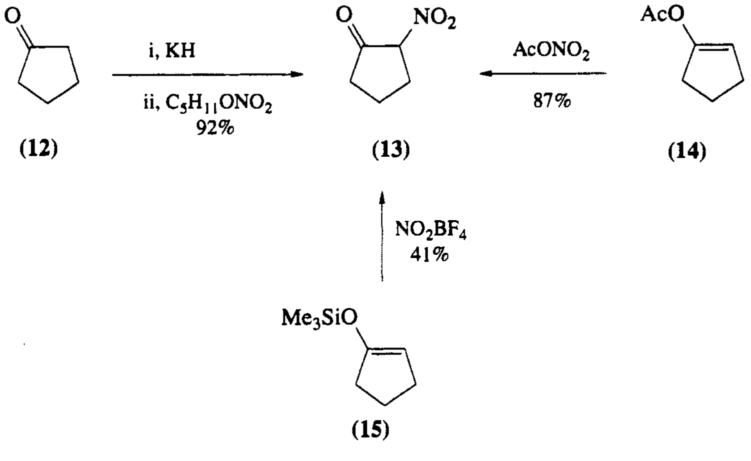

**Scheme 1**

Generating the enolates of substituted cyclic ketones by using potassium hydride leads to the thermodynamic mixture of enolates, and therefore nitration of potassium enolates often does not allow for a regiospecific synthesis of α-nitro ketones. For example, the potassium enolate of 3-methylcyclopentanone (**16**) gives three isomers in a ratio (**17**):(**18**):(**19**) = 2:1:1 (equation 6). On treatment of the potassium enolate of *cis*-3,4-dimethylcyclopentanone (**20**) with pentyl nitrate *trans*-2-nitro-*cis*-3,4-dimethylcyclopentanone (**21**) is formed diastereoselectively (equation 7).[18]

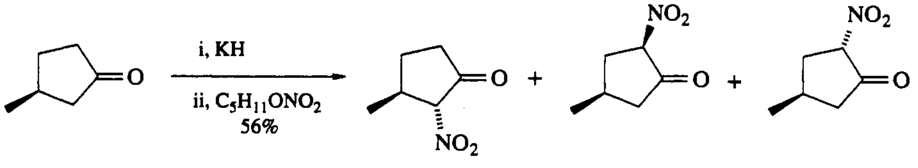

(6)

(**16**) (**17**) 50% (**18**) 25% (**19**) 25%

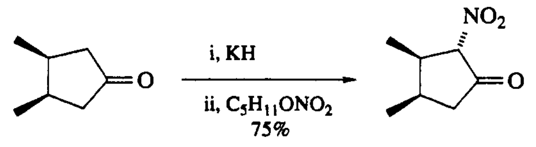

(7)

(**20**) (**21**)

The nitration of enol acetates with acetyl nitrate is a regiospecific electrophilic addition to the β-carbon of the enol acetate, followed by a hydrolytic conversion of the intermediate to the α-nitro ketone. With enol acetates of substituted cyclohexanones the stereochemistry is kinetically established. So, 1-acetoxy-4-methylcyclohexene (**22**) yields the thermodynamically less stable *trans*-4-methyl-2-nitrocylohexanone (**24**) in greater proportion (*cis*:*trans* = 40:60) (equation 8). This mixture can be equilibrated in favor of the thermodynamically more stable *cis* diastereomer (**23**) (*cis*:*trans* = 85:15). Nitration of 1-acetoxy-3-methylcyclohexene (**25**) leads to *trans*-3-methyl-2-nitrocyclohexanone (**26**), which is also the thermodynamically more stable isomer (equation 9).[19] No stereoselection occurs in the kinetically controlled nitration with acetyl nitrate of 1-acetoxy-5-methylcyclohexene (**27**; equation 10), but the 1:1 mixture of the 5-methyl-2-nitrocyclohexanones can be equilibrated in favor of the *trans* diastereomer (**28**) (*cis*:*trans* = 10:90). 2-Alkyl-2-nitrocyclohexanones cannot be prepared in acceptable yields by nitration of the corresponding enol acetates with acetyl nitrate.

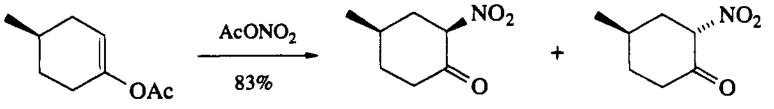

(8)

(**22**) (**23**) 40% (**24**) 60%

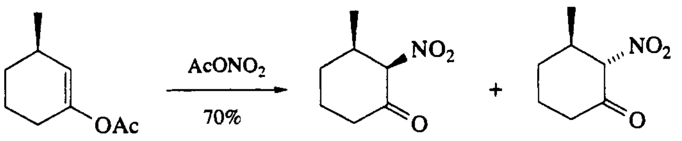

(9)

(**25**) <1% (**26**) >99%

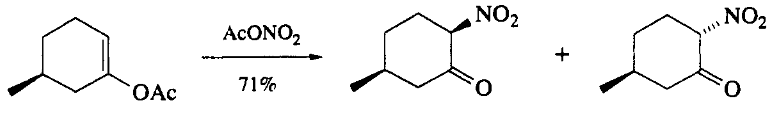

(10)

(**27**) 50% (**28**) 50%

It has been demonstrated that a mixture of ammonium nitrate and trifluoroacetic anhydride is a very effective system for the nitration of enol acetates. It is assumed that trifluoroacetyl nitrate is produced, which is a much more powerful nitrating agent than acetyl nitrate. So, 2-methyl-2-nitrocyclohexanone can be obtained from 2-methyl-1-acetoxycyclohexene in nearly quantitative yield. Also, the enol acetate of decalone (**29**) was quantitatively converted to *trans*-10-nitro-1-decalone (**30**; equation 11).[20]

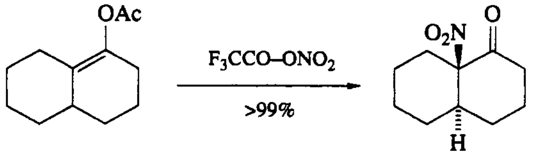

**(29)** **(30)**

(11)

Nitration of 2-methyl-1-(trimethylsiloxy)cyclohexene (**31**) with nitronium tetrafluoroborate leads to 2-methyl-2-nitrocyclohexanone (**32**; equation 12), while 6-methyl-1-(trimethylsiloxy)cyclohexene (**33**) gives under similar conditions a 30:70 mixture of *cis*- and *trans*-6-methyl-2-nitrocyclohexanone (equation 13).[21] The desilylative nitration of allylsilanes with nitronium tetrafluoroborate proceeds readily. The reaction is considered to pass through initial electrophilic attack of the nitronium ion on the allyl system followed by desilylative elimination. So, on treatment of 1-(trimethylsilyl)but-2-ene (**34**) with nitronium tetrafluoroborate the product is 3-nitrobut-1-ene (**35**) and not 1-nitrobut-2-ene (equation 14).[22]

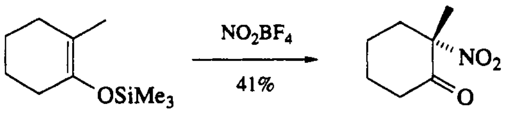

**(31)** **(32)**

(12)

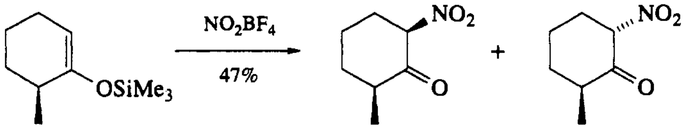

**(33)** 30% 70%

(13)

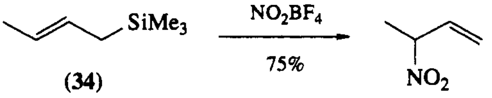

**(34)** **(35)**

(14)

The synthesis of polynitropolycyclic cage molecules has been reviewed.[23]

### *1.4.2.1.2 Conjugated nitroalkenes*

There are reviews dealing with conjugated nitroalkenes in organic synthesis,[24] nitroenamines,[25] the oxyalkylation of carbonyl compounds with conjugated nitroalkenes[26] and the use of conjugated nitroalkenes in the synthesis of heterocyclic compounds.[27] In this section mainly the preparation of nitroalkenes starting from alkenes is described.

In principle nitroalkenes should be available from direct nitration of vinyl carbanions. However, this reaction is not practical due to the potential anionic polymerization. But vinylstannanes obtained from ketones can be used instead of vinyl carbanions. Tetranitromethane is effective in replacing tin by nitro at unsaturated carbon. This method has been used to prepare several alkyl-substituted 1-nitrocyclohexenes and 1-nitrocycloheptenes (Scheme 2).[28]

Dinitrogen tetroxide addition to alkenes in the presence of oxygen leads to mixtures of *vic*-dinitro compounds, β-nitro nitrites and nitrates. Nitroalkenes may be prepared without isolation of the adducts by treating the mixture with basic reagents. 1-Nitrocyclooctene (**37**) can be obtained from cyclooctene (**36**) by this route (equation 15).[29] The same reaction sequence has been used for the regioselective and stereoselective preparation of (*E*)-2-nitroethenyltrimethylsilane (**38**; equation 16).[30] In the presence of iodine with alkenes and dinitrogen tetroxide β-nitroalkyl iodides are formed. These give 1-nitroalkenes

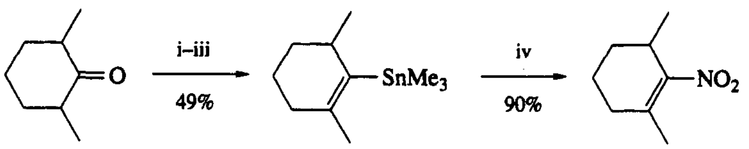
i–iii
49%
SnMe3
iv
90%
NO2

i, 2,4,6-triisopropylbenzenesulfonyl hydrazide; ii, Bu$^s$Li; iii, $Me_3SnCl$; iv, $C(NO_2)_4$

**Scheme 2**

on dehydrohalogenation. Thus, (*E*)-2-phenylbut-2-ene (**39**) yields (*Z*)-2-nitro-3-phenylbut-2-ene (**40**; equation 17),[31] and methyl acrylate yields methyl (*E*)-3-nitroacrylate.[32]

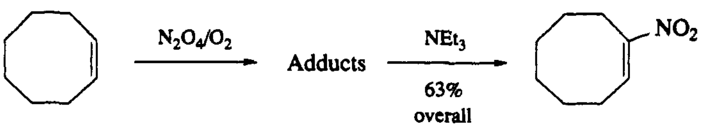
N2O4/O2
Adducts
NEt3
63%
overall
NO2

(15)

**(36)** **(37)**

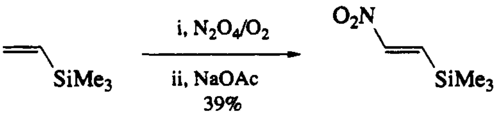
SiMe3
i, N2O4/O2
ii, NaOAc
39%
O2N
SiMe3

(16)

**(38)**

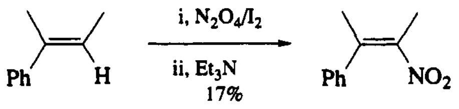
Ph
H
i, N2O4/I2
ii, Et3N
17%
Ph
NO2

(17)

**(39)** **(40)**

Nitryl iodide, generated *in situ* by reaction of silver nitrite with iodine, has been used for chemoselective nitration of substituted styrenes (equation 18).[33] Reaction of alkenes with sodium nitrite and iodine in the presence of ethylene glycol provides 1-nitroalkenes without using a base.[34] Nitrovinylsilanes have been prepared by addition of nitryl chloride to a vinylsilane followed by elimination of hydrogen chloride with base from the resulting chloronitrosilane (equation 19).[30,35] In a similar reaction sequence glycals could be transformed to 2-nitroglycals by treatment with nitronium tetrafluoroborate followed by elimination of hydrogen fluoride.[36]

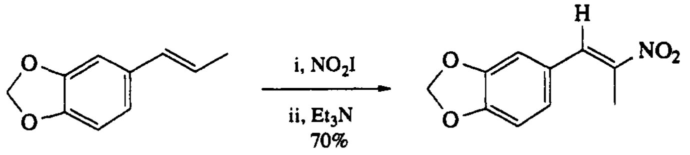
O
O
i, NO2I
ii, Et3N
70%
H
NO2
O
O

(18)

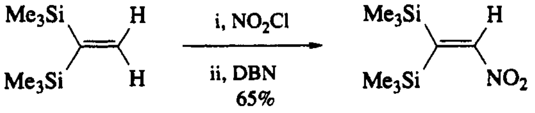
Me3Si
H
Me3Si
H
i, NO2Cl
ii, DBN
65%
Me3Si
H
Me3Si
NO2

(19)

Addition of mercury(II) nitrite, generated *in situ* from mercury(II) chloride and sodium nitrite, provides a general route to 1-nitroalkenes. Thus, on treatment with sodium hydroxide or a tertiary amine the adducts are converted into nitroalkenes in good yields. The clean formation of 2-nitronorbornene from norbornene indicates that carbonium ion rearrangement is not a problem. A further point of interest is the regioselectivity of nitromercuration, illustrated by the nitration of (**42**; Scheme 3).[37] The nitromercuration method has been used for the preparation of 3-nitrocycloalkenones[38] and (*E*)-2-nitroethenyltrimethylsilane.[7]

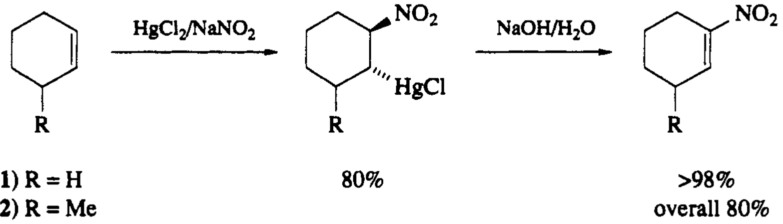

Scheme 3

Another route to conjugated nitroalkenes is based on nitroselenenylation of alkenes. Although the overall yield of nitroalkenes is slightly lower than for nitromercuration, the advantage of nitroselenenylation over nitromercuration is avoidance of aqueous media. Treatment of alkenes with benzene selenyl bromide followed by addition of silver nitrite provides a mixture of 2-nitroalkyl and 2-hydroxyalkyl phenyl selenides. The latter products can be suppressed by addition of mercury(II) chloride. The adducts are converted into conjugated nitroalkenes on oxidation with hydrogen peroxide.[39,40] By using (*E*)- and (*Z*)-oct-4-ene it has been established that the reaction is stereospecific (Scheme 4). Unsymmetrical alkenes give regioisomeric mixtures. Thus on addition, 1-hexene yields Markovnikov product and anti-Markovnikov product in the ratio 78:22.[40] In a similar reaction sequence trialkyl (2-nitro-1-alkenyl) silanes (nitrovinylsilanes) can be prepared starting from vinylsilanes (Scheme 5). In this case the regiochemistry of addition is controlled by the β-effect of the silyl group. This reaction is also stereoselective.[41]

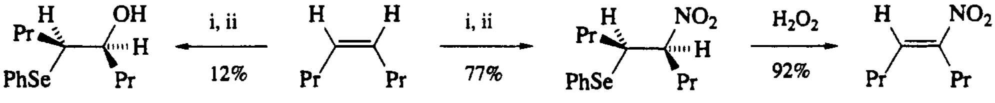

i, PhSeBr; ii, AgNO$_2$/HgCl$_2$

Scheme 4

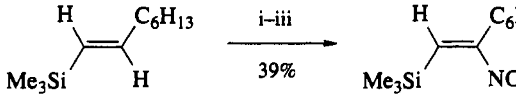

i, PhSeCl; ii, AgNO$_2$/HgCl$_2$; iii, H$_2$O$_2$

Scheme 5

A procedure for the efficient synthesis of 1-nitro-1,3-dienes in two steps involves the *in situ* preparation of trifluoroacetyl nitrate from ammonium nitrate and trifluoroacetic anhydride, and addition to 1,3-dienes to give mixtures of adducts. A mixture of the adducts on treatment with base eliminates to afford 1-nitro-1,3-diene. In the case of isoprene the reaction leads chemo-, regio- and stereo-selectively to (*E*)-2-methyl-1-nitrobuta-1,3-diene (**43**; Scheme 6). In contrast nitrotrifluoroacetoxylation of (*E*)-penta-1,3-diene followed by elimination gives an inseparable mixture of (*E*,*E*)-1-nitropenta-1,3-diene and (*E*)-4-nitropenta-1,3-diene (Scheme 6).[42] Similarly, ethyl vinyl ether has been transformed with acetyl nitrate to ethyl (*E*)-2-nitrovinyl ether.[43]

1-Nitro-2-(trialkylsilyl)alkynes can be synthesized by nitration of bis(trialkylsilyl)alkynes with nitronium tetrafluoroborate or nitronium hexafluorophosphate (equation 20), with nitryl fluoride addition across the triple bond as the major reaction.[44]

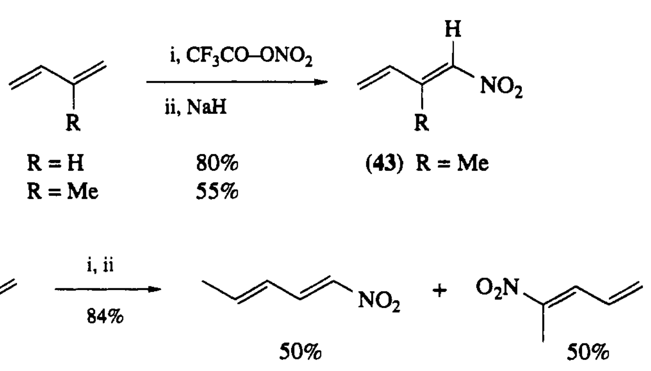

i, $CF_3CO–ONO_2$; ii, AcOK

**Scheme 6**

$$Pr^i_3Si{-}{\equiv}{-}SiMe_3 \xrightarrow[57\%]{NO_2PF_6} Pr^i_3Si{-}{\equiv}{-}NO_2 \qquad (20)$$

### 1.4.2.2 Aromatic Nitro Compounds

This field has been reviewed recently in a monograph.[45] For syntheses of vicinally substituted nitropyridines an extensive review is accessible.[46] In a recent monograph the preparation of nitroazoles has been discussed.[47] Introduction of a nitro group in an aromatic ring is usually carried out *via* electrophilic aromatic substitution using nitric acid, its metal salts, mixed anhydrides, nitrate esters or nitronium salts.[48–50] Most often these methods require subsequent aqueous work-up. In the case of alkylbenzenes this can be avoided by using a perfluorinated resinsulfonic acid (Nafion-H). So, a number of alkylbenzenes have been nitrated with *n*-butyl nitrate, acetone cyanohydrin nitrate or dinitrogen tetroxide over Nafion-H catalyst.[51]

Trifluoroacetic nitrate, prepared *in situ* from ammonium nitrate and trifluoroacetic anhydride, has been used for nitration of aromatic compounds at room temperature with high yields. While benzoic acid gives *m*-nitrobenzoic acid nearly quantitatively, nitrobenzene is not reactive under these conditions. Attack at the *ortho* position rather than the *para* position is observed with activated benzene derivatives like anisole. However, this system oxidizes phenols to quinoid products.[52]

The effect of crown ethers on the selectivity of nitration of aromatic hydrocarbons and anisole has been studied with a mixture of trifluoroacetic anhydride and tetrabutylammonium nitrate as nitration agent. The largest effects on selectivity have been observed with 21-crown-7, which causes *ortho–para*-directing groups to act essentially as *para*-directing groups.[53]

Phenols can be mononitrated in a two-phase system (ether/water) by sodium nitrate and aqueous hydrochloric acid in the presence of a catalytic amount of lanthanum(III) nitrate in yields generally above 80%. Phenol itself gives 2:1 *ortho:para* nitration, while phenols substituted in the *para* position give predominantly *ortho* nitration with some *meta* nitration (equation 21). As shown recently nitration of phenols in the two-phase system occurs even without lanthanum(III) nitrate. By use of sodium nitrate, aqueous sulfuric acid and a catalytic amount of sodium nitrite in the two-phase system mononitration of phenols can be achieved in high yields. Under these conditions starting from 3-substituted phenols in addition to the nitro compounds formation of quinones has been observed.[54,55] Polyhydroxy aromatics are typically difficult to nitrate directly. Thus, 4,6-dinitroresorcinol (**45**) has been synthesized from resorcinol diacetate (**44**) with nitric acid or mixed solutions of nitric acid/sulfuric acid containing urea as a nitrous trap (equation 22).[56]

A useful reagent for the regioselective nitration of aromatic amines is urea nitrate in sulfuric acid. *p*-Nitroanilines are formed exclusively. When the *para* position is blocked, nitration occurs to give the *m*-nitroaniline derivative.[57]

Silica gel supported cerium(IV) ammonium nitrate (CAN) has been employed for controlled nitration of some naphthalene derivatives. While treatment of hydroxynaphthalenes and polynuclear arenes with cerium(IV) ammonium nitrate absorbed on silica gel without a solvent affords mononitro derivatives, the reaction of the same substrates with cerium(IV) ammonium nitrate in solution affords a considerable per-

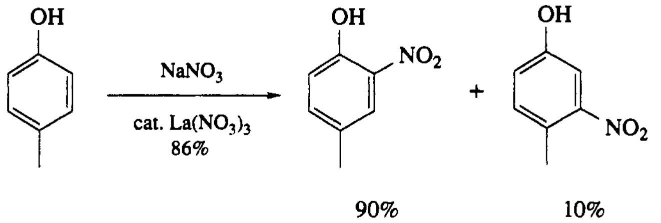

(21)

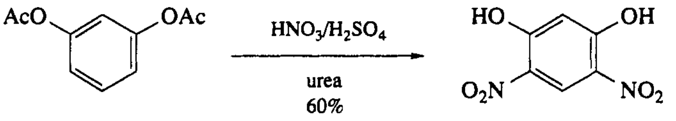

(44) (45)

(22)

centage of dinitro derivatives or quinones. Thus, 1-hydroxynaphthalene (**46**) is converted into a mixture of 4,6-dinitro- and 2,4-dinitro-2-hydroxynaphthalene, when treated with cerium(IV) ammonium nitrate in acetic acid, whereas the 2-nitro- and 4-nitro-naphthalene derivatives (**47**) and (**48**) are obtained when the same nitrating agent on silica gel is used. Under similar conditions 1-methoxynaphthalene (**49**) gives 1-methoxy-4-nitronaphthalene (**50**) exclusively (Scheme 7).[58]

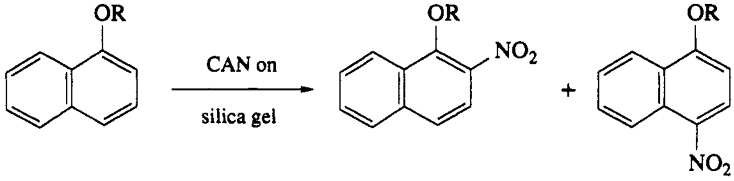

(**46**) R = H 80% (**47**) 53% (**48**) 47%
(**49**) R = Me 65% 0% (**50**) 65%

**Scheme 7**

Novel reagents consisting of metallic nitrates impregnated on montmorillonite have been introduced in aromatic nitration.[59] With clay-supported copper(II) nitrate in the presence of acetic anhydride it is possible to nitrate toluene quantitatively with a high *para* preference (79% *para*, 20% *ortho*, 1% *meta*).[60] Also, good *para* selectivities have been found on nitration of some other aromatic hydrocarbons with copper(II) nitrate on clay.[61] Halobenzenes are mononitrated with clay-supported copper(II) nitrate in the presence of acetic anhydride. Compared to other methods high *para:ortho* ratios are obtained under these conditions.[62]

When nitration of phenols is performed with clay-supported iron(III) nitrate at room temperature, exclusively *o*- and *p*-nitrophenols are formed. No *meta* nitration occurs. With *meta*-substituted phenols, one of the *ortho* positions is favored with respect to the other (Scheme 8).[63]

## 1.4.3 HYDROXYLAMINES

Methods for preparation of hydroxylamine derivatives have been reviewed in detail recently.[64] Here, mainly new developments concerning the synthesis of hydroxylamines by substitution processes with heterobond formation are presented. Reduction of nitro, nitroso, oxime and nitrone derivatives as well as direct oxidation of amines leading to hydroxylamine compounds will not be considered.

### 1.4.3.1 Carbon–Heteroatom Linkage with Nucleophilic Heteroatoms

Direct monoalkylation of hydroxylamine is usually not a good preparative method because of the problems with further alkylation on nitrogen. However, in a one-pot procedure hydroxylamine hydro-

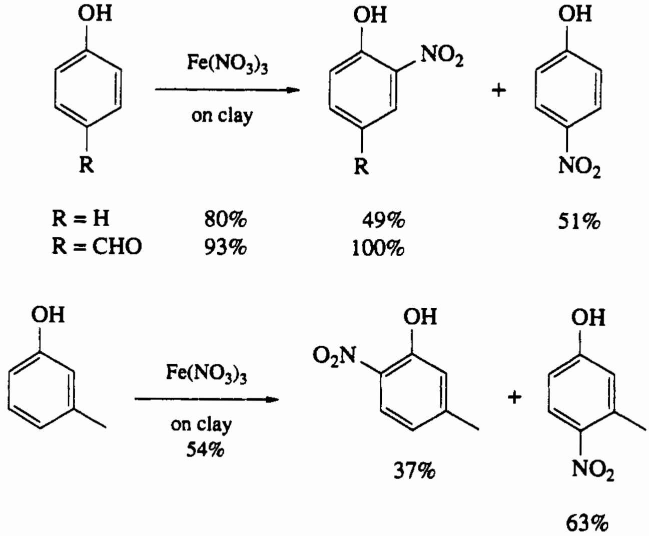
OH
Fe(NO3)3
on clay
OH
NO2
+
OH
R
R
NO2
R = H
R = CHO
80%
93%
49%
100%
51%
OH
Fe(NO3)3
on clay
54%
OH
O2N
+
OH
37%
NO2
63%

**Scheme 8**

chloride has been reacted with propargyl bromide followed by addition of 3-chloropropionyl chloride to give the hydroxamic acid derivative (**51**; Scheme 9).[65]

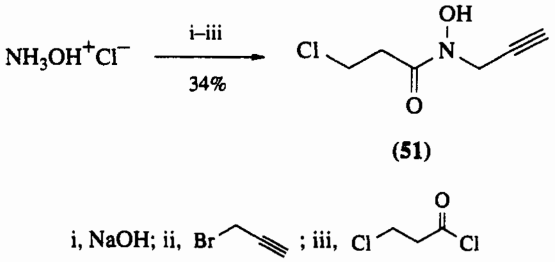
NH3OH+Cl−
i–iii
34%
Cl
OH
N
O
i, NaOH; ii, Br
; iii, Cl
O
Cl

**(51)**

**Scheme 9**

Although several methods have been reported, the synthesis of *N*-monoalkylhydroxylamines from alkyl halides or sulfonates has remained difficult. Relating to this a new preparation of *N*-alkylhydroxylamines is based upon *N*-alkylation of isoxazole derivative (**52**). Besides 2-propyl iodide several primary alkyl halides have been described as the alkylation agent in this procedure (equation 23).[66]

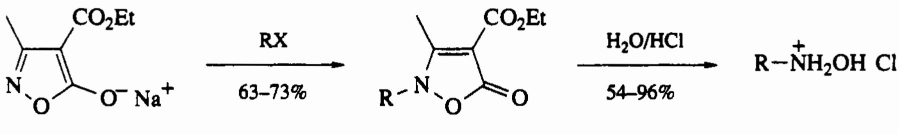
CO2Et
N
O
O− Na+
RX
63–73%
CO2Et
R
N
O
O
H2O/HCl
54–96%
R−NH2OH Cl−

(23)

**(52)**

On application of protecting groups it has to be considered that on deprotection with hydrogen, cleavage of the N—O bond can occur. Thus, the ε-hydroxynorleucine derivative (**53**) was subjected to Mitsunobu reaction with a protected hydroxylamine to yield the *N*-alkylated compound (**54**), but hydrogenolysis gave only lysine (**55**) instead of *N*-hydroxylysine (Scheme 10).[67] Alkylation of the carbamate (**57**), available from di-*t*-butyl dicarbonate (**56**) and *O*-benzylhydroxylamine, with a primary or secondary mesylate or iodide gives carbamates (**58**) in good yields. Similarly, *N*-benzyloxyureas (**61**) have been alkylated exclusively on the benzyloxy-substituted nitrogen to form (**62**). Acidolysis of (**58**) leads to alkylbenzyloxyamines (**59**). Deprotection of (**58**) and (**62**) can be achieved by catalytic transfer hydrogenolysis using ammonium formate and palladium on charcoal (Scheme 11).[68]

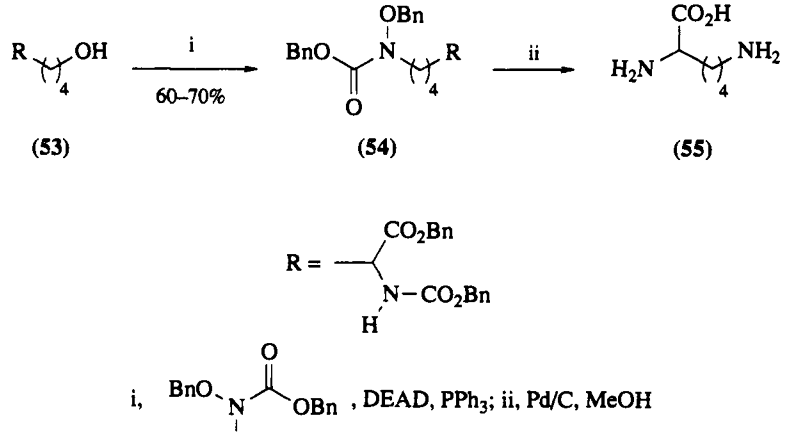
i
60–70%
ii
(53)
(54)
(55)
R =
i, , DEAD, PPh3; ii, Pd/C, MeOH

**Scheme 10**

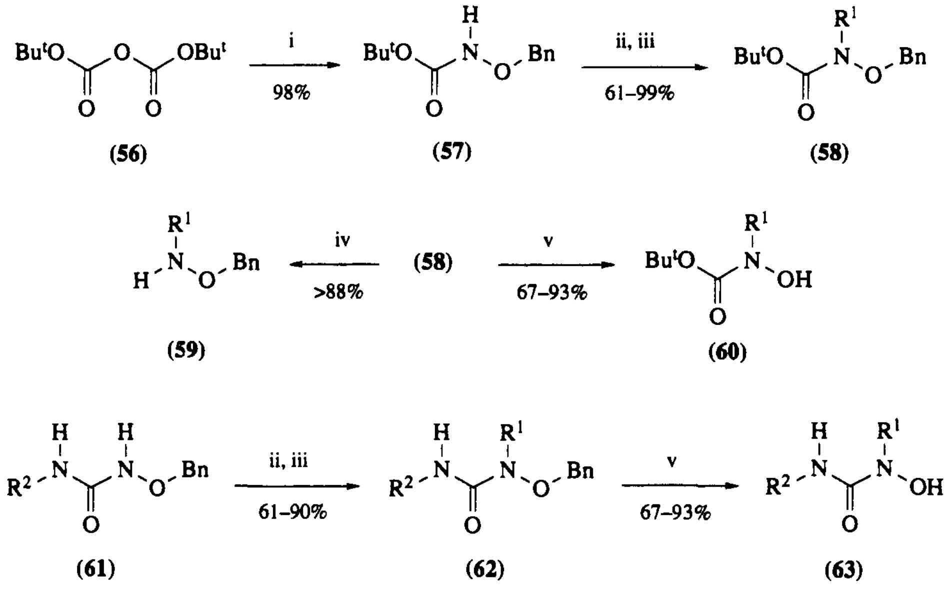
i
98%
ii, iii
61–99%
(56)
(57)
(58)
iv
>88%
v
67–93%
(59)
(60)
ii, iii
61–90%
v
67–93%
(61)
(62)
(63)

i, $H_2N$–OBn; ii, NaH/DMF; iii, $R^1X$; iv, $H^+$; v, ammonium formate, Pd/C

**Scheme 11**

The palladium(0)-catalyzed reaction of allyl esters with hydroxylamine and substituted hydoxylamines is a valuable route to *N*-allylhydroxylamines (equations 24 and 25). The absolute configuration of the products (equation 25) has not been proved. In other examples the regioselectivity of the reaction has been demonstrated.[69]

A number of syntheses of *N*-hydroxy-α-amino acids and derivatives thereof have been reported.[70] α-Bromocarboxylic acids or their *t*-butyl esters can be treated with hydroxylamine or *O*-alkylated hydroxylamines to give the corresponding hydroxylamine derivatives. *N*-Benzyloxy-L-alanine has been obtained by reaction of (*R*)-α-bromopropionic acid with *O*-benzylhydroxylamine. But due to bromide exchange the optical yield was low.[71] Anchimeric assistance of a suitable attached thio group can bring

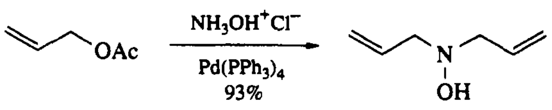
OAc
$NH_3OH^+Cl^-$
$Pd(PPh_3)_4$
93%
N
OH

(24)

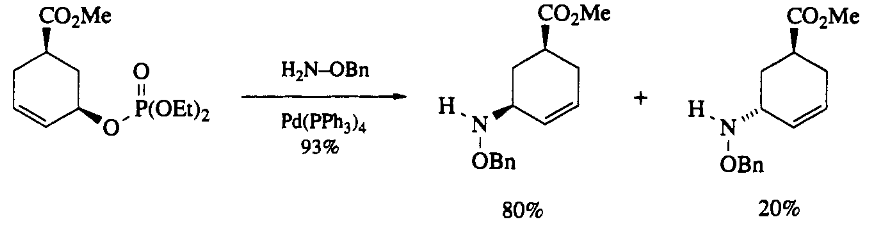

(25)

problems on reaction of α-bromocarboxylic esters with hydroxylamine.[72] By treating triflates of (*R*)- or (*S*)-α-hydroxy esters with *O*-benzylhydroxylamine *O*-benzyl-*N*-hydroxy-α-amino esters (**64**) can be prepared in good optical yields (Scheme 12).[73] The Mitsunobu reaction of aliphatic α-hydroxy esters with *N*-acylated *O*-benzylhydroxylamines provides a route to protected *N*-hydroxy-α-amino acids.[74] Treatment of α-halo ketones with hydroxylamine leads to α-hydroxylaminooximes.[75]

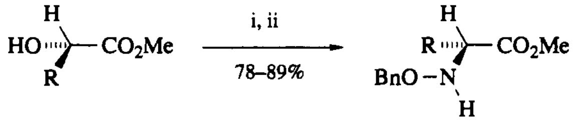

(**64**) 76–100% *ee*

i, $Tf_2O$; ii, BnO–$NH_2$

**Scheme 12**

Hydroxylamines usually react with acid chlorides to give mixtures of *N*-, *O*- and poly-acylated products. In contrast reaction of tris(trimethylsilyl)hydroxylamine (**65**) with aliphatic acid chlorides leads selectively under *N*-monoacylation to the corresponding hydroxamic acids (**66**; equation 26).[76] While diphenylphosphinic chloride (**68**) is attacked by the oxygen of hydroxylamine to yield *O*-(diphenylphosphinyl)hydroxylamine (**67**; Scheme 13), *N*-(diphenylphosphinyl)hydroxylamine (**69**) can be obtained by treatment of diphenylphosphinic chloride with *O*-trimethylsilylhydroxylamine followed by removal of the silyl blocking group (Scheme 13).[77] *O*-Acylation of arylhydroxylamines can be achieved with acyl cyanides.[78]

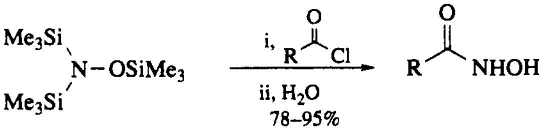

(26)

(**65**) (**66**)

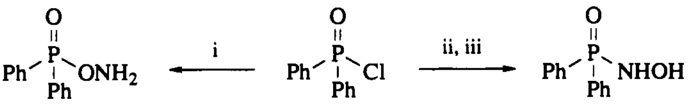

(**67**) (**68**) (**69**)

i, $NH_2OH$; ii, $NH_2OSiMe_3$; iii, MeOH

**Scheme 13**

The aromatic nucleophilic substitution on tricarbonyl(halogenoarene)chromium complexes with *N*-*t*-butyloxycarbonylhydroxylamine provides a convenient route to *O*-arylhydroxylamine derivatives (Scheme 14).[79]

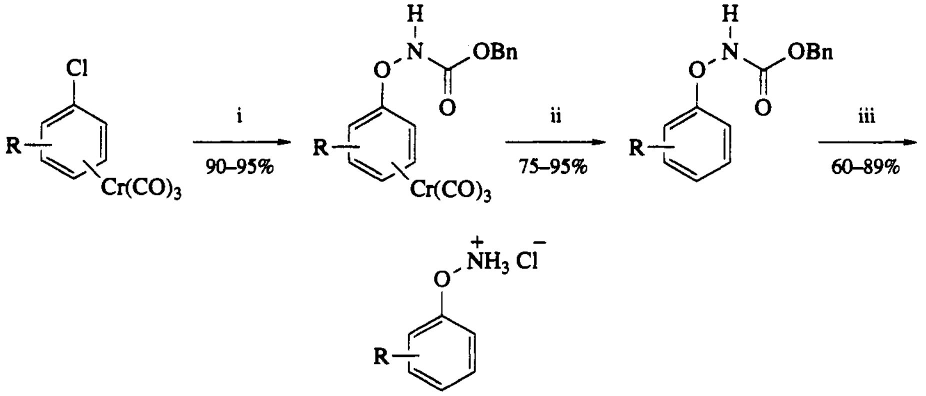

i, HONH–CO$_2$Bu$^t$, KOH; ii, I$_2$, 0 °C; iii, HCl

**Scheme 14**

### 1.4.3.2 Carbon–Nitrogen Linkage *via* Electrophilic Amination

Both inter- and intra-molecular ene reactions of acylnitroso compounds with alkenes provide *N*-alkylhydroxylamine derivatives. The regiochemistry observed is in agreement with C—N bond formation by electrophilic nitrogen ahead of abstraction of allylic hydrogen by nitroso oxygen. Thus, reaction of 1-methylcyclohexene (**70**) with *in situ* generated nitrosocarbonylmethane yields a single product (**71**; equation 27).[80] The chiral α-chloronitroso derivative (**72**) reacts with several alkenes regio- and diastereo-selectively to give nitrone hydrochlorides, which can be hydrolyzed to optically active allylic hydroxylamines (equation 28). The % *ee* values have not so far been determined.[81]

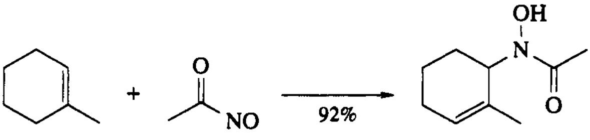

(27)

(**70**) (**71**)

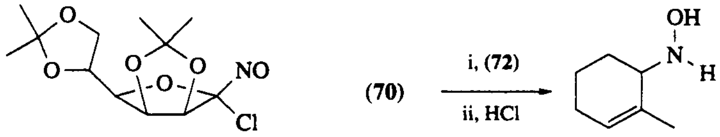

(28)

(**72**)

Bis(silyl)ketene acetals undergo silatropic ene reaction with nitrosobenzene to give *N*-hydroxyamino acid derivatives.[82] When allylmagnesium chloride is reacted with nitroarenes, unstable adducts result. Reduction of these adducts with LAH in the presence of palladium on charcoal leads to *N*-allyl-*N*-arylhydroxylamines (**73**; Scheme 15). With alkyl Grignard reagents this reaction is negligible.[83]

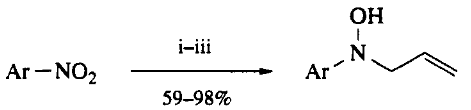

(**73**)

i, allylMgCl; ii, LAH; iii, NH$_4$Cl

**Scheme 15**

### 1.4.3.3 Nitrogen–Oxygen Linkage

A two-step procedure for the oxidation of amines to hydroxylamines involves nucleophilic displacement along the peroxide bond of dibenzoyl peroxide and saponification of the intermediate *O*-benzoylhydroxylamine. Primary and secondary amines have been oxidized in this way (equation 29).[84] Related reactions for transformation of amines to *O*-(arylsulfonyl)- and *O*-phosphinyl-hydroxylamines have been described by means of bis(arylsulfonyl)[85] and bis(diphenylphosphinyl) peroxide, respectively.[86,87]

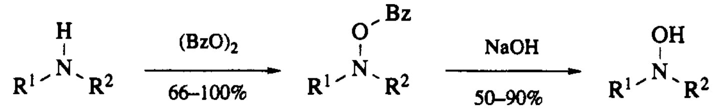

(29)

A method for the synthesis of optically active hydroxylamines from optically active primary amines with retention of configuration is based on the conversion of the amines to corresponding benzylimines followed by oxidation to 3-phenyloxaziridines (**74**). Subsequent hydrolysis leads to hydroxylamines (Scheme 16).[88] This sequence has been extended to the synthesis of optically active *N*-hydroxy-α-amino acid esters.[89]

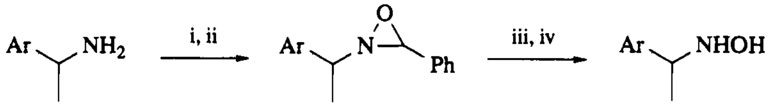

(**74**) overall 28–46%

i, PhCHO; ii, MCPBA; iii, $H_2SO_4$; iv, NaOH

**Scheme 16**

## 1.4.4 HYDRAZINO COMPOUNDS

A detailed review of the literature to 1967 is available, as well as several more recent reviews.[90]

### 1.4.4.1 Carbon–Nitrogen Linkage with Nucleophilic Nitrogen

Direct alkylation of hydrazine itself with halides and sulfates usually gives mixtures of mono- and poly-alkylated hydrazines. It is possible to get useful yields of the monoalkylhydrazine by using an excess of hydrazine. Several specific procedures leading to monoalkylhydrazines are based on selective alkylation of hydrazine derivatives with protecting groups attached. So, easily prepared acetone *N*-(diethoxyphosphoryl)hydrazone (**75**) can be used. Phase-transfer catalyzed *N*-alkylation of (**75**), followed by deprotection with *p*-toluenesulfonic acid provides monoalkylhydrazine sulfonates (**76**; Scheme 17).[91] Similarly, *N*-alkyl-*N*-arylhydrazines have been prepared by phase-transfer catalyzed *N*-alkylation of arylhydrazones (Scheme 18).[92] An efficient, one-pot method for the synthesis of a variety of polysilylated hydrazines employs hexamethyldisilane (equation 30).[93] Polysilylated hydrazines were found to react with aldehydes or ketones to give hydrazones under anhydrous conditions. By treatment with triphenylphosphine and diethyl azodicarboxylate primary and secondary alcohols can be converted to hydrazine derivatives (equation 31).[94]

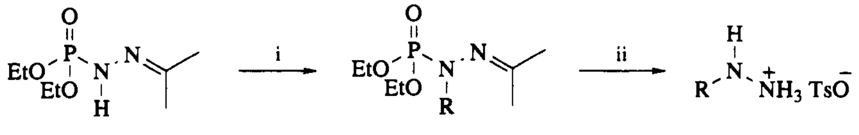

(**75**) overall 47–77% (**76**)

i, RBr, NaOH, $Bu^n{}_4N^+HSO_4^-$ (0.1 equiv.); ii, TsOH, EtOH

**Scheme 17**

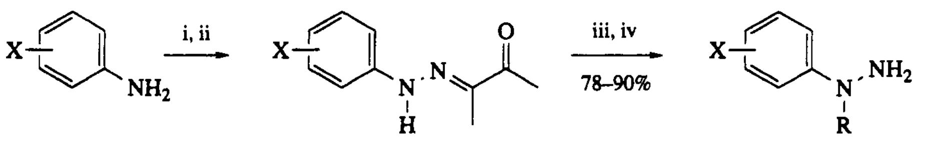
X
NH2
i, ii
X
N
N
H
O
iii, iv
78–90%
X
N
NH2
R

i, $NaNO_2$, HCl; ii, MeCOCHMeCOMe; iii, RBr, NaOH, $BnEt_3N^+Cl^-$; iv, $N_2H_4$

**Scheme 18**

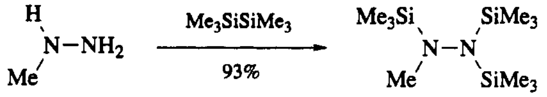
H
N−NH2
Me
Me3SiSiMe3
93%
Me3Si
SiMe3
N−N
Me
SiMe3

(30)

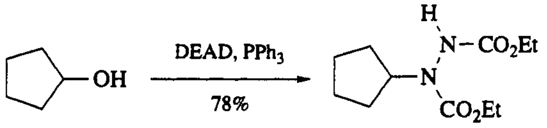
OH
DEAD, PPh3
78%
H
N−CO2Et
N
CO2Et

(31)

Bidentate alkylating agents may react with hydrazines at both nitrogens to close a ring, if the ring size is suitable. If hydrazine itself is used, further alkylation under formation of a second ring to tetrasubstituted hydrazine derivatives sometimes occurs. In these cases a better procedure is to take an azodicarboxylate derivative and remove the protecting group after alkylation.[95]

Alkylation of hydrazine with α,β-unsaturated carbonyl derivatives or carbonyl derivatives with a leaving group in the β-position provides pyrazole derivatives. For example, treatment of the tosylate (**77**), obtained from L-serine, with anhydrous hydrazine gives racemic pyrazolidinone (**78**). It appears that pyrazolidinone (**78**) or one of the intermediates suffers base-catalyzed racemization (equation 32).[96] Starting from β-lactam (**79**) seven-membered cyclic hydrazine (**80**) has been formed by ring closure in an unusually high (84%) yield (equation 33).[97] Reaction of (π-allyl)palladium complex (**81**) with dimethylhydrazine produces exocyclic diene (**82**) in a modest (29%) yield, but this is still more efficient than the reaction of 2,3-bis(chloromethyl)butadiene (**83**) with dimethylhydrazine (equation 34).[98]

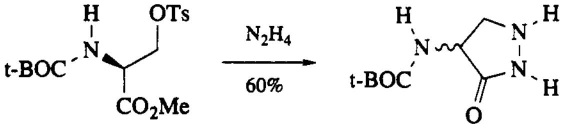
H
OTs
N
t-BOC
CO2Me
N2H4
60%
H
N
t-BOC
N
H
N
H
O

(**77**) (**78**)

(32)

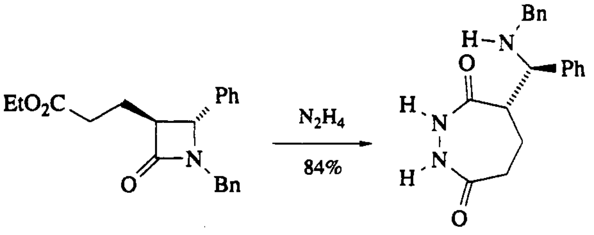
EtO2C
Ph
N
Bn
O
N2H4
84%
Bn
H−N
O
Ph
H
N
N
H
O

(**79**) (**80**)

(33)

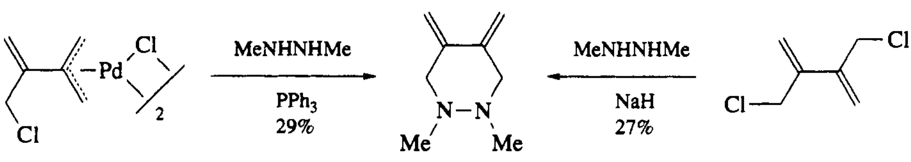
Cl
−Pd
2
Cl
MeNHNHMe
PPh3
29%
N−N
Me
Me
MeNHNHMe
NaH
27%
Cl
Cl

(**81**) (**82**) (**83**)

(34)

### 1.4.4.2 Carbon–Nitrogen Linkage *via* Electrophilic Amination

Azodicarboxylate esters are the reagents of choice for electrophilic *N*-amino amination leading to hydrazine derivatives. Besides Grignard reagents[99] and alkyl or aryl lithium compounds,[100] enolates[101] and silyl enol ethers[102] derived from ketones have been aminated by this method. In particular, di-*t*-butyl azodicarboxylate has been reacted with a variety of chiral enolates (Scheme 19)[103,104] and chiral silyl ketene acetals (Schemes 20 and 21)[105,106] to afford α-hydrazino acid derivatives with high diastereoselectivities in good chemical yields. By the same method α-hydrazino-β-hydroxy esters (**84**) with % *ee* values up to 75% have been obtained from α-hydroxy esters (Scheme 22).[107] An even higher stereoselection results by using dioxanone (**85**) instead of the acyclic β-hydroxy ester (Scheme 23).[108]

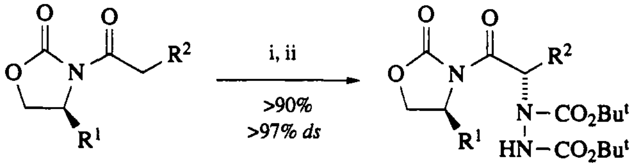
O
O
O
N
$R^2$
$R^1$
i, ii
>90%
>97% *ds*
O
O
O
N
$R^2$
$R^1$
$N-CO_2Bu^t$
$HN-CO_2Bu^t$

$R^1$ = Bn, $Pr^i$

i, LDA; ii, $(Bu^tO_2CN)_2$

**Scheme 19**

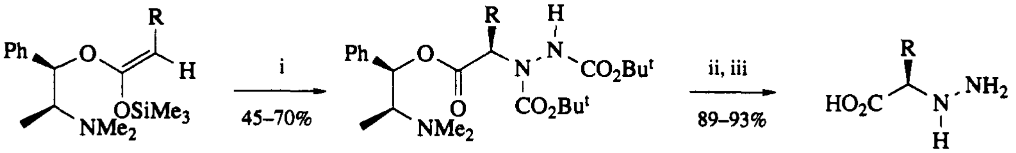
R
Ph
O
H
$OSiMe_3$
$NMe_2$
i
45–70%
R
H
Ph
O
N
N
$CO_2Bu^t$
O
$CO_2Bu^t$
$NMe_2$
ii, iii
89–93%
R
$HO_2C$
N
$NH_2$
H

i, $(Bu^tO_2CN)_2$, $TiCl_4$; ii, TFA; iii, LiOH

78–91% *ee*

**Scheme 20**

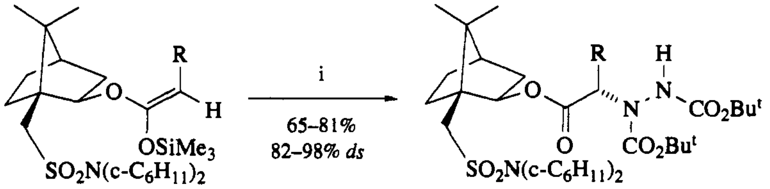
R
O
H
$OSiMe_3$
$SO_2N(c\text{-}C_6H_{11})_2$
i
65–81%
82–98% *ds*
R
H
O
N
N
$CO_2Bu^t$
O
$CO_2Bu^t$
$SO_2N(c\text{-}C_6H_{11})_2$

i, $(Bu^tO_2CN)_2$, $TiCl_4$, $Ti(OPr^i)_4$

**Scheme 21**

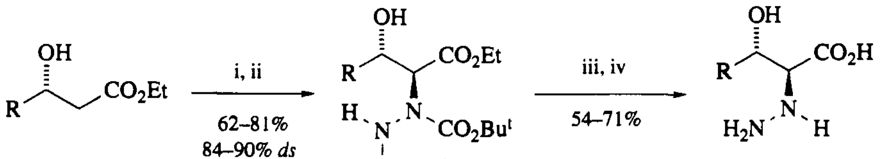
OH
R
$CO_2Et$
i, ii
62–81%
84–90% *ds*
OH
R
$CO_2Et$
H
N
N
$CO_2Bu^t$
$CO_2Bu^t$
iii, iv
54–71%
OH
R
$CO_2H$
$H_2N$
N
H

**(84)**

i, LDA; ii, $(Bu^tO_2CN)_2$; iii, TFA; iv, LiOH

**Scheme 22**

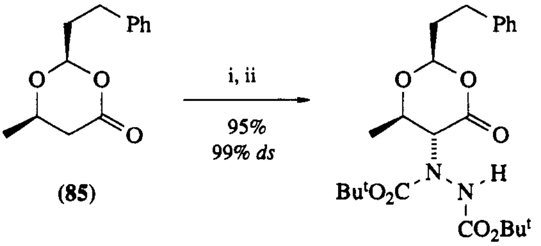

i, LDA; ii, $(Bu^tO_2CN)_2$

Scheme 23

### 1.4.4.3 Nitrogen–Nitrogen Linkage

A widely used method for preparing *N*,*N*-disubstituted hydrazines is the reduction of *N*-nitrosoamines obtained by nitrosation of secondary amines. There are several methods for effecting this reduction based on dissolving metals, low-valent titanium reagents,[109] hydride reagents and catalytic reduction with hydrogen. For example, several chiral auxiliaries derived from (*S*)-proline have been synthesized by reduction of the corresponding *N*-nitrosoamine (Scheme 24).[110] But *N*-nitrosoamines are carcinogenic intermediates. Therefore, an alternative route to (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine ('SAMP' and 'RAMP') (**86**; R = H) has been described. This procedure involves treatment of the urea (**87**) or its enantiomer, obtained from (*S*)- or (*R*)-proline, with potassium hypochlorite followed by elimination of hydrogen chloride with potassium hydroxide (Scheme 24). Yields based on proline range from 50 to 58%.[111]

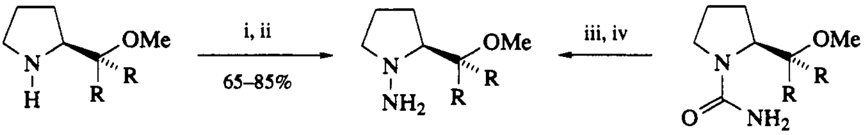

**(86)** **(87)**

i, Bu$^t$ONO; ii, LAH; iii, KOCl; iv, KOH

Scheme 24

Electrophilic *N*-aminations have been performed with hydroxylamine-*O*-sulfonic acid (HOSA),[112] *O*-(2,4-dinitrophenyl)hydroxylamine and *O*-mesitylenesulfonylhydroxylamine. The use of HOSA is mainly restricted to aqueous reaction media. Imide sodium salts of some heterocycles such as theobromine (**88**) can be converted to hydrazine derivatives by treatment with *O*-(diphenylphosphinyl)hydroxylamine (equation 35).[113] This reaction has been extended to synthesis of *N*-arylhydrazines, where R$^2$ and R$^3$ are hydrogen, alkyl or aryl (equation 36).[114] Similarly, trisubstituted hydrazines can be prepared by the use of *N*-aryl-*O*-acetylhydroxylamines and secondary amines.[115] A recent publication[116] concerning the synthesis of 1-acyl-2-alkylhydrazines from hydroxamic acids and amines in the presence of activating agents has been found to be erroneous; no N—N bond formation occurs under these conditions.[117]

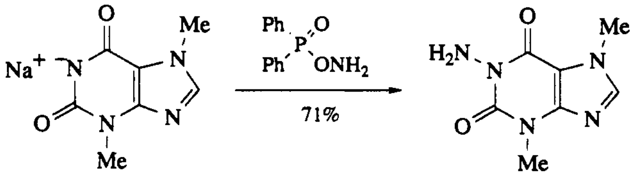

**(88)**

(35)

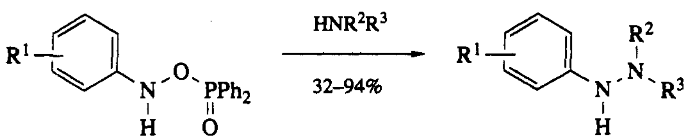
(36)

## 1.4.5 PREPARATION OF DIAZOALKANES

### 1.4.5.1 Properties of Diazoalkanes

The synthesis and properties of diazo compounds have been covered in an excellent review by Regitz and Maas.[118] This section does not attempt to duplicate that review. Rather, two key areas are covered: the most practical methods for the preparation of diazo-containing compounds, and use of these intermediates in organic synthesis. To understand these areas, however, it is important first to appreciate the structure, bonding and reactivity of the diazo functional group.

One model for bonding in a diazo compound would be the ylide (**89**; equation 37).[119] Unlike many other ylides, diazoalkanes are stable to air and water. With acid, however, protonation can lead to the highly reactive salt (**90**), the functional equivalent of the corresponding carbocation. As the substituents on the diazo group are made increasingly electron withdrawing, the ylide becomes less basic, and thus more stable to acid. Reaction of a diazo compound with a transition metal can also often be understood as proceeding *via* initial donation of electron density by (**89**) to a coordinatively unsaturated metal center.

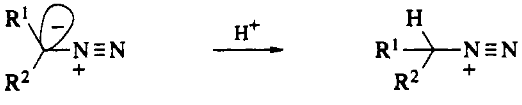
(**89**) (**90**) (37)

The diazo compound can alternatively be viewed as a coordination complex (**91**) between a carbene and $N_2$ (equation 38).[119] The coordination is weak, so any input of energy, either *via* heating or UV radiation, can lead to $N_2$ loss, liberation of the free carbene and subsequent reaction.

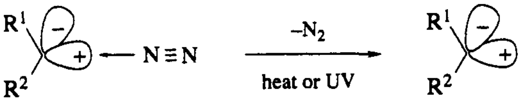
(**91**) (**92**) (38)

It should be remembered that many diazo compounds, especially those having electron-withdrawing groups, are quite stable. Ethyl diazoacetate, for instance, can be stored for years. As methods for the preparation of diazo compounds improve, they will become increasingly important in organic synthesis.

### 1.4.5.2 Diazomethane

The best known and most widely used diazoalkane is diazomethane (**95**; equation 39). Preparative methods for diazomethane involve, in general, the nitrosation of a methylamine derivative (**93**), followed by cleavage under alkaline conditions. Methylamine derivatives used have included the urethanes,[120] ureas,[121] carboxamides,[122] sulfonamides,[123] guanidines[124] and even the methylamine adducts of unsaturated ketones[125] and sulfones.[126] *N*-nitroso-*N*-methyl *p*-toluenesulfonamide (Diazald, Aldrich) is currently the most commonly used diazomethane precursor. Diazomethane is both toxic and explosive. Although in the past it has been purified by codistillation with ether, it is now usually generated, stored and used as an ether solution without distillation.

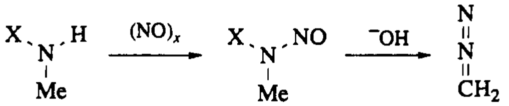

(39)

**(93)** **(94)** **(95)**

### 1.4.5.3 Trimethylsilyldiazomethane

Trimethylsilyldiazomethane (**96**), prepared in excellent yield from chloromethyltrimethylsilane,[127] is now commercially available (Petrarch). Trimethylsilyldiazomethane is readily lithiated and alkylated (equation 40).[128] Synthetic applications of the resultant silyldiazoalkanes (**97**) have not yet been extensively explored. These might, for instance, react smoothly with acid chlorides to give diazoketones (see Section 1.4.6.1).

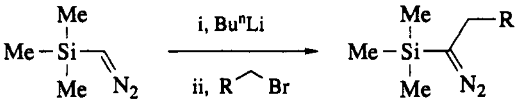

(40)

**(96)** **(97)**

### 1.4.5.4 Higher Diazoalkanes

The synthetic methods outlined above for diazomethane work well, in general, for the higher diazoalkanes. Again, these are usually generated and handled as solutions in diethyl ether. In the special case of the conversion of the amine (**98**) to diazoalkane (**100**), the urethane approach proved most effective (equation 41).[129]

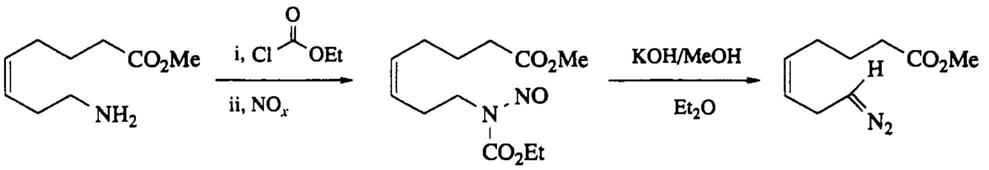

(41)

**(98)** **(99)** **(100)**

The *N*-nitrosation reaction works well for a variety of amine derivatives.[130] The substance to be nitrosated is dissolved in an inert solvent ($CCl_4$ has classically been used, but diethyl ether works just as well) in which anhydrous potassium acetate has been suspended. The brown vapor generated by addition of concentrated sulfuric acid to sodium nitrite (in a separate flask) is then blown through with a gentle stream of nitrogen. Formation of the *N*-nitroso derivative (**99**) is conveniently monitored by TLC. It is usually complete in 1–2 h.

The hydrolysis of (**99**) to diazoalkane (**100**) is a little tricky, since the methyl ester is also subject to saponification. It was found that addition of 4 equiv. of methanol to the 50% KOH/ether mixture, stirred rapidly in an ice–water bath, followed by addition of (**99**), gave optimal yields (30–40%) of (**100**).[129] The reaction mixture must be kept at ice temperature, as warming leads to emulsification and yield loss.

### 1.4.5.5 Aryldiazoalkanes

Aryldiazoalkanes are readily prepared by exposure of the arenesulfonylhydrazone to base (Bamford–Stevens reaction).[131] On addition of sodium methoxide, for instance, to a suspension of 1-naphthaldehyde tosylhydrazone (**101**) in methanol, the solid dissolves, and the solution turns red (equation 42).[132] The diazoalkane (**102**) can be isolated, as a pink-red solid, by dilution with water, extraction with pentane, drying ($Na_2SO_4$) and vacuum concentration. Naphthyldiazomethane reacts readily with acids to give the corresponding esters, which have the advantage, for chromatographic purification or analysis, of being UV-absorbing. An aryldiazoalkane can also be easily prepared by $MnO_2$ oxidation of the hydrazone of the corresponding ketone or aldehyde.[133]

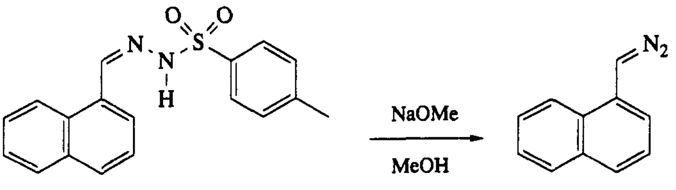

(101) (102) (42)

### 1.4.5.6 Quinone Diazides

Quinone diazides such as **(104)** are readily prepared by nitrosation of 4-aminophenols.[134] On photolysis, **(104)** smoothly cyclizes to **(105)**, a model for the antitumor antibiotic CC-1065 (equation 43).[135]

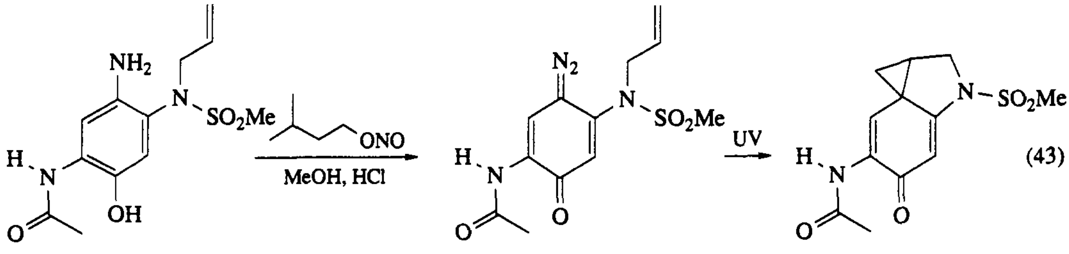

(103) (104) (105) (43)

## 1.4.6 PREPARATION OF α-DIAZO KETONES AND ESTERS

It has not been fully appreciated that α-diazo ketones and esters are easily purified and are quite stable. In the past, such derivatives have been primarily expensive research intermediates. Now, with much better methods available for their preparation, these simple stabilized ylides deserve serious consideration as synthetic intermediates, even on an industrial scale.

### 1.4.6.1 Acyclic α-Diazo Ketones

#### *1.4.6.1.1 From α-amino ketones*

Acylated or sulfonylated α-amino ketones such as **(106)** are smoothly converted *via N*-nitrosation to the corresponding α-diazo ketones (**107**; equation 44).[136] A limitation to this approach has been the difficulty of preparing precursors such as **(106)**, especially given the instability of the precursor α-amino ketones. A recent report that an azide is smoothly converted to the corresponding carboxamide on exposure to triethylphosphine and a carboxylic acid might nicely sidestep this difficulty.[137]

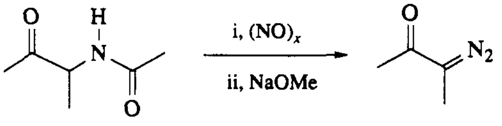

(106) (107) (44)

#### *1.4.6.1.2 From diazoalkanes*

A diazoalkane **(108)** will couple smoothly with an acid chloride or a mixed anhydride to give the corresponding α-diazo ketone (**109**; equation 45).[138] A limitation on this approach is the difficulty of preparing and handling the requisite diazoalkanes (Section 1.4.5.4). Unlike the diazoalkanes, the product α-diazo ketones are stable to silica gel chromatography, and are readily purified.

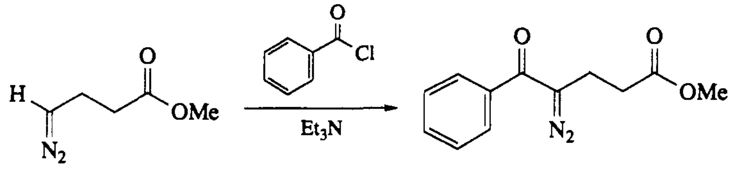

**(108)** **(109)** (45)

### *1.4.6.1.3 By diazo transfer/cyclization*

Diazo transfer from a sulfonyl azide is well known as a method for the preparation of α-diazo active methylene compounds (see Section 1.4.6.4). Application of this method to an α-alkylated 1,3-diketone leads, *via* fragmentation, to the simple α-diazo ketone. As illustrated for (**112**; Scheme 25) fragmentation can be highly chemoselective, so an unsymmetrical diketone can give a single product. The dianion alkylation approach outlined in Scheme 25 is currently the method of choice for preparing practical quantities of simple α-diazo ketones.[139] It should be noted that the sequence dianion alkylation/diazo transfer is most efficiently carried out in the same reaction vessel. A diazomethyl ketone (**115**) can also be prepared by diazo transfer. Thus, formylation of a methyl ketone (**114**) is usually highly regioselective (equation 46). Addition of a sulfonyl azide to the formylation mixture gives directly the diazomethyl ketone.[140]

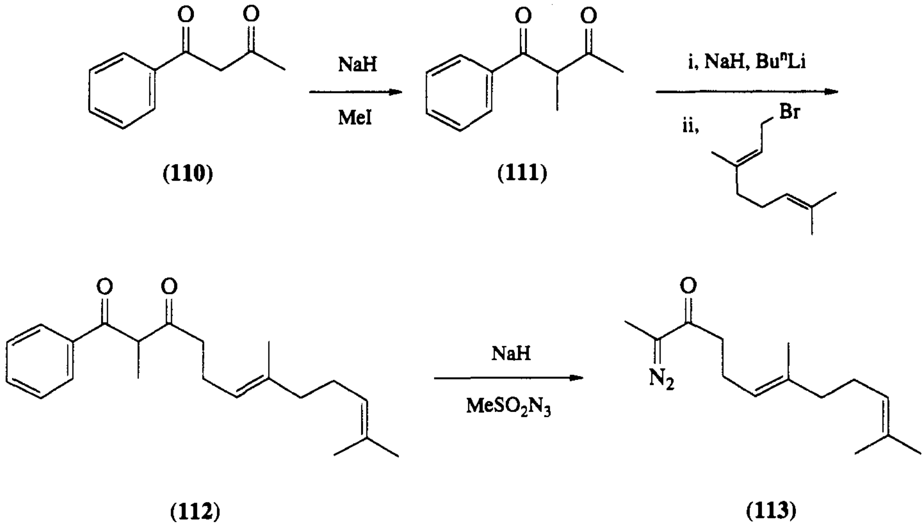

**Scheme 25**

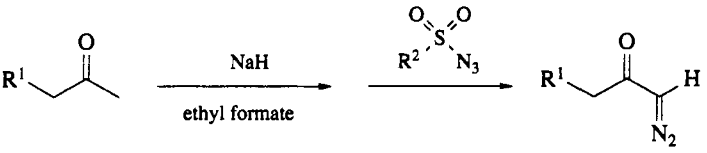

**(114)** **(115)** (46)

## 1.4.6.2 Cyclic α-Diazo Ketones

Usually, a cyclic α-diazo ketone such as (**117**) is prepared by formylation/diazo transfer (equation 47).[141] Such diazo ketones can also be prepared by phase transfer reaction of the parent ketone with

2,4,6-triisopropylbenzenesulfonyl azide, as illustrated for the conversion of (**118**) to (**119**) (equation 48).[142]

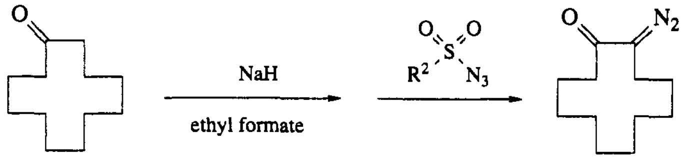

(**116**) (**117**) (47)

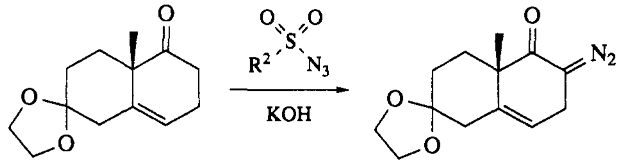

(**118**) (**119**) (48)

### 1.4.6.3 α-Diazo Esters

#### *1.4.6.3.1 Esters of diazoacetic acid*

Two strategies have been developed for the preparation of esters of diazoacetic acid. If the alcohol is inexpensive, it is first converted (diketene) into the corresponding acetoacetate (**120**; equation 49). Diazo transfer with subsequent deacylation then yields the diazoacetate (**121**).[143] If the alcohol is particularly valuable or sensitive, it may alternatively be esterified with a more direct precursor to diazoacetate. One reagent that has been used for this purpose is glyoxalic acid 2,4,6-triisopropylbenzenesulfonylhydrazone (TIPPS) (**123**; equation 50). Esterification of the alcohol (**122**) with (**123**), using dicyclohexylcarbodiimide followed by addition of 4-dimethylaminopyridine, gives the diazoacetate (**124**).[144]

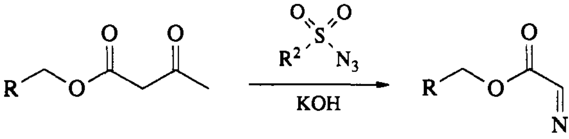

(**120**) (**121**) (49)

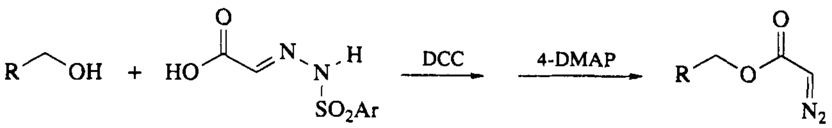

(**122**) (**123**) (**124**) (50)

#### *1.4.6.3.2 Higher α-diazo esters*

As with diazo ketones, an α-diazo ester (**126**) can be prepared by nitrosation of the corresponding α-amino acid (**125**) or a derivative (equation 51).[145] Alternatively, an α-diazo ester (**128**) can be prepared by diazo transfer to an alkylated acetoacetate (**127**), with concomitant deacylation (equation 52).[139]

To prepare an α-diazo ester from the ester (**129**) itself, formylation is effective. Alternatively, it has been reported that trifluoroacetylation of an ester proceeds smoothly (equation 53).[146] The trifluoromethylacetoacetate (**130**) would be expected to react directly with methanesulfonyl azide and sodium hydride to give the α-diazo ester.

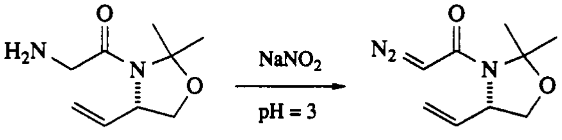

(125) (126)

(51)

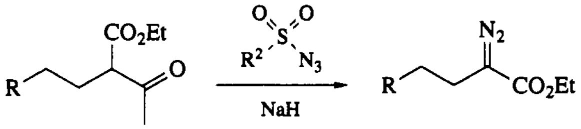

(127) (128)

(52)

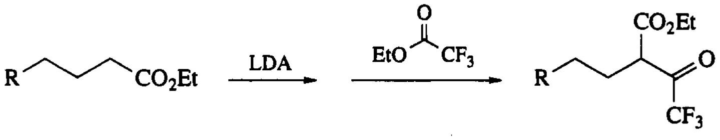

(129) (130)

(53)

## 1.4.6.4 Diazo Transfer to Active Methylene Compounds

### *1.4.6.4.1 Diazo transfer to β-keto esters*

The original Regitz procedure for diazo transfer to a β-keto ester (**131**) used *p*-toluenesulfonyl azide (**132**; equation 54).[143] This reagent works well, and is easy to prepare from the corresponding sulfonyl chloride. A disadvantage of this reagent is that the *p*-toluenesulfonylamide coproduct (**134**), as well as any excess *p*-toluenesulfonyl azide, have to be removed from the product diazo ketone (**133**) before it can be used.

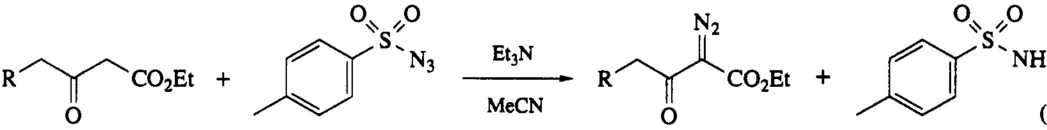

(54)

(131) (132) (133) (134)

Several alternative sulfonyl azides have been used. Hendrickson introduced *p*-carboxybenzenesulfonyl azide (**135**).[147] Both the coproduced sulfonamide and any excess reagent are readily extractable by aqueous base, so product clean-up is easy. One limitation is that the starting sulfonyl chloride is somewhat expensive. Methanesulfonyl azide is much less expensive, yet still offers the same advantage, that the coproduced sulfonamide and excess reagent are readily removed by extraction with aqueous base.[141] Caution is, however, warranted, since methanesulfonyl azide is potentially explosive. Finally, advantage can be taken of the particular product being prepared. In the Merck thienamycin process, for instance, a lipophilic arenesulfonyl azide (**137**) is used. The product diazo ketone, a polar, highly crystalline β-lactam, is easily separated from this reagent and its coproducts.[148]

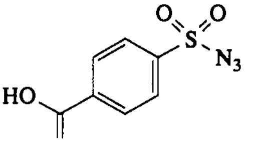

(135)

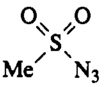

(136)

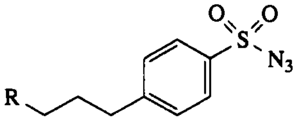

(137)

#### *1.4.6.4.2 Diazo transfer to other active methylene compounds*

Malonate esters and vinylogous malonates,[149] as well as 1,3-diketones, readily undergo diazo transfer. In addition, the less acidic β-keto phosphonates (**138**; equation 55)[150] and β-keto sulfones (**140**; equation 56)[151] have been shown to participate in this reaction.

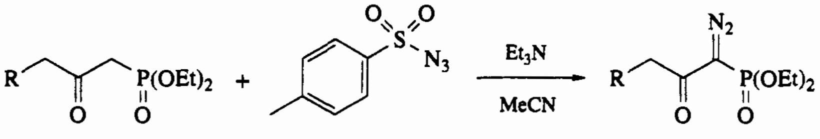

(55)

**(138)** **(139)**

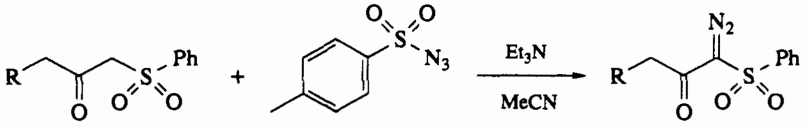

(56)

**(140)** **(141)**

## 1.4.7 SYNTHETIC APPLICATIONS OF DIAZO COMPOUNDS

Many of the reactions of diazo compounds are covered in detail elsewhere in these volumes. The attempt made here is to briefly highlight the diverse reactivity of the diazo functional group.

### 1.4.7.1 Dipolar Cycloaddition

Diazoalkanes undergo smooth 1,3-dipolar cycloaddition. For additions to simple alkenes, this is presumably an electrophilic process. In the example illustrated, the overall process of electrocyclization of (**142**) followed by hydride shift proceeds with remarkable diastereoselectivity (equation 57).[152]

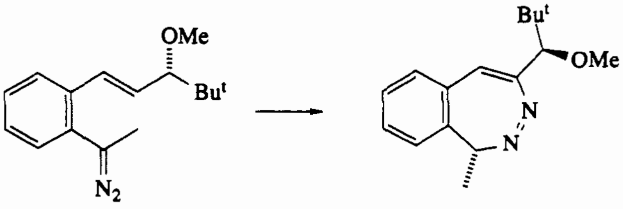

(57)

**(142)** **(143)**

### 1.4.7.2 Alkene Insertion to Make Cyclopropanes

An α-diazo ketone or ester such as (**144**) will, *via* metal-mediated nitrogen loss, insert into an alkene to make the corresponding cyclopropane (**145**; equation 58).[153,154] As illustrated, alkene geometry is retained, as would be expected for a concerted process. Cyclopropane construction by diazo insertion is reviewed in detail elsewhere in these volumes.

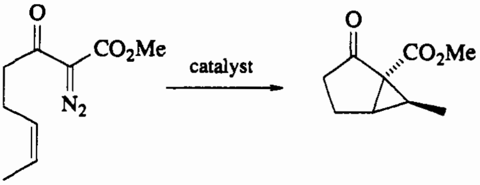

(58)

**(144)** **(145)**

### 1.4.7.3 C—H Insertion

An α-diazo ketone or ester such as (**146**) can also, *via* metal-mediated nitrogen loss, undergo 1,5 C—H insertion, to make the corresponding cyclopentane (**147**; equation 59).[155] This process, most efficiently catalyzed by $Rh^{II}$ dimers, is also reviewed in detail elsewhere in these volumes. It is striking that with copper bronze catalyst, (**146**) gives only intramolecular cyclopropanation.[156]

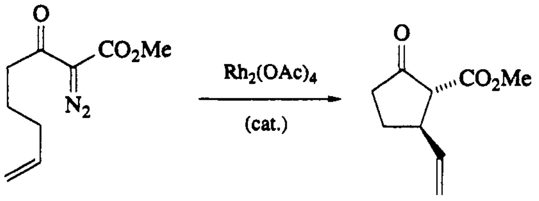

(**146**) (**147**)

(59)

### 1.4.7.4 Wolff Rearrangement/Arndt–Eistert Synthesis

On UV irradiation, an α-diazo ketone such as (**148**), prepared in this case from the parent ketone by formylation/diazo transfer, rearranges with loss of nitrogen to the corresponding ketene (equation 60).[157] In methanol solvent, the methyl ester (**149**) is the product. In aqueous dioxane, the product is the carboxylic acid. It should be noted that substrate (**146**; equation 59), on UV irradiation, gives only the product of Wolff rearrangement, with little trace of either (**147**) or the corresponding cyclopropane.[158] This is significant evidence that both of these latter products are derived from transient organometallic intermediates.

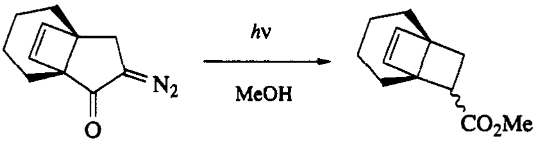

(**148**) (**149**)

(60)

A straight chain diazomethyl ketone will also undergo Wolff rearrangement on irradiation. Such diazomethyl ketones are readily prepared from the corresponding acid chloride (**150**) by exposure to diazomethane or, more conveniently, trimethylsilyldiazomethane (Petrarch).[159] The net one-carbon homologation so effected is known as the Arndt–Eistert synthesis.

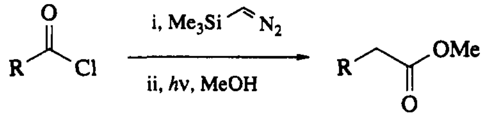

(**150**) (**151**)

(61)

### 1.4.7.5 Hetero-H Insertion

$Rh^{II}$-mediated hetero-H insertion may proceed by initial coordination of the intermediate metal–carbene complex with the nonbonding electrons of the heteroatom. Proton transfer would then give the observed product. This can be an efficient process both for forming C—N bonds, as in the cyclization of (**152**; equation 62),[148] and for C—O bonds, as illustrated by the construction of ether (**155**; equation 63).[160] Si—H insertion of (**156**) was shown to proceed with retention of absolute configuration, as would be expected for a concerted transition metal carbene mediated process (equation 64).[161]

The reactions illustrated in equations (62–64) are each catalyzed by rhodium acetate. Diazo compounds, especially diazoalkanes, can also react by a simple ionic mechanism. The esterification of a carboxylic acid with diazomethane is a familiar example. The ionic pathway is especially likely when the intermediate carbocation would be stabilized. Thus, diazine (**158**) couples smoothly with phenols, presumably by thermal rearrangement to the corresponding diazo sugar, followed by acid-catalyzed $N_2$ loss

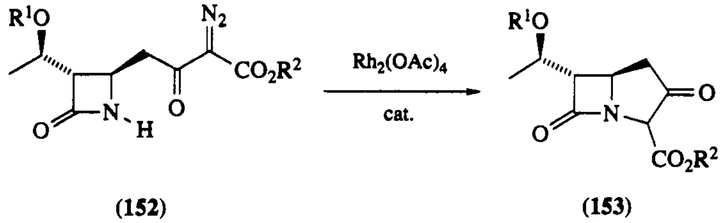
$R^1O$
$N_2$
$CO_2R^2$
O
N
H
$Rh_2(OAc)_4$
cat.
$R^1O$
O
N
$CO_2R^2$
(152)
(153)

(62)

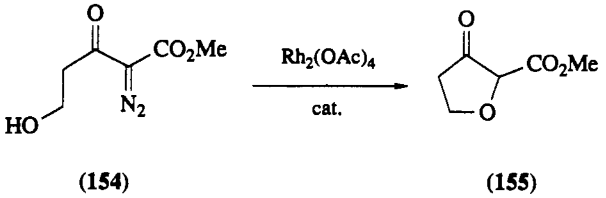
O
$CO_2Me$
$N_2$
HO
$Rh_2(OAc)_4$
cat.
O
$CO_2Me$
O
(154)
(155)

(63)

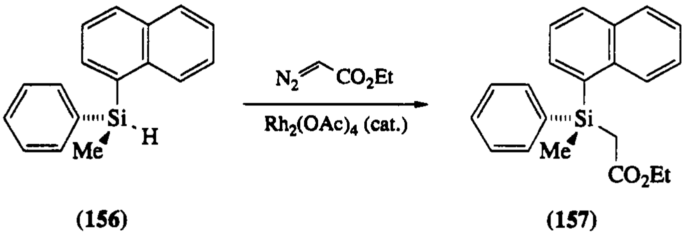
Si
Me
H
$N_2$
$CO_2Et$
$Rh_2(OAc)_4$ (cat.)
Si
Me
$CO_2Et$
(156)
(157)

(64)

(equation 65).[162] If conditions for the alternative transition metal mediated coupling can be developed, diazo sugars may turn out to be effective precursors for stereocontrolled glycoside formation.

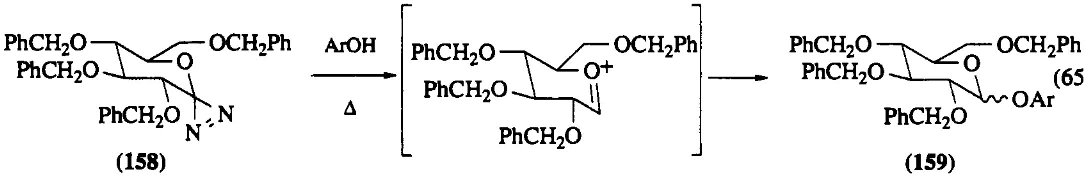
$PhCH_2O$
$PhCH_2O$
$OCH_2Ph$
O
$PhCH_2O$
N
N
(158)
ArOH
Δ
$PhCH_2O$
$OCH_2Ph$
O+
$PhCH_2O$
$PhCH_2O$
$PhCH_2O$
$PhCH_2O$
$OCH_2Ph$
O
OAr
$PhCH_2O$
(65)
(159)

## 1.4.7.6 Ylide Formation

In the examples illustrated above (equations 62–64), the heteroatom had an attached proton, which transferred readily. In the absence of such a proton, the initially-formed ylide can undergo other reactions. One of the more interesting of these is 1,3-dipolar cycloaddition, as illustrated by the conversion of (**160**) to (**161**) (equation 66).[163] Rhodium-mediated diazo addition to an ether is currently the method of choice for preparing such oxonium ylides.

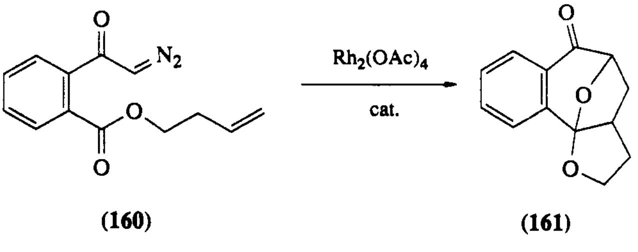
O
$N_2$
O
O
$Rh_2(OAc)_4$
cat.
O
O
O
(160)
(161)

(66)

## 1.4.7.7 Elimination to Make Alkenes

In 1957, Franzen reported that $Ag_2O$ catalyzes the transformation of an α-diazo ketone (**162**) to the corresponding enone (**163**; equation 67).[134] Regitz later made the intriguing observation that for cyclic α-diazo ketones, at least a seven-membered ring is required for efficient conversion to the enone, suggesting that conformational effects may be important.[164] Holt showed that other metallic salts catalyze this transformation, although not as effectively as silver oxide or silver nitrate.[165]

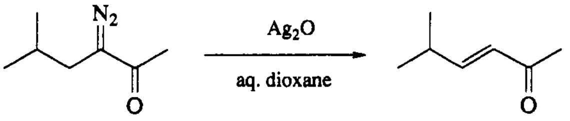

(67)

**(162)** **(163)**

A silyldiazoalkane (**164**) is converted to the alkene (**165**) under $Cu^I$ catalysis. The silyldiazoalkane (**164**) was prepared by deprotonation and alkylation of trimethylsilyldiazomethane.[166]

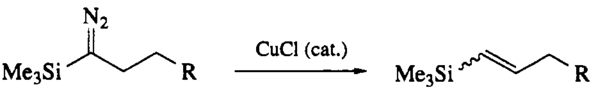

(68)

**(164)** **(165)**

### 1.4.7.8 Homologation of Ketones and Aldehydes

A diazo ester or alkane will react with a ketone, under Lewis acid catalysis, to give the homologated product. This reaction is most often used for one-carbon ring expansion, as illustrated by the conversion of (**166**) to (**167**; equation 69).[167] The regioselectivity of the (**166**) to (**167**) transformation, 98:2 in the example illustrated, was found to depend on both the diazoalkane and the Lewis acid used. With diazomethane and boron trifluoride, a 1:1 mixture of regioisomeric products was observed.

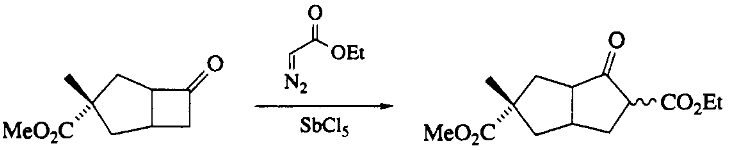

(69)

**(166)** **(167)**

This homologation reaction most likely proceeds *via* nucleophilic addition of the diazo compound to the Lewis acid complexed carbonyl, followed by 1,2-alkyl migration with concomitant loss of $N_2$. Application of this reaction to an aldehyde (**168**) gives, *via* 1,2-hydride shift, the corresponding β-keto ester (**169**; equation 70).[168]

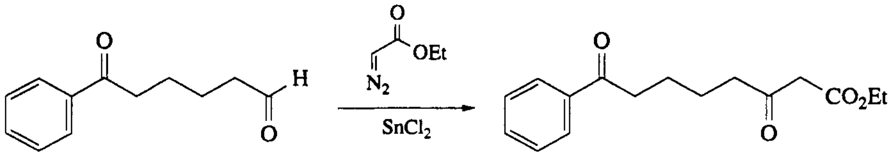

(70)

**(168)** **(169)**

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# 1.5

# Synthesis of Sulfides, Sulfoxides and Sulfones

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## 1.5.1 INTRODUCTION

During the 1980s, organic sulfur compounds have become increasingly useful and important in organic syntheses. Sulfur incorporated into an organic molecule activates, by its electronegativity, the hydrogen atoms situated on the adjacent carbon atom, increasing their thermodynamic acidity. The acidity of a proton α to a sulfoxide group or to a sulfone group falls between those of a benzylic proton and a proton α to a carboxylate function. It has been demonstrated that sulfur groups exert stabilizing effects on the corresponding carbanions that are much larger than those expected from their polar contributions.[1] The stabilizing resonance effect for the phenyl sulfone group was estimated to be equivalent to 33–75 kJ $mol^{-1}$ (8–18 kcal $mol^{-1}$), which is comparable with that of a cyano group but somewhat smaller than that of carbonyl or nitro functions. No data are available for a sulfoxide group and, to our knowledge, the extent of such acidification in β-keto sulfoxides or related compounds has not yet been determined. Another report[2] also showed that the presence of a phenylthio group increases the acidity of cyclohexanone by at least 3 p*K* units, corresponding to a stabilizing effect of the order of 25–42 kJ $mol^{-1}$ (6–10 kcal $mol^{-1}$).[3] This stabilizing effect was attributed to conjugative effects or polarization effects[4] involving the 3*d*-orbitals of sulfur.

The variety of sulfur compounds generating such carbanion structures permitted the development of several synthetic methods for carbon–carbon bond formation.

The basic chemistry of organosulfur compounds has already been reviewed in depth in 'Comprehensive Organic Chemistry',[5] so the purpose of this chapter is to outline the important developments in the use of sulfur-containing reagents in organic syntheses since the reviews cited in refs. 6 and 7, which appeared in 1978, were published.

Because of the large variety of sulfur compounds, this chapter will be limited to thioacetals, sulfides, sulfoxides and sulfones. Many examples, selected from recent total syntheses of natural products, will emphasize the selectivity (chemo-, regio-, diastereo- and enantio-selectivity) of these reactions.

## 1.5.2 SULFIDES

### 1.5.2.1 Thioacetals

Among organic sulfides, those derived from 1,3-dithiane occupy an important place. The interest in these reagents lies not only in their reactivity with electrophilic substrates but also in the synthetic principles which have been developed from work on these compounds. By masking the aldehyde group by the formation of a dithiane, the carbon atom may participate in nucleophilic additions or substitution reactions and after hydrolysis of the thioacetal, the carbonyl group can then be regenerated (Scheme 1).

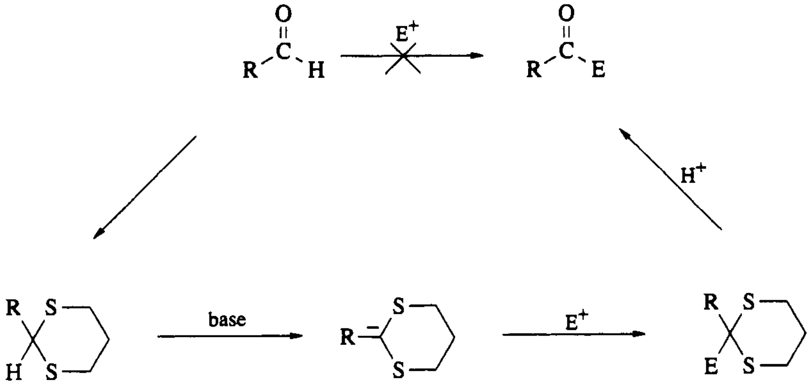

**Scheme 1**

Overall an inversion of polarity of the carbonyl group can thus be achieved; this principle was called 'umpolung' by Seebach.[8] We owe to Corey and Seebach the use of the anions of dithiane, which are more stable than those of noncyclic thioacetals.[9] Although this question was reviewed by Seebach[10] and also by Durst in 'Comprehensive Organic Chemistry',[11] we will briefly comment on the main reactions of the dithiane group.

Dithianes may be prepared by the action of propanethiol on aldehydes or ketones or their acetals in chloroform in the presence of boron trifluoride.[12]

The action of *n*-butyllithium in THF at low temperature leads to the anion. After reaction with an electrophilic compound, the hydrolysis can generally be carried out in polar solvents (acetone, alcohols, acetonitrile) in the presence of mercury(II) chloride or oxide and water.[12–14] In other cases, NBS,[14,15] chloramine T,[16] cerium(IV) ammonium nitrate,[17] *n*-tributyltin hydride,[18] trialkyloxonium tetrafluoroborate,[19] thallium nitrate[20] or photochemistry[21] can be used. Desulfurization by Raney nickel gives hydrocarbons.[22]

Typical examples of the reactions of carbanions α to dithiane are shown in Scheme 2.

Some noncyclic thioacetals are sometimes used for the preparation of keto acids from aryl halides[25] or keto esters[26] by 1,4-addition on α,β-unsaturated ketones (Scheme 3).

Ketene dithioacetals should also be mentioned; these are readily prepared by dehydrogenation of saturated dithioacetals,[27,28] or dihydrohalogenation of 2-dichloromethyl-1,3-dithiane followed by chain extension (Scheme 4).[29]

Wittig-type reactions have also been used to prepare ketene dithioacetals (Scheme 5).[30–36]

A variety of complex molecules have been synthesized by methods involving dithioacetal chemistry. Cyclophanediones have been generated by a sequence employing alkylation of the bisdithianyl derivative of isophthalaldehyde (Scheme 6).[37]

Alnusone, a biphenyl-type natural product, was also synthesized by using a dithianyl reagent to open an epoxide ring (Scheme 7).[38]

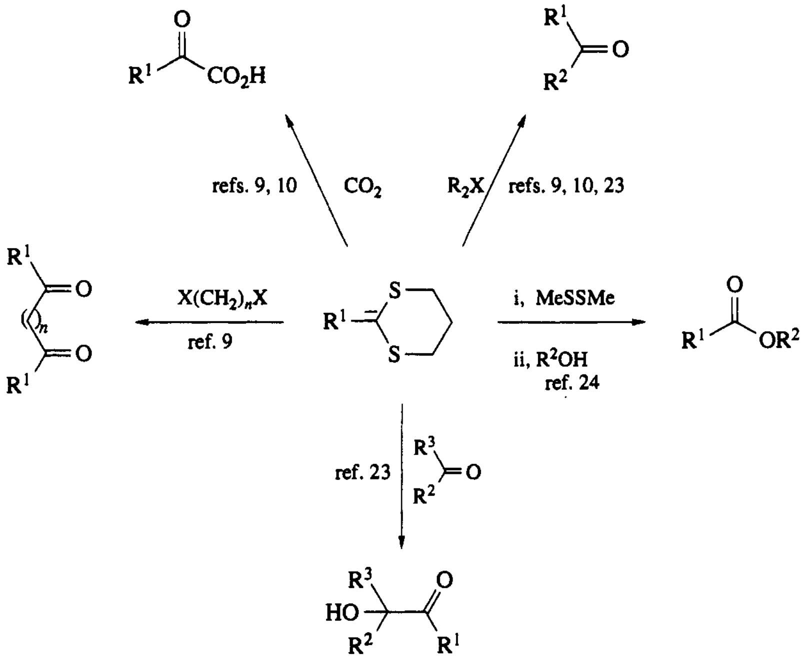
refs. 9, 10
CO2
R2X
refs. 9, 10, 23
X(CH2)nX
ref. 9
i, MeSSMe
ii, R2OH
ref. 24
ref. 23
R1
R2
R3
CO2H
OR2
HO
O
S

Scheme 2

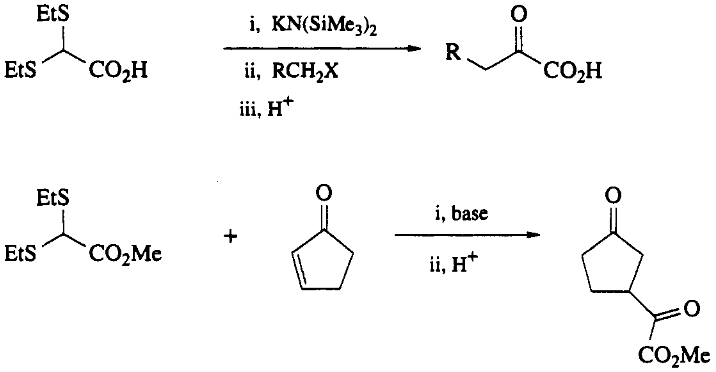
EtS
CO2H
i, KN(SiMe3)2
ii, RCH2X
iii, H+
R
CO2Me
+
i, base
ii, H+
O

Scheme 3

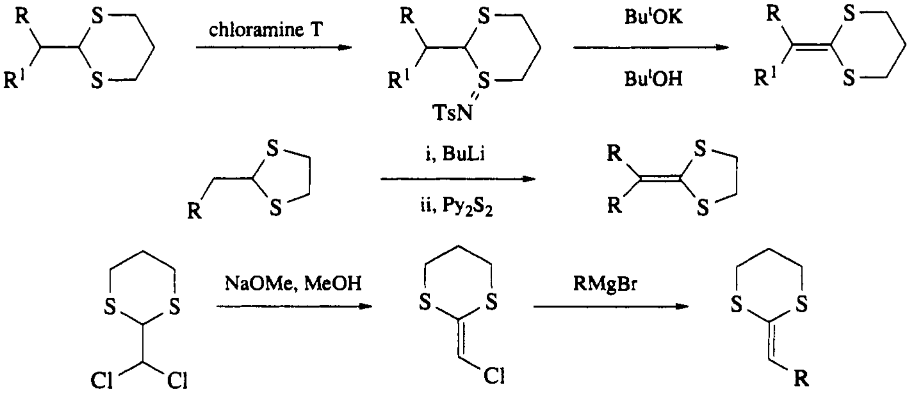
chloramine T
TsN
ButOK
ButOH
i, BuLi
ii, Py2S2
NaOMe, MeOH
RMgBr
R
R1
S
Cl

Scheme 4

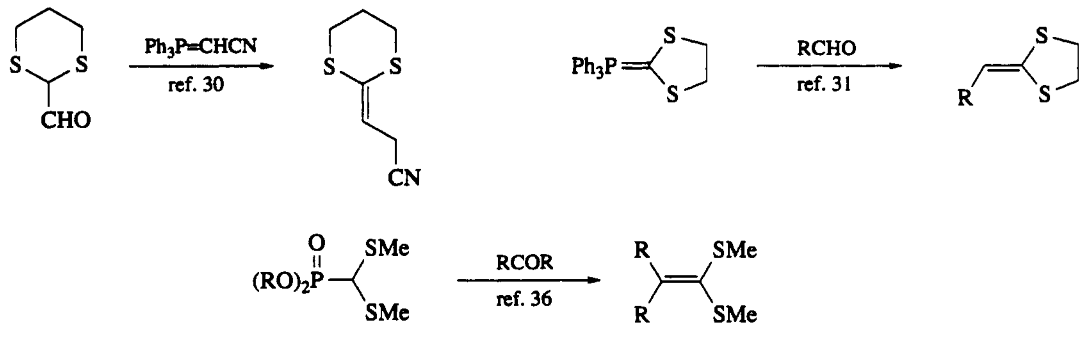
Ph3P=CHCN
ref. 30
CHO
CN
Ph3P
RCHO
ref. 31
R
(RO)2P
SMe
RCOR
ref. 36

Scheme 5

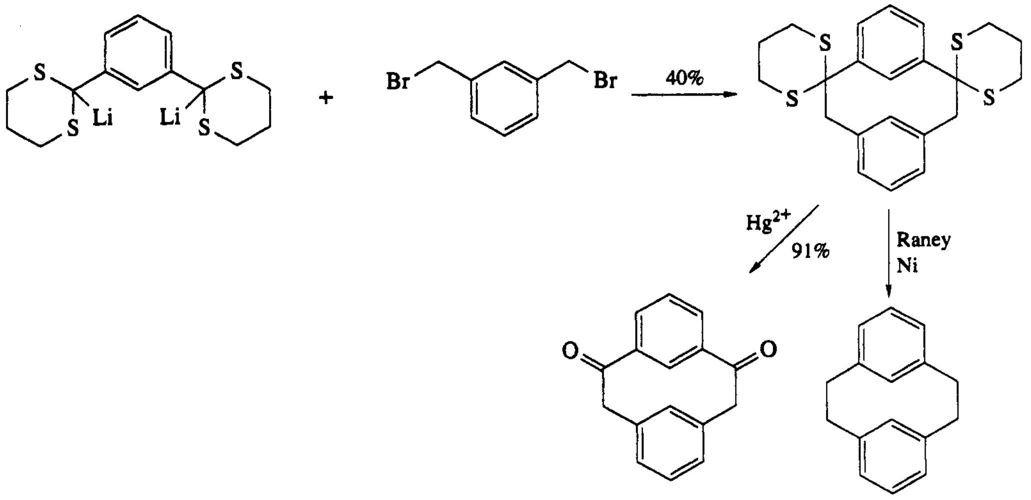
Li
Br
40%
Hg2+
91%
Raney Ni

Scheme 6

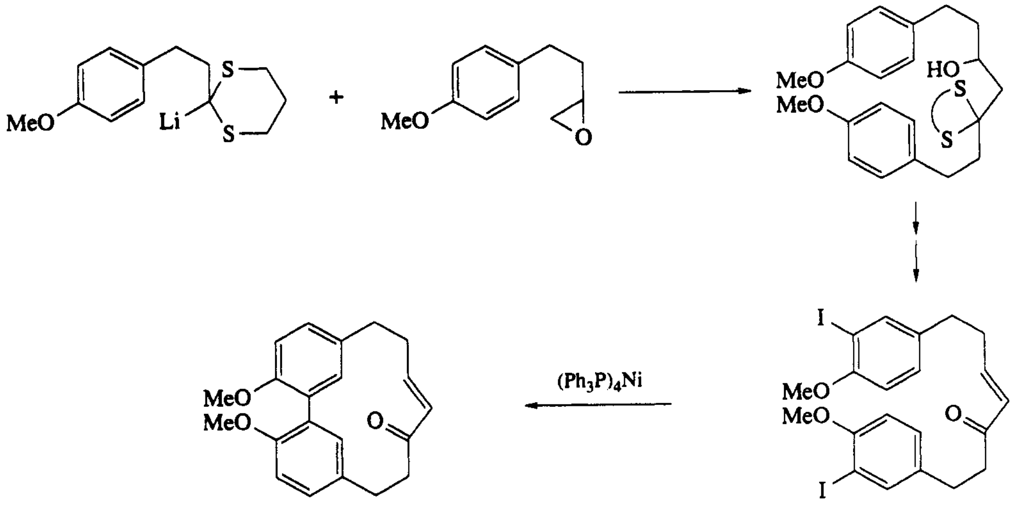
MeO
Li
HO
I
(Ph3P)4Ni

Scheme 7

Another relevant example is the total synthesis of the macrolide glacosporone,[39] a germination self-inhibitor from the fungus *Colletotrichum glocosporioides*. The retrosynthetic scheme shows the important role played by the dithiane anion (Scheme 8).

Finally, the recent total synthesis of zearalenone reported by Rao[40] gives a good illustration of the range of reactions available for organosulfur compounds: the macrocyclization reaction, the formation of the double bond and the introduction of the ketone group were made possible by using sulfur-containing

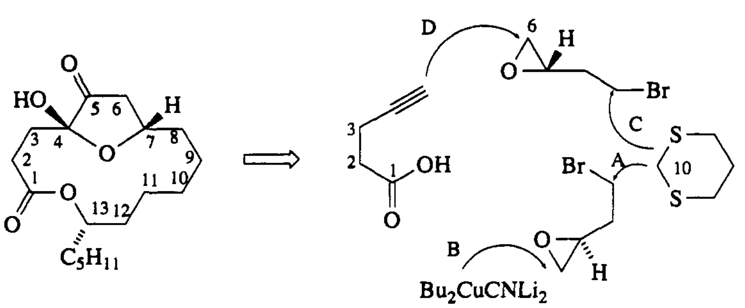

**Scheme 8**

reagents as shown on the retrosynthetic scheme (Scheme 9). The nonaromatic part of the molecule was readily made from dihydropyran *via* thioacetal formation from the corresponding hemiacetal, followed by alkylation of dithiane carbanion (Scheme 10).

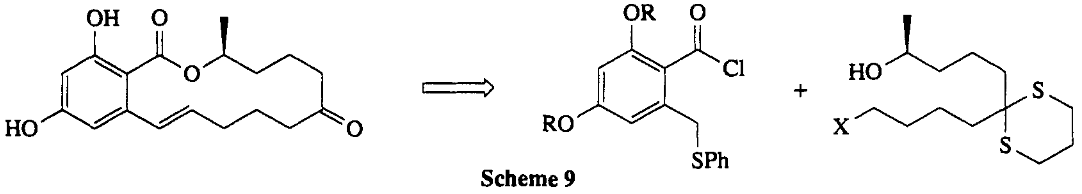

**Scheme 9**

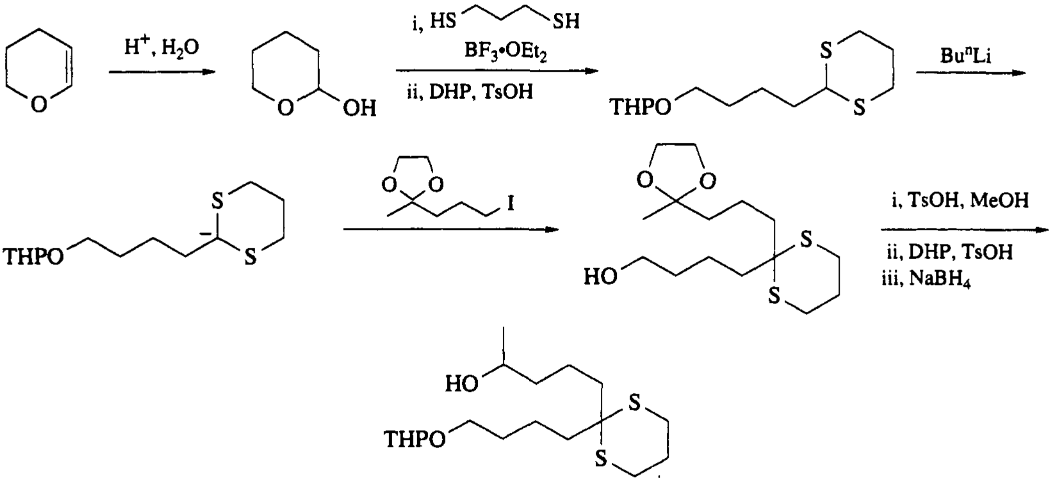

**Scheme 10**

Although benzylic sulfides will be treated later in a separate section, the synthesis of zearalenone gives the first opportunity to mention their synthetic use. The introduction of sulfur to build the aromatic part of zearalenone was done in two different ways:[41,42] displacement of a benzylic bromide by benzenethiol or reaction of diphenyl disulfide with benzylic carbanion (Scheme 11).

Finally, zearalenone was obtained[43] by intramolecular alkylation of the carbanion α to the benzylic sulfide, which occurs readily with potassium hexamethyldisilazane. After cyclization, the double bond was created by oxidation of sulfide to sulfoxide followed by pyrolytic elimination, a technique described in more detail in the next section (Scheme 12).

Recently, Koga[74] found a novel use of dithioacetal as a stereocontrolling unit during alkylation of acyclic α,β-unsaturated esters. Conjugate addition of lithiated dimethyl thioacetals to α,β-unsaturated esters in THF at low temperature, followed by subsequent methylation of the corresponding enolate gave only a single isomer. Alkylation and protonation take place with the electrophile attacking *anti* to the bulky dithioacetal for steric reasons (Scheme 13).

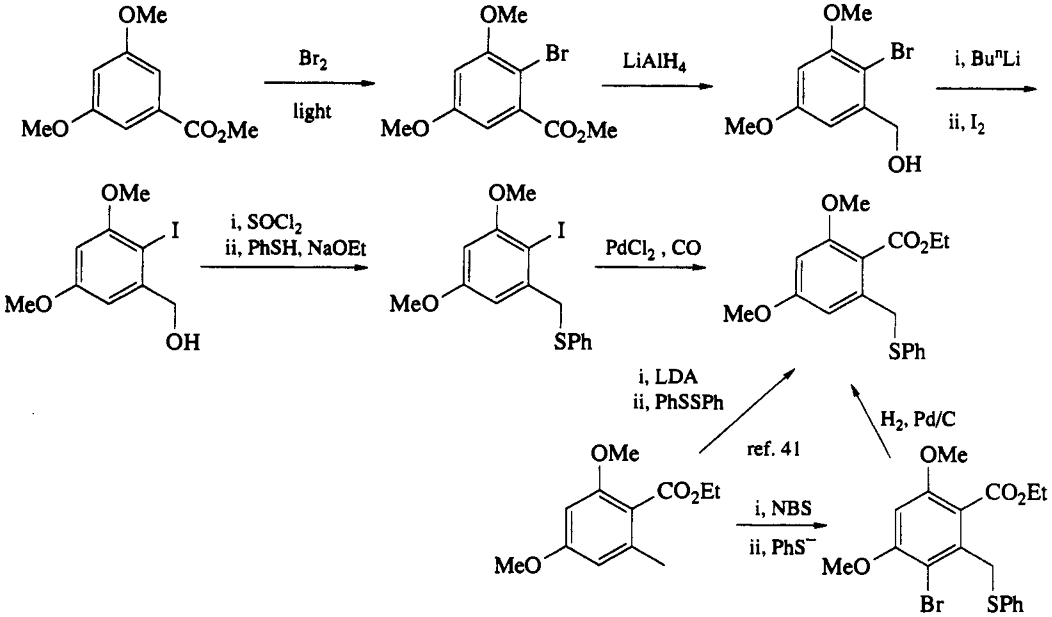

Scheme 11

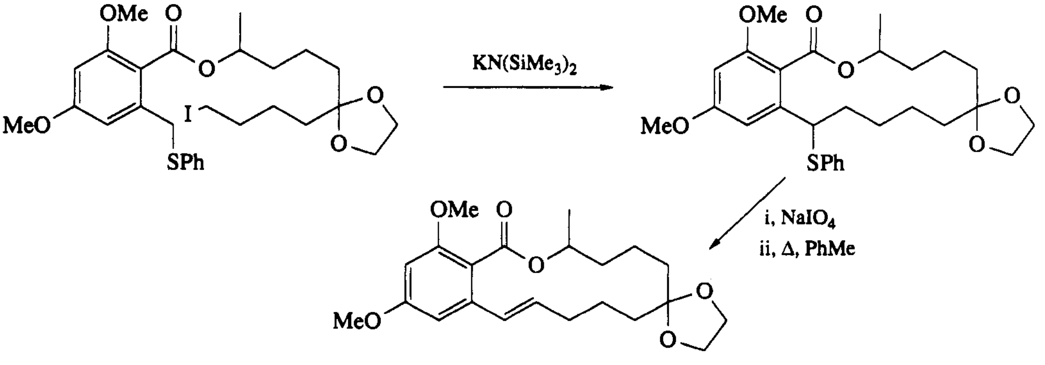

Scheme 12

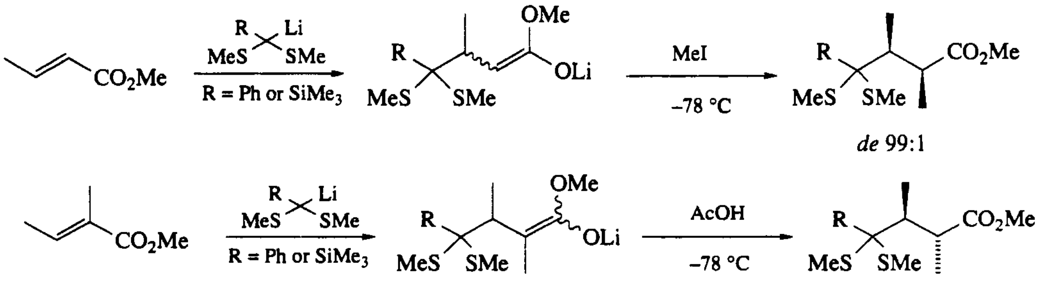

Scheme 13

## 1.5.2.2 Other Sulfides

Benzylic and allylic sulfides have very important applications in organic syntheses.

One of the first papers was published by Corey[44] on the use of bis(methylthio)allyllithium (**1**; Scheme 14) for the synthesis of α,β-unsaturated aldehydes from alkyl halides. The generation of the carbanion as the lithio derivative was readily accomplished by a simple three-step sequence from epichlorohydrin.

Reaction of epichlorohydrin with sodium methanethiolate gave 1,3-bis(methylthio)-2-propanol, which was converted to the sodio derivative and methylated to afford 1,3-bis(methylthio)-2-methoxypropane. Finally, treatment with LDA (1 equiv.) resulted in elimination of methanol to give 1,3-bis(methylthio)propene, whereas reaction with 2 equiv. of LDA gave bis(methylthio)allyllithium, which reacted with 1-bromopentane furnishing 1,3-bis(methylthio)-1-octene, which in turn was converted by hydrolysis with mercury(II) chloride to *trans*-2-octenal (Scheme 14).

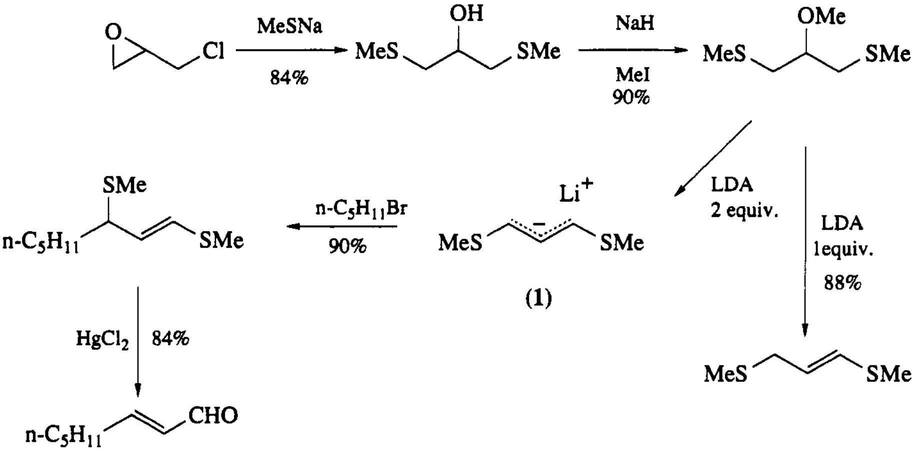

**Scheme 14**

The application of the lithio reagent (**1**) to the conversion of the oxidoacetal to the corresponding hydroxy aldehyde as a key step in a total synthesis of prostaglandin $F_{2\alpha}$ has been described (Scheme 15).[45]

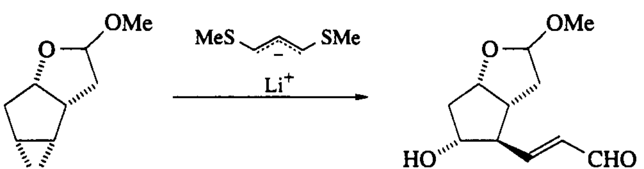

**Scheme 15**

Phenylthiomethyllithium (**2a**) was used for the homologation of primary halides[46] in a two-step sequence: first halogen displacement by reagent (**2a**) or the organocuprate derivative (in the case of allylic compound) and then replacement of the phenylthio group by iodo by heating the sulfide with a large excess of methyl iodide in 1 M sodium iodide solution in DMF (Scheme 16).

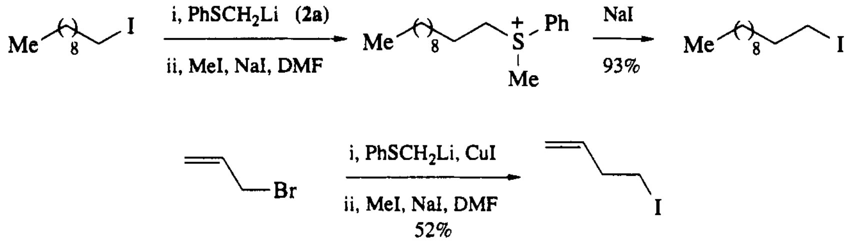

**Scheme 16**

Phenylthiomethyllithium was also used for ketone methylenation,[47,49] mainly in the case of hindered ketones which do not react with the usual Wittig reagent. This is a three-step sequence: the reagent (**2a**) is added, then the resulting alcohol is acylated, and finally the exocyclic methylene is formed by reduction with lithium in ammonia (Scheme 17).

The phenylthiomethyl adduct could also be transformed in one step to methylene with $TiCl_4/LiAlH_4$[48] or to epoxide[50] *via* the corresponding sulfonium salt (Scheme 18).

α-Phenylthiomethyltrimethylsilane (**2b**) was shown to react with alkyl halides or epoxides giving in two steps the corresponding aldehyde.[51–53] This method is interesting because the α-phenylthioalkyl-

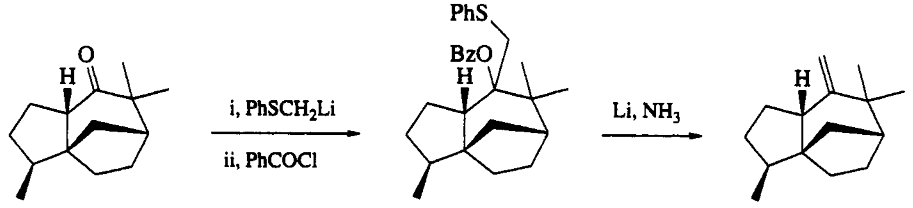

Scheme 17

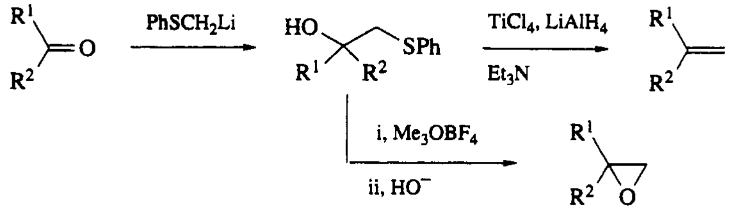

Scheme 18

trimethylsilane obtained in the first step can be oxidized to the corresponding sulfoxide, which undergoes a silyl-Pummerer rearrangement[54,55] giving an *O*-trimethylsilyl hemithioacetal, which is readily hydrolyzed to the aldehyde (Scheme 19).

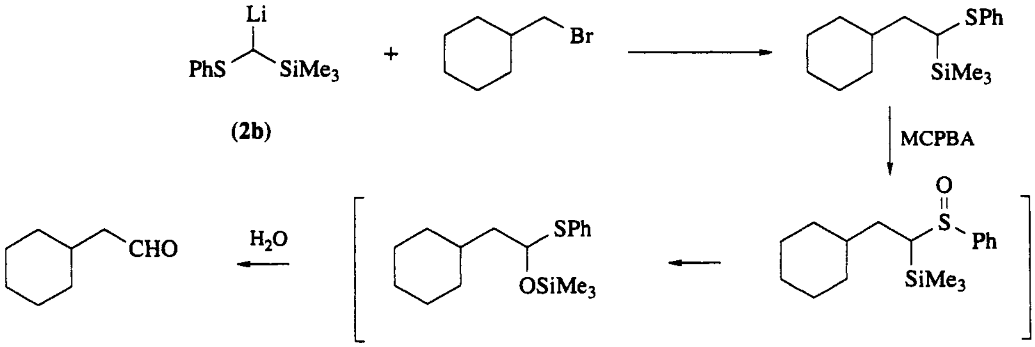

Scheme 19

Tris(phenylthio)methyllithium (**2c**) adds in conjugate fashion to a number of enones,[56,57] and the resulting adduct could then be hydrolyzed into a carboxylic acid ester or aldehyde (Scheme 20).

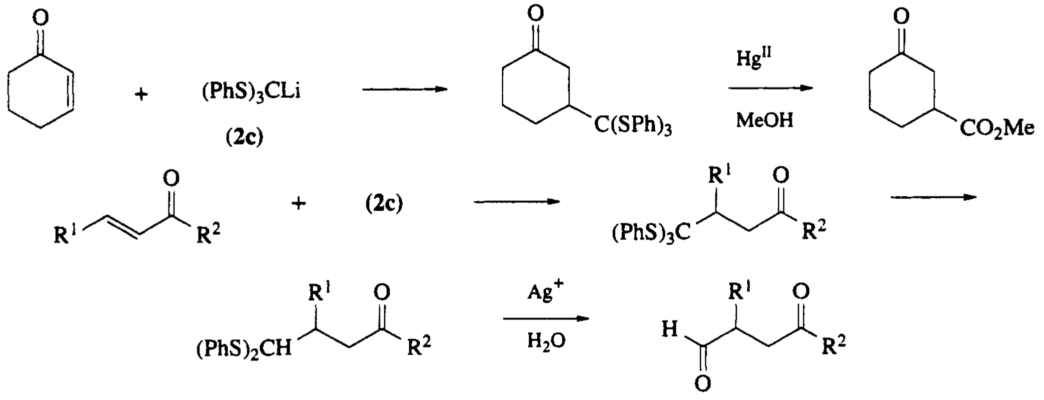

Scheme 20

Michael addition of benzenethiolate to 4-*t*-butyl-1-cyanocyclohexene gives only products containing an axial $PhS^-$ group;[60] the same result was obtained from ethyl 4-*t*-butylcyclohexene-1-carboxylate.[61] In contrast, the addition of diethyl sodiomalonate gave only the equatorial malonate group under thermodynamic or kinetic control (Scheme 21).[58,59] Similar results were observed with the addition of tris(phenylthio)methyllithium (**2c**) on carvone.[62a]

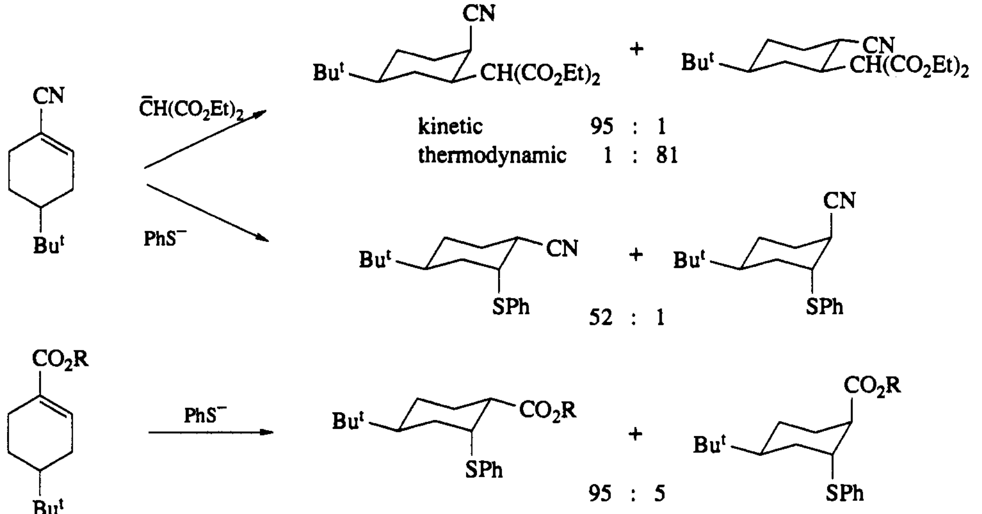
CN
Bu$^t$
$\bar{C}H(CO_2Et)_2$
PhS$^-$
CN
Bu$^t$
$CH(CO_2Et)_2$
+
Bu$^t$
CN
$CH(CO_2Et)_2$
kinetic 95 : 1
thermodynamic 1 : 81
Bu$^t$
CN
SPh
+
Bu$^t$
CN
SPh
52 : 1
$CO_2R$
Bu$^t$
PhS$^-$
Bu$^t$
$CO_2R$
SPh
+
Bu$^t$
$CO_2R$
SPh
95 : 5

**Scheme 21**

The same diastereoselectivity was obtained during the addition of benzenethiol to (–)-carvone;[62b] this was then applied to the preparation of (+)-(2*R*,5*R*)-dihydrocarvone (Scheme 22).

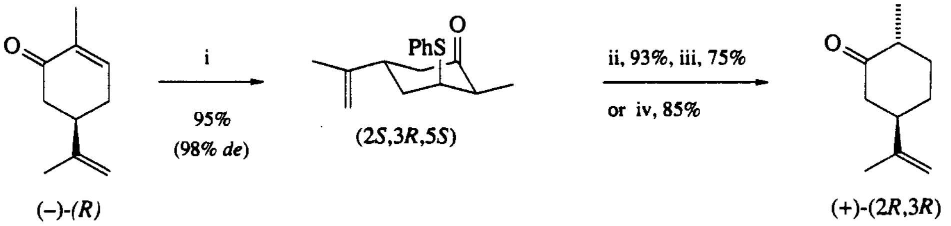
O
i
95%
(98% *de*)
PhS
O
(2*S*,3*R*,5*S*)
ii, 93%, iii, 75%
or iv, 85%
O
(–)-(*R*)
(+)-(2*R*,3*R*)

i, PhSH, $Et_3N$, *n*-hexane, 0 °C; ii, $LiAlH_4$; iii, Li/Pr$^n$NH$_2$; iv, PDC/DMF

**Scheme 22**

Chlorosulfides are often used for vicinal functionalization of alkenes. Silyl enol ethers can react with α-chloromethyl phenyl sulfides (**5**) in the presence of $ZnBr_2$[63] or $TiCl_4$[64] to give the corresponding β-keto sulfide, which could be easily transformed into the α-methylene ketone *via* sulfide oxidation to sulfoxide, followed by pyrolytic elimination (Scheme 23).

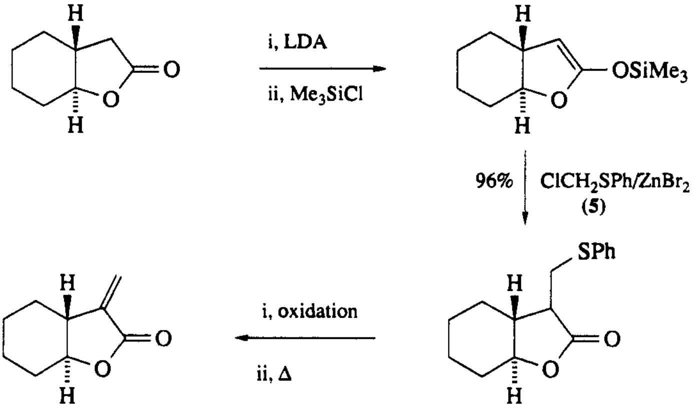
H
O
O
H
i, LDA
ii, $Me_3SiCl$
H
$OSiMe_3$
O
H
96%
$ClCH_2SPh/ZnBr_2$
(**5**)
SPh
H
O
O
H
i, oxidation
ii, Δ
H
O
O
H

**Scheme 23**

Cyclic α-chloro sulfides are easily made from the corresponding alkenes and PhSCl. They have also been reacted with *O*-silylated enolates or allyltrimethylsilanes (Scheme 24a).[65a] A stereoselective synthesis of α-chloro sulfide was also reported[65b] on a camphor derivative (Scheme 24b). A complete review on organic synthesis with α-chloro sulfides was recently published by McKervey.[66]

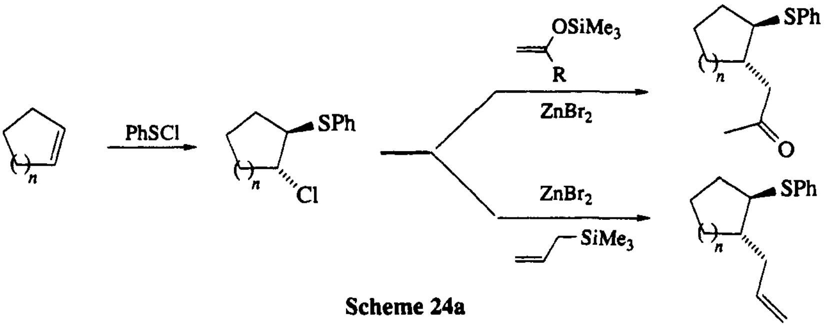
PhSCl
SPh
Cl
n
OSiMe3
R
ZnBr2
ZnBr2
SiMe3
SPh
O
SPh

Scheme 24a

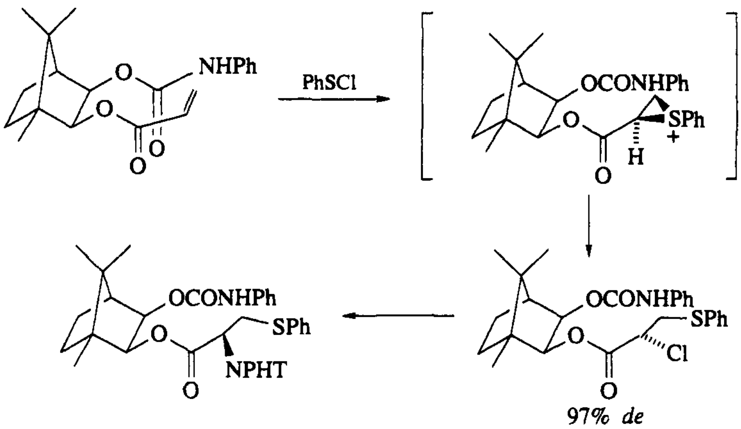
NHPh
O
O
O
O
PhSCl
OCONHPh
O
SPh
+
H
O
OCONHPh
O
SPh
Cl
O
97% de
OCONHPh
O
SPh
NPHT
O

Scheme 24b

Recently Reetz[67] reported on the regio- and stereo-selective carbosulfenylation of alkenes.[67] When *trans*-β-chloro sulfides obtained from cyclic alkenes are allowed to react in a one-pot process with dimethylzinc in the presence of 20 mol % $TiCl_4$, the C—C coupling products are formed with complete retention of configuration. The same is true of noncyclic alkenes. The mechanism should probably proceed by the formation of an episulfonium ion, which is attacked by the complex $[MeTiCl_4]^-$ (Scheme 25).

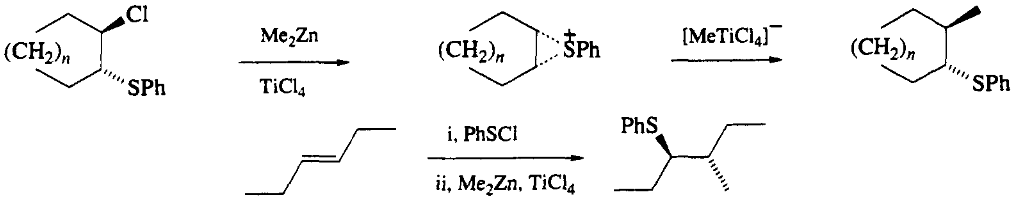
Cl
(CH2)n
SPh
Me2Zn
TiCl4
(CH2)n
+
SPh
[MeTiCl4]−
(CH2)n
SPh
i, PhSCl
ii, Me2Zn, TiCl4
PhS

Scheme 25

Finally, the regioselectivity as well as the 1,2-asymmetric induction were investigated. In the case of optically active 2-methylcyclohexene the regioselectivity was 85%, giving mainly compound (**4**) with 99% diastereofacial selectivity (Scheme 26). For stereoelectronic reasons only (**3**) undergoes a *trans*-1,2-diaxial ring opening to give (**4**) in the chair conformation.

In the case of acyclic alkenes, the carbosulfinylations are likewise regio- and, depending on the nature of the protective group on oxygen, stereo-selective (large protecting groups give smaller 1,2-asymmetric induction; Scheme 26).

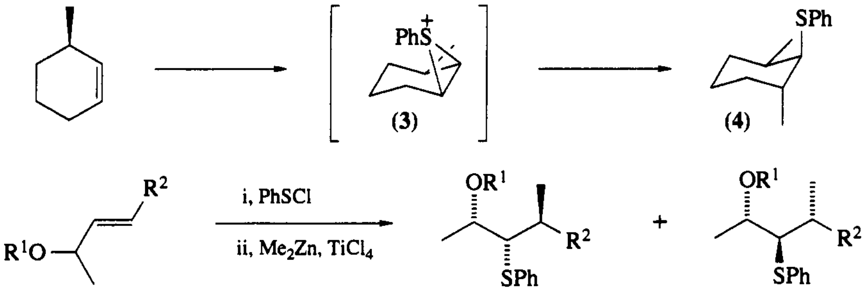

| | | | |
|---|---|---|---|
| $R^1 = Me$ | 99 | : | 1 |
| $R^1 = CH_2Ph$ | 85 | : | 15 |
| $R^1 = SiMe_3$ | 84 | : | 16 |
| $R^1 = SiMe_2Bu^t$ | 60 | : | 40 |

**Scheme 26**

Treatment of cyclopropyl phenyl sulfide with *n*-butyllithium gives α-lithio(phenylthio)cyclopropane, which reacts with electrophilic reagents to give adducts that undergo a variety of transformations, many of which are difficult to achieve by more conventional methodology. Perhaps the most interesting chemistry of cyclopropyl phenyl sulfide involves its reaction with carbonyl compounds,[68,69] giving cyclobutanones or 1-phenylthiocyclobutenes[70] through carbocation rearrangements. After dehydration of the adduct, the resulting vinylcyclopropane could be transformed into cyclopentanone by a known thermal rearrangement (Scheme 27).[71]

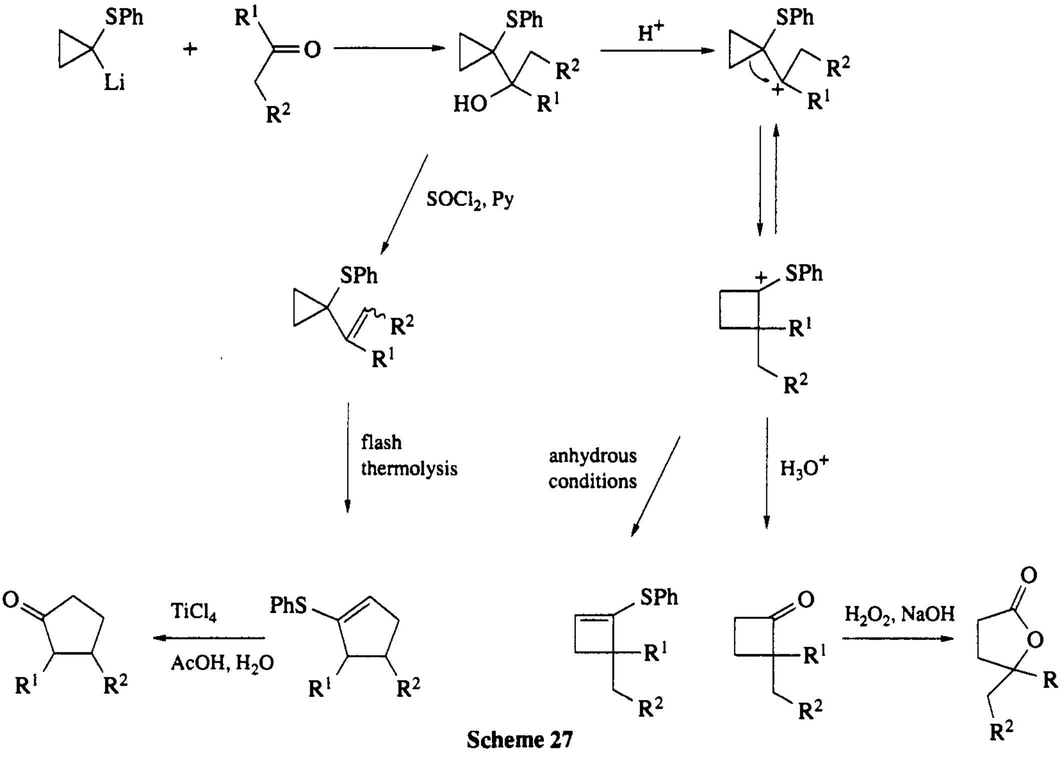

**Scheme 27**

Trost also found[72] that treatment of these cyclobutanones with sodium methoxide and diphenyl disulfide leads to *in situ* bisulfenylation and ring cleavage (secosulfenylation). This was applied to the total synthesis of verrucarol, a complex tetrahydrochromanone substituted at the ring junction by a hydroxymethyl substituent. The synthetic strategy[73] twice used the cyclobutanone formation from 1-lithiocyclopropyl phenyl sulfide and a ketone, followed by the secosulfenylation process and Baeyer–Villiger type rearrangement of cyclobutanone. Only this part of the synthesis is described in Scheme 28.

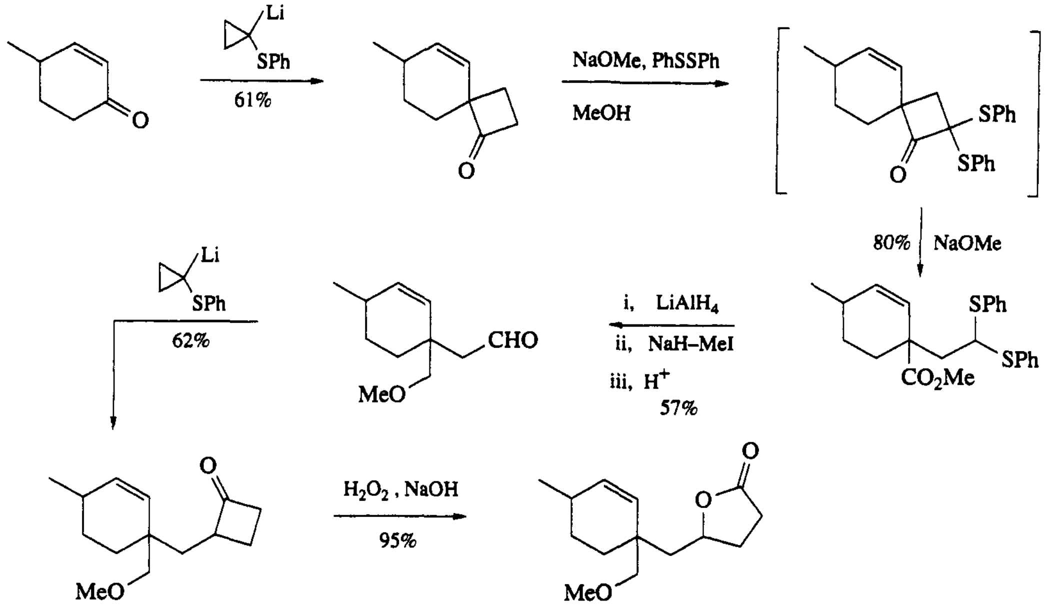

Scheme 28

Sulfides were also involved in a unique three-component, stereospecific Michael addition.[75] The reaction described in Scheme 29 can be explained as follows: regiospecific addition of the nucleophile to the exocyclic double bond of the α-methylenecyclopentenone, followed by trapping of the resulting enolate by methyl acrylate, and attack of the anion thus formed on the endocyclic double bond of the cyclopentenone moiety to result, after protonation, in the bicyclo[2.2.1]heptan-6-one as a single stereoisomer (68% overall yield; Scheme 29).

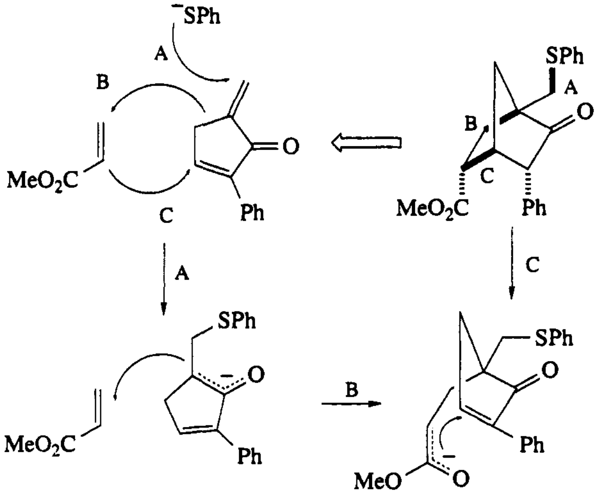

Scheme 29

Sulfide has also been involved in a new two-step annulation method which featured stereospecific formation of three contiguous asymmetric centers.[76] It was found that the lithium dienolate of the vinylogous ester (**6a**) reacts rapidly with the α-thiophenyl butenolide (**6b**) to provide the corresponding adduct as a single diastereoisomer. Subsequent addition of vinyllithium, acidification and cyclization gave the tricyclic lactone (Scheme 30).

A similar highly stereoselective Michael addition has been reported by Uda.[77] The enolate of a substituted cyclohexenone reacted rapidly in a Michael-type addition with methyl α-thiophenylmethacrylate

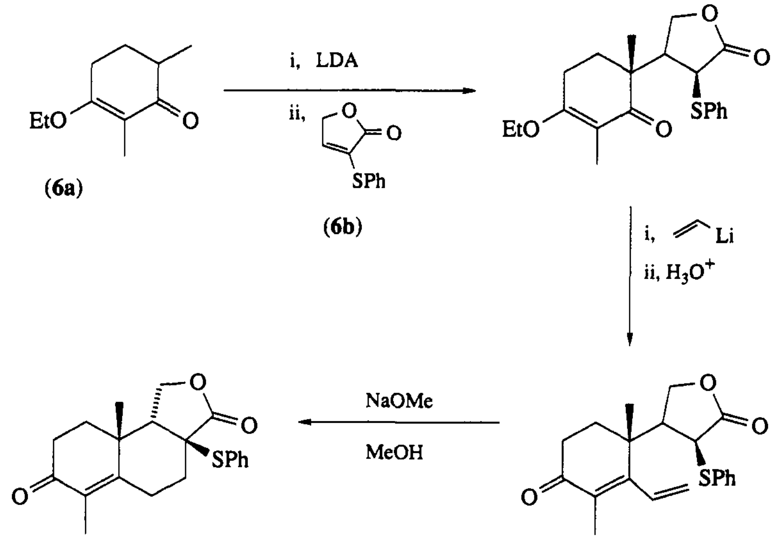

Scheme 30

to provide the corresponding adduct, which, by an intramolecular Michael addition, leads to the substituted [2.2.2]octanone as a single stereoisomer (Scheme 31).

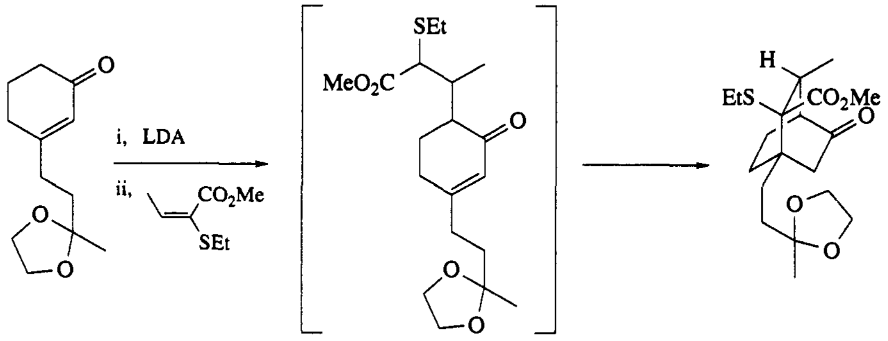

Scheme 31

Allylic sulfides can be coupled with allylic bromides in a process which was first described by Biellmann and applied to the squalene synthesis.[78] Farnesyl sulfide was prepared from 2,4-dinitrophenylfarnesyl oxide and benzenethiolate. Finally, the allylic thiocarbanion was coupled with farnesyl bromide to give, in 82% yield, squalene sulfide, easily transformed to squalene with Li/EtNH$_2$ (Scheme 32).

Several applications of this method appeared in the literature. Furaterpenes can be synthesized in this way; *e.g.* dendrolasin was made from *trans*-ω-chloroperillene and the carbanion of prenyl phenyl sulfide (Scheme 33).[79] Elemol has been synthesized by an intramolecular variant of Biellmann's method (Scheme 34).[80]

Until now, α-lithio ethers were nearly always prepared by deprotonation of an α-carbon atom of an ether having a special anion-stabilizing feature (carbonyl, cyano, phenylthio). An interesting report by Cohen[81] showed that a variety of types of unstabilized and stabilized α-lithio ethers can be readily prepared from α-(phenylthio) ethers by reductive lithiation with lithium 1-(dimethylamino)naphthalenide or lithium naphthalenide. What makes this method one of considerable generality is the ready availability of various types of α-(phenylthio) ether substrates or their vinylogues as shown in Scheme 35.

An example of this method is given by the synthesis of brevicomin.[81] The desired α-(phenylthio) ether (7) was made by Diels–Alder addition of phenyl vinyl sulfide and methyl vinyl ketone. Treatment of (7) with lithium 1-(dimethylamino)naphthalenide, followed by trapping of the anion with propionaldehyde and ring closure to an acetal during the acidic work-up, afforded a mixture of *endo* and *exo* isomers of brevicomin (Scheme 36).

Several other applications of this method have been published. Reductive lithiation of 1-(trimethylsilyl)cyclopropyl phenyl sulfide gives α-lithio(trimethylsilyl)cyclopropane, which reacts with carbonyl

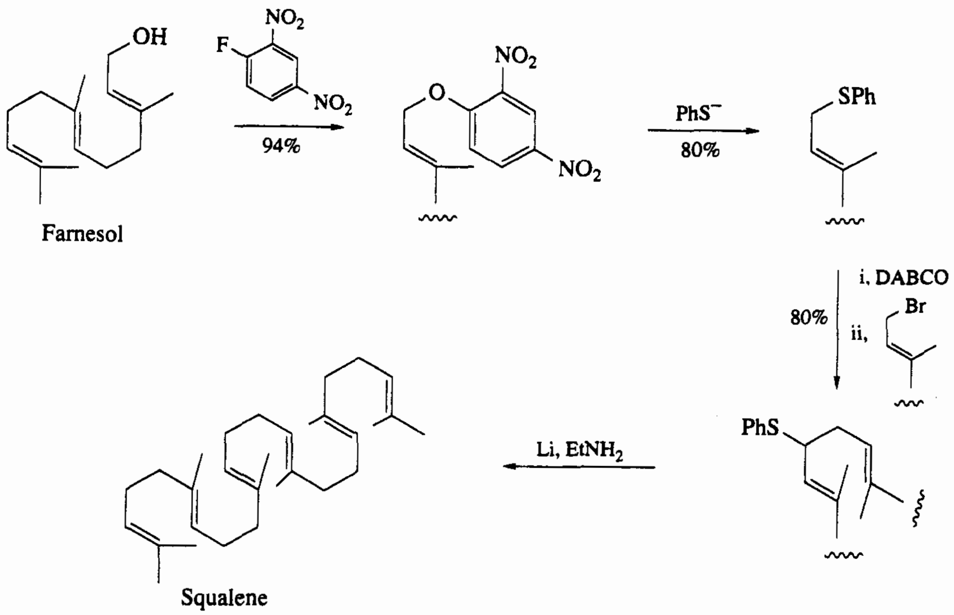
OH
$NO_2$
F
$NO_2$
94%
$NO_2$
O
$NO_2$
$PhS^-$
80%
SPh
Farnesol
i, DABCO
80%
Br
ii,
PhS
Li, $EtNH_2$
Squalene

**Scheme 32**

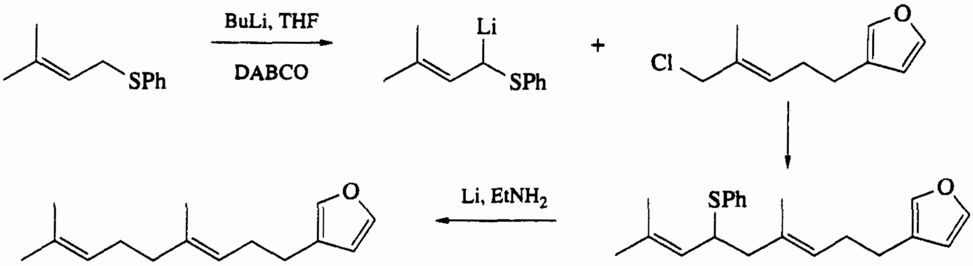
SPh
BuLi, THF
DABCO
Li
SPh
+
Cl
O
Li, $EtNH_2$
SPh
O
O

**Scheme 33**

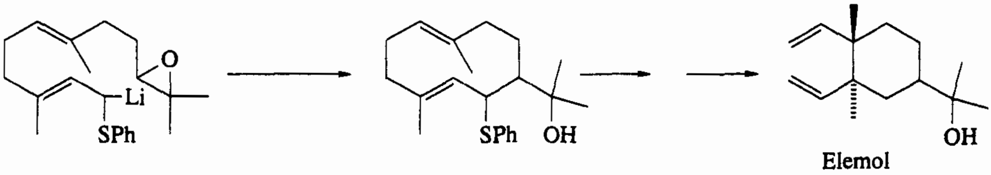
O
Li
SPh
SPh
OH
OH
Elemol

**Scheme 34**

compounds to give 1-(trimethylsilyl)cyclopropylethylenes. Pyrolysis of these compounds provides a new cyclopentane annulation procedure. A unique feature of this process is that the double bond in the vinylsilane is formed in the more highly substituted position (Scheme 37).[88]

The synthesis of (–)-β-selinene from the commercially available (–)-perillaldehyde used a reductive lithiation of 1-methoxycyclopropyl phenyl sulfide, condensation to an aldehyde, acid-catalyzed rearrangement to a vinylcyclobutanone and finally basic 1,3-sigmatropic rearrangement of the corresponding cyclobutanol to cyclohexenol (Scheme 38a).[89a] 1-Phenylthio-1-(trimethylsiloxy)cyclopropane was prepared *via* the silyl-Pummerer rearrangement with high stereoselectivity (Scheme 38b).[89b] (1-Methoxy-1-phenylthio)cyclopropane was also obtained from alkenes *via* Pummerer rearrangement.[89c] 2-Methoxy-3-phenylthiobuta-1,3-diene was also shown to be a novel annelating agent *via* a Diels–Alder reaction (Scheme 38c).

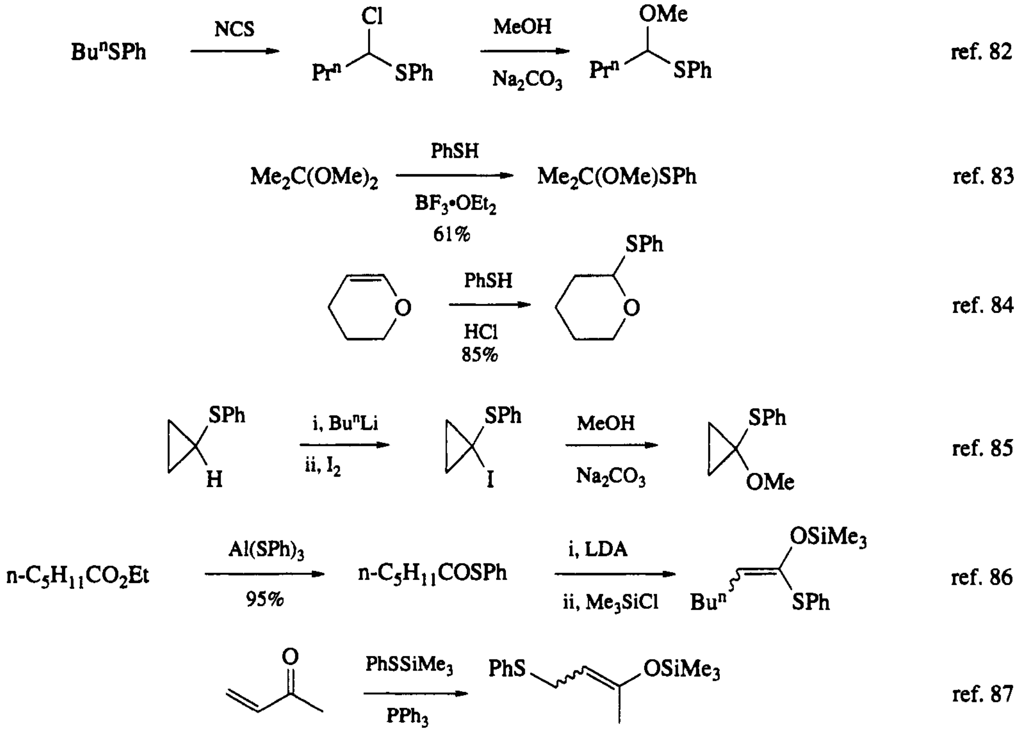
Bu^nSPh
NCS
Cl
Pr^n SPh
MeOH
Na2CO3
OMe
Pr^n SPh
ref. 82
Me2C(OMe)2
PhSH
BF3•OEt2
61%
Me2C(OMe)SPh
ref. 83
O
PhSH
HCl
85%
SPh
O
ref. 84
SPh
H
i, Bu^nLi
ii, I2
SPh
I
MeOH
Na2CO3
SPh
OMe
ref. 85
n-C5H11CO2Et
Al(SPh)3
95%
n-C5H11COSPh
i, LDA
ii, Me3SiCl
OSiMe3
Bu^n
SPh
ref. 86
O
PhSSiMe3
PPh3
PhS
OSiMe3
ref. 87

**Scheme 35**

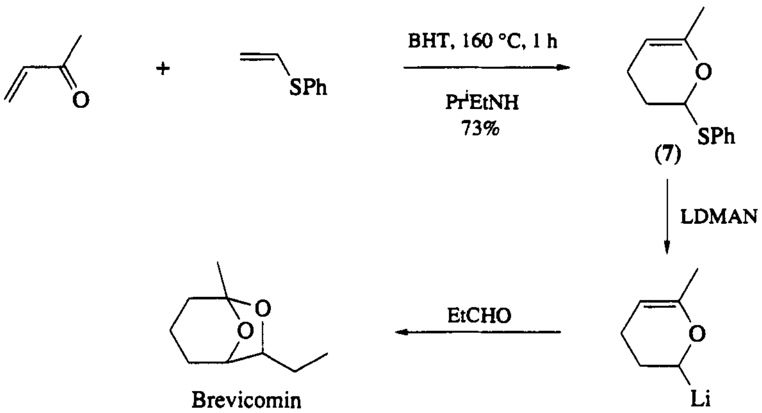
O
+
SPh
BHT, 160 °C, 1 h
Pr^iEtNH
73%
O
SPh
(7)
LDMAN
O
Li
EtCHO
O
O
Brevicomin

**Scheme 36**

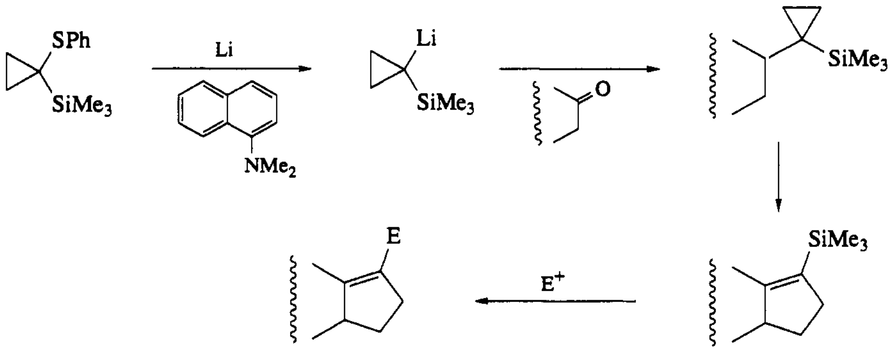
SPh
SiMe3
Li
NMe2
Li
SiMe3
O
SiMe3
E+
E
SiMe3

**Scheme 37**

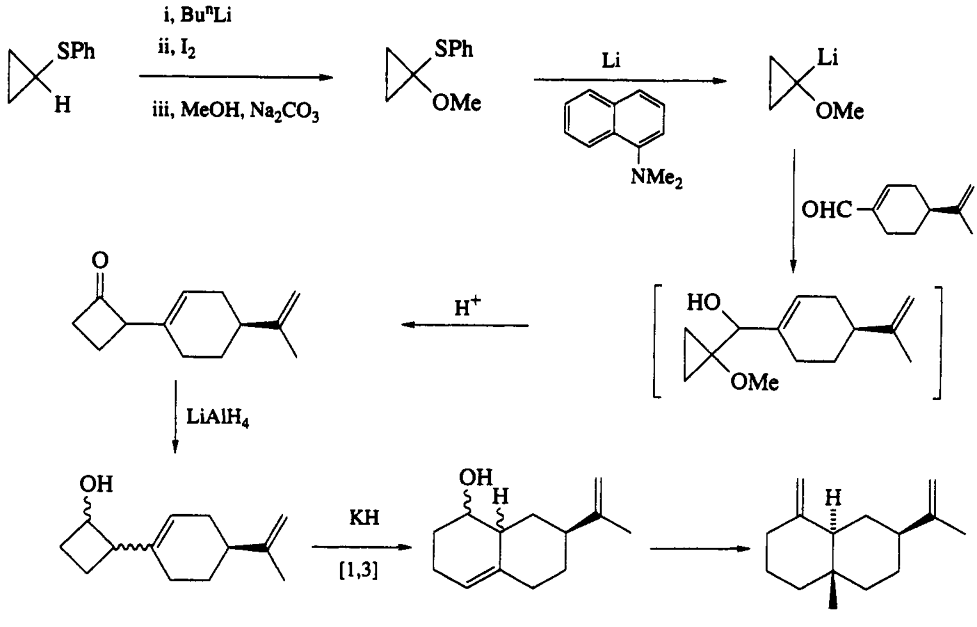
SPh
H
i, Bu$^n$Li
ii, $I_2$
iii, MeOH, $Na_2CO_3$
SPh
OMe
Li
$NMe_2$
Li
OMe
OHC
HO
OMe
H$^+$
O
LiAlH$_4$
OH
KH
[1,3]
OH
H
H

(–)-Selinene

**Scheme 38a**

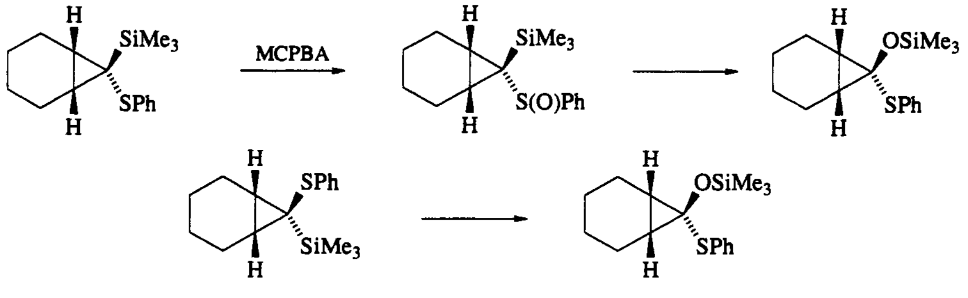
H
SiMe$_3$
SPh
H
MCPBA
H
SiMe$_3$
S(O)Ph
H
H
OSiMe$_3$
SPh
H
H
SPh
SiMe$_3$
H
H
OSiMe$_3$
SPh
H

68% *de*

**Scheme 38b**

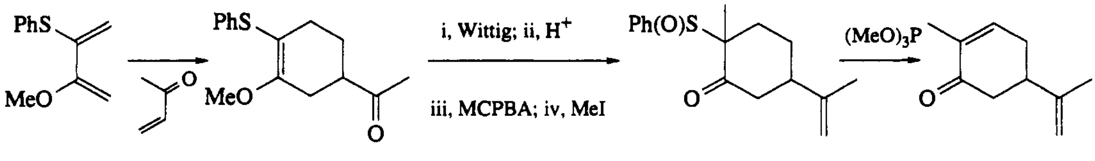
PhS
MeO
PhS
O
MeO
O
i, Wittig; ii, H$^+$
iii, MCPBA; iv, MeI
Ph(O)S
O
(MeO)$_3$P
O

**Scheme 38c**

## 1.5.3 SULFOXIDES

This part concentrates mainly on the utility of chiral sulfoxides in asymmetric synthesis. The main advantage of sulfoxides over the other sulfur functions which are described in this review is indeed their chirality. Sulfoxides are chiral groups which are easy to introduce, easy to remove and give high asymmetric induction in many reactions.[90]

The best way to prepare large quantities of optically active sulfoxides makes use of optically active menthyl sulfinate. By esterification of *p*-toluenesulfinic acid with l-menthol, a mixture of diastereoisomeric menthyl sulfinates is obtained. This esterification reaction shows no particular stereoselectivity and therefore a mixture of the two diastereoisomeric esters was obtained. However, it is possible to equilibrate these diastereoisomers in acidic media and to shift the equilibrium towards the less soluble isomer, (–)-(*S*)-menthyl *p*-toluenesulfinate, which was obtained in 90% yield from the starting *p*-toluenesulfinic acid (Scheme 39).[91]

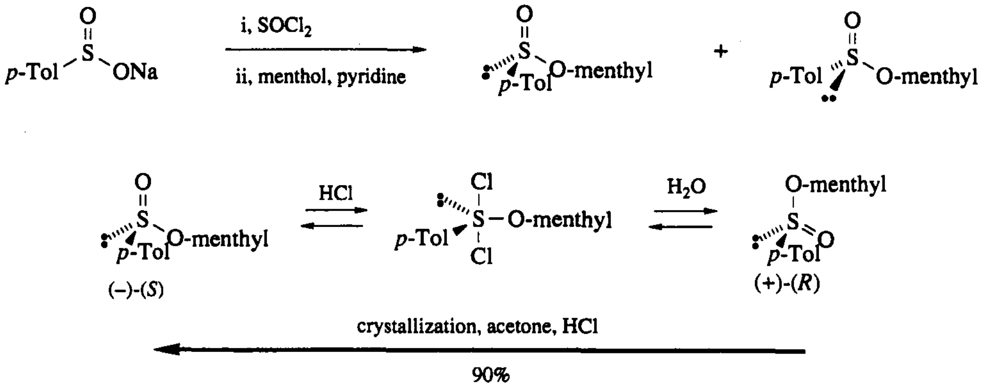
p-Tol
ONa
i, SOCl2
ii, menthol, pyridine
O-menthyl
+
HCl
H2O
Cl
(–)-(S)
(+)-(R)
crystallization, acetone, HCl
90%

Scheme 39

Optically active sulfoxides are readily obtained from menthyl sulfinate by a Grignard reaction. This reaction was originally proposed by Gilman[92] and applied to optically active products by Andersen:[93,94] this is a pure $S_N2$ reaction at sulfur with displacement of the menthoxy group by the Grignard. A great variety of sulfoxides have been prepared by this method;[90,95–105] other organometallics have also been used. A few examples are shown in Scheme 40.

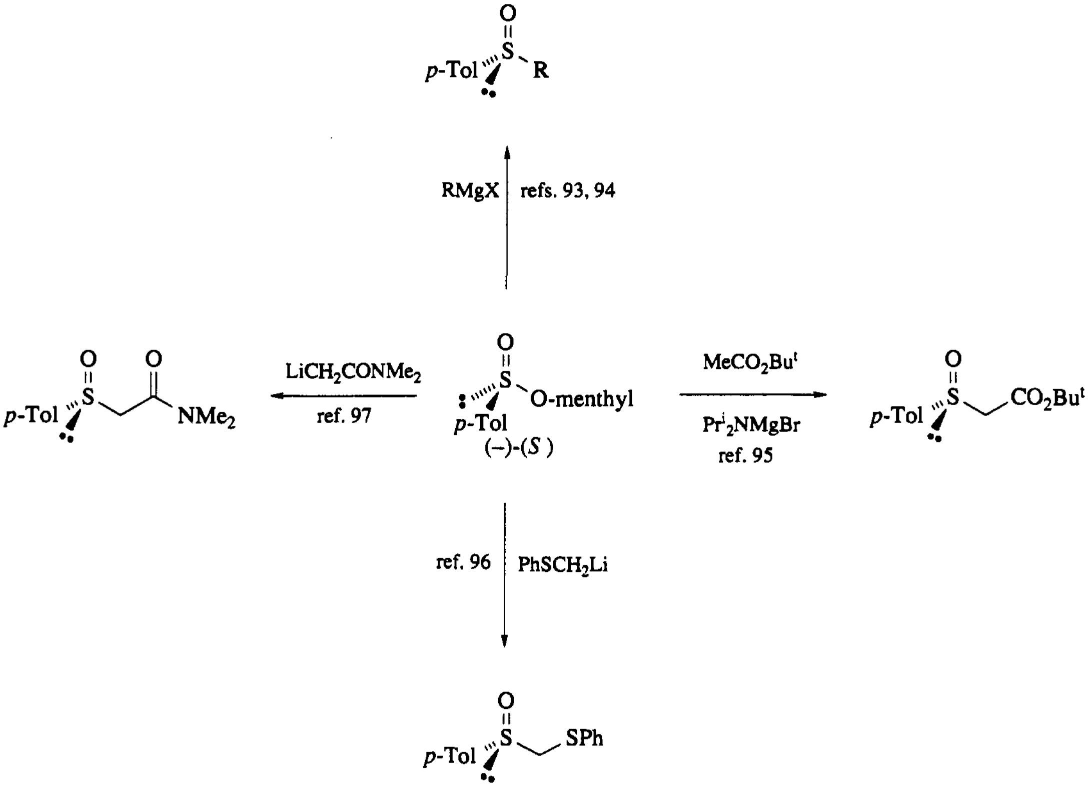
p-Tol
R
RMgX
refs. 93, 94
NMe2
LiCH2CONMe2
ref. 97
O-menthyl
(–)-(S)
MeCO2Bu<sup>t</sup>
Pr<sup>i</sup>2NMgBr
ref. 95
CO2Bu<sup>t</sup>
ref. 96
PhSCH2Li
SPh

Scheme 40

If optically active sulfoxides such as methyl *p*-tolyl sulfoxide give a poor diastereoselectivity when such an α-sulfinyl carbanion is added to a carbonyl,[90] the presence of another function such as ester, sulfide or amide, which has a chelating effect in the transition state, makes optically active α-sulfinyl esters, sulfides or amides very useful in asymmetric aldol-type condensation (Scheme 41).[97,106–109]

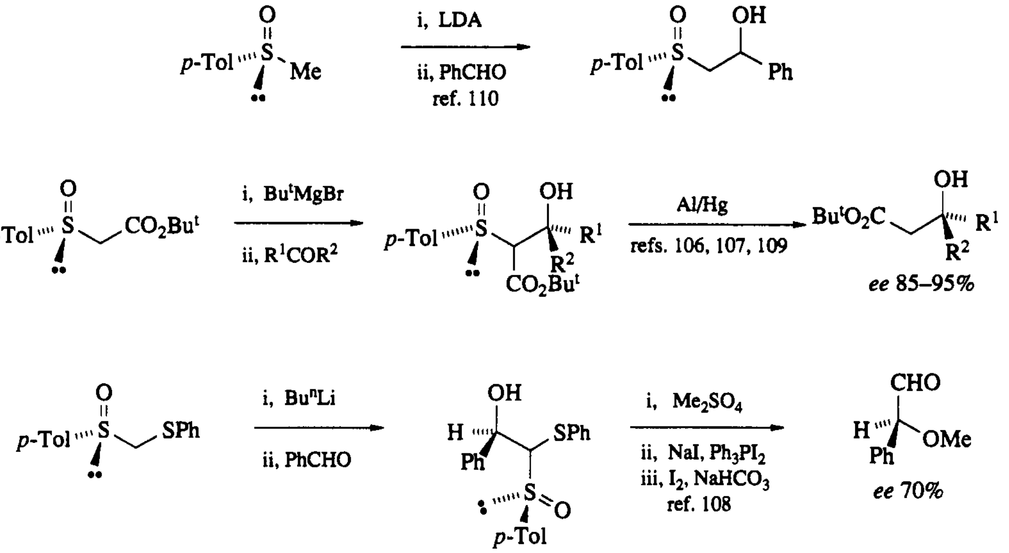

**Scheme 41**

Optically active sulfoxides can also be prepared by asymmetric oxidation of sulfides. However, numerous papers have reported very low enantioselectivity.[111] Only one report,[112–113] using a modified Sharpless reagent, $H_2O/Ti(OPr^i)_4$/diethyl tartrate/$Bu^tOOH$, described asymmetric oxidation of alkyl aryl sulfoxides with good enantiomeric excesses: 75 to 95%.

It should also be mentioned that optically active 2-sulfamyloxaziridines (**8**) afforded high asymmetric induction[114a] for the oxidation of nonfunctionalized sulfides to sulfoxides (53–91% *ee*). The enantioselectivities exhibited by these reagents are comparable to, or in some cases better than, the modified Sharpless reagent reported by Kagan.

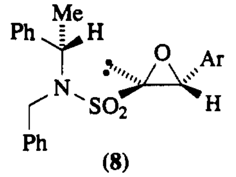

(**8**)

Several papers have also reported asymmetric oxidation of chiral sulfides having a structure derived from camphor.[114b,c]

Optically active vinylic sulfoxides can be prepared by the Andersen synthesis, using (–)-menthyl (–)-(*S*)-*p*-toluenesulfinate and vinylic Grignards,[115,116] or by the Wittig–Horner procedure, using carbonyl compounds and the anion of dimethyl (*R*)-*p*-toluenesulfinylmethanephosphonate, easily made from the corresponding menthyl sulfinate.[117] However, applicability of the former method depends on the availability of stereochemically pure 1-alkenyl halides for preparing Grignard reagents and the latter usually leads to a mixture of (*E*)- and (*Z*)-vinylic sulfoxides. Therefore, it is sometimes easier to prepare the corresponding alkynyl sulfoxide by the Andersen method from alkynyl Grignards and then reduce stereospecifically the triple bond into a *trans* double bond with DIBAL or a *cis* double bond by catalytic hydrogenation using the Wilkinson catalyst (Scheme 42).[118,119]

Vinylic sulfoxides have been used successfully in several Michael-type asymmetric syntheses.[120–124] One typical example is given by the asymmetric synthesis of (–)-methyl jasmonate (Scheme 43).[123]

The CD rings of steroids were synthesized by the same method in high enantiomeric purity.[124]

Vinylic sulfoxides have also been used in asymmetric Diels–Alder reaction.[125–130] A very high diastereoselectivity was observed with optically active sulfinylacrylates. One example[126] is given in Scheme 44.

An interesting observation was reported by Posner who showed that α-pyrone substituted by a sulfoxide[131] or a sulfone[132] reacts rapidly with vinyl ethers, giving a diastereoselective [2 + 4] cycloaddition (Scheme 45). Racemic sulfide, sulfoxide or sulfone was introduced on α-pyrone *via* 3-cuprio-

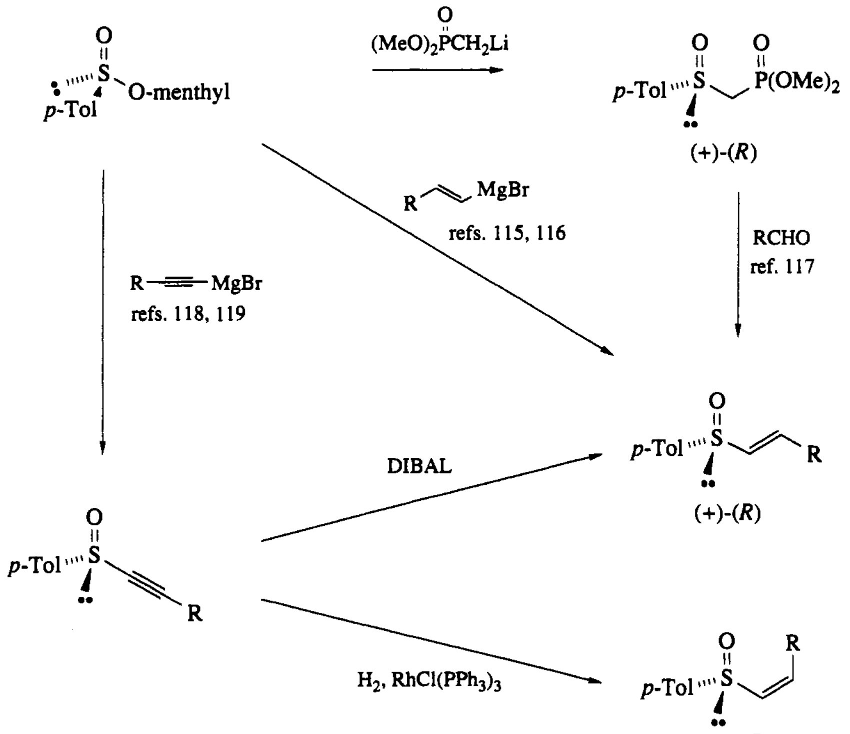
O-menthyl
p-Tol
(MeO)2PCH2Li
P(OMe)2
(+)-(R)
MgBr
refs. 115, 116
RCHO
ref. 117
R—≡—MgBr
refs. 118, 119
DIBAL
H2, RhCl(PPh3)3
(+)-(R)
(+)-(R)

**Scheme 42**

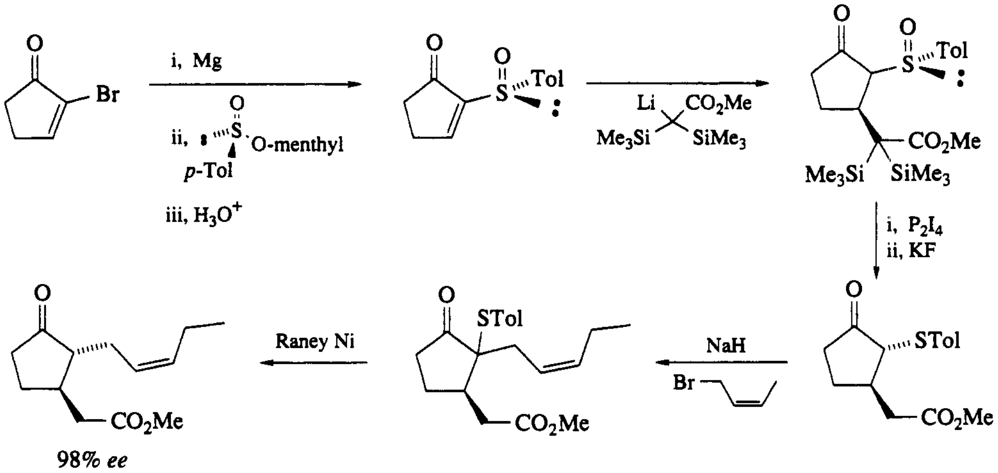
i, Mg
ii, O-menthyl p-Tol
iii, H3O+
Li CO2Me Me3Si SiMe3
i, P2I4
ii, KF
NaH
Raney Ni
STol
CO2Me
98% ee

**Scheme 43**

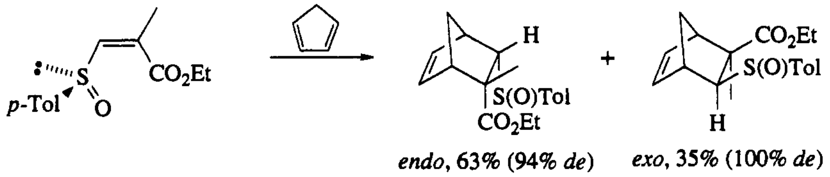
p-Tol
CO2Et
S(O)Tol
endo, 63% (94% de)
exo, 35% (100% de)

**Scheme 44**

2-pyrone.[133] However, optically active pyrone sulfoxide was prepared from (–)-(S)-dihydropyrone sulfoxide by dehydrogenation with $MnO_2$ in low yield.[131]

Vinylic sulfoxides can undergo additive Pummerer rearrangement when they are treated with trichloroacetyl chloride and a zinc/copper couple in refluxing ether giving optically pure γ-butyrolactone

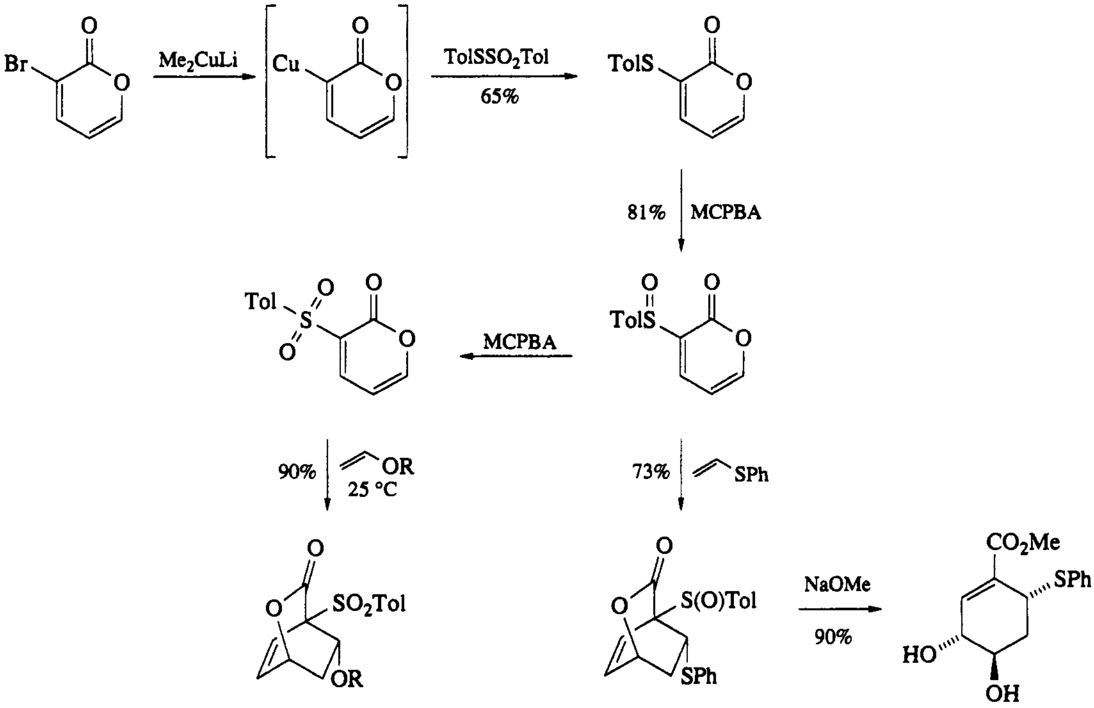
Br
Me2CuLi
Cu
TolSSO2Tol
65%
TolS
81%
MCPBA
MCPBA
Tol
S
TolS
90%
OR
25 °C
73%
SPh
SO2Tol
OR
S(O)Tol
SPh
NaOMe
90%
CO2Me
SPh
HO
OH

**Scheme 45**

(Scheme 46).[134,135] Vinyl sulfoxides also exhibited high chiral induction in the 1,3-dipolar cycloaddition with typical nitrones (Scheme 47).[136]

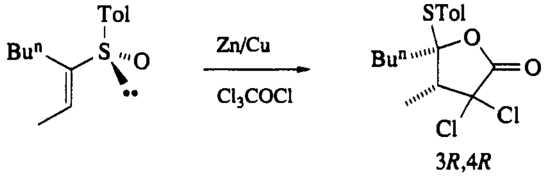
Tol
Bu^n
S
O
Zn/Cu
Cl3COCl
STol
Bu^n
O
O
Cl
Cl
3R,4R

**Scheme 46**

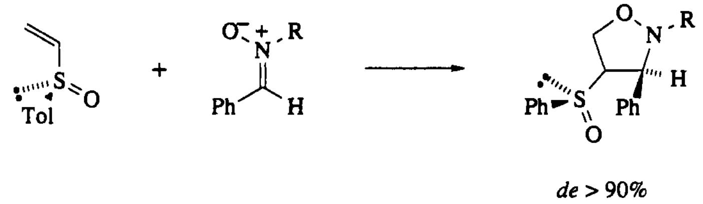
S
O
Tol
+
O⁻ + R
N
Ph
H
O
N
R
H
Ph
S
Ph
O
de > 90%

**Scheme 47**

They can also be used as vinylic carbanion species as shown by the asymmetric synthesis of the chroman ring of vitamin E.[137] The (*E*)/(*Z*) mixture of chiral sulfoxide (**9**) was readily isomerized into the (*E*)-isomer with LDA in THF (the exclusive formation of the (*E*)-isomer was due to the chelation of lithium with an oxygen of the acetal). Condensation to trimethylhydroquinonecarbaldehyde gave only one diastereoisomer and then the cyclization in presence of sodium methoxide was also fully stereoselective (the stereochemistry of the cyclization being controlled by that of the allylic hydroxy group which is eliminated during the cyclization; Scheme 48).

A few other examples are listed in Scheme 49: intramolecular addition of amine giving a good synthesis of (*R*)-(+)-carnegine,[138] synthesis of chiral butenolides by carbonation of vinylic carbanions[139] and conjugate additions of cuprates yielding chiral chromans.[140]

Allylic sulfoxides are also of interest mainly because of the possible sulfoxide/sulfenate rearrangement described by Mislow[141] when he observed that allyl *p*-tolyl sulfoxide racemized in a temperature range

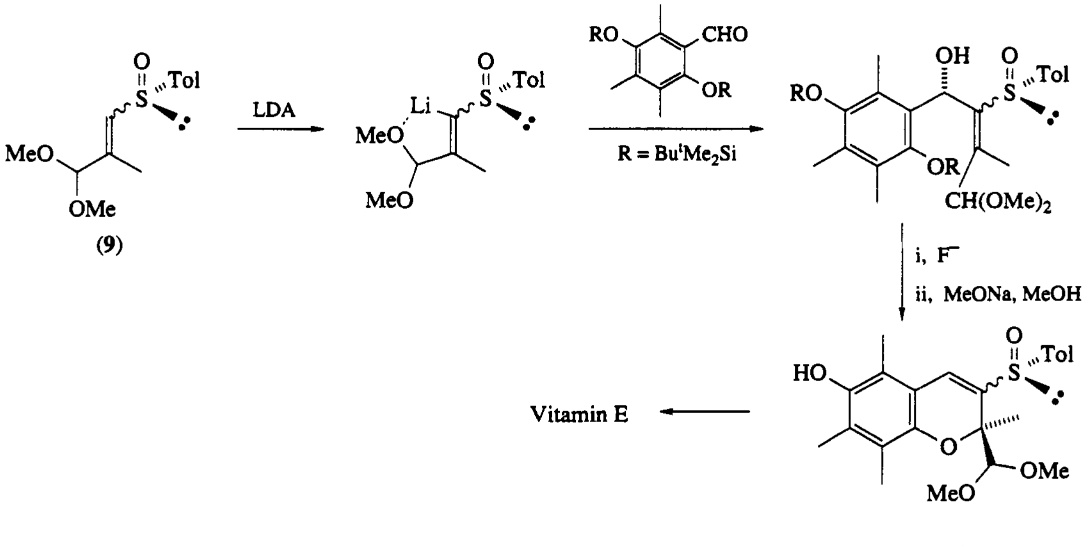
(9)
LDA
R = Bu$^t$Me$_2$Si
i, F$^-$
ii, MeONa, MeOH
Vitamin E
de > 95%

Scheme 48

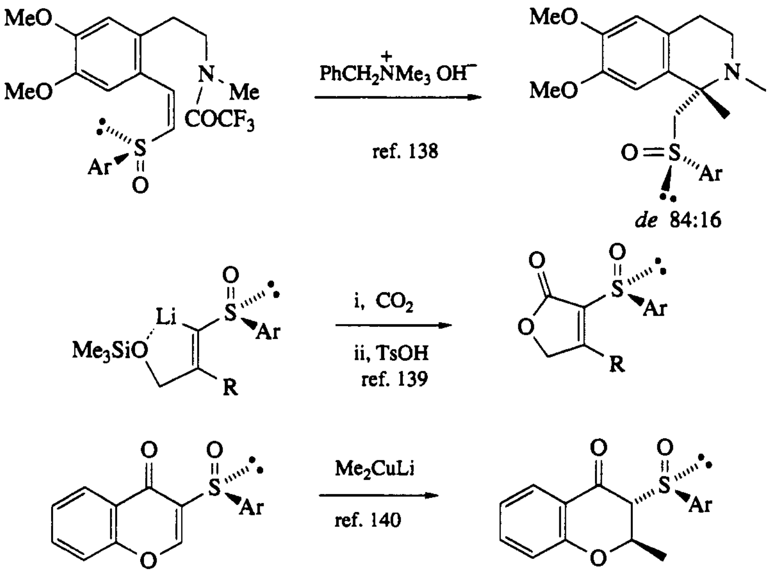
$Ph\overset{+}{C}H_2NMe_3$ OH$^-$
ref. 138
de 84:16
i, CO$_2$
ii, TsOH
ref. 139
Me$_2$CuLi
ref. 140

Scheme 49

(50–70 °C) significantly below the usual racemization temperature of sulfoxides (150 °C and higher; Scheme 50).

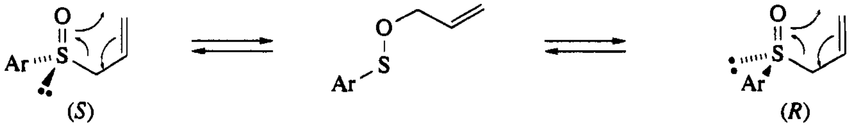

Scheme 50

This 2,3-sigmatropic shift has been of substantial utility since Evans[142] and Hoffmann[143] realized that allyl alcohols can be obtained by intercepting the sulfenate with thiophilic agents. One possible way of preparing optically active allylic sulfoxides, which started to racemize even at 0 °C was the isomerization of the corresponding vinylic sulfoxide followed by the sulfenate rearrangement in the presence of trimethyl phosphite (Scheme 51).[143,144]

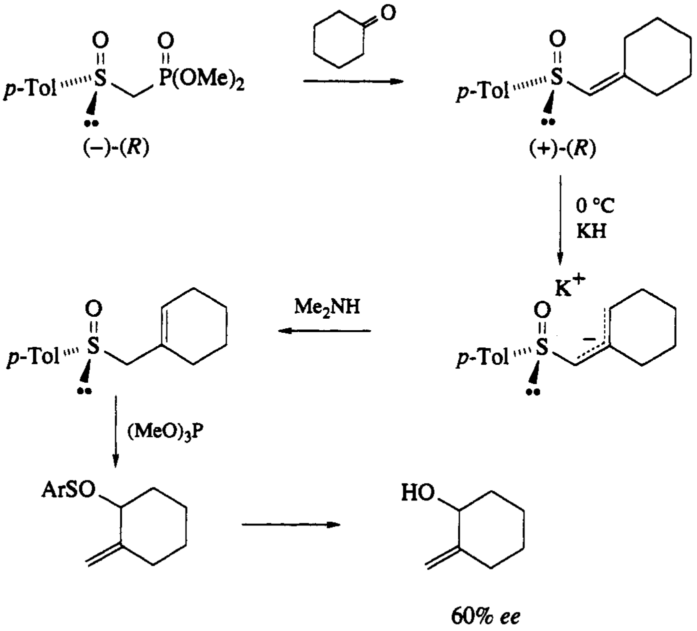

**Scheme 51**

The carbanions of allylic sulfoxides undergo kinetically controlled conjugate additions to give vinylic sulfoxides as a single diastereoisomer (Scheme 52).[145,146]

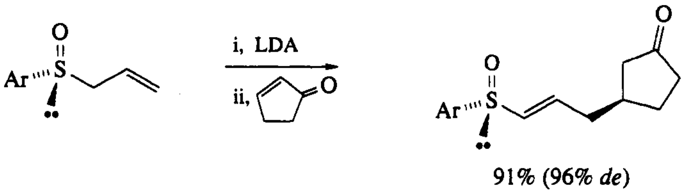

**Scheme 52**

(*E*)- and (*Z*)-allylic sulfoxides bearing alkyl groups at C-3 also undergo highly stereoselective conjugate additions to cyclic enones to give *syn*- and *anti*-vinylic sulfoxides.[146c] Racemic allylic sulfoxides can also be obtained from alkenes by an $EtAlCl_2$-catalyzed ene reaction with *p*-toluenesulfinyl chloride (Scheme 53).[147]

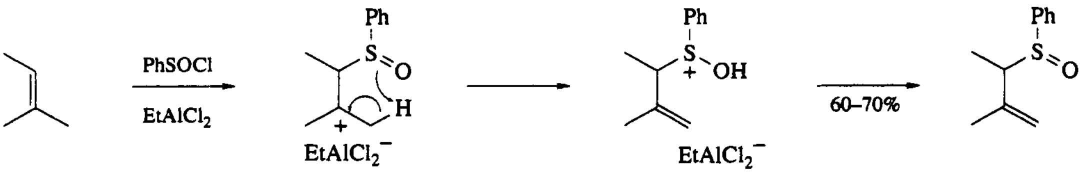

**Scheme 53**

Allylic alcohols can be converted to 1,3-dienes by sequential sulfenate–sulfoxide 2,3-sigmatropic rearrangement and *syn* elimination (Scheme 54).[148] The last step used the pyrolytic elimination of sulfoxide, a *cis* elimination discovered by Cram.[149] A paper published by Trost[150] documented this topic in detail.

A useful synthesis of functionalized dienes from alkenes used the initial formation of a stable π-allyl palladium complex, followed by reaction with α-sulfinyl ester enolate and pyrolytic sulfoxide elimination (Scheme 55).[151]

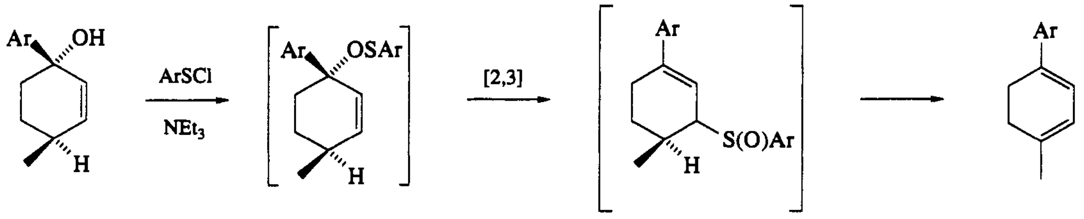
Ar
OH
ArSCl
NEt3
OSAr
H
[2,3]
S(O)Ar

Scheme 54

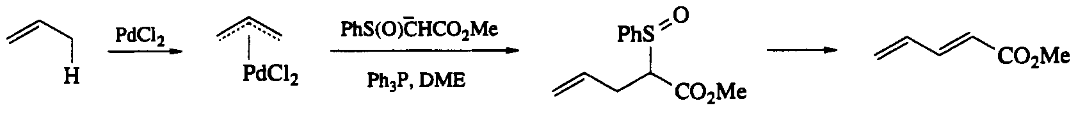
H
PdCl2
PhS(O)CHCO2Me
Ph3P, DME
PhS
O
CO2Me

Scheme 55

Allenic sulfoxides can be made from propargylic sulfenates by a 2,3-sigmatropic shift. In the example reported,[152] the product is not stable at room temperature and undergoes a 1,5-sigmatropic hydrogen shift (Scheme 56). These allenic sulfoxides can react as Michael acceptors (Scheme 57).[153]

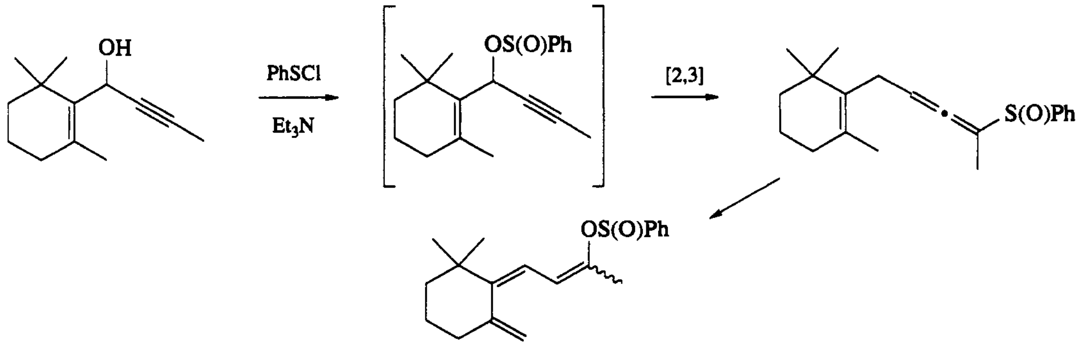
OH
PhSCl
Et3N
OS(O)Ph
[2,3]
S(O)Ph

Scheme 56

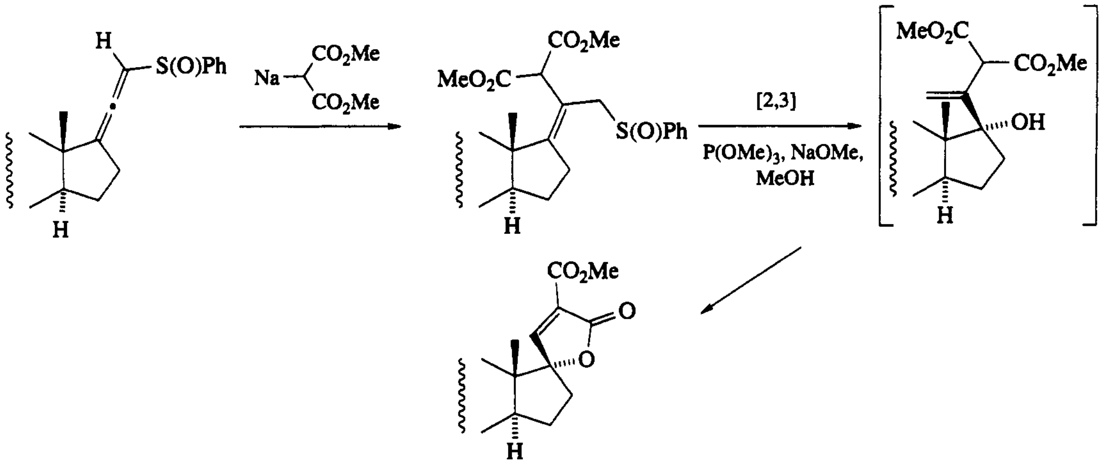
H
S(O)Ph
Na
CO2Me
MeO2C
[2,3]
P(OMe)3, NaOMe, MeOH
OH
O

Scheme 57

Optically active β-keto sulfoxides are readily available from esters and methyl *p*-tolyl sulfoxide. The ketone function can be reduced with metal hydrides (DIBAL and $ZnCl_2$/DIBAL) giving, with very high diastereoselectivity, opposite configurations in the resulting β-hydroxy sulfoxides (Scheme 58).[154,155]

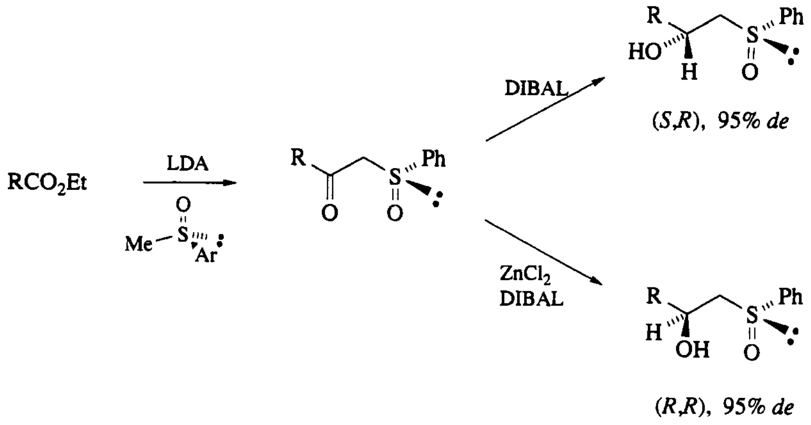

Scheme 58

Chiral β-hydroxy sulfoxides are very good intermediates for the synthesis of optically active alcohols,[156] epoxides[155] or butenolides (Scheme 59).[157]

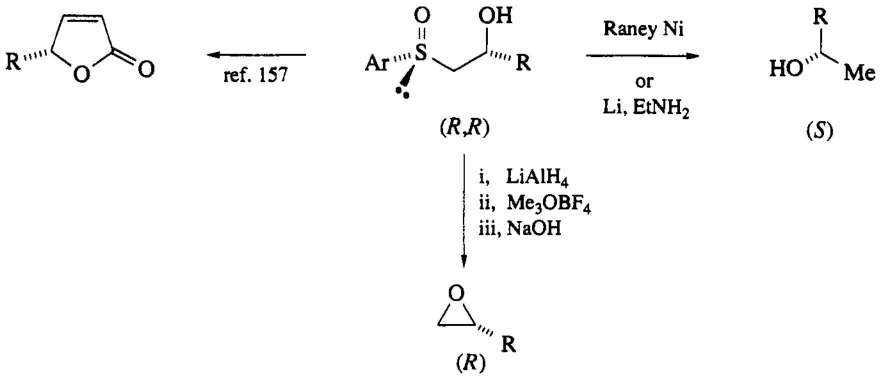

Scheme 59

Allylic and propargylic β-keto sulfoxides could be reduced as well as saturated compounds. Optically active allylic β-hydroxy sulfoxides present some specific interest because of the possible hydroxylation of the double bond leading to vicinal triols. The osmium tetroxide catalyzed hydroxylation reaction of the double bond in the presence of trimethylamine *N*-oxide is highly stereoselective:[158,159] the (*R*,*R*)-β-hydroxy sulfoxide gave only one diastereoisomeric triol as a result of a *cis* hydroxylation of the double bond and a symbiotic effect of the two chiral centers in the asymmetric induction (the (*S*,*R*)-isomer gave a lower *de*).

In the case of the (*S*,*R*)-β-hydroxy sulfoxide, the OH group has to be protected by a trifluoroacetyl group before hydroxylation, which was highly stereoselective and fully controlled by the chiral sulfoxide group.[160] Very similar results were obtained in the case of allylic β-hydroxy sulfoxides having a (*Z*)-geometry on the double bond.[160] Trihydroxy sulfoxides in all possible configurations can therefore be made by this method (Scheme 60).

These trihydroxy sulfoxides are useful molecules in total synthesis because of the possible transformation of the sulfoxide into aldehyde by a Pummerer rearrangement.[159,161] Homoallylic β-hydroxy sulfoxides have also been prepared from β-epoxy sulfoxides, readily obtained from methyl monochloroacetate (Scheme 61a).[162a]

Optically active α-chloro sulfoxides have recently been obtained by a very practical procedure[162b] using NBS and potassium carbonate with the expected inversion of configuration at sulfur. Chloro sulfoxides were shown to be very useful in the synthesis of epoxides[162c] and for α,β-unsaturated ketone homologation (Scheme 61b).[162d]

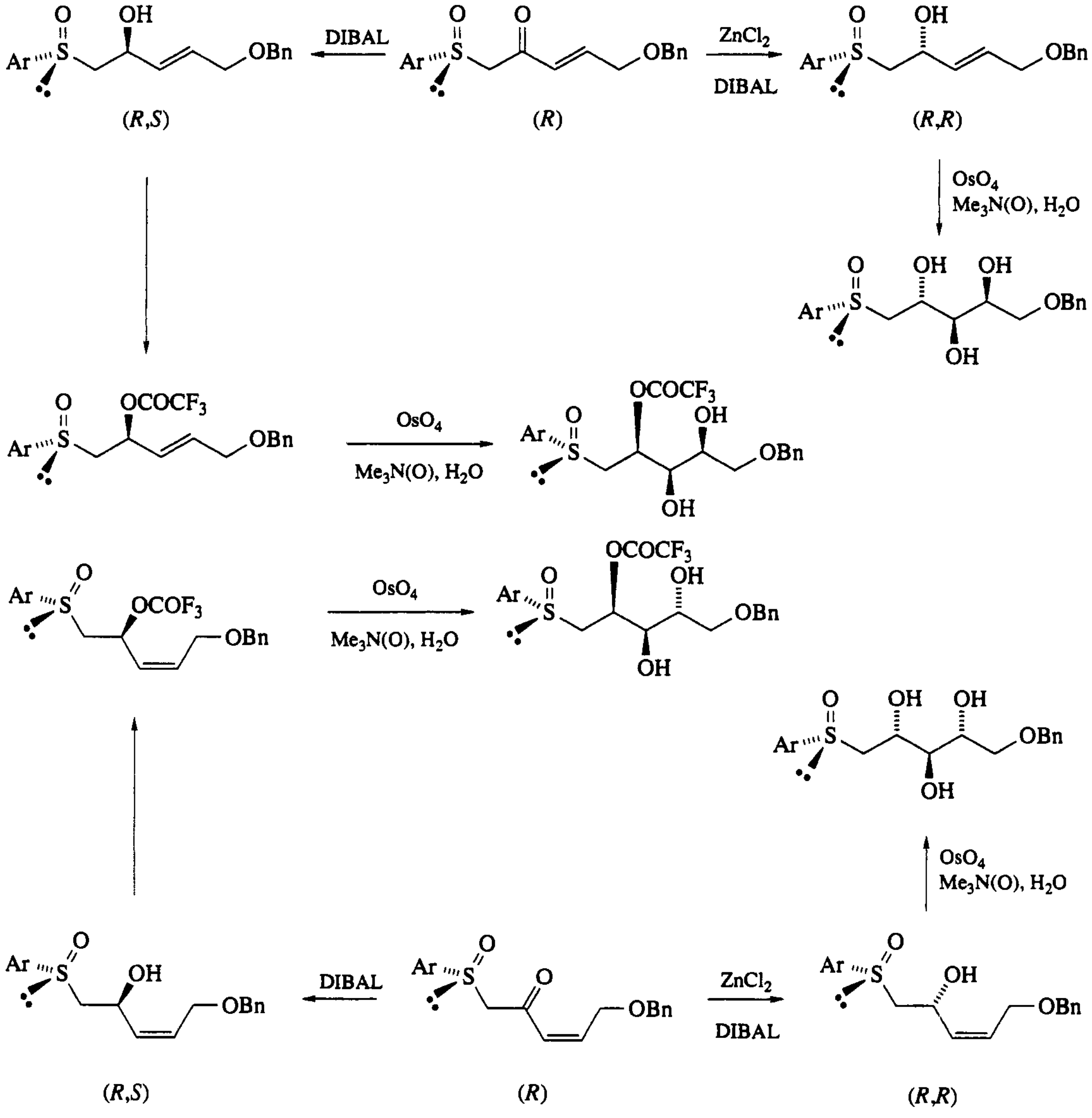

Scheme 60

## 1.5.4 SULFONES

Although Kohler and Tishler[163] reported the metallation of benzyl sulfones in 1935 and Field[164] later used benzyl sulfones in Grignard reactions, the use of new bases and the easy introduction of a sulfonyl group into a molecule *via* alkyl halides and sodium sulfinate resulted in a major development by Julia[165–170] of the synthetic use of sulfones.

The preparation of 3,7-dimethyl-2-*trans*-4-*trans*-6-*trans*-octatrienoic acid (Scheme 62)[165,166] is a good example of the introduction of a sulfonyl group from sodium sulfinate, of the coupling reaction of a sulfonyl carbanion and allylic bromide and finally of the elimination of the sulfonyl group in basic medium giving the all-*trans* compound. The same method was used for vitamin A synthesis (Scheme 63).[168,170]

In a similar way, Grieco[171] reported the synthesis of *trans*-squalene from *trans*-farnesyl acetate and the corresponding sulfone and Liu[176] prepared difluororetinal analogs.

A modification of vitamin A synthesis was reported recently,[172] using addition of allylic sulfone carbanion to aldehyde followed by a basic double elimination[173] of the resulting β-alkoxy sulfone with excellent stereocontrol (Scheme 64).

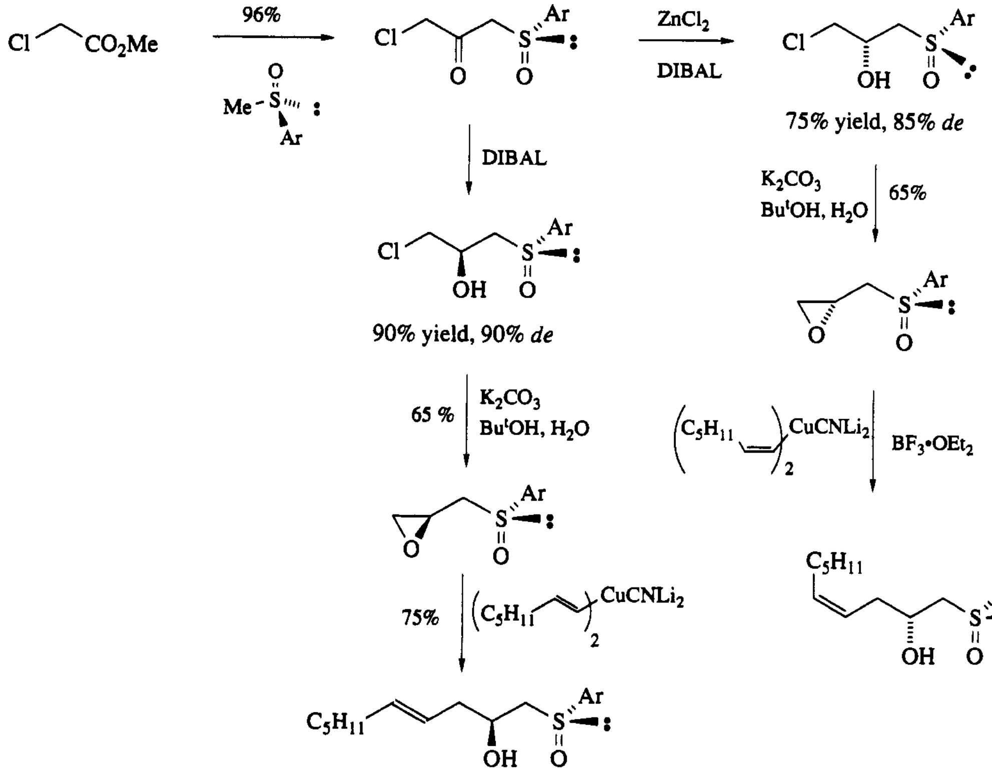
96%
ZnCl2
DIBAL
75% yield, 85% de
DIBAL
K2CO3
Bu'OH, H2O
65%
90% yield, 90% de
65 %
K2CO3
Bu'OH, H2O
BF3•OEt2
CuCNLi2
75%
CuCNLi2

**Scheme 61a**

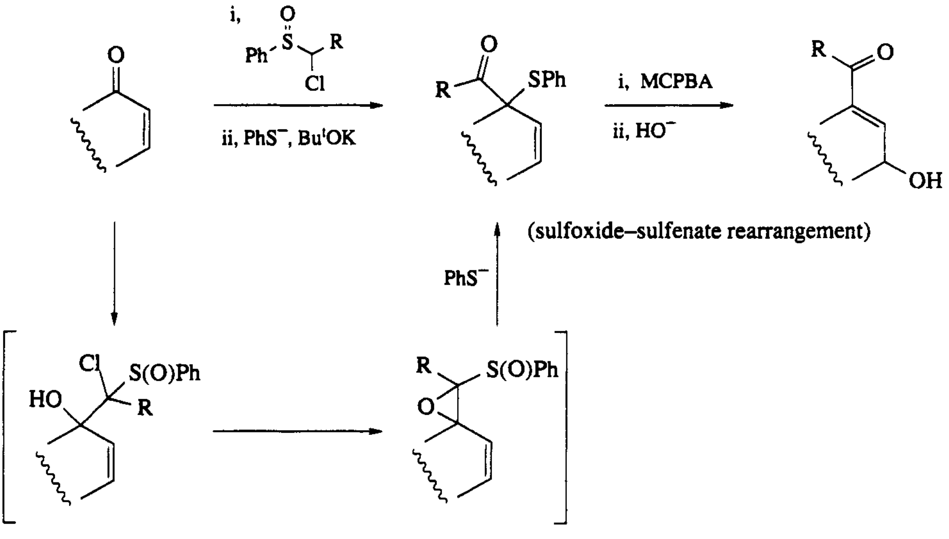
i,
ii, PhS⁻, Bu'OK
i, MCPBA
ii, HO⁻
(sulfoxide–sulfenate rearrangement)
PhS⁻

**Scheme 61b**

Other applications of carbanions α to a sulfone in total syntheses have recently been reported. Most of them used allylic sulfones or allylic halides. Two examples are reported here. In the synthesis of a precursor of cembranolides,[183] a sulfone derived from geranyl bromide was coupled with an allylic alcohol epoxide (Scheme 65). An interesting point was that the coupling reaction gave high yields only when the lithiated sulfone was allowed to react with the epoxymagnesio alkoxide (the lithium salt of the epoxy alcohol did not react at all with the lithiated sulfone).

In the synthesis of an ionophore antibiotic,[184] a bicyclic sulfone made by oxidation of the corresponding sulfide with $PhSeSePh/H_2O_2$ to avoid double bond oxidation was coupled with an allylic bromide in 97% yield and high stereoselectivity. The sulfonyl group was finally eliminated in basic medium to create a *trans*-diene (Scheme 66).

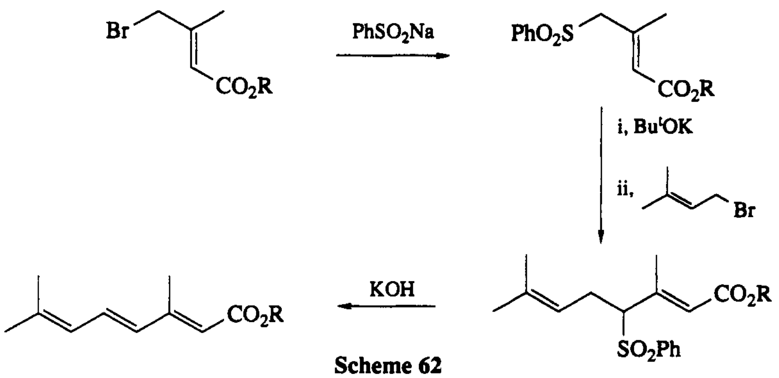
Br
CO2R
PhSO2Na
PhO2S
CO2R
i, ButOK
ii,
Br
CO2R
SO2Ph
KOH
CO2R

**Scheme 62**

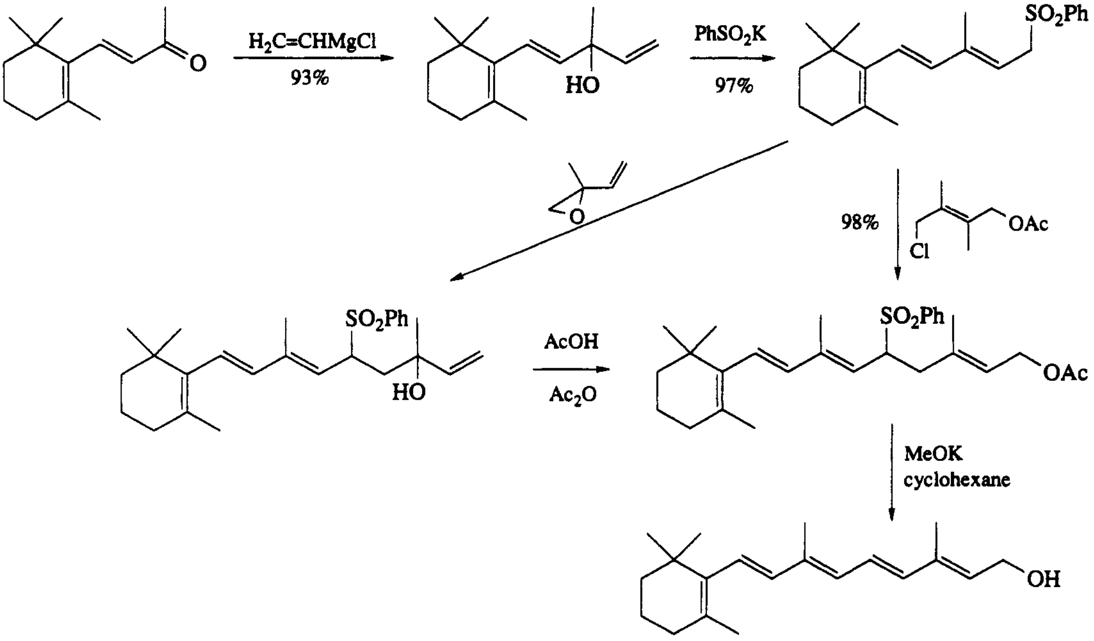
O
H2C=CHMgCl
93%
HO
PhSO2K
97%
SO2Ph
O
98%
Cl
OAc
SO2Ph
HO
AcOH
Ac2O
SO2Ph
OAc
MeOK
cyclohexane
OH

Vitamin A

**Scheme 63**

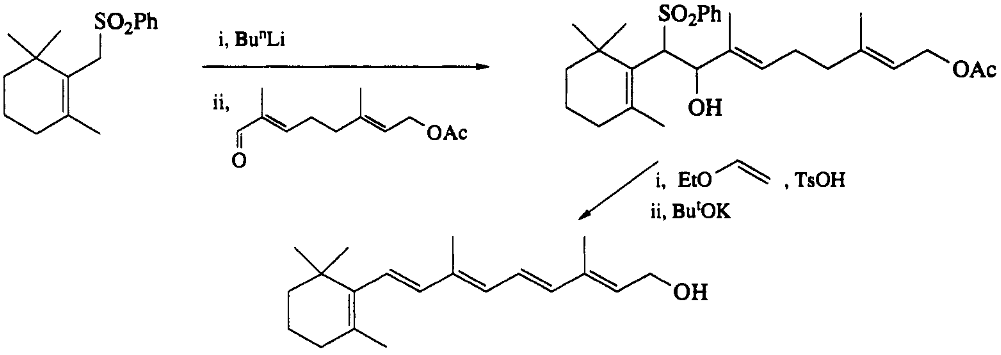
SO2Ph
i, BunLi
ii,
O
OAc
SO2Ph
OH
OAc
i, EtO
, TsOH
ii, ButOK
OH

Vitamin A

**Scheme 64**

γ-Oxo sulfone acetals can be acylated with esters giving, after reductive desulfonylation, a convenient route to γ-keto aldehydes or 1,4-diketones (Scheme 67).[174] The intermolecular acylation of α-sulfonyl carbanions was also used to synthesize γ-butyrolactones.[175]

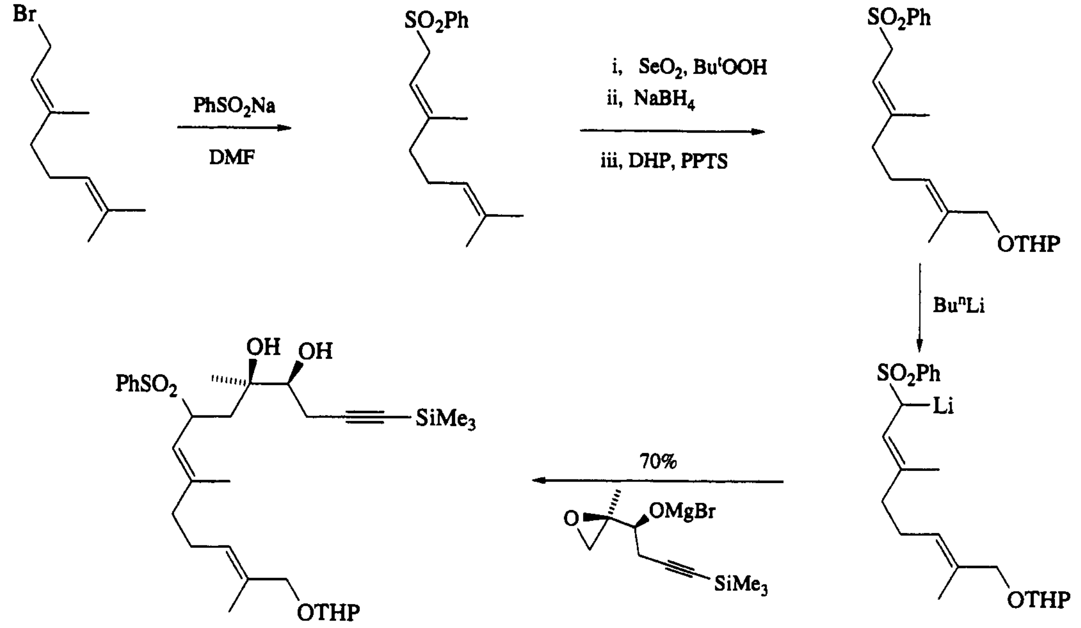
Br
PhSO2Na
DMF
SO2Ph
i, SeO2, ButOOH
ii, NaBH4
iii, DHP, PPTS
OTHP
BunLi
Li
70%
O
OMgBr
SiMe3
OH
PhSO2

Scheme 65

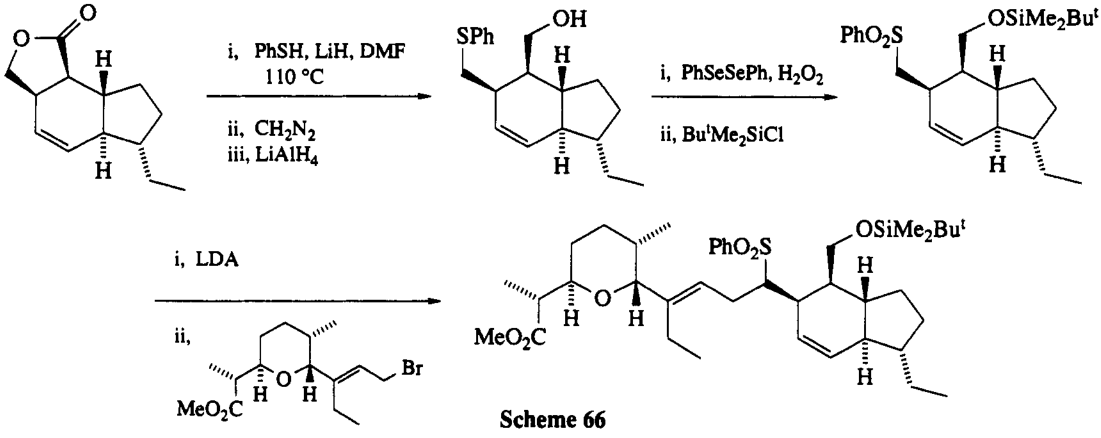
O
H
i, PhSH, LiH, DMF 110 °C
ii, CH2N2
iii, LiAlH4
SPh
OH
i, PhSeSePh, H2O2
ii, ButMe2SiCl
PhO2S
OSiMe2But
i, LDA
ii,
MeO2C
Br

Scheme 66

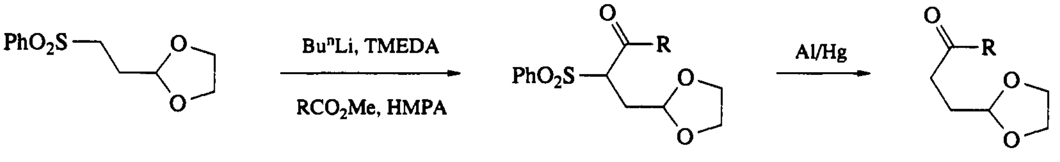
PhO2S
O
BunLi, TMEDA
RCO2Me, HMPA
R
Al/Hg

Scheme 67

The introduction of a sulfonyl group on cyclic compounds allowed γ-alkylation of α,β-unsaturated ketones (Scheme 68).[177]

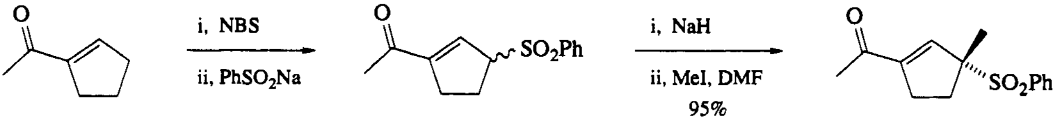
O
i, NBS
ii, PhSO2Na
SO2Ph
i, NaH
ii, MeI, DMF
95%

Scheme 68

α-Pyrone sulfone[132,178a] is indeed, as we have already shown, very reactive in Diels–Alder reactions. The chiron (–)-(**10a**) was obtained with very high diastereoselectivity from α-pyrone sulfone and optically active vinyl ether (Scheme 69). This lactone was later used[178a] in the asymmetric synthesis of (–)-methyltriacetyl-4-epishikimate (**10b**). β-Sulfonylnitroalkenes were also shown to be reactive alkyne equivalents in Diels–Alder reactions.[178b]

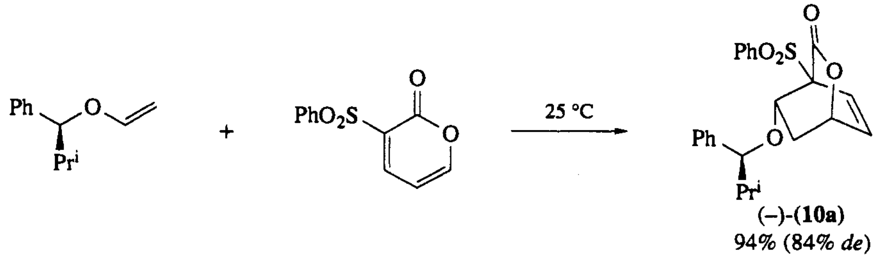

**Scheme 69**

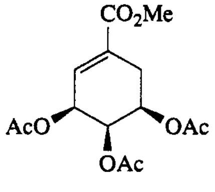

**(10b)**

1,1-Bis(benzenesulfonyl)cyclopropane[179] presents several advantages in organic synthesis: the electron-withdrawing groups on the cyclopropane facilitate its opening by nucleophiles and, since each sulfone can be cleaved to create a carbanionic center, various electrophilic substitutions can be performed. One example is given in Scheme 70.

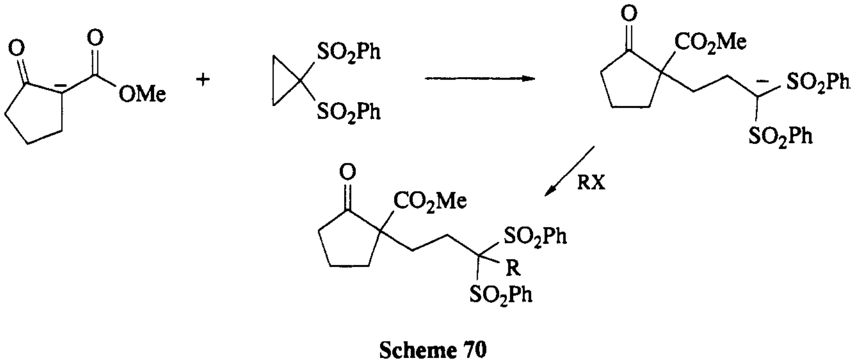

**Scheme 70**

The Ramberg–Bäcklund reaction is a synthetically useful process in which α-haloalkyl sulfones afford alkenes upon treatment with base.[180] Bromomethanesulfonyl bromide (**11**) is a very useful reagent for such reactions with unusual stereochemical features of the reaction with base.[181,182] Adducts between (**11**) and alkenes are formed in nearly quantitative yield by a light-catalyzed free radical addition. Direct treatment of these adducts with DBN afforded vinylic sulfones, which on treatment with Bu$^t$OK gave a highly stereoselective elimination to the corresponding diene, probably *via* a base-catalyzed isomerization to the corresponding allylic sulfone (Scheme 71).

(*E*)-1,3-butadienyl tosyl sulfone was found to react with dialkylcuprates; the alkyl group was added to the terminal double bond and the newly formed double bond has exclusively (*Z*)-geometry (Scheme 72).[185] It is interesting that starting from butadienyl allyl sulfone, the stereochemistry of the double bonds was maintained during the Ramberg–Bäcklund sulfur extrusion.

In similar work, Julia[186] prepared allyl dienyl sulfones from (*Z*)-2-methyl-1,3-butadienylsulfinate. Addition of various nucleophiles to the diene and Ramberg–Bäcklund reaction then yielded isoprenoid compounds (Scheme 73).

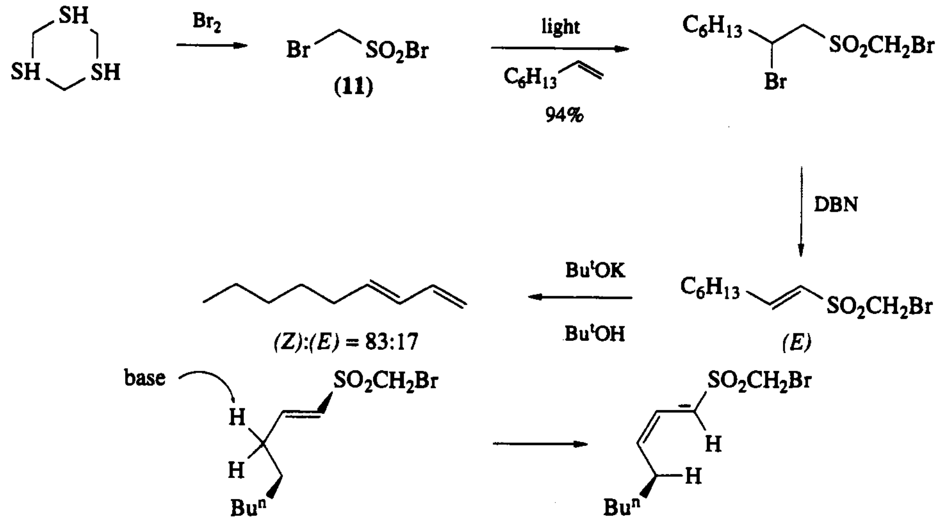
Br2
(11)
light
94%
DBN
Bu'OK
Bu'OH
(Z):(E) = 83:17
(E)
base
Bun

Scheme 71

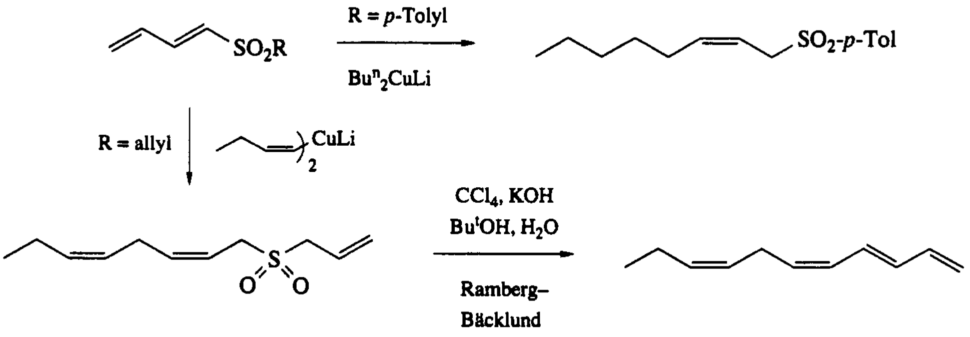
R = p-Tolyl
Bun2CuLi
R = allyl
CuLi
CCl4, KOH
Bu'OH, H2O
Ramberg–
Bäcklund

Scheme 72

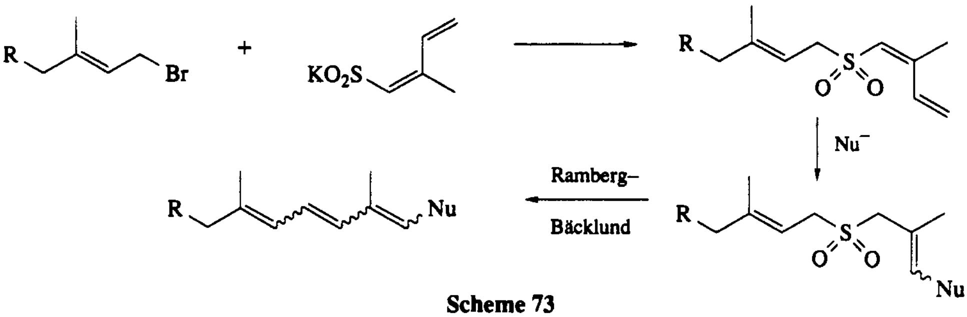
Nu⁻
Ramberg–
Bäcklund

Scheme 73

Oxidation of α-sulfonyl carbanions with copper(II) trifluoromethanesulfonate gives dimers of the original sulfone,[187] while with copper(II) acetate vinylic sulfones were obtained (Scheme 74).[188]

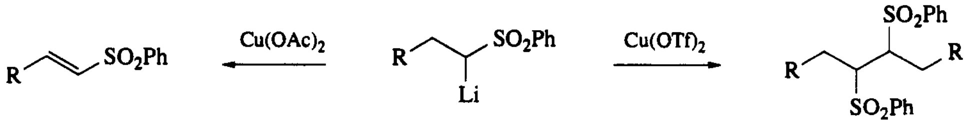
Cu(OAc)2
Cu(OTf)2

Scheme 74

Vinyl sulfones can be easily functionalized in a highly regio- and stereo-selective way: organolithium reagents undergo conjugate addition to afford *trans* adducts in high yield,[189] while organocuprate reagents undergo an amine-directed conjugate addition to afford the *cis* adduct (Scheme 75).[190,191]

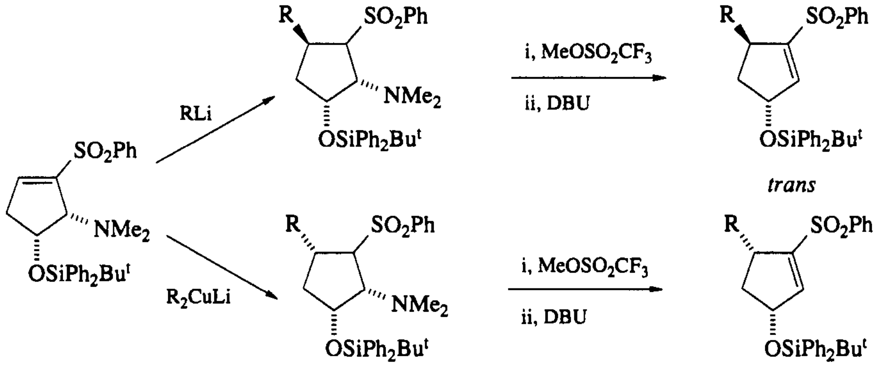
RLi
R₂CuLi
i, MeOSO₂CF₃
ii, DBU
trans
cis

**Scheme 75**

The synthesis of the preceding vinyl amino sulfone offers a very good example of a stereospecific sulfide-directed epoxidation (Scheme 76).[192] Oxidation of optically active sulfide alcohol (**12**; readily made from epoxycyclopentadiene[193] and resolved) with MCPBA affords the corresponding sulfoxide, which is in equilibrium with the sulfenate ester. Treatment with pyridine hydrobromide and then phenyl disulfide and bromine gives the bromodiol (**13**), which is simply cyclized to the epoxide with aqueous sodium hydroxide solution (83% overall yield from the sulfoxide). Treatment of the β-epoxy sulfone with DBU followed by *in situ* silylation with *t*-butyldiphenylsilyl chloride affords an 86% yield of vinyl sulfone (**14**). Mesylation of the alcohol moiety followed by immediate treatment with dimethylamine produces the amino vinyl sulfone *via* a *syn* $S_N2'$ substitution.[189]

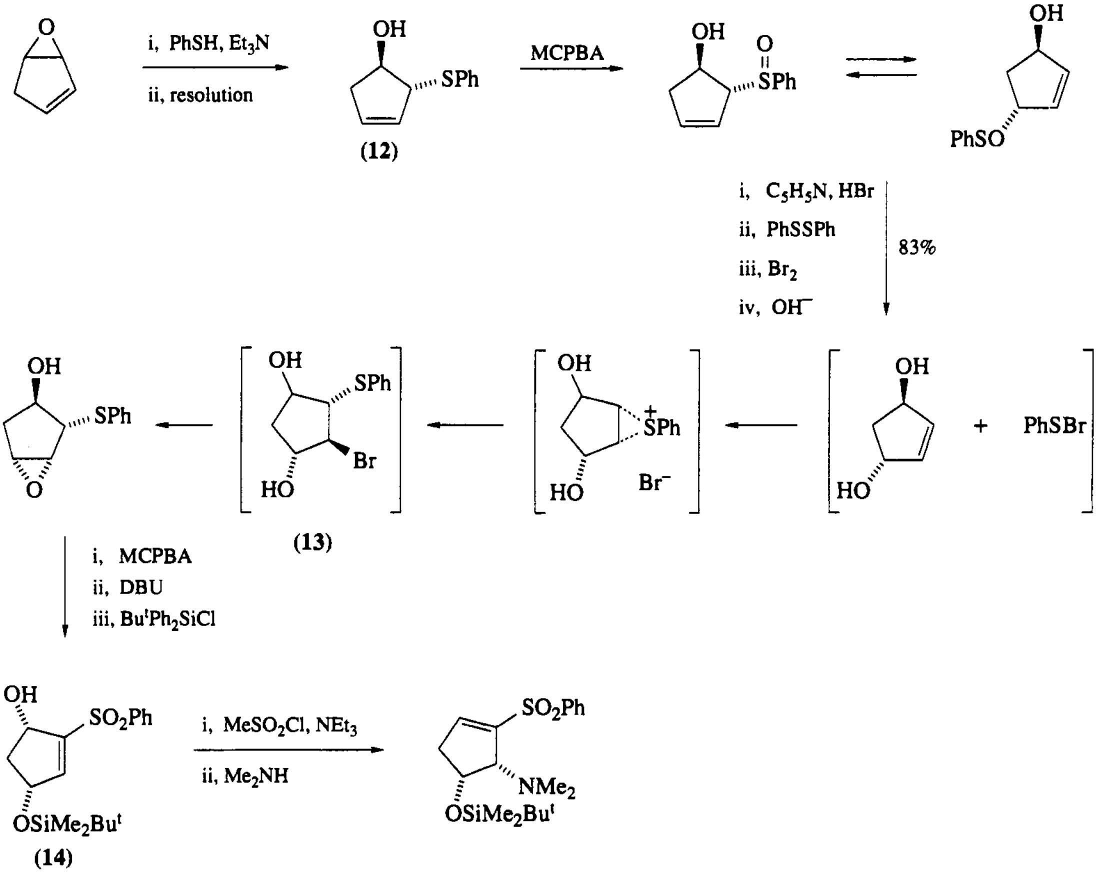
i, PhSH, Et₃N
ii, resolution
(12)
MCPBA
i, C₅H₅N, HBr
ii, PhSSPh
iii, Br₂
iv, OH⁻
83%
(13)
i, MCPBA
ii, DBU
iii, BuᵗPh₂SiCl
(14)
i, MeSO₂Cl, NEt₃
ii, Me₂NH

**Scheme 76**

In a recent total synthesis of (±)-morphine,[194] the key step was a cyclization step induced by intramolecular Michael addition on a vinylic sulfone followed by bromide displacement (Scheme 77). The entire process was highly stereoselective. Methyl-3-phenylsulfonyl orthopropionate was shown to be a good reagent for cyclopentannulation (Scheme 78).[195]

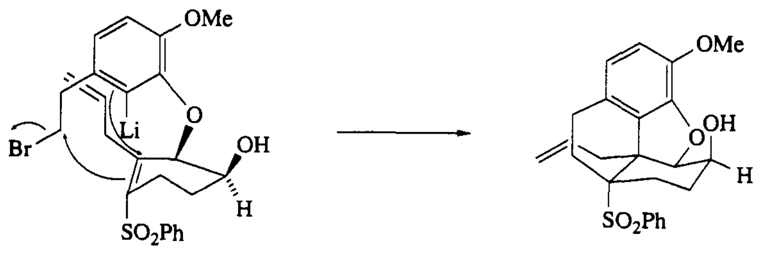
OMe
Li
Br
O
OH
H
SO2Ph
OMe
OH
O
H
SO2Ph

Scheme 77

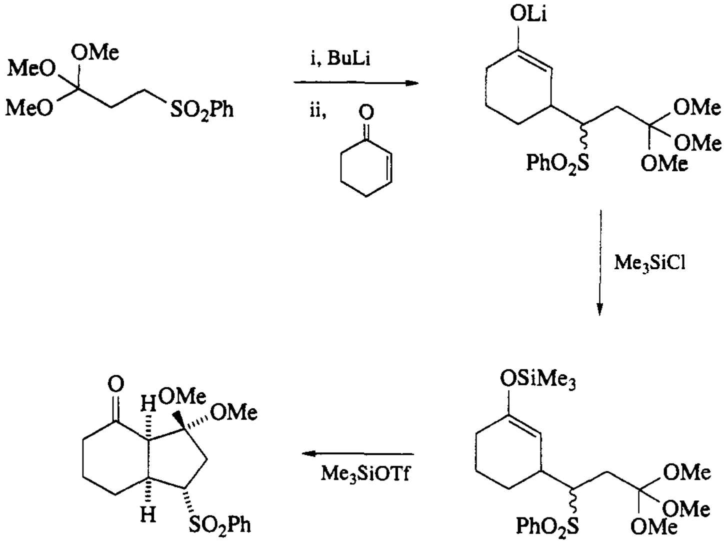
MeO
OMe
MeO
SO2Ph
i, BuLi
ii,
O
OLi
OMe
OMe
PhO2S
OMe
Me3SiCl
OSiMe3
OMe
OMe
PhO2S
OMe
Me3SiOTf
O
H
OMe
OMe
H
SO2Ph

Scheme 78

During the total synthesis of an antileukemia agent, control of the stereochemistry of the C ring formation has been established by a cesium fluoride mediated intramolecular conjugate addition of an α-face α-sulfonyl ester to an α-chloroenone (Scheme 79).[196]

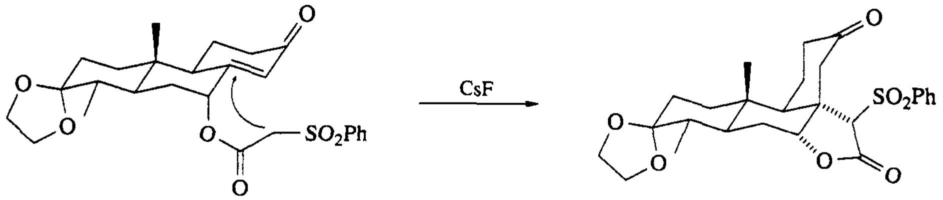
O
O
O
O
SO2Ph
O
CsF
O
SO2Ph
O
O
O
O

Scheme 79

2-Phenylsulfonic allylic bromide (**15**) reacts with aldehydes in the presence of zinc in high yield and high diastereoselectivity giving *syn*-hydroxy sulfones (Scheme 80).[197,198]

A good example of acyclic diastereoselection was reported by Isobe[199] during 'heteroconjugate addition' on vinylic sulfone. The 'heteroalkene' is indeed a vinylic sulfone with an α-chiral center and a hydroxy group in the allylic or homoallylic position. In the allylic case, a complete *syn* diastereoselection was observed during methyllithium addition. This high stereoselectivity can be explained by the following: the nucleophilic carbanion should coordinate with the oxygen atom by a chelation effect through the

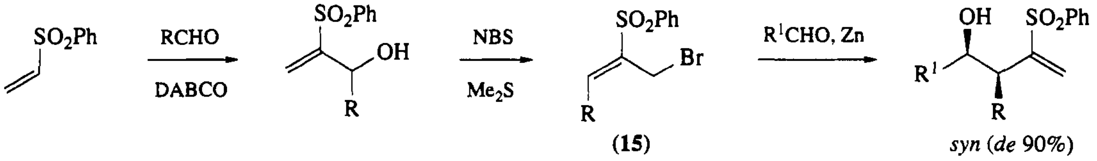

(15)

*syn* (*de* 90%)

**Scheme 80**

lithium cation so that the nucleophile will have a higher opportunity for attacking the alkene from the oxygen face than from the nonchelating carbon face (Scheme 81).

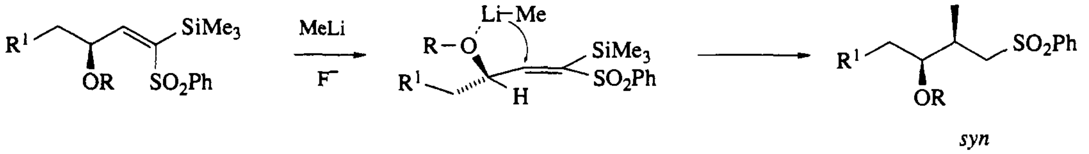

**Scheme 81**

The *anti* diastereoselectivity can be achieved by coordination of the nucleophile to the opposite face of the α-oxygen atom. This was the case with the homoallylic system (Scheme 82).

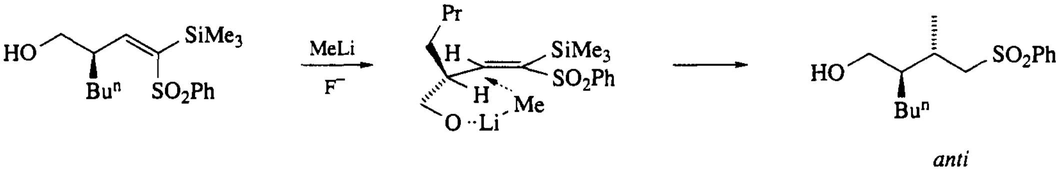

**Scheme 82**

The heteroalkenes were prepared by Peterson-type alkenation of the corresponding aldehydes with bis(trimethylsilyl)phenylthiomethyllithium [$PhS(Me_3Si)_2CLi$] followed by oxidation to sulfones.

Remarkable diastereocontrol was also reported by Trost[200] during alkylation of allylic sulfones with epoxide. A very high kinetic diastereoselectivity was observed in the case of terminal epoxide and branching on the vinyl carbon proximal to sulfone (Scheme 83).

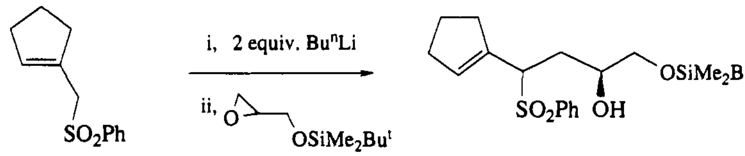

kinetic control, *de* = 97:3

**Scheme 83**

In the other cases, the diastereoselectivity was higher under thermodynamic control. The remarkable ability to obtain γ-hydroxy sulfones with high diastereoselectivity offers the flexibility to transfer stereocontrol to carbon–carbon bond formation by substitution of the sulfone. This is illustrated by the copper cyanide catalyzed coupling of Grignard reagents (Scheme 84).

Sulfones can also be used in Friedel–Crafts-type cyclizations.[201] One example is shown in Scheme 85, where the cyclization in the presence of aluminum chloride of the allylic sulfone occurred in high yield, showing that sulfones can also become electrophiles. Since a tertiary carbanion has about the same stability as a simple allylic cation, tertiary sulfones can also be cyclized (Scheme 85). These last examples illustrated the 'umpolung' provided by the sulfone since carbanion chemistry was used to introduce the 2-methyl groups.

Sulfonyl group substitutions can also be observed with organoaluminum reagents.[202] They proceed with remarkable ease and good chemo- and regio-selectivity and with a strong bias for formation of an axial C—C bond in cyclohexenyl systems. The unique advantage of the sulfone as a leaving group stems from the ease of alkylation α to the sulfone prior to the substitution. The chemoselectivity of this method was tested by its ability to employ carbonyl adducts. Initial complexation of the free alcohol with

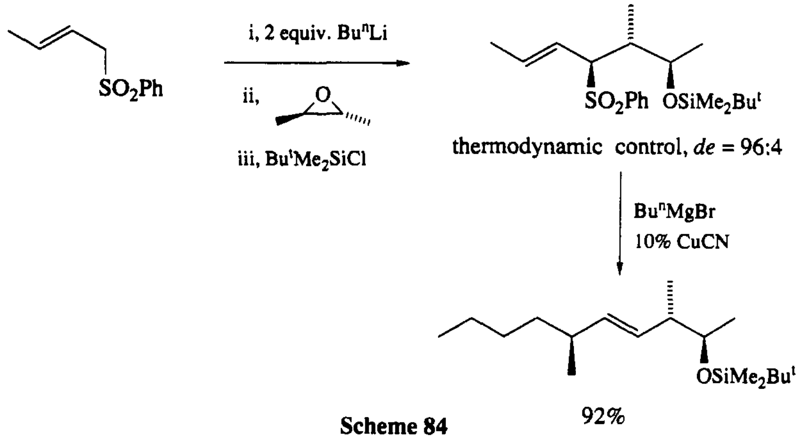

SO2Ph
i, 2 equiv. BunLi
ii,
iii, ButMe2SiCl
SO2Ph OSiMe2But
thermodynamic control, de = 96:4
BunMgBr
10% CuCN
OSiMe2But
92%

**Scheme 84**

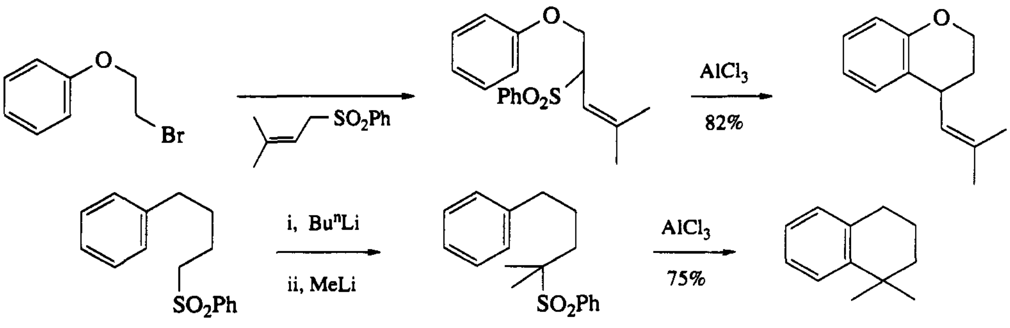

Br
SO2Ph
PhO2S
AlCl3
82%
SO2Ph
i, BunLi
ii, MeLi
SO2Ph
AlCl3
75%

**Scheme 85**

trimethylaluminum, followed by addition of the alkynylalane using ethylaluminum chloride as the Lewis acid gives only the product of substitution of the allylic sulfone with formation of the new C—C bond at the secondary carbon (Scheme 86). The high selectivity for transfer is particularly noteworthy: only alkynyl or vinyl systems are transferred, never alkyl groups.

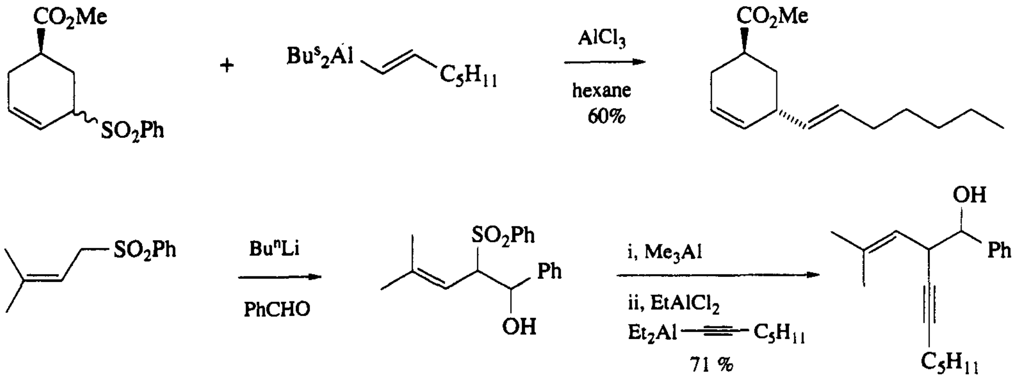

CO2Me
SO2Ph
+
Bus2Al
C5H11
AlCl3
hexane
60%
CO2Me
SO2Ph
BunLi
PhCHO
SO2Ph
Ph
OH
i, Me3Al
ii, EtAlCl2
Et2Al—≡—C5H11
71 %
OH
Ph
C5H11

**Scheme 86**

## 1.5.5 CONCLUSION

The variety and number of examples listed in the literature show the efficiency of sulfur-containing molecules in organic synthesis. In the mid-1960s, organic sulfur chemistry was an area for specialists, but currently almost every organic chemist, in some way or another, encounters organosulfur compounds. It was not, of course, possible to review in this chapter all of the literature work in which sulfur-containing groups serve an important auxiliary function in synthetic sequences. It has, however, been attempted to describe most of the reports which have important applications in selective organic synthesis.

## 1.5.6 REFERENCES

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# 1.6

# Synthesis of Phosphonium Ylides

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## 1.6.1 ALKYLIDENEPHOSPHORANES

### 1.6.1.1 Synthesis from Tertiary Phosphines and Various Compounds

Tertiary phosphines (especially triphenylphosphine) react with various compounds giving rise to the formation of alkylidenephosphoranes.[1–5] By the addition of carbenes and carbenoids, respectively, to tertiary phosphines especially, alkylidenephosphoranes are available which carry one or two halogen atoms at the α-carbon atom (equation 1).

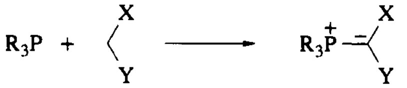

$$R_3P + :C(X)(Y) \longrightarrow R_3\overset{+}{P}-\overset{-}{C}(X)(Y)$$

(1)

The necessary carbene or carbenoid species are generated from di- or tri-halomethanes with bases (organolithium compounds or alkoxides) or by decomposition of sodium trihaloacetates in the presence of a tertiary phosphine. The resulting haloalkylidenephosphoranes are usually not isolated but react with added carbonyl compounds to give alkenes. The *in situ* formation of dichloromethylenetriphenylphosphorane as well as the analog methylthiochloro compound can be achieved in aqueous sodium hydroxide solution under phase transfer conditions.[6] Bis(phenylthio)- and bis(phenylseleno)-methylenetriphenylphosphorane have also been synthesized by the carbenoid method.[7]

Aliphatic diazo compounds may also be used as a source for carbenes, which combine subsequently with tertiary phosphines to give phosphonium ylides. The reaction requires the presence of $Cu^I$ salts, otherwise phosphazines are formed from the diazo compounds and the phosphines.

Alkylidenephosphoranes containing the bis(aryl/alkylsulfonyl)methylene functionality may be obtained from aryliodonium ylides and triphenylphosphine, a carbene mechanism presumably being involved.[8]

Ylide formation by capture of electrophilic carbenes with tertiary phosphines has been shown to be a symmetry-breaking allowed pathway.[9] The reverse process, dissociation of a phosphonium ylide into carbene and phosphine,[10] is in agreement with the concept of phosphonium ylides as phosphine–carbene complexes.[11]

Dihalomethylenephosphoranes are easily available from tetrahalomethanes and tertiary phosphines, especially triphenylphosphine (equation 2). From mixed tetrahalomethanes preferably difluoro- and dichloro-methenylenephosphoranes are formed. The primarily resulting dihalomethylenephosphorane may undergo subsequent reaction giving rise to the formation of a semi-ylide salt (equation 3).[12,13]

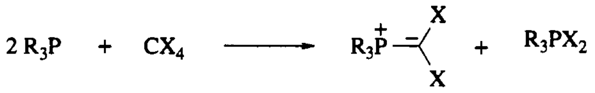
(2)

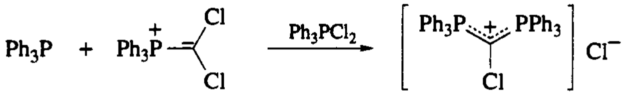
(3)

In contrast to triphenylphosphine alkyldi(*t*-butyl)phosphines react with carbon tetrachloride or tetrabromide to give *P*-halo ylides.[14] Usually dihalo ylides are generated *in situ* in the presence of an aldehyde or a ketone whereby the simultaneously formed dihalotriorganophosphorane reacts with a second mole of the carbonyl compound to give dichloroacetals. The addition of zinc dust proved to be favorable in the synthesis of the difluoro-,[15,16] dibromo-,[17,18] and diiodo-methylenetriphenylphosphoranes.[19] Analogous to tetrahalomethanes trihaloacetates react with triphenylphosphine yielding alkoxycarbonylhalomethylenetriphenylphosphoranes.[5] Also 2,2-dichlorohexafluoropropane seems to react with triphenylphosphine by formation of the corresponding ylide.[20]

Phosphonium ylides are also available from the reaction of trivalent phosphorus compounds with activated C—C multiple bonds.[21–23] Phosphines add to the activated C=C double bond of α,β-unsaturated ketones or carboxylic acid derivatives. The zwitterionic intermediate (generally a phosphonioenolate) undergoes 1,2-prototropic shift giving rise to the formation of an alkylidenephosphorane (equation 4). Ylides generated according to this method *in situ* from acrylic acid derivatives[24,25] are difficult to prepare otherwise, because of the easily occurring Hofmann degradation. Several alternative routes for the stabilization of the zwitterionic intermediate leading to other compounds than the desired ylide have been observed.[23]

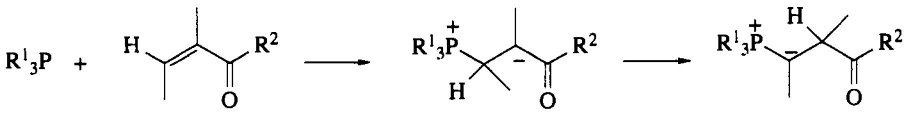
(4)

Alkynes having activated C≡C triple bonds react with tertiary phosphines in the molar ratio 1:2 giving rise to the formation of 1,2-bisylides (equation 5).[23] Beyond that some rather complex reactions between phosphines and alkynes are known; however, these are of no preparative importance as unambiguous routes to ylides.

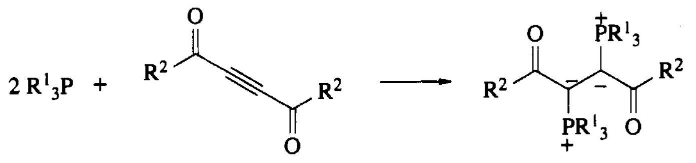
(5)

In addition to the synthetic routes described, tertiary phosphines react with miscellaneous compounds (epoxides, nitrilimines, sulfuranes, amidines) leading to phosphonium ylides.[26] These reactions, however, seem not to represent generally applicable methods for the synthesis of phosphonium ylides.

α-Lithiated tertiary phosphines undergo reaction with electrophiles at phosphorus rather than carbon and thus provide a route to a variety of *P*-substituted phosphonium ylides (equation 6).[26–28]

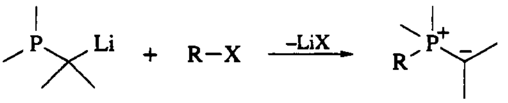

(6)

Dihalotriorganophosphoranes react with activated methylene compounds in the presence of triethylamine yielding stabilized ylides in good yields (equation 7).[29]

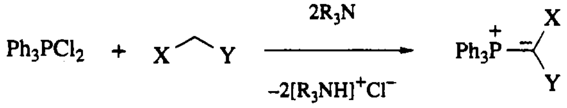

(7)

X, Y = CN, $SO_2R$, $CO_2R$, COR, *etc.*

The generation of an ylide from a phosphine oxide and an alkyne is of interest because it represents the reversal of the known intramolecular Wittig reaction of acylated alkylidenephosphoranes.[30]

## 1.6.1.2 From Phosphonium Salts

### *1.6.1.2.1 Generation with bases*

The most important method of preparing phosphonium ylides is deprotonation of the corresponding phosphonium salts with suitable bases (equation 8).[31–36] In some instances an alternative ylide may be formed instead of that by deprotonation, if the phosphonium salt is carrying another positively charged substituent in the α-position (*e.g.* equation 9).[35,37–40]

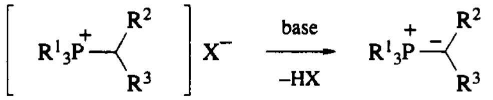

(8)

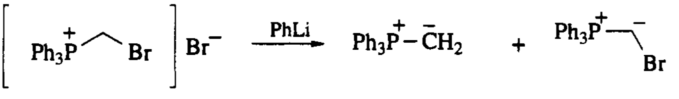

(9)

An alternative route to ylide synthesis *via* α-deprotonation is the abstraction of a proton from the γ-position of a vinylphosphonium salt (equation 10).[41–43] Complications may arise, however, if the phosphonium salt carries a good leaving group in the β-position so that a vinylphosphonium salt may be formed, or if a β-proton is so acidic that a Hofmann elimination is favored.[35,44–47]

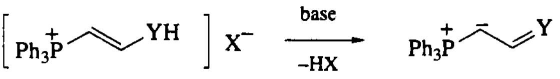

(10)

While triphenylalkylphosphonium salts as ylide precursors unambiguously lead to alkylidenetriphenylphosphoranes, in the case of tetraalkylphosphonium salts ylide formation may take place principally at different α-positions relative to the phosphorus.[48–50] Furthermore an intramolecular transylidation process causes the ligands at the phosphorus in methylenetrialkylphosphoranes to exist alternately as alkyl or as alkylidene substituents, thus giving rise to the formation of isomeric ylides.

The choice of the appropriate base/solvent system for the ylide generation depends on the acidity of the corresponding salt, the stability of the resulting ylide in the reaction medium and the intended application of the ylide. Thus phosphonium salts with electron-withdrawing groups on the α-carbon, which are capable of stabilizing a negative charge, are deprotonated by relatively weak bases, such as dilute aqueous alkali or ammonia. If there are electron-donating substituents on the α-carbon, stronger bases, such as alkyllithium, are required. Highly reactive phosphonium ylides are usually generated in an aprotic medium and mostly are not isolated but reacted *in situ*.[51]

For many reactions with ylides it is very important to use 'salt-free' solutions. This is especially true for lithium salts because they can affect decisively the course of many ylide reactions, especially the stereochemical course of subsequent Wittig reactions.[52–55]

A great variety of bases has been used to generate ylides from the corresponding phosphonium salts: various nitrogen bases, alkoxides, alkali metal hydrides, carbanionic bases, alkali metal hydroxides and carbonates, ethylene oxides, basic ylides and others.[31,35,36]

The use of sodium amide proved to be very successful in the synthesis of nonstabilized ylides free from lithium salts.[35,56] The reaction is usually carried out in liquid ammonia, but also a suspension of sodium amide in benzene or THF can be used. Whereas alkyltriarylphosphonium salts are deprotonated in liquid ammonia, in the case of the corresponding tetraalkyl compounds boiling THF is necessary.[48] Mixtures of dry phosphonium salt and powdered sodium amide can be stored indefinitely and hence provide 'instant ylide' mixtures.[57] Upon addition of an ethereal solvent the ylide is quantitatively generated.

Conversion of phosphonium salts to salt-free solutions of ylides can also be effected with sodium bis(trimethylsilyl)amide.[58] As it is soluble in many solvents, and easy to handle and to weigh out, sodium bis(trimethylsilyl)amide is preferred to sodamide in liquid ammonia in many cases (equation 11).[59] The corresponding potassium and lithium compounds can also be used.[60]

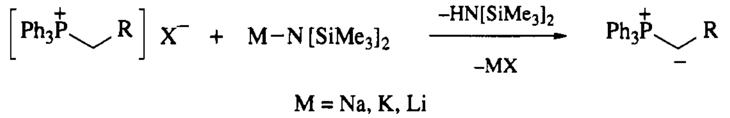

(11)

The anions resulting from dissolving potassium in HMPT are also suitable for generating reactive ylides from their corresponding salts, HMPT also turning out to be a favorable solvent for many ylide reactions (equation 12).[61]

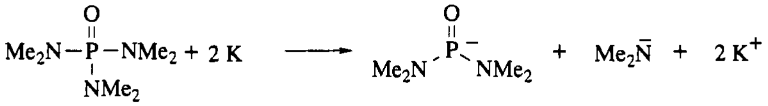

(12)

Apart from the bases mentioned a series of other nitrogen bases (ammonia, triethylamine, pyridine, cyclic amidines, lithium diethylamide, lithium diisopropylamide, lithium piperidide, *etc.*) have been used to deprotonate phosphonium salts.

Many alkoxides (especially sodium methoxide, sodium ethoxide, potassium *t*-butoxide and others) can be used as bases in ylide syntheses (equation 13).[35] The reaction is carried out in the corresponding alcohol or another inert solvent. The alkoxide method has some advantages: alkoxide bases are easy to handle, ylide generation may be effected in a homogeneous phase and phosphonium salts carrying corresponding alkoxycarbonyl groups are not cleaved at the alkoxy function. Since, however, ylides may be quenched by the alcohol produced from the base, they are usually generated in the presence (the temperature playing an important factor[38]) of a carbonyl compound to undergo a Wittig reaction. It seems that among alkoxides potassium *t*-butoxide and sodium as well as potassium *t*-pentylate are most suitable for the generation of reactive ylides.[38,62–64] Alkoxide bases are less suitable for the deprotonation of phosphonium salts carrying activated H atoms in the β-position since alkoxides favor cleavage into a phosphine and an alkene.

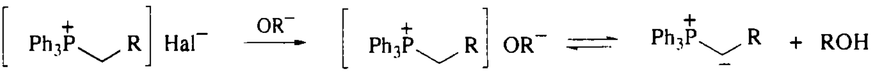

(13)

Very often phosphonium ylides are generated with organolithium compounds (in particular phenyl-, methyl-, *n*-butyl- and *t*-butyl-lithium) as bases.[31,32,34,35] However difficulties may be attached to this method in some cases. When alkyllithium compounds are used, ligand exchange at phosphorus may occur, thus giving rise to the alternative or additional formation of a second ylide. To avoid this phenomenon in the case of triphenylphosphonium salts phenyllithium has to be used as base. Ligand exchange may also be suppressed if one uses, instead of *n*-butyllithium for example, the more bulky tertiary compound.[65] From phosphonium salts carrying halogen at the α-carbon both a proton or a positively charged halogen may be split off and also displacement of an α-halogen by the carbanionic substituent of the lithium compound may occur. β-Substituted phosphonium salts may undergo Hofmann elimination under the influence of organolithium reagents giving rise to the formation of vinyl salts, which subsequently may add a second mole of base at the β-position. Attack of alkyllithium directly at the β-substituent has also been observed.[66] Ylides generated by organolithium compounds may be attacked by excess base yielding metallated ylide species,[39,67] which can act as a more reactive alternative to methylene ylides.[67a,b] Ylides, especially alkylidenetrialkylphosphoranes form complexes with lithium salts,[67f,68] from which the ylide sometimes can be released only at elevated temperatures.

Other carbon bases that have been used successfully to convert phosphonium salts into ylides include sodium methylsulfinate and the corresponding potassium compound[69] (prepared from alkali metal hydride and DMSO), tritylsodium, sodium acetylide and other strongly basic ylides.

Deprotonation of a phosphonium salt by an ylide is a 'transylidation' reaction,[56] which is of importance especially in those cases where ylides are reacted with electrophiles (see Section 1.6.1.3), but may also be applied to isolated phosphonium salts.[35] For an unequivocal reaction the two involved ylides must differ sufficiently with respect to their base strength (as for example in equation 14).

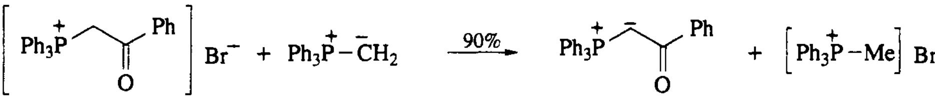
(14)

Aqueous alkali metal hydroxides and carbonates are suitable for the generation of ylides from phosphonium salts, which carry strongly electron-withdrawing groups (*e.g.* acyl, alkoxycarbonyl, cyano, 9-fluorenyl, nitrophenyl and others) at the α-carbon. The resulting stabilized ylides are usually sufficiently stable to be unreactive in water. The above mentioned bases may also be applied to the synthesis of reactive ylides, if the reaction is carried out under phase transfer conditions[46,70–74] in the presence of an aldehyde, which undergoes a Wittig reaction with the *in situ* generated ylide.

Sodium hydride itself, not only its reaction product with DMSO, is also suitable for deprotonation of phosphonium salts and preference has been given to this base over sodium ethoxide.[75]

Ethylene oxide or 1,2-epoxybutane may also be used for the synthesis of ylides.[76] The resulting ylide is in equilibrium with its conjugated salt (equation 15). The use of ethylene oxide offers some advantages over more conventional bases used in Wittig reactions. The application is simple since ylides and most often also phosphonium salts (from phosphine and alkyl halide) need not to be prepared separately. The reaction medium is neutral, so that base-induced side reactions fail to appear. The method is however less applicable to weakly acid phosphonium salts, since deprotonation requires high temperatures (150 °C).

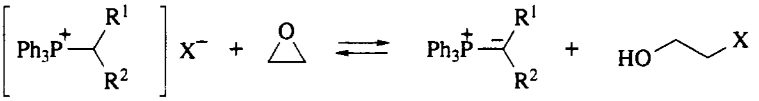
(15)

Another ylide synthesis avoiding basic conditions starts from phosphonium fluorides.[77–79] Fluoride ions are basic enough to play the role of the usually added external base, giving rise to the formation of a phosphonium salt/ylide equilibrium (equation 16).

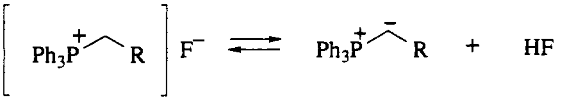
(16)

Ylide generation on alumina or potassium fluoride supported on alumina is of interest since the use of a solvent is unnecessary.[79]

In addition to the generation of phosphonium ylides from phosphonium salts by deprotonation with bases in some instances ylides may result from pyrolysis of phosphonium salts,[80] especially silylated salts (equation 17). Similar fluoride ion induced desilylation (equation 18) of phosphonium salts proved to be a very useful alternative for the synthesis of ylides which are difficult to synthesize by the conventional salt method (as in the case of $R^1$, $R^2$ = alkyl).[81,82] The most effective fluoride source is cesium fluoride and the reaction proceeds at room temperature.

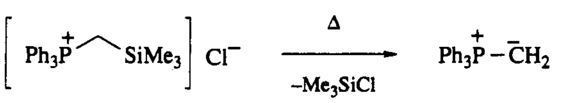

(17)

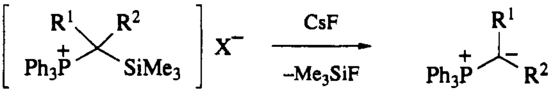

(18)

Phosphonium salts may also be converted to ylides by electrochemical procedures.[80,83] The preparative applicability of these methods, however, seems to be limited.

### *1.6.1.2.2 By addition of nucleophiles to vinyl- and cyclopropyl-triphenylphosphonium salts*

Vinylphosphonium salts are susceptible to nucleophilic attack at the terminal vinyl carbon, thus providing 2-substituted ethylidenephosphoranes (equation 19).[84] This method, developed by Schweizer, has been successfully employed in the addition of a variety of anionic derivatives from alcohols, thiols, amines and others to vinylphosphonium salts, especially to the commercially available vinyltriphenylphosphonium bromide ('Schweizer's reagent').[84–101] The analogous reaction involving alkyl- or aryllithium reagents proceeds in poor yields only, obviously because of ligand exchange processes and a competing elimination reaction transforming the vinyl salt to triphenylphosphine and acetylene. However, when the less basic organolithium cuprates are used as a source of carbanions the desired addition takes place readily.[101] Stabilized carbanions, especially enolate anions, are also well suited as nucleophiles.[92–100]

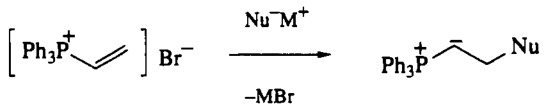

(19)

M = metal; Nu = OR, SR, $NR_2$, $CR_2$, $CR_3$, *etc.*

Ylides generated according to the vinyl salt method are usually not isolated but are quenched *in situ* with a carbonyl compound. Vinylphosphonium salts are most often reacted with nucleophiles containing suitable adjacent carbonyl groups yielding carbonyl substituted ylides, which provides an elegant method for the synthesis of a great variety of cyclic compounds by a subsequent intramolecular Wittig reaction (equation 20). The reaction principle may also be applied to the conjugate addition of a nucleophile to 1,3-butadienyl- and 1,3,5-trienyl-phosphonium salts, leading to the corresponding ylides (*e.g.* equation 21).[84,102,103]

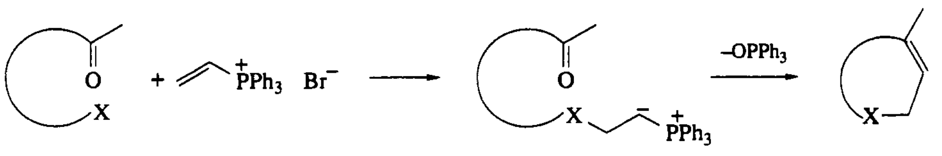

(20)

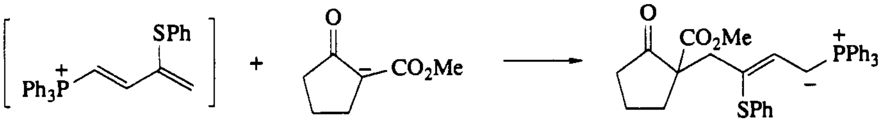

(21)

Ylides may also be generated by nucleophilic ring opening of cyclopropylphosphonium salts (equation 22).[84,104,105] The resulting ylide undergoes intramolecular Wittig reaction if the attacking nucleophile is carrying a carbonyl group.

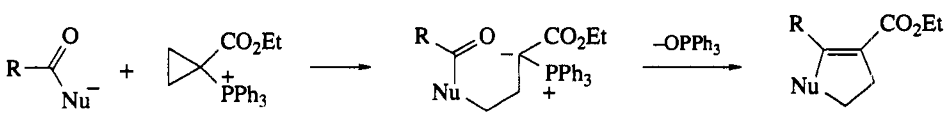

(22)

### 1.6.1.3 From Conversion of Other Phosphonium Ylides

#### *1.6.1.3.1 By substitution of a proton at the ylide carbon atom*

Phosphonium ylides carrying at least one proton at the α-carbon atom react with various electrophilic reagents with formation of α-substituted phosphonium salts or zwitterionic intermediates, from which α-substituted ylides are generated by deprotonation or proton migration, the former reaction being more important (equation 23).[4,106–112]

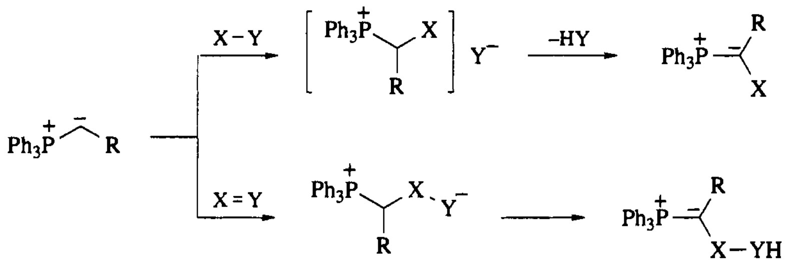

(23)

If the reaction provides a salt whose acidity is greater than that of the starting phosphorane precursor (for example in the case of X = acyl), a second mole of the starting ylide reacts with the intermediate phosphonium salt in a transylidation reaction[56] (*cf.* equation 14) giving rise to the formation of an α-substituted ylide and the conjugated salt of the original ylide. If the proton of the phosphonium salt generated in the first step is not sufficiently acidic for this proton transfer to occur, the phosphonium salt formed in the first step can be isolated and has to be deprotonated by an external base.

Reactions of ylide anions with electrophiles lead directly to substituted ylides.[109,113]

*(i) Substitution by heterofunctional groups*

α-Heterosubstituents influence the stability of phosphonium ylides markedly since σ-donors and π-acceptor groups, *e.g.* electropositive elements, stabilize ylides, whereas π-donors and σ-acceptors, *e.g.* electronegative elements, destabilize them.[9a]

*(a) Substitution by halogen*

Halogenation of strongly basic ylides with free halogen is accompanied by side reactions and is not suitable for preparative application. Stabilized ylides, *e.g.* acyl- or alkoxycarbonyl-methylenephosphoranes, react with free halogen or various halogen carriers to give halogenated phosphonium salts.[114–118] Subsequent α-halo ylide formation may occur *in situ* by a second mole of the original ylide (transylidation), a base added to the reaction mixture at the beginning, or after isolation of the intermediate salt by an external base (equation 24). Suitable halogen carriers are bromo cyanide (in the presence of triethylamine), dichloro- and difluoro-iodobenzene, chloramine T, iodo bromide and perchloryl fluoride.

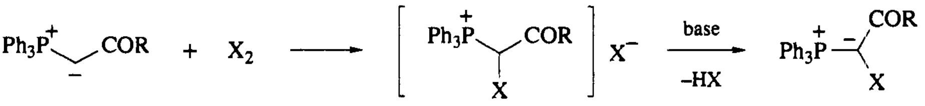

(24)

X = Cl, Br, I; R = alkyl, aryl, *O*-alkyl

*(b) Substitution by elements of Group 6*

Stabilized, as well as basic ylides, react with sulfenyl chlorides in a transylidation reaction to give alkylthiomethylenephosphoranes (equation 25).[119] In methylenetriphenylphosphorane both α-protons may be substituted by sulfenyl groups. The phenylthio and the methylthio group may also be introduced by *N*-methyl-*N*-phenylthioacetamide and dimethylsuccinimidosulfonium chloride, respectively. These methods avoid the disadvantage of requiring two moles of starting ylide as in the reaction with sulfenyl chlorides.

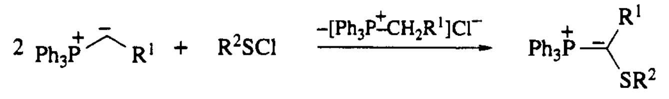

(25)

1-Sulfonylalkylidenephosphoranes are available from simple ylides and sulfonic acid halides or anhydrides in a transylidation reaction (equation 26).[119a] With aromatic sulfonyl chlorides halogenation and sulfenation may occur instead of sulfonation. Aliphatic sulfonyl chlorides give only poor yields of 1-alkanesulfonylalkylidenephosphoranes. Aromatic and aliphatic sulfonyl fluorides are very suitable for the introduction of sulfonyl groups into the α-position of ylides. However, as a consequence of the reaction mechanism (presumably *via* sulfenes) in addition to the expected ylide a rearranged byproduct may be formed (equation 27). 1-Sulfinylalkylidenephosphoranes are synthesized analogously with sulfinyl halides.[119a]

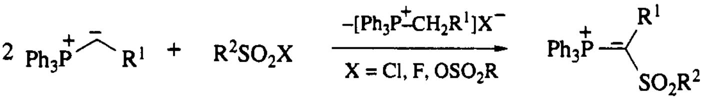

(26)

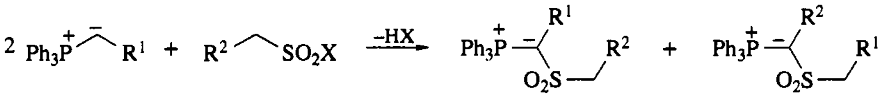

(27)

The transylidation reaction of phenylselenyl bromide with two moles of alkylidenetriphenylphosphorane yields 1-phenylselenoalkylidenetriphenylphosphoranes (equation 28).[119]

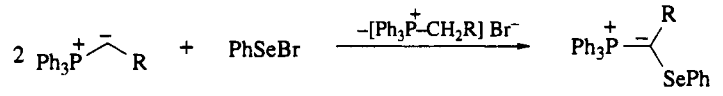

(28)

*(c) Substitution by elements of Group 5*

Acyl ylides add to N=N double bonds of azo compounds giving rise to the formation of 1-*N*-substituted alkylidenephosphoranes (*e.g.* equation 29).[120] It should be mentioned that 1-*N*-substituted ylides, which carry only hydrogen or alkyl groups at the nitrogen, are unknown.[10a]

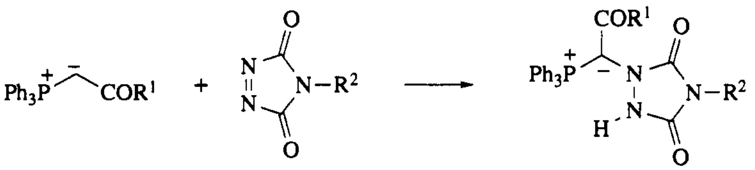

(29)

Coupling of aromatic diazonium salts with stabilized methylenephosphoranes leads to arylazomethylenephosphoranes (equation 30).[121]

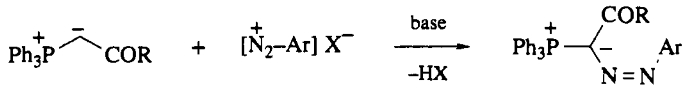

(30)

1-Phosphino-substituted ylides are available from simple ylides and chlorodialkyl- or chlorodiarylphosphines (equation 31).[122,123] It depends upon the conditions of the reaction whether the substituted phosphonium salt or the corresponding ylide can be isolated. Methylenetriphenylphosphorane may undergo double phosphinylation. Phosphino-substituted ylides have also been synthesized using 1-alkyl-2-vinylphosphiranes as reagents.[124]

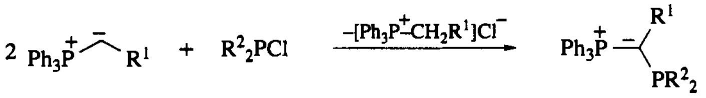
2 Ph3P R1
+ R22PCl
-[Ph3P-CH2R1]Cl−
Ph3P
R1
PR22

(31)

Diphenylphosphinyl chlorides and simple ylides yield 1-diphenylphosphinylalkylidenephosphoranes in a transylidation reaction; the introduction of the thiophosphinyl group may be carried out analogously (equation 32). Synthesis of diethoxy- and diphenoxy-phosphinomethylenetriphenylphosphoranes may be achieved with the corresponding phosphoro chloridates (equation 33).

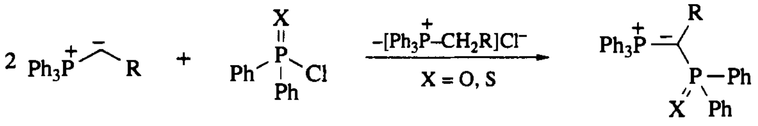
2 Ph3P R
+
-[Ph3P-CH2R]Cl−
X = O, S
Ph3P
R
P−Ph
X Ph

(32)

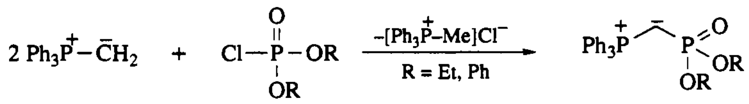
2 Ph3P−CH2
+ Cl−P−OR
-[Ph3P-Me]Cl−
R = Et, Ph
Ph3P
OR

(33)

Apart from the mentioned phosphorus halogen compounds also dichlorophenylphosphine, phosphorus(III) trichloride, phosphorus(III) oxychloride and its thio analog have been reacted with methylenetriphenylphosphorane generating the corresponding phosphorus(III) substituted ylides (*e.g.* equation 34).

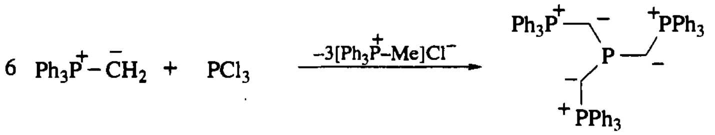
6 Ph3P−CH2 + PCl3
-3[Ph3P-Me]Cl−
Ph3P
PPh3
P
PPh3

(34)

The dimethylstibino group has been introduced by the reaction of lithiated ylide with chlorodimethylstibine (equation 35).[125a] Bis(diphenylstibino)methylenetriphenylphosphorane results from chlorodiphenylstibine and methylenetriphenylphosphorane in a transylidation reaction.[125b]

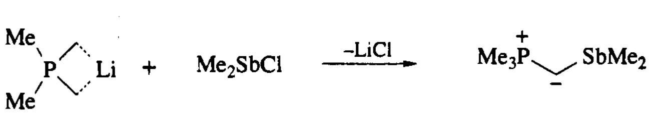
Me
Me
P
Li
+ Me2SbCl
-LiCl
Me3P
SbMe2

(35)

1-Dimethylarsinomethylenetrimethylphosphorane is available by desilylation of the corresponding 1-trimethylsilyl compound (*cf.* Section 1.6.1.3.2)

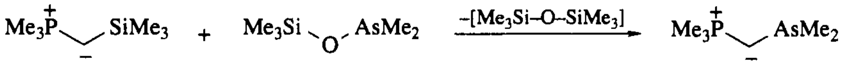
Me3P SiMe3
+ Me3Si O AsMe2
-[Me3Si-O-SiMe3]
Me3P AsMe2

(36)

*(d) Substitution by various element–organic substituents*

α-Silylated alkylidenephosphoranes can be synthesized from simple alkylidenephosphoranes and chlorosilanes (especially chlorotrimethylsilane) by transylidation, since the silyl group stabilizes the resulting ylide (equation 37).[81,126,127]

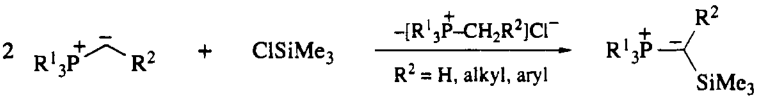
2 R13P R2
+ ClSiMe3
-[R13P-CH2R2]Cl−
R2 = H, alkyl, aryl
R13P
R2
SiMe3

(37)

From methylenephosphoranes ($R^2$ = H) both mono- or bis-silylated products may result.[128] Schmidbaur *et al.* have used a variety of compounds for the silylation of ylides.[126] α-Silylated alkylidenephosphoranes are also formed in the reaction of simple ylides with 2-chloroethylsilane (equation 38), chloromethylsilane (equation 39), siletanes, 1,3-disiletanes (equation 40) and the highly strained hexamethylsilirane (equation 41).[129]

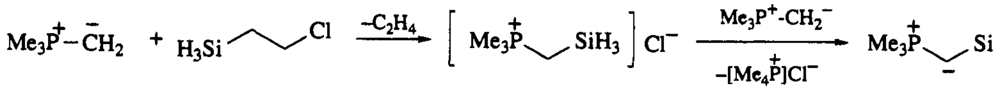
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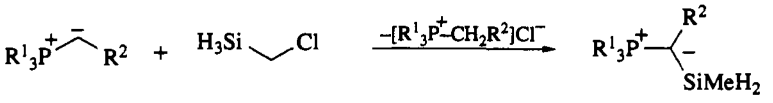
(39)

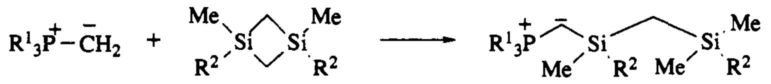
(40)

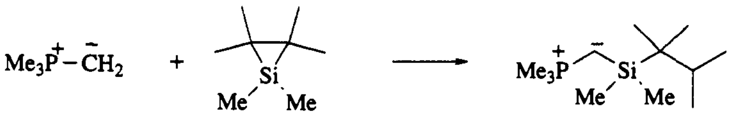
(41)

Reaction of simple ylides with dialkyldihalosilanes leads in a twofold transylidation to the formation of Si-bridged bisphosphoranes (equation 42), which can undergo consecutive reactions with excess starting materials leading to cyclic products. Bis(chlorodimethylsilyl)methane also reacts with dilithiomethylenetrimethylphosphorane to give a methylenephosphorane with an exocyclic ylide function (equation 43).

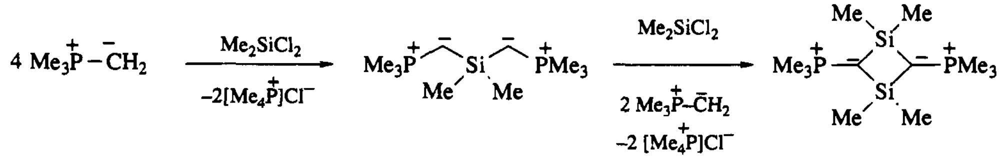
(42)

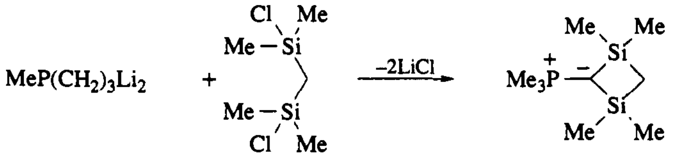
(43)

Analogously to the silyl group the Si—Si unit may be introduced into the α-position of methylenephosphoranes using chlorodisilanes (equations 44 and 45).

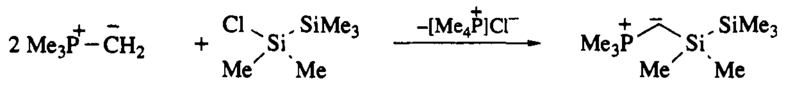
(44)

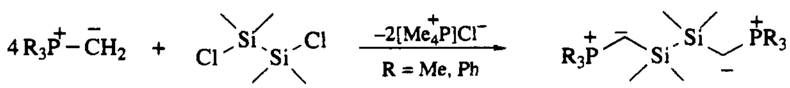
(45)

Germanyl- and stannyl-substituted ylides may be synthesized starting from ylides and germanyl and stannyl chlorides (*e.g.* equation 46).[126] Methylenetriphenylphosphorane is converted into the corresponding disubstituted ylide (equation 47). The monosubstituted derivatives are available by desilylation of 1-trimethylsilylmethylenephosphorane (*cf.* equation 36).

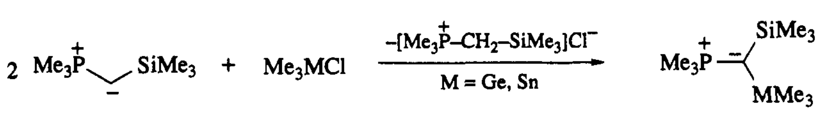
(46)

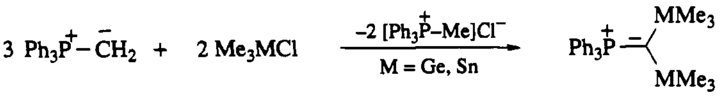
(47)

Stabilized ylides react with mercury(II) chloride giving salts, which can be deprotonated to the corresponding mercury substituted ylides (equation 48).[126] Among reactive ylides only the trimethylsilylmethylenetrimethylphosphorane can be transformed into its mercurated derivative (equation 49).

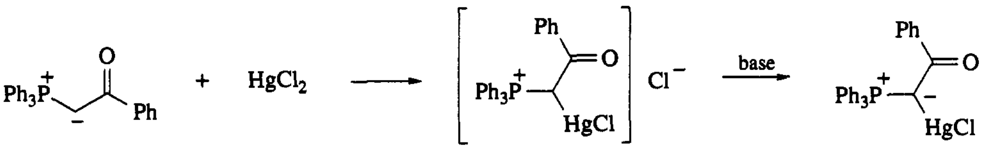
(48)

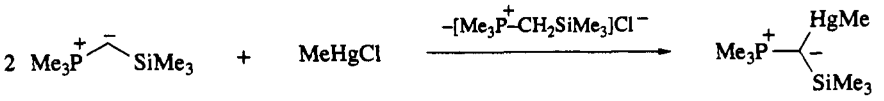
(49)

Dialkylboron-substituted phosphonium ylides have been prepared by reaction of dialkylchloroboranes with alkylidenephosphoranes (equation 50).[130] The reaction of phosphonium ylides with alkyldichloroboranes leads to the formation of boron-bridged 1,3-bisylides (equation 51).[131]

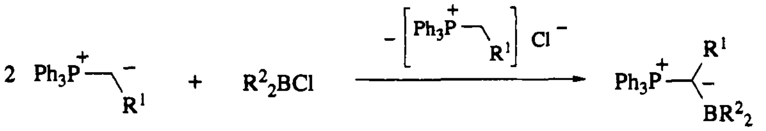
(50)

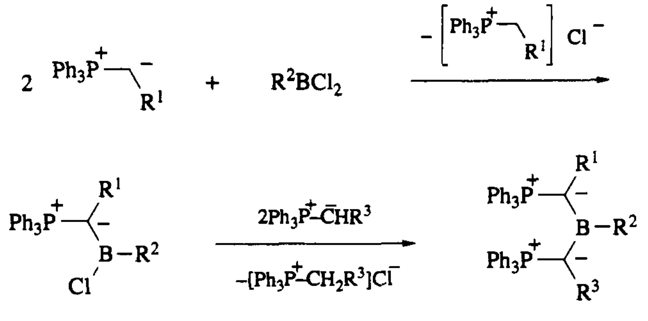
(51)

*(ii) Substitution by carbon substituents*

*(a) By alkyl groups*

Substitution of an α-proton in alkylidenephosphoranes by an alkyl group can be achieved by two alternative routes:[106–108,110–112,132] (a) Michael addition to activated C=C double bonds (equation 52); (b) reaction with alkylating reagents to give phosphonium salts, which are subsequently deprotonated by a second mole of the original ylide (transylidation) or an external base (equation 53). Ylide synthesis according to method (a) is restricted to some special cases.[132] Concerning method (b) it should be mentioned that in some instances the second mole of ylide causes β-elimination (Hofmann degradation) instead of α-elimination (transylidation) of the initially formed salt.[110,111,133]

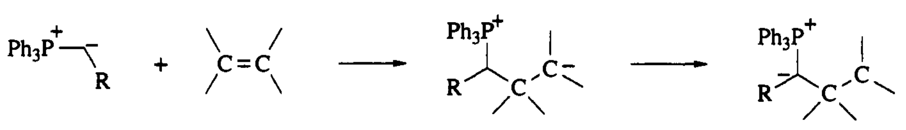

(52)

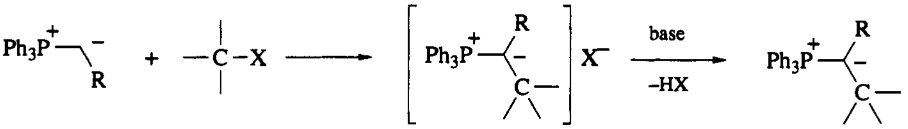

(53)

The reaction of ylides with saturated aliphatic alkyl halides (like methyl iodide, ethyl iodide *etc.*) usually stops at the stage of the alkylated salt because the +*I* effect of the aliphatic substituent causes the resulting salt to be a weaker acid than the conjugated salt of the original ylide (which would result in the course of a transylidation reaction).[56,133,134] However since partial transylidation also occurs between alkylidenephosphoranes and phosphonium salts with equal or not very different base and acid strength,[135] mixtures may result from the reaction with saturated aliphatic alkyl halides. At this point it should be mentioned that the synthesis of dialkylated ylides *via* the salt method is also difficult since the preparation of the necessary phosphonium salt is accompanied by β-elimination. The successful synthesis of dialkylated ylides may be achieved by fluoride ion induced desilylation of α-trimethylsilylphosphonium salts (see equation 18). There is no doubt about the course of ylide alkylation in cases where the inductive effect of the new substituent leads to complete transylidation (*e.g.* equation 54).[134]

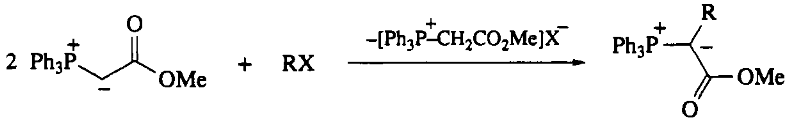

(54)

R = $CH_2CH{=}CH_2$, $CH_2CO_2Me$, $CH_2CN$, $CH_2Ph$, $CH_2CH{=}CHPh$

Ylides with ambident character, like 1-formyl- or 1-acyl-methylenephosphoranes, may be attacked by alkylating reagents (the same is true for acylation) at the α-carbon or at the O atom.[85,136] Bromomethyl acetate *C*-alkylates acylmethylenetriphenylphosphoranes in a transylidation reaction (equation 55).[137] Recently cyanomethylenetriphenylphosphorane has been successfully alkylated *via* its ylide anion, the substituted cyano ylides being accessible more readily in greater variety than previously (equation 56).[113]

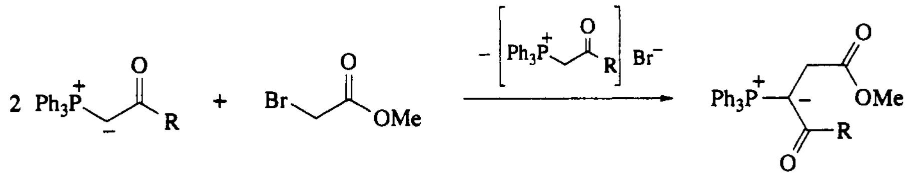

(55)

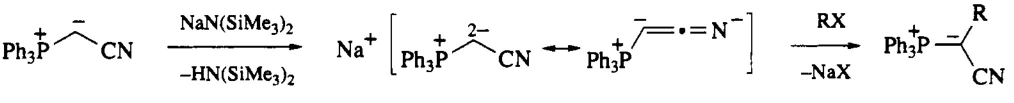

(56)

R = Me, $Bu^n$, $CH_2SiMe_3$, $CH_2Ph$, $CH_2CH{=}CH_2$

Syntheses of complex ylides by alkylation of simple ylides have been achieved in great variety,[110,111,132] using not only alkyl halides (usually containing another functional group) but also other alkylating reagents (Mannich bases,[138] strained cyclic compounds like epoxides,[113b,139] aziridines[140] and siletanes,[141] pyrylium salts[142] and others). Equations (54)–(56), (57),[66] (58),[143] (59),[138] (60)[139a] and (61)[140] give some selected examples.

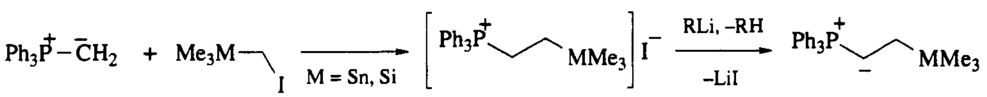

(57)

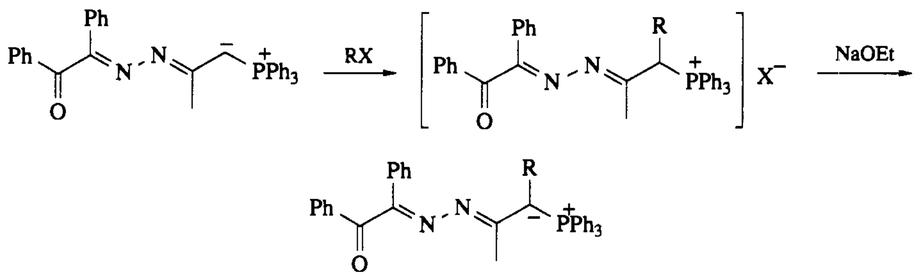

(58)

R = Me, $CH_2CH=CH_2$, $CH_2Ph$

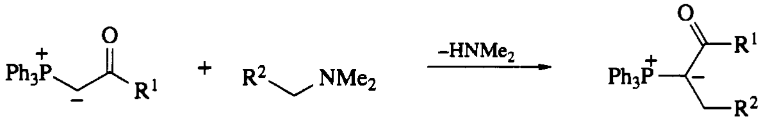

(59)

$R^1$ = OEt, Ph; $R^2$ = Ar, $CH_2CH_2Ar$

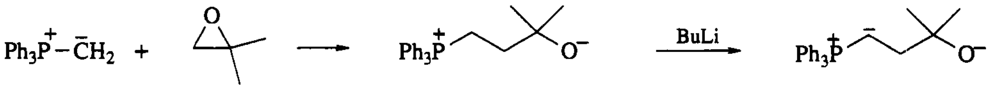

(60)

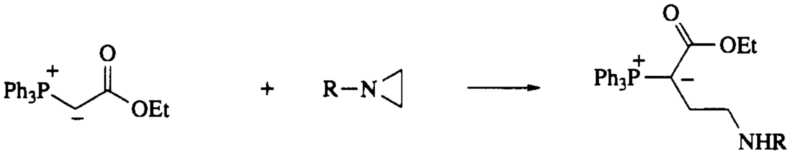

(61)

ω-Haloalkylidenetriphenylphosphoranes undergo intramolecular *C*-alkylation giving rise to the formation of an exocyclic phosphonium salt, which can be deprotonated by a second base (original ylide or an external base) to yield the corresponding exocyclic ylide (equation 62).[144–147]

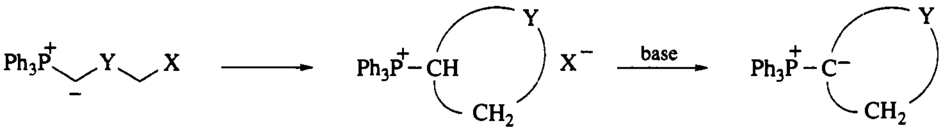

(62)

Differing from this course of reaction, in the case of the analogous trialkyl compounds the P atom may be incorporated into the ring system (equation 63).[148]

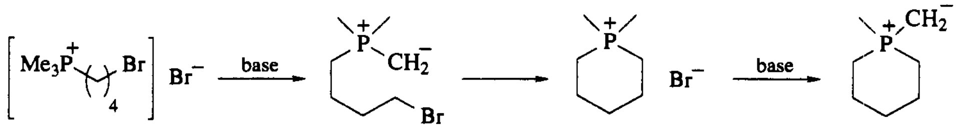

(63)

For a successful intramolecular *C*-alkylation of alkylidenetriphenylphosphoranes it is required that the conjugated salt of the starting ylide can be synthesized from triphenylphosphine and a 1,ω-dihalide. As a consequence of this fact intramolecular *C*-alkylation often fails in the aliphatic series with Y = $(CH_2)_n$, with the exception of $n$ = 1, 2. This difficulty can be overcome by the combination of the inter- and intramolecular *C*-alkylation of ylides (equation 64).[144–146]

Two moles of methylenetriphenylphosphorane are reacted with one mole of a dihalogen compound. In the first step methylenetriphenylphosphorane is *C*-alkylated yielding an ω-halophosphonium salt, which subsequently reacts with a second mole of methylenetriphenylphosphorane forming a transylidation equilibrium with methyltriphenylphosphonium halide and an ω-halogenated ylide. This compound undergoes intramolecular *C*-alkylation, in the course of which the resulting exocyclic phosphonium salt

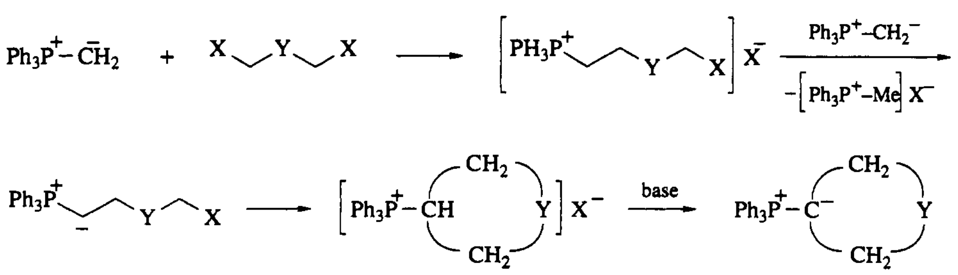

(64)

is formed and precipitates together with the methyltriphenylphosphonium halide (from the transylidation step) from the benzene solution. As a consequence of the precipitation the transylidation equilibrium is permanently disturbed so that the reaction takes place with complete formation of both phosphonium salts. These can be separated by recrystallization from water. From the resulting cycloalkyltriphenylphosphonium salt the corresponding cycloalkylidenetriphenylphosphorane may be generated with a base. Deprotonation may sometimes occur immediately under the influence of a third mole of methylenetriphenylphosphorane. Usually the exocylic alkylidenetriphenylphosphoranes synthesized are not isolated but reacted *in situ*, mostly in a Wittig reaction.

The efficiency of this method is impressively proved by the synthesis of the skeleton of shikimic and chinic acid starting from an open chain sugar derivative and the synthesis of optically active cyclopentanediol synthetic building blocks from tartaric acid.[149]

### *(b) By alkenyl and alkynyl groups*

The alkenylation of alkylidenephosphoranes may be achieved, by analogy to the alkylation, either by Michael addition to conjugated alkynes and allenes or by reaction with alkenylating reagents.[110,111,132b,150,151] Michael addition is restricted to stabilized ylides (*e.g.* equation 65); however, in one case the resulting product has been observed to fragment in a retro-Michael reaction.[152] More reactive alkylidenephosphoranes and alkynes give rise to the formation of four-membered adducts, which undergo ring opening to yield alkenyl-substituted ylides in which the original P—C function has been cleaved.[150] 4-Oxo-2-alkenylidenetriphenylphosphoranes can be prepared from reactive or stabilized ylides and 2-chlorovinyl ketones in a transylidation reaction (equation 66).[150a]

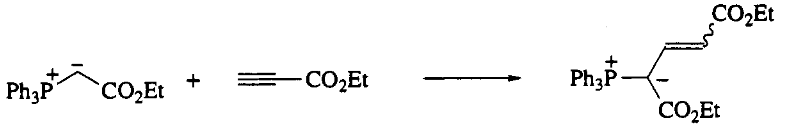

(65)

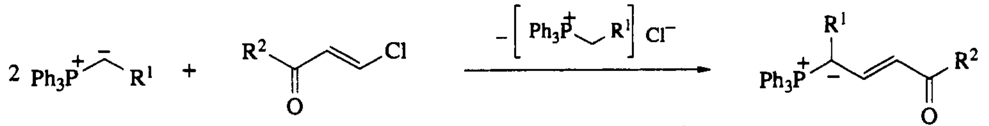

(66)

$R^1$ = $CO_2Et$, COMe, SPh, Ph, $CH_2Ph$, CH=CHMe; $R^2$ = alkyl, phenyl

Methylenetriphenylphosphorane reacts with alkylideneaminodialkylaluminum compounds (available from diisobutylaluminum hydride and nitriles) to give allylidenetriphenylphosphoranes (equation 67). In the case of $R^1$ = *n*-alkyl, $R^2$ = H, predominantly (*Z*)-allylidenephosphoranes are formed; branching of $R^1$ leads to an increasing portion of (*E*)-isomer. The method has also been applied to the synthesis of cyclic and acyclic bisallylidenephosphoranes.[153]

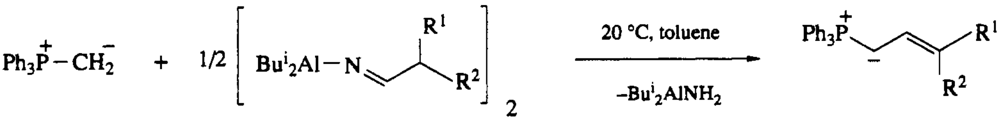

(67)

2,4-Alkadienylidenephosphorane can be synthesized from simple ylides and pyrylium or pyridinium salts (*e.g.* equation 68).[150a] The resulting ylides may undergo spontanous intramolecular Wittig reaction.

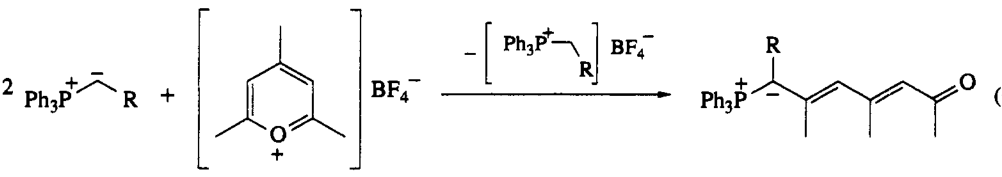
(68)

Esters of aromatic acids react with an excess of methylenetriphenylphosphorane giving rise to the formation of allylidenephosphoranes (equation 69).[150a]

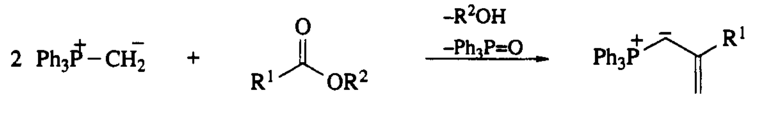
(69)

Alkynyl substituted alkylidenetriphenylphosphoranes are available from the transylidation reaction of methylenetriphenylphosphorane with bromoalkynes (equation 70) or alternatively with 1,1-dibromoalkenes in the presence of a third mole of original ylide.[154]

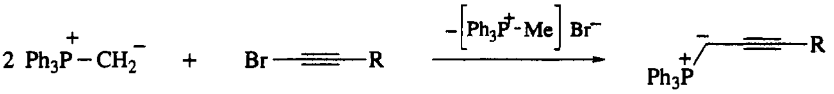
(70)

### *(c) By acyl groups and their derivatives*

Acyl halides, activated esters, carboxylic anhydrides and *N*-acylimidazoles react with alkylidenephosphoranes to yield acylated ylides.[106,110,111,155-157]

Acid chlorides react readily with alkylidenephosphoranes. Owing to the strongly electron-withdrawing effect of the acyl group, the initially formed salt is a sufficiently strong acid to undergo transylidation very easily with a second mole of starting ylide (equation 71). The method has been applied to reactive[158-160] as well as to resonance-stabilized (especially ester-stabilized) ylides,[121d,143,161-164] β-ketoalkylidenephosphoranes however usually yield *O*-acylated products. The second mole of starting ylide necessary for a transylidation may be substituted by triethylamine if the amine is a stronger base than the ylide, as is usual in the case of stabilized phosphoranes.[156,165] Under the influence of the added amine or the original ylide hydrogen chloride may be eliminated from acid chorides containing activated α-hydrogen. The ketenes so formed may react with ylides to give allenes.[166] Acid fluorides have also been used for the acylation of ylides.[167]

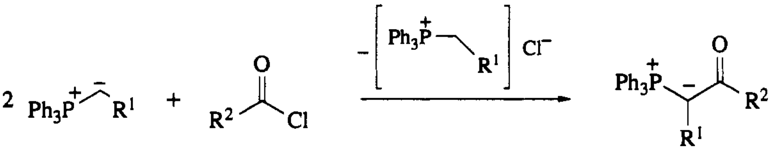
(71)

A disadvantage of the acylation method with acid halides is the requirement of two moles of starting ylide, one acting as a base to deprotonate the initially formed acylated phosphonium salt (although the precipitating salt may be used for the regeneration of the starting ylide). This disadvantage can be removed by the use of thiocarboxylic acid *S*-ethyl esters as acylating reagents (equation 72).[156] The phos-

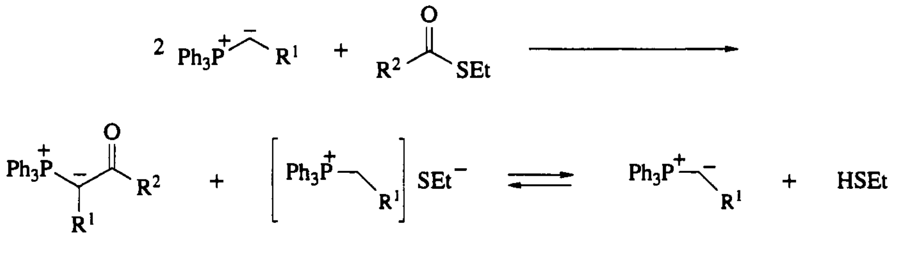
(72)

phonium thiolate initially formed by transylidation eliminates mercaptan thus generating the second mole of starting ylide and removing it from the equilibrium by reaction with further thioester. This method usually supplies purer products and better yields than the acid chloride acylation.

In general, salt-free solutions of ylides do not react with methyl or ethyl esters of carboxylic acids. Better results can be obtained when activated esters (*e.g.* phenyl or pyridyl esters) are used for acylation.[121d,166c] Acylation with carboxylic acid anhydrides also requires only one mole of starting ylide (equation 73).[156,163]

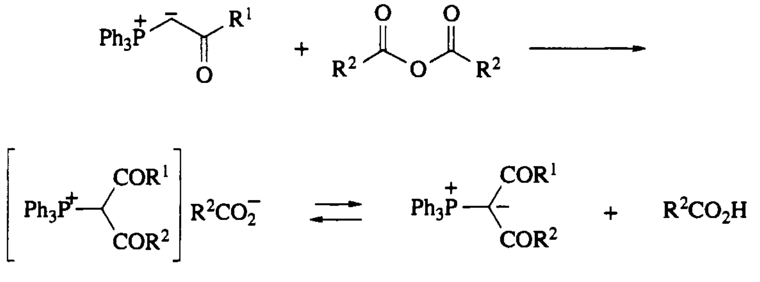

(73)

This route proved to be advantageous in the case of resonance-stabilized ylides since there are no problems in separating the acylated ylide from a phosphonium salt resulting from transylidation, and *O*-acylation does not occur when β-keto ylides are used as starting materials. The acylated ylide is generated from the initially formed phosphonium carboxylate by heating or with an alkali metal hydroxide. Cyclic anhydrides, like succinic or glutaric anhydrides, may also be used as acylating reagents which give rise to the introduction of an ω-carboxy substituted acyl group.[168]

Formylation of alkylidenetriphenylphosphoranes has been achieved with formic esters, *N*-formylimidazole, formyl acetate, chloromethylenedimethylammonium chloride and tetramethylformamidinium chloride. The formamidinium compound leads primarily to vinylphosphonium salts which can be easily hydrolyzed without isolation thus providing a very efficient route to formylalkylidenephosphoranes (equation 74).[169] The preparation of α-formyl substituted ylides with formic ester could be improved by adding tertiary butoxide to the starting ylide before admixture of ethyl formate as formylating reagent, thereby circumventing the necessity for transylidation and increasing the yield drastically.[170]

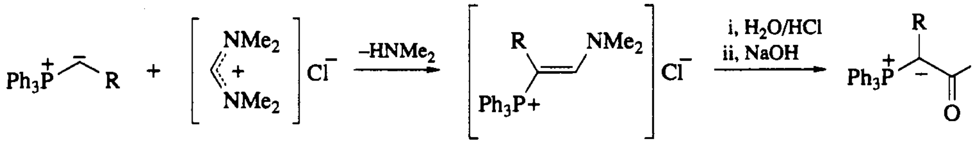

(74)

The introduction of the thioacyl group may be achieved by analogy to the acylation using dithiocarboxylic acid esters (equation 75), however side reactions may occur.[171]

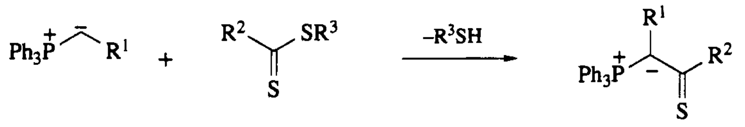

(75)

2-Iminoalkylidenetriphenylphosphoranes result from the transylidation reaction of methylenetriphenylphosphorane with imidoyl chlorides (equation 76),[172a] or from Michael addition of ylides to the C═C bond of ketenimines[172b] (formed from carbodiimide and ylides in the initial step).

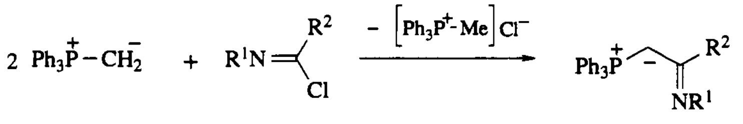

(76)

*(d) By derivatives of the carboxy group*

Ylides carrying α-substituents derived from the carboxy group (alkoxycarbonyl, alkylthiocarbonyl, alkylthiothiocarbonyl, cyano) have been synthesized by different routes.[173,174] Ester-substituted ylides are prepared from simple ylides and alkyl chloroformates in a transylidation reaction (equation 77). Using two moles of potassium bis(trimethylsilyl)amide (one for the generation of the starting ylide from its salt, the other for the deprotonation of the substituted salt) permits efficient carbalkoxylation with only one equivalent of valuable starting ylide.[175]

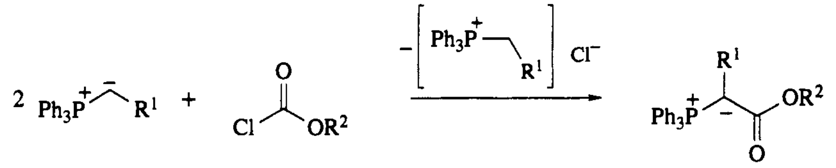

(77)

The synthesis of ylides which are α-substitued with a derivative of the carboxy group can also be achieved *via* the addition of simple ylides to heteroallenes. The reaction with carbon oxysulfide gives rise to the formation of betaines from which alkylthiocarbonylalkylidenephosphoranes may be generated by alkylation and subsequent deprotonation (equation 78; X = O, Y = S).[176] Carbon disulfide reacts in a similar way yielding (alkylthio)thiocarbonyl-substituted ylides (equation 78; X = S, Y = S).[177] These compounds are also available from the reaction of simple ylides with trithiocarbonates or dithiochlorocarbonates in analogy to the acylation of ylides (see equations 71 and 72).[173]

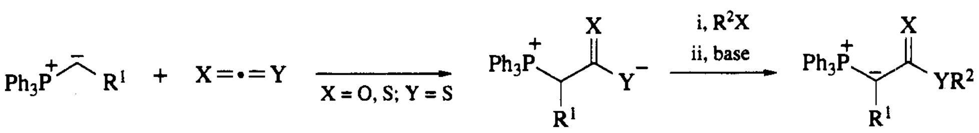

(78)

Alkylidenephosphoranes which carry a carbamoyl or thiocarbamoyl group in the α-position are formed from ylides and isocyanates or thioisocyanates (equation 79).[164,173] If the starting ylide has no activated α-H atom the reaction with thioisocyanates stops at the betaine intermediate (see equation 78) which can subsequently be alkylated and transformed into the corresponding substituted ylide with an external base.

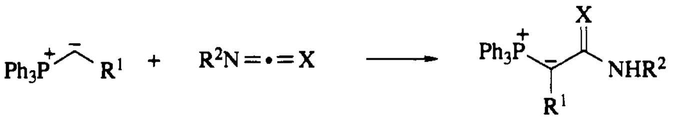

(79)

Carbamoylmethylenephosphoranes can also be synthesized from methylenetriphenylphosphorane and carbamoyl chlorides in a transylidation reaction (equation 80).[158]

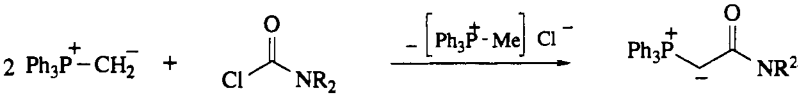

(80)

The cyano group may be introduced into the α-position of ylides by bromocyanide (equation 81) or with cyanic acid aryl esters (equation 82).[173,174]

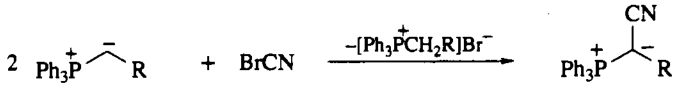

(81)

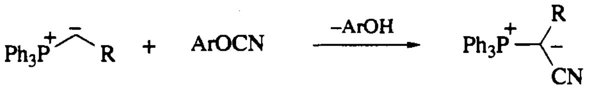

(82)

### (*e*) *By aryl and heteroaryl groups*

The substitution of a H atom at the α-C atom by an aryl group may be achieved with chloropolynitrobenzenes or hexafluorobenzene, whereby transylidation takes place (equation 83).[178,167] A variety of heteroaryl groups can be introduced in an analogous manner.

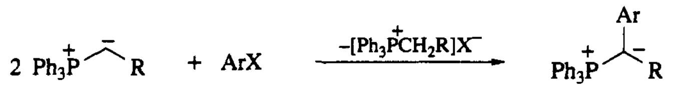

(83)

### *1.6.1.3.2 By substitution of a heterosubstituent at the ylide carbon atom*

Besides protons a series of heteroligands in the α-position of phosphonium ylides can also be substituted, giving rise to the formation of new alkylidenephosphoranes.[179] Halogen atoms have been substituted by carbon groups (with lithium organyls or acyl chlorides) or another halogen. Reaction of α-lithiated ylides (see equation 35) or ylide anions[113] with electrophiles may be considered as substitution of an alkali metal substituent at the ylide carbon atom.

Most important is the substitution of the trimethylsilyl group.[179,180] In this way phosphonium ylides have been generated which could not, or only with difficulties, be synthesized by other methods. Desilylation may be achieved using methanol or trimethylsilanol (substitution of trimethylsilyl by hydrogen), heterosiloxanes (substitution of trimethylsilyl by element–organic groups), acid chlorides, thioesters, anhydrides and trimethylsilyl esters (acylation),[149b,181] and halogenosilanes (transsilylation). Equations (84)–(87) give some examples.

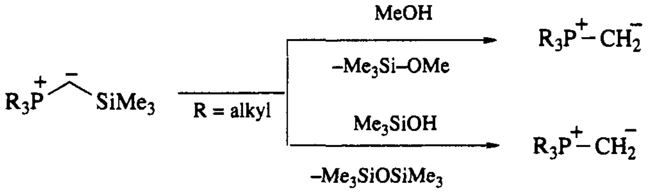

(84)

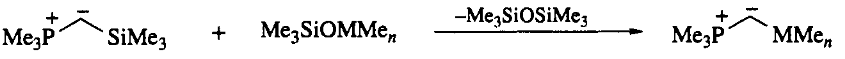

(85)

$n = 2$, M = As; $n = 3$, M = Ge, Sn, Pb

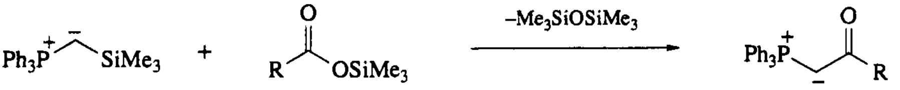

(86)

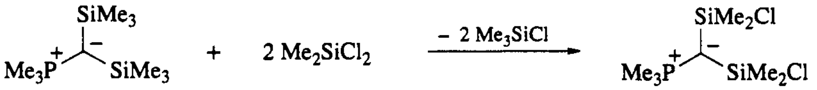

(87)

Ylides add to heteroallenes (see equations 78 and 79). In the case of silyl-substituted ylides the initially formed betaine stabilizes by silyl group migration instead of proton migration.[179]

α-Trimethylsilylalkylidenephosphoranes can be transformed into α-trimethylsilylphosphonium salts which can be desilylated by fluoride ions, thus providing a method of substituting trimethylsilyl by alkyl[81] or iodine[182] (equation 88, see also equation 18)

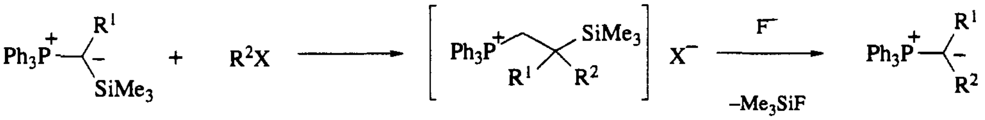

(88)

Dialkylborylalkylidenetriphenylphosphoranes react with polar or polarizable compounds *via* onium complexes to give new ylides, in which the dialkylboryl group has been substituted, and the corresponding organoboron compounds (equation 89).[183]

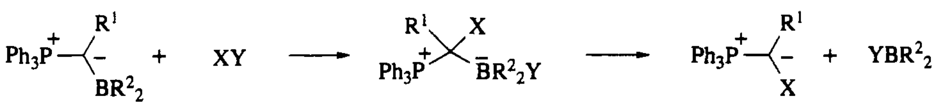

(89)

XY = $Br_2$, DOMe

### *1.6.1.3.3 From reactions which do not take place at the ylide carbon atom*

Many alkylidenephosphoranes can be transformed into new phosphonium ylides by reactions which take place in the side chain of a parent ylide, the α-C atom of the ylide group not being involved.[184]

Allylidenetriphenylphosphoranes react with a series of chloro compounds (alkyl chloroformates, acyl chlorides, 3-chloroacrylates, 2-chlorovinyl ketones, phosphorus chlorides) and other electrophilic compounds at the γ-C atom.[184–188] Abstraction of a proton from the γ-position of the resulting phosphonium salts by a second mole of starting ylide (or proton migration) gives rise to the formation of γ-substituted derivatives of the original allylidenephosphoranes (equation 90).

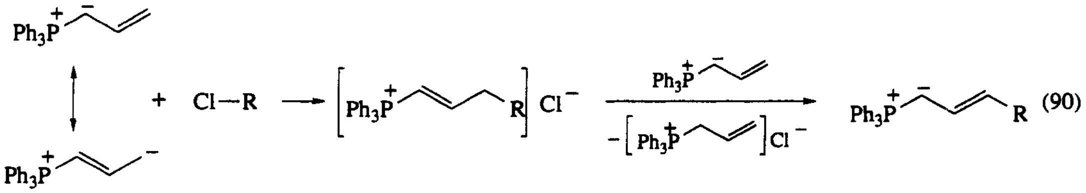

(90)

The extremely stable cyclopentadienylidenetriphenylphosphorane and its derivatives are too inactive to undergo typical ylide reactions. The cyclopentadienyl ring, however, may be substituted by a variety of electrophiles in the 2-position (equation 91).[184]

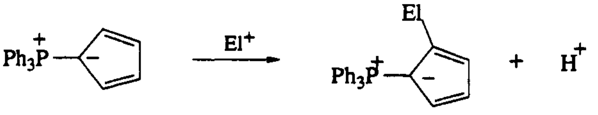

(91)

El = alkyl, acyl, azo, nitro *etc.*

Treatment of acetylmethylenetriphenylphosphorane with *n*-butyllithium or lithium diisopropylamide results in abstraction of a methyl proton to form an ylide anion. Reactions of the 1,3-dicarbanion with electrophilic compounds including alkyl halides, aldehydes, ketones and benzoate esters occurs at the terminal carbanion site to afford a variety of substituted β-ketophosphonium ylides (equation 92).[184,189,190]

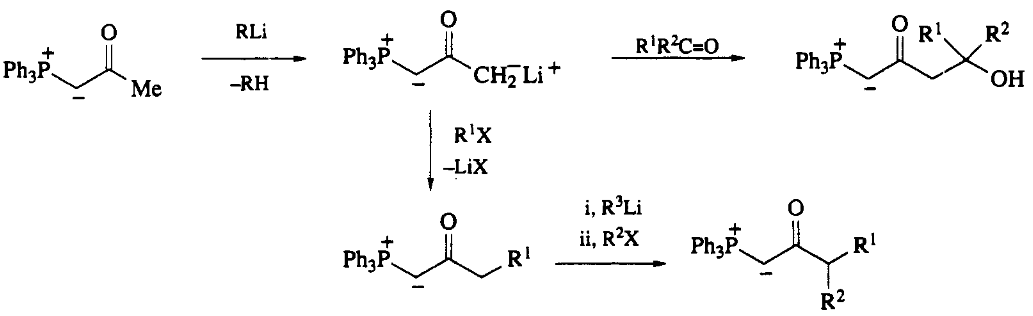

(92)

Converting the resulting monosubstituted ylide into the corresponding secondary ylide anion followed by another alkylation may give rise to the formation of disubstituted 2-oxoalkylidenephosphoranes. The diacetylmethylenetriphenylphosphorane can be deprotonated selectively at one or both methyl groups. Subsequent treatment with an alkyl halide leads to the corresponding mono- or di-alkylated ylide. Ylide anion formation followed by alkylation could also be achieved with the ylide which is readily available from the addition of triphenylphosphine to diethyl fumarate (equation 93).[191]

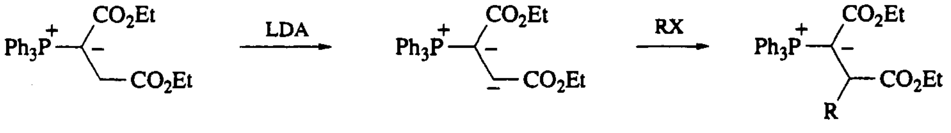

(93)

Another route to substituted ylides *via* ylide anions involves charge-directed addition of a wide range of carbon nucleophiles to γ,δ-unsaturated acylphosphoranes yielding intermediate anions which further react with electrophiles, mostly alkyl halides (equation 94).[161,184,192]

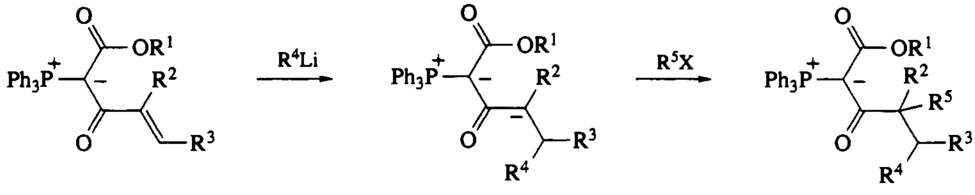
(94)

Generally alkylidenephosphoranes that carry in addition to the ylidic function another reactive site (*e.g.* a second ylide function, an additional phosphonate group, a halogen or a silyl substituent) may react at this additional functional group thus providing a derivative of the original ylide.[184,193–195]

### *1.6.1.3.4 From carbodiphosphoranes*

Carbodiphosphoranes (*cf.* Section 1.6.2.1) react with a series of halogen compounds including bromine, hydrogen chloride, alkyl halides, acyl chlorides, sulfenyl chlorides, diorganohalogenophosphines and silyl chlorides, giving rise to the formation of semi-ylide salts which formally contain an ylidic function, being however best described as salts of diphosphaallyl cations (equation 95).[196–201] Phenylcarbodiphosphoranes are converted by water into stable 1-phosphinylmethylenephosphoranes (equation 96).[196–198]

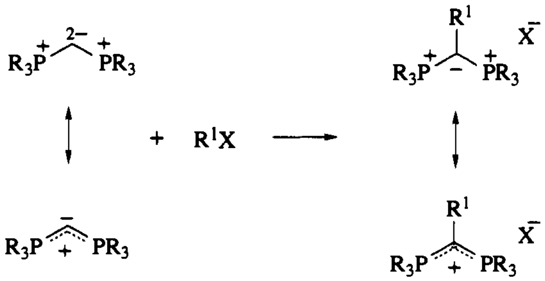
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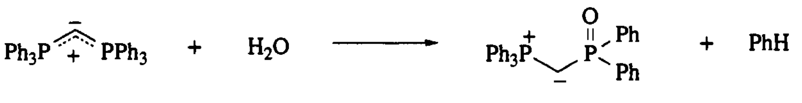
(96)

Borane yields zwitterionic compounds with partial ylide structure (equation 97).[199,201]

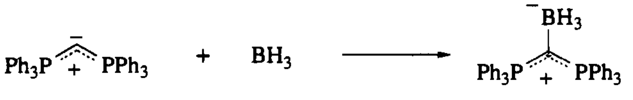
(97)

The reactions with sulfur or selenium result in the formation of betaines, which can be alkylated to give semi-ylide salts (equation 98).[202] The reactions of hexaphenylcarbodiphosphorane with a series of heteroallenes also lead to betaines which on thermolysis yield new cumulated ylides (equation 99, *cf.* equation 120).

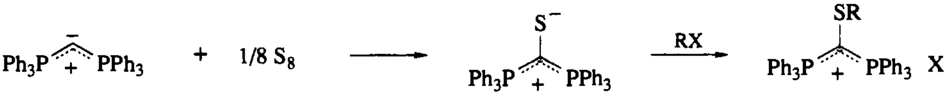
(98)

The bridging oxygen in aromatic carboxylic anhydrides may be exchanged by the ylide function in the reaction with hexaphenylcarbodiphosphorane (*e.g.* equation 100).[203]

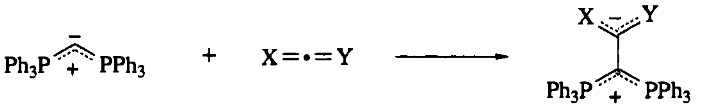

(99)

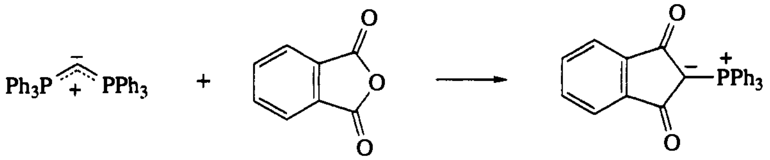

(100)

### 1.6.1.3.5 *From vinylidenephosphoranes*

'Simple' alkylidenephosphoranes can be synthesized from vinylidenephosphoranes by various routes.[204,205]

*(i) By nucleophilic substitution*

Addition of an electrophile to the lone pair of oxo-, thioxo- and imino-vinylidenephosphoranes transforms the nucleophilic $\pi^4$–$\pi^4$ system into the dipolar $\pi^4$–$\pi^2$ system of a ketene. The resulting phosphonium salt becomes a true dipolar ketene which, as such, reacts in a known manner (equation 101). Whenever the anion Nu⁻ is a stronger nucleophile than the original cumulated ylide, the new alkylidenephosphorane will be formed, in which compound ElNu has added to the parent vinylidenephosphorane. If the starting phosphacumulene ylide is a stronger nucleophile than Nu⁻, the intermediate salt always reacts with a second molecule of unreacted ylide in a [2 + 2] cycloaddition to give 1,3-cyclobutanedione derivatives.

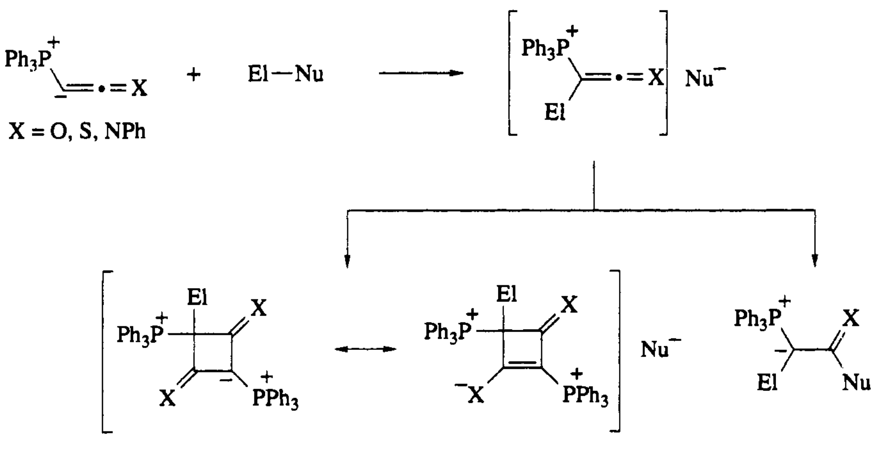

(101)

*(a) From reaction with halogen compounds*

Oxovinylidene- and iminovinylidene-triphenylphosphoranes react with hydrogen chloride in the molar ratio 2:1, leading to 1,3-dioxo- and 1,3-diimino-cyclobutane derivatives, which can be converted into stable exocyclic bisalkylidenephosphoranes by sodium bis(trimethylsilyl)amide (equation 102).

The resulting dimers of the original phosphacumulene ylides are of particular interest because one of their resonance forms represents another type of 'push–pull' cyclobutadiene.

Reactions of oxo- and imino-vinylidenetriphenylphosphoranes with alkyl halides also proceed *via* nucleophilic substitution, which is followed by a [2 + 2] cycloaddition yielding four-membered ylide phosphonium salts (equation 103), which can also be generated from the previously mentioned dimers and alkyl halides. Ring opening of the resulting ylide phosphonium salts with sodium methoxide gives bisylides. Since the ylide flanked by two carbonyl groups in the bisphosphoranes is much more inert than that adjacent to only one CO group, these compounds are easily hydrolyzed by water to monoylides.

The reaction of oxovinylidenetriphenylphosphorane or its dimer with aromatic carboxylic acid chlorides leads not to cyclobutanedione derivatives but to pyrone compounds, which can be converted to open chained bisphosphoranes with sodium methoxide (equation 104).[205] If the acid chlorides carry an

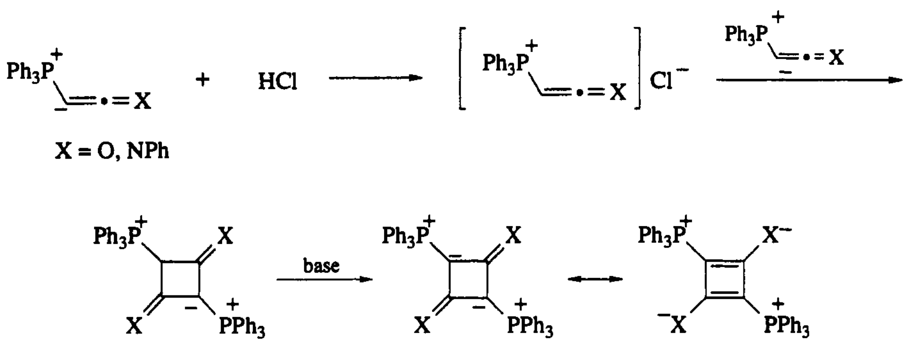

(102)

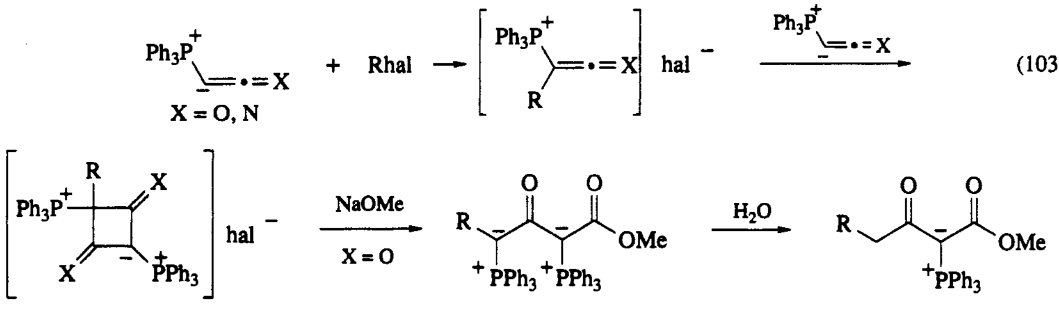

(103)

α-H atom, the resulting ylide phosphonium salts are deprotonated at the vinyl position by excess starting ylide yielding exocyclic bisylides.

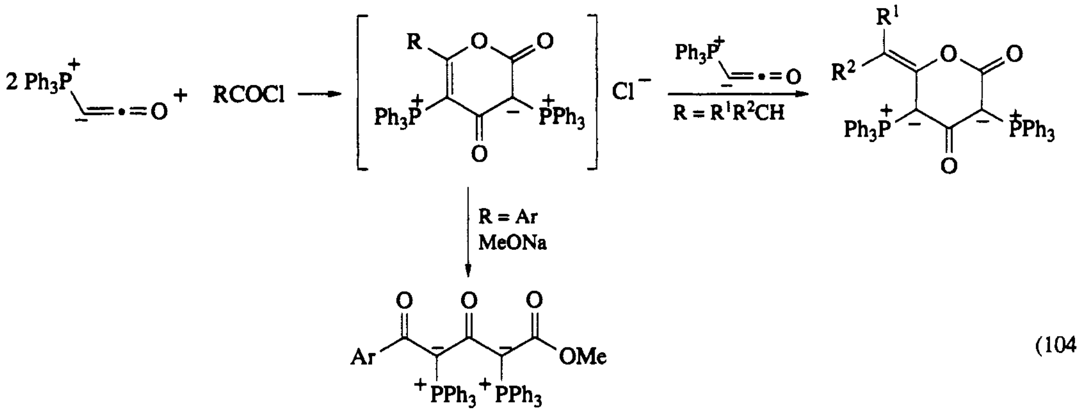

(104)

### (b) From reactions with acidic compounds

In the reaction of OH-, NH-, SH- and CH-acidic compounds with phosphacumulene ylides the anion $Nu^-$ of the initially formed phosphonium salt (*cf.* equation 101) is so nucleophilic, that addition of the anion to give a new alkylidenephosphorane is faster than cycloaddition of a second mole of starting ylide (equation 105).[204,206]

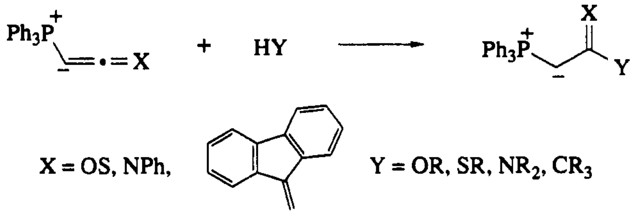

(105)

According to the difference of the ylides in nucleophilicity (NR > O > S) iminovinylidene- and oxovinylidene-phosphorane smoothly add alcohols, thiols and acidic NH compounds, while thioxovinylidenephosphorane reacts readily with thiols and phenols, less rapidly with aliphatic alcohols and does not react with NH-acidic compounds. Strongly activated $CH_2$ groups add readily to iminovinylidenephosphoranes, less rapidly to oxovinylidenephosphorane and not at all to thioxovinylidenephosphorane. (The fluorenylidene derivative is less reactive than iminovinylidenetriphenylphosphorane and more reactive than the oxovinylidene and thioxovinylidene compounds.) By this method a great variety of alkylidenephosphoranes carrying α-substituents derived from the carboxy group can be synthesized.[206]

Carboxylic acids react with phenyliminovinylidenetriphenylphosphorane (equation 106) *via* the intermediates (**1**) with formation of the alkylidenephosphoranes (**2**), which, on heating, rearrange in an intramolecular acyl migration to ylides (**3**). By heating (**2**) in the presence of an alcohol the acyl ylides (**4**) and *N*-phenylurethanes are formed.[206,207] The reaction sequence allows the replacement of the OH group in carboxylic acids by the ylide function.

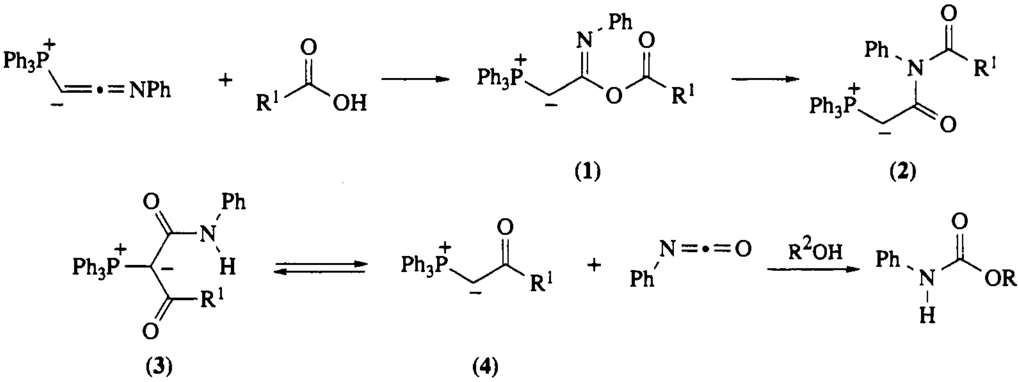

(106)

The addition of acidic compounds to phosphacumulene ylides yielding substituted alkylidenephosphoranes is of particular interest in the reaction of those acidic molecules which carry, besides the Y—H bond, a group capable of cyclization with the ylide function formed by addition.[208–215]

Ethoxy- and diethoxy-vinylidenetriphenylphosphorane add alcohols to the C═C bond according to the general scheme described above yielding orthoester phosphoranes (equation 107).[85,216,217]

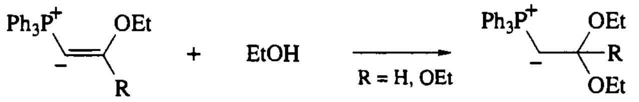

(107)

Because of its enhanced reactivity, diethoxyvinylidenetriphenylphosphorane adds a variety of CH acids, even those which do not react with oxo-, thioxo- and imino-vinylidenetriphenylphosphorane. Irreversible loss of ethanol from the initially formed Michael adduct gives phosphoranes which are vinylogs of β-keto ylides if the starting material is an acidic carbonyl compound (equation 108).[204,216] CH-acidic carbonyl compounds also may add to diethoxyvinylidenetriphenylphosphorane *via* the enolate oxygen, thus leading to orthoester phosphoranes which can undergo intramolecular Wittig reaction.[218]

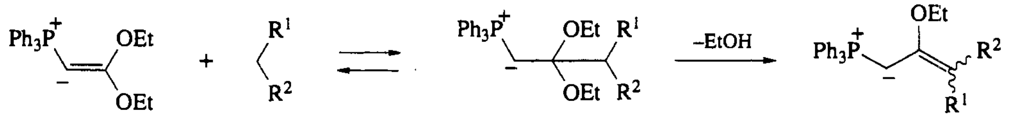

(108)

NH-acidic amines react like CH-acidic compounds. The initially formed Michael adduct loses ethanol giving rise to the formation of ethoxyiminocarbonylmethylenephosphoranes (equation 109).[206]

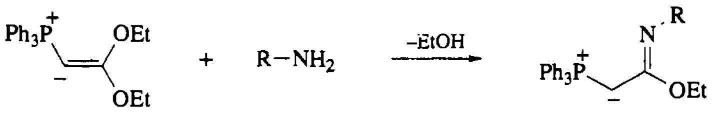

(109)

Strongly CH-acidic compounds, carboxylic acids and thiols react with diethoxyvinylidenetriphenylphosphorane not in the described manner but are ethylated by the ylide (*e.g.* equation 110).

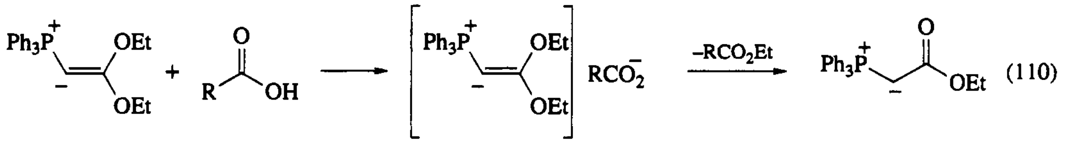
(110)

*(c) From reaction with Grignard compounds*

In the reaction of halogen compounds with oxovinylidenetriphenylphosphorane the initially formed phosphonium salt undergoes cycloaddition with a second molecule of the starting ylide. Umpolung of the reactivity of alkyl halides by transformation into the corresponding Grignard compounds, however, results in the reaction type which occurs in the reaction of acid compounds with oxovinylidenetriphenylphosphorane. Grignard compounds and oxovinylidenetriphenylphosphorane yield addition compounds from which, on subsequent hydrolysis, acyl ylides are formed (equation 111).[219,220]

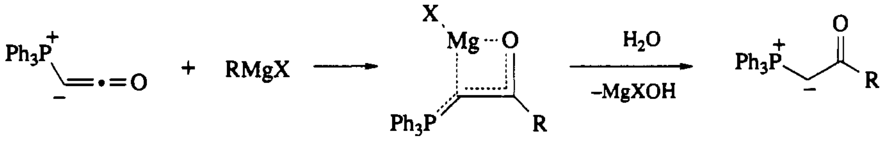
(111)

*(ii) By cycloaddition reactions*

A variety of compounds may undergo cycloaddition at the C=C bond of vinylidenephosphoranes yielding exocyclic ylides.[204,221] [2 + 2] Cycloadditions of *N*-phenyliminovinylidenetriphenylphosphorane to electron poor double bonds of alkenes and imines lead to the formation of four-membered ylides (equation 112).[204,221]

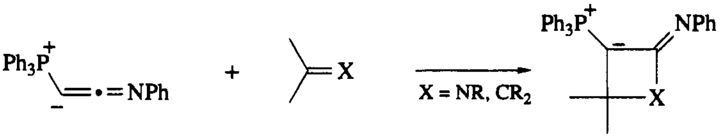
(112)

Alkynes however add to the P–C bond of vinylidenephosphoranes. The initially formed phosphacyclobutenes undergo electrocyclic ring opening to afford open chain ylides.[204,221]

Heteroallenes (*e.g.* carbon disulfide, carbon dioxide, carbon oxysulfide, isocyanates, isothiocyanates, ketenes, ketenimines) and vinylidenephosphoranes can form polar intermediates from which two isomeric products may result in a 1,4-cycloaddition (equation 113).[204,221] The direction of the ring closure depends decisively upon the nucleophilic character of Z compared with that of Y.

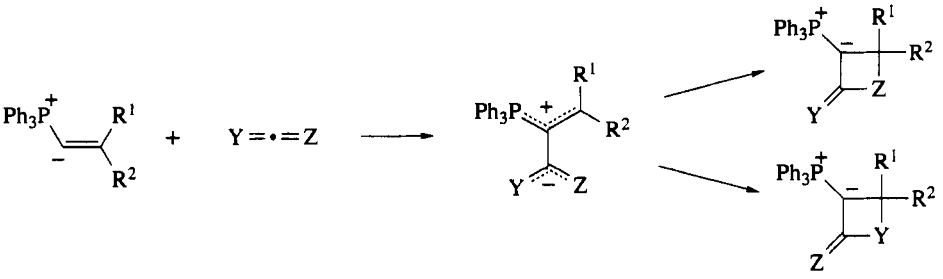
(113)

In the reaction of oxo-, thioxo- and imino-vinylidenetriphenylphosphorane the initially formed cycloadduct (**5**) may undergo electrocyclic ring cleavage followed by a second ring closure thus affording the rearranged isomer (**6**). The overall reaction sequence amounts to exchange of the exocyclic substituent X with the ring member Z. The isomer (**7**) may rearrange analogously. In one case cycloreversion of the four-membered ring occurred (see preparation of thioxovinylidenetriphenylphosphorane).

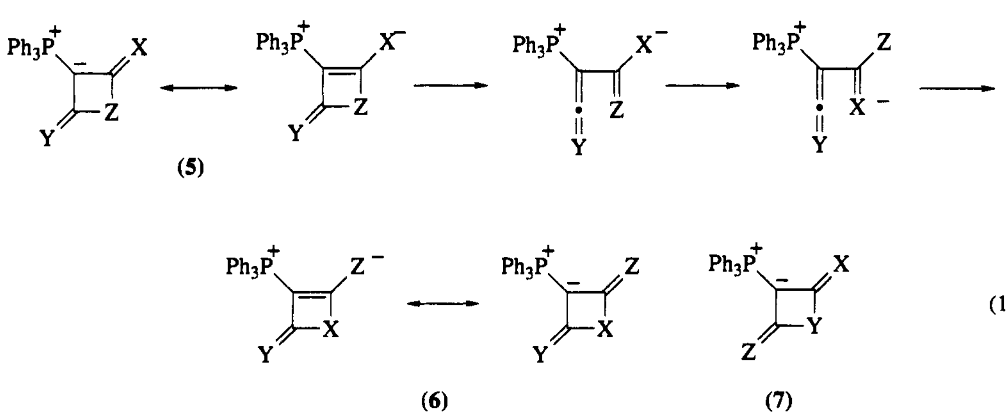
(5)

(6) (7)

(114)

Sometimes [4 + 2] cycloaddition of the dipolar 1:1 intermediate with a second molecule of heteroallene proceeds faster than the 1,4-cyclization, thus leading to six-membered rings (equation 115). Obviously this type of reaction especially occurs if the lifetime of the dipolar intermediate is sufficiently long owing to stabilization of the positive charge. While phenyliminovinylidenetriphenylphosphorane reacts with heteroallenes only in the molar ratio 1:1 the corresponding oxo, thioxo and diethoxy compounds can react both in 1:1 and 1:2 ratio.

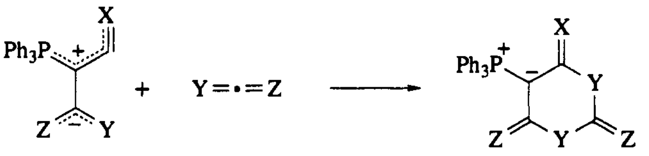
(115)

Diethoxy- and bis(ethylthio)-vinylidenetriphenylphosphorane differ in some instances in their behavior towards heteroallenes from the other vinylidenephosphoranes. The dipolar 1:1 intermediates from diethoxyvinylidenephosphorane and carbon dioxide or carbon disulfide stabilize by migration of an ethyl group to the negative substituent (*cf.* equation 113, $R^1$, $R^2$ = OEt; Y, Z = O or S); on the other hand the 1:2 adducts from the bis(ethylthio) ylide and isocyanates or isothiocyanates do not form six-membered but five-membered rings, which lose triphenylphosphine and hence yield no ylides.[222]

The [2 + 2] cycloaddition and the [4 + 2] addition of vinylidenephosphorane with heteroallenes have been applied to the synthesis of a great variety of four- and six-membered heterocyclic compounds carrying an exocyclic ylide function.[204,221,223]

1,3-Dipolar compounds (*e.g.* azides, nitriloxides and diazo compounds) add to the C=C bond of vinylidenephosphorane, affording five-membered ylidic heterocycles, *e.g.* those based on the 1,2,3-triazole, 1,2-oxazole and pyrazole skeleton from the reactions with *N*-phenyliminovinylidenetriphenylphosphorane (equation 116).

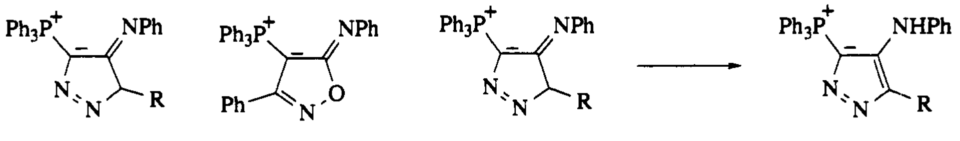
(116)

[4 + 2] Cycloaddition of α,β-unsaturated ketones, acyl ketenes, acyl, thioacyl, imidoyl and vinyl isocyanates, as well as the corresponding isothiocyanates, to the C=C bond of vinylidenephosphoranes leads to the formation of six-membered heterocycles carrying an exocyclic ylide function (*e.g.* equation 117).[204,212,224] In some instances the mentioned thioisocyanates, however, may undergo [2 + 2] cycloaddition at the C=S bond. Interestingly *N*-aryliminovinylidenetriphenylphosphoranes dimerize in a [4 + 2] cycloaddition on heating alone.[225]

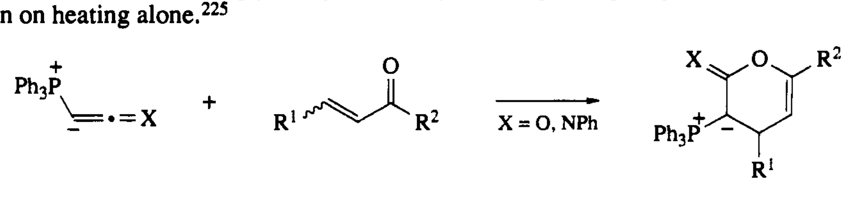
(117)

## 1.6.2 CUMULATED PHOSPHORANES

### 1.6.2.1 Carbodiphosphoranes

Carbodiphosphoranes (bistriorgano)phosphoranylidenemethanes, hexaorganocarbodiphosphoranes) may be generated from suitable phosphonium salt precursors by dehydrohalogenation or dehalogenation.[226] Since the first synthesis of hexaphenylcarbodiphosphorane, a series of symmetrical, unsymmetrical, mixed alkyl/phenyl, cyclic and difunctional carbodiphosphoranes have been prepared. Compounds synthesized until 1984 have been listed.[227]

Stepwise deprotonation of methylenebis(triorgano)phosphonium salts with bases yields carbodiphosphoranes *via* intermediate semi-ylide salts, which may also be accessible by alkylation or phosphinolation of corresponding alkylidenephosphoranes (equation 118).[226–228] It depends on the starting phosphonium salt and the base whether the intermediate ylide salts can be isolated or not. Suitable bases are sodium amide, alkali metal hydrides, alkylidenetrialkylphosphoranes, potassium and lithium organyls. For the synthesis of hexaphenylcarbodiphosphorane improved methods have been reported by which this compound may be generated without isolation of the ylide salt and on a large scale.[201,229]

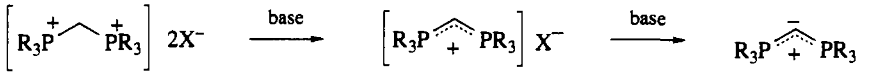

(118)

Hexaphenylcarbodiphosphorane and other carbodiphosphoranes are also available by dechlorination of phosphonium salts (*e.g.* equation 119).[198,226]

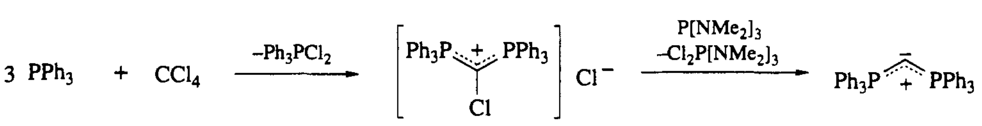

(119)

Hexaphenylcarbodiphosphorane may be stored as a stable adduct formed with sulfur or trimethylchlorosilane, from which it may be regenerated with triethylphosphine or by thermolysis, respectively.[201,202]

As a consequence of their astonishingly high tendency of formation carbodiphosphoranes spontaneously result in some instances from other bisylide precursors by skeletal rearrangement.[227,230] The stability of carbodiphosphoranes is markedly influenced by the nature of the substituents attached to the phosphorus and in the case of cyclic species also in particular by ring strain. As a consequence of these facts carbanion-stabilizing substituents and ring strain effects may cause prototropic rearrangements to afford conjugated isomeric double ylides.[199,231–234]

### 1.6.2.2 Vinylidenephosphoranes

Hexaphenylcarbodiphosphorane reacts with carbon dioxide, carbon disulfide and isothiocyanates to give betaines whose thermolysis affords oxovinylidene-, thioxovinylidene- and iminovinylidene-triphenylphosphoranes (equation 120).[204,235] The corresponding 2,2-di(trifluoromethyl) compound is obtained when the 1,2-oxaphosphetane resulting from hexaphenylcarbodiphosphorane and hexafluoroacetone (equation 121) is heated.

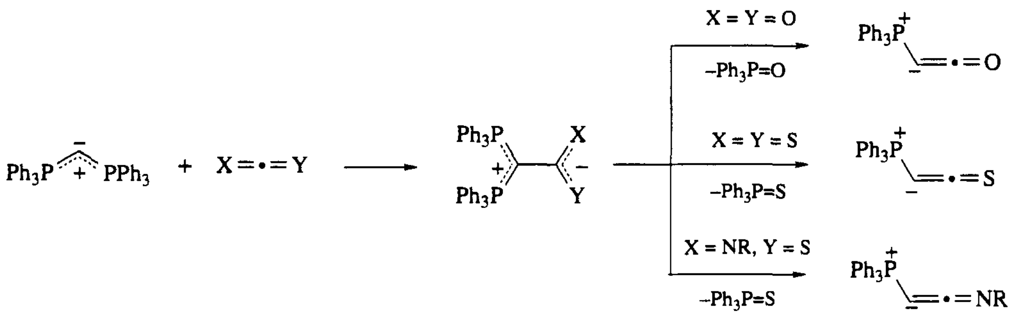

(120)

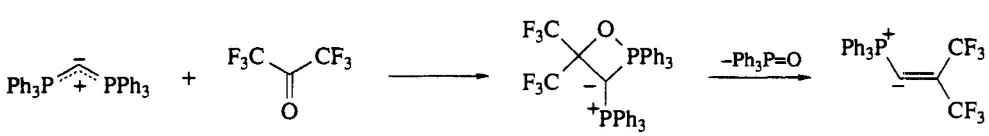

(121)

Thioxovinylidenetriphenylphosphorane is formed when the cycloaddition compound from oxovinylidenetriphenylphosphorane and carbon disulfide decomposes in a cycloreversion (equation 122).[204,235]

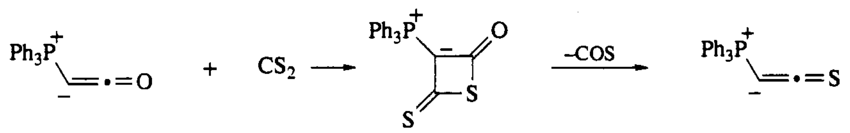

(122)

Methylenetriphenylphosphorane reacts with geminal dihalo compounds (isocyanide dichlorides, thiophosgene and 1,1-dihalo-1-alkenes) in the molar ratio 3:1. The initially formed phosphonium salt undergoes transylidation affording the conjugated ylide from which a third molecule of methylenetriphenylphosphorane removes hydrogen halide thus leading to thioxovinylidene-, iminovinylidene- and 1,2-alkadienylidene-phosphoranes, respectively (equation 123).[204,235] The reaction with 1,1-dihalo-1-alkenes requires electron-accepting substituents $R^1$ and $R^2$. The method is not suitable for the synthesis of oxovinylidenetriphenylphosphorane starting from phosgene. Attempts to generate cumulated species $R_3P{=}C{=}SiR_2$ by dehydrohalogenation of the corresponding β-halogenated ylide precursor were not successful.[67i]

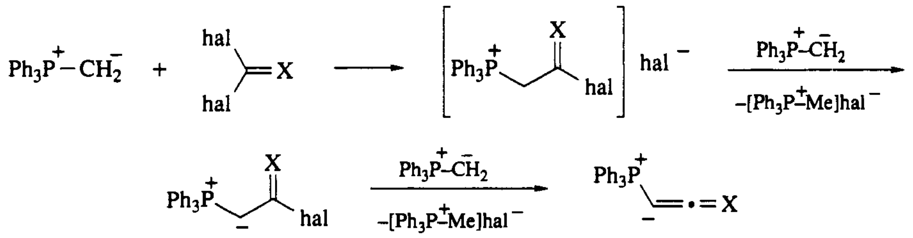

(123)

X = S, NR, $CR^1R^2$; hal = Cl, Br

Reaction of sodium bis(trimethylsilyl)amide with methoxycarbonylmethylenetriphenylphosphorane or its dithio analog leads to β-elimination and formation of oxovinylidene- and thioxovinylidene-triphenylphosphorane, respectively (equation 124).[204,235] The analogous reaction of sodium bis(trimethylsilyl)amide with 2-ethoxyallylidenetriphenylphosphoranes resulting from 2,2-diethoxyvinylidenetriphenylphosphorane and CH acids gives rise to the formation of stable propadienylidenephosphoranes (equation 125).[235]

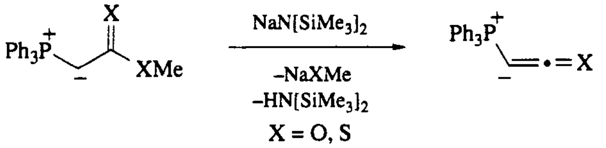

(124)

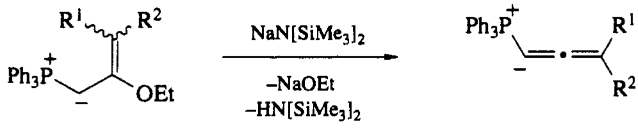

(125)

Finally vinylidenephosphoranes are accessible by α-deprotonation of vinylphosphonium salts with suitable bases, *e.g.* sodium amide, sodium ethoxide or sodium bis(trimethylsilyl)amide (equation 126).[169,204,235]

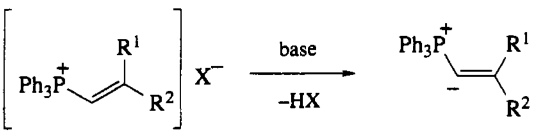
(126)

a, $R^1 = R^2 = OEt$; b, $R^1 = H, R^2 = OEt$; c, $R^1 = S$-alkyl, $R^2 = S$-alkyl; d, $R^1 = H, R^2 = NMe_2$

Propadienylidenephosphoranes have been generated by dehydrohalogenation of 2-halogeno-2-propenyl and propargyl phosphonium salts.[235,236]

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# 1.7

# Synthesis of Halides

ROLF BOHLMANN

*Schering AG, Berlin, Germany*

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## 1.7.1 NUCLEOPHILIC HALOGENATION

The formation of halides by the nucleophilic substitution of leaving groups is commonly used in the synthesis of more elaborate structures. The synthesis of inexpensive bulk chemicals like solvents, however, is mostly done by oxidation or addition reactions. Halides are either used as intermediates or are valuable end products. Authors of publications, especially patent literature, often claim one reaction for three or even four halogens. In practice, this rarely holds true and each of the halogens quite often requires different conditions. The usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$. In dimethylformamide the reverse order $Cl^- > Br^- > I^-$ is observed.[1] This order goes along with the order of the basic strength of the halogens. Thus in some cases the choice of the proper solvent will be the answer to a synthetic problem.

The following chapter deals with the individual halogens separately. A recent survey of the most important methods of preparation of halogen compounds[2] organizes the material in a similar way. This former review also includes tables[3] correlating halogenating agents with the starting materials and halogenated products.

The development in the field of halogenation is not very rapid. Consequently the now almost 30 years old, thoroughly written Volumes 5/3[4] and 5/4[5] of *Houben–Weyl* are still very useful. Fluorination procedures in organic chemistry are developing considerably faster and the field has been reviewed more recently.[6,7]

## 1.7.2 CHLORINATION

The C—Cl bond is less stable than the C—F bond but more stable than the C—Br and the C—I bonds. This means that chlorinated products normally do not suffer from the often undesired instability of bromides or iodides. On the other hand, more severe conditions are normally required to transform the C—Cl bond later in the synthesis when the chloride is not the desired final functionality. If this is no problem, the chloride is the first choice intermediate functionality because chlorine is by far the least expensive and most ready available of all halogens.

### 1.7.2.1 Chlorination of Alkyl Alcohols

The displacement of hydroxy groups by chlorine is of great importance in synthesis.[8] The reaction of hydrochloric acid with tertiary alkyl alcohols proceeds at room temperature within minutes,[9] while secondary alcohols react more slowly and primary alcohols are the least reactive (Scheme 1). A catalyst, usually zinc chloride[10] or phase transfer conditions,[11] is required if the reaction is too slow. Alternatively the use of HMPA as solvent gives good yields of primary halides.[12] Primary alcohols undergo mainly $S_N2$ and tertiary undergo mainly $S_N1$ reactions. The formation of rearrangement and elimination products is a drawback of this reaction. In addition to that problem, chiral alcohols give different degrees of racemization ($S_N1$), inversion ($S_N2$) or retention of configuration. For these and other reasons inorganic acid chlorides like $SOCl_2$, $PCl_3$, $PCl_5$ and $Ph_3PCl_2$ are often employed, as rearrangement products with these reagents are formed only to a small extent.

$$ROH + HCl \longrightarrow RCl$$

R = primary
secondary ↓ increasing rate of reaction
tertiary

Scheme 1

$SOCl_2$ is used extensively in the preparation of chlorides (Scheme 2)[13] although this reaction can give a variety of by-products.[14] Yields are typically in the 70–90% range. In the absence of base retention of configuration is the rule (Scheme 3). This has been explained by an $S_N1$ mechanism or by participation of the solvent.[15] The fact that the secondary chlorosulfite (**1**) gives, on heating, the tertiary chloride (**3**), indicates that an intramolecular single step mechanism is ruled out and an ion pair (**2**) may be involved (Scheme 4).[16] If the reaction is done in the presence of one equivalent of pyridine, inversion ($S_N2$) is likely to occur.[17,18]

$SOCl_2$, like $PCl_3$, still can give products of rearrangement,[19] especially with allylic alcohols. Less rearrangement is observed if DMF[20–23] or HMPA[19] is added. DMF and $SOCl_2$ give the Zollinger reagent (**4**), as in equation (1). Reaction of tertiary alcohols with $PCl_5$ under mild conditions as in equation (2) is a good special method for the synthesis of tertiary chlorides with retention of configuration.[24]

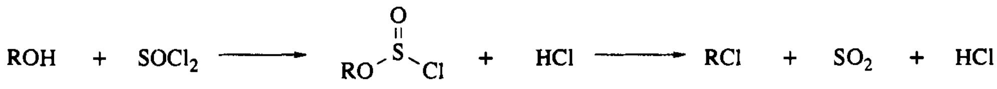

$$ROH + SOCl_2 \longrightarrow RO{-}\overset{O}{\overset{\|}{S}}{-}Cl + HCl \longrightarrow RCl + SO_2 + HCl$$

Scheme 2

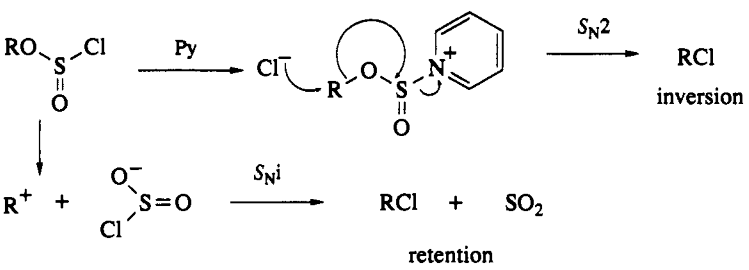

**Scheme 3**

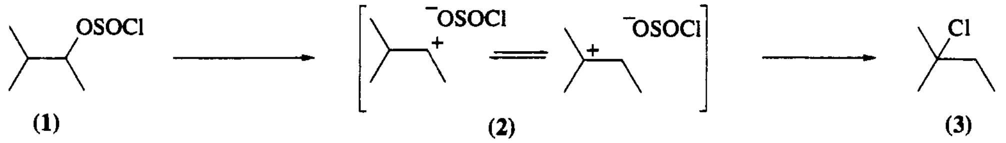

**Scheme 4**

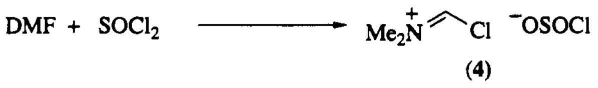

$$\mathrm{DMF + SOCl_2 \longrightarrow Me_2\overset{+}{N}{=}CHCl\ {}^{-}OSOCl}\quad \mathbf{(4)} \qquad (1)$$

$$\mathrm{ROH + PCl_5 \longrightarrow RCl + POCl_3 + HCl} \qquad (2)$$

For other phosphorus reagents good yields, less rearrangement or both are claimed. The reaction of neopentyl alcohol with $Ph_3PCl_2$ gives 92% yield (Scheme 5).[25,26] The use of oxyphosphonium[27] and phosphorus(III)[28] reagents for the replacement of alcoholic hydroxy groups has been reviewed. The system $Ph_3P$–$CCl_4$ (Scheme 6)[29–31] allows the transformation of labile alcohols like geraniol, lincomycines or sugars. Addition of imidazole to $Ph_3PCl_2$ and to the $Ph_3P$–$CCl_4$ system improves the selectivity and reactivity, respectively.[32] With this technique primary hydroxy groups in carbohydrates are selectively substituted, as exemplified in equation (3). $Ph_3P$–hexachloroacetone is another reagent for the formation of chlorides in high yields, with no rearrangement.[33]

$$\mathrm{R_3P + Cl_2 \longrightarrow R_3PCl_2 \xrightarrow{R'OH} R'Cl + HCl + R_3PO}$$

R = Ph, R' = neopentyl; 92%

**Scheme 5**

$$\mathrm{Ph_3P + CCl_4 \longrightarrow Ph_3\overset{+}{P}Cl\ {}^{-}CCl_3 \xrightarrow{ROH}}$$

$$\mathrm{HCCl_3 + Ph_3\overset{+}{P}OR\ Cl^{-} \longrightarrow RCl + Ph_3PO}$$

**Scheme 6**

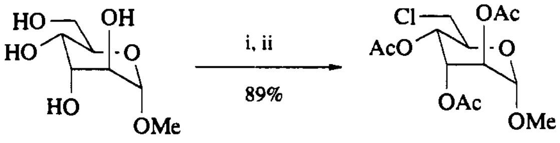

(3)

i, $Ph_3PCl_2$, imidazole; ii, $Ac_2O$, pyridine

The conversion of allylic alcohols into chlorides is complicated by the competition of $S_N2$ and $S_N2'$ reactions (equation 4). $SOCl_2$ and $PCl_3$ give mainly $S_N2'$ reactions.[34] With $Ph_3P$–$CCl_4$[35] or $MeSO_2Cl/LiCl$[36] mainly normal $S_N2$ products are formed.

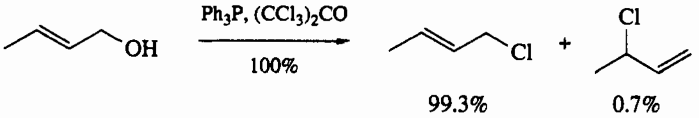

(4)

Alkyl alcohols[37] or enolizable aldehydes are converted in a stereospecific manner to alkyl chlorides or vinyl chlorides in good yields on treatment with a Mukaiyama-type chlorobenzoxazolium salt (Scheme 7).[38] The very good activation of hydroxy groups by the Mitsunobu procedure may be useful in some difficult cases (Scheme 8).[39–42]

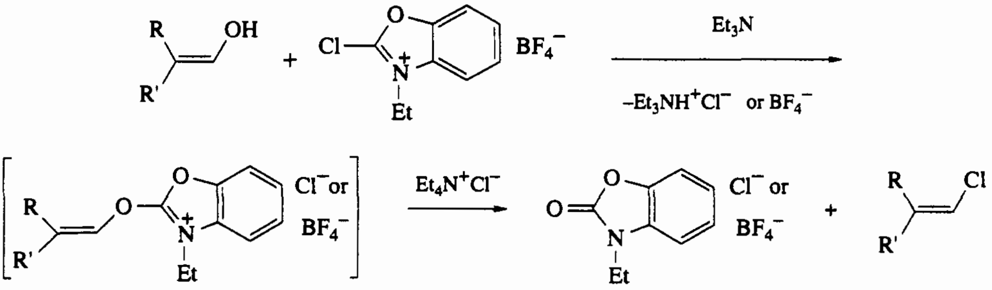

**Scheme 7**

$$\mathrm{ROH} \xrightarrow{\text{i, ii}} \mathrm{RCl}$$

i, $EtO_2CN{=}NCO_2Et$, $Ph_3P$; ii, $Cl^-$

**Scheme 8**

The leaving group is not $OH^-$ but $H_2O$ or $OR^-$. It is a common feature of all the above reactions that the activated species is not isolated. Chlorination of isolated activated alcohols is the subject of the next section.

## 1.7.2.2 Chlorination of Alkyl Alcohol Derivatives

$OH^-$ is not a satisfactory leaving group. A sufficient activation is needed to allow nucleophilic displacements. Tosylates, mesylates, triflates, sulfates and other esters of sulfuric and sulfonic acids are suitable leaving groups for this purpose. They are generally easy to make and stable enough for isolation or purification. Isolation of a stable intermediate often gives cleaner reactions and products.

Neopentyl tosylate reacts with LiCl in HMPA and gives the chloride with clean inversion without rearrangement (equation 5).[43] Another example of this reaction is the conversion of allylic tosylates to chlorides without rearrangement or reaction of the sensitive acetal (equation 6).[44] Dimethylaminopyridine is a useful catalyst for the transformation of hydroxy compounds to chlorides with tosyl chloride.[45]

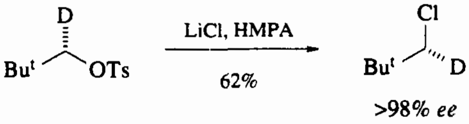

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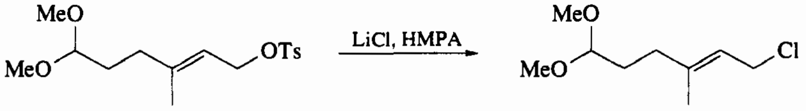

(6)

The opening of γ-lactones with alcoholic hydrogen chloride (equation 7) is a useful example of the otherwise rare cleavage of carboxylic esters to alkyl chlorides.[46]

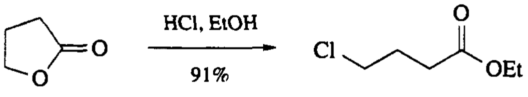

(7)

### 1.7.2.3 Chlorination of Epoxides

The cleavage of dialkyl ethers with hydrogen chloride is rarely successful. A special case is the cleavage of epoxides (Scheme 9), which, due to ring strain, are much more reactive than open chain or larger ring ethers. The mechanism is $S_N2$. This results in formation of a *threo*-chlorohydrin from a *cis*-epoxide and an *erythro* product from a *trans*-epoxide. The regioselectivity of the reaction is satisfactory if one of the two carbon centers can stabilize a positive charge better than the other. An example for good regioselectivity is the opening of epoxy esters (Scheme 10). In the absence of strong electronic effects, hard to predict mixtures of the two possible chlorohydrins are formed.

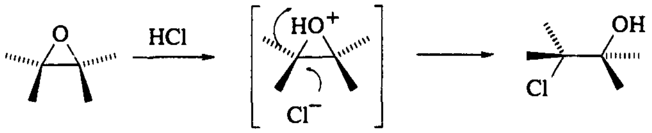

**Scheme 9**

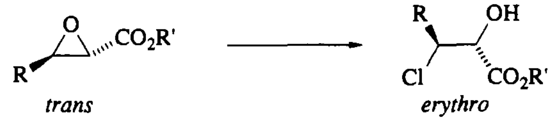

**Scheme 10**

The conversion of epoxides to vicinal dichlorides has been done with $SOCl_2$ and pyridine,[47] $Ph_3P–CCl_4$[48] or $Ph_3PCl_2$.[49] Symmetric *cis*-epoxides give *meso*-dichlorides (equation 8), and the corresponding *trans*-epoxides give D,L-dichlorides. This is a two-step mechanism involving an intermediate chlorohydrin. Two $S_N2$ reactions give inversion at both carbon atoms.

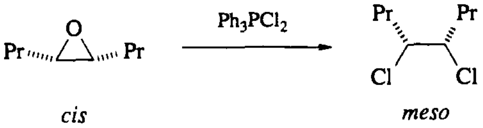

(8)

### 1.7.2.4 Chlorination of Diazo Ketones

Diazo ketones give α-chloro ketones on treatment with hydrogen chloride (equation 9).[50] Diazotization of α-amino acids in the presence of an excess of chloride gives α-chloro acids (Scheme 11).[51] The configurational identity of the amino acids is lost with the achiral diazo intermediate. The reaction becomes useful in cases where the amino acid is easily available and the chloride is not.

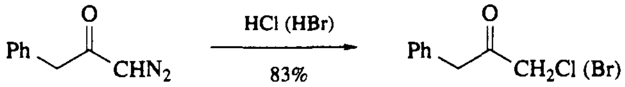

(9)

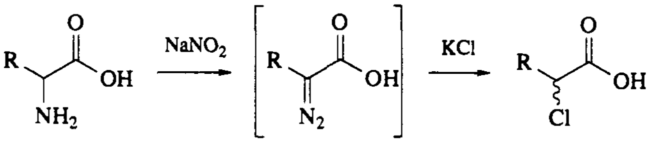

**Scheme 11**

### 1.7.2.5 Chlorination of Diazonium Salts

Phenolic hydroxy groups undergo $S_N$Ar reactions only if the aromatic ring is activated by electron-withdrawing substituents. The replacement of nitrogen in aromatic diazonium salts with hydrogen chloride is by far more common.[52] If the catalyst is copper(I) or copper(II) chloride it is called the Sandmeyer reaction. With copper as catalyst it is called the Gattermann reaction. The choice of catalyst and conditions influences the yields (equation 10).[53] The scope of the reaction is wide. These reactions are useful not only for the formation of aryl chlorides but also of aryl bromides (see Section 1.7.3.5). The synthesis permits the introduction of chlorine with good yields in positions where direct chlorination fails. The mechanism (Scheme 12) is believed to involve a reduction of the diazonium ion to an aryl radical by the copper(I) ion. In the next step the aryl radical reduces copper(II) chloride with aryl–chlorine bond formation.[54]

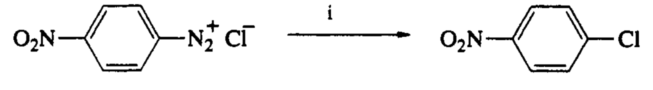

(10)

i, CuCl, acid, 60% or $CuCl_2$, neutral, 85%

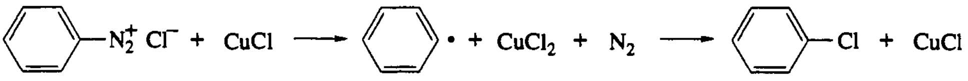

**Scheme 12**

The isolation of the diazonium salt is not always necessary. Several procedures allow the preparation of aryl chlorides from aromatic amines in one step.[55–57]

### 1.7.2.6 Other Chlorinations

*N*-Alkylamides form alkyl chlorides upon treatment with $PCl_5$[58] or $SOCl_2$.[59] Benzamides give better results than aliphatic amides (Scheme 13), with yields sometimes in the region of 80%.

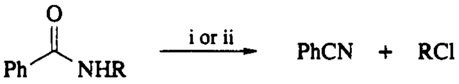

i, $PCl_5$; ii, $SOCl_2$

**Scheme 13**

The replacement of other halogens by chlorine is in most cases a devaluation of the more valuable starting material. If necessary (*e.g.* isotopic labeling), it can be done with LiCl,[60] $AlCl_3$ (equation 11)[61] or copper(I) chloride (equation 12).[62]

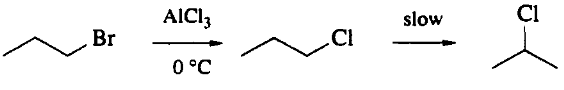

(11)

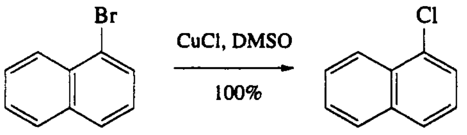

(12)

Substitution of phenolic hydroxy groups is possible if the aromatic ring is activated by electron-withdrawing substituents, as in picric acid (equation 13).[63] The intermediate pyridinium picrate reacts with $POCl_3$ in an $S_N$Ar mode.

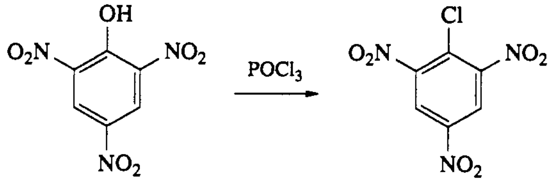

(13)

## 1.7.3 BROMINATION

The C—Br bond is less stable than the C—Cl and C—F bonds. Only the C—I bond is weaker. Organic bromine chemistry is strongly related to organic chlorine reactions. On average brominated compounds are two orders of magnitude more reactive than the chlorinated analogs. Brominated intermediates are often not stable enough for storage or even isolation. On the other hand much milder reaction conditions are required for further transformations of the C—Br bond. In laboratory scale preparations the higher reactivity is often more important than storage or cost considerations. Moreover, smaller brominated molecules have a higher boiling temperature than the chlorinated analogs, so the former are often more easy to handle at atmospheric pressure. Distillation of the less stable bromine compounds may be more critical.

Brominated derivatives are especially useful as precursors for organometallic compounds or free radicals.

### 1.7.3.1 Bromination of Alkyl Alcohols

The substitution of alcoholic hydroxy groups with hydrogen bromide appears to be more common than that with hydrogen chloride.[8] Hydrogen bromide is used as a 48% aqueous solution with[64] or without[65] conc. $H_2SO_4$ in acetic acid,[66] or gaseous.[67]

Primary alcohols prefer an $S_N2$ mechanism. When this mechanism is hindered by steric bulk, the Wagner–Meerwein rearrangement competes with substitution (Scheme 14). Secondary and tertiary alcohols follow an $S_N1$ pathway. The intermediate carbonium ion has the tendency to isomerize to a more stable cation.

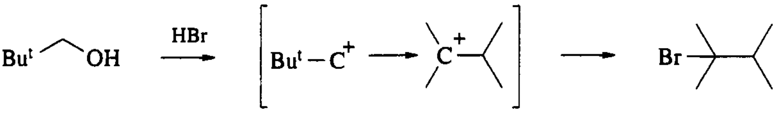

Scheme 14

The use of $PBr_3$[68] avoids rearrangement to some extent, but $PBr_3$ is less easily available than hydrogen bromide. $PBr_5$ can also replace hydroxy groups with bromine. It is, however, even more expensive and difficult to handle than $PBr_3$.

The use of $SOBr_2$ is comparatively much less common than the use of the analog $SOCl_2$. $SOBr_2$ is expensive and less stable than $SOCl_2$, but it gives clean reactions with primary alcohols (equation 14).[69]

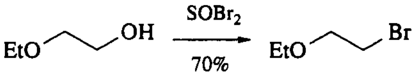

(14)

An alternative to the above-mentioned reagents is the combination of NBS or 1,3-dibromo-5,5-dimethylhydantoin with $Ph_3P$ in DMF (equation 15).[70] In carbohydrate chemistry this reagent gives primary bromides in >70% yield.

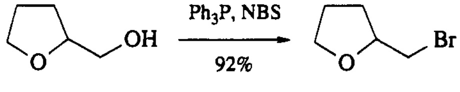

(15)

$Ph_3P$ forms with $Br_2$ the very useful brominating reagent $Ph_3PBr_2$. This can replace aliphatic hydroxy groups without rearrangement or elimination (Scheme 15).[71] Another remarkable reaction of this reagent is the substitution of phenolic hydroxy groups, even if they are not activated (equations 16 and 17).[25,72] The high temperature required for this substitution limits the scope of this reaction, however.

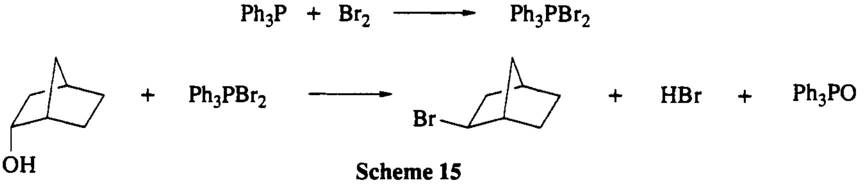

Scheme 15

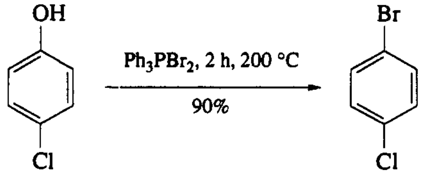

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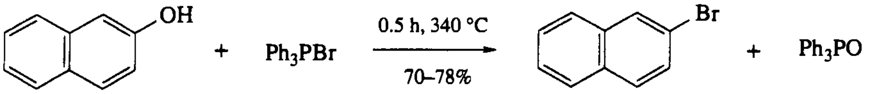

(17)

The system of $Ph_3P$–diethyl azodicarboxylate–hydroxy compound–LiBr allows the formation of alkyl bromides under mild conditions (equation 18).[40–42] An $S_N2$-type displacement of an intermediate alkoxyphosphonium species is generally assumed. Hindered alcohols such as menthol do not give bromides with the Mitsunobu procedure.

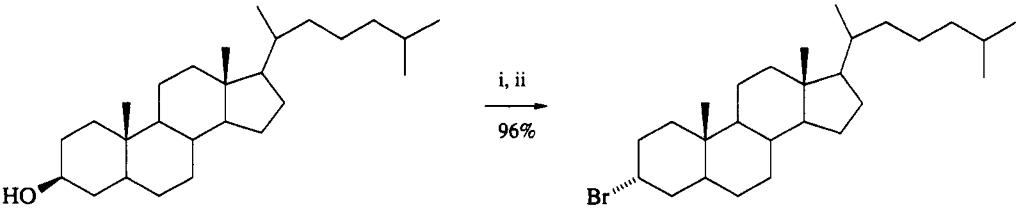

(18)

i, $Ph_3P$, $EtO_2CN{=}NCO_2Et$; ii, LiBr, 20 °C

Good yields of alkyl bromides result from the treatment of alcohols with $Me_3SiBr$ (equation 19)[73] or $Me_3SiCl$ and LiBr.[74,75]

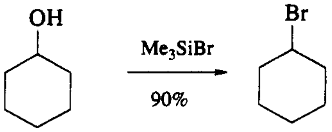

(19)

### 1.7.3.2 Bromination of Alkyl Alcohol Derivatives

The above-mentioned reactions for the introduction of bromine always involve an activation of the alcohol as the first step. In some cases it can be useful to isolate the activated intermediate. The reactions of alkyl mesylates or tosylates with $MgBr_2$ give alkyl bromides under mild conditions with good yields (equation 20).[76] Neopentyl tosylate with LiBr in HMPA gives neopentyl bromide in 67% yield (equation 21).[43] Complete inversion with little or no rearrangement is observed in this difficult case.

Cleavage of dialkyl ethers with $Me_3SiBr$ is strongly catalyzed by 0.1 equiv. of IBr (equation 22).[77] This makes possible synthetic applications which were previously ruled out by low reactivity.

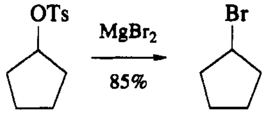

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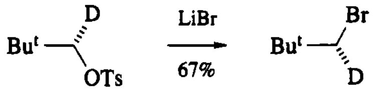

(21)

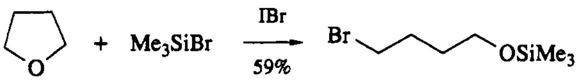

(22)

### 1.7.3.3 Bromination of Epoxides

The reaction of epoxides with hydrogen bromide gives bromohydrins. The mechanism is $S_N2$ as for the analogous chlorination (see Section 1.7.2.3). The cleavage of epoxy cholestanes with hydrogen bromide (Scheme 16) demonstrates the stereochemical features of the reaction.[78] Diaxial opening of the epoxide ring following the Fürst–Plattner rule is the preferred reaction. Bromohydrins formed this way with excellent stereospecificity can undergo further bromination to dibromides. The replacement reactions are most favored when the centers of the reaction are coplanar.

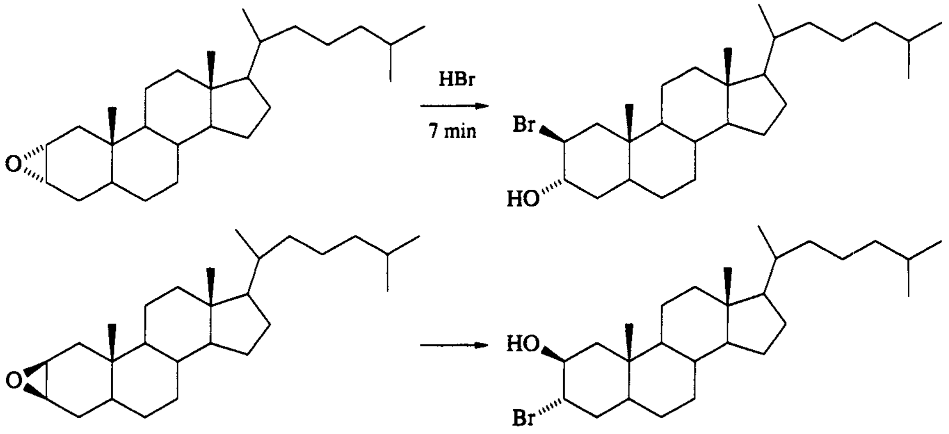

Scheme 16

### 1.7.3.4 Bromination of Diazo Ketones

Diazo ketones are transformed to α-bromo ketones on treatment with hydrogen bromide (equation 9).[79]

### 1.7.3.5 Bromination of Diazonium Salts

The replacement of phenolic hydroxy groups with $Ph_3PBr_2$ (equations 16 and 17) requires 200 °C or more (see Section 1.7.3.1). The transformation of anilines to bromides *via* diazonium salts is a much more general reaction.[52] Copper(I) or copper(II) bromide is the catalyst in case of the Sandmeyer reaction. If copper is used, the reaction is called the Gattermann reaction. These reactions are also known with the analogous chlorine reagents (see Section 1.7.2.5). Yields are in the 90% range and the scope of the reaction is wide. The mechanism is believed to be analogous to the formation of chlorides (Scheme 17).[54]

Isolation of the intermediate diazonium salt can be avoided in many cases. Treatment with *t*-butyl nitrite followed by $CuBr_2$ can give oxidative bromination in addition to replacement of the diazo group

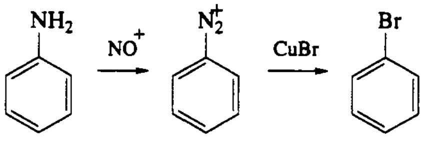

**Scheme 17**

(equations 23 and 24).[57,80] Several other procedures have been described for the preparation of aryl bromides from aromatic amines in one step.[55]

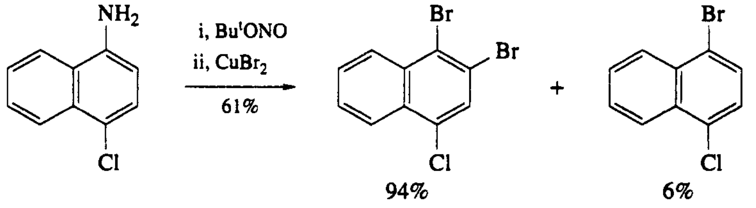

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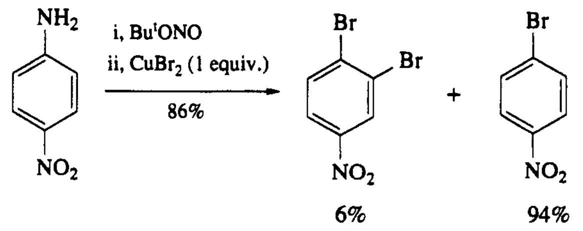

(24)

### 1.7.3.6 Other Brominations

Brominated compounds are more reactive than the analogous chlorinated compounds. Accordingly it is sometimes necessary to exchange chlorine for bromine. This can be achieved by an equilibrium process, called the Finkelstein reaction, if it is possible to shift the equilibrium to the brominated product (Scheme 18). Primary alkyl chlorides react with ethyl bromide in the presence of *N*-methyl-2-pyrrolidone and metal bromides to give alkyl bromides (Scheme 19).[81] Alkyl iodides do not exchange with HBr under normal conditions. The equilibrium is pushed to the alkyl bromide if $I^-$ is selectively removed from the reaction by oxidation with $HNO_3$ to $I_2$ (Scheme 20).[82] An equimolar mixture of HCl and HBr in the presence of $HNO_3$ gives the alkyl bromide as the major product.

$$\mathrm{RCl} + \mathrm{Br}^- \rightleftharpoons \mathrm{RBr} + \mathrm{Cl}^-$$

**Scheme 18**

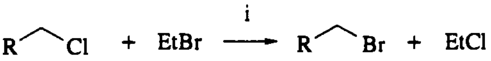

i, *N*-methyl-2-pyrrolidone, MBr

**Scheme 19**

$$\mathrm{RI} + \mathrm{Br}^- \rightleftharpoons \mathrm{RBr} + \mathrm{I}^-$$

$$\mathrm{HNO_3} + \mathrm{I}^- \longrightarrow 0.5\,\mathrm{I_2}$$

**Scheme 20**

Tertiary amines are cleaved with BrCN to give an alkyl bromide and a disubstituted cyanamide (Scheme 21). This process is called the von Braun reaction. Many examples have been reviewed.[58,83] Tertiary amines with different R groups cleave so that the most reactive alkyl bromide is formed. Benzyl and allyl cleave better than alkyl, lower alkyl cleaves better than higher alkyl and aryl is not cleaved at all. The mechanism involves an intermediate *N*-cyanoammonium species, which is substituted by bromide anions (Scheme 22).[84]

$$\mathrm{R_2NR' + BrCN \longrightarrow R'Br + R_2NCN}$$

**Scheme 21**

$$\mathrm{R_3N + BrCN \longrightarrow [Br^- + R_3\overset{+}{N}CN] \longrightarrow RBr + R_2NCN}$$

**Scheme 22**

### 1.7.4 IODINATION

The C—I bond is very unstable and more reactive than C—Br, C—Cl and C—F bonds. Iodine is the most expensive of the common halogens and is much less frequently used in synthesis than bromine, chlorine or fluorine. Organometallic reactions proceed with iodinated aliphatic or aromatic compounds more easily than with the other halogens. Noble metal catalysis with palladium complexes is most effective with iodinated compounds. A useful synthetic procedure is the facile reduction of iodinated derivatives under mild conditions. Replacement of iodine by hydrogen at an $sp^3$ carbon is an exothermic reaction with $\Delta H = -25$ kJ mol$^{-1}$.

Selective reactions of iodide are possible in the presence of other functional groups, including other halides.

#### 1.7.4.1 Iodination of Alkyl Alcohols

Alcohols are converted to iodides with HI in good to high yields (Scheme 23).[8] HI is often prepared *in situ* from potassium iodide and phosphoric acid.[85] The substitution reaction competes with reduction of the alkyl iodide to the alkane.[86] Another problem, namely rearrangement, is common to all acid-catalyzed reactions of alcohols; HI is no exception to this rule.

$$\mathrm{ROH \xrightarrow{HI} RI}$$

**Scheme 23**

A method to avoid unwanted rearrangements involves the use of $PI_3$, which is normally generated from white or red phosphorus and $I_2$ (Scheme 24).[87] This method also suffers from the reducing power of iodide as an alternative pathway.

$$\mathrm{ROH \xrightarrow{red\ P,\ I_2} RI}$$

**Scheme 24**

Phosphite diiodide converts alcohols to iodides.[88] This reagent has been used much less often than the corresponding dibromides or dichlorides. Phosphite methiodides give better yields of iodides in the reaction with primary, secondary and tertiary alcohols and are simple to use.[89] Neopentyl iodide is isolated in 70% yield from the reaction of triphenyl phosphite, neopentyl alcohol and methyl iodide (equation 25). This reaction is remarkable considering the severe steric bulk of the neopentyl group which often makes rearrangement become the major process.

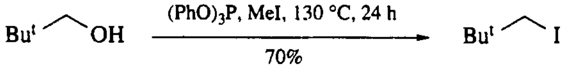

(25)

Diphosphorus tetraiodide is a valuable reagent for the regioselective synthesis of iodoalkanes from alcohols. The reaction occurs stereoselectively in the case of secondary alcohols (equation 26).[90]

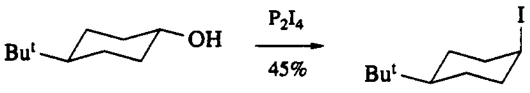

(26)

Trimethylsilyl iodide converts alcohols to iodides.[91] The disadvantage of this method is the expensive reagent, which is avoided if trimethylsilyl chloride and sodium iodide are used instead (equation 27).[92,93] Trimethylsilyl polyphosphate (PPSE), which is prepared from hexamethyldisiloxane and phosphorus pentoxide, also activates alcoholic hydroxy groups for substitutions with iodide anions (equation 28).[94]

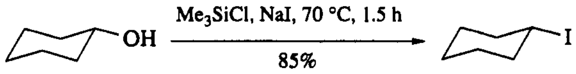

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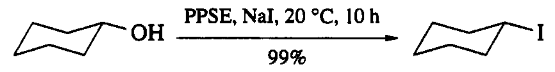

(28)

Activation of alcohols with fluorobenzothiazolium[95] or fluoropyridinium salts,[96] as well as with carbodiimidinium iodide,[97] allows the nucleophilic substitution with iodide to occur under mild conditions with inversion of configuration (equation 29).

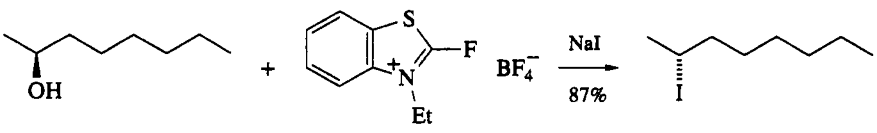

(29)

## 1.7.4.2 Iodination of Alkyl Alcohol Derivatives

Iodide is a very effective nucleophile, although it is still not able to substitute the hydroxy group without activation. The activated intermediates are not isolated in most cases. The iodinated products, however, suffer sometimes from a low stability which limits the period of storage. In such and other cases it may be best to use activated derivatives of alcohols as the stable intermediate.

A general method for the synthesis of alkyl iodides is the reaction of tosylates or methanesulfonates with sodium iodide in acetone or magnesium iodide in diethyl ether (equation 30).[98] The reaction is not always a clean $S_N2$ process. Stereoselectively deuterated neopentyl tosylate, for example, gives with NaI in HMPA only low yields (34%) of the racemic iodide (equation 31).[43] This is in contrast to analogous reactions with bromide and chloride (see Sections 1.7.3.2 and 1.7.2.2), where better yields with complete inversion are observed.

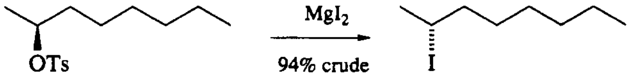

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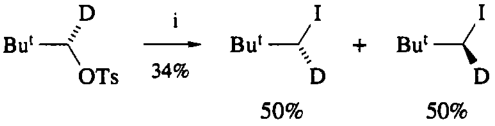

(31)

i, NaI, HMPA, 100 °C, 4 h, 80% conversion

## 1.7.4.3 Iodination of Ethers and Epoxides

Ethers are cleaved by HI faster than by HBr and HCl (Scheme 25). To prevent the undesirable reducing action of the reagent, KI and phosphoric or polyphosphoric acid are used to generate HI *in situ* (equation 32).[99,100] The ether bond is also cleaved by trimethylsilyl iodide (equation 33).[74]

$$\mathrm{ROR'} + \mathrm{HI} \longrightarrow \mathrm{RI} + \mathrm{R'OH}$$

**Scheme 25**

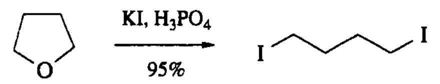

(32)

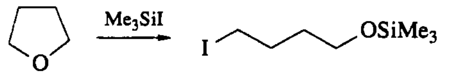

(33)

The release of ring strain in epoxides is probably responsible for the high reactivity of these special ethers. HI opens epoxides under mild conditions stereospecifically to iodohydrins (Scheme 26).[101] The mechanism is similar to the reaction of bromide with epoxides (see Section 1.7.3.3). It should be noted, however, that reduction of epoxides to alkenes may occur if vicinal diiodides are intermediately formed, which can lose $I_2$ under the reaction conditions. With the combination of acyl chloride and NaI unstable diiodides are avoided and 2-iodoethyl esters are formed from oxiranes (Scheme 27).[102]

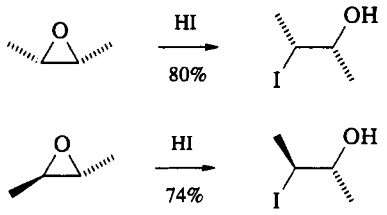

Scheme 26

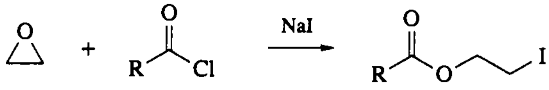

Scheme 27

### 1.7.4.4 Iodination of Carboxylic Esters

LiI in boiling pyridine or other weak nucleophilic bases can cleave alkyl esters to alkyl iodides and lithium carboxylates (Scheme 28). The reaction is mainly used for mild, aprotic cleavage of esters to carboxylates. The high degree of dissociation for LiI and the nucleophilic strength of the iodide ion explain the reaction with esters, which is not useful with the other halides. Trimethylchlorosilane and sodium iodide also give alkyl iodides from esters.[93]

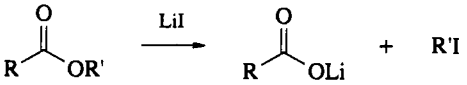

Scheme 28

### 1.7.4.5 Iodination of Diazonium Salts

The transformation of aryl diazonium salts by aryl iodides does not require catalysis by copper or its salts (see Sections 1.7.2.5 and 1.7.3.5). A drawback is unwanted reduction with removal of functionality (equation 34).[103] Diazo ketones are reduced to ketones with HI and do not give halogenated products (Scheme 29).[104]

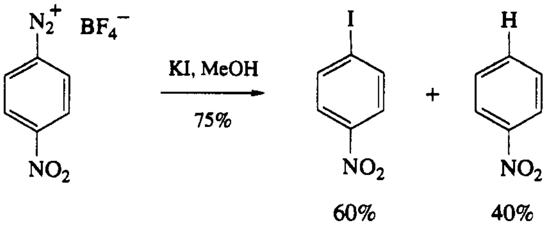

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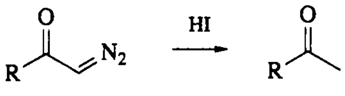

Scheme 29

### 1.7.4.6 Other Iodinations

Halide exchange from the lower halides to iodine is often desirable due to the higher reactivity of iodides in nucleophilic substitutions, reductions, organometallic or radical reactions (Scheme 30). Conversion of chlorides and bromides to iodides with sodium iodide in acetone is called the Finkelstein reaction. This halide exchange is an equilibrium process, which is shifted to the iodinated products due to precipitation of the less soluble sodium bromide or chloride from acetone. Best results are obtained when the reaction mixture is free of water.

$$\mathrm{RX} \xrightarrow{\mathrm{I}^-} \mathrm{RI}$$

Scheme 30

## 1.7.5 FLUORINATION

The C—F bond has a very high dissociation energy (>450 kJ mol$^{-1}$) and it is accordingly seldom used as an intermediate functionality. Poly- and per-fluorinated hydrocarbons are useful due to their inertness and physical properties. Monofluorinated analogs of biologically important compounds often show very different activities to the parent compounds. Fluoroacetic acid, for instance, is highly toxic with an estimated lethal dose of 2–5 mg kg$^{-1}$ and is used as a rodenticide.[105] The discovery that fluorinated cortisol is 10 times more potent than the natural parent compound[106] came totally unexpectedly and was a contradiction to the belief that the natural hormone has the highest achievable potency. Fluorine has several interesting properties which make it a potentially useful substituent in drug molecules. The steric requirements of fluorine and hydrogen are very similar. The metabolism of fluorinated drugs is often inhibited due to the strong C—F bond. The electronegativity of fluorine compared with hydrogen may increase receptor affinity. A recent review[7] focuses on the preparation of biologically active organofluorine compounds.

Formation of the C—F bond mostly requires conditions different from all other carbon–halogen bond formations.

### 1.7.5.1 Fluorination of Alkyl Alcohols

Hydrogen fluoride is only of limited value for the conversion of alcohols to fluorides.[107] Anhydrous HF is a dangerous low boiling liquid (b.p. 19.5 °C), which can cause painful injuries if traces of the acid come into contact with the skin. Only tertiary and secondary alcohols give fluorides, accompanied by elimination products and ethers. Olah's reagent, a mixture of 70% HF and 30% pyridine, is much more convenient to use and often gives better yields (equation 35).[108] The reagent contains a poly(hydrogen fluoride) species, in which each fluorine atom is surrounded by four hydrogen atoms. The poly(hydrogen fluoride) is in equilibrium with some monomeric hydrogen fluoride. The reagent is stable up to 55 °C and often overcomes the need to carry out reactions with corrosive and hazardous anhydrous HF under pressure. The mechanism of the reaction is not clear. In steroid chemistry retention, inversion and scrambling of configuration is observed in related cases with tertiary alcohols (Scheme 31).[109]

$SF_4$ and diethylaminosulfur trifluoride (DAST) give alkyl fluorides not only from tertiary and secondary, as with HF, but also from primary alcohols (equation 36). Reactions with gaseous, corrosive $SF_4$ (b.p. −38 °C) usually require temperatures of 20–100 °C. The special equipment needed for reactions with toxic gases under pressure make the use of $SF_4$ inconvenient. The introduction of DAST has removed the handling problems. DAST is a liquid reagent made from $SF_4$ and trimethylsilyldiethyl-

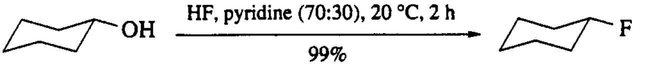

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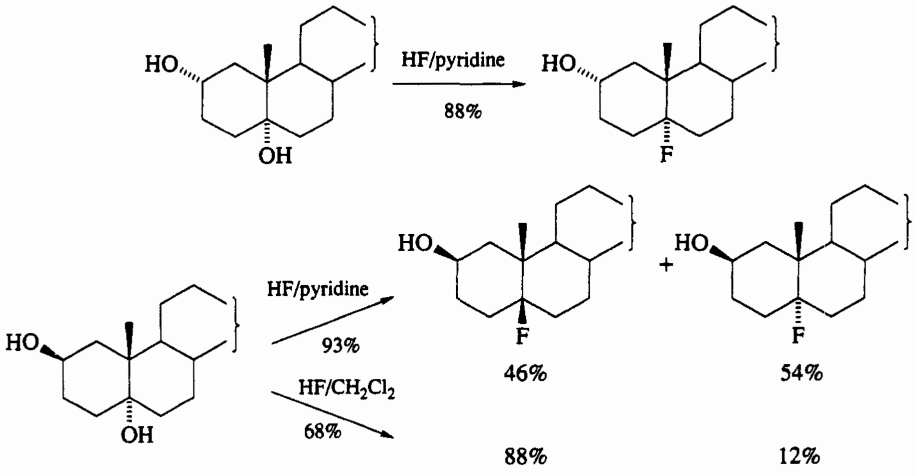

**Scheme 31**

amine. It gives fluoroalkanes from alcohols at lower temperatures (–50 to –78 °C) than $SF_4$ and is safe below 40 °C.[110] Carbenium ion type rearrangement and elimination appear less problematic with DAST than with HF reagents. The stereochemistry of the reaction, however, is still not uniform. In the absence of other directing factors an $S_N2$-type mechanism with inversion of configuration is often observed (equation 37).[111,112] Neighboring group participation, however, results sometimes in retention of configuration (equation 38).[111]

$$n\text{-}C_8H_{17}OH \xrightarrow[90\%]{\text{DAST, -50 °C}} n\text{-}C_8H_{17}F \qquad (36)$$

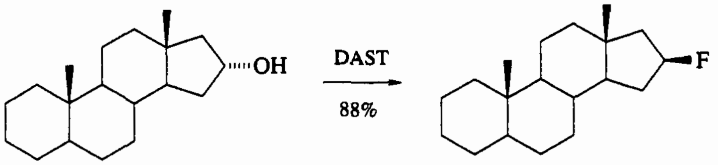

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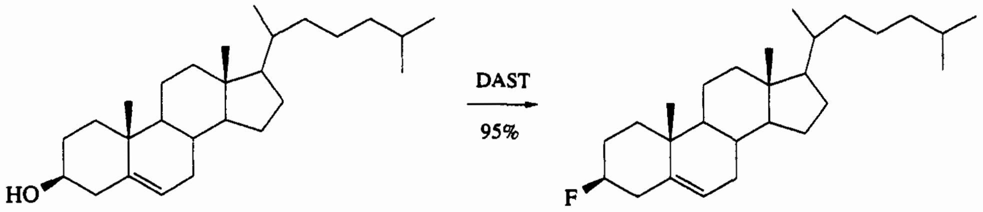

(38)

The fluoroalkylamine reagent (FAR) 2-chloro-1,1,2-trifluorotriethylamine gives alkyl fluorides from alcohols in one step and is known as the Yarovenko reagent.[113] This reagent is less reactive than DAST but was used intensively before the introduction of DAST. Rearrangement and elimination are similar with FAR and DAST (equations 39 and 40).[112,114] This may be explained by the similar mechanism. Activation of the alcohol by intermediate formation of ester-type derivatives is followed by $S_N2$-type displacement by fluoride ion (Scheme 32).

A related group of reagents to FAR and DAST is the phenylfluorophosphoranes. The mechanism is believed to be similar but the reactivity increases with the degree of fluorination. While the di- and trifluorophosphoranes require 150 °C for the conversion of primary alcohols to primary fluorides (equation 41),[115,116] tetrafluorophosphorane converts cholesterol to fluorocholesterin with inversion of configuration at 20 °C (equation 42).[117]

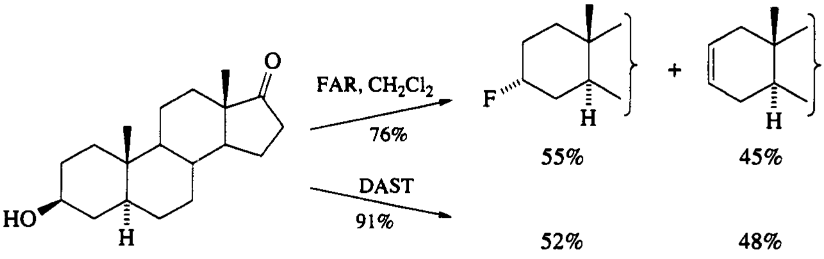

(39)

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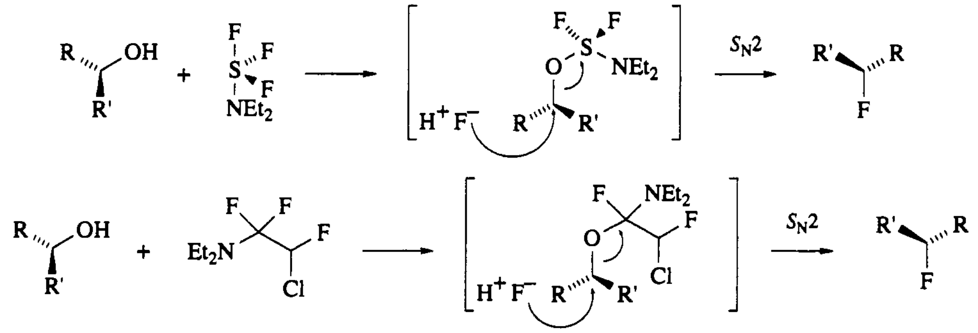

**Scheme 32**

$$\text{n-C}_8\text{H}_{17}\text{OH} \xrightarrow[78\%]{\text{Ph}_3\text{PF}_2,\ 150\ ^\circ\text{C}} \text{n-C}_8\text{H}_{17}\text{F} \tag{41}$$

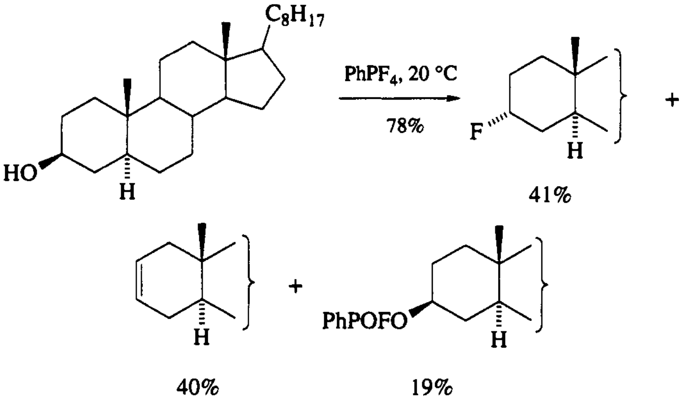

(42)

A preformed complex of diethyl azodicarboxylate/$Ph_3P$ activates primary and secondary alcohols sufficiently for $S_N2$-type reactions with LiF (Scheme 33).[42] This Mitsunobu procedure is a rare example of a reaction useful with all four halogens.

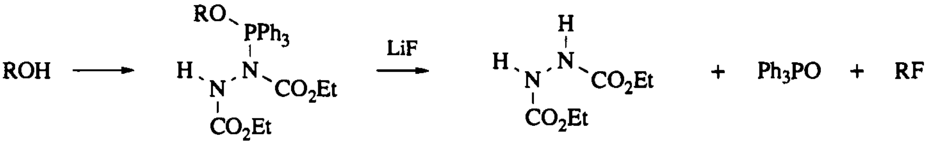

**Scheme 33**

### 1.7.5.2 Fluorination of Alkyl Alcohol Derivatives

The fluoride ion is only a weak nucleophile in water, due to high solvation. Aprotic solvents, however, do not solvate fluoride as readily. Accordingly fluoride is a strong nucleophile in aprotic solvents in the absence of water. Tetrabutylammonium fluoride (TBAF) is a commercial product, which transforms triflates to fluorides with inversion of configuration (equation 43).[118] Triflates react even with the commercial TBAF, although this is not free of water. Partial removal of water from TBAF results not only in a more potent source of nucleophilic fluoride but also in a more potent base; elimination may then become the dominant reaction.[119] If complete removal of water is attempted, the strong base properties cause *E*2 elimination, which decomposes the reagent itself (Scheme 34).[120] With metal fluorides like CsF the reagent itself is perfectly stable.

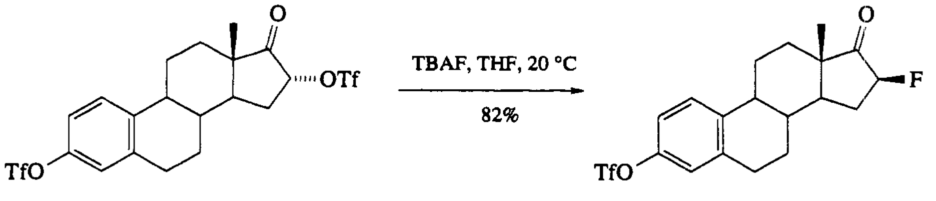

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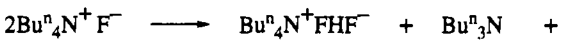

Scheme 34

### 1.7.5.3 Fluorination of Epoxides

Open chain ethers are not cleaved by HF or other fluoride sources. Epoxides, however, are easily opened by HF or $KHF_2$ to fluorohydrins. The reaction has been widely used in steroid chemistry (equation 44).[121] Dexamethasone is still a practical, important corticoid, which is synthesized on an industrial scale with the help of an epoxide-opening reaction (equation 45).[122,123] The low temperature needed for rigid steroidal epoxides and the high regio- and stereo-selectivity are remarkable. HF/pyridine is even more convenient for the opening of rigid epoxides. Side reactions often predominate with nonrigid, less reactive epoxides.[124]

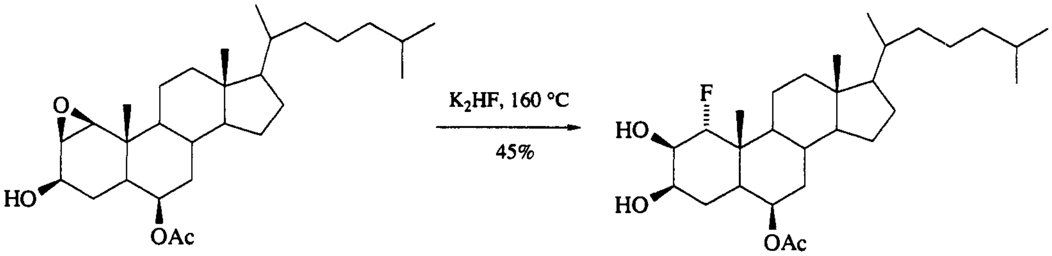

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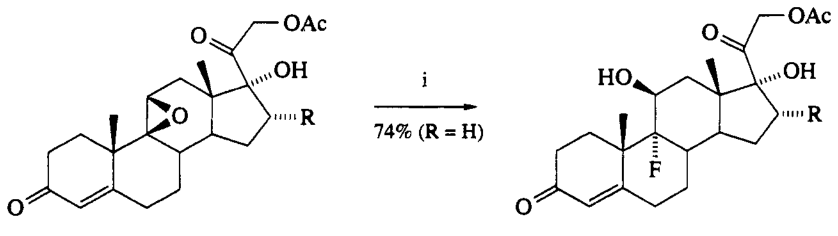

(45)

i, HF, $THF/CHCl_3$, –30 °C, 4 h (Dexamethasone: $\Delta^1$, R = Me)

### 1.7.5.4 Fluorination of Diazo Ketones

Diazo ketones react with HF/pyridine to give the corresponding fluoro ketones (Scheme 35).[108] Reactions in the presence of *N*-halosuccinimides result in the formation of geminally dihalogenated compounds. The mechanism involves initial attack by electrophilic halogen followed by nucleophilic displacement of nitrogen by fluoride ion (Scheme 36). Diazo alkanes give fluoro alkanes with HF/pyridine in good yields (equation 46).

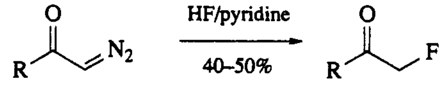

Scheme 35

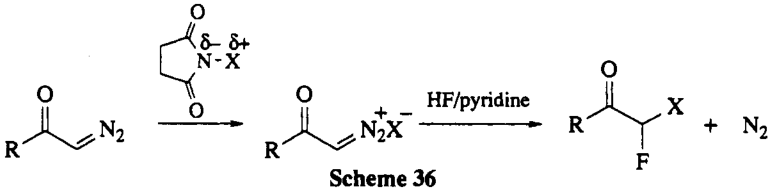

Scheme 36

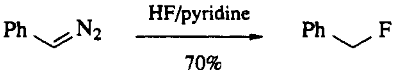

(46)

### 1.7.5.5 Fluorination of Diazonium Salts

Selective introduction of fluorine into an aromatic ring is often achieved by thermal decomposition of diazonium fluoroborates, which is called the Balz–Schiemann reaction (Scheme 37).[125,126] The scope of the reaction is wide and includes heterocyclic compounds (equation 47).[127] The $BF_4^-$ salts are unusually stable for diazonium salts and yields are usually high. In some cases, however, use of $PF_6^-$ or $SbF_6^-$ salts gives improved yields.[128]

$$ArN_2^+BF_4^- \xrightarrow{\Delta} ArF + N_2 + BF_3$$

Scheme 37

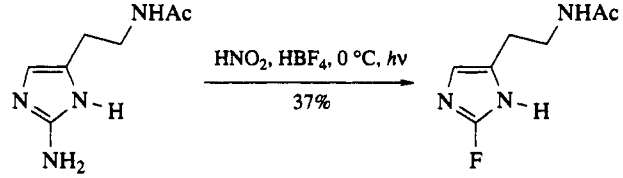

(47)

The mechanism involves a positively charged intermediate, which is attacked by $BF_4^-$ rather than fluoride. The decomposition follows a first-order law, so it is probably of $S_N1$ type.[129]

### 1.7.5.6 Other Fluorinations

The classical route to fluorinated organic compounds is the metathetical halogen–fluorine exchange. Polychloroalkanes are converted to polychlorofluoroalkanes with anhydrous HF. Reactions are carried out in autoclaves at temperatures of 50–150 °C in the presence of catalysts like antimony tri- or pentachloride. Chlorofluorocarbons are produced worldwide in large quantities by this method and used as refrigerants and foamers for plastics. For small scale preparations metal fluorides are more convenient to use. $SbF_3$ gives similar products as anhydrous HF and is activated by the addition of catalysts like chlorine, bromine or $SbCl_5$ (equation 48).[130] The replacement of halogens in polyhalogenated compounds becomes more difficult with increasing fluorination. The formation of perfluoro compounds by replacement of the last fluorine requires severe conditions.

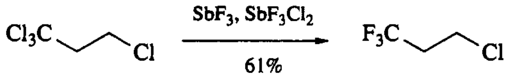

(48)

$SbF_3$ does not exchange single halogens at $sp^3$ or $sp^2$ carbon centers. A more general reagent for the metathetical reaction is KF. Even aromatic (equation 49)[117] or primary alkyl (equation 50)[131] halides are exchanged to fluorides if phase transfer catalysts are used.[132] The classical conditions for a similar reaction give lower yields (equation 51).[133] Addition of CsF to KF results in faster reactions with higher yields (equations 52 and 53).[134]

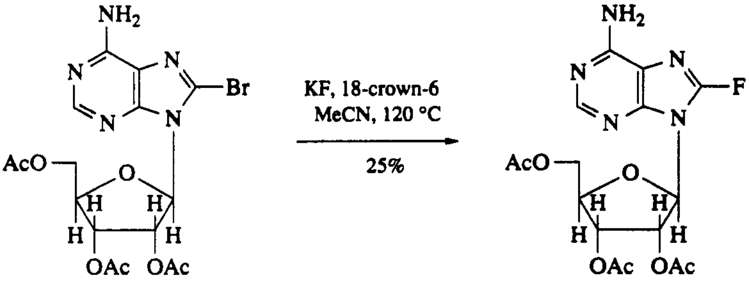

(49)

$$\text{n-C}_8\text{H}_{17}\text{Cl} \xrightarrow[82\%]{\text{aq. KF, }(\text{C}_{16}\text{H}_{33})\text{Bu}_3\text{PBr, 160 °C, 7 h}} \text{n-C}_8\text{H}_{17}\text{F} \qquad (50)$$

$$\text{n-C}_6\text{H}_{13}\text{Cl} \xrightarrow[54\%]{\text{KF, glycol, 180 °C}} \text{n-C}_6\text{H}_{13}\text{F} \qquad (51)$$

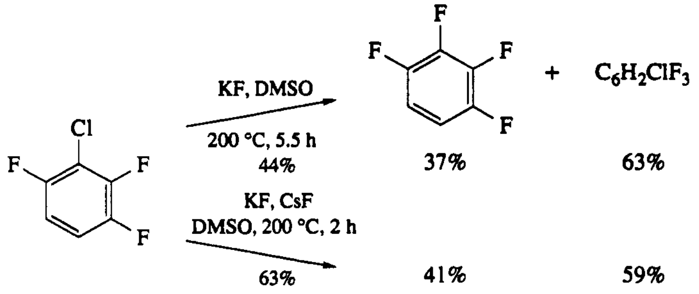

(52)

(53)

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# 1.8

# Synthesis of Pseudohalides, Nitriles and Related Compounds

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## 1.8.1 NITRILES

### 1.8.1.1 Introduction

Nitriles comprise one of the classical functional groups of organic chemistry. The present review deals with useful preparative methods for the synthesis of nitriles by displacement reactions. In view of the extensive current activity in this area, it is necessary to be selective rather than comprehensive. A series of outstanding review articles[1–6] will guarantee rapid acquaintance with the field and some complementary accounts,[7,8] not repeatedly cited, inform of recent developments.

### 1.8.1.2 By Replacement of a Halogen Substituent

#### *1.8.1.2.1 Alkyl halides*

*(i) General remarks*

The transformation of alkyl halides with cyanides (equation 1) represents not only the 'classical' route to nitriles, but, if modified properly, is still of very great practical importance even today. A whole series of review articles[1–6] stress the scope and value of this reaction. Although the substituent 'R' may be varied to a large extent, the primary as well as the benzylic halides generally give higher yields than secondary and tertiary ones, as, with the latter, the formation of alkenes gains in importance. This side reaction as well as the undesired formation of alcohols and ethers, which sometimes takes place in aqueous media or with alcohols as solvent, is of course due to the basicity of the cyanide ion. Under deleterious conditions one may even observe carboxylic acids, which result from the hydrolysis of the nitriles.[2,9] Some of these undesired side reactions may be avoided by the use of CuCN instead of sodium or potassium cyanide.[2]

$$\mathrm{R{-}X} \ + \ \mathrm{MCN} \longrightarrow \mathrm{R{-}CN} \ + \ \mathrm{M{-}X} \qquad (1)$$

X = halogen

As cyanide ions operate as ambident nucleophiles, alkylation reactions may generate isonitriles as well as nitriles (equation 2). A whole range of parameters is responsible for the outcome of reactions of this type and their particular role together with special counter influences is not easily evaluated. There is a large and growing number of papers on this topic, but one can concentrate here on a few selected review articles.[10,11] Suffice it to say that Kornblum's seminal article[12] from 1955 is still of special importance in this field. Pearson's principle of soft and hard acids and bases (HSAB) proved to be particularly helpful in the interpretation of experimental results.[11,13,14]

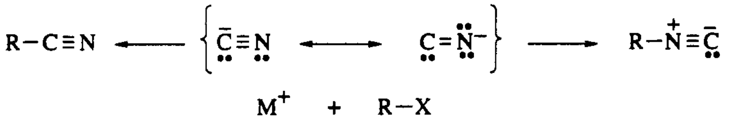

$$\mathrm{R{-}C{\equiv}N} \longleftarrow \left\{ \overset{-}{\mathrm{C}}{\equiv}\mathrm{N} \longleftrightarrow \mathrm{C}{=}\mathrm{N}^{-} \right\} \longrightarrow \mathrm{R{-}}\overset{+}{\mathrm{N}}{\equiv}\overset{-}{\mathrm{C}} \qquad (2)$$
$$\mathrm{M}^{+} \ + \ \mathrm{R{-}X}$$

X = halogen

Of particular preparative value is the observation that ambident anion alkylations, by appropriate choice of reaction conditions, may be manipulated to operate preferentially in one direction. The results of Guillemard's classical work in this area have been reviewed by Kurtz.[2] Although most of the modern investigations do not deal in particular with the nitrile/isonitrile problem, the following rules can be summarized.

(i) Given kinetically controlled reactions, an $S_N1$-type transformation of alkyl halides with cyanide ions should favor the formation of isonitriles. In a charge-controlled reaction the ambident cyanide nucleophile will tend to attack the carbon of the alkyl halide with the more electronegative nitrogen, the center of greater charge density. With $S_N1$ substitutions there will also be a comparatively high positive charge density on the carbon atom of the alkyl halide, although this does not necessarily mean the existence of a discrete cationic intermediate. Even a partially charged carbon atom, according to Pearson's classifications, has to be considered a relatively hard electrophile and should therefore interact most easily with the nitrogen atom of the cyanide ion, which does represent the harder base in this combination,[13] to generate the isonitrile. In Section 1.8.2 the synthetic possibilities will be discussed in detail.

(ii) Accordingly $S_N2$ substitution conditions will favor the formation of nitriles. In an orbital-controlled transformation the less electronegative, but more nucleophilic carbon atom of the $CN^-$ ion will attack the alkyl halide in an $S_N2$-type reaction. The halide-substituted carbon of R—X (X = halogen) may be considered a soft electrophile, thus classifying the formation of nitriles as a soft–soft interaction. Primary halides should therefore be the best candidates for the formation of nitriles and Table 1 proves this for a large number of examples.

If a particular nitrile is being aimed at, there will be no possibility of changing the nature of R in order to promote an $S_N2$ process. Therefore it may be of interest that the nature of the transition state may also be influenced by other parameters. So, important consequences may be expected from changing the

**Table 1** Alkyl Cyanides from the Reaction of Alkyl Halides with CN⁻ Ions

$$\text{R-X} + \text{MCN} \longrightarrow \text{R-CN} + \text{M-X}$$

| *R* | *X* | *MCN* | *Solvent* | *Approx. reaction time* (h) | *Temp.* (°C) | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| $Pr^i$ | Br | NaCN | Glycol | 24 | 60–180 | 39 | 3 |
| $Pr^i$ | Br | $Et_4NCN$ | DMSO | 18 | 50 | 72 | 3, 21 |
| $Bu^n$ | Cl | NaCN | MeOH | 48 | ? | 45 | 3 |
| $Bu^n$ | Cl | NaCN | DMSO | 0.3 | 90–160 | 93 | 3 |
| $Bu^n$ | Cl | KCN | DMSO | 10 | 120–140 | 69 | 3 |
| $Bu^n$ | Cl | NaCN/reversed micelles | | Overnight | 100 | 75 | 22 |
| $Bu^n$ | Br | KCN | PEG[a] | 3 | 110 | 90 | 19 |
| $Bu^n$ | Br | NaCN | DMSO | 0.6 | 60–90 | 92 | 3 |
| $Bu^n$ | Br | $NaCN/Al_2O_3$ | Toluene | 24 | 90 | 93 | 3 |
| $Bu^i$ | Cl | NaCN | DMSO | 0.5 | 80–140 | 88 | 3 |
| $Bu^i$ | Br | NaCN | DMSO | 2 | 70 | 62 | 3 |
| $Bu^s$ | Cl | NaCN | EtOH | 70 | ? | 24 | 3 |
| $Bu^s$ | Cl | KCN | DMSO | 24 | 120–140 | 42 | 3 |
| $Bu^s$ | Cl | NaCN | DMSO | 3 | 90–160 | 69 | 3 |
| $Bu^s$ | Br | NaCN | Glycol | 22 | 70–180 | 0 | 29 |
| $Bu^s$ | Br | NaCN | DMSO | 6 | 70–160 | 41 | 3 |
| $Bu^t$ | Cl | NaCN | Glycol | 6 | 46 | 10 | 3 |
| $Bu^t$ | Cl | NaCN | DMSO | 4 | 130 | 0 | 3 |
| $Bu^t$ | Cl | $TMS\text{-}CN/SnCl_4$ | $CH_2Cl_2$ | 36 | 20 | 64 | 23 |
| $Bu^t$ | Br | NaCN | Glycol | 3 | 70–180 | Low | 29 |
| $n\text{-}C_5H_{11}$ | Cl | NaCN | DMSO | 0.3 | 90–160 | 97 | 3 |
| $n\text{-}C_5H_{11}$ | Br | $Et_4NCN$ | $CH_2Cl_2$ | 2.5 | 35 | 80 | 3, 21 |
| $Bu^tCH_2$ | Br | $Et_4NCN$ | MeCN | 24 | 50 | 55 | 3, 21 |
| $Me_2C(Et)$ | Cl | $TMS\text{-}CN/SnCl_4$ | $CH_2Cl_2$ | 36 | 20 | 75 | 23 |
| Cyclopentyl | Cl | NaCN | DMSO | 3 | 125–130 | 70 | 3 |
| $n\text{-}C_6H_{13}$ | Cl | NaCN | DMSO | 0.3 | 90–160 | 91 | 3 |
| $n\text{-}C_6H_{13}$ | Cl | KCN/crown[a] | MeCN | 2.2 | 83 | 91 | 3 |
| $n\text{-}C_6H_{13}$ | Cl | NaCN/reversed micelles | | Overnight | 100 | 87 | 22 |
| 1-Me-cyclopentyl | Cl | $TMS\text{-}CN/SnCl_4$ | $CH_2Cl_2$ | 32 | 20 | 75 | 23 |
| $n\text{-}C_7H_{15}$ | I | A 26 CN[a] | Benzene | 6 | 80 | 92 | 3 |
| Benzyl | Cl | NaCN | DMSO | 2.5 | 35–40 | 92 | 3 |
| Benzyl | Cl | A 26 CN[a] | Benzene | 2 | 80 | 87 | 3 |
| Benzyl | Cl | KCN/crown[a] | MeCN | 0.4 | 20 | 94 | 3 |
| Benzyl | Cl | LiCN | THF | 6 | 65 | 100 | 20 |
| Benzyl | Br | LiCN | THF | 2 | 65 | 92 | 20 |
| Benzyl | Br | NaCN/reversed micelles | | Overnight | 100 | 87 | 22 |
| $PhCH_2CH_2$ | Cl | NaCN/reversed micelles | | Overnight | 100 | 85 | 22 |
| $n\text{-}C_8H_{17}$ | Cl | NaCN/reversed micelles | | Overnight | 100 | 92 | 22 |
| $n\text{-}C_8H_{17}$ | Cl | $NaCN/R_4P\ Br$ | Water | 2 | 80–100 | 94 | 3 |
| $n\text{-}C_8H_{17}$ | Br | KCN | PEG[a] | 3 | 110 | 94 | 19 |
| $n\text{-}C_8H_{17}$ | I | NaCN or KCN | THF | 15 | 65 | 0 | 20 |
| $n\text{-}C_8H_{17}$ | I | LiCN | THF | 1 | 65 | 90 | 20 |
| 2-Octyl | Cl | NaCN | DMSO | 1 | 90–160 | 70 | 3 |
| Cyclooctyl | Cl | $TMS\text{-}CN/SnCl_4$ | $CH_2Cl_2$ | 32 | 20 | 76 | 23 |
| Cyclooctyl | Cl | LiCN | THF | 6 | 65 | 100 | 20 |
| $n\text{-}C_{10}H_{21}$ | Cl | NaCN | DMSO | 0.3 | 90–160 | 94 | 3 |
| $n\text{-}C_{10}H_{21}$ | Cl | NaCN/reversed micelles | | Overnight | 80 | 85 | 22 |
| $Me_2C(Ph)CH_2$ | Cl | NaCN | DMSO | 24 | 120 | 26 | 3 |

[a] Abbreviations: A 26 CN, Amberlyst A 26 + KCN; crown, 18-crown-6; PEG, polyethyleneglycol.

leaving group. As the polarity of the bond between the leaving group and the carbon atom increases, as shown in equation (3), the likelihood of an $S_N1$ process occurring increases. Within certain limits even the countercation will be able to influence the $S_N1/S_N2$ ratio: with AgCN for instance (sometimes zinc cyanide, CuCN or HgCN have also been used) the initial formation of silver halides ionizes the alkyl halide to a large extent, thus imposing a comparatively high positive charge on the carbon atom. In the transition state there will be a higher positive charge at this center, which, by enhancing the $S_N1$ character, will favor the formation of isonitriles. On the other hand, alkali metal cyanides will be used, if the corresponding nitriles are required. A practical application resulting from these considerations is the optimized preparation of ethyl isocyanide from iodoethane and silver cyanide, as described in *Organic Synthesis*.[15]

$$\xrightarrow[\text{increasing } S_N1 \text{ character}]{X\ =\ I,\ Br,\ Cl,\ OSO_2R} \qquad (3)$$

It should be mentioned briefly that solvation phenomena should also influence the outcome in the case of ambident nucleophiles, at least to the extent to which these reagents are sensitive to solvent effects. With an ambident anion, which is not manipulated by countercations (formation of ion pairs), the more electronegative center should attack preferentially. The more this area is blocked by hydrogen bridges formed in protic solvents, or shielded by countercations, the more likely it is that the less electronegative end will react. If dipolar aprotic solvents are used, which can only solvate the cations, a preferential attack of the nonshielded more electronegative center is to be expected. It must be realized, however, that in substitution reactions employing cyanide ions, dipolar aprotic solvents have not been reported to enhance the formation of isonitriles.[16–18]

Assessing the relative importance of the various factors, which also has to include steric effects, is a complicated task. As already mentioned, nitrile formation in general is favored in these substitution reactions (equation 1), and as isonitriles are normally formed to only a very small extent, they can easily be removed by extraction with diluted mineral acids.

### (ii) Preparative possibilities

As will be shown, a whole range of variations and modifications is known for the reaction of alkyl halides with cyanide ions (equation 4). Without trying to cover every detail, an attempt will be made to mention the most important procedures and to give a few typical examples (see Tables 1 and 2). Despite the diversity of the reaction conditions, a general comparison of their synthetic importance is useful.

$$\mathrm{R{-}X \;+\; MCN \longrightarrow R{-}CN \;+\; M{-}X} \tag{4}$$

R = alkyl, X = halogen

**Table 2** Dinitriles or Halonitriles from Aliphatic Dihalides

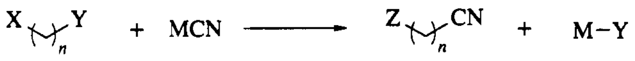

| *n* | *X* | *Y* | *MCN* | *Solvent* | *Approx. reaction time (h)* | *Temp. (°C)* | *Z* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 2 | Cl | Cl | NaCN | DMSO | 0.3 | 90–160 | CN | 56 | 16 |
| 2 | Cl | Cl | NaCN/reversed micelles | | Overnight | 80 | CN | 86 | 22 |
| 2 | Br | Br | $Et_4NCN$ | $CH_2Cl_2$ | 2.5 | 40 | CN | 70 | 21 |
| 3 | Cl | Cl | NaCN | DMSO | 0.5 | 90–160 | CN | 67 | 16 |
| 3 | Cl | Cl | KCN/crown | MeCN | 1.5 | 83 | CN | 97 | 3 |
| 3 | Br | Br | NaCN | $EtOH/H_2O$ | 1.5 | 80–100 | CN | 86 | 30 |
| 3 | Cl | Br | KCN | $EtOH/H_2O$ | 1.5 | 80–100 | Cl | 47 | 31 |
| 3 | F | Br | NaCN | Glycol | 1 | 100 | F | 81 | 32 |
| 4 | Cl | Cl | NaCN | DMSO | 0.5 | 90–160 | CN | 88 | 3, 16 |
| 4 | Cl | Cl | KCN/crown | MeCN | 0.7 | 83 | CN | 95 | 3 |
| 4 | Br | Br | NaCN/reversed micelles | | Overnight | 80 | CN | 92 | 22 |
| 4 | F | Cl | NaCN + NaI | $EtOH/H_2O$ | 12 | 80–100 | F | 76 | 32 |
| 4 | F | Br | NaCN | $EtOH/H_2O$ | 7.5 | 80–100 | F | 82 | 32 |
| 5 | Cl | Cl | NaCN | DMSO | 0.5 | 90–160 | CN | 75 | 16 |
| 5 | Br | Br | $Et_4NCN$ | $CH_2Cl_2$ | 2.5 | 40 | CN | 90 | 21 |

The transformation of alkyl halides into alkanenitriles with cyanide ions has frequently been carried out in protic solvents such as methanol or ethanol, sometimes with the addition of water or acetone, and often at elevated temperatures. Under these conditions reaction rates decrease in the order iodides, bromides, chlorides, as would be expected. Accordingly iodide ions have a catalytic effect and increase reaction rates.[2,4] The use of anhydrous ethylene glycol or di- and poly-ethylene glycols and their corresponding ethers allows the use of higher temperatures, which means better solubility of the alkali metal cyanides.[2,4,19] There is probably additional help from the extensive solvation of the countercations by some of these hydroxy polyethers. While for primary halides yields for nitriles range up to 90% (Table 1), they drop sharply with secondary and tertiary halides.[3]

Particularly good results have been reported (Table 1) with dipolar aprotic solvents like DMSO, DMF, formamide or HMPA,[3,4] which exclusively solvate cations and thus generate highly reactive 'naked' cyanide anions. As a consequence a remarkable increase in reaction rates is observed. The most impressive results were seen with DMSO. Under these conditions even alkyl bromides and chlorides are very useful starting materials and not only primary, but also secondary halides can give rise to high yields if there is not too much steric hindrance (Table 1). Tertiary halides even under these conditions are poor substrates. The cation also may, even if one focuses on alkali metal cyanides, sometimes have a strong influence on reaction rates. With sterically hindered halides for instance, NaCN seems to be superior to the potassium salt in DMSO.[3] Another modification is the use of LiCN in boiling THF; NaCN and KCN fail under these conditions. There has also been a very thorough investigation of the use of tetraalkylammonium cyanides and quite good results were obtained with the tetraethyl or tetrabutyl derivative.[21] Using these highly soluble cyanides, one can run the reaction not only in many polar solvents, *e.g.* acetonitrile, but also in comparatively nonpolar solvents such as $CH_2Cl_2$ and THF, or even benzene or toluene, and at high concentrations. Slowly reacting compounds will again be used in DMSO.[21] Even neopentyl bromide yields 55% of the corresponding nitrile, if treated with tetraethylammonium cyanide in acetonitrile.

Phase transfer catalysis and the use of crown ethers are also of particular advantage in alkanenitrile synthesis (Table 1). Usually quaternary ammonium and phosphonium salts serve quite well as catalysts.[3] Another modification is represented by the use of a solid catalyst, which is insoluble in the two-phase system, for instance alumina or anion-exchange resins (triphase catalysis).[3,7] Crown ethers again capture the cations and generate 'naked' cyanide ions in fairly nonpolar solvents, leading to exceptionally mild reaction conditions.

The use of 'reversed micelles' for the preparation of nitriles is a particularly interesting modern development.[22] Some examples can be found in Table 1.

As discussed above, the classical procedures for the transformation of alkyl halides fail with tertiary derivatives. Trimethylsilyl cyanide (TMS-CN)[23] recently turned out to be the reagent of choice in this case. It may easily be obtained from trimethylchlorosilane,[24-28] but is also available commercially. In this way various *t*-alkyl and cycloalkyl chlorides can be converted to the corresponding nitriles in the presence of a catalytic amount of $SnCl_4$ at room temperature and in solvents such as $CH_2Cl_2$ (equation 5). The yields range between 64 and 80% (Table 1). A sharp drop in yields is observed with educts, however, which have an electron-withdrawing group (EWG) in the neighborhood of the reaction center, as was noticed with 1,1,1,2-tetrachloro-2-methylpropane (yield < 5%) or methyl 2-chloro-2-methylpropanoate (<5%). Isonitriles are not observed in the course of the reaction, although they may play a crucial role in the reaction sequence. A number of observations led to the following mechanism (Scheme 1).[23]

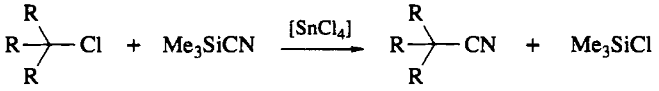

$$R_3C-Cl + Me_3SiCN \xrightarrow{[SnCl_4]} R_3C-CN + Me_3SiCl \qquad (5)$$

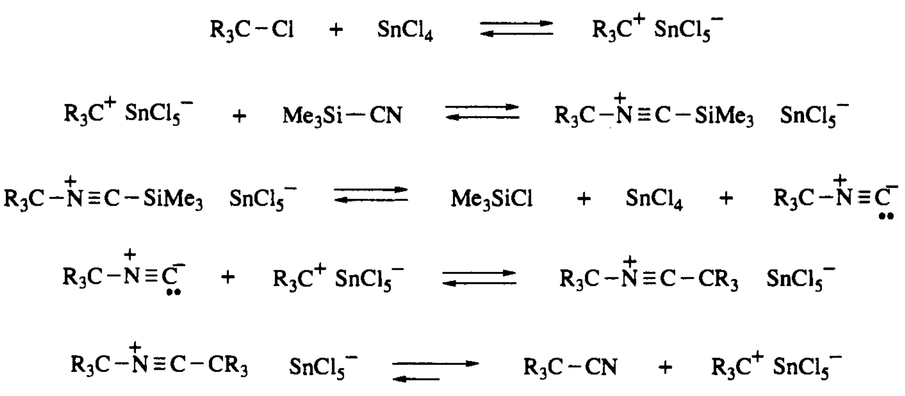

$$R_3C-Cl + SnCl_4 \rightleftharpoons R_3C^+\ SnCl_5^-$$

$$R_3C^+\ SnCl_5^- + Me_3Si-CN \rightleftharpoons R_3C-\overset{+}{N}\equiv C-SiMe_3\ \ SnCl_5^-$$

$$R_3C-\overset{+}{N}\equiv C-SiMe_3\ \ SnCl_5^- \rightleftharpoons Me_3SiCl + SnCl_4 + R_3C-\overset{+}{N}\equiv \underset{\bullet\bullet}{C^-}$$

$$R_3C-\overset{+}{N}\equiv \underset{\bullet\bullet}{C^-} + R_3C^+\ SnCl_5^- \rightleftharpoons R_3C-\overset{+}{N}\equiv C-CR_3\ \ SnCl_5^-$$

$$R_3C-\overset{+}{N}\equiv C-CR_3\ \ SnCl_5^- \rightleftharpoons R_3C-CN + R_3C^+\ SnCl_5^-$$

**Scheme 1**

By using displacement reactions even nitriles that carry a number of functional groups may be prepared. Dinitriles may also be obtained by this method; in the case of ω-chloroalkyl bromides, the bromine atom is exchanged preferentially (equation 6).[2] Dichloro compounds may also be converted into the corresponding dinitriles. This is done mainly in dipolar aprotic solvents such as DMSO or with the help of phase transfer catalysis or crown ethers (Table 2).[3] Generally, the generation of dinitriles does not create any special problems. It should be mentioned that even in γ-halocarboxylic acids a smooth halogen/nitrile exchange is possible.[2]

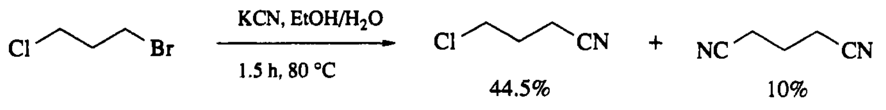

(6)

β,γ-Unsaturated alkanenitriles may often be generated quite easily from allyl halides and cyanide ions. Unfortunately, the preparation of pure compounds suffers sometimes from the formation of rearrangement products (Scheme 2).[2,4] In this case the use of CuCN is expected to be of advantage.[2,4] An 80–84% yield of allyl cyanide may be obtained on treatment of neat allylic bromide with CuCN (Scheme 2).[33] A quite remarkable influence of the reaction conditions is observed, for instance, in the reaction of tetraethylammonium cyanide with allylic bromide.[21] If the cyanide, dissolved in $CH_2Cl_2$, is slowly added to a cold solution of allylic bromide in the same solvent, the main product, allylic cyanide (**1**), will dominate in a 15:1 ratio against crotononitrile (**2**), while the addition of allylic bromide to a boiling solution of the ammonium cyanide in methylene chloride provides 70% (**2**), which is accompanied by only 8% of compound (**1**). On the other hand, 1-bromo-2-butene gives rise to 1-cyano-2-butene exclusively, independent of reaction conditions (Scheme 3).[21] A great number of patents on this topic have been reviewed by Kurtz.[2]

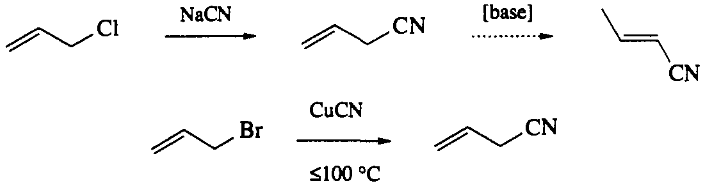

**Scheme 2**

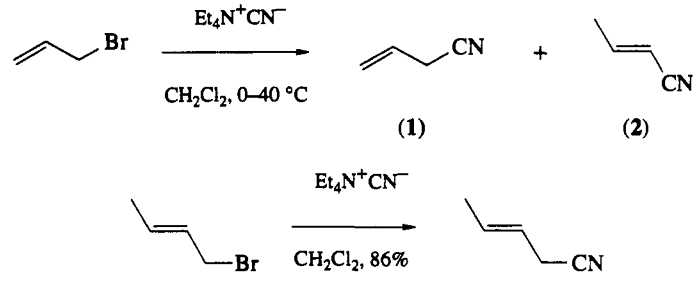

**Scheme 3**

α-Cyano ethers may be obtained from the corresponding halogen precursors (which are quickly destroyed in aqueous or alcoholic solution) with NaCN in DMF or DMSO.[4] Earlier papers recommend the use of CuCN, sometimes without any solvents.[2,4] Good results are reported again for the transformation of α-chloro ethers with tetraethylammonium cyanide in $CH_2Cl_2$,[23] or with TMS-CN/$SnCl_4$ (Scheme 4).[23] In the carbohydrate series nitriles are often prepared by reaction of the corresponding bromo derivative with $Hg(CN)_2$. No special care has to be taken in the formation of alkoxynitriles, where the ether moiety is separated from the nitrile group by at least two carbon atoms.[2]

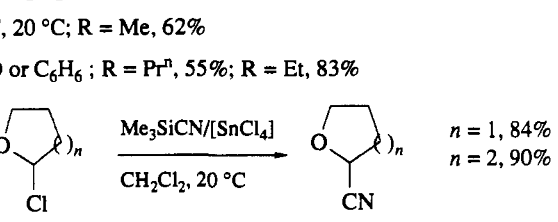

i, $Et_4N^+\ CN^-$, $CH_2Cl_2$, ≤20 °C (ref. 7); R = Me, 67%; R = n-$C_5H_{11}$, 87%

ii, NaCN, DMF, 20 °C; R = Me, 62%

iii, CuCN, $Et_2O$ or $C_6H_6$; R = $Pr^n$, 55%; R = Et, 83%

*n* = 1, 84%
*n* = 2, 90%

**Scheme 4**

In the reaction of 2-hydroxyalkyl halides with cyanide ions the intermediate formation of oxiranes can give rise to rearrangement products. Epoxides may also be encountered if $CN^-$ ions are reacted with α-halo ketones (Scheme 5).[2,3] On heating with quaternary ammonium halides in acetonitrile or DMSO at 80–130 °C these cyanooxiranes (**3**) are converted into 2-cyano ketones (**4**).[21] Phenacyl bromide, in contrast, gives rise to 3-oxo-3-phenylpropionitrile (**5**) on treatment with cyanide ions.[21] Not much is known about the reaction of the corresponding α-halo sulfides with cyanide;[34] ethylthioacetonitrile was obtained from the chloro sulfide by treatment with $Hg(CN)_2$.[35]

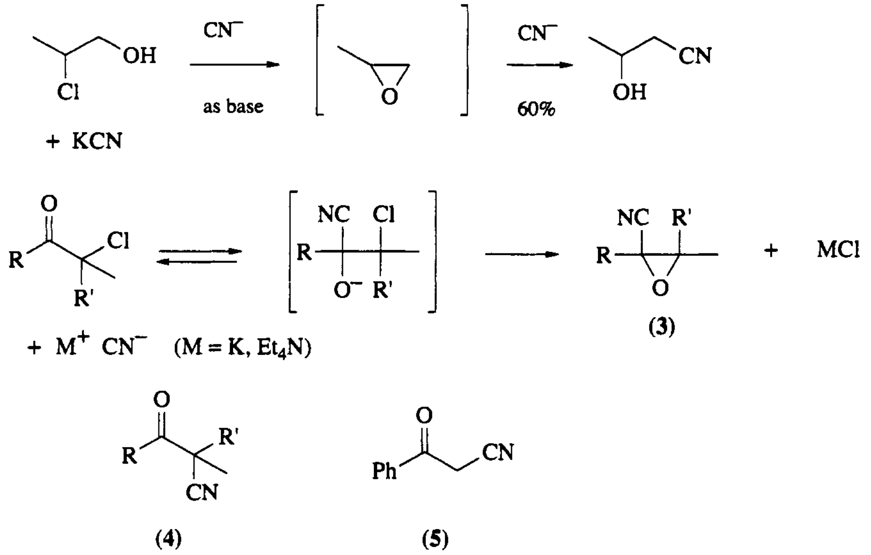

**Scheme 5**

### 1.8.1.2.2 Vinyl and aryl halides

The low reactivity of vinyl halides in nucleophilic displacement reactions is well known. For preparative procedures the use of CuCN, sometimes in the presence of bases like pyridine, at temperatures higher than 200 °C (closed vessel) is recommended.[2,4] This technique may be used to prepare maleonitrile and fumaronitrile from *cis*- and *trans*-1,2-diiodoethylene (equation 7).[2,4]

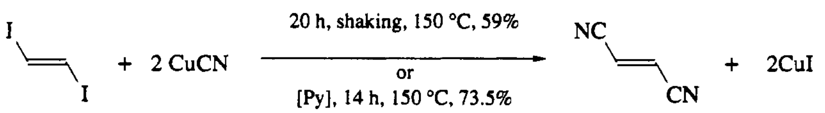

(7)

The reaction of haloquinones with cyanide ions in aqueous ethanol, which yields cyanohydroquinones (Scheme 6),[2] formally represents the same type of reaction. The synthesis of vinyl cyanides from the corresponding halides with KCN in the presence of crown ethers and a $Pd^0$ catalyst can be run under much milder conditions (60–100 °C) in benzene or pyridine as the solvent.[3] The transformations turn out to be nearly stereospecific. Comparable results are obtained at 50 °C with a $Ni^0$ catalyst, prepared *in situ* from bis(triphenylphosphine)bromonickel(II) on treatment with zinc and triphenylphosphine in DMF or DMSO. The stereospecificity is only slightly inferior to the $Pd^0$ catalyst.[3] With both systems yields of more than 90% can be reached. A series of examples is given in a table by Grundmann.[3]

Although the preparation of aryl cyanides from the corresponding halogen compounds is described by the very simple equation (8), the process does not correspond to a simple aromatic substitution reaction. In a series of comprehensive articles[2,3,8,36] various aspects of this transformation are discussed. An excellent review, written by Ellis and Romney-Alexander,[36] should be mentioned in particular, as it provides the literature leading into the modern status of the field.

As a 'classical' technique for the synthesis of aromatic cyanides treatment of the corresponding halides with CuCN has to be cited (Rosenmund–von Braun reaction).[1–4] It is carried out at 150–250 °C, either without any solvent at all, or using pyridine or quinoline, which also operate as complexing agents for the CuCN. Other heavy metal cyanides or hexacyanoferrates have been used in principle, but their

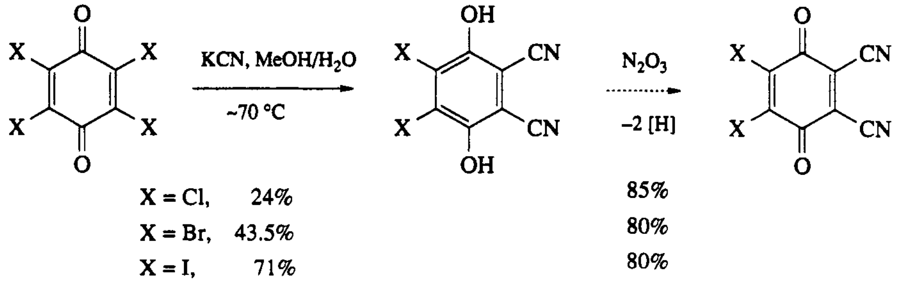

Scheme 6

$$\mathrm{Ar{-}X} + \mathrm{CN^-} \xrightarrow{\Delta} \mathrm{Ar{-}CN} + \mathrm{X^-} \qquad (8)$$

X = halogen

practical importance seems to be low. In recent years DMF, HMPA, NMP or tetramethylurea proved to be very useful solvents. As the reactions with these dipolar aprotic solvents can be run using comparatively mild conditions, it has also been possible to apply this transformation to quite sensitive and nonactivated educts.[3,4,36]

Although aryl iodides represent the most reactive substrates, a very large number of reactions have been run with the bromides, as these are more easily available and still offer satisfactory reactivity. From chloroaryl iodides the corresponding chloronitriles may be obtained with remarkable selectivity. Many heteroaromatic halogen compounds have been transformed into the corresponding nitriles in an analogous manner.[3,4,36]

The substitution pattern of the aromatic ring tends to influence the reaction rates, but the relationship is not very clear cut. Chloro ligands in the 2-position as well as nitro and carboxy groups in the 2- or 4-position seem to increase the reaction rates. There are additional successful transformations with the following substituents: primary amino, tertiary amino, alkoxy, alkylthio, hydroxy, alkyl, formyl, acyl, carboxy, alkoxycarbonyl and nitro groups. Polyhalogenated educts give rise to polynitriles.[8] Starting from 2,4,6-trifluorotricyanobenzene even hexacyanobenzene may be obtained (equation 9).[37]

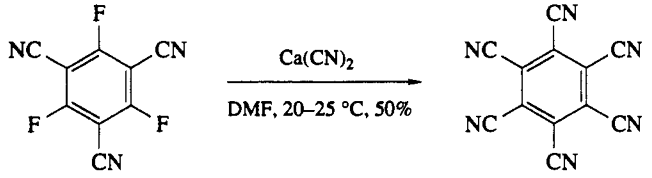

(9)

For work-up of the reaction mixtures, reagents which destroy the nitrile–copper cyanide complexes, for instance $Fe^{III}$/HCl (oxidation of $Cu^{I}$ to $Cu^{II}$, followed by extraction of the nitrile), ethylenediamine (complexation of Cu ions) or an excess of aqueous NaCN (formation of the soluble $NaCu(CN)_2$), proved to be particularly useful.[38] With appropriate *ortho* substituents, such as carboxy groups, cyclization reactions may be observed under the reaction conditions.[4] If treated at higher temperatures with CuCN, *o*-dihalides often provide phthalocyanines.

The mechanism of of these substitution processes, in spite of numerous investigations, is not completely (or not for all variants) solved in detail. As reaction conditions differ very much, one may not even expect a simple homogeneous mechanism. The crucial role of Cu complexes is, however, widely accepted. A very thorough discussion of all aspects can be found in some comprehensive accounts.[36,39]

An excellent overview with numerous tables, providing details on the reaction conditions and disclosing scope and limitations of all transformations of aromatic halogen compounds with CuCN, is provided by Grundmann[3] as well as Ellis and Romney-Alexander[36] (more than 200 examples, some of them with preparative variations). They list various reaction conditions, so that it is not necessary to discuss individual examples here.

Under remarkably mild conditions aromatic cyanides can be prepared from halogen compounds with alkali metal cyanides in the presence of transition metal complexes.[3,36] Complexes of palladium and nickel are particularly useful, for instance tetrakis(triphenylphosphine)palladium(0) (**6**), tris(triphenylphosphine)nickel(0) (**7**) or *trans*-dichlorobis(triphenylphosphine)nickel(II) (**8**; Scheme 7).

| $(Ph_3P)_4Pd$ | $(Ph_3P)_4Ni$ | $Cl_2Ni(PPh_3)_2$ |
|---|---|---|
| **(6)** | **(7)** | **(8)** |

**Scheme 7**

Various cobalt complexes have also been used. While the use of these complexes is more expensive and needs more demanding reaction conditions (oxygen must be strictly excluded), the transformations can be done at comparatively low reaction temperatures. Very often high yields will be obtained at 50–60 °C, and in some cases reactions have even been run at 30 °C. Yields of up to 80–90% are not unusual. The addition of crown ethers proved to be quite helpful in various cases. Instead of alkali metal cyanides, acetone cyanohydrin can also be used.[36] A discussion of relevant mechanistic aspects can be found in eview articles.[3,36,40] Again the aromatic ring may carry various substituents, although *ortho* - ligands tend to give rise to lower yields.[36] Another drawback seems to be the interaction of nitro groups with the catalysts. Depending on the stability of the catalytic system under investigation, one may in principle decide on various polar or nonpolar solvents and details on this matter can again be found from reaction tables provided in the literature.[36] The reaction of aryl iodides with TMS-CN/$(Ph_3P)_4Pd$ in boiling triethylamine was studied recently.[41]

### *1.8.1.2.3 Acyl halides*

The preparation of benzoyl cyanide on distillation of benzoyl chloride and HgCN, which was reported by Liebig and Wöhler in 1832,[42] has to be regarded as a cornerstone in nitrile chemistry, as this documents the first synthesis of an organic nitrile. Today numerous methods for the preparation of these important acylnitriles are known (equation 10). A number of review articles[2,3,7,43–45] provide quick access to the original papers, the very broad patent literature included.

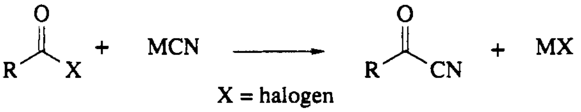

(10)

The most favored technique for quite a while was the transformation of the, compared to acyl chlorides, much more reactive acyl bromides with AgCN or CuCN at elevated temperatures.[2,3,7,45] A whole range of phosphorus compounds may be used as catalyst.[4] Dry alkali metal cyanides were for some time considered to be useless, probably because of their poor solubility in solvents like benzene. Aqueous solvents and alcohols are of course useless, as they react very quickly with the starting material as well as with the product. At this stage the particular sensitivity of acylnitriles to protic solvents and basic or acidic reagents should be mentioned.[2,4] Recently very good results were reported in many cases from the transformation of acid chlorides and CuCN in acetonitrile, which may also operate as a complexing ligand.[3,45] In another modification, aroyl chlorides are treated with CuCN in the presence of LiI in solvents such as diethyl ether.[46] An interesting technique makes use of the reaction of the (difficult to obtain) TlCN with an aroyl chloride in ether or ethyl acetate at room temperature (Scheme 8); high yields of aroyl cyanides are described.[3,45] One cannot apply this method, however, to the preparation of the corresponding aliphatic acyl cyanides, as dimers such as (**9**) are mainly formed under the reaction conditions. If this dimerization is blocked by steric hindrance, it may be possible to isolate the desired acylnitriles. The preparation of 3,3-dimethyl-2-oxobutyronitrile, which was obtained in 45% yield, provides an example of this method.[3] Even cyanoformates can be prepared from chloroformates and TlCN in acceptable yields (Scheme 8).[3] An often quite useful modification, which permits the synthesis of sensitive acyl cyanides, uses the reaction of acyl iodides (which can be generated *in situ* from acid chlorides on treatment with NaI in acetonitrile) with CuCN.[3,47] Although the corresponding isonitriles could well be intermediates, this question is not dealt with by the author[47] (but see also ref. 45). In $CH_2Cl_2$ or acetonitrile good yields are obtained under mild conditions. In the same manner α,β-unsaturated acyl halides and phenyl iodoformate can be transformed into the corresponding nitriles.

Now even alkali metal cyanides are used for the preparation of acylnitriles. The transformation of chloroformates with KCN using phase transfer catalysis can be achieved under very mild conditions. The yields, however, are frequently much lower than those from the TlCN technique.[3,45,48] Probably these deficits may be compensated for by the very convenient operations under phase transfer conditions ($Bu_4N^+Br^-$ in water/$CH_2Cl_2$). The reaction of numerous chloroformates with KCN/18-crown-6 in $CH_2Cl_2$ (equation 11) is reported to give excellent yields.[3,45,49]

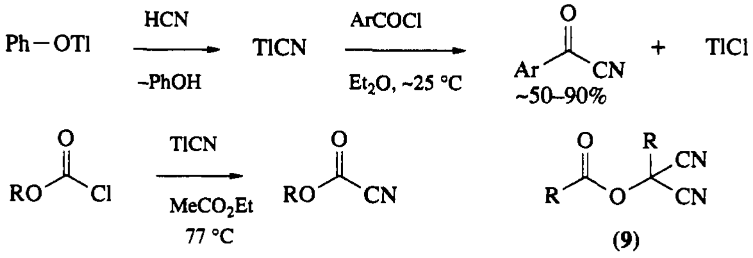

R = alkyl

**Scheme 8**

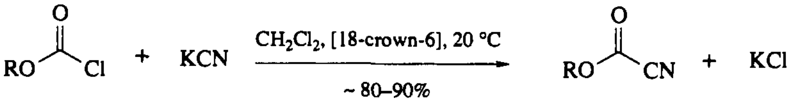

(11)

The recent application of sonochemistry to the reaction of aroyl chlorides with KCN in acetonitrile is very interesting.[3] Aromatic acyl cyanides could also be prepared by reaction of aroyl chlorides with KCN impregnated onto XAD resins.[50] A number of patents describe the results of the two-phase interactions of alkali metal cyanides with a solution of acyl halides or anhydrides in aprotic organic solvents, which in general run in the presence of Cu$^I$ salts.[45]

Due to its excellent solubility in $CH_2Cl_2$, triethylammonium cyanide also serves extremely well in this reaction. The transformation of phenyl chloroformate and (thio)carbamoyl chlorides yields the corresponding nitriles (Scheme 9).[3,21,45] Alkyl chloroformates fail under these conditions as a result of decarboxylation. Trimethylsilyl cyanide (TMS-CN) has also proved to be a very useful reagent for the preparation of acyl cyanides (Scheme 9)[3,45] but see also ref. 47b. The TMS-Cl formed in the process (Scheme 9) is said to be a catalyst in this transformation. The reaction may also be catalyzed by small amounts of other Lewis acids such as $ZnI_2$ or, particularly for aroyl halides, $SnCl_4$. Unsaturated as well as haloalkanoyl chlorides or dicarboxylic acid dichlorides may be transformed in a similar fashion with very satisfactory results. It has to be mentioned, however, that highly reactive or enolizing acylnitriles may suffer from subsequent transformations.[3] In a further modification acylnitriles can also be prepared by reaction of various acid chlorides with cyanotributylstannane,[3,45] although primary and secondary acyl chlorides give rise to acyloxymalodinitriles (**9**).

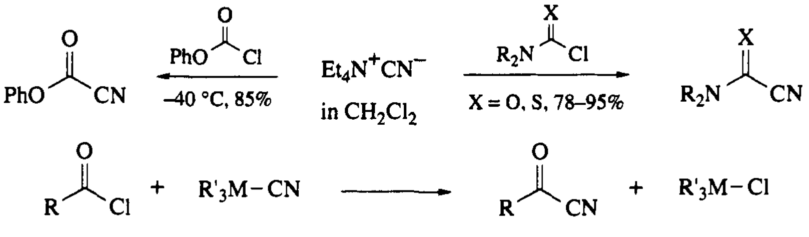

R'$_3$M = Me$_3$Si , Bu$_3$Sn

**Scheme 9**

### 1.8.1.3 Exchange of Oxygen or Sulfur Functionality

The formation of alkanenitriles from alcohols and HCN is of no interest for laboratory preparations. However, a large number of publications, particularly patents, have appeared, which deal with technical applications of this procedure. A few review articles[2–4] serve very well as introductions to this field. Under particularly mild conditions allyl and propargyl alcohols can be transformed into the corresponding nitriles with hydrogen halides in the presence of Cu$^I$ salts.[2,4] The possibility of generating nitriles from alcohols *via* the analogous halides needs no further treatment at this stage.

An attractive procedure for the direct transformation of alcohols into nitriles operates with TMS-CN, generated *in situ* from TMS-Cl and NaCN with catalytic amounts of NaI.[51] The reaction (Scheme 10) is run in DMF/acetonitrile at about 60 °C and leads to good or even excellent yields with primary, secondary and also tertiary alcohols. With 3-β-cholestanol 85% of the nitrile (+ 6% cholest-2-ene) is formed with inversion.[51] Decisive, mechanistically relevant intermediates could be the nitrilium ion (**10**) as well as the oxonium ion (**11**; Scheme 10).[51] The preparation of nitriles from alkanols with KCN, triphenylphosphine and $CX_4$ (X = halogen) in the presence of crown ethers at room temperature (Scheme 11) is restricted to primary alcohols.[52] A second version (Scheme 11), which operates on primary and secondary alcohols, particularly in the carbohydrate series, makes use of triphenylphosphine, tetrachloromethane and DMSO at 90 °C under anhydrous conditions.[3] In the conversion of *o*- and *p*-hydroxybenzyl alcohols to the corresponding arylacetonitriles (NaCN, DMF, 110 °C) quinone methides are discussed as intermediates.[3]

$$\mathrm{ROH} + 2\,\mathrm{NaCN} + 2\,\mathrm{Me_3SiCl} \xrightarrow{[\mathrm{NaI}]} \mathrm{RCN} + \mathrm{HCN} + (\mathrm{Me_3Si})_2\mathrm{O} + 2\mathrm{NaCl}$$

| | | | |
|---|---|---|---|
| R = $PhCH_2$ | 98% | R = $Bu^t$ | 64% |
| R = c-$C_6H_{11}CH_2$ | 93% | R = 1-Me-cyclohexyl | 80% |
| R = n-$C_6H_{13}CHMe$ | 75% | R = 1-adamantyl | 91% |

$$\mathrm{Me_3SiCl} + \mathrm{MeCN} \xrightarrow{[\mathrm{I^-}]} \underset{\textbf{(10)}}{\mathrm{Me{-}C{\equiv}\overset{+}{N}{-}SiMe_3}}\ \mathrm{I^-} + \mathrm{Cl^-}$$

$$\mathrm{Me_3SiCl} + \mathrm{ROH} \xrightarrow[-\mathrm{HCl}]{} \mathrm{R{-}O{-}SiMe_3}$$

$$\mathrm{Me{-}C{\equiv}\overset{+}{N}{-}SiMe_3}\ \mathrm{I^-} + \mathrm{R{-}O{-}SiMe_3} \longrightarrow \mathrm{MeCN} + \underset{\textbf{(11)}}{\mathrm{R{-}\overset{+}{O}(SiMe_3)_2}}\ \mathrm{I^-}$$

$$\mathrm{R{-}\overset{+}{O}(SiMe_3)_2}\ \mathrm{I^-} + \mathrm{CN^-} \xrightarrow{-\mathrm{I^-}} \mathrm{R{-}CN} + (\mathrm{Me_3Si})_2\mathrm{O}$$

**Scheme 10**

$$\mathrm{RCN} \xleftarrow[\text{[18-crown-6]}]{\mathrm{NaCN,\ Bu_3P/CCl_4}} \mathrm{ROH} \xrightarrow[\text{boiling temp.}]{\mathrm{KCN,\ Ph_3P/CCl_4/DMSO}} \mathrm{RCN}$$

| | | | |
|---|---|---|---|
| R = n-$C_8H_{17}$ , | 76% | R = $Bu^n$ , | 85% |
| R = $PhCH_2$ , | 82% | R = 2-octyl , | 70% |
| R = $Ph(CH_2)_2$ , | 75% | | |

**Scheme 11**

One should briefly mention the preparation of cyanoallenes from substituted 2-propynols, KCN and HBr in the presence of CuCN and copper (equation 12).[3] For a mechanistic discussion see ref. 53. In another route to cyanoallenes, the corresponding halides are first prepared from the alcohol and then treated with CuCN.[3]

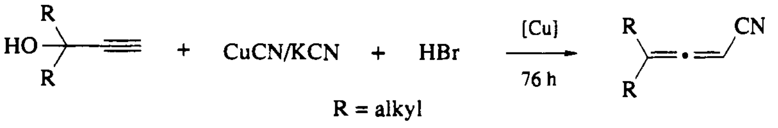

(12)

Various sulfuric and phosphoric acid esters have sometimes been used instead of alcohols as starting materials for the preparation of nitriles.[2,4] Of more general importance are sulfonates, particularly from methane- or *p*-toluene-sulfonic acid, which react in an $S_N2$-type substitution with cyanide ions. The most common starting materials are, as described in Section 1.8.1.2.1, alkyl halides, and if their preparation creates problems, the use of sulfonates may be advantageous.[3] The addition of crown ethers or the application of 'classical' phase transfer conditions may enhance the efficiency of this transformation.[51] The reaction of *n*-octyl methanesulfonate with a saturated aqueous KCN solution, in the presence of crown ether (**12**) at 100 °C, which gives rise to an 80% yield of the corresponding nitrile (Scheme 12), may serve as an example.[54] For the reaction of *n*-octyl bromide with NaCN and crown ether (**13**) for 24 h at 100 °C, a complete failure is reported.[54] The corresponding sulfonate, however, gave rise to 1-cyanooctane on treatment with LiCN in boiling THF.[20] According to literature reports,[3] sulfonic acid aryl and benzyl esters are not converted to nitriles under mild conditions. Carboxylic esters are not useful starting materials for the preparation of nitriles.[2,3] In contrast to this, γ-lactones give rise to the salts of γ-cyanocarboxylic acids without problems. Following a 'classical' procedure,[2] KCN is used without any solvent at 180–200 °C (equation 13). In spite of these forcing conditions, yields tend to be high.[2] There seems to be a possibility for milder reaction conditions by using DMSO as the solvent.[3]

$$\text{n-C}_8\text{H}_{17}-\text{OSO}_2\text{Me} \quad + \quad \text{KCN} \xrightarrow{\text{H}_2\text{O/[(12)]}} \text{n-C}_8\text{H}_{17}\text{CN} \quad + \quad \text{MeSO}_3^-\ \text{K}^+$$

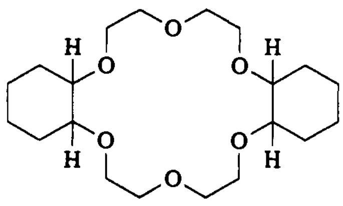

**(12)**

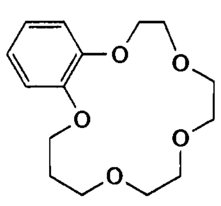

**(13)**

**Scheme 12**

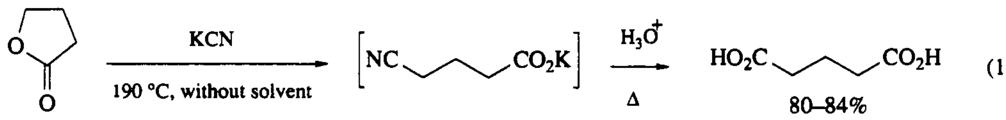

The generation of 3-hydroxypropionitrile from ethylene oxide and HCN in a closed vessel was described in 1878.[55] As the reactivity of epoxides exceeds that of acyclic ethers considerably, oxiranes do represent useful starting materials for hydroxynitriles and their derivatives.[2] For laboratory preparations, the use of alkali metal cyanides (Scheme 13)[56,57] instead of HCN will be more convenient.[3,4] The syntheses of (**14**) and (**15**) (Scheme 13)[57] were accomplished in a buffered ($MgSO_4$) aqueous solution at about pH 9.5. The intermediate formation of epoxides on treatment of 2-halo alcohols with $CN^-$ ions has already been mentioned in Section 1.8.1.2.1.ii.

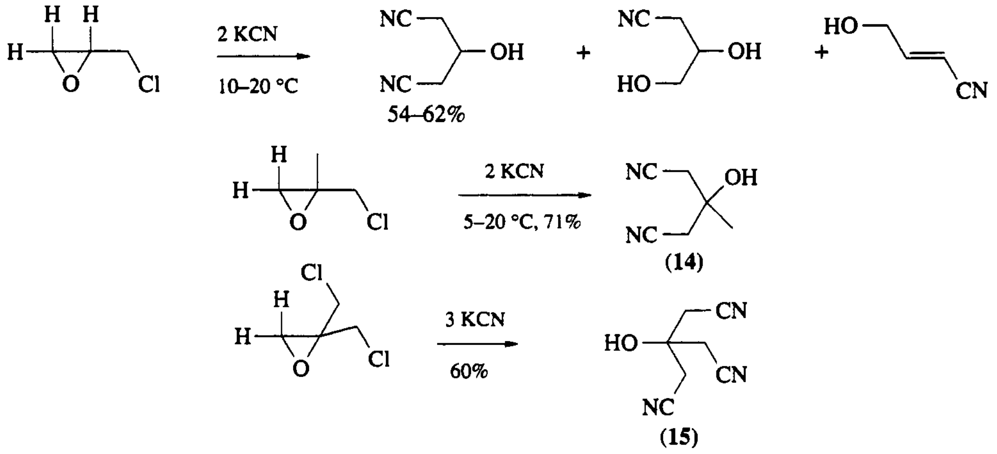

**Scheme 13**

For the synthesis of *trans*-β-cyanohydroxy steroids from the corresponding epoxides treatment with HCN/triethyl aluminum or with diethyl aluminum cyanide proved to be particularly useful.[3]

Recently the transformation of oxiranes with TMS-CN in the presence of Lewis acids, which actually play a major role in this sequence, was investigated in detail. A few examples (Scheme 14)[58,59] were chosen to illustrate the topic.[3]

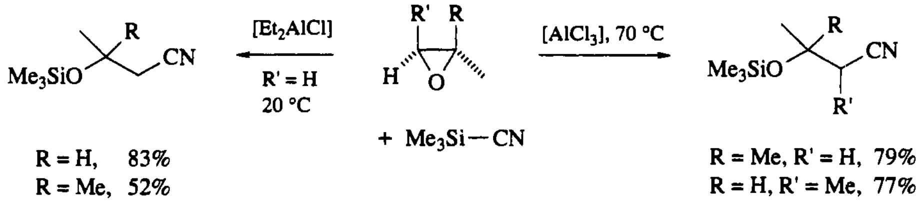
Me3SiO
R
CN
[Et2AlCl]
R' = H
20 °C
R' R
H
O
+ Me3Si—CN
[AlCl3], 70 °C
Me3SiO
R
CN
R'
R = H, 83%
R = Me, 52%
R = Me, R' = H, 79%
R = H, R' = Me, 77%

**Scheme 14**

The same reaction products are obtained from epoxides and TMS-CN in the presence of aluminum alkoxides,[60] samarium, cerium or lanthanum chlorides[61] as well as titanium tetraisopropanoate,[62,63] which may all be considered comparatively 'hard' Lewis acids. On the other hand various groups demonstrated[60,64,65] that 'softer' Lewis acids like zinc, tin and palladium dichloride may give rise to isocyanides (Scheme 15).

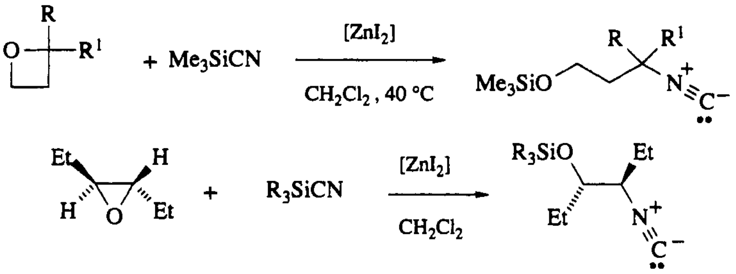
R
O
R1
+ Me3SiCN
[ZnI2]
CH2Cl2, 40 °C
Me3SiO
R
R1
N
+
C
−
Et
H
H
O
Et
+
R3SiCN
[ZnI2]
CH2Cl2
R3SiO
Et
Et
N+
C−

**Scheme 15**

According to a recent report[66] oxiranes yield β-trimethylsilyloxynitriles on treatment with TMS-CN in heptane in the presence of inorganic bases like calcium or magnesium oxide, hydroxyapatite or calcium fluoride, with high regioselectivity (equation 14).

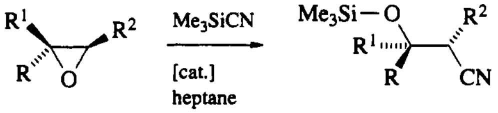
R1
R2
R
O
Me3SiCN
[cat.]
heptane
Me3Si—O
R2
R1
R
CN

(14)

The exchange of alkoxy groups for the cyanide function can also be achieved in acetals (cyclic types like dioxolanes and 1,3-dioxane derivatives included), *S,N*-acetals and ortho esters with the combination of TMS-CN/Lewis acids,[3,67–69] or under neutral conditions with transition metal salts as catalysts (Scheme 16).[70] Furanose derivatives may be treated with TMS-CN in a similar way.[3,67,68]

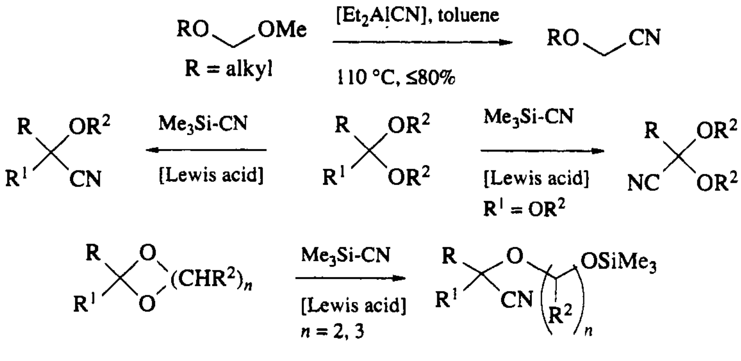
RO
OMe
R = alkyl
[Et2AlCN], toluene
110 °C, ≤80%
RO
CN
R
OR2
R1
CN
Me3Si-CN
[Lewis acid]
R
OR2
R1
OR2
Me3Si-CN
[Lewis acid]
R1 = OR2
R
OR2
NC
OR2
R
O
(CHR2)n
R1
O
Me3Si-CN
[Lewis acid]
n = 2, 3
R
O
OSiMe3
R1
CN
R2
n

**Scheme 16**

Orthocarbonates and their analogs do exchange just one alkoxy group with TMS-CN/$SnCl_4$ (Scheme 17). In earlier papers even the direct reaction with HCN and $ZnCl_2$ at room temperature was reported to give (after several days or even some weeks) high yields.[2,4] Treatment with acetyl cyanide (Scheme 17) represents another possibility for transforming orthoesters into bisalkoxynitriles.[71]

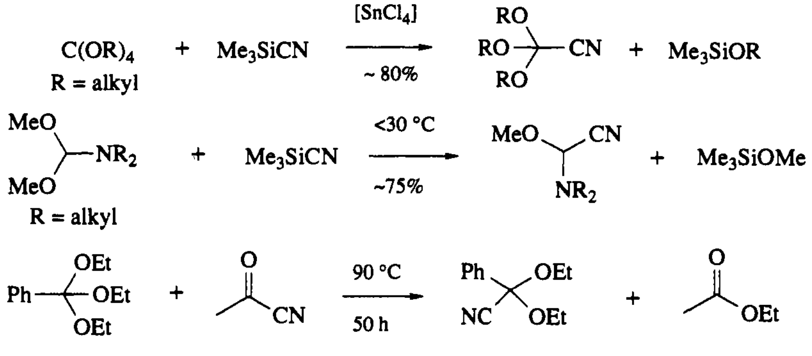

**Scheme 17**

An elegant procedure for generating α-cyano ethers from acyclic or cyclic acetals and ketals is their reaction with *t*-alkyl isocyanides in the presence of an equimolar amount of $TiCl_4$ (Scheme 18).[3,72] The exchange of alkoxy groups against cyanide functions proved to be very important for the preparation of cyanoquinones.[73]

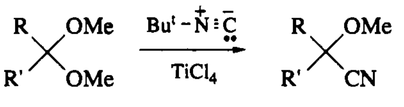

| *R* | *R'* | *Yield* |
|---|---|---|
| $Bu^n$ | H | 81% |
| Ph | H | 96% |
| $-(CH_2)_4-$ | | 86% |
| $-(CH_2)_5-$ | | 92% |

**Scheme 18**

As with oxiranes, ring opening with TMS-CN/$AlCl_3$ can also be carried out with thiiranes.[74] Dialkylaminotrialkylstannanes react with episulfides without anyLewis acid catalysis.[74] For the synthesis of α-cyano sulfides from thioacetals or thioketals with TMS-CN (Scheme 19), $SnCl_4$ proved to be the best catalyst.[34] For the mechanistic interpretation the authors favor the isonitrile (**16**) as a key intermediate. An additional technique for preparing alkylthionitriles uses $Hg(CN)_2$ in the presence of $I_2$, thus reaching yields of up to 80%.[75]

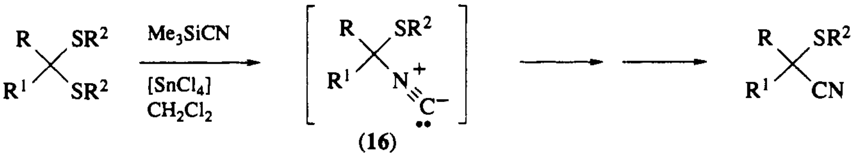

(**16**)

| *R* | *R¹* | *R²* | *Yield* |
|---|---|---|---|
| $Pr^i$ | H | Et | 93% |
| $Bu^t$ | H | Et | 81% |
| c-$C_6H_{11}$ | H | Et | 85% |
| Ph | H | Et | 84% |
| Tol | Me | Et | 70% |
| Et | Et | Ph | 78% |

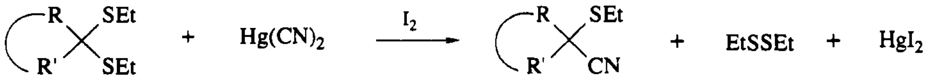

**Scheme 19**

The synthesis of α-methylthionitriles in high yield by 'cyanosulfenylation', *i.e.* addition of dimethyl(methylthio)sulfonium tetrafluoroborate to alkenes, followed by reaction with a CN donator, *e.g.* alkali metal cyanide/$HBF_4$ or TMS-CN (equation 15), was recently described by Trost.[76]

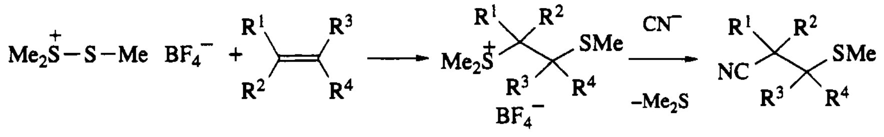

(15)

Sulfoxides may also be used for the preparation of nitriles: alkoxymethyl methyl sulfide, easily obtained from DMSO/acetic anhydride and primary alcohols, gives rise to the corresponding sulfoxides on treatment with MCPBA. By reaction with TMS-CN and $ZnI_2$, 2-alkoxyacetonitriles in good to excellent yields were obtained (Scheme 20).[77]

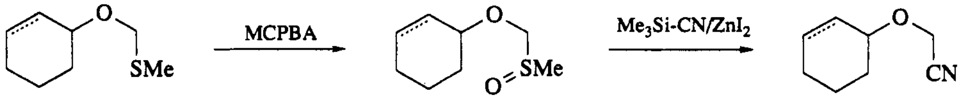

| | | |
|---|---|---|
| cyclohexenyl | 85% | 67% |
| cyclohexyl | 100% | 100% |

**Scheme 20**

The thermal reaction between sulfonates and alkali metal cyanides (equation 16) or potassium hexacyanoferrate is more of historical value.[2,4] The finely powdered, dry and thoroughly mixed starting materials (equation 17) are heated up to 400 °C. For more efficient heat exchange the addition of mineral oil, sand, iron turnings or iron oxide is recommended. In spite of the quite forcing reaction conditions, yields of up to 80% are given in certain cases.[2]

$$ArSO_3M + MCN \xrightarrow{\Delta} Ar-CN + M_2SO_3 \qquad (16)$$

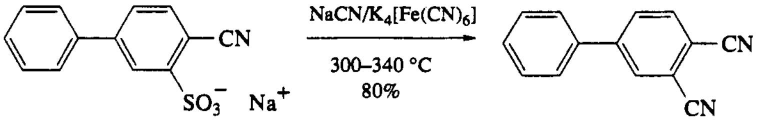

(17)

## 1.8.1.4 Exchange of Other Nitrogen Functionality

A quite important process for the preparation of aromatic nitriles is certainly the substitution of diazo groups by a cyanide function (equation 18). Following this route, the nitro or a primary amino group is, in principle, replaced by a CN ligand. The most important procedures are summarized in review articles[2,4] and in some shorter accounts.[78]

$$Ar-\overset{+}{N_2}\ X^- + CN^- \xrightarrow[\Delta,\ -N_2]{[CuCN]} Ar-CN \qquad (18)$$

The first examples reported by Sandmeyer date back to 1884. The many various preparative procedures differ mainly in the type and the preparation of the copper–cyanide complex which is used.[2,4] In the 'Gattermann procedure' KCN in the presence of Cu powder is used. Generally one tries to avoid the formation of HCN on the addition of alkali metal cyanide to the acidic medium by neutralizing the diazonium salt solution in advance with sodium or barium carbonate. Cyanogen, which is formed from $CN^-$ ions on treatment with $Cu^{II}$ salts, is also a harmful by-product. In this case the addition of sodium hydrogen sulfite (equation 19) proved to be of great value.

$$2\,CuSO_4 + 2\,CN^- + HSO_3^- + H_2O \longrightarrow 2\,CuCN + 3\,HSO_4^- \qquad (19)$$

Better yields were often also obtained by use of the complex copper salt (**17**), prepared *in situ* from KCN and $CuSO_4$ in the presence of $NH_3$ (equation 20). In a thorough investigation Japanese workers[79] recently treated a series of aromatic amines with sodium nitrite in a mixture of polyethylene glycol and $CH_2Cl_2$ with HCl in a little water at 0 °C. After addition of the crystalline complex salt (**17**) the corresponding arenenitriles were obtained in high yield.

$$\mathrm{CuSO_4} + 4\,\mathrm{KCN} + \mathrm{NH_3} \longrightarrow \underset{(\mathbf{17})}{\mathrm{K_2[Cu(NH_3)(CN)_4]}} + \mathrm{K_2SO_4} \qquad (20)$$

The preparation of aromatic nitriles by an $S_{RN}1$ process was described recently.[80] Suitably substituted diazo sulfides, either isolated or only generated *in situ*, reacted with tetrabutylammonium cyanide under photon or electron stimulation (equation 21), leading to aryl cyanides with yields that are comparable with those of the Sandmeyer reaction. Bromo- and chloro-substituted aryl diazo sulfides afforded the corresponding dinitriles in high yields.

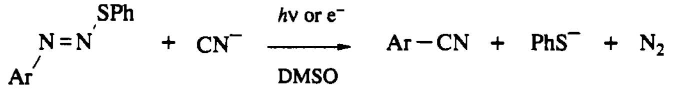

$$\mathrm{Ar{-}N{=}N{-}SPh} + \mathrm{CN^-} \xrightarrow[\text{DMSO}]{h\nu \text{ or } e^-} \mathrm{Ar{-}CN} + \mathrm{PhS^-} + \mathrm{N_2} \qquad (21)$$

The thermally triggered transformation of aromatic nitro halides with KCN is known as the 'von Richter rearrangement'.[3,4,81] The process is illustrated in equation (22). In principle the nitro group is replaced by a cyano group by *cine* substitution, and a carboxylic acid is isolated, but with the carboxy group taking the *ortho* position to the former nitro substituent. The carboxy function is not formed by simple hydrolysis of the nitrile, as was believed for quite a period of time. A number of authors contributed to a better understanding of the reaction mechanism;[81–83] the details of the rearrangement, which involves heterocyclic intermediates, cannot be covered here. The yield of this reaction is generally rather low.

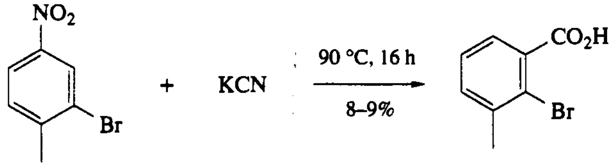

(22)

### 1.8.1.5 Exchange of a Hydrogen

The preparation of nitriles by (formal) exchange of a proton in alkyl-substituted aromatic and heteroaromatic systems, activated methylene compounds *etc*., for a cyanide group, using cyano halides, cyanogen, or aryl cyanates, is described mainly in the patent literature. Operating on contact times of a few seconds, reaction temperatures as high as 1000 °C are proposed.[2–4] The treatment of benzyl cyanide, deprotonated by LDA, with *o*-chlorobenzyl thiocyanate is, owing to mild reaction conditions and high yields, considered to be of some preparative value (Scheme 21).[3] Cyclic 2-cyano ketones may be obtained from the corresponding enolates on treatment with *p*-toluenesulfonyl cyanide.[3]

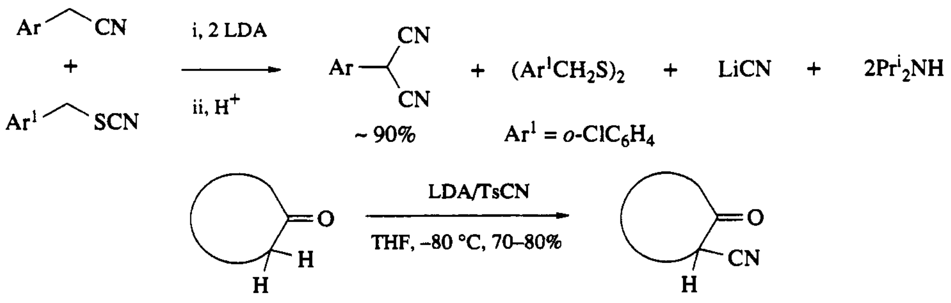

**Scheme 21**

A closer look has to be taken at the transformation of arenes into cyano derivatives. Aromatic starting materials may for instance be converted into nitriles under Friedel–Crafts conditions. Although a number of variations have been described,[2–4] the preparative value of this process seems to be quite low. The method of Houben and Fischer[2–4] gives rise to quite acceptable yields, but the work-up is very tedious (equation 23).[2]

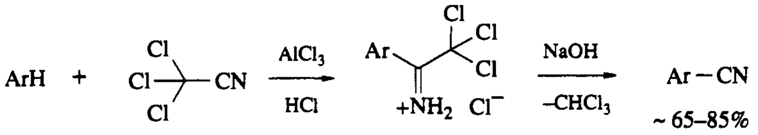
ArH
+
Cl
Cl
Cl
CN
AlCl3
HCl
Ar
Cl
Cl
Cl
+NH2 Cl⁻
NaOH
–CHCl3
Ar–CN
~ 65–85%

(23)

Aroyl cyanides may be obtained from substrates which are not too electron poor on treatment with cyanogen and HF, when the reaction temperature is slowly raised from –30 to 50 °C.[3] Instead of cyanogen, carbonyl cyanide may also be used,[3] but preparation and handling of this reagent is problematic (equation 24).[3]

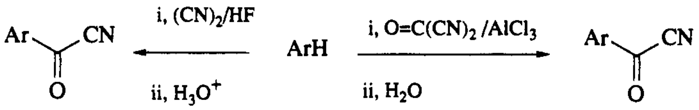
Ar
CN
O
i, (CN)2/HF
ii, H3O+
ArH
i, O=C(CN)2 /AlCl3
ii, H2O
Ar
CN
O

(24)

High yields of α-cyanoazines are obtained from pyridine, quinoline or isoquinoline *N*-oxides and TMS-CN in acetonitrile/triethylamine or in DMF, and also in THF in the presence of tetrabutylammonium fluoride.[3] In another variation TMS-CN together with dimethylcarbamoyl chloride is used. Mechanistically these transformations should be similar to the Reissert reaction and may run through intermediates of type (**18**) and (**19**; Scheme 22).[3]

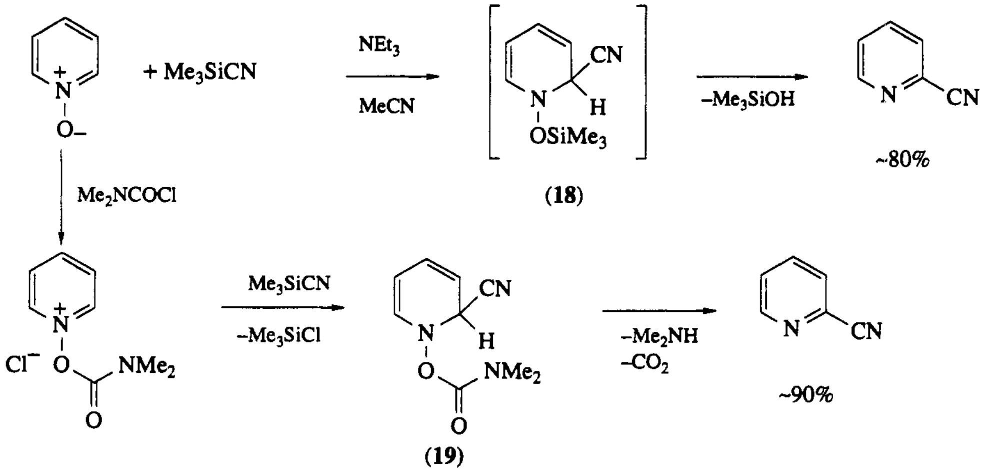
+ Me3SiCN
NEt3
MeCN
CN
N
H
OSiMe3
(18)
–Me3SiOH
N
CN
~80%
Me2NCOCl
Cl⁻
NMe2
Me3SiCN
–Me3SiCl
CN
H
NMe2
(19)
–Me2NH
–CO2
CN
~90%

**Scheme 22**

### 1.8.1.6 Nitriles From Organometallic Compounds

As many organometallic compounds are prepared from the corresponding halides, their transformation into nitriles may in a way be considered as a substitution reaction.[2–4] Of special use is the treatment of aliphatic or aromatic Grignard compounds with cyanogen or halocyanogen. Aryl cyanates also react with Grignard reagents and usually give excellent yields of the corresponding nitriles (Scheme 23).[3] The reaction of lithium arenes and lithium heterocyclic compounds with *N*-methyl-*N*-phenylcyanamide is probably of only limited value (Scheme 23).[3] It should be mentioned that aluminum compounds may also serve for the preparation of acrylonitrile derivatives.[3]

$$\underset{X\,=\,\text{halogen}}{\text{R-MgX}} \xrightarrow[\text{ii, }H_3O^+]{\text{i, X'CN}} \text{R-CN} \xleftarrow[\text{ii, }H_3O^+]{\text{i, ArOCN}} \text{R-MgX}$$

$$\text{ArLi} \xrightarrow[\text{ii, }H_3O^+]{\text{i, PhNMeCN}} \text{ArCN}$$

**Scheme 23**

## 1.8.2 ISONITRILES

A series of papers from Gauthier and Hofmann, which are cited in nearly every review article on isocyanides,[84–92] is considered the real beginning of scientific work on this class of compounds. Lieke,[88,93] however, seems to have encountered isonitriles earlier. This author reports on 'cyanallyl', which was obtained from mercury cyanide with 1 equiv. of allyl iodide in a sealed tube at 100 °C. This 'cyanallyl' has a highly penetrating and most unpleasant smell'. Opening a vessel of the compound will pollute the air inside a room for several days, which is the reason why all work with this material was done in the open air. Hydrolysis of the compound with alcoholic KOH yielded (after acidification) formic acid and not, as the author had expected, crotonic acid. Lieke finishes: 'There was no more material for further investigations and no possibility of preparing more, as there were complaints about the infernal stink from all over the neighborhood'.[93]

Treatment of alkylating agents with metal cyanides should in principle be the method of choice for preparing isocyanides (equation 25). But as the cyanide ion again represents an ambident nucleophile, the well-known problems already discussed will arise (Section 1.8.2.1.i). It remains to be stated that simple alkylation of alkali metal cyanides with halogen compounds or dialkyl sulfates is not useful for the preparation of isonitriles. The formation of nitriles always prevails and isocyanides are at best obtained in yields of up to 25%.[85–88] The prospects are much better in the alkylation of heavy metal cyanides, if the reaction is done under conditions which initially give rise to isocyanide–transition metal complexes (equation 26). These will then be transformed into isonitriles by treatment with KCN. Under optimized conditions this technique yielded 55% of ethyl isocyanide.[15]

$$\text{R}{-}\text{X} + \underset{\bullet\bullet}{\text{N}}{\equiv}\underset{\bullet\bullet}{\text{C}}^{-}\,\text{M}^{+} \longrightarrow \text{R}{-}\overset{+}{\text{N}}{\equiv}\underset{\bullet\bullet}{\overset{-}{\text{C}}} + \text{MX} \tag{25}$$

$$\text{EtI} \xrightarrow[\text{ii, KCN/}H_2O]{\text{i, AgCN, 100 °C}} \text{Et}{-}\overset{+}{\text{N}}{\equiv}\underset{\bullet\bullet}{\overset{-}{\text{C}}} \tag{26}$$

In general, these transformations are run at about 80–100 °C. For preparative use, alkyl iodides proved to be the most useful alkylating agents. CuCN may be used instead of AgCN, in experiments with zinc, cadmium and nickel cyanides; however, a serious decrease in yields was observed.[85–88] Although hexacyano-ferrates and -cobaltates have been recommended in a few cases,[85,88,92] their general use may be rather limited. Remarkable results have, however, been obtained with tetraalkyl- or tetraaryl-ammonium, -phosphonium or -arsonium dicyanoargentates in acetonitrile (Scheme 24).[94] In the diaryl- and triarylmethyl series the bromides or chlorides can be used instead of iodides. The reaction fails, however, with *p*-nitrophenyl derivatives, and aryl iodides and acyl chlorides are not attacked by oniumargentates.

$$2\,\text{MeI} + Ph_4As^+[Ag(CN)_2]^- \longrightarrow 2\,\text{Me}\overset{+}{\text{N}}\overset{-}{\text{C}} + Ph_4As^+[AgI_2]^-$$

$$2\,PhCH_2Br + Me_4N^+[Ag(CN)_2]^- \longrightarrow 2\,PhCH_2\overset{+}{\text{N}}\overset{-}{\text{C}} + Me_4N^+[AgBr_2]^-$$

**Scheme 24**

The quite labile acyl isocyanides on the other hand may be obtained from acyl iodides with AgCN in $CH_2Cl_2$; similarly imidoyl bromides give rise to imidoyl isocyanides (Scheme 25).[95,96] Both types of compounds decompose quite easily under comparatively mild conditions. Acyloxy isocyanides are well known too.[97]

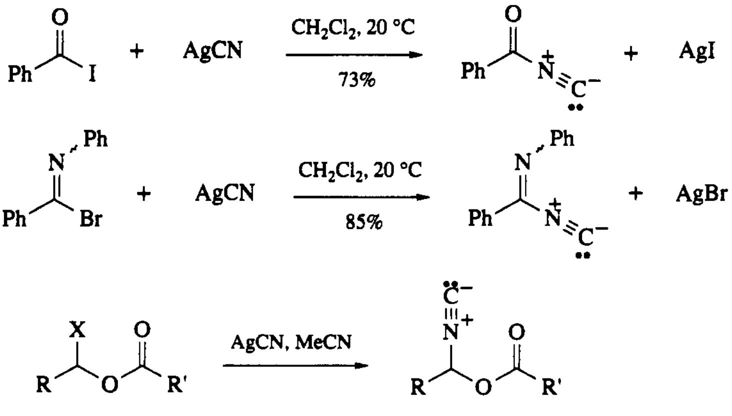

R = Me, X = I, R' = Ph; 79%
R = Ph, X = Br, R' = Bu$^t$; 72%

**Scheme 25**

Silver cyanide is also very useful for the preparation of glycosylisonitriles.[91] Although respectable yields are reported, the reaction is accompanied by anomerization.

In addition to its use in the preparation of nitriles, trimethylsilyl cyanide (TMS-CN) is also becoming a very useful reagent for the preparation of isocyanides. 1-Chloroadamantane, for instance, gives rise to 78% of the corresponding isonitrile in the presence of catalytic amounts of $TiCl_4$ (Scheme 26). Of special interest is the remarkably regioselective and stereoselective synthesis of trimethylsilyloxyalkyl isocyanides (Scheme 26) from oxiranes and TMS-CN in the presence of, for example, zinc halides (see also Section 1.8.1.3).[60,64,65]

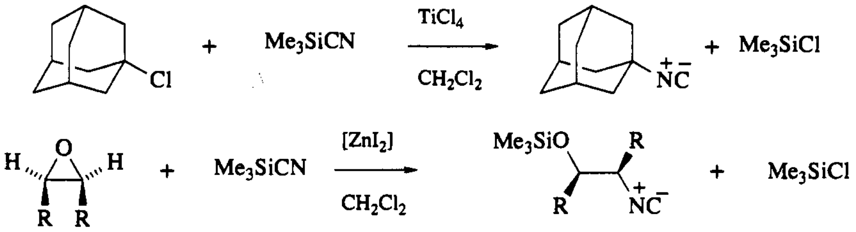

**Scheme 26**

Finally, it should be remembered that isonitriles are not only obtained by substitution processes, but also by alternate routes, which may be of high value. In particular the various techniques for the dehydration of formamides, or the phase transfer version of the classical 'carbylamine' reaction should be noted.[84–92]

## 1.8.3 CYANATES

Attempts to prepare cyanates date back to 1857,[98] but remained unsuccessful for more than 100 years, so that eventually the existence of cyanic esters was questioned. The decisive breakthrough was achieved only about 30 years ago by Stroh and Gerber,[99] when they succeeded in preparing the sterically strongly shielded 2,6-bis(*t*-butylphenyl) cyanate. Today numerous alkyl and aryl cyanates are available and a series of review articles[100–105] provide an excellent overview of the chemistry of this class of compounds. Several tables listing numerous cyanates and the yields from different preparative procedures can be found.[100,103] Discussion of individual examples therefore seems to be unnecessary here. Suffice is to say that, while at the beginning steric protection was believed to be of utmost importance for the stability of the cyanates, it was later realized that sticking to exactly defined reaction conditions is a key measure in preventing secondary reactions.

While aromatic cyanates in their pure state tend to be quite stable compounds, their aliphatic counterparts very often prove to be extremely unstable molecules with an accordingly low preparative value.

Alkyl cyanates are obtained from sterically crowded alcohols or bridgehead derivatives *via* the corresponding alcoholates by treatment with cyanohalides in quite modest yields (Scheme 27). Higher yields and more stable products may be obtained from polyhalogenated alcohols or certain enols. These cyanates show properties comparable to the aromatic series discussed earlier.[106–108]

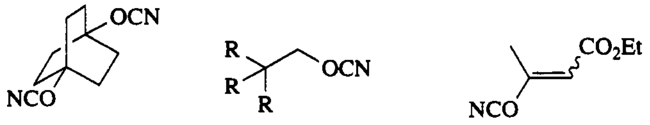

41% R = Me, 4.4%; R = Cl, 93% 73%
R = F, 80%; R = Br, 85%

**Scheme 27**

Further reaction procedures leading to alkyl cyanates[102,103] cannot be discussed here. Mention has to be made, however, of the sometimes particularly useful thermal degradation of 5-alkoxy-1,2,3,4-thiatriazoles, which are often only prepared in solution.[102,103]

The aromatic cyanates are of much more importance. If phenols are treated with cyano halides in such a way as to definitely prevent an excess of the corresponding phenolate, aryl cyanates can be isolated in up to quantitative yields. To achieve this, triethylamine is slowly added to an equimolar mixture of the phenol and the cyano halide in a nonprotic solvent, preferably acetone or *n*-pentane/diethyl ether (equation 27).[109] Heteroaromatic hydroxy compounds can be treated in the same way. The method fails, however, if various electron-attracting substituents are present, as for instance with 2,4-dinitrophenol or polyhalophenols.[108]

$$\mathrm{ArOH} \xrightarrow[\mathrm{NEt_3}]{\mathrm{ClCN}} \mathrm{ArO{-}CN} + \mathrm{Et_3\overset{+}{N}H\ Cl^-} \qquad (27)$$

Martin *et al.*[110] report investigations on the kinetics and the mechanism of aryl cyanate formation from cyanogen bromide and phenols in the presence of different tertiary aliphatic amines. According to Vowinkel,[111] the use of diethyl ether as the solvent at –10 °C raises the yields and various patents describe how the amines can be replaced by sodium hydroxide. There are even reports on work in aqueous solution under phase transfer conditions.[103] With all synthetic variants it is crucial to avoid a surplus of the phenolate as only under these conditions can the often quite fast formation of imino carbonates be prevented (equation 28).

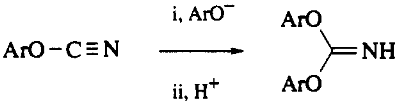

$$\mathrm{ArO{-}C{\equiv}N} \xrightarrow[\text{ii, H}^+]{\text{i, ArO}^-} (\mathrm{ArO})_2\mathrm{C{=}NH}$$

(28)

Treatment of alkyl halides with alkali metal or silver cyanate is of no preparative value for the synthesis of cyanates.[103,112,113] As cyanate ions do represent ambident nucleophiles, Holm and Wentrup[114] tried to reach cyanates under well-defined $S_N1$ conditions (Scheme 28). But even treatment of isopropyl iodide with silver cyanate in nitromethane provided only a very low yield of a 1:1 mixture of isopropyl cyanate and the corresponding isocyanate, and from a reaction of silver cyanate with triphenylchloromethane they isolated only triphenylmethyl isocyanate, although the cyanate may have been an intermediate in this transformation.[114]

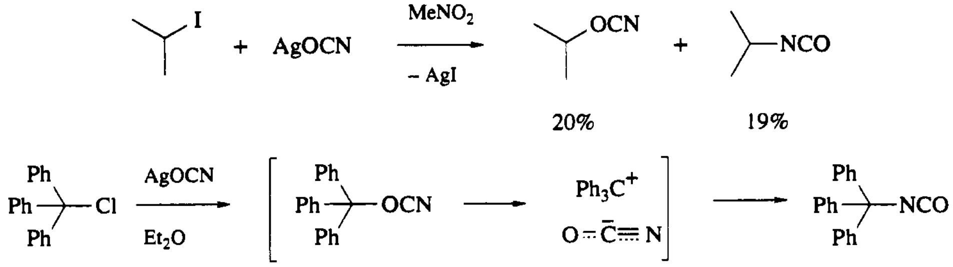

**Scheme 28**

## 1.8.4 AZIDES

### 1.8.4.1 General Remarks

The history of the azides starts in 1864 with the first report on phenyl azide by Griess.[115] In 1990, the first preparation of hydrazoic acid by Curtius had its 100th anniversary.[116] There are many reports on aliphatic and aromatic azides in the literature. In a very recent and thorough review[117] Scriven and Turnbull present a highly impressive list of review articles which have appeared in the 20 years since 1970. Out of the many possibilities for preparing all types of azides, substitution reactions are of special importance. Here again a series of recent review articles[117–123] will guarantee a quick orientation in the field.

### 1.8.4.2 Azides from Halogen, Sulfonate and Sulfate Derivatives

#### *1.8.4.2.1 Alkyl azides*

The reaction of halides or sulfonates with alkali metal azides, mostly $NaN_3$, offers a simple and high yield access to alkyl azides.[118,119] For the preparation of the most simple ones, *e.g.* methyl and ethyl azide, the corresponding sulfates were for a long time considered the only useful starting materials.[118,119] The preparation of azidoethane in ether solution from ethyl iodide and $NaN_3$ was reported recently (Scheme 29).[124] Alkane- and *p*-toluene-sulfonates are well-established starting materials for the preparation of azido carbohydrates.[117,119] Their particular importance rests mainly on the possibility for reductive generation of amino sugars. The crucial role of alkanesulfonates for the generation of alkyl azides is demonstrated by Scriven and Turnbull[117] with numerous examples.

$$R{-}X \quad + \quad N_3^- \longrightarrow R{-}N_3 \quad + \quad X^-$$

$$X = \text{halogen, } OSO_2R', OSO_2OR'$$

$$EtI \quad + \quad NaN_3 \xrightarrow[Et_2O/H_2O]{Bu_4N^+\,BF_4^-} EtN_3 \quad + \quad NaI$$

**Scheme 29**

If alkyl halides are used as starting materials, one is not restricted to iodides, as bromides and chlorides may also be used. So-called activated $NaN_3$[118,119,125] or $AgN_3$ is only necessary in special cases, and may then, however, prove to be of particular advantage.[118] Besides primary alkyl halides, secondary ones may also be considered as starting materials and even some tertiary azides were prepared this way.[117] Some experimental details can be found in Grundmann's review;[118] tables with numerous examples[118,119] provide a very good impression of the scope of this transformation. The high tendency for explosions of many azides, particularly the lower ones, is a good reason to generate and transform these compounds, whenever possible, in solution only.

For a long time protic solvents like methanol or water at temperatures between 60 and 100 °C were considered best. 2-Alkoxyethanols ('carbitols') with their higher boiling points have in the meantime become quite popular.[118,119] Of course dipolar aprotic solvents like DMSO, DMF and also nitrobenzene may be used for the preparation of azides too, although the isolation of reaction products may sometimes be difficult here.[117] Given slowly reacting substrates, the higher solubility of $LiN_3$ may in certain cases provide advantages compared to other alkali metal azides.[117] A combination of $NaN_3$ and $ZnCl_2$ is often recommended, particularly for the generation of tertiary azides.[117,126]

The various phase transfer techniques also led to very good results in azide synthesis. Excellent yields of alkyl azides were secured, for instance, when alkyl bromides were treated with alkali metal azides in the presence of catalytic amounts of tetrabutylammonium bromide or 'aliquat 336' (equation 29).[117,127] The use of crown ethers has been described as well.[117]

A very impressive example consists of the preparation of 3-azido-1,2,4-oxadiazole, which after a series of failures was eventually obtained from the corresponding bromo compound with $LiN_3$ in dry DMF or with $KN_3$ in the presence of 18-crown-6 (Scheme 30).[128]

$$\underset{\mathrm{R = alkyl}}{\mathrm{R{-}Br}} + \mathrm{NaN_3} \xrightarrow[\sim 90\%]{\mathrm{H_2O/aliquat\ 336}} \mathrm{R{-}N_3} + \mathrm{NaBr} \qquad (29)$$

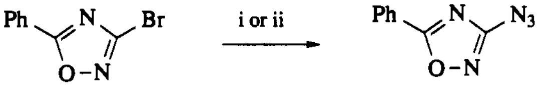

no reaction with:
$NaN_3$, DMF/$H_2O$, 100°C;
$NaN_3$/NaI, 50 °C;
$LiN_3$, MeOH, 65 °C;
$Bu_4N^+N_3^-$, MeCN, 83 °C

i, $KN_3$, DMF, 18-crown-6, 72 h, 90 °C, 50%; ii, $LiN_3$, DMF, 45 h, 90 °C, 50%

Scheme 30

The acceleration of substitution reactions with azides using ultrasound techniques (Scheme 31) has not yet been investigated in detail.[129] Activated primary halides react with trimethylsilyl azide (TMS-A) under particularly mild and absolutely neutral conditions (Scheme 31).[117] Secondary and tertiary cyclic halides were treated with TMS-A/$SnCl_4$ in $CH_2Cl_2$ or $CHCl_3$ to yield the corresponding azido compounds.[117] Very impressive results with yields of about 90% were in this case reported in the adamantane and diamantane series.[117] High solubility in organic solvents is also noticed with acetyl azide, which, prepared *in situ*, has also been used for azide syntheses. The scope of this reaction has still to be determined, however.[117] Hassner[130] noticed nearly quantitative yields of azides when alkyl halides (or tosylates) were treated with polymeric quaternary ammonium azides.

$$\mathrm{R{-}X} + \mathrm{NaN_3} \xrightarrow{\mathrm{H_2O,\ ultrasound}} \mathrm{R{-}N_3} + \mathrm{NaX}$$

R = $HC{\equiv}CCH_2$, X = Br; 88%
R = $NCCH_2$, X = Cl; 64%
R = $H_2C{=}CHCH_2$, X = Br; 91%
R = $H_2C{=}C(Cl)CH_2$, X = Cl; 81%
R = Et, X = Br; 20%

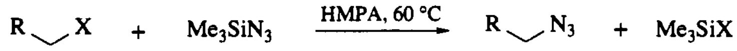

R = $ArCH_2$, $R'_2C{=}CHCH_2$, $NCCH_2$, $EtO_2CCH_2$; 60–87%

Scheme 31

Mechanistically most of these transformations correspond to $S_N2$-type substitutions; chiral substrates react with inversion. In certain cases, however, azides may also be obtained under $S_N1$ conditions.[118,119,126b] Some di- and tri-arylmethanols for instance (Scheme 32) react with $HN_3$ in the presence of trichloroacetic acid *via* the corresponding carbenium ions. Sulfuric acid seems to be inferior for these transformations.[118,119] Under highly acidic conditions the intermediate (**20**) obviously tends to decompose with the elimination of nitrogen (*cf.* Schmidt reaction[117]). $S_N1$ substitution is also highly probable in the reaction of α-halo ethers and sulfides with azide ions.[118,119] In some cases even $S_{RN}1$-type substitution was observed for the halogen/azide exchange.[117]

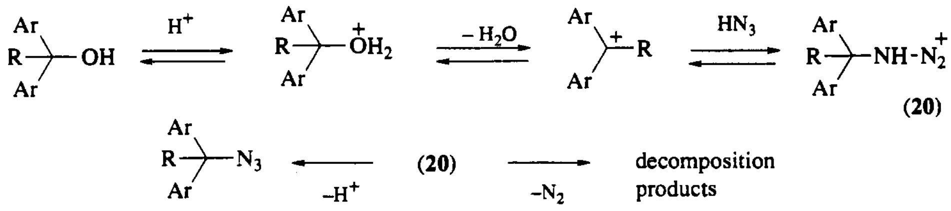

Scheme 32

By starting from the corresponding dihalides, diazides may also be obtained with ease. A list of numerous examples is given by Grundmann.[118] The high tendency of some diazides to explode, has to be mentioned here. For a demonstration of the strong influence of structural parameters on the reactivity of dihalides with azide ions[117] two examples will suffice (Scheme 33): in a sequence of elimination, addition (Michael acceptor) and substitution steps, followed by another β-elimination, 2,3-dibromocarboxylic esters give rise to high yields of the vinyl azides (**21**) with 3 equiv. of $NaN_3$; on the other hand, methyl 2,4-dibromobutanoate yields 80% of the monoazido ester (**22**) with only a very small amount of the corresponding bisazido compound.[131]

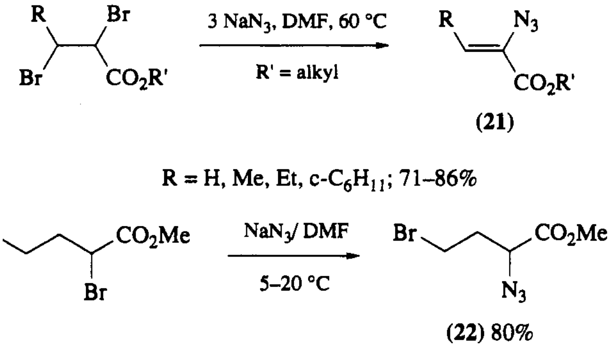

Scheme 33

Vinyl azides are generally prepared from 2-azido halides by elimination,[118,119,132,133] while vinylogous acid chlorides and similar systems may be treated with azide ions directly in an addition–elimination sequence (Scheme 34). With haloquinones smooth transformations into azidoquinones are also observed.[118,119,134,135] Thus all four chloro substituents of chloranil can be successively exchanged with azide ions (Scheme 34).

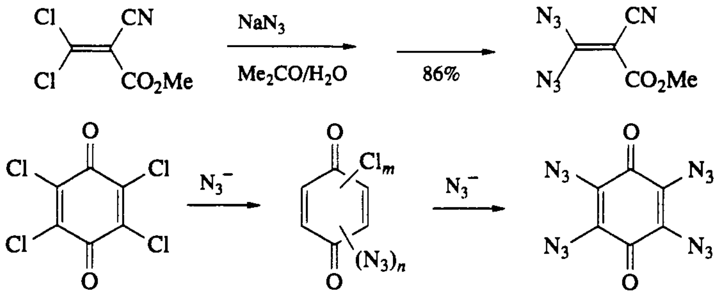

$m = 3, 2, 1$
$n = 1, 2, 3$

Scheme 34

There is still no successful approach to 1-azidoalkynes, although the corresponding phenyl derivative (**23**; Scheme 35) is thought to be a short-lived intermediate in the reaction of chlorophenylacetylene with azide ions.[117,118] In contrast to this, propargylic azide (**24**) and its higher homologs (**25**) can be obtained in the usual way.[117] The formation of these compounds is sometimes accompanied by rearrangements, which also very often take place with azidoallene derivatives; their chemistry was intensively studied recently by Priebe[117] and Banert.[136]

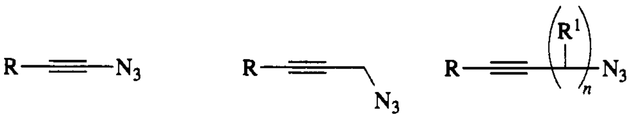

(**23**) R = Ph (**24**) (**25**)

Scheme 35

Mechanistically, there is a range of possibilities for the reaction of allylic halides with azide ions, with many details still open for discussion.[117,119] Besides simple substitution reactions, depending on the structure of the starting materials and the experimental conditions, allylic rearrangements as well as equilibration reactions may be observed.[117,119]

Nucleophilic substitution of functionalized halides may also lead to azides, carrying further functional groups, not only in the 'periphery' of the molecule, but also in the very close neighborhood (α-position). A few examples have been mentioned already. Quite well known are, for instance, α-azido-alkylamines, -carboxylic acid derivatives, ethers, sulfides and ketones, which can be quite simply obtained from the corresponding halo compounds.[117,118] The observation that the chiral substrate (**26**) undergoes the substitution reaction, if tetramethylguanidinium azide is used, with less than 1% epimerization (Scheme 36)[137] merits special interest. In the interaction of azide ions with 3-hydroxy-2-halocarboxylic esters, a rearrangement *via* oxiranes may take place (Scheme 36).[118] Aiming at a stereoselective synthesis of the corresponding amines, a series of azide steroids was prepared,[117,119] starting from the halo derivatives or the corresponding sulfonates. In most cases an $S_N2$-type process, leading to stereochemically well-defined products, was observed.

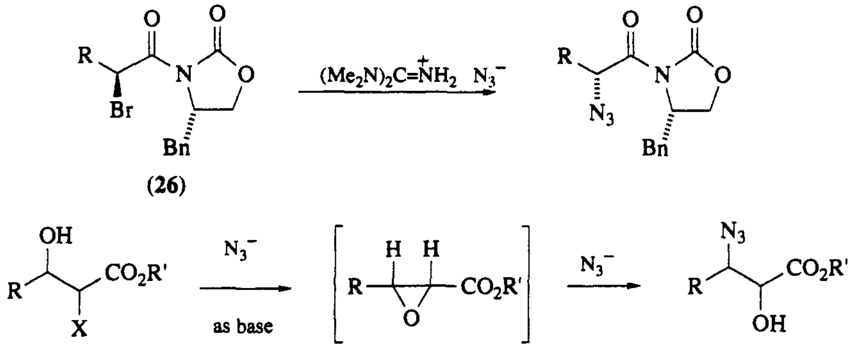

**(26)**

X = halogen, R' = alkyl

**Scheme 36**

### *1.8.4.2.2 Aryl azides*

The synthesis of aromatic azides (Scheme 37) from aryl halides with azide ions ($S_NAr$) is particularly successful with systems that carry an activating substituent, an electron-withdrawing group, either in the *ortho* or the *para* position relative to the potential leaving group.[118,119] A table with numerous examples can be found in the literature.[119] Fluoride ion as a leaving group is superior to the other halides. Dipolar aprotic solvents, such as DMF for instance, have their special merits in these transformations, too. The reaction of 2,4- or 2,6-dinitroaryl halides with azide ions was shown to be accelerated in micelles or in the presence of quaternary ammonium salts.[117]

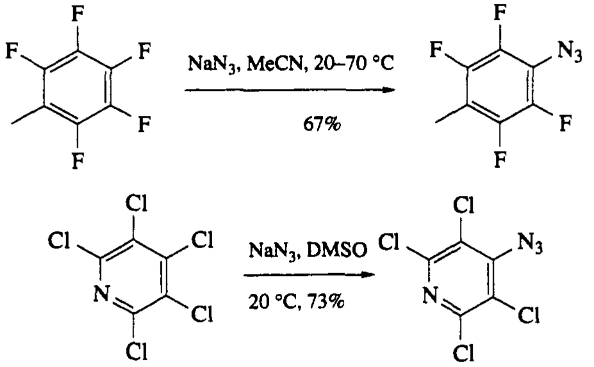

**Scheme 37**

Various perhalo aromatic compounds as well as a series of heterocyclic precursors, such as, for instance, chloro-pyridazine or -triazine derivatives, gave rise to the corresponding azides, too.[117,119,121]

### 1.8.4.2.3 Acyl azides

The preparation of acyl azides by substitution is presented in connection with the Curtius rearrangement in a series of review articles.[117-121,125,138] The most important synthetic methods are discussed in the sequel. The routine technique for the generation of various acyl azides by substitution starts from acyl chlorides and azide ions (equation 30).[119-121,125] The reactions are generally run by mixing an aqueous solution of the azide, mostly $NaN_3$, with a solution of the acid chloride in a water-miscible solvent such as acetone, alcohols, dioxane, HOAc or DMF. The competing solvolysis of the acyl chloride with alcohols must be considered. In certain cases the use of tertiary amines or amine oxides as catalysts is recommended.[120] If suspensions of $NaN_3$ in organic solvents such as pyridine, toluene, xylene or nitrobenzene are used, reaction temperatures often have to be used that lead to the Curtius rearrangement of the required acyl azide.[119,120] In this case the use of 'activated' $NaN_3$ is recommended.[118] Advantages are seen by using $LiN_3$ in DMF,[139] mainly due to its better solubility, and the same holds for a series of tetraalkylammonium azides, which in many cases are thermally quite stable, too.[120] DMSO cannot be used as the solvent here, as it reacts with acyl chlorides quite vigorously at room temperature.[119]

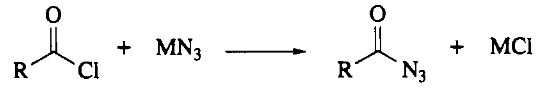

(30)

The reaction of acid chlorides with tetramethylguanidinium azide also proceeds under very mild conditions.[140] Using this technique even *t*-alkyl azidoformates may be prepared (Scheme 38). Quantitative yields of acyl azides (in solution) are reported for the interaction of acid chlorides in toluene with $HN_3$/pyridine at 0 °C. Even sterically hindered educts are smoothly converted into acyl azides.[121] If tetraalkylammonium azides are used, the use of hazardous hydrazoic acid is avoided.[120,121]

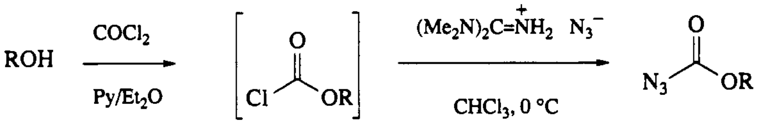

R = Bu$^t$, ~100%; R = *t*-amyl, 84%; R = Ph, 97%

**Scheme 38**

It should be mentioned at this stage that instead of acyl chlorides, mixed anhydrides may also be used for the synthesis of acyl azides. From carboxylic acids and chloroformates/triethylamine, mixed anhydrides are formed, which can directly react with azide ions. Sterically hindered acids fail in this procedure (equation 31).[119-121] The similar synthesis of *t*-butyl azidoformate by reaction of *t*-butylcarbonic diethylphosphoric anhydride with $KN_3$ is described in *Organic Syntheses.*[141]

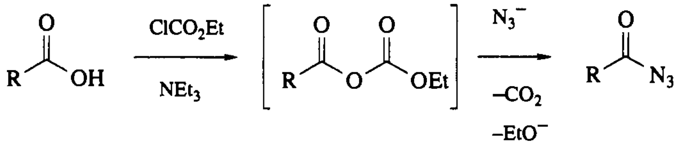

(31)

In synthesizing α,β-epoxyacyl azides Zwanenburg *et al.*[142] noted that treatment of the acid chloride (**28**) with $HN_3$/pyridine is superior to the reaction of mixed anhydrides (**27**), prepared *in situ*, with $NaN_3$ (Scheme 39). Another version of this process uses the transformation of acyloxyiminium salts of type (**29**) (again prepared *in situ*) with $NaN_3$ (Scheme 39).[143] The authors did not isolate the azido derivatives, but used them in a subsequent Curtius rearrangement in boiling toluene. After a final treatment with aniline, yields of the corresponding ureas were between 60 and 80% with alkyl compounds and 86–100% for aryl systems. Palomo *et al.*[144] used a very similar procedure and were able to isolate the azides.

Trimethylsilyl azide (TMS-A) in the presence of catalytic amounts of pyridine turned out to be very useful in the preparation of acyl azides, as this reagent will not only transform acyl chlorides and mixed anhydrides into azides, but also works with reactive esters and lactones (Scheme 40).[121,145] Many of these reactions have, however, been run under conditions which will lead to the Curtius rearrangement of the azide intermediates. Pyridine as a catalyst can be replaced by the combination $KN_3$/18-crown-6.[121] Diazidodiphenylsilane, which was investigated as well, will probably not become a standard reagent.[145]

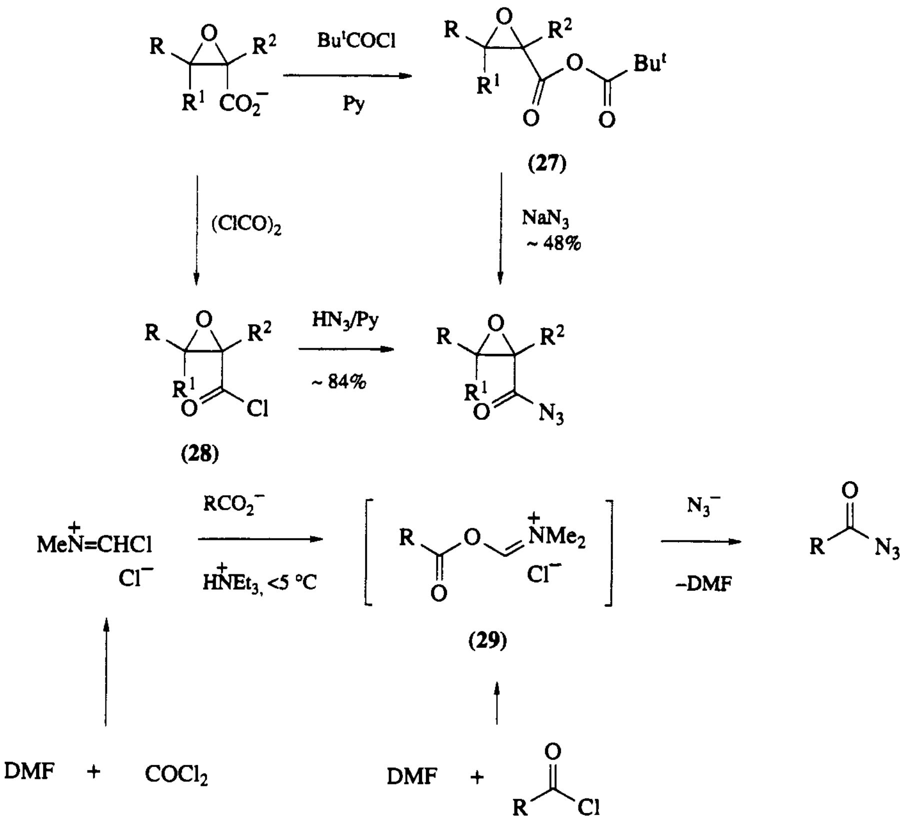
Bu$^t$COCl
Py
(27)
(ClCO)$_2$
NaN$_3$
~ 48%
HN$_3$/Py
~ 84%
(28)
RCO$_2^-$
$H\overset{+}{N}Et_3$, <5 °C
(29)
N$_3^-$
-DMF
DMF + COCl$_2$
DMF

**Scheme 39**

A slight deviation from the routine mechanism is found in the reaction of TMS-A with β-propiolactone (Scheme 40), which generates 75% of the azidosilyl ester (**30**).[144]

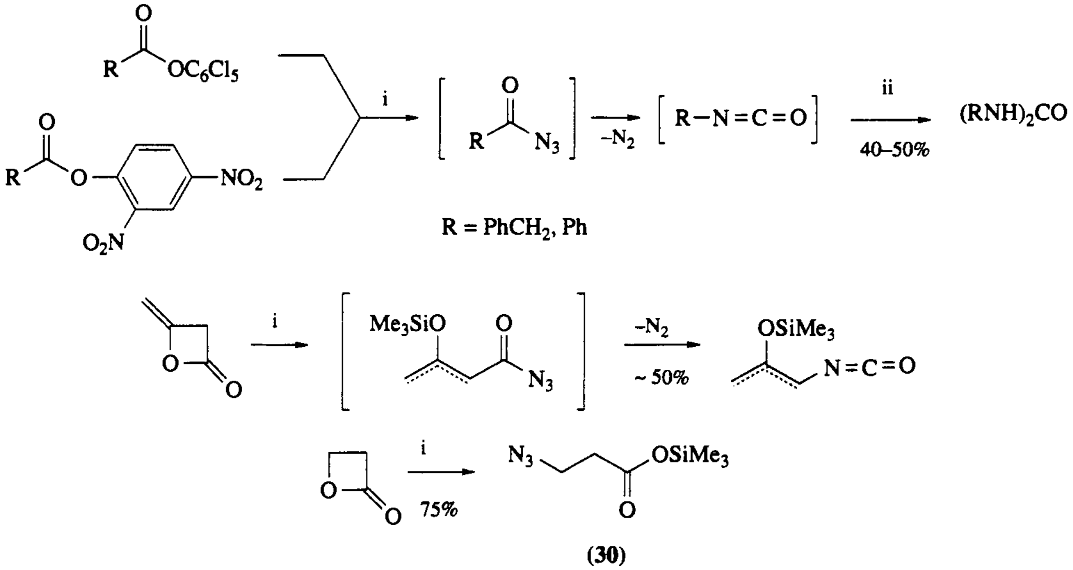
i
$-N_2$
ii
40–50%
(RNH)$_2$CO
R = PhCH$_2$, Ph
~ 50%
75%
(30)

i, Me$_3$SiN$_3$, [Py], dioxane, 100 °C; ii, RNH$_2$

**Scheme 40**

The transformation of aroyl chlorides with TMS-A can be run at 0 °C if a catalytic amount of $ZnI_2$ is used in $CH_2Cl_2$ (equation 32). This provides a simple and high-yielding route to aroyl azides, which may be isolated in a pure state.[146] Electron-donating groups in the aryl group retard the reaction, without, however, influencing yields.

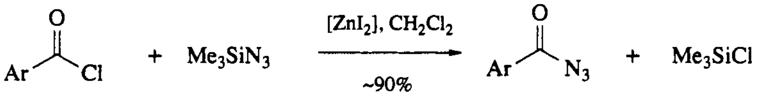

(32)

In a direct route from carboxylic acids to acyl azides diphenyl phosphorazidate is used;[121] probably the reaction passes through a cyclic transition state (Scheme 41). With aromatic and heteroaromatic educts, yields as high as 75% may be obtained.[147] If aliphatic acids are treated under the same conditions, the corresponding azides are, however, immediately transformed into urethanes *via* isocyanates.[148] Aroyl azides can also be obtained in excellent yields by reaction of carboxylic acids with $NaN_3$ and phenyl dichlorophosphate in the presence of tetrabutylammonium bromide or pyridine (Scheme 41).[149]

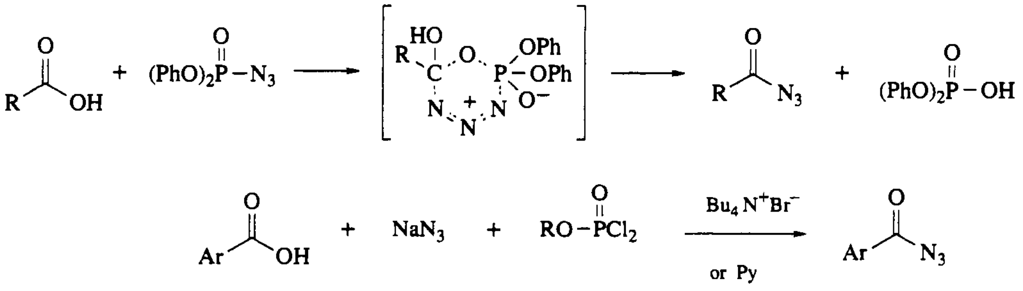

**Scheme 41**

The preparation of acid azides from thiocarboxylic acids/$HN_3$ or from acyl chlorides with dibenzyldimethylammonium azidosulfonate[119] has not yet found broad application (Scheme 42).

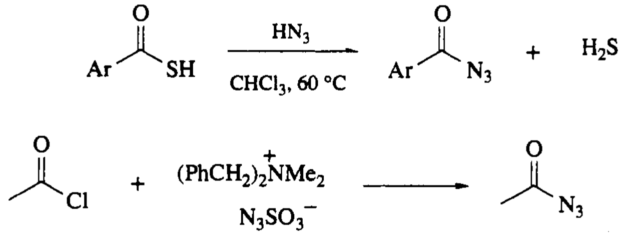

**Scheme 42**

There are great differences in the thermal stabilities of acyl azides. While the aromatic derivatives are considered to be comparatively stable, their aliphatic counterparts very often decompose close to room temperature. As in the course of this destruction the preparatively most useful Curtius rearrangement will take place, this instability is not necessarily a disadvantage.

Owing to the unpredictable tendency of most azides to explode suddenly, it is essential in the preparation of acyl azides to pay strict attention to the necessary precautions.

As demonstrated above, azidoformates, which, like the very similar carbamoyl azides (**30**; equation 33),[119,120,150] play an important role in peptide chemistry and as nitrene precursors,[119,120] can be generated in the usual way. Their thermal stability is generally higher than that of alkanoyl and aroyl azides. The tendency of acyl azides to form 1,2,3,4-oxatriazoles in a cyclization process is extremely low. In contrast to this thioacyl azides, which are only generated on treatment of thioxohydrazides with nitrous acid, seem to be only very short-lived intermediates, which immediately form 1,2,3,4-thiatriazoles as stable end products.[120]

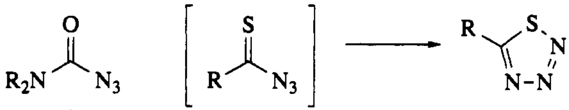

**(30)** (33)

### 1.8.4.2.4 *Further azides of the type RC(=X)N₃*

In the reaction of imidoyl halides with azide ions, imidoyl azides (**31**) are obtained, which caused some interest on account of their ring–chain tautomerism (**31**)/(**32**) (Scheme 43).[119,120] It is not possible, however, to discuss this point in detail here.[117,120,151] The final elucidation of a series of dubious structural assignments had to wait until the advent of modern spectroscopic methods. As expected, the position of this equilibrium is influenced by the nature of substituents R/R′ as well as by temperature and solvents. Electron-withdrawing ligands seem to favor the formation of the tetrazole isomer (**32**). The equilibrium (**31**)/(**32**) does not always operate — there are a number of cases known which show a comparatively high activation barrier.[120] The same problems are encountered with the reaction products from 2-halo-azoles and -azines with azide ions.[118–120]

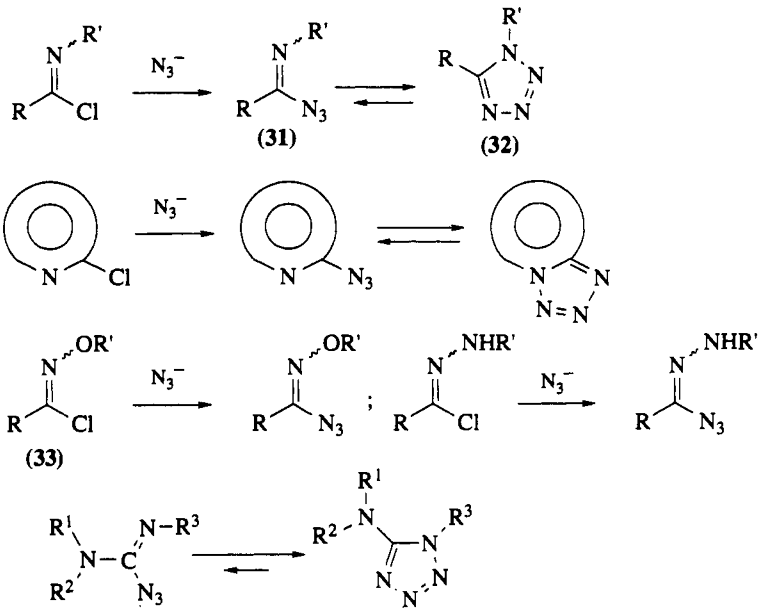

**(31)** **(32)** **(33)** **(34)**

**Scheme 43**

In a similar way to azidoazomethines, the corresponding azido oximes and hydrazides may be obtained (Scheme 43). The formation of cyclic tautomers seems to play only a minor role here.[117,119,120,152] The stereochemical aspects of the transformation of *O*-acylhydroxamoyl chlorides (**33**; R = $^-$Ac) with $N_3$ ions have been studied by Hegarty.[153] Further systems such as the interesting pairs guanyl azides (**34**)/5-aminotetrazoles, are comprehensively discussed by Lwowski.[120]

## 1.8.4.3 Azides by Exchange of Oxygen or Sulfur Functionality

Alcohols may be used in various ways as starting materials for azides. The well-known transformations *via* alkyl halides and sulfonates need not be discussed at this stage again (see Section 1.8.4.2.1). The activation of alcohols *via* phosphonium salts has found application in the carbohydrate series.[117]

The $S_N1$-type transformation of secondary and tertiary alkanols with the help of trichloroacetic acid and hydrazoic acid has also been mentioned in Section 1.8.4.2.1. Several azides, *e.g.* of the adamantane and diamantane series, have been obtained on treatment of the corresponding alcohols with $NaN_3$ and sulfuric acid.[154] As expected, this procedure lends itself particularly well to the formation of tertiary azides.[117] Treatment of tertiary carbinols with $HN_3$ and $BF_3$ or other Lewis acids represents another route to tertiary azido compounds.[117] On the other hand, with primary alcohols this procedure only succeeded when benzylic or allylic alcohols were used (Scheme 44), an observation which, together with the partial racemization noticed in the case of chiral educts, hints at carbenium ion intermediates.[117]

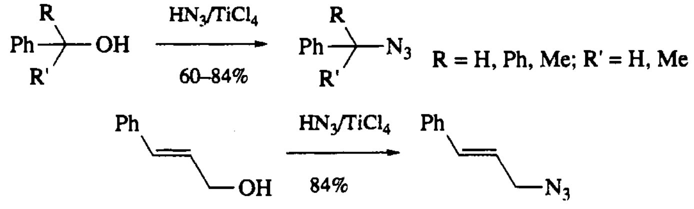

Scheme 44

Walden inversion, on the other hand, is observed in the reaction of alkanols with diethyl azodicarboxylate, triphenylphosphine and $HN_3$ (*cf.* the Mitsunobu reaction).[117,155] There is also some interest in the Pd-catalyzed transformation of allyl acetates into the corresponding azido derivatives.[156] Primary amines can be generated in a one-pot procedure without isolation of these azides, by further treatment with $Ph_3P$ and subsequent hydrolysis (Scheme 45).

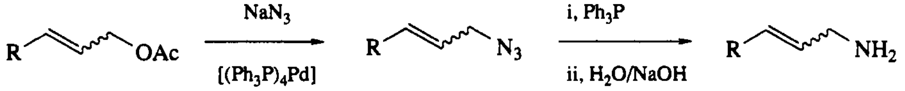

Scheme 45

The direct transformation of carboxylic acids into azides and the ring fission of β-lactones have been discussed in Section 1.8.4.2.3.

Opening of epoxides with azide ions represents a very interesting route to azidocarbinols. The large number of examples quoted in the literature proves the broad scope of this technique.[117-119,157] On treatment of nonsymmetrically substituted oxiranes, the products expected from an $S_N2$ process are usually obtained. In boiling aqueous dioxane, cyclohexene oxide gives rise to 61% of *trans*-2-azidocyclohexanol. The reported formation of (**35**; Scheme 46) with styrene oxide is unexpected,[158b] particularly if the formation of (**36**) from the analogous diphenyl precursor is considered.[158]

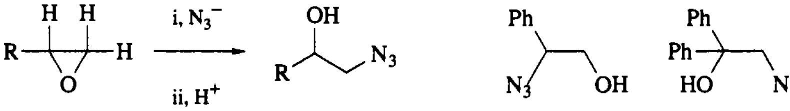

(**35**) 63% (**36**) 73%

Scheme 46

In a recent very thorough investigation, Behrens and Sharpless studied the possibilities for the selective transformation of 2,3-epoxy-carbinols, -acetals and -amides into azidoalkanols (Scheme 47).[159] The regioselectivity of this process turned out to be strongly dependent on steric as well as electronic parameters; it is not possible to discuss details here.

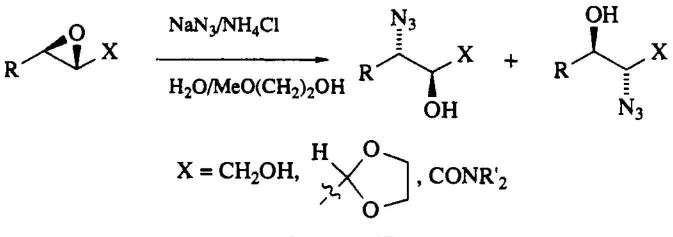

Scheme 47

The special merits of solid-supported sodium azide reagents were intensely investigated recently. Under well-defined reaction conditions very high regioselectivity may be achieved with nonsymmetrically substituted oxiranes.[160] A new approach to an especially mild and selective synthesis of 3-azidodiols was recently described, which involves a highly regio- and stereo-selective ring fission of epoxy alcohols, using TMS-A and $Et_2AlF$ (Scheme 48).[161] For comparison, some results with $NaN_3/NH_4Cl$ are also included.

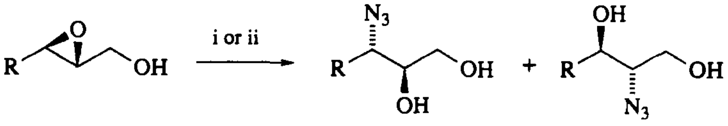
R
O
OH
i or ii
N3
R
OH
OH
+
OH
R
OH
N3

i, $Me_3Si\text{-}A/Et_2AlF$; R = $Pr^i$, 81%, 98:2; R = n-$C_7H_{15}$, 84%, 98:2;
ii, $NaN_3/NH_4Cl$; R = $Pr^i$, 78:22; R = n-$C_7H_{15}$, 90%, 53:47

Scheme 48

α-Azido ethers or even diazides can be obtained on treatment of acetals with $TMS\text{-}A/SnCl_4$ (Scheme 49).[162,163] TMS-A proved also to be the best reagent for the transformation of orthoesters (cyclic ones included) into the corresponding azido derivatives.[164] Cationic species are considered as intermediates.

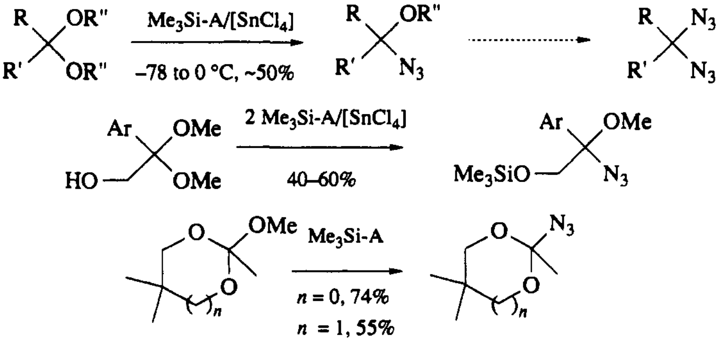
R
OR"
R'
OR"
Me3Si-A/[SnCl4]
-78 to 0 °C, ~50%
R
OR"
R'
N3
R
N3
R'
N3
Ar
OMe
HO
OMe
2 Me3Si-A/[SnCl4]
40–60%
Ar
OMe
Me3SiO
N3
O
OMe
O
n
Me3Si-A
n = 0, 74%
n = 1, 55%
O
N3
O
n

Scheme 49

Thioketals reacted with $IN_3$ to give α-azido sulfides or 1,1-diazides.[165] Treatment of the azido sulfides (**37**) with $SnCl_4$ led to the corresponding imino sulfides; these were also available directly from the thioketals (probably *via* azido sulfides) by reaction with $NaN_3/SnCl_4$ or with $TMS\text{-}A/SnCl_4$ and a catalytic amount of iodine (Scheme 50).

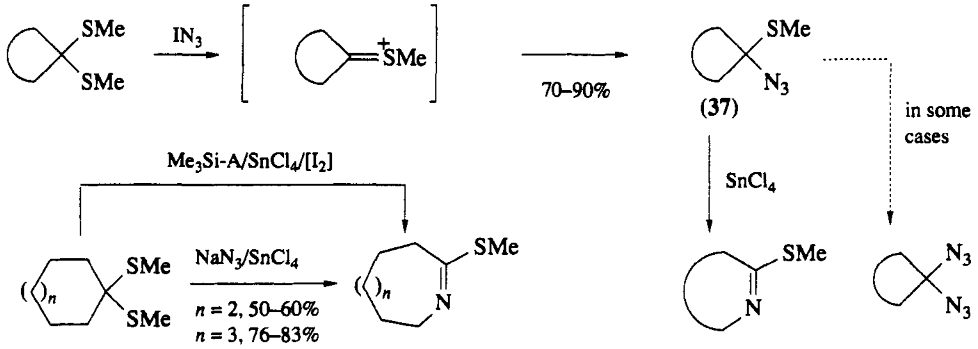
SMe
SMe
IN3
+
SMe
70–90%
SMe
N3
(37)
in some cases
SnCl4
Me3Si-A/SnCl4/[I2]
SMe
SMe
n
NaN3/SnCl4
n = 2, 50–60%
n = 3, 76–83%
SMe
N
n
SMe
N
N3
N3

Scheme 50

### 1.8.4.4 Azides by Exchange of Nitrogen Functionality

In an interesting technique for the preparation of aromatic azides, aryl diazonium salts are treated with azide ions.[117-119] At least in a very formal sense, one can consider this reaction as a substitution process, although the real mechanism of this transformation is much more complicated.[166] An excellent discussion of the mechanistic aspects of the reaction sequence is presented by Biffin *et al.*[119] Without going into details, Scheme 51 illustrates the chemistry involved. The preparative significance becomes obvious from a published table with about 15 examples; sometimes yields of more than 90% were obtained.[119] The aromatic ligand may carry a number of further functional groups and di- or tri-azides can be formed as well as heterocyclic azides. Starting with *N*-(aminophenyl)phthalimide, the azido derivative (**38**) is obtained *via* diazotization, followed by reaction with $HN_3$. Hydrazinolysis of the protecting phthaloyl group (Scheme 52) yields the otherwise inaccesible azidoanilines (**39**).[119] With the 4-, 5- or 6-aminoindoles a remarkable increase of azide yields was noticed when the formation of the diazonium salts was performed in 80% HOAc instead of diluted mineral acids (Scheme 53).[167]

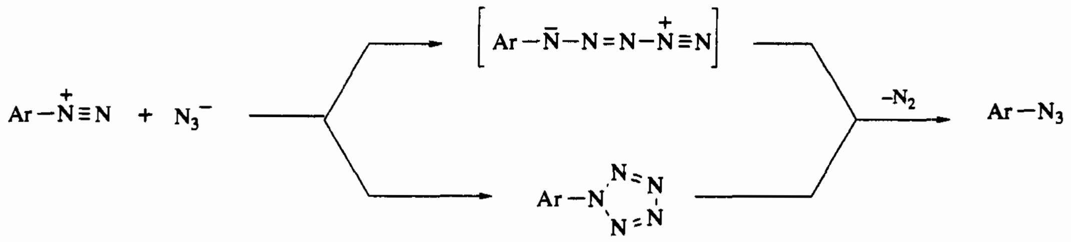

**Scheme 51**

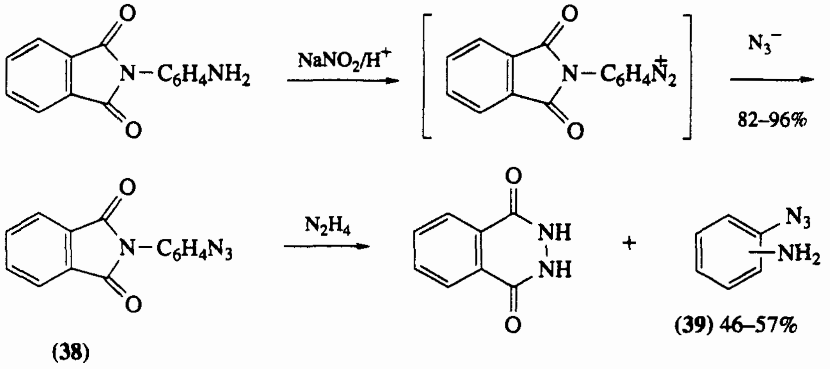

**Scheme 52**

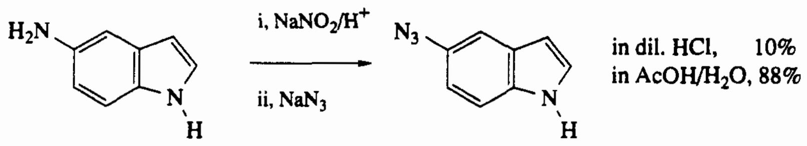

**Scheme 53**

Provided the starting materials are easy to obtain, the interesting reductive substitution of aromatic nitroso compounds (Scheme 54) is also a useful preparative technique.[118,119,168] The mechanistic aspects of the reaction sequence have been discussed.[119]

$$\mathrm{Ar{-}N{=}O} \xrightarrow{\mathrm{HN_3}} \left[\mathrm{Ar{-}N{=}N{-}OH}\right] \xrightarrow[\mathrm{-N_2}]{\mathrm{HN_3}} \mathrm{Ar{-}N_3}$$

**Scheme 54**

*N*-Alkyl and -benzyl substituents can be displaced from 2,4,6-triphenylpyridinium tetrafluoroborates by reaction with azide ions (Scheme 55). This method enables the conversion of primary alkyl- or benzyl-amines to the corresponding azides.[169]

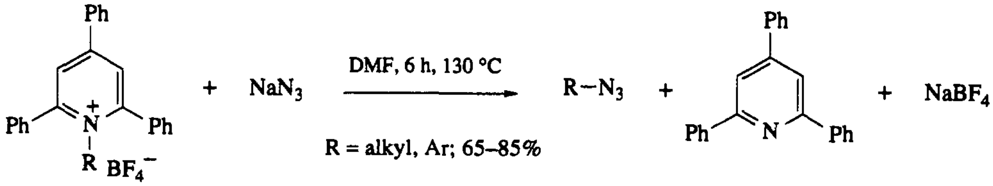

Scheme 55

### 1.8.4.5 Azides by Azide Transfer Reactions

The synthesis of various azido compounds with arene sulfonyl azides has, at least in a formal sense, to be considered as an electrophilic substitution of hydrogen by an azide function.[117,119,122] By this route a number of amines, cyclic derivatives and bridgehead compounds included, after deprotonation with NaH or Grignard reagents, could be transformed into azides in high yield on treatment with arene sulfonyl azides.[117,170] Details cannot be given here. Enolates can also be converted into azido derivatives in a very similar way, *via* triazene intermediates.[117] Evans *et al.*[171] did recently investigate the influence of the countercation, the structure of the transfer azide and work-up conditions on this process.

## ACKNOWLEDGMENTS

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# 1.9
# Ritter-type Reactions

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## 1.9.1 THE RITTER REACTION

The process now known as the Ritter reaction was first described in detail in two papers[1,2] published in 1948. Strongly acidic conditions were used to generate a carbenium ion which underwent nucleophilic attack by a nitrile, and further events leading to the isolated product. In its original and most familiar form, hydrolytic work-up produced an amide. However, later investigations showed that in suitable cases intramolecular cyclization could occur, affording a wide range of heterocyclic materials. Although this very general reaction is justly named for Ritter, who recognized and explored its considerable potential, it is not surprising that a few special cases of Ritter-type processes are described in earlier independent reports.[3–7] Early work on the Ritter reaction is well served by a number of review articles,[8–14] that by Krimen and Cota[12] being especially valuable in the present context.

### 1.9.1.1 Reaction Mechanism

The mechanism of the reaction is illustrated in Scheme 1 for the conversion of *t*-butanol, using sulfuric acid and acetonitrile, into *N*-*t*-butylacetamide. Three intermediates are involved. Firstly, a carbenium ion (**1**) is produced under strongly acidic conditions. This reacts with the nitrile to produce a resonance-stabilized nitrilium ion (**2**), which in turn is converted into the corresponding imidate (**3**). Finally, the latter is hydrolyzed to the amide. Since all three events occur in a one-pot process, frequently in high yield, the Ritter reaction is a simple, efficient and general synthetic procedure.

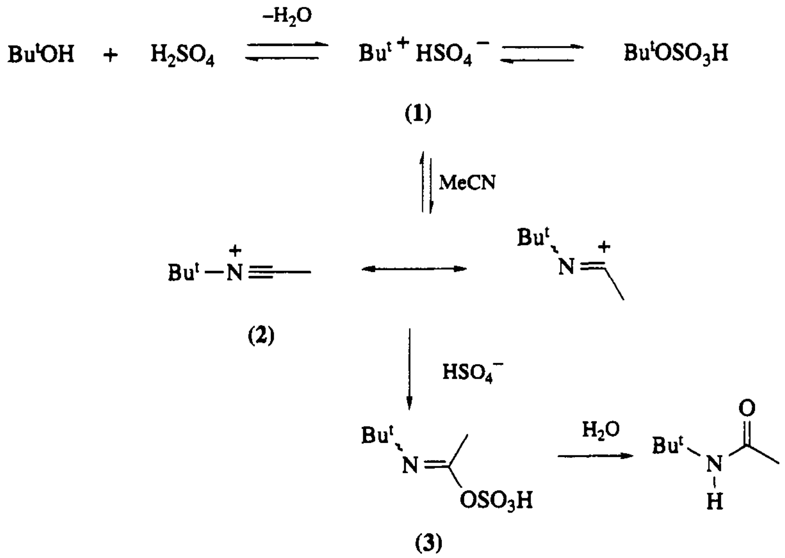

**Scheme 1**

As an alternative to amide formation, intramolecular cyclizations involving the nitrilium ion lead to a variety of heterocyclic systems (Section 1.9.2). Since carbenium ions, or their equivalents, may be produced by means other than strong acid, a number of valuable extensions of the original reaction are possible (Section 1.9.3). In addition, nitrilium and imidate species are also available through other processes, implying that the Ritter reaction has close mechanistic relationships with other well-established reactions and with the chemistry of the isonitriles. These aspects are explored in Section 1.9.4.

The essential details of the reaction mechanism were originally proposed by Ritter and his collaborators,[2,15] and only a brief description of the work supporting this reaction pathway will be presented here. Replacement of the nitrile with the corresponding amide resulted in failure of the reaction, demonstrating that addition of the amide and carbenium ion was not involved.[1] As part of a detailed study using oleic acid, Roe and Swern[16] were not only able to use a variety of acidic media to obtain amide products, but evidence of isomerization due to carbenium ion intermediates was also presented. This expected feature of the above mechanism was thoroughly investigated by Christol, a good illustration[17] of such rearrangement being formation of cation (4), and subsequent isolation of the amine (5), from each of the five alcohol precursors shown in Scheme 2.

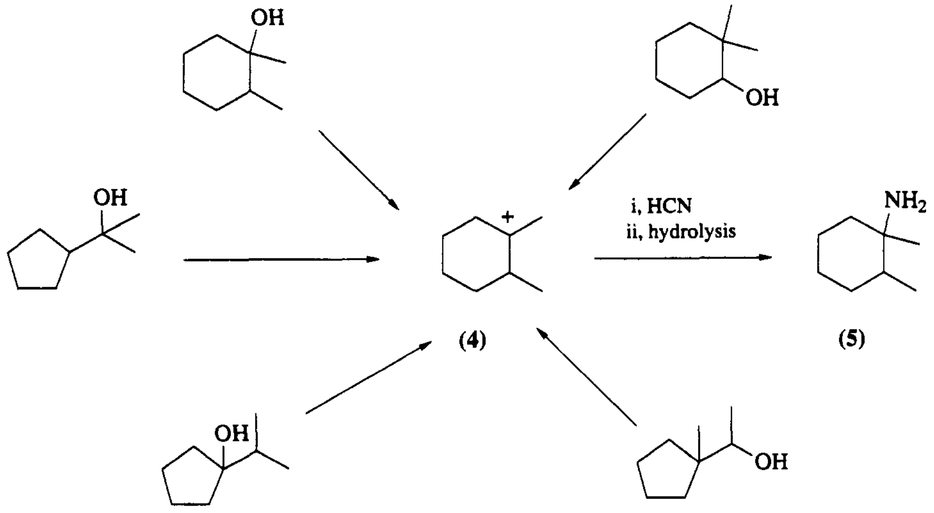

**Scheme 2**

Kinetic measurements on the reaction between *t*-butanol and acrylonitrile in 20–69% sulfuric acid showed it to be first order with respect to both reagents. This led Deno[18] to suggest that the transition state involved nucleophilic attack by the nitrile on the protonated alcohol. However, the latter might better be regarded as a weakly solvated carbenium ion and the process as an '$S_N$ intermediate' reaction.[19] In a later related study (isobutene and acrylonitrile) Glikmans[20] concluded that the reaction involved an ion pair and that the nitrile was associated with both partners in the transition state (**6**). Nitriles are only about half-protonated in 89–100% sulfuric acid and, therefore, nucleophilic behavior presents no difficulty.[21] Retro-Ritter reaction can occur when an *N*-*t*-alkylamide is treated with dehydrating agents such as thionyl chloride or phosphorus(V) oxide.[22] Carbenium ions generated by nonacidic routes also react with nitriles and yield amides on hydrolytic work-up (Section 1.9.3).

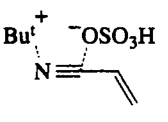

(**6**)

Evidence supporting the involvement of nitrilium ion intermediates is available from the large number of heterocyclic derivatives obtained by intramolecular trapping reactions.[14] Furthermore, independently generated nitrilium salts[23] undergo hydrolysis to Ritter products (Scheme 3).

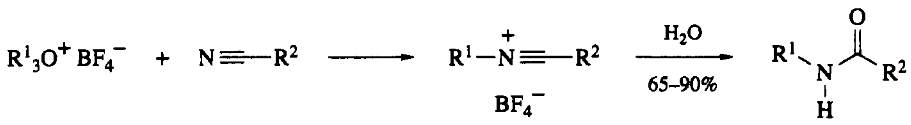

**Scheme 3**

Definitive evidence for the imidate intermediate was provided by Glikmans[24] in 1966. Reaction between isobutene and acrylonitrile in anhydrous acetic acid containing 100% sulfuric acid allowed isolation and characterization of (**7**), which was readily hydrolyzed to the corresponding amide by dehydration of acetic acid (equation 1). Subsequent work by Norell[25] on reactions of alkenes with nitriles in anhydrous liquid hydrogen fluoride allowed isolation of imidoyl fluorides such as (**8**) for the first time. Such materials, obtained pure and fully characterized, react instantly with water to yield the amide (Scheme 4).

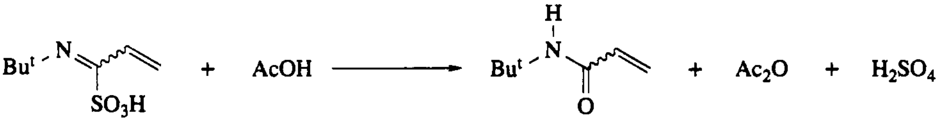

(**7**) (1)

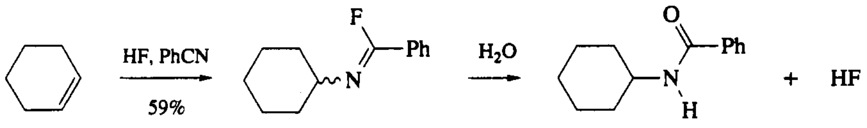

(**8**)

**Scheme 4**

### 1.9.1.2 Reaction Conditions

The precise experimental conditions used can greatly influence the efficiency, or even the course, of the Ritter reaction. Representative procedures are available, along with a comprehensive tabular survey to 1966, in the article by Krimen and Cota.[12] Optimum reaction times (typically 1–24 h) and temperatures (typically 20–50 °C) depend very much on the particular cases. Typical temperatures of 0–10 °C are used when hydrogen cyanide or hydrogen fluoride are employed. Benzenesulfonic, fluoroboric, formic, hydrofluoric, methanesulfonic, perchloric, phosphoric, polyphosphoric, sulfuric, toluenesulfonic and trifluoromethanesulfonic acids are amongst those used to generate the carbenium ion. However, the majority of workers favor sulfuric acid and, in cases where comparative studies have been carried out,[16,24,26] this reagent generally gave the best yields. This may reflect participation of the hydrogensulfate ion during attack by the nitrile reagent.

The best acid concentration depends on the type of substrate[26] but usually 85–90% sulfuric acid is employed. Similarly, for hydrofluoric acid the optimum concentration was 90–100% for linear alkenes and 60–75% for branched alkenes.[27] The function of the water present may be to suppress side reactions by enabling rapid hydrolysis of the imidate to the stable amide product. However, it will also increase the solvent polarity, which is known to enhance the nucleophilicity of the nitrile through solvation and polarization effects.[28] Frequently the reaction is performed using just the nitrile and acid as solvents, but any additional diluent should be polar. Glacial acetic acid is most commonly used, although acetic anhydride, di-*n*-butyl ether, nitrobenzene and dioxane have also found favor. Nonpolar solvents such as carbon tetrachloride or hexane give poor yields,[28] and the reaction fails in the presence of methanol or ethanol.[24] Although acetic acid is the best diluent, formation of acetates can be a significant side reaction,[24,29] and in other cases dilution prevents reaction.[15]

Lewis acids such as tin(IV) chloride,[30] boron trifluoride–acetic acid[16] and boron trifluoride–etherate,[31] are also effective in promoting the Ritter reaction. In general, the original technique is more efficient, but use of Lewis acids can sometimes significantly influence the proportions of products in a mixture and has advantages when relatively sensitive substrates are present.

In reactions where rearrangement is likely, a rule of thumb is that the most stable available carbenium ion will lead to the product. Such thermodynamic control may be used deliberately to carry out complex rearrangements in high yields for suitable cases.[12] When the potential carbenium ions are of similar energy, for example in Ritter reactions of unsaturated fatty acids or esters, then mixtures of products are likely. In such cases, mass spectrometry has proved to be a particularly useful analytical technique.[32,33]

The outcome of the Ritter reaction can also be determined by kinetic control. For example, conflicting reports have appeared in the literature regarding the behavior of alcohol (**9**), the alternative products (**10**)[34] or (**11**)[35] both having been reported. These differences result from the order of addition of the reagents.[36] The amides (**10**) result if the alcohol is mixed first with the nitrile and acetic acid, the sulfuric acid being added last. In this instance (kinetic control), the initial cations are reacted to (**10**) as they are produced. Conversely, if (**9**) is mixed first with the acids, and then the nitrile is added, the products (**11**) result. In this case (thermodynamic control) carbenium ion rearrangement precedes Ritter reaction (Scheme 5). For less clear-cut cases, the use of less acidic conditions and/or lower temperature results in greater isomer selectivity, but at the cost of lower overall yields.[27]

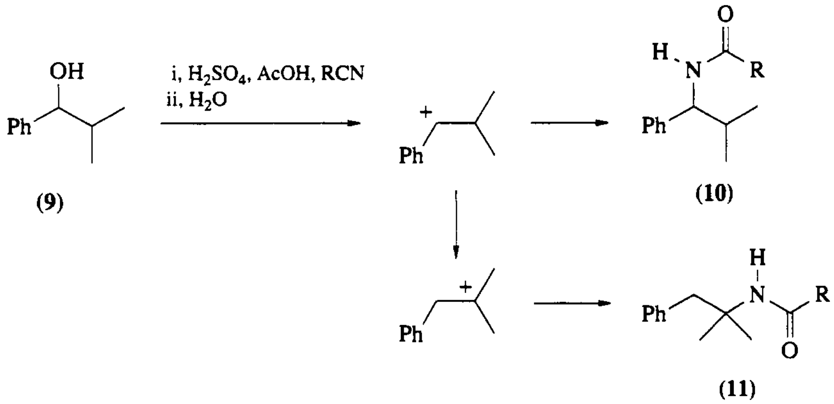

Scheme 5

A good illustration of the interplay of reaction conditions with product formation is provided by the work of Sasaki *et al.*[37] on reactions of 1-hydroxymethyladamantane (**12**) and 3-homoadamantanol (**13**) with sulfuric acid and acetonitrile (Scheme 6). Under a variety of experimental conditions, both alcohols gave a mixture of the acetamides (**14**) and (**15**), but in quite different proportions and total conversions. A selection of these data is present in Table 1. For each entry, a mixture of the alcohol (1.2 mmol) and acetonitrile (76.5 mmol) was added to stirred sulfuric acid (1.5 ml). For the later experiments, $AlCl_3$ (0.6 g) or $BF_3–Et_2O$ (1.5 ml) were added first to the $H_2SO_4$.

The results without Lewis acid demonstrate that the homoadamantane (**14**) is the kinetic product and that the adamantane (**15**) is the thermodynamic product. Addition of Lewis acid to either alcohol decreased the yield of amides. However, while aluminum chloride increased the proportion of the kinetic product, the use of boron trifluoride etherate boosted the proportion of the thermodynamic product.

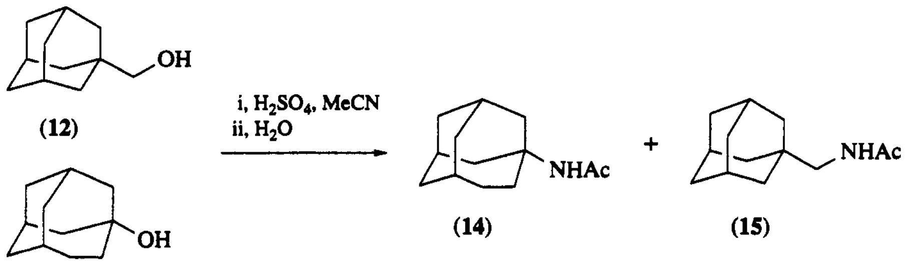

(12)

(13)

(14)

(15)

**Scheme 6**

**Table 1** Correlation of Reaction Conditions for Alcohols (**12**) and (**13**) with the Resulting Kinetic (**14**) and Thermodynamic (**15**) Amide Products[37]

| *Reagent(s)* | *Conditions* | | *Total yield of amides* (%) | *Relative yields* (%) | |
|---|---|---|---|---|---|
| | *Temperature* (°C) | *Time* (h) | | *(14)* | *(15)* |
| (**12**) | 15 | 1 | 20 | 66 | 34 |
| (**12**) | 15 | 24 | 42 | 10 | 90 |
| (**12**) | 50 | 1 | 40 | 2.9 | 97.1 |
| (**12**) | 50 | 24 | 92 | 0.2 | 99.8 |
| (**13**) | 15 | 24 | 93 | 16.5 | 83.5 |
| (**13**) | 50 | 24 | 98 | 10 | 90 |
| (**12**), $AlCl_3$ | 15 | 24 | 23 | 92 | 8 |
| (**12**), $AlCl_3$ | 15 | 96 | 42 | 17 | 83 |
| (**13**), $AlCl_3$ | 15 | 24 | 72 | 31 | 69 |
| (**13**), $BF_3$–$Et_2O$ | 15 | 24 | 76 | 3 | 97 |

### 1.9.1.3 The Nitrile Component

In general, most compounds containing a nitrile group undergo reaction with carbenium ions.[1] Not only are hydrogen cyanide, aliphatic nitriles and aromatic nitriles all effective reagents but the process also occurs with varying degrees of efficiency for nitrile derivatives such as cyanamide, cyanogen and dicyandiamide. Nitriles bearing other functional groups undergo efficient Ritter reaction provided the materials are acid stable, a striking illustration being the tetracycline derivative (**16**; equation 2).[38] Cyanohydrins also undergo Ritter reaction without interference from the hydroxy substituent (equation 3).[39]

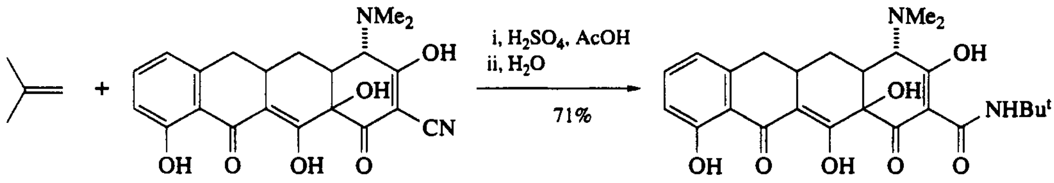

(2)

(**16**)

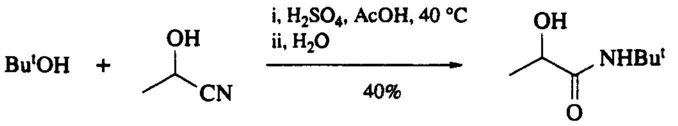

(3)

Conjugated unsaturated nitriles such as acrylonitrile[1] or fumaronitrile (**17**; equation 4)[39] are effective Ritter reagents. More recent work has shown that this is also true of conjugated allenic[40] and alkynic nitriles,[41] as shown in equation (5) and Scheme 7, respectively. Suitably functionalized propiolamides such as (**18**) are readily cyclized, allowing facile preparation of the oxazoline (**19**).[41,42]

Dinitriles such as (**17**) can be used to prepare bisamides or, alternatively, can provide an excellent source of polyamides if glycol, diene,[43] or aldehyde[44,45] carbenium ion sources are utilized.

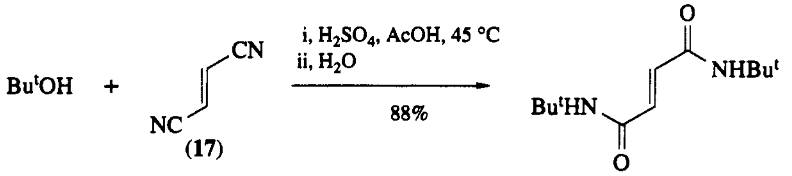

(4)

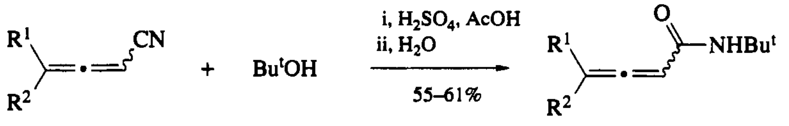

(5)

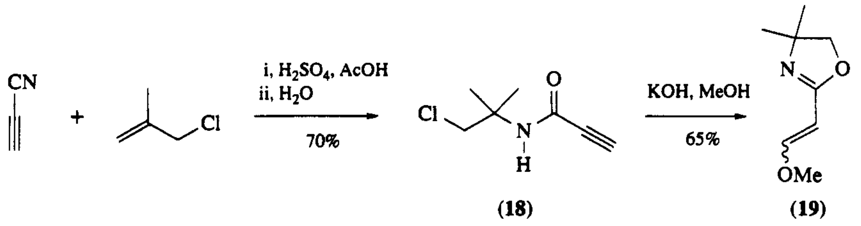

Scheme 7

Hydrogen cyanide, used either directly or generated from cyanide ion *in situ*, is an especially important nitrile source because the *N*-*t*-alkylformamide products can be readily hydrolyzed to the corresponding *N*-*t*-alkylamines.[2] Such materials, frequently of pharmacological interest,[46] could be obtained in principle by either basic or acidic hydrolysis of *N*-*t*-alkylamides. However, alkaline hydrolysis of these compounds can be surprisingly difficult to carry out in some cases.[16] For example, Ritter and Minieri[1] found that *N*-*t*-octylacetamide required prolonged reflux with 0.4 M potassium hydroxide in ethylene glycol to obtain the optimum yield of amine (**20**; equation 6). Under the same conditions, only a 27% conversion of *N*-*t*-amylacetamide was achieved. In contrast, preparation of *N*-*t*-butylamine (**21**) *via* the formamide route (Scheme 8) was possible with shorter reaction time, lower temperature, and in higher yield.[1] Although reagents such as hydrazine,[47] diisobutylaluminum hydride,[48] lithium diethylamide[49] and triethyloxonium tetrafluoroborate[50] have been used in hydrolysis of recalcitrant amides, such difficulties are best avoided by use of the formamide where possible.

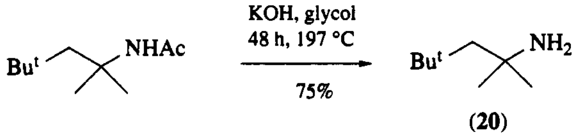

(6)

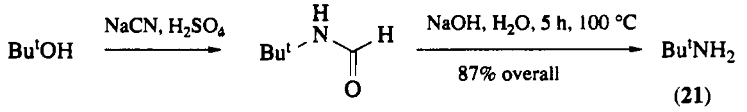

Scheme 8

Although *N*-*s*-alkylamides are hydrolyzed to the corresponding amines under acidic conditions,[51] the *N*-*t*-alkyl derivatives usually undergo alkyl–nitrogen fission, producing alkene or alcohol fragments.[52] Hydrolysis of 3-acetamidohomoadamantane (**22a**) using hydrochloric acid produced a mixture of the compounds (**23a**) and (**24**), while the 1-acetamido isomer (**22b**) gave only chloride (**23b**; equation 7). The absence of amine products from these reactions[53] once again indicates the ease of $A_{AL}1$ hydrolysis[52] to the carbenium ion. If the acidic hydrolysis is conducted in the presence of ethanol, then adamantyl- and homoadamantyl-amides undergo ready deamidation. In this process, illustrated by equation (8), the ethanol acts as a hydride donor, reducing the cation to the hydrocarbon.[54]

A mechanistic limitation of the Ritter reaction is that, while *N*-alkylformamides (and thence primary amines) are readily available, further direct substitution on nitrogen is ruled out. However, simple *N*-alkylation of the formamide may be performed utilizing phase-transfer catalysis. This provides a conven-

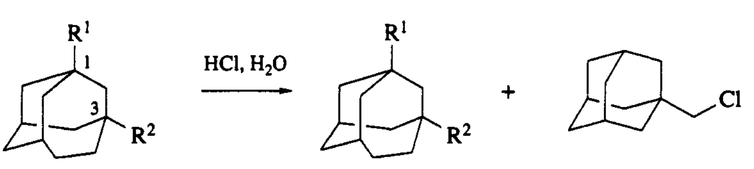
R$^1$
1
3
R$^2$
HCl, H$_2$O
R$^1$
R$^2$
+
Cl

(7)

**(22)** a: R$^1$ = H, R$^2$ = NHAc
b: R$^1$ = NHAc, R$^2$ = H

**(23)** a: R$^1$ = H, R$^2$ = OH, 50%
b: R$^1$ = Cl, R$^2$ = H, 98%

**(24)** 49%

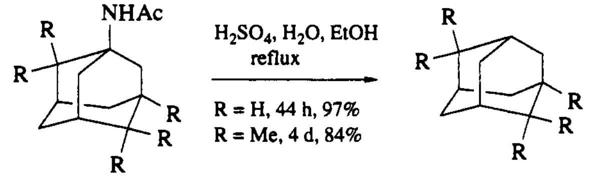
NHAc
R
R
R
R
R
H$_2$SO$_4$, H$_2$O, EtOH
reflux
R = H, 44 h, 97%
R = Me, 4 d, 84%
R
R
R
R
R

(8)

ient indirect route to the *N*,*N*-dialkylformamides (**25**) and the corresponding secondary amines (Scheme 9).[55]

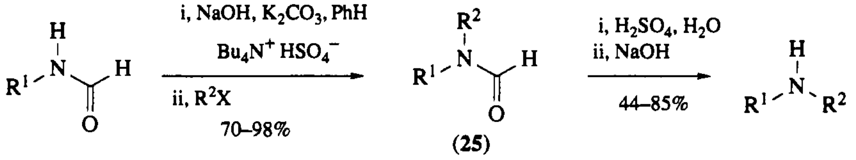
H
R$^1$
N
H
O
i, NaOH, K$_2$CO$_3$, PhH
Bu$_4$N$^+$ HSO$_4^-$
ii, R$^2$X
70–98%
R$^2$
R$^1$
N
H
O
(25)
i, H$_2$SO$_4$, H$_2$O
ii, NaOH
44–85%
H
R$^1$
N
R$^2$

**Scheme 9**

### 1.9.1.4 The Carbenium Ion Source

In principle, any functionality capable of producing a carbenium ion under strongly acidic conditions will be able to participate in a Ritter-type reaction. Such classes of compounds include alcohols, aldehydes, alkanes, alkenes, alkyl halides, carboxylic acids, dienes, epoxides, esters, ethers, glycols, ketones, *N*-methylolamides and oximes. Consequently, an enormous number of examples is reported and only a representative selection can be presented here. A comprehensive listing of examples reported up to 1966 is provided in the review by Krimen and Cota.[12]

Despite the range of sources available, the majority of reactions described have used alcohol or alkene precursors. This reflects both the availability of such materials and their ease of reaction. Typical examples of alkene reagents are shown in equations (9),[56] (10),[30] (11)[24] and (12).[57] When two reactive groups are in close proximity in the substrate it is possible to combine transannular cyclization with Ritter reaction (equation 13).[58,59]

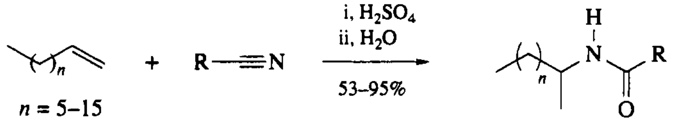
n
n = 5–15
+
R—≡N
i, H$_2$SO$_4$
ii, H$_2$O
53–95%
H
N
R
n
O

(9)

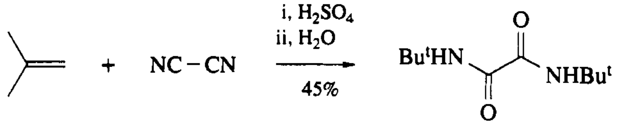
+
NC – CN
i, H$_2$SO$_4$
ii, H$_2$O
45%
O
Bu$^t$HN
NHBu$^t$
O

(10)

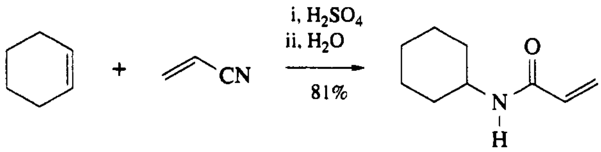
+
CN
i, H$_2$SO$_4$
ii, H$_2$O
81%
O
N
H

(11)

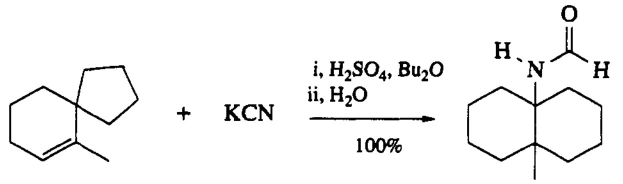
+ KCN
i, H₂SO₄, Bu₂O
ii, H₂O
100%
O
H
N
H

(12)

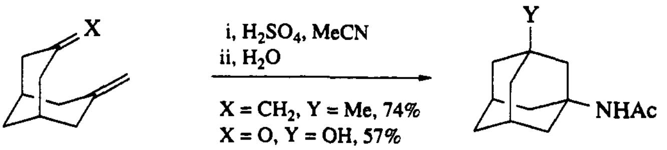
X
i, H₂SO₄, MeCN
ii, H₂O
X = CH₂, Y = Me, 74%
X = O, Y = OH, 57%
Y
NHAc

(13)

Tertiary alcohols tend to react without rearrangement while secondary alcohols are liable to do so, equations (14)[60] and (15),[28] as discussed in Section 1.9.1.2. Primary alcohols normally fail to react with nitriles even under severe conditions,[15] but this restriction does not apply to benzylic examples (equation 16).[29] In appropriate cases,[61] the Ritter reaction can be stereoselective (Scheme 10). Either alcohol isomer, separately or as a mixture, gave identical mixtures of the two amine products, showing that axial attack on the cation was predominant.

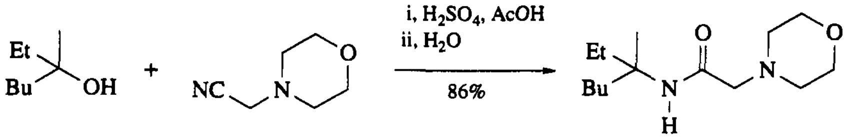
Et
Bu
OH
+
NC
N
O
i, H₂SO₄, AcOH
ii, H₂O
86%
Et
Bu
N
H
O
N
O

(14)

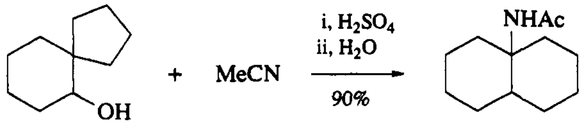
OH
+ MeCN
i, H₂SO₄
ii, H₂O
90%
NHAc

(15)

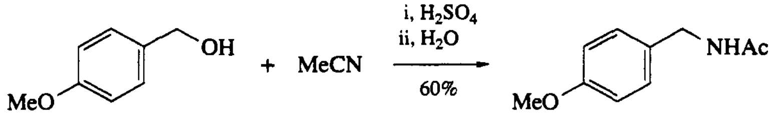
OH
MeO
+ MeCN
i, H₂SO₄
ii, H₂O
60%
NHAc
MeO

(16)

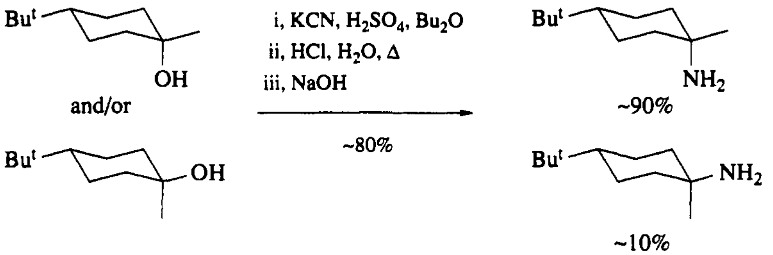
Buᵗ
OH
and/or
Buᵗ
OH
i, KCN, H₂SO₄, Bu₂O
ii, HCl, H₂O, Δ
iii, NaOH
~80%
Buᵗ
NH₂
~90%
Buᵗ
NH₂
~10%

**Scheme 10**

In cases where more than one functional group is present in the substrate, it is usually an alcohol group which is preferred for Ritter reaction, although there are exceptions such as ricinoleic acid.[33] Examples shown here are the diisophorane derivative (**26**; equation 17)[62] and the alkynic alcohol (**27**; Scheme 11).[63] The latter compounds undergo Ritter reaction in only moderate yields because of competing Meyer–Schuster rearrangement to the unsaturated ketone in some cases. Hydrolysis of the product provides either the alkynic amine or, in the case of (**28**), the amino ketone, which undergoes selfcondensation to the dihydropyrazine (**29**). Combination of these processes into a one-pot reaction gives the latter in 54% overall yield.[64]

Similarly, *N*-methylolamides[7] (equation 18)[65,66] and substituted oximes (Scheme 12)[67,68] react specifically through their hydroxy group. Hydroxy esters afford either amido esters[69] or amido acids[70] (equation

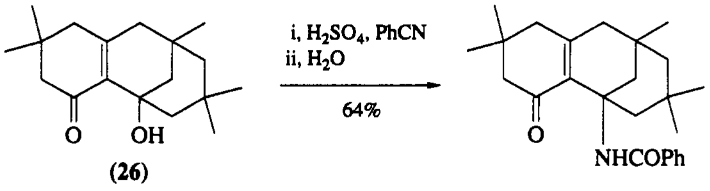
i, H2SO4, PhCN
ii, H2O
64%
O
OH
O
NHCOPh

(26)

(17)

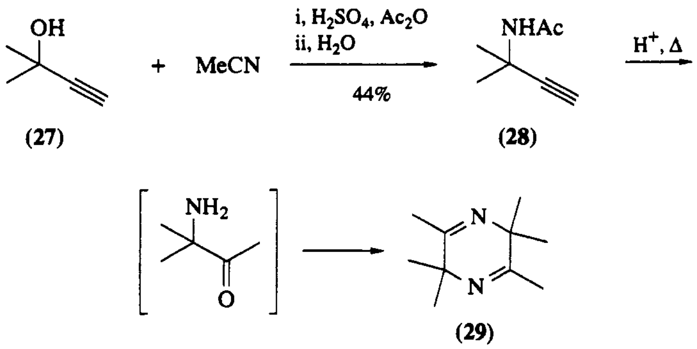
OH
+ MeCN
i, H2SO4, Ac2O
ii, H2O
44%
NHAc
H+, Δ
NH2
O
N
N

(27) (28) (29)

Scheme 11

19), depending on the conditions used. Increased substitution in the starting material results in lower yields due to competing elimination processes.[71,72] Esters of *t*-alcohols should be avoided since these may be regarded as masked *t*-carbenium ions and can participate in Ritter reactions in their own right. Thus, triphenylmethyl formate[73] or *t*-butyl acetate[20,74] produce excellent yields of *N*-*t*-alkylamides when heated with nitriles in the presence of sulfuric acid (equations 20 and 21).

Magat[75] first reported the use of *t*-alkyl halides as Ritter reaction substrates but, in general, these were less satisfactory than the use of the corresponding alcohol or alkene analogs. This process has since come into its own for polycyclic systems, where simple methods of generating bridgehead halides are often available. An early example is Stetter's conversion[76] of 1-bromoadamantane to the acetamide (**30**), there-

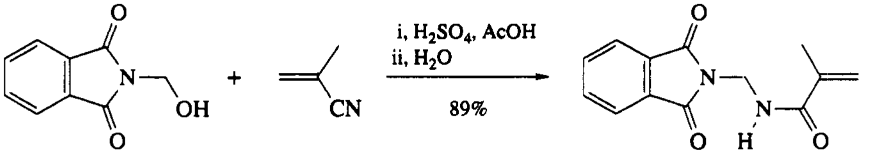
O
N
OH
O
+
CN
i, H2SO4, AcOH
ii, H2O
89%
O
N
N
O H O

(18)

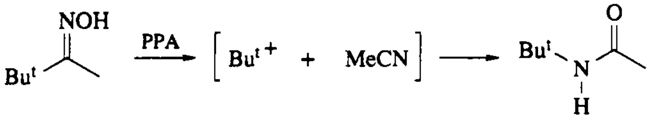
NOH
Bu^t
PPA
Bu^t+ + MeCN
O
Bu^t
N
H

Scheme 12

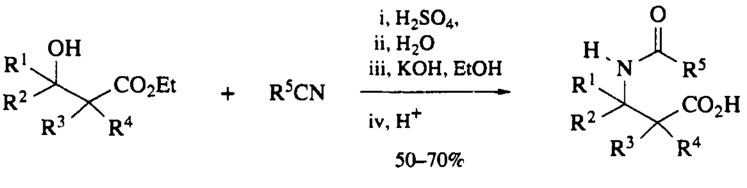
R1
OH
R2
CO2Et
R3 R4
+ R5CN
i, H2SO4,
ii, H2O
iii, KOH, EtOH
iv, H+
50–70%
H
N
O
R5
R1
R2
CO2H
R3 R4

(19)

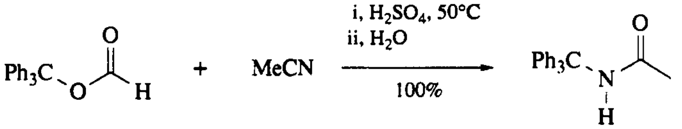
O
Ph3C
O
H
+ MeCN
i, H2SO4, 50°C
ii, H2O
100%
O
Ph3C
N
H

(20)

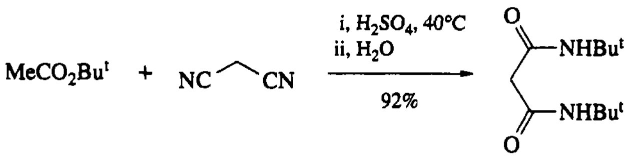

(21)

by providing a simple route to 1-aminoadamantane (**31**; Scheme 13). The discovery that (**31**) alleviates symptoms of Parkinsonism and exhibits antiviral behavior against influenza A[77] has led to considerable interest in the synthesis and testing of related polycyclic amino compounds. A number of these also show significant antiviral activity.

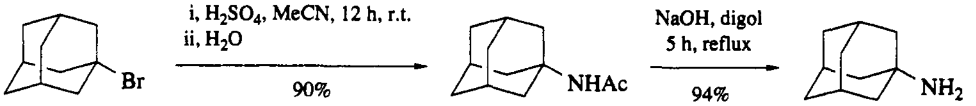

**(30)** **(31)**

**Scheme 13**

Saturated hydrocarbons capable of yielding a *t*-carbenium ion can participate directly in the Ritter reaction[78] provided a suitable hydride acceptor is present, or more efficiently using nitrosonium hexafluorophosphate (equation 22).[79] More recently, Inamoto[80] has described an elegant process whereby bridgehead bromination and Ritter reaction are performed in one step. This procedure is highly efficient for the functionalization of a number of tricyclic hydrocarbons, including conversion of 4-homotwistane (**32**) directly into its 3-acetamido derivative (**33**; equation 23). Although most halides used have been bromides, a recent report[81] indicates that this is not essential. Although the fluorotrishomocubane (**34a**) required more forcing conditions than its bromo analog (**34b**), the yields of amide obtained were identical (equation 24).

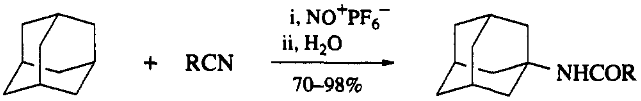

(22)

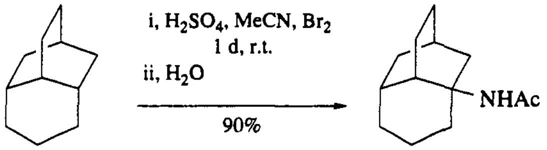

(23)

**(32)** **(33)**

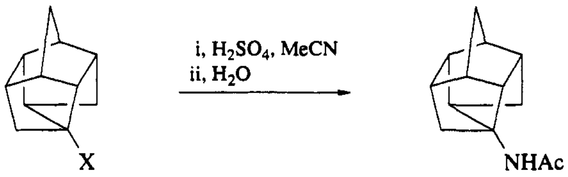

(24)

(**34**) **a**: X = F; 5 h, 95 °C, 61%
**b**: X = Br; 12 h, 20 °C, 62%

In 1876 Hepp and Spiess[3,4] reported that aldehydes react with nitriles under acidic conditions to yield geminal bisamides (equation 25). This process proceeds by a mechanistic pathway which is essentially two consecutive Ritter reactions.[26] In general, ketones do not yield similar products; however, Kozlov[82] has recently obtained a low yield of the geminal bisamide from camphor and acetonitrile. High yields of analogous products from cyclopentanone and cyclohexanone have also been reported.[83]

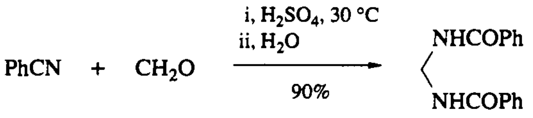

$$\mathrm{PhCN} + \mathrm{CH_2O} \xrightarrow[\text{90\%}]{\text{i, } H_2SO_4\text{, 30 °C; ii, } H_2O} \left\langle \begin{matrix}\mathrm{NHCOPh}\\ \mathrm{NHCOPh}\end{matrix}\right. \qquad (25)$$

More typical behavior of ketones is a condensation process yielding β-acylamino ketones. This process was first reported by Bruson *et al.*[84] who reacted cyclohexanone and nitriles in the presence of anhydrous aluminum chloride and obtained products now known[44] to have the structure (**35**). Such reactions were later studied in more detail by Khorlin[85] using conventional Ritter conditions. β-Acylamino ketones were obtained only from ketones capable of undergoing condensations to produce α,β-unsaturated ketones or ketols, suggesting the intermediacy of such structures in the reaction. This process is shown for acetophenone in Scheme 14. It is well established that α,β-unsaturated acids, esters and ketones yield similar products under Ritter reaction conditions.[69,70]

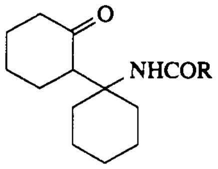

(**35**)

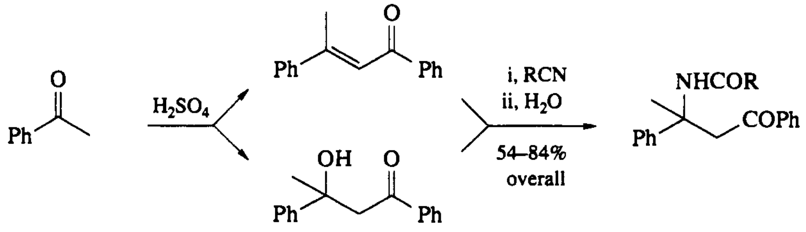

**Scheme 14**

Epoxides react efficiently with nitriles in the presence of either mineral or Lewis acids. Much of this work has been carried out on steroidal systems, which has allowed ready stereochemical analysis of the process. Such reactions yield specifically the *trans*-diaxial α-amido alcohol product, examples from the cholestanol series being shown in equations (26)[86] and (27).[87] Similar stereospecific results can also result from suitable aliphatic cases, as demonstrated by the reaction of methyl *trans*-2-epoxystearate yielding only the *erythro* isomer (**36**; equation 28).[88]

As final examples of the versatility of the Ritter reaction, bridged hemiacetals react by means of their acyclic form in solution to afford amido ketones in good yield (equation 29),[89] while halohydrins give α-amido halides, which are readily cyclized to oxazoline derivatives in an overall stereospecific process.[90]

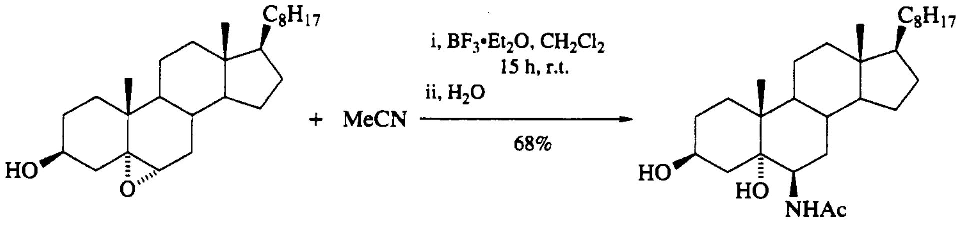

(26)

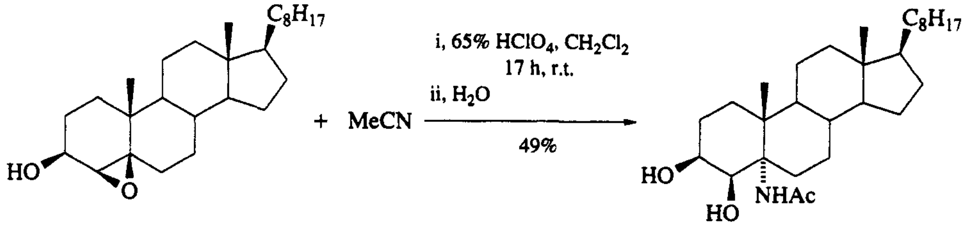
C8H17
HO
O
+ MeCN
i, 65% HClO4, CH2Cl2
17 h, r.t.
ii, H2O
49%
C8H17
HO
HO
NHAc

(27)

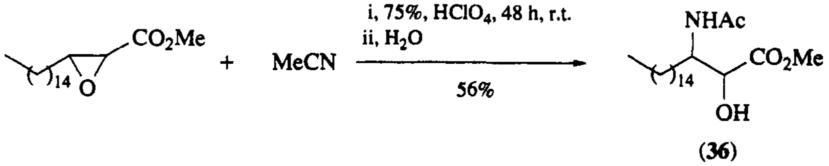
CO2Me
14
O
+ MeCN
i, 75%, HClO4, 48 h, r.t.
ii, H2O
56%
NHAc
CO2Me
14
OH

(28)

(36)

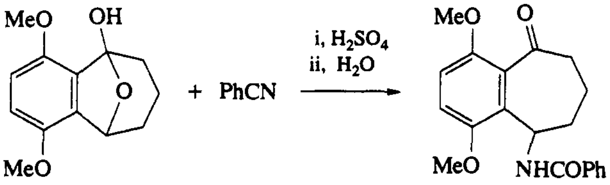
MeO
OH
O
MeO
+ PhCN
i, H2SO4
ii, H2O
MeO
O
MeO
NHCOPh

(29)

## 1.9.2 THE INTRAMOLECULAR RITTER REACTION

The pathways by which nitrile groups can be utilized in the construction of heterocyclic systems have been reviewed by Meyers and Sircar.[14] Two of these routes constitute intramolecular variants of the Ritter reaction and, therefore, are discussed here in detail.

The more common process commences in the normal way, with addition of nitrile and carbenium ion generating a nitrilium species. However, the latter now undergoes intramolecular cyclization with a nucleophilic group in the same molecule to produce a heterocycle of structure (37; Scheme 15). The less common reaction involves initial intramolecular formation of a cyclic nitrilium ion which is then quenched by an external nucleophile, giving products of type (38).

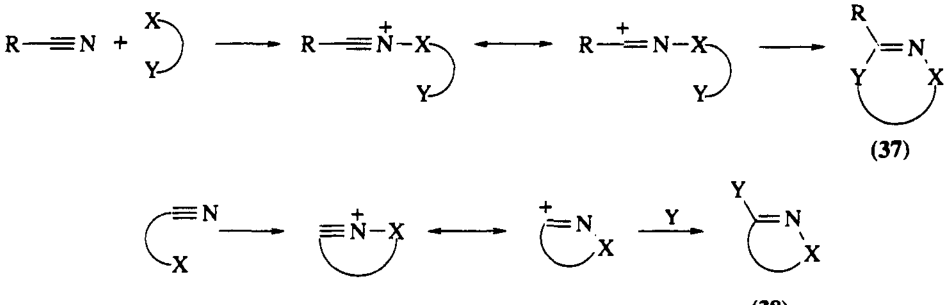
R
N
+
X
Y
R
N
X
Y
+
R
N
X
Y
+
R
N
Y
X
(37)
N
X
N
X
+
N
X
+
Y
Y
N
X

(38)

X = schematic electrophilic group; Y = schematic nucleophilic group

Scheme 15

Only specific ring sizes are available from these procedures since they are constrained by the configuration of the nitrilium intermediate (Section 1.9.4), in addition to the usual factors influencing intramolecular reactions.

### 1.9.2.1 Intramolecular Cyclization of the Nitrilium Ion

In 1952, Ritter and Murphy[91] reported cases of intramolecular Ritter behavior resulting in formation of dihydroisoquinolines from reactions of methyleugenol with nitriles such as veratronitrile (equation 30). Such reactions involve nucleophilic attack by the aromatic ring on the nitrilium ion and are enhanced by the use of Lewis acids. Meerwein[23] reacted a wide range of nitrile–Lewis acid complexes with alkyl and acyl halides, obtaining nitrilium salts such as (**39**) which were readily hydrolyzed to the corresponding amide. A significant advantage of this approach, as illustrated in Scheme 16, is that this Ritter-type process is no longer restricted just to *N*-*t*-alkyl derivatives.

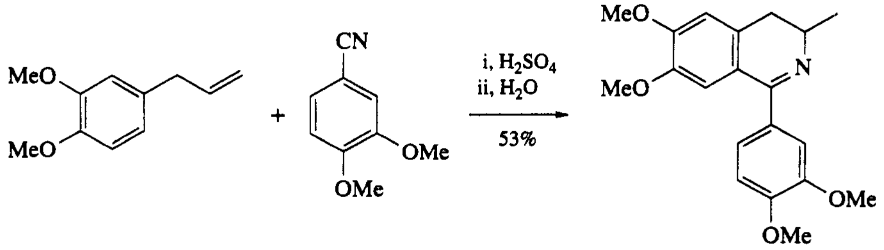

(30)

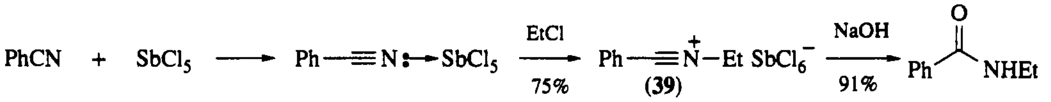

**Scheme 16**

Reaction[92] of aryl nitrilium ions (**40**) or imidoyl chlorides (**41**) with benzonitrile produced the nitrilium species (**42**), which underwent Friedel–Crafts reaction yielding the quinazoline system (**43**; Scheme 17). Generation and cyclization of nitrilium species using Friedel–Crafts reagents has since found widespread favor in heteroaromatic synthesis and such procedures have been reviewed in detail.[10,93] An illustration of its use for a nonbenzenoid aromatic system is given in equation (31).[94]

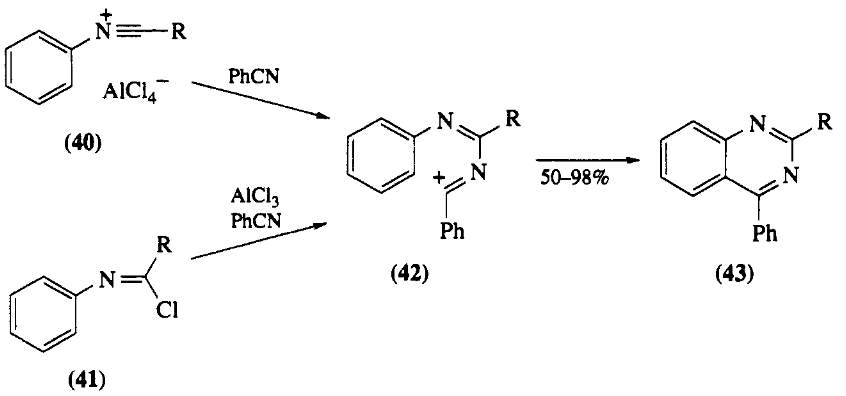

**Scheme 17**

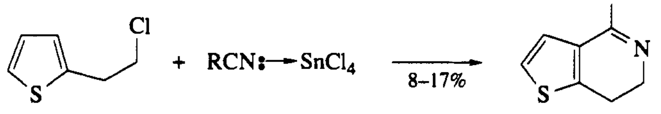

(31)

If the internal nucleophile is an alkenic group, then 5,6-dihydropyridine (Scheme 18)[95–97] or 1-pyrroline (Scheme 19)[95] rings are produced. In a recent development[98] of the latter process, the diol (**44**) follows the same sequence to yield the carbenium ion (**45**; R = Bn). However, this now cyclizes onto the aromatic group originating from the nitrile component and produces the tetrahydrobenz[*f*]indole (**46**) in good yield, with the conventional pyrroline structure (**47**) now being only a minor product. Compound (**46**), present as a tautomeric mixture, was rapidly autoxidized to (**48**; Scheme 20). A further unusual variant of this process is the production of small quantities of the 3-azabicyclo[3.3.0]octanes (**49**) and (**50**) from Ritter reaction of 1-vinylbicyclo[2.1.1]hexane (equation 32).[99]

In 1957 Tillmanns and Ritter reported that reaction of diol (**51**) with nitriles led to dihydro-1,3-oxazine products (**52**)[100,101] instead of yielding bisamides (Scheme 21). In this process the tertiary alcohol group

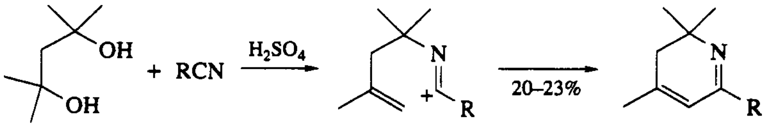
OH
OH
+ RCN
$H_2SO_4$
N
R
20–23%
N
R

Scheme 18

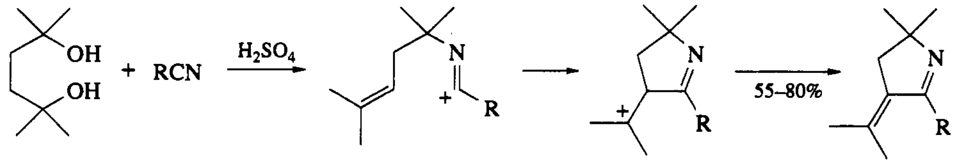
OH
OH
+ RCN
$H_2SO_4$
N
R
N
R
55–80%
N
R

(44)

(45)

Scheme 19

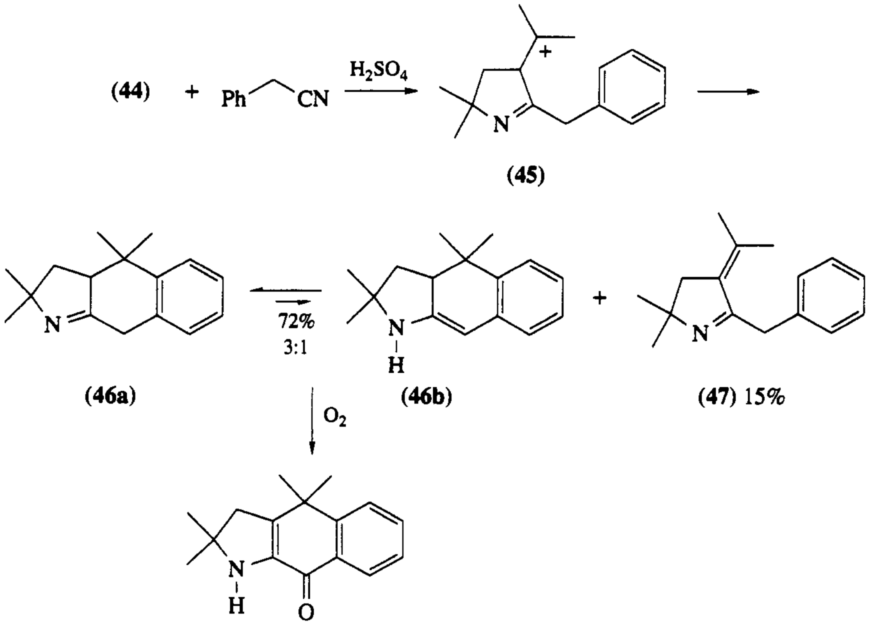
(44) + Ph CN
$H_2SO_4$
N
72%
3:1
N
H
+
N
$O_2$
N
H
O

(45)

(46a)

(46b)

(47) 15%

(48)

Scheme 20

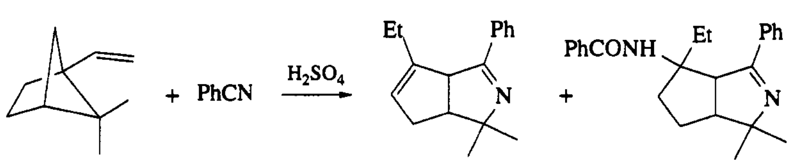
+ PhCN
$H_2SO_4$
Et
Ph
N
+
PhCONH
Et
Ph
N

(32)

(49) 12%

(50) 5%

is converted to a carbenium ion, whereas the secondary alcohol is retained and later acts as the nucleophile which quenches the nitrilium intermediate. Use of a hydroxy group as the internal nucleophile is the most widespread practice and invariably leads to 1,3-oxazine or oxazoline derivatives.

The dihydro-1,3-oxazine route has been extensively investigated by Meyers. Controlled reduction to the tetrahydro derivative (53), followed by hydrolysis, gave good yields of the corresponding aldehyde or deuteriated aldehyde, R—CDO (Scheme 22).[102] Further development of this concept has subsequently given rise to convenient routes to acyclic,[103] α,β-unsaturated,[104] alicyclic,[105] γ-hydroxy[106] and γ-oxo aldehydes.[106] Full synthetic details of these and other variants of the Meyers aldehyde synthesis have been published.[107]

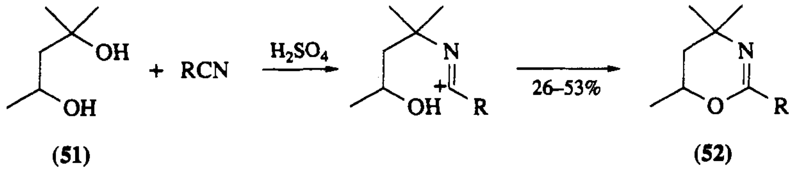
OH
OH
+ RCN
$H_2SO_4$
N
OH
R
26–53%
N
O
R
(51)
(52)

Scheme 21

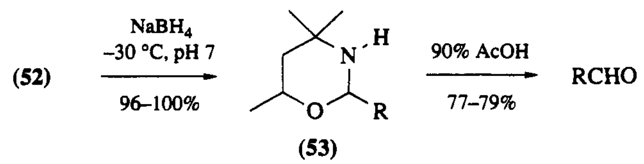
(52)
$NaBH_4$
-30 °C, pH 7
96–100%
N
H
O
R
(53)
90% AcOH
77–79%
RCHO

Scheme 22

Other processes yielding 1,3-oxazine derivatives include the reaction of chloro ketones with Lewis acids (Scheme 23)[108] and reactions of nitriles directly with malonyl chlorides (Scheme 24)[109,110] or related acid chlorides (Scheme 25).[111,112] These processes are also all believed to involve reaction of nitrilium species with an internal oxygen nucleophile.

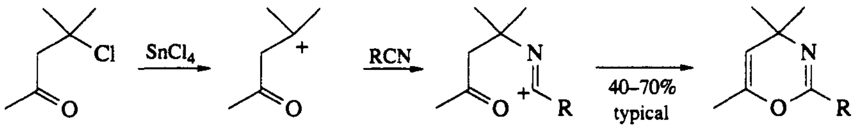
Cl
O
$SnCl_4$
RCN
N
O
R
40–70%
typical
N
O
R

Scheme 23

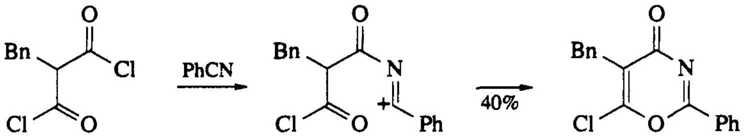
Bn
Cl
Cl
O
O
PhCN
N
Ph
40%

Scheme 24

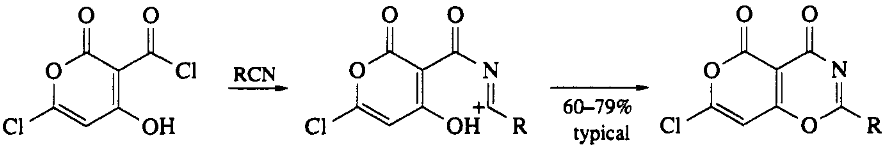
O
Cl
Cl
OH
RCN
N
R
60–79%
typical

Scheme 25

The isolation of oxazole derivatives from Ritter-type reactions dates back to 1893, when Japp and Murray[5] reported that benzoin and sulfuric acid reacted with nitriles (equation 33). Better yields of such products are obtained from reaction of chloro ketones (**54**) with nitrile–$SnCl_4$ complexes (equation 34).[113] Likely mechanisms for these processes have been discussed by Meyers and Sircar.[14]

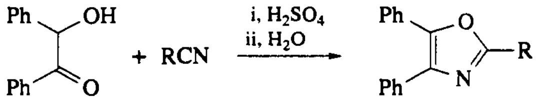
Ph
OH
Ph
O
+ RCN
i, $H_2SO_4$
ii, $H_2O$
Ph
O
R
Ph
N

(33)

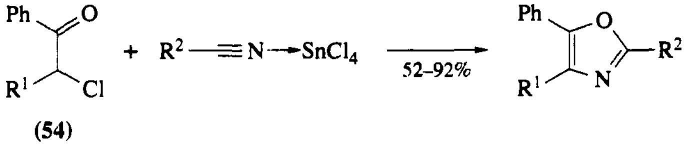
Ph
O
$R^1$
Cl
(54)
+ $R^2$—≡N→$SnCl_4$
52–92%
Ph
O
$R^2$
$R^1$
N

(34)

Japp also found that benzilic acid gave a triphenyloxazolone product with benzonitrile,[114] and later work[115,116] demonstrated that this material was (**55**; Scheme 26). The internal nucleophile in this case is the carbonyl oxygen. More recently, extensions of this type of reaction have been applied to the synthesis of sterically hindered peptides.[117] A further interesting oxazolone synthesis[118] from (**56**) involves nucleophilic attack by the nitrile on a cyclopropenium intermediate and leading ultimately to formation of the spiro derivative (**57**; Scheme 27).

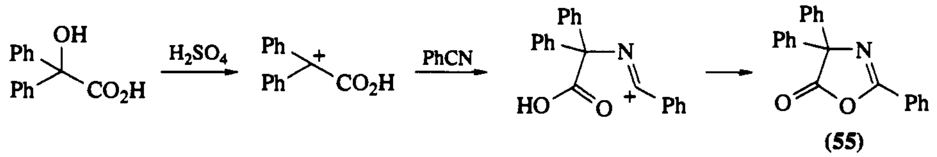

OH
Ph
Ph
CO2H
H2SO4
Ph
+
Ph
CO2H
PhCN
Ph
Ph
N
HO
O
+
Ph
Ph
Ph
N
O
O
Ph

**(55)**

**Scheme 26**

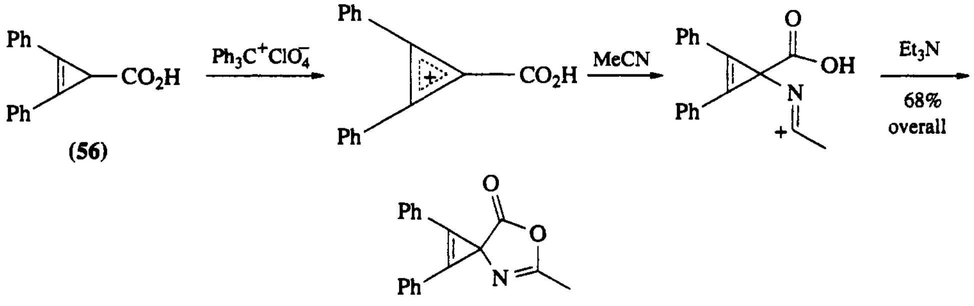

Ph
CO2H
Ph
Ph3C+ClO4−
Ph
+
CO2H
Ph
MeCN
Ph
O
OH
N
+
Ph
Et3N
68%
overall
O
Ph
O
N
Ph

**(56)**

**(57)**

**Scheme 27**

The reaction of epoxides, nitriles and sulfuric acid results in generally poor yields of oxazoline derivatives, and mixtures of isomers may also result (Scheme 28).[119] These difficulties are overcome by the use of epoxy ethers (equation 35).[120,121] As shown in equation (36), oxetanes undergo analogous reactions to afford dihydro-1,3-oxazines in excellent quantities.[122]

When sulfur species act as the internal nucleophile, then thiazoline (**58**) and thiazine (**59**) products result. These processes are analogs of previously discussed oxygen examples,[95] and typical cases are

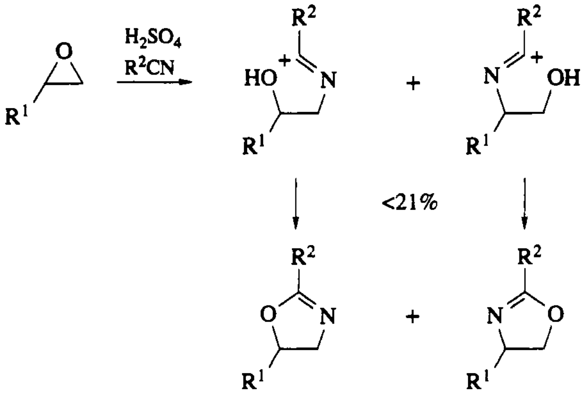

O
R1
H2SO4
R2CN
R2
HO
+
N
R1
+
R2
N
+
OH
R1
<21%
R2
O
N
R1
+
R2
N
O
R1

**Scheme 28**

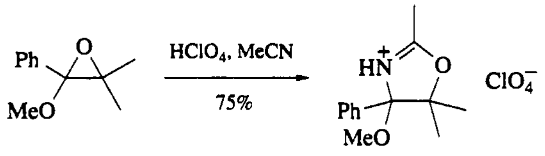

Ph
O
MeO
HClO4, MeCN
75%
HN
+
O
Ph
MeO
ClO4−

(35)

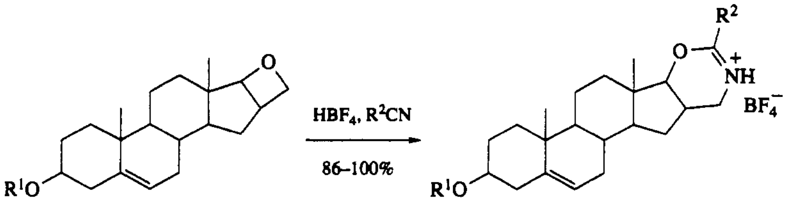
HBF$_4$, R$^2$CN
86–100%
R$^1$O
R$^2$
O
NH
BF$_4^-$

(36)

shown in Scheme 29[123] and equation (37).[124] Episulfides undergo stereospecific ring expansion to thiazoline products in typical yields of 30–80%. Reaction occurs with inversion of configuration,[125,126] as shown in Scheme 30.

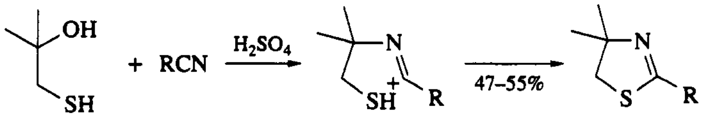
OH
SH
+ RCN
H$_2$SO$_4$
N
SH
R
47–55%
N
S
R

**(58)**

**Scheme 29**

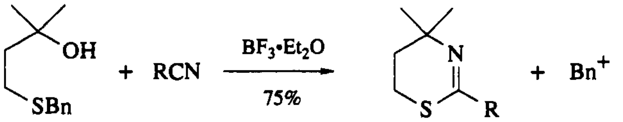
OH
SBn
+ RCN
BF$_3$•Et$_2$O
75%
N
S
R
+ Bn$^+$

**(59)**

(37)

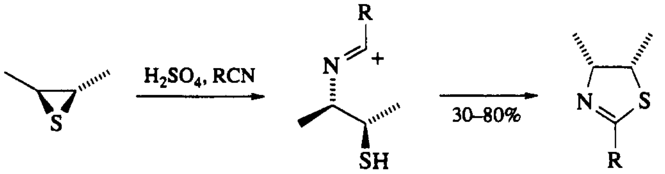
S
H$_2$SO$_4$, RCN
R
N
SH
30–80%
N
S
R

**Scheme 30**

Nitrogen derivatives may also be used to trap nitrilium ions and produce heterocycles. This has been used[127] to produce the 3,4-dihydroquinazoline system (**60**) and the corresponding aromatic derivatives (**61**; Scheme 31; *cf.* Scheme 17[92]). Most examples, however, involve three-membered nitrogen species. Nitriles readily attack aziridinium salts,[128,129] *e.g.* (**62**), producing imidazoline salts (**63**; Scheme 32). Aziridines (Scheme 33) and azirines undergo similar ring expansion under Ritter conditions.[121]

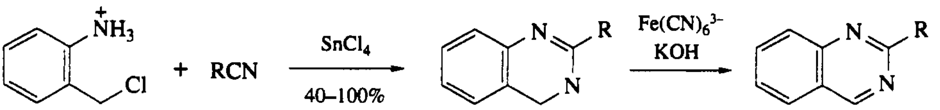
NH$_3^+$
Cl
+ RCN
SnCl$_4$
40–100%
N
R
N
Fe(CN)$_6^{3-}$
KOH
N
R
N

**(60)** **(61)**

**Scheme 31**

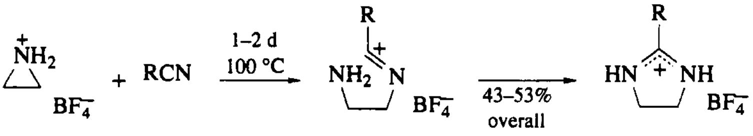
NH$_2^+$
BF$_4^-$
+ RCN
1–2 d
100 °C
R
NH$_2$
N
BF$_4^-$
43–53%
overall
R
HN
NH
BF$_4^-$

**(62)** **(63)**

**Scheme 32**

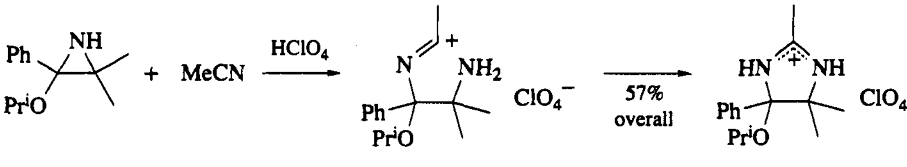
Ph
NH
PriO
+ MeCN
HClO4
N
NH2
+
Ph
PriO
ClO4−
57%
overall
HN
+
NH
Ph
PriO
ClO4−

Scheme 33

Until recently, the intramolecular cyclization procedure had been used only to synthesize fused heterocyclic structures. The first report[31] of a bridged product, in 1978, involved only a minor amount (9%) of an azabicyclo[3.3.1]nonane derivative obtained from the reaction of *cis*-carveol with acetonitrile and $BF_3$–$Et_2O$. However, several effective examples are now known. These all involve reaction of the nitrilium intermediate with an internal alkenic nucleophile to yield a 1-azacyclohexene ring and a new carbenium ion which undergoes conventional, but stereospecific, Ritter reaction from the least hindered face. Such reactions are typified by formation of the multicyclic structures (**64**; equation 38)[130] and (**65**; equation 39),[131] and have considerable potential in the synthesis of complex nitrogen heterocyclic systems since suitable optically pure substrates should undergo completely stereospecific conversions. This has been confirmed by Marschoff[132] in an elegant study on (*R*)-(+)-limonene (**66**) and (1*S*)-(−)-β-pinene (**67**), which produced opposite enantiomers of the bicyclic amide (**68**; Scheme 34).

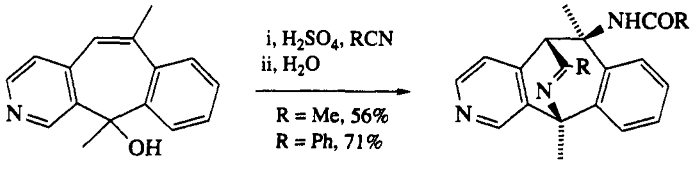
N
OH
i, H2SO4, RCN
ii, H2O
R = Me, 56%
R = Ph, 71%
NHCOR
R
N
N

(**64**)

(38)

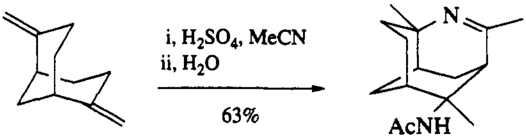
i, H2SO4, MeCN
ii, H2O
63%
N
AcNH

(**65**)

(39)

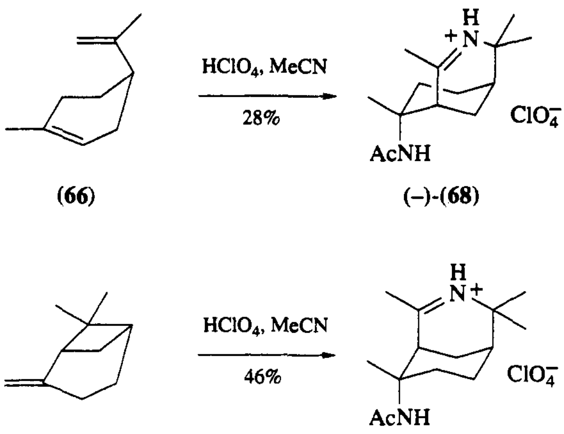
HClO4, MeCN
28%
H
+N
ClO4−
AcNH
HClO4, MeCN
46%
H
N+
ClO4−
AcNH

(**66**) (−)-(**68**)

(**67**) (+)-(**68**)

Scheme 34

### 1.9.2.2 Intramolecular Formation of the Nitrilium Ion

Intramolecular reaction of a nitrile group and a carbenium ion can produce a cyclic nitrilium intermediate leading to Ritter-type products after reaction with an external nucleophile (Scheme 15). Geometrical considerations determine that six-membered rings are the smallest available by this mechanism. The carbenium ion is most commonly generated from an alkene, oxime, ketone or a second nitrile group.

Conversion of 3-cyano-4-stilbazole (**69**) into a tetrahydrocopyrine derivative illustrates the use of an alkenic group as the cation precursor (Scheme 35).[133] Such processes are frequently less clear-cut; for example, reaction of either the unsaturated nitrile (**70**) or oxime (**71**) resulted[134] in competitive cyclizations to the minor Ritter product (**72**) and the major Hoesch product (**73**; Scheme 36). Similar competing processes have been observed for spirocyclohexanone oximes,[135] but in other cases no cyclic products were produced at all.[136]

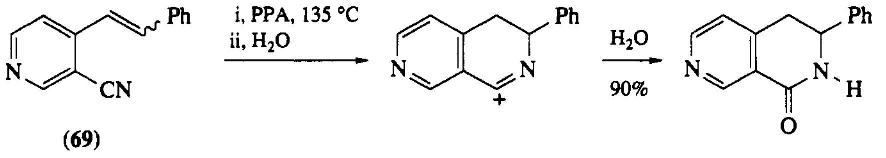

**Scheme 35**

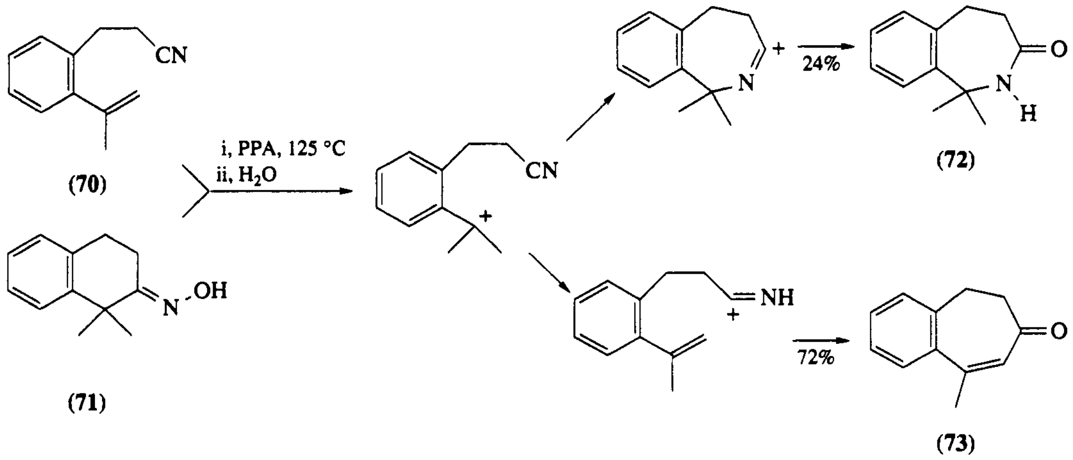

**Scheme 36**

Reports of five-membered ring formation involving this mechanism remain unauthenticated. Formation of an oxazolidinone product from Ritter reaction of cyclohexanone and cyclohexanone cyanohydrin[137] has been shown by Ducker[138] to result from an alternative pathway. Although 4-methyl-3-pentenonitrile did undergo intramolecular cyclization, this did not involve pyrrolidone formation.[139] Rather a novel dimeric process took place, leading to formation of a monocyclic (**74**) and a bicyclic (**75**) product. The latter was readily ring opened to (**74**) using silver oxide and water (Scheme 37).

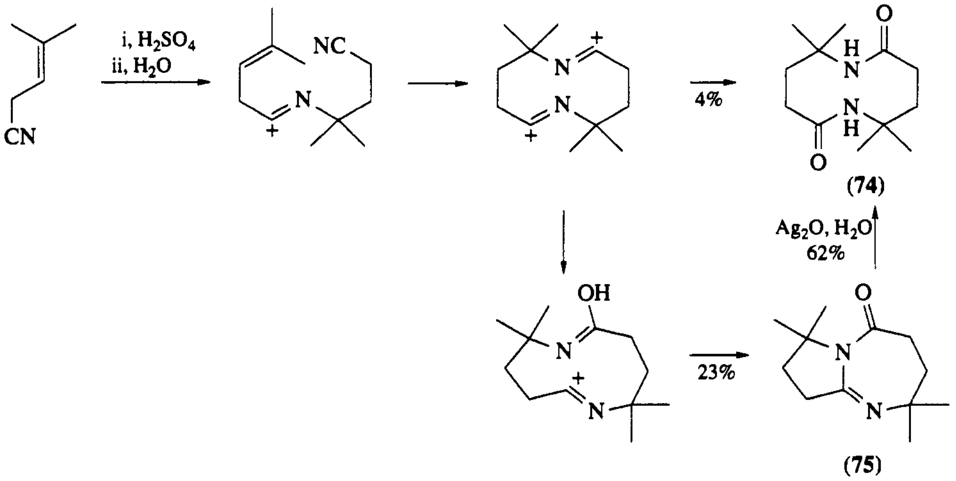

**Scheme 37**

It has been known for many years that δ-ketonitriles produce 2-pyridone derivatives under acidic conditions,[140] and such processes have been reviewed by Meyers.[14] Such reactions generally yield reduced derivatives, but in some cases (*e.g.* Scheme 38) *in situ* oxidation produces the aromatic compounds directly.[141] A further interesting example is conversion of the pimelonitrile derivative (**76**) into the bicyclic product (**77**) by means of sequential Ritter and Hoesch processes in a one-pot reaction (Scheme 39).[142]

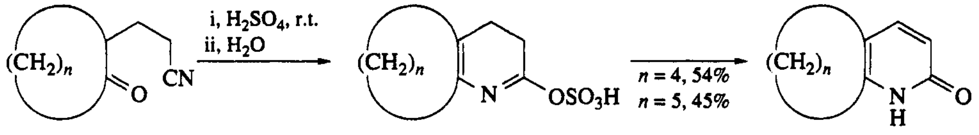

**Scheme 38**

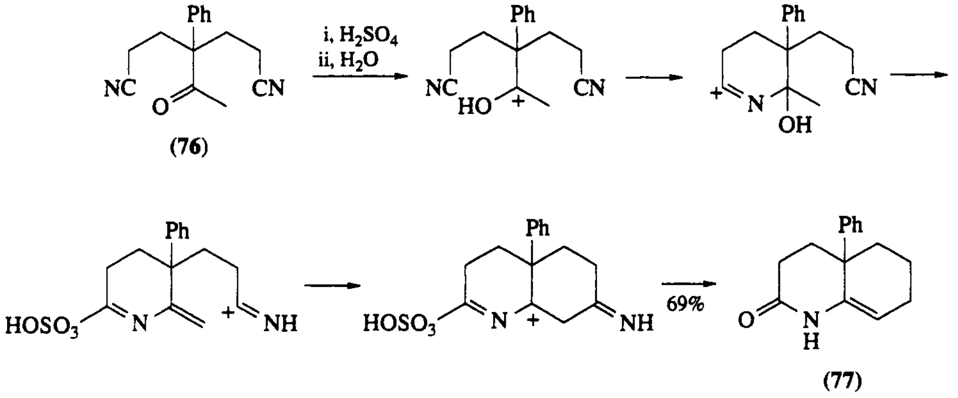

**Scheme 39**

Cyclization of α,ω-dinitriles under acidic conditions has been reviewed thoroughly by Johnson and Madronero.[10] Anhydrous hydrogen halides are favored for such reactions and a wide range of five-, six- and seven-numbered heterocyclic systems are produced.

## 1.9.3 EXTENSIONS OF THE ORIGINAL REACTION

The Ritter reaction as originally reported involved generation of a carbenium ion intermediate under strongly acidic conditions, followed by reaction with the nitrile component. Not surprisingly, other means of generating the carbenium ion, or related chemical species, also result in Ritter-type processes. These newer developments have greatly added to the overall synthetic versatility of the reaction over recent years.

### 1.9.3.1 Physical Techniques

Carbenium ions generated by nonacidic routes also react with nitriles and yield amides on hydrolytic work-up. Such experiments[143] have included oxidation of free radicals (Scheme 40) using $Cu^{2+}$. Similarly, Cacace *et al.*[144] produced carbenium ions including s-$C_3H_7^+$, s-$C_4H_9^+$ and t-$C_4H_9^+$ by radiolysis, and observed reaction with nitriles and water leading to *N*-alkylamides. Ritter-type products have also been isolated from a number of organic photochemical reactions carried out in nitrile solvents. For example, photolysis of dibenzyldimethylammonium chloride (**78**) in acetonitrile resulted[145] in a mixture of products including toluene, dibenzyl, benzyl chloride and *N*-benzylacetamide (**79**). The small amounts of amide produced were postulated to result from the sequence shown in Scheme 41.

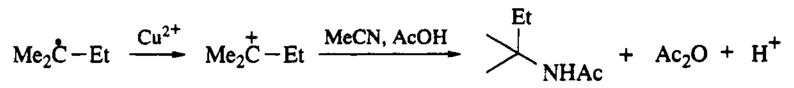

**Scheme 40**

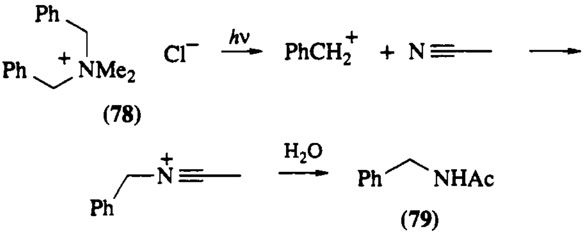

**Scheme 41**

Cristol has carried out photochemical studies on a range of cyclic halogenated substrates which yield Ritter-type products.[146] Irradiation of the dihalides (**80**) in acetonitrile normally affords a mixture of the isomeric products (**81**) and (**82**; X = halogen), plus polar material. However, when the solvent was switched to 5% aqueous acetonitrile, significant amounts of the additional products (**81**; X = OH; 15%) and (**81**; X = NHAc; 16%), plus traces of (**82**; X = NHAc) were isolated (equation 40). These new substances are believed to result from nucleophilic attack by water or acetonitrile on a ground state carbenium ion-like intermediate. A number of further, closely related reactions of this type have been described.[147-149] These photolyses consistently yield amide products but, unfortunately from the synthetic viewpoint, mixtures are often produced, and overall yields of the amides are not generally high.

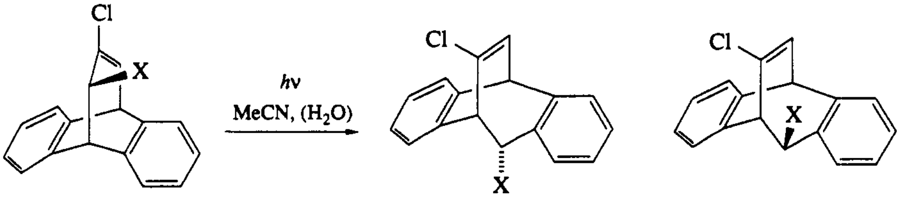

(**80**) X = Cl, Br (**81**) (**82**) (40)

The physical technique with the greatest potential for synthetic applications of Ritter-type reactions is electrochemistry. A selection only of examples is discussed here. Synthetic chemists unfamiliar with this technique will find the review by Eberson and Nyberg[150] an informative and entertaining introduction to this area. Electrochemical Ritter reactions may be performed through anodic substitution of a hydrogen by the nitrile, followed by hydrolysis of the nitrilium ion intermediate, as shown in Scheme 42. The majority of reactions investigated have been anodic acetamidations using hydrocarbons, alkyl halides, esters or ketones as the substrate. In some cases, such as reaction of the adamantane derivatives (**83**),[151] the yields of amide product are excellent (Scheme 43).

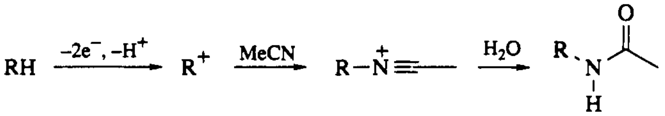

**Scheme 42**

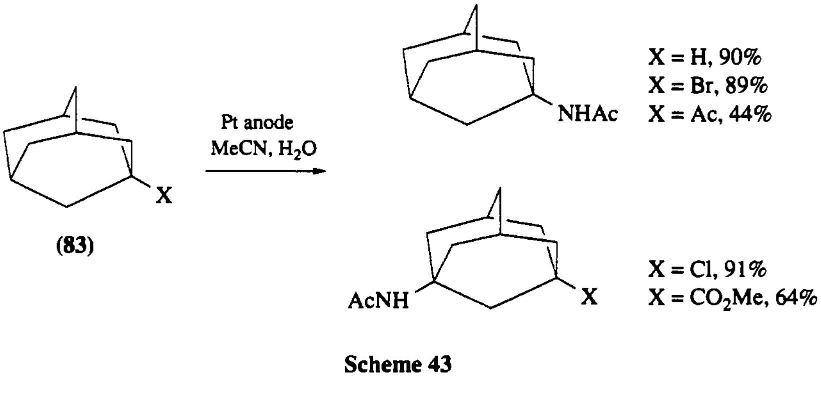

**Scheme 43**

Anodic oxidation of *n*-alkanes in acetonitrile results in mixtures of *N*-*s*-alkylacetamides but skeletal rearrangement of the intermediate *s*-carbenium ions is not observed.[152] Aromatic compounds can undergo direct acetamidation in the ring. Thus, acetophenone, which normally undergoes electrophilic aromatic substitution at the *meta* position, affords the *o*- and *p*-acetamides (Scheme 44).[153] Anthracene is cleanly converted into the acetamide (**84**) when the reaction is performed in the presence of TFAA as water scavenger (equation 41).[154]

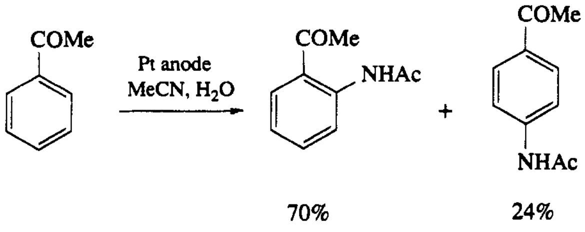
COMe
Pt anode
MeCN, H2O
COMe
NHAc
+
COMe
NHAc
70%
24%

**Scheme 44**

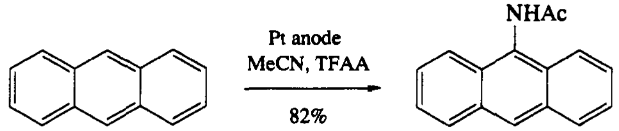
Pt anode
MeCN, TFAA
82%
NHAc

(**84**)

(41)

Generally, α-branched ketones undergo α-cleavage followed by acetamidation (equation 42),[155] while unbranched or remotely branched ketones result in substitution at remote (γ, δ and ε) positions (equation 43).[156] These modes of reaction are direct analogs of behavior in ketone photochemistry (Norrish Type I and II processes) and mass spectrometry (α-cleavage and McLafferty rearrangement). However, the electrochemical intramolecular hydrogen abstraction is much less selective, which detracts from the synthetic opportunities in being able to functionalize unactivated hydrocarbon groups at remote sites. On the other hand, acyclic esters tend to be more selective than the ketones, generally providing ω-1-substituted products (equation 44).[157]

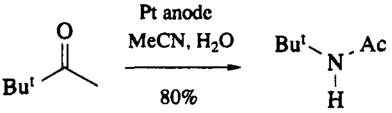
O
Bu^t
Pt anode
MeCN, H2O
80%
Bu^t
N
Ac
H

(42)

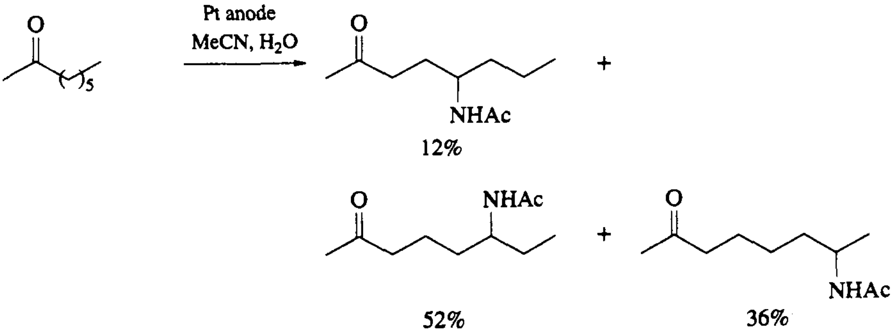
O
5
Pt anode
MeCN, H2O
O
NHAc
12%
+
O
NHAc
+
O
NHAc
52%
36%

(43)

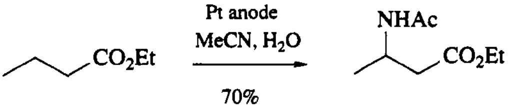
CO2Et
Pt anode
MeCN, H2O
70%
NHAc
CO2Et

(44)

### 1.9.3.2 Metallic Reagents

The scope of the Ritter reaction can also be extended by avoiding strong acid as the carbenium ion initiator. In at least one case it is possible to omit this reagent entirely because of the facility of $S_N1$ reaction. Thus, reflux of *t*-butyl bromide in acetonitrile or propionitrile for 24 h led to formation of *N*-*t*-butylamide products.[158] Less commonly used initiators have included cation exchange resins[159] and clayfen.[160] In this latter case, the clay-supported iron(III) nitrate is believed to give rise to nitrosonium ions, which react with the alkyl halide substrate to produce a carbenium ion. Yields of amide from this technique are generally modest (21–35%).

Earlier mention has been made of the use of Lewis acid and Friedel–Crafts reagents as initiators of carbenium ion formation. Another versatile device is to employ a metal to assist in generation of the carbenium ion. In its simplest form, addition of silver(I) ion to an alkyl halide is an excellent technique for encouraging reaction by means of the $S_N1$ pathway. This process was first applied to the Ritter reaction by Cast and Stevens,[161] but yields obtained were modest. A recent elegant application of this technique is the two-step conversion of dodecahedrane into its acetamide derivative (Scheme 45).[162]

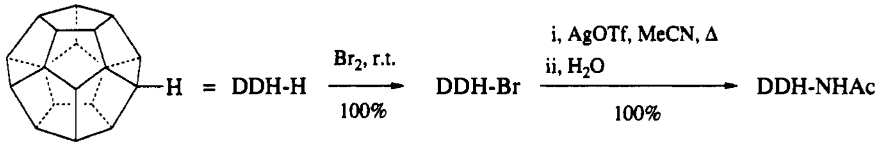

Scheme 45

Silver-assisted solvolysis of the trianisylvinyl bromide (**85**) produces a vinyl cation, which then undergoes Ritter reaction, yielding the amide (**86**; Scheme 46).[163] Other less reactive triarylvinyl bromides (**87**) required much higher temperatures for generation of the cation, and silver triflate proved a better reagent.[164] Under these conditions the intermediate nitrilium ion performed an intramolecular electrophilic aromatic substitution, producing the highly substituted isoquinolines (**88**). This conversion may also be carried out photochemically at low temperature, but in variable yield (12–77%) since the vinyl radical initially produced can carry out hydrogen abstraction reactions in competition with being oxidized to the vinyl cation. Superior yields were obtained by combining the procedures and performing sequential thermal and photochemical steps (Scheme 47).[164]

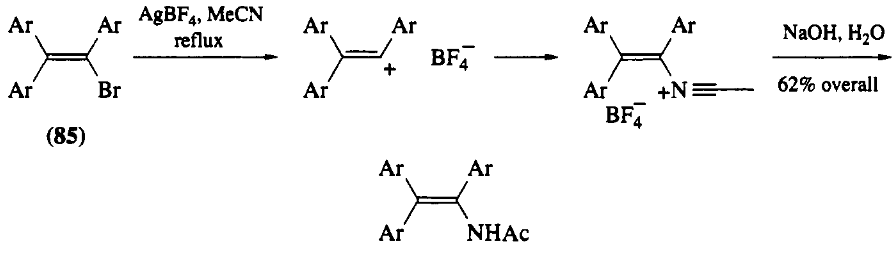

Scheme 46

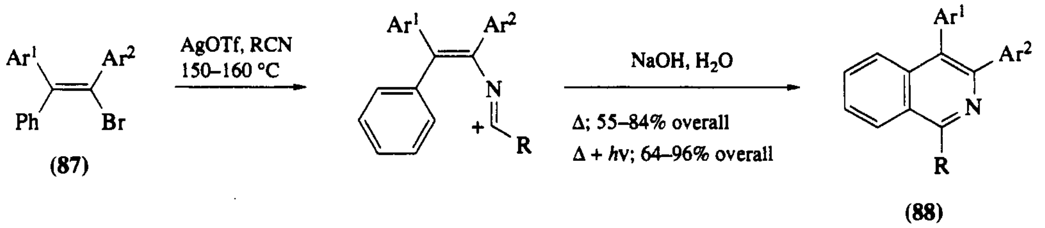

Scheme 47

Some years ago it was reported that cyclohexene reacted with mercury(II) nitrate and acetonitrile in nitric acid to give the metallic derivative (**89**), which, in turn, underwent demercuration with sodium amalgam, producing the corresponding amide (Scheme 48).[165] Later investigators[166–168] found that less severe conditions were adequate, requiring only a solution of anhydrous mercury(II) nitrate in the nitrile, and sodium borohydride, respectively. This process is analogous to the more familiar procedure developed by Brown for the hydration of alkenes using mercury(II) acetate.[169] It shares the advantage of that process in that it proceeds *via* a bridged mercurinium ion rather than a carbenium ion and, therefore, it is less prone to rearrangement. Thus, for example, the alkene (**90**) is converted into amide (**91**) in excellent yield and without formation of isomeric side products (Scheme 49).[167] Unfortunately, many alkenes fail to react in this process due to steric effects resulting from the bulky mercury reagent. When this does occur, reduction of the organomercurial intermediate produces β-amido radicals which may be coupled with electron-deficient alkenes to produce nitrogen heterocyclic products.[170,171]

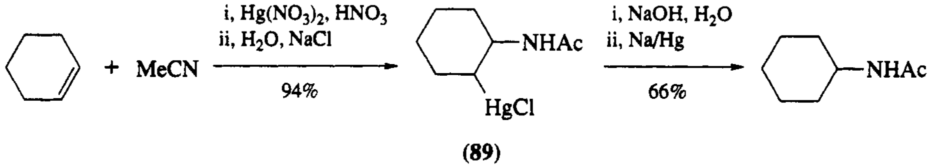

**Scheme 48**

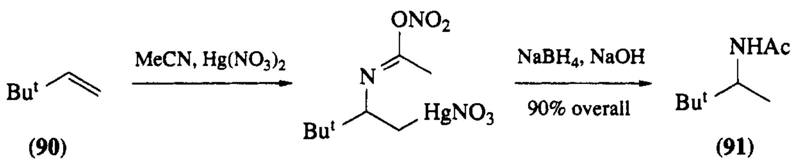

**Scheme 49**

When Delpech and Khuong-Huu[172] applied this procedure to a trisubstituted steroidal alkene, they obtained four isomeric unsaturated amide products. In crowded cases the mercuration can therefore proceed by means of an allylic oxidation pathway with concomitant rearrangement.[173] In contrast, the reaction of (–)-α-pinene (**92**) with acetonitrile and mercury(II) nitrate gave a good yield of either of the racemic 3-azabicyclo[3.3.1]nonene derivatives (**93**) or (**94**), depending on the work-up conditions used.[174] The mechanism proposed (Scheme 50) involves an intramolecular nitrilium ion cyclization similar to those discussed in Section 1.9.2. Reaction of (**94**) with aqueous formaldehyde produced the azaadamantanol (**95**) *via* another novel pathway involving loss of the C(4)-methyl group of (**94**) as acetaldehyde. Replacement of water by alternative nucleophiles allows access to a range of substituted azaadamantanes, avoiding previous multistep procedures.

This mercuration reaction has been adapted by Stevens and Kenney[175] to perform elegant stereospecific syntheses of the *Aristotelia* indole alkaloids (+)-makomakine (**97**) and (+)-aristoteline (**98**) from (–)-β-pinene and indol-3-ylacetonitrile (**96**) in only two and three steps, respectively (Scheme 51). A similar procedure from (+)-α-pinene yielded racemic hobartine (**99**) in 11% overall yield. Enantiospecificity is not observed in this reaction for the same reasons encountered during the preparations of (**93**) and (**94**).[174]

Whereas palladium(II) salts frequently react with aromatic substrates causing direct palladation, the strongly electrophilic complex (**100**) is known to interact with alkenes and induce reactions involving incipient carbenium ions. Hegedus[176] has recently demonstrated that reaction of (**100**) with a variety of alkenes can be followed by nucleophilic attack by nitriles in a palladium-assisted version of the Ritter reaction. This process is illustrated (Scheme 52) for the reaction of (**100**) with *N*-allylskatole in nitrile solvents. Initial reaction yields the σ-alkylpalladium(II) complex (**101**), which is stabilized by chelation. On reduction with sodium borohydride stereospecific reduction to the *syn*-1,2,3,4-tetrahydropyrazino[1.2-*a*]indoles (**102**) occurs, or work-up using benzylamine affords the pyrazinoindole (**103**). Alternatively, treatment of (**101**) with carbon monoxide leads to insertion, producing the acylpalladium complex (**104**) and leading to isolation of the esters (**105**).

Other examples from this study indicate that the reaction path followed by the nitrilium ion depends very much on the nature of the nucleophiles present. Thus, the allylindole (**106**) produced the imidate (**107**) through reaction of the nitrilium ion with methanol in preference to the electron-rich heterocyclic system (equation 45). In contrast, alcohol (**108**) underwent effective intramolecular cyclization (equation 46).

It is also reported that palladium(II) chloride is a suitable catalyst for Ritter reactions conducted at elevated temperature and pressure.[177]

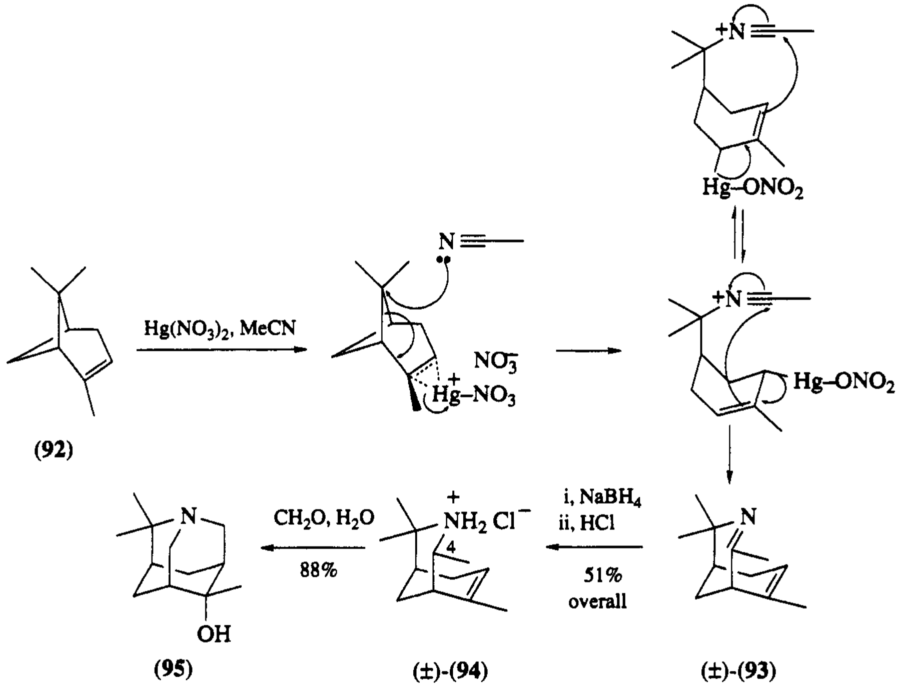
Hg(NO3)2, MeCN
(92)
NO3−
Hg–NO3
Hg–ONO2
+N
N
i, NaBH4
ii, HCl
51%
overall
CH2O, H2O
88%
NH2 Cl−
4
OH
(95)
(±)-(94)
(±)-(93)

**Scheme 50**

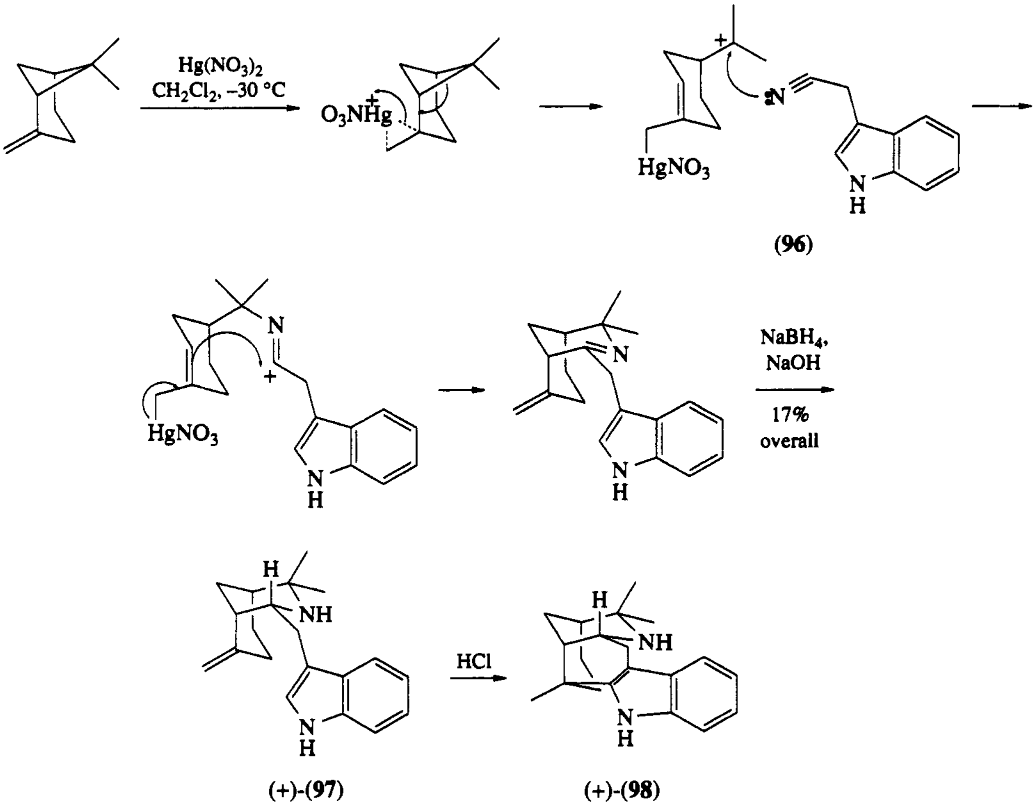
Hg(NO3)2
CH2Cl2, −30 °C
O3NHg
HgNO3
N
N
H
(96)
NaBH4,
NaOH
17%
overall
NH
HCl
(+)-(97)
(+)-(98)

**Scheme 51**

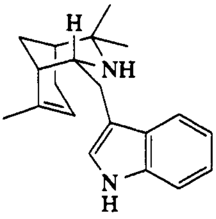

(±)-(99)

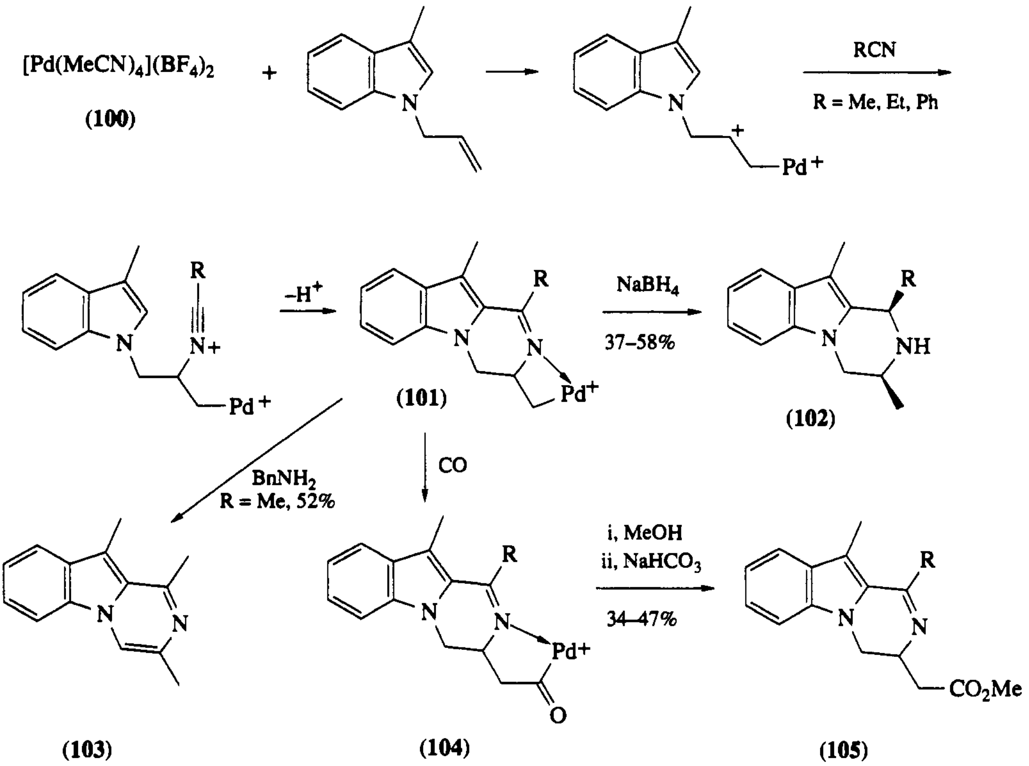
[Pd(MeCN)4](BF4)2
(100)
RCN
R = Me, Et, Ph
Pd+
-H+
R
N+
NaBH4
37–58%
NH
(101)
(102)
BnNH2
R = Me, 52%
CO
i, MeOH
ii, NaHCO3
34–47%
Pd+
O
CO2Me
(103)
(104)
(105)

Scheme 52

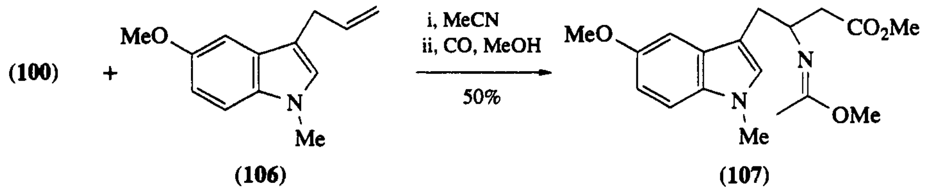
(100)
MeO
N
Me
i, MeCN
ii, CO, MeOH
50%
CO2Me
OMe
(106)
(107)

(45)

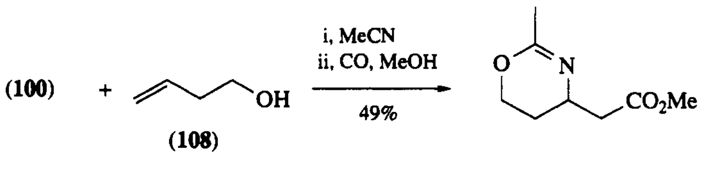
(100)
OH
(108)
i, MeCN
ii, CO, MeOH
49%
O
N
CO2Me

(46)

Top and Jaouen[178,179] have found that an effective means of controlling carbenium ion reactivity is to employ temporary stabilization of the ion by means of a suitable organometallic complex. Thus, while benzyl alcohol gives a 48% yield of *N*-benzylacetamide under conventional conditions,[29] the use of

($\eta^6$-benzyl alcohol)tricarbonylchromium (**109**) gave more than double that yield of the complexed acetamide (**110**; equation 47).

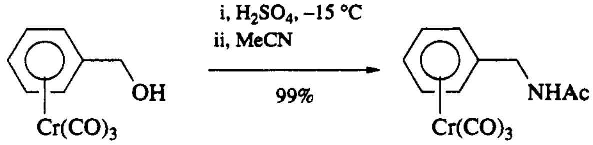

(**109**) (**110**) (47)

Similarly, several nitriles (such as $ClCH_2CN$ and *o*-$MeC_6H_4CN$) which tend to react poorly in the conventional reaction now reacted most efficiency (98 and 83%, respectively) with the stabilized benzyl cation. Tertiary carbenium ions were so stabilized that no Ritter reaction took place and the behavior of secondary ions depended on the particular case (Scheme 53). Complexed propargyl alcohol (**111**) was converted into the complexed acetamide (**112**) without encountering the customary acid-catalyzed rearrangement problems (equation 48).

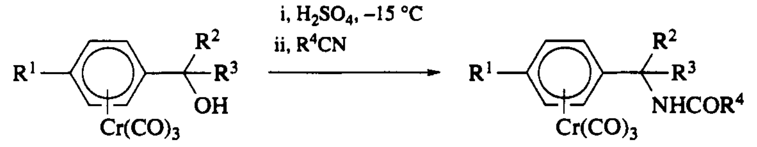

| *R¹* | *R²* | *R³* | *R⁴ = Me* | *R⁴ = Ph* |
|---|---|---|---|---|
| *p*-MeO | Me | H | 99% | 84% |
| H | Ph | H | 82% | 0% |
| H | Me | Me | 0% | 0% |

**Scheme 53**

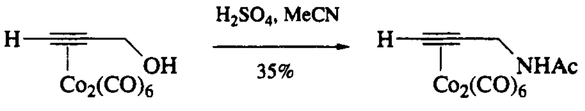

(**111**) (**112**) (48)

Complexation of the $Cr(CO)_3$ group to an aromatic ring imparts a three-dimensional structure to the molecule which can be exploited in asymmetric syntheses.[179,180] Reaction of alcohol (**113**) with $Cr(CO)_6$ was followed by resolution. Complex (**114**) underwent Ritter reaction in acetonitrile yielding the complexed amide (**115**; Scheme 54). Decomplexation gave the free chiral amide whose optical purity (92%) indicated that this process took place with almost complete retention. In contrast, the indanol complex (**116**) was transformed into the Ritter product (**117**) with complete inversion of configuration (equation 49). Convincing explanations of these different stereochemical results have been provided.[179,180] These results are significant in foreshadowing future possibilities for the synthesis of chiral amides and amines by Ritter-type reactions.

### 1.9.3.3 Generation of Onium Intermediates

Electrophilic attack of alkenic groups provides a variety of cationic species available for Ritter-type reaction with nitriles, but avoiding strongly acidic conditions. Such processes involving bridged onium ions are also subject to the usual regio- and stereo-chemical factors in the ring-opening step.

Both nitronium and nitrosonium salts are effective initiators but with quite different results. Thus, propene and nitronium fluoroborate react[181] to produce the secondary α-nitrocarbenium ion which undergoes Ritter reaction with acetonitrile to yield amide (**118**). Under similar conditions, nitrosonium fluoroborate leads to heterocyclic products.[182,183] Intramolecular reaction of the nitroso and nitrilium groups, followed by prototropic shifts, affords the *N*-hydroxy imidazolium salt (**119**). This may be either neutralized to produce the *N*-oxide or reduced to the imidazole (**120**; Scheme 55).

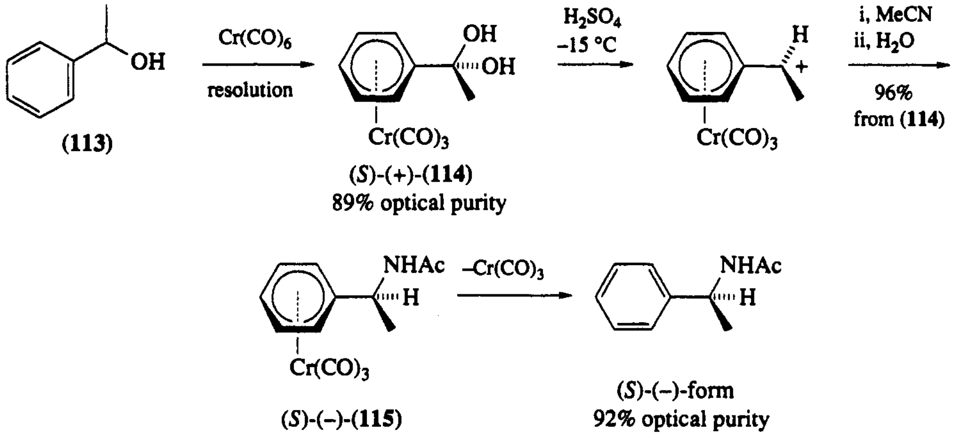
(113)
Cr(CO)6
resolution
Cr(CO)3
(S)-(+)-(114)
89% optical purity
H2SO4
-15 °C
i, MeCN
ii, H2O
96%
from (114)
NHAc
-Cr(CO)3
(S)-(–)-(115)
(S)-(–)-form
92% optical purity

Scheme 54

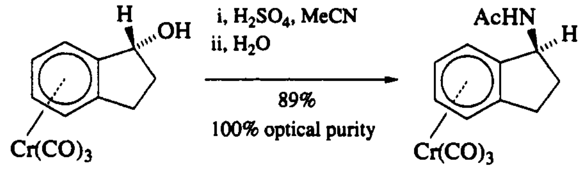
i, H2SO4, MeCN
ii, H2O
89%
100% optical purity
Cr(CO)3
AcHN

(1*R*)-(**116**) (1*S*)-(**117**) (49)

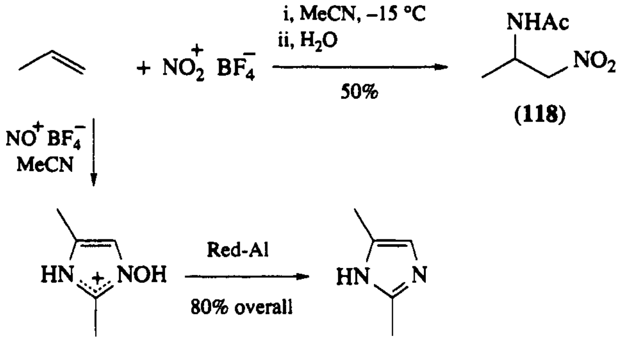
i, MeCN, -15 °C
ii, H2O
50%
(118)
NO+BF4−
MeCN
Red-Al
80% overall
(119)
(120)

Scheme 55

Cairns[184] demonstrated that, as initiator, chlorine provided a convenient synthesis of *N*-(2-chloroalkyl)amides (Scheme 56). In cases where the intermediate imidoyl chloride (**121**) was formed from a nitrile with no α-hydrogen atoms, then this material could be separated from the vicinal dichloride side product by distillation. Otherwise, loss of hydrogen chloride and further reaction was likely, making immediate hydrolysis to the amide desirable. One example of the use of bromine, with cyclohexene and acetonitrile, was also described, producing *N*-(2-bromocyclohexyl)acetamide (**122**) in 26% yield. Hassner[185] has since reported that this type of reaction is best carried out in the presence of silver ion, which removes bromide from solution, thus suppressing the competing formation of vicinal dibromide. Amide (**122**) was now obtained in 70% overall yield (Scheme 57). The use of alkenes, halogen and nitriles or nitrile derivatives (R—SCN, $R_2N$—CN, Cl—CN, R—OCN) has been extensively studied by Beger as a synthetic route to imidate species and derived five-membered heterocyclic systems.[186–190] This methodology can also be combined with that of the intramolecular Ritter process to synthesize 3,3-disubstituted isoquinoline derivatives (**123**) not available by Bischler–Napieralski reaction (Scheme 58).[191] Reduction affords the fused aziridines (**124**). Utilization of aziridinium species in Ritter-type processes has already been discussed (Section 1.9.2.1).[128,129]

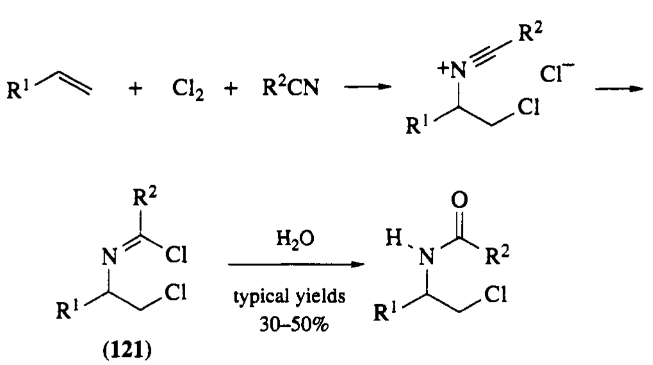

Scheme 56

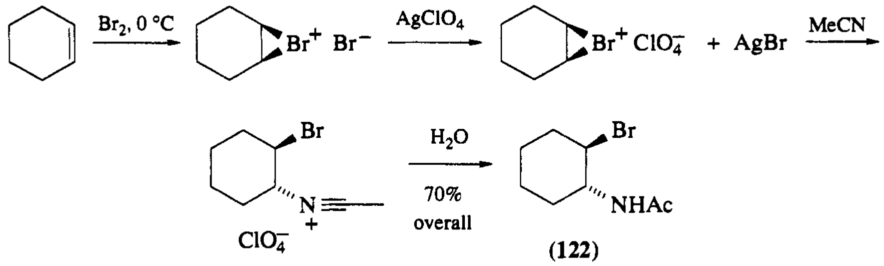

Scheme 57

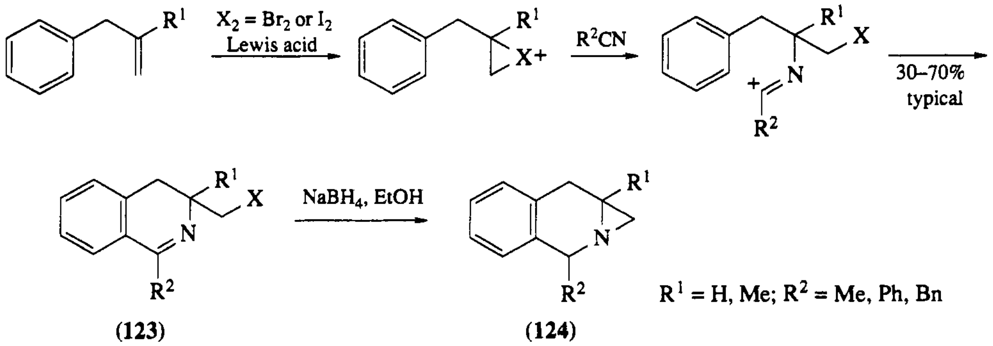

$R^1$ = H, Me; $R^2$ = Me, Ph, Bn

Scheme 58

Generally, iodine azide adds to an alkene by an ionic pathway, yielding a *trans* addition product;[192] however, in a few cases nitrile reagents compete successfully with azide ion in attacking the iodonium intermediate. Thus, α-pinene was converted into tetrazole (**125**) in a one-pot reaction in near quantitative yield (Scheme 59).[193] This type of process is far from general.

More recently, these concepts have been extended to include a range of elegant amidoselenation processes. Alkenes react with benzeneselenenyl chloride and nitriles to yield β-amido phenyl selenides in excellent yield.[194,195] Oxidative elimination of the latter provides the corresponding allylic amides (Scheme 60). Since the reaction proceeds *via* an episelenonium intermediate, the amido selenides are formed with *trans* stereospecificity. However, when applied to nonsymmetrical alkenes (equation 50)[195] it only proceeds with regioselectivity.

An alternative approach[196] is to use the readily available β-hydroxy phenyl selenides as Ritter substrates. Amide formation occurs with retention of configuration, indicating that fission of the carbon–oxygen bond is assisted by the neighboring phenylseleno group (Scheme 61). Diphenyl diselenide and iodine react with 1,5-dienes to give carbocyclic products. Initial formation of the episelenonium ion is followed by intramolecular attack and subsequent Ritter reaction (Scheme 62).[197]

Vankar and Rao[198] have shown that the cationic intermediate (**126**) in the Pummerer reaction can be intercepted by nitriles producing the amido sulfides (**127**). The moderate yield of these novel products is a consequence of competition with the normal Pummerer process (Scheme 63).

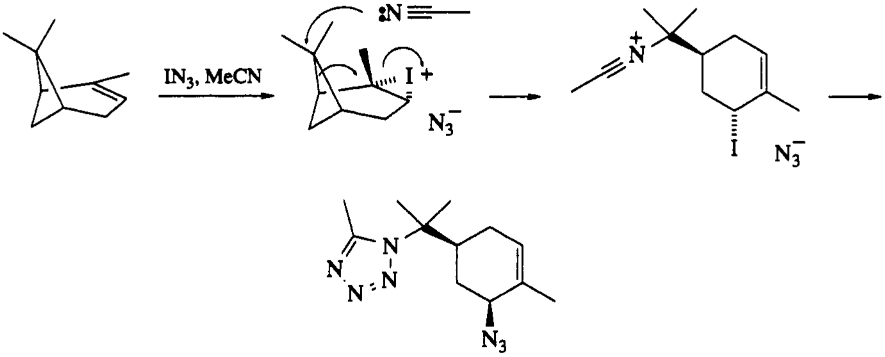
IN$_3$, MeCN
:N≡
I+
$N_3^-$
$\overset{+}{N}$
I
$N_3^-$
N
N
N
N
$N_3$

(125)

Scheme 59

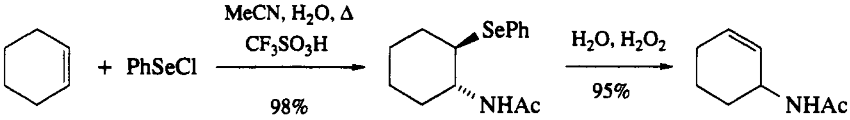
+ PhSeCl
MeCN, H$_2$O, Δ
CF$_3$SO$_3$H
98%
SePh
NHAc
H$_2$O, H$_2$O$_2$
95%
NHAc

Scheme 60

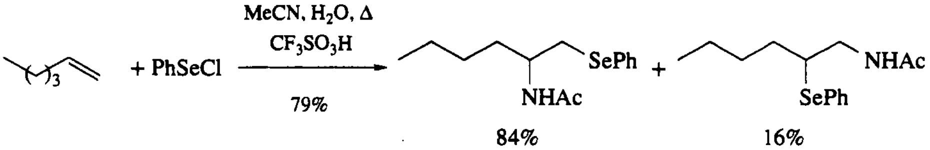
3
+ PhSeCl
MeCN, H$_2$O, Δ
CF$_3$SO$_3$H
79%
SePh
NHAc
84%
+
NHAc
SePh
16%

(50)

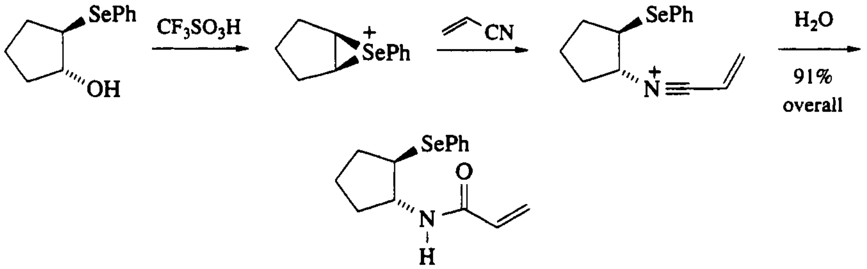
SePh
OH
CF$_3$SO$_3$H
+
SePh
CN
SePh
$\overset{+}{N}$
H$_2$O
91%
overall
SePh
O
N
H

Scheme 61

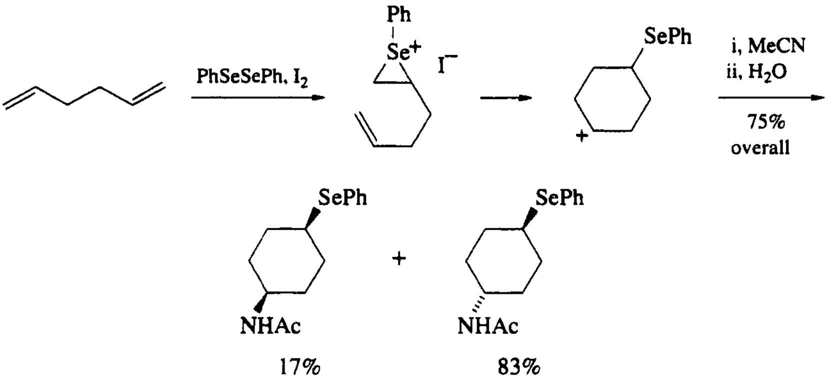
PhSeSePh, I$_2$
Ph
Se+
I$^-$
SePh
+
i, MeCN
ii, H$_2$O
75%
overall
SePh
NHAc
17%
+
SePh
NHAc
83%

Scheme 62

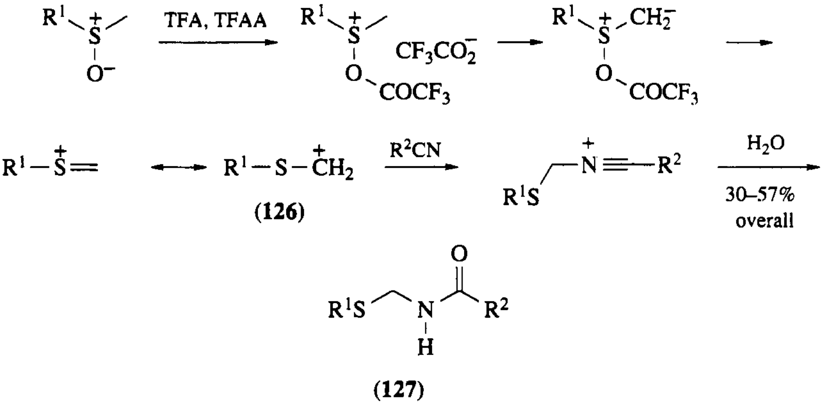

Scheme 63

## 1.9.4 RELATED PROCESSES

### 1.9.4.1 Relationship of Ritter and Other Reactions

Over recent years it has become clear that certain organic reactions share common intermediates and therefore have a closer relationship than previously suspected. The first step of the Ritter reaction is production of a carbenium ion, as originally reported under strongly acidic conditions, where Wagner–Meerwein rearrangements are liable to be encountered. As discussed in Section 1.9.3, alternative means of generating carbocationic species have resulted in a resurgence in Ritter-type chemistry. The recent report[199] that carbenium and nitrilium ions may be generated under mild conditions in the absence of strong electrophiles is therefore of considerable interest. Related carbenium ion reactions are those with thiocyanates yielding *N*-alkyl thiocarbamates,[200,201] and with carbon monoxide followed by hydrolysis yielding carboxylic acids (the Koch–Haaf reaction).[202] The relationship between the latter reaction and the Ritter process has been examined in detail.[203]

Trapping of the carbenium ion by a nitrile produces a nitrilium ion (**128**). Although such species were proposed by Hantzsch[204] in 1931, chemical syntheses did not become available for some time.[23,205] Major routes to such species now include: (i) alkylation of nitriles; (ii) reaction of imidoyl halides with Lewis acid;[206] (iii) 1,1-addition to isonitriles;[207] and (iv) reaction of ketenimines with electrophiles (Scheme 64).[208] From $^1H$, $^{13}C$ and $^{15}N$ NMR data, Olah and Kiovsky[209] concluded that nitrilium ions and protonated nitriles had a linear structure. This is supported by low temperature X-ray studies on *N*-(2,6-dimethylphenyl)acetonitrilium tetrafluoroborate where the angles $R^1$—C—N (179.2°) and C—N—$R^2$ (177.4°) were found. The C—N bond length of 1.15 A° indicated that form (**128a**) is the major contributor to the structure. However, CNDO/2 calculations revealed that, while the positive charge was spread over the entire acetonitrilium group, the carbon atom derived from the nitrile carried the most density. This may be largely due to polarization effects involving the tetrafluoroborate counterion.[210] More recently, the crystal structure of an organometallic nitrilium ion derived from *t*-butyl isocyanide has been obtained. This is significantly bent at nitrogen (169.5°), indicating a contribution from the ketenimine resonance form.[211]

Nitrilium chemistry ranges far beyond hydrolysis to an amide (Ritter reaction) or cyclization (intramolecular Ritter reaction). The generation of nitrilium triflate salts, often in high yield (72–95%),[212] has permitted detailed study of such processes.[213–215] In particular, evidence for the intermediacy of the nitrilium ion in the Beckmann rearrangement,[216,217] von Braun amide degradation[218] and Bischler–Napieralski reaction[219] has been presented. Fodor and Nagubandi[206,220,221] have done much to clarify the interplay of these previously unrecognized relationships of named reactions,[222] as illustrated in Scheme 65 for structures (**129**)–(**137**). This summary may readily be extended to include analogs of the Bischler–Napieralski reaction such as the Pictet–Gams isoquinoline synthesis and Pictet–Hubert (Morgan–Walls) phenanthridine synthesis, as well as offshoots incorporating carbenium ion and imidate chemistry.

It has been shown[208,223] that appropriately substituted nitrilium ions undergo stereospecific attack by nucleophiles to produce only the (*Z*)-isomer (**138**), *i.e.* approach of nucleophile $Y^-$ is concomitant with development of the *trans*-nitrogen lone pair (Scheme 66). While this stereospecificity may be completely general, it can only be proven for cases where addition is faster than nitrogen inversion in (**138**). The

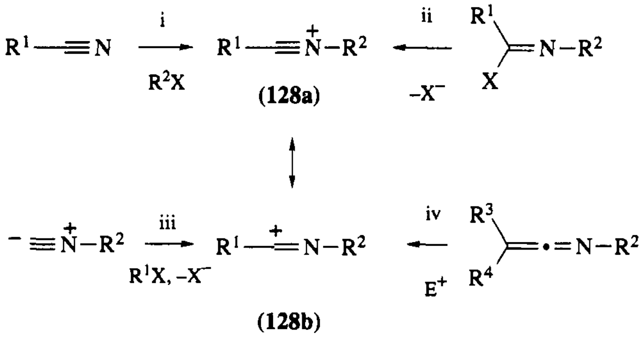

Scheme 64

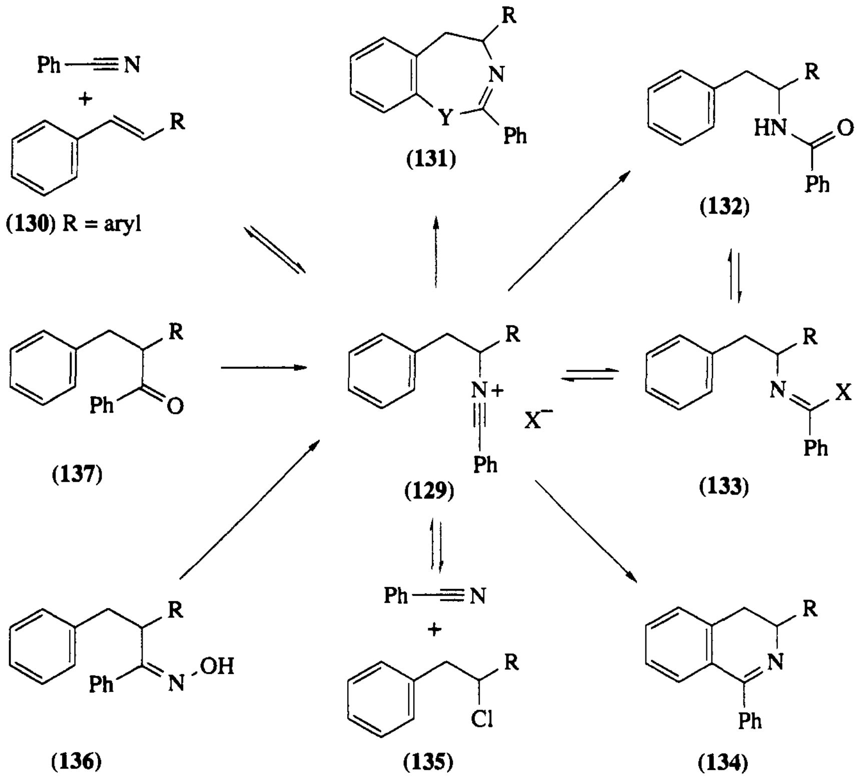

**KEY**: **Reaction name**: functional group conversion; steps involved; typical reagents

**Ritter reaction**: alkene *(etc.)* into amide, sequence **(130)** → carbenium ion → **(129)** → **(133)** → **(132)** or **(130)** → **(129)** → **(132)**; $H_2SO_4$ then $H_2O$ ($X = SO_3H$).

**Retro-Ritter reaction**: amide into alkene; reverse sequence to above; $SOCl_2$ or $P_4O_{10}$.

**Intramolecular Ritter reaction**: alkene *(etc.)* into heterocycle; sequence **(130)** → carbenium ion → **(129)** → **(131)** (where Y is a nucleophilic substituent); $H_2SO_4$ then $H_2O$.

**Bischler–Napieralski reaction**: β-phenethylamide into 3,4-dihydroisoquinoline; sequence **(132)** → **(133)** → **(129)** → **(134)**; $P_4O_{10}$ or $POCl_3$ plus Lewis acid.

**Beckmann rearrangement**; ketoxime into amide; sequence **(136)** → **(129)** → **(132)**; $PCl_5$.

**Schmidt reaction**: ketone *(etc.)* into amide; sequence **(137)** → **(129)** → **(132)**; $HN_3$ and $H_2SO_4$.

**von Braun reaction** (modified): amide into alkyl halide and nitrile; sequence **(132)** → **(133)** → **(129)** → carbenium ion → **(135)**; $PCl_5$.

**Scheme 65** Schematic summary of some major nitrilium ion reaction pathways major cases studied have therefore employed substituents ($R^2$ = OR, $NR_2$, $N{=}CR_2$ and SR) which retard inversion of the imidoyl nitrogen atom. Consequently, previously unknown materials such as *O*-acylisoamides (**139**) may be readily obtained (equation 51).[224] Such *O*-acylated products may be generated in the presence of amines as *in situ* acyl transfer reagents for peptide synthesis.[225] It seems likely that these stereochemical considerations are a major factor in the success of intramolecular Ritter cyclizations (Section 1.9.2.1).

As an extension of the amidoseleniation processes discussed previously,[194–197] imidates (the third Ritter intermediate) may be utilized as precursors for the synthesis of cyclic amides (Scheme 67)[226] and lactams (equation 52).[227] Such combination of imidate and onium ion processes has much potential for further extension of Ritter-type chemistry.

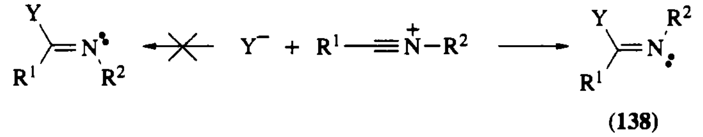

**(138)**

**Scheme 66**

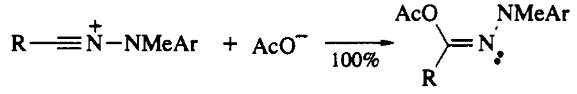

**(139)**

(51)

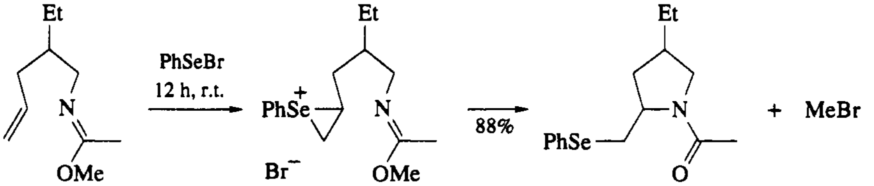

**Scheme 67**

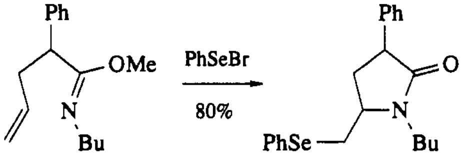

(52)

### 1.9.4.2 Isonitriles and Ritter-type processes

Although the isomeric nitrile (R—CN) and the isonitrile (R—NC) functional groups have structural characteristics leading to their own unique chemistry,[207,228,229] the two have much in common. They share properties such as a linear configuration, triple bonding between carbon and nitrogen, low steric demand, polarizability and similar bond strengths. Both have large and similar dipole moments, for example 3.9 D for benzonitrile and 3.5 D for phenyl isocyanide.[230] Not surprisingly, there are therefore occasions when their chemistry becomes closely related.

In valence bond terms, the isonitrile (isocyanide) group requires representation as two resonance structures (**140a**) and (**140b**), but physical properties indicate that the dipolar contribution (**140a**) is the major one. The isonitrile structure involves divalent carbon,[230] a property shared only with carbon monoxide and fulminates (R—O—NC) as isolable entities. Since the latter are notoriously reactive materials, this singles out the isonitriles as the only stable family of organic compounds which are formally divalent.

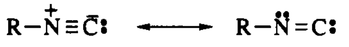

$$R-\overset{+}{N}\equiv\overset{-}{C}: \longleftrightarrow R-\ddot{N}=C:$$

**(140a)** **(140b)**

Formerly, isonitriles were perhaps best known to many chemists through the indescribably vile odor[231] of volatile members of the series encountered during the Hofmann carbylamine test for primary amines.[232] Over recent years, however, isonitriles have come into their own as versatile synthetic reagents. Several reliable preparative methods now allow ready access to this family of substances and their remarkable chemistry.[207,233] Biological pathways to isonitriles are also known, the first such substance isolated being the antibiotic xanthocillin (**141**), isolated from *Penicillium notatum*.[234,235] Isonitrile compounds are also isolated fairly frequently from marine sources.[236]

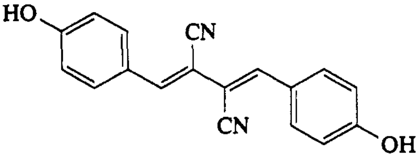

**(141)**

It has been known for many years that on strong heating isonitriles isomerize to nitriles[237] in an exothermic, unimolecular process. For example,[238] kinetic work on *p*-tolyl isocyanide demonstrated that clean isomerization to *p*-tolunitrile took place in solution at 200 °C with an energy of activation of 154 kJ mol$^{-1}$. Cyclobutyl isocyanide underwent rearrangement to cyclobutanenitrile without ring-contraction or ring-opening side products being formed.[239] Furthermore, the homochiral isonitrile (**142**) underwent rearrangement (equation 53) with almost complete retention of configuration. It is therefore believed that the thermal isomerization process is a concerted reaction.[240] However, more recently, evidence for a competing radical process in solution reactions has been presented.[241,242] At the lower reaction temperatures normally employed in organic synthesis, these isomerization processes are not a complicating factor.

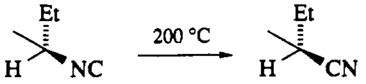

**(142)**

(53)

A further bridge between the chemistry of the two functional groups is formation of nitrilium ions. Nucleophilic attack on a carbenium ion by the carbon atom of an isonitrile produces a nitrilium ion (**143**) identical in all respects with that resulting from Ritter reaction (Scheme 68). In practice this process is less common than might be expected since the procedure for generating carbenium ions for Ritter reaction is through use of strong acid which would destroy the isonitrile. Thus, the tropylium ion reacts with isonitriles (Scheme 69)[243] to give a nitrilium intermediate which is hydrolyzed to the corresponding amide in traditional Ritter fashion. In a related process (Scheme 70) the benzyne precursor (**144**) reacts with cyclohexyl isocyanide to produce the amide (**145**). Here, nucleophilic attack on benzyne was followed by dehydration of the *t*-butanol solvent to yield the stable products.[244] A further interesting example[245] involves reaction of the cyclobutadiene complex (**146**) with cyclohexyl isocyanide (Scheme 71).

Acidic hydrolysis of isonitriles proceeds in two steps to the *N*-formamide and subsequently to the amine derivatives in common with nitrilium ions produced in the Ritter reaction using hydrogen

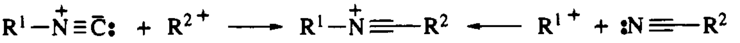

$$R^1{-}\overset{+}{N}{\equiv}\bar{C}{:} \; + \; R^{2+} \longrightarrow R^1{-}\overset{+}{N}{\equiv}{-}R^2 \longleftarrow R^{1+} + {:}N{\equiv}{-}R^2$$

**(143)**

**Scheme 68**

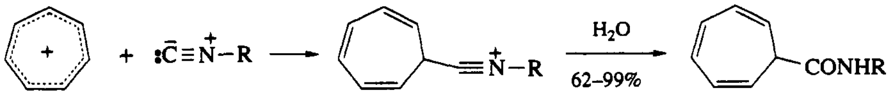

**Scheme 69**

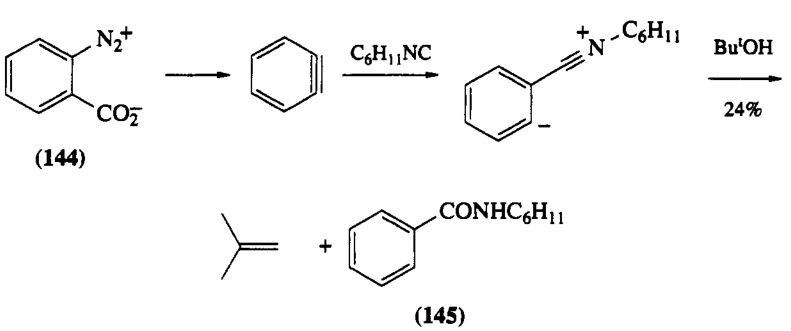

**Scheme 70**

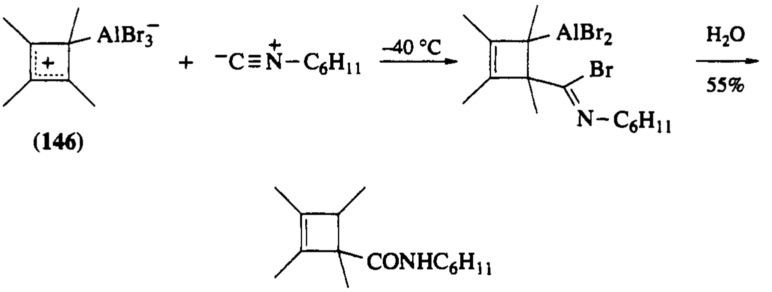

**Scheme 71**

cyanide.[246] In another parallel with chemistry discussed earlier, isonitriles may also be employed in aldehyde syntheses, including production of C(1)-labeled derivatives.[247,248] Coordination of an isonitrile to a metal leads to a rich range of chemistry.[207,249] In the presence of catalytic amounts of metal ion, the hydroxyalkyl isocyanides (**147**) are cyclized in quantitative yield to the 2-oxazoline and dihydro-1,3-oxazine derivatives (equation 54).[250] This process is analogous to the intramolecular Ritter process.

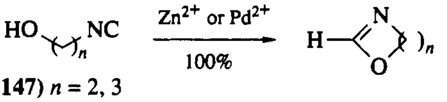

(54)

A major reaction of isonitriles is α-addition of a reagent XY to the formally divalent carbon atom (equation 55), thereby yielding imidate or imidoyl products[251] and providing a further direct connection with Ritter-type reactivity. Indeed, on occasion, isonitriles have been obtained from Ritter reactions *via* such intermediates.[25,27] Recent elegant work by Livinghouse[252–254] illustrates how isonitrile chemistry is intermeshed with Ritter-type processes. Isonitriles react with acyl halides (Scheme 72) to produce keto-imidoyl halides, *e.g.* (**148**), from which the acylnitrilium ion (**149**) may be generated through reaction with silver salts. In this example, the reactive intermediate cyclizes readily and in high yield to the corresponding dihydroisoquinoline. A range of nitrogen heterocyclic systems has been synthesized using this methodology.

Isonitriles can otherwise attain tetravalent respectability by participating in cyclization reactions,[207,255] and in multicomponent condensations such as the Passerini[207] (3-component) and Ugi (4-component) reactions.[207,256] Nitrilium-type intermediates are implicated in many of these processes. These isonitrile reactions of major synthetic importance are discussed in detail elsewhere in this compendium.

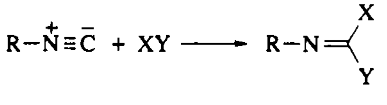

$$R-\overset{+}{N}\equiv\overset{-}{C} + XY \longrightarrow R-N=C\begin{matrix}X\\Y\end{matrix} \qquad (55)$$

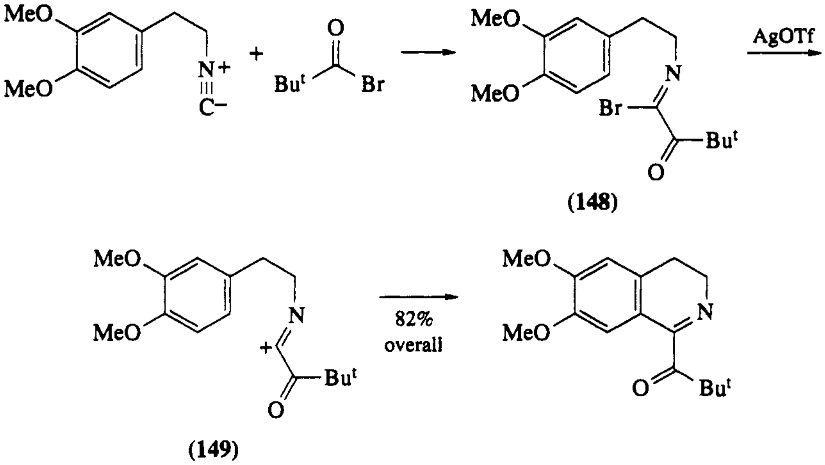

Scheme 72

## 1.9.5 REFERENCES

1. J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045.
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# 2.1
# Synthesis of Acid Halides, Anhydrides and Related Compounds

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## 2.1.1 INTRODUCTION

Activation of the carbonyl group is the major purpose for the generation of the carboxylic acid derivatives treated in this chapter. They are of importance as intermediates in the preparation of other functionalized organic molecules. The electronic character of the substituents at the carbonyl group of the carboxylic acid increases the electrophilicity of the carbonyl C atom and, therefore, facilitates the attack by nucleophiles. The different electron-withdrawing power of the halogen atoms, the acyl group in anhydrides or the cyano group in α-ketonitriles allows a fine tuning of the electronic character of the carbonyl C atom. This can be used successfully for adapting the reactivity in the desired direction. Although acid chlorides represent the biggest number of acyl derivatives and, therefore, are used preferentially for synthetic purposes, it is sometimes of advantage to rely on other acyl compounds. α-Ketonitriles form a separate class of acid derivatives. Besides being mild acylating agents they can undergo a number of useful synthetic reactions.

The preparation of the acid derivatives is organized according to their precursors. The synthetic method of choice in a particular case will depend on a number of factors of which the presence of other functional groups in the molecule under study is not the least important. The methods will be evaluated with respect to their scope of application. The chemistry of acid halides has been reviewed.[1] Methods of preparation are treated in Houben–Weyl[2] as well as in other reference books.[3,4] This applies also to acid anhydrides[5] and α-ketonitriles.[6]

## 2.1.2 ACID HALIDES

No explicit subdivision according to the type of halide will be made, *i.e.* the preparation of acid fluorides, chlorides, bromides and iodides will be treated simultaneously.

### 2.1.2.1 Acid Halides from Carboxylic Acids

The most widely used synthesis of acid chlorides is based on the reaction of a free carboxylic acid with thionyl chloride. A number of examples of this reaction can be found.[7] The mechanism seems to involve an intermediate chloro sulfite, which is transformed to the acid chloride (equation 1).[8] Polar solvents normally increase the reaction rates.[9]

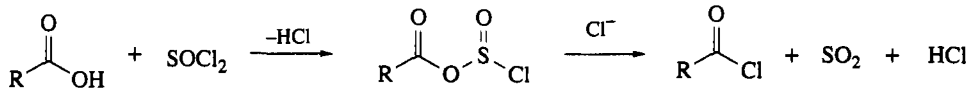

(1)

The reactions can be catalyzed effectively by various additives. It has been shown that dimethylformamide constitutes an effective catalyst in many cases, the reaction being thought to proceed *via* an intermediate imidoyl chloride (equation 2).[10] The catalytic effect may be so pronounced that otherwise unreactive carboxylic acids can be transformed to their acid chlorides. An example is trichloroacetic acid which reacts only in the presence of *N*,*N*-dimethylformamide with thionyl chloride.[10] Interestingly, this reaction can also be accomplished in the presence of an alkali metal chloride.[1] Other catalysts being used include pyridine[11] and triphenylphosphine.[12] The latter converts iso- and tere-phthalic acid quantitatively to the corresponding acid dichlorides.

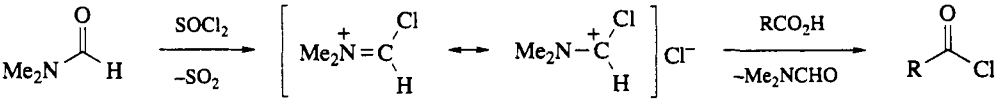

(2)

The nature of the catalyst seems to be important if additional functional groups are present. Thus, a complicating factor may be that double bonds in a molecule add the evolving hydrogen chloride. By using hexamethylphosphoramide and thionyl chloride at low temperature (–20 °C) this side reaction can be suppressed and in the case of acrylic acid, acryloyl chloride is formed in 80% yield.[13] The reactivity towards thionyl chloride is such that there is a correlation with the acidity of the acids: the stronger the acid the less reactive it is. A rate acceleration can be achieved in strongly polar solvents.

Phosphorus chlorides, $PCl_3$, $PCl_5$ and $POCl_3$, are common reagents for preparing acid chlorides of a variety of carboxylic acids. A comprehensive discussion of these reagents has been given by Ansell.[1] In these cases the reaction conditions, with regard to relative amount of phosphorus halide, solvent, temperature *etc.*, are important parameters for successful applications, *i.e.* tolerable yields. The often sluggish reactions with these phosphorus halides do not recommend them as reagents. Side reactions, *e.g.* oxidations at higher temperatures, and difficulties in the handling of $PCl_5$ have led to their replacement by other reagents.

Modified phosphorus halides, which allow more controlled reaction conditions, have been developed more recently. Thus 2,2,2-tribromo- and 2,2,2-trichloro-1,3,2-benzodioxaphospholes (**1a**) and (**1b**),[14–16] as well as dichloro- and dibromo-phosphoranes (**2a**) and (**2b**)[17] have been used successfully in the preparation of a number of aromatic and aliphatic acid halides. These reactions can be carried out at room temperature or slightly above and convert carboxylic acids or anhydrides in good yield to the acid halides. Also, unsaturated acids tolerate these reaction conditions. In many cases products can be isolated by distilling the acid halide directly from the reaction mixture. An advantage of these reagents is their solubility in organic solvents like diethyl ether, chloroform or benzene. Some examples are given in Table 1.

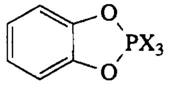

$Ph_3PX_2$

**(1a)** X = Cl
**(1b)** X = Br

**(2a)** X = Cl
**(2b)** X = Br

**Table 1** Acid Chlorides and Acid Bromides from Free Carboxylic Acid and Reagents **(1a)** and **(1b)**

| *Acid* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| $MeCO_2H$ | **(1a)** | MeCOCl | 67 | 15 |
| $ClCH_2CO_2H$ | **(1a)** | $ClCH_2COCl$ | 77 | 15 |
| $ClCH_2CO_2H$ | **(1b)** | $ClCH_2COBr$ | 80 | 16 |
| $EtCO_2H$ | **(1b)** | EtCOBr | 78 | 16 |
| $PhCO_2H$ | **(2a)** | PhCOCl | 63 | 14 |
| $Me_2C{=}CHCO_2H$ | **(2b)** | $Me_2C{=}CHCOBr$ | 50 | 17 |
| $PhCH{=}CHCO_2H$ | **(2b)** | $PhCH{=}CHCOBr$ | 76 | 17 |
| $C_6H_{11}CO_2H$ | **(2b)** | $C_6H_{11}COBr$ | 71 | 17 |

Problems of isolation which may arise for higher boiling or temperature sensitive acid halides can be circumvented by the use of polymer-bound phosphorus halides. Thus, a suspension of trisubstituted phosphine dichlorides, chemically connected to cross-linked polystyrene, reacted with carboxylic acids in methylene chloride almost quantitatively according to equation (3).[18]

Product isolation is very simple as only the solvent has to be removed after separation from the polymer. The polymer can be returned to the active chlorinating agent by reaction with carbonyl chloride. A variation of this procedure does not require polymer-bound phosphorus halide but uses Lewis acid–Lewis base complexes between anion-exchange resins, such as Amberlite IRA 93, and phosphorus pentachloride (equation 4).[19] Again, isolation of the resultant acid chloride is simple and the exhausted polymer can be regenerated for further use by simply washing it with aqueous acidic and basic solutions. Yields range from 51% for crotonic acid chloride to 86% for decanoic acid chloride.

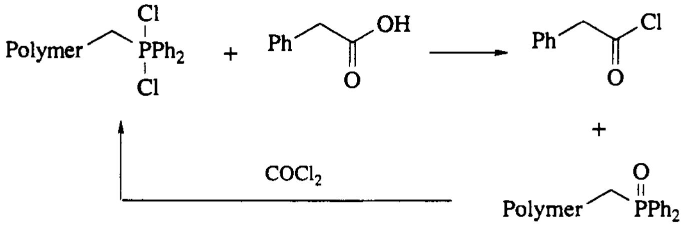

(3)

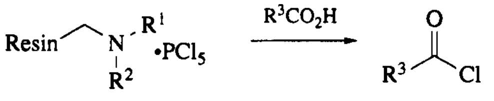

(4)

The reactions of thionyl chloride and phosphorus halides, also in their polymer-modified form, involve the formation of hydrogen halide and cannot, therefore, be applied without complications to acid sensitive compounds. The combination of triphenylphosphine and tetrachloromethane as reagent provides conditions under which, for instance, pelargonic acid can be converted to the acid chloride in good yield according to equation (5).[20] This method has been recently applied to polymer-bound triphenylphosphine.[21] Table 2 lists some examples of acids treated in this manner.

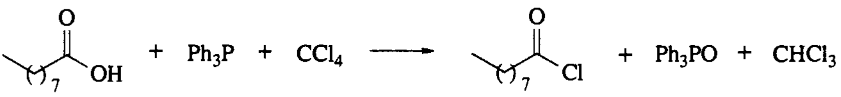

(5)

**Table 2** Conversion of Acids to Acid Chlorides by Treatment with Phosphine Resin[a] (2 equiv.) in Carbon Tetrachloride under Reflux for 4 h

| *Acid* | *Yield (%)* |
|---|---|
| *n*-Octanoic | 63 |
| Phenylacetic | 50 |
| Stearic | 82 |
| Phenoxyacetic | 50 |
| Cinnamic | 77 |
| Benzoic | 90 |
| β-Naphthoic | 84 |
| α-Furoic | 82 |

[a] 1% cross-linked polymer containing 2.50 mmol of phosphine per g.

Whereas the need to prepare the polymer might count against this technique, the commercial availability of a polymer obtained from polymerization of diphenyl-*p*-styrylphosphine would make this procedure more attractive (equation 6).[22] The process has also been tried successfully for the conversion of alcohols to alkyl chlorides. There are, however, limitations in the fact that the starting material cannot be regenerated for the reaction with carbon tetrachloride. In this respect the above mentioned reagent of Relles and Schluenz might prove superior even though it has the drawback of acidic conditions.[18]

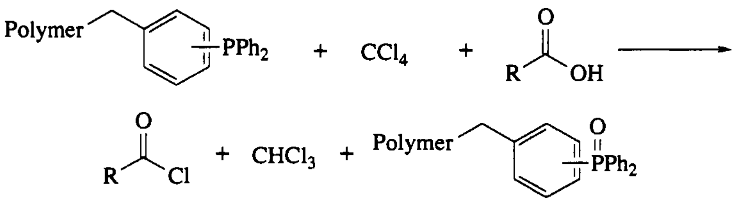

(6)

For acid-sensitive carboxylic acids it may sometimes be advantageous to use easily accessible acid halides of other carboxylic acids as halogen transfer agents. In this case an equilibrium is established between the carboxylic acid, its acid halide, the halogenating agent and its reaction product, respectively. This procedure is of particular interest if the desired product has a lower boiling point than the reagent.[23] Thus, acrylic acid can be converted to its acid chloride in 76% yield by use of benzoyl chloride as reagent (equation 7).[24] If higher boiling acid chlorides are desired then phthaloyl chloride may be a suitable reagent.[25,26] In this way maleic anhydride gives in the presence of $ZnCl_2$ *ca.* 90% fumaryl chloride. Benzenesulfonyl chloride has also been used in this context.[27] Polymer-bound aroyl chloride may be an alternative.[28]

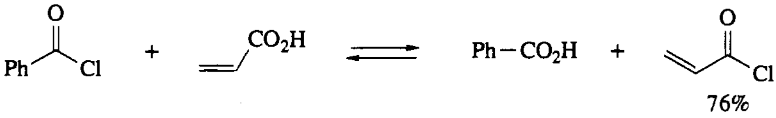

(7)

An extension of this methodology which, however, again involves the generation of hydrogen halide is the application of carbonyl chloride and oxalyl chloride (equations 8 and 9). As in the case of thionyl chloride only gaseous byproducts are formed, thus facilitating the isolation of the products. These reagents are in many cases a true alternative to the thionyl halides, sometimes giving even better yields and requiring less drastic reaction conditions. For a thorough discussion see Ansell.[1] Large scale syntheses in high yield either continuously or in batches seem to be possible by these procedures. A variety of catalysts has been applied successfully. For a list of references see Houben–Weyl.[2]

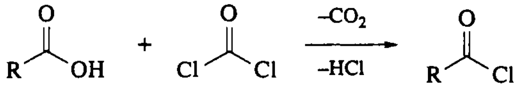

(8)

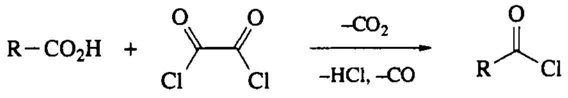

(9)

A method for converting carboxylic acids under neutral conditions to the corresponding acid chlorides is available with α-halogenated ethers as reagents. Thus it has been shown that 2-chlorodioxin can give acid chlorides of a variety of acids in good yield.[29] The method, however, has not received wide application. Instead α,α-dichloromethyl methyl ether, which can be prepared easily,[30] has replaced other α-haloethers as reagents.[31] In Table 3 some examples are listed.

**Table 3** Acid Chlorides from the Reaction of Dichloromethyl Methyl Ether[a] with Carboxylic Acids

| *Acid* | *Product* | *Yield (%)* |
|---|---|---|
| $Cl_3CCO_2H$ | $Cl_3CCOCl$ | 88 |
| $CH_2(CO_2H)_2$ | $CH_2(COCl)_2$ | 88 |
| $(CH_2CH_2CO_2H)_2$ | $(CH_2CH_2COCl)_2$ | 96 |
| $PhCO_2H$ | $PhCOCl$ | 96 |
| $PhCH_2CO_2H$ | $PhCH_2COCl$ | 92 |

[a] The reagent is used in 25% excess in the presence of 0.001 mol % $ZnCl_2$.

Sometimes the addition of a small amount of $ZnCl_2$ as a catalyst is recommended, *e.g.* succinic acid is transformed to the dichloride only in the presence of this catalyst. It has to be noticed, however, that under these conditions hydrogen chloride is evolved and, therefore, acid sensitive compounds cannot be taken. *N*-acylamino acid chlorides[32] and chlorides of fully acetylated sugar acids[33] are also obtainable in yields of 70% or more. Whereas most reagents seem to be unsuited to the preparation of acid halides of α-keto acids, dichloromethyl methyl ether is successful in this reaction (equation 10).[34] Pyruvyl chloride can now be made in *ca.* 50% yield.[35] In some examples the corresponding α,α-dibromomethyl methyl ether has also been tested.[36]

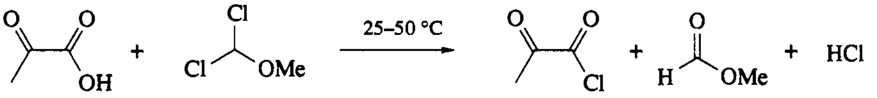

(10)

There are as shown a number of reagents for the preparation of acid chlorides; acid bromides are also produced by similar reactions, *e.g.* with thionyl bromide.[37] A general approach to obtain acid halides of fluorine, chlorine, bromine and iodine has been described by Ghosez *et al.* (equation 11).[38] 1-Dimethylamino-1-chloro-2-methylpropene, which is accessible from *N*,*N*-dimethylisobutyroamide,[39] is a generally applicable reagent for this purpose. The other halo derivatives can be formed by halogen exchange. Under very mild conditions, *i.e.* at room temperature or below in dichloromethane as solvent, the acid halides are obtained in high yield (Table 4). No hydrogen halide is evolved, so acid labile compounds

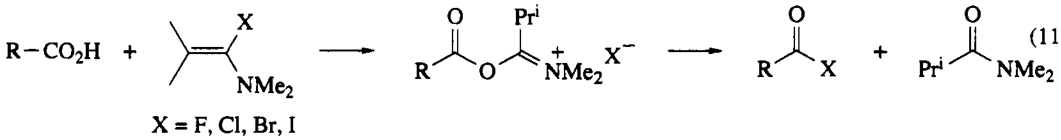

(11)

**Table 4** Preparation of Acyl Halides RCOX[a] According to equation (11)

| *R* | *X* | *Yield (%)*[b] |
|---|---|---|
| $Cl_3C$ | Cl | 100 |
| $Bu^t$ | Cl | 100 |
| $H_2C{=}CH$ | Cl | 96 |
| MeCO[c] | Cl | 100 |
| Pyrrol-2-yl | Cl | 100 |
| Furan-2-yl | Cl | 100 |
| H[d] | Cl | 94 |
| $Cl_3C$ | F | 100 |
| $Bu^t$ | F | 100 |
| H | F | 100 |
| $Bu^t$ | Br | 100 |
| $H_2C{=}CH$ | Br | 100 |
| H | Br | 100 |
| Me | I | 100 |
| $Bu^t$ | I | 100 |
| H[e] | I | 100 |

[a] Reactions were carried out at 20 °C unless otherwise stated. [b] Determined by NMR spectroscopy. [c] −20 °C. [d] −60 °C. [e] −20 °C.

can also be subjected to this reaction. Also thermally unstable acid halides such as formyl chloride or formyl iodide can be made due to the high reactivity of the halogenating agent, which permits the use of temperatures as low as –60 °C.

Some special procedures for the preparation of acid fluorides from carboxylic acids will be added at this point. Several reagents have been suggested recently. Olah proposed the adduct of pyridine and $SeF_4$.[40] In halogenated solvents at room temperature the acid fluorides are normally isolated in yields greater than 80%. Similar good results were reported for cyanuric fluoride, which is prepared from cyanuric chloride with hydrogen fluoride.[41] The reactions are carried out in acetonitrile in the presence of pyridine. Double bonds, triple bonds and hydroxy groups are tolerated under these conditions. These new methods seem to be superior to sulfur tetrafluoride for the generation of acid fluorides.[42]

### 2.1.2.2 Acid Halides from Acid Halides by Transformation

As a synthetic approach this reaction is valuable for the generation of acid bromides, acid iodides and acid fluorides. The readily accessible acid chlorides are a convenient starting material. Thus, it is possible to react acid chlorides with hydrogen fluoride, hydrogen bromide or hydrogen iodide to obtain the corresponding acid halides.[43]

More recent approaches which avoid acidic conditions are based on the application of trimethylsilyl bromide or iodide (equation 12).[44] With aliphatic acid halides a high reactivity (often the reaction is exothermic) is observed. The isolation of the products can be effected immediately after the addition of trimethylsilyl halide is complete. With aromatic halides heating is sometimes required. Easy work-up is possible, because only the low boiling trimethylsilyl chloride has to be removed before the product is isolated by distillation. Table 5 gives some examples.

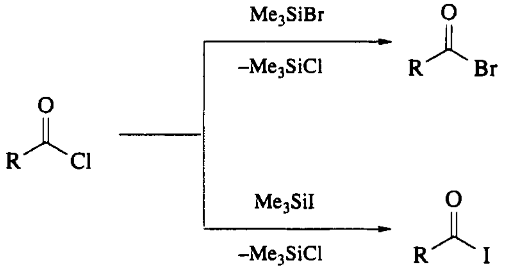

(12)

**Table 5** Acid Bromides and Acid Iodides from Acid Chlorides *via* Reaction with Trimethylsilyl bromide or Iodide

| *Product* | *Yield (%)* | *Product* | *Yield (%)* |
|---|---|---|---|
| EtCOBr | 74 | MeCOI | 46 |
| $Pr^nCOBr$ | 89 | EtCOI | 93 |
| PhCOBr | 79 | $Pr^nCOI$ | 86 |
| $(COBr)_2$ | 85 | PhCOI | 83 |
| $(H_2CCOBr)_2$ | 78 | | |

Another versatile pathway to acid iodides was described by Hoffmann (equation 13).[45] Aliphatic and aromatic acid iodides are prepared in high yields from acid chlorides by reaction with sodium iodide in acetonitrile. A large number of alkanoyl, alkenoyl and aroyl iodides can be prepared in good yields from the corresponding acid chlorides. In the same way it was possible for the first time to obtain diiodides from aliphatic and aromatic dicarboxylic acids.[46] The conversion of acid chlorides to iodides by sodium iodide had been known before;[47,48] the reaction conditions proposed by Hoffmann, however, are milder and the yields are higher.

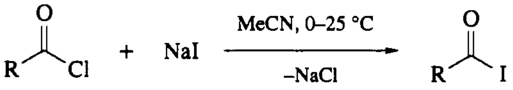

(13)

The transhalogenation reaction has been applied widely to the preparation of acid fluorides.[1] Newer developments include the use of dialkylaminotrifluorosulfonate as reagent (equation 14).[49] This compound not only converts a variety of organic acid chlorides to acid fluorides but is also able to produce thionyl fluoride from thionyl chloride as well as other fluorides of inorganic acids. A mixture of pyridine (30%) and hydrogen fluoride (70%) has been proposed as a replacement for hydrogen fluoride itself, because it is a stabilized, less volatile form of HF (equation 15). This is a versatile reagent which among many other fluorinations can produce acid fluorides in excellent yields.[50]

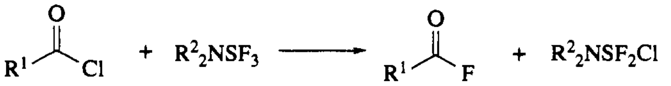

(14)

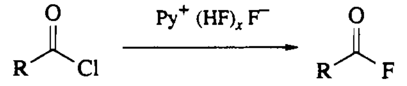

(15)

### 2.1.2.3 Acid Halides from Acid Anhydrides

Acid anhydrides as activated derivatives of carboxylic acids have found little attention for the preparation of acid halides. Their use can be justified if they are obtained from other sources than from carboxylic acids, *e.g.* phthalic anhydride from the oxidation of naphthalene or *o*-xylene. It is, therefore, no surprise that there exist patents to convert phthalic anhydride to phthalic acid dichloride with carbonyl dichloride in the presence of catalysts.[2,51–53] However, there are some methods available; thus α,α-dichloromethyl methyl ether will convert acid anhydrides to acid chlorides[31] and brenzcatechyl phosphorus tribromide will also achieve this transformation.[36] Fluorides may be prepared similarly with the pyridine/HF mixture of Olah.[50]

### 2.1.2.4 Acid Halides from Carboxylic Acid Esters

If carboxylic acid esters are readily available, they provide a convenient basis for the preparation of acid halides. Modified phosphorus halides, like 2,2,2-trichloro-1,3,2-benzodioxaphosphole can be applied successfully.[15] This reagent forms first a 1,1-dichloroalkyl ether, which decomposes to the acid chloride (equation 16). The reaction conditions are rather drastic. For instance *n*-butyl benzoate has to be heated for 4 h at 180 °C in order to get a 90% yield of benzoyl chloride. The only stable and isolable 1,1-dichloro ether is α,α-dichloromethyl methyl ether, which, as described above, is used as a mild reagent for the conversion of carboxylic acids to their chlorides. Similarly severe conditions are required if the chlorine or bromine adduct of triphenylphosphine is selected.[54,55] This reaction may be catalyzed by $BF_3$. It has been applied successfully to unsaturated esters and to the cleavage of lactones.

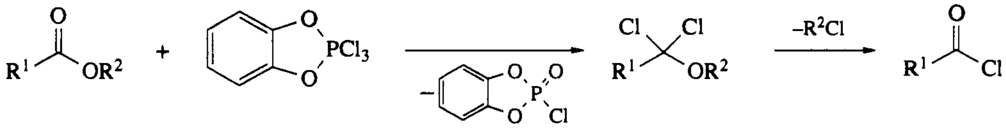

(16)

Neutral conditions are also realized if trimethylsilyl esters are reacted with dibromotriphenylphosphine.[56] This reaction, as shown in equation (17), can also be applied to sterically hindered trialkylsilyl esters.[57]

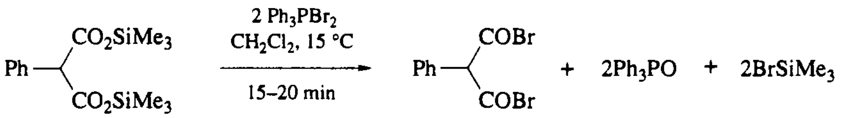

(17)

A general route to acid fluorides, chlorides, bromides and iodides is provided by the reaction of enol esters, such as isopropenyl esters, with the appropriate hydrogen halide (equation 18).[58,59] Phthalic acid dichloride in the presence of chlorosulfonic acid has been proposed as a reagent for the conversion of carboxylic esters to acid chlorides in high yield, as is shown in equation (19) for the cleavage of the ethyl ester of chlorofluoroacetic acid.[60]

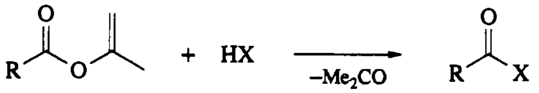

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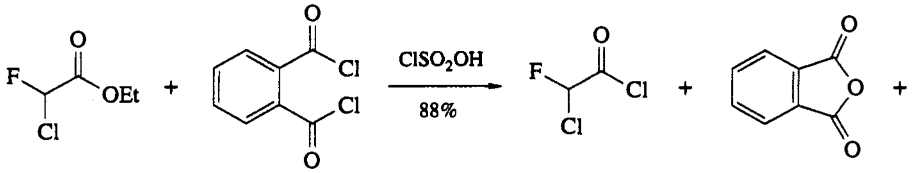

(19)

## 2.1.2.5 Acid Halides from Acyl Amides and Hydrazides

Staab introduced azolides as versatile reagents in organic synthesis.[61] The reaction of carbonyldiimidazolide with carboxylic acids produces imidazolides under mild conditions which can be converted by the action of hydrogen halides to acid halides in high yield (equation 20). The method does not even require the isolation of the imidazolides, but can be carried out as a one-pot synthesis.[62] The possibility of carrying out this reaction at low temperatures allows the preparation of temperature sensitive compounds. Formyl chloride, which decomposes at −40 °C, has been prepared in this way.

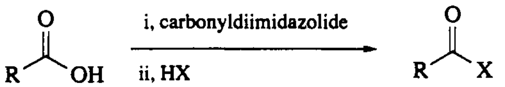

(20)

Other possibilities include the reaction of hydrazides with hydrogen chloride in nitromethane or methylene chloride.[63] Also thionyl chloride or sulfuryl chloride will produce acid chlorides from hydrazides,[64] although these reactions seem to be of limited scope.

## 2.1.2.6 Acid Halides from Aldehydes

Aldehydes were among the first compounds to be converted to acid chlorides. Thus, Liebig and Woehler reported the formation of benzoyl chloride from benzaldehyde.[65] A discussion of acid halide syntheses starting from aldehydes is given in ref. 1. Most of these reactions seem to be of free radical character, carried out using reagents like *t*-butyl hypochlorite, *N*-chlorosuccinimide or *N*-bromosuccinimide. In special cases where aldehydes are readily available and where functional groups prevent the application of other methods, these reagents might constitute an alternative for the preparation of acid halides. The use of *N*-bromosuccinimide for the direct oxidation of aldehydes to acid bromides has been taken up recently.[66] Iodobenzene dichloride has also been described as a reagent for producing acid halides directly from aldehydes.[67]

## 2.1.2.7 Acid Halides by Introduction of a Halocarbonyl Group

The conversion of an organic compound to an acid halide by introduction of a halocarbonyl group directly is an attractive synthetic possibility. Thus, acid halides can be obtained if hydrocarbons are reacted with oxalyl chloride in the presence of free radical initiators like dibenzoyl peroxide. Obviously, this will not be a very selective procedure and only highly symmetrical compounds with preferentially one type of CH bond will lead to acceptable selectivity and yield. Kharash showed that cyclohexane can give cyclohexanecarboxylic acid chloride in 65% yield according to equation (21).[68] Higher selectivity can be expected if functionalized compounds render one kind of CH bond particularly reactive towards free radical abstraction. Substituted malonic acid dibromides are formed in this way by reaction of acid bromides with oxalyl bromide in yields ranging from 40 to 70%.[69] A radical chain reaction in tetrachloromethane in the presence of carbon monoxide is another alternative.[70,71]

In principle the possibility of introducing a halocarbonyl into aromatic compounds with carbonyl dichloride in the presence of Lewis acids exists. In practice it is difficult to stop the reaction after the first electrophilic substitution, because the reaction products themselves can react further to give ketones.[72] However, there are exceptions. Thiophene reacts with phosgene in the presence of aluminum trichloride to give 2-chlorocarbonylthiophene almost quantitatively.[73]

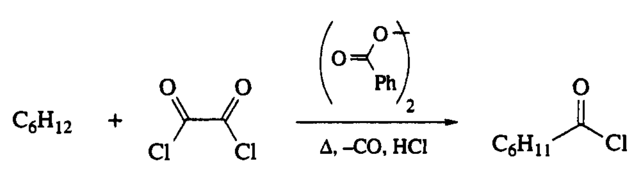
(21)

An attractive pathway with a lot of potential uses the transition metal mediated reaction of organic halides with carbon monoxide.[74–76] Suitable substrates are organic halides capable of oxidative addition to low-valent transition metal compounds. Insertion of carbon monoxide and reductive elimination of an acid halide will complete the catalytic cycle. In this way it was shown that allyl chloride yields butenoic acid chloride in >80% yield according to equation (22).[77,78] As well as palladium, rhodium and iridium also act catalytically.[2] It is of no surprise that allylic halides, benzylic halides and aryl halides in particular are readily converted to acid halides. Simple aliphatic halides undergo the oxidative addition step more slowly and, if they carry hydrogen atoms on an $sp^3$ hybridized C atom in the β-position to the halogen atom, may give alkenes *via* β-hydrogen elimination. Alkenes can also be converted to acid halides with carbon monoxide in the presence of transition metal catalysts in solvents such as methylene chloride or tetrachloromethane.[79]

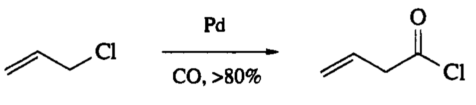
(22)

### 2.1.2.8 Miscellaneous Methods of Preparation of Acid Halides

There are a number of specialized methods for the preparation of acid halides which, however, do not seem to have general applicability. For a summary see ref. 1.

## 2.1.3 ACID ANHYDRIDES AND MIXED ANHYDRIDES

Acid anhydrides play a similar role in organic chemistry to acid halides. The enhanced electrophilic character of the carbonyl groups renders them valuable intermediates in organic syntheses. Several general approaches exist for their preparation and depending on the availability of the starting material or the presence of sensitive functional groups one or the other procedure may be the method of choice for their generation.[80]

### 2.1.3.1 Acid Anhydrides from Carboxylic Acids by Dehydration

The most general procedure for the preparation of acid anhydrides starts from free carboxylic acids which are activated by suitable reagents in order to make the overall bimolecular dehydration process feasible under moderately mild conditions. Thermal dehydration, in principle the simplest method (equation 23), is only of limited preparative value giving the acid anhydride only in low yield.[81,82] Even in special cases, where dicarboxylic acids may form five- or six-membered rings, anhydride formation requires dehydration agents. In the simplest case concentrated sulfuric acid may be applied.[83] For some examples see ref. 80. The advantage of an intramolecular dehydration, which is favored entropically, is lost in longer chain α,ω-dicarboxylic acids where normally intermolecular reactions with the formation of polymers is the result. In general more specific reagents have to be found to effect the elimination of water from two molecules of carboxylic acid to form an acid anhydride.

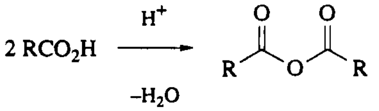
(23)

If thionyl chloride is used for activation, it is possible to react the carboxylic acid in the presence of 0.5 equiv. of the reagent. The acid halide formed initially reacts further with free carboxylic acid under elimination of hydrogen chloride. Two modes of operation are possible: either the free acid is boiled under reflux in a solvent in the presence of thionyl chloride[84] or the reaction is carried out in the presence of pyridine as base.[85] Pyridine not only traps the liberated hydrogen chloride but takes part in the mechanism of formation of the acid anhydride, allowing milder conditions than in its absence. Mostly simple aliphatic carboxylic acids have been converted to their anhydrides by this method. The just described processes lead to acid anhydrides *via* the reaction of acid halides formed *in situ* with free carboxylic acid. In some cases, and in particular if mixed anhydrides are desired, it is advantageous to react isolated acid halides with carboxylic acids. This reaction is either carried out in inert solvents in the presence of bases such as pyridine[86] (Schotten–Baumann reaction) or in aqueous medium in the presence of sodium bicarbonate.[87] Acid anhydrides of higher boiling long chain aliphatic acids can be generated by simply heating an approximate 1:1 mixture of acid and acid halide and recrystallizing the product.[88]

An acyl transfer agent which can be used for the synthesis of acid anhydrides is obtained from the reaction of an acid chloride with 4-benzylpyridine (equation 24).[89] In this way benzoic acid anhydride and cinnamic acid anhydride were obtained in 72% and 57% yields, respectively. As the intermediate, 1-acyl-4-benzylidene-1,4-dihydropyridines, can be isolated, this procedure should be well suited for the preparation of mixed anhydrides. Mixed aromatic and aliphatic anhydrides can be prepared with 2-benzoylthio-1-methylpyridinium chloride and salts of carboxylic acids.[90] These reactions are carried out in aqueous solution. They make use of the high reactivity of esters of thiocarboxylic esters towards nucleophiles. The mixed anhydrides of benzoic acid with 3-phenylpropanoic acid, phenoxyacetic acid, isobutyric acid, *p*-toluic acid and cinnamic acid were formed in 82, 79, 61, 91 and 66% yields, respectively.

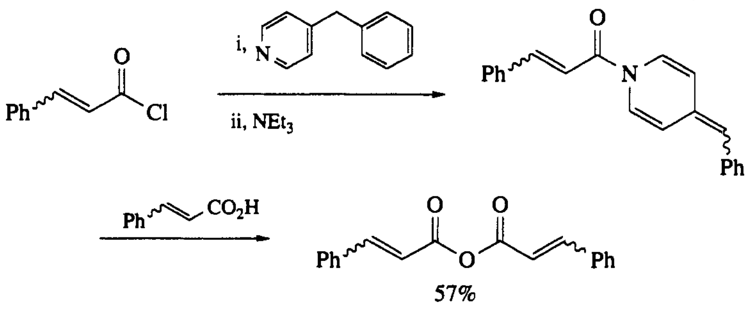

(24)

Activation of carboxylic acids by phosphorus acid halides in the form of different derivatives (3–7) has been used extensively in more recent years. These methods have been tested not only for saturated aliphatic or aromatic carboxylic acids but also for functionalized derivatives. In Table 6 some examples are collected where (3) and (4) were applied successfully.[91] The reactions are carried out at room temperature in acetone or dichloromethane by treatment of the carboxylic acid with 1 equiv. of triethylamine or *N*-ethylpiperidine and 0.5 equiv. of the reagent (equation 25). The anhydrides are either collected by filtration or recovered by evaporation of the solvent after washing with water.

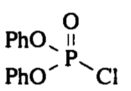

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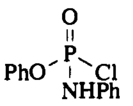

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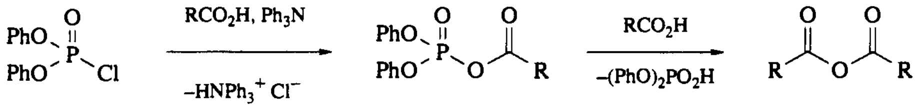

(25)

**Table 6** Symmetrical Carboxylic Acid Anhydrides from Carboxylic Acids and Reagents (3) and (4)

| *$RCO_2H$* | *Reagent* | *Yield (%)* |
|---|---|---|
| Ph | (3) | 98 |
| | (4) | 97 |
| 3,5-$Ph(NO_2)_2$ | (3) | 54 |
| | (4) | 60 |
| 4-$PhNO_2$ | (3) | 91 |
| $Bu^t$ | (3) | 90 |
| n-$C_{11}H_{23}$ | (3) | 90 |
| | (4) | 91 |
| $Ph(CO)_2NCH_2$ | (3) | 98 |

A still greater number of acid anhydrides has been prepared with reagent (**5**), which is obtained easily from phosphorus pentachloride.[92] The reactions take place at room temperature in the presence of a tertiary base. Selected examples are given in Table 7. Anhydride formation was also reported with (**6**) and (**7**).[93] Dihalide derivatives of phosphorus oxychloride have been tested as well.[94,95]

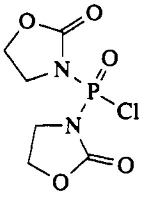

(**5**)

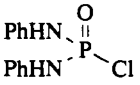

(**6**)

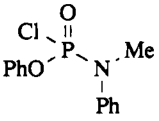

(**7**)

**Table 7** Acid Anhydrides from Carboxylic Acids and Reagent (**5**)

| *$RCO_2H$* | *Yield (%)* | *$RCO_2H$* | *Yield (%)* |
|---|---|---|---|
| $Pr^n$ | 95 | 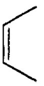 | 82 |
| $BrCH_2$ | 92 | 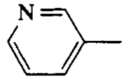 | 96 |
| $Bu^t$ | 90 | 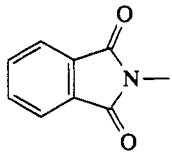 | 97 |
| MeHC=CH | 100 | 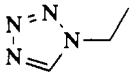 | 75 |
| PhCH=CH | 97 | | |

A procedure which converts carboxylic acids under very mild conditions to acid anhydrides was discovered in the reaction of 2 equiv. of acid with carbon tetrachloride in the presence of 1 equiv. of hexamethylphosphoramide and 1 equiv. of triethylamine in THF at –70 °C (equation 26). The anhydride of cyclopropanecarboxylic acid is, for example, formed in 76% yield.[96] The reaction can be modified in the sense that preformed chlorotrisdimethylaminophosphonium perchlorate is used as reagent. At room temperature acids are transformed into anhydrides in very good yield according to equation (27).[97] The latter reagent can be applied successfully to the coupling of amino acids to form peptides.

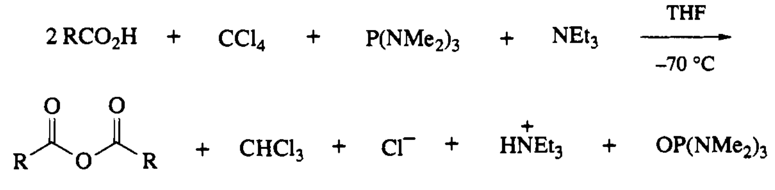

$$2\,RCO_2H + CCl_4 + P(NMe_2)_3 + NEt_3 \xrightarrow[-70\ ^\circ C]{THF} RC(O)OC(O)R + CHCl_3 + Cl^- + H\overset{+}{N}Et_3 + OP(NMe_2)_3 \qquad (26)$$

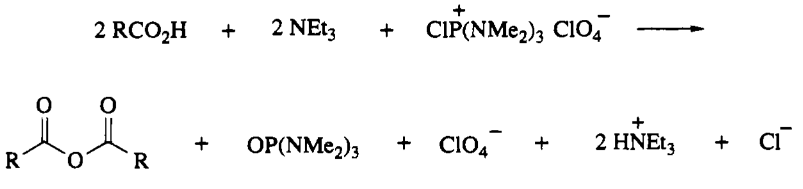

$$2\,RCO_2H + 2\,NEt_3 + Cl\overset{+}{P}(NMe_2)_3\,ClO_4^- \longrightarrow RC(O)OC(O)R + OP(NMe_2)_3 + ClO_4^- + 2\,H\overset{+}{N}Et_3 + Cl^- \qquad (27)$$

On the basis of organomercury compounds Mukaiyama introduced a method for the production of acid anhydrides. Thus the reaction of diphenylmercury with carboxylic acids in the presence of tri-*n*-butylphosphine leads to anhydrides of aliphatic and aromatic carboxylic acids in yields of *ca.* 80% (equation 28).[98] The reaction is regarded as proceeding through initial formation of phenylmercury(II) carboxylates. Oxidation–reduction reactions with tri-*n*-butylphosphine as reducing agent and electron deficient alkenes as oxidizing agents were also proposed as a means of obtaining acid anhydrides from carboxylic acids (equation 29).[99] *trans*-Dibenzoylethylene as electron acceptor in this reaction allows the preparation of aliphatic acid anhydrides in good yield. Quinoidal systems[100] or azodicarboxylates[101] can also assume the role of the electron acceptor.

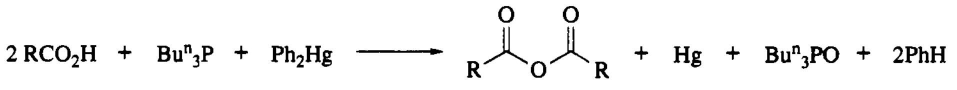

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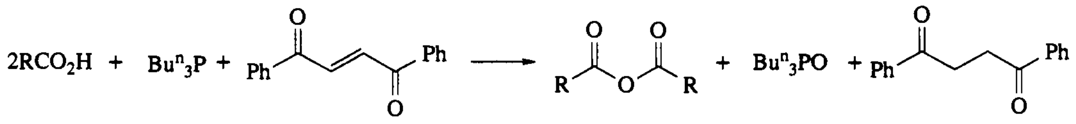

(29)

One of the most widely applied methods of synthesis for acid anhydrides consists of the reaction of a free carboxylic acid with an acid anhydride, in particular with acetic anhydride as dehydrating agent.[102,103] The process (equation 30) involves the intermediate formation of a mixed anhydride and is normally driven to completion by distilling off acetic acid. Acetic anhydride is used as solvent. The method can be used in all those cases where the desired product has a higher boiling point than acetic acid. The yields are good to excellent. Acid halides can be considered as mixed anhydrides of an organic and an inorganic acid. It is therefore obvious that they may be chosen as activated derivatives of carboxylic acids from which acid anhydrides can be formed conveniently. Both aliphatic and aromatic acid anhydrides are accessible by this approach. The reaction is favorably carried out in the presence of pyridine, which forms an acylpyridinium salt with the acid halide. The yields are >80%.[104]

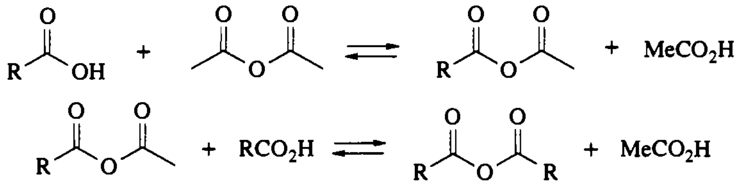

(30)

Carbonyl dichloride can be taken similarly to form acid anhydrides (equation 31). *Via* a mixed anhydride and in the presence of triethylamine, it is possible to prepare symmetrical anhydrides in high yield.[105,106] A variation provides ethyl chloroformate as reagent.[107,108] In a first step the carboxylic acid is ethoxycarbonylated in the presence of triethylamine and then reacted with free carboxylic acid to form the acid anhydride (equation 32). As the intermediate can be isolated, this is a good method of forming mixed anhydrides.[109] In addition it seems to be particularly suitable for functionalized carboxylic acids such as hydroxy acids.[110] Polymer-bound chloroformates may be advantageous in some cases.[111,112]

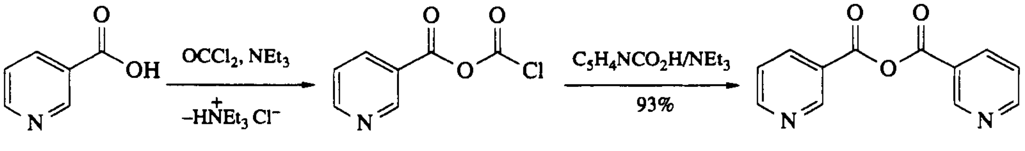

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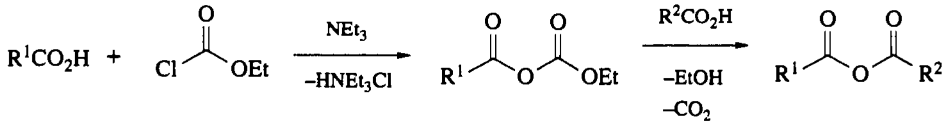

(32)

An analogous methodology can be seen in the proposal to use chloroformamidinium salts as dehydrating agents.[113] *N,N,N′,N′*-Tetramethylchloroformamidinium chloride, used as the condensation agent, is easily available by the reaction of *N,N,N′,N′*-tetramethylurea and oxalyl dichloride. The reaction of carboxylic acids (equation 33) can be achieved at –30 °C in the presence of triethylamine. Thus, for instance, 2-furoic acid, cinnamic acid and crotonic acid yield the anhydrides in 84%, 83% and 83%, respectively.

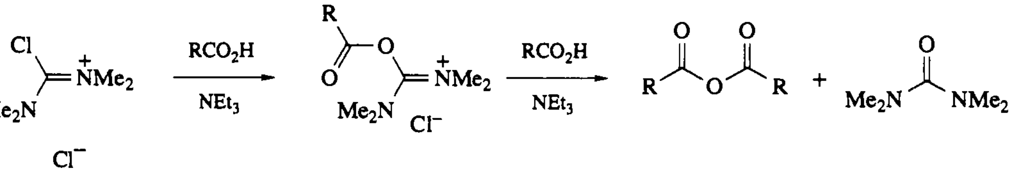

(33)

Carbodiimides, in particular dicyclohexylcarbodiimide, have been applied in many syntheses where dehydration had to be performed under mild conditions. It is therefore no surprise that this reagent was also introduced for the synthesis of acid anhydrides from carboxylic acids.[114,115] In order to avoid *N*-acylation the reactions are carried out at low temperature. First *O*-acylisoureas are formed, which then react further with free acid to the acid anhydride (equation 34). The reaction has been exploited in particular for the preparation of peptides.[116] *N*-alkoxycarbonyl-protected amino acids can be transformed in high yield to the corresponding anhydrides, which themselves are activated acid derivatives and may be converted to peptides. As in many other examples polymer-bound carbodiimides may prove superior sometimes, as the isolation of the products is facilitated. Easy preparation of acid anhydrides is possible in this way.[117]

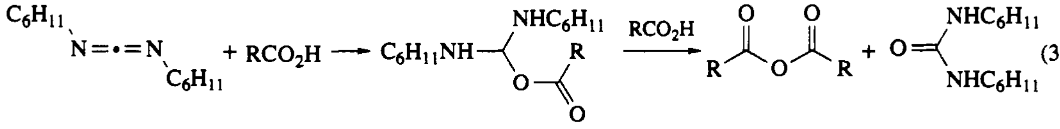

(34)

The use of imidazolides in organic synthesis has been propagated by Staab and coworkers.[118,119] Acid anhydrides can also be prepared with carbonyldiimidazolide. The reaction of a carboxylic acid with this reagent leads to acid anhydride if the transacylation equilibrium (equation 35) can be shifted to the side of the anhydride. This is possible either if the acid is used in twofold excess and forms an insoluble salt with the liberated imidazole or if trifluoro- or trichloro-acetylimidazolide is taken as the reagent. Symmetrical acid anhydrides can be obtained in a number of cases in good yield according to equation (36).[120]

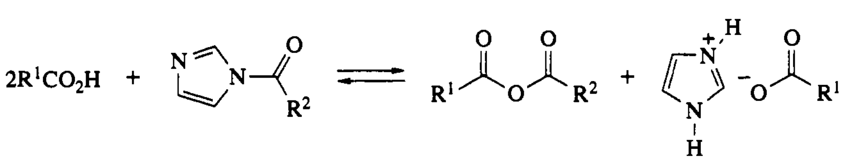

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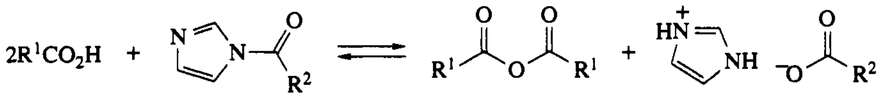

(36)

$R^2 = CCl_3, CF_3$

Another general approach to acid anhydrides from carboxylic acids was developed with esters of cyanuric acid as reagents (equation 37).[121] If the reactions are carried out in solvents like carbon tetrachloride or benzene, the resulting aryl esters of carbaminic acid are insoluble and can be removed by filtration.

Chlorosulfonyl isocyanate was introduced by Olah for the preparation of acid anhydrides. Under very mild conditions it is even possible to obtain formic acid anhydride.[122] This method has been applied successfully to other examples (equation 38).[123]

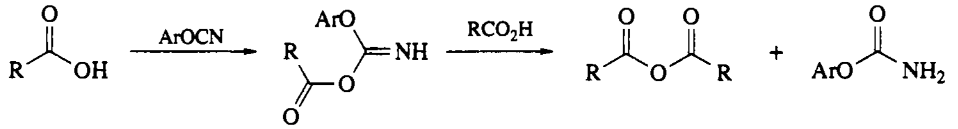
(37)

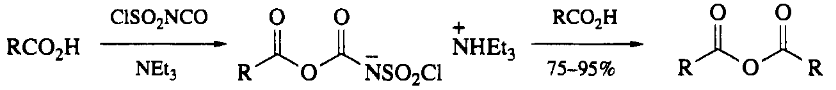
(38)

### 2.1.3.2 Acid Anhydrides from Carboxylic Acid Salts and Acid Halides

One of the classic procedures for the preparation of acid anhydrides is based on the reaction of metal salts of acids with acid halides. It offers the opportunity to obtain symmetrical and unsymmetrical acid anhydrides. A number of different metal salts have been applied over the years.

For the reaction of sodium salts with acid halides a procedure was developed which allows preparation of acid anhydrides in aqueous solution in the presence of a tertiary base (Table 8).

**Table 8** Acid Anhydrides from the Reaction of Sodium Carboxylates with Acyl Chlorides

| *$R^1COCl$* | *$R^2CO_2Na$* | *Yield (%)* |
|---|---|---|
| Ph | Ph | 97 |
| Ph | *o*-ClPh | 79 |
| *o*-ClPh | Ph | 96 |
| Ph | *p*-BrPh | 75 |
| Ph | *p*-$O_2$NPh | 64 |
| $Me(CH_2)_5$ | $Me(CH_2)_5$ | 94 |
| $Me(CH_2)_{14}$ | $Me(CH_2)_{14}$ | 75 |

Pyridine is used in catalytic amounts and acylpyridinium salts are assumed to be the reactive acylating agents. The method can be applied to the synthesis of both symmetrical and unsymmetrical acid anhydrides.[124] These can also be obtained in many cases directly from the acid halide and the sodium carboxylate without using a solvent or a catalyst. This approach has been described for a number of mixed acid anhydrides. Thus acetic palmitic anhydride (70%), butyric myristic anhydride (81%) and caproic lauric anhydride (85%) were prepared by heating the components for 2 h at 90 °C.[125] These anhydrides were successfully employed for the *N*-acylation of amino sugars.[126]

Peptides are also acetylated with the mixed anhydride of acetic acid and formic acid. The latter is made by the reaction of acetyl chloride with sodium formate in yields of 80–90%.[127] Mixed formic anhydrides with several carboxylic acids are obtainable with a copolymer of 4-vinylpyridine 1-oxide as catalyst. The reactions are carried out in acetonitrile with equimolar amounts of acid chloride and sodium formate. In most cases the mixed anhydride is the major product (Table 9).[128] The reactions are thought to proceed according to equation (39).

A solid phase copolymer of 4-vinylpyridine is a highly effective catalyst for the synthesis of acid anhydrides from mixtures containing equimolar quantities of carboxylic acids and acid chlorides.[129] The reaction can be simplified even more if a mixture of carboxylic acid and one-half equivalent of thionyl chloride in dichloromethane is treated with the solid state copolymer of 4-vinylpyridine. The conversion is accomplished equally well in batch or column mode.[130] Some examples are given in Table 10.

**Table 9** Mixed Formic Anhydrides from the Reaction of Acyl Halides with Sodium Formate

| *Reactants RCOCl* | *Yield (%)* | *Anhydrides (mole ratio)*<br>*RCOOOCH* | <br>*RCOOOCR* |
|---|---|---|---|
| Me | 7 | 0.00 | 1.00 |
| $Me_3C$ | 48 | 0.83 | 0.17 |
| Ph | 60 | 0.85 | 0.15 |
| *p*-MeO—Ph | 89 | 0.97 | 0.03 |
| Ph—CH═CH | 72 | 0.96 | 0.04 |

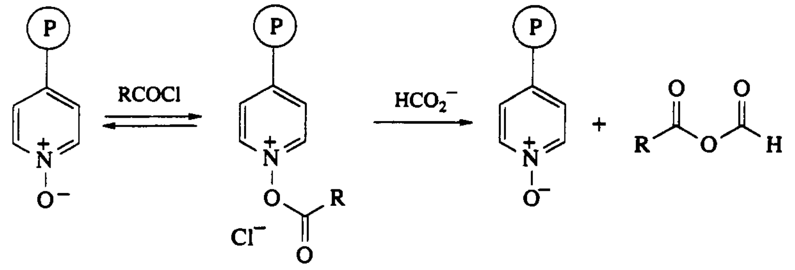

(39)

**Table 10** Conversion of Carboxylic Acids to Acid Anhydrides with a Copolymer of 4-Vinylpyridine

| *Reactant* | *Anhydride (%)* | *Production mode* |
|---|---|---|
| $MeCO_2H$ | 89 | Batch |
| $EtCO_2H$ | 96 | Batch |
| $Me_2CHCO_2H$ | 95 | Batch |
| $H_2C{=}CHCO_2H$ | 52 | Batch |
| $H_2C{=}C(Me)CO_2H$ | 86 | Batch |
| $MeCO_2H$ | 89 | Column |
| $EtCO_2H$ | 95 | Column |
| $Bu^tCO_2H$ | 97 | Column |
| $PhCO_2H$ | 99 | Column |

Several other metal salts have been proposed to react with acid halides to give acid anhydrides in good yield. Thus, thallium carboxylates in etheral suspension may be treated with acid halides to lead to acid anhydrides in high yield. The method has the advantage that thallium chloride can be separated by filtration and the product is isolated after evaporation of the solvent.[131] Another synthetic possibility exists in the desulfurization of thioesters with mercury(II) carboxylates.[132] Mercury(II) carboxylates can also be reacted with triethyl phosphite or tri-*n*-butylphosphine to provide acid anhydrides in yields of 60–80%.[133] Another possibility is offered by the reaction of 1 mol of *N*,*N*-dicyclohexylthiourea and 2 mol of silver or mercury(II) carboxylates.[134] Mixed carboxylatocarbamato anhydrides follow from the room temperature reaction of *N*,*N*-dialkylcarbamato metal derivatives with acid chlorides. Either Na, $Cu^{II}$, $Ti^{III}$ or $V^{III}$ are employed.[135]

### 2.1.3.3 Acid Anhydrides by Miscellaneous Methods

Mild dehydrating agents are available in yneamines[136] and 1-alkoxyalkynes.[137] They have been applied occasionally to the preparation of acid anhydrides.[136–139] The great advantage of these reagents is that the reaction takes place under neutral conditions and, therefore, acid anhydrides of acid sensitive compounds can be obtained. An extension of this approach was described recently. Trimethylsilylethoxyacetylene, which can be prepared from ethoxyacetylene, serves as a very mild dehydrating agent.[140] By means of this compound various types of acid sensitive carboxylic acid anhydrides can be made quantitatively or almost quantitatively (equation 40). Some examples are collected in Table 11.

Direct catalytic oxidative carbonylation to form acid anhydrides was achieved with arylmercury acetate.[141] Palladium(II) salts are taken as catalysts. Aromatic compounds such as benzene, toluene, anisole, furan, thiophene and naphthalene can be converted catalytically with palladium(II) acetate and an excess of 1,2-dibromoethane to acid anhydrides in yields of 30–60%.[142]

Of commercial interest is the preparation of acid anhydrides from hydrocarbons by direct oxidation. This methodology has been developed in particular for the synthesis of cyclic anhydrides, which are then introduced for the production of polymers.[143]

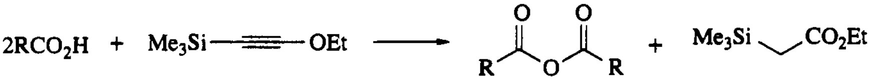

(40)

**Table 11** Synthesis of Carboxylic Acid Anhydrides by Reaction with Trimethylsilylethoxyacetylene

| *Acid* | *Product* | *Yield (%)* |
|---|---|---|
| 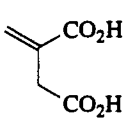 | 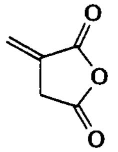 | Quantitative |
| 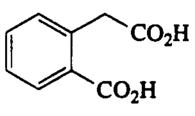 | 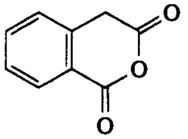 | Quantitative |
| 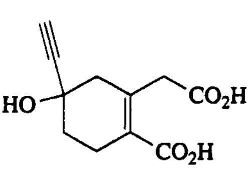 | 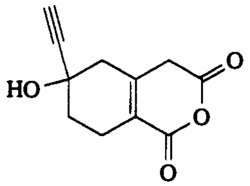 | 99 |
| 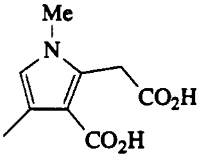 | 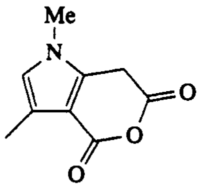 | 90 |

## 2.1.4 α-KETONITRILES

The characteristic feature of α-ketonitriles is the presence of two functional groups, which are capable of adding nucleophiles, next to each other. The electron-withdrawing character of the cyano group leads to enhanced electrophilicity of the carbonyl group, even though the carbonyl activity is less pronounced than in acid halides. Also, the cyano group displays increased reactivity towards nucleophiles as a consequence of the directly attached carbonyl group. These compounds are valuable intermediates for the synthesis of heterocycles. An earlier review[144] has found an actualization more recently.[145] Some information on their preparation can be obtained from Houben–Weyl.[146,147] The synthesis of acyl cyanides starts in general from cyanuric acid or its metal salts and reacts them with acid halides. Most α-ketonitriles are colorless liquids or solids. In the preparation of these compounds it has to be considered that they are mild acylating agents, that they dimerize in the presence of excess cyanide ion and that enolizable derivatives are converted in the presence of base to acylated enols (equation 41).

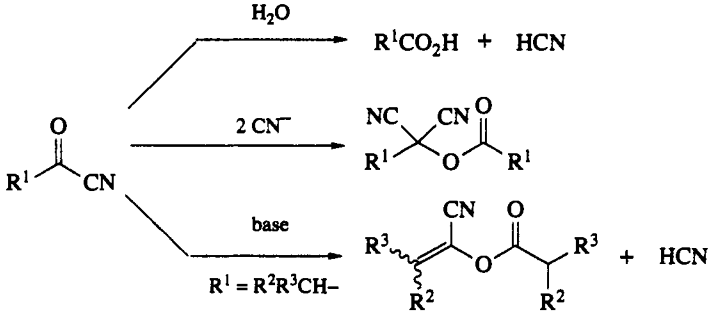

(41)

### 2.1.4.1 α-Ketonitriles from Acid Halides

Due to the sensitivity of acyl cyanides towards excess cyanide ions it is in general advisable not to use alkali metal cyanides as reagents unless special conditions are secured. Therefore, in most cases cyanides of heavy metals (low concentration of free cyanide) have been applied. These transformations require rather drastic conditions, which restricts the application mainly to the preparation of aromatic acyl cyanides. The latter can be obtained in good yield if copper(I) cyanide is heated with acid chlorides in aromatic solvents for several hours at temperatures of 160 °C.[148] More recent developments are based on the same strategy, but allow the application of milder conditions. In most cases acid chlorides are converted to acyl cyanides. Some reagents and the reaction conditions for their application according to equation (42) are collected in Table 12.

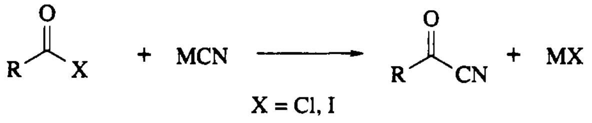

(42)

**Table 12** Preparation of Acyl Cyanides from Acyl Halides

| *MCN* | *Conditions* | *R in RCOX* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| CuCN | MeCN, 40–60 °C, 1 h | Alkyl | 50–75 | 149 |
| CuCN | LiI, $Et_2O$, 30 °C 2 h or MeCN 80 °C | Alkyl, aryl | 50–75 | 150 |
| TlCN | $Et_2O$, $MeCO_2R$, 20 °C, 1–3 h | Aryl | 45–89 | 151 |
| NaCN<br>(CuCN) | Organic solvent<br>50–300 °C | Alkyl, aryl | 50–95 | 152 |
| KCN | 18-Crown-6 $CH_2Cl_2$ | RO | 62–94 | 153 |
| $Et_4NCN$ | $CH_2Cl_2$, –40 to +20 °C | $R_2N$, PhO | *ca.* 90 | 154 |
| NaCN | Tetra-*n*-butylammonium bromide, $CH_2Cl_2$, $H_2O$ | Aryl | 20–75 | 155 |
| $Bu^n{}_3SnCN$ | 75 °C, 5 min | Aryl | 80–95 | 156 |

Compared to the older procedures the use of acid iodides in acetonitrile or dichloromethane as solvent constituted a remarkable improvement.[149] Aromatic and aliphatic acyl cyanides are accessible by this route. For example acyl cyanides of cinnamic acid and phenylacetic acid could be obtained in 53% and 49% yields. Copper(I) cyanide in diethyl ether in the presence of lithium iodide gave α-cyano ketones in 50–70%.[150] The reaction can be carried out at room temperature in diethyl ether or slightly above or at 80 °C in acetonitrile. It is not possible to obtain the acyl cyanide from acryloyl chloride, chloroformate or oxalyl chloride by this approach.

Thallium(I) cyanide was introduced by Taylor and McKillop as a reagent.[151] Aromatic and heteroaromatic acyl cyanides are produced in good yield, whereas aliphatic acid halides lead under these conditions mainly to dimerization products. 18-Crown-6 is a good catalyst for the preparation of cyanoformate in methylene chloride with potassium cyanide and chloroformates.[153] Similarly, tetraethylammonium cyanide gives cyanoformates in high yield under very mild conditions.[154] Aroyl cyanides are generated easily by phase transfer catalysis with tetra-*n*-butylammonium bromide.[155] Tri-*n*-butyltin cyanide proved successful only with aromatic acid halides, leading to dimerization products with aliphatic compounds.[156]

A general method for the preparation of α-cyano ketones from acid halides was developed recently (equation 43).[157,158] With trimethylsilyl cyanide as reagent a great number of acyl cyanides can be prepared under mild conditions in high yield. In particular the synthetically useful aliphatic derivatives have become accessible by this reaction. Table 13 lists examples for aliphatic, α,β-unsaturated and benzylic acyl cyanides. The procedure is very simple in that trimethylsilyl cyanide and acid chloride are mixed and kept without solvent. The reaction is followed by IR spectroscopy. As soon as all of the trimethylsilyl cyanide is consumed, the product can be isolated, normally by distillation, or directly used for further reactions.

Sometimes a Lewis acid such as zinc iodide is added in catalytic amounts. Side reactions may sometimes occur if acyl cyanides carry hydrogen atoms in the α-position and are, therefore, enolizable. In those examples trimethylsilyl chloride, which is formed during the reaction, may react to give trimethylsilylated enol ethers (**8**). This methodology can be applied successfully to the synthesis of such com-

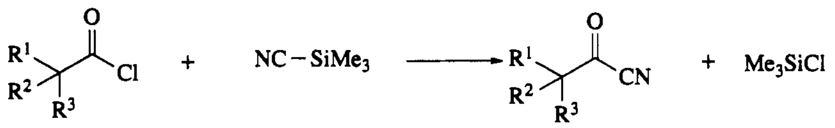
(43)

**Table 13** Synthesis of Aliphatic, α,β-Unsaturated and Benzylic Acyl Cyanides

| *$R^1, R^2, R^3$* | *Yield (%)*[a] | *$R^1, R^2, R^3$* | *Yield (%)*[a] |
|---|---|---|---|
| H, H, H | 100 | $PhCH_2$, Me, H | 100 |
| Me, H, H | 94 | $-(CH_2)_5-$, H | 100 |
| Et, H, H | 92 | Me, Me, Me | 91 |
| $-(CH_2)_2-$, H, H | 100 | Me, Cl, H | 90 |
| $CH_2{=}CH{-}CH_2$, H, H | 100 | Me, Br, H | 81 |
| $Me{-}CH{=}$, H | 90 | Me, I, H | 100 |
| Ph, Ph, H | 100 | Cl, H, H | 53 |
| $Ph{-}CHMe$, H, H | 100 | Br, Et, H | 64 |
| $MeO{-}CH_2$, H, H | 80 | Br, $Pr^i$, H | 100 |
| Me, Me, H | 92 | Br, Br, H | 69 |
| Ph, Me, H | 100 | $Cl_2C{=}CCl{-}CCl{=}$, Cl | 46 |

[a] Yields and purity determined by IR spectroscopy.

pounds.[145] Sometimes excess trimethylsilyl cyanide may add to the carbonyl group of the α-ketonitrile leading to compounds of type (**9**). The latter reaction is predominant for carbonyl chloride, oxalyl chloride and trifluoroacetyl chloride. Compounds of type (**8**) can be taken to generate α-halo substituted acyl cyanides through reaction with halogens.

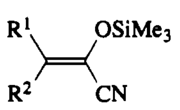
(**8**)

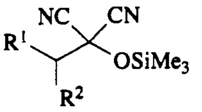
(**9**)

### 2.1.4.2 α-Ketonitriles by Miscellaneous Methods

α-Cyano ketones have been prepared from derivatives of aldehydes and ketones (equation 44),[159] in particular aromatic derivatives. Oxidation of aromatic cyanohydrins (equation 45) is another possibility.[160] More recently catalytic cyanocarbonylation of aryl iodides has been advanced.[161]

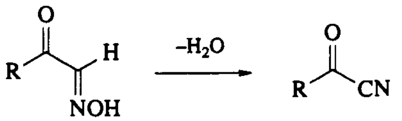
(44)

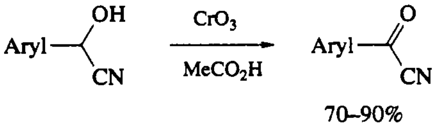
(45)

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# 2.2

# Synthesis of Esters, Activated Esters and Lactones

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## 2.2.1 FORMATION OF ESTERS AND ACTIVATED ESTERS

### 2.2.1.1 General Introduction

The formation and further transformation of esters belongs to the fundamentals of organic chemistry. Moreover, some esters have enormous importance; for example triglycerides (**1**), in the form of fats and oils, are produced in million ton quantities for a number of applications. Other esters, *e.g.* (**2**) and (**3**), are olifactory components; waxes, *e.g.* (**4**), are used commercially to protect metallic surfaces against corrosion. Aspartame (**5**) is an important artificial sweetener, and pyrethrin (**6**) is the prototype of the pyrethroids, an unusually potent class of insecticides.[1] Apart from these more applied considerations, esters are important synthetic intermediates in a number of multistep sequences. Striking examples are chain elongations *via* Horner alkenation or α-alkylations of ester enolates, in particular the ones stereocontrolled by chiral auxiliaries.[2]

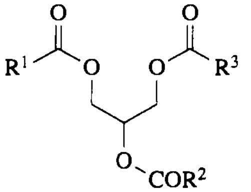

(**1**)

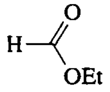

(**2**)

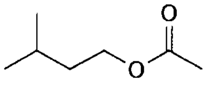

(**3**)

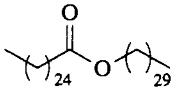

(**4**)

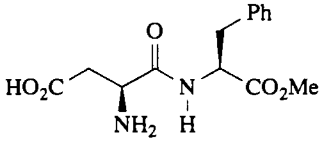

(**5**)

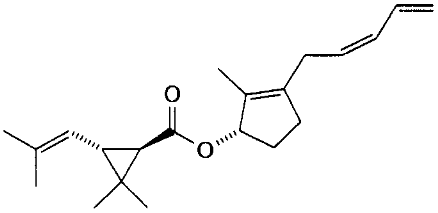

(**6**)

The simplest route to esters is the esterification of carboxylic acids. This subject has been covered in a number of more or less comprehensive reviews.[3] Therefore, the present report can be restricted to the most significant and recent developments.

### 2.2.1.2 Synthesis of Esters by Acyl Transfer to Alcohols (Carboxy Group Activation, CGA)

This method for the synthesis of esters is the most common method (equation 1). The carboxylic acid or an activated derivative thereof (**7**) is treated with the alcohol (**8**), generally in presence of a base, so that eventually the activating group X is replaced by the $OR^2$ moiety to form the ester (**9**). In effect this reaction is an $S_N$ process at a trigonal carbon center and may proceed *via* an addition–elimination ('$S_N2$') or an elimination–addition ('$S_N1$') sequence. In either case, the configuration with respect to the $R^2$—O bond is retained and no $^{18}O$ exchange of this oxygen is observed.[4] X must be a good leaving group on one hand as in the aliphatic $S_N$ reactions and, additionally, its electron donation to the carbonyl function must be minimalized.

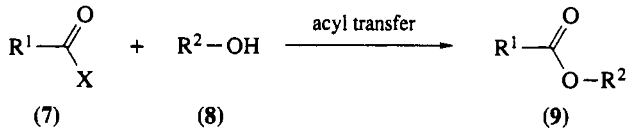

(7) (8) (9)

(1)

X = $^{+}OH_2$, $^{+}OHR$, $^{+}NR_3$, F, Cl, Br, $SR^3$, 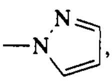 , $OPPh_3$, $OSO_2R^3$, $\overset{O}{\overset{\|}{OCR^3}}$

### 2.2.1.2.1 *Esters from carboxylic acids and alcohols under acid catalysis: the* $A_{AC}2$ *and* $A_{AC}1$ *mechanism*

This method is extremely simple and is to be preferred if one of the components is cheap and both the acid and the alcohol do not contain acid sensitive functional groups. As catalysts conc. HCl (Fischer–Spei esterification), anhydrous sulfuric acid or *p*-toluenesulfonic acid or acidic ion exchange resins may be employed. The alcohol generally serves as the solvent, if permitted by its costs, otherwise toluene or xylenes may also be used. A very efficient catalyst is graphite bisulfate in cyclohexane.[5] The reaction generally leads to an equilibrium mixture consisting of about 80% of the ester and 20% of the components. Complete ester formation can be accomplished either by using the alcohol in large excess, *e.g.* as the solvent, or by removing the water from the mixture, for example by means of a Dean–Stark apparatus or a desiccating agent, preferrably 3Å molecular sieve. Volatile esters may be removed from the mixture by distillation. Instead of the proton acids mentioned above, Lewis acids such as boron trifluoride or polymer-supported aluminum chloride and chlorosilanes, may also be used. The advantage of these procedures lies in the high yields and the purity of the esters. Table 1 shows some illustrative examples.

**Table 1** Acid-catalyzed Esterifications

$$R^1CO_2H + R^2OH \longrightarrow R^1CO_2R^2 + H_2O$$

| *$R^1$* | *$R^2$* | *Catalyst* | *Removal of $H_2O$* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| Citric acid (triester) | Et | HCl | $CaCl_2$ | 68 | 6 |
| Citric acid (triester) | Et | $H_2SO_4$ | Two phase with toluene | 80 | 6 |
| MeCH(OH) | Et | *p*-TsOH | Azeotropic with toluene | 90 | 7 |
| $(EtO)_2CH$ | Et | *p*-TsOH | | 88 | 8 |
| $C_8H_{17}$ | Me | $H_2SO_4$ | Molecular sieve 3Å | 96 | 9 |
| Me | Ph | $H_3BO_3/H_2SO_4$ | Azeotropic with xylene | 86 | 10 |
| Me | $Pr^i$ | Amberlite IR 20 | $CaSO_4$ | 100 | 11 |
| PhCO | 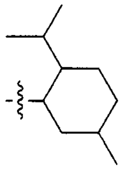 | Graphite–bisulfate | — | 50 | 12 |
| $4\text{-}NH_2C_6H_4SCH_2$ | Me | $BF_3\cdot OEt_2$ | — | 78 | 13 |
| 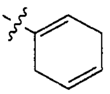 | Et | $BF_3\cdot OEt_2$ | — | 66 | 14 |
| Et | $Bu^n$ | $AlCl_3$/polystyrene | — | 97 | 15 |
| 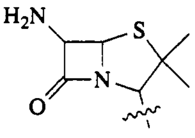 | Me | $Me_3SiCl$ | — | 84 | 16 |

The widely accepted mechanism of the acid-catalyzed esterification is designated as the $A_{AC}2$ process (A = acid catalysis, AC = acyl transfer, 2 = bimolecular). As shown in Schemes 1a and 1b the rate-determining step is the reversible attack of the alcohol at the carbonyl function of the activated species (**10**) and (**12**). Two modes of proton (or Lewis acid) activation may be distinguished: either protonation of the OH function (Scheme 1a), leading to (**10**) and (**11**), or protonation of the carbonyl oxygen (Scheme 1b), leading to (**12**) and (**13**). Although the first mechanism is generally formulated in the literature, the second mechanism appears far more plausible regarding the site of the initial protonation,[17] as well as the lesser degree of charge separation in the crucial intermediates (**11**) *versus* (**13**).

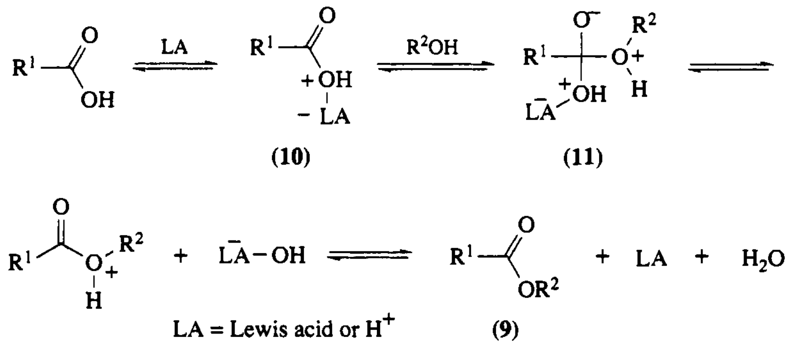

**Scheme 1a**

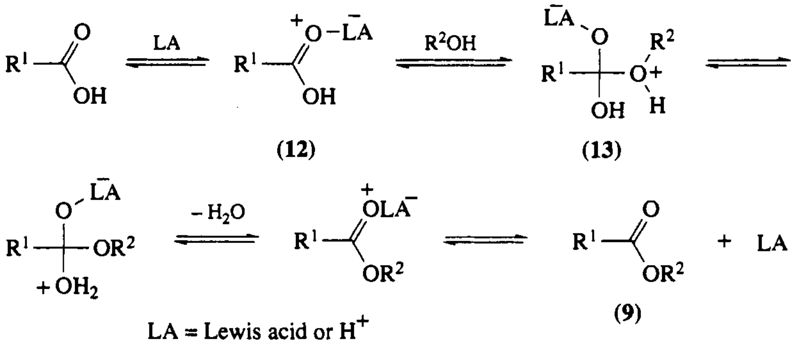

**Scheme 1b**

*(i) Scope and limitation of the $A_{AC}2$ esterifications*

The greatest advantage of the method lies in its simplicity; however, the rather severe conditions (extended heating in presence of a mineral acid) makes it questionable for sensitive substrates. Additionally, α- and β-branching in the carboxylic acid strongly retards the reaction, so that for example, acids (**14**)–(**16**) are too hindered to react. On the other hand, α- and β-branching in the alcohol induces dehydration.

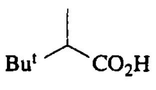

(**14**)

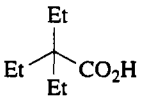

(**15**)

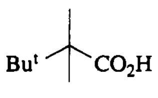

(**16**)

*(ii) The $A_{AC}1$ mechanism*

This mechanism (A = acid catalyzed, AC = acyl transfer, 1 = unimolecular) is observed in the esterification of 2,4,6-trisubstituted benzoic acids with R groups of moderate +M effect (*e.g.* methyl).[17] The $A_{AC}2$ mechanism is blocked by the steric interference of the *ortho* substituents. Therefore, the acylium cation (**17**) is generated with anhydrous sulfuric acid and then treated with the alcohol (equation 2).[18] R groups with strong +M effects, like methoxy, are not tolerable, as the aromatic nucleus undergoes sulfonation under the conditions. A variation of the $A_{AC}1$ mechanism for aliphatic acids is achieved by using the fluorides and antimony pentafluoride to generate the acylium ion (**18**),[19] which reacts even with strongly hindered alcohols to form the esters (equation 3).

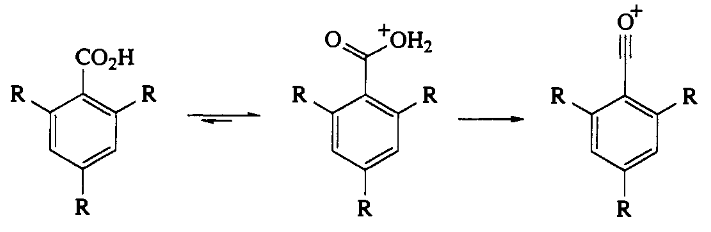

**(17)**

(2)

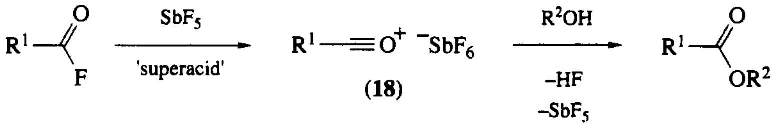

(3)

### *2.2.1.2.2 Acyl transfer via anhydrides and acid chlorides*

In contrast to the $A_{AC}$ esterifications this method makes use of preformed CGA species (**19**) and (**20**) to which the alcohol is added. The formation of acid chlorides[20] requires strong Lewis acids like thionyl or oxalyl chloride, which may react with acid sensitive functions in the molecule and also cause epimerization of chiral α-centers in the substrate molecule. On the other hand, using anhydrides (**20**) for esterification means to lose 1 mol equiv. of the acid. Thus, both (**19**) and (**20**) should preferentially be used for inexpensive carboxylic acids with a low degree of functionalization. Typical and frequently encountered examples in multistep syntheses are benzoylation and acetylation of primary and secondary alcohols, whereas tertiary alcohols are generally too hindered to react, unless a strong base catalyst (*e.g.* calcium hydride)[21] is added. The acetylations are normally performed in pyridine at 0–25 °C. Acid catalysis is less common. Acid chlorides can be used in pyridine or in dichloromethane with triethylamine as the base. In any case, the anhydride should be preferred, as the reaction mixture remains almost neutral throughout the reaction and the yields are higher, particularly if the acylation is catalyzed with *N*,*N*-dimethylaminopyridine (DMAP; **21**) or, even better, 4-pyrrolidinopyridine (PPY; **22**).[22] Regular conditions are 0.05–0.2 mol equiv. of the catalyst in aprotic solvents (hexane, dichloromethane, THF, pyridine) at room temperature. Rate enhancements compared to the uncatalyzed reactions are several powers of ten, so that even hindered hydroxy functions (*e.g.* in **23** or **24**) are smoothly acylated.

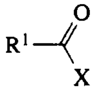

**(19)**

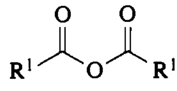

**(20)**

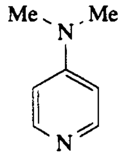

**(21)** DMAP

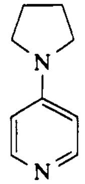

**(22)** PPY

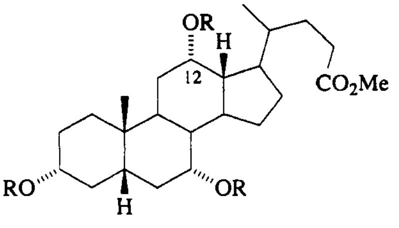

**(23)** a: R = H
b: R = COMe

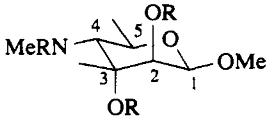

**(24)** a: R = H
b: R = COMe

### *(i) Mechanistic aspects*

Mechanistically, the alcoholysis of acid chlorides may proceed *via* a one step $S_N2$-like mechanism or more frequently, *via* the usual tetrahedral intermediate.[23] The reaction is accelerated by electron-withdrawing substituents in the chloride and hardly affected by steric hindrance. On the other hand, benzoyl chlorides with electron-releasing substituents in the aromatic nucleus undoubtedly react *via* an $S_N1$-like mechanism, especially in protic solvents.[24] Anhydrides prefer the normal addition–elimination pathway, the rate-determining step being the formation of the tetrahedral intermediate. The drastic effect of the catalysts (**21**) and (**22**) may be attributed to the initial formation of the acyl pyridinium salt (**25**), in which $X^-$ serves as the base for the deprotonation of the alcohol during its nucleophilic attack on the carbonyl group (equation 4). This explains why acid chlorides show much smaller rate enhancements with (**21**) and (**22**) than anhydrides, although the equilibrium concentration of (**25a**) is much higher than that of (**25b**). However, chloride is a much weaker base than the carboxylate and cannot remove the proton from the alcohol with similar efficiency. Additionally, $X^-$ must be close to the reaction site, which means that (**25**) is more efficient an acylating agent as a contact than as a solvent-separated ion pair. In fact, the rates are much higher in unpolar than in polar solvents.

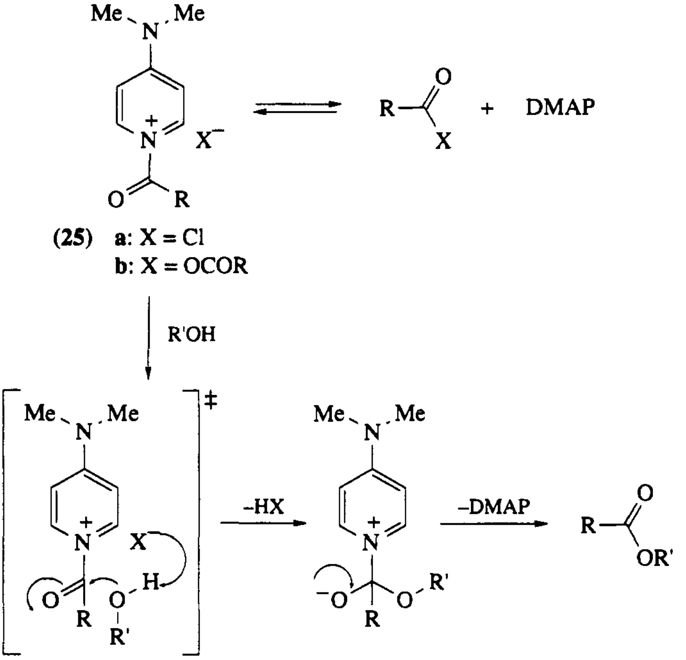

(**25**) **a**: X = Cl
**b**: X = OCOR

(4)

### *2.2.1.2.3 Acylation with mixed anhydrides and activated esters*

This acylation process is of the utmost importance. In the first step, the carboxylic acid is treated with an activating agent X—Y to form the CGA species (**26**), which acylates the alcohol in the second step. X is a substituent with a strongly electron-withdrawing –I- or –M-effect and Y is a good leaving group. If X contains an acyl function, as in cases a–d, (**26**) is a mixed anhydride; otherwise, for instance in cases e–i, (**26**) is classified as an activated ester. In both types, the activating effect of X is two-fold ('double activation')[25] in facilitating the nucleophilic attack of the alcohol.

As shown in Scheme 2, the electron-withdrawing character of X enhances the electropositive nature of the carbonyl carbon in (**26**). The second, and equally important, effect is the ability of X to accept the proton from the alcohol. In this manner the effective nucleophilicity of the alcohol is drastically increased in the immediate proximity to the reactive center. Thus, (**26**) behaves very similarly to (**25**), with the only difference that (**26**) is neutral and (**25**) is an ion pair. As an additional benefit of the proton transfer, the leaving group quality of the OX fragment is also greatly improved.

Mixed anhydrides from carboxylic acids (**26a**) have to be so devised that the desired acyl group is transferred. This can be achieved in two ways. The first one is to block the undesired carbonyl position by steric (*e.g.* **26aa**; equation 5) or electronic (*e.g.* **26ab**; equation 6) deactivation. The second one, as illustrated by (**26ac**; equation 7) is to allow the reversible attack of both carbonyl groups; the desired acyl transfer is accomplished by the better leaving group quality of the trifluoroacetate. Specifically, the

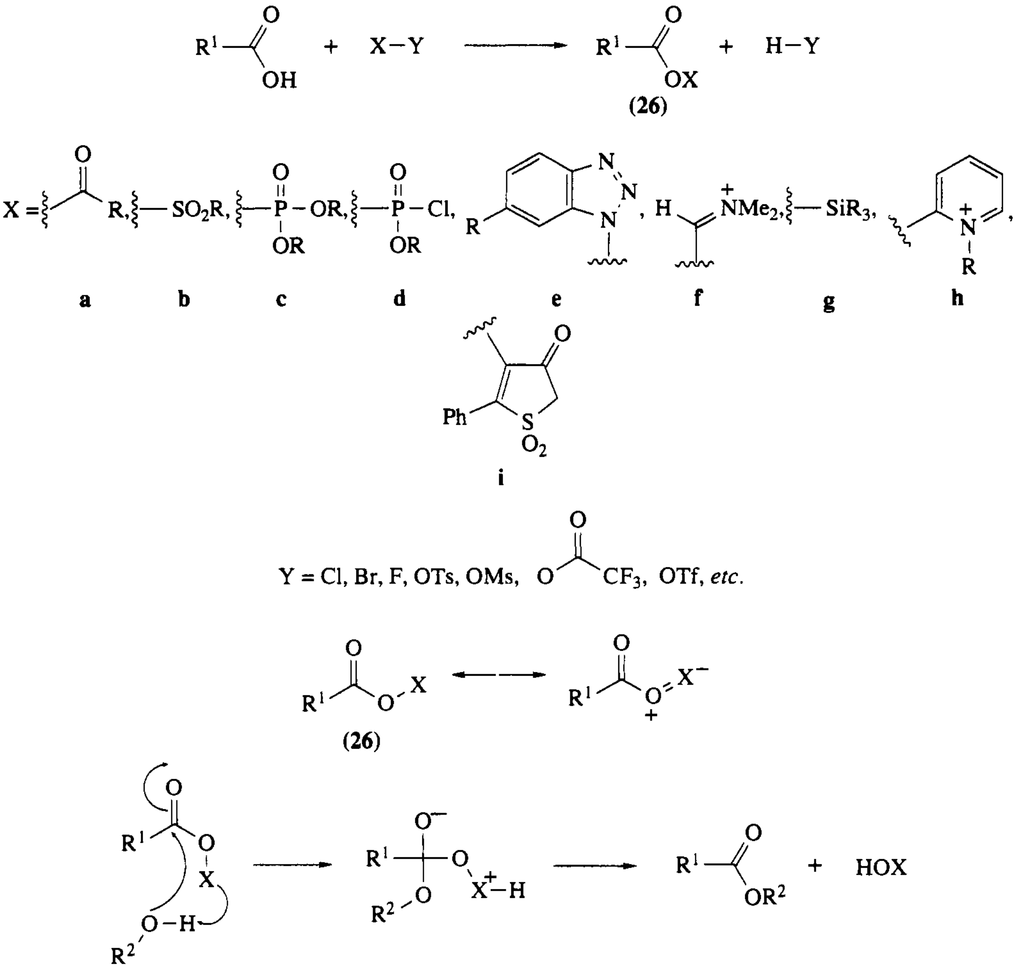
R¹ + X−Y → R¹ + H−Y
OH
OX
(26)
X =
a
b
c
d
e
f
g
h
i
R, SO₂R, P−OR, P−Cl, OR, NMe₂, SiR₃
Ph
S
O₂
Y = Cl, Br, F, OTs, OMs, CF₃, OTf, etc.
(26)
HOX
OR²

Scheme 2

mixed anhydrides (**26aa**) and (**26ab**) are prepared from the carboxylic acid and 2,4,6-trichlorobenzoyl chloride and methyl(ethyl)chloroformate in an aprotic solvent (THF, dichloromethane, *etc.*) in the presence of triethylamine. In the case of (**26aa**), the solvent is then replaced by benzene and the alcohol and a catalytic amount of DMAP (**21**) are added (equation 5).[26] On the other hand, (**26ab**) is heated to eliminate carbon dioxide under formation of the ester. This reaction, however, requires an $R^1$ group with electron-withdrawing substituents (equation 6).[27] (**26ac**) is formed from the carboxylic acid and trifluoroacetic anhydride in benzene at about 50 °C, then the alcohol is added without a catalyst (equation 7).[28]

Similarly, the acyl tosylates (**26b**) are prepared from the acid and tosyl chloride in pyridine at 0 °C; then the alcohol is added (equation 8). In view of the basic medium this method is particularly suited for acid sensitive alcohols (tertiary, propargylic, allylic or homoallylic).[29] The acyl phosphate (**26c**) is made

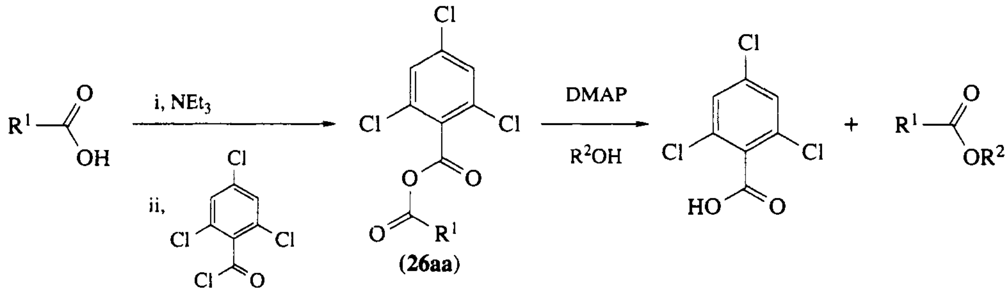
R¹
OH
i, NEt₃
ii,
Cl
Cl
Cl
Cl
(26aa)
DMAP
R²OH
HO
+
OR²

(5)

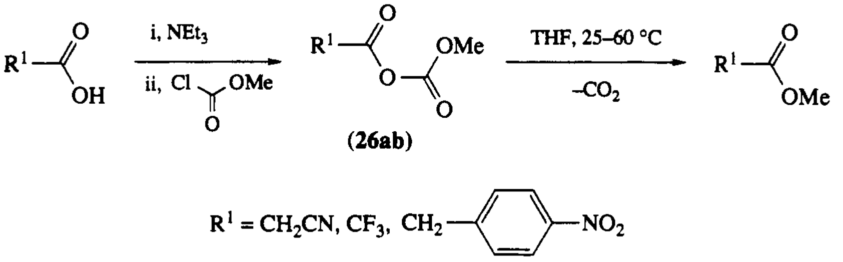

i, NEt3
ii, Cl OMe
THF, 25–60 °C
-CO2
(26ab)
R1 = CH2CN, CF3, CH2 NO2

(6)

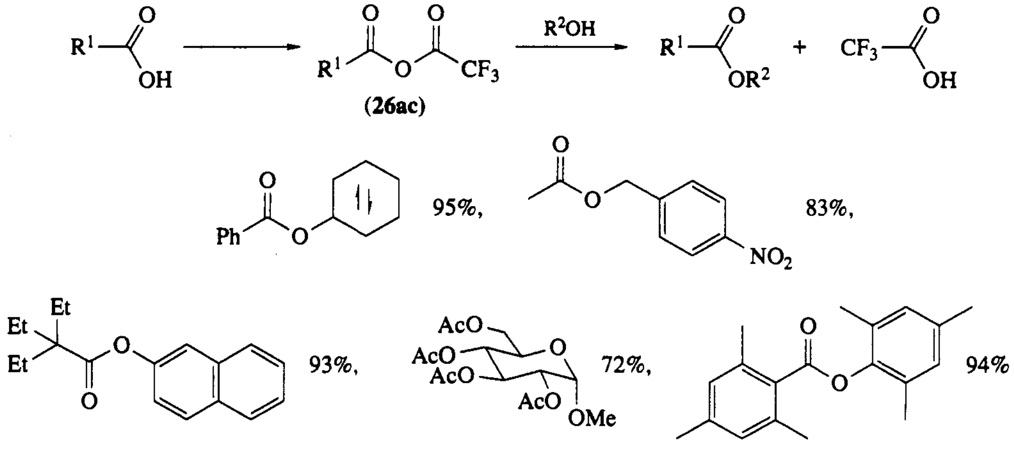

R2OH
(26ac)
95%,
83%,
93%,
72%,
94%

(7)

from the carboxylic acid and the chlorophosphate[27] in the presence of triethylamine. The alcohol only reacts with the mixed anhydride (**26c**) and not with the chlorophosphate, which means that it can be added together with the carboxylic acid (equation 9).[30] In a similar way, phosphoric ester dichlorides may be reacted with carboxylic acids to form mixed anhydrides (**26d**) in DMF and after addition of the alcohol component, esters are formed in high yields.[31]

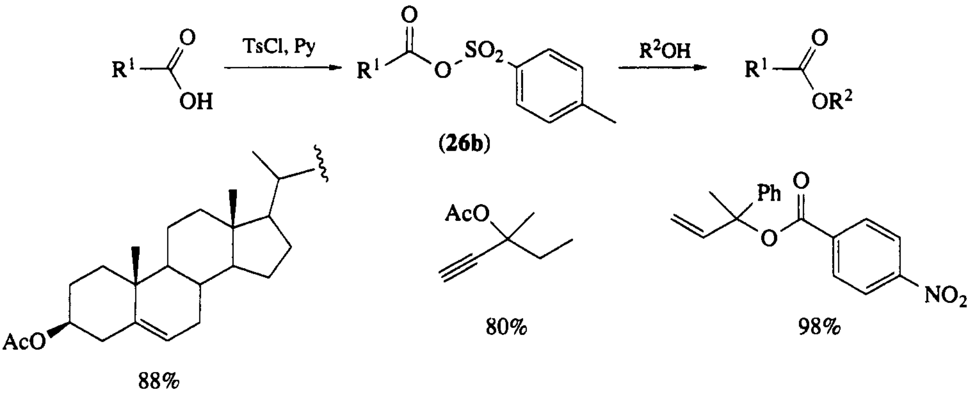

TsCl, Py
R2OH
(26b)
80%
98%
88%

(8)

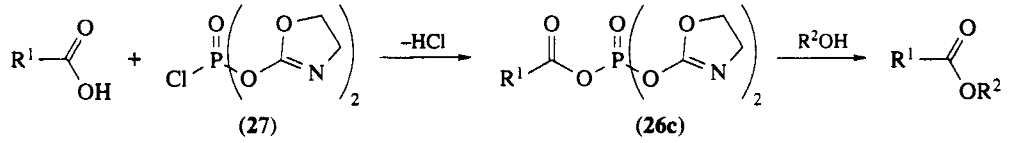

-HCl
R2OH
(27)
(26c)

(9)

### *(i) Activated esters*

Like the mixed anhydrides, activated esters may also be represented by the general formula (**26**). The only difference between mixed anhydrides and activated esters lies in the fact that HOX corresponds to a carboxylic or inorganic proton acid in the case of the mixed anhydrides and to an (acidified) alcohol in the case of the activated esters. In all other respects the overall procedure is very similar to that used for mixed anhydrides. For example (equation 10), the 1-acyloxy-1,2,3-triazole derivatives (**26e**) are formed from the carboxylic acid and the benzenesulfonates (**28**). Triethylamine is used to neutralize the sulfonic acid and to catalyze reaction of the alcohol with (**26e**).[32] The advantage of this method lies in the high selectivity; primary alcohols are acylated with high preference over secondary ones (see Section 2.2.1.6).

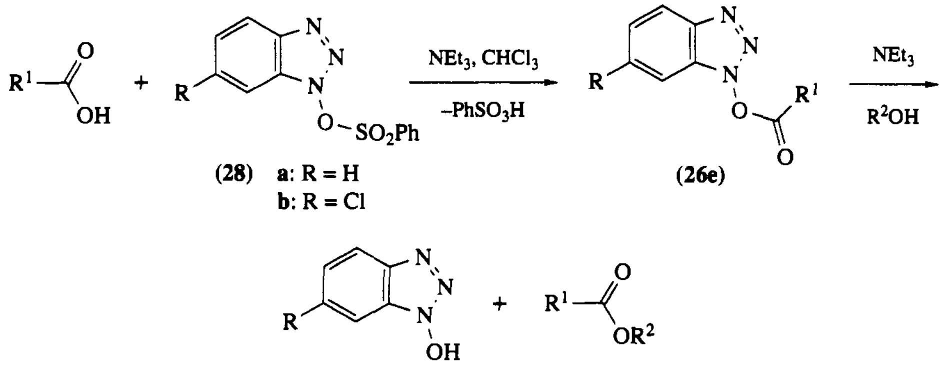

(**28**) **a**: R = H
**b**: R = Cl

(**26e**)

(10)

Chloroformamidinium chlorides (**29**) are generated from DMF and oxalyl chloride in acetonitrile. After addition of the carboxylic acid the activated ester (**26f**) is formed and treated with a solution of the alcohol in pyridine.[33] Phenyl, alkyl and even *t*-butyl esters may be prepared in yields of greater than 80% (equation 11). Reagent (**31**), accessible from (**30**) and oxalyl chloride (equation 12) behaves quite similarly to (**29**).[34] The use of silyl esters (**26g**), which are formed *in situ* in the presence of the alcohol and react then to the esters, has already been mentioned in Section 2.2.1.2.1. An application is described in Table 1.

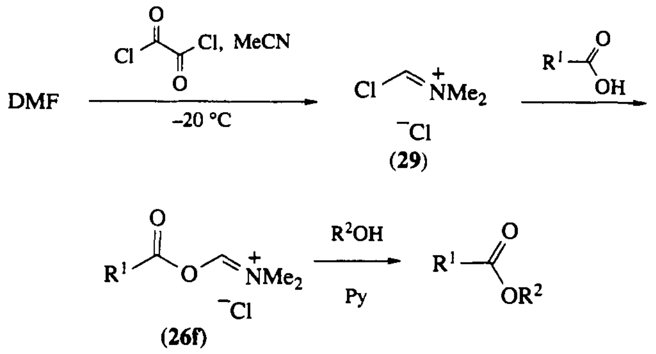

(**29**)

(**26f**)

(11)

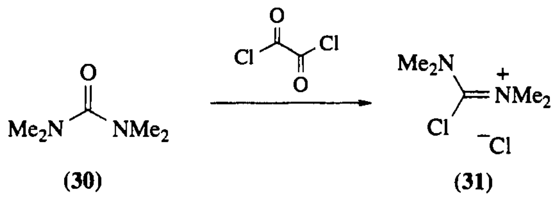

(**30**) (**31**)

(12)

2-Acyloxypyridinium salts (**26h**) acylate various primary, secondary and tertiary alcohols under very mild conditions. All components (carboxylic acid, **32**, tributylamine and the alcohol) are stirred in dichloromethane at room temperature for several hours[35] to form the desired ester and pyridine (**33**; equation 13). The ester is isolated by chromatography. The synthesis of benzyl phenylpropiolate (**35**) may serve as an example (equation 14).

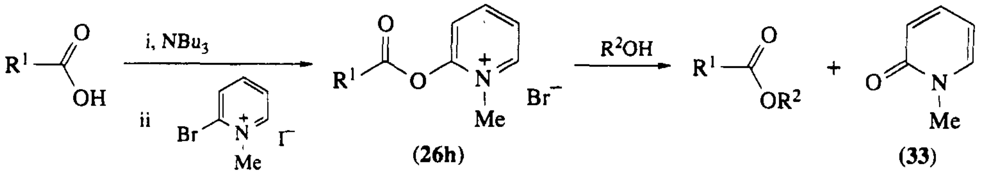

(**32**) (**26h**) (**33**)

(13)

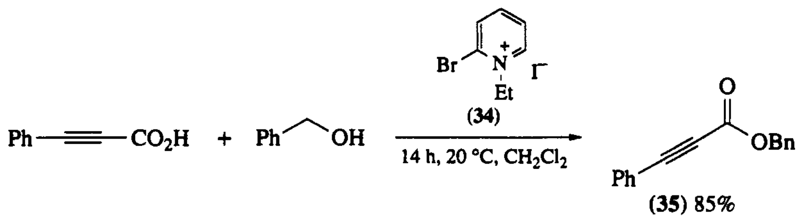

(14)

The novel carbonate (**36**) has been developed by Steglich and coworkers[36] to solve a fundamental problem in solid-phase peptide synthesis, *i.e.* the attachment of the terminal *N*-protected amino acid to the Merrifield resin without racemization. To this end, the Fmoc-protected acid is treated with (**36**) to form the activated ester (**26i**), which may be isolated, and is then added together with Hünig's base to the *p*-benzyloxybenzyl alcohol substituted resin. Under elimination of (**38**) the desired immobilized ester (**39**) is formed, from which the Fmoc group is removed with piperidine. The next amino acid can be condensed to the amino group, again using (**36**) as the coupling agent (equation 15).[36]

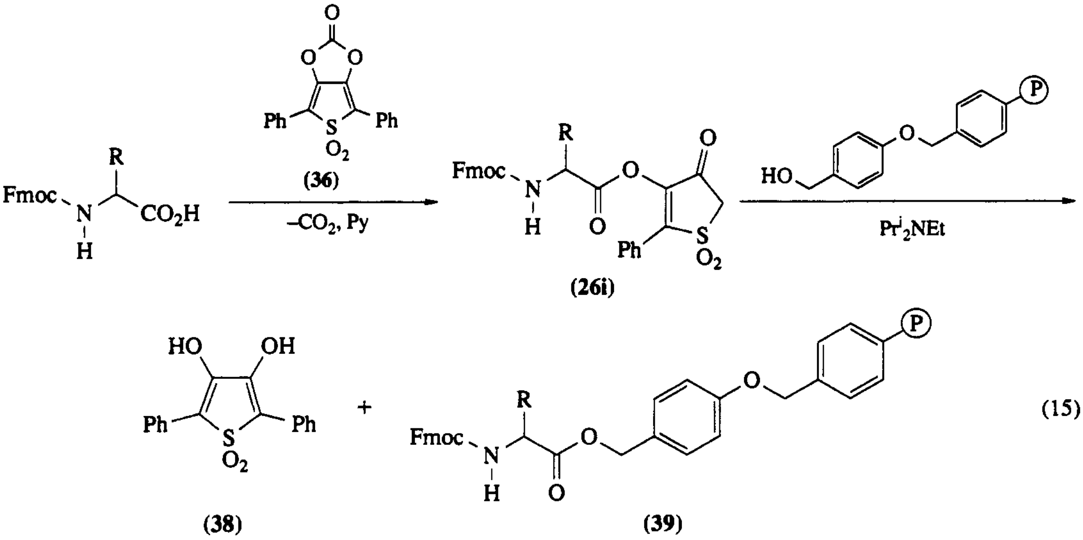

(15)

## 2.2.1.2.4 *Acylation with ketenes*

Ketenes are highly reactive acylating agents. However, they have found only limited application, as they are not as readily available as the other acylating agents described so far. The only exception is ketene itself, which is produced on a large scale industrially and is used for the acylation of acetic acid to acetic anhydride (1986, 1.6 millions of tons[37]). A minor amount (1986, 63 000 tons[37]) of ketene is dimerized to diketene (**40**), which is used to acylate alcohols to various esters of acetoacetic acid (equation 16). The corresponding amides are prepared analogously.

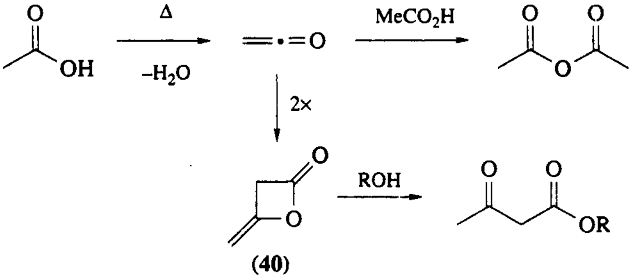

(16)

#### *2.2.1.2.5 Acylation with* N*-acylimidazoles*

This method was introduced by Staab[38] and is suitable for the acylation of primary, secondary and tertiary alcohols. First the carboxylic acid is converted into the imidazolide (**42**) with carbonyldiimidazole (**41**), and then the alcohol is added together with a catalytic amount of strong base (alkoxide). The ester is formed at room temperature within a few hours (equation 17). If functional groups in the acid or alcohol prevent the use of base, the imidazolide and the alcohol have to be heated to 70 °C for 1–2 h.

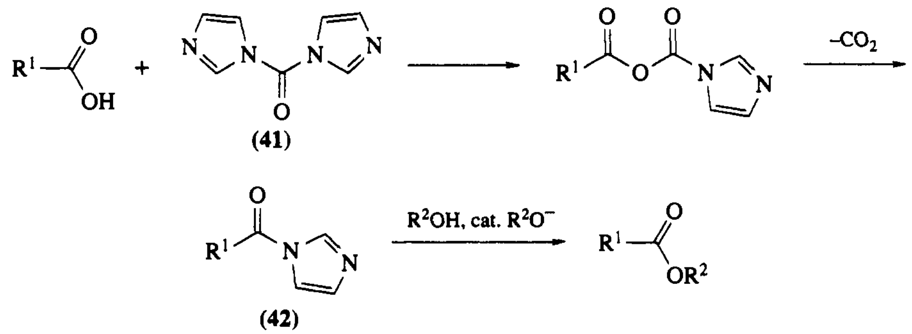

(17)

### 2.2.1.3 Esters from Carboxylic Acids and Alcohols *via* Hydroxy Group Activation (HGA)

This type is a one-pot reaction with all components present from the beginning. The alcohol is first converted into an $S_N$-activated (HGA) species (**43**), which undergoes an OX displacement with the carboxylic acid to form the ester (equation 18). Two methods are known to fit into this general scheme: the Mitsunobu reaction[39] and the Vorbrüggen–Eschenmoser reaction.[40]

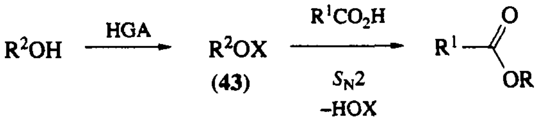

(18)

#### *2.2.1.3.1 Mitsunobu reaction*

This method is unusually mild, using neutral conditions and low temperatures (20 °C and less). It tolerates a number of functional groups in the components (*e.g.* acetals, esters, alkenes, *etc.*). The alcohol, the carboxylic acid and triphenylphosphine are treated dropwise in an inert solvent (dichloromethane, THF, ether) with diethyl azodicarboxylate (DEAD). The ester is formed rapidly. However, tedious chromatography is frequently required to remove the by-products, triphenylphosphane oxide and hydrazo ester. The main value of the reaction lies in the clean inversion of configuration at a secondary carbinol center and in its selectivity towards primary hydroxy groups (*vide infra*). Inversions are usually performed with benzoic or *p*-nitrobenzoic acid. The benzoates are purified and saponified with aqueous base to furnish the inverted alcohols in overall yields of *ca.* 50%. Elimination is the main side reaction. Thus, from (**44**) 75% of the desired $S_N$2 product (**45**) is formed, along with 25% of the elimination product (**46**) (equation 19).[41] The mechanism of the reaction has been clarified to the point that betaine (**47**) is the pri-

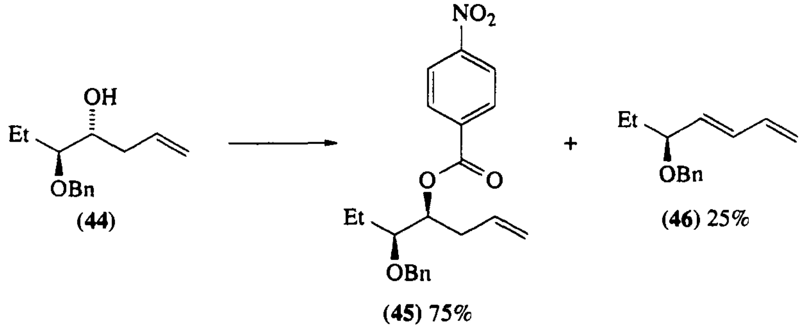

(19)

mary intermediate from which the triphenylphosphonium moiety is transferred to the alcohol from (**49**) to form the HGA species (**48**). The rate-determining step is the final $S_N2$ reaction with the carboxylate (equation 20).[42]

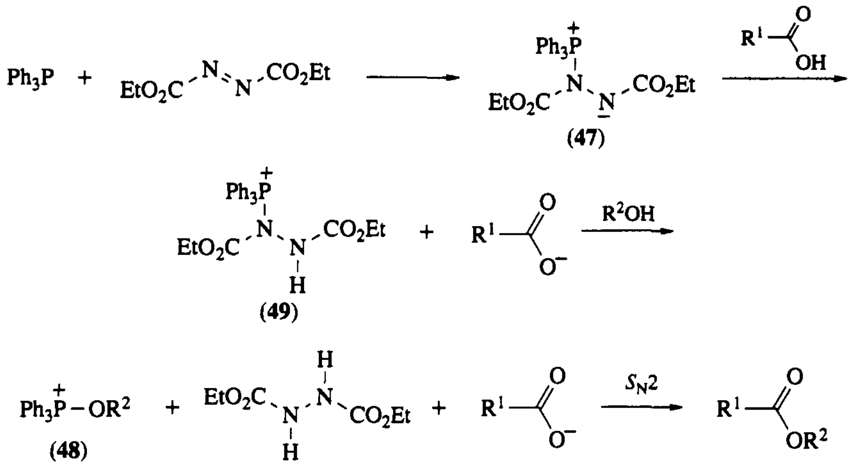

(20)

### 2.2.1.3.2 *Eschenmoser–Vorbrüggen reaction*

In this reaction the carboxylic acid is heated together with formamidacetals (**50**) in an inert solvent (benzene, *etc.*). The products are the ester, DMF and alcohol $R^2OH$. Only $S_N2$ active $R^2$ groups like methyl, ethyl, benzyl *etc.* can be transferred. Mechanistic studies have shown that the HGA species (**52**) is generated from (**50**) *via* elimination of $R^2OH$ under proton donation from the carboxylic acid. The carboxylate in turn undergoes an $S_N2$ displacement with (**52**) to form the ester and DMF (equation 21).

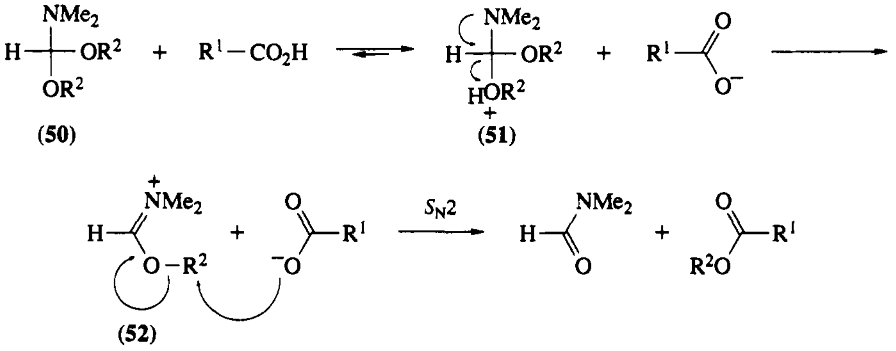

(21)

## 2.2.1.4 CGA and HGA Esterifications at Will: the DCC Method

A reagent which allows both CGA and HGA esterifications is DCC (dicyclohexylcarbodiimide; **53**; $R^3$ = cyclohexyl). CGA esterifications are accomplished by treating a mixture of the carboxylic acid and the alcohol with DCC in hexane or pyridine with a catalytic amount of *p*-TsOH. The *O*-acylisourea (**54**) is postulated as intermediate, which reacts with the alcohol under elimination of the urea (**56**) and formation of the desired ester. The urea is removed by filtration (equation 22).[43] This method is highly recommendable if both the carboxylic acid and the alcohol are valuable and bear sensitive functional groups. Numerous applications in natural product synthesis have been reported.[44]

DMAP catalyzes the reaction most efficiently.[45] From (**54**) and excess carboxylic acid (**56**) the already described ion pair (**25**) is formed, which then acts as the acylating species proper. However, the carboxylate is not wasted in this case, as it reacts immediately with (**53**) and is thus recycled.[46] Thus, the DCC method can also be used for acylations with symmetrical anhydrides; now both acyl moieties are used in the esterification (equation 23).[46] The HGA variant is less common. To this end, the alcohol is first

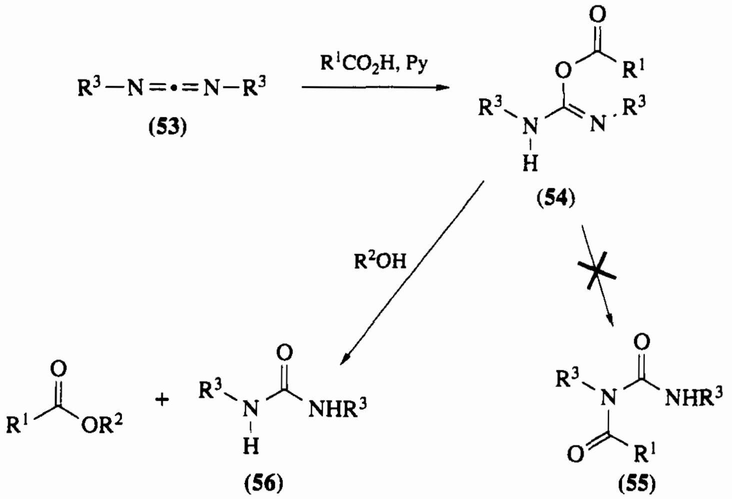

(22)

added to DCC under copper(I) catalysis to form the *O*-alkylisourea derivative (**57**), which is isolated and treated with the acid to form the ester *via* $S_N2$ displacement.[47] In effect, this reaction constitutes an alternative to the Mitsunobu reaction. The carboxylic acid used for the inversion of secondary carbinols is formic acid; the formates are saponified with methoxide (equation 24). The inversion of carbinols (**58**)–(**60**) proceeds with high overall yields.[48]

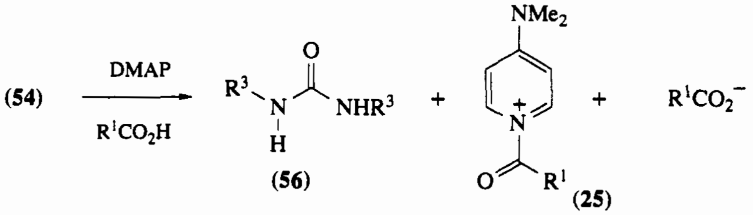

(23)

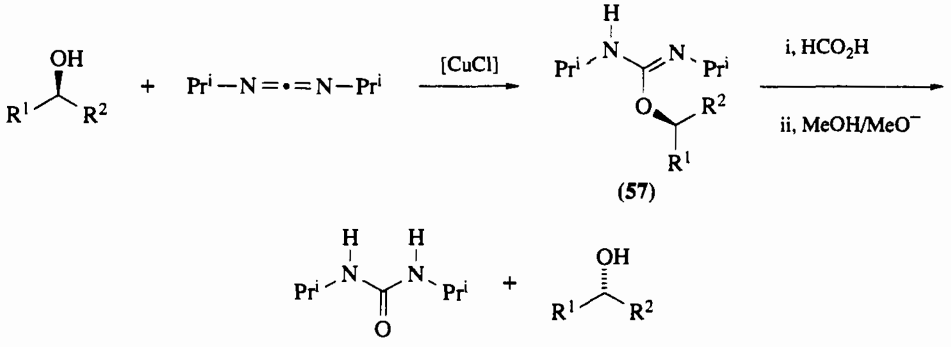

(24)

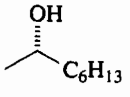

(**58**)

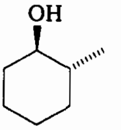

(**59**)

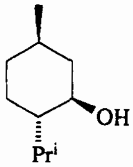

(**60**)

### 2.2.1.5 Alkylative Esterification

This type of esterification largely resembles the HGA reactions described in Section 2.2.1.3, with the only difference that the alkylating species is now an alkyl halide or tosylate or some quasi-carbenium ion instead of an activated alcohol (**43**). The most straightforward way of achieving alkylative esterification is by the treatment of carboxylate salts with an alkylating agent $R^2X$ (Table 2).

**Table 2** Alkylative Esterification

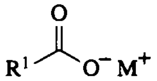
+ $R^2X$ X = OTs, OMs, Cl, Br

| *Compound* | *Ester* | *M* | *X* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| **(61a)** | 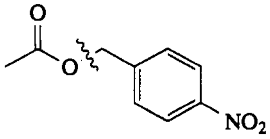 | Na | Cl | 82 | 49 |
| **(61b)** | 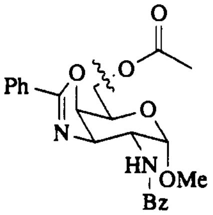 | Na | OMs | 40 | 50 |
| **(61c)** | 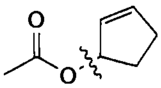 | Na | Cl | 80 | 51 |
| **(61d)** | 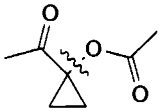 | Ag | Br | 65 | 52 |
| **(61e)** | 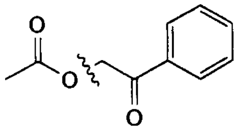 | K | Br | Quantitative | 53 |
| **(61f)** | 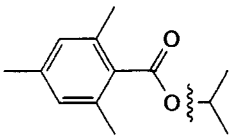 | Na | Br | Quantitative | 54 |
| **(61g)** | 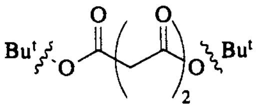 | Ag | I | 68 | 55 |
| (61h) | 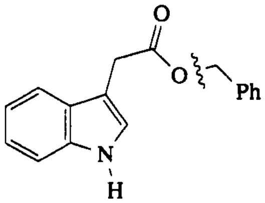 | 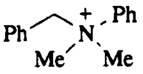 | | 68 | 56 |

It will be noted from examples (**61a**)–(**61g**) that a wide variety of carboxylates can be used, suitable cations being Na, K or Ag. In particular $Ag^+$ in combination with an alkyl bromide or iodide permits the $S_N$ reaction even at branched $sp^3$-centers (**61d, 61f** and **61g**). Example (**61h**) illustrates the use of quaternary ammonium carboxylates in which on heating the alkyl substituent with the highest $S_N2$ activity (*e.g.* benzyl > ethyl or methyl) is transferred from N to O. The advantage of the alkylative esterification lies in the neutral conditions under which acid sensitive functional groups can survive (*e.g.* **61b** and **61c**). Like the Mitsunobu reaction and the CuCl-catalyzed DCC activation the alkylative esterification may be used for the inversion of configuration at secondary carbinol centers. For instance, lactic ester (**62**) is mesylated and then heated with cesium propionate in DMF[57] to give (**63**; equation 25). Diazoalkanes (**64**) react with carboxylic acids under proton transfer to give the diazonium carboxylate (**65**),[58] which collapses into the ester and nitrogen (equation 26). This method is the best for methylating sensitive carboxylic acids like (**66**).[59] The extension to diazoalkanes other than diazomethane, however, has been prohibited by their poor availability and the potential danger in handling these compounds. An established procedure for preparing *t*-butyl esters is the treatment of carboxylic acids with isobutene and strong acid in aprotic solvents (equation 27).[60]

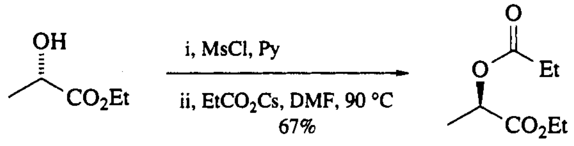

(**62**) (**63**) (25)

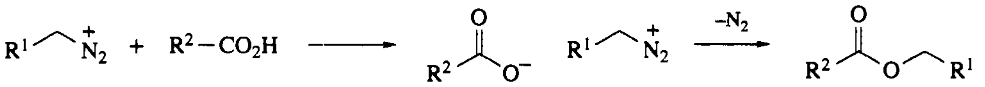

(**64**) (**65**) (26)

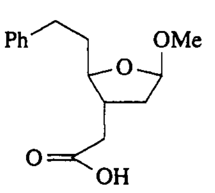

(**66**)

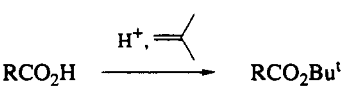

(27)

### 2.2.1.6 Selective Monoacylation of Polyols

One of the fundamental operations in multistep syntheses is the selective acylation of polyols, mainly for protection purposes, as selectivity in favor of one out of several hydroxy groups in general is far easier to get by acylation than by alkylation. The differentiation between tertiary and secondary or primary OH groups presents no problems, as tertiary groups are acylated only under forced conditions. Standard conditions (*e.g.* acetic anhydride or benzoyl chloride in pyridine) leave tertiary hydroxy groups untouched. Thus, only the secondary OH function in (**67**) is acetylated.[61] Even strongly hindered primary OH functions, *e.g* the one marked in (**68**), are unreactive.[62] A crucial problem, however, is the differentiation of primary and secondary positions, especially in 1,2-diols like (**70**), (**71**), (**75**) or (**76**). A variety of methods have been developed to solve this problem by selective benzoylation of the primary OH group with reagents like benzoyl cyanide, benzoylimidazole and benzoyltetrazole.[63] Recently, 1-benzoyl oxybenzotriazole (**69**) has been reported to furnish product ratios of primary to secondary benzoates of >90:10[64] in a number of cases, *e.g.* (**70**)–(**72**). The reagent even differentiates between secondary OH groups. So the marked positions in (**73**) and (**74**) are benzoylated with >90% selectivity. In favorable cases, primary OH functions in 1,2-diols can be selectively benzoylated simply by using benzoyl chloride in pyridine at –20 °C. (**75**) and (**76**) form the primary monobenzoates under these conditions with no concomitant acylation of the secondary position, but with formation of 5–10% of the dibenzoate.[65] Monobenzoylation of primary OH groups can also be achieved by the Mitsunobu reaction (Table 3).[39]

However, this method fails for 1,2-diols like (**79**) or (**81**), from which the epoxides (**80**) and (**82**) are generated (equations 28 and 29). This involves an $S_N2$-type cyclization with retention at the secondary

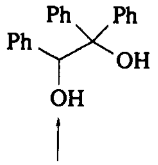

**(67)**

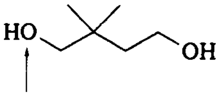

**(68)**

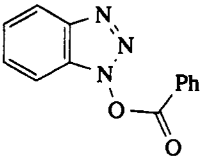

**(69)**

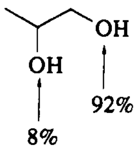

**(70)**

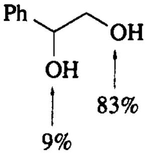

**(71)**

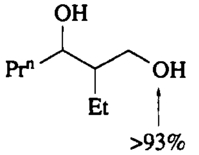

**(72)**

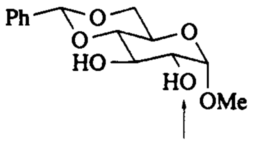

**(73)**

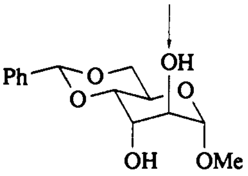

**(74)**

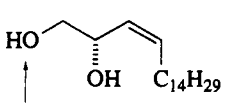

**(75)**

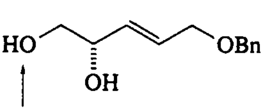

**(76)**

**Table 3** Selective Monobenzoylation under Mitsunobu Conditions[39]

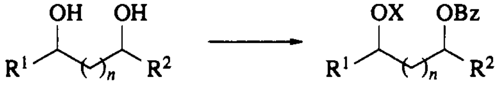

**(77)** **(78)**

| *n* | *R*$^1$ | *R*$^2$ | *X* | *Yield (%)* *X = H* | *X = Bz* |
|---|---|---|---|---|---|
| 1 | H | H | H or Bz | 65 | 12 |
| 2 | H | H | H or Bz | 66 | 15 |
| 1 | Me | H | H or Bz | 70 | 7 |
| 1 | Me | Me | H or Bz | 57 | 20 |

center.[66] The comparison between the *cis*- and *trans*-cyclohexane diols (**81**) and (**83**) is quite informative. Only the *trans* isomer gives the epoxide (equation 29), whereas the *cis* compound is monobenzoylated (equation 30). In suitable cases selective acylations with $Ac_2O$ may be achieved by utilizing conformational effects. For instance, in the forskolin precursor (**86**) only the marked OH group is acetylated under standard conditions. Due to the rigid conformation of the molecule this is the only secondary equatorial hydroxy function, whereas the other ones are either tertiary or axial.[67] Sometimes the need arises to get selective acylation of a secondary position in the presence of a primary one. This can be achieved by first peracetylating the compound and removing the more unhindered primary acetate with mild base. In this way, (**85b**) has been prepared from (**85a**) with perfect regiocontrol.[68] Further selective acylations are described in Section 2.2.1.8.

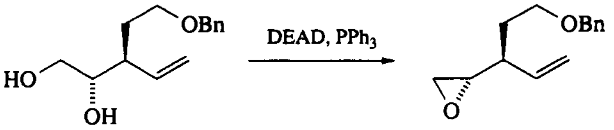

**(79)** **(80)** 75% (28)

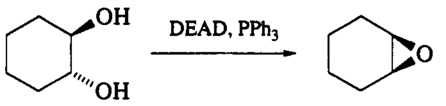

(81) (82) 80%

(29)

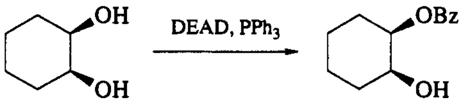

(83) (84) 22%

(30)

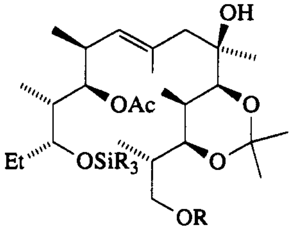

(85) a: R = Ac
b: R = H

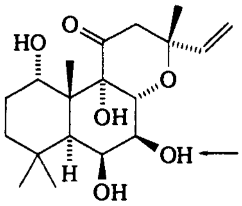

(86)

### 2.2.1.7 Transesterifications

Transesterifications can, in principle, be performed by reaction of esters with alcohols, carboxylic acids and other esters. All three types are reversible, so that the equilibrium has to be shifted to the desired side either by applying an excess of the reagent or by removing a volatile product *via* distillation. In all cases acid or base catalysis is required. In laboratory practice the most common transesterification method is the reaction of valuable esters with an excess of a cheap alcohol under the catalysis of a mild base. Examples are given in Table 4. Recently, $Ti(OPr^i)_4$ has been recommended as an exceptionally mild and efficient transesterification catalyst.[72] Thus, the dimethyl ester (**87**) is cleanly converted into (**88**) without affecting the acetonide ring (equation 31). The alcohol need not necessarily be identical with the OR group in the titanate, as this exchange is slow compared to the transesterification itself. Transesterifications of β-keto esters are most efficiently catalyzed with DMAP, as illustrated by equation 32.[73]

**Table 4** Transesterification of Esters and Alcohols

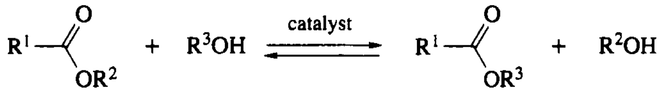

$$R^1C(O)OR^2 + R^3OH \overset{\text{catalyst}}{\rightleftharpoons} R^1C(O)OR^3 + R^2OH$$

| $R^1$ | $R^2$ | $R^3$ | Catalyst | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 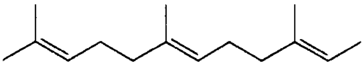 | Me | Et | KCN | 85 | 69 |
| $C_6H_{13}$ | Me | $Bu^t$ | Molecular sieves | 83 | 70 |
| 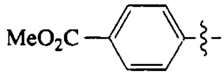 $MeO_2C$ | Me | 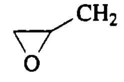 $CH_2$ | TlCl | 94 | 71 |

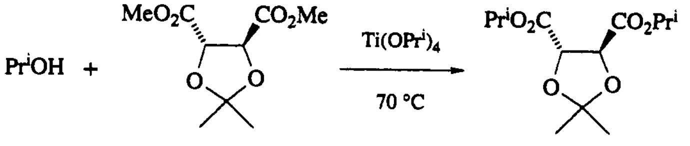

**(87)** **(88)** 91%

(31)

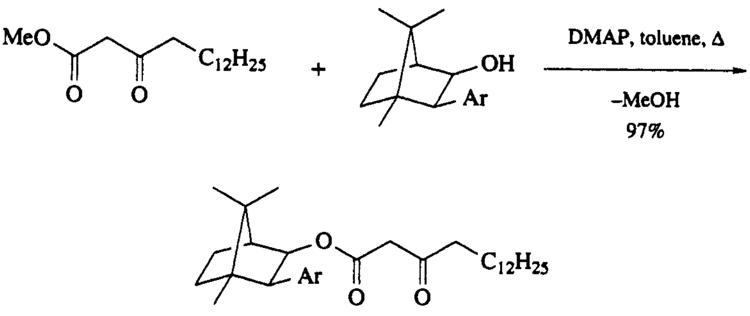

Ar = 1-naphthyl

(32)

#### 2.2.1.8 Enzymatic Acylations and Deacylations

Enzymatic transacylations have received enormous attention in recent years.[74] The enzymes generally employed are lipases from microorganisms like *Candida cylindracea*, *Rhizopus arrhizus* or *Chromobacterium viscosum*, or from mammalian liver, like porcine pancreatic lipase (PPL). Ester hydrolysis is normally performed in water, sometimes with organic solvents (acetone or acetonitrile) as additives, whereas the acylations are run as transesterifications of the alcohol with esters with the enzyme in organic solvents (ether, benzene, *etc.*). The enzyme may be used as a crude extract or in purified form, sometimes entrapped in sepharose or in chromosorb as a solid support. The great advantage of the enzymatic process lies in its high chemo- and stereo-selectivity. For example selective monoacetylations of the primary OH function in methyl furanosides of D-ribose, D-arabinose, D-xylose and 2-deoxy-D-ribose with crude PPL in THF, using 2,2,2-trifluoroethyl acetate as the acyl donor, have been reported.[75] Optical resolution of racemic mixtures of alcohols can be efficiently achieved by enzymatic acylation or transesterification. In the ideal case, only one enantiomer is reactive, the other remains unchanged. In this way a variety of γ-branched alcohols (**89**) have been resolved with high *ee* values in both the ester and the remaining alcohol (Table 5 and equation 33).[76] α-Branched alcohols have been resolved with similar efficiency (Table 6 and equation 34).[76] The enzymes used were HLCE and yeast lipase on sepharose or chromosorb in water and the acyl-donating ester as solvent.

On the other hand, resolution of racemic α-halo carboxylic acids (**93**) with butanol can be effected with lipase (Table 7 and equation 35).[77] Applications of enzyme-catalyzed acyl transfer reactions, among many others, are the synthesis of the pheromone (*S*)-sulcatol (**95**; equation 36)[78] and of (*R*)-glycidylbu-

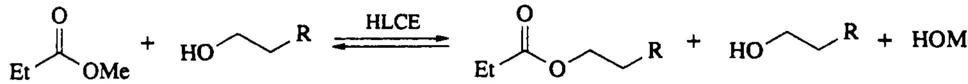

(33)

(*R,S*)-(**89**) (*S*)-(**90**) (*R*)-(**89**)

Table 5 Enzymatic Resolution of Alcohols by Transesterification with Hog Liver Carboxylate Esterase (HLCE) (equation 33)

| *R* | % *ee* (*S*)-(**90**) | % *ee* (*R*)-(**89**) |
|---|---|---|
| CH(OMe)Me | 98 | — |
| CH(Me)Et | 94 | 94 |
| CH(Me)(CH$_2$)$_3$CHMe$_2$ | 95 | 97 |
| CH(Me)CH$_2$CH$_2$CH═CMe$_2$ | 96 | 97 |

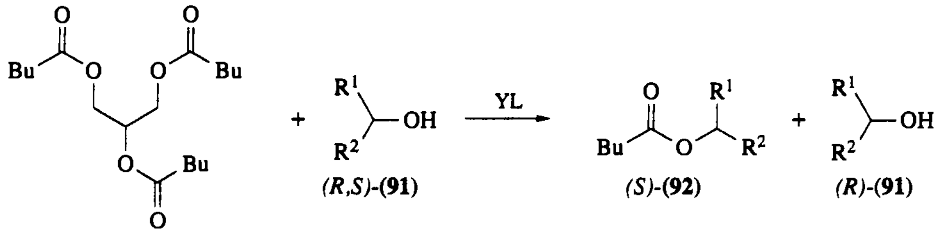

(34)

**Table 6** Enzymatic Resolution of Alcohols by Transesterification with Yeast Lipase (YL) (equation 34)

| *R*$^1$ | *R*$^2$ | (% ee) *(S)-(***92***)* | *(R)-(***91***)* |
|---|---|---|---|
| Me | Et | 98 | 97 |
| Me | $C_6H_{13}$ | 98 | 89 |
| H | $CHClCH_2Cl$ | 93 | 88 |

tyrate (**96**), which serves as the starting material for the β-blocker propranolol (**97**). Enzymatic esterification of racemic menthol (**98**) with hexanoic acid leads to optically pure ester (equation 37).[79]

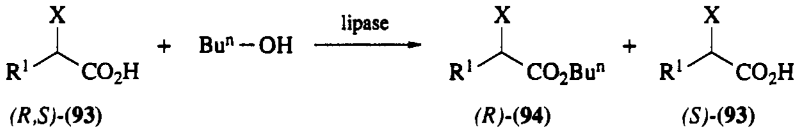

(35)

**Table 7** Enzymatic Resolution of α-Halocarboxylic Acids (equation 35)

| *R*$^1$ | *X* | (% ee) *(R)-(***94***)* | *(S)-(***93***)* |
|---|---|---|---|
| Me | Br | 96 | 99.6 |
| Me | Cl | 95 | 95 |
| Bu | Br | 99 | 62/73 |
| Ph | Cl | 99 | — |

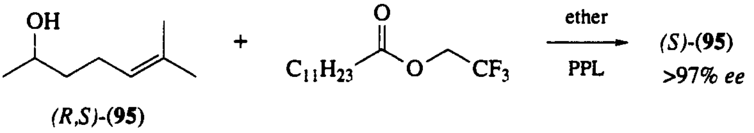

(36)

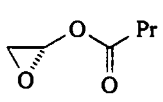

**(96)**

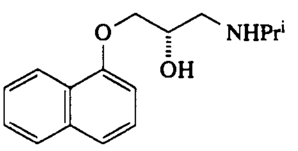

**(97)**

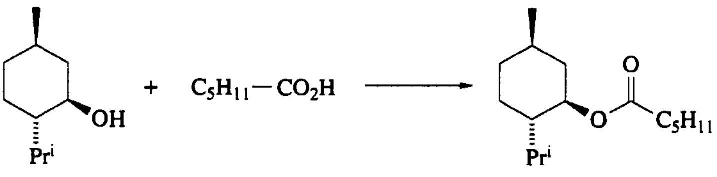

(**98**) racemate

100% *ee*

(37)

In contrast to the procedures described so far which all have to use a large excess of one component (ester in equations 33, 34 and 36, alcohol in equation 35 or acid in equation 37) direct enzymatic acylation with isopropenyl acetate or acetic anhydride[80] requires only stoichiometric amounts of the reagents (equations 38 and 39). Both acetate, **(100)** and **(102)**, and alcohol, **(99)** and **(101)**, are obtained with high enantioselectivity.

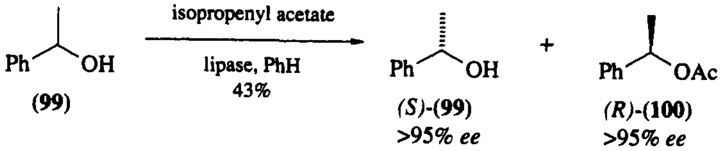

(38)

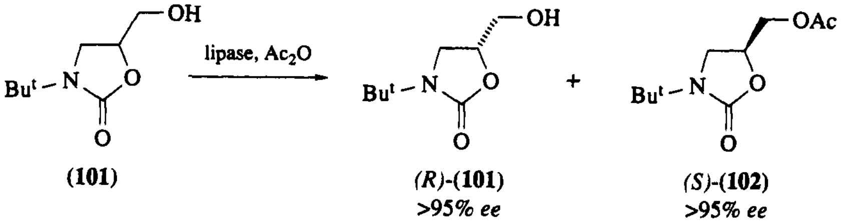

(39)

Enantiotopically selective ester hydrolysis can also be achieved enzymatically (Table 8). Either one ester group in a *meso*-diester **(103)**–**(106)** or one acetate in a *meso*-diacetate **(107)**–**(111)** are saponified with PLE or other lipases. In favorable cases enzymatic acylation and deacylation are stereochemically complementary and may thus be combined to gain access to both enantiomers, as illustrated by the example in Table 9.[89]

## 2.2.2 SYNTHESIS OF LACTONES

Lactones are intramolecularly formed esters of hydroxy carboxylic acids and may, consequently, be prepared by cycloacylating or cycloalkylating processes. The CGA intermediate **(116)** has to be formed from **(115)** by means of some activating agent, whereas cycloalkylation presupposes the carboxylate **(119)**, with some leaving group Y in the ω-position. Y may be an oxygen-leaving group (HGA mechanism) or a halogen. The most significant difference between cycloacylation and cycloalkylation is the retention and inversion of the configurations of the ω-center, respectively. Most lactonizations proceed *via* cycloacylation.

### 2.2.2.1 Synthesis of α-Lactones

α-Lactones have no significance in synthesis, but in their own right they are interesting, highly strained, and hence, transient species. Classical work has provided evidence that the hydrolysis of α-bromopropionic acid in mild base proceeds *via* **(121)**, which is then opened with inversion of configuration, so that the overall result is retention of configuration at the α-center.[90]

α-Lactones of type **(122)** may be generated photolytically in a frozen matrix and polymerize at higher temperature.[91]

### 2.2.2.2 Synthesis of β-Lactones

β-Lactones are normally stable compounds, which have found ample application as synthetic intermediates,[92] and, quite recently, have been detected as the central structural unit in physiologically active natural products like obaflorin **(123)**[93a] and lipstatin **(124)**.[93b] Characteristic applications of β-lactones in synthesis are the stereospecific $CO_2$ elimination to form di- and tri-substituted alkenes (*e.g.* from **125**; equation 40)[94] or Grignard addition to the carbonyl group (*e.g.* equation 41).[95] Particularly useful is the formation of β-lactone enolates **(126)**, which react with a variety of electrophiles (EX) with high stereocontrol (equation 42).[96] Organocuprates may be used in chain elongations to form β-branched carboxylic acids (equation 43).[97]

**Table 8** Enzymatic Enantioselective Hydrolysis of *meso*-Diesters or Diacetates

| *Compound* | *Diester or diacetate* | *% ee* | *Ref.* |
|---|---|---|---|
| **(103)** | 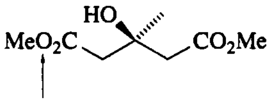 | 99 | 81 |
| **(104)** | 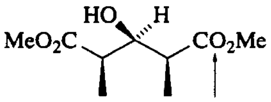 | 98 | 82 |
| **(105)** | 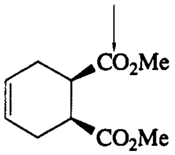 | 98 | 83 |
| **(106)** | 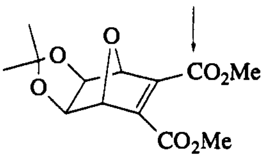 | 77 | 84 |
| **(107)** | 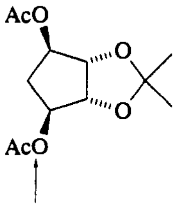 | 98 | 85 |
| **(108)** | 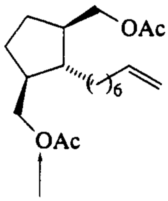 | 99 | 86 |
| **(109)** | 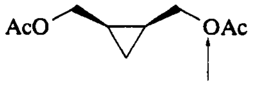 | 93 | 87 |
| **(110)** | 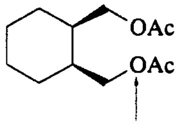 | 87 | 87 |
| **(111)** | 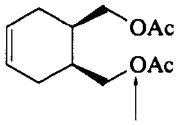 | 95 | 88 |

**Table 9** Complementary Enzymatic Acylation and Deacylation

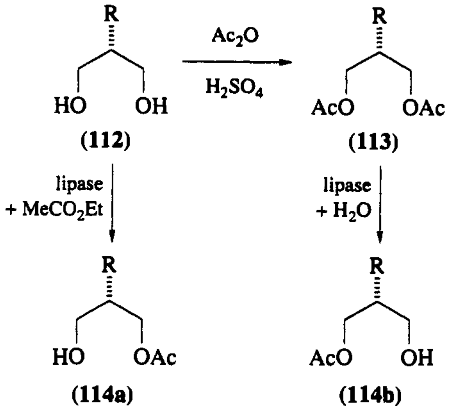
R
HO
OH
(112)
Ac2O
H2SO4
R
AcO
OAc
(113)
lipase
+ MeCO2Et
lipase
+ H2O
R
HO
OAc
(114a)
R
AcO
OH
(114b)

|  | (% ee) |  |
|---|---|---|
| *R* | *(114a)* | *(114b)* |
| $CH_2CH_2CH{=}CH_2$ | 90 | >95 |
| Ph | 92 | >95 |
| $CH_2Ph$ | 13 | 61 |
| $C_6H_{11}$ | 58 | 60 |

*Cycloacylation*

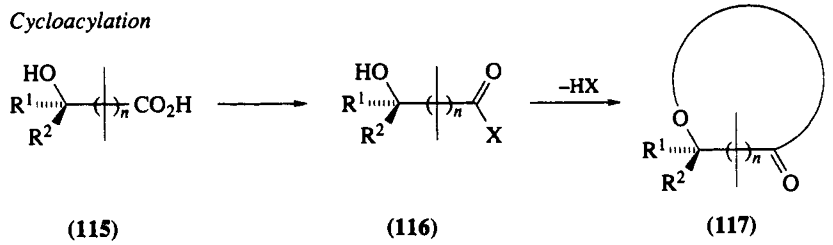
HO
R1
R2
n
CO2H
(115)
HO
R1
R2
n
O
X
(116)
-HX
O
R1
R2
n
O
(117)

*Cycloalkylation*

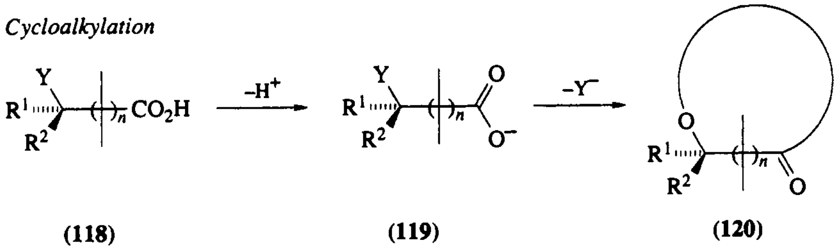
Y
R1
R2
n
CO2H
(118)
-H+
Y
R1
R2
n
O
O−
(119)
-Y−
O
R1
R2
n
O
(120)

**a**, Y = Hal; **b**, Y = OZ

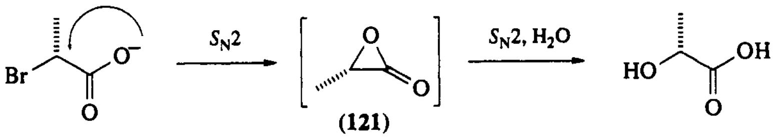
Br
O−
O
SN2
O
O
(121)
SN2, H2O
HO
OH
O

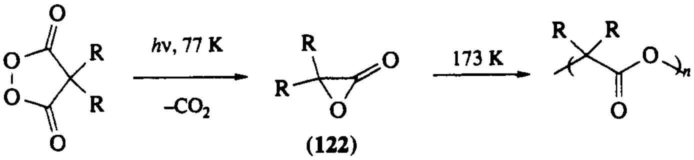
O
O
O
O
O
R
R
hν, 77 K
−CO2
R
R
O
O
(122)
173 K
R
R
O
O
n

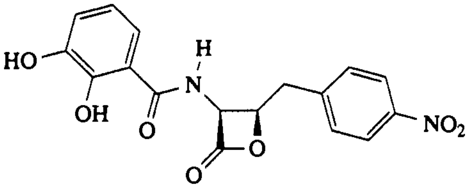

**(123)**

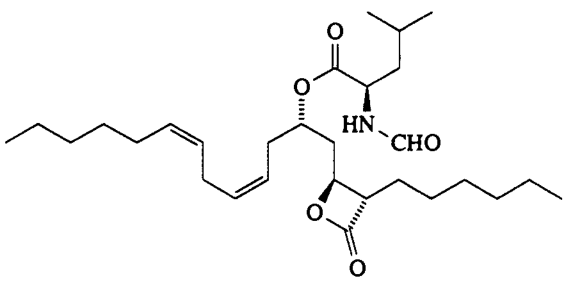

**(124)**

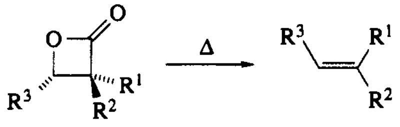

**(125)**

(40)

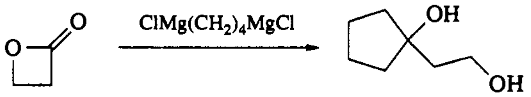

(41)

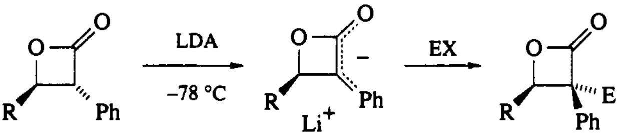

**(126)**

(42)

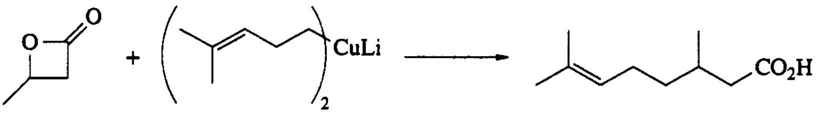

(43)

### 2.2.2.2.1 β-Lactones via cycloalkylation

It has been shown that β-bromocarboxylic acids like (**127**) and (**129**) cyclize with mild base to form β-lactones like (**128**; equation 44)[98] and (**130**; equation 45).[99] The reaction is mostly accompanied by fragmentation to the alkene, as shown by the conversion of (**131**) into (**132**) and (**133**) (equation 46).[100] In this particular example, only *trans*-β-lactone (**132**) was found, inspite of the *threo* configuration of (**131**), which indicates an $S_N1$- rather than an $S_N2$-type cyclization.

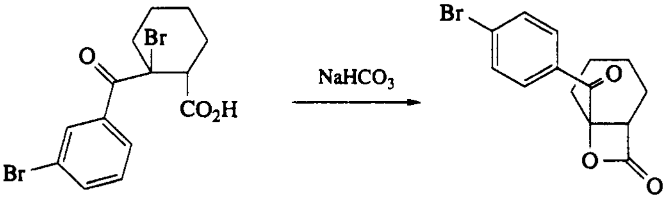

**(127)** **(128)**

(44)

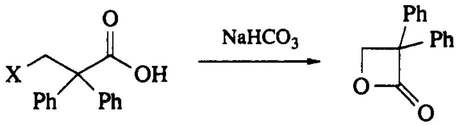

**(129)** X = Cl, Br, I **(130)**

(45)

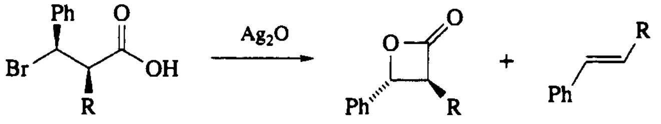

(131) R = Me, Et (132) 17% (133) 40%

(46)

### 2.2.2.2.2 *β-Lactones* via *cycloacylation*

Cycloacylation of β-hydroxy carboxylic acids can be accomplished with various dehydrating agents. For example (**134**) has been converted into the δ-lactone acetal (**135**) with orthoformate. On heating, (**135**) loses methyl formate under formation of the β-lactone (equation 47).[101] β-Hydroxy thiol esters like (**136**) have been reported to form β-lactones under retention of configuration in high yields (equation 48).[102]

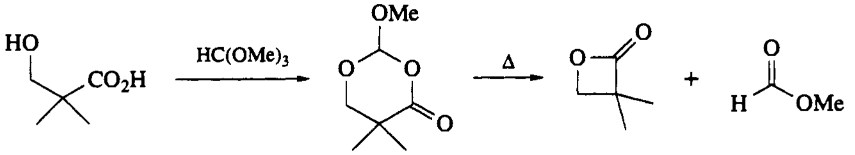

(134) (135)

(47)

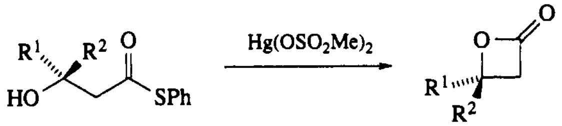

(136)

(48)

The method of choice, however, is the reaction of (**137**) with benzenesulfonyl chloride in pyridine at low temperature (equation 49). This conversion proceeds *via* (**138**) with strict retention of configuration and is compatible with a variety of substituents (Table 10).[103] However, it fails for small substituents (**137l** and **137m**) in which case only polyesters are formed. In cyclic systems like (**140**) β-lactone formation cannot occur if the carboxy and the hydroxy functions are *trans* (equation 50) In this case the di-

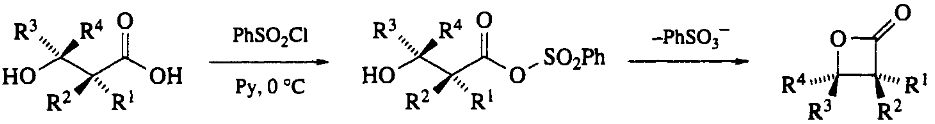

(137) (138) (139)

(49)

**Table 10** β-Lactones from (137) and Benzenesulfonyl Chloride (equation 49)

| *Compound* | *R*$^1$ | *R*$^2$ | *R*$^3$ | *R*$^4$ | *Yield (%)* |
|---|---|---|---|---|---|
| (137a) | Me | OMe | Pr$^n$ | Pr$^n$ | 77 |
| (137b) | Me | Me | H | Ph | 95 |
| (137c) | H | Bu$^t$ | Ph | Ph | 100 |
| (137d) | Bu$^t$ | H | H | Ph | 88 |
| (137e) | Bu$^t$ | H | Ph | H | 73 |
| (137f) | Me | H | H | Ph | 81 |
| (137g) | Me | H | Ph | H | 15 |
| (137h) | Ph | H | H | Bu$^t$ | 92 |
| (137i) | Ph | H | Bu$^t$ | H | 85 |
| (137j) | Ph | H | H | Me | 15 |
| (137k) | Ph | H | Ph | H | 15 |
| (137l) | Me | H | H | Me | — |
| (137m) | Me | H | H | Et | — |
| (137n) | Bu$^t$ | H | H | 2-Thienyl | 83 |
| (137o) | Bu$^t$ | H | 2-Thienyl | H | — |

sulfonated anhydride (**143**) is formed in *ca.* 40% yield, presumably *via* (**142**) as an intermediate.[104] Alkene formation is the main reaction for systems with strongly electron-donating substituents in the β-position (*e.g.* **137a**). Presumably these β-lactones are unstable and eliminate carbon dioxide very rapidly.[105]

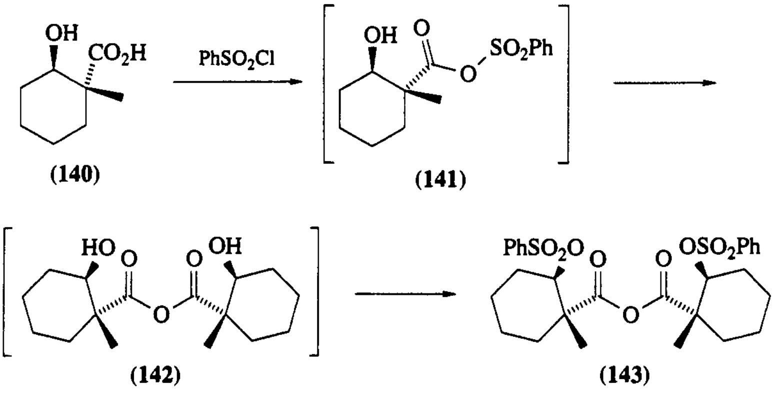
OH
CO2H
PhSO2Cl
OH
O
SO2Ph
O
(140)
(141)
HO
O
O
OH
O
(142)
PhSO2O
O
O
OSO2Ph
O
(143)

(50)

### 2.2.2.2.3 β-Lactones from β-hydroxy carboxylic acids with HGA and CGA reagents

*(i) Mitsunobu conditions*

Under Mitsunobu conditions ('*anti*') *threo*-hydroxy carboxylic acids (**144**) form (*Z*)- and (*E*)-alkenes (**150**) and (**151**) and *cis*- and *trans*-β-lactones (**152**) and (**149**) in various ratios, depending on $R^1$ and $R^2$ (Table 11). The mechanism (Scheme 3) involves a competition between the HGA and CGA intermediates (**145**) and (**146**). For $R^2$ with a high +M effect (*e.g.* Ph, 2-thienyl *etc.*), the zwitterion (**147**) also has to be considered. After rotation to (**148**), intermediate (**145**) gives rise to the products (**151**) and (**152**). *Via* (**146**) the lactone (**149**) is generated. It is obvious from Table 11 that only large $R^1$ and $R^2$ groups lead to CGA (**144d** and **144i**), whereas the rest prefer the HGA pathway.[106]

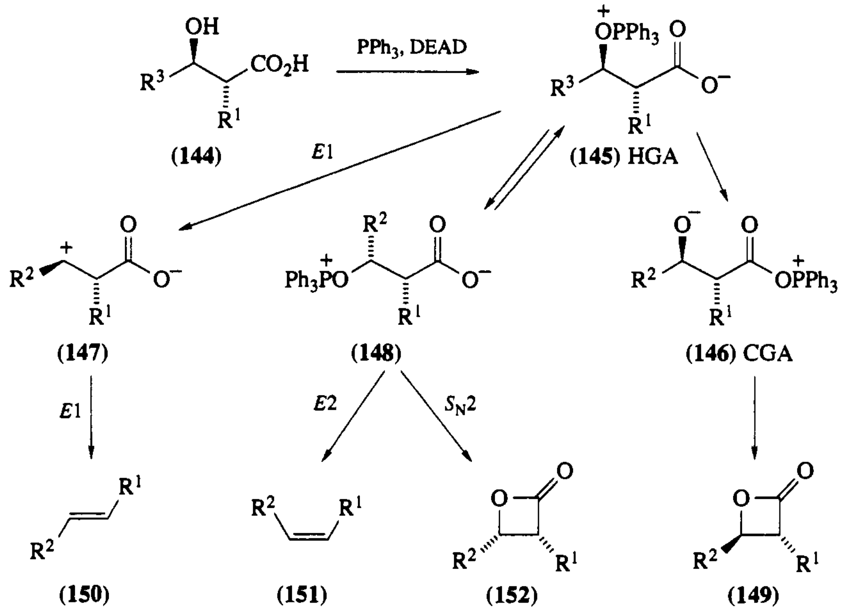
OH
R3
CO2H
R1
(144)
PPh3, DEAD
E1
+
OPPh3
O
R3
O−
R1
(145) HGA
O
+
R2
O−
R1
(147)
R2
O
+
Ph3PO
O−
R1
(148)
O−
O
R2
+
OPPh3
R1
(146) CGA
E1
E2
SN2
R1
R2
(150)
R2
R1
(151)
O
O
R2
R1
(152)
O
O
R2
R1
(149)

**Scheme 3**

**Table 11** CGA *versus* HGA Reaction of *anti*-Acids (**144**) under Mitsunobi Conditions (Scheme 3)

| *Compound* | *R*$^1$ | *R*$^2$ | *Yield (%)* (**150**) | (**151**) | (**152**) | (**149**) | *Total yield (%)* | *Prevailing mechanism* |
|---|---|---|---|---|---|---|---|---|
| (**144a**) | Ph | Me | — | 88 | 12 | — | 85 | HGA |
| (**144b**) | Ph | Et | — | 83 | 17 | — | 82 | HGA |
| (**144c**) | Ph | Pr$^i$ | — | 80 | — | 20 | 92 | HGA |
| (**144d**) | Ph | Bu$^t$ | — | — | — | 100 | 92 | CGA |
| (**144e**) | Me | Ph | 11 | 63 | 36 | — | 83 | HGA |
| (**144f**) | Et | Ph | 17 | 60 | 23 | — | 87 | HGA |
| (**144g**) | Pr$^i$ | Ph | 81 | 12 | — | 7 | 81 | HGA |
| (**144h**) | Bu$^t$ | Ph | 66 | — | — | 34 | 92 | HGA |
| (**144i**) | Bu$^t$ | Bu$^t$ | — | — | — | 100 | 83 | CGA |

By contrast, ('*syn*') *erythro*-hydroxy carboxylic acids (**153**) react *via* HGA exclusively to form the (*E*)-alkene (**150**), along with minor amounts of *cis*-β-lactone (**149**) *via* (**154**) (Scheme 4 and Table 12).[107]

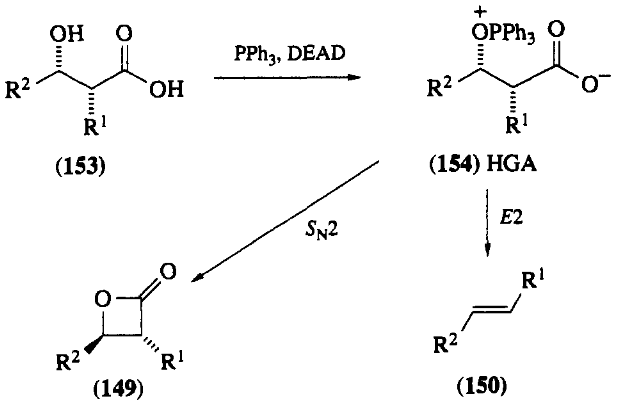

**Scheme 4**

**Table 12** Product Ratios in the Reaction of (**153**) with DEAD/PPh$_3$ (Scheme 4)

| *Compound* | *R*$^1$ | *R*$^2$ | *Yield (%)* (**149**) | (**150**) | *Total yield (%)* |
|---|---|---|---|---|---|
| (**153a**) | Ph | Me | 8 | 92 | 79 |
| (**153b**) | Ph | Et | — | 100 | 82 |
| (**153c**) | Ph | Pr$^i$ | — | 100 | 91 |
| (**153d**) | Ph | Bu$^t$ | — | — | — |
| (**153e**) | Me | Ph | 25 | 75 | 87 |
| (**153f**) | Et | Ph | 24 | 76 | 83 |
| (**153g**) | Pr$^i$ | Ph | 21 | 79 | 88 |
| (**153h**) | Bu$^t$ | Ph | — | 100 | 90 |
| (**153i**) | Ph | H | 100 | — | 30 |

### *(ii) Vorbrüggen–Eschenmoser conditions*

*Threo*-acids (**144**) react with DMF dimethyl acetal (**155**) at room temperature to give alkenes (**150**) and (**151**) along with the methyl ester (**159**) in varying ratios (Table 13). The mechanism (Scheme 5) suggests the initial formation of an ion pair (**156**) and (**157**), which either collapses to (**159**) (irreversibly) or (**158**) (reversibly). From (**158**) *E*1 and *E*2 fragmentations are possible, generating (**151**) and (**150**), respectively.[108] In general it may be stated that activating, *e.g.* aryl, substituents in the R$^2$ position are required for alkene formation. No β-lactones are formed from (**144**), quite in contrast to the '*erythro*' analogs (**153**) (Scheme 6 and Table 14), which react to (**149**), (**150**) and (**160**).[108] However, the overall yields of β-lactones (**149**) do not exceed 36% (**153g**).

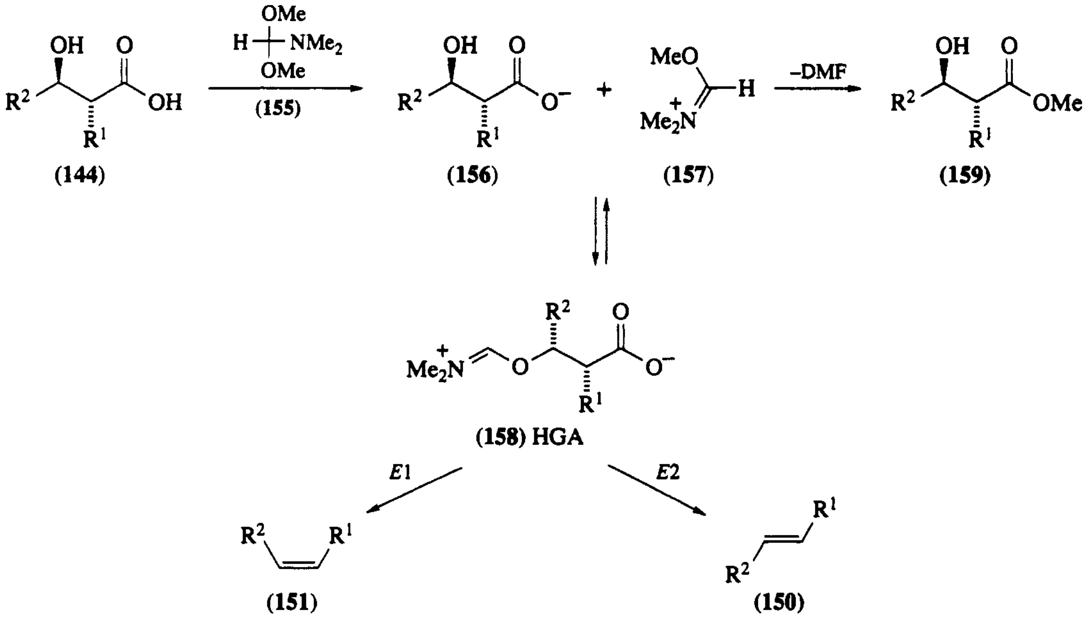
(155)
-DMF
(144)
(156)
(157)
(159)
(158) HGA
E1
E2
(151)
(150)

**Scheme 5**

**Table 13** Product Ratios in the Reaction of (**144**) with DMF Dimethyl Acetal (**155**; Scheme 5)

| *Compound* | *R*$^1$ | *R*$^2$ | *Yield (%)*<br>*(***150***)+(***151***)* | *Yield (%)*<br>*(***159***)* | *Total yield (%)* |
|---|---|---|---|---|---|
| (**144a**) | Ph | Me | 9 | 91 | 76 |
| (**144c**) | Ph | Pr$^i$ | <2 | >98 | 75 |
| (**144d**) | Ph | Bu$^t$ | <2 | >98 | 92 |
| (**144e**) | Me | Ph | 61 | 39 | 81 |
| (**144g**) | Pr$^i$ | Ph | 91 | 9 | 88 |
| (**144h**) | Bu$^t$ | Ph | 95 | 5 | 89 |
| (**144j**) | Ph | 2-Thienyl | >98 | <2 | 75 |

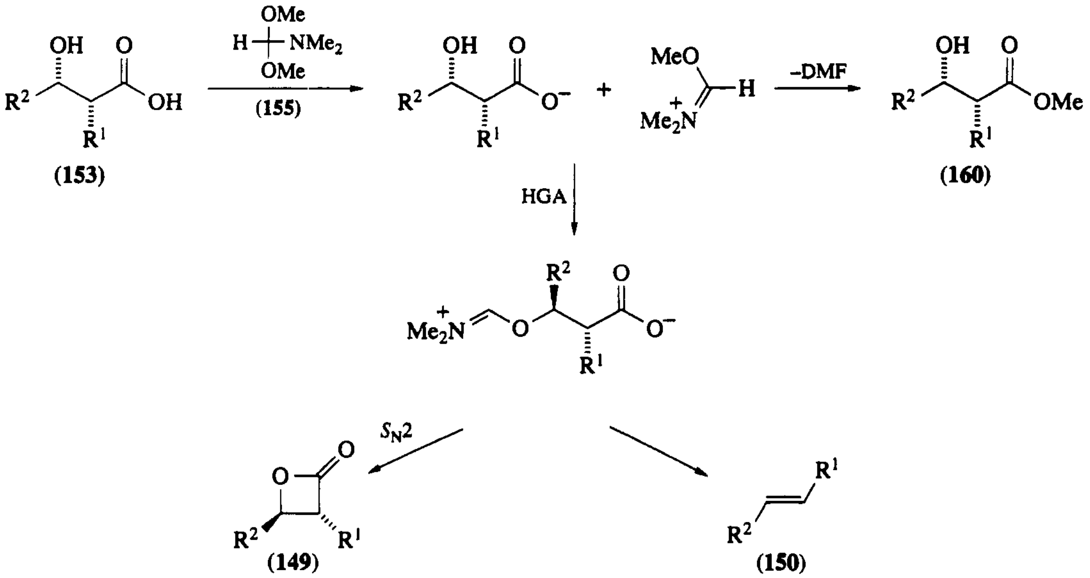
(155)
-DMF
HGA
(153)
(160)
SN2
(149)
(150)

**Scheme 6**

**Table 14** Product Ratios in the Reaction of (**153**) with DMF Dimethyl Acetal (**155**; Scheme 6)

| *Compound* | $R^1$ | $R^2$ | *Yield (%)* (**160**) | (**149**) | (**150**) | *Total yield (%)* |
|---|---|---|---|---|---|---|
| (**153a**) | Ph | Me | 41 | 16 | 43 | 75 |
| (**153b**) | Ph | Et | 35 | 10 | 55 | 72 |
| (**153c**) | Ph | $Pr^i$ | 42 | 22 | 58 | 80 |
| (**153d**) | Ph | $Bu^t$ | 29 | 22 | 71 | 85 |
| (**153e**) | Me | Ph | <2 | 7 | 93 | 87 |
| (**153f**) | Et | Ph | <2 | 15 | 85 | 82 |
| (**153g**) | $Pr^i$ | Ph | <2 | 40 | 60 | 90 |
| (**153h**) | $Bu^t$ | Ph | <2 | <2 | 98 | 90 |

#### 2.2.2.2.4 *β-Lactones* via *C—C connections*

Although C—C connecting reactions are discussed elsewhere in 'Comprehensive Organic Synthesis',[109] it may be mentioned that epoxides react regioselectively with carbon monoxide under rhodium catalysis (equation 51)[110] and benzyl bromides undergo carbonylation and subsequent lactonization under the influence of a $Pd^{II}$ catalyst (equation 52).[111] The [2 + 2] cycloaddition of ketenes to carbonyl compounds, catalyzed by Lewis acids, is a familiar route to β-lactones (equation 53).[112]

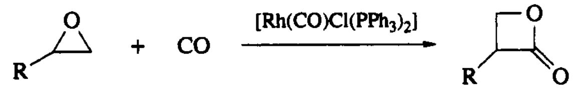

R = Me, Ph

(51)

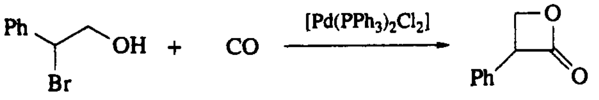

(52)

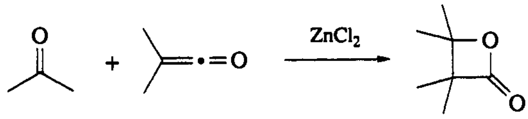

(53)

### 2.2.2.3 Synthesis of γ-Lactones

γ-Lactones are among the most abundant substructures in natural products.[113] This fact had kindled enormous activity in the field of γ-lactone synthesis.[114] γ-Lactones have been prepared by direct cycloacylation of γ-hydroxy acids, either as such or generated as transient intermediates, and by cycloalkylation, either of γ-halocarboxylates or of β,γ- or γ,δ-unsaturated acids by additions to the double bond.

#### 2.2.2.3.1 *γ-Lactones* via *direct cycloacylation of γ-hydroxy acids or derivatives*

As indicated in equation (54) γ-lactones may be generated from γ-hydroxy acids, esters or amides, generally under acid catalysis. For esters and amides also base catalysis is appropriate. The rate of cyclization varies with the degree of substitution along the carbon chain. Bulky substituents, particularly if they have to be arranged *cis* to each other during ring formation, retard the reaction. For example (**161**) takes several days at 25 °C (equation 55),[115] whereas (**162**) only requires 14 h to form the lactone (equation 56).[116]

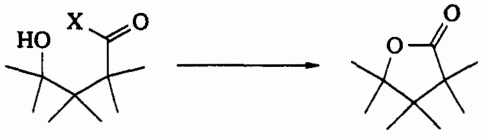

X = OH, OR, $NR_2$

(54)

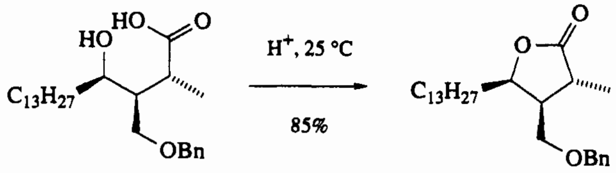
HO
HO
O
$C_{13}H_{27}$
OBn
$H^+$, 25 °C
85%
O
O
$C_{13}H_{27}$
OBn

(**161**)

(55)

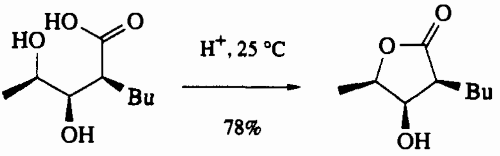
HO
HO
O
Bu
OH
$H^+$, 25 °C
78%
O
O
Bu
OH

(**162**)

(56)

The different rates of cyclization of the four diastereomeric hydroxy acids (**163**), (**165**), (**167**) and (**169**) have been utilized for separating (**163**) and (**165**) from (**167**) and (**169**). On treatment with dilute sulfuric acid in acetonitrile (**167**) and (**169**) spontaneously form the lactones (**168**) and (**170**), whereas (**163**) and (**165**) remain unchanged and can be cyclized only by treatment with acetic anhydride in pyridine (equations 57–60).[117]

In cyclic systems like (**171**), (**173**), (**175**) and (**177**) strain arguments are even more important. All four acids form the lactones only on heating to >130 °C, but the yields reflect the highly different ring strain encountered: the most favorable diequatorial lactone (**172**) is formed quantitatively (equation 61), whereas the strained diastereomers (**174**), (**176**) and (**178**) form reluctantly (equations 62–64).[118] The ring clo-

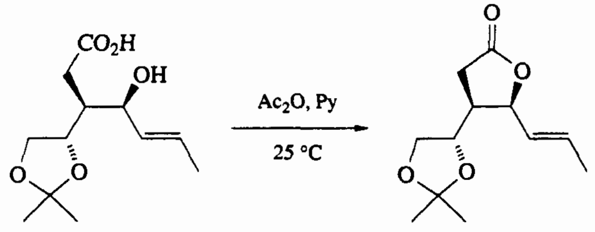
$CO_2H$
OH
O
O
$Ac_2O$, Py
25 °C
O
O
O
O

(**163**) (**164**)

(57)

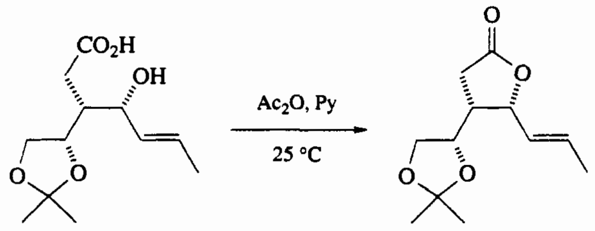
$CO_2H$
OH
O
O
$Ac_2O$, Py
25 °C
O
O
O
O

(**165**) (**166**)

(58)

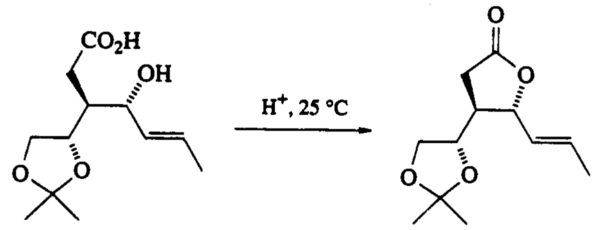

**(167)** **(168)**

(59)

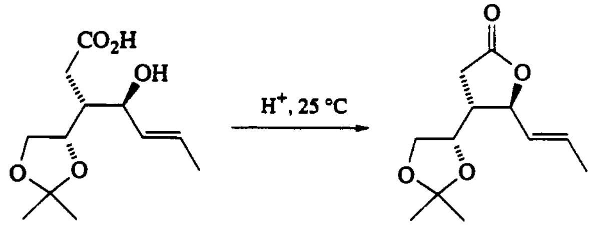

**(169)** **(170)**

(60)

sure of (**179**) to the bridged lactone (**180**) requires prolonged heating with acetic anhydride (equation 65).[119]

Lactonization may sometimes be combined with deketalization, as shown by equation (66).[120] The γ-lactone is formed in preference to the δ-lactone, in analogy to related observations.[121] Transketalization is also shown by (**183**), which forms the β-anomer of (**184**) with >10:1 selectivity (equation 67).[59]

The examples in equations (68–70) demonstrate that unsaturated γ-lactones are also accessible by the usual cyclization. The case of (**185**) shows that again the five-membered lactone is preferred.[122] The (*E*)-

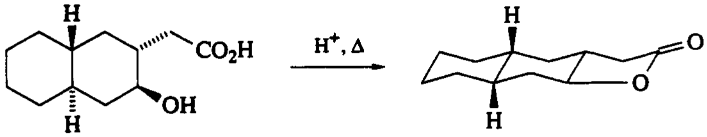

**(171)** **(172)** 97%

(61)

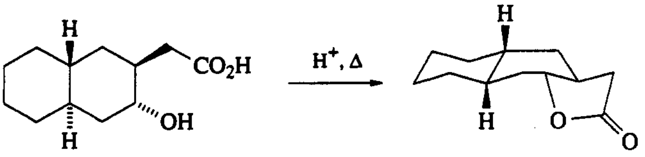

**(173)** **(174)** 73%

(62)

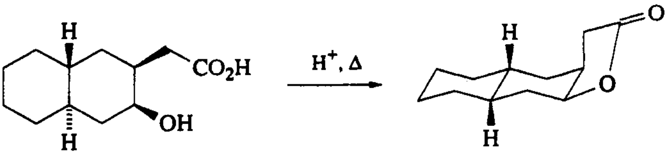

**(175)** **(176)** 75%

(63)

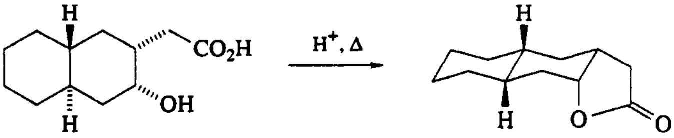

**(177)** **(178)** 40%

(64)

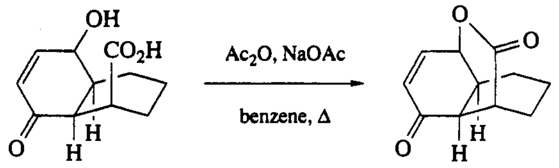
OH
CO2H
Ac2O, NaOAc
benzene, Δ
H
H
O
O
H
H

**(179)** **(180)** 66%

(65)

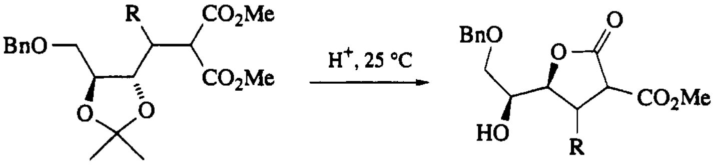
R
CO2Me
BnO
CO2Me
O
O
H+, 25 °C
BnO
O
O
CO2Me
HO
R

**(181)** **(182)**

(66)

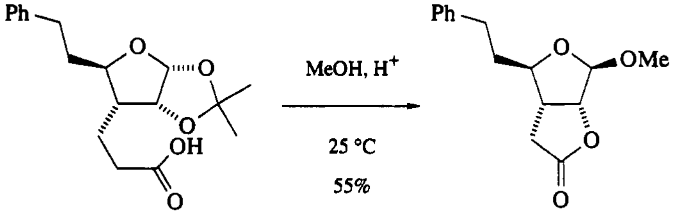
Ph
O
O
O
OH
O
MeOH, H+
25 °C
55%
Ph
O
OMe
O
O

**(183)** **(184)**

(67)

isomer of (**185**) does not cyclize, but undergoes deketalization to form the diol ester instead.[120] The DCC-mediated cyclization of (**187**) to (**188**) is noteworthy, as it starts from the ester and obviously proceeds under HGA.[123]

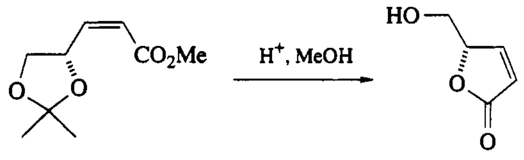
CO2Me
O
O
H+, MeOH
HO
O
O

**(185)** **(186)**

(68)

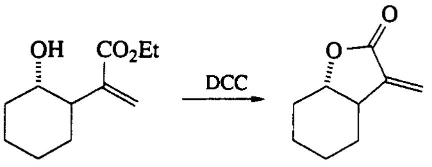
OH
CO2Et
DCC
O
O

**(187)** **(188)**

(69)

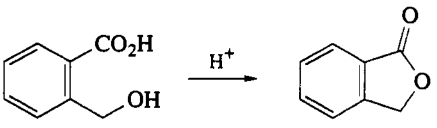

**(189)** **(190)**

(70)

Equations (71) and (72) illustrate the use of hydroxy amides as γ-lactone presursors. Prolonged heating with strong base and subsequent acidification produces (**192**) and (**194**) in almost quantitative yields.[124]

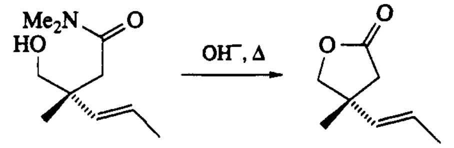

**(191)** **(192)**

(71)

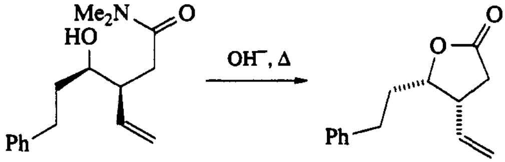

**(193)** **(194)**

(72)

### 2.2.2.3.2 *γ-Lactones by* in situ *cyclization of γ-hydroxy carboxylic acid intermediates*

In this section sequences are described in the course of which γ-hydroxy carboxylic acid derivatives are formed and immediately cyclized to γ-lactones. For instance, γ-keto ester (**195**) is reduced with 'super hydride' to give the alkoxide ester (**196**) with 7:1 selectivity (equation 73); (**196**) cannot be isolated, due to the rapid formation of lactone (**197**).[125] Similarly, cuprates add to γ-aldehydo esters with high selectivity to form *trans*-4,5-disubstituted γ-lactones after acidification (equation 74).[126]

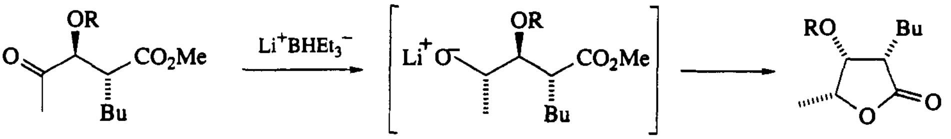

**(195)** R = COBu$^i$ **(196)** **(197)**

(73)

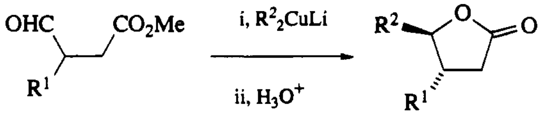

(74)

Another possibility is the addition of malonate anions to epoxides (equation 75), which, *via* the alkoxide ester (**199**), deliver the lactone ester (**200**) immediately.[127] This concept has been used in the nonstereocontrolled synthesis of protolichesterinic acid ester (**203**) from (**201**) *via* (**202**; equation 76).[128]

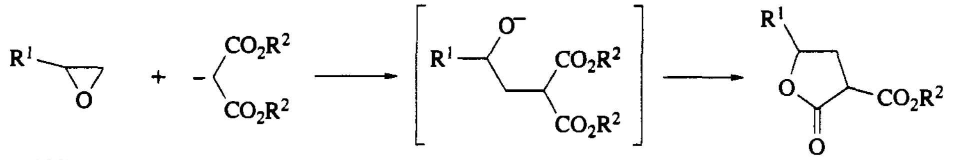

**(198)** **(199)** **(200)**

(75)

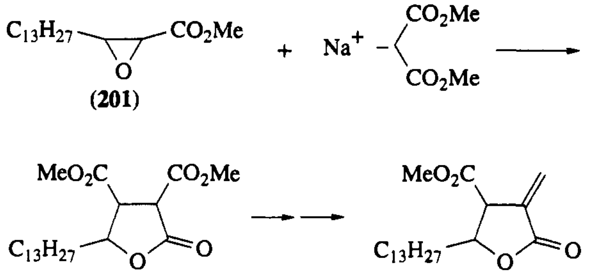

**(201)** **(202)** **(203)**

(76)

Instead of malonic esters the lithium dianions of carboxylic acids may also be used, as shown by equation (77).[129] Enantioselective γ-lactone formation has been achieved by Meyers as a ramification of his well-known oxazoline alkylations. As illustrated by equation (78), (**206**) is deprotonated and alkylated with ethylene oxide to give (**207**), which in a second alkylation step furnishes (**208**) diastereoselectively. The oxazoline ring so far has served as a carboxy synthon. Unmasking with acid immediately generates the α-substituted optically active γ-lactone (**209**).[130]

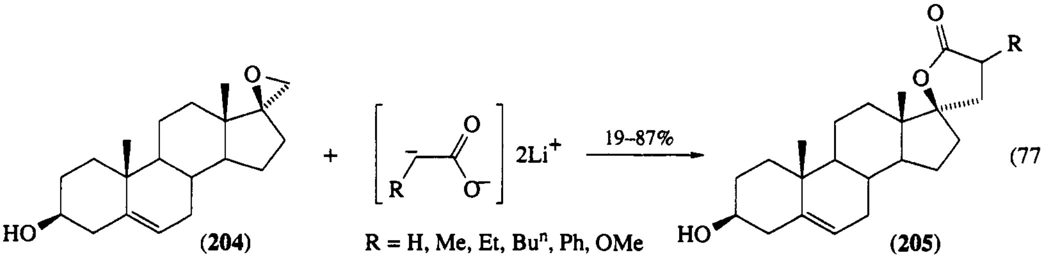
(204)
19–87%
2Li+
R = H, Me, Et, Bu^n, Ph, OMe
(205)

(77)

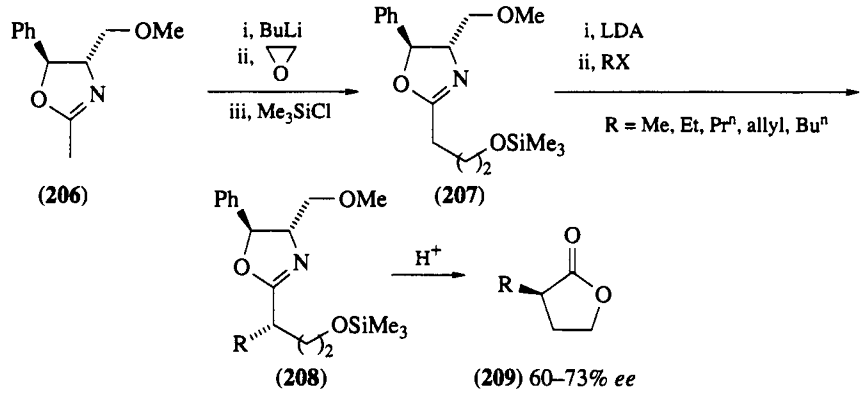
(206)
i, BuLi
ii, ▽O
iii, Me3SiCl
(207)
i, LDA
ii, RX
R = Me, Et, Pr^n, allyl, Bu^n
(208)
H+
(209) 60–73% ee

(78)

Instead of epoxides carbonyl compounds may be used as electrophiles to generate the γ-hydroxy carboxylic acid intermediate. In the classical Stobbe reaction (equation 79) succinic esters are deprotonated and treated with aldehydes or ketones to form, *via* the unstable adduct (**211**), the paraconic ester (**212**).[131]

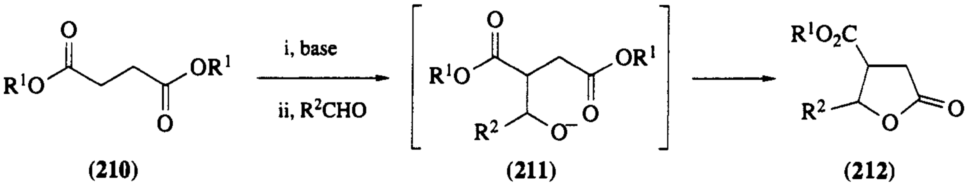
(210)
i, base
ii, R2CHO
(211)
(212)

(79)

A more recent and stereocontrolled version of the Stobbe reaction is shown in equation (80). β-Lactone ester (**213**) is deprotonated to the enolate (**214**), which adds aldehydes to give either monocyclic

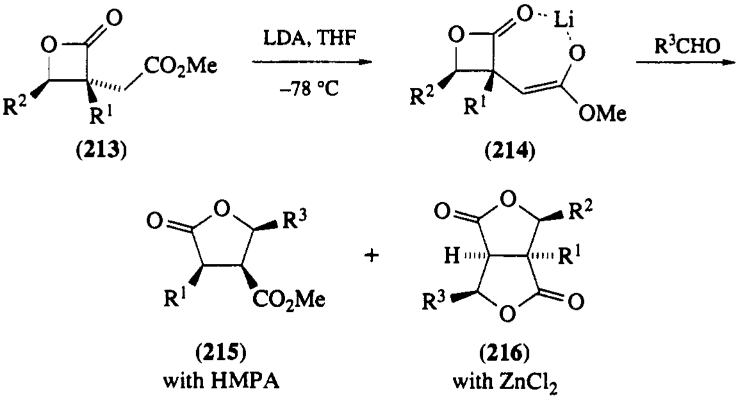
(213)
LDA, THF
–78 °C
(214)
R3CHO
(215)
with HMPA
(216)
with ZnCl2

(80)

paraconic esters (**215**) or bicyclic γ-lactones (**216**). In the presence of HMPA (**215**) is formed preferentially, and in the presence of zinc(II) chloride (**216**) is formed (preferentially), in both cases with a high degree of stereocontrol.

A mechanistic rationalization is given in Scheme 7 (HMPA additive) and Scheme 8 ($ZnCl_2$ additive) respectively. In both Schemes analogous adducts (**218**) and (**223**) are formed stereoselectively, which rearrange to the γ-lactone alkoxides (**219**) and (**224**). In the presence of HMPA, retroaldol cleavage to

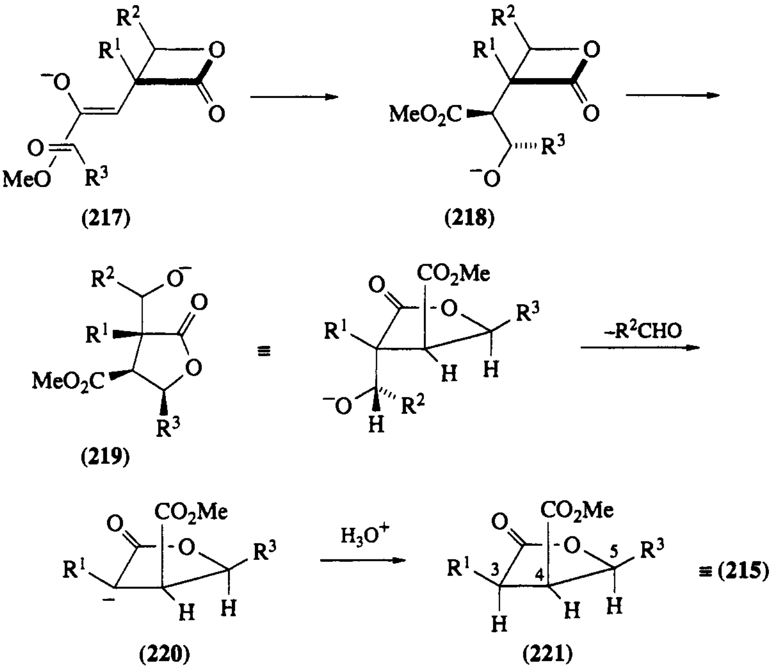

**Scheme 7**

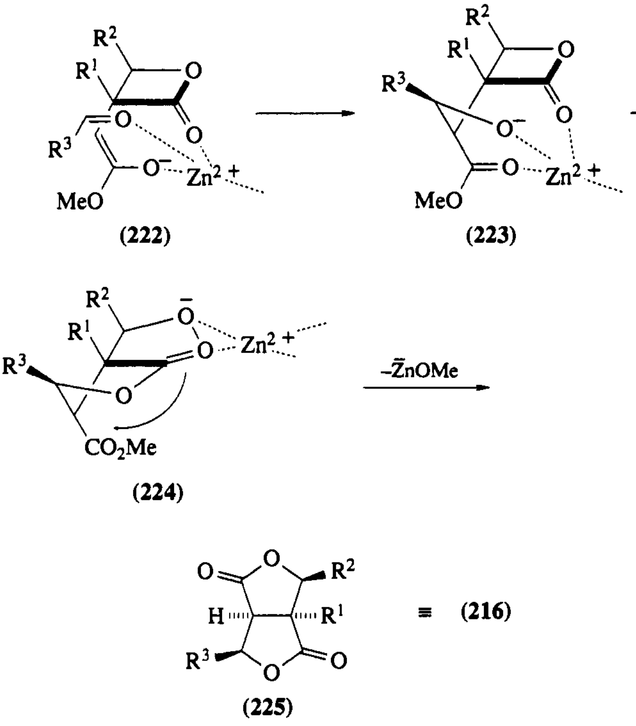

**Scheme 8**

(**220**) occurs, and after protonation (**221**) is formed. In the presence of the chelating Zn ion, by contrast, a second lactone ring is closed between the ester group and the alkoxide anion, generating (**225**).[125]

Similar condensations can be accomplished with other types of stabilized carbanions, *e.g.* sulfonyl anions, as illustrated by equation (81). The resulting sulfonyl lactone (**228**) eliminates sulfinic acid on treatment with *p*-TsOH to furnish the α,β-unsaturated system (**229**).[132] Spirolactonization is the result of the Reformatsky reaction of ester (**231**) with cyclic ketones.[133] In equation (82), this reaction is applied to the synthesis of the lysergic acid precursor (**232**), which is formed stereoselectively from (**230**).[134]

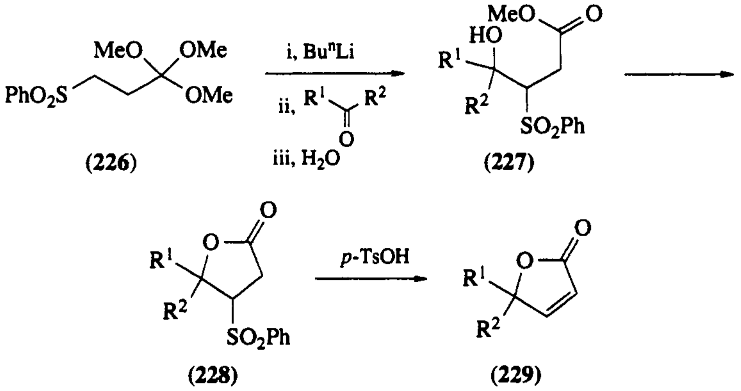
MeO
OMe
PhO2S
OMe
(226)
i, BunLi
ii, R1 R2 O
iii, H2O
MeO
O
HO
R1
R2
SO2Ph
(227)
R1
O
O
R2
SO2Ph
(228)
p-TsOH
O
R1
O
R2
(229)

(81)

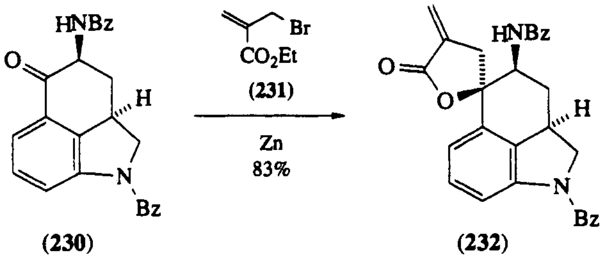
HNBz
O
H
N
Bz
(230)
Br
CO2Et
(231)
Zn
83%
O
O
HNBz
H
N
Bz
(232)

(82)

A carbocyclic ring and a γ-lactone may be created in a concise manner by using the Sakurai cyclization of (**233**) to (**234**) and closing the lactone in the usual manner under acid catalysis (equation 83).[135] The C—C connection required to generate the γ-hydroxy carboxylic acid may be performed by means of a pericyclic arrangement. For instance, the allylic alcohol (**236**) reacts with an orthoester to form, *via* (**237**), the hydroxy ester (**238**), which cyclizes under the conditions to (**239a**). For unsymmetrically substituted alcohols (**236**), the regioisomer (**239b**) is also formed in comparable amounts (equation 84).[136]

γ-Lactones may be the result of an oxidative cyclization of 1,4-butanediol derivatives (**240**). On treatment with silver carbonate on Celite (Fetizon's reagent) (**242**) is formed, presumably *via* lactol (**241**) (equation 85).[137] A lactol–lactone oxidation is the ultimate step in a rather complex sequence (equation 86). Cyclopropane ester (**243**) may undergo aldol-type additions to give (**244**), which on fluoride treatment opens the cyclopropane ring and gives first the aldehyde (**245**) and then the lactol (**246**). PCC oxidation leads eventually to the paraconic ester (**247**). Although a high degree of substitution is available, the stereocontrol is low.[138]

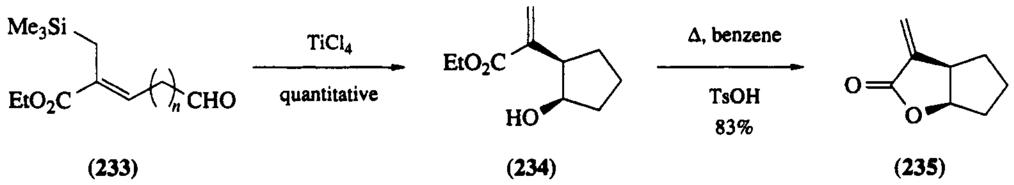
Me3Si
EtO2C
n
CHO
(233)
TiCl4
quantitative
EtO2C
HO
(234)
Δ, benzene
TsOH
83%
O
O
(235)

(83)

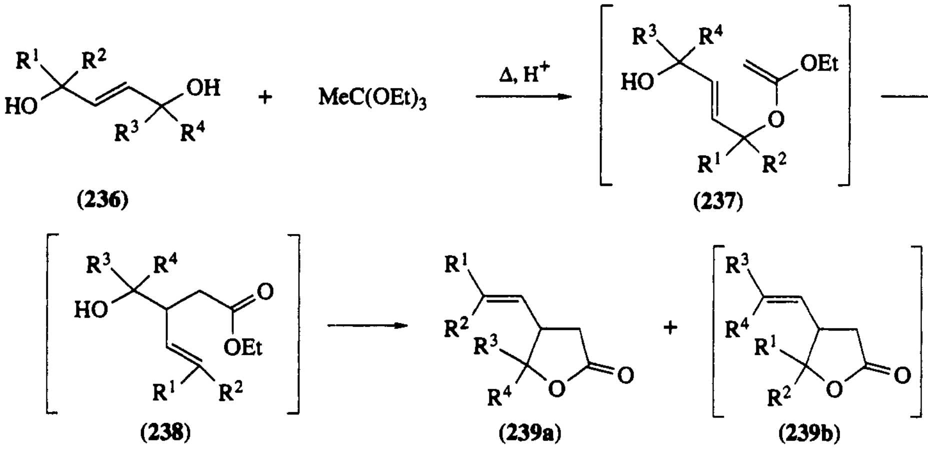

(84)

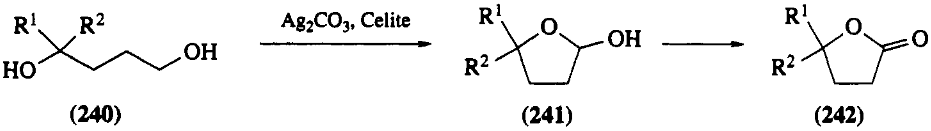

(85)

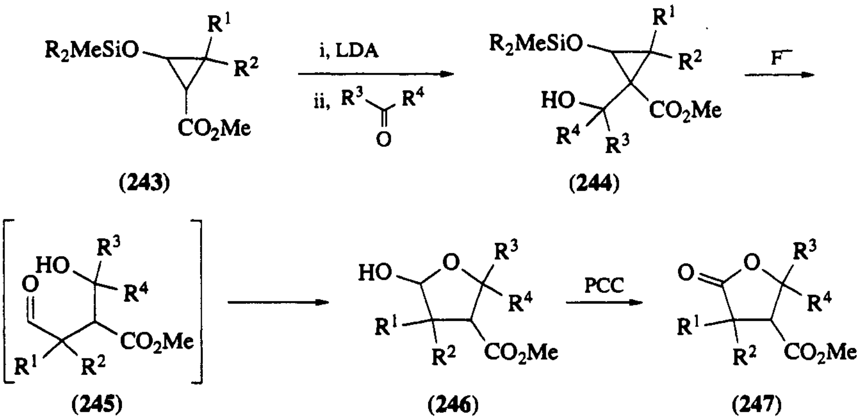

(86)

### *2.2.2.3.3 γ-Lactones via cycloalkylation*

There are numerous variations of cycloalkylating lactone formations. They may be classified into HGA ring closure of γ-hydroxy acids or esters, $S_N2$ ring closure of γ-bromocarboxylates, lactonizations under participation of alkenic double bonds or γ-lactone formation by carbenium rearrangements.

### *(i) HGA lactonization of γ-hydroxy acids*

Such cases are extremely rare, as the normal mode of action involves CGA mechanisms. However, Trost *et al.* have shown (equation 87) that in cases where the normal CGA reaction is prohibited due to ring strain, HGA ring closure under Mitsunobu conditions may be accomplished, *e.g.* from (**248**) to (**249**).[139] In contrast, hydroxy acid (**250**) has been found to undergo CGA ring closure to (**251**) spontaneously, as well as under Mitsunobu treatment. However, HGA reactions can be accomplished (equation 88) by preparing the mesylate (**252**) with sulfene, and by subsequent $S_N2$ cyclization with base to form (**252**).[140] An acid-catalyzed HGA lactonization has been reported for the hydroxypyrrolidines (**254**) and (**256**), both of which, under acid treatment, form the lactone (**255**), presumably *via* (**257**; equation 89).[141]

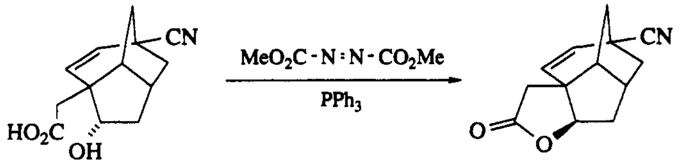
CN
HO2C
OH
MeO2C-N=N-CO2Me
PPh3
CN
O
O

**(248)** **(249)** 92%

(87)

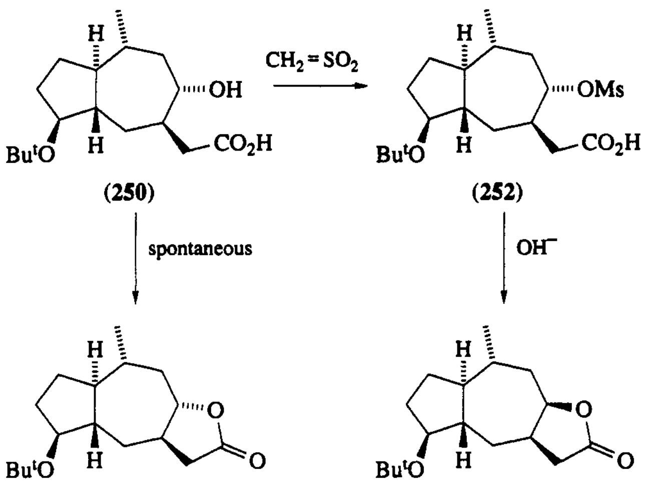
H
OH
Bu^tO
H
CO2H
CH2=SO2
H
OMs
Bu^tO
H
CO2H
spontaneous
OH⁻
H
O
Bu^tO
H
O
H
O
Bu^tO
H
O

**(250)** **(252)** **(251)** **(253)**

(88)

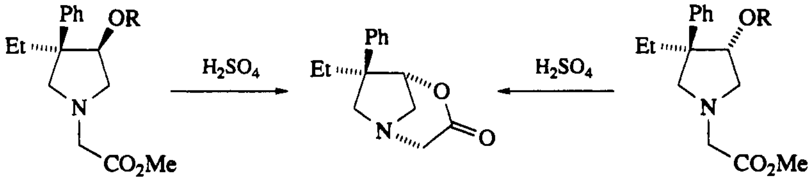
Ph
OR
Et
N
CO2Me
H2SO4
Ph
Et
O
N
O
H2SO4
Ph
OR
Et
N
CO2Me

**(254)** R = H, Ac **(255)** **(256)**

(89)

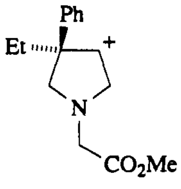
Ph
Et
+
N
CO2Me

**(257)**

## *(ii) γ-Bromo carboxylates*

γ-Lactones may be obtained from (**258**) with strong base (equation 90). The reaction may be reversed by ring opening with hydrobromic acid, which is by far the more important process. The inversion of configuration on ring closure is demonstrated by means of the cyclic derivative (**259**; equation 91).[142]

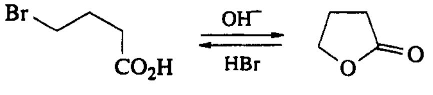
Br
CO2H
OH⁻
HBr
O
O

**(258)**

(90)

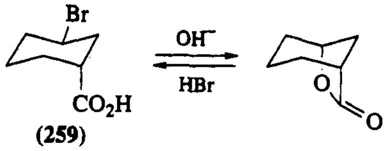
Br
OH⁻
HBr
CO₂H
O
O

(259)

(91)

*(iii) γ-Lactonization of unsaturated carboxylic acids*[143]

Usually γ,δ-unsaturated acids (**260**) are employed in these lactonizations. The initial step involves an electrophilic attack at the double bond, either by a proton or a reagent X—Y (**264**). An activated species (**261**) is thus generated, suitable for the nucleophilic addition of the carboxy group, which in principle may close to a six- or five-membered lactone ring (**263** or **262**; equation 92). Normally, (**262**) is preferred on the basis of vector approach analysis.[144]

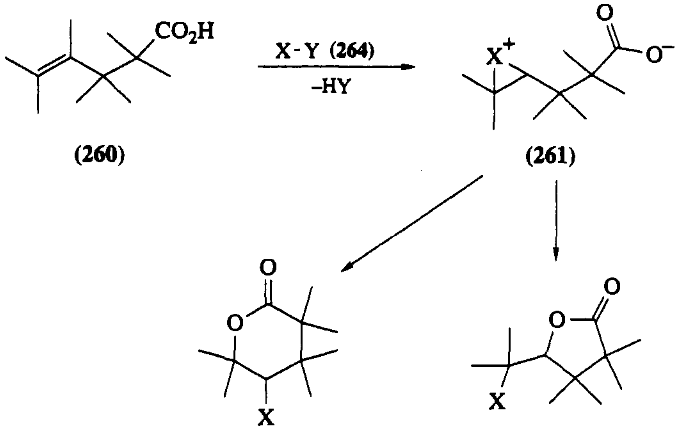
CO₂H
X-Y (264)
-HY
X⁺
O
O⁻
O
O
X
O
O
X

(260) (261) (263) (262)

(92)

Equations (93–96) describe proton-catalyzed lactonizations. One can see that even for the β,γ-unsaturated acids (**265**)[145] and (**267**)[146] the γ-lactone prevails; whether this is by kinetic or thermodynamic con-

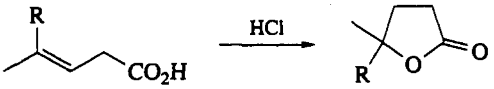
R
CO₂H
HCl
R
O
O

(265) (266)

(93)

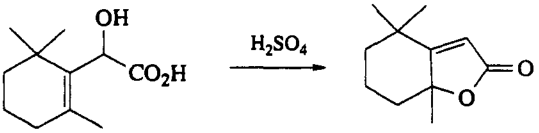
OH
CO₂H
H₂SO₄
O
O

(267) (268)

(94)

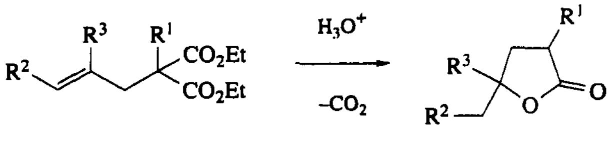
R³
R¹
R²
CO₂Et
CO₂Et
H₃O⁺
-CO₂
R¹
R³
R²
O
O

(269) (270)

$R^1$ = H, Bu; $R^2$ = H, Bu, $C_5H_{11}$; $R^3$ = H, Me

(95)

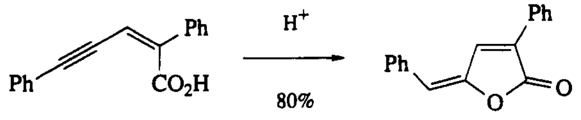

**(271)** **(272)**

(96)

trol remains unclear. The malonic esters (**269**)[147] are decarboxylated after lactonization. The enyne acid (**271**) is lactonized at the triple bond without affecting the alkenic moiety (equation 96).[148]

Hydroxylactonizations (equations 97–99) involve the formation of a stable and, in general, stereochemically defined epoxide intermediate with peroxy acids. In an ensuing step these epoxides are cyclized with acid catalysis under the participation of the carboxylic group. If steric reasons prohibit ring closure, as in equation (98), the diol acid (**278**) is formed instead of the hydroxy lactone (**275**).[149] Equation (99)[150] shows an example for the stereocontrol of the epoxidation step by an axially oriented carboxy group, which is then in an appropriate position to close the lactone ring (**281**).

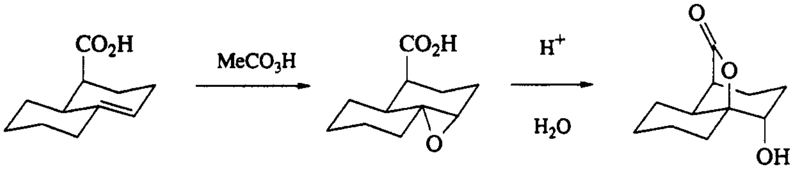

**(273)** **(274)** **(275)**

(97)

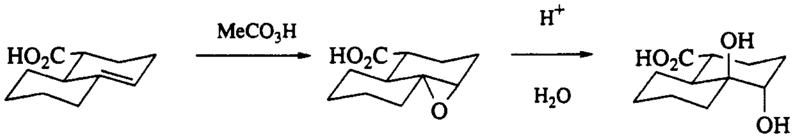

**(276)** **(277)** **(278)**

(98)

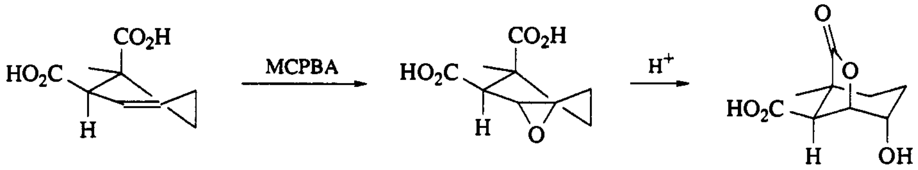

**(279)** **(280)** **(281)**

(99)

Equation (100)[116] illustrates the lactonization of a β,γ-epoxy acid. Only the γ-lactone (**283**) is formed, with inversion of configuration.

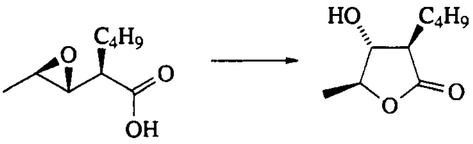

**(282)** **(283)**

(100)

Halolactonizations have been used extensively for achieving high degrees of functionalization in a regio- and stereo-controlled manner.[151] The conversion of (**284**) into (**285**; equation 101)[152] is a key step in Corey's prostaglandin synthesis to prepare the central intermediate (**286**). For β,γ-unsaturated acids like (**287**) the β-lactone (**288**) is formed under kinetic control, which then equilibrates to the γ-lactone isomer (**289**; equation 102).[153]

In acyclic systems like (**290**) the facial selectivity of the double bond addition may be directed by a free OH function (Scheme 9).[154] It can also be shown that the regiocontrol depends on the reagent. Mercurilactonizations (equation 103)[155] are related to halolactonizations. The C—Hg bond may be cleaved reductively by a radical process.

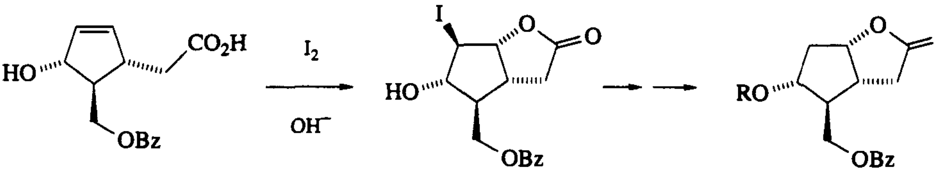
CO$_2$H
HO
OBz
I$_2$
OH$^-$
I
O
O
HO
OBz
O
O
RO
OBz

**(284)** **(285)** **(286)** (101)

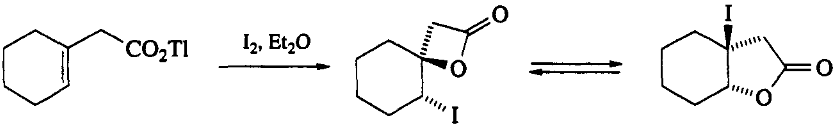
CO$_2$Tl
I$_2$, Et$_2$O
O
O
I
I
O
O

**(287)** **(288)** **(289)** (102)

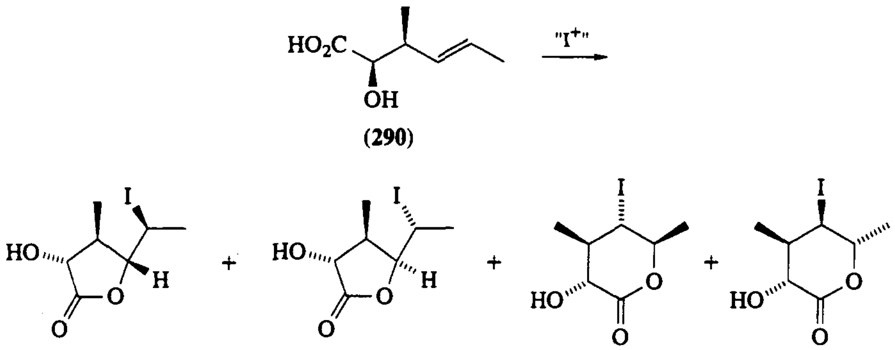
HO$_2$C
OH
"I$^+$"
I
HO
H
O
O
+
I
HO
H
O
O
+
I
HO
O
O
+
I
HO
O
O

**(290)**

**(291)** **(292)** **(293)** **(294)**

| $I^+$ | *(291)* | : | *(292)* | : | *(293)* | : | *(294)* |
|---|---|---|---|---|---|---|---|
| NIS, CHCl$_3$ | 2 | : | 2 | : | 3 | : | 1 |
| I$_2$, CHCl$_3$ | >20 | : | 1 | : | 0 | : | 0 |

**Scheme 9**

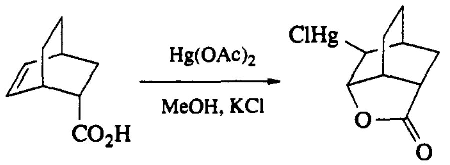
CO$_2$H
Hg(OAc)$_2$
MeOH, KCl
ClHg
O
O

**(295)** (103)

### (iv) *γ-Lactones* via *rearrangements*

Under MgBr$_2$ catalysis β-lactones like (**296**) rearrange to γ-lactones (**297**) under dyotropic migration of an alkyl or hydrogen substituent (equation 104).[156] The stereochemistry as shown in the stereoformulae (**302**) and (**303**) requires an antiperiplanar arrangement of the migrating groups. In cyclic systems spiroannulation and angular annulation may be achieved, depending on the ring sizes (equations 105 and 106).[157]

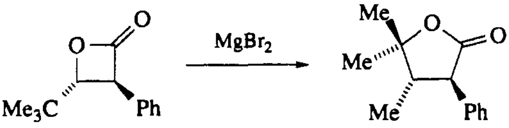
O
O
Me$_3$C
Ph
MgBr$_2$
Me
O
O
Me
Me
Ph

**(296)** **(297)** (104)

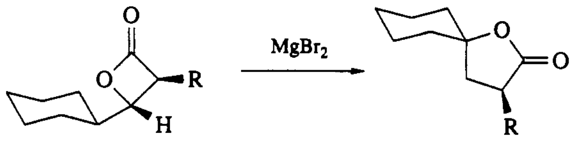

**(298)** **(299)** (105)

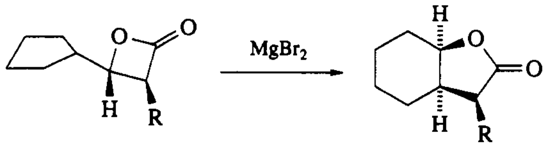

**(300)** R = Ph, SPh, OPh **(301)** (106)

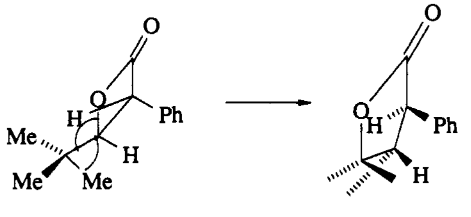

**(302)** **(303)**

An interesting and potentially useful sequence is shown in equation (107). Cyclopropane esters (**305**) may be prepared by the addition of diazo esters (**304**) to double bonds under elimination of nitrogen. After saponification the acid is *O*-protonated to open the cyclopropane ring, and the resulting carbenium ion (**306**) is trapped by lactonization. In effect a γ-lactone has been annulated to a double bond in a regiodefined manner.[158–160] Examples are given in Scheme 10. A related reaction involves the conversion of the cyclopropane ester (**307**) into the lactone (**308**; equation 108).[161]

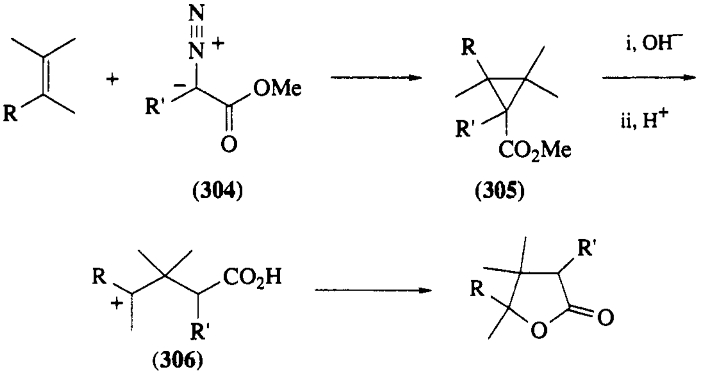

**(304)** **(305)** **(306)** (107)

### 2.2.2.3.4 *γ-Lactones* via *carbonylation of homoallylic alcohols*

It has been shown recently[162] that homoallylic alcohols (**309**) undergo regiocontrolled carbonylation–lactonization to form (**310**) or (**311**) in good yield (equation 109). In the reaction of *cis*-3-hexenol, (**315**) is formed as a side product to (**313**), presumably *via* the isomerization of intermediate (**312**) to (**314**) (Scheme 11).

A direct way to α,β-unsaturated γ-lactones involves the Pd-catalyzed carbonylation of *cis*-vinyl iodides (**316**; equation 110).[163] In a similar way *exo*-methylene lactones[319] may be prepared from the alkynols (**318**; equation 111).[164]

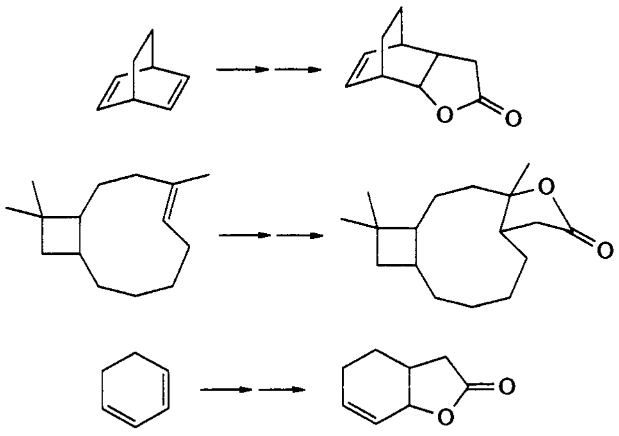

**Scheme 10**

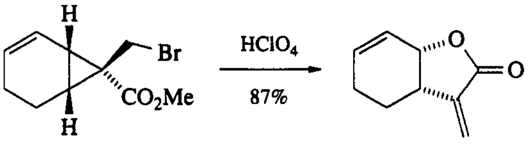
H
Br
$CO_2Me$
H
$HClO_4$
87%
O
O

(307) (308) (108)

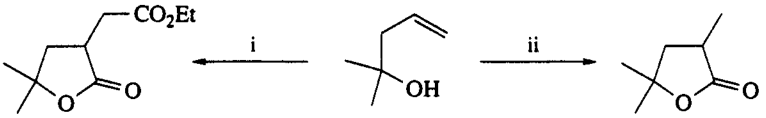
$CO_2Et$
O
O
i
OH
ii
O
O

(310) (309) (311) (109)

i, $PdCl_2$, $CuCl_2$, CO, $MeC(OEt)_3$, MeOH, propylene oxide; ii, $PdCl_2$, $CuCl_2$, CO, HCl

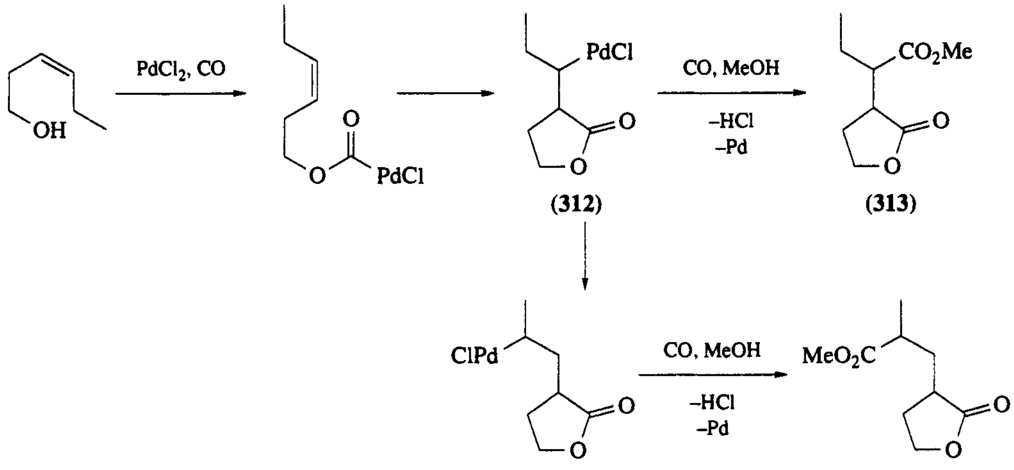
OH
$PdCl_2$, CO
O
O
PdCl
PdCl
O
O
(312)
CO, MeOH
–HCl
–Pd
$CO_2Me$
O
O
(313)
ClPd
O
O
CO, MeOH
–HCl
–Pd
$MeO_2C$
O
O

(314) (315)

**Scheme 11**

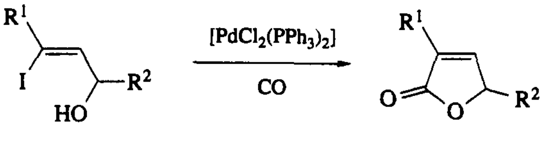
R1
I
R2
HO
[PdCl2(PPh3)2]
CO
R1
O
O
R2

**(316)** **(317)** (110)

$R^1$ = H, Me, Ph; $R^2$ = H, Me, Ph; 46–100%

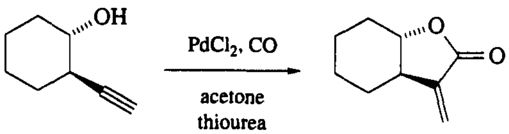
OH
PdCl2, CO
acetone
thiourea
O
O

**(318)** **(319)** (111)

### 2.2.2.3.5 *γ-Lactones from furans*

A fundamentally different route to unsaturated lactones involves the oxidation of furanes (*e.g.* **320**) with NBS and subsequent debromination with Zn to give the butenolide (**321**; equation 112). The alternative regioisomer (**323**) may be prepared by using MCPBA as the oxidant to furnish the hydroxy lactone (**322**), which is then reduced to (**323**; equation 113).[165]

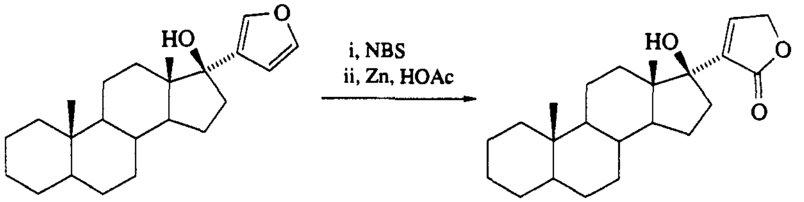
HO
O
i, NBS
ii, Zn, HOAc
HO
O
O

**(320)** **(321)** (112)

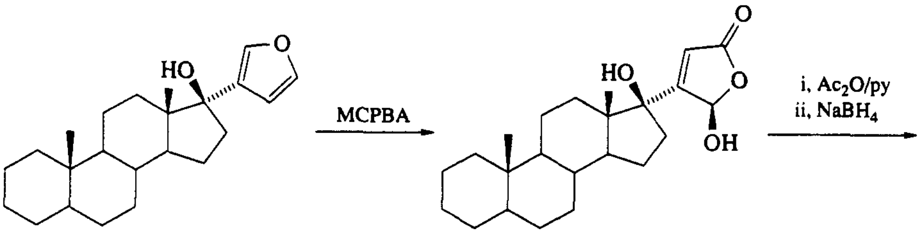
HO
O
MCPBA
O
HO
O
OH
i, Ac2O/py
ii, NaBH4

**(320)** **(322)**

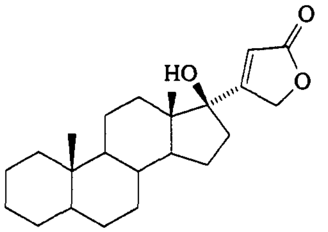

**(323)** (113)

### 2.2.2.4 Synthesis of δ-Lactones

The methods applied for the synthesis of δ-lactones are very similar to those described for γ-lactones. In general, the tendency to form a six-membered ring is slightly lower than that for γ-lactonization. This is illustrated by equation (114); δ-hydroxy esters polymerize on acid treatment. Depolymerization takes place on heating, and the δ-lactone is formed.[166] Strained δ-lactones may be closed using acetic anhydride activation (**324**; equation 115),[119] whereas transannulations to decalin systems readily occur on heating (equation 116).[118] δ-Lactones can be efficiently prepared by glycol cleavage of 1,2,6-triols (**326**; equation 117). The lactol (**327**) is oxidized to (**328**) with PCC.[167]

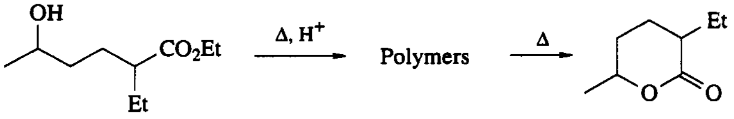
OH
CO2Et
Et
Δ, H+
Polymers
Δ
Et
O
O

(114)

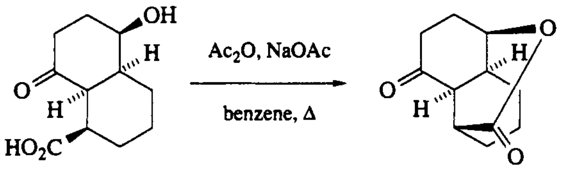
OH
H
O
H
HO2C
Ac2O, NaOAc
benzene, Δ
O
H
O
H
O

**(324)**

(115)

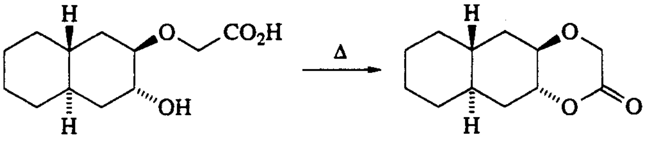
H
O
CO2H
OH
H
Δ
H
O
O
O
H

**(325)**

(116)

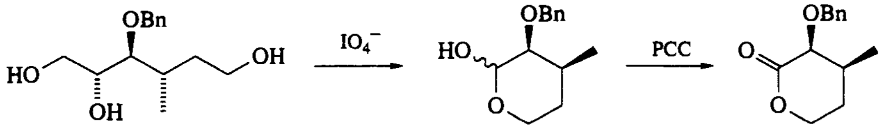
OBn
HO
OH
OH
IO4−
OBn
HO
O
PCC
OBn
O
O

**(326)** **(327)** **(328)**

(117)

Meyers' approach to α-chiral lactones may be expanded to the δ-lactone series with *ee* values comparable to those achieved for lactones (equation 118).[168] Mercuri- and similarly halo-lactonizations of δ,ε-unsaturated carboxylic acid derivatives are an efficient way to achieve stereocontrolled heteroatom–carbon ring closure, *e.g.* of (**333**) to (**334**; equation 119).[143]

An interesting case of a δ-lactonization under inversion of configuration has been reported by Prasit and Rockach (equation 120).[169] Triol ester, (**335**), with a good leaving group in the terminal position undergoes a Payne rearrangement to (**336**) and (**337**) with aqueous base, and (**337**) cyclizes to form (**338**). As in the γ-lactone series, lactonization may be preceded by a C—C connecting process. For instance, as shown in equation (121), enamine alkylation generates a δ-keto ester, which after saponification, reduction and acidification delivers the δ-lactone.[170]

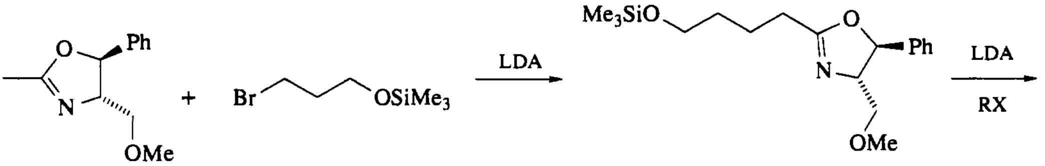
O
Ph
N
OMe
+
Br
OSiMe3
LDA
Me3SiO
O
Ph
N
OMe
LDA
RX

**(329)** **(330)**

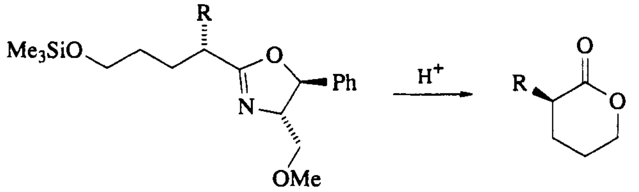
R
Me3SiO
O
Ph
N
OMe
H+
O
R
O

**(331)** **(332)** 52–70% *ee*

(118)

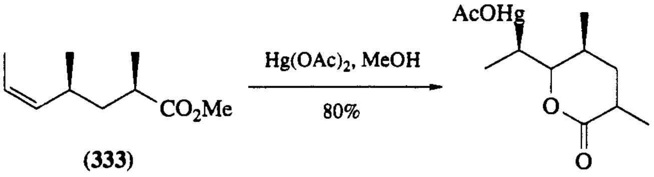
CO2Me
Hg(OAc)2, MeOH
80%
AcOHg
O
O

**(333)** **(334)**

(119)

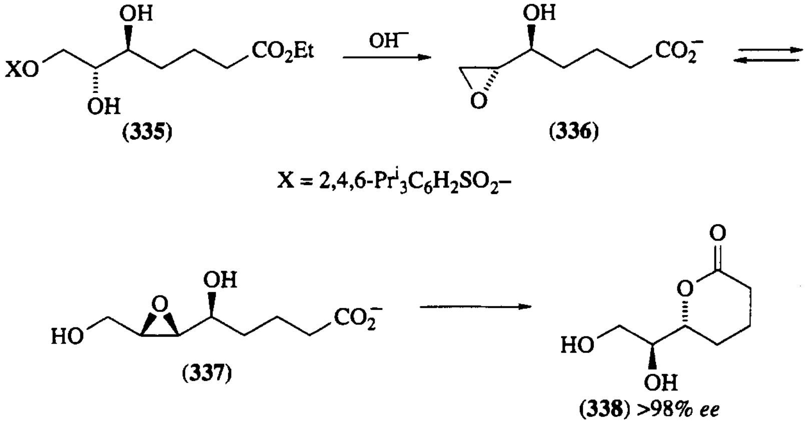
OH
XO
CO2Et
OH
OH⁻
OH
CO2⁻
O
OH
HO
O
CO2⁻
O
O
HO
OH

**(335)** **(336)**

$X = 2,4,6\text{-}Pr^i_3C_6H_2SO_2\text{–}$

**(337)** **(338)** >98% *ee*

(120)

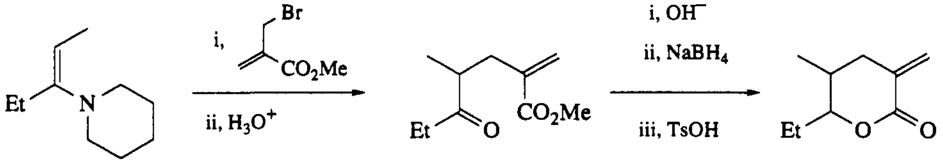
Et
N
i,
Br
CO2Me
ii, H3O+
Et
O
CO2Me
i, OH⁻
ii, NaBH4
iii, TsOH
Et
O
O

(121)

### 2.2.2.5 Enantioselective Lactonization

Much attention has been devoted to asymmetric lactonization of *meso*-hydroxy acids. In the case of 4-hydroxypimelate (*S*)-camphorsulfonic acid [(*S*)-CSA] has been found to deliver a proton enantioselectively to the *pro-R* appendage. In this way lactone (**340**) is generated with 94% *ee* (equation 122).[171] A different approach has been used in the case of (**341**). An axially chiral binaphthylamine is used as an auxiliary for forming the dimamide (**342**), which is hydrolyzed enantioselectively to the mono amide (**343**). In this way an optically active lactone is created, which is removed from the auxiliary by acylation of the free amino group, and reduction of the amide to form (**344**). To secure the configuration and the optical purity, (**344**) was converted into the known derivative (**345**; equation 123).[172]

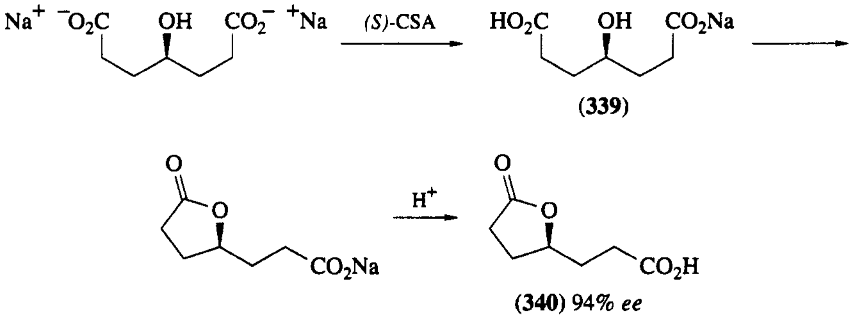
Na+ ⁻O2C
OH
CO2⁻ +Na
(S)-CSA
HO2C
OH
CO2Na
O
O
CO2Na
H+
O
O
CO2H

**(339)**

**(340)** 94% *ee*

(122)

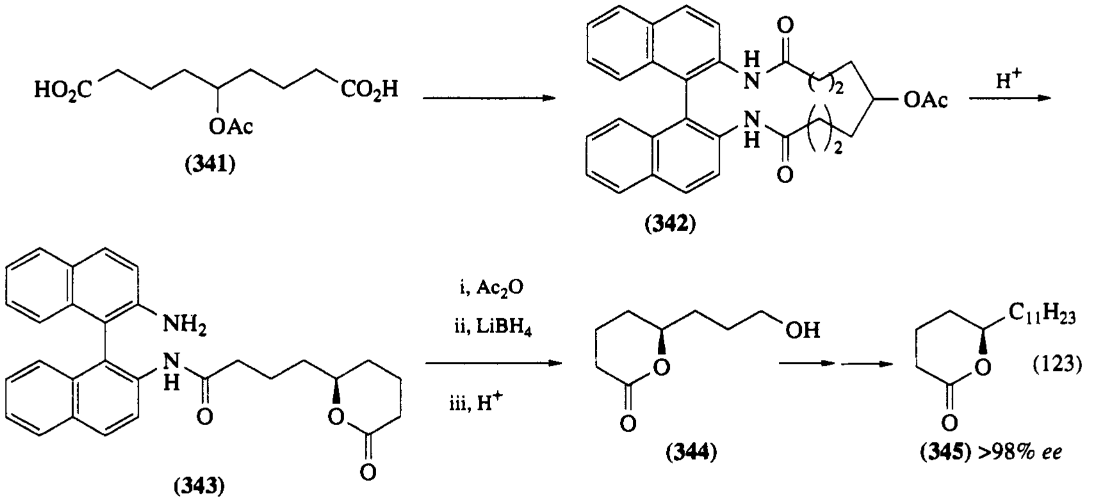
**(341)** **(342)** **(343)** **(344)** **(345)** >98% *ee*

## 2.2.2.6 Macrolactonization

The synthesis of lactones with ring sizes of more than nine (macrolides) has been one of the central objectives in the past 10 years.[173] In most cases these syntheses involve the construction of an acyclic ω-hydroxy carboxylic acid ('seco-acid') by a number of C—C connecting steps, which eventually is submitted to the lactonization process proper. After the lactonization, some deprotecting steps have to follow to establish the desired functionality. For the lactonization essentially the same methods are used as those described in Section 2.2.1 for esterifications. The crucial problem, however, in lactonizing a seco-acid (**346**) is to avoid polymerization and to direct the reaction either to a monomeric (macrolide) or a dimeric ('diolide') lactone. Polymerization in general can be overcome, to a certain degree, by employing high dilution conditions. The dichotomy of macrolide *versus* diolide can be influenced by the proper choice of the reagent; for instance, Mitsunobu conditions preferentially lead to diolides, whereas most other reagents induce macrolide formation (Scheme 12).

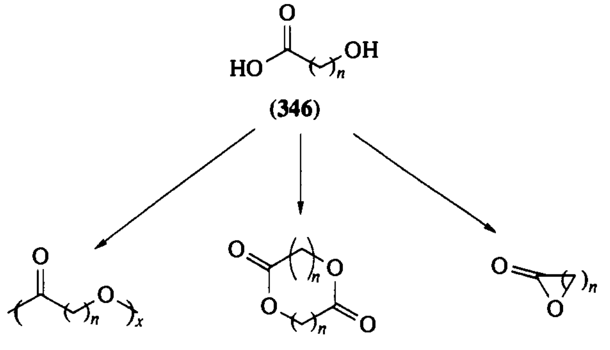
**(346)**

**Scheme 12**

A controlled way to achieve diolide formation is the application of protecting groups for the hydroxy function of one hydroxy acid moiety and the carboxy group of the other and thus to prepare a seco-acid (**347**) by esterification (equation 124). After deprotection, (**347**) may be lactonized to the diolide. In macrolactonization one encounters frequently the situation that the seco-acid has more than one hydroxy group suitable for ring formation. To avoid lactones of undesired ring sizes, protective groups have to be attached to the unwanted positions in course of the synthesis of the seco-acid which are stable under the lactonization conditions, and can be removed without destroying the lactone ring. In the following discussion the subdivisions follow the reagents employed for lactonization rather than the target structures envisaged. As for the esterifications one may distinguish macrolactonizations with retention of configuration (cycloacylations) or inversion of configuration (cycloalkylation). It will be noted that for one and the same seco-acid type, different lactonizing agents have been used, which suggests that the choice of these reagents has been made according to the personal taste and experience of the individual author, and not following a deeper rationale.

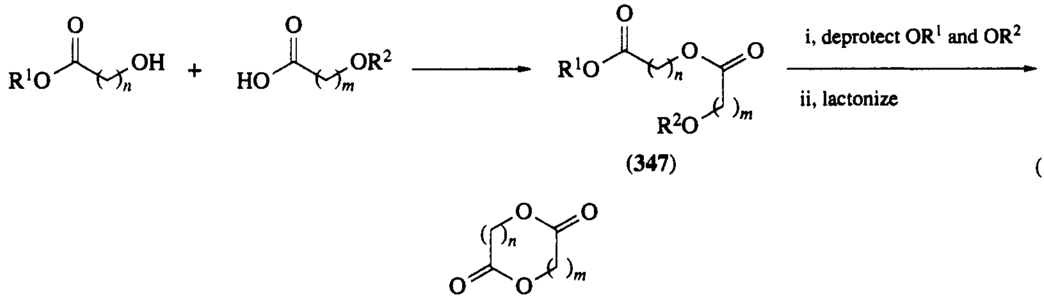

**(347)** (124)

**(348)** Diolide

### *2.2.2.6.1 Cycloacylating macrolactonization*

*(i) Macrolactonization of hydroxy esters under base catalysis*

The simplest way of macrolactonization is the use of acid or base catalysis so that after the ring closure no tedious separation of the lactone from auxiliary by-products is required. However, there are only very few such examples. The 16-membered macrolide ring of milbemycin β3 is closed very efficiently by simply treating the hydroxy ester (**349**) with potassium hydride. OH deprotonation induces ring formation with retention of configuration to (**350**; equation 125).[174]

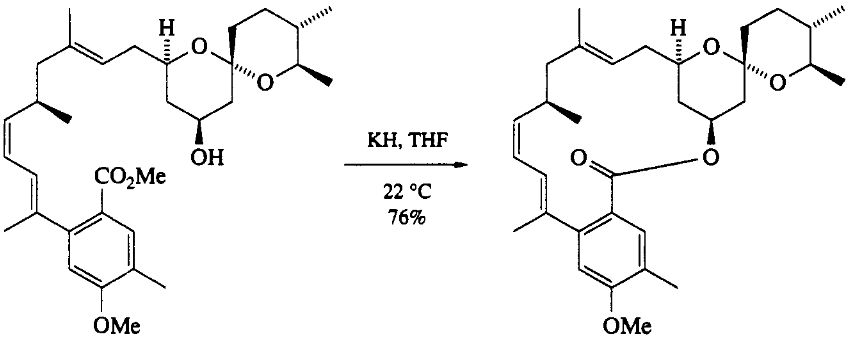

**(349)** **(350)** (→ Milbemycin $\beta_3$) (125)

*(ii) Macrolactonization with mixed anhydrides*

The formation of mixed anhydrides, which in some cases may be isolated, is an established method. For instance, racemic zearalenone (**352**) has been obtained by treating the seco-acid (**351**) with trifluoroacetic anhydride (equation 126).[175] Similarly, antimycin $A_3$ has been prepared.[176] A more modern procedure makes use of Yamaguchi's 2,4,6-benzoyl chloride esterification.[26] For example, a synthesis of methynolide is based on the lactonization of the alkynic seco-acid (**353**) to (**354**; equation 127).[177]

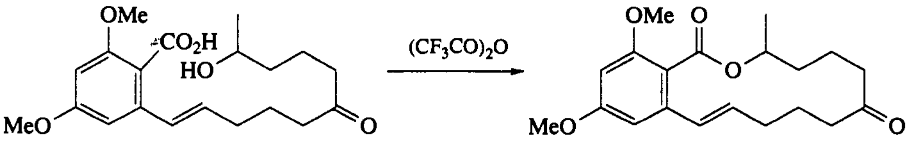

**(351)** **(352)** (→ Zearalenone) (126)

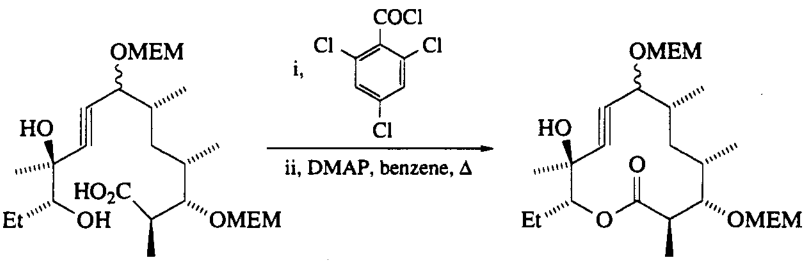
OMEM
HO
HO2C
Et
OH
OMEM
i, COCl, Cl, Cl, Cl
ii, DMAP, benzene, Δ
OMEM
HO
O
Et
O
OMEM

(127)

**(353)** **(354)**

(→ Methynolide)

A more complex hydroxy acid is lactonized in a synthesis of (9*S*)-9-dihydroerythronolide A, albeit in low yield (equation 128).[178] By acid treatment (**356**) is deprotected to give the desired target molecule. The presence of $sp^2$-centers in the seco-acid obviously facilitates lactonization, as shown by the preparation of the mycinolide V precursor (**357**; equation 129).[179] A mixed carbonate is used in the synthesis of the tylonolide precursor (**358**; equation 130).[180] In general, DMAP catalysis is helpful in the ring closing step in most cases.

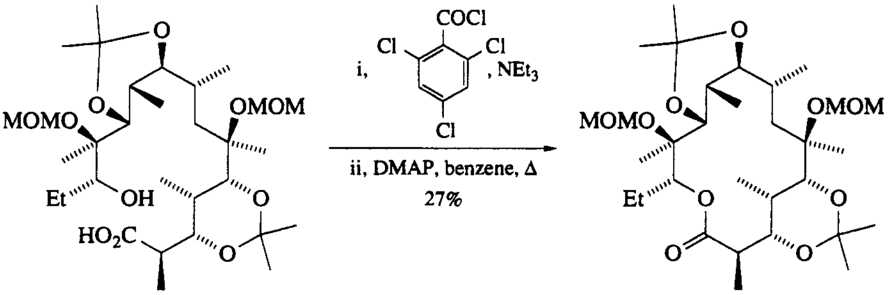
O
MOMO
O
OMOM
Et
OH
O
HO2C
O
i, COCl, Cl, Cl, Cl, NEt3
ii, DMAP, benzene, Δ
27%
O
MOMO
O
OMOM
Et
O
O
O
O

(128)

**(355)** **(356)**

(→ (9*S*)-9-Dihydroerthronolide)

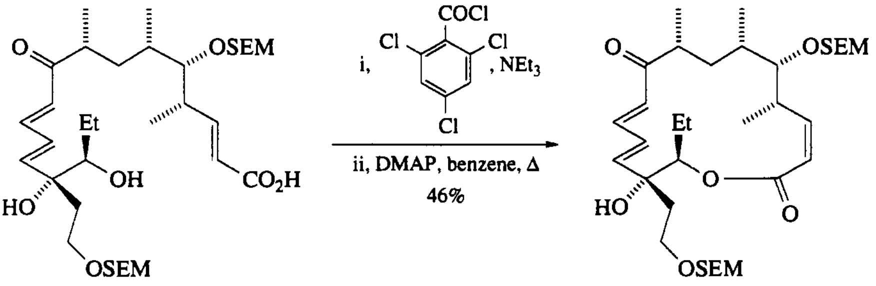
O
OSEM
Et
OH
CO2H
HO
OSEM
i, COCl, Cl, Cl, Cl, NEt3
ii, DMAP, benzene, Δ
46%
O
OSEM
Et
O
O
HO
OSEM

(129)

**(357)**

(→ Mycinolide V)

*(iii) Thiol ester mediated macrolactonization*

Although thiol esters are not common for normal esterifications they have found ample application in macrolactonization. Thus, the Corey–Nicolaou procedure which uses Mukaiyama's preparation of 2-thiopyridyl esters *via* a redox condensation[181] is one of the most general and efficient macrolactonization methods described so far. By forming a chelate hydrogen bridge double activation is achieved to facilitate the conversion of the activated ester (**359**) into the tetrahedral intermediate (**360**), which eliminates thiopyridone to form the lactone (equation 131).[182] The method has been applied to the syntheses of zearalenone (*via* **361**),[182] brefeldin A (*via* **362**),[183] tylonolide (*via* **363**),[184] and (+)-18-deoxynargenicin $A_1$ (*via* **364**) (note that no protective groups are necessary for the OH on ring c).[185]

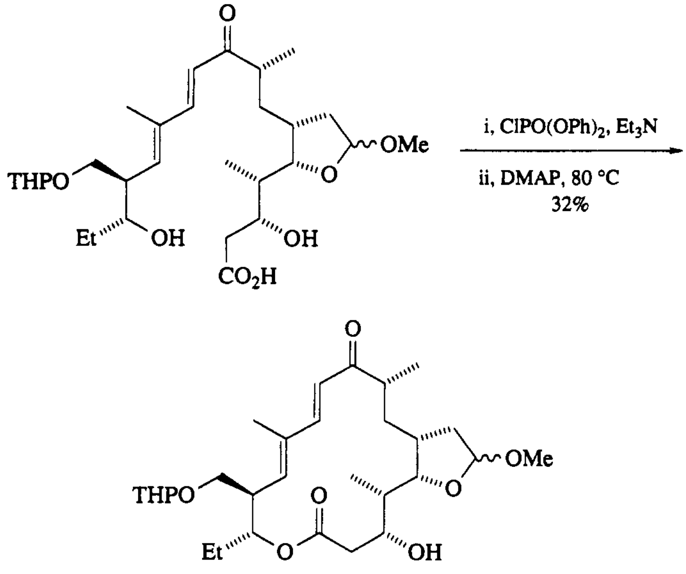

**(358)**
(→ Tylonolide)

(130)

In all cases, the indicated *O*-acyl bond is closed following Corey's original procedure.[182] In the case of the vermiculine precursor (**365**) diolide formation to (**366**) is observed (equation 132).[186] To meet the special requirements of his erythronolide A and B syntheses Corey developed a diimidazolyl disulfide (**367**) by which (**368**) is obtained from the seco-acid in acceptable yields.[187] The same reagent has been used in a recent synthesis of erythronolide B (*via* **369**).[188a] Gerlach has found that silver(I) ions drastically enhance the rate of the lactonization,[188b] presumably by forming a silver–thiol bond in the activating complex. Masamune also has resorted to thiol ester activation in his macrolide syntheses. In contrast to Corey he used the *t*-butyl thiol esters (*e.g.* **370**), which are lactonized under treatment with copper(I) triflate to remove the thiol, and Hünig's base to abstract the OH proton. In this way a respectable yield of

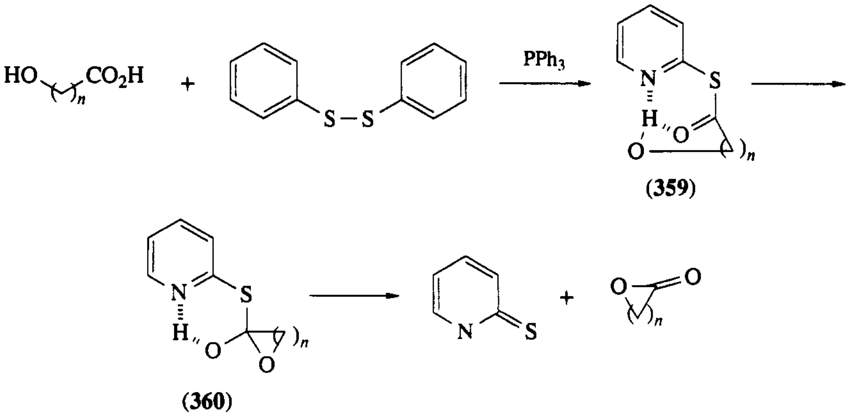

**(359)**

**(360)**

(131)

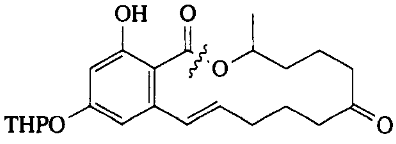

**(361)**

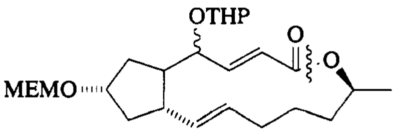

**(362)** 44%
i, dipyridyl disulfide, PPh$_3$; ii, xylene, Δ
(→ Brefeldin A)

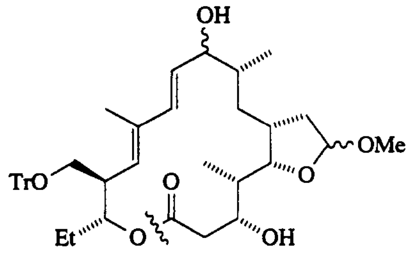
OH
OMe
TrO
O
Et
O
O
OH

**(363)**
i, dipyridyl disulfide, $PPh_3$; ii, toluene, Δ
(→ Tylonolide)

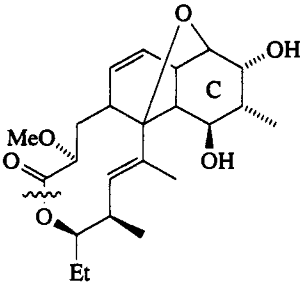
O
OH
C
MeO
O
OH
O
Et

**(364)** 20%
i, dipyridyl disulfide, $PPh_3$; ii, xylene, Δ
(→ (+)-18-Deoxynargenicin $A_1$)

the 6-deoxyerythronolide B precursor (**371**) is obtained (equation 133).[189] In the first synthesis of methymycin (*via* **372**), mercury(II) methanesulfonate was used in a phosphate buffer.[190]

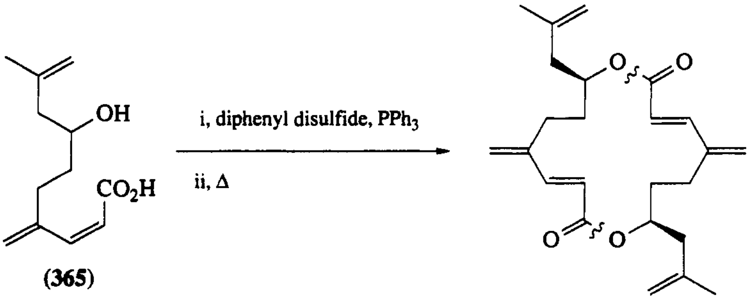
OH
$CO_2H$
i, diphenyl disulfide, $PPh_3$
ii, Δ
O
O
O
O

**(365)**

**(366)**
(→ Vermiculine)

(132)

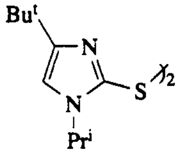
$Bu^t$
N
N
S
$\frac{}{}$2
$Pr^i$

**(367)**

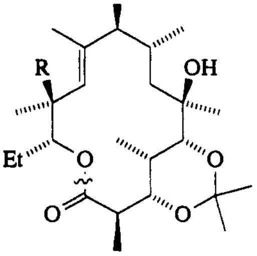
OH
R
OH
Et
O
O
O
O

**(368)**

i, (**367**), $PPh_3$; ii, toluene, Δ
R = H, 50%; R = OMTM, 30%
(→ Erythronolides A and B)

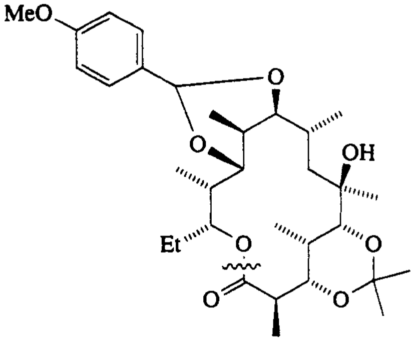
MeO
O
O
OH
Et
O
O
O
O

**(369)** 72%
(→ Erythronolide B)

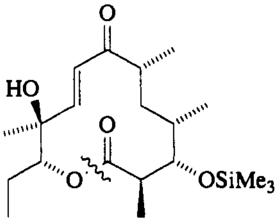
O
HO
O
O
$OSiMe_3$

**(372)** 30%
(→ Methymycin)

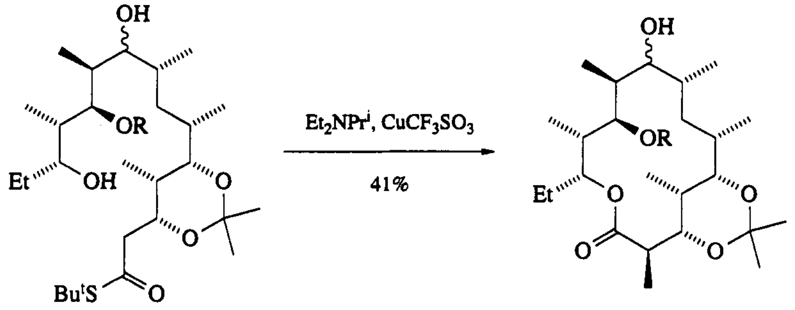

(133)

**(370)** **(371)**

(→ 6-Deoxyerythronolide B)

### *(iv) Macrolactonization* via *activated amides*

Staab's *N*,*N*-carbonyldiimidazolide method has been applied in a synthesis of pyrenophorine (*via* **373**), in which the indicated bond has been closed.[191] More recently, the usual activated amide (**374**) has been used to obtain the *N*-protected antimycin A3 derivative (**374**) under acid catalysis (equation 134).[192]

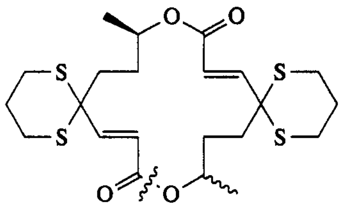

**(373)**

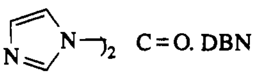

(→ Pyrenophorin)

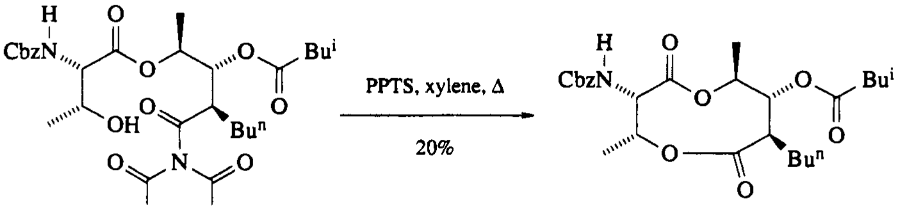

(134)

**(374)** **(375)**

(→ Antimycin A$_3$)

### *(v) Macrolactonization* via *activated esters*

DCC coupling serves in Stork's erythronolide A synthesis for closing the lactone (**376**) at the indicated C—O bond.[193] A modified DCC-type reagent (**378**) was successful in the preparation of the milbemycin β3 precursor (**377**).[194] The resulting urea derivative is water soluble and can thus be easily separated from (**377**) during work-up. An interesting enol ester type activation has been devised by Gais *et al.* to prepare the brefeldin A precursor (**383**; equation 135).[195] The hydroxy acid (**379**) adds the carboxy oxygen to the triple bond of the ynamine ketone (**380**) to form the enol ester (**381**), which spontaneously forms (**382**) *via* a 1,5-acyl migration in 96% yield. Under acid catalysis (**382**) lactonizes to (**383**).

Mukaiyama's 2-halopyridinium activation has also been applied to macrolactonization, to prepare, for instance, the brefeldin A intermediates (**384**)[196] and (**385**).[197] In a very elegant synthesis of (+)-aspicilin the macrolactonization has been performed with the aid of a hydroxy ketene intermediate (**387**), which had been generated *in situ* by the photolytic ring opening of (**386**). The primary macrolide (**388**) is then converted into (**389**) by elimination of sulfinate and acetyl azide (equation 136).[198] A cyclic alkoxy stannylene carboxylate (**391**) has been employed in a number of model macrolactonizations leading to nodusmycin, ingramycin and others (equation 137).[199] Compound (**391**) is readily formed from the hydroxy acid (**390**) and Bu2SnO. As in Corey's method, intramolecular hydrogen bridging is postulated to effect double activation.

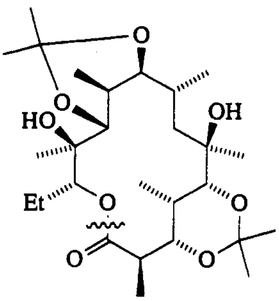
O
HO
OH
Et
O
O
O
O
O

(**376**) 65%
DCC, DMAP, TFA, Δ in $CHCl_3$
(→ Erythronolide A)

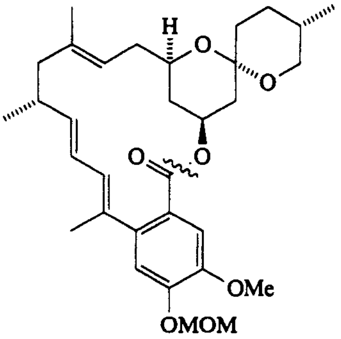
H
O
O
O
O
OMe
OMOM

(**377**)
(→ Milbemycin $\beta_3$)

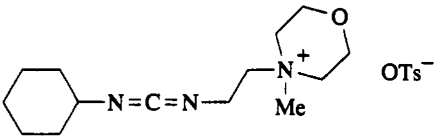
N=C=N
O
N+
Me
OTs−

(**378**)

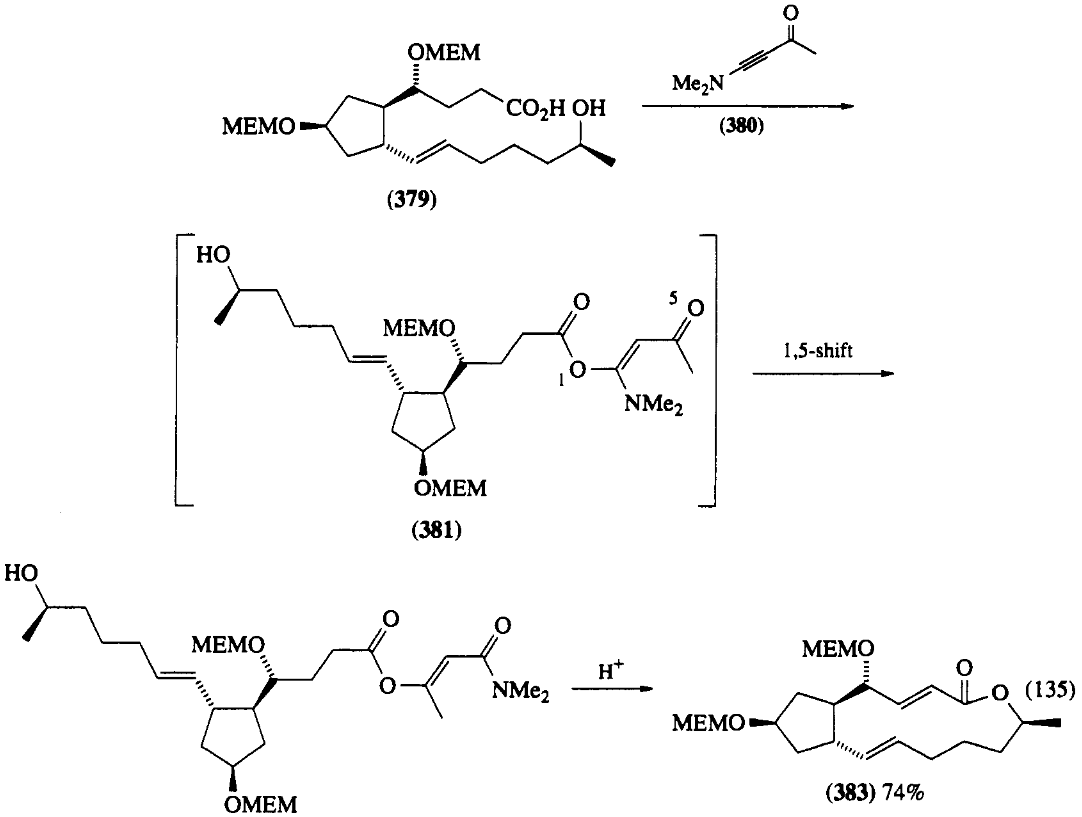
OMEM
MEMO
CO2H OH
O
Me2N
(380)
HO
MEMO
O
5
O
1
O
NMe2
OMEM
1,5-shift
HO
MEMO
O
O
O
NMe2
OMEM
H+
MEMO
O
O
(135)
MEMO

(**379**)

(**381**)

(**382**) 96%

(**383**) 74%
(→ Brefeldin A)

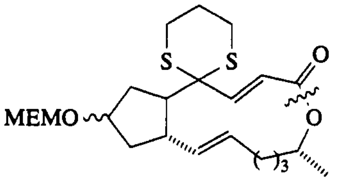

**(384)** 57%

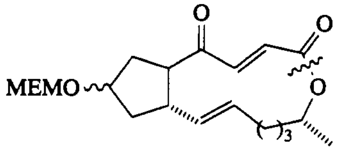

**(385)** 37%

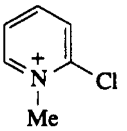

$I^-$, $Et_3N$, MeCN

(→ Brefeldin A)

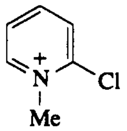

$BF_4^-$, $Et_3N$, $CH_2Cl_2$

(→ Brefeldin A)

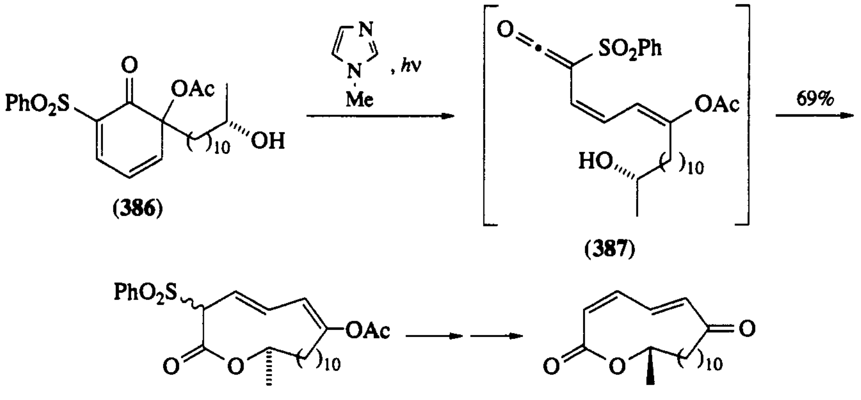
PhO2S
OAc
OH
10
N
Me
, hν
SO2Ph
OAc
HO
10
69%
PhO2S
OAc
10
O
10

**(386)** **(387)** **(388)** **(389)**

(→ (+)-Aspicilin)

(136)

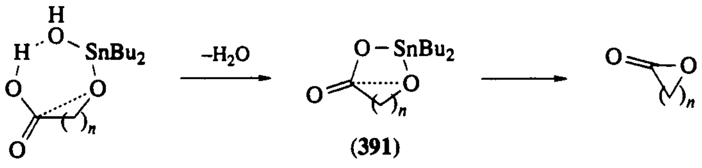
H
H
O
SnBu2
O
O
O
n
-H2O
O–SnBu2
O
O
n
O
O
n

**(390)** **(391)**

applied to nodusmycin, ingramycin, *etc.*

(137)

### *2.2.2.6.2 Cycloalkylating macrolactonization*

The Mitsunobu procedure has found considerable application, so it has been used for diolide formation in pyrenophorin (equation 138)[200] and colletodiol[201] syntheses. Yamaguchi's method[26] is much inferior.[202] As expected, the ring closure in equation (138) proceeds with inversion of configuration. In a

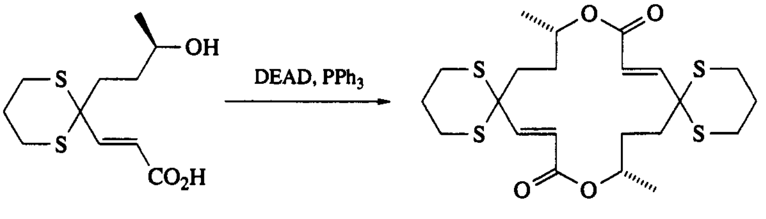
OH
S
S
CO2H
DEAD, PPh3
O
O
S
S
S
S
O
O

(→ Pyrenophorin)

(138)

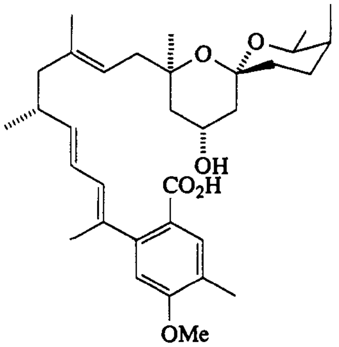

**(392)** 77%

(→ (+)-Milbemycin $\beta_3$)

recent synthesis of milbemycin $\beta_3$ Mitsunobu's reagent was used for achieving the required inversion of the carbinol center during lactonization of the seco-acid (**392**).[203] Classical $S_N2$ lactonizations have been rarely performed. Kellogg has applied his alkylative esterification in the lactonization of (**393**) to the zearalenone precursor (**394**; equation 139).[204]

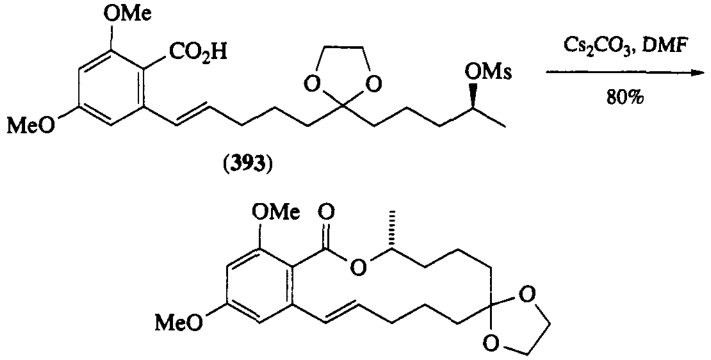

**(393)**

**(394)**

(→ Zearalenone)

(139)

### 2.2.2.6.3 *Enzymatic macrolactonization*

So far, enzymatic macrolactonizations are on a model stage yet. Sih has tested the enantio- and diastereo-selectivity in the diolide formation from racemic (**395**). With lipase, high enantiomer selection in favor of the (*R*,*R*)-(**396**) has been observed, whereas the diastereoselection is disappointingly low (equation 140).[205]

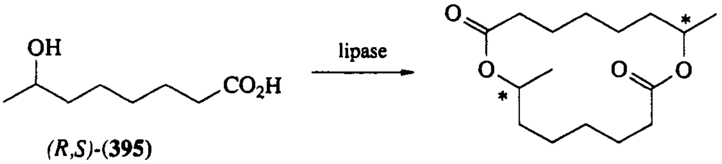

*(R,S)*-(**395**)

**(396)**

*ee (R,R):(S,S)* = 96:4

*de (R,R) + (S,S):(R,S)* = 12:5

(140)

## 2.2.3 REFERENCES

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2. D. A. Evans, *Asymm. Synth.*, 1984, **3B**, 1.
3. (a) M. A. Ogliaruso and J. F. Wolfe, in 'The Chemistry of Functional Groups', ed. S. Patai, Wiley, Chichester, Suppl. B, part 1, p. 411; (b) H. Pielartzik, B. Irmisch-Pielartzik and T. Eicher in *Methoden Org. Chem. (Houben-Weyl)*, 1985, **5**, (E), 659; (c) I. O. Sutherland, in 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, p. 869.

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# 2.3

# Synthesis of Amides and Related Compounds

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## 2.3.1 AMIDES

The chemistry of amides has a long history, and since the end of the last century a plethora of synthetic methods has been developed.

The occurrence of the amide group in important technical polymers (*e.g.* polyacrylamides, nylon polyamide), in drugs (*e.g.* β-lactam antibiotics), in peptides and proteins has stimulated research leading to safe, simple, and in the case of α-asymmetric carboxylic acids nearly racemization-free, condensation methods.

The synthesis of amides was recently reviewed by several authors. Short contributions came from Smith,[1] and Millar and Springall.[2] Especially due to practical aspects, those by Beckwith,[3] Challis and Challis,[4] Sandler and Karo,[5] and Döpp and Döpp[6] are more detailed.

With respect to peptide chemistry, Wünsch[7] discussed the scope and limitations of nearly all known procedures, and Merrifield and Barany[8] reviewed the application of several methods to solid phase peptide chemistry.

## 2.3.1.1 Carboxylic Acids and Amines

### *2.3.1.1.1 Dehydration of ammonium salts*

With simple carboxylic acids and amines, direct conversion to amides takes place at elevated temperatures (equation 1).[9] Generally, this reaction may be catalyzed by acid[10] or by cation exchange resin.[11] Addition of ammonium carbonate or urea[12] as a source of ammonia reduces reaction temperatures and improves yields.

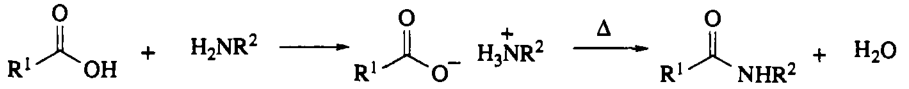

(1)

### *2.3.1.1.2 Activation of the carboxy group (acylation of amines)*

This is the most useful method of amide formation (equation 2). An activated carboxylic acid acylates ammonia, primary or secondary amines by a formal $S_N2$ substitution of leaving group X. The reactivity of the acylating reagent depends on the acidity of HX, and therefore the order of reactivity is RCOHal > $(RCO)_2O \approx RCON_3 > RCO_2R > RCONH_2 > RCOR$. Moreover, the reaction rate increases with higher nucleophilicity of the amine as well as base or acid catalysis.

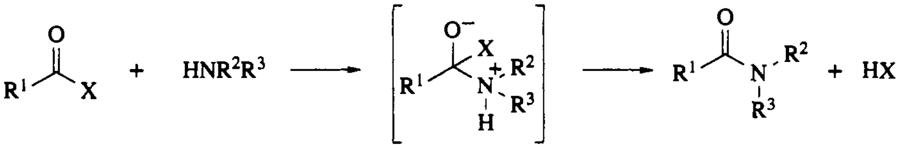

(2)

In the case of peptide synthesis one always has to take the double functionality of α-amino acids into account. Therefore, protection of one of these groups is necessary to direct peptide bond formation to a defined product. Moreover, the protection group has to be stable against the peptide bond-forming reaction and should be easily cleaved to generate an appropriate functional group for the next coupling.

With the exception of glycine, all proteinogenic α-amino acids are chiral. The prevention of racemization in the case of the most commonly used α-protected amino acids is a prerequisite of successful peptide synthesis. *N*-acylamino acids might lose their stereochemistry according to the mechanism shown in Scheme 1. The proper choice of the protection group (*e.g.* urethane-derived), activation method and additives has to be made carefully.

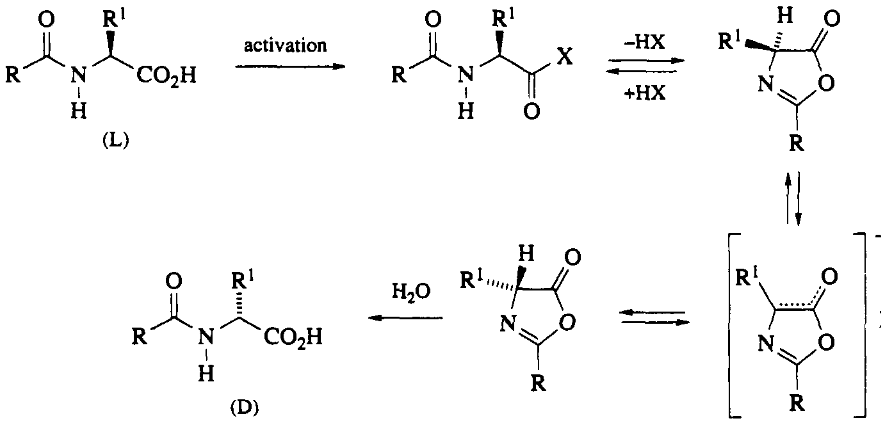

Scheme 1

Though the amide (peptide) forming reaction may be carried out by the use of hundreds of reagents and procedures, it is advisable to concentrate first on the most often applied reagents and conditions published in the literature. A further advantage is that these reagents are mostly commercially available.

### *(i) Carboxylic acid halides*

Activation of the carboxylic acid can easily be accomplished by the classical thionyl chloride method.[13,14] To generate acid chlorides under mild conditions without the evolution of gaseous HCl the reaction is carried out in $SOCl_2$/DMF[15] or started with the dicyclohexylammonium salt of the carboxylic acid.[16] Addition of DMF accelerates the reaction.[17] An imide chloride is considered to be the reactive species (Scheme 2). Other methods include activation with cyanuric chloride[18] or triphenylphosphine/tetrachloromethane.[19,20]

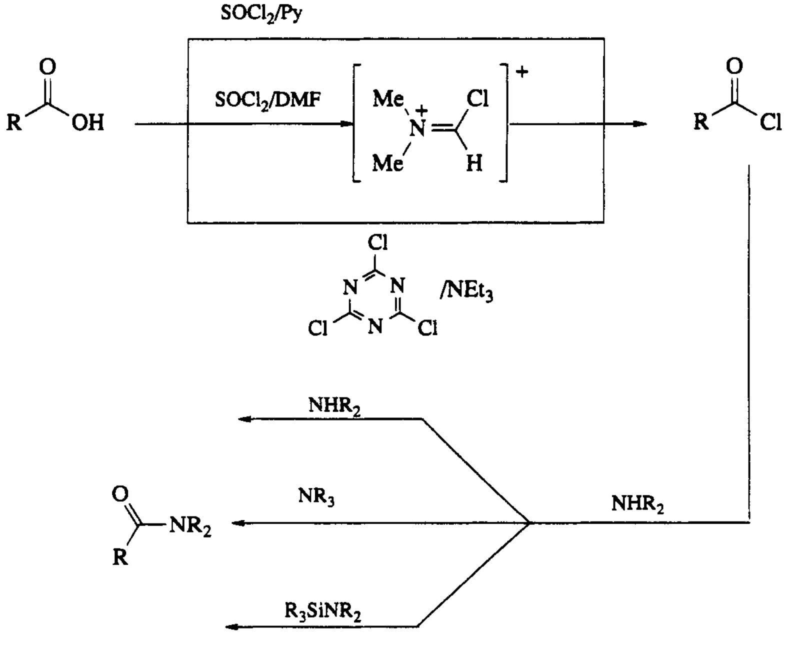

**Scheme 2**

Conversion to the corresponding amides with ammonia, primary or secondary amines proceeds by adding two equivalents of amine (to trap excess hydrogen chloride),[21] refluxing with one equivalent of amine in aromatic solvents,[22] or reacting with dialkylaminotrimethylsilane[23] under formation of the volatile trimethylchlorosilane. The latter method has advantages especially in the preparation of sterically hindered amides like acetic acid *t*-butylamide.[24]

For peptide chemistry, protected amino acid chlorides are too highly activated and therefore not used due to their racemization tendency, reactions with amino acid side chains (*e.g.* asparagin), loss of selectivity against nucleophiles and the formation of internal Leuchs' anhydrides.[25]

Carboxylic acid fluorides are more stable to water and other nucleophiles. They are readily prepared by the use of cyanuric fluoride and converted to amides by silylated amines.[26] In contrast to the chlorides, protected amino acid fluorides exert virtually no racemization in peptide coupling.[27]

### *(ii) Carboxylic acid anhydrides*

#### *(a) Intramolecular.*

The preparation and use of α-amino-*N*-carboxylic anhydrides (NCA) and α-amino-*N*-thiocarboxylic anhydrides (NTA) for peptide synthesis was recently reviewed.[28] The main advantage of this coupling method lies in its simplicity. Protection of the nitrogen and activation of the carboxy group are achieved in one step (equation 3). NCAs (X = O) are prepared by the method of Leuchs, starting with *N*-substituted oxycarbonyl amino acid halides[29,30] and subsequent cyclization, or by the method of Fuchs–Farthing,[31,32] condensing the parent amino acid with phosgene. An alternative procedure that avoids gaseous phosgene uses trichloromethylchloroformate (TCF)[33] at elevated temperatures with a drastic reduction of reaction times. The preferred method of preparing NTAs (X = S) starts with *N*-alkoxythiocarbonyl amino acids and cyclization with $PBr_3$ at low temperature.[34–36] Alternatives starting with amino acid thiocarbamates or α-amino thioacids are more tedious and necessitate additional steps resulting in lower yields. Both NCAs and NTAs can be obtained in moderate to good yield with an optical purity exceeding 98% *ee*.

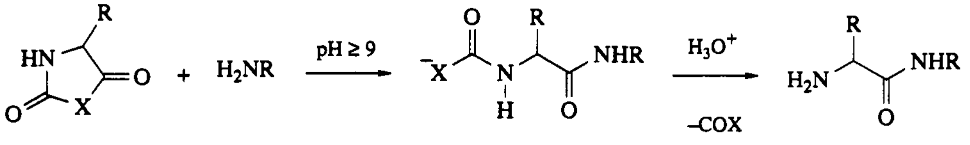

(3)

X = O (NCA); X = S (NTA)

For peptide coupling, only lysine and cysteine have to be protected in their side chains. In NCA couplings, reaction parameters have to be carefully controlled:[37] rapid mixing, temperature (*ca.* 0 °C) and pH (optimum pH 10.2). Under these conditions racemization is virtually absent. In the case of NTAs, the coupling pH is lower (pH ≈ 9) and the overall yield is somewhat higher. Due to their generally higher racemization tendency, only the use of glycine-, alanine- and histidine-NTA is recommended in comparison to the NCAs.

The NCA/NTA technology has found application in the synthesis of fragments of ribonuclease A,[38] as well as in the large scale synthesis of ACE inhibitor precursors of enalapril[39,40] and the artificial sweetener aspartam.[35]

*(b) Intermolecular symmetric.*

Symmetrical anhydrides are prepared according to reactions reviewed in Chapter 2.1 of this volume. Advantageously, in contrast to unsymmetric anhydrides nucleophilic attack on both possible carbonyls gives the correct product. The disadvantage is the waste of one equivalent of carboxylic acid (which will be recovered in the case of expensive protected amino acids). The most widely used is acetic anhydride,[6] which acetylates amines under mild conditions.

In peptide chemistry two methods are used frequently. The reaction of phosgene with protected amino acids leads to symmetric anhydrides (equation 4), after disproportionation and release of carbon dioxide, which can be readily used to build up a growing peptide chain.[41,42] More recently, symmetrical amino acid anhydrides have been generated by carbodiimides like DCC,[43,44] water soluble carbodiimide[45] and diisopropylcarbodiimides[46] *in situ*. They are extensively applied to automated solid phase peptide synthesis. Attention has to be paid to the proper solvent system, as aprotic dipolar solvents tend to slow down reactions and increase formation of side products.[43]

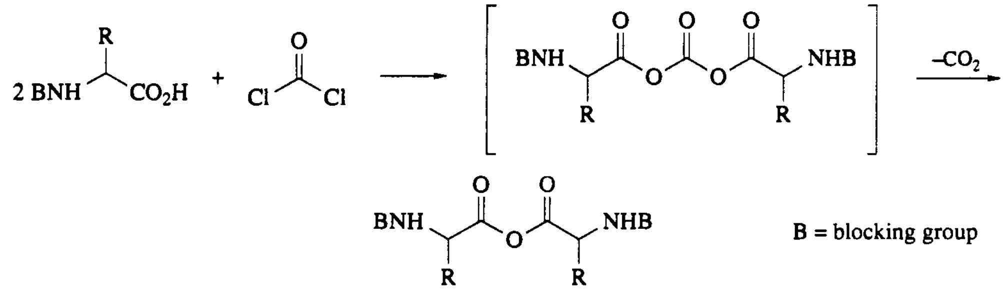

B = blocking group (4)

*(c) Intermolecular mixed from* C*-acids.*

In mixed anhydrides, the difference between the two carbonyl groups with respect to their electrophilic character should be pronounced.

Formylation of amines is performed with formic acid/acetic acid anhydride.[47] The application of other mixed anhydrides with acetic acid as well as benzoic acid[48] is less favorable, because both possible amides will form in varying amounts.

An improvement resulting in a decreased amount of the second acylation product is the introduction of mixed anhydrides with α-branched carboxylic acids like isovaleric[49] and pivalic acid,[50] due to deactivating electronic and steric effects.

In peptide chemistry, activation with pivalic acid mixed anhydrides allows condensation with α-alkyl-α-amino acids (*e.g.* Aib),[51] *N*-methyl-α-amino acids[52] (resulting in the total synthesis of cyclosporin A) and Boc-Asn.[53]

Mixed anhydrides of carbonic acid half esters contain an activating carbonyl group with reduced electrophilic character (due to lone pairs of electrons on the vicinal oxygen atom) and are rapidly amidated by amines. The anhydride is formed at low temperature in the presence of tertiary amines (equation 5).

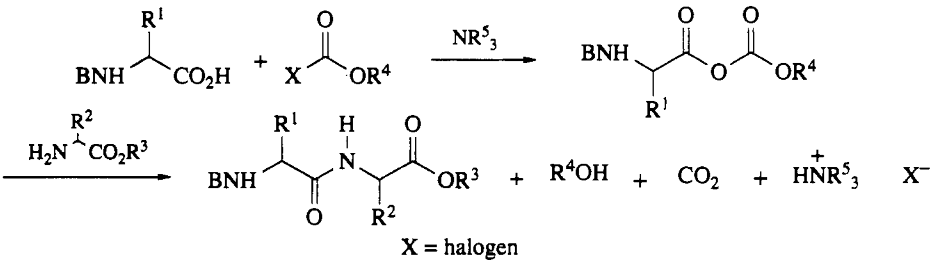

(5)

Isobutyl chloroformate is most frequently applied in peptide chemistry,[54–56] followed by ethyl chloroformate (see Table 1).[57] The advantage of this method is that the mixed anhydride does not have to be isolated, and during work-up only carbonic acid half esters are formed, which decompose to an alcohol and carbon dioxide. Only in the case of sterically hindered amino acids does the opening of the anhydride at the undesired carbonyl occur in considerable amounts. Furthermore, short activation times (30 s) at low temperatures lead to peptides with minimal racemization.[55] With isopropenyl chloroformate[58] the mixed anhydride is prepared at room temperature, and during reaction only acetone and carbon dioxide are formed.

**Table 1** Amides *via* Mixed Anhydrides: Use of *C*-acids

| *Reagent* | *Structure* | *Ref.* |
|---|---|---|
| Ethyl chloroformate | 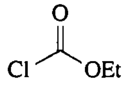 | 57 |
| Isobutyl chloroformate | 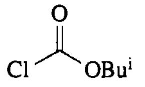 | 54, 55 |
| 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) | 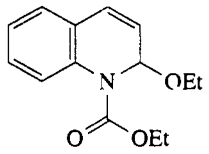 | 59 |
| 2-Isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ) | 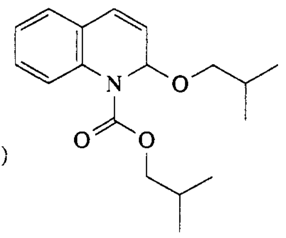 | 60, 61 |
| 2-Propenyl chloroformate | 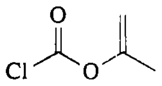 | 58 |

The coupling reagents EEDQ[59] and IIDQ[60,61] permit the formation of amides from carboxylic acids and amines in one pot, at ambient temperatures, without the need for a tertiary base (equation 6).

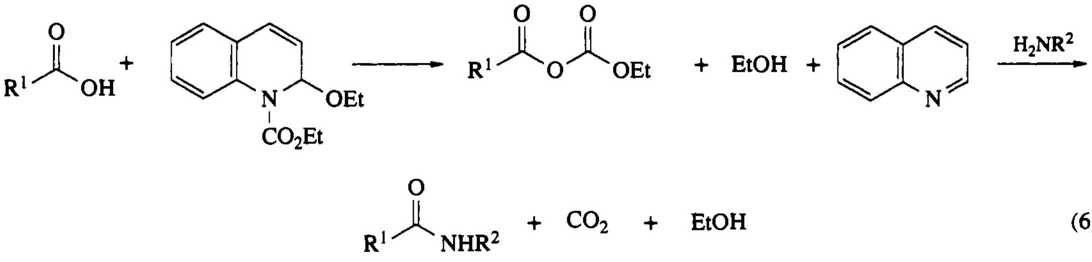

(6)

Carbodiimides are the major coupling reagents in peptide chemistry and are frequently used in solution as well as in solid phase synthesis (Table 2).

**Table 2** Amides *via* Mixed Anhydrides: Use of *C*-acids

| *Reagent* | *Structure* | *Ref.* |
|---|---|---|
| Dicyclohexylcarbodiimide (DCC) | 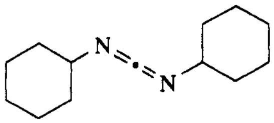 | 62 |
| Diisopropylcarbodiimide (DIC) | 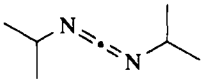 | 66, 67 |
| 1-Cyclohexyl-3-(2-*N*-methylmorpholiniumylethyl)-carbodiimide-*p*-toluenesulfonate | 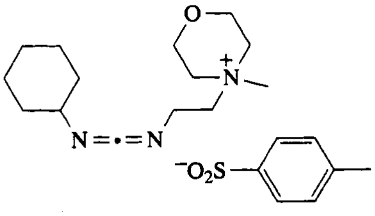 | 63 |
| 1-Ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC) | 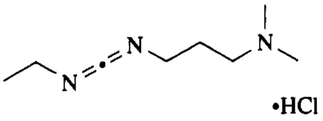 | 64 |
| Ethylphenylcarbodiimide | 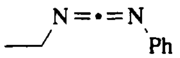 | 68 |
| Ethoxyethyne | ≡—OEt | 75 |
| 4-Dimethylamino-3-butyn-2-one | 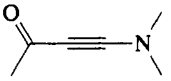 | 76 |
| 1-(4-Chlorophenyl)-3-(4-methylpiperazinyl)-2-propyn-1-one | 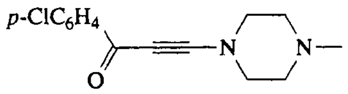 | 77 |
| Trimethylsilylethoxyethyne | EtO—≡—SiMe$_3$ | 74 |
| 2-Morpholinylethyl isocyanide | 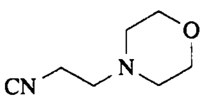 | 73 |
| t-Butyl isocyanide | $Bu^tNC$ | 71, 72 |

The reaction proceeds *via* a 1,2-addition of carboxylic acids to the carbodiimides to give acyllactims (Scheme 3), and leads to the peptide after nucleophilic attack of an amine. The by-product of this reaction, *N,N'*-dicyclohexylurea in DCC-mediated couplings,[62] is easily removed by filtration from the reaction mixture. Because it is not completely insoluble in most organic solvents, contamination of the products occur. The introduction of water soluble carbodiimides[63–65] facilitates the work-up procedure by extracting the urea with water. Diisopropylcarbodiimide[66,67] is frequently used in solid phase synthesis,[46] because its corresponding urea is soluble in a variety of organic solvents and readily removed by filtration.

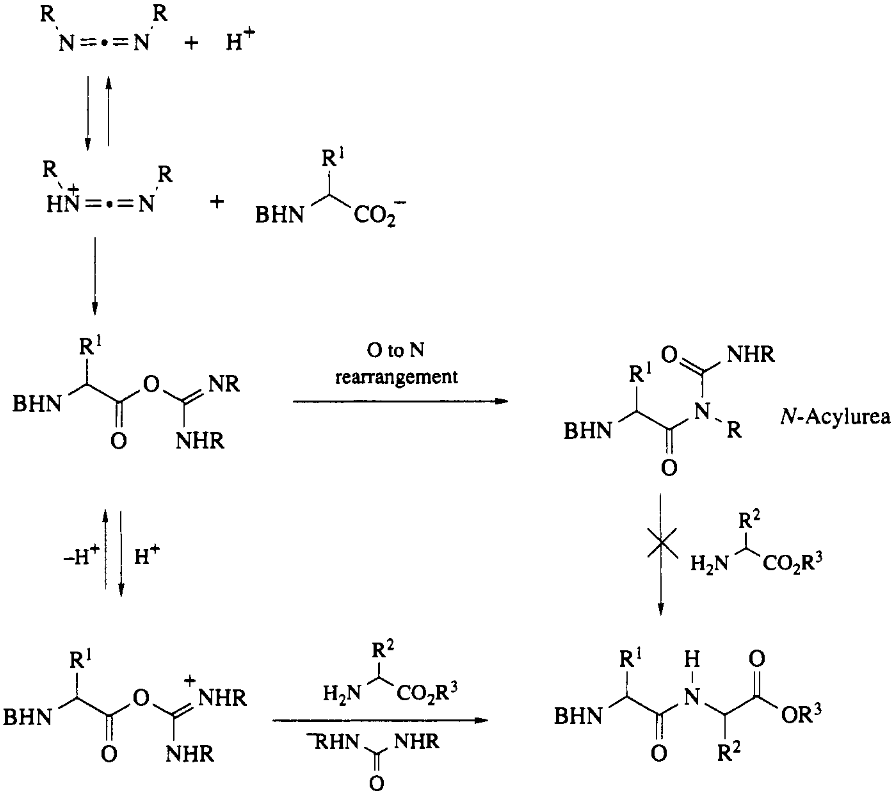

B = blocking group

**Scheme 3**

Two side reactions, the O to N acyl shift and racemization, limit the application to some extent. Lower reaction temperatures, shorter reaction times or the use of unsymmetric carbodiimides[68] suppress these reactions. The addition of reactive nucleophiles will be discussed in a later section (active esters).

Dicyclohexylcarbodiimide has been used in the acylation of all common amino acids and is the most familiar condensation reagent in peptide chemistry, in spite of its skin-irritating and allergic properties. Outside peptide chemistry, dicyclohexylcarbodiimide has been used only infrequently for the condensation of carboxylic acids and amines, probably due to its high costs.

α,β-Unsaturated carboxylic acids[69] and α-oxocarboxylic acids[70] give low yields of amides. The condensation of carboxylic acids with isocyanides is related to that of carbodiimides (equation 7).[71–73] The mild reaction conditions tolerate unprotected hydroxy groups of amino acids even with long reaction times. Generation of side products like acylureas is not possible and racemization is lower than with DCC.

2-Morpholinylethyl isocyanide[73] gives good results in fragment condensations and the by-product is simply removed by acid washing.

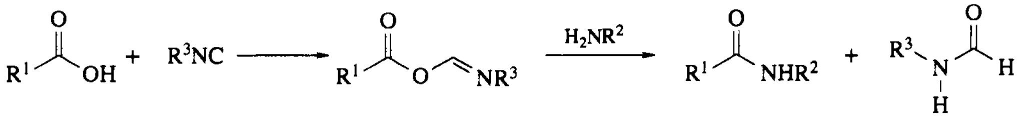
(7)

Activation by addition of a carboxylic acid to a triple bond occurs with ethyl ethynyl ether,[74,75] which forms amides *via* reactive enol esters. The reaction is catalyzed by mercury(II) oxide under almost neutral conditions. Push–pull alkynes exert higher reactivity.[76,77] The intermediate enol esters (Scheme 4) rearrange and react with the amino function of a second amino acid. Hydroxy, thiol and imidazole functional groups do not have to be protected. The degree of racemization is low, and yields are good in the case of small peptides.

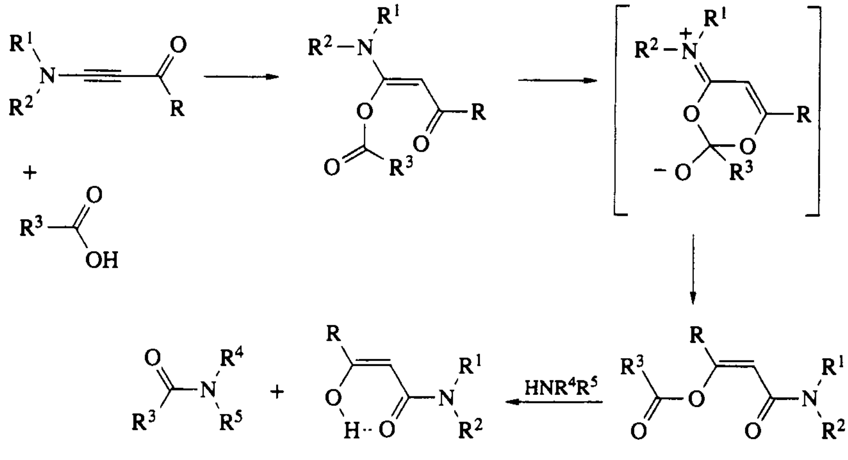

**Scheme 4**

*(d) Intermolecular mixed from S-acids.*

Activation of aliphatic and aromatic carboxylic acids with sulfuric acid derivatives yields amides (Table 3). Sulfuryl chloride fluoride and primary amines[78] or chlorosulfonyl isocyanate and secondary amines[79] are used as reaction partners.

Activation with sulfonic acid chlorides[80,81] is more general, rendering amides with the possible participation of symmetric anhydrides after disproportionation.[82] This method has also found use in the synthesis of modern β-lactam antibiotics.[83] However, in peptide chemistry this activation method leads to unwanted side reactions, like formation of nitriles in the cases of glutamine and asparagine,[84] and racemization.[85] In a convenient one-pot procedure, the carboxylic acids are activated by sulfonyl chlorides under solid–liquid phase transfer conditions using solid potassium carbonate as base and a lipophilic ammonium salt as catalyst.[86]

**Table 3** Amides *via* Mixed Anhydrides: Use of *S*-acids

| *Reagent* | *Structure* | *Ref.* |
|---|---|---|
| Sulfuryl chloride fluoride | $SO_2ClF$ | 78 |
| Chlorosulfonyl isocyanate | $ClO_2S\text{–}N{=}\bullet{=}O$ | 79 |
| Methanesulfonyl chloride | $MeSO_2Cl$ | 80 |
| Methanesulfonyl chloride | $MeSO_2Cl$<br>(Phase transfer conditions) | 86 |
| 2-Mesitylenesulfonyl chloride | 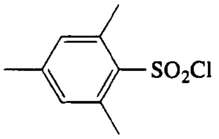 | 81 |
| *p*-Toluenesulfonyl chloride | 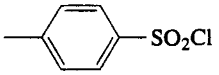 |  |

### *(e) Intermolecular mixed from* P-*acids.*

In recent years organophosphorus reagents have received much attention (Table 4). Their mixed carboxylic–phosphorous acid anhydrides are very reactive intermediates and are opened chemoselectively by nitrogen nucleophiles to give amides. The by-products in these coupling reactions are mostly water soluble, oxygen-containing phosphorus compounds. Therefore, medium scale technical syntheses of amides and peptides are also feasible.[87,88] The tendency for disproportionation to the symmetrical anhydrides is small.[89,90] Most of these reagents activate urethane-blocked amino acids without racemization,[91] while others are rapidly converted to their corresponding azides (DPPA)[92] or active esters[93–96] (BNPP,[97,98] BOP[99,100] and NPTP[101]; *cf.* Section 2.3.1.1.2.iii.a).

Advantages have been claimed for DPPCl[89] and BOP-Cl[102–104] in the condensation of *N*-methylamino acids, namely high yields and low racemization rates. For cyclization to cyclopeptides both DPPA[92,105] and (5-nitropyridyl)diphenylphosphinate,[96] to β-lactams NPTP[101] and DMPC,[106] have been applied.

DPPA, the Bates reagent and BOP are toxic, the latter due to the formation of HMPA. A substitute for the widely used BOP is TBTU [174], which releases tetramethylurea as a harmless side product.

The redox coupling found by Mukaiyama makes use of the facile oxidation of phosphines and the strength of the P—O bond (Table 5). In each case the reaction proceeds *via* an acyloxyphosphonium intermediate (equation 8). The oxidation is carried out by disulfides[108–110] and related compounds,[111,112] DEAD,[113] and halogens.[114–117] Although this method has been applied to the solid phase synthesis of peptides, it has not found broad application.

### *(f) Intermolecular mixed from* N-*acids.*

Carboxylic acid azides give rise to three different reactions under different conditions. Azide coupling (equation 9) was the earliest method[131] in peptide synthesis and is still one of the most important in fragment condensation[132] and preparation of cyclic peptides due to its almost complete lack of racemization. At elevated temperatures a frequent side reaction is the Curtius rearrangement. Trapping of the intermediate isocyanate with amines (equation 10) gives urea derivatives and with carboxylic acids rearranged amides are obtained (equation 11).[133]

Carboxylic acid azides are prepared from carboxylic acid halides or from amino acid/peptide esters *via* hydrazides, followed by nitrosylation with nitrous acid in water[134] or with alkyl nitrites in organic solvents.[135] Also, the aforementioned diphenylphosphorazidate (*cf.* Section 2.3.1.1.2.2.ii.e) is often used in this preparation method starting from carboxylic acids.

Activation of carboxylic acids with carbonyldiimidazole (equation 12) and subsequent reaction with amines gives amides and peptides in good yield.[136–138] Through the same intermediate, the activation also occurs with the more stable *N,N'*-oxalyldiimidazole[139] and the mixture of triphenyl phosphite and imidazole.[140]

Imidazolides are powerful acylating agents. Therefore moisture has to be excluded and the acids have to be preactivated before addition of the amine. The tendency toward racemization is low, especially in DMF. The by-products of the reaction, imidazole and carbon dioxide, are easily removable. Other activating reagents (Table 6) can be applied. The advantage of COMODD[141] and *N,N'*-carbonyldi-2-thione-1,3-thiazolidine[142] is that the activated carboxylic acids are stable and isolable.

### *(iii) Carboxylic acid esters*

The direct aminolysis of unactivated esters and lactones is particularly difficult with secondary amines, since even primary amines require temperatures higher than 200 °C.[143] Application of high pressure (8 kbar, 1 bar = 100 kPa) at lower temperatures (room temperature to 45 °C) makes this reaction possible.[144] Sodium cyanide catalyzes this reaction at atmospheric pressure and it proceeds without racemization of amino acid esters.[145]

Alternative methods include deprotonation of the amine, to enhance its nucleophilicity, by one equivalent of sodium methoxide,[146] sodium amide, metallic sodium,[147] *n*-butyllithium,[148] sodium hydride in dimethyl sulfoxide[149] or Grignard reagent.[150] Under less drastic basic conditions 2-hydroxypyridine catalyzes the reaction at elevated temperatures (130–170 °C).[151]

Treatment of the parent ester with Lewis acids like boron tribromide and subsequent addition of amine results in amides in good yields.[152]

**Table 4** Amides *via* Mixed Anhydrides: Use of *P*-acids

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| 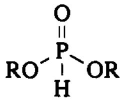<br>Phosphorous acids | Diphenyl phosphite | 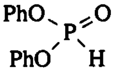 | 118 |
| 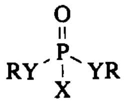<br>Phosphoric acids | Diethyl phosphorobromidate | 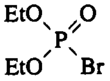 | 91 |
| Y = O, NR | Diethyl phosphorochloridate | 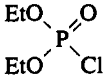 | 119 |
| | Diethylphosphoryl cyanide (DEPC) | 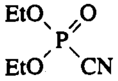 | 120 |
| | Diethyl-1-(benzo-1,2,3-triazolyl)phosphonate | 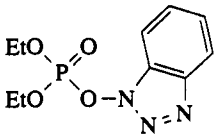 | 93 |
| | Diphenyl chlorophosphate | 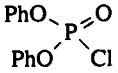 | 121 |
| | Diphenylphosphoryl azide (DPPA) | 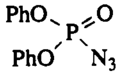 | 92, 105 |
| | 2-Pyridone diphenyl phosphate | 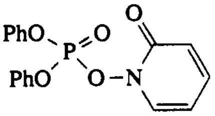 | 94 |
| | Norborn-5-ene-2,3-dicarboximidoyl diphenyl phosphate (NDPP) | 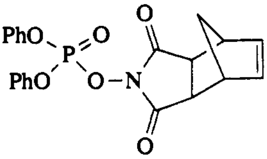 | 95 |
| | Bis(5'-nitro-2'-pyridyl) 2,2,2-trichloroethyl phosphate (NPTP) | 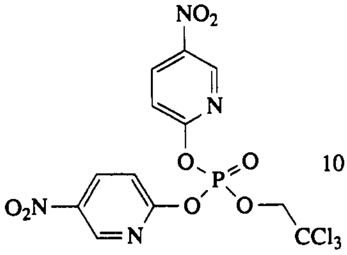 | 101 |

**Table 4** *(continued)*

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| 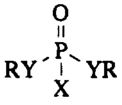<br>Phosphoric acids<br>Y = O, NR | Bisoxazolidonylphosphoroxy chloride | 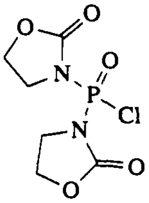 | 102 |
| | Phenyl *N*-phenylphosphoramidochloridate | 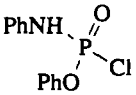 | 122 |
| | *N*,*N*-Dimethylphosphoramidic dichloride (DMPC) | 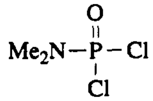 $Me_2N-P(=O)(Cl)-Cl$ | 106 |
| | Diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate | 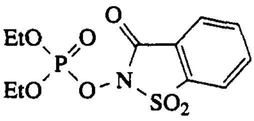 | 123 |
| 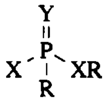<br>Phosphonic acids<br>X = O, NR, S<br>Y = O, S | *n*-Propylphosphonic anhydride (n-PPA) | 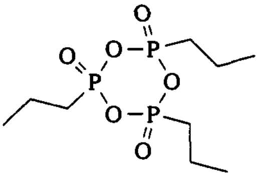 | 124 |
| | Bis(*o*-nitrophenyl) phenylphosphonate (BNPP) | 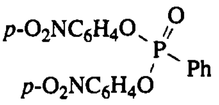 | 97, 98 |
| | Lawesson reagent | 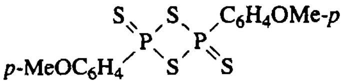 | 125 |
| | 1,4,6,9-Dioxa-5-phosphaspiro[4.4]dibenzononane | 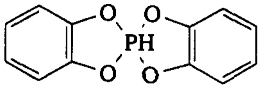 | 126 |
| | 3,3'-(Phenylphosphinylidene)bis(2(3*H*)-benzoxazolone | 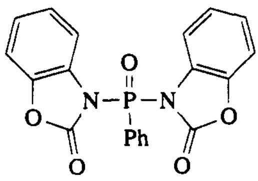 | 127 |
| 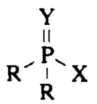<br>Phosphinic acids<br>Y = O, S | Diphenylphosphine chloride (DPPCl) | 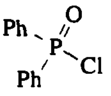 | 89, 90 |

**Table 4** *(continued)*

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| 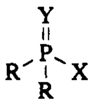<br>Phosphinic acids<br>Y = O, S | Ethylmethylphosphinic anhydride (EMPA) | 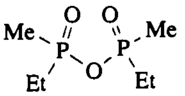 | 87 |
| | 2-(5-Nitropyridyl) diphenylphosphinate | 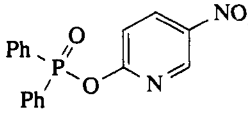 | 96 |
| | 3,3'-(Phenylphosphinylidene)bis(2(3*H*)benzoxazole) | 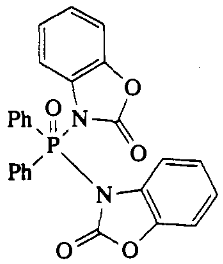 | 85 |
| | 1-Oxo-1-chlorophospholane | 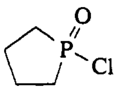 | 88 |
| 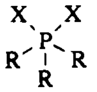 | Bis(2,2,2-trifluoroethoxy)triphenylphosphorane | 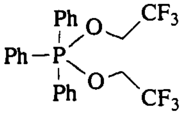 | 128 |
| | Bis(trifluorosulfonyl)triphenylphosphane | 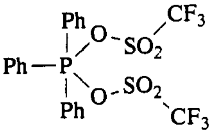 | 129 |
| 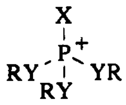 | Tris(dimethylamino)phosphonium anhydride bis(tetrafluoroborate) (Bate's reagent) | 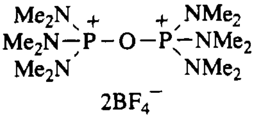 | 107 |
| | Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) | 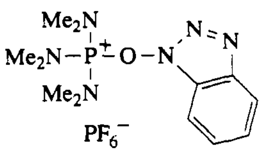 | 99, 100 |

A mild and general method involves pretreatment of amines with one equivalent of trimethylaluminum followed by addition of the ester or lactone.[153] Similarly $RhCl_3$ catalyzes amide bond formation leading to diketopiperazines.[154]

Some simple examples exploit the electrochemical amidation of esters with amines in the cathodic compartment.[155]

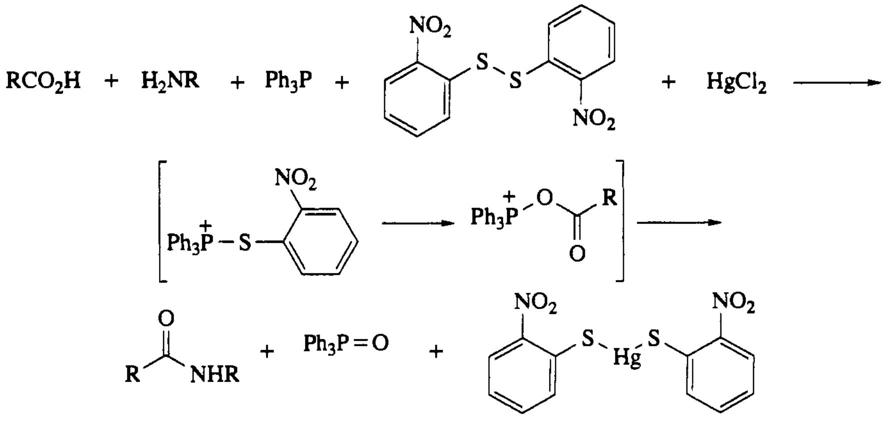
RCO2H + H2NR + Ph3P +
+ HgCl2
Ph3P=O

(8)

**Table 5** Amides *via* Mixed Anhydrides: Use of *P*-acids (Oxidation–Reduction)

| *Structure* | *Ref.* | *Structure* | *Ref.* |
|---|---|---|---|
| $Ph_3P/CCl_4$ | 114 | $Ph_3P$/DEAD | 113 |
| $Ph_3P$/NBS | 115 | 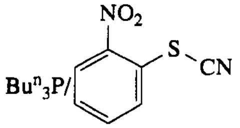 | 111 |
| 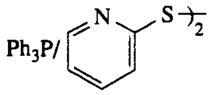 | 108, 109 | 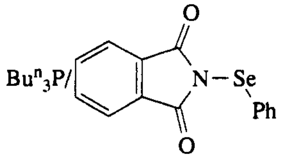 | 112 |
| 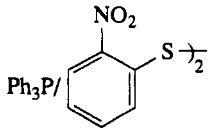 | 110 | $(Me_2N)_3P/Cl_2$ or $C_2Cl_6$ | 116, 117 |
| 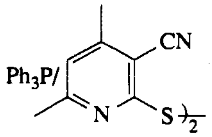 | 130 | | |

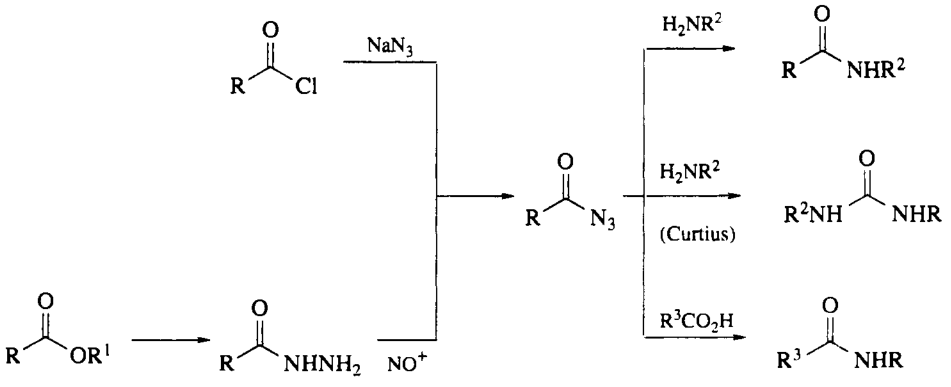
NaN3
H2NR2
H2NR2
(Curtius)
R3CO2H
NO+

(9)

(10)

(11)

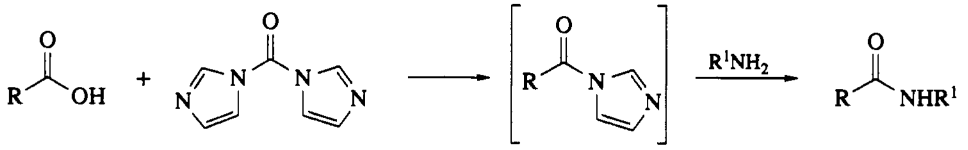
(12)

**Table 6** Amides *via* Mixed Anhydrides: Use of *N*-acids

| *Reagent* | *Structure* | *Ref.* |
|---|---|---|
| 2,2'-Carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) (COMODD) | 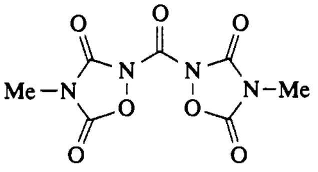 | 141 |
| 1,1'-Carbonyldiimidazole | 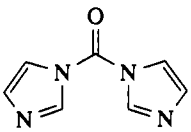 | 136 |
| *N*,*N*'-Carbonyldiimido-2-thiono-1,3-thiazolidine | 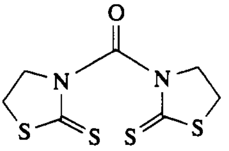 | 142 |
| *N*,*N*'-Carbonyldiimidotriazole | 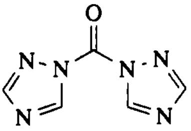 | 143 |
| *N*,*N*'-Oxalyldiimidazole | 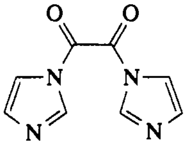 | 139 |
| Azide | $N_3$ | 131 |
| Triphenyl phosphite, imidazole | $(PhO)_3P$, 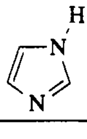 | 140 |

*(a) Intermolecular from active esters.*

To facilitate the amidation of esters, phenols substituted with strongly electron-withdrawing groups have been applied to this reaction. The nucleophile, a primary or secondary amine, only attacks the ester bond at the electrophilic carbonyl group. This reaction has found broad acceptance in peptide chemistry, also due to the fact that many active esters are available as crystalline compounds. Table 7 shows the most important groups. Aromatic alcohols like *p*-nitrophenols[156] or pentafluorophenols[157] are often used to prepare active esters, the latter compounds being used in combination with the *N*-amino protecting group FMOC in solid phase synthesis. These aminolyses can further be catalyzed by the addition of hydroxybenzotriazole.[158]

*O*-Acyl derivatives of substituted hydroxylamines react readily with amines and amino acids with almost no racemization due to an anchimeric assistance (equation 13) in the transition state. The active esters are prepared either by the activation reagents shown in Table 7 or by activation with DCC and trapping by the hydroxylamine. TBTU[174] reacts fast and has found increasing interest in solid phase synthesis. Following a similar mechanism, oxime esters[159,160] are also used for activation.

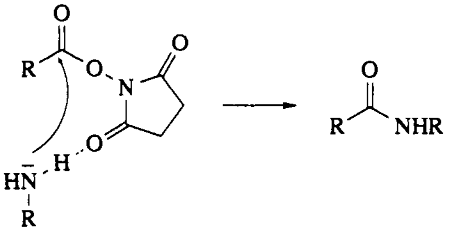

(13)

*C*-Terminal amino acid oxime esters on a polymeric phase have been applied to solid phase peptide synthesis;[161] the protected peptide is cleaved by amino acid esters and other nucleophiles.

Enol ester intermediates are formed from cyclic carbonates,[162,163] a color change indicating the progress of the reaction.

### *(b) Intermolecular from active thioesters.*

In analogy to the active esters, thioesters are prepared by condensation of thiols with carboxylic acids/DCC[178] or carboxylic acid chlorides.[179–181] Aryl thioesters react readily with nucleophiles like amines to give amides. Peptides are prepared without racemization. In the case of *t*-butyl thioesters activation is accomplished by treatment with $AgO_2CCF_3$.

2,2′-Pyridine disulfide reacts with triphenylphosphine and carboxylic acids to yield active thioesters, which can be amidated with secondary amines.

Due to their obnoxious smell and catalyst-poisoning properties, active thioesters have only encountered limited use.

### *(c) Miscellaneous.*

Lewis acids like tetrachlorosilane in pyridine[182,183] or titanium tetrachloride[184] are reported to give simple amides in moderate yields. Boron trifluoride etherate in the presence of a strong base amidates carboxylic acids in an excess of primary amine.[185] These reactions have not found broad application.

### *(d) Enzyme-catalyzed peptide bond formation.*

The fact that hundreds of coupling reagents have been developed for peptide chemistry demonstrates that there is still a need for general methods with high reaction rates employing equimolar amounts of carboxy and amino components without racemization.[186,187]

Hydrolyzing enzymes, especially proteases, constitute an alternative to chemical synthesis. The principal advantages are the use of unprotected side chain amino acids (except cysteine), racemization-free couplings (especially in fragment couplings) and the specificity of the involved enzyme. As a consequence, the number of synthetic steps is drastically reduced and the procedures are environmentally safe.

The peptide-forming reaction can be carried out under thermodynamic or kinetic control (equation 14). The equilibrium between substrates and product is unfavorable for the peptide (endergonic process due to a loss in entropy). Shifting the equilibrium to the right (increasing $K_{syn}$) is achieved by optimizing the reaction conditions through increasing $K_{ion}$ by proper choice of pH, use of water miscible organic solvents and use of biphasic systems. The reversal of hydrolysis by formation of insoluble products or extraction of products increases the yield.

For these thermodynamically controlled syntheses a variety of enzymes may be used, *e.g.* serine proteases like chymotrypsin[188] and trypsin,[189] cysteine proteases (thiol proteases) like papain,[190,191] aspartate proteases like pepsin[192] and metalloproteases like thermolysin.[193]

Kinetically controlled syntheses, which are more often studied, can only be carried out by enzymes forming a reactive acyl–enzyme intermediate (serine or cysteine protease, Scheme 5). The reaction starts with weakly activated amino acids (*e.g.* esters), and the rapidly formed reactive intermediate RCOE is attacked by nucleophiles like amines and water. If $k_4 \gg k_3$ and $k_4[H_2NR'] > k_3[H_2O]$, the desired peptide accumulates. Short reaction times, low enzyme concentrations and the danger of secondary hydrolysis of the peptide product are characteristics of these reactions. The optimal pH usually lies above pH 8.

Immobilized enzymes which have the same efficiency as soluble enzymes can easily be recovered and reused and exert no proteolytic activities on synthesized peptides.[194]

**Table 7** Amides *via* Active Esters

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| Aromatic compounds | *p*-Nitrophenol | 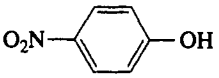 | 156 |
| | 2,4,5-Trichlorophenol | 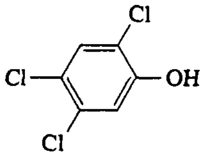 | 164 |
| | Pentafluorophenol | 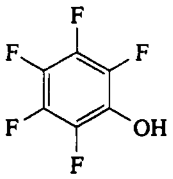 | 157 |
| | (*p*-Hydroxyphenyl)dimethylsulfonium methyl sulfate (HODMSP *x* $MeSO_4$) | 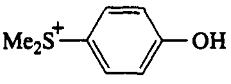 | 165 |
| | 2-Chloro-4,6-disubstituted-1,3,5-triazines | 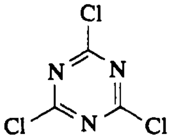 | 166 |
| | 2-Chloro-1-methylpyridinium iodide (CMPI) | 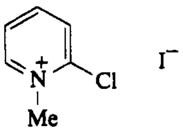 | 167 |
| | 2-Fluoro-1-ethylpyridinium iodide | 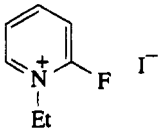 | 168 |
| | 2-Pyridone | 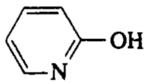 | 169 |
| Hydroxylamines | *N*-Hydroxysuccinimide | 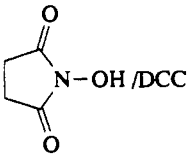 | 158 |
| | 1-Hydroxybenzotriazole | 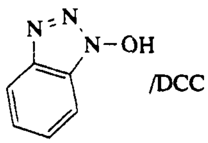 | 158 |

**Table 7** *(continued)*

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| Hydroxylamines | 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine | 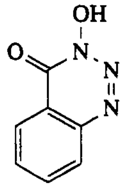 /DCC | 170 |
| | Bis(1-benzotriazolyl) carbonate | 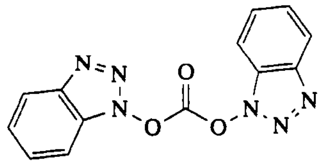 | 171 |
| | Bis(1-benzotriazolyl) oxalate | 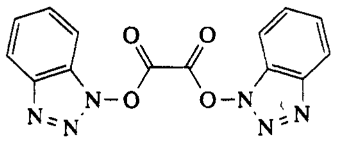 | 172 |
| | Bis(*N*-succinimidyl) oxalate | 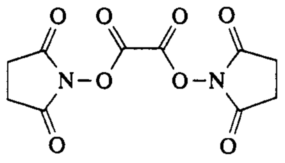 | 172 |
| | Bis(*N*-succinimidyl) carbonate | 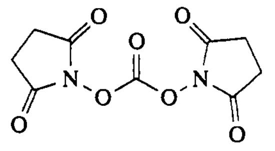 | 173 |
| | 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate | 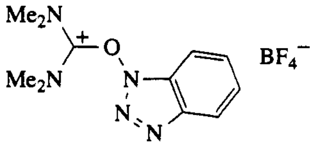 | 174 |
| | *N*-Hydroxypyridone | 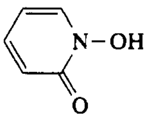 | 175 |
| | *N*-Hydroxypiperidine | 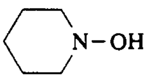 | 176 |
| | *N*-Hydroxy-5-norbornene-2,3-dicarboxamide | 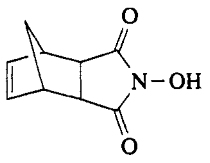 | 177 |

**Table 7** *(continued)*

| *Class* | *Reagent* | *Structure* | *Ref.* |
|---|---|---|---|
| Oximes | *syn*-Phenylpyridyl *O*-acetyloxime | 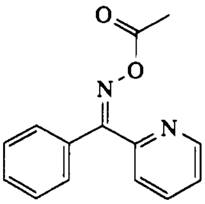 | 159 |
| | | 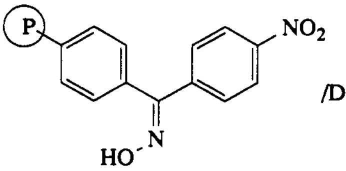 /DCC | 160 |
| Enol esters | Steglich's reagent | 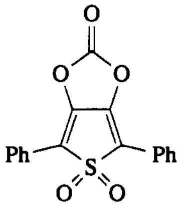 | 162, 163 |

$$\mathrm{RCO_2^-} + \mathrm{H_3\overset{+}{N}R'} \overset{K_{\mathrm{ion}}}{\rightleftharpoons} \mathrm{RCO_2H} + \mathrm{H_2NR'} \overset{K_{\mathrm{inv}}}{\rightleftharpoons} \mathrm{RCONHR'} + \mathrm{H_2O} \qquad (14)$$

$$K_{\mathrm{syn}} = K_{\mathrm{ion}} + K_{\mathrm{inv}}$$

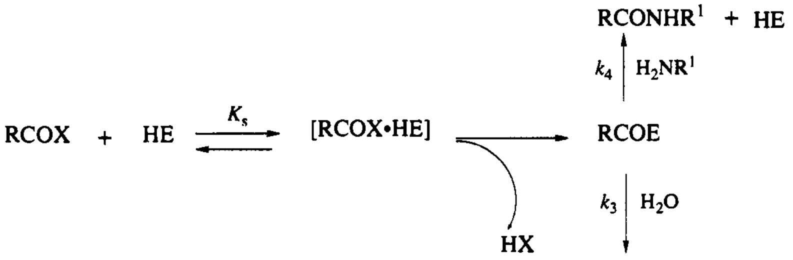
RCONHR¹ + HE
k4
H2NR¹
RCOX + HE
Ks
[RCOX•HE]
RCOE
HX
k3
H2O
RCO2H + HE

E = enzyme

**Scheme 5**

Enzymatic methods were applied to the synthesis of aspartame (equation 15),[195] an artificial sweetener.

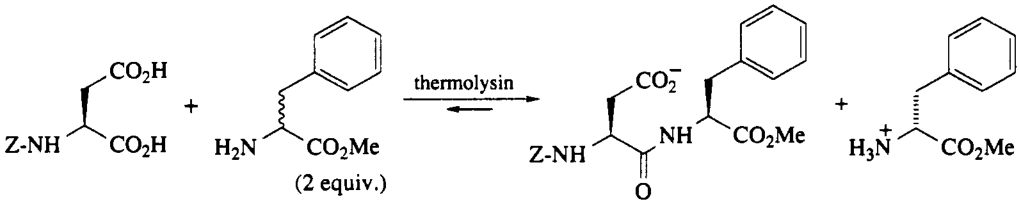
CO2H
Z-NH
CO2H
+
H2N
CO2Me
(2 equiv.)
thermolysin
CO2−
Z-NH
NH
CO2Me
O
+
H3N+
CO2Me

(15)

In the case of thermolysin, a thermodynamically controlled reaction takes place. Only L-Phe reacts with the side chain unprotected L-Asp. The reaction proceeds to the product side by the formation of an insoluble salt with the remaining D-Phe.

Enkephalins, hormones with morphine-like activities, have been synthesized with chymotrypsin and papain[196] as well as carboxypeptidase Y[197] under kinetically controlled conditions.[190]

Further commercial interest was found by the transpeptidation reaction of porcine insulin to human insulin, the latter only differing in the last amino acid of the B-chain (Ala-B30 to Thr-B30). This reaction proceeds under kinetic control with trypsin,[198,199] carboxypeptidase Y[200] or *achromobacter lyticus* protease I.[201]

The enzymatic method was extended using chemically modified serine proteases like thiolsubtilisin[202] for the synthesis of the ribonuclease $T_1$ (12–23) fragment.

Recent progress was made in the incorporation of D-amino acids in peptides *via* subtilisin-mediated syntheses in organic solvents[203] or in the application of the nonproteolytic lipases[204] in anhydrous organic solvents.

In general, the enzymatic methods cannot be used universally and have to be optimized for each peptide synthesis. High specificity of an enzyme drastically reduces its wide application; broad specificity has the advantage of universal use, but suffers from early proteolytic cleavage of products.

### *2.3.1.1.3 Activation of the amino group*

A conceptual alternative way to the activation of the carboxylic acid function is the reaction of carboxylic acids with amino groups activated as isocyanates[205,206] and isothiocyanates (equation 16).[207] Preparation of these derivatives is racemization free. The reaction proceeds *via* mixed acid anhydrides in aromatic hydrocarbon solvents at elevated temperatures, and decarboxylation leads to the *N*-substituted amide. Pyridine as solvent enhances the conversion rate but increases also the amount of the urea side product *via* disproportionation.[205] Application to peptide chemistry is limited, because peptide ester fragments tend to form hydantoins.[205]

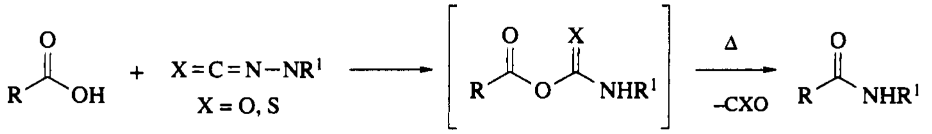

(16)

Reaction with *N*-urea-protected amino acids is racemization free, whereas the fragment condensation shows considerable racemization.[208] The analogous condensation with isothiocyanates[207] runs at higher temperatures.

Activation of organic azides with trivalent phosphines under mild conditions followed by reaction with carboxylic acids leads to amides *via* iminophosphoranes in moderate to good yields (equation 17).[209] The driving force of this method lies in the intramolecularity of the acyl transfer and the expulsion of a thermodynamically stable end product.

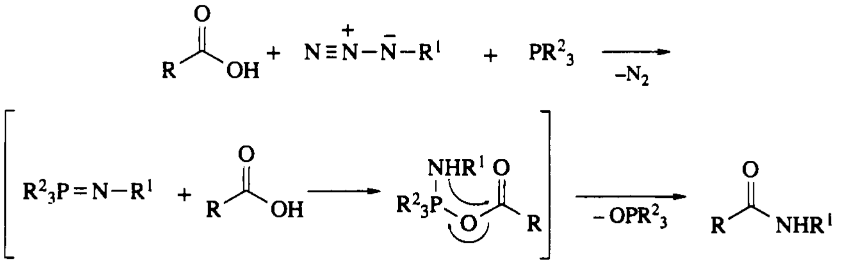

(17)

## 2.3.1.2 Alkylation and Arylation of Amides

The preparation of *N*,*N*-disubstituted amides is easily performed with sodium salts of *N*-monosubstituted amides and alkyl bromides or iodides.[210]

Under phase transfer conditions (boiling benzene, 50% aquous sodium hydroxide solution and tetra-*n*-butylammonium hydrogenphosphate) benzamides are monoalkylated.[211] In the solid–liquid PTC system potassium hydride, tetrahydrofuran and 18-crown-6, acidic trifluoroacetamides are rapidly deprotonated and alkylated with lower alkyl, allyl and benzyl halogenides in high yield.[212] Methylation of trifluoroacetamides is carried out under less basic conditions in KOH/acetone.[213] A similar reaction in KOH/DMSO generally allows the efficient reaction of benzamide and acetanilide with primary alkyl halides; with secondary halides only moderate yields are accomplished, whereas tertiary halogenides are not alkylated due to dehydrohalogenation.[214]

The photochemical 1,2-addition of *N*-halogen amides to alkenes results in a mixture of diastereomers (equation 18).[215]

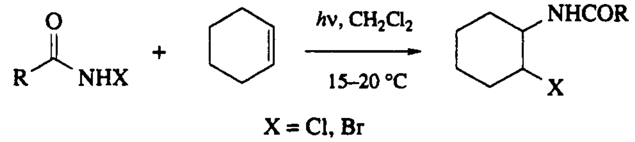

(18)

*N*-Arylation of benzamide or acetamide is possible under drastic reaction conditions in aryl halides as solvent and at high temperatures,[216] with copper powder as catalyst. A simplified procedure, using tris(3,6-dioxaheptyl)amine (TDA-1) and copper(I) chloride as PTC system, performs this reaction with quasi-stoichiometric quantities of bromobenzene under relatively mild conditions.[217]

The addition of mercury(II) nitrate activated alkenes to amides follows the rule of Markovnikov. Subsequent $NaBH_4$ demercuriation leads to more highly substituted amides in moderate to good yields.[218]

An efficient two-step procedure for the *N*-methylation of amides (equation 19) involves the preparation of intermediate methylols with subsequent reduction using triethylsilane, hydrogen/Pd–C[219] or cyanoborohydride.[220,221]

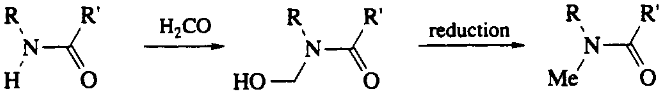

(19)

### 2.3.1.3 Nitriles

### *2.3.1.3.1 Hydration*

Under neutral conditions and at high temperatures (*ca.* 180 °C) nitriles react with water to give amides (equation 20). ZnO and CdO are efficient catalysts.[222] To accelerate the reaction rate, acid treatment under a variety of conditions can be carried out: hydrochloric acid,[223] hydrogen chloride or bromide in formic acid,[224] alcoholic hydrogen chloride solutions,[225–227] polyphosphoric acid[228,229] and boron trifluoride in aqueous acetic acid[228] are all effective.

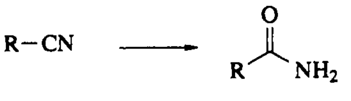

(20)

Alternatively, applying basic reaction conditions, partial hydrolysis with hydroxide-loaded anion exchangers in boiling water leads to aromatic amides in good yield.[230–232]

Hydrolysis with powdered potassium hydroxide or potassium fluoride on alumina[233] in *t*-butyl alcohol converts nitriles to amides without further hydrolysis to carboxlic acids.[234] Under similar conditions, addition of alkyl halides gives *N*-alkylcarboxyamides.[235] Less drastic acidic or basic hydrolysis conditions involve disproportionation of alkaline hydrogen peroxide with concomitant hydration of the nitrile (equation 21).[236,237]

Aromatic nitriles generally afford amides in yields of 80–90%, but in the aliphatic series only 50–60% yields are achieved.

A modification of this method using phase transfer catalysis leads to improved yields in shorter reaction times.[238]

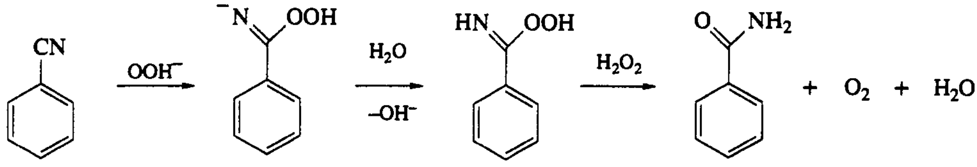

(21)

With the help of metal catalysis amidation takes place at room temperature under apparently neutral conditions. Manganese dioxide in large quantities,[239] or, even better, manganese dioxide on silica gel,[240] is well suited to this conversion. Even compounds with functional groups labile to manganese dioxide, for example benzylic groups, are suited for the hydration. With pentacarbonylmanganese bromide, nitrile hydration takes place under PTC conditions.[241]

Copper(0) catalyzes the hydration of sensitive nitriles like 2-acrylamide.[242]

Other processes involving metal catalysts like nickel(II), zinc(II), palladium(II) and ruthenium(I) have not found broad application, but a related amidation of nitriles uses the ruthenium catalyst $[RuH_2(PPh_3)_4]$.[243]

### *2.3.1.3.2 Ritter-type reactions*

In general, treatment of carbonium ions with nitriles under a variety of conditions yields *N*-substituted amines.[244] Anodic oxidation in acetonitrile converts selected aliphatic compounds to acetamides, *e.g.* adamantane to adamantylacetamide (equation 22).[245]

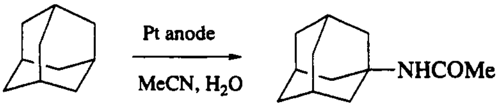

(22)

Alkenes and alcohols condense with nitriles under drastic acidic conditions. In most cases sulfuric acid is used either neat or with solvents such as acetic acid.[244,246] In liquid hydrogen fluoride containing defined amounts of water, nitriles react with linear or branched alkenes to form amides in good yields.[247]

Treatment of allylsilanes and allylstannanes with thallium(III) salts in acetonitrile activates the alkene for nucleophilic attack of the nitrile group. The generated nitrilium cation (equation 23) is hydrolyzed to the corresponding *N*-allylamide.[248]

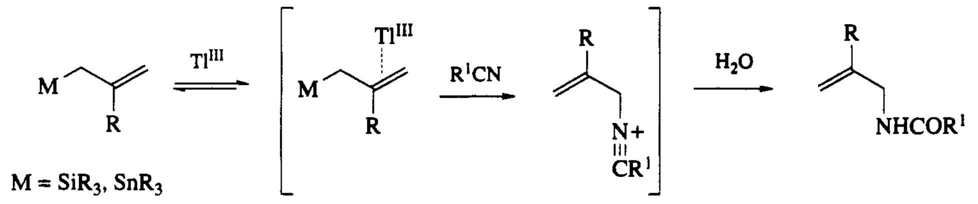

(23)

Allyl halides react with acetonitriles after anodic oxidation[245,249] under acidic conditions[244,250] or in the presence of nitrosonium hexafluorophosphate[251] to give the corresponding amides.

Vinyl cations, generated from β-arylvinyl bromides by silver(I)-assisted solvolysis or by photolysis, are trapped by nitriles to yield isoquinolines (equation 24).[252]

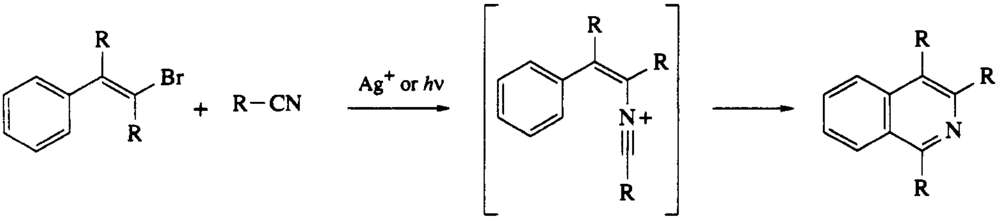

(24)

The reaction of nitriles with carbon monoxide, carbonyl compounds, carboxylates, ketenes, 1-aminoalkynes and carbenes has been reviewed recently.[250]

### 2.3.1.4 Oxidation

Oxidation of amines containing α-hydrogen atoms is of variable difficulty (equation 25). Permanganate oxidation of 1-aryl-5-(tertiary)amino-*v*-triazoles leads to the corresponding amides.[253] Benzyl(triethyl)ammonium permanganate[254] oxidizes a variety of simple, substituted amines. Tertiary amines give good yields of amides, but secondary and primary amines give moderate yields due to the formation of imines.

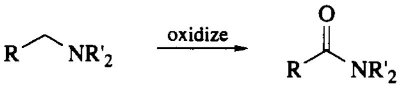

(25)

A similar selective oxidation of *N*-methyl groups has been accomplished with osmium tetroxide in the alkaloids delphinine and mesaconitine.[255]

Lactams are formed by bromination (bromine, *N*-bromosuccinimide) of cyclic tertiary amines, resulting in an intermediate iminium salt that can be isolated.[256] Oxidation by metal oxides,[257] autoxidation,[258] photochemical oxidation[259] and electrooxidation[260] are alternatives with limited scope.

The oxidation of aldehydes in the presence of amines occurs at low temperatures with nickel peroxide.[261] Similarly, the oxidation of aromatic aldehydes with manganese dioxide[262] or ruthenium chloride[263] in the presence of sodium cyanide and an amine leads to the corresponding amides.

The dipeptide sweetener aspartame has been synthesized *via* an oxaziridine, which was rearranged by irradiation with UV light (equation 26).[264]

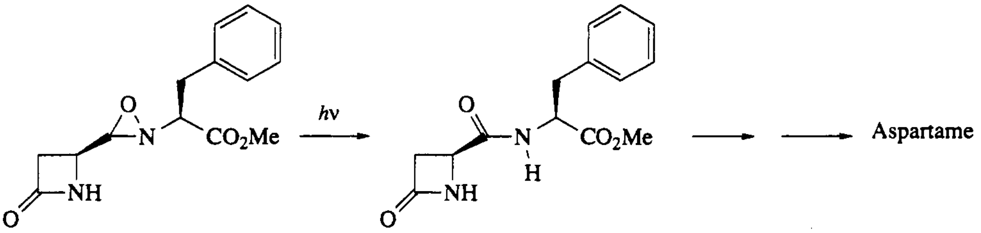

(26)

Aldehyde bisulfite adducts are oxidized by dimethyl sulfoxide/acetic anhydride and converted to simple amides in good yield.[265]

In the oxidative decyanation of dialkylaminophenylacetonitriles under phase transfer conditions the generated α-carbanion is oxidized by a stream of oxygen (equation 27).[266] Catalytically, a direct conversion occurs with the system consisting of $Pd(OAc)_2$, benzyl bromide and potassium carbonate.[267]

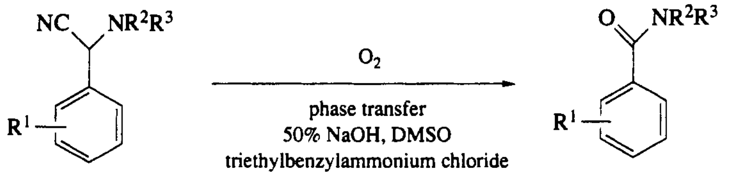

(27)

Oxidations of hydroxamic acids[268] by periodate (assumed to involve a nitrosylacyl intermediate) and of hydrazides[269] by potassium ferrocyanide, followed by quenching with amines, are of limited preparative value.

### 2.3.1.5 Reduction

Under mild conditions, titanium trichloride reduces hydroxamic acids to the corresponding amides and lactams (including β-lactams) in good yield (equation 28).[270]

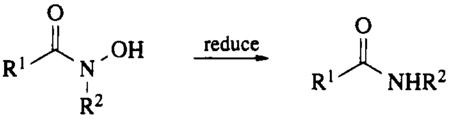

(28)

Brief heating of hydroxamic acids in phosphorus tribromide/benzene,[271] as well as treatment with Raney-Ni,[272] results in the formation of lactams.

Isoxazole derivatives, considered as cyclic β-ketohydroxamic acids, are opened by hydrogenation over palladium or platinum[273] to give the corresponding β-ketoamides in excellent yields (equation 29).

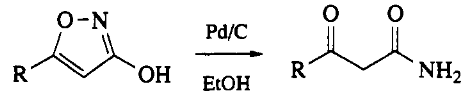

(29)

Thionyl chloride reacts with *N*-arylhydroxamic acids to form the corresponding amides *via* ortho-halogenation (equation 30).[274]

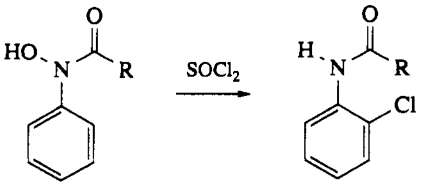

(30)

Hydrazides are hydrogenated by a substantial excess of Raney nickel.[275] Phenylhydrazides are reductively cleaved over palladium/charcoal as catalyst, and the corresponding amides are obtained in good yields.[276]

The reductive cleavage of benzoyl azide runs at low temperature with tetracarbonylhydridoferrate, $[HFe(CO)_4]^-$,[277] and with diphosphorus tetraiodide in benzene under reflux.[278] Curtius rearrangement side products are not observed.

### 2.3.1.6 Thioamides

Due to the ease of preparation of thioamides (*cf.* Chapter 2.4. of this volume) there is considerable interest in the desulfurization of these to the corresponding amides (equation 31).

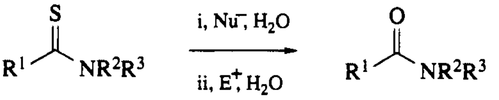

(31)

With the exception of a few examples of nucleophilic attack on the thiocarbonyl group, including a more recently published method using sodium hydroxide under phase transfer conditions,[279,280] most conversions are carried out with oxidative reagents. Sodium peroxide,[281] dimethyl sulfoxide with acid[282] or iodine,[283] selenium-derived reagents[284,285] and bis(*p*-methoxyphenyl)telluroxide[286] have been used.

Catalytic amounts of halogen accelerate the conversion, especially with strong base under phase transfer conditions.[280,287] *m*-Chloroperbenzoic acid reacts with thiolactams and thioamides and gives good yields of amides with precipitation of sulfur.[288]

Alkylation of thioamides with Meerwein's reagent (trialkoxonium fluoroborate)[289] proceeds *via* a thioiminoester and subsequent base hydrolysis with sodium carbonate (equation 32). For the synthesis of 2-pyridones from 2-thiopyridones, chloroacetic acid has been used.[290] Mild reaction conditions are provided by nitrosyl species which are derived from a variety of reagents: excess $NaNO_2/HCl$[291] in aqueous medium, nitrosonium tetrafluoroborate[292] in dichloromethane, dinitrogen tetroxide[293] in acetonitrile at low temperature and *t*-butyl thionitrate.[294]

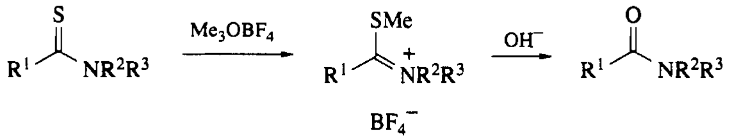

(32)

### 2.3.1.7 Rearrangements

#### *2.3.1.7.1 Beckmann, Schmidt*

The Beckmann rearrangement converts oximes to amides or lactams and was reviewed recently (equation 33).[295]

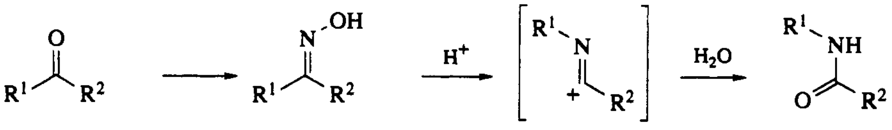
(33)

In general, this rearrangement is stereospecific, involving the migration of the residue *anti* to the leaving group on nitrogen. The reaction usually occurs under acidic conditions. $PCl_5$ in ether,[296] thionyl chloride in dioxane,[297] boric acid[298] and more frequently polyphosporic acid[299] are used at elevated temperatures. Due to its viscosity and low dissolving ability resulting in large reaction volumes, polyphosphoric acid can be effectively replaced by trimethylsilylpolyphosphate[300] (readily prepared from phosphorus pentoxide and hexamethyldisiloxane) or the two phase system polyphosphoric acid/xylene.[301] The mildly basic hexamethylphosphoramide causes rearrangement at higher temperatures.

Activation of the oxime with benzenesulfonyl chloride or *p*-toluenesulfonyl chloride leads to sulfonate esters which undergo the Beckmann reaction with or without isolation.[302,303] The sulfonate esters also rearrange under mild reaction conditions on silica gel.[304] Under neutral conditions, *N,N*-carbonyldiimidazole activates oximes in the presence of allyl bromide, followed by spontaneous Beckmann rearrangement.[305]

Dependent on the stereochemistry of the oxime sulfonate and the different groups $R^1$, $R^2$, in many cases only one preferred stereoisomer rearranges. In hydrochloric acid/acetic acid, isomerization gives rise to only one final product.[306]

Hydroxylamine sulfonic acid,[307] hydroxylamine and catalytic amounts of trifluoromethanesulfonic acid,[308] or *O*-mesitylenesulfonylhydroxylamine[309] converts ketones directly to the lactams under mild conditions (reflux in formic acid).

The Schmidt reaction is closely related to the Beckmann reaction (equation 34). Acyclic and cyclic ketones are transformed to amides and lactams by treatment with hydrogen azide.[310,311] With bridged bicyclic ketones, the regioselectivity of the migration is opposite to the direction of the Beckmann reaction.[311,312] The Schmidt reaction has been applied to asymmetric synthesis starting from optically active α,α-dialkylated β-keto esters. High chemical and optical yields have been obtained (equation 35).[313]

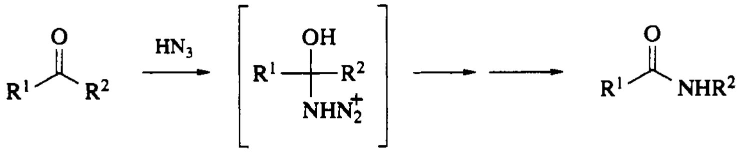
(34)

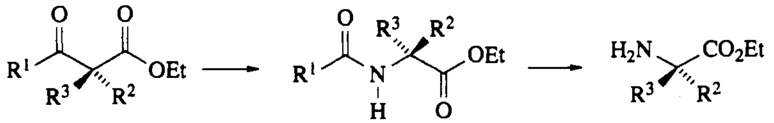
(35)

#### *2.3.1.7.2 Willgerodt*

In the Willgerodt reaction, aryl alkyl ketones react with sulfur and ammonium hydroxide to give amides with the same number of carbon atoms (equation 36).[314] In an extension, aliphatic ketones,[315] aldehydes[316] and unsaturated hydrocarbons[317] also can be used as starting materials.

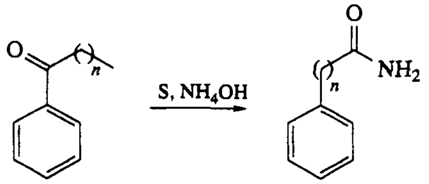
O
n
S, NH4OH
O
n
NH2

(36)

The Kindler modification of the Willgerodt reaction uses sulfur and dry amines, ammonia, primary amines or secondary amines, which leads to the formation of thioamides (conversion of thioamides to amides *cf.* Section 2.3.1.7).[318] This reaction can also be extended to aldehydes,[319] hydrocarbons[320] and heterocyclic ketones.[321] Due to the usually low to moderate yields this reaction has not found general application.

### *2.3.1.7.3 Ugi four component reaction*

The four component condensation (Ugi reaction)[322-324] converts a mixture of substituted amine, isonitrile, aldehyde (or ketone) and carboxylic acid (Scheme 6) to α-acylaminocarboxylic acid amides (pathway a), to diacylamines (pathway b) and to α-aminocarboxylic acid amides (pathway c).[325]

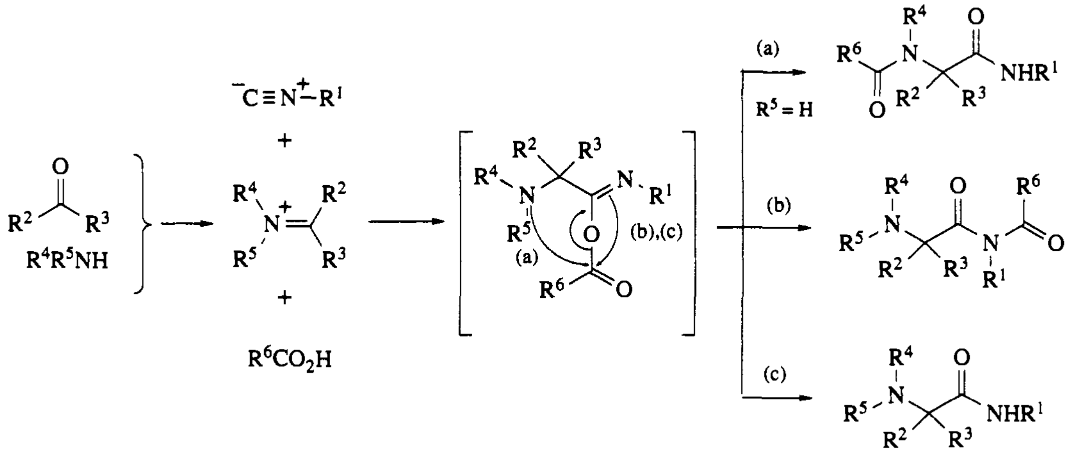
O
R2
R3
R4R5NH
⁻C≡N⁺–R1
+
R4
R2
N
R5
R3
+
R6CO2H
R2
R3
R4
N
N
R1
R5
O
(b),(c)
(a)
R6
O
(a)
R5 = H
R4
O
R6
N
NHR1
O
R2
R3
(b)
R4
O
R6
R5
N
N
O
R2
R3
R1
(c)
R4
O
R5
N
NHR1
R2
R3

**Scheme 6**

Also, β-lactams are obtained in high yield by the reaction of β-aminocarboxylic acids with aldehydes and isocyanides.[324,326]

Tripeptides can be obtained in good yields by reacting primary amines with aldehydes leading to the intermediate Schiff base. Applying pathway (b; Scheme 6) with isocyanide amino acid esters and *N*-protected amino acids, the Ugi reaction occurs[322,323] with good yields (equation 37). Asymmetric induction on the new stereogenic centre (*) is low, but can be enhanced by the use of chiral amines.

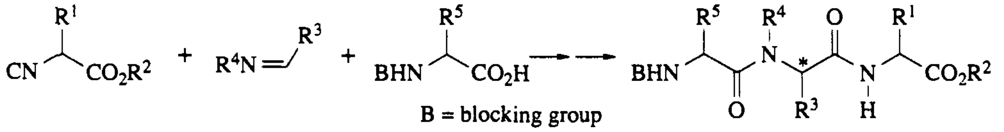
R1
CN
CO2R2
+
R3
R4N
+
R5
BHN
CO2H
B = blocking group
R5
R4
O
R1
BHN
N
*
N
CO2R2
O
R3
H

(37)

A stereochemical control of the Ugi reaction can be effected with carbohydrates as chiral templates (*e.g.* tetrakis(*O*-pivaloyl)galactosylamine), which gives rise to easily separable amides. From these a variety of non-natural amino acids can be derived after acidic hydrolysis.[327] The Passerini reaction,[328] related to the Ugi rearrangement, gives α-hydroxyamides. A modification of this reaction using titanium tetrachloride gives α-branched amides in high yields *via* *C*-metalated imidoyl chlorides[329] (equation 38).

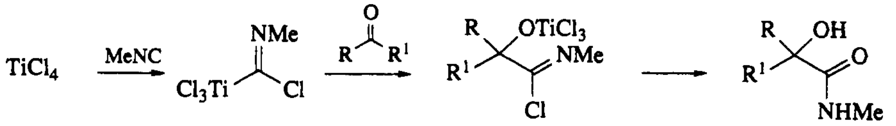
(38)

### 2.3.1.7.4 Miscellaneous

The amide acetal Claisen rearrangement[330] and the ynamine Claisen rearrangement[331,332] proceed *via* a common [3,3] sigmatropic shift of *N,O*-ketene acetals (equation 39) and lead to $\gamma,\delta$-unsaturated amides under mild conditions. Modification of this procedure involves the use of 3-(trimethylsilyl)allyl alcohols for the preparation of $\beta,\gamma$-unsaturated amides,[333] or conversion of propargyl alcohols to $\beta$-allenic amides, which may be rearranged to 2,4-dienamides.[334] Similarly, allylic and propargylic imidic esters[335] undergo stereospecific [3,3] sigmatropic rearrangement to allylic acetamides.

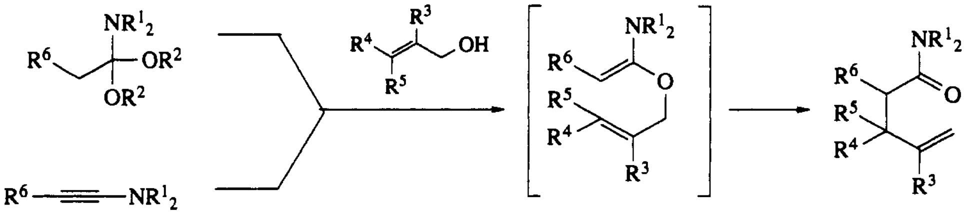
(39)

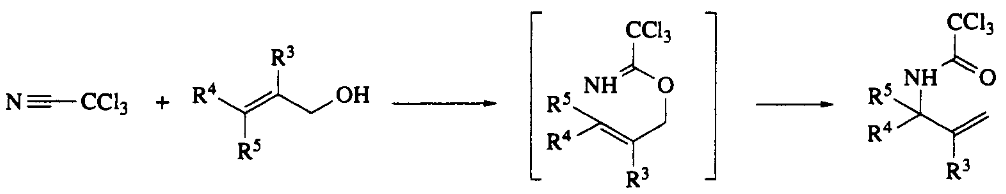
(40)

With trichloroacetimidates, 1,3-conversion of allylic alcohols to allylic amines proceeds smoothly (equation 40).

### 2.3.1.8 Construction of the Carbon Frame

In the Heck reaction, aryl, heterocyclic and vinyl halides[336,337] or aryl triflates[338] react with excess carbon monoxide and primary or secondary amines to give substituted amides, in the presence of a palladium(II) catalyst (equation 41). *Cis*- and *trans*-vinyl halides react stereoselectively.

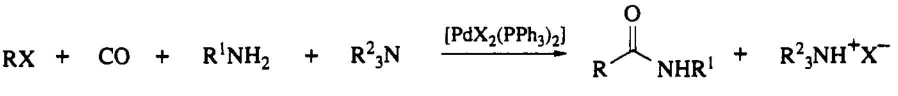

$$RX + CO + R^1NH_2 + R^2{}_3N \xrightarrow{[PdX_2(PPh_3)_2]} RC(O)NHR^1 + R^2{}_3NH^+X^- \quad (41)$$

Intramolecularly, insertion of carbon monoxide into vinyl halides bearing a secondary amino group yields $\alpha$-methylene five-, six- and seven-membered ring lactams.[339]

Catalytic double carbonylation of organohalogen compounds[340,341] or simple alkenes[342] needs higher CO pressures (10 atm at room temperature), and mainly provides $\alpha$-ketoamides.

Substituted benzyl alcohols can be converted with cobalt carbonyl to the homologous amides under mild conditions, even using sterically hindered secondary amines (equation 42).

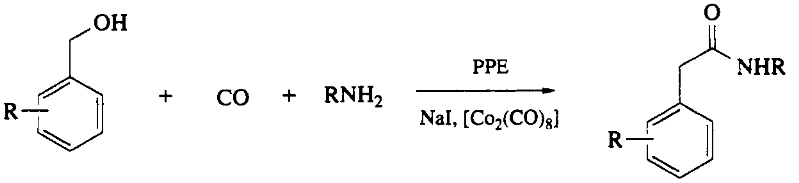
(42)

Vinyl bromides are directly aminocarbonylated by nickel carbonyl and amines.[343] Very similarly, $Rh_6(CO)_{16}$ and $Bu_4NCl$ as catalyst convert allylphosphates to β,γ-unsaturated amides *via* π-allylrhodium complexes (equation 43).[344] Although palladium(0) complexes are more reactive than rhodium(I) complexes, palladium(0) complexes undergo side reactions, like reductive elimination in the presence of carbon monoxide, and direct nucleophilic attack by amines.

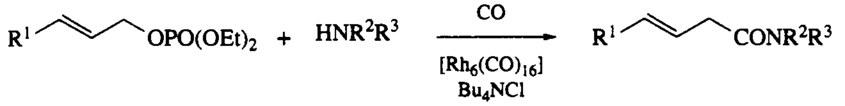

(43)

The Haller–Bauer reaction is applied to nonenolizable ketones which react with fresh sodium amide to form amides (equation 44).[345] Cleavage of aliphatic or alicyclic phenyl ketones to produce tertiary carboxamides is the most useful. With equivalent amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO) the reaction proceeds under milder conditions.[346]

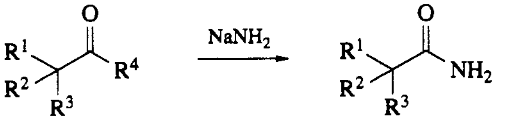

(44)

## 2.3.2 LACTAMS

### 2.3.2.1 Intramolecular Acylation of Amino Acid Derivatives

Generally, the formation of lactams follows the same activation procedures as those discussed in Section 2.3.1.1.

To minimize dimerization products, intramolecular condensations have to be carried out under carefully controlled conditions and in high dilution. The formation of small rings obeys the Baldwin rules (equation 45).[347]

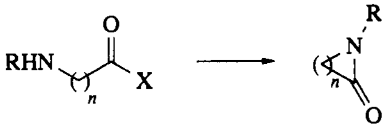

(45)

$n \geq 2$; X = OR, OH

Simple five-, six- and seven-membered lactams are obtained under cyclodehydration conditions by boiling ω-amino acids and alumina or silica gel in excess toluene.[348]

Metal compounds like organostannyl oxides[349] and titanium(IV) alkoxides[350] have been used in the synthesis of macrocyclic lactams.

Reduced copper–titanium catalysts convert ε-aminocapronitrile to ε-caprolactam.[351]

Intramolecular opening of *N*-(haloalkyl)azetidin-2-ones *via trans* amidation affords medium and unstrained ring azalactams.[352]

For the preparation of cyclic peptides, standard procedures are still the azide and the active ester method. In a variety of bicyclic analogs of somatostatin, azide coupling is applied twice and yields can be improved by catalysis with *N*-hydroxybenzotriazole.[353]

Cyclopeptide alkaloids are prepared in good yield by catalytic hydrogenation of pentafluorophenyl esters of ω-(*Z*)-aminocarbocyxlic acids. The slow release of the amino function under these conditions minimizes dimerization.[354]

Other masked forms of the ω-amino function include the azido function, which can be readily reduced by triphenylphosphine[355] and the nitro function, which can be reduced by standard hydrogenating procedures including an electrochemical process.[356]

### 2.3.2.2 Intramolecular Alkylation of Amide Derivatives

Cyclization of ω-halocarboxamides (equation 46) requires the use of metallic amides and hydrides under anhydrous conditions. Phase transfer catalysis with strongly basic ion exchange resins in 50% sodium hydroxide solution give four- to seven-membered lactams in good to excellent yield.[357]

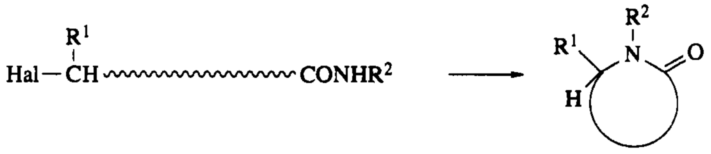

(46)

Reaction of *N*-alkylalkenamides with organoselenium compounds activates the double bond and gives rise to lactams (equation 47).[358]

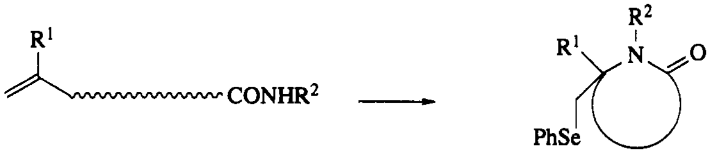

(47)

In total syntheses of β-lactam antibiotics, the formation of 2-azetidinones is crucial. In a biomimetic synthesis, the N—C4 bond is best closed by the open chain hydroxamate (equation 48),[359] because, depending on the different p$K_a$ values of the three potentially ionizable positions, only the ring-forming amide is ionized. β-halohydroxamates are cyclized by base treatment, whereas β-hydroxyhydroxamates cyclize *via* the Mitsunobu reaction (diethyl azodicarboxylate, $Ph_3P$).[360] More highly substituted precursors yield isomeric β-lactams after rearrangement.[361]

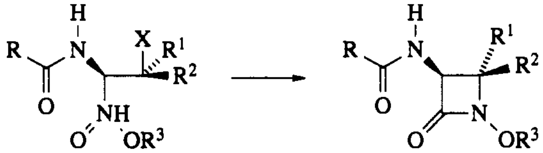

(48)

Under oxidative (iodosobenzene diacetate, $I_2$) and photolytic conditions some nonactivated amides from the alkaloid and steroid series form lactams *via* radical mechanisms.[362]

### 2.3.2.3 Construction of the Carbon Frame

The main principles of lactam, especially β-lactam, formation by cycloaddition, exemplified by equation (49),[363] are described in Volume 5, Part 2 of this series.

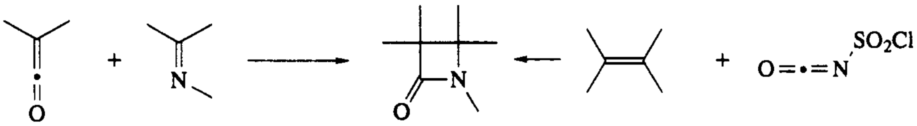

(49)

Chain elongation leading to ring enlargement of lactams takes place in the ZIP reaction (equation 50),[364] where derivatives of trimethylenediamines isomerize to lactams containing a secondary amine and a monosubstituted amide. The reaction sequence can be repeated several times to gain access to larger ring systems.

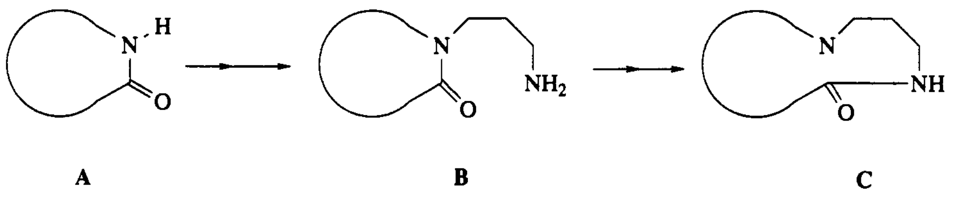

(50)

In a modified reaction sequence starting with cyclic α-nitro ketones the same reaction leads to nitrolactams, which can be converted to ketolactams in moderate yields (equation 51).[365] The same class of compounds is obtained when α-alkylamino-β-diketo derivatives are treated with base.[366]

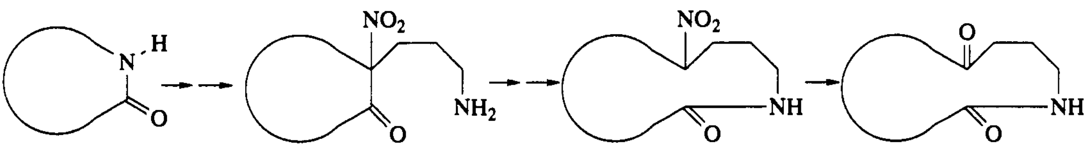

(51)

## 2.3.3 IMIDES

Imides are monoacyl derivatives of amides or lactams and are used as valuable intermediates in organic synthesis as well as in biologically active compounds like drugs, fungicides and herbicides.

The preparation of imides was reviewed recently and many methods are recommended.[3–6,367] Under somewhat drastic conditions (≈ 200 °C) dicarboxylic acids react with ammonia, or compounds which are able to produce ammonia like urea, thiourea, formamide, sulfamic acid, ammonium carbonate and others to form cyclic imides (equation 52).[367] Monoammonium salts of dicarboxylic acids give imides under pyrolytic conditions when distilled under reduced pressure.[368]

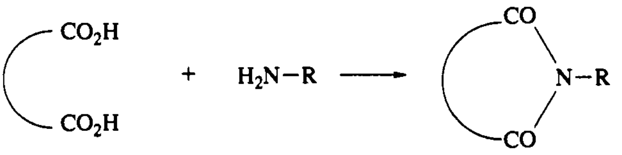

(52)

Ammonia and amines react with partially or fully activated carboxylic acid derivatives (acylating reagents) like acid anhydrides, acid halides, ammonium salts of monoesters, monoamides with heating, diesters under basic conditions and dinitriles after partial hydrolysis.[367]

Intramolecular cyclization occurs with carboxylic acid nitriles, amide nitriles, and ester amides under strongly basic and anhydrous conditions.

To avoid gaseous ammonia dicarboxylic anhydrides are heated with a slight excess of urea, until the cessation of gas evolution indicates completion of the reaction.[368]

Under milder, neutral conditions, organometallics like 1,1-dimethylstannocene (equation 53) react as Lewis acid and dehydrating reagents at room temperature with cyclic anhydrides and amines.[369]

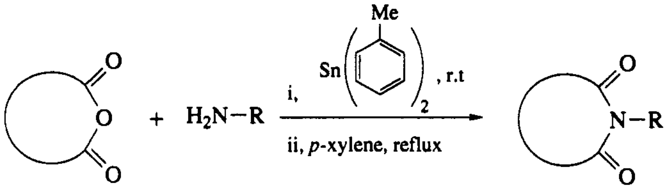

(53)

Acylation of amide bonds in peptides can be accomplished by silylation with trimethylsilyl chloride followed by treatment with acid chlorides.[370] A modified procedure has been applied to acylation of the sensitive β-lactam antibiotic cephamycin, where silylamides like trimethylsilylurethane trap generated HCl (equation 54).[371]

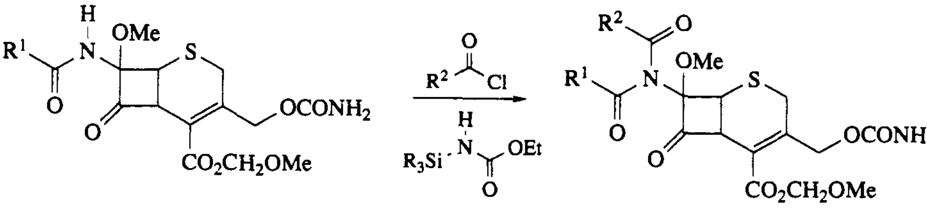

(54)

Diketenes react with carboxamides in the presence of trimethylsilyl iodide to yield *N*-acetoacetylcarboxamides (equation 55).[372]

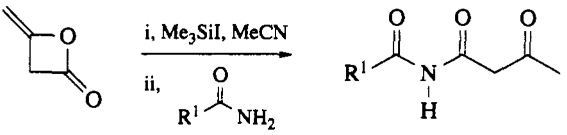

(55)

With the powerful formylation reagent *N*,*N*-diformylacetamide imides are obtained from amides or lactams in good yield (equation 56).[373] Oxidation reactions also have found some application in the synthesis of imides. For example, catalytic amounts of ruthenium tetroxide and 10% aqueous $NaIO_4$ as cooxidant in an optimized reaction medium (ethyl acetate–water) oxidize acyclic amides to imides.[374] The reaction rate is inversely related to the electron-withdrawing power of the acyl group, *i.e.* the electron density at the nitrogen atom (equation 57).

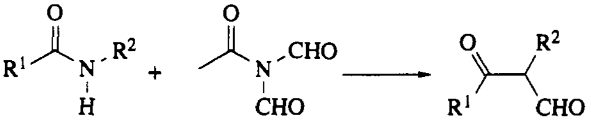

(56)

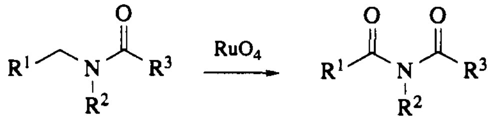

(57)

According to the same procedure, *N*-alkyllactams are converted to cyclic imides, where the position of the new carbonyl group depends on the ring size of the lactam.[375] Racemization of chiral *N*-acyl-pyrrolidines or -piperidines can be ruled out.[376,377]

Electrochemical anodic oxidation of amides and *N*-alkyllactams can be carried out with *N*-hydroxyphthalimide as mediator.[378] Oxidation takes place predominantly at the endocyclic carbon α to the nitrogen. The susceptibility of five-membered rings to oxidation is much higher than that of six-membered rings.

A photocatalytic oxidation takes place in a suspension of titanium(IV) oxide and five-membered or six-membered ring lactams.[379]

Reaction of nitrones with aroyl chlorides in the presence of triethylamine yields *N*,*N*-diacylamines (equation 58).[380] The reaction can be rationalized by formation of an aroyloxy(benzylidene)ammonium chloride, with elimination of the carboxylic acid and readdition of carboxylate to the nitrilium ion followed by 1,3-acyl shift to give the *N*,*N*-diacylamine.

Transition metal complexes are used as catalysts and as reagents in the synthesis of imides. Molybdenum hexacarbonyl activates strained aziridines and allows the nucleophilic attack of carbanions. Intramolecular rearrangement and a final oxidation yields imides completely stereospecifically (equation 59).[381] Dicobalt octacarbonyl catalyzes the conversion of β,γ-unsaturated amides to imides in the presence of carbon monoxide (equation 60).[382]

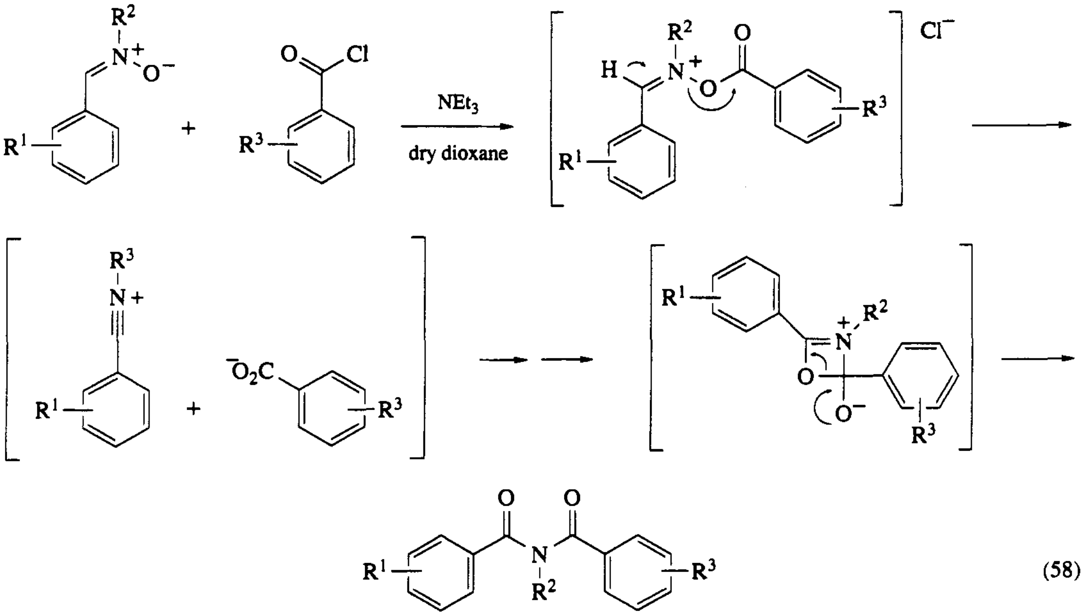

(58)

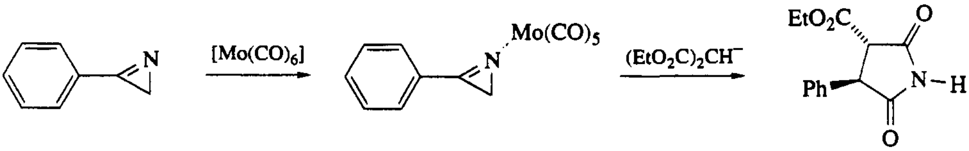

(59)

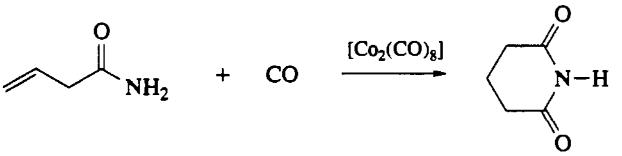

(60)

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# 2.4

# Synthesis of Thioamides and Thiolactams

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## 2.4.1 INTRODUCTION

The size difference between carbon and sulfur atoms leads to relatively inefficient overlap of π-orbitals in the C=S bond. Consequently, thiocarbonyl compounds are in general highly reactive and have a tendency to di-, oligo- or poly-merize. This is particularly true for thioaldehydes, thioketones,[1] and thioketenes.[2] In contrast, thioamides (**1**) are usually perfectly stable and can be handled without problems. This stability can be understood in terms of a pronounced resonance interaction between the C=S π-bond and the nonbonding electron pair on nitrogen. The analogous electron delocalization prevails in thiolactams.[3]

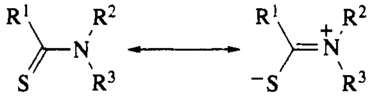

(**1**)

A large body of work has been directed toward synthesis and applications of thioamides.[4–7] The most important uses are as synthetic intermediates[5,8–10] and in heterocyclic synthesis.[5,11,12] Among the wealth of synthetic methods that lead to thioamides, thioacylation routes are certainly of prime importance.

Alternatively, for *N*-monosubstituted thioamides, methods based on nucleophilic addition of hydride, carbanions, or cyanide to isothiocyanates are available,[4,5,7] and, quite often, thionation of the corresponding amides provides a convenient route to thioamides (*cf.* Volume 6, Chapters 4.1 and 4.3).[13]

## 2.4.2 THIOACYLATION OF AMINES

### 2.4.2.1 Thioacylation with *O*-Alkyl Thiocarboxylates

Nucleophilic attack of ammonia or of a primary or secondary amine on an *O*-alkyl thiocarboxylate (**2**) provides a formally straightforward approach to thioamides and a number of examples have been reported (equation 1).[14,15] However, some limitations should be noted. Thus, there is a tendency of esters (**2**) to rearrange to their *S*-alkyl isomers on heating (*cf.* Volume 6, Chapter 2.5)[15] and these yield amides with amines rather than thioamides. Besides, excess primary amine will lead to amidine formation, or the tetrahedral intermediate of the substitution reaction may break down to an imidate rather than a thioamide (*cf.* Volume 6, Chapter 2.7). These unwanted side reactions are favoured in polar, protic solvents such as ethanol. In contrast, THF has proven to be particularly useful in the synthesis of tertiary thioamides according to equation (1).[14] For improved reactivity in the preparation of *N*-aryl derivatives and milder reaction conditions, it is advantageous to employ the amine in the form of its Mg salt.[14]

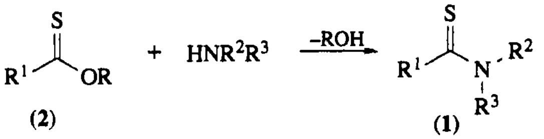

(1)

No activation is required in the synthesis of thioformamides using HCSOEt; this particularly reactive thioester allows one to work at 0 °C and offers the best route to the unsubstituted thioformamide (**1**; $R^1 = R^2 = R^3 = H$; 90%)[16] or *N*-alkylthioformamides.[16,17] This reagent has also been successfully employed in the thioformylation of hydroxylamines to give thioformohydroxamic acids (**1**; $R^1 = H$, $R^2 = OR^4$)[18] and, in a basic medium, also of hydrazines to give thioformohydrazides (**1**; $R^1 = H$, $R^2 = NR^4R^5$).[19]

Using primary aliphatic amines, ring opening of isocoumarin-derived thiolactones (**3**) according to equation (2) offers a convenient access to *o*-(2-oxoalkyl)thiobenzamides (**4**) with yields in the 80% range; aromatic amines give side reactions.[20]

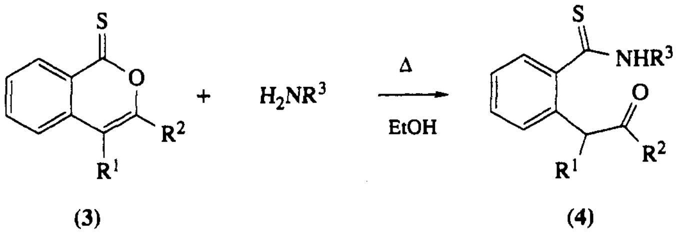

(2)

*O*-Methyl thiocarboxylates are very suitable for the *N*-thioacylation of *N*-unprotected amino acids. Thus, shaking a heterogenous mixture of PhCSOMe in ether and the amino acid in aq. NaOH gives good yields of *N*-thiobenzoylated material.[21] Using *O*-alkyl thiocarboxylates of amino acids (**2**; $R^1 = R^2NHCHR^3$), the approach has been extended to synthesize endothiopeptides such as (**5**);[22-24] formation of imidates may interfere with the desired process.[23] The reaction has been carried out in water/THF using $Na_2CO_3$[24] or as shown in equation (3).[22]

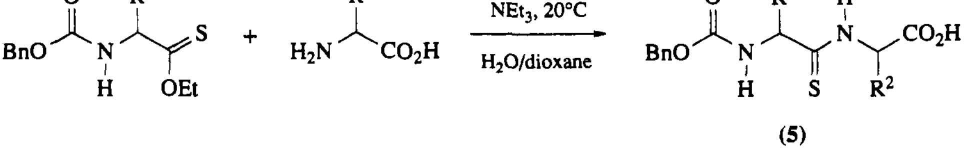

(3)

$R^1 = R^2 = Me$, 45%; $R^1 = Bn$, $R^2 = Me$, 57%

### 2.4.2.2 Thioacylation with 3*H*-1,2-Dithiol-3-ones

Cleavage of the S—S bond in 3*H*-1,2-dithiol-3-ones (**6**) by nucleophiles liberates the latent thioamide group. Piperidine in DMF or DMSO[25] and Grignard reagents[26,27] have been employed and allow synthesis of malonic acid monothioamides (Scheme 1).

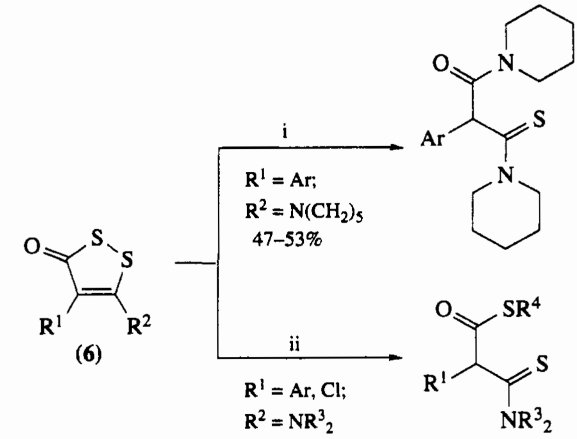

i, $HN(CH_2)_5$; ii, $R^4MgBr$ in THF, then quench with $H_2O$

**Scheme 1**

### 2.4.2.3 Thioacylation with Dithiocarboxylic Acids

Contrary to carboxylic acids which, under normal conditions, only give salts with amines, dithiocarboxylic acids, $RCS_2H$, are quite reactive in nucleophilic displacement reactions. However, the compounds are unpleasant to handle and, due to their limited stability, often give only low yields of thioamides in the reaction with amines.[1,28,29] The approach was successfully employed in the synthesis of thiobenzoyl azolides, *e. g.* in the formation of (**7**) according to equation (4).[30]

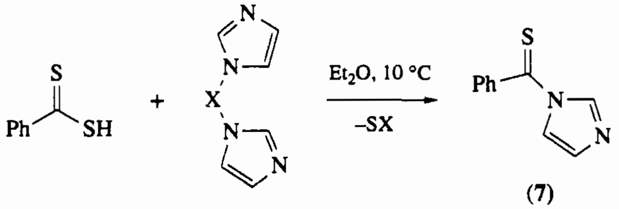

(**7**)

X = CO, 78%; X = CS, 77%; X = SO, 64% (4)

Phenyldithioacetic acid (**8**) allows thioacylation of the 7-amino group in penicillanate (**9**); the resulting highly nucleophilic thioamide (**10**) gives intramolecular trapping of the sulfenic acid, RSOH, which is in thermal equilibrium with the thiazolidine *S*-oxide moiety in (**10**; Scheme 2).[31]

Thioacylation reactions with dithiocarboxylic acids are not limited to amines, but, employing the Mg salt, can also be carried out with hydroxylamine to give thiohydroxamic acids[18] or with hydrazine and some substituted hydrazines to provide thiohydrazides.[19]

The reaction of CH acidic compounds with $CS_2$ in the presence of excess base yields dianions of dithiocarboxylic acids.[32] Starting from camphor, neutralization with HCl and addition of primary amines yields 3-oxonorbornanethiocarboxamides (**11**) with undefined stereochemistry (Scheme 3).[33]

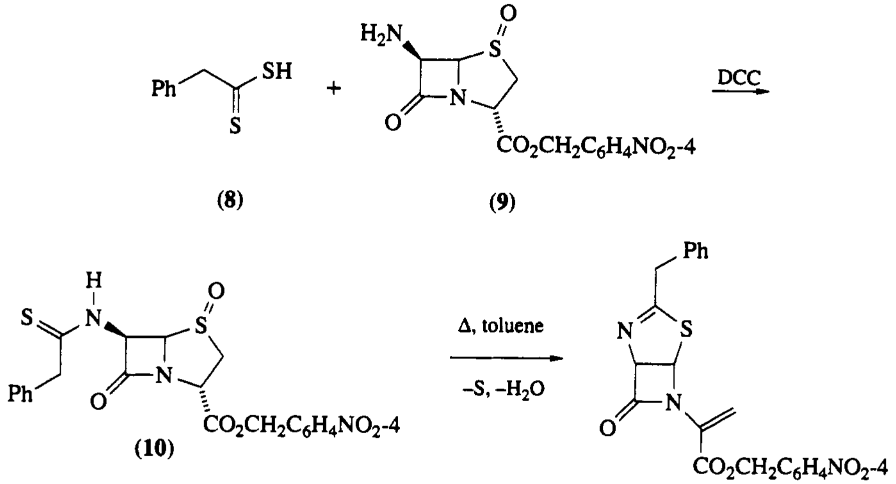

**(8)** **(9)** **(10)**

**Scheme 2**

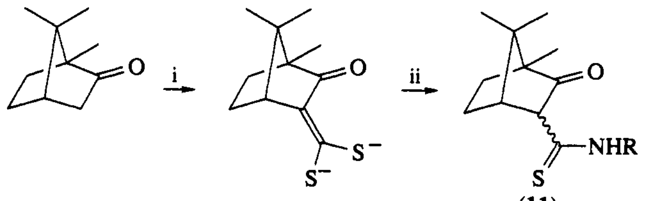

**(11)**

i, $NaNH_2$, $CS_2$; ii, HCl, then $RNH_2$ or $ArNH_2$ in $Et_2O$ or PhH

**Scheme 3**

### 2.4.2.4 Thioacylation with Thioacyl Chlorides

Thioacyl chlorides, RCSCl, are powerful thioacylating agents as is obvious from the quantitative thiobenzoylation of the only moderately nucleophilic nitrogen in thiocarbamate (**13**; equation 5).[34] However, severe limitations are the difficult accessibility of thioacyl chlorides and their thermal lability.[35] Even if they are prepared from dithiocarboxylic acids using an improved procedure,[36] only thioaroyl chlorides, particularly PhCSCl (**12**), can be handled sufficiently easily to be used in synthetic work. Thus, various azoles react with (**12**) to furnish *N*-thiobenzoyl azolides (**14**) in the presence of excess azole or $NEt_3$ (equation 6); a particularly clean and fast reaction is achieved if *N*-silylated azoles are employed.[30] However, considering the fact that the chloride has to be prepared from the dithiocarboxylic acid, the approach of equation (4) presents a shortcut to the products.

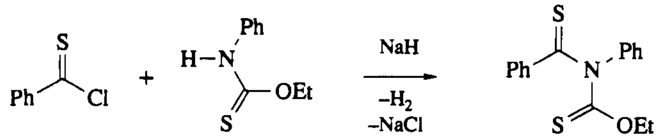

**(12)** **(13)**

(5)

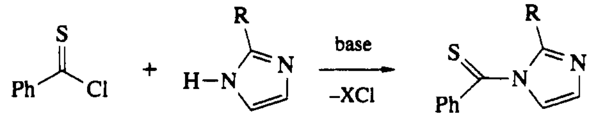

**(12)** **(14)**

R = H, 87%; R = Me, 47%

(6)

In contrast to thioacyl chlorides, thiophosgene, $CSCl_2$, is readily accessible and conveniently handled making it an important reagent in the synthesis of thiocarbamoyl chlorides (**15**; $ClCSNR_2$),[37] *O*-alkyl thiourethanes ($ROCSNR'_2$),[38] and thioureas ($R_2NCSNR_2$) (*cf.* Volume 6, Chapter 2.8).[39,40]

On the other hand, thiocarbamoyl chlorides (**15**) may be used in thioamide synthesis, though *via* carbon–carbon bond formation in Friedel–Crafts-type reactions (*cf.* Volume 2, Chapter 3.1). The approach is limited to fairly electron-rich aromatics such as alkylbenzenes, anisole, and furan, but fails for benzene; equation (7) gives some details.[41,42] Phenol does not require a Lewis acid catalyst in the reaction with $H_2NCSCl$, but gives a mixture of 2-/4-hydroxythiobenzamides along with *O*-phenyl thiocarbamate.[43]

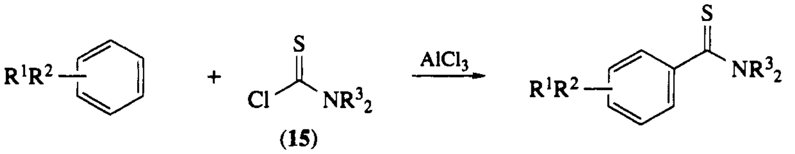

(**15**)

(7)

$R^1 = R^3 = Me, R^2 = H$, 53% (ref. 41); $R^1 = R^2 = Me, R^3 = H$, 61% (ref. 42);
$R^1 = OMe, R^2 = H, R^3 = Me$, 77% (ref. 41); $R^1 = R^2 = OMe, R^3 = Me$, 56% (ref. 41)

Another application of thiocarbamoyl chlorides (**15**) and related activated thiocarbonic acid derivatives in thioamide synthesis is found in their reaction with carbanions of highly CH acidic compounds $EWG_2CH_2$ to give thioamides $EWG_2CHCSNR_2$.[7,44]

### 2.4.2.5 Thioacylation with Dithiocarboxylates

Dithiocarboxylates, $R^1CSSR^2$, give a faster reaction with amines than *O*-alkyl thiocarboxylates (**2**; *cf.* Section 2.4.2.1).[45] As shown in equation (8), this pronounced reactivity may lead to an undesired *in situ* reaction with the liberated ammonia to give a primary thioamide, when the ester is generated by thiolysis of a thioimidate.[23]

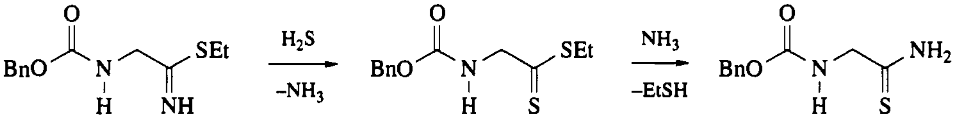

(8)

On the other hand, dithiocarboxylates allow the chemoselective thioacylation of the amine moiety in tryptamine or tryptophane (**16**; equation 9).[46]

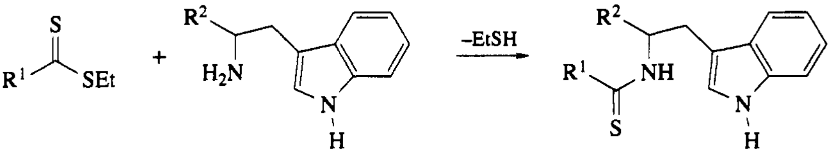

(**16**)

$R^1$ = Me, Br, Ph; $R^2 = H, CO_2Me$

(9)

Dithiocarboxylates are particularly useful reagents in the thioacylation of the terminal amino group in peptides. Combination with a subsequent cleavage by anhydrous TFA results in a modified Edman degradation[47] and a protocol has been worked out with conditions that are compatible with the ones required for an automatic sequential analysis (Scheme 4).[48]

By analogy with the reaction of equation (3) *N*-protected dithiocarboxylates of amino acids react with amino acids or peptides with a free $NH_2$ group to give endothiopeptides.[23,49] A systematic study of thio analogs of enkephalin revealed that attempted removal of benzyloxycarbonyl protective groups with HBr/HOAc results in decomposition, but that the t-BOC group can be cleanly cleaved from the product using liquid HF/anisole.[23] Therefore, dithiocarboxylates, t-$BOCNHCHR^1CSSR^2$, appear to be the reagents of choice in endothiopeptide synthesis.

Thioamide synthesis from dithiocarboxylates and amines under basic conditions gives thiols as rather unpleasant parallel products. This problem is avoided by using *S*-thioacylated thioglycolic acids (**17**), as

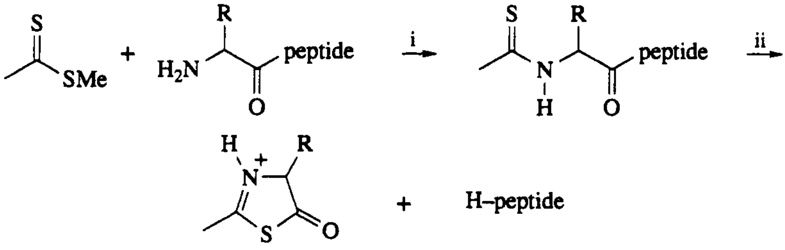

i, $\text{NEt}_3$ or $\overset{+}{\text{H}}\text{NEt}_3\text{OAc}^-$ in DMF; ii, anhydrous TFA

Scheme 4

was first suggested by Holmberg.[50] As shown in equation (10) these esters display the usual reactivity of dithiocarboxylates,[28,51,52] but displacement reactions yield the thiol (**18**), which is soluble in aqueous base and so readily disposed of. However, esters (**17**) may fail to thioacylate sterically hindered amines and the derivative with $R^1$ = H is too labile to be used in thioformylations.

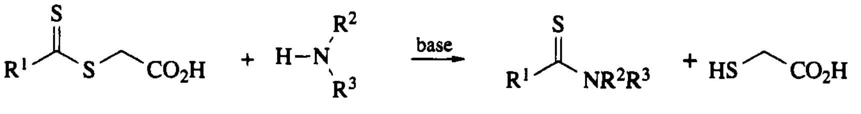

(10)

(**17**) (**1**) (**18**)

Several uses of the reaction in equation (10) for the *N*-thioacylation of amino acids, their esters, or amides have been reported.[21,53,54] It is noteworthy that these reactions occur without racemization allowing a CD study of *N*-thioacyl amino acids.[55] Moreover, the reaction of equation (10) is not limited to amines or amino groups, but has also been employed to thioacylate hydrazines and hydroxylamines to give thiohydrazides[19,56] and thiohydroxamic acids,[18] respectively.

In a heterocyclic environment, the dithiocarboxylate functionality may give a more complex reaction pattern, as shown by dithiolactones (**19**). Here, secondary aliphatic amines lead to ring cleavage providing 2-(thioacylamino)thiobenzamides (**20**),[57] whereas primary aliphatic or aromatic amines give thiolactams (**21**; Scheme 5).[58]

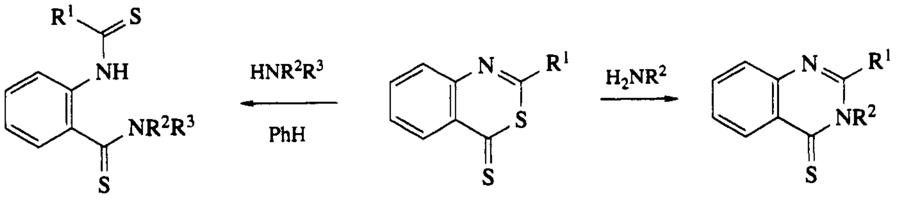

(**20**) (**19**) (**21**)

Scheme 5

In accord with the special reactivity of a dithiocarboxylate moiety, *O*,*S*-dialkyl dithiocarbonates, ROCSSR′, yield *O*-alkyl thiourethanes, ROCSNR′$_2$, on addition of amines.[38] Similarly, trithiocarbonates, $(\text{RS})_2\text{CS}$, yield thioureas.[39,40,59]

### 2.4.2.6 Thioacylation with Thioamides

Whether transamidation of a thioamide by addition of an amine is feasible depends on the interplay of the nucleophilicity of the incoming amine and the leaving-group ability of the amine to be replaced. The reaction is of particular importance in using some *N*-thioacylated heterocycles such as the benzoxazole derivative (**22**),[60] the succinimide (**23**),[61] and azoles (**24**) (equations 11–13).[30] The last mentioned approach appears to be the most general and proceeds under particularly mild conditions; in contrast to the reaction of equation (10), the method allows the thiobenzoylation of *N*-methylaniline, PhNHMe, using the imidazole derivative (**24**; $R^3$ = Me). The reactivity of the reagent can be further increased by employing azoles with more ring nitrogens and could be extended to the synthesis of thiohydrazides.[30]

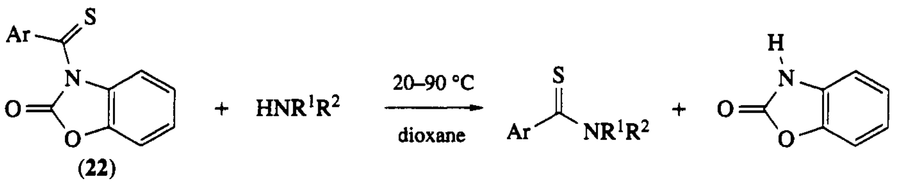

**(22)**

(11)

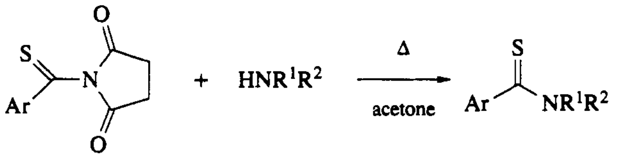

**(23)**

(12)

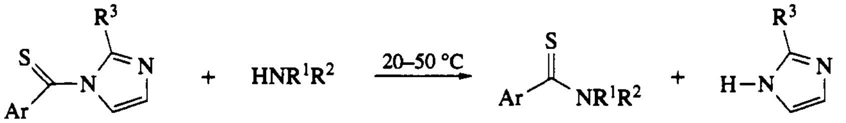

**(24)**

(13)

Cleavage of the *N*-acyl thioamide moiety in the 4-thiouracil (**25**) gives an example for the conversion of a thiolactam into a thioamide (yield 25%; equation 14).[62]

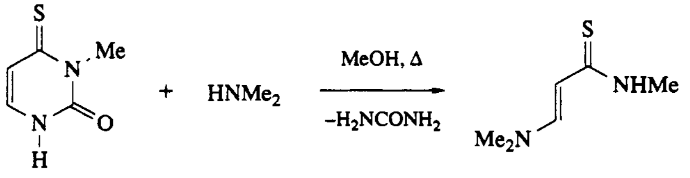

**(25)**

(14)

Heating of dithiooxamide (**26**) with primary amines yields the corresponding *N*-alkyl derivatives (**27**);[63] the reaction is catalyzed by acid with even $CO_2$ being effective (equation 15).[5,64]

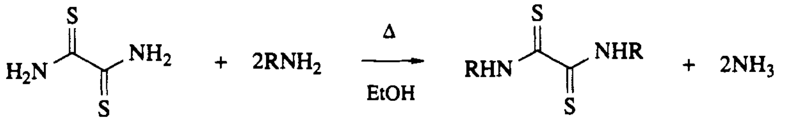

**(26)** **(27)**

(15)

In a number of reactions thioamides are converted into other thioamides by C—C bond formation (Scheme 6). Examples from Seebach's umpolung chemistry include *C*-lithiation of $HCSNMe_2$ and subsequent reaction with electrophiles to give (**28**)[8] and deprotonation of one of the *N*-methyl groups in $Bu^tCSNMe_2$ and again electrophilic addition to yield products (**29**).[9]

Another possibility to obtain thioamides from thioamides is *via* electrophilic attack in the α-position (Scheme 6). Thus, aldol-type reactions are feasible and proceed with high *erythro* selectivity providing (**30**),[65] or even allowing optically active products (*cf.* Volume 2, Chapter 1.6).[66] Heating with a formamide *O,N*-acetal gives an α,β-unsaturated thioamide (**31**) in a sequence of electrophilic attack and elimination.[67,68]

Finally, thioamides can be modified *via* their *S*-silylated derivatives (**32**). With Lewis acid catalysis, addition of a Schiff base yields β-aminothioamides (**33**) as a mixture of diastereomers (Scheme 7).[69]

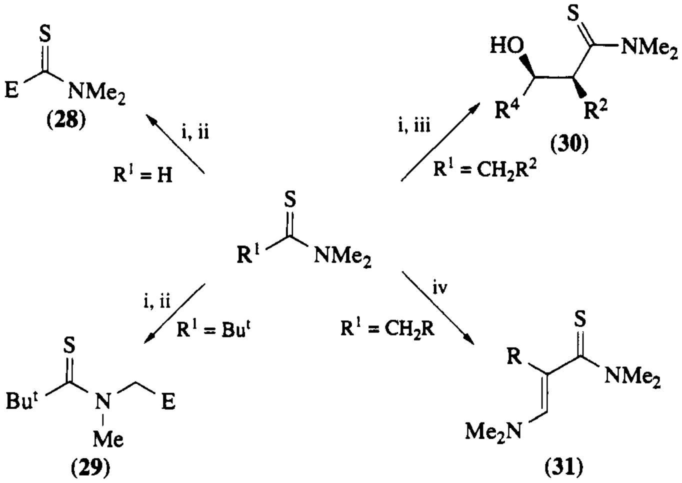

i, LDA; ii, $E^+$; iii, $R^4CHO$; iv, $(Me_2N)CHOBu^t$

**Scheme 6**

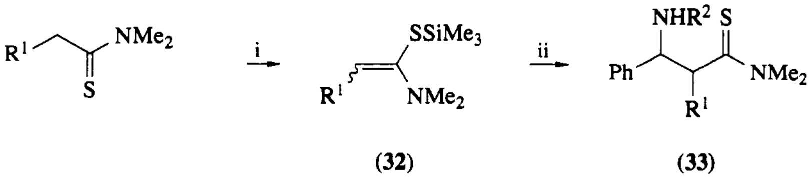

i, LDA, then $Me_3SiCl$; ii, $PhCH{=}NR^2$, $ZnBr_2$ or $SnCl_4$, then $H^+$

**Scheme 7**

### 2.4.2.7 Thioacylation with Thioketenes or Thioketene Equivalents

Thioketenes (**34**) have a nonstabilized C═S group and consequently, except for sterically hindered examples,[70,71] exhibit a high tendency to oligo- or poly-merize.[2] Their application in synthesis depends on the availability of convenient routes to generate these species and, at least for the more elusive examples, trap them *in situ*. Recently, a number of routes to thioketenes have been developed, allowing them now to be considered as useful reagents.[2] The most handy methods to obtain thioketenes are based on: the flash-vacuum pyrolysis of 1,2,3-thiadiazoles (**35**);[72,73] the thionation of sterically hindered acyl chlorides (**36**);[70,71] the [3 + 2] cycloreversion of modified 2-alkylidene-1,3-dithiolanes (**37**);[74] and the 3,3-sigmatropic rearrangement of alkynyl allyl sulfides (**38**; Scheme 8).[75]

Thioketenes (**34**) are highly electrophilic and give a smooth reaction with ammonia or amines. In fact, addition of a secondary amine offers the best way to scavenge a suspected thioketene.[2] But the approach also deserves interest from the point of view of thioamide synthesis as it allows very mild and nonreducing conditions, tolerating the presence of sensitive additional functional groups such as cyano, nitro, or sulfonyl residues (equation 16).[74]

In the reaction of alkynyl thiolates (**39**) with excess diethylamine, the amine provides the proton to generate an aldothioketene (**40**) and, at the same time, serves as the trapping reagent (Scheme 9).[76]

Bis(trimethylsilyl)thioketene (**41**) gives a smooth reaction with amines, but one silyl group is always displaced in the process yielding thioamides (**42**; equation 17).[77]

Alknyl silyl sulfides, $R^1C{\equiv}CSSiR^2_3$, which are readily obtained by silylation of anions (**39**), react as thioketene equivalents. Thus, β-thiolactams are formed in the reaction with C═N systems (*cf.* Volume 5, Chapter 2.2)[3] and thioamides on addition of amines;[78,79] equation (18) shows a typical example.[79] This approach has great promise for the thioacylation of very sensitive natural products.

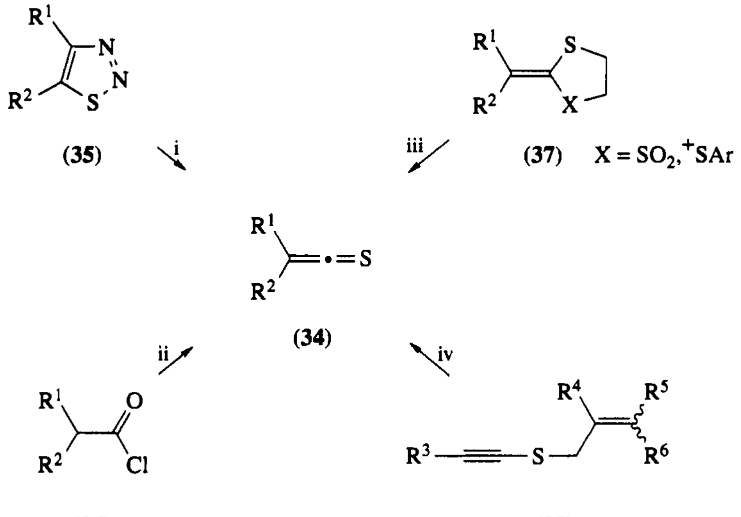

**(35)** **(37)** X = $SO_2$, $^+SAr$

**(34)**

**(36)** **(38)**

i, 530 °C, $10^{-4}$ Torr; ii, $P_2S_5$, Py; iii, base; iv, heat

**Scheme 8**

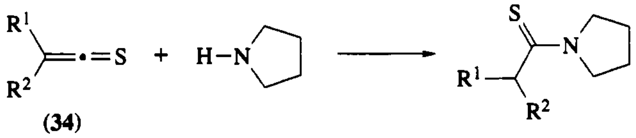

**(34)**

(16)

$R^1 = NO_2$, $R^2 = H$, 53%; $R^1 = PhSO_2$, $R^2 = H$, 38%; $R^1 = NC$, $R^2 = Ph$, 82%

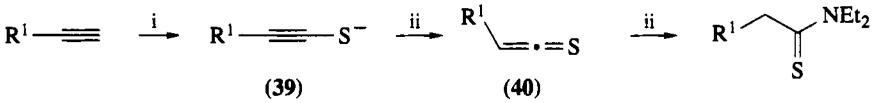

**(39)** **(40)**

i, $LiNEt_2$, then $S_8$; ii, $HNEt_2$

**Scheme 9**

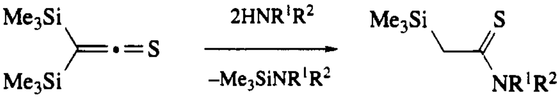

$2HNR^1R^2$
$-Me_3SiNR^1R^2$

**(41)** **(42)**

(17)

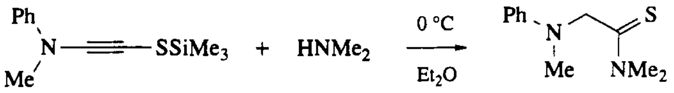

45%

(18)

### 2.4.2.8 Thioacylation with Carbon Disulfide

At elevated temperatures and under pressure, carbon disulfide converts triethylamine into thioformamide (**43**) in 49% yield (equation 19); similarly, the reagent yields thioformamides (23–36%) from the corresponding amides.[80]

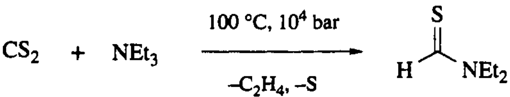

$CS_2$ + $NEt_3$
100 °C, $10^4$ bar
$-C_2H_4$, –S
S
H
$NEt_2$

(**43**)

(19)

Thiolactams (**46**) are isolated on addition of carbon disulfide to cyclic nitrones (**44**); the products are formed in a sequence of [3 + 2] cycloaddition giving (**45**) and cycloreversion (equation 20).[81]

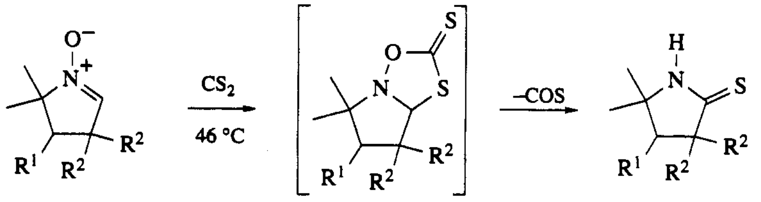

$O^-$
$N^+$
$R^2$
$R^1$
$R^2$
$CS_2$
46 °C
O
S
N
S
$R^2$
$R^1$
$R^2$
–COS
H
N
S
$R^2$
$R^1$
$R^2$

(20)

(**44**) (**45**) (**46**)

$R^1 = R^2 = H$, 45%; $R^1 = H$, $R^2 = Me$, 62%; $R^1 = Ph$, $R^2 = H$, 62%

Use of carbon disulfide has particular significance for the synthesis of dithiocarbamates[82] and thioureas in thioacylation reactions.[39,40,82]

## 2.4.3 THIOLYSIS OF IMIDOCARBOXYLIC ACID DERIVATIVES

### 2.4.3.1 Thiolysis of Imidoyl Chlorides

Thiolysis of imidoyl chlorides offers a straightforward route to thioamides. The formation of *N*-sulfonyl thioamides (**47**) in equation (21) gives an example,[83] but the method works particularly well for the synthesis of *N,N*-disubstituted thioamides including thiolactams from the corresponding imidium chlorides, $R^1C({=}NR^2)Cl$.[84] Quite often, the chlorides are generated *in situ* from the corresponding amides by the action of $COCl_2$ so that the overall process represents an alternative to the thionation of amides.[13] In a useful modification, $HS(S)P(OEt)_2$ is used to achieve the thiolysis and allows very high yields of thiobenzamides and of dithiooxamides; nitro-substituted derivatives are not reduced under the reaction conditions.[85] Thiourea has been employed to convert α-chlorine-substituted azines (**48**) into thiolactams (**50**); as shown in equation (22), thiuronium salts (**49**) are supposed to be intermediates in this transformation.[86]

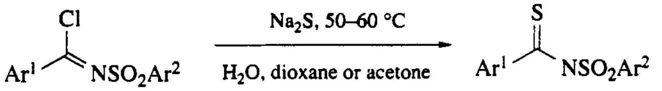

Cl
$Ar^1$
$NSO_2Ar^2$
$Na_2S$, 50–60 °C
$H_2O$, dioxane or acetone
S
$Ar^1$
$NSO_2Ar^2$

(**47**)

(21)

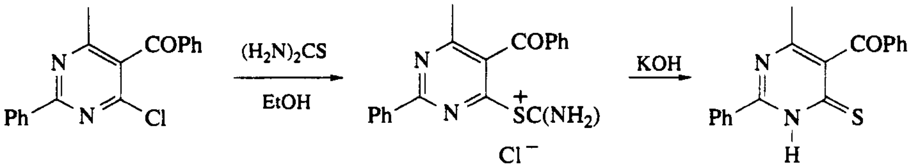

N
COPh
Ph
N
Cl
$(H_2N)_2CS$
EtOH
N
COPh
Ph
N
$\overset{+}{S}C(NH_2)$
$Cl^-$
KOH
N
COPh
Ph
N
S
H

(22)

(**48**) (**49**) (**50**)

The reaction of tertiary amides with phosgene immonium chloride (**51**) allows this approach to be extended to the synthesis of thiomalonamides (**52**; equation 23).[87]

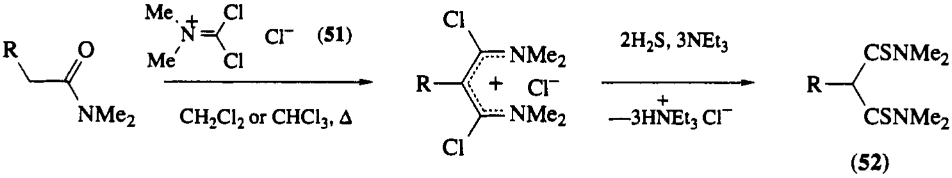
Me
N
Cl
Cl⁻ (51)
Me
Cl
R
O
NMe2
CH2Cl2 or CHCl3, Δ
Cl
NMe2
R
+ Cl⁻
NMe2
Cl
2H2S, 3NEt3
—3HNEt3 Cl⁻
CSNMe2
R
CSNMe2
(52)

(23)

R = H, 70%; R = Et, 83%; R = Ph, 55%

The thiolysis of imidoyl chlorides has proven to be particularly useful in the synthesis of α-chlorothioamides. Thus, chlorine can be added to trichlorovinylamines (**53**) and the resulting imidium salt (**54**) thiolyzed to give trichlorothioacetamides (**55**; equation 24).[88] Similarly, addition of HCl and $H_2S$ to di- or tri-chlorovinylamines (**53**) yields tertiary mono- and di-chlorothioacetamides, respectively.[88] In a recent modification, α,α-dichlorination of propionimidium salt (**56**) giving (**57**) is achieved and, subsequently, thiolysis and dehydrohalogenation using $AlCl_3$-modified triethylamine to obtain α-chlorothioacrylamides (**58**; equation 25).[89]

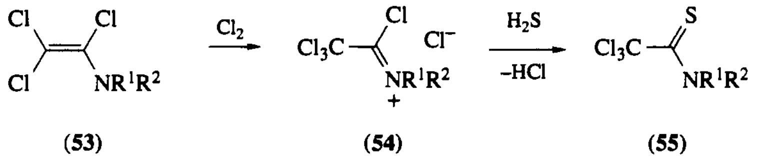
Cl
Cl
Cl
NR1R2
(53)
Cl2
Cl
Cl3C
Cl⁻
NR1R2
+
(54)
H2S
-HCl
S
Cl3C
NR1R2
(55)

(24)

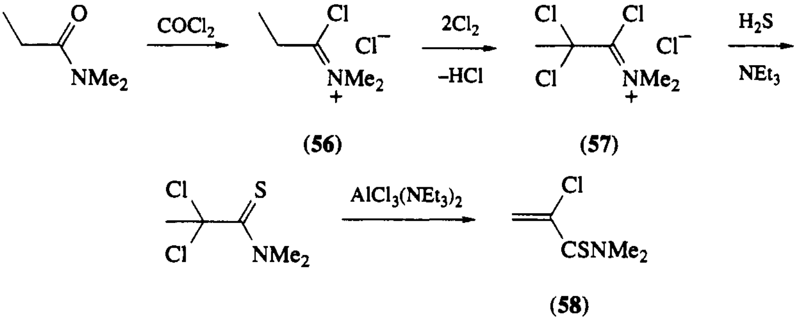
O
NMe2
COCl2
Cl
Cl⁻
NMe2
+
(56)
2Cl2
-HCl
Cl
Cl
Cl
Cl⁻
NMe2
+
(57)
H2S
NEt3
Cl
S
Cl
NMe2
AlCl3(NEt3)2
Cl
CSNMe2
(58)

(25)

The reaction of benzimidium chlorides (**59**) with dithiocarbamate (**60**) yields a thioimidate (**61**) as primary product which rearranges in a Chapman-type interchange of heteroatoms to give the thioacylated thiobenzamide (**62**) in almost quantitative yield (equation 26).[34]

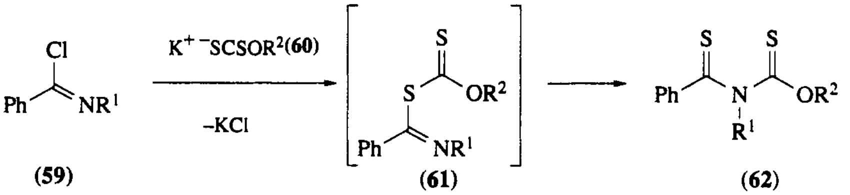
Cl
Ph
NR1
(59)
K+ ⁻SCSOR2(60)
-KCl
S
S
OR2
Ph
NR1
(61)
S
S
Ph
N
OR2
R1
(62)

(26)

### 2.4.3.2 Thiolysis of Imidates

The most common source of imidates is nitriles (*cf.* Volume 6, Chapter 2.7) and, as these can be directly transformed into thioamides (*cf.* Section 2.4.3.4), this one-step approach is usually preferred. Moreover, depending on the reaction conditions and the substitution pattern, thiolysis of imidates may give thioesters rather than thioamides (*cf.* Volume 6, Chapter 2.5).[21] However, some high-yield applications of imidates in thioamide synthesis have been reported and are detailed in equations (27)[90] and (28).[91]

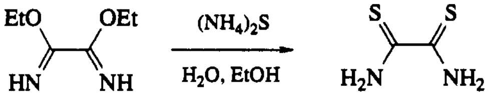

(26)

(27)

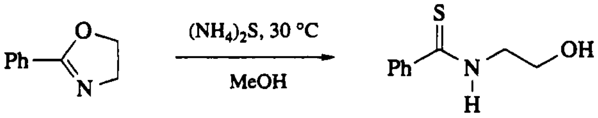

(28)

*N*-Substituted thiolactams (**65**) are obtained from lactams (**63**) in 55–100% yield by alkylation with Meerwein reagent and subsequent thiolysis of the resulting imidium salt (**64**; equation 29).[92] The approach has been extended to other thiolactams and acyclic examples employing a cyanohydrin derivative (**66**; equation 30).[93] Similarly, *N*,*N*-acetals of formyl cyanide, $(R_2N)_2CHC{\equiv}N$, yield thioformamides on treatment with $H_2S$.[94]

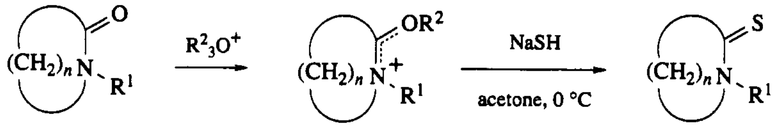

(63) (64) (65)

$R^1$ = Me, $(CH_2)_3F$; $R^1 \neq$ H; $n$ = 3, 4

(29)

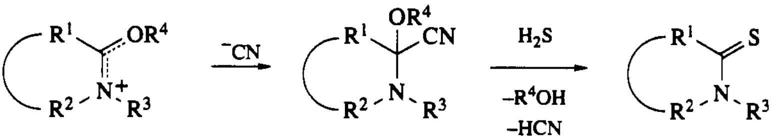

(66)

(30)

### 2.4.3.3 Thiolysis of Amidines

Thiolysis of *N*-monosubstituted amidines, $R^1C({=}NH)HNR^2$, proceeds unselectively giving a mixture of thioamides $R^1C(S)NH_2$ and $R^1C(S)NHR^2$.[95] However, *N*,*N*-disubstituted examples (**67**) can be cleanly transformed into tertiary thioamides (**68**; equation 31).[95]

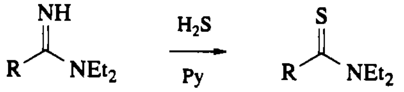

(67) (68)

(31)

Cyclic amidinium salts (**71**) are obtained by [2 + 2] cycloaddition of ketenimmonium compounds (**69**) to Schiff bases (**70**; $R^3$ = H, Ph, $MeO_2C$) or thioimidates (**70**; $R^3$ = SBn); their thiolysis provides an elegant access to β-thiolactams (**72**; equation 32).[96]

### 2.4.3.4 Thiolysis of Nitriles

Addition of $H_2S$ to nitriles (**73**) represents an important method for the synthesis of primary thioamides (**74**; equation 33). The reaction is carried out under base or acid catalysis. The base-catalyzed process is particularly useful in the preparation of aromatic thioamides, *i.e.* for R = aryl, hetaryl in (**73**); triethylamine in molar proportion or pyridine, which at the same time also serves as solvent, are employed most commonly.[97] The approach tolerates the presence of various other functionalities such as an amide,[98] hydrazone,[99] enamine,[68] α-oxo,[100] α-acetoxy[101] or α-amino group.[102] Moreover, the reaction has been applied to the synthesis of thioasparagine as such[103] or incorporated into a dipeptide, as shown

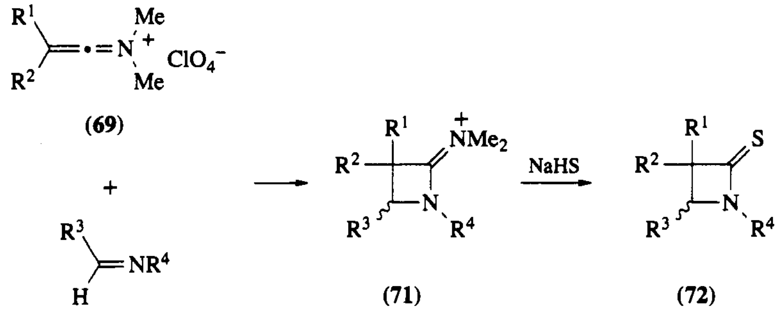

**(69)** **(70)** **(71)** **(72)** (32)

in equation (34).[104] Alternatively, a basic ion-exchange resin in methanol has been suggested to catalyze the transformation of nitriles (**73**) into thioamides (**74**).[105]

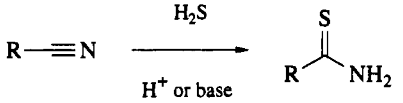

**(73)** **(74)** (33)

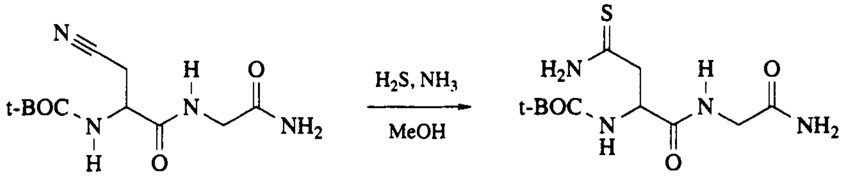

(34)

Without special measures, aliphatic nitriles (**73**; R = alkyl) often give low yields in the base-catalyzed thiolysis.[106] It has proven advantageous to work in the presence of diethylamine, a tetraalkylammonium hydroxide, or a guanidine derivative in DMF, DMSO or sulfolane; these conditions allow one to work at atmospheric pressure and provide aliphatic thioamides in medium to good yields.[107] However, as detailed in Scheme 10, pressure is required in the phase transfer modification of the reaction which gives excellent yields for aromatic (R = Ph, 3-pyridyl) and moderate to good yields starting from aliphatic substrates (R = Bn, Pr).[108] Similarly, 13–17 atm of $H_2S$ are a prerequisite in the synthesis of thioformamide, $HCSNH_2$, from HCN with addition of triethylamine[109] or of a basic ion-exchange resin.[110] In the presence of the $Cu(NH_3)_4^{2+}$ cation, NaCN reacts with $H_2S$ to yield 77% dithiooxamide (**26**).[111]

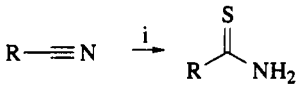

**(73)** **(74)**

i, $Na_2S$, $H_2S$ (2 atm), $R'_4NCl$ or dibenzo-18-crown-6 in $H_2O$, PhH

**Scheme 10**

According to equation (35), heating of nitriles (**73**) with dithiocarbamate (**75**) gives up to 80% of *N*,*N*-dimethylthioamides (**76**).[112] In a related reaction, *N*-mono- and *N*,*N*-di-substituted thioformamides are isolated on heating HCN and $H_2S$ in the presence of an amine.[94,109,113]

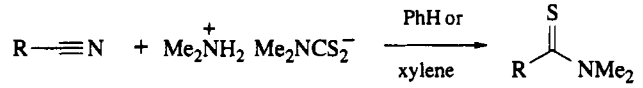

**(73)** **(75)** **(76)** (35)

The thiolysis of nitrile groups can also be applied to cyanamides giving thioureas.[39,40,114]

In the acid-catalyzed thiolysis of nitriles (73) $H_2S$ is commonly replaced by appropriate precursors or equivalents. Thus, thioacids, RCOSH, have been used together with HCl[115] or $SnCl_4$.[116] Thioacetamide (77) is a very convenient source of $H_2S$; as shown in equation (36), an equilibrium is established which is shifted to the right, if the liberated MeCN is removed by distillation.[117] Alternative sources of $H_2S$ are dithiophosphoric, $HSP(=S)(OR)_2$ with R = Et[118] or $Pr^i$,[119] or phosphinodithioic acid derivatives, $HSPPh_2(=S)$.[120] The last mentioned approach allows the elegant synthesis of α-hydroxythioamides (78) in Scheme 11.[121]

Heating of $P_4S_{10}$ with nitriles (73) yields adducts incorporating a $P_4$ tetrahedron; hydrolytic cleavage furnishes thioamides.[122]

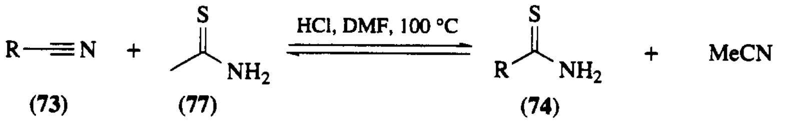

(36)

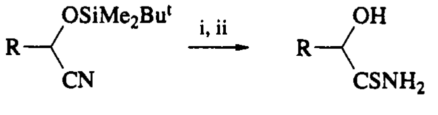

(78)

i, $Ph_2P(S)SH$, 60 °C, $Pr^iOH$; ii, TBAF

**Scheme 11**

## 2.4.4 THIOLYSIS OF 1,1,1-TRIHALIDES

In a process reminiscent of isonitrile hydrolysis, dichlorocarbene as generated from $CHCl_3$ reacts with $H_2S$ in the presence of primary or secondary amines to yield thioformamides (79; equation 37).[123] If pressure is employed, $CCl_4$ or $Cl_3CCCl_3$ can also be used with the latter giving dithiooxamides (27), *e.g.* with $BuNH_2$, 65% of BuNHCSCSNHBu.[124]

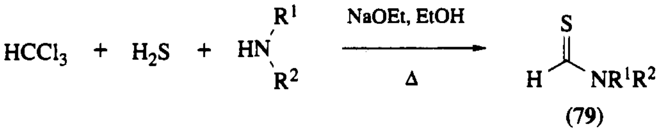

(37)

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# 2.5

# Synthesis of Thioesters and Thiolactones

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## 2.5.1 INTRODUCTION

Three different types of thiocarboxylic esters (and also thiolactones) exist: the thiol, thioxo- and dithioesters which, according to the IUPAC rules, are named *S*-alkyl (*S*-aryl) carbothioates (**1**), *O*-alkyl (*O*-aryl) carbothioates (**2**) or alkyl (aryl) carbodithioates (**3**). Acylation-type reactions were used for the first preparations of thiol carboxylic esters (**1**) by Tjuttschew (1863),[1] Saytzeff and Lukaschewicz (1868)[2] and Michler (1875).[3] Thioxocarboxylic esters (**2**) were first obtained *via* an acylation route by Matsui (1908).[4] On the other hand, alkyl dithiobenzoates (**3**; $R^1$ = Ph), which were first mentioned in a patent by Bloch and Höhn (1908),[5a] and alkyl alkanedithioates (**3**; $R^1$ = Me, Et, $PhCH_2$), first described by Houben and Schultze (1910),[5b] were prepared by alkylation of the corresponding metal carbodithioates.

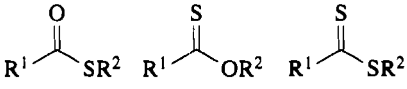

**(1)** **(2)** **(3)**

Some structural characteristics and significant spectroscopic properties of thiocarboxylic esters are compiled in Table 1. These data might be helpful for preparative work. The IR frequencies of the CX—SR group are especially indicative of a thioester even if strong vibrational coupling occurs, as in the case of (**2**) and (**3**). The best and unequivocal spectroscopic feature is the $^{13}C$ NMR signal of the CX carbon atom. The CS groups of thioxo- (**2**) and dithio-esters (**3**) can be distinguished in most cases since the chemical shifts are clearly different. It should be mentioned, however, that the intensity of the signals is sometimes extremely low and the lines can thus be detected only at high signal-to-noise ratios.

**Table 1** Physical and Spectroscopic Data of Thiocarboxylic Esters

| $R^1$—CX—$YR^2$ | *(1)* $X = O, Y = S$ | *(2)* $X = S, Y = O$ | *(3)* $X = Y = S$ | *Refs.* |
|---|---|---|---|---|
| *d* (C—X) (pm) | 119–121 | 161–163 | 160–167 | 6–13 |
| *d* (C—Y) (pm) | 174–178 | 132–137 | 168–175 | 6–13 |
| $\mu$ (D) | 1.3–1.7 | 2.1–2.6 | 1.7–1.9 | 6,14 |
| $\lambda_{max}$ (nm) | 232 | 400–440 | 450–530 | 6,14 |
| [log $\varepsilon$] | [3.7] | [1.2–2.0] | [1.2–2.1] | |
| | | 250–290 | 300–330 | |
| | | [4.0–4.3] | [3.8–4.3] | |
| $\nu_{CX}$ (cm$^{-1}$) | 1660–1715 | 1000–1050 | 980–1030 | 6,14–18 |
| | | 1200–1230 | 1180–1250 | |
| $\delta_{CX}{}^{13}C$ (p.p.m.) | 190–200 | 210–230 | 225–245 | 6,14,19–22 |

Thiocarboxylic esters do not play a major role in biochemistry, with the one exception of acetyl-CoA (**4**; R = Me), the prototype of acyl-CoAs (**4**), which represent important energy rich intermediates in amino acid, lipid and glucose metabolism.[23] In fact the thiol esters (**4**) fit in with the scope of this chapter. They are often formed by acylation reactions and themselves react as acylating agents.

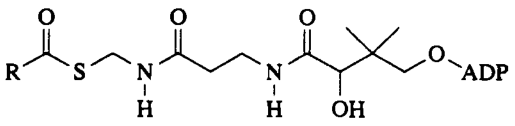

(**4**)

Although acylation reactions rank among the best-known methods for the synthesis of thiocarboxylic *S*-esters (**1**), there exist other important and convenient routes,[6,24] *e.g.* the alkylation of thiocarboxylate anions (equation 1) or radical addition of thiocarboxylic acids to carbon–carbon double bonds (equation 2). These methods are not dealt with here (*cf.* Volume 4, Chapter 1.5).

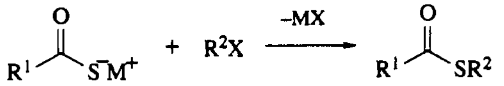

(1)

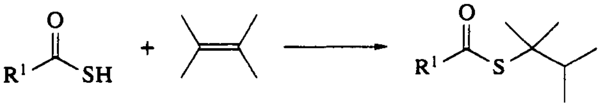

(2)

Alternatives to the acylation-type reaction are even more important in the thioxo- and dithio-carboxylic ester series[6,14,15,24–29] since dithiocarboxylate salts are most conveniently obtained from a variety of precursors and can be not only alkylated but also arylated by arenediazonium hydrogen sulfates (equation 3).[14,30] An advantage of the latter method is that no thiophenols are needed, which are necessary, but sometimes not easily obtained, educts in most other *S*-aryl thiocarboxylate preparations (*cf.* Chapter 1.5).

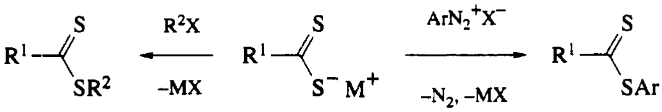

(3)

In the last decade the methods of converting carbonyl to the corresponding thiocarbonyl compounds have been substantially improved.[6,15,25–28] Therefore, thioxo- as well as dithio-carboxylic esters are accessible from esters, thiol esters and even carboxylic acids by reacting them with phosphorus pentasulfide or 1,3,2,4-dithiadiphosphetane 2,4-disulfides such as Lawesson's[19] or Davy's[31] reagent (equation 4; *cf.* Chapter 4.1, this volume).

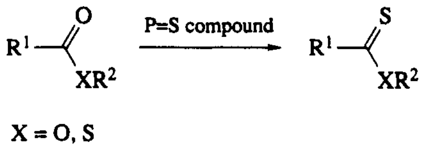

(4)

Finally, sigmatropic processes (*cf.* Volume 5, Part 7) are useful procedures for the preparation of certain thioxo- and dithio-carboxylic esters.

## 2.5.2 THIOL ESTERS AND THIOL LACTONES

Thiol carboxylic esters (**1**) are the most common compounds among the three types of thioester. They are activated derivatives of carboxylic acids and exhibit acylating properties similar to those of carboxylic acid anhydrides. They have therefore found widespread application in synthetic chemistry and have been used for preparing esters, amides and peptides, especially macrocyclic ketones and lactones. Several review articles concerning the chemistry of thiol carboxylic esters[6,24,32,33] and thiol lactones[34] have appeared.

### 2.5.2.1 Acylation of Thiols with Carboxylic Acids

Unlike carboxylic esters, open-chained *S*-alkyl thiocarboxylates cannot be obtained by direct proton-catalyzed esterification. Whereas thiocarboxylic acids react with alcohols to form esters as expected, thiol esters are formed on reaction of carboxylic acids with thiols, but the equilibrium is shifted towards the educts and the reaction is not useful for synthetic purposes. Therefore, activation is necessary and several methods have been developed to meet this requirement.

Condensing agents that are well known for peptide synthesis are also very suitable for the preparation of thiol carboxylic esters.

DCC can be used to prepare *S*-alkyl and *S*-aryl thiocarboxylates (**1**) from carboxylic acids and thiols according to equation (5).[35] This method has been successfully applied to the synthesis of thiol esters with sensitive substituents, *e.g.* *S*-methyl thioacrylate, a natural product.[36] In particular, *N*-protected amino acid and peptide *S*-phenyl esters, which are useful building blocks in peptide synthesis, are obtained in excellent yields without racemization.[37] *N*-Hydroxyphthalimide[38] and DMAP[39] have been used as cocatalysts to facilitate the reaction. The preparation of the Wittig reagent (**5**) by this route[39] is shown in equation (6).

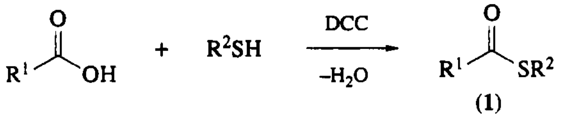

(5)

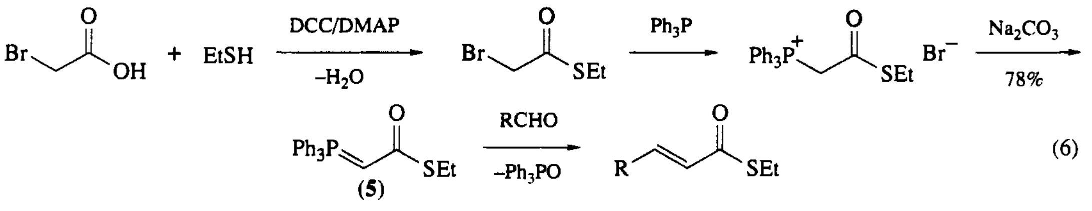

(6)

Activation of the carboxyl group is also achieved by various phosphorus compounds (**6**–**16**; *cf.* Table 2). Obviously, mixed anhydrides are the reactive intermediates, but these need not be isolated. The yields are generally high. *S*-Alkyl monothiomalonates and *S*,*S*′-dialkyl dithiomalonates are obtained by means of (**15**). *N*-Protected amino or hydroxy as well as 6-acylaminothiopenicillanic acids (**17**) can be converted to the corresponding thiol esters without racemization if (**11**), (**12**) or (**13**) are used as activators. Steric hindrance by bulky groups $R^1$ or $R^2$ during the formation of the carbon–sulfur bond in (**1**) is overcome by using (**8**), (**9**) or (**13**) as catalysts. This is important since the *t*-butylthiocarbonyl group is a good protecting group during the synthesis of macrocyclic lactones.[42,51,52] Antibiotics of the macrolide type have also been prepared *via* thiol esters, which were obtained by selective activation of the corresponding ω-hydroxycarboxylic acids with carbonyldiimidazole or similar reagents.[53–56]

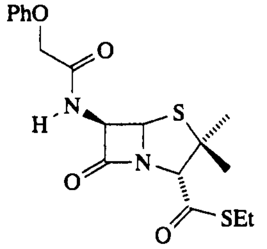

(**17**)

**Table 2** Phosphorus Compounds $R^1R^2P(O)X$ used as Activators for the Preparation of Thiol Carboxylic Esters (**1**)

| *Compound* | $R^1$ | $R^2$ | *X* | *Refs.* |
|---|---|---|---|---|
| (**6**) | Cl | Cl | Cl | 40 |
| (**7**) | Ph | Ph | Cl | 38,41 |
| (**8**) | OEt | OEt | Cl | 42 |
| (**9**) | OPh | Cl | Cl | 43 |
| (**10**) | $NMe_2$ | Cl | Cl | 44 |
| (**11**) | OEt | OEt | CN | 45,46 |
| (**12**) | OPh | OPh | $N_3$ | 45,46 |
| (**13**) | OPh | OPh | ODO[a] | 47 |
| (**14**)[b] | SPh | SPh | SPh | 48 |
| (**15**) | | Ethyl polyphosphate | | 49 |
| (**16**) | | Hexachlorocyclotri(phosphazene) | | 50 |

[a]2-Oxo-2,3-dihydro-1,3-oxazolyl; [b]$(PhS)_3PS$/imidazole.

2-Halo-pyridinium or -benzothiazolium salts[56,57] have been applied in the preparation of *S*-alkyl or *S*-aryl carbothioates from carboxylic acids *via* acyloxypyridinium salts (*cf.* equation 7).

Another efficient method seems to be Mukaiyama's[58] redox condensation, which has found widespread application in total syntheses of natural products. Originally *S*-(2-pyridyl)carbothioates (**18**), obtained from carboxylic acids, 2,2′-dipyridyl disulfide and triphenylphosphine (equation 8), were used in follow-up reactions.[59] The use of (**18**) has been reviewed in the literature.[51,52,60–63]

Carboxylic esters, especially lactones, are conveniently obtained *via* the pyridyl thioesters (**18**). Some examples are given in Scheme 1.[64] The 2-pyridyl thiol ester method can be further improved if silver ions ($AgClO_4$) are used as activators.[65] Corey and Brunelle[66] have also introduced other heterocyclic disulfides, and (**19**) was found to be superior to other reagents tested for the formation of lactones from ω-hydroxyalkanoic acids.

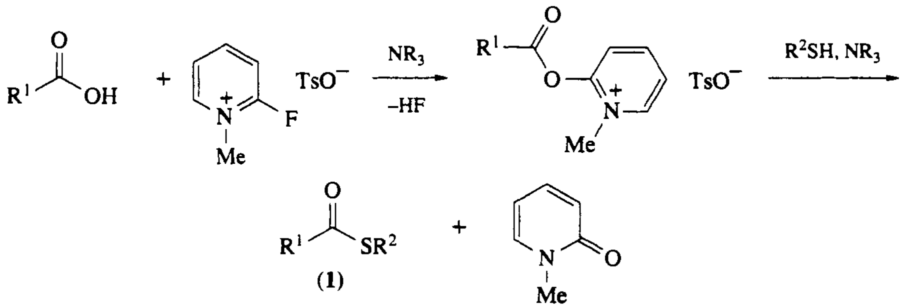

(7)

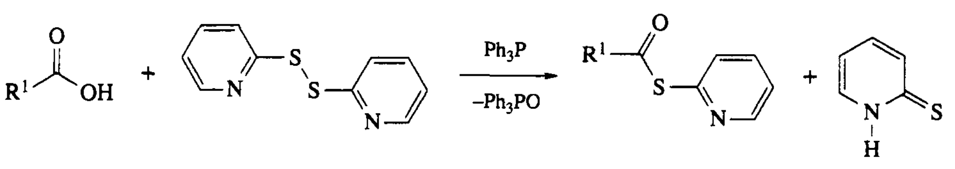

**(18)**

(8)

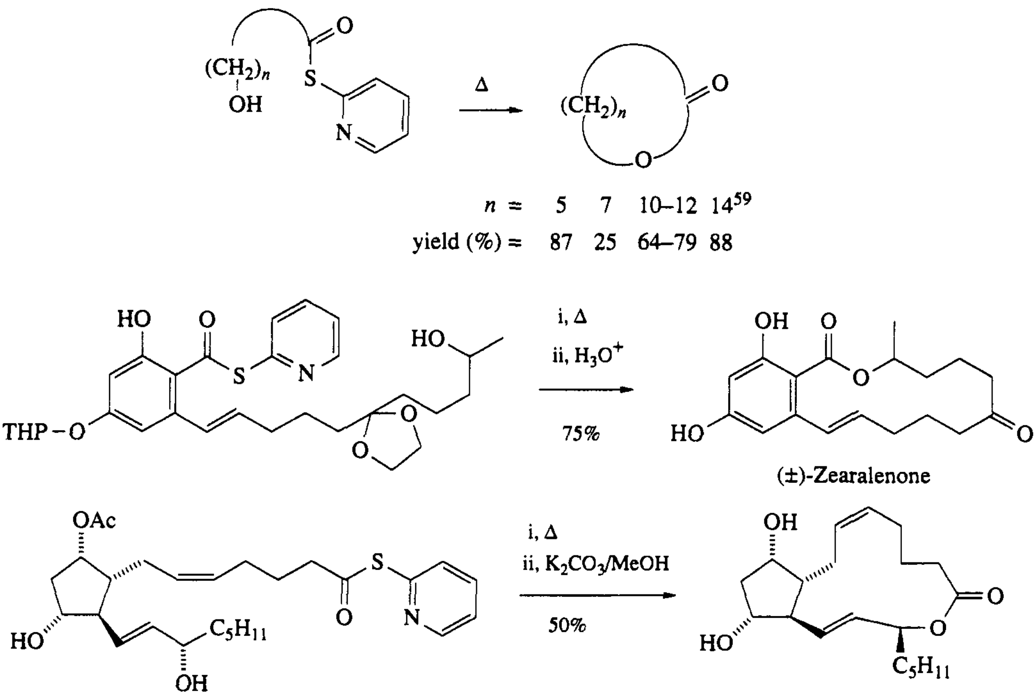

$n$ = 5 7 10–12 14[59]
yield (%) = 87 25 64–79 88

(±)-Zearalenone

PGF$_{2\alpha}$-1,15-lactone[64]

**Scheme 1**

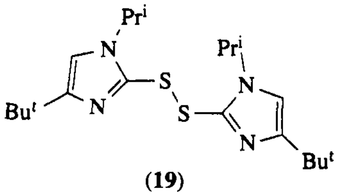

**(19)**

Grignard reaction of (**18**) yields open-chained as well as cyclic ketones, including natural products such as jasmone, in a selective way since formation of carbinols or Claisen-type condensation products is completely inhibited (equation 9).[58,67]

The use of diphenyl disulfide in the presence of triphenylphosphine to prepare thiol carboxylic esters has been described in the recent literature[68] and even *S*-alkyl alkanethioates can be obtained in good yields if DMAP is used as the base in the second step (*cf.* equation 10).[69]

*S*-Methyl[70] and *S*-aryl[71] thiocarboxylic esters can also be prepared directly from carboxylic acids if thiocyanates or chlorothioformates[72] are used instead of thiols (equations 11 and 12).

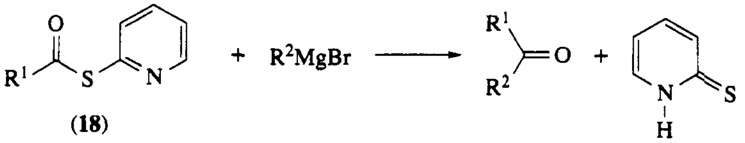

(9)

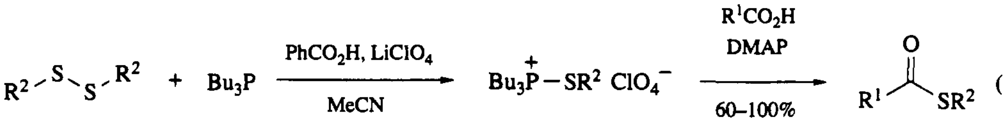
PhCO₂H, LiClO₄
MeCN
Bu₃P
Bu₃P⁺–SR² ClO₄⁻
R¹CO₂H
DMAP
60–100%
SR²

(10)

$R^2$ = Me, Et, Bu, PhCH$_2$, Ph

(1) $R^1$ = C$_6$H$_{13}$, Ph

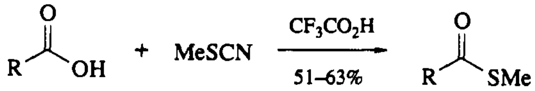
MeSCN
CF₃CO₂H
51–63%
SMe

(11)

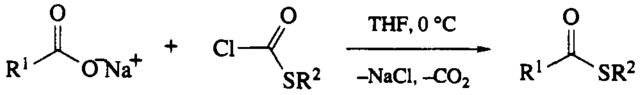
THF, 0 °C
–NaCl, –CO₂

(12)

(1)

Finally, it should be mentioned that γ- and δ-thiol lactones are in many cases formed simply by heating the corresponding mercaptocarboxylic acids[34] or by treating them with phosphorus pentoxide.[73] The β-thiolactone (**20**) has also been obtained by flash pyrolysis of 3-mercapto-2-naphthoic acid (equation 13).[74]

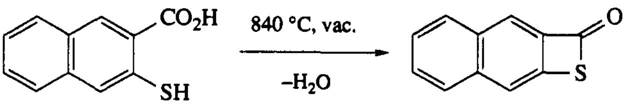
CO₂H
SH
840 °C, vac.
–H₂O
O
S

(13)

(**20**) 25%

## 2.5.2.2 Acylation of Thiols with Acyl Halides

Reaction of thiols or thiolates with acyl halides, chlorides in particular, represents the standard method for preparing thiol carboxylic esters (*cf.* ref. 33 and the literature cited therein). Since thiols are strong nucleophiles, the acylation even takes place in the absence of base. However, to obtain excellent yields under mild conditions, tertiary amines are added or metal (Si, Sn, Tl$^{I}$ Cu$^{I}$) derivatives of the thiols are used. The following examples demonstrate the scope of the method.

Thallium(I) thiolates have been introduced by Masamune *et al.*[75,76] Their use is especially advantageous if *S*-*t*-butyl thiocarboxylic esters are to be prepared which can serve as educts for macrolide synthesis. Zearalenone dimethyl ether ethylene acetal (**22**; *cf.* also Scheme 1) was obtained from the corresponding acid chloride and thallium(I) α-methylpropanethiolate *via* the *S*-*t*-butyl benzenecarbothioate (**21**; equation 14)

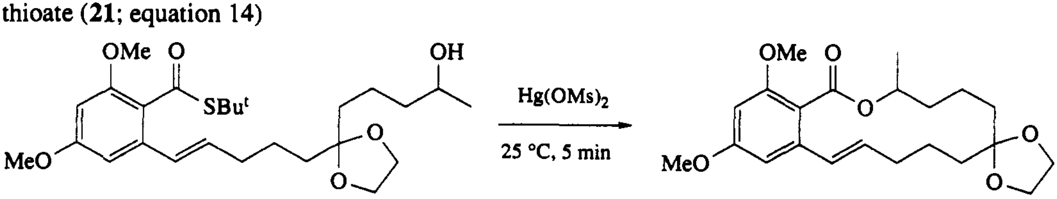
OMe O
SBuᵗ
OH
MeO
Hg(OMs)₂
25 °C, 5 min

(14)

(**21**) (**22**) 90%

*S*-*t*-Butyl thiocarboxylic esters are also accessible from acyl chlorides and *t*-butylthiotrimethylsilane in the presence of potassium fluoride and dicyclohexyl-18-crown-6 (equation 15).[33,77]

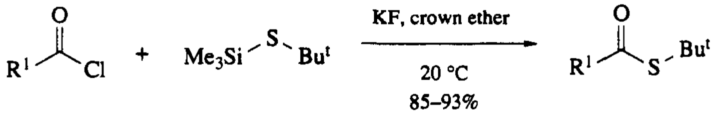
Me₃Si
Buᵗ
KF, crown ether
20 °C
85–93%

(15)

Stannyl thiolates[33,78] were recently shown to be applicable to the formation of the macrocyclic polythiolactones (**23**) and (**24**), according to equation (16).[79]

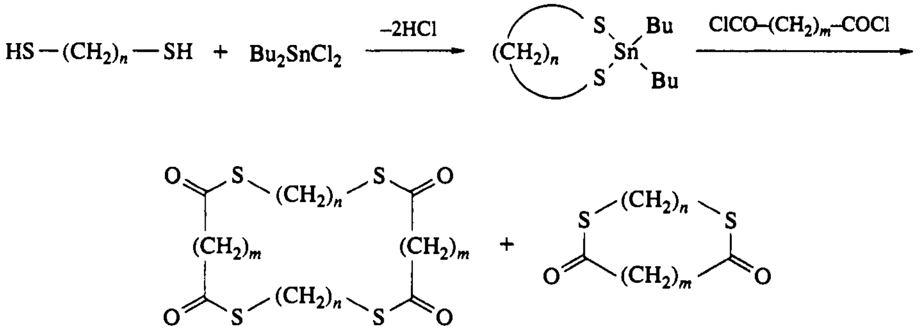

(**23**) (**24**)

(16)

Several optically active *S*-(2-methylbutyl) alkanethioates (**25**)[80] and the naturally occurring thiocarboxylic esters (**26**)[81] and (**27**)[82] were synthesized from the corresponding acid chlorides and thiols, as well as *S*-phenyl arenecarbothioates and thiocinnamates, which are applicable for the preparation of radio-labeled CoA derivatives (**14**; equation 17),[83] and the acyl sulfenates (**28**) occurring in the cultural media of *Pseudomonas* species (equation 18).[84]

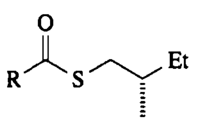

*(S)*-(**25**)

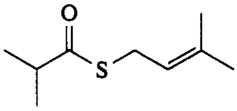

(**26**)

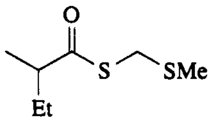

(**27**)

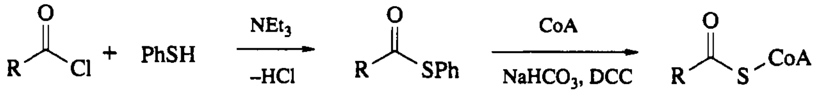

(**14**)

(17)

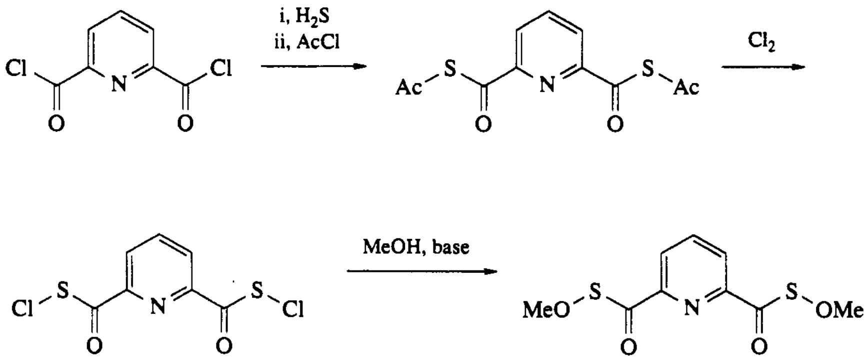

(**28**)

(18)

Special thiol carboxylic esters (**29**) were prepared from aroyl halides and arene thiolates.[85] These 4,4′-disubstituted *S*-aryl arenecarbothioates might gain importance from a practical point of view, since they exhibit liquid crystal properties and could be useful as components of a display cell. Another thiocarboxylic ester (**30**), which was obtained from a zinc thiochelate and benzoyl chloride (equation 19),[86] might be potentially useful as a precursor for organic conductors.

Thiol carboxylic esters of an unusual type are formed if thioamides react with acyl chlorides. 2-Acylthiopyridine *N*-oxides, which are yellow crystalline compounds, are the primary reaction products

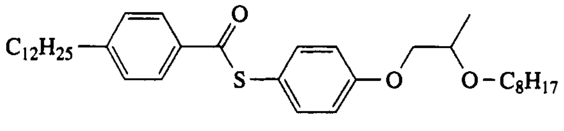

$C_{12}H_{25}$
O
S
O
$O-C_8H_{17}$

**(29)**

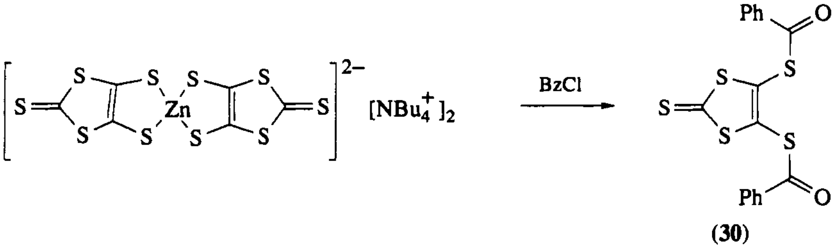

$[NBu_4^+]_2$
2–
Zn
BzCl
Ph
O
S

**(30)**

(19)

of *N*-hydroxy-α-thiopyridone and acyl chlorides. They undergo spontaneous rearrangement to yield the *N*-acyloxy-α-thiopyridones (**31**), which are new and versatile sources of alkyl radicals for use in organic synthesis. Reductive decarboxylation of (**31**) takes place on photolysis or thermolysis in the presence of a suitable hydrogen donor HX (*e.g.* $Bu^tSH$) and alkanes $R^1H$ are formed in high yields (Scheme 2).[87] Addition of electron poor alkenes leads to products (**32**) in which a carbon–carbon and a carbon–sulfur bond have been formed (Scheme 2).[87] The related 2-acylthio-*N*-alkylpyridinium salts (**33**) can serve as water soluble acylating agents for phenols, amines or carboxylic acids according to equation (20).[88]

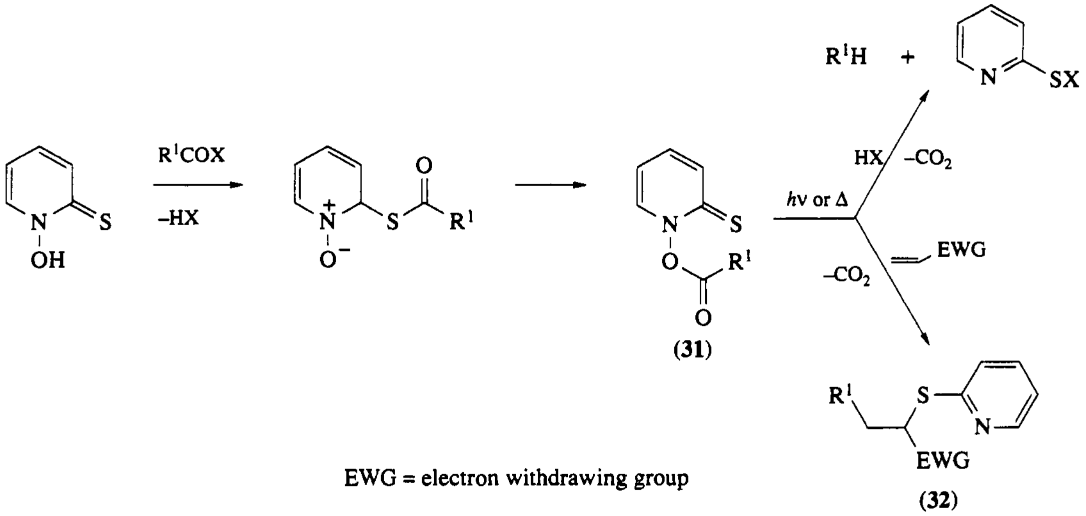

$R^1COX$
–HX
$R^1H$ +
SX
HX
$-CO_2$
hν or Δ
EWG
$-CO_2$
(31)
(32)

EWG = electron withdrawing group

**Scheme 2**

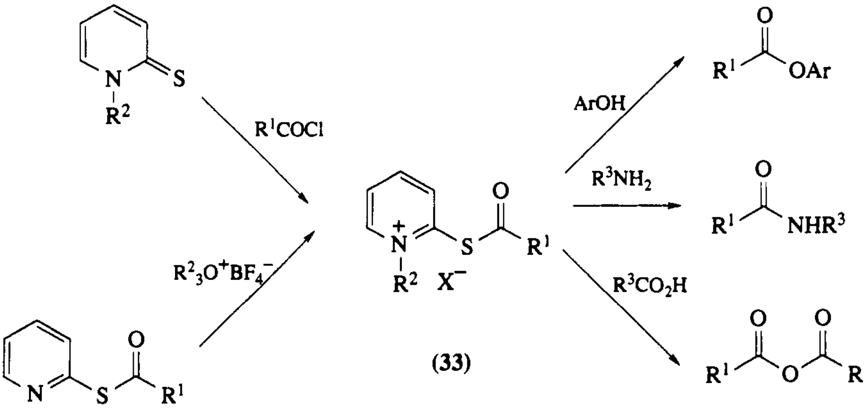

$R^1COCl$
$R^2_3O^+BF_4^-$
$R^2$
$X^-$
(33)
ArOH
$R^3NH_2$
$R^3CO_2H$
OAr
$NHR^3$
$R^3$

(20)

The open-chained thioacetamide, on the other hand, yields iminium salts (**34**) on acylation. Reaction of (**34**) with alkyl halides and subsequent hydrolysis results in the formation of thiocarboxylic esters (**1**).[89] This reaction is actually performed in one step under phase transfer catalysis (equation 21). No unpleasant smelling thiols or thiocarboxylic acids are required as educts, the yields are high and a large variety of substituents $R^1$ and $R^2$ are possible.[89]

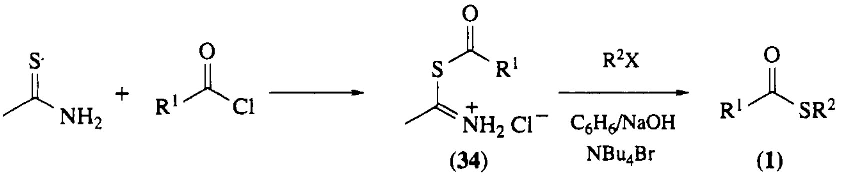

(21)

$R^1$ = *n*-alkyl, $Bu^t$, Ar, PhCH=CH; $R^2$ = *n*-alkyl, $PhCH_2$, $MeCH=CH-CH_2$

### 2.5.2.3 Acylation of Thiols with Anhydrides, Ketenes and Esters

Acid anhydrides in the presence of basic catalysts can be used instead of acyl chlorides in acylation reactions of thiols.[33] Mixed anhydrides of *N*-protected amino acids and ethyl carbonate yield the corresponding *S*-*t*-butyl thiocarboxylic esters, which are useful reagents for peptide syntheses (equation 22).[90]

Acylation of thiols with ketenes (equation 23) is a method of long standing.[33] In many cases the yields are nearly quantitative. Functionalities such as acetamino groups or carbon–carbon double bonds in the thiol are not attacked under the mild reaction conditions and optically active thiol esters are obtained without racemization.[33,78]

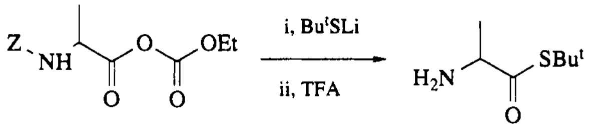

(22)

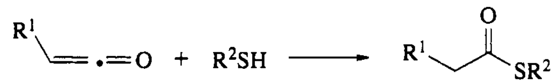

(23)

Metal thiolates or benzenethiols in the presence of triethylamine also react very smoothly with diketene to yield *S*-alkyl (**35**)[91] or *S*-aryl acetothioacetates (**36**).[92] The β-keto thioesters (**35**) can be used in exceptionally mild preparations of β-keto amides (**37**),[93] whereas (**36**) can be cyclized by Lewis acids to form thiocumarins (**38**).[92] The *S*-*t*-butyl thiol ester (**35**) is also a suitable substrate for *C*-alkylation in the β-position or, after double deprotonation, in the δ-position (Scheme 3).[91]

Acylation of a simple thiol with an alkyl carboxylate is not a very suitable method for preparation of *S*-alkyl thiocarboxylates. Transesterification is, however, possible if either the thiol or the carboxylic ester is activated. The enhanced reactivity of boron, aluminum and silicon thiolates has been utilized for the synthesis of a large variety of thiocarboxylic *S*-esters, including hydroxy derivatives (from lactones).[33] α,β-Unsaturated thiol esters, *e.g.* cinnamoyl or 2-butenoyl derivatives, are also accessible. Michael addition, an undesirable side reaction of thiols, is completely avoided if alkyl trimethylsilyl sulfides or tris(arylthio)boranes are applied.[33]

Phenyl carboxylates are reactive enough to form thiocarboxylic esters directly with thiols or thiolate anions.[33] This reaction was applied for the preparation of polyhexamethylene thioterephthalates (equation 24).[94]

The highly activated 4-acyloxypyridines react with thiols under particularly mild conditions (room temperature, no acids or bases) to form *S*-alkyl or *S*-phenyl carbothioates in excellent yields (equation 25).[33,95]

As expected, formation of five- and six-membered thiolactones is a favored process. It occurs easily therefore, even with unactivated esters,[34] as for instance in the case of thiocumarins (**38**) and dihydrothiocumarins (**39**; Scheme 4).[96]

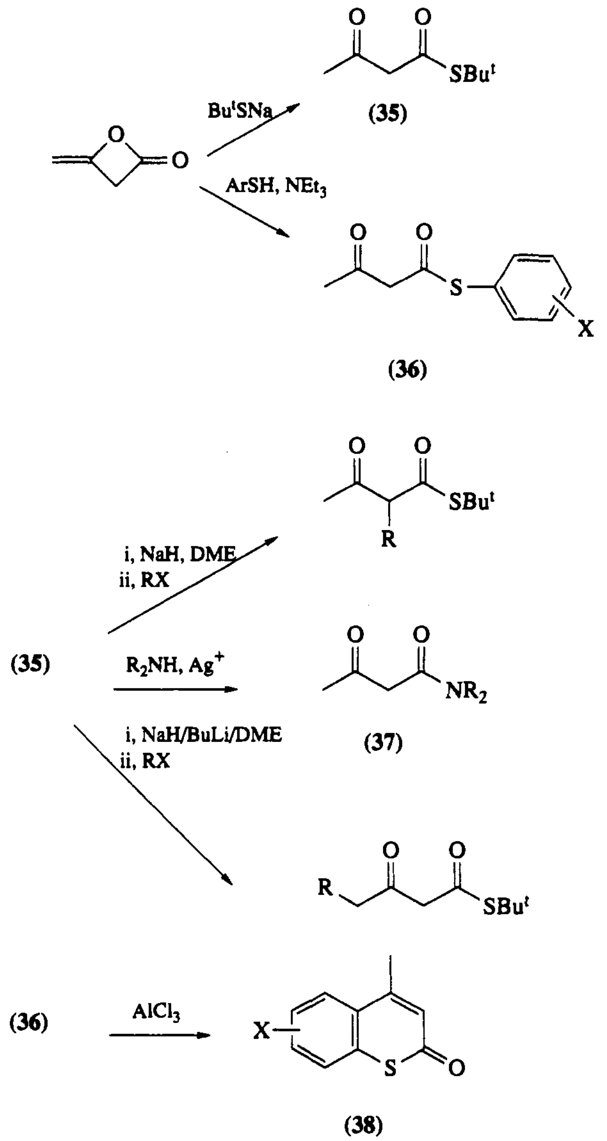
Bu$^t$SNa
(35)
ArSH, NEt$_3$
(36)
i, NaH, DME
ii, RX
(35)
R$_2$NH, Ag$^+$
(37)
i, NaH/BuLi/DME
ii, RX
(36)
AlCl$_3$
(38)

**Scheme 3**

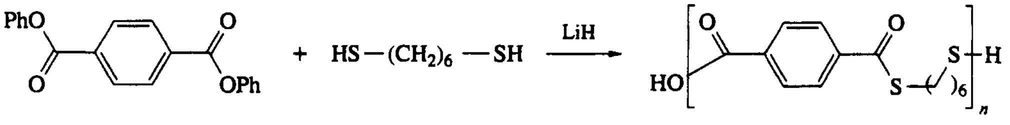

(24)

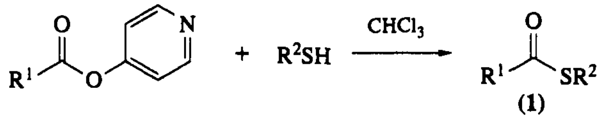

(25)

### 2.5.2.4 Acylation of Water (Hydrolysis) with Imidothioates, Thioorthoesters and Ketene *S,S*-Acetals

Imidothioates are easily accessible from nitriles (equation 26)[6] or, in special cases, from alkyl thiocyanates (equation 27).[97] Their hydrolysis represents a route to thiol carboxylic esters.[6,33,97] However, the alternative, formation of amides, is not easy to avoid and the yields are therefore often low.[33,98]

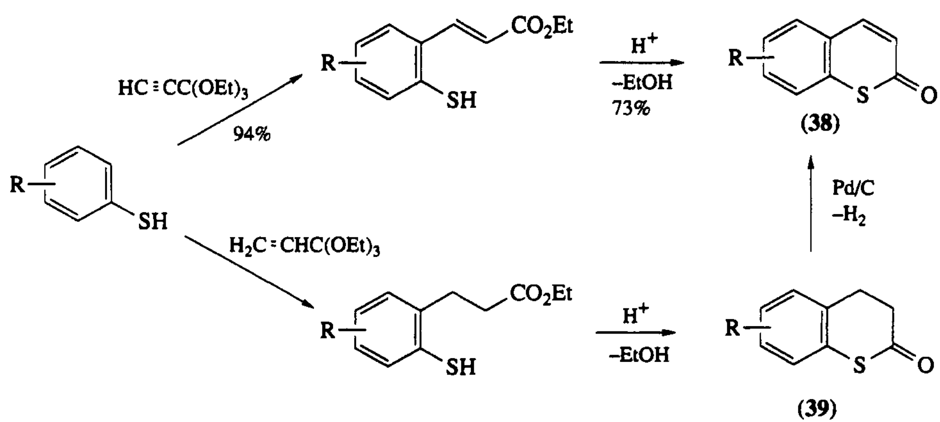

Scheme 4

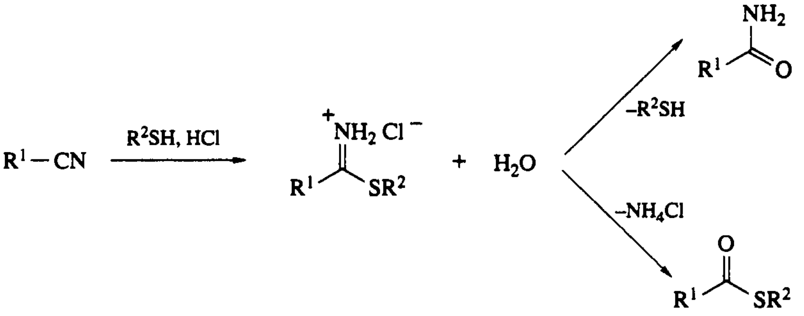

(26)

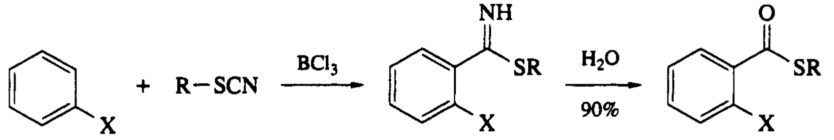

(27)

Thioorthoesters[6] as well as α,α-dihalo sulfides and related compounds may be partially hydrolyzed to yield thiol carboxylic esters.[99] This reaction has been utilized in a sarcomycin synthesis (equation 28).[99]

Ketene *S*,*S*-acetals are also hydrolyzed with aqueous acid *via* dithioorthoesters as has been shown recently,[100] and thiol carboxylic esters are obtained in good yields (equation 29).[6]

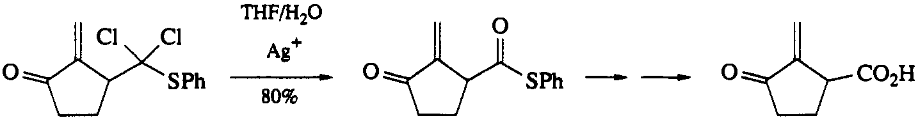

(28)

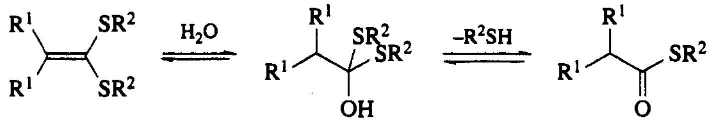

(29)

### 2.5.2.5 Acylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

Although reactions of this type are dealt with in other volumes or chapters of this book, a short overview should be given here because in some cases they represent interesting and useful methods for the synthesis of thiol carboxylic esters.

Friedel–Crafts acylation of arenes (*cf.* Volume 2, Chapter 3.1) can be achieved with *S*-aryl or *S*-*n*-alkyl chlorothioformates in good to moderate yields (equation 30).[33]

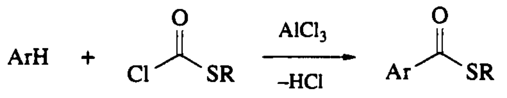

(30)

*S*,*S*-Dimethyl dithiocarbonate also reacts with carbonyl-stabilized carbanions (equation 31).[33]

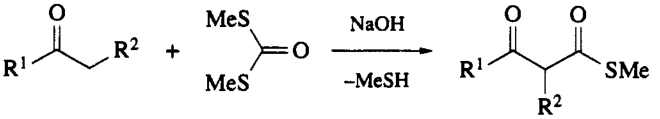

(31)

The Grignard reaction (*cf.* Volume 1, Chapter 1.16) was recently used in a highly efficient route to ketones through sequential coupling of *S*-phenyl chlorothioformate in the presence of transition metal catalysts (equation 32).[101]

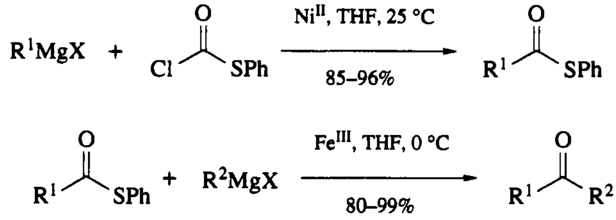

(32)

Claisen (*cf.* Volume 2, Chapter 3.4) and Dieckmann (*cf.* Volume 2, Chapter 3.5) condensation reactions work well with thiocarboxylic esters (equations 33 and 34).[33]

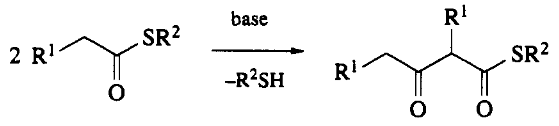

(33)

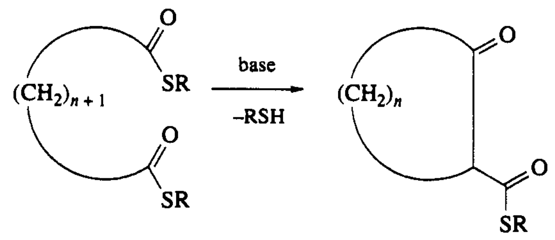

(34)

Magnesium or lithium enolates of thiol carboxylic esters can be acylated with suitable reagents (*cf.* Volume 2, Part 1).[33] Highly functionalized new derivatives are obtained. The example shown in equation (35)[33,102] is closely related to the *C*-acylation of malonyl-CoA with acetyl-CoA, which plays an important role in the biosynthesis of polypeptides and fatty acids. (*S*)-4-Hydroxy-5-methyl-3-oxo-hexanoyl-L-leucine esters (**41**), 2-demethyl analogs of the Hip-Leu moiety of didemnin antibiotics, can be prepared *via* the β-keto thiol carboxylic esters (**40**; equation 36).[103]

*S*-Alkyl arenecarbothioates (**42**), on the other hand, undergo deprotonation at the *S*-alkyl group. The resulting dipole-stabilized carbanions may be acylated by the starting compound (**42**) to form *S*-(2-oxoalkyl) arenethioates (equation 37).[33]

## 2.5.3 THIOXOESTERS AND THIOXOLACTONES

Thioxocarboxylic esters are the least conveniently available type of thioester because of their decreased stability. Oxidation or hydrolysis to form the corresponding esters occurs very easily and thiol esters are formed by rearrangement. On the other hand, the pronounced reactivity makes them promising candidates for synthetic utilization. This valuable chemical property of thioxocarboxylic esters has only

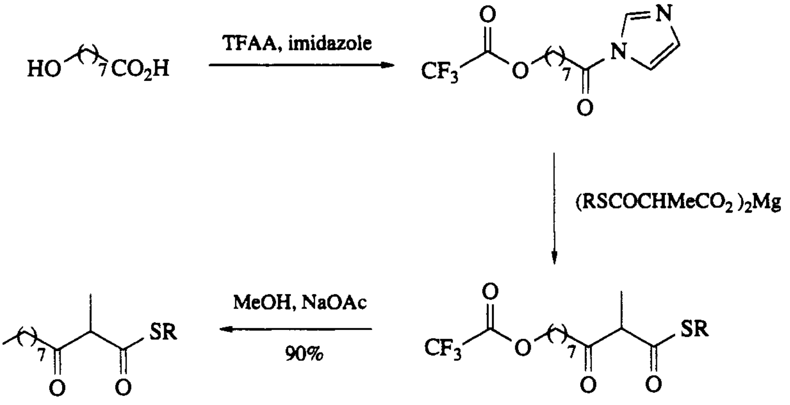
TFAA, imidazole
(RSCOCHMeCO2)2Mg
MeOH, NaOAc
90%

(35)

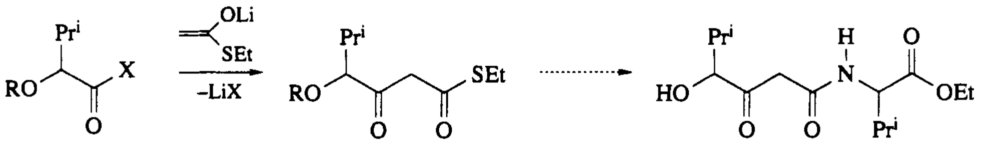

**(40)** **(41)**

(36)

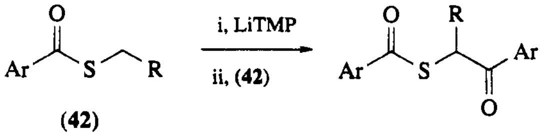
i, LiTMP
ii, (42)

**(42)**

(37)

recently attracted attention. Primary, secondary and tertiary alcohols are, for instance, reducible to the corresponding hydrocarbons *via* thioxoesters (equation 38).[28,104]

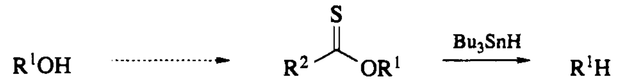

(38)

Reductive desulfurization of the thiocarbonyl group with Raney nickel results in good yields of ethers.[28] 3′-*O*-Benzyl-2′-deoxy-5-trifluoromethyl-β-uridine (**43**), claimed as a possible antitumor agent, has been prepared in this way (equation 39).[105]

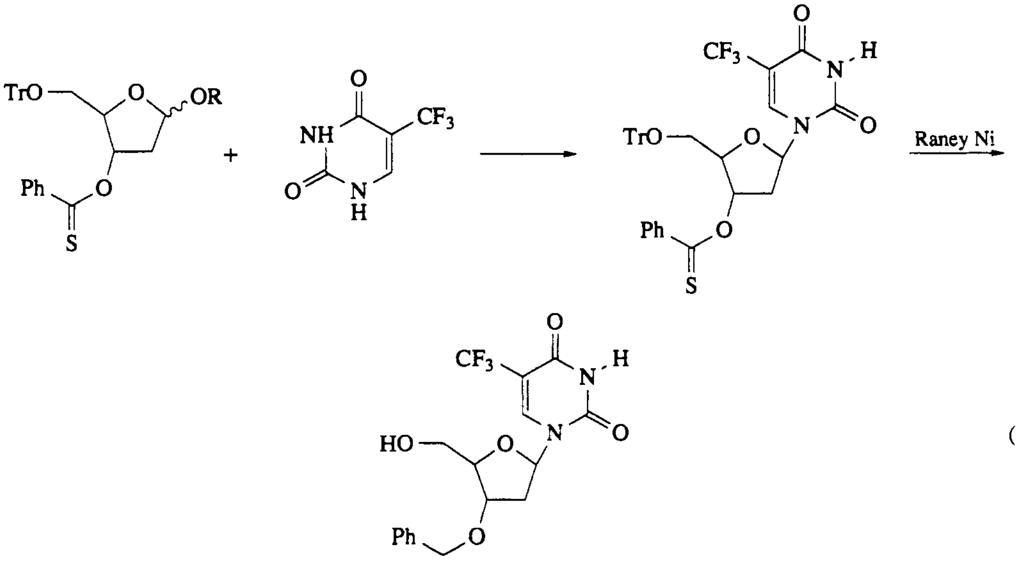

**(43)**

(39)

Nicolaou and coworkers have not only used thioxocarboxylic esters as precursors of the first stable 1,2-dithietane,[106] but also as a photochemical approach to the oxepane system (equation 40),[106–109] which could be useful in a total synthesis of brevetoxin B.[109]

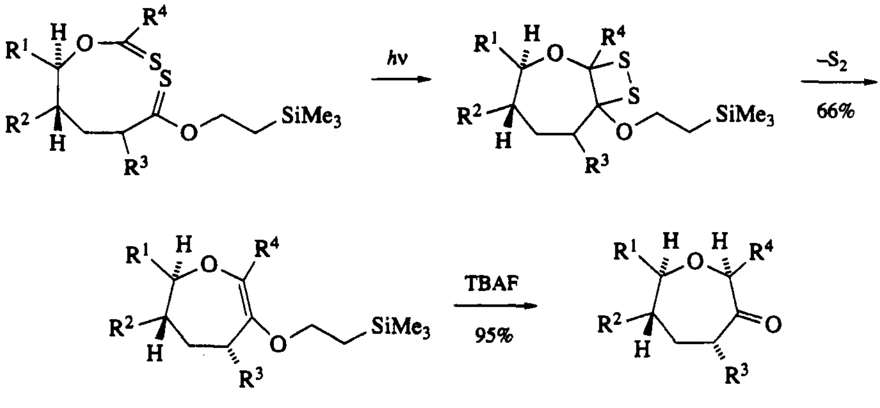

(40)

On account of the increased attention the class of thioxocarboxylic esters has recently gained, new and successful efforts have led to a considerable improvement in the methods that are available for the preparation of these compounds. The advances in this field are clearly described in several review articles and monographs which have appeared in the last decade.[6,14,15,25,28]

### 2.5.3.1 Thioacylation of Alcohols and Phenols with Thioacyl Halides

Thioacyl halides are not easily accessible. Aliphatic derivatives, in particular, can only be isolated in rare cases. Thioacylations of alcohols are therefore less important as synthetic methods than acylation of thiols with acyl halides. Nevertheless, a variety of *O*-alkyl and *O*-aryl arenecarbothioates (**2**) have been obtained according to equation (41).[6,14,25,28]

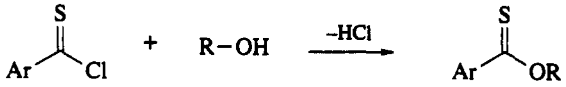

(41)

**(2)**

A stable aliphatic thioacyl chloride (**44**) was obtained according to equation (42) and used in alcoholysis reactions to prepare thioxo malonates (**45**).[110] A mixture of sulfenyl chloride (**46**) and trisulfide (**47**), which does not however contain an α-oxothioacyl chloride,[111] also yields thioxoesters on base-catalyzed reaction with methanol (equation 43).[111]

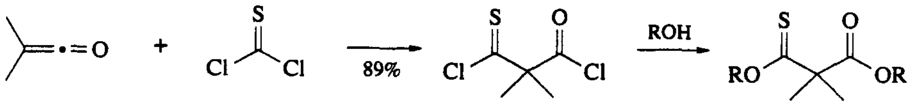

(42)

**(44)** **(45)** R = Me, Ph

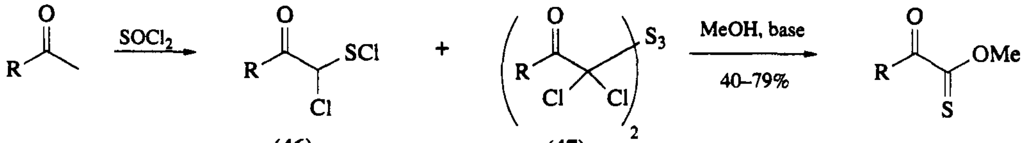

(43)

**(46)** **(47)**

Interestingly, *O*-trimethylsilyl carbothioates are formed if acyl chlorides react with trimethylsilyl sulfides (equation 44)[14,25] or *N*-trimethylsilylthioacetamide (equation 45).[112] This is obviously due to the strong silicon–oxygen bond present in the products. *O*-Alkyl perfluoroalkanethioates, *e.g.* (**48**) and (**49**), were also obtained by alcoholysis of perfluoroalkane thiocarbonyl chlorides.[6,14,25,28]

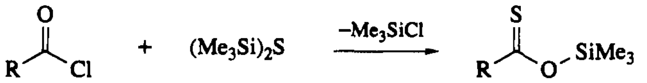

(44)

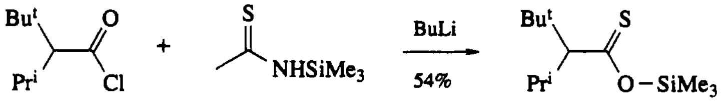

(45)

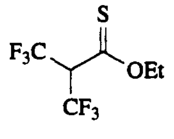

**(48)**

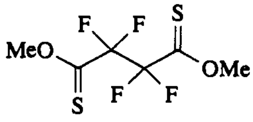

**(49)**

### 2.5.3.2 Thioacylation of Alcohols and Phenols with Anhydrides, Thioketenes, Thioesters and Dithioesters

The utility of various thioxo- and dithio-carboxylic anhydrides was recently reviewed by Martin and Barnikow,[113] who pointed out that bisthioacylthioanhydrides and the mixed anhydrides of dithiocarboxylic and diphenyldithiophosphinic acids are effective thioacylating agents for alcohols (equation 46), whereas carboxylic dithiocarboxylic anhydrides transfer an acyl group to a nucleophile.

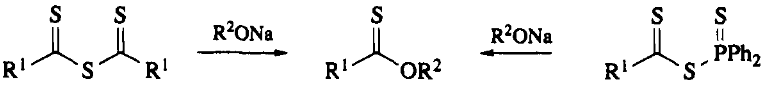

(46)

Thioketenes are stable isolable compounds only if the heterocumulene system is protected against dimerization by bulky substituents or perfluoroalkyl groups.[114] In these cases they are suitable educts for addition of hydroxylic compounds.[6,14,25,28,114,115] This reaction is also possible for the ylid (**50**). The resulting thioxoester (**51**) does not however react with *p*-nitrobenzaldehyde in a Wittig reaction.[115]

$Ph_3P{=}{\bullet}{=}{\bullet}{=}S$

**(50)**

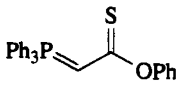

**(51)**

Furthermore, transient thioketenes with a wide variety of substituents R$^1$ and R$^2$, including hydrogen, can be generated by flash vacuum thermolysis of 1,2,3-thiadiazoles.[114] By *in situ* reactions thioxoesters are formed with alcohols (equation 47).

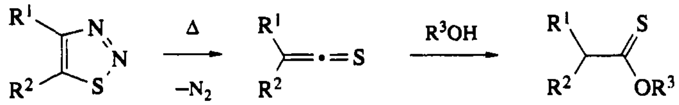

(47)

Interconversion of a thioxocarboxylic ester with an alcohol can be achieved in the presence of a base.[25,28] The reaction takes place with high yields if amino alcohols or diols are used. A series of macrocyclic polyether thioxoesters has been prepared by treating *O,O'*-diethyl dithiooxalate and *O,O'*-dimethyl 2,6-pyridinedicarbothioate with glycols. Methanol or ethanol were removed from the equilibrium mixture by distillation or adsorption in molecular sieves (equation 48).[28,116]

Transesterification of dithiocarboxylic esters with alcohols or alcoholates occurs in the presence of bases. In particular, the highly reactive sodium salts of methoxycarbonyl carbodithioates are used, which can be applied conveniently in aqueous solution or, if hydrolysis has to be avoided, in dry

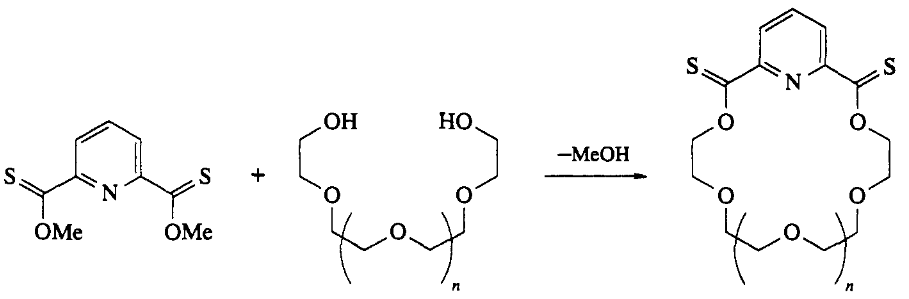

(48)

$n =$ 2 3 4 5
yield $=$ 71 39 26 10 %

THF.[14,25,28,117,118] For instance, the thioxobenzoylcholine (**52**), which is a powerful *N*-thiobenzoylating agent itself and can be advantageously used in peptide sequence analysis, was prepared according to equation (49).[118]

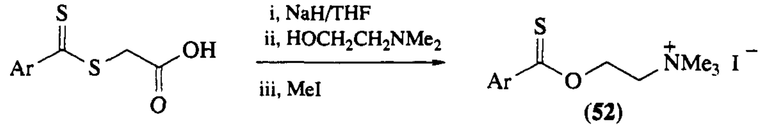

**(52)**

(49)

The above-mentioned *O*-deoxyribosyl thiobenzoate (*cf.* equation 39) was obtained from 1,5-protected deoxyribose and phenyl dithiobenzoate.[105] Also vinyl arenecarbodithioates were shown to be applicable for the synthesis of thioxoesters.[119]

The interesting *O*-alkyl ferrocenecarbothioates are available from *S*-methyl ferrocenecarbodithioate.[120] Instead of thioxo- or dithio-carboxylic esters thioacylimidazoles were successfully applied in certain cases,[6] for instance in preparing 2′- (**53**) or 3′-*O*-(*N*-acetylthioleucyl)adenosine 5′-phosphate.[121]

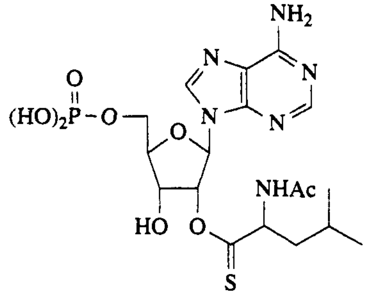

**(53)**

### 2.5.3.3 Acylation of Hydrogen Sulfide (Sulfhydrolysis) with Imidates and Orthoesters

Sulfhydrolysis of imidates is one of the most powerful tools in the field of thioxoester synthesis.[6,14,15,25,28] Advantageously, hydrochlorides or acetates are used as substrates instead of the free bases. Nitriles are useful precursors, but in some cases amides or imidochlorides are preferred as the starting material, according to Scheme 5.[6,14,15,25,28]

This method can be applied with almost every substituent $R^1$ and $R^2$. Thioxoesters of dicarboxylic acids can also be prepared *via* the imidates. Fully characterized authentic compounds of this type were, however, not obtained until the 1970s. Synthetic problems arise especially if the thioxoester groups are close enough to each other to permit formation of heterocycles during their synthesis.

Dialkyl bisthioxooxalates are obtained if the sulfhydrolysis is performed in the presence of acetic acid (equation 50).[122,123] The method also works successfully in the case of the homologous dicarboxylic acids (equation 51),[21,124] including the unsaturated fumaric acid.[20] The preparation and further reaction of the appropriate imidates is not always straightforward. As Hartke and coworkers[20,21,124] have shown, special substituents $R^2$ at the nitrogen atoms and carefully chosen reaction conditions are required in order to get high yields and pure products.

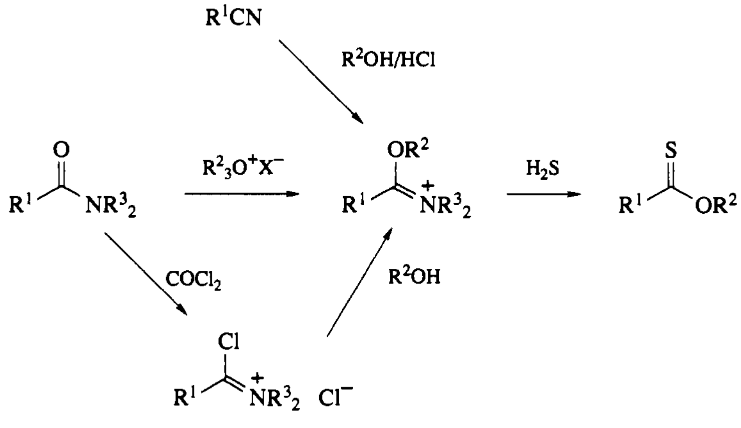

**Scheme 5**

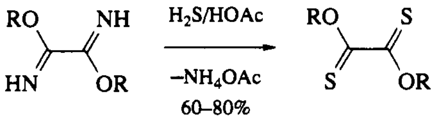

(50)

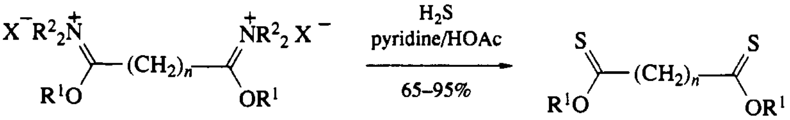

(51)

$2R^2$ = 2H, 2Me, $-(CH_2)_5-$ $n$ = 1–5; $R^1$ = Me, Et

Sulfhydrolysis of imidates is also the method of choice for preparing *O*-*t*-alkyl thioformates (equation 52),[104] *O*-methyl 2-hydroxy-, 2-mesyloxy- and 2-acetoxy-thiocarboxylic esters (**54**),[125] and especially the thioxoesters of amino acids and peptides. The first examples of the latter class of compound were described by Ried and von der Emden (1960).[126] More recently the preparation as well as the biochemical behavior, the thioacylating properties in particular (*cf.* Section 2.4, this volume), have been intensely studied[126–130] and thioxoesters of amino acids with different protecting groups (**55**) have been explored. Attempts to improve the leaving properties of the alkoxy groups by introduction of a 2-nitro substituent resulted in poorer yields of thioxoesters.[127]

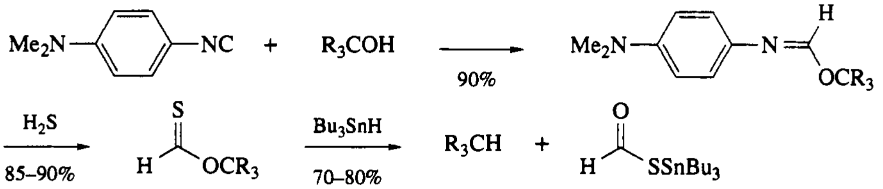

(52)

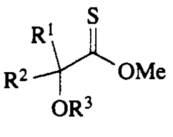

**(54)** $R^1$ = H, $R^2$ = Ph
$R^1$ = $R^2$ = Me
$R^3$ = H, Ms, Ts

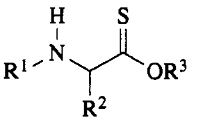

**(55)**
$R^1$ = Ac,[128] Bz,[128, 129] Z,[126, 127, 129]
t-BOC,[130] Ts,[126] Phth,[126] Fmoc[127]

A special route from imidates to *O*-ethyl arenecarbothioates *via* *O*,*N*-acetals of α-keto nitriles as intermediates is also suitable for the preparation of nitro derivatives which are difficult to obtain in good yields by other methods (equation 53).[131]

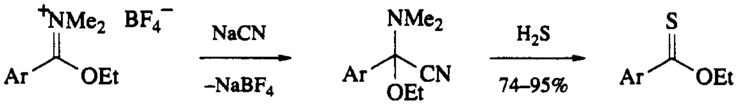

$^+NMe_2$ $BF_4^-$
Ar
OEt
NaCN
$-NaBF_4$
$NMe_2$
Ar
CN
OEt
$H_2S$
74–95%
S
Ar
OEt

(53)

Orthoesters undergo sulfhydrolysis in the presence of proton or Lewis acids ($ZnCl_2$, $FeCl_3$).[25] This method is still the best for the preparation of *O*-ethyl thioformate.[25,132]

In a similar way to the formation of open-chain thioxocarboxylic esters, thioxolactones are obtained from cyclic imidates.[28] Kaloustian *et al.*[133] have studied this reaction and its mechanism in detail. It is closely related to the sulfhydrolysis of dialkoxycarbenium ions, which also results in the formation of thioxoesters or thioxolactones (Scheme 6).[134]

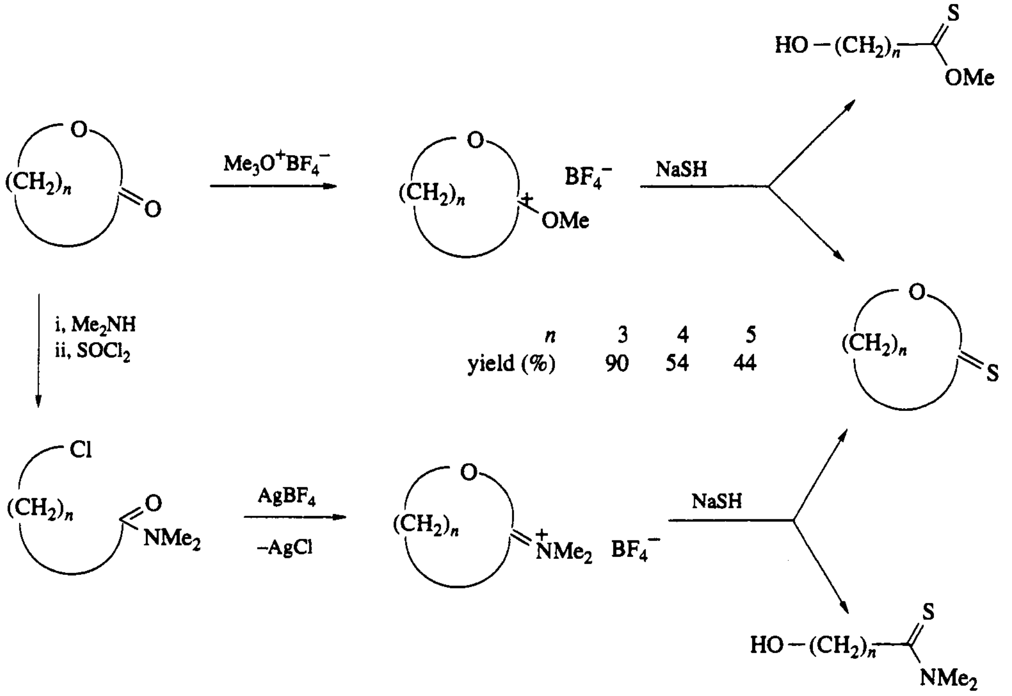

$HO-(CH_2)_n$
S
OMe
O
$(CH_2)_n$
O
$Me_3O^+BF_4^-$
$BF_4^-$
OMe
NaSH
i, $Me_2NH$
ii, $SOCl_2$
n 3 4 5
yield (%) 90 54 44
S
Cl
AgBF4
−AgCl
$NMe_2$
$NMe_2$ $BF_4^-$
NaSH
$HO-(CH_2)_n$
S
$NMe_2$

**Scheme 6**

*O*,*O*-Dimethyl monothiomaleate (**56**) and monothiofumarate (**57**) are formed in a complicated reaction from 2,5-dimethoxythiophene *via* an intermediate of the orthoester type.[135] *O*-Trimethylsilyl ketene-*O*,*O*-acetals are readily formed from carboxylic esters and can be transformed to thioxoesters, without being isolated, by reaction with hydrogen sulfide, according to equation (54).[136] Methyl thioxoarachidonate (**58**) was prepared by this route.[136]

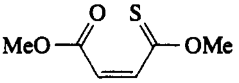

**(56)**

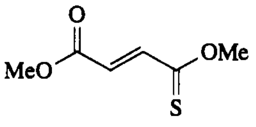

**(57)**

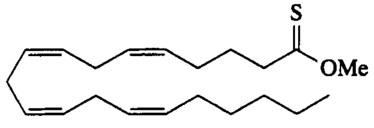

**(58)**

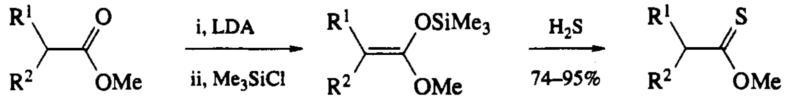

(54)

### 2.5.3.4 Thioacylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

As with the thiol ester series (Section 2.5.2.5) acylation reactions of this type are treated in other parts of this work. However, the most important synthetic reactions should be mentioned here.

Friedel–Crafts thioacylation (*cf.* Volume 2, Chapter 3.1) can be performed with *O*-aryl chlorothioformates (equation 55). The yields are only moderate and no *O*-alkyl derivatives are available.[25]

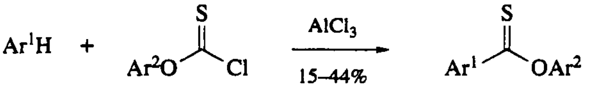

(55)

Carbanions (*cf.* Chapter 2, Chapter 3.4) derived from ketones, hydrazones or phosphonates react with *O*-alkyl chlorothioformates or thiocarbonates, resulting in *O*-alkyl β-oxo- (**59**),[137] β-hydrazono- (**60**)[138] or α,β-unsaturated-carbothioates (equation 56).[139]

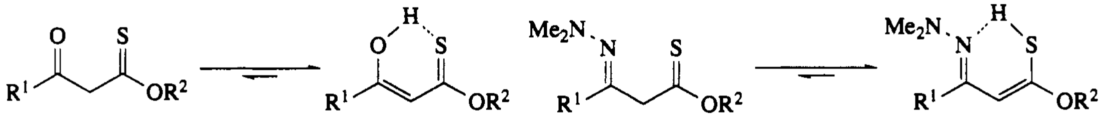

**(59)** **(60)**

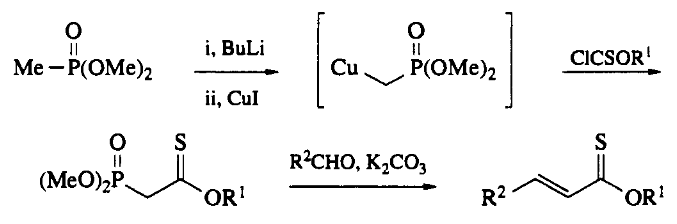

(56)

## 2.5.4 DITHIOCARBOXYLIC ESTERS AND DITHIOLACTONES

Although, presumably, dithiocarboxylic esters are prepared by alkylation of the strongly nucleophilic dithiocarboxylate salts in most cases (Section 2.5.1), thioacylation procedures provide a valuable alternative.[6,14,15,26,27,29,140,141] In particular, the sulfhydrolysis of imidothioates (Section 2.5.4.3) has retained its importance due to the convenient availability of the starting material, a nitrile or thioamide.

### 2.5.4.1 Thioacylation of Thiols with Thioacyl Halides, Thioacyl Anhydrides and Thioketenes

Thioacyl halides react with thiols in the presence of base and high yields of alkyl or aryl dithiocarboxylates (**3**) are obtained according to equation (57).[26]

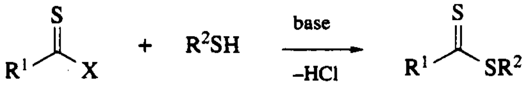

(57)

**(3)**

Thiols can also be thioacylated, in the same way as alcohols (Section 2.5.3.2),[113] by reaction with bisthioacyl thioanhydrides (equation 58). The preparation of aromatic as well as aliphatic thioanhydrides is possible according to novel procedures described by Kato *et al.*,[142–144] *e.g.* from the corresponding dithiocarboxylic acids and DCC[142] or 2-chloro-*N*-methylpyridinium iodide.[143] Even sterically hindered dithioesters are obtained (equation 58).[144]

Phenyl carbodithioates are obtained in acceptable yields by an intramolecular thioacylation according to equation (59).[145] The intermediate mixed thiocarboxylic thiocarbonic acid anhydride is not isolated but spontaneously eliminates carbon oxysulfide.

Thioacyl diphenylthiophosphinyl sulfides are useful thioacylating reagents too, which give dithioesters in good yields under mild reaction conditions (equation 60).[146]

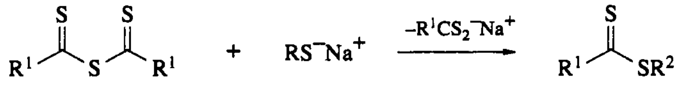

(58)

(3) $R^1 = Pr^i$, $R^2 = Bu^t$; 20%

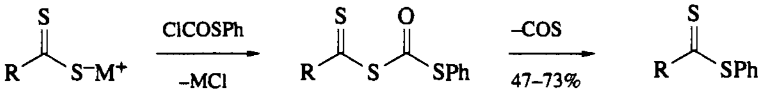

(59)

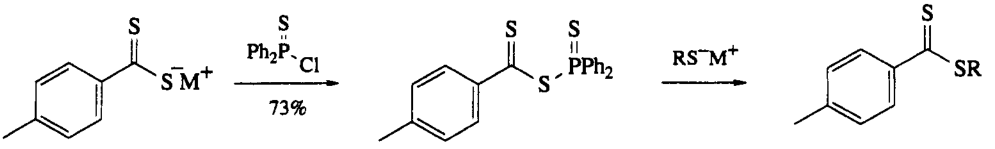

(60)

R = Et, M = Li; 74%
R = Ph, M = Na; 90%

Stable, as well as transient, thioketenes give dithiocarboxylic esters on reaction with thiols (equation 61).[114]

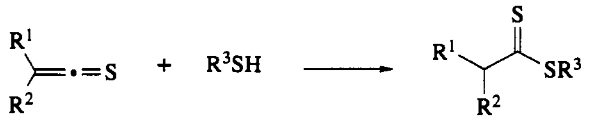

(61)

### 2.5.4.2 Transesterification of Thiols

The interchange reaction between a thioxoester and a thiol does not, in general, represent a meaningful synthetic procedure since dithioesters are more readily available than thioxoesters in most cases. However, *O*,*S*-diethyl trithiomalonate (**61b**) and diethyl tetrathiomalonate (**61c**) were prepared from *O*,*O*-diethyl dithiomalonate (**61a**).[21] On the other hand, the transformation of one dithiocarboxylic ester into another can be a useful and practicable reaction. For instance, ethyl arenecarbodithioates are interconverted to 2-dialkylaminoethyl arenecarbodithioates,[14] according to equation (62).

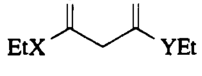

(**61a**) X = Y = O
(**61b**) X = O, Y = S
(**61c**) X = Y = S

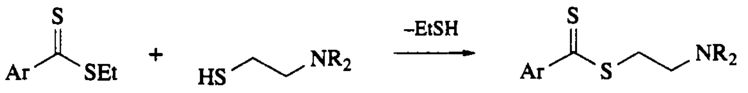

(62)

The highly activated sodium salts of carboxymethyl carbodithioates, which can be easily obtained by alkylation of sodium carbodithioates with bromoacetic acid,[14,147,148] have especially found application for the thioacylation of thiols.[6,14] Since the products are insoluble in water, the equilibrium reaction (equation 63) is shifted to the product side. Also vinyl arenecarbodithioates are reactive enough to be interconverted with potassium alkanethiolates.[119]

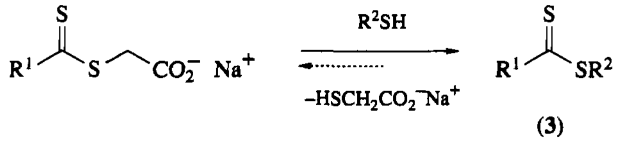

(63)

The unnatural coenzyme A dithioesters were synthesized by transesterification and their reactions with enzymes (acetyl transferase) studied.[149]

### 2.5.4.3 Acylation of Hydrogen Sulfide (Sulfhydrolysis) with Imidothioates and Related Compounds

Imidothioates in the neutral or ionic form are the most generally applied educts for the preparation of dithiocarboxylic esters. They are themselves prepared from nitriles, thioamides or isothiocyanates, and react with hydrogen sulfide under appropriate conditions to yield the dithioesters (Scheme 7).[6,14,26,27,29,141] Interesting examples (**62**)–(**73**) were described in the recent literature.

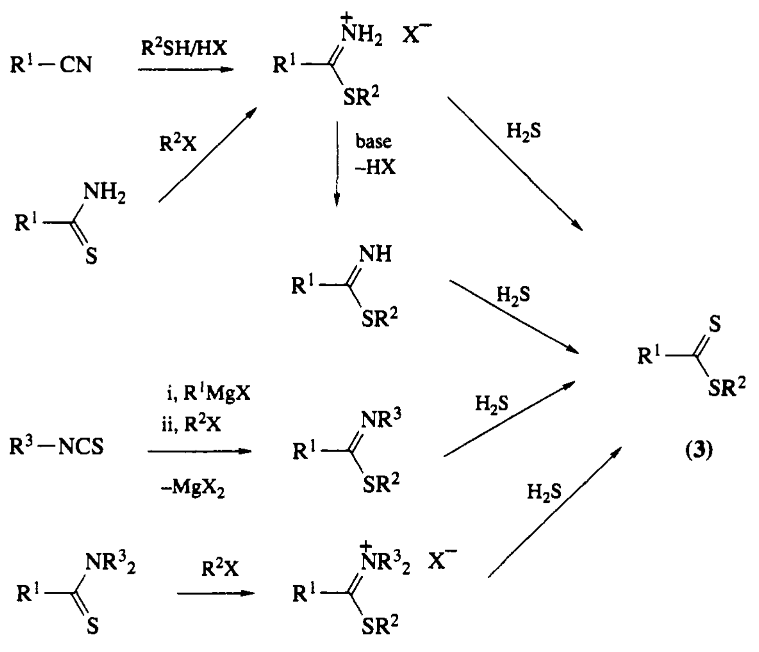

Scheme 7

Nitriles can be used as starting material for the bisdithioesters (**62**; $n = 4, 5, 10$),[124,150] whereas the derivatives with shorter chain lengths (**62**; $n = 1–3$),[21,124] as well as methyl dithiocinnamate (**63**),[20] are accessible from *N,N*-disubstituted thioamides *via* the corresponding imidothioate iodides. Methyl dithioacrylate (**65**), the simplest unsaturated dithioester, was prepared by flash vacuum thermolysis of a precursor dithioester (**64**), which had been obtained from the corresponding nitrile (equation 64).[151] It can be isolated as a red monomeric compound at 77 K but dimerizes rapidly at room temperature. The $\beta,\gamma$-unsaturated isoprene derivative (**66**)[152] and the methyl 2-arylpropanedithioates (**67**)[141] were prepared from phenyl isothiocyanate and used as educts for syntheses of lavandulal and *ar*-curcumene. Also ethyl furane-3-carbodithioate (**68**), as prepared from the nitrile, has found application in syntheses of the natural products egona ketone and *ar*-turmerone.[141]

Markedly branched alkyl 3,3,3-trialkylpropanedithioates (**69**) can be prepared by 1,4-addition of organometallics to $\alpha,\beta$-unsaturated imidothioates and subsequent sulfhydrolysis of the ketene *S,N*-acetals according to equation (65).[141,153]

Dithioesters of various amino acids with different *N*-protecting groups have been prepared. The corresponding nitriles are suitable educts in many cases (**70**).[154,155] Using $^{13}C$ sodium cyanide or $^{15}N$ ammonium chloride as starting material, Storer *et al.*[154] were able to prepare the respective isotopically labeled

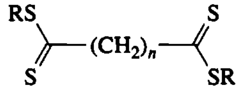

**(62)** $n = 1\text{–}5, 10$

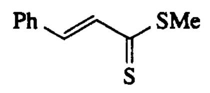

**(63)**

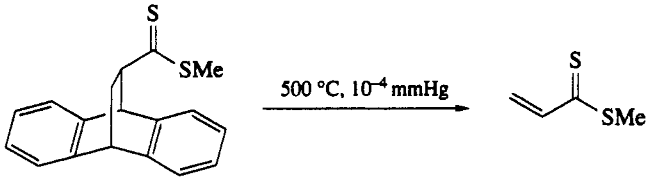

**(64)** **(65)**

(64)

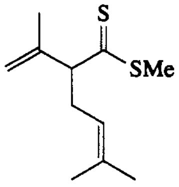

**(66)**

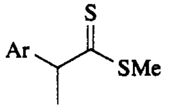

**(67)**

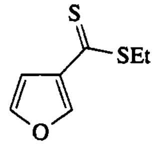

**(68)**

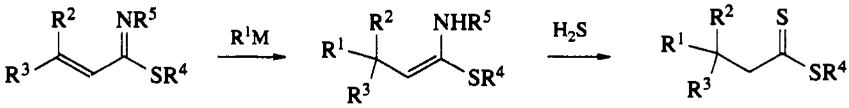

**(69)**

(65)

amino acid dithioesters, model compounds for studies on enzyme–substrate complexes. However, *N*-*t*-butyloxycarbonyl derivatives (**71**)[130] cannot be obtained in this way, since obviously deprotection occurs under the strongly acidic conditions of the first step. Instead, amino acid thiopiperidides have been successfully used.[130] Levesques *et al.* have prepared polydithioesters of type (**72**) from polyacrylonitrile[156] and (**73**) from polyethylene oxide *via* the polythioamide.[157]

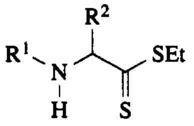

**(70)** $R^1$ = Ac, Bz, $PhCH_2CO$, Z

**(71)** $R^1$ = t-BOC

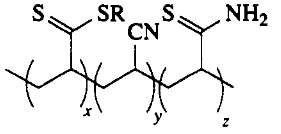

**(72)**

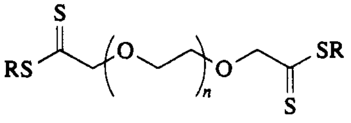

**(73)**

### 2.5.4.4 Dithiocarboxylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

As in previous sections of this chapter, only short comments will be made on this type of thioacylation. Reaction of benzene and activated arenes with alkyl or aryl chlorodithioformates under Friedel–Crafts conditions or with (alkylthio)thiocarbonyl hexafluoroantimonates, $(RSC{=}S)^+\ SbF_6^-$,[158] results in formation of the corresponding arenecarbodithioates.[6,14,26,27,156] Three interesting new examples, (**74**),[159] (**75**)[160] and (**76**),[156] may illustrate the scope of the reaction.

Methyl chlorodithioformate has also been used to prepare the methyl cyclopropanecarbodithioate (**77**; equation 66),[161] whereas dimethyl trithiocarbonate was reacted with the carbanions of ketones[162] and

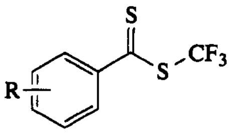

**(74)** R = H, F, $CF_3$, OMe

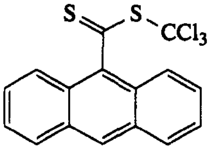

**(75)**

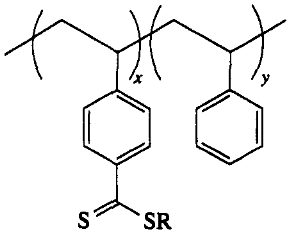

**(76)**

other compounds with activated methyl or methylene groups[163] to yield, for example, the methyl carbodithioates **(78)**[162] and **(79)**.[163]

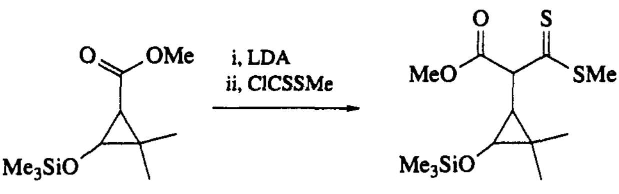

(66)

**(77)**

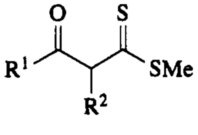

**(78)**

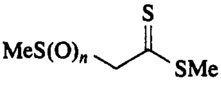

**(79)** $n = 1, 2$

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# 2.6

# Selenoesters of All Oxidation States

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## 2.6.1 INTRODUCTION

As well as thiol esters, selenol esters (**1**) frequently exhibit a high and selective reactivity toward nucleophiles, which is enhanced even further by activation with heavy ions or oxidizing agents. These properties make selenol esters valuable acyl transfer agents. This review deals with general methods for the synthesis of selenol esters and their reactivity as acyl transfer agents. Furthermore, selenoesters (**2**), isomeric compounds of selenol esters, and their derivatives selenoamides (**3**) are also described. These compounds show the characteristic reactivity based on the carbon–selenium double bond.

Hitherto known reviews for the chemistry of selenol esters and their derivatives are shown in refs. 1–5.

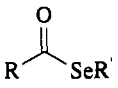

(1)

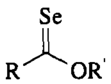

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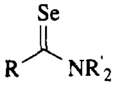

(3)

## 2.6.2 SELENOL ESTERS

### 2.6.2.1 Preparation

Many methods for the preparation of selenol esters have been developed. These can be classified into the following five general methods according to the types of reaction.

#### *2.6.2.1.1 Acylation of selenols and their metal salts*

In 1962 Renson *et al.* reported that a variety of selenol esters can be synthesized by the reaction of the appropriate acyl chlorides with selenols in the presence of pyridine.[6,7] Selenols can easily be prepared from elemental selenium and the corresponding Grignard reagents. In addition to simple selenol esters, α,β-unsaturated selenol esters (**4**) and (**5**) and *o*-substituted aromatic selenol esters (**6**) have been obtained by this method, as shown in Scheme 1. Butyl selenol esters are generally colorless or light yellow liquids, whereas the phenyl or substituted phenyl selenol esters are white solids, which are easily purified by recrystallization. More recently other groups have used Renson's method to synthesize similar selenol esters.[8–10]

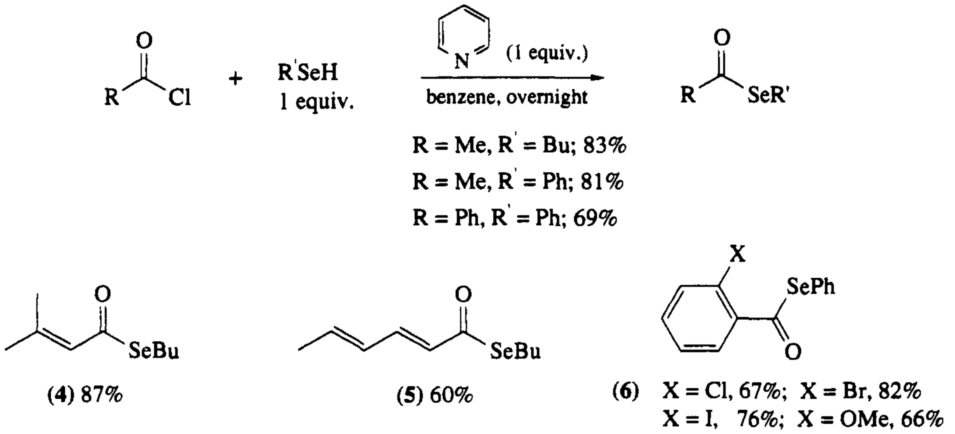

R = Me, R' = Bu; 83%
R = Me, R' = Ph; 81%
R = Ph, R' = Ph; 69%

(**4**) 87%

(**5**) 60%

(**6**) X = Cl, 67%; X = Br, 82%
X = I, 76%; X = OMe, 66%

**Scheme 1**

It has been reported that some selenols are directly acylated by carboxylic acids to give selenol esters.[11–14] For example, heating of 4-hydroselenobutyric acid at about 160 °C resulted in ring closure to give the corresponding γ-lactone (equation 1).[11]

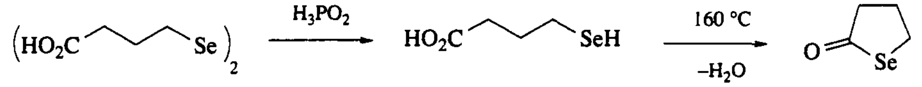 (1)

Areneselenyl magnesium bromide has been reported to react with *p*-substituted benzoyl halides, giving aromatic selenol esters[15–17] as the first examples exhibiting liquid crystal properties (equation 2).[15]

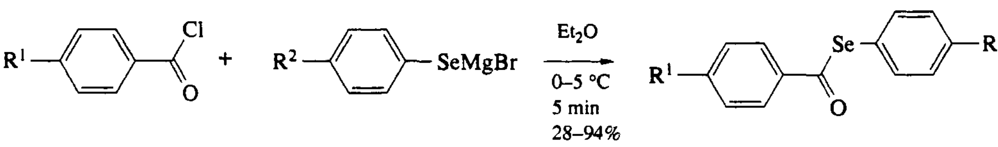 (2)

Alkali metal salts of selenol can also be used in the synthesis of selenol esters.[17–22] Axial and equatorial selenol esters of cholestane and androstanone have been prepared from the potassium salt (**7**) and benzoyl chloride (Scheme 2 illustrates the axial isomer).[18]

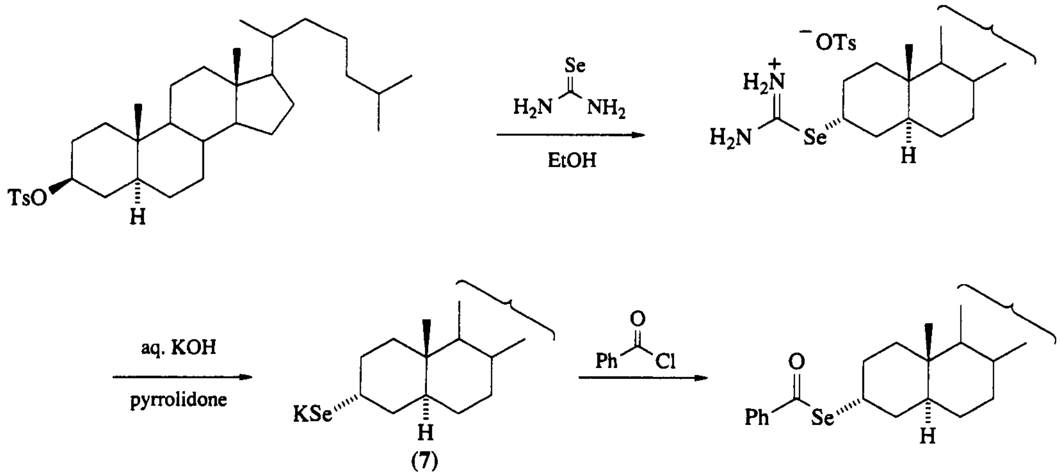
TsO
H
Se
H2N NH2
EtOH
OTs
H2N
H2N Se
H
aq. KOH
pyrrolidone
KSe
H
(7)
O
Ph Cl
O
Ph Se
H

**Scheme 2**

Reaction of acyl or aroyl halides with thallium(I) phenyl selenide, prepared by the reaction of either thallium(I) ethoxide or thallium(I) phenoxide with benzeneselenol, gave the corresponding phenyl selenol esters in yields over 97% (equation 3).[23]

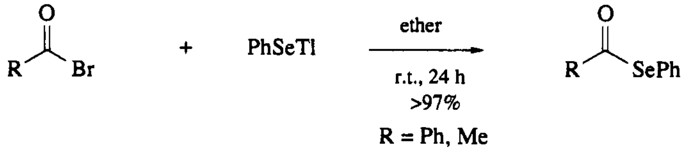
O
R Br
+
PhSeTl
ether
r.t., 24 h
>97%
R = Ph, Me
O
R SePh

(3)

Tetraethylammonium borohydride reduces diphenyl diselenide to phenylselenolate anion. When an acyl halide is added to the toluene solution of phenylselenolate anion, the corresponding acylation product is isolated in good yield (equation 4).[24] Resin-supported phenyl selenide anion underwent acylation with acetyl chloride under mild reaction conditions.[25]

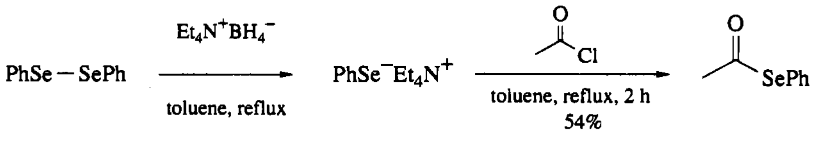
PhSe—SePh
Et4N+BH4−
toluene, reflux
PhSe−Et4N+
O
Cl
toluene, reflux, 2 h
54%
O
SePh

(4)

Selenol esters have also been prepared from trimethylsilyl selenides and acyl halides, as shown in equation (5).[26]

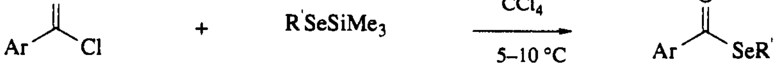
O
Ar Cl
+
R'SeSiMe3
CCl4
5–10 °C
O
Ar SeR'

(5)

A mild and convenient method has been attained by using the imidazolide (**8**; equation 6) or triazolide (**9**; equation 7) of carboxylic acids as a key intermediate. Treatment of an imidazolide of carboxylic acid with 1.2 equiv. of benzeneselenol and 0.02 equiv. of sodium phenoxide provided the selenol ester in a quantitative yield.[27] In the case of the triazolide of carboxylic acids, the reaction proceeded in the absence of base.[28]

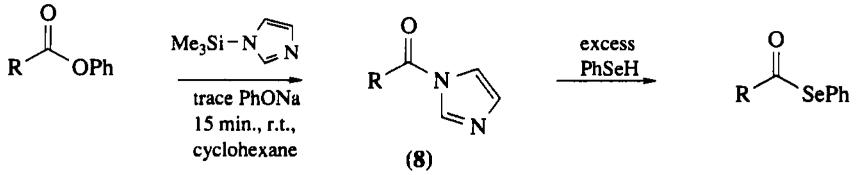
O
R OPh
Me3Si−N N
trace PhONa
15 min., r.t.,
cyclohexane
O
R N
N
(8)
excess
PhSeH
O
R SePh

(6)

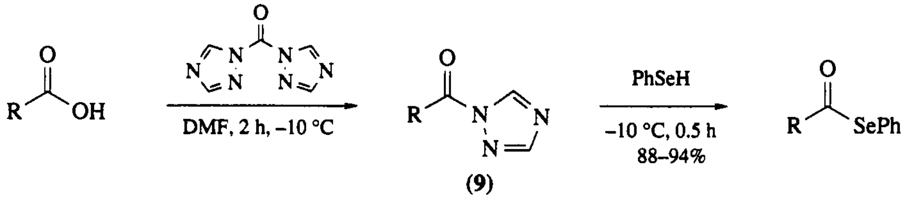

Reaction of some vinyl esters (**10**; Scheme 3) of carboxylic acids with selenolate gave the corresponding selenol esters in high yields because of the good leaving ability of enolate.[29]

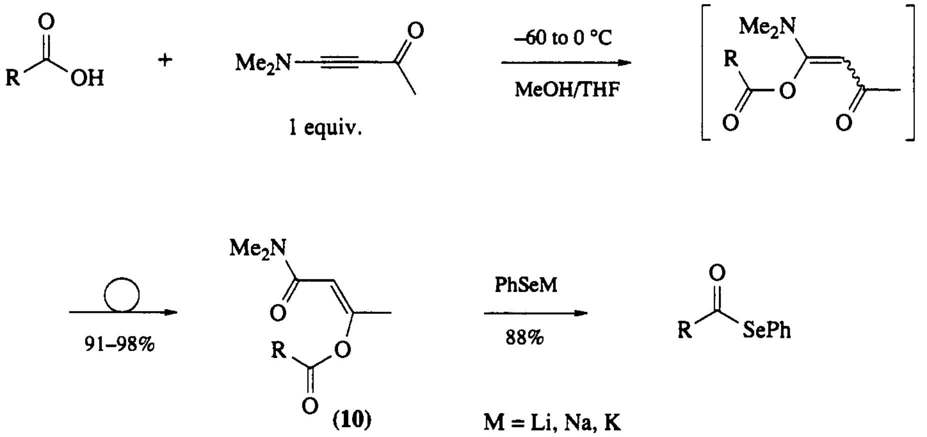

Scheme 3

Reaction of carboxylic acids with phenyl dichlorophosphate, followed by the addition of benzeneselenol to the mixture afforded selenol esters (Scheme 4).[30] The reaction is assumed to proceed *via* the pentacovalent oxyphosphorane intermediates (**11a**) and (**11b**).

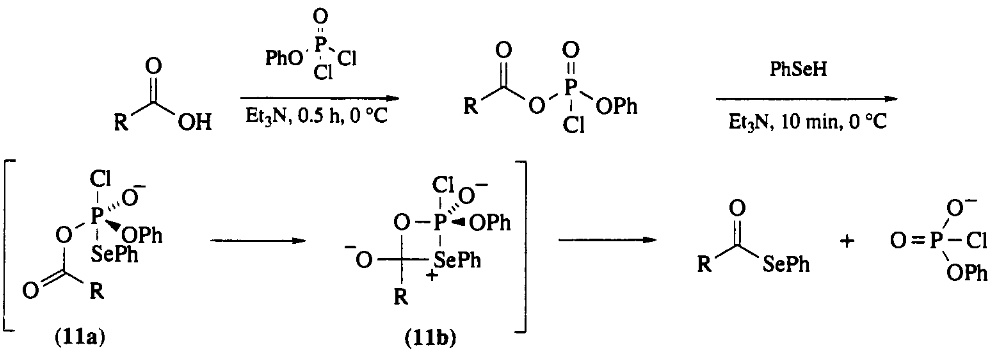

Scheme 4

It has recently been disclosed that the electrophilic cleavage of zirconocene complex (**12**; Scheme 5) leads easily to new *Se,Se′*-disubstituted derivatives of benzene-1,2-diselenol (**13**) in good yields, with quantitative recovery of the organometallic moiety of the reagent.[31,32]

### *2.6.2.1.2 Alkylation of selenocarboxylates*

As well as acylation of selenols, alkylation of selenocarboxylates with alkyl halides is one of the most straightforward methods for synthesis of selenol esters. However, known examples of selenol esters synthesized using this strategy have been limited to a few cases,[33–37] due to the difficulty of the preparation of selenocarboxylates.

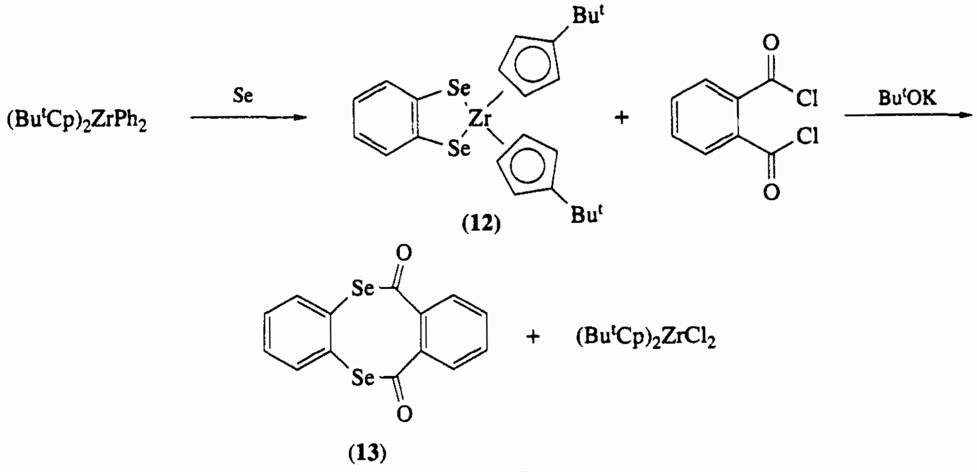
(Bu$^t$Cp)$_2$ZrPh$_2$
Se
Bu$^t$
Se
Zr
Se
Bu$^t$
(12)
O
Cl
Cl
O
+
Bu$^t$OK
O
Se
Se
O
(13)
+ (Bu$^t$Cp)$_2$ZrCl$_2$

**Scheme 5**

Jensen *et al.* reported that selenobenzoic *Se*-acid (**14**; equation 8) is formed as the primary product of the reaction of benzoyl chloride with hydrogen selenide in pyridine, but (**14**) is a very unstable liquid that reversibly loses hydrogen selenide to give dibenzoyl selenide. On rapid treatment with *p*-nitrobenzyl bromide, the selenobenzoic *Se*-acid formed *in situ* produced (*p*-nitrobenzyl)selenobenzoate in high yield.[33]

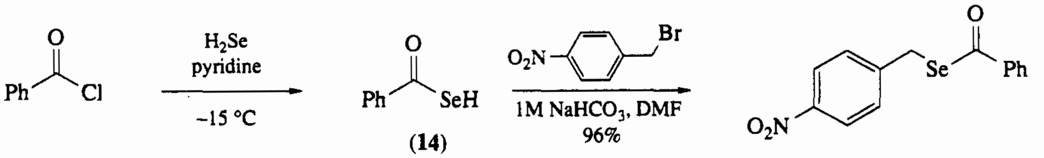 (8)
Ph
Cl
H$_2$Se
pyridine
−15 °C
Ph
SeH
(14)
O$_2$N
Br
1M NaHCO$_3$, DMF
96%
Se
Ph
O$_2$N

Potassium selenocarboxylates, which are useful starting materials for the preparation of selenol esters,[34,35] can be prepared by the reaction of diacyl selenides with methanolic potassium hydroxide (equation 9).

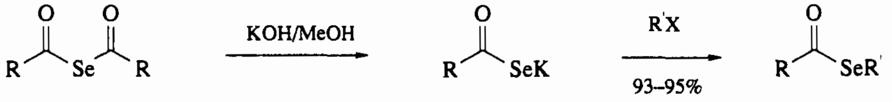 (9)
R
Se
R
KOH/MeOH
R
SeK
R′X
93–95%
R
SeR′

R = Ph, *p*-Cl-$C_6H_4$, n-$C_{17}H_{35}$; R′ = Me, PhCOCH$_2$

Piperidinium selenocarboxylates (**15**; equation 10) have been isolated in high yields from the reaction between diacyl diselenides and piperidine. The salts (**15**) dissolved in common protic and aprotic solvents and readily reacted with alkylating agents such as phenacyl bromide to give the corresponding esters in almost quantitative yields.[36,37]

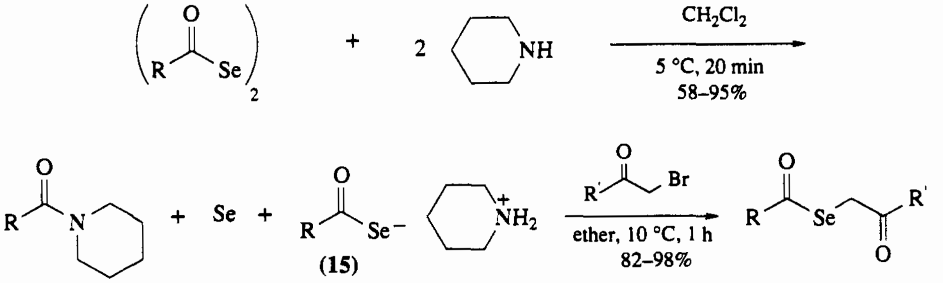 (10)
R
Se
2
+ 2
NH
CH$_2$Cl$_2$
5 °C, 20 min
58–95%
R
N
+ Se +
R
Se$^-$
(15)
NH$_2$
R′
Br
ether, 10 °C, 1 h
82–98%
R
Se
R′

### *2.6.2.1.3 Reaction of esters with aluminum selenolate*

One of the most general methods for synthesis of selenol esters uses dimethylaluminum methylselenolate (**16**), which has been found to be a remarkably efficient and versatile reagent for the conversion of *O*-alkyl esters to their corresponding methylselenol esters under mild conditions.[38,39] The reagent (**16**) is conveniently prepared by heating a toluene solution of trimethylaluminum with powdered selenium for 2 h under reflux. The transformation of various esters to selenol esters can be completed within 1 h. Representative results are shown in Scheme 6 (**17–23**). This method can also be applied to cyclic esters (**19**) and esters (**20**)–(**23**) containing other functional groups.

Reaction of methyl *trans*-4-*t*-butylcyclohexanecarboxylate (**24b**; equation 12) with (**16**) proceeded much faster than the reaction of the *cis* isomer (**24a**; equation 11), a result suggesting that this method is highly sensitive to steric factors.[40–42]

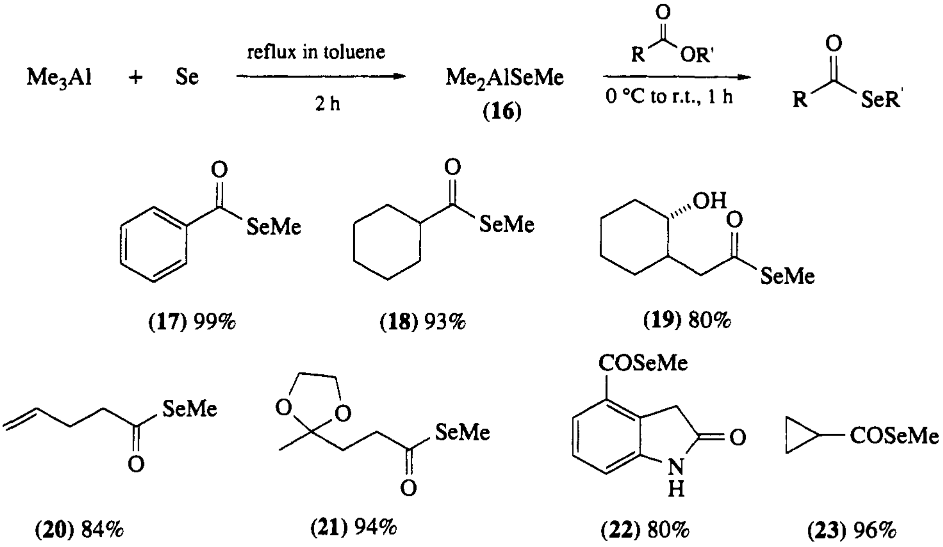
$Me_3Al$
+
Se
reflux in toluene
2 h
$Me_2AlSeMe$
(16)
R
OR'
O
0 °C to r.t., 1 h
R
SeR'
O
SeMe
(17) 99%
SeMe
(18) 93%
OH
SeMe
(19) 80%
SeMe
(20) 84%
SeMe
(21) 94%
COSeMe
N
H
(22) 80%
COSeMe
(23) 96%

**Scheme 6**

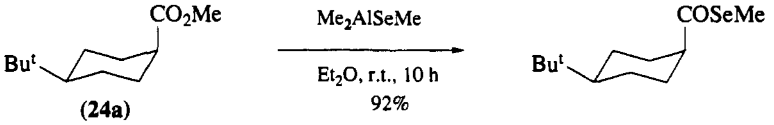
$CO_2Me$
$Bu^t$
(24a)
$Me_2AlSeMe$
$Et_2O$, r.t., 10 h
92%
COSeMe
$Bu^t$

(11)

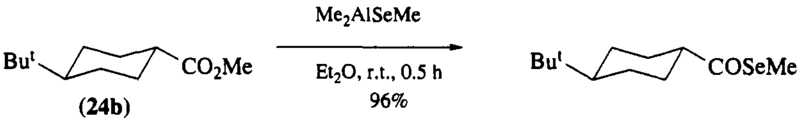
$Bu^t$
$CO_2Me$
(24b)
$Me_2AlSeMe$
$Et_2O$, r.t., 0.5 h
96%
$Bu^t$
COSeMe

(12)

### *2.6.2.1.4 Reaction of carboxylic acids with selenocyanates or* N*-PSP in the presence of trialkylphosphine*

It has been reported that aryl selenocyanate (**25**; Scheme 7) reacts with carboxylic acids in the presence of tributylphosphine under mild conditions, giving rise to selenol esters in good yields.[43] The process may involve the reaction of carboxylic acids with selenophosphonium salt (**26**), which is the key intermediate.

Since phenyl selenocyanate (**25**; Ar = Ph) is a sensitive liquid, which slowly decomposes on storage during a few days, an improved method using *N*-phenylselenophthalimide (*N*-PSP; **27**), a stable crystalline compound, has been developed.[44,45] In general, the yields of selenol esters prepared from *N*-PSP/$Bu_3P$ are higher than those obtained employing ArSeCN/$Bu_3P$.

*N*-Acetylselenenamide (**28**) can also be used in place of (**25**) or (**27**).[46]

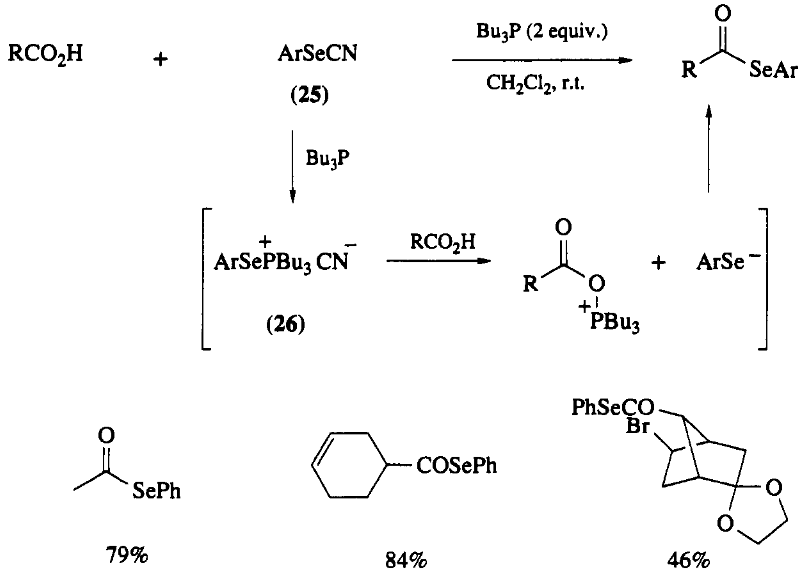
RCO₂H
+
ArSeCN
(25)
Bu₃P (2 equiv.)
CH₂Cl₂, r.t.
SeAr
Bu₃P
ArSePBu₃ CN
(26)
RCO₂H
PBu₃
+ ArSe⁻
SePh
79%
COSePh
84%
PhSeCO
Br
46%

**Scheme 7**

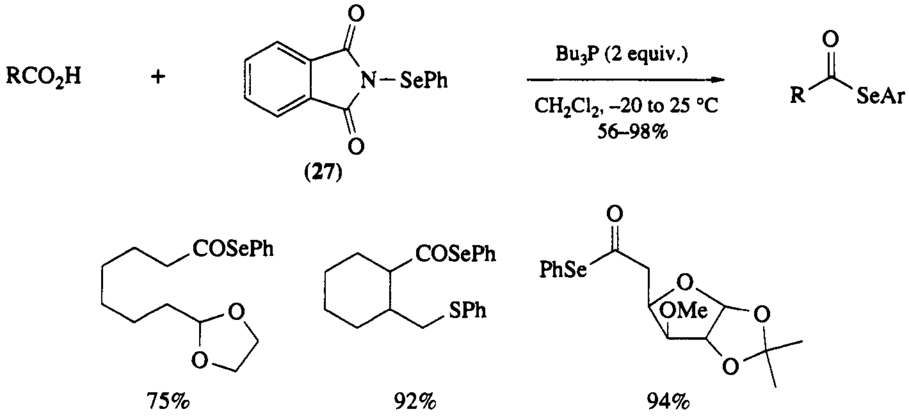
RCO₂H
+
N–SePh
(27)
Bu₃P (2 equiv.)
CH₂Cl₂, -20 to 25 °C
56–98%
SeAr
COSePh
75%
COSePh
SPh
92%
PhSe
OMe
94%

**Scheme 8**

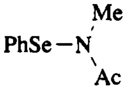

$$\text{PhSe}-\text{N}(\text{Me})(\text{Ac})$$

**(28)**

### *2.6.2.1.5 Miscellaneous*

The reaction of *N*-acylhydrazines with benzeneseleninic acid (**29**; Scheme 9) in the presence of triphenylphosphine afforded high yields of diverse selenol esters.[47–49] Alkyl, cycloalkyl and aryl selenol esters were prepared, even in the case of the highly hindered compounds (**30**) and (**31**).

The removal of sulfur and selenium atoms from compounds (**32**) and (**33**) using triphenylphosphine easily furnished the corresponding selenol esters (equation 13).[50,51]

Diaryl diselenides reacted with carbon monoxide (5–100 atm) at 100–200 °C, in the presence of $Co_2(CO)_8$ as a catalyst, to give the corresponding selenol esters of aromatic carboxylic acids in 21–96% yields (equation 14).[52]

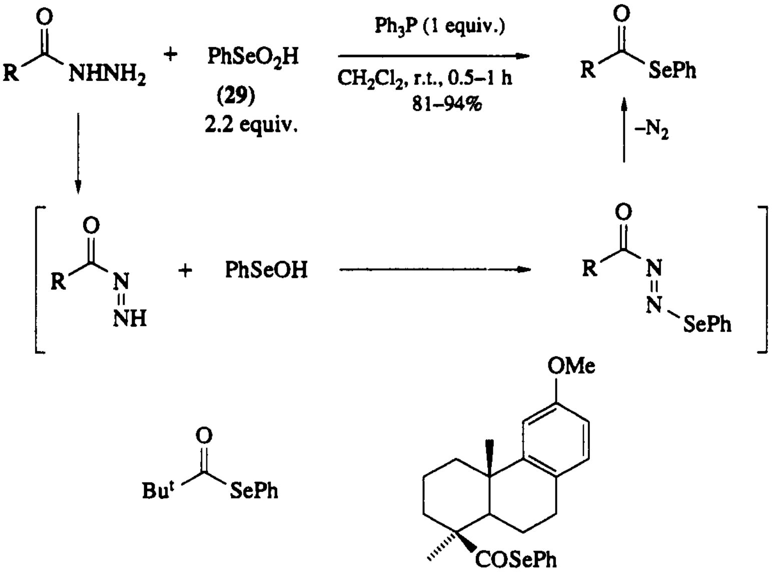
R
NHNH2
+
PhSeO2H
(29)
2.2 equiv.
Ph3P (1 equiv.)
CH2Cl2, r.t., 0.5–1 h
81–94%
SePh
–N2
PhSeOH
NH
N
SePh
OMe
But
COSePh

(30) 83%

(31) 84%

**Scheme 9**

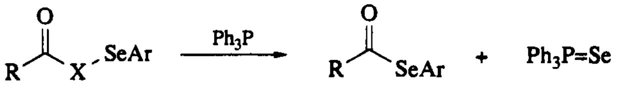
R
X
SeAr
Ph3P
R
SeAr
+
Ph3P=Se

(32) X = S
(33) X = Se

(13)

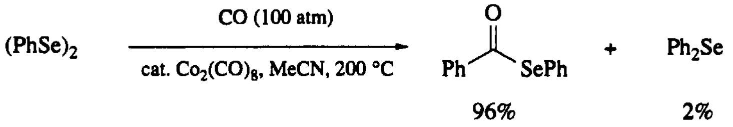
(PhSe)2
CO (100 atm)
cat. Co2(CO)8, MeCN, 200 °C
Ph
SePh
+
Ph2Se
96%
2%

(14)

### 2.6.2.2 Reactions

Selenol esters are expected to be a more reactive species than the corresponding thiol esters or oxo esters due to the comparatively weak bonding between carbon and selenium. The ability of the selenol esters to serve as active acyl transfer agents has been readily demonstrated by the easy conversion of the selenol ester (**34**; equation 15) to its corresponding acid (**35**), ester (**36**) or amide (**37**).[38,53] This acyl–selenium bond cleavage has also been promoted by $\mathrm{Cu^I}$ and $\mathrm{Cu^{II}}$ salts.[38,39] The isopropylidene derivative (**38**; equation 16) of ribofuranosylacetate has been converted to a lactone (**40**) in good yield *via* the selenol ester (**39**).

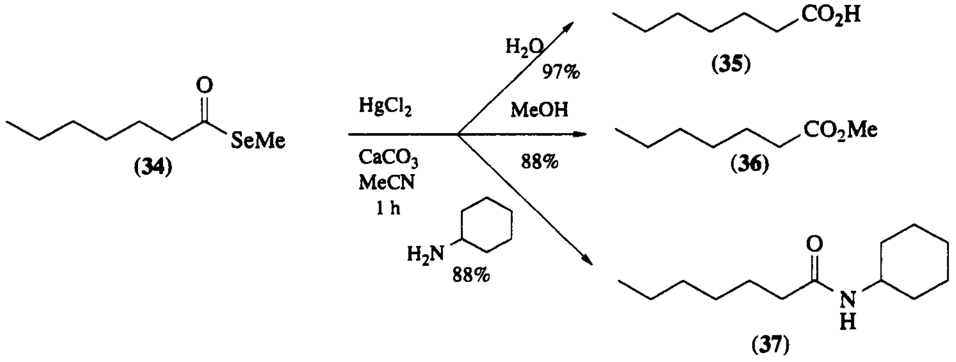
SeMe
(34)
HgCl2
CaCO3
MeCN
1 h
H2O
97%
MeOH
88%
H2N
88%
CO2H
(35)
CO2Me
(36)
N
H
(37)

(15)

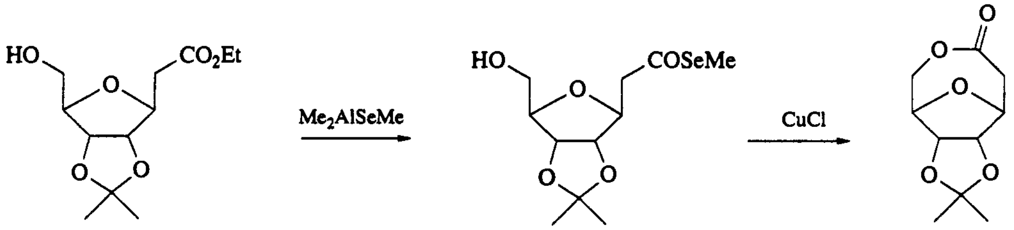

**(38)** **(39)** **(40)** (16)

Single-step conversion of carboxylic acids to amides has been achieved using the *N*-PSP/$Bu_3P$ reaction system in the presence of amines (equation 17).[44,45]

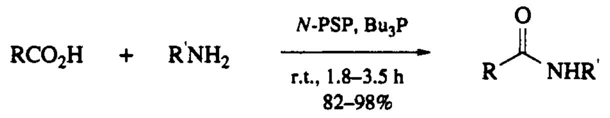

$$RCO_2H + R'NH_2 \xrightarrow[\text{r.t., 1.8–3.5 h}]{N\text{-PSP, }Bu_3P} RC(O)NHR' \qquad (17)$$

82–98%

Some examples of carbon–carbon bond formation by the reaction of selenol esters with carbon nucleophiles have been reported. *Se*-Acylmethyl selenocarboxylates (**41**) readily extruded selenium by treatment with potassium *t*-pentoxide to form 1,3-diketones in good yields.[35] A proposed pathway is outlined in Scheme 10.

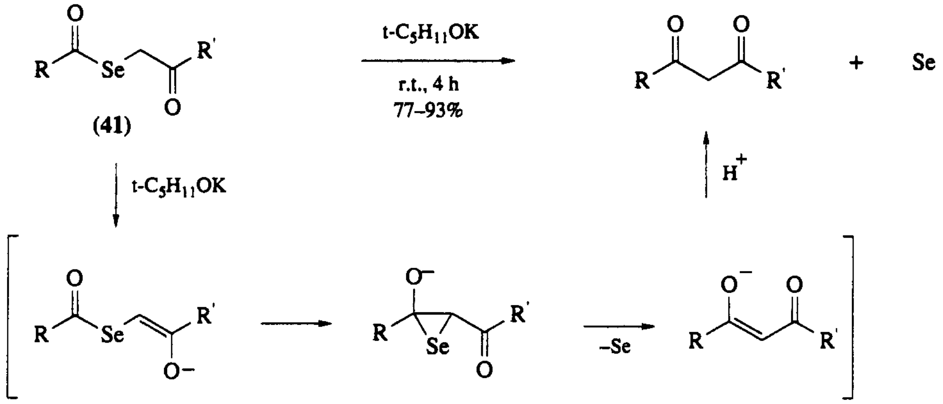

**(41)**

**Scheme 10**

A mild and efficient transformation of esters into ketones *via* selenol esters has been developed. Selenol esters smoothly reacted with organocuprates to produce ketones in excellent yields (equation 18).[40] Reaction with a vinylcopper(I) reagent gave α,β-unsaturated ketones (equation 19).[54] Butylmanganese chloride also transformed selenol esters into ketones, although 3 equiv. of the reagent are required to complete the reaction. $Me_2Cd$ and PhHgBr were not effective for this transformation.

The copper or copper(I) iodide-catalyzed insertion of diazomethane into the acyl–selenium linkage of selenol esters was reported to afford the corresponding ketones as the chief products.[55,56] A nonconcerted mechanism involving a tetrahedral intermediate (**42**; Scheme 11) has been suggested.

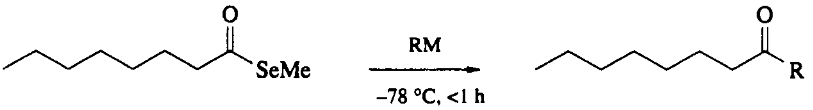

(18)

RM = $Me_2CuLi$; $Bu_2CuLi$; $Bu^tCuSPhLi$ R = Me, 98%; R = Bu, 96%; R = $Bu^t$, 98%

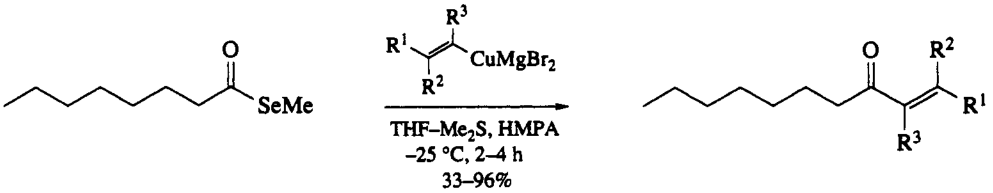
O
SeMe
R^3
R^1
CuMgBr_2
R^2
THF-Me_2S, HMPA
-25 °C, 2–4 h
33–96%
O
R^2
R^1
R^3

(19)

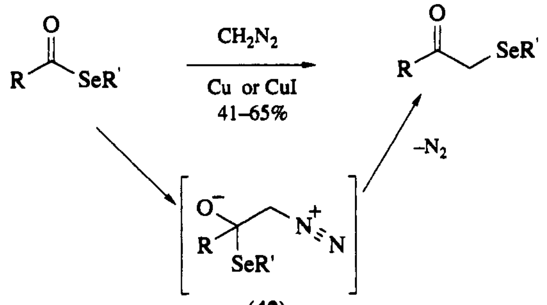
O
R
SeR'
CH_2N_2
Cu or CuI
41–65%
O
R
SeR'
-N_2
O^-
R
SeR'
N^+
N

**(42)**

**Scheme 11**

Moreover, the selenol esters can acylate reactive arenes and heteroaromatic compounds when copper(I) triflate is employed as the selenophilic metal cation.[39,57] The acylation of aromatics by use of the benzene complex of copper(I) triflate (**43**; Scheme 12) was complete within an hour at room temperature, with benzene as solvent, and the acylation products were obtained in high yields. Intramolecular acylation was examined successfully, as shown in equation (20).

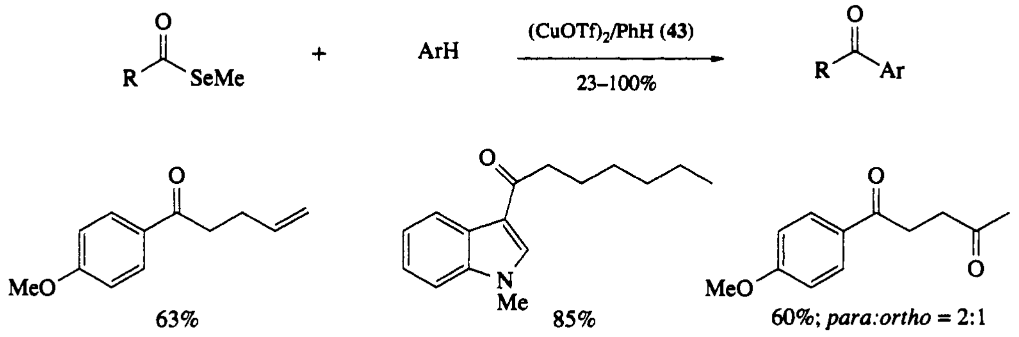
O
R
SeMe
+
ArH
(CuOTf)_2/PhH (43)
23–100%
O
R
Ar
O
MeO
63%
O
N
Me
85%
O
MeO
O
60%; para:ortho = 2:1

**Scheme 12**

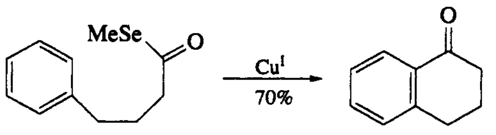
MeSe
O
Cu^I
70%
O

(20)

Selenol esters also reacted with isonitrile (**44**; Scheme 13) at room temperature for 6–20 h in the presence of 1.5 equiv. of copper(I) oxide and triethylamine (or DBU) to give oxazole (**45**).[39,57] The reaction presumably proceeds through an intermediate β-ketoisonitrile (**46**), and copper(I) oxide functions as a reagent for complexation to the selenium moiety.

Recently it has become apparent that phenyl selenides (**47**; Scheme 14) are efficiently reduced to alkanes (**48**) with tin hydride by a free radical process.[58]

The reaction of selenol esters with tributyltin hydride resulted in the formation of the corresponding aldehydes (**49**) and alkanes (**50**).[59,60] The formation ratio of aldehydes to alkanes depends on the reaction temperature, as exemplified in Scheme 15. When the reaction was carried out with UV irradiation at ambient temperature, the aldehyde was formed predominantly, in high yields.

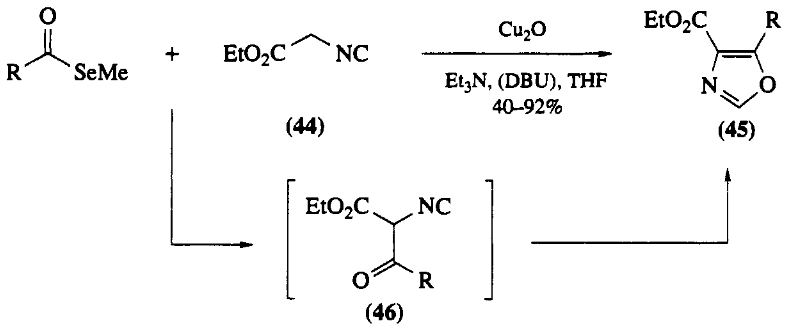
R
SeMe
O
+
EtO2C
NC
(44)
Cu2O
Et3N, (DBU), THF
40–92%
EtO2C
R
N
O
(45)
EtO2C
NC
O
R
(46)

**Scheme 13**

$$\begin{tikzcd}
\underset{(47)}{\text{R-SePh}} \arrow[rr, "\text{Bu}^n_3\text{SnH}", "\text{AIBN}"'] \arrow[dr, "\text{Bu}^n_3\text{Sn}\bullet", "-\text{Bu}^n_3\text{SnSePh}"'] & & \underset{(48)}{\text{R-H}} \\
& \text{R}\bullet \arrow[ur, "\text{Bu}^n_3\text{SnH}", "-\text{Bu}^n_3\text{Sn}\bullet"'] &
\end{tikzcd}$$

**Scheme 14**

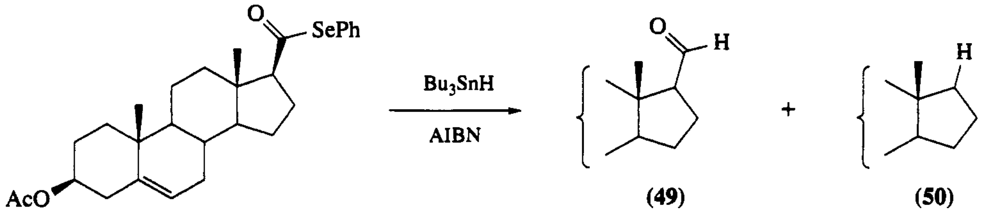
O
SePh
AcO
$Bu_3SnH$
AIBN
O
H
+
H

| | (49) | (50) |
|---|---|---|
| benzene, 80 °C | 82% | 17% |
| mesitylene, 164 °C | 18% | 80% |

**Scheme 15**

A new method for the transformation of —$CO_2H$ to —H has been attained by formation of the selenol ester from carboxylic acid, followed by its reduction.[59–64] Owing to high chemoselectivity and mild reaction conditions, this method is often utilized for the synthesis of natural products (equation 21).[30]

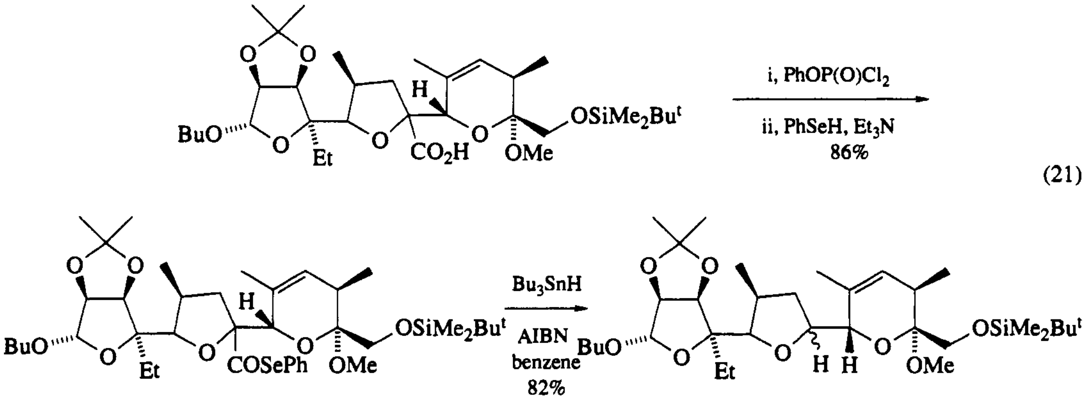
O
O
BuO
O
Et
O
H
CO2H
O
OMe
OSiMe2Bu$^t$
i, PhOP(O)Cl2
ii, PhSeH, Et3N
86%
COSePh
Bu3SnH
AIBN
benzene
82%
H H

(21)

Intramolecular capture of the acyl radical formed *in situ* from a selenol ester and tin hydride has been examined successfully.[65] Phenyl selenol esters (**51**), with an unsaturated functional group (C═C *etc.*) at the appropriate position of the molecule, reacted with 1.2 equiv. of tin hydride in the presence of 0.05 equiv. of AIBN in benzene under reflux to yield ketones (**52**) through radical cyclization of the acyl radical (**53**; Scheme 16).[65,66]

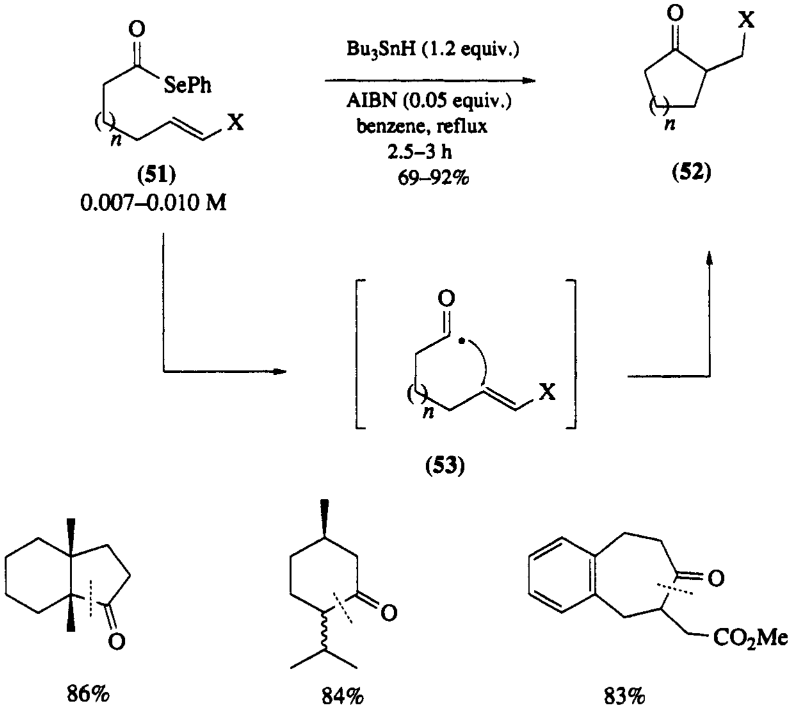
O
SePh
X
n
(51)
0.007–0.010 M
$Bu_3SnH$ (1.2 equiv.)
AIBN (0.05 equiv.)
benzene, reflux
2.5–3 h
69–92%
O
X
n
(52)
O
n
X
(53)
O
86%
O
84%
O
$CO_2Me$
83%

**Scheme 16**

It was reported that UV irradiation of *o*-substituted aromatic selenol esters (**54**) led to the 5*H*-[1]benzoselenino[2,3-*b*]pyridine (**55**) ring system *via* a selenol ester–seleninone transformation.[67,68]

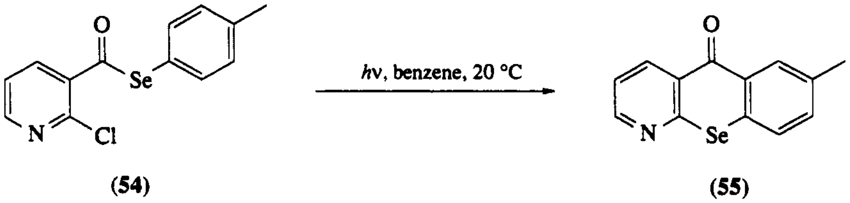
O
Se
N
Cl
(54)
*h*ν, benzene, 20 °C
O
N
Se
(55)

(22)

## 2.6.3 SELENOESTERS

### 2.6.3.1 Preparation

In an earlier investigation, aryl selenoesters have been prepared by the reaction of hydrogen selenide with imido esters (**56**; equation 24), but the yields were very low (**56**; R = Ph, 5.6%; **56**; R = *p*-tol 3%).[69,70] The yield was somewhat improved by employing methyl benzimidate hydrochloride (**57**; equation 23) as the starting material.[71]

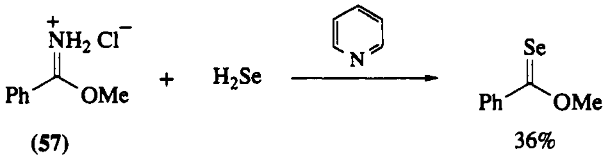
$\overset{+}{N}H_2\,Cl^-$
Ph
OMe
(57)
+
$H_2Se$
N
Se
Ph
OMe
36%

(23)

A practically useful method for synthesis of selenoesters has been developed by Barton *et al.* A wide range of aliphatic and aromatic selenoesters have been synthesized from the appropriate *N*,*N*-disubstituted imidoyl chlorides (**58**) using sodium hydrogen selenide to introduce selenium.[72,73] Imidoyl chlorides (**58**) can be obtained by the reaction of amides with phosgene. Representative results are shown in Scheme 17 (formulae **59**–**61**).

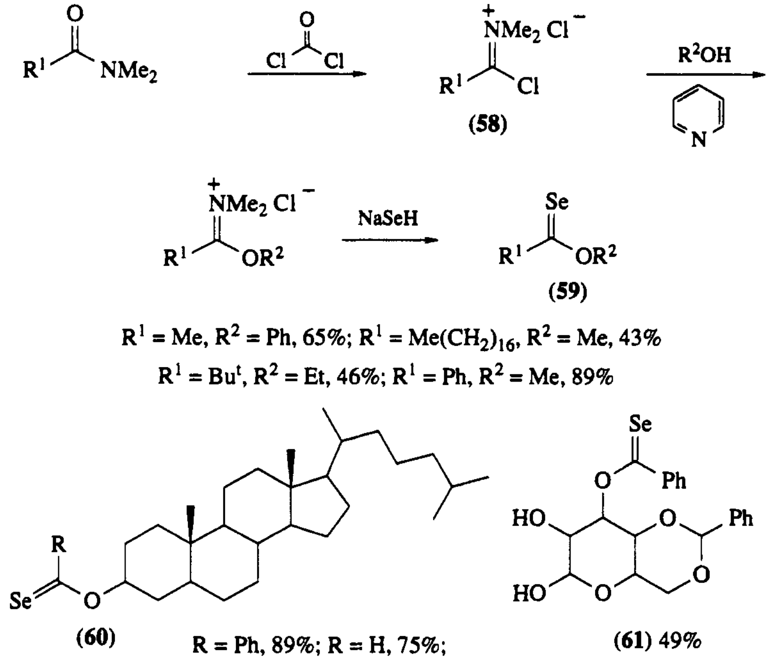

(**58**)

(**59**)

$R^1$ = Me, $R^2$ = Ph, 65%; $R^1$ = $Me(CH_2)_{16}$, $R^2$ = Me, 43%
$R^1$ = $Bu^t$, $R^2$ = Et, 46%; $R^1$ = Ph, $R^2$ = Me, 89%

(**60**) R = Ph, 89%; R = H, 75%;
R = Me, 74%

(**61**) 49%

**Scheme 17**

Cohen investigated in detail the addition of hydrogen selenide to imido esters (**56**), and found that selenoesters can be prepared by the reaction at –20 to –30 °C in the presence of pyridine–triethylamine.[74]

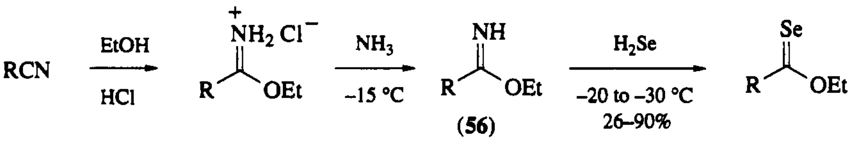

(**56**) (24)

α-Substituted selenoesters (**64**) have been synthesized by the reaction of alcohols with arylethynylselenolate salts (**63**), prepared from 4-aryl-1,2,3-selenadiazoles (**62**).[75]

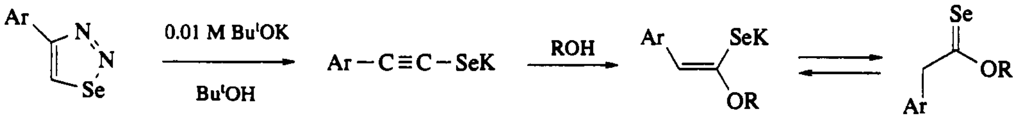

(**62**) (**63**) (**64**)

**Scheme 18**

The transition metal complex pentacarbonyl(methoxyarylcarbene)chromium(0) (**65**), gave selenoesters on treatment with elemental selenium.[76]

Although alkylation of potassium selenobenzoate with alkyl halides led to the formation of selenol esters *via Se*-alkylation, as described in Section 2.6.2.1.1 (equation 9), the reaction of (**66**; equation 26) with trimethylsilyl chloride proceeded through *O*-silylation to give trimethylsilyl selenobenzoate (**67**) in 68% yield.[77] The driving force of the reaction may be due to the strong affinity of silicon for oxygen.

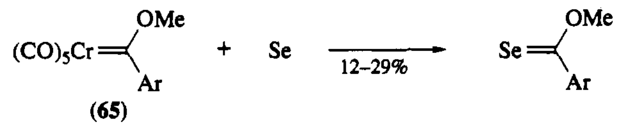
OMe
(CO)5Cr
Ar
(65)
+ Se
12–29%
OMe
Se
Ar

(25)

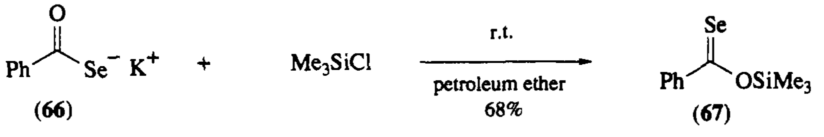
O
Ph
Se⁻ K⁺
(66)
+
Me3SiCl
r.t.
petroleum ether
68%
Se
Ph
OSiMe3
(67)

(26)

The aliphatic selenoesters are generally yellow liquids, while the aromatic esters are deep red oils, the latter being more stable. However, after 2–3 days, these begin to decompose slowly, accompanied by the deposition of elemental selenium, although they can be stored in a refrigerator for a few months without any such precipitation.[74]

### 2.6.3.2 Reactions

Owing to the high polarizability of the carbon–selenium double bond, selenoesters can easily be attacked by nucleophiles. This property makes a selenoester a useful reagent for the synthesis of heterocycles.[78–83] Condensation of selenoesters with bifunctional aromatic or aliphatic amines has yielded a variety of nitrogen-containing heterocyclic compounds (Scheme 19).

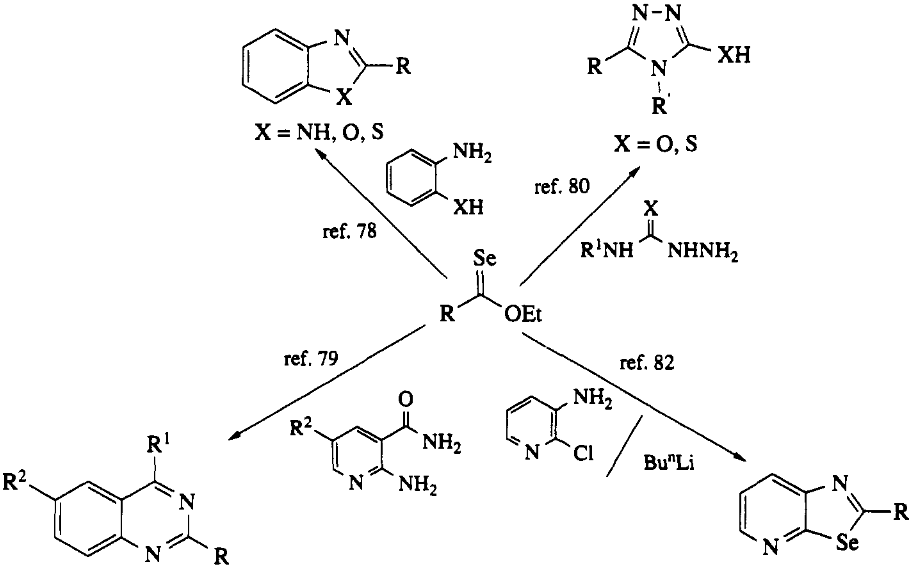
N
R
X
X = NH, O, S
NH2
XH
ref. 78
N-N
R
XH
N
R'
X = O, S
ref. 80
X
R¹NH
NHNH2
Se
R
OEt
ref. 79
ref. 82
O
R²
NH2
N
NH2
NH2
N
Cl
BuⁿLi
R¹
R²
N
N
R
N
R
N
Se

Scheme 19

Selenazofurin (**72**), a promising antitumor agent, has been synthesized from methyl 2,5-anhydroallonimidate (**68**), as illustrated in Scheme 20. The key step of the synthesis is the formation of the selenazole (**71**) by the condensation of the selenoester (**69**) with ethyl 2-amino-2-cyanoacetate (**70**).[83]

In order to clarify the fundamental chemical reactivity of selenoesters, Barton *et al.* investigated their reaction behavior towards a number of common reagents.[72] The reduction of selenoesters was examined using sodium borohydride–triphenylphosphine or Raney nickel (W-2). In both cases, the corresponding ether (**73**) was obtained in high yield. On the other hand, selenoesters were converted into their parent oxocarbonyl derivatives (**76**) in high yield on treatment with oxidizing agents such as benzeneseleninic anhydride (**74**)[84,85] and bis(*p*-methoxyphenyl) telluroxide (**75**; Scheme 21).[86]

The reaction of a selenoester with the methylene Wittig reagent (**77**) readily produces the vinyl ether (**78**; equation 27).[72]

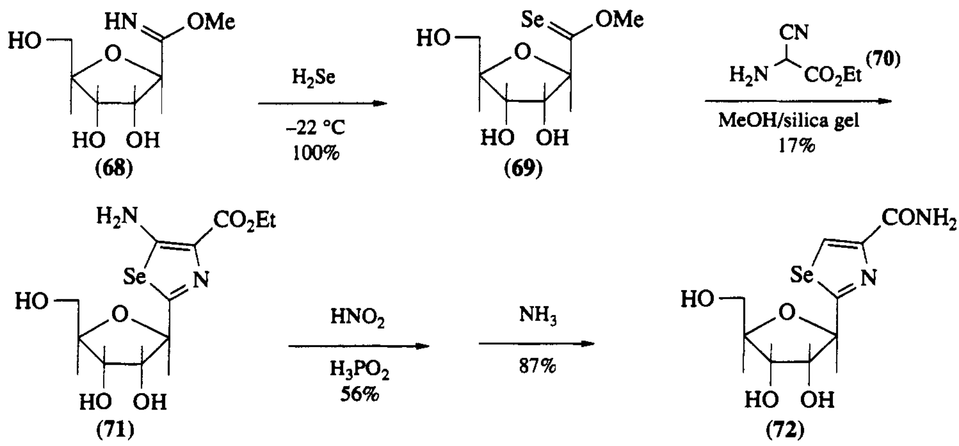
HN
OMe
HO
O
HO OH
(68)
H2Se
-22 °C
100%
Se
OMe
HO
O
HO OH
(69)
CN
H2N
CO2Et
(70)
MeOH/silica gel
17%
H2N
CO2Et
Se
N
HO
O
HO OH
(71)
HNO2
H3PO2
56%
NH3
87%
CONH2
Se
N
HO
O
HO OH
(72)

**Scheme 20**

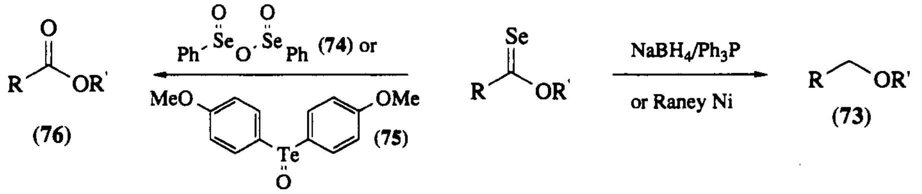
O
R
OR'
(76)
O O
Ph Se O Se Ph (74) or
MeO
OMe
Te
O
(75)
Se
R
OR'
NaBH4/Ph3P
or Raney Ni
R
OR'
(73)

**Scheme 21**

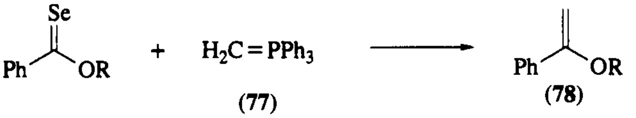
Se
Ph
OR
+
H2C=PPh3
(77)
Ph
OR
(78)

(27)

During these investigations, it was observed that the selenoester reacts with triphenylphosphine in the presence of atmospheric oxygen to give the parent ester.[72] Hansen investigated in detail the reactions between triethylphosphine and a number of aliphatic and aromatic selenoesters.[87] Under oxygen-free conditions, the reaction of aliphatic selenoesters with triethylphosphine gave a purple intermediate, which was quenched with atmospheric oxygen to give the corresponding esters (**79**). In the case of aromatic selenoesters, the same reaction under oxygen-free conditions led to deselenative coupling to afford α-dialkoxy-stilbenes (**80**) and -dibenzyls (**81**). When the reaction was carried out in cyclohexene, 7-alkoxy-7-phenylbicyclo[4.1.0]heptanes (**82**) were formed. These results suggest the formation of α-alkoxycarbene (**84**). The presence of benzaldehyde in the reaction mixture led to α-alkoxystilbenes (**83**; Scheme 22).

Recently, the synthesis of selenoaldehyde was examined by the reaction of *O*-alkyl selenoformates (**85**) with aryllithium.[88–90] 2,4,6-Tri-*t*-butylphenyllithium reacted with selenoformates (**85**) at three different sites, *i.e.* the selenoformyl carbon, the selenoformyl hydrogen and the selenium, to give several reaction products including 6,8-di-*t*-butyl-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin (**86**). The formation of (**86**) is explained in terms of the intermediacy of 2,4,6-tri-*t*-butylselenobenzaldehyde (**87**; Scheme 23).

Selenoesters have easily undergone exchange reactions with sulfur to give the corresponding thioesters (**88**), on heating with elemental sulfur (equation 28).[91,92]

Some other reactions concerning selenoesters are shown in refs. 93 and 94.

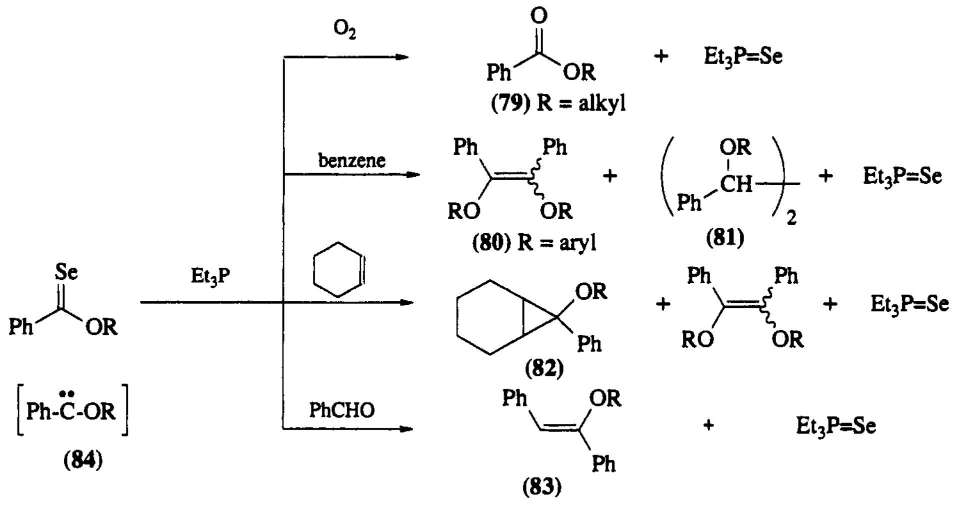
O2
benzene
PhCHO
Et3P
(79) R = alkyl
(80) R = aryl
(81)
(82)
(83)
(84)
Et3P=Se

Scheme 22

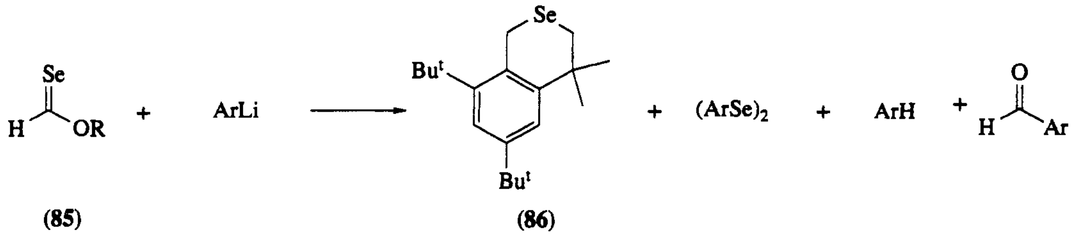
(85)
(86)
ArLi
(ArSe)2
ArH

R = Bu$^t$, cholesteryl; Ar = 2,4,6-tri-*t*-butylphenyl

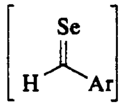

(87)

Scheme 23

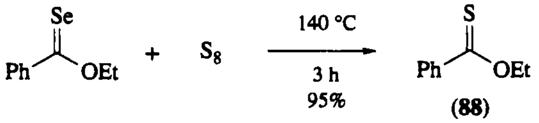
140 °C
3 h
95%
(88)

(28)

## 2.6.4 SELENOAMIDES

### 2.6.4.1 Preparation

#### *2.6.4.1.1* N-*Unsubstituted selenoamides*

In general, *N*-unsubstituted selenoamides have been prepared by the addition of hydrogen selenide to the corresponding nitriles in the presence of base.

In an earlier investigation of the synthesis of aromatic selenoamides, gaseous hydrogen selenide was directly introduced into the reaction vessel. The first report[95] described the synthesis of benzeneselenoamide by the reaction of benzonitrile with hydrogen selenide in ethanolic ammonia (equation 29), while its 4-methyl derivative was synthesized under similar conditions.[96]

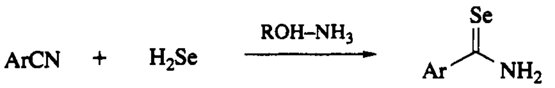
ArCN
+
H2Se
ROH-NH3
Se
Ar
NH2

(29)

In order to avoid the handling of poisonous hydrogen selenide, two other useful syntheses have been devised. One method[97] uses the reaction of aromatic nitriles with aluminum selenide in the presence of pyridine, triethylamine and water (Scheme 24), while the other[98] is performed by the reaction of nitriles with selenium, carbon monoxide and water in the presence of triethylamine (Scheme 25). These methods are exceedingly convenient in terms of manipulation without the isolation of hydrogen selenide for the preparation of selenoamides. Using these methods, a variety of aromatic and heterocyclic selenoamides can be obtained from the corresponding nitriles in high yields.

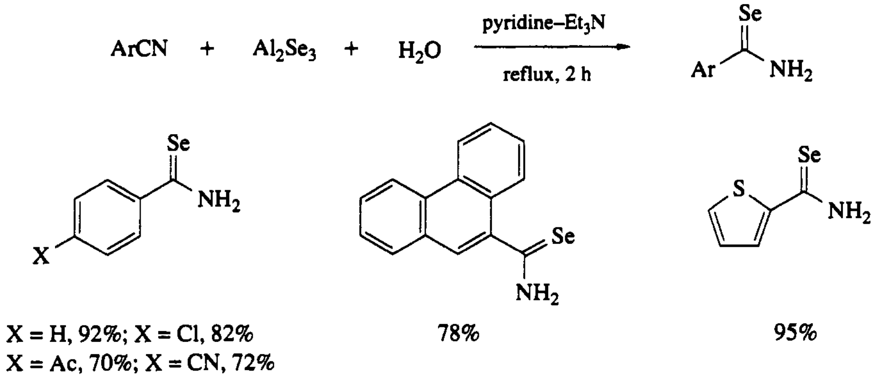
ArCN
+
Al2Se3
+
H2O
pyridine–Et3N
reflux, 2 h
Se
Ar
NH2
Se
NH2
X
Se
NH2
S
Se
NH2
X = H, 92%; X = Cl, 82%
X = Ac, 70%; X = CN, 72%
78%
95%

Scheme 24

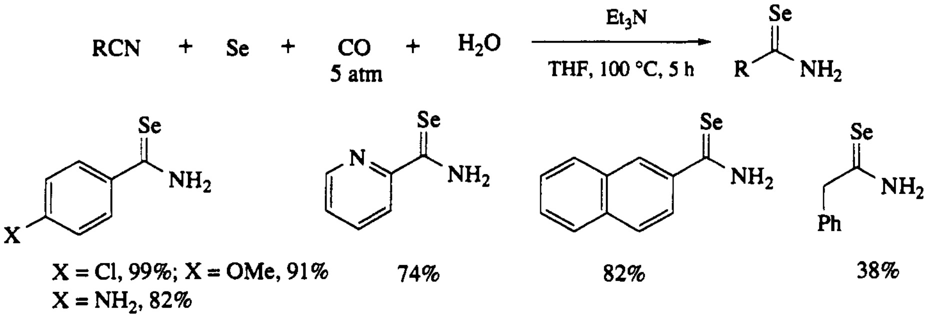
RCN
+
Se
+
CO
5 atm
+
H2O
Et3N
THF, 100 °C, 5 h
Se
R
NH2
Se
NH2
X
N
Se
NH2
Se
NH2
Se
NH2
Ph
X = Cl, 99%; X = OMe, 91%
X = NH2, 82%
74%
82%
38%

Scheme 25

The aromatic selenoamides are generally yellow solids and are stable enough under nitrogen at ordinary temperature to be kept for several weeks in high purity. On exposure to air, they gradually decompose into the starting nitriles, elemental selenium and water, at room temperature or below. These observations suggest that the selenoamides are in equilibrium with the corresponding nitriles and hydrogen selenide (equation 30).[98]

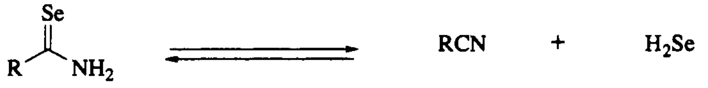
Se
R
NH2
RCN
+
H2Se

(30)

In contrast to aromatic selenoamides, little is known about the isolation of *N*-unsubstituted aliphatic selenoamides, which lack the stabilizing conjugation between the aromatic ring and the selenocarbonyl group. Hitherto known procedures are Kindler's method,[99–101] using the reaction of nitriles with hydrogen selenide in the presence of sodium ethoxide (equation 31), and the method using nitriles and Se–CO–$H_2O$ (Scheme 25).

Treatment of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-1-carbonitrile (**89**) with liquid hydrogen selenide, with 4-(dimethylamino)pyridine as the catalyst, provided 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonselenoamide (**90**). Compound (**90**) was treated with ethyl bromopyruvate to provide ethyl 2-(2,3,5-tri-*O*-ben-

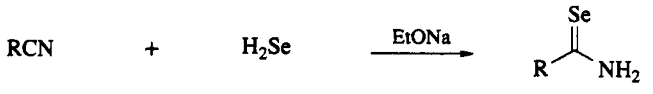

$$\mathrm{RCN} + \mathrm{H_2Se} \xrightarrow{\mathrm{EtONa}} \mathrm{RC(=Se)NH_2} \qquad (31)$$

R = Me, 77%; R = $PhCH_2$, ~100%;
R = $H_2NC(=Se)CH_2$, 36%

zoyl-D-ribofuranosyl)selenazole-4-carboxylate (**91**), followed by ammonolysis to give 2-β-D-ribofuranosylselenazole-4-carboxamide (**72**) as a promising antitumor agent.[102]

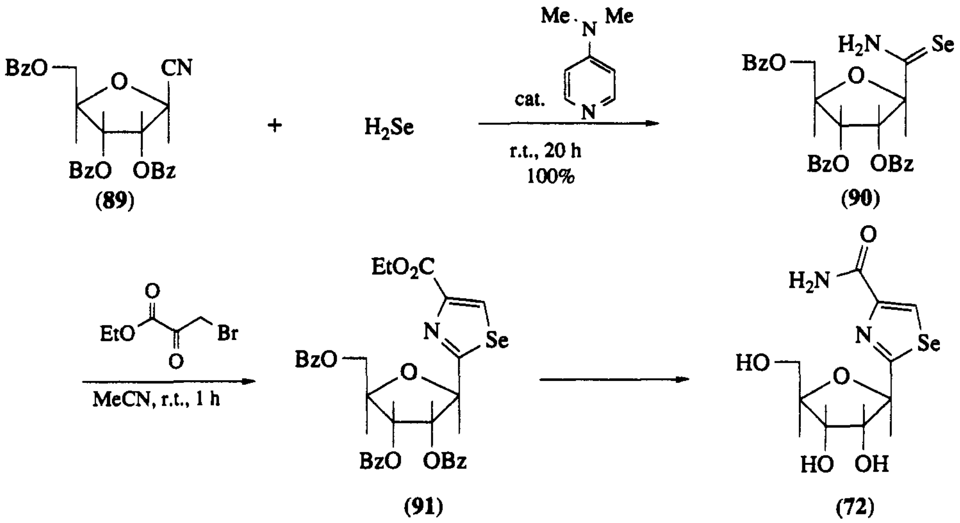

**Scheme 26**

### 2.6.4.1.2 *N-Substituted selenoamides*

*N*-substituted aliphatic selenoamides have been obtained on treatment of the corresponding amides with phosphorus pentaselenide in refluxing benzene,[101,103] but the yields were generally low (equation 32). Aromatic selenoamides can be obtained in moderate to high yields by the same method.[104] Improved yields of unhindered aliphatic selenoamides were obtained by heating the analogous amides with phosphorus pentaselenide in the presence of barium carbonate in boiling xylene.[105] Synthesis of selenolactams ($n$ = 3–5, 7 and 11) was accomplished by heating a mixture of the lactam with red phosphorus and gray selenium in refluxing xylene for 24 h.[106]

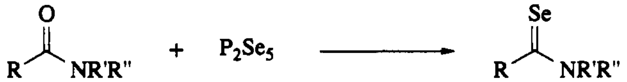

$$\mathrm{RC(=O)NR'R''} + \mathrm{P_2Se_5} \longrightarrow \mathrm{RC(=Se)NR'R''} \qquad (32)$$

R' = alkyl; R'' = alkyl or H

| *Ref.* | *R* | *Condition* | *Additive* | *Yield* |
|---|---|---|---|---|
| 101, 103 | Alkyl | Benzene reflux | None | <23% |
| 104 | Aryl | Pyridine reflux | None | 52–82% |
| 105 | Alkyl | Xylene reflux | $BaCO_3$ | <61% |

The reaction of an imidoyl chloride with sodium hydrogen selenide gave high yield of the selenoamide (equation 33).[107]

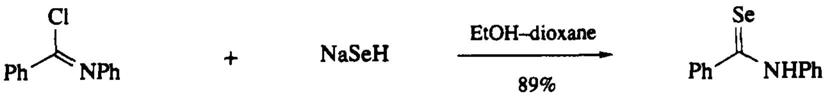

$$\mathrm{PhC(Cl)=NPh} + \mathrm{NaSeH} \xrightarrow[89\%]{\text{EtOH–dioxane}} \mathrm{PhC(=Se)NHPh} \qquad (33)$$

Convenient one-pot syntheses of *N*-substituted selenoamides from nitriles, metallic selenium, carbon monoxide, water and amines have been developed on the basis of an amino group exchange reaction between the *N*-unsubstituted selenoamides formed *in situ* and the primary or secondary amines.[108] Aromatic or aliphatic, and *N*-mono- or *N*,*N*-di-substituted selenoamides can be obtained in good yields by this method (Scheme 27).

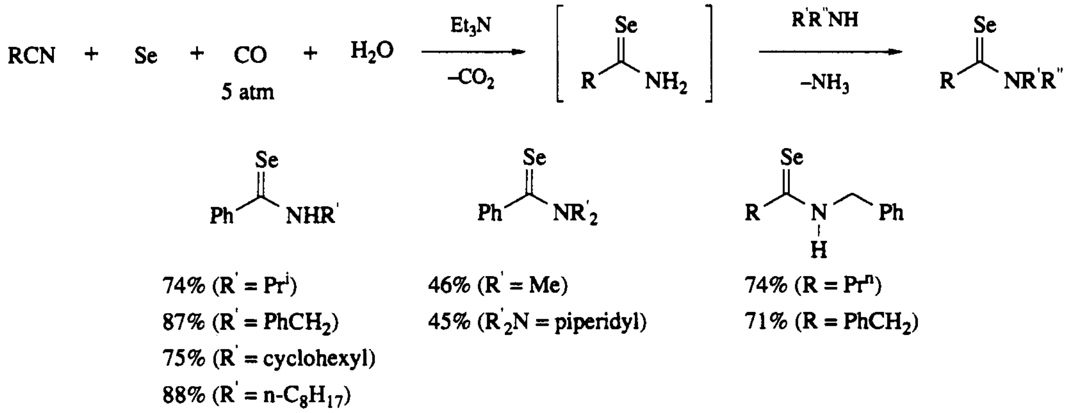
RCN + Se + CO + H2O
5 atm
Et3N
-CO2
Se
R NH2
R'R''NH
-NH3
Se
R NR'R''
Se
Ph NHR'
74% (R' = Pr$^i$)
87% (R' = PhCH2)
75% (R' = cyclohexyl)
88% (R' = n-C8H17)
Se
Ph NR'2
46% (R' = Me)
45% (R'2N = piperidyl)
Se
R N Ph
H
74% (R = Pr$^n$)
71% (R = PhCH2)

**Scheme 27**

In the cases of primary amines, the corresponding selenoamides have also been obtained from nitriles, selenium, carbon monoxide and excess primary amines by a single step mixing at the beginning of the reaction (Scheme 28).[108]

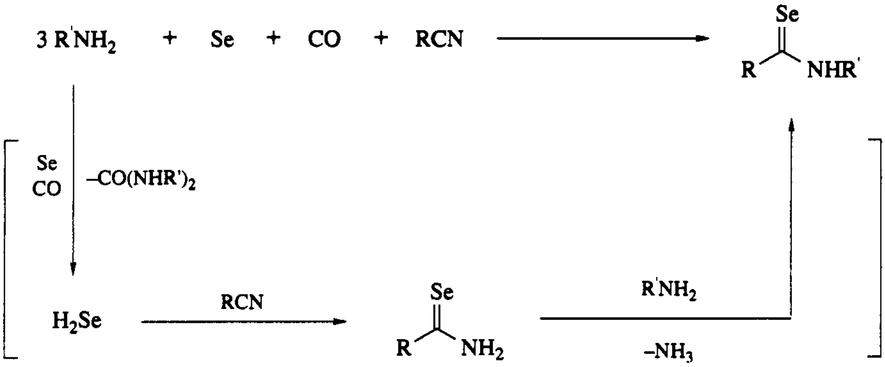
3 R'NH2 + Se + CO + RCN
Se
R NHR'
Se
CO
-CO(NHR')2
H2Se
RCN
Se
R NH2
R'NH2
-NH3

**Scheme 28**

A method for synthesis using the reaction of selenoesters with amines or their magnesium salts has been reported.[74] The reaction of aliphatic selenoesters with various primary alkylamide magnesium bromides in diethyl ether gave *N*-monosubstituted selenoamides, whereas direct addition of secondary amines to selenoesters afforded *N*,*N*-disubstituted selenoamides (Scheme 29).

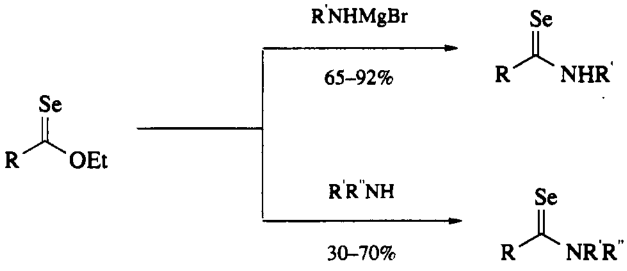
Se
R OEt
R'NHMgBr
65–92%
Se
R NHR'
R'R''NH
30–70%
Se
R NR'R''

**Scheme 29**

Based on the observation that 1,2,3-selenadiazoles can be converted to selenoesters (Scheme 18), Yalpani *et al.* have found that reacting 5-unsubstituted 1,2,3-selenadiazoles with various amines gave, in most cases, quantitative yields of the selenoamides (equation 34).[109,110]

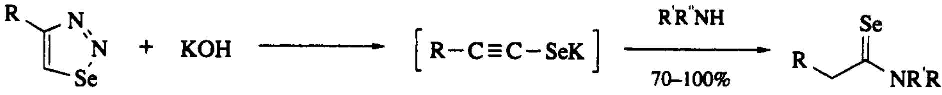
R
N
N
Se
+ KOH
R−C≡C−SeK
R'R''NH
70–100%
Se
R
NR'R''

(34)

Selenoamides have been prepared in good yields by adding selenium powder to a solution of lithium acetylides in an excess of diethylamine (equation 35).[111]

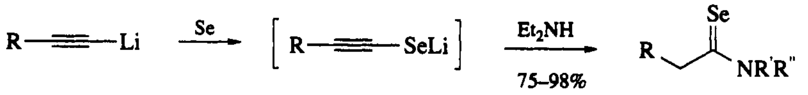
R—≡—Li
Se
R—≡—SeLi
Et₂NH
75–98%
Se
R
NR'R''

(35)

A few methods for the synthesis of selenoformamides have been reported. (Mercaptomethylene)imminium salt (**92**) reacted with NaSeH to give the corresponding selenoformamide (equation 36).[112]

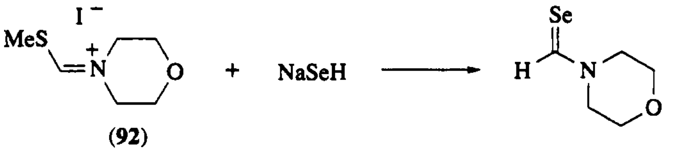
I⁻
MeS
+
N
O
+ NaSeH
Se
H
N
O

(**92**)

(36)

An alternative synthetic route to selenoformamides has been developed by the reaction of carbon diselenide with phenylmethaneselenol to produce triselenocarbonate (**93**), which reacts with primary or secondary amines to give the selenoformamide (Scheme 30).[113]

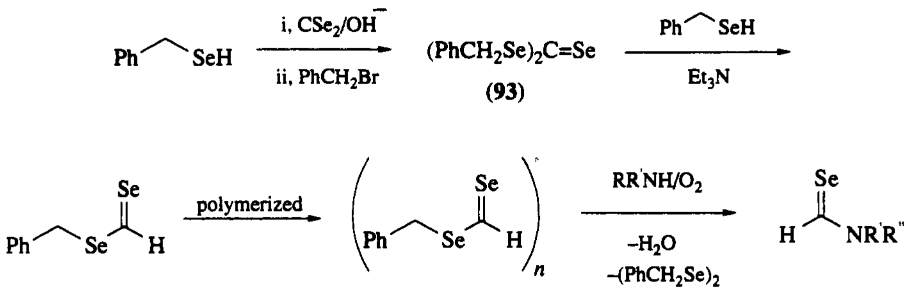
Ph
SeH
i, CSe₂/OH⁻
ii, PhCH₂Br
(PhCH₂Se)₂C=Se
(93)
Ph
SeH
Et₃N
Se
Ph
Se
H
polymerized
Se
Ph
Se
H
n
RR'NH/O₂
-H₂O
-(PhCH₂Se)₂
Se
H
NR'R''

**Scheme 30**

The *N*,*N*-dimethylaminomethylenamino compounds (**95**), obtained from amines and dimethylformamide diacetal (**94**), react smoothly with hydrogen selenide to give the desired selenoformamides (equation 37).[114]

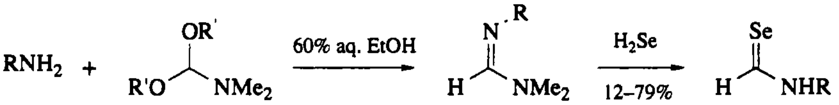
RNH₂ +
OR'
R'O
NMe₂
60% aq. EtOH
R
N
H
NMe₂
H₂Se
12–79%
Se
H
NHR

(37)

(**94**) (**95**)

Some other methods for the synthesis of selenoamides are shown in Schemes 31[115] and 32.[116]

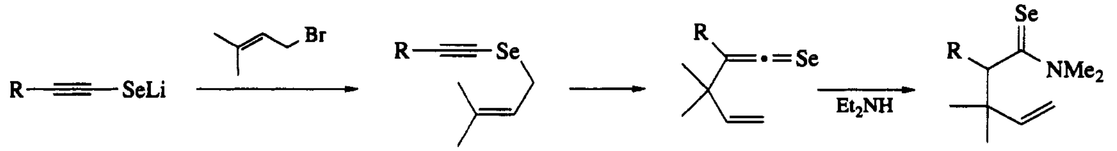
R—≡—SeLi
Br
R—≡—Se
R
•=Se
Et$_2$NH
Se
R
NMe$_2$
5–37%

Scheme 31

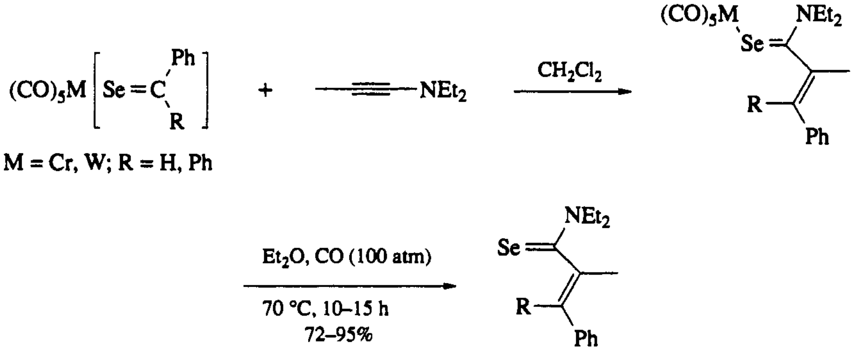
(CO)$_5$M
Se=C
Ph
R
M = Cr, W; R = H, Ph
+
—≡—NEt$_2$
CH$_2$Cl$_2$
(CO)$_5$M
Se
NEt$_2$
R
Ph
Et$_2$O, CO (100 atm)
70 °C, 10–15 h
72–95%
Se
NEt$_2$
R
Ph

Scheme 32

### 2.6.4.2 Reactions

As with selenoesters, selenoamides are excellent reagents for the synthesis of selenium-containing heterocycles.[117–122] Anhydro-2,3,5-triphenyl-4-hydroxyselenazolium hydroxide (**96**), as the first mesoionic selenium heterocycle,[107] selenophene derivatives (**97**)[118–121] and 1,3-selenazoles (**98**)[122] have been synthesized as shown in Scheme 33 and equations (38) and (39).

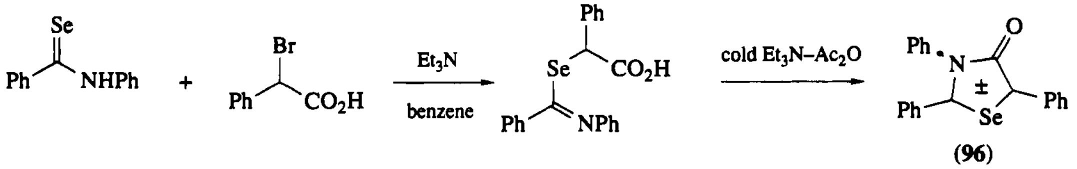
Se
Ph
NHPh
+
Br
Ph
CO$_2$H
Et$_3$N
benzene
Ph
Se
CO$_2$H
Ph
NPh
cold Et$_3$N-Ac$_2$O
Ph
N
O
±
Ph
Se
Ph

**(96)**

Scheme 33

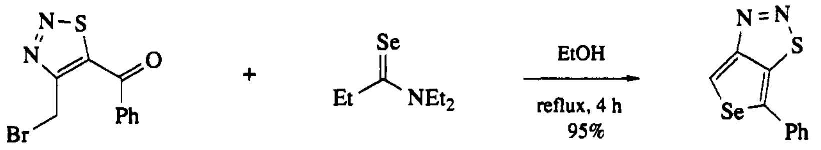
N–S
N
O
Ph
Br
+
Se
Et
NEt$_2$
EtOH
reflux, 4 h
95%
N=N
S
Se
Ph

(38)

**(97)**

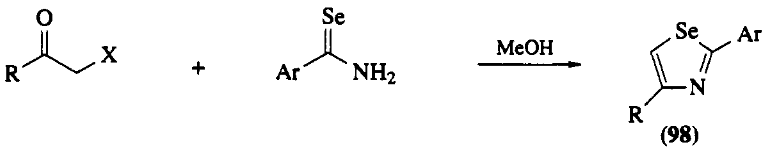
O
R
X
+
Se
Ar
NH$_2$
MeOH
Se
Ar
N
R

(39)

**(98)**

It has recently been reported that selenoamide is a useful reagent for the stereospecific deoxygenation of epoxides under mild conditions.[123] This deoxygenation can be applied to various epoxides, *i.e.* mono-, di- and tri-substituted epoxides and cyclic epoxides. A suggested reaction path is illustrated in Scheme 34.

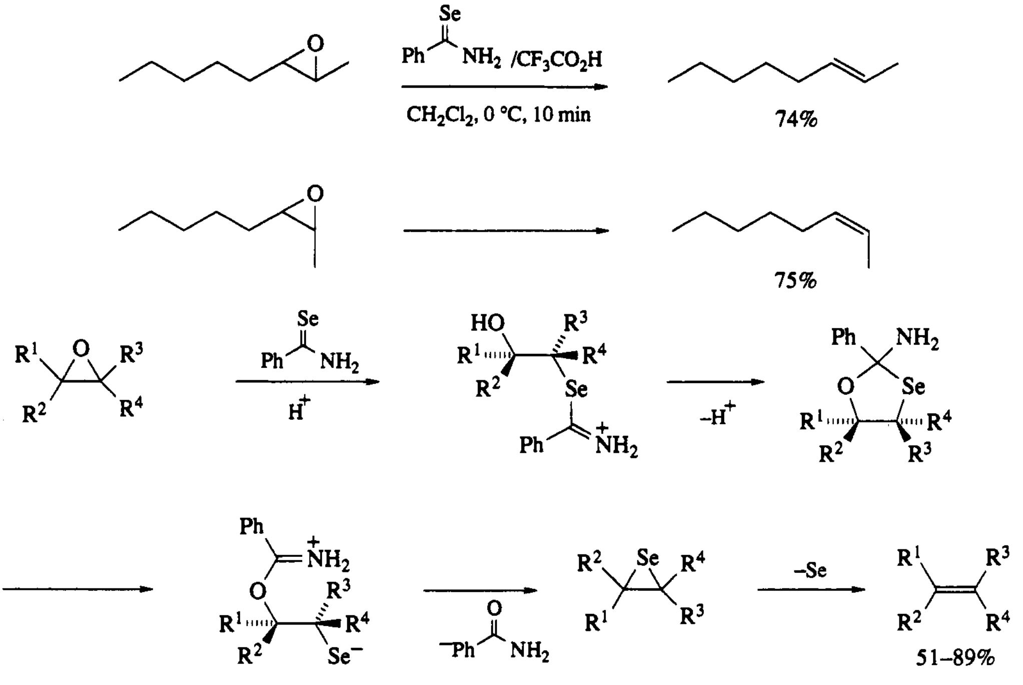

Scheme 34

Some other reactions are shown in refs. 91, 124 and 125.

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# 2.7

# Synthesis of Iminium Salts, Orthoesters and Related Compounds

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## 2.7.1 INTRODUCTION AND SCOPE

This chapter deals with 'activated amides', *i.e.* salt-like compounds, imino derivatives of carboxylic acids as well as compounds which formally arise by complete esterification or amidation of carboxylic orthoacids.

Well known compounds of this type are Vilsmeier–Haack adducts, imino esters, amidines, carboxylic orthoesters, orthoamides *etc.*, which have proven their synthetic utility in thousands of reactions. As a consequence of the synthetic importance of these compounds, more or less extensive reviews are available for all of them.

There exists a series of compounds which can also be regarded as activated amides, *e.g.* α-haloenamines, ketene *O,N*-acetals, ketene aminals or ynamines, which are not dealt with in this chapter. To show the scope of the contribution, the formulae of all the types of compounds which are treated in the text, together with references of the relevant reviews are listed in Table 1.

## 2.7.2 SALT-LIKE COMPOUNDS (IMINIUM SALTS)

### 2.7.2.1 Adducts from Amides (Thioamides) and Acylating Reagents

### *2.7.2.1.1 Phosphorus oxychloride and phosphorsulfur trichloride*

In preparative organic chemistry adducts from *N*-formylamines, *e.g.* *N*-methylformanilide and *N,N*-dimethylformamide, and $POCl_3$, which are used to formylate activated aromatic compounds and alkenes, are very important.[4] For these purposes it is not necessary to isolate the amide/$POCl_3$ adducts; usually they are prepared *in situ*. As a consequence of this only a few acid amide/$POCl_3$ adducts have been prepared in the pure state; examples are the adducts of $POCl_3$ with *N*-methylformanilide and *N,N*-dimethylformamide.[5] Elemental analysis revealed that adduct formation takes place in a 1:1 ratio. There has been much confusion on the constitution of these compounds.[1–5,7] There is no doubt that in solution adduct formation proceeds *via* attack at the carbonyl oxygen of the amide. This primary product (**1**) reacts further to give a salt (**2**) consisting of a chloromethyleneiminium ion with dichlorophosphate as the counterion (equation 1).

In formylation reactions both types of iminium compounds may act as electrophilic reagents. It has been demonstrated that the DMF–$POCl_3$ adduct is more reactive in formylation reactions than *N,N*-dimethylchloromethyleniminium chloride, which has the same cation. This indicates that the more reactive primary adduct from DMF and $POCl_3$ is the formylation species. But this conclusion is not fully convincing, because ion pair formation may take place in different amounts, meaning that in iminium chlorides there are more ion pairs than in the corresponding dichlorophosphates. Many reactions are known in which $POCl_3$ is used as a condensating agent, which indicates that there are adducts formed which act as reactive intermediates. From such experiments one may conclude that nearly all types of amides form adducts with $POCl_3$. Some examples of amides used in such reactions are: formamide, *N*-monosubstituted formamides,[5] *N,N*-disubstituted formamides,[4,5,7]· *N*-monosubstituted acetamides,[39,40] *N,N*-disubstituted acetamides,[41–44] mono- and di-substituted propionamides,[39,45] chloroacetamides,[39,46] phenylacetamides,[45] monosubstituted[40] and disubstituted[41] isobutyramides, malono ester amides,[47–54] cyanoacetamides,[45,55,56] *N*-monosubstituted[40,46,57] and disubstituted[41,46,58–60] benzamides, secondary aromatic[61] and higher aliphatic amides[61] as well as secondary[46] and tertiary[46,60] heterocyclic carboxamides, acylhydrazides[62–66] and lactams.[4,5,67–76]

**Table 1**

| *Formula* | *Type of compound* | *Ref.* |
|---|---|---|
| 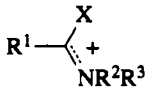 $[R^1C(X){=}NR^2R^3]^+\ Y^-$ (X ≠ halogen) | Adducts from amides and acylating reagents | 1–7 |
| 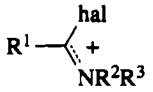 $[R^1C(hal){=}NR^2R^3]^+\ Y^-$ | Halomethyleneiminium salts | 1–9 |
| 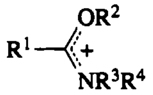 $[R^1C(OR^2){=}NR^3R^4]^+\ Y^-$ | Alkoxymethyleneiminium salts | 6, 7, 10 |
| 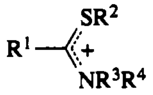 $[R^1C(SR^2){=}NR^3R^4]^+\ Y^-$ | Alkylmercaptomethyleneiminium salts | 7, 11–13 |
| 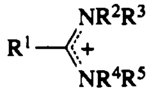 $[R^1C(NR^2R^3){=}NR^4R^5]^+\ Y^-$ | Amidinium salts | 7, 14 |
| 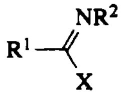 $R^1C(X){=}NR^2$ X = halogen | Imidoyl halides | 1–3, 7 |
| 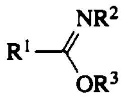 $R^1C(OR^3){=}NR^2$ | Imidic acid esters (imidates, imino esters)<br>Lactimidic acid esters<br>Cyclic imidates | 7, 15, 16<br>17<br>12, 19 |
| 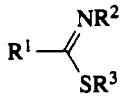 $R^1C(SR^3){=}NR^2$ | Imidic acid thioesters (thioimidates, imino thioesters) | 7, 12 |
| 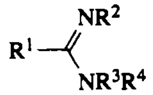 $R^1C(NR^3R^4){=}NR^2$ | Amidines | 7, 20, 21 |
| 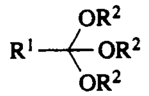 $R^1C(OR^2)_3$ | Carboxylic orthoacid esters | 7 |
| 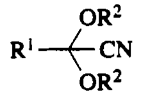 $R^1C(OR^2)_2CN$ | 2,2-Bis(alkoxy)carbonitriles | 28, 29 |
| 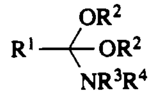 $R^1C(OR^2)_2NR^3R^4$ | Amide acetals<br>Lactam acetals<br>Bicyclic amide acetals | 6, 7, 24, 28, 30–35<br>7, 24, 28, 34, 35<br>24, 36 |
| 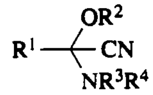 $R^1C(OR^2)(CN)NR^3R^4$ | 2-Alkoxy-2-dialkylaminocarbonitriles | 7, 28, 29, 35 |
| 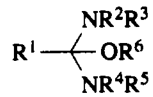 $R^1C(NR^2R^3)(OR^6)NR^4R^5$ | Bis(dialkylamino)alkoxyalkanes (aminal esters) | 6, 7, 24, 28, 32, 35 |

**Table 1** *(continued)*

| *Formula* | *Type of compound* | *Ref.* |
|---|---|---|
| 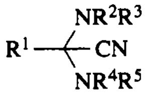 | 2,2-Bis(dialkylamino)carbonitriles | 7, 28, 29, 35 |
| 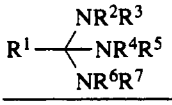 | Tris(dialkylamino)alkanes | 6, 7, 24, 28, 32, 35 |

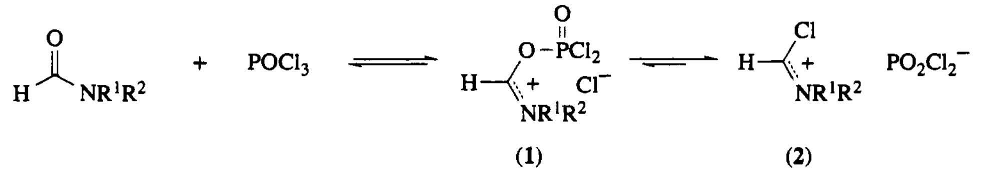
(1)

(1) (2)

The adducts have been used for preparation of heterocyclic compounds,[4,5,37,46–48,52–54,56,59,63] in Beckmann rearrangement,[43] for cyclizations,[4,5,38,40,44,45,57,62,64,66,68] (a review covering cyclizations under Vilsmeier–Haack conditions is available[77]), for preparation of amidines,[5,7,39,41,42,55,76] in von Braun degradation,[61] in rearrangements,[68] in condensation reactions,[69] in substitution of aromatic compounds,[4,6,7,71,74] in reduction of amides,[72] in amide dimerization[73] and for preparation of isonitriles.[5] The adduct from DMF and $POBr_3$ was used for similar purposes.[4,5,7,78–81] The adduct formation either from thioamides and $POCl_3$ or amides and $PSCl_3$ has been studied.[82] The adduct of *N*,*N*-dimethylthioformamide with $POCl_3$ is said to be more reactive than the oxygen analog adduct.[4,5,7] It has been demonstrated that DMF undergoes selfcondensation with $PSCl_3$ to give *N*,*N*-dimethylglyoxylicthioamide (**3**) on hydrolysis (equation 2).[5]

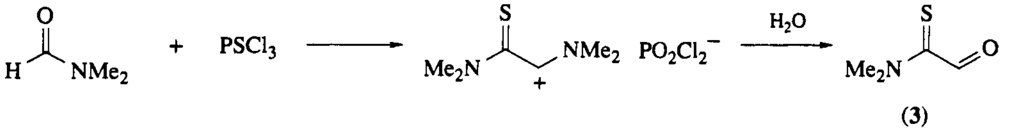
(2)

(3)

For preparative purposes it should be kept in mind that the use of these adducts, *e.g.* for C—C bond forming reactions,[1–4,6,83] can be restricted by several side reactions,[84] depending on the structure of the adducts. *N*,*N*-Unsubstituted adducts can decompose to nitriles by loss of HCl and $HOPOCl_2$ (this procedure was often used to prepare nitriles from amides[5,85–87]). *N*-Monosubstituted amides can split off $HOPOCl_2$ giving imidoyl chlorides (a reaction which is a standard procedure in heterocyclic chemistry, whenever a CONH unit is to be converted into a CCl═N unit); the imide chlorides thus formed on heating can lose alkyl chlorides—a process which is well known as von Braun degradation.[1–3,5,61] Adducts of *N*-monosubstituted formamides, especially in the presence of bases, furnish isonitriles by elimination of HCl and $HOPOCl_2$. This reaction is a very important method for the preparation of isonitriles.[1,5,88–97] Finally adducts derived from tertiary carboxamides, with $CH_2$—, or at least CH—, groups in the α-position to the amide function, can undergo selfcondensation, yielding products which can be regarded as adducts of $POCl_3$ with 2,3-disubstituted 3-chloroacrylic acid amides, which after hydrolysis afford β-keto acid amides.[1–5,7] In other cases heterocycles have been prepared by this type of condensation.[4,98]

Acid amide–triphenylphosphine dihalide adducts (**4**) have found wide application in organic synthesis.[5,7] Synthetic equivalents are adducts (**5**) from acid amides and triphenylphosphine/$CCl_4$, which are prepared *in situ* from the educts.[5,7] With these reagents the following transformations have been performed: dehydration of amides or aldoximes to nitriles, preparation of isonitriles from secondary formamides, preparation of imidoyl halides from amides or acylhydrazines and preparation of ketene imines from amides. Using polymer-supported triphenylphosphine the work-up procedure is much easier to achieve.[99] Triphenylphosphine can be replaced by tris(dialkylamino)phosphines.[5,7] Instead of $CCl_4$ hexachloroethane, hexabromoethane or 1,1,2,2-tetrabromo-1,2-dichloroethane can be used;[100] the adducts thus formed are assumed to be more effective than those from the triphenylphosphine/$CCl_4$ system.

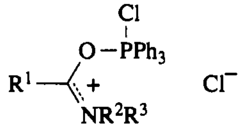

**(4)**

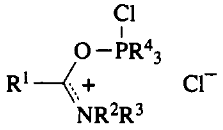

**(5)**

Adducts (**6**) and (**7**) from amides and chlorophosphoric acid aryl esters or dichlorophosphoric acid aryl esters respectively are well known.[5,7] The adducts are formed in a 1:1 ratio. They have been applied to the synthesis of mixed anhydrides from diarylphosphoric acids and carboxylic acids, as well as mixed substituted esters of pyrophosphoric acid. The adduct formation between primary or secondary carboxamides and dichlorophosphates has been used to prepare nitriles and isonitriles respectively.[5] The adduct from DMF and phenyldichlorophosphate is a useful reagent for the preparation of: carboxylic acid esters from the corresponding acids and alcohols,[101] β-lactams from imines and carboxylic acids,[102] carboxylic acid anhydrides,[103] carboxylic acid esters and thiol esters.[103] Adducts of amides with ester amides or diamides of chlorophosphoric acid have been studied.[103,104]

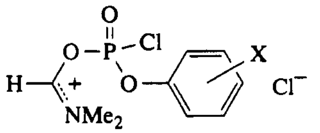

**(6)**

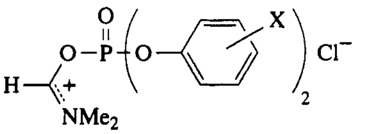

**(7)**

A still unresolved problem is the structure of the often used adducts from phosphorus trihalides and carboxylic acid amides, which might be described by the formulae (**8**) or (**9**). With the aid of *in situ* generated adducts of acid amides and $PX_3$ amidines,[5,7] isonitriles,[5] quinazolinones,[105] alkyl chlorides,[5] aminomethylenediphosphonic acids,[5,106] carbamoyl halides,[5] triformylaminomethane,[5,7] 1,3,4-oxadiazoles,[107] sulfides (from sulfoxides),[108,109] nitriles (from primary nitro compounds)[110] and bromoquinolines (from methoxyquinolines)[111] have been prepared.

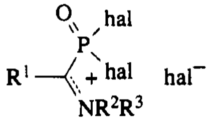

**(8)**

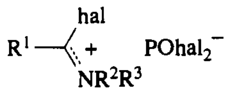

**(9)**

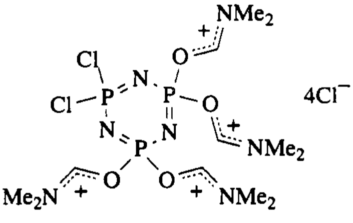

**(10)**

The adduct of DMF and dichlorophenylphosphine has been used to convert primary aromatic amides to nitriles by dehydration,[112] as well as to synthesize 2,5-diaryl-1,3,4-oxadiazoles from *N,N'*-diacylhydrazides.[113]

Phosphorus nitrile chloride forms adduct (**10**) with DMF in the ratio 1:4, which is useful for the preparation of formamidines and azavinylogous formamidinium salts.[5] It is supposed that the dehydration of primary amides to nitriles with $(PNCl_2)_3$ as well as the formation of 2-alkylbenzothiazoles from 2-(methylthio)anilides and $(PNCl_2)_3$ in the presence of triethylamine proceed *via* similar adducts.[114]

### *2.7.2.1.2 Adducts from acid amides and sulfur compounds*

Sulfonyl halides (*e.g.* benzenesulfonyl chloride) form adducts (**11**) with acid amides in an equilibrium reaction.[5] From these adducts or *via* adducts of this type *O*-sulfonated lactim ethers, isonitriles, adenine, nitriles, amidines, amidinium salts and formic acid esters were prepared.[5] The adducts from DMF and chlorosulfonamides (**12**) can be used to prepare amidines or amidrazones.[5] *N*-Chlorosulfonylcarboxylic acid amides yield nitriles on treatment with DMF or other tertiary amides, presumably *via* an acid amide sulfonyl chloride complex (**13**; equation 3).[5]

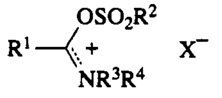

**(11)**

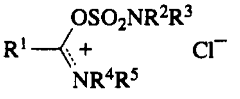

**(12)**

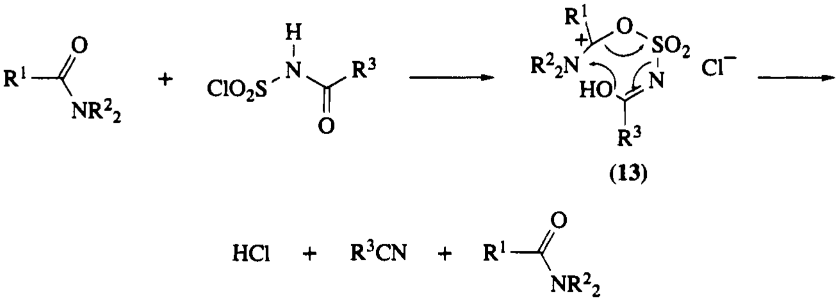

**(13)**

(3)

In contrast to these adducts the DMF–sulfuryl chloride adduct (**14**) has been prepared in a pure state.[5,7] It thermally decomposes to *N*,*N*-dimethylcarbamoyl chloride.[5] Secondary formamides form similar adducts, which on heating afford isocyanates.[5] Aromatic compounds such as anisole are not formylated by the DMF–$SO_2Cl_2$ adduct but chlorosulfonated.[5] This reaction was also performed with thiophenes; 2-thiophenecarbaldehydes are formed as byproducts.[115] The formation of triformaminomethane from formamide and $SO_2Cl_2$ has been reported.[5]

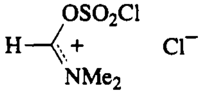

**(14)**

Thionyl chloride forms a fairly stable primary adduct (**15**) with DMF, which has been isolated.[5,7] On heating it decomposes to $SO_2$ and *N*,*N*-dimethylformamide chloride (equation 4).[5] Treatment of the adduct (**15**) with carboxylic acids affords iminium salts (**16**; equation 5) in which the carboxylic acid function is strongly activated, *e.g.* for amide formation.[116] With imines β-lactams are formed, sodium azide is converted to acyl azides.[117]

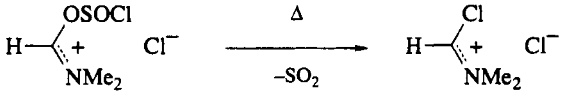

**(15)**

(4)

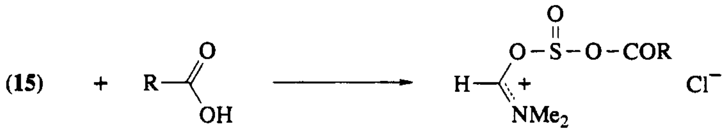

**(16)**

(5)

### 2.7.2.1.3 *Adducts from amides and carbonic acid derivatives*

Phosgene and tertiary carboxylic acid amides form very labile adducts (**17**; equation 6; not yet isolated or used for preparative purposes as such), which decompose with loss of $CO_2$ very rapidly to give amide chlorides (see Section 2.7.2.2.1.i). Decomposition with evolution of $CO_2$ is a common fate of primary adducts of carbonic acid chloride derivatives. Primary adducts from DMF and chloroformic acid esters (**18**), for example, decompose immediately to give alkoxymethyleneiminium chlorides, which react to give alkyl chlorides and DMF (equation 7).[5,118] Adducts (**19**) from secondary and tertiary carboxamides and *N*,*N*-dialkylcarbamoyl chlorides are formed at elevated temperatures (about 120 °C). However, under these conditions the adducts thus formed decompose to yield amidinium salts (equation 8).[5]

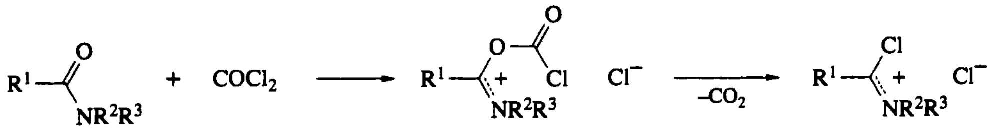
(6)

**(17)**

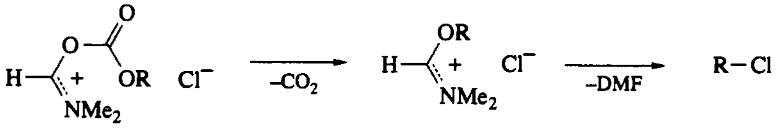
(7)

**(18)**

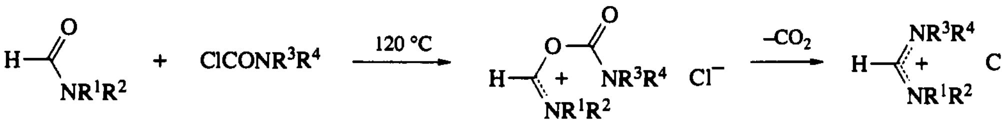
(8)

**(19)**

Adduct formation between cyanogen chloride and DMF was proposed to explain the complex product mixture, which was obtained by reaction of these educts at 150 °C (equation 9).[5] More important are adducts (**20**) from cyanuric acid chloride and tertiary formamides. These compounds are formed in a 1:2 ratio and they are isolable when DMF or *N*-formylpyrrolidine is used.[5,121] The adducts have been used to formylate ketones at the α-$CH_2$ groups,[122] sterically hindered phenols can be formylated at the oxygen,[123] amides are dehydrated to nitriles[124] and secondary formamides are transformed to isonitriles.[5] Using these adducts, amidines,[5] *N*-acylamidines,[123] alkyl halides[5] and amidinium salts[5] have been synthesized. In the preparation of these adducts an excess of amide must be avoided, because the 2:1 adducts (**20**) react with further tertiary formamide to give a labile, not isolable 1:3 adduct (**21**; equation 11), which, in the presence of excess amide, decomposes with great ease with evolution of $CO_2$ to give azavinylogous formamidinium salts.[5] The mechanism of this complex reaction has been established.[125]

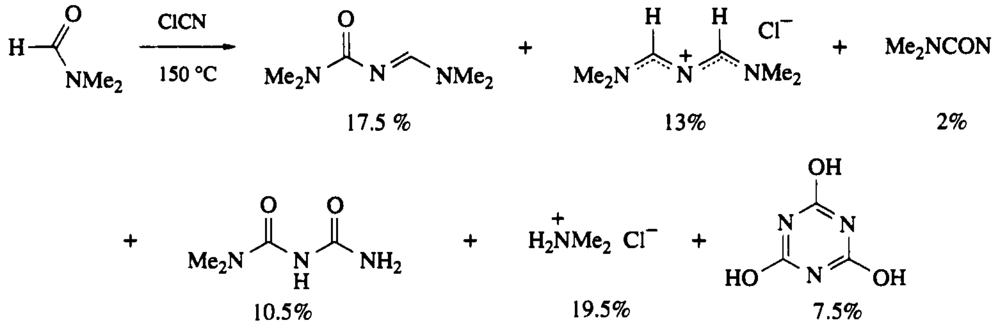

(9)

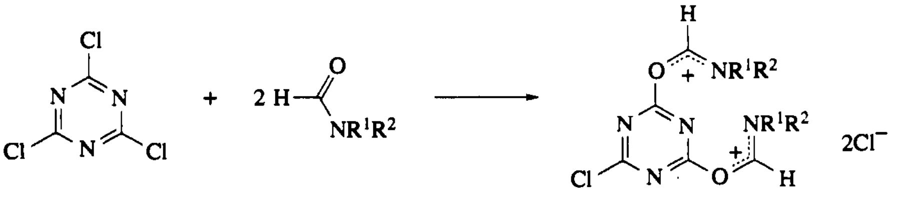
(10)

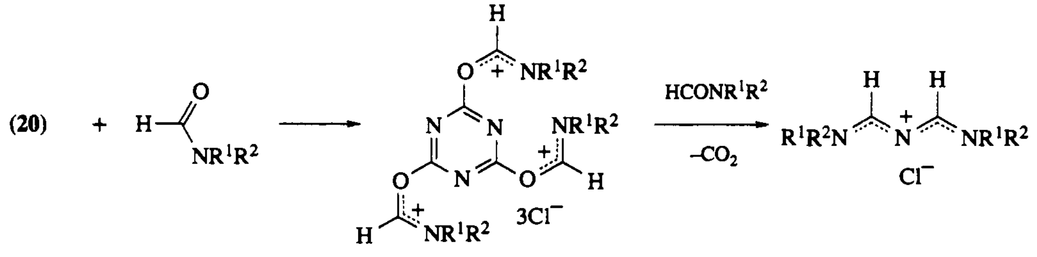
**(21)** (11)

### *2.7.2.1.4 Adducts from acid amides and carboxylic acid derivatives*

Conductivity measurements have revealed that DMF and carboxylic acid chlorides form salt-like adducts (**22**) in an equilibrium reaction (equation 12).[5,7] Such adducts can be prepared either from DMF and acid halides (chlorides and bromides)[5] or from chloromethyleneiminium salts and salts of carboxylic acids.[5,126] Acyloxyiminium salts (**23**) can be prepared in the pure state by reacting acid amides with carboxylic acid chlorides in the presence of silver trifluoromethanesulfonate (equation 13).[127] Salts of type (**24**; equation 14) are regarded as being intermediates in the synthesis of ketones from carboxylic acids and Grignard reagents in the presence of α-chloroenamines[128] as well as in the preparation of acyl halides (F, Cl, Br, I) by action of α-haloenamines on carboxylic acids.[129]

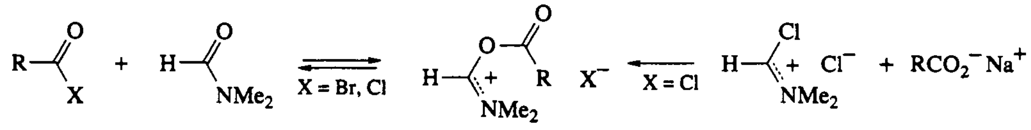
**(22)** (12)

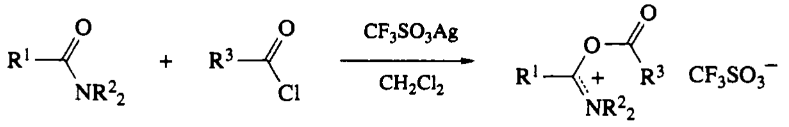
**(23)** (13)

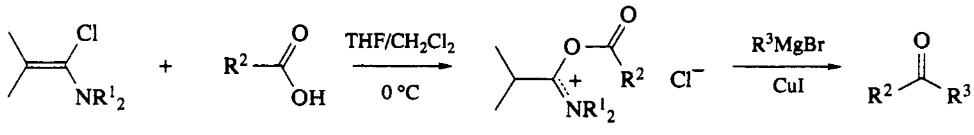
**(24)** (14)

Acid amide–acid halide adducts have been used in synthetic organic chemistry to prepare various types of compounds (see Table 2).

Crystalline adducts from thioamides and aromatic acid chlorides are well known.[5] A very convenient synthesis of diacyl sulfides[139] and thiocarboxylic acids[139,140] proceeds *via* adducts of thio-DMF with acid chlorides.

From formylation reactions of CH-acidic compounds, which take place if mixtures of carboxylic acid amides and anhydrides are used as formylating agents, it was concluded that the latter compounds form similar adducts to those from amides and acid halides.[5]

**Table 2** Preparative Applications of Acid Amide–Acid Chloride Adducts

| *Starting amides* | *Ref.* | *Products* | *Ref.* | *Products* | *Ref.* |
|---|---|---|---|---|---|
| Formamide | 5, 130 | Formimino ester hydrochlorides | 5 | Tris(1-methyl-3-indolyl)methane | 132 |
| Vinylogous formamides | 5 | Orthoesters | 130 | Vinylogous amidinium salts | 5 |
|  |  | Amidines | 5 | Formylindoles | 131, 134 |
| DMF | 5, 131–135 | Amidinium salts | 133 | Formates | 135 |
|  |  | Carbonates | 5 | Aldehydes | 137, 138 |
|  |  | Trisformamidomethane | 5 | *N*-Substituted hydroxamic acids | 126 |
|  |  | Acid anhydrides | 5, 136 |  |  |
|  |  | Acyl azides | 5 |  |  |

## 2.7.2.2 Halomethyleneiminium Salts (Amide Halides)

### *2.7.2.2.1 From halogenating reagents and acid amides*

*(i) Phosgene, diphosgene, carbonyl dibromide, carbonyl difluoride, oxalyl dihalides*

Phosgene, as well as the easier to handle 'diphosgene' (chloroformic acid trichloromethyl ester)[141] or 'triphosgene' (carbonic acid bis(trichloromethyl) ester) transform primary, secondary and tertiary amides and thioamides to chloromethyleneiminium chlorides (**25**; equation 15),[1,7–9] whereby the reaction with thioamides is of broader scope and proceeds with fewer side reactions. The amide chlorides derived from primary and secondary amides can lose HCl, giving nitriles or imidoyl halides, respectively.[9] *N*-Substituted formamides can be converted to isonitriles *via* amide halides.[9]

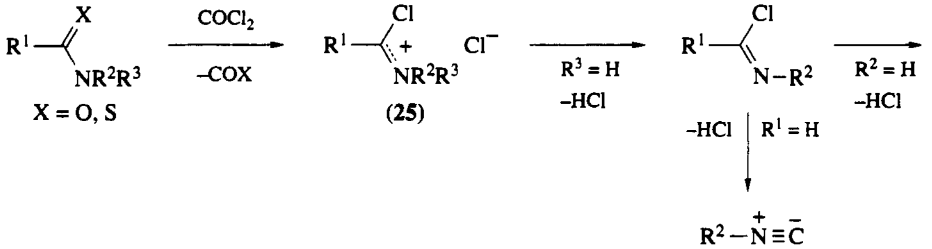

**(25)**

(15)

It should be noted that amide chlorides bearing strong electron acceptors (*e.g.* $CCl_3$, $CF_3$, CN, $CO_2R$, $ClCNMe_2$ groups) in the α-position readily undergo rearrangement to α,α′-dichloroamines (**26**; equation 16).[142–144] Oxalyl chloride has been used to prepare amide chlorides (*e.g.* **27**; equation 17) from tertiary amides; side reactions are known if α-halogenated amides or thioamides containing α-$CH_2$ groups are used in this reaction.[5] From carbonyl dibromide and tertiary carboxamides the corresponding bromomethyleneiminium salts (**28**; Scheme 1) were synthesized, which often possess $Br_3^-$ as a counterion from which $Br_2$ can be split off by treatment with cyclohexene.[7,9] The action of carbonyl difluoride on tertiary amides gives rise to formation of α,α-difluoroamines (**29**),[7,9,145] which seem to be dissociated only to a very small extent.[7,9,146,147]

*(ii) Phosphorus compounds*

Wallach was the first (1874) to report on the transformation of carboxylic acid amides to amide chlorides by treatment with $PCl_5$;[7–9] various types of amides were converted by this reagent to chloromethyleneiminium chlorides (**30**; equation 18).[7–9,148,149] Side reactions can include the α-chlorination of the amide chloride.[8,9] If excess $PCl_5$ is used, the formation of iminium salts with complex ions (**31**) has been reported.[150] The very labile bromomethyleneiminium bromides (**32**; equation 19) can be obtained by action of $PBr_5$ on tertiary amides.[7,9] The iodomethyleneiminium salt (**33**) was prepared from DMF and diphosphorus tetraiodide in $CS_2$.[151]

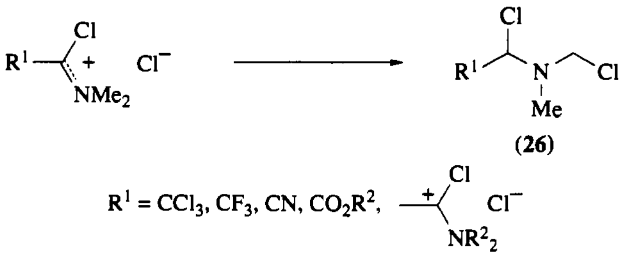

**(26)**

(16)

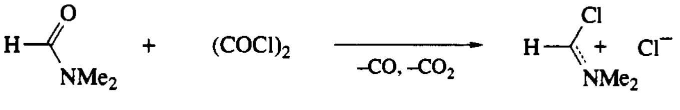

**(27)**

(17)

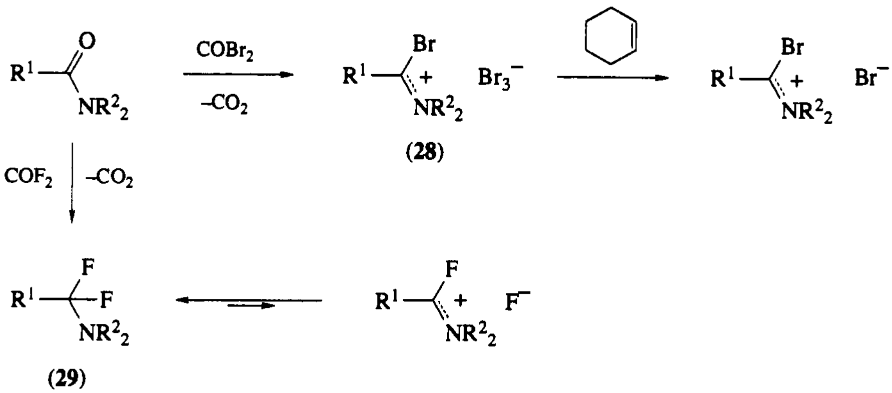

Scheme 1

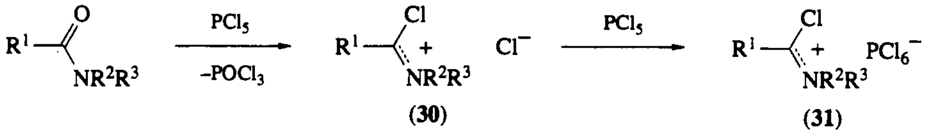

(18)

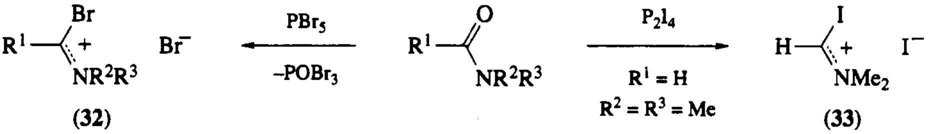

(19)

*(iii) Sulfur compounds*

Thionyl chloride was often used to synthesize amide chlorides from amides. The mechanism of this reaction has been thoroughly studied.[9] According to these investigations a primary adduct is formed (**34**; equation 20), which loses $SO_2$ in a reversible reaction to give the amide chloride (compare Section 2.7.2.1.2).[9] Mixtures of $SOCl_2$ with $PCl_5$ have also been used to convert amides to amide chlorides.[152] Amide fluorides (α,α-difluoroamines) (**35**; equation 21) can be obtained by the action of sulfur tetrafluoride on amides[7,9,153] or thioamides.[9,154] In the presence of KF tertiary formamides react with $SF_4$ to give α,α,α-trifluorodialkylamines.[155]

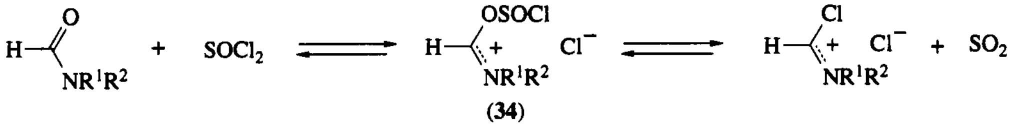

(20)

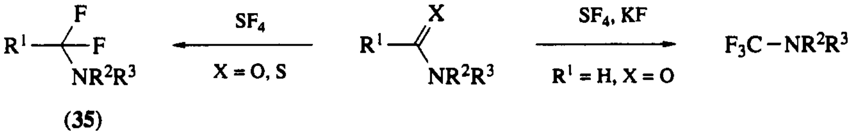

(21)

*(iv) Miscellaneous reagents*

A very efficient preparation of amide chlorides comprises the action of elemental chlorine on thioamides in $CH_2Cl_2$ or $CCl_4$; even amide chlorides which possess electron-attracting substituents in the α-position have been prepared in this way.[7,9,143,156]

DMF was converted to the corresponding iminium salt (**27**) by the following reagents:[5] perfluorobutyryl chloride, 2,2-dichlorobenzodioxole (**36**) and 2,2,2-trichlorobenzodioxaphosphole (**37**).

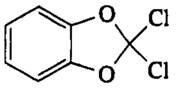

**(36)**

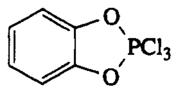

**(37)**

### 2.7.2.2.2 By addition reactions

#### (i) Hydrogen halides to nitriles or imidoyl halides

The formation of amide chlorides from nitriles and hydrogen halides under anhydrous conditions is a well-known reaction of wide scope.[7,9] There has been some confusion on the nature of the reaction products, but it has turned out that the isolable species are amide chlorides. The thermal stability of the addition products strongly depends on the acidity of the hydrogen halide used. Iodides are more stable than bromides, which in turn are more stable than the chlorides. As a consequence, thermally stable HCl adducts (**38**; equation 22) can be prepared if Lewis acids are present, which incorporate the chlorine anion to give a less basic anion (**39**).

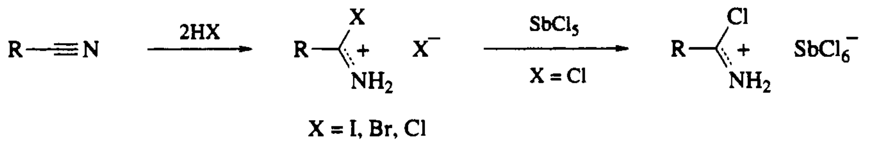

**(38)** **(39)** (22)

The reaction of fluorinating reagents such as $F_2$,[157] $HgF_2$,[158] $CoF_3$[159] and $AgF_2$,[159] in the presence of halogens[158] or interhalogen compounds,[157] with nitriles produces *N*-halogenated amide fluorides (*e.g.* **40** and **41**; equation 23). *N*-Alkylated imidoyl halides add HCl or HBr to give the corresponding iminium salts (**42**; equation 24).[7,9]

$$\underset{\mathbf{(40)}}{RCF_2NClF} \xleftarrow{F_2,\ ClF} R{\equiv}N \xrightarrow{Cl_2,\ HgF_2} \underset{\mathbf{(41)}}{RCF_2NCl_2} \qquad (23)$$

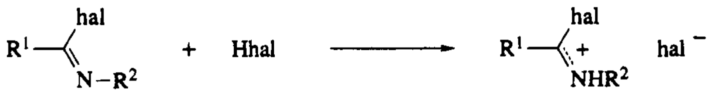

**(42)** (24)

#### (ii) Hydrogen halides or halogens to α-chloroenamines or ynamines

Hydrogen halides (*e.g.* HCl) or halogens (*e.g.* $Cl_2$) add to chloroenamines to give amide chlorides (**43** and **44**; equation 25). The HCl addition seems to proceed reversibly.[9] By addition of HCl or $Cl_2$ to ynamines the iminium salts (**45**; equation 26) and (**46**; equation 27) were synthesized.[9,143]

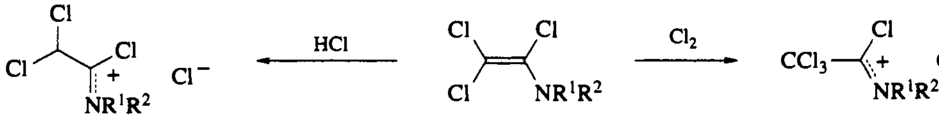

**(43)** **(44)** (25)

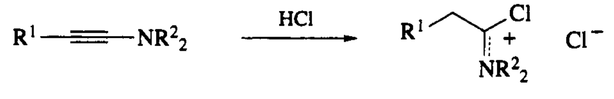

(45)

(26)

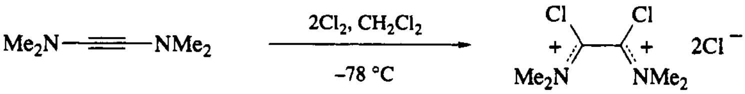

(46)

(27)

*(iii) Amines to 1,1-dihalogenated alkenes*

Perfluoroalkenes[9,160] and perfluorinated chloroalkenes[161] add secondary amines to give α,α-difluoroamines (**47**; equation 28). The *N*-halogenated amine (**48**) reacts with perhalogenated alkenes in a similar fashion. (equation 29).[162]

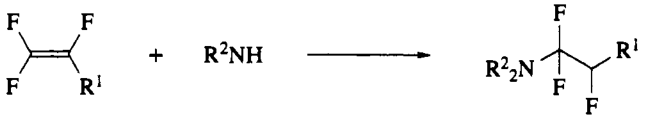

$R^1$ = F, CF$_3$

(47)

(28)

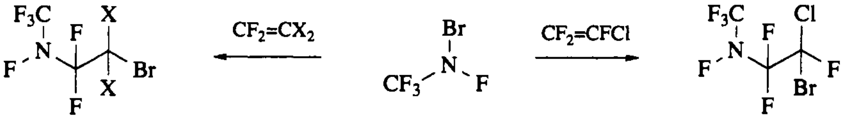

X = F, Cl, Br

(48)

(29)

*(iv) Dihalocarbenes to C═N group containing compounds*

Dihalocarbenes generated from haloforms and strong bases (*e.g.* alkoxides) or from haloforms and alkali metal hydroxides under phase transfer conditions[9,163–165] or organomercurytrihalomethanes,[9] add to azomethines to yield 2,2-dihaloaziridines (**49**; equation 30). The following carbenes have been used for such purposes: dichlorocarbene,[1,9,163–168] dibromocarbene,[165–167] difluorocarbene,[169,170] bromochlorocarbene[167] and bromofluorocarbene.[167] The addition of dihalocarbenes to azoxybenzene[9,171] or azobenzene affords dihaloaziridines (*e.g.* **50**; equation 31) among other products.

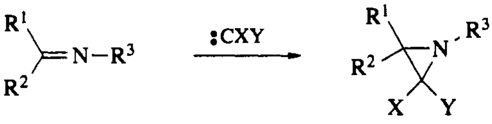

(49)

(30)

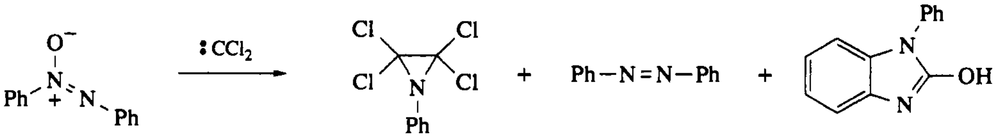

(50)

(31)

### 2.7.2.2.3 *From dihalomethyleneiminium salts (phosgene iminium salts, PI salts)*

Dihalomethyleneiminium salts undergo condensation reactions with CH-acidic compounds such as ketones, carboxylic acid chlorides, nitriles and amides, to give amide halides, *e.g.* (**51**; equation

32).[7,9,172–174] Amide chlorides were obtained by the same method from enamines,[9,172] fulvenes,[175] barbituric acid derivatives[176] or pyridopyrimidines[177] and PI salts (*e.g.* **52**; equation 33).

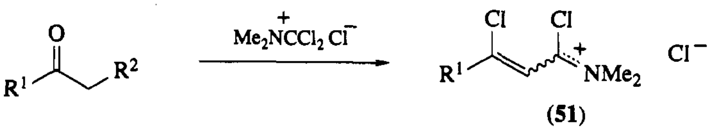

(32)

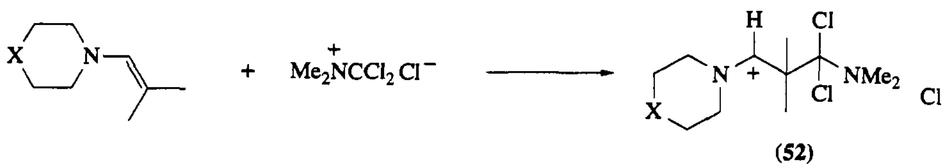

(33)

### 2.7.2.2.4 *From halomethyleneiminium salts*

*(i) By halogenation*

Amide chlorides which contain an α-CH or α-$CH_2$ group readily undergo chlorination in these positions. The amide chlorides thus formed were not isolated but their hydrolysis products, α-chlorinated amides (**53**) and (**54**; Scheme 2)[8,9,144] were formed.[8,9,144]

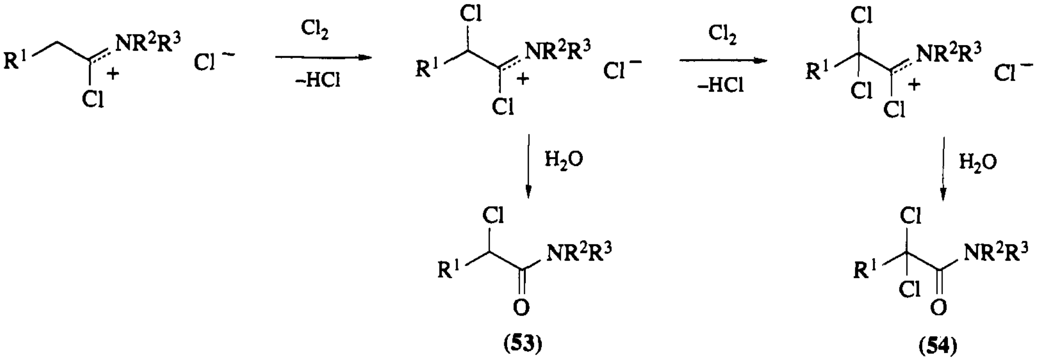

**Scheme 2**

*(ii) By diazocoupling*

In a few examples it was demonstrated that diazonium salts are capable of coupling with amide chlorides in the α-position yielding hydrazones of α-keto acid amide chlorides (**55**; equation 34).[8,9]

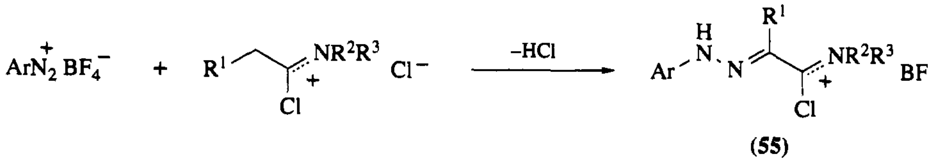

(34)

*(iii) By condensation with carbonyl compounds or by selfcondensation*

Although the selfcondensation of amide chlorides proceeds well to give amide chlorides derived from β-keto acids (**56**; equation 35) this reaction has only been used to synthesize β-keto acid amides, which result after hydrolysis of the condensation products (**56**), and not to prepare the salts (**56**) in the pure state. The condensation reaction of aromatic aldehydes with the *N*,*N*-dimethylacetamide–$POCl_3$ adduct in the presence of $HClO_4$ affords iminium salts (**57**; equation 36), which are hydrolyzed to cinnamic acid amides.[178]

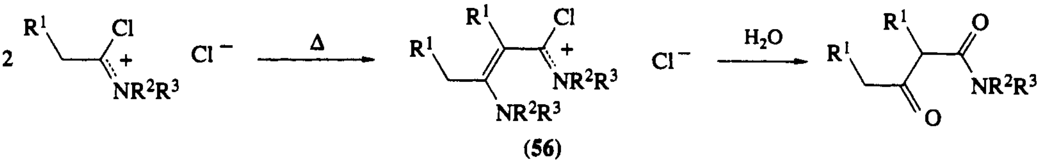
2
$R^1$
Cl
+
$NR^2R^3$
$Cl^-$
Δ
$R^1$
Cl
$R^1$
+
$NR^2R^3$
$NR^2R^3$
(56)
$Cl^-$
$H_2O$
$R^1$
O
$R^1$
$NR^2R^3$
O

(35)

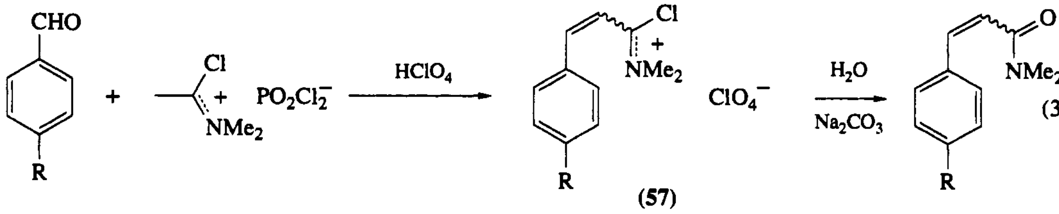
CHO
R
+
Cl
+
$PO_2Cl_2^-$
$NMe_2$
$HClO_4$
Cl
+
$NMe_2$
R
(57)
$ClO_4^-$
$H_2O$
$Na_2CO_3$
O
$NMe_2$
R

(36)

*(iv) By halogen exchange or anion exchange reactions*

Both chlorines in the iminium chloride (**27**) can be replaced by fluorine, bromine or iodine, giving compounds (**58**)–(**60**) (Scheme 3) if the salt is treated with the corresponding hydrogen halide under anhydrous conditions.[7,9] By chloro–iodo exchange with HI from the 3-chloroacrylamide chloride the corresponding amide iodide (**61**; equation 37) was prepared.[179] Dimethylformamide chloride (**27**) is converted by methyl iodide to dimethylformamide iodide (**59**).[180] Remarkably the difluoro compound (**60**) is a nonionic, distillable liquid which can be ionized by addition of boron trifluoride.[9]

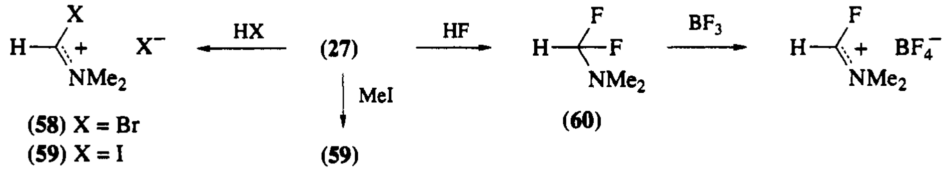
X
H
+
$X^-$
$NMe_2$
(58) X = Br
(59) X = I
HX
(27)
MeI
(59)
HF
F
H
F
$NMe_2$
(60)
$BF_3$
F
H
+
$BF_4^-$
$NMe_2$

Scheme 3

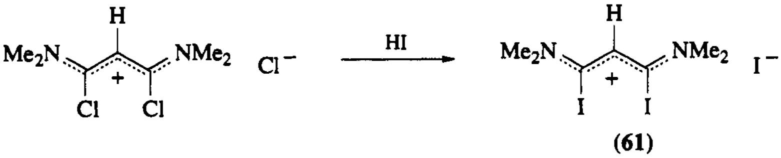
H
$Me_2N$
$NMe_2$
+
Cl
Cl
$Cl^-$
HI
H
$Me_2N$
$NMe_2$
+
I
I
$I^-$
(61)

(37)

*(v) Miscellaneous methods*

Octafluoroisobutene reacts with phenyl azides, presumably *via* a triazole which loses nitrogen to give the difluoroaziridine (**62**; equation 38).[170] *N*-Aryltrichloroethylamines are cyclized to dichloroaziridines (**63**; equation 39) on treatment with potassium *t*-butoxide.[181] A related procedure is the reduction of trichloroacetophenone imines by $LiAlH_4$, which can be stopped at the stage of the dichloroaziridines (**64**; equation 40).[182] Triethylamine splits off hydrogen iodide from the iminium salt (**61**) to give the 2-propinylium iodide (**65**; equation 41).[179] With fluorosulfonic acid methyl ester the imidoyl chloride (**66**) was methylated to yield the iminium salt (**67**, equation 42).[183]

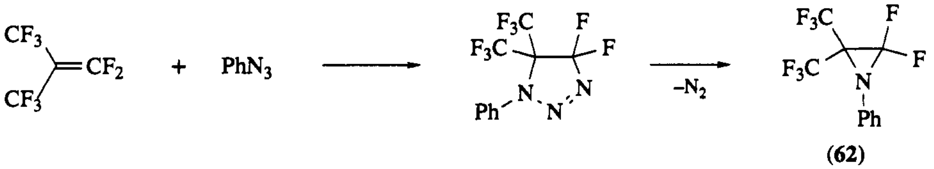

(38)

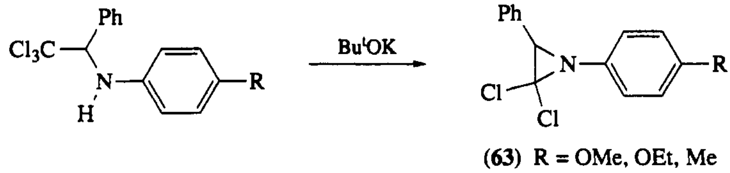

(39)

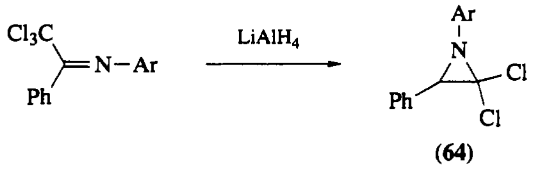

(40)

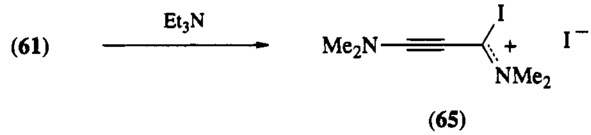

(41)

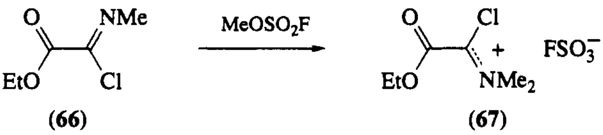

(42)

## 2.7.2.3 Alkoxymethyleneiminium Salts

### *2.7.2.3.1 From amides and alkylating reagents*

Fifty years ago Meerwein demonstrated that tertiary oxonium salts alkylate amides at the oxygen of the carbonyl group.[7,10] Since then a lot of amides have been converted by these reagents to the corresponding iminium salts (**68**; Scheme 4). The results show that there is little restriction in the use of this procedure. Only strongly electron-attracting groups eventually, in connection with high steric efficiency, are able to prevent the alkylation of the oxygen of the amide function. Thus *N*,*N*-dimethyltrichloroacetamide or *N*,*N*-dimethylcarbamoyl chloride do not react with triethyloxonium tetrafluoroborate.[10] If other functional groups are present in the amide molecule which are sensitive to strong alkylating reagents, *e.g.* orthoester structures,[10] thiadiazoline compounds,[184] amino groups *etc.*, they may also be attacked or degraded; however, there are known alkylations of 4-amino-5-aminocarbonylimidazolyl nucleosides at the oxygen of the amide function.[185] Steric effects alone seem not to be able to block the reaction as can be seen from the alkylation of isobutyramides[186] or pivalic acid dimethylamide.[10] No restrictions of the alkylation procedure are known either in the series of aromatic acid amides[7,10,187–189] or in the case of *N*,*N*-diaryl-substituted carboxylic acid amides. Triple bonds[10,190,191] and double bonds[10,192] can be present in the amide molecule.

Oxonium salts alkylate diamides of dicarboxylic acids twice, provided the amide groups are separated by at least two carbon atoms,[10,193,194] thus the bis(dimethylamides) of maleic acid or terephthalic acid have been converted to dications (**69**; Scheme 4) by means of oxonium salts.[10]

*N*-Acylimino compounds are converted by oxonium salts to iminium salts, which can be regarded as azaallenium salts.[195–198] A lot of lactams have been alkylated by oxonium salts at the carbonyl oxygen to give salts of type (**70**; equation 43).[7,10,199–207]

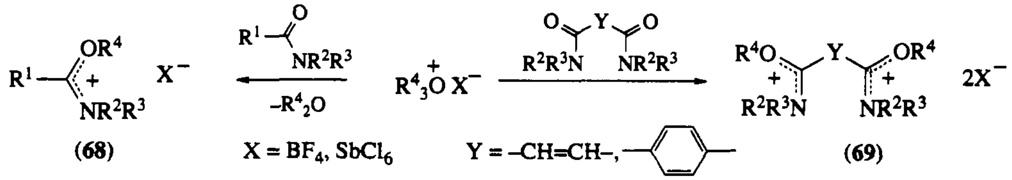
OR4
R1
NR2R3
X−
R1
O
NR2R3
−R42O
R43O X−
O Y O
R2R3N NR2R3
R4O Y OR4
R2R3N NR2R3
2X−
(68)
X = BF4, SbCl6
Y = -CH=CH-,
(69)

$R^1$ = H, alkyl, $RC_6H_4$, $CH_2Cl$, $CHCl_2$, $CH(OR)_2$, RC≡C, RCH=CH;
$R^2$, $R^3$ = H, alkyl, aryl, $=CR^5R^6$ ($R^6$ = alkyl, aryl, OR)

**Scheme 4**

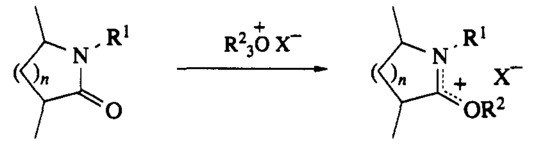
N R1
( )n
O
R23O X−
N R1
X−
OR2

(43)

**(70)** $R^3$ = Me, Et; X = $BF_4$

The action of oxonium salts on vinylogous amides affords iminium salts (**71**; equation 44), which are useful for synthetic purposes in heterocyclic chemistry.[10,208–211,214] Alkyldiphenylsulfonium tetrafluoroborates (**72**; equation 45) were recommended as reagents which alkylate amides and lactams under smooth conditions.[212] With the aid of fluorosulfonic acid esters[7,10,186,213] as well as with trifluoromethanesulfonic acid esters,[7,10,214,215] which have alkylation power comparable to oxonium salts, iminium salts, *e.g.* (**73**) and (**74**; Scheme 5), could be synthesized from amides,[186,214] vinylogous amides[213] and lactams.[215] Trimethylsilyloxymethyleneiminium salts (**75**; equation 46) are accessible by reacting trimethylsilyltrifluoromethanesulfonate with amides.[216,217]

Although carboxonium salts (**76**; equation 47) are easily available and of high alkylation power, they have found little application for alkylation of amide groups.[10]

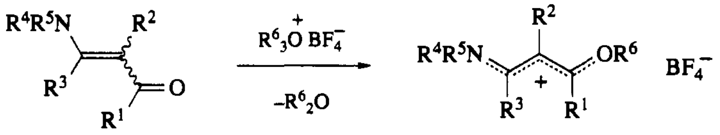
R4R5N R2
R3 O
R1
R63O BF4−
−R62O
R2
R4R5N OR6
R3 R1
BF4−

(44)

**(71)**

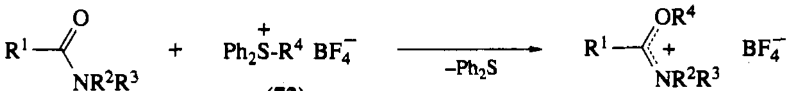
R1
O
NR2R3
Ph2S-R4 BF4−
−Ph2S
OR4
R1
NR2R3
BF4−

**(72)**

(45)

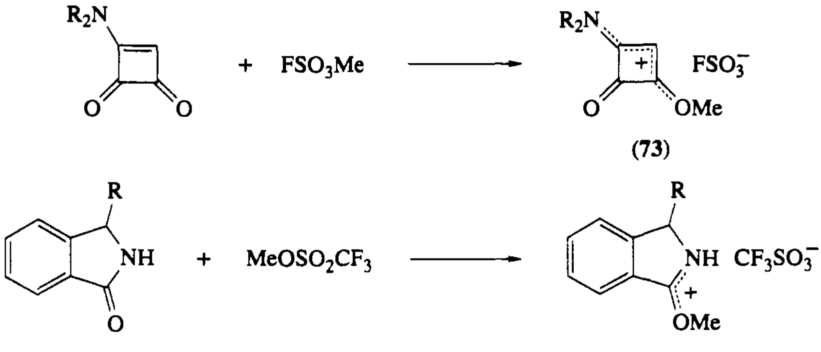
R2N
O O
FSO3Me
R2N
FSO3−
O OMe
R
NH
O
MeOSO2CF3
R
NH CF3SO3−
OMe

**(73)**

**(74)**

**Scheme 5**

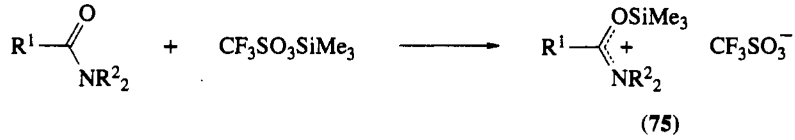
**(75)**

(46)

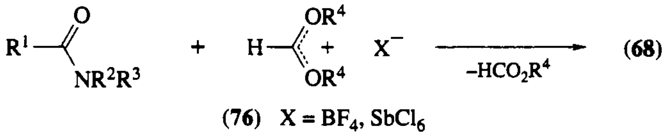
**(76)** $X = BF_4, SbCl_6$

(47)

Dialkyl sulfates alkylate acid amides in an equilibrium reaction at the carbonyl oxygen to give iminium salts (**77**; equation 48).[7,10] The position of the equilibrium depends on the nature of the substituents: bulky and electron-attracting groups shift it to the starting compounds. Fortunately in the case of the most important iminium salts, derived from *N,N*-dialkylated formamides or acetamides, the position of the equilibrium is situated far on the side of the iminium compounds, so that this reaction is by far the most convenient way to produce salts derived from formamides and acetamides. The alkylation is slow at room temperature, it can be accelerated by heating the components up to 80 °C. Higher temperatures should not be applied in order to avoid side reactions. *N*-Monosubstituted formamides react with dimethyl sulfate in a molar ratio of 2:1, yielding *N,N'*-disubstituted formamidinium salts (**78**; equation 49); formamide itself reacts in a more complicated way to give tris(formylamino)methane (**79**).[10]

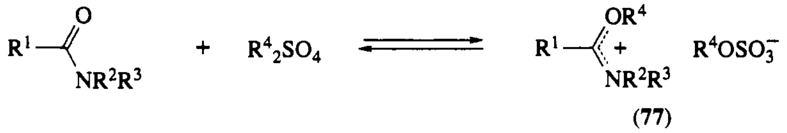
**(77)**

(48)

$R^1 = H$, alkyl ($C_1$–$C_5$), Ph, $PhCH_2$, $CH_2CONR_2$

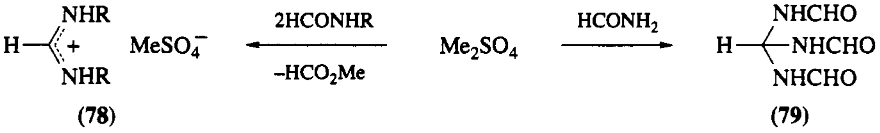
**(78)** **(79)**

(49)

In the alkylation of lactams the equilibrium position also lies at the side of the iminium compounds (**80**; equation 50), so it is not surprising that 4- to 12-membered ring lactams have been methylated by dimethyl sulfate to produce the corresponding cyclic iminium salts.[10]

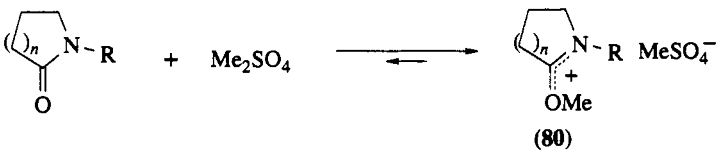
**(80)**

(50)

The alkylation of amides by alkyl halides or simple sulfonic acid esters is usually of little importance because the alkylation equilibrium is placed on the side of the starting compounds. This is not the case, however, in either the alkylation of vinylogous amides (which has been achieved even with alkyl iodides[218]) or if intramolecular alkylation is possible, *e.g.* in *N*-(2-haloethyl)amides. In the latter case cyclic iminium compounds (**81**; equation 51) are readily available by replacing the more nucleophilic halide by less nucleophilic complex anions, which can be achieved by addition of Lewis acids or $AgBF_4$.[10,219]

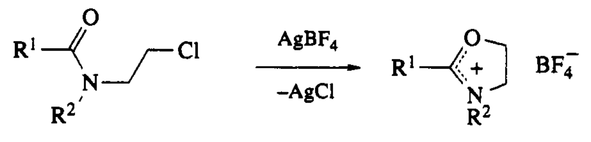

**(81)**

(51)

### 2.7.2.3.2 *From carboxylic acid amides and acylating reagents*

Primary and secondary amides and thioamides react with alkyl chloroformates with loss of $CO_2$ or COS, forming iminium chlorides (**82**; equation 52). In some cases this method is complementary to the Pinner imido ester hydrochloride synthesis.[7,10] The iminium salt (**83**; Scheme 6) formed by action of ethyl chloroformate on DMF is labile and decomposes rapidly to ethyl chloride. If the reaction is performed in the presence of $NaBF_4$, the iminium salt (**85**) is isolable. Aryl chloroformates react in the same fashion with DMF or DMA, but in these cases the aryloxymethyleneiminium compounds are fairly stable, so this reaction is an important method for the preparation of compounds of this type.[7,10] Succinic acid monoamides, phthalic acid monoamides and related compounds are cyclized to iminium salts (**86**; equation 53) by treatment with acetic anhydride and $HClO_4$.[220] With the aid of trifluoromethanesulfonic anhydride lactams and amides can be converted to dication ether salts (**87**) and (**88**; Scheme 7).[221,222]

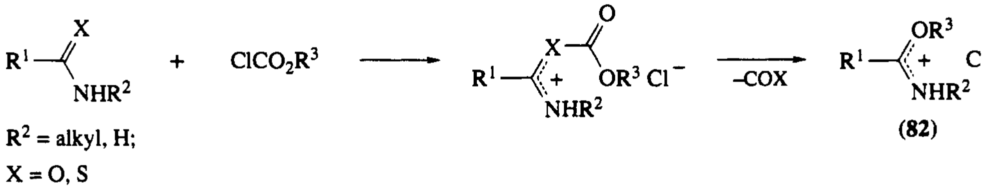

**(82)**

(52)

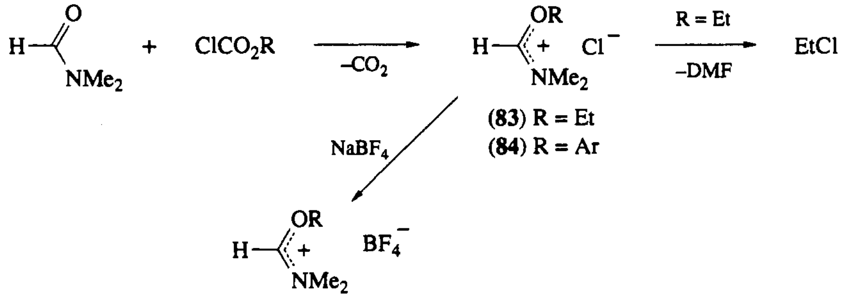

**(83)** R = Et
**(84)** R = Ar
**(85)**

**Scheme 6**

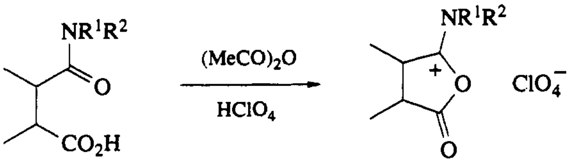

**(86)**

(53)

### 2.7.2.3.3 *By alkylation or acylation of imino esters*

Alkylation and acylation of imino esters proceeds at the nitrogen of the imino ester function. In many cases it is not advisable to use alkyl halides or acyl halides for such reactions because the iminium salts (**89**) or (**90**; Scheme 8) are readily dealkylated by the halide anions. This can be prevented by the use of stronger alkylating reagents, *e.g.* tertiary oxonium salts, dialkyl sulfates or alkyl triflates, which produce in the course of the alkylation only anions with low nucleophilicity.[10,223,224] Heterocycles containing

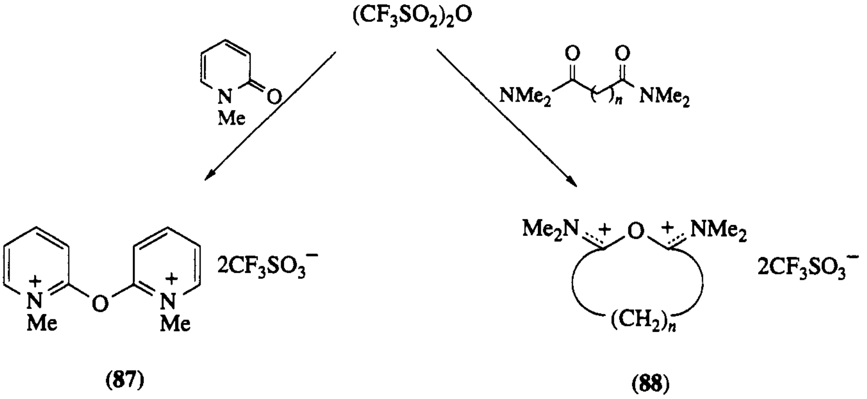
(CF3SO2)2O
N
Me
O
O
O
NMe2
n
NMe2
+
N
Me
O
+
N
Me
2CF3SO3−
Me2N
+
O
+
NMe2
(CH2)n
2CF3SO3−
(87)
(88)

Scheme 7

imino ester structures, *e.g.* 1,3-oxazolines or lactim ethers, can be transformed easily by alkylation to the corresponding heterocyclic iminium compounds.$^{10}$

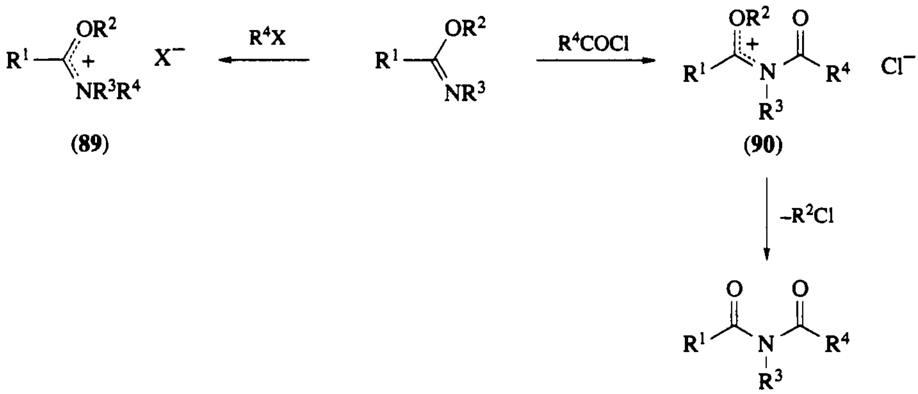
OR2
R1
+
NR3R4
X−
(89)
R4X
OR2
R1
NR3
R4COCl
OR2
O
+
R1
N
R4
Cl−
R3
(90)
-R2Cl
O
O
R1
N
R4
R3

Scheme 8

#### 2.7.2.3.4 *From halomethyleneiminium salts and related compounds*

The reaction of amide chlorides with alcohols to yield alkoxymethyleneiminium salts, *e.g.* (**91**) and (**92**; Scheme 9), is important for the preparation of cations with bulky alkoxy groups, *e.g.* $t$-butoxy. These alcoholysis reactions demand the presence of salts with less nucleophilic anions in order to avoid dealkylation of the cations. This difficulty does not arise if the iminium hexachloroantimonates, which are obtained from the chlorides by addition of SbCl$_5$, are used for alcoholysis.$^{7,10}$ A convenient route to $N$-unsubstituted salts (**93**; equation 54) is the alcoholysis of the formamide–benzoyl chloride adduct.$^{7,10}$ The reaction of phenols with dimethylformamide chloride (**27**) affords aryloxymethyleneiminium salts (**94**; equation 55) which are hard to prepare by other methods. By addition of alkynols to the $\alpha$-haloenamine (**95**) alkoxymethyleneiminium salts have been obtained (equation 56).$^{225}$

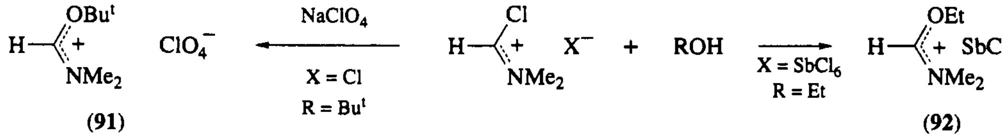
OBut
H
+
NMe2
ClO4−
(91)
NaClO4
X = Cl
R = But
Cl
H
+
NMe2
X−
+
ROH
X = SbCl6
R = Et
OEt
H
+
SbCl6−
NMe2
(92)

Scheme 9

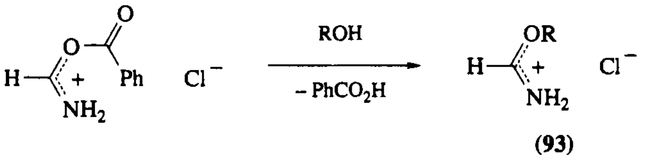
O
O
H
+
Ph
NH2
Cl−
ROH
- PhCO2H
OR
H
+
NH2
Cl−
(93)

(54)

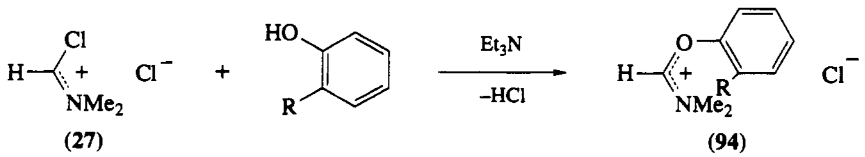

(55)

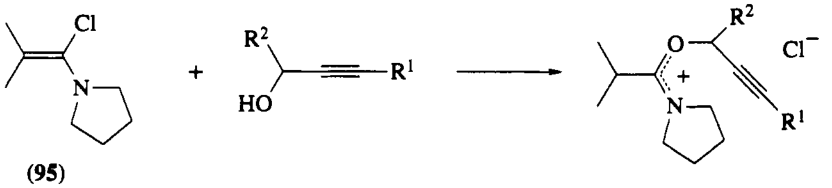

(56)

### 2.7.2.3.5 *From orthoamide derivatives and related compounds*

Strong Lewis acids abstract alkoxide groups from amide acetals or lactam acetals to give the corresponding iminium salts, *e.g.* (**96**; Scheme 10). Alkoxide transfer from amide acetals to less stable carbenium ions is also a route from amide acetals to iminium compounds (**97**).

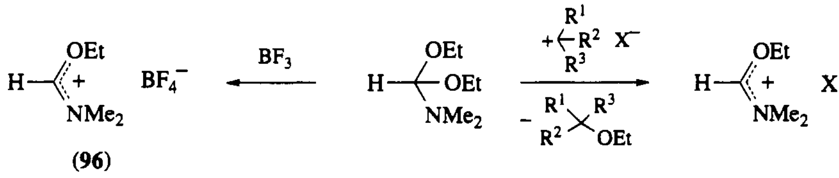

$R^1 = H, R^2 = R^3 = OEt; X = BF_4$ (**96**)

or $X = SbCl_6$ (**97**)

$R^1 = R^2 = R^3 = Ph; X = BF_4$

**Scheme 10**

Protonation of ketene *O*,*N*-acetals with strong acids gives rise to the formation of iminium compounds, *e.g.* (**98**; equation 57). Ketene *O*,*N*-acetals are transformed by alkyl halides or acyl halides to α-substituted amides *via* unstable iminium salts (**99**; equation 58).[10] Iminium compounds of this type are isolable if they are immediately precipitated, *e.g.* as perchlorate salts (**100**; equation 59).[227] Heterocumulenes such as isocyanates,[10] isothiocyanates[10] or $SO_2$[226] form 1,4-dipoles with ketene *O*,*N*-acetals, which can be stabilized by protonation with perchloric acid to give salts, *e.g.* (**101**; equation 60).

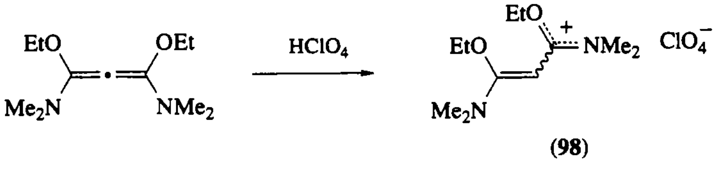

(57)

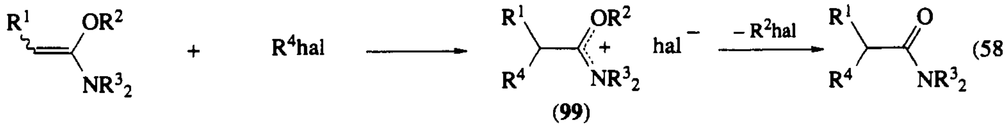

(58)

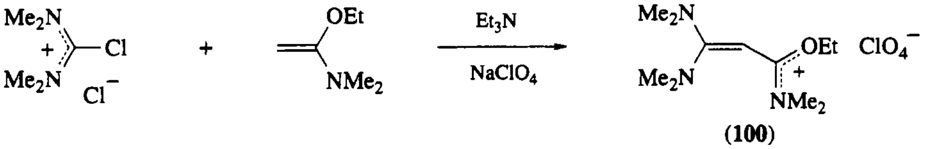

(59)

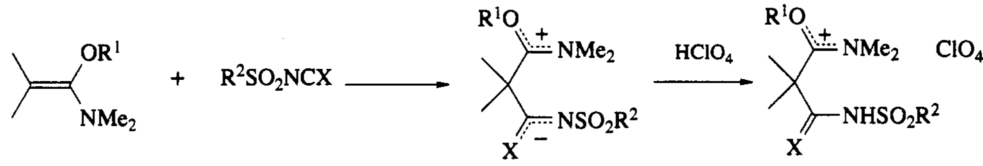

(60)

**(101)**

### 2.7.2.3.6 *From carboxonium salts*

Dialkylcarboxonium ions possess a very high alkylation power. If they are reacted with amines or amine derivatives, the substitution of the alkoxy group by the amino compound competes with the dealkylation of the carboxonium ion. Therefore only a few examples for the preparation of iminium salts are known, *e.g.* (**102**; equation 61), from carboxonium salts.[10,228,229]

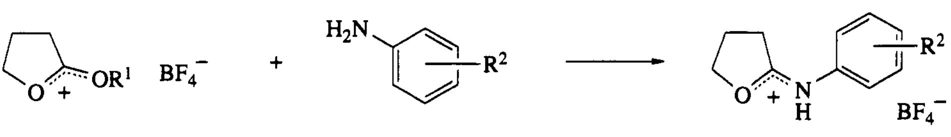

(61)

$R^2$ = 4-Me, 4-Cl, 2-$CO_2Et$

**(102)**

### 2.7.2.3.7 *From nitriles or nitrilium salts*

The addition of water-free alcohols to the nitrile group in the presence of HCl or HBr in a temperature range of 0–5 °C is a versatile synthesis for *N*-unsubstituted alkoxymethyleneiminium salts. Detailed reviews on these reactions have been published.[16,230,231] More recently it has been demonstrated that 'imido ester hydrochlorides' can be prepared, *e.g.* (**103**; equation 62), from heterocyclic nitriles[232,233] even if they have strong basic character.[232–234] The transformations of α-aryloxynitriles,[237] adamantanedicarbonitriles,[237] glycosidic-bound oxynitriles[238] and benzonitriles[239,240] with highly reactive functional groups, *e.g.* enol ether structures, to the corresponding imido ester hydrohalides have been described. Nitrilium salts add alcohols and phenols to give *N*-monosubstituted alkoxymethyleneiminium salts (**104**; equation 63).[7,10,241,242]

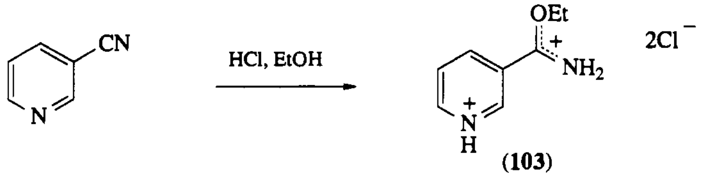

(62)

**(103)**

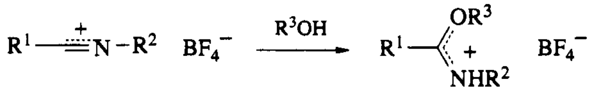

(63)

**(104)**

### 2.7.2.3.8 *Miscellaneous methods*

In alkoxymethyleneiminium salts the anions are exchangeable ($Cl^-$ *versus* $ClO_4^-$ or $SbCl_6^-$ *etc.*). This procedure can be used to purify the iminium compounds for analytical purposes. Tetraphenylborates (**105**), which are easy to obtain from the iminium salt and sodium tetraphenylborate in dry acetonitrile (equation 64), and which crystallize easily, are suitable reagents. The carbon skeleton of α,β-unsaturated alkoxymethyleneiminium compounds can be altered by cycloadditions, *e.g.* Diels–Alder reactions, to give compounds of type (**106**; equation 65).[7,10]

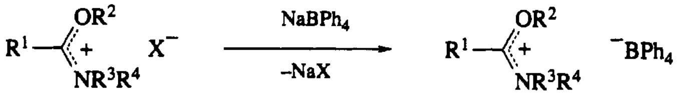

(105)

(64)

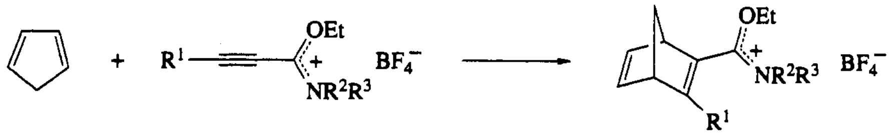

(106)

(65)

### 2.7.2.4 Alkylmercaptomethyleneiminium Salts

#### *2.7.2.4.1 From thioamides and alkylating reagents*

The high nucleophilicity of sulfur facilitates the alkylation of thioamides. The alkylation of thioamides and thiolactams is a long-known synthesis of alkylmercaptomethyleneiminium compounds (**107**; equation 66), which has been reviewed several times.[7,11–13,243] Nearly all types of alkylating reagents and amides were used for these reactions (see Table 3).

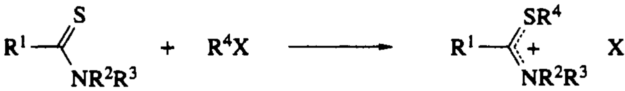

(107)

(66)

$R^1$ = alkyl, $Bu^t$, $Ar(CH_2)_n$, Ar;
$R^1$, $R^3$ = H, alkyl, aryl;
$R^4$ = alkyl, $ArCH_2$, $RCOCH_2$

If the substrate molecule contains further nucleophilic centers, these can be attacked first. With powerful alkylating reagents both functions are alkylated,[13,279] *e.g.* in (**108**) and (**109**; Scheme 11). Tertiary alkyl halides, *e.g.* trityl chloride, under basic conditions can alkylate primary thioamides at the nitrogen of the thioamide group.[13] From thio-DMF and 2,4-dinitrochlorobenzene the corresponding *S*-arylmethyleneiminium compound was prepared.[285]

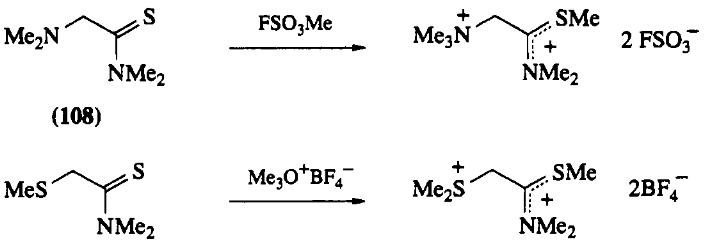

(108)

(109)

Scheme 11

#### *2.7.2.4.2 From thioamides and acylating reagents*

A simple and efficient route to alkylmercaptomethyleneiminium salts (**110**; equation 67) is the action of alkyl thiochloroformates on thioamides.[7,13,286] β-Chlorovinyl ketones react with thioamides to form iminium compounds (**111**; equation 68),[13,287,288] which can serve as precursors for 1,3-thiazinium salts.[288] Bromine forms labile *S*-bromoiminium salts (**112**) with thioamides,[289,290] which react with enamines to give *S*-vinyl-substituted salts (**113**; equation 69).[290]

**Table 3** Alkylating Reagents and Thioamides Suited as Starting Compounds for Alkylmercaptomethyleneiminium Compounds

| *Alkylating reagents* | *Ref.* | *Thioamides* | *Ref.* | *Thioamides* | *Ref.* |
|---|---|---|---|---|---|
| Alkyl iodides | 244–261 | Simple saturated aliphatic thioamides | 263, 265, 275, 279, 281 | Ester thioamides of aliphatic dicarboxylic acids | 253 |
| Alkyl bromides | 252, 254, 262–266 | | | | |
| Alkyl chlorides | 254, 263, 266–268 | Arylalkythiocarbonamides | 244, 246, 250, 257, 258 | Dithioamides of dicarboxylic acids | 284 |
| | | | | Four-membered thiolactams | 277 |
| | | | | Five-membered thiolactams | 254, 255, 261, 266, 270, 272, 276, 280, 283 |
| α-Halocarboxylic acid esters | 263, 269–272 | Long-chain aliphatic thioamides | 248 | | |
| α-Halo ketones | 273–276 | | | | |
| Dialkyl sulfates | 12 | Aromatic thioamides | 249, 251, 253, 259, 260, 269, 271 | | |
| Alkyl fluorosulfonates | 277–279 | | | Six-membered thiolactams | 253, 261, 273, 274 |
| | | | | Seven-membered thiolactams | 256 |
| Trifluoromethanesulfonic acid esters | 280 | Vinylogous thioamides | 245, 247, 252, 253, 282 | | |
| Oxonium salts | 279, 281–284 | | | | |
| | | Unsaturated thioamides | 268 | | |
| | | Chain-branched aliphatic thioamides | 250, 278 | | |
| | | Malonanilidedimethylthioamide | 268 | | |

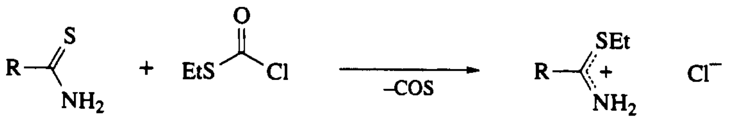

**(110)**

(67)

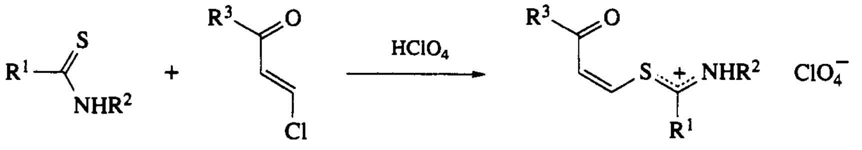

**(111)**

(68)

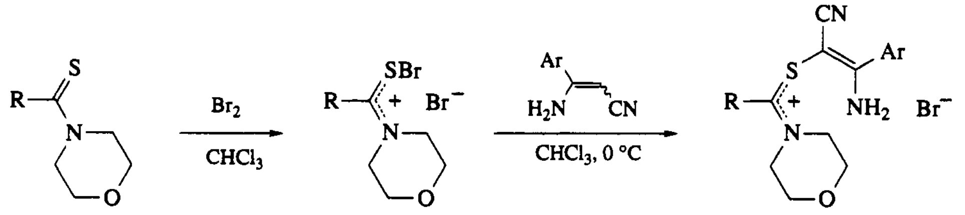

**(112)** **(113)**

(69)

### 2.7.2.4.3 *From thioimido esters by alkylation or acylation*

Alkylation of thioimino esters affords salts of type (**107**). This procedure was not often applied as the thioimido esters needed are usually prepared *via* alkylmercaptomethyleneiminium compounds. Provided there is an acceptable way to synthesize the imino ester, the method is of particular use if strong nucleophilic groups are present in a thioamide molecule so that a direct route to the iminium compound *via* alkylation of the amide is not possible. The nucleophilicity of the thioimido ester function exceeds even that of amino groups, as can be seen by the reaction of the thioimino ester (**114**; equation 70) with alkyl iodides.[13] Heterocycles containing the thioimino ester structure are easy to alkylate at the nitrogen. In this way a great number of 1,3-thiazolium salts, *e.g.* (**115**; equation 71), have been prepared. Alkylating reagents used in such processes were: alkyl iodides,[291–295] alkyl bromides,[293,296] toluenesulfonic acid methyl ester,[297] dimethyl sulfate[298] and triethyloxonium tetrafluoroborate.[299]

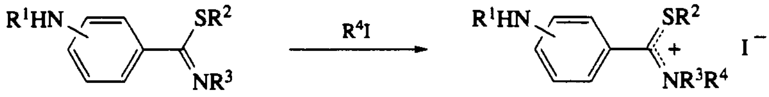

*(o,p)* **(114)**

(70)

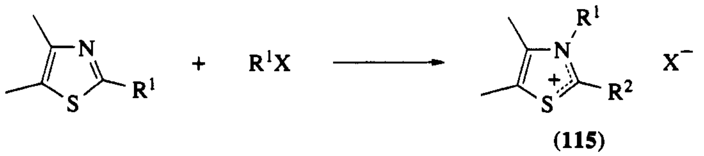

**(115)**

(71)

Generally the acylation of thioimino esters takes place at the nitrogen, the salts (**116**; equation 72) thus formed were not usually isolated but reacted further, *e.g.* deprotonated.

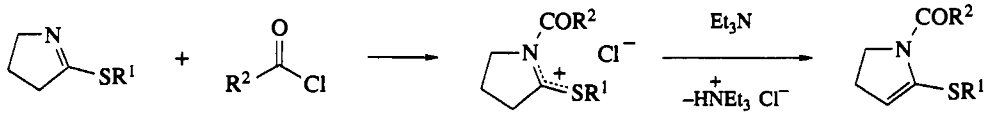

**(116)** (72)

#### 2.7.2.4.4 *From other methyleneiminium salts*

It is well known that the action of mercapto group containing compounds on chloromethyleneiminium salts affords alkylmercaptomethyleneiminium salts, *e.g.* (**117**; equation 73); this type of reaction has only rarely found application.[13]

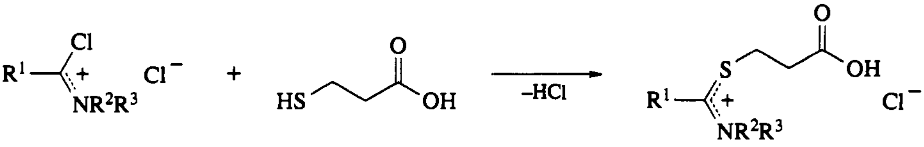

**(117)** (73)

#### 2.7.2.4.5 *By addition of SH group containing compounds to nitriles*

Thiols and benzenethiols add to nitriles in the presence of hydrogen halides to give *N*-unsubstituted iminium salts, *e.g.* (**118**, equation 74).[13,300] The reaction seems to have no advantage over other known preparative procedures.

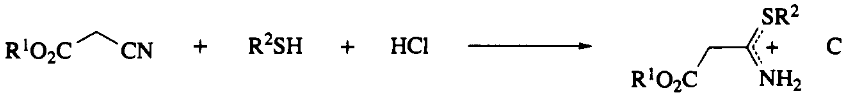

**(118)** (74)

#### 2.7.2.4.6 *By rearrangement of thioamides*

Thioamides with bulky substituents bound to the nitrogen can be rearranged to iminium compounds (**119**; equation 75) by treatment with HCl, provided the bulky groups can form stable carbenium ions.[7,13]

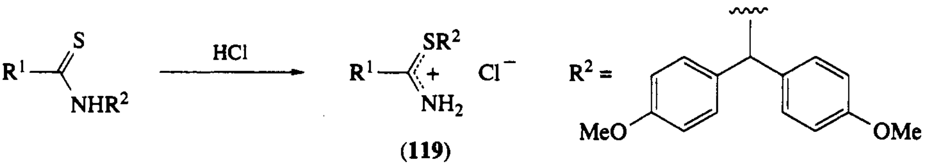

**(119)** (75)

#### 2.7.2.4.7 *From orthoamide derivatives and related compounds*

Ketene *S*,*N*-acetals are usually attacked by electrophilic reagents at the β-carbon, yielding iminium salts, thus ketene *S*,*N*-acetals have been alkylated and acylated. Similar reactions are described with chloroformic acid esters, cyanuric chloride, *m*-nitrophenylsulfenyl chloride, 2,4-dinitrochlorobenzene, 3-chloro-2-cyanoacrylonitriles and 2-chlorovinyl phenyl ketone. Usually it is not the initially formed iminium compounds but the substituted ketene *S*,*N*-acetals which are isolated, *e.g.* (**120**) and (**121**; Scheme 12).[13]

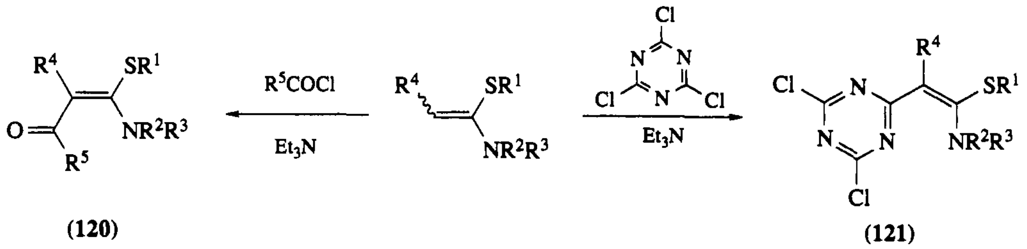

**(120)** **(121)**

**Scheme 12**

#### 2.7.2.4.8 *From orthocarbonic acid derivatives*

It was demonstrated that indole and substituted pyrroles undergo electrophilic substitution with alkylmercaptochloromethyleneiminium chlorides giving heterocyclic iminium chlorides (**122**; equation 76).[7,12] Probably this reaction type is of more general applicability.

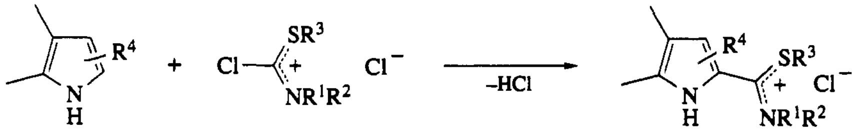 (76)

**(122)**

#### 2.7.2.4.9 *Miscellaneous methods*

*N*-Sulfinyldimethylammonium tetrafluoroborate transforms methyl dithiobenzoate to the corresponding iminium salt (**123**; equation 77).[301]

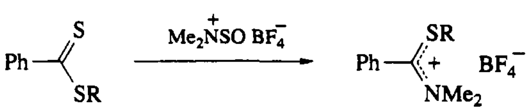 (77)

**(123)**

### 2.7.2.5 Amidinium Salts (Aminomethyleneiminium Salts)

#### 2.7.2.5.1 *From amide–acylating reagent adducts and amines or amine derivatives*

The adducts from secondary or tertiary carboxylic acid amides and $POCl_3$, $PCl_3$, $(PNCl_2)_3$, $RSO_2Cl$ and $R^1R^2NSO_2Cl$ (see Section 2.7.2.1) react with compounds containing primary or secondary amino groups to give amidinium salts (**124**; Scheme 13), but these are usually hard to isolate from the mixtures of amidinium and ammonium salts formed. Therefore in general the reaction mixture is made alkaline and the released amidine is extracted with organic solvents;[7,14] so this reaction is best suited to the preparation of *N,N'*-disubstituted or *N,N',N'*-trisubstituted amidines rather than the synthesis of the corresponding salts. Under certain circumstances the amidinium salts (**125**) are isolable by addition of NaI, $NaClO_4$ or $HClO_4$ *etc.* using the fact that amidinium ions with iodine or $ClO_4$ anions form only slightly soluble salts.

A versatile method for the preparation of *N,N,N',N'*-tetrasubstituted formamidinium salts[7,14,302,303] and *N,N,N'*-trisubstituted carbonamidinium salts[119,120] is the thermal decomposition of the *in situ* formed adducts, *e.g.* (**126**; equation 78), from secondary or tertiary formamides or higher secondary carboxylic acid amides with *N,N*-dialkylcarbamoyl chlorides. By the same procedure vinylogous amides have been converted to vinylogous salts (**127**; equation 79).[304] Similarly the adducts (**128**; equation 80) formed from phenylisocyanide dichloride with tertiary formamides decompose on heating to give formamidinium salts (**129**).[7,14] The 2:1 DMF–cyanuric acid adduct (**20**) has been used to prepare *N,N,N'*-trisubstituted formamidinium salts (**130**; equation 81).[14] The *in situ* formed adducts of DMF with trimethylhalosilanes react with arylamines to yield *N,N'*-diarylformamidinium salts (**131**; equation 82).[305]

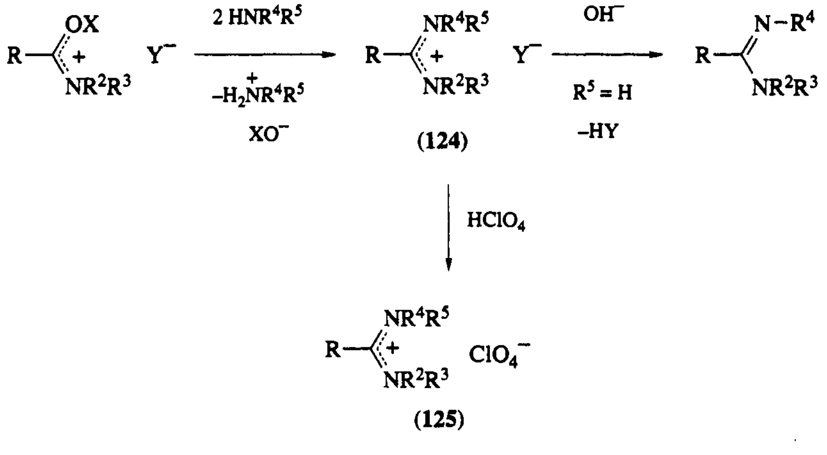

Scheme 13

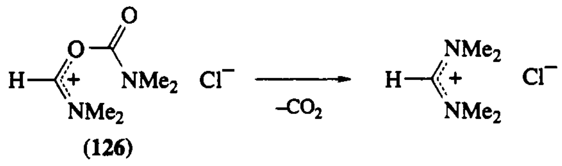

(78)

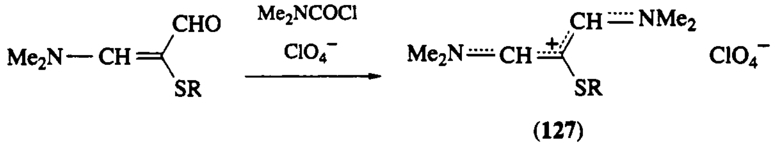

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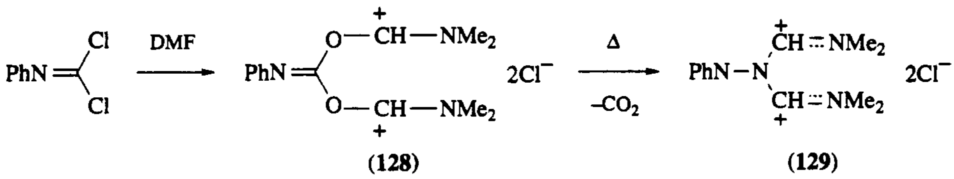

(80)

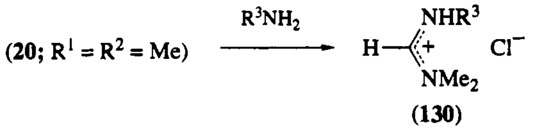

(81)

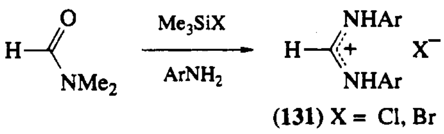

(82)

### 2.7.2.5.2 *From carboxylic acids, amines and various condensing agents*

A very simple procedure for the preparation of amidinium salts is the condensation of carboxylic acids with excess amine in the presence of $POCl_3$.[7,14] Using this method, the selfcondensation reaction of amide–$POCl_3$ adducts is suppressed. The salts are usually isolated as perchlorates (**132**; Scheme 14). In a related reaction benzoic acid is transformed by means of *N*,*N*′-dimethylethylenediamine and $TiCl_4$ to the imidazolium chloride, which was separated as the $PF_6^-$ salt (**133**).[14]

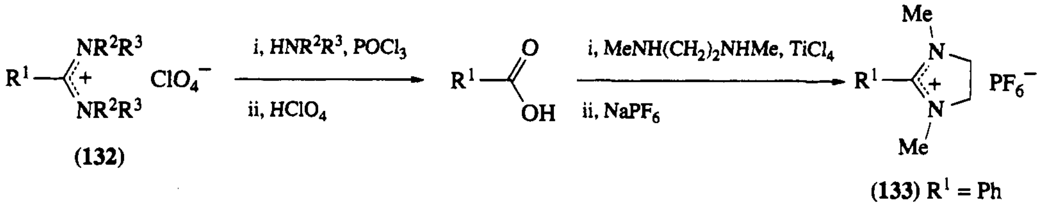

Scheme 14

### 2.7.2.5.3 *From iminium salts*

The reaction of amide chlorides with primary and secondary amines or amine derivatives yields amidinium salts (**134**; Scheme 15).[7,14,306] In the course of the reactions HCl is produced, which converts the amino compound to its hydrochloride. The salt mixtures thus formed are difficult to separate. Provided the amidinium compound in the mixture is at most an *N,N′,N′*-trisubstituted one, separation can be achieved *via* the free amidine, which, after separation, is easily converted to the desired amidinium salt (**135**) by acidification with water-free acids. From salt mixtures containing *N,N,N′,N′*-tetrasubstituted amidinium salts, the pure amidinium compound, *e.g.* (**136**) can sometimes be isolated *via* anion exchange by addition of $HClO_4$, $NaClO_4$[156] or NaI (in acetone/acetonitrile).

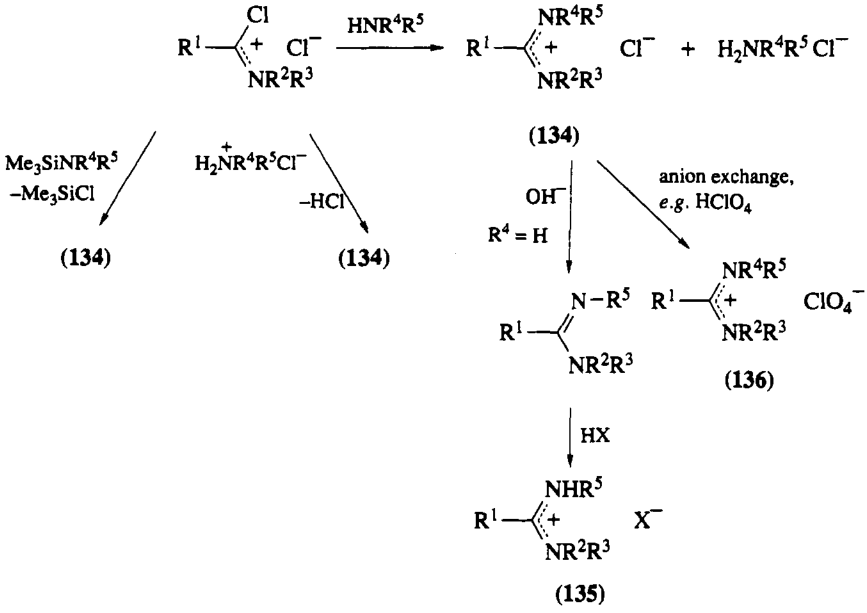

Scheme 15

Some ideas exist on circumventing the problem. Amine hydrochlorides at higher temperatures are in equilibrium with HCl and the amine. Provided the amide chloride is thermally stable (no von Braun degradation, no selfcondensation), which is true for a lot of aromatic amide chlorides or formamide chlorides, the amine hydrochloride can be reacted at elevated temperatures (150–170 °C) for strongly basic aliphatic amines, whereas weakly basic aromatic amides react under more gentle conditions. In another approach, instead of the amine the *N,N*-dialkylsilylamine is used, hence trimethylsilyl chloride is formed as a byproduct, which can be removed by distillation.

The reaction of amide chlorides with *N*-unsubstituted carbaminic acid esters or *N,N,N′*-trisubstituted ureas or thioureas affords the corresponding amidinium salts in good yields.[14,307]

By treatment of alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts with primary or secondary amines the alkoxy group or the alkylmercapto group, respectively, is replaced by the amino group forming amidinium salts (**137**; Scheme 16). The byproducts, alcohols or thiols, are easy to remove by distillation *in vacuo*. Especially in the case of alkoxymethyleneiminium salts it is necessary for the reaction temperature to be as low as possible to suppress the competing dealkylation of the salt (**138**) by the amine giving rise to ammonium salt formation.

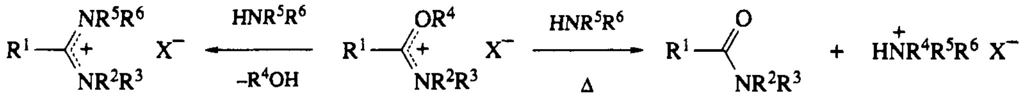

**(137)** **(138)**

**Scheme 16**

Since alkoxymethyleneiminium salts with nearly any substitution pattern are easy to prepare, this amidine synthesis has attained widespread application. Thus *N*-unsubstituted,[235–240] *N*-monosubstituted[7,14] and *N*,*N*-disubstituted alkoxymethyleneiminium salts (**138**)[7,14] have been transformed to amidinium salts (**137**) by treatment with ammonia,[235–240] primary and secondary amines and amine derivatives.[7,10,14]

It has been noted in some exchange reactions, performed under neutral conditions, that the amino group and not the alkoxy group is replaced.[10] 1,2-Diamines[308] and 1,3-diamines[7,10,14] react with iminium salts, *e.g.* (**139**) by substitution of both the alkoxy and the amino group.[7,10,14] In lactim ester salts (**140**; equation 84) the alkoxy groups can be replaced in the same fashion.[7,10,14]

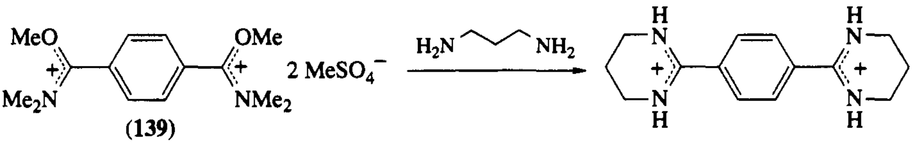

**(139)** (83)

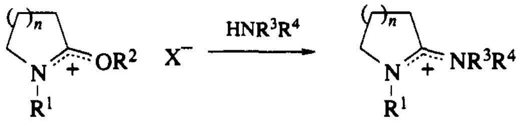

**(140)** (84)

From alkylmercaptomethyleneiminium salts various types of amidinium salts have been synthesized. Ammonia,[309] primary and secondary amines,[7,13,14] hydrazines[7,13,14,309] and *N*-unsubstituted[310,312] and *N*-monosubstituted hydrazones[311–313] were the reaction partners. Side reactions can include the dealkylation of the iminium salt by the amine. If *N*,*N*-unsubstituted salts (**141**; equation 85) are treated with amines, the desired exchange reaction can be accompanied by nitrile formation.

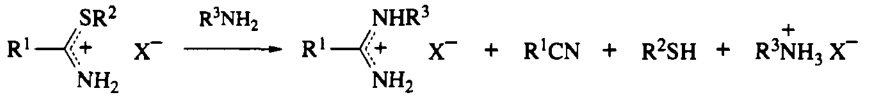

**(141)** (85)

Amidinium salts can also serve as starting materials for transamination reactions, *e.g.* Scheme 17.[7,14,314] The condensation of orthoamides with amidinium salts containing α-$CH_2$ groups affords α,β-unsaturated amidinium salts, *e.g.* (**144**; equation 86).[315]

### *2.7.2.5.4 From imidoyl compounds*

Imidoyl halides react with NH- and $NH_2$-containing compounds to give amidinium salts,[1–3] which were sometimes isolated,[14,316] but the free amidine bases were usually prepared from them. Since amidines are converted by water-free acids to the corresponding amidinium salts, amidinium salts with nearly every desired anion are accessible by this procedure. The alkylation of *N*,*N*,*N*′-trisubstituted amidines,[317] as well as those of symmetrically *N*,*N*′-disubstituted, *N*-monosubstituted and *N*-unsubstituted amidines are unambigous reactions. By this method a lot of amidinium salts, *e.g.* (**145**), (**146**) and (**147**) (equation 87), have been prepared. The alkylation of *N*-monosubstituted and *N*,*N*′-unsymmetrically substituted amidines can give rise to product mixtures of amidinium salts.[14]

1,1,2-Trimethyl-4-phenylbenzamidrazone reacts with methyl iodide uniformly to give (**148**; Scheme 18), whereas 1,1,4-trisubstituted amidrazones (**149**) yielded product mixtures by attack of the alkylating

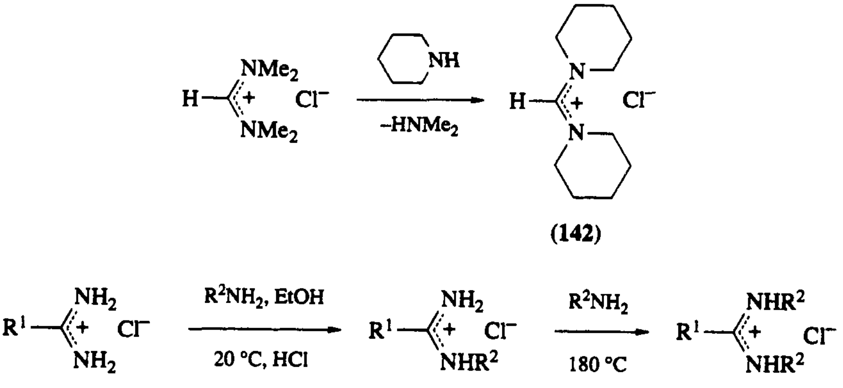

(142)

(143)

Scheme 17

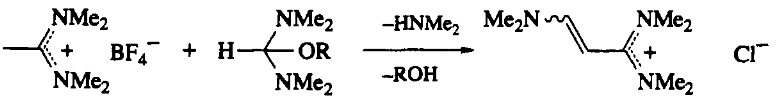

(144)

(86)

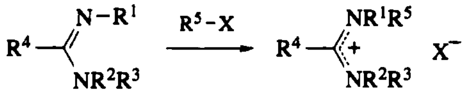

(87)

(145) $R^1 = R^2 = R^3 = H$
(146) $R^1 = R^2 =$ alkyl, aryl, $R^3 = H$
(147) $R^1, R^2, R^3 =$ alkyl

reagent on both nitrogens of the hydrazino group.[318] By alkylation of 2-acylimidazoles[319] or acylation of 1-methylimidazole[320] as well as by methylation of imidazolines[321] imidazolium salts are accessible.

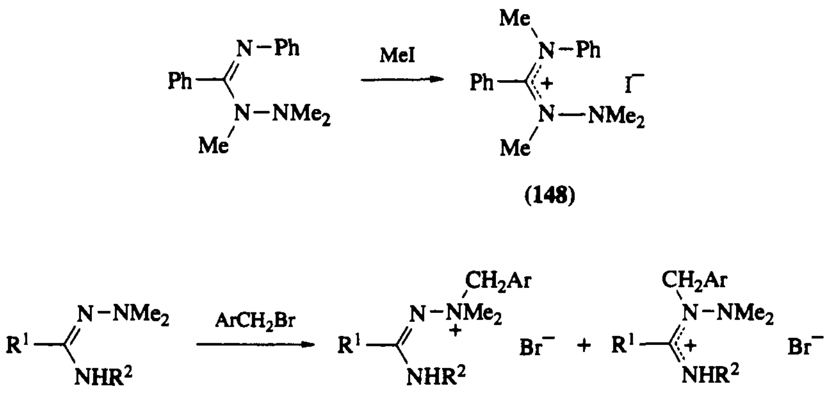

(148)

(149)

Scheme 18

### 2.7.2.5.5 From nitriles or nitrilium salts

Simple ammonium salts, as well as those derived from primary and secondary amines add to nitriles on heating. The yields can often be increased by application of pressure. By this method *N*-monosubstituted and *N*,*N*-disubstituted amidinium salts can be prepared.[14,20] The action of chloromethyleneiminium salts on nitriles gives rise to formation of 3-chloro-2-azapropenium salts (**150**; equation 88), the reaction has to be catalyzed by HCl in the case of aromatic nitriles. The salts (**150**) can be transformed to other amidinium salts by treatment with various nucleophiles (*e.g.* $H_2O$, $H_2S$, $ArNH_2$). Recently a review covering these reactions has appeared.[322]

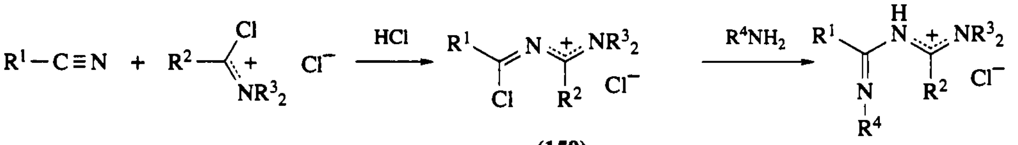

**(150)**

(88)

Nitrilium salts add amines and amine derivatives readily to give amidinium salts (**151**; equation 89). Alkaline work-up procedures often give the free amidines rather than the amidinium salts as the products. In these studies primary and secondary amines[7,14,323-325] and amino acids[14] have been used.

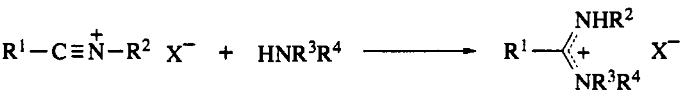

$$R^1-C\equiv\overset{+}{N}-R^2\ X^- + HNR^3R^4 \longrightarrow R^1-\overset{NHR^2}{\underset{NR^3R^4}{C}}{}^{+}\ X^-$$

$X = BF_4, FeCl_4, SbCl_6, CF_3SO_3$

**(151)**

(89)

1,2-Diaminomaleic acid dinitrile[326] as well as imines[327] were added to give the amidinium salts (**152**) and (**153**; Scheme 19), respectively. The amidinium salts (**152**) are useful for the synthesis of imidazoles.

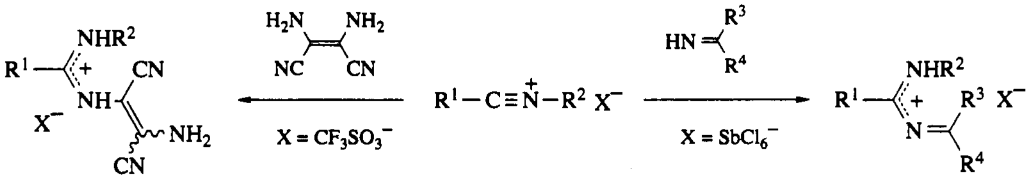

**(152)** $R^1 = R^2 = Me$

**(153)** $R^2 = Pr^i$, $R^3 = Bu^t$

**Scheme 19**

### 2.7.2.5.6 *From isonitriles*

Amine hydrochlorides as well as hydroxylamine hydrochlorides add to isonitriles to produce formamidinium salts (**154**; equation 90).[14]

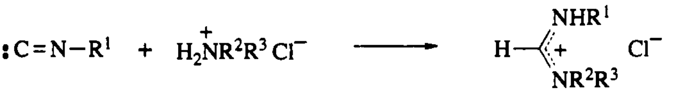

$$:C=N-R^1 + H_2\overset{+}{N}R^2R^3\,Cl^- \longrightarrow H-\overset{NHR^1}{\underset{NR^2R^3}{C}}{}^{+}\ Cl^-$$

(90)

**(154)** $R^2 = H$, $R^3 = Ar$; $R^2 = alkyl$, $R^3 = OH$

### 2.7.2.5.7 *From thioamides, thioxo esters, thioureas, amides and various reagents*

The reaction of amine hydrochlorides with thioxoesters affords amidinium salts (**155**; equation 91).[14] Formamidinium salts (**156**; equation 92) with bulky substituents at the nitrogens can be obtained by oxidation of *N*,*N*,*N*′-trisubstituted or *N*,*N*′-disubstituted thioureas with peracetic acid.[7,14] Byproducts in this reaction can be ureas and thiourea trioxides. β-Dimethylaminoacrolein reacts with dimethylamine hydrochloride to give (**157**; equation 93), the parent compound of the vinylogous amidinium salt series.[328,329] From *N*,*N*-dimethylthiobenzamide and *N*-sulfinyldimethylammonium tetrafluoroborate the benzamidinium salt (**158**; equation 94) was prepared.[301]

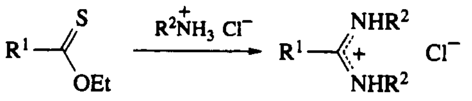

(155)

(91)

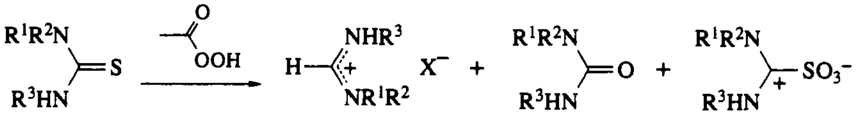

(156)

(92)

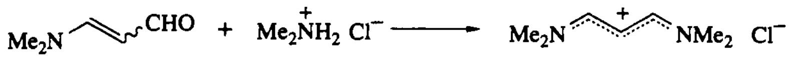

(157)

(93)

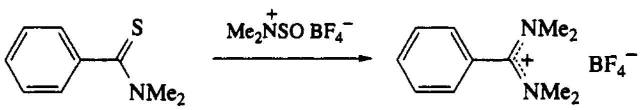

(158)

(94)

### 2.7.2.5.8 From orthoesters, orthoamide derivatives and related compounds

*N,N'*-Disubstituted amidinium salts (**159**; Scheme 20) and *N,N,N',N'*-tetramethylformamidinium perchlorate (**160**) have been prepared by action of orthoesters on the appropriate ammonium salts.[7,14] Formamidinium salts (**161**) can be synthesized in a similar fashion from amide acetals and salts of secondary amines.[7,330] Generally the amidine salt formation by treatment of aminal esters or tris(dialkylamino)alkanes with hydrogen halides is of little synthetic interest since *N,N,N',N'*-tetraalkylcarbonamidinium salts thus formed are usually the starting compounds for the synthesis of the corresponding orthoamide derivatives.[7,14] Only in cases where the orthoamides are readily available by other methods is this route acceptable; examples are the synthesis of *N,N'*-dialkyl-*N,N'*-diarylformamidinium salts (**162**; equation 95) or *N,N'*-diacylamidinium salts (**163**). Instead of hydrogen halides or mineral acids, acid halides or Lewis acids can be used for such purposes. From tris(dialkylamino)methanes and $CS_2$ formamidinium *N,N*-dialkyldithiocarbaminates were obtained;[7,330] in a similar reaction an amidinium salt has been prepared from tris(dimethylamino)methane and iron pentacarbonyl.[331]

Ketene aminals can be transformed by various electrophilic reagents to amidinium salts, thus mineral acids, alkyl halides, *N,N*-dialkyliminium salts, alkoxymethyleneiminium salts, formamidinium salts,[14] acyl halides,[14] diazonium salts, vinylogous amidinium salts,[332,333] sulfonyl halides, ketene dichlorides[334]

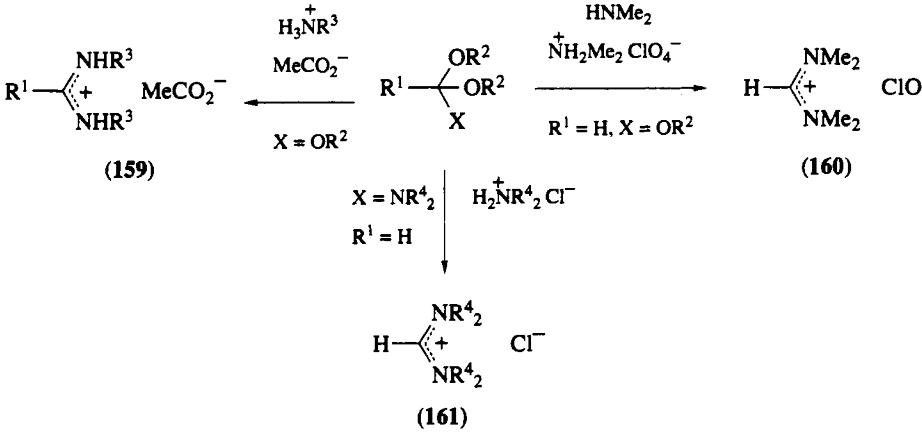

(159) (160) (161)

Scheme 20

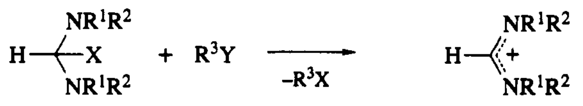

(95)

X = OR, $NR^1R^2$; $R^3$ = H, Y = hal, $HSO_4$; $R^3$ = RCO, Y = hal

**(162)** $R^1$ = alkyl, $R^2$ = aryl

**(163)** $R^1$ = H, $R^2$ = COR, $CO_2R$

and dithiolium salts[335] have been reacted with ketene aminals to give amidinium salts, *e.g.* **(164)**–**(169)** (Scheme 21). Heterocumulenes react with ketene aminals to form dipoles, which, with strong acids, yield amidinium salts, *e.g.* (**170**; equation 96).[14]

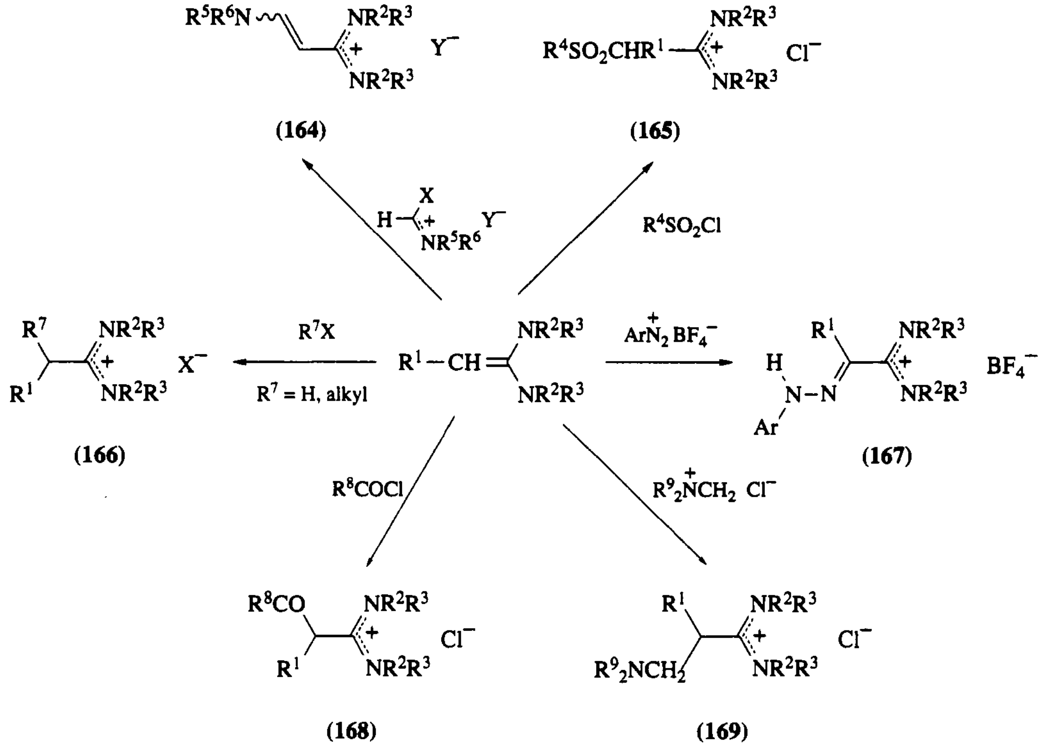

**Scheme 21**

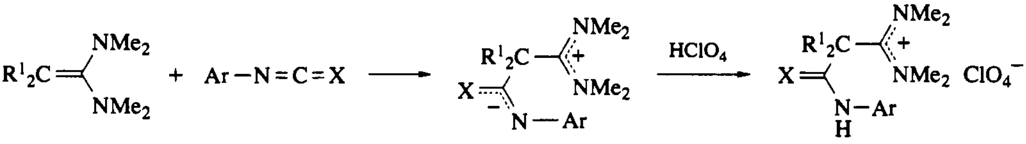

(96)

**(170)**

β-Ketoketene aminals[333,336] as well as β-(methylmercaptothiocarbonyl) ketene aminals[335] can be alkylated at the oxygen or sulfur, respectively, to afford the corresponding amidinium salts (**171**; equation 97). Ketene aminals, being electron rich compounds, are easily oxidized to yield amidinium salts. In the course of such investigations interesting results were obtained, for example dimerizations or cyclizations can occur[7,14,337–339] as well as formation of simple amidinium salts. By oxidation amidinium salts can be synthesized which are accessible only with difficulty by other methods, *e.g.* (**172**), (**173**) and (**174**) (Scheme 22).

The oxidation of triaminoethylenes (*e.g.* with $Br_2$) and tetraaminoethylenes (with $N_2O_4$, $Cu^+$, $Ag^+$, $Br_2$, $CCl_4$, $C_2Cl_6$) occurs with extreme ease to give bisamidinium salts, *e.g.* (**175**; equation 98) and (**176**; equation 99).[7,14] Even on reaction with malonodinitrile the oxamidinium system (**175**) is formed.

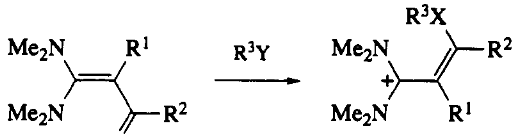 (97)

**(171)** X = O, S

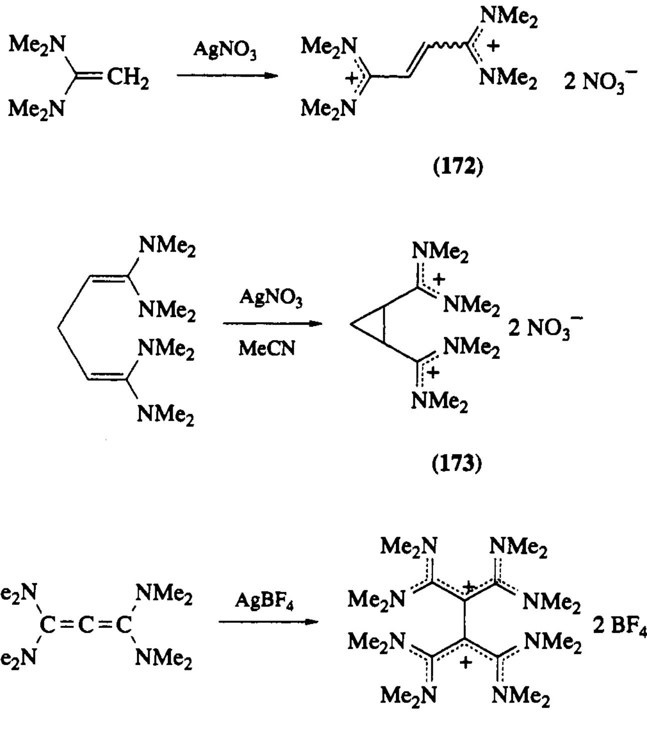

**(172)**

**(173)**

**(174)**

**Scheme 22**

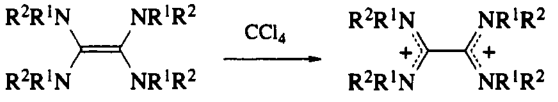 (98)

**(175)**

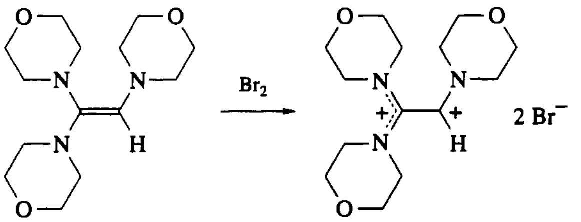 (99)

**(176)**

The reaction of α-chloroenamines with primary or secondary amines affords amidinium salts, *e.g.* (**177**; equation 100).[340] In most cases not the amidinium salts but their deprotonation products (ketene animals or amidines) have been isolated; these reactions have been reviewed.[341] Imino compounds undergo cycloadditions with α-haloenamines in which α-azetidylideneammonium salts (**178**; equation 101) are formed.[341-343] Ynamines are converted to amidinium salts, *e.g.* (**179**), (**180**) and (**181**) (Scheme

23), by halogenation, alkylation and *via* cycloaddition with methyleneiminium salts. These reactions have been thoroughly reviewed.[344]

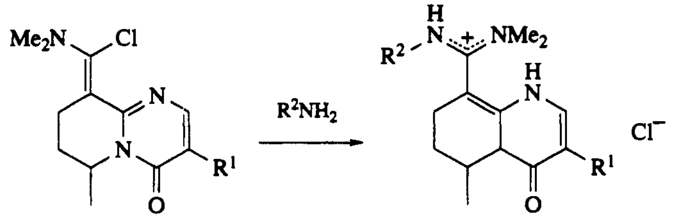

**(177)**

(100)

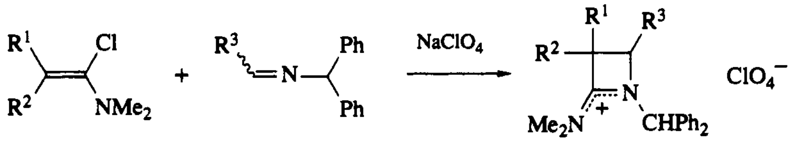

**(178)**

(101)

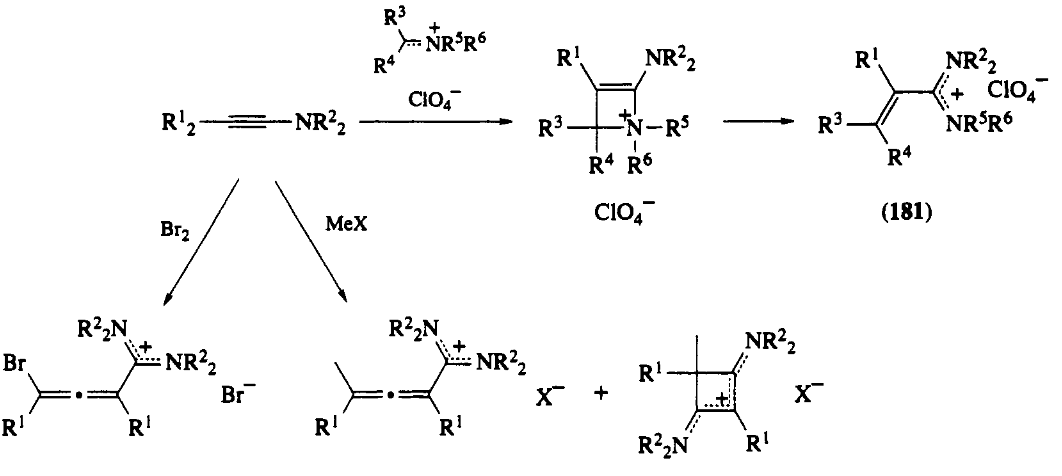

**(181)**

**(179)** **(180)**

Scheme 23

### 2.7.2.5.9 *From halogen compounds*

By action of excess secondary amine on chloroform in the presence of sodium alkoxide some formamidinium salts (**182**; equation 102) have been prepared.[14] The aminolysis of β,β-dichlorovinyl ketones or trihalocyclopropenes gives rise to the amidinium salts (**183**) and (**184**) (Scheme 24), respectively.[14]

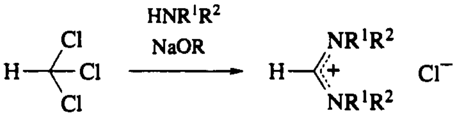

(102)

**(182)** $R^1$–$R^2$ = $(CH_2)_n$, $n$ = 4, 5; $R^1$ = $R^2$ = Et

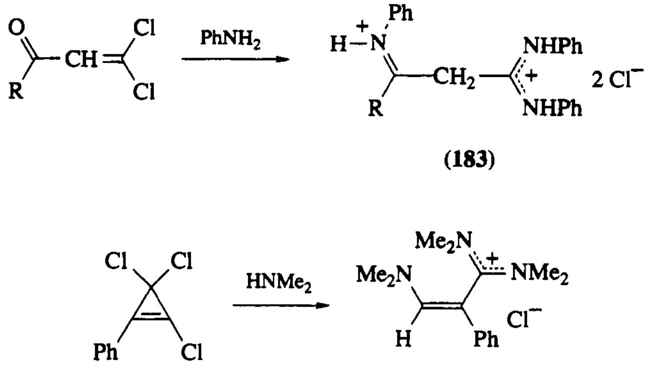

**(183)**

**(184)**

Scheme 24

### 2.7.2.5.10 *Vinylogous and azavinylogous amidinium salts*

Many vinylogous amidinium salts, *e.g.* **(185)** and **(186)** (Scheme 25), are readily available by double formylation of $CH_2$-acidic or alkenic compounds.[4] Reviews on the chemistry of vinylogous amidinium salts are available.[345] The first azavinylogous formamidinium salt (**187**; Scheme 26) was prepared in 1960 by reaction of DMF with cyanuric chloride.[14] The mechanism of this reaction has been established.[125,346] Based on these findings new methods for the synthesis of these compounds were developed, *e.g.* the reaction of isocyanatomethyleneiminium salts with tertiary formamides affords salts (**187**).[125,346] In the synthesis of the salts (**187**) cyanuric chloride can be replaced by phosphorus nitride chloride $(PNCl_2)_3$.[314]

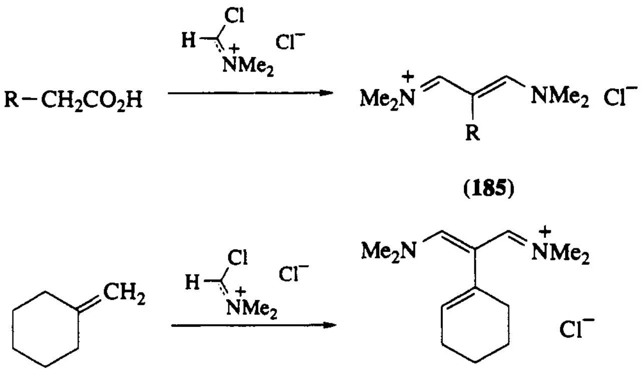

**(185)**

**(186)**

Scheme 25

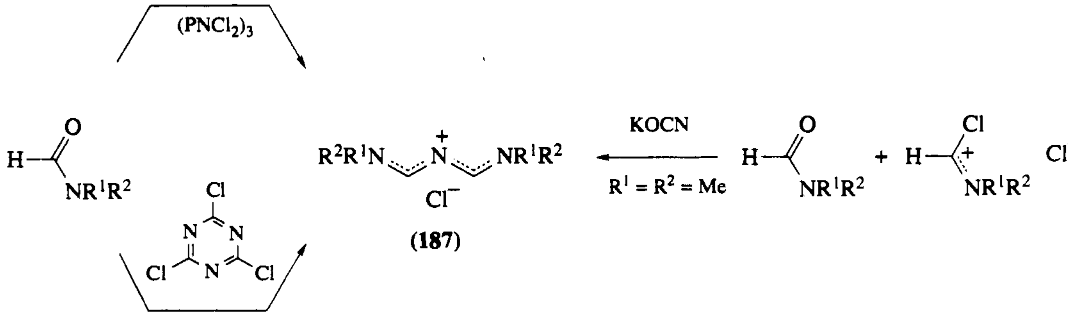

**(187)**

Scheme 26

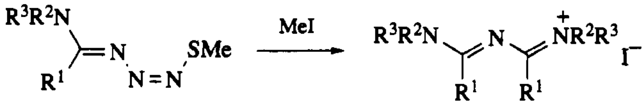

(103)

**(188)**

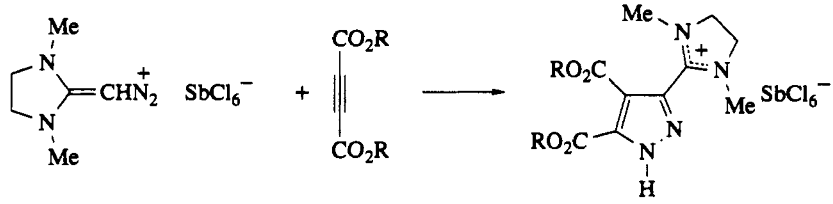

(104)

**(189)** **(190)**

#### 2.7.2.5.11 *Miscellaneous methods*

Azavinylogous amidinium salts (**188**; equation 103) were obtained by treatment of triazenes with methyl iodide.[347] Acetylenedicarboxylic acid ester reacts with the diazonium salt (**189**; equation 104) *via* cycloaddition to give the imidazolium salt (**190**).[348]

In diazophosphoryl compounds (**191**) electrophilic substitution occurs on treatment with bis(formamidinium) ether salts (**192**) to afford the diazoamidinium salts (**193**; equation 105).[349] In the alkylation of 1,3-dialkyl-5,5-dimethylhexahydropyrimidines with alkyl iodides mixtures of ammonium salts and iminium compounds (**194**; equation 106) result, which can be the sole products if $R^1$, $R^2$ and $R^3$ are bulky groups.[350]

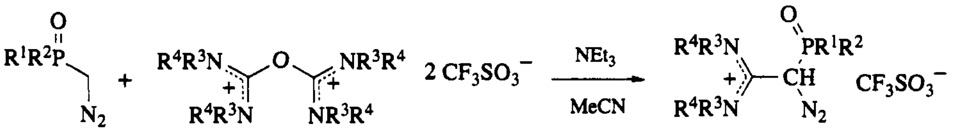

(105)

**(191)** **(192)** **(193)**

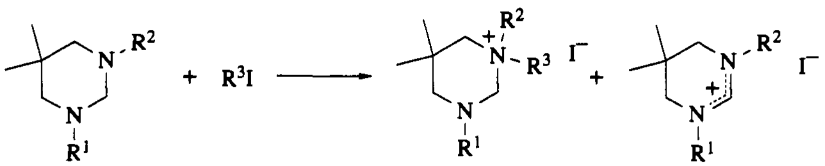

(106)

**(194)**

## 2.7.3 IMIDOYL COMPOUNDS

### 2.7.3.1 Imidoyl Halides

#### 2.7.3.1.1 *From amides, thioamides and halogenating reagents*

*(i) Phosgene, diphosgene, carbonyl difluoride, oxalyl dichloride*

Phosgene is a suitable reagent for converting secondary amides[1-3,351,352] and *N*-unsubstituted lactams[353] to imide chlorides, *e.g.* (**195**) and (**196**) (Scheme 27). The substituents at nitrogen might be saturated aliphatic or aromatic groups, but even unsaturated groups seem to be possible.[352] The reaction, which can be catalyzed with pyridine,[351] has been performed with aliphatic,[1–3,351] aromatic[1–3,352] and heterocyclic[352] amides. Phosgene can be replaced by the easier to handle 'diphosgene' (chloroformic acid trichloromethyl ester)[354] or triphosgene [bis(trichloromethyl)carbonate]. These methods have the advantage that only gaseous byproducts are formed, which facilitates product isolation. *N*-Monoalkylated formamides react with phosgene *via* the imidoyl chloride to *N*-dichloromethylformamidinium chlorides (**197**; equation 107).[1,3,9] Carbonyl difluoride is not suited to such reactions,[1–3,9] *e.g.* *N*-methylformamide is attacked at nitrogen and not at oxygen. Oxalyl chloride, is not very effective either for the preparation of imidoyl chlorides,[355] at elevated temperatures it reacts at the amide nitrogen.[5,356]

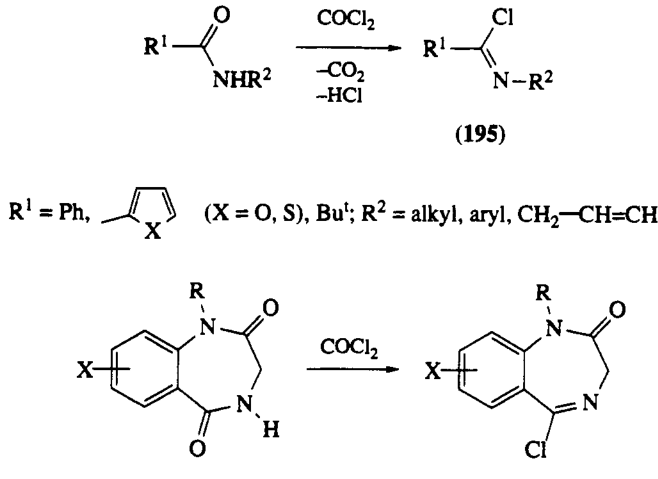

(195)

(196)

Scheme 27

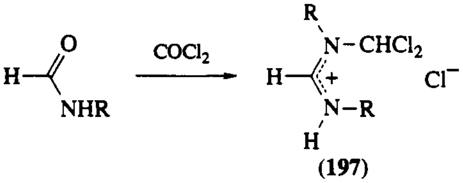

(197)

(107)

## (ii) *Phosphorus pentahalides, phosphorus trihalides, triarylphosphorane dihalides, tetraarylphosphorane halides, triphenylphosphine/carbon tetrahalides*

Wallach[1,3,7,9] in 1874 introduced $PCl_5$ as a reagent for the preparation of amide and imide chlorides from amides. Since that time this procedure has been developed to a standard procedure and several reviews deal with this topic.[1–3,357] Amides of aliphatic,[355,358–362] aromatic[355,363–367] and heterocyclic[368,369] acids bearing aliphatic,[358,362,364,365,368] aromatic[359,360,369] or heterocyclic[361,363,367] substituents or acyl groups[366] at nitrogen, as well as lactams[370,371] and dibenzamidoalkenes[372] have been transformed by this method to the corresponding imidoyl chlorides. *N,N'*-Dialkyloxamides react with $PCl_5$ *via* unstable imidoyl chlorides to give 4-chloroimidazoles (**198**; equation 108),[1,3] whereas imide chlorides of *N,N'*-diaryl oxamides can be prepared in the pure state.[3] *N,N'*-diarylmalondiamides react with $PCl_5$ to give the α,α-dichlorinated bisimide chlorides (**199**; equation 109).[373,374]

In general in the preparation of imide chlorides excess $PCl_5$ should not be used if α-chlorination is undesired. In contrast to triple bonds, double bonds conjugated with the amide carbonyl group do not add the HCl set free in the course of imidoyl chloride formation.[1] In the case of α,α,α-trihalogenated amides

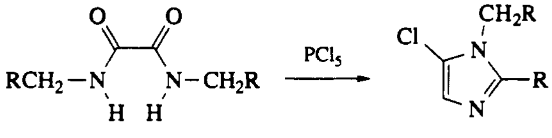

(198)

(108)

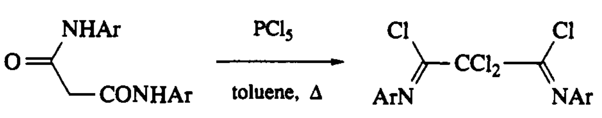

(109)

**(199)**

side reactions are known, which arise from the attack of the $PCl_5$ molecule at the amide nitrogen, *e.g.* formation of compounds (**200**) and (**201**) (equation 110).[1,3,355]

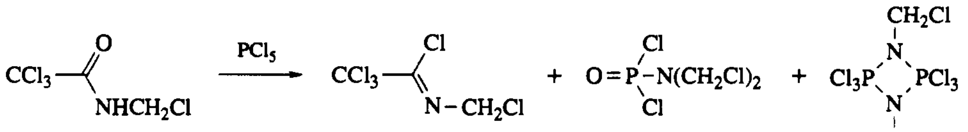

(110)

**(200)** **(201)**

If α-CH bonds are present in the imide chloride molecule selfcondensation can occur at elevated temperatures to yield compounds (**202**; equation 111),[355] a fact which should be kept in mind when choosing the reaction conditions. Starting with *N*-arylethylcarbonamides the imidoyl chlorides can cyclize to give heterocyclic compounds[376–378] (Bischler–Napieralksi reaction[375]), *e.g.* (**203**; equation 112). For such cyclizations $POCl_3$ has also been used as the condensing agent.[379–382] Treatment of ketoximes with $PCl_5$ affords imidoyl chlorides (**204**; equation 113), which readily cyclize to yield isoquinoline derivatives.[382–384]

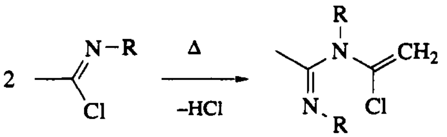

(111)

**(202)**

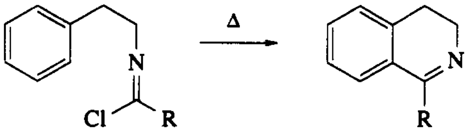

(112)

**(203)**

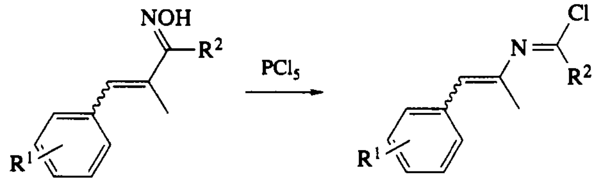

(113)

**(204)**

Other phosphorus compounds, *e.g.* $PBr_5$,[1,3] mixtures of $PBr_3$ and $Br_2$[3] or $PCl_3/Cl_2$[3] and phenyltetrachlorophosphorane ($PhPCl_4$)[3] have been used to convert amides to imidoyl halides. The formation of imidoyl halides proceeds under mild conditions by action of triphenylphosphine/$CCl_4$ or triphenylphosphine dihalides on secondary amides[385,386] or ketoximes.[387] The work-up procedure can be facilitated by use of polymer-supported triphenylphosphine/$CCl_4$.[99] By the action of $POCl_3$, phenyl- or methyl-phosphonic acid dichloride on aminocarboxylic acid thiol esters in the presence of triethylamine the imidoyl chlorides (**205**; equation 114) are formed in moderate to good yields.[388] The mechanism of this reaction has not been established. The methylene dialkylchlorophosphorane (**206**; equation 115) allows the conversion of secondary aromatic amides to imidoyl chlorides under very mild conditions.[389]

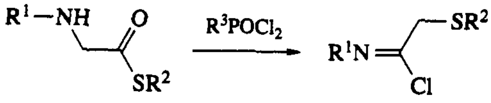
R¹—NH
O
SR²
R³POCl₂
R¹N
SR²
Cl

(114)

**(205)**

$R^1 = Bu^n, R^2 = Bu^i$

$R^3 = Cl$, 50%; $R^3 = Me$, 90%; $R^3 = Ph$, 96%

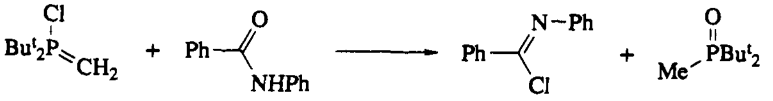
Cl
Bu^t₂P
CH₂
+
Ph
O
NHPh
Ph
N−Ph
Cl
+
O
Me
PBu^t₂

**(206)**

(115)

*(iii) Thionyl halides, nitrosyl chloride*

Thionyl chloride is a versatile reagent for transforming secondary amides[9,357,390,391] and lactams [392] to imidoyl chlorides, *e.g.* (**207**; Scheme 28) because only gaseous byproducts are formed. Thionyl chloride can be used in excess. Even from the Ni complexes of *N*-benzoylthioureas and $SOCl_2$ imide chlorides (**208**) could be prepared.[393]

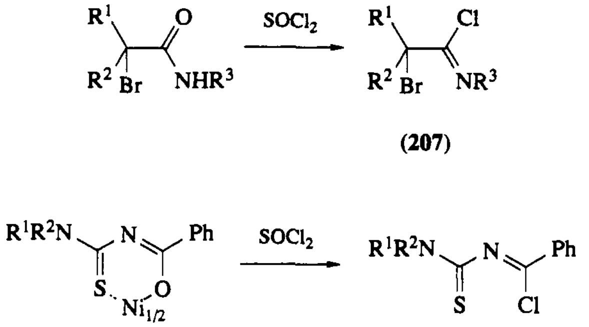
R¹
O
R²
Br
NHR³
SOCl₂
R¹
Cl
R²
Br
NR³
R¹R²N
N
Ph
S
O
Ni₁/₂
SOCl₂
R¹R²N
N
Ph
S
Cl

**(207)**

**(208)**

**Scheme 28**

The action of nitrosyl chloride on thioamides affords imidoyl chlorides with moderate yields.[3] α-Halogenated secondary amides react with boron trihalides or alkylhaloboranes to give imidoyl halides (**209**; equation 116) in low to moderate yields.[394]

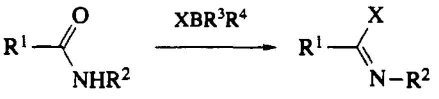
O
R¹
NHR²
XBR³R⁴
X
R¹
N−R²

(116)

**(209)**

$R^1 = CF_3, CHCl_2, CCl_3$ ; $X = Cl, Br$; $R^3, R^4 = Ph, Me, Cl, Br$

### *2.7.3.1.2 From isonitriles, nitriles and ketene imines*

Isonitriles add carboxylic acid chlorides to yield α-oxoimidoyl chlorides (**210**; equation 117).[1,3,5,395,396] With copper catalysis, from perfluorinated alkyl iodides and isonitriles imidoyl iodides (**211**; equation 118) can be obtained.[397,398] Alkenes react with nitriles in the presence of HF[399] or $Cl_2$[400,401] to afford the corresponding imidoyl derivatives (**212**; equation 119). By addition of chlorine[3] or arenesulfenyl chlorides[402–404] to ketene imines the α-substituted imidoyl chlorides (**213**) and (**214**) can be prepared (Scheme 29).

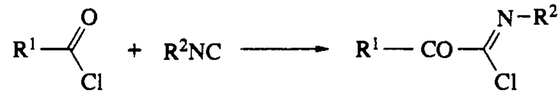

(117)

**(210)**

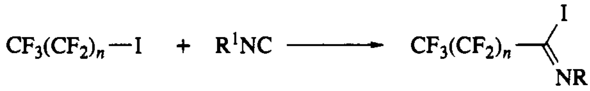

(118)

$R^1$ = alkyl, aryl **(211)**

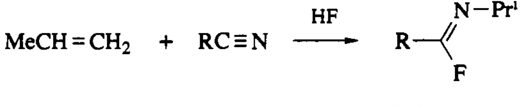

(119)

**(212)** R = H, alkyl

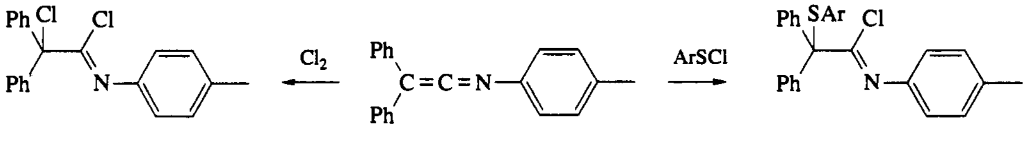

**(213)** **(214)**

**Scheme 29**

### 2.7.3.1.3 *From imines by oxidation*

High temperature chlorination of imines makes a few special (perhalogenated) imidoyl chlorides accessible.[357] From the preparative point of view the oxidation of aldimines with *t*-butyl hypochlorite or alkali metal hypochlorite[1,405] is more convenient and of broader scope for the synthesis of imidoyl chlorides (**215**; Scheme 30). Aldimines are converted to imidoyl chlorides (**215**) by heating with $PCl_5$ in xylene.[406]

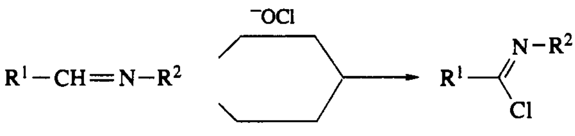

**(215)**

**Scheme 30**

### 2.7.3.1.4 *From amines and haloalkanes or haloalkenes*

At temperatures of about 500 °C pentafluorophenyltrichloromethane reacts with perfluorinated aromatic or heterocyclic amines to give imidoyl chlorides (yields 23–77%), *e.g.* (**216**; Scheme 31).[407] Chlorotrifluoroethylene reacts with 1-phenylethylamine to give the imidoyl chloride (**217**) in high yields.[408] The action of perfluoroisobutene on trimethylsilylacetamide or *N*-chloroacetamide gives rise to formation of the *N*-acetylimidoyl fluorides (**218**) and (**219**).[409]

### 2.7.3.1.5 *From imidoyl halides*

Imidoyl chlorides are transformed to the fluorides (**220**; equation 120) by reaction with CsF (at elevated temperatures)[386] or with KF and crown ethers.[410] On heating with triethylamine the *N*-benzyltrifluo-

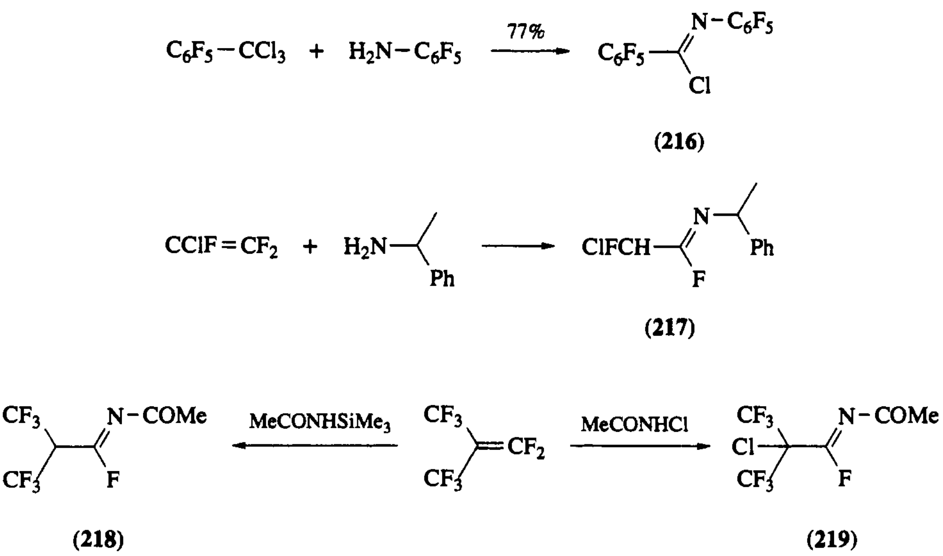
77%
(216)
(217)
MeCONHSiMe₃
MeCONHCl
(218)
(219)

**Scheme 31**

roacetimidoyl chlorides (**221**; equation 121) isomerize *via* the isolable imines (**222**) to yield the *N*-trifluoroethylbenzimidoyl chlorides (**223**).[411,412]

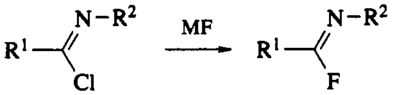

(120)

**(220)**

$R^1$ = Me, $CCl_3$, Ph; $R^2$ = $C_6H_{11}$, Me, $CH_2Cl$

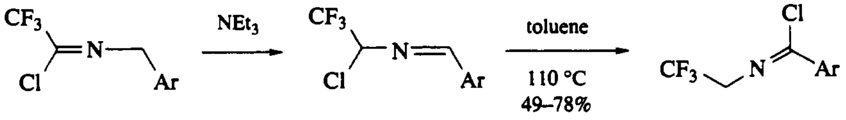
NEt₃
toluene
110 °C
49–78%

(121)

**(221)** **(222)** **(223)**

### 2.7.3.1.6 Miscellaneous methods

Chlorine adds to *N*-trichlorovinylbenzaldehydeimine to give the *N*-benzylideneamide chloride (**224**) which is in equilibrium with the imidoyl chloride (**225**; equation 122).[413] The action of trimethylsilyl iodide or diethylaluminum iodide on *O*-acylketoximes affords imidoyl iodides (**226**; equation 123) with excellent yields.[414]

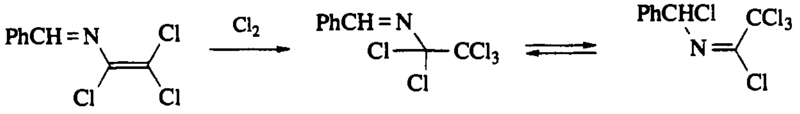

(122)

**(224)** **(225)**

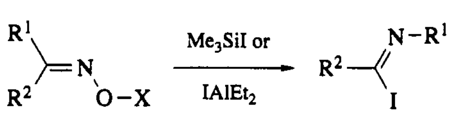

(123)

**(226)**

X = SO$_2$Me, CO$_2$Et, COMe, COPh; R$^1$ = R$^2$ = Me, Et; R$^1$–R$^2$ = (CH$_2$)$_n$ , *n* = 5, 11; R$^1$ = Ph, R$^2$ = Me

## 2.7.3.2 Imidates (Imidic Acid Esters, Imido Esters, Imidoates)

### *2.7.3.2.1 From alkoxymethyleneiminium salts or nitrilium salts*

*N*-Unsubstituted and *N*-monosubstituted alkoxymethyleneiminium salts are readily deprotonated by bases like tertiary amines, carbonates, alkoxides *etc.* to give the corresponding imidates (**227**; Scheme 32). By the same procedure cyclic imidates (lactim esters) (**228**) can be prepared. The iminium salts needed are readily available (see Section 2.7.2.3); often they were synthesized and transformed to the imidates without further purification. The Pinner synthesis, which produces the *N*-unsubstituted salts, is widely applicable and has been reviewed several times[7,15–17,22] (for some more recent examples see Section 2.7.2.3.7). To demonstrate the range of the reaction, a selection of nitriles, which have been transformed *via* Pinner synthesis to the corresponding imidates (**229**; equation 124) is compiled in Table 4.

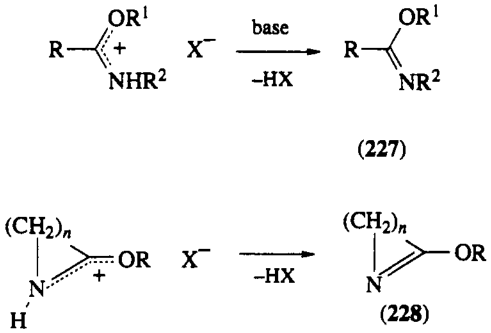

**(227)**

**(228)**

**Scheme 32**

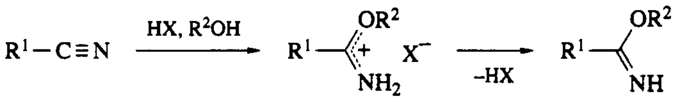

(124)

**(229)**

Not only the Pinner synthesis provides alkoxymethyleneiminium salts; the action of chloroformic acid esters on primary or secondary amides or thioamides[7,10,16] as well as on lactams[424] is a versatile method to get these salts and from them the imino esters, *e.g.* (**230**; equation 125). Primary and secondary amides have been alkylated by several reagents and the iminium salts thus formed were converted to imino esters with the aid of bases. A collection of imino esters prepared by this method can be found in a review;[10] the more recent results listed in Table 5 demonstrate the scope of this procedure.

The addition of alcohols to nitrilium salts gives rise to formation of alkoxymethyleneiminium salts, which react with bases to yield imido esters (**231**; Scheme 33).[241,242] By deprotonation of carboxylic acid amides ambident anions are formed, which can be alkylated in the presence of silver ions to give imido esters, *e.g.* (**232**).[463–466] Secondary amides react with trifluoroacetic acid anhydride or trifluorosulfonic acid anhydride to give mixed anhydrides of imidic acids (**233**).[467]

**Table 4** Nitriles which are Suited for Pinner Synthesis

| *Nitrile* | *Ref.* | *Nitrile* | *Ref.* |
|---|---|---|---|
| Cyanocytidine | 415 | 5-Cyano-3-pyridinecarbonic acid ester | 419 |
| *o*-Azidobenzonitrile | 416 | | |
| 2,6-Dimethoxybenzoyl cyanide | 417 | 3-Chloro-4-pyridinecarbonitrile | 420 |
| 3,5-Di(*t*-butyl)-4-hydroxybenzonitrile | 418 | 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carbonitrile | 421 |
| Substituted phenylacetonitriles and 3-phenylpropionitrile | 418 | Long-chain ($C_{11}$–$C_{18}$) nitriles | 422 |
| Alkylmercaptoacetonitriles and alkylmercaptopropionitriles | 418 | Cyanoacetic acid ester | 423 |

**Table 5** Alkylating Reagents and Carboxylic Acid Amides as Starting Materials for Imidates

| *Alkylating reagent* | *Ref.* | *Amides* | *Ref.* |
|---|---|---|---|
| Dimethyl sulfate | 425–429 | 5-Amino-4-imidazolecarbonamides | 185 |
| Trimethyloxonium tetrafluoroborate | 430–443 | (Optically active) acetamides | 448, 462 |
| Triethyloxonium tetrafluoroborate | 203, 425, 426, 429, 444–461 | Propionamides | 448 |
| | | Benzamide | 462 |
| Methyl trifluoromethanesulfonate | 215, 462 | Dihydroxypyrmidones | 429 |
| | | Acrylamide | 445 |
| | | Crotonamide | 445 |
| | | Cinnamic acid amide | 445 |
| | | Five-membered lactams | 203, 215, 425, 430, 444, 449 |
| | | Six-membered lactams | 425, 451–453, 462 |
| | | Seven-membered lactams | 425, 438, 445, 446, 456, 461 |
| | | Eight-membered lactams | 427, 428, 457, 458 |
| | | Nine-membered lactams | 439, 440 |
| | | 13-membered lactams | 441, 442 |
| | | Bicyclic [2.2.2] lactams | 437 |
| | | Bicyclic [3.2.1] lactams | 426 |
| | | 2,5-Diketopiperazines (→ monoethers) | 454 |
| | | 1-Aza[14]annulen-2-one | 459, 460 |
| | | 1-Aza[16]annulen-2-one | 459, 460 |
| | | 1-Aza[18]annulen-2-one | 459, 460 |

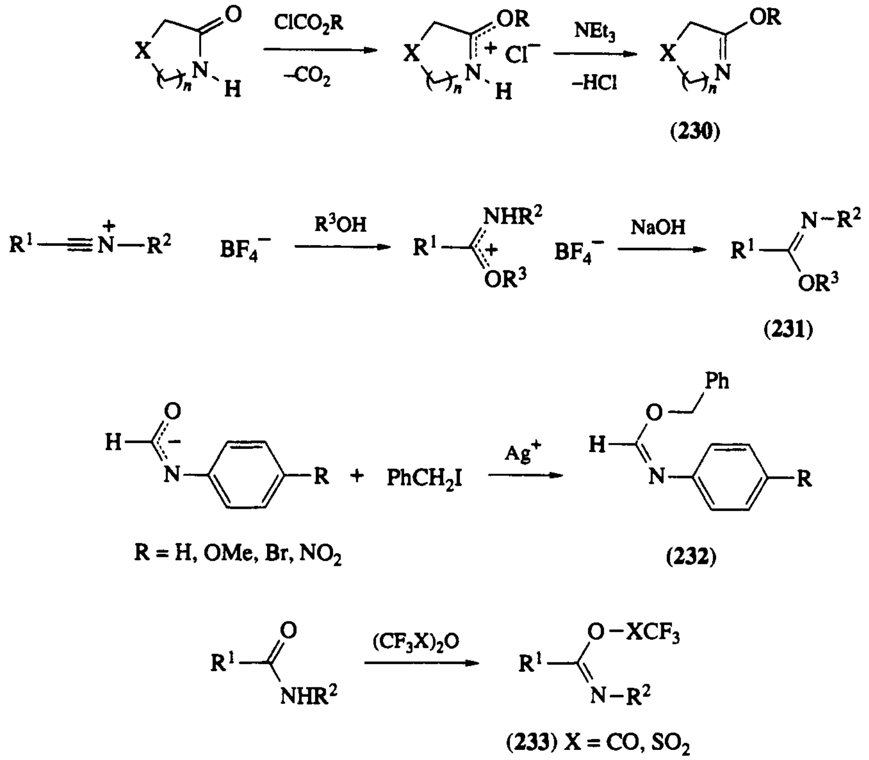

(125)

(230)

(231)

R = H, OMe, Br, $NO_2$

(232)

(233) X = CO, $SO_2$

Scheme 33

### 2.7.3.2.2 *From imidoyl halides and related compounds*

Mixed anhydrides (**234**; equation 126) are formed in the reaction of silver benzoate with imidoyl chlorides.[16] Imidoyl chlorides react with alcohols or phenols in the presence of base (alkoxide, tertiary amine) to give imidates, *e.g.* (**235**; equation 127).[3,364,370,468–474] This method is especially useful for the preparation of arylimidates; the reaction can be performed under phase transfer catalysis.[470] In the Lewis acid catalyzed reaction of polyoxymethylene with the benzimide chloride (**236**; equation 128) the chloromethylbenzimidate (**237**) is formed.[355]

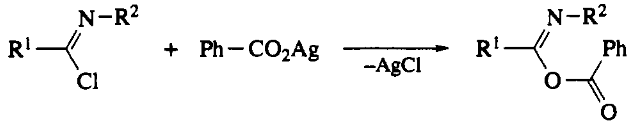

(126)

(234)

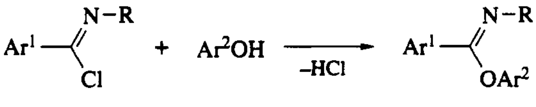

(127)

(235)

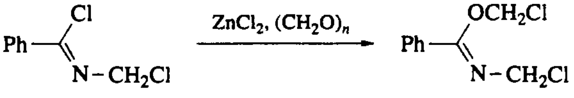

(128)

(236) (237)

### *2.7.3.2.3 From carboxylic orthoesters, carboxylic orthoamide derivatives and related compounds*

Orthoesters react with primary amines to give imino esters (**238**; equation 129). The condensation proceeds usually at temperatures above 100 °C and can be catalyzed by mineral acids, sulfonic acids, Lewis acids and carboxylic acid anhydrides.

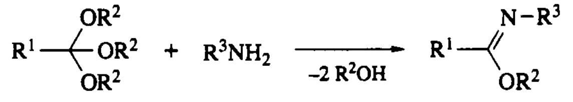

(129)

**(238)**

This reaction was often used to transform primary heterocyclic amines to imino esters. The following selection of more recent examples will demonstrate the range of the method. Orthoesters of formic acid,[16,369,475–489] acetic acid[484,485,489–491] and propionic acid[484] have been reacted with substituted anilines,[475,484,485,488–490] naphthylamines,[16,369,481,485,489] aminouracil,[486] aminoimidazoles,[476,482] aminoquinolines,[369] aminothiophenes,[479] aminopyrans,[480] aminopyrimidines,[369] aminomalonodinitrile,[477,478] aminomalono esters[483,487] and amino acid esters[491] to give imidates. According to this scheme the following compounds can be converted to imino esters: cyanamide, *O*-protected hydroxylamines, hydrazines and hydrazine derivatives, phosphorus amides, sulfonamides *etc.* Such reactions have been reviewed.[7,15,16] Ketene acetals react with primary amines to give imino esters, *e.g.* (**239**; equation 130).[492,493]

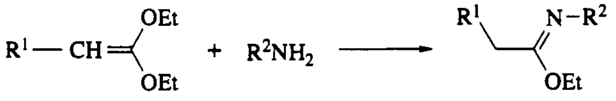

(130)

**(239)**

### *2.7.3.2.4 From nitriles and isonitriles*

The base-catalyzed addition of alcohols to nitriles to give imidates proceeds well, if there are electron-attracting groups in the α-position. In such cases the Pinner synthesis is less effective, because nitrile basicity is less. This shows that both methods are complementary.[16] Recently attention has been paid to the long-known addition of alcohols to trichloroacetonitrile,[16] since it was found that imidates prepared from protected saccharides, amino alcohols *etc.* and trichloroacetonitrile are useful reagents for the synthesis of nucleosides,[494] disaccharides and other natural products.[495] The trichloroacetimidic acid esters (**240**; equation 131) of fluorinated,[16] unsaturated aliphatic alcohols[496–500] and benzyl alcohol[500] have been prepared for synthetic purposes.

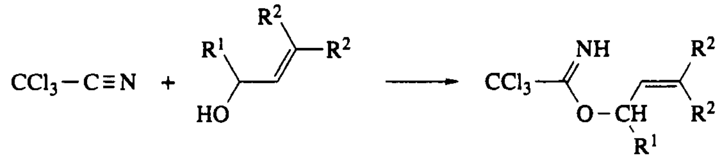

(131)

**(240)**

Addition of alcohols to nitriles was preferably used for the synthesis of aromatic or heterocyclic carboxylic acid imide esters, *e.g.* (**241**; equation 132),[501–504] as well as for α-arylamino- or α-arylmercaptocarboxylic acid imide esters[505] and for bicyclobutanimidic acid esters.[506] By condensation of dichloroacetonitrile with ketones in the presence of alkoxide oxiranylimido esters (**242**; equation 133) are accessible.[507] Formimido esters (**243**; equation 134) can be prepared by copper compound catalyzed addition of alcohols to isonitriles.[16,508,509] From alkylaminomethoxycarbene–gold complexes formimino esters have been obtained.[510] Isonitriles react with aldehyde *O,N*-acetals to give α-aminoacetimidates (**244**; Scheme 34).[511] Under diethylaluminum chloride catalysis the addition of α,β-unsaturated ketones to isonitriles is possible, affording imino esters (**245**).[512]

Various acids (nitrobenzoic acids, picric acid, toluenesulfonic and phosphonic acids) have been reacted with isonitriles to give mixed anhydrides (**246**; equation 135).[513,514]

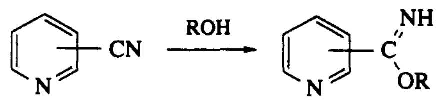
ROH
CN
NH
C
OR
N

(132)

**(241)**

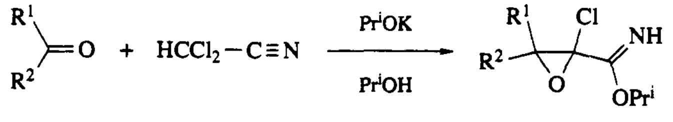
R1
R2
O
HCCl2−C≡N
PriOK
PriOH
Cl
NH
O
OPri

(133)

**(242)**

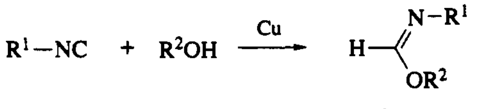
R1−NC
R2OH
Cu
N−R1
H
OR2

(134)

**(243)** $R^2$ = alkyl, aryl

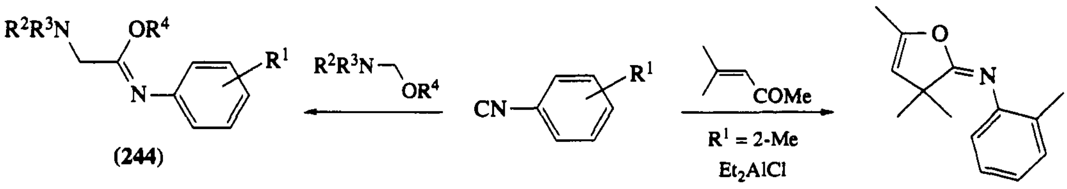
R2R3N
OR4
R1
N
(244)
R2R3N
OR4
CN
R1
COMe
R1 = 2-Me
Et2AlCl
O
N

**(245)**

**Scheme 34**

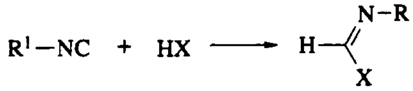
R1−NC
HX
N−R
H
X

(135)

**(246)** X = $ArCO_2$, $ArSO_3$, ArO, $ArPO_3H$

### 2.7.3.2.5 *From imidates*

Transesterification of imidates is a well-known reaction, which is catalyzed preferably by alkoxides.[16] In *O*-phosphorylated compounds (**247**; equation 136) such an exchange occurs with ease.[515] From imidates and 1,2- and 1,3-amino alcohols 1,3-oxazolines[16,516–518] and 1,3-oxazines,[519] respectively, were synthesized.

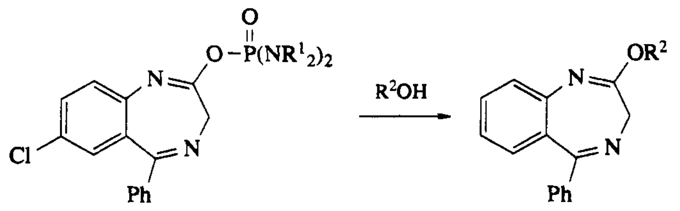
O
O−P(NR12)2
N
Cl
N
Ph
R2OH
OR2
N
N
Ph

(136)

**(247)**

2-Alkyloxazolines and 2-alkyloxazines are weakly CH-acidic compounds. The carbanions derived from them have been reacted with a variety of electrophiles to give substituted 'cyclic imidates', *e.g.* (**248**; equation 137). Reviews on such synthetic procedures are available.[520–522]

2-Alkylbenzoxazoles were condensed with esters of aromatic acid esters to give 2-phenacylbenzoxazoles (**249**; equation 138).[523] 2-Alkyloxazoles are acylated by electrophiles, *e.g.* anhydrides, catalyzed

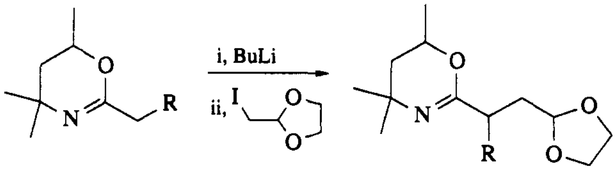

**(248)**

(137)

by Lewis acids,[524] to produce the enols (**250**; equation 139). *N*-Unsubstituted imidates have been transformed to *N*-carboxylated and acylated imidates (**251**)–(**253**) (Scheme 35) by reaction with isocyanates,[525] isothiocyanates,[526] chloroformic acid esters[527] or acid chlorides.[447,528–530] In the course of such reactions cyclizations can occur to give heterocycles, *e.g.* (**254**; Scheme 36);[531] a very useful synthesis for amino acid derivatives, *e.g.* (**255**), is based on the anions derived from 2,5-dialkoxy-3,6-dihydropyrazines. These applications have been reviewed.[532,533] *N*-Unsubstituted imino esters are phosphorylated at nitrogen, to give compounds (**256**; equation 140) by treatment with dialkyl phosphites in the presence of $CCl_4$/triethylamine.[534]

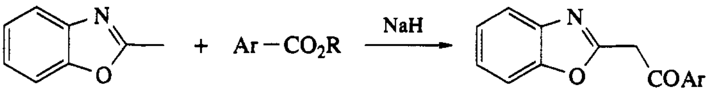

**(249)**

(138)

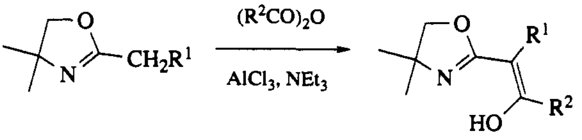

**(250)**

(139)

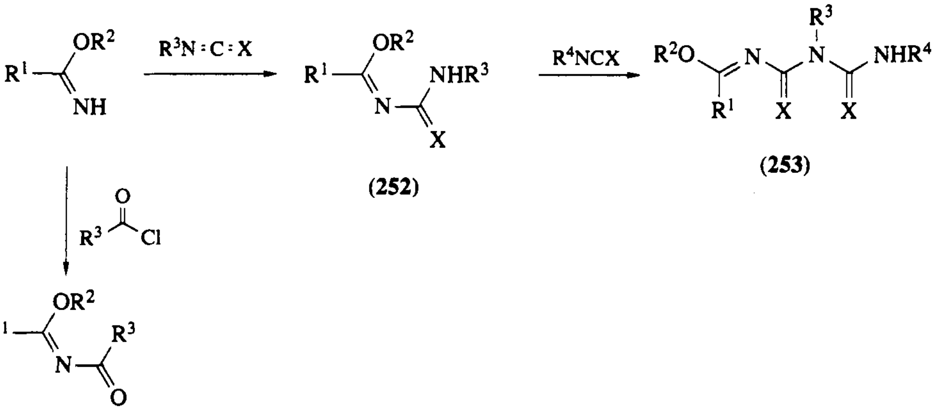

**(252)**

**(253)**

**(251)**

**Scheme 35**

### 2.7.3.2.6 *Miscellaneous methods*

Under the influence of bases *N*-acylaminosulfonium salts are rearranged to imino esters (**257**; equation 141).[535,536] Photolysis of aromatic or heterocyclic azides in the presence of alkoxides affords imino esters, *e.g.* (**258**; equation 142).[537–541]

1-Azirines can be transformed to imino esters (**259**) and (**260**) (Scheme 37) by addition of alcohols[542] or 'alkoxy carbenes'[543] respectively. By sodium methoxide catalyzed addition of methanol to the ketene imine (**261**; Scheme 38) the imino ester (**262**) is obtainable.[544] Keteneimines undergo photoinduced addi-

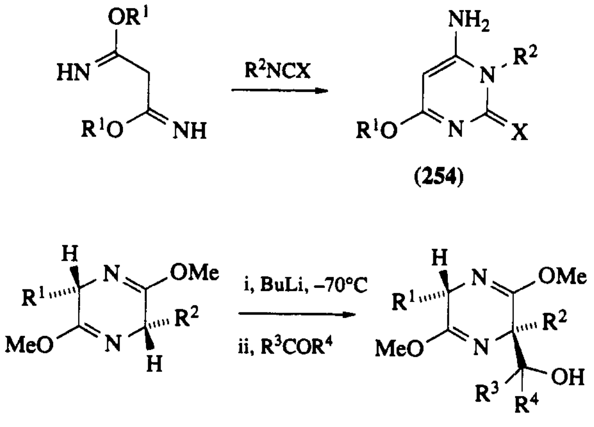

(254)

(255)

Scheme 36

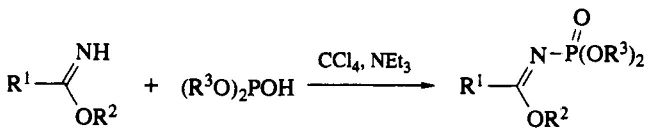

(256)

(140)

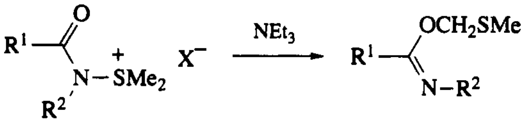

(257)

(141)

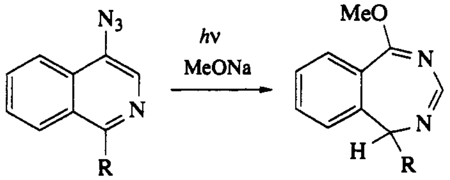

(258)

(142)

tion to quinones to yield imidates (**263**).[545] Oxidative dimerization of oxazolines allows the preparation of 2,2′-bisoxazolines (**264**; equation 143).[546] On heating oxime carbonates are transformed to arylimidates (**265**; equation 144); the reaction seems to be related to the Beckmann rearrangement.[547]

## 2.7.3.3 Thioimidates

### *2.7.3.3.1 From alkylmercaptomethyleneiminium salts*

Due to the high nucleophilicity of sulfur it is easy to alkylate primary and secondary thioamides as well as thiolactams, even with reagents of low alkylating ability (compare Section 2.7.2.4.1). Deprotonation of these salts, often without previous isolation or purification, affords thioimidates (**266**; equation 145).[16,548] A selection of compounds accessible by this procedure can be found in ref. 13. Some more recent results are briefly summarized in Table 6.

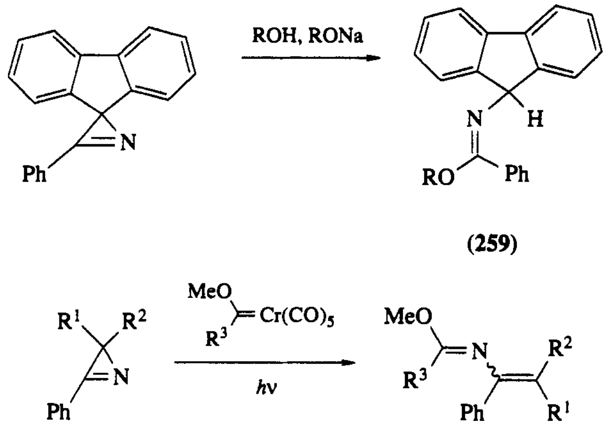
ROH, RONa
Ph
N
N
H
RO
Ph
MeO
Cr(CO)5
R3
hv
R1
R2
N
Ph
MeO
N
R2
R3
Ph
R1

(259)

(260)

**Scheme 37**

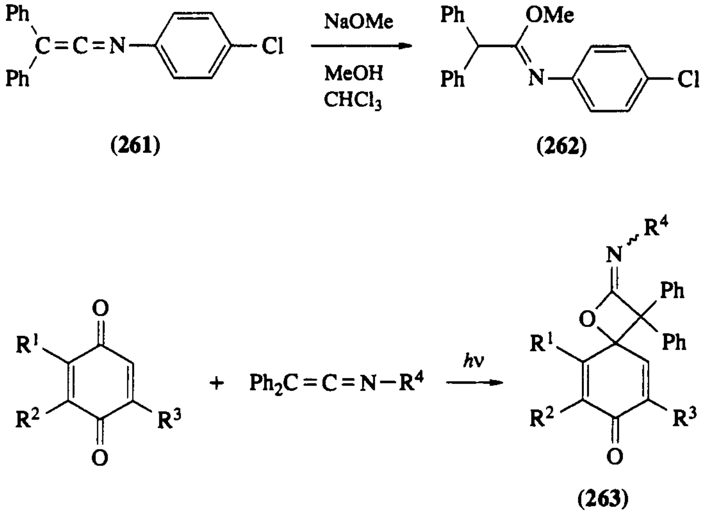
Ph
C=C=N
Ph
Cl
NaOMe
MeOH
CHCl3
Ph
OMe
Ph
N
Cl
O
R1
R2
R3
O
+ Ph2C=C=N−R4
hv
R4
N
Ph
O
Ph
R1
R2
R3
O

(261)

(262)

(263)

**Scheme 38**

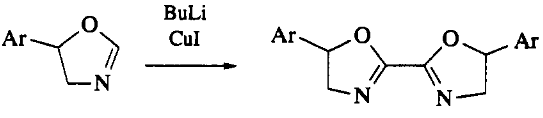 (143)
Ar
O
N
BuLi
CuI
Ar
O
N
O
N
Ar

(264)

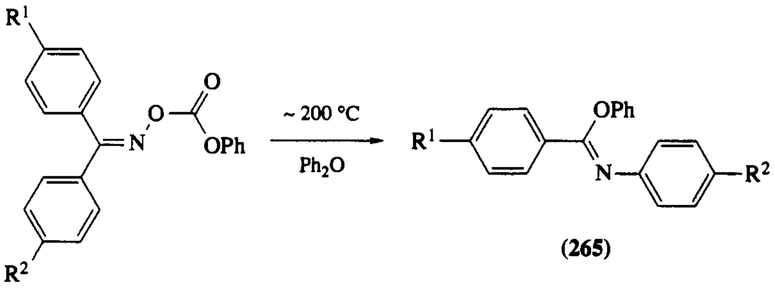 (144)
R1
O
O
N
OPh
R2
~ 200 °C
Ph2O
R1
OPh
N
R2

(265)

Alkylmercaptomethyleneiminium salts (**267**; Scheme 39), which are accessible either by addition of thiols to the nitrile function in the presence of hydrogen halides[16] or by reaction of chloroformic acid thioethyl ester with thioamides,[286,576] can also be transformed to the corresponding thioimidates (**268**).

**Table 6** Starting Compounds for the Synthesis of Thioimidates by Alkylation of Thioamides

| *Alkylating reagent* | *Ref.* | *Thioamide* | *Ref.* |
|---|---|---|---|
| Alkyl halides | 535–563 | *N*-Thioformylaminoisobutyric acid ester | 553 |
| Benzyl halides | 556, 564, 565 | | |
| Benzylammonium salts | 556 | Secondary thioformamides | 556, 572 |
| Allyl halides | 567 | Thioacetamide | 564 |
| Dialkyl sulfates | 445 | *N*-Toluenesulfonyloxymethylthioacetamide | 549 |
| α-Halo ketones | 554 | | |
| α-Halo esters | 556, 562, 568–570 | Secondary thioacetamides | 567, 572 |
| α-Halonitriles | 562, 570 | 4-Substituted thiobenzamides | 561, 563, 565 |
| Oxonium salts | 571–575 | *N*-Phosphorylated thiobenzamides | 570 |
| | | *N*-Toluenesulfonyloxymethylenethiobenzamide | 549 |
| | | *N*-Benzoylthiobenzamide | 559 |
| | | *N*,*N'*-Bis(thiobenzoyl)alkylenediamines | 550 |
| | | Five-membered thiolactams | 540, 560, 568, 569, 571 |
| | | Six-membered thiolactams | 552, 560 |
| | | Seven-membered thiolactams | 445, 552, 573 |
| | | Eight-membered thiolactams | 557 |
| | | Imidazolethiocarbonamides | 551, 555 |
| | | 2-Thiono-1-azapenam derivatives | 562 |
| | | Thioamide *S*-oxides (alkylation at oxygen) | 574, 575 |

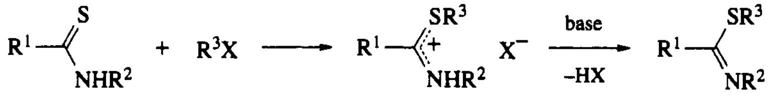
R¹
S
NHR²
+ R³X
SR³
+
X⁻
base
-HX
NR²

(266)

(145)

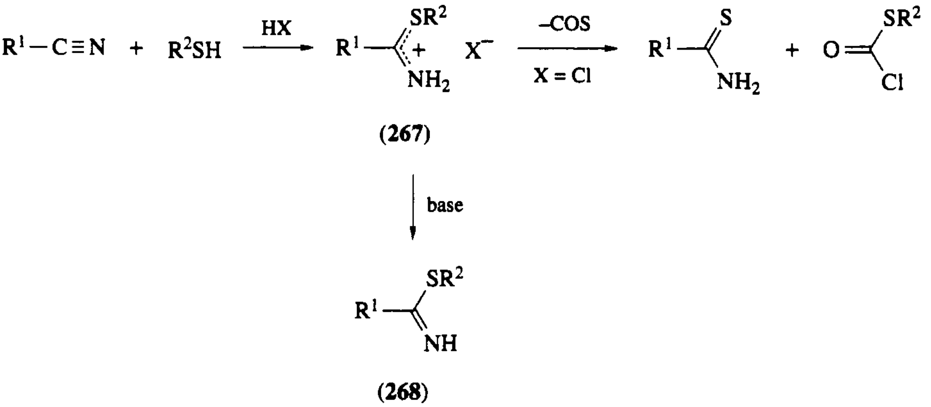
R¹—C≡N + R²SH
HX
SR²
NH₂
X⁻
–COS
X = Cl
S
+ O
Cl
(267)
base
NH
(268)

Scheme 39

### 2.7.3.3.2 *From imidoyl halides*

Although long known, the reaction of imidoyl halides with thiolates to give thioimidates is of less importance.[1,470,577] In special cases, such as the synthesis of multifunctional thioimidates, *e.g.* (**269**; equation 146), this method can be of interest.[577]

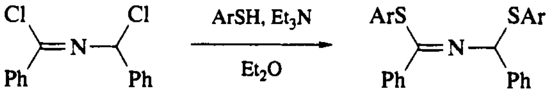
Cl
Ph
N
ArSH, Et₃N
Et₂O
ArS
SAr

(146)

Ar = 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$ (**269**)

Benzimidoyl chlorides and *N*,*N*-dimethyl-*N*′-thiobenzoylformamidine react to afford thioimidic acid anhydrides (**270**; Scheme 40).[578] Spirocyclic thioimino esters have been prepared from benzimidoyl chlorides and thiazolin-5-thiones.[579] Carboxylic acid imidothio acid anhydrides (**271**) can be synthesized from carboxylic acid chlorides and secondary thioamides.[580]

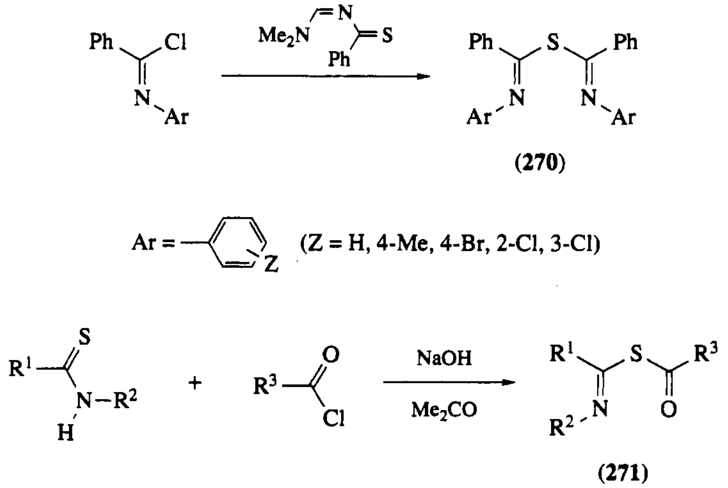
Ph
Cl
N
Ar
Me₂N
S
(270)
Ar =
Z
(Z = H, 4-Me, 4-Br, 2-Cl, 3-Cl)
R¹
N—R²
H
+
R³
O
Cl
NaOH
Me₂CO
R¹
R³
R²
(271)

Scheme 40

### *2.7.3.3.3 From nitriles and isonitriles*

Catalyzed by bases, thiols add to the nitrile function to give thioimidates. The reaction is facilitated if electron-attracting groups are present in the α-position to the nitrile group. Very often the thioimidates thus formed were not isolated but reacted further to other products, *e.g.* (**272**) and (**273**; Scheme 41).[581-583]

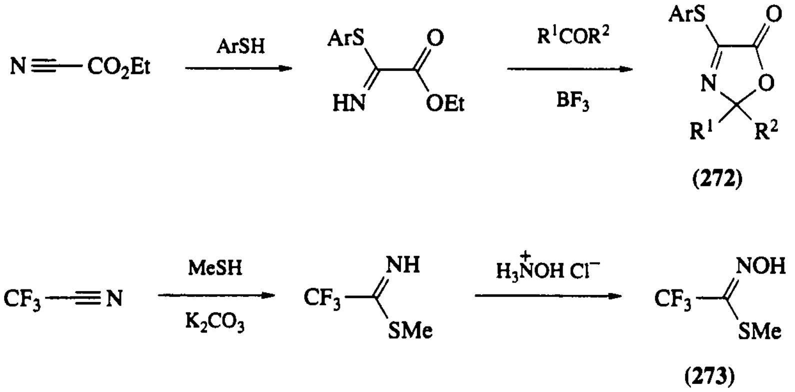
N≡—CO2Et
ArSH
ArS
O
HN
OEt
R1COR2
BF3
ArS
O
N
O
R1
R2
(272)
CF3—≡N
MeSH
K2CO3
CF3
NH
SMe
H3N+OH Cl−
CF3
NOH
SMe
(273)

**Scheme 41**

By addition of thiols to isonitriles thioformimidates (**274**; equation 147) are accessible.[509] 2-Methylpropaneisonitrile inserts into the thietane system to give triiminothiolanes (**275**; Scheme 42).[584] A related insertion of isonitriles into a C—S bond was observed in the reaction of alkylmercaptocyanoacetic acid esters, labile thioimidates (**276**) are the products.[585,586] The addition of thiocarboxylic acids to isonitriles, giving mixed anhydrides of thioformimidic acids and carboxylic acids has been studied.[587]

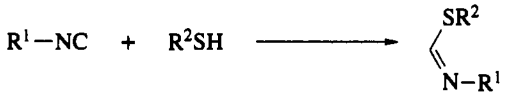
R1—NC
+
R2SH
SR2
N—R1

(147)

(**274**)

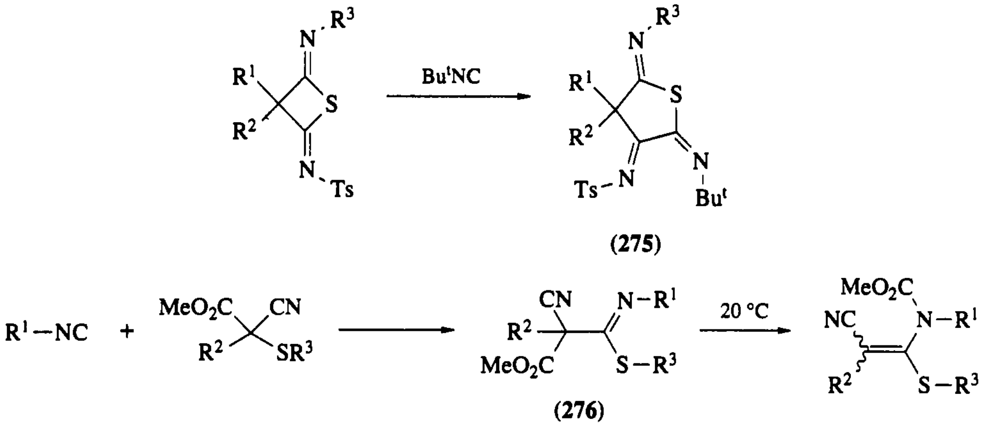
N
R3
R1
S
R2
N
Ts
BuᵗNC
N
R3
R1
S
R2
Ts-N
N
Buᵗ
(275)
R1—NC
+
MeO2C
CN
R2
SR3
CN
N—R1
R2
MeO2C
S—R3
(276)
20 °C
MeO2C
NC
N—R1
R2
S—R3

**Scheme 42**

### *2.7.3.3.4 From activated aromatic compounds, alkenes, carbanions and carbenes*

The alkylmercaptomethyleneiminium salts (**277**; equation 148) can be synthesized by the action of alkyl isothiocyanates on resorcinol in the presence of HCl or $ZnCl_2$.[588] Isothiocyanates react with the ketene *O,N*-acetal (**278**; equation 149) to give primary products (**279**), which are stabilized by transalkylation to the thioimidates (**280**).[589] Similar transalkylation reactions were observed in the reactions of dimethylformamide acetals with aryl isothiocyanates giving thioimidates (**281**; equation 150).[590,591]

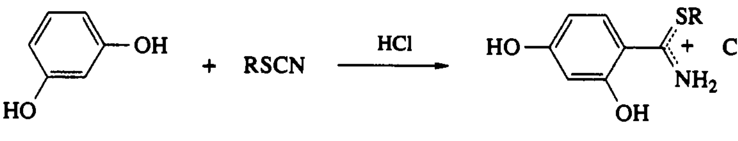

**(277)**

(148)

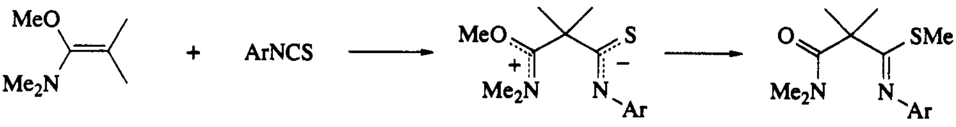

**(278)** **(279)** **(280)**

(149)

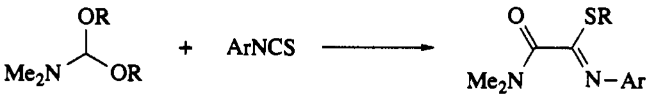

**(281)**

(150)

Benzothiazole can be metallated by treatment with butyllithium; the compound thus formed reacts with various electrophiles to furnish 2-substituted benzothiazoles, *e.g.* (**282**; equation 151).[592]

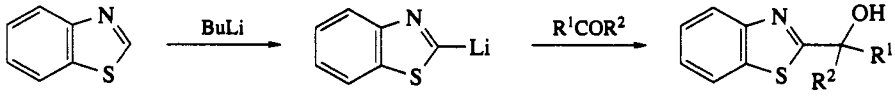

**(282)**

(151)

### *2.7.3.3.5 From thioimidates*

In 2-methyl-1,3-thiazolines the α-CH bonds are acidic enough to be metallated. These carbanions have been alkylated, acylated, *etc.* to give 2-substituted-1,3-thiazolines, *e.g.* (**283**; equation 152). The thiazoline ring system is quite easy to reduce, the thiadiazolidines thus formed suffer hydrolytic ring opening to give aldehydes.[593,594] The whole sequence is a versatile aldehyde synthesis, which has been reviewed.[595] Isocyanates carboxylate the five-membered thiolactim ether (**284**; Scheme 43) at C-3 of the ring system to give the thiolactim ether (**285**), whereas six- and seven-membered lactim ethers are attacked at the ring-nitrogen to afford ketene *S,N*-acetals (**286**).[596] By acylation of thioimidates the new thioimidates (**287**; equation 153) were obtained, which are in equilibrium with ketene *S,N*-acetals.[597]

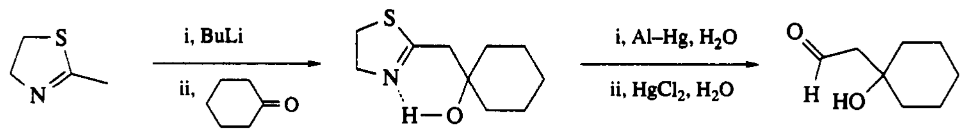

**(283)**

(152)

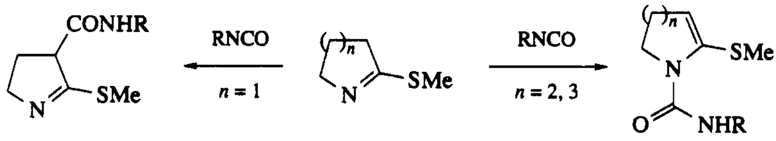

**(285)** **(284)** $n = 1$ **(286)**

**Scheme 43**

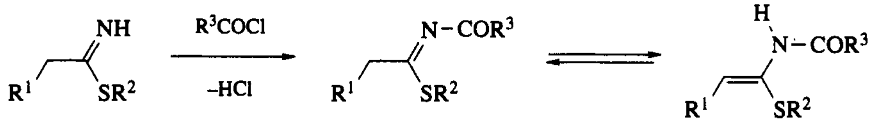
NH
R$^3$COCl
-HCl
R$^1$
SR$^2$
N-COR$^3$
H

(287)

(153)

### 2.7.3.3.6 Miscellaneous methods

Secondary thioamides react with dimethylcyanomethyl radicals to give thioimidic acid anhydrides (**288**; Scheme 44), in poor yields,[598] whereas with phenyl radicals phenylthioimidates (**289**) are obtained in fairly good yields.[599] Thiolactim ethers (**290**; equation 154) (ring size 6–9) have been prepared by rearrangement of 1-azido-1-methylmercaptocycloalkanes.[600]

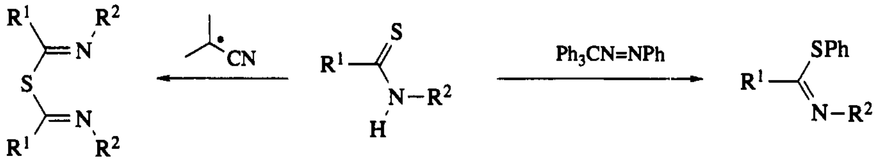
R$^1$
R$^2$
N
S
CN
Ph$_3$CN=NPh
SPh
N-R$^2$
H

(288)

(289)

**Scheme 44**

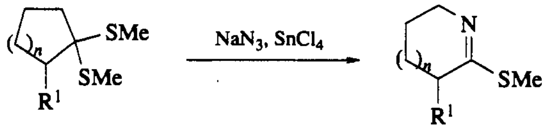
SMe
SMe
R$^1$
n
NaN$_3$, SnCl$_4$
N

(290)

(154)

Oxime sulfonates were rearranged in the presence of diisobutylaluminum methyl sulfide to produce methylthioimidates, *e.g.* (**291**; equation 155), and methylthiolactim ethers in good yields.[601] The adducts formed in the reaction of Grignard reagents with trimethylsilylmethyl isothiocyanate can be alkylated to furnish the *N*-trimethylsilylmethylthioimidates (**292**; equation 156).[602,603]

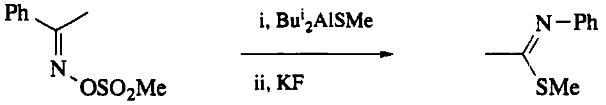
Ph
N
OSO$_2$Me
i, Bu$^i_2$AlSMe
ii, KF
N-Ph
SMe

(291)

(155)

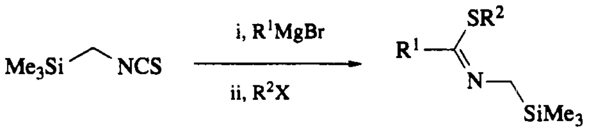
Me$_3$Si
NCS
i, R$^1$MgBr
ii, R$^2$X
SR$^2$
R$^1$
N
SiMe$_3$

(292)

(156)

## 2.7.3.4 Amidines

### 2.7.3.4.1 From iminium salts

#### (i) Adducts from amides with acylating reagents

Adducts from tertiary amides (mostly DMF) or lactams with POCl$_3$ or PCl$_3$ were reacted with different kinds of primary amines and amine derivatives to give amidinium salts which were deprotonated to produce the free amidine, *e.g.* (**293**; equation 157). This amidine synthesis is a standard procedure. A collection of examples demonstrating the scope of the method is available.[5,14] The following selection of more recent examples will underline the importance of this synthetic procedure.

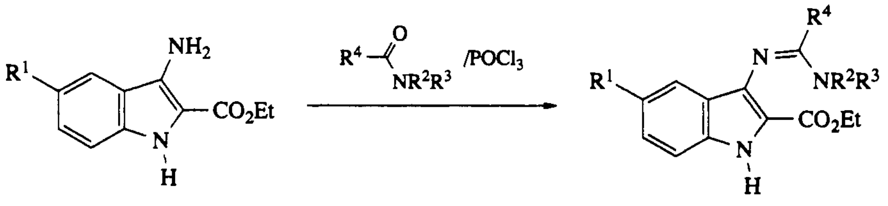

(157)

(**293**)

Adducts from $POCl_3$ and formamides,[604–617] acetamides,[39,42,615] malono ester amides,[47,48] cyanoacetamides[55,56] or lactams[618] have been transformed to amidines by reaction with the following amino compounds: 2-acylaminothiophenes,[607] 2-aminoisoxazole,[604] 4-aminotriazole,[605] 3-aminoimidazole,[610] aminoindoles,[608,611,615] 2-acylaminoanthraquinones,[606] 2,6-diaminoanthraquinone,[42,56] 6-aminouracil,[609] *N*-arylacetamides,[612] *N,N*-disubstituted thioureas,[613] *N*-arylchloroacetamides,[612] anilines,[55,614,618] *o*-phenylenediamines,[47,48] anthranilic acid amide[617] and acylaminobenzothiophene.[613]

Some of these transformations were accompanied by additional reactions, *e.g.* formylation of the aromatic[39] or heteroaromatic[607,608,615] nucleus or CH-acidic methyl groups;[609] further dehydration of amides to nitriles was observed.[617] Adducts from amides and $PCl_3$,[612] sulfonyl halides[42] or $SO_2Cl_2/SOCl_2$[619] from which amidines can be obtained by reaction with amine derivatives (compare Section 2.7.2.5 and refs. 5 and 14) have not found wide application for this purpose. An interesting reaction is the preparation of the amidine (**294**; equation 158) from *N*-pentafluorophenylformamide.[619] By thermal decomposition of the adducts from secondary amides and *N,N*-dialkylcarbamoyl chlorides amidinium salts were synthesized from which the amidines (**295**; equation 159) were set free by treatment with bases.[119,120]

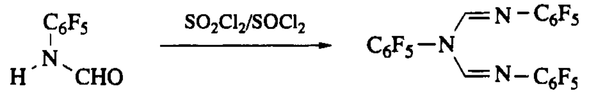

(158)

(**294**)

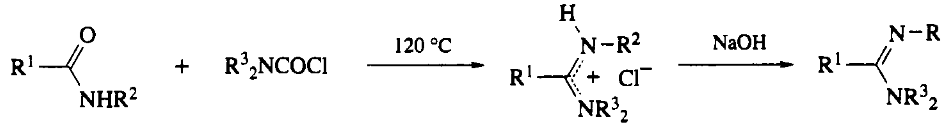

(159)

(**295**)

### *(ii) From halomethyleneiminium compounds or nitrilium salts*

It is well known that halomethyleneiminium salts, often prepared *in situ* (see Section 2.7.2.2) react with ammonium salts, primary amines, secondary amides, urea and *N*-substituted ureas to afford amidinium salts, from which the free amidines can be obtained by addition of bases.[8,14] Some recent results are given below. Dimethylformamide chloride[306,612,620] and other *N,N*-disubstituted formamide chlorides[620,621] were reacted with acetanilides,[612] chloroacetanilides,[612] 6-aminopenam derivatives,[621] 2-aminopyrimidine,[306] 4-aminouracil,[306] 2-amino-4-chloropyridazine,[306] 2-aminothiazole,[306] 2-aminobenzothiazole[306] and thiobenzamides[620] to give the amidines *via* the amidinium salts. In the reaction of *N,N*-disubstituted formamide chlorides with thiobenzamides the solvent seems to be decisive for the course of the reaction. In tertiary formamides the thiobenzamides are desulfurized to nitriles, whereas in $CHCl_3$ or $CCl_4$ amidinium salts (**296**; Scheme 45) are formed.[620] From trimethylsilyl isocyanate and the fluorinated amine (**297**) the *N*-fluorocarbonylamidine (**298**) is accessible.[622]

In the reaction of dimethylformamide chloride with the imidoyl cyanide (**299**; equation 160) the amidine (**300**) is formed.[623] Isoxazolines, prepared from amide chlorides and hydroxylamine, rearrange on heating or irradiation to give 2-aminoazirine (**301**; Scheme 46).[624] Azirines (**302**) can also be prepared by treating chloroenamines with base and sodium azide.[341,625]

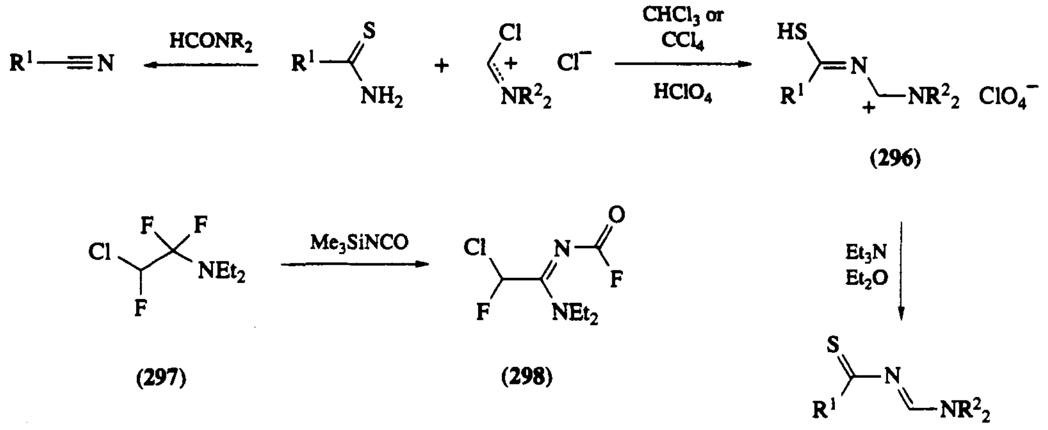
HCONR2
CHCl3 or CCl4
HClO4
Et3N
Et2O
Me3SiNCO
(296)
(297)
(298)

**Scheme 45**

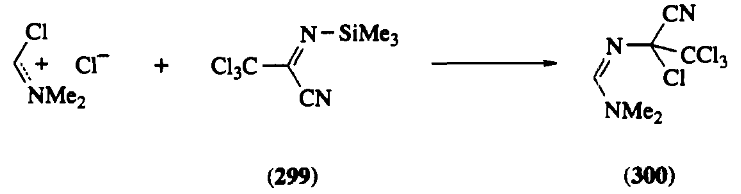

(160)

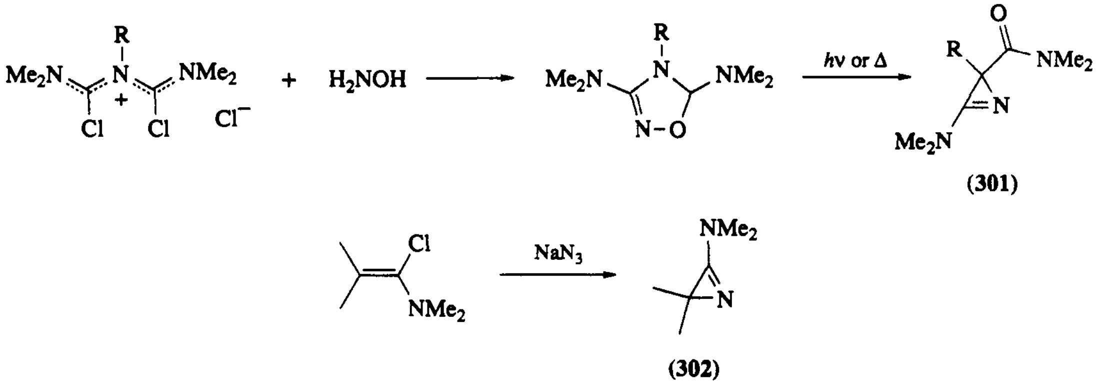
H2NOH
hν or Δ
NaN3
(301)
(302)

**Scheme 46**

Dehydrohalogenation of amide chlorides affords α-chloroenamines, which undergo cycloaddition with *N*-diphenylmethylaldimines to furnish azetidinium salts (**303**; equation 161). From these salts the diphenylmethyl group can be removed by hydrogenation, subsequent deprotonation yields 2-amino-1-azetines.[342,626] The addition of primary or secondary amines to nitrilium salts gives rise to formation of amidinium salts[5,323–325,627] and amidines respectively, *e.g.* (**304**; equation 162). In a similar reaction from copper(I) imidazolide, *t*-butyl bromide and nitriles amidines (**305**; equation 163) were prepared.[628]

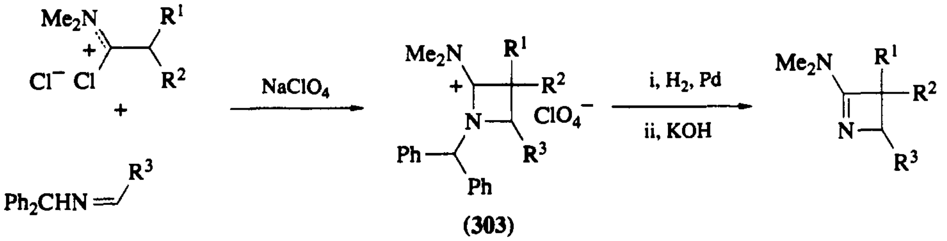
NaClO4
i, H2, Pd
ii, KOH
(303)

(161)

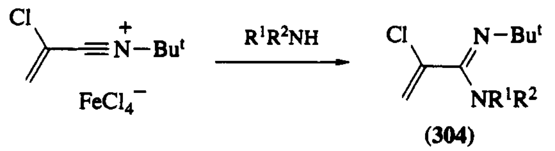

**(304)**

(162)

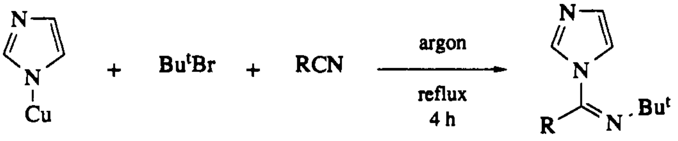

**(305)**

(163)

### *(iii) From alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts*

The action of ammonia, primary and secondary amines on alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts affords amidinium salts. Provided the educts are chosen in such a manner that the substitution pattern of the resulting amidinium salts does not exceed that of *N,N,N'*-trisubstituted salts, the amidines can be released from the salts by addition of bases[9–15] (see also Section 2.7.2.5.3). Very often the alkoxymethyleneiminium salts were prepared *in situ* and reacted without further purification with the amino compound to give the desired amidine. This amidine synthesis is of special synthetic interest, since it was stated that formamidines, derived from alicyclic amines, *e.g.* (**306**; equation 164), which are simple to obtain by this method, are readily transformed to reactive carbanions.[629–631] Heterocycles, *e.g.* (**307**; equation 165), containing amidine structures, are accessible by reaction of appropriate difunctional compounds with iminium salts.[632]

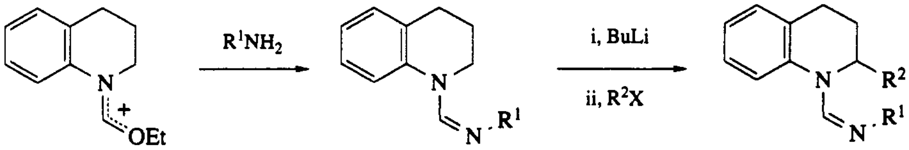

**(306)**

(164)

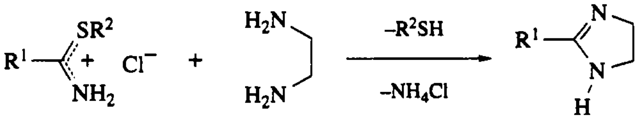

**(307)**

(165)

### *(iv) From amidinium salts*

Amidinium salts (obtainable by various methods, compare Section 2.7.2.5) which are not peralkylated at nitrogen are converted to amidines by treatment with strong bases, *e.g.* aqueous alkali metal hydroxides, alcoholic alkoxides,[633] tertiary amines *etc.* As already mentioned it is not difficult to alkylate amidines (see Section 2.7.2.5.4), thus by subsequent alkylation and deprotonation reactions amidines can be synthesized carrying the desired substituents at nitrogen, *e.g.* (**308**; Scheme 47).[14,634] A series of *N,N,N'*-trisubstituted formamidines have been prepared by reaction of anilines with the azavinylogous formamidinium salt (**309**).[635]

## *2.7.3.4.2 From carboxylic acids or carboxylic acid amides and amines in the presence of condensing agents*

Heating of secondary carboxylic acid amides with HMPA gives rise to formation of *N*-substituted *N',N'*-dimethylamidines (**310**; Scheme 48).[636,637] In this procedure the secondary amide can be replaced by a ketoxime in which at least one substituent has to be an aromatic one.[638] Similar methods were de-

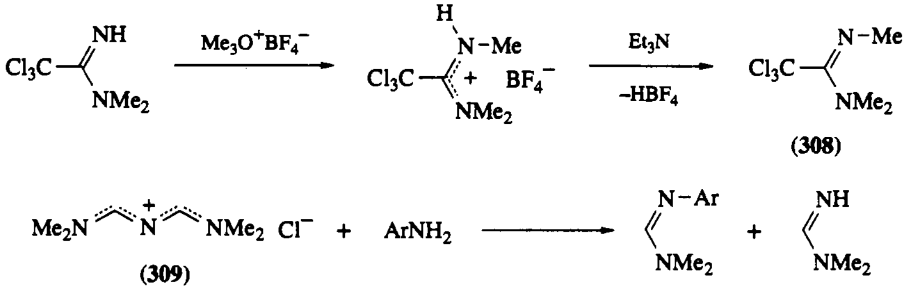

(308)

(309)

Scheme 47

veloped and thus formamidines were prepared by heating $P_4O_{10}$ with mixtures of *N*,*N*-dialkylformamides with secondary carboxylic acid amides,[639] or by reacting secondary amides with mixtures of $P_4O_{10}$ and secondary amines.[640] Even carboxylic acids can be transformed to amidines by reaction with anilines and polyphosphorus acid trimethylsilyl ester,[641,642] or with mixtures of $P_4O_{10}$, alkylammonium chlorides and *N*,*N*-dimethylcyclohexylamine.[643] Iminophosphoranes (**311**; Scheme 49)[644] or cyclotrisilazanes (**312**)[645] react with DMF to yield formamidines.

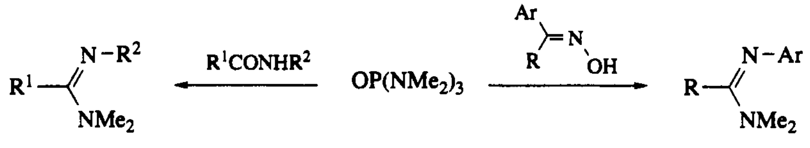

(310)

Scheme 48

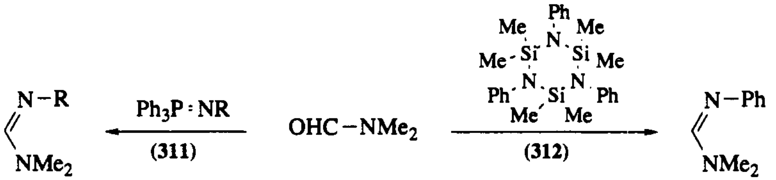

Scheme 49

Tetrakis(dimethylamino)titanium is a useful reagent for preparing amidines from secondary amides.[646] From *N*,*N*′-thionyldiimidazole and secondary amides of both aromatic and aliphatic carboxylic acids amidines (**313**; Scheme 50) are formed under mild conditions in moderate to good yields.[647] *N*-Tosylamidines (**314**) can be obtained by reacting secondary thioamides (aliphatic and aromatic) with tosyl azide.[648] Thiobenzamides have been condensed with anilines to afford amidines (**315**).[648] Thioamides can be converted to amidines, *e.g.* (**316**), by treatment with ammonia in the presence of mercury acetate.[317]

### 2.7.3.4.3 *From nitriles, isonitriles, ketene imines, carbodiimides and cyanamides*

The addition of ammonia, primary and secondary amines to the nitrile group proceeds well if electron-attracting groups are present in the α-position to the nitrile function. Thus it is well known that amines add rapidly to trihaloacetonitriles[634,649,650] or cyanogen[651] to give amidines (**317**) and (**318**) respectively (Scheme 51). Recently it was reported that the addition of aliphatic amines and diamines to aliphatic or aromatic nitriles, respectively, proceeds with good yields if lanthanide triflates are present as catalysts.[652]

Metal amides can be added to ordinary nitriles (*e.g.* lithium, sodium or magnesium amides), thus forming amide imide salts, which on addition of water or alcohol afford amidines.[20,21] Some recent results demonstrate the wide applicability of the method, *e.g.* from metal amides and trialkoxyacetonitriles, trialkoxyacetamidines (**319**; Scheme 52)[653] were prepared and from lithium imides and nitriles *N*-alkylideneamidines (**320**)[654] could be synthesized.

The addition of amines to isonitriles, catalyzed by copper compounds, furnishes formamidines.[509] The method has found further application, *e.g.* piperidine was added to benzeneisonitrile[655] or to trimethylsilylmethaneisonitrile[656] to give the amidine (**321**; Scheme 53). *N*-Sulfonylformamidines (**322**) were the

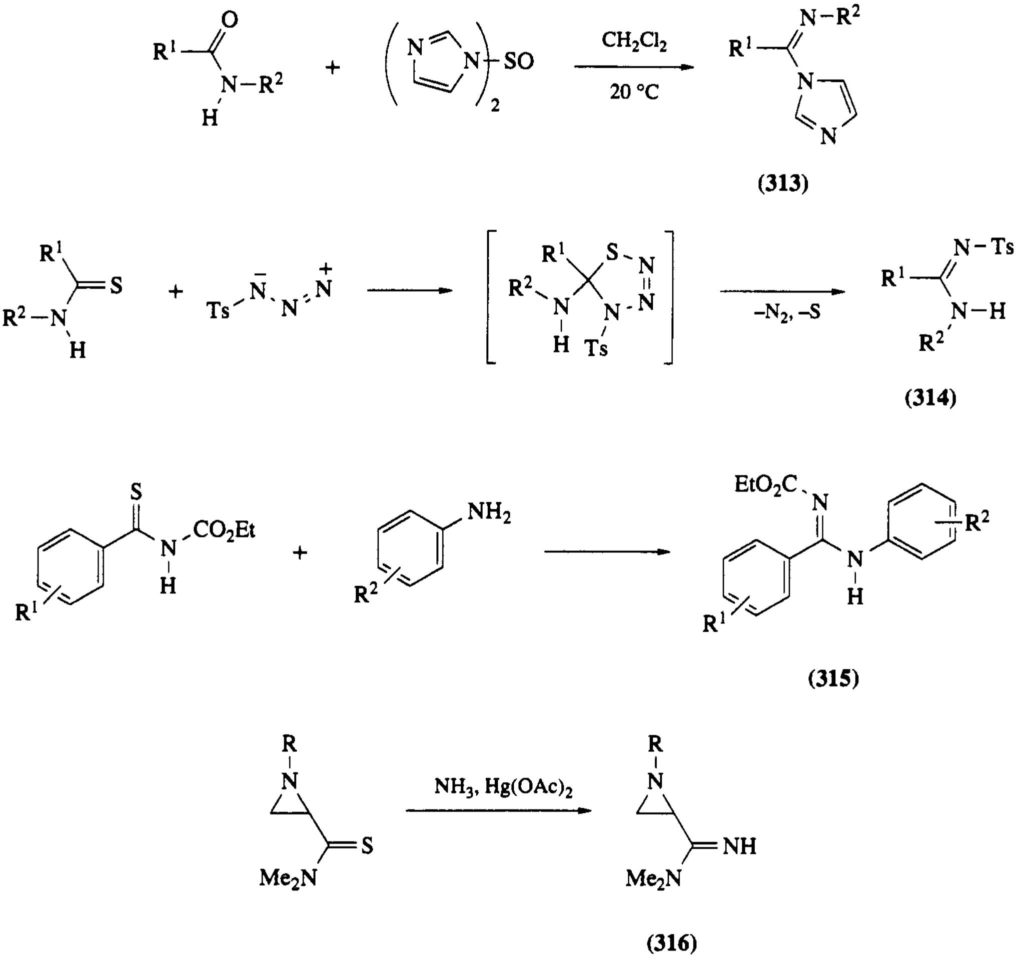

Scheme 50

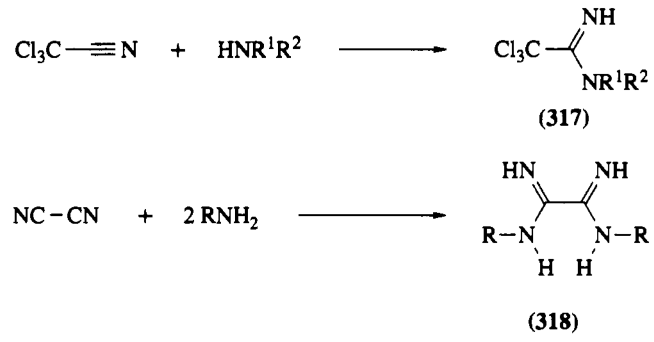

Scheme 51

products when sulfonamides were reacted with isonitriles.[657] It has turned out that silver chloride catalyzes the addition of aziridine to isonitriles to produce formamidines (**323**).[658]

*N*-Vinylformamidines (**324**; equation 166) are accessible from the reaction of aldehydes with isocyanoacetic acid esters and amines.[659,660] Isonitriles can insert into the C—N bond of aminals with formation of α-aminoacetamidines (**325**) and (**326**) (equation 167).[661,662] From ketene imines and primary[663,664] or secondary[664,665] amines amidines (**327**; Scheme 54) have been prepared; the ketene imines needed can be generated *in situ* from isoxazoles.[666] In the presence of triethylamine from the ketene imine (**328**) and the urethane (**329**), the iminoaziridine (**330**) is obtainable.[667] Ketene imines with *N*-sulfinyldimethylammonium tetrafluoroborate form adducts (**331**), which are decomposed by aqueous alkali to yield amidines in good yields.[668]

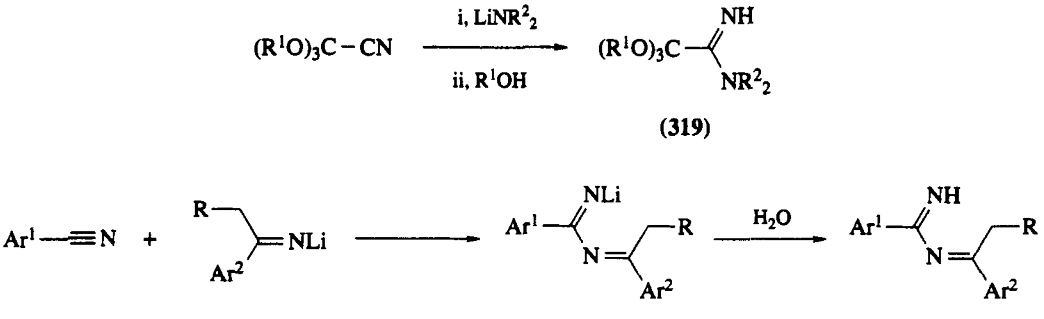
i, $LiNR^2_2$
ii, $R^1OH$
$H_2O$

(319)

(320)

**Scheme 52**

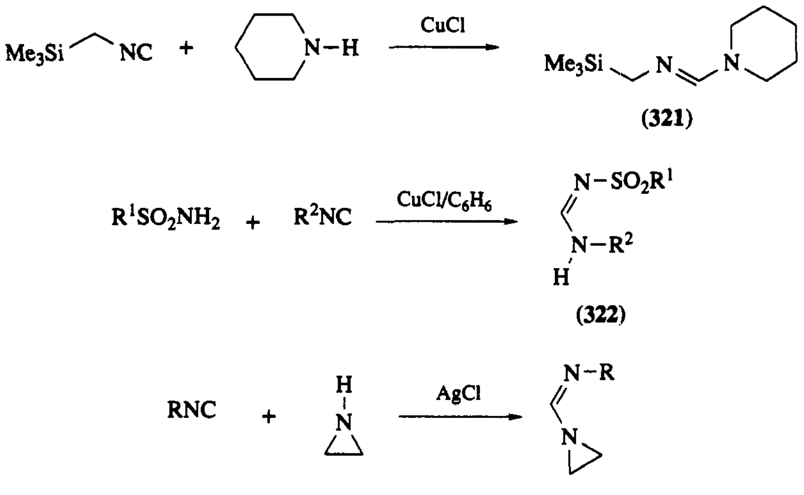
CuCl
$CuCl/C_6H_6$
AgCl

(321)

(322)

(323)

**Scheme 53**

Carbodiimides (332; Scheme 55) form amidines on treatment with: $NaBH_4$ in alcohols,[669] Grignard reagents,[20] sodium phenylacetylide,[20] carbon monoxide in the presence of *s*-butyl- or t-butyl-lithium[670] and nitrones catalyzed by $HBF_4$.[671] In the reaction of stannylated or silylated ynamines with carbodiimides

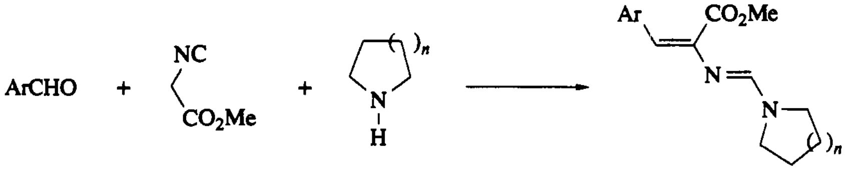

(324)

(166)

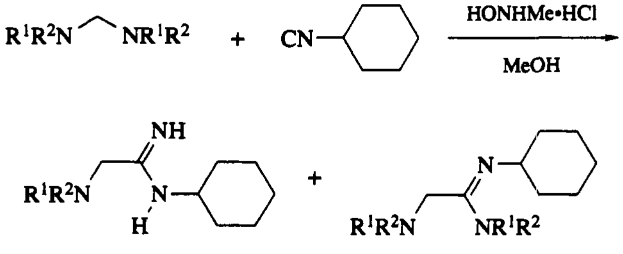
HONHMe•HCl
MeOH

(325) (326)

(167)

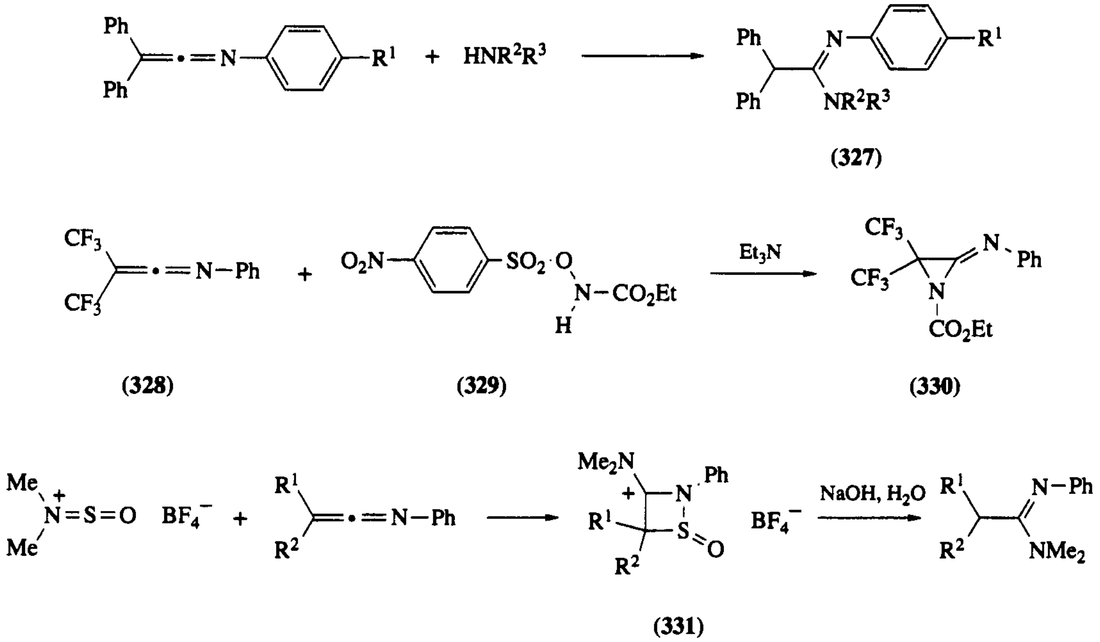
(327)
(328)
(329)
(330)
(331)

**Scheme 54**

propiolamidines (**333**; equation 168) are byproducts.[672] *N,N*-Disubstituted cyanamides react with Grignard reagents to yield amidines (**334**; equation 169).[20]

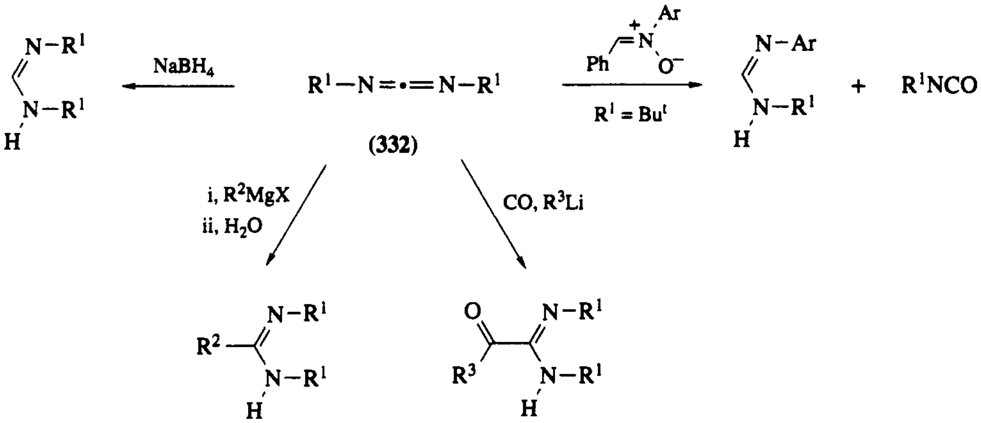

**Scheme 55**

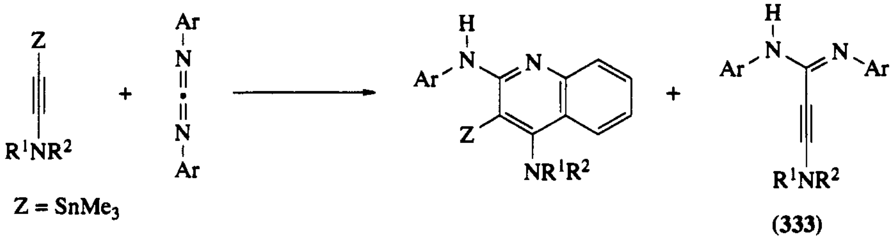

(168)

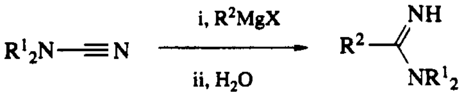

(169)

### *2.7.3.4.4 From 1,1-dihaloalkenes or ynamines*

In β,β-dichlorovinyl sulfones aromatic amines replace both chlorine atoms to furnish β-sulfonylacetamidines (**335**; equation 170).[673,674] 3-Aminopropiolamidines (**336**; equation 171) are accessible from lithio ynamines and carbodiimides after hydrolysis of the initially formed adduct.[675] From ynamines and *N*-sulfinyltosylamide the amidines (**337**; Scheme 56) are formed *via* cycloaddition and cycloreversion steps.[676] In a similar way from ynamines and *N*-sulfonylimines or *N*-phenylsulfonylthioimidates amidines (**338**) and (**339**), respectively, can be prepared.[677]

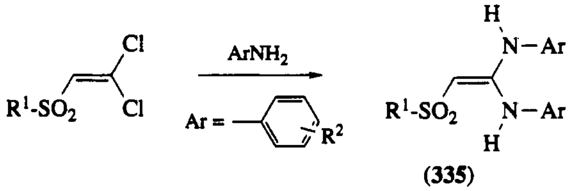

Cl
R$^1$-SO$_2$
Cl
ArNH$_2$
Ar =
R$^2$
H
N−Ar
R$^1$-SO$_2$
N−Ar
H

**(335)**

(170)

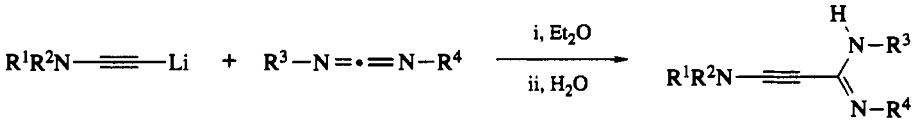

R$^1$R$^2$N
Li
+
R$^3$−N=•=N−R$^4$
i, Et$_2$O
ii, H$_2$O
H
N−R$^3$
R$^1$R$^2$N
N−R$^4$

**(336)**

(171)

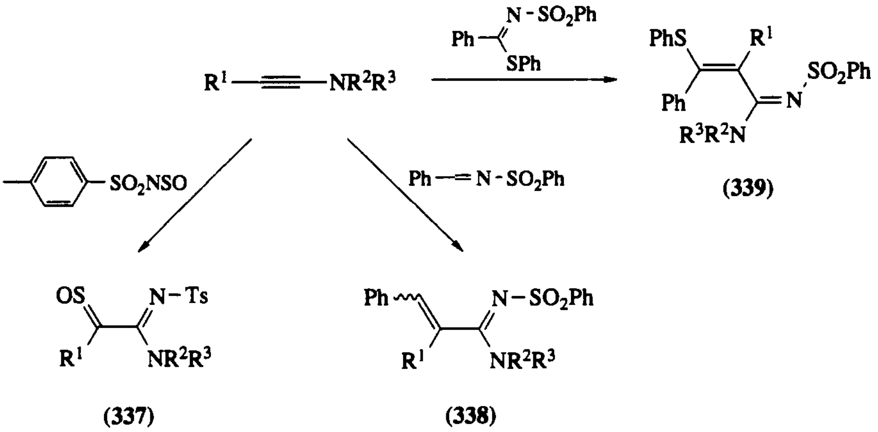

R$^1$
NR$^2$R$^3$
N-SO$_2$Ph
Ph
SPh
PhS
R$^1$
SO$_2$Ph
Ph
N
R$^3$R$^2$N
(339)
SO$_2$NSO
Ph—=N-SO$_2$Ph
OS
N−Ts
R$^1$
NR$^2$R$^3$
(337)
Ph
N−SO$_2$Ph
R$^1$
NR$^2$R$^3$
(338)

**Scheme 56**

### *2.7.3.4.5 From imidoyl compounds*

As already mentioned the action of ammonia, primary and secondary amines on imidoyl halides affords amidinium salts, from which the amidines (**340**; Scheme 57) can be set free by treatment with bases (see Section 2.7.2.5.3 and 2.7.2.5.4). In imidates[42,421,479–482,488,490,678,679] and thioimidates[500,552,563] the alkoxy groups and alkylmercapto groups respectively are readily replaced by amino groups giving amidines (**340**).

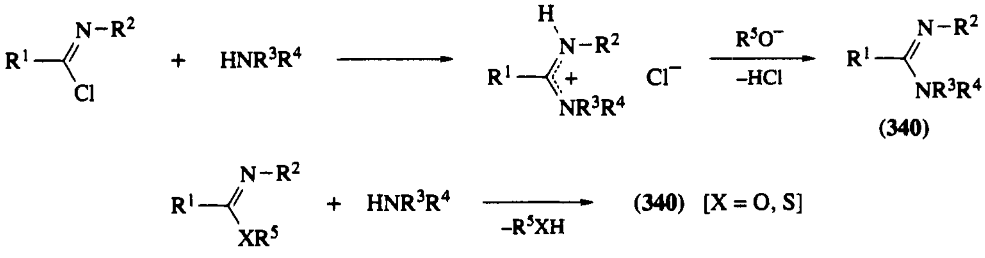

N−R$^2$
R$^1$
Cl
+
HNR$^3$R$^4$
H
N−R$^2$
R$^1$
+
NR$^3$R$^4$
Cl$^-$
R$^5$O$^-$
-HCl
N−R$^2$
R$^1$
NR$^3$R$^4$
(340)
N−R$^2$
R$^1$
XR$^5$
+
HNR$^3$R$^4$
-R$^5$XH
(340) [X = O, S]

**Scheme 57**

In amidines transamination is possible,[680–683] especially useful for such purposes are imidoylimidazolides, *e.g.* (**341**; equation 172).[680] In some cases it is useful to prepare amidines by ring opening of suitable heterocycles, which can be achieved by treatment with amines or other nucleophilic (basic) compounds. Examples are the synthesis of amidines from 1,3,5-oxadiazinium salts (**342**),[684,685] 3-amino-1,2-benzisothiazoles (**343**),[686] 2-ethoxycarbonyl-3,1-benzoxazin-4(4*H*)-one (**344**),[687] 1,2,5-oxadiazolo[3,4]pyrimidine 1-oxides (pyrimidofuroxans; **345**)[688] and 1,2,4,6-thiatriazenium-5-olate 1,1-dioxides (**346**)[689] as shown in Scheme 58.

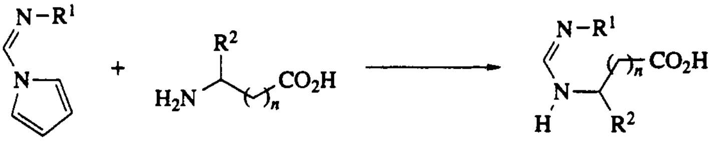
N–R¹
R²
CO₂H
H₂N
n
+
N–R¹
CO₂H
N
H
R²

(172)

**(341)**

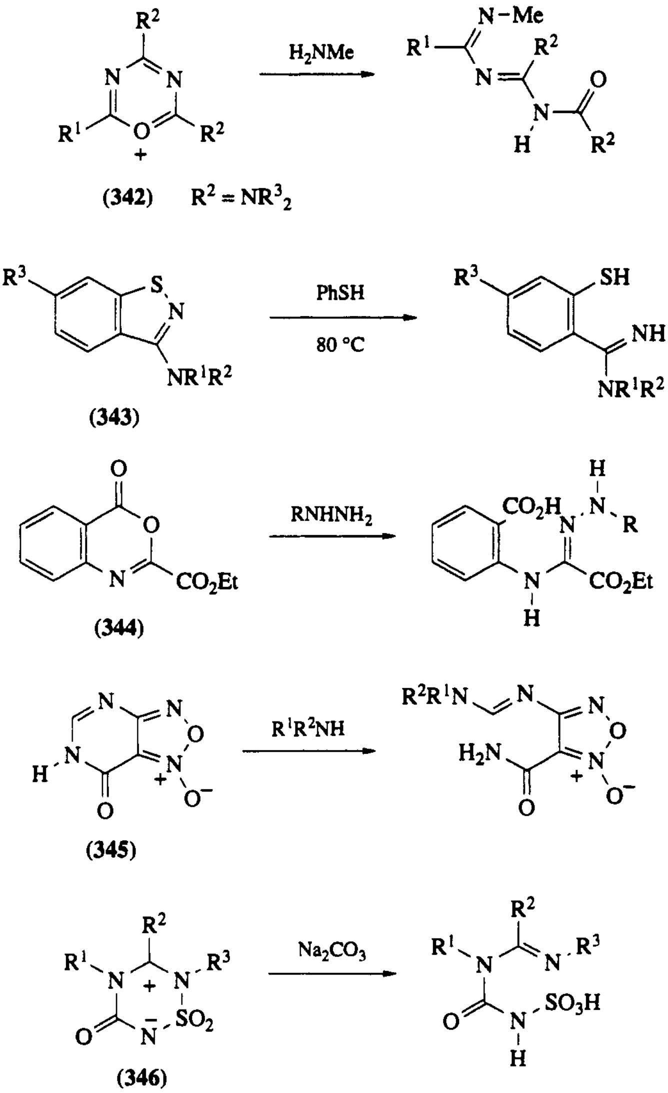
H₂NMe
N–Me
PhSH
80 °C
SH
NH
RNHNH₂
CO₂H
CO₂Et
R¹R²NH
R²R¹N
H₂N
Na₂CO₃
SO₃H

**(342)** $R^2 = NR^3_2$

**(343)**

**(344)**

**(345)**

**(346)**

**Scheme 58**

Amidines with a more complicated substitution pattern have been prepared from amidines by alkylation—either at nitrogen[690–692] or at nitrogen substituents.[693,694] Variations at these positions have been achieved by heteroarylation,[695] acylation,[675,696,697] vinylation[698] or carboxylation with phosgene,[699] thiophosgene,[699] isocyanide dichlorides[699] or isothiocyanates.[700] Some interesting amidines, *e.g.* (**347**)–(**352**) (Scheme 59), have been prepared in this manner. The amidine skeleton can also be varied by halogenation,[325,667] hydrolysis,[622] isomerization[658] or catalytic hydrogenation[655] or other addition reactions if there are C=C double bonds present as in (**353**; equation 173) for example.[701]

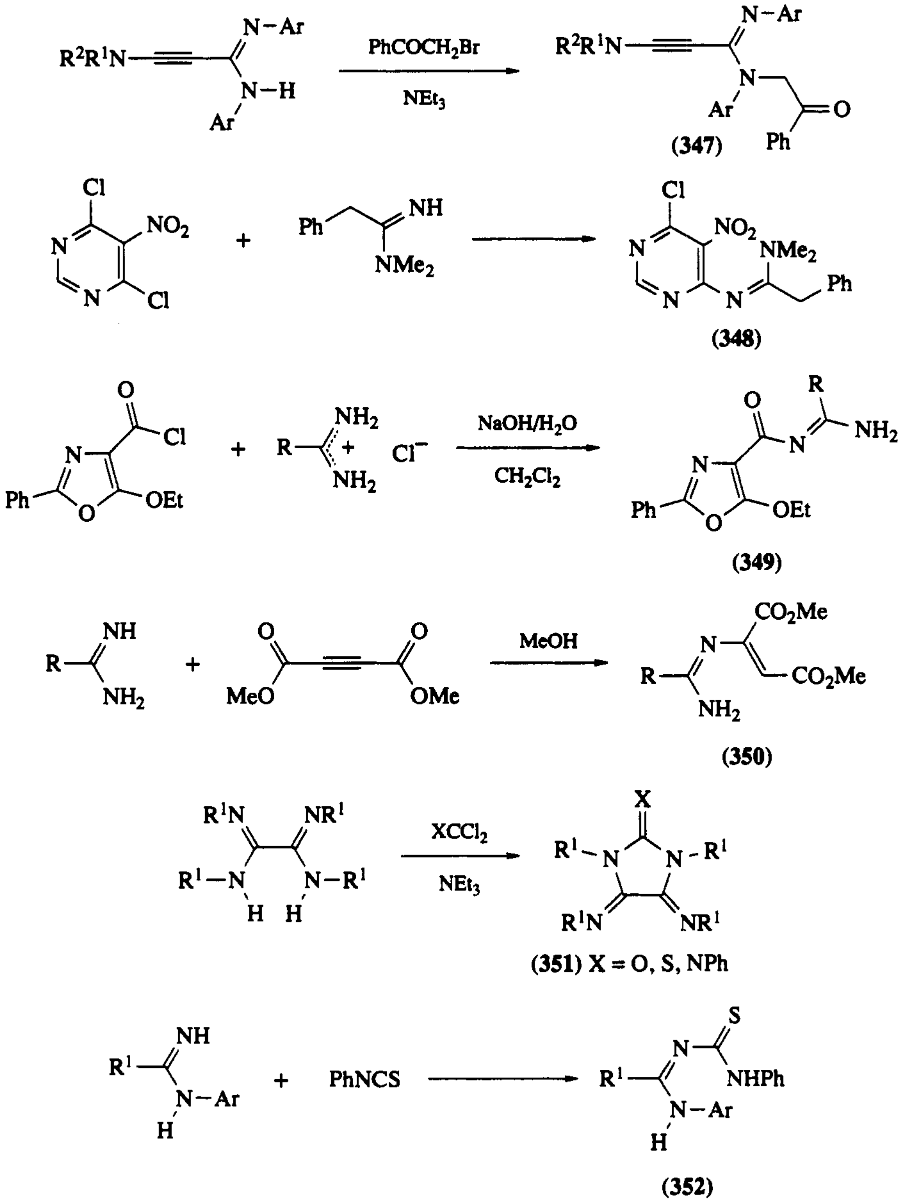

(**347**)

(**348**)

(**349**)

(**350**)

(**351**) X = O, S, NPh

(**352**)

**Scheme 59**

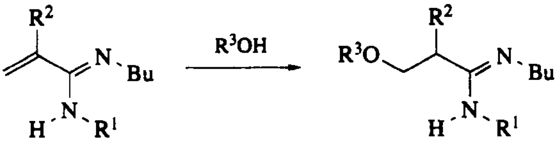

(**353**)

(173)

### *2.7.3.4.6 From orthoesters, orthoamides and related compounds*

Orthoesters react with excess amines, catalyzed by acids, to afford amidines;[702–704] imino esters are isolable intermediates (see Section 2.7.3.2.3). A lot of *N*-naphthylformamidines,[702] *N*-pyridylformamidines[703] and *N*,*N*′-diphenylformamidines (**354**; Scheme 60)[704] were prepared by this method. In a similar reaction from dichlorofluoromethane and pentafluoroformanilide the formamidine (**355**) was prepared.[705] The condensation of NH-acidic compounds with orthoamide derivatives affords amidines (**356**) and (**357**) (Scheme 61). This is one of the most general and easy to perform syntheses of amidines, which has found wide application in the last 15 years. In Tables 7a and 7b are compiled orthoamide derivatives and amino compounds which have been reacted to give amidines.

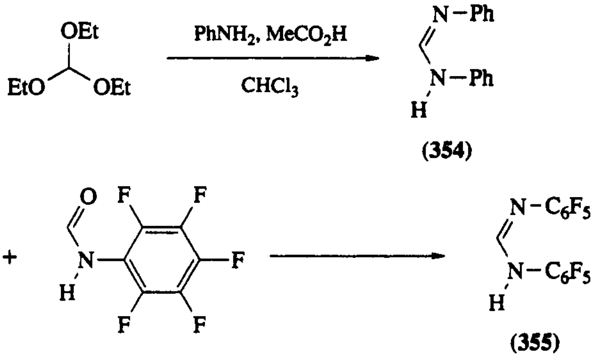
OEt
EtO
OEt
PhNH2, MeCO2H
CHCl3
N–Ph
N–Ph
H
(354)
HCF2Cl
+
O
F
F
N
H
F
F
F
N–C6F5
N–C6F5
H
(355)

**Scheme 60**

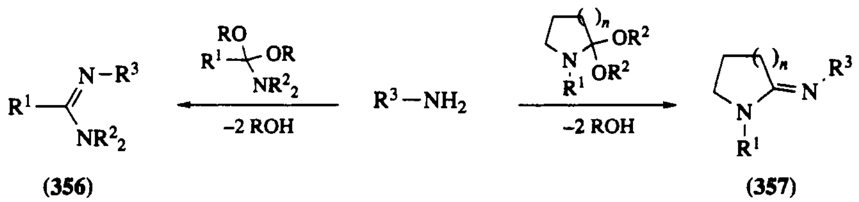
N–R3
R1
NR22
(356)
RO
R1
OR
NR22
–2 ROH
R3–NH2
)n
OR2
N
R1
OR2
–2 ROH
)n
R3
N
N
R1
(357)

**Scheme 61**

In addition to the construction of the amidine structure *N*-alkylation reactions can occur;[722,723] ring opening in the case of heterocyclic amines[728] and formylation of acidic methylene or methyl groups.[760,761,795] The reaction of formamide with excess *N*,*N*-dialkylformamide acetals deviates from this reaction pattern, here azavinylogous formamide acetals (**358**; Scheme 62) are formed.[796] *N*,*N*-Dialkyl-*N*′-formylformamidines (**359**) can be prepared either by action of *N*,*N*-dialkylformamide acetals on bis(trimethylsilyl)formamide[797] or by treatment of azavinylogous amide acetals (**358**) with trimethylchlorosilane.[798]

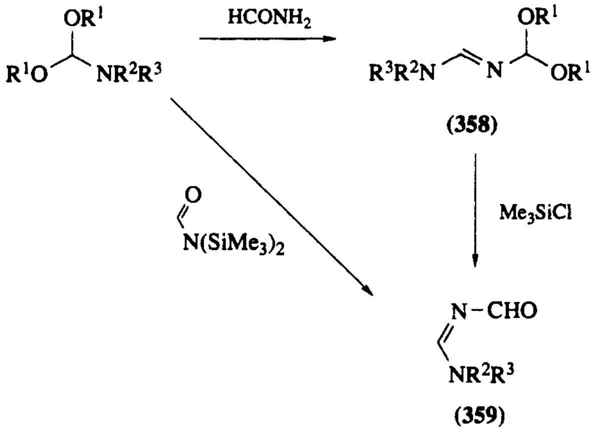
OR1
R1O
NR2R3
HCONH2
OR1
R3R2N
N
OR1
(358)
O
N(SiMe3)2
Me3SiCl
N–CHO
NR2R3
(359)

**Scheme 62**

**Table 7a** Amidines from Orthoamide Derivatives and Amino Compounds

| *Orthoamide derivatives* | *Ref.* |
|---|---|
| *N*,*N*-Dimethylformamide acetals | 42, 706–782 |
| *N*-Formylpyrrolidine acetals | 760, 783 |
| *N*-Formylpiperidine acetals | 754 |
| *N*-Formylmorpholine acetals | 754, 760 |
| *N*,*N*-Dimethylacetamide acetals | 724, 729, 741, 747, 756–758, 765, 775, 779–781, 784–787 |
| *N*-Acetylpiperidine acetal | 788 |
| *N*-Acetyl-*N*′-(2-pyridyl)piperazine acetal | 788 |
| *N*,*N*-Dimethylbenzamide acetals | 772, 775 |
| *N*-Alkylpyrrolidone acetals | 729, 731, 763, 765, 780, 784, 785, 787, 789–794 |
| *N*-Methylpiperidone acetals | 729, 763, 765, 784, 785,789–792 |

**Table 7b** Amidines from Orthoamide Derivatives and Amino Compounds

| *Amino compounds* | *Ref.* |
|---|---|
| Aminoanthraquinones | 42, 787, 794 |
| Anilines | 715, 719, 720, 731, 759 |
| Aminocoumarins | 736 |
| Aminoindazoles | 712 |
| Aminopurines | 721, 730 |
| Aminopyridines | 713, 715, 716, 726, 741, 782, 785 |
| Aminopyrimidines | 715, 718, 743, 744, 747, 784 |
| Aminouracils | 706–708, 795 |
| Aminopyrazines | 714, 717, 746, 747 |
| Aminopyridazines | 739,747 |
| Aminoquinazolines | 710 |
| Amino-1,2,4-triazines | 715, 747 |
| Amino-1,2,4-triazoles | 715 |
| Aminopteridines | 709, 714 |
| Aminobenzimidazole | 715 |
| Aminopyrimidopyrimidines | 716 |
| Aminobenzotriazines | 724 |
| Cytosines | 722, 723 |
| Pyrazinethionhydroxamic acid amide | 725 |
| Aminothiazoles | 727 |
| Aminothiophenes | 727, 788 |
| Aminopyrazoles | 728, 729, 733, 738, 745 |
| Aminoisoxazoles | 728 |
| Pyrroloazepinones | 729 |
| Aminotriazolopyrimidines | 732 |
| Aminotetrahydronaphthyridines | 734 |
| Aminopyrazolopyridines | 735 |
| Aminopyridazinones | 739 |
| Aminopyridopyrimidines | 740 |
| Amino-1,3,4-thiadiazoles | 742 |
| Aminoimidazoles | 742 |
| Sulfonamides | 748 |
| Amino sugars | 749 |
| *N*-Arylbenzamidines | 750 |
| Thioamides | 751–754, 756, 760, 781 |
| Benzylamines | 755 |
| Aromatic acid amides | 757, 758 |

Formamidines are accessible from 2-dialkylamino-2-alkoxyacetonitriles (**360**; Scheme 63) and primary amines.[799] The action of HCN on the nitriles (**360**) gives rise to formation of *N*-vinylamidines (**361**).[800] Formamidines (**362**) are formed from bis(dialkylamino)acetonitriles and isocyanates in excellent yields.[801,802] This reaction is interesting from the mechanistic point of view.

### *2.7.3.4.7 Miscellaneous methods*

Anilines[803,804] and heterocyclic amines[805,806] react with 1,3,5-triazine to furnish formamidines, *e.g.* (**363**) and (**364**) (Scheme 64). $CH_2$-acidic compounds, *e.g.* nitriles, can be formylated by heating with 1,3,5-triazine. In the course of such reactions the enamines thus obtained can be converted to formamid-

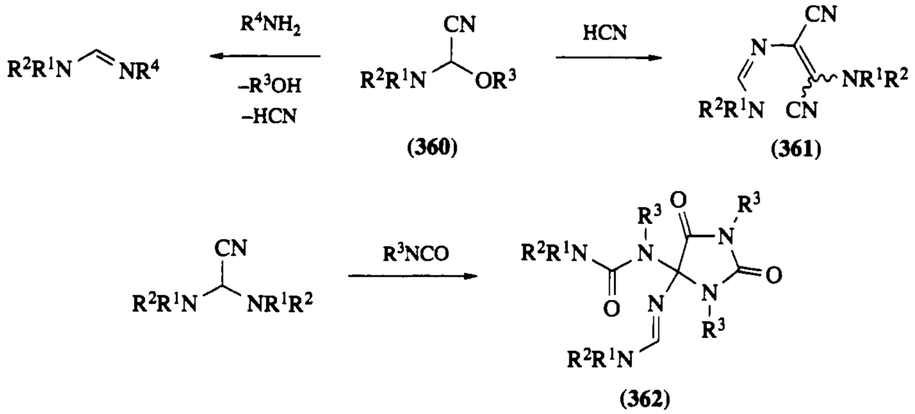
R⁴NH₂
-R³OH
-HCN
HCN
R³NCO
(360)
(361)
(362)

**Scheme 63**

ines (**365**) if secondary amines are present.[807,808] From hydrocyanic acid and primary amines *N,N'*-disubstituted formamidines were prepared.[809] The mercury acetate catalyzed addition of aromatic amines to acetylene affords acetamidines (**366**; Scheme 65);[810] in a similar procedure α-arylaminopropionamidines (**367**) from propargyl alcohol and arylamines have been prepared.[811,812] 1,2-Diaminoethylenes react with aryl azides or tosyl azide to give α-aminoamidines (**368**; equation 174).[813,814] Amidines (**369**) and (**370**) (Scheme 66) are accessible from thioureas by desulfurization with Raney nickel[815] or by sulfide contraction.[816] In an unexpected reaction sequence α-ketoamidines (**371**; equation 175) are produced from enamines and nitrosobenzene in moderate yields.[817]

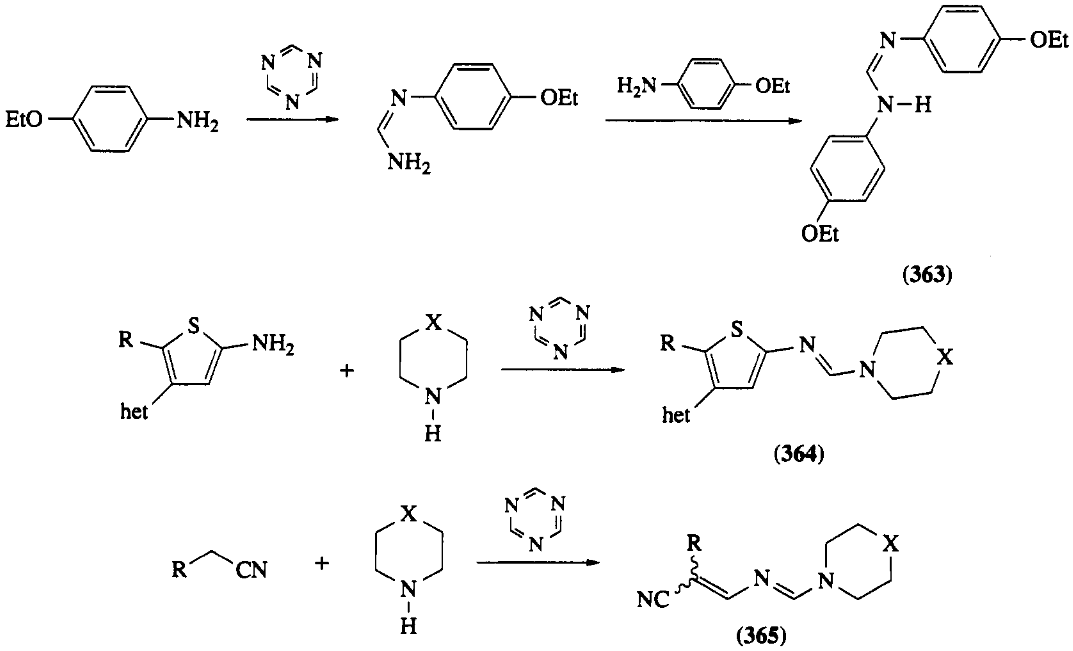

**Scheme 64**

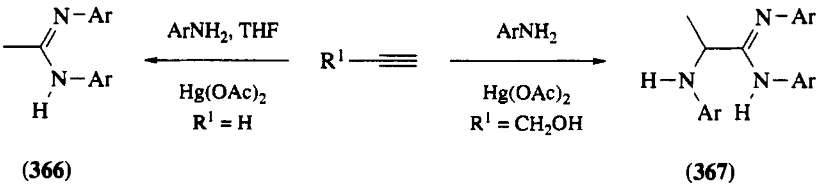
ArNH₂, THF
Hg(OAc)₂
R¹ = H
ArNH₂
Hg(OAc)₂
R¹ = CH₂OH
(366)
(367)

**Scheme 65**

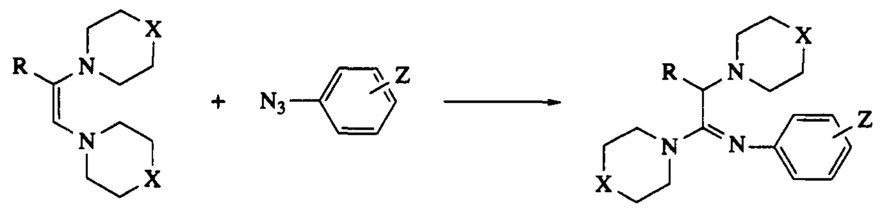

(174)

(368)

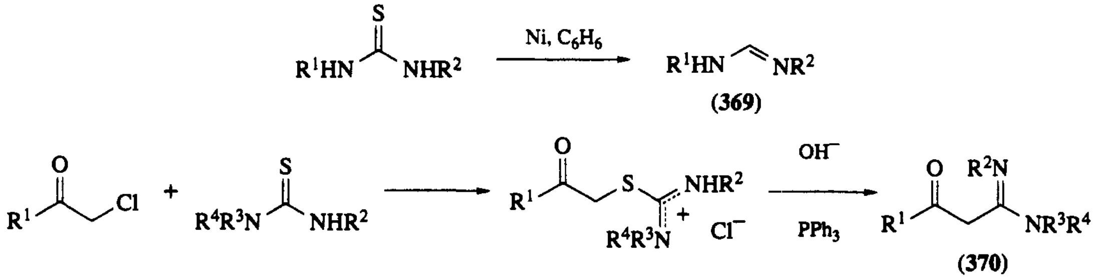

(369)

(370)

Scheme 66

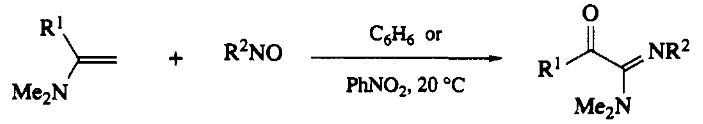

(175)

(371)

## 2.7.4 CARBOXYLIC ORTHOACID DERIVATIVES

### 2.7.4.1 Carboxylic Orthoesters

#### *2.7.4.1.1 From 1,1,1-trihaloalkanes, α,α-dihalo ethers, haloalkenes, ketene acetals and alkoxyalkynes*

The preparation of orthoformic acid esters from chloroform and alkali metal alkoxides is a long known procedure,[7,22–27] which can be performed under phase transfer catalysis.[818] If small amounts of alcohol are present in the phase-catalyzed process, cyclopropanes (**372**; Scheme 67) can be produced by addition of dichlorocarbene to 1,2-dialkoxy-1,2-dichloroethylenes, which are thought to be intermediates.[819] Alkenes of this kind, *e.g.* (**373**; equation 176), have been observed as byproducts in the synthesis of tri-*t*-butylorthoformate from chlorodifluoromethane or dichlorofluoromethane and potassium *t*-butoxide.[820] Trimethoxyacetonitrile was prepared from trichloroacetonitrile and sodium methoxide.[821]

In the reaction of geminal trihaloalkanes with alkoxides elimination (alkene formation) is preferred over substitution (orthoester formation). There are a few known exeptions, *e.g.* the preparation of β-keto orthoesters (**374**; equation 177) from fluorinated ketones,[822] or the synthesis of trimethoxymethylalkyne from 1,4-dichloro-2,3-dibromo-2-butene.[823] Triaryl orthoesters can be prepared from perhalogenated alkenes,[824] dichloronitroalkenes (**375**; Scheme 68),[825,826] dihalomethylenefuranone[827] or, very favorably, from dichloromethyl aryl ethers (**376**)[828] and phenoxides. In general the action of alkoxides on α,α-dichloro ethers is a reliable method for the preparation of substituted orthoesters like 2,2,2-trialkoxyacetic acid esters[829,830] or pentaalkoxyethanes.[831] Aromatic and heteroaromatic orthoesters, *e.g.* orthobenzoic acid esters[7,22,24] or the bisorthoesters (**377**)[832] and (**378**)[833] can be synthesized from the corresponding trihalomethyl compounds.

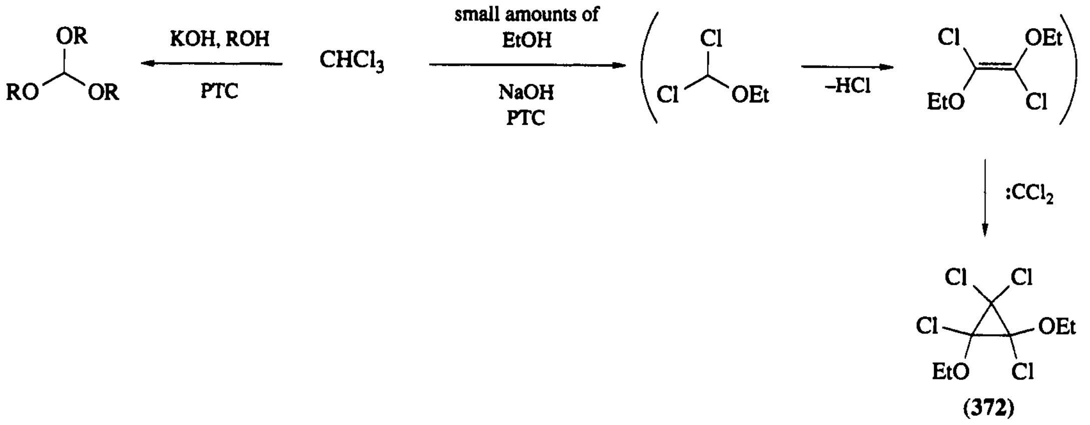
KOH, ROH
PTC
CHCl3
small amounts of EtOH
NaOH
PTC
-HCl
:CCl2
(372)

**Scheme 67**

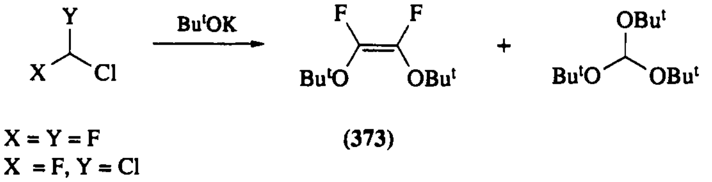
Bu$^t$OK
X = Y = F
X = F, Y = Cl
(373)

(176)

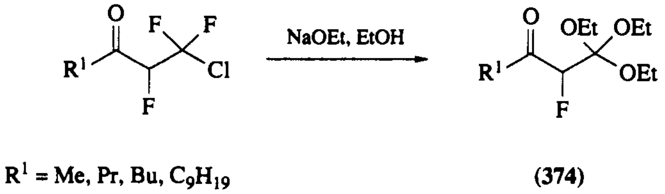
NaOEt, EtOH
R$^1$ = Me, Pr, Bu, C$_9$H$_{19}$
(374)

(177)

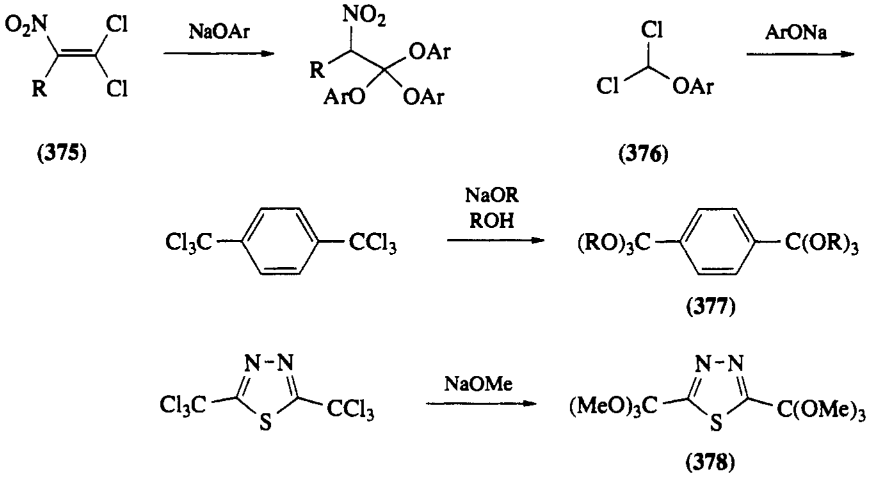
NaOAr
(375)
ArONa
(376)
NaOR
ROH
(377)
NaOMe
(378)

**Scheme 68**

In the reaction of sodium methoxide with 3-trichloromethylpyridine the nicotinecarbaldehyde acetal (**379**; Scheme 69) is formed, whereas by action of methoxide on 2,6-dichloro-3-trichloromethylpyridine the orthoester (**380**) is accessible.[834] The 1,1-dichloro-2-acylcyclopropanes on treatment with sodium methoxide undergo ring enlargement to yield the cyclic orthoester (**381**; equation 178).[835,836] A mixture of isomeric cyclopentadiene carboxylic orthoacid esters results when the bis(methylthio)fulvene (**382**; equation 179) is reacted with excess alkoxide.[837]

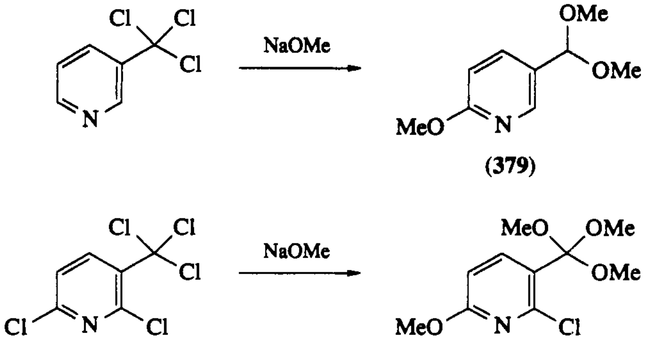

**(379)**

**(380)**

**Scheme 69**

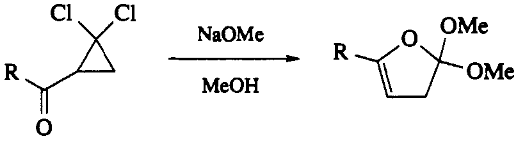

**(381)**

(178)

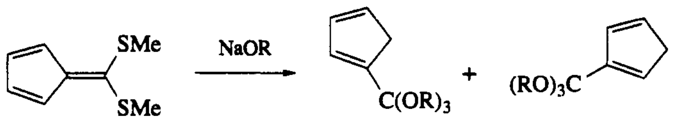

**(382)**

(179)

Mixed substituted orthoesters, *e.g.* (**383**; equation 180), can be obtained by addition of alcohols to ketene *O,O*-acetals.$^{838}$ With the aid of phosphoranes containing a ketene *O,O*-acetal structure, various orthoesters, *e.g.* (**384**) and (**385**) (Scheme 70) were prepared.$^{839-844}$ Cyclic orthoesters (**386**)–(**390**) (Scheme 71) are formed in cycloaddition reactions of ketene *O,O*-acetals with aldehydes,$^{845-848}$ ketones,$^{847,848}$ acyl cyanides,$^{849}$ oxiranes,$^{850}$ α-keto esters,$^{851}$ α-diketones$^{852}$ or ketones$^{853}$ (with irradiation), α,β-unsaturated aldehydes and ketones$^{854-856}$ (under pressure or catalyzed by $ZnCl_2$), diazoacetophenone,$^{857,858}$ diazoacetone$^{858}$ and azodicarboxylate.$^{859}$

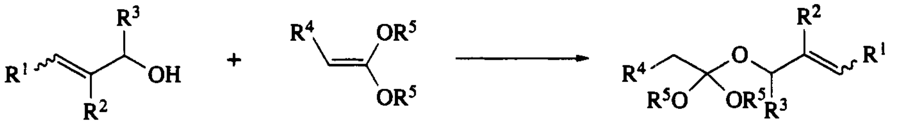

**(383)**

(180)

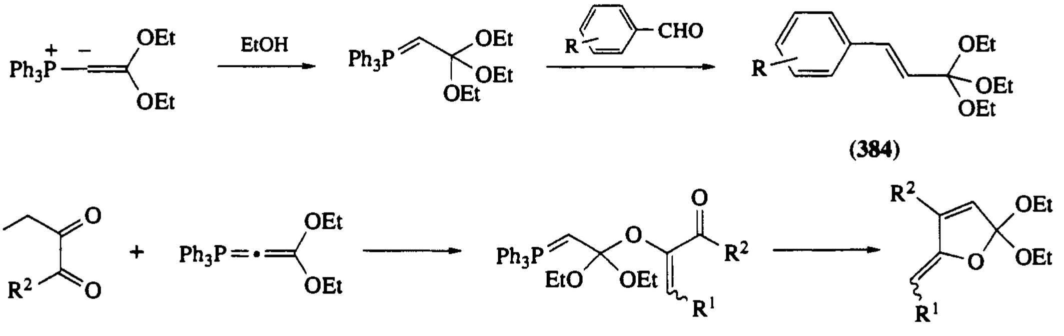

**(384)**

**(385)**

**Scheme 70**

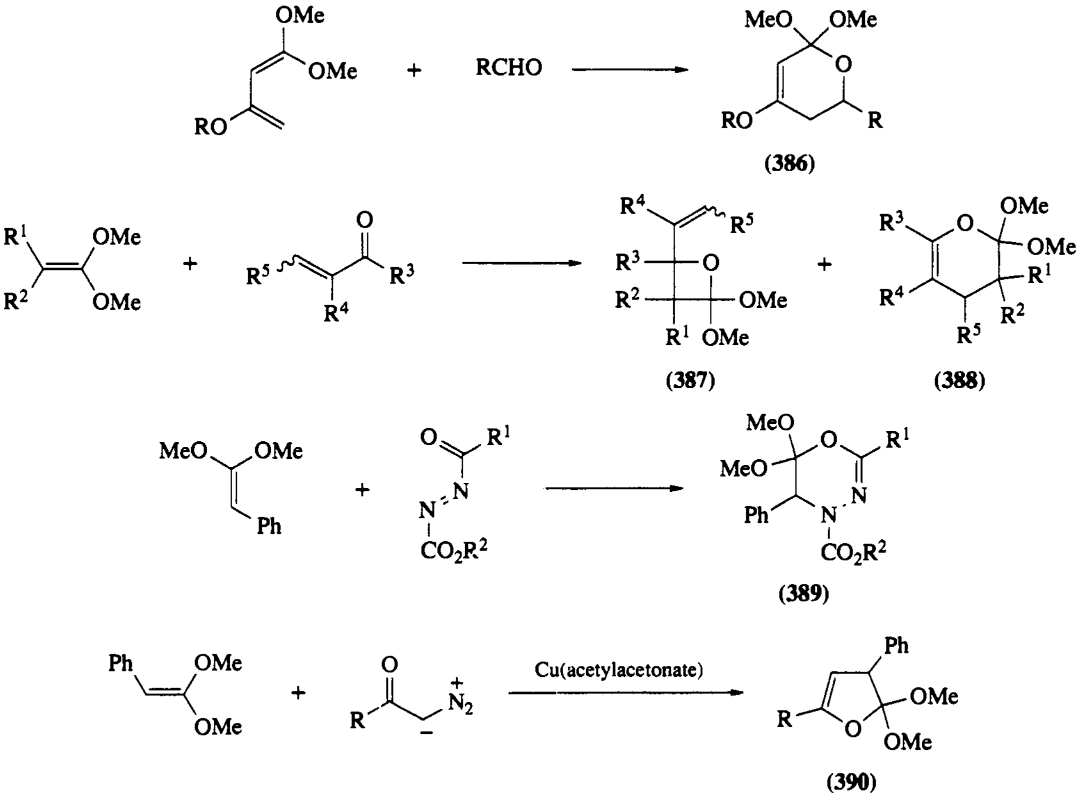
OMe
OMe
RO
+
RCHO
MeO
OMe
O
RO
R
(386)
R1
OMe
R2
OMe
+
O
R5
R3
R4
R4
R5
R3
O
R2
OMe
R1
OMe
(387)
+
R3
O
OMe
OMe
R1
R4
R2
R5
(388)
MeO
OMe
Ph
+
O
R1
N
N
CO2R2
MeO
MeO
O
R1
N
Ph
N
CO2R2
(389)
Ph
OMe
OMe
+
O
R
N2
Cu(acetylacetonate)
Ph
OMe
R
O
OMe
(390)

**Scheme 71**

Ethoxyacetylene adds, catalyzed by mercury acetate and $ZnCl_2$, aliphatic or aromatic alcohols to produce mixed substituted orthoesters, *e.g.* (**391**)–(**393**) (Scheme 72).[860] Acyl ketenes are formed on thermolysis of 1,3-dioxin-4-ones, which can be trapped with ketene acetals to give orthoesters (**394**; equation 181).[861–863] 2,2-Dialkoxydihydrofurans (**395**; equation 182) are accessible by addition of ketones to cyclopropenone acetals.[864] Treatment of 2-chloro-2,3-dimethoxy-1,4-dioxane with sodium methoxide affords the 2,2,3-trimethoxy-1,4-dioxane (**396**; equation 183).[865]

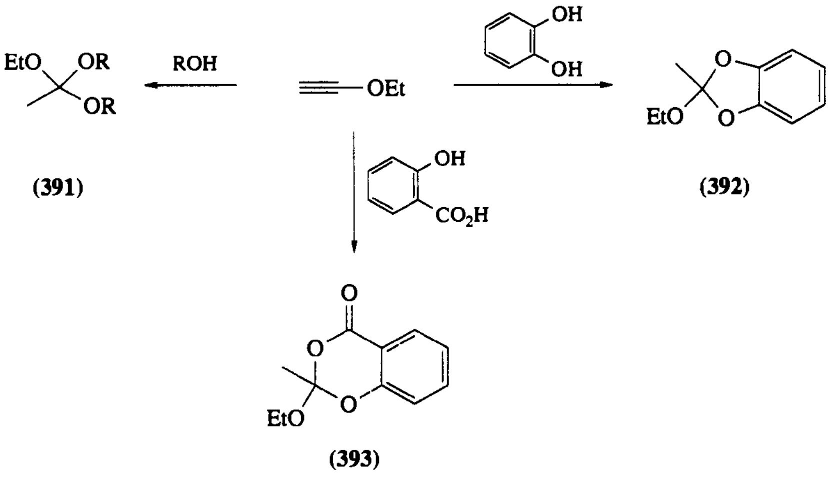
EtO
OR
OR
(391)
ROH
OEt
OH
OH
O
EtO
O
(392)
OH
CO2H
O
O
EtO
O
(393)

**Scheme 72**

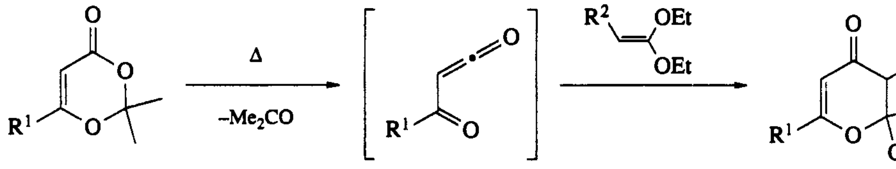
Δ
$-Me_2CO$
$R^1$
$R^2$
OEt
OEt

**(394)**

(181)

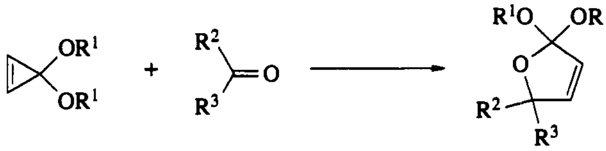
$OR^1$
$R^2$
$R^3$
$R^1O$

**(395)**

(182)

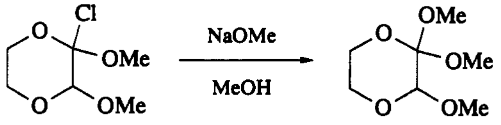
Cl
OMe
NaOMe
MeOH

**(396)**

(183)

### 2.7.4.1.2 *From esters and diols or epoxides*

Spirocyclic orthoesters, *e.g.* (**397**; equation 184), have been synthesized by Lewis acid catalyzed addition of epoxides to lactones.[866,867] Lactones can be transformed to spirocyclic orthoesters, *e.g.* (**398**) and (**399**) (Scheme 73), by treatment with mixtures of either diols and orthoformates[868] or 1,2-bis(trimethylsiloxy)alkanes and trimethylsilyl triflate.[869,870]

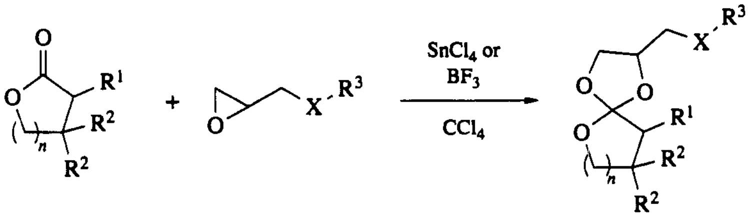
$R^1$
$R^2$
$R^3$
X
$SnCl_4$ or $BF_3$
$CCl_4$
n

**(397)**

(184)

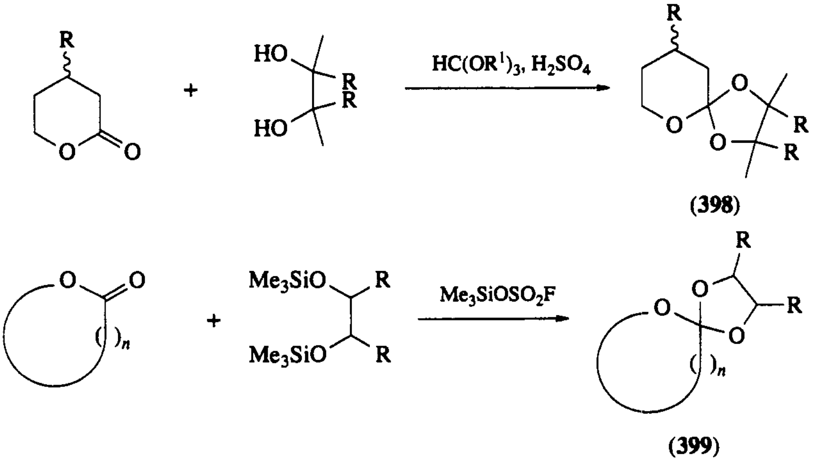
R
HO
$HC(OR^1)_3$, $H_2SO_4$
$Me_3SiO$
$Me_3SiOSO_2F$
n

**(398)**

**(399)**

**Scheme 73**

### 2.7.4.1.3 By oxidation of carbonyl compounds and derivatives

By electrochemical oxidation in alcoholic solution, *e.g.* in the presence of alkoxides, of aldehyde acetals or 1,3-dioxolanes derived from aldehydes orthoesters, *e.g.* (**400**; equation 185), can be obtained.[871–873] Orthobenzoates (**401**; equation 186) are accessible by electrolysis of substituted toluenes in the presence of triarylamines in solvents such as methanol/methylene chloride.[874] Decarboxylation and subsequent electrochemical oxidation of the dicarbonic acid (**402**; equation 187) in methanol affords cyclic orthoesters (**403**).[875]

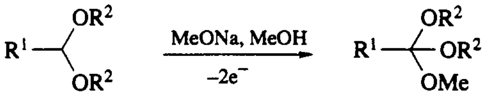

OR²
R¹
OR²
MeONa, MeOH
-2e⁻
-2H⁺
OR²
R¹
OR²
OMe

(**400**)

(185)

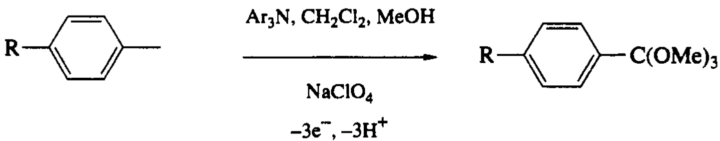

R
Ar₃N, CH₂Cl₂, MeOH
NaClO₄
-3e⁻, -3H⁺
R
C(OMe)₃

(**401**)

(186)

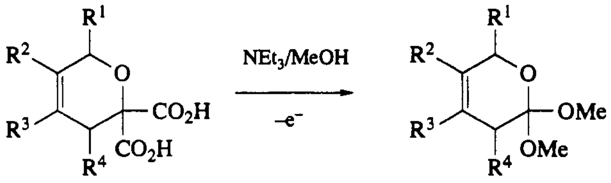

R¹
R²
O
CO₂H
R³
CO₂H
R⁴
NEt₃/MeOH
-e⁻
R¹
R²
O
OMe
R³
OMe
R⁴

(**402**) (**403**)

(187)

### 2.7.4.1.4 From carboxonium salts, alkoxymethyleneiminium salts and related compounds (including amide acetals)

The reaction of lactones with trialkyloxonium salts furnishes lactonium salts, *e.g.* (**404**; equation 188), which react with alkoxides to give cyclic orthoesters.[22,24,27,876–878]

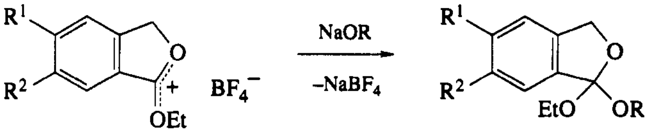

R¹
O
+
R²
OEt
BF₄⁻
NaOR
-NaBF₄
R¹
O
R²
EtO
OR

(**404**)

(188)

By means of silver salts, alcohols and 2,6-dimethylpyridine 'sugar orthoesters' (**405**; equation 189) have been prepared from *O*-acetylated glycosyl halides.[879] Bicyclic orthoesters (**407**; equation 190) are accessible by rearrangement of the esters (**406**).[880] Excess oxalyl chloride reacts with tetrahydrocarbazole to give the acid chloride (**408**; equation 191) which is converted by alcohols to orthoesters (**409**).[881,882]

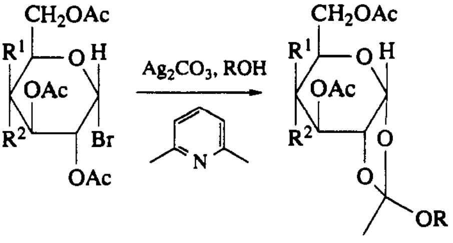

CH₂OAc
R¹
O
H
OAc
R²
Br
OAc
Ag₂CO₃, ROH
N
CH₂OAc
R¹
O
H
OAc
R²
O
O
OR

(**405**)

(189)

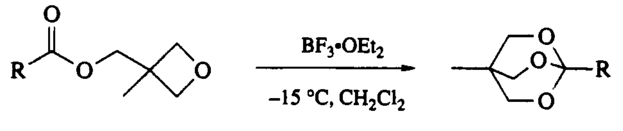

**(406)** **(407)** (190)

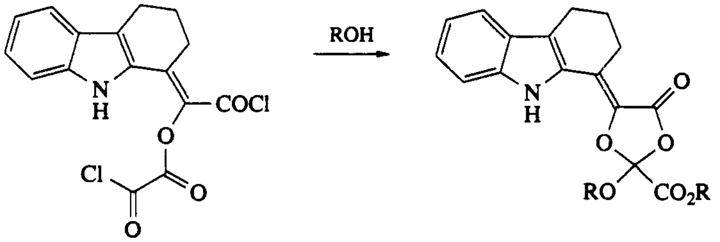

**(408)** **(409)** (191)

Pinner synthesis of orthoesters starting from alkoxymethyleneiminium salts (**410**; equation 192) (imino ester hydrohalides) is a standard procedure, which has been reviewed several times.[15,16,22,24,27] For some more recent results see ref. 7. Closely related to this reaction is the alcoholysis of *N*-alkyl- and *N*,*N*-dialkyl-alkoxymethyleneiminium salts[7] or acid amide–acid halide adducts.[883] Orthoesters are formed *via* *N*,*N*-dialkylalkoxymethyleneiminium salts when amide acetals (**411**; Scheme 74) are alcoholyzed in the presence of acetic acid.[7,214,884]

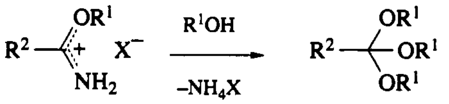

**(410)** (192)

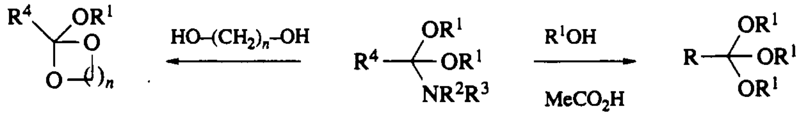

**(411)**

**Scheme 74**

### 2.7.4.1.5 *From orthocarbonic esters and related compounds (including trialkoxycarbenium ions)*

Orthocarbonates react with Grignard reagents to give orthocarboxylates (**412**; equation 193) in usually only moderate yields, because the orthoesters thus formed can react further with the Grignard reagent yielding acetals or ethers.[7,22,24,27,885,886] This side reaction can be suppressed by the use of trialkoxyacetonitriles instead of orthocarbonates.[887] From organolithium compounds and trialkoxycarbenium salts orthoesters (**413**) and (**414**) (Scheme 75) were synthesized.[888–890] The action of organolithium compounds on trialkoxyacetonitriles furnishes α-iminoorthocarboxylates (**415**; equation 194).[891] The reaction of tetraethylorthocarbonate with phenylacetylene can be catalyzed by $ZnCl_2$ and gives the phenylorthopropiolate (**416**; equation 195) in low yields.[22,24]

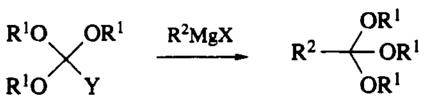

Y = OR, CN **(412)** (193)

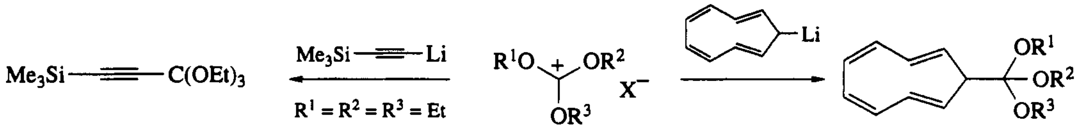

**(413)** **(414)**

**Scheme 75**

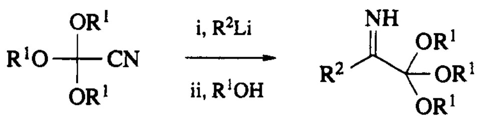

(194)

**(415)**

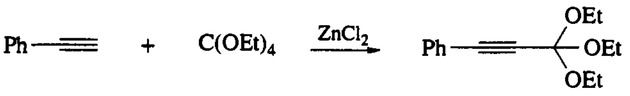

(195)

**(416)**

### 2.7.4.1.6 *From orthoesters*

The preparation of orthoesters from orthoesters by acid-catalyzed transesterification is a standard procedure, which has been reviewed several times.[7,22–27] Advantageous starting compounds are the methyl- or ethyl-orthoesters. Transesterification works well if primary alcohols are used whereas with secondary alcohols complete exchange of all alkoxy groups is difficult to achieve. Mixed substituted orthoesters are the products if tertiary[7] or sterically hindered[892] alcohols are used for transesterification. By this method mixed substituted orthoesters with aryloxy[7,893] or vinyloxy groups,[7,894,895] *e.g.* (**417**; equation 196), have been prepared. With diols and triols transesterification proceeds rapidly,[7,865,896,897] therefore it is not surprising that even acyloins (as 'endiols'),[898] nucleosides,[899,900] dihydroxylactones,[901] inositol,[902] alkaloids (germine),[903] *etc.* have been incorporated into the orthoester function. In a pyridine-catalyzed bromination orthoesters can be brominated to give $\alpha$-bromo orthoesters, from which esters of orthoalkynecarboxylic acids can be prepared.[904] Triethylorthopropiolate has been used in alkynylation reactions giving orthoesters (**418**; Scheme 76).[905] From orthoacrylic and orthopropiolic acid triethyl ester and catechol

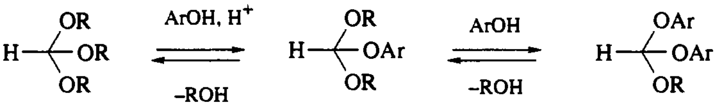

(196)

**(417)**

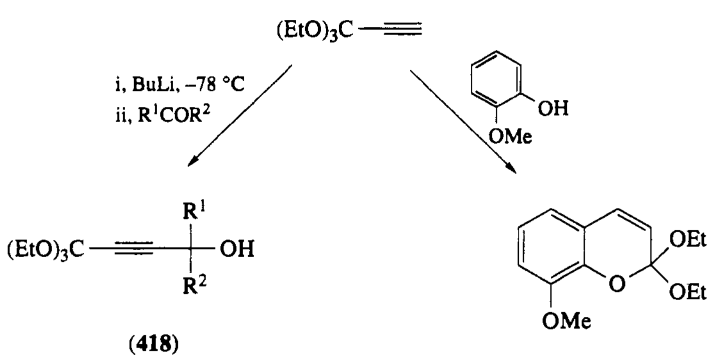

**(418)** **(419)**

**Scheme 76**

monomethyl ether cumarin derivatives (**419**) are accessible.[906] A reactive bis(spiro)orthoester (**420**; equation 197) was synthesized from a trioxaspirononane.[907]

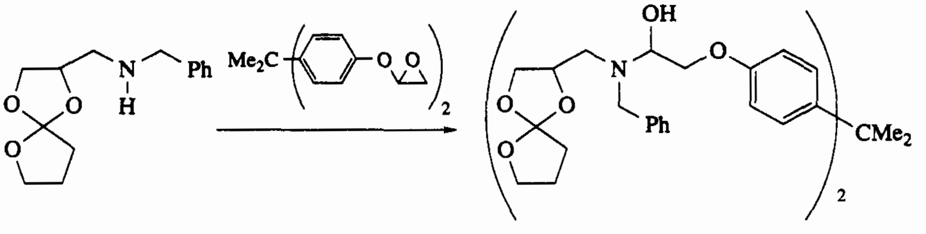

(197)

(**420**)

### 2.7.4.1.7 *Miscellaneous methods*

3-Iodotriethylorthotrithiobenzoate, a readily accessible compound, on reaction with methanol loses ethanethiol to give the methylorthobenzoate (**421**; equation 198).[908] Dialkoxydibutylstannanes convert dithiocarboxylic acid esters to orthoesters (**422**; equation 199).[909] From orthoesters and chloral the orthoesters (**423**; equation 200) can be synthesized.[910]

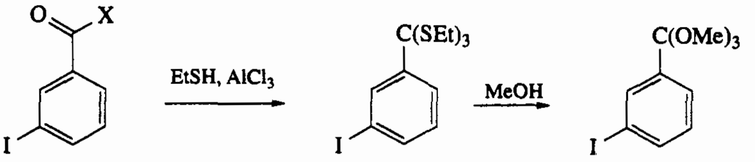

(198)

(**421**)

X = OMe, Cl

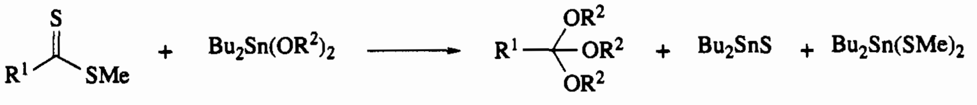

$$R^1C(=S)SMe + Bu_2Sn(OR^2)_2 \longrightarrow R^1C(OR^2)_3 + Bu_2SnS + Bu_2Sn(SMe)_2 \quad (199)$$

(**422**)

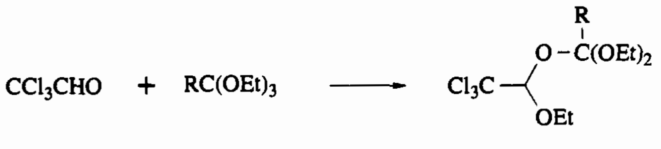

$$CCl_3CHO + RC(OEt)_3 \longrightarrow Cl_3C\text{-}CH(OEt)\text{-}O\text{-}C(R)(OEt)_2 \quad (200)$$

(**423**)

## 2.7.4.2 2,2-Bis(dialkoxy)carbonitriles

### 2.7.4.2.1 *From orthoesters, ketene* O,O*-acetals and cyanating reagents*

Orthoesters react with hydrocyanic acid, catalyzed by $ZnCl_2$, to give 2,2-dialkoxycarbonitriles (**424**; equation 201).[911] These nitriles can also be obtained by treatment of orthoesters with acyl cyanides[912] or trimethylsilyl cyanide in the presence of Lewis acids ($BF_3$, $SnCl_2$).[913–915] Cyanoselenation of ketene *O,O*-acetals affords the nitriles (**425**; Scheme 77),[916,917] from which other compounds of this type can be prepared, *e.g.* (**426**) and (**427**), by splitting off the phenylselenyl group. The acetonitrile derivative (**428**; equation 202) is a byproduct (23%) in the photochemical cycloaddition of ketene diethylacetal to 6-cyanouracil.[918]

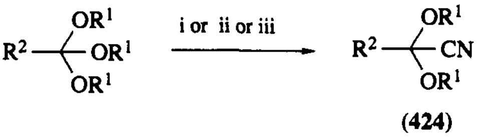
i or ii or iii

(424)

(201)

i, HCN, $ZnCl_2$; ii, $R^3COCN$; iii, $Me_3SiCN$, $SnCl_2$

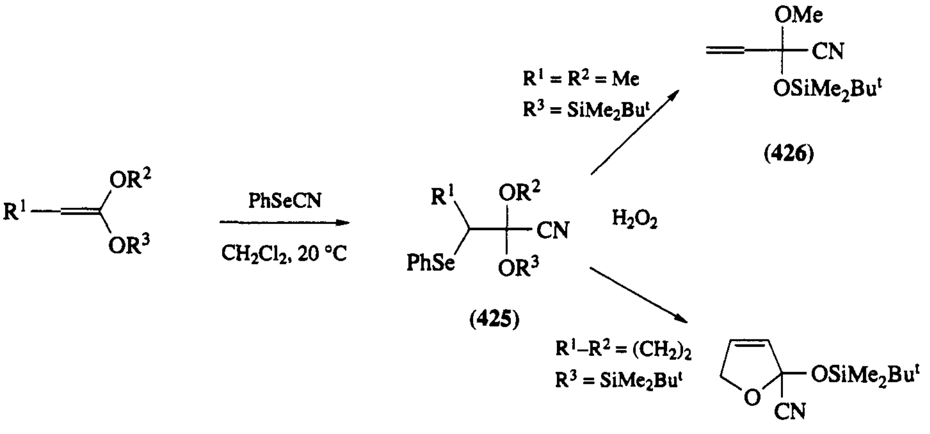
PhSeCN
$CH_2Cl_2$, 20 °C
$H_2O_2$
$R^1 = R^2 = Me$
$R^3 = SiMe_2Bu^t$
$R^1$-$R^2 = (CH_2)_2$
$R^3 = SiMe_2Bu^t$

(425) (426) (427)

Scheme 77

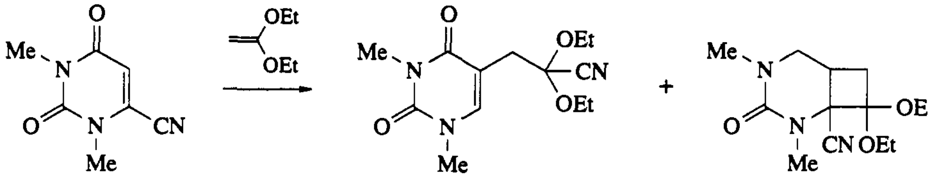

(428)

(202)

## 2.7.4.2.2 *From dialkoxyhalomethanes or dialkoxycarbenium salts*

Chlorodiphenoxymethane[919] as well as 1,3-dioxolanylium salts[920] react with suitable cyanides to give the corresponding nitriles (**429**) and (**430**) (Scheme 78), respectively. The cyanodioxolanes (**430**) can serve as cyanide carriers to noncylic carboxonium ions giving, for example, diethoxyacetonitrile (**431**).[921]

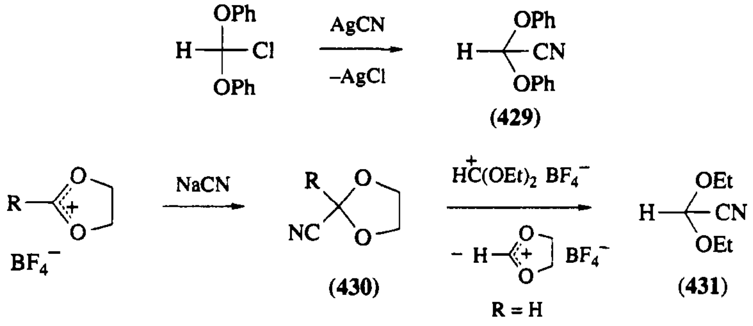
AgCN
-AgCl
NaCN
$H\overset{+}{C}(OEt)_2\ BF_4^-$
$BF_4^-$
R = H

(429) (430) (431)

Scheme 78

#### 2.7.4.2.3 Dehydration of 2,2-dialkoxycarboxylic acid amides

The dehydration of 2,2-dialkoxyacetamides can be achieved by means of $POCl_3$/pyridine or trifluoroacetic anhydride and furnishes 2,2-dialkoxyacetonitriles (**432**; equation 203).[922–926]

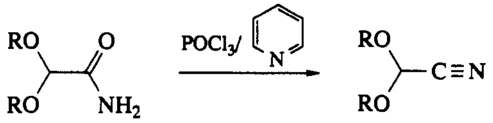
RO
RO
O
NH2
POCl3/
N
RO
RO
C≡N

(203)

**(432)**

### 2.7.4.3 Amide Acetals (Including Lactam Acetals)

#### 2.7.4.3.1 From amide halides (halomethyleneiminium salts)

*N*,*N*-Disubstituted chloromethyleneiminium chlorides (compare Section 2.7.2.2) react with alcoholic alkoxides at temperatures below 0 °C to give amide acetals (**433**; Scheme 79, yields 30–70%).[7–9,24,28,30,32,35] By the same method lactam acetals (**435**) are accessible. From dimethylformamide chloride and catechols the amide acetals (**434**) were prepared.[7,28,32,35] The bicyclic amide acetals (**436**) have been obtained from phenols, formamide and $POCl_3$.[927]

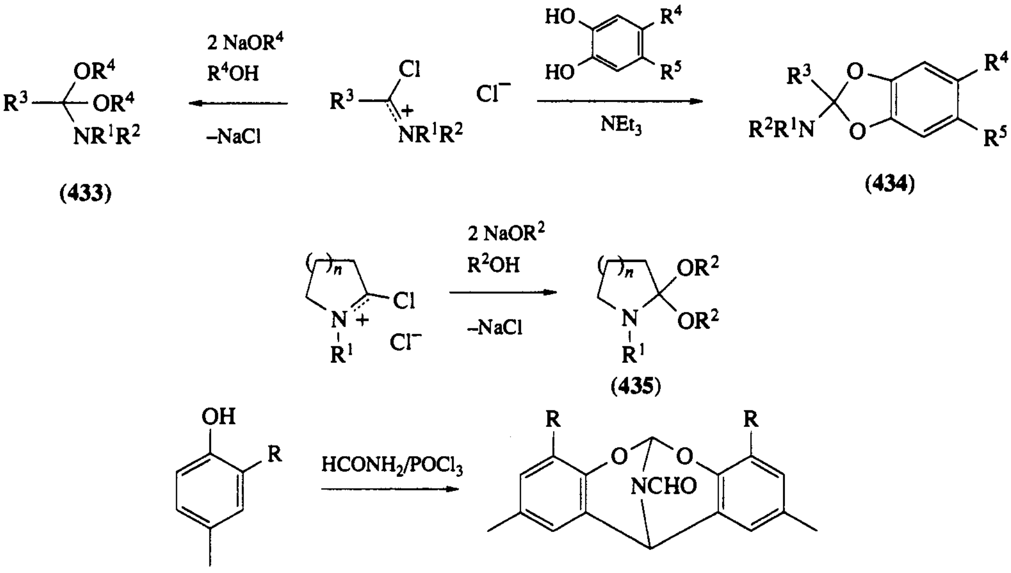
OR4
R3
OR4
NR1R2
2 NaOR4
R4OH
-NaCl
Cl
R3
+
NR1R2
Cl−
HO
HO
R4
R5
NEt3
R3
R2R1N
O
O
R4
R5
(433)
(434)
Cl
N +
R1
Cl−
n
2 NaOR2
R2OH
-NaCl
n
OR2
OR2
N
R1
(435)
OH
R
HCONH2/POCl3
R
R
O
O
NCHO
(436)

Scheme 79

In a usually less favorable procedure formamide acetals (**437**; equation 204) are accessible from chloroform or trichloroacetic acid esters and mixtures of secondary amines and alkoxides;[7,28,35] dichlorocarbene is thought to be an intermediate. Chloromethoxycarbene, generated from the diazirine (**438**; equation 205) inserts into the NH bond of diethylamine to yield the amide acetal (**439**).[928] The undissociated α,α-difluorotrialkylamines (**440**; Scheme 80) react with the alkali metal salts of diols to afford 1,3-dioxanes or 1,3-dioxolanes.[7,9,28,32,35,929,930] Noncyclic amide acetals can be prepared in the same manner.

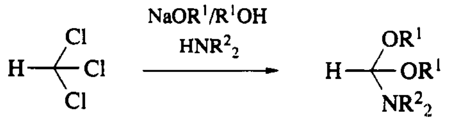
Cl
H
Cl
Cl
NaOR1/R1OH
HNR22
OR1
H
OR1
NR22

(204)

**(437)**

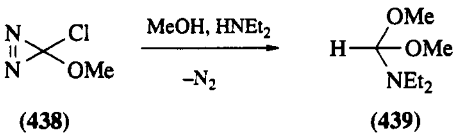

(205)

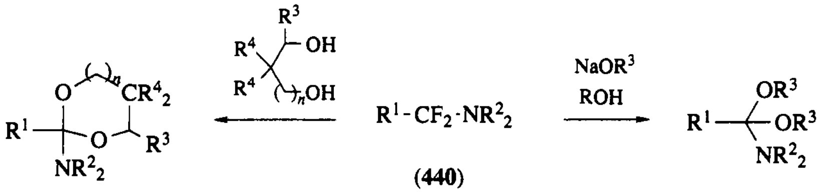

Scheme 80

### 2.7.4.3.2 *From alkoxymethyleneiminium salts*

*N*,*N*-Disubstituted alkoxymethyleneiminium salts are converted by alkoxides to amide acetals.[7,10,24,28,32,35,634,829,931] Usually the alkoxides are applied in alcoholic solution; however, if alkoxymethyleneiminium salts having aromatic or electron-attracting groups bound to nitrogen are used, it is favorable to use alcohol-free alkoxides suspended in solvents of low polarity, *e.g.* diethyl ether or THF, to avoid orthoester formation. Since alkoxymethyleneiminium salts are easy to obtain (see Section 2.7.2.3) this procedure is the most convenient method for the preparation of amide acetals and lactam acetals and has found widespread application.

One side reaction, which is regarded as thermodynamically controlled, in this synthesis can be ether formation by dealkylation of the alkoxymethyleneiminium salt (**441**; Scheme 81). This type of reaction dominates if bulky groups are present in the iminium compound or if the reaction temperature (which should be kept below 0 °C) was chosen too high. Another side reaction is ketene *O*,*N*-acetal formation by deprotonation of the iminium salt, which can become the main reaction provided acidifying groups are present in the α-position to the iminium group. By the same reaction sequence vinylogous amide acetals (**442**) have been synthesized.[28,32]

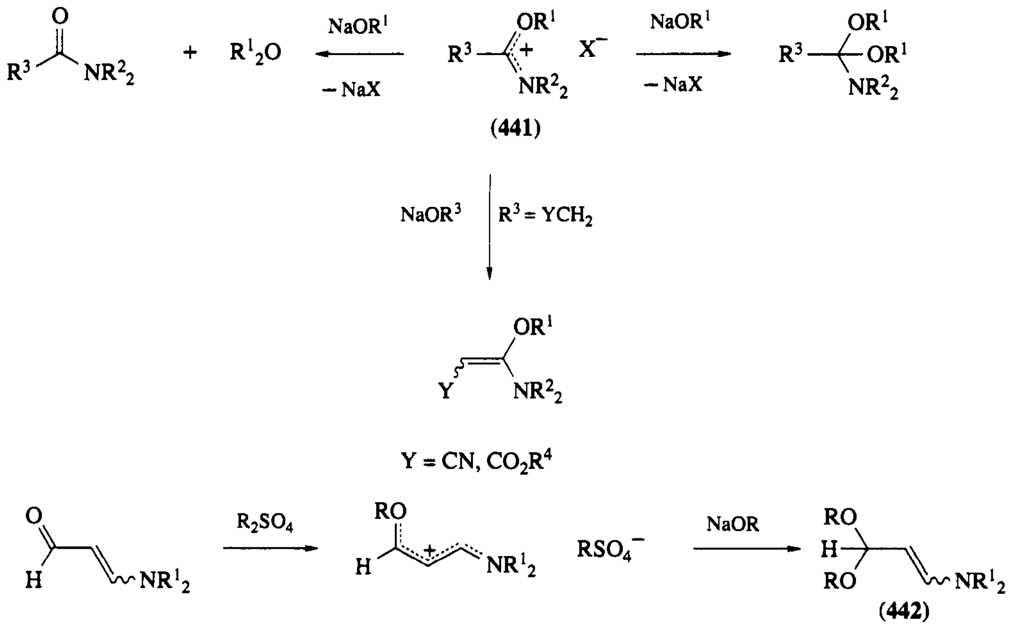

Scheme 81

Alkylmercaptomethyleneiminium salts as well as alkoxymethyleneiminium salts are transformed to amide thioacetals (**443**; equation 206) by alkali metal thiolates and thiols.[7,28,32,35] The action of alcoholic alkoxides on 2-alkoxy-2-dialkylaminocarbonitriles (**444**; equation 207) produces amide acetals.[7,634] Spirocyclic amide acetals (**446**; Scheme 82) were prepared from oxazolium salts (**445**) and substituted salicyl aldehydes.[932,933] The addition of alcohols to the 1,3-oxazolium-4-olate (**447**) affords heterocyclic amide acetals (**448**).[934]

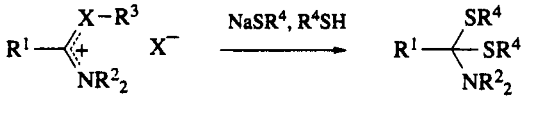
X−R³
R¹
+
X⁻
NR²₂
X = O, S
NaSR⁴, R⁴SH
SR⁴
R¹
SR⁴
NR²₂

**(443)** (206)

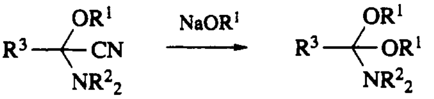
OR¹
R³
CN
NR²₂
NaOR¹
OR¹
R³
OR¹
NR²₂

**(444)** (207)

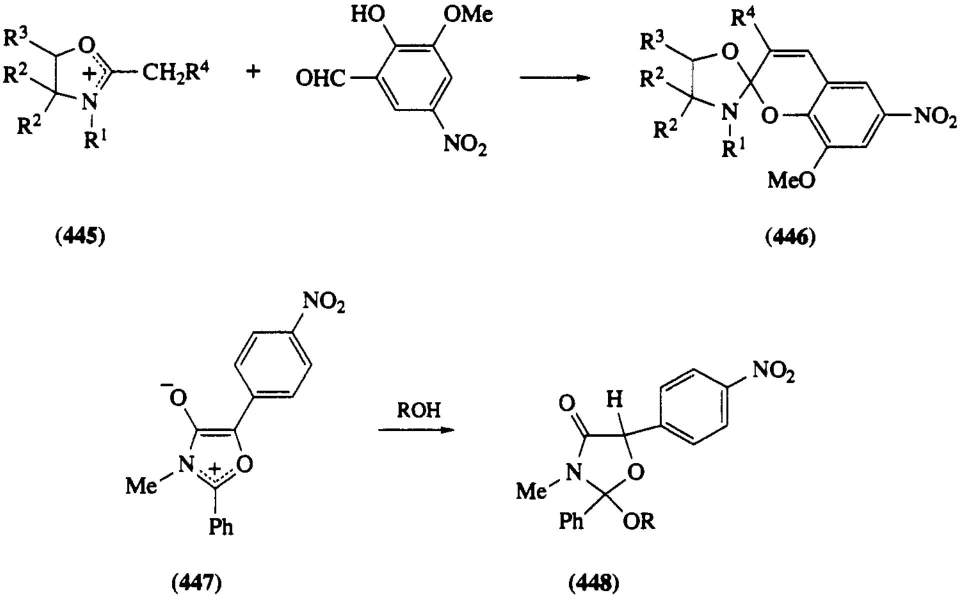
R³
O
R²
+
CH₂R⁴
R²
N
R¹
+
HO
OMe
OHC
NO₂
R⁴
R³
O
R²
N
O
NO₂
R²
R¹
MeO
NO₂
⁻O
N
+
O
Me
Ph
ROH
O
H
NO₂
N
O
Me
Ph
OR

**(445)** **(446)**

**(447)** **(448)**

**Scheme 82**

### *2.7.4.3.3 From amidinium salts*

An important synthesis for formamide acetals with bulky alkoxy groups or with *N*-aryl substituents starts from the corresponding formamidinium salts or from bis(dialkylamino)acetonitriles; the reaction with alcoholic alkoxides furnishes the amide acetals (**449**; Scheme 83).[7,14,28,32,35] In the reaction of the azavinylogous formamidinium salt (**450**) with methanolic methoxide a mixture of *N*,*N*-dimethylformamide dimethyl acetal and its azavinylogous derivative is produced.[14,28,29]

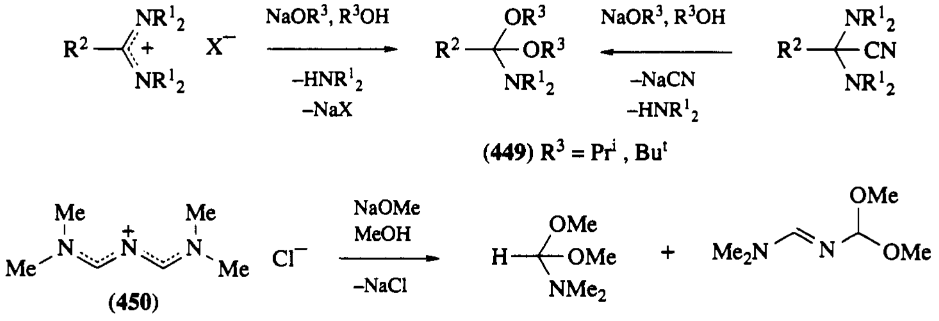

**Scheme 83**

### *2.7.4.3.4 By acetalization of amides; by addition reactions to nitriles, lactim ethers or* N*-acylimino esters*

The action of a Zn/Cu couple on 1,3-dibromo ketones and secondary amides yields 2-dialkylamino-1,3-dioxolanes (**451**; equation 208).[935] Fluorosulfonic peracid anhydride adds to trifluoroacetonitrile to give an 'amide acetal' (**452**; equation 209).[936] In the addition of (*Z*)-2-butene-1,4-diol to trichloroacetonitrile, catalyzed by sodium, the 1,3-dioxepin (**453**; equation 210) is produced.[937] Bicyclic amide acetals (**454**; equation 211) are byproducts in the reaction of lactim ethers with diketene.[938] The methyl esters of perfluorinated carboxylic acids react with diethanolamine to afford bicyclic amide acetals (**455**; equation 212).[939] Heating of maleic anilides (**456**; equation 213) with acetic acid anhydride/sodium acetate gives heterocyclic compounds (**457**) containing an amide acetal structure.[940]

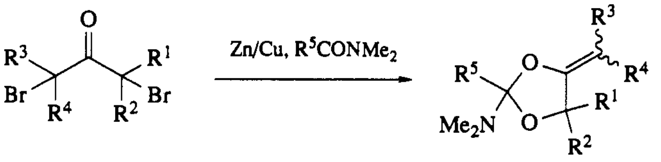

**(451)**

(208)

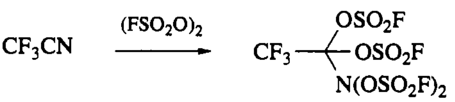

**(452)**

(209)

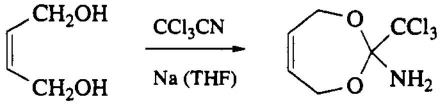

**(453)**

(210)

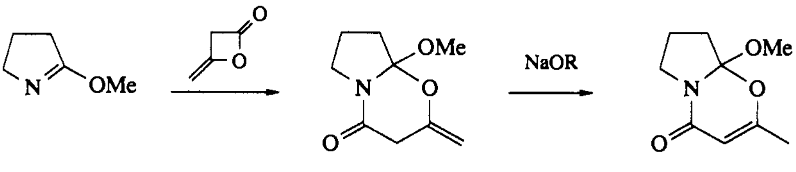

**(454)**

(211)

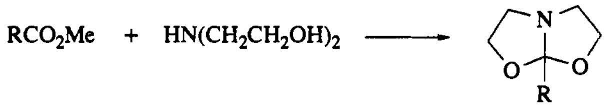
RCO2Me + HN(CH2CH2OH)2
N
O
O
R

**(455)** R = $CF_3$, $C_7F_{15}$

(212)

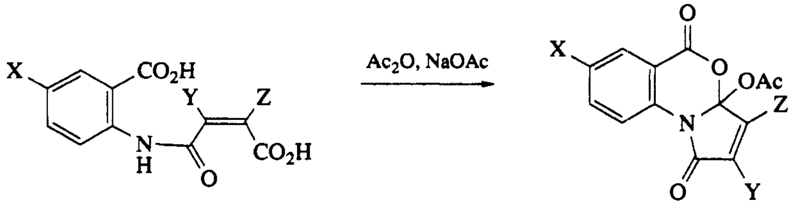
X
CO2H
Y
Z
N
H
O
CO2H
Ac2O, NaOAc
O
O
OAc
Z
N
O
Y

**(456)** **(457)**

(213)

### 2.7.4.3.5 *From orthoesters and related compounds*

In orthoesters (**458**; Scheme 84) one alkoxy group can be replaced by aminoacyl groups, by aminosulfonyl groups or by the 1-imidazolyl group on reaction with ureas,[941,942] imides,[943,944] salicylamide,[945] *N*-alkylsulfonamides[946,947] in the presence of Lewis acids[948,949] or with imidazoles[944,950,951] under acid catalysis.[950,951] Excess aryl isocyanates convert orthoformates to acetals of parabanic acid.[952]

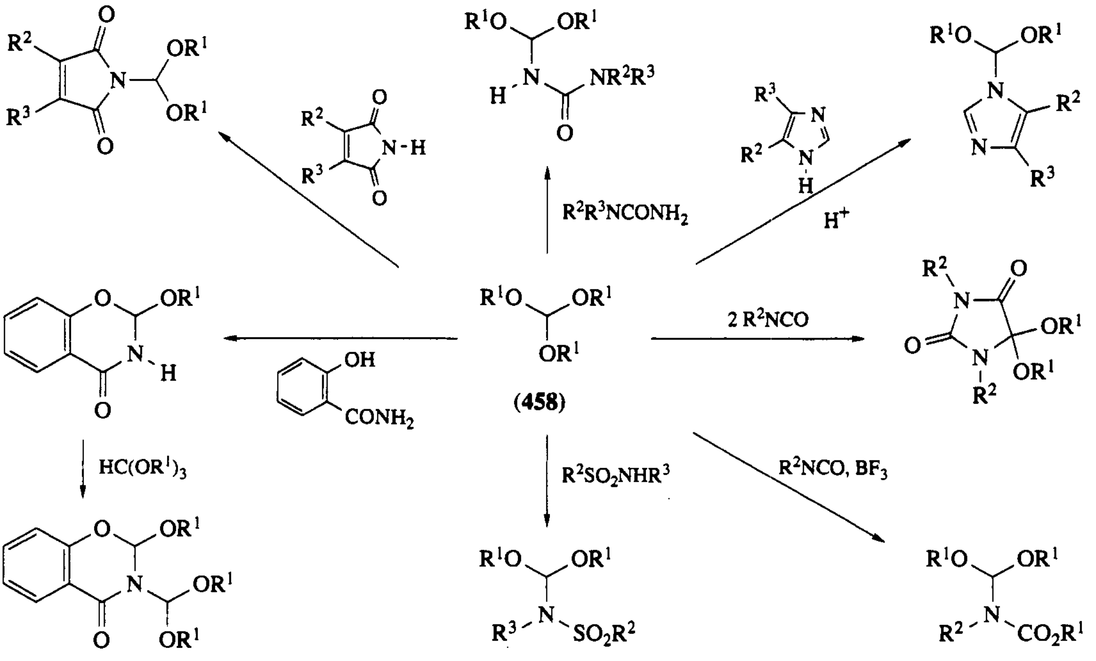
R²R³NCONH₂
H⁺
2 R²NCO
R²NCO, BF₃
R²SO₂NHR³
HC(OR¹)₃
(458)

Scheme 84

The reaction of chlorodiphenoxymethane with dimethylamine yields the amide acetal (**459**; equation 214).[953] Dialkoxymethyl groups can be transferred by means of dialkoxyalkyltriethylammonium tetrafluoroborate (**460**; equation 215) to primary amines and amides, amidines, secondary amines and amides once or twice to give amide acetals (**461**) and (**462**).[7,28,29] Azodiazoles, *e.g.* (**463**) and (**464**) (Scheme 85), add to ketene dimethylacetal to give lactam acetals.[954,955]

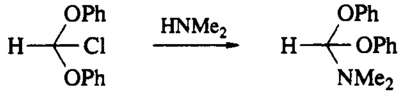

OPh
H
Cl
OPh
HNMe$_2$
OPh
H
OPh
NMe$_2$

**(459)**

(214)

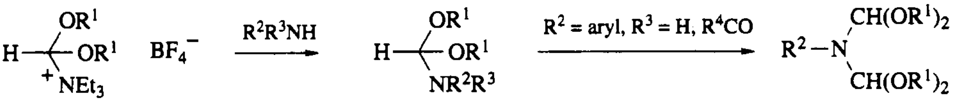

OR$^1$
H
OR$^1$
BF$_4^-$
$^+$NEt$_3$
R$^2$R$^3$NH
OR$^1$
H
OR$^1$
NR$^2$R$^3$
R$^2$ = aryl, R$^3$ = H, R$^4$CO
CH(OR$^1$)$_2$
R$^2$–N
CH(OR$^1$)$_2$

**(460)** **(461)** R$^2$ = R$^3$ = alkyl; **(462)**

R$^2$ = alkyl, R$^3$ = CH=NR;

R$^2$ = alkyl, R$^3$ = COR

(215)

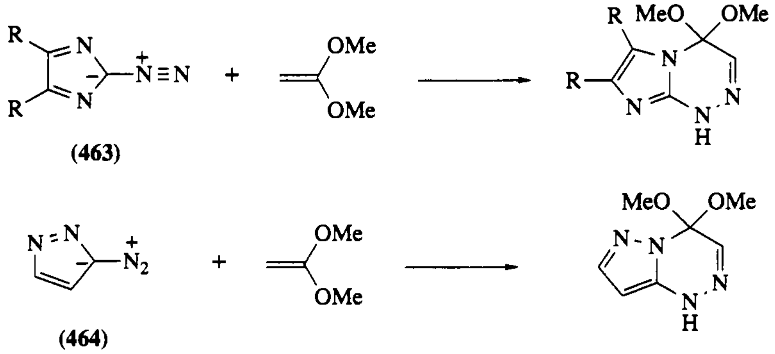

R
N
N
R
N≡N
+
OMe
OMe
R MeO OMe
R
N
N
N
N
H
N=N
N$_2$
+
OMe
OMe
MeO OMe
N-N
N
N
H

**(463)**

**(464)**

**Scheme 85**

### *2.7.4.3.6 From orthoamide derivatives and related compounds*

Transacetalization, usually starting from the dimethyl acetal, is an important method for the preparation of amide acetals (**465**; Scheme 86) with long chain or secondary alkyl groups.[7,24,28,31,32,35] Recently a method was described which allows the preparation of even the di-*t*-butyl acetal of DMF by transacetalization.[956] To achieve good yields it is necessary to drive the equilibrium reaction to completion by distilling off the alcohol formed. Cyclic acetals (**467**) or dithioacetals (**466**) can be more easily synthesized by transacetalization.[7,24,28,31,32,35]

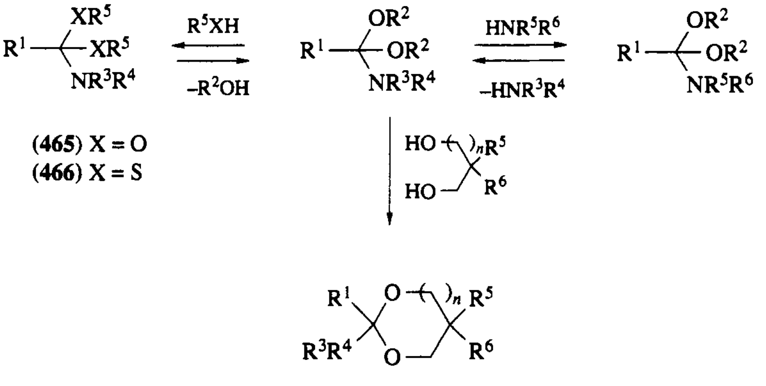

XR$^5$
R$^1$
XR$^5$
NR$^3$R$^4$
R$^5$XH
-R$^2$OH
OR$^2$
R$^1$
OR$^2$
NR$^3$R$^4$
HNR$^5$R$^6$
-HNR$^3$R$^4$
OR$^2$
R$^1$
OR$^2$
NR$^5$R$^6$
HO
$)_n$R$^5$
HO
R$^6$
R$^1$
O
$)_n$ R$^5$
R$^3$R$^4$
O
R$^6$

**(465)** X = O

**(466)** X = S

**(467)**

**Scheme 86**

Transamination of amide acetals is possible and of synthetic value if high boiling, strongly nucleophilic secondary amines are to be introduced.[7,957] Ketene *O,N*-acetals add alcohols to yield amide acetals (**468**; equation 216).[7,27–29,35] From tetrakis(dimethylamino)ethylene and methanol a mixture of amide acetals, *e.g.* (**469**) and (**470**; equation 217), is formed.[7,28,29,35] Azavinylogous formamide acetals (**471**; equation 218) are accessible by the action of formide acetals on tris(formylamino)methane[958] or formamide.[796]

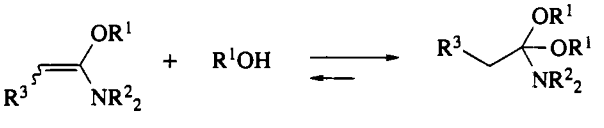

(216)

**(468)**

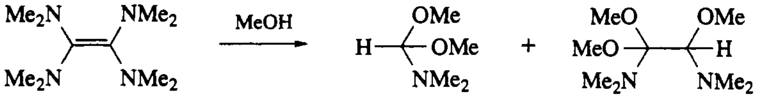

(217)

**(469)** **(470)**

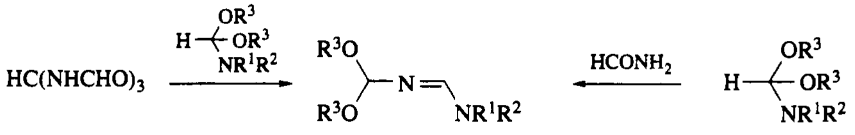

(218)

**(471)**

### 2.7.4.3.7 Miscellaneous methods

Photodecomposition of the diazo group containing acetals (**472**; Scheme 87) furnishes lactam acetals (**473**); similar compounds are accessible from ketenes and azidoformates.[7,27–29,35] From 1,3-dioxolanes and azidoformate the aminodioxolanes (**474**) were prepared.[7,27–29,35]

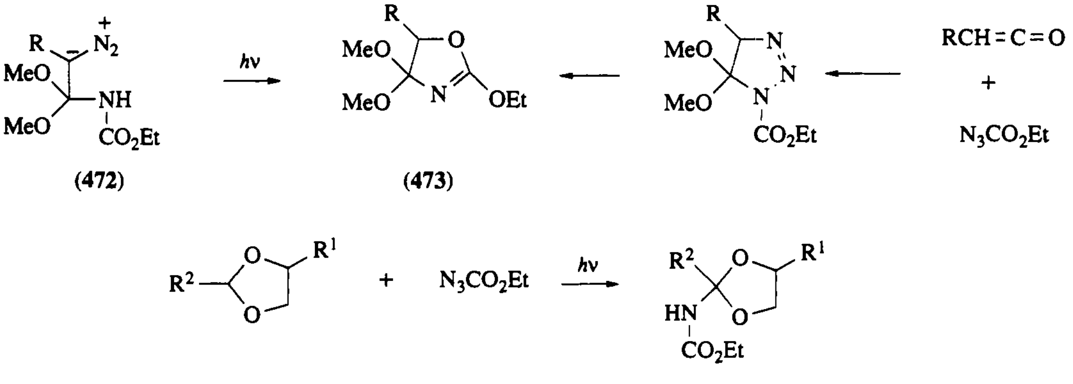

**(472)** **(473)** **(474)**

Scheme 87

The electrolysis of DMF in alcohols affords a product mixture in which amide acetals, *e.g.* (**475**) and (**476**) (equation 219), are present.[959] The heterocyclic amide acetal (**479**; equation 220) was obtained by reaction of the ynamine (**478**) with the *o*-quinonimine derivative (**477**).[960] An azomethine ylide, generated *in situ* from the iminium salts (**480**; equation 221), transforms *m*-nitrobenzaldehyde to the oxazolidine derivative (**481**).[961]

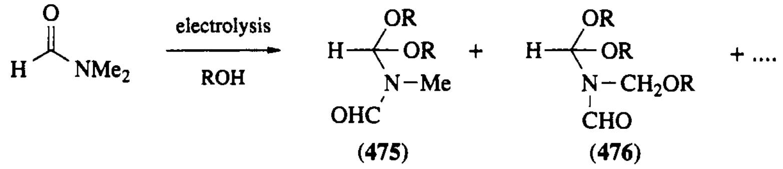
electrolysis
ROH
NMe2
OR
N-Me
OHC
(475)
N-CH2OR
CHO
(476)
+ ....

(219)

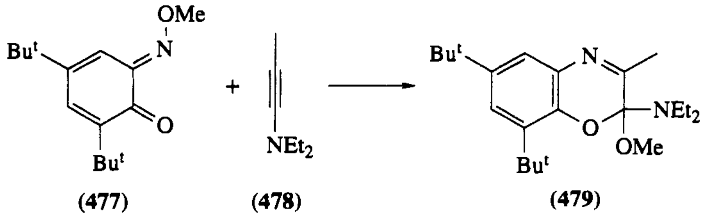
OMe
Bu^t
O
NEt2
(477)
(478)
(479)
OMe

(220)

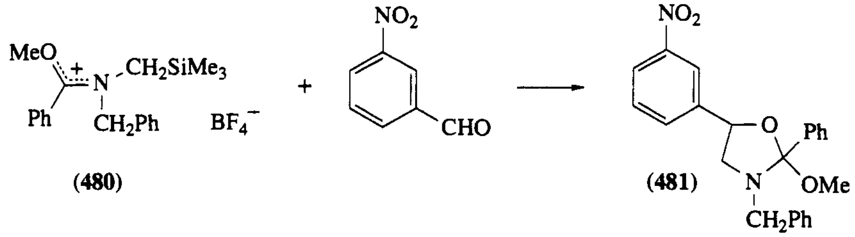
MeO
CH2SiMe3
Ph
CH2Ph
BF4−
(480)
NO2
CHO
(481)
Ph
OMe
CH2Ph

(221)

### 2.7.4.4 2-Alkoxy-2-dialkylaminocarbonitriles

#### *2.7.4.4.1 From amide acetals and cyanating reagents*

Amide acetals on treatment with hydrocyanic acid,[28,29,35,962] acyl cyanides[28,29,45] or trimethylsilyl cyanide[963] yield 2-alkoxy-2-dialkylaminocarbonitriles (**482**; Scheme 88). A similar cleavage has been performed with azavinylogous amide acetals (**483**).[798]

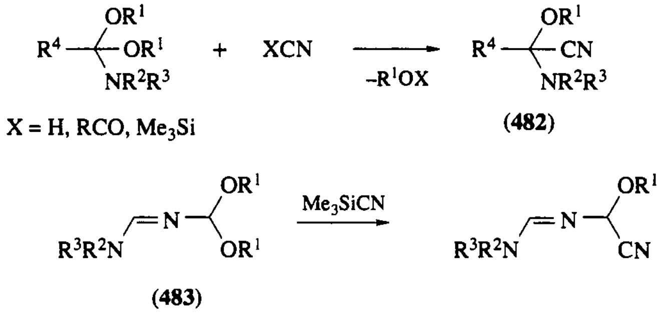
OR1
R4
OR1
NR2R3
+ XCN
-R1OX
CN
X = H, RCO, Me3Si
(482)
R3R2N
Me3SiCN
(483)

Scheme 88

#### *2.7.4.4.2 From alkoxymethyleneiminium salts and alkali metal cyanides*

In the most favorable preparative method for the synthesis of nitriles (**482**; equation 222) alkoxymethyleneiminium salts serve as starting materials, their reaction with alkali metal cyanides in a two-phase system (water/benzene or water/cyclohexane) affords the desired compounds in good yields.[28,29,35,962] An analogous reaction has been performed in acetonitrile.[964]

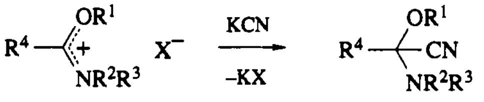

$X = MeSO_4, BF_4$ **(482)**

(222)

### *2.7.4.4.3 From alkoxydialkylaminoacetonitriles*

On heating with higher boiling alcohols alkoxy group exchange occurs in the nitriles (**484**; equation 223), thus furnishing new nitriles (**485**).[962]

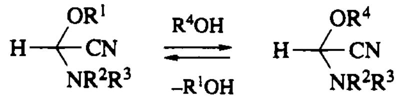

**(484)** **(485)**

(223)

## 2.7.4.5 Aminal Esters (Bis(dialkylamino)alkoxyalkanes)

### *2.7.4.5.1 From 1,1,1-trihaloalkanes or orthoesters*

In the presence of alkoxides chloroform reacts with secondary amines or aziridines to yield a mixture of aminal esters (**486**), amide acetals (**487**) and tris(dialkylamino)methanes (**488**; equation 224). Predominantly aminal esters (**489**; equation 225) are formed in the reaction of dichloromethyl ether with aziridines and sodium hydroxide.[7,28,29,35] The heterocyclic aminal ester (**491**; equation 226) was prepared from the perimidine (**490**) and triethyl orthoformate.[965]

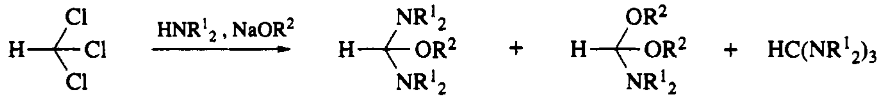

**(486)** **(487)** **(488)**

(224)

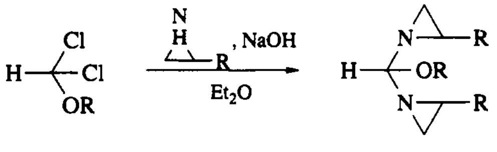

**(489)**

(225)

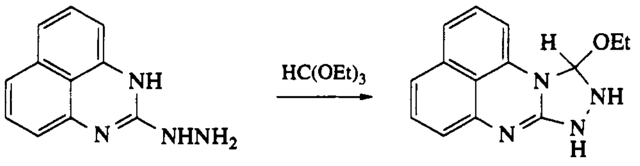

**(490)** **(491)**

(226)

### *2.7.4.5.2 From acid amides, lactamidines and cyclic imino esters*

By electrolysis of 2-bromoamides in DMF the aminal esters (**492**; Scheme 89) are accessible.[966] In the reaction of benzoylphenyl ketene with the isoquinolinedione (**493**) the heterocyclic aminal ester (**494**) is formed.[967] Another heterocyclic aminal ester (**496**) was obtained from a hydrazinoyl chloride and a benzoxazine derivative (**495**).[968]

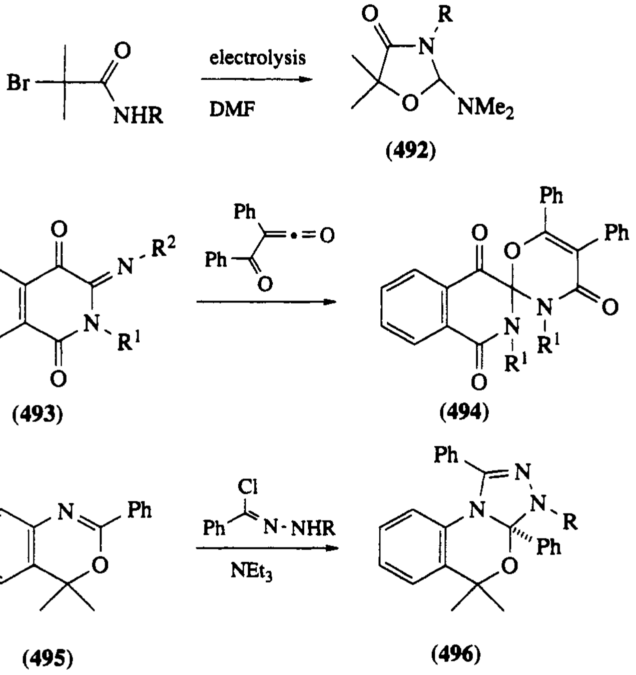
Br
O
NHR
electrolysis
DMF
O
R
N
O
NMe2
(492)
O
N
R2
N
R1
O
(493)
Ph
Ph
O
Ph
O
O
Ph
Ph
N
O
N
R1
R1
O
(494)
N
Ph
O
(495)
Cl
Ph
N-NHR
NEt3
Ph
N
N
N
R
Ph
O
(496)

**Scheme 89**

### *2.7.4.5.3 From amidinium salts and related compounds*

*N,N,N′,N′*-Tetraalkylformamidinium salts[7,28,29,35] and *N,N′*-dimethyl-*N,N′*-diphenylformamidinium tetrafluoroborate[7,28,29,35] in ether, hexane, benzene or cyclohexane, have been treated with alcohol-free alkoxides to yield aminal esters (**497**; Scheme 90). By a similar procedure aminal esters (**498**) were obtained from 2,2-bis(dialkylamino)carbonitriles in good yields.[7,28,29,35]

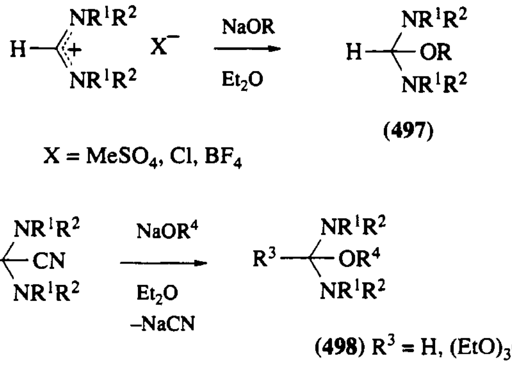
NR1R2
H
+
NR1R2
X−
NaOR
Et2O
NR1R2
H
OR
NR1R2
(497)
X = MeSO4, Cl, BF4
NR1R2
R3
CN
NR1R2
NaOR4
Et2O
−NaCN
NR1R2
R3
OR4
NR1R2
(498) R3 = H, (EtO)3C

**Scheme 90**

2,4,5-Tris(diethylamino)imidazolium chloride adds ethoxide to give the heterocyclic aminal ester (**499**; Scheme 91).[969,970] Treatment of 3-bromo-3-phenyldiazirine with methoxide at low temperatures affords the labile 3-methoxy-3-phenyldiazirine (**500**),[971] which can be regarded, from its substitution pat-tem, as an aminal ester. From vinylogous[7,28,29,35,972] and azavinylogous amidinium salts[973] the corresponding aminal esters (**501**) are accessible.

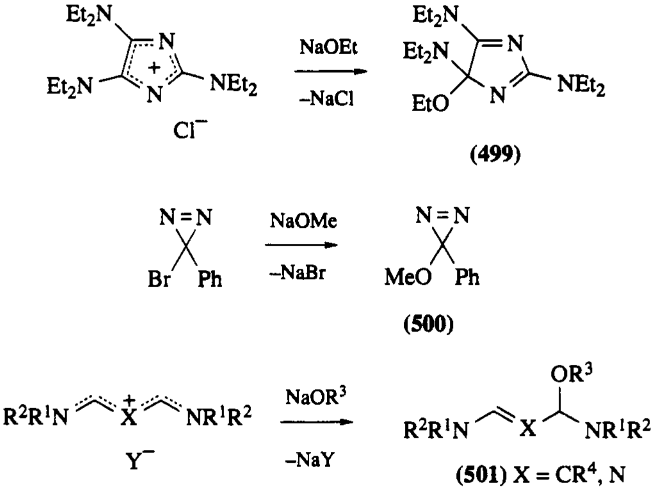
(**499**)

(**500**)

(**501**) X = CR$^4$, N

**Scheme 91**

### 2.7.4.5.4 *From orthoamide derivatives and related compounds*

Amide acetals react with isocyanates and isothiocyanates to form *O,N*-acetals of parabanic acid (**502**) or dithioparabanic acid (**503**; Scheme 92).[7,28,29,35] The same type of compounds can be prepared from isocyanates and 2-alkoxy-2-dialkylaminoacetonitriles.[802] From bis(trimethylsilyl)acetamide and isocyanates the heterocyclic aminal esters (**504**) were obtained.[974] Alcoholysis of trisaminoalkane derivatives furnishes aminal esters.[974] This method is only of interest if the trisamino compound is easy to prepare, *e.g.* (**505**; equation 227).[801,802] In transamination reactions of amide acetals aminal esters (**506**) and (**507**) (equation 228) are formed among other products.[7,28,29,35,975]

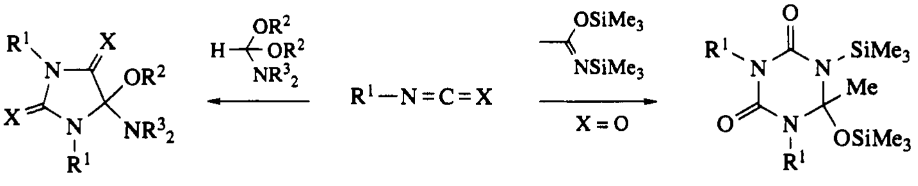
(**502**) X = O
(**503**) X = S

**Scheme 92**

(**504**)

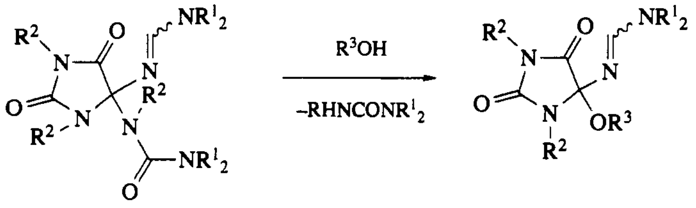
(**505**)

(227)

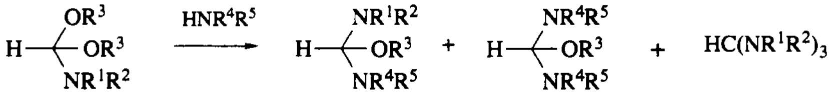
(**506**) (**507**)

(228)

### *2.7.4.5.5 Miscellaneous methods*

2-Aminopyridine reacts with α-alkoxy-α-chloroalkyl isocyanates (**508**) to give heterocyclic aminal esters (**509**; equation 229).[976]

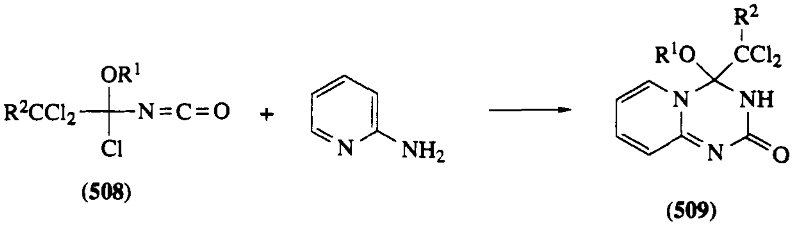

(**508**) (**509**) (229)

## 2.7.4.6 2,2-Bis(dialkylamino)carbonitriles

### *2.7.4.6.1 From 2,2-dihalocarbonitriles and amines*

Dibromoacetonitrile reacts with morpholine to form bis(morpholino)acetonitrile (**510**; Scheme 93).[28,29,35,977] The acrylonitriles (**511**) are cyclized to the imidazolines (**512**) by treatment with NCS and nicotinic acid amide.[978]

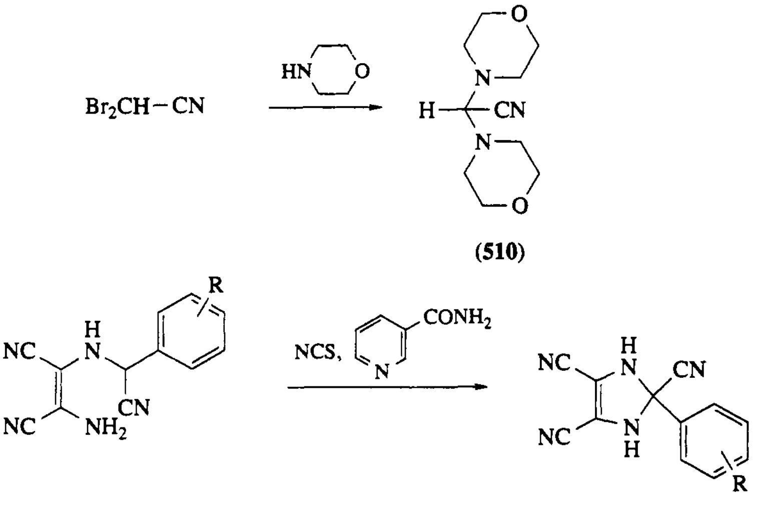

Scheme 93

### *2.7.4.6.2 From secondary amines and hydrocyanic acid*

Alicyclic amines react with water-free HCN, probably *via* amidines (**513**; equation 230) and trisaminomethanes (**514**), to yield the corresponding bis(dialkylamino)acetonitriles (**515**).[28,29,35,977,979]

### *2.7.4.6.3 From ketene aminals, aminal esters and tris(dialkylamino)alkanes*

Hydrocyanic acid adds to bis(dimethylamino)ethylene (**516**) to give 2,2-bis(dimethylamino)propionitrile (**517**; Scheme 94).[28,29,35,977] By cleavage of aminal esters with acyl cyanides or hydrocyanic acid α,α-diaminonitriles (**518**) are accessible; trisaminomethanes have also been cleaved by HCN to give nitriles (**518**).[28,29,35,977]

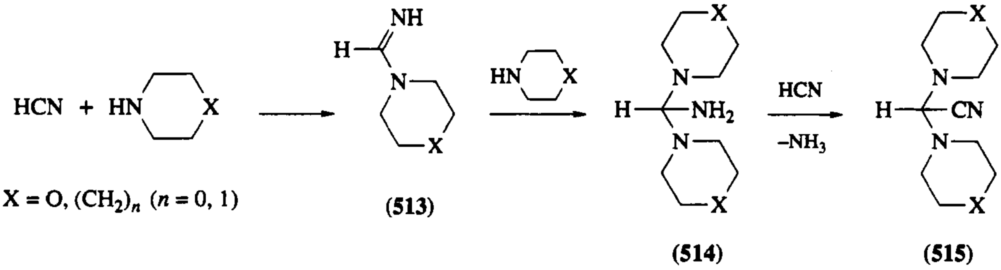

**(513)** **(514)** **(515)** (230)

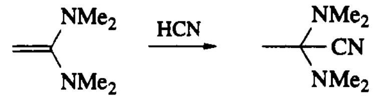

**(516)** **(517)**

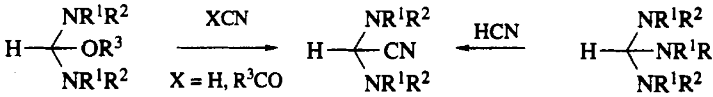

**(518)**

**Scheme 94**

### 2.7.4.6.4 *From amidinium salts and alkali metal cyanides*

In a two-phase system (water/cyclohexane) amidinium salts react with alkali metal cyanides to form bis(dialkylamino)carbonitriles (**519**; equation 231).[28,29,35,977] With the aid of tetraethylammonium cyanide the aziridinium salt (**520**; equation 232) was transformed to the nitrile (**521**).[980]

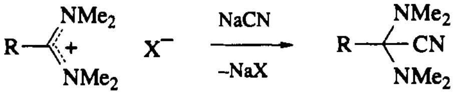

**(519)** (231)

$R = H, X = MeSO_4$

$R = CCl_3, X = BF_4$

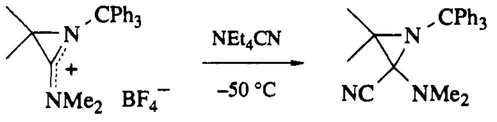

**(520)** **(521)** (232)

### 2.7.4.6.5 *From 2-alkoxy-2-dialkylaminocarbonitriles and related compounds*

On treatment with secondary amines 2-alkoxy-2-dialkylaminocarbonitriles readily exchange their alkoxy groups *versus* dialkylamino groups; mixed substituted nitriles (**522**; equation 233) can be prepared in this way.[28,29,35,977] At elevated temperatures an exchange of the amino group occurs additionally. This procedure is useful in the preparation of nitriles bearing alicyclic amino groups.[28,29,35,977,981]

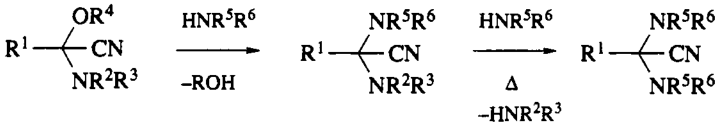

(522)

(233)

### *2.7.4.6.6 Miscellaneous methods*

Thionylbisimidazolide (**523**) reacts with benzoyl cyanide to give α,α-bis(imidazolyl)benzyl cyanide (**524**; equation 234).[982]

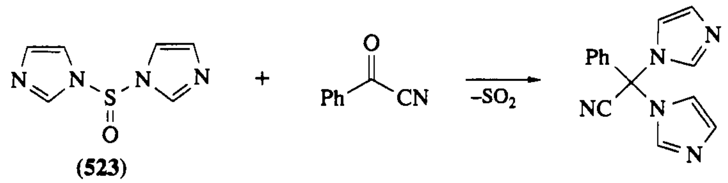

(523)

(524)

(234)

## 2.7.4.7 Tris(dialkylamino)alkanes

### *2.7.4.7.1 From 1,1,1-trihaloalkanes, amide halides and related compounds*

The reaction of chloroform with imidazoles,[983,984] benzimidazoles[985] and secondary amines (especially alicyclic amines) in the presence of alkoxides or hydroxides, as well as the reaction of chlorodifluoromethane with sodium *N*-alkyl-*N*-arylamides furnishes trisaminomethanes (**525**) and (**526**) (Scheme 95), respectively.[7,28,29,35] Aziridine transforms fluorodialkyl sulfide (**527**) to the orthoamide (**528**; equation 235).[7]

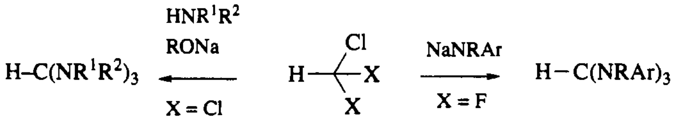

(525)

(526)

**Scheme 95**

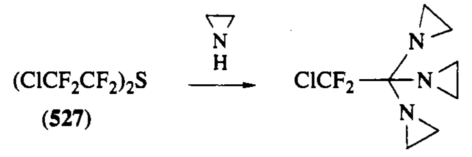

(527)

(528)

(235)

### *2.7.4.7.2 From amides, amidines and imidates*

Tetrakis(dimethylamino)titanium converts DMF to tris(dimethylamino)methane (**529**; equation 236).[7,28,29,35] This compound is also formed in the reaction of *N,N,N',N'*-tetramethyloxamide with the titanium reagent,[7] whereas amides which have α-CH bonds are converted to ketene aminals.[7,28,29,35] Cyclic and spirocyclic compounds, containing the substitution pattern of a trisamino compound, are formed in the reaction of *N,N*-dialkylformamides or *N'*-aryl-*N,N*-dialkylformamidines with aryl isocyanates.[7] Similar compounds, *e.g.* (**530**; equation 237), are produced in the reaction of imidazolines[986] or lactamidines[987] with isocyanates.

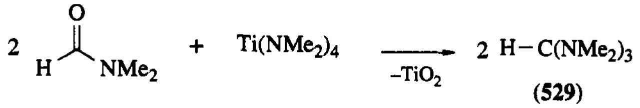

**(529)**

(236)

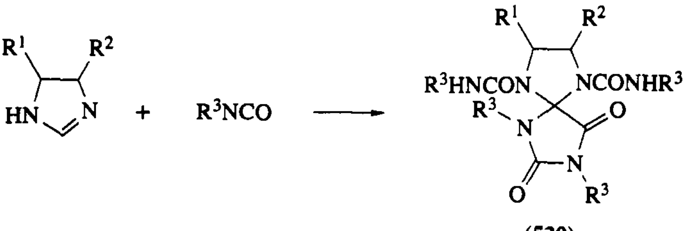

**(530)**

(237)

### 2.7.4.7.3 From amide halides and related compounds

*N,N*-Dimethylformamide chloride reacts with the alkali metal salts of phthalimide, saccharin or dimethylamine to give trisaminomethanes, *e.g.* (**531**), (**532**) and (**529**), respectively.[7,28,29,35] The preparation of tris(formamido)methane (**533**; equation 239) proceeds *via* iminium salts, which are formed as intermediates in the reaction of alkylating reagents (dialkyl sulfates, sulfonic acid esters, oxonium salts) or acylating reagents ($POCl_3$, $PCl_3$, $SO_2Cl_2$) with formamide.[7,28,29,35]

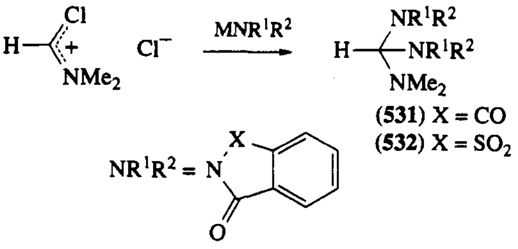

**(531)** X = CO
**(532)** X = SO$_2$

(238)

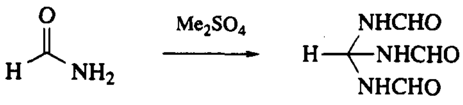

**(533)**

(239)

### 2.7.4.7.4 From amidinium salts or 2,2-bis(dialkylamino)carbonitriles

*N,N,N′,N′*-Tetrasubstituted formamidinium salts as well as bis(dialkylamino)acetonitriles have been reacted with alkali metal amides of secondary amines to give tris(dialkylamino)methanes (**534**; Scheme 96).[7,28,29,35]

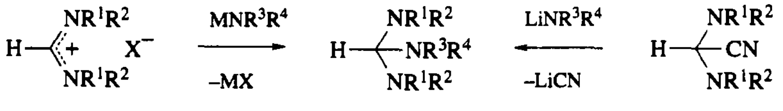

**(534)**

**Scheme 96**

### 2.7.4.7.5 From orthoesters, orthoamides and related compounds

Orthoformates have been reacted with secondary aliphatic amines,[7,28,29,35] *N*-alkylanilines,[7] 1,3,5-triaminocyclohexanes[7] and cyclic triamines[988,989] to afford trisaminomethane derivatives, *e.g.* (**535**) and (**536**) (Scheme 97), usually in unsatisfactory yields. Better results have been reported when orthoformates were replaced by amide acetals.[988,990,991]

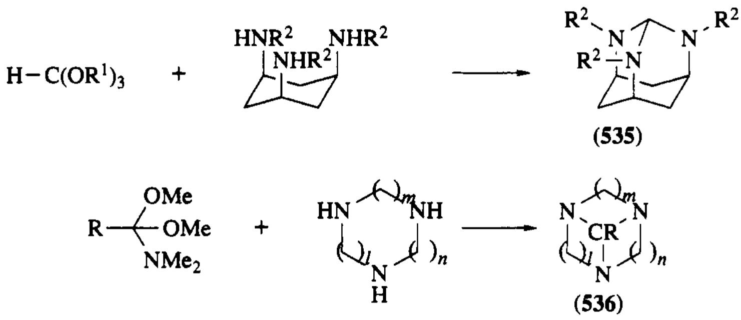
H−C(OR¹)₃
+
HNR² NHR²
NHR²
R²
N
N
R²
R²−N
(535)
OMe
R—OMe
NMe₂
+
HN
NH
m
N
H
n
N
N
CR
N
m
n
(536)

Scheme 97

In the acid-catalyzed reactions of orthoformates with primary carbon acid amides or urethanes tris(acylamino)methanes (**537**; Scheme 98) are formed with good yields.[7,28,29,35] Dimethylaminodi(phthalimido)methane (**531**) is accessible from phthalimide and DMF diethyldithioacetal.[7] Lithium dimethylamide, prepared *in situ* from lithium and dimethylamine in HMPA converts orthoformates to tris(dimethylamino)methane (**529**).[28]

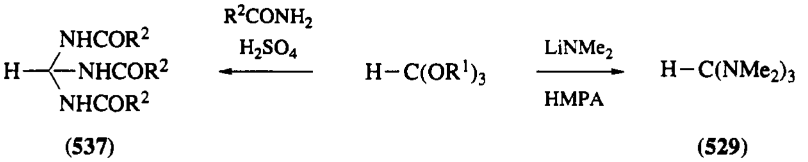
NHCOR²
H—NHCOR²
NHCOR²
(537)
R²CONH₂
H₂SO₄
H−C(OR¹)₃
LiNMe₂
HMPA
H−C(NMe₂)₃
(529)

Scheme 98

On heating amide acetals (**538**; equation 240), or better aminal esters, with amines (preferably alicyclic amines) an equilibrium with the corresponding trisaminomethane is established. To achieve good yields of the orthoamide it is necessary to distill off the alcohol formed. Tris(dimethylamino)methane (**529**) is readily transaminated with high-boiling amines to give orthoamides, *e.g.* (**539**) and (**540**) (Scheme 99).[7] Parabanic acid aminals (**541**; equation 241) are formed in good yields in the reaction of 2,2-bis(dialkylamino)acetonitriles with isocyanates.[801,802]

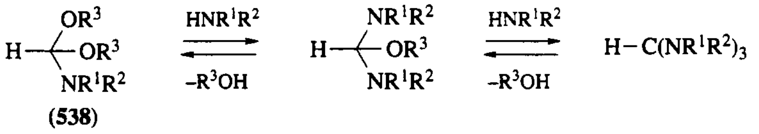
OR³
H—OR³
NR¹R²
(538)
HNR¹R²
-R³OH
NR¹R²
H—OR³
NR¹R²
HNR¹R²
-R³OH
H−C(NR¹R²)₃

$$\mathrm{H{-}C(OR^3)_2(NR^1R^2)} \underset{-\mathrm{R^3OH}}{\overset{\mathrm{HNR^1R^2}}{\rightleftharpoons}} \mathrm{H{-}C(OR^3)(NR^1R^2)_2} \underset{-\mathrm{R^3OH}}{\overset{\mathrm{HNR^1R^2}}{\rightleftharpoons}} \mathrm{H{-}C(NR^1R^2)_3} \qquad (240)$$

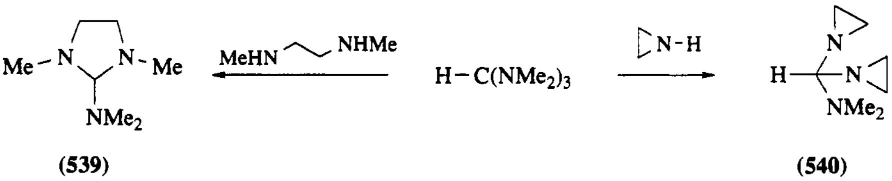
Me
N
N
Me
NMe₂
(539)
MeHN
NHMe
H−C(NMe₂)₃
N−H
N
H—N
NMe₂
(540)

Scheme 99

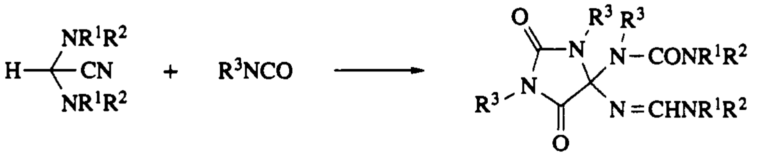

**(541)**

(241)

### 2.7.4.7.6 From guanidinium salts or orthocarbonic acid derivatives

*N,N,N′,N′,N″,N″*-Hexamethylguanidinium chloride (**542**; Scheme 100) is readily reduced by means of NaH in the presence of sodium alkoxyaluminates, boronic acid esters or aluminum alkoxides.[7] Organometallic derivatives such as phenyllithium, 2-thienyllithium or 2-furanyllithium or sodium acetylides add to the guanidinium salt to give the corresponding orthoamides. From tetrakis(dimethylamino)methane and phenylacetylene 1-phenyltris(dimethylamino)-1-propyne (**543**; equation 242) was prepared.[992]

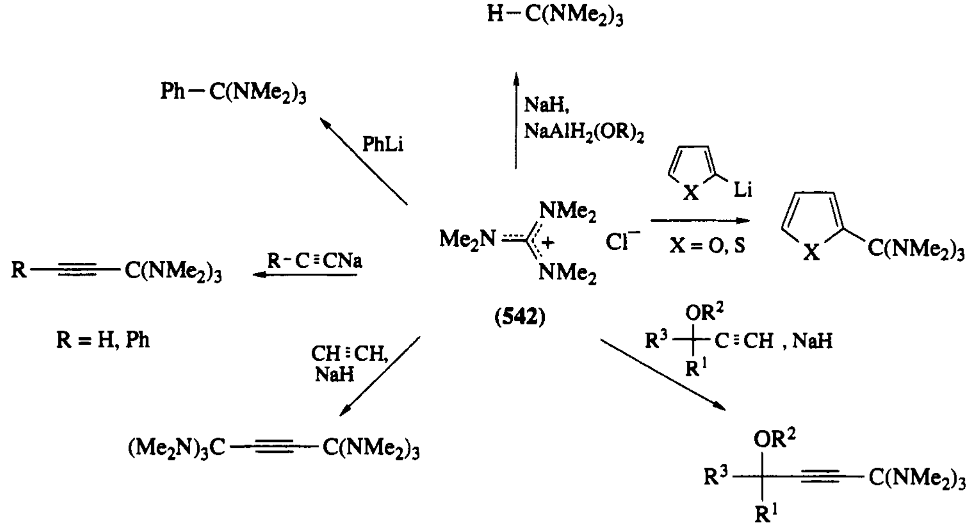

H−C(NMe2)3
NaH, NaAlH2(OR)2
Ph−C(NMe2)3
PhLi
Li
X
X = O, S
C(NMe2)3
Me2N
NMe2
Cl⁻
(542)
R−≡−C(NMe2)3
R−C≡CNa
R = H, Ph
CH≡CH, NaH
(Me2N)3C−≡−C(NMe2)3
OR2
R3
R1
C≡CH, NaH

**Scheme 100**

$$\mathrm{C(NMe_2)_4} \xrightarrow{\mathrm{Ph}-\equiv} \mathrm{Ph}-\equiv-\mathrm{C(NMe_2)_3} \qquad (242)$$

**(543)**

### 2.7.4.7.7 From ketene aminals

Hydrazinoyl chlorides react with ketene aminals in the presence of triethylamine to give diaminopyrazolines (**544**; equation 243).[993] From tetraaminoethylenes and amines or amine derivatives or heterocumulenes tris(amino)methane derivatives, *e.g.* (**545**) and (**546**) (Scheme 101) are formed. Reactions of this type have been reviewed.[994]

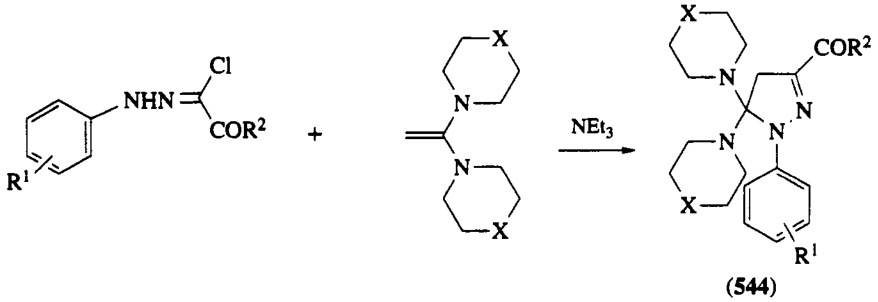

**(544)**

(243)

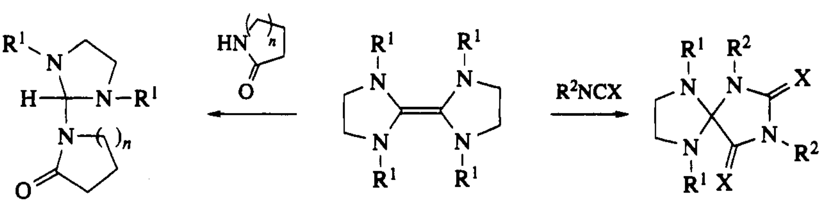

(545)

(546)

Scheme 101

### 2.7.4.7.8 Miscellaneous methods

Heterocyclic compounds possessing the structural pattern of orthoamides were obtained by spirocyclization of isocyanates in the presence of triethylsilane catalyzed by a ruthenium cluster (equation 244).[995,996]

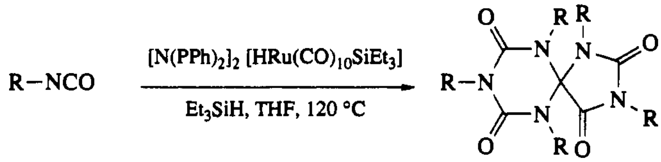

(244)

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# 2.8
# Inorganic Acid Derivatives

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## 2.8.1 INTRODUCTION

An organic phosphoric acid is a well recognized structural unit appearing in a number of biologically important substances such as nucleic acids, phospholipids, and inositol phosphates, and, accordingly, efforts to construct the structure have extensively been made so far, providing many ways to the organic phosphoric acid derivatives.[1] Among the existing methods, the most straightforward and synthetically useful one is phosphorylation of protic substances. In phosphorylation, of great importance is discovery of effective phosphorylating agents. In addition, invention of the protecting groups for a phosphoric acid moiety is sometimes an essential problem, because the many important classes of biochemical substances discussed above are phosphomonoesters or phosphodiesters, which generally are derived by deprotection of the corresponding phosphotriester precursors. This chapter describes methods of phosphorylation, which are classified by the type of phosphorylating agents employed, and makes brief discussion on the protecting groups.

## 2.8.2 USE OF PENTAVALENT PHOSPHORUS REAGENTS

Pentavalent phosphorus compounds with a suitable leaving group, listed below, serve effectively as phosphorylating agents for some protic substrates such as alcohols, phenols, primary and secondary amines, thiols, phosphates, *etc.*

### 2.8.2.1 Halophosphates

Three types of chlorophosphates, *i.e.* phosphorus oxychloride ($POCl_3$), phosphorodichloridates [$(RO)POCl_2$], and phosphorochloridates [$(RO)_2POCl$], are among the most widely employed phosphorylating agents for the synthesis of organic phosphoric acid derivatives.[2] The reaction with chlorophosphates is usually promoted by tertiary amines, including trialkylamines, pyridine and its analogs, DBU, *N*-alkylazoles, *etc.* Use of 1-methyl-5-chloroimidazole effects phosphorylation of sterically hindered alcohols (equation 1).[3] In place of amines, molecular sieves can be used as acid scavengers.[4] Trialkyl phosphates also assist the phosphorylation (equation 2).[5] Less reactive phosphorofluoridates are usable for some limited cases. The reagents cannot be activated by the ordinarily used amines such as trialkylamines, pyridine and related compounds,[6] but are effected by use of DBU as a base (equation 3).[7] There is little example of phosphorylation using bromophosphates.

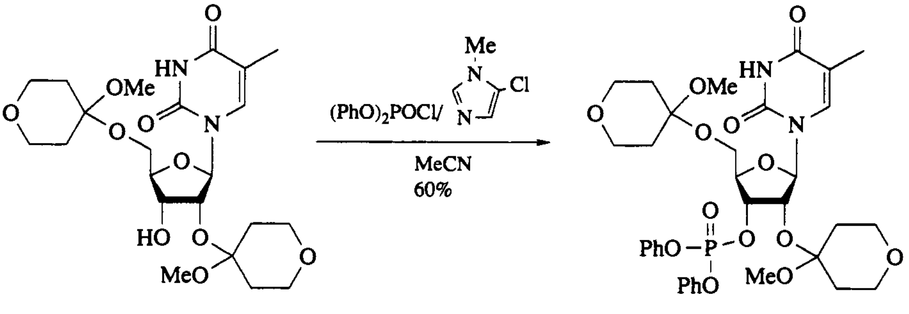

(1)

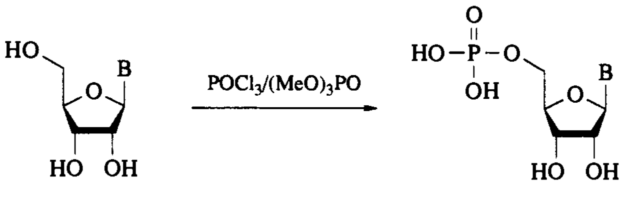

(2)

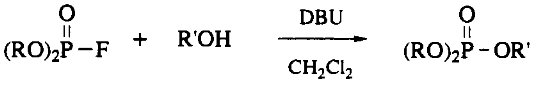

$$(RO)_2\overset{O}{\overset{\|}{P}}-F \;+\; R'OH \xrightarrow[CH_2Cl_2]{DBU} (RO)_2\overset{O}{\overset{\|}{P}}-OR'$$

(3)

Phosphorus oxychloride is a suitable reagent for preparation of the symmetrically substituted phosphotriesters of type $(RO)_3PO$. The preparation is easily achieved by treatment of phosphorus oxychloride with 3 equiv. of alcohols or their metal salts. The reaction is generally promoted by a base or acid. Titanium trichloride is a particularly effective catalyst for the reaction.[8] Conversion of $POCl_3$ to unsymmetrically substituted phosphotriesters is achievable with difficulty. Phosphorochloridates and phosphorodichloridates have been used for the preparation of mixed tertiary phosphoric esters of type $(RO)_mPO(OR')_n$ ($m = 1$, $n = 2$, or $m = 2$, $n = 1$) in a very wide variety.[9] Reaction of phosphorus oxychloride and 1 or 2 equiv. of alcohols followed by hydrolysis forms phosphomonoesters or phosphodiesters, respectively. The hydrolysis may be generally effected by dilute aqueous alkali. Some phosphorodichloridate intermediates are easily hydrolyzed by water. For example, the phosphorylation of a ribonucleoside (**1**; equation 4) with phosphorus oxychloride in an aqueous pyridine–acetonitrile mixture furnishes the nucleoside 5′-monophosphate (**2**) in excellent yield.[10]

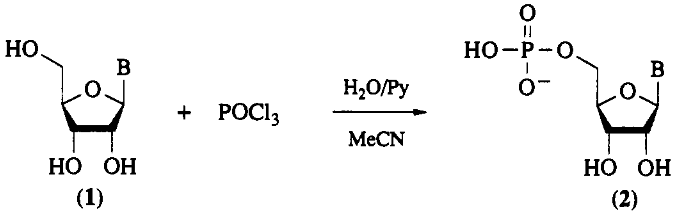

(4)

When alcohols are activated as the alkoxides, the phosphorylation is greatly accelerated. Activators employable are potassium *t*-butoxide,[11,12] thallium ethoxide,[13,14] alkyllithiums,[7,11,14] *t*-butylmagnesium chloride,[15] dibutylstannoxane,[16] *etc.* Phosphorylation *via* an aluminum alkoxide like $LiAl(OAr)_3(OR)$ or $Al(OAr)_2(OR)$, where Ar is *o*-chlorophenyl or *p*-nitrophenyl, also proceeds smoothly.[17] The lithium[7] and potassium[12] alkoxides react with not only chlorophosphates but also phosphorofluoridates (equation 5). The hydroxy activation procedure frequently reverses the reactivity of nitrogen and oxygen atoms toward the phosphorochloridate. Thus, this approach is often efficient for nucleotide synthesis. Particularly useful is the activation as the magnesium or aluminum alkoxides, and the phosphorylation of *N*-unprotected nucleosides proceeds in a perfect *O*-selective manner. No protection of amino function is necessary. For instance, when the cytidine derivative (**3**; equation 6) is treated with 1 equiv. of *t*-butylmagnesium chloride followed by $(CH_2{=}CHCH_2O)_2POCl$ in THF, the phosphate (**4**) is obtained in quantitative yield.[15] Choice of the activator is important in phosphorylation of an anomeric hydroxy of a carbohydrate. The stereochemistry of the product is highly dependent on the activator and reaction conditions employed. When the 1α-hydroxylaminosugar (**5**) is phosphorylated with dibenzyl phosphorochloridate by the aid of thallium ethoxide in acetonitrile, anomerization occurs to afford the β-glycosyl phosphate (**6**; equation 7). By contrast, the reaction promoted by *n*-butyllithium in hexane, which can generate the carbohydrate alkoxide at lower temperature (–70 °C), brings about no anomerization to give the α-phosphate (**7**; equation 8).[14] On the other hand, in phosphorylation of the thallium alkoxide of glucopyranose (**8**; equation 9) the solvent affects the stereochemistry of the product.[13] Formation of the α-anomer predominates in acetonitrile. On the other hand, the β-anomer is a major product in benzene. Phosphorylation of hydroxyaryl compounds is also accelerated by hydroxy activation. Preparation of triaryl phosphates can be readily achieved by reacting phosphorus oxychloride with the sodium salt of the hydroxyaryl compound in a two-phase system using a phase-transfer catalyst, tricaprylmethylammonium chloride.[18]

### 2.8.2.2 Phosphoric–Arenesulfonic Anhydrides

Mixed anhydrides of phosphoric acids and arenesulfonic acids, which are intermediately generated by the condensation of phosphodiesters and arenesulfonyl chlorides[19,20] or arenesulfonyl amides,[21–25] are more reactive phosphorylating agents than chlorophosphates. Arenesulfonylamides generally give higher coupling yields than arenesulfonyl chlorides. Benzenesulfonyl, 2,4,6-trimethylbenzenesulfonyl, 2,4,6-triisopropylbenzenesulfonyl (TPS), *p*-nitrobenzenesulfonyl, *etc.*, are effective as arenesulfonyl parts. Azoles such as imidazole,[21] *N*-methylimidazole,[25] triazole,[22,23] 3-nitrotriazole,[24] and tetrazole[24] are usable as the amine of the sulfonylamides (equation 10). In general, the phosphorylation proceeds

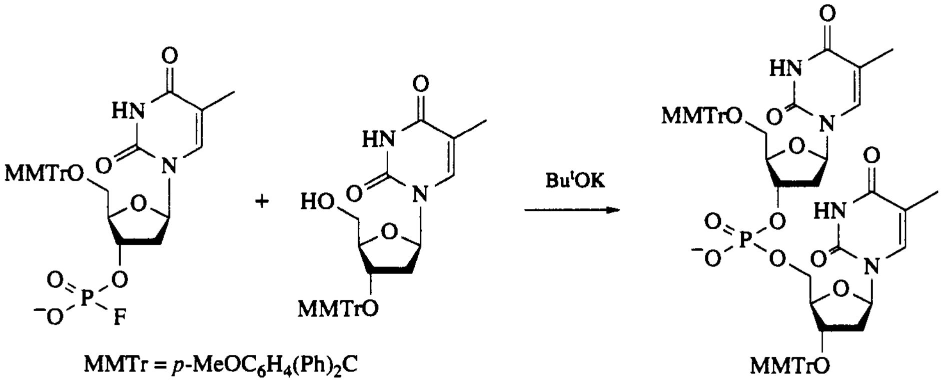

MMTr = $p$-$MeOC_6H_4(Ph)_2C$

(5)

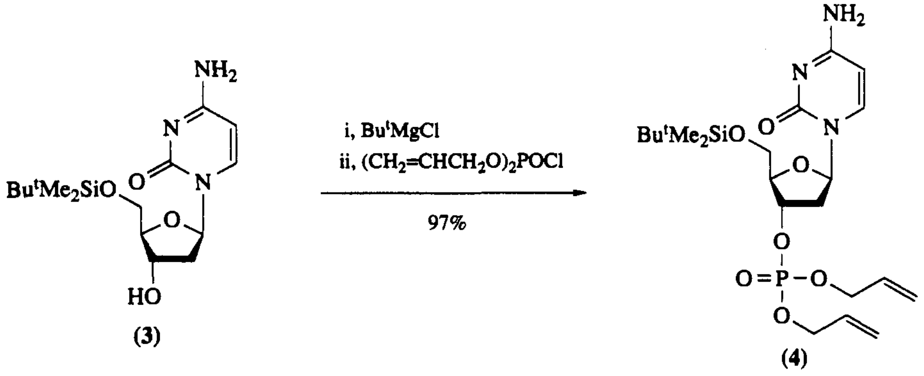

(6)

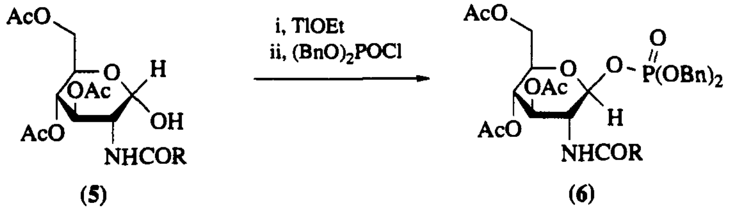

(7)

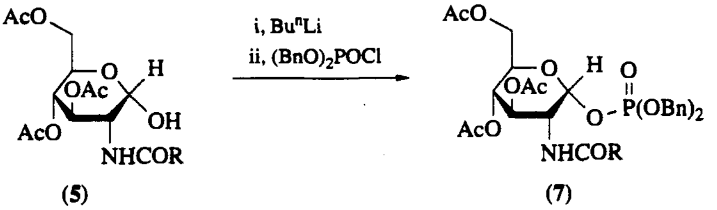

(8)

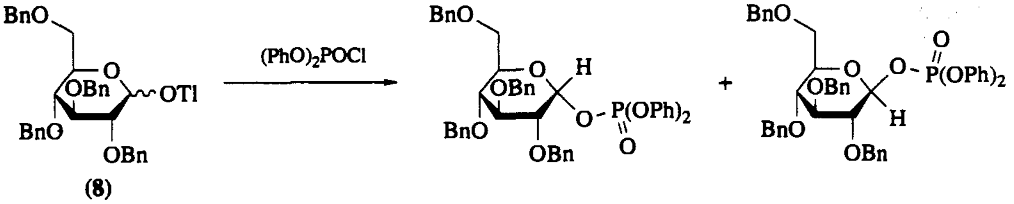

(9)

| | | |
|---|---|---|
| MeCN | 100 | 0 |
| $C_6H_6$ | 15 | 85 |

smoothly with the assistance of tertiary amines at room temperature or below it. According to this procedure, sulfonylation of alcohols competes with the phosphorylation.[26] The undesired reaction can be prevented to a considerable extent by the use of bulky sulfonyl reagents such as TPS derivatives.[26] Certain 4-substituted pyridine *N*-oxides promoted phosphorylation using arenesulfonyl chlorides. The 1-oxido-4-alkoxy-2-picolyl protecting group of phosphodiesters greatly accelerates the internucleotide bond formation with arenesulfonyl chlorides (equation 11).[27] A similar effect is observed with 4-alkoxy-2-picolyl,[27] 1-oxido-2-picolyl,[27] or a 2-(1-methylimidazole-2-yl)phenyl group.[28,29] The sulfonyl amide (**9**)[30] greatly accelerates the internucleotide linkage formation in pyridine. In nucleotide synthesis, use of a condensing agent that is easily separable from the product is essential for obtaining a high yield. Quinonesulfonyl chloride (**10**)[31] and the disulfonyl dichlorides (**11**)[32] and (**12**)[33] in the presence of 1*H*-tetrazole are such activators. The internucleotide bond formation with the sulfonylamide (**13**) proceeds in a diastereoselective manner to give the phosphotriester (**14**; equation 12) as a single isomer.[34]

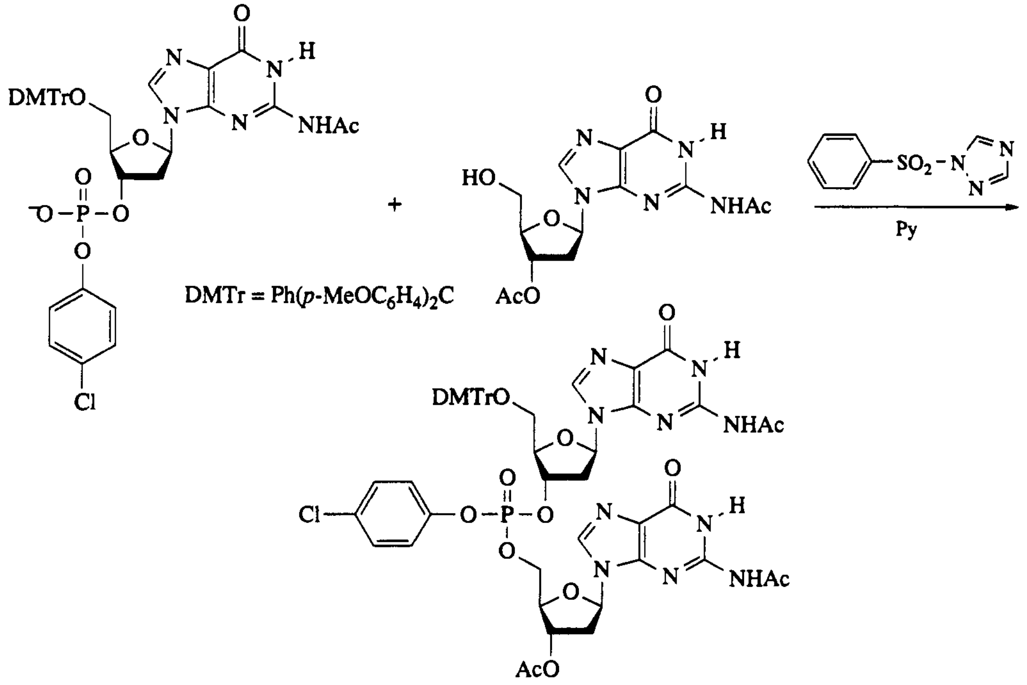
DMTrO
NHAc
HO
AcO
DMTr = Ph($p$-MeOC$_6$H$_4$)$_2$C
SO$_2$
Py
Cl

(10)

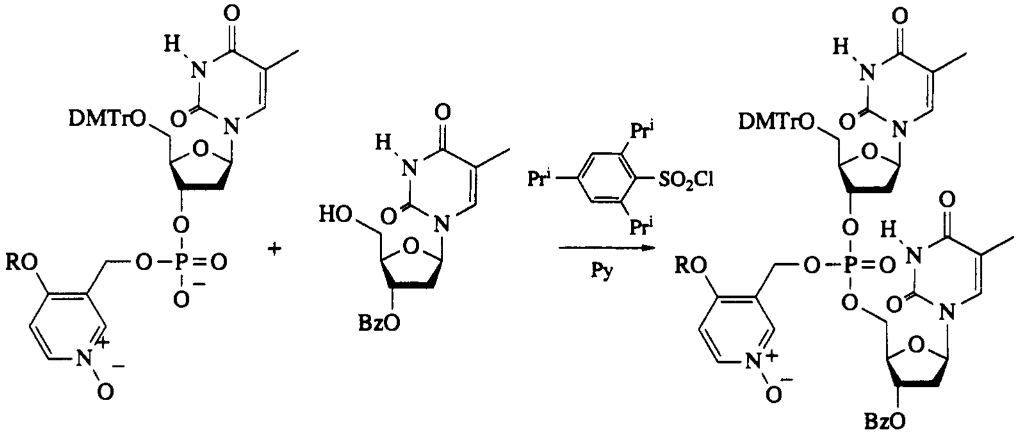
DMTrO
RO
HO
BzO
Pr$^i$
SO$_2$Cl
Py

(11)

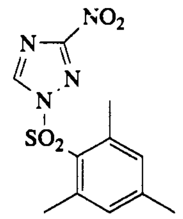

**(9)**

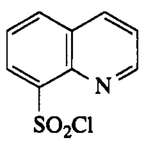

**(10)**

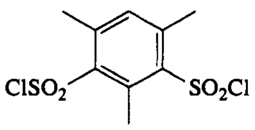
ClSO$_2$
SO$_2$Cl

**(11)**

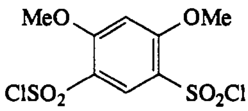
MeO
OMe
ClSO$_2$
SO$_2$Cl

**(12)**

### 2.8.2.3 Pyrophosphates

Free pyrophosphoric acid (phosphoric anhydride) and $P^1$,$P^2$-pyrophosphoric diesters are stable under standard basic conditions and serve as phosphorylating agents only in some limited cases. An example is the trichloroacetonitrile-aided phosphorylation using a *syn*-dialkyl pyrophosphoric diester (equation 13).[35] The tetraalkyl esters contrast with the dissociated compounds, being convenient phosphorylating agents. Among the tetraalkyl pyrophosphates, symmetrical derivatives are widely employable as the monophosphorylating agents (equation 14).[36,37] The unsymmetrical pyrophosphates are not always

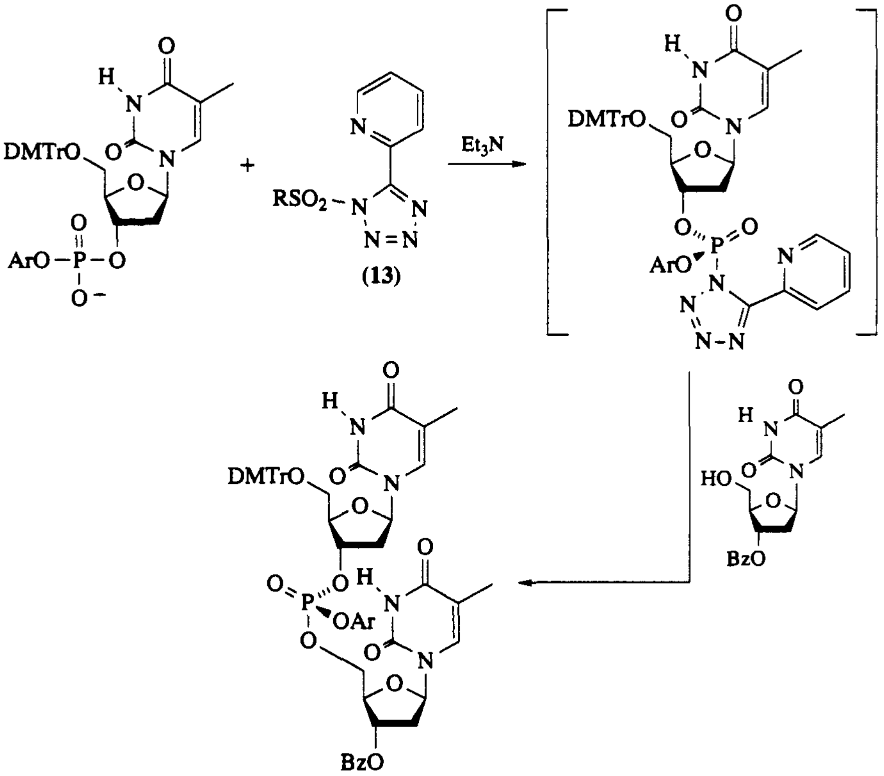

**(14)** Ar = $o$-ClC$_6$H$_4$

(12)

useful, because they react usually at two reactive sites to give a mixture of phosphates. In such cases, the selective preparation may be realized by designing the structure of a phosphoryl moiety which acts as the leaving group. In unsymmetrical pyrophosphates, the more acidic phosphate moiety generally acts as a leaving group. Reagents designed according to such consideration are the diaryl phosphorochloridates (**15**) or (**16**). The reagent (**16**) assists condensation of the thiophosphodiester (**17**; equation 15) and the 5′-free nucleotide (**18**) in the presence of 3-nitrotriazole to give exclusively the dinucleoside phosphate (**19**).[38] In this phosphorylation, the mixed phosphoric anhydride is the intermediate. The reagent (**20**)[39] has a similar effect. Pentavalent phosphorous trichlorides (**21**)[40] and (**22**)[41] and the dichloride analog (**23**)[41] are also useful condensing agents. Preparation of the nucleoside diphosphate (**24**; equation 16) and triphosphate (**25**; equation 16) is achieved using Bu$^n_2$PSBr. The reaction is believed to proceed *via* a mixed pyrophosphate-type intermediate.[42]

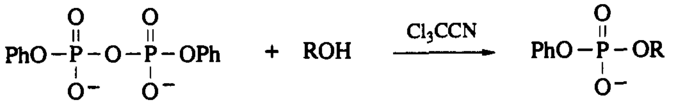

$$\mathrm{PhO-\underset{O^-}{\overset{O}{\overset{\|}{P}}}-O-\underset{O^-}{\overset{O}{\overset{\|}{P}}}-OPh} \quad + \quad \mathrm{ROH} \quad \xrightarrow{\mathrm{Cl_3CCN}} \quad \mathrm{PhO-\underset{O^-}{\overset{O}{\overset{\|}{P}}}-OR} \qquad (13)$$

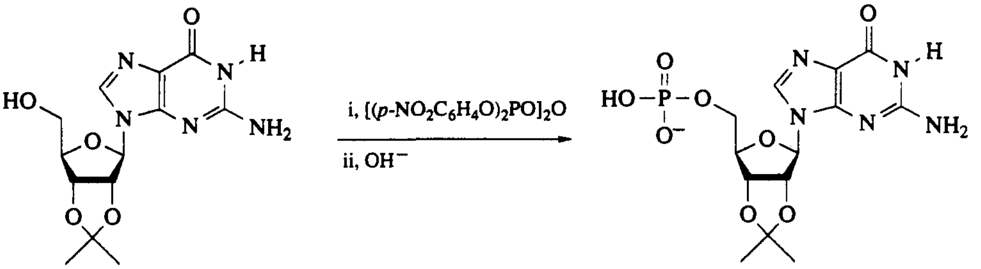

(14)

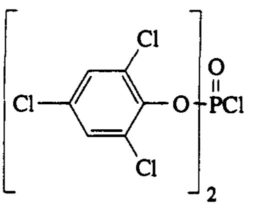

**(15)**

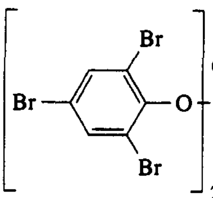

**(16)**

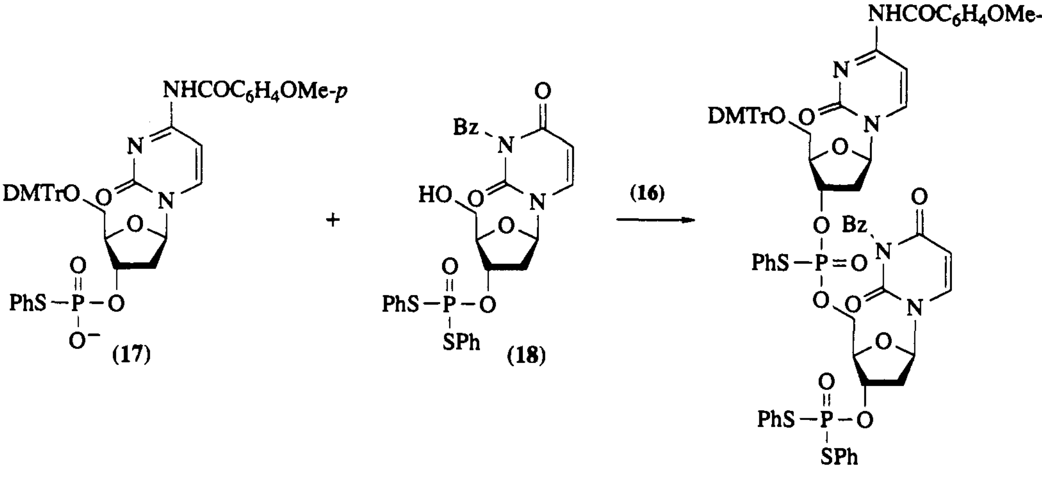

(15)

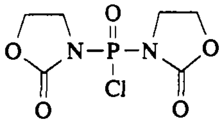

**(20)**

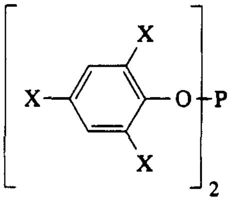

**(21)** $X = Cl$
**(22)** $X = Br$

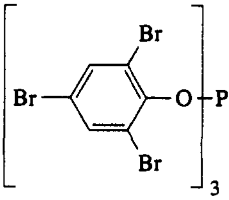

**(23)**

### 2.8.2.4 Acyl Phosphates

Nucleophilic attack of alcohol to acyl phosphates usually occurs predominately at the carbonyl carbon atom, producing carboxylic esters but not phosphates.[43] In contrast, some kinds of phosphoric monoesters or amines react with the mixed anhydrides at the phosphorus atom. An example is when monoethyl phosphate is treated with acetic anhydride or acetyl chloride in pyridine, the acetyl phosphate occurs intermediately, which in turn condenses with the second ethyl phosphate to give diethyl phosphate (equation 17).[44] A similar reaction is conducted by use of ketene dimer in place of the acetylating reagents (equation 18).[45] Triethylamine-promoted reaction of dialkyl phosphates and trifluoroacetic anhydride produces tetraalkyl pyrophosphates.[46] These reactions are presumed to involve an acyl phosphate as the intermediate. Both methods cannot be used for specific synthesis of unsymmetrical pyrophosphates. Condensation of the acyl phosphate (**26**; equation 19) and aniline exclusively occurs with a P—O bond fission to give the phosphoramidate (**27**).[47] Reaction of protection-free 2′-deoxyribonucleoside 5′-monophosphate with mesitylenecarbonyl chloride followed by methanol in pyridine gives the methyl ester of the nucleotide (equation 20).[48] This procedure is applicable to the 3′-phosphate of oligonucleotide, dCpApAp.[48]

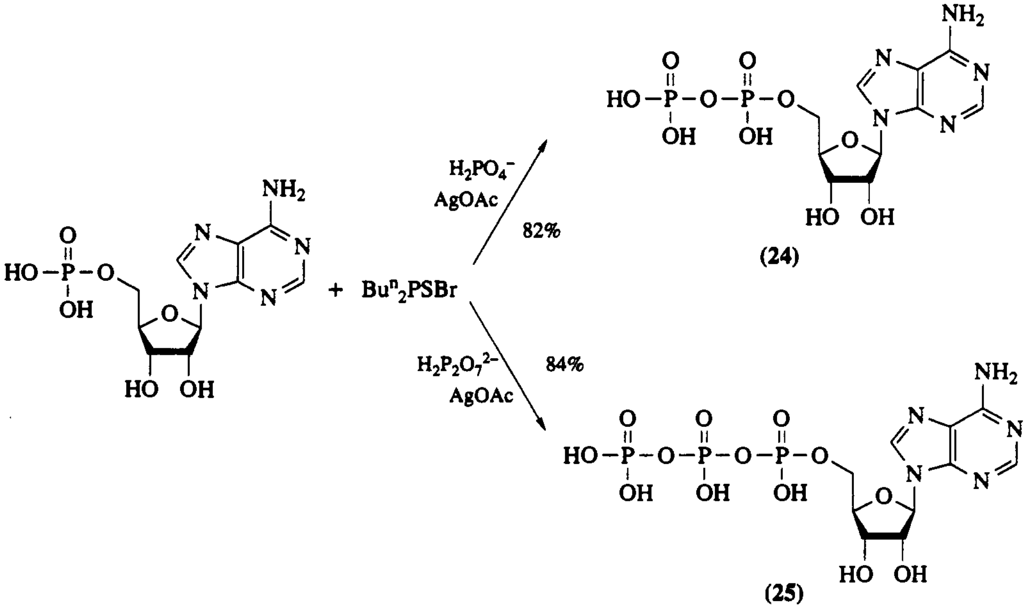
NH2
O
HO-P-O
OH
N
HO OH
+ Bun2PSBr
H2PO4-
AgOAc
82%
H2P2O7 2-
AgOAc
84%

(24)

(25)

(16)

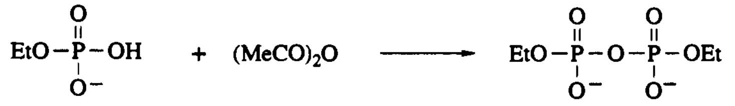

$$\mathrm{EtO{-}P(O)(O^-){-}OH + (MeCO)_2O \longrightarrow EtO{-}P(O)(O^-){-}O{-}P(O)(O^-){-}OEt} \qquad (17)$$

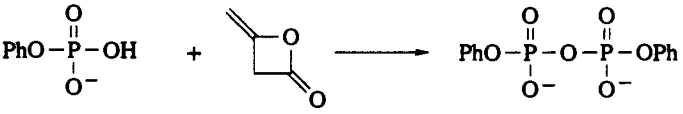
PhO-P-OH
O-
+
O
O
PhO-P-O-P-OPh
O- O-

(18)

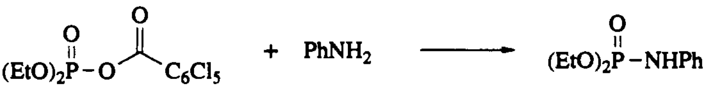

$$\mathrm{(EtO)_2P(O){-}O{-}C(O){-}C_6Cl_5 + PhNH_2 \longrightarrow (EtO)_2P(O){-}NHPh} \qquad (19)$$

(26) (27)

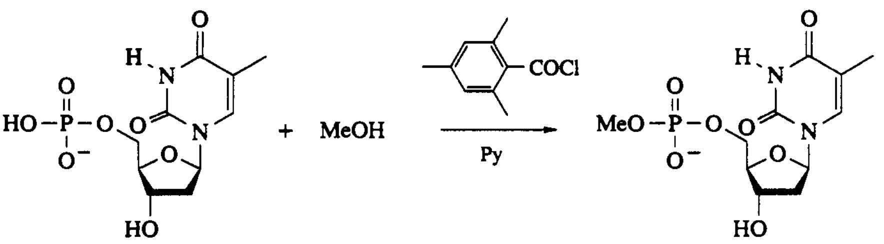
HO-P-O
O-
H
N
O
HO
+ MeOH
COCl
Py
MeO-P-O
O-

(20)

### 2.8.2.5 Phosphoryl Phenoxides and Related Compounds

Some kinds of phosphoryl phenoxides (phenyl phosphates) are useful and easily handled phosphorylating agents. Although a phosphoryl 4-nitrophenoxide does not serve as an efficient phosphorylating agent for alcohols in an ordinary procedure using a tertiary amine as an activator, because of the low reactivity, the phenoxide reacts very smoothly with the alkoxide to give the corresponding phosphate in high yield (equation 21).[8,11] The 2,4,6-trinitrophenoxide analog (**28**) is also a potential phosphorylating agent.[49] The alkyl-2-chloromethyl-4-nitrophenyl hydrogen phosphate (**29**; equation 22) is activated by pyridine to condense with an alcohol, giving the phosphodiester (**30**).[50] Similarly, the phosphoryl phenoxide (**31**; equation 23) reacts with cytidine 5′-monophosphate in the presence of triethylamine to form the diphosphate (**32**).[51]

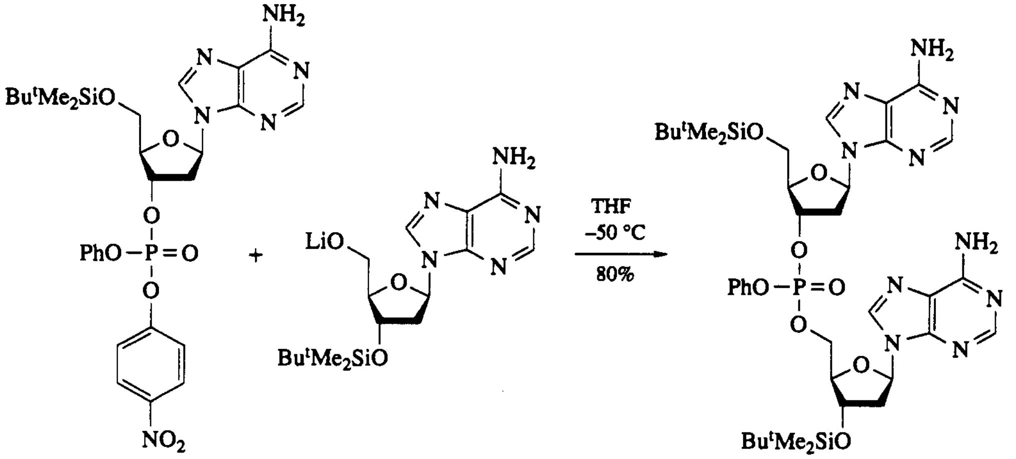

(21)

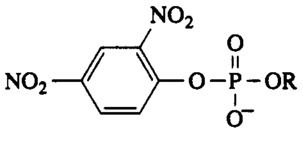

**(28)**

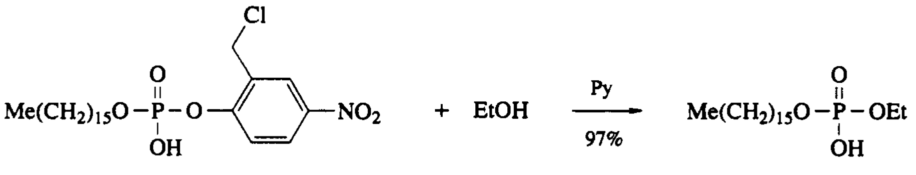

**(29)** **(30)** (22)

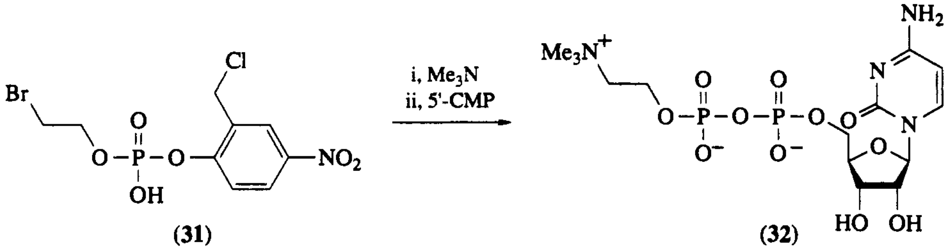

**(31)** **(32)** (23)

2-Dimethylamino-4-nitrophenyl dihydrogen phosphate (**33**; equation 24) in the presence of an acidic promotor such as acetic acid, trifluoroacetic acid, or $BF_3$–etherate in pyridine, is also a useful reagent.[52] The phosphorylation using (**33**) proceeds selectively on primary alcohols. Furthermore, it is noteworthy that (**33**) shows no interaction with the amino group in the reaction of amino alcohols. Thus, ribonucleoside 5′-monophosphates are directly prepared from amino-free nucleosides.[53] Phosphorylation using the 8-quinolyl phosphate (**34**; equation 25), in which the quinolyl moiety is activated by copper(II) ion through chelation, takes place readily with the assistance of copper(II) chloride.[54] Similarly, the aryl phosphate (**35**; equation 26) is activated by a $Cu^{II}$ salt. Condensation of (**35**) and the phosphodiester (**36**) gives the pyrophosphoric ester (**37**).[55] The coupling of 5-chloro-8-quinolyl phosphate (**38**; equation 27) and the ribonucleoside (**39**) is promoted by cesium fluoride in acetonitrile to give the dinucleoside phosphate (**40**).[56] Oxidation of the monophosphate of a naphthaquinol (**41**; equation 28) by bromine generates metaphosphate, serving as a highly reactive phosphorylating agent.[57] This method is applicable to formation of 2′,3′-*O*-protected adenosine 5′-diphosphate from the corresponding monophosphate.[58] The 2-hydroxypyridyl phosphoric diester (**42**) in the presence of pyridine or tertiary amines is usable for phosphorylation of amines, alcohols, and phosphomonoesters, giving phosphoramidates, phosphodiesters, and unsymmetrical pyrophosphates, respectively.[59] For example, the reagent (**43**; equation 29) reacts with the nucleoside 5′-monophosphate (**44**) in pyridine to give the diphosphate (**45**).[60] The aryl phosphate (**46**), derived as an intermediate by the condensation of cyanuric chloride and phosphomonoester, acts similarly.[61]

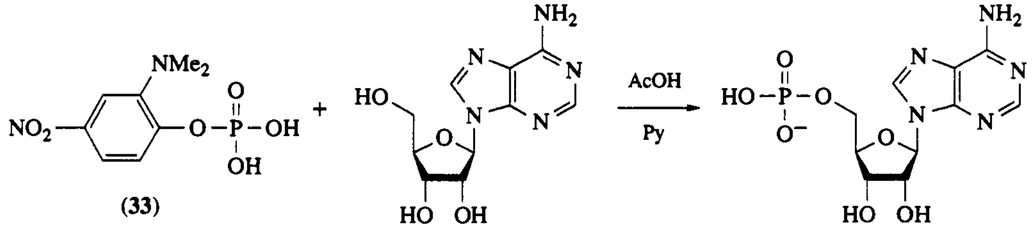

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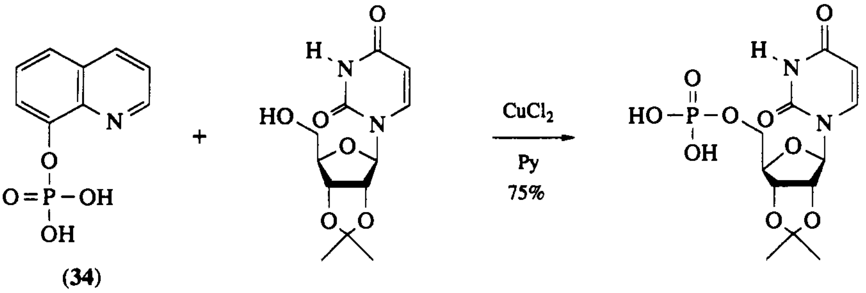

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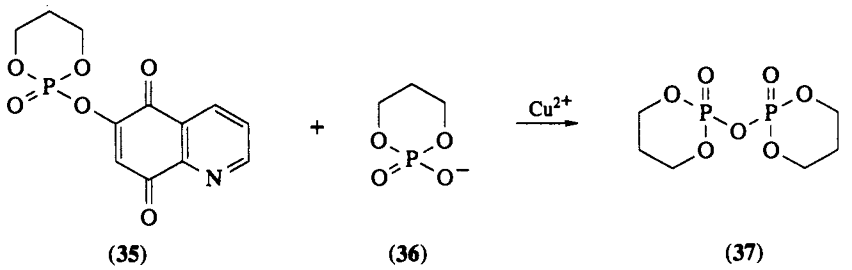

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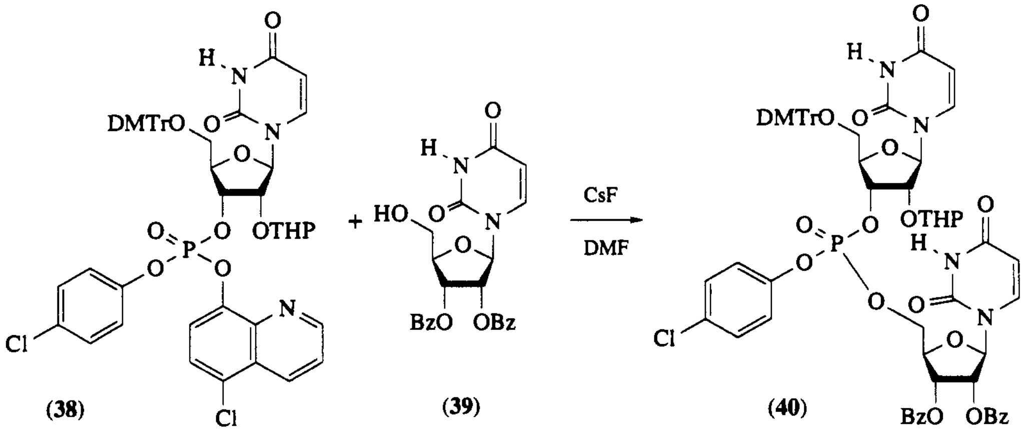

(27)

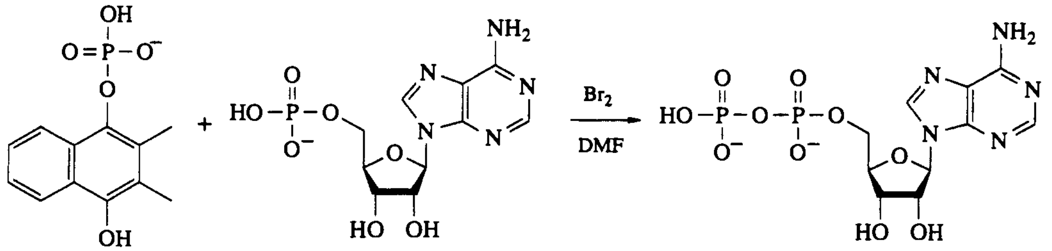

(41)

(28)

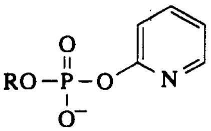

(42)

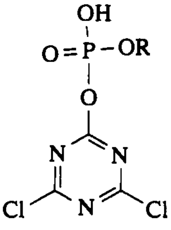

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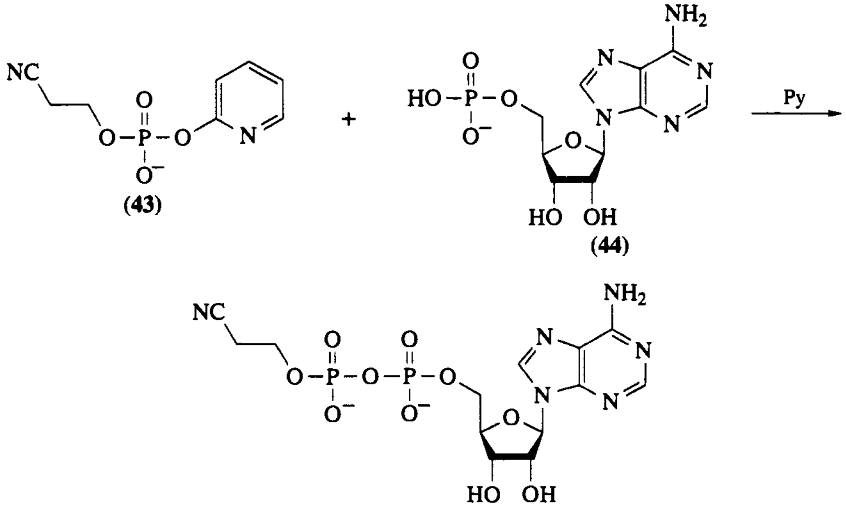

(43)

(44)

(45)

(29)

### 2.8.2.6 Vinyl Phosphates and Related Compounds

Vinyl phosphates, including imino ether-type derivatives, easily undergo transesterification with alcohols with the aid of a base or an acid to give new phosphoric esters.[62] In some cases, the vinyl phosphates are not isolable and thus the intermediates prepared *in situ* are used without purification. Condensation of phosphomonoesters and hydroxylic substrates with DCC in the presence of amines such as triethylamine, pyridine, *etc.*, belongs to this category.[63] This method has been widely employed in oligonucleotide synthesis (equation 30).[64] The reaction, however, particularly of hindered alcohols is very slow. For example, condensation of the ribonucleoside 3′-phosphate (**47**; equation 31) and 5′-free ribonucleoside (**48**) requires more than 4 d.[64] In contrast, a similar reaction with TPS chloride is completed within 6–7 h.[65] Preparation of unsymmetrical pyrophosphates with DCC has invariably led to the formation of mixed products.[66] Cyclohexyl isocyanide is capable of activating phosphomonoesters in a similar way to DCC, assisting the coupling with alcohols (equation 32).[67] Imidoyl phosphates (**49**; equation 33), formed as reactive intermediates by treatment of phosphoric monoesters with trichloroacetonitrile in pyridine, react with alcohols to give unsymmetrical diesters.[68] This method is also effective for the preparation of pyrophosphates. Aryl cyanates behave similarly to trichloroacetonitrile. When a phosphomonoester is treated with the cyanate, dimerization of the phosphates occurs to afford a pyrophosphate (equation 34). The pyrophosphate is activated again by the cyanate to react with an alcohol or an amine, giving an unsymmetrical phosphodiester or a phosphoramidate, respectively.[69] Condensation of DMF and a phosphorochloridate or a phosphorodichloridate also gives an imino ether-type active ester (**50**; equation 35; X = OR or Cl), which acts, in the presence of a tertiary amine, as the phosphorylating agent for phosphomonoesters, carboxylic acids, amino acids, *etc.*[70] An example is the reaction of (**50**; X = OEt) and triethylammonium benzoate to give the mixed anhydride (**51**). The internucleotide linkage formation using *N*-ethyl-5-phenylisoxazolium fluoroborate (**52**; equation 36) goes through a similar pathway.[71,72] The alkoxyvinyl ester of phosphoric acid (**53**), prepared by the addition of a phosphodiester to an alkoxyalkyne, is also an active phosphorylating agent.[73,74] Rapid phosphorylation of alcoholic, phenolic and nucleosidic hydroxy groups, phosphoric acids, amines, and carboxylic acids is achievable with (**53**).[73] This reaction is catalyzed by an $Hg^{II}$ salt.[73] Reaction of a trialkyl phosphite and α-bromocyanoacetamide gives a vinyl or iminyl phosphate intermediate, (**54**) or (**55**), both of which serve as phosphorylating agents toward alcohols, phosphodiesters, and amines.[75] Dibromomalonamide in place of bromocyanoacetamide is also employable.[76] The ketene acetal-type phosphates (**56**) or (**57**), derived from trichloroacetic acid and diethyl bromomalonate, respectively, in a similar manner, react with acetic acid to give the phosphoric–acetic mixed anhydrides.[77]

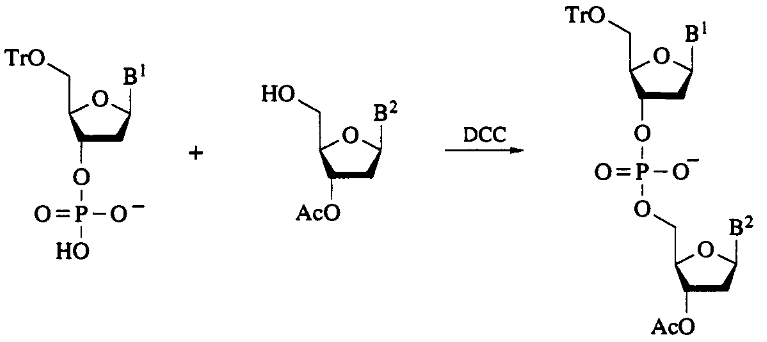

(30)

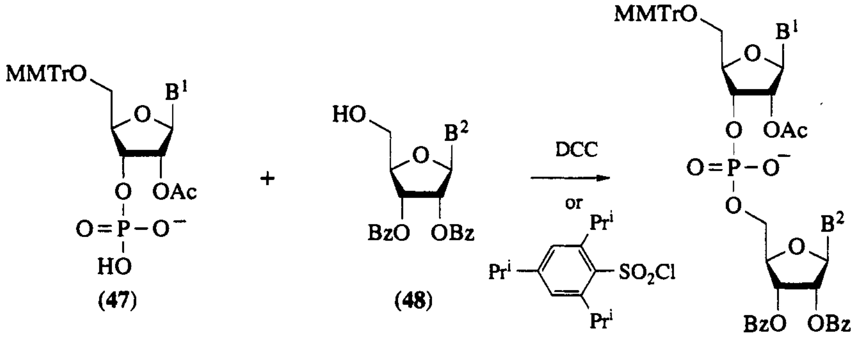

(31)

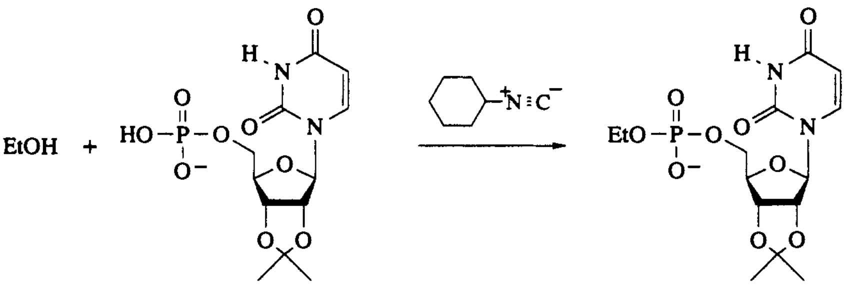

(32)

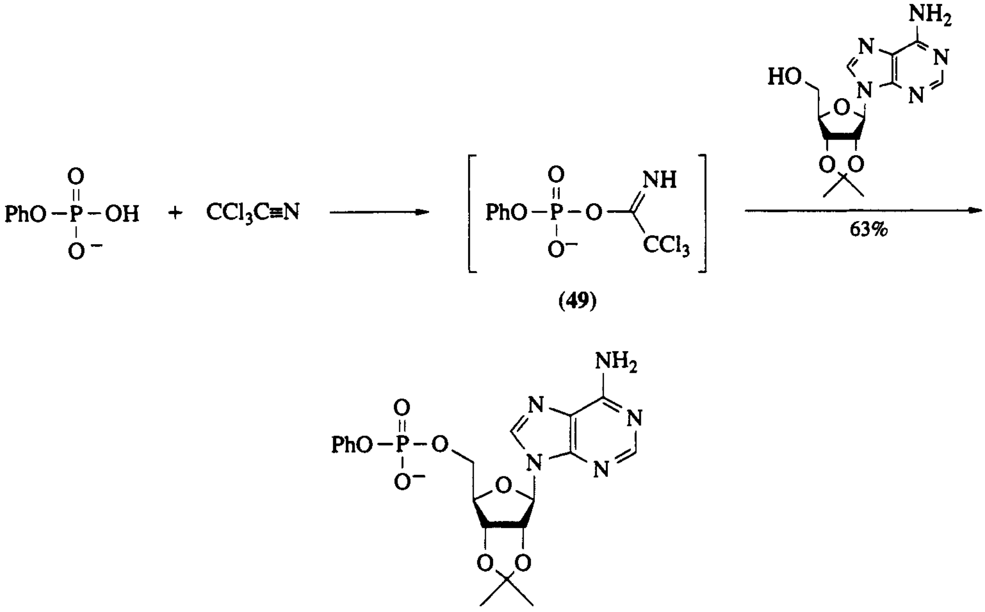

PhO–P(O)(O⁻)–OH
CCl3C≡N
PhO–P(O)(O⁻)–O–C(=NH)CCl3
(49)
NH2
HO
63%
PhO–P(O)(O⁻)–O

(33)

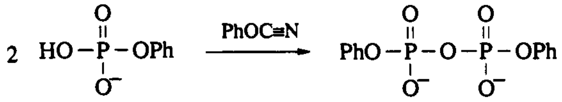

$$2\ \mathrm{HO{-}\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}{-}OPh} \xrightarrow{\mathrm{PhOC{\equiv}N}} \mathrm{PhO{-}\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}{-}O{-}\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}{-}OPh}$$

(34)

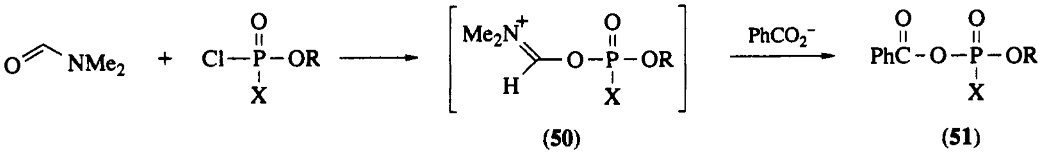

NMe2
Cl–P(O)(X)–OR
Me2N+
H
O–P(O)(X)–OR
(50)
PhCO2⁻
PhC(O)–O–P(O)(X)–OR
(51)

(35)

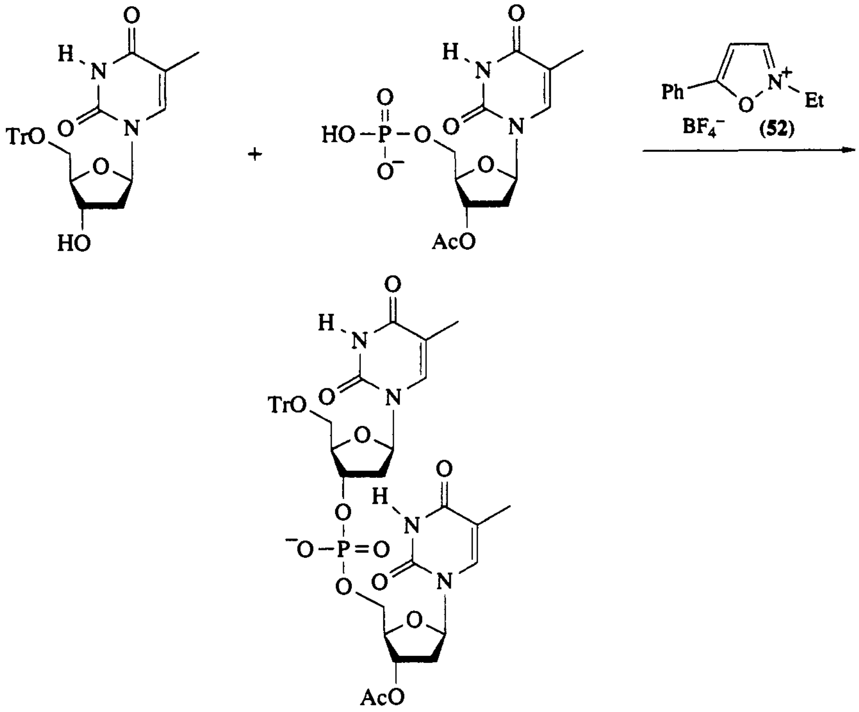

TrO
HO
HO–P(O)(O⁻)–O
AcO
Ph
N+
Et
BF4⁻
(52)
TrO
⁻O–P=O
AcO

(36)

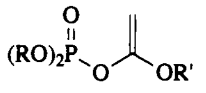

**(53)**

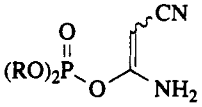

**(54)**

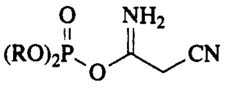

**(55)**

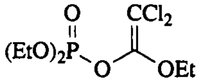

**(56)**

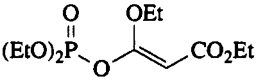

**(57)**

### 2.8.2.7 Phosphoramidates and Related Compounds

Aliphatic amides of phosphoric acid (phosphoramidates) are rather stable and do not react with alcohols. On the other hand, condensation of some of the amidates and phosphates takes place easily to give pyrophosphates. Thus, the phosphoramidates serve as useful reagents for the preparation of unsymmetrical pyrophosphates.[78–80] Among the amidates, the morpholidate is the most useful reagent, because of ready accessibility and high reactivity.[80] This approach is effective for the synthesis of the nucleoside 5′-triphosphates by coupling of nucleoside 5′-monophosphates and pyrophosphate (equation 37).[81,82] *N*-Acylphosphoramidates, in contrast to the free amidates, phosphorylate alcohols under neutral or acidic conditions (equation 38).[83] The phosphoryloxazolides (**58**) and (**59**) are activated by $Zr(acac)_4$, serving as useful reagents for the phosphorylation of alcohols.[84] The phosphorohydrazidate (**60**) is oxidized by iodine or NBS to generate an active species capable of phosphorylating phosphate anions.[85] High yields of unsymmetrical pyrophosphates can be obtained by this method. Similarly, oxidative phosphorylation is accomplished using the phosphoramidate (**61**; equation 39), where triphenylmethyl fluoroborate or cerium(IV) ammonium nitrate is used as the oxidizing agent.[86] Photochemical oxidative phosphoryl transfer to alcohols is also achievable with (**61**).[86] Although unlike other systems containing a phosphorus–nitrogen bond, the phosphoroguanidates (**62**; equation 40) show remarkable chemical stability, the compounds undergo nucleophilic attack at the phosphorus atom with consequent phosphoryl transfer by the action of zinc and manganese(II) cations. Thus, the cross coupling between benzyl hydrogen phosphoroguanidate (**62**; R = $PhCH_2$) and phenyl dihydrogen phosphate is effectively promoted by zinc acetate to afford the pyrophosphate (**63**).[87] Related *N*-acylphosphoroguanidates (**64**) function as phosphorylating agents under weakly basic conditions.[88] *N*-Phosphorylimidazoles are highly reactive, particularly under acidic conditions, being capable of transferring a phosphoryl group to protic compounds. Reactivity of the phosphorylimidazole to phosphate or pyrophosphate anions is usually higher than to alcohols and therefore the reagent is widely employed for the preparation of diphosphates (equation 41)[89–92] or triphosphates.[93,94] Phosphoryltriazoles are also good phosphorylating agents.[95,96] Oligoadenylates with a 2′–5′ phosphoric linkage are prepared by $Pb^{2+}$ ion catalyzed condensation of adenosine 5′-phosphorimidazolide.[93] The trimer (**65**; equation 42) is a major product.

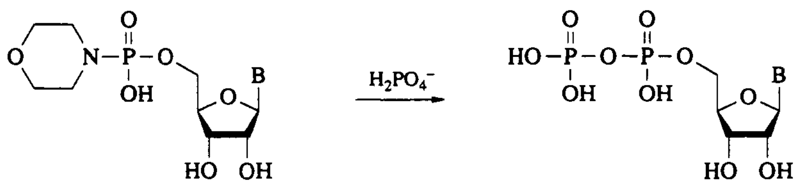

(37)

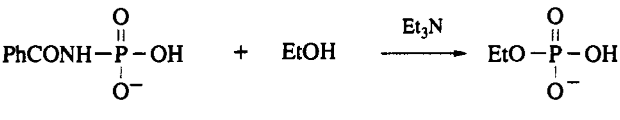

$$PhCONH-\underset{O^-}{\overset{O}{\overset{\|}{P}}}-OH + EtOH \xrightarrow{Et_3N} EtO-\underset{O^-}{\overset{O}{\overset{\|}{P}}}-OH \qquad (38)$$

### 2.8.2.8 Phosphorothioates

The nucleoside phosphorothioate (**66**; equation 43) reacts with tributylammonium phosphate in the presence of silver nitrate to give the nucleoside 5′-diphosphite (**67**).[97]

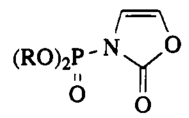

**(58)**

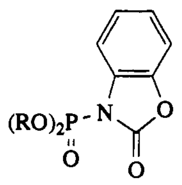

**(59)**

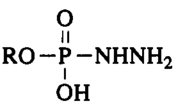

**(60)**

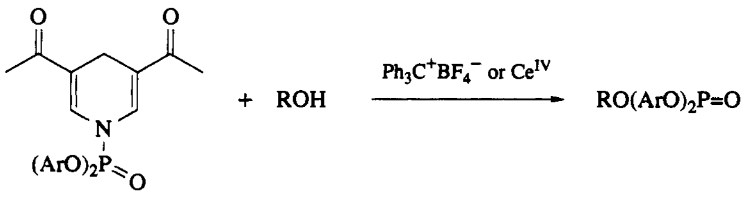

**(61)**

(39)

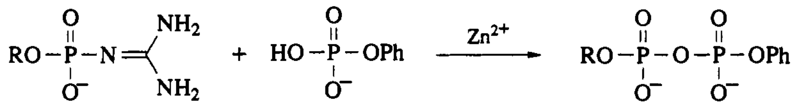

**(62)** **(63)**

(40)

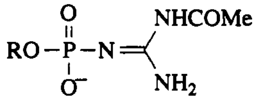

**(64)**

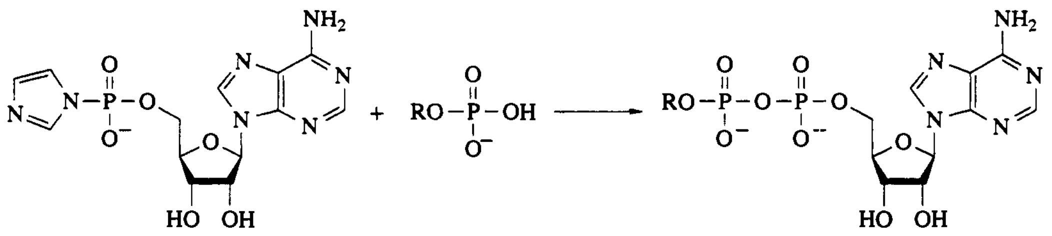

(41)

## 2.8.2.9 Triphenylphosphonium Salts of Phosphoric Acid Esters

Phosphorylation of alcohols and amines forming mixed esters of phosphoric acid and phosphoramidates, respectively, is effected by triphenylphosphine and 2,2′-dipyridyl disulfide.[98] The reaction passes through a triphenylphosphonium phosphate of type (**68**; equation 44) as an active intermediate. Formation of an internucleotide linkage can be achieved by this method.[99,100] Dimerization of monoesters of phosphoric acid producing dialkyl pyrophosphates is achieved using tributylphosphine and dibenzoylethylene or *p*-quinonedibenzimide (equation 45). A phosphonium phosphate is the active intermediate of this reaction.[101]

## 2.8.2.10 Miscellaneous

Esterification of dialkyl phosphates is carried out with diethyl azodicarboxylate and triphenylphosphine (equation 46).[102] This condensation is applicable to phosphorylation of pyrimidine nucleosides. The trichloromethanephosphonic acid derivative (**69**; equation 47) serves as a phosphorylating agent of ribonucleosides, affording the 2′- and 3′-monophosphates.[103] Ethyl vinyl ether assisted the dimeric condensation of diethyl hydrogen phosphate giving tetraethyl pyrophosphate (equation 48).[45]

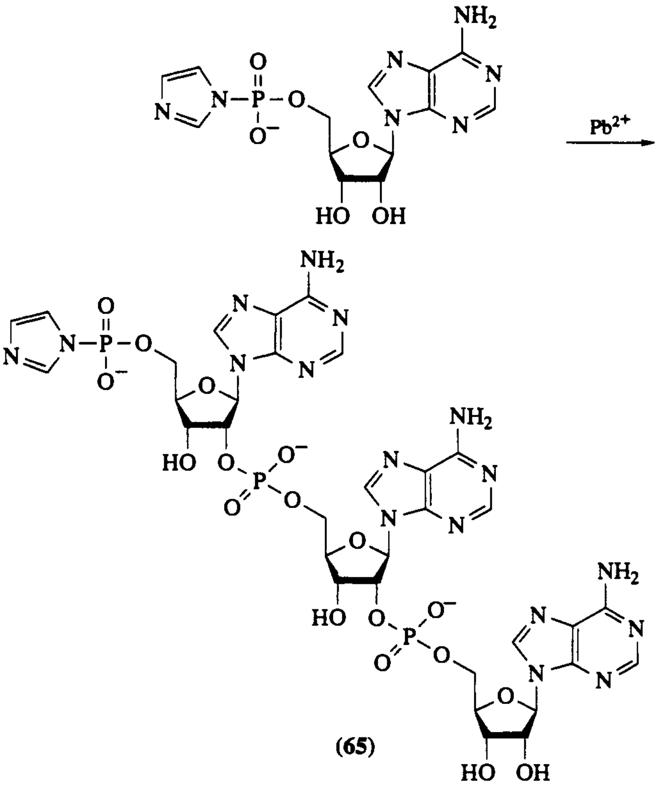

(65)

(42)

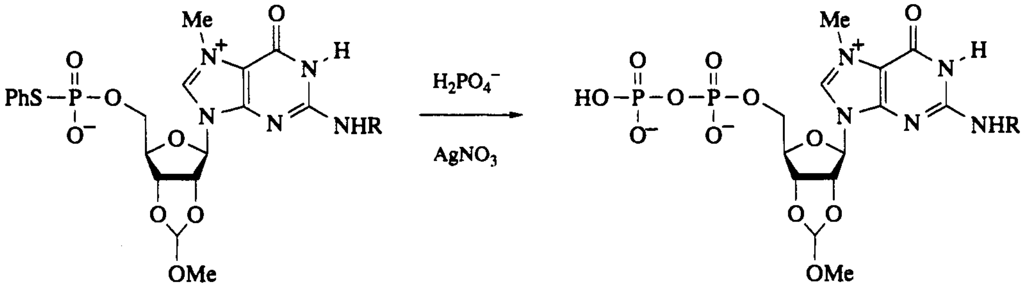

(66) R = $(p\text{-MeOC}_6H_4)_3C$

(67)

(43)

## 2.8.3 USE OF TRIVALENT PHOSPHORUS REAGENTS

Phosphorylation of alcohols can also be achieved through the phosphitylation with some kinds of trivalent phosphorus reagents followed by oxidation. The phosphitylating agents are generally more reactive than the corresponding pentavalent analogs. Thus this approach has been used very frequently for the preparation of phosphoryl derivatives of less reactive alcohols, such as nucleosides.[104]

### 2.8.3.1 Phosphorochloridites (Chloroalkoxyphosphines) and Related Compounds

Phosphorochloridites are highly reactive reagents, undergoing condensation with alcohols in the presence of an acid scavenger at low temperature. For instance, reaction of the 2′,3′-*O*-protected ribonucleoside (**70**; equation 49) with phosphorus trichloride in the presence of trimethyl phosphate takes place at 0 °C, to afford, after oxidation with chlorine followed by hydrolysis, the nucleoside 5′-monophosophate (**71**).[105] Preparation of alkyl dihydrogen phosphates is performed through condensation of an alcohol and diethylthiochlorophosphine, giving (**72**; equation 50), followed by oxidation and hydrolysis uisng aqueous iodine.[106]

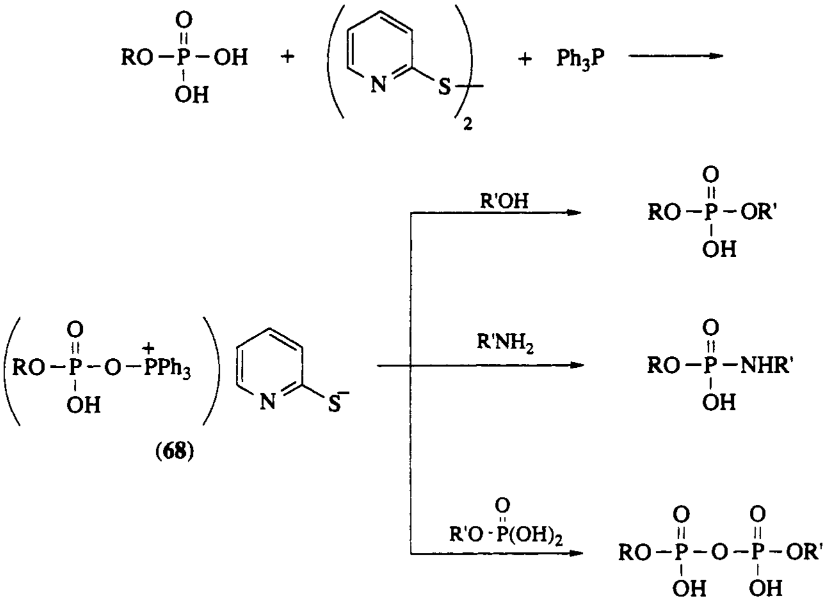

RO–P(O)(OH)–OH
Ph3P
R'OH
R'NH2
R'O·P(O)(OH)2
RO–P(O)(OH)–OR'
RO–P(O)(OH)–NHR'
RO–P(O)(OH)–O–P(O)(OH)–OR'
(68)

(44)

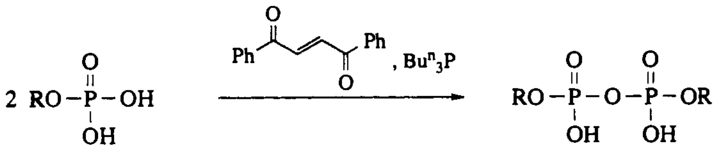

2 RO–P(O)(OH)–OH
, Bun3P
RO–P(O)(OH)–O–P(O)(OH)–OR

(45)

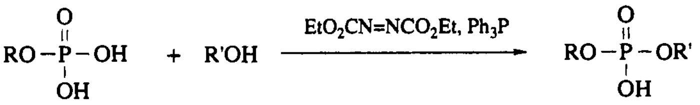

$$RO-\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OH}{|}}{P}}}-OH + R'OH \xrightarrow{EtO_2CN{=}NCO_2Et,\ Ph_3P} RO-\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OH}{|}}{P}}}-OR'$$

(46)

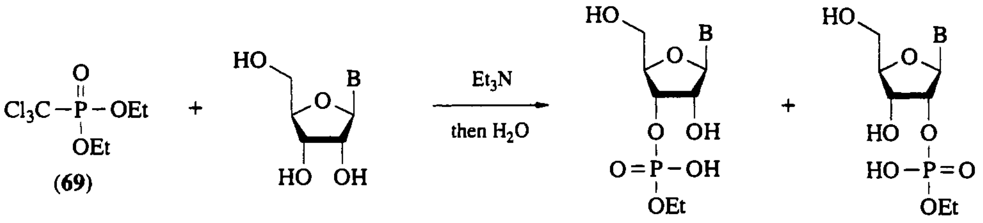

Cl3C–P(O)(OEt)–OEt
(69)
HO
B
HO OH
Et3N
then H2O
O OH
O=P–OH
OEt
HO O
HO–P=O
OEt

(47)

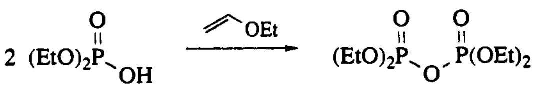

$$2\ (EtO)_2\overset{\displaystyle O}{\overset{\|}{P}}\text{–}OH \xrightarrow{\text{CH}_2\text{=CHOEt}} (EtO)_2\overset{\displaystyle O}{\overset{\|}{P}}\text{–O–}\overset{\displaystyle O}{\overset{\|}{P}}(OEt)_2$$

(48)

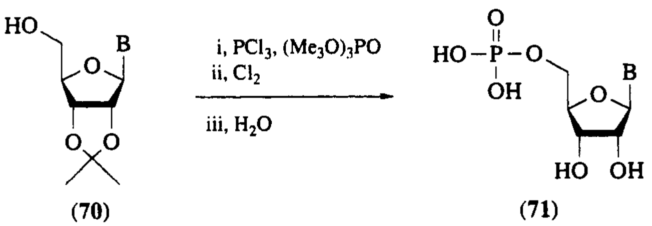

HO
B
(70)
i, PCl3, (Me3O)3PO
ii, Cl2
iii, H2O
HO–P(O)(OH)–O
B
HO OH
(71)

(49)

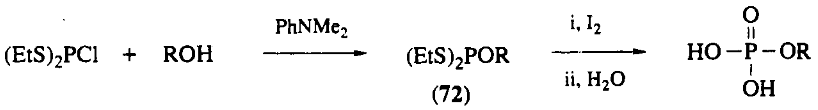

$$(EtS)_2PCl + ROH \xrightarrow{PhNMe_2} \underset{(72)}{(EtS)_2POR} \xrightarrow[\text{ii, }H_2O]{\text{i, }I_2} HO-\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OH}{|}}{P}}}-OR$$

(50)

### 2.8.3.2 Phosphoramidites (Dialkylaminodialkoxyphosphines)

When phosphoramidites are activated by weak acids such as *N*-methylanilinium trifluoroacetate,[107] 1*H*-tetrazole,[108] 5-methyltetrazole,[109] 5-methylthiotetrazole, 5-(4-nitrophenyl)tetrazole,[110] *etc.*, the reagents react with alcohols, forming phosphites, which can be transferred to the phosphates by oxidation. For example, the methyltetrazole-assisted condensation of phosphoramidite (**73**; equation 51) and an alcohol followed by oxidation with MCPBA gives the phosphate (**74**).[111] Use of DMAP as an additive accelerates the reaction.[111] Choice of amino group of the amidite reagents affects the reactivity and stability. From the synthetic point of view, diethylamidites, diisopropylamidites, and morpholidites are most efficient reagents. In general, the phosphoramidites are more stable than the corresponding phosphorochloridites and some of the reagents can be purified by silica gel chromatography. Thus the reagents are frequently employed for the synthesis of oligonucleotides.

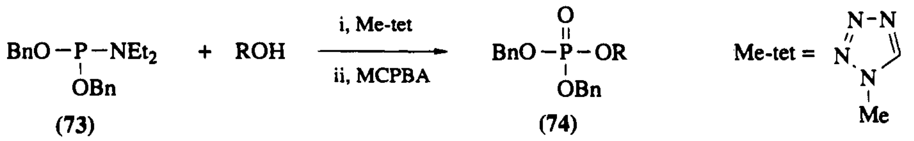

$$\underset{\text{OBn}}{\text{BnO}-\overset{|}{\text{P}}-\text{NEt}_2} + \text{ROH} \xrightarrow[\text{ii, MCPBA}]{\text{i, Me-tet}} \underset{\text{OBn}}{\text{BnO}-\overset{\text{O}}{\overset{\|}{\text{P}}}-\text{OR}} \qquad (51)$$

**(73)** **(74)**

### 2.8.3.3 Phosphorothioites (Alkylthiodialkoxyphosphines)

The dinucleoside phosphate (**77**; equation 52) is prepared by oxidative coupling of the nucleoside phosphothioiten (**75**) and the nucleoside (**76**) using iodine followed by aqueous treatment.[112]

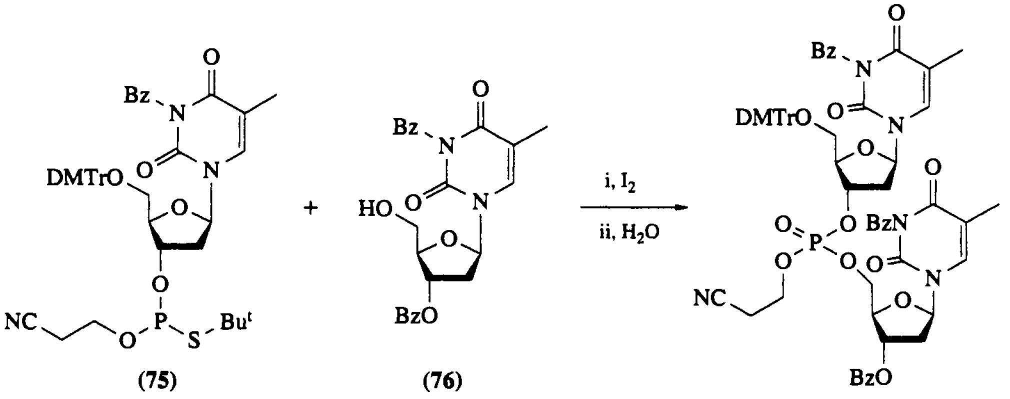

**(75)** **(76)** **(77)** (52)

## 2.8.4 BIFUNCTIONAL PHOSPHORYLATING AGENTS AND RELATED REAGENTS USEFUL FOR SYNTHESIS OF FULLY UNSYMMETRICAL PHOSPHOTRIESTERS

Preparation of the fully unsymmetrical phosphotriesters (RO)(R′O)(R″O)PO is very important for the synthesis of oligonucleotides, but it is far from easy. Reaction of $POCl_3$ or $PCl_3$ and three kinds of alcohols generally occurs at random to give a mixture of possible trialkyl phosphates or trialkyl phosphites, respectively. In contrast, use of bifunctional phosphorylating or phosphitylating agents like $(RO)POX_2$, (RO)POXY, $(RO)PX_2$, and (RO)PXY, where X and Y are leaving groups, sometimes brings about success. According to this approach, the desired phosphotriesters can be prepared in one pot without isolation of the intermediate formed by condensation of the first alcohol.

### 2.8.4.1 $(RO)POX_2$-type Reagents

The phosphorobistriazolide (**78**; equation 53) reacts with 1 equiv. of an alcohol without any activator to give the corresponding monotriazole (**79**), which then condenses the second alcohol with the aid of an amine to give the fully unsymmetrical phosphotriester (**80**).[113,114] A similar stepwise condensation is achieved by use of the phosphorobis(nitrobenzotriazolide) (**81**)[115] or phosphorobis(1-hydroxybenzotriazolide) (**82**).[116] The phosphorobis(oxazolide) (**83**; equation 54) also serves as the bifunctional reagent. In this case, Mn(acac)$_3$ and Zr(acac)$_4$ catalyze the first and second steps, respectively.[83]

### 2.8.4.2 (RO)PX$_2$-type Reagents

In general, monoesterification takes place in the reaction of a phosphorodichloridite and 1 equiv. of an alcohol in the presence of an amine at low temperature. The condensation with the second alcohol requires an elevated temperature. Thus, an internucleotide bond can be constructed *via* the coupling of (**84**; equation 55) and a nucleoside, forming the phosphorochloridite intermediate (**85**), and the subsequent condensation with another nucleoside.[117] 1*H*-Tetrazole-promoted esterification of the bisphosphoramidite of type (**86**) with two kinds of alcohol occurs in a similar manner.[118,119] The latter procedure is much more efficient for the synthesis of oligonucleotides, because the phosphorodichloridite reagent is too labile in air and cannot be stored for a long period without decomposition. Long sequences of DNA can be prepared by a procedure based on the bisphosphoramidite method.[120]

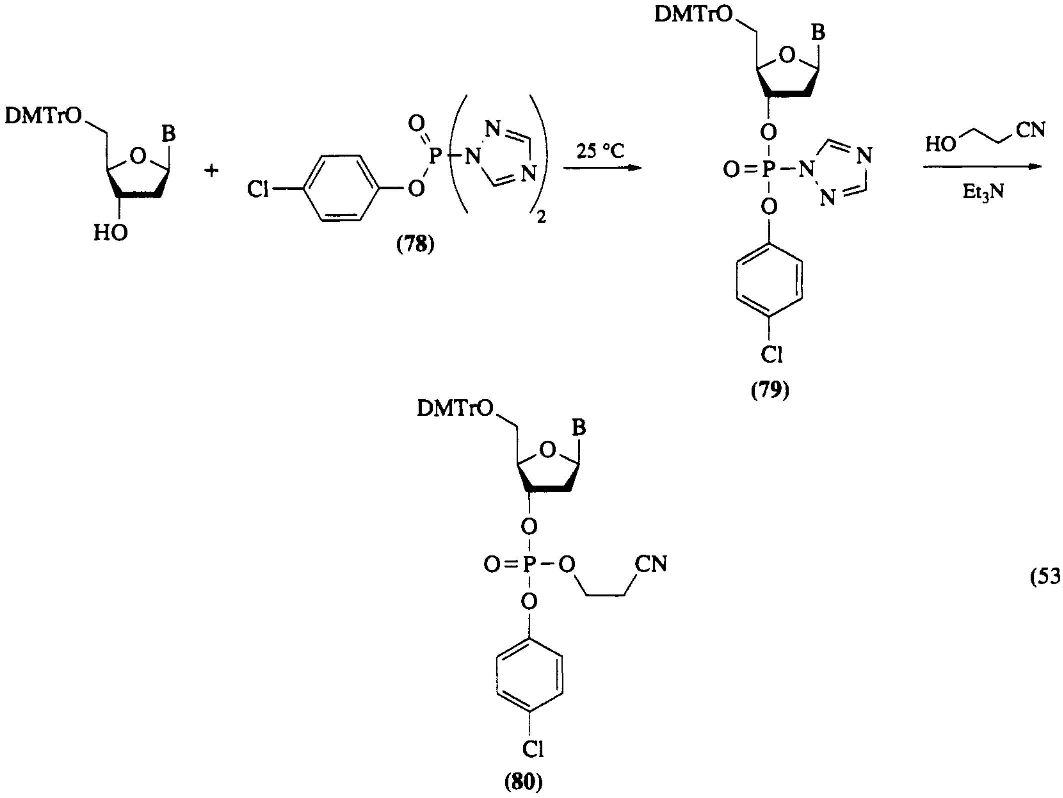

(53)

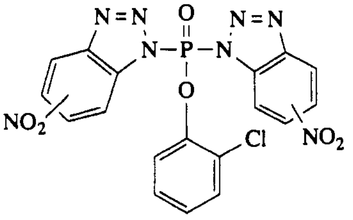

**(81)**

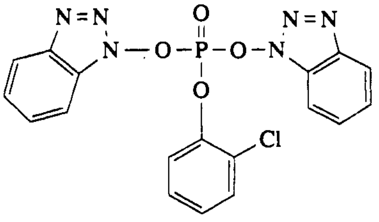

**(82)**

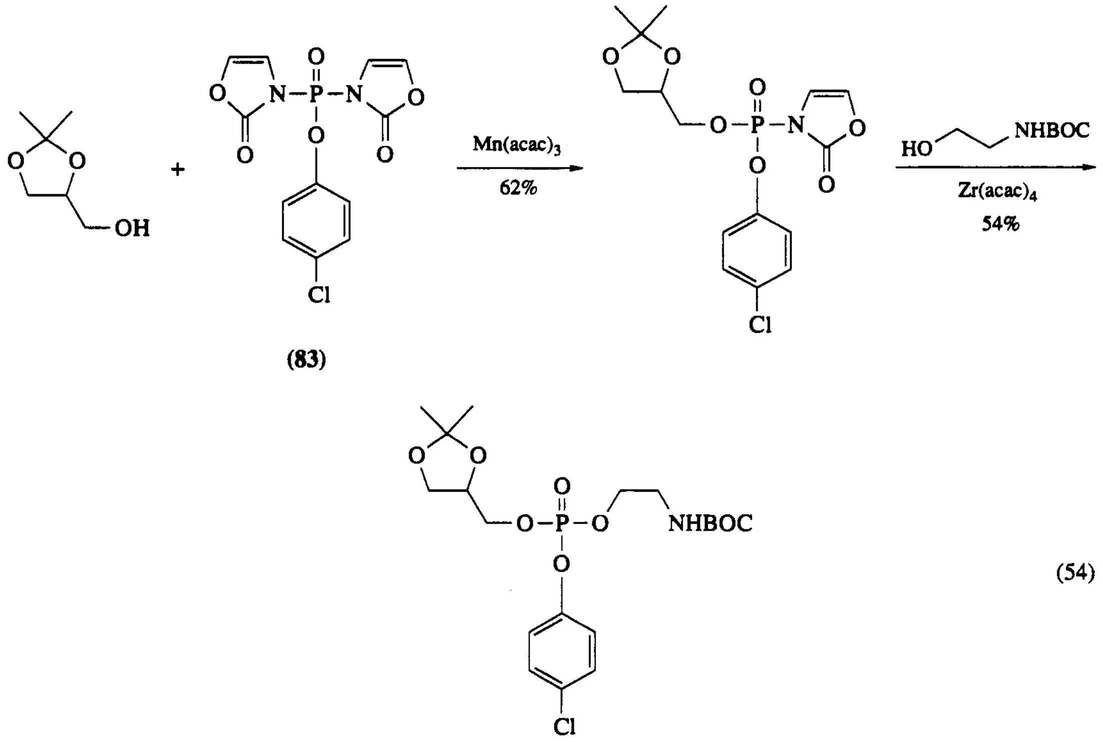

(54)

### 2.8.4.3 (RO)POXY-type Reagents

When the cyclic enediol ester of phosphoric acid (**87**; equation 56)[121] is reacted with the diol (**88**), the cyclic phosphate (**89**) is obtained in a single step.[122] Use of the chlorophosphoryl analog (**90**; equation 57) effects the two-step preparation of the phospholiposterol (**91**).[121,123] The pyrophosphate-type compound (**92**) has a similar reactivity.

The method using (**90**) or (**92**) is applied to the synthesis of many phospholipids and their analogs, oligonucleotides, *etc.*[121,124–127] Interribonucleotide bond formation is accomplished by the successive condensation of the chlorophosphorylnitrobenzotriazolide (**93**; equation 58) and the 3′-free ribonucleoside (**94**) assisted by pyridine, followed by the 5′-free derivative (**95**) promoted by 2,6-lutidine, affording (**96**).[128]

The *p*-nitrophenyl phosphorochloridate (**97**; equation 59) acts as the bifunctional phosphorylating agent when used with 2 equiv. of magnesium alkoxide. The internucleotide linkage formation *via* alcohol activation does not require protectors on all the amino groups of the nucleoside bases.[129] The chlorophosphoromorpholidite (**98**) is a usable bifunctional reagent for the preparation of nucleoside di- and tri-phosphates.[130]

### 2.8.4.4 (RO)PXY-type Reagents

The chlorophosphoramidite (**99**; equation 60)[131] reacts with 1 equiv. of an alcohol in the presence of a tertiary amine to form the unsymmetrical phosphoramidite (**100**), which in turn condenses another alcohol, by the assistance of 1*H*-tetrazole to afford, after oxidation, the unsymmetrical phosphorotriester (**101**). This method has been successfully applied to the synthesis of long DNA sequences. The *H*-phosphonate (**102**; equation 61) exists in an equilibrium mixture with the valence tautomer, phosphite ester (**103**). The phosphite ester (**104**; equation 62) can be activated by pivaroyl chloride in the presence of pyridine to form the mixed anhydride, which reacts with an alcohol to give, after iodine oxidation, the phosphodiester (**105**).[132,133]

The phosphite method is effective for the synthesis of DNA oligomers, because the preparation requires no protection of the phosphoric acid moieties.[132,133]

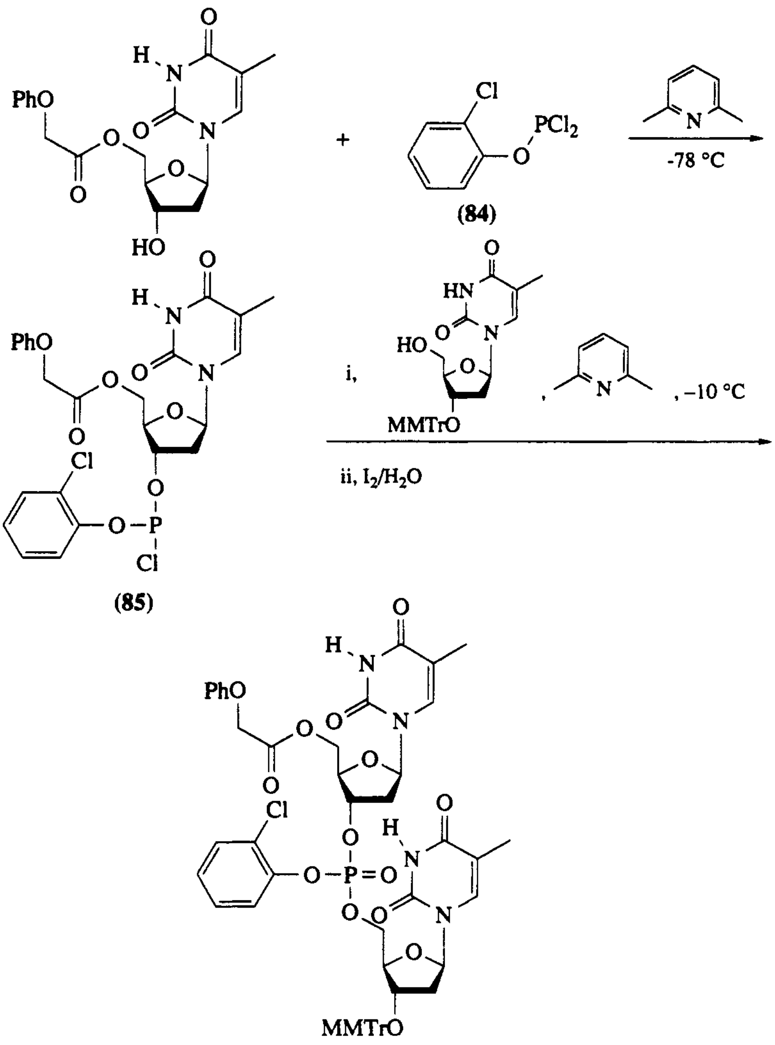

(84)

(85)

(55)

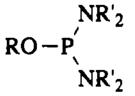

$$\text{RO-P}\begin{matrix}\text{NR}'_2\\ \\ \text{NR}'_2\end{matrix}$$

(86)

## 2.8.5 PROTECTING GROUPS OF PHOSPHORIC ACID

When the preparation of phosphomonoesters or -diesters is exemplified, two types of protecting group are conceivable. One is the protector removed *via* a P—O bond fission and the other through a C—O bond cleavage. In the former case, there is the possibility that a P—O bond fission between undesired positions competes. Use of the latter protector may prevent such side reaction. Thus, at present, the protecting groups belonging to the latter strategy are much more widely employed.

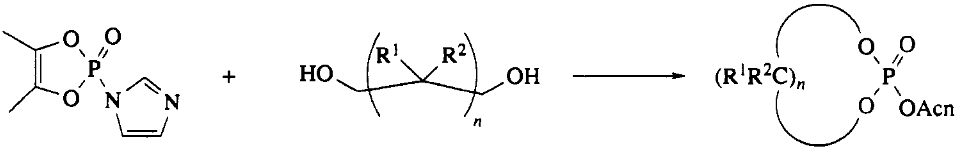

(56)

(87) (88) (89) Acn = CH(Me)COMe

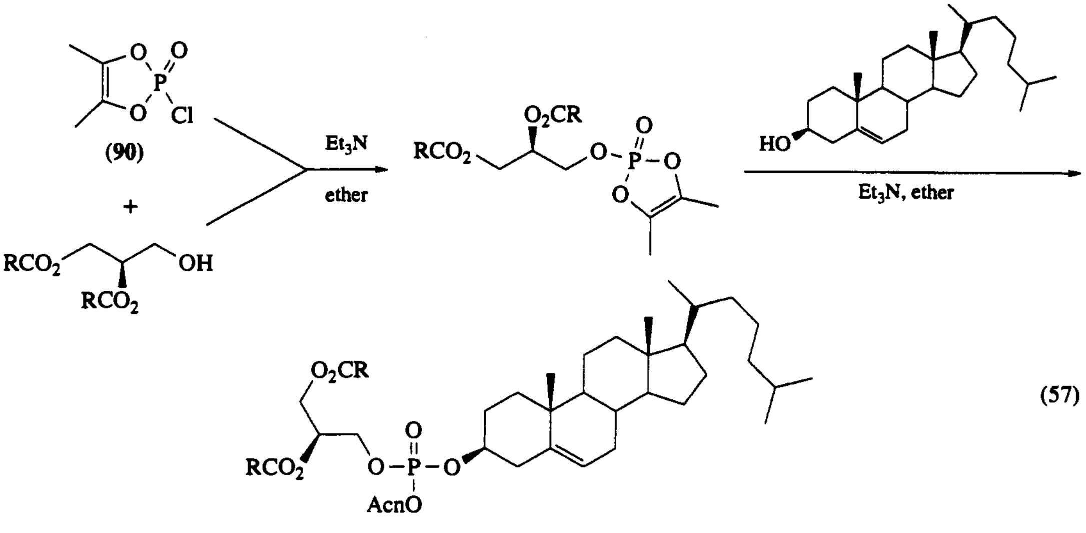
(90)
+
RCO2
OH
RCO2
Et3N
ether
O2CR
RCO2
O
HO
Et3N, ether
O2CR
RCO2
O
AcnO

(91)

(57)

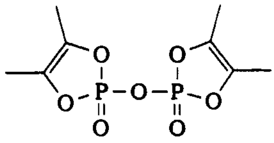

(92)

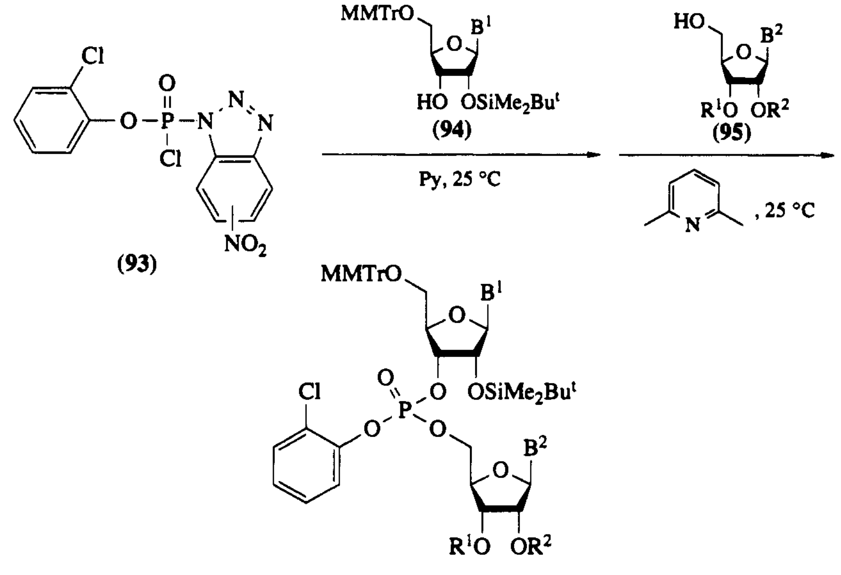
Cl
O
NO2
(93)
MMTrO
B1
HO OSiMe2Bu^t
(94)
Py, 25 °C
HO
B2
R1O OR2
(95)
, 25 °C
MMTrO
B1
Cl
OSiMe2Bu^t
B2
R1O OR2

(96)

(58)

### 2.8.5.1 Aryl Groups

Aryl groups are widely employed as the protector. Some kinds of phenyl derivatives can be removed by basic hydrolysis. The removal, particularly from phosphodiesters, frequently requires high temperature.[134,135] For example, the 4-chloro-2-nitrophenyl ester (**106**; equation 63) is hydrolyzed by sodium

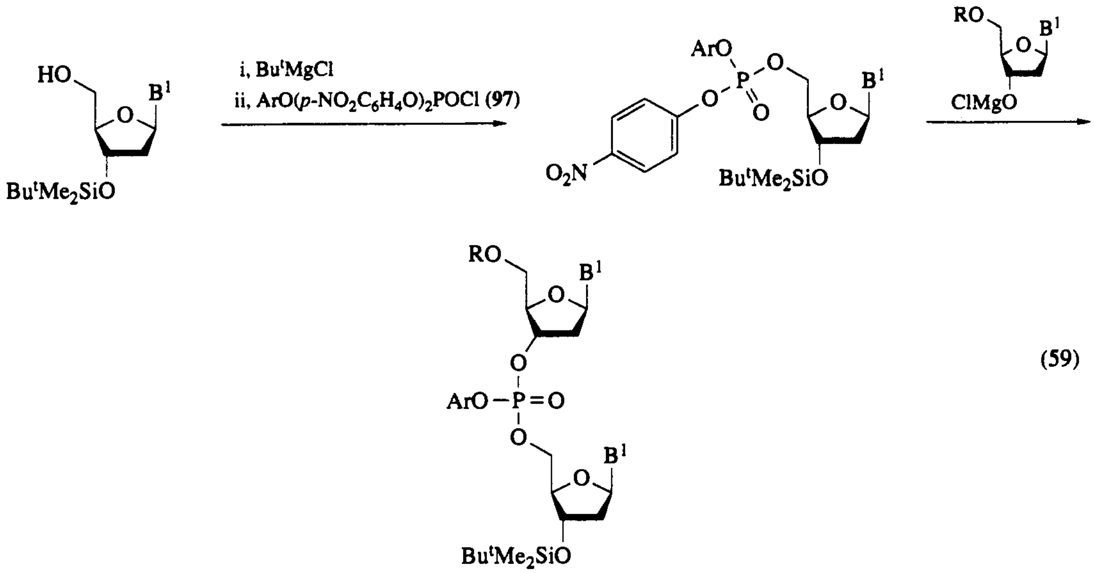

HO
B1
Bu'Me2SiO
i, Bu'MgCl
ii, ArO(p-NO2C6H4O)2POCl (97)
ArO
O2N
RO
ClMgO
ArO-P=O

(59)

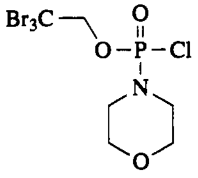

Br3C
O
O-P-Cl
N

**(98)**

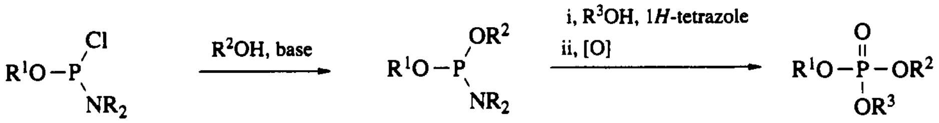

R2OH, base
i, R3OH, 1H-tetrazole
ii, [O]

**(99)** **(100)** **(101)** (60)

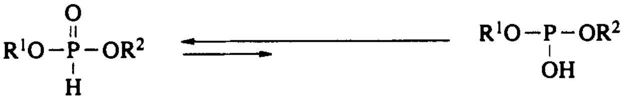

**(102)** **(103)** (61)

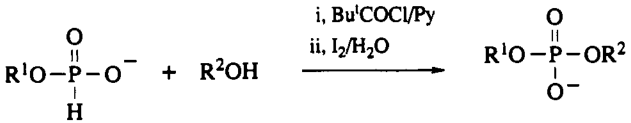

i, Bu'COCl/Py
ii, I2/H2O

**(104)** **(105)** (62)

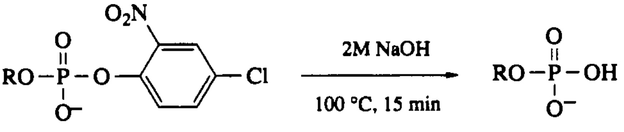

2M NaOH
100 °C, 15 min

**(106)** (63)

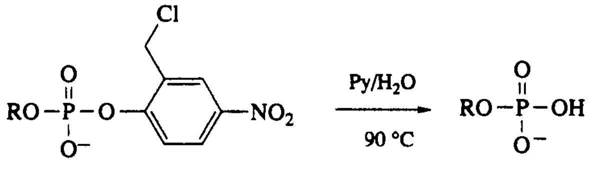

(64)

**(107)**

hydroxide at 100 °C.[136] Similarly, hydrolysis of the 2-chloromethyl-4-nitrophenyl analog (**107**; equation 64) takes place using aqueous pyridine at 90 °C.[137]

The base hydrolysis under harsh conditions very often brings about undesired cleavage of phosphates. In contrast, removal of an *o*- or *p*-chlorophenyl protecting group by $N^1,N^1,N^2,N^2$-tetramethylguanidinium *syn*-*p*-nitrobenzaldoxymate (NBO) (**108**; equation 65) or *syn*-pyridin-2-aldoxymate (PAO) (**109**) is achievable at room temperature and no side reaction occurs.[129,138] The 8-quinolyl phosphate (**110**; equation 66) is also hydrolyzed under mild conditions with the assistance of a stoichiometric amount of $ZnCl_2$ or $CuCl_2$ salt.[139]

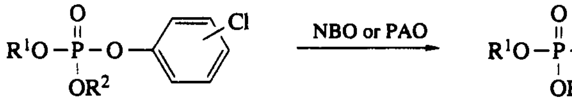

(65)

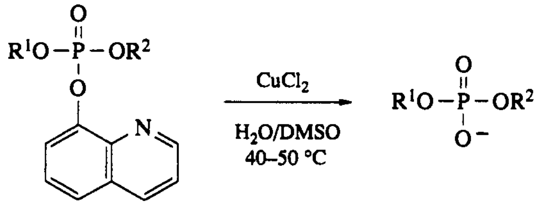

(66)

**(110)**

The 2-*t*-butylphenyl group, which is removed by hydrogenolysis on platinum oxide, is usable in some limited cases (equation 67).[140] 2-Hydroxyphenyl is a useful protecting group in conversion of phosphodiesters to phosphomonoesters. The deprotection is carried out by the oxidative treatment.[141]

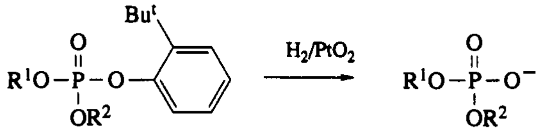

(67)

### 2.8.5.2 Alkyl Groups

Methyl is an easily employable protecting group. Deprotection is effected by thiophenol/triethylamine,[142] metal thiophenoxides,[143,144] dimethyl sulfide/methanesulfonic acid,[145] *t*-butylamine,[146] *etc.* (equation 68). The reaction using potassium thiophenoxide is greatly accelerated by addition of a catalytic amount of dicyclohexyl-18-crown-6.[144] When the demethylation of the methyl ester of nucleoside 5′-phosphoric acid is carried out with thiophenol in the presence of triethylamine, attack of the thiophenoxide to the 5′-carbon of the nucleoside takes place competitively.[142] This side reaction can be prevented to a considerable extent by use of 2-thiopyridine (**111**), 2-thiobenzoxazole (**112**), or 2-thiobenzothiazole (**113**) in place of thiophenol.[147] An allyl group is an excellent protector, removable using a palladium(0) catalyst in the presence of nucleophiles such as primary or secondary amines, and their salts of formic acid (equation 69).[15,120,148] Removal of the allyl protector is effected by sodium iodide in hot acetone.[149] The allyl protection is successfuly applied in oligo-DNA synthesis.[120] Benzyl is the protecting group and is removable by hydrogenolysis, using platinum or palladium metal as the catalyst (equation 70).[101,150] An *o*-nitrobenzyl group is a photolabile protector (equation 71). The reaction conditions do not affect purine or pyrimidine bases of nucleosides.[151] A 1-oxido-2-pyridylmethyl group is also use-

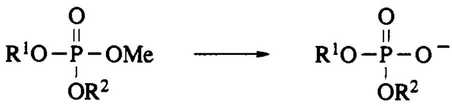
(68)

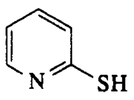
**(111)**

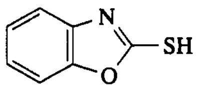
**(112)**

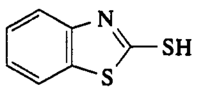
**(113)**

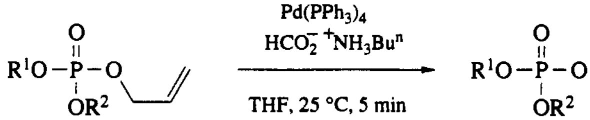

(69)

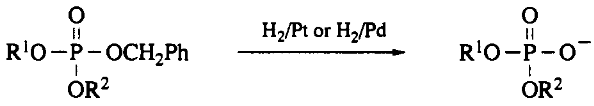

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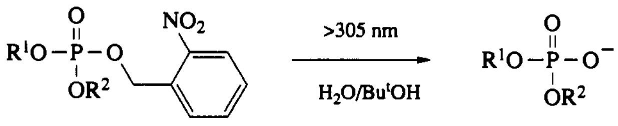

(71)

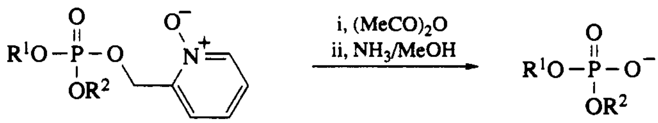

(72)

ful for protection of phosphoric acid, which is deblocked by treatment with acetic anhydride followed by methanolic ammonia (equation 72).[152]

Protecting groups that are removed through a β-elimination mechanism are widely used in oligonucleotide synthesis. 2-Cyanoethyl (equation 73) and related protection can be deprotected by treatment with a base encompassing methanolic ammonia, DBU, *etc.*[146,153] 2-*p*-Nitrophenyl,[154] 2-pyridylethyl,[155] 2-(arylaminocarbonyl)ethyl[156] and 2-(arylsulfonyl)- or 2-(alkylsulfonyl)-ethyl groups[156,157] are similarly usable (equations 74–76). The sulfonylethyl function is usually generated from an arylthioethyl analog by oxidation with sodium periodate or NBS. The fluorene-9-methyl group is another example belonging to this category.[158] Deprotection is conducted by treatment with pyridine containing concentrated ammonia (equation 77). The 2,2,2-trichloroethyl[159,160] or 2,2,2-tribromoethyl groups[131] are protectors reductively removed by treatment with a Zn/Cu couple (equation 78).[159,160] The presence of acetylacetone as an additive in DMF greatly promoted the reaction.[161] A similar effect is observed with anthranic acid in pyridine.[160] The 2,2,2-trichloro-1,1-dimethyl group is also a useful protector, which can be removed with a mixture of triethylamine, tributylphosphine, and DMF (equation 79).[162] A 1-acetylethyl group is readily removed under mild basic conditions (equation 80).[121,163]

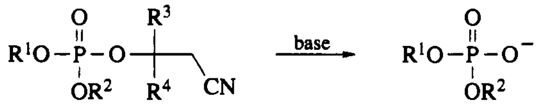

(73)

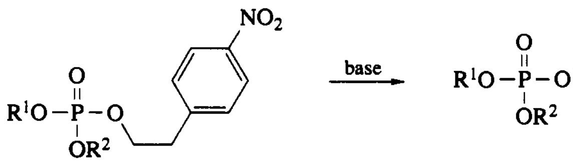

(74)

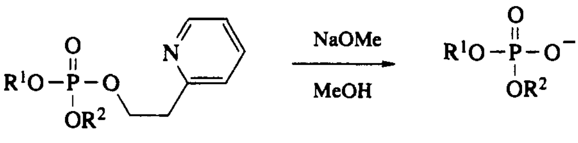

(75)

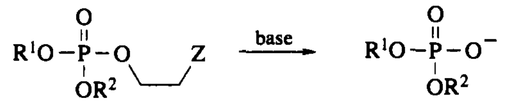

$Z = CONHC_6H_4R^3, SO_2R^3$

(76)

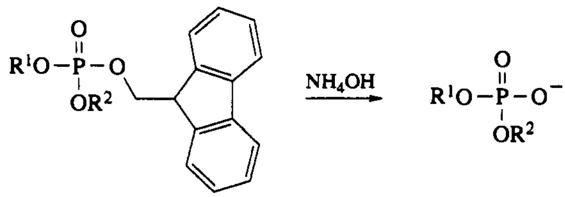

(77)

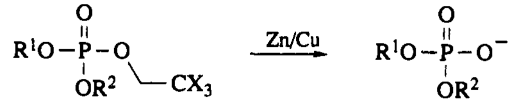

X = Cl, Br

(78)

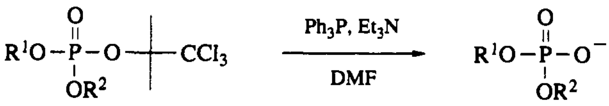

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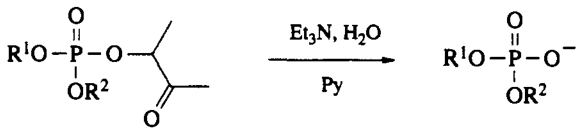

(80)

### 2.8.5.3 Miscellaneous

Thiophosphates can be converted to the phosphates by treatment with tributyltin oxide followed by water (equation 81).[164] Accordingly, the thiophenol is regarded as the protecting group in a formal sense. The transformation is also achieved by oxidative reaction with aqueous iodine (equation 82).[165] Certain kinds of amines also act formally as the protector. When phosphoramidates are treated with isoamyl nitrite in a mixture of pyridine and acetic acid, followed by water, hydrolysis occurs to give the phosphates (equation 83).[166,167] 2,2′-Diaminobiphenyl serves as a bifunctional protecting group deprotectable under similar conditions. Thus, the phosphorodiamidate (**114**; equation 84) is hydrolyzed to the phosphomonoester (**115**).[168] The deprotection is remarkably accelerated by addition of silver acetate and benzoic anhydride.

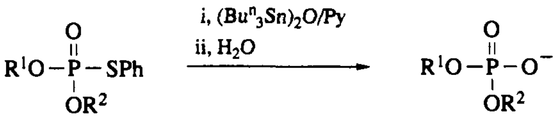

$$\mathrm{R^1O{-}\underset{OR^2}{\overset{O}{P}}{-}SPh} \xrightarrow{\text{i, }(\mathrm{Bu^n{}_3Sn})_2\mathrm{O/Py};\ \text{ii, }\mathrm{H_2O}} \mathrm{R^1O{-}\underset{OR^2}{\overset{O}{P}}{-}O^-} \qquad (81)$$

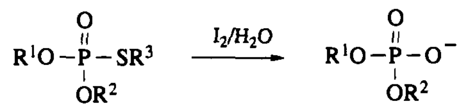

$$\mathrm{R^1O{-}\underset{OR^2}{\overset{O}{P}}{-}SR^3} \xrightarrow{\mathrm{I_2/H_2O}} \mathrm{R^1O{-}\underset{OR^2}{\overset{O}{P}}{-}O^-} \qquad (82)$$

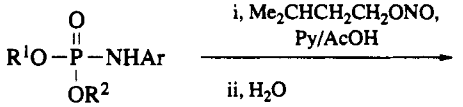

$$\mathrm{R^1O{-}\underset{OR^2}{\overset{O}{\overset{\|}{P}}}{-}NHAr} \xrightarrow[\text{ii, H}_2\text{O}]{\text{i, Me}_2\text{CHCH}_2\text{CH}_2\text{ONO, Py/AcOH}} \mathrm{R^1O{-}\underset{OR^2}{\overset{O}{\overset{\|}{P}}}{-}O^-} \qquad (83)$$

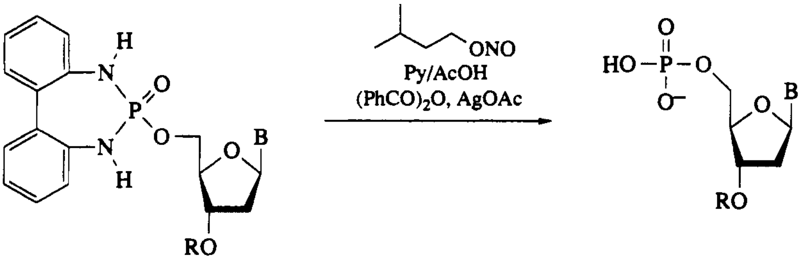

**(114)** **(115)**

(84)

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# 3.1

# Protecting Groups

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## 3.1.1 PRINCIPAL DEMANDS FOR AND ON FUNCTIONAL GROUP PROTECTION

There is hardly any area of preparative organic chemistry in which the proper use of protecting groups is not a prerequisite for the successful achievement of the goals aimed at. For this reason such blocking functions have been developed for nearly 100 years by numerous researchers from all disciplines of organic chemistry, and consequently solutions to the existing problems have been devised, making use of various synthetic transformations. It was Fischer who, among his many important contributions to chemistry, first realized that the application of protecting functions is often a necessity for a successful synthesis. Thus, he introduced the isopropylidene ketal in carbohydrate chemistry[1] (see Section 3.1.3), and for the first time used both the chloroacetyl moiety and a urethane, namely the ethoxycarbonyl group, as

N-terminal-protecting groups (see Section 3.1.2.1) in the selective synthesis of peptides.[2] However, although Fischer tackled the problem, he could not provide reliable blocking functions to address the prevailing synthetic problems in peptide chemistry. It was not until 1932 that the decisive breakthrough for the invention of easily and selectively removable protecting groups was achieved. In this year Bergmann and Zervas reported on the use of the benzyloxycarbonyl (Z, Cbo) group (see Section 3.1.2.1) in peptide synthesis[3] and thereby opened up this new field of organic chemistry. Since then the discipline has continued to grow steadily.

During the past decades the highly selective construction of polyfunctional molecules, *e.g.* nucleotides, oligosaccharides, peptides and glycopeptides, and complex natural products like alkaloids, the macrolide and polyether antibiotics and the prostaglandins, has seen dramatic improvements in the state of the art. These achievements were only possible through the extensive use of protecting groups, which in numerous cases had to be newly designed to overcome the emerging difficulties in the experimental realization of the synthetic plans. The studies aiming at the successful total synthesis of palytoxin,[4] the most complex acyclic compound known to date, provide an impressive example of this. Today, therefore, protecting group chemistry is more important than ever. This review intends to summarize the most practical and commonly used blocking functions, and to offer to the interested reader solutions to prevailing problems, rather than to be a complete summary of all protecting groups described.[5] Very detailed and helpful compilations of the developments reported in the literature up to 1979 are available,[5] and the data collected by Greene in this book have provided the basis for a computerized method to choose the correct protecting group combination in retrosynthetic analysis.[6]

A good protecting group has to meet numerous demands, which themselves heavily depend on the chemical nature of the function to be protected, the other structural elements present in the compound to be transformed and especially the types of reaction to be carried out in subsequent steps. Thus, the benzyloxycarbonyl (Z) group is very efficient for the protection of the amino group during the formation of peptide bonds. If, however, an alkylation of the α-carbon of an amino acid *via* the corresponding enolate is desired it cannot be used, and the nitrogen is best converted to an imine. The second example depicted in Scheme 1 also demonstrates that by a proper choice of the reagent used for protection, further directing effects, like the introduction of sterical bias, can be exerted.

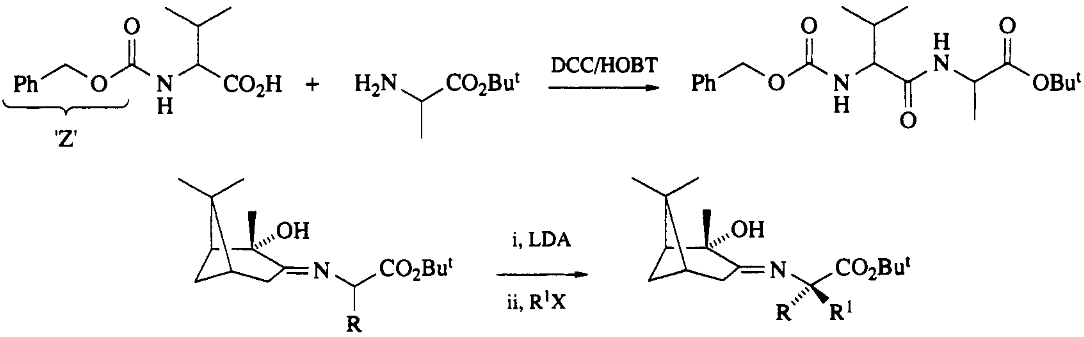

Scheme 1

The major criteria that must be fulfilled by a protecting group are that: (i) it must exclude the protected functional group from participating in the reaction to be carried out; (ii) it must ensure that the protected functional group is not damaged during the projected synthetic transformation; (iii) it must itself be stable during the projected reaction, but at the same time must be removable after this reaction under conditions which will cause no damage to the newly synthesized structure; and (iv) it should not exhibit a destabilizing, but rather a stabilizing, influence on the compound to be protected (*e.g.* epimerizations and racemizations should be suppressed).

For practical reasons a blocking group should, in addition, display the following properties: (i) it should be easy to introduce and to remove, and the reagents for introduction and removal should be readily available, stable and easy to handle; (ii) the protected compound should be easy to characterize, in particular the protecting group should neither possess nor introduce a chiral center; (iii) the solubility of the protected product should be favorably influenced; (iv) it should be put on, and removed from, a functional group in high yields and, after deprotection, the reaction products should be readily separable from the freed compound; and (v) a participation of the protecting group during the reaction must be either unequivocal or excluded.

If several blocking functions are present in a given compound it may be desirable to remove them all in one step. However, the more demanding task, which usually has to be fulfilled in a reaction sequence, is that each single protecting group must be selectively removable, leaving the other blocking functions intact. This strategy has been addressed as 'the principle of orthogonal stability' of protecting groups.[7]

These criteria are highly demanding and, not surprisingly, most of the blocking groups which have been introduced fail to meet them all. On the other hand this is not always necessary. Depending on the synthetic problem to be addressed it is often sufficient that the protecting functions used display only some of the desired properties.

In the synthesis of complex molecules containing numerous different functional groups the interdependence of protecting groups extended by regio- and stereo-chemical requirements creates multidimensional problems which can only be solved by means of a subtle and versatile blocking group strategy. Frequently the overcoming of one problem creates a new one, as, for instance, had to be learned in attempting the synthesis of glycopeptides of type (**1**), representing partial structures of virus envelope glycoproteins and containing the α-fucosyl chitobiose core.[8] For immunological evaluations of such glycoprotein segments all blocking functions must be removable. Furthermore, the exactly specified extension of the peptide part and the coupling of the nondeformed glycopeptide to carrier proteins is highly desirable. This can only be achieved with N- and C-terminal-protecting groups which are orthogonally stable to each other, and which can be selectively removed without affecting the blocking functions and the sensitive glycosidic bonds in the saccharide part. However, the task is even more complex, because the construction of the saccharides themselves involves numerous regio- and stereo-chemical problems.

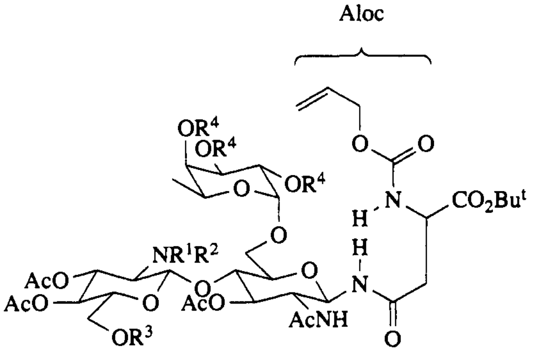

(**1a**) $R^1 = Ac, R^2 = H, R^3 = R^4 = Bn$
(**1b**) $R^1 = R^3 = R^4 = Ac, R^2 = H$

For syntheses of saccharide side chains of *N*-glycopeptides it is generally advantageous to use the anomeric azide group as the blocked form of the amino function, as can be demonstrated for the chitobiose derivatives (**2**). The azide does not usually interfere with ester formations and cleavages, nucleophilic substitutions, acetal formations, acetal reductions and acetal hydrolyses, or interfere with glycosylation reactions. A precondition for the construction of the α-fucoside linkage in (**1**) is that the fucosyl donor (**3**), to be connected with the chitobiose acceptor (**2**), carries nonneighboring group active blocking functions, *i.e.* ether-type protection. This is most commonly achieved with *O*-benzyl-protected fucosyl halides (**3a**). Thus, under *in situ* anomerization conditions[9] (**3a**) and (**2a**) give the desired α-fucosyl chitobiosyl azide (**4a**) with complete stereoselectivity.[8] As a consequence of the benzyl ether protection, the azide in (**4a**) cannot be reduced to the required glycosylamine by usual hydrogenation with palladium or platinum catalysts. The reduction is, however, accomplished using neutral Raney nickel. The amine thus obtained is then condensed with *N*-allyloxycarbonyl (Aloc) aspartic acid α-mono *t*-butyl ester to furnish the conjugate (**1a**). The selective removal of the Aloc group by means of the palladium(0)-catalyzed allyl transfer to dimedone allows N-terminal peptide chain extension without destruction of the complex conjugate. The planned subsequent removal of the C-terminal *t*-butyl ester from the trisaccharide peptide (**5a**) was expected to open the way for the coupling of the synthetic glycopeptide to a carrier protein. However, in contrast to the safe and selective removal of the Aloc group, the treatment of (**5a**) with trifluoroacetic acid resulted in complete cleavage of the fucoside bond. After a synthesis of about 30 steps this result was quite discouraging. It illustrates the fatal consequence of the fact that, although all other demands on selective protecting group chemistry are fulfilled, the sensitivity of the fucoside bond in (**5a**) is incompatible with a selective *t*-butyl ester cleavage. In this situation, two principally different ways could lead to the aimed selective carboxy deprotection of (**5**). The first, and probably more generally applicable one, would consist in a substitution of the carboxy protecting group by another blocking function. Of course, the properties of this substitute may necessitate a modification of the whole synthetic strategy to avoid new undesired interferences. On the other hand, for glycopeptide syntheses a further property of a correctly chosen fucoside-protecting group might advantageously be exploited: the stabilizing effect towards acids exerted by acyl protection in the carbohydrate.

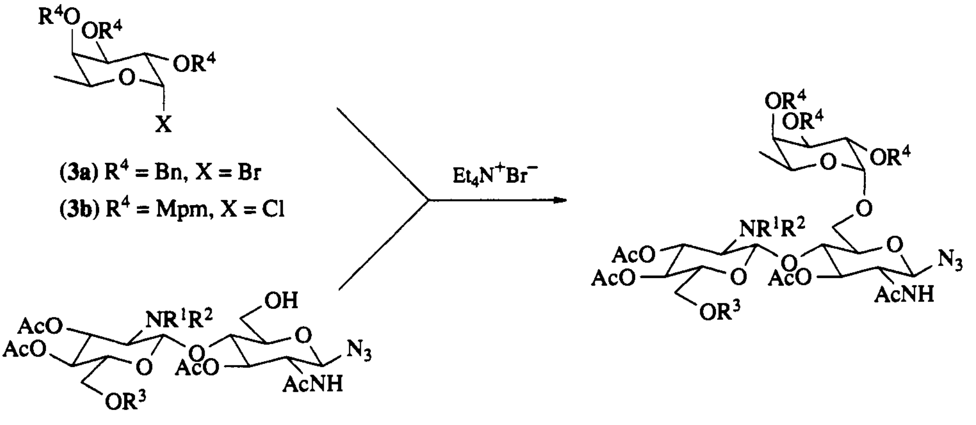

(1)

(**3a**) $R^4$ = Bn, X = Br
(**3b**) $R^4$ = Mpm, X = Cl

(**2a**) $R^1$ = Ac, $R^2$ = H, $R^3$ = Bn
(**2b**) $R^1$ = $R^2$ = Pht, $R^3$ = Ac

(**4a**) $R^1$= Ac, $R^2$ = H, $R^3$ = $R^4$ = Bn
(**4b**) $R^1$ = $R^2$ = Pht, $R^3$ = Ac, $R^4$ = Mpm
(**4c**) $R^1$ = $R^3$ = $R^4$ = Ac, $R^2$ = H

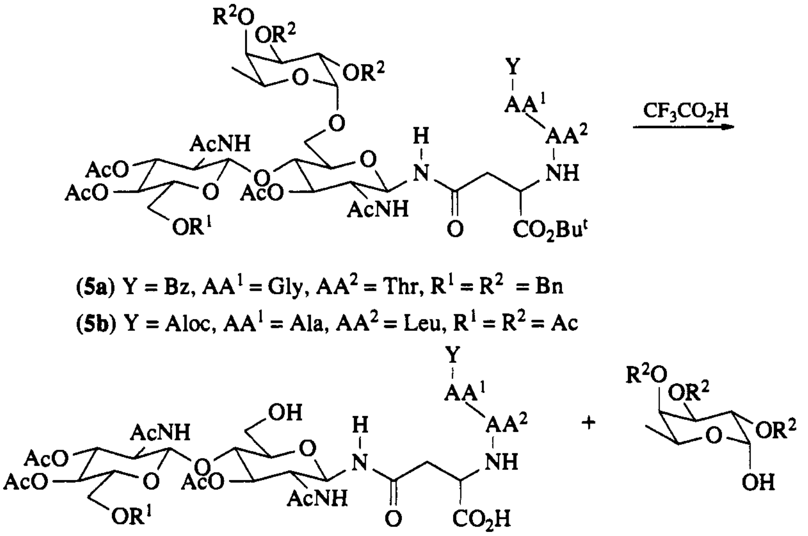

(**5a**) Y = Bz, $AA^1$ = Gly, $AA^2$ = Thr, $R^1$ = $R^2$ = Bn
(**5b**) Y = Aloc, $AA^1$ = Ala, $AA^2$ = Leu, $R^1$ = $R^2$ = Ac

(2)

Experiences in glycopeptide synthesis suggested that acyl protecting functions in the saccharide part enhance the stability of intersaccharidic bonds towards acids.[10] Therefore a new concept was developed, based on the exchange of the fucose-protecting groups in (**4b**) immediately after formation of the α-fucosidic bond. The acid sensitive 4-methoxybenzyl (Mpm) ether protection requires a special construction of the fucosyl donor (**3b**). However, after linking to the acceptor (**2b**) the ether protecting groups are removable from the trisaccharide (**4b**) by means of an oxidation method which does not affect the azide group. Subsequent hydrazinolysis of the phthaloyl moiety and acetylation of the free amino and hydroxy groups furnishes the fully acetylated trisaccharide (**4c**). After hydrogenation the liberated amine is transformed into the conjugate (**1b**) which after N-terminal deblocking is chain-elongated to give the trisaccharide tripeptide (**5b**). The removal of the *t*-butyl ester protection from (**5b**) can now be achieved with complete selectivity by using trifluoroacetic acid. The selectively deblocked compound (**6**) allows for C-terminal chain extension as well as for coupling to a protein carrier.[8] The successful deblocking of (**5b**) as opposed to (**5a**) illustrates the manifold interdependency of properties in protecting group chemistry. It is also a highlighting example which demonstrates that the protecting group (here the acetyl group) not only serves to mask a functionality (in **5b** the hydroxy groups of fucose) but also may strongly influence other structures present (in this example the fucoside bond). Therefore, the realization of a planned synthesis aiming at a complex structure critically depends on the protecting group strategy chosen.

**(5b)**

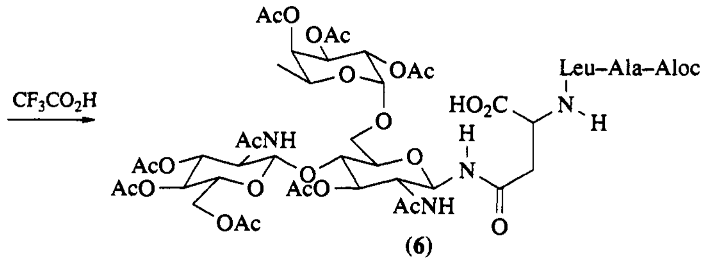

**(6)** (3)

## 3.1.2 AMINO-PROTECTING GROUPS

Amino-protecting groups are extensively used in peptide chemistry.[11] During the formation of a specific peptide bond between two amino acids, one amino function has to remain blocked to ensure the formation of only a single amino acid sequence. Together with the reversible masking of the nucleobases in nucleotide synthesis[12] and the protection of nitrogen atoms in alkaloid synthesis, this constitutes the most important area of application for amino-protecting groups.[5]

### 3.1.2.1 Urethane Protecting Groups

In peptide synthesis the use of a suitable protection for the N-terminal amino group is required not only to prevent the formation of a complex mixture of oligo- and cyclo-peptides, but an additional demand on the functionality applied for this purpose is that it should prevent possible racemization of the activated amino acid. Racemization usually takes place *via* an intermediate oxazolone (**7**) that forms readily from *N*-acyl-protected amino acids (Scheme 2). This side reaction can be mostly suppressed by using a carbamate as an N-terminal-protecting group. Therefore, nearly all blocking functions currently applied in this field are of the urethane type.

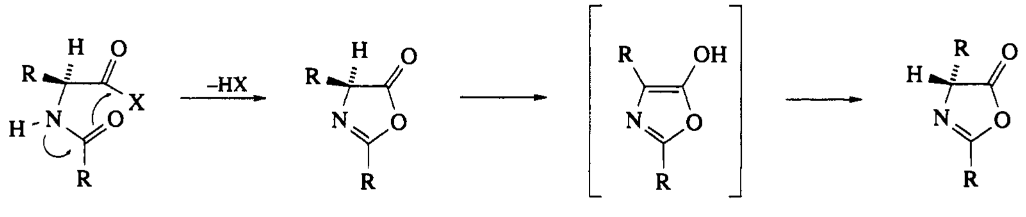

(7)

**Scheme 2**

Since their invention by Bergmann and Zervas in 1932, benzyl carbamates have been widely used as protecting groups. They are easily introduced *via* the corresponding chloroformates[3,11] or the *p*-nitrophenyl carbonates (**8**; Scheme 3).[13] The benzyloxycarbonyl (Z, Cbo) group[3] is stable during the formation of the peptide bond, but can be selectively removed under a variety of conditions. Thus, hydrogenolysis over palladium catalysts in the presence of hydrogen (or hydrogen donors like cyclohexene,[14a] cyclohexadiene[14b] or formic acid)[15] is effective. Furthermore, the group can be cleaved off using sodium in liquid ammonia, or strong acids like HBr/HOAc[17a] and 70% HF/pyridine.[17b] It is, however, stable to hydrazine, to warm acetic acid and to trifluoroacetic acid at room temperature, *i.e.* the conditions used to cleave *t*-butyl carbamates and *t*-butyl esters.

By introducing substituents into the benzylic system, its stability towards acids or reduction can be varied. Electron-withdrawing substituents in the aromatic ring increase acid stability and may accelerate the cleavage by hydrogenolysis. Thus, the 4-nitro-Z group (NZ)[18] and the (isonicotinyl)oxycarbonyl group (Inoc)[23] are stable towards HBr/HOAc but are more quickly removed by hydrogenation than the Z group. On the other hand introduction of electron-donating substituents promotes acid sensitivity, *e.g.* the 4-methoxy-Z group (MOZ)[19] is attacked by trifluoroacetic acid at 0 °C, conditions under which a benzyl

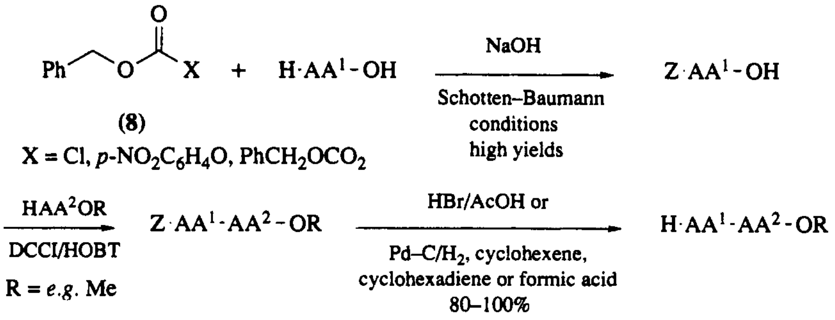
(8)
X = Cl, p-NO₂C₆H₄O, PhCH₂OCO₂
NaOH
Schotten–Baumann conditions high yields
Z AA¹-OH
HAA²OR
DCCI/HOBT
R = e.g. Me
Z AA¹-AA²-OR
HBr/AcOH or
Pd–C/H₂, cyclohexene, cyclohexadiene or formic acid
80–100%
H AA¹-AA²-OR

**Scheme 3**

carbamate is stable. The even more electron-rich 2-(3,5-dimethoxyphenyl)-2-propoxycarbonyl (Ddz) group (see Table 1)[24] is cleaved by 5% TFA in methylene chloride. Table 1 shows a selection of the most commonly used benzyl-type urethane protecting groups. For an extensive compilation of the numerous variants of the Z group see especially Wünsch in ref. 11a.

**Table 1** Selected Benzyl Urethane-type Protecting Groups

| *Benzylic system* | *Abbreviation* | *Stable to* | *Removal by* | *Ref.* |
|---|---|---|---|---|
| 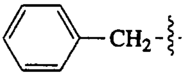 | Z | Base, TFA, $H_2NNH_2$ | $H_2$/Pd, Na/$NH_3$, $Et_3SiH$, $PdCl_2$/$Et_3N$ | 13–17 |
| 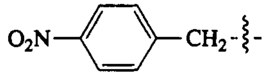 | NZ | Base, TFA, HBr/AcOH | $H_2$/Pd increased, $e^-$/1.2 V, $R_4N^+ X^-$ | 18 |
| 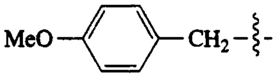 | MOZ | Base | $H_2$/Pd, TFA | 19 |
| 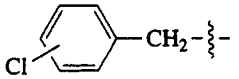 | CZ | Base, TFA | HBr/AcOH, decreased; $H_2$/Ph | 20, 21 |
| 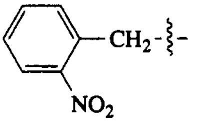 | (2-$NO_2$)Z | Base, TFA | Like NZ, *hv* | 22 |
| 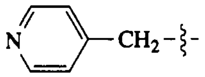 | Inoc | Base, TFA | $H_2$/Pd, Zn/AcOH | 23 |
| 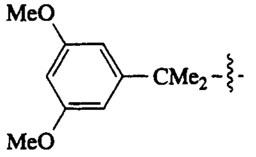 | Ddz | Base | 5% TFA/$CH_2Cl_2$, *hv* | 24 |
| 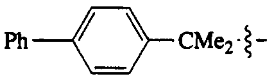 | Bpoc | Base | 80% AcOH/$H_2O$ | 25 |

It is not only benzyl-type urethanes which are widely used for the blocking of amino groups. This goal may also successfully be achieved by the application of alkyl urethanes. Among these, the *t*-butoxycarbonyl group (t-BOC or Boc), introduced in 1957,[26] deserves special mention. Today it probably is the most frequently used amino-protecting function in peptide synthesis. The t-BOC group can be easily introduced using *t*-butoxycarbonyl azide,[27] the commercially available pyrocarbonate[28] or an oxime reagent (t-BOC-ON; **9**).[29]

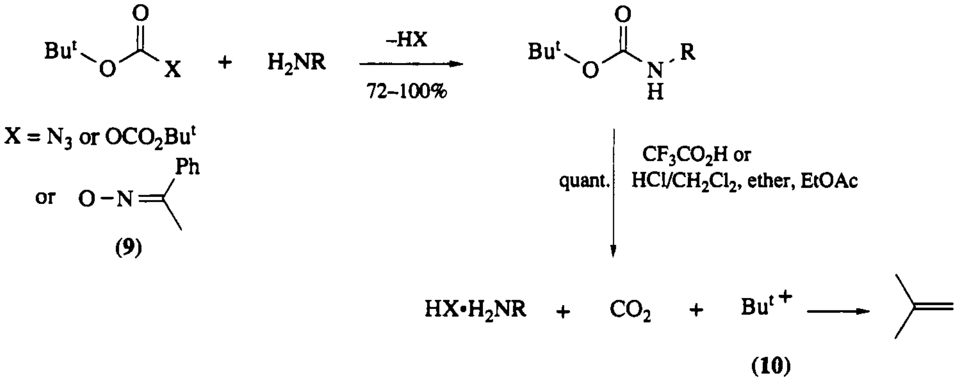

**Scheme 4**

It is stable towards bases and reduction with hydrogen and sodium in liquid ammonia. Its removal can be accomplished with the aid of hydrochloric acid in dichloromethane, ether and ethyl acetate[30] or by using trifluoroacetic acid (neat or dissolved in dichloromethane).[31] Under these conditions the Z group remains unaffected, so that the t-BOC group appears to be an ideal complement to it. During the acid-catalyzed cleavage the *t*-butyl cation (**10**) is formed, which then eliminates a proton to give isobutene (Scheme 4). If, however, nucleophilic reagents are present, *e.g.* mercapto groups as in cysteine, they may be attacked by the cation giving rise to undesired side products. To circumvent this difficulty thiophenol or ethanedithiol should be added as scavengers.[31] Deprotection of t-BOC amino acids and peptide derivatives is also achieved by treatment with trimethylsilyl trifluoromethanesulfonate,[32a–c] and the reagent generated from phenol and trimethylsilyl chloride.[32d]

The underlying principle for the advantageous properties of the t-BOC group, that is the stabilization of the cation formed during acid-catalyzed deprotection by adjacent substituents exerting +I effects, was also adopted for the development of similar blocking functions with varied acid sensitivity. The most important ones among them are presented in Table 2. Once more, introduction of –I substituents causes increased acid stability. In addition, the Ddz and the 2-(4-biphenyl)-2-propoxycarbonyl (Bpoc) groups mentioned in Table 1 may be considered as intermediates between t-BOC- and Z-type protection.

**Table 2** Selected Acid Labile Protecting Groups

| *Protecting group* | *Abbreviation* | *Removal by* | *Ref.* |
|---|---|---|---|
| 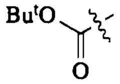 | t-BOC | TFA, HCl/solvent, $Me_3SiOTf$ | 26–32 |
| 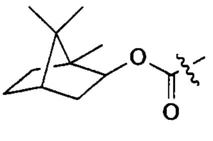 | Iboc | TFA | 33 |
| 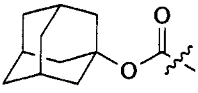 | Adoc | TFA | 34 |
| 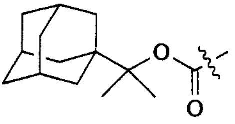 | Adpoc | 3% $TFA/CH_2Cl_2$ | 35 |
| 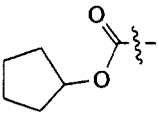 | Cpc | HBr/AcOH | 36 |

Whereas the Z- and the t-BOC-based urethane protecting groups are characterized by their sensitivity towards hydrogenation and/or acids, in recent years a new class of protecting functions which are removable by treatment with bases has been developed. In 1970 Carpino and coworkers introduced the 9-fluorenylmethoxycarbonyl (Fmoc) group for N-terminal protection in peptide synthesis (Scheme 5).[37] Fmoc-protected amines and amino acids are easily formed in the reaction of the amino compound with the chloroformate. After condensation to dipeptides the amino function can be liberated by treatment with bases like piperidine, morpholine, ammonia or ethanolamine. Acids, such as HBr/HOAc or TFA, however, do not affect the Fmoc group. The ease of removal of the Fmoc group has allowed for a new strategy in solid-phase peptide synthesis which is becoming increasingly popular.[38] A certain drawback of the Fmoc methodology, however, is that the protected derivatives (**11**) are sometimes not easily soluble in organic solvents and that the amino group liberated can react with the dibenzofulvene formed, giving rise to undesired side products. The latter reaction can be prevented by using cyclic amines in the deprotection step. In addition, the Fmoc function can be removed by hydrogenolysis. Here, the homobenzylic position is attacked by hydrogen in the presence of a freshly prepared Pd catalyst. This type of reaction appears to be general, since the parent 2-phenylethoxycarbonyl group is also sensitive to hydrogenation and can too be used as an N-terminal-protecting group for the synthesis of peptides (Scheme 5).[39]

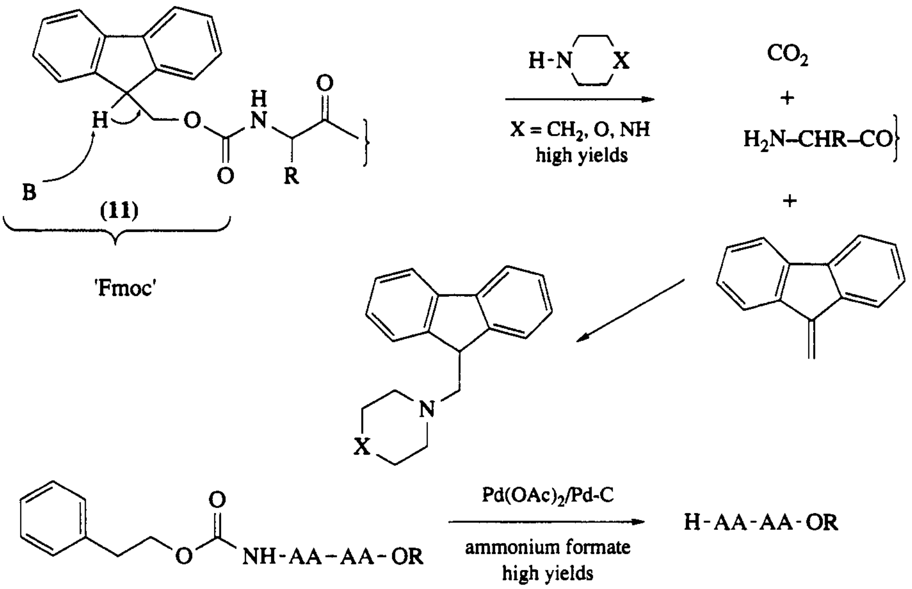

**Scheme 5**

The underlying principle in the cleavage of the Fmoc protecting group is that the base abstracts the bisbenzylic proton from the cyclopentadiene part. The aromatic fluorenyl carbanion generated undergoes an *E1cB* β-elimination reaction. Similar processes are also exploited in several other protecting techniques. Thus, in the tolyl-[40] and methyl-sulfonylethyl[41] carbamates the acidifying functionality is a sulfone (equation 4). The protecting groups can be removed by treatment with bases of the strength of dilute NaOH, but are not attacked by strong acids. Compared to the Fmoc group, these protecting functions are less sensitive to bases. They are stable towards primary and secondary amines in aprotic solvents. Therefore, Tesser and coworkers[41b] designed the 2-[4-(methylsulfonyl)phenylsulfonyl]ethoxycarbonyl (Mpc) group as a new amino-protecting group which is only slightly more stable than the Fmoc group, resists hydrogenation and whose cleavage product does not polymerize spontaneously. The triphenylphosphonioethoxycarbonyl (Peoc) function[42] is even more base labile than the Fmoc group and is cleaved at pH 8.4. Its extreme acid stability allows the preparation of Peoc amino acid chlorides which appear to be very useful in the synthesis of strained cyclic depsipeptides.[43] Acid-stable analogs of the t-BOC group were created following these guidelines, resulting in the use of the 'Cyano-Boc' (CBoc)[44] and the β-trichloro-Boc (TcBoc)[45] groups. Both are stable to trifluoroacetic acid. The CBoc protection is lost at pH 10 (see equation 4) and the TcBoc function can be removed reductively with zinc in acetic acid (see equation 5) or using the supernucleophile lithium cobalt(I) phthalocyanine. The nucleophilic attack at a heteroatom in the β-position of a substituted ethyl carbamate, exploited in the deprotection of the TcBoc group, also forms the basis for the cleavage of 2-haloethyl carbamates[46] and the 2-trimethylsilylethyl carbamate.[47]

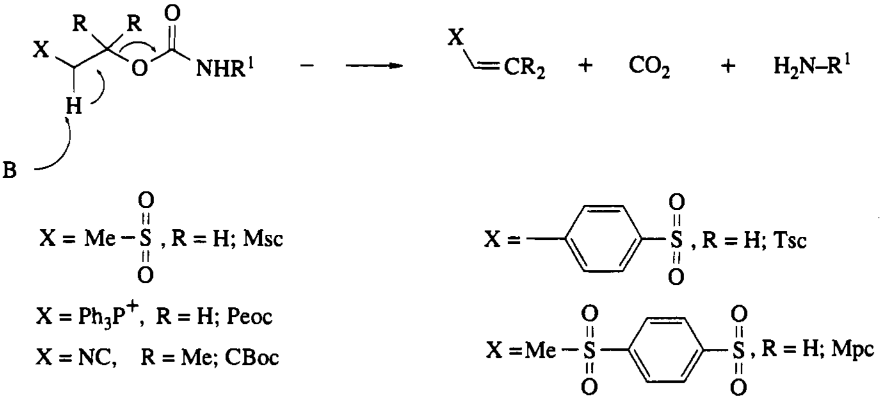

(4)

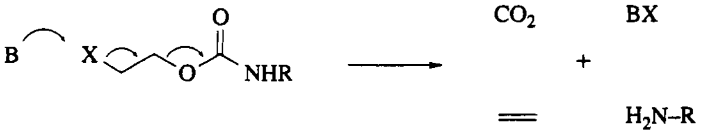

(5)

X = Cl, B = Zn/AcOH or cobalt(I) phthalocyanine (ref. 46a)

X = Br, B = Zn/AcOH, electrolysis or cobalt(I) phthalocyanine (ref. 46b)

X = I, B = Zn/MeOH (ref. 46d)

X = $Me_3Si$, B = KF or $Bu_4N^+F^-$ (ref. 47)

Not only β-elimination reactions were introduced for fragmentation-induced deblocking. The *m*-chloro-*p*-acyloxybenzyl carbamates (**12**),[48] the *p*-(dihydroxyboryl)benzyl carbamate (**13**)[49] and the 5-benzisoxazolylmethoxycarbonyl group (**14**)[50] can all be regarded as substituted Z groups. On the one hand they can be cleaved by hydrogenolysis. Alternatively, however, treatment with base (for **12** and **14**) or $H_2O_2$ at pH 9.5 (for **13**) results in the formation of a phenolate which then decomposes to a quinomethane, $CO_2$ and the free amine (Scheme 6).

An inherent disadvantage of the very base- and acid-labile protecting groups is that their reactivity retained during the projected synthetic steps (which make the protection necessary) must be considered. Therefore, side reactions and unwanted loss of the blocking groups become possible. In particular, when several protecting functions of comparable sensitivities are present at the same time, the selective liberation of one functionality may be complicated. These difficulties can be overcome by applying protecting groups which are introduced in a chemically stable form, and which, if deprotection is desired, are modified to yield a chemically sensitive structure. Protecting functions of this type are called 'two-step protecting groups'. This principle was first developed in the form of the 2-methylthioethyl ester as a carboxy-protecting group.[51] On the basis of this concept, the 2-(methylthio)ethoxycarbonyl (Mtc)[52] and the (1,3-dithian-2-yl)methoxycarbonyl (Dmoc)[53] groups were designed for amino protection (Scheme 7). Both are relatively stable towards acids and bases, but, after oxidation of the sulfurs to sulfones, base-induced β-elimination liberates the amino function. The acidifying influence exerted by the oxidized Dmoc group is so strong that the deprotection occurs at pH 7.5.

Applying the same principle, 2- and 4-pyridylethoxycarbonyl (2- and 4-Pyoc)[54] structures can be sensitized by methylation of the pyridine nitrogen. Subsequent treatment with the weak base morpholine ($pK_a \approx 8.3$) in dichloromethane already induces fragmentation and the formerly protected amino group is liberated (Scheme 8). This method proved to be successful in the synthesis of acid- and base-sensitive *O*-glycopeptides with tumor-associated antigen structure.[53b]

Further examples for this type of protecting group strategy were developed for amides and esters (*vide infra*; levulinyl esters, azidobutyryl esters and *o*-nitrophenylpropionyl amides). Although the two-step protecting groups circumvent the presence of potentially labile structures for protection, they require the use of further chemical transformations which might also harm other parts of the molecule to be deprotected (*e.g.* the methylations of the Pyoc groups and the oxidations of the Dmoc and the Mtc groups de-

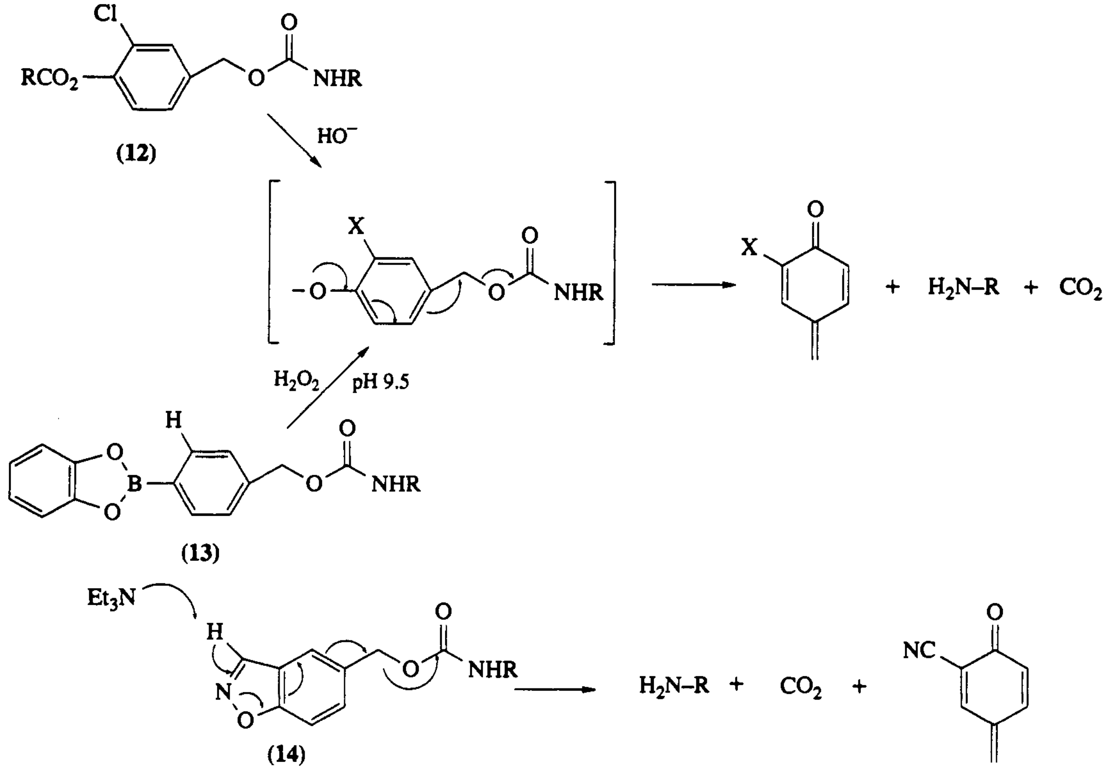

Scheme 6

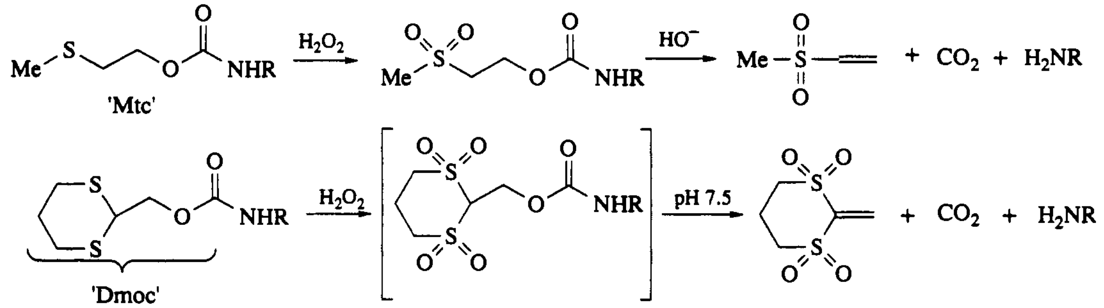

Scheme 7

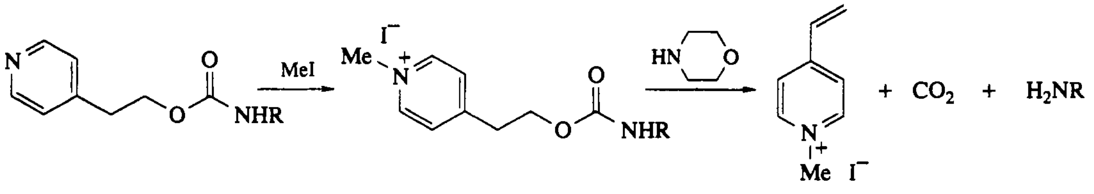

Scheme 8

scribed above cannot be performed in the presence of methionine, cysteine or tryptophan). This disadvantage may be overcome by initiating the protecting group removal through the action of a reagent which is unreactive towards the other functionalities present, but at the same time regio- and chemoselectively activates the desired group without performing a chemical transformation. This principle could be realized in the allyl esters (see Section 3.1.5.1) and the allyloxycarbonyl (Aloc) group (Scheme 9).[55] This long-known amino-protecting function[56] is easily introduced using chloroformic acid allyl ester and is stable towards bases and strong acids. The removal of the Aloc group can be accomplished under nearly neutral conditions by palladium(0)-catalyzed allyl transfer to weakly basic nucleophiles like morpholine (**18**) or CH-acidic compounds like dimedone (**16**) and *N*,*N*′-dimethylbarbituric acid (**17**).[57]

Recently, tributyltin hydride was described as the allyl-trapping reagent in this amino-deblocking reaction.[58] The earlier reported method,[59] unknown at that time in peptide chemistry, consisted in the use of 2-ethylhexanoic acid ions as the allyl-trapping nucleophiles. However, this nucleophile is not generally applicable for amino deblocking because of the more rapidly occurring competing reaction of the liberated amino group itself as the allyl-accepting nucleophile. During the deprotection reaction the palladium catalyst interacts as the electron donor with the allylic system and forms a π-allylpalladium complex (**15**) which then is attacked by the nucleophile, liberating the $Pd^0$ compound again. This protecting principle proved to be particularly advantageous for the construction of biologically important and chemically very sensitive glycopeptides.[10] An example in which the removal of the Aloc group was carried out in the presence of complex structures being sensitive to acids and bases is mentioned in Section 3.1.1. One of the decisive applications of the Aloc protecting principle is shown in Scheme 10.[8]

Allyl-type protection is becoming increasingly popular. In addition to the use of Aloc amino acids in peptide synthesis,[8,55–58] it has been applied to the blocking of alcohols, phenols, phosphates and carboxylic acids (see the respective chapters and references given in ref. 58) and also for the introduction of a new linking principle for solid-phase peptide synthesis, making removal of the synthesized peptide under nearly neutral conditions possible.[60] Several modifications of the parent system as well as the allyl-trapping reagents have been described.[58–61] However, the most reliable and advantageous nucleophile for the removal of the Aloc moiety appears to be *N,N′*-dimethylbarbituric acid (**17**).[57] It not only undergoes no side reactions (the tin hydride may reduce enones; dimedone may form enamines with amino groups) but it also protonates liberated amino groups, thereby protecting them from further electrophilic attack. Its anion is a very weak base unable to cause racemization. In other developments no additional nucleophile is needed since the substituted allylic moiety under the conditions applied eliminates a β-hydrogen (in boiling dioxane) to form a diene[61] or is attacked by the liberated carboxylate (see Section 3.1.5.1). Among the substituted modifications of the Aloc group, the cinnamyloxycarbonyl analog[62] shows an increased acid sensitivity and is not reliably stable during *t*-butyl ester cleavage. In contrast, the *p*-nitrocinnamyloxycarbonyl (Noc) group[57] is not only completely stable towards trifluoroacetic acid but also resists rhodium(I)-catalyzed isomerization of the allyl system which is used for allyl ester deblocking.[63]

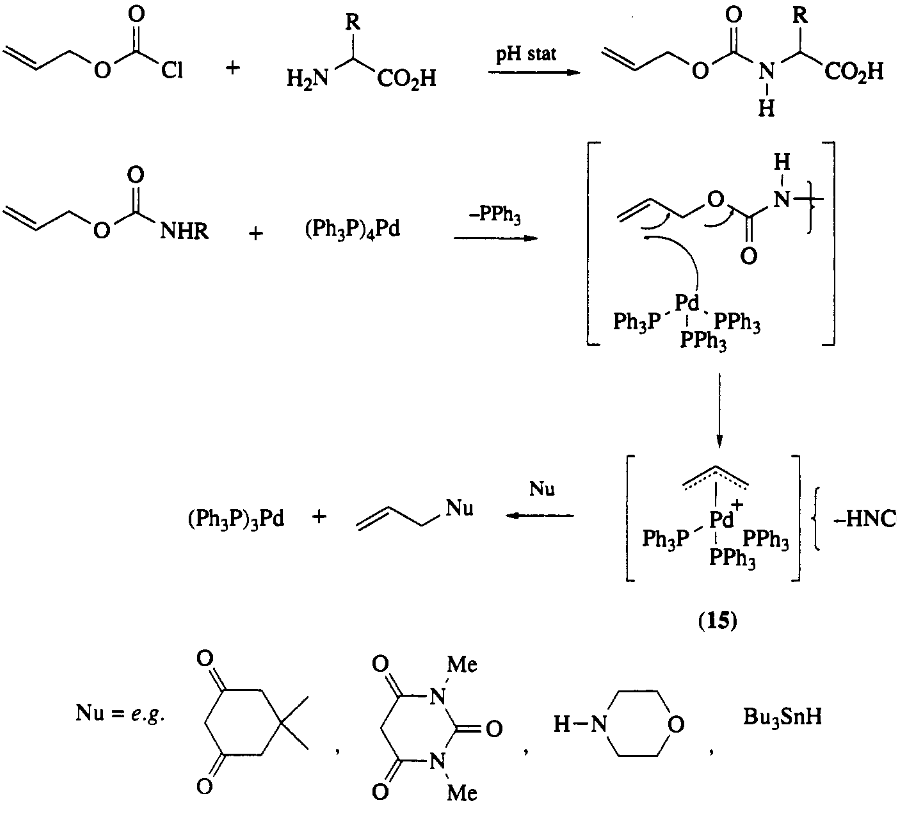

(**15**)

(**16**) (**17**) (**18**)

**Scheme 9**

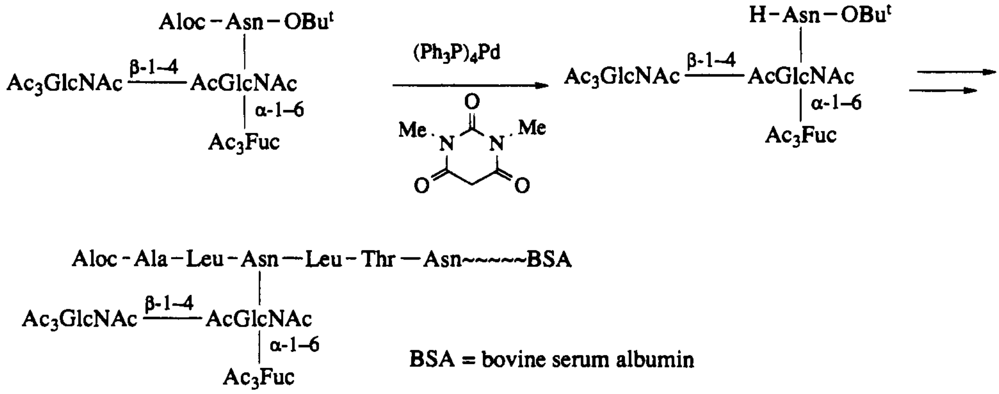
Aloc-Asn-OBu^t
Ac3GlcNAc β-1-4 AcGlcNAc
α-1-6
Ac3Fuc
(Ph3P)4Pd
Me N N Me
O
O O
H-Asn-OBu^t
Ac3GlcNAc β-1-4 AcGlcNAc
α-1-6
Ac3Fuc
Aloc-Ala-Leu-Asn—Leu-Thr—Asn~~~~~BSA
Ac3GlcNAc β-1-4 AcGlcNAc
α-1-6
Ac3Fuc

BSA = bovine serum albumin

**Scheme 10**

### 3.1.2.2 Acyl Protecting Groups

Amides can in most cases be readily synthesized from activated derivatives of carboxylic acids and amines. They are fairly stable and often need harsh conditions for their removal. On the one hand this prompted a search for advanced methods for their selective cleavage; on the other, however, amides generally are used for the protection of chemically stable compounds, *e.g.* in nucleotide chemistry. In more recent developments, acceleration of the deprotection reaction by intramolecular attack and the advantageous properties of amido hydrolases have been exploited.

The most simple amide function is the *N*-formyl group, used by Fischer.[64] Its removal could be carried out using acid or base, but newer methods have applied oxidation with $H_2O_2$[65] or reduction to an acetal.[66] Acetamides also usually require strongly acidic or basic conditions for their hydrolysis. However, a much milder method, which leaves *O*-acetates untouched, consists of the *O*-alkylation of the amide group with oxonium salts, followed by hydrolysis of the imidate formed (Scheme 11).[67] Substituted acetates in many cases can be cleaved by much milder processes. Thus, mono-, di- and trichloro- as well as trifluoro-acetamides[68] are more easily hydrolyzed by acids or bases. The removal of a further class of substituted acetamides is based on the generation of a nucleophile in the molecule followed by its intramolecular attack on the amide group. In such a transformation *o*-nitrophenylacetamides after hydrogenation to the corresponding amino compounds break down to the free amine and the cyclic amide.[69] The same principle is realized in the *o*-nitrophenoxyacetamide,[70] the 3-(*o*-nitrophenyl)propionamide (**19**)[71] and the *o*-nitrocinnamide (Scheme 12).[72] A particularly interesting example of this type consists of the removal of the chloroacetyl group, applied by Fischer,[73] but only as a precursor for glycine, after treatment with *N*-thiocarbamoylpiperidine.[74]

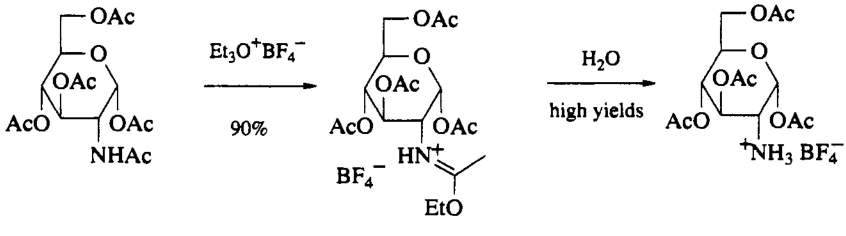
OAc
O
OAc
AcO
OAc
NHAc
Et3O+BF4−
90%
OAc
O
OAc
AcO
OAc
HN+
BF4−
EtO
H2O
high yields
OAc
O
OAc
AcO
OAc
+NH3 BF4−

**Scheme 11**

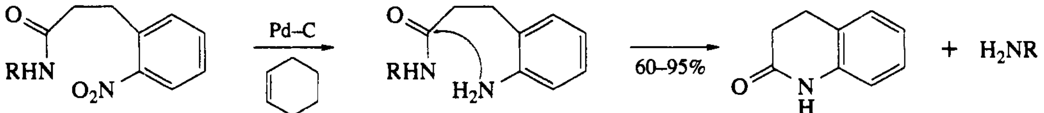
O
RHN
O2N
Pd–C
O
RHN
H2N
60–95%
O
N
H
+ H2NR

(**19**)

**Scheme 12**

In nucleotide chemistry amide-type protecting functions have proven to be very useful and are widely used. The amino group in guanine is usually blocked as the isobutyramide (**20**), adenine is masked as the

*N*-benzamide (**21**) and cytosine as the benzamide (**22**) or the 4-methoxybenzamide.[12,75] These derivatives all must be cleaved with strong bases, *e.g.* 9 M $NH_3$.

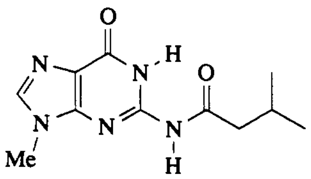

**(20)**

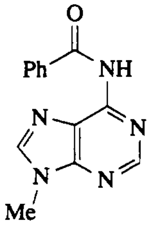

**(21)**

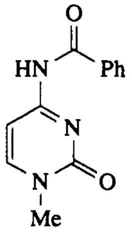

**(22)**

In peptide, as well as in carbohydrate chemistry, phthalimides (Pht) are applied for the temporary protection of primary amino functions.[76] They are easily introduced *via* phthalic anhydride or *N*-ethoxycarbonylphthalimide.[77] The Pht group is stable to acids and provides neighboring group assistance in glycosylations. It can finally be removed with hydrazine or hydrazine acetate (Scheme 13). Among analogous diacylamide protections the dithiasuccinyl (Dts) group (equation 6) should be mentioned.[78] It resists acids, but is easily cleaved by thiols and obviously has advantageous properties in solid-phase synthesis. The introduction of the Dts group requires several steps. Furthermore, the protected form exhibits remarkable carbonyl activity, which limits its application.

The great chemical stability and lack of reactivity under mild conditions for deprotection has greatly hampered the widespread application of amides in protecting group chemistry. However, recent developments in this area may suggest that proteases and amidohydrolases of broad substrate specificity can serve to overcome these drawbacks. Thus, 3-phenylpropionamides and *N*-benzoylphenylalanine amides are attacked by chymotrypsin (pH 7, 37 °C).[79] The application of penicillin acylase for the selective removal of the phenylacetamido residue from peptides (**23**; equation 7) and carbohydrates[80] is also promising.

Besides the protecting groups based on carboxylic acid amides, the attention should also be drawn to derivatives of other acids. Arylsulfonamides are stable to bases and to catalytic reduction, but may be cleaved with sodium in liquid ammonia or butanol and heating in strong acids. The most commonly used

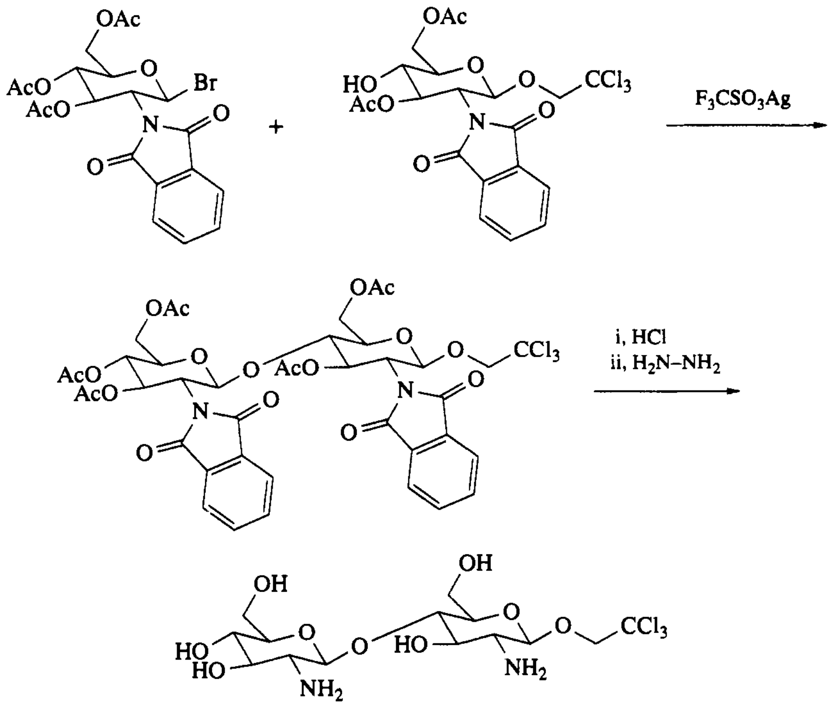

**Scheme 13**

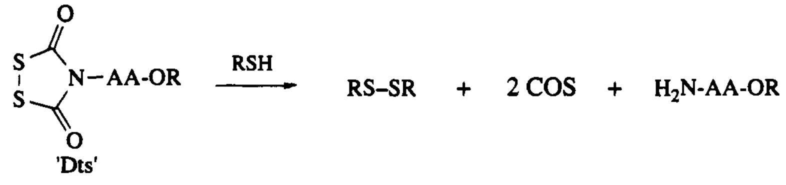

(6)

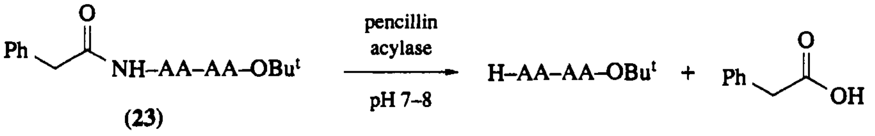

(7)

sulfonamide is the tolylsulfonyl (Tos) group which can also be removed by photolysis and cathodic reduction.[81] A modern alternative, especially recommended for the protection of the arginine guanidino function, is the 4-methoxy-2,3,6-trimethylphenylsulfonyl (Mtr) group[82] which can be cleaved off with trifluoroacetic acid. The acid sensitivity of this group has been even more enhanced by conformational optimizing of the +M effect in the form of the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) group[83] shown in equation (8).

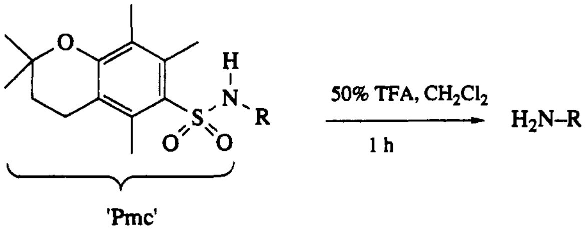

(8)

Among the phosphorus-containing blocking functions the diphenylphosphinyl (Dpp)[84] and the diphenylthiophosphinyl (Ppt)[85] groups were advantageously applied in peptide synthesis. Both are resistant to mild alkaline hydrolysis, hydrazinolysis and hydrogenation, but are readily cleaved with trifluoroacetic acid without intermediary formation of carbocations. *N*-Sulfenyl derivatives of amines are conveniently prepared from the sulfenyl halides. They can be cleaved by acid hydrolysis, nucleophiles and Raney Ni/$H_2$. Here the *o*-nitrophenylsulfenyl (Nps) group,[86] which has extensively been used in peptide chemistry,[87] is the most representative example (Scheme 14).

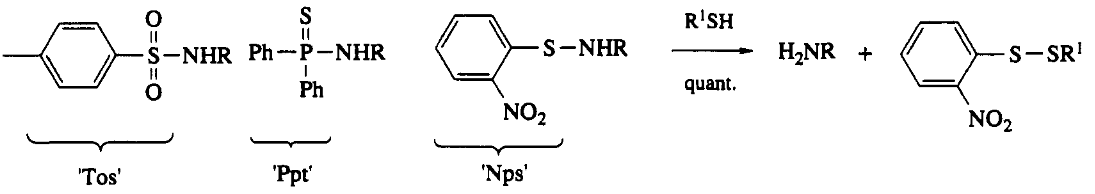

**Scheme 14**

### 3.1.2.3 Alkyl and Alkylidene Protecting Groups

In numerous applications the presence of acyl protecting groups cannot be tolerated. In these cases *N*-alkyl protection often provides a viable alternative. For instance, the *N*-benzyl group proved to be the only reliable choice for amino protection in the racemization-free synthesis of α-amino aldehydes (**24**) from amino acids (Scheme 15).[88] Its removal is best accomplished by catalytic transfer hydrogenolysis[89] or with sodium in liquid ammonia.[90]

Allyl- (**25**) and phenacyl-amines (**26**) are also practical alternatives. They can be cleaved after isomerization of the allyl moiety to the acid sensitive vinyl amines,[91] or with zinc in acetic acid.[92] The bulky triphenylmethyl (Tr) group (**27**), readily removed by mild acid hydrolysis, possesses advantageous shielding properties and has found applications in the protection of amino acids (Scheme 16).[93]

Amines and β-keto carbonyl compounds form enamines in high yields. This reaction has been used to protect amino acids and amino acid esters (Scheme 17).[94] Enamines (**28**) from acyclic β-dicarbonyl com-

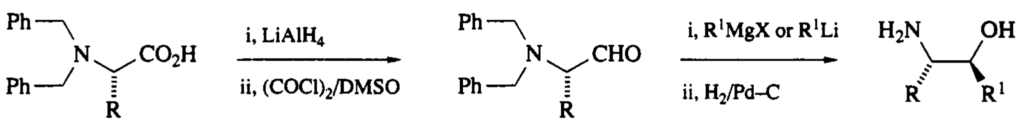
i, LiAlH$_4$
ii, (COCl)$_2$/DMSO
i, R$^1$MgX or R$^1$Li
ii, H$_2$/Pd–C

**(24)**

**Scheme 15**

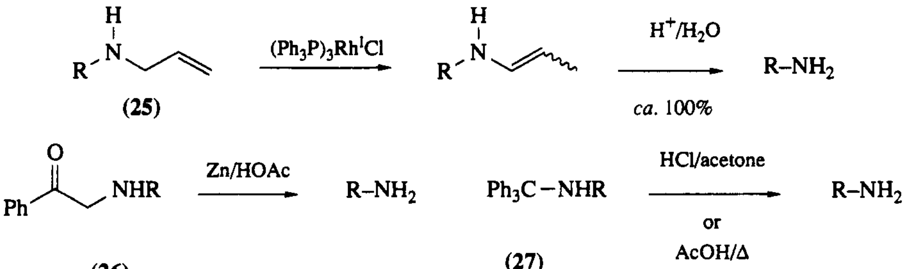
(Ph$_3$P)$_3$Rh$^I$Cl
H$^+$/H$_2$O
R–NH$_2$
ca. 100%
Zn/HOAc
R–NH$_2$
Ph$_3$C–NHR
HCl/acetone
or
AcOH/Δ
86%
R–NH$_2$

**(25)** **(26)** **(27)**

**Scheme 16**

pounds are sensitive to acid hydrolysis, but those derived from cyclic carbonyl compounds (**29**) are more stable because of the missing intramolecular hydrogen bonding.[94b]

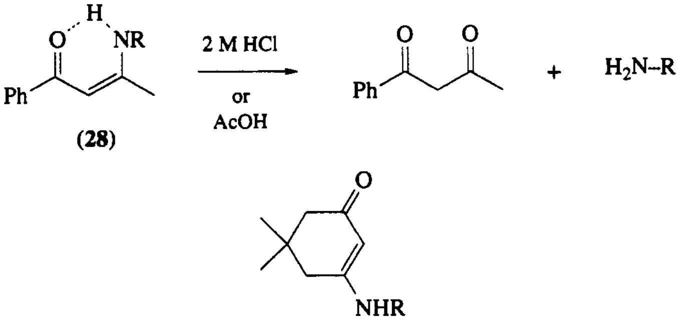
2 M HCl
or
AcOH
+ H$_2$N–R

**(28)** **(29)**

**Scheme 17**

Imines were extensively applied for the protection of the amino group in the synthesis of unusual amino acids. They have been used in both chiral and achiral form (see Scheme 1), and in the first case high asymmetric induction was achieved.[95] The most common derivative is the *N*-benzylideneimine[96] but ketones have also been used for this purpose,[97] as is demonstrated in Scheme 18.

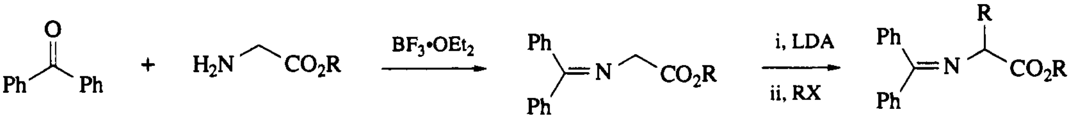
BF$_3$•OEt$_2$
i, LDA
ii, RX

**Scheme 18**

### 3.1.2.4 Special Amino-protecting Groups

Amines are known to coordinate to various metal ions and this has been exploited for their temporary protection, *e.g.* as zinc and copper(II) chelates.[11,98] For the selective functionalization of the ε-amino group of lysine, the phenolic hydroxy group of tyrosine or the side chain carboxylic acids in aspartic and glutamic acid, the α-amino and the α-carboxy groups are protected as copper chelates. After the desired reaction has been carried out, the metal ion is removed with 2 M HCl or even better with thioacetamide, EDTA or hydrogen sulfide (Scheme 19).

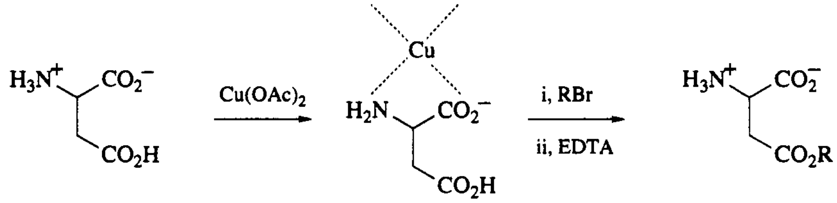

Scheme 19

Azido groups constitute protected forms and precursors for amines and have been used in this sense, for instance, in carbohydrate chemistry. Here for the stereoselective synthesis of α-glycosides a non-neighboring group active substituent in the 2-position of the glycosyl donor is needed and the azido group serves well (Scheme 20).[99] After the glycoside has been constructed, the azide is reduced to the amine with nickel boride,[99b] thioacetic acid,[100a] $H_2S$[100b] or tertiary phosphines in the presence of water.[10,101] In addition, the anomeric center of carbohydrate amines can be masked in the form of a 1-azide which is stable under a variety of conditions.[8,102] For a further example see the use of 4-azidobutyryl esters (Section 3.1.5.1).

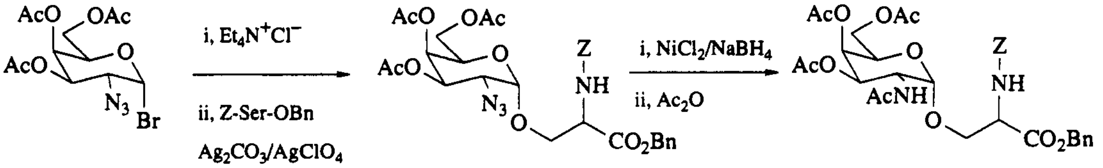

Scheme 20

Recently silicon-based protection has matured into a new broad area of protecting group chemistry (see Section 3.1.3.2) and amines can also be conveniently blocked with appropriate silicon reagents. In organometallic syntheses, *e.g.* in the alkylation of amino acid enolates, the so-called stabase adducts (**30**) serve to temporarily protect the α-amino group (Scheme 21).[103] In the absence of hard nucleophiles, in particular of O-nucleophiles, the Si—N bonds are stable, but deprotection is readily effected in the presence of water and acids.

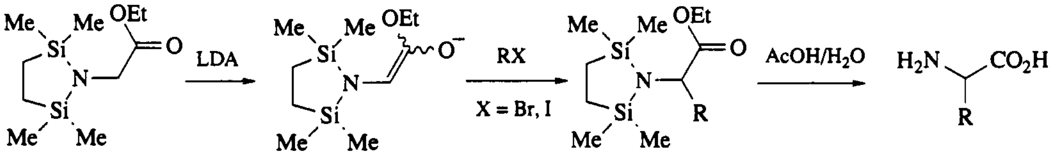

(**30**)

R = *e.g.* methyl, allyl, propargyl

Scheme 21

### 3.1.3 ALCOHOL-PROTECTING GROUPS[104]

In carbohydrate and nucleotide chemistry one of the regularly arising problems is the selective protection and liberation of a specific hydroxy function in the presence of several others of comparable reactivity. Also, in steroids, hydroxy acids and some amino acids alcoholic functions frequently have to be masked. In addition, for the successful completion of most total syntheses of complex natural products, in particular macrolide and polyether antibiotics and prostaglandins, numerous problems of hydroxy protection have to be solved, and many new developments stem from this area. Isolated hydroxy groups are generally protected as ethers, acetals and esters, while 1,2- and 1,3-diols are best masked *via* the formation of cyclic acetals and ketals. Whereas simple alkyl ethers are resistant to mild cleavage conditions, acetals are hydrolyzed under mild acid catalysis. In general, benzyl-type protecting groups are removed by hydrogenolysis, silyl ethers by reaction with fluoride ions or under slightly acidic conditions and several 2-substituted ethyl ethers can be cleaved by β-elimination reactions.

### 3.1.3.1 Ether and Acyclic Acetal Protecting Groups[104]

Ethers usually are prepared by the Williamson ether synthesis, *i.e.* by nucleophilic displacement on alkyl halides or sulfates. The system silver oxide/alkyl halide is also efficient. The numerous variations in ether-forming reactions cannot be outlined in this survey. They are covered in extensive reviews.[104] Among the more recent contributions the acceleration of etherifications by phase transfer catalysis[105] and the ether formation with methyl triflate in pyridine[106] should be noted. The cleavage of simple alkyl ethers by acids occurs only under drastic conditions; therefore, they have mainly been used, not as protecting groups, but rather as a means of functionalization to obtain more favorable properties for analytical techniques. Thus, after permethylation, carbohydrates can be analyzed conveniently by gas chromatography and mass spectrometry.[107] Recently the introduction of iodotrimethylsilane for the cleavage of methyl ethers,[108] shown in equation (9), offered new opportunities. Disadvantages of this method are that the relatively aggressive reagent also attacks other functionalities (esters, urethanes, other ethers) and that alkyl iodides are formed. This can be overcome by using $SiCl_4$/NaI or $SiMeCl_3$/NaI.[109] Further milder methods for the cleavage of methyl ethers involve combinations of Lewis acids with soft nucleophiles, *e.g.* $BF_3$/thiol and $AlCl_3$/EtSH (equation 10).[110]

$$\text{R–OMe} \xrightarrow[\text{ii, H}_2\text{O} \atop \text{70–80\%}]{\text{i, Me}_3\text{SiI}} \text{R–OH} + \text{MeOH} \qquad (9)$$

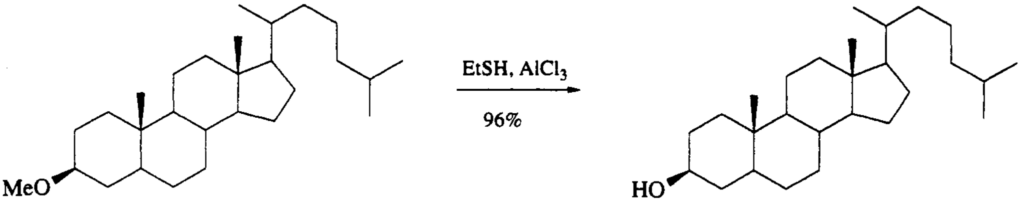

(10)

To overcome the difficulties encountered in the application of simple alkyl ethers, suitably substituted ether variants were introduced. Many of these systems were developed by Corey and Bock.[111] and are nowadays widely used in natural product synthesis. In general, these groups protect the hydroxy functions as acyclic acetals. The most common ones are derived from formaldehyde and synthesized by a Williamson reaction with halomethyl alkyl ethers (Scheme 22). According to this method methoxymethyl (MOM) ethers (**31**) are formed in yields of 80–86%.[112a] They may alternatively be obtained from formaldehyde dimethyl acetal by transacetalization.[112b] The MOM group is readily removed under acidic conditions or again by transacetalization with thiophenol.[113] The benzyloxymethyl (BOM)[114] and *t*-butyloxymethyl groups[115] can be similarly introduced. The BOM group is cleaved by hydrogenolysis or with sodium in ammonia, the *t*-butyl acetal hydrolyzes readily in aqueous trifluoroacetic acid (Scheme 23).

The methylthiomethyl (MTM) ethers (**32**), mainly applied in natural product synthesis, represent thioacetals of formaldehyde. These ethers again are formed by Williamson-type reactions; however, the

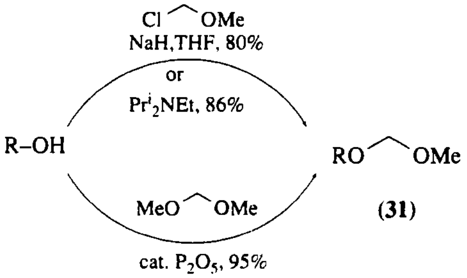

**Scheme 22**

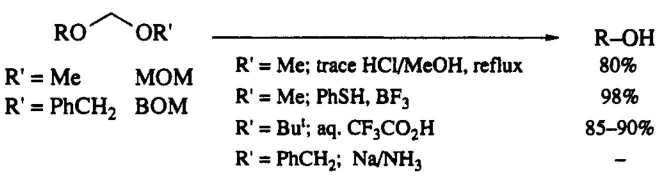
RO⌒OR'
R' = Me MOM
R' = PhCH$_2$ BOM
R' = Me; trace HCl/MeOH, reflux
R' = Me; PhSH, BF$_3$
R' = Bu$^t$; aq. CF$_3$CO$_2$H
R' = PhCH$_2$; Na/NH$_3$
R–OH
80%
98%
85–90%
-

Scheme 23

chloromethyl acetal must be converted *in situ* to the iodide[111] or activated with Ag$^+$.[116] Further methods for MTM introduction consist of a Pummerer rearrangement with dimethyl sulfoxide (DMSO) and acetic anhydride[117a] or treatment of the respective alcohol with dimethyl sulfide in the presence of dibenzoyl peroxide (Scheme 24).[117b]

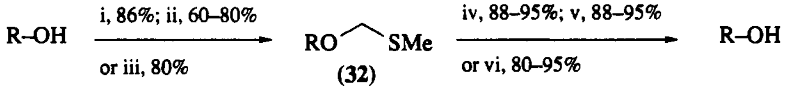
R–OH
i, 86%; ii, 60–80%
or iii, 80%
RO⌒SMe
(32)
iv, 88–95%; v, 88–95%
or vi, 80–95%
R–OH

i, NaH then NaI/ClCH$_2$SMe; ii, ClCH$_2$SMe, AgNO$_3$/NEt$_3$;
iii, DMSO, Ac$_2$O, AcOH, r.t; iv, HgCl$_2$, MeCN/H$_2$O, r.t.;
v, AgNO$_3$, THF/H$_2$O, r.t.; vi, MeI, NaHCO$_3$, acetone/H$_2$O

Scheme 24

Formaldehyde acetals are effectively labilized by Lewis acids like ZnBr$_2$ or TiCl$_4$ if a second oxygen atom in a β-position promotes the coordination of the metal. This is used in the removal of the 2-methoxyethoxymethyl (MEM) ethers (**33**; Scheme 25).[118] They were designed to protect alcohols with formation and cleavage under aprotic conditions and were advantageously used in syntheses of brefeldin A (**34**)[118] and gibberelic acid.[119] A variant of this type of protecting group is the 2-methoxyphenoxymethyl moiety.[120]

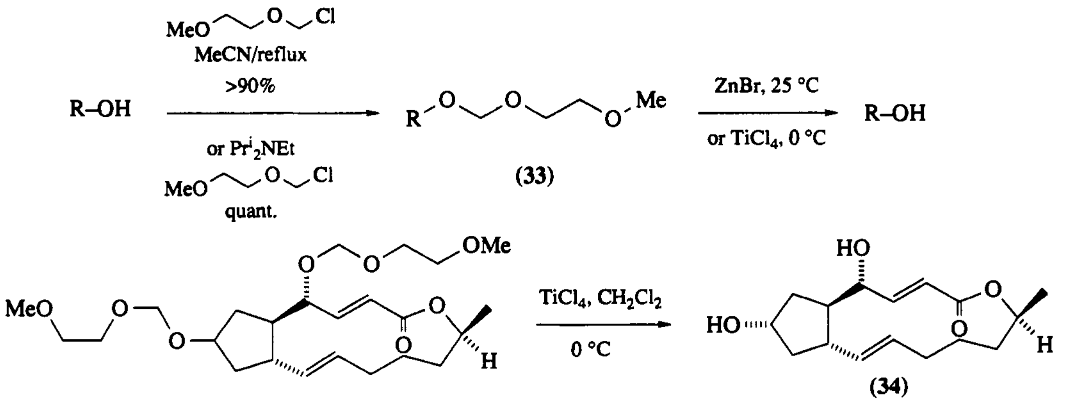
R–OH
MeO⌒O⌒Cl
MeCN/reflux
>90%
or Pr$^i_2$NEt
MeO⌒O⌒Cl
quant.
(33)
ZnBr, 25 °C
or TiCl$_4$, 0 °C
R–OH
MeO
O
O
O
OMe
O
O
O
H
TiCl$_4$, CH$_2$Cl$_2$
0 °C
HO
HO
O
O
H
(34)

Scheme 25

For the liberation of acetal-masked alcohols under nonacidic conditions, β-eliminations, already mentioned in Section 3.1.2.1, were adopted. Following this concept the 2,2,2-trichloroethoxymethyl (**35**)[121] and the 2-(trimethylsilyl)ethoxymethyl (SEM) ethers (**36**)[122] were proposed. Both are introduced *via* Williamson syntheses and their removal is initiated by treatment with Zn or Zn/Cu in methanol[121] or by fluoride-induced β-elimination[122] respectively. Similarly, the trichloroethyl ether had already been applied in carbohydrate chemistry (Scheme 26).[123]

Before all these acetal-based protecting groups were introduced, the tetrahydropyranyl (THP) ether had found extensive use in organic synthesis.[124] It can easily be synthesized from a variety of hydroxy-containing compounds like carbohydrates, amino acids, steroids and nucleotides by the acid-catalyzed reaction with dihydropyran. It is stable to bases, but the protection is removed through acidic hydrolysis with hydrochloric acid, toluenesulfonic acid or acidic ion-exchange resin (Scheme 27). In the case of acid sensitive substrates, *e.g.* containing an epoxide or a further acetal, pyridinium *p*-toluenesulfonate should be applied for particularly mild deprotection conditions.[125]

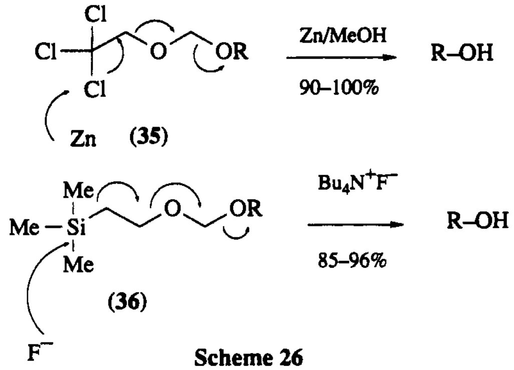
Cl
Cl
Cl
O
OR
Zn
Zn/MeOH
90–100%
R–OH
Me
Me – Si
Me
O
OR
$F^-$
$Bu_4N^+F^-$
85–96%
R–OH

(35)

(36)

**Scheme 26**

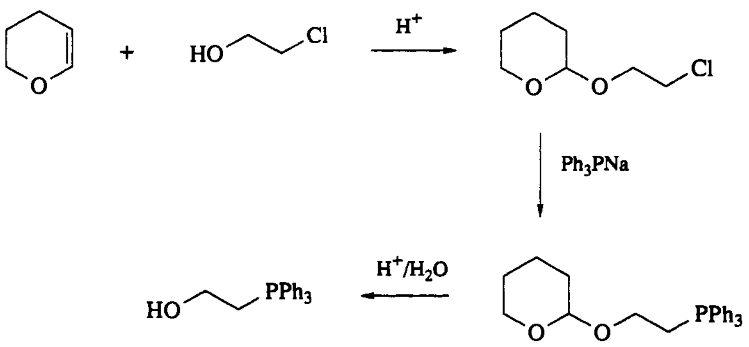
O
+
HO
Cl
$H^+$
O
O
Cl
$Ph_3PNa$
HO
$PPh_3$
$H^+/H_2O$
O
O
$PPh_3$

**Scheme 27**

As a similar protecting function the 1-ethoxyethyl ether, formed by reaction of the alcohol with ethyl vinyl ether, was introduced (Scheme 28). It displayed advantageous properties for the construction of oligonucleotides since it could be cleaved with 5% acetic acid without affecting the internucleotide bond.[126]

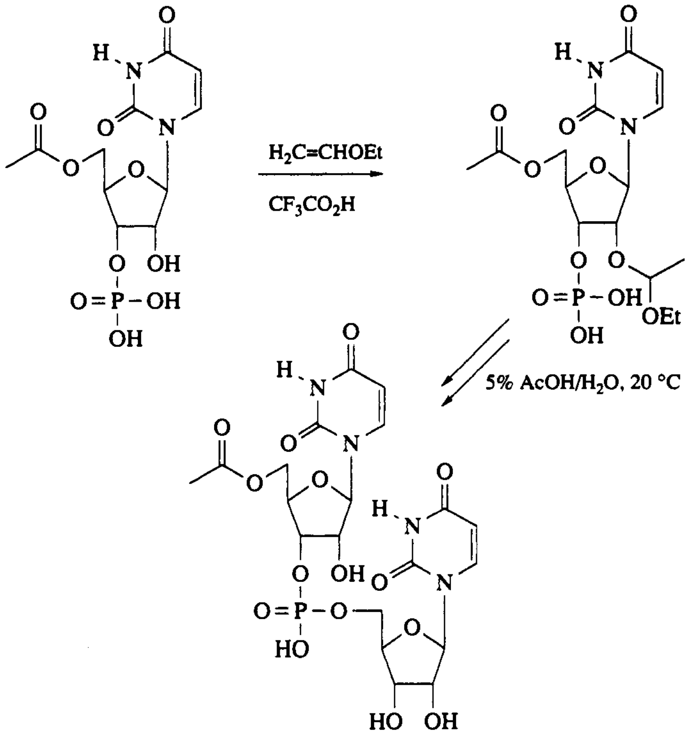
$H_2C{=}CHOEt$
$CF_3CO_2H$
5% $AcOH/H_2O$, 20 °C
O=P–OH
OH
OEt
HO
HO OH

**Scheme 28**

An inherent disadvantage of the THP and acetaldehyde acetals is that they contain a new chiral center, giving rise to mixtures of diastereomers if chiral alcohols are involved. This can be overcome by the use of 4-methoxytetrahydropyranyl ethers (Scheme 29).[127] They are extensively applied in oligonucleotide synthesis. The analogous thiopyranyl compounds are hydrolyzed five times more quickly, but their *S,S*-dioxides 2000 times more slowly, than the corresponding oxygen compounds.

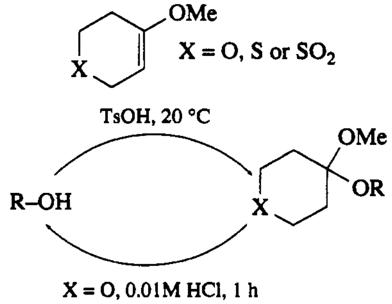

**Scheme 29**

An important family of acid labile ether protecting groups consists of the trityl (Tr) group and its substituted variants. Due to their high steric demand, trityl ethers are mainly used to selectively mask primary alcohols in the presence of secondary ones. Consequently, the major fields of their application are carbohydrate and nucleotide chemistry. Thus, in the presence of pyridine, trityl chloride selectively reacts with the 6-OH group of glucose (Scheme 30),[128] and also other mono- and di-saccharides can be selectively substituted. The Tr protecting function is also introduced using a variety of other reagents, *e.g.* 1-tritylpyridinium tetrafluoroborate or tritylated pyridones.[128] The latter reagents in particular react with high substrate selectivity and allow the protection under neutral conditions. The removal of the trityl group is carried out with the aid of mineral acids, Lewis acids ($ZnCl_2$) or, most mildly, with silica gel.[129] Although the conditions for trityl removal cannot be described as harsh, they were not mild enough to prevent hydrolysis of *N*-glycosidic bonds when this protecting group was used for the protection of the 5′-OH group of purine nucleosides. Therefore, Khorana introduced the monomethoxytrityl (Mmt) and the dimethoxytrityl (Dmt) groups,[130] which are widely applied in nucleotide chemistry. The addition of each *p*-methoxy substituent increases the rate of hydrolysis by about one order of magnitude. The times required for the hydrolysis of the uridine derivatives (**37**) in 80% aqueous acetic acid at 20 °C are given in Scheme 31. As is evident, the Mmt and the Dmt ether[131] are the most advantageous protecting groups because they are not too sensitive, but at the same time are readily removed. An interesting variant of the trityl group, also suitable for the blocking of primary hydroxys, is the 'tritylon' group (Scheme 32). It is more stable towards acids, but removable with hydrazine in an interesting 1,6-elimination reaction.[132]

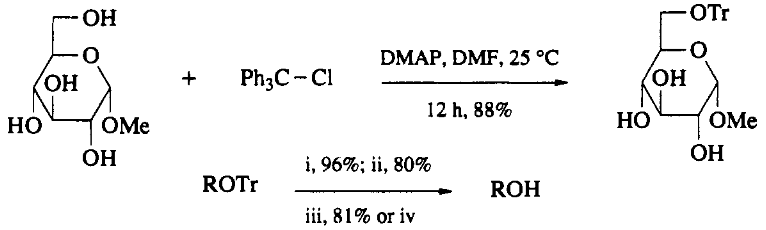

i, HOAc, 56 °C; ii, $BF_3 \cdot Et_2O$, thiol; iii, $SiO_2$, PhH, 25 °C; iv, TsOH, MeOH, 25 °C

**Scheme 30**

In amino acid chemistry *t*-butyl ethers are also used successfully for the protection of the serine and threonine hydroxy groups.[133a] They are formed by the addition of the alcohols to isobutene and are cleaved with TFA and HBr/AcOH. *t*-Butyl trichloroacetimidate is also a convenient reagent for their introduction.[133b] However, the preparation of *O*-*t*-butyl serine and threonine themselves requires several steps including methyl or *p*-nitrobenzyl esters as intermediates.[133c]

Acidic conditions for hydroxy deprotection can be avoided if benzyl-type ethers are used as the blocking functions. They can be prepared from the alcohols by alkylation with benzyl halide/sodium hydride in DMSO or benzyl halide/silver(I) oxide in DMF (the silver salt does not cause acyl migration as a side

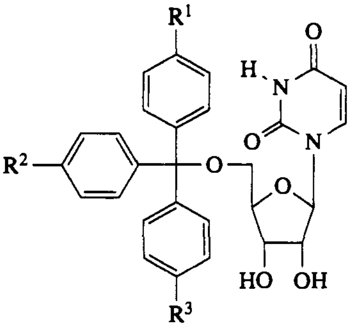
R¹
R²
R³
O
H
N
O
N
O
O
HO OH

(37)

| | | |
|---|---|---|
| $R^1 = R^2 = R^3 = H$ | Tr, | 48 h |
| $R^1 = OMe, R^2 = R^3 = H$ | Mmt, | 2.2 h |
| $R^1 = R^2 = OMe, R^3 = H$ | Dmt, | 1.15 min |
| $R^1 = R^2 = R = OMe$, | | 6 s |

**Scheme 31**

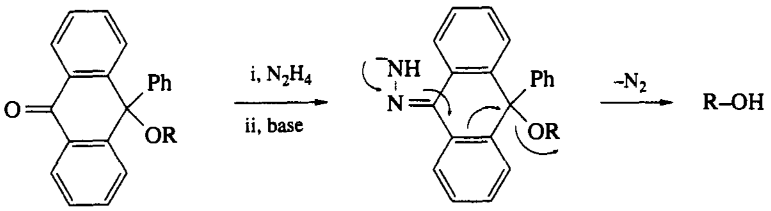
O
Ph
OR
i, N₂H₄
ii, base
NH
N
Ph
OR
-N₂
R–OH

**Scheme 32**

reaction).[134] For base labile compounds benzyl trichloroacetimidate is the reagent of choice (Scheme 33).[135] Also regioselective benzylation of 1,2-diols can be achieved from an intermediary dibutylstannylidene acetal (see Section 3.1.3.4). Benzyl ethers are stable to bases and weak acids, as used to cleave acetals. Their removal can, however, be easily accomplished by catalytic reduction with palladium[136a–c] or better with $Pd(OH)_2$ (Pearlman's catalyst),[136d] although steric hindrance sometimes poses a problem.[136] Furthermore, iodotrimethylsilane, the system thiol/$BF_3{\cdot}OEt_2$ (*vide supra*) and electrochemical methods are effective. The benzylic $CH_2$ group can also be oxidized using, for instance, ruthenium dioxide/sodium periodate to furnish base labile benzoic acid esters (Scheme 34).[137]

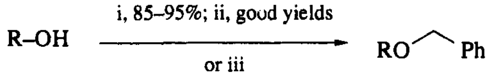
i, 85–95%; ii, good yields
R–OH
or iii
RO
Ph

i, $PhCh_2Cl$, NaH (or $NaNH_2$, NaOH)/DMSO, 20 °C, 1–3 h; ii, $PhCH_2Cl(Br)$, $Ag_2O$, DMF, 25 °C;
iii, $BF_3{\cdot}OEt_2$, $CCl_3C(=NH)OCH_2Ph$

**Scheme 33**

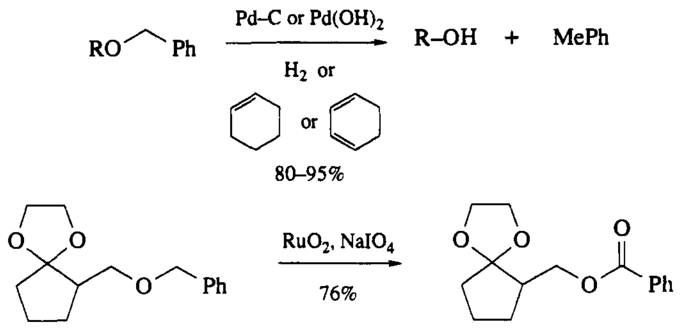
RO
Ph
Pd–C or Pd(OH)₂
H₂ or
or
80–95%
R–OH + MePh
O
O
O
Ph
RuO₂, NaIO₄
76%
O
O
O
O
Ph

**Scheme 34**

Introduction of substituents into the aromatic ring makes the benzylic system prone to further deblocking methods. Thus, *o*-nitrobenzyl ethers, available from *o*-nitrobenzyl bromide, are cleaved photolytically[138] and the mono- and di-methoxybenzyl groups (Mpm and Dmpm) are removable by oxidation with ammonium cerium nitrate[139] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[140] An example chosen from a chiral pool synthesis is given in Scheme 35.

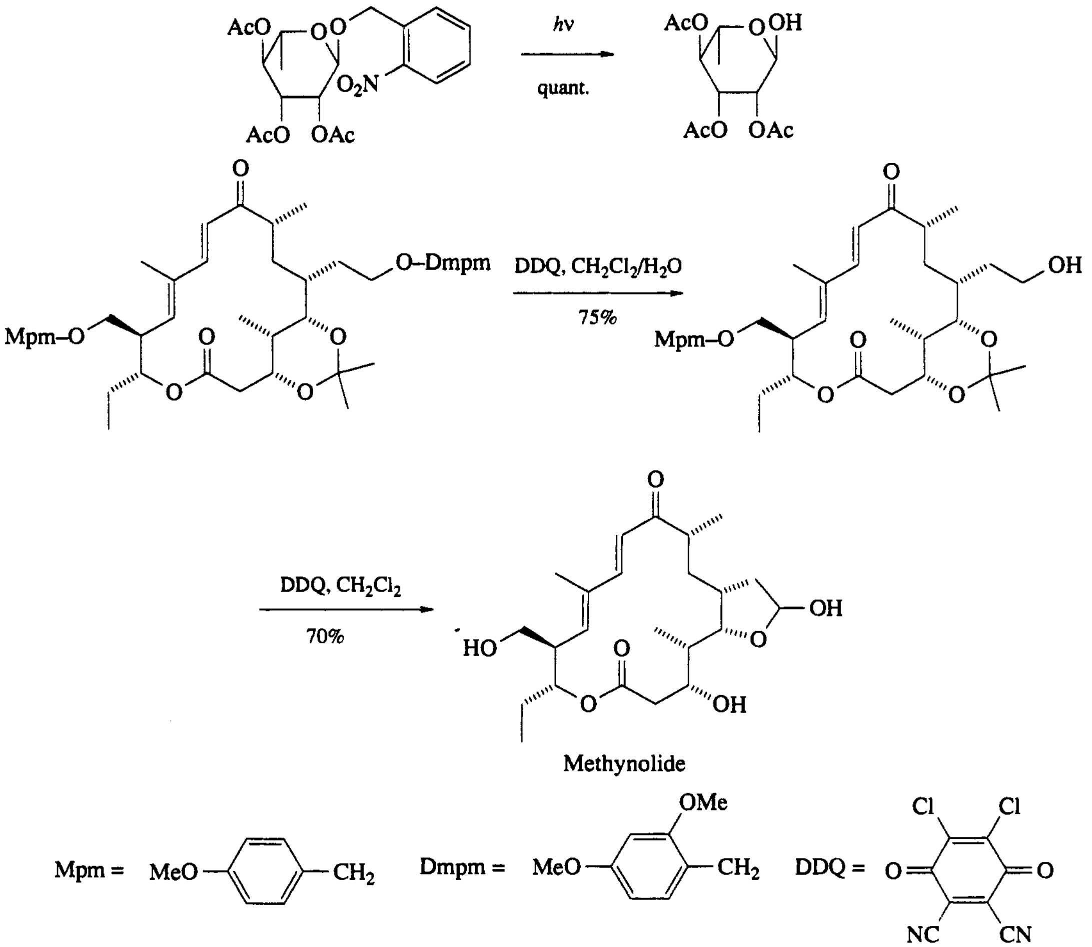

**Scheme 35**

The major areas of application for benzyl-type protecting groups are polyol, nucleotide, and, in general, carbohydrate chemistry. In this latter field these ethers do not only serve to effect protection, but also function as nonneighboring group active substituents in the stereoselective construction of α-glycosides.[141]

A protecting group which is gaining increasing importance is found in the allyl ethers (Scheme 36). They are also synthesized *via* alkylation with allyl bromide and base, or under acidic conditions with allyl trichloroacetimidate.[142] The advantage of this group lies in the possibility to isomerize it to very acid labile propenyl ethers using either potassium *t*-butoxide[143] or, even better, a rhodium(I)[144] or iridium complex.[145] This method for the removal of allyl ethers is often used in carbohydrate chemistry. This deblocking principle allowed, for instance, the selective cleavage of the allyl fucoside (**38**) in the presence of the very acid sensitive Mpm ether groups.[8] The isomerization of the allyl system can also be carried out with palladium on carbon in the presence of acids.[146] These conditions are so mild that benzyl ethers, nitriles, epoxides, esters and α,β-unsaturated structures remain intact.

### 3.1.3.2 Silyl Protecting Groups[147]

The arsenal for hydroxy protection has been considerably enriched by the introduction of silyl ethers in the early 1970s and many of the decisive developments in this area were made by Corey *et al.* Since then a boom of applications has emerged, and in numerous complex total syntheses to date a silyl protecting group has been involved. Natural product synthesis, in particular the construction of prostaglan-

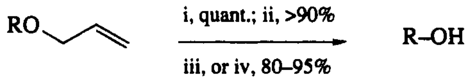

i, $KOBu^t/DMSO$, 100 °C, then 0.1 M HCl or $HgCl_2/HgO$; ii, $(Ph_3P)_3Rh^ICl$, DABCO, EtOH, $H_2O$, reflux then $Hg^{II}$, pH 2; iii, $[Ir(COD)(PMePh_2)]^+PF_6^-$ then $H^+$; iv, Pd/C–$H_2O$, MeOH, 60–80 °C, cat. TsOH or $HClO_4$

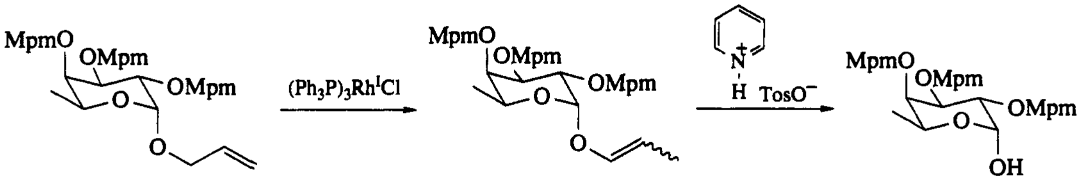

**(38)**

**Scheme 36**

dins but also nucleoside and, increasingly, carbohydrate chemistry, is the major discipline in which protection by silyl groups is applied.

The widespread use of these blocking groups is due to the widely adjustable stability which different trialkylsilyl groups can exhibit towards acid- and base-induced hydrolysis and towards fluoride ion mediated cleavage. The ease of hydrolysis of silyl ethers is mainly influenced by the steric bulk of the ligands at silicon. The more bulky the substituents are, the higher is the stability of the silyl ether to acidic and basic hydrolysis. Furthermore, in silyl ethers silicon is prone to react with hard nucleophiles, whereas at the same time electrophiles can attack the oxygen atom. Therefore, electron-withdrawing groups at the silicon increase the stability of a silyl ether to acidic hydrolysis and decrease the stability to basic hydrolysis, and *vice versa* for electron-donating substituents. The general stabilities of trialkylsilyl ethers $R^1R^2R^3SiO$ towards acid-catalyzed and base-catalyzed solvolysis were determined and found to be in agreement with these general considerations (Scheme 37).[147,148]

*Relative stabilities of trialkylsilyl ethers towards acid-catalyzed solvolysis*

$Me_3Si \approx PhMe_2Si \approx Ph_2MeSi < Et_3Si \approx Pr^iMe_2Si \approx Pr_3Si \approx Bu_3Si < Ph_3Si < Pr^i_2MeSi < Bu^tMe_2Si <$
$thexylMe_2Si < Pr^i_3Si < Bu^tPh_2Si < TrMe_2Si < Bu^t_2MeSi$

*Relative stabilities of trialkylsilyl ethers towards base-catalyzed solvolysis*

$PhMe_2Si \approx Ph_2MeSi \approx Ph_3Si \approx Me_3Si < Pr^iMe_2Si \approx Et_3Si < Pr_3Si < Bu_3Si < Pr^i_2MeSi < Bu^tPh_2Si \approx$
$Bu^tMe_2Si < thexylMe_2Si < Pr^i_3Si < Bu^t_2MeSi$

**Scheme 37**

The rate of cleavage with fluoride ions, *e.g.* tetrabutylammonium fluoride, approximately parallels the orders given for basic hydrolysis.

Trimethylsilyl (TMS) ethers have been widely used for the protection of alcohols and even today it is probably the most important silyl blocking group. The TMS group can be introduced under basic, neutral or acidic conditions by choosing the appropriate reagent.[149] As shown in equation (11), the silylation is achieved with trimethylsilyl chloride in the presence of a base like pyridine or triethylamine. The reaction can be accelerated by the addition of DMSO, hexamethyl phosphoric acid triamide, DABCO or imidazole. Alternatively, hexamethyldisilazane[150] and trimethylsilyldiethylamine can be used. The latter reagent is very sensitive to the steric environment of the hydroxy group to be masked. In the cyclohexane series, for instance, it attacks only equatorial alcohols and it effectively differentiates between hydroxy groups in prostaglandins (see Scheme 38).[151]

$$R{-}OH \;+\; Cl{-}SiMe_3 \xrightarrow[\text{THF or ether}\atop \textit{ca. } 90\%]{\text{base}} R{-}O{-}SiMe_3 \qquad (11)$$

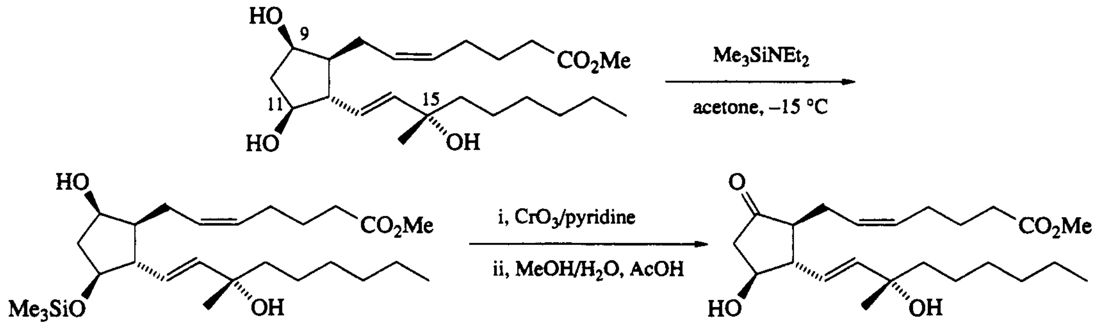
HO
9
11
HO
15
OH
CO2Me
Me3SiNEt2
acetone, –15 °C
HO
Me3SiO
OH
CO2Me
i, CrO3/pyridine
ii, MeOH/H2O, AcOH
O
HO
OH
CO2Me

Order of reactivity: 11 > 15 >> 9

Scheme 38

For the introduction of the TMS group under neutral conditions, trimethylsilyl chloride can be activated with lithium sulfide.[152] Also trimethylsilylketene acetals (**39**), silyl enol ethers (**40**) (in particular those of pentane-2,4-dione), *N*-trimethylsilylacetamide (**41**), *N*,*O*-bis(trimethylsilyl)acetamide (**42**), *N*,*N'*-bis(trimethylsilyl)urea (**43**) and *N*,*O*-bis(trimethylsilyl)carbamate (**44**) are effective silylating agents under neutral conditions (Scheme 39).[147]

$$\mathrm{R{-}OH + Li_2S + Cl{-}SiMe_3 \xrightarrow[75\text{–}95\%]{\text{MeCN, 25 °C}} R{-}OSiMe_3 + 2\,LiCl + H_2S}$$

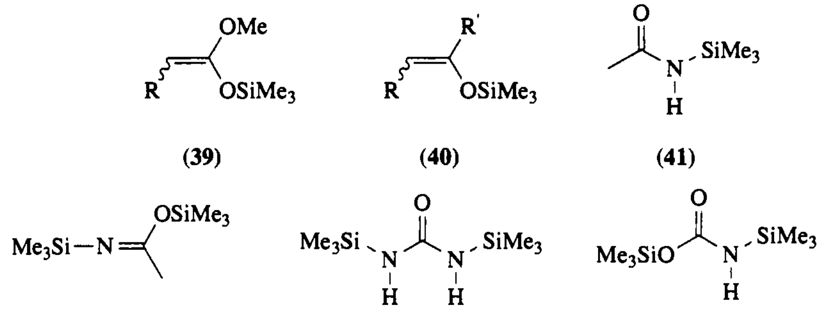
OMe
R
OSiMe3
R'
R
OSiMe3
O
N
SiMe3
H
OSiMe3
Me3Si—N
O
Me3Si
N
N
SiMe3
H
H
O
Me3SiO
N
SiMe3
H

(**39**) (**40**) (**41**)

(**42**) (**43**) (**44**)

Scheme 39

For the introduction of TMS groups under acidic conditions, trimethylsilyltriflate, hexamethyldisilazane and also allyltrimethylsilane (**45**)[153] have been successfully applied. The allylsilane offers the advantage of being stable to hydrolysis. The mechanism proposed for its reaction with alcohols is shown in equation (12). It involves an initial protonation of the double bond. The 1-silylisopropyl cation formed is then attacked by the alcohol at the silicon to produce the silyl ether and propene.

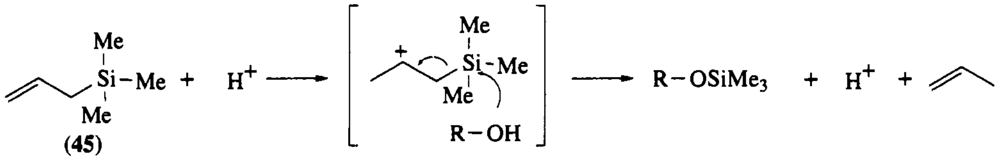
Me
Si–Me
Me
(45)
+ H+
+
Me
Si–Me
Me
R–OH
R–OSiMe3 + H+ +

(12)

The TMS group is stable under a variety of conditions, *e.g.* Grignard reactions, Wittig reactions, reductions with DIBALH, Collins oxidation[154] and epoxidations with MCPBA. However, strongly basic conditions occurring in organometallic reactions as, for instance, in the treatment of (**46a**) with butyllithium, may result in a silyl migration (**46b** to **46c**; Scheme 40; reverse Brook rearrangement).[155] A severe drawback of the TMS group is its tendency to hydrolyze, which also prevents chromatography on silica gel. Because of this sensitivity the deprotection of the TMS ethers can be achieved readily by basic or acidic hydrolysis or alcoholysis. Alternatively, the use of fluorides, *e.g.* tetrabutylammonium fluoride in anhydrous THF,[156] is the method of choice (see equation 13).

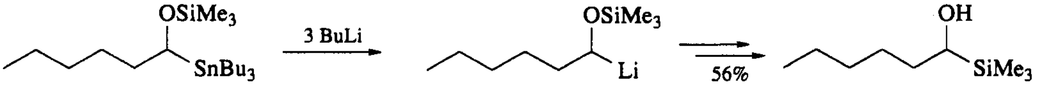

**(46a)** **(46b)** **(46c)**

Scheme 40

$$R{-}OSiMe_3 \xrightarrow[\text{iii or iv}]{\text{i, 100\%; ii, 100\%;}} R{-}OH \qquad (13)$$

i, MeOH/AcOH or citric acid, 20 °C; ii, MeOH/$K_2CO_3$, 0 °C; iii, MeOH/THF; iv, $Bu^n{}_4N^+F^-$/THF or KF/DMF

It should finally be pointed out that trimethylsilyl ethers can also be transformed directly into other functionalities. Oxidation with NBS leads to ketones and aldehydes,[157] treatment with $LiAlH_4/AlCl_3$ results in deoxygenation of the alcohol,[147] reaction with carboxylic acid anhydrides in the presence of $BF_3{\cdot}OEt_2$ produces esters[158] and on treatment with $Ph_3P{\cdot}Br_2$ acid bromides are formed directly from TMS esters.[159]

The *t*-butyldimethylsilyl (TBDMS) group was introduced by Stork[160] and Corey,[156] and since then has become one of the most popular hydroxy-protecting groups. It is more stable to hydrolysis than the TMS group but can still be removed selectively. TBDMS ethers can be formed with the aid of a variety of introducing reagents (equation 14). The one most often applied is *t*-butyldimethylsilyl chloride with imidazole in DMF,[156] with DMAP/$Et_3NH$ in DMF or with silver nitrate in pyridine.[161] In addition, the same types of reagents already described for the formation of TMS ethers can be used for the introduction of the TBDMS group. Thus, under acidic conditions the corresponding silylketene acetals, silyl enol ethers and allyl-*t*-butyldimethylsilane are applied. TBDMS-Cl can, too, be activated with lithium sulfide under essentially neutral conditions. Also *N*-methyl-*N*-(*t*-butyldimethylsilyl)-acetamide and -trifluoroacetamide and the analogous *N*,*O*-bis(*t*-butyldimethylsilyl) derivatives deliver the TBDMS group under neutral conditions. These reagents show markedly better silylating properties than the silyl chloride and serve to overcome problems with low reactivity towards hindered secondary and tertiary alcohols. Exceptionally reactive introducing reagents are TBDMS triflate and perchlorate.

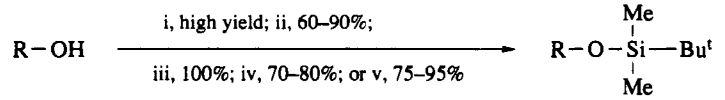

$$R{-}OH \xrightarrow[\text{iii, 100\%; iv, 70–80\%; or v, 75–95\%}]{\text{i, high yield; ii, 60–90\%;}} R{-}O{-}\overset{Me}{\underset{Me}{Si}}{-}Bu^t \qquad (14)$$

i, $Bu^tMe_2SiCl$/imidazole, DMF; ii, $Bu^tMe_2SiCl$/DMAP, $NEt_3$, DMF;
iii, $Bu^tMe_2SiOClO_3$/pyridine; iv, $Bu^tMe_2SiCH_2CH{=}CH_2$, TsOH, MeCN;
v, $Bu^tMe_2SiCl$, $Li_2S$, MeCN, 25 °C. For further introducing reagents see text

TBDMS ethers are stable under a great variety of conditions, some of which are Wittig reaction, reduction with Zn/MeOH, $H_2$/Pd–C, Na/$NH_3$ and DIBAL-H, oxidation with $CrO_3$/pyridine,[162] $H_2O_2/OH^-$ or $RuO_2$, MeI/$Ag_2O$, $K_2CO_3$/MeOH, acidic removal of a THP ether,[163] reactions with organocopper reagents, mesylation, treatment with $KOBu^t$/DMF or $Pr^iMgI$/–78 °C and even the elimination of the β-trimethylsilyl ethyl ester protecting group with fluoride.[164a] This resistance has allowed the application of this silyl protecting group in numerous syntheses (an example is given in Scheme 41).[164b] It found a particularly broad application in the chemistry of prostaglandins[165] and carbohydrates.[166] Thus, the TBDMS group is the most popular silyl protecting group in nucleoside chemistry.[147,167] It is useful for the selective protection of the 5′-OH group or for the simultaneous masking of the 2′- and the 5′-OH groups. Also 3′,5′-diprotected compounds were obtained (Scheme 42).

*t*-Butyldimethylsilyl ethers can be cleaved by methods similar to those reported for the trimethylsilyl group (Scheme 43). The usual reagent is tetrabutylammonium fluoride at 25 °C.[156] However, the fluoride ion is a strong base and may cause severe side reactions. In these cases either mixtures of aqueous HF/MeCN or THF/$H_2O$/AcOH[156] can alternatively be applied. Acetic acid may be replaced by weakly acidic ion-exchange resins. Alternative sources of fluoride are $BF_3$ and tetrafluoroborates. In addition, $Ac_2O/FeCl_3$ cleaves the silyl ethers to produce the corresponding acetates. One of the problems arising

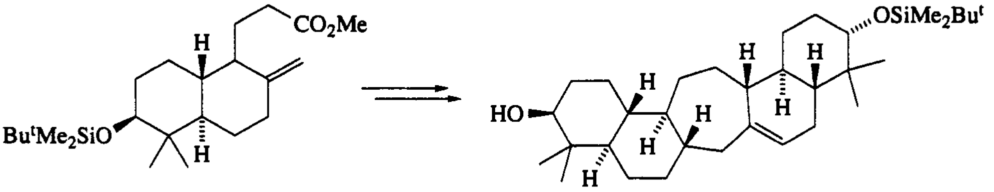
H
$CO_2Me$
$Bu^tMe_2SiO$
H
$OSiMe_2Bu^t$
HO
H
H
H
H
H
H
H

The $Bu^tMe_2Si$ group was cleaved with tetra-*n*-butylammonium fluoride in THF at 70 °C for 12 h

**Scheme 41**

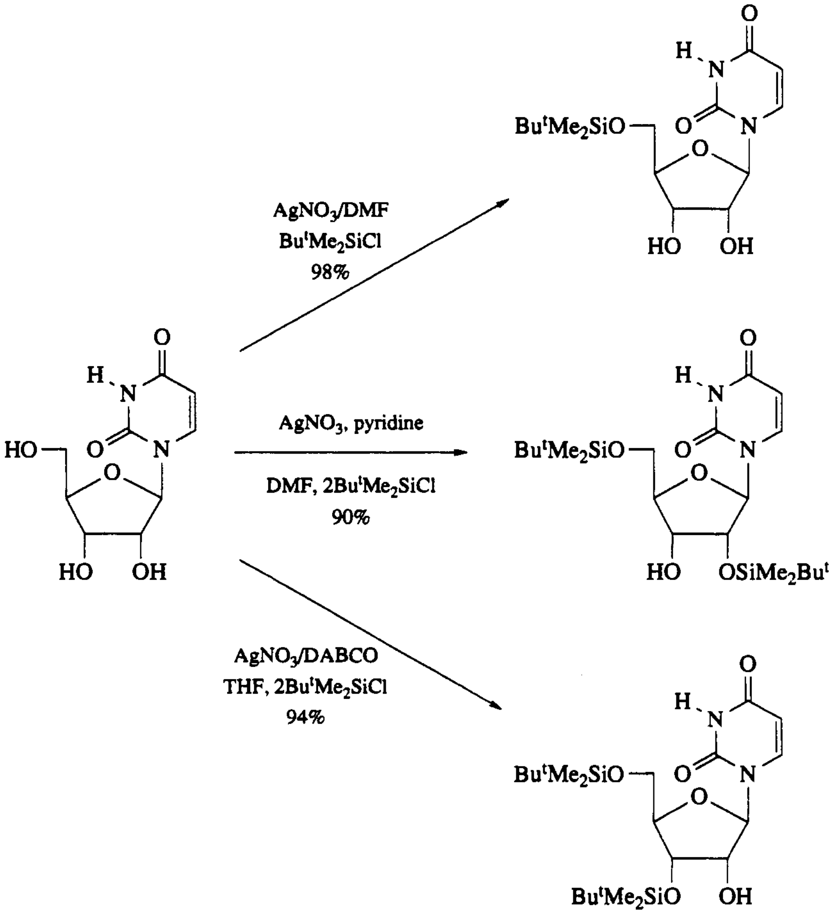
$AgNO_3/DMF$
$Bu^tMe_2SiCl$
98%
$AgNO_3$, pyridine
DMF, $2Bu^tMe_2SiCl$
90%
$AgNO_3/DABCO$
THF, $2Bu^tMe_2SiCl$
94%
HO
HO
OH
$Bu^tMe_2SiO$
HO
OH
$Bu^tMe_2SiO$
HO
$OSiMe_2Bu^t$
$Bu^tMe_2SiO$
$Bu^tMe_2SiO$
OH
O
H
N
N
O

**Scheme 42**

during the removal of the TBDMS blocking group is that in acylated substrates, particularly under basic conditions, the acyl groups and also the silyl group itself may migrate.[168]

$$R-OSiMe_2Bu^t \xrightarrow[\text{iii, high yields; iv, high yields; or v, 70–90\%}]{\text{i, 100\%; ii, 90–100\%}} R-OH$$

i, $Bu^n{}_4N^+F^-$, THF, 25 °C; ii, aq. HF/MeCN (95:5), 20 °C; iii, $AcOH/H_2O/THF$, 20–80 °C;

iv, Dowex 50W-X8, MeOH, 20 °C; v, $BF_3{\bullet}OEt_2$, 0–25 °C

**Scheme 43**

Silyl protecting groups other than TMS and TBDMS are usually applied only if a modified acid stability is wanted. Thus, the triethylsilyl (TES) group[169] shows a sensitivity to hydrolysis and nucleophilic attack intermediate between the TMS and the TBDMS groups. The triisopropylsilyl (TIPS),[170] the *t*-butyldiphenylsilyl (TBDPS)[171] and the thexyldimethylsilyl (TDS)[172] groups are considerably more stable towards 1% HCl and aqueous NaOH than the TBDMS group. The TDS group can, in addition, be regarded as a replacement for the TBDMS protecting group since the silyl chloride used for its introduction is less expensive and easier to handle (equation 15).

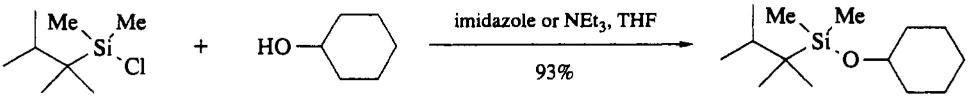

(15)

The respective introducing reagents may also be sterically more demanding and give better selectivities in the protection of polyfunctional molecules. This is mainly exploited in nucleotide chemistry. Also, stereochemical bias may be introduced with the aid of appropriate silyl protection. As shown in equation (16), tribenzylsilyl and tri-*p*-xylylsilyl ethers were used to control the stereochemistry of epoxidation in prostaglandin syntheses.[173]

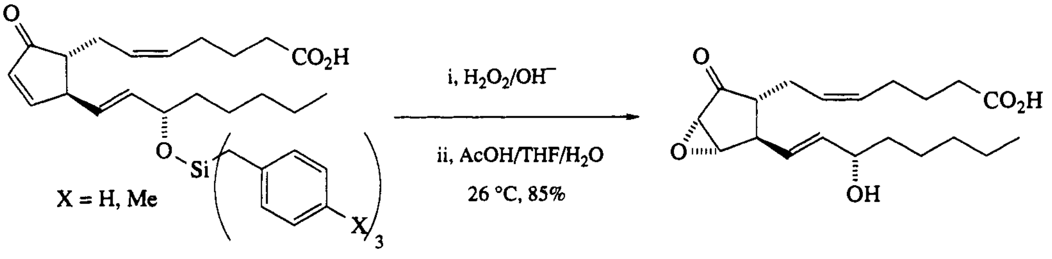

(16)

### 3.1.3.3 Ester and Carbonate Protecting Groups

Esters can be prepared from alcohols and activated forms of carboxylic acids by a variety of methods.[174] Carboxylic acid esters are mainly base labile and, therefore, they complement the acid sensitive ether protecting groups. A variety of esters can be used for simpler and for more complex problems. Here, only the most practical groups will be treated. The application of esters as protected forms is frequently complicated by the possibility of acyl migration which may occur under basic, acidic and also neutral conditions.[175]

Acetates and benzoates are widely used in carbohydrate chemistry. Their introduction is readily achieved *via* the acyl chlorides or the anhydrides. The reactivity of these reagents is greatly enhanced by the addition of 4-dimethylaminopyridine, and unreactive alcohols can usually be acylated this way.[176] The removal of these ester blocking groups can be carried out in several ways. Alkaline saponification, treatment with $K_2CO_3$ in aqueous methanol, ammonia in methanol and, as a particularly mild method, KCN in ethanol[177] are effective for the cleavage of acetates. In addition, hydrazine in methanol is a very advantageous reagent to achieve this aim. Its use proved to be the method of choice for the removal of *O*-acetyl and *O*-benzoyl groups from very base labile glycopeptides (equation 17).[178]

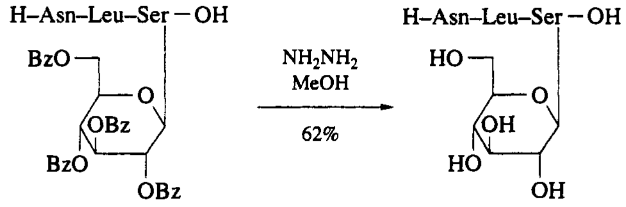

(17)

Acetates and benzoates not only serve to mask the OH groups in sugars, they also display neighboring group assistance in the stereoselective construction of 1,2-*trans*-glycosides.[141]

The major side reaction in this glycosylation reaction is the formation of an orthoester. This can, however, be suppressed if the sterically demanding pivaloyl group is used as the blocking group of the 2-hydroxy function of the glycosylating compound. Here the *trans*-glycosides are isolated in high yields without orthoester formation (Scheme 44).[179] Even earlier pivaloates had been introduced for the selective masking of 5′-hydroxys in nucleosides.[180] For their removal transesterification with sodium methylate in methanol or, according to Gassman *et al.*, 'anhydrous hydroxide' ($KOBu^t/H_2O$ 8:2, 20 °C, 3 h, 94%) has to be applied.[181] Under these conditions tertiary amides also are hydrolyzed.

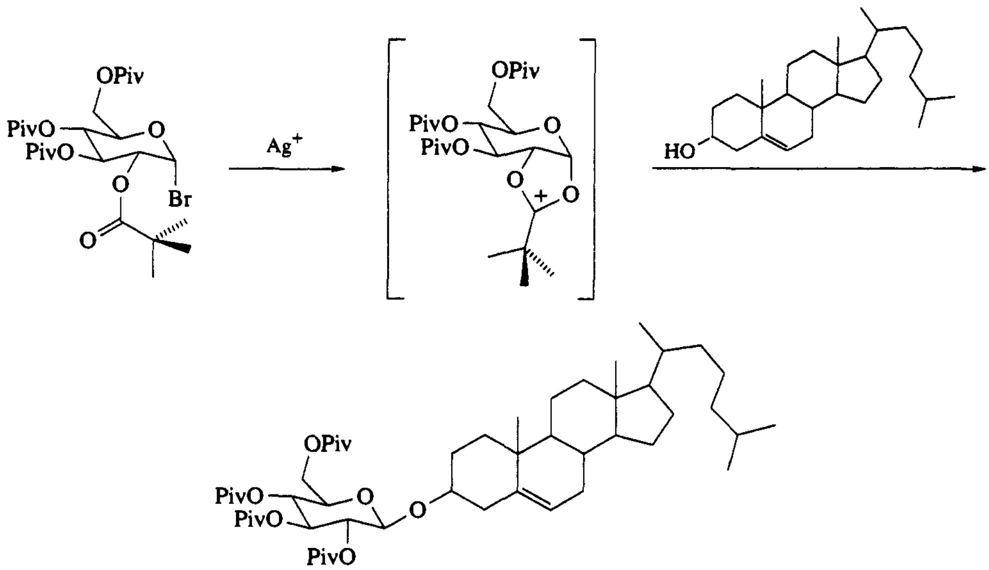

Scheme 44

Recently the enzyme-catalyzed hydrolysis of pivaloates from carbohydrates was reported.[182] In general, enzymatic methods could prove to be viable alternatives to traditional chemical transformations since enzymes mostly operate under exceptionally mild conditions and with selectivities which are otherwise hard to achieve.[183] An example is given in equation (18). Also trypsin and chymotrypsin may be applied.[184]

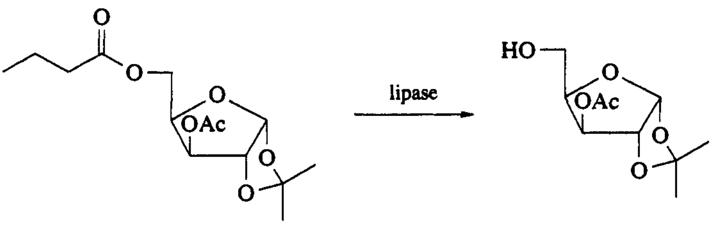

(18)

By introducing substituents into the acetyl or benzoyl groups the stability of the derived esters towards basic hydrolysis can be varied. In accordance with the Hammett principle, the order of increasing reactivity given in Scheme 45 is valid.

$$\mathrm{Bu^tCO < MeCO < MeOCH_2CO < PhOCH_2CO < HCO < ClCH_2CO < Cl_2CHCO < Cl_3CCO < F_3CCO}$$

$$\mathrm{PhCO} < p\text{-}\mathrm{NO_2C_6H_4CO} < o\text{-}\mathrm{BrC_6H_4CO} < \mathrm{MeCO}$$

Scheme 45

Methoxyacetates and phenoxyacetates serve as protecting groups in nucleoside synthesis.[185] They are cleaved by aqueous ammonia 20 and 50 times faster respectively than acetic acid esters. In the aromatic series the *p*-nitrobenzoates often show the advantageous tendency to crystallize.

In analogy to methods developed in peptide chemistry, acyl groups can be removed *via* a secondary intramolecular transformation (Scheme 47). For instance, chloroacetyl esters (**47**) are cleaved with thiourea[186a] or hydrazinedithiocarbonate[186b] by the formation of a heterocycle. Similarly γ-oxo carboxylic acid esters (**48**) are labile towards hydrazine. This is the basis for the cleavage of the benzoylpropionates and the levulinic acid esters.[187] Under nearly neutral conditions initially a hydrazone is formed, which then intramolecularly attacks the ester bond. By this method a levulinic group can be selectively removed in the presence of acetates. Alternatively, the levulinates can also be cleaved by initial reduction of the ketone with $NaBH_4$, to an alcohol.[188] Similarly, crotonates and methoxycrotonates (**49**) first undergo a Michael addition with hydrazine followed by an intramolecular reaction.[189] Further methods for the generation of a nucleophile which then attacks intramolecularly consist in the reduction of a nitro or an azido group in 4-nitro and 4-azido carboxylic acid esters (**50**).[190]

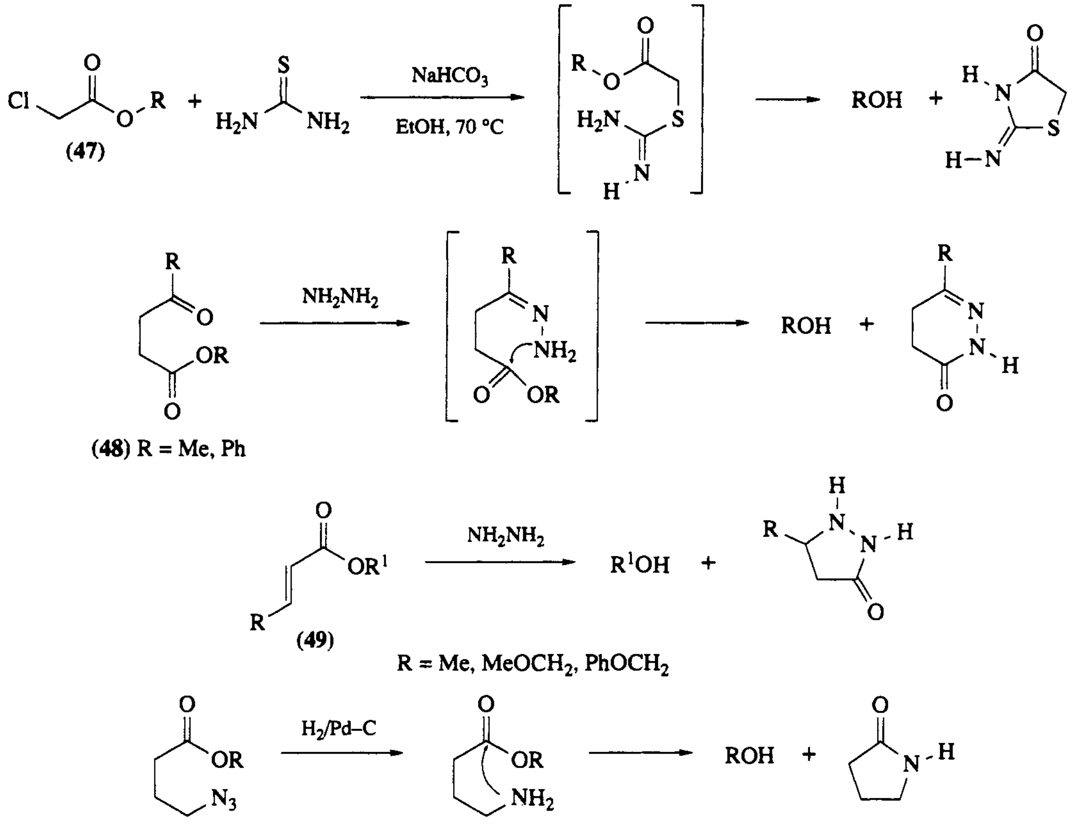
(47)
NaHCO3
EtOH, 70 °C
ROH
(48) R = Me, Ph
NH2NH2
ROH
(49)
NH2NH2
R1OH
R = Me, MeOCH2, PhOCH2
(50)
H2/Pd–C
ROH

Scheme 46

Several of the urethane protecting groups described in Section 3.1.2.1 can analogously be used as carbonates for the protection of alcohols, too.[5,104] Thus, the 2-arylsulfonylethyl[191] (deblocking with ammonia), the 9-fluorenylmethyl[192] (deblocking with ammonia), the 2-phosphonioethyl[43,193] (deblocking with dimethylamine in methanol), the benzyl and substituted benzyl,[194,195] the allyl (deblocking by $Pd^0$-catalyzed hydride transfer,[196] trapping with 2-ethylhexanoate[59] or catalyzed isomerization[144]), the 2,2,2-trichloroethyl[46c,197a] (deblocking by reduction) and the 2-(trimethylsilyl)ethyl carbonates[197b] have been applied successfully. Allyl carbonates (**51**) prove to be particularly valuable. On the one hand they can be removed completely using $Pd^0$ and tri-*n*-butylstannane, or on the other hand they can be decarboxylated to give the corresponding allyl ethers (Scheme 47).[196]

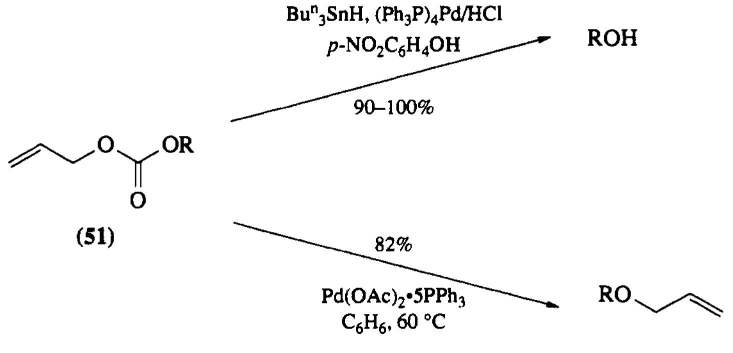
Bu^n3SnH, (Ph3P)4Pd/HCl
p-NO2C6H4OH
ROH
90–100%
(51)
82%
Pd(OAc)2•5PPh3
C6H6, 60 °C

Scheme 47

### 3.1.3.4 Protecting Groups for 1,2- and 1,3-Diols

Compounds bearing *cis*-1,2-diols and *cis*- and *trans*-1,3-diols can be protected as cyclic acetals and ketals or cyclic orthoesters. As has been shown for ethers, these blocking groups are stable to bases but are labile to acids. Diol protection as cyclic esters, sensitive to basic conditions, is also possible. More recent developments have involved cyclic silylene, siloxanylidene and stannoxane derivatives.

Cyclic acetals and ketals are of particular importance in carbohydrate chemistry. They can be formed by the reaction of the diol and a carbonyl component in the presence of an acid or a Lewis acid.[2,198] Also transacetalization of a ketal or acetal with the diol can be carried out. Finally geminal dibromides and dichlorides can be used as introducing reagents. In the acid-catalyzed acetalizations polyols can give rise to five-, six- or seven-membered rings. Here different carbonyl reagents prefer different ring sizes. As an empirical rule, aldehydes like formaldehyde, acetaldehyde and aromatic aldehydes react to give 6-ring acetals (1,3-dioxanes; **52a**), and aliphatic ketones like acetone, cyclopentanone and cyclohexanone form 5-ring ketals (1,3-dioxolanes; **52b**) (Scheme 48).[198] However, the particular method for the introduction as well as the acid catalyst may also influence which product is preferred. Thus, in the reaction of glycerol with benzaldehyde dimethyl acetal only the formation of the 1,3-dioxolane derivative is observed, but on prolonged standing it isomerizes to the 1,3-dioxane. With benzaldehyde itself, however, a mixture of both isomers is isolated.[199]

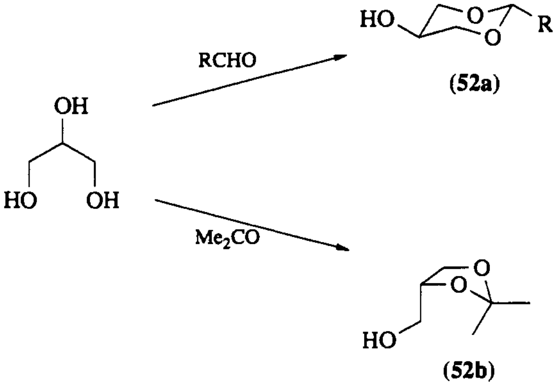

Scheme 48

The most important and widely used ketal is the acetonide.[2] It is prepared by the reaction of the diol with acetone[200] or acetone dimethyl acetal[201] and an acid catalyst. Also 2-alkoxy and 2-silyloxy propenes can be applied for this purpose (Scheme 49).[202] In the reactions with carbohydrates furanose rings are formed if possible, but under kinetically controlled conditions also 1,3-dioxanes may be constructed. In the cases of hexoses which do not contain *cis*-1,2-diols the reaction usually involves the 6-OH group.

For the removal of the isopropylidene ketal a variety of acid-catalyzed hydrolyses have been described. Typical conditions are: Dowex 50-W (H$^+$)/H$_2$O, 70 °C and 60–80% HOAc, 25 °C or reflux.

Other ketals which are frequently used if a modified acid stability is wanted are the cyclopentylidene, the cyclohexylidene and the cycloheptylidene ketals. They are readily prepared by the reaction of a diol and the cycloalkanone in the presence of ethyl orthoformate and mesitylenesulfonic acid.[203] The relative rates of their acid-catalyzed hydrolysis are given in Scheme 50.

The most important acetal protecting function is the benzylidene group. It is formed from the diol and benzaldehyde or its dimethyl acetal under acidic catalysis (Scheme 51).[104,204] The Williamson reaction of the diols with benzylidene bromide in the presence of pyridine is also effective.[204,205] The benzylidene group constitutes an important blocking and regiodifferentiating principle in carbohydrate chemistry. This is due to the fact that it can be easily removed by acidic hydrolysis and hydrogenation and that, on the other hand, it can be regioselectively opened, thereby providing a route for the selective liberation and protection of OH groups. As is shown in Scheme 52, by treatment with NaCNBH$_3$ in the presence of acids in THF the 4,6-*O*-benzylidene function in protected glucose is converted to the 6-benzyl ether (**53**).[206] Alternatively the application of LiAlH$_4$/AlCl$_3$ produces the 4-benzyl ether (**54**).[207] Whereas the former method can be used with ester- and ether-protected carbohydrates, only ether protecting groups are tolerated in the second case. In similar reactions NBS transforms the benzylidene group to the 4-benzoate.[208] In analogous reactions 4-methoxybenzylidene acetals can be regioselectively opened and oxidized with dichlorodicyano-*p*-quinone (DDQ)[209] or ammonium cerium nitrate[139] to give the *p*-methoxybenzoates or deprotected compounds.

In addition to the ketals and the acetals, cyclic orthoesters are sometimes used for the protection of 1,2-diols. They are more readily cleaved by acids than the acetonides. In nucleoside chemistry formic acid, acetic acid and benzoic acid orthoesters were applied to temporarily mask the carbohydrate part.[210] Also the methoxyacetic acid orthoester (**55**) was useful because it allowed the selective liberation of the 3′-

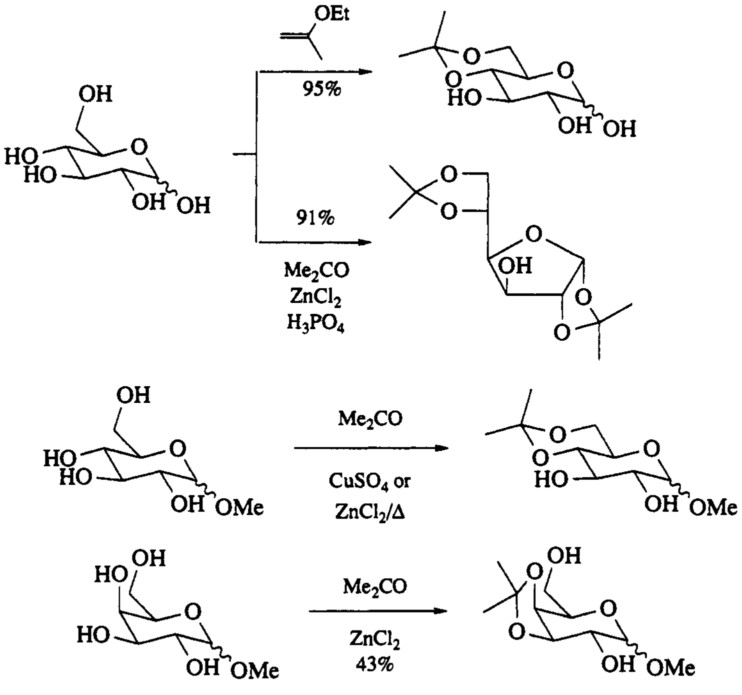
OEt
95%
91%
Me2CO
ZnCl2
H3PO4
Me2CO
CuSO4 or
ZnCl2/Δ
Me2CO
ZnCl2
43%

**Scheme 49**

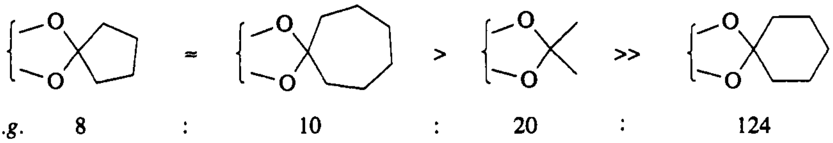
≈
>
>>
e.g. 8 : 10 : 20 : 124

for 1,2-*O*-alkylidene-α-D-glucopyranoses

**Scheme 50**

and the 2′-hydroxy groups.[211] During its cleavage the protecting function is converted to the base labile ester (**56**; Scheme 53).

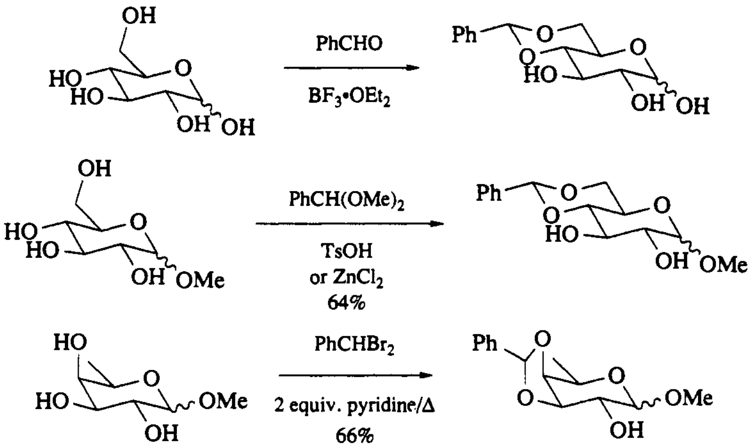
PhCHO
BF3•OEt2
PhCH(OMe)2
TsOH
or ZnCl2
64%
PhCHBr2
2 equiv. pyridine/Δ
66%

**Scheme 51**

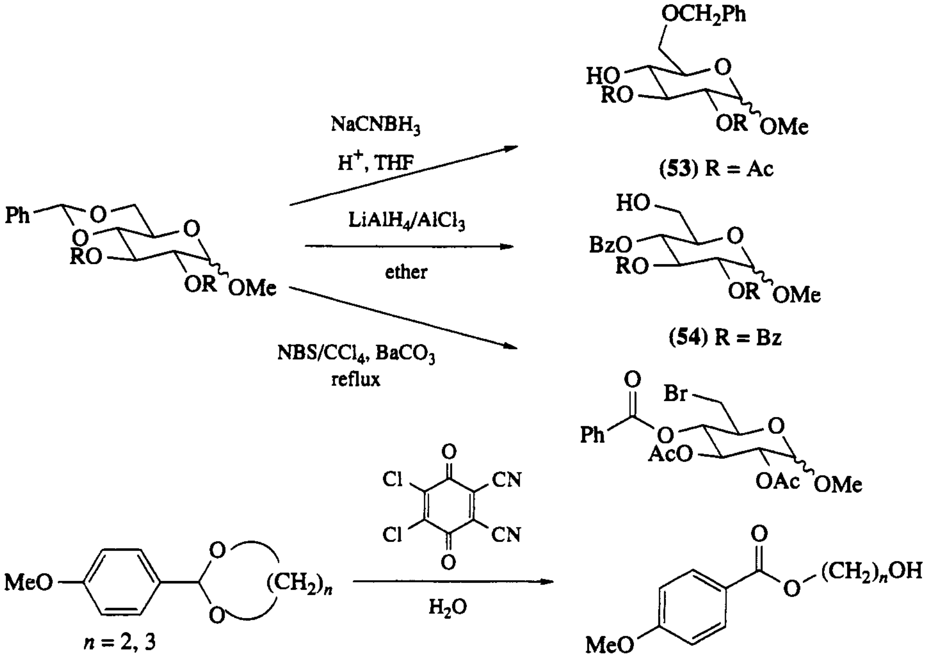

Scheme 52

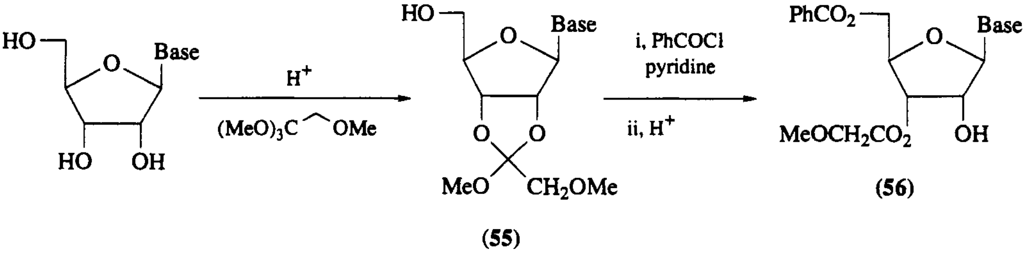

Scheme 53

Besides the many acid sensitive derivatives, base labile protecting groups for 1,2-diols were also recommended. With phosgene or a chloroformate, cyclic carbonates are formed from *cis*- and *trans*-diols.$^{210,212}$ They are stable to the conditions that hydrolyze acetals but are readily removed by saponification. Cyclic boronates may also be used, but their application is limited because they hydrolyze very rapidly.$^{213}$

Finally, silicon and tin reagents offer the possibility to protect diol systems. The 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) (TIPDS)$^{214}$ group is introduced *via* the 1,3-dichloro derivative. With 1,3-diol structures of nucleosides, carbohydrates or glycerol it forms eight-membered rings (Scheme 54). This protecting group is stable to water, 0.3 M TosOH, 10% TFA/CHCl$_3$, amines, the conditions for the introduction of THP, sulfonyl and trityl groups and the isomerization of an allyl to a propenyl ether. Its removal is accomplished with tri- or tetra-*n*-butylammonium fluoride, 0.2 M HCl/MeOH and 0.2 M NaOH in dioxane/water. In addition the 3'- and the 5'-OH groups of nucleosides can selectively be liberated and the siloxanylidene group can be isomerized under acidic conditions (see Scheme 54).$^{214}$

Diisopropyl- and di-*t*-butyl-silylene (DTBS) derivatives constitute further interesting protecting groups for 1,2-, 1,3- and 1,4-diols. These compounds are obtained from the dichlorosilanes or the ditriflates.$^{215}$ An example for the use of the di-*t*-butylsilylene group is given in Scheme 55. It demonstrates that the blocking group is cleaved under mild acidic conditions with pyridinium fluoride. The TBDMS ether, the 4-methoxyphenyl sulfide and the sensitive β-ketol system present remain unaffected.

More sensitive than silicon-derived compounds are dialkoxystannanes.$^{216}$ They are formed in good yields on treatment of the respective diols with dibutyltin oxide. The particular advantage offered by this protecting technique is that it allows for regioselective acylations and alkylations of diol structures.$^{217}$ Two examples are given in Scheme 56.

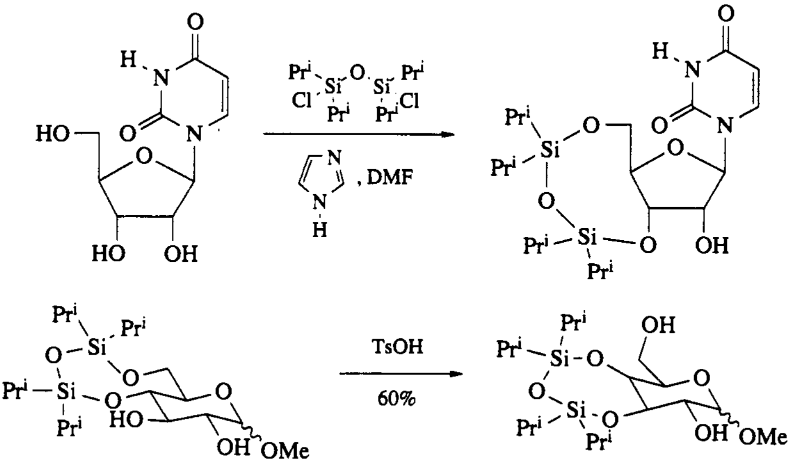

Scheme 54

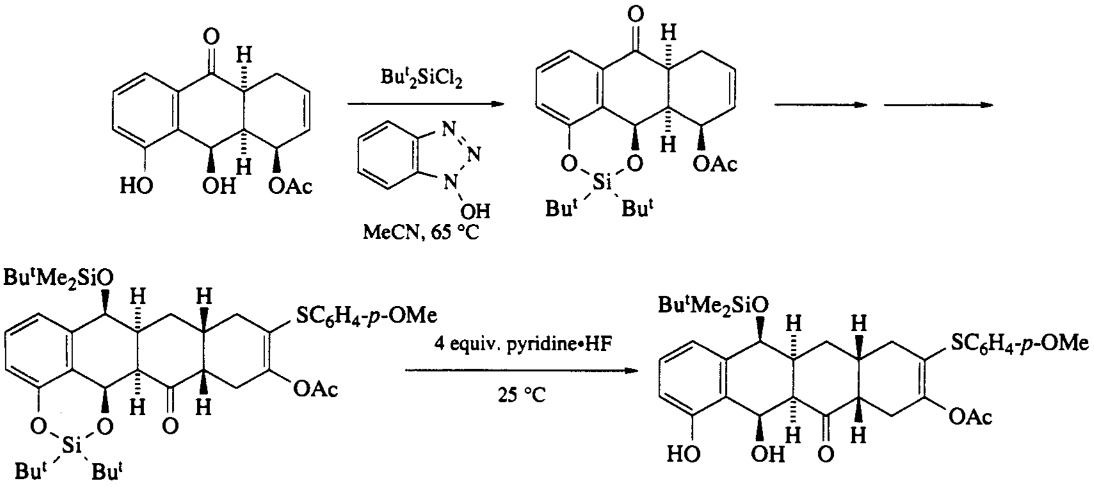
Bu$^t_2$SiCl$_2$
MeCN, 65 °C
4 equiv. pyridine•HF
25 °C

Scheme 55

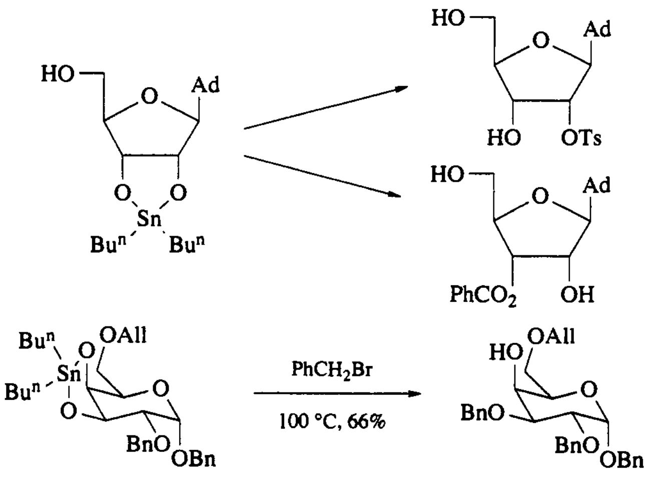
PhCH$_2$Br
100 °C, 66%

Scheme 56

### 3.1.4 THIOL-PROTECTING GROUPS[5,218]

The protection of the thiol group is a serious problem in peptide synthesis if cysteine is involved. Blocking can be achieved as a thiol ester, a sulfide or as a disulfide from which the thiol must be regenerated by reduction. The protection of cysteine through *S*-acyl or *S*-alkoxycarbonyl derivatives embodies the danger of β-elimination under formation of alkenic structures. Also these thiol ester derivatives display considerable acylating properties towards amines and alcohols. Therefore, *S*-alkyl protecting groups and disulfides are used almost exclusively.

Due to the pronounced nucleophilicity of the SH group, the *S*-benzyl ether (**57**) can directly be prepared from cysteine and benzyl chloride in high yield. It is stable towards acid, but removable with sodium in ammonia[16,219] or electrolysis.

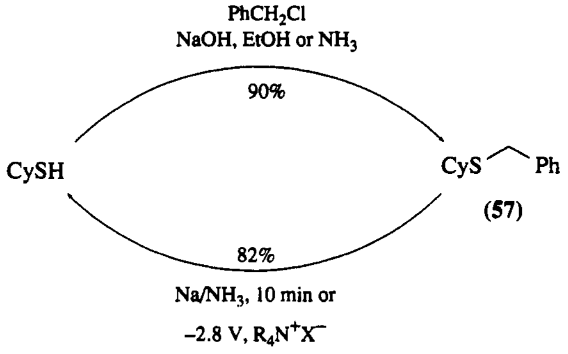

**Scheme 57**

Also the trityl group was applied for the masking of SH functions.[220] The sulfides were prepared by the reaction of the thiol with trityl chloride (75% yield) or from trityl alcohol and the thiol in the presence of anhydrous TFA (85–90% yield). The cleavage of this group can be carried out under several conditions (Scheme 58).[221] It is sensitive to acids (*e.g.* trifluoroacetic acid/ethanethiol 1:1) and to heavy metals. Thiocyanogen $(SCN)_2$ oxidizes *S*-trityl ethers to the disulfides and iodine converts *S*-tritylcysteine derivatives to cystine structures.

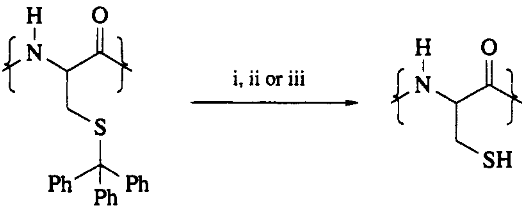

i, HCl/aq. AcOH, 90 °C; ii, $Hg(OAc)_2/EtOH/\Delta$ then $H_2S$; iii, $AgNO_3/EtOH/pyridine$, 90 °C then $H_2S$

**Scheme 58**

*t*-Butyl sulfides, like *t*-butyl ethers, are formed from the thiol and isobutene under acidic conditions.[222] They are stable to HBr/AcOH and TFA but are cleaved with HF/anisole. Mercury salts in combination with acids also liberate the thiol function (Scheme 59).[222] In addition to these *S*-alkyl protecting methods, several of the acetalic blocking groups used for alcohols can be applied to the SH function (*e.g.* BOM, MOM, THP). An advantageous thioacetal is found in the *S*-acetamidomethyl (Acm) protecting group (Scheme 60).[223] Cysteine can be masked with this function under acidic conditions and its removal is accomplished with $Hg^{2+}$ in aqueous acid. Alternatively with *o*-nitrobenzenesulfenyl chloride the disulfide is obtained, which must be cleaved with mercaptoethanol or $NaBH_4$.[224]

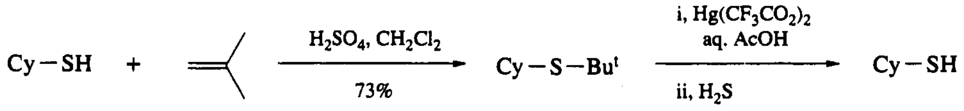

**Scheme 59**

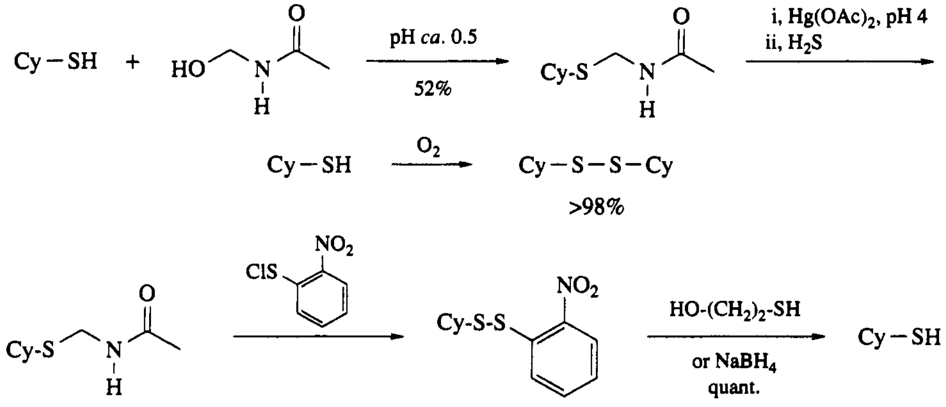

Scheme 60

Disulfides can also, in general, be prepared from a thiol by oxidation ($O_2$, $H_2O_2$, $I_2$). The symmetrical or unsymmetrical disulfides must finally be reduced, for instance with other thiols, $NaBH_4$ or $LiAlH_4$, to liberate the SH group again. The unsymmetrical disulfide with *t*-butyl thiol has been used for the protection of cysteine in peptides.[225] As is shown in equation (19) its cleavage was successfully achieved with $NaBH_4$.

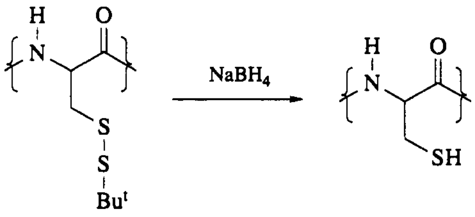

(19)

## 3.1.5 CARBOXY-PROTECTING GROUPS[5,11c,11d,226,227]

The carboxylic acid group represents one of the central functionalities in organic chemistry and, due to its reactivity, it must be protected in the majority of reactions involving other parts of a given molecule. In comparison to amino protection the masking and liberation of carboxylic acids pose less severe problems. Usually esters are chosen for this purpose, and the great variety of methods for their formation is well documented.[174,227] In contrast to amides and urethanes, esters can be hydrolyzed under relatively mild acidic or basic conditions. The ester cleavage often can be carried out without racemization of optically active compounds. Therefore, in numerous cases simple alkyl esters fulfill the demands for the temporary protection of carboxylic acid groups. However, for the cases in which milder deprotection techniques are required, nearly all the reliable methods already described as urethane protection principles for the amino function can be applied in the form of the analogous esters. Therefore, they are presented in this section mainly in tabular surveys. For detailed discussions see Section 3.1.2.1. In addition to chemical methods, increasing numbers of reports on enzymes attacking esters and amides under mild conditions can be found in the recent literature,[228] and it must be expected that these techniques will receive more and more attention for the selective removal of ester protecting functions.

### 3.1.5.1 Ester Protecting Groups

The most simple esters are the methyl and higher *n*-alkyl esters which can be prepared by numerous methods.[226,227] They usually are cleaved by saponification with base but also the application of trimethylsilyl iodide is efficient.[229] This reaction belongs to the mildest methods for ester cleavage, which generally consist in the treatment with nucleophiles effecting an $S_N2$ displacement of the carboxylate (Scheme 61).[227,229,230] For this transformation various anions (iodide, chloride, cyanide, thiocyanate, thiolate) or neutral molecules (thiols, amines) are applied in dipolar aprotic media. In the reaction of trimethylsilyl iodide with esters the silyl group acts as an activating Lewis acid, while the iodine attacks as the nucleophile. If thiols are used, the reaction can also be accelerated by adding a strong Lewis acid ($AlCl_3$, $AlBr_3$, $BCl_3$) which complexes the carbonyl oxygen and thereby activates the ester group (Scheme 61).[231] Of the metal halides employed in this deprotection technique the use of lithium iodide in pyridine is probably the method of choice for $S_N2$ dealkylation of esters. It also allows differentiations between similar esters in a given molecule because the accessibility of the ester alkyl carbon atom determines the ease of these ester cleavages (Scheme 62). If electron-withdrawing groups are bound to the methyl group of methyl esters, functionalities are generated which are considerably more reactive towards nucleophiles. Thus, the phenacyl ester, easily prepared by reaction of a carboxylate with phenacyl bromide, is cleaved with zinc in acetic acid[232] or sodium thiophenoxide.[233] Furthermore, the α-methylphenacyl ester can be removed photolytically or by hydrazinolysis.[234] The phthaloylmethyl group is also attacked by thiophenoxide[232a] or zinc, or alternatively by hydrazine or diethylamine in methanol (see Table 3). As the carboxy group generally is a much better leaving group than an alcohol, acetal-type protecting functions corresponding to those mentioned in Section 3.1.3.1 can also be used in the form of the α-alkoxyalkyl esters. They are in most cases synthesized in good yields by nucleophilic substitution of the halogen at the respective halomethyl alkyl ether by a carboxylate. For the cleavage of these groups, methods similar to those reported for the acetal-type protection of alcohols were devised. A selection of the proven blocking groups belonging to this class and conditions for their removal is given in Table 3.

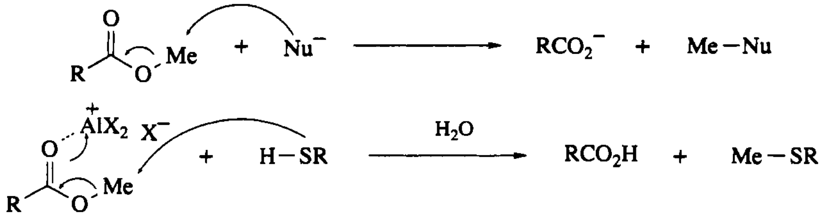

**Scheme 61**

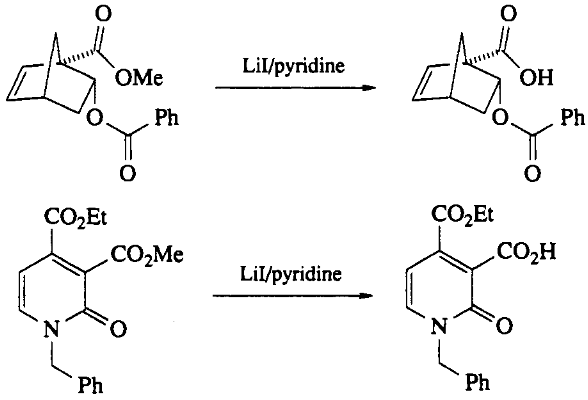

**Scheme 62**

In analogy to the β-substituted ethyl urethanes the corresponding β-substituted ethyl esters are cleaved in reductive fragmentations and β-elimination reactions. This allows deprotections under very mild conditions using various reagents (Table 4, see Sections 3.1.2.1 and 3.1.3.1), which can often be applied as alternatives to each other. It should be noted that the methylthioethyl,[51] the pyridylethyl[244] and the 1,3-dithianylmethyl esters[245] are two-step protecting groups which offer the additional advantage of being stable during the synthetic transformations of the protected compounds. After chemoselective labilization they can be removed under very mild conditions. To this category of protecting functions the cinnamoyl esters (**58**) must be added, since they can be cleaved in nearly neutral media by a method which is also based on a β-elimination (Scheme 63).[247] After methoxymercuration, the organomercury intermediate is fragmented by attack of thiocyanate at the thiophilic Hg atom. β-Substituted ethyl ester groups proved to be particularly well suited for the construction of sensitive glycopeptides. An example in which a synthesis of *N*-glycopeptides is highlighted is depicted in Scheme 64.[248] Here, the selective C-terminal deblocking and the subsequent extension of the peptide chain are achieved with the aid of the dithianylmethyl ester as a two-step protecting group. After oxidation of the sulfurs to the disulfones, the whole ester becomes so labile that it immediately hydrolyzes under the weakly basic reaction conditions (pH 7–8).

**Table 3** Substituted Methyl Esters, R—COO—R′, as Carboxy-protecting Groups

| *R′* | *Abbreviation* | *Removal by* | *Ref.* |
|---|---|---|---|
| Me | Me | $HO^-$; LiI/pyridine; $Me_3SiI$ if possible | 174, 229–231 |
| $CH_2C(O)Ph$ | Pac | NaSPh; Zn/AcOH; $h\nu$ | 232–234 |
| 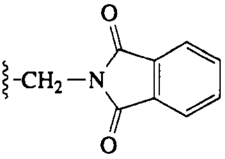 | Ptm | Zn/AcOH; $NH_2$—$NH_2$;<br>HCl or HBr/EtOAc | 235 |
| $CH_2OMe$ | MOM | $R_3SiBr$, trace MeOH | 236 |
| $CH_2O(CH_2)_2OMe$ | MEM | 3 M HCl, THF | 237 |
| $CH_2OCH_2Ph$ | BOM | $H_2$/Pd-C, EtOH | 238 |
| $CH_2SMe$ | MTM | i, $HgCl_2$/MeCN-$H_2O$; ii, $H_2S$ if possible or i, MeI or $H_2O_2$; ii, NaOH | 239 |

**Table 4** β-Substituted Ethyl Esters, $RCO_2R'$, as Carboxy-protecting Groups

| *R′* | *Abbreviation* | *Removal by* | *Ref.* |
|---|---|---|---|
| 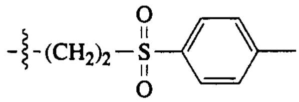 | Tse | 1 M NaOH; KCN or $Na_2CO_3$, dioxane/$H_2O$ | 240 |
| $-(CH_2)_2-S-Me$ | Mte | i, $H_2O_2$; ii, pH 10–11 | 51 |
| $-(CH_2)_2-SiMe_3$ | Tmse | $R_4N^+ F^-$ | 241 |
| $-CH_2-CCl_3$ | Tce | Zn/AcOH or THF; electrolysis | 242 |
| $-(CH_2)_2-Br(I)$ | Br(I)Et | Zn/AcOH; $S^{2-}$ or $^-S(CH_2)_2S^-$; electrolysis; Co(I)-phthalocyanine | 243 |
| 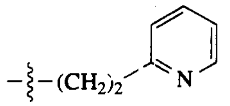 | 2-Pet | i, MeI; ii, morpholine | 244 |
| 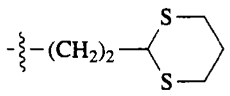 | Dim | i, $H_2O_2$; ii, pH 7–8 | 245 |
| 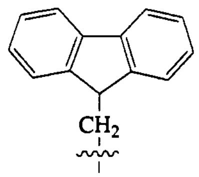 | Fm | $Et_2NH$ | 246 |

Of great importance in peptide chemistry are the *t*-butyl, benzyl and substituted benzyl esters.[11c,11d,174,226] They are more stable to acids than the corresponding urethanes. Benzyl and substituted benzyl esters can be prepared by azeotropic esterification with the respective benzyl alcohol, by activating the carboxy group, *e.g.* with dicyclohexylcarbodiimide (DCC) or by reacting a carboxylate with a benzyl halide (Scheme 65). The latter $S_N2$-type ester formation is particularly efficient if cesium carboxylates are employed.[249] Under the conditions required for this reaction the racemization of α-chiral car-

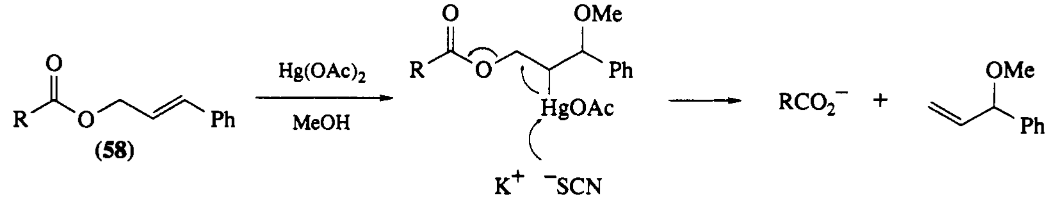

**Scheme 63**

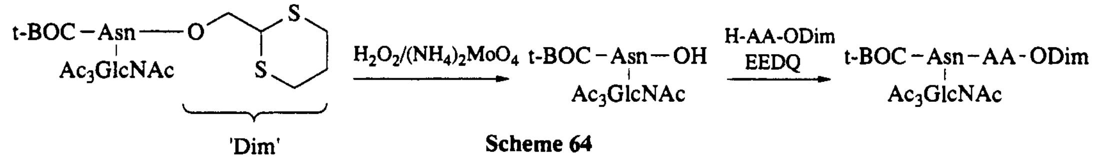

**Scheme 64**

boxylic acids can be minimized. All benzyl-type esters are cleaveable by hydrogenolysis. Furthermore, it should be noted that catalytic transfer hydrogenation can be useful to remove these groups from sulfur-containing compounds.[250] Whereas simple unsubstituted benzyl esters are hydrolyzed by HBr/AcOH, the properties of the substituted variants depend on the substituent in the aromatic ring (see Section 3.1.2.1). Electron-withdrawing groups, *e.g.* the nitro group,[251] enhance the acid stability of the esters. In contrast, electron-donating substituents induce an increased sensitivity towards acids. Thus, the 4-methoxybenzyl esters are already cleaved by trifluoroacetic acid at 0 °C.[252] In addition, the substituents can serve to introduce solubilizing properties as is the case for 4-sulfobenzyl esters[253] and for 4-picolyl esters.[254] The picolyl ester, furthermore, is resistant towards acids and allows the protected compound to be purified by ion-exchange techniques. Since the hydrogenation of picolyl esters may be very slow, the electrochemical reduction at a mercury electrode at least in some cases appears to be more favorable. Benzyl esters also form the basis for several photosensitive protecting groups. Thus, for instance, *o*-nitrobenzhydryl and 2,4-dinitrobenzenesulfenyl esters can be photolyzed under neutral conditions.[255] As is to be expected, the 9-anthrylmethyl ester is also an acid sensitive protecting function. Interestingly, it is very reactive towards thiolate anions in hexamethyl phosphoric triamide.[256] The most commonly used benzyl-type esters are shown in Table 5. Phenyl esters, or aryl esters in general, constitute blocking groups of carboxylic acids of only limited applicability. For most purposes their acylating ability is too high. They are readily removed, exploiting the α-effect of peroxide anions in moderately basic media.[257]

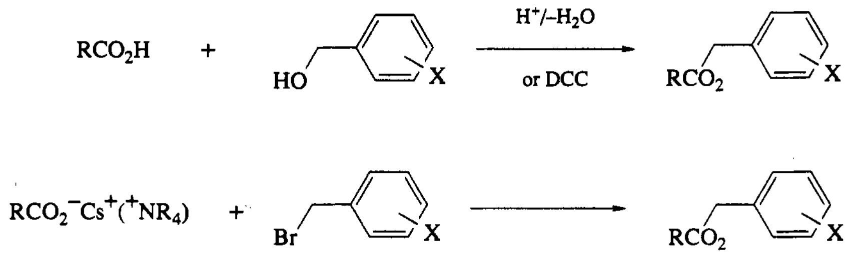

**Scheme 65**

*t*-Butyl esters[11c,11d,226,227] are among the most important carboxy-protecting groups. They are stable under basic conditions and towards hydrazine and ammonolysis. The *t*-butyl ester protection is readily removed with trifluoroacetic acid, HBr/AcOH, formic acid or toluenesulfonic acid. The formation of these esters is most frequently carried out by the reaction of the acid with isobutene under acidic catalysis (Scheme 66).[258] However, transesterification of acetic acid *t*-butyl ester catalyzed by perchloric acid[259] and the reaction of an acid chloride or the mixed anhydride with 2,4,6-trichlorobenzoic acid[260] with *t*-butyl alcohol are effective (Scheme 66). A very mild method consists in the recently described esterification using *t*-butyl trichloroacetimidate.[261] *t*-Butyl esters are completely stable under conditions required for hydrogenolytic removal of benzyloxycarbonyl and related groups. The acidolysis of *t*-butyl esters can selectively be achieved in the presence of the N-terminal Z, and suitably substituted Z, groups. These orthogonal stabilities form the basis for numerous successful peptide syntheses. Under the weakly acidic conditions used for the acidolytic removal of the 2-(4-biphenyl)-2-propoxycarbonyl (Bpoc) group, the *t*-butyl ester remains untouched.[262] However, this acid stability is not reliably sufficient to allow the

**Table 5** Substituted Benzyl Esters, $RCO_2R'$, as Carboxy-protecting Groups

| *R'* | *Abbreviation* | *Removal by* | *Ref.* |
|---|---|---|---|
| 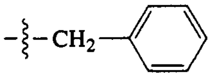 | Bn | Pd–C, $H_2$, $HCO_2H$/MeOH, cyclohexadiene or cyclohexene; $OH^-$; HBr/AcOH; $NaNH_3$ liq. | 11c, 11d, 226, 227 |
| 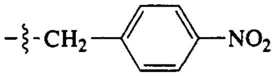 | Nb | $H_2$/Pd–C; $OH^-$; Na/$NH_3$ liq.; stable to HBr | 251 |
| 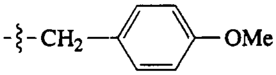 | Mob | $H_2$/Pd–C; Na/$NH_3$ liq.; $CF_3CO_2H$, 0 °C | 252 |
| 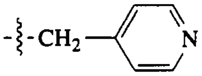 | Pic | $H_2$/Pd–C; electrolysis; very stable towards acids | 254 |
| 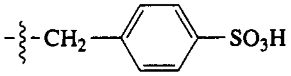 | — | $H_2$/Pd; NaOH/$H_2O$/dioxane | 253 |
| 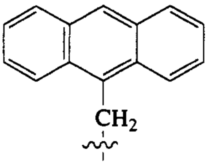 | Anm | HBr/AcOH; 0.1 M NaOH; NaSMe/HMPA | 256 |

selective removal of N-terminal *t*-butyloxycarbonyl groups.[263] It seems that the treatment with trimethylsilyl perchlorate[32a] can provide a possibility for the chemoselective differentiation between Boc and *t*-butyl ester protection. It should also be noted that the application of one equivalent of *p*-toluenesulfonic acid in ether/ethanol mixtures results in the selective cleavage of the N-terminal Boc group, while the C-terminal *t*-butyl esters remain intact.[264] As is well known, these esters are quite resistant towards nucleophilic attack. One severe exception to this generalization is observed in the synthesis of peptides involving aspartic acid β-*t*-butyl ester units. On treatment with alkali, amines or hydrazine, cyclization to the corresponding aspartimide derivatives occurs. The analogous side reaction is also observed for glutamic acid γ-*t*-butyl esters, but only to a lesser extent.[265]

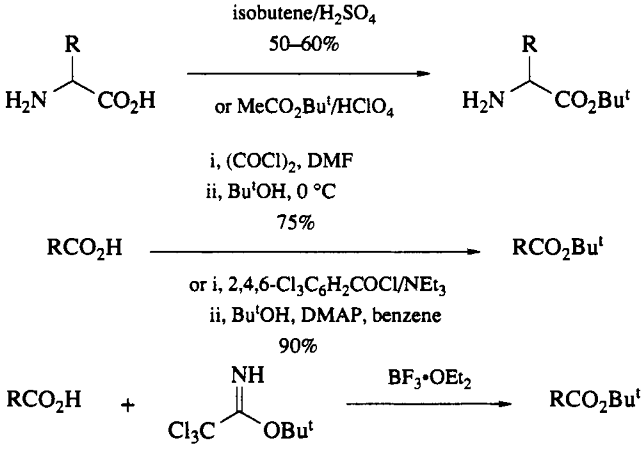

**Scheme 66**

As has already been detailed for the allyloxycarbonyl (Aloc) moiety, allyl esters also proved to be very versatile and useful carboxy-protecting groups. They can be easily constructed by azeotropic esterification or nucleophilic displacement on allylic halides.[63,266] For the cleavage of these esters lithium dimethylcuprate can be used. However, a much milder method is found in the $Rh^I$-catalyzed isomerization of the allyl moiety to a propenyl ester which immediately hydrolyzes under the reaction conditions (Scheme 67).[63,267] Even milder is the $Pd^0$-catalyzed allyl transfer to morpholine as an accepting nucleophile.[10,266,267] The removal of allyl ester protection has earlier been used in particular in β-lactam antibiotic synthesis in the sense of a $Pd^0$-mediated transesterification.[59] By applying a substituted derivative, the addition of an external nucleophile can be circumvented. Thus, 4-(trimethylsilyl)-2-buten-1-yl esters (**59**)[268] react with $Pd^0$ to form a π-allylpalladium complex. This species then undergoes desilylation by the liberated carboxylate to give butadiene and a trimethylsilyl ester (Scheme 68).

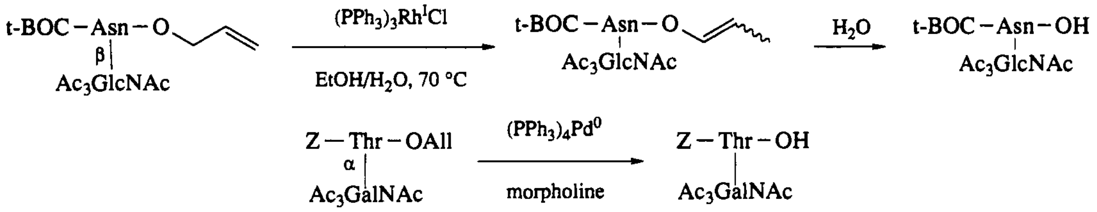

**Scheme 67**

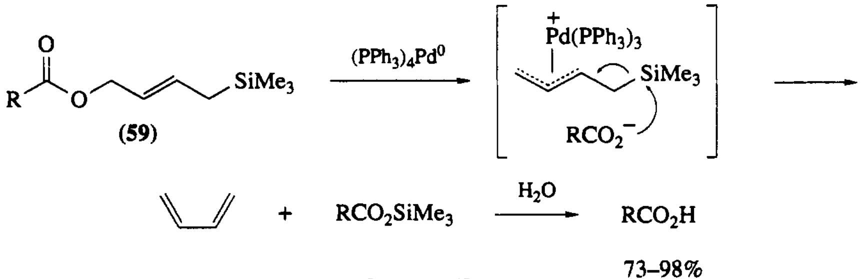

**Scheme 68**

### 3.1.5.2 Polymer Esters as Protecting and Anchoring Groups

One of the milestones in preparative organic synthesis is certainly the concept of synthesizing peptides on a solid supporting phase, invented by Merrifield.[269] Therefore, polymer-linked protecting groups[270] shall be briefly discussed here. In the original form as well as in most of the commonly applied variants of this principle, the C-terminal amino acid is attached to a resin *via* a benzyl ester-type linkage. The coupling to the polymer is preferably carried out by reacting the salts of *N*-protected amino acids with benzyl halide groups of the polymer, in the most simple case with chloromethyl polystyrene (**61**).[269] As shown in equation (20), a particularly efficient anchoring without racemization is accomplished if the cesium salts (**60**) are used.[249] Alternative condensations of *N*-protected amino acids with polymeric benzyl alcohols often suffer from the partial racemization of the activated amino acid derivative. As the selectively removable amino-protecting group (PG) in this concept, the *t*-butyloxycarbonyl function (t-BOC, see Section 3.1.2.1) is most commonly used. Its removal from the polymer-linked amino acid derivative (**62**) is achieved with trifluoroacetic acid without affecting the polymer benzyl ester bond. After construction of the desired peptide (**63**) by sequential chain extension,[271] the final detachment of the free peptide (**64**) requires treatment with strong acids which simultaneously cleave off the N-terminal and side chain protecting groups. A mixture of liquid hydrogen fluoride and anisole[272] is widely used for this aim. It often yields the peptides almost quantitatively. The anisole serves as a suitable scavenger for the generated carbocations and thus prevents their reaction with nucleophilic functionalities of the peptide (equation 21). Numerous efforts to optimize the concept of solid-phase synthesis[270,271] involve the application of different N-terminal and side chain blocking groups, generation of improved accessibilities of functional groups by using polyamides,[38] or even soluble polyethylene glycol as the polymeric backbone,[273] and modified benzyl ester anchorages. The acid stability of this benzyl ester linkage is increased by electron-withdrawing substituents in the aromatic ring.[269] In this sense, a useful method was developed on the basis of the *p*-hydroxymethylphenylacetic acid,[274] which, furthermore, provides an improved anchoring strategy using preformed benzyl esters (**65**) of the *N*-protected amino acids ('handle strategy', see equation 22). The separately synthesized handle ester (**65**) can be purified and its condensation with aminomethyl polystyrene is not accompanied by racemization. Compared with the simple benzyl ester (**63**), the Pam-linked benzyl ester in (**66**) displays about a 100-fold greater stability towards acids. In contrast, electron-donating substituents enhance the acid sensitivity of polymer benzyl esters as has been demonstrated for *p*-alkoxybenzyl ester anchoring groups.[275] Even more acid labile are the dialkoxybenzyl ester linkages[276,277] which are already cleaved by 1% trifluoroacetic acid in dichloromethane. Solid-phase peptide syntheses on these resins are carried out with the N-terminal Fmoc group[37,38] (see Section 3.1.2.1), which is selectively removable under weakly basic conditions.

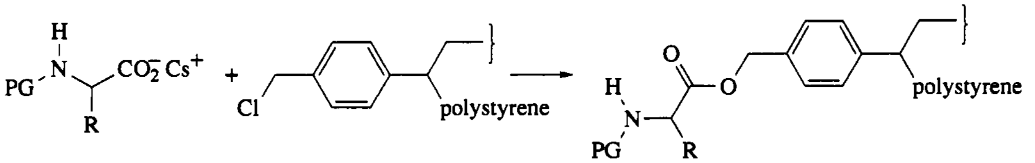

**(60)** **(61)** **(62)** (20)

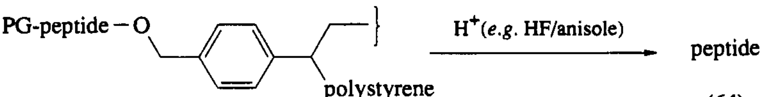

**(63)** **(64)** (21)

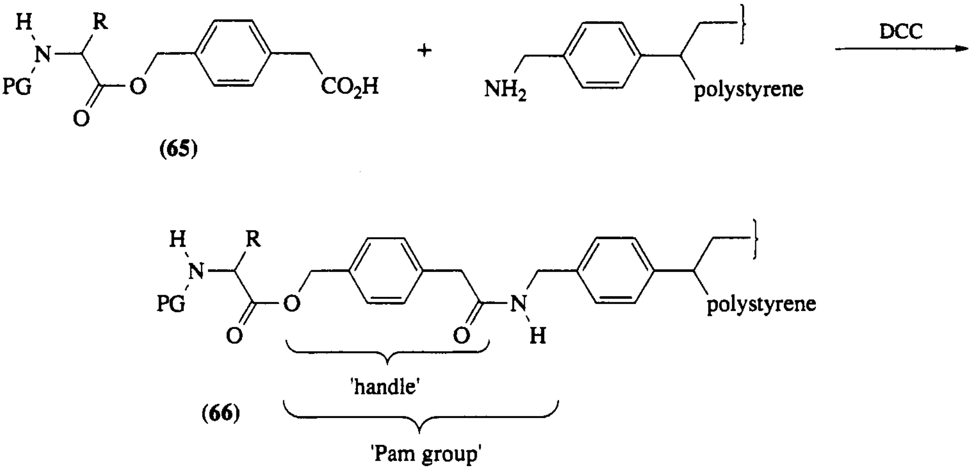

**(65)**

**(66)** (22)

A new type of anchorage, stable towards trifluoroacetic acid, and at the same time cleavable under almost neutral conditions was developed on the basis of the allyl ester and its palladium(0)-catalyzed removal. For instance, the very acid and base sensitive *O*-glycosyl serine peptide (**68**) can be selectively released from its polymer-protected derivative (**67**), bound to hydroxycrotonyl aminomethyl polystyrene (Hycram resin)[60] by application of the $Pd^0$-catalyzed allyl transfer to morpholine[55,266] or a different suitable weakly basic nucleophile.[57,278] The stability of the allylic anchoring group allows the use of the acid sensitive t-BOC or, alternatively, the base labile Fmoc group as temporary amino protection. Under the neutral detachment conditions (equation 23) *N*- and side chain protecting groups remain unaffected. The obtained peptide fragments can immediately be used for fragment condensations.

As has been demonstrated in Section 3.1.2.4, complexation of amino groups offers a quite different concept for reversible protection. Making use of this principle, the coordination of chromium carbyne complexes with amino acids was described as a new amino protection.[279] Similarly, bis(ethylenediamine)cobalt(III) complexes of amino acids constitute a new interesting method for protection[280] which recently was extended to the development of a new type of anchoring in solid-phase synthesis (Scheme 69).[281] First, a t-BOC amino acid is condensed with the aquabis(ethylenediamine)cobalt(III) complex of *p*-aminomethylbenzoic acid. The handle obtained in this way is then linked to aminomethyl polystyrene to give the anchored amino acid (**69**). Due to the sufficient stability of the complex towards

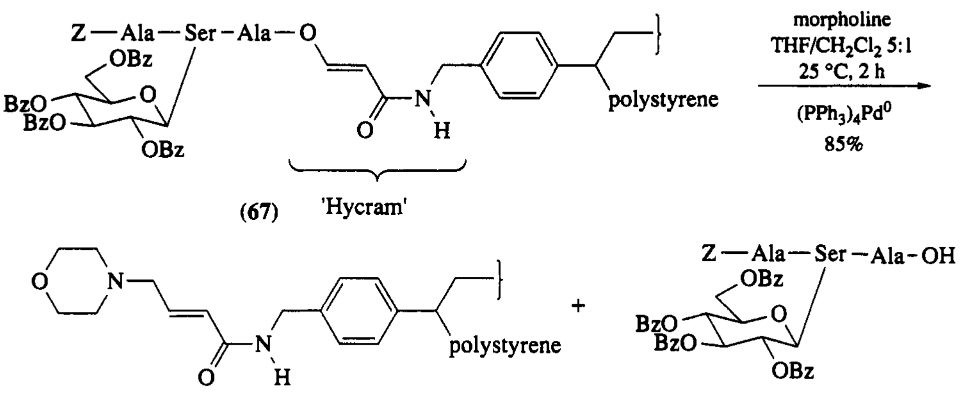
Z—Ala—Ser—Ala—O
OBz
BzO
BzO
O
OBz
N
H
O
polystyrene
morpholine
THF/CH2Cl2 5:1
25 °C, 2 h
(PPh3)4Pd0
85%
O
N
N
H
O
polystyrene
+
Z—Ala—Ser—Ala-OH
OBz
BzO
BzO
O
OBz

(67) 'Hycram'

(68)

(23)

acids, the t-BOC group can be selectively removed. Subsequent chain extension delivers the polymer-linked peptide (**70**) from which the *N*-t-BOC peptide (**71**) is released by destruction of its cobalt complex with mercaptoethanol. Both allyl ester anchoring and amino acid complexation need further testing in syntheses of larger peptides.

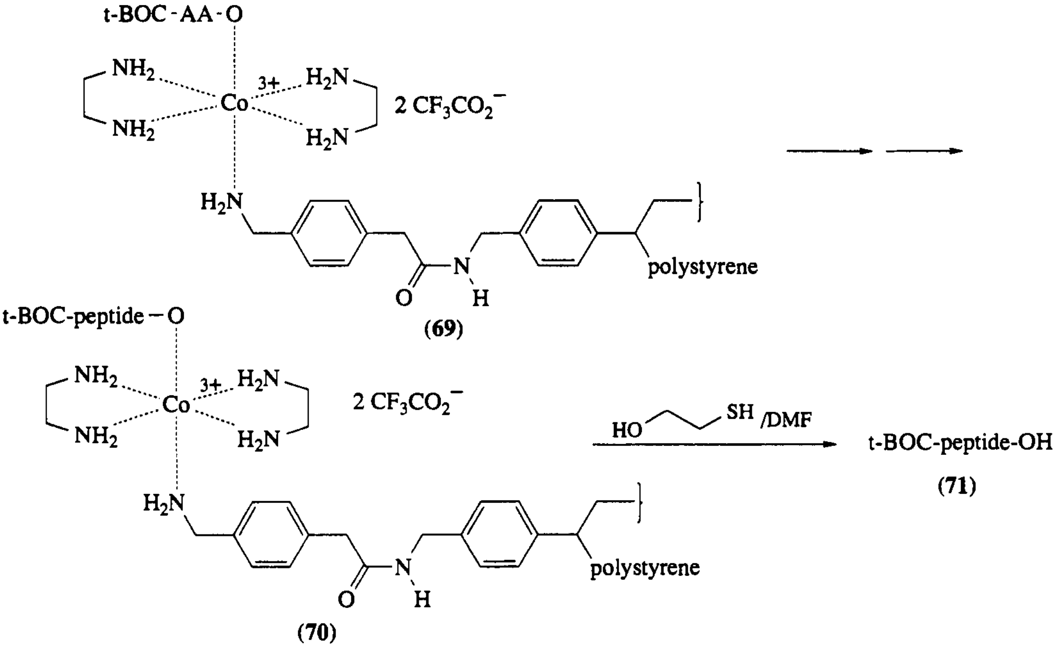
t-BOC-AA-O
NH2
NH2
3+
Co
H2N
H2N
2 CF3CO2−
H2N
N
H
O
polystyrene
t-BOC-peptide – O
NH2
NH2
3+
Co
H2N
H2N
2 CF3CO2−
HO
SH
/DMF
t-BOC-peptide-OH
H2N
N
H
O
polystyrene

(69)

(71)

(70)

Scheme 69

### 3.1.5.3 Amide Protecting Groups

Amides are only in isolated cases employed as blocking groups for carboxylic acids. However, their use may be advantageous since they can be removed easily by *O*-alkylation[282] and subsequent hydrolysis of the imidate formed (Scheme 70). An alternative, known for a long time,[283] consists of nitrosation and hydrolysis of the diazonium intermediate. These strategies were applied by Woodward[284] and Eschenmoser,[285] respectively, in their syntheses of vitamin $B_{12}$. Nitrosation can be achieved by using $N_2O_4$, butyl nitrite, nitrosyl chloride or nitrosonium tetrafluoroborate. The conversion to imidates usually is effected with Meerwein salts[286] or, following Eschenmoser's method, using the extremely reactive *N*-alkyl-*N*-vinylnitrosonium ion, derived from the α-chloronitrone by treatment with $AgBF_4$ (Scheme 70). Alkyl diphenyl sulfonium salts have also been described as *O*-alkylating reagents for amides.[287] An additional method for the cleavage of tertiary amides consists in the use of 'anhydrous hydroxide' (see Section 3.1.3.3).[181]

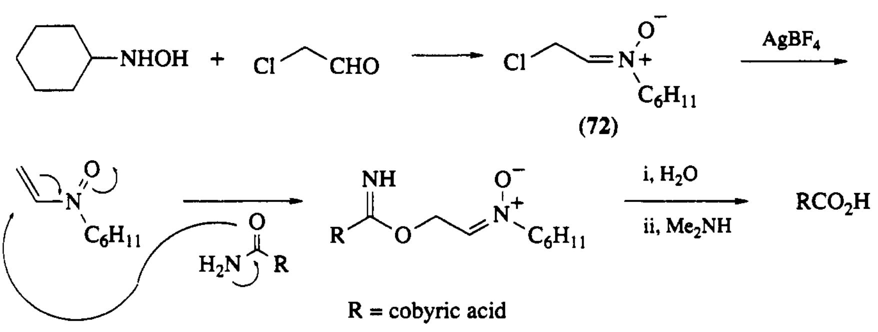

R = cobyric acid

**Scheme 70**

### 3.1.5.4 Protection of Carboxylic Groups in Organometallic Transformations

Carboxylic acids and esters frequently must be protected against the attack of organometallic reagents, *e.g.* metal alkyls and hydrides, and reducing agents like $LiAlH_4$. For this purpose they usually are converted to orthoesters, oxazolines or oxazoles.

Acyclic orthoesters can be used for the masking of carboxylic acids; however, they are very sensitive to hydrolysis and are affected by Grignard reagents. Therefore, the more stable 3,4,10-trioxa-3-adamantyl group (**73**), derived from *cis*-phloroglucit (*r*-1,*c*-3,*c*-5-trihydroxycyclohexan) and orthocarboxylic acid trimethyl or triethyl esters, was introduced (see Scheme 71).[288] It is resistant to treatment with Grignard compounds, reduction with $LiAlH_4$, and can be converted to Grignard reagents,[289] ready for reactions with various electrophiles like acetaldehyde, methyl vinyl ketone, alkyl halides and epoxides (Scheme 71). For the hydrolysis of these orthoesters to the free carboxylic acids heating with 1–2 M $H_2SO_4$/dioxane (1:1) is necessary (Scheme 72). Alternatively, heating with 0.01 M $H_2SO_4$ for 10 min leads to 3,5-dihydroxy-1-cyclohexyl esters, which can then be saponified with base.

The problems with the inaccessibility and relatively slow cleavage rates of these adamantoid orthoesters were overcome by the introduction of cyclic ortho esters (**74**) derived from 2,2-bishydroxymethyl-1-propanol.[290] They are prepared either from trialkylorthoesters by ortho ester exchange[290] or, most advantageously, directly from the carboxylic acids by esterification with 3-methyl-3-hydroxyethyl oxetane (obtained from the triol $MeC(CH_2OH)_3$ and subsequent rearrangement with $BF_3{\cdot}OEt_2$; Scheme 73).[291] The oxabicyclo[2.2.2]octyl ortho esters (OBO esters; **74**) thus obtained are still stable during chromatography but can be readily removed in high yields by subsequent treatment with acid (pH 3) and a base to cleave the intermediately formed ester.[290,292] The advantageous properties of this ortho ester

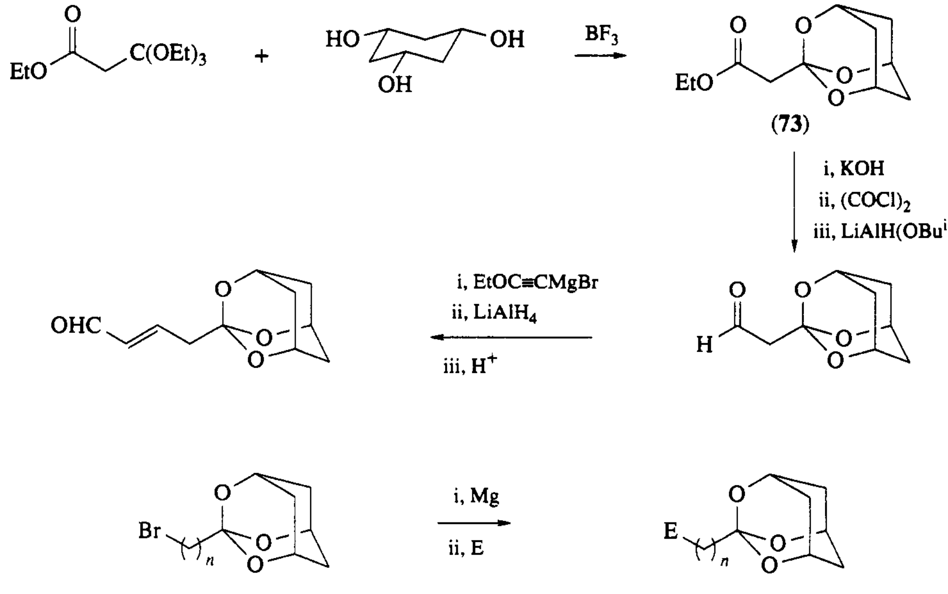

**Scheme 71**

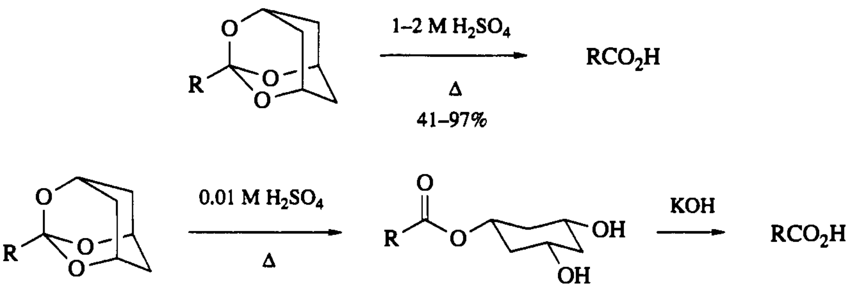
1–2 M H2SO4
Δ
41–97%
RCO2H
0.01 M H2SO4
Δ
KOH
RCO2H
OH
OH

Scheme 72

protecting group were, for instance, exploited in the synthesis of a metabolite of prostaglandin $D_2$,[293] the eicosanoid hybridalactone[292] and ginkgolide B.[294]

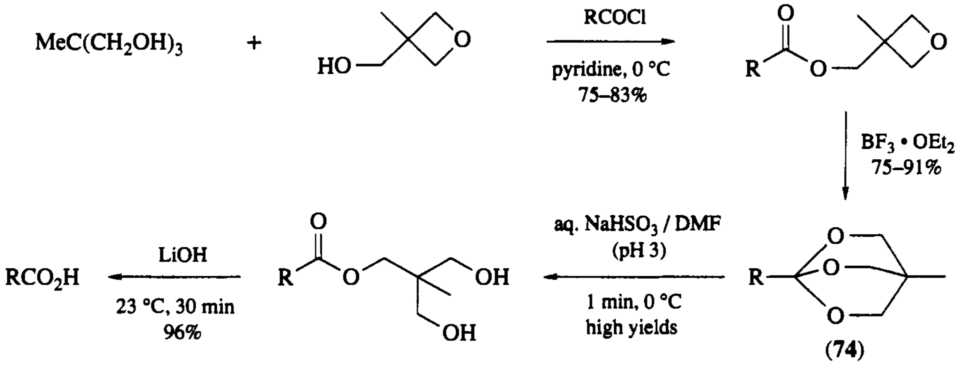
MeC(CH2OH)3
+
HO
RCOCl
pyridine, 0 °C
75–83%
BF3 • OEt2
75–91%
aq. NaHSO3 / DMF
(pH 3)
1 min, 0 °C
high yields
(74)
LiOH
23 °C, 30 min
96%
RCO2H

Scheme 73

Oxazolines (**75**) may be formed from carboxylic acids by condensation with either 2-amino alcohols or aziridines (Scheme 74). They are stable to Grignard reagents and to $LiAlH_4$ and are cleaved either by acid-catalyzed hydrolysis or alcoholysis.[295] A disadvantage of the oxazolines is that they retain reactivity towards alkylating reagents. On the other hand, this forms the basis for an alternative deprotection in the presence of acid sensitive structures. After methylation the oxazolines can be hydrolyzed to the free acids with 2 M NaOH (94% yield).[296]

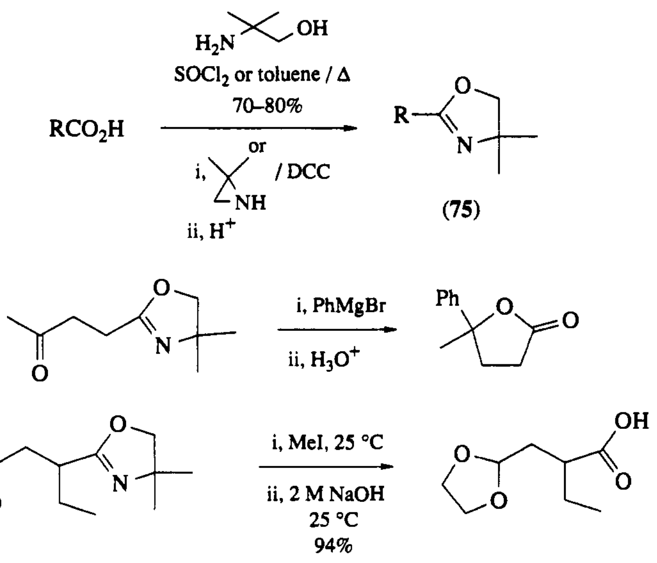
H2N
OH
SOCl2 or toluene / Δ
70–80%
RCO2H
or
i,
NH
/ DCC
ii, H+
(75)
i, PhMgBr
ii, H3O+
Ph
i, MeI, 25 °C
ii, 2 M NaOH
25 °C
94%
OH

Scheme 74

4,5-Diphenyl oxazoles (**76**)[297] may be prepared from carboxylic acids and benzoin by esterification, followed by treatment with ammonium acetate in glacial acetic acid in overall yields of 80–85% (Scheme 75). The heterocycles thus obtained can be functionalized in numerous ways (alkylations, Friedel–Crafts reactions, reduction with $NaBH_4$, *etc.*). If desired, the original carboxylic function may be regenerated in a reaction with singlet oxygen in high yields. In fact, what is obtained from this reaction is a triamide (*e.g.* **77**) which represents an activated acylating agent and which may be used directly for lactonizations and lactam formations. As an example for this conversion a synthesis of recifeiolide is detailed in Scheme 76.

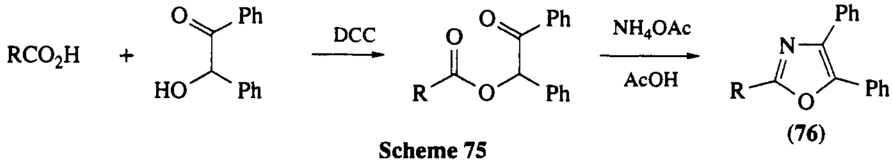

**Scheme 75**

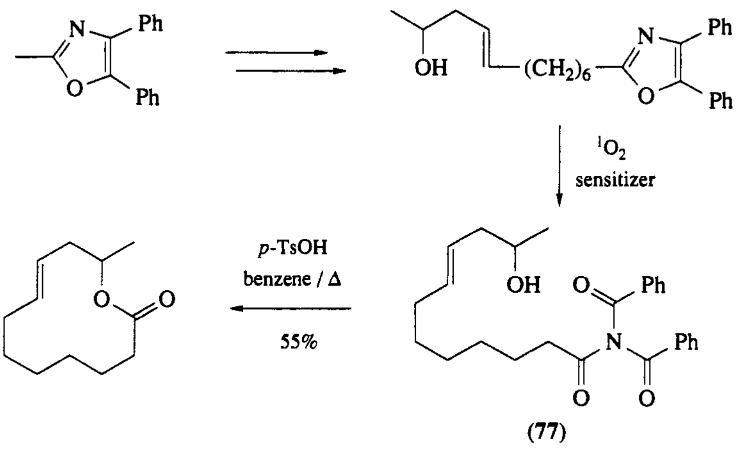

**Scheme 76**

### 3.1.6 CARBONYL-PROTECTING GROUPS[5,298]

In the course of complex syntheses, for instance in total syntheses of natural products, carbonyl groups often must be protected against nucleophilic attack, *e.g.* by organometallic compounds and strong bases, reduction, and sometimes also oxidation. To achieve this aim, the carbonyl functions generally are transformed into suitable acetals, thioacetals, hydrazones, oximes and cyanohydrins. In addition, they can be converted to enamines, enol ethers and silylenol ethers. In these derivatives the carbonyl function is desensitized towards attack under neutral and basic conditions. Most of the protecting groups can be removed by treatment with acids or Lewis acids. In particular, the oxygen acetals and ketals are readily cleaved by acidic hydrolysis and are stable to oxidants and heavy metal ions. In contrast, thio-acetals and -ketals are cleaved by a wide range of oxidants and, under neutral conditions, by mercury(II), silver(I) or copper(II) salts. Due to the pronounced differences in reactivity between the different carbonyl groups, in many cases a reactive $C{=}O$ group may be protected selectively in the presence of less reactive ones.

#### 3.1.6.1 Acyclic and Cyclic Acetals and Ketals

Dialkyl acetals and ketals can easily be formed from carbonyl compounds with alcohols under acidic conditions. Some representative examples for the great variety of methods available for this transformation are given in Scheme 77. As is demonstrated, both simple alcohols themselves or formic acid ortho esters can be used for acetal formation in the presence of hydrochloric acid,[299] toluenesulfonic acid[300] or activated alumina (Montmorrilonite clay K-10).[301] Owing to different carbonyl reactivities, regio- and chemo-selective differentiation is often realizable, as has been shown, for example, on androstane-3,17-dione (**78**). Acid-catalyzed acetalization selectively delivers the 3-ketal, whereas the sterically hindered 17-carbonyl function remains unaffected. Under neutral conditions the reactions are promoted by catalysis with lanthanide ions.[302] An interesting acetal formation consists of the electrochemical oxidation of α-silyl ethers, *e.g.* **(79)**.[303] The classical method for the cleavage of acetals is acidic hydrolysis.[304] With trifluoroacetic acid the dimethyl acetal **(80)** is selectively hydrolyzed while the cyclic acetal and the dithioacetal remain intact.[304] The acid sensitivity of dimethyl or diethyl acetals, *e.g.* in **(81)**, allows the regeneration of the carbonyl group even in the presence of a cyclopropane structure.[305] However, transacetalization[306] and, in particular, the cleavage with trimethylsilyl iodide[307] offer alternatives (Scheme 78).

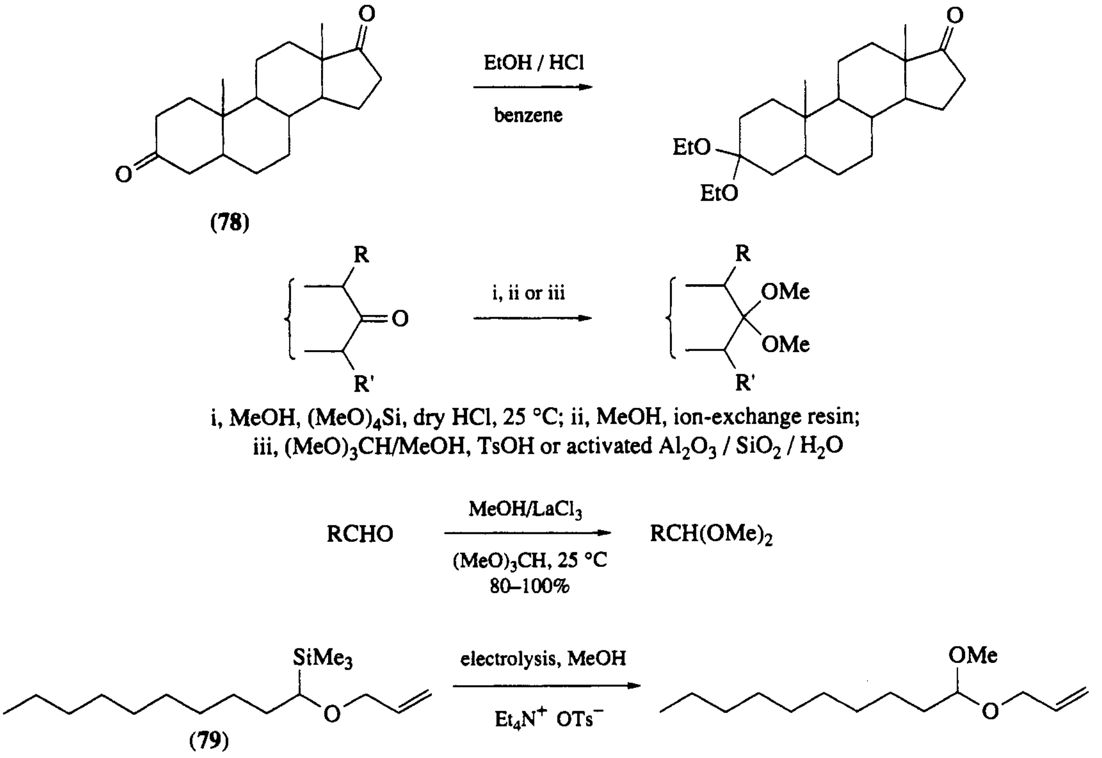
O
EtOH / HCl
benzene
O
EtO
EtO
(78)
R
O
i, ii or iii
R
OMe
OMe
R'
R'
MeOH/LaCl$_3$
RCHO
RCH(OMe)$_2$
(MeO)$_3$CH, 25 °C
80–100%
SiMe$_3$
electrolysis, MeOH
OMe
O
Et$_4$N$^+$ OTs$^-$
O
(79)

i, MeOH, (MeO)$_4$Si, dry HCl, 25 °C; ii, MeOH, ion-exchange resin;
iii, (MeO)$_3$CH/MeOH, TsOH or activated Al$_2$O$_3$ / SiO$_2$ / H$_2$O

Scheme 77

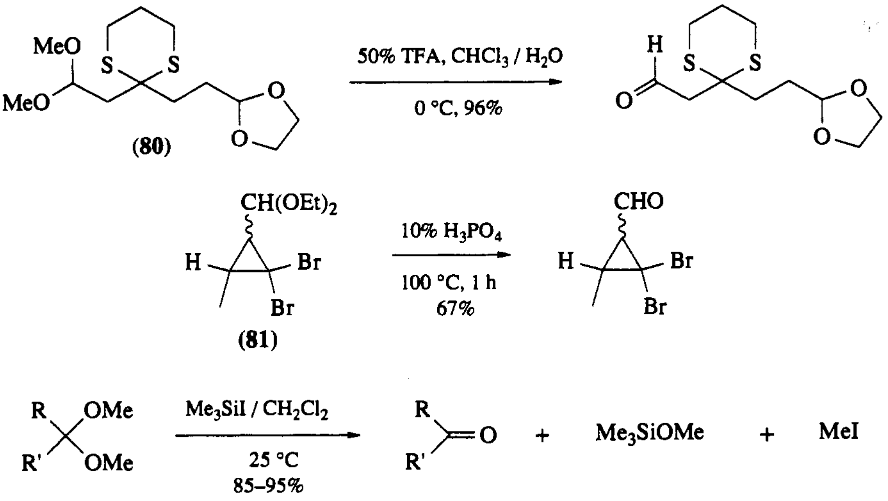
MeO
MeO
S
S
O
O
(80)
50% TFA, CHCl$_3$ / H$_2$O
0 °C, 96%
H
O
S
S
O
O
CH(OEt)$_2$
H
Br
Br
(81)
10% H$_3$PO$_4$
100 °C, 1 h
67%
CHO
H
Br
Br
R
OMe
R'
OMe
Me$_3$SiI / CH$_2$Cl$_2$
25 °C
85–95%
R
O
R'
+
Me$_3$SiOMe
+
MeI

Scheme 78

More popular than the acyclic acetals are 1,3-dioxanes and 1,3-dioxolanes in carbonyl protection. A great variety of techniques, mainly based on the acid-catalyzed reaction of the respective diol with the carbonyl compound, were developed.[308] Recently an improved procedure was described in which trimethylsilyl chloride was used as the condensing reagent.[309] Particularly mild conditions are found in the transacetalization with 2-dimethylamino-1,3-dioxolane (**82**), which has been extensively used for the regioselective functionalization of steroid ketones (see equation 24).[310] As a rule, 1,3-dioxolanes and -dioxanes are more stable than acyclic acetals (see Scheme 78).[304] This has been exploited, for instance, in the synthesis of the manoalide analog (**84**) from the precursor (**83**; Scheme 79).[311] The hydrolysis of these acetals is usually carried out with dilute acid[312] or by acid-catalyzed transketalization, as for example in the synthesis of walburganal (**85**; Scheme 80).[314] As a general rule, for the hydrolysis of cyclic acetals it was found that 1,3-dioxanes derived from ketones hydrolyze faster than the corresponding 1,3-dioxolanes. For aldehyde derivatives the reversed order is commonly observed.[315] The acidolytic regeneration of ketones from their dioxolanes takes place under relatively mild conditions. Even acid sensitive structures, *e.g.* the cyclopropane in (**86**), can be conserved. This has been used in the synthesis of sirenine.[312] Since the dioxane and dioxolane protection are reliably stable to strong nucleophiles and bases, organometallic reactions can be performed on compounds protected in this way, without destruction of the blocked form (see, for example, the transformation of (**87**) to (**88**)[313] shown in equation 25). Much milder and nonacidic conditions for the deprotection can be applied if functionalized acetals and ketals are introduced. Thus, bis(2,2,2-trichloroethyl) acetals, 5,5-dibromo-1,3-dioxanes and 4-bromomethyl-1,3-dioxolanes can be removed with zinc in organic solvents.[316] The synthesis of the bis(trichloroethyl) acetals is favorably carried out by an acid-catalyzed exchange reaction with the corresponding dimethyl or diethyl acetals.[316a] From acyclic[317] and cyclic dibenzyl acetals and ketals, as for instance (**89**),[318] the carbonyl group can be regenerated by hydrogenation. Interestingly, the seven-membered cyclic dibenzyl acetal is removable with conservation of the cyclopropane, which is usually prone to hydrogenolytic ring opening.[318a] The cyclic benzyl-type acetal also proved to be an efficient carbonyl-protecting group in pheromone synthesis.[318b] In addition, 5-methylene-1,3-dioxanes[319] can be regarded as cyclic allyl ethers which are cleaved under mild conditions either after isomerization or with the aid of oxidizing reagents. Finally, the deprotection principle used for amino protection in the 2- and 4-Pyoc urethanes (see Section 3.1.2.1) has been adapted for the design of acetals being labile after methylation of the pyridine nitrogen (Scheme 81).[320]

### 3.1.6.2 Acyclic and Cyclic Dithioacetals and Dithioketals

Carbonyl functions often are protected as thioacetals, because these derivatives are stable to acids and bases. Dithio-acetals and -ketals generally are prepared by reaction of the carbonyl compound with a thiol in the presence of an acid catalyst. This transformation has been used in carbohydrate chemistry for a long time to lock aldoses in their acyclic forms (see equation 26).[322] In recent years, this blocking principle for carbohydrates has been exploited in several chiral pool syntheses.[323] Several other methods for

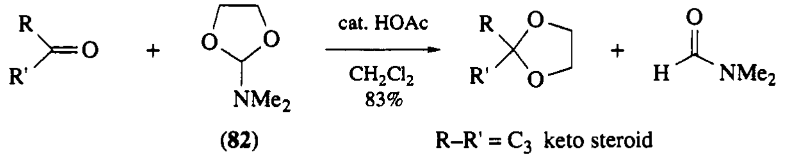

(24)

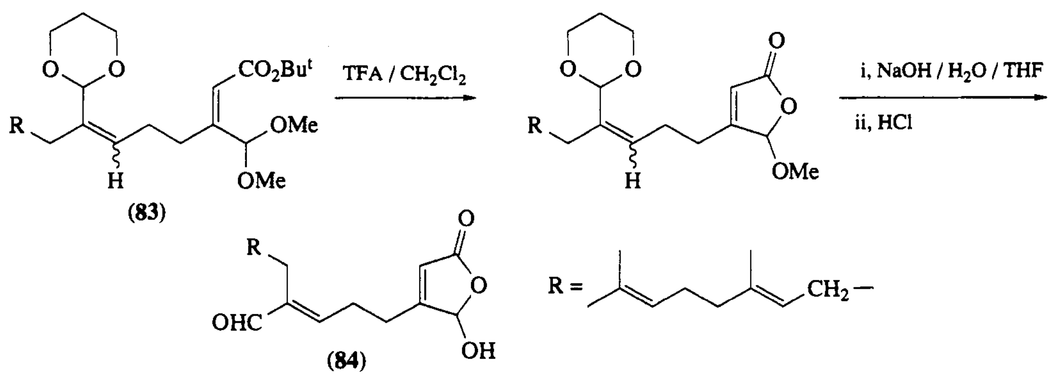

Scheme 79

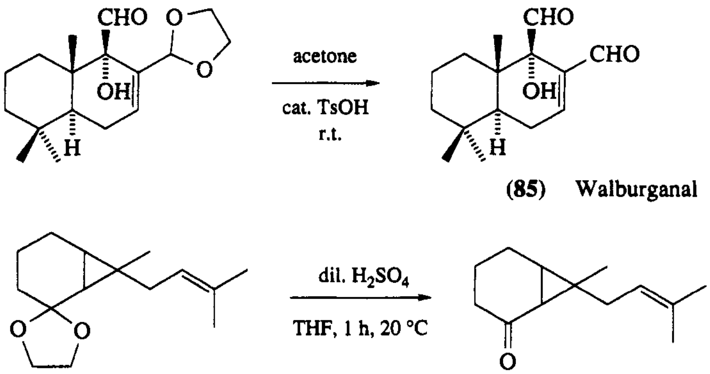

CHO
OH
H
acetone
cat. TsOH
r.t.
CHO
CHO
OH
H
dil. $H_2SO_4$
THF, 1 h, 20 °C
O

**(85)** Walburganal

**(86)**

Scheme 80

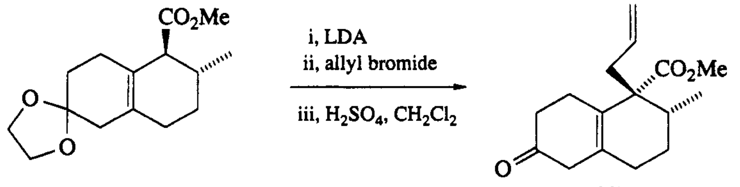

$CO_2Me$
i, LDA
ii, allyl bromide
iii, $H_2SO_4$, $CH_2Cl_2$
$CO_2Me$
O

**(87)** **(88)**

(25)

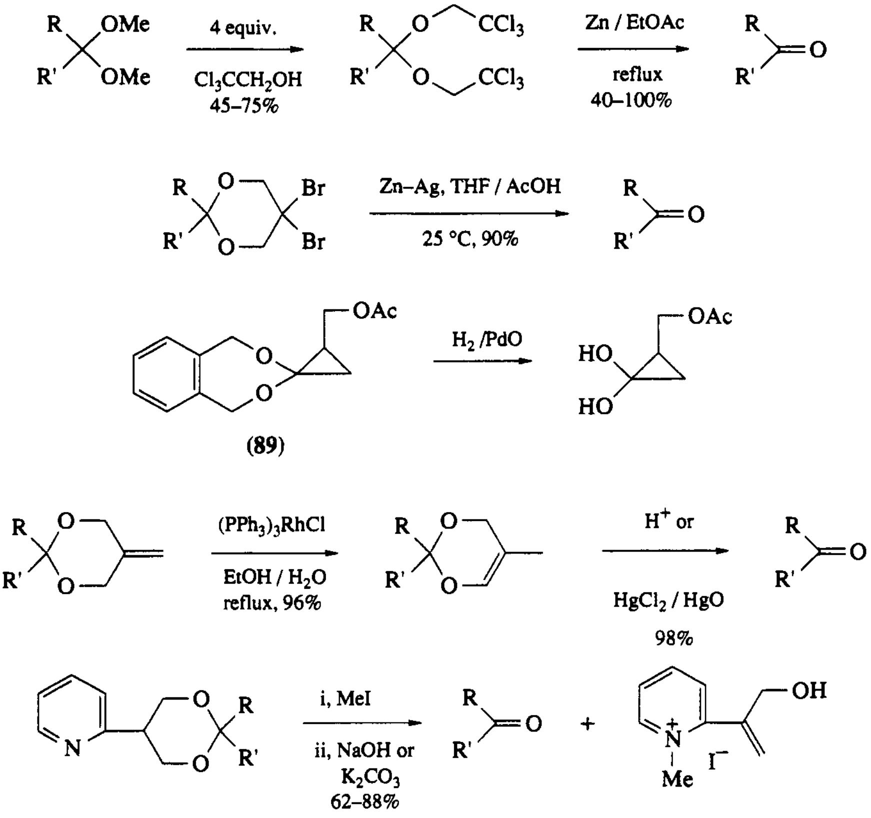

R
R'
OMe
OMe
4 equiv.
$Cl_3CCH_2OH$
45–75%
$CCl_3$
$CCl_3$
Zn / EtOAc
reflux
40–100%
Br
Br
Zn–Ag, THF / AcOH
25 °C, 90%
OAc
$H_2$ /PdO
HO
HO
(89)
$(PPh_3)_3RhCl$
EtOH / $H_2O$
reflux, 96%
$H^+$ or
$HgCl_2$ / HgO
98%
i, MeI
ii, NaOH or
$K_2CO_3$
62–88%
OH
Me
$I^-$

Scheme 81

the execution of this reaction are available,[5,321] including the use of $BF_3 \cdot OEt_2$ or $ZnCl_2$ as Lewis acids, the application of thiol esters of boric acid and a combination of trimethylsilyl chloride with thiols. In general, the thioacetals are cleaved by the action of silver, copper or mercury salts.[324] Electrophilic attack or oxidation of the sulfurs are also recommended.[321,325] Some representative examples are given in Scheme 82.

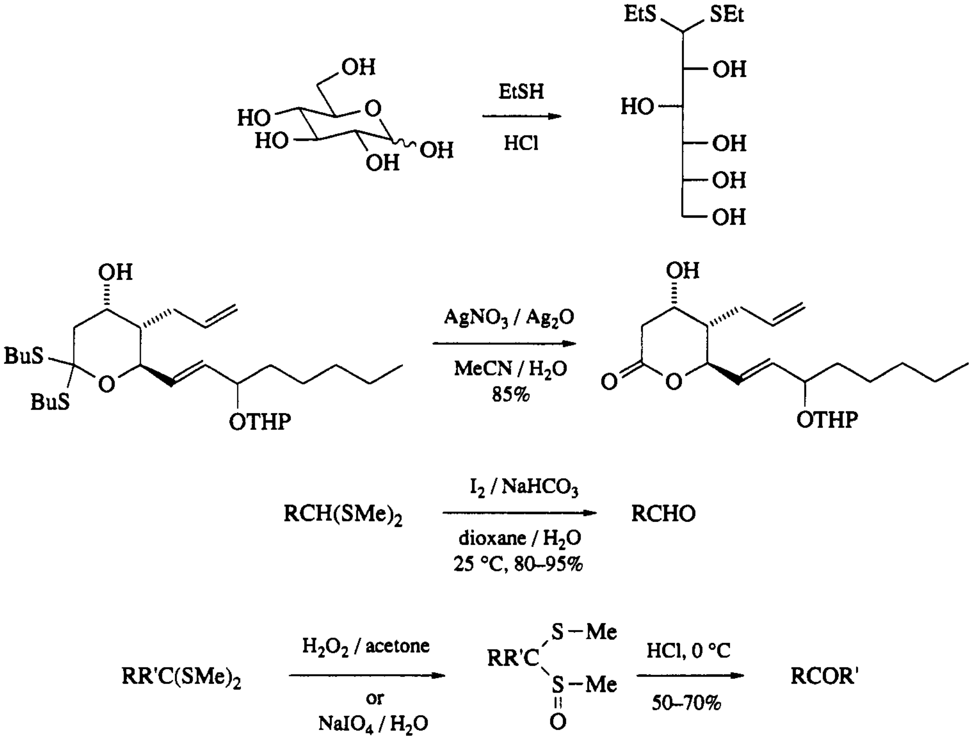

EtSH
HCl
EtS
SEt
HO
OH
BuS
OTHP
AgNO₃ / Ag₂O
MeCN / H₂O
85%
RCH(SMe)₂
I₂ / NaHCO₃
dioxane / H₂O
25 °C, 80–95%
RCHO
RR'C(SMe)₂
H₂O₂ / acetone
or
NaIO₄ / H₂O
S–Me
HCl, 0 °C
50–70%
RCOR'

(26)

**Scheme 82**

Very popular and widely used protected forms of aldehydes and ketones are found in the dithiolanes and dithianes. The use of these blocking groups has raised a new strategy for electrophilic substitutions at the carbonyl carbon. This method was developed and introduced by Corey and Seebach[326] and is termed 'umpolung of the reactivity'.[321,326,327] The cyclic dithioacetals are easily formed from the carbonyl compounds and the dithiols under the influence of Lewis acids, acids and boron reagents (Scheme 83). Several methods are available for the subsequent liberation of the carbonyl groups from these very acid-stable ketals and acetals. They all are based on the conversion of the sulfurs to better leaving groups, followed by hydrolysis (Scheme 84).[321] The modification of the sulfides can be achieved by complexation with thiophilic heavy metal ions like $Ag^+$, $Hg^{2+}$ and $Cu^{2+}$, by oxidation of the sulfurs, with, *e.g.* iodine, halosuccinimides, ammonium cerium nitrate, $NaIO_4$, chloramine T, singlet oxygen, and also by their conversion to sulfonium salts through alkylation with methyl iodide or oxonium salts.[321] Finally, transthioacetalization under weakly acidic conditions is successful (Scheme 85).[328]

The dithiane method is extensively applied in the construction of complex molecules. Some representative examples[329] are given in Scheme 86. The diastereoselective attack of the 2-methyl-1,3-dithianyl anion at the *si*-face of the ulose (**90**) is a crucial step in a synthesis of methylaldgaroside B (**91**).[329a]

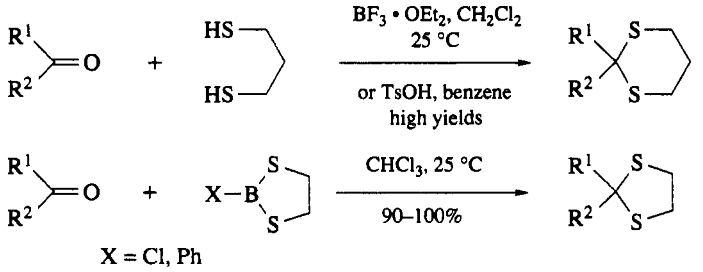

R¹
R²
O
+
HS
HS
BF₃ • OEt₂, CH₂Cl₂
25 °C
or TsOH, benzene
high yields
S
X–B
CHCl₃, 25 °C
90–100%
X = Cl, Ph

**Scheme 83**

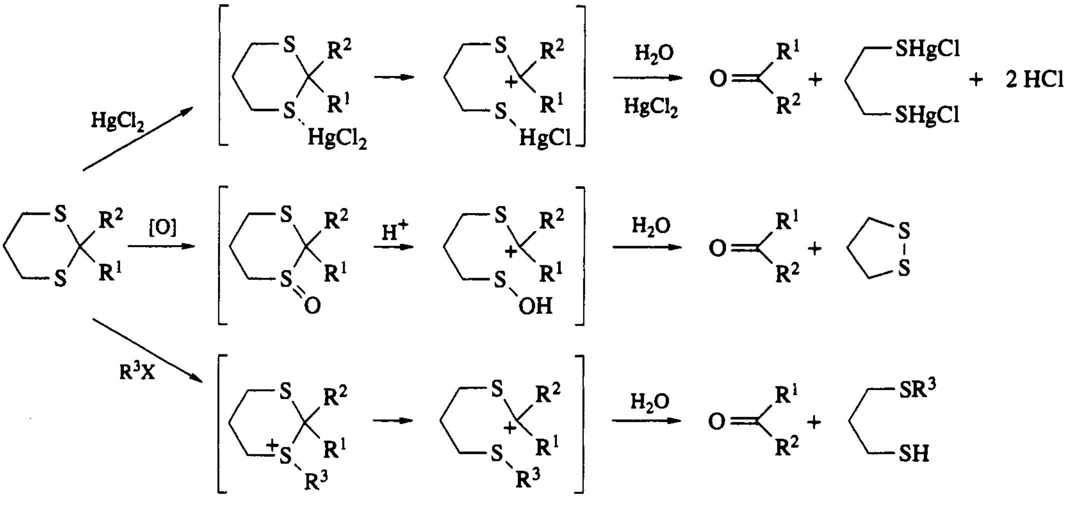

Scheme 84

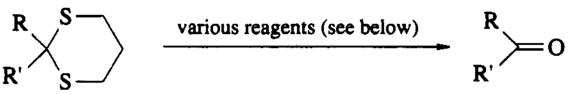

$CuCl_2$ / CuO, acetone, Δ, 85%

$AgNO_3$, EtOH / $H_2O$, 50 °C, 55%

HgO, $BF_3$, THF / $H_2O$, 86%

NBS, $H_2O$ / MeCN or acetone, 70–100%

$I_2$, DMSO, 90 °C, 75–85%

isopentyl nitrite, 65%

$Ce(NH_4)_2(NO_3)_6$, MeCN / $H_2O$, 70–87%

$O_2$ /*hν*, 60–80%

MeI, MeOH / $H_2O$, Δ, 60–80%

$Et_3O^+BF_4^-$, 3% aq. $CuSO_4$, 81%

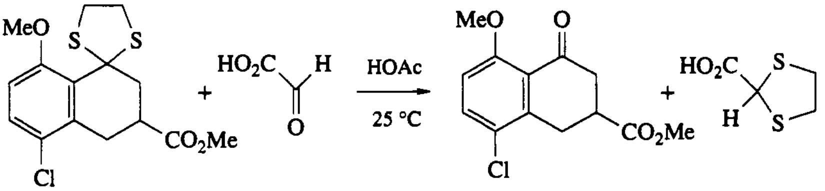

Scheme 85

The second example involves the diastereoselective reaction of the dithianyl anion with the epoxide (**92**) to achieve the construction of maytansine.[329b] However, not only the opportunities offered by the umpolung concept are of preparative interest. The high stability of the cyclic dithioacetals is also a very valuable property for syntheses of complex compounds. This has recently been demonstrated in the construction of 11-deoxydaunomycin and its analogs.[330] The hydroquinone monoallyl ether derivative (**93**) contains a carbonyl function protected as the dithiolane, whereas the enolized β-dicarbonyl structure is underivatized (equation 27). At 240 °C this compound undergoes a Claisen rearrangement which induces a cascade of reactions, including an intramolecular Diels–Alder reaction and a double bond isomerization. The tricyclic compound (**94**) thus formed serves as a key intermediate in the synthesis of daunomycin derivatives.[330] After oxidation of ring B, the regeneration of the ketone from the dithiolane allows the annelation of the fourth ring to furnish the complete daunomycin skeleton.

1,3-Oxa-thiolanes and -thianes combine the properties of oxygen and sulfur acetals. Thus they can be cleaved with mercury salts and are also more labile towards acids than the sulfur analogs.[331] In addition, oxazolidines, imidazolidines and thiazolidines can be used for the protection of aldehydes and ketones;[5] however, they have not found a broader use in protecting group chemistry.

An acid-resistant protecting principle for carbonyl groups consists of the α,α-dicyanoethylene derivatives (**96**). They are obtained from carbonyl compounds, *e.g.* pyrrole aldehydes (**95**), by Knoevenagel condensation with malodinitrile.[332] In general, mineral acids and Lewis acids, which are used in Friedel–

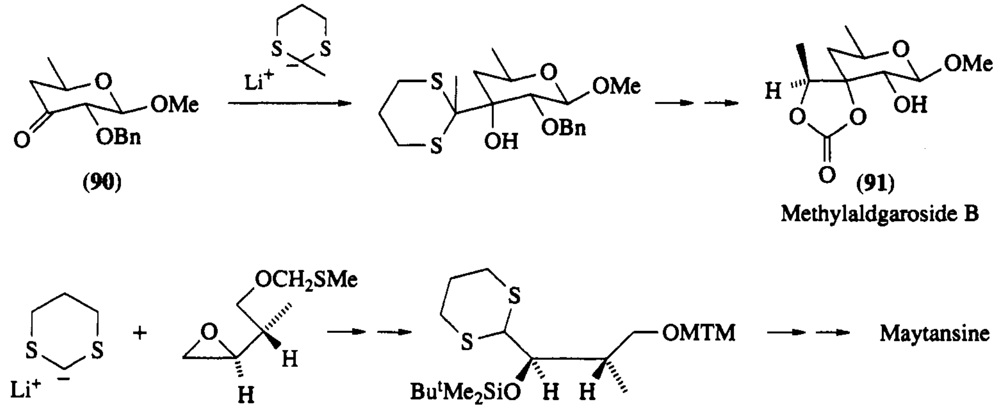

(90) (91) (92)

**Scheme 86**

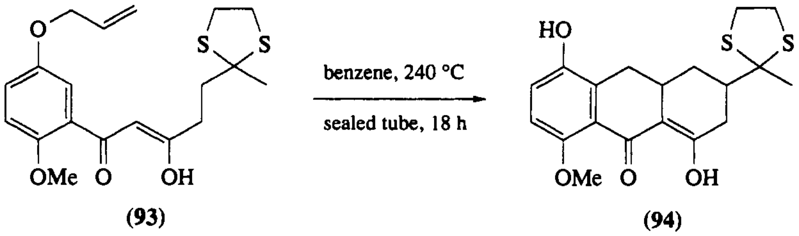

(93) (94) (27)

Crafts reactions, and oxidizing reagents like chlorine do not destroy this protection. The regeneration of the carbonyl functions has to be carried out with concentrated aqueous alkali and proceeds as a tandem hetero Michael addition/retro aldol reaction (Scheme 87). Although these drastic conditions set a limit to the general application of this protecting group, it has successfully been used in porphyrine total syntheses.[332]

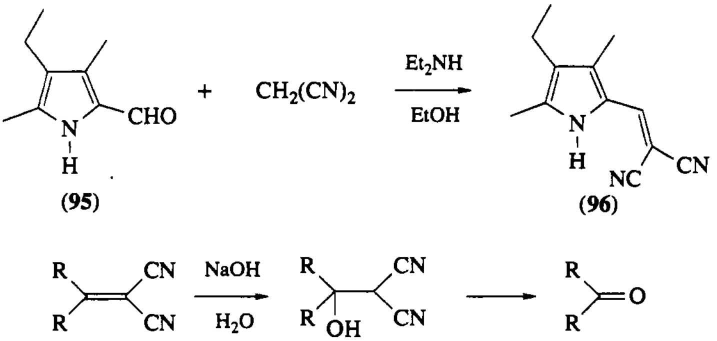

(95) (96)

**Scheme 87**

### 3.1.6.3 *O*-Substituted Cyanohydrins[147]

Cyanohydrins of aldehydes and ketones may be considered as protected forms of the carbonyl compounds. If they are further *O*-alkylated with vinyl ethers, the acetals formed constitute base resistant protection. Such *O*-acetals and aldehyde cyanohydrins have been subjected to deprotonation and umpolung transformations.[333] Actually, the benzoin condensation[334] has to be considered as the first reaction based on umpolung at the carbonyl carbon. In benzoin condensations the cyanide ion can further be substituted by thiazolium salts.[335] Their anions react with aldehydes to give the aldol-type adducts (**97**). After the following crucial transfer of the proton from the carbonyl carbon to the oxygen (enabled by the electron-withdrawing effect of the thiazolium group), electrophiles can attack. In contrast to the cyanide-catalyzed reaction, aliphatic aldehydes can be used here. The preparative value of this group was increased still further when it could be demonstrated that α,β-unsaturated ketones, esters and nitriles undergo vinylogous addition with the intermediate (**98**). Thus, they deliver 1,4-diketones, keto esters and keto nitriles (Scheme 88).[336] The principle demonstrated in these chemical transformations is also of fundamental biological relevance. For example, the reaction of the intermediate, corresponding to (**98**), formed from pyruvate (acetaldehyde) and thiamine pyrophosphate (vitamin $B_1$) with lipoic acid is a key step in the pathway which links glycolysis and the citric acid cycle. A protecting group related to the thiazolium adduct has recently been found in the hydroxyalkylation products (**99**) of *N*-methyl imidazole.[337] After activation by *N*-alkylation, the carbonyl compounds are regenerated by treatment with aqueous base (see Scheme 89).

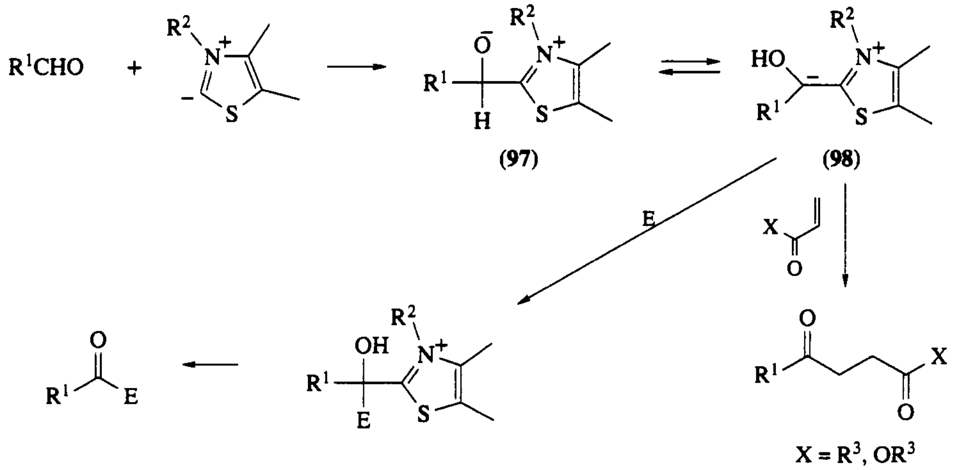

**Scheme 88**

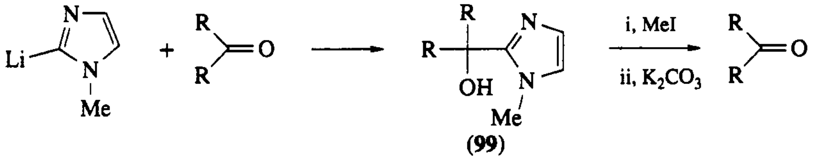

**Scheme 89**

Aldehydes and ketones can also be protected as *O*-trimethylsilyl cyanohydrins by reaction with trimethylsilyl cyanide under catalysis with zinc iodide, cyanide ions, tetra-*n*-butylammonium fluoride or triphenylphosphine.[338] The resulting silyl cyanohydrins are stable to sodium hydride, amines, hydrogenation with Lindlar's catalyst, $NaCNBH_3$, $CrO_3$/pyridine and thionyl chloride and can therefore be advantageously used in multistep synthesis. An example which shows a synthesis of partial structures of prostaglandins is depicted in Scheme 90.[339] Here, the cleavage is carried out with $NaBH_4$ in methanol. *O*-Trimethylsilyl cyanohydrins are particularly useful for the monoprotection of *p*-benzoquinones,[340] because they allow the functionalization of the remaining unprotected carbonyl group, *e.g.* by addition of organometallic reagents (Scheme 91). Furthermore, if an α-hydrogen is present, the silylated cyanohydrins offer an additional possibility for umpolung of carbonyl groups, *e.g.* alkylation of the former carbonyl carbon (Scheme 91).[340] The reformation of the carbonyl groups from the protected forms can usually be achieved in dilute aqueous acid or base and with fluoride ions, *e.g.* silver fluoride in aqueous THF.

### 3.1.6.4 Substituted Hydrazones and Oximes[5]

For decades oximes and hydrazones have been used for the derivatization of carbonyl compounds and are mainly applied for carbonyl group characterization in analytical procedures. However, they can also be applied as viable protecting groups in complex reaction schemes. For instance in the synthesis of erythronolide A[341] a carbonyl group had to be converted to an oxime to allow the selective removal of the remaining isopropylidene protecting group without side reactions. The reconversion of the oxime to the carbonyl compound proceeds by *N*-nitrosation (Scheme 92). The previously attempted removal of the

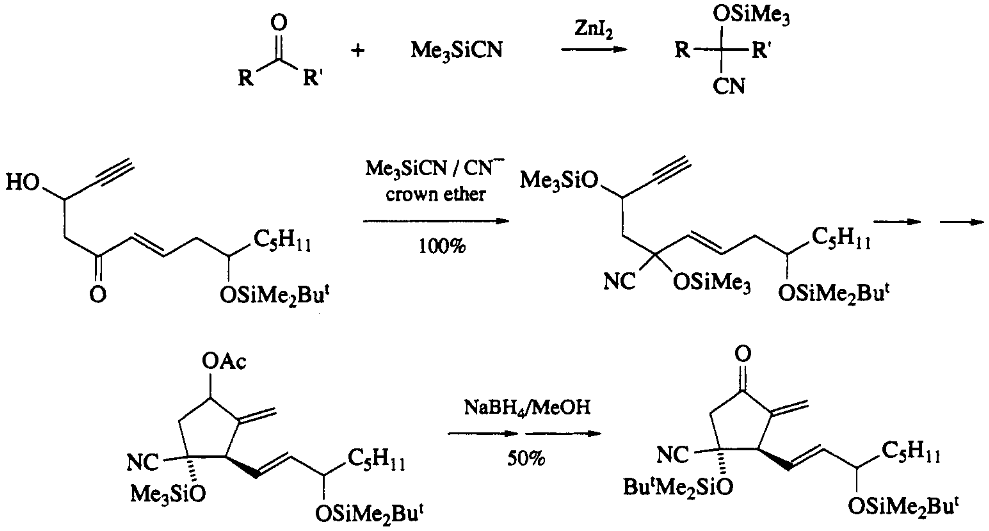
ZnI2
Me3SiCN
Me3SiCN / CN⁻
crown ether
100%
NaBH4/MeOH
50%

**Scheme 90**

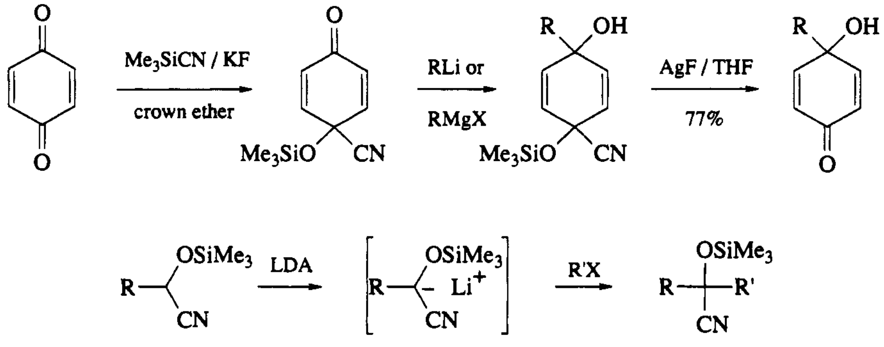
Me3SiCN / KF
crown ether
RLi or
RMgX
AgF / THF
77%
LDA
R'X

**Scheme 91**

isopropylidene protecting function in the presence of the unprotected keto group could not successfully be carried out. Oximes are mainly cleaved by oxidation, reduction or hydrolysis.

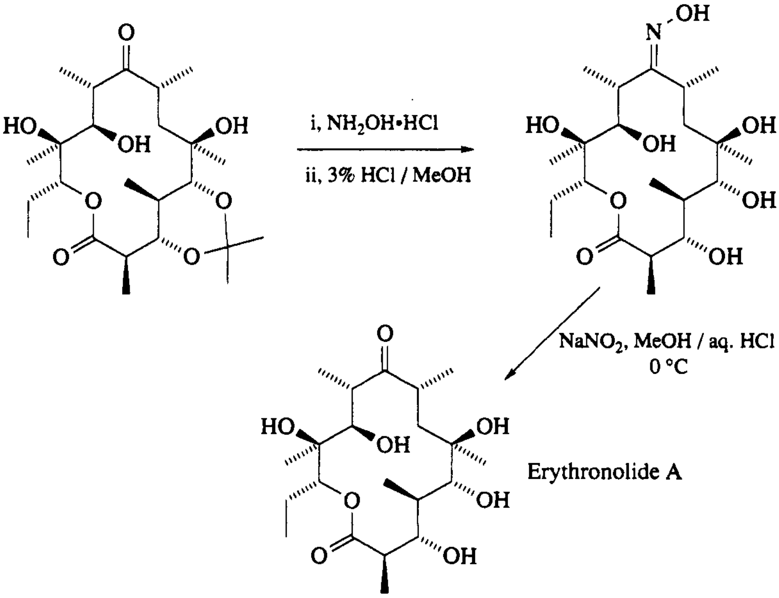
i, NH2OH•HCl
ii, 3% HCl / MeOH
NaNO2, MeOH / aq. HCl
0 °C
Erythronolide A

**Scheme 92**

*N,N*-Dialkylhydrazones are often converted into the carbonyl form by a variety of oxidative methods. The respective compounds (like **100**) shown in Scheme 93, derived from proline-based systems (RAMP and SAMP), are widely used as potent chiral auxiliaries and have provided a very versatile method for the diastereoselective α-alkylation of ketones.[342] SAMP and RAMP hydrazones can be cleaved with $O_3$, by reductive techniques and by hydrolysis with strong acids.

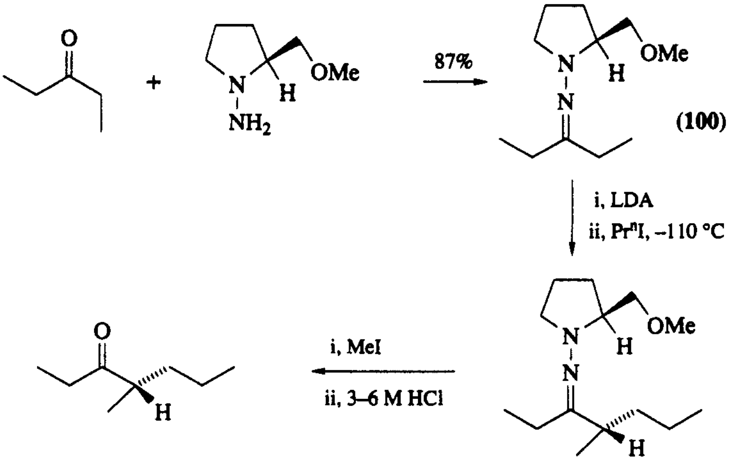

Scheme 93

### 3.1.6.5 Monoprotection of Dicarbonyl Compounds

β-Diketones often are protected as enol ethers or enamines and these selectively functionalized compounds may be subjected to complementary transformations (Scheme 94).[343] Also silylenes can be prepared from diketones and β-hydroxycarbonyl compounds by reaction with dimethyldicyanosilane.[344] Naturally, these blocking groups are relatively sensitive to hydrolysis. On the other hand, partial solvolysis can open a route to monoprotected derivatives (*e.g.* **101**), usually blocked at the sterically less demanding carbonyl function as *O*-silyl cyanohydrins (see Scheme 95). Deprotection is finally achieved with silver fluoride in THF.

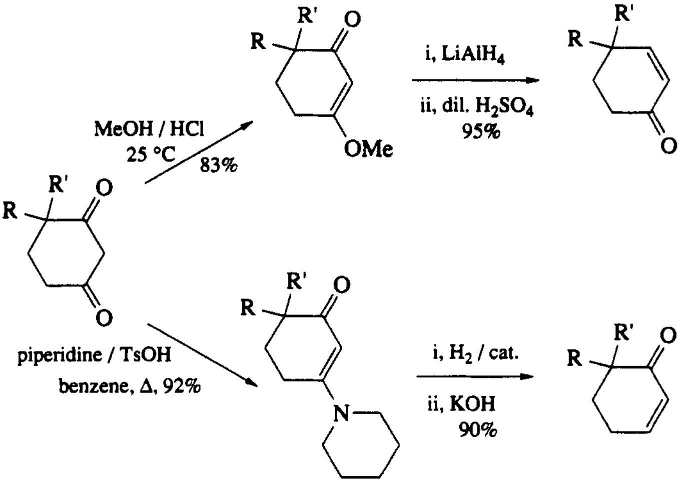

Scheme 94

## 3.1.7 PROTECTION OF ALKENES AND ALKYNES[345]

Unsaturated carbon–carbon bonds are central structural elements of numerous chemical entities. The construction of these bonds can be carried out by a variety of reactions. In many chemical transform-

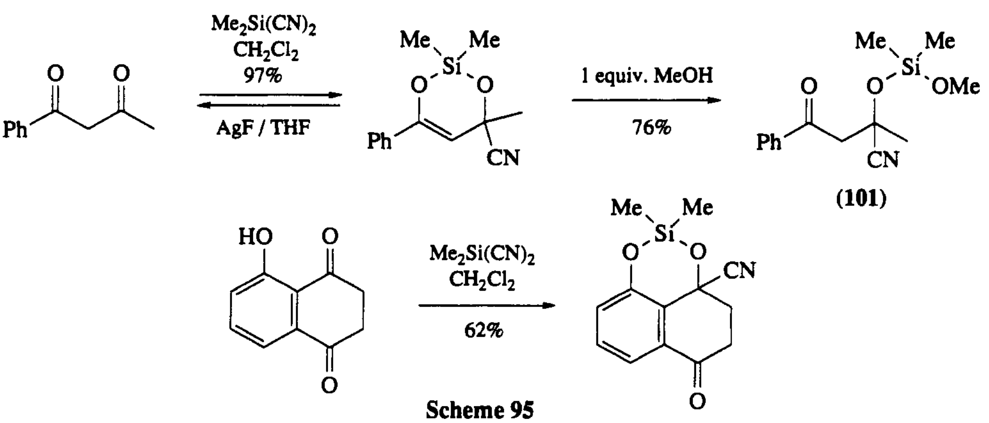

(101)

Scheme 95

ations a special masking of double and triple bonds is not necessary. However, the high reactivity of π- and π*-orbitals of these bonds, particularly against soft electrophiles or nucleophiles, makes them sensitive to oxidation, reduction and addition processes. Although modern mild variants of such reactions which were harmful to double and triple bonds have been introduced in the last decades, this reactivity still demands effective methods for multiple bond protection. In most cases this goal can be achieved by conversion of alkenes to addition products from which the double bonds can be regenerated. Alternatively, complexation by transition metals can also be utilized for the temporary protection of alkenes, 1,3-dienes and alkynes.

### 3.1.7.1 Protection of Alkenes[345,346]

The ease and the stereospecificity of bromine addition to alkenes, together with the possibility of regeneration of the double bond under conservation of the original stereochemistry, render the bromination reaction one of the most common methods for protection of alkenes. The dibromides of alkenes are conveniently obtained by using bromine itself or reagents like pyridinium hydrobromide perbromide ($C_5H_5N\cdot HBr_3$).[347] These bromo adducts are, for instance, stable during reactions with ozone, $CrO_3$, $KMnO_4$ and $OsO_4$. They are also efficiently protected forms during addition reactions and hydrogenolysis.[345] For the regeneration of the double bond numerous methods are available,[345,348,349] *e.g.* treatment of the dibromides with metals[345] (zinc, magnesium, sodium, lithium or sodium amalgam, iron graphite[350]), metal ions of sufficient electron-donating potential[345,351] ($Cr^{II}$, $Fe^{II}$, $Ti^{II}$, $Co^{II}$, $Ni^{II}$, $Sn^{II}$) and various nucleophilic reagents[345] (halides,[352] thiolates,[353] selenides,[354] tellurides,[355] phosphites, phosphines, $LiAlH_4$, Grignard reagents). Also electrochemical methods are often effective.[356] Some selected examples for the protection of double bonds in the form of dibromides and for their reconversion to the alkenic structures under different conditions are shown in Scheme 96. Most of these methods are stereospecific and proceed through an *anti* elimination of the bromides. The most widely employed reagent for this conversion is zinc dust. The reaction is usually carried out in acetic acid or in ethanol.[345,346,357] However, problems frequently arise by possible side reactions of the solvent with the substrate (*e.g.* acetylation of alcohols). In these cases the other methods described above offer viable alternatives to achieve the synthetic goals. Problems caused by debromination at higher temperatures or instability of the dibromides in a reduction step can be overcome by employing dichlorides[358] or halohydrins[359] as protecting groups. In addition halohydrin acetates may serve as the blocked forms. They are obtained by treatment of the alkene with aqueous *N*-bromosuccinimide and subsequent acetylation. They are relatively stable to acid, mild alkali and oxidation with chromic acid. The alkene can be regenerated from the β-haloalkyl acetate by using a zinc–copper couple.[360]

Alkenes are converted to epoxides by oxidation with peroxy acids, and thereby they are protected with regard to certain chemical transformations. Alkaline hydrogen peroxide selectively attacks enone double bonds in the presence of other alkenes. The epoxides can be transformed back to alkenes by reduction–dehydration sequences[361] or using triphenylphosphine,[362] chromous salts, zinc, or sodium iodide and acetic acid.[363] A more advantageous and fairly general method consists, however, of the treatment of epoxides with dimethyl diazomalonate in the presence of catalytic amounts of binuclear rhodium(II) carboxylate salts.[364] This deoxygenation proceeds under neutral conditions and without isomerization or cyclopropanation of the liberated alkene (Scheme 97). Furthermore, epoxides can be converted to alkenes with the aid of various metal carbonyl complexes. Thus, they may be nucleophilically opened with

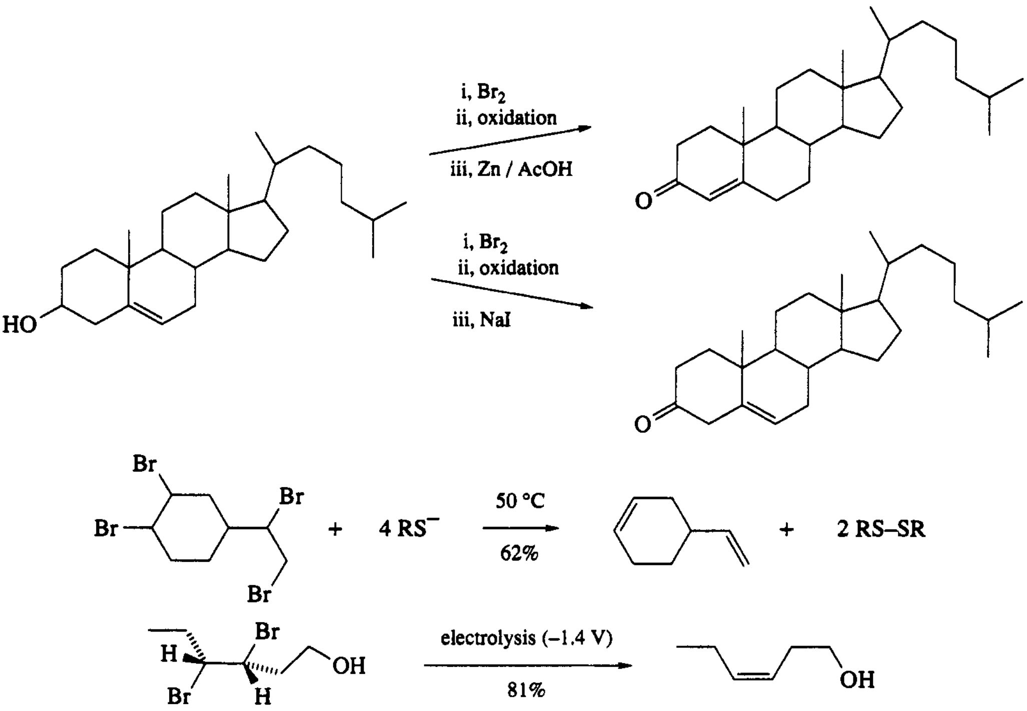
i, Br2
ii, oxidation
iii, Zn / AcOH
i, Br2
ii, oxidation
iii, NaI
HO
O
O
Br
Br
Br
Br
+
4 RS⁻
50 °C
62%
+
2 RS–SR
H
Br
Br
H
OH
electrolysis (–1.4 V)
81%
OH

Scheme 96

$CpFe(CO)_2^-$ $Na^+$ and after treatment with acid and decomplexation with sodium iodide in acetone the free alkene is isolated (Scheme 97).[365] In addition, certain metal carbonyls like $Co_2(CO)_8$,[366] $Fe(CO)_5$[367] and $Mo(CO)_6$[368] effectively deoxygenate epoxy-esters and -ketones. Also low-valent tungsten species[369] and metallocenes[370] may be used for the regeneration of alkenes.

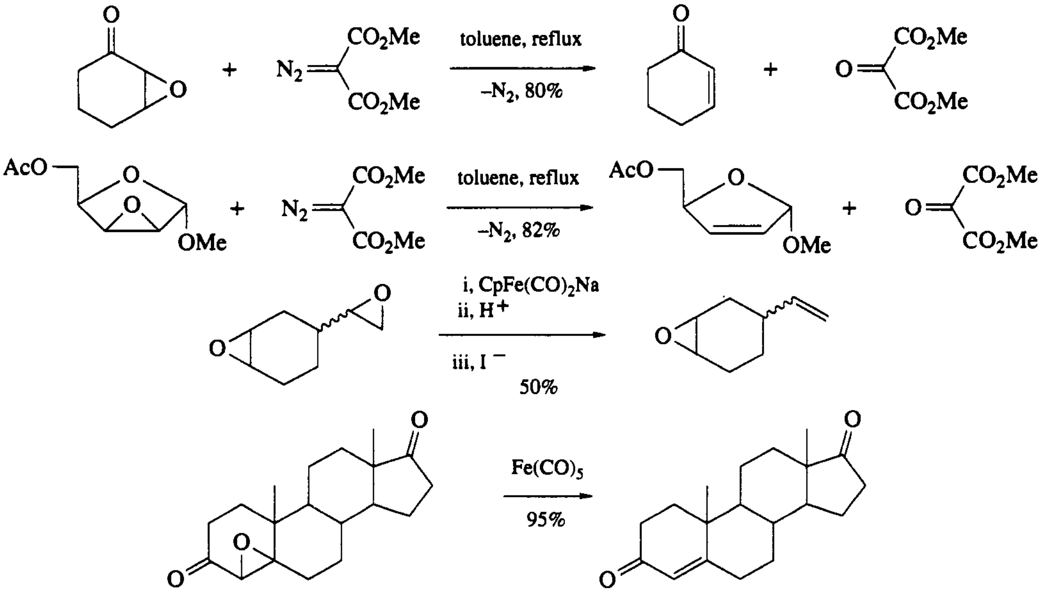
O
O
+
N2
CO2Me
CO2Me
toluene, reflux
–N2, 80%
O
+
O
CO2Me
CO2Me
AcO
O
O
OMe
+
N2
CO2Me
CO2Me
toluene, reflux
–N2, 82%
AcO
O
OMe
+
O
CO2Me
CO2Me
O
O
i, CpFe(CO)2Na
ii, H+
iii, I⁻
50%
O
O
O
O
Fe(CO)5
95%
O
O

Scheme 97

1,2-Diols are easily accessible from alkenes by the reaction with osmium tetroxide, and constitute another protection of the double bond since a variety of methods for the reformation of the alkenes from them is available.[371] Among the important methods which proceed stereospecifically, the desulfurization of 2-thioxo-1,3-dioxolanes (*e.g.* **102**, Corey–Winter reaction),[372] the acid-catalyzed decomposition of

2-ethoxy- or 2-dialkylamino-1,3-dioxolanes (Eastwood procedure)[373] and the base-induced fragmentation of 2-phenyl-1,3-dioxolanes[374] must be mentioned. In the Corey–Winter method cyclic thioxocarbonates, readily prepared from vicinal diols by reaction with thiophosgene or *N,N'*-thiocarbonyldiimidazole, are fragmented by heating with trivalent phosphorus compounds, commonly with trialkyl phosphites (Scheme 98). Although this transformation requires prolonged heating at elevated temperatures and, occasionally, undesired side reactions are observed, it often is superior to the other methods. Thus, it can be advantageously used for the preparation of unsaturated sugars (*e.g.* **103**). However, bicyclo[2.2.1]hept-2-enes and related alkenes cannot be synthesized by this method. For their construction the thioxocarbonates can instead be decomposed with other reagents (Raney Ni, $Fe(CO)_5$, $Ni^0$ complexes) in good yields.[371] In the Eastwood deoxygenation, vicinal diols are treated with ethyl orthoformate at elevated temperatures (100–180 °C), followed by continued heating at higher temperatures (160–220 °C) in the presence of a carboxylic acid. In this reaction sequence, 2-ethoxy-1,3-dioxolanes (**104**) are formed initially. In the following acid-catalyzed reaction they eliminate ethanol and the resulting carbocation captures the carboxylate. Finally rearrangement to the desired alkene takes place (Scheme 99). Lower reaction temperatures are needed if first 2-dialkylamino-1,3-dioxolanes are formed by reaction of the diols with dimethylformamide dimethyl acetal. In the presence of acetic anhydride or after alkylation with methyl iodide the alkenes are obtained at temperatures around 90–115 °C. The reaction even proceeds at 20–50 °C if a combination of trifluoromethanesulfonic anhydride with diisopropylethylamine is used (Scheme 99).[375] The mechanism proposed for this reaction involves the attachment of the anhydride at the nitrogen and the subsequent formation of a nitrogen ylide intermediate which fragments to the alkene. The Eastwood procedure possesses the advantage of being a one-pot alkene synthesis, but the strongly electrophilic conditions and the high temperatures usually required are limiting for its application. The third procedure mentioned, the rearrangement of 2-phenyl-1,3-dioxolanes, requires the use of *n*-butyllithium. This circumstance makes the method inapplicable to many substrates and, consequently, it has found only a few applications in organic synthesis. In addition to these fairly stereospecific alkene syntheses several other procedures are available for the formation of a double bond from 1,2-diols.[345] Among them are the reduction–elimination of cyclic phosphates and phosphoramidates,[376] as well as titanium- and tungsten-mediated deoxygenations (Scheme 100).[377] Also, the treatment of vicinal sulfonate esters (*e.g.* **105**) with nucleophiles (Scheme 100, Tipson–Cohen reaction),[378] which is often used in carbohydrate chemistry, the reductive elimination of vicinal dimesylates[379] and the radical decomposition of vicinal dixanthates (*e.g.* **106**) induced by tri-*n*-butyl tin hydride[380] allow the regeneration of alkenes from vicinal diols (Scheme 100). The latter reaction occurs under neutral and relatively mild conditions and gives predominantly the more stable isomer of the alkene. This method is also mainly applied in the construction of unsaturated carbohydrates.

The double bonds of enones easily undergo Michael additions and this may be used for their temporary masking. Thus dimethylamine[381] or, better, propanethiol[382] may be added to the conjugated system. From the adducts thus formed, the alkene may finally be recovered *via* pyrolysis of the derived methiodide. In a recent development the silylcuprate derived from dimethylphenylsilyllithium and copper iodide is added to the β-position of enones. The silyl ketones (**107**) produced in this way can conveniently be used for further syntheses. The double bond may be reobtained by bromination followed by desilylbromination (Scheme 101).[383] The sequence was, for instance, successful in syntheses of carvone (**108**) and dehydrojasmone.

Alkenes and dienes react with each other in Diels–Alder reactions to form cyclic adducts and the reversal of this transformation can be exploited for the regeneration of the desired alkenes at a later stage

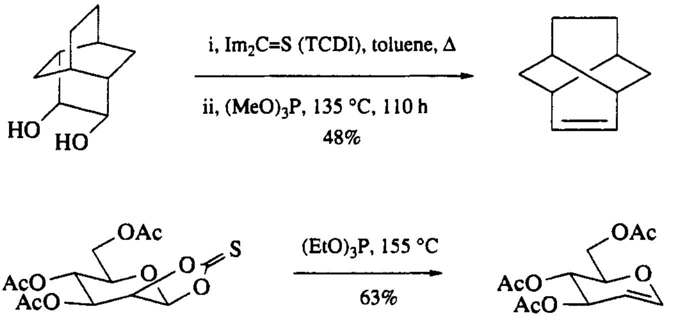
HO
HO
i, Im$_2$C=S (TCDI), toluene, Δ
ii, (MeO)$_3$P, 135 °C, 110 h
48%
OAc
AcO
AcO
O
O
O
S
(EtO)$_3$P, 155 °C
63%
OAc
AcO
AcO
O

**(102)** **(103)**

**Scheme 98**

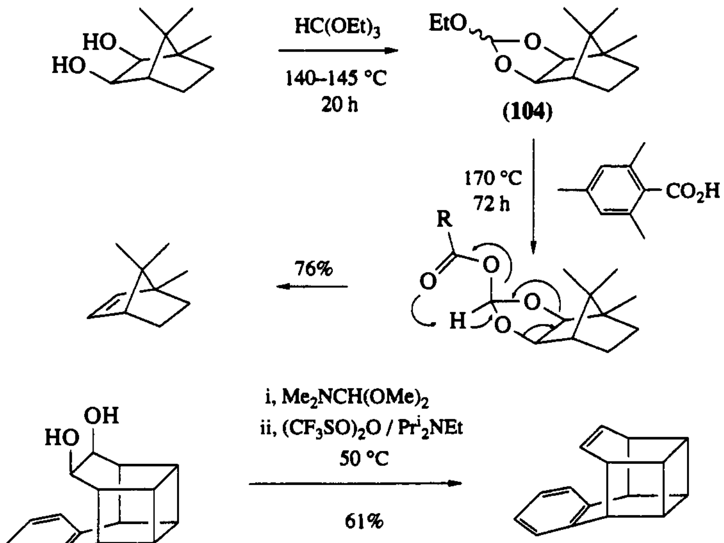
HO
HO
$HC(OEt)_3$
140–145 °C
20 h
EtO
O
O
(104)
170 °C
72 h
$CO_2H$
R
O
O
O
O
H
O
76%
i, $Me_2NCH(OMe)_2$
ii, $(CF_3SO)_2O$ / $Pr^i_2NEt$
50 °C
61%
OH
HO

**Scheme 99**

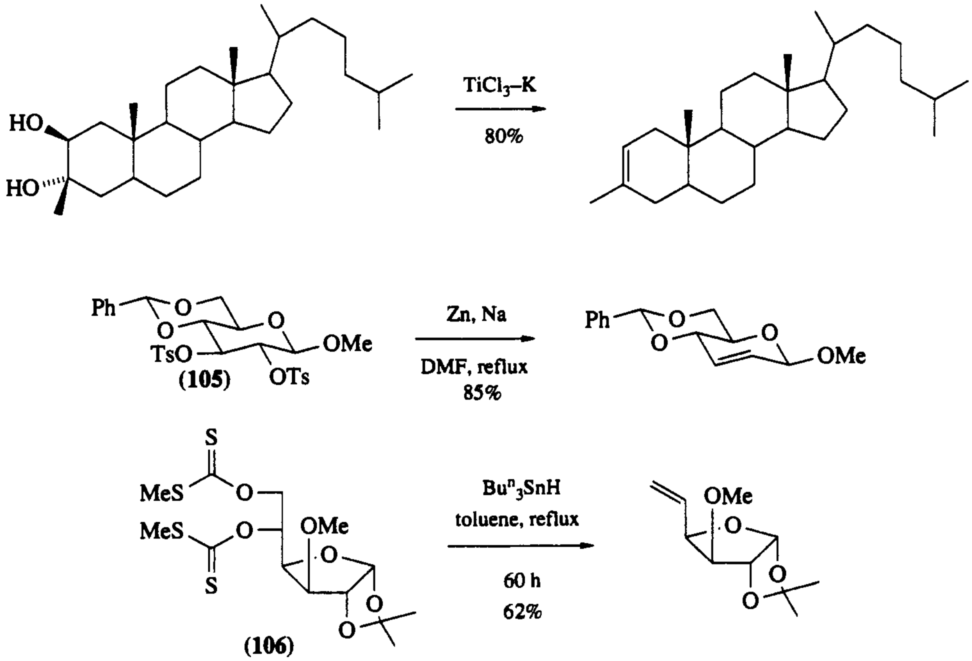
HO
HO
$TiCl_3$–K
80%
Ph
O
O
O
OMe
TsO
(105)
OTs
Zn, Na
DMF, reflux
85%
Ph
O
O
O
OMe
S
MeS
O
MeS
O
S
OMe
O
O
O
(106)
$Bu^n_3SnH$
toluene, reflux
60 h
62%
OMe
O
O
O

**Scheme 100**

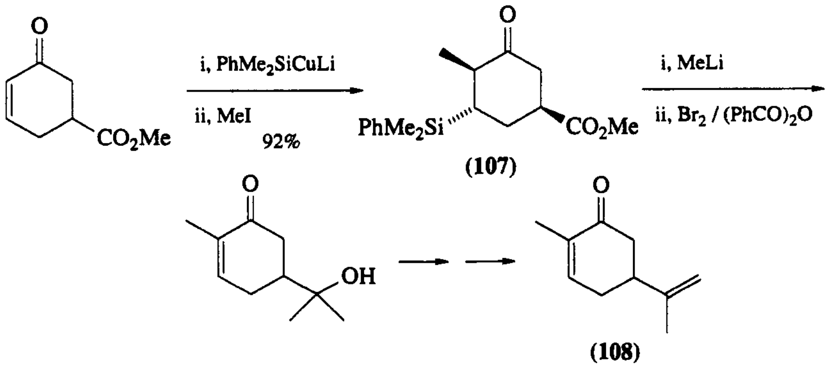
O
$CO_2Me$
i, $PhMe_2SiCuLi$
ii, MeI
92%
O
$PhMe_2Si$
$CO_2Me$
(107)
i, MeLi
ii, $Br_2$ / $(PhCO)_2O$
O
OH
O
(108)

**Scheme 101**

of a synthesis. The retro Diels–Alder reaction usually requires high temperatures to proceed. This has for a long time hampered the application of this methodology as a strategy for protection. However, the correct choice of the dienes employed in the reaction and the invention of new techniques, like flash vacuum pyrolysis and infrared laser beams, have allowed to use the [4π + 2π] cycloreversion as a key step in the generation of complex natural products.[384] The dienes which are often used to protect double bonds are anthracene, cyclopentadiene, dimethylfulvene and 1-methoxy-1,3-cyclohexadiene. In Scheme 102 some applications of these protecting techniques are given. Dicyclopentadiene (**110**) serves, for instance, as the starting material for a synthesis of jasmone (**109**),[385] a cyclopentenoid compound. Numerous other cyclopentenones, for example multifidene (**111**), have been generated in this way. The elimination of dimethylfulvene (**112**) has been applied in the construction of quinone epoxides which were converted into natural products, as is briefly illustrated for senepoxyde (**113**).[386] Although the activation energy for the retro Diels–Alder reaction involving cyclopentadiene is relatively low (*e.g.* $E_A$ for the retroreaction of *endo*-bicyclo[2.2.1]hept-2-ene-5-carbaldehyde is 33.6 kcal mol$^{-1}$),[387] dimethylfulvene is ejected even more easily (at temperatures of 150–190 °C). Anthracene also is an easily available protecting group for a double bond. It can, for example, be used for the synthesis of butenolides like tuli-

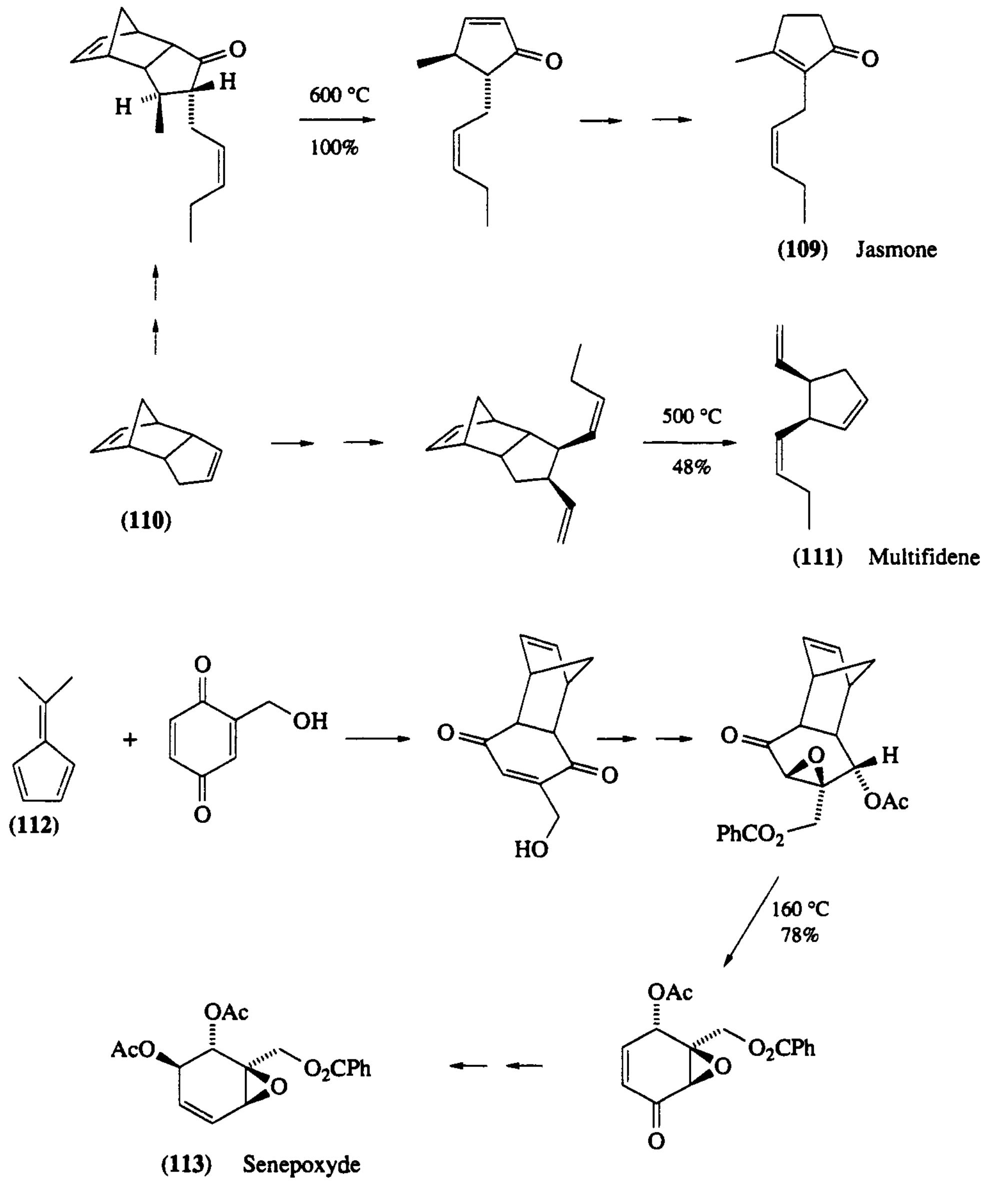

Scheme 102

paline A.[388] In addition to the chemical derivatizations described above, alkenes may be protected by the formation of complexes with some metals or their ions. Thus, coordination to silver ions protects double bonds from hydrogenation.[389] Alternatively, iron tricarbonyl complexes were used to mask double bonds during oxidation of an alcohol to a ketone.[390] Coordination of an alkene to the cyclopentadienyliron dicarbonyl cation to give the cations $CpFe(CO)_2(alkene)^+$ reduces its reactivity towards electrophilic attack and this may be used as a convenient protection method.[346] This masking can be introduced by ligand exchange reactions in which the alkene substitutes for the isobutene of the corresponding isobutene complex. In polyenes selective coordination of the most strained or the terminal double bond can be achieved. Double bonds masked in this way withstand hydrogenation,[391] treatment with mercury(II) acetate,[392] and bromination (Scheme 103).[391,392] Reactions of these types may, therefore, be performed selectively on the unblocked multiple bonds of the same polyenes. The release of the alkene is simply effected by treatment with sodium iodide in acetone. Terminal alkenes can be selectively and reversibly functionalized by alkyl exchange with organoaluminum compounds to form an aluminum alkyl, which must finally be decomposed again in a second exchange reaction with another alkene (*e.g.* 1-dodecene).[393]

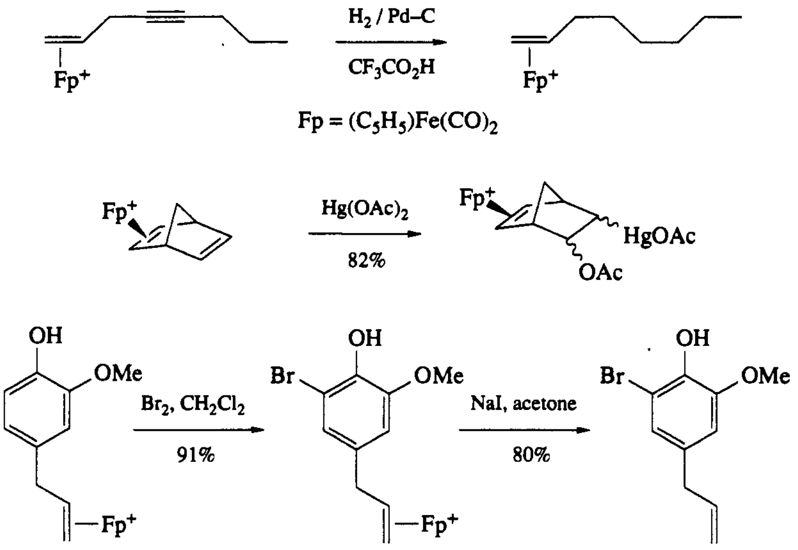

**Scheme 103**

### 3.1.7.2 Protection of 1,3-Dienes[346,384]

Dienes may be protected as their Diels–Alder adducts and, like the dienophiles, they can be regenerated from the adduct by pyrolysis. Thus, conjugated steroidal dienes have been masked by reaction with 4-phenyl-1,2,4-triazoline 3,5-dione (**114**).[394] The parent systems are reobtained[384] after treatment of the cycloadduct with $LiAlH_4$, with $K_2CO_3$ or by using tetramethylguanidine or 1,3,5-collidine at relatively low temperatures. This methodology was, for instance, successfully applied in syntheses of metabolites of vitamin $D_3$, starting from ergosterol or provitamin $D_3$ (Scheme 104).[394,395] Also, dienes may be protected as cyclic sulfones and reobtained from their sulfur dioxide adducts in a cheletropic reaction. This approach has become important in the construction of various natural products like terpenes, steroids, alkaloids and pheromones[384] (as an example the synthesis of aspidospermine (**115**) is outlined in Scheme 105).[396]

Conjugated as well as nonconjugated dienes can be converted to irontricarbonyl complexes by reaction with iron carbonyls like $Fe(CO)_5$, $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$.[397] In these complexes their reactivity differs from that of the uncomplexed ligand. This phenomenon can be exploited as a means of the protection of 1,3-dienes under varying conditions.[346,399] 1,3-Diene complexes of this kind are not affected during hydroboration,[398,399] reductions[398–400] with $LiAlH_4/AlCl_3$, $NaBH_4$, and with $H_2$/Pd–C or $H_2/PtO_2$. They also withstand oxidation with $OsO_4$, treatment with $SO_3$/pyridine, Sharpless epoxidations ($VO(acac)_2/Bu^tO_2H$)[399,401] as well as Friedel–Crafts acylations, treatment with cyanogen bromide, cyclopropanation conditions[400,402] and treatment with strong bases[401–403] as for example lithium alkyls, Grignard compounds and Wittig reagents. Furthermore, they do not participate in Diels–Alder reactions and

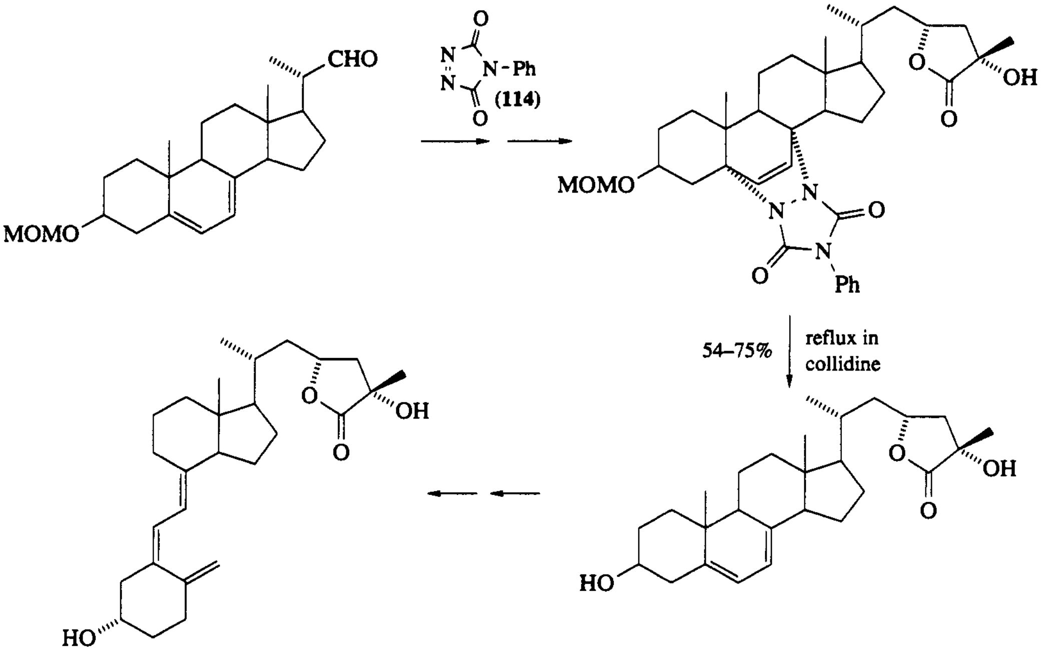
CHO
MOMO
O
N
N-Ph
N
(114)
O
MOMO
OH
O
N
N
O
N
Ph
54–75%
reflux in
collidine
HO
OH
O
HO

**Scheme 104**

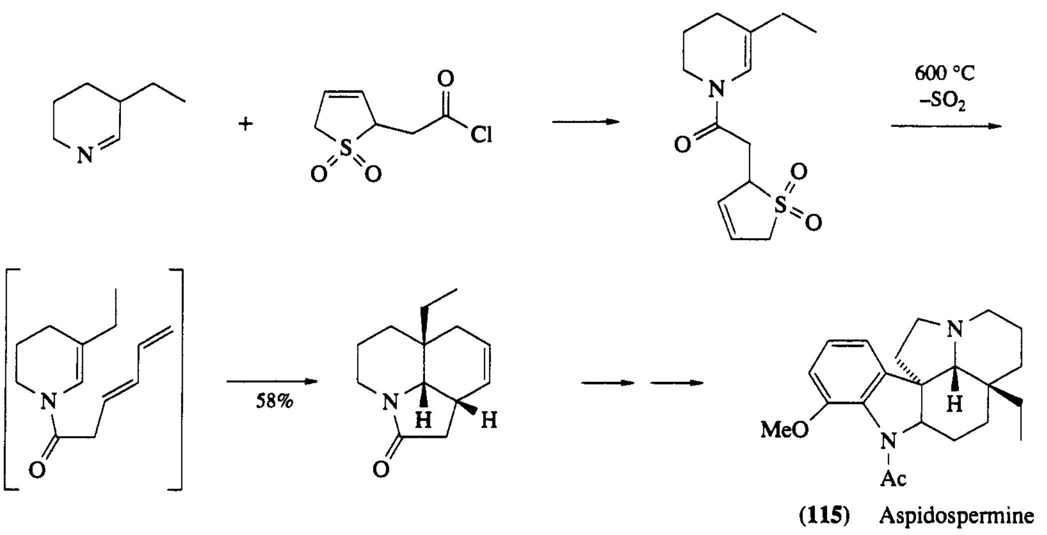
N
+
O
Cl
S
O
O
N
O
S
O
O
600 °C
-SO2
N
O
58%
N
H
H
O
N
H
MeO
N
Ac
(115) Aspidospermine

**Scheme 105**

1,3-dipolar cycloadditions.[404] Selected examples, illustrating the efficiency of this selective diene protection, are depicted in Scheme 106. The blocking of the diene structure of ergosterol opens a route for the selective hydrogenation, oxidation and hydroboration of the isolated side chain double bond.[399] Protection of the diene part of tropone opens the way for cycloaddition reactions on the remaining unmasked double bond. In contrast, unprotected tropone would undergo ring expansion reactions with diazomethane.[404b] In particular, it should be noted that in the $Fe(CO)_3$ complexes the dienes are not only protected but even stabilized. Thus, for instance, 1,3-butadien-1-ol and -2-ol are prevented from rearranging to their respective keto tautomers by coordination to $Fe(CO)_3$.[405] In addition, the highly reactive cyclobutadiene can be isolated as its complexes with transition metals. The dienes may be regenerated from their complexes by treatment with oxidizing agents, *e.g.* $Fe^{III}$, $Cu^{II}$ or $Ce^{IV}$ salts, trimethylamine *N*-oxide and pyridinium chlorochromate.[397–404]

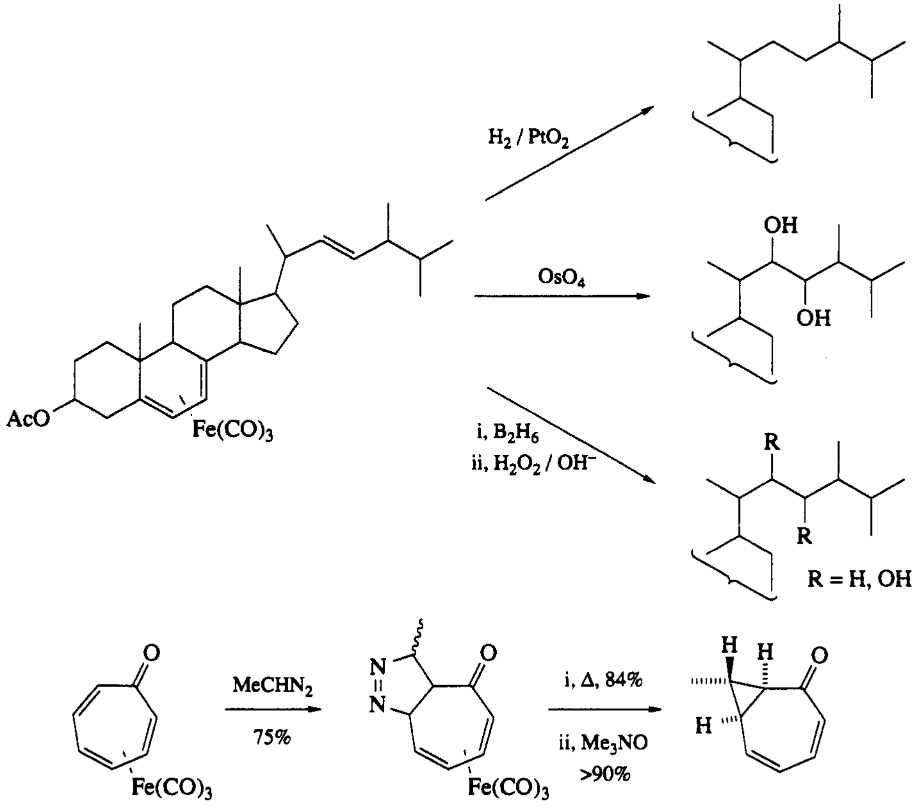

Scheme 106

### 3.1.7.3 Protection of Alkynes[346]

Like the double bond, the carbon–carbon triple bond is susceptible to many of the common addition reactions. In some cases, such as reduction, hydroboration and acid-catalyzed hydration, it is even more reactive. A very efficient method for the protection of the triple bond is found in the alkynedicobalt hexacarbonyl complexes (*e.g.* **117** and **118**), readily formed by the reaction of the respective alkyne with dicobalt octacarbonyl.[406,407] In eneynes this complexation is specific for the triple bond. The remaining alkenes can be reduced with diimide or borane[407] as is illustrated for the ethynylation product (**116**) of 5-dehydro androsterone in Scheme 107. Alkynic alkenes and alcohols complexed in this way show an increased structural stability. This has been used for the construction of a variety of substituted alkynic compounds uncontaminated by allenic isomers (Scheme 107) and in syntheses of insect pheromones.[408] From the protecting cobalt clusters, the parent alkynes can easily be regenerated by treatment with iron(III) nitrate,[407] ammonium cerium nitrate[406] or trimethylamine *N*-oxide.[409]

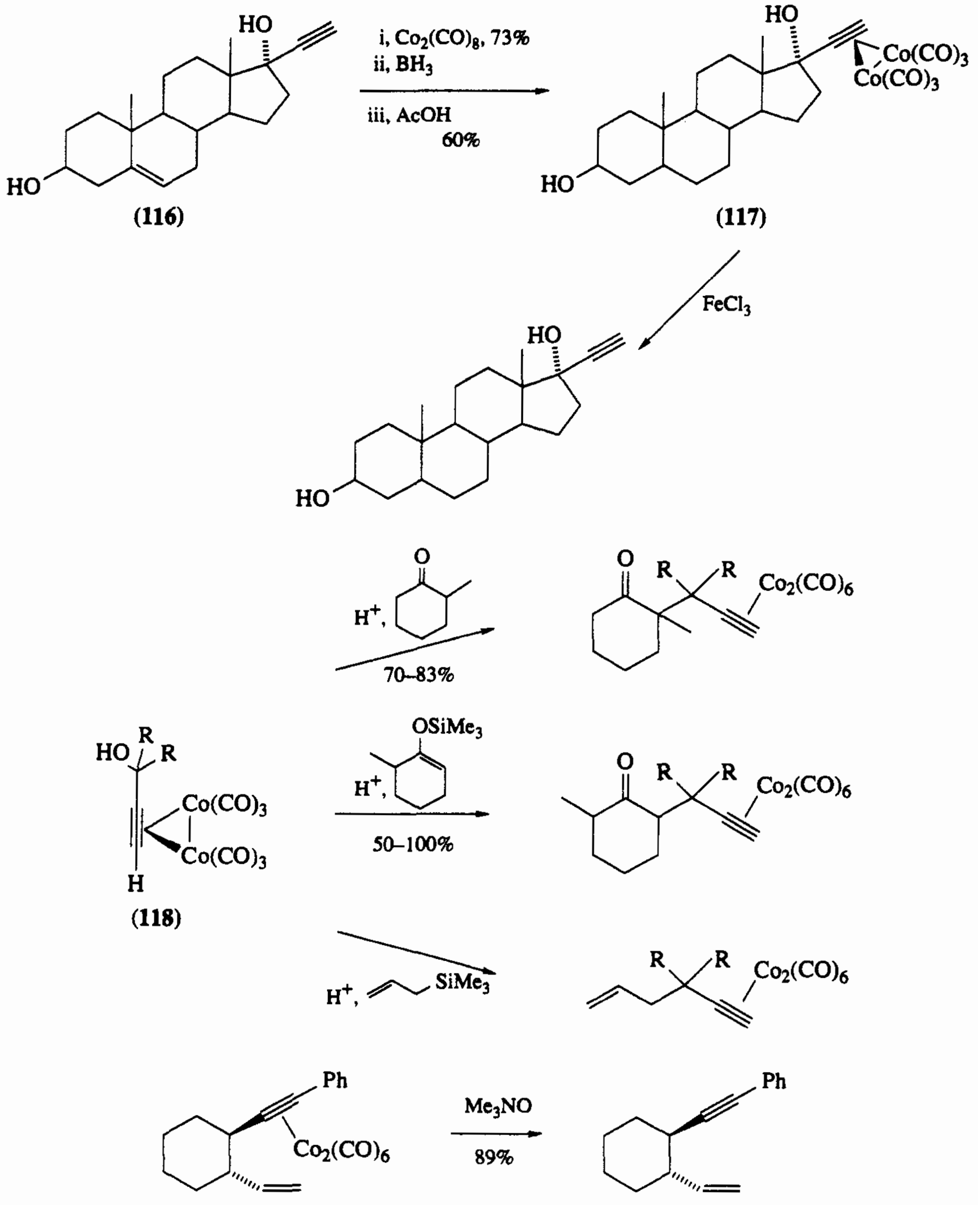
HO
HO
(116)
i, $Co_2(CO)_8$, 73%
ii, $BH_3$
iii, AcOH
60%
HO
$Co(CO)_3$
$Co(CO)_3$
HO
(117)
$FeCl_3$
HO
HO
O
$H^+$,
70–83%
O
R
R
$Co_2(CO)_6$
HO
R
R
$Co(CO)_3$
$Co(CO)_3$
H
(118)
$OSiMe_3$
$H^+$,
50–100%
O
R
R
$Co_2(CO)_6$
$H^+$,
$SiMe_3$
R
R
$Co_2(CO)_6$
Ph
$Co_2(CO)_6$
$Me_3NO$
89%
Ph

Scheme 107

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# 4.1

# Carbonyl Group Derivatization

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## 4.1.1 INTRODUCTION

Enamines, imines, hydrazones and oximes represent the common nitrogen derivatives of ketones and aldehydes (Scheme 1). Both hydrazones and oximes were of importance before the availability of modern spectral techniques for the conversion of liquid carbonyl-containing compounds into solid materials that could be correlated with known samples by melting point and mixed melting point methods. While these applications have all but disappeared, these derivatives, as well as enamines and imines, have emerged as important intermediary species in overall transformations that effect substitution $\alpha$ to the original carbonyl group. Much of this work is based on the seminal contributions of Stork.[1–4]

While enamines are structurally distinguished from the other three derivatives by the absence of the carbon–nitrogen double bond, they serve in substitution reactions in the same conceptual way: that is, the

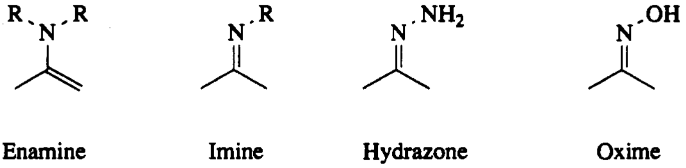

Scheme 1

substitution process involves, overall, the replacement of a hydrogen atom by a different atom, usually carbon, and these species provide an avenue for removal of the α-hydrogen as the first operation. Thus, direct formation of enamines from aldehydes and ketones involves removal of this hydrogen, while reactions that proceed through the other derivatives involve separate steps, usually treatment with a strong base (Scheme 2). The resulting anions are structurally similar to enamines and, indeed, have been referred to as metalloenamines.

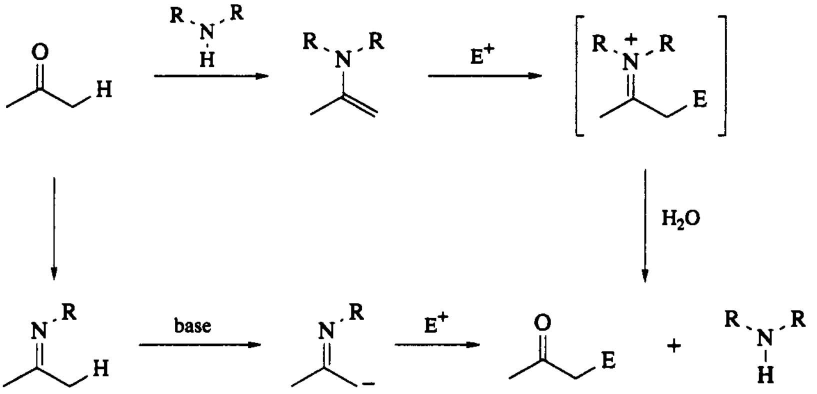

Scheme 2

There are other applications of these derivatives. For example, imines can be reduced to amines (equation 1),[5] oximes can undergo rearrangement under strongly acidic (or dehydrating) conditions to form amides (equation 2),[6] and the treatment of tosylhydrazones with strong bases can provide an excellent method for reductive elimination to form alkenes (equation 3).[7]

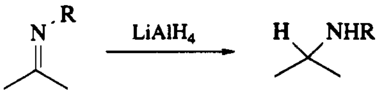

(1)

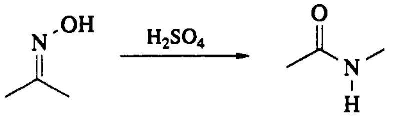

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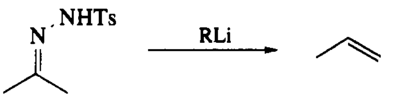

(3)

A number of comprehensive reviews of enamine and imine chemistry have appeared.[8–17] Sections in other volumes of this series will concentrate explicitly on carbon–carbon bond forming reactions that use these species. They will be treated here mainly from the perspectives of methods for their formation and of their unique structural features.

## 4.1.2 ENAMINES

### 4.1.2.1 Formation

The reaction between all classes of amines (except tertiary) and either ketones or aldehydes is usually straightforward and generally leads to imines in the case of primary amines and to enamines with secondary amines, which bear only one labile proton on nitrogen (equation 4).

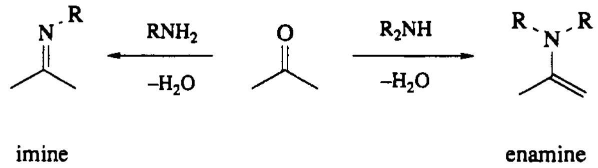

(4)

It is generally conceded that some method of removal of the water that is coproduced in both reactions is required to effect maximal conversion of ketones to imines or enamines. Indeed, the variations between the different methods for enamine formation center on the techniques employed for driving the reaction to completion. The simple method of azeotropic removal of water when effecting reaction in a hydrocarbon solvent such as benzene or toluene in the presence of an acid catalyst represents the classical method for enamine formation. Qualitative rates of reaction of three commonly used amines are in the order: pyrrolidine > morpholine > piperidine. The rate of reaction of pyrrolidine with various ketones proceeds in the following order: cyclopentanone > cyclohexanone > cycloheptanone > 2-methylcyclohexanone > acetone.[18,19] Alternatively, chemical drying agents can be employed with the advantage that the conversion to enamine can be effected more rapidly and that elevated temperatures (reflux) need not be employed. Molecular sieves not only provide a means for water removal but have also been shown to have catalytic, rate-enhancing effects on enamine formation,[20–22] most likely as the result of the binding agent.[21] Reaction between simple secondary amines and hindered ketones, including the relatively unreactive methyl ketones, can be quite slow. Titanium tetrachloride has been used in such cases as both a strong Lewis acid and a powerful dehydrating agent,[23] and an extensive study has been carried out in order to find optimum conditions for its application.[24] Two significant conclusions from this latter study are that: (i) complexation of the amine and titanium tetrachloride before addition to the ketone provides enhanced rates; and (ii) a large excess of amine is required, presumably to effect deprotonation of an intermediate complex.

In a similar vein, 3 equiv. of trimethylsilyldimethylamine have been used at room temperature to form the enamine from cyclohexanone, conditions under which the water is presumably consumed as hexamethyldisiloxane (equation 5).[25] This method has been extended to the formation of *N,N*-dimethylenamines from unsaturated aldehydes.[26] Alternatively, enamines have also been obtained by converting the carbonyl compound to a ketal before reaction with the amine.[27] The first process is endothermic but can be readily driven to completion and provides the driving force for formation of the enamine.

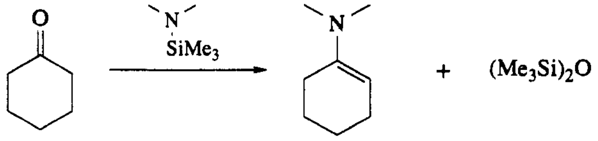

(5)

Two unusual and useful methods for enamine formation involving carbon–carbon bond formation[28–36] have been developed from the pioneering work of Martin[28–30] and are illustrated in equations (6)[28] and (7).[36] The moderate overall yields in both processes are offset by the complexity of alternative pathways for accomplishing the same transformation.

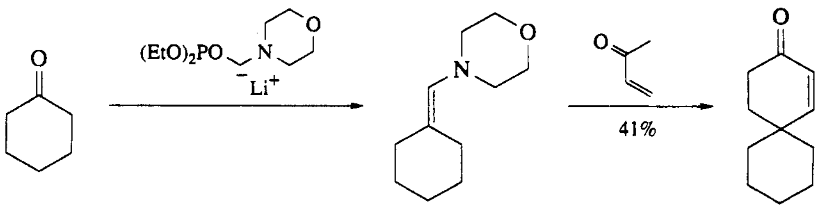

(6)

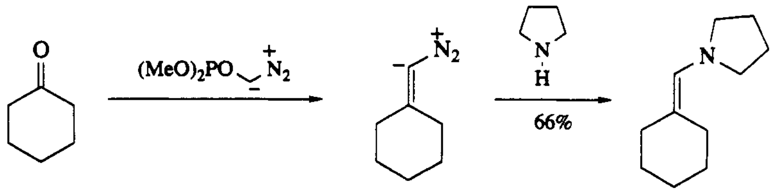

(7)

The transformation illustrated in equation (8) effects a net conversion of an acid to the enamine of the corresponding aldehyde, but does so by decarboxylation (rather than by reduction).[37]

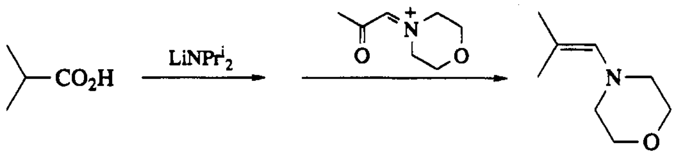

(8)

The formation of enamines from acyclic methyl ketones is often complicated by reaction of the enamine with the ketone. In a cleverly devised process, Ahlbrecht first converted acetone to a cyanoamine, which is then transformed into the enamine by potassium *t*-butoxide induced loss of hydrogen cyanide (equation 9).[38]

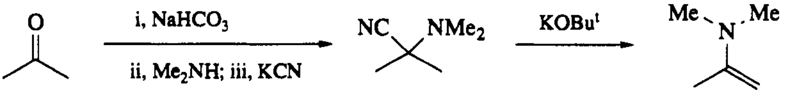

(9)

Enamines that would formally be derived from ammonium cannot be formed by any process that would expose the product to either acid or base, since the conversion to the imine is exothermic as both the carbon–nitrogen π-bond (74 kcal mol$^{-1}$; 1 cal = 4.18 J) and carbon–hydrogen bond (99 kcal mol$^{-1}$) are stronger than the carbon–carbon π-bond (63 kcal mol$^{-1}$) and nitrogen–hydrogen bond (93 kcal mol$^{-1}$). However, ethenamine and several substituted analogs have been prepared for spectral analysis (at low temperature) by retro-Diels–Alder reactions (equation 10).[39]

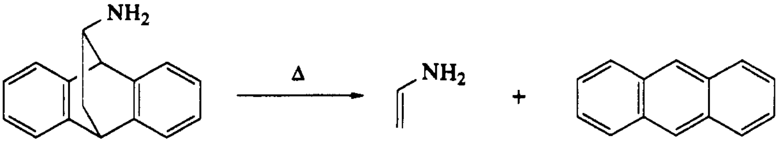

(10)

As will be further detailed in Section 4.1.2.2, it is possible to effect equilibration of allylamines and the corresponding enamines (for example, equation 11). Such a procedure obviously lacks generality, as in the majority of cases the allylamine would be more difficult to prepare than the enamine. Furthermore, and more importantly, such a sequence for forming enamines removes the ketone functionality from its central role in the synthetic sequence.

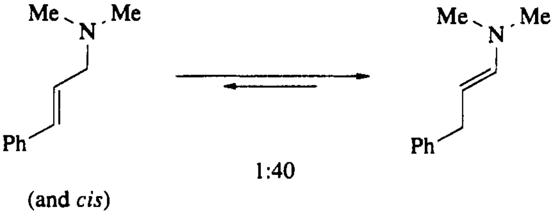

(11)

### 4.1.2.2 Structure and Chemical Properties

The structure of enamines, on first inspection, would seem straightforward, and, indeed, most elementary texts present a simplistic picture in which the nitrogen is fully $sp^2$-hybridized with complete $p$-orbital overlap between nitrogen and the carbon–carbon π-bond system (**1**).

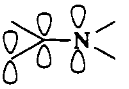

**(1)**

The energetic significance of this overlap can be concluded from a combined analysis of a number of studies. The energy difference between *N*-allyl- and *N*-propenyl-piperidine was determined indirectly by heats of hydrogenation to be 5.0 kcal mol$^{-1}$ (in favor of the enamine form) (Scheme 3).[40] Approximately 2.5 kcal mol$^{-1}$ of this difference can be attributed to the greater stability inherent in the more substituted alkene isomer.[41] Doering has pointed out that the remaining difference of 2.5 kcal mol$^{-1}$ could, in principle, be the result of either nitrogen lone pair, π-system overlap or a change in the energy of the σ-bond between nitrogen and either an $sp^2$ or $sp^3$ carbon.[42] In an imaginative experiment, he determined the equilibrium ratio between the allylamine and enamine below (equation 12) to be nearly 1:1, demonstrating that there is essentially no difference in energy between the allylamine and enamine in the absence of lone pair, π-system overlap. (The bridgehead lone pair must be orthogonal to the carbon–carbon π-bond in this system.)

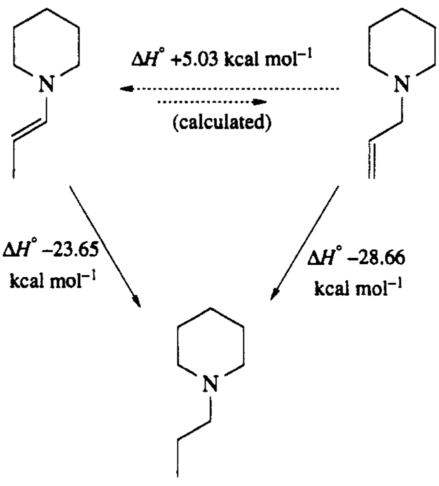
N
ΔH° +5.03 kcal mol$^{-1}$
(calculated)
N
ΔH° −23.65 kcal mol$^{-1}$
ΔH° −28.66 kcal mol$^{-1}$
N

**Scheme 3**

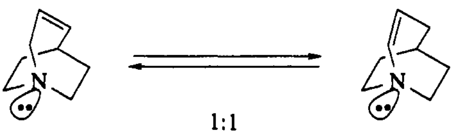

(12)

Other determinations of the energy difference between an allylamine and an enamine include the equilibration of the species in equations (11),[44] (13)[43] and (14).[45,46]

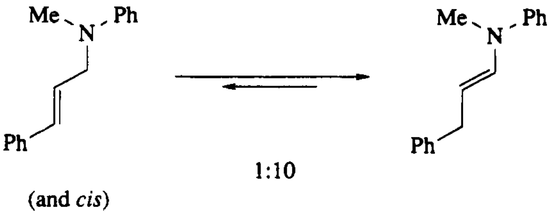

(13)

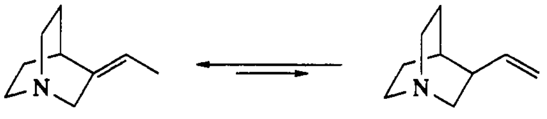

16:1

(14)

In theory, the energetic advantage that results from lone pair π-system overlap could be directly assessed by determining the barrier to rotation about the carbon–nitrogen σ-bond. Unfortunately, the barrier appears to be too low for determination by NMR spectroscopic techniques. Philipsborn has shown that there is a good correlation between the barrier to rotation about this bond and the $^{15}N$ NMR chemical shift for enamines with extended conjugation, resulting in higher and measurable barriers (vinylogous amides, for example).[47] Extrapolation of these observations to simple enamines leads to a predicted barrier of 5 kcal $mol^{-1}$, corresponding well with a barrier of 6 kcal $mol^{-1}$ calculated by Dixon using PRDDO and *ab initio* calculations with a variety of basis sets.[48] The chemical shift of the vinylic hydrogen can be correlated in a similar fashion.[49]

An extensive collection of single-crystal, X-ray structural determinations resulting from a collaboration between Eschenmoser and Dunitz on a variety of enamines provides interesting insight into the conformation about the nitrogen–carbon σ-bond as well as the degree of planarity (hybridization) at nitrogen.[50] The three examples shown in Scheme 4 illustrate the range of possibilities found, with nitrogen varying from nearly perfectly planar to nearly pyramidal. (The values provided are a measure of the degree, in angstroms, to which the nitrogen atom lies out of the plane defined by its three attached carbon atoms.)

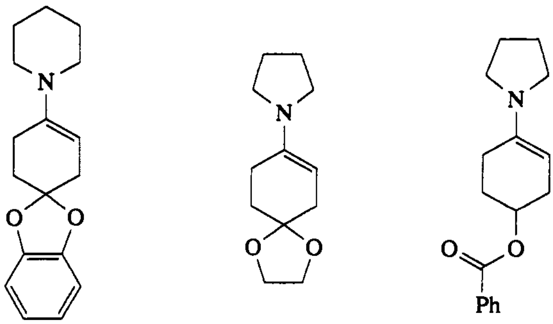

0.325 Å
0.311

0.196 Å
0.120

0.013 Å

**Scheme 4**

Caution should always be exercised in extrapolating solid state structural information to the analysis of arrangements in solution and, indeed, the unit cells of two of the crystals contain different molecules with significant differences in arrangements. Nonetheless, the large number of examples in this study provide a statistical basis for concluding that the energetics of overlap are affected in only a minor way by the hybridization state at nitrogen. Further, the energetics of alignment of the lone pair with the π-system appears to be quite soft and overridden by an apparent favoring of arrangements in which the bond from nitrogen to one of the two substituents of the amine moiety is nearly eclipsed with the carbon–carbon double bond (Figure 1).[50]

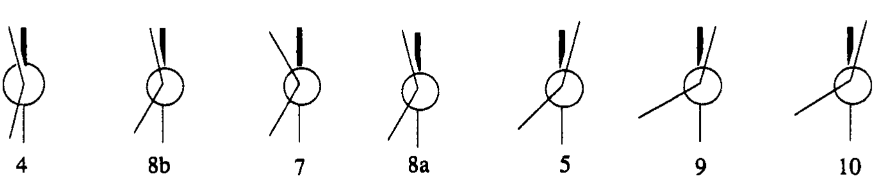

**Figure 1** Newman projections of various enamines looking down the N–C bond (the C=C bond is maintained in the vertical position throughout)[50]

For applications of enamines as reactive derivatives of ketones and aldehydes, the major structural question for those derived from unsymmetrical ketones is that of regiochemistry. The ratio of less to more substituted forms for a series of 10 enamines derived from various amines and methylcyclohexanone has been summarized by Thompson from various literature studies (Scheme 5).[51]

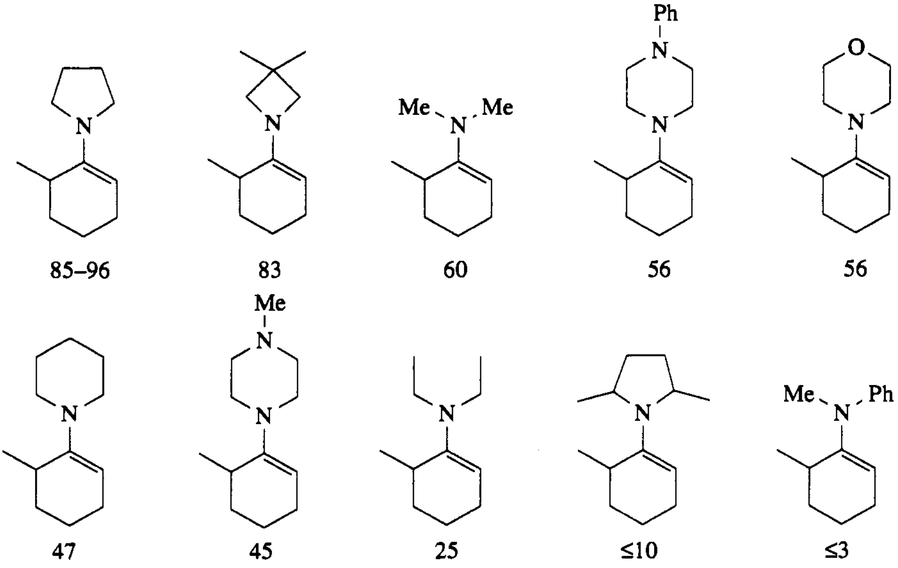

**Scheme 5**

While it is probably reasonable to draw general trends from this series, it should be kept in mind that most of the data came from different laboratories, as indeed there are four different reports for the simple pyrrolidine enamine that account for the range from 85 to 96%. Some of the factors that contribute to determining the regioisomeric composition of enamines are $A^{1,3}$-strain, which destabilizes the more substituted isomer, and $A^{1,2}$-strain, which destabilizes the less substituted isomer (Scheme 6).[52] The former effect was used by Johnson to effectively convert *cis*-2,4-dimethylcyclohexanone to the *trans* isomer through formation of the less substituted pyrrolidine enamime, where a pseudo-axial orientation of the 2-methyl group reduces the level of $A^{1,2}$-strain (equation 15).[53,54]

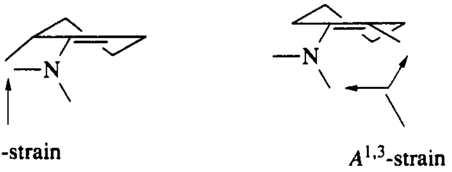

**Scheme 6**

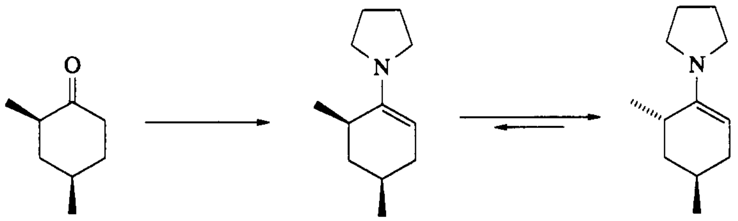

(15)

The degree to which each of the effects will impact the respective isomer will depend not only on the amine substituents but also on the specific structure of the ketone involved. For example, and rather surprisingly, it has been shown that $A^{1,3}$-strain can be sufficiently greater that $A^{1,2}$-strain so as to favor the less substituted enamine, even when the substituent is an alkoxycarbonyl group capable of adding stability to the more substituted form through extended conjugation (equation 16).[55,56] Further, it has been established, at least with some enamines, that interconversion of the two regioisomers occurs at a rate competitive with alkylation and, therefore, that the ground state composition of the starting enamine does not directly correlate with product composition. For example, the two regioisomeric enamines derived from 3-methylcyclohexanone (Scheme 7) have been shown to be in rapid equilibrium, providing a product ratio upon reaction with β-nitrostyrene that differed markedly from that of the starting enamine.[57-59]

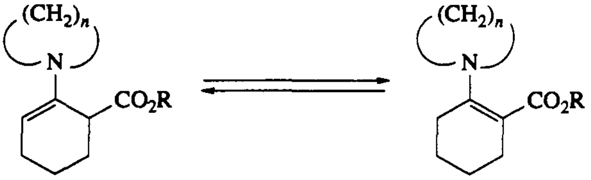

(16)

*Percentage of more substituted isomer*

| | 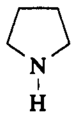 | 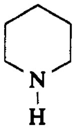 | 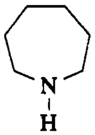 |
|---|---|---|---|
| R = Me | 95 | 34 | 75 |
| R = Et | 88 | 25 | 64 |
| R = Pr$^i$ | 85 | 25 | 64 |

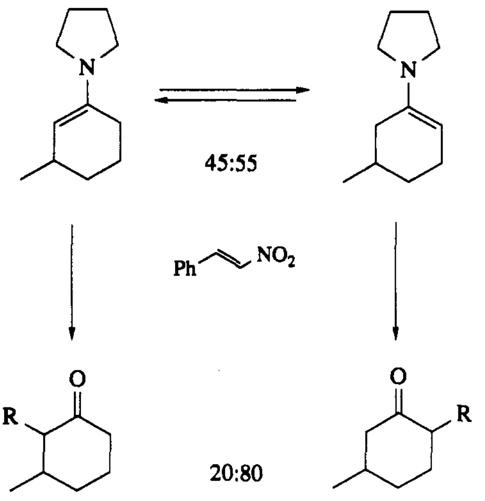

**Scheme 7**

Interpretation of these studies, as well as those involving reaction with methyl acrylate and acrylonitrile as electrophiles,[60] are complicated by the possibility that these reactions are reversible. Conversely, reaction with molecular bromine is considerably faster than regioisomerization, an observation that has been used to prepare separate samples of 2-bromo-6-methyl- and 2-bromo-2-methyl-cyclohexanone.[61] Thus, in the reaction of a nearly one to one mixture of the less and more substituted enamines derived from methylcyclohexanone with 0.5 equiv. of bromine, only the less substituted isomer is converted to the intermediate immonium ion, which precipitates from ether solution at –50 °C (Scheme 8). Separation, and then addition of more bromine to the filtrate, then effected reaction of the more substituted isomer.

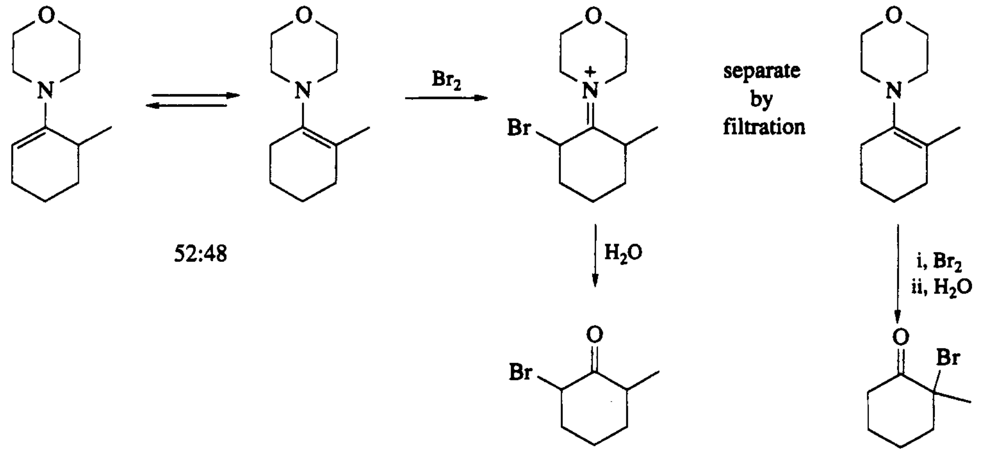

**Scheme 8**

### 4.1.2.3 Spectral Properties

#### *4.1.2.3.1 Photoelectron spectra*

Extensive measurements of ionization potentials of various enamines by photoelectron spectroscopy from a number of separate investigations[62-66] have been nicely tabulated by Hickmott[67] and, more recently, by Vocelle.[68] Conclusions from these data concerning the degree of lone pair, π-system conjugation for different enamines seem valid as they are consistent with other spectroscopic and chemical observations. On the other hand, the presumption that the nitrogen is pyramidal because the first ionization band is quite broad as a result of a large geometry change between the neutral ground state and the radical cation is more speculative.

#### *4.1.2.3.2 Ultraviolet spectra*

The UV absorption spectra of simple enamines as well as those with extended carbon–carbon π-conjugation are quite broad. A correlation with photoelectron spectra has also been made.[69]

#### *4.1.2.3.3 Infrared spectra*

The π-bond stretching of enamines is only slightly affected by interaction with the nitrogen lone pair.[8] It might be argued that the relatively greater shift of the absorption for the less substituted isomer as compared with the more substituted isomer (relative to a tri- or tetra-substituted alkene[70] at 1670 $cm^{-1}$) is an indication of greater lone pair delocalization in the former (Scheme 9).

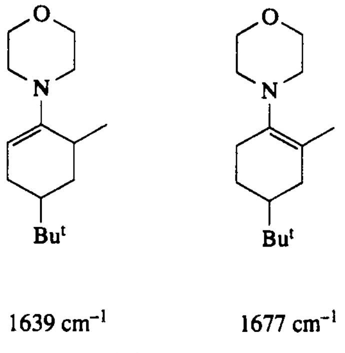

**Scheme 9**

### *4.1.2.3.4 Carbon NMR spectra*

A number of early studies established the value of carbon NMR spectroscopy for the analysis of the composition of enamines, especially with regard to regiochemistry for those derived from unsymmetrical ketones and to stereochemistry for enamines of acyclic ketones as well as of aldehydes.[71–73] A more recent survey by Paquer provides valuable information for the prediction of the expected chemical shift for new systems.[74] While only morpholine enamines were directly examined, the anticipated shift corrections for those derived from both pyrrolidine and piperidine are given. Two approaches are provided by these authors; the first provides appropriate shift-of-shift values for both the α- and β-carbon relative to the corresponding alkene (Scheme 10).[75] These are quite consistent for the α-carbon, ranging from +16.7 to +21.3 δ for the α-carbon of enamines derived from five-, six-, seven- and eight-membered ring ketones. Similarly, the shift-of-shift values for the β-carbon relative to the corresponding alkene ranged from –22.3 to –32.8 when the β-carbon had one hydrogen and from –6.5 to –10.9 when the β-carbon was fully substituted. Both the relatively large variation in the shift-of-shift of the β-carbon and the decrease in this value upon further substitution by carbon correlate well with the degree of anticipated delocalization of the nitrogen lone pair. Similar observations were also made for a series of eight enamines derived from acyclic ketones. These results are also summarized in Scheme 10.

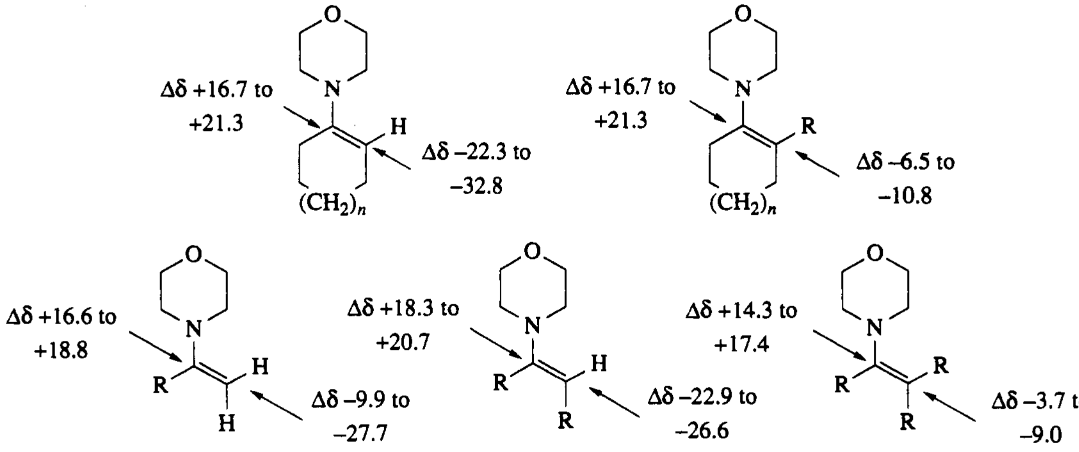

**Scheme 10**

An alternative process for predicting the chemical shifts of both the α- and β-carbons without reference to the parent alkene is also provided. This latter method is amazingly accurate and will find use especially where the spectrum for the appropriate alkene is not available. Notice the large shift of shift effect on both the α- and β-carbons for added substituents on the β-carbon. Thus, analysis of ratios and assignment of regiochemistry to enamines derived from unsymmetrical ketones becomes a trivial matter by $^{13}C$ NMR spectral analysis. There is also a large difference in the shift of shift value for the β-carbon for adding an additional substituent either *cis* (23.4) or *trans* (13.3) to the nitrogen, permitting ready and reliable assignment of stereochemistry about the enamine π-bond for those derived from aldehydes and acyclic ketones (Scheme 11).

### *4.1.2.3.5 Proton NMR spectra*

The proton NMR spectra of enamines have been examined for some time,[76,77] and represented the first reliable technique for assigning the regiochemistry of those enamines derived from unsymmetrical ketones, although of course there will be no vinylic hydrogen absorption for enamines upon formation of the π-bond toward the side of the ketone that is disubstituted. Shown in Scheme 12 are shift values for the vinylic hydrogen of enamines derived from a variety of ketones and amines.[76]

The shift values obtained in $CDCl_3$ are at approximately 0.1 p.p.m. lower field. The large upfield shift of this proton from simple alkenes is, of course, the result of lone pair electron delocalization into the π-system, resulting in an increase in electron density at the β-carbon. The ease with which this delocalization can occur crudely correlates with the kinetic reactivity of the various enamines where the most reactive are generally the pyrrolidine enamines.[12,77,78] A similar analysis of the proton spectra for enamines derived from 2-butanone and a variety of amines has also been made.[79] Again, the pyrrolidine enamine absorption occurs upfield from both the piperidine and morpholine enamines. The vinylic

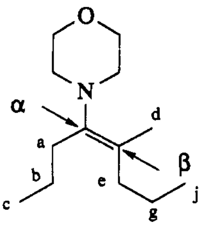

*For C-α*

To base of 147.00 p.p.m. add for nonhydrogen

| | |
|---|---|
| a 4.68 | e −5.93 |
| b 4.30 | g −1.46 |
| c −0.92 | j −1.25 |
| d −6.26 | |

For five-membered ring add 5.88

*For C-β*

To base of 84.40 p.p.m. add for nonhydrogen

| | |
|---|---|
| a 0.45 | e 13.29 |
| b 0.51 | g 6.10 |
| c 1.06 | j −4.79 |
| d 23.37 | |

For five-membered ring add −2.12

**Scheme 11**

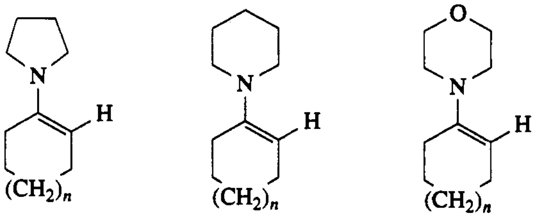

*Chemical shift of the vinylic hydrogen in p.p.m.(δ) downfield from TMS*

| $n$ | | | |
|---|---|---|---|
| 0 | 3.92 | 4.25 | 4.35 |
| 1 | 4.13 | 4.53 | 4.57 |
| 2 | 4.37 | 4.75 | |
| 3 | 4.08 | 4.48 | |
| 5 | 3.97 | 4.30 | |

**Scheme 12**

hydrogen of the (*E*)-isomer is found to be consistently (0.1 to 0.7 p.p.m.) upfield from the (*Z*)-isomer and it is probable that this also results from greater lone pair delocalization in the former since overlap in the (*Z*)-isomer can be inhibited as the result of $A^{1,3}$-strain. A similar study of enamines of propiophenone has also been reported.[80a]

The configuration about the carbon–carbon π-bond of enamines derived from acyclic ketones can, at least in principle, be derived from NOE enhancement between the carbons α to the nitrogen and the vinylic hydrogen.[80b] For example, that of the enamine derived from propiophenone and dimethylamine (where the hydrogen is *cis* to the amine unit, *i.e.* the (*E*)-isomer) exhibits an enhancement of 23% in the vinylic hydrogen upon irradiation of the methyl groups attached to nitrogen. The generality of this observation has not been demonstrated and, further, in those cases where only the (*Z*)-isomer was obtained the evidence would be negative. In summary, it would appear that carbon NMR spectral analysis represents by far the best technique for determining the regio- and stereo-chemistry of enamines.

### 4.1.2.4 General Reactions

Enamines are employed in the majority of cases as a means of activating the α-carbon as a nucleophile for reaction with an electrophilic carbon partner (Scheme 13). In the historical picture of the development of methods for α-alkylation of ketones and aldehydes, they represented a significant advance over the use of alkaline earth metal enolates, which had been employed up to that point. More recently developed techniques that involve the formation of enolates (as well as imine and hydrazone anions, *vide infra*) with lithium amide bases have proved superior in most cases both in terms of regiochemical control and in limiting the process to monosubstitution. Nonetheless, these methods universally involve strongly basic reactions, and enamine alkylation stands uniquely apart from other methods in being essentially neutral.

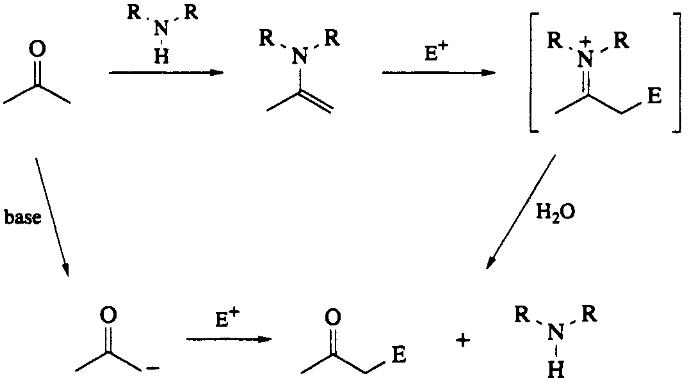

Scheme 13

There are a number of side processes in the reactions of enamines that can divert material from the (usually) desired monoalkylation product at the less substituted side. These include *N*-alkylation (which in rare cases is reversible), reaction at the more substituted α-carbon, and di- and higher alkylation (equation 17). Furthermore, conditions for maximum conversion to monoalkylation relative to dialkylation product generally result in incomplete alkylation of the enamine which is then converted, upon hydrolysis, to the original ketone or aldehyde.

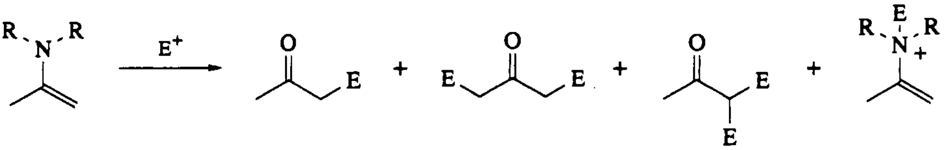

(17)

A variety of secondary amines have been used for enamine alkylation.[81-83] Nonetheless, the three most commonly used, pyrrolidine, piperidine and morpholine, appear to still represent the best compromise between ease of access to the amine and formation of the enamine and the degree of conversion to monoalkylated product.[81] Pyrrolidine appears to be the best amine for the specific case where the electrophilic partner for the enamine is a Michael acceptor, such as an α,β-unsaturated ester,[84,85] and enamines derived from this base are generally more reactive than the piperidine and morpholine analogs.[3] The use of optically active amines for asymmetric induction will be covered in Section 4.1.2.5.

A range of electrophilic partners have been employed in reactions with enamines, ranging from simple alkyl halides (and sulfonates) to acylating agents such as carboxylic acid chlorides and to electrophilic alkenes such as the aforementioned unsaturated esters. Specific examples are provided in equations (18), (19) and (20). Appropriately, all three examples are from Stork.[3] The reaction with α,β-unsaturated ketones has special significance as a variant of the Robinson ring annelation technique[86] (equation 21).[87] in which the second stage is the cyclization of a diketone through formation of the enamine of one ketone group. This process can be effected with a high degree of asymmetric induction with the amino acid proline as a catalyst. This aspect will be covered in detail in Section 4.1.2.5.

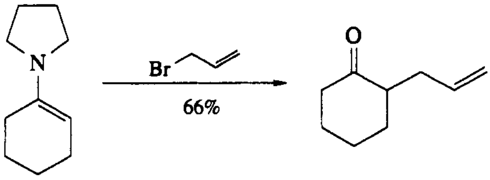

(18)

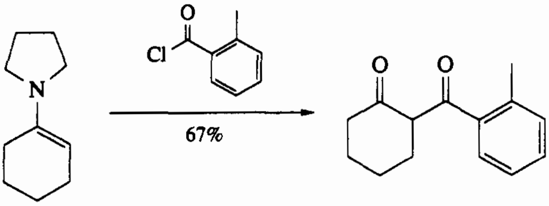

(19)

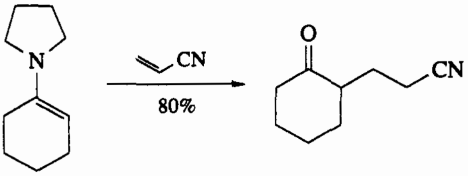

(20)

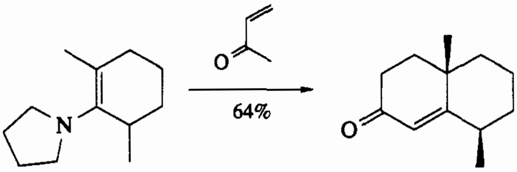

(21)

Recent reports from Takazawa[88–90] provide the background for the reaction of enamines with aldehydes and acetals as well as with orthoesters in the presence of Lewis acids (equations 22[89] and 23[90]). For these reactions it was found that the enamine from morpholine provided the highest yield as did the use of boron trifloride etherate as a Lewis acid (in stoichiometric amounts).

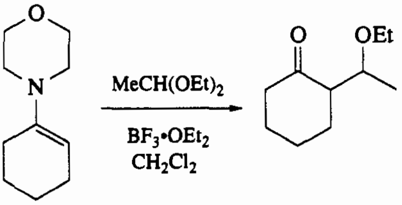
O
N
$MeCH(OEt)_2$
$BF_3{\bullet}OEt_2$
$CH_2Cl_2$
O
OEt

(22)

76% (mixture of diastereomers)

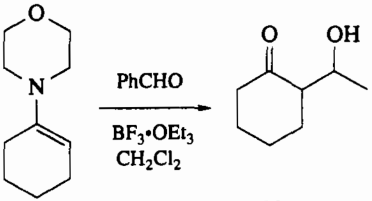
O
N
PhCHO
$BF_3{\bullet}OEt_3$
$CH_2Cl_2$
O
OH

(23)

92%; *erythro*:*threo* = 78:22

Sequential reaction at both positions α to a carbonyl group (as its enamine derivative) with a bifunctional electrophile provides for ring formation, as illustrated in equation (24) by the preparation of a bicyclo[3.2.1]octane bridged system from a cyclopentanone.[91] Alternatively, spiro systems can also be formed, as in equation (25).[92] A comprehensive study with a variety of bifunctional electrophiles has been reported recently.[93]

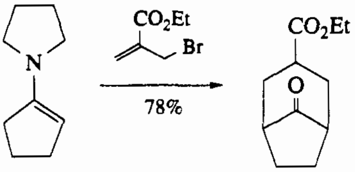
N
$CO_2Et$
Br
78%
$CO_2Et$
O

(24)

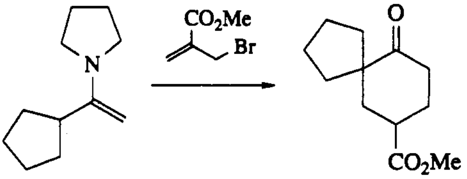

(25)

A number of atypical reactions of enamines have been developed. For example, hydroboration–oxidation affords stereochemically defined, vicinal amino alcohols (equation 26).[94] Similarly, enamines have been shown to undergo reaction with diazomethane to form substituted cyclopropanes. These materials can be further transformed to α-alkylated ketones by thermolysis followed by hydrolysis (equation 27).[95]

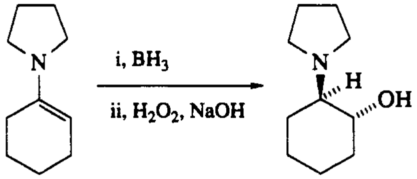

(26)

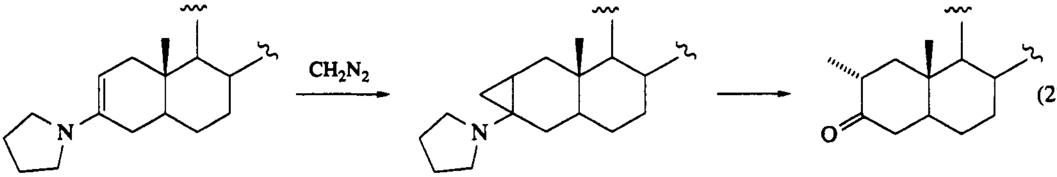

(27)

### 4.1.2.5 Stereochemical Features

Control of absolute stereochemistry in ketone alkylation through the use of chirality in the amine component of an enamine represents a nearly ideal case for asymmetric induction where the chiral auxiliary is present in an equimolar amount. The formation of enamines is generally straightforward, cleavage of the product immonium ion is trivial in most cases, and the amine can be readily separated from the prouct for recovery and reuse. Indeed, the first example of such a process was reported by Yamada in 1969 using proline esters as the chiral amine (equation 28).[96–98]

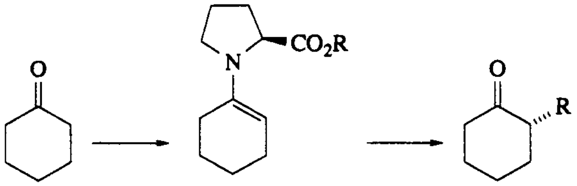

(28)

However, the maximum level of stereochemical control in these processes with a variety of electrophiles ($CH_2{=}CHCO_2Me$, $CH_2{=}CHCN$, $BrCH_2CH{=}CH_2$, $BrCH_2CO_2Et$) was below 60% optical purity (corresponding to a ratio no better than 4:1). These results appear to be the result of kinetic control in the transition state for carbon–carbon bond formation. On the other hand, reactions with methyl vinyl ketone can be run under either kinetic or thermodynamic control and the level of stereochemical control is higher under the latter conditions.[99,100] Likewise, the enamine from 2-methoxymethylpyrrolidine (derived from proline) adds in a Michael fashion to nitrostyrenes (equation 29)[101–103] and in a simple addition mode to acyliminoacetates (equation 30)[104] with very high levels of asymmetric induction.

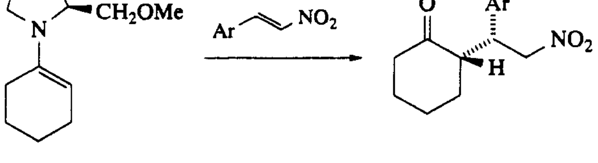

(29)

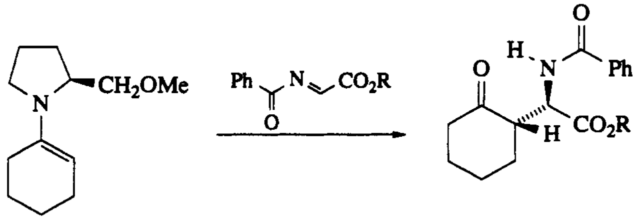

(30)

Similarly, reaction of an enamine derived from the pyrrolinylamide of proline with methyl vinyl ketone afforded an entry to the natural product mesembrine (equation 31).[105-107]

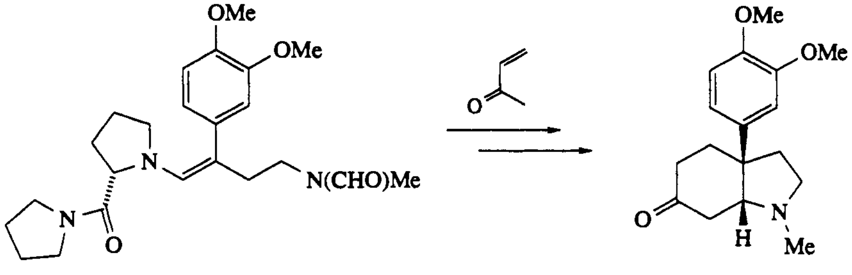

(31)

Mesembrine

In an analogous fashion, the enamine derived from cyclohexanone and trimethylsiloxymethylpyrroline undergoes reaction with methyl acrylate with good levels of stereochemical control, while enamines derived from a noncyclic chiral amine gave poorer results.[108] Protonation of enamines under both thermodynamic and kinetic control has provided optically active products, though generally at less than practical levels.[109] The 'deracemization' illustrated in equation (32) represents an interesting example of this process.[110] Likewise, reaction of a chiral proline-derived enamine with a nitrene led to reasonable levels of stereochemical control but to poor chemical yield (equation 33).[111]

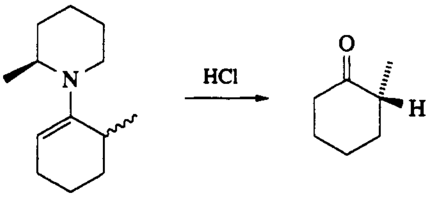

(32)

from racemic ketone

20% *ee*

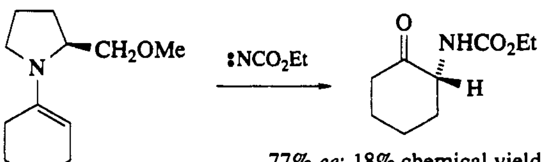

(33)

77% *ee*; 18% chemical yield

In 1977, we proposed that use of an unsymmetrical amine in such a reaction would lead to reaction from both rotational isomers (about the nitrogen–carbon formal single bond), reducing the level of stereochemical control.[112] As an alternative, the $C_2$ symmetrical amine *trans*-2,5-dimethylpyrrolidine was prepared in optically pure form and shown to be superior (equation 34). Other applications of this amine have followed from other research groups, including the alkylation of a vinylogous ester enolate derived from a β-keto ester vinylogous amide (Scheme 14).[113] We have recently introduced a new tricyclic chiral amine (**2**) and demonstrated its superior stereochemical directing ability in the same sequence.[114]

Schreiber has recently demonstrated excellent control of asymmetric induction in the intramolecular reaction of *in situ* prepared aldehyde enamines with unsaturated aldehydes (equation 35).[115,116] The

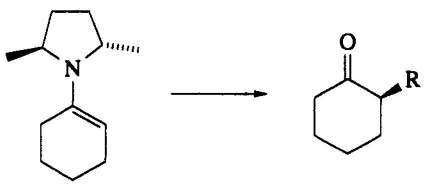

(34)

| R = | *ee* (%) |
|---|---|
| Me | 83 |
| Pr$^n$ | 93 |
| $CH_2CH{=}CH_2$ | 82 |

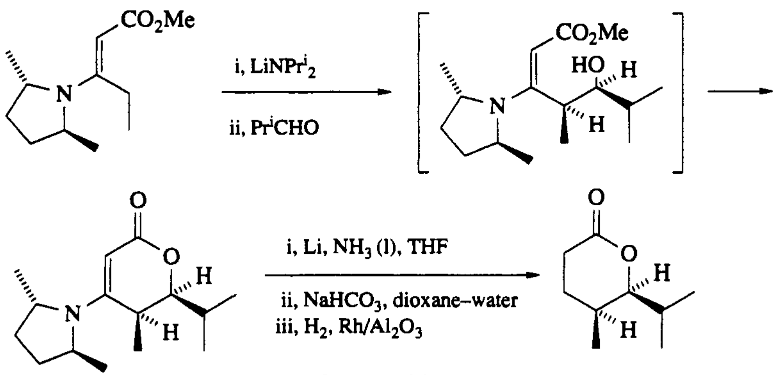

**Scheme 14**

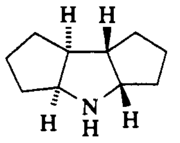

**(2)**

five-membered amine used has the feature that one of the carbons α to nitrogen bears a bulky *t*-butyl substituent that disfavors reaction from one of the two enamine rotamers.

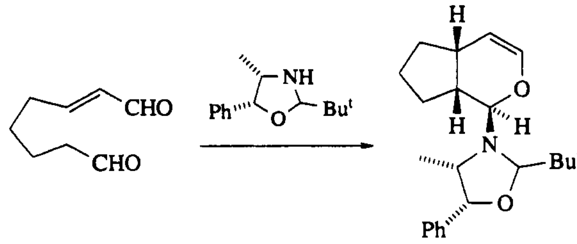

(35)

The most interesting and practical asymmetric induction process that involves enamines is the proline-catalyzed conversion of the prochiral triketone in Scheme 15 to the cyclic aldol condensation product[117] or to the aldol product.[118] The course of the reaction is determined by the presence (or absence) of a strong acid such as hydrochloric acid as a cocatalyst. As a result of both the practical significance of the product(s) as synthetic intermediate(s) and the catalytic nature of this process, there has been a high level of interest directed at establishing the mechanistic pathway for these reactions.[119-124]

The most interesting observation relative to the mechanism of stereochemical control is that the level of asymmetric induction is *not* linear with the enantiomeric excess of the proline catalyst.[124] From these observations it can be concluded that (at least) two molecules of proline are involved at the stage where the stereochemical outcome is determined. While the intermediacy of an enamine is not required by any of the observations made to date on this reaction, it would appear probable.

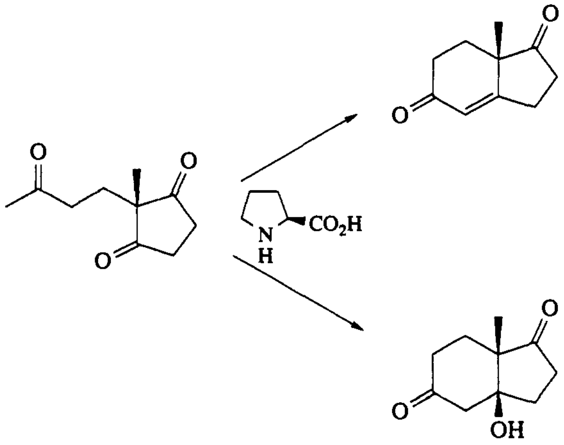

Scheme 15

## 4.1.3 IMINES AND DERIVED ANIONS

Use of imines as synthetic intermediates has been limited to mainly two processes: reduction to amines, and as precursors to azaallyl anions for reaction with a variety of electrophiles (equation 36). The former transformation can often provide the best access to highly substituted amines and the latter represents one of the highest yield methods for carbon–carbon bond formation α to the carbonyl group of an aldehyde or ketone. Thus, the following sections will deal not only with imines but also with the properties and chemical reactions of the derived anions. Several reviews are available (in addition to those that cover both enamine and imine anion chemistry)[15–17] as the result of recently uncovered methods for asymmetric induction through reactions of the anions.[125,126]

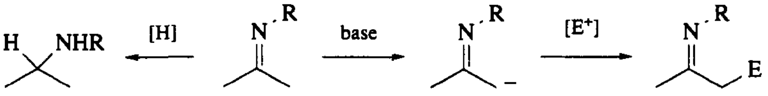

(36)

### 4.1.3.1 Formation

The reaction of a primary amine with a ketone to form an imine is generally quite straightforward, with the techniques typically used for water removal in the formation of enamines (see Section 4.1.2.1) also applicable here. As with the formation of enamines from aldehydes, preparation of the corresponding aldehyde imines can be difficult, especially with relatively unhindered aldehydes where formation of the double amine addition product can occur. However, these aminals often undergo loss of one amine unit thermally (typically during distillation) to generate the imine (Scheme 16).[127]

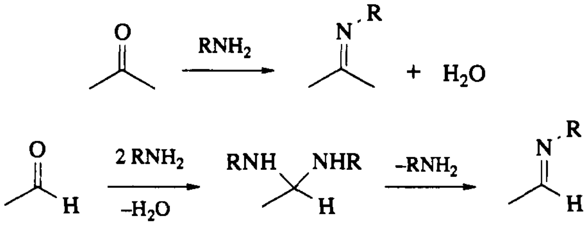

Scheme 16

Reaction of an imine with a strong base represents the most straightforward avenue for the formation of imine anions. The first bases used were lithium dialkylamides and Grignard reagents (equation 37) employed in the seminal studies of Wittig[128] and Stork.[129] The rate of deprotonation with both reagents is relatively low (for example in comparison to the reaction of ketones with dialkylamide bases) and the use of Grignard reagents requires elevated temperatures. Interestingly, the rate of deprotonation of a secondary amine by an alkyllithium is faster than reaction of the alkyllithium with the imine. Thus, the amine can be used in less than stoichiometric amounts.[128] Furthermore, it has been shown that methyllithium acts preferentially as a base with imines, providing little of the addition product.[128]

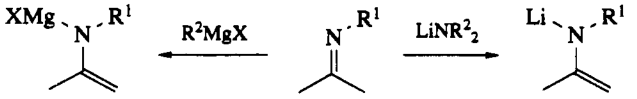

(37)

Formation of an imine from a symmetrical ketone effects a desymmetrization of the two α-carbons. The deprotonation of such imines has been extensively investigated by Bergbreiter and Newcomb.[125,130] In general, there is little observed selectivity for deprotonation by lithium dialkylamide bases, as, for example, with the 3-pentanone imine in equation (38).

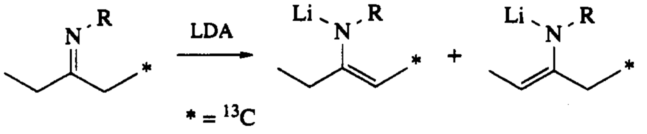

(38)

R = $Bu^t$ 30 : 70

= c-$C_6H_{11}$ 53 : 47

The regiochemistry of deprotonation of imines derived from unsymmetrical ketones is of special significance for the synthetic applications of these anions for carbon–carbon bond formation. This selectivity is sensitive to both the amine moiety and the base used. With imines derived from cyclohexyl- or *t*-butylamine, deprotonation with either Grignard reagents or lithium dialkylamide bases will result in high selectivity (>98:2) for removal of the proton on the less substituted α-carbon as in equations (39)[128] and (40).[131]

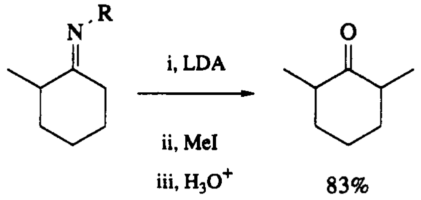

(39)

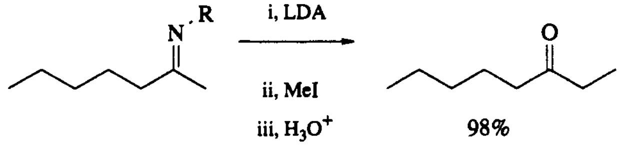

(40)

Conversely, Hosomi and Sakurai have shown that deprotonation with alkyllithium reagents occurs predominantly at the more substituted side of the cyclohexylimine of 2-methylcyclohexanone (equation 41).[132] However, the low yield in this sequence (as compared with, for example, equations 39 and 40) places this route to 2,2-disubstituted systems only equal with other techniques such as those that employ the more stable enolate-derived 2-alkyl cyclic ketones. Further, in no case did deprotonation of an unsymmetrical, acyclic ketone imine with an alkyllithium result in synthetically usable selectivity for the more substituted carbon.

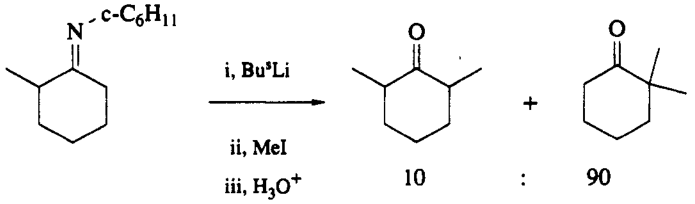

(41)

Knorr has studied both the kinetic and thermodynamic selectivity for the two geometric isomers about the carbon–carbon π-bond system in anions derived from acyclic ketones and aldehydes.[133] Thus, deprotonation of imines at –70 °C with lithium diisopropylamide in THF led to a mixture of (*E*)- and (*Z*)-anions where a small but consistent preference for the former was observed (equation 42). No change was observed upon heating these mixtures at 60 °C, although addition of an excess of the original imine, as a proton source, led to slow but essentially quantitative conversion of the (*E*)- to the (*Z*)-isomer. For the one aldehyde-derived system studied, the (*E*)-isomer was favored. The half-life for this isomerization varied with substituents from less than 10 min to 5 h at room temperature. The half-life for the example given in equation (42) was 30 min. It was also demonstrated that protonation of these anions occurred on nitrogen with apparent kinetic control and that the resulting secondary amine derived enamines were sufficiently stable (relative to rearrangement to the isomeric imines) for spectral analysis.

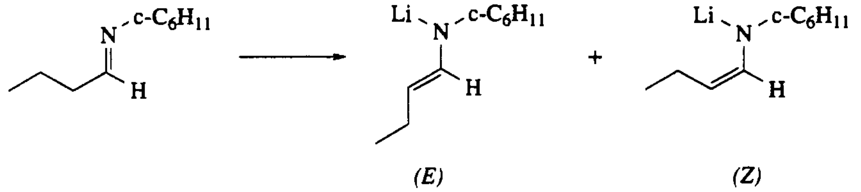

(42)

There are a number of indirect, yet valuable, methods for the preparation of imine anions. The more important of these provide convenient access to regiochemically defined anions, especially those that would otherwise be derived by deprotonation at the more substituted α-carbon. For example, Wender reported that reduction of imines derived from α,β-unsaturated ketones leads to lithium substituted anions, in analogy to the reduction of the ketones themselves (equation 43).[134]

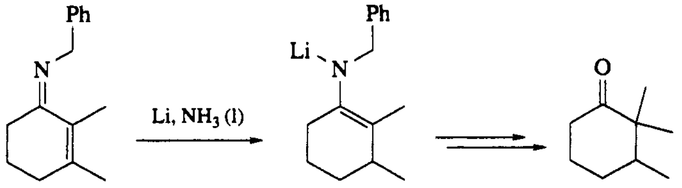

(43)

Imines derived from benzylamine and α,β-unsaturated ketones which represent 1-azadiene systems can be isomerized to the corresponding 2-azadienes with potassium *t*-butoxide. Addition of *t*-butyllithium occurs smoothly to afford simple imine anions that undergo alkylation in the usual fashion.[134,135] The two examples provided in Scheme 17 illustrate the power of this method to provide either α,α- or α,α′-substitution. On the other hand, reaction of similar 1-azadiene systems with Grignard reagents results in addition to form the imine anion directly (equation 44).[136] This example represents one of the early contributions to asymmetric induction in this area and will be elaborated in Section 4.1.3.5.

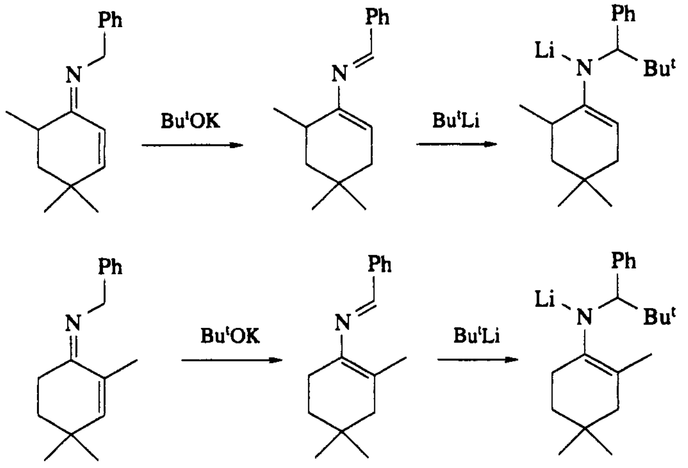

**Scheme 17**

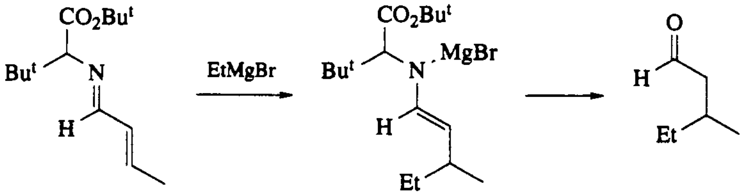
CO2Bu^t
Bu^t
N
H
EtMgBr
CO2Bu^t
Bu^t
N
MgBr
H
Et
O
H
Et

(44)

Martin has provided a useful procedure for geminal disubstitution at the carbonyl carbon of ketones.[137,138] Reaction of, for example, cyclohexanone (equation 45) with a phosphonate anion provides an alternative to Wender's route to 2-azadienes described above.

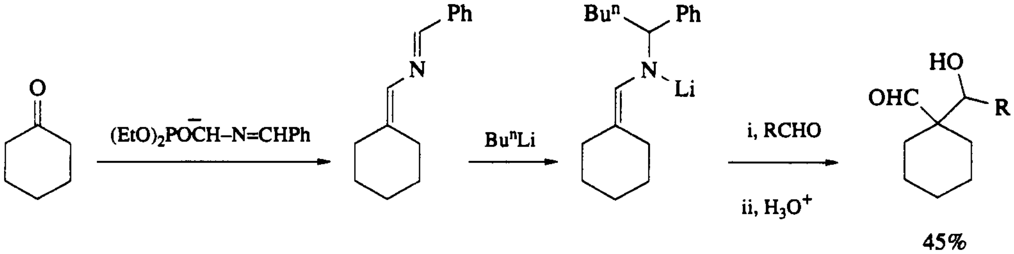
O
(EtO)2POCH-N=CHPh
Ph
N
Bu^nLi
Bu^n
Ph
N
Li
i, RCHO
ii, H3O+
HO
OHC
R
45%

(45)

Bergbreiter and Newcomb have shown that the benzylamine imine of 3-pentanone is deprotonated by lithium diisopropylamide selectively at the benzylic position of a 2-azaallyllithium system that slowly isomerizes by a protonation–deprotonation sequence to afford the 1-azaallyl system (equation 46).[139]

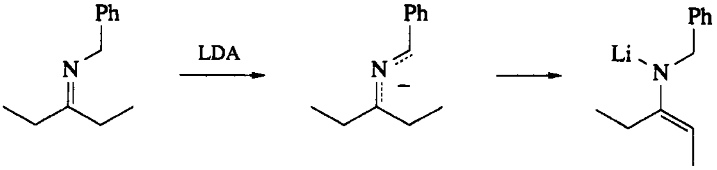
Ph
N
LDA
Ph
N
–
Ph
Li
N

(46)

Stork has demonstrated that, in analogy with enolate chemistry, deprotonation of α,β-unsaturated imines with butyllithium under kinetic control produces the 'cross-conjugated' anion.[140] Conversely, use of slightly less than 1 equiv. of lithium diisopropylamide leads ultimately (by equilibration) to the conjugated system (equation 47).

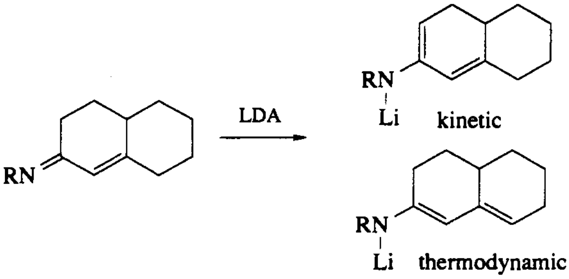
RN
LDA
RN
Li
kinetic
RN
Li
thermodynamic

(47)

Enders[141] has shown that *N*-trimethylsilyl enamines[142,143] [*N*,*N*-bis(trimethylsilyl) enamines have also been prepared[144]] undergo reaction with methyllithium to afford imine anions (equation 48).

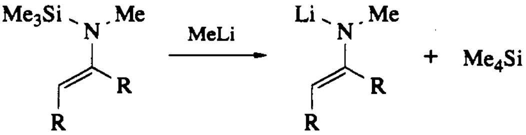
Me3Si
N
Me
R
R
MeLi
Li
N
Me
R
R
+ Me4Si

(48)

### 4.1.3.2 Structure and Chemical Properties

The structures of imines are generally devoid of the subtleties that permeate the same discussion of enamines. While two regiochemically distinct enamines can be derived from unsymmetrical ketones (each with two possible geometric isomers in the case of acyclic ketones), the corresponding imines show only geometric isomerism (equation 49). As would be expected, the preferred isomer is generally that which disposes the substituent on nitrogen *anti* to the larger carbon substituent.

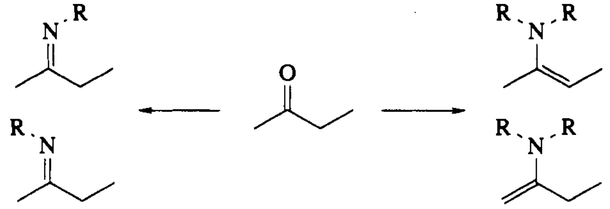

(49)

On the other hand, the conversion of imines to their anions raises issues of regio- and stereo-chemistry (geometric) and is fully as complex an issue as the formation of enamines. The structural analysis of imine anions is further complicated by questions relating to the nature of bonding to the metal. In addition to extensive investigations by NMR spectroscopic techniques (see Section 4.1.3.3.2), there exists one single-crystal X-ray structural determination (Figure 2).[145] Unfortunately, the imine anion is significantly different to those used for synthetic purposes in that the nitrogen is directly substituted with a benzene ring. Thus, the orientations about bonds and the nature of the coordination to lithium that are present in this example may not be of use in explaining the properties and reactions of the imine anions derived from cyclohexyl- and *t*-butyl-amine. Note especially the coordination of lithium to the aromatic ring. The presence of a dimeric structure with two lithium atoms associated with each azaallyl anion unit is consistent with at least some of the spectral studies and is, indeed, quite reasonable. The ultimate usefulness of such ground state structural details to an understanding of the reactions of these species will probably not be resolved in the near future since dissociation pathways can be expected to be rapid. These reactions thus provide pathways for reactions occurring *via* higher energy monomeric species or, conversely, *via* even more highly aggregated clusters.

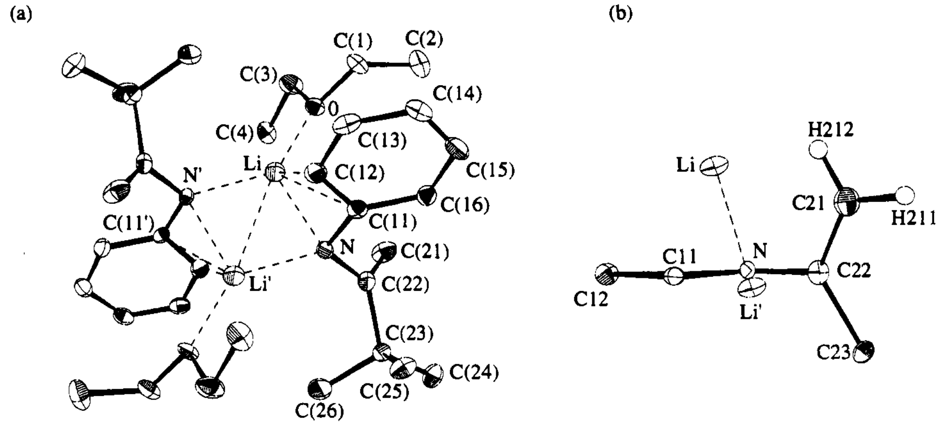

**Figure 2** (a) Molecular structure of the dimer [CH$_2$C=CBu$^t$NPh)Li(OEt$_2$)]$_2$. Ellipsoids correspond to 50% probability. Distances: Li—Li', 2.544(2); Li—N, 2.076(2); Li—N', 2.000(2); Li—O, 1.937(2); Li—C(11), 2.437(2); N—C(11), 1.380(1); N—C(22), 1.436(1); C(22)—C(21), 1.326(1); O—C$_{av}$, 1.443 Å. Angles: Li—N—C(11), 87.28(7); Li—N'—C(11), 119.36(7); Li—N—Li', 77.22(7); N—Li—N', 102.78(7); N—Li—O, 121.93(9); N'—Li—O, 134.7(1); C(22)—N—C(11), 116.61(7)°. (b) Partial structure of the monomer viewing the dimer shown in (a) from the right and along the bisector of the angle C(22)—N—C(11)[145]

A number of investigators have examined the ease of isomerization about the formal carbon–carbon bond in imine anions.[133,146–149] Bergbreiter and Newcomb determined an energy barrier of approximately 17 kcal mol$^{-1}$ for rotation about this bond in both the lithium imine anions derived from cyclohexyl- and *t*-butyl-amine addition to acetaldehyde.[146] The barrier for rotation for the corresponding anion derived from propionaldehyde was approximately 23 kcal $mol^{-1}$. Similar observations for the magnesium anions were made by Koga.[148] On the other hand, theoretical calculations (*ab initio*) by Fraser and Houk provide predicted barriers for the carbon–nitrogen bond of 16 kcal $mol^{-1}$ and for the carbon–carbon bond of 45 kcal $mol^{-1}$.[150]

### 4.1.3.3 Spectral Properties

The unusual regiochemical and stereochemical features that are part of both the formation of imine anions and their subsequent reaction as nucleophiles have spawned considerable interest in deriving details of the bonding, especially of the metal, in these species.

#### *4.1.3.3.1 Infrared spectra*

The carbon–nitrogen double bond behaves in the IR region as would be expected, exhibiting stretching absorptions in the range 1690 to 1640 $cm^{-1}$.[151] No IR spectra for imine anions appear to have been reported.

#### *4.1.3.3.2 Carbon and proton NMR spectra*

$^{13}C$ NMR spectroscopy has served as the major tool for investigating the solution structure of imine anions. Analysis of these spectra is made difficult by the number of possible isomers and by the complication of an unknown state of aggregation. Thus, interpretation of the significance of these various observations and possible application to new systems is best done through reference to the original literature.[141,152–156]

### 4.1.3.4 General Reactions

The two major synthetic applications of imine derivatives of ketones and aldehydes are: (i) for reduction to amines; and (ii) for formation of carbon–carbon bonds at the α-position to the original carbonyl group. Both topics are covered extensively in other volumes in this series and thus will be treated only briefly here.

A variety of reducing agents have been used for the conversion of imines to amines.[157–164] The examples in equations (50)[162,163] and (51)[157] are typical. The relatively slow destruction of sodium cyanoborohydride in slightly acid aqueous solutions allows the process of imine formation to be carried out simultaneously with reduction.[162–164] Apparently, the protonated imine is the species that is reduced and this process occurs significantly faster than reduction of the original carbonyl compound by this reagent. A recent report by Nose indicated that diborane in methanol will reduce only imines and no other functionality.[165] Apparently, the diborane reacts rapidly with methanol to form a derived reagent.

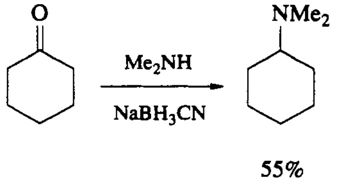

(50)

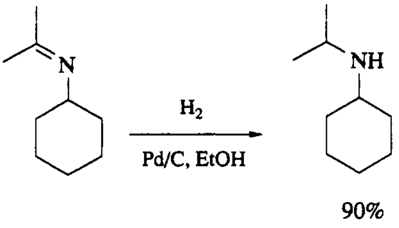

(51)

The alkylation of carbonyl groups through imine anions as the reactive nucleophile often represents (along with the corresponding chemistry of hydrazone anions) the very best procedure for accomplishing carbon–carbon bond formation α to a carbonyl group.[15,17,125,126] Indeed, in those cases where comparisons have been made, both the yield of the process and the level of conversion are superior with imine anions, as compared to reactions using enolate chemistry. The sole exceptions to this general rule are those systems where other functionality prevents the use of the strongly basic conditions required by all methods for formation of the anions. In such cases, enamine alkylation represents the method of choice.

In general, formation of the anion from an imine will occur at the least substituted α-carbon, and thus the overall process of alkylation *via* imine anions is generally limited to substitution at a methylene or methyl group. There are, however, alternative techniques for the formation of these anions that provide some access to more substituted species (see Section 4.1.3.1). It would appear that the comparative success of imine anion alkylations is the result of a comparatively slow rate of proton exchange between the product imine and the anion and to an almost total lack of reaction at nitrogen. Indeed, both of these factors may be the result of the same feature of imine anions that contrasts with corresponding enolates: given heteroatom coordination to the metal from an $sp^2$ lone pair on nitrogen, the remaining unshared electron density is delocalized in the π-system. In contrast, a similar bonding arrangement in enolates leaves one $sp^2$ lone pair 'free' to act as a base or a nucleophile (Scheme 18).

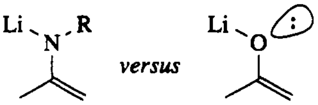

**Scheme 18**

Recently, Hickmott has reported an unusual reaction in which methyl acrylate underwent reaction with the relatively small amount of enamine present in equilibrium with the imine of a 2-methylcyclohexanone.[166] In all cases the major product was the 2,2-disubstituted isomer, although the reaction yields were in general low (13–64%). Previous reports of this unusual carbon–carbon bond forming reaction are rare.[167]

### 4.1.3.5 Stereochemical Features

The synthetic implications of carbon–carbon bond formation *via* imine anions gained additional significance with the first report by Horeau[168] of asymmetric induction in the alkylation of the anion derived from isobornylamine and cyclohexanone.[126] However, the degree of stereochemical control in the formation of 2-methylcyclohexanone by this process (72% *ee*) was below the synthetically useful level. Additionally, incorporation of other alkyl groups afforded even lower levels of asymmetric induction. Further studies by Yamada with a variety of chiral amines did not improve on these results.[169]

Both Meyers[170,171] and Whitesell[172] independently ascribed the less than ideal level of asymmetric induction to the possibility that reaction was taking place from two or more rotamers of the anion and designed chiral amines incorporating a second, oxygen ligand for the metal involved (equations 52 and 53). These ideas came from previous[173] and concurrent[112] activities in each group to design more rigid systems for asymmetric induction. Both of these methods for the alkylation of cyclohexanone afforded improved and practical levels of control and amazingly consistent results given the difference in the metal involved (lithium *versus* magnesium).

Similar studies have been carried out for control of absolute stereochemistry in the alkylation of aldehydes *via* imine anions. Fraser examined the reactions of the imine anion derived from α-phenylethylamine with lithium as the counterion where optimum conditions afforded approximately 70% optical

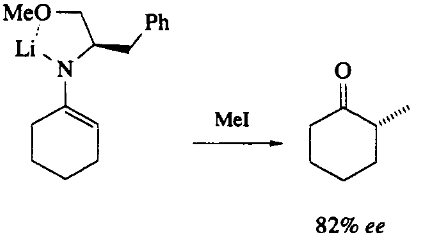

(52)

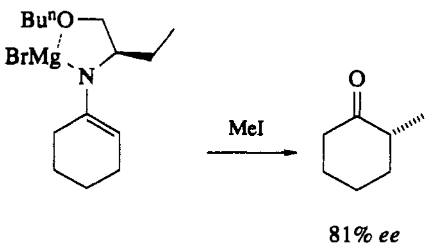

(53)

purities.[174] Meyers extended his studies with chelating chiral auxiliaries and found, surprisingly, that alkylation of octanal afforded optimized levels of control (17 to 54%) inferior to those observed in the alkylation of cyclohexanone.[175] Examination of a range of chelating auxiliaries (all *trans*, vicinal alkoxyaminocyclohexane derivatives) led to improved but still less than practical levels of control (75%).[176]

Other chelating auxiliaries for imine anion alkylation have been developed. Hashimoto and Koga used *t*-butyl esters of the amino acids leucine and valine, where the chelating functionality is presumably the ester carbonyl oxygen.[177,178] Saigo examined the influence of the metal counterion and found large differences, with zinc species providing the highest levels of control with 2-methoxy-1,2-diphenylethylamine as auxiliary.[179] Asymmetric induction in the reactions of imine anions with tin as the counterion has also been examined.[180] McArthur has shown that the chiral auxiliary can be bound to a polymer, thus facilitating recovery for reuse.[181,182]

In an unusual variation, Hashimoto and Koga found that Grignard reagents add to the β-carbon of imines derived from α,β-unsaturated aldehydes (rather than acting as base to form the anions).[183,184] High levels of asymmetric induction (91 to 95%) were observed with the *t*-butyl ester of leucine as the chiral auxiliary (equation 54).

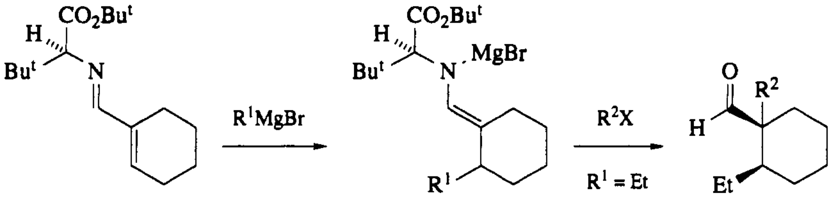

(54)

## 4.1.4 HHYDRAZONES, OXIMES AND DERIVED ANIONS

The synthetic uses of hydrazones and oximes for carbon–carbon bond formation differ little from those of imines as their anions represent enolate equivalents except for certain methods that have been developed for asymmetric induction. Conversely, the formal replacement of the carbon substituent of imines by a heteroatom (nitrogen for hydrazones and oxygen for imines) opens reaction pathways such as the Beckmann rearrangement of oximes and the Wolff–Kishner and Shapiro reductions of hydrazones that have no analogy in the chemistry of imines.

### 4.1.4.1 Formation

Methods for the preparation of hydrazones and oximes differ little from those used for the synthesis of imines from ketones and aldehydes in that the appropriate nitrogen species and the ketone are mixed. However, the equilibrium for the majority of reactions of ketones and aldehydes with hydrazines and hydroxylamine favor the product hydrazones and oximes and removal of the water formed by the condensation is not required.[185,186] Acid catalysis is complicated by the basicity of the reagent and, for example, the maximum rate of oxime formation is at approximately pH 4.[187] Complicating reactions can occur such as the 1:2 combination of hydrazine with two ketones or aldehydes to form azines but this is not a problem with the substituted hydrazines that are used for asymmetric induction.

Of special importance to the applications of hydrazones and oximes to carbon–carbon bond formation is the observation that these derivatives are considerably more resistant to hydrolysis than are either enamines or imines. Thus, methods for mild regeneration of the carbonyl group from these derivatives are especially significant. Among the reagents/systems developed are: oxidation with bromine;[188] reaction with thallium[189] or sodium nitrate in trifluoroacetic acid;[191] reaction with dinitrogen tetroxide;[190] oxidation with periodate;[192,193] and oxidation with *m*-chloroperbenzoic acid.[194]

### 4.1.4.2 Structure and Chemical Properties

Many of the same features of imine and imine anion structure previously discussed (Section 4.1.3.2) are apparent with hydrazones and their anions and with oxime ether anions. A number of investigations of the structure of *N,N*-dialkylhydrazone and oxime ether anions as well as oxime dianions have been carried out, Most notable are the experimental studies of Collum and Clardy,[195–198] and the theoretical treatment by Glaser and Streitwieser.[199,200] As might be expected, and as was observed for lithiated imine anions (*vida supra*), lithiated hydrazones exist in the solid as aggregates, with two lithiums coordinated to the aza anion system (Figure 3).[195]

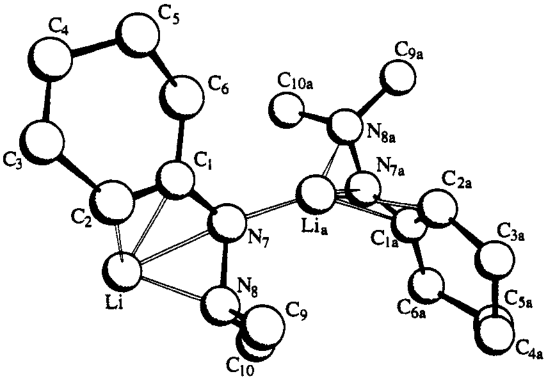

**Figure 3** Molecular structure of the asymmetric unit of lithiated cyclohexanone dimethylhydrazone polymer (hydrogen positions have been left off for clarity)[195]

Note that one of the lithiums is associated with the nitrogen $sp^2$ lone pair, while the other is π-bound to the three atoms of the allylic anion. As with the structure of imine anions, there appears to be no simple answer for the unusual properties of these anions, especially in asymmetric induction, and the interested reader is referred to the original literature.

### 4.1.4.3 Spectral Properties

#### *4.1.4.3.1 Infrared spectra*

A systematic survey of the IR spectra of hydrazones and oximes has been carried out and summarized by Bellamy.[201] Values for the carbon–nitrogen double bond do not differ greatly, and are surprisingly similar for oximes and imines.

#### *4.1.4.3.2 Proton NMR, carbon NMR and ultraviolet spectra*

A very complete treatment of the proton and carbon NMR spectra as well as the UV absorption spectra of *N,N*-dialkylhydrazones has been reported by Grundemann.[202]

### 4.1.4.4 General Reactions

In addition to carbon–carbon bond forming reactions of derived anions, hydrazones and oximes are important derivatives of carbonyl groups for the Beckmann rearrangement (of oximes to amides, equation 55)[203,204] and the Shapiro reaction (tosylhydrazones to alkenes, equation 56).[205,206] Of historical significance is the Wolff–Kishner reduction of ketones *via* their hydrazones (equation 57).[207] The procedure is rarely employed since the conditions of this procedure are considerably harsher than those of more recently developed sequences.

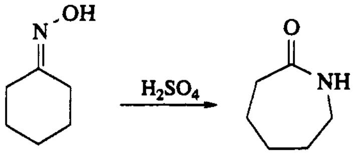

(55)

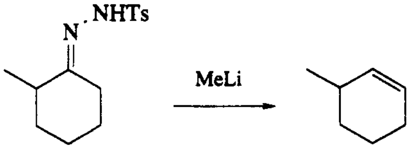

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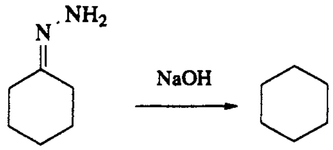

(57)

### 4.1.4.5 Stereochemical Features

The application of hydrazone and oxime anions for carbon–carbon bond formation generally offers no advantages to the use of imine anions and, significantly, the hydrolysis of the hydrazone or oxime products to form the product carbonyl group is substantially more difficult than is the cleavage of an imine. The notable exception is in the area of asymmetric induction where powerful direction has been obtained with chiral hydrazone anions. This area has been explored fully by Enders[208–213] following initial observations of Enders and Corey.[214,215] Enders has recently reviewed these contributions.[211,212]

The basic concept, although most likely not the detailed mechanism, of the Enders asymmetric induction follows from the chelation-controlled asymmetric alkylation of imine anions introduced by Meyers[170,171] and Whitesell.[172] The hydrazones derived from either the (*S*)- or the (*R*)-enantiomer of *N*-amino-2-methoxymethylpyrrolidine (SAMP and RAMP, derived from the amino acid proline) can be converted to anions that undergo reaction with a variety of electrophiles. After hydrolysis of the product hydrazones, the alkylated ketones can be obtained with good to excellent levels of optical purity (Scheme 19).

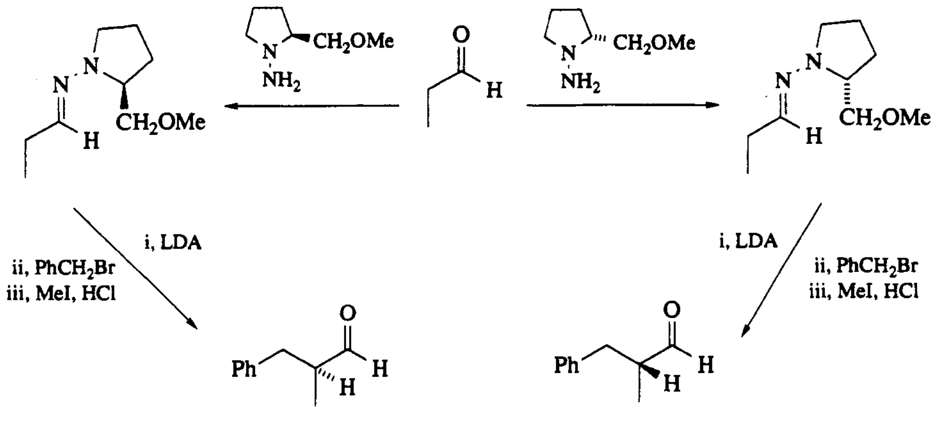

**Scheme 19**

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# 4.2
# Use of Carbonyl Derivatives for Heterocyclic Synthesis

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## 4.2.1 INTRODUCTION

The carbonyl group and its derivatives occupy a central position in synthetic organic chemistry. In the preparation of heterocyclic compounds, they may play a multiple role: they provide the reactive species required for the crucial ring-closing bond formation and, simultaneously, act as valuable sources for the heteroatom in the ring produced.

In view of the vast scope of this synthetic field, the present review is not intended to provide a complete account of this subject, but rather to emphasize certain selected points. As already indicated by the title, only carbonyl derivatives will be dealt with, particularly heteroatom-type or positively charged analogs of carbonyl groups, not carbonyl compounds themselves (unless they serve as starting material for the carbonyl derivatives). In addition, carbonyl derivatives with more than one heteroatom (such as the aldehyde-derived nitrones), which can be utilized for 1,3-dipolar cycloadditions,[1] had to be omitted, due to the restricted space.

For the chosen examples, the, inevitably subjective, emphasis was laid preferentially on the synthetic use of the presented reactions and on their applicability to the synthesis of natural products or other important molecules which prove difficult to synthesize, rather than on mechanistic or theoretical aspects, unless these are essential for the prediction of the chemo-, regio- or stereo-selective outcome of the reaction.

The article is subdivided according to the gross reaction types and the reactive species involved, for the convenience of the reader. Wherever possible, not only the carbonyl derivatives and their reactions are presented, but also modern synthetic trends and strategies which benefit from them.

## 4.2.2 CYCLIZATION REACTIONS INVOLVING NUCLEOPHILIC ATTACK ON CARBONYL DERIVATIVES

### 4.2.2.1 Reactions Involving Imines or Iminium Ions

#### *4.2.2.1.1 Creation of the reactive species and general aspects*

For a long time, iminium ions (**2**; Scheme 1) have been recognized as useful functional groups in the synthesis of important and demanding heterocyclic ring systems. Milder methods of iminium preparation, efficient modern strategies (such as tandem techniques, intramolecular reactions, *etc.*) and the use of attractive new counter-nucleophiles demonstrate the still-increasing value of these nitrogen-containing carbonyl derivatives as indispensible synthetic tools.[2]

Iminium salts (**2**) can commonly be prepared from the reaction of amines with aldehydes or ketones (**1**; Scheme 1). With formaldehyde as the carbonyl precursor, Eschweiler–Clark-type methylation reactions may occur when using reducing acids such as formic acid.[3,4] Alternatively, other $sp^3$-type, nitrogen-free carbonyl derivatives (**3**), such as acetals[5] and hemiacetals,[6,7] can be used, where this is favorable. Highly electron-poor carbonyls, such as chloral (*cf.* Scheme 10),[8] may show distinctly decreased reactivity in aqueous solution, due to the extended hydrate formation.

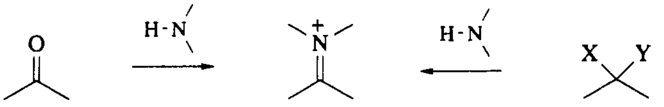

(**1**) (**2**) (**3**) X, Y = OR, OH

**Scheme 1**

Furthermore, iminium ions (**2**) can be generated from enamines (**4**) and imines (**5**), by reaction with electrophiles such as H+ (Scheme 2; for corresponding acylation reactions, see Section 4.2.2.2).[9]

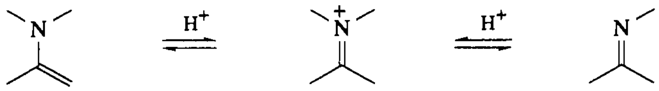

(**4**) (**2**) (**5**)

**Scheme 2**

Other $sp^3$-type, nitrogen-containing carbonyl derivatives (**6**), such as α-amino alcohols,[10] α-amino ethers[11] (*e.g.* oxazolidines[12]), α-amino sulfides (*e.g.* thiazolidines[13]) and α-amino nitriles,[14] are efficient sources for iminium ions (Scheme 3).

Similarly, though not starting from carbonyl precursors, iminium ions can be prepared from tertiary amines (**7**) by oxidative *N*-functionalization and subsequent β-elimination,[15] as employed in the Polonovski reaction (*cf.* Section 4.7),[16] and by decarbonylation of α-amino acids (Scheme 4).[17,18]

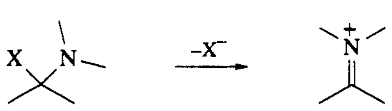

**(6)** X = NR$_2$, OR, CN

**Scheme 3**

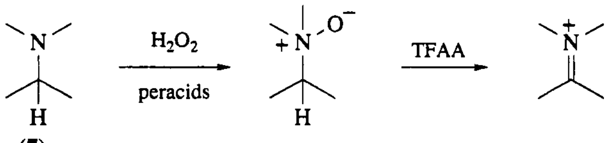

**(7)**

**Scheme 4**

Increasing importance has to be attributed to modern 'tandem' (or 'cascade') techniques—reaction sequences that can be performed as a one-pot procedure because the first reaction step creates the arrangement of functional groups needed for the second to occur. Schemes 5–7 present some *in situ* preparations for iminium species, which can then react further with appropriate nucleophiles that are already present (preferably in the same molecule). Most elegantly, *in situ* generation of iminium ions for tandem processes was performed by a 3,3-sigmatropic (aza-Cope-type) rearrangement (Scheme 5),[19] but also by initial Michael-type addition reactions to vinyl-substituted 1,2,3-tricarbonyls (Scheme 6)[10] or to electron-deficient alkynes *via* enamines (Scheme 7).[20]

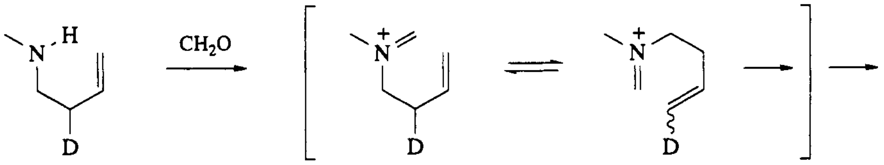

D = donor substituent

**Scheme 5**

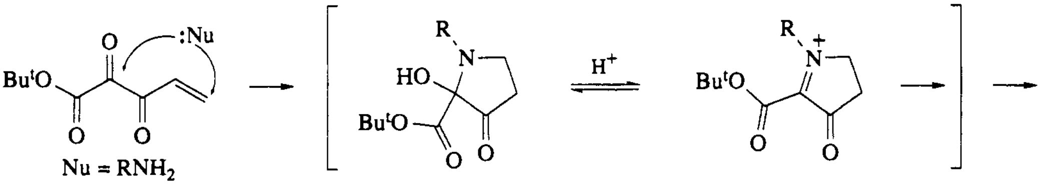

**Scheme 6**

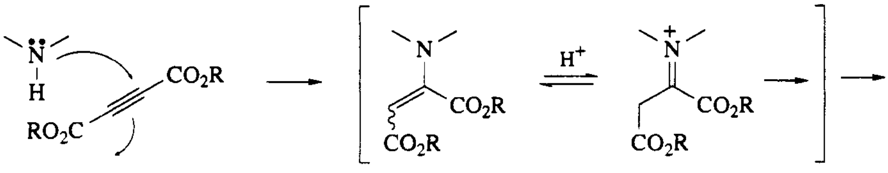

**Scheme 7**

Iminium cations are comparatively weak electrophiles and consequently require quite reactive nucleophiles. This limitation offers the advantage that intramolecular reactions, which lead to heterocyclic ring systems, are strongly favored over intermolecular ones.

### *4.2.2.1.2 Cyclization reactions*

#### *(i) With aromatic nucleophiles*

The most prominent intramolecular reaction of iminium ions with aromatic C-nucleophiles is the long-known Pictet–Spengler condensation[21] of 2-phenylethylamines (**8**) with reactive carbonyl compounds (**9**)—by far the most important route to natural and synthetic tetrahydroisoquinolines (**10**; Scheme 8).

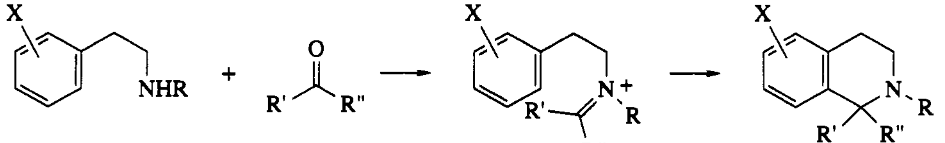

**(8)** **(9)** **(10)**

**Scheme 8**

Plants have taken advantage of this successful synthetic principle for their enzymatic production of isoquinoline[22] (as well as β-carboline[23]) alkaloids.[24] In the chemical laboratory, this synthetic approach has been exploited for nearly 80 years in numerous biomimetic-type syntheses.[25] This special form of the Mannich reaction requires electron-rich aromatics, if possible with free phenolic oxygen functions in *ortho* or *para* positions (Scheme 9). As for the carbonyl compound, aldehydes or 1,2-dicarbonyls (and very recently 1,2,3-tricarbonyls[26,27]) are preferred. Due to the mild 'physiological' reaction conditions required with such ideally reactive partners (often pH = 7, room temperature, aqueous medium), this condensation was also found to play a role in human organisms, leading to endogenous 'mammalian alkaloids'.[28,29,22]

Pictet–Spengler reactions with dopamine-type 2-arylethylamines (**11**) usually proceed with high regioselectivity, *para* to the activating group, thus leading to 6,7-dihydroxytetrahydroisoquinolines (**12**; Scheme 9). Only for smaller aldehydes, especially formaldehyde (R = H), have appreciable amounts of *ortho*-cyclized products (**13**) been reported, especially at neutral pH.[30]

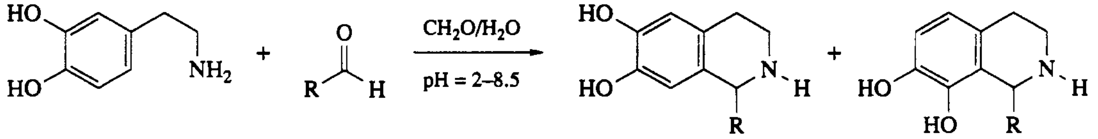

**(11)** **(12)** **(13)**

| *R* | *pH* | *Ratio (12):(13)* |
|---|---|---|
| H | 2 | 87:13 |
| H | 7 | 50:50 |
| Me | 2 | 100:0 |
| Me | 7 | 75:25 |

**Scheme 9**

Some aldehydes require special reaction conditions, *e.g.* chloral (**14**), which, due to extended hydration, does not undergo a Pictet–Spengler reaction with dopamine (**11**) in aqueous solution but can be condensed very efficiently in organic acids, such as trifluoroacetic acid, to give the 1-trichloromethyltetrahydroisoquinoline (**15**) in high yield (Scheme 10).[8]

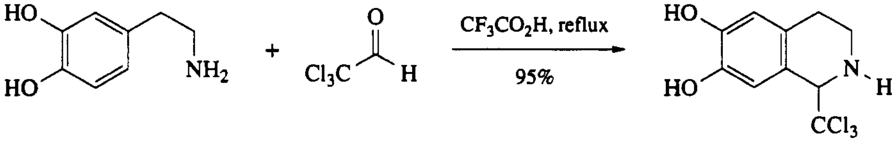

**(11)** **(14)** **(15)**

**Scheme 10**

Furthermore, nonaqueous, especially nonprotic, solvents allow Pictet–Spengler condensation reactions to occur with acid-labile aldehydes[31] (*e.g.* when bearing additional acetal functions) and may significantly influence the stereoselectivity (see below).

Isotope-labeling experiments and the secondary formation of regioisomers show that the Pictet–Spengler condensation may be reversible under more vigorous conditions.[32]

Starting from (3-indolyl)-2-ethylamines (**16**), such as tryptamine, and aldehydes (**17**), the Pictet–Spengler reaction has been broadly extended to the synthesis of tetrahydro-β-carbolines (**18**), the most important synthetic access to such indole alkaloids (Scheme 11). Early findings[33–36] and newer results[37] suggest an initial attack of the iminium salt (**19**) at the reactive 3-position (Scheme 11), rather than the expected 'direct' ring closure at C-2. The intermediate spiroindolenine (**20**) (which can be trapped by *in situ* hydrogenation[38]) is thought to undergo a Wagner–Meerwein-type rearrangement to (**21**).

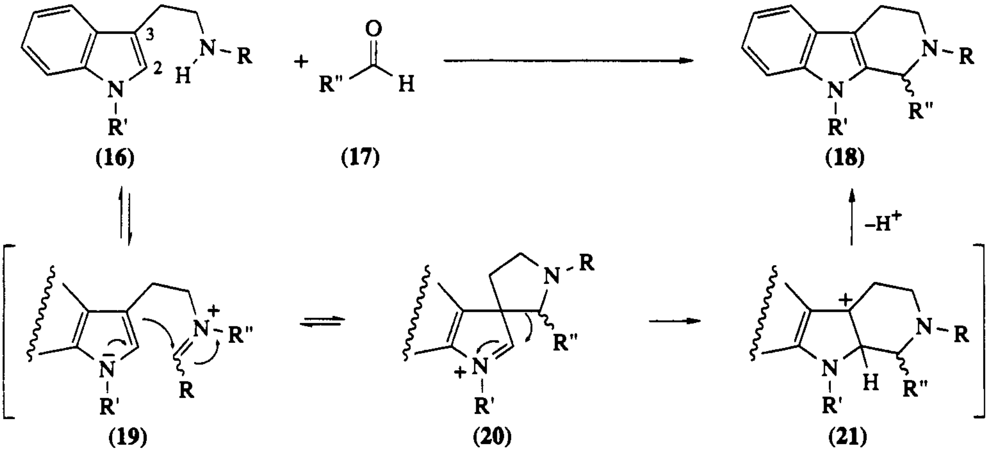

**Scheme 11**

In view of the multifold important biological activities[39] of isoquinoline and β-carboline alkaloids, increasing efforts have been made to perform Pictet–Spengler reactions stereoselectively. The most obvious chiral auxiliary to induce asymmetric control is the stereogenic center of the corresponding aromatic amino acids, such as DOPA or tryptophan.

Thus, at low temperatures, tryptophan esters (**22**) with nonalkylated, primary amino functions condense with aldehydes to give tetrahydro-β-carbolines with predominantly *cis* configuration (Scheme 12).[40] At higher temperatures, *e.g.* in refluxing benzene, the diastereomeric ratio is reversed, giving mainly the *trans* product. Under these thermodynamically controlled conditions, however, extended racemization may become an additional serious problem.

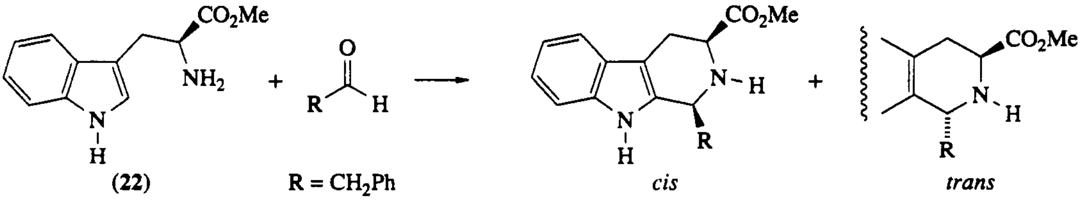

| *Temperature* | *Solvent* | *Yield (%)* | *cis/trans ratio* | *ee (%)* |
|---|---|---|---|---|
| 0 °C | $CH_2Cl_2$ | 74 | 82:18 | 90 |
| 40 °C | $CH_2Cl_2$ | 72 | 45:55 | |
| r.t. | Benzene | 65 | 78:22 | |
| 80 °C | Benzene | 76 | 37:63 | 11 |

**Scheme 12**

For an efficient, directed synthesis of *trans*-tetrahydro-β-carbolines such as (**24**), hydrocarbyl (*e.g.* benzyl) substituents at the amino function[41] and at the pyrrole nitrogen of the tryptophan ester, as in (**23**), are favored (Scheme 13).[42] Under kinetically controlled nonacidic conditions, small amounts of the corresponding *cis* isomer (**25**) are formed.[43] The latter can be completely converted into the *trans* product (**24**) by heating in methanolic HCl (1%). Alternatively, the Pictet–Spengler reaction can be carried out directly in an acidic medium, obviously under thermodynamic control (to give *trans* products almost exclusively).[42] Moreover, under these reaction conditions, the *N*-benzyl group allows a complete retention of optical purity, as the epimerization occurs at C-1 solely, not at C-3.

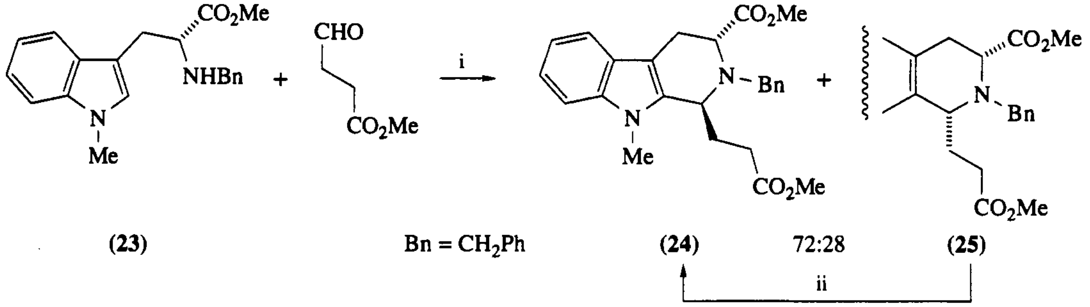

i, PhH, Δ, 10 h, 90%; ii, MeOH–HCl, Δ

**Scheme 13**

On the basis of a rapid and reversible[44] spiroindolenine mechanism, a pathway for the Pictet–Spengler reaction was proposed recently, which is consistent with all these stereochemical findings.[45]

The amino acid derived carboxy group can be utilized as a functionality for further synthetic manipulations, *e.g.* for cyclization reactions to 1,3-bridged β-carbolines, using the Dieckmann reaction, a promising stereocontrolled approach to macroline-related alkaloids (Scheme 14).[43,46]

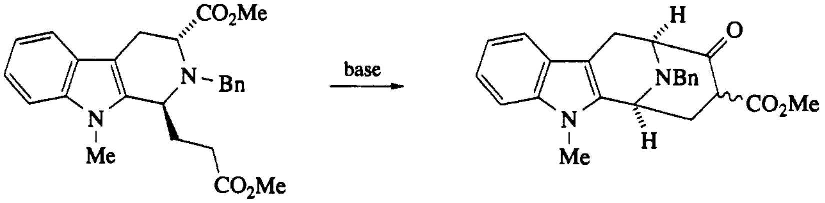

**Scheme 14**

Alternatively, after having governed the stereochemistry at C-1, the carboxy group at C-3 can be eliminated (Scheme 15), *e.g.* according to Yamada's method.[47,48] Such as overall enantioselective synthesis of optically pure 1-alkyltetrahydro-β-carbolines from the 'chiral pool', optionally with (*R*) or (*S*) configuration, has been applied in numerous indol alkaloid syntheses.[49–51]

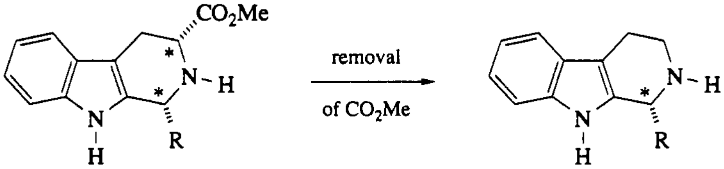

**Scheme 15**

A regio- and stereo-controlled Pictet–Spengler reaction in the field of tetrahydroisoquinolines is the condensation of the secondary amine (**26**) with acetaldehyde (Scheme 16). At pH 11.5, the *trans* product (**27**), with the free phenolic OH-group at C-6, a key intermediate in the total synthesis of the naphthylisoquinoline alkaloid (–)-ancistrocladine (**28**),[52–54] is obtained in good yield.[55] This yield can be further upgraded by epimerization at C-1 of the analogous *cis* diastereomer (6.5%). Alternatively, the corresponding 6-methoxy-8-hydroxy regioisomer, which was required for the first total synthesis of the related alkaloid ancistrocladisine,[56] can be attained as the main product by running the reaction at pH 2.[55]

Besides these influences exerted by C(3)- and N-substituents, asymmetric induction may also be achieved by the use of chiral aldehydes. Thus, reaction of dopamine (**11**) with (*R*)-(+)-glyceraldehyde (**29**) affords the tetrahydroisoquinoline (**30**) in excellent yield (93%) and high diastereoselectivity (9:1; Scheme 17).[57] The broader synthetic applicability of this approach is exemplified by the oxidative cleav-

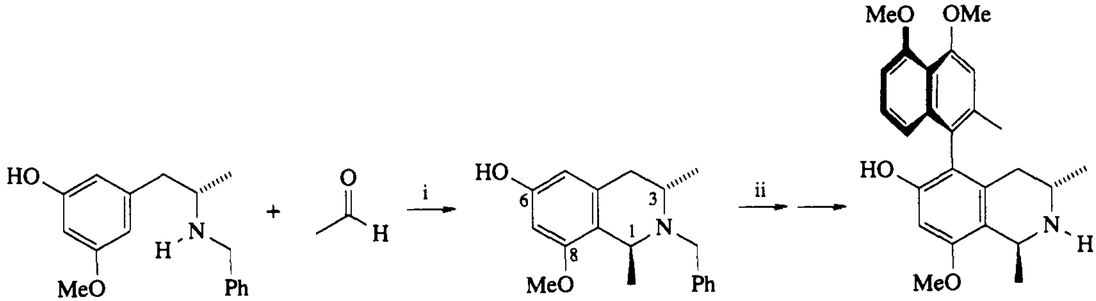

HO
MeO
H
N
Ph
+
O
H
i
HO
6
3
1
8
N
MeO
Ph
ii
MeO
OMe
HO
N
H
MeO

**(26)** **(27)** **(28)** (–)-Ancistrocladine

i, $H_2O/Pr^iOH$ (2:1), pH = 11.5, 78%; ii, regio- and stereo-selective aryl coupling

**Scheme 16**

age of the chiral auxiliary and the subsequent transformation into various optically active alkaloids, such as (*S*)-(–)-carnegine (**31**).[57]

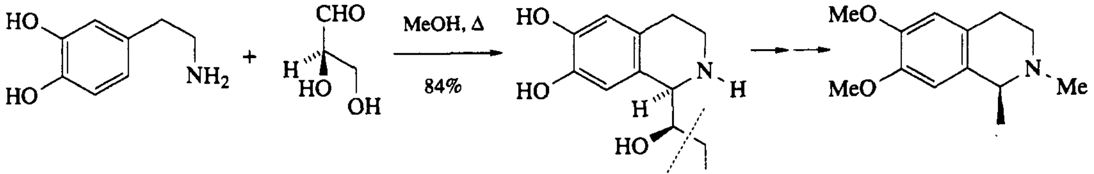

HO
HO
$NH_2$
+
CHO
H
HO
OH
MeOH, Δ
84%
HO
HO
N
H
H
HO
OH
MeO
MeO
N
Me

**(11)** **(29)** **(30)** **(31)** (*S*)-(–)-Carnegine

**Scheme 17**

Several modifications of the Pictet–Spengler reaction have been developed.[58] From these, only two, both relying on iminium salt generation from intermediate enamines, will be presented here. The first one is the acid-catalyzed cyclization of the dienamine (**32**), which is one of the key steps in an elegant total synthesis of (+)-geissoschizine and related alkaloids (Scheme 18).[59] As in previous similar cases,[50] the tryptophan-derived amide function governs the stereochemical outcome at C-1 much more efficiently than the analogous ester group. After the stereocontrolled ring closure, the amide can be removed by reduction of the corresponding nitrile.

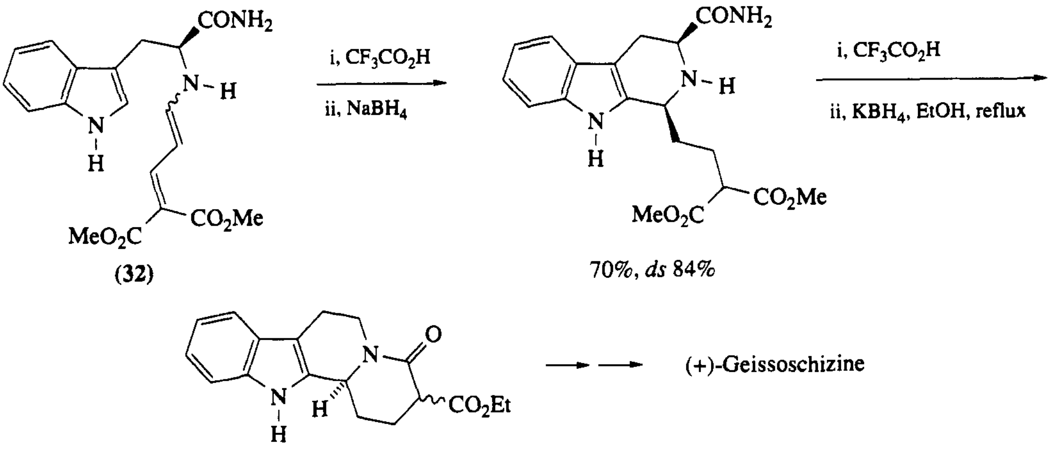

$CONH_2$
N
H
N
H
$MeO_2C$
$CO_2Me$
(32)
i, $CF_3CO_2H$
ii, $NaBH_4$
$CONH_2$
N
H
N
H
$MeO_2C$
$CO_2Me$
70%, *ds* 84%
i, $CF_3CO_2H$
ii, $KBH_4$, EtOH, reflux
N
H
H
N
O
$CO_2Et$
(+)-Geissoschizine

**Scheme 18**

The second procedure worth presenting involves the Michael addition of tryptophan ester (**22**) to propynoate ester (**33**; R = H) to give (**34**; R = H), and subsequent acid-induced cyclization *via* the iminium salt (**35**; R = H; Scheme 19),[60,61] to afford tetrahydro-β-carboline (**36**; R = H), which could not be prepared by the 'simple' Pictet–Spengler reaction with malonic hemialdehyde.[20] Again, asymmetric induction can be achieved through the amino acid derived ester function. Extension of this procedure to dimethyl butynedioate (**33**; R = $CO_2Me_3$) lowers the diastereoselectivity (Scheme 19), but simultaneously strongly enhances the reaction rate and the yield, and gives rise to 1,1-disubstituted (formally, ketosuccinic acid derived) tetrahydro-β-carbolines (**36**; R = $CO_2Me_3$), which are key intermediates for the synthesis of alkaloids of the ajmaline group.

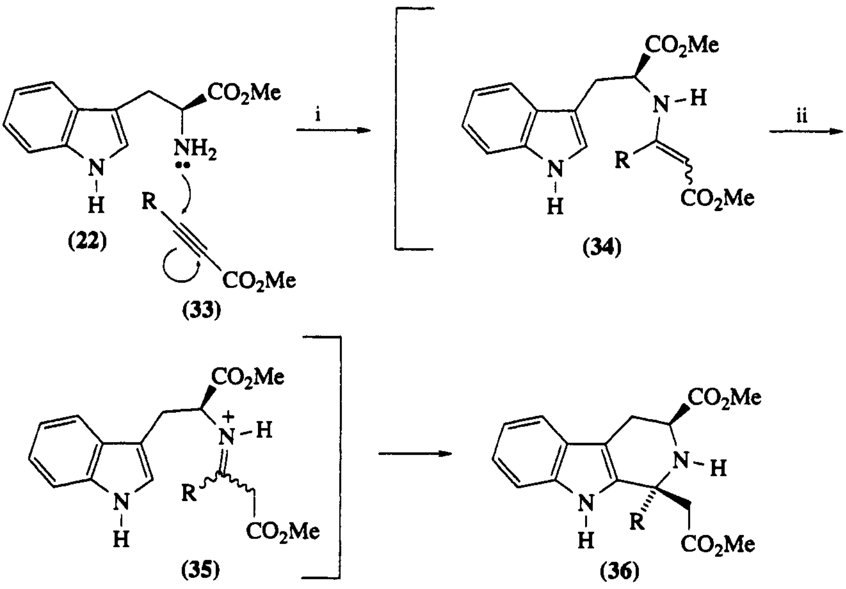

i, $CHCl_3$, r.t.; ii, TFA/$CHCl_3$, r.t.; 50%, *ds* 71% (R = H); 91%, *ds* 68% (R = $CO_2Me$)

**Scheme 19**

*(ii) With vinylic and alkynic C-nucleophiles*

Under the assistance of external nucleophiles, simple, nonactivated alkenes can undergo intramolecular attack to give nitrogen-containing heterocyclic compounds, *via* the iminium salt.

Alkynes are more susceptible than alkenes to external soft nucleophiles, as demonstrated in the reaction of (**37**) with formaldehyde, where an excess of NaI dramatically changes the cyclization mode (Scheme 20).[62]

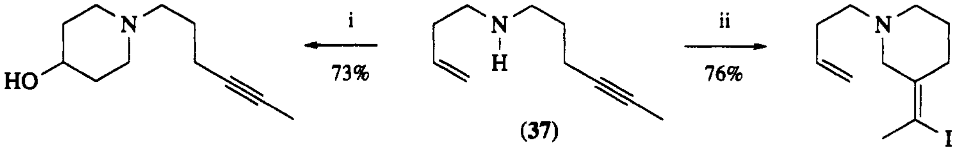

i, $CH_2O$, $H_2O$, camphorsulfonic acid (CSA); ii, as in i, excess NaI

**Scheme 20**

Starting from homoallylic amines (such as **38**; Scheme 21) and, for example, formaldehyde, the initially formed iminium species (**40**) may, before cyclizing to (**39**), suffer a rapid charge-accelerated 3,3-sigmatropic rearrangement to (**41**), the relevance of which was shown by reductive trapping.[63] More recent investigations with related optically active substances show that, depending on the electronic nature of the substrate, cyclization may occur with or without a preceding aza-Cope rearrangement.[64]

On the basis of this rearrangement, an efficient synthetic route to pyrrolidines such as (**46**) was developed by Overman, starting from oxazolidine (**42**), *via* hydroxylated homoallylic imines such as (**43**; Scheme 22).[19] Mechanistically, the formation of (**46**) may be explained as a tandem-type combination of a cationic aza-Cope rearrangement with a subsequent Mannich cyclization (route a) or, alternatively, as an alkene–iminium ion cyclization/pinacolic rearrangement sequence (route b).

Some evidence for the mechanism being reaction mode (a) comes from the conversion of optically active oxazolidine (**42**) to a racemic mixture of pyrrolidine (**46**; Scheme 22),[19] obviously *via* the achiral intermediate (**44**), since in a pinacolic-type rearrangement *via* (**45**), the chiral information would have been

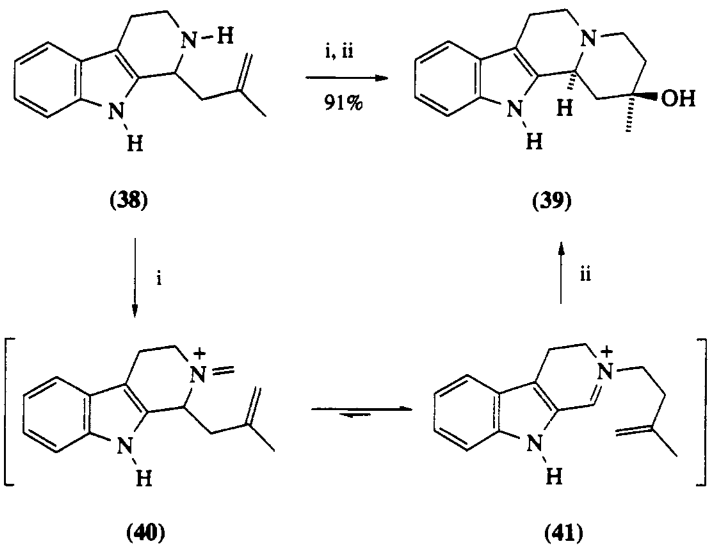
N-H
N
H
i, ii
91%
N
N H
H
OH
(38)
(39)
i
ii
+
N=
N
H
+
N
N
H
(40)
(41)

i, AcOH/$H_2O$, formalin, 3 h, r.t.; ii, $H_2O$, 24 h, r.t.

**Scheme 21**

expected to be conserved. In consequence, this example reveals the limited stereochemical use of this strategy for the synthesis of enantiomerically pure compounds.

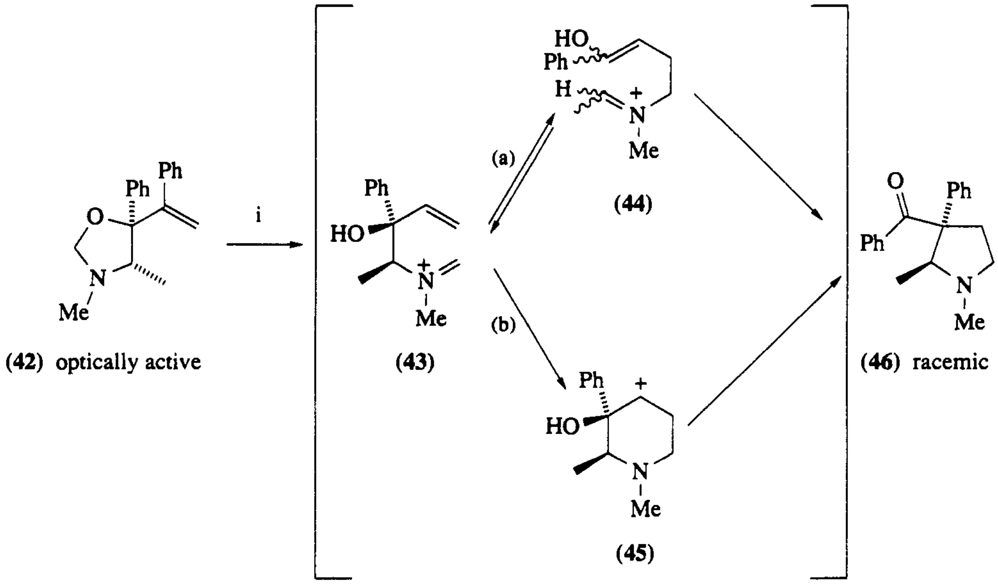
Ph
Ph
O
N
Me
(42) optically active
i
Ph
HO
+
N
Me
(43)
(a)
(b)
HO
Ph
H
+
N
Me
(44)
Ph +
HO
N
Me
(45)
O
Ph
Ph
N
Me
(46) racemic

i, toluene, CSA, 60 °C, 1.5 h

**Scheme 22**

On the other hand, the alkaloid (–)-crinine (**47**) can be prepared in enantiomerically pure form by a similar approach (Scheme 23),[12,65] possibly due to the different reaction conditions applied or because of the additional chiral *N*-phenylethyl residue. This method also applied very well for other nitrogen-containing heterocycles,[66] including other ring sizes.

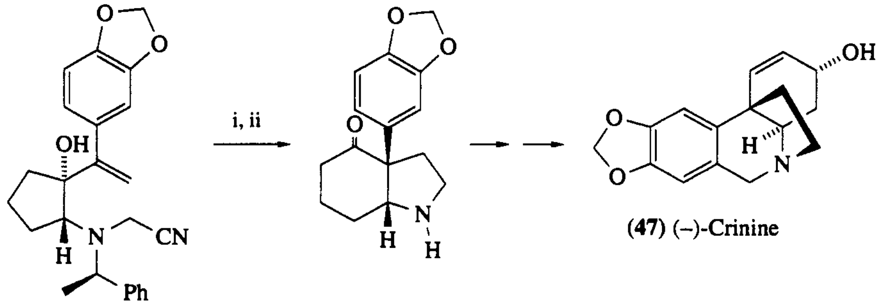

(47) (–)-Crinine

i, $AgNO_3$, EtOH, 25 °C, 3 h, 80%; ii, ammonium formate, Pd/C, 100 °C, 0.5 h, 94%

Scheme 23

During the last few years, silyl-substituted alkenes in particular have emerged as potent 'terminators' for regio- and stereo-selective iminium ion initiated cyclization reactions.[67] In principle, such ring closure reactions proceed either in an endocyclic (types a and c) or exocyclic fashion (type b)[68] with respect to the terminating alkene, and in an endocyclic (types a and b) or exocyclic mode (type c) with respect to the iminium function (Scheme 24), with the C=C double bond being retained in its place and the silyl group substituted with retention of configuration.

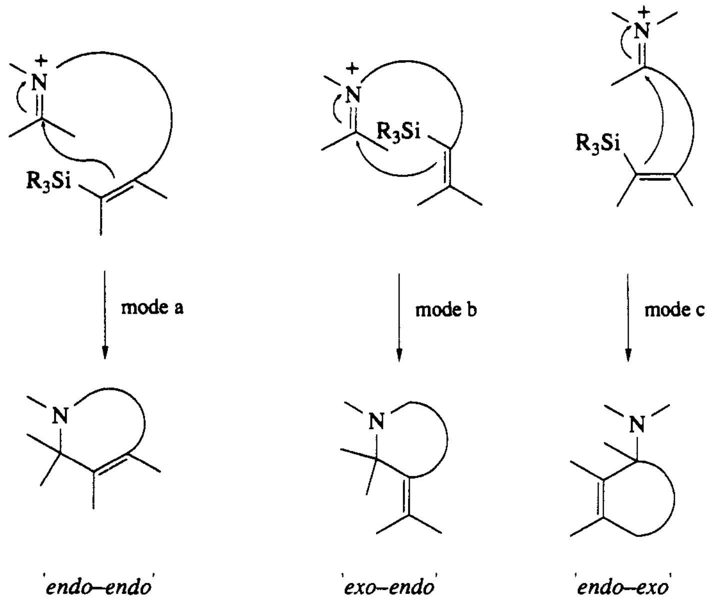

Scheme 24

Correspondingly, this stereospecificity may inevitably require the correct configuration to exist in the starting material, as illustrated by comparative reactions of the diastereomeric vinylsilanes (**48**) and (**50**; Scheme 25).[69] While (**48**) smoothly cyclizes to give the hexahydroindole (**49**), reaction of (**50**) completely fails, proceeding at least 7000 times more slowly. This can be rationalized by considering the geometry of the ring-closed species (**52**) that is primarily formed. For steric reasons, only the β-silyl carbenium ion (**52**), as obtained from the (*Z*)-isomer (**51**), can profit from the 'β-effect', the typical stabilizing interaction of the empty carbenium *p*-orbital with the C—Si σ-bond.

The reverse case, a cyclization in an endocyclic fashion with respect to the iminium salt and in an exocyclic way with respect to the vinylsilane part, is represented by the first enantioselective synthesis of (+)-pumiliotoxin A (Scheme 26), which establishes, for the first time, the complete stereostructure of this famous cardiac-active poisonous alkaloid obtained from frogs.[70] The key step, the impressively stereo-

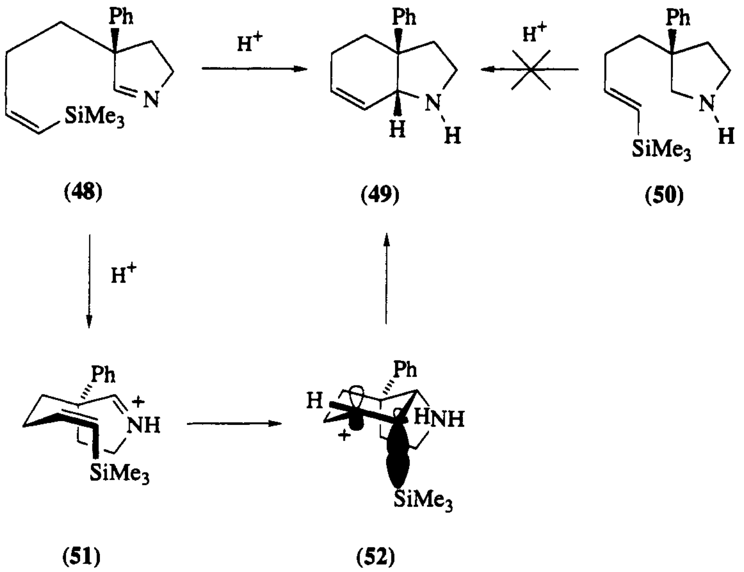
Ph
SiMe3
N
H+
H
(48)
(49)
(50)
(51)
(52)
HNH
NH
+

Scheme 25

specific conversion of (**53**) into the alkylideneindolizidine (**54**), with the correct (*Z*)-configuration at the exocyclic double bond, is performed under near neutral conditions. Another impressive example is the stereocontrolled total synthesis of the indole alkaloid (+)-geissoschizine.[59]

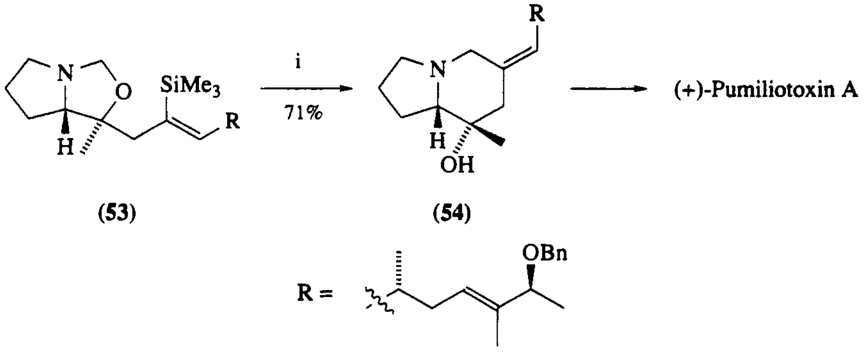
SiMe3
R
i
71%
N
O
H
OH
(+)-Pumiliotoxin A
(53)
(54)
R =
OBn

i, pyridine–TsOH, MeOH, pH ≈ 4.5, 80 °C

Scheme 26

Trialkylsilyl groups may assist imine-initiated cyclization reactions as alkylic as well as vinylic substituents. Thus, in the presence of desilylating reagents, such as $Bu_4NF$ or LiI, the allylsilane (**55**) is cyclized diastereoselectively to give the 2,6-disubstituted *cis*-4-methylenepiperidine (**56**), which can be dehydrogenated to give the aromatic pyridine (**57**; Scheme 27).[71]

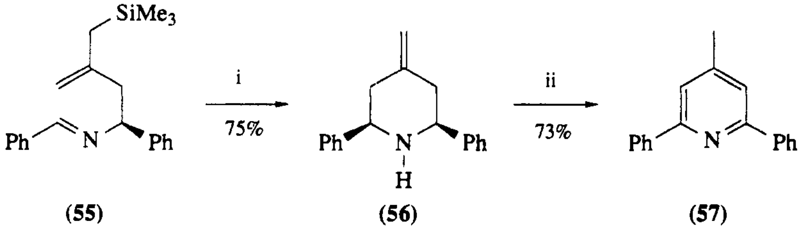
SiMe3
Ph
N
i
75%
ii
73%
H
(55)
(56)
(57)

LiI, THF, 40 °C; ii, $Hg(OAc)_2$, AcOH, Δ

Scheme 27

*(iii) With heteroatom nucleophiles*

Far less important for the synthesis of important molecular frameworks are cyclization reactions involving attack of heteroatom nucleophiles on carbonyl derivatives, since these reactions are not concerned with carbon–carbon bond formation but rather with transforming the carbonyl derivatives into other carbonyl derivatives, such as the reductive cyclization of (**58**) to give the cyclic *O,N*-acetal (**59**; Scheme 28).[72]

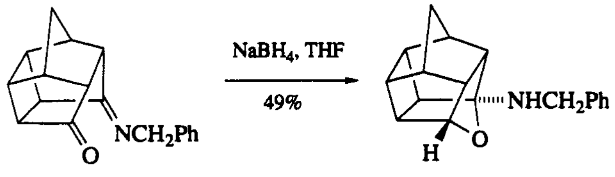

**(58)** **(59)**

**Scheme 28**

### 4.2.2.2 Reactions Involving Acyliminium Ions

#### *4.2.2.2.1 Creation of the reactive species and general aspects*

*N*-Acylated iminium ions have gained increasing importance in the past few years.[73] As the less electron-rich counterparts of the aforementioned 'softer' iminium ions, they offer strongly enhanced reactivities towards nucleophiles, combined with the attractive possibility of introducing additional functionalities (*e.g.* the amide group) into the desired heterocycles.

The $sp^2$-type hybridized ionic acyliminium species (**60**) are in chemical equilibrium with the corresponding covalently bound $sp^3$-type species (**61**; Scheme 29).[74]

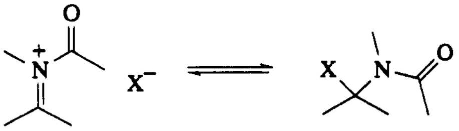

**(60)** **(61)** X = OR, OH, Hal, *etc.*

**Scheme 29**

In analogy to the synthesis of iminium salts (Section 4.2.2.1.), acyliminium ions (**60**) can be obtained from carbonyl precursors (**1**), such as ketones or aldehydes, and carboxylic acid amides (**62**; Scheme 30). In addition, other amides can be used, such as *p*-toluenesulfonamides, which lead to the corresponding *N*-tosylated iminium salts.[75]

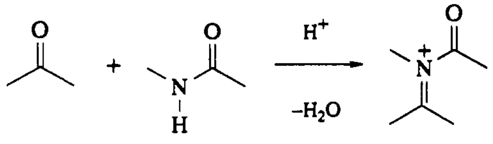

**(1)** **(62)** **(60)**

**Scheme 30**

Acyliminium ions can also be created by treatment of the easily accessible enamides (**63**) with protic acids (Scheme 31; see also Section 4.2.2.1). Alternatively, transformation of enamides (**63**) to (**60**) can be achieved with C-electrophiles, by simultaneous formation of carbon–carbon bonds (*cf.* Scheme 37).[76]

In contrast, considerably less importance can be attributed to the comparable preparation of (**60**) from acylimines (**64**; Scheme 31), by protonation for example,[77] due to their usually pronounced instability,

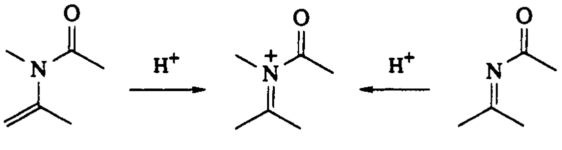

**(63)** **(60)** **(64)**

**Scheme 31**

for which only few exceptions have been described.[78,79] Acyliminium ions (**60**) can also be generated by *N*-acylation of imines (**5**), *e.g.* with acyl halides (**65**; Scheme 32).

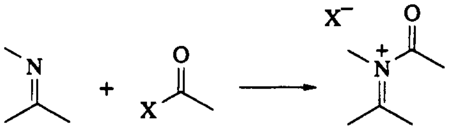

**(5)** **(65)** **(60)** X = Hal

**Scheme 32**

The preparation of acyliminium ions is not restricted to aldehyde or ketone derivatives as starting materials, but can also use the more highly oxidized carboxylic acid amides as precursors, *e.g.* reduction of imides (**66**) affords (**67**; Scheme 33).[80,81] For constitutionally unsymmetrical imides, regiocontrol can be achieved in many cases by the choice of the appropriate hydride-transfer reagent.[82]

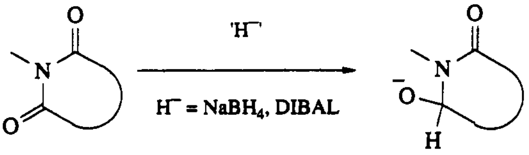

**(66)** **(67)**

**Scheme 33**

Similarly, addition of C-nucleophiles 'R⁻'[83] (such as Grignard reagents) to cyclic imides (**66**) leads to acyliminium ions, *via* their $sp^3$-type precursors (**68**; Scheme 34). Again, regioselectivity is observed for unsymmetrical imides, which are attacked preferably at the less-hindered carbonyl group.[84] A disadvantage of this procedure may be seen in occasional side reactions, such as ring opening or over-alkylation.

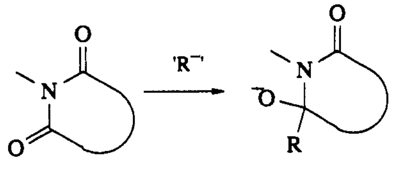

**(66)** **(68)**

**Scheme 34**

Other oxidative methods have been mentioned,[85,86] such as the transformation of enamides (**63**) to α-hydroxylated acyliminium salts (**70**), *via* the hemiaminals (**69**).[87]

Compared with the simple iminium ions, the enhanced reactivity of acyliminium salts opens up a greatly enlarged spectrum of counter-nucleophiles, which now includes alkenes and aromatic compounds possessing no donor substituents (see Section 4.2.2.2.2).

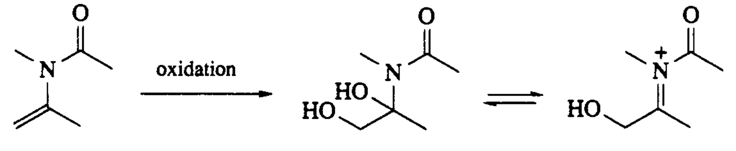

**(63)** **(69)** **(70)**

Scheme 35

### 4.2.2.2.2 Cyclization reactions

*(i) With aromatic carbon nucleophiles*

'Normal' Pictet–Spengler-type cyclization reactions of 2-arylethylamines and reactive carbonyl compounds require activated aromatic systems, ideally with unprotected phenolic oxygen functions in *ortho* and *para* positions (Section 4.2.2.1). The high reactivity of acyliminium salts, however, allows very effective analogous ring closure reactions, even for the oxygen-deficient 2-phenylethylamine *via* its formamide (**71**), which may be prepared *in situ* (Scheme 36).[88] Similar tetrahydroisoquinoline syntheses were achieved in good to excellent yields *via* the corresponding tosylamides.[75]

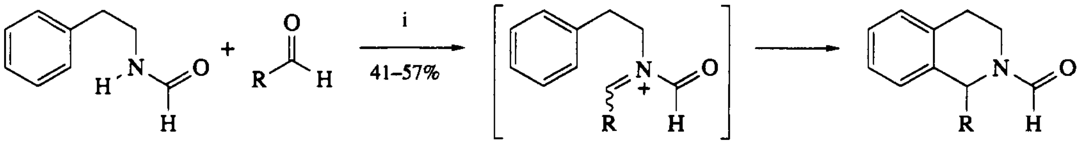

**(71)**

i, AcOH/TFA, 5–10 h, Δ; R = H, Me, Ph, 4-$O_2NC_6H_4$

Scheme 36

In a very elegant tandem-type combination of such a modified Pictet–Spengler condensation and an initial Pummerer reaction (*e.g.* Section 4.2.2.4), the polycyclic framework (**75**) of the erythrina alkaloid (**76**; Scheme 37) is formed diastereoselectively, in a single step, from (**72**) in 72% yield; the required acyliminium ion (**74**) is created by an intramolecular alkylation of the intermediate enamide (**73**).[76]

In addition analogous β-carboline syntheses with tryptamine and α,β-unsaturated aldehydes, hitherto impossible even under acid catalysis,[89] were found to proceed very smoothly *via* acyliminium salts (**78**), induced by *in situ* acylation of the intermediate imine (**77**) with methyl chloroformate,[90] allowing a first directed total synthesis of the indole alkaloid borrerine (**79**; Scheme 38).

An impressive acyliminium ion initiated cyclization to the β-carboline system, combined with the simultaneous formation of an additional seven-membered ring, is found in the synthesis of the vasodilating alkaloid vincamine (**80**), as outlined in Scheme 39.[91]

*(ii) With alkenic carbon nucleophiles*

As mentioned previously, acyliminium ions are electrophilic enough to react intramolecularly even with nonactivated alkenic π-systems. These cyclization reactions have been recognized and elaborated as valuable tools in the stereoselective total synthesis of quinolizidine, indolizidine and pyrrolizidine alkaloids.[92,93] A typical example from Speckamp's laboratory is the highly stereospecific acid-catalyzed cyclization of (**81**) to (**83**; Scheme 40), presumably *via* the corresponding acyliminium ion (**82**).[94]

Analogously, other more complex natural products, such as the antiulcerogenically active alkaloid matrine (**85**), can be built up with high stereocontrol (Scheme 41), with an enol ether function as a more electron-rich nucleophile for the intermediate iminium ion (**84**).[95]

Special steric or electronic influences may thwart the expected reaction pathway, as in the regio- and stereo-selective conversion of (**86**) to the pyrrolizidine (**87**; Scheme 42).[96] This surprising formation of a five- instead of a six-membered ring is interpreted in terms of an aza-Cope equilibrium between the expected iminium salt (**88**) and its isomer (**89**). The latter finally cyclizes regioselectively in an exo-type mode to give (**87**). Further support for this assumption was obtained from quenching experiments with related compounds.[97]

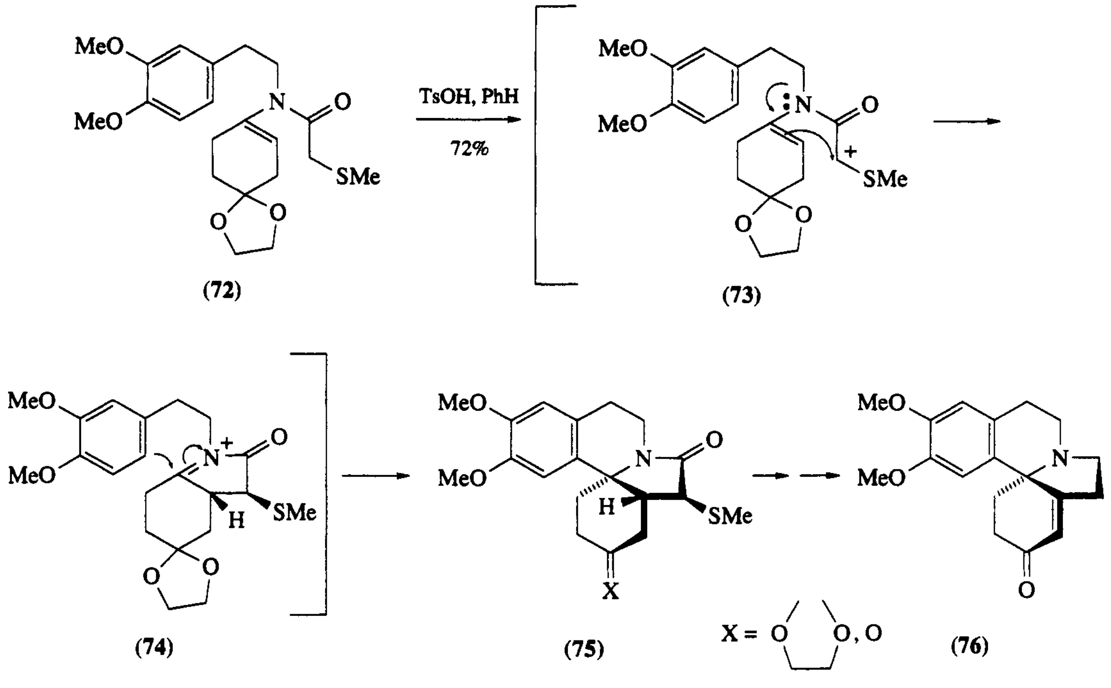
MeO
MeO
N
O
SMe
O
O
(72)
TsOH, PhH
72%
(73)
+
(74)
H
(75)
X
X = O O, O
(76)

**Scheme 37**

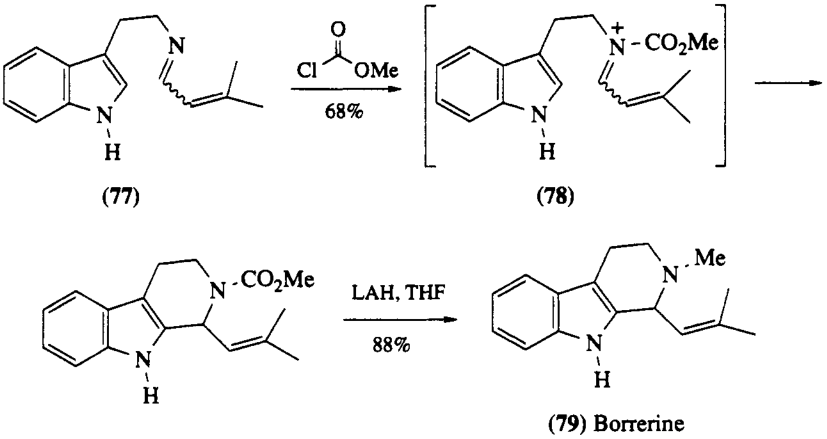
N
N
H
(77)
O
Cl OMe
68%
+
N - CO2Me
(78)
N - CO2Me
LAH, THF
88%
N - Me
(79) Borrerine

**Scheme 38**

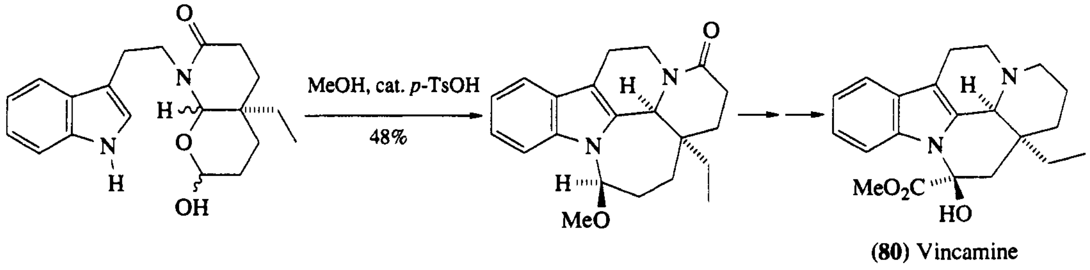
O
N
H
N
O
OH
MeOH, cat. p-TsOH
48%
H
MeO
MeO2C
HO
(80) Vincamine

**Scheme 39**

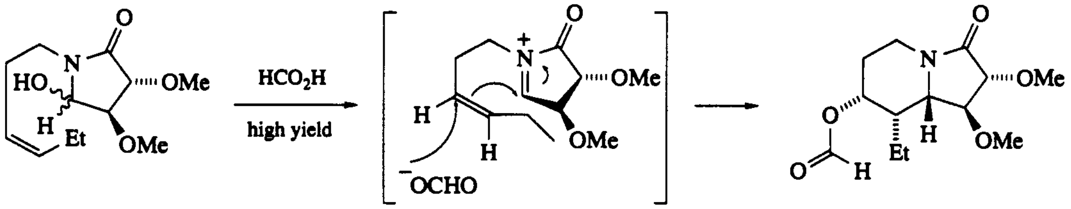
HCO2H
high yield

**(81)** **(82)** **(83)**

**Scheme 40**

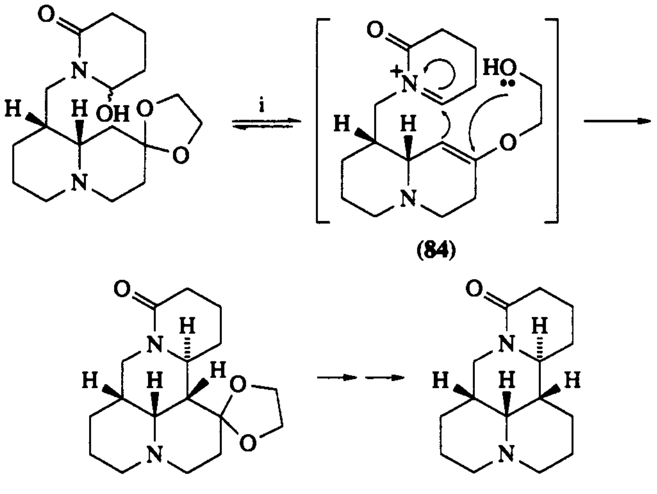

**(84)**

**(85)** Matrine

i, MSA, $CHCl_3$, 25 °C, 20 h

**Scheme 41**

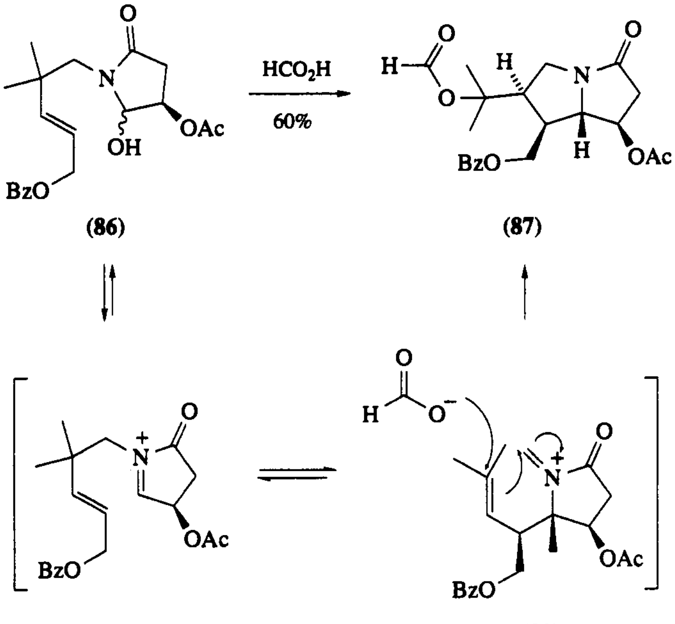

**(86)** **(87)**

**(88)** **(89)**

**Scheme 42**

Instead of being captured by external or internal heteroatom nucleophiles as in the preceding examples, the cationic intermediate resulting from the initial ring closure can eventually undergo a further cyclization reaction with additional C-nucleophiles present in the same molecule. Such a tandem-type reaction cascade from (**90**) to (**92**), *via* the intermediate acyliminium salt (**91**), is presented in Scheme 43.[98]

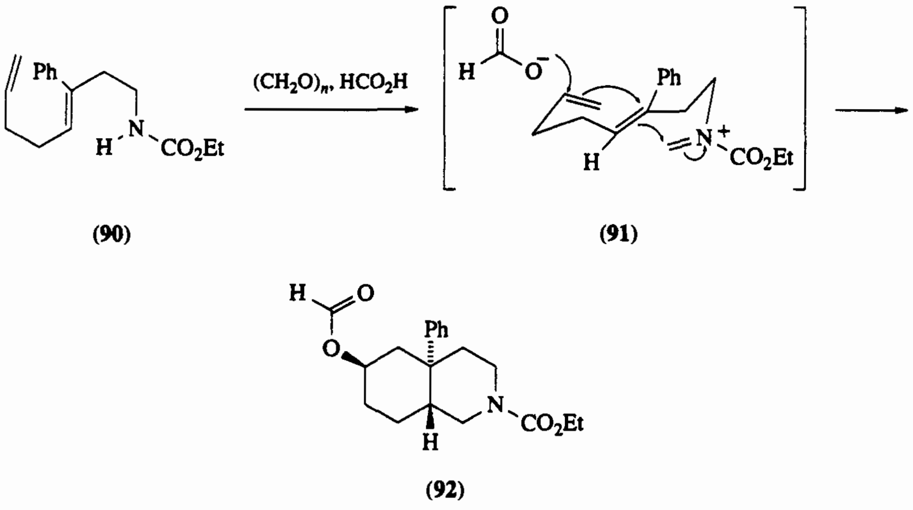

(**90**) (**91**) (**92**)

**Scheme 43**

### 4.2.2.3 Reactions Involving Oxocarbenium Ions

#### *4.2.2.3.1 Creation of the reactive species*

The use of oxocarbenium ions provides an efficient method for the preparation of heterocycles, especially of medium-sized cyclic ethers.

Most commonly, oxocarbenium ions (**94**) are formed from acetals (**93**), by treatment with either Brønsted or Lewis acids (Scheme 44).[99] In a similar way, α-halo ethers (**95**) have also been used as potent sources of oxocarbenium ions.[100]

Alternatively, they can be prepared by an electrophilic attack of Brønsted or Lewis acids, or alkyl halides, at the carbonyl oxygen of, for example, ketones (**1**; Scheme 45.[101]

Although detectable by spectroscopic methods,[102] oxocarbenium ions are highly reactive intermediates, prone to nucleophilic attack.

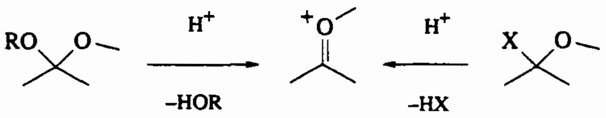

(**93**) (**94**) (**95**)

**Scheme 44**

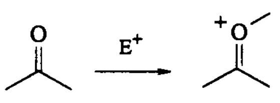

**(1)** **(94)**

$E^+ = H^+$, Lewis acids, carbon electrophiles

Scheme 45

#### *4.2.2.3.2 Cyclization reactions*

Oxocarbenium ions may react with carbon and hetereoatom nucleophiles. In intramolecular reactions, the attacking nucleophile may be attached either to the oxygen or to the carbon atom of the oxocarbenium unit (Scheme 46), thus allowing ring closure reactions to occur in an endocyclic (type a) or exocyclic (type b)[68] fashion.

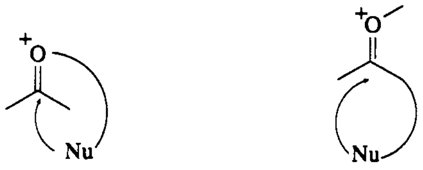

mode a

mode b

Scheme 46

Exo- and endo-cyclic ring closure reactions using O-nucleophiles transform oxocarbenium ions into cyclic acetals. As an example of an endocyclic cyclization, epoxide ring opening of (**96**) with lithium dimethyl cuprate, and subsequent treatment of the resulting alcohol with acid, smoothly gives the bicyclic acetal (**97**),[103] a key intermediate in the total synthesis of tirandamycic acid (Scheme 47).[104]

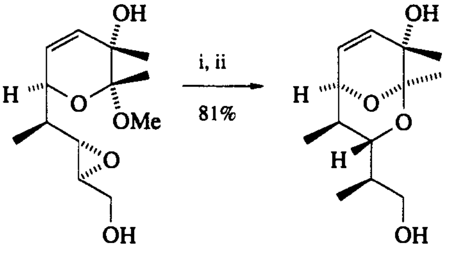

**(96)** **(97)**

i, $Me_2CuLi$, $Et_2O$, 0 °C; ii, $CHCl_3$, TsOH (trace)

Scheme 47

Out of numerous endo-type multiple ring closure cascades, only the double cyclization of (**98**) is mentioned here. This leads to the bis(spiroacetal) entity (**99**; Scheme 48), which is present in polyether antibiotics, insect pheromones and other important natural products.[105]

Though intensively exploited (*e.g.* in carbohydrate chemistry), reactions of oxocarbenium ions with heteroatom nucleophiles will not be treated further in this chapter, since they all lead back to carbonyl derivatives such as acetals. Instead, particular emphasis is laid on syntheses of heterocycles that involve carbon–carbon bond formation.

However, for ring closure reactions that use C-nucleophiles in the exocyclic fashion, heterocyclic products can be expected only under special conditions, namely when an additional heteroatom is present within the ring-closing loop. The most important exo mode reaction of oxocarbenium ions with aromatic

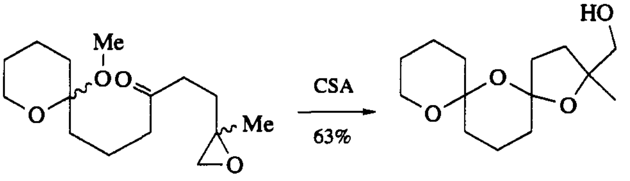

'one single diastereomer'

**(98)** **(99)**

Scheme 48

C-nucleophiles is the Pomeranz–Fritsch type synthesis of isoquinolines,[53] including Bobbit's improved modification.[106] For a mild ring closure without epimerization, electron-releasing *ortho* or *para* substituents are obligatory (Scheme 49); this situation nicely complements the substitution pattern required for corresponding Pictet–Spengler reactions (Section 4.2.2.1), due to the different ring closure site. For a given target molecule like (**100**; Scheme 49; *cf.* also Scheme 16), lack of reactivity can be compensated for by additional alkoxy groups, which can be removed selectively after the ring closure.[107]

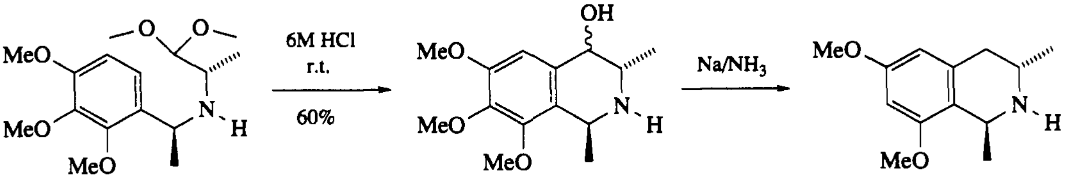

**(100)**

Scheme 49

Similarly, the nucleophile may also be an activated alkene, such as the allylsilane moiety in (**101**; Scheme 50),[108] which cyclizes diastereoselectively, though under partial racemization, to the piperidine (**103**). The cyclization proceeds *via* the energetically favorable transition state (**102**), which avoids steric repulsion between the acetal oxygen and trimethylsilylmethyl group, and minimizes A-strain[109] with the methyl group.

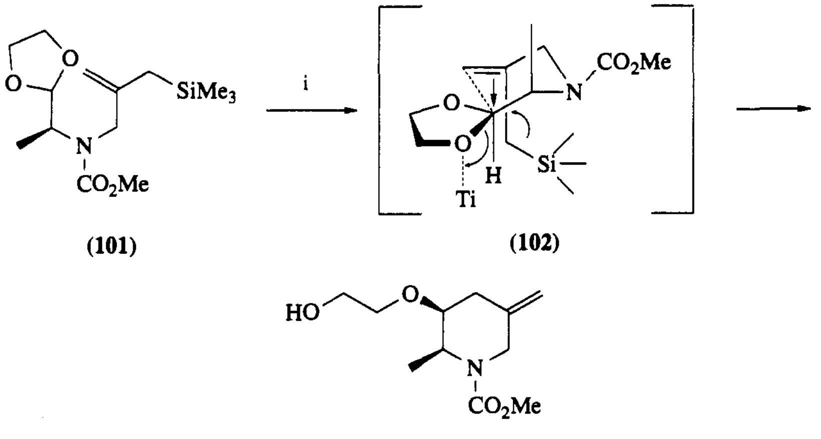

**(101)** **(102)**

**(103)**

i, $TiCl_3(OPr^i)$, '100%' *de*, 82–83% *ee*

Scheme 50

Considerably more important are reactions involving an endocyclic attack of C-nucleophiles. Besides rarer reactions with aromatic nucleophiles[110] (the oxa analog of the Pictet–Spengler reaction) the use of vinylic nucleophiles especially provides an efficient route to 'critical', medium-sized oxygen-containing heterocycles. Thus, even nonactivated alkenes like (**104**) readily undergo acid-catalyzed cyclization in remarkable yields (Scheme 51).[111]

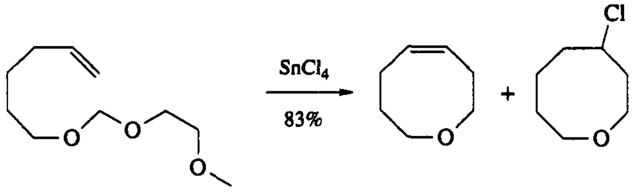

(**104**) 2:1

**Scheme 51**

A different outcome in the presence of an additional vinylic oxygen was observed by Overman's group (Scheme 52).[112] The formation of the five-membered cyclic ether (**108**) is rationalized in terms of an $SnCl_4$-mediated acetal ring opening of (**105**), subsequent cyclization of (**106**) to (**107**), followed by a ring contraction to (**108**) by a pinacol-type rearrangement. This stereocontrolled reaction proved to be applicable to the synthesis of related natural products.[112]

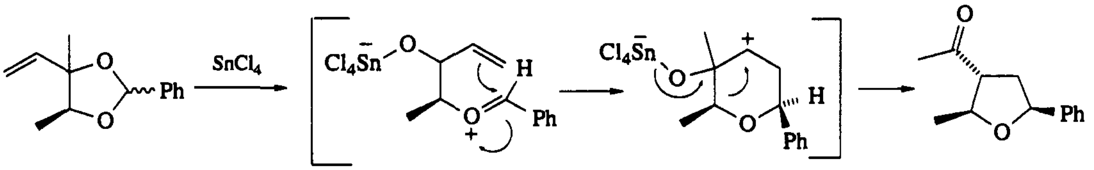

(**105**) (**106**) (**107**) (**108**)

**Scheme 52**

Vinylsilanes as nucleophilic 'terminators' offer several additional advantages over ordinary nonactivated alkenes (*cf.* Section 4.2.2.1). The silyl group is readily substituted stereo- and regio-selectively by the electrophilic carbon atom of the oxocarbenium ion, as demonstrated in Overman's synthesis of alkylidenetetrahydropyran (**109**; Scheme 53).[113] This strategy was also applied to the preparation of five- and seven-membered cyclic ethers.[113]

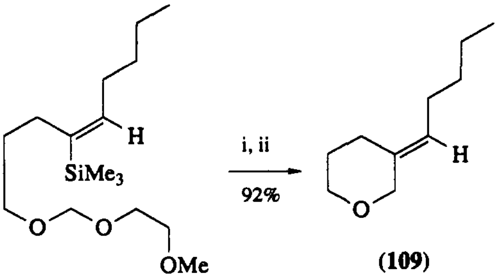

(**109**)

i, 2–8 equiv. $SnCl_4$, –20 °C; ii, aq. NaOH, –70 °C

**Scheme 53**

An impressive application is the highly stereocontrolled and enantioselective synthesis of (–)-laurenyne (**113**; Scheme 54).[114] The key step is the cyclization of the mixed acetal (**110**) to give the oxocene (**112**), with the required endocyclic unsaturation at the correct position. The formation of this eight-membered cyclic ether, instead of the corresponding seven-membered ring with an exocyclic double bond, may be rationalized[111] by an intramolecular ene-type reaction of the intermediate oxocarbenium ion (**111**).

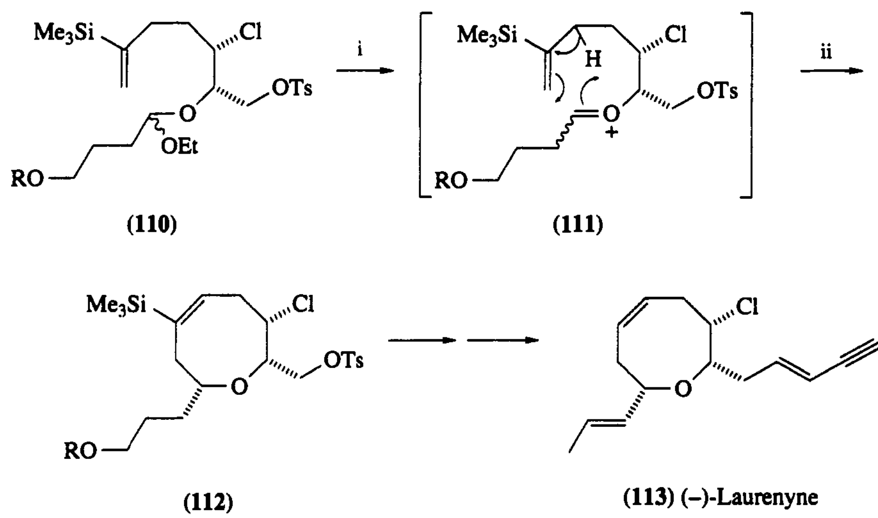

(110) (111) (112) (113) (–)-Laurenyne

i, 2 equiv. $SnCl_4$, 0 °C, $CH_2Cl_2$; ii, $Bu^n{}_4NF$–THF

Scheme 54

## 4.2.2.4 Reactions Involving Thiocarbenium Ions

### *4.2.2.4.1 Creation of the reactive species*

In analogy to the preparation of iminium salts, thiocarbenium ions (**115**) can be created by treatment of carbonyl compounds (**1**) with thiols,[115] by alkylating (or Lewis acid catalyzed) cleavage of dithioacetals[116] (**114**) or by protonation of vinyl sulfides (thio enol ethers) (**116**; Scheme 55).[116]

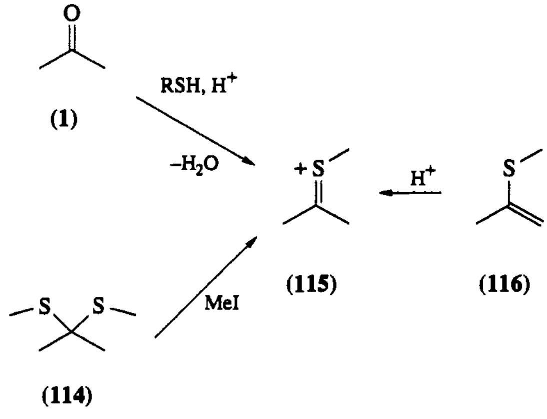

(1) (115) (116) (114)

Scheme 55

Most efficiently, however, thiocarbenium ions (**115**) can be prepared from sulfides (**117**), by *S*-oxidation, transformation of the introduced oxygen into a good leaving group (*e.g.* into the trifluoroacetate) and subsequent β-elimination—the Pummerer-type route (Scheme 56; see also Chapter 4.7).[117]

Alternatively, the sulfides can be *C*-oxidized (*e.g.* with *N*-chlorosuccinimide) to yield α-halo sufides (**118**), which easily decompose to afford the thiocarbenium salt (**115**; Scheme 57).[118]

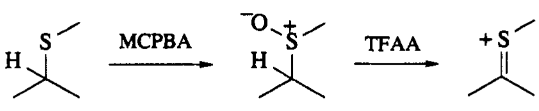

**(117)** **(115)**

Scheme 56

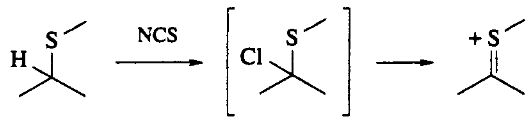

**(118)** **(115)**

Scheme 57

### 4.2.2.4.2 Cyclization reactions

As for the corresponding iminium and oxocarbenium ions, thiocarbenium salts can undergo endo- or exo-cyclic ring closure reactions. Again, carbon–carbon bond formation by exocyclic-type reactions lead to heterocyclic systems only 'by chance', namely when an additional heteroatom is located in the chain that will form the ring, *e.g.* the thiol-assisted annulation of (**119**) to give (**120**; Scheme 58).[115]

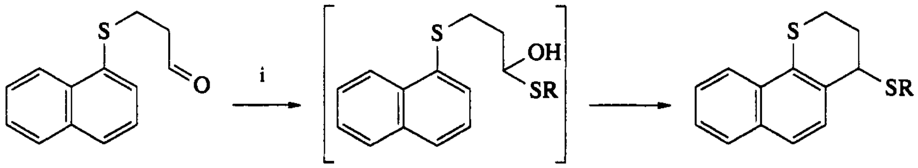

**(119)** **(120)**

i, RSH, 0.1M $H_2SO_4$, PhH, high yield

Scheme 58

Especially when combined with the Pummerer-type preparation, thiocarbenium species become valuable carbon electrophiles for various ring closure reactions. At nearly any time in the course of the synthesis, the thiocarbenium species can be set free, *e.g.* from the nonproblematical sulfide function under essentially mild, oxidative conditions, as demonstrated in the synthesis of the pentacyclic precursor (**122**) to aspidospermine alkaloids[119] from (**121**; Scheme 59). The sulfur, if not required for the target molecule, can be taken away reductively, after the ring closure reaction (*cf.* Scheme 37, Section 4.2.2.1).

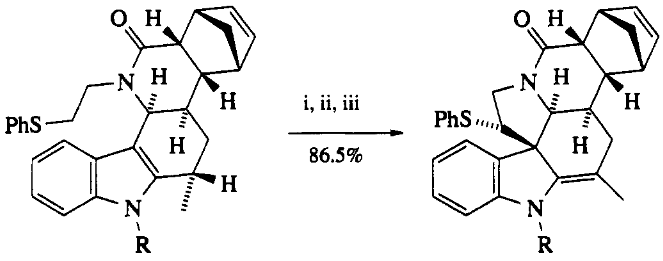

**(121)** **(122)**

i, MCPBA, $NaHCO_3$, $CH_2Cl_2$; ii, TFAA, $CH_2Cl_2$, 0 °C, 1 h; iii, toluene, 1.5 h, Δ

Scheme 59

Only very rarely have endo-type cyclization reactions triggered by thiocarbenium ions been achieved. One interesting example,[116] involving an aromatic C-nucleophile, is the sulfur analog of the Pictet–Spengler reaction, leading to (**125**), presumably *via* (**124**; Scheme 60). Besides the vinyl sulfide (**123**), the corresponding dithioacetal can also be utilized.

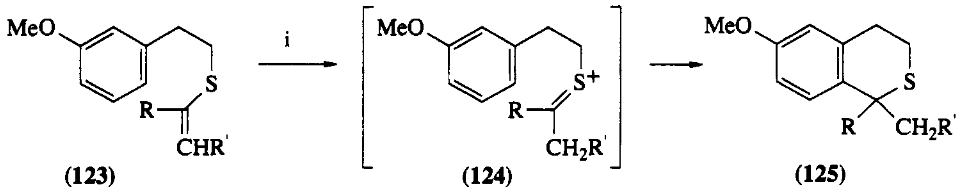

(**123**) (**124**) (**125**)

i, $HClO_4$ (70%), 25 °C, 2–3 h, 'high yield'

**Scheme 60**

## 4.2.3 CYCLIZATION REACTIONS INVOLVING ELECTROPHILIC OR RADICAL ATTACK ON CARBONYL DERIVATIVES

### 4.2.3.1 By Electrophilic Attack

Generally, cyclization reactions using carbonyl derivatives involve an intramolecular nucleophilic attack on the carbon atom of the heterocarbonyl group. Sometimes, especially in domino-type reaction cascades, (hetero)carbonyl groups undergo nucleophilic and electrophilic ring closure reactions 'simultaneously' (*cf.* Scheme 48, Section 4.2.2.3). Far less frequently, the cyclization reaction results exclusively from an intramolecular electrophilic attack on carbonyl derivatives, the reaction then usually being triggered by the attack of an external nucleophile. This is the case in the formation of the aziridine (**127**) from the α-haloimine (**126**; Scheme 61),[120] a key step in the first biomimetic synthesis of scandine (**128**) and the structurally related meloscine. A similar cyclization, albeit with a carbonyl group itself rather than a carbonyl derivative, is found in Scheme 28 (Section 4.2.2.1). However, compared with cyclization reactions by nucleophilic attack on heterocarbonyl groups, this reaction type has received only relatively marginal attention and will not be treated further in this chapter.

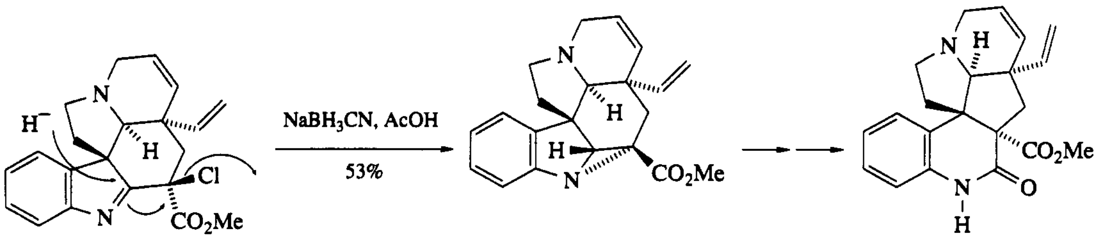

(**126**) (**127**) (**128**) Scandine

**Scheme 61**

### 4.2.3.2 By Radical Attack

Compared with the numerous efficient syntheses based on nucleophilic/electrophilic or concerted (*cf.* Section 4.2.4) cyclization reactions of carbonyl derivatives, very little synthetic applications have been described that rely on radical-induced ring closure reactions, such as the reductive cyclization of δ-unsaturated iminium salts like (**129**) using samarium diiodide, which affords (**132**) as the only bicyclic product (Scheme 62).[121] The reaction is believed to proceed by single electron transfer, going through the α-amino radical (**130**), which cyclizes in an exocyclic mode to give the denoted product (**132**) *via* the benzylic carbon radical (**131**).

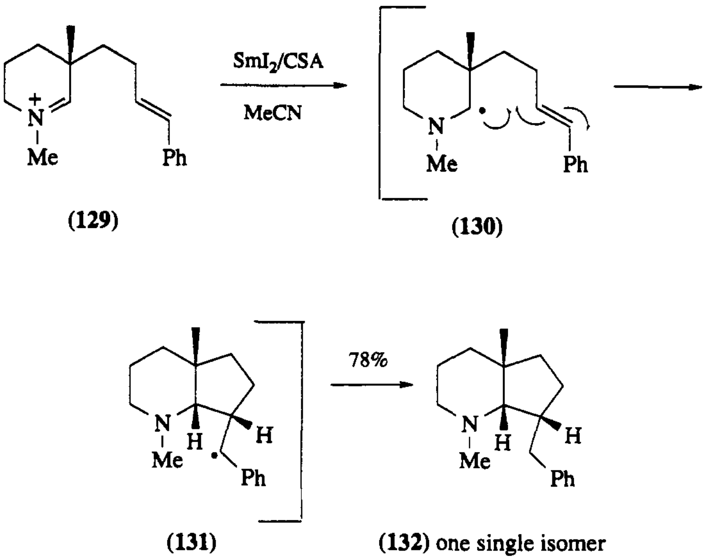

Scheme 62

Besides such free radical induced reactions, cyclization reactions involving carbonyl derivatives may of course have partial or complete radical character (such as some [2 + 2] cycloaddition reactions[122]), but will be dealt with in Section 4.2.4 for reasons of lucidity and simplicity.

## 4.2.4 CONCERTED REACTIONS

### 4.2.4.1 [4 + 2] Cycloadditions (Hetero Diels–Alder Reactions)

#### *4.2.4.1.1 General aspects*

During the last few years, pericyclic reactions, especially hetero [4 + 2] cycloadditions, have increasingly been utilized as pivotal steps in the total synthesis of heterocyclic natural products. This vast field of hetero Diels–Alder reactions has been thoroughly reviewed recently.[123] Because of the intentions (and limitations) of the present chapter, all that will be done is to highlight some of the modern trends, such as the control of regio- and stereo-selectivity by intramolecular processes, the *in situ* generation of highly reactive $\pi$-systems, *e.g.* by cycloreversion, and, finally, tandem-type strategies, such as ring contraction reactions subsequent to the cycloaddition.[124]

#### *4.2.4.1.2 Carbonyl derivatives as dienophiles*

From the numerous $\pi$-systems investigated, nitrogen-containing dienophiles[78] are the most typical carbonyl derivatives for hetero Diels–Alder reactions. Simple imines, however, are quite unreactive and require highly reactive dienes as counterparts.[125,126] In contrast, electron-deficient species, such as iminium salts (**134**; Scheme 63) or *N*-acylimines (**137**; Scheme 64), do undergo [4 + 2] cycloadditions with normal nonactivated dienes. Thus, the intramolecular Diels–Alder reaction of the iminium species (**134**), created *in situ* from the aldehyde (**133**) and ammonia, gives the octahydroquinoline (**135**), which can be hydrogenated to afford the 8a-epimer of pumiliotoxin C (Scheme 63).[127]

Both reaction partners, *i.e.* the diene and the dienophile, may simultaneously be set free *in situ*, as illustrated in the total synthesis of the indolizidine alkaloid elaeokanine A (**139**; Scheme 64).[128] Flash pyrolysis of (**136**) yields (**138**), presumably *via* the nonisolable dieneacylimine (**137**).

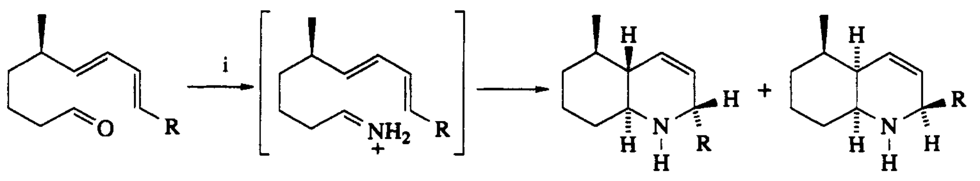

**(133)** R = $Pr^n$ **(134)** **(135)** 2.2:1

i, $NH_4Cl$, $H_2O$–EtOH, 75 °C, 55%

Scheme 63

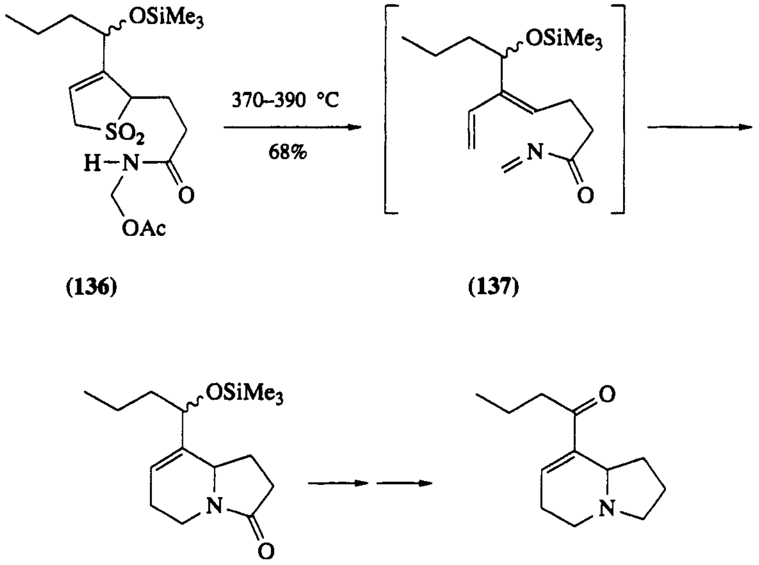

**(138)** **(139)** Elaeokanine A

Scheme 64

In the presence of very reactive dienes, such as *o*-quinodimethanes, even electron-rich dienophiles, such as oxime ethers, can be reacted, as exemplified in the intramolecular cycloaddition of (**143**; Scheme 65),[129] which is created *in situ* by an initial [2 + 2 + 2] cycloaddition reaction of (**140**) with (**141**) and subsequent electrocyclic ring opening of the resulting benzocyclobutene (**142**). This strategy has been applied recently to a novel isoquinoline synthesis.[130]

For such electron-rich dienophiles, Diels–Alder reactions with unfavorable electron demand become possible when assisted by intramolecularity and high dilution, as in Oppolzer's total synthesis of lysergic acid (Scheme 66),[131] where the labile transient diene is set free by cycloreversion.

### *4.2.4.1.3 Carbonyl derivatives as dienes*

1-Azabutadiene systems, as more or less formal carbonyl derivatives, have been used for [4 + 2] cycloaddition reactions. The fluoride-induced stereoselective transformation of (**144**) to the polycyclic steroid-like system (**145**), obviously proceeding *via* the corresponding reactive aza-*o*-quinodimethane (Scheme 67),[132] shows the synthetic utility of such heterodienes.

Where no assistance can be expected from intramolecularity, or from a reactive rearomatizing *o*-quinodimethane system as above, [4 + 2] cycloadditions with inverse[133] electron demand are required. Thus, reaction of the 2-aza-1,3-butadiene (**146**) with the electron-rich enamine (**147**) at room temperature affords the octahydroisoquinoline (**148**) in high regio- and diastereo-selectivity (Scheme 68).[134]

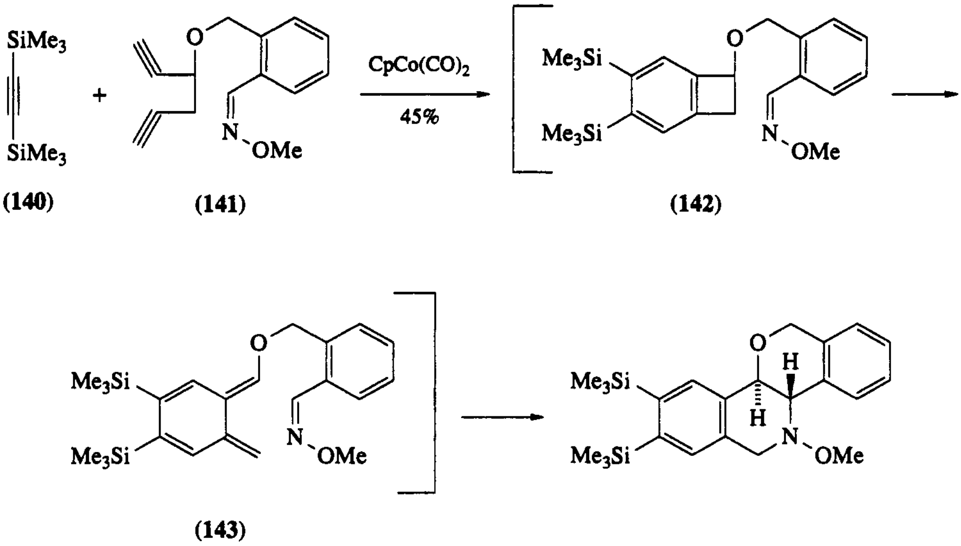
SiMe3
SiMe3
+
O
N
OMe
CpCo(CO)2
45%
Me3Si
Me3Si
O
N
OMe
(140)
(141)
(142)
Me3Si
Me3Si
O
N
OMe
(143)
Me3Si
Me3Si
O
H
H
N
OMe

**Scheme 65**

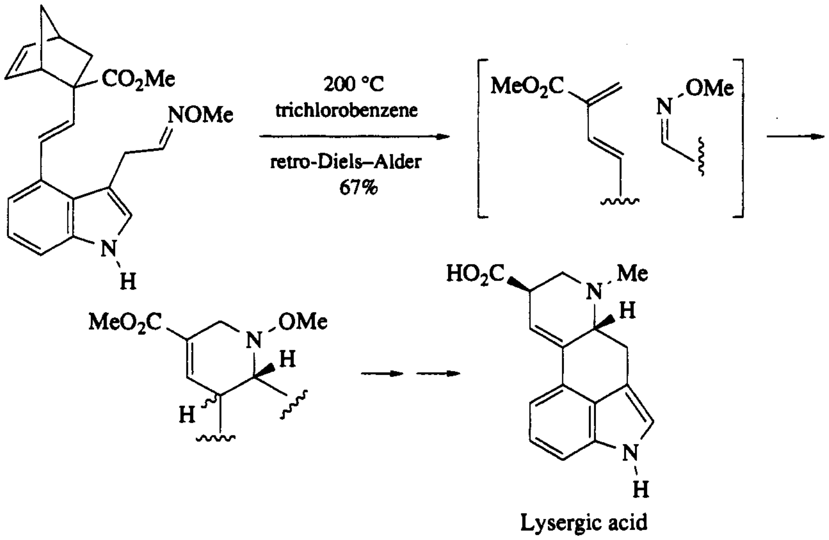
CO2Me
NOMe
N
H
200 °C
trichlorobenzene
retro-Diels–Alder
67%
MeO2C
N
OMe
MeO2C
N
OMe
H
H
HO2C
N
Me
H
N
H
Lysergic acid

**Scheme 66**

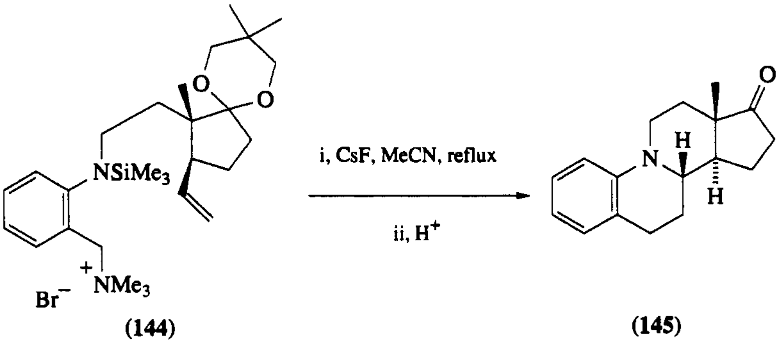
O
O
NSiMe3
+
NMe3
Br−
i, CsF, MeCN, reflux
ii, H+
O
N
H
H
(144)
(145)

**Scheme 67**

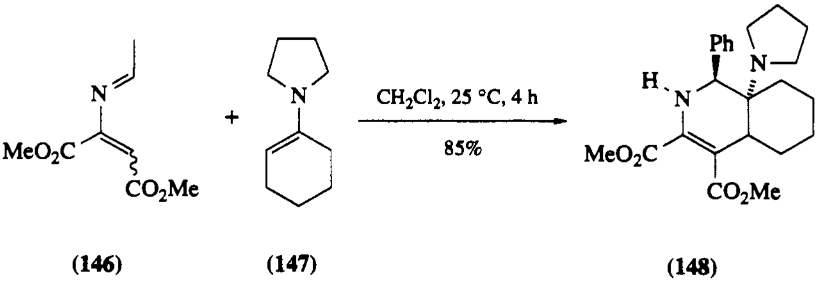
MeO2C
CO2Me
N
+
N
CH2Cl2, 25 °C, 4 h
85%
Ph
H
N
N
MeO2C
CO2Me
(146)
(147)
(148)

Scheme 68

### 4.2.4.2 [2 + 2] Cycloaddition Reactions

The most prominent hetero [2 + 2] cycloaddition reaction is the Paterno–Büchi reaction[135] of alkenes with carbonyl compounds, such as aldehydes or ketones. Among the corresponding reactions of carbonyl derivatives, the ketene–imine addition, the so-called Staudinger reaction, deserves particular attention, as it provides efficient straightforward access to the β-lactam system.[136] The synthetic value of this procedure not only comes from the diastereoselectivity concerning the relative configuration [(*E*)-imines usually afford *cis*-azetidinones; see Scheme 69], but also from the establishment of absolute stereochemical control, by using transient or permanent chiral auxiliary groups located, for example, in the ketene part. Thus, treatment of the imine (**150**) with the oxazolidine-substituted ketene (**149**; Scheme 69) mainly yields the β-lactam (**151**) with excellent 1,2-asymmetric induction (no formation of *trans*-azetidinones) and good diastereoselectivity (92:8) with respect to the chiral residue.[137,138] In the course of the further β-lactam synthesis, the phenylglycinol-derived chiral auxiliary is cleaved reductively. On the basis of this strategy, further β-lactams have been synthesized more recently.[139]

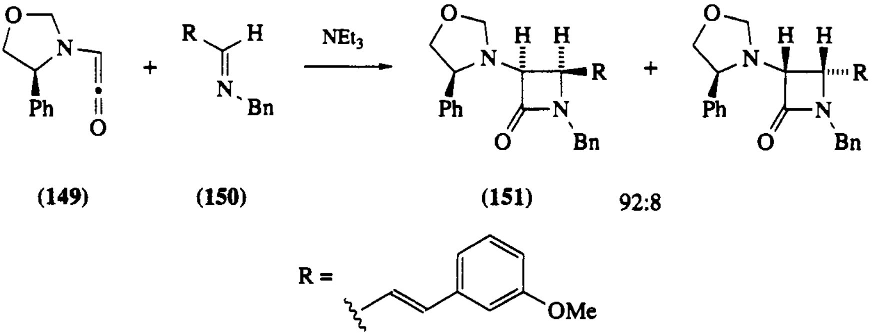
O
N
Ph
O
+
R
H
N
Bn
NEt3
O
N
Ph
H H
R
N
O
Bn
+
O
N
Ph
H H
R
N
O
Bn
(149)
(150)
(151)
92:8
R =
OMe

Scheme 69

For the preparation of optically active β-lactams (**154**) with relative *trans* configuration (*e.g.* for the synthesis of '(+)-PS-5'), the [2 + 2] cycloaddition of ester enolates such as (**152**) and *N*-trialkylsilylimines (**153**) is an appropriate strategy (Scheme 70).[140] In this case, chirality is introduced by the imino moiety.

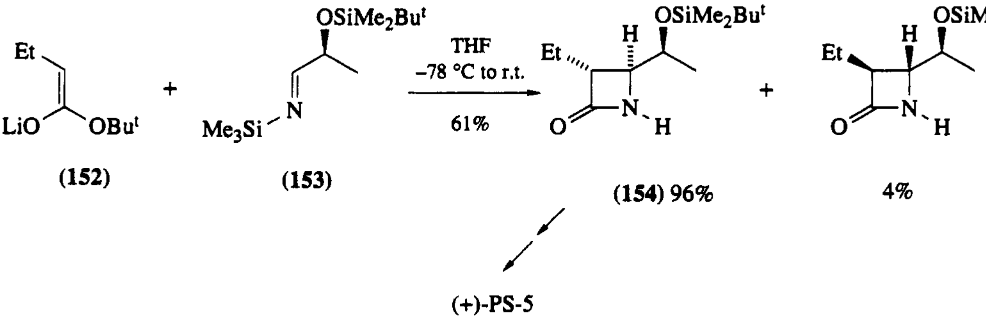
Et
LiO
OBu$^t$
+
OSiMe$_2$Bu$^t$
N
Me$_3$Si
THF
−78 °C to r.t.
61%
Et
H
OSiMe$_2$Bu$^t$
O
N
H
+
Et
H
OSiMe$_2$Bu$^t$
O
N
H
(152)
(153)
(154) 96%
4%
(+)-PS-5

Scheme 70

Apart from numerous similar β-lactam syntheses,[141-143] the very promising photolytic [2 + 2] cycloaddition of imines (or the corresponding hexahydro-1,3,5-triazenes respectively)[122] to chromium carbene complexes that leads to norcardicin precursors[144] merits special interest.

## 4.2.5 CONCLUDING REMARKS

Heterocyclic compounds are of great interest not only as useful synthetic auxiliaries but also as natural products (or merely synthetic compounds) of biological and medicinal relevance. This review was intended to demonstrate that carbonyl derivatives constitute versatile reactive species for the efficient regio- and stereo-controlled synthesis of demanding heterocyclic molecules. The different reactive carbonyl-derived species could not be covered exhaustively in a chapter of this size, but it is hoped that some salient features of this important subject have been highlighted.

## ACKNOWLEDGEMENT

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# 4.3

# Functional Group Transformations *via* Carbonyl Derivatives

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## 4.3.1 BECKMANN REARRANGEMENT

The Beckmann rearrangement is the skeletal rearrangement of aldoximes and ketoximes in the presence of certain acids, including Lewis acids, to give amides or lactams. Since the first discovery of this rearrangement by Beckmann in 1886,[1] successive investigations have largely clarified its scope, reaction mechanism, and the stereochemical configurations of the oximes employed. Accordingly, the Beckmann rearrangement has become an increasingly important synthetic tool in organic chemistry and it has been reviewed several times.[2–6] It is one of the most reliable ways of incorporating the nitrogen atom efficiently into both acyclic and alicyclic systems, thereby providing a powerful method for a variety of natural product syntheses.

### 4.3.1.1 Synthetic Utility of the Beckmann Rearrangement

Most ketoximes will undergo the normal Beckmann rearrangement under the proper acidic or neutral conditions to yield an amide or a mixture of amides, and a wide variety of examples are listed in reviews.[2,6] Polyphosphoric acid continues to be a common reagent for the Beckmann rearrangement. However, in view of the viscosity and utility in a large molar excess as a solvent, polyphosphoric acid has several drawbacks in the work-up step. A recent procedure suggests the use of xylene as a cosolvent.[7] Under these conditions the reaction temperature is easily controlled and the yields are the same or better than those obtained in polyphosphoric acid alone.

Several reagents for effecting the Beckmann rearrangement of the oxime (**1**) to give the lactam (**2**) have been evaluated with a view to the synthesis of a structural analog of the natural product, muscarine. The best results are obtained with a 10:1 mixture of methanesulfonic acid and phophorus pentoxide (equation 1).[8]

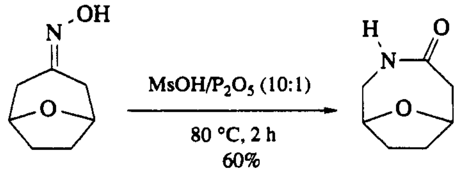

(1)

(**1**) (**2**)

The combination of benzenesulfonyl chloride and *p*-toluenesulfonyl chloride with base is highly effective for the Beckmann transformation. The oxime (**3**) of 4,9-methano[11]annulenone, when heated with *p*-toluenesulfonyl chloride in pyridine, gives the desired lactam (**4**) in 26% yield (equation 2).[9,10] Attempted rearrangement of (**3**) with $PCl_5$ is fruitless. Oximes that are prone to the Beckmann fragmentation can often be rearranged by use of these reagents. Spirooxime (**5**) successfully rearranges to the lactam (**6**; equation 3), the key intermediate for the synthesis of pharmacologically important alkaloid perhydrohistrionicotoxin.[11] An interesting case of regiochemical control has been observed in the Beckmann rearrangement of the oxime (**7**). Thus, heating of (**7**) in polyphosphoric acid produces exclusively the abnormal lactam (**8**), suggesting the acid-catalyzed *syn*/*anti* oxime isomerization prior to rearrangement. By contrast, solvolysis of the corresponding oxime tosylate (**9**) yields the normal Beckmann lactam (**10**) under essentially neutral conditions (equation 4).[12]

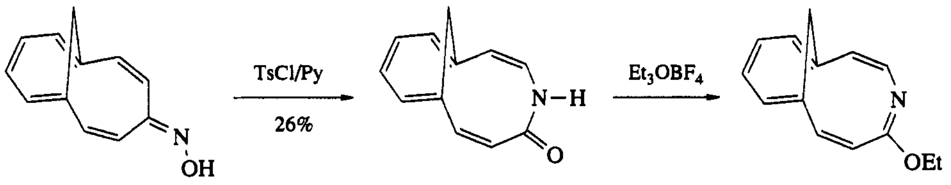

(2)

(**3**) (**4**)

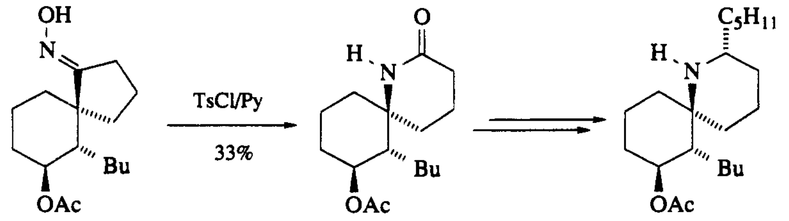

(3)

(**5**) (**6**) Perhydrohistrionicotoxin

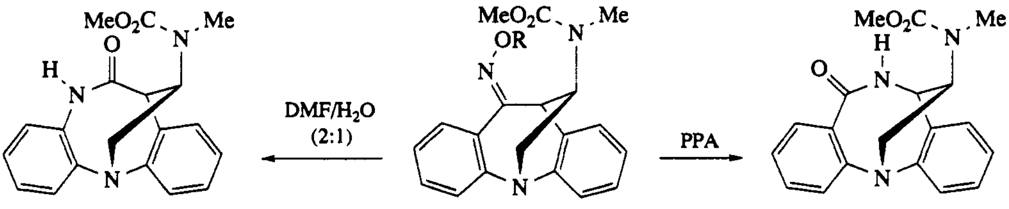

(4)

(**10**) (**7**) R = H (**8**)

(**9**) R = Ts

Hydroxylamine-*O*-sulfonic acid or *O*-mesitylenesulfonylhydroxylamine (Tamura's reagent)[13] are effective catalysts for the conversion of ketones directly to lactams. For example, the rearrangement of

$C_5$–$C_{12}$ cycloalkanones with hydroxylamine-*O*-sulfonic acid produces the corresponding lactams in 80–83% yield.[14] Abnormal Beckmann rearrangement, where the migration of the more-substituted α-carbon takes place predominantly, is observed on treatment of cyclopropyl ketone (**11**) with hydroxylamine-*O*-sulfonic acid to furnish the lactam (**12**) as the sole isolable product in 86% yield (equation 5).[15] In contrast, heating of the oxime of (**11**) with polyphosphoric acid affords a mixture of (**12**) and its isomeric lactam. The utility of this reagent in the synthesis of various heterocycles has been reviewed by Wallace.[16] Although the Beckmann rearrangement of ketone (**13**) cannot be accomplished by standard methods, *O*-mesitylenesulfonylhydroxylamine enables the facile transformation of the ketone (**13**) to the crystalline lactam (**14**) in 55% yield along with 15% of the isomeric lactam (**15**; equation 6).[17]

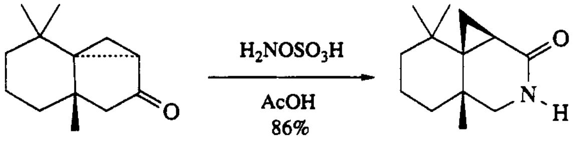

**(11)** **(12)** (5)

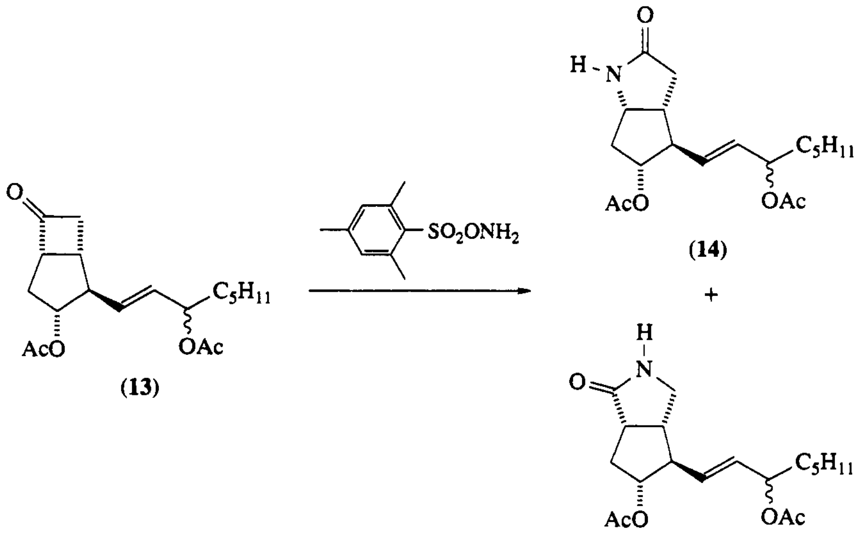

**(13)** **(14)** **(15)** (6)

A regio- and stereo-selective ring expansion of the *O*-mesitylenesulfonyl oxime of an unsymmetrical cyclobutanone (**16**) has been observed under the influence of a basic alumina (equation 7).[18] In the rearrangement of *O*-mesitylenesulfonyl oxime (**17**) the activated alumina is found to be superior to basic alumina which causes the formation of oxazoline derivative (**18**) as a side product (equation 8).[19]

α-Hydroxy ketoximes are prone to undergo the Beckmann fragmentation with a variety of reagents which generally induce the Beckmann rearrangement. However, photoreaction of cyclic α-hydroxy ketoxime (**19**) in MeOH gives two structurally isomeric lactams, (**20**) and (**21**), possessing a hydroxy group

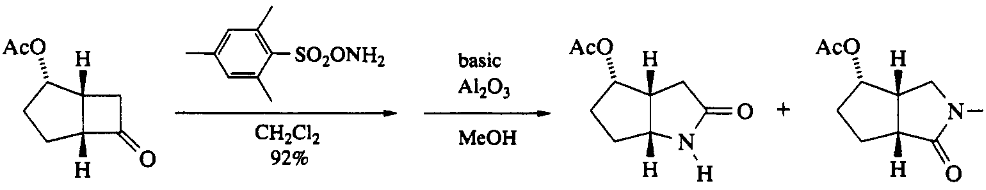

(7)

**(16)**

–10 °C, 5:1
25 °C, 2:1

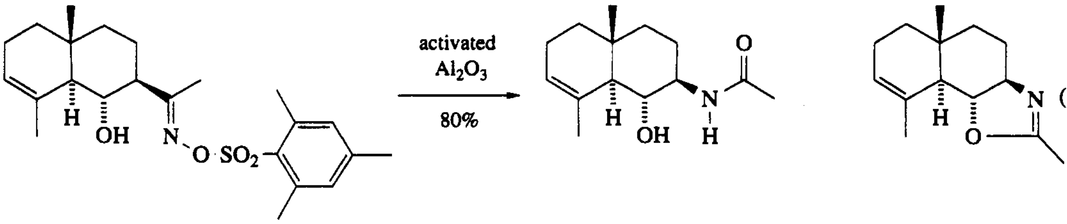

(8)

**(17)** **(18)**

adjacent to the amide group (equation 9).[20] Another feature of the photoreactions of oximes is their reluctance towards the Beckmann fragmentation, as demonstrated in equation (10).[21]

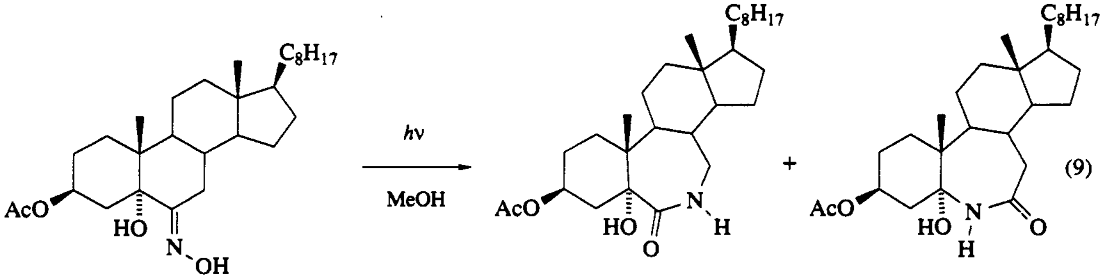

(9)

**(19)** **(20)** 15% **(21)** 21%

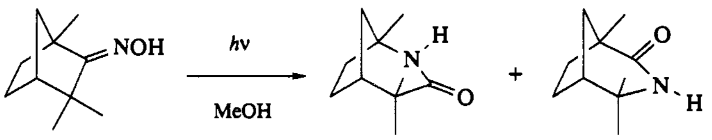

(10)

13% 13%

Beckmann rearrangement of α,β-unsaturated oximes usually gives rise to α,β-unsaturated lactams. However, treatment of unsaturated *N*-methyl nitrone (**22**) with *p*-toluenesulfonyl chloride in pyridine leads to selective migration of the vinylic rather than the alkyl bond, producing enamide (**23**) in 60% yield (equation 11).[22]

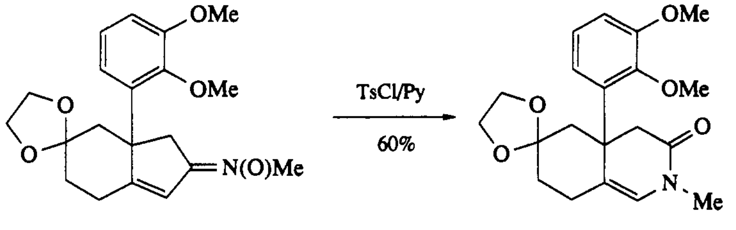

(11)

**(22)** **(23)**

### 4.3.1.2 Trapping of the Beckmann Intermediate with Heteroatoms

One synthetically interesting development in the Beckmann rearrangement is the trapping of the intermediate nitrilium ion with heteroatom nucleophiles other than water, since the resulting imine derivatives may be further manipulated into various amine derivatives.

Intramolecular participation of a neighboring hydroxy group is observed in the rearrangement of erythromycin A oxime (**24**) with *p*-toluenesulfonyl chloride and sodium hydrogencarbonate in acetone–water (equation 12).[23] Interestingly, with the same reagent in pyridine–ether only the normal rearrangement product (**25**) is formed.

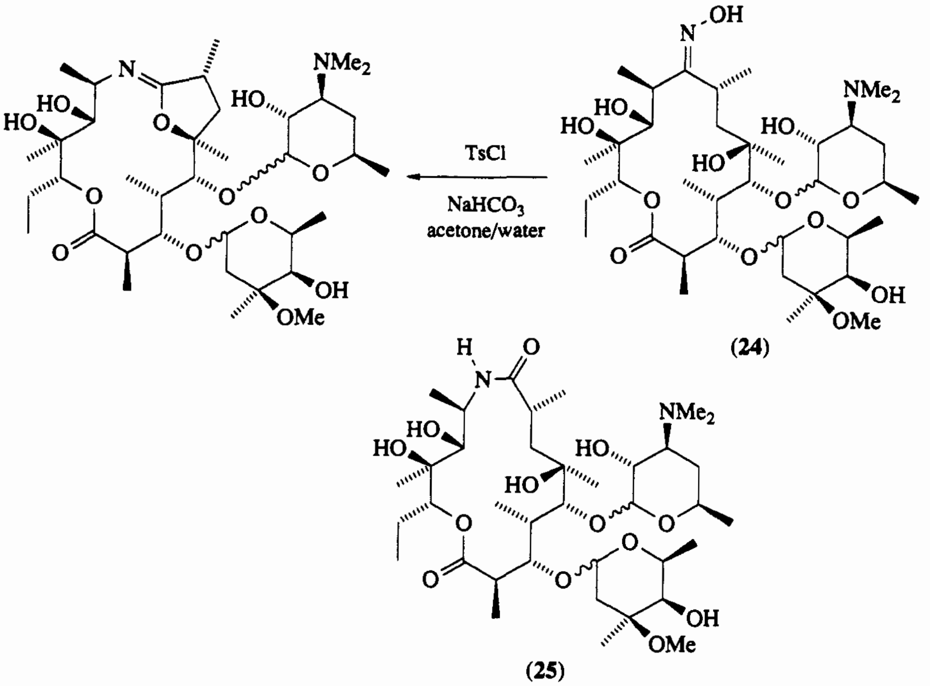

(24)

(25)

(12)

Preparation of imidoyl chlorides is usually effected by using phosphorus pentachloride or triphenylphosphine–carbon tetrachloride.[24] A recent example indicates the utility of imidoyl chloride (**26**) in the synthesis of the potential antidepressant (**27**; equation 13).[25]

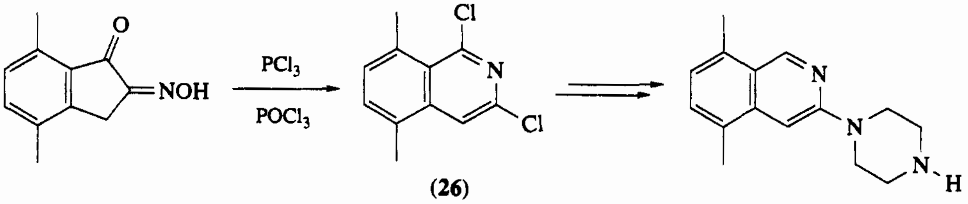

(**26**)

(**27**)

(13)

Although imidoyl iodides are chemically labile, their *in situ* generation from oxime derivatives with trimethylsilyl iodide or diethylaluminum iodide has been ascertained spectroscopically (equation 14).[26,27] The synthetic utility of these reactive species has been demonstrated by further reacting them with external nucleophiles such as thiolates or Grignard reagents. For example, the imidoyl iodide (**28**), generated from acetophenone oxime carbonate with trimethylsilyl iodide, is further transformed to ethylthioimidate (**29**) and α-alkylated amine (**30**), respectively (Scheme 1 and equation 15).

A highly efficient and general approach for the synthesis of thioimidates from oxime sulfonates has been developed which involves the use of dialkylaluminum thiolates both as initiators of the Beckmann rearrangement and as trapping agents, *via* thiolate nucleophiles, of the intermediate nitrilium ions. The regiochemistry of this reaction follows the general rule of the Beckmann rearrangement and preferential migration of the group *anti* to the oxime sulfonate is rigorously observed, as shown in equations (16) and (17).[28]

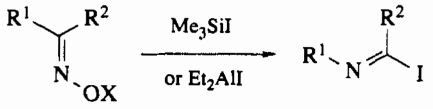

(14)

X = Ac, COPh, CO$_2$Et, Ms

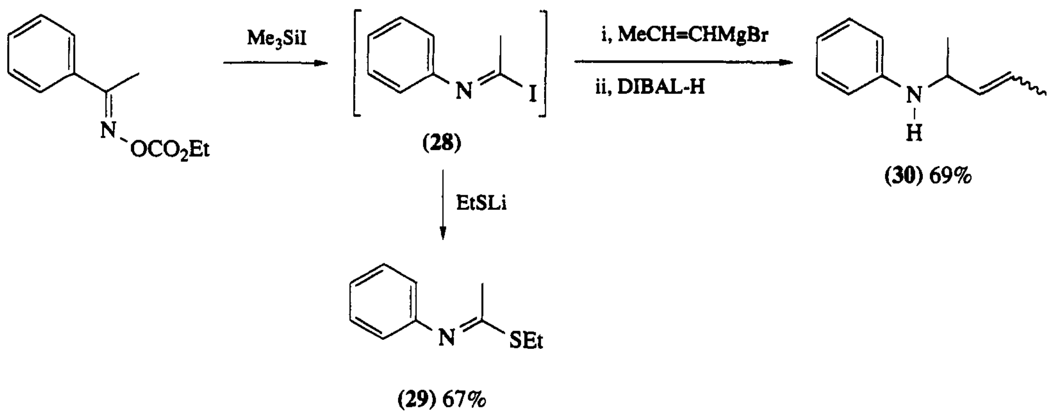
N
OCO$_2$Et
Me$_3$SiI
N
I
(28)
i, MeCH=CHMgBr
ii, DIBAL-H
N
H
(30) 69%
EtSLi
N
SEt
(29) 67%

**Scheme 1**

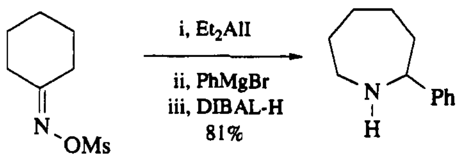
N
OMs
i, Et$_2$AlI
ii, PhMgBr
iii, DIBAL-H
81%
N
H
Ph

(15)

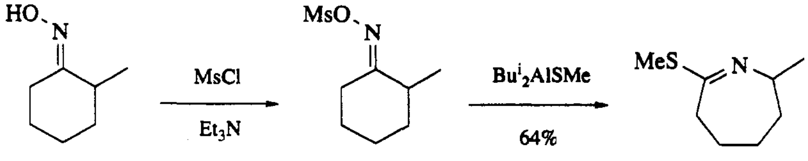
HO
N
MsCl
Et$_3$N
MsO
N
Bu$^i_2$AlSMe
64%
MeS
N

(16)

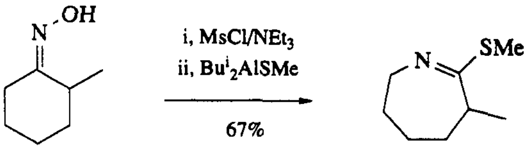
N
OH
i, MsCl/NEt$_3$
ii, Bu$^i_2$AlSMe
67%
N
SMe

(17)

This aluminum method, in principle, is applicable to a synthesis of other heterosubstituted imino derivatives, since the preparations of various organoaluminum reagents of type $R_2AlX$ are well established. For instance, treatment of oxime sulfonate (**31**) with dimethylaluminum selenomethylate yields methylselenoimidate (**32**) in 71% yield (equation 18).[28]

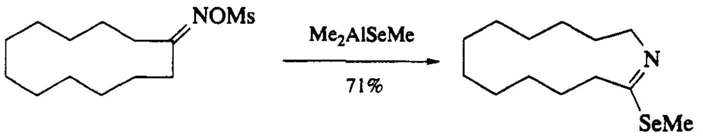
NOMs
Me$_2$AlSeMe
71%
N
SeMe

(18)

**(31)** **(32)**

The combination of diethylaluminum chloride with trimethylsilyl cyanide has been successfully utilized for the general synthesis of imidoyl cyanides from various oxime sulfonates (equation 19).[28]

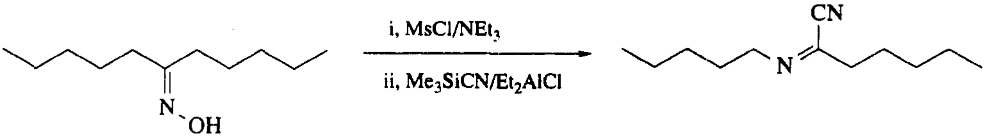
N
OH
i, MsCl/NEt$_3$
ii, Me$_3$SiCN/Et$_2$AlCl
CN
N

(19)

The reductive Beckmann rearrangement of oximes has been effected with several types of aluminum hydride reagents. Early examples exhibited only moderate regioselectivity, giving mixtures of primary amines and rearranged secondary amines. Recently, diisobutylaluminum hydride was reported to be most satisfactory for this type of transformation (equation 20).[29] Here dichloromethane is the solvent of choice, and attempted use of ethereal solvents results in the formation of a mixture of primary and secondary amines.[30]

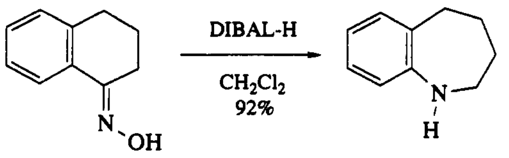

(20)

An unexpected reductive rearrangement was observed in the reaction of the dioxime (33) with diisobutylaluminum hydride in dichloromethane, leading to the diamine (34; equation 21).[31] It should be noted that attempted reaction of (33) under various Beckmann rearrangement conditions resulted either in extensive decomposition or fragmentation.

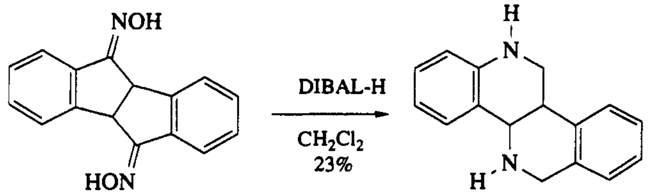

(33) (34)

(21)

### 4.3.1.3 Beckmann Rearrangement–Alkylation Sequence

A most exciting advance in Beckmann rearrangement chemistry is the successive Beckmann rearrangement–alkylation sequence promoted by certain organometallic reagents. Here, organoaluminum reagents behave in an amphoteric manner, inducing the Beckmann rearrangement of oxime sulfonates as well as capturing the intermediate nitrilium ion with the carbon nucleophile from aluminum.[28,32] For example, treatment of oxime mesylate (35) with diethyl(1-hexynyl)aluminum in $CH_2Cl_2$ gives after reduction of the intermediate imine (36) with DIBAL-H, the amine (37) with rigorous regioselectivity (Scheme 2). Further alkylation is achieved with allylmagnesium bromide to furnish the amine (38). This approach possesses a vast potential in the area of alkaloid synthesis, as demonstrated by the facile synthesis of coniine and pumiliotoxin C (equations 22 and 23).

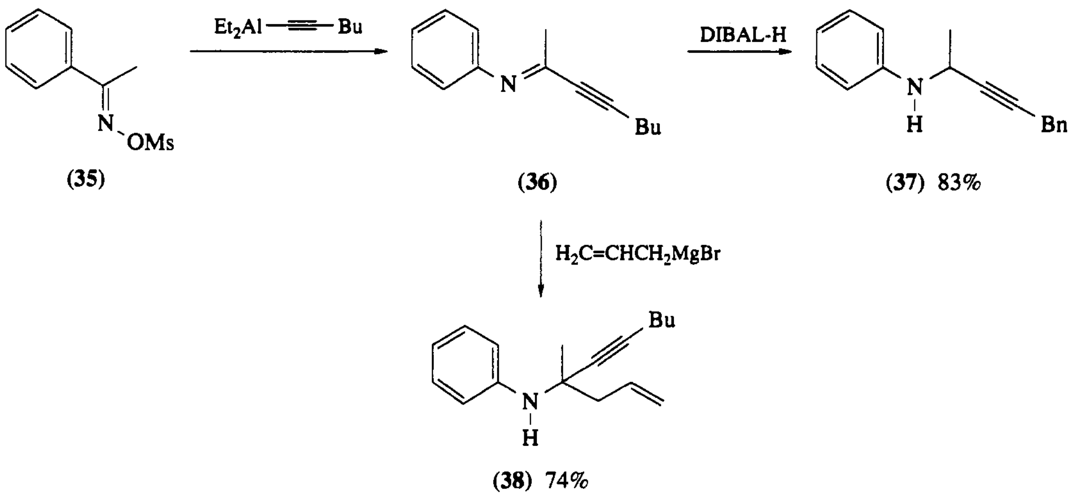

(35) (36) (37) 83%

(38) 74%

Scheme 2

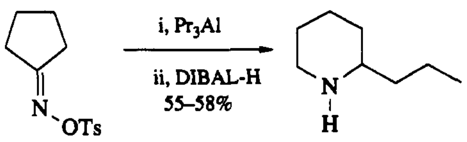

Coniine

(22)

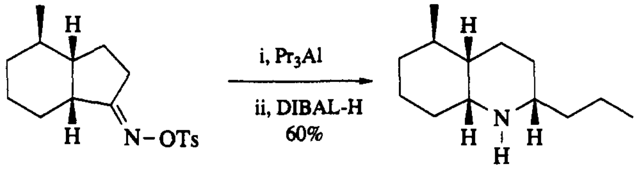

Pumiliotoxin C

(23)

Grignard reagents have also been found to be effective for these types of transformations (equation 24), but not with cyclopentanone oxime sulfonate.[33]

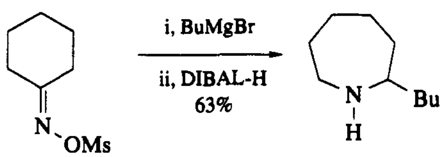

(24)

The isolable imine (**39**), which is obtainable by the rearrangement of 2-undecylcyclopentanone oxime mesylate with $Me_3Al$, can be transformed to either the *cis* or *trans* isomer with high stereoselectivity depending on the choice of the reducing agents (Scheme 3). Reduction of (**39**) with $Me_3Al–LiAlH_4$ completes a short synthesis of solenopsin A (**40**).[34]

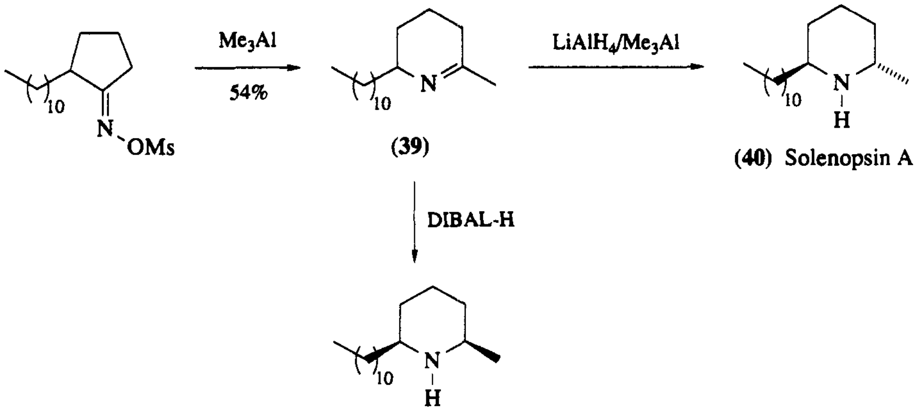

**Scheme 3**

Trapping of the Beckmann intermediates with enol silyl ethers affords facile entry to a variety of enamino ketones.[35] This condensation takes place with retention of regiochemical integrity in both oxime sulfonates and enol silyl ethers. Reaction of 6-methyl-1-(trimethylsiloxy)-1-cyclohexene (**41**) or 1-methyl-2-(trimethylsiloxy)-1-cyclohexene (**42**) with cyclohexanone oxime mesylate furnishes (**43**) or (**44**), respectively, as the sole isolable products (equation 25). Another striking feature of the reaction is the high chemospecificity. The condensation of the enol silyl ether (**45**), derived from *p*-acetoxyacetophenone, occurs in a chemospecific fashion with cyclododecanone oxime mesylate, the acetoxy moiety remaining intact (equation 26). Oxime sulfonates of aromatic ketones and cyclopentanones are not employable since complex reaction mixtures are formed.

Beckmann rearrangement of phthalimide derivative (**46**) is induced by aluminum chloride in benzene and terminated by electrophilic aromatic substitution, as shown in equation (27).[36]

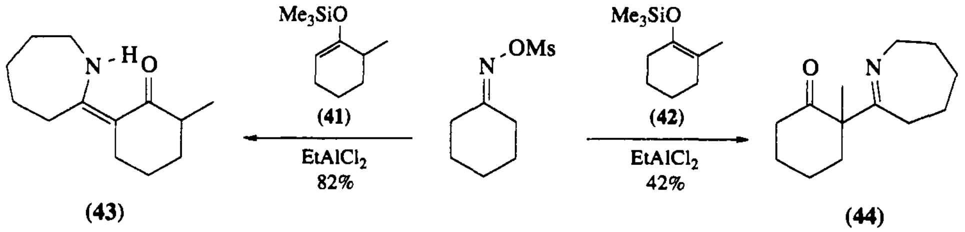

(25)

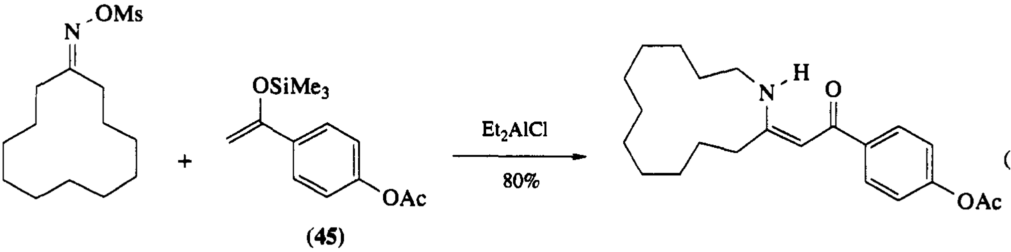

(26)

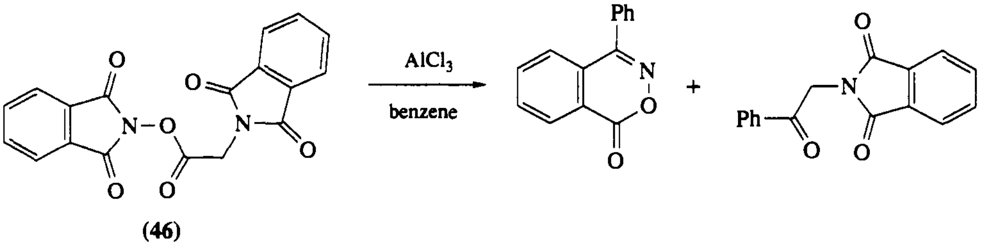

(27)

### 4.3.1.4 Beckmann Rearrangement–Cyclization Sequence

The efficient activation of oxime sulfonates by organoaluminum reagents enables the intramolecular cyclization of alkenic oxime mesylates, which involves the electrophilic addition of the intermediate nitrilium ion to the double bond. This results in the direct formation of a wide variety of structurally diverse carbocyclic and heterocyclic systems. Four distinct cyclization modes, *i.e. endo*(B)-*endo*, *endo*(B)-*exo*, *exo*(B)-*endo* and *exo*(B)-*exo* are possible, as shown in Scheme 4.[37] The values in parentheses refer to the yields obtained using $SnCl_4$.

The *endo*(B) cyclizations are highly useful in natural product syntheses. Solenopsin B can be prepared *via* the *endo*(B)-*endo* cyclization in two steps from a simple acyclic precursor (equation 28). Analogous *endo*(B) cyclizations have been utilized as key steps in synthetically important transformations (equations 29 and 30).[38]

The alkenic cyclizations described above are terminated by deprotonation, yielding unsaturated imines. The intermediate carbocations, however, may also be captured by carbon nucleophiles to afford saturated imines. For example, treatment of the oxime mesylate (**47**) with $Me_3Al$ followed by reduction with DIBAH predominantly produces the methylated product (**48**; equation 31).[37]

The similar *endo*(B)-*exo* cyclizations have been effected with phosphorus pentoxide and more recently with trimethylsilyl polyphosphate (equation 32 and 33).[39–41] The starting alkenic oximes are readily obtainable by the alkylation of the oxime dianion. Hence the overall process provides convenient access to the stereospecific synthesis of various heterocycles bearing substituents in the desired positions.

The Beckmann rearrangement–cyclization sequence terminated by aromatic moieties is fairly general. Recent examples of isoquinoline and dihydroisoquinoline synthesis exhibit two-step sequences using phosphorus pentachloride and phosphorus pentoxide *via* the cyclization of the intermediate imidoyl chlorides (equation 34).[42]

Indoloisoquinoline skeletons can be readily constructed, *via* intramolecular cyclization, by treatment of the indole aldoxime (**49**) with sulfuric acid in refluxing ethanol (equation 35).[43] This example is rather unusual, since the rearrangement of aldoximes to formamides is difficult to achieve.

*endo*(B)–*endo* cyclization

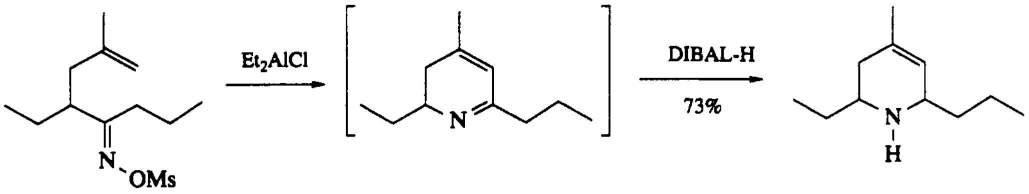

N
OMs
$Et_2AlCl$
N
DIBAL-H
73%
N
H

*endo*(B)–*exo* cyclization

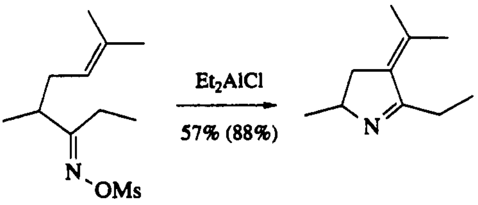

N
OMs
$Et_2AlCl$
57% (88%)
N

*exo*(B)–*endo* cyclization

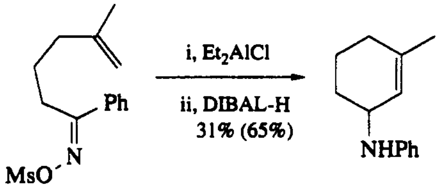

Ph
MsO
N
i, $Et_2AlCl$
ii, DIBAL-H
31% (65%)
NHPh

*exo*(B)–*exo* cyclization

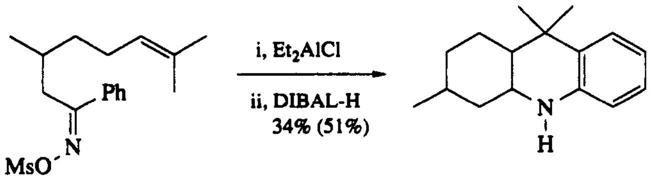

Ph
MsO
N
i, $Et_2AlCl$
ii, DIBAL-H
34% (51%)
N
H

**Scheme 4**

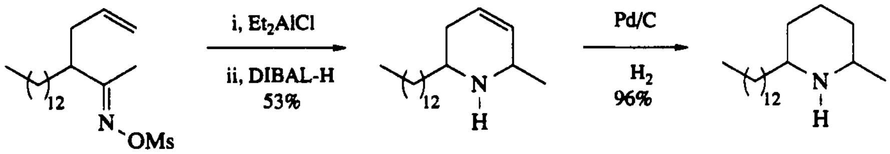

12
N
OMs
i, $Et_2AlCl$
ii, DIBAL-H
53%
12
N
H
Pd/C
$H_2$
96%
12
N
H

Solenopsin B

(28)

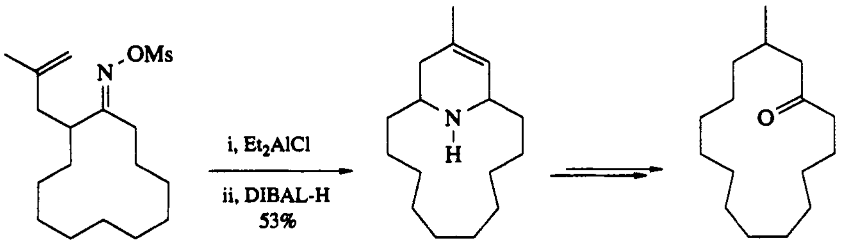

N
OMs
i, $Et_2AlCl$
ii, DIBAL-H
53%
N
H
O

Muscone

(29)

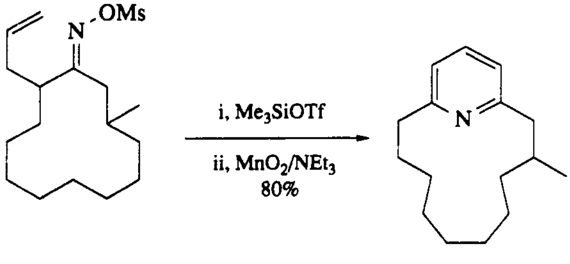
OMs
N
i, Me$_3$SiOTf
ii, MnO$_2$/NEt$_3$
80%
N

Muscopyridine

(30)

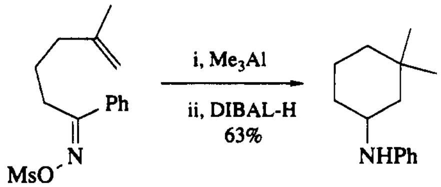
Ph
MsO
N
i, Me$_3$Al
ii, DIBAL-H
63%
NHPh

**(47)** **(48)**

(31)

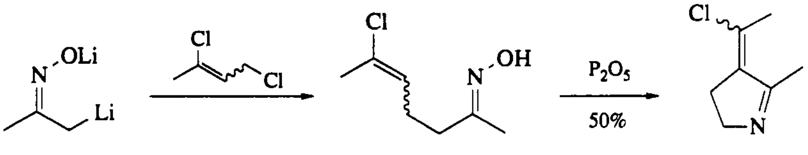
OLi
N
Li
Cl
Cl
Cl
OH
N
P$_2$O$_5$
50%
Cl
N

(32)

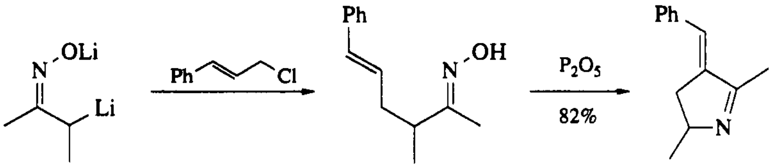
OLi
N
Li
Ph
Cl
Ph
OH
N
P$_2$O$_5$
82%
Ph
N

(33)

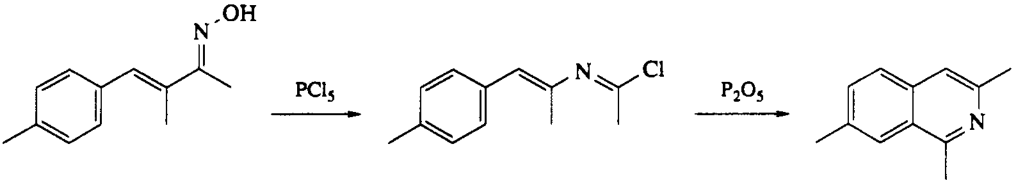
OH
N
PCl$_5$
N
Cl
P$_2$O$_5$
N

(34)

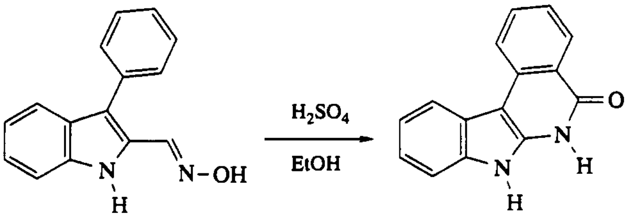
N
H
N-OH
H$_2$SO$_4$
EtOH
O
N
H
N
H

**(49)**

(35)

### 4.3.1.5 Beckmann Fragmentations

Oximes that have quaternary carbons adjacent to the oxime carbon are prone to undergo fragmentation as a major reaction pathway, furnishing nitriles. Steroidal ketoxime (**50**) and tetrahydrofuranyl ketoxime (**52**) give nitriles (**51**) and (**53**), respectively, as major products (equations 36 and 37).[44,45]

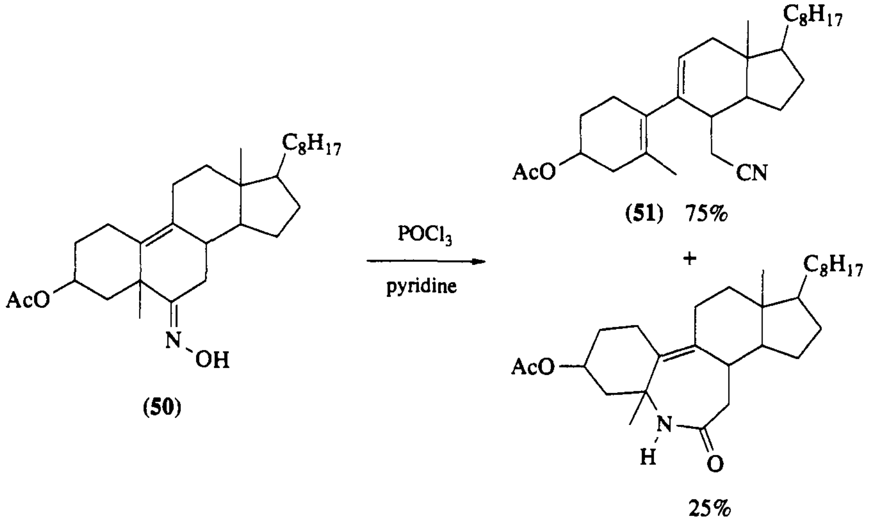
$C_8H_{17}$
AcO
N
OH
(50)
POCl$_3$
pyridine
$C_8H_{17}$
AcO
CN
(51) 75%
+
$C_8H_{17}$
AcO
N
H
O
25%

(36)

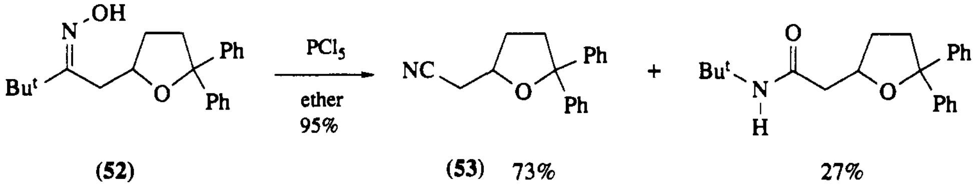
OH
N
Bu$^t$
O
Ph
Ph
(52)
PCl$_5$
ether
95%
NC
O
Ph
Ph
(53) 73%
+
O
Bu$^t$
N
H
O
Ph
Ph
27%

(37)

In the course of an asymmetric synthesis of steroids, iodocamphor oxime (**54**) was converted to a 1:1 mixture of chiral cyclopentenyl cyanides, (**55**) and (**56**), on treatment with *p*-toluenesulfonyl chloride in pyridine at 0 °C (equation 38).[46] Notably, equilibration of this mixture with anhydrous trifluoroacetic acid afforded essentially pure (**56**), in 81% yield, which was further elaborated in the synthesis of chiral *trans*-hydrindenone.

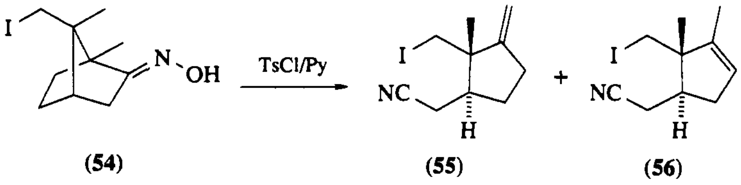
I
N
OH
(54)
TsCl/Py
I
NC
H
(55)
+
I
NC
H
(56)

(38)

The presence of α-substituents such as carbonyl, amino, hydroxy, alkoxy or alkylthio groups on oxime substrates also promotes the Beckmann fragmentation to nitriles under thermal or acid-catalyzed conditions. A recent example demonstrates the synthesis of functionalized nitriles by the regioselective sulfenylation–alkylation of cyclic oximes *via* their dianions and subsequent regioselective ring cleavage (equation 39).[47] Acetals of 1,2-dione monooximes are susceptible to the Beckmann fragmentation in the presence of trimethyl orthoformate and methanesulfonic acid (equation 40).[48]

The trimethylsilyl group can rigorously control and direct the Beckmann fragmentation leading to the regio- and stereo-specific formation of unsaturated nitriles (equations 41 to 43).[49,50] Oxime acetate (**57**) fragments to the *cis*-alkenic nitrile (**58**) in 90% yield, whereas its epimer (**59**) affords the *trans*-alkenic nitrile (**60**) in 94% yield under the same conditions. Furthermore, fluoride-induced fragmentation can re-

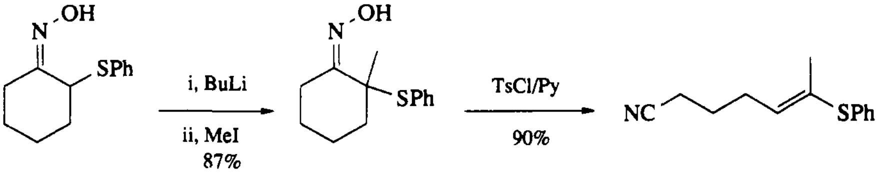
OH
N
SPh
i, BuLi
ii, MeI
87%
OH
N
SPh
TsCl/Py
90%
NC
SPh

(39)

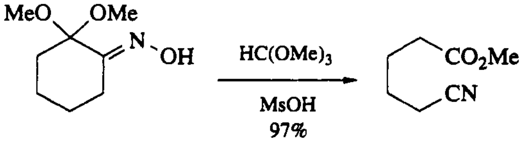
MeO
OMe
N
OH
HC(OMe)3
MsOH
97%
CO2Me
CN

(40)

sult in the stereochemical reversal of the alkenic bond, as shown in the equation (43). This approach is applicable to the synthesis of some insect pheromones.

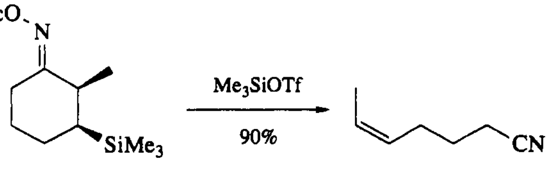
AcO
N
SiMe3
Me3SiOTf
90%
CN

**(57)** **(58)**

(41)

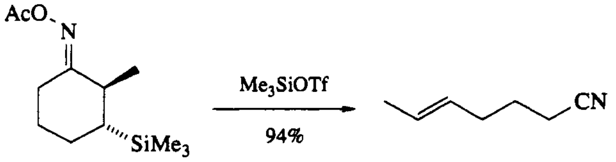
AcO
N
SiMe3
Me3SiOTf
94%
CN

**(59)** **(60)**

(42)

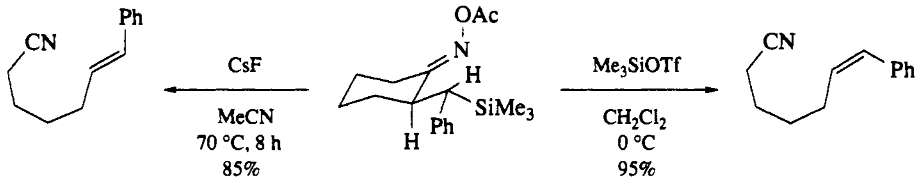
CN
Ph
CsF
MeCN
70 °C, 8 h
85%
OAc
N
H
SiMe3
Ph
H
Me3SiOTf
CH2Cl2
0 °C
95%
CN
Ph

(43)

Aldoxime fragmentation is a well-known process for nitrile synthesis, and numerous reagents have been developed for this purpose. Trimethylsilyl iodide was recently found to be effective as a dehydration agent.[27]

Closely related to the aldoxime fragmentation is the base-catalyzed ring cleavage of C(3)-substituted isoxazoles.[51] Quite recently a novel base-catalyzed isoxazole–oxazole ring transformation was realized in the conversion of ethyl 5-hydroxy-3-(5-methylisoxazol-4-yl)isoxazole-4-carboxylate (**61**) into ethyl 4-cyano-5-methyloxazol-2-ylacetate (**62**; Scheme 5).[52]

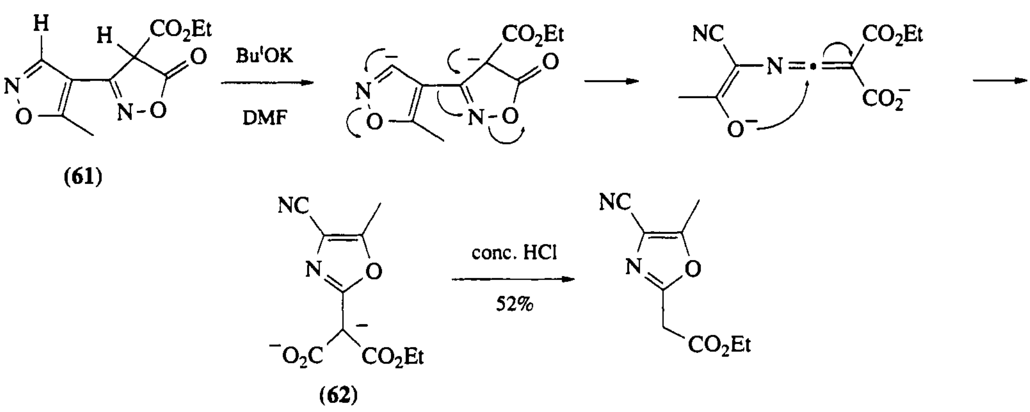
H
H
CO2Et
O
N
O
N-O
Bu^tOK
DMF
CO2Et
O
N
O
N-O
NC
N
CO2Et
CO2−
O−
NC
N
O
−O2C
CO2Et
conc. HCl
52%
NC
N
O
CO2Et

**(61)**

**(62)**

**Scheme 5**

## 4.3.2 BAMFORD–STEVENS REACTION

The Bamford–Stevens reaction is the base-catalyzed decomposition of arenesulfonylhydrazones of aldehydes and ketones, leading to the formation of alkenes and/or cyclopropanes. There are several important general reviews in this area of organic synthesis.[53–55] Since the reactions are mostly carried out either in protic or in aprotic solvents, the reaction types are divided into the protic and aprotic Bamford–Stevens processes. This section reviews recent examples in the synthesis of alkenes and cyclopropanes from arenesulfonylhydrazones, which is closely related to the following Shapiro reaction.

### 4.3.2.1 Protic Bamford–Stevens Process

The original Bamford–Stevens reaction employs protic solvents in the decomposition of a tosylhydrazone with a strong base. Ethylene glycol is the most popular and reliable solvent. The tosylhydrazone (**63**), bearing an adjacent cyclopropyl group, decomposes on treatment with sodium methoxide in ethylene glycol to give four alkenic products (equation 44).[56] Possible mechanisms in the formation of these products are in agreement with previous mechanistic conclusions concerning tosylhydrazone decompositions.[53] Very often different behavior is observed in the decomposition of tosylhydrazones of aliphatic ketones under protic or aprotic Bamford–Stevens conditions. For example, in the case of the protic medium, reaction of oxabicyclic ketone tosylhydrazone (**64**) with sodium in ethylene glycol at 115–120 °C yields hydroxy ketone (**67**), mainly *via* the intermediate diazo compound (**65**) followed by the *exo*-diazonium cation (**66**). In contrast, (**64**), subjected to the aprotic condition (excess sodium methoxide in diglyme at 135–140 °C), gives diazetine (**69**) *via* carbene intermediate (**68**; Scheme 6).[57]

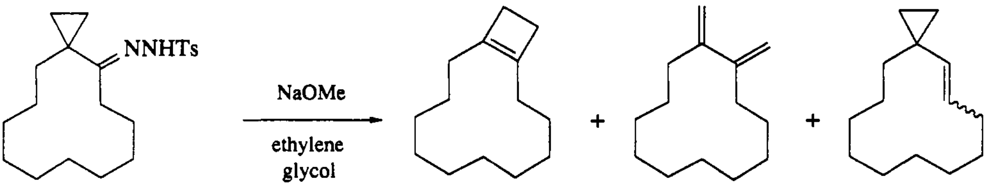

(44)

(**63**) 60% 10% 30%

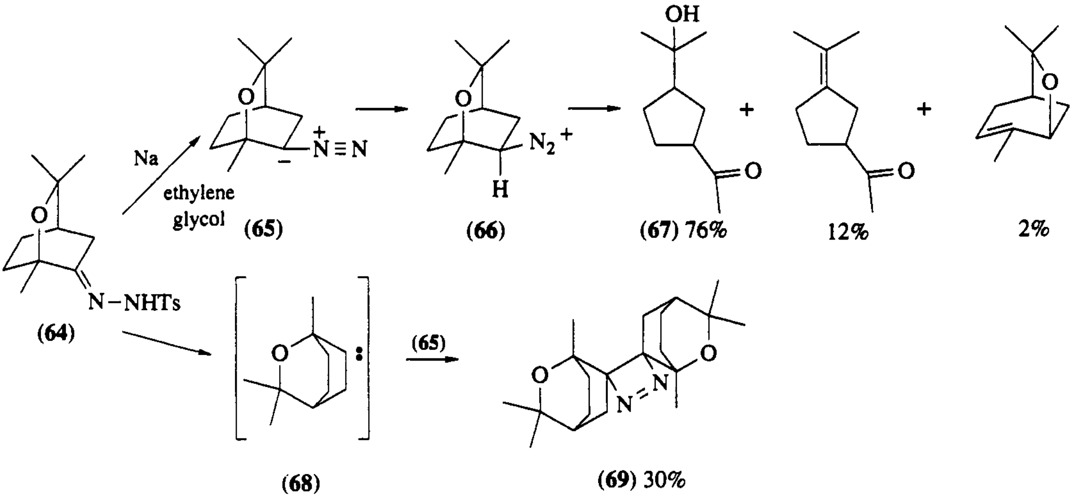

Scheme 6

Interesting stereochemical aspects of the protic Bamford–Stevens reactions of the epimeric 7-oxohexahydrocannabinol tosylhydrazone acetates (**70**) and (**72**) have been recently demonstrated. When the axial epimer (**70**) was added to sodium ethylene glycol, the ring expansion product (**71**) was obtained in 38% yield. On the other hand, reaction of the equatorial epimer (**72**) under the same conditions yielded (**73**) in 56% yield (equations 45 and 46).[58] Notably, the aprotic Bamford–Stevens reaction of the axial epimer (**70**) gave rise to (**73**) (30–40% yield) after acetylation.

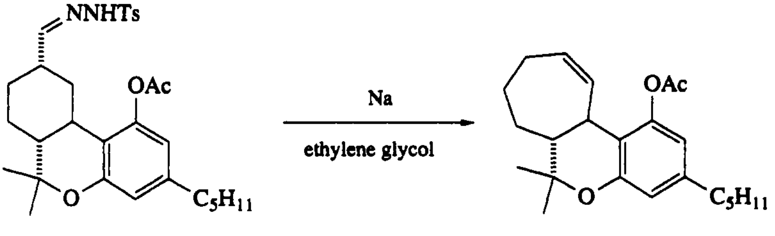

**(70)** **(71)**

(45)

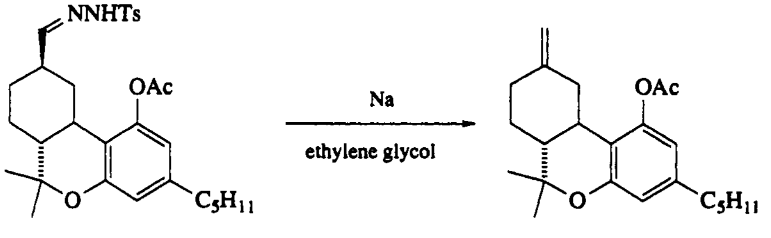

**(72)** **(73)**

(46)

The protic Bamford–Stevens reaction has been successfully utilized in the asymmetric synthesis of the naturally occurring sesquiterpenes (+)-α-eudesmol and (–)-α-selinene. Here, the more-substituted alkene was formed preferentially (equation 47).[59]

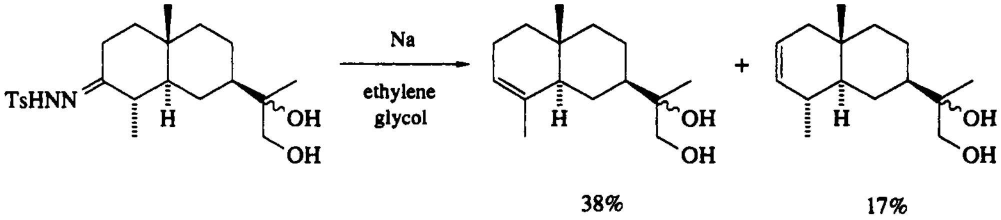

(47)

### 4.3.2.2 Aprotic Bamford–Stevens Process

The aprotic reaction is usually executed with bases in a solvent of little or no proton-donating ability, such as diglyme or diethyl carbitol. These conditions provide convenient ways of carbene generation from tosyl hydrazones, which collapse to rearranged alkenes and insertion products as exemplified in the decomposition of cyclooctanone tosylhydrazone on treatment with sodium methoxide in diethyl carbitol or with KH/18-crown-6 in diglyme (equation 48).[60] In a more complex example, pyrolytic or photolytic decomposition of the lithium salt of the substrate (**74**; Scheme 7) results in the formation of (**77**) to (**82**).[60] The formation of (**77**) to (**79**) is thought to occur *via* the singlet carbene (**75**), while (**80**) to (**82**) are generated *via* the triplet carbene (**76**), or a closely related species.

A structurally intriguing dimethyl[6]ditriaxane (**84**) has been synthesized from the polycyclic diketone tosylhydrazone (**83**) by the aprotic Bamford–Stevens reaction *via* a carbenic intermediate (equation 49).[61]

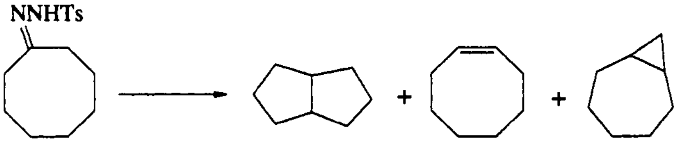

(48)

| | | | |
|---|---|---|---|
| KH/18-crown-6 | 45% | 47% | 8% |
| NaOMe | 46% | 45% | 9% |

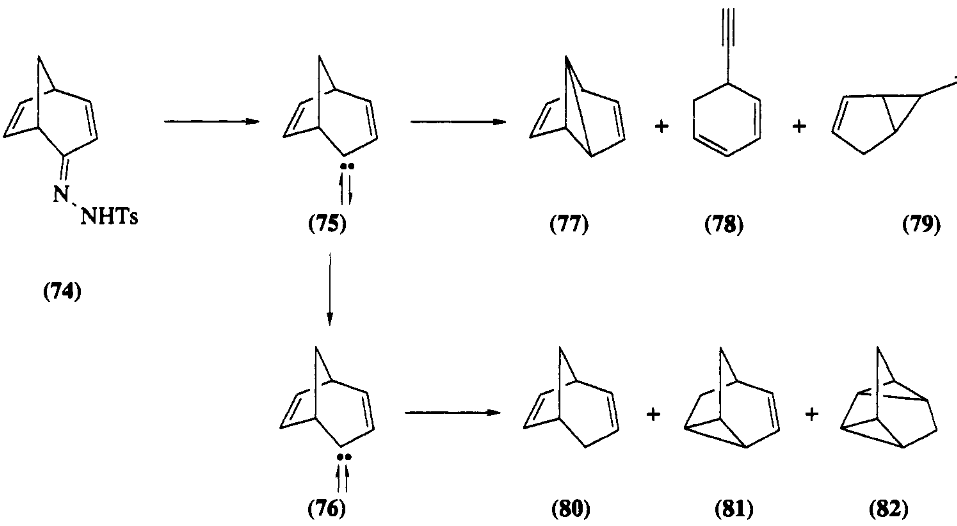
NHTs
(74)
(75)
(76)
(77)
(78)
(79)
(80)
(81)
(82)

**Scheme 7**

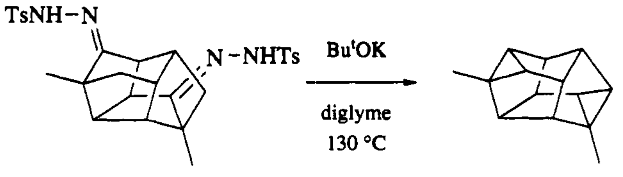
TsNH–N
N–NHTs
Bu$^t$OK
diglyme
130 °C

(83) (84) (49)

The aprotic Bamford–Stevens reaction has been utilized for the development of a methodology towards 1,2-carbonyl transposition in natural product synthesis. The example in Scheme 8 illustrates the regiocontrolled alkene formation for the synthesis of hirsutic acid.[62]

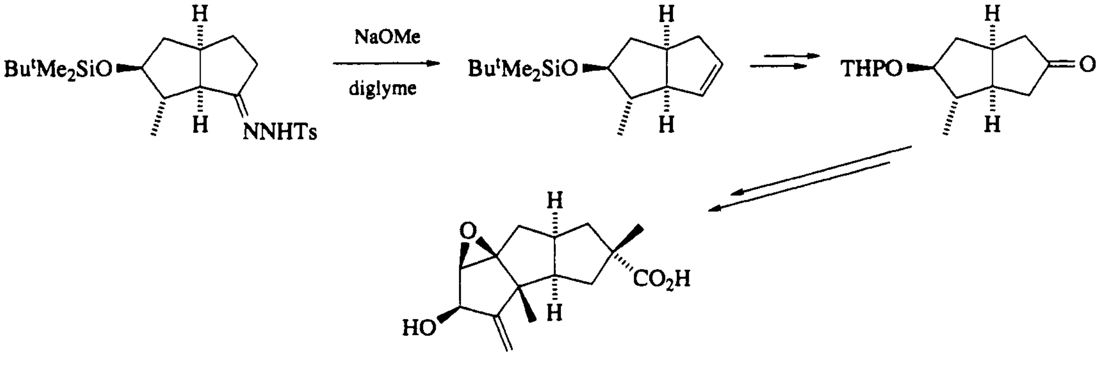
H
Bu$^t$Me$_2$SiO
H
NNHTs
NaOMe
diglyme
H
Bu$^t$Me$_2$SiO
H
H
THPO
O
H
O
H
CO$_2$H
HO
H

Hirsutic acid

**Scheme 8**

A non-Kekule molecule, a *m*-xylylene (**88**), has been generated by the Bamford–Stevens reaction of a fulvene–ketene adduct (**85**), *via* the homofulvene (**87**) from the intermediate carbene (**86**). This unstable intermediate readily dimerizes to octamethyl[2.2]metacyclophane (**89**; Scheme 9).[63]

The Bamford–Stevens reaction is the key step in a convenient procedure for the conversion of aldehydes and ketones into the corresponding diazoalkanes. Here, the use of 2,4,6-triisopropylbenzenesulfonylhydrazone (trisylhydrazone) is far superior to the use of the more common tosylhydrazones (equation 50).[64] This behavior is attributed to the greater release of steric compression in the decomposition of *ortho*-substituted arenesulfonylhydrazones.

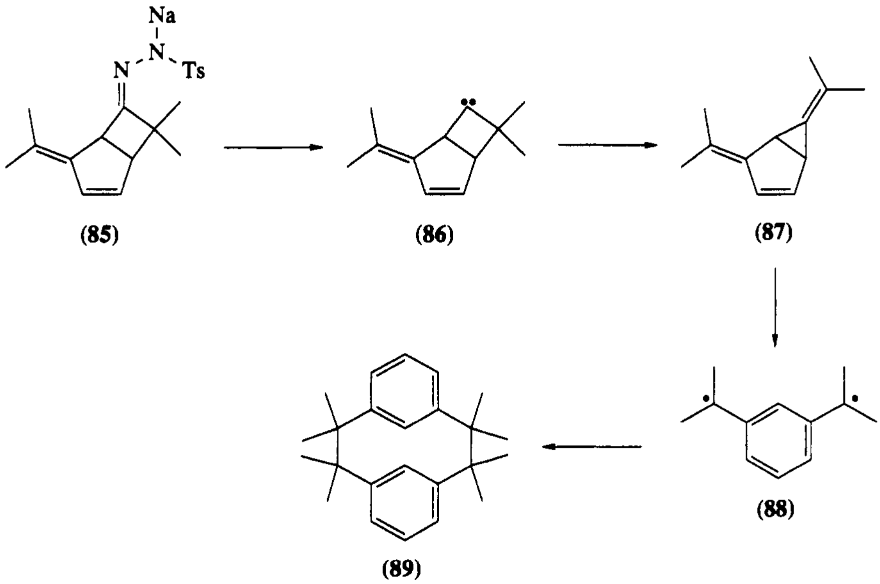

**Scheme 9**

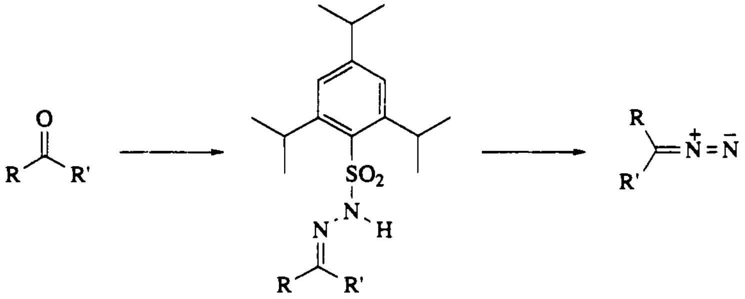

(50)

Mechanistic information on the photolytic Bamford–Stevens reaction is provided by the successful isolation of a diazo hydrocarbon as a reaction intermediate from the direct photolysis of a tosylhydrazone sodium salt (**90**; Scheme 10).[65] This study also clarifies that the 'carbene' derived thermally and that derived photolytically behave differently with respect to the stereoselectivity of the 1,2-hydrogen shift that produces the alkene.

The Bamford–Stevens reaction is particularly effective for the generation of 9-phenyl-1(9)-homocubene (**93**), the most twisted alkene yet known.[66] Thus, thermolysis of the cubyl phenyl ketone tosylhydrazone (**91**) in ethanolic sodium ethoxide or photolysis of the diazo compound (**92**) in ethanol both give good conversions to a 3:2 mixture of the isomeric ethers (**95**) and (**96**) (Scheme 11). The formation of (**96**) suggests the intervention of 1-phenyl-9-homocubylidene (**94**) *via* the rearrangement of (**93**).

Mesitylene-2-sulfonylhydrazone is found to be particularly effective in the Eschenmoser fragmentation reaction. For example, reaction of the epoxy ketone of type (**97**) gives rise to the corresponding cycloalkynone in reasonable yield (equation 51).[67] The same reaction with tosylhydrazone failed, however.

## 4.3.3 SHAPIRO REACTION

The title reaction represents the decomposition of arenesulfonylhydrazones with alkyllithium reagents to furnish unrearranged, less-substituted alkenes almost exclusively. The *in situ* generated alkenyllithium reagents can be further elaborated by reaction with an electrophile. Since the electrophile can be easily varied, the Shapiro reaction permits the convenient transformation of a ketone into a single substituted alkene in a synthetically useful way.[53,68] This section will highlight the versatility of this reaction in selective organic synthesis.

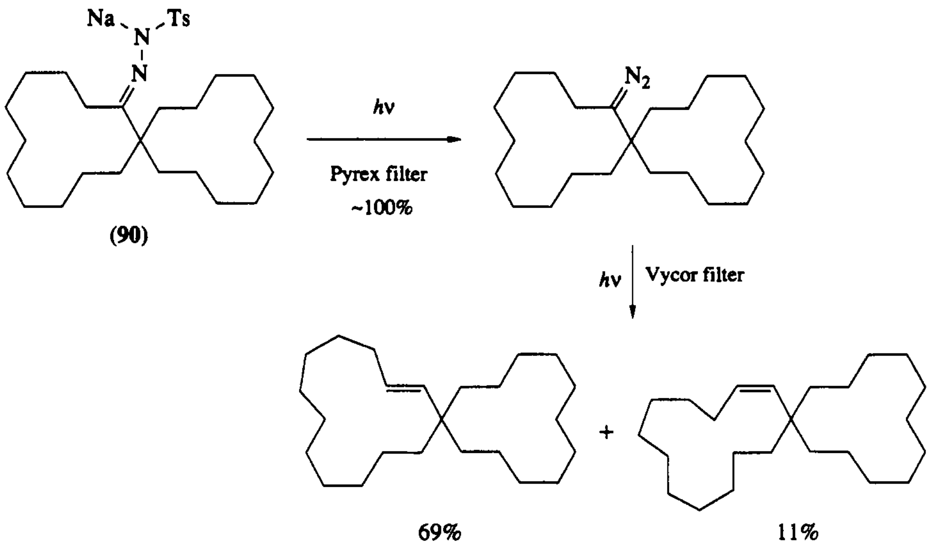
Na
N
Ts
N
N
(90)
hν
Pyrex filter
~100%
$N_2$
hν
Vycor filter
+
69%
11%

Scheme 10

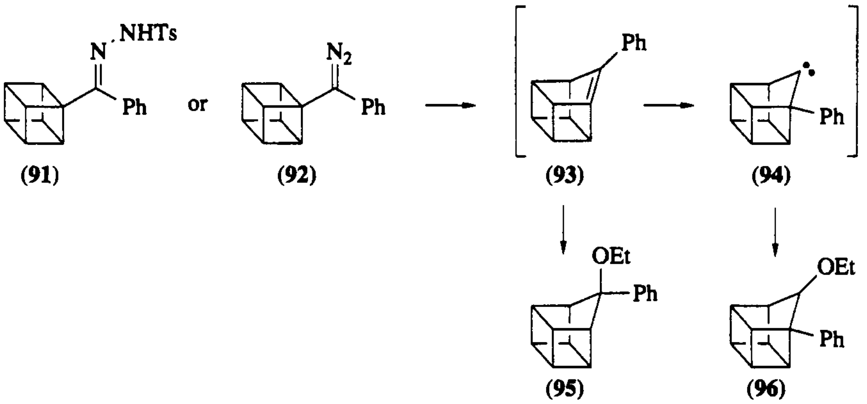
N
NHTs
Ph
(91)
or
$N_2$
Ph
(92)
Ph
(93)
Ph
(94)
OEt
Ph
(95)
OEt
Ph
(96)

Scheme 11

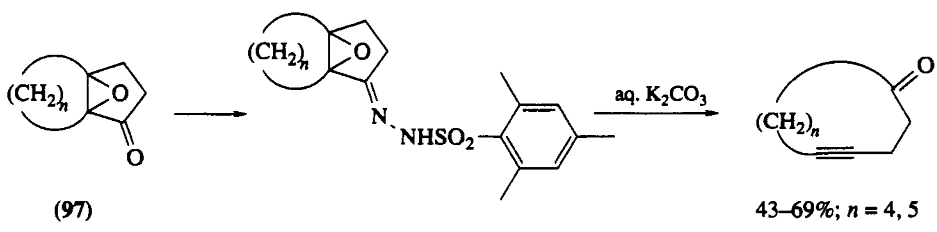
$(CH_2)_n$
O
O
(97)
$(CH_2)_n$
O
N
$NHSO_2$
aq. $K_2CO_3$
O
$(CH_2)_n$
43–69%; n = 4, 5

(51)

The original Shapiro reaction involves the preparation of unfunctionalized alkenes from ketone tosylhydrazones by quenching of the *in situ* generated alkenyllithium reagents with water. Recent applications of this reaction in natural product synthesis include the synthesis of 9(0)-methanoprostacyclin (Scheme 12),[62] the *in vitro* conversion of humulene to $\Delta^{8(13)}$-capnellene (Scheme 13),[69] the synthesis of the basic skeleton of isoatisirene (equation 52)[70] and the total synthesis of the eudesmanolides rothin A and rothin B (equation 53).[71]

New methods for the 1,2-transposition and alkylative 1,2-transposition of carbonyl groups *via* vinylsilanes or vinyl sulfides have been explored which are based on the Shapiro reaction as the key reaction (Schemes 14 and 15).[72–74] These methodologies have been further extended to regiocontrolled enone transpositions.[75]

As already demonstrated in the Bamford–Stevens reaction, 2,4,6-triisopropylhydrazones (trisylhydrazones) are also found to undergo fragmentation more easily than the corresponding tosylhydrazones in

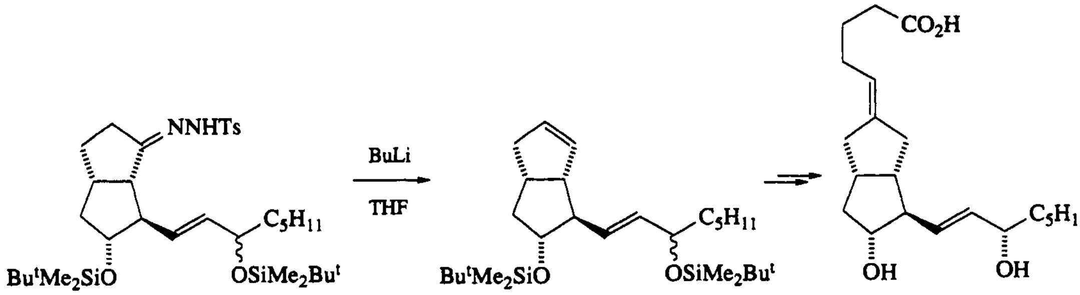

9(0)-Methanoprostacyclin

**Scheme 12**

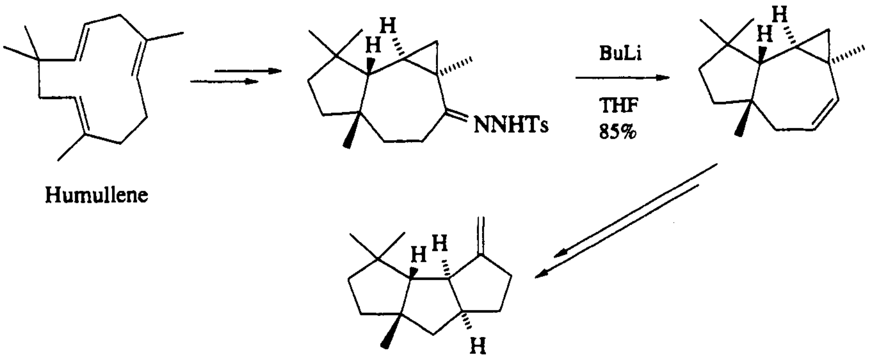

Humullene

$\Delta^{8(13)}$-Capnellene

**Scheme 13**

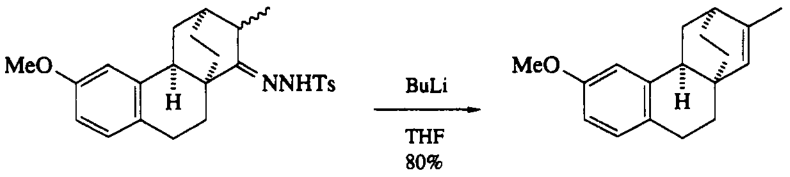

(52)

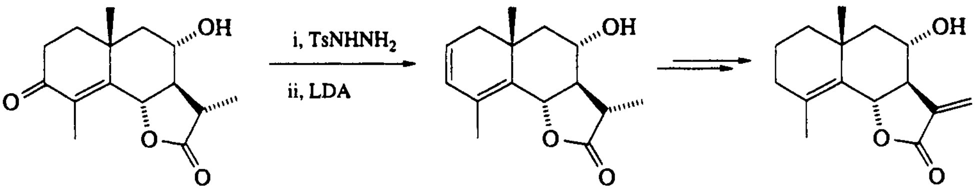

(53)

Rothin A

the Shapiro reaction.[76] In fact, the conversion of the hydrazone (**98**) to the annulene (**99**) is much improved by using trisylhydrazone (Scheme 16).[77]

The modified Shapiro reaction is quite effective for the regioselective generation of 1-octen-2-yl-lithium (**100**) from an (*E,Z*)-mixture of 2-octanone trisylhydrazones (Scheme 17).[78] Here, the use of hexane–TMEDA is crucial for regiospecifically obtaining the less-substituted alkenyllithium reagent. In THF the regioselectivity is controlled by the stereochemistry of the hydrazones, and the ratio of a 1-octene/2-octene product is identical with that of the original hydrazone mixture. In contrast, the more-substituted regioisomeric alkenyllithium reagent (**101**) has been successfully generated, as outlined in Scheme 18.[79] The regiospecifically generated alkenyllithium reagent can be trapped with a variety of electrophiles, as illustrated in Scheme 19.[78,80]

Reactive alkenyl anions prepared by the Shapiro reaction from trisylhydrazones of polyenones and their smooth 1,2-addition to polyenals provides a new route to the versatile synthesis of hydroxymethyl-

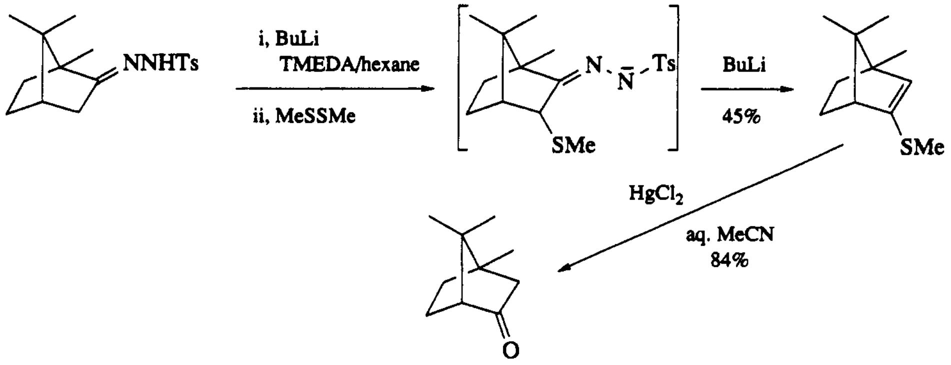
NNHTs
i, BuLi
TMEDA/hexane
ii, MeSSMe
N
N
Ts
SMe
BuLi
45%
SMe
HgCl2
aq. MeCN
84%
O

Scheme 14

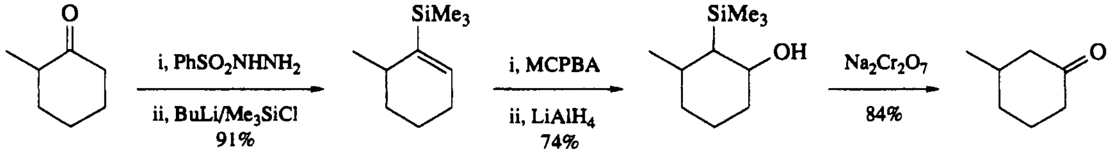
O
i, PhSO2NHNH2
ii, BuLi/Me3SiCl
91%
SiMe3
i, MCPBA
ii, LiAlH4
74%
SiMe3
OH
Na2Cr2O7
84%
O

Scheme 15

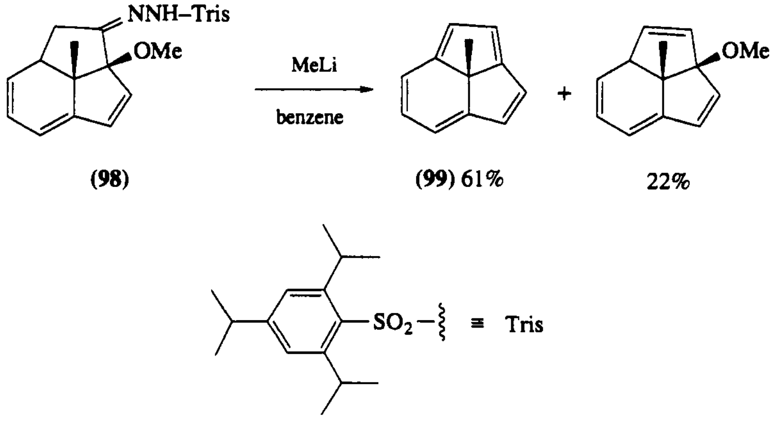
NNH–Tris
OMe
MeLi
benzene
+
OMe
(98)
(99) 61%
22%
SO2
≡ Tris

Scheme 16

carotenoids. A typical example is the facile synthesis of optically active carotenediol (**102**), a model compound structurally very close to loroxanthin (Scheme 20).[81]

A new enephosphinilation of ketones has been developed, based on the Shapiro decomposition of trisylhydrazones with BuLi followed by trapping with chlorodiphenylphosphine (Scheme 21).[82] Oxidation of the resulting vinylphosphines with 30% hydrogen peroxide or 40% peroxyacetic acid/sodium carbonate yields the corresponding phosphine oxides.

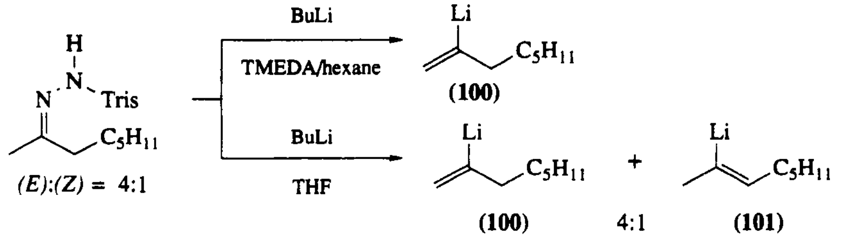
H
N
N
Tris
C5H11
(E):(Z) = 4:1
BuLi
TMEDA/hexane
BuLi
THF
Li
C5H11
(100)
Li
C5H11
+
Li
C5H11
(100)
4:1
(101)

Scheme 17

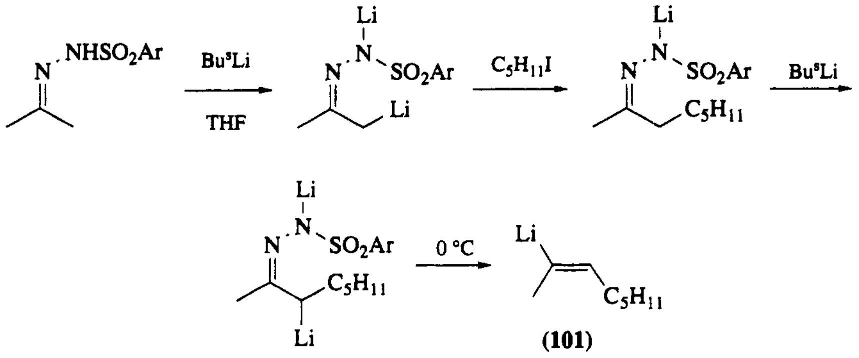

Scheme 18

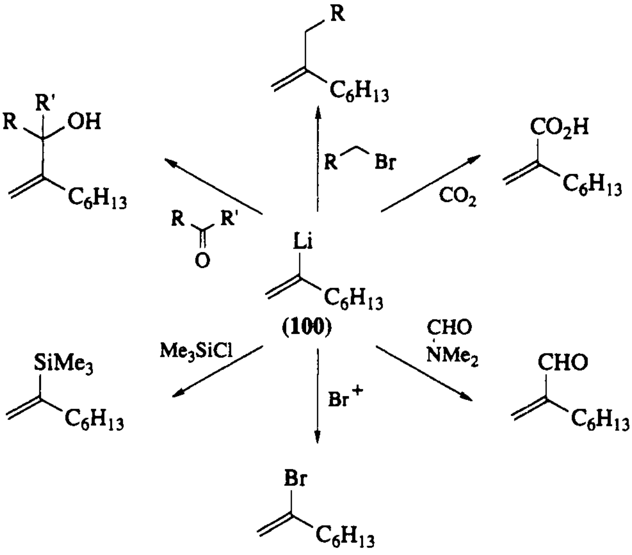

Scheme 19

The modified Shapiro reaction usually requires the use of an excess of base along with a coordinating solvent such as TMEDA: this hampers the clean generation of alkenylcuprate reagents from trisylhydrazones. However, treatment of trisylhydrazones with 2 equiv. of $Bu^tLi$ in THF successfully gives the desired alkenyllithium reagents. Subsequent transmetallation with phenylthiocopper affords the corresponding mixed alkenylcuprates which smoothly undergo conjugate additions to enones (equation 54).[83]

Intramolecular cyclization of an ω-chloro ketone trisylhydrazone *via* the *in situ* generated alkenyllithium has been achieved efficiently, thereby providing a new approach to the synthesis of various unsaturated carbocycles (equation 55).[84]

Amidorazones are very useful as acyl anion equivalents. For example, trisylamidorazones on treatment with $Bu^tLi$ yield α-lithioenamines which subsequently react with electrophiles to give ketones (Scheme 22).[85]

The synthon of the α-acrylate anion is available from a secondary α-keto carboxamide by the Shapiro reaction.[86] The secondary α-ketoamide trisylhydrazones are prepared in a 'one-pot' synthesis by reaction of the isocyanides with acid chloride, water and trisylhydrazine in sequence. In DME solvent, the hydrazone (**103**) is smoothly metallated with BuLi to give the trianion (**104**). Allylation of the trianion (**104**) gives the hydrazone (**105**). Alternatively, warming (**104**) up to room temperature yields the dianion (**106**) which can be intercepted with several electrophiles (Scheme 23). The adduct (**107**) is readily transformed into the *trans*-iodo lactone (**108**) stereospecifically (equation 56). This chemistry also has been applied to a new synthesis of β-lactams (Scheme 24).[87]

The ability of the trisylhydrazone dianion to undergo alkylation further enhances the synthetic potential of the Shapiro reaction. The initial carbonyl alkylation of acetone trisylhydrazone dianion, followed by fragmentation to the functionalized alkenyllithium reagent and subsequent trapping with carbon diox-

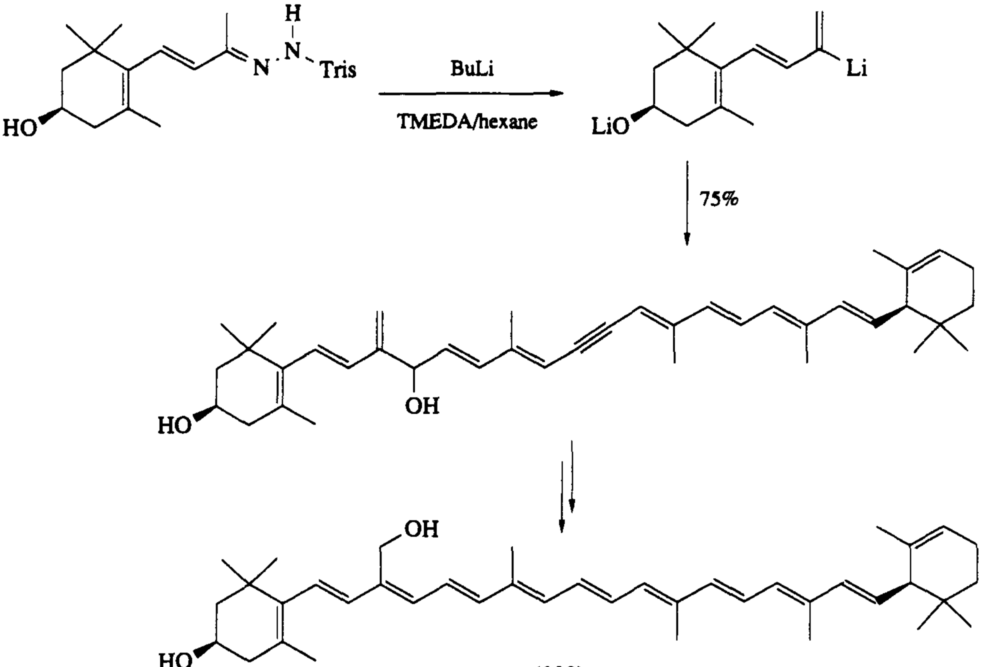
H
N
N
Tris
HO
BuLi
TMEDA/hexane
Li
LiO
75%
OH
HO
OH
HO

**(102)**

**Scheme 20**

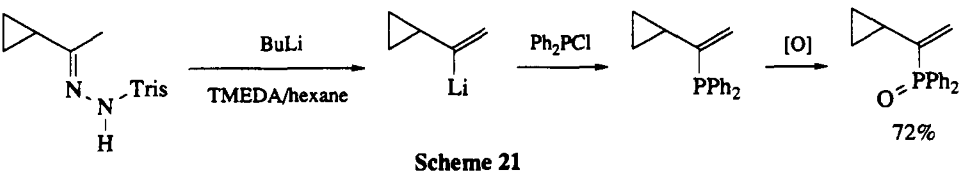
N
N
Tris
H
BuLi
TMEDA/hexane
Li
Ph₂PCl
PPh₂
[O]
O
PPh₂
72%

**Scheme 21**

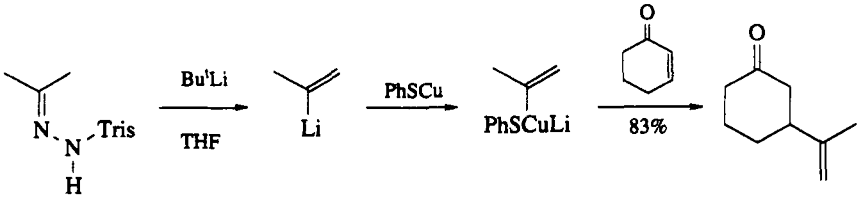
N
N
Tris
H
Bu^tLi
THF
Li
PhSCu
PhSCuLi
O
83%
O

(54)

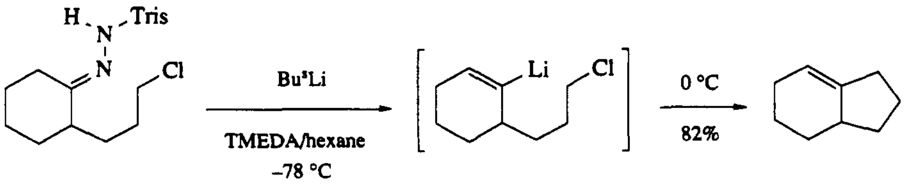
H
N
Tris
N
Cl
Bu^sLi
TMEDA/hexane
-78 °C
Li
Cl
0 °C
82%

(55)

ide provides a novel route to α-methylene-γ-lactones (equation 57).[88] The important 3,5-dimethylene-tetrahydrofuran-2-one unit found in natural products such as obtsusilactones and mahubenolides is also available by this procedure (Scheme 25).[89,90] In the total synthesis of ovalicin, the vinylstannane (**109**) is obtained from acetone trisylhydrazone in a 'one-pot' synthesis (equation 58).[91]

1,3-Diphenylacetone tosylhydrazone can be used as an indicator in the assay of organolithium reagents (equation 59).[92] Here, the end point, the formation of the orange dianion, is sharp and easily observed.

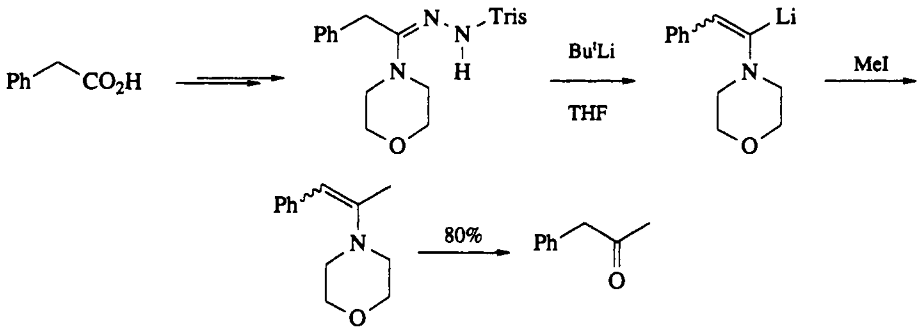
Ph
CO2H
Tris
N
H
O
Bu'Li
THF
Li
MeI
80%

**Scheme 22**

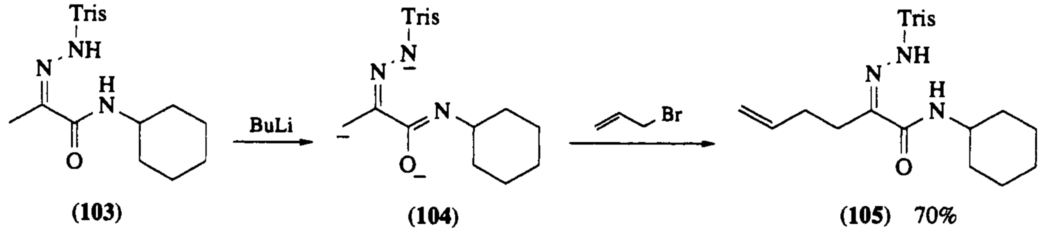
Tris
NH
N
H
O
(103)
BuLi
(104)
Br
(105) 70%
D
82%
(106)
OH
59%

**Scheme 23**

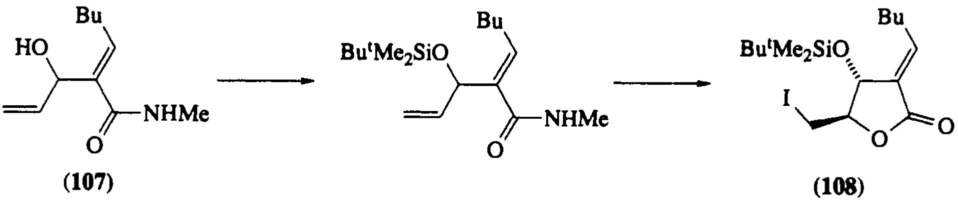
Bu
HO
NHMe
O
(107)
Bu'Me2SiO
I
(108)

(56)

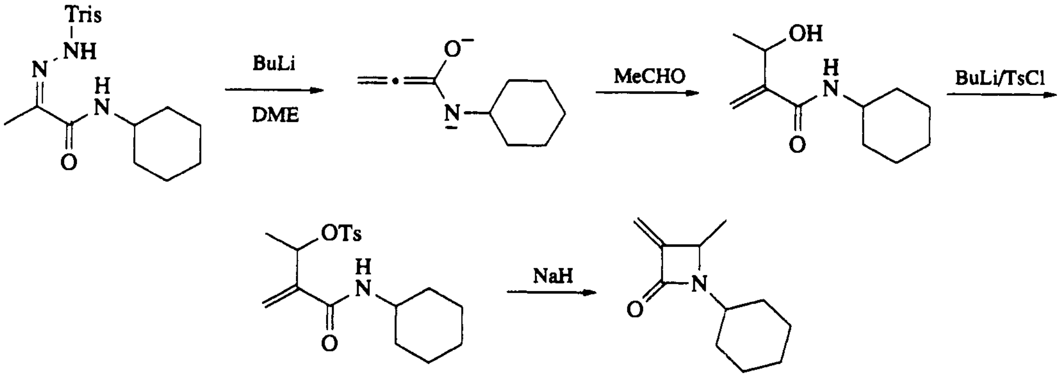
Tris
NH
N
H
O
BuLi
DME
MeCHO
OH
BuLi/TsCl
OTs
NaH

**Scheme 24**

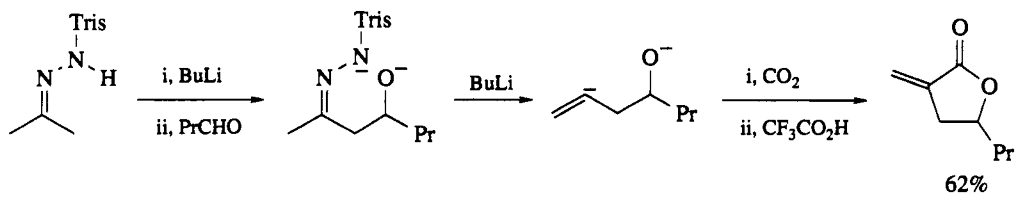
Tris
i, BuLi
ii, PrCHO
BuLi
i, CO₂
ii, CF₃CO₂H
Pr
62%

(57)

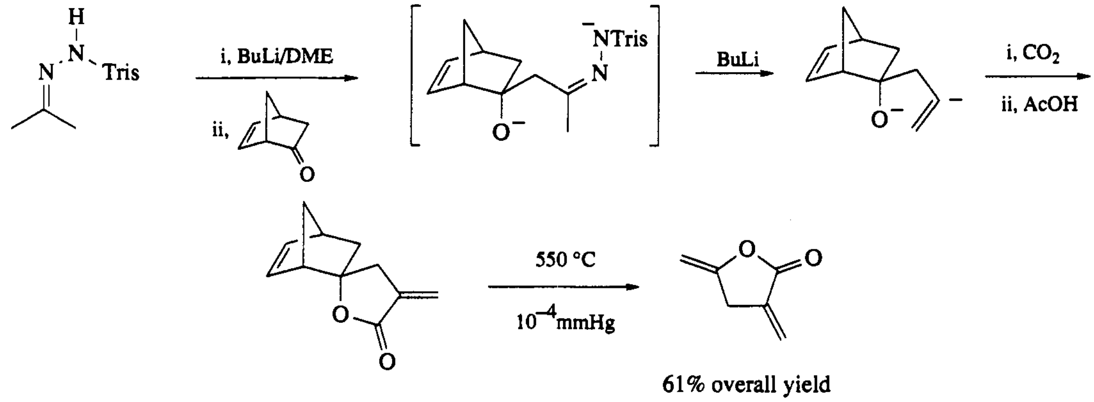
i, BuLi/DME
ii,
NTris
BuLi
i, CO₂
ii, AcOH
550 °C
10⁻⁴mmHg
61% overall yield

**Scheme 25**

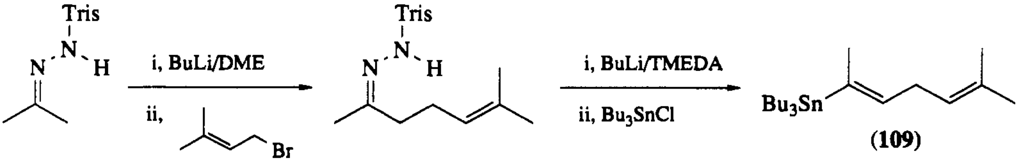
Tris
i, BuLi/DME
ii,
Br
i, BuLi/TMEDA
ii, Bu₃SnCl
Bu₃Sn
(109)

(58)

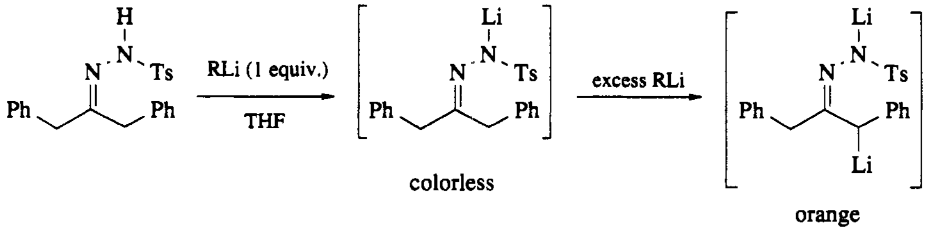
Ts
Ph
RLi (1 equiv.)
THF
Li
colorless
excess RLi
orange

(59)

## 4.3.4 NEBER REARRANGEMENT

The Neber rearrangement involves the base-catalyzed conversion of oxime tosylates, quaternary salts of hydrazones or *N*-chloroimines to α-amino ketones *via* isolable azirine intermediates (equation 60).[93-95]

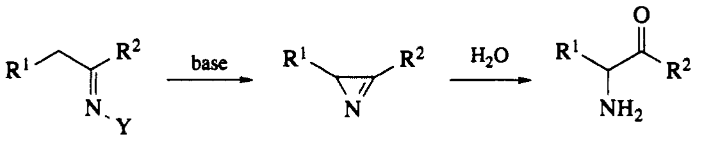
base
H₂O
R¹
R²
NH₂

(60)

Y = OTs, NMe$_3$X, Cl

From mechanistic studies on the Neber reaction, the 2*H*-azirine has been shown to be a distinct intermediate formed by ring closure of a vinyl nitrene.[96] The evidence for the vinyl nitrene has resulted from the reported lack of stereospecificity in converting the (*E*)- and (*Z*)-isomers of *O*-tosyloximes to the same α-amino ketone. Although a vinyl nitrene has been suggested as a possible intermediate in the thermal and photochemical preparations of the azirine ring, direct evidence for such a species is lacking. In this context, the configurational stereospecificity in a modified Neber reaction has been studied with oxime carbamates in order to elucidate the mechanism of this reaction. Thus, oxidation of (*E*)-α,α-bis(methylthio)oxime carbamate (**110**) with $KMnO_4$ or MCPBA yields functionalized 2*H*-azirine derivatives (**111**) or (**112**) exclusively (Scheme 26).[97] On the other hand, reaction of the corresponding (*Z*)-isomer (**113**) results only in oxidation at sulfur (Scheme 27). These observations imply that the involvement of a vinyl nitrene intermediate seems unlikely in the conversion of the oxime carbamate to the 2*H*-azirine.

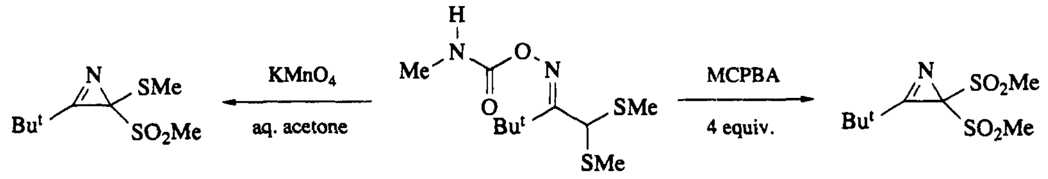

(**111**) 81% (**110**) (**112**) 55%

Scheme 26

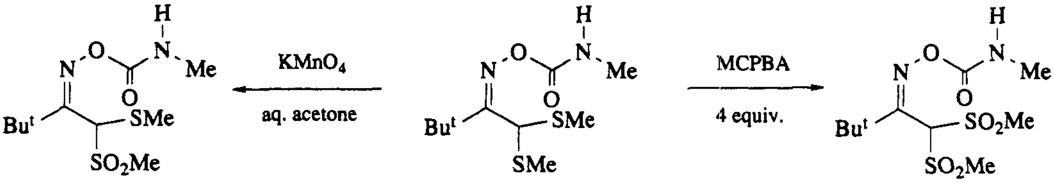

95% (**113**) 38%

Scheme 27

Since α-amino ketones are useful intermediates for the preparation of a variety of heterocycles, including imidazoles, oxazoles and pyrazines, the Neber rearrangement is of high synthetic value particularly in the pharmacological fields. Tetrahydroindenoisoquinoline (**115**) has been synthesized *via* the Neber rearrangement of (**114**) in order to study the structural requirement necessary for interaction with dopamine receptor binding sites (equation 61).[98] Another example is the synthesis of a rigid dopamine congener, naphthoxazine (**117**), starting from methoxytetralone (**116**), *via* a seven-step sequence (equation 62).[99,100] In a search for a new structural type of β-adrenergic antagonist, a series of *trans*-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol (**118**) and 6-(*N*-substituted amino)-3-arylcyclohex-2-enol (**119**) derivatives have been synthesized by using similar methodologies (equations 63 and 64).[101,102]

In the synthesis of various heterocycles from α-amino ketones, pyrazine formation can be a complicating side reaction due to the tendency of the α-amino ketone to dimerize. One way of avoiding this problem would be to generate the α-amino ketone in a protected form, specifically, as an α-amino acetal. Such derivatives allow the manipulation of the amino moiety as desired. Accordingly, the azirine intermediates derived from oxime tosylates by the Neber rearrangement are subsequently treated with acidic ethanol to furnish the corresponding α-amino acetals (equation 65).[103]

A new variant of the Neber rearrangement has been reported recently which involves the treatment of amidoxime-*O*-tosylate (**120**) with sodium methoxide affording 2-amino-1-aziridine (**121**), a useful intermediate for the synthesis of a large array of heterocyclic compounds. None of possible pyrazolone (**122**) or cyanamide (**123**) derivatives were detected in the reaction mixture (Scheme 28).[104]

The Neber rearrangement of dimethylhydrazone quaternary salts to α-amino ketones is a well-studied reaction. However, when this reaction is carried out at temperatures below those of normal Neber condi-

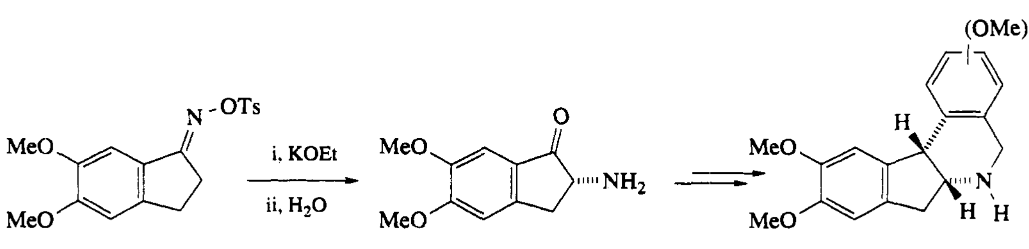

(61)

(**114**) (**115**)

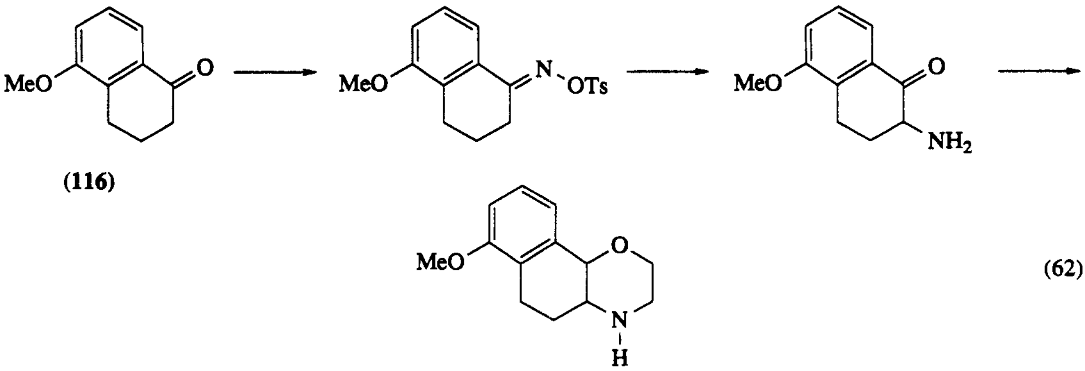
MeO
O
MeO
N
OTs
MeO
O
NH₂
MeO
O
N
H

**(116)**

**(117)** Naphthoxazine

(62)

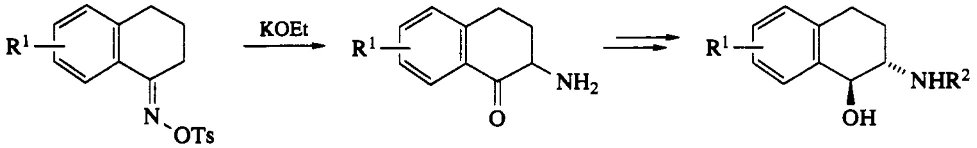
R¹
N
OTs
KOEt
R¹
NH₂
O
R¹
NHR²
OH

(63)

**(118)**

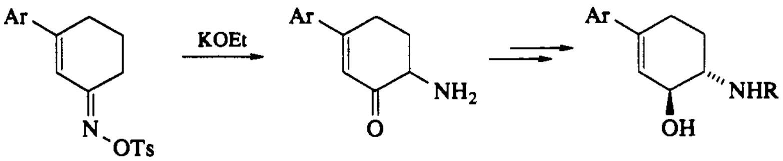
Ar
N
OTs
KOEt
Ar
NH₂
O
Ar
NHR
OH

(64)

**(119)**

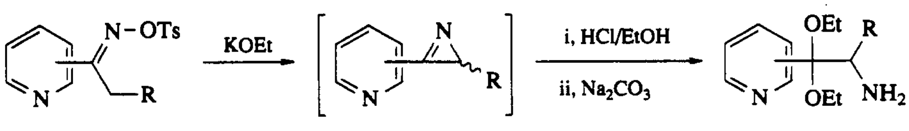
N–OTs
N
R
KOEt
N
N
R
i, HCl/EtOH
ii, Na₂CO₃
OEt
R
N
OEt
NH₂

(65)

R = H or Me

40–70%

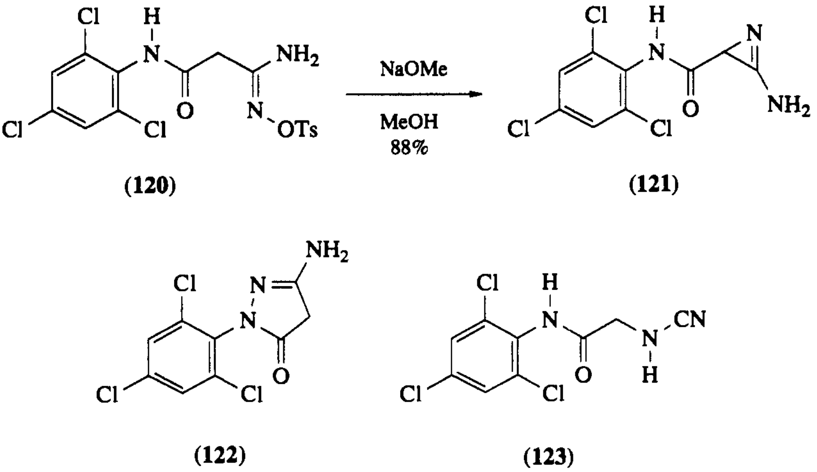
Cl
H
N
NH₂
Cl
Cl
O
N
OTs
NaOMe
MeOH
88%
Cl
H
N
N
Cl
Cl
O
NH₂
(120)
(121)
NH₂
Cl
N
N
Cl
Cl
O
Cl
H
N
N
CN
Cl
Cl
O
H
(122)
(123)

Scheme 28

tions, the methiodide (**124**) of 2-phenylcyclohexanone dimethylhydrazone gives varying amounts of 2-phenylcyclohexanone and the Mannich product (**125**) arising from this ketone (Scheme 29).[105] The normal Neber product can be made to predominate by adding the quaternary salt (**124**) portionwise to a refluxing solution of sodium ethoxide in ethanol.

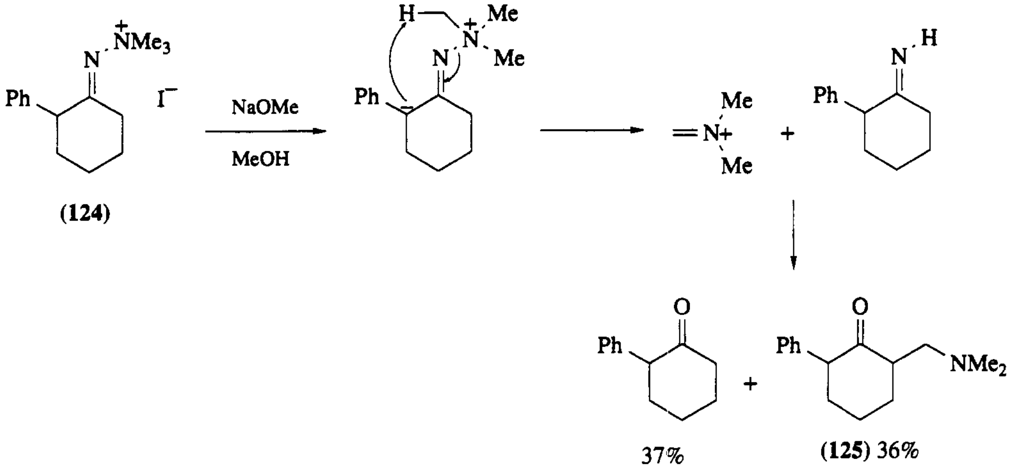
NMe3
N
Ph
I⁻
(124)
NaOMe
MeOH
H
Me
N
N
Me
Ph
Me
=N+
Me
+
N
H
Ph
O
Ph
+
O
Ph
NMe2
37%
(125) 36%

**Scheme 29**

Attempted synthesis of the bis(2*H*-azirine) system from the 2,3-dimethyl-1,4-diphenyl-1,4-butanedione bis(hydrazonium) salt under basic conditions gives 3,4-dimethyl-2,5-diphenylpyrrole in 89% yield (equation 66).[106]

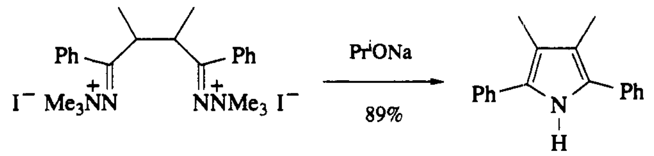
Ph
Ph
I⁻ Me3NN
NNMe3 I⁻
PriONa
89%
Ph
N
H
Ph

(66)

## 4.3.5 AMADORI REARRANGEMENT

The Amadori rearrangement represents a conversion of *N*-glycosides of aldoses to *N*-glycosides of the corresponding ketones by acid or base catalysis, as shown in the preparation of 1-alkylamino-1-deoxy-(+)-fructose (**127b**) from (+)-glucosylamine (**126**; equation 67).[107,108] Compounds of the type (**127a**) and (**127b**) are known as 'Amadori compounds'. A variety of Lewis acids such as $CuCl_2$, $MgCl_2$, $HgBr_2$, $CdCl_2$, $AlCl_3$, $AsCl_3$, $FeCl_3$ and $SnCl_4$ have been employed as catalysts for the rearrangement of *N*-(+)-glucosylamines containing aromatic aglycons.[109]

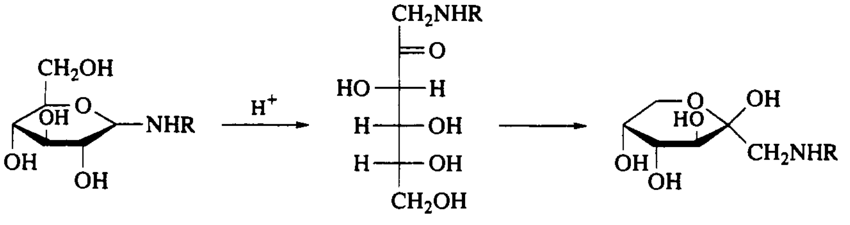
CH2OH
O
OH
NHR
OH
OH
H+
CH2NHR
O
HO
H
H
OH
H
OH
CH2OH
O
OH
HO
CH2NHR
OH
OH

(67)

**(126)** **(127a)** **(127b)**

A recent example involves the synthesis of *N*-glycosyl derivatives of polyene macrolide antibiotics, such as the preparation of *N*-(deoxyfructosyl)nystatin (**128**) by reaction of nystatin with (+)-glucose (Scheme 30).[110]

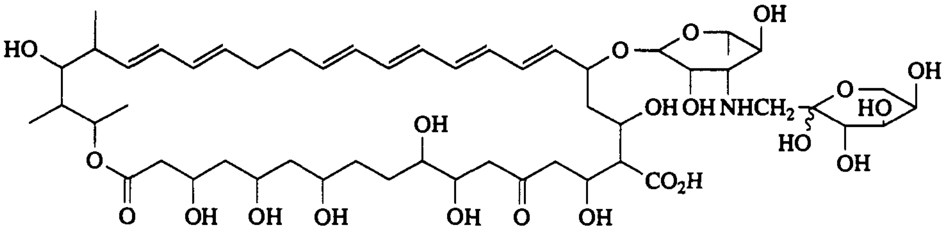

**(128)**

**Scheme 30**

In spite of their physiological and toxicological importance the Amadori compounds have been investigated until recently only in relatively few biological materials. This is due to the tedious procedures for their isolation and purification from the reaction medium. In this context, a new route to the Amadori compounds (**130**) has been developed starting from fructose (**129**; equation 68), thereby avoiding the formation of undesirable by-products from thermal degradation of amino acids, from Amadori compounds themselves, and due to sugar caramelization.[111]

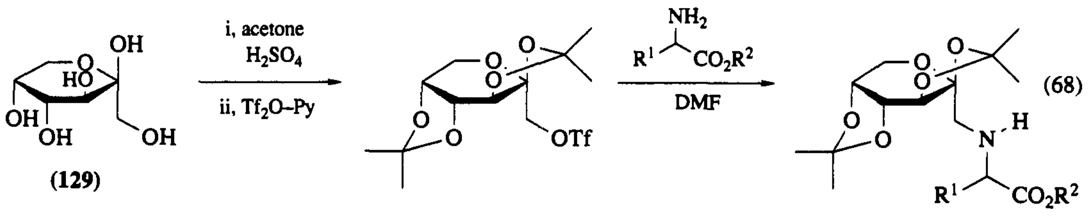

**(129)** **(130)** (68)

The equilibrium mixture of various Amadori products in dimethyl sulfoxide-$d_6$ has been studied qualitatively and quantitatively by $^{13}$C NMR spectroscopy. The position of the equilibrium varies considerably depending on the substituents on the carbohydrates (Scheme 31).[112]

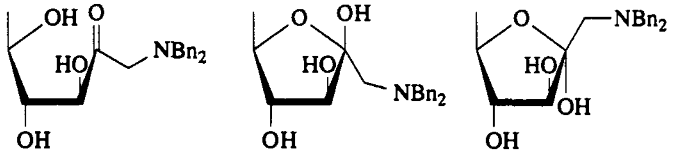

27% 49% 24%

**Scheme 31**

The Schiff base adducts of glyceraldehyde with the amino groups of hemoglobin A are found to undergo Amadori rearrangement to give stable ketoamine adducts, a reaction analogous to the nonenzymic glycosylation of proteins (Scheme 32).[113–118] In the presence of sodium cyanoborohydride, the incorporation of glyceraldehyde into hemoglobin is faster than that in its absence, suggesting that Amadori rearrangement is the rate-limiting step in nonenzymic glycosylation.

Lithium aldimine (**131**), an acyl anion equivalent derived from an isocyanide and an organolithium reagent, adds to aldehydes giving, after quenching with water, α-amino ketones (**134**) *via* the Amadori rearrangement (Scheme 33).[119] The α-amino ketone (**134**) results from a double tautomerization of α-hydroxy imine (**132**), formed initially after quenching with water. Thus, the imine (**132**) isomerizes to enolamine (**133**), which in turn tautomerizes to the observed product (**134**).

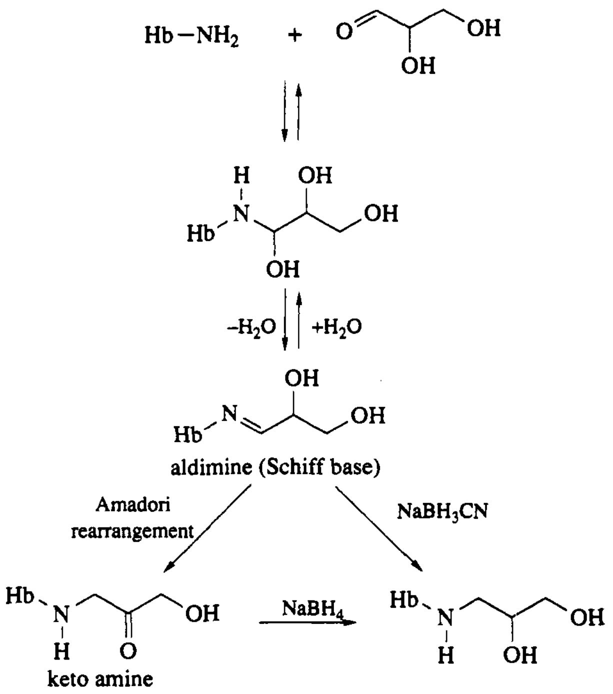
$Hb-NH_2$
+
OH
OH
H
OH
N
Hb
OH
OH
$-H_2O$
$+H_2O$
OH
N
Hb
OH
aldimine (Schiff base)
Amadori rearrangement
$NaBH_3CN$
Hb
N
H
O
OH
keto amine
$NaBH_4$
Hb
N
H
OH
OH

**Scheme 32**

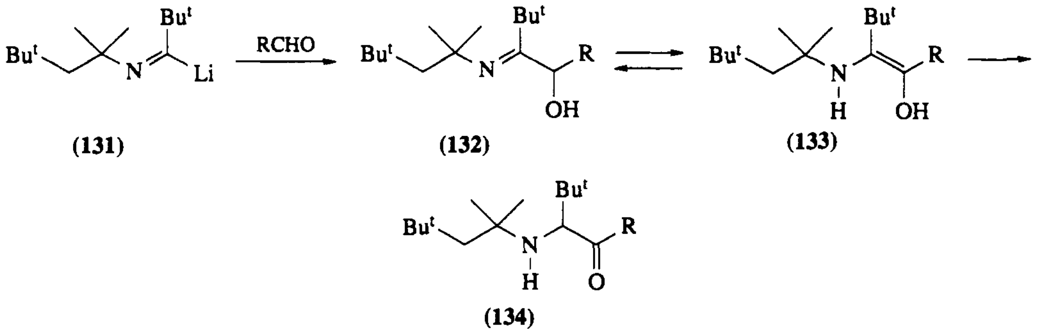
Bu$^t$
Bu$^t$
N
Li
(131)
RCHO
Bu$^t$
Bu$^t$
N
R
OH
(132)
Bu$^t$
Bu$^t$
N
H
R
OH
(133)
Bu$^t$
Bu$^t$
N
H
R
O
(134)

**Scheme 33**

## 4.3.6 REFERENCES

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2. L. G. Donaruma and W. Z. Heldt, *Org. React. (N. Y.)*, 1960, **11**, 1.
3. P. A. S. Smith, *Mol. Rearrangements*, 1963, 457.
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# 4.4
# Degradation Reactions

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## 4.4.1 FROM CARBOXYLIC ACIDS TO AMINES

### 4.4.1.1 General Aspects

Degradation reactions of carboxylic acids and their derivatives to amines and their derivatives with one less carbon unit[1–5] involve rearrangements of a carbon to an electron deficient nitrogen atom as key steps, namely the Hofmann (H),[6,7] Curtius (C),[8,9] Schmidt (S)[10–13] and Lossen (L)[14,15] rearrangements, as shown in Scheme 1.

The overall process of going from carboxylic acids to amines is known as the Hofmann, Curtius, Schmidt or Lossen 'reaction', but these are quite often described as 'rearrangements' and sometimes called 'degradations'. These reactions were all discovered in the late 19th century (Hofmann, 1881; Curtius, 1890; Lossen, 1872) except for the Schmidt reaction (1923). Since these reactions provide a practical procedure for replacing a carboxy group by an amino group, they have been extensively used since their discoveries. Inspection of *Chemical Abstracts* between 1967 and 1988 has revealed that the numbers of papers related to these four rearrangement reactions are 233 for the Hofmann reaction, 522 for the Curtius reaction, 332 for the Schmidt reaction (including the Schmidt reaction of ketones, aldehydes and others) and 57 for the Lossen reaction.

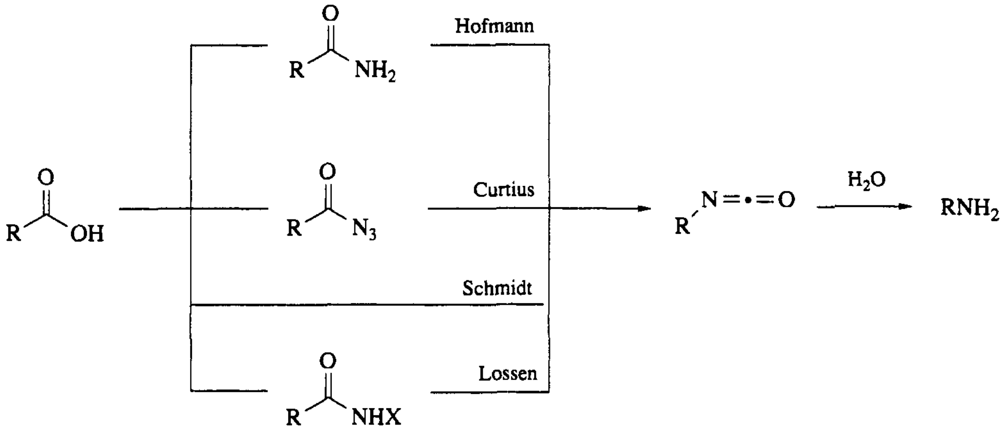

**Scheme 1**

The common initial products of the rearrangements are isocyanates, which readily react with all types of compounds containing—OH, —NH or —SH functions, giving amines, ureas, urethanes, thiourethanes, amides *etc.* (Scheme 2).[16] Isolation of the isocyanates may be possible under some reaction conditions, especially in the Curtius reaction when the rearrangement is conducted in aprotic solvents, but usually the solvolytic conversion of isocyanates occurs to give amines or ureas.

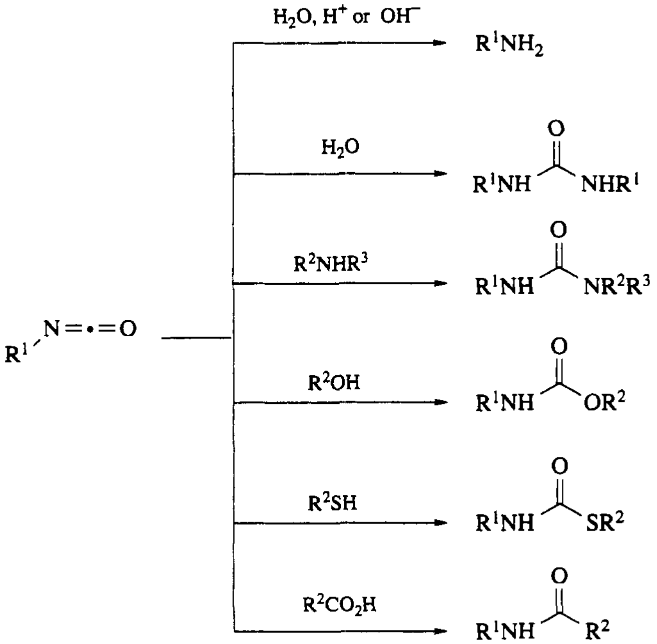

**Scheme 2**

The Hofmann reaction[6,7] involves the conversion of carboxylic primary amides to primary amines or their derivatives. Generally, alkaline hypohalites or a combination of halogens and alkaline hydroxides are used in aqueous solutions. The rearrangement generally occurs by heating. The intermediate isocyanates are easily hydrolyzed to amines under the reaction conditions, as shown in Scheme 3. When sodium methoxide in methanol is used in place of aqueous alkaline hydroxide, the corresponding methylurethanes are formed and may be hydrolyzed to yield amines.

The Hofmann reaction is applicable to the preparation of a wide variety of aliphatic, aromatic and heterocyclic amines, and is suitable for large-scale preparative work, since it is safe and relatively inexpensive to carry out, especially when chlorine and sodium hydroxide can be used.

Oxidizing agents such as lead tetraacetate or [*I,I*-bis(trifluoroacetoxy)iodo]benzene can also be used for the Hofmann reaction. The usual Hofmann reaction shown in Scheme 3 proceeds under alkaline con-

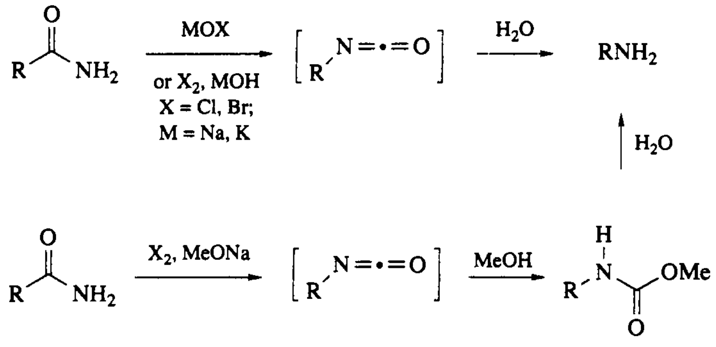

**Scheme 3**

ditions; hence, it can not be applied to compounds containing alkali labile functions. For these compounds, the alternative Hofmann reaction (equation 1) can be used, since it proceeds under mildly acidic conditions.

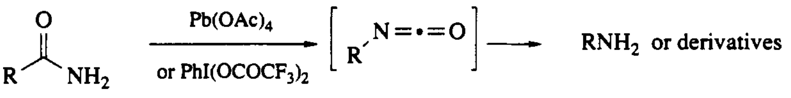

(1)

The Curtius reaction[8,9] involves the thermal rearrangement of acyl azides, with expulsion of nitrogen, to produce isocyanates. Although the rearrangement of acyl azides proceeds by photochemical means at lower temperatures, photolysis has no advantage over thermolysis from preparative points of view. Preparation of acyl azides is conducted in three ways, shown in Scheme 4. A common classical route to acyl azides involves the preparation of acyl hydrazides by the action of hydrazine on esters, followed by treatment of hydrazides with nitrous acid or alkyl nitrites. Interaction of acyl chlorides with sodium azide also gives acyl azides. Mixed anhydrides prepared from carboxylic acids and alkyl chloroformates are useful alternatives for acyl chlorides, giving acyl azides when reacted with sodium azide. The hydrazide method requires more steps and is less convenient than the other methods. Although the acyl chloride method is convenient, it is sometimes difficult to obtain pure acyl chlorides efficiently from acids, since decomposition or isomerization occurs in the presence of mineral acids. In contrast to these, the mixed anhydride method proceeds under mild reaction conditions and mostly gives satisfactory results. The overall process of converting carboxylic acids to amines or their derivatives through the corresponding acyl azides is commonly referred to as the Curtius reaction. Since the Curtius reaction proceeds under relatively mild conditions, it is suitable for sensitive compounds and can be carried out on a wide variety of acids.

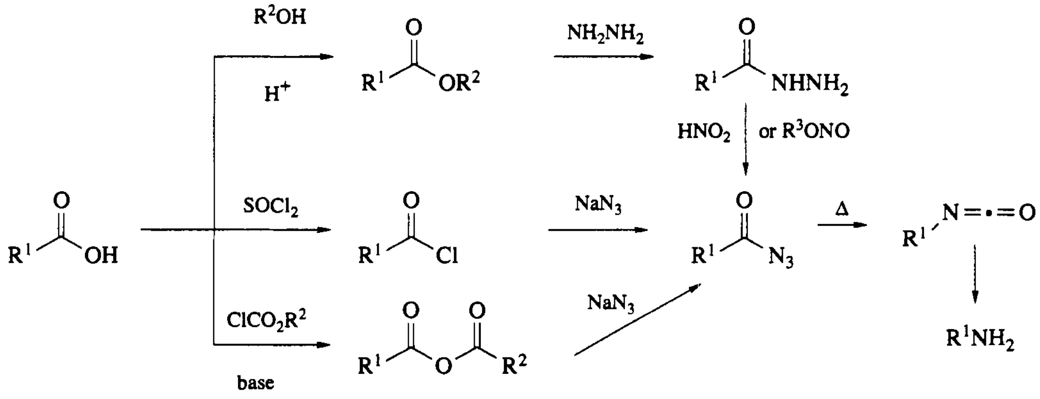

**Scheme 4**

One of the most useful variants of the Curtius reaction is the reaction of carboxylic acids with diphenyl phosphorazidate (DPPA; $(PhO)_2P(O)N_3$) in the presence of base, such as triethylamine (equation 2).[17,18]

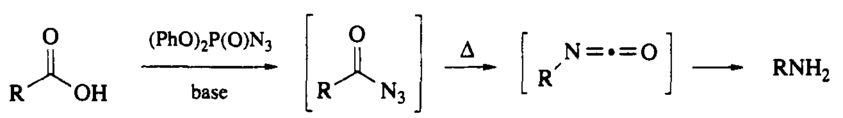

(2)

The Schmidt reaction[10–13] is the name given to a group of reactions which involve the addition of hydrazoic acid to carboxylic acids, ketones and aldehydes, alcohols and alkenes under strongly acidic conditions. The most common reaction is the reaction with carboxylic acids, which give amines in a single step (equation 3). Usually, a mixture of sodium azide and sulfuric acid is used to conduct the reaction, though the use of a solution of free hydrazoic acid together with sulfuric acid sometimes gives better results. The Schmidt reaction often gives higher yields than the other rearrangement reactions since it is a one-step reaction. However, the strongly acidic conditions preclude the use of carboxylic acids containing strongly acid labile or reactive functions. Advantages and drawbacks of the Hofmann, Curtius and Schmidt reactions carried out before 1946 have been discussed in ref.8.

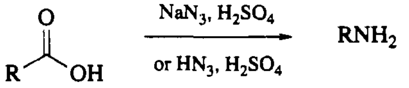

(3)

Reaction of ketones with hydrazoic acid proceeds similarly to the Beckmann rearrangement to give amides, while aldehydes yield nitriles and formamides under analogous reaction conditions (equations 4 and 5).

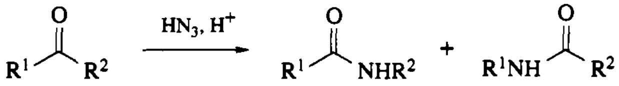

(4)

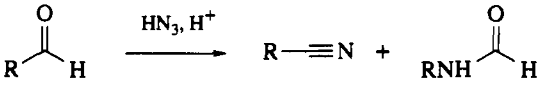

(5)

The fourth related rearrangement reaction is the Lossen reaction,[14,15] which generally occurs by base treatment of *O*-substituted hydroxamic acids which possess electron-withdrawing functions at the oxygen atom (*e.g.* *O*-acylhydroxamic acids), giving amines *via* isocyanates (equation 6). Preliminary *O*-activation (*e.g.* *O*-acylation) of hydroxamic acids is essential for a smooth rearrangement, otherwise it will not occur. The Lossen reaction is not as useful as the other three rearrangements since hydroxamic acids are not readily available.

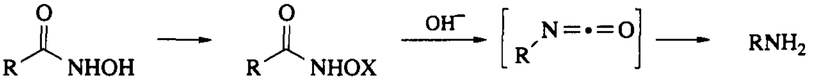

(6)

### 4.4.1.2 Mechanism and Stereoselectivity

The Hofmann, Curtius, Schmidt and Lossen rearrangements generally involve nucleophilic migrations from a carbon to an electron deficient nitrogen center (Scheme 5), giving isocyanates as the initial products, which undergo further reactions as already shown in Scheme 2.

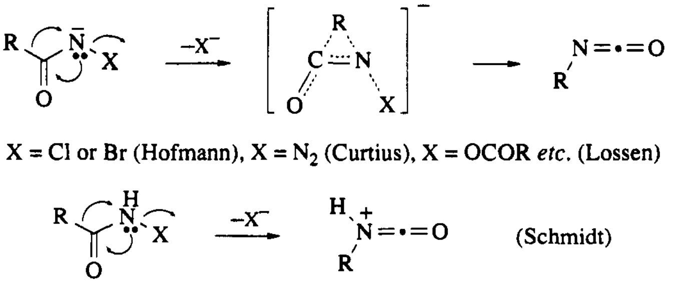

X = Cl or Br (Hofmann), X = N$_2$ (Curtius), X = OCOR *etc.* (Lossen)

Scheme 5

Mechanistic studies on these four rearrangements[2,3,9] have revealed that: (i) these are concerted intramolecular rearrangements; (ii) stereochemical configurations of the migrating groups are completely retained; (iii) the kinetics are first order; and (iv) neither free carbonium ions nor radical intermediates are formed during the rearrangements.

The first intermediates of the Hofmann reaction are *N*-haloamides (*e.g.* **1**), which are subsequently converted to alkaline salts (*e.g.* **2**). Both intermediates can be isolated under carefully controlled conditions. Kinetic evidence on both the substituent[19] and isotope[20] effects in the Hofmann rearrangement of various *N*-halobenzamides (**1**) in an aqueous sodium hydroxide solution strongly support a concerted mechanism, involving the bridged anion (**3**), shown in Scheme 6.

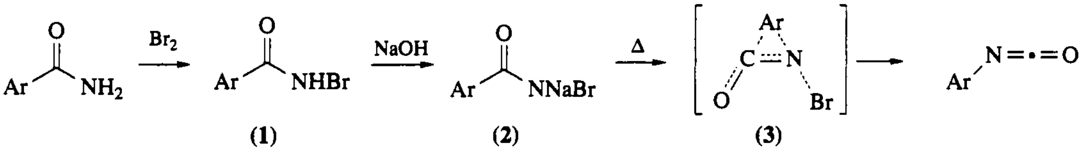

**Scheme 6**

Practically, the carbon–nitrogen rearrangements occur with almost complete retention of optical and geometrical configurations. (*S*)-(+)-2-Phenylpropionic acid (**4**) and its derivatives undergo the Hofmann, Curtius, Schmidt and Lossen rearrangements to give (*S*)-(–)-1-phenylethylamine (**5**) with more than 99% retention of configuration.[21,22] Strong alkaline conditions used in the Hofmann reaction cause some racemization (*ca.* 4%) before the rearrangement (equation 7).

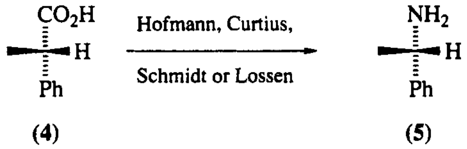

(7)

Conversion of (*S*)-2-cyano-2-methyl-3-phenylpropionic acid (**6**) to (*S*)-α-methylphenylalanine (**7**) through the Hofmann and Curtius rearrangements followed by hydrolysis also proceed with nearly complete retention of configuration (equation 8).[23]

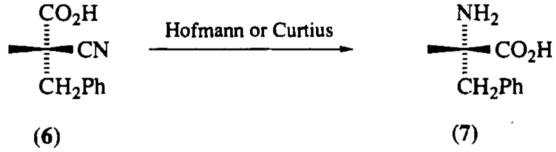

(8)

The four rearrangements may be utilized for the determination of absolute configurations by correlation to compounds of established configurations. Thus, the absolute configurations of two binaphthyl derivatives (**8** and **9**) have been determined by utilizing the Curtius rearrangement (Scheme 7).[24]

Perfect retention of the geometrical configurations has been observed in the Curtius rearrangement of *cis*- and *trans*-crotonyl azides (**10**), which respectively give *cis*- and *trans*-propenyl isocyanates (**11**), characterized as their urea derivatives (**12**; Scheme 8).[25] The *cis* isomers (**10b**) and (**11b**) tend to isomerize thermally to the *trans* isomers (**10a**) and (**11a**) respectively.

The Curtius rearrangements of some *trans*-cinnamoyl azides (**13**), obtained by treatment of the corresponding chlorides with sodium azide, smoothly give *trans*-β-styryl isocyanates (**14**), which are efficiently isomerized in an inert solvent at 250 °C to produce 1-isoquinolone derivatives (**15**; equation 9).[26] The isomerization proceeds more conveniently at 140 °C in the presence of iodine.

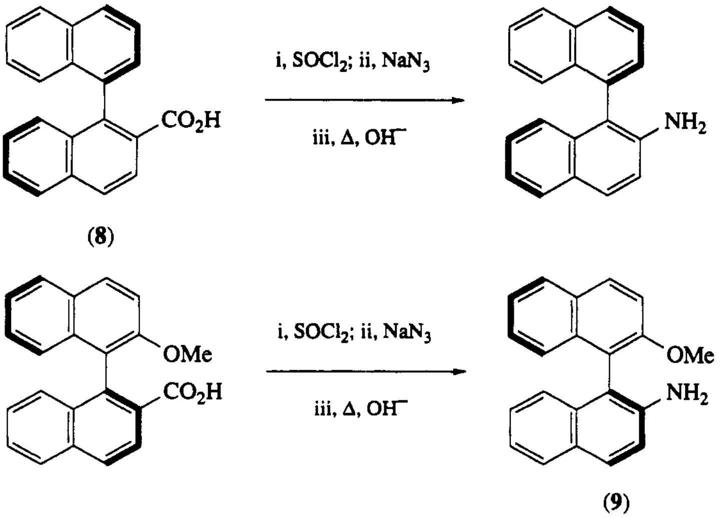
CO2H
i, SOCl2; ii, NaN3
iii, Δ, OH−
NH2
(8)
OMe
CO2H
i, SOCl2; ii, NaN3
iii, Δ, OH−
OMe
NH2
(9)

**Scheme 7**

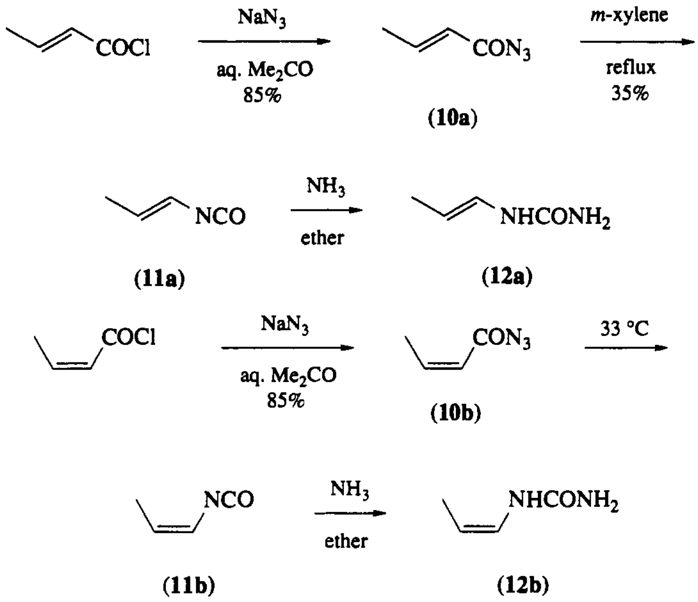
COCl
NaN3
aq. Me2CO
85%
CON3
(10a)
m-xylene
reflux
35%
NCO
NH3
ether
NHCONH2
(11a)
(12a)
COCl
NaN3
aq. Me2CO
85%
CON3
(10b)
33 °C
NCO
NH3
ether
NHCONH2
(11b)
(12b)

**Scheme 8**

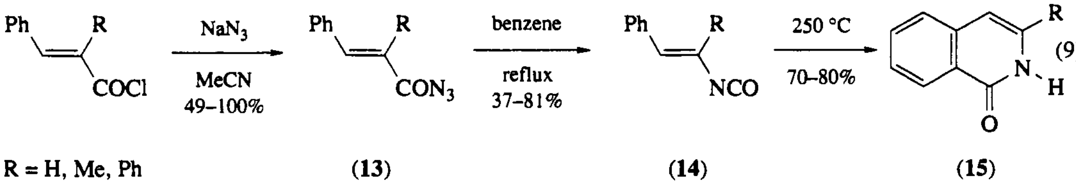
Ph
R
COCl
NaN3
MeCN
49–100%
Ph
R
CON3
benzene
reflux
37–81%
Ph
R
NCO
250 °C
70–80%
R
(9)
N
H
O
R = H, Me, Ph
(13)
(14)
(15)

## 4.4.2 THE HOFMANN REACTION

### 4.4.2.1 Under Basic Conditions

The classical and most standard reaction conditions of the Hofmann rearrangement use sodium or potassium hypobromite (or bromine with sodium or potassium hydroxide) under aqueous conditions.

Sodium or potassium hypobromite may be replaced with the other alkaline hypohalites such as sodium hypochlorite, calcium hypochlorite or barium hypobromite. The other alternative reagent used under aqueous alkaline conditions is sodium bromite ($NaBrO_2$) in the presence of a catalytic amount of sodium bromide[27] or a calculated amount of benzyltrimethylammonium bromide ($PhCH_2N^+Me_3Br^-$).[28]

Neopentylglycine (**17**) is conveniently prepared from neopentylmalonamic acid (**16**) by the action of hypobromite (equation 10).[29] The method using the carbon–nitrogen rearrangements of malonic half-acid derivatives is one of the classical methods for the preparation of α-amino acids.

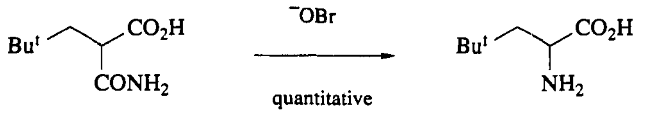

(**16**) (**17**)

(10)

The Hofmann reaction under basic conditions is apparently suitable for degradation of acid sensitive compounds, *e.g.* acetals, without any change at their acid sensitive functions (equation 11).[30]

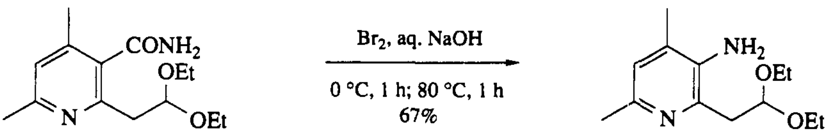

(**18**) (**19**)

(11)

Isocyanates, the initial products of the Hofmann rearrangement, usually undergo solvolysis to give amines, as described earlier (Section 4.4.1.1). However, a two-phase Hofmann reaction using phase transfer catalysts allows isolation of reactive isocyanates (equation 12).[31] The phase transfer catalyst is essential for the formation of primary and secondary isocyanates, while tertiary isocyanates are formed without the catalyst. Shorter reaction times at room temperature as well as high dilution conditions minimize the formation of by-products such as dialkylureas or acylalkylureas. Chlorine in place of bromine considerably decreases the yield of isocyanates.

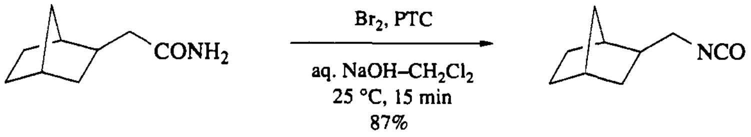

(12)

PTC = $Bu_4N^+HSO_4^-$, $PhCH_2N^+Et_3Cl^-$, or $Bu_4P^+Br^-$

Although the Hofmann reaction is applicable to various amides under usual aqueous alkaline conditions, it sometimes proceeds sluggishly, especially in the rearrangement of hydrophobic amides such as aliphatic amides containing a longer carbon chain. However, use of bromine and sodium methoxide gives better results though the product is a methylurethane, as already shown in Scheme 3. This methoxide method is classified into three approaches according to the order of mixing reagents: (i) addition of bromine to a methanolic solution of an amide and sodium methoxide (the Jeffreys' method, J);[6,7,32] (ii) use of a methanolic solution of bromine in the Jeffreys' method (the Nagai–Matsuo method, N);[7,33,34] and (iii) addition of bromine to sodium methoxide in methanol to produce methyl hypobromite, followed by addition of amides (the Radlick and Brown method, R),[35,36] shown in Scheme 9. The last method is utilized for the amide (**20**), which is highly susceptible to electrophilic addition reactions.[35]

The electroorganic method also induces the Hofmann reaction, by use of potassium bromide as a catalytic mediator, giving methylurethanes.[37] Since the reaction proceeds without heating under neutral conditions, this method can be applied to a base labile epoxyamide (**21**), which gives unidentified products with no epoxide function when treated under the usual alkaline conditions of the Hofmann reaction (equation 13).

An attempted Hofmann reaction of phosphonoacetamides (**22**) with alkaline sodium hypobromite shows a dramatic substituent effect (Scheme 10).[38] The rearrangement occurs when the alkyl residue (R) is ethyl or phenyl, while only bromination occurs when R is hydrogen or benzyl.

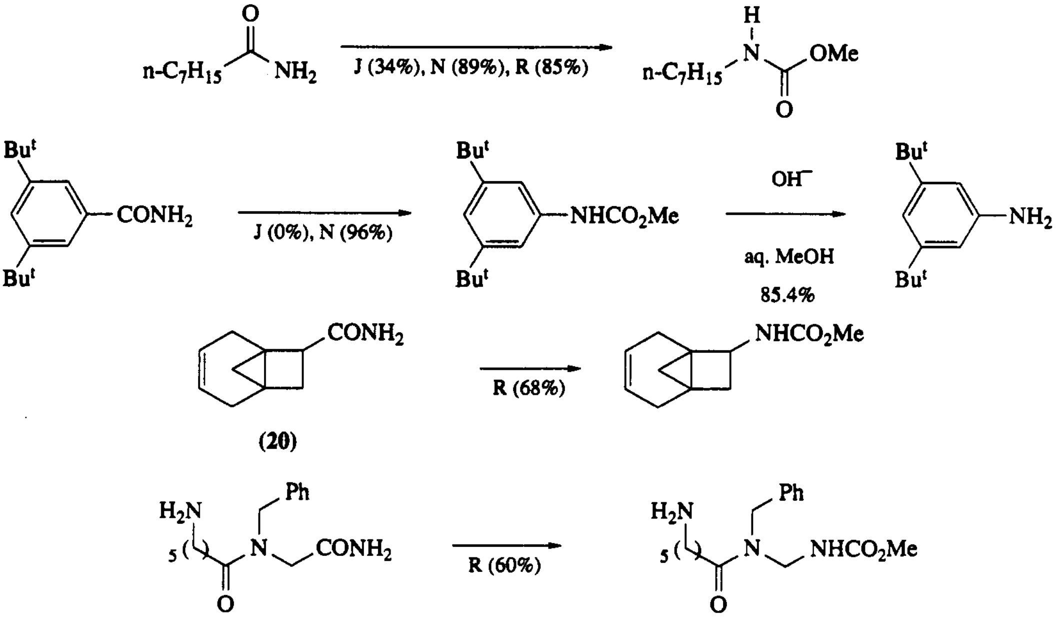
n-C7H15
NH2
J (34%), N (89%), R (85%)
OMe
Bu<sup>t</sup>
CONH2
J (0%), N (96%)
NHCO2Me
OH⁻
aq. MeOH
85.4%
NH2
R (68%)
H2N
Ph
R (60%)

**(20)**

**Scheme 9**

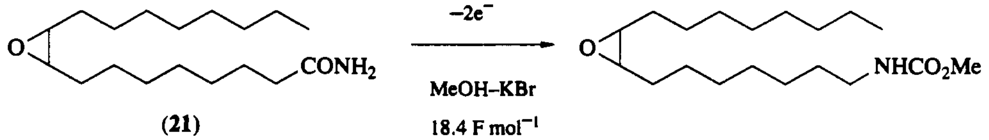
CONH2
−2e⁻
MeOH–KBr
18.4 F mol⁻¹
NHCO2Me

**(21)** (13)

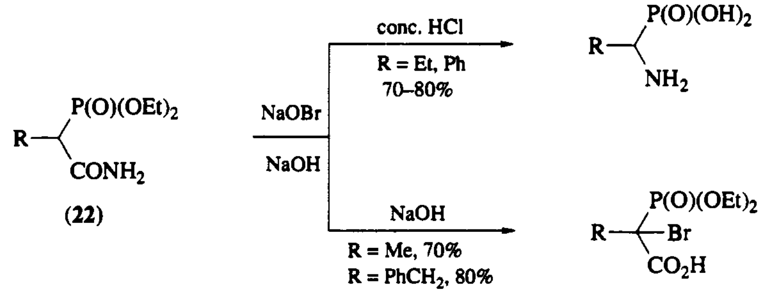
P(O)(OEt)2
R
CONH2
NaOBr
NaOH
conc. HCl
R = Et, Ph
70–80%
P(O)(OH)2
NH2
NaOH
R = Me, 70%
R = PhCH2, 80%
Br
CO2H

**(22)**

**Scheme 10**

Phthalimides undergo the Hofmann reaction by an initial hydrolytic ring-opening, giving the *N*-haloamides formed from either of the free imides or the *N*-haloimides, followed by their rearrangement to give anthranilic acids.[39] The regioselectivity in the Hofmann rearrangement of *N*-chloro-4,4-dialkylhomophthalimides (**23**) is governed by the bulkiness of the 4,4-dialkyl groups.[40] The imides containing small substituents give rise to indolinones (**24**), while isoindolinones (**25**) are formed from the imides containing bulky substituents (equation 14).

(*S*)-*N*-Carbamoylalanine (**26**) also undergoes the Hofmann rearrangement to give (*S*)-*N*-aminoalanine (**27**), by use of sodium hypochlorite but not hypobromite (equation 15).[41]

### 4.4.2.2 Under Acidic Conditions

The oxidative Hofmann rearrangement of primary carboxamides occurs by use of lead tetraacetate (LTA) and several hypervalent organoiodine compounds $IF_5$ (**28**), $PhI(OCOCF_3)_2$ (**29**), PhI(OH)OTs (**30**) and PhIO (**31**) under mildly acidic conditions.

Although some conflicting results have been presented by Beckwith[42] and Baumgarten,[43] LTA is still an interesting reagent for the oxidative rearrangement. LTA in benzene converts primary amides to acyl-

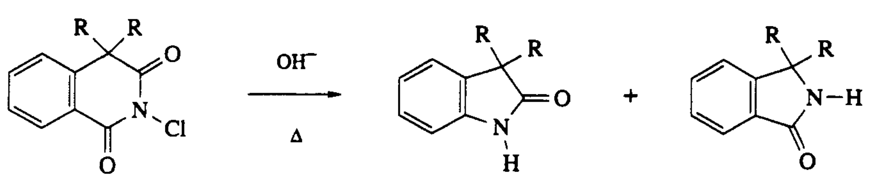

**(23)** **(24)** **(25)** (14)

| | % | % |
|---|---|---|
| R = Me | 68 | – |
| R = Et | – | 58 |
| R = $H_2C{=}CHCH_2$ | 47 | 31 |
| R, R = $(CH_2)_4$ | 74 | – |

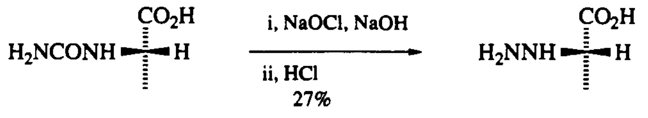

**(26)** **(27)** (15)

amines, together with a small amount of dialkylureas.[42] The reaction, which may also be conducted in acetic acid or benzene–acetic acid, is catalyzed by pyridine. Acetic acid may be replaced with other carboxylic acids (equation 16).

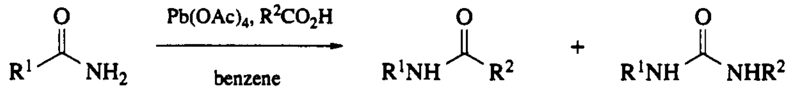

(16)

With LTA in refluxing *t*-butyl alcohol, *t*-butyl carbamates are conveniently produced from various amides (equation 17).[43] Triethylamine, tin(IV) chloride and dibutylstannyl dilaurate are effective catalysts for the reaction of the intermediate isocyanates and *t*-butyl alcohol. When the reaction is run in dimethylformamide, isocyanates can be isolated and easily converted to ureas with *t*-butylamine (equation 18).[43]

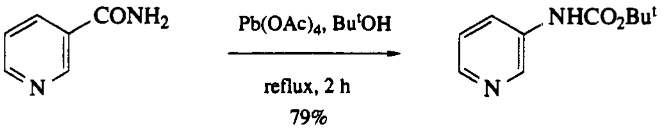

(17)

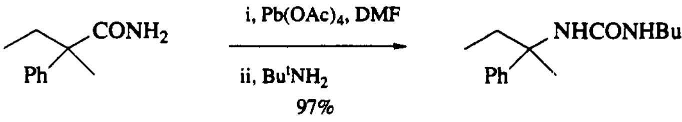

(18)

In addition, both primary and secondary alcohols can be used, alone or together with benzene.[42] Pyridine also serves as a catalyst. The method is applicable to a wide variety of amides and alcohols, including compounds containing alkenic, ester, aromatic and other reactive functions, as shown in Scheme 11.

The oxidative rearrangement with LTA also proceeds with retention of configuration about the migrating carbon atom, as shown in equations (19)[43] and (20).[44]

Iodine pentafluoride (**28**) in hot pyridine works like LTA as a Hofmann reagent for aliphatic primary carboxamides (equation 21).[45] Iodination occurs together with rearrangement when benzamide is treated under similar reaction conditions.

[*I,I*-Bis(trifluoroacetoxy)iodo]benzene (PIFA; **29**) also brings about the facile oxidative rearrangement of aliphatic amides to amines in mildly acidic (pH 1–3) 50% aqueous acetonitrile at room temperature within several hours, as shown in equation (22).[46,47] The reagent cannot be applied to the formation of aromatic amines since the latter are further oxidized. The intermediates of the reaction are isocyanates, which are rapidly hydrolyzed to amines under mildly acidic conditions. The acidic conditions protect the

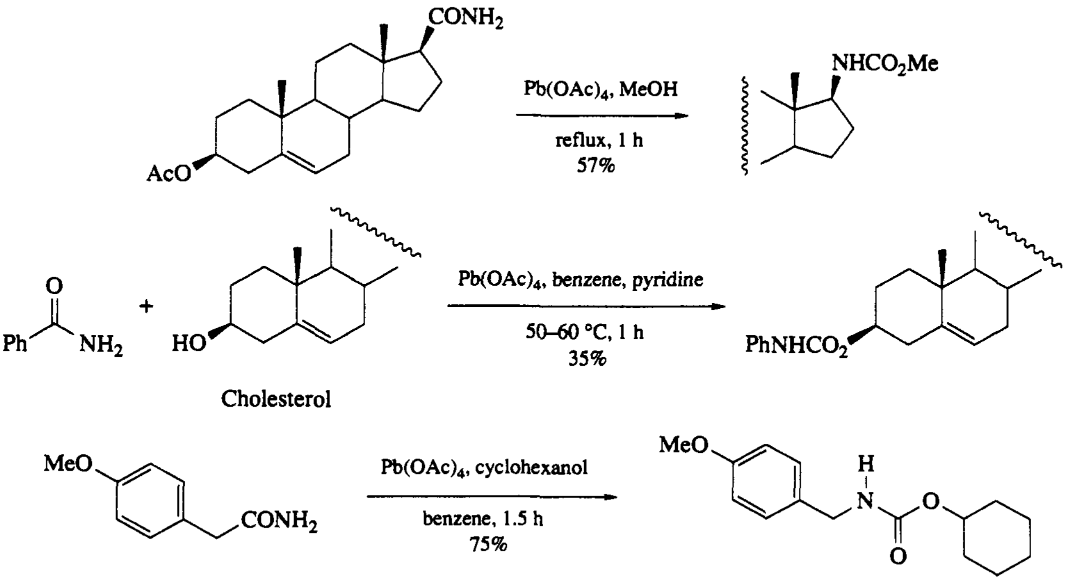
CONH2
AcO
Pb(OAc)4, MeOH
reflux, 1 h
57%
NHCO2Me
O
Ph
NH2
+
HO
Cholesterol
Pb(OAc)4, benzene, pyridine
50–60 °C, 1 h
35%
PhNHCO2
MeO
CONH2
Pb(OAc)4, cyclohexanol
benzene, 1.5 h
75%
MeO
H
N
O
O

**Scheme 11**

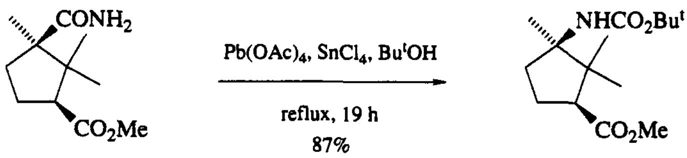
CONH2
CO2Me
Pb(OAc)4, SnCl4, ButOH
reflux, 19 h
87%
NHCO2But
CO2Me

(19)

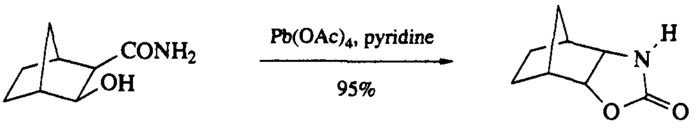
CONH2
OH
Pb(OAc)4, pyridine
95%
H
N
O
O

(20)

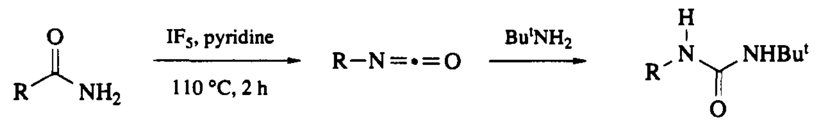
O
R
NH2
IF5, pyridine
110 °C, 2 h
R—N=•=O
ButNH2
H
N
R
NHBut
O

(21)

product amines from reacting with the intermediate isocyanates and forming ureas. The reaction is catalyzed by pyridine though this is not strictly necessary.

$$\underset{(\mathbf{29})}{\mathrm{RCONH_2} + \mathrm{PhI(OCOCF_3)_2}} + \mathrm{H_2O} \longrightarrow \mathrm{RNH_3^+} + \mathrm{CO_2} + \mathrm{PhI} + 2\mathrm{CF_3CO_2^-} + \mathrm{H^+} \quad (22)$$

PIFA easily converts succinic acid derivatives (**32**) to β-alanine derivatives (**33**).[47] Limited use of PIFA (1 equiv.) allows the rearrangement of 3-cyclohexene-1-carboxamide (**34**) without oxidation of the double bond, as shown in Scheme 12. Cyclohexanone is obtained by the PIFA oxidation of 1-cyclohexenecarboxamide (**35**). Selective oxidation of the primary amide (**36**) occurs without effect on secondary or tertiary amides in the same molecule.[47] The rearrangement of the cyclopropane derivative (**37**) accompanies the ring cleavage to give the β-alanine derivative (**38**) after treatment with benzyloxycarbonyl chloride.[48]

Retention of configuration during the Hofmann reaction promoted with PIFA has been rigorously demonstrated in the rearrangements of (*S*)-(+)-2-phenylpropionamide (**39**)[47] as well as the peptide derivative (**40**),[49] as shown in Scheme 13. The latter reaction can be employed in the sequential degradation of carboxy terminal peptides[50] as well as modifications of peptides.[51]

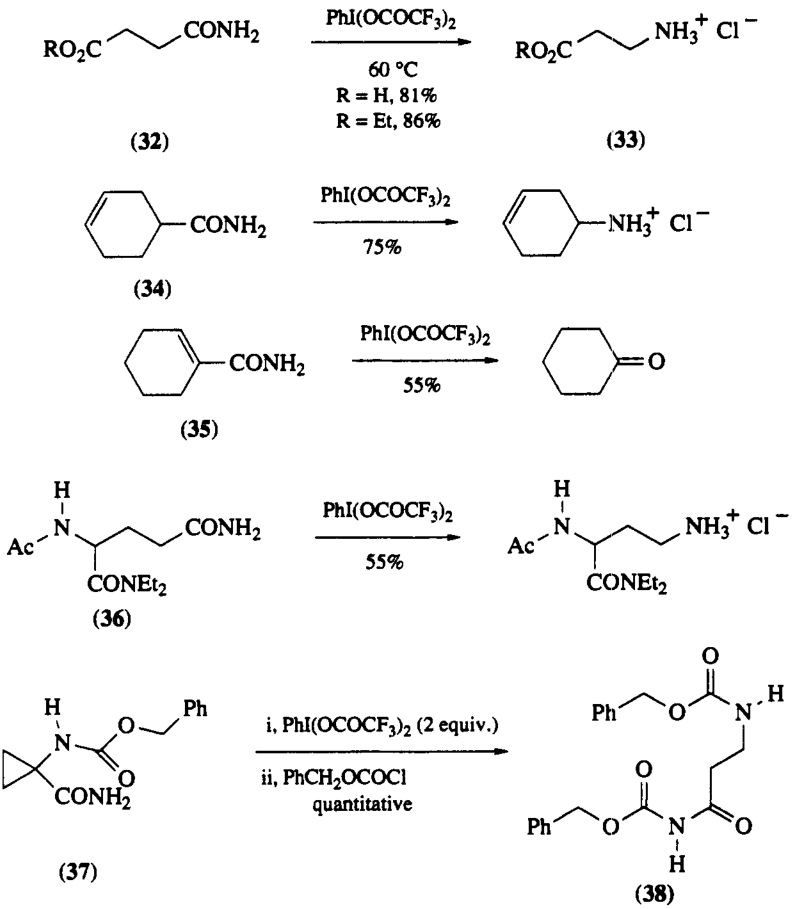
RO2C CONH2
PhI(OCOCF3)2
60 °C
R = H, 81%
R = Et, 86%
RO2C NH3+ Cl−
(32)
(33)
CONH2
PhI(OCOCF3)2
75%
NH3+ Cl−
(34)
CONH2
PhI(OCOCF3)2
55%
O
(35)
H
N
Ac
CONH2
CONEt2
PhI(OCOCF3)2
55%
NH3+ Cl−
(36)
H
N
O
Ph
O
CONH2
i, PhI(OCOCF3)2 (2 equiv.)
ii, PhCH2OCOCl
quantitative
(37)
(38)

**Scheme 12**

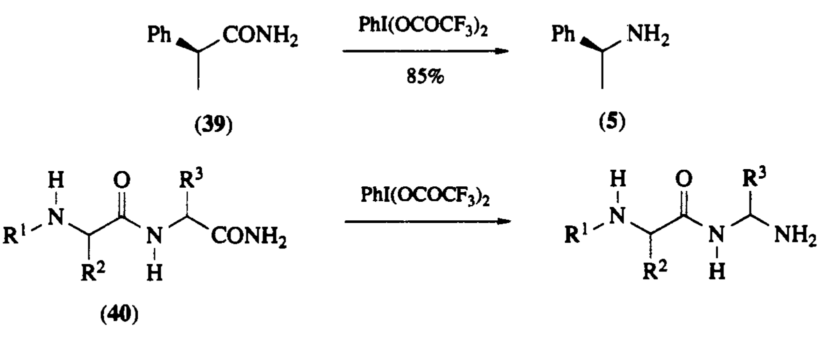
Ph
CONH2
PhI(OCOCF3)2
85%
NH2
(39)
(5)
H O R3
R1 N N CONH2
R2 H
PhI(OCOCF3)2
NH2
(40)

**Scheme 13**

Hydroxy(tosyloxy)iodobenzene (HTIB; **30**) is another hypervalent organoiodine compound which acts as a Hofmann reagent,[52] converting aliphatic carboxamides to alkylammonium tosylates in refluxing acetonitrile (equation 23).

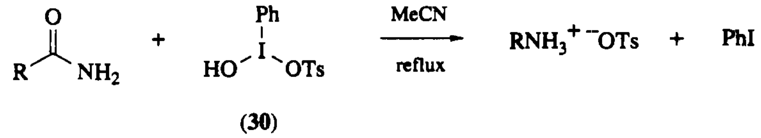
O
R NH2
+
Ph
I
HO OTs
MeCN
reflux
RNH3+ −OTs + PhI

(30)

(23)

HTIB is particularly useful for the degradation of long chain amides,[53] in contrast to the classical Hofmann reaction under alkaline conditions (see Section 4.4.2.1). The double bonds remain intact with

HTIB. In the reaction with malonamide, however, only tosylation at the active methylene carbon occurs (Scheme 14).[52]

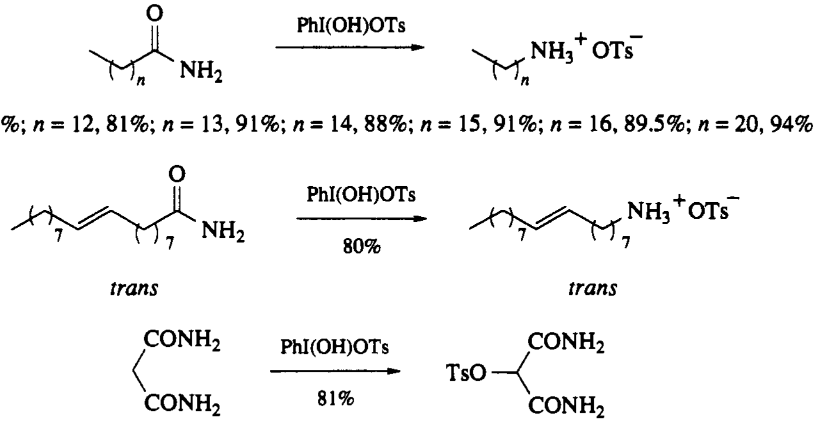
O
NH2
PhI(OH)OTs
NH3+ OTs−
n
n = 11, 90%; n = 12, 81%; n = 13, 91%; n = 14, 88%; n = 15, 91%; n = 16, 89.5%; n = 20, 94%
O
NH2
PhI(OH)OTs
80%
NH3+OTs−
7
trans
trans
CONH2
CONH2
PhI(OH)OTs
81%
TsO
CONH2
CONH2

**Scheme 14**

Iodosylbenzene (**31**), together with formic acid, can also be used for the oxidative Hofmann reaction[54] in an acetonitrile–water mixture (3:1) at room temperature (equation 24). The reaction behavior of (**31**) is quite similar to that of PIFA.

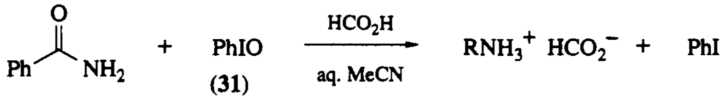
O
Ph
NH2
+
PhIO
(31)
HCO2H
aq. MeCN
RNH3+ HCO2− + PhI

(24)

## 4.4.3 THE CURTIUS REACTION

### 4.4.3.1 *Via* Hydrazides

As described earlier (Section 4.4.1.1), the intermediates of the Curtius reaction are acyl azides, which thermally rearrange to isocyanates. One of the classical procedures[8,9] for the preparation of acyl azides consists of the formation of hydrazides from esters and hydrazine, followed by treatment of the hydrazides with nitrous acid, generated from sodium nitrite and acetic, hydrochloric or sulfuric acid. Acyl azides are commonly used in the crude state or in solution since they are thermally unstable and potentially explosive.

Conversion of phosphonoacetic esters (**41**) to aminophosphonic acids (**42**) is conveniently carried out by chemoselective reaction of (**41**) with hydrazine, followed by the Curtius rearrangement without isolation of any intermediates (equation 25).[55]

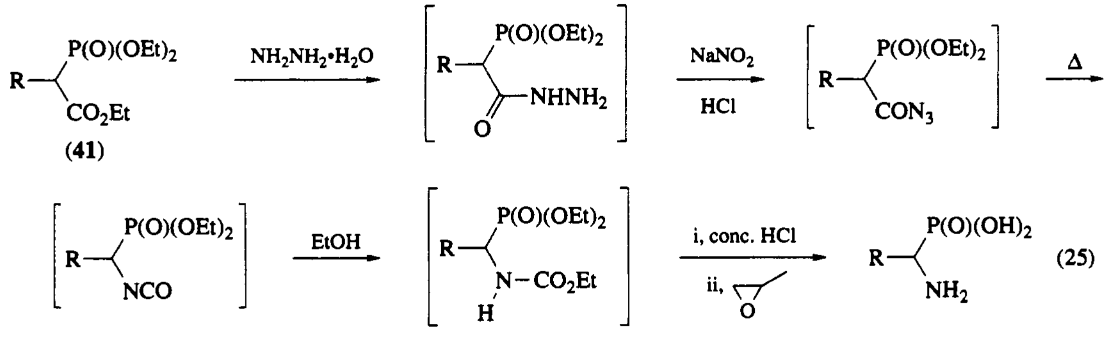
P(O)(OEt)2
R
CO2Et
(41)
NH2NH2•H2O
P(O)(OEt)2
R
NHNH2
O
NaNO2
HCl
P(O)(OEt)2
R
CON3
Δ
P(O)(OEt)2
R
NCO
EtOH
P(O)(OEt)2
R
N−CO2Et
H
i, conc. HCl
ii,
O
P(O)(OH)2
R
NH2

(25)

R = H, 54%; R = Me, 80%; R = PhCH$_2$, 56% (**42**)

The pyrazole derivatives (**44**), prepared from the lactones (**43**), give the cyclized (**45** and **46**) or uncyclized products (**47**) by the Curtius rearrangement, depending on the substrates and reaction solvents (Scheme 15).[56]

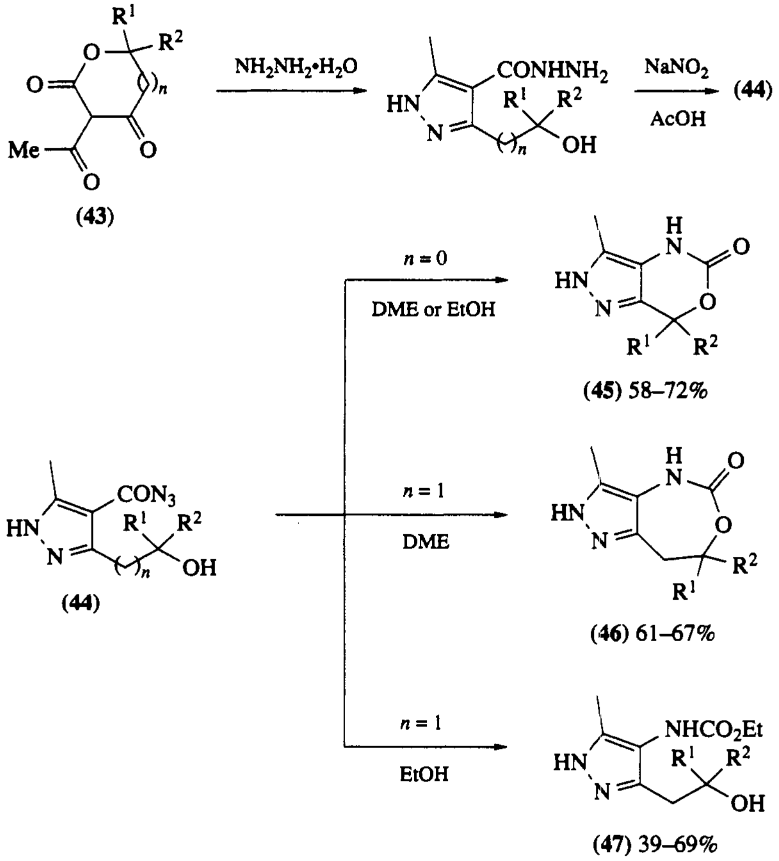

**Scheme 15**

The Curtius rearrangement of the acyl azide derived from optically pure α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA; **48**) also proceeds with retention of configuration, giving α-methoxy-α-(trifluoromethyl)benzyl isocyanate (**49**; equation 26).[57] The isocyanate (**49**) is useful for the determination of the enantiomeric composition of optically active primary and secondary amines.

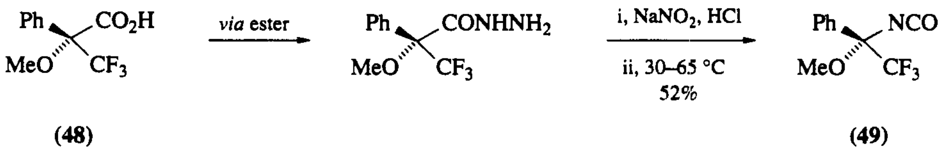

(26)

Alkyl nitrites[58] and nitrogen tetroxide[59,60] together with acid are also effective for the formation of acyl azides from hydrazides under anhydrous conditions. As shown in Scheme 16, the Curtius reaction is especially suitable for the formation of complex reactive molecules.

### 4.4.3.2 *Via* Acyl Chlorides

Formation of acyl azides from acyl chlorides is also a classical procedure[8,9] for the Curtius reaction. Sodium azide is used for the azidation under aqueous and anhydrous conditions, called the wet and dry methods respectively (equations 27[61] and 28[62]).

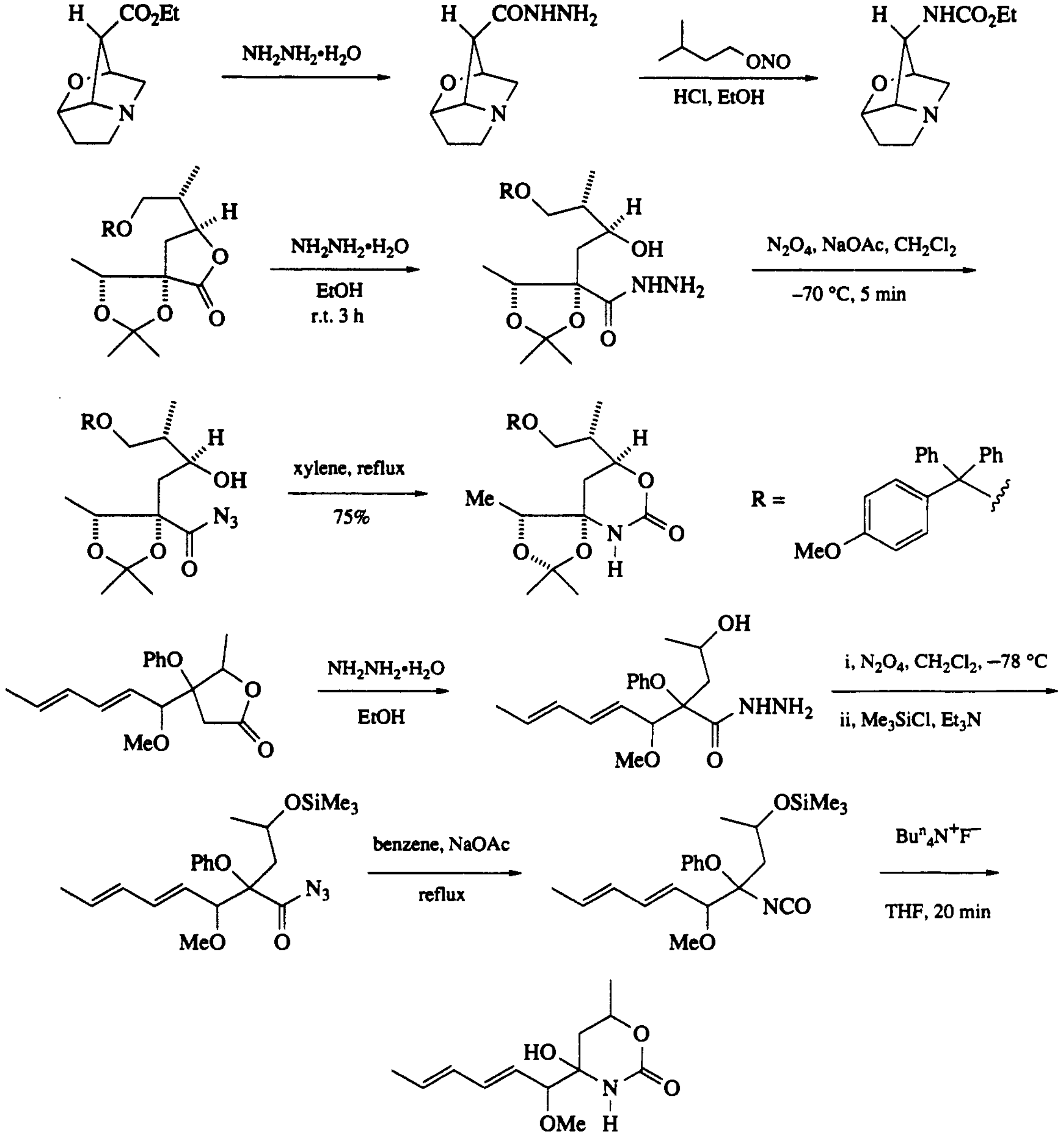

H CO2Et
NH2NH2•H2O
H CONHNH2
ONO
HCl, EtOH
H NHCO2Et
RO
NH2NH2•H2O
EtOH
r.t. 3 h
OH
NHNH2
N2O4, NaOAc, CH2Cl2
-70 °C, 5 min
N3
xylene, reflux
75%
Me
R =
Ph Ph
MeO
PhO
MeO
NH2NH2•H2O
EtOH
OH
NHNH2
i, N2O4, CH2Cl2, −78 °C
ii, Me3SiCl, Et3N
OSiMe3
benzene, NaOAc
reflux
NCO
Bun4N+F−
THF, 20 min
HO
OMe H

Scheme 16

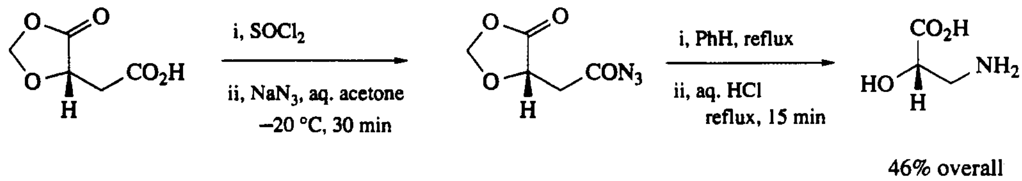

CO2H
i, SOCl2
ii, NaN3, aq. acetone
−20 °C, 30 min
CON3
i, PhH, reflux
ii, aq. HCl
reflux, 15 min
CO2H
HO
NH2
H
46% overall

(27)

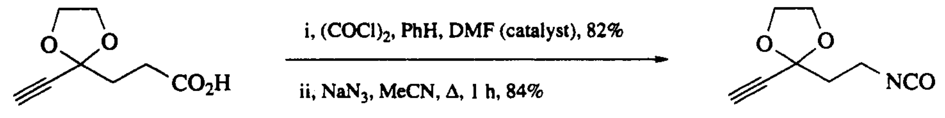

CO2H
i, (COCl)2, PhH, DMF (catalyst), 82%
ii, NaN3, MeCN, Δ, 1 h, 84%
NCO

(28)

Trapping of isocyanates, the intermediates of the Curtius reaction, is usually carried out with methanol, ethanol, *t*-butyl alcohol or benzyl alcohol. Use of 9-anthrylmethanol (AnOH) gives the corresponding urethanes, which can be converted to amines by treatment with sodium ethanethiolate under neutral conditions (equation 29).[63]

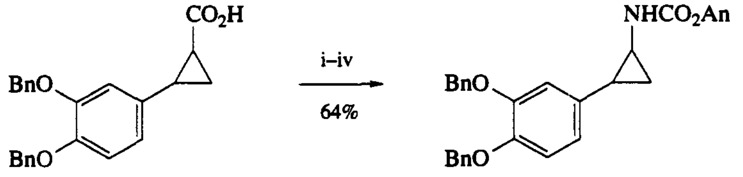
CO2H
BnO
BnO
i–iv
64%
NHCO2An
BnO
BnO

(29)

i, $SOCl_2$; ii, $NaN_3$; iii, Δ, toluene; iv, AnOH

A useful variant of the Curtius reaction comprises the reaction of acyl chlorides in dichloromethane with sodium azide under phase transfer conditions, followed by treatment of the dried dichloromethane solution, which contains acyl azides, with a slight excess of trifluoroacetic acid. The resulting trifluoroacetamides can easily be cleaved with potassium carbonate in aqueous methanol at room temperature, giving the amines (equation 30).[64]

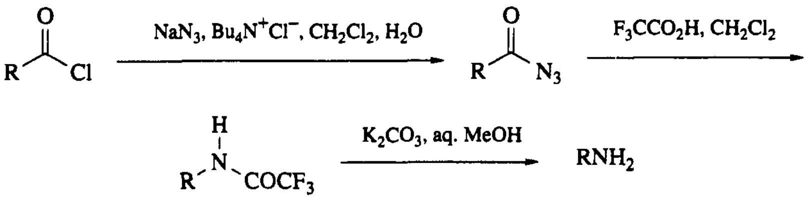
NaN3, Bu4N+Cl−, CH2Cl2, H2O
F3CCO2H, CH2Cl2
K2CO3, aq. MeOH
RNH2

(30)

In place of sodium azide, which has low solubility in common organic media, use of a mixture of hydrazoic acid and pyridine,[65] tetrabutylammonium azide[66] or tetramethylguanidinium azide[67] has been recommended. One of the most useful and safe alternatives is trimethylsilyl azide (**50**), which reacts with various acyl chlorides or anhydrides to give isocyanates directly, under thermal conditions (Scheme 17).[68,69]

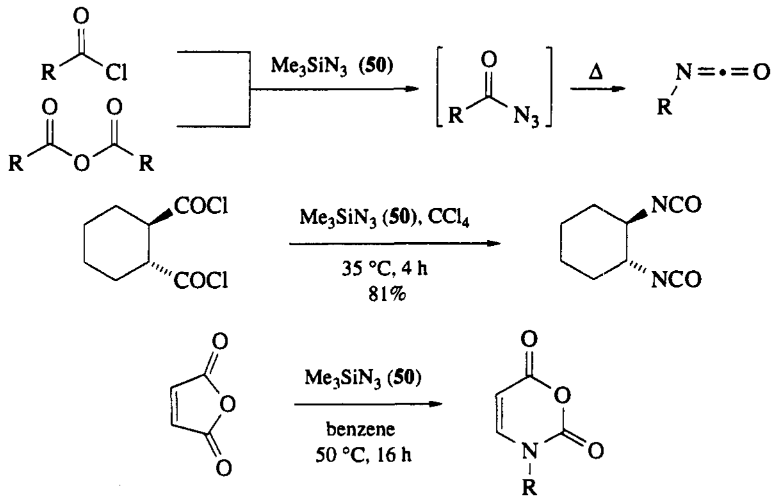
Me3SiN3 (50)
Δ
N=•=O
Me3SiN3 (50), CCl4
35 °C, 4 h
81%
COCl
COCl
NCO
NCO
Me3SiN3 (50)
benzene
50 °C, 16 h

R = $Me_3Si$, 15%; R = H, 52%

**Scheme 17**

When the usual reaction conditions using trimethylsilyl azide (**50**) are not suitable for the Curtius reaction, addition of catalytic amounts of powdered potassium azide and 18-crown-6 is quite effective in conducting the reaction (equation 31).[70]

Tributylstannyl azide (**51**), prepared from tributylstannyl chloride and sodium azide, is also useful for the direct conversion of acyl chlorides to isocyanates (equation 32).[71] In addition, succinic anhydride

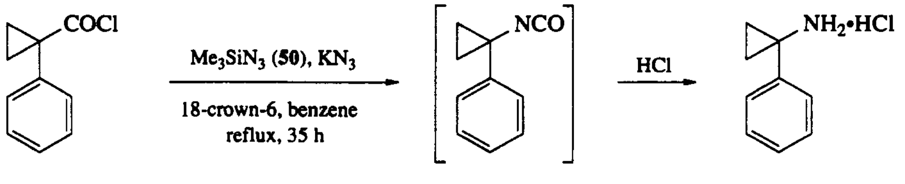
COCl
Me$_3$SiN$_3$ (50), KN$_3$
18-crown-6, benzene
reflux, 35 h
NCO
HCl
NH$_2$•HCl

88% overall

(31)

reacts with (**51**) to give tributylstannyl 3-isocyanatopropionate (**52**), which on treatment with benzyl alcohol and then aqueous alkali affords *N*-benzyloxycarbonyl-β-alanine (**53**; equation 33).

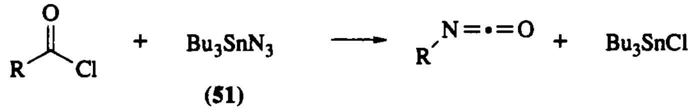
O
R
Cl
+
Bu$_3$SnN$_3$
(51)
N=•=O
R
+
Bu$_3$SnCl

(32)

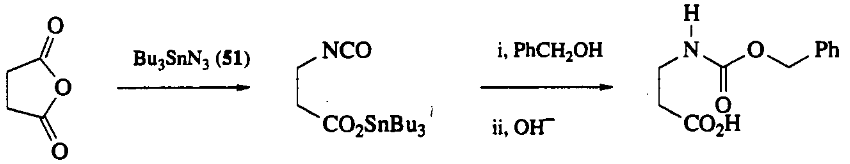
O
O
O
Bu$_3$SnN$_3$ (51)
NCO
CO$_2$SnBu$_3$
i, PhCH$_2$OH
ii, OH$^-$
H
N
O
Ph
O
CO$_2$H

(**52**)

(**53**) 35% overall

(33)

Acyl chlorides may be replaced with imidazolides, which react with sodium azide to give acyl azides. In the reaction shown in equation (34), 2-trimethylsilylethanol is used for trapping the isocyanate.[72] The resulting 2-trimethylsilylethyl ester is easily cleaved with tetra-*n*-butylammonium fluoride.

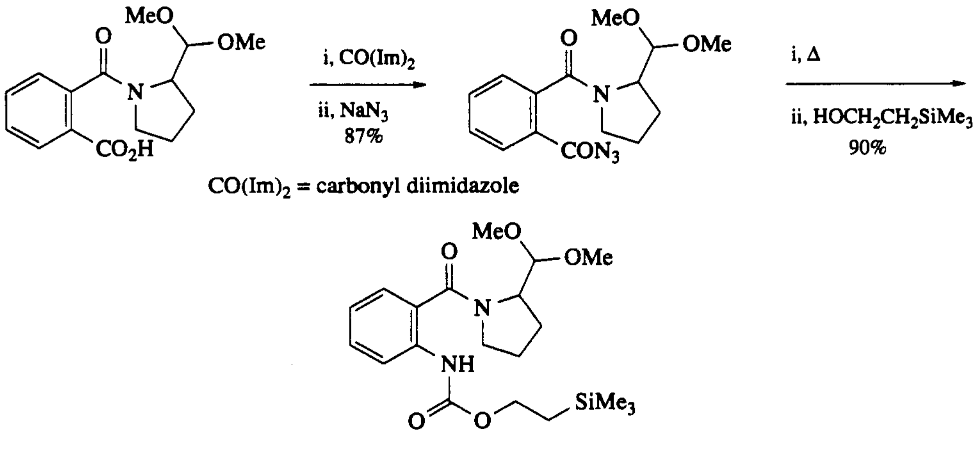
MeO
O
OMe
N
CO$_2$H
i, CO(Im)$_2$
ii, NaN$_3$
87%
MeO
O
OMe
N
CON$_3$
i, Δ
ii, HOCH$_2$CH$_2$SiMe$_3$
90%
MeO
O
OMe
N
NH
O
O
SiMe$_3$

CO(Im)$_2$ = carbonyl diimidazole

(34)

*N*,*N*-Dimethylchlorosulfitomethaniminium chloride (**54**), prepared from thionyl chloride and dimethylformamide, together with sodium azide is useful for the direct preparation of acyl azides from carboxylic acids (equation 35).[73]

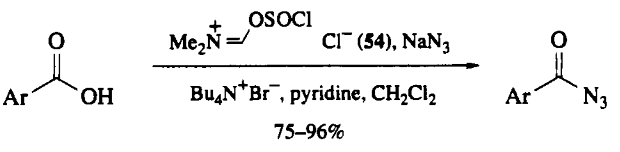
O
Ar
OH
+
Me$_2$N=
OSOCl
Cl$^-$ (54), NaN$_3$
Bu$_4$N$^+$Br$^-$, pyridine, CH$_2$Cl$_2$
75–96%
O
Ar
N$_3$

(35)

### 4.4.3.3 *Via* Mixed Anhydrides

Mixed carboxylic–carbonic anhydrides, prepared from carboxylic acids and alkyl chloroformates in the presence of base, are easily converted to acyl azides by the action of sodium azide. Since the reaction sequence from carboxylic acids to acyl azides proceeds under mild conditions, it has a broad applicability. *cis*-2-Phenylcyclopropanecarboxylic acid (**55**) is easily converted to *cis*-2-phenylcyclopropylamine (**56**), without isomerization to the *trans* isomer, by consecutive treatment with: (i) ethyl chloroformate in the presence of triethylamine; (ii) sodium azide; (iii) refluxing toluene; and (iv) hydrochloric acid, without purification of the intermediates (equation 36).[74]

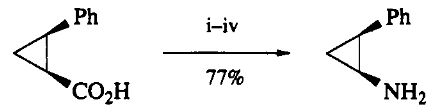

**(55)** **(56)** (36)

i, $ClCO_2Et$, $Et_3N$, aq. $Me_2CO$, 0 °C, 30 min; ii, $NaN_3$ in water, 0 °C, 1 h; iii, toluene, reflux; iv, 20% aq. HCl, reflux, 9 h

Various *trans*-1-*N*-acylamino-1,3-butadienes (**58**) are prepared from 2,4-pentadienoic acids (**57**) by the mixed anhydride method (equation 37).[75] The procedure is reproducible when *N*,*N*-diisopropylethylamine is used in place of triethylamine.

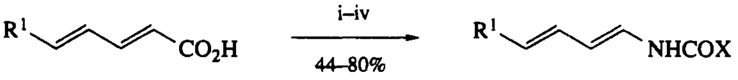

**(57)** **(58)** (37)

i, $ClCO_2Et$, $Pr^i_2NEt$, 0 °C, 30 min; ii, $NaN_3$ in water, 0 °C, 30 min; iii, toluene; iv, XH ($R^2OH$, $R^3NHR^4$ or $R^5SH$), reflux

The mixed anhydride method is analogously and conveniently applied to the preparation of α-amino acids (**60**) from malonic acid half-esters (**59**; equations 38 and 39).[76,77]

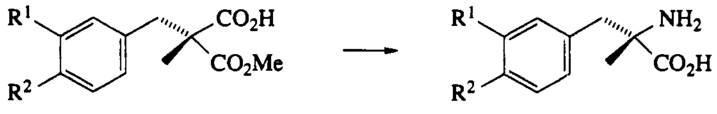

**(59a)** **(60a)** (38)

$R^1 = R^2 =$ H, 86%; $R^1 =$ MeO, $R^2 =$ H, 63%; $R^1 = R^2 =$ Me, 74%

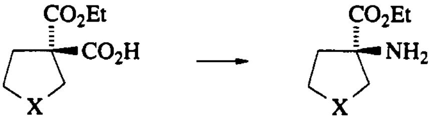

**(59b)** X = NH, S **(60b)** (39)

### 4.4.3.4 By Use of Diphenyl Phosphorazidate

Diphenyl phosphorazidate (DPPA; $(PhO)_2P(O)N_3$) is a useful and versatile reagent in organic synthesis,[78] and can be conveniently used for the Curtius reaction under mild reaction conditions, using carboxylic acids as a starting material.[17,18] Exchange of the azide group occurs from DPPA to carboxylic acids in the presence of base, *e.g.* triethylamine, giving acyl azides. When the reaction is conducted under thermal conditions, the rearrangement occurs *in situ* to give isocyanates in a single step. Addition of water, or preferably a mineral acid, to the reaction mixture containing isocyanates gives amines in a one-pot process, while addition of alcohols yield urethanes. When this modified Curtius reaction is carried out in refluxing *t*-butyl alcohol, *t*-butylurethanes are formed in a single process from carboxylic acids. The modified Curtius reaction using DPPA is similar to the Schmidt reaction in the sense that carboxylic acids yield amines or their derivatives in a one-pot process, but is more like the Curtius reaction from a mechanistic point of view.[18] Since the reaction proceeds under mild and neutral conditions, it has a broad applicability.

Acyl azides (**61**)[79] and (**62**)[80] and isocyanate (**63**),[81] the reaction intermediates of the modified Curtius reaction using DPPA, have been isolated in a pure state, since they are relatively thermally stable, and further converted to urethanes or ureas by the addition of alcohols or amines respectively.

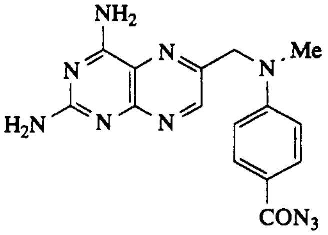
NH2
N
N
Me
H2N
N
N
CON3

(**61**)

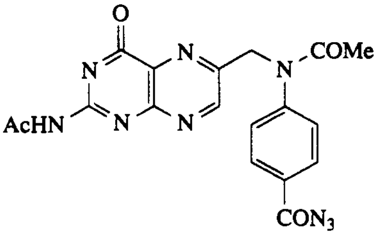
O
N
N
COMe
AcHN
N
N
CON3

(**62**)

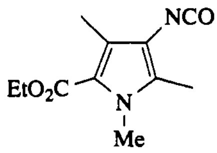
NCO
EtO2C
N
Me

(**63**)

Pyridine-2-carboxylic acid (**64**), which is known to fail in the Schmidt reaction, smoothly undergoes the reaction with DPPA to give the *t*-butylurethane (**65**).[18] The potassium salt of penicillin G (**66**) also gives the *t*-butylurethane (**67**) in a single operation. Although levulinic acid (**68**) gives the *t*-butylurethane (**69**) together with the carbamoyl azide (**70**) in unsatisfactory yields, the corresponding acetal derivative (**71**) smoothly undergoes the rearrangement to give the urethane (**72**) in good yield, together with small amounts of the carbamoyl azide (**73**) and the benzyl ester (**74**; Scheme 18).[18]

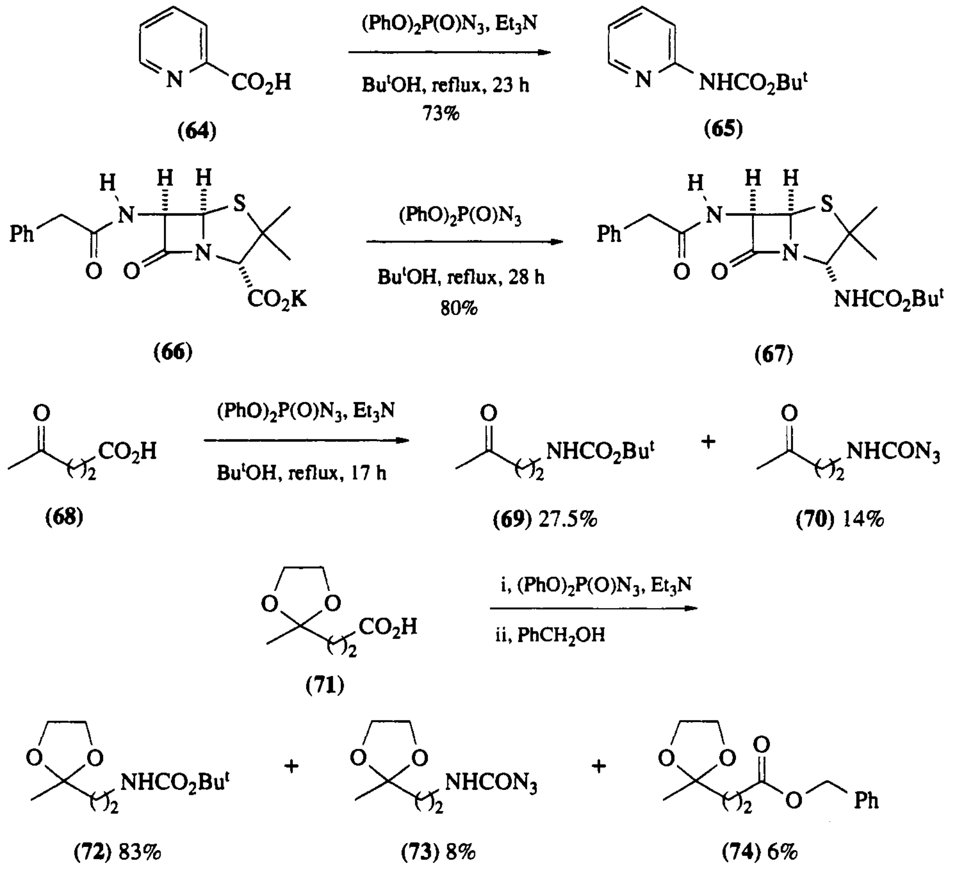
N
CO2H
(64)
(PhO)2P(O)N3, Et3N
ButOH, reflux, 23 h
73%
N
NHCO2But
(65)
H H H
Ph
N
S
O O
N
CO2K
(66)
(PhO)2P(O)N3
ButOH, reflux, 28 h
80%
H H H
Ph
N
S
O O
N
NHCO2But
(67)
O
CO2H
2
(68)
(PhO)2P(O)N3, Et3N
ButOH, reflux, 17 h
O
NHCO2But
2
(69) 27.5%
+
O
NHCON3
2
(70) 14%
O O
CO2H
2
(71)
i, (PhO)2P(O)N3, Et3N
ii, PhCH2OH
O O
NHCO2But
2
(72) 83%
+
O O
NHCON3
2
(73) 8%
+
O O O
2
O
Ph
(74) 6%

**Scheme 18**

Reaction procedures affect the products when malonic acid half-esters (**75**) with an acidic hydrogen at the $\alpha$-position are subjected to the modified Curtius reaction.[82,83] The usual one-pot procedure, in which alcohols are present from the beginning, affords esters (**76**), whereas the two-in-one procedure, in which alcohols are added after the formation of isocyanates, conveniently produces urethanes (**77**; Scheme 19). Formation of esters can be explained by the generation of ketene intermediates in equilibrium with acyl azides. The former irreversibly react with alcohols to give esters.[83] Malonic acid half-esters with no acidic hydrogen, *e.g.* (**78**), do not undergo the esterification but give the rearranged products, *e.g.* (**79**), even in the one-pot procedure since no ketene intermediates can be formed (Scheme 19).

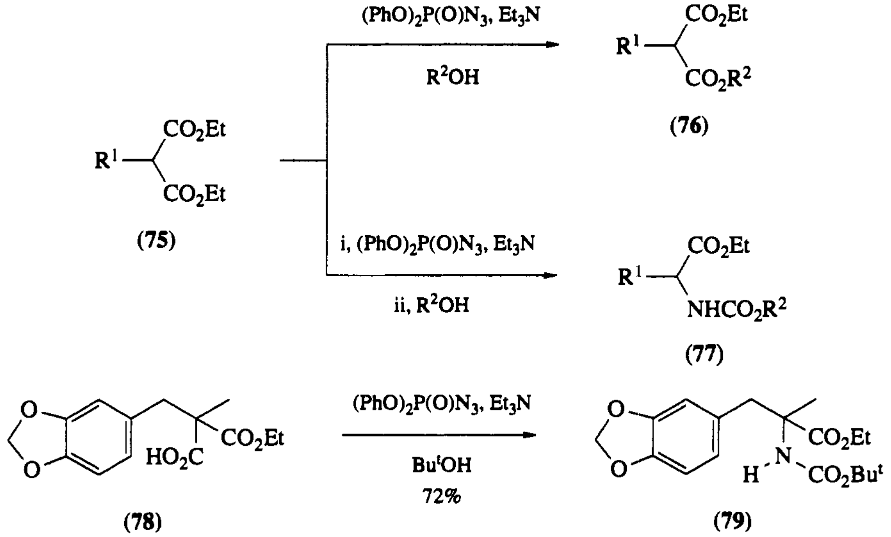

$CO_2Et$
$R^1$
$CO_2Et$
(75)
$(PhO)_2P(O)N_3$, $Et_3N$
$R^2OH$
$CO_2R^2$
(76)
i, $(PhO)_2P(O)N_3$, $Et_3N$
ii, $R^2OH$
$NHCO_2R^2$
(77)
O
$HO_2C$
(78)
$Bu^tOH$
72%
H
N
$CO_2Bu^t$
(79)

**Scheme 19**

The one-step modified Curtius reaction of *N*-benzyloxycarbonyl-L-proline (**80**) gives the allophanate (**82**) as the major product in addition to the expected urethane (**81a**).[84] However, the use of *t*-butyl carbamate (**83**) as an additive changes the reaction course and the desired carbamate (**81b**), though accompanied by racemization, is obtained in good yield. Similarly, the β-carboline derivative (**84**) also affords a mixture of the urethane (**85**) and the allophanate (**86**), with the latter as the major product, by a one-step procedure.[85] The two-step procedure, however, produces more of the urethane (**85**; Scheme 20).

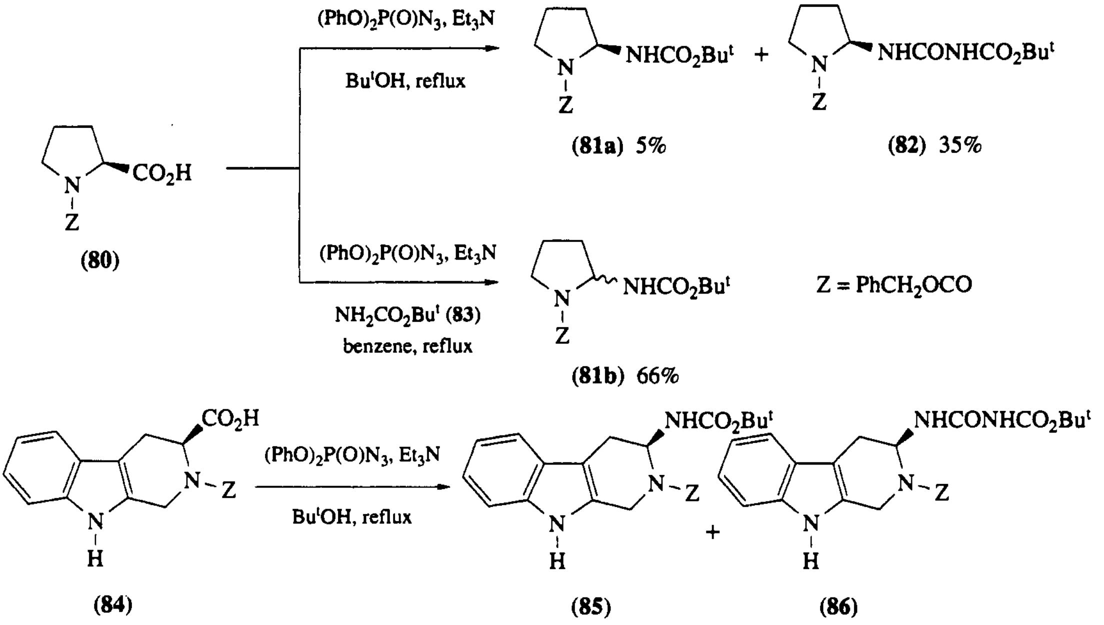

$CO_2H$
N
Z
(80)
$(PhO)_2P(O)N_3$, $Et_3N$
$Bu^tOH$, reflux
$NHCO_2Bu^t$
+
$NHCONHCO_2Bu^t$
(81a) 5%
(82) 35%
$NH_2CO_2Bu^t$ (83)
benzene, reflux
(81b) 66%
Z = $PhCH_2OCO$
H
(84)
(85)
(86)

| | (85) | (86) |
|---|---|---|
| one-step procedure | 10% | 32% |
| two-step procedure | 22% | – |

**Scheme 20**

Within the total synthesis of the antitumor antibiotics streptonigrin and lavendamycin, sterically hindered polyfunctional pyridinecarboxylic acids (**87**–**89**) have been conveniently converted to their corresponding amines by treatment with DPPA–triethylamine in refluxing benzene for 1–25 h, followed by a brief reflux after addition of water.[86–90]

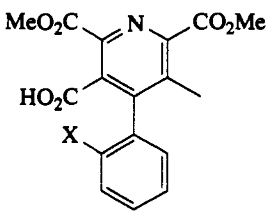
MeO2C
N
CO2Me
HO2C
X

(**87a**) X = H, 60% (ref. 86)
(**87b**) X = Br, 71% (ref. 87)

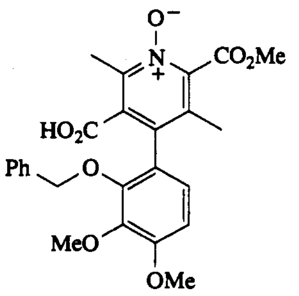
O−
N
+
CO2Me
HO2C
Ph
O
MeO
OMe

(**88**) 83% (ref. 88)

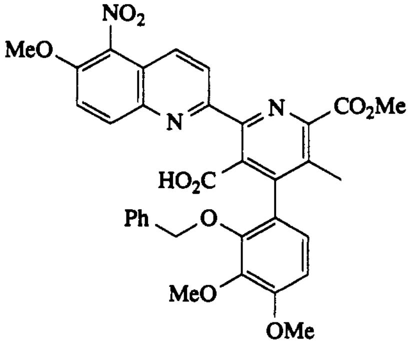
NO2
MeO
N
N
CO2Me
HO2C
Ph
O
MeO
OMe

(**89**) 43% (refs. 89, 90)

Sensitive molecules such as (**90**),[91] (**92**),[92] and (**94**)[93] smoothly undergo the modified Curtius reaction with DPPA to give the corresponding carbamates (**91**), (**93**) and (**95**), as shown in Scheme 21.

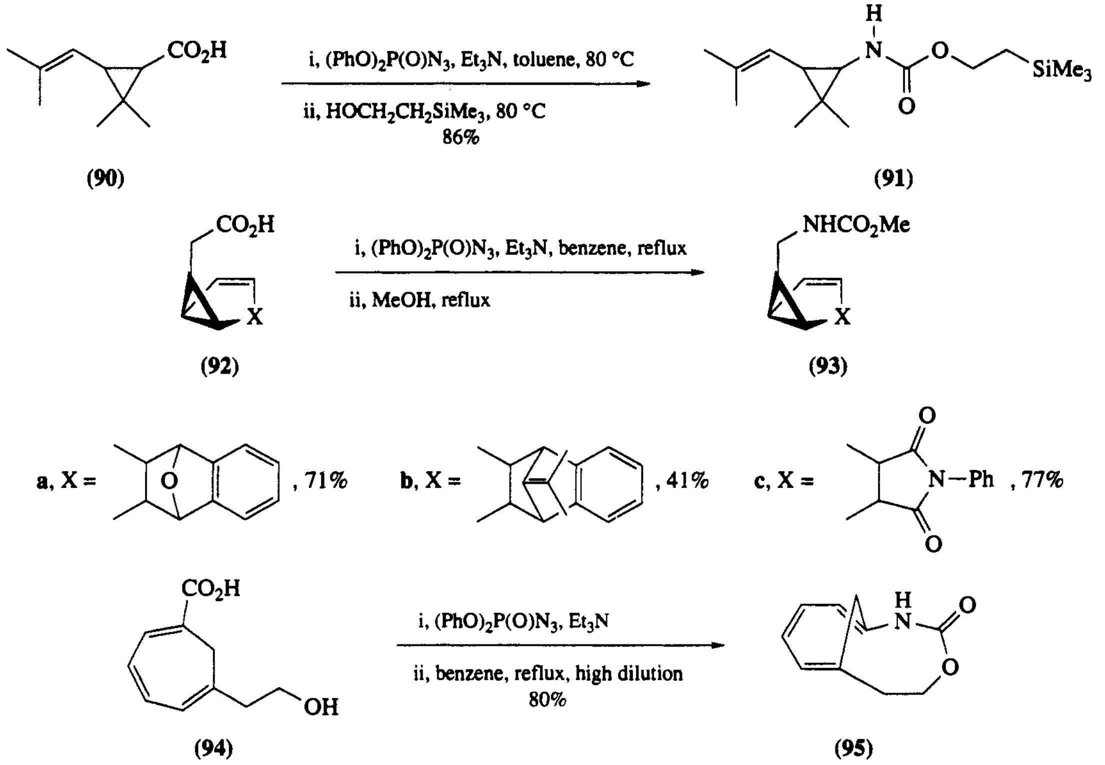
CO2H
i, (PhO)2P(O)N3, Et3N, toluene, 80 °C
ii, HOCH2CH2SiMe3, 80 °C
86%
H
N
O
O
SiMe3
(90)
(91)
CO2H
X
i, (PhO)2P(O)N3, Et3N, benzene, reflux
ii, MeOH, reflux
NHCO2Me
X
(92)
(93)
a, X =
O
, 71%
b, X =
, 41%
c, X =
O
N–Ph
, 77%
O
CO2H
OH
i, (PhO)2P(O)N3, Et3N
ii, benzene, reflux, high dilution
80%
H
N
O
O
(94)
(95)

**Scheme 21**

Analogously, the Curtius rearrangement followed by an intramolecular cyclization easily occurs by the reaction of DPPA with hydroxycarboxylic acids (**96**) and (**98**), giving cyclic carbamates (**97**)[94] and (**99**; equations 40 and 41).[95]

Rearrangement of β-alanine and succinic acid derivatives (**100** and **102**) gives 1-acyl-2-imidazolidinones (**101**) and β-alanine derivatives (**103**) respectively (Scheme 22).[96] However, the *N*-methylcarbox-

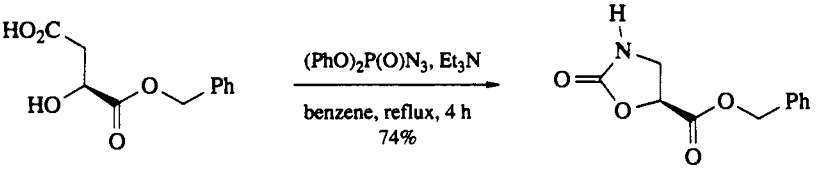
(PhO)2P(O)N3, Et3N
benzene, reflux, 4 h
74%

**(96)** **(97)** (40)

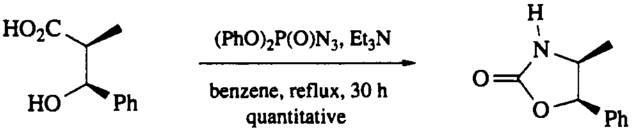
(PhO)2P(O)N3, Et3N
benzene, reflux, 30 h
quantitative

**(98)** **(99)** (41)

amide function has been found to have a deleterious effect and the compounds (**104a**) and (**104b**) afford a complex mixture of products.

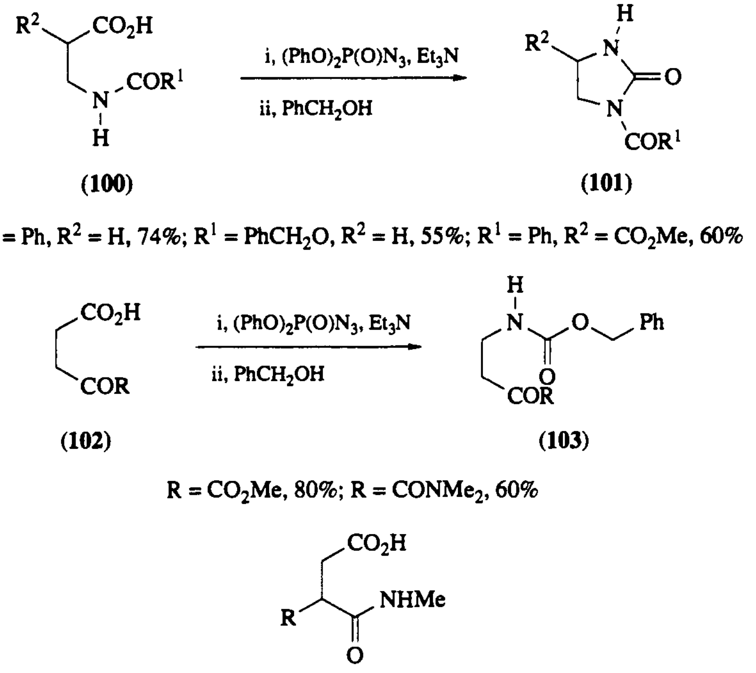
i, (PhO)2P(O)N3, Et3N
ii, PhCH2OH
i, (PhO)2P(O)N3, Et3N
ii, PhCH2OH

**(100)** **(101)**

$R^1$ = Ph, $R^2$ = H, 74%; $R^1$ = $PhCH_2O$, $R^2$ = H, 55%; $R^1$ = Ph, $R^2$ = $CO_2Me$, 60%

**(102)** **(103)**

R = $CO_2Me$, 80%; R = $CONMe_2$, 60%

(**104a**) R = H
(**104b**) R = PhCONH

**Scheme 22**

1-Aryl-1,2,4-triazolin-5-ones (**106**) are conveniently prepared from arylhydrazones of α-keto acids (**105**) by the Curtius rearrangement with DPPA, followed by an intramolecular cyclization (equation 42).[97]

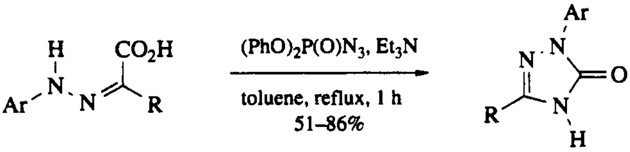
(PhO)2P(O)N3, Et3N
toluene, reflux, 1 h
51–86%

**(105)** **(106)** (42)

1-Cyclohexenyl isocyanate (**108**), produced from 1-cyclohexenecarboxylic acid (**107**) and DPPA *in situ*, reacts with 1-(*N*-pyrrolidinyl)cyclohexene (**109**) to give the pyridone derivative (**110**; equation 43).[98] The similar vinyl isocyanate–enamine cyclocondensation presents a general method for the preparation of various pyridone derivatives.

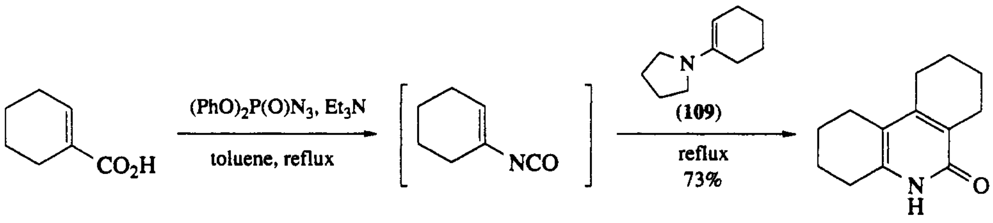
CO2H
(PhO)2P(O)N3, Et3N
toluene, reflux
NCO
N
(109)
reflux
73%
N
H
O

(43)

**(107)** **(108)** **(110)**

Preparation of α-amino acid amides of aromatic amines (**111**) is easily conducted as a one-pot procedure by the modified Curtius reaction of aromatic carboxylic acids with DPPA, followed by reaction with *N*-protected α-amino acids (equation 44).[99] By this method, *N*-*t*-butoxycarbonyl-L-leucine *p*-nitroanilide, which serves as a substrate for leucine aminopeptidase after deblocking of its *t*-butoxycarbonyl group, has been efficiently prepared from *p*-nitrobenzoic acid and *N*-*t*-butoxycarbonyl-L-leucine.

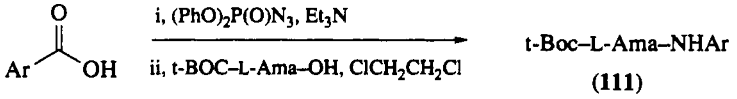
O
Ar
OH
i, (PhO)2P(O)N3, Et3N
ii, t-BOC-L-Ama-OH, ClCH2CH2Cl
t-Boc-L-Ama-NHAr

**(111)** (44)

t-BOC = Bu$^t$OCO; Ama = amino acid residue

Analogs of DPPA such as diethyl phosphorazidate (**112**),[18] di-*p*-nitrophenyl phosphorazidate (**113**)[100] and phenyl *N*-phenylphosphoramidoazidate (**114**)[101] can also be used for the Curtius reaction. Di-*p*-nitrophenyl phosphorazidate (**113**) has been proposed as a reagent for the determination of the carboxy terminal residue of peptides.[100] A simple protected form of diaminomethane (**116**), an interesting building block for peptide mimetics, has been prepared from *t*-butoxycarbonylglycine (**115**) using di-*p*-nitrophenyl phosphorazidate (**113**; Scheme 23).[102] Phenyl *N*-phenylphosphoramidoazidate (**114**) has been utilized for the preparation of *N*,*N*′-diarylureas (**117**) from aromatic carboxylic acids and aromatic primary amines.[101]

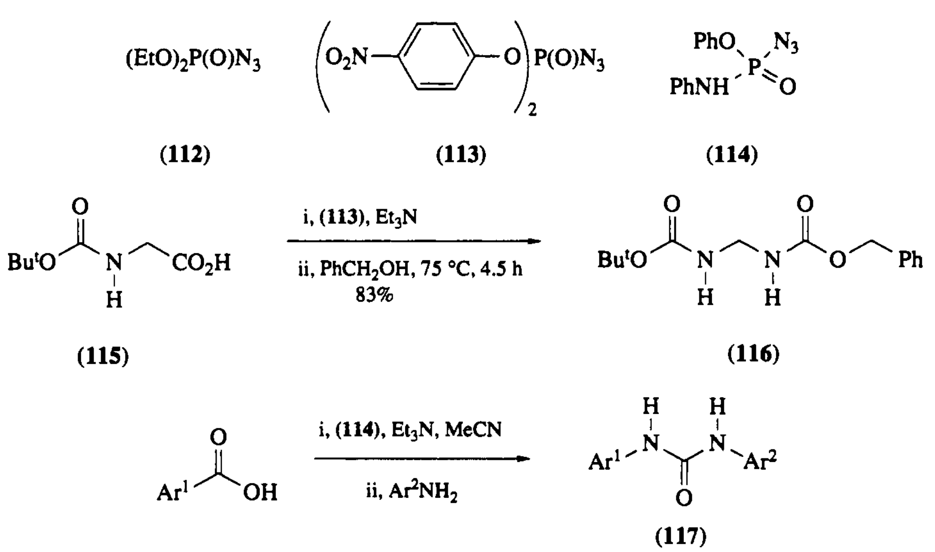
(EtO)2P(O)N3
(112)
O2N
O
P(O)N3
2
(113)
PhO
N3
P
PhNH
O
(114)
Bu$^t$O
N
H
CO2H
(115)
i, (113), Et3N
ii, PhCH2OH, 75 °C, 4.5 h
83%
Bu$^t$O
N
H
N
H
O
Ph
(116)
Ar1
OH
i, (114), Et3N, MeCN
ii, Ar2NH2
H
N
Ar1
Ar2
O
(117)

**Scheme 23**

## 4.4.4 THE SCHMIDT REACTION

### 4.4.4.1 With Carboxylic Acids

The Schmidt reaction[10–13] is usually carried out using a mixture of sodium azide and sulfuric acid, which generates hydrazoic acid. Free hydrazoic acid together with sulfuric acid may also be used. Although the Schmidt reaction of carboxylic acids is quite useful for the preparation of amines with one less carbon unit, it is less flexible than the other rearrangements since it requires hazardous hydrazoic acid and strongly acidic conditions. Since hydrazoic acid is very poisonous and potentially explosive, the reaction should be conducted under an efficient hood and precautions should be taken against explosion, especially in a large-scale preparation. In place of sulfuric acid, polyphosphoric acid and trifluoroacetic acid–trifluoroacetic anhydride may be used. Usual solvents are chloroform, 1,2-dichloroethane and benzene.

Aliphatic carboxylic acids, even in the case of a sterically hindered carboxylic acid such as (**118**), are usually converted to the corresponding amines, *e.g.* (**119**), by the Schmidt reaction (equation 45).[103]

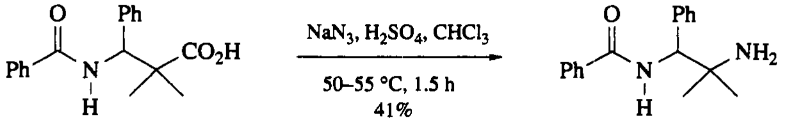
O
Ph
Ph
N
H
$CO_2H$
$NaN_3$, $H_2SO_4$, $CHCl_3$
50–55 °C, 1.5 h
41%
O
Ph
Ph
N
H
$NH_2$

(**118**) (**119**) (45)

Both phenylacetic and 3-phenylpropionic acids (**120**) easily undergo the Schmidt reaction under the standard conditions using sulfuric acid, giving the corresponding amines (**121**).[104] 4-Phenylbutyric acid (**122**), however, produces the cyclic lactam (**123**), in addition to the sulfonated amine (**124**). Replacement of sulfuric acid with polyphosphoric acid again affords the lactam (**123**) mainly, together with 3-phenylpropylamine (**125**) as a minor product. In the rearrangement of 5-phenylpentanoic acid (**126**), only the sulfonated amine (**127**) is obtained, as shown in Scheme 24.

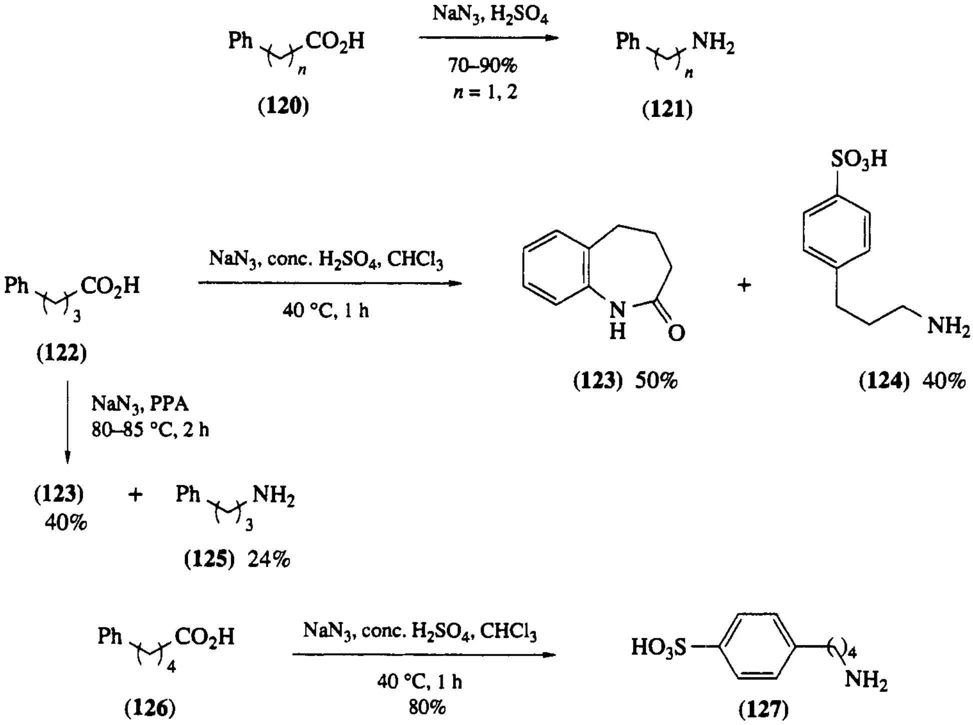
Ph
$CO_2H$
n
(120)
$NaN_3$, $H_2SO_4$
70–90%
n = 1, 2
Ph
$NH_2$
n
(121)
Ph
$CO_2H$
3
(122)
$NaN_3$, conc. $H_2SO_4$, $CHCl_3$
40 °C, 1 h
N
H
O
(123) 50%
+
$SO_3H$
$NH_2$
(124) 40%
$NaN_3$, PPA
80–85 °C, 2 h
(123)
40%
+
Ph
$NH_2$
3
(125) 24%
Ph
$CO_2H$
4
(126)
$NaN_3$, conc. $H_2SO_4$, $CHCl_3$
40 °C, 1 h
80%
$HO_3S$
4
$NH_2$
(127)

**Scheme 24**

Treatment of 2-phenylhexanoic acid (**128**) with sodium azide in polyphosphoric acid furnishes the expected amine (**129**) together with aniline (**130**) in a nearly equal ratio, as shown in Scheme 25.[105] 2-Phenyl-2-methylhexanoic acid (**131**) gives aniline (**130**) only and no Schmidt product is obtained. Similar treatment of diphenylacetic, 2,2-diphenylpropionic and triphenylacetic acids mainly gives the unchanged starting materials. Except in the case of triphenylacetic acid, a small amount of aniline (**130**) is formed. The above anomalous formation of aniline can be explained by the decarboxylation at the initial step to form a benzyl-type cation (**132**), which reacts with hydrazoic acid, followed by rearrangement with concomitant expulsion of nitrogen and then hydrolysis.

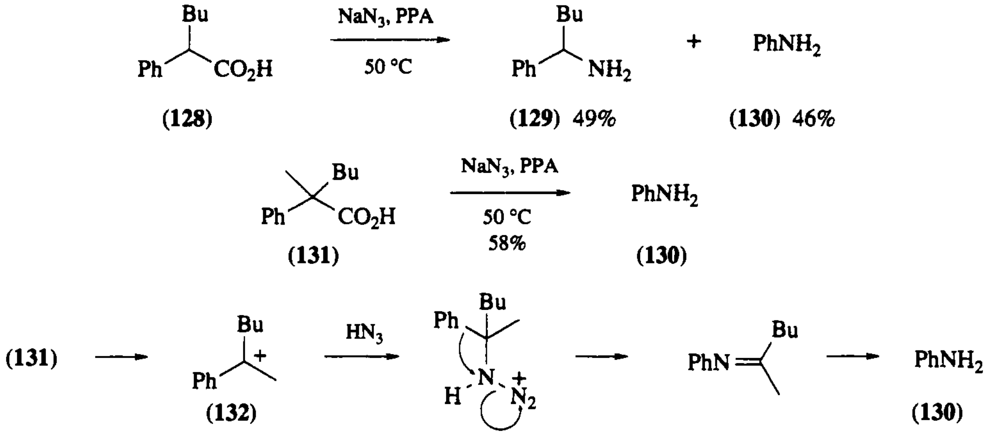

(128)
NaN$_3$, PPA
50 °C
(129) 49%
+ PhNH$_2$
(130) 46%
(131)
NaN$_3$, PPA
50 °C
58%
PhNH$_2$
(130)
(131)
(132)
HN$_3$
PhN
PhNH$_2$
(130)

**Scheme 25**

(*E*)-Hex-3-ene-1,6-dioic acid (**133**) undergoes the Schmidt reaction with 1 equiv. of sodium azide to give (*E*)-5-aminopent-3-enoic acid (**134**) in moderate yield, shown in Scheme 26. The Schmidt reaction of the corresponding (*Z*)-isomer (**135**) analogously proceeds to give the (*Z*)-amino acid (**136**) though with much lower efficiency.[106] Furthermore, hex-3-yne-1,6-dioic acid (**137**) gives the Schmidt product (**138**) in very low yield, presumably because of competing additions of hydrazoic acid to the triple bond.

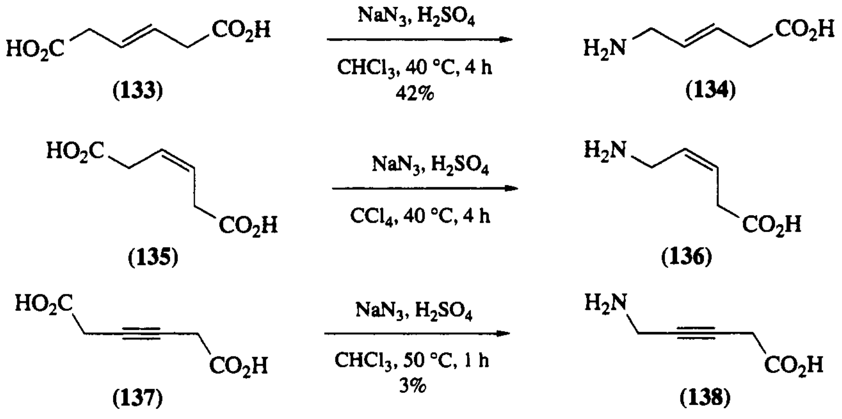

(133)
NaN$_3$, H$_2$SO$_4$
CHCl$_3$, 40 °C, 4 h
42%
(134)
(135)
NaN$_3$, H$_2$SO$_4$
CCl$_4$, 40 °C, 4 h
(136)
(137)
NaN$_3$, H$_2$SO$_4$
CHCl$_3$, 50 °C, 1 h
3%
(138)

**Scheme 26**

The absolute configuration of (+)-*trans*-cyclopentane-1,3-dicarboxylic acid (**139**) has been determined to be (1*S*, 3*S*) by the correlation with *trans*-(1*S*, 3*S*)-3-aminocyclopentanecarboxylic acid (**140**) through the Schmidt reaction (equation 46).[107]

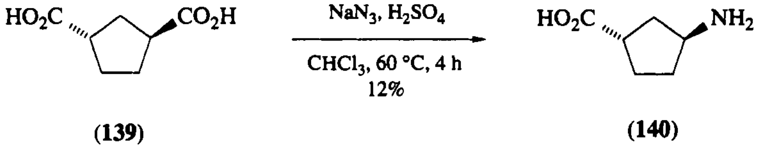

NaN$_3$, H$_2$SO$_4$
CHCl$_3$, 60 °C, 4 h
12%

(46)

(**139**) (**140**)

Aromatic carboxylic acids, *e.g.* (**141**),[108] also undergo the Schmidt reaction to give amines, *e.g.* (**142**), in a single operation. Although the Schmidt reaction of 2′,4,4′,6,6′-pentanitrobiphenyl-2-carboxylic acid (**143a**) proceeds to give the amine (**144a**) in 49% yield, the corresponding 2′,4′,6′-trinitro analog (**143b**) affords only unchanged starting material (Scheme 27).[109] In the latter case, however, conversion to the amine (**144b**) has been achieved by the Curtius reaction *via* the acyl chloride.

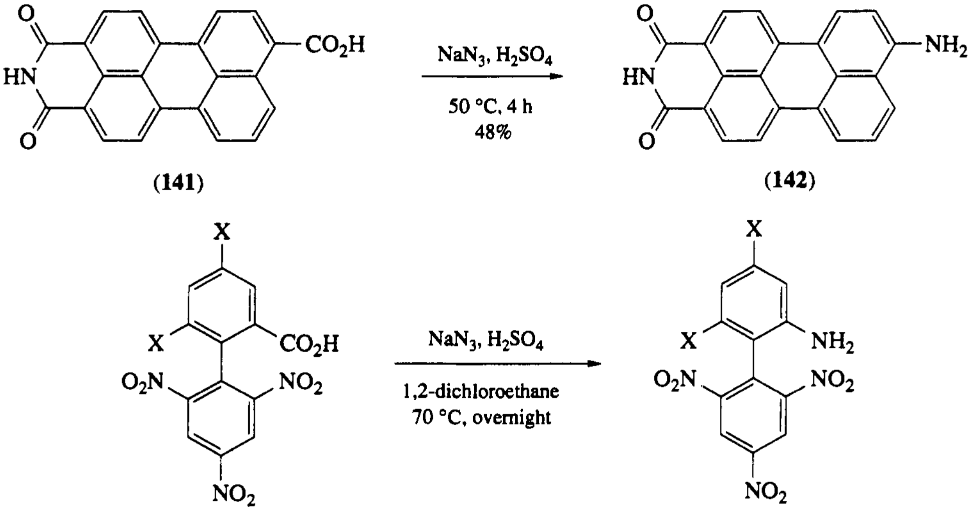

**(141)** **(142)**

**(143a,b)** a: X = $NO_2$, b: X = H **(144a,b)**

**Scheme 27**

Treatment of phthalic acid (**145**) with sodium azide under acidic conditions has been reported[110] to give various products: anthranilic acid (**147**) and a trace of *o*-phenylenediamine (**148**) in concentrated sulfuric acid; and anthranilazide (**149**) and benzimidazol-2-one (**150**) in 90% sulfuric acid. Analogously, phthalic anhydride (**146**) gives the following products: anthranilic acid (**147**), benzimidazol-2-one (**150**) and some 3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride) (**151**) in sulfuric acid; and benzimidazol-2-one (**150**) in acetic acid. A recent report[110] has revealed that the Schmidt reaction of phthalic acid (**145**) in 90–98% sulfuric acid gives anthranilic acid (**147**) and anthranilazide (**149**) (major products) by a process thought to involve 3,1-benzoxazine-2,4(1*H*)-dione (**151**) as an intermediate. Benzimidazol-2-one (**150**) is produced in this reaction by a secondary process from anthranilazide (**149**). Photolysis of (**149**) also produces (**150**).

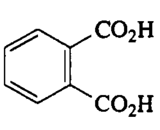

**(145)**

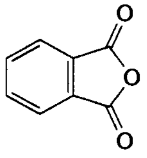

**(146)**

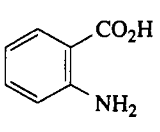

**(147)**

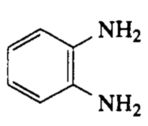

**(148)**

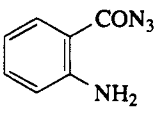

**(149)**

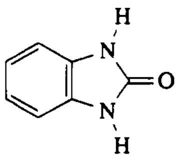

**(150)**

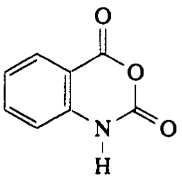

**(151)**

Under the Schmidt reaction conditions, the lactol (**152**) of 4-formyl-5-phenanthroic acid gives 1-azapyren-2(1*H*)-one (**153**) and phenathrene-4,5-dicarboximide (**154**).[110] The compound (**153**) may be formed by attack of hydrazoic acid at the latent aldehyde site in preference to the carboxy site (see Section 4.4.4.2). Phenanthrene-4,5-dicarboxylic acid (**155**), obtained by oxidation of (**152**), similarly affords

(**153**) as the major product. Diphenic acid (**156**) also undergoes the Schmidt reaction to give 2,2′-diaminobiphenyl (**157**) and phenanthridone (**158**) in proportions dependent on the sulfuric acid concentration, as shown in Scheme 28.

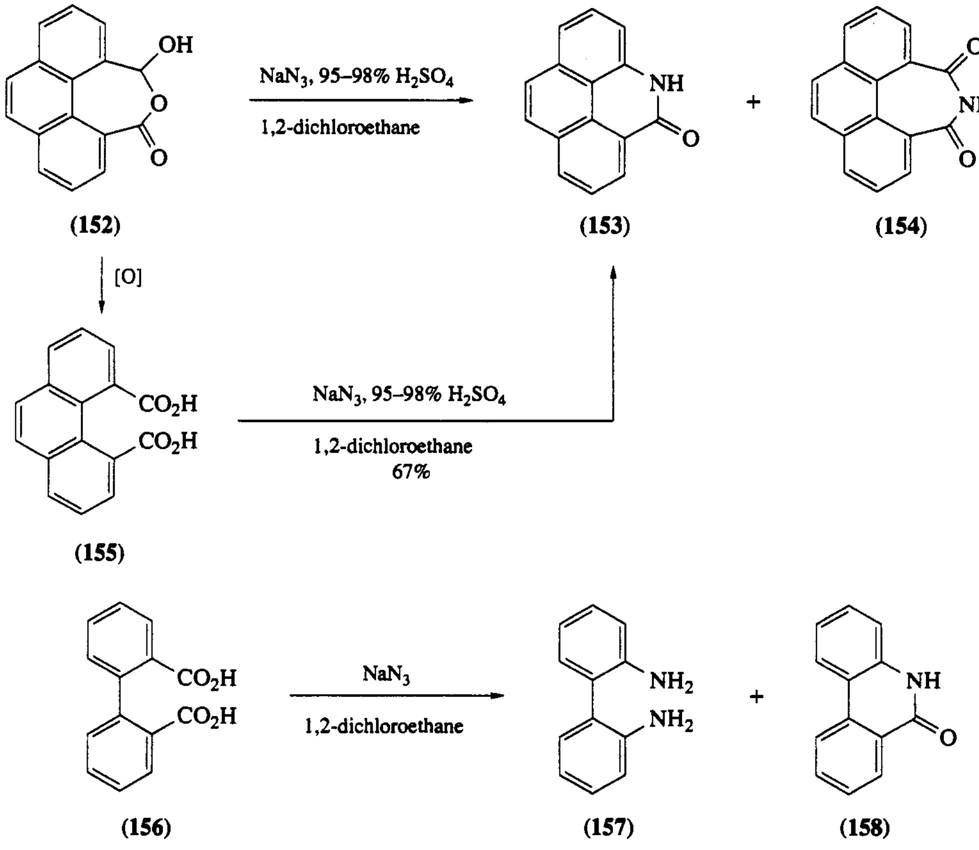

**(152)** **(153)** **(154)**

**(155)**

**(156)** **(157)** **(158)**

| | | |
|---|---|---|
| 95–98% $H_2SO_4$ : | 43% | 6% |
| 90% $H_2SO_4$ : | 5% | 56% |

**Scheme 28**

### 4.4.4.2 With Ketones

In addition to carboxylic acids, hydrazoic acid reacts with ketones, aldehydes, alcohols and alkenes under strongly acidic conditions. Among them, the Schmidt reaction of ketones[10–12] has been most studied because of its synthetic possibilities as well as its similarity to the Beckmann rearrangement (Section 4.3.1). A drawback of the Schmidt reaction of unsymmetrical ketones is that which one of its substituents will migrate depends on the structures and reaction conditions (see equation 4 in Section 4.4.1.1). Regioselective migration, however, has been observed in many cases. Although the Schmidt reaction with ketones does not strictly belong with the degradation reactions reviewed in this chapter, it will be discussed here briefly since it is often used and its reaction procedure and mechanism are very similar to those of the Schmidt reaction with carboxylic acids.

In general, ketones are preferentially attacked by hydrazoic acid when both ketonic and carboxylic groups are present in the same molecule (*cf.* conversion of **152** to **153** in Scheme 28). Thus, treatment of the ketophenolic acid (**159**) with sodium azide in phosphoric acid chemo- and regio-selectively gives the lactam–lactone (**160**) as the sole product (equation 47).[111]

The Schmidt rearrangement of optically active α,α-bisalkylated β-keto esters (**161**) regioselectively proceeds to give *N*-acyl α-alkylated α-amino acid esters (**162**) with retention of configuration and little or no racemization.[112] Acid hydrolysis of (**162**), followed by treatment with propylene oxide, affords α-alkylated α-amino acids (**163**) in high yield and optical purity (equation 48).

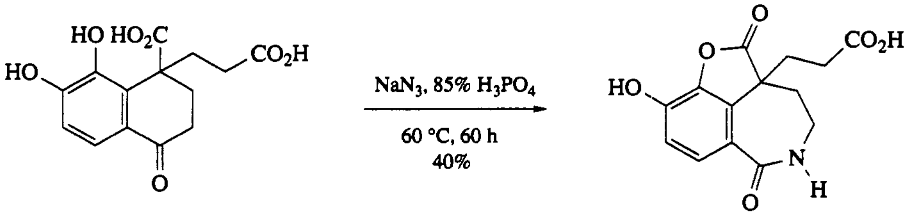

**(159)** **(160)**

(47)

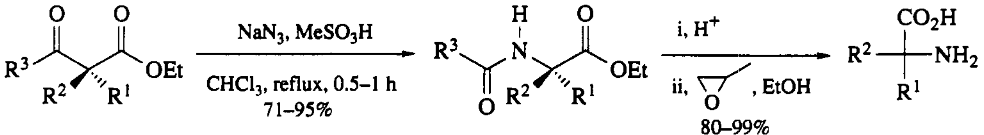

**(161)** **(162)** **(163)**

(48)

4-Acetyl-3-arylsydnones (**164**) undergo the regioselective Schmidt reaction to give 3-arylsydnone-4-*N*-methylcarboxamides (**165**) in good yields without formation of 4-acetamidosydnones (equation 49).[113] In contrast to this, the Beckmann rearrangement of the oxime of (**164**, Ar = phenyl) does not proceed at all.

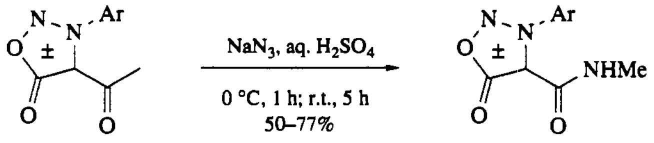

**(164)** **(165)**

(49)

An interesting version of the Schmidt or Beckmann rearrangement utilizes thioketals (**166**), which generate thionium ions (**167**) as carbonyl substitutes, giving amides (**169**) or imino sulfides (**170**) *via* α-azido sulfides (**168**), as shown in Scheme 29.[114] Thus, amides or lactams can be obtained in good yields by treatment of thioketals (**166**) with iodine azide ($IN_3$), followed by the rearrangement of the resulting α-azido sulfides (**168**) with trifluoroacetic acid. This method may be superior to the normal Schmidt or Beckmann rearrangement. For example, the rearrangement of the oxime (**171**) leads to the lactam (**174**) in very poor yield under Beckmann conditions but the yield is greatly increased by starting with the thioketal (**172**) and going *via* the α-azido sulfide (**173**). The thioketal (**175**) is also smoothly converted to *N*-*t*-butylacetamide (**177**) *via* the α-azido sulfide (**176**), while the Schmidt reaction of pinacolone exclusively affords fragmentation products.[114]

Imino sulfides (*e.g.* **180**), regarded as an activated form of amides, can be prepared in a single step from thioketals (*e.g.* **179**) by the action of sodium or trimethylsilyl azide, tin(IV) chloride and a trace of iodine (equation 50).[114]

Another version of the Schmidt-type rearrangement starts from silyl enol ethers (**181**) prepared from acylbenzenes and does not need any acid catalysts.[115] The silyl enol ethers (**181**) react with *N*-chlorosuccinimide (NCS) in the presence of sodium azide and benzyltriethylammonium chloride to give chloro azido derivatives (**182**) *via* siloxycarbinyl cations. Subsequent thermal rearrangement of the azido products (**182**) leads to anilide derivatives (**183**; equation 51).

## 4.4.5 THE LOSSEN REACTION

### 4.4.5.1 Under Basic Conditions

The Lossen reaction[14,15] is the rearrangement of hydroxamic acids, which are prepared from acids, acyl chlorides and esters. It is usually conducted under alkaline conditions. Initial attachment of electron-withdrawing groups to the oxygen atom of the hydroxamic acids is essential to conduct the reaction; the

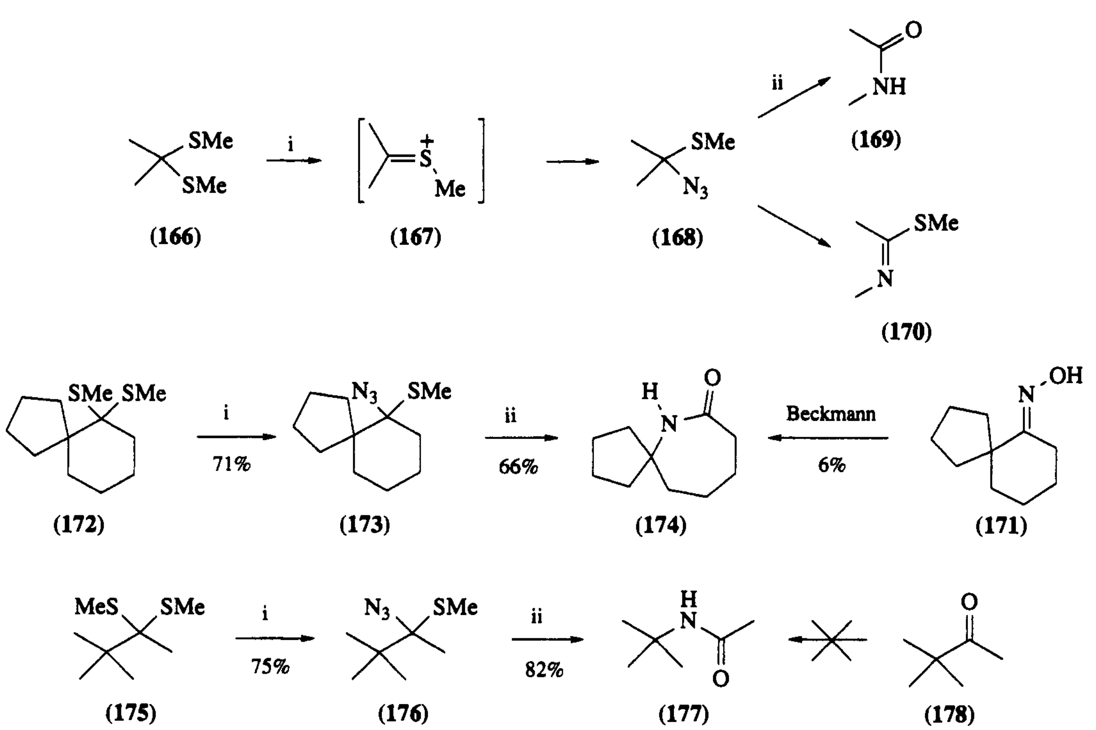

i, $IN_3$, $CH_2Cl_2$–MeCN, –78 °C, 2 h; ii, $CF_3CO_2H$, $CHCl_3$

**Scheme 29**

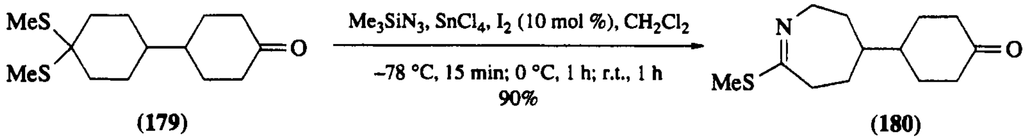
(179)
$Me_3SiN_3$, $SnCl_4$, $I_2$ (10 mol %), $CH_2Cl_2$
–78 °C, 15 min; 0 °C, 1 h; r.t., 1 h
90%
(180)

(50)

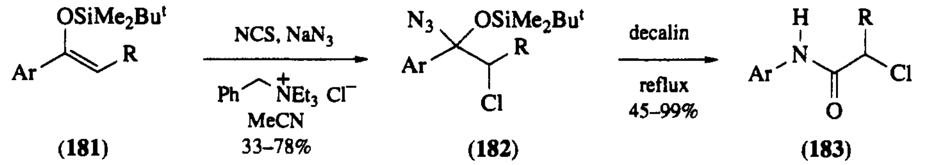

(51)

rate of the Lossen rearrangement is directly proportional to the acidity of these groups, which act as leaving groups, or their conjugate acids, where the leaving groups are basic anions.[116] *O*-Acylhydroxamic acids are most often used, though *O*-sulfonyl or *O*-phosphoryl derivatives may also be employed.

The Lossen reaction of peptide carboxylic acids has been investigated in order to determine the carboxy terminal amino acid residue of peptides.[117] The procedure first involves the formation of *O*-pivaloylhydroxamic acids (**187**) by condensation of peptide carboxylic acids (**184**) with *O*-pivaloylhydroxylamine (**185**) using a water soluble carbodimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (**186**). The Lossen rearrangement of (**187**) occurs at pH 8.5 and 50 °C to give a mixture of isocyanates (**188**) and their reaction products, which, on acidic hydrolysis, afford the aldehydes (**189**), ammonia and amino acids, as shown in Scheme 30.[117] Identification of aldehydes determines the C-terminal amino acids of the original peptides.

The bishydroxamate (**190**) prepared from ethyl succinate partially undergoes the Lossen rearrangement with benzenesulfonyl chloride in pyridine to give the uracil derivative (**191**).[118] Treatment of (**191**) with ammonia or various amines yields a mixture of 1,2-bis(ureido)ethanes (**193**) and 1-carboxamido-2-imidazolidones (**194**) *via* the Lossen product, while a hydroxide ion initiated Lossen rearrangement of (**191**) leads to ethylenediamine (**195**), as shown in Scheme 31. *N*-Benzenesulfonyloxysuccinimide (**196**) also undergoes the Lossen reaction with amines to give β-ureidopropionamides (**197**).[118]

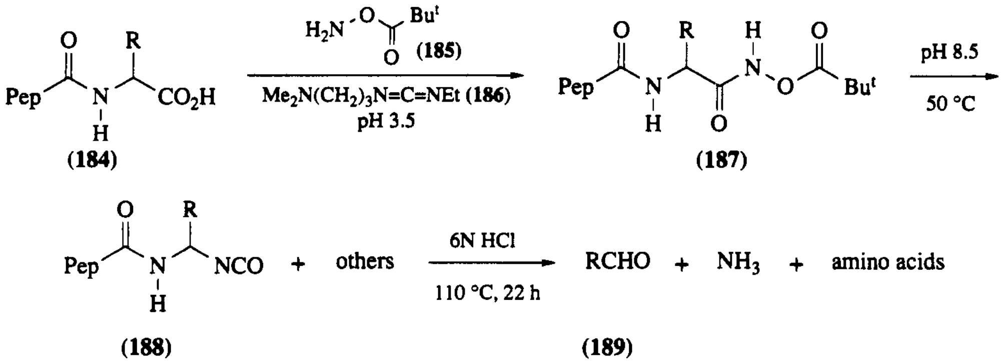
(184)
(185)
$H_2NOC(O)Bu^t$
$Me_2N(CH_2)_3N=C=NEt$ (186)
pH 3.5
(187)
pH 8.5
50 °C
(188)
others
6N HCl
110 °C, 22 h
RCHO + $NH_3$ + amino acids
(189)

**Scheme 30**

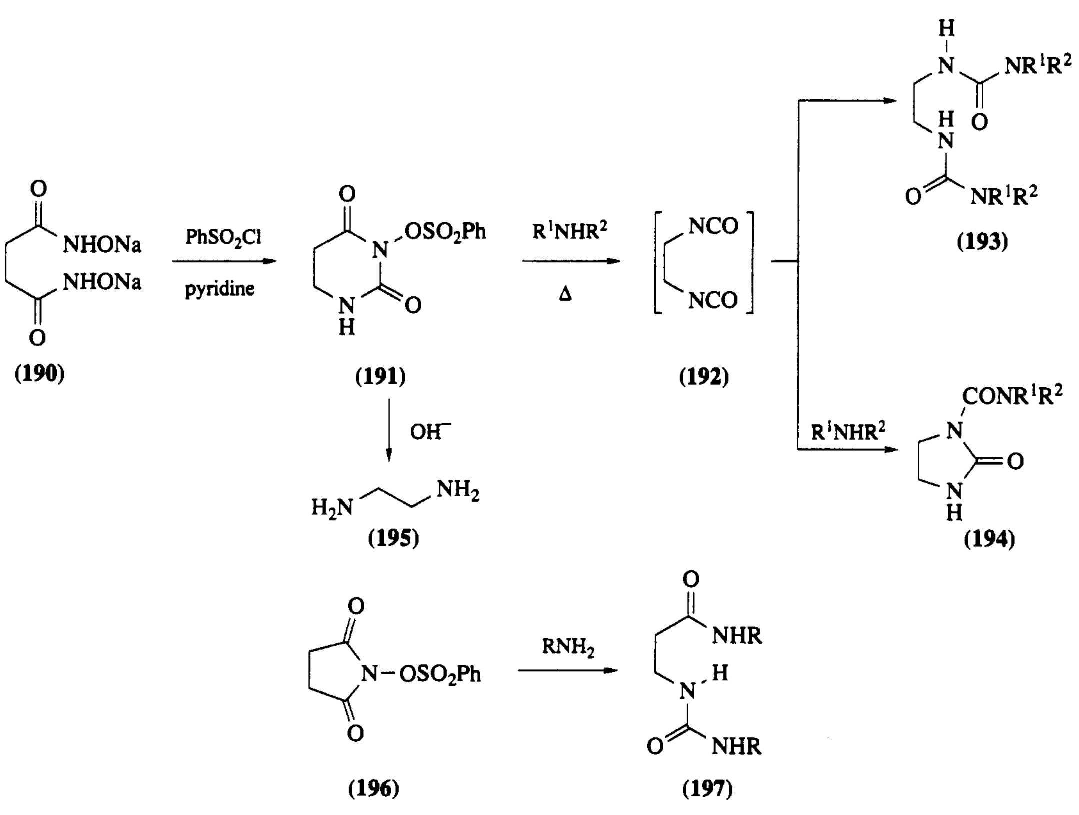
(190)
$PhSO_2Cl$
pyridine
(191)
$R^1NHR^2$
Δ
(192)
(193)
$R^1NHR^2$
(194)
$OH^-$
(195)
(196)
$RNH_2$
(197)

**Scheme 31**

Although the Lossen reaction of *O*-acylated derivatives of the amide oxime (**198**) has failed, its mesylate (**199**) easily gives the Lossen product (**200**) under alkaline conditions (equation 52).[119]

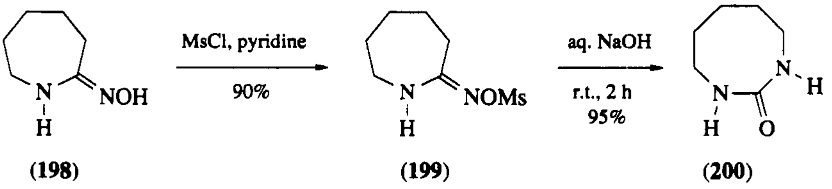
MsCl, pyridine
90%
aq. NaOH
r.t., 2 h
95%
(198)
(199)
(200)

(52)

### 4.4.5.2 Under Neutral Conditions

A useful variant of the Lossen reaction proceeds under neutral conditions without any prior treatment of the hydroxamic acids. This 'amide modification' of the Lossen rearrangement involves a short heating of the hydroxamic acid in formamide to give amines.[120–122] Anthranilohydroxamic acid[120] and pyridinecarbohydroxamic acids[121] undergo the rearrangement to produce benzimidazol-2-one and aminopyridines respectively. The Lossen rearrangement of the hydroxamic acid (**201**) derived from quinolinic acid regioselectively occurs to give 2-aminonicotinic acid (**204**) in good yield *via* the isocyanate (**202**) and then the Leuchs anhydride-type intermediate (**203**; equation 53).[121] The latter intermediate (**203**) is also obtained when the disodium salt of (**201**) is heated with benzenesulfonyl chloride.

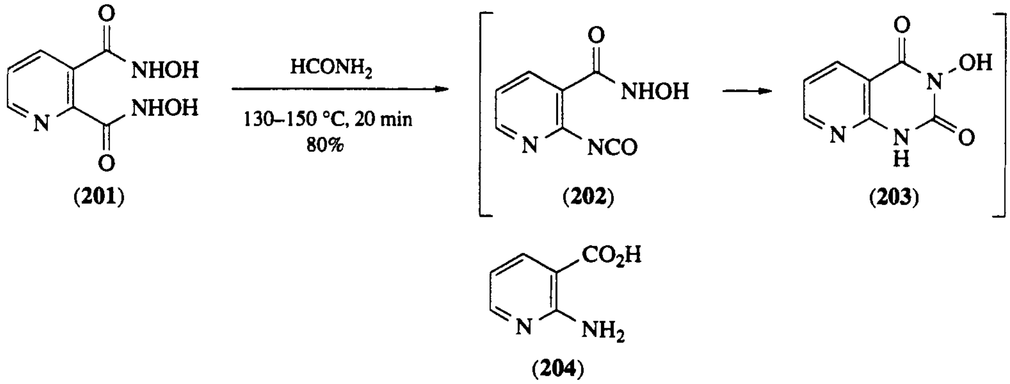

(**201**) (**202**) (**203**) (**204**)

(53)

Short heating of 4-quinolinecarbohydroxamic acid (**205**) with formamide affords 4-aminoquinoline (**207**) *via* the isocyanate (**206**), while use of a large excess of formamide and increasing the temperature slowly give *N*-(4-quinolyl)urea (**208**) exclusively, as shown in Scheme 32.[122] Intermediacy of *O*-formates or equivalents has been suggested in the above modification of the Lossen reaction.[121]

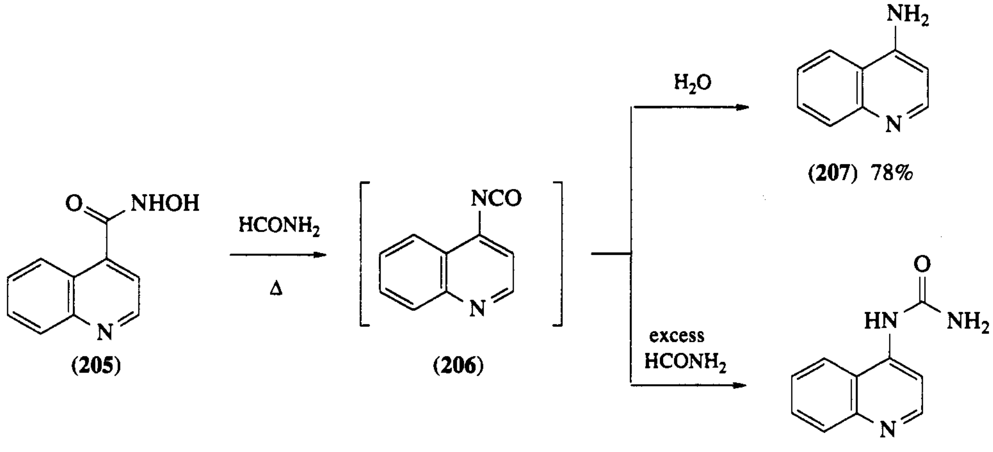

(**205**) (**206**) (**207**) 78% (**208**) 67%

Scheme 32

*N*,*N*′-Dicyclohexylcarbodiimide (DCC) also mediates the Lossen reaction of hydroxamic acids under neutral conditions.[123,124] In the conversion of the hydroxamic acid (**209**) to the tricyclic compound (**210**), the Lossen rearrangement is accompanied by an intramolecular cycloaddition (equation 54).[123]

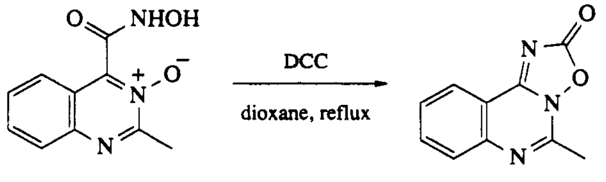

(**209**) (**210**)

(54)

A combination of triphenylphosphine and diethyl azodicarboxylate (the Mitsunobu reagent)[125] is useful for the rapid conversion of aromatic hydroxamic acids (**211**) to *O*-(*N*-arylcarbamyl)hydroxamates (**212**), products of the Lossen rearrangement.[126] In some cases, a spontaneous second Lossen rearrangement occurs to give diarylureas (**213**), as shown in Scheme 33. The yields of (**212**) and (**213**) are 70–85%. The intermediacy of the phosphonium salts (**214**) has been suggested.

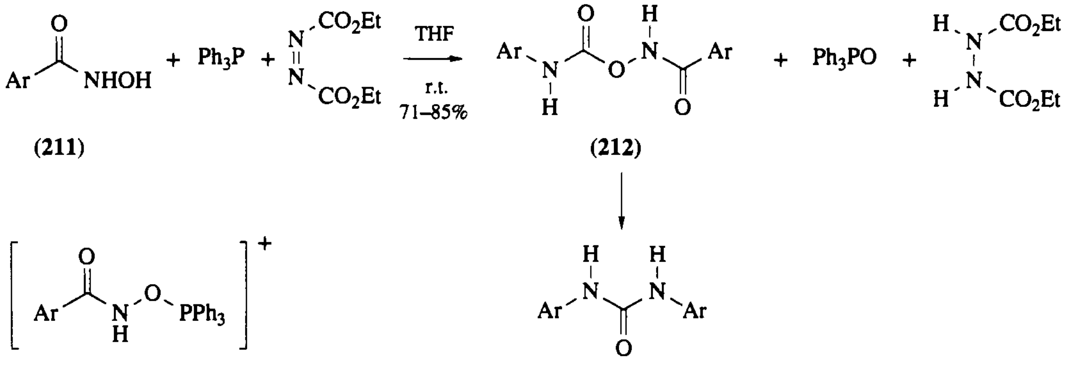

(**211**) (**212**) (**214**) (**213**)

Scheme 33

### 4.4.5.3 Under Acidic Conditions

Aromatic carboxylic acids can be converted to aromatic amines in a single operation by the action of polyphosphoric acid and hydroxylamine[127] or nitromethane.[128] The intermediates are hydroxamic acids which are activated by phosphorylation with polyphosphoric acid and undergo the rearrangement (equation 55). When nitromethane is used, hydroxylamine is first formed by the action of polyphosphoric acid. This one-step Lossen reaction works well with aromatic acids containing electron-donating substituents, but fails or gives poor yield with aliphatic acids and with aromatic acids containing electron-withdrawing groups.

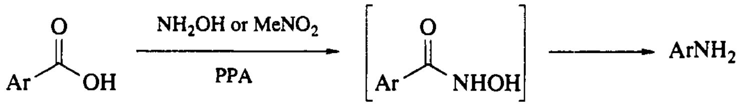

(55)

Hydroxylamine-*O*-sulfonic acid can be also used for the Lossen rearrangement. Heating acids with hydroxylamine-*O*-sulfonic acid in hot mineral oil[128] or polyphosphoric acid[129] affords amines, though the reaction conditions for this transformation still need to be optimized (equations 56 and 57).

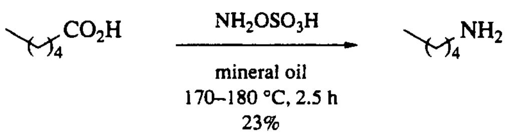

(56)

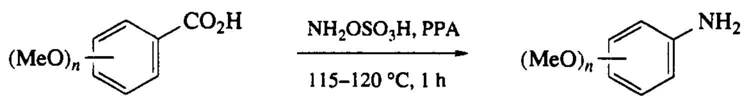

(57)

4-methoxy, 35%; 2,4-dimethoxy, 25%

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# 4.5

# Functional Group Transformations *via* Allyl Rearrangement

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## 4.5.1 INTRODUCTION

Functionalized allylic systems are not only often part of target molecules but also have potential as versatile synthetic intermediates. They can frequently be used to generate multifunctional compounds by further elaboration of the C═C bond, namely by reduction (*e.g.* hydrogenation)[1] or oxidation (*e.g.* to alcohols, diols, oxiranes, aldehydes or ketones)[2] or by diverse addition reactions.[3] As such reactions can very often be performed with remarkable stereocontrol by means of the allylic functionality, especially in intramolecular reactions, the potential of functionalized allylic systems is immense.

Another fascinating, unique property of allylic systems is their propensity for allylic rearrangement with transfer of functionality from one end of the allylic system to the other and concomitant double bond shift with or without transformation of functional groups. In the latter case (X = Y; equation 1) a reaction is synthetically useful only in unsymmetrical cases for a 1,3-transposition of the functional group.

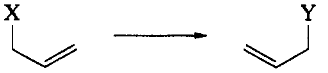

(1)

Such reactivity is likewise known for propargylic systems leading to allenic systems (equation 2).[4]

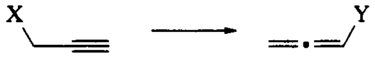

(2)

The usefulness of these allylic or propargylic rearrangements in synthesis is obvious as they allow 1,3-transposition of functionality, permitting allylic functional group transformation. There are quite a number of functional group transformations *via* allyl rearrangements known, proceeding either by intermolecular or by intramolecular reactions, and by different reaction mechanisms. Desirable features for a valuable synthetic procedure are the following: (i) the reaction should be regiospecific, leading only in one direction; (ii) the stereochemistry of the double bond should be controllable in a predictable manner; (iii) high optical yields should be possible with chiral systems. Intramolecular reactions are the more likely to comply with these requirements as they proceed very often by a concerted mechanism *via* rigid, cyclic, five- or six-membered transition states, leading to high stereocontrol. Prominent examples are 2,3- and 3,3-sigmatropic rearrangements such as the Wittig or the Claisen rearrangements. In intermolecular reactions, especially when a reactive intermediate, *e.g.* a more or less free allylic anion, carbenium ion or radical is involved, the regioselectivity is already a problem as the reactive intermediate can be captured at either end of the allylic system and the proportion of the attack will be mainly influenced by steric factors. In nucleophilic and electrophilic substitutions this notorious problem refers to the competition of $S_N$ and $S_N'$ or $S_E$ and $S_E'$ reactivity; in the reaction of allyl metal compounds with electrophiles it reflects the α- *versus* γ-reactivity of the allylic 'carbanionic' species.

A general discussion of such inherent problems and the principles of allylic rearrangements will be presented first, followed by specific examples of functional group transformations, which will be systematically surveyed regardless of the mechanism involved.

Such a systematic review is especially useful since a knowledge of the functional group transformation is essential in retrosynthetic analysis.[5] In the so-called 'transform'-based strategy 'functional group interchanges' (or 'interconversions'; FGI) or 'functional group transpositions' (FGT) are applied to simplify a target molecule and one has to look for synthetic reactions which allow these transformations to perform.

## 4.5.1.1 Intermolecular Reactions with Allylic Rearrangement

### *4.5.1.1.1 Substitution reactions with double bond shift*

Substitution reactions with allylic rearrangement are known in nucleophilic $S_N$ as well as in electrophilic $S_E$ reactions (Scheme 1).[6]

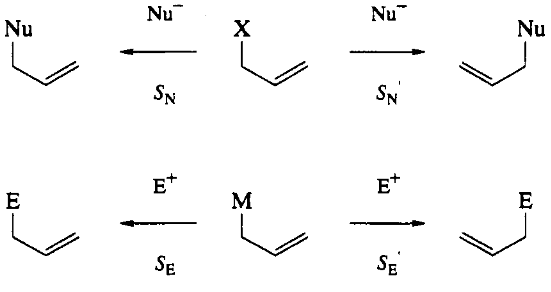

**Scheme 1**

The exchange of an allylic functional group with double bond shift by a nucleophilic substitution generally presents problems because the competing direct substitution is very often the dominating reaction. The proportion of *S*N to *S*N′ reaction is mainly determined by steric effects, the attack of the nucleophile being preferred at the least hindered site. Under equilibrating conditions the thermodynamic stabilities of the products will be decisive. So the substitution pattern of the allylic substrate plays the most important role for regiochemical control. Whereas with systems with the leaving group in a primary or secondary position one normally gets a mixture of products, substitution of a leaving group at a tertiary position will proceed with allylic rearrangement. With regard to stereochemistry, reaction conditions which favor a bimolecular reaction mechanism are to be preferred because in the case of an allylic carbenium ion the stereochemical integrity will be lost. Although there is still a dispute about the preferred mode of an *S*N2′ reaction,[7] there seems to be a preference for *syn* attack of the nucleophile not only in cyclic but also in acyclic cases (Scheme 2).

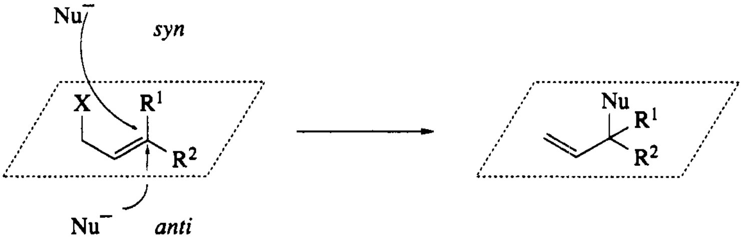

**Scheme 2**

Valuable preparative applications are rare and especially in ring-forming reactions other stereochemical factors such as ring strain and conformational effects will determine the stereochemistry. However the use of metal compounds to influence regio- and stereo-selectivity continues to excite interest.[8] For C—C bond formation the coupling of allylic acetates with organocuprates offers broad synthetic potential as it generally seems to proceed with double bond shift.[9]

In recent years there has been an impressive development in transition metal promoted substitution reactions which can also be utilized for transforming allylic functionalities. An especially useful process, already extensively used in organic synthesis, is the the Pd$^0$-catalyzed nucleophilic substitution of allylic substrates.[10,11] The stereochemical outcome of the reaction can be explained by a widely accepted model which involves a two-step sequence: (i) formation of a π-allyl intermediate with inversion of configuration; and (ii) the attack of the incoming nucleophile either directly on the allyl ligand, especially with soft nucleophiles, again with inversion of configuration thereby leading to an overall retention of stereochemistry, or, with hard nucleophiles, primarily on the metal center followed by an internal transfer to the allyl system with retention effecting a net inversion of stereochemistry (Scheme 3).

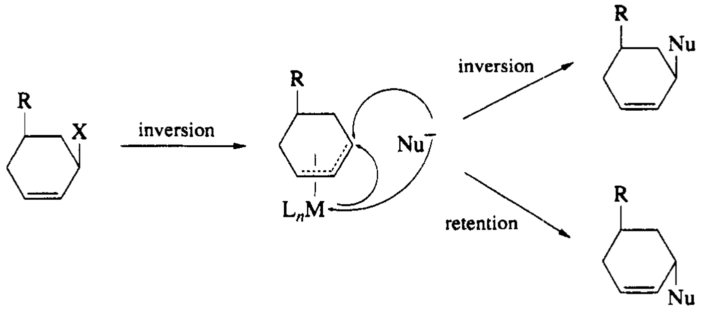

**Scheme 3**

A wide range of allylic leaving groups, including acetates and other esters, ethers, alcohols, amines, sulfinates, epoxide and nitro groups, can be substituted by a variety of heteroatom and carbon nucleophiles most commonly by stabilized carbanions and amines. However control of regioselectivity still remains one of the most difficult and challenging problems: although reaction of the less substituted end of the allyl system usually predominates, a number of variables influence the regioselectivity and it is difficult to draw any general conclusion. In the context discussed here it is especially necessary to point out that the regioisomeric nature of the product is not directly influenced by the regiochemistry of the starting material as a common π-allyl intermediate is formed from regioisomers, independent of the geometry of the double bond. Other factors will determine whether a formal $S_N2$ or $S_N2'$ reaction occurs (Scheme 4).

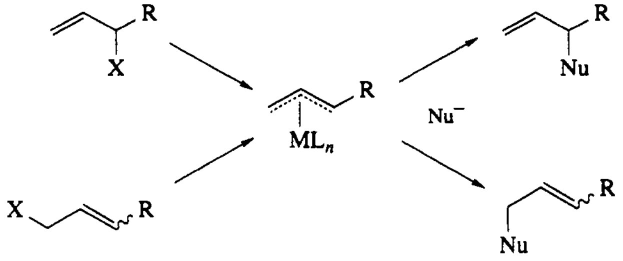

**Scheme 4**

Beside the fascinating aspect that the reactions can be brought about catalytically with the possibility of asymmetric induction by optically active catalysts,[10] the mildness of the reaction conditions, allowing many functional groups to be tolerated, will increase the number of applications in the future.

Electrophilic substitutions can also be used for functional group transformation with allyl rearrangement. In some respects electrophilic substitutions are even better than nucleophilic substitutions as the normal mode of electrophilic substitution is by a formal $S_E2'$ mechanism with double bond shift. Allylsilanes[12] and allylstannanes[13] especially can be employed for such reactions with electrophiles. As these compounds can be generated stereospecifically (in contrast to allylic Grignard reagents which would be equilibrated to the different geometrical isomers) and react with a wide variety of electrophiles they constitute a valuable tool for synthetic purposes, being 'stable' equivalents of allyl anions, the reactivity decreasing from allyltin to allylsilicon compounds. Regarding stereochemistry, it is almost generally found that the $S_E'$ reactions take place with *anti* stereochemistry (Scheme 5).

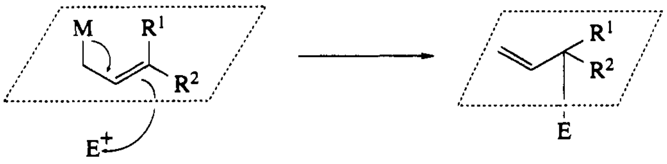

**Scheme 5**

Lastly it should be mentioned that appropriate allylic substrates can also be substituted in a radical $S_H'$ reaction with rearrangement, but the synthetic applications are rather limited.[14] Quite a different intermolecular reaction, where an allylic shift occurs, is the ene reaction, in which an allylic hydrogen is substituted in a concerted process *via* a six-membered transition state (equation 3).

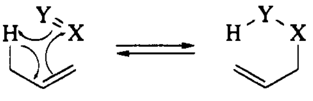

(3)

In recent years this reaction has frequently been utilized for allylic functionalization and there are some interesting applications in synthesis.[15] In connection with the topic of this chapter only the retro-ene reaction has to be taken into consideration here.

### 4.5.1.1.2 *Reactions of allylmetal compounds with electrophiles*

Rearrangement of an allylic (or propargylic or allenic) system is effected if the derived anion, either in form of an organometallic compound[16] or a heteroatom-stabilized 'carbanion',[17] is attacked by electrophiles at the γ-position. However, competing α-reactivity is most often observed as well, and a lot of experimental material exists with respect to this problem,[18] but generalizations are difficult to make.[19] The regioselectivity depends on different factors, not least on the nature of the electrophile, so that it can dramatically change from one electrophile to the other. Regioselectivity is more of a problem in alkylation than in the reaction with a carbonyl group, but by change of the 'counterion', transforming an allyllithium into a copper or a titanium compound, one can often direct alkylation to occur at the γ-position. Some allylic compounds, namely boron, aluminum, titanium, silicon and tin derivatives, exhibit mainly γ-selectivity in addition reactions to a carbonyl group,[20] apparently because of a tight, highly organized chair transition state with distinct Lewis acid–carbonyl interaction (Scheme 6).

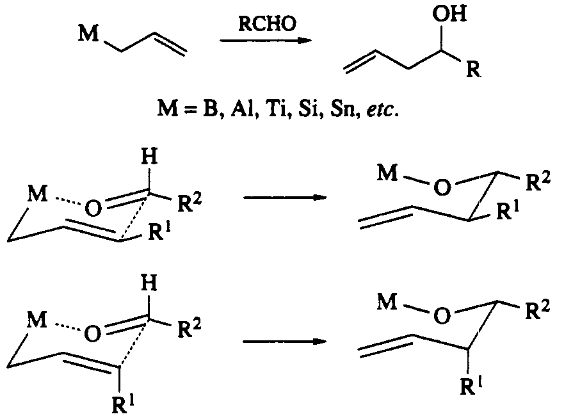

M = B, Al, Ti, Si, Sn, *etc.*

**Scheme 6**

In accordance with this model one finds diastereoselectively *anti* products on reaction of aldehydes with (*E*)-allyl compounds, whereas allyl systems with the (*Z*)-configuration give mainly *syn* products and it is even possible to effect asymmetric induction. As the double bond of the product can be oxidatively cleaved to a C═O group, the reaction can be regarded as a stereoselective aldol reaction, an aspect which explains the widespread interest in this type of reaction. With heterosubstituted allylic anions it is sometimes possible to effect predominantly γ-attack with different electrophiles by the choice of the heteroatom.[21] For instance it is well known that with sulfur substituents like —SR, —SOR or —$SO_2R$ the α-attack dominates, but doubly lithiated allenethiol possesses high γ-reactivity and can be used as a homoenolate anion equivalent in reaction with electrophiles such as alkyl halides (Scheme 7).[22]

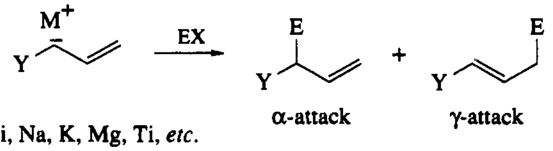

M = Li, Na, K, Mg, Ti, *etc.*

Y = OR, SR, SOR, $SO_2R$, $NR_2$, $SiR_3$, $POR_2$, *etc.*

**Scheme 7**

On the other hand the inherent α-selectivity of allylsulfur carbanions can sometimes be transformed to a γ-reactivity by a sigmatropic rearrangement, earning in addition the stereoselectivity typical for such reactions (see Section 4.5.2.3). Due to their significance in synthesis a lot of work has been done on reactions of heteroatom-substituted allyl anions with special emphasis on their use as homoenolate anion equivalents.[23,24] The more recent developments, with the possibility of introducing diastereoselectivity, will be discussed later in Section 4.5.3.2.1.

### 4.5.1.2 Intramolecular Allylic Rearrangements

A versatile and very powerful strategy for functional group transformation *via* allyl rearrangement involves intramolecular reactions of the 2,3-[25] and 3,3-sigmatropic[26] type, as exemplified in generalized form in Scheme 8.

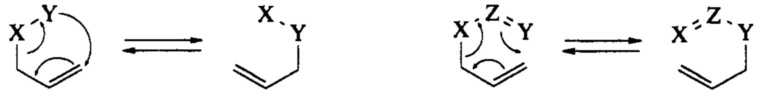

**Scheme 8**

The outstanding significance of these reactions in synthesis originates from the high stereochemical control and the possibility of transferring chirality associated with the internal migration of an allyl group due to the highly ordered cyclic transition states of such processes.[27,28] In contrast to the 3,3-sigmatropic rearrangement, the diastereoselectivity with regard to newly formed adjacent stereogenic centers is normally lower in 2,3-sigmatropic processes, because the ratio of diastereomers is not controlled by the significant energy difference between a chair and a boat conformation of the six-membered transition state, but by the much lower energy difference between *endo* and *exo* five-membered envelope transition states.

Besides the high stereochemical control of 2,3- and 3,3-sigmatropic rearrangements it is their obvious generality with respect to hetereoatom variation which has led to numerous synthetically useful applications. Even though not all possibilities have been examined yet, an impressive number of combinations of heteroatoms X and Y in the 2,3- and X, Y and Z in the 3,3-sigmatropic reactions have been realized.

#### 4.5.1.2.1 2,3-Sigmatropic rearrangements

Quite a number of synthetically useful transformations in allylic systems belong to this class of reactions, namely the Wittig–ether rearrangement,[29,30] the Stevens–Sommelet rearrangement of ammonium ylides,[31] the Meisenheimer rearrangement of amine oxides,[32] the Büchi rearrangement[33] and the Mislow allyl sulfoxide–allyl sulfenate rearrangement.[34] Some of them are relevant to the subject of this review for heteroatom to heteroatom or heteroatom to carbon transformation and will be systematically presented with examples in the appropriate section. A thorough general discussion of 2,3-sigmatropic reactions is given in Chapter 4.6, Volume 6.[25]

#### 4.5.1.2.2 3,3-Sigmatropic rearrangements

This category encompasses the Cope (X = Y = Z = C),[26] the Claisen (X = O, Y = Z = C)[26,35] and other hetero-Cope rearrangements.[36] Even though a concerted mechanism is not always certain, especially not with multiheteroatom systems and in some catalyzed versions,[37] a high degree of stereoselectivity in the formation of double bonds and stereogenic centers is normally found which allows very useful synthetic applications in the hetero-Cope cases. In the all-carbon case only the oxy-Cope rearrangement is of synthetic relevance (equation 4).[38,39]

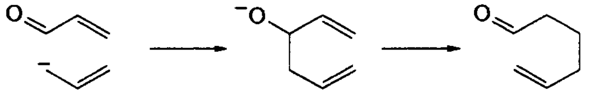

(1)

(4)

Considering that the system (1) is generated by the 1,2-addition of an allyl anion to an α,β-unsaturated carbonyl system, the rearrangement allows an indirect clean 1,4-addition to the α,β-unsaturated carbonyl system.

## 4.5.2 1,3-HETEROATOM TRANSPOSITIONS

### 4.5.2.1 Oxygen–Halogen Transpositions

The transformation of an allylic alcohol to an allylic halide (equation 5) or the reverse reaction normally leads to a mixture of isomers of direct and allylic substitution products. Only when tertiary allylic alcohols are employed or a rearrangement leads to extended conjugation of double bonds does a transposition of functionality occur predominantly.[40] While a number of procedures have been developed for the conversion of allylic alcohols to halides without rearrangement,[41] there seems to be only one reaction where a cleanly rearranged product is obtainable in a substitution of a primary or secondary allylic (and propargylic) hydroxy group to a chloride, that is by thionyl chloride in ether, probably by a cyclic $S_Ni$ process. The regioselectivity is worse in other solvents and is lost in the presence of a base. In accordance with the mechanism it is a *syn* facial substitution, as has been demonstrated in cyclic cases (equation 6)[42] or with optically active propargyl alcohols, which give rise to optically active chloroallenes (equation 7).[43]

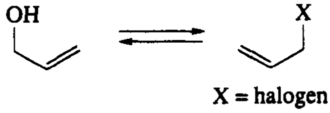

(5)

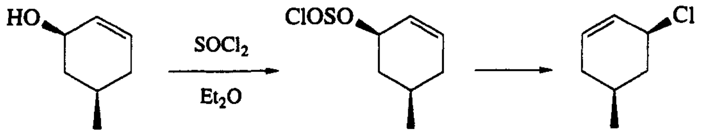

(6)

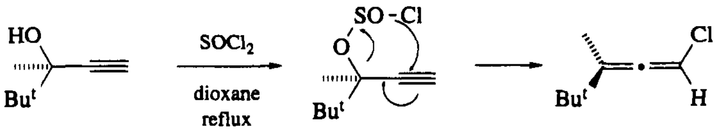

(7)

Recently a remarkable sequence of substitution reactions was published providing the first general method for the generation of primary allyl acetates from primary, secondary and tertiary alcohols.[44] Interestingly, the first reaction of the transformation of allyl alcohols (**2**) with anhydrous magnesium iodide in benzene gives regiospecifically the rearranged primary allylic iodides (**3**) from which the corresponding primary allylic acetates (**4**) can be obtained without rearrangement with anhydrous sodium acetate in dimethylformamide (equation 8).

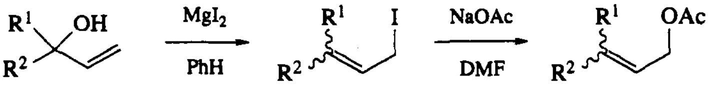

**(2)** **(3)** **(4)**

(8)

A substitution of an allylic halide by an oxygen function is a problem with regard to regioselectivity too. Clean allylic rearrangements can be observed with tertiary halides and in intramolecular substitutions. In the latter case steric requirements seem to dictate the stereochemistry and examples with *syn*[45] and *anti* $S_N'$[46] substitutions are known. A unique regiospecific method for the transformation of allylic iodides to rearranged allylic alcohols, which may be rather general, uses an intramolecular rearrangement of a derived allylic iodoso compound (equation 9).[47]

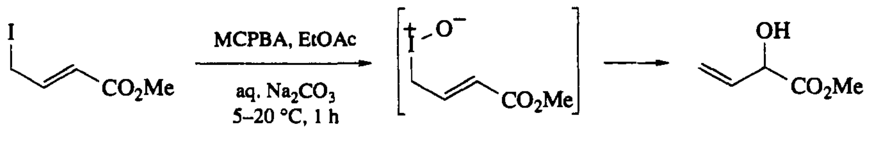

(9)

### 4.5.2.2 Oxygen–Oxygen Transpositions

The best known example of this kind is the rearrangement of allyl acetates, a synthetically very useful reaction, especially in the case of tertiary systems (equation 10). These undergo isomerization sometimes even under the conditions of acetylation.[48] Otherwise, Lewis acid catalysis, preferably with $PdCl_2(MeCN)_2$, will bring about the isomerization smoothly (equation 11).[49]

The analogous reactions of acetates of primary and secondary allyl alcohols normally lead to equilibrium mixtures only slightly favoring primary allyl acetates. The equilibration of allyl alcohols by the Pd-catalyzed equilibration of derived esters or carbamates has some advantages in comparison with the

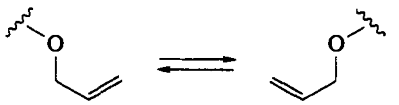

(10)

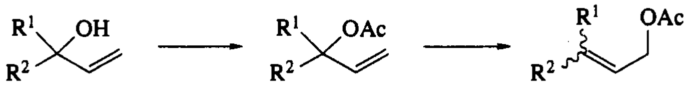

(11)

classical acid-catalyzed isomerization of allyl alcohols, which proceeds *via* allyl cations giving: high yield; no complication by dehydration, cyclization or skeletal rearrangement; and as a consequence of its 3,3-sigmatropic character clean suprafacial stereoselection (equation 12).[49]

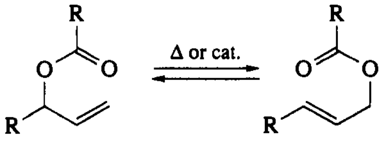

(12)

In an interesting example where steric effects seem to drive the reaction in the required direction the reaction proceeds by complete transfer of chirality (equation 13).[50]

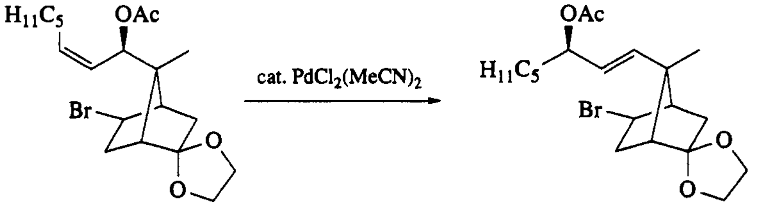

(13)

Other examples where secondary allyl esters are rearranged in one direction are found in the carbohydrate field with glycals.[51] In the case of propargylic oxygen functionalities a 1,3-shift is also possible. With propargylic alcohols this is the classical Meyer–Schuster reaction,[52] which has been extensively used for the preparation of α,β-unsaturated carbonyl compounds. Besides acid catalysts such as sulfuric, hydrochloric or acetic acid, which may give rise to unselective rearrangements and side reactions, oxo derivatives of vanadium, molybdenum or tungsten have been used.[53] Recently titanium/copper-based catalysts have been recommended for the reaction (equation 14).[54]

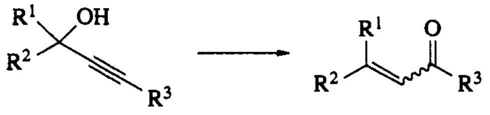

(14)

The isomerization of propargylic alcohols to α,β-unsaturated carbonyl compounds can also be effected by means of the rearrangement of derived propargylic esters (**5**) *via* allenic esters (**6**; equation 15).[55]

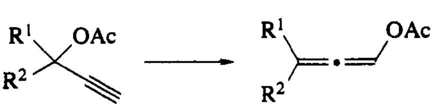

**(5)** **(6)**

(15)

The rearrangement can be catalytically brought about with silver and copper salts[56] or more recently with Pd$^{II}$ compounds.[57] α,β-Unsaturated carbonyl compounds are also often formed under rearrangement on oxidation of allylic alcohols, especially when they are tertiary. This process can serve to perform a 1,3-transposition of carbonyl groups in α,β-unsaturated ketones (Scheme 9).[58]

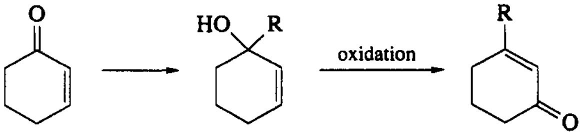

**Scheme 9**

There are some other methods for 1,3-oxygen–oxygen transposition of allylic alcohols which are not based on intra- or inter-molecular substitutions but on epoxidation of the allylic alcohol followed by a reductive rearrangement, so that the problem of regioselectivity can be avoided. One example is the so-called Wharton procedure[59] which seems to be very generally usable and is depicted in Scheme 10 for cyclohexenol. As the epoxidation of such cyclic allyl alcohols with peracids exhibits high diastereoselectivity the sequence permits a *syn* facial 1,3-migration of the hydroxy group with synthetically valuable chirality transfer (Scheme 10).

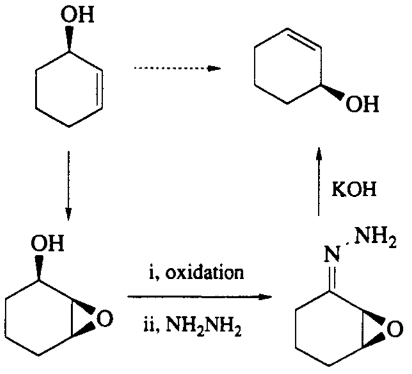

**Scheme 10**

Another method, where a different reduction methodology is employed, can be used to generate secondary and tertiary allylic alcohols from primary ones,[60] and when this method is used in combination with Sharpless asymmetric epoxidation enantioselectivity may even be achieved (Scheme 11).[61]

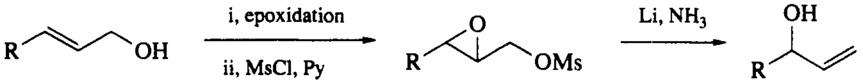

**Scheme 11**

### 4.5.2.3 Oxygen–Sulfur Transpositions

The synthetically most useful oxygen–sulfur transpositions (equation 16) are the allyl sulfenate–allyl sulfoxide and the propargyl sulfenate–allene sulfoxide rearrangements, the driving force of both being the formation of the strong S═O bond at the cost of the weak O—S bond (Scheme 12).[62]

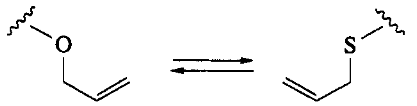

(16)

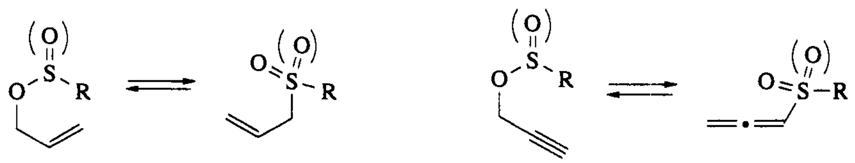

**Scheme 12**

The rearrangements take place most often spontaneously below room temperature with allyl and propargyl sulfenates. The corresponding sulfinates require much higher temperatures to be rearranged to the sulfones and the reaction is no longer reversible.[63]

As a consequence of the 2,3-sigmatropic nature of the rearrangements they are accompanied by high stereoselectivity allowing 1,3-chirality transfer and efficient control of the double bond configuration, giving predominantly *trans* geometry. Furthermore in the sulfenate–sulfoxide case the opportunity for chirality transfer from carbon to sulfur and *vice versa* exists, but its applicability in synthesis is limited since racemization is possible due to the reversibility of the allyl sulfenate–sulfoxide rearrangement.

On the other hand the reversible nature of the allyl sulfenate–sulfoxide rearrangement can be used very efficiently for the facile interconversion of allylic sulfoxides and alcohols *via* their sulfenate esters (Scheme 13).

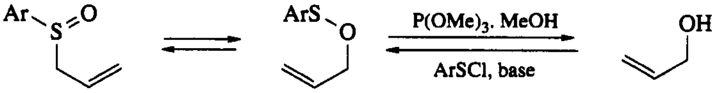

Ar
S
O
ArS
O
P(OMe)3, MeOH
ArSCl, base
OH

Scheme 13

Even though the sulfenate ester is usually in low equilibrium concentration with the isomeric sulfoxide, it can be trapped by thiophiles like trimethyl phosphite, leading eventually to complete formation of the alcohol.

The synthetic potential of these transformations was first fully recognized by Evans[64] and they have been utilized since in various versions in numerous applications, some of which are discussed here.

Evans' rather general route to γ-substituted allyl alcohols is depicted in a specific example, which demonstrates the stereochemical outcome of the suprafacial rearrangements in cyclic systems (Scheme 14).[65]

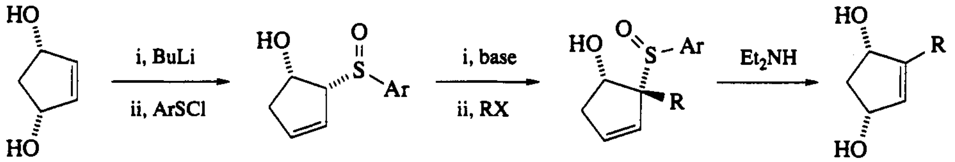

HO
HO
i, BuLi
ii, ArSCl
HO
O
S
Ar
i, base
ii, RX
HO
O
S
Ar
R
Et2NH
HO
R
HO

Scheme 14

The methodology of using allyl alcohols as $d^3$-synthons of type (7) has proven to be a very general one, providing an easy and highly stereoselective route to allylic alcohols with exclusive formation of (*E*)-double bonds in acyclic systems, even in the case of trisubstituted alkenes (Scheme 15).[66]

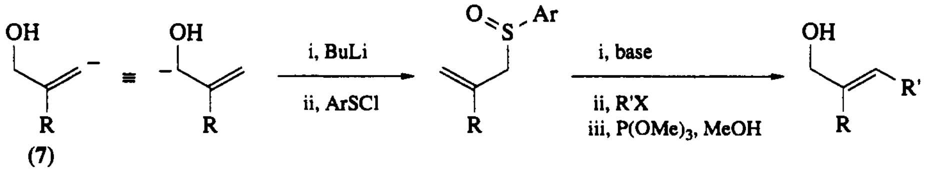

OH
R
(7)
≡
OH
R
i, BuLi
ii, ArSCl
O
S
Ar
R
i, base
ii, R'X
iii, P(OMe)3, MeOH
OH
R'
R

Scheme 15

In an acyclic situation the transformations can also lead to complete 1,3-chirality transfer, as exemplified by remarkable studies in the prostaglandin field (Scheme 16).[67]

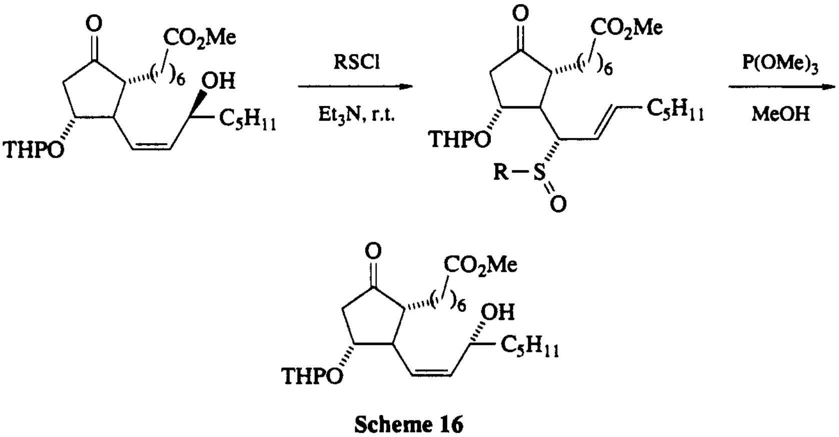

O
CO2Me
( )6
OH
C5H11
THPO
RSCl
Et3N, r.t.
O
CO2Me
( )6
C5H11
THPO
R–S
O
P(OMe)3
MeOH
O
CO2Me
( )6
OH
C5H11
THPO

Scheme 16

Other examples of directed epimerization of allyl alcohols by such processes are known, *e.g.* in the case of the bicyclic system (**8**) an *exo* to *endo* ratio of 8 to 1 was obtained starting from the more accessible *endo*-alcohol (**8**; equation 17).[68]

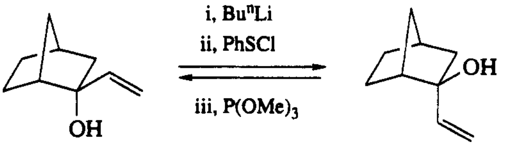
OH
i, Bu$^n$Li
ii, PhSCl
iii, P(OMe)$_3$
OH

(**8**) (**9**) (17)

Allyl sulfoxide systems appropriate for a transformation to allylic alcohols can also be generated by other preparative methods, *e.g.* by isomerization of aryl vinyl sulfoxides. Such an isomerization occurs in connection with a Knoevenagel reaction of (**10**) with aldehydes leading finally to γ-hydroxy-α,β-unsaturated systems (**11**), which can easily be transformed into α,β-unsaturated γ-lactones (**12**; Scheme 17).[69]

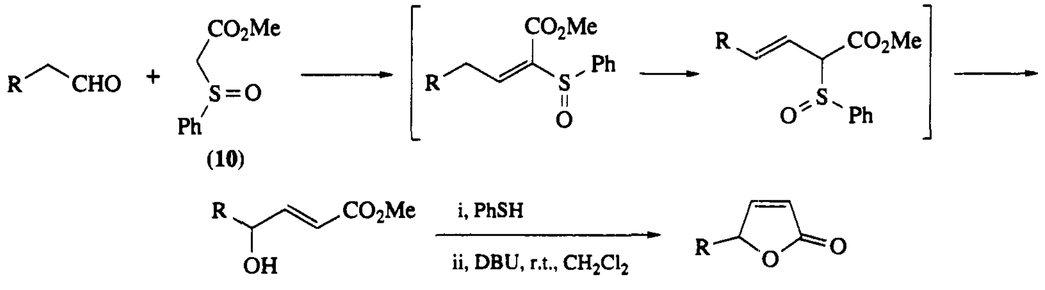
R
CHO
+
CO$_2$Me
S=O
Ph
(10)
CO$_2$Me
R
S
Ph
O
R
CO$_2$Me
O
S
Ph
R
CO$_2$Me
OH
(11)
i, PhSH
ii, DBU, r.t., CH$_2$Cl$_2$
R
O
O
(12)

**Scheme 17**

Hoffmann has used an isomerization of readily available aryl vinyl sulfoxides, which can be obtained in optically active form, to study the possibility of generating optically active allyl alcohols by employing chirality transfer from sulfur to carbon.[70] While this synthetic route (Scheme 18) to allylic alcohols generally works well and gives good yields, the optical yields which could be obtained are only satisfactory in some cases, *e.g.* (*R*)-(*Z*)-sulfoxide (**13**) gave the (*S*)-(+)-octenol (**14**) with greater than 80% optical purity, whereas the (*R*)-(*E*)-isomer (**15**) yielded only 29% of the (*R*)-(–)-enantiomer (**16**; Scheme 19).

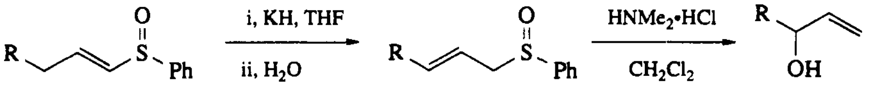
O
R
S
Ph
i, KH, THF
ii, H$_2$O
O
R
S
Ph
HNMe$_2$•HCl
CH$_2$Cl$_2$
R
OH

**Scheme 18**

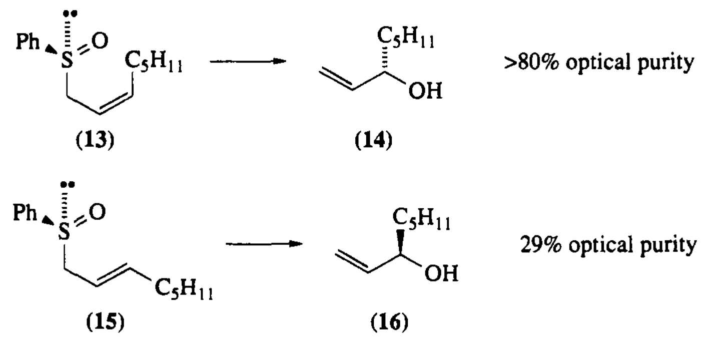
Ph
S
O
C$_5$H$_{11}$
(13)
C$_5$H$_{11}$
OH
(14)
>80% optical purity
Ph
S
O
C$_5$H$_{11}$
(15)
C$_5$H$_{11}$
OH
(16)
29% optical purity

**Scheme 19**

Besides the low optical yields of the reaction the known hazard of racemization and (*E*)/(*Z*)-isomerization of optically active allylic sulfoxides, which can only be avoided below 0 °C, limits the synthetic utility of such a process.

Clean conjugate addition of appropriate nucleophiles to allenic sulfoxides has been used to produce allylic sulfoxide systems. Horner has described the formation of functionalized allylic alcohols when adding nucleophiles like amines, alcohols or thiols to allenic sulfoxides in excess.[71] If the addition is performed with equimolar amounts at lower temperature, so that the 2,3-sigmatropic rearrangement is avoided, the intermediate addition products (enamines or enol ethers) can be hydrolyzed to the synthetically valuable β-keto sulfoxides (Scheme 20).[72]

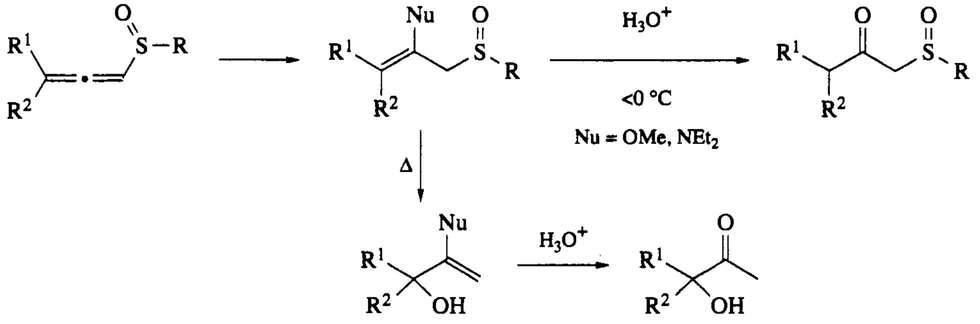

Scheme 20

The overall process, considering that the propargylic alcohols are generated from carbonyl compounds, constitutes a reductive nucleophilic substitution with additional introduction of the synthetically valuable sulfoxide functionality.

An impressive application, where the stereochemical consequences of unsaturated sulfoxide–sulfenate rearrangements are convincingly utilized, provides an efficient and stereoselective method for the corticosteroid side chain formation, starting from 17-keto steroids (Scheme 21).[73]

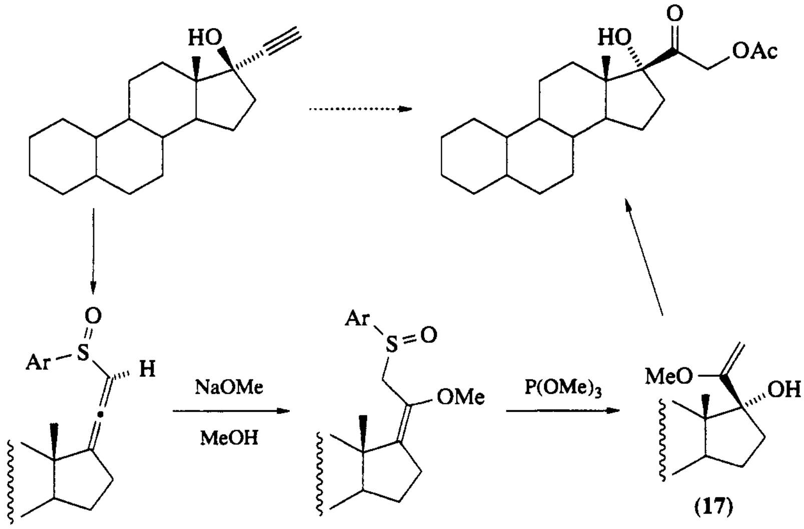

(17)

Scheme 21

Under the influence of the angular methyl group the addition of acetylene occurs from the α-side, giving the opposite configuration at C-17 to that required for the corticosteroids, but the rearrangement of the diastereomeric methanol adducts of the derived allenic sulfoxide is also forced to proceed at the α-side, leading finally to the correct configuration. The elaboration of the required side chain in (17) can easily be accomplished.

The addition of allylic alcohols to electrophilic allenes leads to another interesting possibility for their use in synthesis. The addition products respresent Claisen systems and can be forced to rearrange. More valuable applications of this principle will be discussed in Section 4.5.3.1.3. In the case of allenic sulfoxides the rearrangement is followed by elimination of sulfinic acid, giving easy access to conjugated dienones (Scheme 22).[74]

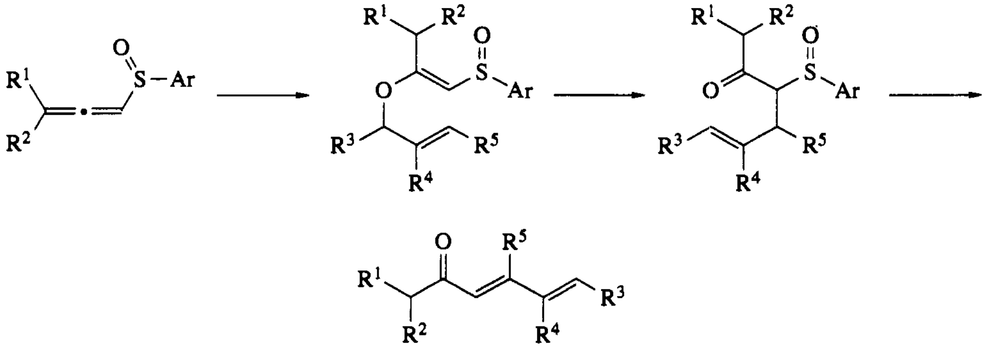

**Scheme 22**

When adding malonic ester anion to an allenic sulfoxide, rearrangement of the derived addition product leads to an allylic alcohol which cyclizes to (**18**) and isomerizes to the isolated product (**19**). If one alkylates the intermediate carbanion one gets an entry to a β-methylenelactone system (**18**; Scheme 23).[75]

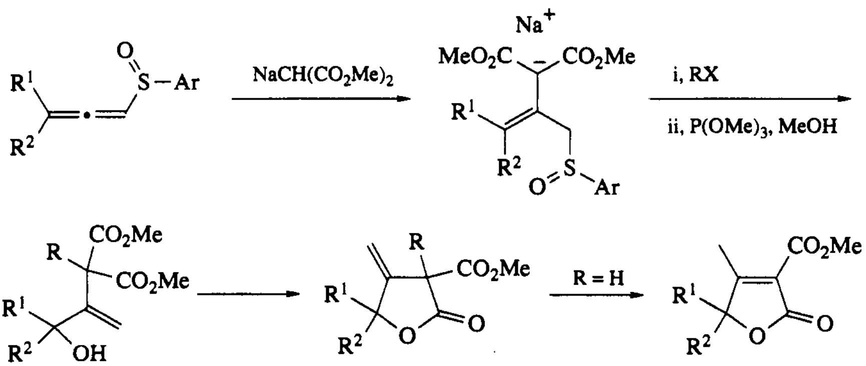

(**18**) (**19**)

**Scheme 23**

In all the examples discussed, unsaturated aryl-substituted sulfur compounds were used. But one is not restricted to this substitution if synthetic purposes require otherwise. One example is depicted in Scheme 24. Combining the rearrangement in turn with a Ramberg–Bäcklund extrusion of $SO_2$ leads to a relatively facile synthesis of conjugated dienoic acids.[76]

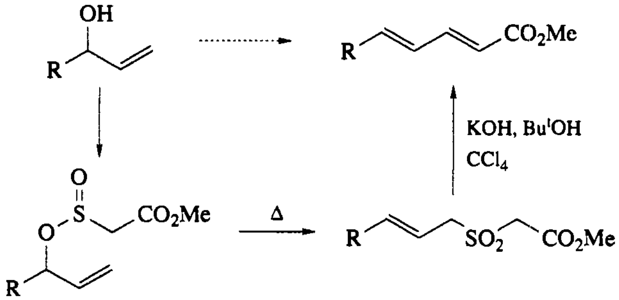

**Scheme 24**

Unsaturated sulfinamides can also be obtained by a 2,3-sigmatropic rearrangement, again very easily affording the product with (*E*)-double bond geometry in most cases (Scheme 25).[77]

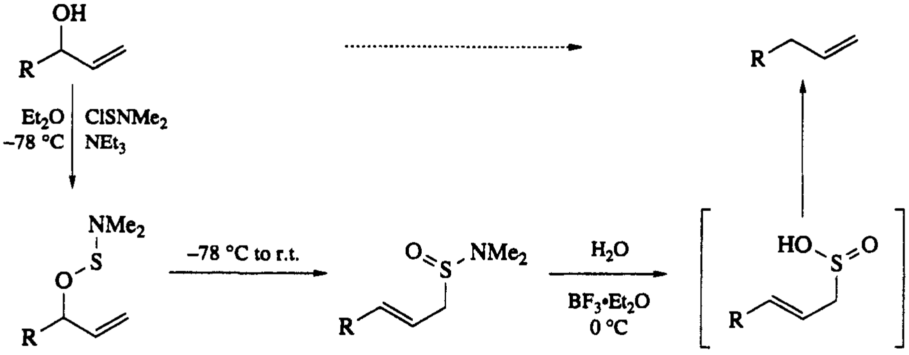

**Scheme 25**

When the allylic sulfinamides are hydrolyzed under special conditions (classical methods like alkali- or acid-catalyzed hydrolysis did not work properly) the obtained allylic sulfinic acids are unstable and will fragment smoothly again with allylic rearrangement into terminal alkenes.

There is one other synthetically interesting O → S transformation based on a hetero-Cope reaction, which is worth mentioning here. This rearrangement (equation 18) is so easy that on attempting to prepare allylic xanthates (**20**) one isolates instead the rearranged (*E*)-thiocarbonates (**21**),[78] which can be used in synthesis, *e.g.* as protected thiol derivatives[79] or as precursors for allylic radicals.[80]

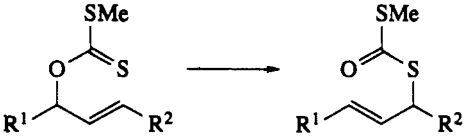

**(20)** **(21)**

(18)

### 4.5.2.4 Oxygen–Nitrogen Transpositions

A direct *N*-substitution of an allylic substrate with an oxygen leaving group (equation 19) lacks generality and the problem of regio- and stereo-selectivity also arises in Pd-catalyzed reactions. Such a substitution *via* π-allyl–palladium intermediates may be useful in cases where the steric situation allows only one mode of attack, as exemplified in the key step of an ibegamine synthesis by Trost, where the intramolecular reaction leads to clean allylic *syn* substitution (equation 20).[81]

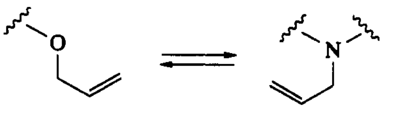

(19)

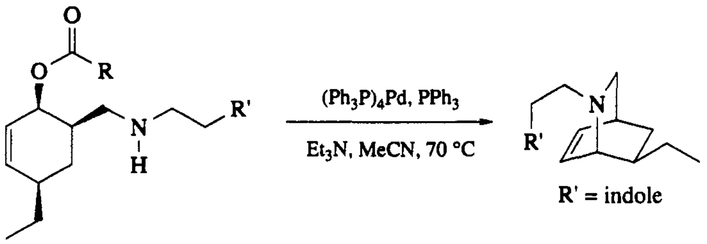

(20)

An intermolecular reaction, again with overall *syn* $S_N'$ substitution, was successfully applied in a synthesis of the carbocyclic nucleoside analog aristeromycin to introduce the nitrogen base stereoselectively (equation 21),[82] although with heteronucleophiles, unlike the case of carbon nucleophiles, a lower propensity for attack distal to oxygen to give the 1,4-product with vinyloxiranes exists.

Recently even asymmetric allylic substitution reactions using optically active Pd catalysts have become known.[83,84] An example of an intramolecular allylic substitution with nitrogen is seen in equation (22).

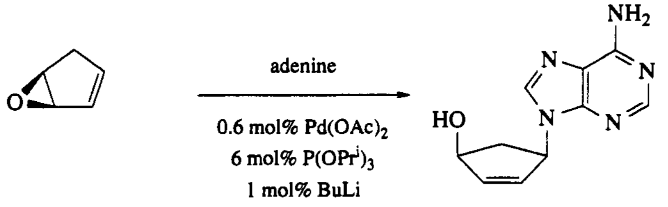

(21)

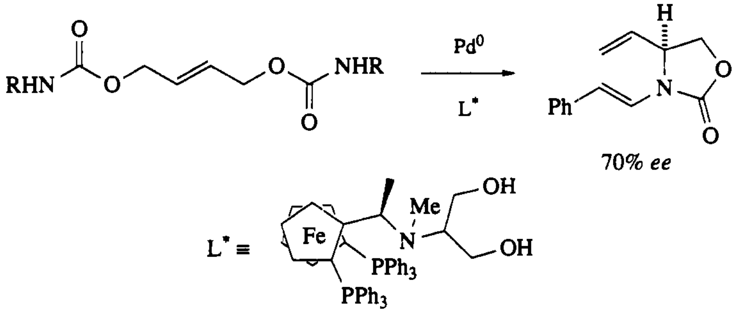

(22)

The most reliable methods for allylic O → N conversions are based on intramolecular rearrangements. For example, the rearrangements of allylic *N*-phenylimidates have long been known, but the required temperature of 200 °C limits synthetic applications. With trichloromethylacetimidates, which are easily prepared and rearrange at much lower temperatures, Overman has introduced a very useful method for the allylic transformation of a hydroxy group into an amino function (Scheme 26),[85] leading to a general synthesis of allylic amines with the stereochemical features expected from a 3,3-sigmatropic rearrangement.[86,87] Catalysis with Pd$^{II}$ or Hg$^{II}$ salts has proven to be effective in some cases.[88]

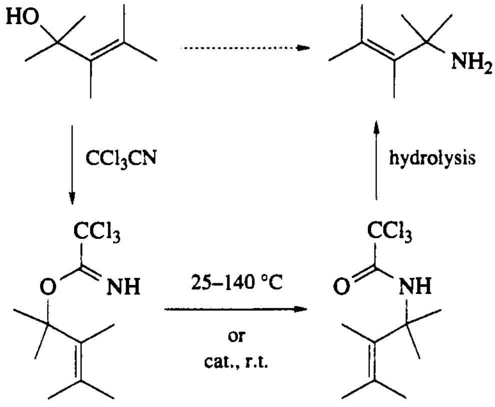

**Scheme 26**

Thermal rearrangement of imidate esters of propargylic alcohols leads *via* *N*-acylaminoallenes to *N*-acyl-1-amino-1,3-dienes or *N*-acyl-2-amino-1,3-dienes, depending upon the substitution of the propargylic alcohol (Scheme 27).[85]

It is interesting to note that in the case of *N*-acyl-1-amino-1,3-dienes the (1*Z*,3*E*)-isomer is probably formed because a 1,5-sigmatropic hydrogen migration is involved in the tautomerization. If X is not the $CCl_3$ group but a potential leaving group such as the pyrrolidine function, the intermediate diene will react further by elimination of HX to a (1*Z*,3*E*)-diene isocyanate (**22**), which undergoes electrocyclic ring closure to yield ultimately a substituted 2-pyridone system (Scheme 28).

With another hetero-Cope reaction one is able to introduce an aryl-substituted amino group (Scheme 29).[89]

Not a 3,3-sigmatropic but an *S*Ni-like reaction is involved in an oxygen–nitrogen transposition which allows the introduction of a secondary amine function (Scheme 30).[90]

There are not many examples of the direct transformation of an allylic amino to a rearranged oxygen functionality. One example is found in the Meisenheimer rearrangement of amine oxides, which occurs with almost complete chirality transfer, as seen in equation (23).[91]

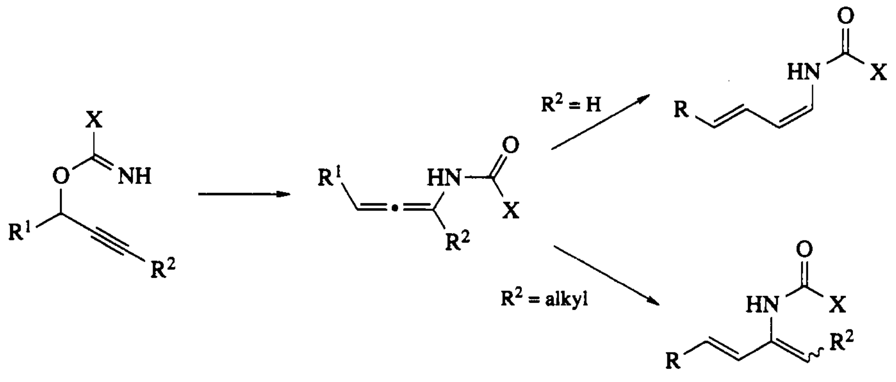

Scheme 27

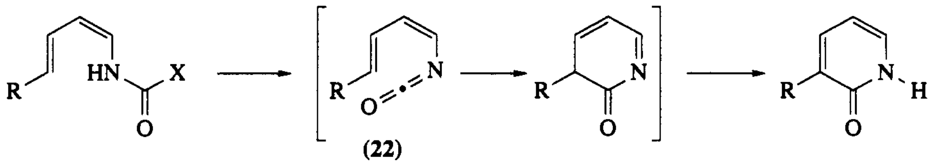

(22)

Scheme 28

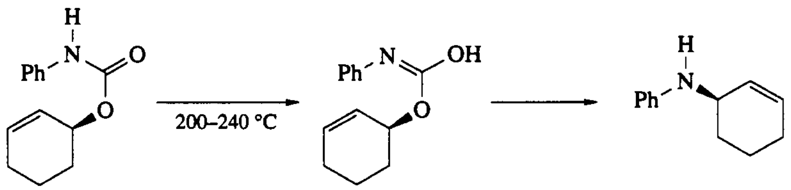

Scheme 29

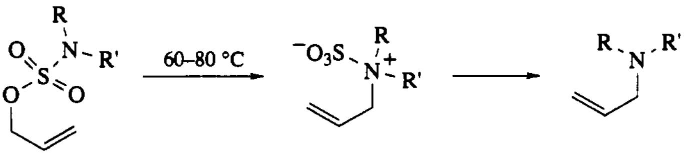

Scheme 30

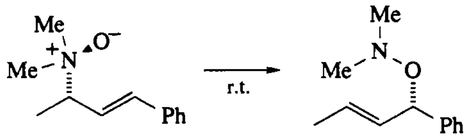

(23)

### 4.5.2.5 Oxygen–Phosphorus Transpositions

In an analogous reaction to that of sulfenates, unsaturated esters of P$^{III}$ compounds rearrange easily (equation 24) to corresponding allyl- and allenyl-phosphoryl compounds because the strong heteroatom–oxygen double bond is formed (Scheme 31).[92]

This reaction presents a very efficient way of preparing many kinds of unsaturated phosphoryl systems, *e.g.* phosphonic acid chlorides (X = Cl) phosphonates (X = OR) or phosphine oxides (X = alkyl, aryl), tolerating almost all types of substitution at the carbon chain.[92,93] The chemistry of allylic phospho-

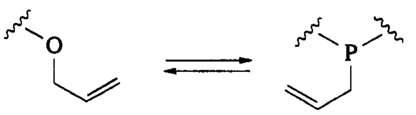

(24)

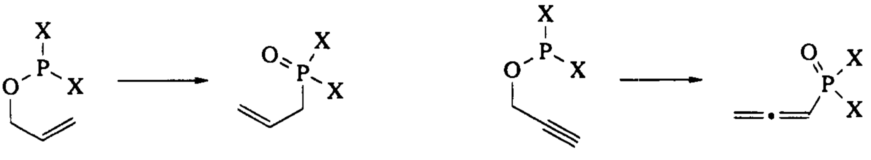

**Scheme 31**

ryl compounds is not as rich as that of allylic sulfoxides, as in contrast to an S=O group the P=O group is difficult to remove from an organic compound except by an alkenation reaction[94] and in some cases, from an allylic position, by reduction with $LiAlH_4$ accompanied by an allylic shift.[95]

This reactivity has been used preparatively in combination with the known tendency of allylic phosphonates to be alkylated in the α-position (Scheme 32).[95]

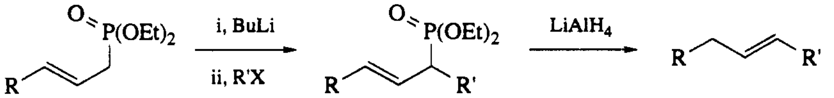

**Scheme 32**

Interestingly, an alkenation reaction can even be brought about with an allenic phosphonate leading to cumulatrienes.[96] A very useful application of allenic phosphoryl compounds is due to their electrophilic properties, which allow easy addition of nucleophiles like alcohols or amines. The adducts can be hydrolyzed to β-keto phosphonates. The reaction sequence starting from propargylic alcohols can even be performed as a 'one-pot reaction', thus constituting a convenient and very general synthetic route to this important class of organophosphorus compounds (Scheme 33).[97,98]

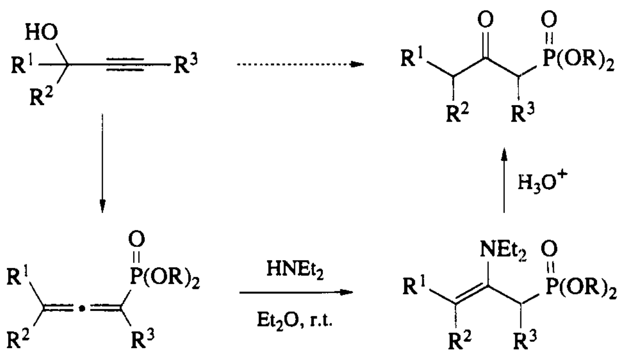

**Scheme 33**

Recently an allylic phosphonate has been shown to react as an allylic phosphonate cation by transformation to a π-allyl–palladium complex, susceptible to attack by nucleophiles such as stabilized carbanions (Scheme 34).[99]

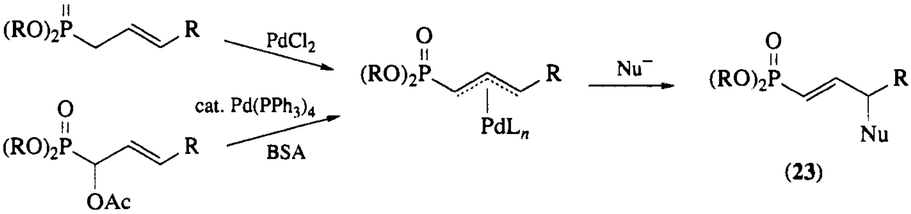

**(23)**

**Scheme 34**

Starting from the readily available α-acetoxyallyl phosphonates, reaction to the γ-substituted systems (**23**) takes place under Pd catalysis.

### 4.5.2.6 Sulfur–Sulfur Transpositions

The only synthetic application of an allylic S → S transposition (equation 25) seems to be in the synthesis of (*E*)-α,β-unsaturated aldehydes *via* a 3,3-sigmatropic rearrangement of allylic dithiocarbamates (Scheme 35).[100]

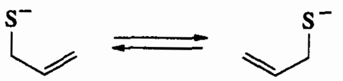

(25)

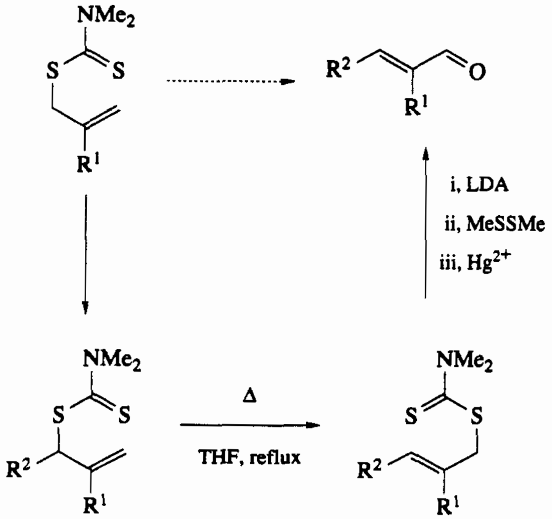

NMe2
S
S
R1
R2
O
R1
i, LDA
ii, MeSSMe
iii, Hg2+
NMe2
S
S
R2
R1
Δ
THF, reflux
NMe2
S
S
R2
R1

Scheme 35

### 4.5.2.7 Sulfur–Nitrogen Transpositions

Allylic sulfides can be transformed by a 2,3-sigmatropic rearrangement into allylic nitrogen derivatives (equation 26) *via* a sulfimide intermediate (Scheme 36).[101,102]

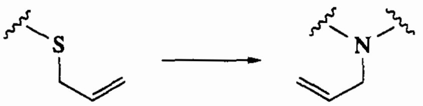

(26)

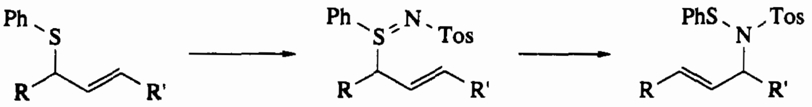

Ph
S
R
R'
Ph
S
N
Tos
R
R'
PhS
N
Tos
R
R'

Scheme 36

The reaction is analogous to the allyl sulfenate–allyl sulfoxide rearrangement and is also known in the selenium case.[103] As sulfur and selenium functionalities are common activating groups in organic synthesis, this highly stereocontrolled transformation can sometimes be very useful.

3,3-Sigmatropic rearrangements have also found use in allylic S → N transposition. The rearrangement of allyl thiocyanates to allyl isothiocyanates (equation 27)[104] belongs to this class as does the rearrangement of *S*-allyl thioimidates (equation 28).[105]

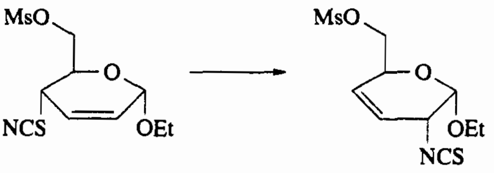

MsO
O
NCS
OEt
MsO
O
OEt
NCS

(27)

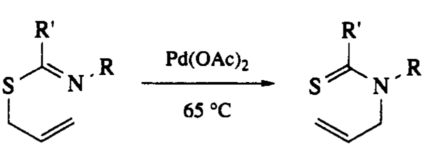

(28)

In the latter case the S → N allyl group migration is only efficient when Pd$^{\text{II}}$ catalysis is employed, otherwise, at much higher temperatures, a double bond isomerization occurs first and is then followed by an S → C allyl shift by means of a thio-Claisen rearrangement. As the appropriate *S*-allyl thioimidates are easily prepared by alkylation of thioamides with allyl halides, the overall process is an $S_N'$ substitution of an allylic halide by an amine, a reaction which is difficult to achieve directly.

## 4.5.3 1,3-HETEROATOM TO CARBON TRANSPOSITIONS

1,3-Heteroatom to carbon transposition is represented in equation (29).

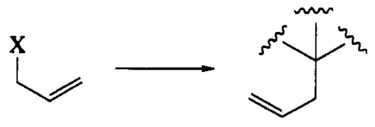

(29)

### 4.5.3.1 C—C Bond Formation by Nucleophilic Attack on the Allylic System

When there is the intention of effecting an allylic rearrangement in the C—C bond formation step, it is obvious that intramolecular processes are principally better than intermolecular ones as there always exists the competition of $S_N$ *versus* $S_N'$ reactions with intermolecular processes, although there have been a number of improvements regarding this problem in recent years. Because of the huge amount of literature only selected examples, which demonstrate the general trends, can be presented here.

#### *4.5.3.1.1 Allylic substitution with carbon nucleophiles*

Allylation of an organometallic reagent is an important carbon–carbon bond forming reaction (equation 30).

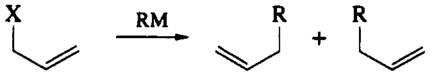

(30)

Besides ordinary halides and sulfonic acid esters, the development of transition metal catalyzed processes has enabled allylic alcohols, acetates, carbonates, vinyl epoxides and vinyllactones also to be successfully employed as allylic substrates.

With alkyl-lithium and -magnesium compounds (the most common organometallic reagents) the regioselectivity of the reaction with an allylic electrophile is the primary problem. Normally a mixture of $S_N$ and $S_N'$ products is obtained. The readily available organozinc reagents (prepared *in situ* from RLi and $ZnCl_2$ in THF) undergo highly regio- and chemo-selective allylation reactions under mild conditions, where the regioselection can be completely changed from $S_N$ to $S_N'$ simply by changing the catalyst from a nickel-based to a copper-based one (Scheme 37).[106]

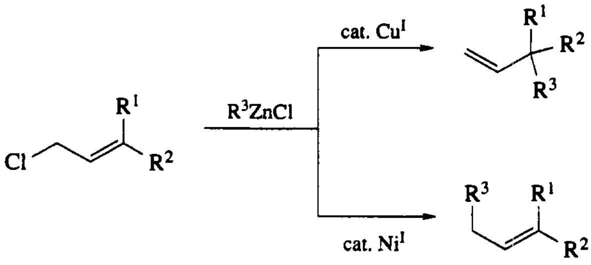

**Scheme 37**

The observed regioselectivity (92–98%) compares favorably with that of the more elaborate stoichiometric reagent $RCu{\cdot}BF_3$, which was used previously,[107] even for the reaction in which a sterically congested quaternary center is created. Generally Cu organic compounds are known to prefer γ-attack on allylic substrates, especially with allylic acetates and vinyloxiranes, in most cases with *anti* stereoselectivity.[108] Two examples are shown in equations (31)[109] and (32).[8]

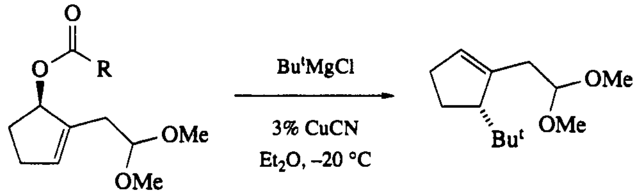

(31)

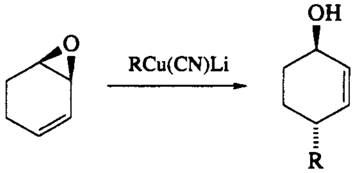

(32)

The $S_N2'$ addition of organocopper reagents to vinyloxiranes is now a well-established synthetic route to allylic alcohols, often giving remarkable stereocontrol.[8]

Recently an example of a virtually complete diastereofacial selectivity in the $S_N'$ allylation of organocopper/zinc reagents was reported.[110] The best results were achieved with a new 'zinc cuprate' reagent, the structure of which has not yet been elucidated (equation 33). This reagent was developed as a catalytic system for zinc alkyl reagents.

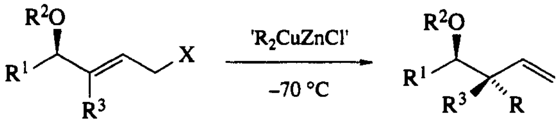

**(24)**

(33)

A single diastereomer was formed by *anti* attack on (**24**; equation 33) with 98% regioselectivity, regardless of the nature of the substituent $R^1$ on the stereogenic center, the $R^2$-protecting group on oxygen or the nature of the leaving group. The reaction of the *cis* isomers of (**24**) was also *anti* selective.

Another fascinating development in the field of allylic alkylation is the $Pd^0$-catalyzed nucleophilic substitution of allylic compounds.[10,11] Allylic acetates are by far the most often used allylic substrates, but many others are possible, and vinyloxiranes and vinyllactones especially offer many useful synthetic opportunities. Stabilized carbanions are mainly employed as nucleophiles for allylic alkylations, although other nucleophiles, *e.g.* simple zinc or boron enolates can be employed.[111] As a consequence of the reaction mechanism, with the formation of a π-allyl intermediate, the regioselectivity is not determined by the position of the leaving group but by other factors, mainly steric ones. The stereoselectivity, however, is normally very high, resulting usually in retention of configuration due to a double inversion during the reaction. Therefore a high degree of 1,3-chirality transfer may occur if the substitution reaction proceeds with double bond shift.

The optically active allylic lactone (**25**; equation 34), for example, reacted with sodium malonate in the presence of $Pd(PPh_3)_4$ to give stereospecifically the acid (**26**), which was utilized for the generation of the side chain of vitamin K.[112]

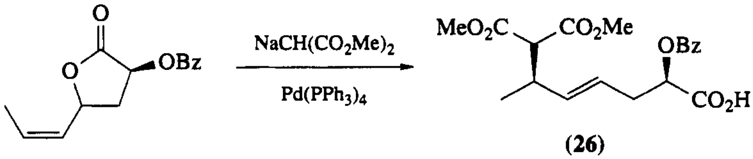

**(25)** **(26)**

(34)

However, Pd-catalyzed allylic alkylations have found more applications in intra- rather than in intermolecular substitution reactions. Many of these alkylations are highly regio- and stereo-selective and occur with allylic rearrangement and are applied to construct various carbo- and hetero-cyclic systems.[113,114] Some illustrative examples are shown in equations (35)–(37).[115–118]

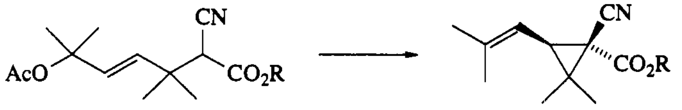

(35)

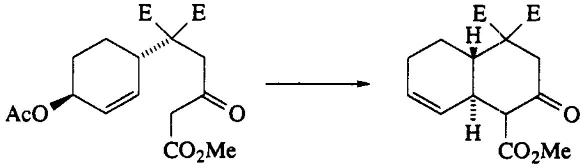

(36)

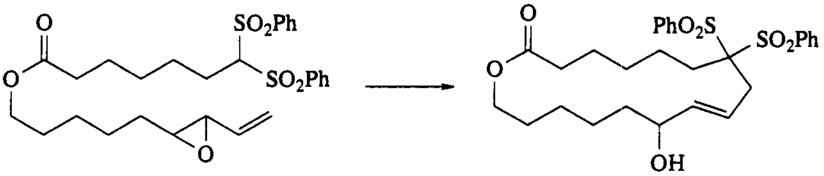

(37)

A most spectacular stereochemical aspect of the Pd-catalyzed reactions is the possibility of creating new stereogenic centers in the allylic substrate or in the nucleophile when chiral phosphine–palladium complexes are employed. Although the full potential of these reactions has still to be exploited, the results thus far are promising and the first successful applications have become known (*e.g.* equation 38).[119]

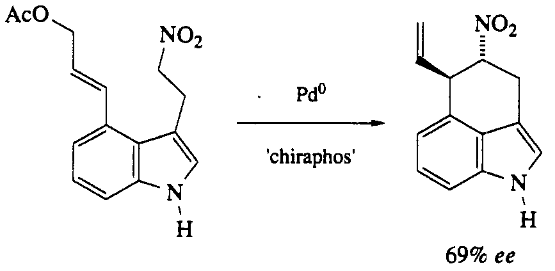

(38)

Yet another development which is worth mentioning in this context is the $S_N'$ substitution of acetals of unsaturated carbonyl compounds. The phenomenon that the reaction of an allylic acetal with a Grignard reagent in the presence of CuBr may occur as a vinylogous substitution with double bond shift has been long known.[120] The reaction can be utilized in an efficient synthesis of 3-substituted propionaldehydes using the acrolein acetal as a homoenolate cation equivalent (Scheme 38).[121]

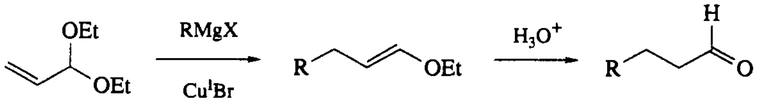

**Scheme 38**

This type of reaction attracted broad interest when it was discovered that high regioselectivity can also be effected with organoaluminum compounds and other nucleophiles in the presence of Lewis acids and that by employing chiral cyclic acetals (from optically active 1,2- or 1,3-diols) diastereoselective transformations can be realized.[122,123] Such reactions are synthetically very valuable when considering that the overall process represents an enantioselective Michael addition, where the chiral auxiliary can be recycled (Scheme 39).[124]

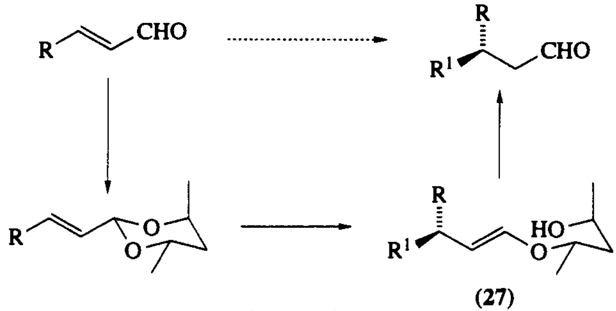

**Scheme 39**

The stereochemical outcome of the reaction is in most cases consistent with an *anti* $S_N2'$ substitution in a transoid transition, leading to the (*E*)-enol ethers (**27**). Whereas acetals of α,β-unsaturated aldehydes react regioselectively only with 'soft' alkenyl- and aryl-copper reagents, the reaction of α,β-unsaturated ketals always affords the $S_N'$-product, also with aliphatic copper compounds. With cyclic enones, like cyclohexenone ketals, however, the diastereoselectivity is poor (only up to 26% *de*). In contrast organoaluminum compounds seem to give generally better regio- and diastereo-selectivity. In this case another advantage is that inexpensive tartaric acid derived acetals can be employed successfully, affording diastereoselectivities of up to 78%, even with a cyclohexenone system (Scheme 40).[125]

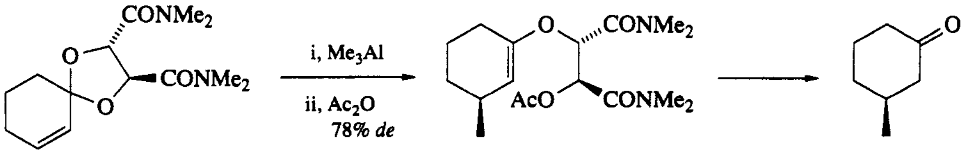

**Scheme 40**

Even though the regio- and diastereo-selectivities of these reactions are not yet satisfactory in many cases, the potential of this type of conjugate addition is obvious.[126]

### *4.5.3.1.2 Transformation of allyl alcohols to rearranged homoallyl alcohols or β,γ-unsaturated carbonyl compounds*

A synthetically very useful method for regiospecific carbon–carbon bond formation by an allylic transposition is provided by the 2,3-Wittig rearrangement of α-allyloxy carbanions (**29**; Scheme 41).[29,30]

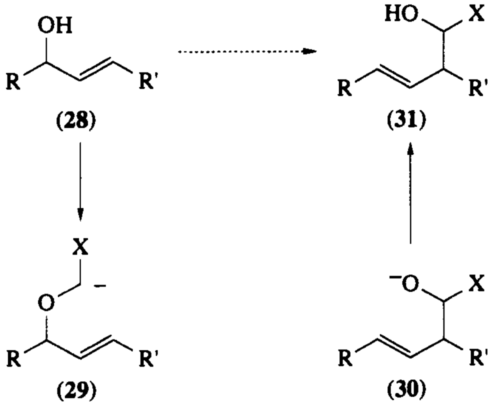

**Scheme 41**

Since the appropriate allylic ethers, as starting material, are generated normally from allyl alcohols, the 2,3-Wittig rearrangement permits easy construction of homoallyl alcohol systems (**31**) from allyl alcohols (**28**). Due to its sigmatropic nature the rearrangement possesses several stereochemical features which make it an increasingly important tool for the stereorational synthesis of highly functionalized acyclic and macrocyclic systems: (i) generation of specific alkene geometries with preferential formation of an (*E*)-double bond; (ii) diastereoselective creation of vicinal chiral centers; and (iii) potential 1,3- and 1,4-transfer of chirality.

The required allyloxy carbanion may be generated either by direct deprotonation with a strong base, by transmetalation of Sn-substituted systems[127] or, most recently, by reductive lithiation.[128] In the former case substituents X, which facilitate carbanion formation, are helpful for a clean reaction by establishing regioselective deprotonation at temperatures low enough to avoid competing 1,2-shifts. Typical synthetically useful substituents include phenyl, vinyl, alkynic or alkoxycarbonyl groups. The propargylic variants possess particular advantages: one gets an unusually high level of either diastereoselection by proper choice of the geometry of the allyl system and the rearrangement product contains unique multifunctionality for further synthetic transformations (Scheme 42).[129]

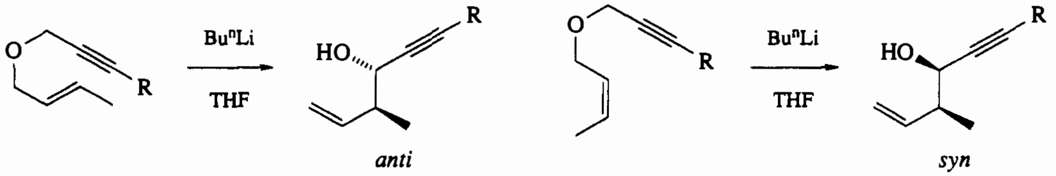

**Scheme 42**

In the case of X = $CO_2H$ (Scheme 41) the product of the rearrangement is an unsaturated α-hydroxycarboxylic acid which may be converted to an aldehyde by oxidation, thus allowing a stereoselective synthesis of β,γ-unsaturated aldehydes (Scheme 43).[130]

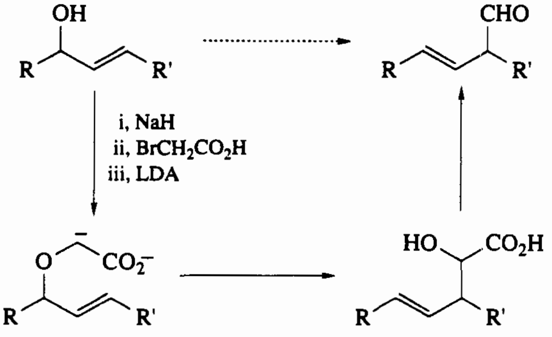

**Scheme 43**

With a ketone function as an activating group (X = RC=O) a Wittig rearrangement is induced on silylation with TMS-Cl and triethylamine in DMF; interestingly no competing Claisen rearrangement is observed.[131] The rearranged product can be cleaved to a β,γ-unsaturated ketone (Scheme 44).

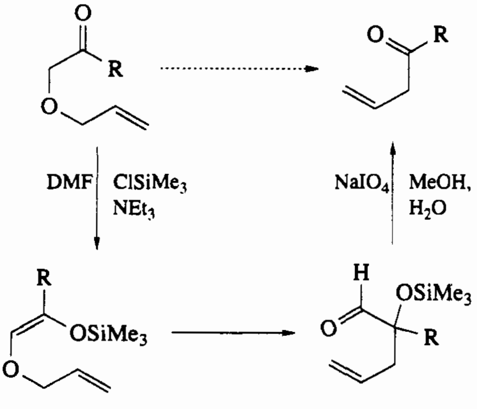

**Scheme 44**

If X in Scheme 41 represents a cyanide group (X = CN) the rearrangement of the anion leads to a cyanohydrin anion as the product, which can yield a carbonyl function directly.[132] The reaction is not only known for allylic ethers but also for propargylic ethers, giving access to allenic carbonyl compounds in the latter case (equation 39).[133]

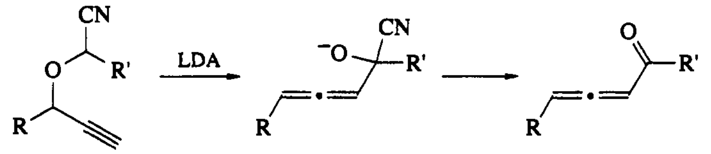

(39)

With a phenylsulfonyl group as X (Scheme 41) the intermediate, after rearrangement, will decompose directly to an aldehyde function, which reacts with excess alkyllithium to form an unsaturated alcohol.[134] The often efficient transfer of chirality from C-1 of an optically active allylic alcohol to the newly created stereogenic centers at C-3 and/or C-4 is another valuable aspect of the 2,3-Wittig rearrangement which has already found extensive use in natural product synthesis.[30]

With regard to asymmetric synthesis, the possibility that a stereogenic center outside the sigmatropic framework can direct the stereochemical outcome of the electrocyclic process has been intensively exploited recently.[30] One method for asymmetric induction has been realized with X representing a chiral carboxylic acid derivative. From the various chiral auxiliaries studied, the $C_2$ symmetrical amide (**32**) seems to be the most effective,[135] giving (*via* its zirconium enolate) essentially 100% diastereoselectivity and *erythro* selection, thus permitting ready access to optically active α-hydroxycarboxylic acids (equation 40).

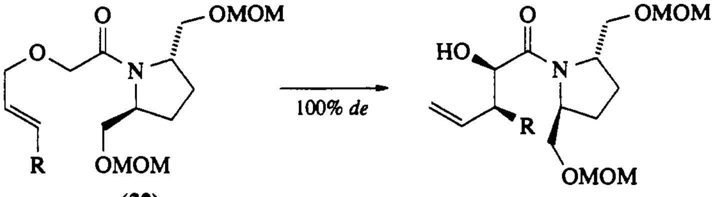

**(32)**

(40)

Another system which affords rearrangement products of high optical purity uses the diastereofacial selection of an 8-phenylmenthol-derived ester.[136]

Interestingly an asymmetric induction can also be caused by an external stereocenter in the allylic moiety of the anionic Wittig system, as has been demonstrated recently (Scheme 45).[137]

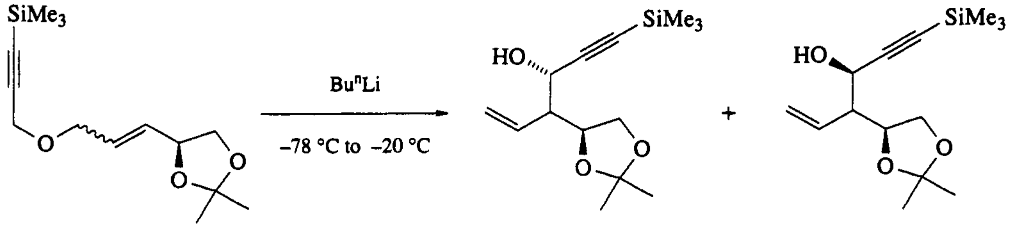

*(Z)* 0 : 100
*(E)* 83 : 17

**Scheme 45**

Lastly it should be mentioned that a 2,3-Wittig rearrangement can be coupled with other sigmatropic processes in synthetically valuable 'tandem' sequences. An illustrative example is a 'tandem' 2,3-Wittig–oxy-Cope rearrangement, which provides a versatile route to δ,ε-unsaturated carbonyl compounds (Scheme 46).[138]

It is remarkable that the (*E*)/(*Z*)-stereochemistry of the oxy-Cope product is not dependent on the *erythro*/*threo* ratio of the 2,3-Wittig rearrangement but on the specific rearrangement procedures used: thermal rearrangement exhibits higher (*E*)-selectivity (92–95%) than the anionic oxy-Cope and siloxy-Cope variants.

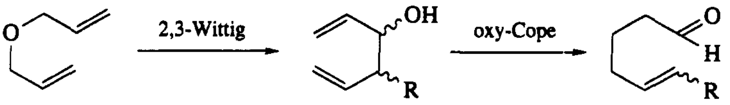

**Scheme 46**

A reaction which transforms allylic alcohols to homologous β,γ-unsaturated amides by means of a 2,3-sigmatropic process was first described by Büchi.[33] When an allyl alcohol is heated with *N*,*N*-dimethylformamide acetal, a rearrangement occurs apparently involving a nucleophilic carbene as an intermediate, leading to a product with 95–100% (*E*)-geometry of the double bond (Scheme 47).

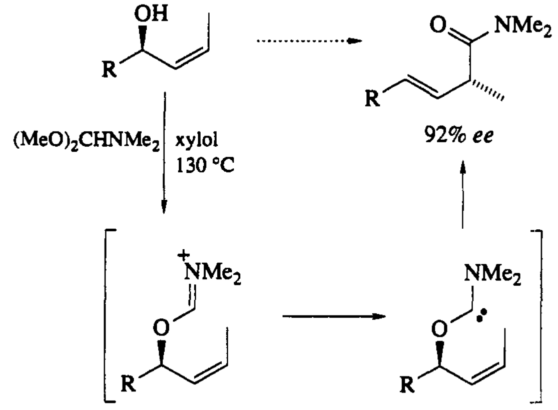

**Scheme 47**

The Büchi rearrangement has found synthetic use, *e.g.* for the synthesis of chiral isoprenoid building blocks, as it also allows effective 1,3-transfer of chirality.[139]

### 4.5.3.1.3 *Transformation of allyl hetero- to homoallyl hetero-systems*

One possibility of transforming allyl hetero- to homoallyl hetero-systems is by 2,3-sigmatropic rearrangements analogous to the 2,3-Wittig reaction, namely its *thio* and *aza* counterparts, where an allyl group migrates from a sulfur or nitrogen instead of an oxygen atom to an adjacent carbanionic center (Scheme 48).[30] In these cases the corresponding nitrogen or sulfur ylides are also able to rearrange in the same manner. In all cases an electron-withdrawing group Y is normally present to facilitate and direct carbanion formation.

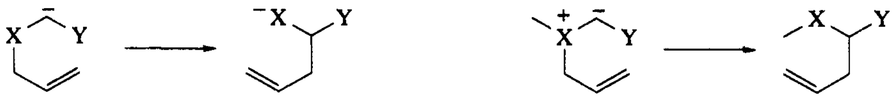

X = S, NR; Y = electron-withdrawing group

**Scheme 48**

Whereas the thio-2,3-Wittig reaction is well recognized and used, particularly in terpene synthesis (*e.g.* Scheme 49),[140] the amino counterpart is less studied.

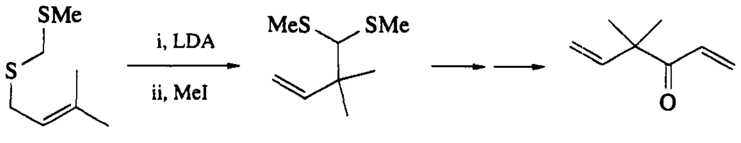

**Scheme 49**

The variants with allylic ammonium[31] and sulfonium ylides[141] are well known and correspond to the Sommelet–Hauser and the Stevens rearrangement.[31] Two representative examples are shown in Schemes 50 and 51.

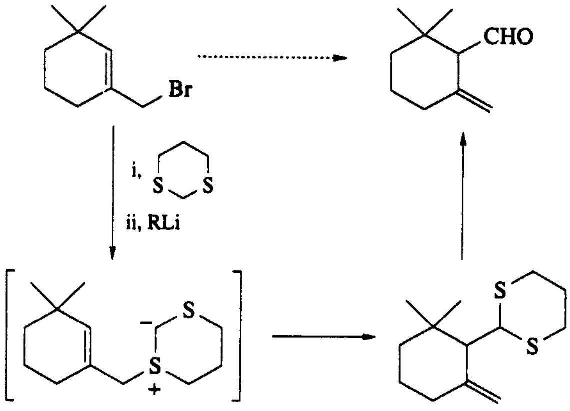

Br
CHO
i, S S
ii, RLi
S
S
+
S
S

Scheme 50

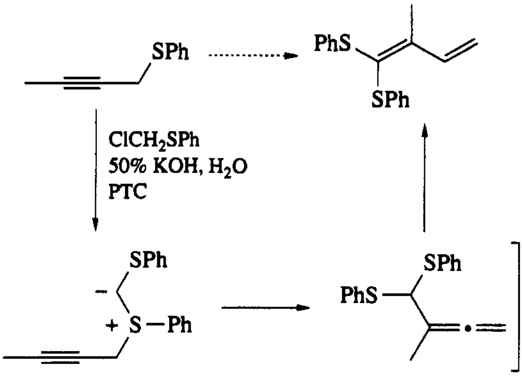

SPh
PhS
SPh
ClCH$_2$SPh
50% KOH, H$_2$O
PTC
SPh
S—Ph
SPh
PhS

Scheme 51

In Scheme 50 it can be seen that the reaction can be used for the conversion of an allylic halide to an allylically shifted formyl group.[142] A 1,1-dithio-1,3-butadiene system, synthesized *via* rearrangement of the ylide,[143] is also accessible by a different kind of 2,3-sigmatropic rearrangement involving a nucleophilic carbene intermediate (Scheme 52).[144] The same type of rearrangement has found synthetic application in a bakkenolid A synthesis.[145]

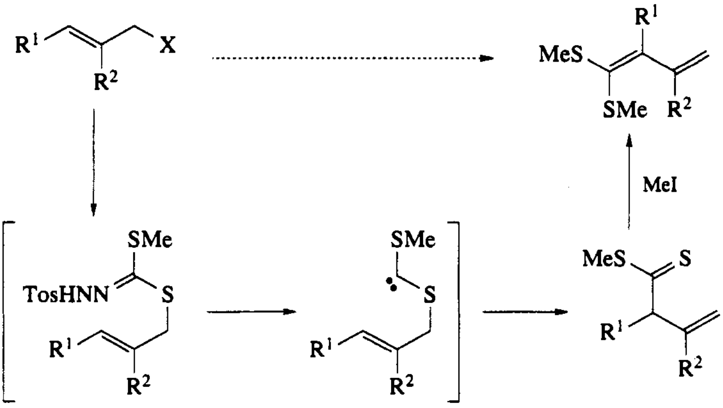

R$^1$
X
R$^2$
R$^1$
MeS
SMe
R$^2$
MeI
SMe
TosHNN
S
R$^1$
R$^2$
SMe
S
R$^1$
R$^2$
MeS
S
R$^1$
R$^2$

Scheme 52

With the aid of a nitrogen ylide rearrangement, it is possible to transform an allylic secondary amine to an unsaturated carbonyl system, in certain circumstances with transfer of chirality (Scheme 53).[27]

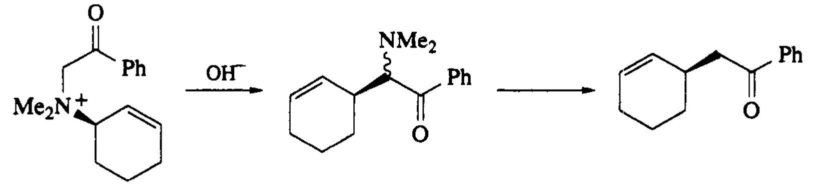

**Scheme 53**

Especially interesting is the possibility for asymmetric synthesis by employing amino acid derived ylide systems (*e.g.* **33**; Scheme 54), which allows the synthesis of optically active β,γ-unsaturated aldehydes.[146]

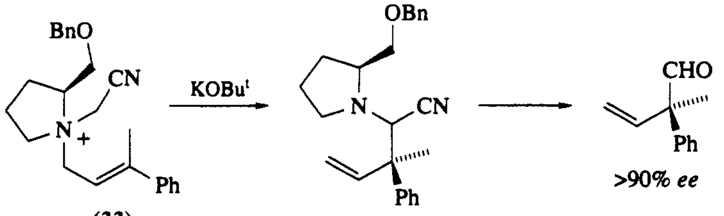

**(33)**

**Scheme 54**

2,3-Sigmatropic rearrangements of cyclic sulfonium and ammonium ylides have been extensively used in ring contraction and ring enlargement methods.[147] An example is shown in Scheme 55.

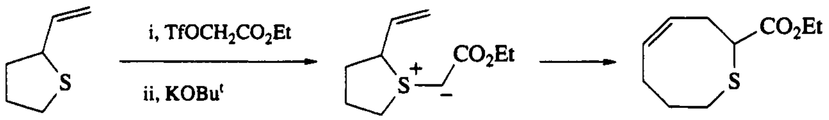

**Scheme 55**

#### *4.5.3.1.4 Transformation of allyl alcohols and allylamines to γ,δ-unsaturated carbonyl compounds*

One of the most versatile and useful allylic rearrangements is the aliphatic Claisen rearrangement with its different variants, which allows an easy, very general access to γ,δ-unsaturated carbonyl compounds (Scheme 56).[35,36]

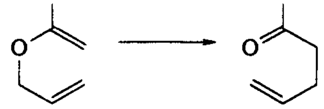

$X = H, OR, NR_2, O^-, CH_2^-$

**Scheme 56**

This 3,3-sigmatropic rearrangement's extraordinary role in synthesis results from several characteristic features: (i) a wide range of carbonyl derivatives is available with variation of X in Scheme 56 (aldehydes, ketones, acids, esters, lactones, thioesters and amides); (ii) more functionalized derivatives may be employed; and (iii) high stereoselectivity in the formation of double bonds and new stereocenters is usually observed. Therefore the Claisen rearrangement has found extensive use particularly for the stereocontrolled construction of acyclic systems.[148] Of special significance is the stereoselective generation of vicinal centers from terminal monosubstituted double bonds, depending upon their configuration, and the possibility of transferring chirality along the allyl system (Scheme 57).

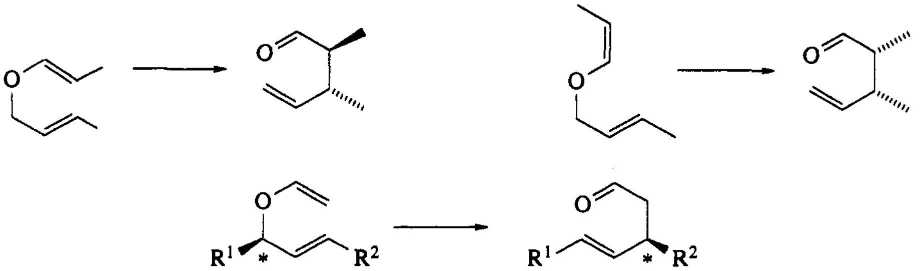

Scheme 57

It is now well established that the rearrangement proceeds more easily the more electron-donating the substituent X is. With an anionic X-group the reaction may take place below room temperature. In the case of X = O the ester enolate Claisen variant is represented, with X = C it is the 'carbanion-accelerated' version of the Claisen rearrangement that takes place. Another possibility to moderate the rather drastic conditions for the classical type of the Claisen rearrangement, is to catalyze the reaction,[37] a development which bears high potential, particularly with regard to control of stereochemistry.[149–151] Nakai has described the diastereocontrolled rearrangement of cyclic enol ethers, which is dependent upon the catalyst employed.[151] Starting from (**34**) in the presence of 2,6-dimethylphenol the *anti* product (**35**; Scheme 58) results, which is also the main product in the thermal reaction without a catalyst; under catalysis with a Pd complex at room temperature the *syn* product (**36**) is formed. This striking result is explained by a change in the transition state comformation: in the phenol-catalyzed reaction a usual chair conformation is involved, whereas a complexation of the 1,5-diene with the Pd catalyst leads to a boat transition state (Scheme 58).

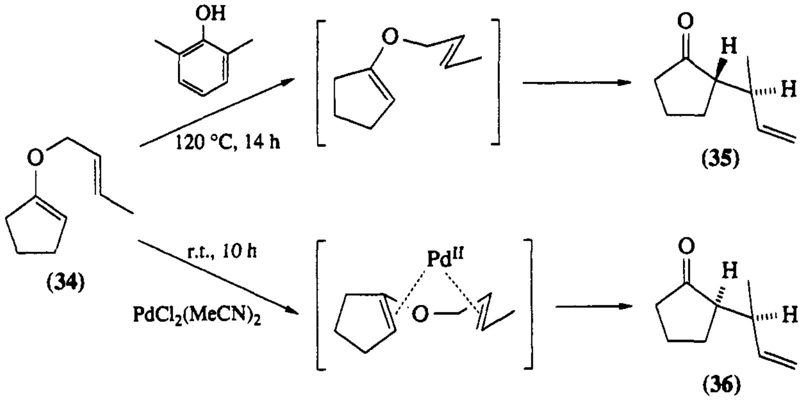

Scheme 58

Another unprecedented stereochemical control in a Claisen rearrangement was reported recently by Yamamoto using organoaluminum reagents (Scheme 59).[152] Sometimes (*e.g.* with R = $Cu_2CH{=}CH{-}C_5H_{11}$) complete reversal of double bond geometry could be achieved simply by modifying the bulky aluminum catalyst.

To exploit the whole capacity of the Claisen rearrangement, appropriate methods for the preparation of the allyl vinyl ethers starting from allyl alcohols are necessary. The classical approach involves vinylation with simple vinyl ethers or acetals. Unfortunately these methods fail with more complex systems and do not allow, except in the case of cyclic enol ethers, control of the stereochemistry of the substituted enol ether double bond. Until recently it was only possible to generate such substituted systems with appreciable stereocontrol *via* ketene *N,O*-acetals.[153,154] Their preparation by addition of allyl alcohols to substituted ynamines can lead to adducts of either (*E*)- or (Z)-geometry, depending upon the conditions used (Scheme 60).

The principally practicable route to allyl vinyl ethers by alkenation of allyl formates, has not yet been exploited in this context.[155] In another approach, the nucleophilic addition of allylic alcohols to alkynic esters, one observes the exclusive formation of *trans*-enol ethers;[156,157] the stereochemical information is lost, however, after the rearrangement, due to enolization of the formed formylacetic acid derivatives. On the other hand the nucleophilic addition of allyl alcohols to acceptor-substituted allenes like allenic sulfones or phosphonates offers a novel route with fascinating potential.[158–160] Such systems that are readily

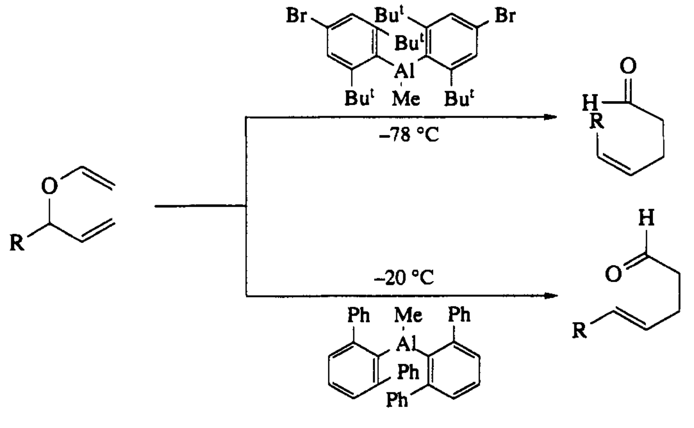

Br
Bu^t
Bu^t
Br
Al
Bu^t Me Bu^t
−78 °C
O
H
R
O
R
H
O
−20 °C
R
Ph Me Ph
Al
Ph
Ph

Scheme 59

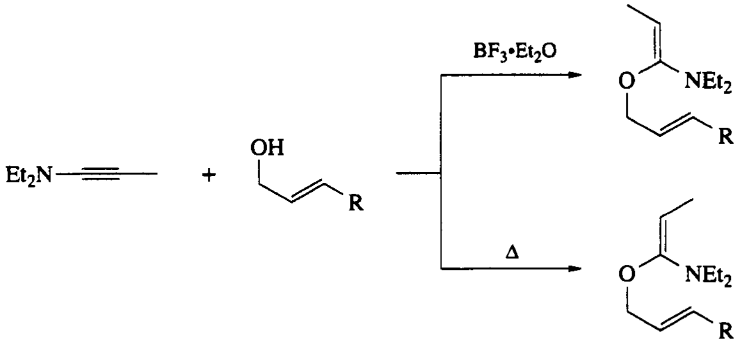

BF3•Et2O
O
NEt2
R
Et2N
+
OH
R
Δ
O
NEt2
R

Scheme 60

accessible *via* a 2,3-sigmatropic rearrangement, allow the easy synthesis of $\alpha,\beta$- or $\beta,\gamma$-unsaturated adducts, depending upon the substitution pattern of the allene and the reaction conditions (Scheme 61).

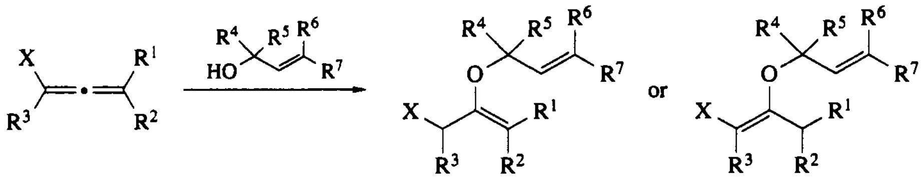

X
R1
R3
R2
R4
R5 R6
HO
R7
R4
R5 R6
O
R7
X
R1
R3 R2
or
R4
R5 R6
O
R7
X
R1
R3 R2

Scheme 61

In an extensive study Denmark could elaborate conditions to control the formation of the conjugated or the (in most cases thermodynamically more stable) deconjugated system.[159] With terminal monofunctionalized allenic sulfones one observes predominantly attack from the sterically less hindered face of the allene leading to *trans* adducts (equation 41).

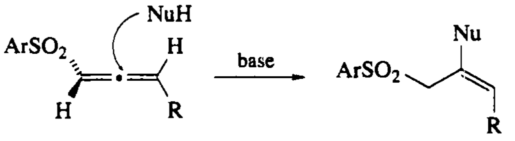

NuH
ArSO2
H
H
R
base
Nu
ArSO2
R

(41)

The adducts of the reaction of allyl alcohols with allenic sulfones are especially interesting as they allow the carbanion-accelerated Claisen rearrangement to take place. By deprotonation, or directly by addition of an allyl alcoholate anion, a system is generated, which rearranges much more easily than the uncharged system and with high diastereoselectivity (Scheme 62).

Even highly functionalized systems with vicinal quaternary centers can be prepared very readily.

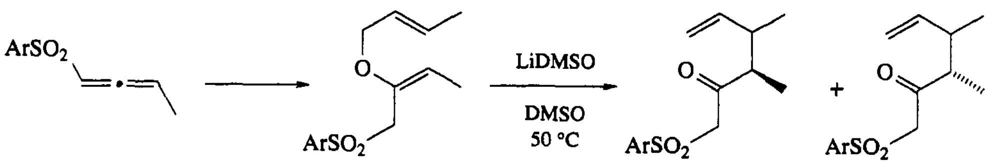

**Scheme 62**

A new perspective was opened up recently when Denmark demonstrated that with chirally modified phosphoryl-activated allenes an asymmetric induction could be effected.[160] From easily generated allenyl phosphoramidates containing an optically active amino alcohol, the diastereomeric adducts (**37**) and (**39**) could be obtained by addition of allyl alcohol. When the separated adducts were employed in the carbanionic Claisen rearrangement, a remarkable asymmetric induction (90:10) could be achieved with preferential formation of the diastereomers (**38**) or (**40**) respectively, whereas in a thermal reaction no stereoselection was observed (Scheme 63). Another example of an asymmetric induction in Claisen rearrangements is reported by Welch.[161]

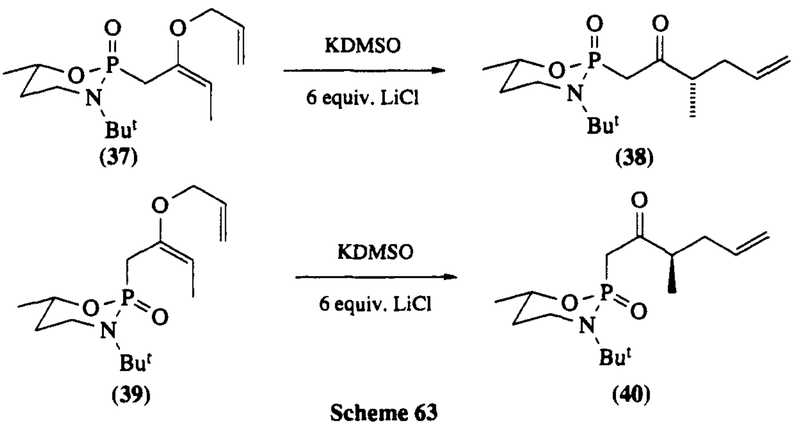

**Scheme 63**

From the different variants of the Claisen rearrangement the reaction of allyl ester enolates or the derived silylated ketene acetals has found the most widespread application. The apparent reason for this popularity is that the starting material is generated by a simple esterification and the rearrangement takes place under very mild conditions so that even difficult C—C bond formations can be effected after having joined two readily accessible partners together. The method proved the more attractive after Ireland had developed conditions to influence the geometry of the enolates, formed by a strong, non-nucleophilic base like LDA, by appropriate choice of the solvent so that a diastereoselective control of the rearrangement is possible: in THF the (*E*)-enolate is formed predominantly, whereas on adding HMPT the ratio of the isomers is practically reversed (Scheme 64).[162]

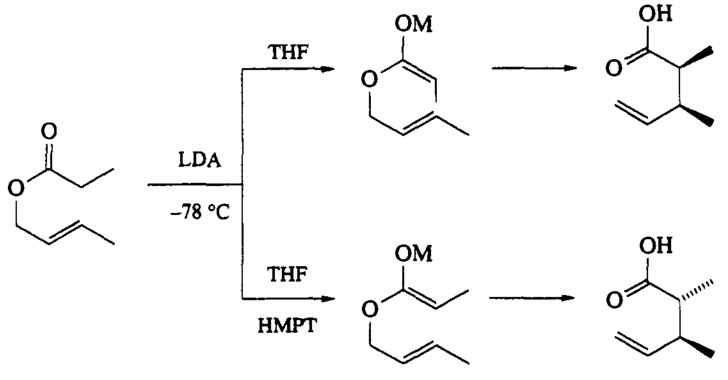

M = Li or SiMe$_3$

**Scheme 64**

To avoid complications with the reactive enolates and to preserve the stereochemistry it has proven practical to employ the derived silyl enol ethers, formed by trapping the enolates with chlorotrialkylsilane instead of the enolates themselves. The rearrangement of the silyl enol ethers takes place under mild conditions, too, often at room temperature, and exhibits all the characteristics of 3,3-sigmatropic rearrangements, namely high stereoselectivity in the formation of double bonds and stereocenters.

The potential of the ester enolate Claisen rearrangement for the stereocontrolled synthesis of highly functionalized, complex systems has been demonstrated in numerous applications in natural product synthesis. Utilizing the 1,3-chirality transfer Ireland has synthesized oxygen heterocycles with chiral side chains, such as are found as units in polyether antibiotics and macrolides, starting from enantiomerically pure furanoid or pyranoid glycal systems of type (**41**), which are easily accessible from carbohydrates (Scheme 65).[163–168]

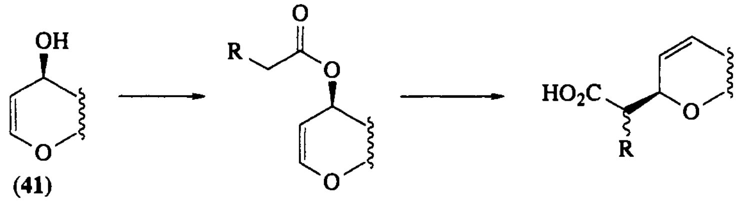

(**41**)

**Scheme 65**

Interesting possibilities arise when unsaturated lactones are employed in the enolate-Claisen rearrangement: either ring enlargements[169] or ring contractions[170] can be promoted (Scheme 66).

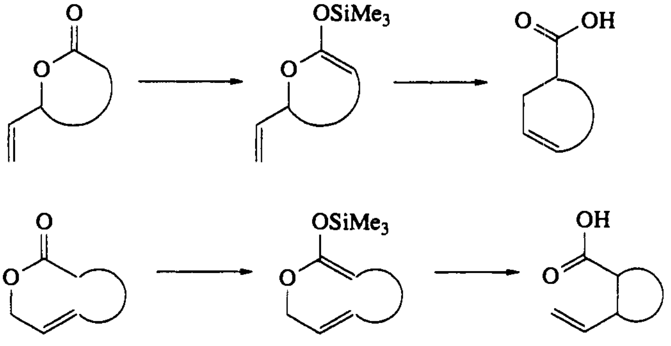

**Scheme 66**

Versatile procedures have been developped particularly for the latter sequence;[171,172] one illustrative example, leading to a simple synthesis of *cis*-chrysanthemum acid, is shown in Scheme 67.[173]

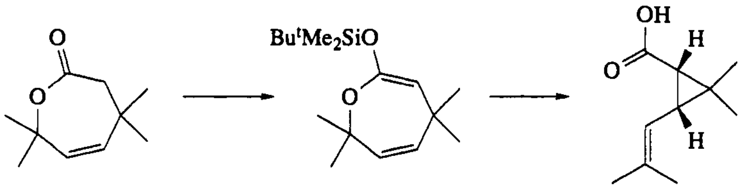

**Scheme 67**

The deliberate control of stereochemistry is the most fascinating aspect of the Ireland–Claisen rearrangement. Another possibility for influencing the geometry when forming the enolate emerges with allylic acetic acid esters containing substituents in the α-position, which are capable of chelating. A selective entry to the diastereomeric series becomes possible due to intramolecular coordination of the corresponding lithium enolates (Scheme 68).[174]

New prospects are opened up with glycolate ester derivatives having an incorporated stereogenic center outside the Claisen system which may cause asymmetric induction during the rearrangement, as can be seen in a recent example (Scheme 69).[175]

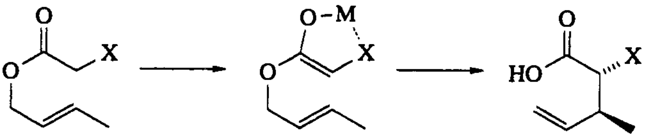

$X = O^-, OR, NR_2, CH_2C(O^-)HR$

**Scheme 68**

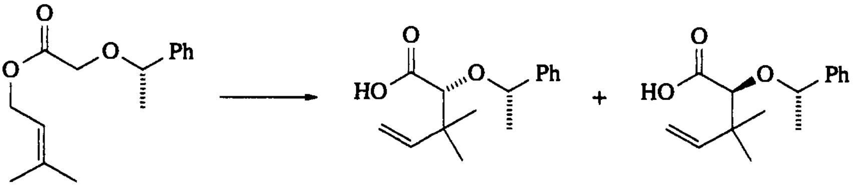

**Scheme 69**

Finally some selected examples will further demonstrate the synthetic versatility of the Claisen rearrangement when different functionalities in either the allyl or the vinyl part of the system are present (Scheme 70).[176–178] By appropriate choice of substituents in strategically important positions, systems can be built up which are suitable for further elaboration in a synthetic scheme.

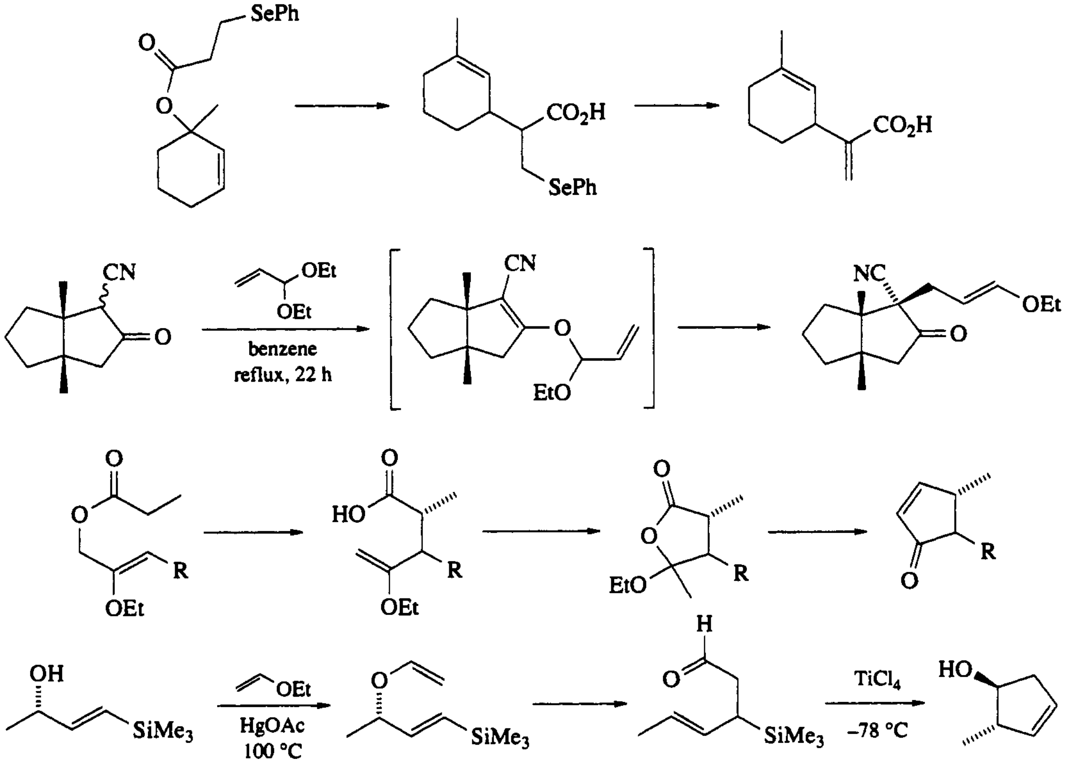

**Scheme 70**

Besides alkoxy groups in positions which allow the generation of 1,5- or 1,4-dicarbonyl compounds respectively, silicon substituents also offer many opportunities.[179]

A further aspect of the generality of Claisen-type rearrangements is that the oxygen atom can be replaced by nitrogen or sulfur, leading to the amino- or thio-Claisen[180] variants. They can also be viewed as hetero-Cope rearrangements, so that the amino-Claisen is also known as a 3-aza-Cope rearrangement (Scheme 71).

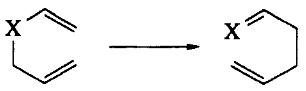

X = S, NR

Scheme 71

The aza-Cope rearrangement generally requires higher temperatures than the corresponding oxa analog, but quaternization or catalysis may allow milder conditions to be used.

The thio-Claisen rearrangement has its special value when the specific reactivity of a sulfur function, *e.g.* its carbanion-stabilizing effect or the high nucleophilicity of S, can be utilized, as in syntheses of $\gamma$-keto aldehydes (Scheme 72)[181] or thioamides (Scheme 73).[182]

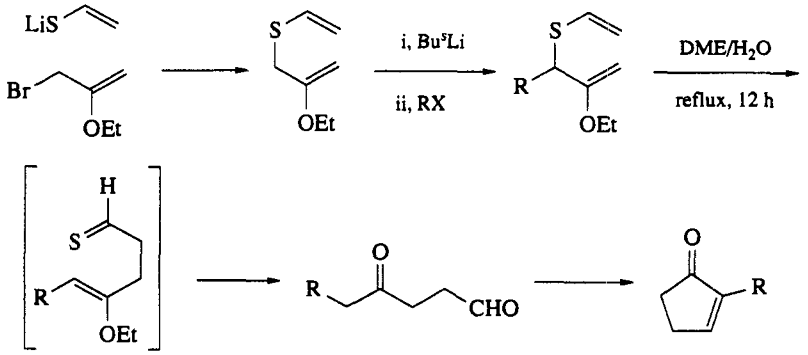

Scheme 72

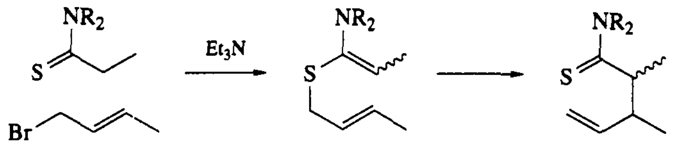

Scheme 73

Beside the simple allylic N → C transformation, which allows an allylation in the $\alpha$-position of aldehydes avoiding completely the problem of *O*- *versus C*-alkylation (Scheme 74),[183] the amino-Claisen rearrangement seems especially suited for effecting asymmetric induction by employing optically active amine systems.[184,185]

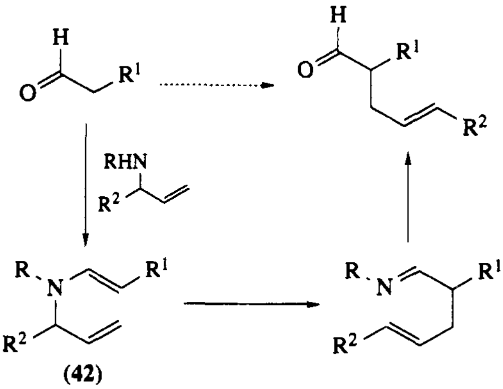

Scheme 74

With a chiral auxiliary in (**42**) such as 1-phenylethylamine (R = CHMePh), the diastereomeric excess in the reaction is low (*de* < 30%) and only improves somewhat when $TiCl_4$ catalysis is used to lower the temperature and simultaneous 1,4- and 1,5-asymmetric induction is attempted.[184] A more promising approach was found in the amino-Claisen rearrangement of *N*-allylketene *N,O*-acetals (**44**), which are easily derived from optically active oxazolines (**43**) by alkylation with tosylated allyl alcohols and subsequent deprotonation (Scheme 75).[185]

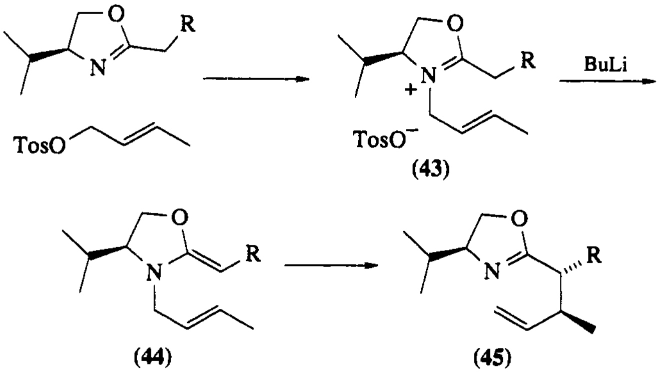

**Scheme 75**

Four diastereomeric rearranged oxazolines were obtained with (**45**) as the main product. Obviously, the relative diastereoselection, influenced by the stereogenic center, is acceptable, but the internal diastereoselection, which is controlled by the ketene *N,O*-acetal double bond in (**44**), could be better.

Finally it should be mentioned that most Claisen rearrangements are also possible with propargylvinyl systems leading to allenic derivatives, and very often providing efficient syntheses of functionalized allenes. From a stereochemical point of view such an approach is of special interest as it offers the opportunity of transferring chirality from a centrodissymmetric compound to an axial dissymmetric one. A rare application in synthesis is depicted in equation (42).[186]

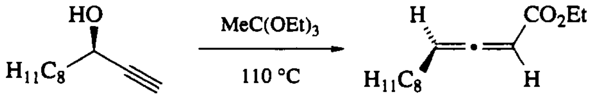

(42)

### 4.5.3.2 C—C Bond Formation with the Allyl System as the Nucleophile

There are two main synthetic applications where the reaction of an allyl system with electrophiles is accompanied by an allylic rearrangement. One consists of the use of heteroatom-substituted allylic anions as homoenolate anion equivalents and the other represents a synthetically valuable alternative to the aldol reaction by addition of allyl metal compounds to aldehydes.

#### *4.5.3.2.1 Heteroatom-substituted allylic anions as homoenolate anion equivalents*

Heteroatom-substituted allylic anions can serve as homoenolate anion equivalents in reaction with electrophiles, when γ-attack can be realized and the formed vinyl heterocompound can be hydrolyzed to an aldehyde (Scheme 76).[23,24]

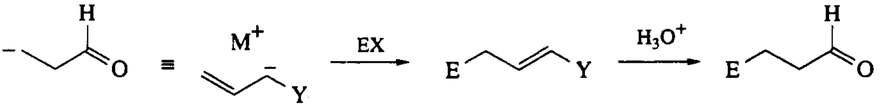

Y = $NR_2$, OR, SR, $SiR_3$, *etc.*

**Scheme 76**

The potential of homoenolate anions on reaction with different electrophiles (Scheme 77) is evident and explains why a great deal of effort has been expended to get high γ-selectivity in reactions of such allyl metal compounds.

Whereas with most alkylating agents the α,γ-selectivity is still a problem and one has often to rely on the more pronounced γ-selectivity of Cu and Ti derivatives, γ-selective addition is, however, normally observed with oxiranes, leading to 1,5-oxygen-substituted systems (**46**). A 1,4-relationship of oxygen

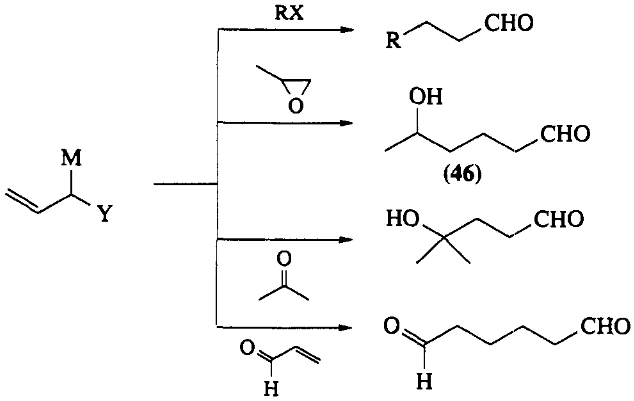

Scheme 77

functions is obtained on γ-selective addition to a carbonyl group, whereas conjugate addition to an α,β-unsaturated carbonyl compound leads to a 1,6-relationship. Conceptually it is interesting that the last arrangement also results when an α-selective 1,2-addition to an α,β-unsaturated carbonyl compound can be accomplished, since the product can be induced to undergo an oxy-Cope rearrangement. The idea has been realized by Evans who could bring about the addition of oxygen-substituted anions to acyclic and cyclic α,β-enones γ-regioselectively after their conversion to organo-zinc or -cadmium reagents (Scheme 78).

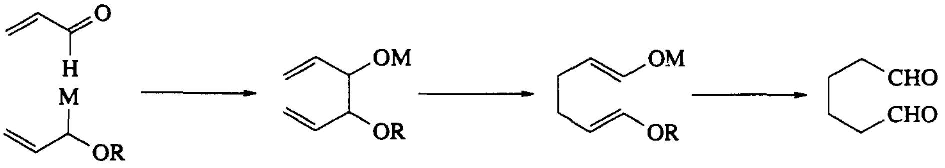

Scheme 78

The addition of heteroatom-substituted allylic anions to aldehydes has found particular interest as it represents a homoaldol reaction. Metalated allyl carbamates seem to be the most valuable reagents developed for this purpose as they are prepared easily and exhibit high γ-selectivity and diastereoselectivity, at best in their titanated form (Scheme 79).[187]

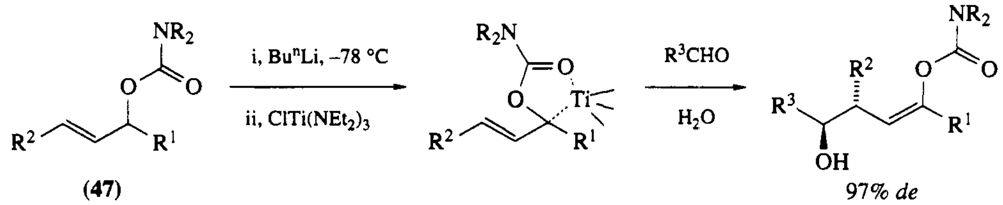

Scheme 79

It is especially remarkable that optically active homoaldol adducts can be obtained when enantiomerically pure 2-alkenyl carbamates (**47**; $R^1$ = alkyl) are employed.[188] Apparently the deprotonation occurs with retention of configuration and leads to configurationally stable lithium derivatives, which, after metal exchange with $Ti(OPr^i)_4$, again with retention, add to aldehydes with efficient 1,3-chirality transfer coupled with enantiofacial differentiation at the carbonyl group, indicating a rigid six-membered transition state. Recently even an asymmetric homoaldol reaction by enantioselective lithiation of prochiral primary alkenyl carbamates in the presence of (–)-sparteine was reported.[189]

Several other chiral homoenolate anion equivalents have been successfully exploited for asymmetric homoaldol reactions, *e.g.* (**48**) and (**49**),[190,191] but their preparation seems more laborious than that of the carbamates (**47**).

The 1,4-addition reaction of stabilized allylic carbanions with conjugated enones is normally complicated by the ambident reactivity of the carbanion. Clean γ-selective conjugate addition to cyclic enones, however, has been observed with lithiated allylic sulfoxides, phosphine oxides and phosphonates

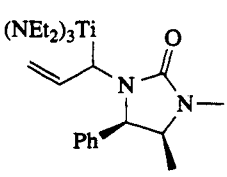

**(48)**

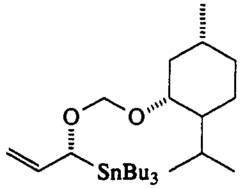

**(49)**

(Scheme 80).[192] The reactions exhibit high diastereoselectivity, probably due to a 10-membered *trans*-decalyl-like transition state, and with chiral allyl phosphonyl anions of type (**50**) even good asymmetric induction could be accomplished.[193]

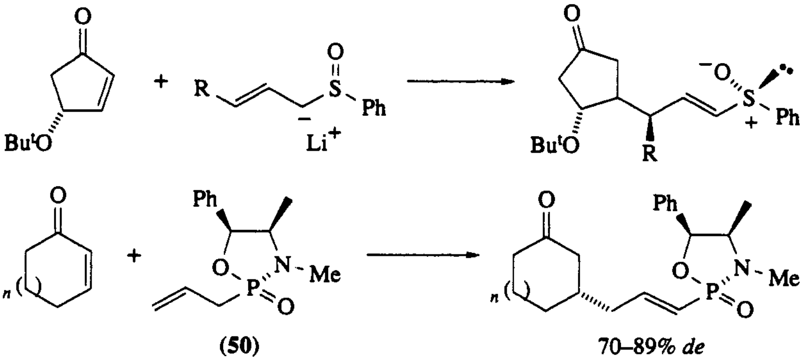

Scheme 80

### *4.5.3.2.2 Addition of allylmetal compounds to aldehydes: synthesis of homoallylic alcohols*

The allylation of aldehydes plays an important role in stereoselective synthesis since in one step several stereogenic centers can be generated and the resulting homoallylic alcohols can be oxidized to β-hydroxycarbonyl compounds, so that the overall process represents an indirect aldol reaction. By employing allyl metal compounds with M = Al, B, Si, Sn, Ti the addition occurs generally with allylic rearrangement under high diastereocontrol, leading to *anti* or *syn* products, respectively, depending upon the geometry of the double bond in the educt (Scheme 81).[194]

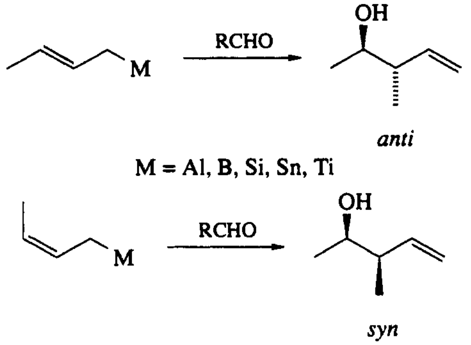

Scheme 81

With allyltin derivatives a change of the relative configurations at the newly formed stereogenic centers is observed when the reaction, which is rather slow without a catalyst, is performed in the presence of BF$_3$, apparently as a consequence of the now open transition state with BF$_3$ activation of the carbonyl group and the reaction not going *via* a cyclic, six-membered transition state as is usual.[13]

Allylboronates,[195,196] however, have attracted most interest, as they are easily prepared, stand out because of their high degree of chemoselectivity and, as it has turned out in several investigations, can be chirally modified to generate systems (**51**)–(**53**),[197–199] which allow highly enantioselective formation of homoallyl alcohols.

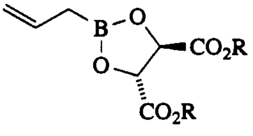

**(51)**

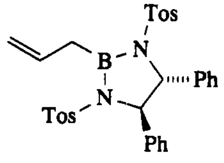

**(52)**

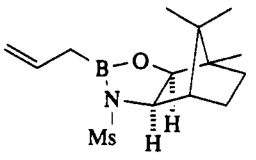

**(53)**

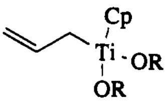

**(54)**

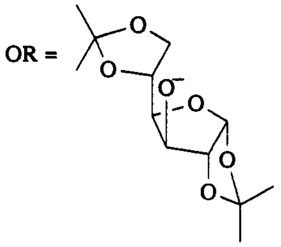

Allenylboronic acid, readily accessible from propargylic halides, on esterification with tartaric acid esters can also be induced to add to aldehydes with high enantioselectivity to give homopropargylic alcohols (Scheme 82).$^{200}$

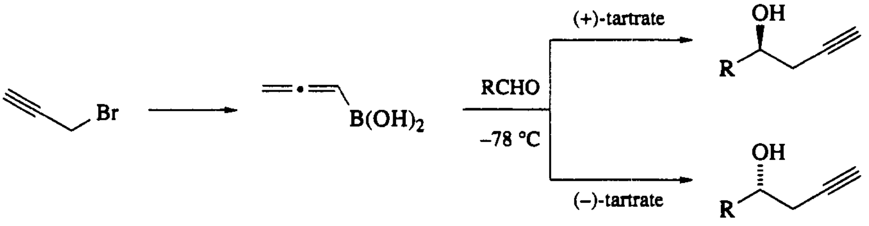

**Scheme 82**

Another promising asymmetric allylation of aldehydes, mediated by a D-glucose-derived titanium reagent (**54**), has recently been described.$^{201}$

## 4.5.4 1,3-HETEROATOM–HYDROGEN TRANSPOSITIONS

1,3-Heteroatom to hydrogen transpositions in allylic systems (equation 43) can be observed in different reactions, namely the protonation of allyl metal compounds, in reductions of allyl heterocompounds and in retro-ene reactions. Except for the last reaction, which proceeds by a cyclic transition state, the problem of regioselectivity restricts the synthetic value of such reactions and it is only in specific cases that this can be overcome.

Allylic or propargylic metal compounds are often intermediates in isomerization reactions of unsaturated systems (see Section 4.5.5); the product distribution on protonation depends very much on the substitution and the conditions of hydrolysis and most often mixtures of isomers are obtained. In contrast double bond shift generally occurs on protodesilylation of allylic silanes by acids, a reaction which takes place stereospecifically *anti*.$^{12}$ Only when intramolecular delivery of the proton in a chair-like transition state is possible may a different kind of stereoselectivity be effective and good 1,3- or 1,4-induction in hydrogen transfer be observed (Scheme 83).$^{202}$

Reductive removal of an allylic heteroatom functionality is a synthetically very useful operation if it can be effected in a regioselective manner. It seems generally easier to find conditions for reduction without a double bond shift than with clean allylic rearrangement. An exception is found in the reduction of allylic phosphonates with LiAlH$_4$,$^{95}$ most likely because of a preceding complexation of the reducing agent with the phosphoryl group and then an internal hydride transfer. Such a reactivity, where the hydride reagent is directed by a functionality in the molecule, is probably the rationale for most of the re-

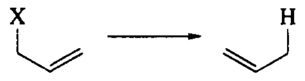

(43)

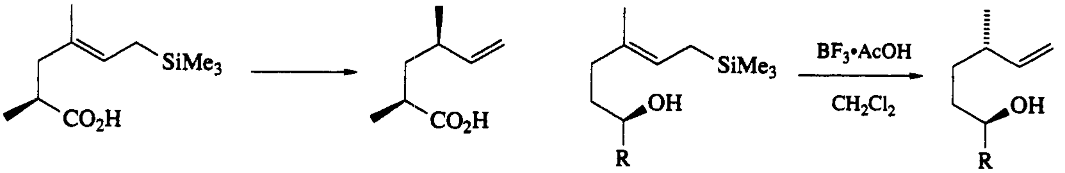

Scheme 83

ductions which proceed with allylic rearrangement. An example where an interesting chirality transfer results is seen in equation (44).[203]

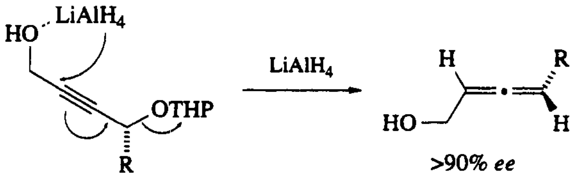

(44)

While in propargylic systems a vinylogous reduction is the normal reactivity, in allylic systems a double bond shift on reduction is realized more generally only when terminal alkenes are produced. Especially interesting in this respect is the Pd-catalyzed hydrogenolysis of allylic acetates (X = OAc) with ammonium formate (equation 45).[204]

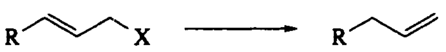

(45)

The removal of an allylic functionality is always accompanied by an allylic rearrangement when it proceeds by a retro-ene reaction. In most cases such a reaction requires high temperatures as in the thermolysis of allylic or, preparatively more useful, propargylic ethers (Scheme 84),[205] but allylic sulfinic acids undergo fragmentation slightly above room temperature[77,206] with the potential of high stereocontrol, as the example demonstrates (equation 46).[206]

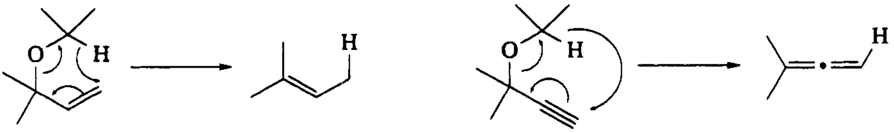

Scheme 84

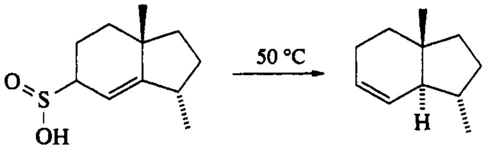

(46)

## 4.5.5 1,3-HYDROGEN-HYDROGEN TRANSPOSITIONS: ISOMERIZATION OF ALLYL AND PROPARGYL SYSTEMS

Prototopic rearrangements of allylic (equation 47) and propargylic systems sometimes provide useful synthetic transformations of unsaturated compounds; in such cases the regioselectivity presents no difficulties. Due to the easy and clean isomerization of allyl ethers to vinyl ethers with $(Ph_3P)_3RhCl$ or KOBu$^t$/DMSO an allyl ether can serve as a protecting group for a hydroxy function.[207] With chiral rhodium complexes such a migration of the double bond can even be brought about in an asymmetric manner, giving rise to chiral enamines (**56**) from allylamines (**55**; Scheme 85).[208]

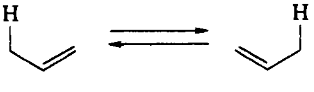

(47)

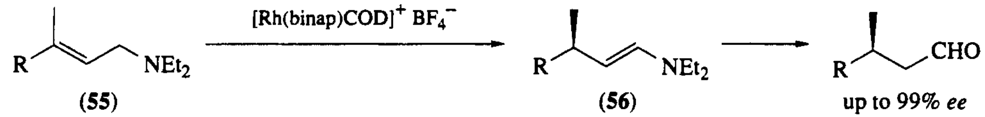

Scheme 85

The base-catalyzed isomerization of propargylic systems can in some cases be used for easy access to heterosubstituted allenes, *e.g.* for alkoxy-substituted allenes starting from the ether of a propargylic alcohol. The problem is that in many other systems an equilibrium exists where the isomerization does not stop at the allenic stage but also leads to the alkynic isomer (Scheme 86). There are relatively few examples where a 1,3-sigmatropic hydrogen shift leads to a synthetically useful isomerization. One example has been found in the thermal rearrangement of β-allenic esters to (2*E*,4*Z*)-dienoic esters over an alumina catalyst, in high yield, with 90–100% stereospecificity (equation 48).[209]

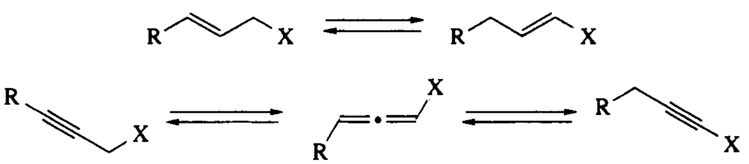

Scheme 86

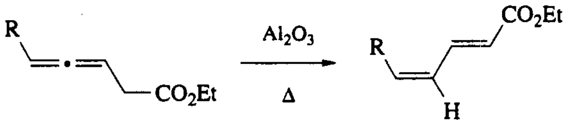

(48)

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# 4.6
# 2,3-Sigmatropic Rearrangements

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## 4.6.1 INTRODUCTION

'2,3-Sigmatropic rearrangement' is termed the 1,3-shift of an allylic atom pair —X—Y with a concomitant 1,2-shift of an electron pair from Y to X (Scheme 1). It is symmetry allowed as a concerted suprafacial process.

The substrate of a 2,3-sigmatropic rearrangement contains an allylic (**1a**), benzylic (**1b**), propargylic (**1c**) or allenylic (**1d**) C—X bond. It can be anionic (Y = $CR_2^-$) or neutral (*inter alia* **1** = ylide or carbene). The X-part of the migrating —X—Y atom pair must be a heteroatom since part of the driving force of a 2,3-sigmatropic rearrangement is provided by the better stabilization of the migrating electron pair on X *vs.* Y. This driving force is big enough to make 2,3-sigmatropic rearrangements irreversible, a noteworthy exception being the sulfoxide–sulfenate rearrangement —X—Y pairs which were rearranged successfully in this fashion are summarized elsewhere.[1–3]

2,3-Sigmatropic rearrangement is a method for the synthesis of functionalized alkenes, aromatics, allenes or alkynes. The C—X bond of the starting material (**1**) serves to introduce the C—Y bond into the molecular framework regioselectively and often stereoselectively. The newly formed C—X bond can be carbon–carbon or carbon–heteroatom. In the following, 2,3-rearrangements will be discussed in this order.

2,3-Rearrangements were reviewed with particular emphasis on their stereochemistry by Hoffmann[3] and Hill.[4] Individual treatments are available for the sulfoxide–sulfenate rearrangement,[5] sulfonium ylide rearrangement[6] and 2,3-Wittig rearrangement.[7] Some aspects of 2,3-shifts in selenium containing compounds are covered in ref. 8. A substrate-oriented discussion of the 2,3-Wittig rearrangement is Marshall's contribution in Volume 3, Chapter 3.11. Supplementary material on ylide rearrangements and allene synthesis *via* 2,3-sigmatropic rearrangements is contained in refs. 9 and 10, respectively.

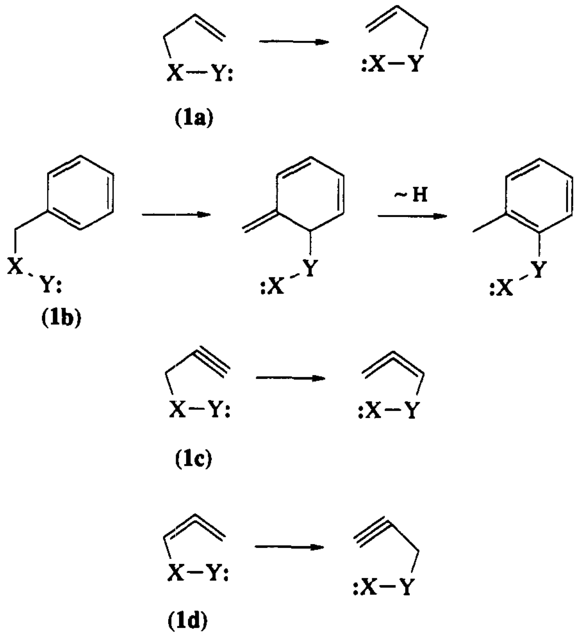
X—Y:
:X—Y
(1a)
X
Y:
(1b)
:X
Y
~H
:X
Y
X—Y:
:X—Y
(1c)
X—Y:
:X—Y
(1d)

Scheme 1 2,3-Sigmatropic rearrangements

## 4.6.2 FORMATION OF CARBON–CARBON BONDS

### 4.6.2.1 Rearrangement of Ethers

2,3-Sigmatropic rearrangements of ethers are usually performed as Wittig rearrangements of metalated ethers. Usually, the substrate is allylic (**2**). Only a few examples are known for propargylic ethers (**3**; equation 1). The 2,3-Wittig rearrangement of allylic ethers is increasingly used in synthetic work. A remarkable application is Marshall's synthesis of the cerembrolide precursor (**5**; equation 2).[11,12]

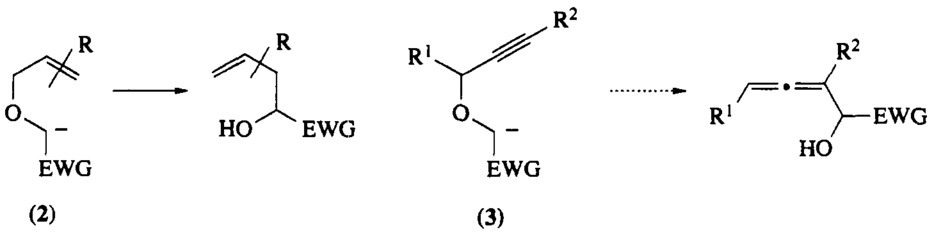
R
O
EWG
(2)
R
HO
EWG
R$^2$
R$^1$
O
EWG
(3)
R$^2$
R$^1$
EWG
HO

(1)

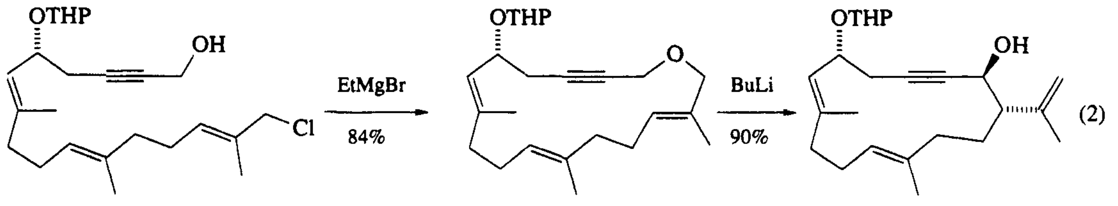
OTHP
OH
Cl
EtMgBr
84%
OTHP
O
BuLi
90%
OTHP
OH

(2)

(**4**) (**5**) 81% + 19% isomers

Rearrangements *via* oxonium ylides are scarce.[9c,13,14] Nonetheless, interesting structures were prepared from ylides like (**6**; equation 3)[15] or (**7**; equation 4).[16] The potential of ylide rearrangement methodology in the context of total synthesis is unexplored, but interesting target molecules are already identified.[16]

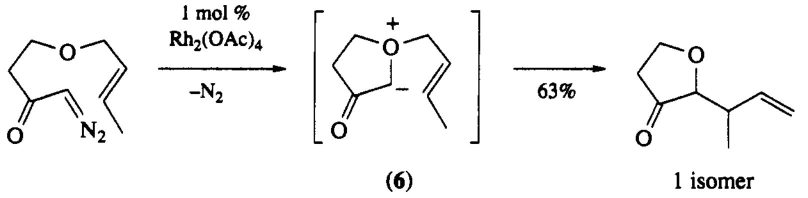

(6)

(3)

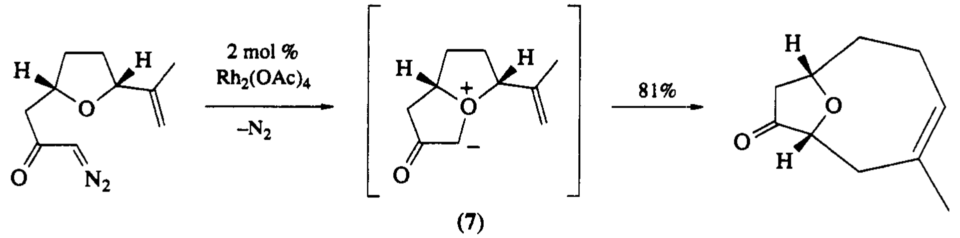

(7)

(4)

The transition state of the 2,3-Wittig rearrangement is visualized as envelope (**8**) by Nakai[7] or envelope (**9**) by Midland.[17] Small sets of experimental results were interpreted successfully with these pictures. However, (**8**) and (**9**) fail to accommodate the whole set of data. A modified transition state (**10**) is therefore suggested. In (**10**), the lone pair attacks the C=C bond from the rear. This direction of approach circumvents an antibonding interaction with the orbital on the nonattacked $sp^2$-center. A second modification concerns the geometry of the carbanion moiety of the rearranging species; unless it is integrated in an enolate or an azaenolate (where planarity is assumed; *vide infra*), it should be pyramidal as shown. Finally, pyramidalization of the double bond is expected in the transition state due to the beginning rehybridization from $sp^2$ to $sp^3$. Indeed, a transition state structure very similar to (**10**) was found by means of MM2/STO-3G calculations starting from lithio allyl methyl ether;[18] computationally, however, the ensuing reaction was not a 2,3-shift.

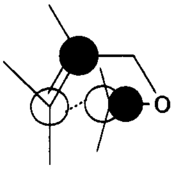

(**8**) Nakai

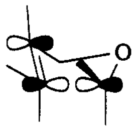

(**9**) Midland

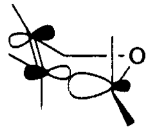

(**10**) Modified

### 4.6.2.1.1 (E)/(Z)-Selectivity

Disubstituted alkenes with a *trans* double bond can be generated routinely from Wittig rearrangements; in the case of ester enolate Wittig rearrangements, *cis* selectivity can be achieved. For trisubstituted alkenes, (*E*)- and (*Z*)-selective syntheses are known.

The Still–Wittig rearrangement of stannylated *cis*-ethers (**11**) gives *trans* homoallylic alcohols (**12**) selectively (equation 5).[19] If the underlying alcohols ($R^2$ = Me) are rearranged under Büchi's conditions (DMF acetal, xylene, reflux), *trans* selectivity is achieved, too, but yields are lower (41–49%).[23]

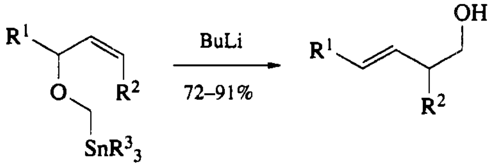

(**11**) (**12**)

(5)

The Büchi rearrangement is stereochemically superior to the Still–Wittig rearrangement when one elaborates secondary allylic alcohols (**13**) with or without a *trans* alkenic substituent. In these cases, the Büchi rearrangement gives preponderantly or exclusively *trans* product (equation 6).[23,24] The corresponding Still–Wittig rearrangements of (**14**; $R^2$ = H, Me) give alcohols as *cis*/*trans* mixtures (equation

7).[19,21] Alkenic stereoselection in the Still–Wittig rearrangement results presumably from conformational control in a very early transition state (Scheme 2).[19] There, the substituent $R^\alpha$ prefers equatorial (**15**) over axial (**16**) orientation, if the 1,2-allylic strain is smaller than the 1,3-allylic strain, and *vice versa*.[25] This implies *trans* products in the former (*vide supra*) and (*Z*)-products in the latter case (*vide infra*).

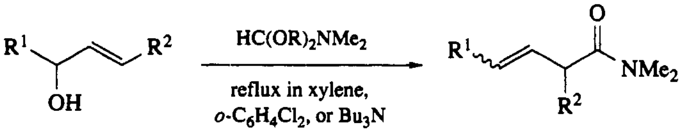

R1
R2
OH
HC(OR)2NMe2
reflux in xylene,
o-C6H4Cl2, or Bu3N
66–76%
R1
O
NMe2
R2

(**13**) 87–100% *trans* (6)

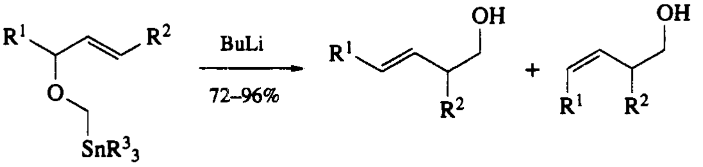

R1
R2
O
SnR33
BuLi
72–96%
R1
OH
R2
+
OH
R1
R2

(**14**) 35–53% : 65–47% (7)

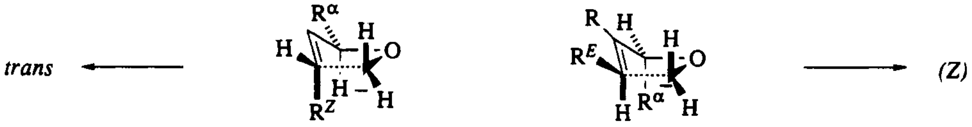

trans
Rα
H
H
O
H
RZ
H
R
H
RE
H
O
H
Rα
H
(Z)

(**15**) no 1,3 allyl strain (**16**) no 1,2 allyl strain

**Scheme 2** *Cis*/*trans* selectivity of the Still–Wittig rearrangement

Secondary anions amenable to 2,3-Wittig rearrangements contain a stabilizing electron-withdrawing group (EWG). The EWG can be 'hydrocarbon' (vinyl, alkynyl, aryl) or 'acyl' (acid, ester, amide, imido ester). Ethers (**17**) with EWG = hydrocarbon furnish homoallylic alcohols (**18**) containing one new stereocenter with 93–100% *trans* selectivity (equation 8).[26–30] If similar homoallylic alcohols with two new stereocenters are required, *trans* selective access along with 91–99% *syn* diastereoselection is straightforward starting from *cis* ethers (**19**; equation 9).[17,31–35]

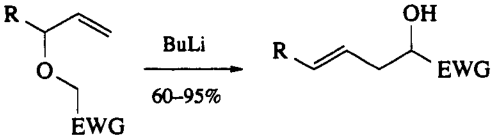

R
O
EWG
BuLi
60–95%
R
OH
EWG

(**17**) (**18**) 93–100% *trans* (8)

EWG = $H_2C{=}CH$, $H_2C{=}CMe$, Ph, 9-fluorenyl, $HC{\equiv}C$, $MeC{\equiv}C$, $Me_3SiC{\equiv}C$

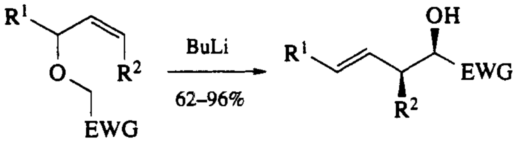

R1
O
R2
EWG
BuLi
62–96%
R1
OH
EWG
R2

*cis*-(**19**) 91–99% *syn* >98% *trans* (9)

EWG = $H_2C{=}CH$, $H_2C{=}CMe$, Ph, $HC{\equiv}C$, $MeC{\equiv}C$, $Me_3SiC{\equiv}C$

*Trans* configuration in the homoallylic alcohol with concomitant *anti* diastereoselectivity is observed starting from the *trans* ethers (**20**; equation 10) (Table 1). The comparatively low simple diastereoselectivity of these reactions (60–91%) reflects the general difficulty in obtaining *anti* products from 2,3-Wittig rearrangements (*cf.* Section 4.6.2.1.2).

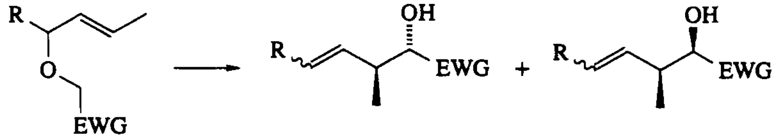

**(20)** *trans* **(21)** *anti* **(22)** *syn* (10)

**Table 1** *Trans* Selective Formation of Homoallylic Alcohols With *Anti* Configuration[a]

| *EWG* | *R* | *Yield (%)* | *Trans (%)* | *Anti (%)* | *Ref.* |
|---|---|---|---|---|---|
| $H_2C{=}CH$— | Pr$^i$ | 75 | 100 | 60 | 17 |
| Ph— | Pr$^i$ | 95 | 82 | 76 | 17 |
| $HC{\equiv}C$— | Me/Pr$^i$ | 62/63 | 100/92 | 91/89 | 31/17 |

[a] See equation (10).

Acids (**23**) give unsaturated hydroxy acids (**24**) with more than 95% *trans* selectivity *via* their dianions (equation 11).[36] Under Nakai's oxonium ylide rearrangement conditions,[14] acid (**23**; R = Me) preferred the *cis* product although only slightly (57:43 ratio). The methyl ester derived from the same acid showed little, albeit complementary, *cis:trans* selectivity when rearranged *via* its tetrabutylammonium enolate[37] (22:78) and an oxonium ylide[14] (69:31). It is unknown, how this ester rearranges as a lithium enolate, but the stereorandom reaction of an isopropyl ester upon treatment with LDA discourages the expectation of selectivity.[38] However, by adding complexes $MCp_2Cl_2$ of tetravalent transition metals (Ti, Zr, Hf) to the lithio enolates of isopropyl esters (**25**) at −100 °C and warming up subsequently, Katsuki attained an astonishing level of 93–99% *cis* selectivity (equation 12).[38,39] In addition, these reactions are highly *syn* selective.

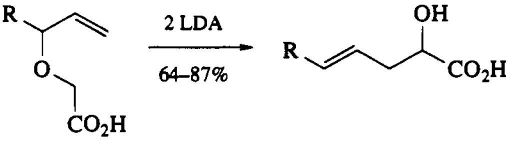

(11)

**(23)** **(24)** >95% *trans*

R = Me, n-$C_5H_{11}$, n-$C_7H_{15}$

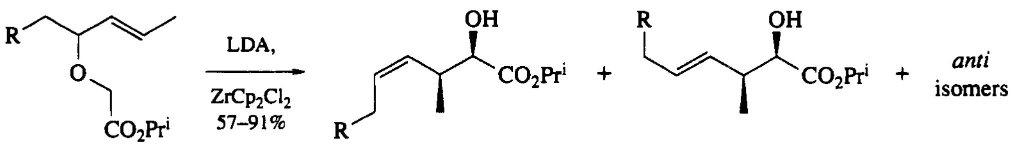

(12)

**(25)** **(26)** *syn*, *cis* 93–99 : **(27)** 0–4 : **(28)** 0–3

R = H, n-$C_7H_{15}$, $BnOCH_2$, $BnOCH_2CH_2$, PhS

Ti, Zr and Hf enolates do not react *via* a transition state (**29**) akin to the (**70**) proposed later for enolates with lithium as a small counterion. With its large counterion, (**29**) would exhibit a destabilizing interaction between the voluminous cyclopentadienyl ligands and the substituent $R^\alpha$. No such interaction occurs in the preferred transition state (**30**). (**30**) precedes *cis*-alkenes (**31**) with *syn* configuration (Scheme 3).

The side chain of Katsuki's esters (**25**) turned out less innocent in these rearrangements than its location 'outside of the cyclic transition state' suggests. In fact, an appropriately placed oxygen atom in the side chain of such esters (**32**; equation 13) can steer the double bond geometry of the reaction product. Compare, for example, the stereochemically complementary results reported for ester (**25**; side chain = *n*-heptyl)[38] and (**32a**; side chain = $BnOCH_2$).[39] With $ZrCp_2Cl_2$ as additive, the first reaction is 99% *cis*

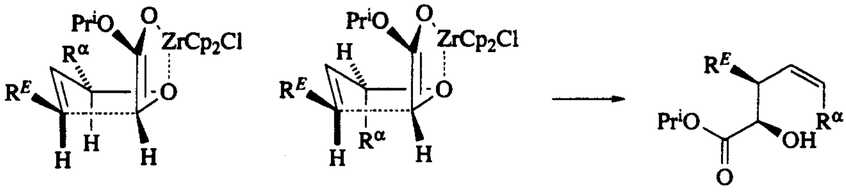

**(29)** **(30)** **(31)** *cis, syn*

**Scheme 3** Transition states rationalizing *cis* and *syn* selectivity of Wittig rearrangements with EWG = acyl (large counterion)

selective, while the second furnished a 3:2 mixture of *trans* and *cis* isomers. For all of the oxygenated esters (**32**), the geometry of the newly formed double bond could be varied from preferentially *cis* to preferentially *trans* (Table 2).[39] Notice that part of the stereocontrol stems from tuning the size and the acidity of the metal core in the added $MCp_2Cl_2$ (Ti → Zr → Hf).

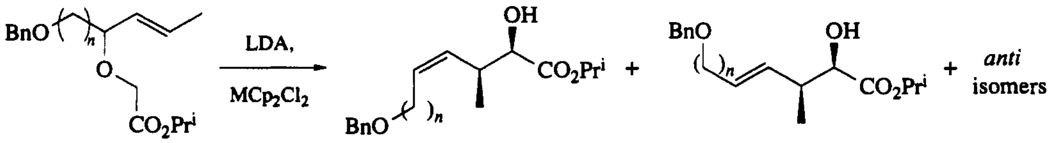

(13)

**(32)** **(33)** *syn, cis* **(34)** *syn, trans* **(35)**

**Table 2** Counterion Effects on the *cis/trans* Selectivity of Ester Enolate Wittig Rearrangements[a]

| *(32)* | *n* | *M* | *Yield (%)* | *(33):(34):(35)* |
|---|---|---|---|---|
| (a) | 1 | Ti | 72 | 2:96:2 |
| | | Zr | 53 | 40:60:0 |
| (b) | 2 | Ti | 31 | 16:65:19 |
| | | Zr | 62 | 96:2:2 |
| (c) | 3 | Ti | 37 | 21:43:36 |
| | | Zr | 57 | 94:4:2 |

[a] See equation (13).

The Zr enolate of ester (**25**; R = H) should rearrange *via* transition state (**37**) where methyl as the side chain points downward. This follows from the discussion of Scheme 3 (*vide supra*). In contrast, the side chain $BnOCH_2$ of ester (**32a**) is located on the upper face of transition state (**38**). There, its oxygen atom is complexed by the metal. One stereochemical consequence is the *trans* configuration in the rearrangement product. The other consequence is opposite absolute configurations at the newly formed stereocenters in *trans*-(**39**) *vs*. *cis*-(**36**). This aspect will be emphasized later (*vide infra*).

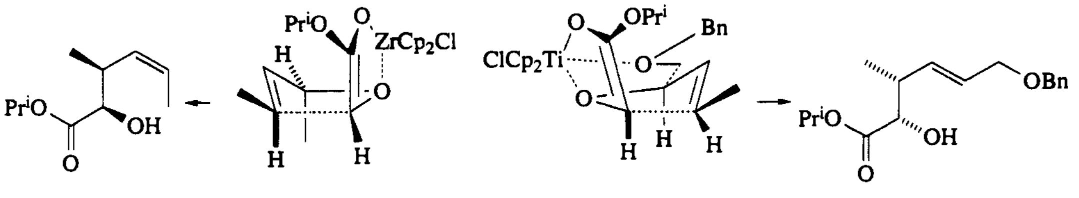

**(36)** *cis*, (2*R*) **(37)** **(38)** **(39)** *trans*, (2*S*)

**Scheme 4** Transition states rationalizing the *cis* and *trans* dichotomy of Katsuki's Wittig rearrangements

Another example of remote control of *cis/trans* selectivity was provided by Kallmerten.[40] He studied Wittig rearrangements of the tertiary oxazolinyl ethers (**40**; equation 14) (Table 3).[40] By changing (off the pericyclic transition state) a methyl group into MOMO the previous 72:28 (*Z*)-selectivity was completely inverted into >100:1 (*E*)-selectivity. Remarkably, the MOMO effect depends heavily on which of the diastereomers is used: **(41b)** gave a nearly balanced ratio of (*E*)- and (*Z*)-isomers (64:36), which falls far behind the perfect (*E*)-selectivity displayed by the epimer **(41c)**.

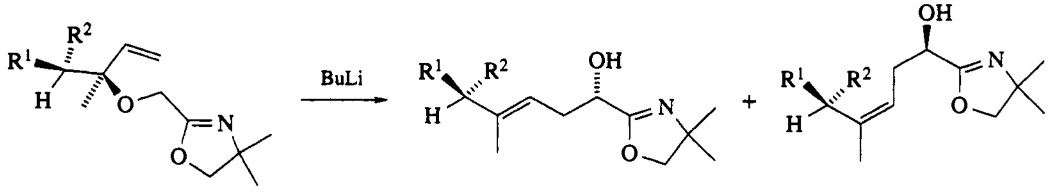

(14)

**(40)** **(41)** *(E)* **(42)** *(Z)*

**Table 3** Remote Control of the (*E*)/(*Z*) Selectivity in the 2,3-Wittig Rearrangements of Oxazolinyl Anions[a]

| *(40)* | *R*$^1$ | *R*$^2$ | *Yield (%)* | *(E):(Z)* |
|---|---|---|---|---|
| (a) | Me | Me | — | 28:72 |
| (b) | Me | MOMO | 95 | 64:36 |
| (c) | MOMO | Me | 82 | >100:<1 |

[a] See equation (14).

Wittig rearrangements other than those just mentioned or Büchi rearrangements do not necessarily lead to stereochemically pure triply substituted alkenes (Scheme 5). However, with appropriate substrates, (*E*)- and (*Z*)-selectivity can be realized. The most noteworthy among these stereoselective transformations is the (*Z*)-selective Still–Wittig rearrangement.[19] The homoallylic alcohol **(46)**, for example, gave **(47)** as a 96.5:3.5 mixture of (*Z*)- and (*E*)-isomers (equation 15).[42] Conveniently, the formation of the $Bu_3SnCH_2$ ether and the subsequent rearrangement can be performed in a one-pot operation;[19] for similar applications see ref. 43.

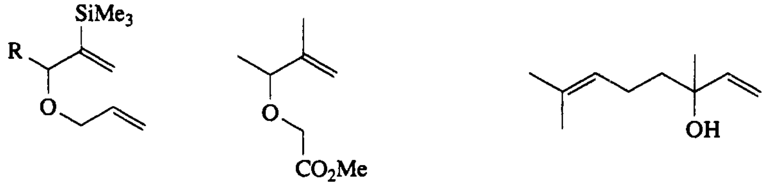

**(43)** → *(E):(Z)*

R = Me, 36:64
R = n-$C_5H_{11}$, 33:67

**(44)** → *(E):(Z)* = 31:69

**(45)** → isomeric ratio = 58:42

**Scheme 5** Substrates of nonstereoselective Wittig (**43**[41,27] and **44**[14]) or Buchi (**45**)[24] rearrangements

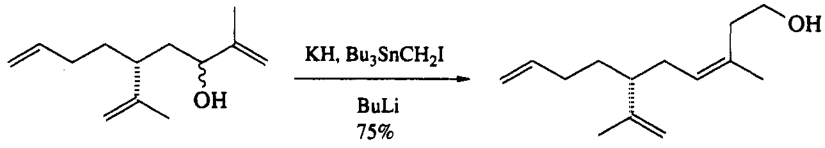

(15)

**(46)** **(47)** *(Z):(E)* = 96.5:3.5

Unequalled in elegance is the double Still–Wittig rearrangement of **(48)**, which gave the bis-(*Z,Z*)-homoallylic alcohol **(49)** in 95% isomeric purity (equation 16).[44] (*Z*)-Selectivity has also been noted for the Wittig rearrangement of an acid dianion (equation 17).[36]

The transformation **(50)** → **(51)** includes a 2,3-rearrangement (Scheme 6).[45] It exhibits (*E*)-selectivity and allows incorporation of a nucleophile *in situ*. The nucleophile can be adjusted to the synthetic demands. Upon reduction of the aldehyde intermediate **(53)**, a primary homoallylic alcohol **(54)** should be formed. This would constitute the (*E*)-selective complement of Still's (*Z*)-selective synthesis[24] (*vide supra*).

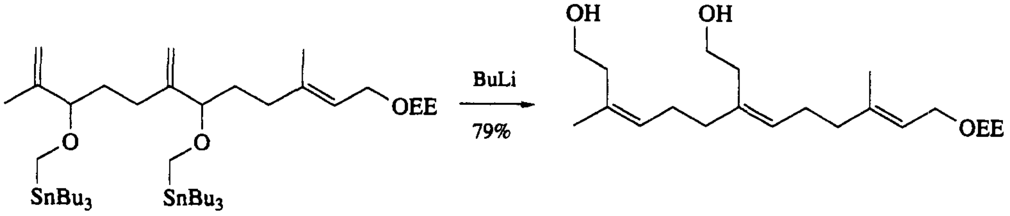

(16)

**(48)** **(49)** >95% *(Z, Z, E)*

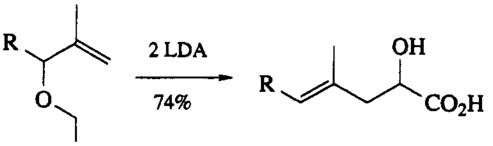

(17)

R = n-$C_5H_{11}$, >95% *(E)*

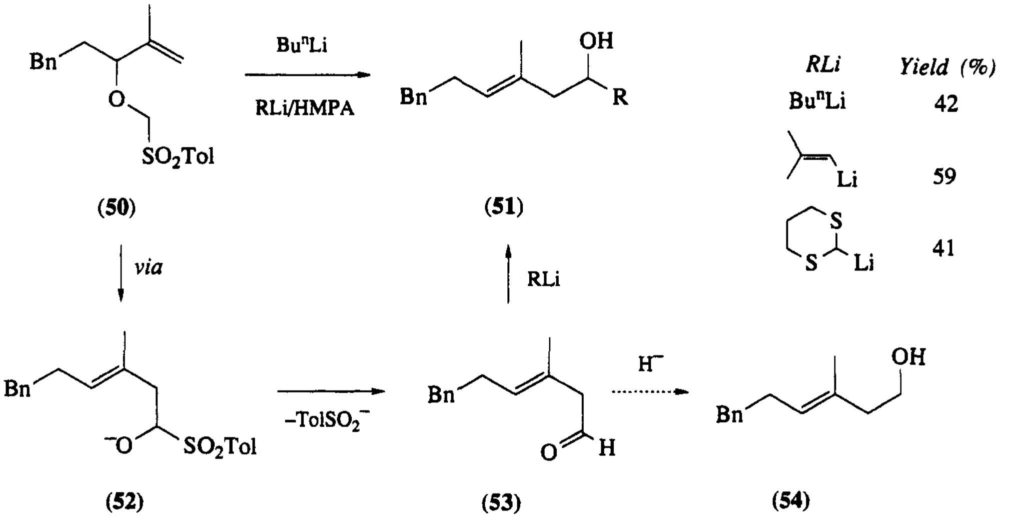

**Scheme 6**

Silicon-containing substrates acquired some merit in the stereoselective synthesis of alkenes *via* 2,3-rearrangements (Scheme 7). Starting from the terminally silylated ether (**55**), one (*Z*)-bond is generated by the Wittig rearrangement; a second (*Z*)-bond is introduced by an ensuing Peterson elimination.[46] Pattenden presented a potentially generally applicable concept: by desilylation, he 'translated' the (*E*)-selective rearrangement of the internally silylated ether (**57**) into the (*Z*)-configuration of (**58**).[27]

### *4.6.2.1.2 Diastereocontrol*

Nakai, Midland, Katsuki and others have studied *syn/anti* selective 2,3-Wittig rearrangements extensively. It is not yet possible to unambiguously explain all results, but a number of stereochemically useful transformations have emerged. The simple diastereoselectivity of 2,3-Wittig rearrangements of ethers (Scheme 8) with EWG = hydrocarbon (Table 4) can be summarized as follows: (i) *cis/trans* isomeric ethers give epimeric products; (ii) *cis*-ethers react more selectively than their *trans* isomers; (iii) *cis*-derived diastereoselectivities are hardly affected by structural variation of the starting material, while they are affected profoundly in the *trans* series; (iv) *cis*-ethers give homoallylic alcohols with *syn* configuration and, if possible, a *trans* C=C bond. Products are at least 90%, often 95% and occasionally 100% isomerically pure (exception: 72% *syn* in entry 5); and (v) *trans*-ethers lead usually to the *anti* diastereomer (exceptions: entries 6, 13 and 15). 90% selectivity is rare (entries 9 and 11) and if occasionally

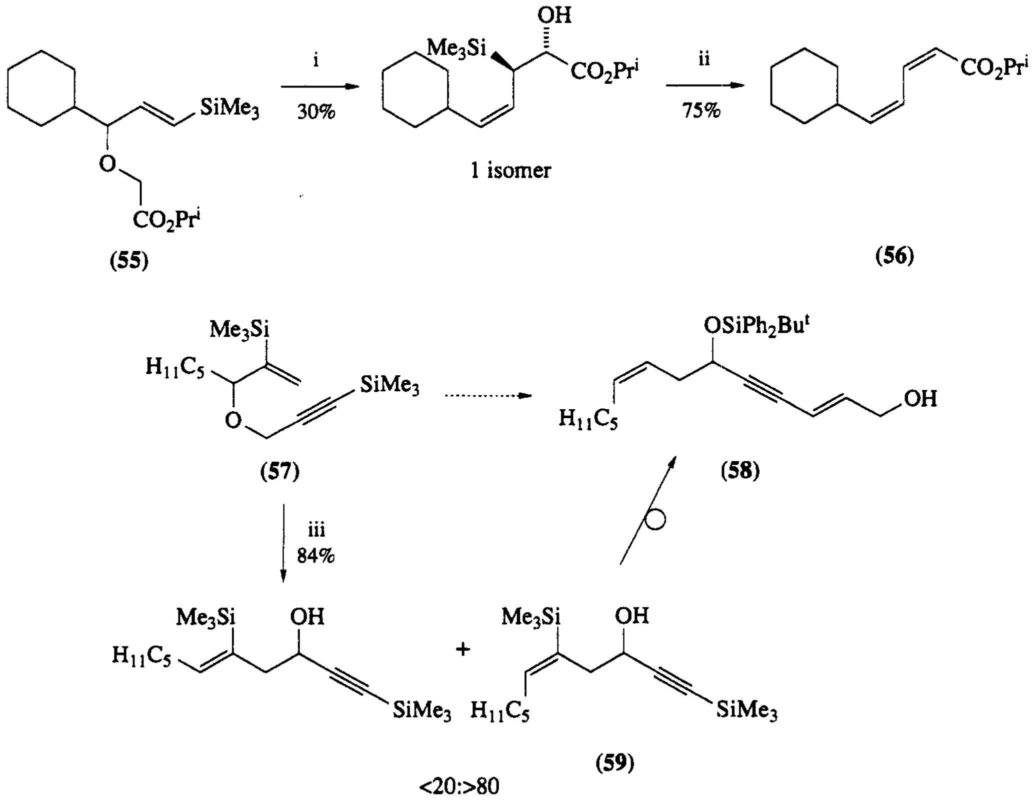

i, LDA, $ZrCp_2Cl_2$ (method: equation 12); ii, $BF_3{\bullet}OEt_2$; iii, BuLi (*cf.* **43**; Scheme 5)

**Scheme 7** Silicon assistance in stereoselective alkene synthesis *via* 2,3-Wittig rearrangements

encountered (EWG = substituted alkynyl) not so in general: compare the 1:99 *syn*:*anti* ratio of entry 11 with the reversed 73:27 ratio of entry 13.

These diastereoselectivities can be rationalized by transition state (**64**; Scheme 9). A pyramidal configuration of the anionic center is assumed (*cf.* nonplanarity of a benzylic[50] or an allylic anion[51]). This leaves more space for an equatorial substituent EWG (**64**) than for an axial EWG (**65**). The resulting product structure (**63**) agrees well with the general trends of Table 4. The finer issue — why (**64**) is preferred over (**65**) in the case of (*Z*) *vs.* (*E*)-alkenes — remains unexplained.

*Syn*/*anti* selectivities of 2,3-Wittig rearrangements of ethers (Scheme 10) with EWG = acyl are compiled in Table 5. Oxonium ylide rearrangements are included (entries 2 and 7). The following observations can be made: (i) (*Z*)-ethers give useless *syn*/*anti* mixtures (exception: entry 4); (ii) (*E*)-ethers give *syn* products with selectivities between close to 90% and 100%; and (iii) branching of the vinylic substituent was probed in entry 4 (EWG = $CO_2R$). When compared to the ester enolate rearrangements of entries 3 and 5 with linear alkyl groups as vinylic substituents, the proportion of *anti* product is dramatically increased. In fact, the rearrangement product obtained from the (*Z*)-ether is exclusively *anti*. To branch the vinylic substituent might be a worthwhile consideration in other cases, too, when a homoallylic alcohol with *anti* stereochemistry is required.

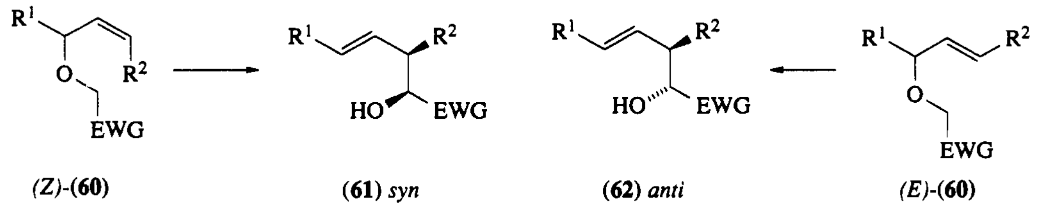

**Scheme 8**

**Table 4** Wittig Rearrangements of (*E*)/(*Z*) Isomeric Ethers with EWG = Hydrocarbon[a,b]

| *Entry* | *EWG* | *$R^1$* | *$R^2$* | *From (Z)-(60)* *Yield (%)* | *From (Z)-(60)* *Syn (%)* | *From (E)-(60)* *Yield (%)* | *From (E)-(60)* *Anti (%)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | $H_2C{=}CH$— | H | Me | 88 | 92 | 81 | 84 | 26 |
| 2 | | $Pr^i$ | Me | 84 | 92 | 75 | 60 | 17 |
| 3 | $H_2C{=}CMe$— | H | Me | 71 | 95 | 70 | 72 | 26 |
| 4 | | $Pr^i$ | Me | 93 | 93 | 89 | 56[c] | 17 |
| 5 | $PhCH{=}CH$— | H | Me | 70–98 | 72 | 70–98 | 76 | 47 |
| 6 | Ph | H | Me | 70–98 | 95 | 70–98 | 39 | 47 |
| 7 | | $Pr^i$ | Me | 89 | 93 | 95 | 76[d] | 17 |
| 8 | $MeOC_6H_4$— | H | Me | 70–98 | 100 | 70–98 | 60 | 47 |
| 9 | $HC{\equiv}C$— | H | Me | 56 | 90 | 72 | 99 | 31 |
| 10 | | $Pr^i$ | Me | 89 | 91 | 63 | 89[e] | 17 |
| 11 | $MeC{\equiv}C$— | H | Me | 55 | 100 | 65 | 99 | 31 |
| 12 | | H | f | 62 | 98 | 73 | 77 | 48 |
| 13 | $Me_3SiC{\equiv}C$— | H | Me | 74 | 100 | 72 | 27 | 31 |
| 14 | | H | f | 77–87 | 100 | 84–86 | 85–87 | 48,49 |
| 15 | | H | g | 77 | 99 | 93 | 41 | 48 |
| 16 | | $Pr^i$ | h | >85 | >98 | — | — | 33 |

[a] See Scheme 8. [b] In this and the following tables, *syn/anti* ratios are given for starting materials of 100% geometrical purity wherever possible; these ratios are either experimental or calculated from data referring to less than 100% sterically pure allylic ethers.[c–e] In addition, 11, 22 and 9 rel-% of (*Z*)-isomer(s) with unassigned configuration(s) were found.[f] $R^2$ = 2,2-Dimethyl-1,3-dioxolan-4-yl.[g] $R^2$ = TBDMSO—CHMe—.[h] $R^2$ = TBDMSO—$CH_2$—.

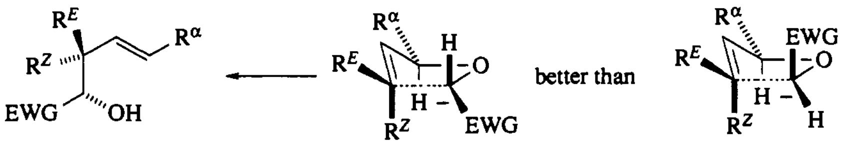

**(63)** **(64)** **(65)**

**Scheme 9** Transition states rationalizing *syn*/*anti* selectivities of Wittig rearrangements with EWG = hydrocarbon

The 'metalated ethers' with EWG = acyl are simply enolates and azaenolates. These allow for intramolecular bridging *via* the $Li^+$ cation (Scheme 11). Agreement with the experiments would be attained if such bridging was favored on the *endo* face of the five-membered transition state (**70**). Indeed, the atom H-2 in the enolate is less sterically hindered in *endo*-(**70**) *vs.* *exo*-(**71**). In (**70**), the H-2 is directed towards a small hydrogen atom, while it would be confronted with the larger alkyl group $R^E$ in (**71**).

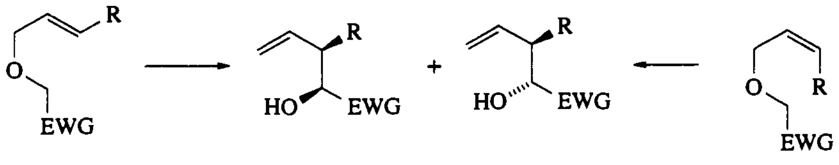

*(E)*-(**66**) (**67**) *syn* (**68**) *anti* *(Z)*-(**66**)

**Scheme 10**

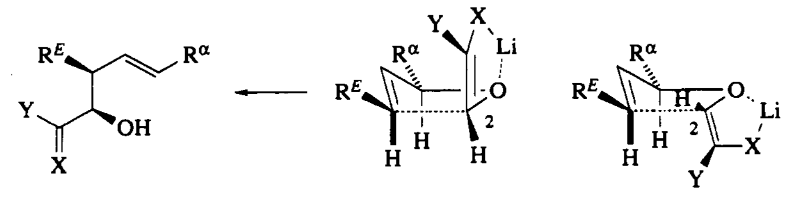

(**69**) *trans, syn* (**70**) (**71**)

**Scheme 11** Transition states rationalizing the diastereoselectivity of Wittig rearrangements with EWG = acyl

Nakai's oxonium ylide rearrangement (Table 5, entry 7) is believed to proceed *via* (**76**) to give *syn*-(**77**) and *anti*-(**78**; Scheme 12), respectively.[14] These diastereoselectivities are difficult to understand in view of the strikingly deviating selectivities reported for the related ylide (**73**).[13] Presumably, one deals with different reactive species. Speculatively, ylide (**76**) cyclizes to (**80**), a zwitterionic isomer of a ketene Si-acetal (Scheme 13). (**80**) would resemble sterically the transition state (**70**) of ester enolate Wittig rearrangements (Scheme 11). Accordingly, the *syn*/*anti* selectivities resulting from (**80**) are similar to those explained *via* (**70**). (**73**), on the other hand, can hardly react other than *via* transition state (**79**). (**79**) resembles the transition state (**64**) of Wittig rearrangements with EWG = hydrocarbon and shows equal *syn*:*anti* ratios.

**Table 5** 2,3-Rearrangements of (*E*)/(*Z*) Isomeric Ethers with EWG = Acyl[a,b]

| *Entry* | *EWG* | *R* | *From (E)-(66)* | | *From (Z)-(66)* | | *Ref.* |
|---|---|---|---|---|---|---|---|
| | | | *Yield (%)* | *Syn (%)* | *Yield (%)* | *Syn:anti* | |
| 1 | $CO_2H$ | Me | 60 | 32 | 73 | 77:23 | 36 |
| 2 | | Me[c] | 92 | 88 | — | — | 14 |
| 3 | $CO_2$—menthyl | Me, Bu[n] | 75–88 | 92–93 | — | — | 52 |
| 4 | $CO_2R$ | d | 40–75 | *ca.* 32–80 | 40–79 | 0:100 | 53 |
| 5 | $CO_2Pr^i$ | Me | 14 | 82 | 20 | 67:33 | 38 |
| 6 | | Me[e] | 47 | 98 | 15 | 88:12 | 38 |
| 7 | $CO_2Me$ | Me[c] | 83 | 95 | 86 | 50:50 | 14 |
| 8 | 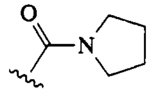 | Me | 98 | 96 | — | — | 54 |
| 9 | 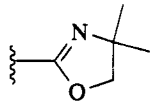 | Me | 80 | 89 | 80 | 18–24:82–76[f] | 55 |
| 10 | 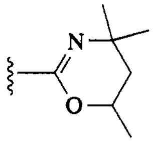 | Me | 92 | 100 | 82 | 64:36 | 55 |

[a] See Scheme 10. [b] See footnote b of Table 4. [c] With $Me_3SiOTf/NEt_3$. [d] R = 2,2-Dimethyl-1,3-dioxolan-4-yl. [e] In the presence of $ZrCp_2Cl_2$. [f] Ref. 55 is ambiguous with 28:78 given for the (*E*):(*Z*) mixture ($\Sigma \neq 100\%$).

Taking the product-oriented view, homoallylic alcohols (**82**; equation 18) with *syn* configuration can be prepared from (*E*)- or (*Z*)-alkenes in 95% isomeric purity (Table 6). Less numerous and less selective — but again including the choice of (*E*)- or (*Z*)-ethers as starting materials — are the syntheses of the *anti* epimers (**84**; equation 19) (Table 7).

Perfect *anti* selectivities may also result where they would not have been predicted on the basis of much less satisfactory model studies (*cf.* Table 5, entries 1 and 9). Pertinent examples are the Wittig rearrangements of the sterically demanding acid (**85**; equation 20)[57,58] or of the oxazoline (**87**; equation 21).[40] The highly *syn*,*cis* selective synthesis of homoallylic alcohols (**26**) from isopropyl esters was discussed earlier in a different context (equation 12, Scheme 3).[38,39]

Axial *vs.* equatorial selectivities of Wittig rearrangements were studied with the *t*-butylcyclohexane derivatives (**89**; equation 22) (Table 8). The lithio dianion of acid (**89a**) prefers equatorial attack. The $Bu^tO_2C$ (**89b**) and $Me_3SiC{\equiv}C$ substituted ethers (**89c**) undergo nonstereoselective rearrangements. The Still–Wittig reaction of (**89d**) is the only one among all known 2,3-sigmatropic shifts on this skeleton that prefers axial attack (67:33).

The conversion of the cyclopentenyl alcohol (**92**) into the homoallylic alcohol (**93**) occurs by a diastereoselective Still–Wittig rearrangement on the less hindered face of the molecule (equation 23).[60]

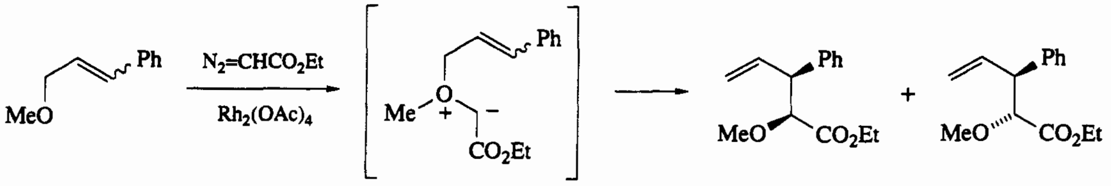
Ph
MeO
N$_2$=CHCO$_2$Et
Rh$_2$(OAc)$_4$
Ph
Me
O
+
−
CO$_2$Et
Ph
MeO
CO$_2$Et
+
Ph
MeO
CO$_2$Et

**(72)** **(73)** **(74)** *syn* **(75)** *anti*

From (*E*)-(**72**) 17 : 83
From (*Z*)-(**72**) 94 : 6

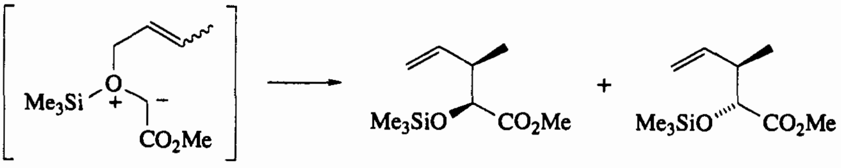
Me$_3$Si
O
+
−
CO$_2$Me
Me$_3$SiO
CO$_2$Me
+
Me$_3$SiO
CO$_2$Me

**(76)** **(77)** *syn* **(78)** *anti*

From (*E*)-(**76**) 95 : 5
From (*Z*)-(**76**) 50 : 50

**Scheme 12** Oxonium ylide rearrangements

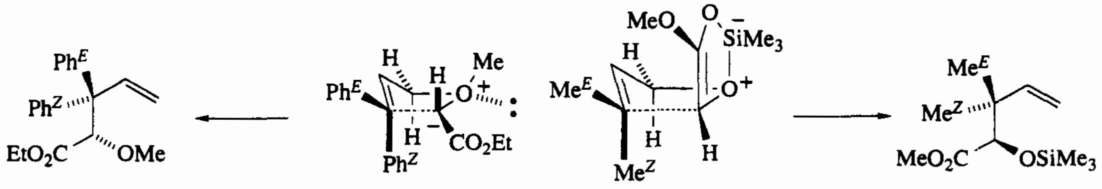
Ph$^E$
Ph$^Z$
EtO$_2$C
OMe
H
Me
Ph$^E$
H
O
+
H
CO$_2$Et
Ph$^Z$
MeO
O
−
SiMe$_3$
H
Me$^E$
O+
H
H
Me$^Z$
Me$^E$
Me$^Z$
MeO$_2$C
OSiMe$_3$

**(74/75)** **(79)** **(80)** **(77/78)**

**Scheme 13** Transition states of oxonium ylide rearrangements

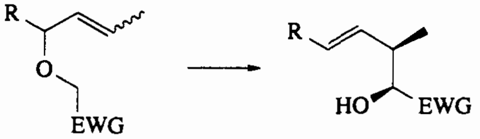
R
O
EWG
R
HO
EWG

**(81)** **(82)** *syn* (18)

### *4.6.2.1.3 Control of the absolute configuration of the rearrangement product*

The absolute configuration of Wittig rearrangement products can be controlled starting from chiral ethers (**94**; Scheme 14). In the formation of (**95a**) configurational control stems from chirality transfer. Product types (**95b**)–(**95d**) are configurationally enriched through the influence of asymmetric induction. In the metalated ether (**94a**) the chiral center is a part of the five-atom backbone involved in the sigmatropic process. In the anions (**94b**)–(**94d**), the chiral center is only attached to the backbone in question. No matter where the location of the chiral center is in (**94b**)–(**94d**), it induces the formation of products with defined absolute configurations.

Complete chirality transfer from *cis*-ethers (**96**; equation 24) to homoallylic alcohols (**97**) was the cornerstone for numerous applications of the Wittig rearrangement in natural product synthesis (Table 9). The predictability of the absolute configuration of the rearranged product on the basis of a suprafacial bond shift and the ready availability of optically active starting materials make these reactions attractive.

**Table 6** Synthesis of *Syn* Homoallylic Alcohols[a,b]

| *(81)* | *EWG* | *R* | *Yield (%)* | *Syn (%)* | *Ref.* | *Ref. for similar results* |
|---|---|---|---|---|---|---|
| (*E*) | 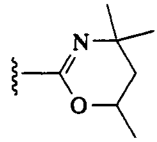 | H | 92 | 100 | 55 | |
| | 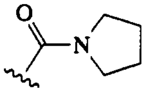 | H | 98 | 96 | 54 | 56 |
| | $CO_2Pr^i$ | H | 47 | 98 | 38[c] | |
| | $CO_2Me$ | H | 83 | 97 | 14[d] | |
| (*Z*) | $Me_3SiC{\equiv}C$— | $Pr^i$ | 62 | >98 | 48 | 31, 48, 49 |
| | $MeC{\equiv}C$— | H | 55 | 100 | 31 | 48 |
| | $MeOC_6H_4$— | H | 70–98 | 100 | 47 | 47 |
| | $H_2C{=}CMe$— | $Pr^i$ | 93 | 97 | 35 | 26, 34 |

[a] See equation (18). [b] See footnote b of Table 4. [c] LDA, $ZrCp_2Cl_2$. [d] $Me_3SiOTf$ mediated rearrangement of the isolated ketene Si-acetal.

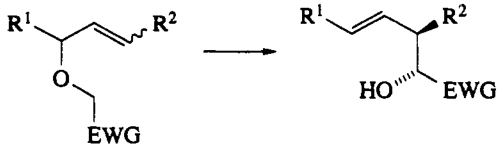

**(83)** **(84)** *anti*

(19)

**Table 7** Synthesis of *Anti* Homoallylic Alcohols[a,b]

| *(83)* | *EWG* | *$R^1$* | *$R^2$* | *Yield (%)* | *Anti (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| (*E*) | $MeC{\equiv}C$— | H | Me | 65 | 99 | 31 |
| (*E*) | $HC{\equiv}C$— | H | Me | 72 | 99 | 31 |
| | | $Pr^i$ | Me | 63 | 89[c] | 17 |
| (*Z*) | $CO_2R$ | H | 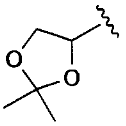 | 40–79 | 100 | 53 |

[a] See equation (19). [b] See footnote b of Table 4. [c] Together with 9 rel-% of (*Z*)-isomer(s) with unassigned configuration(s).

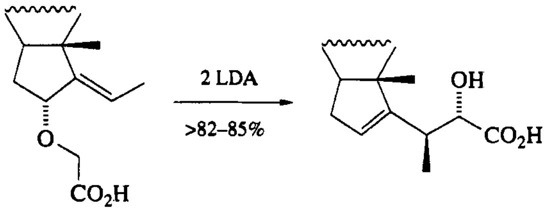

**(85)** **(86)** >98:<2

(20)

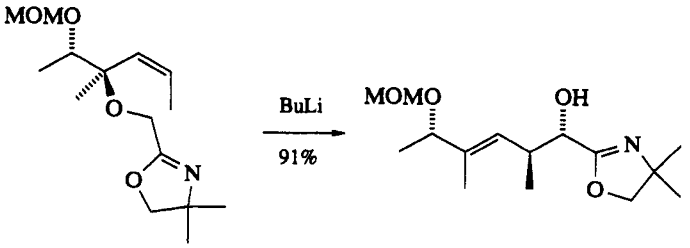
MOMO
O
O
N
BuLi
91%
MOMO
OH
N
O

(21)

**(87)** **(88)** >100:1

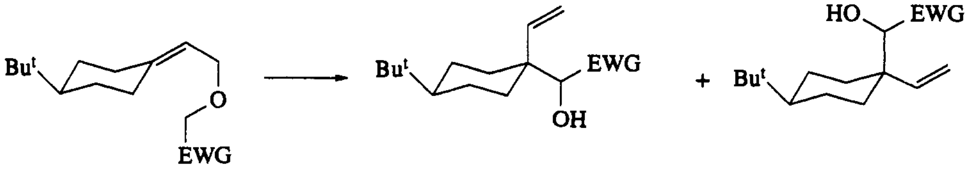
Bu^t
O
EWG
Bu^t
EWG
OH
+
HO
EWG
Bu^t

(22)

**(89)** **(90)** equatorial attack **(91)** axial attack

**Table 8** Wittig Rearrangements in Conformationally Fixed Cyclohexanes[a]

| *(89)* | *EWG* | *Yield (%)* | *(90):(91)* | *Ref.* |
|---|---|---|---|---|
| (a) | $CO_2H$ | 63 | *ca.* 100:*ca.* 0 | 36 |
| (b) | $CO_2Bu^t$ | 51 | 71:29 | 59 |
| (c) | $Me_3SiC{\equiv}C$— | 74 | 55:45 | 59 |
| (d) | $Bu_3Sn^b$ | 86 | 34:66 | 59 |

[a] See equation (22). [b] EWG = H in (90) and (91).

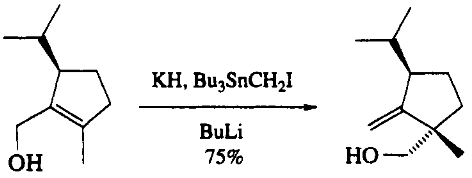
OH
KH, Bu₃SnCH₂I
BuLi
75%
HO

(23)

**(92)** **(93)**

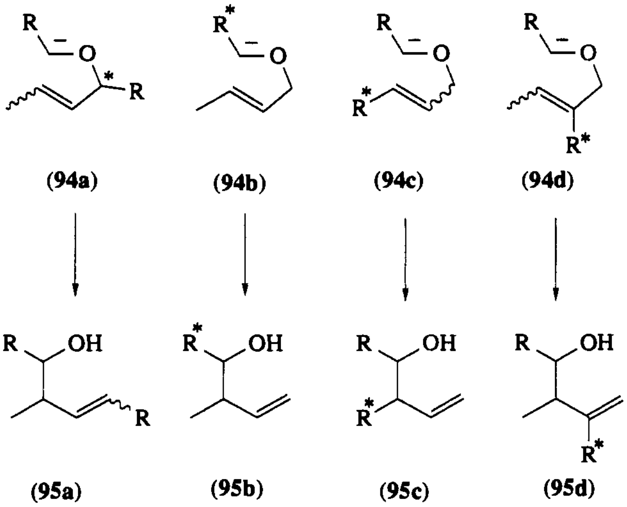
R
O
*
R
(94a)
R*
O
(94b)
R
O
R*
(94c)
R
O
R*
(94d)
R
OH
R
(95a)
R*
OH
(95b)
R
OH
R*
(95c)
R
OH
R*
(95d)

**Scheme 14**

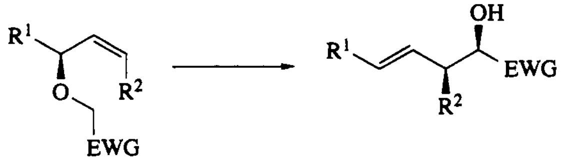

(96) (97) *syn*, 1 enantiomer (24)

**Table 9** Chirality Transfer in 2,3-Wittig rearrangements[a]

| *EWG* | *$R^1$* | *$R^2$* | *Yield (%)* | *Ref.* | *Synthesis use* |
|---|---|---|---|---|---|
| $Me_3Sn$[b] | $R^n$ | Me | 80 | 20 | Steroid side chain |
|  | $R^s$ | $—CMe_2OTBDMS$ | 82–84 | 22 | Steroid side chain |
| $H_2C{=}CMe—$ | $Pr^i$ | Me | 93 | 35 | Prelog–Djerassi lactone |
| $Me_3SiC{\equiv}C—$ | Me | Me | >64 | 61 | Pheromone |
|  | Me | $Bu^n$ | 96 | 32 | Blastmycinone |
|  | $Pr^i$ | $—CH_2OTBDMS$ | >85 | 33 | Talaromycin |

[a] See equation (24). [b] EWG = H in (97)

Allylic alcohols with a *trans* double bond give product mixtures in the Still–Wittig rearrangement (*cf.* equation 7[21]). Advantageously, such substrates (*e.g.* **98**) can be converted to homoallylic alcohols with 100% chirality transfer by the Büchi rearrangement (equation 25).[23]

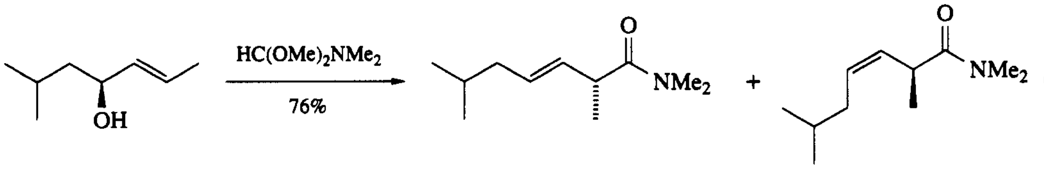

**(98)** **(99)** 87:13 **(100)** (25)

Proper variation of a 'remote' substituent allowed selective conversion of different alcohols (**101**) of identical stereostructure into hydroxy acids (**36**)[38] and (**39**)[39] of opposite absolute configurations (Scheme 15). The underlying reason was already presented *en passant* in Scheme 4.

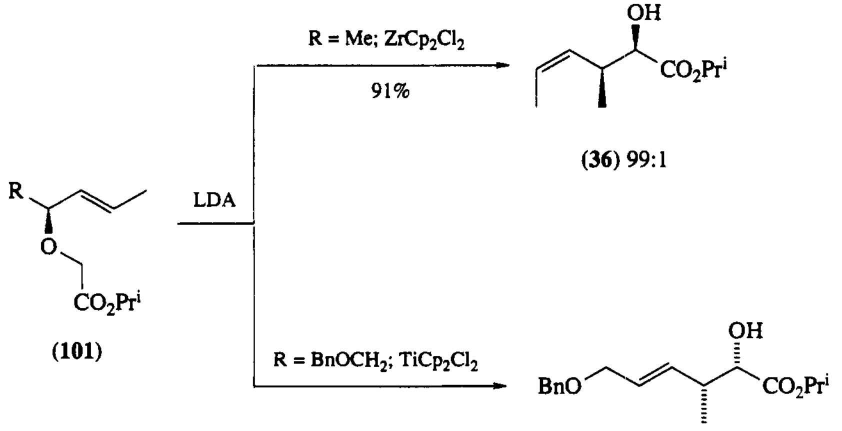

**(101)** **(36)** 99:1 **(39)**

**Scheme 15**

Skilful use of chelation by the oxygen bridge was made in the elaboration of oxazoline (**102**) to the rearranged (**104**). Only one out of eight possible stereoisomers was formed (equation 26).[62] Highly efficient chirality transfer from similar substrates with the Still–Wittig rearrangement is also known.[63]

Chirality transfer out of a cycle was used repeatedly in steroid side chain synthesis (equation 27;[64] *cf.* equation 20[57,58]). The rigidity of the substrate grants high stereocontrol. The advantage of an unequivocal

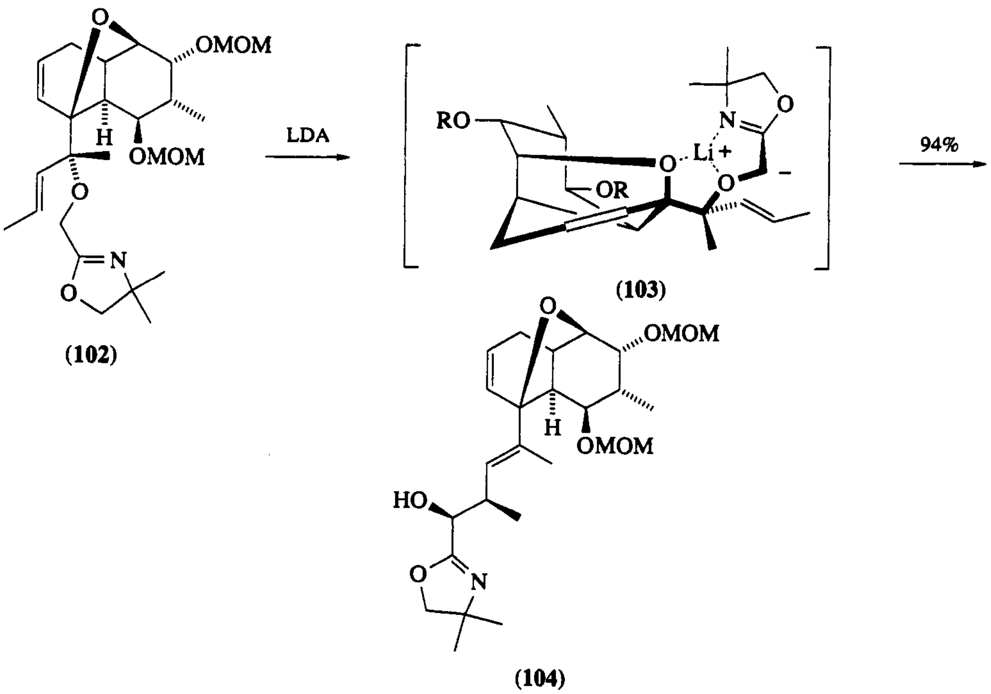

OMOM
H
OMOM
O
N
O
LDA
RO
N
O
Li+
O
OR
94%
O
OMOM
H
OMOM
HO
O
N

(102)

(103)

(104)

(26)

orientation of the rearranging moiety with respect to the attacked C=C bond is shared by chirality transfer within cycles. The one-pot two-step conversion of alcohol (**107**) into its homolog (**108**) illustrates how a hydroxy group serves to direct a hydroxymethyl group to a given face of a molecule (equation 28).[65] For successful chirality transfer, dissociative 1,2- or 2,3-pathways must not interfere; this was, however, reported occasionally starting from substituted 2-cyclohexenols under Wittig[19,7] or Büchi rearrangement conditions.[23]

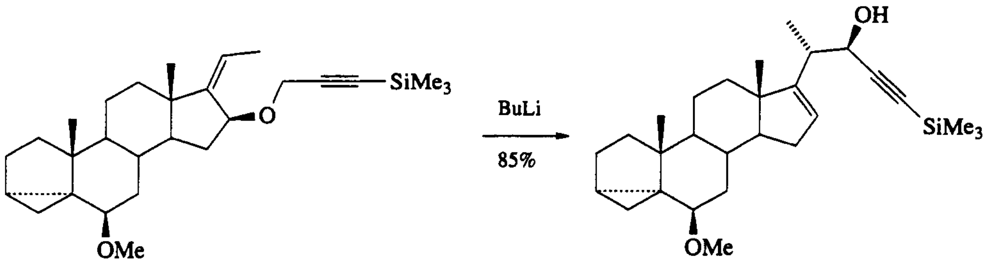

SiMe3
O
OMe
BuLi
85%
OH
SiMe3
OMe

(27)

(105)

(106)

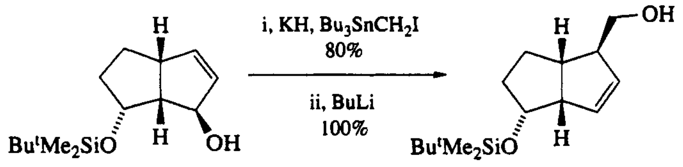

H
Bu'Me2SiO
H
OH
i, KH, Bu3SnCH2I
80%
ii, BuLi
100%
H
OH
Bu'Me2SiO
H

(28)

(107)

(108)

How a CH2OH group can be guided into a molecule by means of a hydroxy group which is carried through a Still–Wittig rearrangement, is nicely demonstrated in the total synthesis of laurenene (**109**; Scheme 16).[66] Since Me2CuLi introduced the missing methyl group into (**110**) from the wrong, *i.e.* bottom, face, recourse was made to a rearrangement *via* alcohol (**112**). It delivered the CH2OH entity from the desired, *i.e.* top, face into (**111**). Finally, it was unmasked to the methyl group of the target molecule.

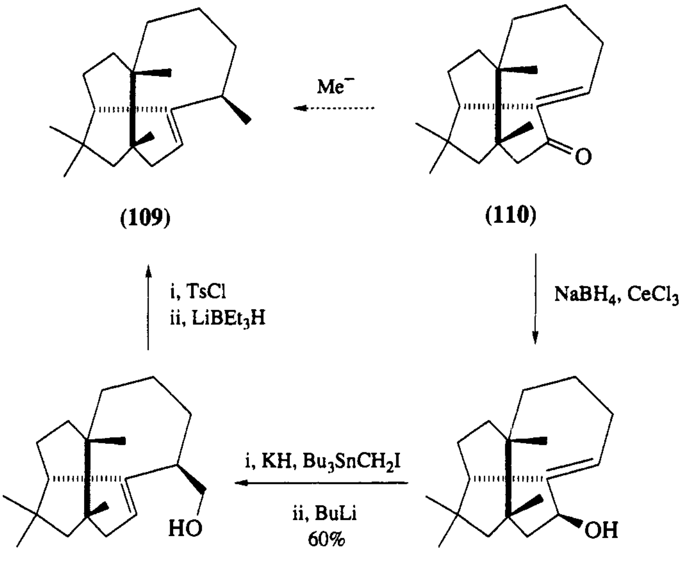

**(109)** **(110)** **(111)** **(112)**

**Scheme 16**

Chirality transfer through a Still–Wittig reaction provided the *C*-glycoside (**113**) from the enol ether (equation 29).[67] The low yield (25%) was mainly due to protonation of the intervening oxyanion to the methyl ether (**114**) prior to rearrangement. Presumably, this side reaction could have been suppressed with HMPA as cosolvent.[68]

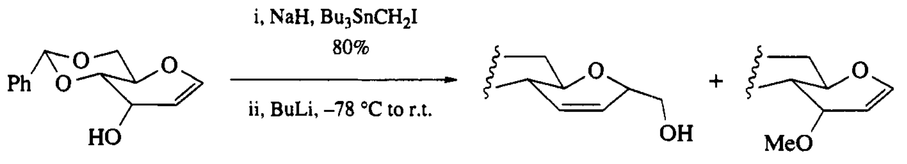

(29)

**(113)** **(114)**

Asymmetric induction by a chiral substituent in the anion moiety provides efficient access to homoallylic alcohols with (*S*)- (Scheme 17) or (*R*)-configuration (Scheme 18), respectively. Optically active alcohols with defined absolute and concomitant *anti* configuration have not yet been prepared with satisfactory selectivity.

A chiral anion moiety dictates the stereochemistry of the macrocyclic ring contraction (**4**) → (**5**) of a lithiated allylic propargylic ether (equation 2); scope and utility of such reactions are detailed in Volume 3, Chapter 3.11. Chiral allyl moieties also effect stereocontrol in the Wittig rearrangement of ethers (**116**). There, the chirality resides in an allylic C—O bond. Depending on the size of the neighboring R group, the epimers (**117**)/(**118**; equation 30) result in ratios ranging from 96:4–45:55 (Table 10).[68]

The main product is thought to arise from transition state (**119**; Scheme 19).[68] (**119**) is stabilized through the antiperiplanar alignment of the allylic $^*$C—O orbital with respect to the approaching carbanion.[71] This geometry entails the formation of the *syn* product (**117**). The diastereomeric transition state (**120**) is caused by the alkyl substituent striving for the least hindered orientation with respect to the pericyclic transition state. (**120**) competes with the electronically favored (**119**) only if R is sterically demanding.

MOM and MEM protecting groups induce *syn* selectivity in this type of rearrangement more efficiently than benzyl groups; (**122**) is the only detectable isomer obtained from MEM ether (**121**; equation 31).[68] The mode of action of these auxiliaries can be understood by secondary orbital interactions in transition state (**123**). The amino group of allylamine (**124**) acts as a similar inducer of asymmetry. This compound, again, led to a single rearrangement product (**125**; equation 32).[72] Carbamate (**126**), likewise, gave only one rearranged alcohol in 88% yield.[72]

Asymmetric induction plus simple diastereoselectivity is observed in the Wittig rearrangements of ester (**127**; equation 33)[53] or silyl ether (**130**; equation 34).[48,49] The configuration of the allylic carbon is identical in the two reactions and analogous to that of the foregoing examples. Interestingly, the accompanying *syn*/*anti* preferences are complementary: the C—OH bond is oriented downward in (**128**) and upward in (**131**). How the C—OH bond is arranged with respect to the vinyl group depends on the size of the carbanionic substituent. The alkynyl group of transition state (**132**) protrudes unhindered over the heterocycle, whereas the voluminous ester moiety of transition state (**129**) is pushed away from the dioxolane.

Asymmetric induction of the same kind controls the configuration at the allylic methine carbon in compound (**134**); (**134**) results from a chain-elongating Wittig rearrangement (mechanism: Scheme 6) of sulfone (**133**; equation 35).[73] Surprisingly, the sense of the asymmetric induction in the rearrangement of silyl ether (**135**; equation 36)[48] is opposite to that of more than a dozen other (*E*)-ethers.[49,53,68,72]

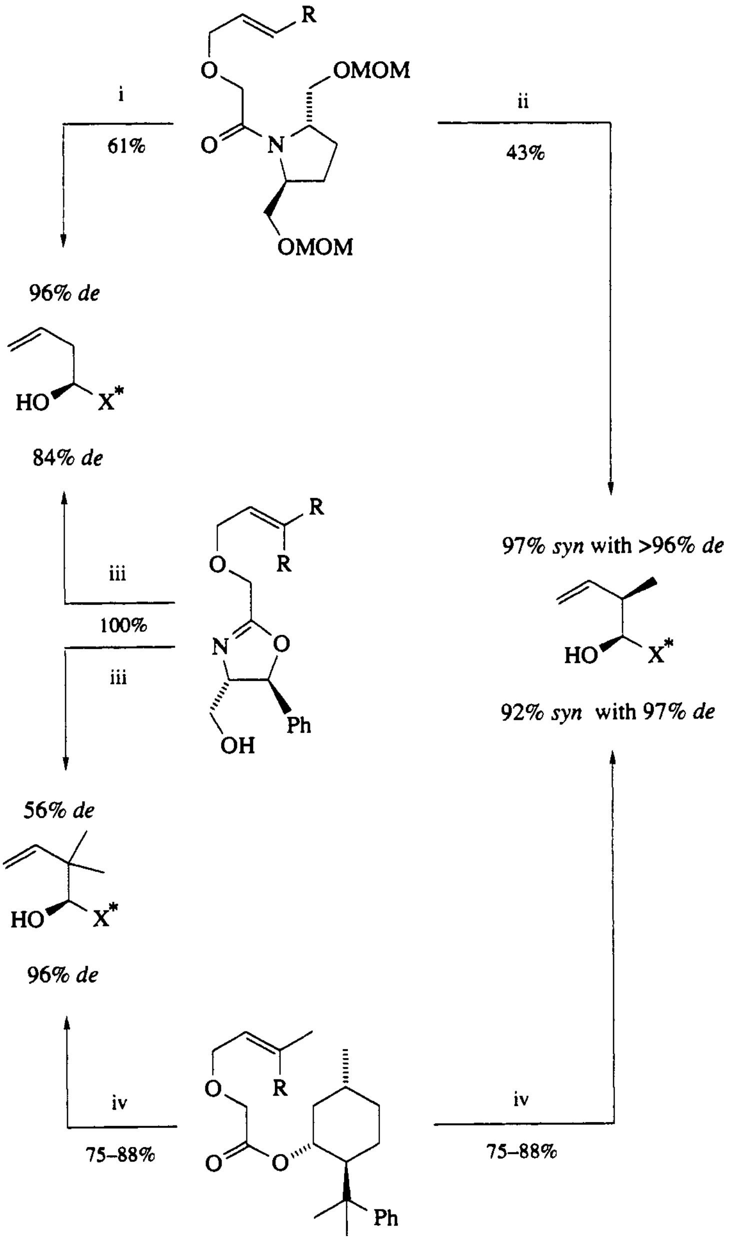

i, BuLi;[56] ii BuLi, $ZrCp_2Cl_2$;[56] iii,KH;[69] iv, LDA[52]

**Scheme 17** Synthesis of masked hydroxy acids with (2*S*) configuration

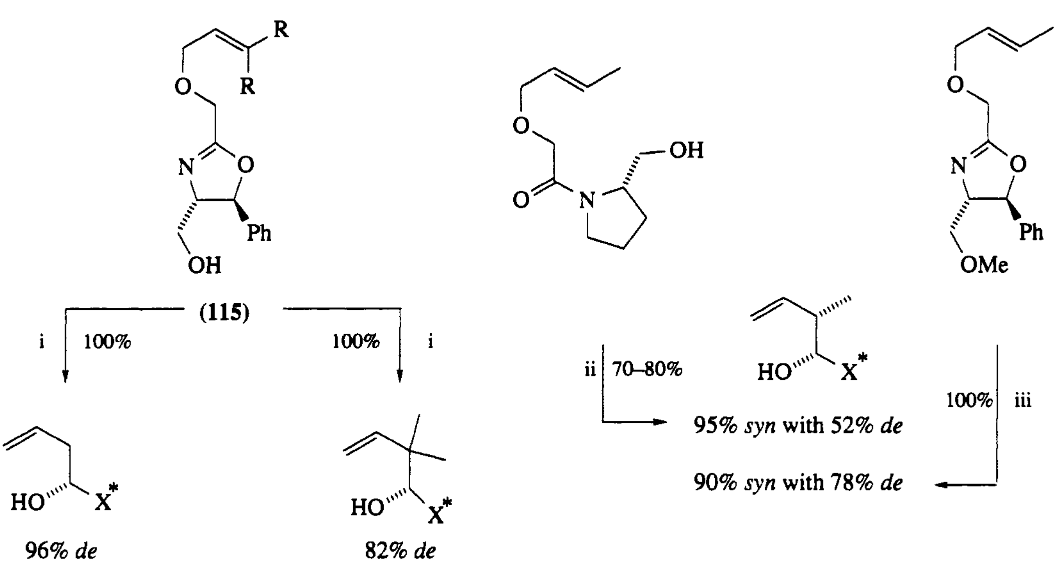
R
O
R
N
O
Ph
OH
(115)
i
100%
100%
i
HO
X*
96% de
HO
X*
82% de
O
O
N
OH
ii
70–80%
HO
X*
95% syn with 52% de
90% syn with 78% de
O
N
O
Ph
OMe
100%
iii

i, KH, 18-crown-6;[69] ii, LDA;[54] iii, BuLi[70]

**Scheme 18** Synthesis of masked hydroxy acids with (2*R*) configuration

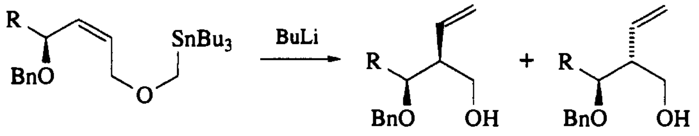
R
BnO
SnBu$_3$
O
BuLi
R
BnO
OH
+
R
BnO
OH

**(116)** **(117)** **(118)** (30)

**Table 10** Asymmetric Induction in Wittig Rearrangements of Allylic Ethers[a]

| *R* | *Yield (%)* | *(117):(118)* |
|---|---|---|
| $BnCH_2$— | 81 | 96:4 |
| $Pr^i$ | 78 | 93:7 |
| Ph | 71 | 89:11 |
| $Bu^t$ | 67 | 45:55 |

[a]See equation (30).

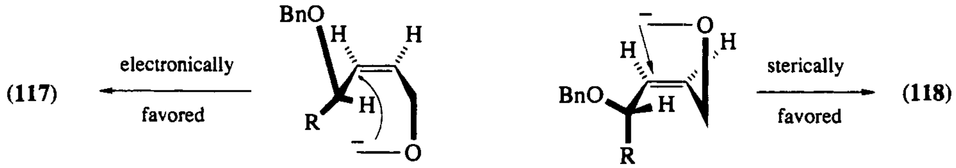
(117)
electronically
favored
BnO
H
H
R
H
O
O
H
H
BnO
H
R
sterically
favored
(118)

**(119)** **(120)**

**Scheme 19** Transition states of Wittig rearrangements under the influence of asymmetric induction

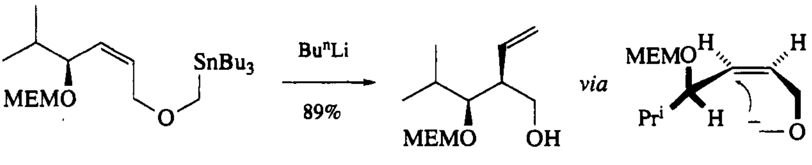
MEMO
SnBu$_3$
O
Bu$^n$Li
89%
MEMO
OH
via
MEMO
H
H
Pr$^i$
H
O

**(121)** **(122)** **(123)** (31)

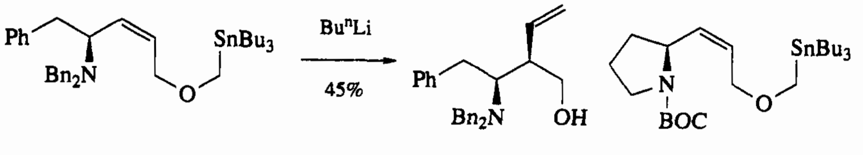

Ph
Bn$_2$N
O
SnBu$_3$
Bu$^n$Li
45%
Ph
Bn$_2$N
OH
N
BOC
O
SnBu$_3$

(32)

**(124)** **(125)** **(126)**

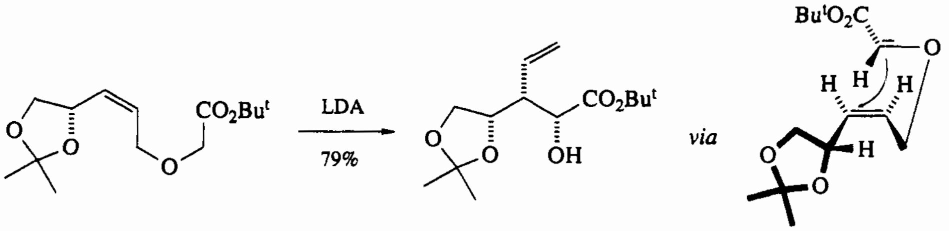

O
O
O
CO$_2$Bu$^t$
LDA
79%
O
O
CO$_2$Bu$^t$
OH
via
Bu$^t$O$_2$C
O
H H H
O
H
O

(33)

**(127)** **(128)** **(129)**

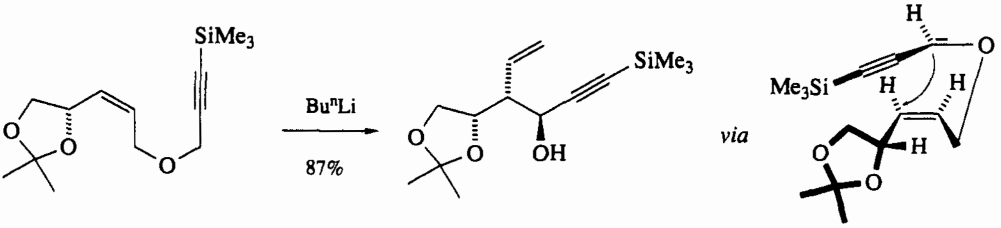

SiMe$_3$
O
O
O
Bu$^n$Li
87%
SiMe$_3$
O
O
OH
via
H
O
Me$_3$Si
H H
O
H
O

(34)

**(130)** **(131)** **(132)**

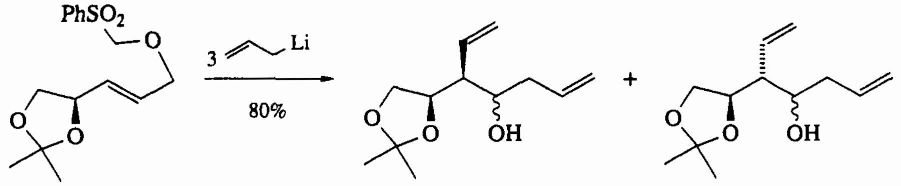

PhSO$_2$
O
O
O
3
Li
80%
O
O
OH
+
O
O
OH

(35)

**(133)** **(134)** 93:7

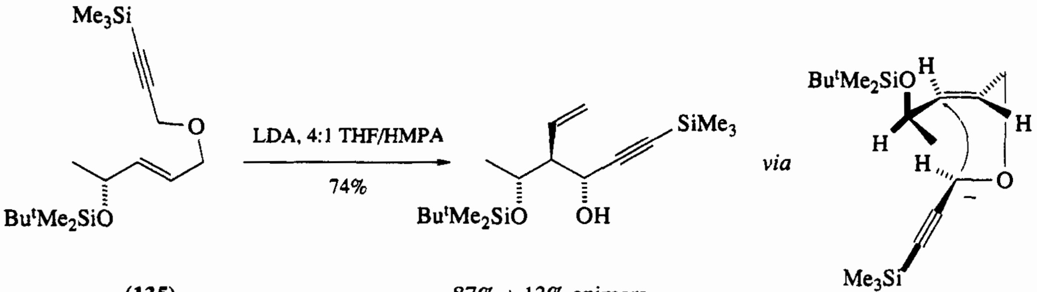

Me$_3$Si
O
Bu$^t$Me$_2$SiO
LDA, 4:1 THF/HMPA
74%
SiMe$_3$
Bu$^t$Me$_2$SiO
OH
via
Bu$^t$Me$_2$SiO
H
H
H
H
O
Me$_3$Si

(36)

**(135)** 87% + 13% epimers

### 4.6.2.2 Rearrangement of Sulfides and Amines

2,3-Sigmatropic rearrangements of allylic nitrogen or sulfur compounds are usually performed with ylides. Of the corresponding anionic 2,3-rearrangements, thia-Wittig rearrangements are known, their aza counterparts virtually not. Even the thia-Wittig rearrangements have been rarely used apart from early model studies. Multistep syntheses of some of the starting materials,[74] suspected noncompatibility of other functionality with the strongly basic thio anion and the attractiveness of the sulfonium ylide rearrangement as a methodological alternative played their role in discouraging from applications.

Onium salt precursors for ylide rearrangements are easily obtained from amines or sulfides by alkylation. The direct transformation of sulfides into sulfonium ylides is possible, too. To this end, sulfides are reacted with carbenoids like $CH_2I_2/ZnEt_2$,[75] $(MeO_2C)_2C{=}N_2/CuSO_4$,[76] $(EtO_2C)_2C{=}N_2/Rh_2(OAc)_4$[77] or $LiC{\equiv}CCMe_2Cl$.[78] In a related approach, the reaction with benzyne was used to transform a sulfide (**136**) to a sulfonium ylide (**137**) in a single operation. (**137**) rearranged under the reaction conditions and gave one major product (**138**) in high yield (Scheme 20).[79]

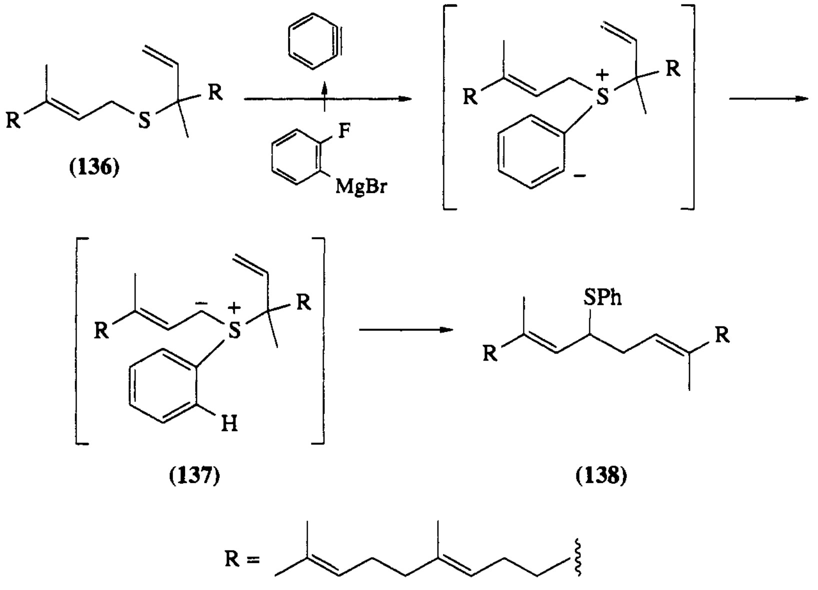

Scheme 20

Sulfonium methylides can also be prepared from sulfides by treatment with $Me_3SiCH_2OTf$ followed by desilylation with CsF.[80] This method allows the regioselective generation of sulfonium ylides (*i.e.* **140**),[81] which would not form under equilibrium deprotonation conditions (*cf.* **139** → **141**; Scheme 21).[82] Neither the (*Z*)-selective (90:10) formation of a trisubstituted alkene[76] nor enantioselective versions[83,84] have become essentials of ylide rearrangement methodology. Far more important are aspects of regio- and diastereo-control.

### *4.6.2.2.1 Regioselectivity*

The base-induced 2,3-shift in a benzyltrialkylammonium halide (Sommelet–Hauser synthesis) effects an *ortho*-selective aminomethylation of aromatics. A variation (*ortho*-selective formylation) is shown in equation (37).[85] Unfortunately, the 1,2-Stevens rearrangement (→ 10% **143**) of the intervening ylide competes with the 2,3-pathway (→ **142**). A reliable tool to circumvent this very general difficulty is still unknown.[86] Nonetheless, 2,3-rearrangement pathways can be very efficient as demonstrated by the synthesis of the cyclic amine (**144**; equation 38).[87]

Sulfur ylides are also apt to introduce carbon atoms regioselectively into aromatic frameworks (equation 39).[88]

### *4.6.2.2.2 Diastereoselectivity*

If opportunity is given, a (thiolated) carbon atom can be transferred from a sulfur ylide to a double bond with diastereocontrol. The carbon remains on that side of the molecule which contained the sulfur initially (*e.g.* equation 40).[75] By similar chirality transfer, the β-oriented phenylthio group of octalin (**147**) determines the β-orientation of the transposed $PhSCH_2$ unit in the reaction product (**148**; equation 41).[89] The efficient formation of a quaternary center from (**147**) is all the more remarkable since an

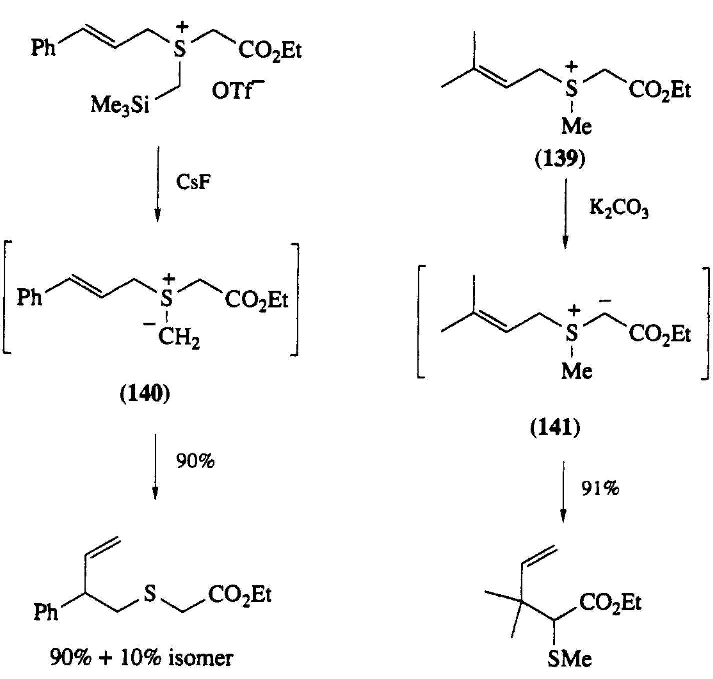
Ph
CO₂Et
Me₃Si
OTf⁻
CsF
(140)
90%
90% + 10% isomer
(139)
Me
K₂CO₃
(141)
91%
SMe

**Scheme 21**

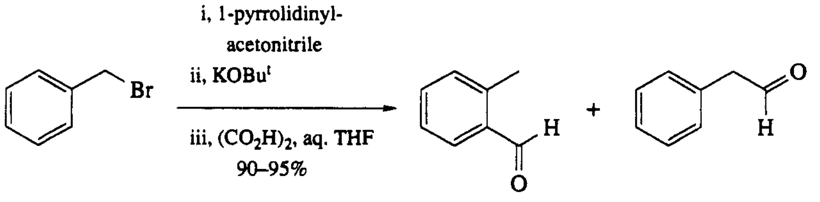
i, 1-pyrrolidinyl-acetonitrile
ii, KOBu$^t$
iii, $(CO_2H)_2$, aq. THF
90–95%
Br
H
O

(142) 90:10 (143)

(37)

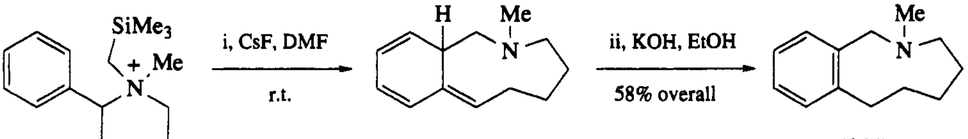
SiMe₃
Me
N
i, CsF, DMF
r.t.
H
ii, KOH, EtOH
58% overall

stable! (144)

(38)

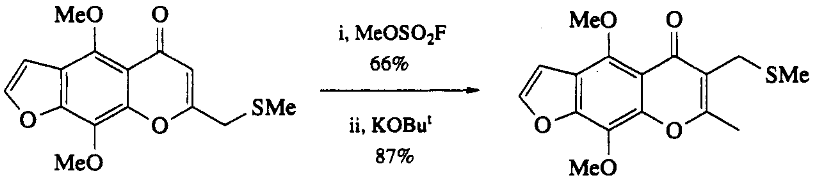
MeO
O
SMe
i, MeOSO₂F
66%
ii, KOBu$^t$
87%

(145) (146)

(39)

electron rich C═C bond is attacked. Attempted 2,3-Wittig rearrangements of the structurally related stannyl ether (**149**) were sluggish and accompanied by decomposition and 1,2-rearrangement.[19]

Chirality transfer in acyclic substrates has received little attention so far. However, the complete stereoselectivity of the rearrangement (**150**) → (**151**; equation 42) indicates a potential not yet fully appreciated.[90]

Ylides may attack preponderantly one of the two diastereotopic faces of a C═C bond in the course of a 2,3-sigmatropic shift. Facial selectivity with respect to exocyclic C═C bonds will be considered first.

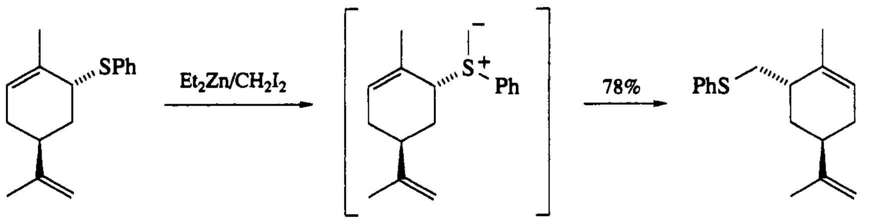
SPh
Et2Zn/CH2I2
S+
Ph
78%
PhS

(40)

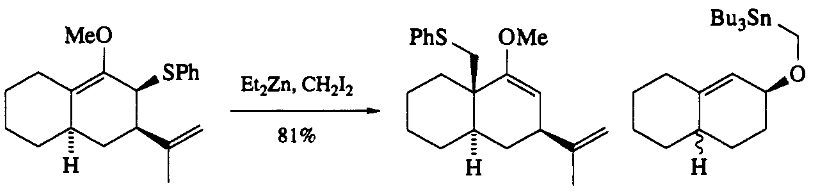
MeO
SPh
H
Et2Zn, CH2I2
81%
PhS
OMe
H
Bu3Sn
O
H

**(147)** **(148)** **(149)**

(41)

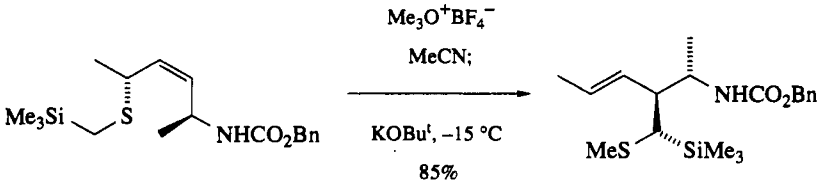
Me3Si
S
NHCO2Bn
Me3O+BF4−
MeCN;
KOBut, −15 °C
85%
NHCO2Bn
MeS
SiMe3

**(150)** **(151)**

(42)

Equatorial attack was reported for the rearrangements of sulfonium and nitrogen ylides in the conformationally fixed $Bu^t$-substituted cyclohexanes (**152**; equation 43)[1] and (**153**; equation 44),[91] respectively.

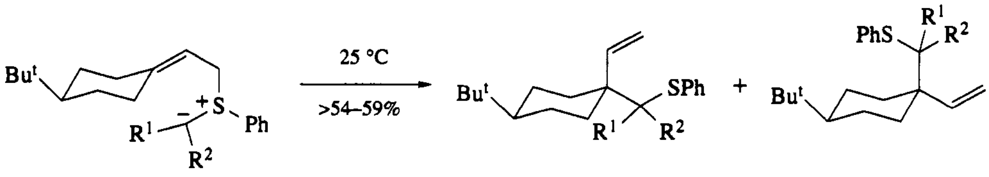
But
S
Ph
R1
R2
25 °C
>54–59%
But
SPh
R1
R2
+
PhS
R1
R2
But

**(152)**

(43)

| *R¹* | *R²* | *Equatorial attack* | : | *Axial attack* |
|---|---|---|---|---|
| Cl | Cl[a] | 97 | | 3 |
| H | $CO_2Et$ | 91 | | 9 |

[a] Product: $R^1,R^2$ = C=O

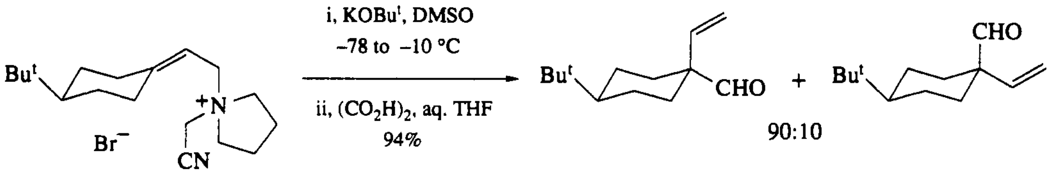
But
+N
Br−
CN
i, KOBut, DMSO
−78 to −10 °C
ii, (CO2H)2, aq. THF
94%
But
CHO
+
But
CHO

**(153)**

90:10

equatorial attack axial attack

(44)

A thia-Wittig rearrangement in the methylenecyclopentane (**154**) proceeded to (**155**) without formation of the epimer (equation 45).[1] Obviously, the reaction proceeds on the less hindered (convex) face of the bicyclic framework. Equally high diastereoselectivity — unassigned, but presumably also on the less hindered (*exo*) face — is recorded for the 2,3-rearrangement of a methylenecyclopentane-derived sulfur ylide.[75]

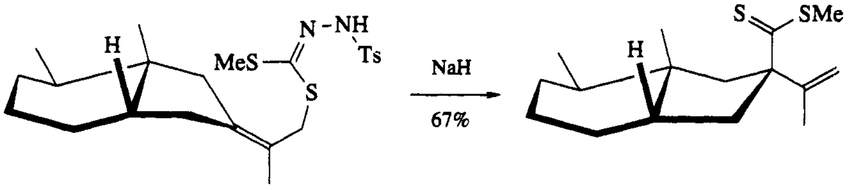
H
MeS
N-NH
Ts
S
NaH
67%
H
S
SMe

(154) (155)

(45)

Surprisingly, a methylenecyclohexane-derived carbazate akin to (**154**) gave negligibly more equatorial (55%) than axial attack when treated under the same conditions. When the rearrangement was initiated with 10 mol % Cu(acac)$_2$, equatorial attack amounted to 65%.[74] The first observation is clearly inconsistent with Evans' reaction (**154**) → (**155**). The copper catalysis of the second process suggests the existence of a synthetically unexplored second rearrangement mechanism through a carbenoid.

The conformationally fixed six-membered ring (**156**) contains an endocyclic C═C bond. (**156**) displays axial selectivity in the 2,3-sigmatropic shift of the corresponding sulfur ylide (equation 46).[92] Unselective, on the other hand, is the seemingly related rearrangement (**157a**) → (**158a/159a**) of a nitrogen ylide (equation 47).[91] In this system, axial attack is in part (80%) restored upon replacing the alkenic hydrogen of (**157a**) by a methyl group in (**157b**).[91]

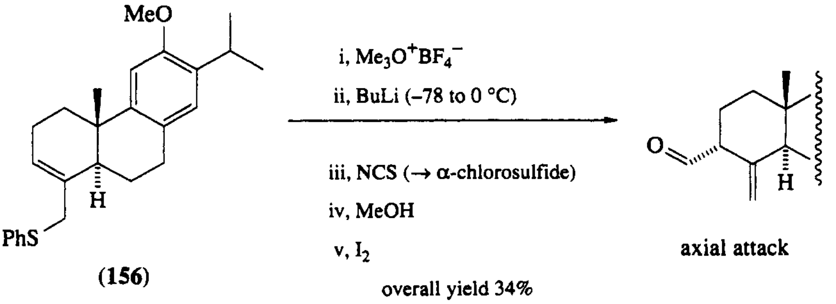
MeO
H
PhS
i, Me$_3$O$^+$BF$_4^-$
ii, BuLi (–78 to 0 °C)
iii, NCS (→ α-chlorosulfide)
iv, MeOH
v, I$_2$
overall yield 34%
O
H
axial attack

(156)

(46)

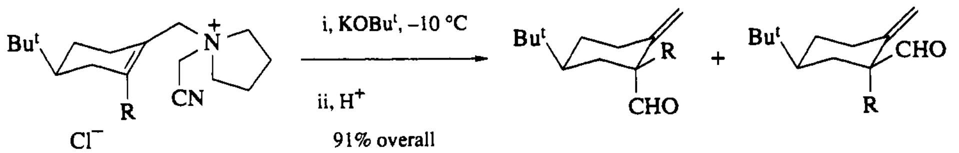
Bu$^t$
N
+
CN
R
Cl$^-$
i, KOBu$^t$, –10 °C
ii, H$^+$
91% overall
Bu$^t$
R
CHO
+
Bu$^t$
CHO
R

(157) (158) (159)

(47)

| | R | Axial attack | : | Equatorial attack |
|---|---|---|---|---|
| (a) | H | 57 | : | 43 |
| (b) | Me | 80 | : | 20 |

That isomerization of the β,γ-unsaturated aldehyde to the conjugated isomer during hydrolysis is negligible as in the case of (**158a/159a**; equation 47) is no standard feature of this reaction.[93] Presumably, smaller strain of the deconjugated isomer contributes to leaving certain of these aldehydes unaltered. Mostly due to this hindrance of isomerization, the carboxylation (**160**) → (**161**) could be accomplished with excellent stereocontrol (equation 48).[94]

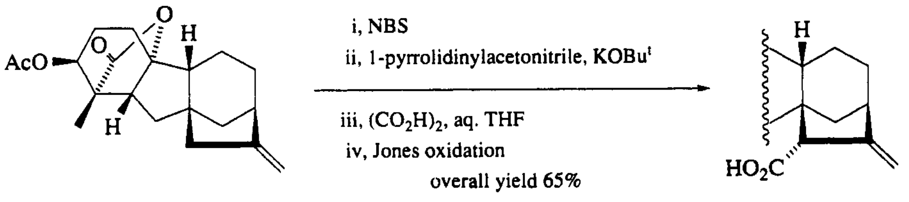
AcO
O
O
H
H
i, NBS
ii, 1-pyrrolidinylacetonitrile, KOBu$^t$
iii, (CO$_2$H)$_2$, aq. THF
iv, Jones oxidation
overall yield 65%
H
HO$_2$C

(160) (161)

(48)

Ylides with substituted carbanions can form vicinal stereocenters upon 2,3-rearrangement. In acyclic compounds, little stereocontrol[9b,95] is documented more often than good control.[96] Cyclic ylides, on the other hand, exhibit high stereoselectivities for ring contractions *via* 2,3-sigmatropic shifts. The oldest and still the most impressive among such reactions is Yoshimoto's transformation of the cephalosporin (**162**) into the penicillin skeleton (**163**). Diastereoselectivity follows from an *exo* preference of the ester group in transition state (**164**; equation 49).[97]

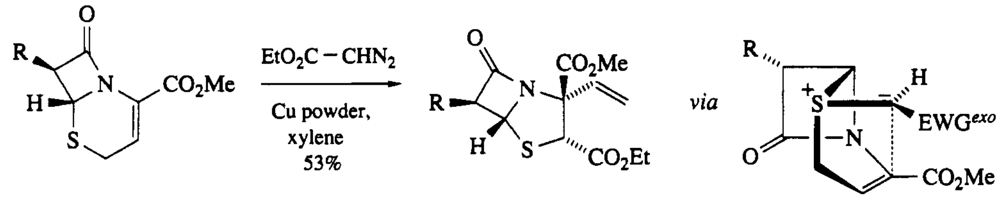

(**162**) R = NHCOBn (**163**) (**164**) (49)

Turning to ammonium ylides, the *cis* selective ring contraction of the ylide (**165**) is noteworthy (equation 50).[98] From the product structure, again an *exo* preference is deduced for the electron-withdrawing group (here: benzoyl) in the corresponding transition state (**166**). Notice the similarity of transition states (**166**; nitrogen ylide) and (**164**; sulfur ylide). The (*Z*)-configuration of the rearranged piperidine (**167**) follows from similar considerations (equation 51).[99] The yield of this reaction, in the course of which a quaternary stereocenter is created, is remarkably good (75%).

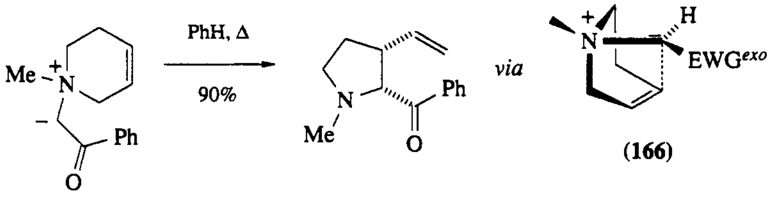

(**165**) (**166**) (50)

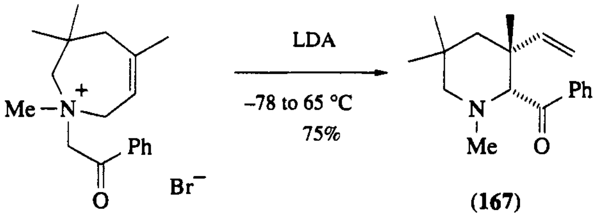

(**167**) (51)

An interesting ring contraction of the eight-membered heterocycle (**168**) furnished the spirocycle (**169**) in which the aromaticity is lost (equation 52).[100] Unfortunately, the stereochemical integrity of the rearrangement product was not commented upon. Ylides are used for ring expansion reactions likewise. The *cis* and *trans* isomeric ylides (**170**) and (**173**) lead to the same rearrangement product (**172** ≡ **175**) with a *trans* double bond (Scheme 22).[101] This result can be rationalized on the assumption that in each of the transition states (**171**/**174**) the ester enolate is equatorial.

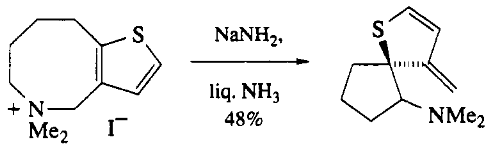

(**168**) (**169**) (52)

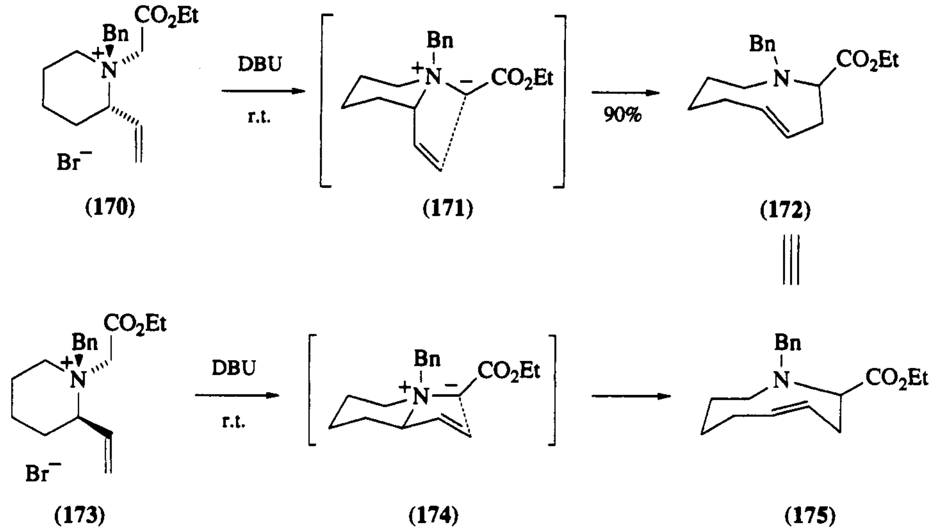
CO2Et
Bn
N
Br⁻
DBU
r.t.
Bn
N
CO2Et
90%
Bn
N
CO2Et
(170)
(171)
(172)
CO2Et
Bn
N
Br⁻
DBU
r.t.
Bn
N
CO2Et
Bn
N
CO2Et
(173)
(174)
(175)

**Scheme 22**

In an interesting variation of these rearrangements, a Bu$^t$ group was introduced into ylide (**171**) to lock the enolate side chain axially and the vinyl group equatorially (*e.g.* **176**). This turns the geometry of the rearrangement product *cis* (equation 53).[102]

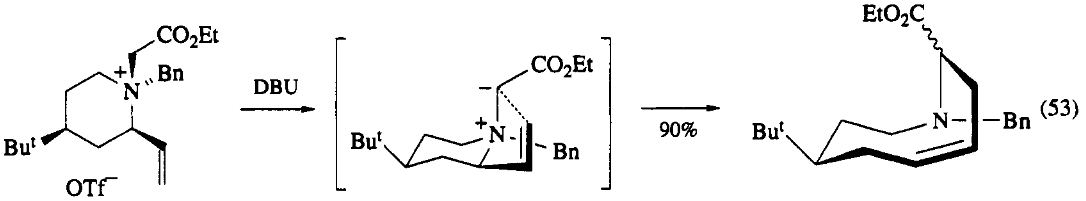
CO2Et
Bn
N
Bu$^t$
OTf⁻
DBU
CO2Et
Bu$^t$
N
Bn
90%
EtO2C
Bu$^t$
N
Bn
(53)

**(176)**

Comparable *cis/trans* selectivities and similar conformational effects on them were studied in ring enlargements of cyclic sulfonium ylides.[103] Rearrangements of sulfur ylides performed in repetition were used for stepwise ring expansion 5- → 8- → 11- → 14- → 17-membered.[104] Synthesis applications of sulfonium ylide mediated ring expansions are mostly due to Vedejs.[6] For example, the key step of his total synthesis of zygosporin[105] was an intramolecular allylation of type (**177**) → (**178**; equation 54).[106] An ylide (**178**) is formed initially in which the sulfur brings the previously separated termini of the molecule close to each other. This sets the stage for an ensuing efficient (93% yield) sigmatropic bond shift.

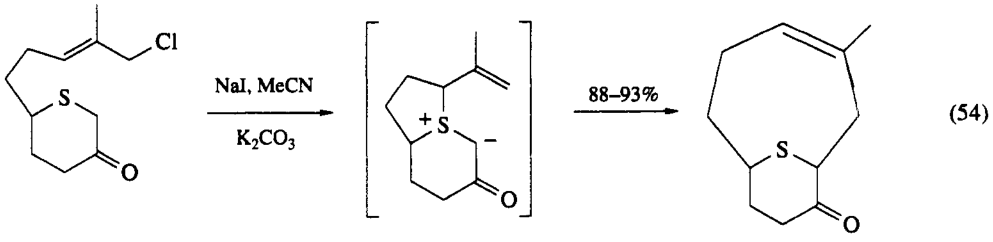
Cl
S
O
NaI, MeCN
K2CO3
+S
O
88–93%
S
O
(54)

**(177)** **(178)**

The 2,3-rearrangement (**179**) → (**180**) indicates the possibility of obtaining ring-expanded products with high diastereocontrol. Only one (**180**) of four possible stereoisomers was formed (equation 55).[107a] Subsequently, the ester group of the first rearrangement product (**180**) was transformed into another C═C bond. Thus, a second ring expansion *via* a sulfonium ylide could be performed carrying the material further towards methinolide.[107b]

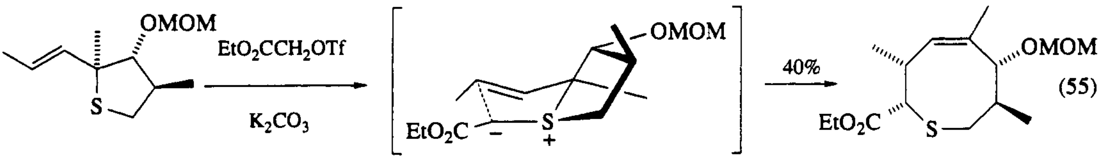

(55)

**(179)** **(180)**

## 4.6.3 FORMATION OF CARBON-HETEROATOM BONDS

### 4.6.3.1 Sulfoxide–Sulfenate Rearrangement

The interconversion of C—O and C—S bonds is realized by the 2,3-sigmatropic shift of β,γ-unsaturated sulfoxides/sulfenates. In a higher oxidation state a sulfone–sulfinate 2,3-rearrangement is known; this is of little importance in synthetic chemistry as it is associated with a stepwise rearrangement mechanism which interferes even in slightly hindered substrates.[108]

Allylic sulfoxides (**181**) and sulfenates (**182**) are related by a reversible reaction (equation 56). The equilibrium is shifted towards the sulfoxide. Due to the low barrier associated with this 2,3-shift optically active allylic sulfoxides can racemize at room temperature.[109] Accordingly, the reaction of an alcohol (**183**) with PhSCl *via* sulfenate (**182**) continues through the 2,3-rearrangement to the sulfoxide. Allylic sulfenates are very seldom isolable.[110] When, conversely, an allylic sulfoxide (**181**) is heated in the presence of a thiophile ($P(OMe)_3$, $R_2NH$, NaSR), the sulfenate (**182**) is removed from the equilibrium mixture by O—S bond cleavage. The ultimate reaction product obtained from an allylic sulfoxide, therefore, is an allylic alcohol (equation 56).

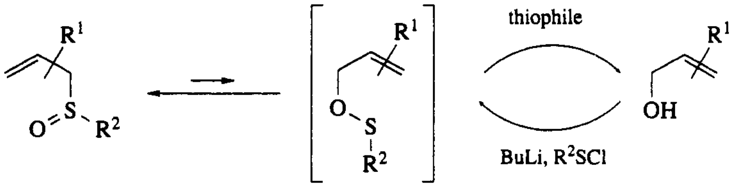

(56)

**(181)** **(182)** **(183)**

In such desulfurizing 2,3-rearrangements, the alcohol is usually sought and the thiophile–SR molecule undesired. One of the few instances where the thio compound was desired, is the conversion of sulfoxide (**184**) into a penem (equation 57).[111]

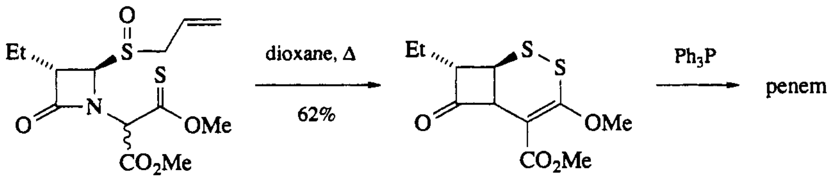

(57)

**(184)**

The stereochemical course of sulfoxide–sulfenate rearrangements was reviewed by Hoffmann in detail.[3] The results can be summarized as follows: (i) chirality transfer from the stereocenter on sulfur to carbon is only observed for sulfoxides without α-substituents (left-hand part of Scheme 23). Then, the (*Z*)-isomers react preferentially *via* the *endo* transition state (**185**) with up to 90% chirality transfer. (*E*)-Sulfoxides are less selective and therefore worthless as precursors for optically active rearrangement products. (ii) Any substituent $R^{\alpha}$ of the sulfoxide overrides stereocontrol originating in the stereocenter on sulfur (right hand part of Scheme 23). How chirality is transmitted is here determined exclusively by the desire of $R^{\alpha}$ to be quasi-equatorial in the transition state (**187**). At the same time, this orientation of $R^{\alpha}$ is tantamount to a *trans* configuration in the rearranged alcohol.

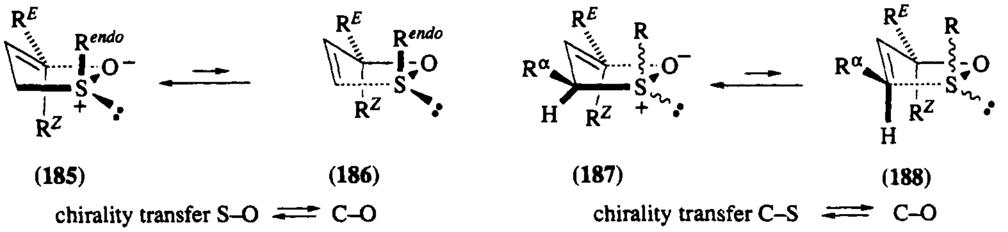
R^E
R^endo
O⁻
S
R^Z
+
O
R^α
H
R

(185) (186) (187) (188)

chirality transfer S–O ⇌ C–O chirality transfer C–S ⇌ C–O

Scheme 23

### *4.6.3.1.1 Chirality transfer and diastereoselectivity*

Chirality transfer from the C—S bond of sulfoxide (**189**) to the C—O bond of the sphingosine derivative (**190**) gave a single isomer (equation 58).[112] This type of chirality transfer will become more popular due to Whitesell's synthesis of suitable homochiral sulfoxides (equation 59).[113]

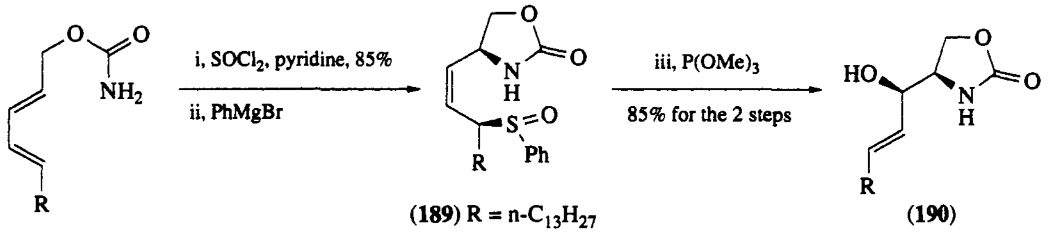
NH2
R
i, SOCl2, pyridine, 85%
ii, PhMgBr
N
H
S=O
Ph
iii, P(OMe)3
85% for the 2 steps
HO
(189) R = n-C13H27
(190)

(58)

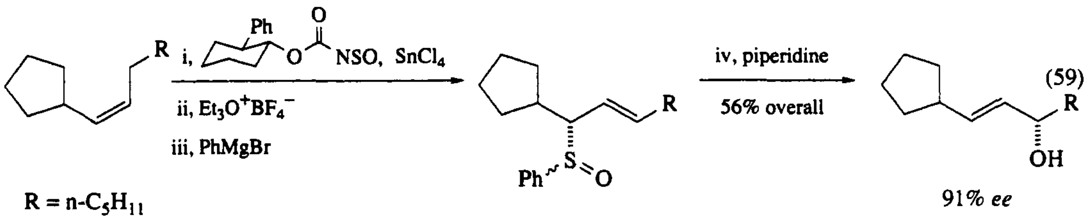
R
i, Ph O NSO, SnCl4
ii, Et3O+BF4−
iii, PhMgBr
R = n-C5H11
Ph S O
iv, piperidine
56% overall
OH
91% ee

(59)

Chirality transfer in cycloalkenes is a more common practice. Equations (60)–(62) illustrate stereoselective syntheses of cyclohexenols.[110,114,115] Similar functionalizations of medium-sized rings are also known (10-membered[116] and 14-membered[117]). The many different ways to access allylic sulfoxides make their rearrangements a particularly versatile tool.

Unlike the foregoing rearrangements, that of sulfoxides (**191**) and (**193**) was accomplished with only one of the epimers (equation 63).[118] The reactive epimer was believed to be (**191**) because of its similarity with the favorable transition state (**185**) from Scheme 23. Going from the sulfenate (**194**) to sulfoxide (**195**; equation 64),[119] the phenyl group prefers the opposite orientation compared with the

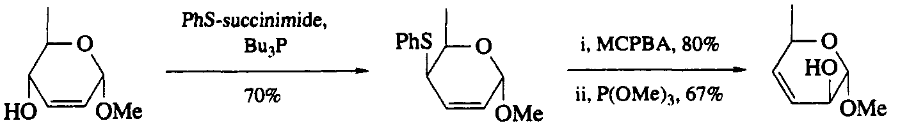
O
HO
OMe
PhS-succinimide,
Bu3P
70%
PhS
i, MCPBA, 80%
ii, P(OMe)3, 67%
HO

(60)

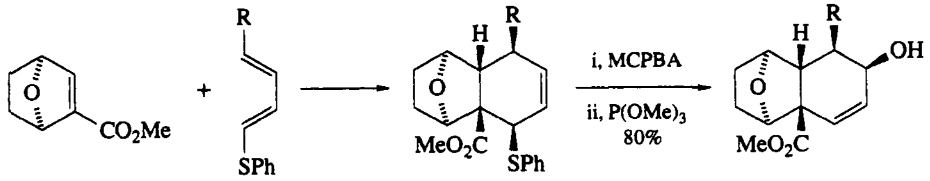
O
CO2Me
+
R
SPh
H
MeO2C
i, MCPBA
ii, P(OMe)3
80%
OH

(61)

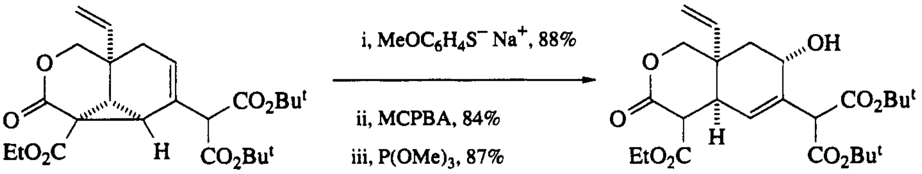

(62)

rearrangement (**191**) → (**192**). Obviously, the stereochemistry of equations (62) and (63) warrants a reconsideration.[120]

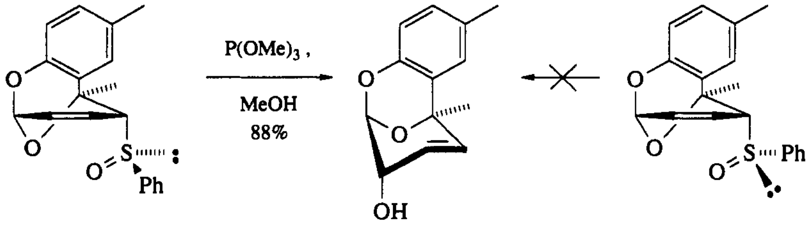

(**191**) (**192**) (**193**) (63)

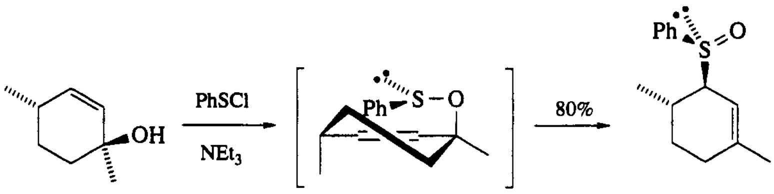

(**194**) (**195**) (64)

In the *exo*-methylenecyclohexane (**196**) two diastereotopic faces of a C=C bond are available for the sulfoxide rearrangement. Under various desulfurization conditions the less hindered equatorial attack predominates (equation 65).[121] The greatest equatorial selectivity (92:8) was observed with the strongest thiophiles, *i.e.* $P(OMe)_3$ or $P(NEt_2)_3$. Piperidine gave less equatorial alcohol (66:34). Presumably, $P(OMe)_3$ captures the kinetically formed mixture of sulfenates, while partial equilibration of the isomers precedes the S—O bond cleavage with piperidine.

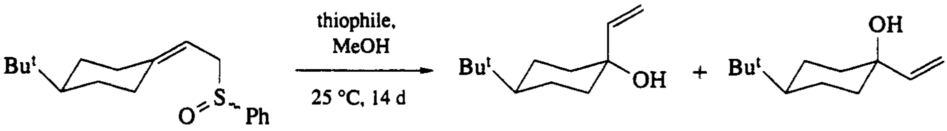

(**196**) (65)

| *Thiophile* | *Yield (%)* | *Equatorial attack* | : | *Axial attack* |
|---|---|---|---|---|
| LiBH₃CN | 24 | 58 | : | 42 |
| Piperidine | 90 | 66 | : | 34 |
| PhS⁻ | 99 | 88 | : | 12 |
| P(OMe)₃, P(NEt₂)₃ | 99 | 92 | : | 8 |

The *exo*-methylenecyclopentane (**197**) is also functionalized on the less hindered side upon rearrangement (Scheme 24).[122] The isomeric sulfoxide *epi*-(**197**) gave the same product (**198**) but more slowly. The retarding effect is due to the enforced *exo* orientation of the phenyl group in the transition state while *endo* is preferred (*cf.* Scheme 23).

Selective attack on one of the two diastereotopic faces of an endocyclic alkene (**199**) is encountered occasionally.[123] However, in the absence of an α-substituent, the chiral center on the sulfur of (**199**) exerts stereochemical control itself (*cf.* **185** in Scheme 23). Hence, selectivities caused by the ring factors

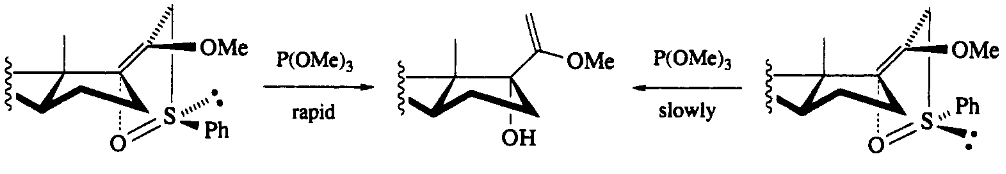
OMe
S
Ph
O
P(OMe)3
rapid
OMe
OH
P(OMe)3
slowly
OMe
Ph
S
O

**(197)** **(198)** *epi*-**(197)**

**Scheme 24**

may be compensated for in part.[124,125] In case of lack of diastereofacial selectivity in the 2,3-rearrangement of sulfoxide (**199**), stereocontrol can be restored in a secondary sulfoxide (**200**; Scheme 25).[126] The propensity of the side chain to become a *trans* alkenic substituent (*cf.* Scheme 23) provides the key control element.

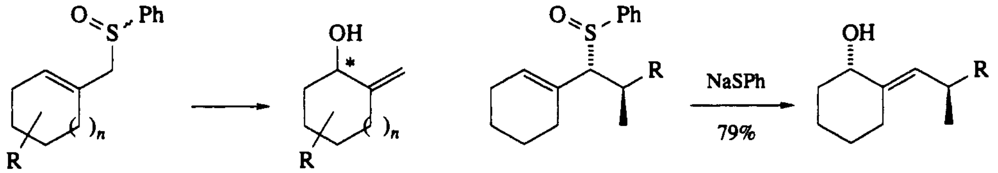
O
S
Ph
)n
R
OH
*
)n
R
O
S
Ph
R
NaSPh
79%
OH
R

**(199)** **(200)**

**Scheme 25**

### 4.6.3.1.2 Miscellaneous applications

A useful extension of sulfoxide–sulfenate rearrangements exploits the greater stability of allylic *vs.* vinylic sulfoxides.[127] For example, the Knoevenagel product (**202**) is deconjugated under the conditions of its formation. This sets the stage for a 2,3-rearrangement in the same pot (equation 66).[128] Optically active condensation products give hydroxy esters (**201**) with 64–72% *ee*.[129] 50–80% *ee* were reported for the analogous synthesis of the corresponding hydroxy nitriles.[130] The reaction of β-keto sulfoxides with aldehydes follows the same course of events (equation 67).[131]

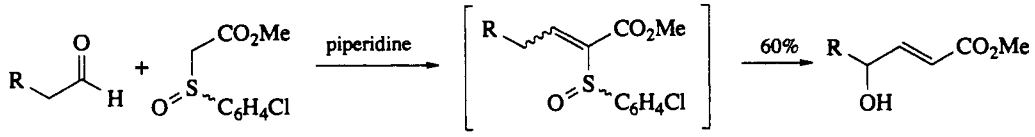
O
R
H
+
CO2Me
O
S
C6H4Cl
piperidine
R
CO2Me
O
S
C6H4Cl
60%
R
CO2Me
OH

(66)

**(201)**

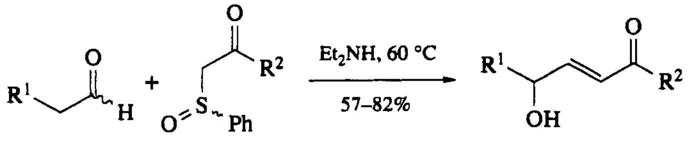
O
R1
H
+
O
R2
O
S
Ph
Et2NH, 60 °C
57–82%
R1
O
R2
OH

(67)

Sulfenate → sulfoxide and sulfoxide → sulfenate rearrangements were combined in the inversion of secondary[132] or tertiary allylic alcohols (equation 68).[133]

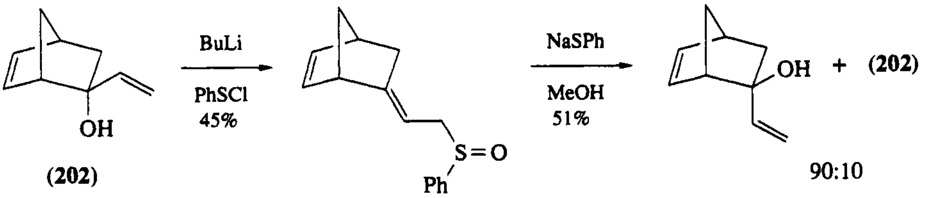
OH
BuLi
PhSCl
45%
S=O
Ph
NaSPh
MeOH
51%
OH
+ (202)
90:10

(68)

**(202)**

A beautiful application of two consecutive 2,3-sigmatropic shifts was provided by Corey (equation 69).[134] In a one-pot operation he elaborated sulfoxide (**203**) into sulfoxide (**204**), which gave an α,β,γ,δ-unsaturated aldehyde by a Pummerer rearrangement (for a similar application see ref. 135).

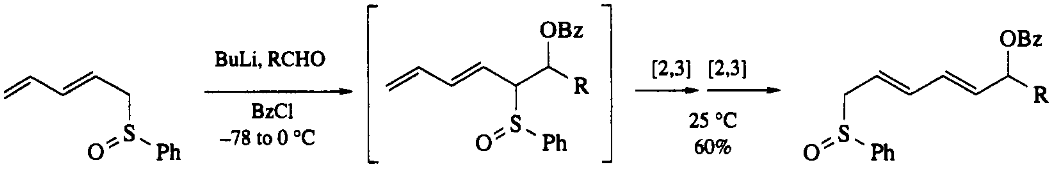

BuLi, RCHO
BzCl
-78 to 0 °C
OBz
R
O=S-Ph
[2,3] [2,3]
25 °C
60%

(69)

**(203)** **(204)**

The role of allylic sulfoxides as homoaldol equivalents in the synthesis of (*E*)-allylic alcohols was summarized earlier.[5] A more recent finding is that allylic sulfoxides are precursors for conjugated dienes (equation 70).[136] The elimination is regioselective but stereorandom. The 2,3-rearrangement of propargylic sulfenates gives allenyl sulfoxides. Allenyl sulfoxides are valuable synthetic intermediates. They can be converted into stereochemically homogeneous allenes, *e.g.* (**205**; equation 71).[137]

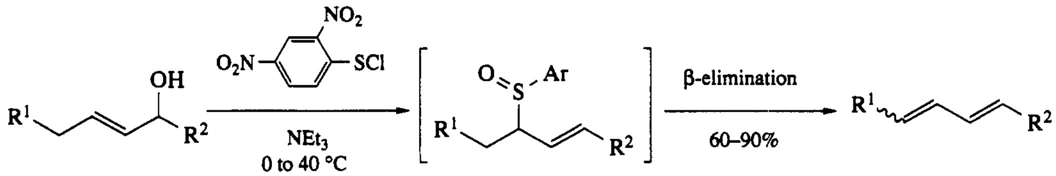

OH
R1
R2
NO2
O2N
SCl
NEt3
0 to 40 °C
O
S
Ar
β-elimination
60–90%

(70)

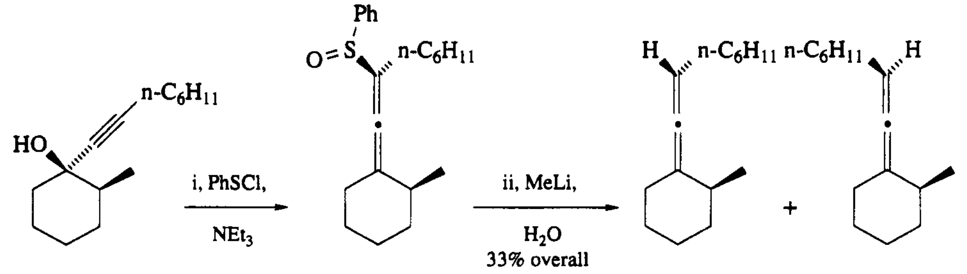

HO
n-C6H11
i, PhSCl,
NEt3
Ph
O=S
n-C6H11
ii, MeLi,
H2O
33% overall
H
n-C6H11
n-C6H11
H
+

(71)

**(205)** 96:4

Altenbach used the Michael addition of sodium methyl malonate to allene (**206**) for a diastereoselective spiroannulation to a steroid (equation 72).[138] Or, in imaginative work by Okamura, allenyl sulfoxides were transformed into enantiomerically pure hydrocarbons by pericyclic reactions like electrocyclic ring closure (equation 73)[139] or intramolecular cycloaddition (equation 74).[140] Note that the starting materials (propargylic alcohols) are readily accessible as single enantiomers.

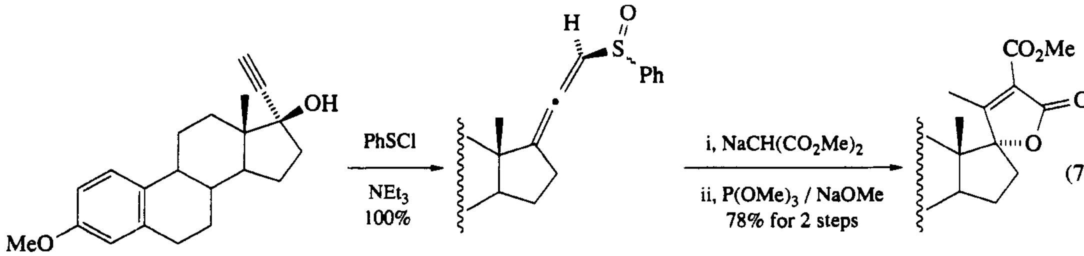

OH
MeO
PhSCl
NEt3
100%
H
O
S
Ph
i, NaCH(CO2Me)2
ii, P(OMe)3 / NaOMe
78% for 2 steps
CO2Me
O
O

(72)

**(206)**

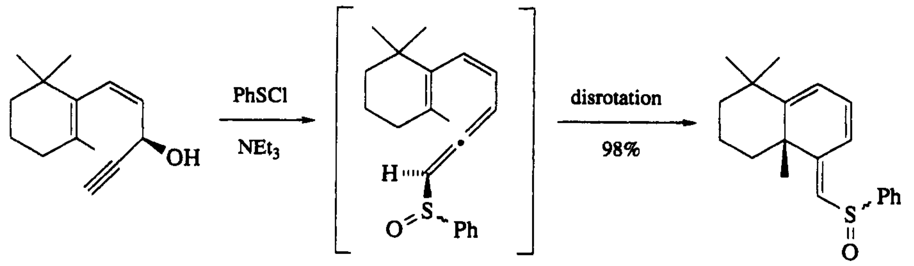

OH
PhSCl
NEt₃
H
O
S
Ph
disrotation
98%
Ph
S
O

(73)

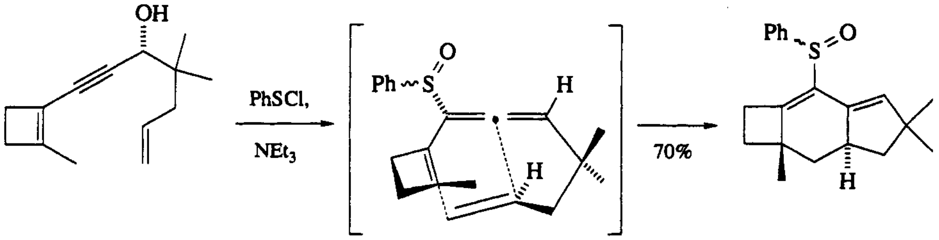

OH
PhSCl,
NEt₃
O
Ph
S
H
H
70%
Ph
S
O
H

(74)

### 4.6.3.2 Selenoxide–Selenate Rearrangement

According to Reich, selenoxides (**207b**) rearrange to selenates (**208b**) extremely fast compared with the reaction rate going from sulfoxide (**207a**) to sulfenate (**208a**; equation 75).[141] In addition, the more stable in a pair of isomers is structurally different, *i.e.* sulfoxide and selenate, respectively. Probably, this relationship reflects the smaller overlap in Se=O *vs.* S=O double bonds. From the equilibrium constant $K_{eq}$, one obtains 11 kcal $mol^{-1}$ (1 cal = 4.18 J) driving force for the conversion of a selenoxide into a selenate. This amount is sufficient to overcome the aromaticity of furan (**209**; equation 76).[141]

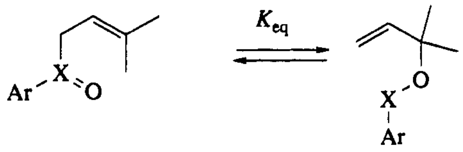

Ar
X
O
$K_{eq}$
O
X
Ar

**(207)** Ar = 4-$O_2NC_6H_4$ **(208)**

| | *X* | $K_{eq}$ | $\Delta G^\ddagger$ *(207) → (208)* (kcal $mol^{-1}$) |
|---|---|---|---|
| **(a)** | S | 0.042 | 19.8 (–30 °C) |
| **(b)** | Se | $10^{12}$ | 13.5 (–80 °C) |

(75)

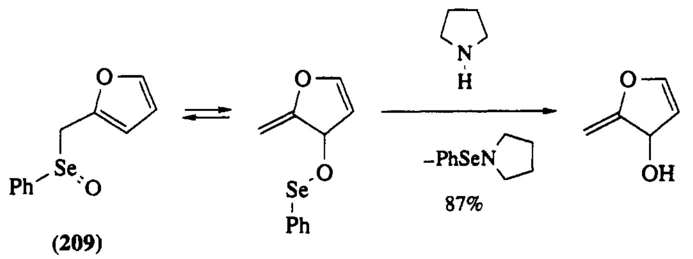

O
Ph
Se
O
O
O
Se
Ph
N
H
-PhSeN
87%
O
OH

**(209)**

(76)

In fact, allylic selenoxides (**207b**) are so unstable with respect to their rearrangement products that they are never (**209** is an exception) isolated. The oxidation of an allylic selenide leads, after hydrolysis, directly to the rearranged alcohol. Equation (77) demonstrates how such a rearrangement can be incorporated in the diastereoselective 1,3-transposition of an allylic alcohol.[142]

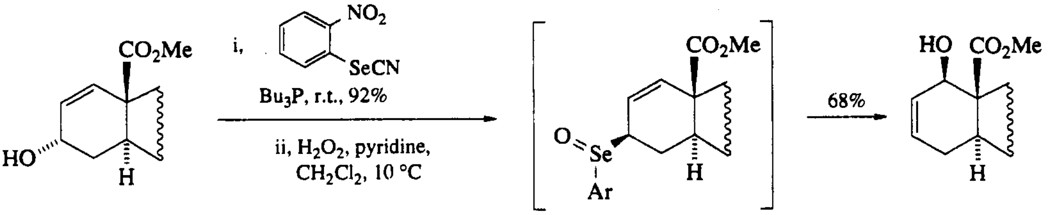

CO₂Me
HO
H
i, NO₂ SeCN
Bu₃P, r.t., 92%
ii, H₂O₂, pyridine, CH₂Cl₂, 10 °C
CO₂Me
O
Se
Ar
H
68%
HO CO₂Me
H

(77)

Sulfide and selenide precursors for 2,3-rearrangements can be obtained stereochemically pure by chalcogeno-etherifications (equation 78).[143] From these precursors thio-(**211**) and seleno-(**211**) were prepared by oxidation. While the sulfoxide refused to rearrange to alcohol (**212**) under various conditions, the selenoxide did so even at 0 °C. Here, the extra driving force of selenoxide *vs.* sulfoxide rearrangements was an essential; it pushed the selenoxide through a transition state obviously too sterically hindered for the less reactive sulfur analog.

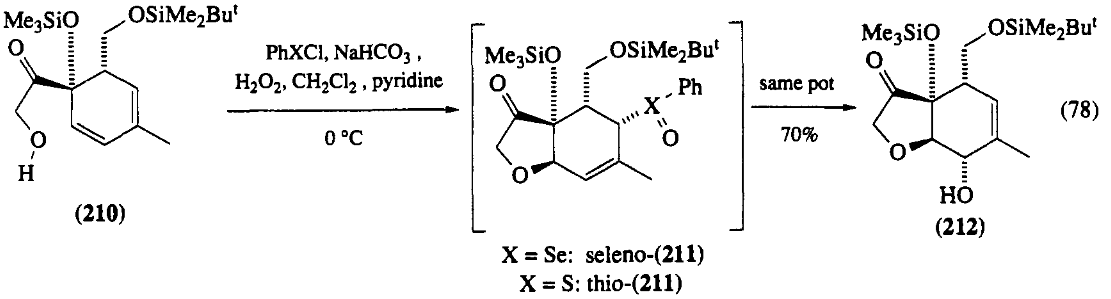
Me₃SiO
OSiMe₂Buᵗ
O
O
H
(210)
PhXCl, NaHCO₃,
H₂O₂, CH₂Cl₂, pyridine
0 °C
X
Ph
O
same pot
70%
HO
(212)
(78)
X = Se: seleno-(211)
X = S: thio-(211)

To use a selenate instead of a sulfoxide rearrangement for the preparation of allylic alcohols can be advantageous if silicon is present in the starting material. Vedejs found that the allylsilane (**213**) could be selenylated to give (**214**; equation 79);[144] this reaction includes a rapid 1,3-shift of the initially formed selenide. Oxidation and 2,3-rearrangement to the alcohol (**215**) followed uneventfully.

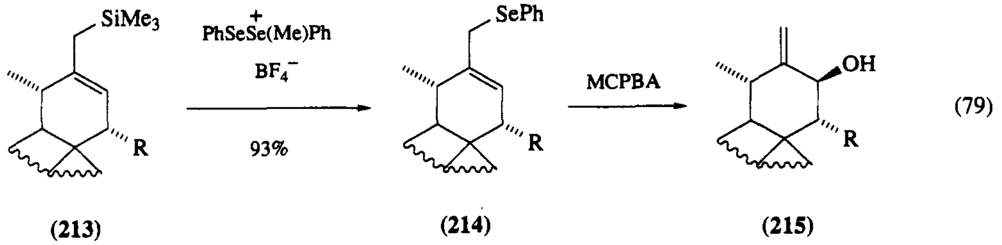
SiMe₃
R
(213)
PhSeSe(Me)Ph +
BF₄⁻
93%
SePh
R
(214)
MCPBA
OH
R
(215)
(79)

### 4.6.3.3 Introduction of Allylic Nitrogen

Primary and secondary allylic amines can be prepared from allylic selenides.[145] Chirality transfer from the C—Se to the C—N bond may be included for stereocontrol (equation 80).

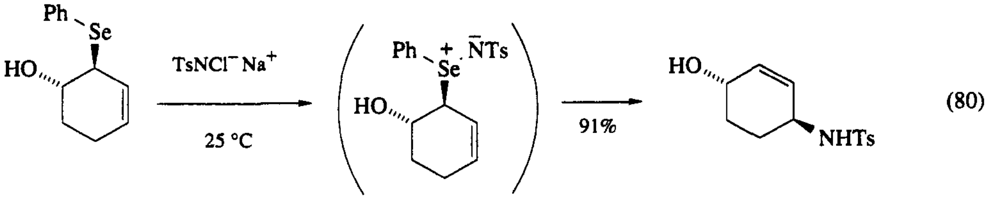
Ph
Se
HO
TsNCl⁻Na⁺
25 °C
Ph + NTs
Se
HO
91%
HO
NHTs
(80)

A similar amination is known in the sulfur series (equation 81).[146] Here, the reactive species is generated *in situ* from (**216**). Deprotonation and reprotonation isomerize the vinylsulfimide (**216**) to an allylsulfimide which gives the amino compound (**217**). (**217**) exhibits the expected (*cf.* Scheme 25) (*E*)-configuration of the C=C bond.

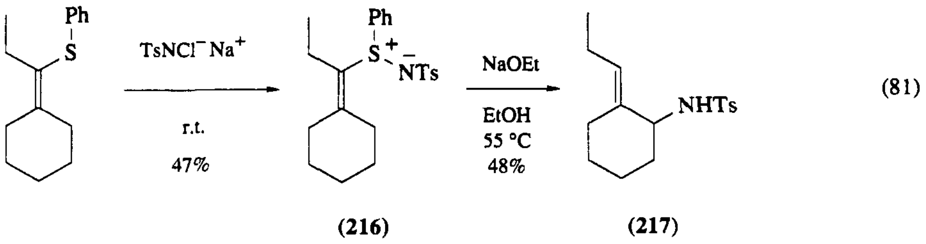
Ph
S
TsNCl⁻Na⁺
r.t.
47%
Ph
S + −
NTs
(216)
NaOEt
EtOH
55 °C
48%
NHTs
(217)
(81)

[4 + 2] cycloadditions and 2,3-rearrangements are involved in *cis* vicinal bisaminations of certain 1,3-dienes (Scheme 26).[147,148] In these reactions, chirality is transferred from C—Se or C—S bonds to C—N bonds.

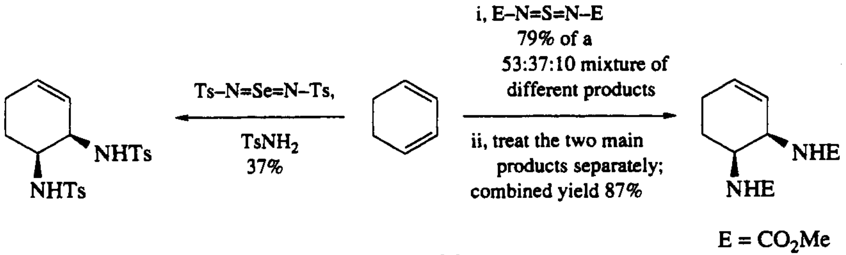

Scheme 26

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# 4.7

# Polonovski- and Pummerer-type Reactions and the Nef Reaction

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## 4.7.1 INTRODUCTION

In 1927 the Polonovskis reported their discovery that treatment of a tertiary amine *N*-oxide with acetic anhydride or acetyl chloride results in a rearrangement in which one of the alkyl groups attached to nitrogen is cleaved and the *N*-acetyl derivative of the corresponding secondary amine and aldehyde are obtained (equation 1).[1,2] Although originally considered to be a mild method for *N*-demethylation of tertiary amines, it is now recognized that the Polonovski reaction provides ready access to iminium ions, enamines, tertiary amides and/or secondary amines and aldehydes.[3–6]

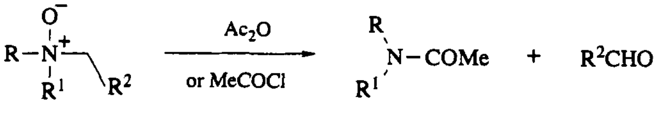

(1)

The central feature of this reaction is the transformation of an *N*-oxide to an iminium ion intermediate. Depending upon the *N*-oxide structure and the acid anhydride or other activating reagent employed, this can occur through loss of an α-hydrogen or through fragmentation of a Cα–carbon bond (equation 2).

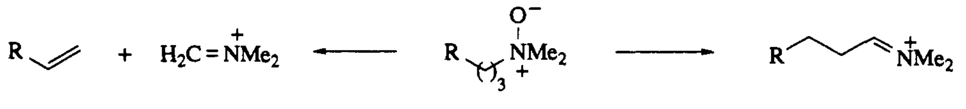
(2)

In principle, any reagent capable of activating the *N*-oxide oxygen can promote the Polonovski reaction. However, acid anhydrides, and in particular trifluoroacetic anhydride (the modified Polonovski reaction), are usually employed. The discussion in this chapter will therefore be limited mainly to the use of acid anhydrides. Brief mention is made in Sections 4.7.2.5 and 4.7.2.6 of the use of iron salts, sulfur dioxide and organo-silicon and -selenium derivatives as activating agents.

Also discovered near the beginning of the century,[7] the Pummerer reaction can be broadly defined as a reaction in which a sulfoxide bearing at least one α-hydrogen can readily be transformed to α-substituted sulfides upon treatment with electrophilic reagents.[8–11] The net result is a redox reaction in which the sulfoxide group is reduced to the sulfide and the α-carbon is oxidized. When acetic or trifluoroacetic anhydride is used as the activating reagent, acyloxy sulfides are formed (equation 3). These labile products are readily hydrolyzed in aqueous media to the corresponding thiol, formaldehyde and either acetic or trifluoroacetic acid.

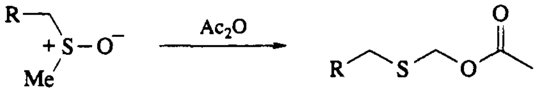

(3)

In many respects the Pummerer reaction can be regarded as the sulfur version of the Polonovski reaction (and *vice versa*), and by analogy to the Polonovski reaction the central intermediate is a sulfur-stabilized carbocation (thionium ion). Although the existence of this species is only transient, it reacts to give a number of different products, *e.g.* α-acetoxy sulfides, vinyl sulfides, cationic cyclization products, *etc.*, depending upon the sulfoxide structure and reaction conditions. Other reaction pathways are specific to the Pummerer reaction as a result of sulfur's ability to expand its valence shell (additive Pummerer reactions). A moderate degree of asymmetric induction is also observed in certain Pummerer reactions, where optically pure sulfoxides are substrates.

Although the emphasis in this chapter is placed on the use of acid anhydrides in the Pummerer reaction, a number of other activating reagents, *e.g.* acids, in particular *p*-toluenesulfonic acid, and trialkylsilyl halides, have been employed. Mention of these reagents is made in cases where their use leads to an improvement in yields or selectivity, or to a transformation which is not possible using an acid anhydride. Acetyl chloride is usually not employed in the Pummerer reaction because of the simultaneous presence of acetate ion and chloride ion in the reaction medium. The product of these reactions is predominantly the thioacetal derived from spontaneous decomposition of the initially formed α-acetoxy sulfide.

The reaction of sulfides bearing α-methylene hydrogens with halogenating agents, to form α-halo sulfides, can be classified as a Pummerer reaction of halosulfonium salts.[8] With chlorine and bromine it is sometimes difficult to limit the reaction to monosubstitution. However, monosubstituted products are produced in high yields using *N*-halosuccinimides, sulfuryl and thionyl chloride and cyclic phosphorus chlorides. The α-halo sulfides obtained in these reactions react in an identical fashion to the α-acyloxy sulfides obtained in the classical Pummerer reaction of a sulfoxide.

The Nef reaction, discovered in 1894, involves the transformation of a carbon bearing a primary or a secondary nitro group to the corresponding aldehyde or ketone (equation 4).[12] The addition of acetylides to aldehydes or ketones is also sometimes referred to as the Nef reaction, since the first example was also reported by Nef.[13] The resultant alcohol may be looked upon as a protected form of the alkynic group, which is easily regenerated according to a 'retro-Nef reaction' (equation 5).[14]

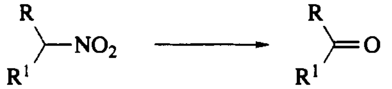

(4)

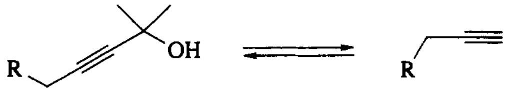

(5)

In this chapter the Nef reaction refers to the reaction of nitroalkanes. As nitro compounds are readily available and can be involved in a variety of reactions, the Nef reaction often represents the key transformation in a reaction sequence. A review of this topic appeared in 1990[15] and an article has been published on the chemistry of nitroaliphatic compounds, including the Nef reaction.[16]

## 4.7.2 THE POLONOVSKI REACTION

### 4.7.2.1 Mechanism

The first step in the Polonovski reaction of an amine *N*-oxide with an acid anhydride, acyl chloride or chloroformate ester is the formation of the *O*-acylimonium salt (**1**; Scheme 1). Such species are highly unstable. However, they can be detected *in situ* ($^1$H NMR), and in certain cases actually isolated, if prepared using powerful acylating agents such as acetyl perchlorate.[17]

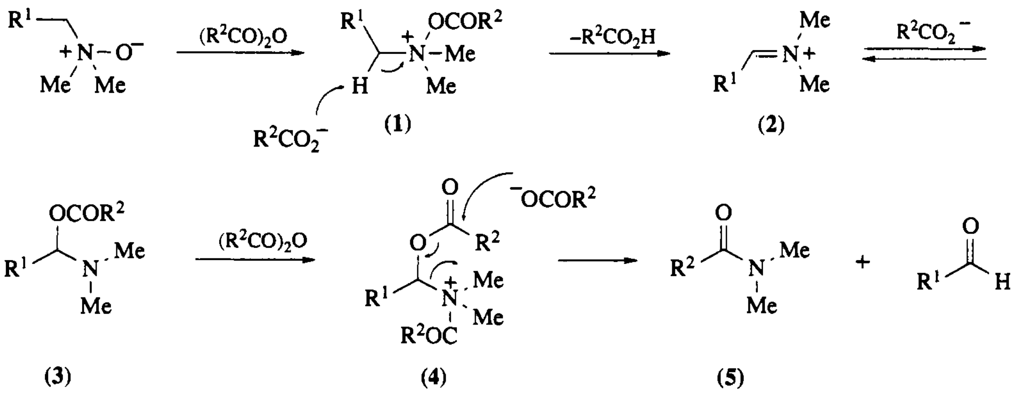

Scheme 1

The conversion of (**1**) to the iminium ion (**2**) occurs by an ionic *E*2-type elimination mechanism.[17-19] In support of this mechanism, the Polonovski reaction is accelerated by the addition of acetate ion or amine bases, and markedly decelerated when carried out in acidic media. These observations point to the involvement of the counterion $R^2CO_2^-$ in the removal of the proton from the α-carbon. Further support comes from studies which demonstrate that there is a pronounced preference in nonbiased systems for loss of the hydrogen which is antiperiplanar to the N—O bond.

The subsequent position of the equilibrium reaction between the iminium ions (**2**) and their addition products (**3**) is a function of both the nucleophilicity of the counterion $R^2CO_2^-$ and the acidity of the reaction medium. When $R^2CO_2^-$ is an acetate anion, this equilibrium is displaced entirely toward intermediates (**3**). Such α-acetoxymethylamines are very labile entities; however, under special conditions they can be isolated.[20] In the presence of trifluoroacetic acid, intermediate (3) reverts back to the iminium ion. This reversibility and the low nucleophilicity of the trifluoroacetate anion explain why the modified Polonovski reaction using trifluoroacetic anhydride does not proceed beyond the iminium ion stage. This characteristic of the modified Polonovski reaction has considerable synthetic potential, as discussed in the following sections.

The elaboration of the acetoxymethylamines (3) to the corresponding tertiary amides (5) can occur during aqueous work-up and *in situ* under nonhydrolytic conditions by reaction with a further molecule of acetic anhydride, followed by acetate ion promoted fragmentation of intermediates (4).

The alternative Polonovski reaction mode, in which $C_\alpha$—C bond cleavage is observed, can occur if two conditions are met (equation 6): (i) the $C_\alpha$—C bond to be broken is activated towards cleavage by an adjacent electron-donating center (double bond, aromatic ring or heteroatom); and (ii) the $C_\alpha$—C and N—O bonds are antiperiplanar.

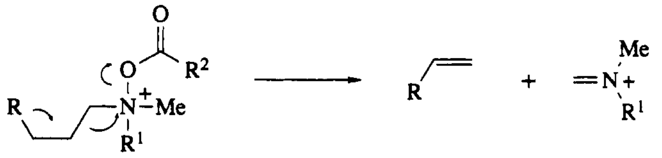

(6) (7) (8)

(6)

The reaction by which (6) is transformed to (7) and the iminium ion (8) is, in fact, a manifestation of the Grob fragmentation,[21] and is of considerable interest because extensive modification of the tertiary amine structure is achieved in a single operation.

## 4.7.2.2 Carbon–Hydrogen Elimination Reactions

As mentioned above, the capacity of the intermediate iminium ion (2) to condense with its counterion is a crucial product-determining step. This is illustrated by the reaction of trimethylamine *N*-oxide with acetic and trifluoroacetic anhydride (Scheme 2). With acetic anhydride the *N*-demethylated product dimethylacetamide is formed in high yield,[18] whereas with trifluoroacetic anhydride under similar conditions the iminium ion (9), a synthetically useful Mannich reagent, is generated in nearly quantitative yield.[22]

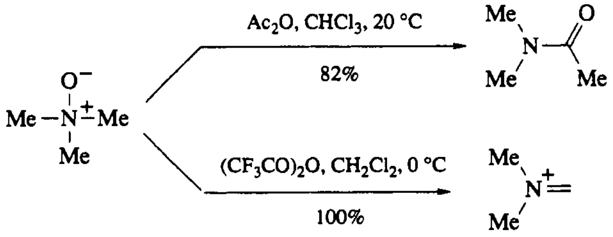

(9)

Scheme 2

### 4.7.2.2.1 *Regio- and stereo-chemistry*

For an unsymmetrical *N*-oxide the regiochemistry of the Polonovski reaction is determined by a preference for loss of a proton from either of the carbon centers α to the nitrogen in the step which forms the iminium ion, as illustrated in Scheme 1. The anhydride plays a fundamental role in the orientation of this *E*2 elimination reaction, since both the base and the leaving group on the nitrogen are derived from it. As a rule it is found that the thermodynamically more stable iminium ion is produced when trifluoroacetic anhydride is employed, while with acetic anhydride the product obtained generally depends upon the kinetic acidity of the α-hydrogens. These results reflect the fact that with trifluoroacetic anhydride an excellent leaving group is generated along with a weak base, whereas with acetic anhydride a comparatively poor leaving group and a much stronger base are produced.

These arguments are evoked to explain the results obtained in the reaction of *N*-oxide (**10**) with different acid anhydrides (Scheme 3).[23] Thus with stronger bases ($Et_3N > MeCO_2^- > Cl^-$) the *E*1cB character of the transition state is considered to be enhanced, favoring the formation of (**12**) *via* the less stable iminium ion intermediate (**11**). Opposed to this is the trend with better leaving groups ($CF_3SO_3^- > CF_3CO_2^- > MeCO_2^-$) towards formation of compound (**14**) *via* the more stable iminium ion (**13**).

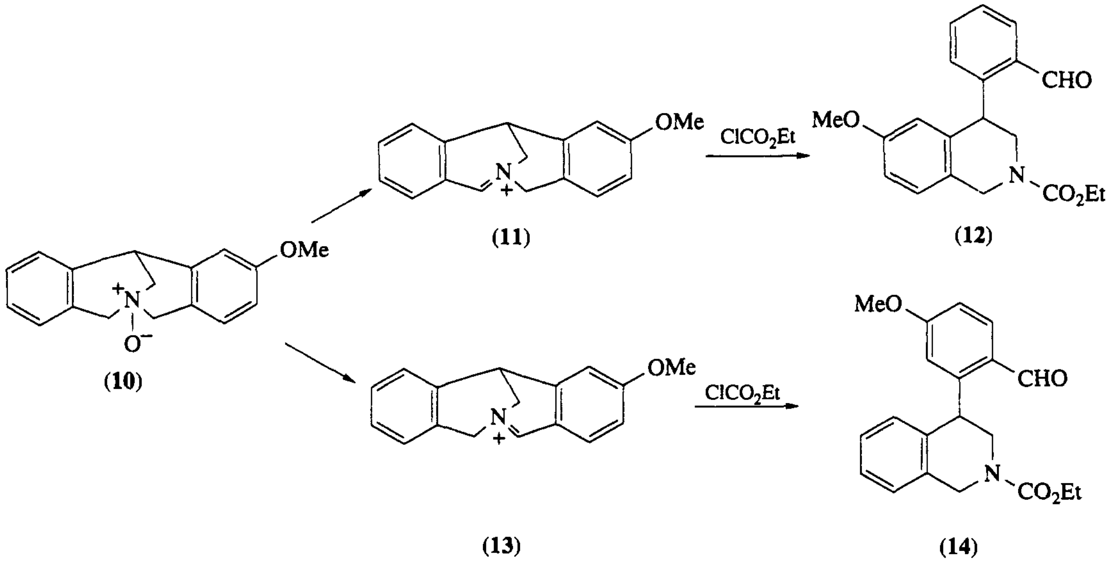

| | *(12):(14)* | *Yield (%)* | | *(12):(14)* | *Yield (%)* |
|---|---|---|---|---|---|
| $Ac_2O$, 12 h | 2:1 | 75 | $(CF_3CO)_2O$ | 1:1 | 95 |
| $Ac_2O$, $Et_3N$, 30 min | 3:1 | 71 | $(CF_3SO_2)_2O$ | 1:5 | 89 |
| MeCOCl | 1:1 | 92 | $CF_3SO_2Cl$ | 1:2 | 25 |

**Scheme 3**

As might be expected, when the acidity of an α-hydrogen is increased by the presence of an adjacent electron-withdrawing group, double bond or aromatic ring, the Polonovski reaction occurs predominantly, if not exclusively, in the direction of the activated center. However, the influence of such a group is overcome if the *N*-oxide is incorporated into a piperidine ring as in (**15**; equation 7). The greater stability of the intermediate endocyclic iminium ions is responsible for this effect.

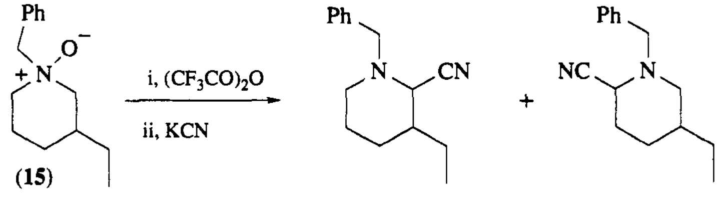

(7)

Unfortunately, in 3-alkyl-substituted piperidine *N*-oxides there is generally little discrimination between the ring α-carbon centers, and mixtures of regioisomeric products are obtained. When a $\Delta^{3,4}$ double bond is present in the starting *N*-oxide, however, this functionality will direct the Polonovski reaction towards elimination of one of the allylic hydrogens. Thus, the (*Z*)-ethylidene product (**18**) is obtained from (**16**) after reduction of the conjugated iminium ion intermediate (**17**; equation 8).[24]

Formation of exocyclic iminium ions can be achieved under special circumstances where a functionality other than hydrogen is lost during the elimination step. One version of this technique takes advantage of the fact that carboxylic acid esters are readily hydrolyzed to the parent acids during *N*-oxide formation with hydrogen peroxide. Thus, on sequential treatment of the *N*-oxide (**19**) with hydrogen peroxide, trifluoroacetic acid and potassium cyanide the exocyclic, rather than the endocyclic, aminonitrile (**20**) is produced in 48% yield (equation 9).[25]

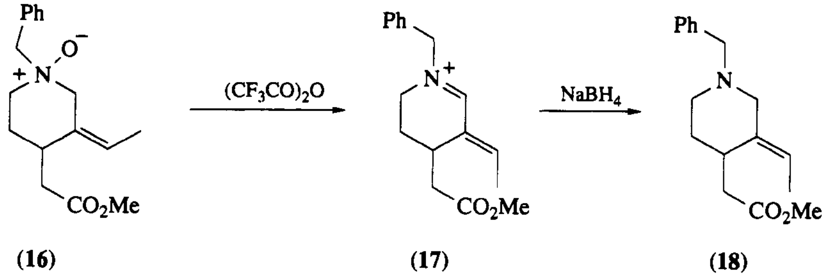

(8)

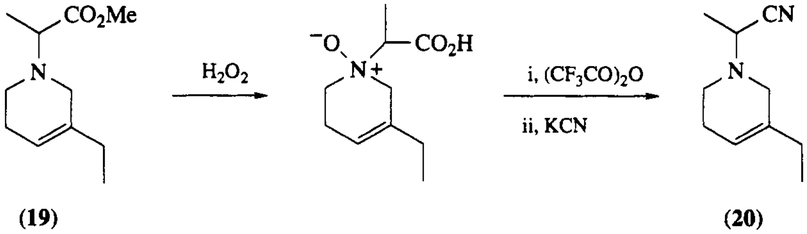

(9)

Studies of the Polonovski reaction in conformationally rigid polycyclic systems reveal the stereochemical requirements for the elimination step. For example, the 6β,7β-dideutero derivative (**22**) of nupharidine is converted on reaction with acetic anhydride into $\Delta^6$-dehydrodeoxynupharidine (**24**) containing a single deuterium atom at C$_\alpha$ (Scheme 4).[26]

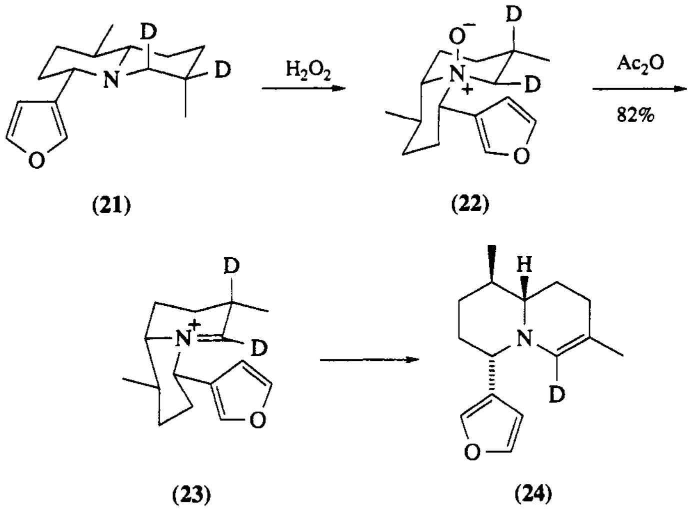

Scheme 4

The formation of the intermediate iminium ion (**23**) in the reaction thus involves loss of the 6α-H which is *trans* diaxial, *i.e.* antiperiplanar, to the N—O bond of (**22**). Although the *N*-oxide (**22**) could conceivably undergo the Polonovski reaction *via* its alternative *cis*-decalin conformer, this is highly improbable because in this conformation the three ring substituents would be axially oriented. Accordingly, the structure of an *N*-oxide cannot always be correlated with that of the free base because of the possibility of nitrogen inversion (compare **21** with **22**).

A similar high degree of stereoselectivity is observed in the Polonovski reaction of coccinelline (**25**; equation 10), which produces enamine (**26**) through loss of the *trans* diaxial hydrogen.[27]

The situation is more complicated in cyclic systems such as the indoloquinolizidine *N*-oxide (**27a,b**), where one of the α-carbon centers is activated by the presence of an aromatic (indole) substituent, as compound (**28**) is obtained from both the *cis* and *trans* isomers of (**27**; Scheme 5).[28] Since the relative rates and yields of the two reactions are comparable, it appears that *anti* elimination is not an absolute requirement for this and related Polonovski reactions.

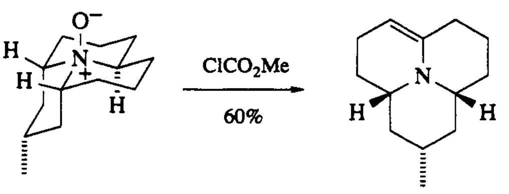

**(25)** **(26)** (10)

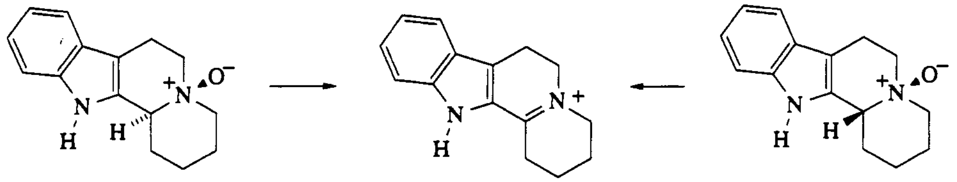

**(27a)** **(28)** **(27b)**

**Scheme 5**

For pyrrolidine *N*-oxides, one might *a priori* anticipate iminium ion formation to occur by a *syn* elimination process, since the N—O and adjacent $C_\alpha$—H bonds cannot become antiperiplanar to each other. However, the *N*-oxide (**29a**) of the steroid alkaloid conanine reacts with acetic and trifluoroacetic anhydride exclusively by the *anti* pathway to give the exocyclic enamine (**30**; Scheme 6).[29] Release of steric strain between the C-16 methylene and the ring methyl substituent is undoubtedly a major driving force in this reaction. More revealing is the reaction of *N*-oxide (**29b**), which would give the same enamine product if a *syn* pathway is favored. The observed formation of compounds (**31**) and (**32**) argues in favor of the *anti* elimination.

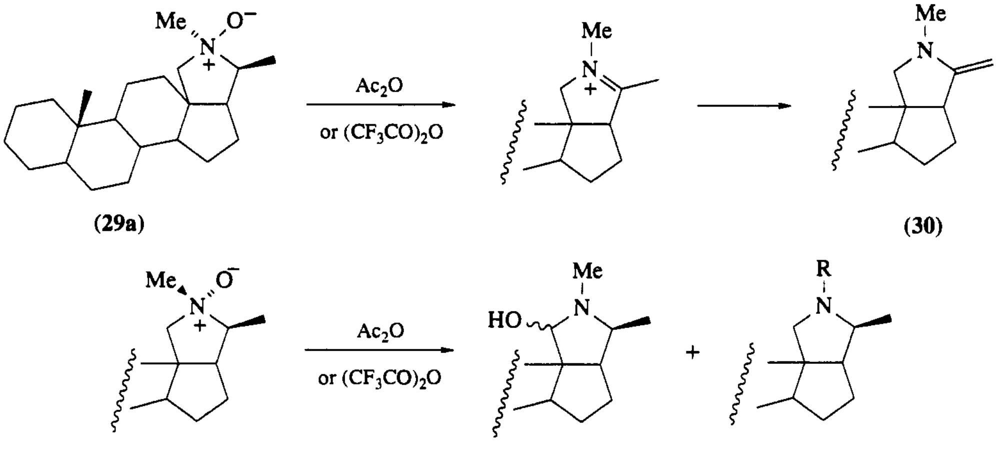

**(29a)** **(30)**

**(29b)** **(31)** 1:4 **(32)**

R = COMe (from $Ac_2O$);
R = H (from $(CF_3CO)_2O$)

**Scheme 6**

To date no reports of the Polonovski reaction of *N*-oxides of four- or seven- and higher-membered cyclic tertiary amines have appeared. Aziridine *N*-oxides can be prepared by ozonolysis of *N*-*t*-butylaziridine; however, these compounds are unstable above 0 °C.[30] At higher temperatures compound (**33**) undergoes first-order decomposition to ethylene and 2-methyl-2-nitrosopropane (equation 11).

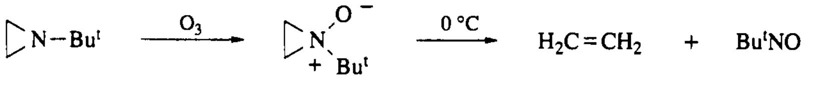

$$\text{N-Bu}^t \xrightarrow{O_3} (\mathbf{33}) \xrightarrow{0\,^\circ C} H_2C{=}CH_2 + Bu^tNO \qquad (11)$$

**(33)**

#### *4.7.2.2.2 Iminium ion cyclizations*

Iminium ion cyclizations such as the Pictet–Spengler reaction have been widely used in alkaloid chemistry to create a carbon–carbon bond between the carbon α to the basic nitrogen and an aromatic ring. The requisite iminium ions in these reactions are often readily available *via* the modified Polonovski reaction. Although two steps, *N*-oxide formation and reaction with trifluoroacetic anhydride, are involved, this approach is often preferable to the reaction of a tertiary amine with mercury(II) acetate, in which it is necessary to destroy the amine–mercury complex at the end of the reaction. In this way the secoheteroyohimbinoid *N*-oxide (**34**) was cyclized selectively to akuammigine (**35**; equation 12).[31] Using mercury(II) acetate a nearly equal mixture of (**35**) and its C-3 β-H epimer tetrahydroalstonine is obtained.

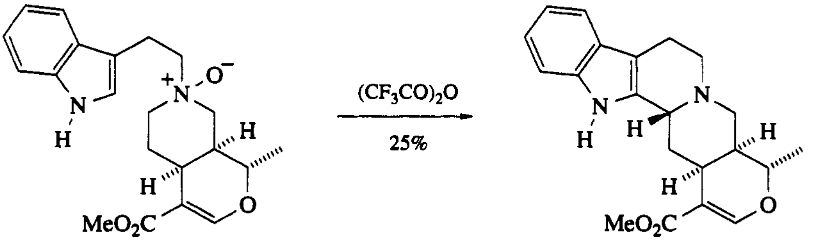

(**34**) (**35**) (12)

Carbon–carbon bond formation by intramolecular cyclization of conjugated iminium ions is also possible, as illustrated by the transformation of amine oxide (**36**) to (**37**), a key intermediate in the synthesis of the pyridocarbazole alkaloid ellipticine (**38**; Scheme 7).[32]

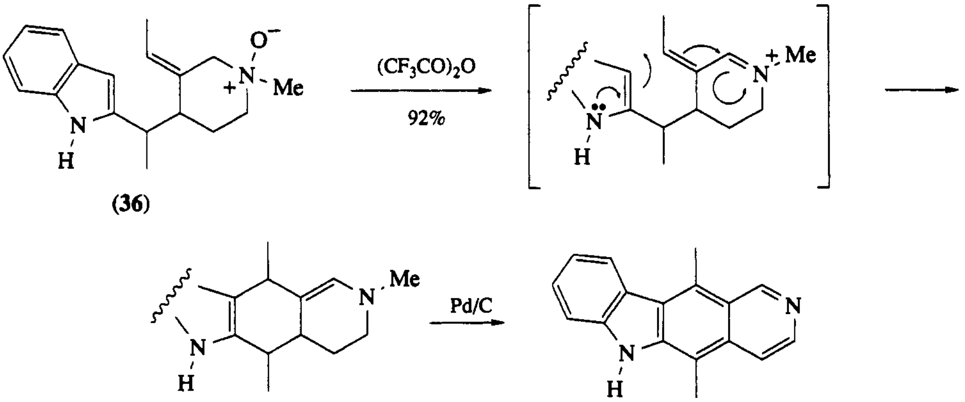

(**36**) (**37**) (**38**)

**Scheme 7**

With few exceptions the activation of a methyl group in an iminium ion cyclization is not efficient under modified Polonovski conditions. However, the yields of such reactions are significantly improved by using iron salts or sulfur dioxide as the activator (see Section 4.7.2.5).

#### *4.7.2.2.3 Formation of α-cyanoamines and related iminium ion reactions*

In a number of instances the iminium ion intermediates formed under Polonovski conditions are too reactive or labile to be employed as such in projected syntheses. The acidity of the Polonovski reaction medium is sometimes a further problem when considering *in situ* reactions with organometallic reagents and other carbon nucleophiles. One technique that can circumvent this problem is to convert these labile iminium ion intermediates into their more stable α-cyanoamine derivatives. There are two advantages to this approach. First, the reaction of cyanide ion with iminium salts generally gives high yields, and secondly, the resultant α-cyanoamines react efficiently as 'iminium ion equivalents' with a wide range of nucleophilic reagents. An additional gain is the possibility of effecting an 'umpolung' of the normal reactivity of iminium ions *via* the reaction of α-cyanoamine anions with electrophiles. The dual reactivity of these cyanide adducts thus broadens considerably the scope of application of iminium ions in synthetic chemistry.

The use of α-cyanoamines in place of their less stable iminium ion precursors often results in high product yields in the Pictet–Spengler and other ring closure reactions. Thus, the Polonovski-derived α-cyanoamine (**39a**) cyclized to (**40**) in 84% yield, whereas reaction of the tertiary amine (**39b**) with mercury(II) acetate was unsuccessful (equation 13).[33] The conversion of unstable 5,6-dihydropyridinium salts (**41**), obtained by reaction of tetrahydropyridine *N*-oxides with trifluoroacetic anhydride, into the stable, synthetically versatile tetrahydropyridine-2-carbonitrile (**42**) is another area in which use of this methodology has met with particular success (equation 14).[34]

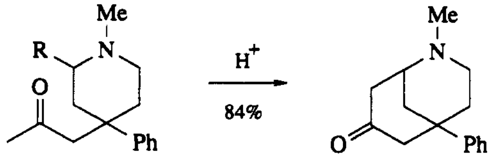

(**39a**) R = CN
(**39b**) R = H

(**40**)

(13)

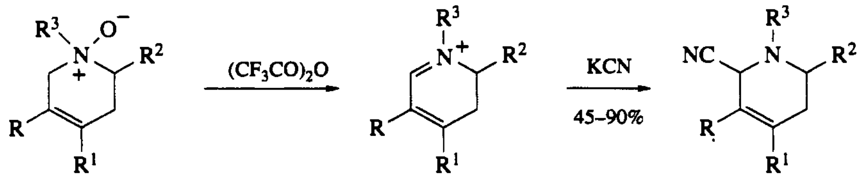

(**41**) (**42**)

(14)

The intramolecular reaction of an iminium ion with an oxygen nucleophile is the key step in the synthesis of dihydromancunine (**43**; equation 15).[35]

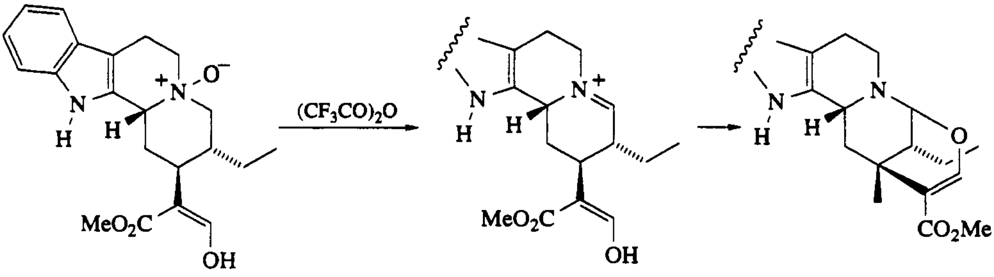

(15)

(**43**)

### 4.7.2.2.4 *Enamines*

Enamines can be obtained as the products of the Polonovski reaction of amine oxides and, in particular, by reaction of piperidine *N*-oxides with acetic anhydride. This is primarily due to the fact that when acetate is the counterion the intermediate iminium ions are labile and readily tautomerize. The formation of enamines during the Polonovski reaction is also favored by the presence of a base. In fact, enamines are often obtained in high yield from the reaction of an *N*-oxide with trifluoroacetic anhydride in the presence of triethylamine or pyridine. Conversion of intermediate iminium ions, generated under modified Polonovski conditions, to enamine products can also occur during hydrolytic work-up.

Reaction of the *N*-oxide (**44**) with acetic anhydride–pyridine provides a direct means for the *in situ* generation of the highly reactive dehydrosecodine intermediate (**45**).[36] This species undergoes spontaneous cyclization to give vincadifformine (**46**; 12%) *via* an intramolecular Michael reaction followed by B/C ring closure (Scheme 8). ψ-Vincadifformine (**48**) is also produced in this reaction *via* the enamine

(**47**), since a simple ethyl side chain in the starting *N*-oxide has no 'directing effect' on the iminium ion forming step.

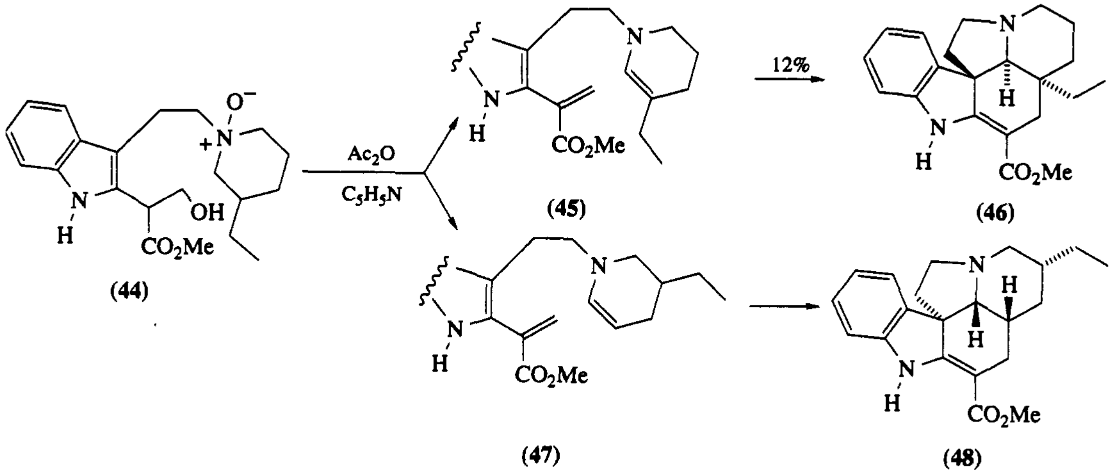

Ac$_2$O
C$_5$H$_5$N
12%
(44)
(45)
(46)
(47)
(48)
CO$_2$Me
OH
O$^-$
N
H

**Scheme 8**

The Polonovski reaction also provides a solution to the difficult problem of cleaving the glycoside bond linking an amino sugar to the aglycone in tysolin (**49**) and related 16-macrolide antibiotics. The idea is to generate an endocyclic enamine (**51**) so that the lone pair of electrons on nitrogen can assist in breaking the glycoside bond through a vinylogous β-elimination reaction (Scheme 9). Using acetic anhydride, the yield of the desired hemiacetal (**50**) is only 10%.[37] However, as might be expected under modified Polonovski conditions (trifluoroacetic anhydride–pyridine), the yield of (**50**) is significantly increased (65%).[38]

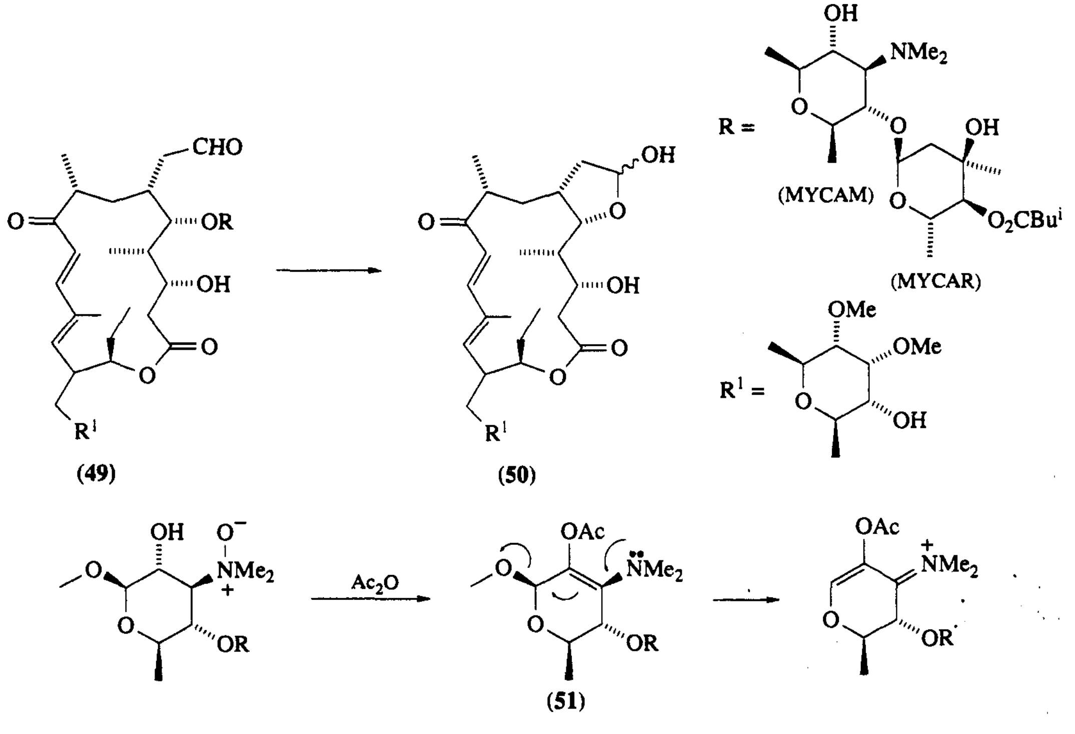

CHO
OR
OH
O
R$^1$
(49)
(50)
R =
NMe$_2$
(MYCAM)
O$_2$CBu$^i$
(MYCAR)
OMe
R$^1$ =
Ac$_2$O
OAc
(51)

**Scheme 9**

The enamino ketone (**54**) can also be prepared by a Polonovski approach, involving either sequential addition of *m*-chloroperbenzoic acid, acetic anhydride and triethylamine to a cooled solution of (**52**) in methylene chloride[39] or reaction of the *N*-oxide (**53**) with trifluoroacetic anhydride (Scheme 10).[40] Although the latter approach involves three distinct steps, the overall yield of (**54**) is higher.

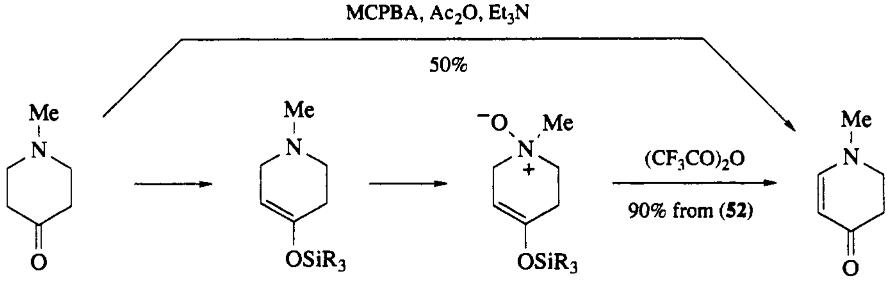

(**52**) (**53**) (**54**)

**Scheme 10**

#### *4.7.2.2.5 Pyrrole ring formation and other reactions of five-membered rings*

Although in cyclic systems studied to date the *N*-oxide function has been for the most part incorporated into a six-membered ring system, there are several examples where pyrrolidine or dihydropyrrole *N*-oxides are the substrates. For instance, the reaction of amine oxide (**55**) with acetic anhydride at 0 °C provides a convenient route to the *N*-alkylisoindole (**56**; equation 16).[41]

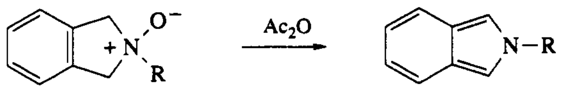

(16)

(**55**) (**56**)

The mitosane *N*-oxide derivative (**57**) is similarly converted into the pyrroloindole derivative (**58**) in high yield upon reaction with acetic anhydride in chloroform (equation 17).[42] The corresponding reaction of the 1,2-diacetoxy derivative (**59**) is more complex, however, as there is no directing functionality to orient the reaction (Scheme 11). One of the reaction products (**62**) is viewed as being formed *via* intermediates (**60**) and (**61**). If this mechanistic rationale is correct then the transformation of (**59**) to (**62**) represents a new manifestation of the Polonovski reaction.

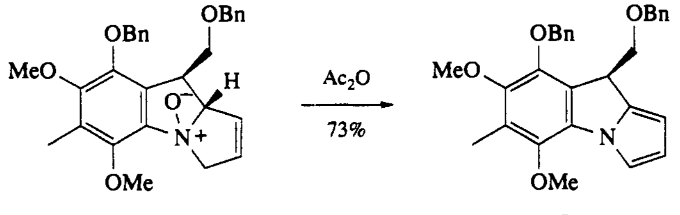

(17)

(**57**) (**58**)

### 4.7.2.3 Carbon–Carbon Fragmentation Reactions

As outlined in the section on mechanism, Polonovski reactions in which intermediate iminium ions are produced by fragmentation of the $C_\alpha$–carbon bond are of considerable interest in synthesis since extensive modification in structure is achieved in a single operation. However, not every *N*-oxide substrate can react in this manner. In fact, for this reaction mode to become operative, the $C_\alpha$–carbon bond to be broken must be both activated toward cleavage by an adjacent electron-donating center (double bond, aromatic ring or heteroatom) and be oriented antiperiplanar to the N—O bond.

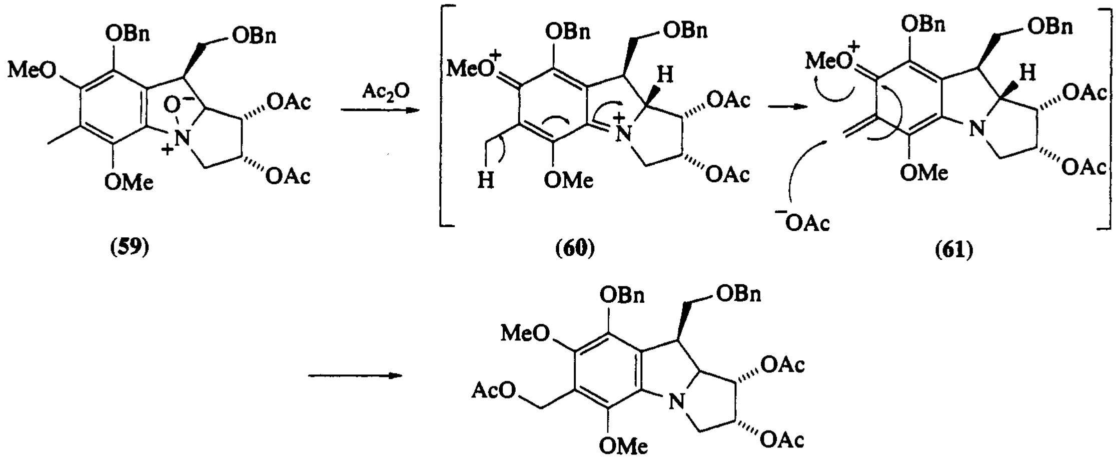

(59) (60) (61)

(62)

**Scheme 11**

The first example of this fragmentation reaction to be described is the conversion of the *N*-oxide (**63**) to the 17-oxa-D-homoandrostane derivative (**65**; Scheme 12).[43] The crucial step in this transformation involves the participation of the lone pair of electrons on oxygen in the departure of trifluoroacetate ion from the *O*-acylimonium salt intermediate (**64**).

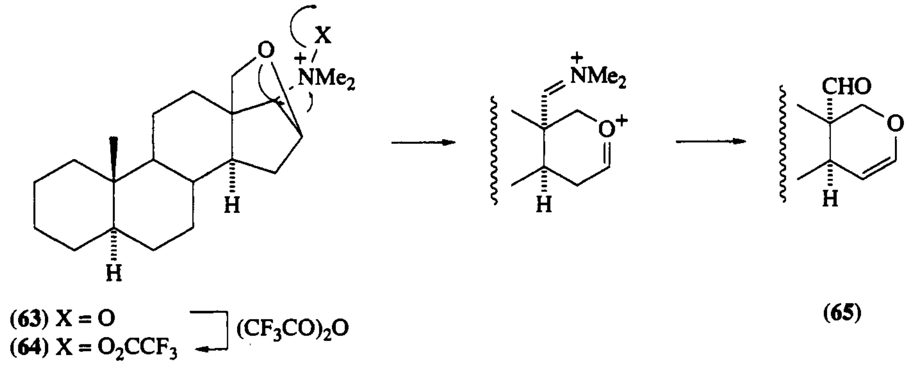

(65)

**Scheme 12**

Phenethylamine-type *N*-oxides also undergo carbon–carbon bond fragmentation under modified Polonovski conditions, as illustrated by the reaction of *N*,*N*-dimethyltryptamine *N*-oxide (**66**), wherein cleavage of the side chain is facilitated through participation of the electrons on the indole nitrogen (equation 18).[44] The ease with which *N*-oxide (**66**) undergoes fragmentation implies that the *in vivo* equivalent of this reaction is important in the biosynthesis of certain indole alkaloids, such as ellipticine (**38**)[45] and vallesamine (**67**; Scheme 13),[46] whose derivation from tryptophan is not immediately obvious.

Without doubt the most relevant and spectacular application of the Polonovski reaction is the development of the first successful method of preparation of the indole antitumor agent vinblastine (**68**). This

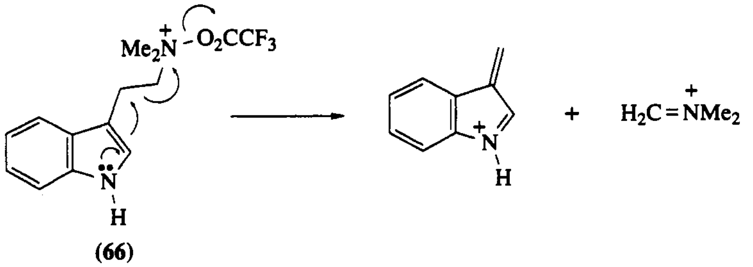

(66) (18)

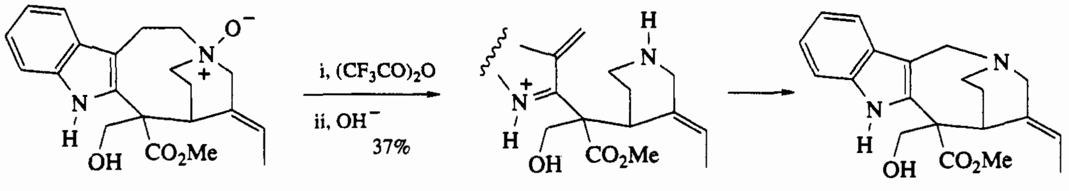

**(67)**

**Scheme 13**

difficult problem was resolved by reacting catharanthine *N*-oxide (**69**) with trifluoroacetic anhydride at > –50 °C in the presence of vindoline (**70**), followed by treatment with sodium borohydride (Scheme 14).[47,48] In this way the natural configuration dimer (**71**) is obtained in 50% yield along with only minor amounts of (**72**).

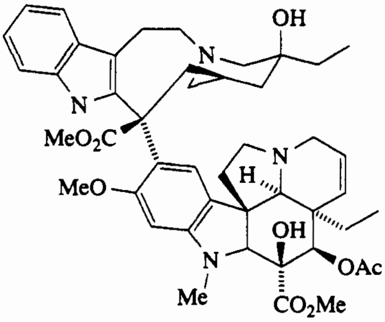

**(68)**

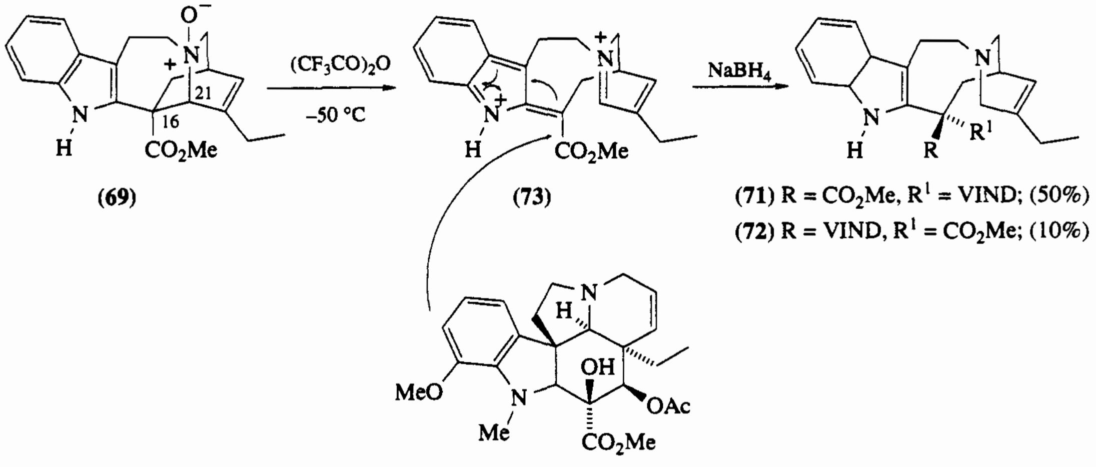

**(69)**

**(73)**

(**71**) R = $CO_2Me$, $R^1$ = VIND; (50%)
(**72**) R = VIND, $R^1$ = $CO_2Me$; (10%)

(**70**) VIND

**Scheme 14**

Although the precise mechanism of the coupling reaction is not thoroughly established, one can visualize the formation of (**71**) as arising from initial fragmentation of the C(16)—C(21) bond of (**69**), followed by condensation of vindoline with the more accessible α face of the iminium ion (**73**). The impact of the Polonovski approach in this area is emphasized by the fact that all other attempts to couple vindoline with 16,21-seco derivatives of catharanthine lead invariably to formation of the unnatural dimer. A Polonovski reaction was also a key step in the subsequent elaboration of anhydrovinblastine (**71**) to (**68**).[49]

### 4.7.2.4 Other Reactions

In several instances reaction of an amine oxide with an acid anhydride triggers a process in which the amine oxide nitrogen is converted into a leaving group and the $C_\alpha$—N bond is cleaved (Scheme 15).[50] Interestingly, these reactions occur to the exclusion of the Polonovski pathways, *i.e.* elimination of the benzylic α-hydrogen or fragmentation of the phenethylamine chain.

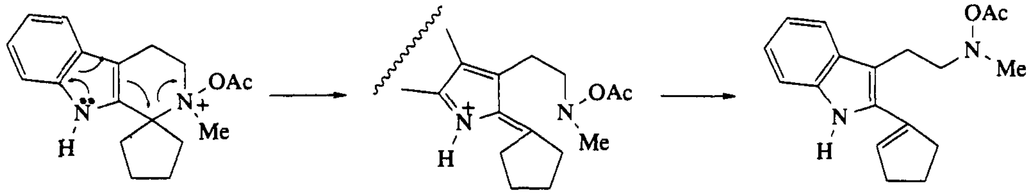

**Scheme 15**

In a number of reactions the Polonovski products are obtained directly on reaction of a tertiary amine with peroxy acids. This can happen when the peroxy acid is present in excess, in which case it acts as both the oxidizing and activating agent, or when an appropriately positioned acid or amide group, which can act as an internal activator, is present in the *N*-oxide. The latter situation is illustrated by the efficient conversion of compound (**74**) to the benzimidazole (**75**; Scheme 16).[51]

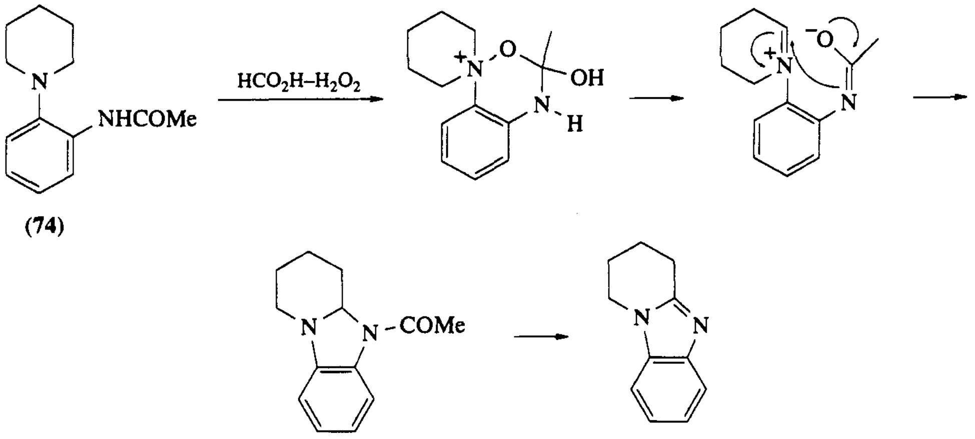

(**74**)

(**75**)

**Scheme 16**

There is one special example involving the reaction of 1,4-diazepine *N*-oxides such as (**76**), a trisubstituted nitrone, with acetic anhydride which has repeatedly been referred to as a Polonovski reaction, because the acetate group is introduced at the saturated C-3 position in the product (**77**).[52] However, an alternative mechanism proposed for this reaction appears more likely (Scheme 17) as it conserves all the aspects of the chemistry of nitrones with the slight variation that the elements of acetic acid are eliminated through loss of the C-3 proton.[53]

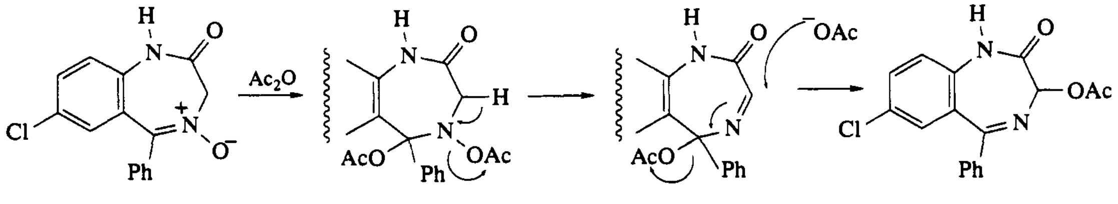

(**76**)

(**77**)

**Scheme 17**

#### 4.7.2.5 Iron Salts and Sulfur Dioxide as Activators in the Polonovski Reaction

Iron(II) salts and sulfur dioxide activate *N*-oxides in the Polonovski reaction. The mechanism by which iminium ions are generated is different in both cases. In the iron reaction an $Fe^{II}/Fe^{III}$ redox process occurs involving two one-electron transfer steps,[54,55] whereas in the sulfur dioxide reaction an intramolecular ionic mechanism is evoked.[56] A major distinguishing feature between these Polonovski reaction variants and the classical reaction using acid anhydrides is that they exhibit a marked preference for oxidation at the methyl carbon center of *N*-methyl-substituted amine oxides. The yields of these reactions are generally moderate, however, as reduction of the *N*-oxide to the tertiary amine is a competing side reaction. In fact, both iron salts and sulfur dioxide (at elevated temperatures) have been employed as reagents to deoxygenate amine oxides selectively. Attention must, therefore, be paid to experimental conditions (temperature, solvent, pH, concentration of reactants, *etc.*) in order to optimize the formation of the desired Polonovski products.

The Pictet–Spengler cyclization of *N,N*-dimethyltryptamine *N*-oxide (**66**) to the tetrahydrocarboline (**78**) using sulfur dioxide in anhydrous formic acid[57] and the selective *N*-dealkylation of the morphinan *N*-oxide (**79**) using catalytic quantities of iron(II) chloride[58] (equations 19 and 20) illustrate the advantages of using these activating reagents in the Polonovski reaction.

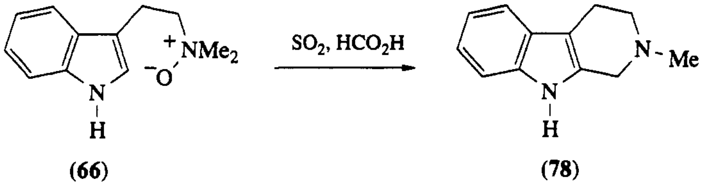

(19)

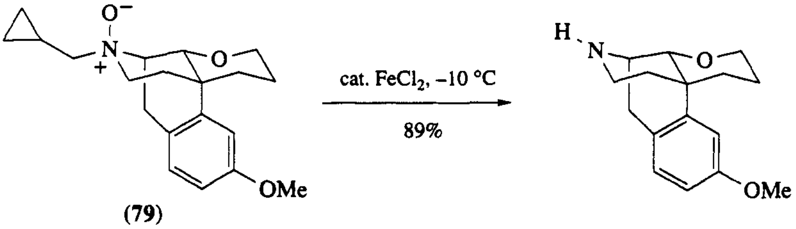

(20)

Finally, mention should be made of the use of iron porphyrins as catalysts in the Polonovski reaction. An added feature of this approach is that the *N*-oxide can act as an oxygen source for other synthetically useful, iron porphyrin catalyzed transformations.

#### 4.7.2.6 Silicon and Selenium Polonovski Reactions

*t*-Butyldimethylsilyl triflate promotes the rearrangement of *N*-oxides to α-silyloxyamines (**81**) *via* the *O*-silylimonium salts (**80a**; Scheme 18).[59] The intermediate (**80a**) is remarkably stable, however, and strong bases such as methyl- or butyl-lithium are required to promote the transformation to (**81**). At present it has not been determined whether this reaction occurs by an elimination–addition mechanism, as in the conventional Polonovski reaction (Scheme 1), or by formation of an anion at the α-carbon center followed by migration of the silyloxy groups in a manner analogous to the Stevens rearrangement.

In a second variation, benzenselenyl triflate is employed as the activator and α-selenyloxyamines (**82**) are obtained.[60] The interesting feature of this reaction is that the *O*-selenylimonium salts (**81b**) are labile, and quantitative rearrangement to (**82**) is observed using weaker bases, such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The α-silyl- and α-selenyl-oxyamines obtained are reactive towards both electrophiles and nucleophiles, the typical procedure involving addition of the appropriate reagent to a solution of (**80a**) or (**80b**) in THF generated *in situ* (Scheme 18).

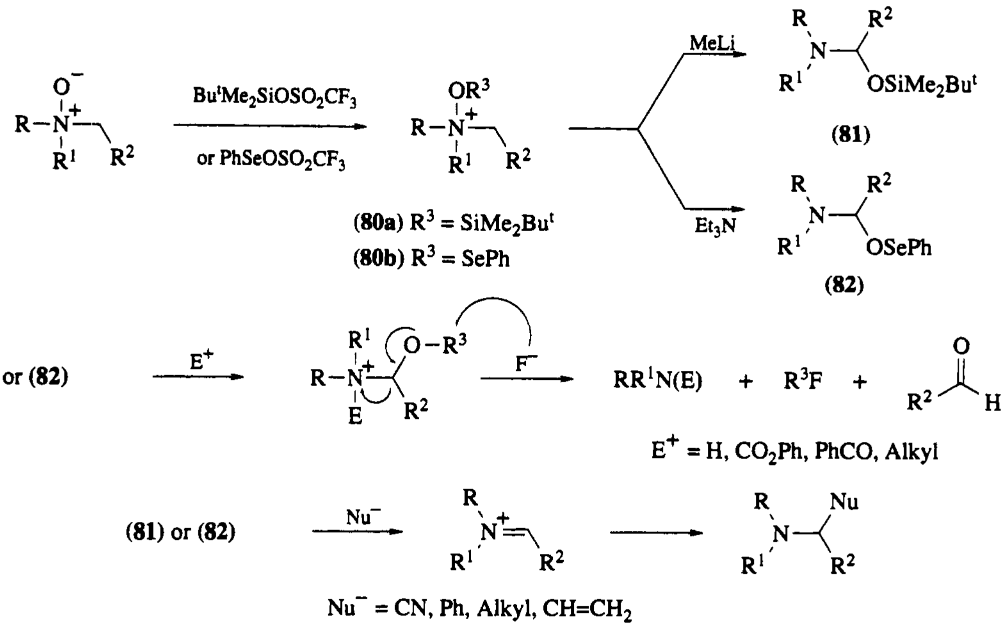
Bu<sup>t</sup>Me2SiOSO2CF3
or PhSeOSO2CF3
MeLi
Et3N
(81)
(82)
(80a) R3 = SiMe2Bu<sup>t</sup>
(80b) R3 = SePh
(81) or (82)
E+
F−
RR1N(E) + R3F +
E+ = H, CO2Ph, PhCO, Alkyl
Nu−
Nu− = CN, Ph, Alkyl, CH=CH2

Scheme 18

## 4.7.3 THE PUMMERER REACTION

### 4.7.3.1 Mechanism, Regio- and Stereo-chemistry

The mechanism of the Pummerer reaction can essentially be broken down into four steps (equations 21–24).[8–11] The initial step involves acylation of the sulfoxide oxygen to form an acyloxysulfonium salt (**83**). In the following step, removal of a proton from the α-carbon of (**83**) produces an acylsulfonium ylide (**84**). This ylide subsequently undergoes concurrent electron reorganization and S—O bond cleavage to give the ion pair (**85**). In the final step, condensation of acetate ion with the sulfur-stabilized carbocation gives the α-acyloxy sulfide product (**86**).

The acyloxysulfonium salts (**83**) are markedly more stable than the corresponding *N*-acyloxyimonium salts generated in the Polonovski reaction (Scheme 1). In contrast, although there is substantial kinetic isotope$^{18}$O labeling and Hammett correlation data in favor of the formation of ylide (**84**) and carbocation (ion pair) (**85**), neither of these intermediates has been identified or characterized spectroscopically. The high reactivity of thionium ions is reflected by the fact that they react with weakly nucleophilic trifluoroacetate ion to give α-trifluoroacetoxy sulfides as products. Iminium ions generated in the modified Polonovski reaction are stable in the presence of $CF_3CO_2^-$.

Variations on the mechanism presented in equations (21) and (22) occur since, depending upon the sulfoxide structure and the acid anhydride employed, any one of the steps 1 to 3 can be rate determining. The mode by which migration of the acyloxy group to the α-carbon center in step 4 occurs is also dependent upon these factors. Generally, this involves an intermolecular process. However, a growing number of cases exist in which this step occurs intramolecularly *via* a tight ion pair. Intramolecular acyloxy migration is one prerequisite for asymmetric induction in the Pummerer reaction.

The most extensively investigated class of Pummerer reactions involves the reaction of aryl alkyl sulfoxides, acyclic dialkyl sulfoxides or cyclic sulfoxides with acid anhydrides. In these reactions proton removal is rate determining and the product regiochemistry is determined by the kinetic acidities of the α-protons, *i.e.* $CH_2COR > CH_2CN > PhCH_2 > CH_3 >$ *n*-alkyl > *s*-alkyl. These reactions are highly susceptible to steric effects, however, as suggested by the formation of nearly equal amounts of compounds (**88**) and (**89**) in the reaction of benzyl methyl sulfoxide (**87**) with acetic anhydride (equation 25).[8,61]

The elimination of acetic acid from the initially formed acylsulfonium salt in the reaction of sulfoxides (**87**) and (**90a,b**; Scheme 19) is considered to involve a concerted nonsynchronous *E*2-type mechanism, rather than the stepwise process depicted in equations (22) and (23).[62,63] In the latter study, retention of

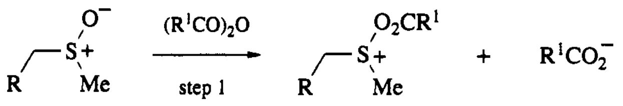

**(83)**

(21)

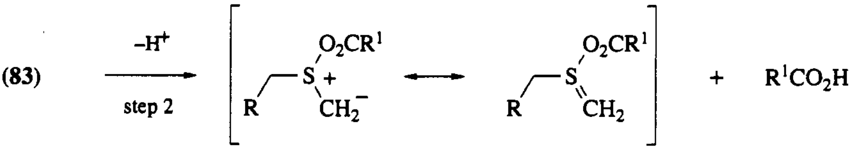

**(84)**

(22)

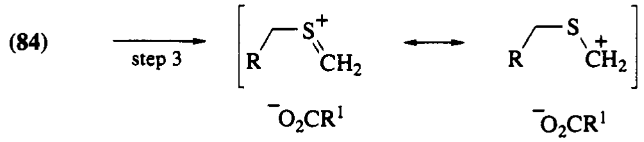

**(85)**

(23)

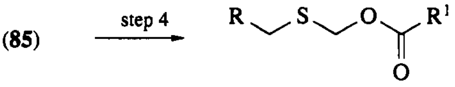

**(86)**

(24)

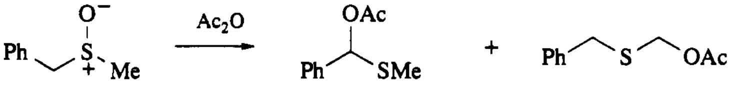

**(87)** **(88)** **(89)**

(25)

the deuterium label in the product (**91**) from both reactions strongly suggests that formation of a thionium ion intermediate involves a stereospecific *anti* elimination.

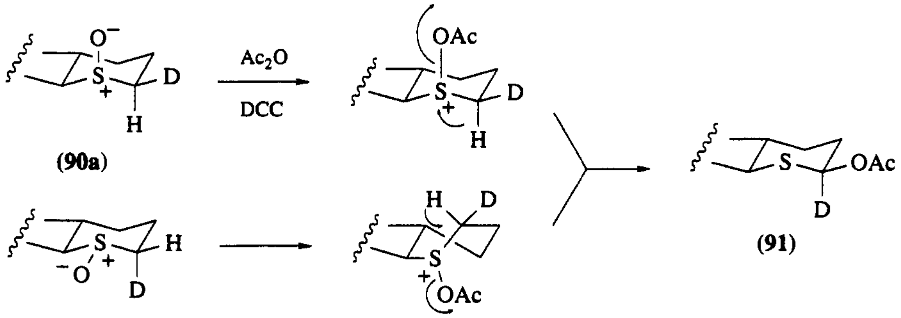

Scheme 19

In this class of Pummerer reactions subsequent formation of the α-acyloxy sulfide involves, in the majority of instances, an intermolecular acyloxy migration. The reaction of *p*-tolyl benzyl sulfoxide with acetic anhydride is an exception. However, even in this case no asymmetric induction is observed.[64]

The third step in the Pummerer reaction is rate determining in reactions in which proton removal is fast and reversible and S—O bond cleavage is slow. These '*E*1cB' Pummerer reactions are observed when R′ (equation 26) is an electron-withdrawing group such as cyano, carbonyl, alkynyl or cyclopropyl. The presence of these groups facilitates proton removal while at the same time retarding departure of the leaving group due to strong inductive effects.

An important feature of these reactions is that acyloxy migration occurs intramolecularly. Moderate (30–70% *ee*) induction of asymmetry at the α-carbon is observed. In fact, Pummerer reactions in which chiral transfer occurs are almost exclusively restricted to this category. The very tight nature of the α-thiocarbenium–acetate ion pair and very rapid recombination (ion pair return) are considered to be two

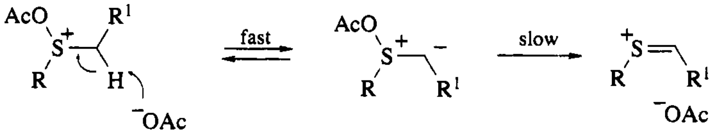

(26)

important factors in this process. Another aspect of equal importance is the preference for one ylide conformer in the transition state leading to the ion pair. In the absence of such a bias racemic products are obtained. In the reaction of (–)-*N,N*-dimethyl-*p*-tolylsulfinylacetamide (**92**) with acetic anhydride (Scheme 20), correlation of the absolute stereochemistry of the starting material with the reaction product (**93**) provided evidence suggesting that the sterically less-hindered conformer (**94**) is preferred in the ylide to ion pair transition state.[65]

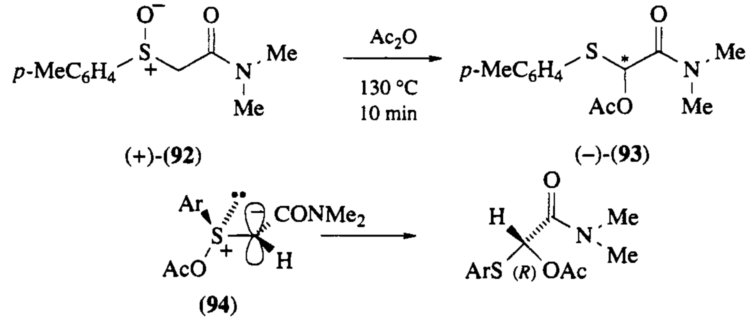

**Scheme 20**

Several factors contribute to the fact that the extent of chiral transfer in the Pummerer is only moderate. These include the acidity of the reaction medium, oxygen exchange and the lifetimes of the ylide and ion pair intermediates. Although the Pummerer reaction is accelerated by the presence or addition of acid, its presence also influences the tightness of the ion pair. Oxygen exchange, through which the starting chiral sulfoxide is racemized, is a problem in all Pummerer reactions. This process is particularly rapid when trifluoroacetic anhydride is employed. Naturally, for any asymmetric induction to be possible the lifetime of the ion pair must be very short. The longer the existence of this species, the greater is the chance that acyloxy migration will occur intermolecularly and/or that rotation about the S—C bond will occur.

Pummerer reactions in which acylation of the sulfoxide oxygen is rate determining are rare, having been demonstrated for the reaction of DMSO with acid anhydrides and for the reaction of *O*-carboxyphenyl sulfoxides such as (**95**). This latter reaction (Scheme 21) is particularly interesting in that formation of the acyloxysulfonium intermediate (**98**) occurs by two competing intramolecular pathways, involving either reaction of the sulfoxide oxygen with the activated *O*-carboxy group in (**96**) or displacement of acetate ion from (**97**).[66] The two pathways are not equivalent, as the former, which predominates when DCC is used as the activating agent, involves retention of configuration, whereas the latter, which predominates under acetic anhydride conditions, occurs with inversion. In agreement with this picture (+)-(**95**) reacts with DCC to give (–)-(**99**) (29.9% optical purity) and with acetic anhydride to give (+)-(**99**) (11% optical purity).

### 4.7.3.2 Preparation and Elaboration of α-Acyloxy Sulfides

When acetic anhydride is employed in the Pummerer reaction, reflux temperatures are generally required. However, at elevated temperatures α-acetoxy sulfides are labile and if a β-hydrogen is present elimination of acetic acid and formation of a vinyl sulfide becomes a competing reaction (*cf.* Section 4.7.3.5). This problem is reduced by addition of sodium acetate to the reaction medium[67] or by using trifluoroacetic anhydride.[68,69] With this more reactive activating agent, high yield conversion of sulfoxides to α-trifluoroacetoxy sulfides is achieved under much milder conditions (0–20 °C). These reactions can be further accelerated by addition of a hindered base. However, once again, if a β-hydrogen is present in the sulfoxide substrate, vinyl sulfide formation may be favored.

α-Acyloxy sulfides undergo a variety of synthetically useful transformations. Of particular interest is the fact that these *O,S*-acetals are readily hydrolyzed to aldehydes. α-Trifluoroacetoxy sulfides are very

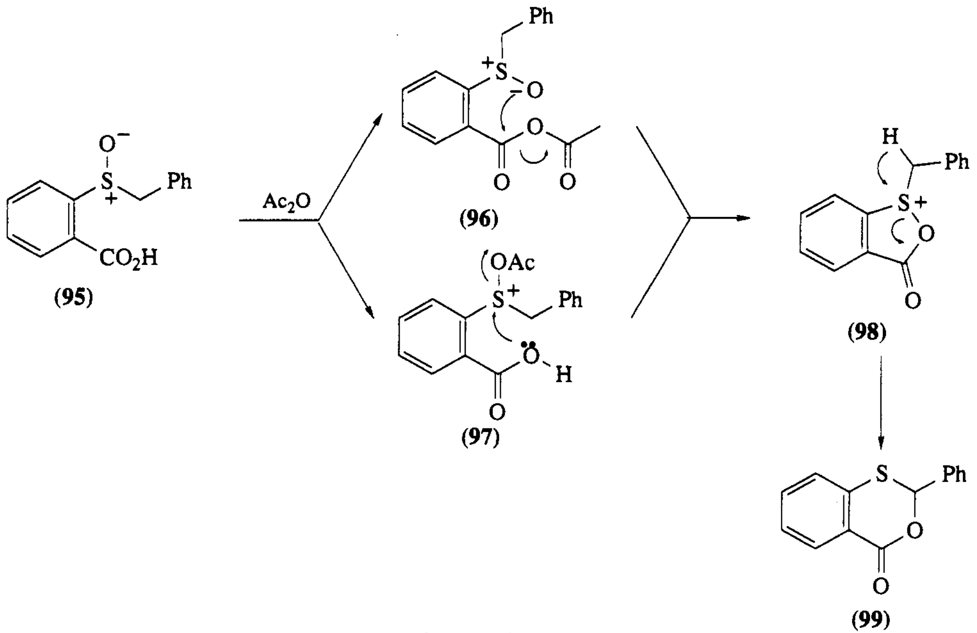

Scheme 21

prone to reaction under acid and base hydrolysis conditions, and often simple treatment of these Pummerer products with aqueous sodium hydrogen carbonate is sufficient to liberate the aldehyde.[68,70] Aldehydes are also obtained by partial reduction of the ester carbonyl of α-acetoxy sulfides using diisobutylaluminum hydride at –78 °C.[71] The Pummerer reaction thus provides a direct means for the conversion of a sulfoxide to an aldehyde, the versatility of this transformation in synthesis being augmented by the fact that sulfoxides are accessible by a number of different routes.

These two points are illustrated by the approach for the synthesis of deoxyleukotriene D (**105**; Scheme 22).[72] The required sulfoxide (**102**) for the Pummerer reaction step was obtained by reaction of the conjugate base of another sulfoxide (**100**) (a 4-formyl-*trans,trans*-buta-1,3-dienyl anion equivalent) with methyl 5-formylpentanoate. On warming, the resultant product (**101**) undergoes a spontaneous 3,2 double sigmatropic rearrangement giving (**102**). Pummerer reaction of (**102**) followed by hydrolysis of the intermediate acetoxy sulfide (**103**) furnished aldehyde (**104**). Compound (**104**) was subsequently converted to leukotriene (**105**) using Wittig chemistry.

Several methods have been developed which permit the direct conversion of α-acyloxy sulfides to acetals. This can be achieved by treatment with mercury(II) acetate and *p*-toluenesulfonic acid in methanol, or even more directly by effecting the Pummerer reaction with iodine in methanol.[73,74] α-Keto acetals are similarly obtained in high yields from the reaction of β-keto sulfoxides in refluxing methanol containing iodine.[74]

Interestingly, the α-acetoxy sulfides (**106**) obtained from the reaction of β-keto sulfoxides with acetic anhydride containing sodium acetate undergo *in situ* oxidation–reduction and acyl transfer, giving α-acetoxy thiol esters (**107**) as products (Scheme 23).[75] Yields in this process are generally high.

Selective transformation of α-acetoxy sulfides to primary alcohols is achieved using $LiAlH_4$, diisobutylaluminum hydride at 0 °C and sodium borohydride in ethanol at room temperature.[76–78] Selective reduction of the Pummerer product (**108**) to the primary alcohol (**109**) is a key step in the elegant approach developed for the synthesis of monosaccharides (Scheme 24).[76]

### 4.7.3.3 Inter- and Intra-molecular Reactions of α-Acyloxy Sulfides or their Thionium Ion Precursors with Nucleophiles

As α-acyloxy sulfides are relatively labile entities, inter- and intra-molecular displacement of the acyloxy group by a nucleophile is possible. For example, reaction of 1-*O*-acetyl-4-thiotetroses such as (**110**) with pyrimidine and purine bases in acidic media provides a convenient route to biologically interesting thionucleosides (**111**; equation 27).[79] The reaction with internal nucleophiles is illustrated by the conversion of sulfoxide (**112**) to the 2,6-epithio-3-benzazocine (**114**; Scheme 25).[80] Heating sulfoxide (**112**) in acetic anhydride for 24 hours leads to a mixture of compounds (**113**; 34%), (**114**; 18%) and the *N*-acetyl

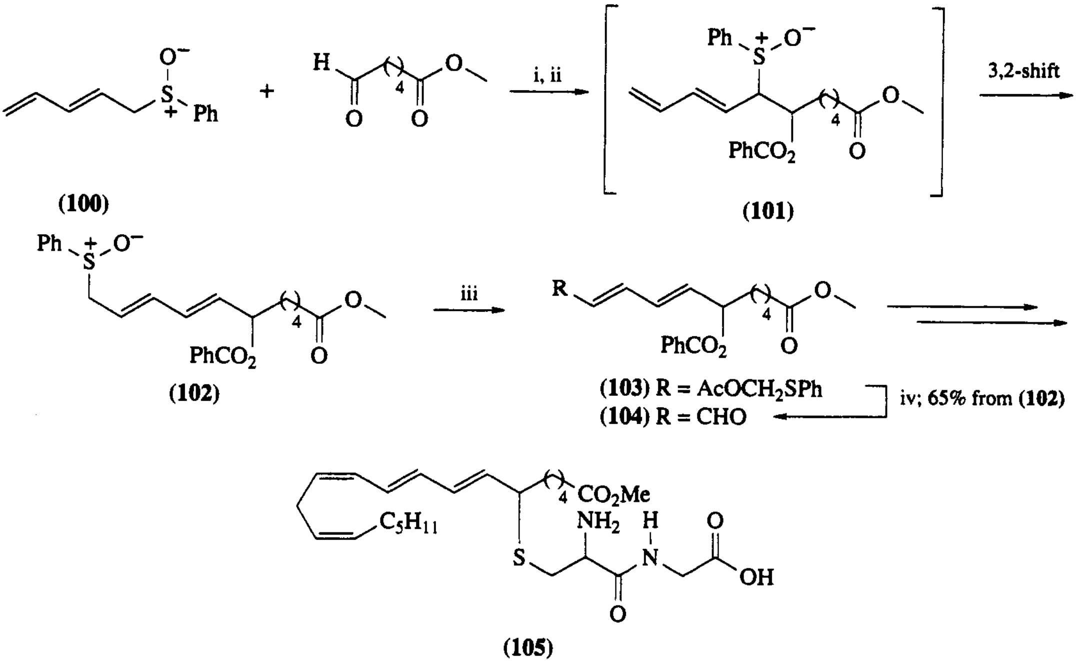

i, $Bu^nLi$, THF, –78 to –40 °C; ii, PhCOCl, THF, –40 to 0 °C;
iii, TFAA–$Ac_2O$, NaOAc, AcOH, 2,6-lutidine, 0 to 25 °C; iv, $CaCO_3$, $HgCl_2$, MeCN–$H_2O$

Scheme 22

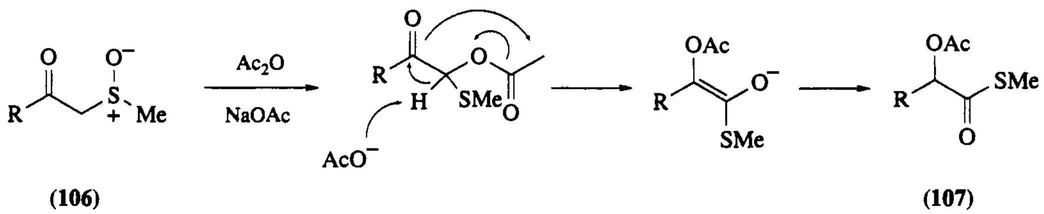

Scheme 23

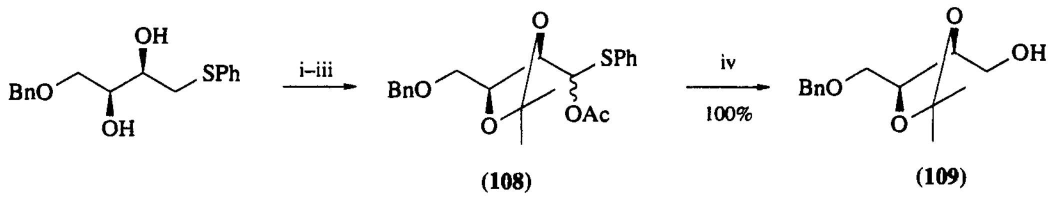

i, $MeC(OMe)_2Me$, $H^+$; ii, MCPBA, $CH_2Cl_2$, –20 °C; iii, $Ac_2O$, NaOAc, heat; iv, $LiAlH_4$, ether, 0 °C

Scheme 24

derivative of (**113**; 45%). The overall yield of product (**114**) is considerably increased, however, by the two-step procedure in which (**113**) is formed selectively by brief treatment of sulfoxide (**112**) with acetic anhydride, followed by subsequent intramolecular capture by nitrogen of the thionium ion generated from (**113**) under thermal conditions.

A biomimetic synthesis of β-lactams is similarly achieved by treatment of optically pure sulfoxide (**115**; R = H) with trimethylsilyl triflate and diisopropylethylamine (DIPEA; Scheme 26).[81,82]

Compound (**116**) is obtained in 41% chemical yield and 67% *ee*, one of the highest reported cases of asymmetric induction in the Pummerer reaction. The use of a silicon activating reagent in this reaction is crucial as the reaction of sulfoxide (**115**; R = Me) with trifluoroacetic anhydride gave compound (**119**), presumably *via* intermediates (**117**) and (**118**). This latter result points to the possibility that this and

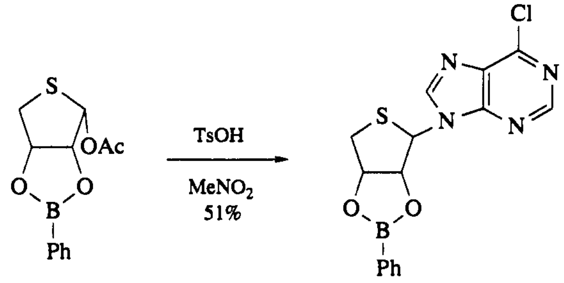

(110) (111)

(27)

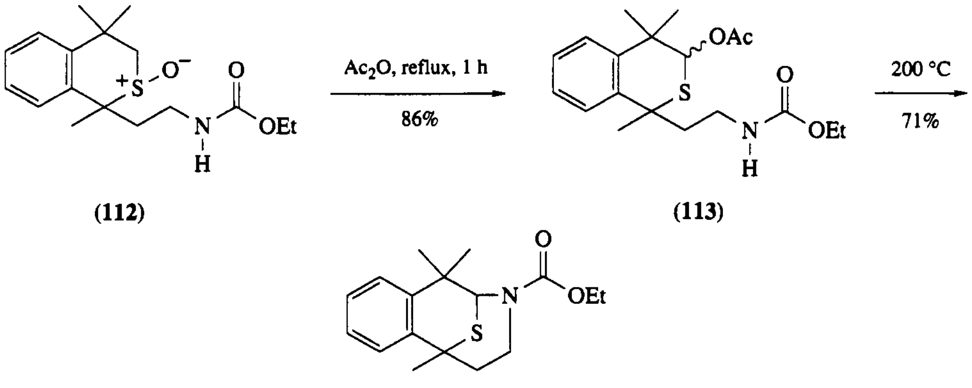

(112) (113)

(114)

Scheme 25

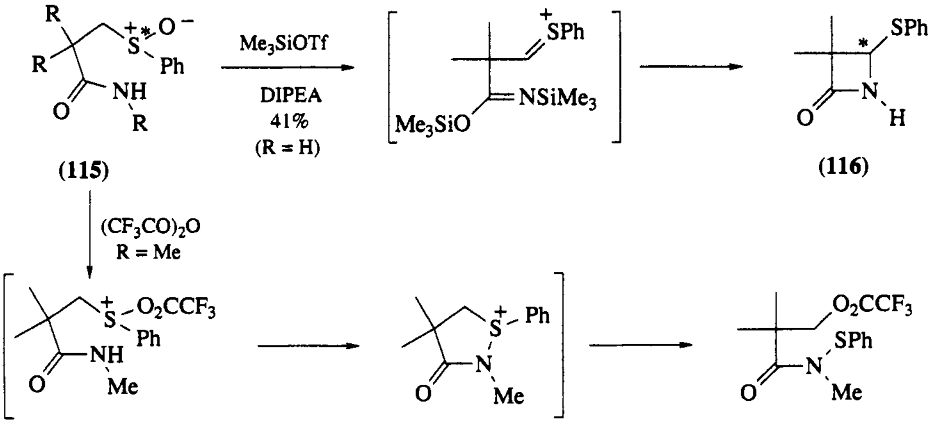

(115) (116)

(117) (118) (119)

Scheme 26

other intramolecular Pummerer reactions may occur by an additive Pummerer mechanism (*cf.* Scheme 21 and Section 4.3.3.6).

Conjugate addition to vinylthionium ions is observed in the reaction of allylic sulfoxide (**120**) with enol silyl ethers in the presence of trimethylsilyl triflate and diisopropylethylamine (Scheme 27).$^{83}$ However, in certain cases moderate yields were obtained. This has been traced to a competing reaction of the intermediate (**121**) with the tertiary amine base to give the quaternary ammonium salt (**122**).

### 4.7.3.4 Reactions of α-Acyl Sulfides with π-Systems

α-Acylthionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently in inter- and intra-molecular reactions with aromatic and heteroaromatic

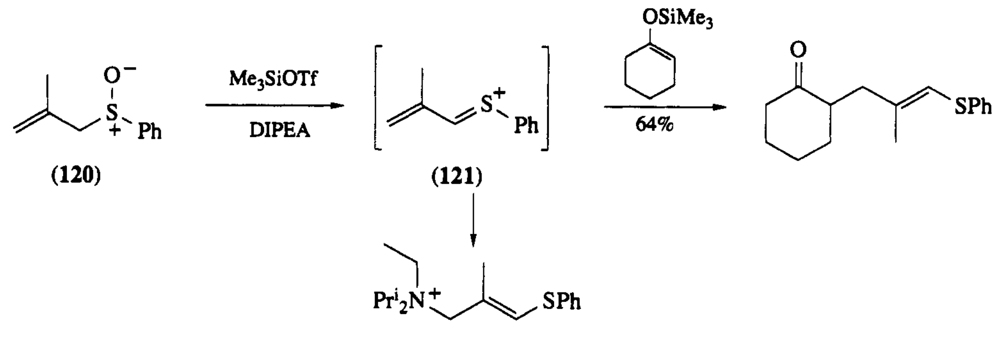

(120) (121) (122)

Scheme 27

systems as well as carbon–carbon double bonds. Pioneered by Yonemitsu and coworkers,[84] the key step in a number of elegant alkaloid syntheses involves intramolecular reaction of α-acylthionium ions with aromatic rings. The synthesis of the *Aspidosperma* indole alkaloid kopsanone (**125**) by Magnus and Gallagher[85] is a particularly good illustration of this approach (Scheme 28), as it not only demonstrates how the Pummerer reaction of α-acyl sulfoxides can be used to construct the alkaloid D-ring (**123** → **124**), but also shows in subsequent steps how the same sulfur atom can be used to introduce other functionality into the molecule.

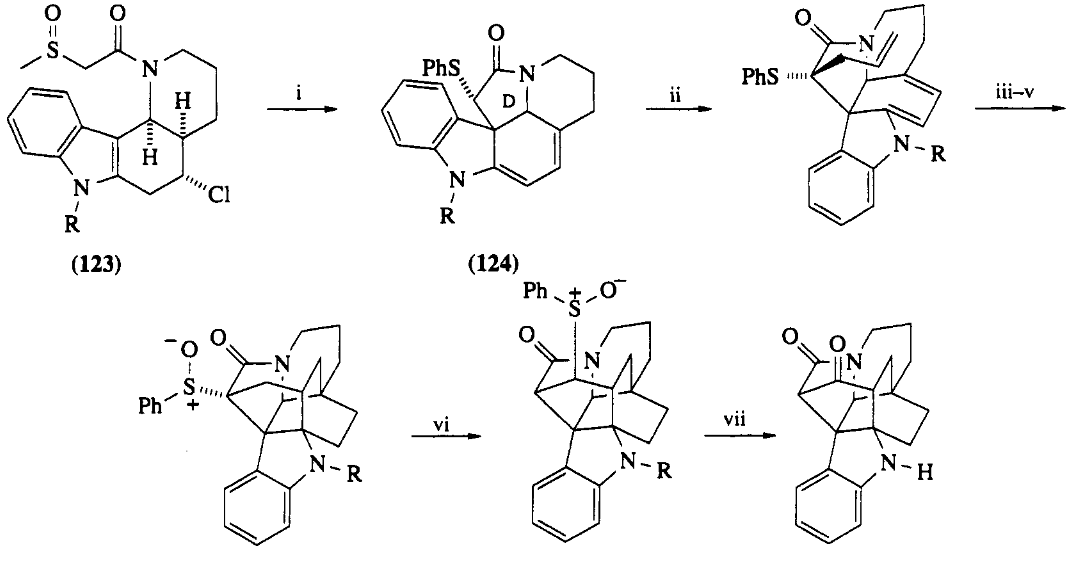

(123) (124) (125)

i, TFAA, $CH_2Cl_2$, 0 °C then 130 °C, PhCl; ii, $KN(SiMe_3)_2$, THF, 0 °C, allyl bromide; iii, 100 °C; iv, $TsNHNH_2$, NaOAc, EtOH; v, MCPBA; vi, AcOH, 230 °C; vii, TFAA, $CH_2Cl_2$, 0 °C, then PhCl, TFA, 130 °C

Scheme 28

Non-nucleophilic activating agents, such as *p*-toluenesulfonic acid, are generally used to generate the intermediate thionium ions. The use of trifluoroacetic anhydride in the Pummerer step of the kopsanone synthesis is feasible, since at elevated temperatures an equilibrium is established between the thionium ion and trifluoroacetoxy sulfide intermediates. Trifluoroacetic anhydride in combination with a Lewis acid can also be used. Under these latter conditions efficient intermolecular reactions of acylthionium ions with aromatic systems are observed.[86]

A detailed study of the Pummerer reaction of a series of *N*-alkenyl-α-sulfinylacetamides has shown that, depending upon the number and position of methyl groups on the double bond, five- or six-membered ring lactams are obtained.[87] This reaction has been applied to a concise synthesis of the erythrinane alkaloid derivative (**129**; Scheme 29).[88] On reaction of sulfoxide (**126**) with *p*-toluenesulfonic acid in dichloroethane an α-acylthionium ion (**127**) is produced, which undergoes cationic alkene cyclization generating the iminium ion intermediate (**128**), which in turn condenses with the aromatic ring giving (**129**).

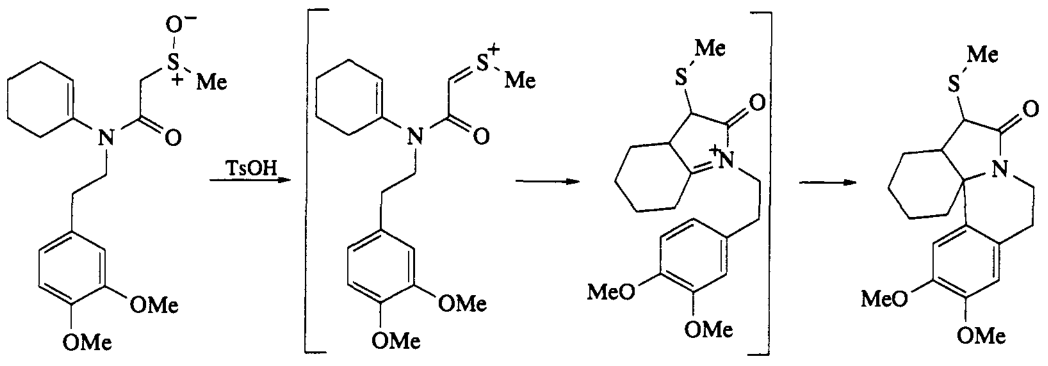

**(126)** **(127)** **(128)** **(129)**

**Scheme 29**

α-Acylthionium ions also undergo intermolecular cationic alkene cyclizations or 'ene'-type reactions with alkenes bearing at least one allylic hydrogen, as illustrated in Scheme 30 for the synthesis of pellitorine (**130**).[89] 4-Chlorophenylthiomethyl trifluoroacetate (**131**) and the chlorosulfide (**132**) are also good initiators of these 'ene'-type reactions.[90,91]

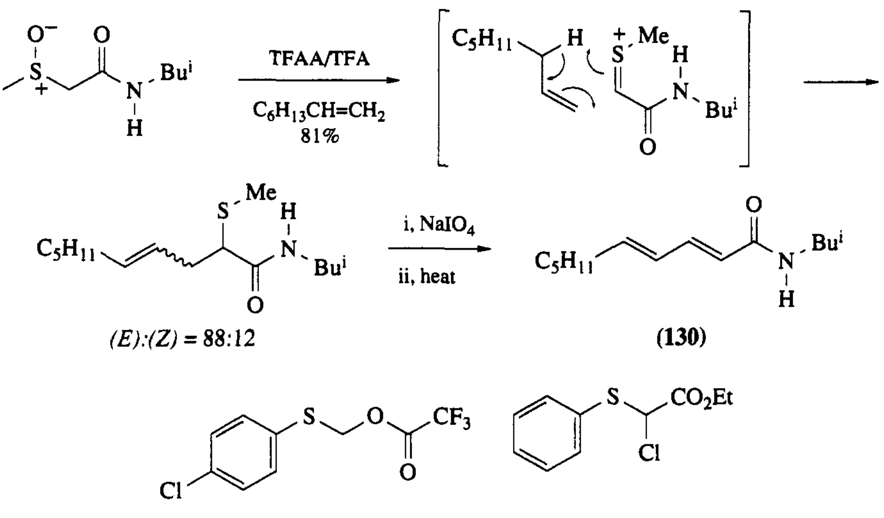

*(E):(Z)* = 88:12

**(130)**

**(131)** **(132)**

**Scheme 30**

## 4.7.3.5 Vinyl Sulfides

Vinyl sulfides and the corresponding sulfoxides are versatile reagents which react as Michael acceptors, Diels–Alder dienophiles, annelating agents and carbonyl equivalents. They are also interesting substrates for extended enolate chemistry.

Vinyl sulfides are prepared from sulfoxides under a variety of conditions. These include reaction with acetic anhydride at reflux, with trifluoroacetic anhydride in the presence of an amine base[92] and with acetic anhydride in the presence of an acid catalyst.[93] In fact, precautions must be taken in certain Pummerer reactions discussed in the preceding sections to avoid competing vinyl sulfide formation.

Reaction of 2-phenylsulfinyl esters such as (**133**) with acetic anhydride is slow at room temperature, but when a catalytic amount of methanesulfonic acid is present in the reaction medium, conversion to the vinyl sulfide (**134**) is complete after a few hours at 20–40 °C (Scheme 31).$^{94,95}$ Mixtures of (*E*)/(*Z*) isomers are usually obtained, with the (*Z*)-isomer generally being the more stable. These isomers are interconverted on heating, a process which occurs slowly on standing, even in the dark. The discovery that photochemical or free radical induced 1,3-shift of the PhS group in (**135**) to the γ-position can be effected offers an additional opportunity to modulate the α/γ selectivity in the extended enolate chemistry of α,β-unsaturated carbonyl systems.

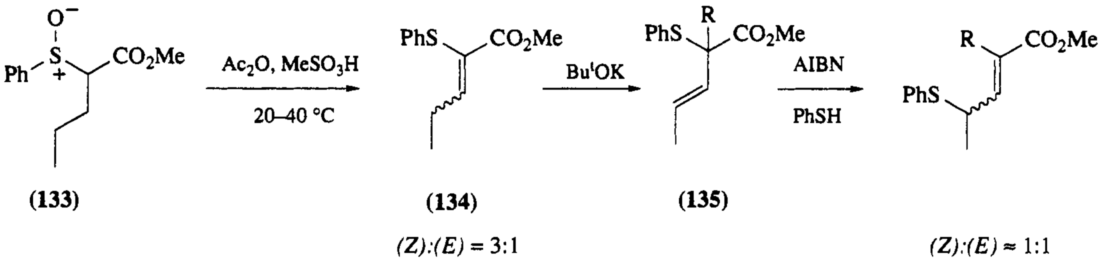

Scheme 31

Trimethylsilyl iodide (TMS-I) can be used as an activating agent in the conversion of sulfoxides to vinyl sulfides providing a sufficiently reactive hindered base, *i.e.* DIPEA, is employed (Scheme 32).$^{96}$ When dibutyl sulfoxide (**136**) is treated with TMS-I in the presence of HMDS rapid formation of dibutyl sulfide and iodine is observed, indicating that HMDS is too weak a base to effect deprotonation at a rate competitive with iodide ion displacement. Note also that this procedure can be used to prepare 1-thiophenyl-1,3-butadienes (**137**) and that either allylic or vinyl sulfoxides can be used as the precursors to these synthetically useful dienes.

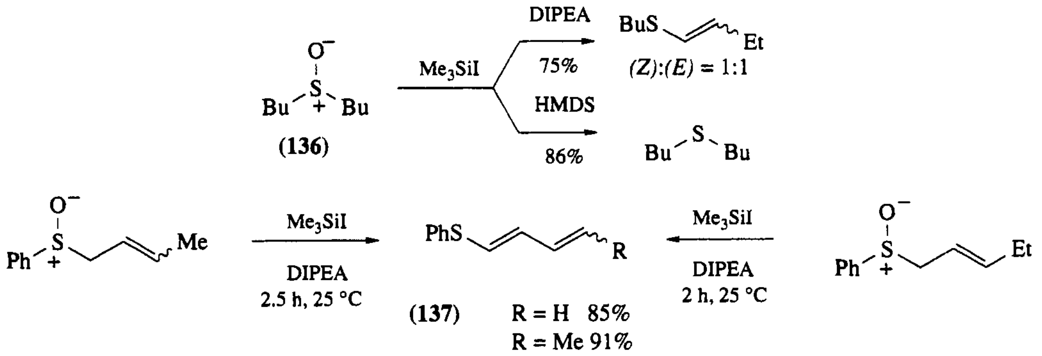

Scheme 32

### 4.7.3.6 Additive and Vinylogous Additive Pummerer Reactions

The additive Pummerer reaction is a reaction in which displacement of the acyloxy group in the initially formed acyloxysulfonium salt by an internal nucleophile occurs to give a new positively charged sulfur species (Scheme 33). A number of pathways are open for the subsequent reaction of intermediate (**138**), including elimination of the proton α to the sulfur to give a thionium ion (pathway a), displacement of the sulfur from the α′-carbon by an external nucleophile (pathway b), elimination of a β-proton with formation of an alkene and (**139**) (pathway c) and loss of a proton from the carbon atom α to 'Nu' with formation of (**140**; pathway d).

The reactions of *O*-carboxyphenyl sulfoxides (**95**) and sulfoxide (**115**) encountered earlier (Schemes 21 and 26) are examples of the additive Pummerer reaction in which pathways a and b are operative.

A Pummerer reaction which proceeds *via* pathway c is observed when the tetrahydrothiazepine *N*-oxide (**141**) is treated with acetic anhydride and sodium acetate (Scheme 34).$^{97}$ In this reaction highly efficient rearrangement to the isothiazoline derivative (**143**) occurs *via* formation and stereoselective eliminative ring opening of the bicyclic intermediate (**142**). Interestingly, the sulfoxide obtained when

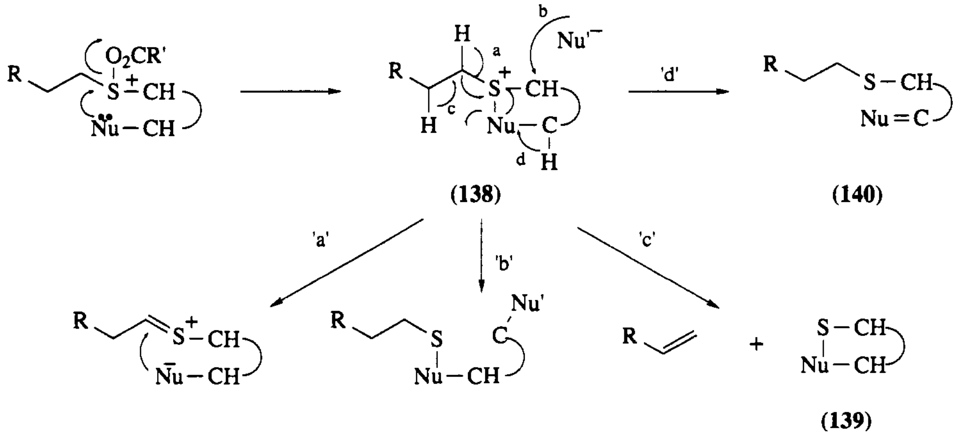
(138)
(140)
(139)
'a'
'b'
'c'
'd'

Scheme 33

the two phenyl substituents in (**141**) are replaced by *t*-butyl groups undergoes a normal Pummerer reaction.

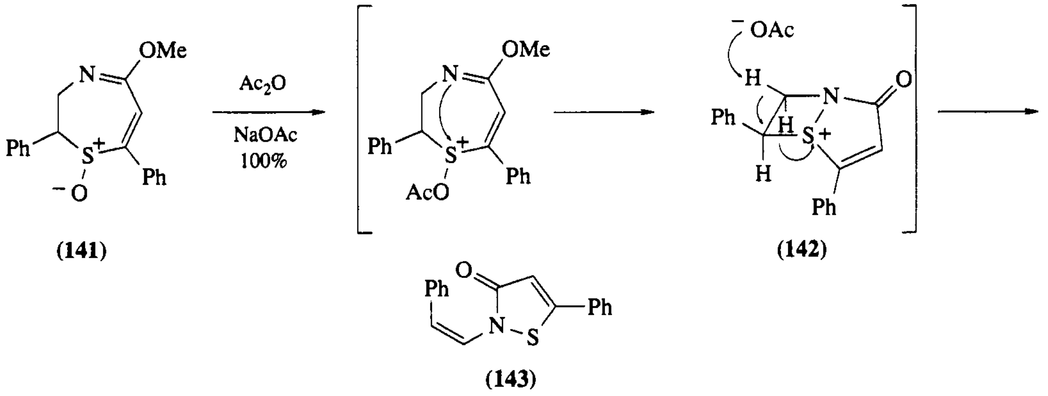
Ac$_2$O
NaOAc
100%
(141)
(142)
(143)

Scheme 34

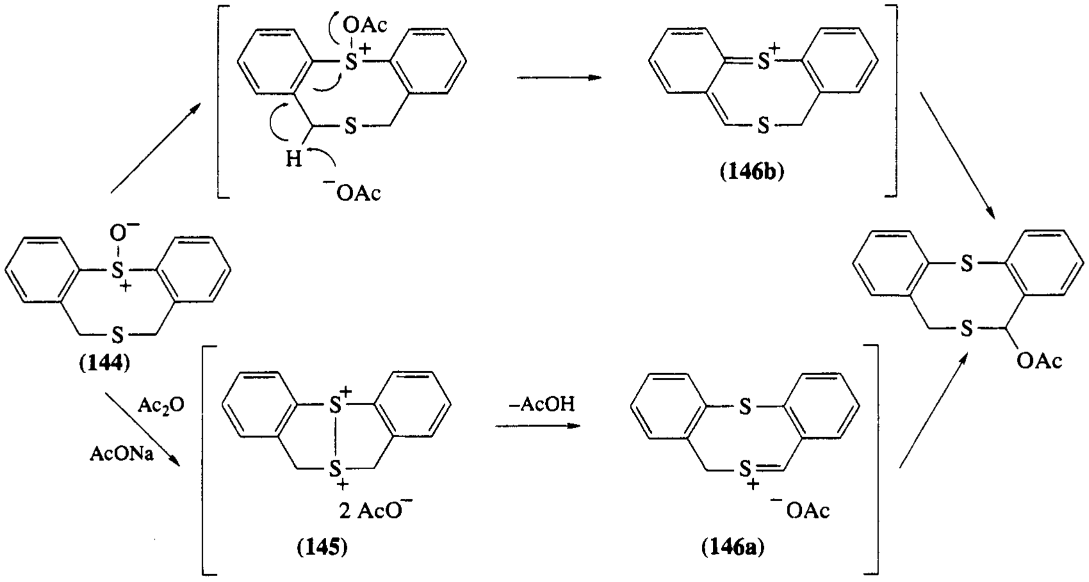
(144)
Ac$_2$O
AcONa
(145)
2 AcO$^-$
–AcOH
(146a)
(146b)

Scheme 35

In the reaction of sulfoxide (**144**) with acetic anhydride the available evidence points to the formation of the disulfide dication intermediate (**145**) and subsequent rate-determining loss of a benzylic proton to give (**146a**; pathway d; Scheme 35).[98] On the basis of experiments conducted on related substrates the alternative mechanism involving the formation of the quinidomethide intermediate (**146b**) was ruled out.

Vinyl sulfoxides also partake in additive Pummerer reactions. Of particular interest in this category are cases where the sulfoxide activating agent also provides the internal nucleophile. Two general pathways for such vinylogous additive Pummerer reactions are presented in Scheme 36.[99]

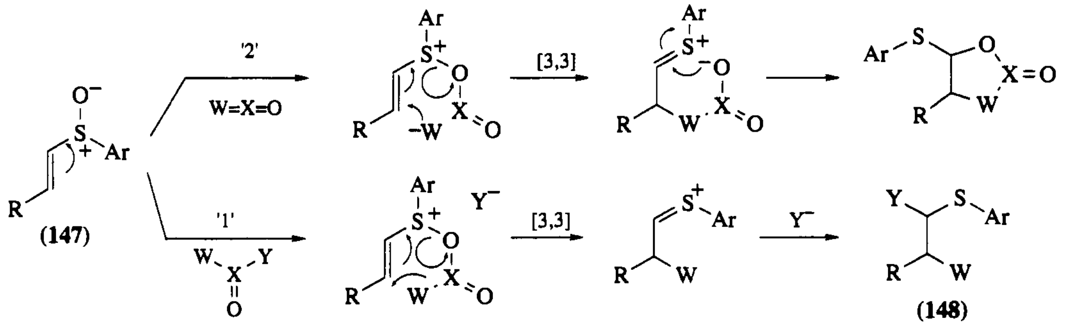

**Scheme 36**

The reaction of sulfoxide (**147**) with thionyl chloride, which produces α,β-dichlorosulfides (**148**; Y = W = Cl) in 85–95% yields, is an example of pathway 1.[99] Illustrating pathway 2 is the remarkable enantiospecific formation of lactone (**150**) from the reaction of dichloroketene with the chiral sulfoxide (**149**; equation 28).[100]

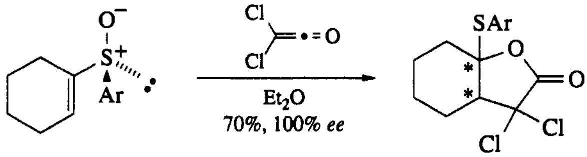

(**149**) (**150**) (28)

### 4.7.3.7 Sila-Pummerer Reactions: Preparation of Trimethylsiloxy Sulfides

In the sila-Pummerer reaction, aryl or alkyl trimethylsilyl sulfides (**151**) rearrange to the corresponding trimethylsiloxy sulfides (**153**) *via* a mechanism in which the key step is a stereocontrolled 1,3-shift of the silyl group in (**151**) from carbon to oxygen, producing ylide (**152**; Scheme 37).[101] Gentle heating is generally all that is required to induce this Pummerer reaction. In fact, the reaction often occurs spontaneously during preparation of the sulfoxide.

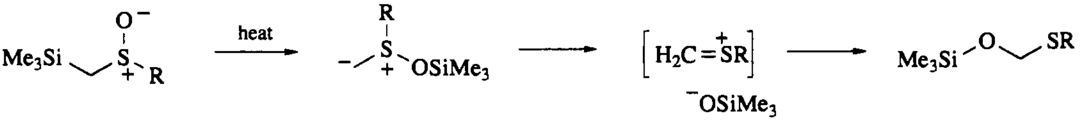

(**151**) (**152**) (**153**)

**Scheme 37**

The sila-Pummerer reaction is of considerable synthetic use as the *O,S*-acetal products can be hydrolyzed to give aldehydes under particularly mild conditions (*cf.* Section 4.7.3). Of added interest is the possibility of contracting the starting trialkylsilyl sulfides using reagents such as the conjugate base of $Me_3SiCH_2SR$ (**154**) and $Me_3SiCH_2SH$ (**155**).

In the synthesis of the novel prostacyclin analog (**157**) an aldehyde group was introduced at the 2-position by regiospecific ring opening of the epoxide (**156**) with the lithium anion of (**154**) and subsequent sila-Pummerer reaction (Scheme 38).[102] The aldehyde derivative (**157**) was obtained directly from the Pummerer reaction after work-up with aqueous $CuSO_4$ solution.

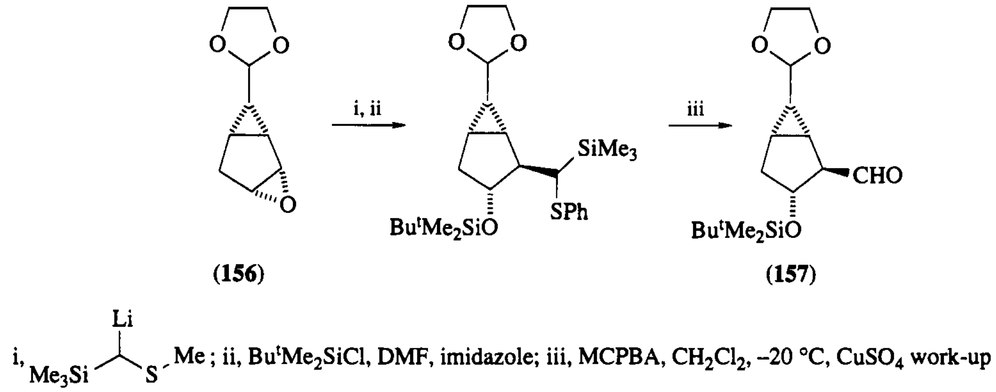
i, ii
iii
SiMe3
SPh
CHO
Bu'Me2SiO
Bu'Me2SiO
Li
Me3Si
S
Me

(**156**) (**157**)

i, Me ; ii, $Bu^tMe_2SiCl$, DMF, imidazole; iii, MCPBA, $CH_2Cl_2$, –20 °C, $CuSO_4$ work-up

**Scheme 38**

The synthesis of α-cyclocitral (**161**) in Scheme 39 illustrates further how trimethylsilyl sulfides can be synthesized and readily converted to aldehydes by the sila-Pummerer reaction.[103] Compound (**159**) was prepared by a route involving a 2,3-sigmatropic rearrangement of the ylide derived from intermediate (**158**). The sila-Pummerer rearrangement of the sulfoxide derived from (**158**) occurred below room temperature. Unfortunately, however, the enhanced rate of the rearrangement to (**160**) conferred by the methyl substituent on the intermediate sulfoxide was accompanied by greater than normal difficulty in the *O*,*S*-acetal hydrolysis step.

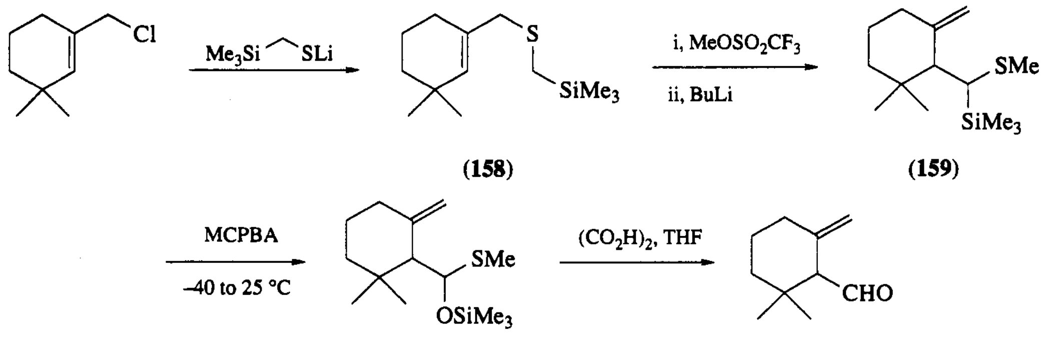
Cl
Me3Si SLi
S
SiMe3
i, MeOSO2CF3
ii, BuLi
SMe
SiMe3
MCPBA
–40 to 25 °C
SMe
OSiMe3
(CO2H)2, THF
CHO

(**158**) (**159**)

(**160**) (**161**)

**Scheme 39**

A recent study demonstrates that trimethylsiloxy sulfides can also be prepared by the reaction of sulfoxides with *O*-silylated ketene acetals (Scheme 40).[104] Although by definition this transformation is not a sila-Pummerer reaction, it provides the first set of conditions by which compounds (**153**) are prepared using a silicon activating reagent.

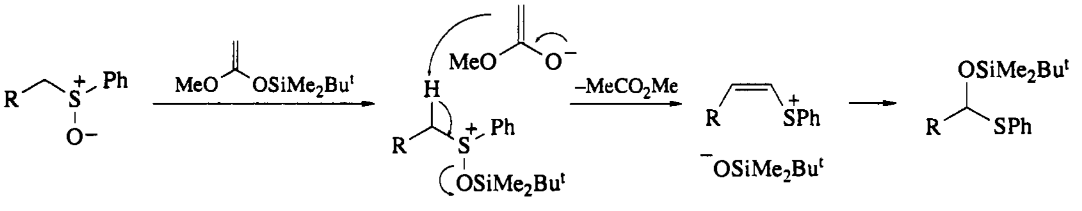
R
S
Ph
O–
MeO OSiMe2Bu'
MeO
O–
H
R
S
Ph
OSiMe2Bu'
–MeCO2Me
R
SPh
–OSiMe2Bu'
OSiMe2Bu'
R
SPh

**Scheme 40**

### 4.7.3.8 The Abnormal Pummerer Reaction

Morin *et al.* showed that the reaction of penicillin sulfoxides (**162**) with refluxing acetic anhydride leads to formation of the ring-expanded cepham derivatives (**165**) and compound (**166**; Scheme 41).[105] Although this transformation was effected under Pummerer conditions, it occurs by a different mechanism, hence the term 'Abnormal Pummerer reaction'.

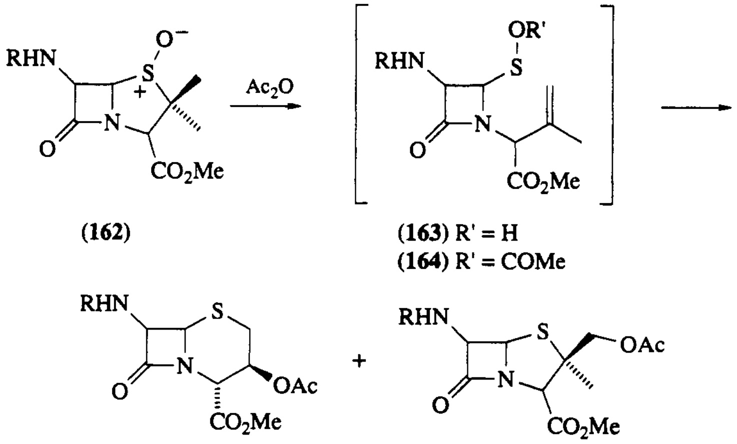

(**162**)

(**163**) R' = H
(**164**) R' = COMe

(**165**) (**166**)

Scheme 41

Rearrangements of this type are generally observed when there are no α-hydrogens in the sulfoxide substrate and many examples of the reaction are now known. The mechanism by which they occur is dependent upon the sulfoxide structure.[106] In the reaction of sulfoxide (**162**) the sulfenic acid (**163**) or its *O*-acetyl derivative are presumed to be intermediates. The former would arise from a 2,3-sigmatropic shift of the hydrogen of the C-2 alkyl group and the latter from an eliminative ring opening in which positive sulfur is the leaving group.

### 4.7.3.9 Other Activating Reagents

Acid anhydrides and/or acids are employed in the majority of synthetic applications of the Pummerer reaction. However, there are a number of other reagents which activate the sulfoxide oxygen in the Pummerer reaction. The use of organosilicon reagents is discussed in Sections 4.7.3.3, 4.7.3.5 and 4.7.3.7 in connection with the preparation of trimethylsiloxy sulfides and vinyl sulfides. Recently it was shown that the trimethylsilyl ester of polyphosphoric acid also promotes the Pummerer rearrangement.[107]

Isopropenyl acetate acts as an acetyl transfer reagent in vinylogous additive Pummerer reactions, providing an efficient means for the conversion of vinyl sulfoxides to α-acyl sulfides (**167**; equation 29).[108]

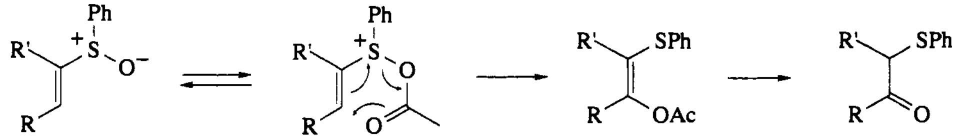

(29)

(**167**)

Interestingly, carboxylic acids can be converted into the corresponding methylthiomethyl derivatives (**169**) in high yield by the addition of a solution of DMSO and *t*-butyl bromide to a suspension of the carboxylic acid in DMSO containing a weak base (Scheme 42).[109] This transformation is believed to involve activation of the sulfoxide through formation of (**168**), followed by displacement of the *t*-butoxide anion by the carboxylic acid and a normal Pummerer reaction.

α-Fluoro sulfides are conveniently prepared by the Pummerer-type reaction of sulfoxides with (diethylamino)sulfur trifluoride (DAST).[110] Thallium(III) nitrate[111] and phenyl iodosylbis(trifluoroacetate)[112] have also been employed as activating agents in Pummerer-type reactions.

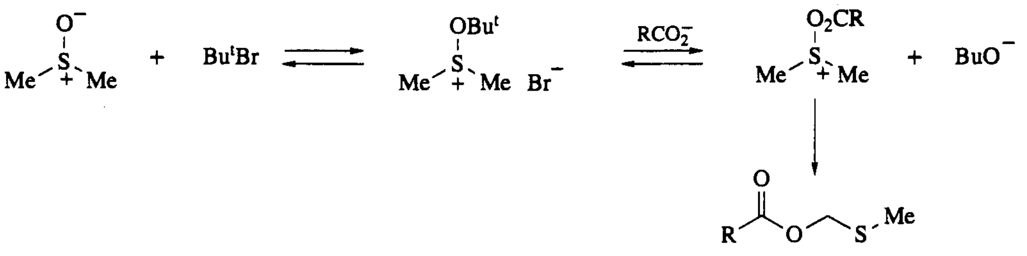

Scheme 42

**(169)**

## 4.7.4 THE NEF REACTION

### 4.7.4.1 Mechanism

In most cases the Nef reaction is characterized by treatment of nitro compounds with a mineral or organic base to give a nitronate salt, which is subsequently hydrolyzed, oxidized or reduced to afford a carbonyl derivative.

### *4.7.4.1.1 Hydrolysis of salts of nitroalkanes*

The original procedure for the Nef reaction involved the aqueous sulfuric acid hydrolysis of the salts (**170**) obtained by the treatment of primary and secondary nitroalkanes with sodium hydroxide (equation 30).[15] In contrast, if a neutral primary nitro derivative is treated in hot concentrated mineral acid, the corresponding carboxylic acid (**172**) is formed *via* the hydroxamic acid (**171**; equation 31). This reaction is known as the Meyer reaction and was first described in 1873.[113] Protonation of salts of nitroalkanes occurs preferentially at the oxygen atom to give the *aci* form (**173**; equation 32).

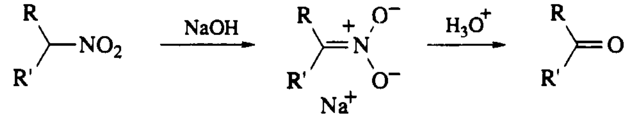

**(170)**

(30)

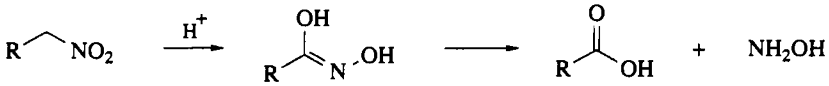

**(171)** **(172)**

(31)

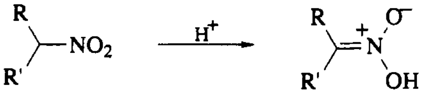

**(173)**

(32)

A kinetic study of the effect of water on the hydrolysis of (**173**) established the existence of two reaction pathways leading to the carbonyl derivatives, depending on water concentration.[114] The unsatisfactory results observed in many instances led to modifications of the hydrolysis conditions. The supposed limitation of the Nef reaction due to steric hindrance is probably a result of the low solubility of nitroalkanes in aqueous alkali, as demonstrated by the success of the reaction if THF–$H_2O$,[115] alcoholic sodium hydroxide[116] or alkoxide[117] is used. Silica gel[118-120] as a reaction medium is of great advantage when the use of organic solvents is undesirable. A two-layer method represents an improvement for the conversion of aromatic nitroalkanes.[121]

#### *4.7.4.1.2 Oxidation reactions*

The oxidizing agents usually employed for cleavage of double bonds are able to transform nitronate anions into carbonyl derivatives. The permanganate ion oxidation has been well studied.[122] The stepwise formation of the activated complex (**174**) as the slow step is a possibility but the formation of (**175**) *via* a concerted *cis* cycloaddition could also be the rate-limiting step (equation 33). Although the yield is generally high, oxidizable functions such as double bonds and hydroxy groups do not survive or at least result in decreased yields. Among modifications of methods using $KMnO_4$ as an oxidant, two interesting improvements have been described.[123–125] The electronic similarity of nitronates and enols led to the use of epoxidizing agents on nitronates[126–128] or their trialkylsilyl derivatives.[129] An α-hydroxy nitro compound is thought to be the intermediate leading to the carbonyl derivative. *m*-Iodylbenzoic acid, a reagent for cleaving glycols, also oxidized secondary nitronates to ketones (equation 34).[130]

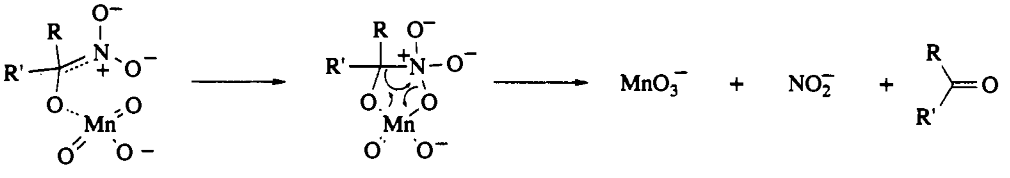

(**174**) (**175**)

(33)

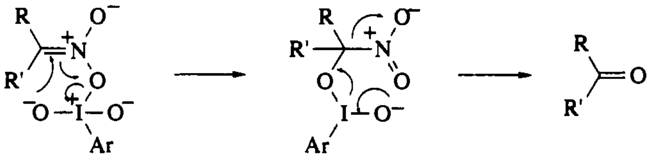

(**176**) (**177**)

(34)

#### *4.7.4.1.3 Reduction reactions*

Reagents such as $TiCl_3$,[131,132] $VCl_2$[133] and $CrCl_2$[134,135] are able to reduce nitro compounds to oximes and/or imines, which in turn are rapidly hydrolyzed to carbonyl derivatives. These reactions are usually performed in an acidic medium; however, to improve the yield a variety of pH conditions have been studied.

Reactions of titanium(III) chloride, one of the most useful reducing agents, can be carried out on free nitro compounds or on nitronate anions. The mechanisms of these two cases are thought to proceed by different pathways.

Since oximes are reduced to imines with buffered aqueous $TiCl_3$, one can assume that reduction of nitronate anions might progress through a similar mechanism. With regard to the reduction of nitro compounds themselves, there is some evidence for the intermediacy of a nitroso compound (**178**; Scheme 43). Indeed, at low pH tautomerization of (**178**) to oxime (**179**) would be rapid, whereas with $TiCl_3$–$NH_4OAc$ at pH 6 the nitro group is trapped to give only pyrroline (**183**), due to slow tautomerism.

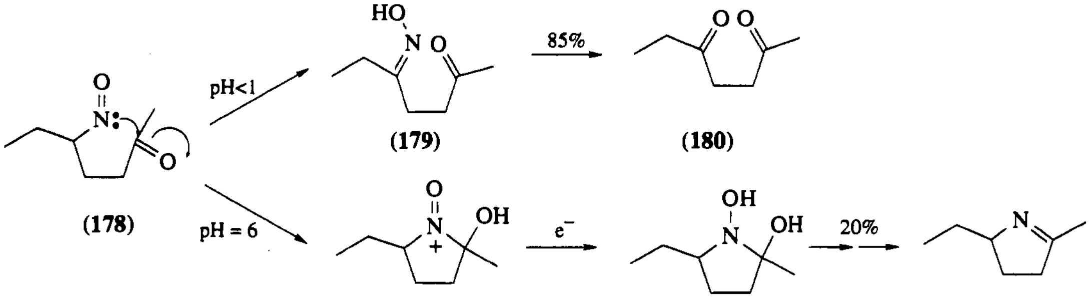

(**178**) (**179**) (**180**) (**181**) (**182**) (**183**)

Scheme 43

### 4.7.4.2 Scope and Limitations

The Nef reaction often represents the key transformation in a reaction sequence in which it is involved. The synthesis of simple aliphatic ketones or aldehydes is probably not the most useful application of the Nef reaction. More important is the access to dicarbonyl compounds for intramolecular cyclization reactions leading to a large variety of carbocycles or heterocycles. However, the method can be capricious and success depends on the structure of the substrate. In order to overcome synthetic drawbacks, several roundabout methods have been devised for application to peculiar polyfunctionalized molecules. The number of modifications of the Nef reaction which can be carried out under a wide variety of conditions clearly reveals that no procedure is of general application. The scope and limitations of the different modifications will be discussed considering the structure of desired carbonyl derivative.

#### *4.7.4.2.1 Simple aldehydes and ketones*

Most of the methods allow preparation of simple alphatic and aromatic aldehydes and ketones. With some oxidants competitive transformation of aldehydes to carboxylic acids is observed. For high molecular weight compounds the yield drops under hydrolytic conditions because of poor aqueous solubility of these derivatives; in contrast this inconvenience does not exist in alcoholic media.[117] Some methods require apparatus which is not always available or compatible with large-scale reactions, *e.g.* electrolysis,[136–138] ozonolysis[139,140] or singlet oxygen reactions.[141] $TiCl_3$ reduction exhibits some general character but yields are dependent on pH conditions (see above) if other functional groups are present in the molecule. Ozone[139,140] reacts with monosubstituted alkenes which are inert to singlet oxygen[141] and $TiCl_3$.

Cetyltrimethylammonium permanganate (CTAP),[123] a stable quaternary ammonium salt, provides a valuable modification of the original permanganate procedure for selective conversion of substrates containing alkenic and hydroxy groups. Yields are good to excellent (Scheme 44) and large quantities of substrate can be transformed.

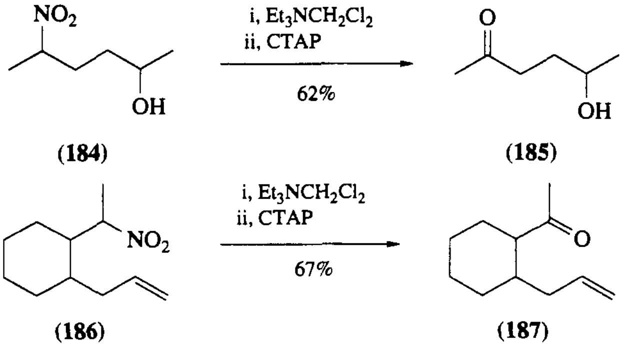

Scheme 44

α,β-Unsaturated nitroalkenes give 1,4-addition with reducing agents. Thus lithium tri-*s*-butylborohydride[142] and chromium(II) chloride[135] give the corresponding nitroalkanes, which are subsequently transformed into the saturated ketones. The same mechanism is followed when 1-nitrocyclooctene (**188**) is treated in a one-pot reaction with base (NaOH or NaOMe) then reduced by $TiCl_3$; the α-hydroxy or α-methoxy ketones are formed in excellent yields (Scheme 45).

The ester function is in general unaffected by most of the Nef reaction conditions. Of particular interest are those reactions using methanol or ethanol as the solvent for hydrolysis.[116,117] It is worth noting that treatment of a nitronate salt by sulfuric acid in absolute methanol at −10 °C yields dimethyl acetal, *i.e.* a protected form of the aldehyde.[143] For solid phase hydrolysis, silica gel[118–120] or potassium permanganate supported on silica gel[144–146] are remarkably efficient reagents, especially for small scale reactions.

##### *(i) Elongation reactions*

The base-catalyzed addition of nitromethane to an aldehyde according to the Henry reaction, followed by the Nef reaction, is a classical method for elongation of the carbon chain in carbohydrate chemistry[4,147] Facile β-elimination of the hydroxy group allows the synthesis of α,β-unsaturated aldehydes or

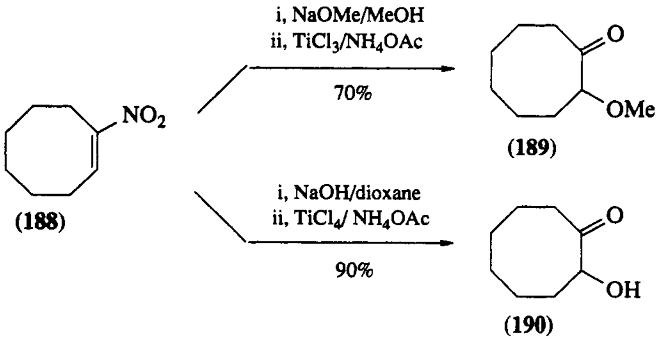
NO2
(188)
i, NaOMe/MeOH
ii, TiCl3/NH4OAc
70%
O
OMe
(189)
i, NaOH/dioxane
ii, TiCl4/ NH4OAc
90%
O
OH
(190)

**Scheme 45**

deoxy sugars after hydrogenation of the double bond.[147] Homologation of an aldehyde in a polyfunctional synthetic intermediate (**191**) is accomplished efficiently (equation 35).[117]

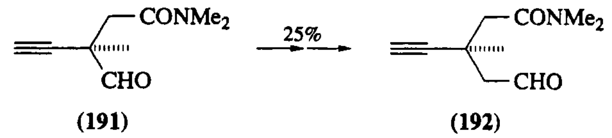
CONMe2
CHO
(191)
25%
CONMe2
CHO
(192)

(35)

### 4.7.4.2.2 α-*Substituted ketones*

α-Alkoxycarbonyl compounds are part of macrolide antibiotics and polyether ionophores. In contrast to aldehydes, α-substituted ketones are difficult to synthesize by known methods. A straightforward manner of solving this problem is the one-pot 1,4-addition of alkoxides to nitroalkenes, followed by a Nef reaction, a process suitable for both cyclic or alicyclic ketones (*e.g.* **193**, **195**; Scheme 46).[129] The combination of these two reactions also provides a valuable route to α-sulfenylated ketones (**197**; Scheme 46).[125]

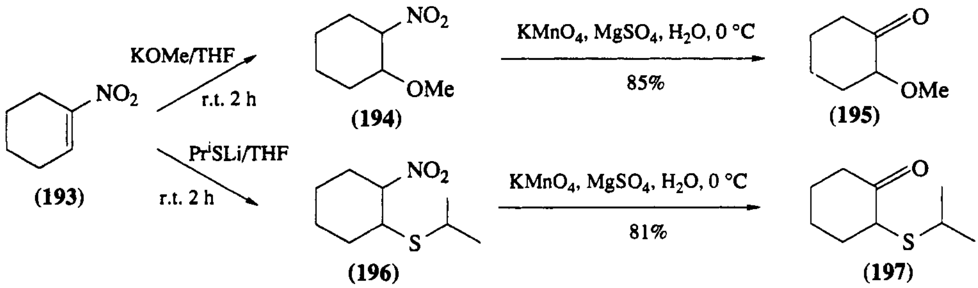
NO2
(193)
KOMe/THF
r.t. 2 h
Pr$^i$SLi/THF
r.t. 2 h
NO2
OMe
(194)
NO2
S
(196)
KMnO4, MgSO4, H2O, 0 °C
85%
KMnO4, MgSO4, H2O, 0 °C
81%
O
OMe
(195)
O
S
(197)

**Scheme 46**

Very mild conditions, which do not affect enol ethers, involve treatment of trialkylsilyl nitronates with MCPBA (equation 36)[129]. Nitro derivatives themselves do not react with MCPBA.

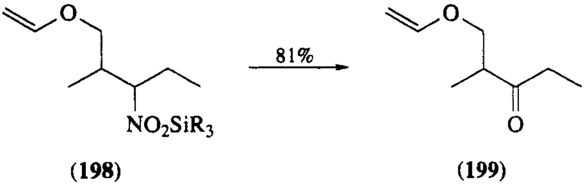
O
NO2SiR3
(198)
81%
O
O
(199)

(36)

Preparation of α-fluoro ketones or aldehydes can also be achieved by cerium ammonium nitrate[148] oxidation of the corresponding silyl nitronates. *C*-acylation compounds derived from nitroalkanes can be transformed into α-diketones or keto esters. This procedure, while theoretically interesting, has not been extensively explored because acylation of the nitronate anion often occurs at oxygen.

#### 4.7.4.2.3 1,3-Dicarbonyl compounds

1,3-Dinitroalkanes, obtained by condensation of nitroalkane Mannich base with other nitroalkanes or by Michael addition of nitroalkanes to nitroalkenes give 1,3-diones only when a secondary amine is used as base;[149] however, yields are moderate (~ 40%).

Interestingly, hydrazines react with 1,3-dinitroalkanes to afford pyrazoles, in most cases in high yields (equation 37).[150]

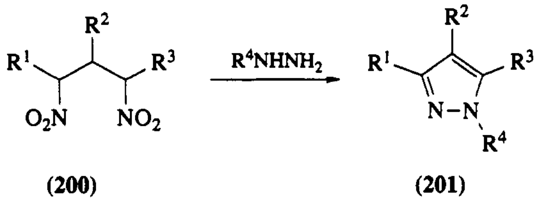

(37)

#### 4.7.4.2.4 1,4-Dicarbonyl compounds

1,4-Dicarbonyl compounds are valuable intermediates in the preparation of natural products and related compounds containing pyrrole, thiophene, furan or cyclopentenone ring systems.

Reaction of nitroalkanes with Michael acceptors, followed by the Nef reaction, represents a versatile synthetic route for the preparation of 4-oxoalkanals,[138] 1,4-diketones[146] and 4-oxo esters.[143]

##### (i) 4-Oxoalkanals

The sensitivity of 4-oxoalkanals requires that special care be taken in their preparation.

The Michael reaction of nitroalkanes with acrolein, catalyzed by tributylphosphine, followed by acetalization of the resultant adduct, led to 1,1-ethanediyldioxy-4-nitroalkane (**202**), which is oxidized by an electrolytic procedure[138] to 4-oxoalkanal 1-acetal, the protected form of the expected 4-oxoalkanal (**203**; Scheme 47).

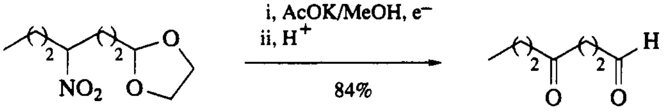

**(202)** **(203)**

**Scheme 47**

Aqueous acid hydrolysis of the primary nitro derivative (**204**) gives the desired keto aldehyde (**205**) in moderate yield (Scheme 48).[115]

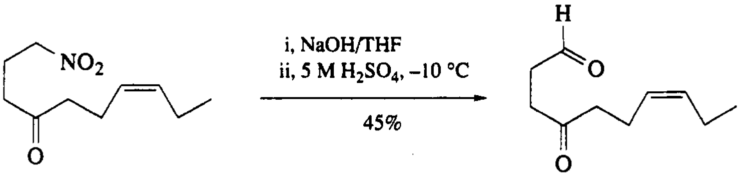

**(204)** **(205)**

**Scheme 48**

The utility of the Nef reaction in the synthesis of prostanoic acids is illustrated by the preparation of the key cyclopentanecarbaldehydes (**207**)[151] and (**209**)[152] (Scheme 49).

Selectively protected keto aldehyde (**209**) is prepared by $KMnO_4$ oxidation of (**208**).

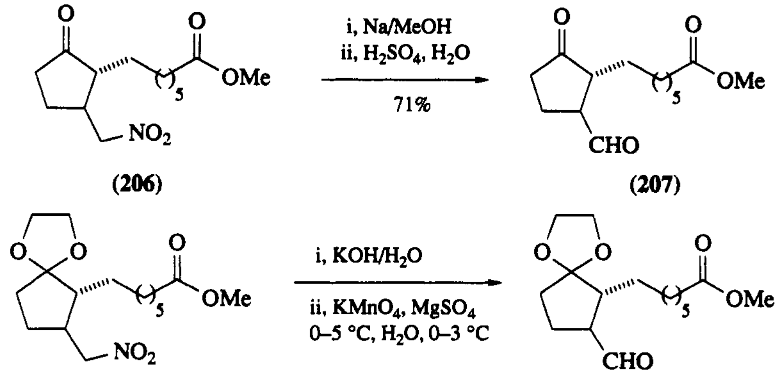

i, Na/MeOH
ii, $H_2SO_4$, $H_2O$
71%
OMe
$NO_2$
CHO
i, KOH/$H_2O$
ii, $KMnO_4$, $MgSO_4$
0–5 °C, $H_2O$, 0–3 °C

**(206)** **(207)** **(208)** **(209)**

**Scheme 49**

*(ii) 1,4-Diketones*

Efforts have been devoted to the synthesis of 1,4-diketones as key intermediates for the synthesis of the cyclopentenone ring found in jasmone and its derivatives.

Many reaction conditions can be efficiently utilized for the Nef reaction leading to robust 1,4-diketones.[116,118,120,123,128,136,139,141,146]

Mild procedures are required for the preparation of 1,4-diketones which incorporate unsaturations. The most straightforward route to (*Z*)-jasmone (**213**) illustrates the efficiency of $TiCl_3$ reduction of (**210**) to give the diketone (**211**) in 85% yield (Scheme 50).[153]

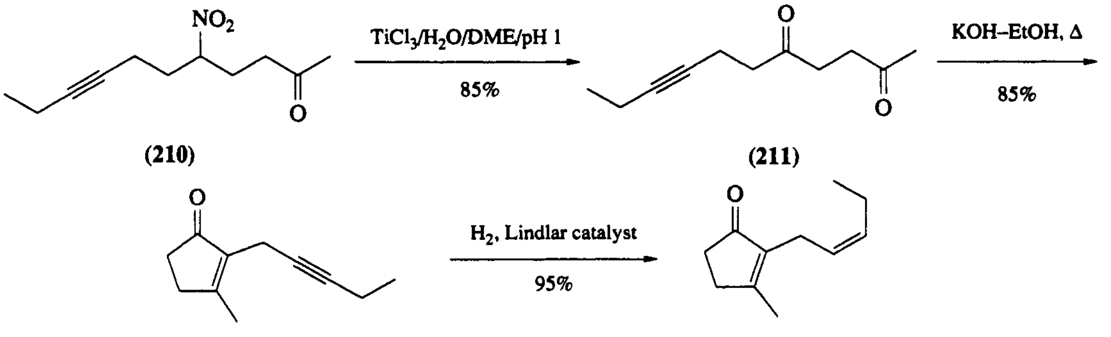

$NO_2$
$TiCl_3/H_2O/DME/pH$ 1
85%
KOH–EtOH, Δ
85%
$H_2$, Lindlar catalyst
95%

**(210)** **(211)** **(212)** **(213)**

**Scheme 50**

Acid hydrolysis of the ethylenic nitro derivative (**214**) gave (**215**; Scheme 51) in good yields when the reaction temperature was kept at –15 °C to avoid isomerization of the double bond.

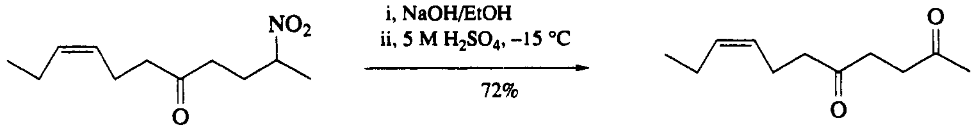

$NO_2$
i, NaOH/EtOH
ii, 5 M $H_2SO_4$, –15 °C
72%

**(214)** **(215)**

**Scheme 51**

The $TiCl_3$ conditions are the most appropriate for the one-pot synthesis of the 6-oxo-PGE$_1$ derivative (**217**; Scheme 52).[154]

The use of supported $KMnO_4$ is disavantaged by the removal of the dicarbonyl compound from the surface of the silica gel and the yields are not convenient for large scale experiments.[144,146] *m*-Iodylbenzoic acid[130] is a mild oxidative reagent which does not affect the dithiolane moiety of the monoprotected 1,4-diketone (**219**; Scheme 53).

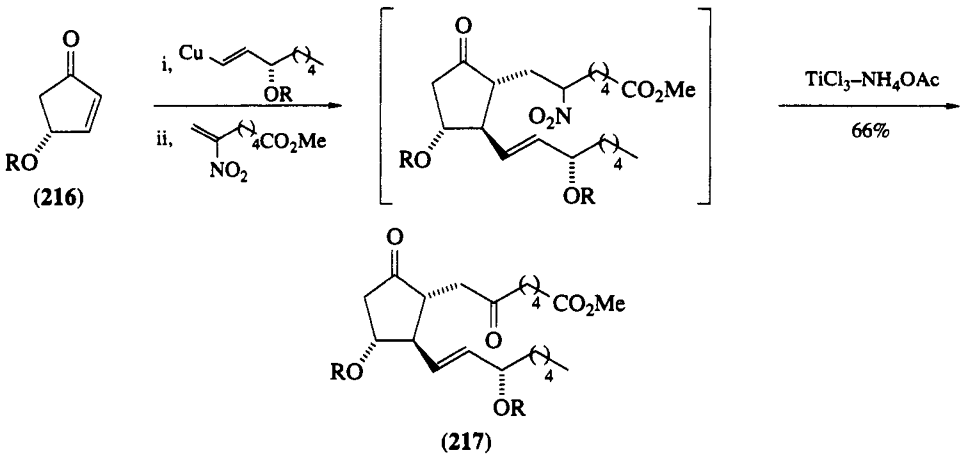
i, Cu, OR, 4
ii, NO2, 4CO2Me
TiCl3–NH4OAc
66%
CO2Me
O2N
RO
OR

(216)

(217)

Scheme 52

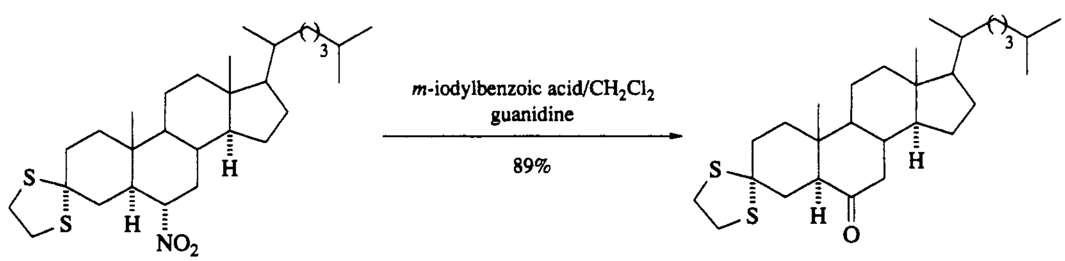
*m*-iodylbenzoic acid/CH2Cl2
guanidine
89%
S
H
NO2
O
3

(218) (219)

Scheme 53

2,3-Unsaturated 1,4-diketones are available from the corresponding nitro ketones by adsorption on silica gel,[118] oxidation with peroxodisulfate[155] or reduction with ascorbic acid (equation 38).

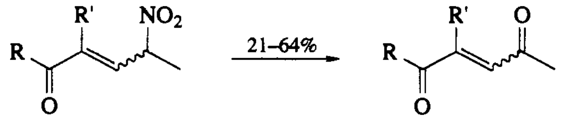
R
R'
NO2
O
21–64%

(220) (221) (38)

### (iii) *Formation of heterocycles*

Intramolecular reactions of nitronic acids, obtained from nitroalkenes and acetoacetate, lead to furans or *N*-substituted pyrroles, depending on the organic base which is used (Scheme 54).[156,157]

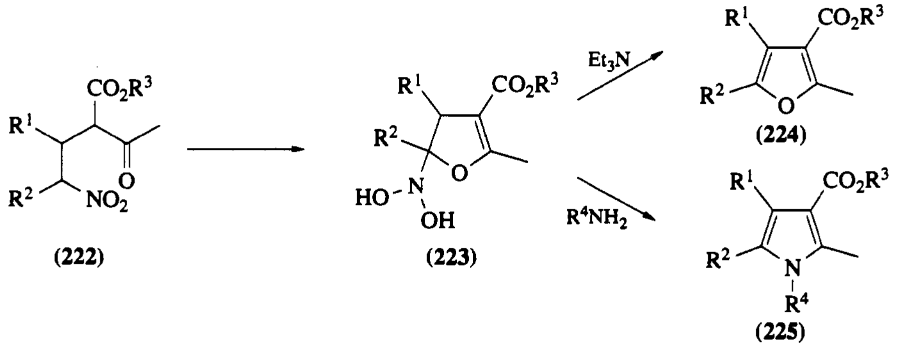
CO2R3
R1
R2
NO2
HO
N
OH
Et3N
R4NH2
(222)
(223)
(224)
(225)

Scheme 54

Primary amines or tertiary amines afford respectively only furans (**224**) or *N*-substituted pyrroles (**225**).

The reaction in the presence of secondary amines gives a mixture of pyrrole and furan.

### *(iv) 4-Oxo Esters*

Amongst numerous methods available, the Nef reaction appears to be the most flexible procedure for the synthesis of 4-oxo-3-alkylbutanoates (**228**); (Scheme 55), intermediates in the preparation of dienes used for cycloaddition reactions.

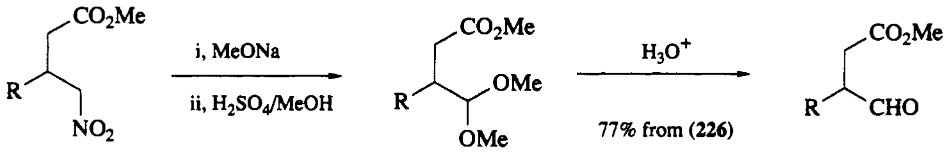

**(226)** **(227)** **(228)**

**Scheme 55**

### *4.7.4.2.5 1,5-Dicarbonyl compounds*

A general route for the regiospecific synthesis of 3-alkylbenzopyran-1-ones,[158] which occur in natural products, is based upon the formation of nitroalkyl-susbtituted isobenzofuranones from Henry condensation of nitroalkanes with phthalaldehydic acids.

Amongst several Nef conditions,[127,128,131,132,154] utilization of hydrolysis in methanolic phase gave the best yields of the carboxy acetal (**232**) mixed with the keto acid (**231**), which led to the desired compound (**233**) after dehydration (Scheme 56).

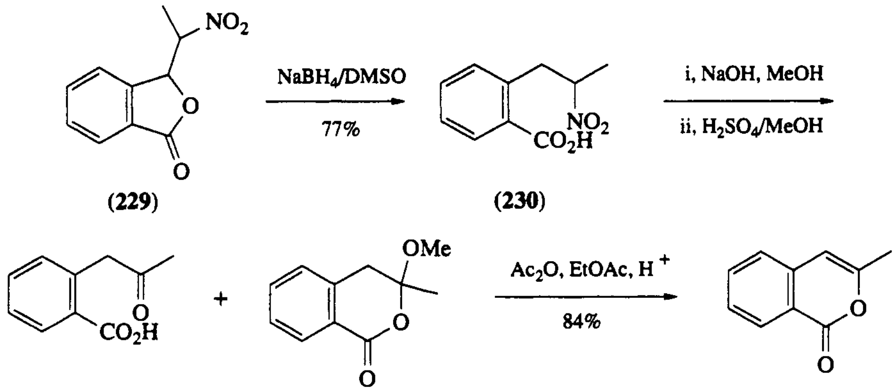

**(229)** **(230)**

**(231)** **(232)** **(233)**

**Scheme 56**

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# 5.1

# Eliminations to Form Alkenes, Allenes and Alkynes and Related Reactions

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## 5.1.1 INTRODUCTION

If a molecule loses two atoms or groups, which will not be replaced by other atoms or groups, this reaction is called an elimination reaction. These reactions may be catalyzed by base, acid, iodine, metals or application of heat. Table 1 gives a survey of the possible elimination reactions and their products.

**Table 1** Possible Elimination Reactions

| *Substrate*[a] | *Name* | *Products* |
|---|---|---|
| 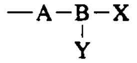 $-A-\underset{Y}{\underset{\mid}{B}}-X$ | 1,1- or α-elimination | Carbenes, nitrenes |
| 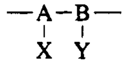 $-\underset{X}{\underset{\mid}{A}}-\underset{Y}{\underset{\mid}{B}}-$ | 1,2- or β-elimination | Alkenes, alkynes, allenes |
| 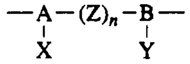 $-\underset{X}{\underset{\mid}{A}}-(Z)_n-\underset{Y}{\underset{\mid}{B}}-$<br>$n = 1, 2$ | 1,($n$ + 2)-elimination | Cumulenes, conjugated dienes, ring systems |
| 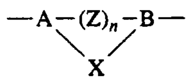<br>$n = 0, 1, 2$ | Extrusions | Alkenes, alkynes, aromatic systems |

[a] X and Y represent leaving groups.

This article concentrates on the most important type of elimination reaction from the preparative point of view: β-elimination in solution.

## 5.1.2 MECHANISMS

A β-elimination is characterized as shown in Scheme 1.

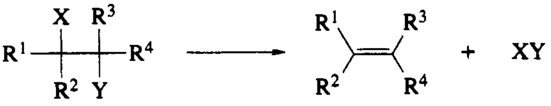

**Scheme 1**

Depending upon the sequence of C—X and C—Y cleavage, a distinction is made between three possible mechanisms, described in the following sections, but one should always bear in mind that all three mechanisms are idealized extremes and that borderline cases exist.

### 5.1.2.1 The *E*1 Mechanism (Elimination, Monomolecular)[1]

In the case of an *E*1 reaction (*e.g.* HY elimination) a two-step process is involved (see Scheme 2). In the first step (slow, rate-determining) the leaving group Y departs from the substrate as an anion and a carbocation is formed. Since the latter is also the intermediate of an $S_N1$ reaction, the $S_N1$ substitution may be a competing reaction. In the second step (fast) the positively charged substrate molecule will lose a proton from C-β to a base (*e.g.* the solvent).

Characteristic features of this mechanism are that: (i) the rate of the reaction does not depend on the concentration of the base and the kinetics are first order (in substrate); (ii) the reaction may not be stereospecific; (iii) the elimination/substitution ratio is mostly independent of the leaving group (but in solvents of low ionization energy ion pairs are formed and then the ratio depends upon the leaving group); (iv) by-products are formed *via* rearrangements; (v) the reaction is reversible; (vi) generally the most stable alkene is formed (Zaitsev orientation; see Section 5.1.2.5)

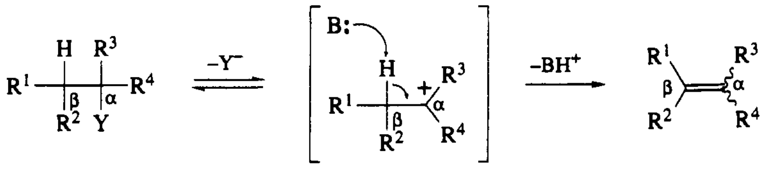

Scheme 2

Because the characteristics (ii)–(v) are generally undesirable for preparative work, *E*1 conditions should be avoided if complications can arise.

*E*1 reactions are favored by: (i) substitution of substrate in the α-position with alkyl or aryl groups, because they stabilize carbocations (for this reason primary alkyl halides generally do not react *via* an *E*1 mechanism); (ii) polar protic solvents (*e.g.* $H_2O$, ROH, $HCO_2H$); (iii) substitution of the substrate in the β-position with alkyl substituents, because of the less-hindered transition state of the *E*1 reaction (change from $sp^3$ to $sp^2$) compared to $S_N1$ and *E*2 reactions; (iv) a good leaving group Y (*e.g.* $OH_2^+$).

These points may be illustrated by two examples: acid-catalyzed dehydration of tertiary alcohols (Scheme 3),[2] and solvolytic dehydrohalogenation of secondary alkyl halides (Scheme 4).[3]

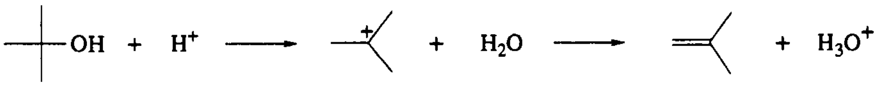

Scheme 3

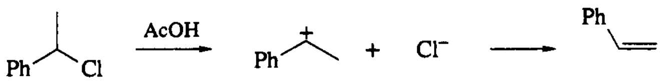

Scheme 4

### 5.1.2.2 The *E*1c*B* Mechanism (Elimination, Monomolecular, Conjugate Base)

Like the *E*1 reaction, the *E*1c*B* reaction takes place by a two-step process (Scheme 5). However, the substrate molecule now loses a proton to the attacking base in a fast and reversible step, and a carbanion is formed at C-β. The second step (slow, rate-determining) is the departure of the leaving group Y.

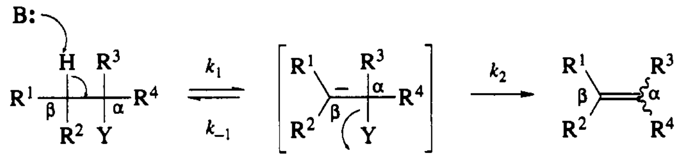

Scheme 5

This mechanism is characteristic of substrates having a poor leaving group, such as fluorine, but a very acidic proton at the β-position. Depending on the conditions of the reaction, four limiting cases can be considered: (i) $k_1 > k_2$, $k_{-1} \gg k_2$ ($E1cB_{\mathrm{R}}$; R = reversible), *i.e.* a reversible reaction with specific base catalysis; (ii) $E1cB_{\mathrm{IP}}$ (IP = ion pair), where there is no free carbanion, the protonated base stays close to the substrate and there is no H/D isotope effect, because the proton abstraction is not rate determining; (iii) $k_2 \gg k_{-1}$ ($E1cB_{\mathrm{IRR}}$; IRR = irreversible), where Y is a very good leaving group and the proton abstraction is rate determining, so the reaction is irreversible and exhibits general base catalysis; (iv) $k_1 \gg k_2$ ($E1_{\mathrm{anion}}$), where a stable carbanion is formed, which is slowly converted to the product.

These four cases are illustrated in Table 2.[4]

An example of the *E*1c*B* elimination, the dehydrofluorination of $X_2CH—CF_3$ (X = Hal), is shown in Scheme 6 (F = poor leaving group; acidic proton at C-β).[5]

**Table 2** Kinetic Predictions for Base-induced β-Eliminations

| *Mechanism* | *Kinetic order*[a] | *β-Hydrogen exchange faster than elimination* | *General or specific base catalysis* | $k_H/k_D$ | *Electron withdrawal at C-β*[d] | *Electron release at C-α*[d] | *Leaving group isotope effect or element effect* |
|---|---|---|---|---|---|---|---|
| $E1_{\text{anion}}$ | 1 | Yes | General[c] | 1.0 | Rate decrease | Rate increase | Substantial |
| $E1cB_{\text{R}}$ | 2 | Yes | Specific | 1.0 | Small rate increase | Small rate increase | Substantial |
| $E1cB_{\text{IP}}$ | 2 | No | General[e] | 1.0–1.2 | Small rate increase | Small rate increase | Substantial |
| $E1cB_{\text{IRR}}$ | 2 | No | General | 2–8 | Rate increase | Little effect | Small to negligible |
| $E2$[b] | 2 | No | General | 2–8 | Rate increase | Small rate increase | Small |

[a] All mechanisms exhibit first-order kinetics in substrate. [b] Only transition states with considerable carbanion character are considered in this table. [c] Specific base catalysis predicted if extent of substrate ionization reduced from almost complete. [d] Effect on rate assuming no change in mechanism is caused, as steric factors upon substitution at C-α and C-β have not been considered. The rate predictions are geared to substituent effects such as these giving rise to Hammett reaction constants on β- and α-aryl substitution. [e] Depends on whether ion pair assists in removal of leaving group.

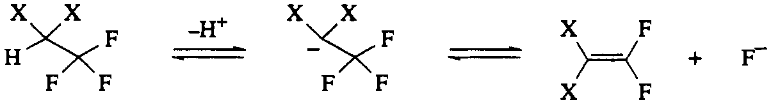

Scheme 6

### 5.1.2.3 The *E*2 Mechanism (Elimination, Bimolecular)

In contrast to the mechanisms mentioned before, *E*2 elimination takes place in a concerted, but not necessarily synchronous, manner. While the attacking base is abstracting a proton from C-β, cleavage of the C(α)—Y bond is progressing. In the transition state all five atoms or groups are coplanar and a double bond is subsequently formed between C-α and C-β (Scheme 7).

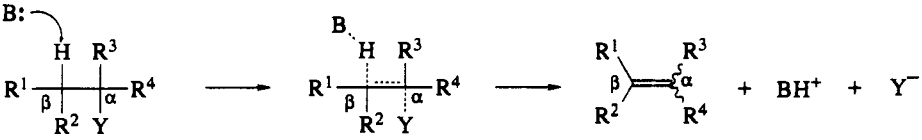

Scheme 7

The characteristics of this mechanism are that: (i) the attacking base and the substrate both take part in the rate-determining step, which has second-order kinetics overall (first-order in base and first-order in substrate); (ii) a large primary isotope effect is usually observed; (iii) since the mechanisms of *S*N2 and *E*2 differ much more than those of *S*N1 and *E*1 reactions, the substitution/elimination ratio can be controlled in most cases by choosing appropriate conditions; (iv) no rearrangement reactions are observed; (v) the rate of elimination depends upon the strength of the base; (vi) the stereospecificity of an *E*2 reaction depends on the conditions (see Section 5.1.2.4).

These characteristics are excellent for preparative work, so synthetic chemists usually try to run elimination reactions under *E*2 conditions. To pull an elimination into the favorable *E*2 region, the following conditions have to be observed: (i) the leaving group Y should have a poor tendency to leave the substrate and low electron-withdrawing power (*e.g.* $NR_3^+$, $PR_3^+$, $SR_2^+$); (ii) use of a strong base in high concentration; (iii) the C-α atom should be sterically hindered by branching, so that the substitution reaction is rendered more difficult, if this is possible in view of the synthetic target; (iv) the attacking center of the base should be sterically hindered in order that only the proton at C-β, and not C-α, can be reached; (v) the solvent must be polar aprotic (*e.g.* DMF, DMSO).

The *E*1 and *E*1c*B* mechanisms are regarded as the two extreme cases[6] and the *E*2 mechanism lies somewhere between them. Whether the transition state of an elimination is more *E*1-like, more *E*1c*B*-like or exactly *E*2 depends upon the substrate, the leaving group, the attacking base and the medium of the reaction.

For example, if the substrate has a poor leaving group, the attacking base will abstract the proton at C-β a little earlier than the bond between C-α and Y is cleaved. This leads to a transition state with more

*E*1*cB* character. On the other hand, if the substrate has an electron-releasing group at C-α, the acidity of the proton at C-β will be reduced and now the leaving group is able to leave the substrate a little earlier. This gives a transition state with more *E*1 character.[7]

### 5.1.2.4 Stereoselectivity

Stereoselectivity means the specific formation of either (*E*)- or (*Z*)-alkenes. Unlike the *E*1-reaction, which has only poor stereoselectivity because of the intermediate formation of a planar carbocation, the stereoselectivity of the *E*2 reaction is very high. In the transition state all five groups or atoms involved must be coplanar. This implies a dihedral angle between C(β)—H and C(α)—Y of either 0° (ecliptic arrangement, synperiplanar) or 180° (staggered arrangement, antiperiplanar).

Because the ecliptic arrangement is energetically unfavorable, *E*2 reactions prefer *anti* elimination. This is also shown by frontier orbital arguments.[8]

Usually this antiperiplanar conformation is easy to reach for acyclic compounds, because of the low energy barrier between the conformations.

There may also exist an interaction between the base and C-α, especially for weak attacking bases, which has already nucleophilic quality. It is to be supposed that such eliminations will proceed *via* the transition state shown in Scheme 8.[9]

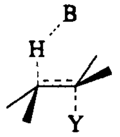

**Scheme 8**

The dehydrobromination of 1,2-dibromo-1,2-diphenylethane is an example of *anti* elimination. The reaction of the *meso* isomer (**4**) results in the formation of (*E*)-bromostilbene (**5**). The same reaction with the (±)-isomer (**6**) gives (*Z*)-bromostilbene (**7**; Scheme 9).[10]

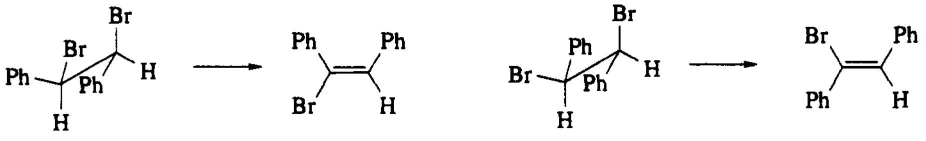

(**4**) (**5**) (**6**) (**7**)

**Scheme 9**

The preference for *anti* elimination is especially evident in reactions with systems of fixed configuration such as vinylic haloalkenes. Usually those reactions use the *E*1*cB* pathway, because of the relatively high acidity of the vinylic proton. However, if this proton is not especially activated by electron-withdrawing groups at C-β and if the attacking base is not too strong, the reaction is shifted into the *E*2 region. The reaction of the *cis*-alkene (**10**) leads to the allene (**11**) rather than to the alkyne (**9**; Scheme 10).[11] If the substrate does not have this choice, the reaction will proceed *via* a *syn* elimination and the rate is strongly decreased.[12]

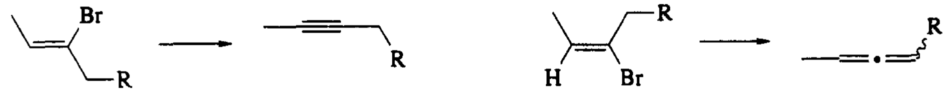

(**8**) (**9**) (**10**) (**11**)

**Scheme 10**

Another case is the elimination reaction in cyclic systems. In such systems the conformation is determined by the flexibility or rigidity of the ring. The following correlation between ring size and degree of selectivity is observed (Table 3).[13]

**Table 3** The Effect of Ring Size on the Percentage of *Syn* Elimination Product

| *Ring size* | *Syn elimination (%)* | *Ring size* | *Syn elimination (%)* |
|---|---|---|---|
| Cyclobutyl | 90 | Cyclohexyl | 4 |
| Cyclopentyl | 46 | Cycloheptyl | 37 |

The table shows that *E*2 eliminations, particularly in five- and seven-membered ring systems, are not completely stereospecific, but four- and six-membered rings exhibit strong preferences. Six-membered rings in particular show distinct *anti* selectivity, because it is very easy for such systems to reach the *trans*-diaxial conformation (**12**) (Scheme 11; Barton's rule).[14] This *anti* selectivity can be seen very clearly in the elimination reaction with the isomers of 1,2,3,4,5,6-hexachlorocyclohexane. The isomer (**13**), which has no Cl *trans* to an H, loses HCl about 7000 times more slowly than the slowest of the other isomers.[15]

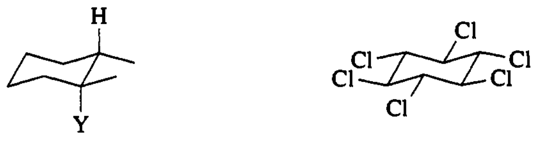

**(12)** **(13)**

**Scheme 11**

*Syn* elimination in *E*2 reactions will be observed if: (i) it is impossible for H and Y to reach antiperiplanar conformation (see Scheme 12);[16] (ii) one *syn*-H ($H^1$ in **15**) is more acidic than all the others ($H^2$ and $H^3$ in **15**; Scheme 13);[17] (iii) *syn* elimination is sterically privileged (and furthermore the attacking base, *e.g.* $OH^-$, may operate as a complexing reagent; Scheme 14);[18] or (iv) the counterion of the attacking base is able to form an ion pair with the substrate, although if the reaction is performed in the presence of crown ethers the relative rate of *syn* elimination is rapidly decreased (Scheme 15).[19]

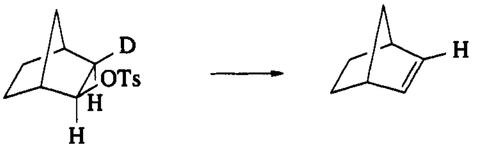

**(14)**

**Scheme 12**

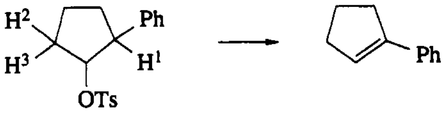

**(15)**

**Scheme 13**

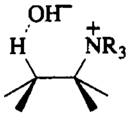

**(16)**

**Scheme 14**

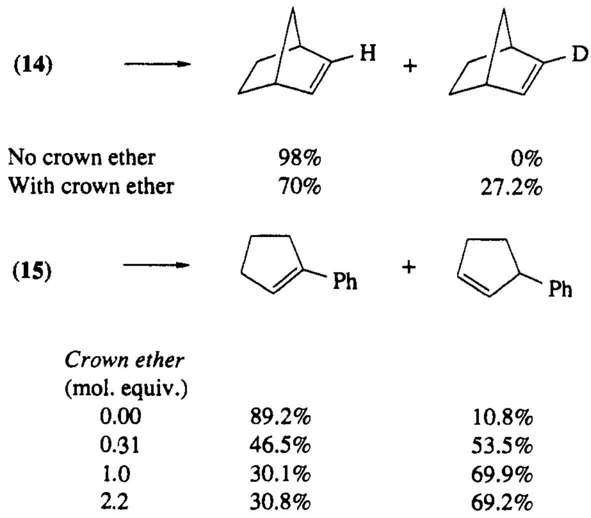

| (14) | | |
|---|---|---|
| No crown ether | 98% | 0% |
| With crown ether | 70% | 27.2% |

| *Crown ether* (mol. equiv.) | | |
|---|---|---|
| 0.00 | 89.2% | 10.8% |
| 0.31 | 46.5% | 53.5% |
| 1.0 | 30.1% | 69.9% |
| 2.2 | 30.8% | 69.2% |

**Scheme 15**

### 5.1.2.5 Orientation

If a substrate molecule has more than one β-H atom, the elimination reaction may lead to more than one alkene. The orientation is called Zaitsev orientation[20] if the resulting double bond has the largest numbers of substituents possible; this means that the proton is abstracted from the most highly substituted carbon. If the elimination reaction runs the other way, the orientation is called Hofmann orientation.[21] In general, the Zaitsev product is thermodynamically more stable than the Hofmann product, due to hyperconjugation (Scheme 16).

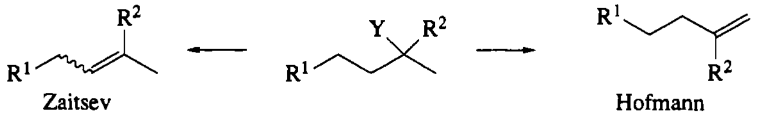

**Scheme 16**

The orientation also depends on other factors. If there is a choice between the formation of a conjugated or unconjugated double bond, usually the conjugated system is formed. Furthermore, a double bond will never be formed to a bridgehead carbon atom if the ring size is not large enough (Bredt's rule).[22]

In addition the orientation depends upon the following factors: (i) the acidity of the β-H atom; (ii) the reactivity and character of the leaving group; (iii) the strength of the attacking base; (iv) the sizes of the attacking base and the substrate.

These points are illustrated by the following examples.

A fluoroalkane reacts with a strong base in an *E*1*cB* reaction because it has a poor leaving group and an acidic proton in the β-position. If there are several β-protons, the one leading to the most stable carbanion will be abstracted, thus a Hofmann product is formed. If there is a better leaving group, the reaction is moved into the *E*1 region. Now all factors which stabilize carbocations are important, *e.g.* high substitution at C-β; this means that the Zaitsev product is formed (Table 4).[23]

*E*2 reactions have their own rules: (i) if the leaving group is uncharged (*i.e.* negatively charged after cleavage) Zaitsev orientation is preferred; (ii) if the leaving group is charged (*i.e.* uncharged after the reaction) Hofmann orientation is preferred in acyclic systems and Zaitsev orientation in six-membered rings.

The effect of base strength is illustrated by the reaction shown in Scheme 17.

With the poor base potassium benzoate only 7.2% Hofmann product (**22**) could be obtained; with the strong base potassium *t*-butoxide the yield is raised to 20%.[24]

Table 5 demonstrates the effect of steric hindrance of the base.[25]

The larger the attacking base, the smaller is the proportion of Zaitsev product. Every kind of steric hindrance (in the substrate as well as in the leaving group or the attacking base) will make the transition

**Table 4** The Effect of the Leaving Group on Orientation

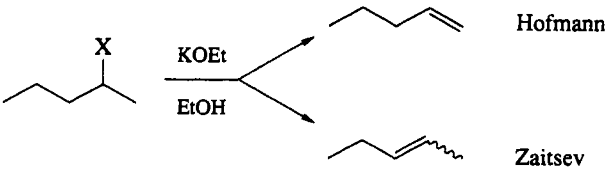

| *X* = | *F* | *Cl* | *Br* | *I* |
|---|---|---|---|---|
| Zaitsev product (%) | 17 | 64 | 75 | 80 |
| Hofmann product (%) | 83 | 36 | 25 | 20 |

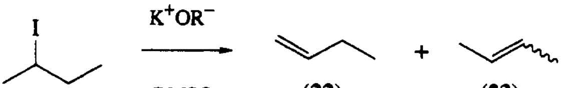

(22) (23)

**Scheme 17**

**Table 5** The Effect of the Bulkiness of the Attacking Base on Orientation

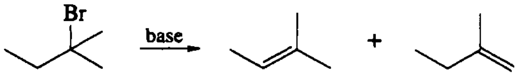

| *Base* | *1-Alkene (%)* | *Base* | *1-Alkene (%)* |
|---|---|---|---|
| EtOK | 38 | 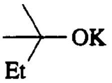 | 78 |
| $Bu^tOK$ | 73 | 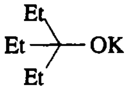 | 89 |

state which leads to the Zaitsev product energetically more unfavorable, so that the formation of the Hofmann product is preferred.

If steric hindrance is not significant, electronic effects will predominate. Finally, it should be noted that there is a statistical factor in favor of the Hofmann elimination, because there are usually more protons that can be eliminated on the Hofmann side.

### 5.1.2.6 *E1 versus E2 versus E1cB*

### *5.1.2.6.1 The effect of substituents*

The *E*1 mechanism is preferred if α-alkyl and α-aryl groups are in the substrate, because they stabilize carbocations. This mechanism is also supported by β-alkyl groups, because they decrease the acidity of β-protons. On the other hand, β-aryl groups favor the *E*1c*B* mechanism, as they stabilize carbanions by conjugative effects. Electron-withdrawing groups (*e.g.* $NO_2$, $SO_2Ar$) move the reaction towards *E*1c*B*, especially in connection with poor leaving groups.

#### *5.1.2.6.2 The attacking base*

In *E*1 reactions the solvent usually operates as the attacking base. If a base is added, the mechanism can be pushed into the *E*2 region. Preparatively useful examples use $OH^-$, $OR^-$ or $NH_2^-$, with their conjugate acids as solvents. A highly concentrated strong base moves the mechanism towards *E*1*cB* and a weak base in a polar aprotic solvent promotes an *E*2 mechanism.

#### *5.1.2.6.3 The leaving group*

A good leaving group favors *E*1 and *E*2 mechanisms, whereas a poor leaving group, especially if it is positively charged, favors *E*1*cB*, bacause of the increasing acidity of the β-H atom. Very good leaving groups shift the mechanism towards the *E*1 end of the spectrum.

#### *5.1.2.6.4 The medium*

A more polar medium favors the more ionic mechanisms, *i.e.* *E*1 or *E*1*cB*. Addition of crown ethers can move a reaction from *E*1 to the *E*2 mechanism.

### 5.1.2.7 The Elimination/Substitution Ratio

#### *5.1.2.7.1 The effect of substituents*

In general, elimination is increased by nearly all electron-withdrawing groups (*e.g.* $CF_3$, $NO_2$, $SO_2Ar$, CN, C=O, $CO_2Et$, *etc.*) because they (i) increase the acidity of β-H atoms; (ii) stabilize carbanions; and (iii) stabilize double bonds by conjugative effects. Because of (i) and (ii), the effect of electron-withdrawing substituents in the β-position is more pronounced than in the α-position.

If the reaction has second-order kinetics, elimination is preferred if the substrate has α-branching (*e.g.* *t*-butyl) groups. One reason for this is the statistical factor: there are more protons which can be eliminated. Secondly, there is a steric factor: the nucleophilic attack on the α-C is hindered. Thirdly, branching at α-C accelerates elimination, due to greater hyperconjugative stabilization of the double bond being formed.

If the reaction obeys first-order kinetics, the same factors promote elimination. A branching at the β-position promotes *E*2, and for steric reasons *E*1 is also promoted. But if the leaving group is charged, the *E*2 proportion is decreased; electron-withdrawing groups promote elimination and move the mechanism toward *E*1*cB*.

In general, therefore, overcrowded substrates prefer elimination, because the product is less hindered than the substitution product.

#### *5.1.2.7.2 The attacking base*

Strong bases favor elimination rather than substitution and the *E*2 mechanism rather than *E*1, particularly if they are highly concentrated. Reaction with low concentrations of base or no base in ionizing solvents promotes $S_N1$ rather than *E*1. Strong nucleophiles or weak bases favor substitution, unless the solvent is polar aprotic, in which case an *E*2 reaction is preferred.

#### *5.1.2.7.3 The leaving group*

If first-order kinetics apply, the elimination/substitution ratio is independent of the leaving group as long as there is no formation of ion pairs. With second-order kinetics only iodine (of the halogens) affects the ratio; it favors elimination. If the leaving group is OTs, substitution is preferred. On the other hand elimination is promoted if the leaving group is positively charged. The following sequence is observed:[26] OTs < Br < $^+SMe_2$ < $^+NMe_3$.

#### *5.1.2.7.4 The medium*

*(i) Solvent*

The more polar the solvent, the more substitution product will be produced, *e.g.* alcoholic KOH favors elimination and aqueous KOH favors substitution. In most solvents the $S_N1$ reaction predominates over the *E*1 reaction. An *E*1 reaction is best carried out in a weakly nucleophilic polar solvent.

*(ii) Temperature*

Raising the temperature promotes elimination, since the activation energy is higher for elimination than for substitution. There are more bond changes in elimination reactions, so the entropic factor becomes important. This means that the factor $T\Delta S^*$ will be the determining factor at higher temperatures in the Gibbs–Helmholtz equation $\Delta G^* = \Delta H^* - T\Delta S^*$ and will more than compensate for an unfavorable enthalpy of activation.

## 5.1.3 ALKENES

### 5.1.3.1 Dehydrohalogenation of Alkyl Halides

The general reaction for the dehydrohalogenation of alkyl halides is shown in Scheme 18.

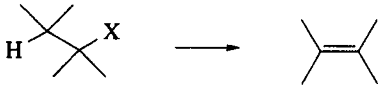

**Scheme 18**

This is a very useful reaction, which can be carried out with iodides, bromides, chlorides and fluorides.[27] The main problems are competing substitution reactions, orientation of the double bond (Zaitsev *versus* Hofmann) and the diastereoselectivity (*E versus Z*). By selecting the proper conditions it is possible in most cases to obtain the desired compound. The rate of elimination depends strongly on the leaving group (iodides usually eliminate much more quickly than bromides and chlorides), the structure of the substrate, the solvent and the base. The bases most frequently used are alkali metal hydroxides in alcohols or dipolar aprotic solvents, alkoxides in the corresponding alcohol or in DMSO, and alkali metal amides in $NH_3$ or inert solvents. Hydroxide ion has also been used for elimination in phase transfer catalysis.[28] Tertiary amines, *e.g.* pyridine, quinoline and dimethylaniline, are usually applied at higher temperatures; sterically hindered amines, *e.g.* ethyldicyclohexylamine (Hünig bases) or the bicyclic amidines 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[29] are used when substitution reactions are competing. The ratio of elimination to substitution product can also be increased by raising the reaction temperature.

The regiochemistry of the elimination, if the basic structure is given, can be influenced by the choice of the leaving group and the base. Fluorides yield the Hofmann product preferentially, while iodides afford the Zaitsev product. Strong bulky bases, *e.g.* $KOBu^t$ in $Bu^tOH$, increase the proportion of Hofmann product. The advantage of the bulky base is lost in DMSO.[30]

Table 6 shows the results of treating acyclic chloro- or bromo-alkanes with certain bases.

In eliminations from alkyl halides, an increase in the proportion of the 1-alkene (Hofmann product) is often accompanied by a decrease in the (*E*)/(*Z*) 2-alkene ratio as the base/solvent system is changed from EtOK/EtOH to $Bu^tOK/Bu^tOH$ (see Table 7).[30]

In the first three eliminations in Table 7 the associated base is the main reacting species, whereas in the last three eliminations it is the dissociated base.

However, with β-phenyl-substituted compounds the effects of base association on double bond orientation are opposite to those shown in Table 7. Here the (*E*)/(*Z*) ratios are larger with the associated than with the dissociated base.[33]

Alkali metal organometallics, when used as bases in elimination reactions, often afford many by-products; however, with triphenylmethylpotassium good results were obtained.[34] On the other hand, some weak bases, such as alkali halides, sometimes in the presence of the corresponding carbonates, in DMF or HMPA have been used successfully for eliminations.[31,35] In some cases, dehydrohalogenation has

**Table 6** Results of Base Treatment of an Acyclic Chloro- or Bromo-alkane[31]

| *Base* | | *Elimination* | | | | |
|---|---|---|---|---|---|---|
| | *Primary* | *Secondary* | *Tertiary* | *BZ*[a] | *Orientation*[e] | *(E)/(Z) ratio*[f] |
| NaOMe/MeOH | –[d] | (+)[c] | +[b] | – | 70% Z[g] | 4.0 |
| KOBu$^t$/Bu$^t$OH | – | + | + | + | 85% H[h] | 1.5 |
| KOBu$^t$/DMSO | + | + | + | + | 55% H | 4.5 |
| Quinoline | (+) | (+) | + | + | 85% Z | 2.5 |
| Triethylamine | – | (+) | + | – | Z | |
| Hünig bases | + | + | + | + | 75% Z | |
| Amidines | – | + | + | (+) | 80% Z | |
| Alkali metal amides | (+) | + | + | – | Z | |
| Alkali metal halides | – | (+) | + | – | Z | |
| Solvolysis | – | – | (+) | (+) | Z | |
| Pyrolysis | + | + | + | + | 60% Z | 2.5 |

[a] BZ, benzyl. [b] +, clean elimination without concomitant substitution. [c] (+), some substitution competing. [d] –, unsatisfactory for preparative purposes. [e] Standard deviation +/– 5%. [f] Standard deviation +/– 0.5. [g] Z, Zaitsev. [h] H, Hofmann.

**Table 7** Orientation and Diastereoselectivity in Some Eliminations from 2-Iodobutane at 50 °C[32]

| *Base/solvent* | *1-Butene (%)* | *(E)/(Z) ratio for 2-butene* |
|---|---|---|
| EtOK/EtOH | 11.7 | 3.25 |
| Bu$^t$OK/Bu$^t$OH | 34 | 2.17 |
| Et$_3$COK/Et$_3$COH | 49.3 | 1.50 |
| Bu$^t$OK/DMSO | 20.7 | 2.99 |
| Et$_3$COK/DMSO | 20.9 | 3.13 |
| EtONa/DMSO | 17.1 | 3.32 |

been accomplished by heating in DMF[36] or HMPA[37] without the addition of any other reagent; however, if the resulting HX is not removed from the reaction mixture immediately, rearrangement products *via* carbenium ion intermediates will be formed.

### 5.1.3.2 Dehalogenation of 1,2-Dihalides

The general reaction for the dehalogenation of 1,2-dihalides is shown in Scheme 19.

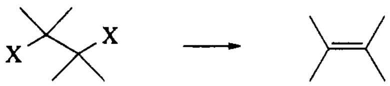

**Scheme 19**

Dehalogenation can be effected with many metals, *e.g.* zinc,[38,39] magnesium,[39] lithium[39] and sodium in ammonia.[40] Other reagents are sodium naphthalenide,[41] phenyllithium, lithium aluminum hydride,[42] chromium(II) chloride,[43] sodium iodide,[44] sodium sulfide[45] and sodium selenide.[46] Usually good yields are obtained in these reactions; however, since the best route to the starting material is halogen addition to an alkene, the preparative value is limited. An advantage over dehydrohalogenation is the fixed position of the formed double bond. The mechanisms of the dehalogenations are complex and depend on the particular conditions.[47] The reactions are sometimes stereospecifically *anti*, but in other cases no stereospecificity has been observed.[48]

### 5.1.3.3 Dehydration of Alcohols

The general reaction for the dehydration of alcohols is shown in Scheme 20.

Since OH is a poor leaving group, catalysts which convert the OH group to a better leaving group, or high temperatures have to be used for this type of elimination. However, with strong acids, *e.g.* $H_2SO_4$, $H_3PO_4$, TsOH, rearrangements and ether formation can be observed, because then a carbenium ion intermediate may be formed (*E*1 conditions).

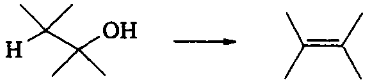

Scheme 20

For volatile alcohols, up to 1-dodecanol, vapor phase eliminations over $Al_2O_3$[49] or $ThO_2$[50] are excellent methods, since no significant side reactions occur. Another way of avoiding competing side reactions is the formation of appropriate esters and their subsequent pyrolysis or treatment with base. For the pyrolysis acetates and xanthogenates[51] and for base-catalyzed eliminations tosylates,[52] mesylates or triflates are usually used. The use of bis(tetra-*n*-butylammonium) oxalate is recommended to induce elimination rather than substitution in tosylates.[53] Heating of arenesulfonates in polar aprotic solvents, such as DMSO[54] or HMPA,[55] gives the corresponding alkenes in high yields. For some problematic eliminations, $Ph_2S[OC(CF_3)_2Ph]_2$[56] or $MeO_2CNSO_2NEt_3$[57] have been used with excellent results for secondary and tertiary alcohols (Scheme 21).

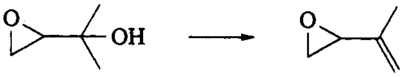

Scheme 21

Another interesting alkene synthesis starts from a cyclopropyl-substituted alcohol, which, on reaction with magnesium halides,[58] is converted to a haloalkene; $Me_3SiX$ has also been used in this type of reaction (Scheme 22).[59]

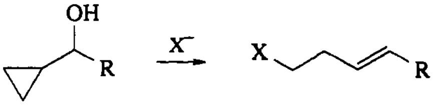

Scheme 22

### 5.1.3.4 Alkenes from Ethers

With some very strong bases, such as alkyl-sodium or -lithium compounds or sodium amide, ethers can be converted to alkenes (Scheme 23).[60] The reaction is supported by electron-withdrawing groups in the β-position; thus, $EtOCH_2CH(CO_2R)_2$ can be converted to $H_2C{=}C(CO_2R)_2$ (retro-Michael-type reaction).

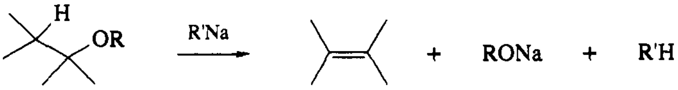

Scheme 23

The conversion of epoxides to allylic alcohols (Scheme 24) can also be considered here. A variety of reagents, including lithium diethylamide,[61] *t*-butyldimethylsilyl iodide,[62] a dialkylboryl triflate[63] and an ethylaluminum dialkylamide[64] have been used successfully.

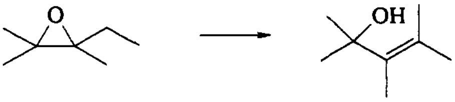

Scheme 24

### 5.1.3.5 Alkenes from Quaternary Ammonium Salts

The general reaction for obtaining alkenes from quaternary ammonium salts is shown in Scheme 25.

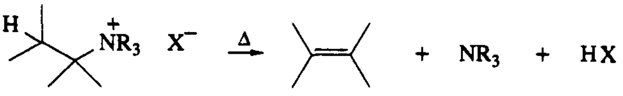

**Scheme 25**

In this reaction two different procedures have been used. The first is the classical Hofmann degradation, which prepares the alkene by thermal decomposition of the quaternary ammonium hydroxide.[65] Hofmann orientation is generally observed in acyclic and Zaitsev orientation in cyclohexyl substrates. The second is the treatment of quaternary ammonium halides with very strong bases, *e.g.* PhLi, $KNH_2$ in liquid $NH_3$.[65,66] The formation of the alkene proceeds *via* an *E*1 mechanism, which means a *syn* elimination in contrast to the *anti* elimination which is observed in most of the classical Hofmann degradations. In some cases this type of elimination can also be accomplished by heating the salt with KOH in polyethylene glycol monomethyl ether.[67]

Sulfonium compounds yield alkenes in reactions which are analogous to the ammonium compounds.

### 5.1.3.6 Alkenes from *p*-Toluenesulfonylhydrazones

Scheme 26 illustrates the general reaction for the generation of alkenes from *p*-toluenesulfonylhydrazones (tosylhydrazones).

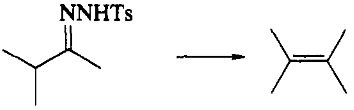

**Scheme 26**

The reaction of a tosylhydrazone with at least 2 equiv. of an alkyllithium reagent in ether or hexane generates the dianion (Shapiro reaction); this gives, after loss of $Ts^-$ and $N_2$, the vinyllithium compound, which can be trapped by a variety of electrophiles, *e.g.* $H^+$, $CO_2$, DMF (Scheme 27).[68] The less-substituted alkene is formed predominantly under these conditions.

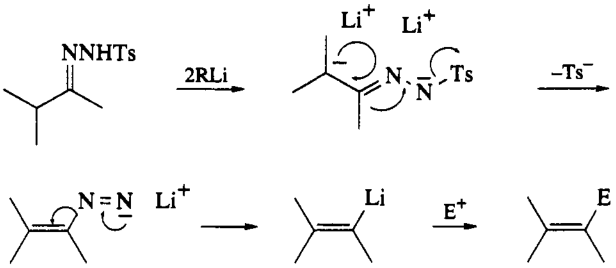

**Scheme 27**

The reaction of tosylhydrazones with sodium in ethylene glycol to give alkenes had been observed before (Bamford–Stevens reaction);[69] other bases, *e.g.* NaOMe,[70] alkali metal hydrides[71] and $NaNH_2$[72] were also used. However, in these cases side reactions occur and, in contrast to the Shapiro reaction, the more highly substituted alkene is predominantly formed. Two mechanisms are discussed for these reactions: a mechanism *via* a carbenium ion, which usually takes place in protic solvents, and a carbene mechanism in aprotic solvents (Scheme 28). In both cases diazo compounds are intermediates, which can sometimes be isolated.[73]

In the absence of protons, the carbene is formed after loss of nitrogen and subsequent or concerted migration of hydrogen affords the alkene; insertion reactions or migration of other groups can lead to side products. In the presence of protic solvents, a carbenium ion is formed *via* a diazonium ion; this carbenium ion may then lose a proton to give the alkene or may give other reactions typical of carbenium ions.

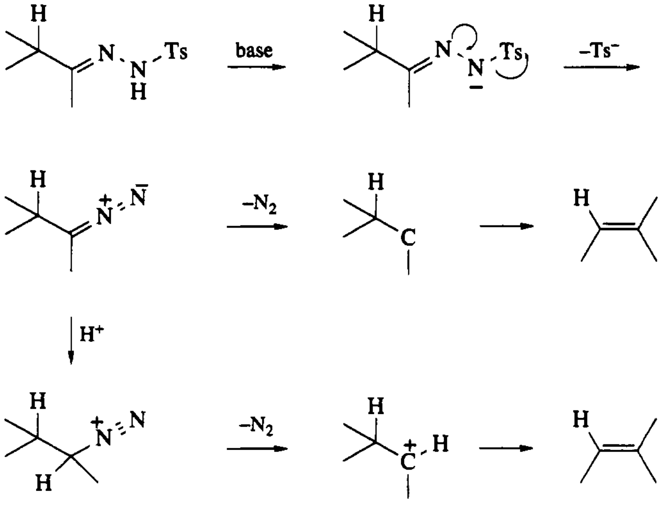

Scheme 28

In the oxidative decomposition of 1-*N*-aminotriazolines, two molecules of nitrogen are lost from the nitrene intermediate. The oxidation of an aminotriazoline with lead tetraacetate was used for the synthesis of a strongly pyramidalized alkene (Scheme 29).[74]

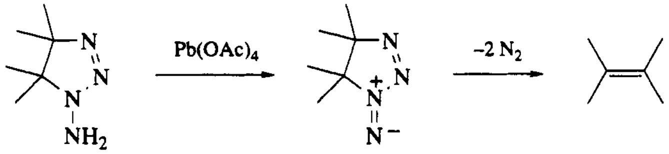

Scheme 29

## 5.1.4 ALKYNES

The methods for the synthesis of alkynes have been extensively reviewed in the past 20 years;[75] two books, which deal particularly with the preparative aspects of alkyne chemistry, have been published.[76]

Except for the syntheses of acetylene and propyne, which are prepared in technical processes from carbides, from methane by oxidation, or by electric arc processes, all carbon–carbon triple bonds must be generated by an elimination reaction. Again, as in the synthesis of alkenes, the most important is the dehydrohalogenation.

### 5.1.4.1 Dehydrohalogenation of 1,2- or 1,1-Dihaloalkanes

Scheme 30 illustrates the general reaction for the dehydrohalogenation of 1,2- and 1,1-dihaloalkanes.

In most cases, bromo or chloro derivatives are used as starting materials. The 1,2-dihaloalkanes are usually prepared from the alkenes by halogen addition, the 1,1-dihaloalkanes from the corresponding carbonyl compounds with $PCl_5$ or other acid chlorides (Scheme 31). Some 1,1-dichloroalkanes can be prepared from vinyl chloride by addition of a secondary or tertiary alkyl chloride (Scheme 32). The 1-haloalkenes can be prepared from either the 1,2- or the 1,1-dihaloalkanes by elimination of 1 mol of hydrogen halide or by a Wittig reaction (Scheme 33).

Bromo compounds generally eliminate faster than the corresponding chloro compounds. Electron-withdrawing substituents in the substrate facilitate the elimination.

To accomplish the elimination, the substrate must be treated with a base. Whereas elimination of 1 mol HX from chloro- or bromo-alkanes can be effected with a weaker base, *e.g.* tertiary amines or $K_2CO_3$, the elimination of the second mole of HX requires stronger bases, *e.g.* $NaNH_2$, $LiNPr^i_2$ or RLi. Thus,

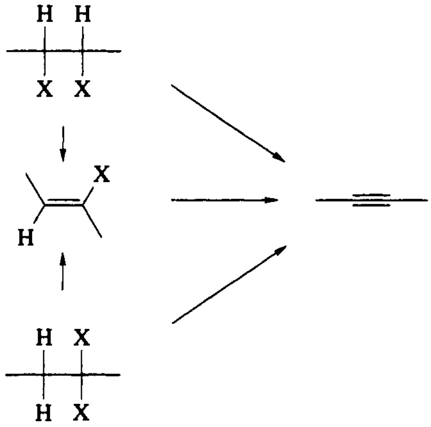

Scheme 30

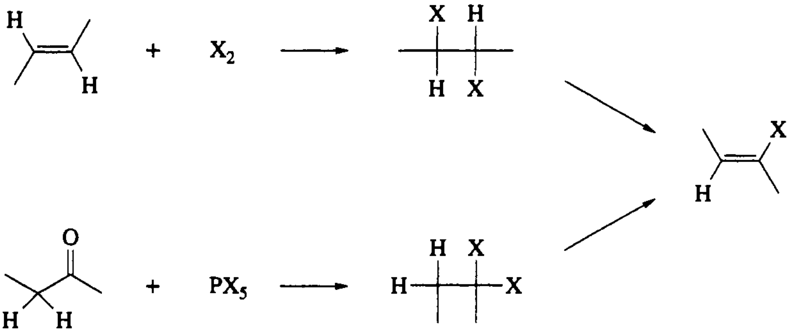

Scheme 31

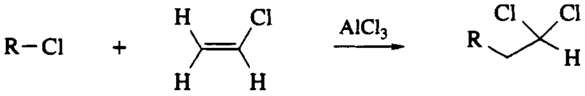

Scheme 32

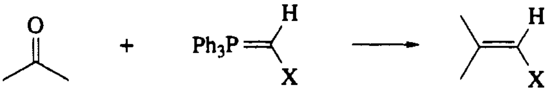

Scheme 33

treatment of 1,2-dibromocyclooctane with KOBu$^t$ yields 1-bromocyclooctene, which can be converted to cyclooctyne with LDA (Scheme 34).[77]

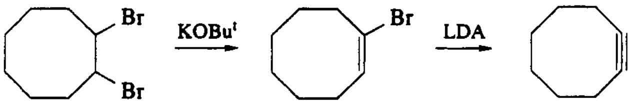

Scheme 34

The formation of the allene, sometimes a serious complication in alkyne synthesis, is not a problem in this case, because 1,2-cyclooctadiene, once formed, dimerizes readily and can therefore be easily removed from cyclooctyne by distillation.

The oxygen bases, alkali metal carbonates, alkali metal hydroxides and alkoxides are used to a large extent. The solvents are alcohols, ether, THF, dioxane, glycol or glycol ethers (for higher temperatures), DMSO, HMPA or crown ethers. The latter three increase basicity by generating 'naked' anions, because the cations are strongly solvated.

Alkali metal carbonates, being weak bases, can only eliminate to the alkyne if a strongly electron-withdrawing group facilitates elimination. Thus, the bromovinyl ketones (both *cis* and *trans*) can be converted to the alkynic ketone with $K_2CO_3$ (Scheme 35); the elimination from the educt having H and Br in a *trans* configuration is about 10 times faster.[78]

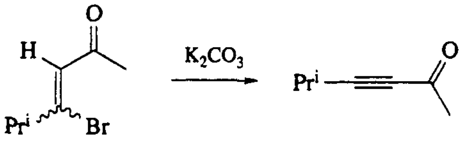

Scheme 35

The use of KOH in alcohols is a convenient method for preparing acetylenes (Schemes 36[79] and 37[80]). However, when the corresponding ester is treated with sodium ethoxide in ethanol, the major product is the vinyl ether, which is formed by a nucleophilic addition of ethoxide to the activated triple bond (Scheme 38).[81]

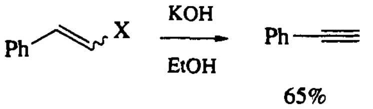

Scheme 36

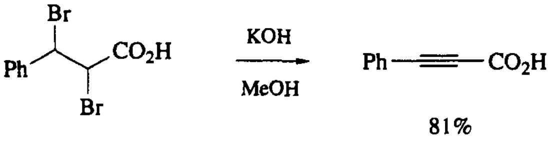

Scheme 37

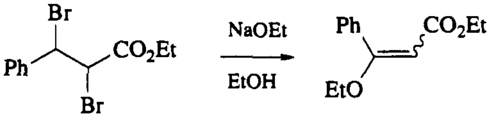

Scheme 38

As mentioned before, allenes can be formed by prototropic rearrangement of alkynes or, if an appropriate hydrogen is present in the allylic position, by direct elimination. The bromovinyl ether yields, in a *trans* elimination, the alkyne ether (Scheme 39), but the other isomer, where *trans* elimination is not possible, gives both the alkynyl ether and the allenyl ether (Scheme 40).[82] This corresponds to the problem of Hofmann and Zaitsev orientation in alkene synthesis.

Use of KOH without a solvent prevents the alcohol addition to the alkyne formed; usually the alkynes are directly distilled from the mixture of their halogenated precursors and KOH (Schemes 41[83] and 42[84]).

The alkali metal amides are stronger bases than the alkoxides. Therefore, in many reactions milder conditions can be applied; sodium amide in liquid $NH_3$ is most widely used. In contrast to the oxygen

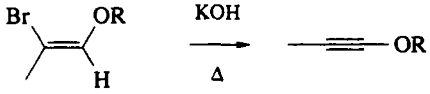

Scheme 39

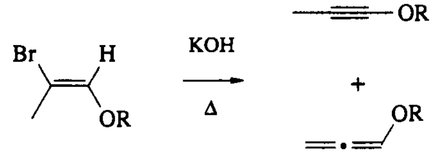

**Scheme 40**

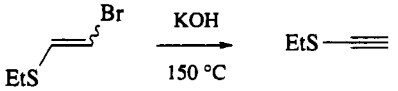

**Scheme 41**

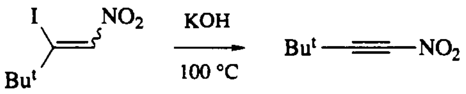

**Scheme 42**

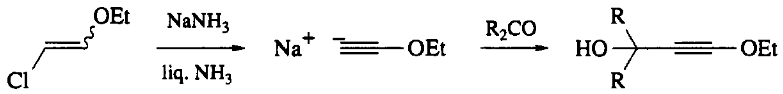

**Scheme 43**

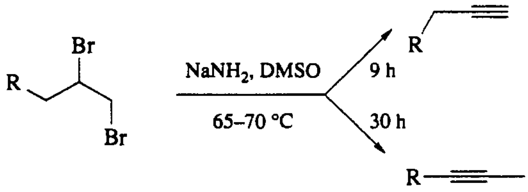

R = n-$C_8H_{17}$, n-$C_{11}H_{23}$ to n-$C_{14}H_{29}$

**Scheme 44**

bases, both *cis*- and *trans*-haloalkenes are converted to the alkyne; in the preparation of terminal alkynes no isomeric allenes or alkynes are formed, since the sodium salt of the terminal alkyne precipitates. This sodium alkynide can be used immediately for further reactions, *e.g.* with ketones (Scheme 43).[85] In DMSO the sodium alkynides are soluble and the terminal alkynes can, under equilibrium conditions, isomerize to the more stable internal alkynes (Scheme 44).[86] Lithium dialkylamides have been used successfully in the preparation of aryl- and alkyl-alkynes[77,87] and in the synthesis of ynamines, where elimination and concurrent substitution took place.[88]

Butyllithium is an excellent reagent for the dehydrohalogenation of 1-chloroalkenes or 1,1-dichloroalkanes to terminal alkynes;[89] the organolithium compound must be added dropwise to avoid alkylation of the intermediate carbenoids, leading to alkenes. Three equivalents of alkyllithium are necessary to convert the 1,1-dichloroalkane to the alkyne (two equivalents from 1-chloroalkenes; Scheme 45).

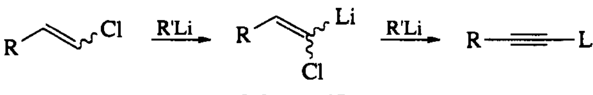

**Scheme 45**

Sodium hydride can be used as a dehydrohalogenating agent in dipolar aprotic solvents, such as DMSO or HMPA. Halostilbenes have been converted to the corresponding diarylalkynes in this way.[90]

### 5.1.4.2 Elimination of 'Acids' Other Than Hydrogen Halides

If the anions of these acids are good leaving groups, elimination from their enol esters can be effected by the bases used for elimination of hydrogen halides. Enol triflates, on treatment with pyridine (Scheme 46),[91] 2,6-di-*t*-butyl phenoxide (Scheme 47)[92] or potassium *t*-butoxide (Scheme 48)[93] yield the corresponding alkynes.

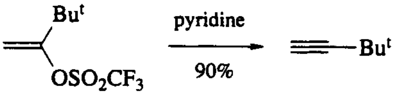

**Scheme 46**

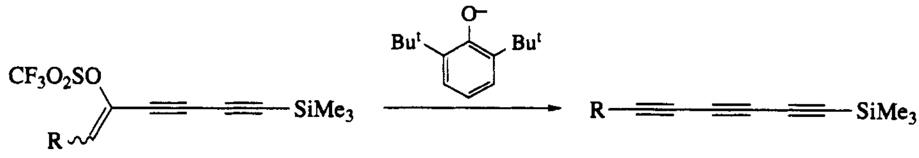

**Scheme 47**

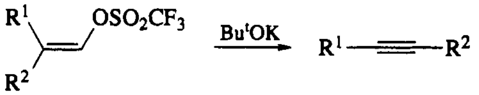

$R^1, R^2$ = H, Pr$^n$; Ph, Ph; Ph, Me

**Scheme 48**

Enol phosphates treated with $NaNH_2$ in liquid ammonia[94] or with lithium dialkylamides[95] give the alkynes in good yields (Scheme 49).[96] Vinyl selenoxides can also be used as a starting material for the preparation of alkynes. Thermolysis at 85–95 °C takes place in the presence of DABCO if a *syn* elimination to the alkyne is possible (Scheme 50). If a *syn* elimination to an alkyne is blocked by a substituent, allene formation can occur.[97]

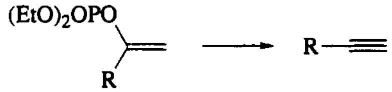

**Scheme 49**

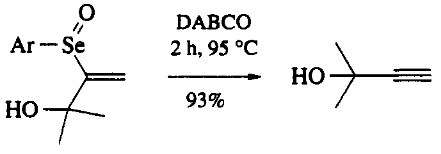

**Scheme 50**

Ynamines have been prepared from ketene *S*,*N*-acetals on treatment with lithium dialkylamides or $NaNH_2$ (Scheme 51).[98]

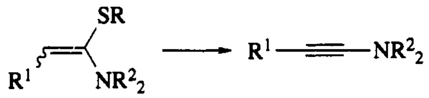

**Scheme 51**

A one-step dehydration of ketones to alkynes is possible in some cases. Aryl ketones can be converted to arylalkynes by treatment with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of triethylamine at room temperature (Scheme 52).[99]

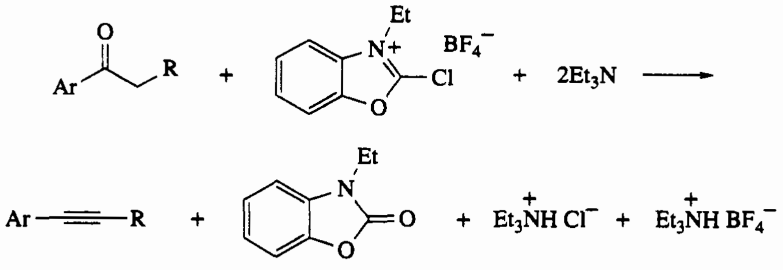

**Scheme 52**

Alkynic ketones can be prepared in good yields from β-diketones using α,α-difluoroalkylamines and KF (Scheme 53).[100]

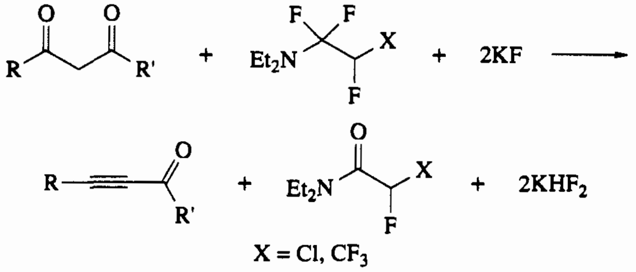

**Scheme 53**

Some 17β-alkynic steroids were formed from hindered 20-oxo compounds *via* thermolysis of Grignard-derived enolates (Scheme 54).[101]

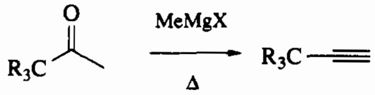

**Scheme 54**

### 5.1.4.3 Dehalogenation of 1,1- or 1,2-Dihaloalkenes and Other Eliminations of Two Vicinal Leaving Groups

The general reaction for the dehalogenation of 1,1- and 1,2-dihaloalkenes is shown in Scheme 55.

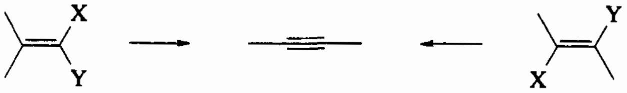

**Scheme 55**

As in the preparation of alkenes, dehalogenation leading to alkynes has been effected mainly by zinc (Scheme 56),[102] magnesium (Scheme 57)[103] and organolithium (Scheme 58)[104] compounds. Since in most cases the best route to 1,2-dihaloalkenes is halogen addition to alkynes, this method is of limited preparative value. Advantages over dehydrohalogenation are the fixed position of the resulting triple bond and the exclusion of allene formation.

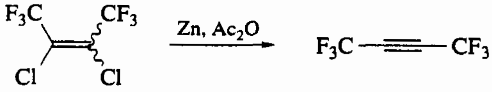

**Scheme 56**

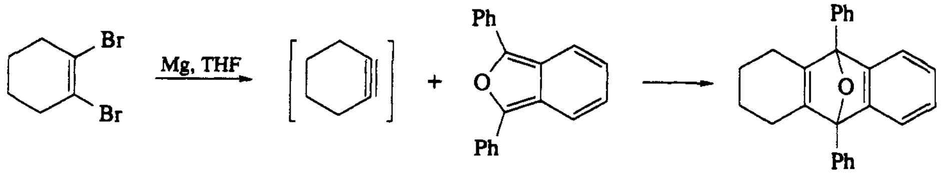

**Scheme 57**

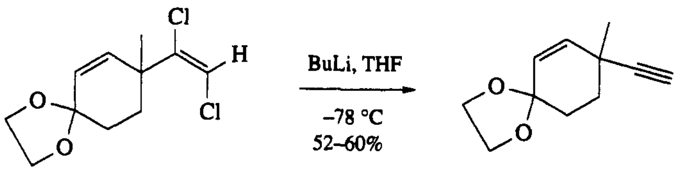

**Scheme 58**

Organolithium compounds can also induce the rearrangement of 1,1-diaryl vinyl dichlorides and dibromides (Fritsch–Buttenberg–Wiechell rearrangement) to diarylalkynes;[105] *p,p'*-bridged cyclic diarylalkynes[106] can be prepared *via* this route (Scheme 59).

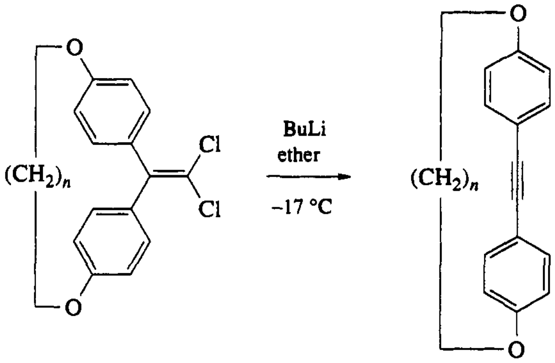

$n$ = 11, 23%; $n$ = 12, 47%; $n$ = 13, 75%;
$n$ = 14, 90%; $n$ = 18, 75%

**Scheme 59**

Elimination of two unlike leaving groups with a metal is realized in the synthesis of alkynes from 1-sulfonylenol-2-phosphates with sodium in liquid ammonia or sodium amalgam in THF (Scheme 60).[107]

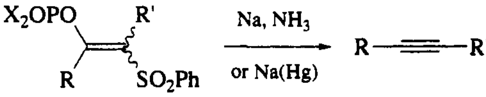

**Scheme 60**

### 5.1.4.4 Oxidative Decomposition of 1,2-Dihydrazones and 1-Amino-1,2,3-triazoles

1,2-Dihydrazones can be oxidized to alkynes with $O_2$ (CuCl as a catalyst),[108] HgO,[109–111] $F_3CCO_2Ag$[112,113] and $Pb(OAc)_4$ (Scheme 61).[114] 1-Amino-1,2,3-triazoles, which are sometimes observed as by-products in the HgO oxidation of 1,2-dihydrazones, can be oxidized with $Pb(OAc)_4$ to give alkynes. Cyclooctyne[115] has been prepared and cycloheptyne and cyclohexyne[116] have been generated by this method (Scheme 62). The 1-tosylamino-1,2,3-triazoles can also be used as educts for alkyne synthesis; the anions are decomposed to yield the corresponding alkyne, $N_2$ and toluenesulfinate (Scheme 63).[117]

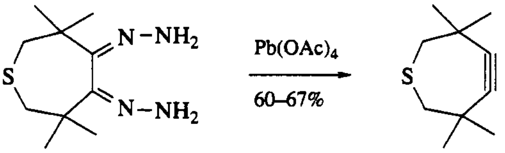

Scheme 61

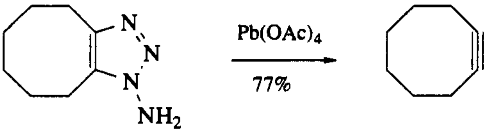

Scheme 62

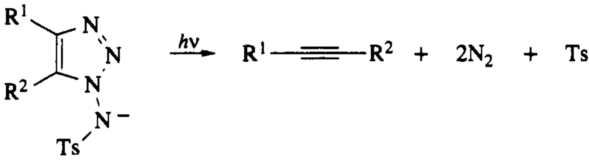

Scheme 63

### 5.1.4.5 Elimination from 1,2,3-Selenadiazoles

Many 1,2,3-selenadiazoles, which are prepared from semicarbazones and $SeO_2$, give alkynes on pyrolysis (Scheme 64). $R^1$ and $R^2$ can be H, alkyl and aryl, and $R^1$ can also be CN and $CO_2Et$.[118]

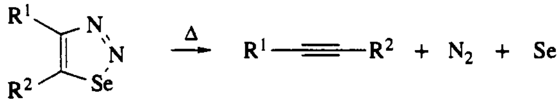

Scheme 64

## 5.1.5 ALLENES

In general, allenes are prepared by the same types of reactions which lead to alkenes: elimination of hydrogen halides, halogens and water from adjacent carbon atoms. However, some methods are characteristic of allene synthesis, *e.g.* the dehalogenation of *gem*-dihalocyclopropanes, rearrangement of alkynes and the 1,4-addition to vinylalkynes.

### 5.1.5.1 Dehydrohalogenation of Vinylic or Allylic Halides

The general reaction for the dehydrohalogenation of vinylic and allylic halides is shown in Scheme 65.

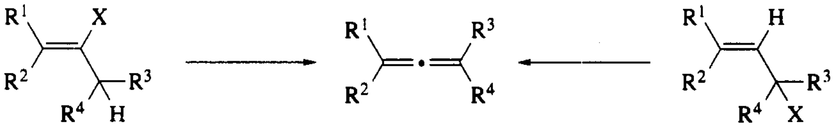

Scheme 65

The base-induced dehydrohalogenation of vinyl halides and allyl halides often gives low yields of allenes because of the competing reaction to alkynes; alkynes can either be formed by direct elimination from vinyl halides or by isomerization of the allene first formed to the isomeric alkyne. Since it has been established that *anti* elimination of hydrogen halide from vinyl halides to yield alkynes is much faster than *syn* elimination, the proper choice of the starting material is often important for a successful allene synthesis. When (*E*)-4-bromo-4-octene was treated with NaOMe, the sole product was 3,4-octadiene, whereas the corresponding *Z*-educt yielded 4-octyne (Scheme 66).[119]

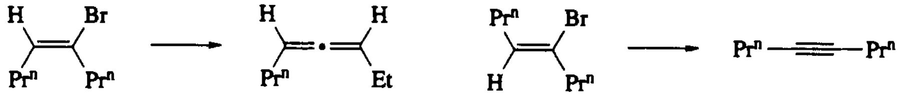

Scheme 66

### 5.1.5.2 Dehalogenation of 2,3-Dihalopropenes

The general reaction for dehalogenation of 2,3-dihalopropenes is shown in Scheme 67.

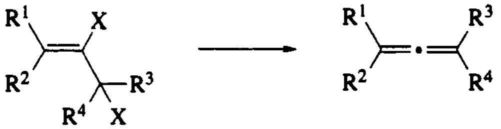

Scheme 67

The dehalogenation of 2,3-dihalopropenes with zinc dust gives allenes in high yields. Ethanol has often been used as a solvent, but sometimes alkenic impurities were observed in the allene. This can be avoided by the use of butyl or isopentyl acetate as a solvent.[120]

### 5.1.5.3 Dehydration of Allylic Alcohols

The general reaction for the dehydration of allylic alcohols is shown in Scheme 68.

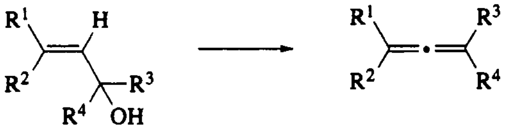

Scheme 68

Dehydration of allylic alcohols with strong acid leads to allenes if an isomerization to an alkyne is not possible. This method has been used for the synthesis of tetraarylallenes[121] and tetra-*t*-butylallene.[122] This method was also used for the first synthesis of an optically active allene by an enantioselective dehydration using (+)-camphorsulfonic acid.[123]

### 5.1.5.4 Dehalogenation of *gem*-Dibromocyclopropanes

The general reaction for the dehalogenation of *gem*-dibromocyclopropanes is shown in Scheme 69.

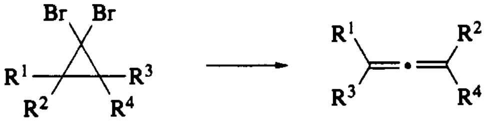

Scheme 69

The dehalogenation of *gem*-dibromocyclopropanes is a general route to a great variety of allenes. For the dehalogenation magnesium and sodium[124] were first used; later methyllithium[125] was successfully applied. 1,2-Cyclononadiene was prepared in this way;[126] by using optically active *trans*-cyclooctene as an educt, optically active 1,2-cyclononadiene was obtained (Scheme 70).

Attempts to isolate unsubstituted cyclic allenes with less than nine carbons were not successful. The highly strained 1,2-cyclooctadiene was generated as a short-lived intermediate; it dimerized to give a 1,2-dimethylenecyclobutane.[127] In addition several by-products were obtained (Scheme 71).

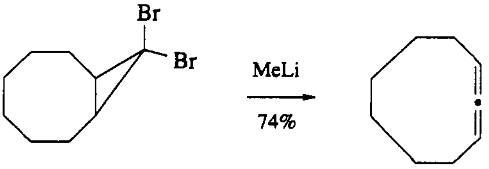

Scheme 70

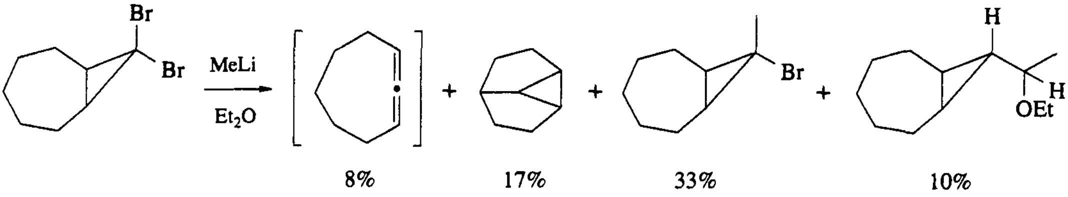

Scheme 71

Another limitation of this procedure occurs in the case of tetraalkyl-substituted dibromocyclopropanes; they do not yield allenes, but rather bicyclobutanes (Scheme 72).[128,129] However, tetrasubstituted dibromocyclopropanes with two aryl substituents do give allenes, at least as a by-product.[129]

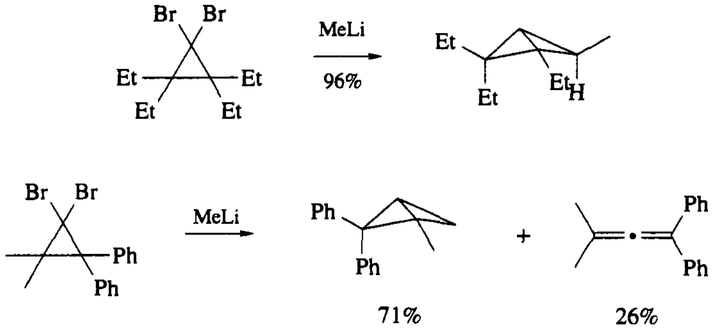

Scheme 72

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# 5.2

# Reductive Elimination, Vicinal Deoxygenation and Vicinal Desilylation

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## 5.2.1 INTRODUCTION

In this chapter we deal with the regio- and stereo-controlled synthesis of alkenes by reductive elimination of 1,2-disubstituted alkanes. Where appropriate the related 1,4-elimination reactions leading to conjugated dienes will also be considered. The principal criterion for inclusion here is synthetic utility, and reactions such as the Julia alkenation are given prominence because they incorporate a reductive elimination as a key step in a sequence which is connective. Consequently such reductive eliminations should not be considered in isolation, but as an integral part of a sequence which achieves regio- and stereo-controlled synthesis of an alkene but, more importantly, also achieves the union of two fragments or the creation of a ring.

In the narrower context of simple functional group manipulation, reductive eliminations have proved valuable in the vicinal deoxygenation of cheap and readily available natural products such as carbohydrates to give synthetically useful fragments. However, comparatively few of the vast array of reductive eliminations recently reported were deemed worthy of inclusion because the reagents required were esoteric, expensive or obnoxious, or because the 1,2-disubstituted alkanes were themselves prepared from alkenes. Unless there are very pressing reasons, one cannot advocate the synthesis of alkenes from alkenes: to travel in circles is the domain of astronomers not chemists!

At the end of the chapter we briefly consider some reactions such as the fluoride-induced elimination of β-silyl sulfones, which are not reductive eliminations but which have been included because of their relation to the Julia alkenation.

## 5.2.2 REDUCTIVE ELIMINATION OF VICINAL HALOGEN DERIVATIVES

### 5.2.2.1 1,2- and 1,4-Dihalides

The reductive elimination of vicinal dihalides has been extensively investigated and early work up to 1971 has been reviewed by Schlosser.[1] The reaction is generally *anti* stereoselective with *vic*-dibromides and can be achieved by a wide range of reagents under mild conditions.[2-4] Since the *vic*-dihalide substrates are usually prepared stereoselectively by *anti* addition of halogens to alkenes, the reaction is of only limited synthetic value. Equation (1) illustrates a practical use of reductive elimination in the isolation of a natural product. Saponification of raw linseed oil followed by treatment with bromine gives a crystalline hexabromostearic acid (**1**), which undergoes efficient stereoselective reductive elimination to give the highly air sensitive linolenic acid (**2**) in 25% overall yield.[5]

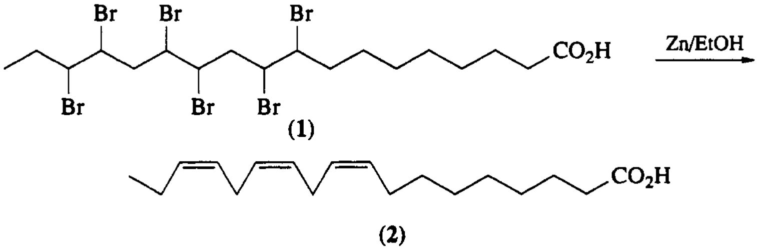

(1)

The reductive elimination of *vic*-bromochlorides and *vic*-dichlorides with metals such as zinc is much less stereoselective than the corresponding *vic*-dibromides. However, with NaI in DMF the reductions are highly stereoselective and proceed with a net *syn* elimination. These observations have been used to effect an alkene inversion as shown in Scheme 1 for the preparation of the sex pheromone (**3**) of the oriental fruit moth.[6,7] Treatment of *vic*-dichlorides with sodium phenylselenolate also results in a *syn* elimination.[8]

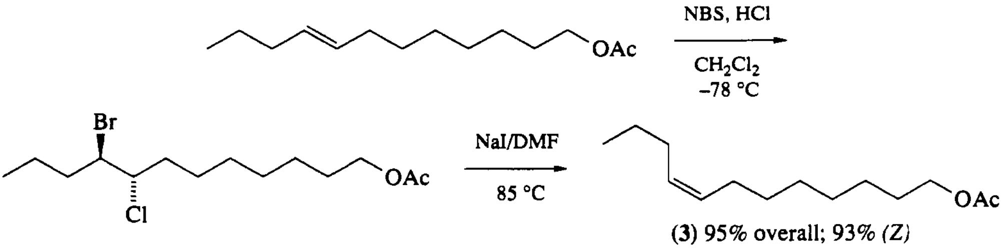

**Scheme 1**

A combination of a photochemical [2 + 2] cycloaddition of dichloroethylene to enone (**4**), followed by a reductive elimination, was used to prepare the tricyclic cyclobutene (**5**), which served as a precursor to the highly strained 8-carboxy[6]paracyclophane (**6**; Scheme 2).[9] A similar strategy has been used to prepare other strained propellanes.[10]

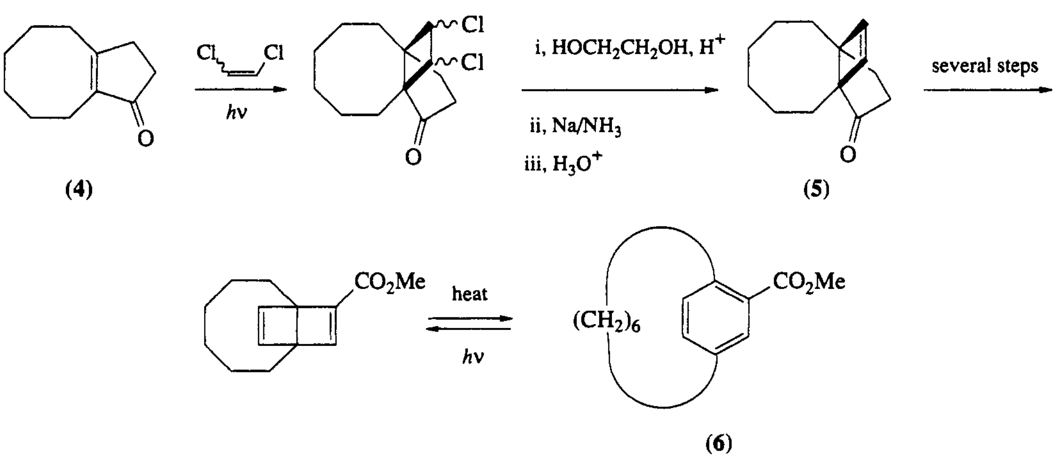

Scheme 2

$o$-Quinodimethanes are highly reactive dienes, which have been trapped both intramolecularly and intermolecularly with dienophiles and used as valuable intermediates in the synthesis of natural products.[11] These intermediates were first generated unwittingly by Finkelstein[12] in 1910, who treated the tetrabromide (**7**) with NaI to give the dibromobenzocyclobutene (**8**; equation 2) but it was not until 1957 that Cava and Napier[13] first proposed the generation of the $o$-quinodimethane system by a reductive 1,4-elimination. A recent synthesis of 4-demethoxydaunorubicin (equation 3) illustrates the generation and trapping of an $o$-quinodimethane using the Finkelstein method.[14] Recently a wide range of reducing agents have been employed to generate $o$-quinodimethanes, including Zn in association with ultrasonic irradiation,[15] $CrCl_2$[16] and a variety of metals.[17] Similar conditions can be used[18] to effect 1,4-elimination of diiodides for the generation of 1,3-dienes (equation 4).

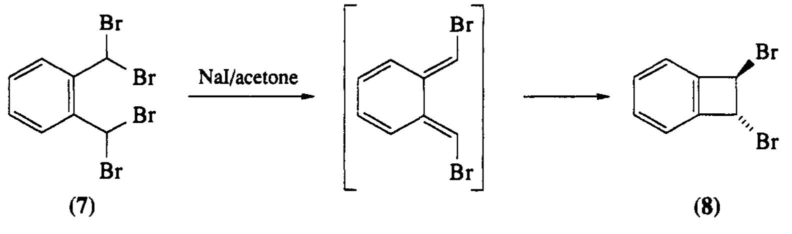

(2)

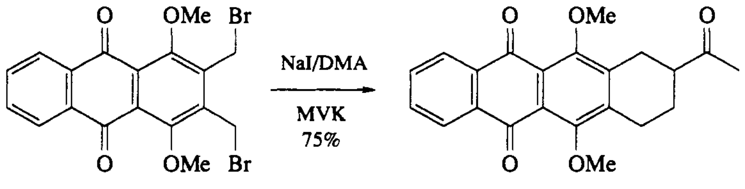

(3)

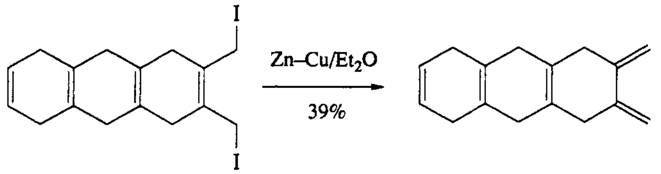

(4)

### 5.2.2.2 Halohydrins

Many of the same reagents that reduce *vic*-dihalides also reduce halohydrins with similar regiochemical and stereochemical advantages. However, halohydrins are more useful alkene precursors because they can be prepared by a greater variety of methods. The Fischer–Zach synthesis of 3,4,6-tri-*O*-acetyl-D-glucal (**11**; Scheme 3) reported in 1913 is one of the first synthetically useful applications of reductive elimination reactions to the manipulation of natural products and the method is still widely used today.[19]

In the key step, the glycosyl bromide (**10**) was treated with Zn in acetic acid in conditions typical of those of dissolving metal reduction, and this has led to the speculation that the elimination occurs by addition of two electrons from the metal to the C-1 carbonium ion formed by ionization of the halide, followed by elimination of the adjacent acetoxy group. Alternatively, organozinc intermediates could be involved. Protic solvents are necessary for the reaction and acetic acid can be replaced by ethanol or 1-propanol but if still milder conditions are required, the elimination can be effected with trimethyl phosphite.[20]

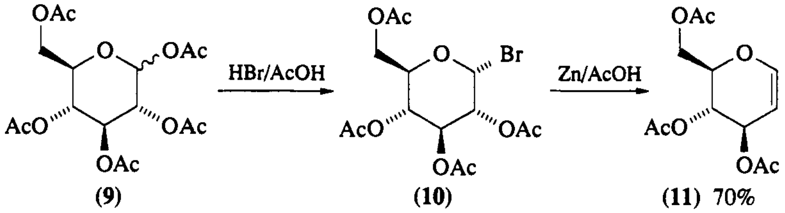

**Scheme 3**

Furanoid glycals are not stable to the acidic conditions used to prepare the pyranoid congeners. Scheme 4 illustrates a very mild method for preparing furanosyl chlorides, which undergo efficient reductive elimination on treatment with lithium in liquid ammonia.[21] Alternatively, a Zn–Ag couple adsorbed on graphite will reduce furanosyl bromides[22] and the corresponding chlorides react with the radical anion prepared from naphthalene and sodium.[23]

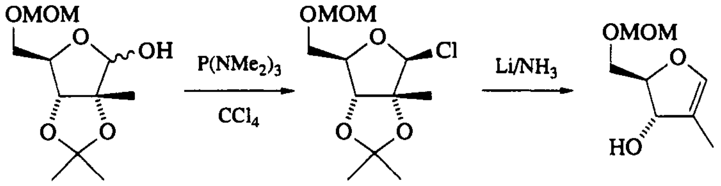

**Scheme 4**

Reductive elimination reactions have provided a rich mine of methodology for the modification of carbohydrate precursors into useful chiral building blocks. The two examples included here come from a synthesis of the antibiotic pseudomonic acid (Scheme 5)[24] and the Ferrier synthesis of 6-deoxyinonose triesters from pyranose acetates (Scheme 6).[25] An efficient and highly regioselective synthesis of the 6-bromoglycoside (**13**) by oxidative cleavage of the 4,6-benzylidene acetal (**12**) with *N*-bromosuccinimide, followed by reductive cleavage of the ring, gave an aldehyde, which was further reduced to the fragment (**14**) having three contiguous chiral centres. In the 6-deoxyinonose synthesis the requisite halogen atom was introduced stereo- and regio-selectively by a photochemically induced bromination of β-D-glucose pentaacetate (**15**). Reductive elimination then afforded the exocyclic 6-deoxy-5-enose sugar (**16**), which rearranged on treatment with $Hg(OAc)_2$ to the carbocyclic 6-deoxyinosose (**17**).

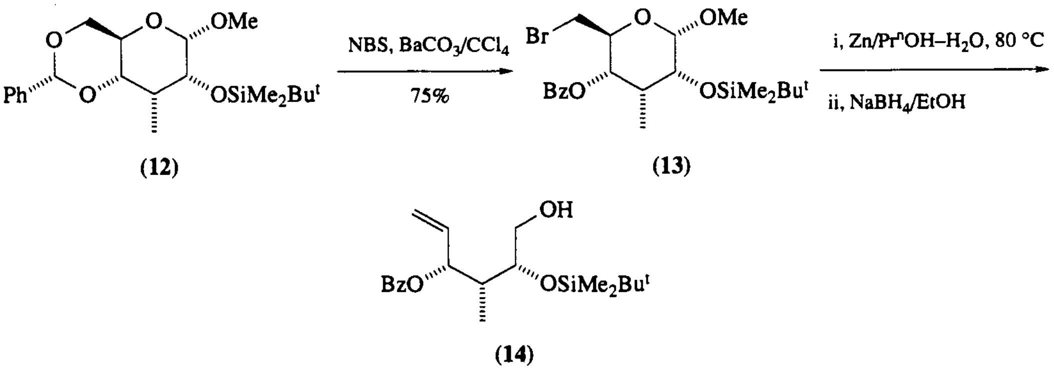

**Scheme 5**

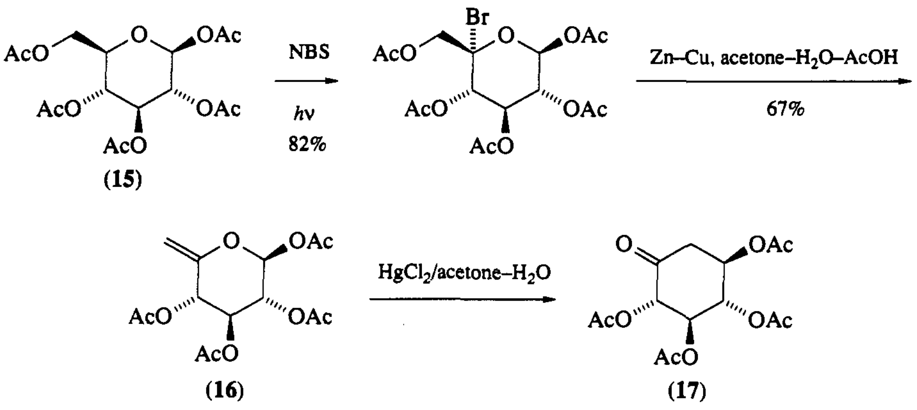
(15)
NBS
hν
82%
Zn–Cu, acetone–H2O–AcOH
67%
(16)
HgCl2/acetone–H2O
(17)

Scheme 6

A pair of reductive eliminations on chlorohydrin intermediates was used to achieve regioselective introduction of alkene functionality in a synthesis of (**18**), a precursor of the sesquiterpenoid pentalenene (Scheme 7).[26] Key steps in Tochtermann's synthesis of [6]-paracyclophane derivative (**21**; Scheme 8)[27] were bromination of the bridged oxepine (**19**) followed by reductive elimination of the resultant dibromooxirane (**20**).

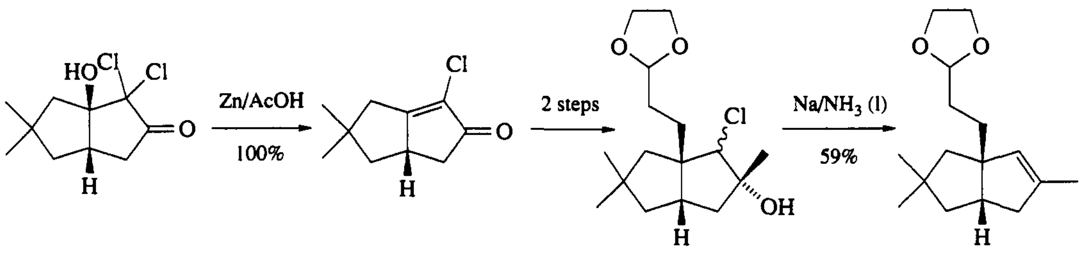
Zn/AcOH
100%
2 steps
Na/NH3 (l)
59%

Scheme 7

(18)

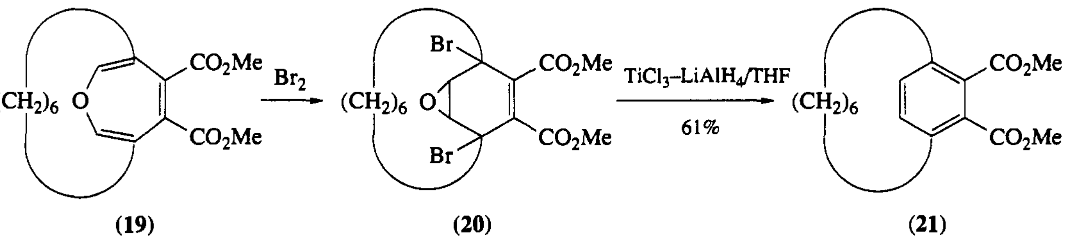
Br2
TiCl3–LiAlH4/THF
61%
(19)
(20)
(21)

Scheme 8

Reductive eliminations of halohydrin derivatives can also be used to prepare functionalized alkenes. Trihalomethanes react chemoselectively with aldehydes in the presence of ketones[28] in a reaction initiated by $CrCl_2$. The (*E*)-isomer of the alkenyl iodide was formed stereoselectively in the example in equation (5).

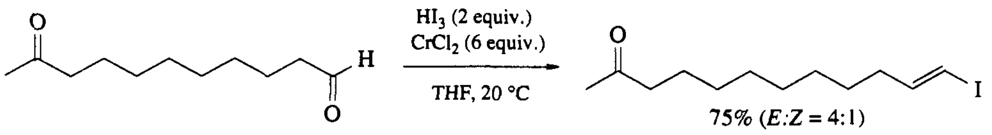
HI3 (2 equiv.)
CrCl2 (6 equiv.)
THF, 20 °C
75% (E:Z = 4:1)

(5)

A stereoselective synthesis of the (*Z*)-isomer of α,β-unsaturated esters (Scheme 9) from α-phenylthio-β-keto esters results from an iodide-induced *anti* elimination of the pyridinium salt (**22**).[29] An analogous reaction based on a β-phenylseleno alcohol derivative (Scheme 10) was exploited in a synthesis of the sesquiterpenoid confertin.[30] A notable feature of this sequence is the use of phenylselenoacetaldehyde as a vinyl cation equivalent.[31]

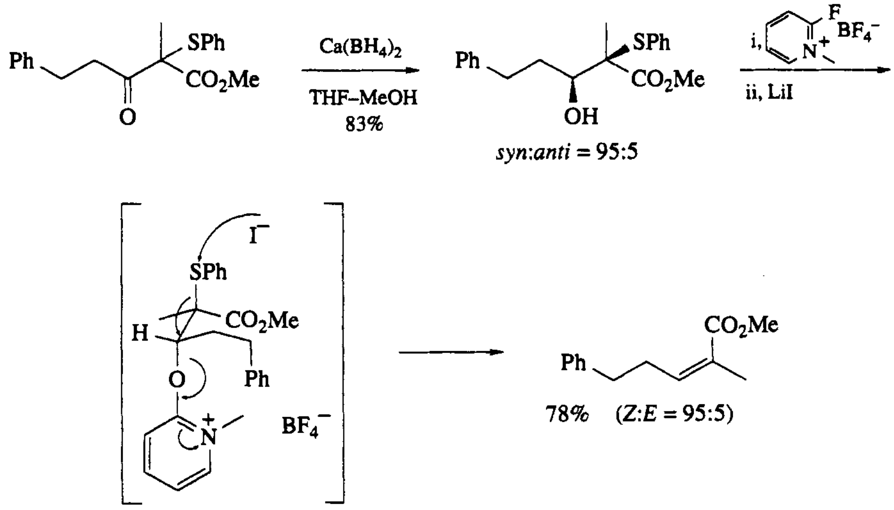

**(22)**

**Scheme 9**

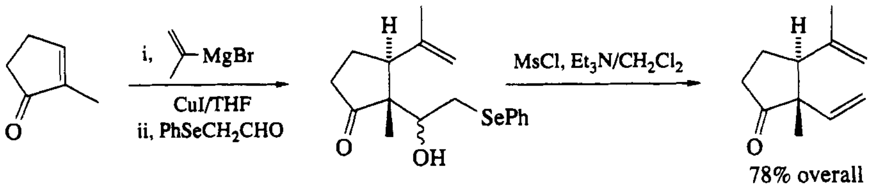

**Scheme 10**

## 5.2.3 REDUCTIVE ELIMINATION OF OXIRANES AND THIIRANES

The earliest general method for the reductive deoxygenation of oxiranes to alkenes involved multistep procedures in which halohydrins were intermediates. Cornforth,[32] for example, used an oxirane deoxygenation in an early synthesis of squalene (Scheme 11). Diastereoselective double addition of homogeranyllithium (**23**) to the dichloro diketone (**24**) gave the bis(chlorohydrin) (**25**), which was first converted to the diepoxide (**26**). Subsequent treatment with NaI and Zn in HOAc buffered with NaOAc gave squalene (**27**).

By using $POCl_3$ in pyridine in the reductive elimination of an iodohydrin intermediate (Scheme 12), the acid sensitive α,β-unsaturated acetal (**28**) was prepared.[33]

The stereoselective reductive deoxygenation of aliphatic *cis*-oxiranes to the corresponding *cis*-alkenes *via* iodohydrin intermediates has been accomplished by convenient one-pot procedures (equations 6 and 7).[34,35]

For the one-step conversion of oxiranes to alkenes a variety of reducing metals have been used, including Li,[36] $Ti^0$,[37] low-valent Nb,[38] $Cr^{II}$,[39] and $Sm^{II}$.[40] In the latter case, HMPA and *N*,*N*-dimethylaminoethanol facilitate the reaction.[41] Reaction of 2 equiv. of $Bu^nLi$ with $WCl_6$ produces a reagent which effects efficient deoxygenation of oxiranes, as exemplified in equation (8).[42] This reagent is particularly valuable for the deoxygenation of tri- and tetra-substituted oxiranes and is compatible with ethers and esters, although aldehydes and ketones reductively couple with it.

A synthesis of *trans*-γ-irone (**29**; Scheme 13) achieved the introduction of an exocyclic methylene adjacent to a hindered centre *via* reductive deoxygenation of an oxirane with a low-valent Ti reagent.[43]

The reductive desulfurization of thiiranes has been accomplished with Raney nickel, Li in $EtNH_2$, Zn in HOAc, $Bu_3SnH$, and $P_2I_4$ in DMF but the reaction has seldom been applied to organic synthesis.[44] A noteworthy procedure for preparing moderately hindered tetrasubstituted alkenes, which proceeds *via* a thiirane intermediate, was developed independently by Barton[45] and Kellogg.[46] The procedure, illustrated in Scheme 14 for the preparation of (**34**), involved reaction of thiocamphor (**30**) with diazoalkane

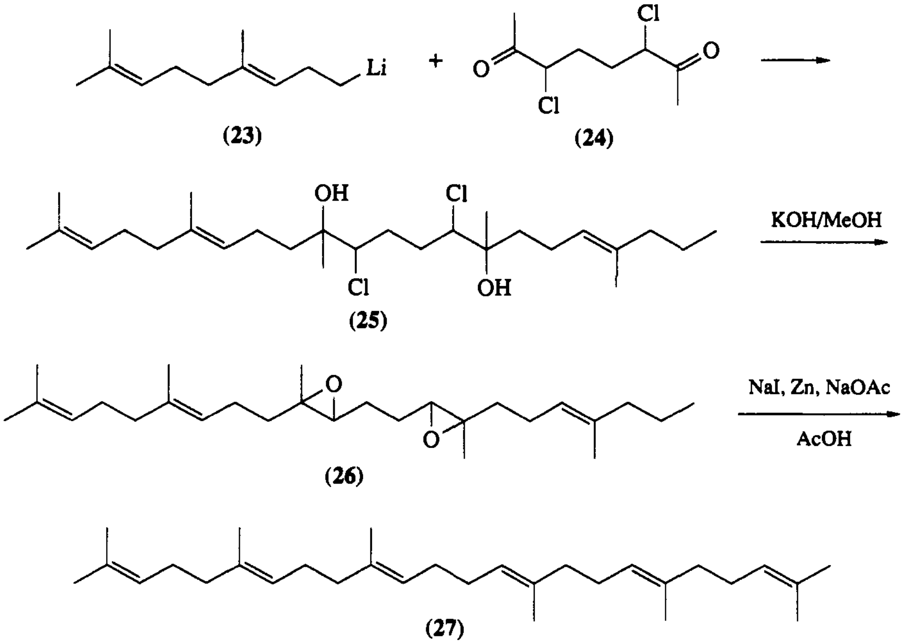
Li
+
Cl
O
O
Cl
(23)
(24)
OH
Cl
Cl
OH
(25)
KOH/MeOH
O
O
(26)
NaI, Zn, NaOAc
AcOH
(27)

**Scheme 11**

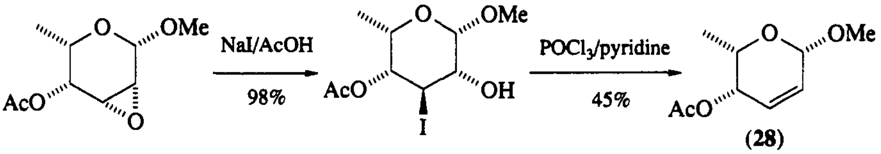
O
OMe
AcO
O
NaI/AcOH
98%
O
OMe
AcO
OH
I
POCl$_3$/pyridine
45%
O
OMe
AcO
(28)

**Scheme 12**

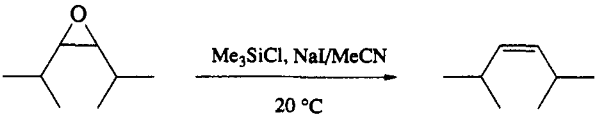
O
Me$_3$SiCl, NaI/MeCN
20 °C

(6)

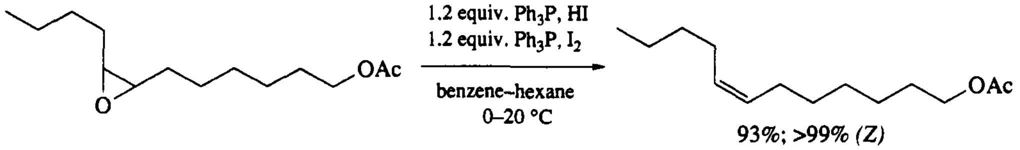
O
OAc
1.2 equiv. Ph$_3$P, HI
1.2 equiv. Ph$_3$P, I$_2$
benzene–hexane
0–20 °C
OAc
93%; >99% *(Z)*

(7)

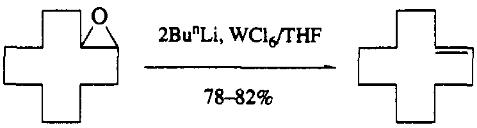
O
2Bu$^n$Li, WCl$_6$/THF
78–82%

(8)

**(31)** to give the 1,3,4-thiadiazole **(32)**, which, on heating with $Bu_3P$, extruded $N_2$ to afford thiirane **(33)**. However, under the reaction conditions, **(33)** underwent reductive desulfurization to the alkene **(34)** with concomitant formation of $Bu_3P{=}S$. An alternative method involving the generation of the analogous 1,3,4-selenadiazoles, followed by thermal extrusion of $N_2$ and Se metal, can be applied to even more hindered alkenes.[47]

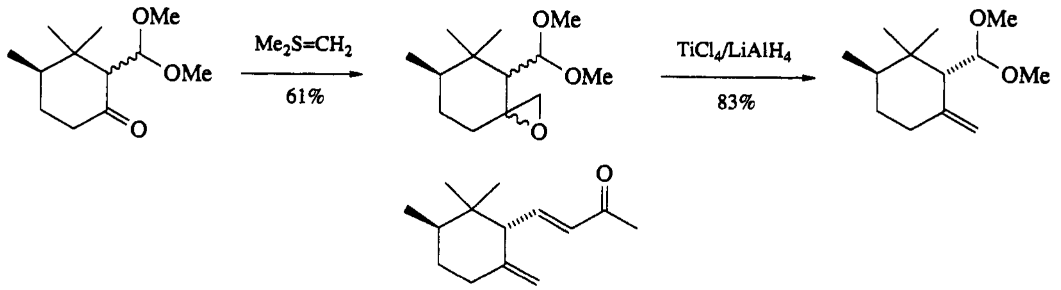

(29)

Scheme 13

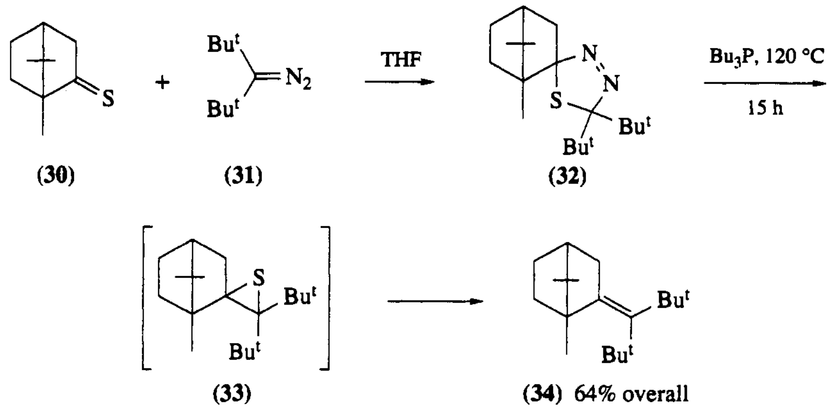

Scheme 14

## 5.2.4 DEOXYGENATION OF *VIC*-DIOLS

### 5.2.4.1 Fragmentation of Thioxocarbonates

The regio- and stereo-selective deoxygenation of *vic*-diols to alkenes based on the *syn* elimination of cyclic derivatives provides an especially valuable method for the modification of carbohydrates and the synthesis of strained or twisted alkenes.[48] The first generally useful method reported in 1963 by Corey and Winter[49] involves a two-step procedure involving conversion of the *vic*-diol to a cyclic thionocarbonate (1,3-dioxolane-2-thione) followed by stereospecific fragmentation on heating with trivalent phosphorus compounds. The procedure and mechanism of the reaction are illustrated in Scheme 15 for the synthesis of optically active *trans*-cyclooctene (**39**).[50] Resolution of *trans*-cyclooctane-1,2-diol *via* the monophthalate ester gave the enantiomer (**35**), which was converted to the thioxocarbonate (**36**) by refluxing with thiocarbonyldiimidazole (TCDI) in toluene. The resultant thioxocarbonate was then heated with triisooctyl phosphite at 135 °C for 17 h, during which time the product was removed from the reaction mixture in a stream of $N_2$. Optically active *trans*-cyclooctene was thus obtained in 84% yield in >99% isomeric purity.

The mechanism of the reaction involves nucleophilic attack by the phosphite on the sulfur atom of (**36**) to give the 1,3-dipole (**37**), which is converted to ylide (**38**) either by cyclization–desulfurization (path a) or α-elimination–carbene capture (path b). Concerted 1,3-dipolar cycloreversion of the ylide then gives the product. Alternatively, direct stereospecific 1,3-dipolar cycloreversion of zwitterion (**37**) may account for the product.

If the alkene is too unstable to permit isolation, it may be trapped *in situ* with a suitable reagent. The highly strained bridgehead alkene (**40**; Scheme 16) was prepared and trapped in this way as a Diels–Alder adduct with 1,3-diphenylisobenzofuran (**41**).[51]

The high temperatures and protracted reaction times required for the Corey–Winter reaction can lead to detrimental side reactions. Much lower reaction temperatures can be achieved by using 1,3-dimethyl-

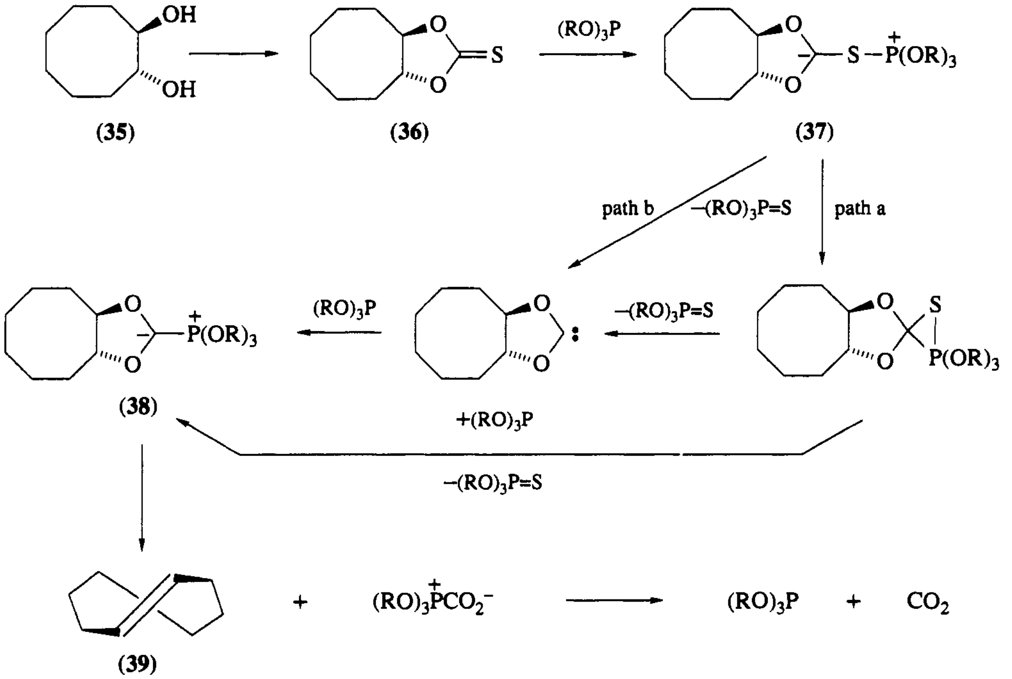
OH
OH
(35)
O
S
O
(36)
(RO)3P
O
S – P(OR)3
O
(37)
path b
–(RO)3P=S
path a
O
P(OR)3
O
(38)
(RO)3P
O
O
–(RO)3P=S
O
S
O
P(OR)3
+(RO)3P
–(RO)3P=S
(39)
+
(RO)3PCO2−
(RO)3P
+
CO2

Scheme 15

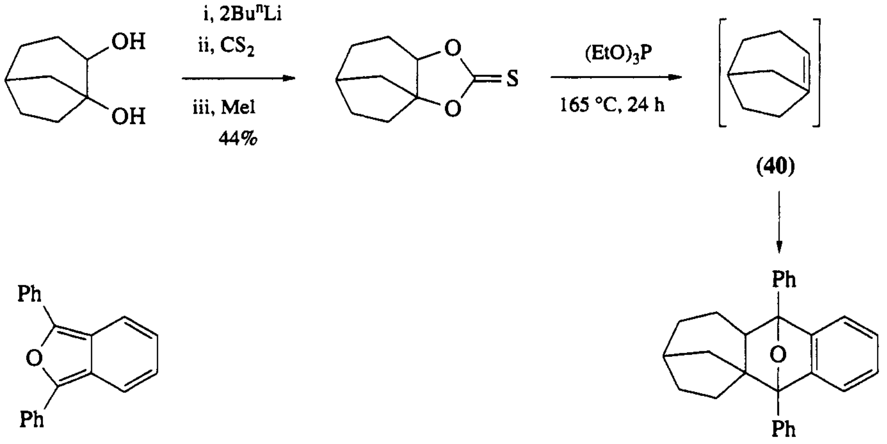
OH
OH
i, 2BunLi
ii, CS2
iii, MeI
44%
O
S
O
(EtO)3P
165 °C, 24 h
(40)
Ph
O
Ph
Ph
O
Ph
(41)

Scheme 16

2-phenyl-1,3,2-diazaphospholidine (**42**) as the thiophile, as shown in Scheme 17.[52] The reagent (**42**) is prepared in one step (70% yield) from *sym*-dimethylethylenediamine and dichlorophenylphosphine.

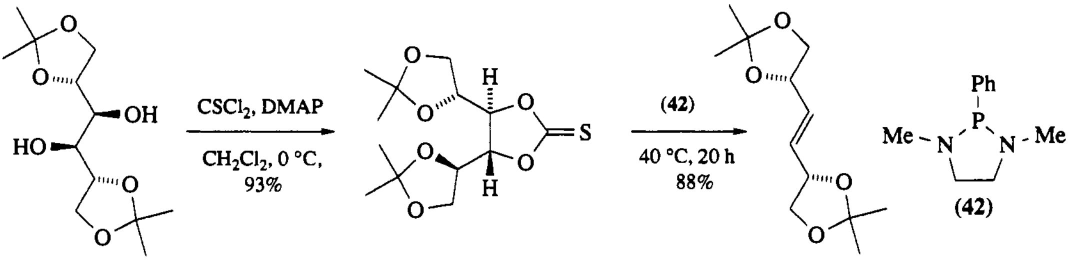
O
O
OH
HO
O
O
CSCl2, DMAP
CH2Cl2, 0 °C,
93%
O
O
H
O
S
O
O
O
H
(42)
40 °C, 20 h
88%
O
O
O
O
Ph
P
Me
N
N
Me
(42)

Scheme 17

### 5.2.4.2 Fragmentation of 2-Methoxy-, 2-Acetoxy- and 2-Dimethylamino-1,3-dioxolanes

Eastwood[53] has devised an alternative one-pot deoxygenation of *vic*-diols which, like the Corey–Winter reaction, depends upon the fragmentation of a 1,3-dioxolane intermediate. The reagents required are cheaper and less obnoxious than the Corey–Winter sequence and the procedure is amenable to large scale operation. For example (+)-5-*O*-methyl-D-ribonolactone (**43**) was converted to the 2-methoxy-1,3-dioxolane (**44**) on heating with excess triethyl orthoformate (Scheme 18); subsequent heating at 176 °C gave $CO_2$, EtOH and the butenolide (**45**).[54] A trace of HOAc is frequently used to catalyze the fragmentation. The mechanism of the reaction has been examined in some detail.[48]

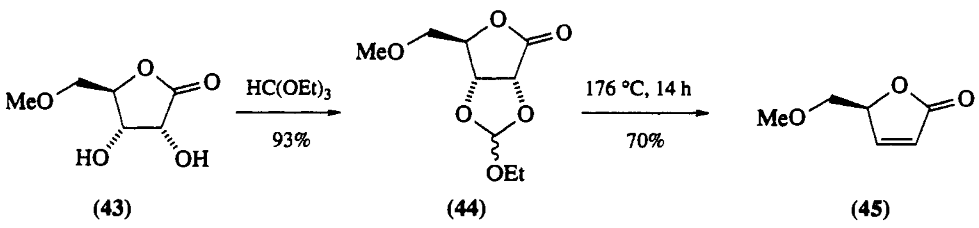

**Scheme 18**

2-Dimethylamino-1,3-dioxolanes, prepared by the reaction of the diol with dimethylformamide dimethylacetal, react *in situ* with MeI to give quaternary ammonium salts, which typically fragment at lower temperature (110–130 °C) to give the alkene, $CO_2$ and $Me_3NHI$.[55] For acid sensitive compounds such as the unsaturated acetal (**46**; equation 9), these conditions are superior to the original Eastwood procedure. Fragmentation of the 2-dimethylamino-1,3-dioxolane can also be effected by $Ac_2O$[56] and in some cases this modification is preferred, since the weakly nucleophilic acetate by-product causes fewer serious side reactions than iodide.[57,58]

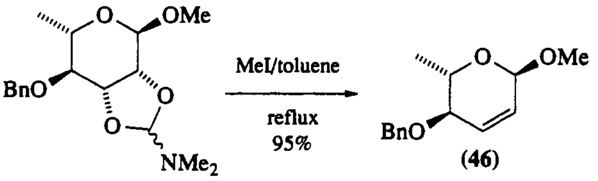

(9)

Stereospecific conversion of *vic*-diols into alkenes can also be achieved at moderate temperatures *via* 2-acetoxy-1,3-dioxolanes. These are generated as intermediates by heating a 2-methoxy-1,3-dioxolane with $Ac_2O$. The acid sensitive trisubstituted alkene (**48**) was efficiently prepared by this method as shown in Scheme 19.[59]

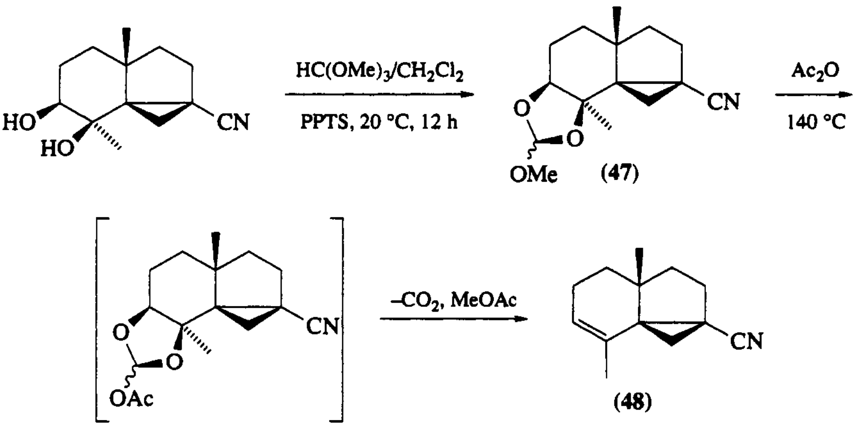

**Scheme 19**

### 5.2.4.3 Reductive Elimination of Cyclic Phosphates

The cyclic phosphate and phosphoramidate derivatives of *vic*-diols undergo a two-step reductive elimination on treatment with Li/$NH_3$, Na–naphthalene, $TiCl_4$–Mg(Hg) or $TiCl_4$–K.[60] In acyclic systems the reaction is only moderately stereoselective.[60] The reaction has particular value in the synthesis of tetrasubstituted alkenes from highly hindered *vic*-diols. Scheme 20 illustrates its use in the synthesis of [10,10]-betweenanene (**49**).[61]

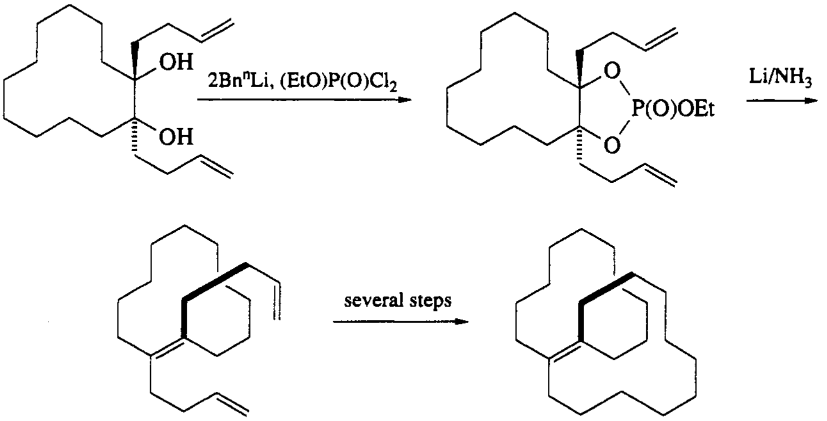

**(49)**

**Scheme 20**

### 5.2.4.4 Transition Metal Mediated Deoxygenation of *vic*-Diols

The McMurry reaction[62] is a powerful and versatile method for synthesizing a wide variety of alkenes. The intramolecular variant of the reaction is especially useful for preparing medium ring cycloalkenes, as illustrated in equation (10) for the synthesis of humulene (**50**).[63] Two distinct stages are involved: (i) reductive coupling of a dicarbonyl to produce a *vic*-diolate (**51**), bound to $Ti^I$ embedded in a $Ti^0$ matrix; and (ii) stepwise fragmentation to the alkene and $Ti^{II}$ oxide (Scheme 21). It is only the second stage of the process, the fragmentation of the *vic*-diolate intermediate, that will be discussed here; for a fuller discussion of the McMurry reaction see Volume 1, Chapter 3.1.

A $Ti^0$ reagent, prepared by the reaction of $TiCl_3$ with K metal, provides a one-step procedure for the deoxygenation of *vic*-diols. The reaction is run in refluxing THF in the presence of excess K metal to convert the diol to the diolate (**52**), which then reacts with $Ti^0$ to form the same intermediate (**51**) implicated in the McMurry coupling. Acyclic systems reduce with little stereoselectivity (equation 11) and *trans*-diols deoxygenate as readily as the corresponding *cis* isomers (equation 12). These results are in accord with the mechanism outlined in Scheme 21 in which the reaction takes place on the surface of a $Ti^0$ particle and the loss of stereochemistry is explained by the stepwise fragmentation of the bound diolate.[64] The utility of the reaction is limited by the incompatibility of many functional groups to the powerful reducing conditions. Thus ketones, thioketones, acyloins, bromohydrins, oxiranes, cyanohydrins and allylic or benzylic alcohols are some of the functional groups which are affected by the reagent. Related deoxygenations of *vic*-diols can be achieved using potassium hexachlorotungstate.[65]

Allylic 1,4-diols also deoxygenate to give conjugated dienes using a $Ti^0$ catalyst prepared from $TiCl_4$ and LAH[66] or $TiCl_3$ and LAH. The latter reagent mixture has been exploited in a synthesis of vitamin A (**53**; equation 13).[67]

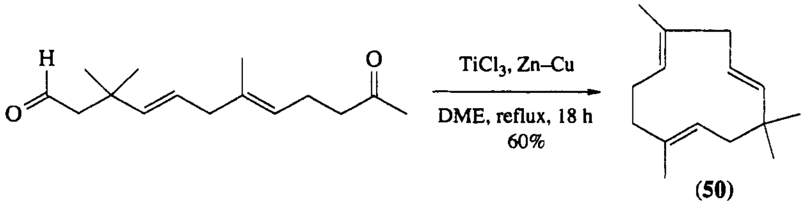

**(50)**

(10)

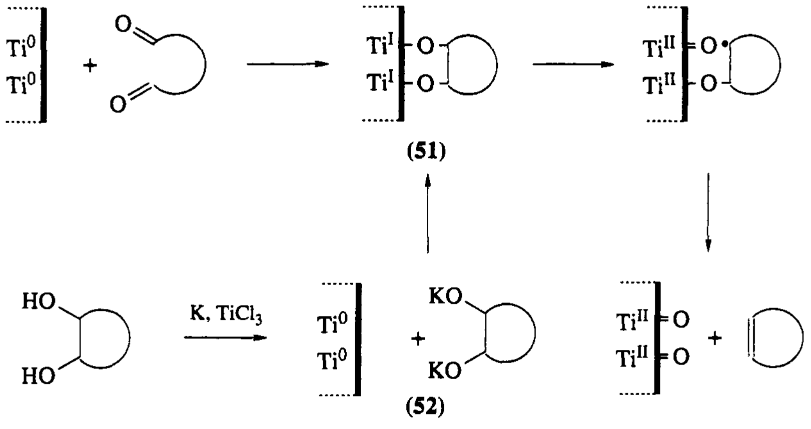
Ti$^0$
Ti$^0$
O
O
Ti$^I$
Ti$^I$
O
O
(51)
Ti$^{II}$
Ti$^{II}$
O
O
HO
HO
K, TiCl$_3$
Ti$^0$
Ti$^0$
KO
KO
(52)
Ti$^{II}$
Ti$^{II}$
O
O

**Scheme 21**

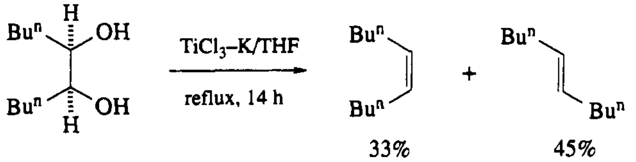
H
Bu$^n$
OH
Bu$^n$
OH
H
TiCl$_3$–K/THF
reflux, 14 h
Bu$^n$
Bu$^n$
33%
Bu$^n$
Bu$^n$
45%

(11)

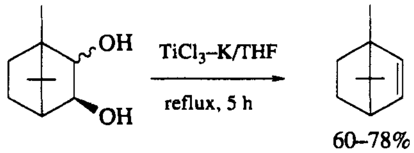
OH
OH
TiCl$_3$–K/THF
reflux, 5 h
60–78%

(12)

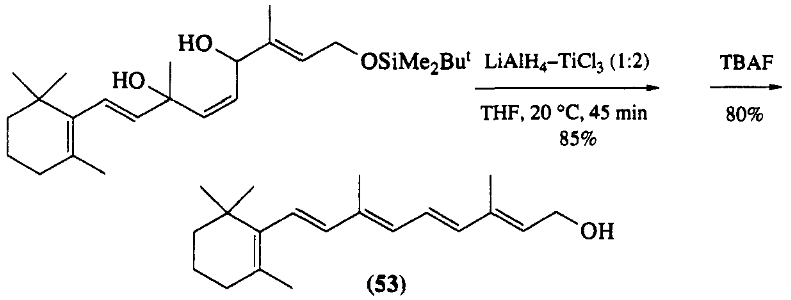
HO
HO
OSiMe$_2$Bu$^t$
LiAlH$_4$–TiCl$_3$ (1:2)
THF, 20 °C, 45 min
85%
TBAF
80%
OH
(53)

(13)

### 5.2.4.5 Reductive Elimination of Acyclic *vic*-Diester Derivatives

The generation of an alkene by the reaction of a *vic*-disulfonate ester with iodide (the Tipson–Cohen reaction) has been known since 1943 and in some cases it has proved useful where other methods have failed, as in the preparation of the spirocyclic triene (**54**; Scheme 22).[68] The mechanism probably involves an initial nucleophilic displacement to give an iodohydrin sulfonate, which then undergoes iodide-induced elimination to the alkene. Methanesulfonates can be used as well as arenesulfonates.

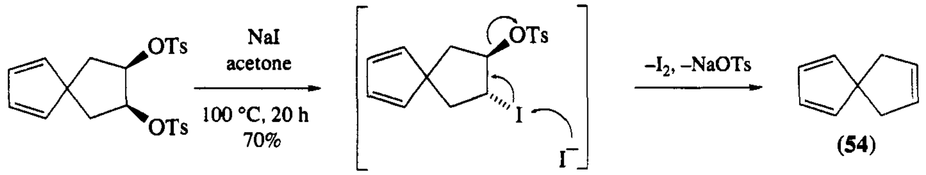
OTs
OTs
NaI
acetone
100 °C, 20 h
70%
OTs
I
I$^-$
–I$_2$, –NaOTs
(54)

**Scheme 22**

The reaction has been most often applied to the synthesis of cycloalkenes, since the acyclic version shows low stereoselectivity. A modification of the original Tipson–Cohen conditions has been developed by Fraser-Reid and coworkers[69] for the elaboration of carbohydrate derivatives, in which sodium iodide in conjunction with Zn or Zn–Cu couple in refluxing DMF is used to effect the elimination. As can be seen from the examples shown in equations (14) and (15), the reaction proceeds with equal ease for both *cis* and *trans* isomers.

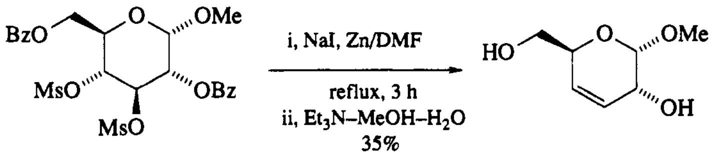

(14)

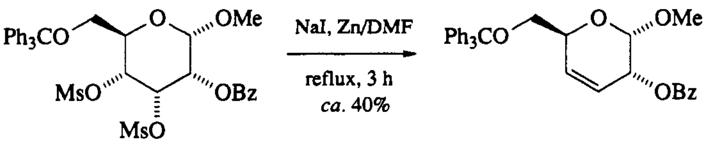

(15)

A one-pot conversion of *vic*-diols to alkenes can be achieved at room temperature using TMS-I generated *in situ* (equation 16).[70]

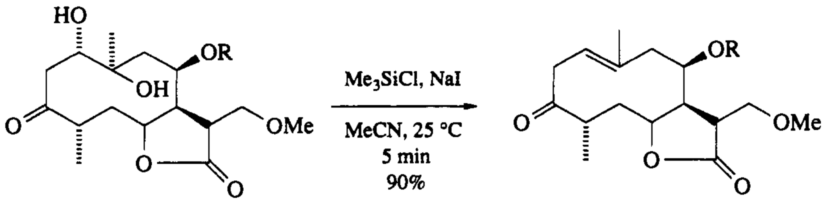

(16)

Barton and coworkers developed a very useful procedure for the deoxygenation of alcohols, which involves conversion of the alcohol to the corresponding xanthate derivative followed by reaction with $Bu_3SnH$.[71] When applied to the bis(xanthates) derived from *vic*-diols the reaction gives alkenes, as illustrated in equation (17).[72] Once again alkene formation is independent of the stereochemistry of the starting diols.

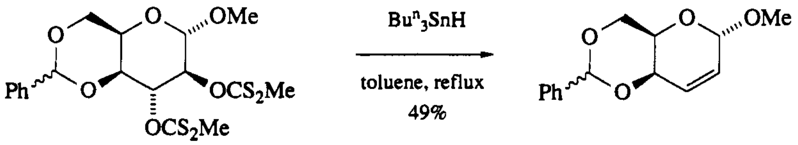

(17)

## 5.2.5 CONNECTIVE ALKENE SYNTHESES *VIA* REDUCTIVE ELIMINATION

### 5.2.5.1 The Julia Alkenation

In 1973 Julia and Paris[73] reported a new alkene synthesis which, like the Horner–Wittig reaction, is connective and regiospecific. A subsequent study of its scope and stereochemistry led to improved reaction conditions, which have since been widely adopted.[74] The Julia alkenation consists of four distinct stages, as exemplified in Scheme 23 by the synthesis of the fragment (**60**) of moenocinol.[75] These are: (i) metalation of the aryl alkyl sulfone (**55**); (ii) condensation of the α-metalated sulfone (**56**) with the aldehyde (**57**) to give a β-arylsulfonyl alkoxide adduct (**58**); (iii) functionalization of the adduct to give the β-benzoyloxy sulfone (**59**); and (iv) reductive elimination of the β-benzoyloxy sulfone using Na-Hg to generate the diene (**60**).

The first three stages can be performed in a single reaction vessel, although the overall yield of the sequence can be improved by isolating the β-hydroxy sulfone at the second stage and functionalizing the hydroxy group in a separate step. Purification of intermediates is not normally required.

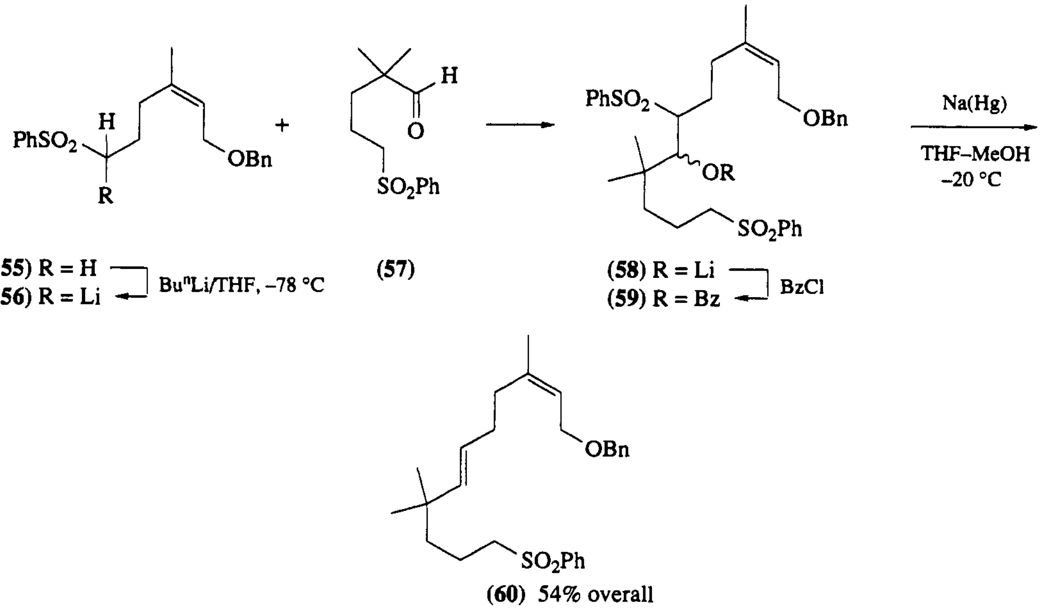

**Scheme 23**

By comparison with the Horner–Wittig reaction, the Julia alkenation has two principal assets. First, as the nucleophilic partner in the connective step (stage 2), sulfones are used, which are often more readily available and more easily purified than the corresponding phosphonium salts. Secondly, the 1,2-disubstituted alkenes produced in the key reductive elimination step have predominantly (*E*)-stereochemistry. One detraction of the Julia alkenation is its length — it can be foiled at any one of the four stages. In practice, stage 2, the condensation of the metalated sulfone with the carbonyl, is usually the most problematic but in certain circumstances all of the stages have their pitfalls. These will be examined individually below.

### *5.2.5.1.1 Scope and limitations*

#### *(i) Sulfone metalation*

Aryl alkyl sulfones are about as acidic as esters. They react rapidly with $Bu^nLi$ or LDA in THF at –78 °C to give homogeneous solutions of α-lithiated sulfones, which are bright yellow in the case of simple aryl alkyl sulfones to red-orange in the case of aryl allyl sulfones. The corresponding magnesio derivatives can be prepared by addition of EtMgBr to a solution of the sulfone in THF followed by a brief period at reflux or, more conveniently, by transmetalation of the lithio derivative with anhydrous $MgBr_2$, prepared by reacting Mg with 1,2-dibromoethane in THF. The magnesio derivatives are only faintly colored.

Problems have been encountered in the metalation of phenyl alkyl sulfones with $Bu^nLi$ when the α-protons are hindered. In such cases, competitive abstraction of the protons *ortho* to the sulfone group on the aryl ring may take place but this can be avoided by using LDA as the base.

#### *(ii) Condensation of metalated sulfones with carbonyls*

The addition of metalated sulfones to aldehydes or ketones is a reversible reaction and the principal cause of failure in the Julia alkenation results from an unfavorable equilibrium at this stage. The reverse reaction is favored when the β-alkoxy sulfone adduct is sterically encumbered. Adducts derived from ketones are more vulnerable than those derived from aldehydes. Stabilization of the sulfone anion by conjugation with an aromatic ring or chelation with a proximate heteroatom are also important contributors to favoring the reverse reaction. However, by varying the metal counterion, the position of equilibrium can be adjusted. For example, the lithio derivative of the sulfone (**61**; Scheme 24) failed to condense with the aldehyde (**62**) but the desired adduct (**64**) could be obtained in 81% yield from the corresponding magnesio derivative.[76] Successful addition was only achieved by adding a solution of LDA to a mixture of the sulfone, the aldehyde and excess $MgBr_2$ in THF at −110 °C. These unusual conditions were determined by the instability of the metalated derivatives of the sulfone. The beneficial effect of magnesium has been exploited by others.[77–80]

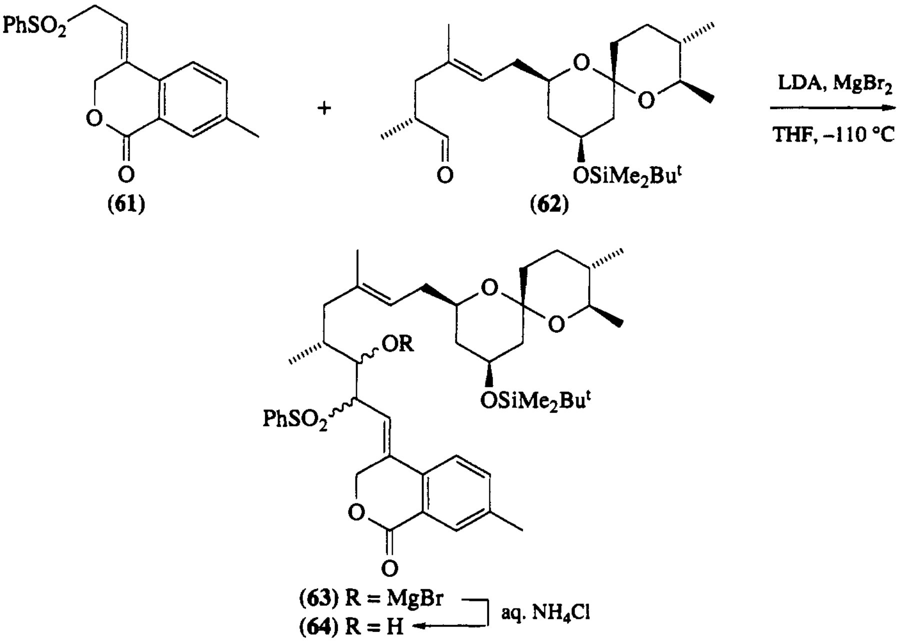
PhSO2
OSiMe2Bu^t
LDA, MgBr2
THF, −110 °C
OR
PhSO2
OSiMe2Bu^t

(**61**) (**62**)

(**63**) R = MgBr
(**64**) R = H
aq. $NH_4Cl$
81% overall

**Scheme 24**

Neither the lithio nor the magnesio derivatives of the sulfone (**65**) reacted with the aldehyde (**66**). However, the 'ate' complex derived from the lithio derivative and $BF_3$ gave a 90% yield of the desired adduct (**67**), which was transformed to the alkene (**68**) in the usual way (Scheme 25).[81]

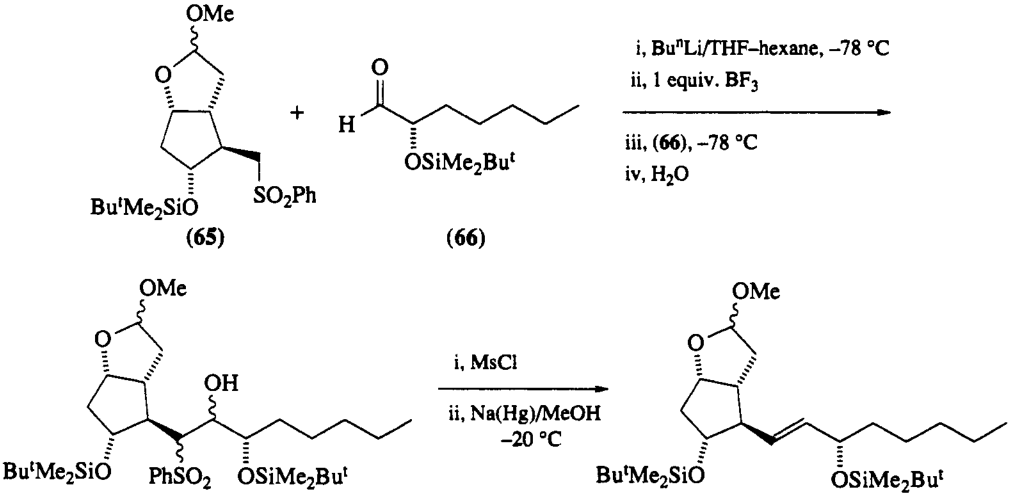
OMe
Bu^tMe2SiO
SO2Ph
H
OSiMe2Bu^t
i, Bu^nLi/THF–hexane, −78 °C
ii, 1 equiv. BF3
iii, (66), −78 °C
iv, H2O
OMe
OH
Bu^tMe2SiO
PhSO2
OSiMe2Bu^t
i, MsCl
ii, Na(Hg)/MeOH
−20 °C
OMe
Bu^tMe2SiO
OSiMe2Bu^t

(**65**) (**66**)

(**67**) (**68**) 76% overall

**Scheme 25**

An interesting divergence in behavior between the lithio and magnesio derivatives of the sulfone (**69**) has emerged from studies on the synthesis of the antibiotic pseudomonic acid C. The lithio derivative of

(**69**; Scheme 26) formed a stable chelate with the proximate oxygen, which prevented addition to the aldehyde (**70**). The magnesio derivative, on the other hand, acted as a reducing agent, giving (**71**) and (**72**) as the main products.[74] However, by reversing the functionality, the lithio derivative of sulfone (**73**) successfully condensed with the aldehyde (**74**).[82]

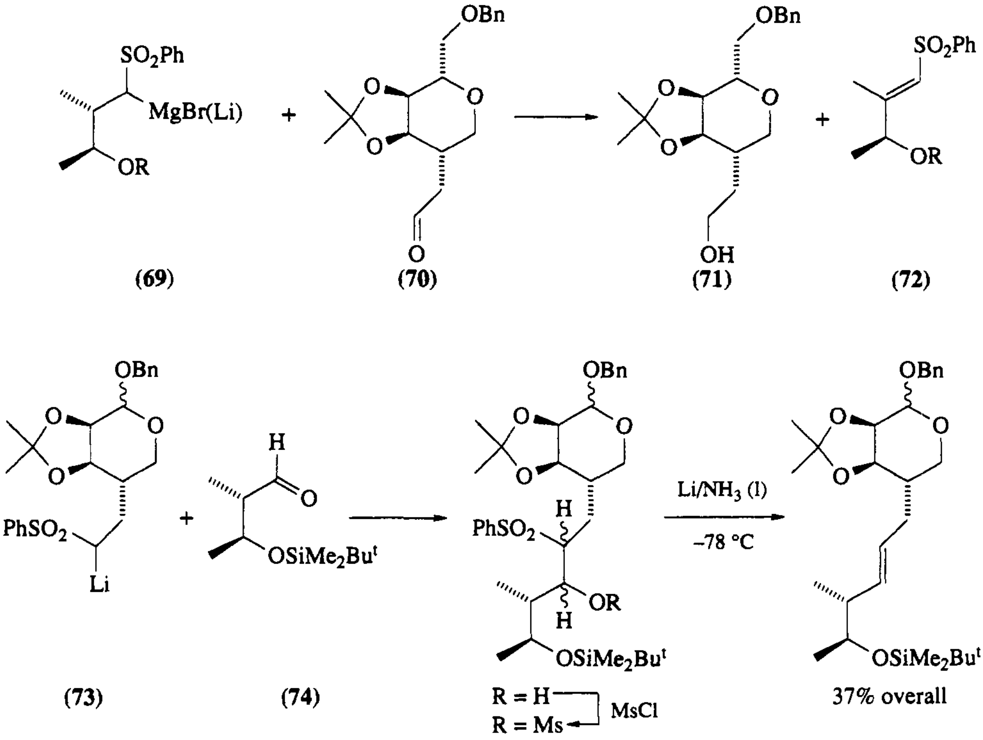

**Scheme 26**

Metalated sulfones with β leaving groups can be generated at low temperature and trapped with electrophiles. For example the α-lithio sulfone (**76**; Scheme 27) was prepared by metalation with LDA at –90 °C in 9:1 THF–HMPA and condensed with aldehyde (**75**). Acetylation of the adduct followed by reductive elimination gave an intermediate in the synthesis of the antibiotic ingramycin.[83]

The unfavorable equilibrium in the condensation of metalated sulfones with carbonyls can be surmounted in other ways. For example, β-keto sulfones, which are prepared by condensation of metalated sulfones with esters, are efficiently reduced to β-hydroxy sulfones with $NaBH_4$. These reactions were deployed in the preparation of the (*E*)-alkene in the side chain of the intermediate (**77**; Scheme 28) on the way to brefeldin A.[84]

Another method for securing union of the sulfone and carbonyl fragments involves trapping the intermediate alkoxide by an intramolecular alkylation. This procedure was used in the synthesis of the diumycinol intermediate (**78**; Scheme 29).[85]

### *(iii) Preparation of the β-acyloxy sulfone*

In many cases functionalization of the adduct (stage 3) is superfluous since β-hydroxy sulfones undergo reductive elimination under the usual Julia alkenation conditions. However, the yields are usually lower than the corresponding reductive elimination with the more reactive β-acetoxy, β-benzoyloxy or β-methanesulfonyloxy sulfones owing to competing retroaldolization under the basic conditions of the reaction. A further complication is reductive desulfonylation, as shown in equation (18).[86]

### *(iv) Reductive elimination*

The reductive elimination step is effected by adding an excess of 5.65% Na(Hg) (2.5 mg atom of Na $g^{-1}$) to an efficiently stirred solution of the sulfone in 3:1 THF–MeOH at –20 °C. A protic solvent is essential for the reaction and a detailed study[77] revealed that MeOH was superior to EtOH or $Pr^iOH$ at low

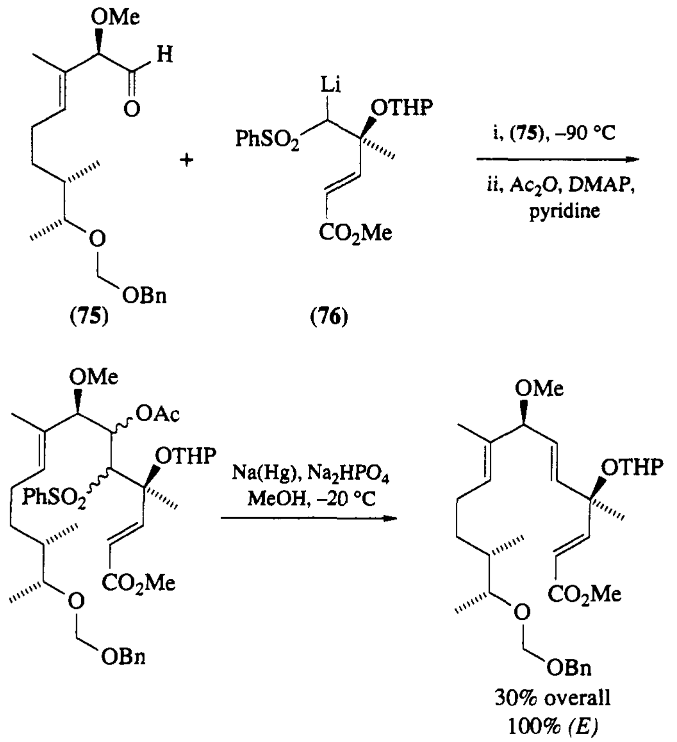
OMe
H
O
OBn
(75)
+
Li
OTHP
PhSO2
CO2Me
(76)
i, (75), -90 °C
ii, Ac2O, DMAP, pyridine
OAc
Na(Hg), Na2HPO4
MeOH, -20 °C
30% overall
100% (E)

Scheme 27

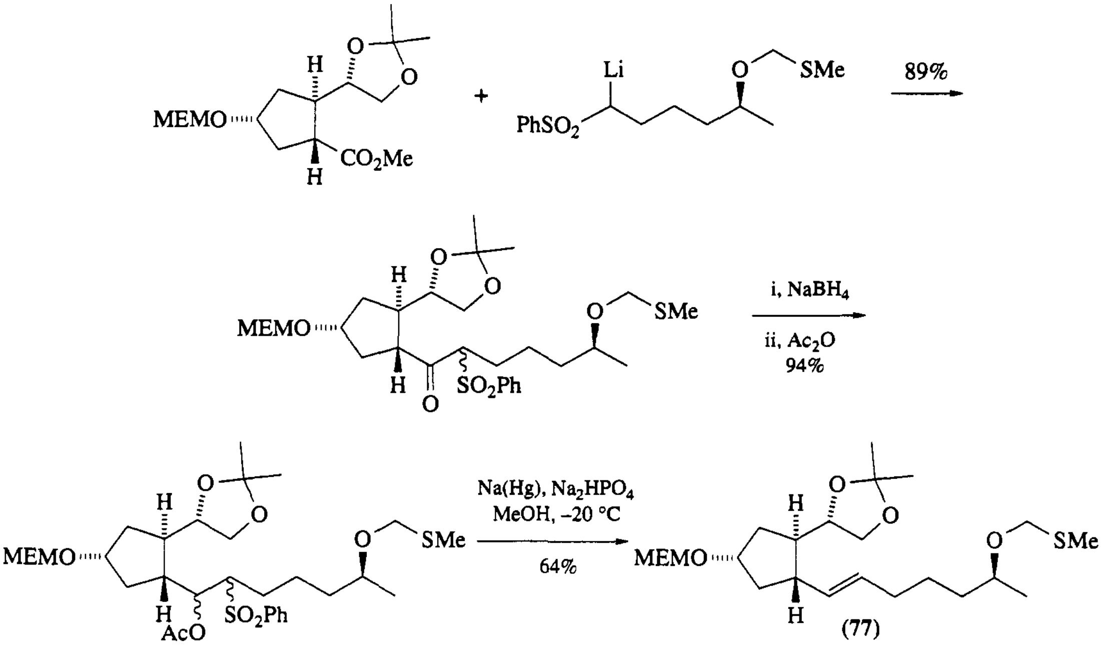
MEMO
H
O
CO2Me
+
Li
PhSO2
SMe
89%
SO2Ph
i, NaBH4
ii, Ac2O
94%
AcO
Na(Hg), Na2HPO4
MeOH, -20 °C
64%
(77)

Scheme 28

temperature. The THF or other cosolvents are needed to improve solubility of the organic substrates and diminish the rate of reaction of the Na(Hg) with the MeOH. The formation of NaOMe — an agent of serious side reactions — is slow at −20 °C and its effects can be ameliorated but not altogether suppressed by the addition of $Na_2HPO_4$ as a heterogeneous base scavenger.[87]

Electrochemical methods,[88] $Li/NH_3$ (l)[82] and modified Beauvault–Blanc reduction conditions[86,89] have also been used to effect reductive elimination. An example of the latter reaction is illustrated in equation (19).

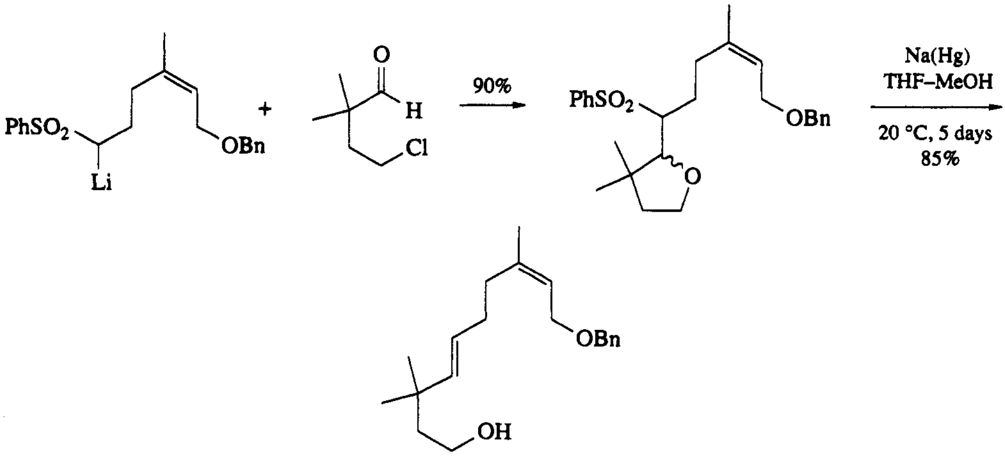
PhSO2
Li
OBn
+
O
H
Cl
90%
PhSO2
OBn
O
Na(Hg)
THF–MeOH
20 °C, 5 days
85%
OBn
OH

**(78)**

**Scheme 29**

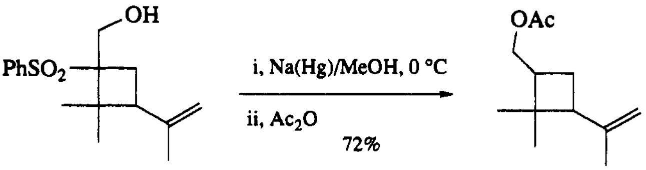
OH
PhSO2
i, Na(Hg)/MeOH, 0 °C
ii, Ac2O
72%
OAc

(18)

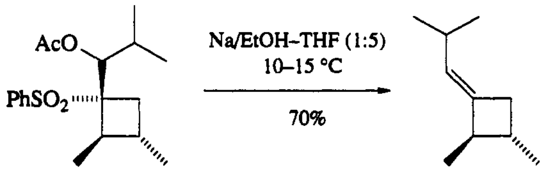
AcO
PhSO2
Na/EtOH–THF (1:5)
10–15 °C
70%

(19)

The rate of reductive elimination can vary considerably depending on the β-substituent and the structure of the product. Formation of conjugated dienes and trienes is fast (*ca.* 15–30 min) — especially when the sulfone occupies an allylic position; simple alkenes require 1–5 h. Although methanesulfonates, benzoates and acetates react at roughly similar rates, reductive elimination of β-alkoxy sulfones requires higher temperatures and longer reaction times. The large rate difference depending on leaving group and product structure is illustrated by comparing the reductive elimination in Scheme 29 (ether oxygen leaving group, 5 d at room temperature) with the formation of the conjugated triene in the tachysterol derivative (**79**) (30 min, –20 °C) shown in equation (20).[90] The reductive elimination shown in Scheme 27 gives further testimony to the importance of leaving group structure on the course of the reaction. In this case elimination can take place in either of two directions. Nevertheless the reaction was regioselective in the direction of the better leaving group (acetate), even though the alternative mode of elimination would have generated a conjugated diene ester containing a trisubstituted double bond.

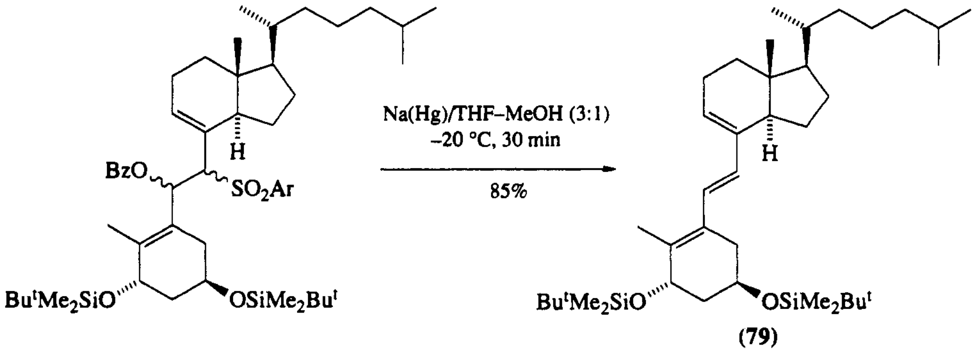
H
BzO
SO2Ar
Bu^tMe2SiO
OSiMe2Bu^t
Na(Hg)/THF–MeOH (3:1)
–20 °C, 30 min
85%
H
Bu^tMe2SiO
OSiMe2Bu^t

**(79)**

(20)

### *5.2.5.1.2 Stereochemistry*

The stereochemistry of the alkene is independent of the stereochemistry of the β-acyloxy sulfone precursor.[77,91] Thus reductive elimination of the pure diastereomeric β-acetoxy sulfones (**80**) and (**81**) gave the triene (**82**; Scheme 30). Similar results have been reported for β-hydroxy sulfones.[78] These results can be interpreted in terms of an intermediate carbanion (or radical) derived from electron transfer from the metal to the sulfone group, followed by elimination of benzenesulfinate anion (or radical) in which the *p*-orbital is *trans* coplanar to the acetoxy group and the substituents as far apart as possible. According to this view the overall stereochemistry is governed by steric interactions of the substituents and assumes that the intermediate anion or radical has sufficient lifetime to equilibrate. There are two further implications: firstly, the alkenes obtained should represent the thermodynamic mixture and secondly, increased branching, especially on those carbons adjacent to the carbons bearing the arylsulfonyl and the acyloxy groups, should increase stereoselectivity.[92] As can be seen from Table 1 this is the case. Furthermore, it can be seen from entries 2 and 3 that interchanging the position of the sulfone and the acyloxy groups has no effect on the stereochemical outcome of the reaction.

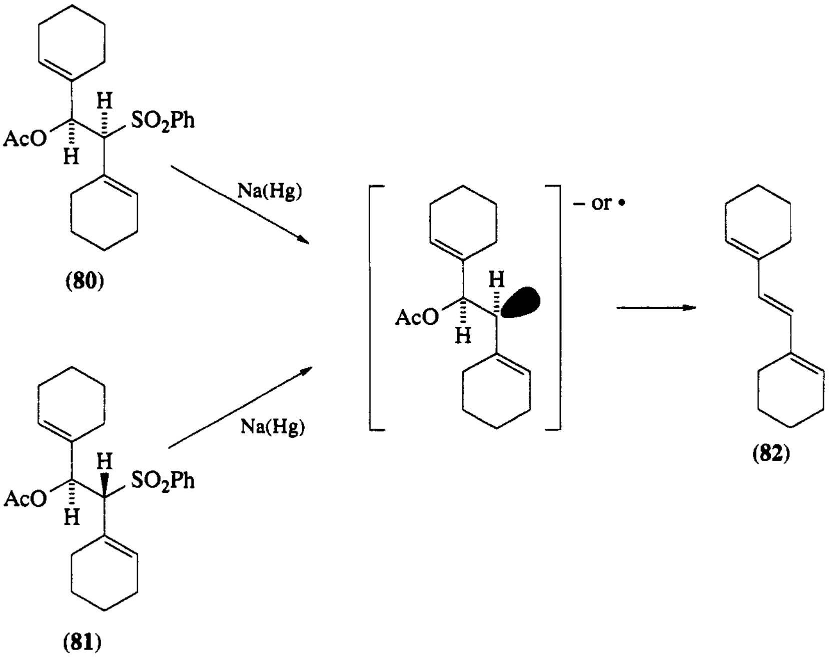

**Scheme 30**

Adverse conformational effects can affect the reductive elimination. For example, in the cholestane derivative (**83**; equation 21), the *trans* diequatorial substituents cannot achieve a *trans* coplanar relation demanded by the mechanism suggested in Scheme 30 unless the ring undergoes an unfavorable conformational change to a boat. Consequently only a 15% yield of cholest-2-ene (**84**) was obtained, along with 15% of the benzoate (**85**) derived from protonation of the carbanion before elimination could occur. It is noteworthy that the reductive elimination of (**83**) is unusually slow at –20 °C and could only be effected with a large excess of Na(Hg) at room temperature. This suggests that there may be a stereoelectronic advantage in the reductive elimination in a coplanar relation between the arylsulfonyl and the acyloxy leaving groups. The rate advantage in a *trans* coplanar relation between leaving groups in other reductive eliminations is well known.[93,94]

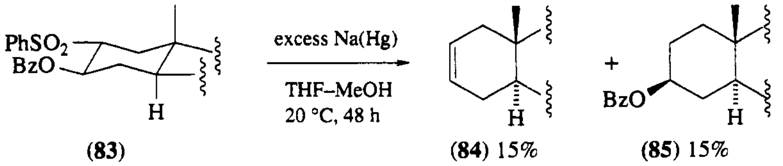

(21)

**Table 1** Scope and Stereochemistry of Alkenes from Reductive Elimination of β-Substituted Sulfones

| *Entry* | *Alkene* [a] | *Yield (%)* | *[E:Z] ratio* | *Ref.* | *Entry* | *Alkene* [a] | *Yield (%)* | *[E:Z] ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 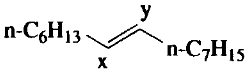  n-C6H13<br>y<br>x<br>n-C7H15 | 53 | 4:1 | 92 | 7 | 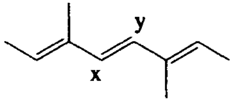 | 61 | 98:2 | 92 |
| 2 | 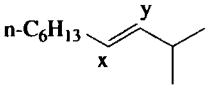 | 63 | 9:1 | 92 | 8 | 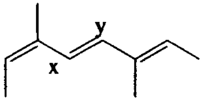 | 75 | 98:2 | 92 |
| 3 | 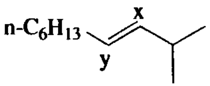 | 68 | 9:1 | 92 | 9 | 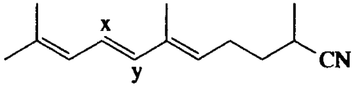 | 47 | 12:1 | 96 |
| 4 | 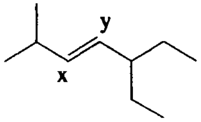 | 71 | 100:1 | 92 | 10 | 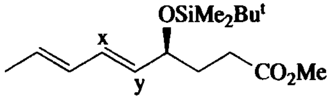  OSiMe2Bu<sup>t</sup><br>x<br>y<br>CO2Me | 81 | — | 97 |
| 5 | 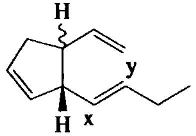 | 33 | 6:1 | 95 | 11 | 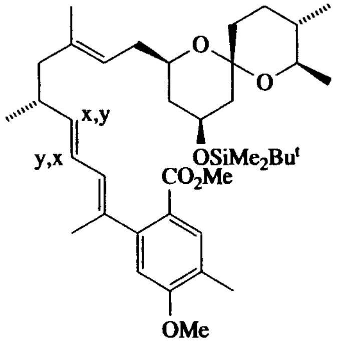  O<br>O<br>x,y<br>y,x<br>OSiMe2Bu<sup>t</sup><br>CO2Me<br>OMe | 70 | 100:0 | 98 |
| 6 | 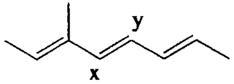 | 68 | 97:3 | 92 | | | | | |

**Table 1** *(continued)*

| *Entry* | *Alkene* [a] | *Yield (%)* | *[E:Z] ratio* | *Ref.* | *Entry* | *Alkene* [a] | *Yield (%)* | *[E:Z] ratio* | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|
| 12 | 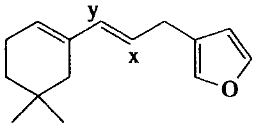 | 65 | 6:1 | 99 | 17 | 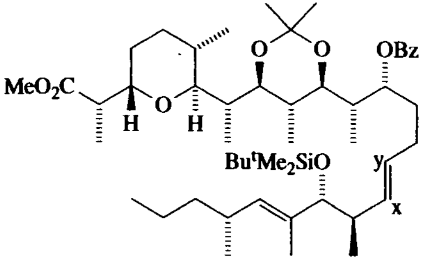 MeO$_2$C<br>O<br>H<br>H<br>O<br>O<br>OBz<br>Bu$^t$Me$_2$SiO<br>y<br>x | 50 | 8:1 | 80 |
| 13 | 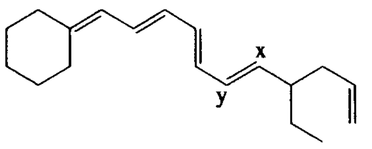 | 49 | 10:1 | 100 | | | | | |
| 14 | 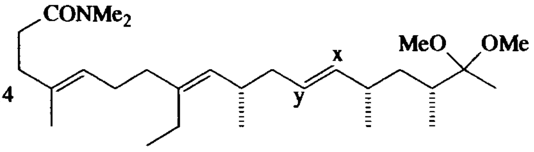 CONMe$_2$<br>x<br>MeO<br>OMe<br>y | 68 | 4:1 | 101 | 18 | 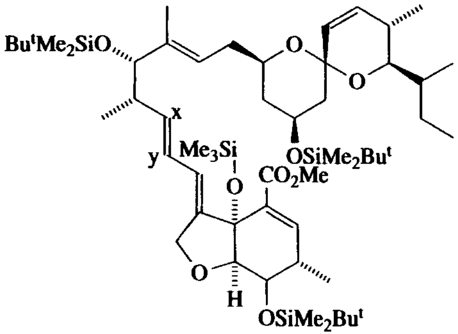 Bu$^t$Me$_2$SiO<br>O<br>O<br>x<br>y<br>Me$_3$Si<br>O<br>OSiMe$_2$Bu$^t$<br>CO$_2$Me<br>O<br>H<br>OSiMe$_2$Bu$^t$ | 47 | 100:0 | 104 |
| 15 | 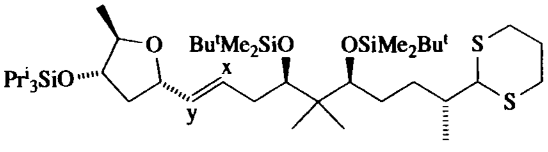 O<br>Pr$^i_3$SiO<br>Bu$^t$Me$_2$SiO<br>x<br>y<br>OSiMe$_2$Bu$^t$<br>S<br>S | 46 | 100:0 | 102 | | | | | |
| 16 | 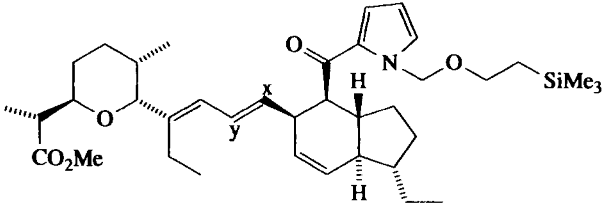 O<br>CO$_2$Me<br>x<br>y<br>O<br>N<br>O<br>SiMe$_3$<br>H<br>H | 53 | 100:0 | 103 | | | | | |

[a] x and y represent the site of the aryl sulfonyl and β-substituent respectively in the β-substituted precursor. y = OH, OMs, OBz or OAc.

### *5.2.5.1.3 Trisubstituted alkene synthesis*

A serious obstacle to the use of the Julia alkenation for the synthesis of trisubstituted alkenes is illustrated in Scheme 31. Addition of cyclohexanone to the lithiated sulfone (**86**) gave intermediate (**87**), which could not be acylated under the reaction conditions because of the sterically hindered tertiary alkoxide. Owing to an unfavorable equilibrium, (**87**) reverted back to starting materials. However, by reversing the functionality of the fragments a stable adduct (**88**) was formed in which the less hindered secondary alkoxide was acylated and the resultant β-benzoyloxy sulfone (**89**) reductively eliminated to the alkene (**90**) in 54% overall yield. Trisubstituted alkenes have been generated by reductive elimination of β-hydroxy sulfones[105,106] but, in general, retroaldol reactions compete.

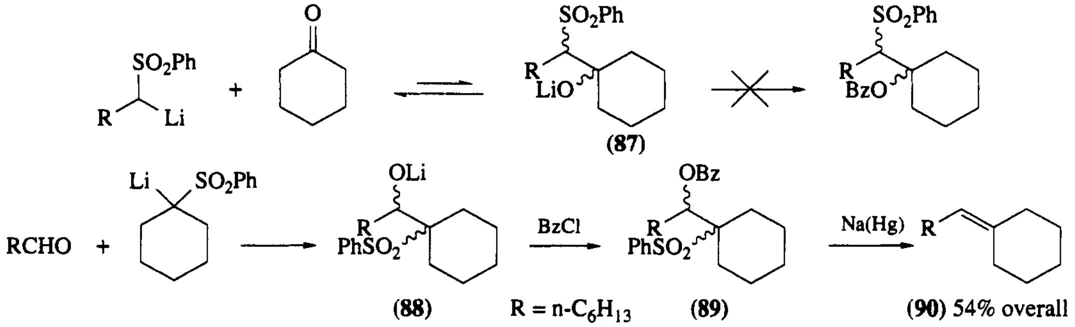
SO2Ph
R
Li
+
O
SO2Ph
R
LiO
(87)
SO2Ph
R
BzO
RCHO
+
Li
SO2Ph
OLi
R
PhSO2
(88)
BzCl
R = n-C6H13
OBz
R
PhSO2
(89)
Na(Hg)
R
(90) 54% overall

**Scheme 31**

Little is known about the stereochemistry of trisubstituted alkene formation in the Julia alkenation. In a synthesis of milbemycin $\beta_3$ Barrett and coworkers[107] generated intermediate (**91**; equation 22) as a mixture of isomers ($E$:$Z$ = 5:3) by reductive elimination of a β-acetoxy sulfone; however, a similar reductive elimination on the β-hydroxy sulfone shown in equation (23) gave a single isomer.[104] The marked difference in the yield of these two transformations reflects the advantage of suppressing the retroaldolization reaction by acylation.

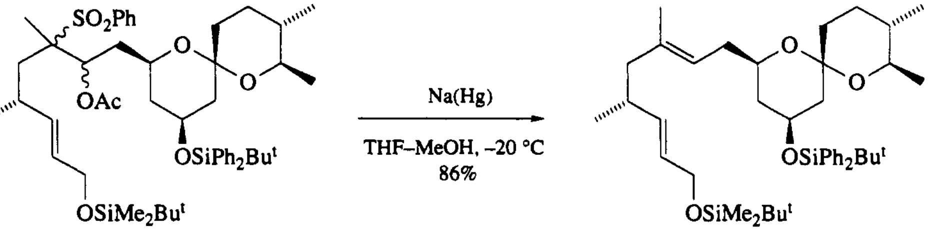
SO2Ph
OAc
O
O
OSiPh2Bu^t
OSiMe2Bu^t
Na(Hg)
THF–MeOH, –20 °C
86%
O
O
OSiPh2Bu^t
OSiMe2Bu^t

**(91)** $E$:$Z$ = 5:3 (22)

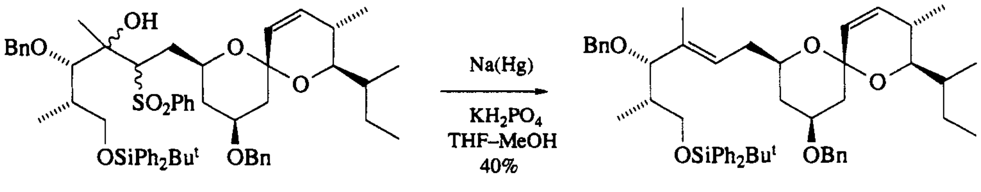
BnO
OH
SO2Ph
O
O
OSiPh2Bu^t
OBn
Na(Hg)
KH2PO4
THF–MeOH
40%
BnO
O
O
OSiPh2Bu^t
OBn

(23)

### *5.2.5.1.4 Variations*

#### *(i) Reductive elimination of 2,3-epoxy sulfones*

A three-stage synthesis of allylic alcohols has been devised (Scheme 32),[108] which consists of: (i) alkylation of a sulfone-stabilized allylic carbanion; (ii) peroxy acid oxidation of the allylic sulfone to give a 2,3-epoxy sulfone; and (iii) reductive elimination of the 2,3-epoxy sulfone to give the allylic alcohol. The overall strategy is similar to that of the Evans–Mislow allylic alcohol synthesis based on the 2,3-sigmatropic rearrangement of allylic sulfoxides.[109] However, there are regiochemical advantages to the sulfone-based method exemplified by comparing the alkylation of (**92**) (*n*-hexyl bromide, 96% yield, exclusive α-alkylation) with the corresponding sulfoxide (*n*-hexyl iodide, 42% yield, α:γ = 2:5).[110]

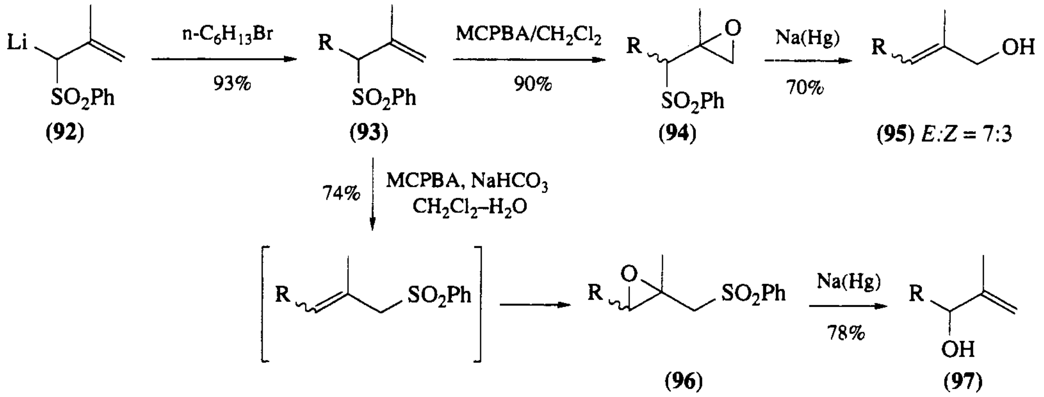

**Scheme 32**

A disadvantage of this procedure is that reductive cleavage of the epoxy sulfones leading to trisubstituted alkenes, *e.g.* (**95**), is not stereoselective. However, formation of disubsituted alkenes follows the trends found in the standard Julia alkenation in that *trans*-alkenes are favored (equation 24) and proximate branching increases the stereoselectivity (equation 25). Unlike the standard Julia alkenation, the stereochemistry of the epoxy sulfone reductive elimination depends on the stereochemistry of the precursor.[111]

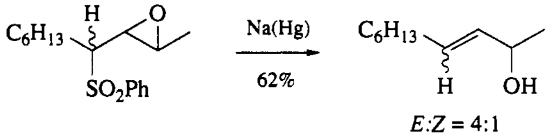

(24)

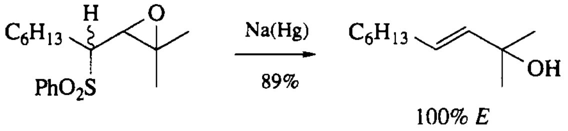

(25)

The scope of the sulfone-based allylic alcohol synthesis is enhanced by the discovery that certain allylic sulfones undergo a 1,3-rearrangement, caused by *m*-chloroperbenzoic acid and $NaHCO_3$ in aqueous dichloromethane. Under these conditions epoxidation of the allylic sulfone (**93**; Scheme 32) gave the rearranged epoxy sulfone (**96**) in 79% yield. Subsequent reductive elimination of (**96**) gave the regioisomeric allylic alcohol (**97**). A radical chain mechanism has been proposed for the rearrangement, which is restricted to those allylic sulfones in which the arylsulfonyl group can migrate from a more- to a less-substituted carbon.

### *(ii) Radical-mediated reductive elimination*

The greatest drawback to the Julia alkenation is the inherent limitation in scale imposed by the use of Na(Hg) as the reducing agent and the inconvenient temperature used in the reductive elimination step. A potential solution to the problem of scale has been provided by Lythgoe and Waterhouse,[112] who reported that thiocarbonyl derivatives of β-hydroxy sulfones undergo reductive elimination at elevated temperature on treatment with $Bu_3SnH$. The reductive elimination of the xanthate derivative (**98**; equation 26) illustrates the value of the reaction in the elaboration of the side chain of pseudomonic acid[113] — a problem which has resisted efficient solution using standard Wittig or Julia methodology. The principal impediment to the use of the reaction in the synthesis of conjugated alkenes is the ease with which allylic xanthates undergo 3,3-sigmatropic rearrangement to dithiocarbonates.[114,115]

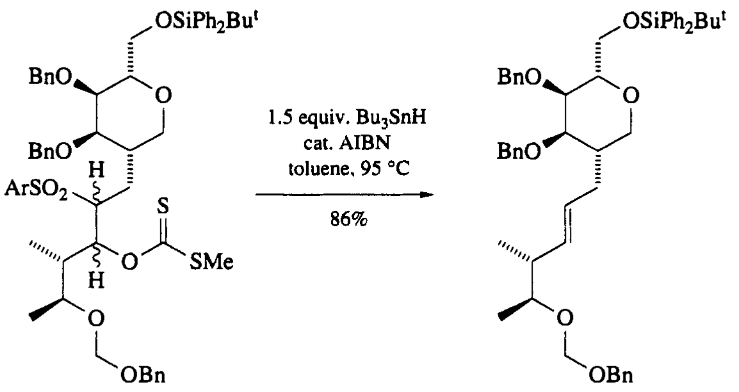

**(98)**

$E$:$Z$ = 85:15

(26)

*(iii) Reductive elimination of β-hydroxy sulfoximines*

Sulfoximines are N-analogs of sulfones and their β-hydroxy derivatives, which are less prone to retroaldolization, undergo reductive elimination on treatment with Al(Hg) in aqueous THF containing some acetic acid. The reaction takes place at room temperature or below. Despite these marked advantages, the sulfoximine modification of the Julia alkenation has not found wide acceptance, primarily because the sulfoximines are less readily available and less robust than the corresponding sulfones. Furthermore, the reductive eliminations of β-hydroxysulfoximines tend to be less *trans* stereoselective than the sulfone-based reactions and the stereochemistry of the product is influenced by the stereochemistry of the starting β-hydroxysulfoximine.[116] However, in certain instances the reaction has provided a useful alternative method for introducing a methylene in sterically demanding environments, as illustrated in the transformations depicted in Scheme 33, which were used in a synthesis of the alkaloids picrotoxinin and coriamyrtin.[117] Similar transformations were used in a synthesis of a thromboxane $A_2$ agonist.[118] The chromatographic resolution of optically active β-hydroxysulfoximines has resulted in methodology which leads to ketone methylenation and resolution.[116]

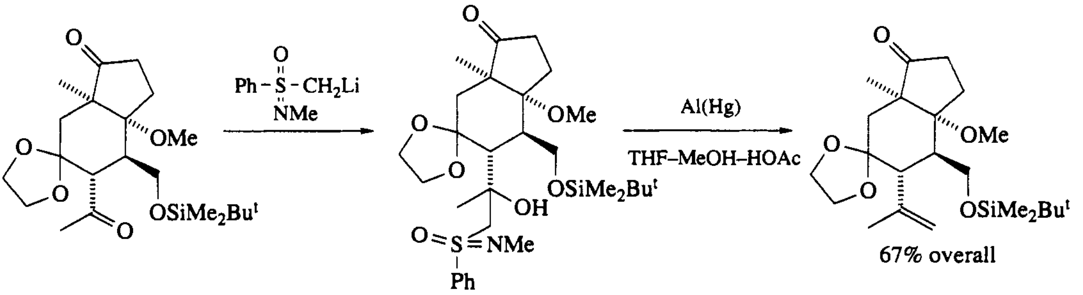

**Scheme 33**

*(iv) Reductive elimination of β-arylsulfonyl enol esters*

A connective synthesis of alkynes inspired by the Julia alkenation was developed by Lythgoe and coworkers for the synthesis of 1α-hydroxyvitamin $D_3$,[90,119] as shown in Scheme 34. The β-keto sulfone (**101**) derived by condensation of the the metalated sulfone (**99**) with the ester (**100**) was converted to the enol phosphate (**102**), which on reductive elimination gave the enynene (**103**).

The precise conditions for the reductive elimination are important. Use of Na(Hg) in THF–MeOH[95] or THF alone gives messy reactions, owing to substantial cleavage of the P—O bond of the enol phosphate but this can be avoided with Na(Hg) in THF–DMSO. Alternatively, Na in liquid ammonia can be used to effect the reductive elimination but the reaction must be very carefully controlled in order to avoid reduction of the alkyne to a *trans*-alkene.[120] A deliberate over-reduction of the initial alkyne product to an alkene was used in a synthesis of the intermediate (**104**) in a synthesis of brefeldin (Scheme 35).[121]

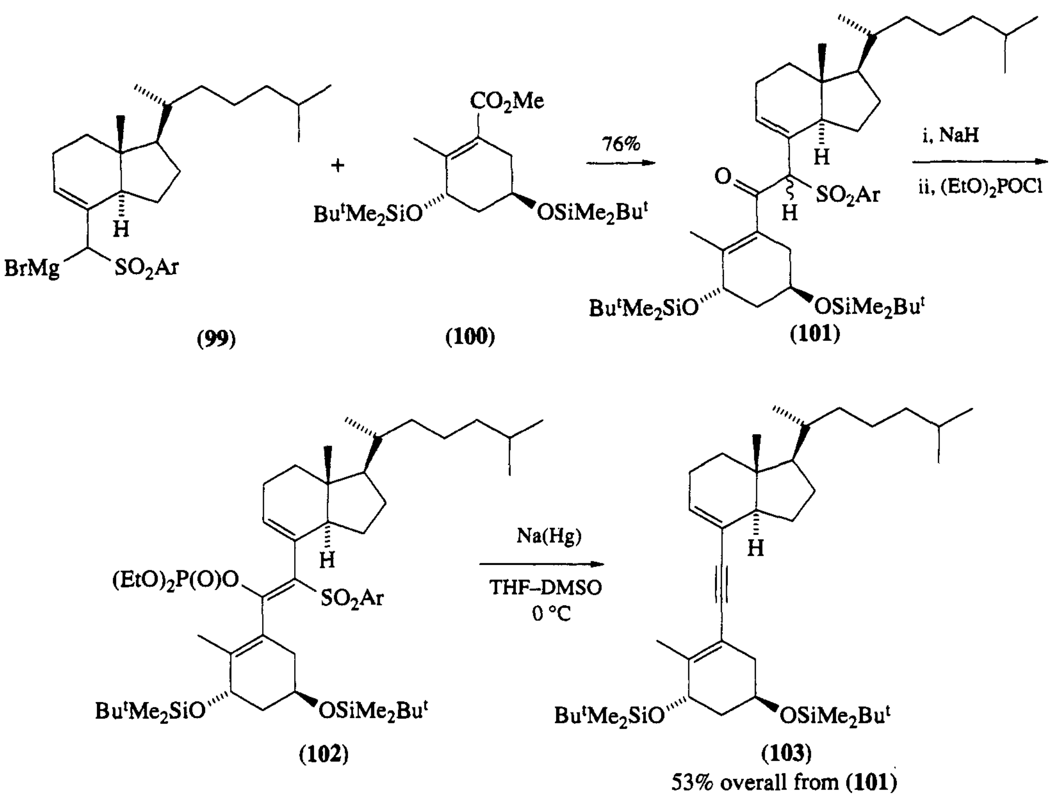
BrMg
SO2Ar
H
(99)
+
CO2Me
Bu'Me2SiO
OSiMe2Bu'
(100)
76%
O
H
SO2Ar
H
(101)
i, NaH
ii, (EtO)2POCl
(EtO)2P(O)O
SO2Ar
(102)
Na(Hg)
THF–DMSO
0 °C
(103)
53% overall from (101)

Scheme 34

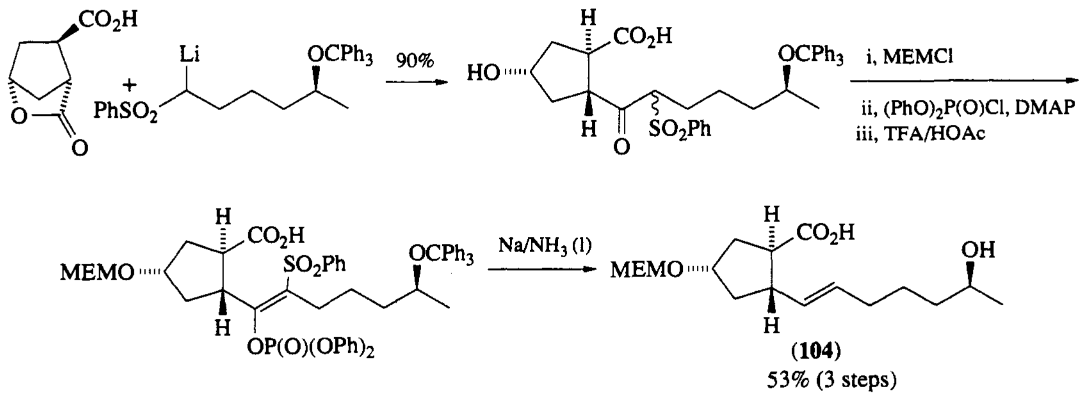
CO2H
O
O
+
Li
PhSO2
OCPh3
90%
HO
H
CO2H
H
O
SO2Ph
OCPh3
i, MEMCl
ii, (PhO)2P(O)Cl, DMAP
iii, TFA/HOAc
MEMO
H
CO2H
SO2Ph
OCPh3
H
OP(O)(OPh)2
Na/NH3 (l)
MEMO
H
CO2H
OH
H
(104)
53% (3 steps)

Scheme 35

### (v) *Reductive elimination of 1,2-disulfones*

A new method for introducing an ethylenic bridge *via* a cycloaddition reaction makes use of either (*Z*)-1,2-di(phenylsulfonyl)ethylene (**105**) or the less reactive (*E*)-isomer as synthetic equivalents of acetylene.[122] The high activation due to the two sulfonyl groups promotes cycloaddition even to very unreactive dienes. The removal of the two sulfonyl groups for the required formation of the carbon–carbon double bond is achieved by reduction at room temperature with Na(Hg) in methanol buffered with $NaH_2PO_4$[123] or Mg in MeOH at 50 °C.[124] These properties, associated with the stability of the reagents and the ease of performance of the reactions, make this method a very useful synthetic tool for the preparation of polycyclic dienes and a valid alternative to the commonly available reagents that largely depend upon oxidative methods.

The synthesis of the diene (**107**) from the quadricyclane cycloadduct (**106**) reflects the value of the method (Scheme 36).

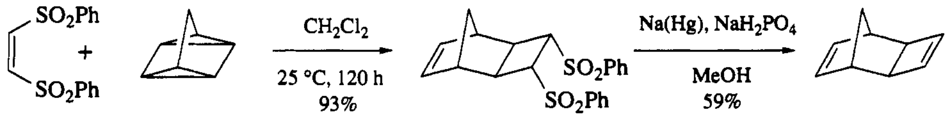

**(105)** **(106)** **(107)**

**Scheme 36**

### 5.2.5.2 Reductive Elimination of β-Substituted Nitroalkanes

The anions of nitroalkanes (nitronates) can be used as precursors in a connective and regiospecific synthesis of tetrasubstituted alkenes. They are easily formed on reaction with LiOMe and undergo oxidative dimerization in the presence of bromine.[125] The resultant 1,2-dinitroalkanes (Scheme 37) participate in a reductive elimination involving an $E_{RC}1$ radical chain mechanism when irradiated in the presence of $Na_2S$, PhSNa or the lithium nitronate derived from 2-nitropropane.

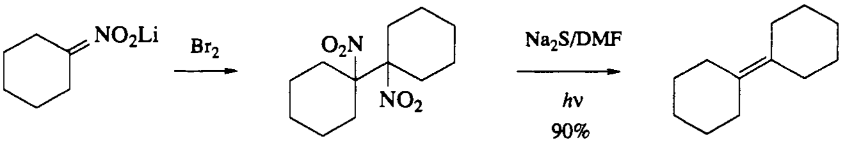

**Scheme 37**

An alternative procedure (Scheme 38) affords a connective synthesis of unsymmetrical tetrasubstituted alkenes.[126] In this case the lithium nitronate reacted with a 1,1-dinitroalkane to give the 1,2-dinitroalkane intermediate. Reductive elimination was effected by Ca(Hg) in DMF–HMPA.

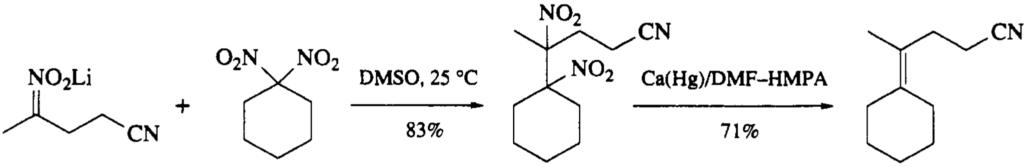

**Scheme 38**

The power of the nitroalkane coupling procedure was exploited by Vasella and coworkers[127] in order to fuse two furanose derivatives to form the unique enediol ether (**111**). Coupling of the lithiated nitrofuranose (**108**) with the 1-nitrofuranosyl bromide (**109**) took place on irradiation to afford the dinitrododecadiulose derivative (**110**), which then underwent reductive elimination on treatment with $Na_2S$.

A major drawback to the 1,2-dinitroalkane approach to tetrasubstituted alkenes is its poor stereoselectivity. Thus treatment of the *erythro*- and *threo*-1,2-dinitroalkanes (**112** and **113**; Scheme 40) respectively with $Bu_3SnH$ in refluxing benzene gave the alkene as a 1:1 mixture of isomers.[128] By contrast, the reductive elimination of certain β-nitro sulfones is stereospecific because the elimination of the radical intermediate is faster than bond rotation. For example, treatment of the β-nitro sulfones (**114**) and (**116**) with $Bu_3SnH$ gave the alkenes (**115**) and (**117**) with high efficiency and stereoselectivity (equations 27 and 28).

The synthesis of the requisite β-nitro sulfones is accomplished by reacting a carbanion stabilized with a cyano and arylsulfonyl group with a 1-bromonitroalkane, as shown in equation (29).[129] Carbanions stabilized by one arylsulfonyl group or by an arylsulfonyl and nitro group do not react.

β-Phenylsulfonylnitroethylene (**118**) has been used as an alkyne equivalent in cycloaddition reactions because the cycloadducts undergo reductive elimination to the alkene (Scheme 41).[130]

## 5.2.6 VICINAL DESILYLATION

The formation of an Si—F bond (142 kcal $mol^{-1}$; 1 cal = 4.18 J) is a highly exothermic process, which provides the driving force for a number of synthetically useful reactions. Fluoride initially attacks an empty 3*d*-orbital of silicon to form a pentacoordinate siliconate species. In molecules containing a leav-

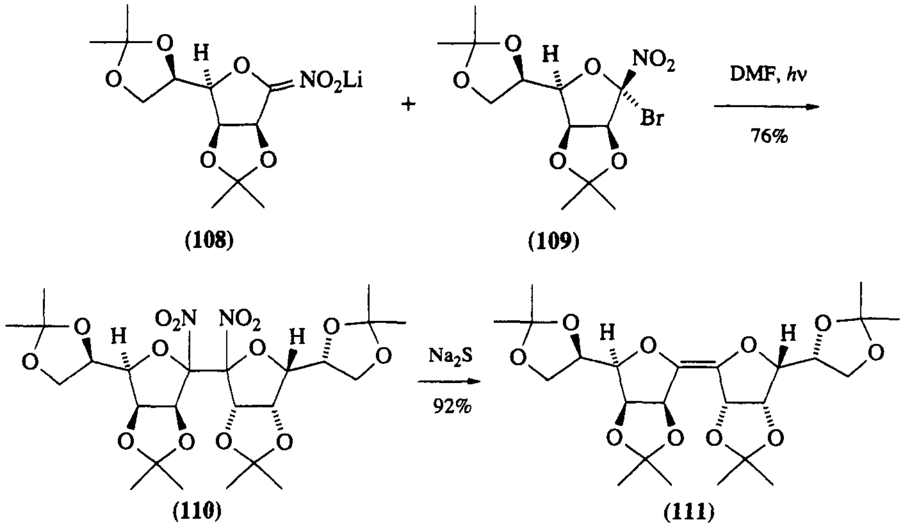
$NO_2Li$
+
$NO_2$
Br
DMF, hv
76%
(108)
(109)
$O_2N$
$NO_2$
$Na_2S$
92%
(110)
(111)

**Scheme 39**

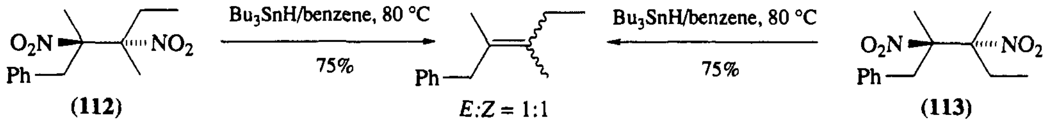
$Bu_3SnH$/benzene, 80 °C
75%
$Bu_3SnH$/benzene, 80 °C
75%
$O_2N$
$NO_2$
Ph
(112)
(113)
E:Z = 1:1

**Scheme 40**

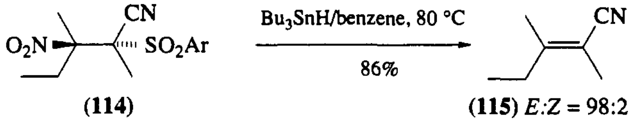
$O_2N$
CN
$SO_2Ar$
$Bu_3SnH$/benzene, 80 °C
86%
(114)
(115) E:Z = 98:2

(27)

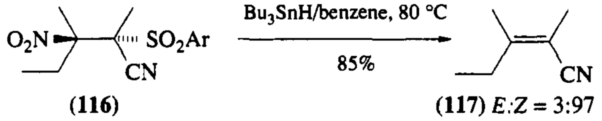
$O_2N$
$SO_2Ar$
CN
$Bu_3SnH$/benzene, 80 °C
85%
(116)
(117) E:Z = 3:97

(28)

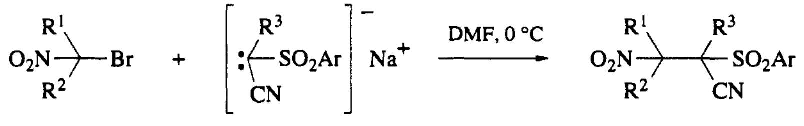
$R^1$
$O_2N$
Br
$R^2$
+
$R^3$
$SO_2Ar$
CN
$Na^+$
DMF, 0 °C

(29)

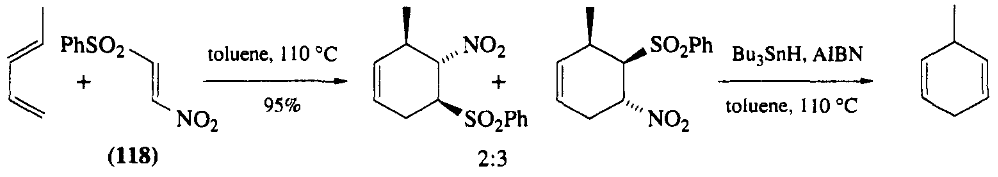
$PhSO_2$
+
$NO_2$
(118)
toluene, 110 °C
95%
$NO_2$
+
$SO_2Ph$
$SO_2Ph$
$NO_2$
2:3
$Bu_3SnH$, AIBN
toluene, 110 °C

**Scheme 41**

ing group β to the siliconate, elimination takes place to generate an alkene. Among the leaving groups which have proved effective are arylsulfonyl, halide, ester, trialkylammonium and ether groups. A brief review of the fluoride-induced 1,2-, 1,4- and 1,6-elimination of silanes has appeared.[131]

### 5.2.6.1 β-Silyl Sulfones

The fluoride-induced elimination of β-trimethylsilyl sulfones to give terminal alkenes was first reported in 1979.[132] The β-silyl sulfone (**120**; Scheme 42), prepared by the alkylation of the readily available crystalline sulfone (**119**), undergoes elimination on warming with TBAF in THF to give 1-decene in 80% yield. A second alkylation–elimination sequence can then be performed to give a 1,1-dialkylethylene derivative (**121**). Thus, the sulfone (**119**) may serve as a synthon for $CH_2{=}CH^-$ or $CH_2{=}C^{2-}$ in which the alkene is liberated under specific and mild conditions. Scheme 43 illustrates an application of the β-silyl sulfone elimination to the introduction of the C-11 methylene of moenocinol (**122**).[77]

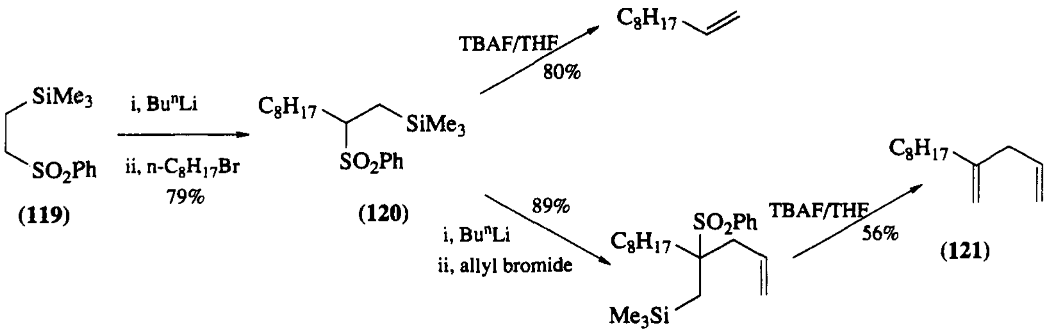

Scheme 42

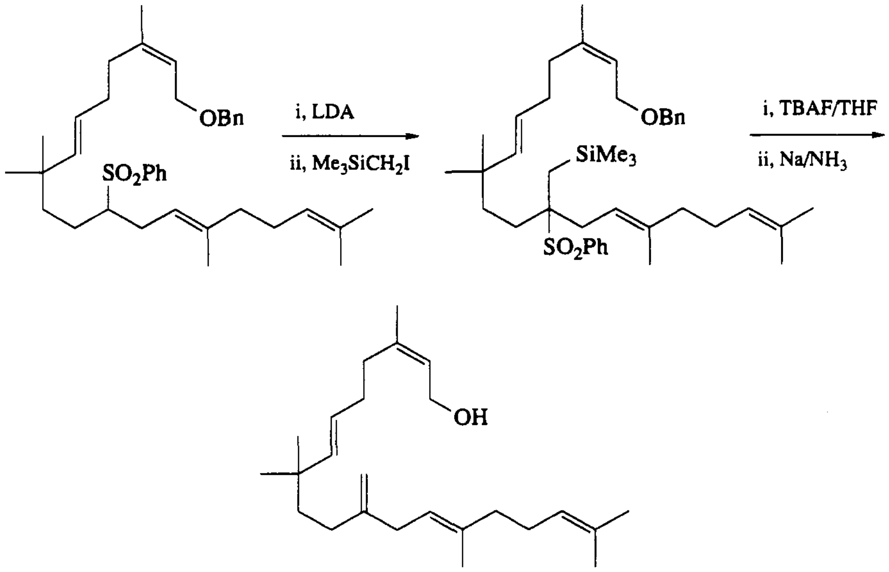

(**122**) 40% overall

Scheme 43

A major detraction to the β-silyl sulfone route to alkenes is its narrow scope, owing to the paucity of methods for preparing the requisite β-silyl sulfones. The method has so far been largely restricted to monosubstituted and 1,1-disubstituted ethylene derivatives because the β-silyl sulfones have usually been most conveniently and economically prepared by the alkylation of a sulfone anion with iodomethyltrimethylsilane. Unfortunately higher haloalkylsilanes are difficult to prepare and their alkylation chemistry remains unexplored.

Sammes and coworkers[133] devised a promising solution to the synthesis of substituted β-silyl sulfones, which has been exploited in a new approach to the antibiotic bicyclomycin (Scheme 44). In their approach the β-silyl sulfone (**125**) was prepared by conjugate addition of the lithium enolate of the monoimino ether derivative (**123**) of a dioxopiperazine to the unsaturated β-silyl sulfone (**124**). After oxidative cyclization to the bicyclic system (**126**), the latent alkene functionality was unleashed in 89% yield on treatment with TBAF in THF at room temperature to give the basic skeleton of bicyclomycin.

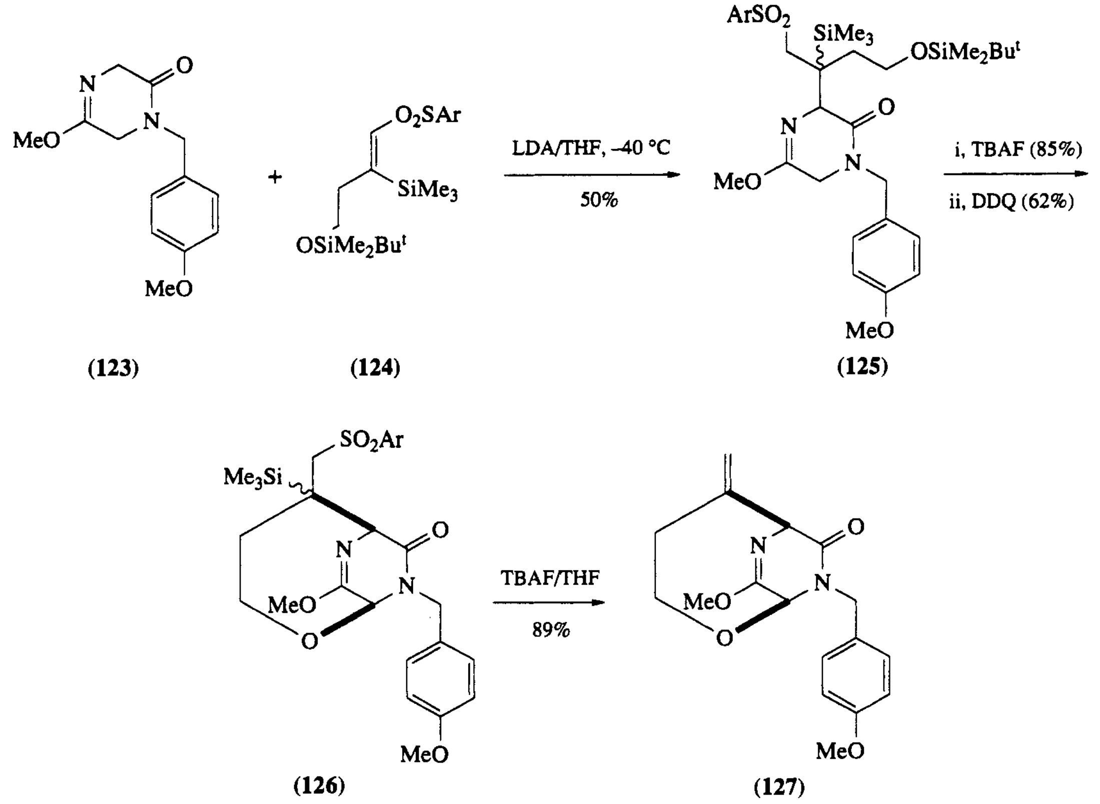
MeO
N
O
N
MeO
(123)
+
O2SAr
SiMe3
OSiMe2Bu^t
(124)
LDA/THF, –40 °C
50%
ArSO2
SiMe3
OSiMe2Bu^t
(125)
i, TBAF (85%)
ii, DDQ (62%)
SO2Ar
Me3Si
(126)
TBAF/THF
89%
(127)

Scheme 44

(*E*)-1-Trimethylsilyl-2-phenylsulfonylethylene (**128**) has been exploited as an alkyne equivalent since it undergoes Diels–Alder cycloadditions with relatively reactive dienes to give β-silyl sulfones, which can then be eliminated to the alkene (Scheme 45).[134] However, (**128**) is a poorer dienophile than the 1,2-disulfone (**105**) but it has the advantage that the α-position of the sulfone in the cycloadduct can be alkylated prior to fluoride-induced elimination.

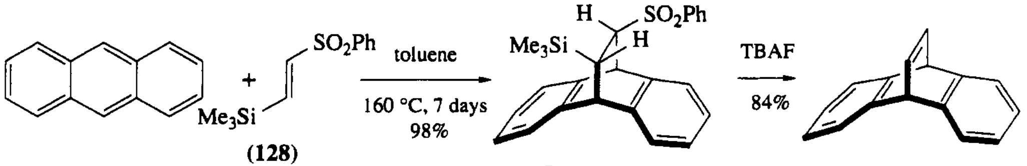
+
SO2Ph
Me3Si
(128)
toluene
160 °C, 7 days
98%
H
SO2Ph
Me3Si
H
TBAF
84%

Scheme 45

A fluoride-induced 1,4-elimination reaction illustrates the use of 1-trimethylsilyl-4-phenylsulfonyl-2-butene (**129**) as a synthon for a butadiene anion (Scheme 46).[135] The elimination is stereoselective, giving the (*E*)-diene (**130**) exclusively.

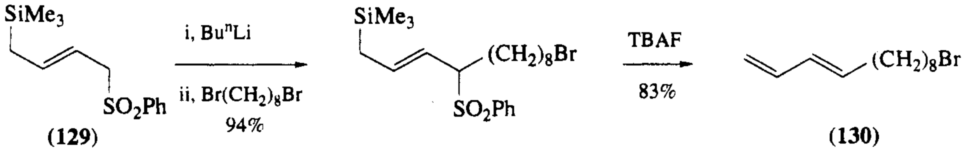
SiMe3
SO2Ph
(129)
i, Bu^nLi
ii, Br(CH2)8Br
94%
SiMe3
(CH2)8Br
SO2Ph
TBAF
83%
(CH2)8Br
(130)

Scheme 46

Fluoride also has a high affinity for tin and the analogous β-stannyl sulfone elimination is an efficient and fast reaction.[136] The requisite β-stannyl sulfones are prepared by alkylation of the sulfone anions as in the silicon case; however, the iodoalkylstannanes react faster [relative rate order $Me_3SiCH_2I$ (1),

$Bu_3SnCH_2I$ (600), $Me_3SnCH_2I$ and $Bu^nI$ (10 000). Fluoride-induced elimination takes place at 0 °C in less than 5 minutes (Scheme 47). Nitrile anions alkylate even faster than sulfones with $Bu_3SnCH_2I$, but the subsequent elimination requires MeLi. Both reactions proceed in good yield (Scheme 48).[137] Silica gel is also effective in causing elimination of β-trialkylstannyl sulfones to alkenes.[138]

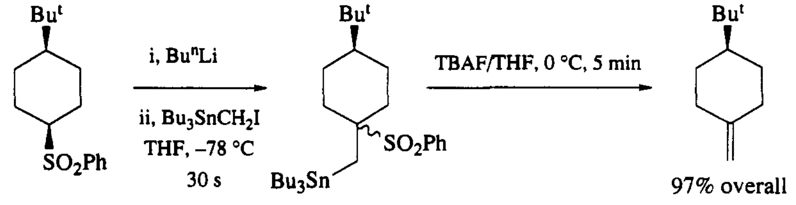
Bu<sup>t</sup>
SO2Ph
i, BunLi
ii, Bu3SnCH2I
THF, –78 °C
30 s
Bu3Sn
SO2Ph
TBAF/THF, 0 °C, 5 min
97% overall

Scheme 47

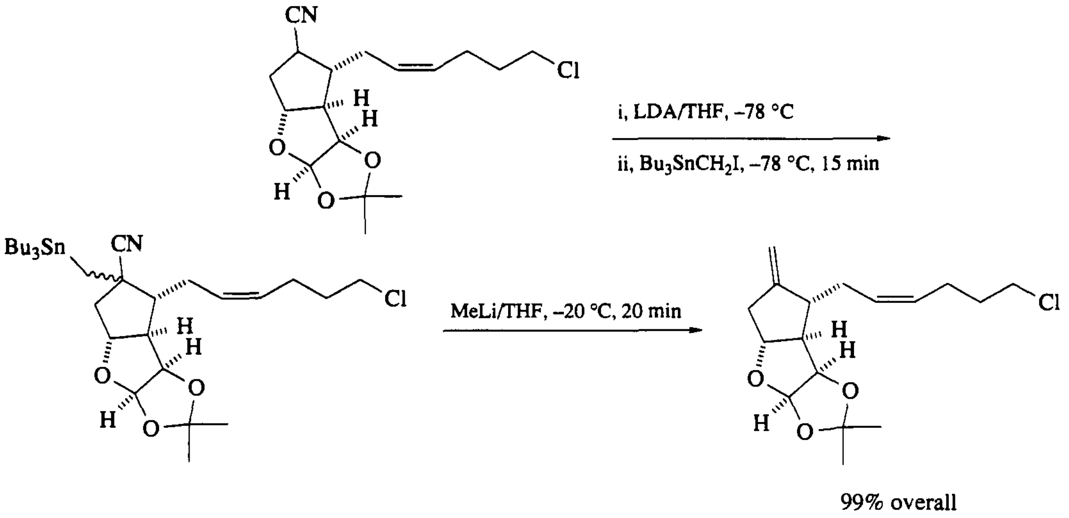
CN
Cl
H
H
O
O
H
O
i, LDA/THF, –78 °C
ii, Bu3SnCH2I, –78 °C, 15 min
Bu3Sn
CN
MeLi/THF, –20 °C, 20 min
99% overall

Scheme 48

## 5.2.6.2 β-Silylhaloalkanes

The fluoride-induced fragmentation of β-silylhaloalkanes is a clean and efficient reaction which has been limited by the relative inaccessibility of the starting material. Fleming and Goldhill[139] have exploited the easy introduction of a bromine atom α to a ketone as a means for introducing unsaturation adjacent to a ketone function in a regiocontrolled fashion. Scheme 49 shows how the β-silylketone (**131**) serves as a masked version of the enone (**133**). The regioselectivity of the kinetically controlled bromination reaction is noteworthy. In all the examples studied there is a bias in favor of the side of the ketone on which the silyl group is placed, regardless of the level of substitution at that site. Thus bromination of (**131**) gave a 65% yield of the desired bromo ketone (**132**) along with a further 15% of the regioisomer. This is surprising since a trimethylsilyl group is both bulky and a π-electron-donating substituent, and would on both counts be expected to deter enolization towards itself, yet the opposite is actually the case. The desilylbromination can be achieved with NaF in aqueous ethanol, as illustrated, or with benzyltrimethylammonium fluoride (BTAF) in THF. These transformations can also be adapted to the synthesis of α-methylenelactones.

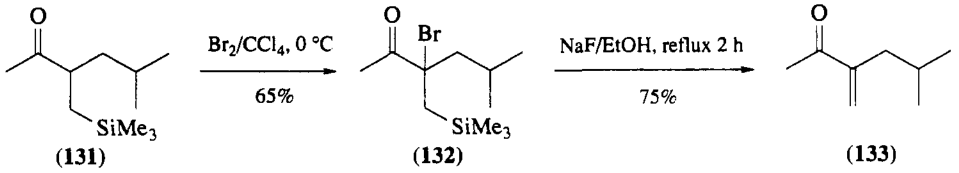
O
SiMe3
(131)
Br2/CCl4, 0 °C
65%
O
Br
SiMe3
(132)
NaF/EtOH, reflux 2 h
75%
O
(133)

Scheme 49

A fluoride-induced desilylchlorination of α-chloro-β-silyl ketones has been used to prepare α-methylenecyclobutanones and α-methylenecyclopentanones (Scheme 50).[140] In this case, the requisite α-chloro-β-silylcyclobutanone precursor (**135**) was prepared by an efficient [2 + 2] cycloaddition of chloro[(trimethylsilyl)methyl]ketene (**134**) with 3,4-dihydro-2*H*-pyran.

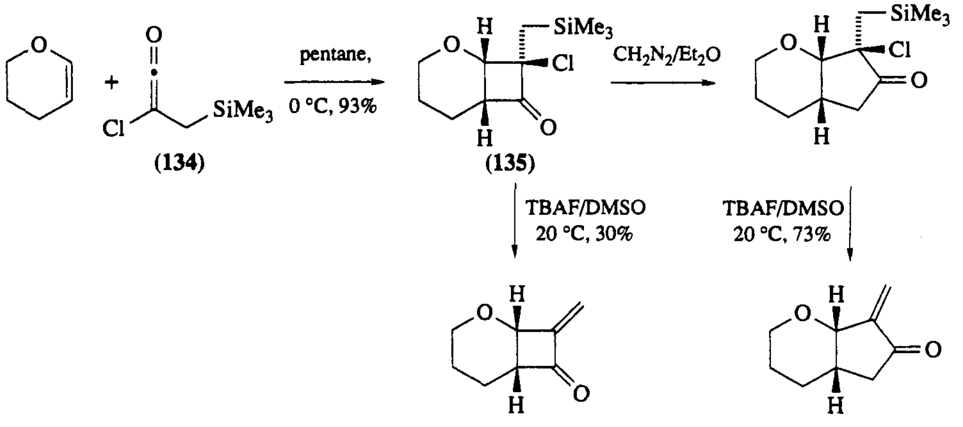

**Scheme 50**

The desilylhalogenation reaction has been used to good effect in the preparation of highly reactive alkenes since the alkali metal or tetraalkylammonium fluorides used to induce the reaction and the fluorosilane by-products are largely inert. For example, the bridgehead alkene (**137**) was generated as a reactive intermediate from the desilylbromination of the β-silyl bromide (**136**) using BTAF in THF (equation 30).[141] Similarly, the highly reactive allene oxide (**139**) was generated from the β-silyl chloride (**138**; equation 31) on treatment with CsF and the product isolated by blowing a stream of $N_2$ through the reaction mixture.[142] Other allene oxides with less bulky substituents are too reactive to be isolated but they have been generated as transient intermediates by the same procedure. Heterolysis of the allene oxide moiety leads to an oxyallyl 1,3-dipole which can be trapped by 1,3-dipolar cycloaddition (Scheme 51)[143] or, in special cases, rearrange to an isolable cyclopropanone.

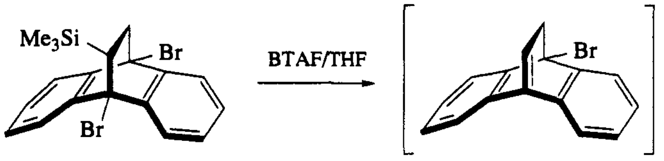

(**136**) (**137**) (30)

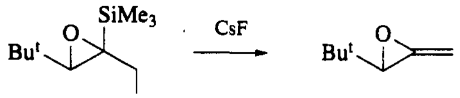

(**138**) (**139**) (31)

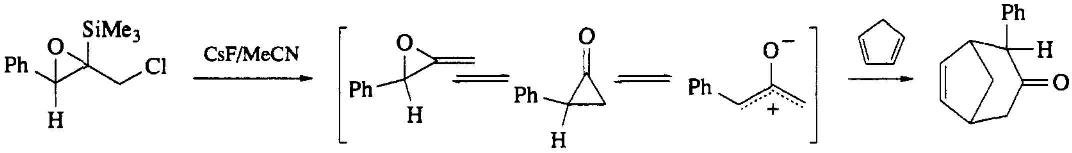

**Scheme 51**

### 5.2.6.3 β-Silyl Esters and Ethers

The efficiency and specificity of the fragmentation of β-silyl-substituted derivatives have great value in the design of new protecting groups[144] — a subject treated in greater detail in part 3 of this volume. Carboxylic acids, for example, are easily protected as their 2-(trimethylsilyl)ethyl esters, which are about as stable as ethyl esters under most reaction conditions. However, on treatment with TBAF they fragment to give $Me_3SiF$, ethylene and the tetrabutylammonium salt of the acid. The conditions for the deprotection are sufficiently mild for amino acids to be liberated without racemization. Equation (32) gives an example of the generation of a highly unstable carboxylic acid salt using this method[145] and equation (33) illustrates the chemospecific liberation and subsequent reaction of a carboxylic acid intermediate in the presence of an ester function.[146]

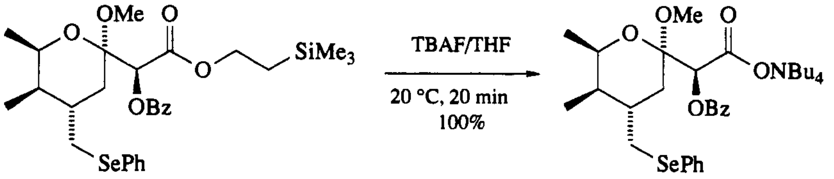
OMe
O
O
O
SiMe3
OBz
SePh
TBAF/THF
20 °C, 20 min
100%
OMe
O
O
ONBu4
OBz
SePh

(32)

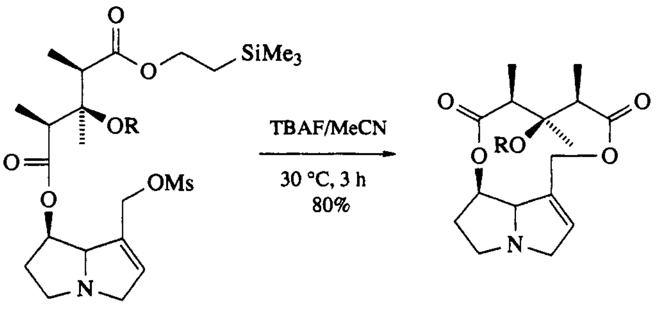
O
O
SiMe3
OR
O
O
OMs
N
TBAF/MeCN
30 °C, 3 h
80%
O
O
RO
O
O
N

(33)

Primary, secondary and tertiary alcohols can be protected in good yield as their 2-(trimethylsilyl)ethoxymethyl ethers (abbreviated SEM ethers) by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in dichloromethane in the presence of $Pr^i_2NEt$.[147] The resultant ethers are stable to the conditions used to remove THP and TMS ethers (3:1:1 THF:HOAc:$H_2O$). Deprotection takes place on treatment with TBAF in THF at 45 °C.

Fluoride-induced fragmentation reactions were used in two stages of a synthesis of hexahydrocannabinol methyl ether (**144**; Scheme 52).[148] One of the phenolic hydroxy functions in the resorcinol derivative (**140**) was selectively liberated from the SEM ether to give the diol (**141**), which was converted to the *bis* (trimethylsilyl) ether (**142**). Subsequent treatment with CsF resulted in a 1,4-elimination to the *o*-quinone methide (**143**) intermediate, which underwent an intramolecular [4 + 2] cycloaddition to give the product in good yield.

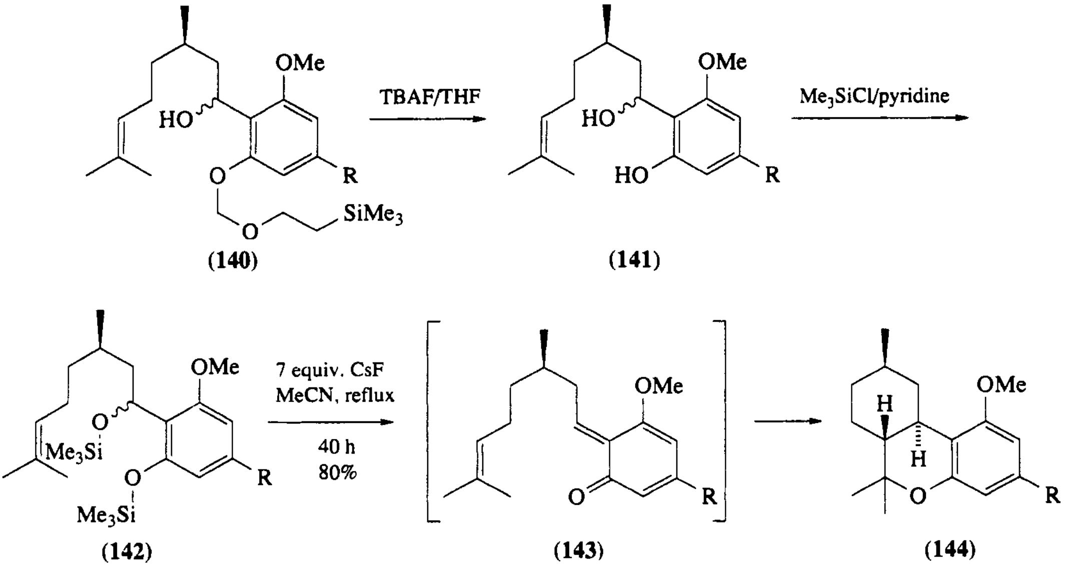
OMe
HO
O
R
O
SiMe3
(140)
TBAF/THF
OMe
HO
HO
R
(141)
Me3SiCl/pyridine
OMe
O
Me3Si
O
R
Me3Si
(142)
7 equiv. CsF
MeCN, reflux
40 h
80%
OMe
O
R
(143)
H
H
OMe
O
R
(144)

Scheme 52

### 5.2.6.4 *o*-Quinodimethanes *via* 1,4-Fragmentation

This last section deals with the generation of *o*-quinodimethanes using fluoride-induced fragmentation reactions. Strictly speaking these are not vicinal desilylations but they bear a close affinity to the reactions discussed above.

Ito and coworkers[149] developed a mild and efficient procedure for generating *o*-quinodimethanes[11] as reactive intermediates in [4 + 2] cycloadditions. The key step in the sequence, illustrated here by the synthesis of Estrone methyl ether (**146**; Scheme 53) involves a fluoride-induced fragmentation of the *o*-[α-(trimethylsilyl)alkyl]benzyltrimethylammonium iodide (**144**) to give the *o*-quinodimethane (**145**), which underwent stereoselective intramolecular [4 + 2] cycloaddition to give the desired tetracyclic framework in (**146**). The entire process was conducted at room temperature. The annulation reaction is not limited to intramolecular cycloadditions; intermolecular versions of the reaction proceed equally well.

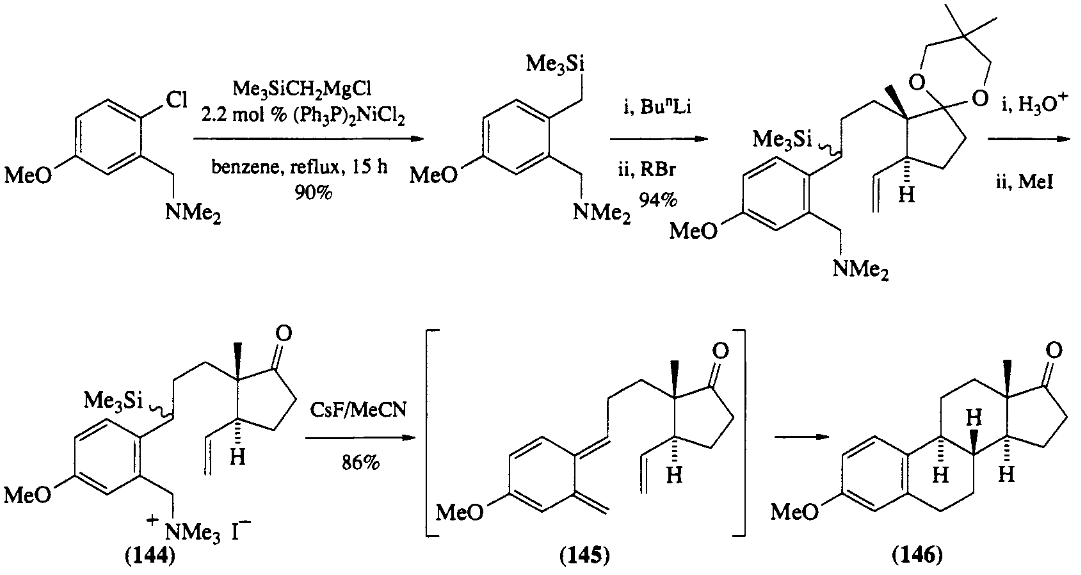
MeO
Cl
NMe2
Me3SiCH2MgCl
2.2 mol % (Ph3P)2NiCl2
benzene, reflux, 15 h
90%
Me3Si
MeO
NMe2
i, BunLi
ii, RBr
94%
Me3Si
O
O
MeO
NMe2
H
i, H3O+
ii, MeI
Me3Si
O
H
MeO
+ NMe3 I−
(144)
CsF/MeCN
86%
O
MeO
H
(145)
O
H
H
H
MeO
(146)

**Scheme 53**

Contemporaneous with the work of Ito was a synthesis of 11-α-hydroxyestrone methyl ether (**148**) by Magnus and coworkers (Scheme 54)[150] in which the requisite *o*-quinodimethane intermediate was generated by the fragmentation of the *o*-[(trimethylsilyl)methyl]aryl oxirane derivative (**147**) using CsF.

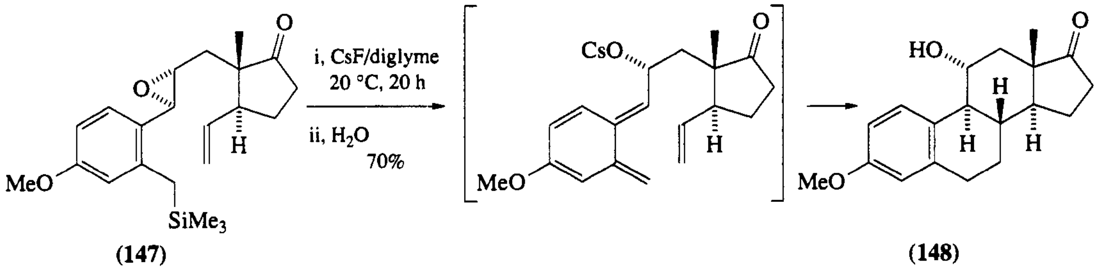
O
O
H
MeO
SiMe3
(147)
i, CsF/diglyme
20 °C, 20 h
ii, H2O
70%
CsO
O
H
MeO
HO
O
H
H
H
MeO
(148)

**Scheme 54**

The synthesis of *O*-quinodimethanes has recently been reviewed.[151]

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# 5.3

# The Cope Elimination, Sulfoxide Elimination and Related Thermal Reactions

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## 5.3.1 INTRODUCTION

This chapter is concerned with a group of thermally induced elimination reactions widely used for the introduction of carbon–carbon double bonds into complex molecules. These reactions form a discrete group of elimination reactions in that they proceed with *syn* stereochemistry *via* concerted cyclic transition states.[1,2] Related *syn* elimination processes are believed to be involved in other elimination reactions, *e.g.* alcohol dehydration using the Burgess reagent,[3] but are not discussed here. One of the advantages of the *syn* elimination reactions discussed in this chapter is that they do not require the use of strongly acidic or basic reagents; they are simply carried out by heating the substrate to the required temperature.

## 5.3.2 COPE ELIMINATION

### 5.3.2.1 Introduction

Tertiary amine oxides fragment on heating to give an alkene and an *N,N*-dialkylhydroxylamine (*e.g.* equations 1 and 2). This reaction was studied extensively by Cope, and is commonly referred to as the 'Cope elimination'.[4]

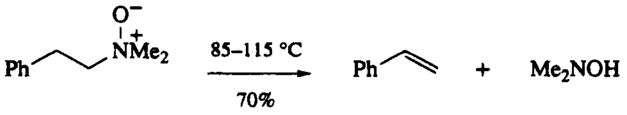

(1)

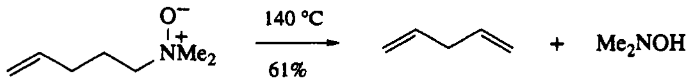

(2)

Early stereochemical evidence supported the *syn* elimination mechanism outlined in equation (3). Pyrolysis of the *erythro*-2-amino-3-phenylbutane (**1**) gave mainly the (*Z*)-alkene (**2**; equation 4), whereas the *threo* isomer (**4**) gave more of the (*E*)-alkene (**3**; equation 5).[5,6] This stereochemistry has since been confirmed by deuterium labeling, the *trans*-labeled cyclooctyldimethylamine oxide (**5**) giving *cis*-cyclooctene with no loss of label, and the *cis*-labeled isomer (**6**) giving partially labeled product (78% $d_1$, 22% $d_0$) consistent with an isotope effect of about 3.[7]

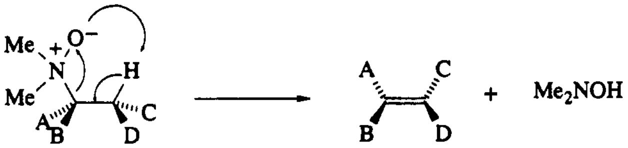

(3)

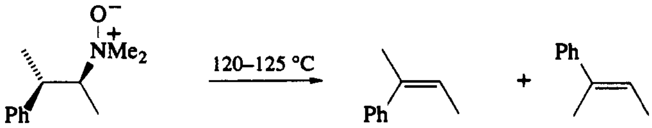

(4)

(**1**) (**2**) 95:5 (**3**)

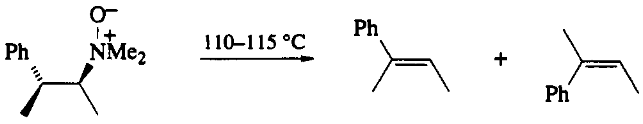

(5)

(**4**) (**3**) 99.7:0.3 (**2**)

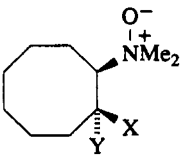

(**5**) X = H, Y =D
(**6**) X = D, Y = H

Kinetic isotope effects have been used to probe the Cope elimination mechanism in more detail. In diglyme the β-deuterium isotope effect was found to be temperature independent, consistent with a nonlinear hydrogen transfer *via* a bent cyclic transition state (**7**).[8] In contrast, a substantial temperature dependence of the β-deuterium isotope effect was found in DMSO, suggesting that a linear hydrogen transfer was involved, possibly *via* the transition state (**8**), involving a molecule of DMSO.[8,9]

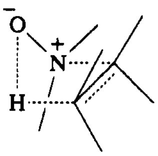

(**7**)

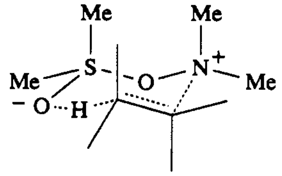

(**8**)

The observation of large $^{14}C$ isotope effects in thermal decomposition of both α- and β-($^{14}C$)-labeled (2-phenylethyl)dimethylamine oxide (**9**), together with linear free energy data, has been interpreted in terms of a transition state for elimination in which there is considerable cleavage of both the C(α)—N and C(β)—H bonds, significant carbanionic character on the β-carbon and little carbon–carbon double bond development.[10] However, the development of significant double bond character in the transition state was postulated to explain the exclusive formation of *cis*-cyclooctene from cyclooctyldimethylamine oxide.[7] This contrasts with the formation of mixtures of *cis*- and *trans*-cyclooctenes from fragmentation of the ylide generated from the quaternary ammonium salt (**10**) using strong base.[11]

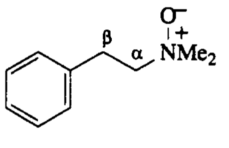

(**9**)

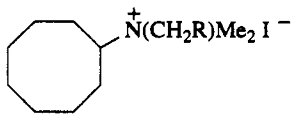

(**10**)

The Cope elimination has been used less widely than the Hofmann elimination of quaternary ammonium hydroxides, but in some cases has advantages in terms of the ease of manipulation and lack of product isomerization, *e.g.* nonconjugated alkenes can be obtained without double bond migration, as in equation (2).[4]

Tertiary amines can be converted into amine oxides using a variety of oxidizing agents, including aqueous hydrogen peroxide, peroxy acids and ozone. Often the amine oxides are not purified. Instead any excess of the oxidant is destroyed, and the amine oxide solution concentrated to leave a crude material, which is then pyrolyzed under reduced pressure with the alkene removed as it is formed.[4] Alternatively the elimination can be carried out in solution with significant rate enhancements being observed in DMSO.[6] This was originally explained in terms of increased basicity of the amine oxide in the dipolar aprotic solvent, but may be due to a change of mechanism as indicated above.[9]

### 5.3.2.2 Stereo- and Regio-chemistry

The Cope elimination has been used to synthesize a variety of acyclic alkenes. 1,2-Disubstituted acyclic alkenes are usually obtained with the (*E*)-stereochemistry because of steric hindrance to (*Z*)-alkene formation. The stereochemistry of trisubstituted alkenes is determined by the configuration of the starting amine oxide and is not usually affected by subsequent isomerization.[4]

Cyclic alkenes synthesized by the Cope elimination include small ring cycloalkenes, *e.g.* cyclobutene[12] and the thiete 1,1-dioxide (**11**; equation 6).[13] However, the Cope elimination route to the spirodiene (**12**; equation 7) was less efficient than the analogous Hofmann procedure.[14] The stereochemistry of cyclic alkenes prepared by the Cope elimination depends upon the ring size with *cis*-cycloalkenes being obtained for eight-membered and smaller rings, and *trans*-cycloalkenes being obtained for larger rings.[15]

For acyclic compounds the regioselectivity depends upon statistical factors and the relative acidities of the different β-hydrogens, the elimination preferring to take place towards the most acidic hydrogen. This can also influence the regioselectivity of elimination from alicyclic compounds, *e.g.* the α,β-unsaturated carbonyl compound (**14**) was obtained from the β-aminocarbonyl compound (**13**),[16] and the allylic alcohol (**16**) was the major product obtained on oxidation and pyrolysis of the hydroxyamine (**15**).[17]

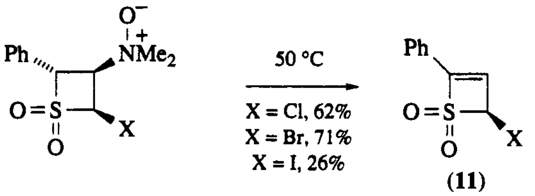
Ph
$O^-$
NMe2
O=S
O
X
50 °C
X = Cl, 62%
X = Br, 71%
X = I, 26%
Ph
O=S
O
X

(11)

(6)

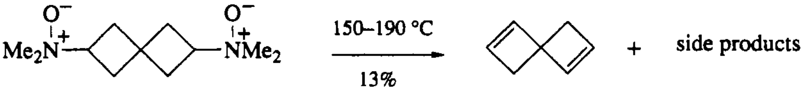
$O^-$
$Me_2N^+$
$O^-$
$NMe_2$
150–190 °C
13%
+
side products

(12)

(7)

However, for alicyclic compounds the product composition can also be controlled by the necessity of achieving a cyclic transition state. Thus whereas the dimethylmenthylamine oxide (**17**) gave a mixture of 2- and 3-menthenes (**19**) and (**20**), only the 2-isomer (**19**) was obtained from neomenthylamine oxide (**18**).[18] High regioselectivities have also been obtained from some steroidal tertiary amine oxides.[19]

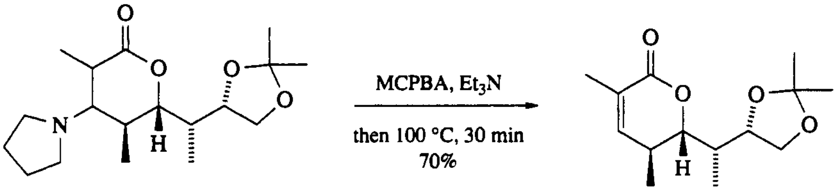
O
O
N
H
O
O
MCPBA, Et3N
then 100 °C, 30 min
70%
O
O
H
O
O

(13) (14)

(8)

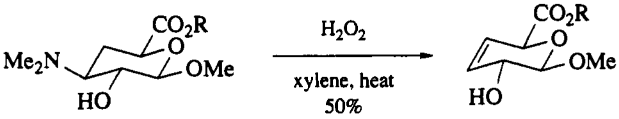
CO2R
O
Me2N
OMe
HO
H2O2
xylene, heat
50%
CO2R
O
OMe
HO

(15) (16)

(9)

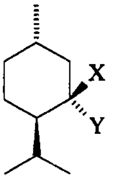

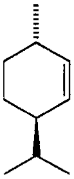

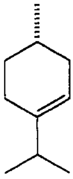

(17) X = H, Y = N(O)$Me_2$
(18) X = N(O)$Me_2$, Y = H

(19)

(20)

The preference for endo- or exo-cyclic elimination depends on the ring size. The cyclopentyl- and cycloheptyl-dimethylamine oxides (**21**; *n* = 5, 7) give more of the endocyclic alkene (**22**; *n* = 5, 7) whereas the cyclohexylamine oxide (**21**; *n* = 6) gives predominantly the exocyclic alkene (**23**; *n* = 6) because the six-membered ring has to adopt an unfavorable boat conformation in the transition state for endocyclic elimination (equation 10).[20]

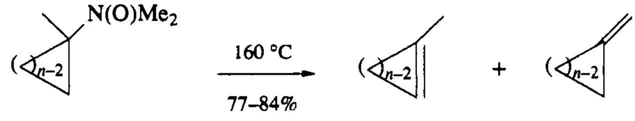
N(O)Me2
n–2
160 °C
77–84%
n–2
+
n–2

(21) (22) (23)

(10)

**Table 1** Endo- *vs.* Exo-cyclic Elimination from Amine Oxide Pyrolysis

| *Amine oxide (**21**) n* | *Endo (**22**) (%)* | *Exo (**23**) (%)* |
|---|---|---|
| 5 | 97.5 | 2.5 |
| 6 | 2.8 | 97.2 |
| 7 | 84.8 | 15.2 |

Exocyclic alkenes can also be prepared using dimethylaminomethylcycloalkanes,[21] *e.g.* pyrolysis of the trisamine oxide (**24**) gave trimethylenecyclobutane (**25**; equation 11). In this case the analogous Hofmann elimination was accompanied by double bond migration and gave dimethylene-1-methylcyclobutene (**26**).[22] Terminal double bonds can also be introduced using Cope eliminations. An example is found in the synthesis of the vinyl steroid (**27**; equation 12).[23]

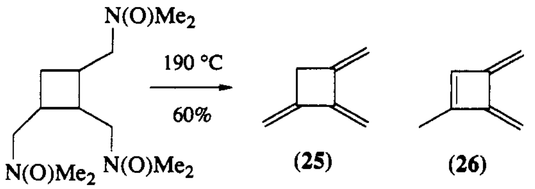

(**24**) (**25**) (**26**)

(11)

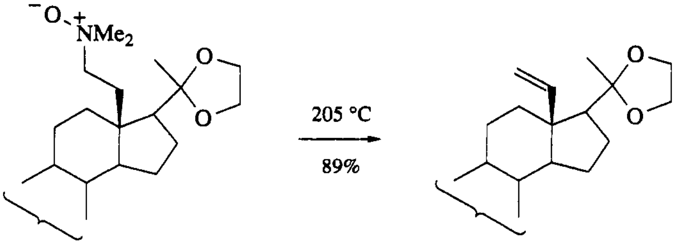

(**27**)

(12)

The success of ring-opening Cope eliminations of heterocyclic amine oxides depends upon the accessibility of the five-membered ring transition state. *N*-Methylpiperidine oxide (**28**) does not undergo ring opening even at 240 °C in a sealed tube, although the analogous seven- and eight-membered ring amines fragment at 165 °C. The α-methylamine oxide (**29**) fragments cleanly at 160–165 °C, whereas its epimer (**30**) gives no identifiable products on pyrolysis (equation 13).[24]

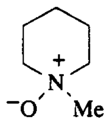

(**28**)

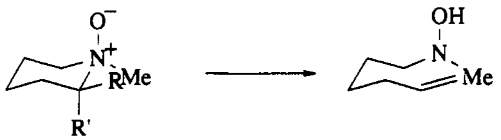

(13)

(**29**) R = Me, R' = H
(**30**) R = H, R' = Me

72% (38% after redistillation)

### 5.3.2.3 Side Reactions

The Cope elimination for alkyldimethylamine oxides is generally reliable providing the cyclic transition state can be attained. However, allylic and benzylic amine oxides undergo a competing rearrangement, the Meisenheimer rearrangement, which gives rise to *O*-substituted hydroxylamines as well as the desired alkene, *e.g.* thermolysis of the cyclooctenyldimethylamine oxide (**31**; equation 14) gives a mixture of *cis,cis*-cycloocta-1,3-diene (**32**) and the *O*-cyclooctenyl-*N*,*N*-dimethylhydroxylamine (**33**).[25] The Meisenheimer rearrangement of allylic amine oxides is believed to involve a concerted 2,3-shift,[26] whereas radical pair intermediates are involved in the rearrangement of benzylic amine oxides.[27]

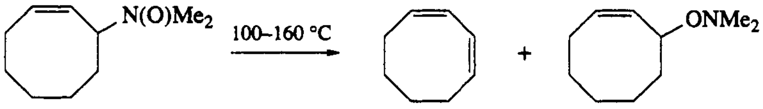

(**31**) (**32**) 50% (**33**) 19%

(14)

The Meisenheimer rearrangement can compete with the formation of highly strained alkenes. The pyrolysis of the homoadamantylamine oxide (**34**; equation 15) gave a mixture of products, including hydrocarbons believed to have been formed by dimerization of 3-homoadamantene (**36**), which was trapped by 1,3-diphenylisobenzofuran, and the Meisenheimer product (**35**).[28]

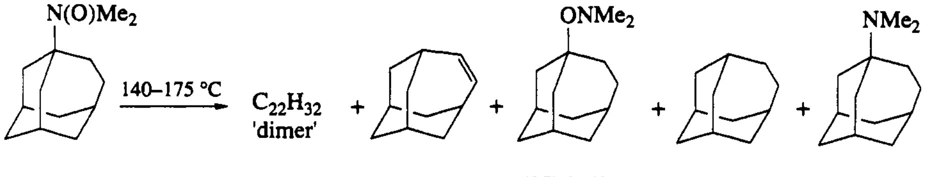

(**34**) 9% 5% (**35**) 25% 29% 12%

(15)

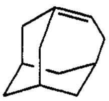

(**36**)

Normally the Cope elimination is carried out by thermolysis of the amine oxide under reduced pressure with removal of the alkene as it is formed. However, if carried out in a closed system, secondary products can be formed by oxidation of the *N*,*N*-dialkylhydroxylamine by unchanged amine oxide to form a nitrone, which then adds to the alkene (Scheme 1).[29]

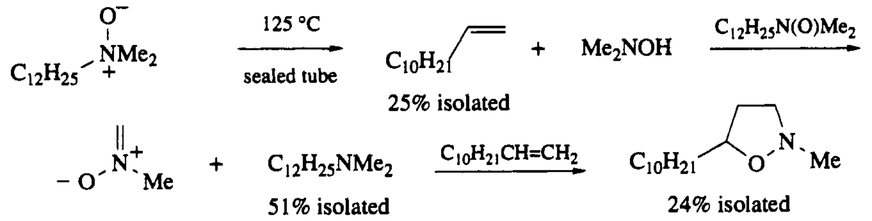

**Scheme 1**

## 5.3.3 SULFOXIDE ELIMINATION

### 5.3.3.1 Introduction

Sulfoxides fragment on heating to form alkenes and sulfenic acids. This reaction, known for over a century, has been developed into a useful alkene synthesis,[30,31] particularly for the synthesis of α,β-unsaturated carbonyl compounds as illustrated in equations (16)–(18).[32–35]

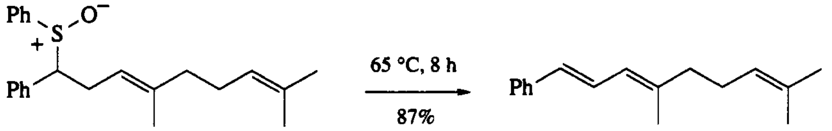
Ph
S
O⁻
+
Ph
65 °C, 8 h
87%
Ph

(16)

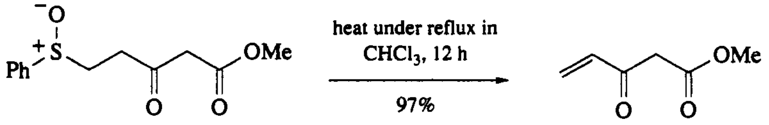
⁻O
+ S
Ph
OMe
O
O
heat under reflux in
CHCl₃, 12 h
97%
OMe
O
O

(17)

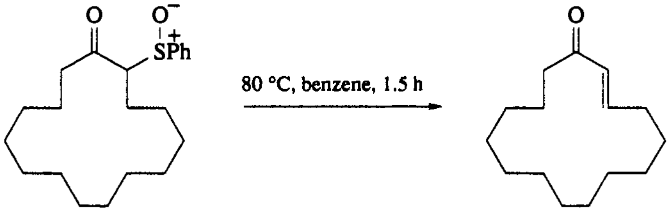
O
O⁻
+
SPh
80 °C, benzene, 1.5 h
O

(18)

The stereochemistry of trisubstituted alkene formation was demonstrated by Kingsbury and Cram who found that the *erythro*-sulfoxide (**37**) gave mainly the (*E*)-alkene (**38**; equation 19) with the (*Z*)-alkene (**40**; equation 20) being the major product from thermolysis of the *threo*-sulfoxide (**39**). The rate and stereochemistry of elimination was found to be independent of solvent, and so the concerted *syn* elimination mechanism outlined in equation (21) was proposed.[36] The variation of the β-deuterium isotope effect with temperature is consistent with a linear hydrogen transfer,[8] and the elimination has been found to be reversible, with sulfenic acids being trapped both inter- and intra-molecularly by addition to alkenes to give sulfoxides (Schemes 2 and 3).[37,38]

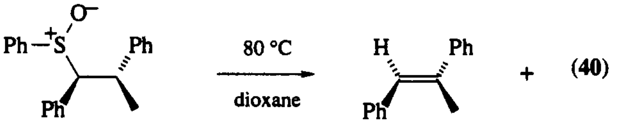
O⁻
Ph
+
S
Ph
Ph
80 °C
dioxane
H
Ph
Ph
+
(40)

**(37)** **(38)** 90:10

(19)

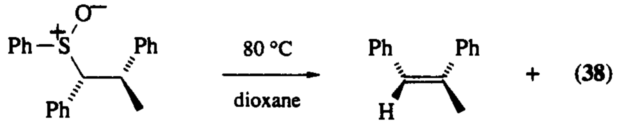
O⁻
Ph
+
S
Ph
Ph
80 °C
dioxane
Ph
Ph
H
+
(38)

**(39)** **(40)** 90:10

(20)

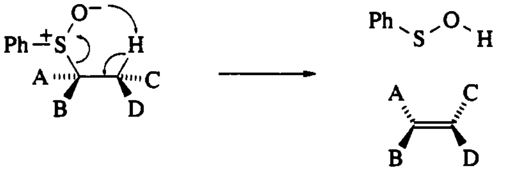
O⁻
Ph
±
S
H
A
C
B
D
Ph
S
O
H
A
C
B
D

(21)

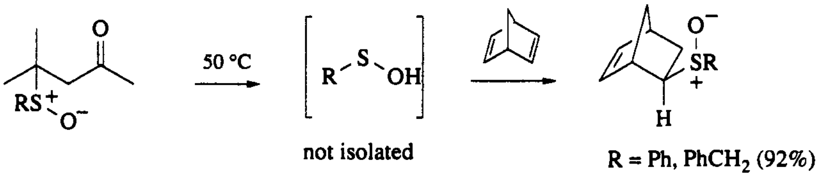
O
RS
+
O⁻
50 °C
R
S
OH
not isolated
O⁻
SR
+
H
R = Ph, PhCH₂ (92%)

**Scheme 2**

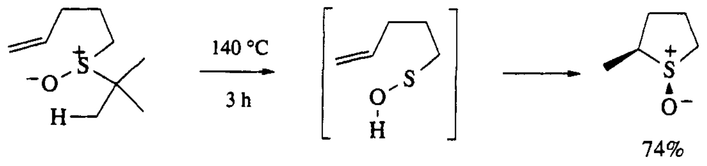

**Scheme 3**

The temperatures required for sulfoxide elimination depend upon the stability of the alkene being formed, with temperatures in the range 50–110 °C commonly used for conjugated alkenes. Phenyl sulfoxides fragment faster than the analogous methyl sulfoxides.[32] The reaction has also been used for the generation of sulfenic acids and this will be briefly discussed in Section 5.3.3.3.3.

### 5.3.3.2 Stereo- and Regio-chemistry

Acyclic 1,2-disubstituted alkenes from sulfoxide pyrolyses are obtained with the *trans* geometry because of increased torsional interaction in the transition state leading to the *cis* isomer (*e.g.* equation 22).[39] The stereochemistry of tri- and tetra-substituted alkenes is determined by the stereochemistry of the precursor sulfoxides and is predictable on the basis of the *syn* elimination mechanism. In practice the stereospecific synthesis of such alkenes is limited by the availability of isomerically pure starting materials.

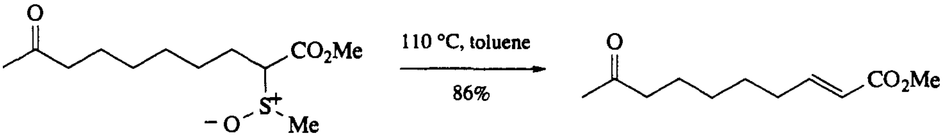 (22)

Sulfoxide fragmentation for acyclic sulfoxides takes place towards the most acidic β-hydrogen with the following order being observed in acyclic systems: $C{=}CCH_2 \approx C{\equiv}CCH_2 > ArCH_2 \approx CH_3 > CH_2 >> CH$.[32] For example, elimination of sulfoxide (**41**) takes place towards the more acidic methyl group to give the α-methylenelactone (**42**; Scheme 4) after cyclization.[40] In contrast, fragmentation of cyclic sulfoxides shows a preference for endocyclic elimination, *e.g.* thermolyses of the lactone sulfoxides (**43**)[39] and (**45**)[41] give more of the endocyclic alkenes (**44**; equation 23) and (**46**; equation 24), respectively, perhaps reflecting the increased stability of the endocyclic alkenes.

For sulfoxides with β-silyl substituents there is some preference for elimination to take place towards the silyl group. On protodesilylation both the allyl- and vinyl-silanes formed give the same alkene, so providing a regioselective and high yielding alkene synthesis (Scheme 5).[42] If there is no β-hydrogen,

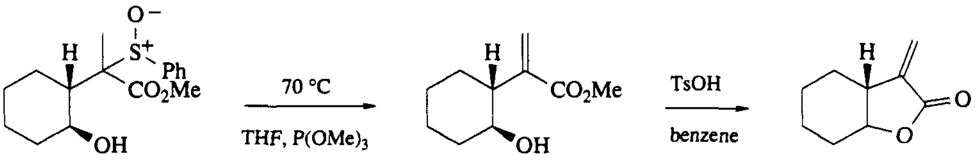

(**41**) **Scheme 4** (**42**)

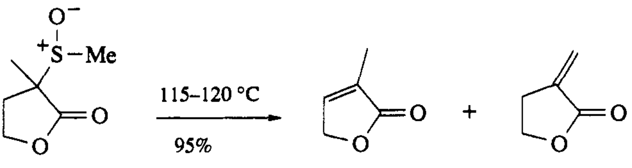 (23)

(**43**) (**44**) 87:13

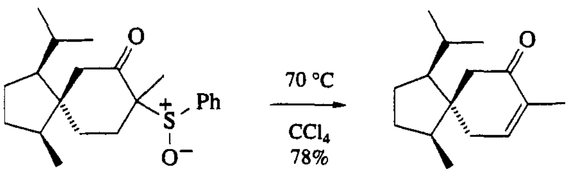

**(45)** **(46)**

(24)

β-silyl sulfoxides undergo a *syn* elimination of the silylsulfenate (equation 25), which can also be used for the synthesis of alkynes providing the silyl and sulfoxide substituents are *cis* disposed (equation 26).[43]

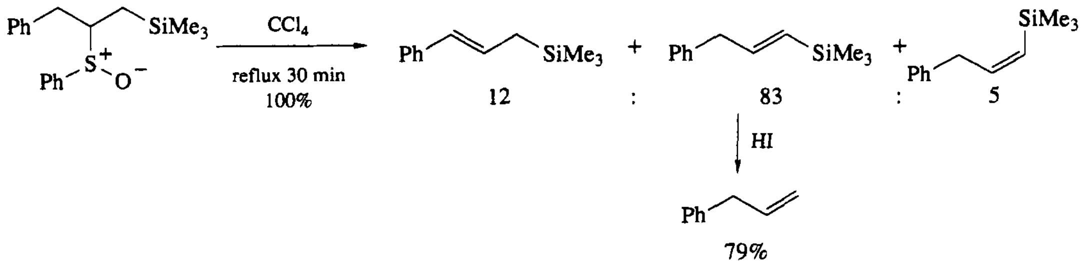

**Scheme 5**

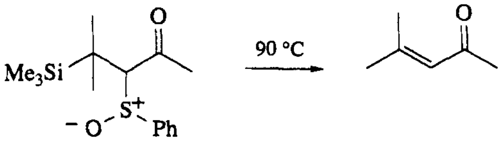

(25)

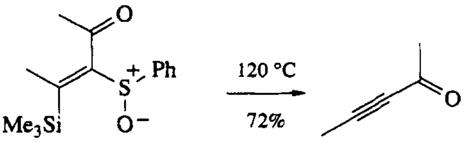

(26)

Most of the sulfoxides discussed above were generated by oxidation of the corresponding sulfide. This would have given mixtures of diastereoisomers due to the chirality of the sulfoxide group, but the isomers were not separated. However, the influence of the configuration at sulfur on the regioselectivity of sulfoxide elimination has been examined for a series of steroidal sulfoxides.[44] For 3α-alkylsulfinyl-5α-cholestanes the regioselectivity depends upon the configuration at sulfur and the bulk of the alkyl group. Thermolysis of the (*S*)-sulfoxide (**47**) gave a mixture of the 2- and 3-cholestenes (**51**) and (**52**), ratio 70:30, respectively, whereas the (*R*)-sulfoxide (**49**) gave more of the 3-cholestene (**52**); ratio (**51**):(**52**) = 30:70 in this case.[44] When the 3-(1-adamantyl)sulfinylcholestanes (**48**) and (**50**) were pyrolyzed at 110 °C the eliminations were completely regioselective, the (*S*)-isomer (**48**) giving only the 2-cholestene (**51**), and the (*R*)-isomer giving only the 3-cholestene (**52**).[45] These regioselectivities were explained in terms of steric interactions in the transition states for elimination. For the (*S*)-isomers (**47**) and (**48**) the conformation (**53**) leading to the 2-cholestene is less hindered than conformation (**54**). From these results it would appear that the sulfoxide configuration can influence the regioselectivity of elimination, at least in sterically hindered systems where the acidities of the β-hydrogens are similar.

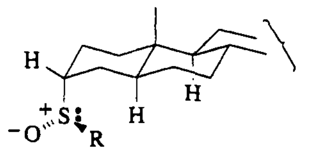

(**47**) R = Bu$^t$

(**48**) R = 1-adamantyl

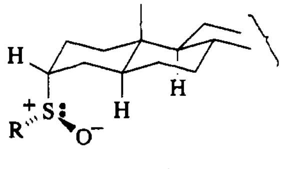

(**49**) R = Bu$^t$

(**50**) R = 1-adamantyl

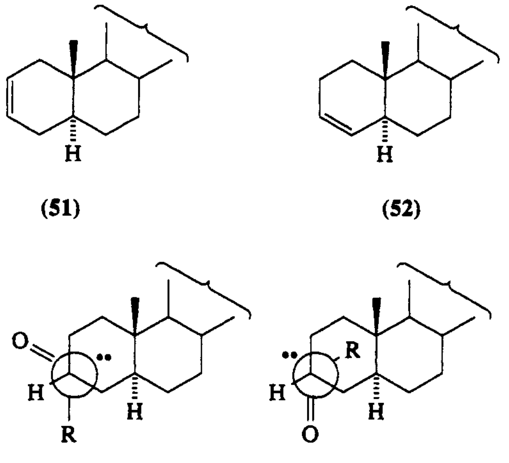

(51) (52)

(53) (54)

**Figure 1**

The use of optically active sulfoxides for the synthesis of optically active alkenes has been reported,[46] *e.g.* the (*S*)-sulfoxide (**55**) gave the (*S*)-alkene (**56**) on heating at 250 °C (equation 27). However, the observed enantiomeric excesses were only modest and the reactions were only carried out to low conversions.

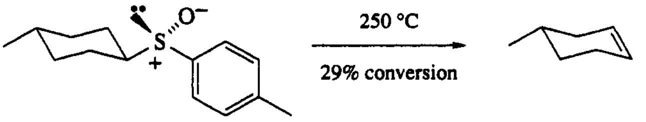

(**55**) (**56**) 47% *ee* (27)

### 5.3.3.3 Applications of Sulfoxide Elimination in Synthesis

#### *5.3.3.3.1 Alkene synthesis*

α-Sulfinyl carbonyl compounds fragment on thermolysis under mild conditions to give α,β-unsaturated carbonyl compounds.[30–32] The preparation of these compounds by α-sulfenylation of esters and ketones followed by oxidation has been developed by Trost and coworkers.[47] Treatment of an ester or ketone with a strong base, often LDA, followed by quenching the enolate anion with dimethyl or diphenyl disulfide, provides the α-sulfenylated carbonyl compound, which can be oxidized by a suitable oxidant, *e.g.* MCPBA or $NaIO_4$. Ketone enolates tend to be less reactive than ester enolates towards disulfides, the more reactive diphenyl disulfide being the preferred reagent for such cases. Indeed, the dilithiated keto ester (**57**) can be sulfenylated regioselectively α to the ester using dimethyl disulfide to give the α,β-unsaturated ester (**58**; equation 28) after oxidative elimination.[39] Unsymmetric ketones can be sulfenylated regioselectively using diphenyl disulfide, but the more reactive phenylbenzenethiosulfonate gives improved regioselectivity (*e.g.* equation 29).[32,47] The phenylsulfenylation and oxidative elimination of β-dicarbonyl compounds has also been used for the synthesis of 1,1-dicarbonyl-substituted alkenes, *e.g.* butenolides (**59**) and (**60**; R = Me, Pr$^i$, Bu$^t$).[48]

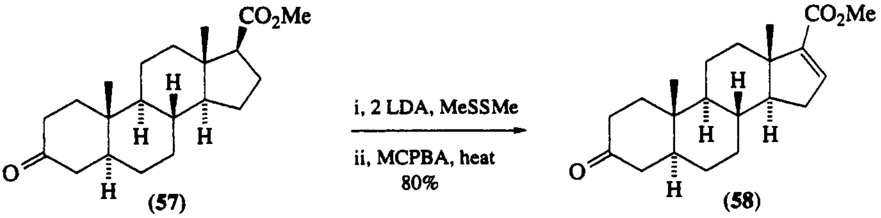

(**57**) (**58**) (28)

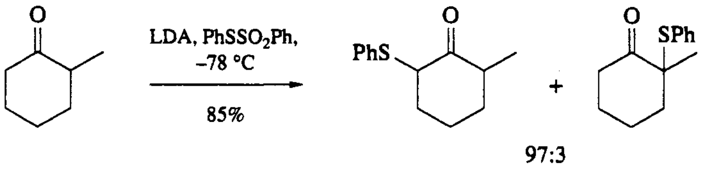
O
LDA, PhSSO2Ph,
-78 °C
85%
PhS
O
+
O
SPh
97:3

(29)

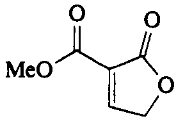

**(59)**

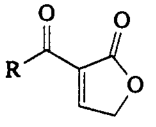

**(60)**

The intermediate α-sulfenyl carbonyl compounds may be alkylated prior to oxidative elimination. Phenylsulfenylation of the *cis*-fused butyrolactone (**61**), followed by methylation and oxidative elimination, gave the α-methylenebutyrolactone (**62**) because endocyclic elimination is sterically inhibited (Scheme 6). For the *trans*-fused butyrolactone (**63**), the alkylation was carried out first to ensure exocyclic elimination (Scheme 7).[49] The intermediate α-sulfinylcarbonyl compounds may also be modified before elimination, the alkylation of keto sulfoxides (**64**) providing a useful synthesis of α,β-unsaturated γ-keto esters (**65**; Scheme 8).[50–52] In some cases the use of an excess of strong base provides a dimetallated species which can be alkylated at the more reactive site before elimination, *e.g.* an approach to α′-alkylated vinyl ketones (Scheme 9).[53]

An alternative synthesis of α-methylene ketones and esters is provided by enolate alkylation using benzyl bromomethyl sulfide followed by oxidative elimination (Scheme 10).[54] The addition of sodium thiophenoxide to α-methylenebutyrolactones has been recommended for protection of the sensitive double bond, which can be regenerated by oxidative elimination.[55]

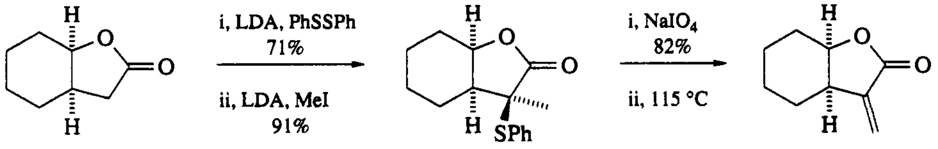
H
O
O
H
i, LDA, PhSSPh
71%
ii, LDA, MeI
91%
H
O
O
H
SPh
i, NaIO4
82%
ii, 115 °C
H
O
O
H

**(61)** **(62)**

**Scheme 6**

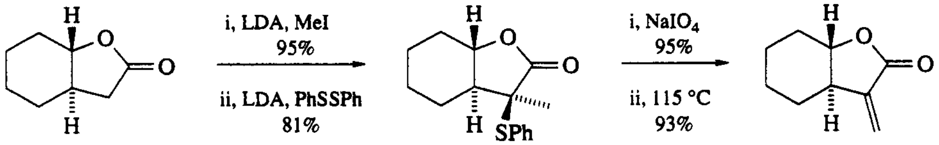
H
O
O
H
i, LDA, MeI
95%
ii, LDA, PhSSPh
81%
H
O
O
H
SPh
i, NaIO4
95%
ii, 115 °C
93%
H
O
O
H

**(63)**

**Scheme 7**

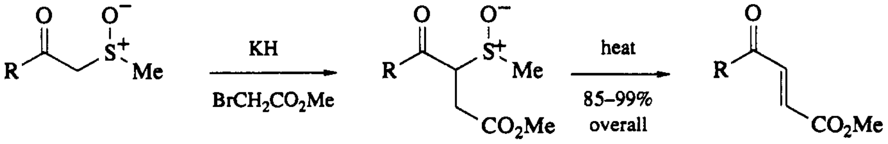
O
O−
S+
R
Me
KH
BrCH2CO2Me
O
O−
S+
R
Me
CO2Me
heat
85–99%
overall
O
R
CO2Me

**(64)** **(65)**

**Scheme 8**

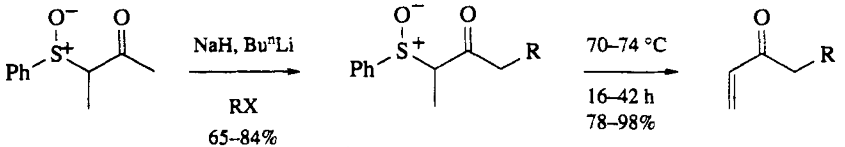

**Scheme 9**

α-Phenylsulfenylvinyl ketones, *e.g.* (**66**), are good Michael acceptors.[56] The intramolecular alkylation of sulfides has provided a route to large-ring compounds,[57] and aldol condensations of the β-phenylsulfinylcarboxylic acid have been used to prepare 5-substituted butenolides (Scheme 11).[58] α,β-Unsaturated lactones have also been prepared by intramolecular acylation of sulfoxides.[59]

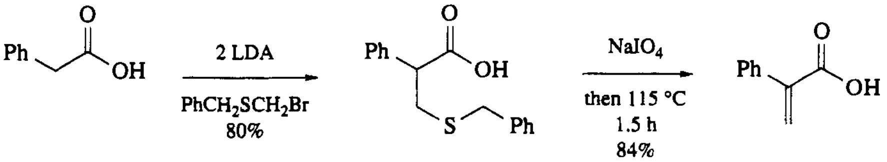

**Scheme 10**

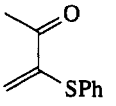

(**66**)

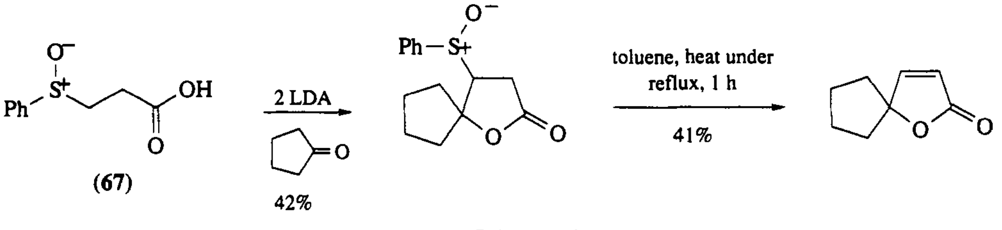

**Scheme 11**

From these examples it can be seen that sulfoxide pyrolysis has been widely used for the synthesis of α,β-unsaturated carbonyl compounds. Sulfoxide pyrolysis has also been used for the synthesis of other types of alkene although the temperatures required are usually higher, *e.g.* equation (30).[33,60,61] The alkylation of dimsyl sodium followed by pyrolysis has been used as an alternative to the Wittig reaction for the synthesis of terminal alkenes (Scheme 12),[62] and Michael addition to phenyl vinyl sulfoxide followed by pyrolysis was used in a novel approach to α-vinylcarbonyl compounds in which the vinyl sulfoxide is being used as the synthetic equivalent of the vinyl cation (Scheme 13).[63] For β-hydroxy sulfoxides the elimination takes place away from the hydroxy group to give allylic alcohols, but higher temperatures are required than for elimination from the corresponding hydroxy selenoxides, which are readily available by epoxide opening and which also give allylic alcohols (Section 5.3.4.2.2).[64] Ketones are formed if the elimination can only take place towards the hydroxy substituent (equation 31)[65] and vinyl chlorides can be obtained from α-chloro sulfoxides.[66]

Allylic sulfoxides are known to equilibrate with their isomeric sulfenates *via* a 2,3-sigmatropic shift, which has been developed into a useful allylic alcohol synthesis when the unstable sulfenate is trapped (Scheme 14).[67] However, this rearrangement is reversible and so need not necessarily interfere with pyrolytic elimination of the sulfoxide, *e.g.* the long-chain hydroxydiene (**69**) was obtained on pyrolysis of the sulfoxide (**68**; equation 32).[68] A study of substitution effects on the relative rates of rearrangement

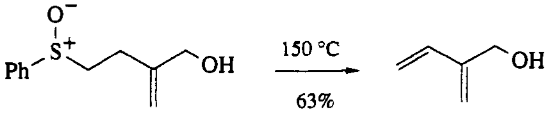

(30)

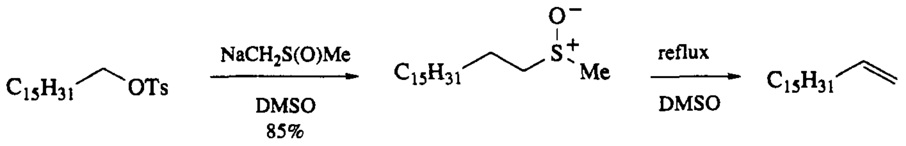

Scheme 12

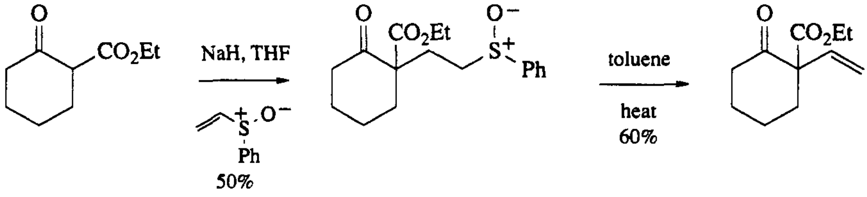

Scheme 13

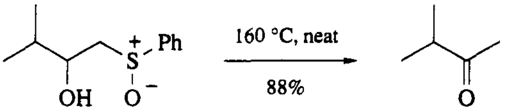

(31)

and elimination of alkyl aryl sulfoxides has shown that the elimination is favoured by electron-withdrawing substituents in the aryl ring.[69] Analogous 1,4-eliminations have also been studied.[70]

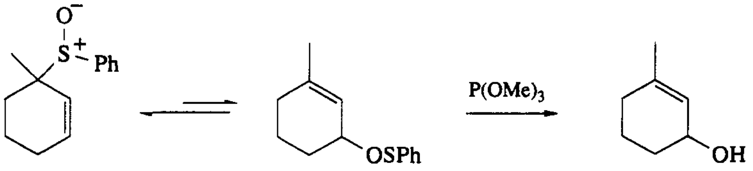

Scheme 14

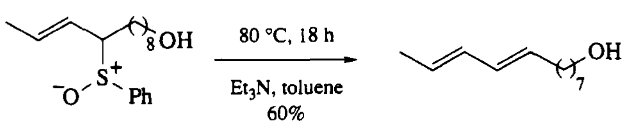

**(68)** **(69)**

(32)

### 5.3.3.3.2 *Vinyl sulfoxides as dienophiles*

Vinyl sulfoxides are useful Diels–Alder dienophiles. Thermolysis of the adducts gives rise to alkenes *via* sulfoxide elimination and so over the two steps the vinyl sulfoxides are the synthetic equivalents of alkynes, *e.g.* phenyl vinyl sulfoxide reacts with anthracene and 1,4-diphenylbuta-1,3-diene with concomitant sulfoxide elimination under the Diels–Alder conditions to give adducts (**70**) and (**71**; Scheme 15).[71] β-Phenylsulfinyl-α,β-unsaturated-carbonyl compounds have also been used as Diels–Alder dienophiles in chemistry developed for a synthesis of disodium prephenate and epiprephenate.[72,73] With the electron rich diene (**72**), vinyl sulfoxides (**73**) and (**75**) gave rise to products (**74**; equation 33) and (**76**; equation 34) after hydrolysis.[72] For the prephenate synthesis the phenylsulfinylmethylenelactone (**77**) was used, giving cyclohexadienone (**78**; Scheme 16) after sulfoxide elimination and hydrolysis.[73]

### 5.3.3.3.3 *Sulfoxide elimination for sulfenic acid generation*

So far in this chapter sulfoxide pyrolysis has been discussed in connection with alkene synthesis. However, the other products of these reactions, the sulfenic acids, are also of interest, and have been generated for study by several methods including sulfoxide pyrolysis. Thermolysis of di-*t*-butyl sulfoxide (**79**;

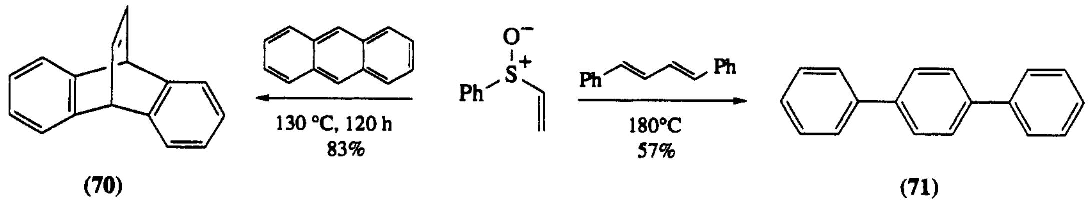
(70)
130 °C, 120 h
83%
Ph
O⁻
S⁺
Ph
Ph
180°C
57%
(71)

Scheme 15

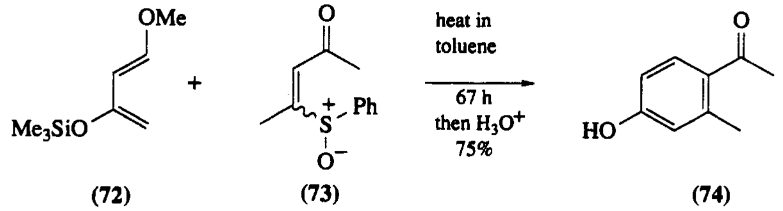
OMe
Me3SiO
+
O
Ph
S
O⁻
heat in toluene
67 h
then H3O+
75%
O
HO
(72)
(73)
(74)

(33)

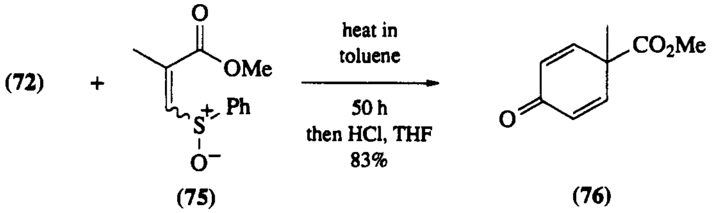
(72)
+
O
OMe
Ph
S
O⁻
heat in toluene
50 h
then HCl, THF
83%
CO2Me
O
(75)
(76)

(34)

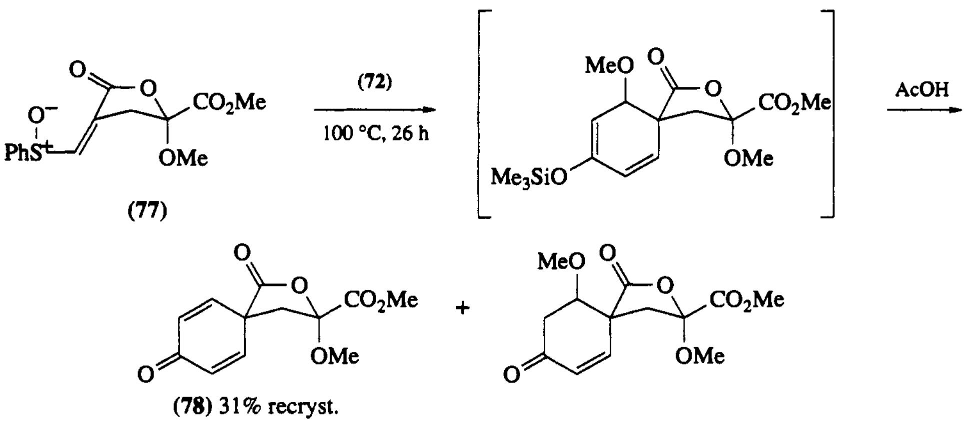
O
O
O⁻
PhS⁺
CO2Me
OMe
(77)
(72)
100 °C, 26 h
MeO
O
O
CO2Me
OMe
Me3SiO
AcOH
O
O
CO2Me
OMe
O
+
MeO
O
O
CO2Me
OMe
O
(78) 31% recryst.

Scheme 16

Scheme 17) at 80 °C generates 2-methylpropanesulfenic acid (**80**), which was trapped by ethyl acrylate to give the sulfoxide (**81**), formation of sulfoxide (**81**) corresponding to the reverse of sulfoxide elimination.[74] 2-Methylpropanesulfenic acid (**80**), generated by elimination from di-*t*-butyl sulfoxide, has also been trapped by addition to dienes to give (*t*-butylsulfinyl)alkenes; these eliminate 2-methylpropene to release the alkenesulfenic acids, which then cyclize. For example, di-*t*-butyl sulfoxide (**79**; Scheme 18) and hexa-1,5-diene gave the alkenyl sulfoxide (**82**) after heating at 130 °C for 5 min. Further heating of this sulfoxide eliminated 2-methylpropene and released the alkenesulfenic acid, which cyclized to give the *cis*- and *trans*-dimethylthiolane 1-oxides (**83**) and (**84**).[38,75] This intramolecular addition of sulfenic acids to alkenes has been used for the synthesis of thietanoprostanoids (Scheme 19).[76]

Sulfenic acids also react with alkynes,[74] and (*t*-butylsulfinyl)alkynes (**85**) eliminate 2-methylpropene on thermolysis to give the (*E*)-alkenyl sulfoxides (**87**) stereoselectively *via* cyclization of the intermediate sulfenic acids (**86**; Scheme 20).[77] The stereochemistry of the adduct (**87**) is established by the mechanism of sulfenic acid addition. For the intermolecular trapping of sulfenic acids by alkynes, generation of the sulfenic acids by thermolysis of the corresponding β-sulfinylpropionitrile (**88**; equation 35) is the preferred route.[77] Sterically hindered sulfenic acids have also been generated by flash vacuum pyrolysis of sulfoxides and trapped intermolecularly by alkynes.[78]

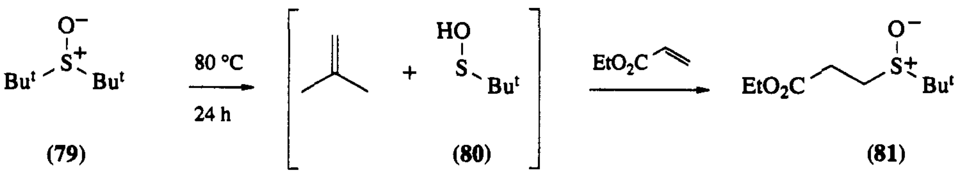

Scheme 17

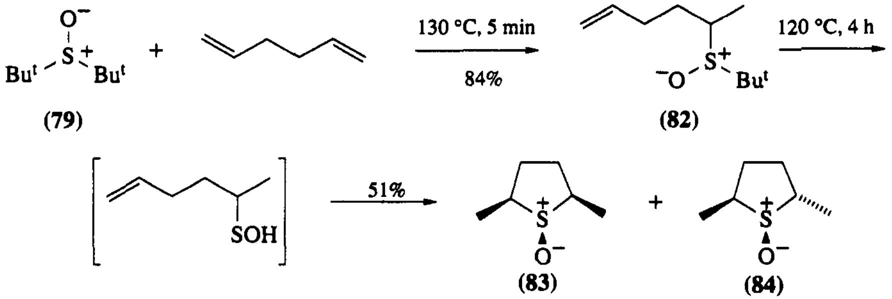

Scheme 18

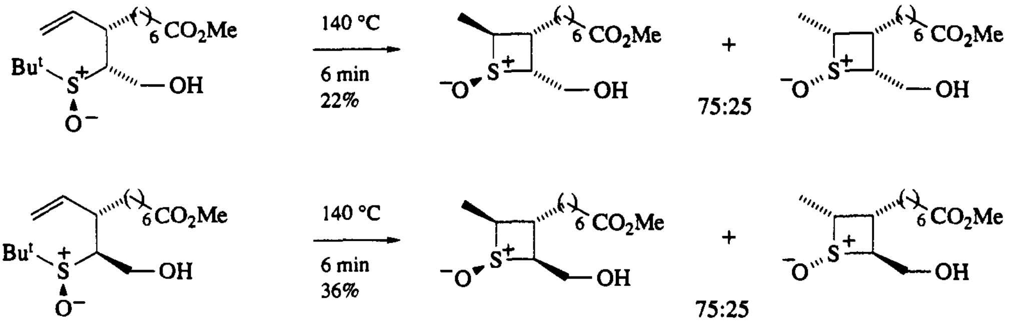

Scheme 19

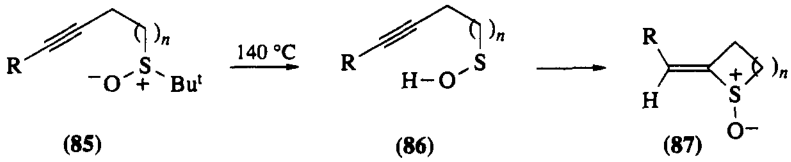

Scheme 20

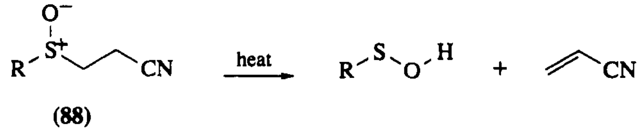

(35)

Unsaturated sulfenic acids have been generated by thermolysis of cyclic sulfoxides.[79] This has proved to be particularly important for the conversion of penicillins into cephalosporins, and the chemistry of penicillin sulfoxides has been widely studied in this respect.[80] Thus thermolysis of penicillin sulfoxides (**89**) and (**92**) generates the corresponding sulfenic acid (**90**; Scheme 21), which in the presence of acid catalysts undergoes electrophilic intramolecular alkene addition to give mixtures of cephems (**93**) and cephams (**94**) with the ratio of products being dependent upon the reaction conditions used. The intermediate sulfenic acids (**90**) have also been trapped as their silyl ethers (**91**), from which the parent sulfenic acids can be regenerated, reduced to thiols (**95**), which cyclize to form thiazolines (**96**), and used to prepare mixed disulfides (**97**). This elegant chemistry has been thoroughly reviewed,[80] and may find applications in other areas of organic synthesis.

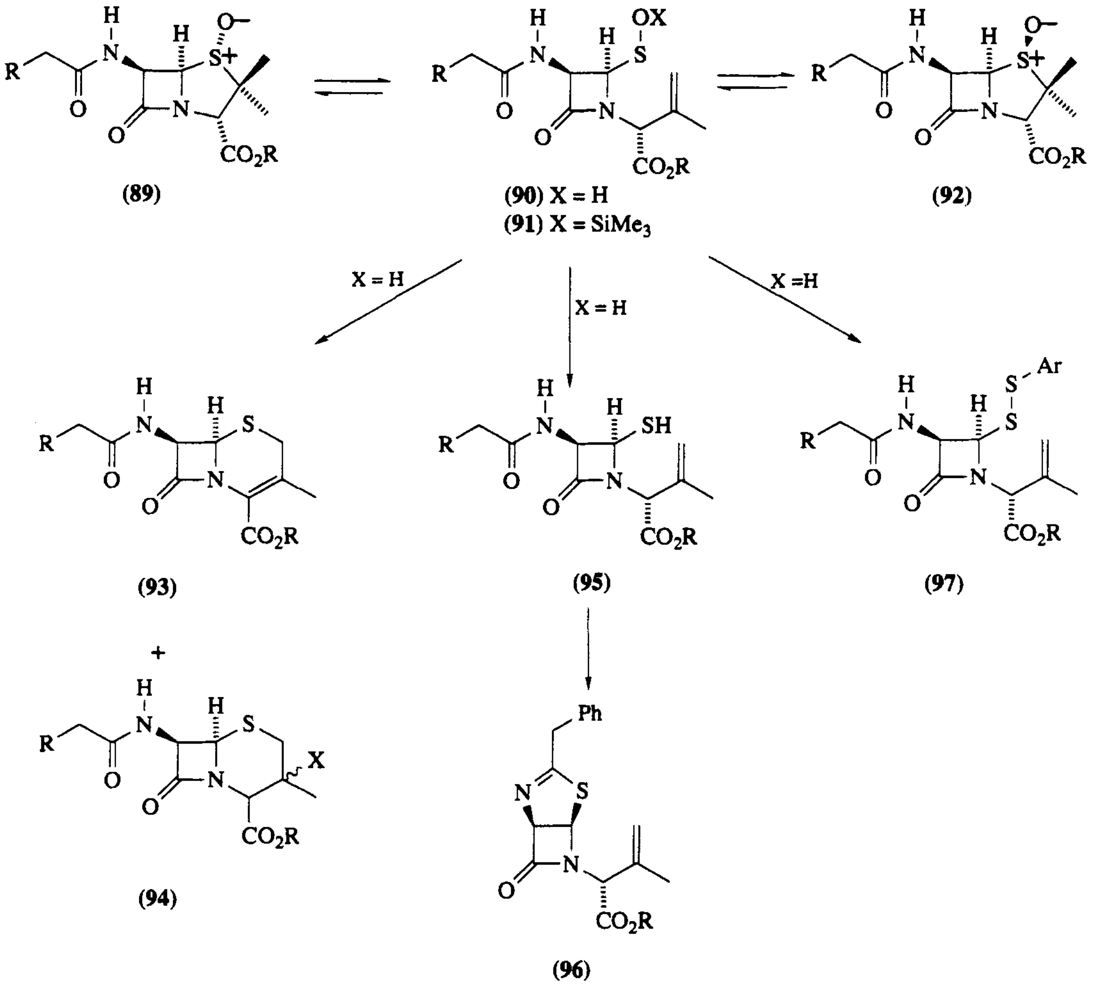

Scheme 21

## 5.3.4 SELENOXIDE ELIMINATION

### 5.3.4.1 Introduction: Stereo- and Regio-chemistry

The instability of alkyl selenoxides had been known for many years but it was not until the early 1970s that the *syn* elimination of selenoxides was recognized and developed into a useful synthesis of alkenes.[81] In 1970, the two 5β-cholestane selenoxides (**98**; equation 36), epimeric at selenium, were separated, and shown to fragment readily, albeit at different rates, to give cholest-6-ene (**99**) regioselectively.[82] The *syn* elimination mechanism outlined in equation (37) was proposed to account for the regioselectivity of these eliminations. The more labile epimer was assigned the (*S*)-configuration at selenium by analogy with the corresponding sulfoxide since it would be expected to encounter less steric hindrance than the other isomer in the conformation required for fragmentation.[82] The *syn* stereochemistry of selenoxide elimination has since been confirmed (Scheme 22).[83]

Selenoxide elimination is now widely used for the synthesis of α,β-unsaturated carbonyl compounds,[84] allyl alcohols[85–87] and terminal alkenes[88] since it proceeds under milder conditions than those required for sulfoxide or any of the other eliminations discussed in this chapter. The selenoxides are usually generated by oxidation of the parent selenide using hydrogen peroxide, sodium periodide, a peroxy acid or ozone, and are not usually isolated, the selenoxide fragmenting *in situ*. The other product of the elimination, the selenenic acid, needs to be removed from the reaction mixture as efficiently as possible. It can disproportionate with any remaining selenoxide to form the corresponding selenide and seleninic acid, or undergo electrophilic addition to the alkene to form a β-hydroxy selenide, as shown in

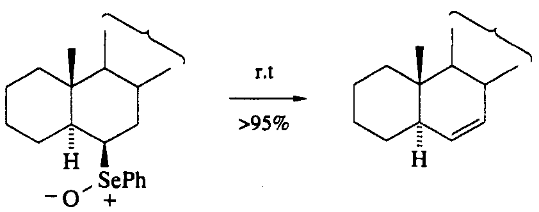
SePh
r.t
>95%
H
H

**(98)** **(99)**

(36)

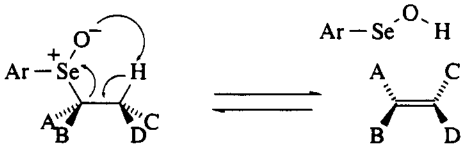
Ar—Se
A
B
C
D
H
Ar—Se
O
H

(37)

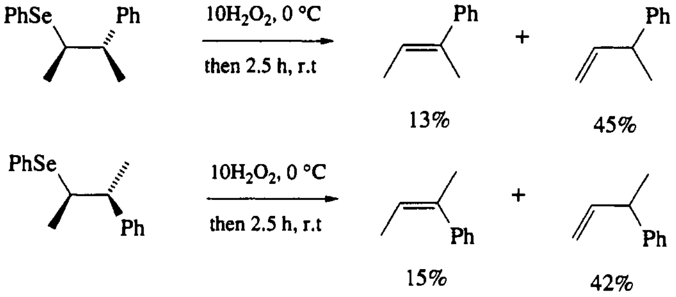
PhSe
Ph
10H2O2, 0 °C
then 2.5 h, r.t
Ph
Ph
13%
45%
PhSe
Ph
10H2O2, 0 °C
then 2.5 h, r.t
Ph
Ph
15%
42%

**Scheme 22**

Scheme 23.[87–90] To avoid these side reactions an excess of oxidant is frequently used to oxidize the selenenic acid as quickly as it is formed to the corresponding seleninic acid. Alternatively an amine can be added to convert the selenenic acid into the selenenamide.[81]

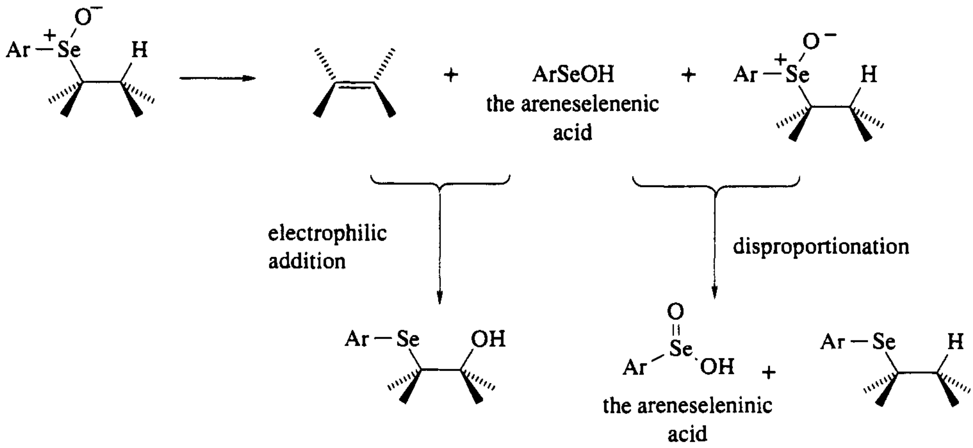
Ar—Se
H
ArSeOH
the areneselenenic acid
Ar—Se
H
electrophilic addition
disproportionation
Ar—Se
OH
Ar
Se
OH
the areneseleninic acid
Ar—Se
H

**Scheme 23**

As with amine oxides and sulfoxides, acyclic 1,2-disubstituted alkenes are usually obtained with the (*E*)-stereochemistry, although the formation of α,β-unsaturated nitriles is reported to give a mixture of (*E*)- and (*Z*)-isomers.[91] For cyclic alkenes, the stereochemistry of double bond formation depends upon ring size. However, it can be affected by conformational factors, *e.g.* cyclododecyl phenyl selenide gives a mixture of *cis*- and *trans*-cyclododecenes on oxidative elimination (equation 38)[83] but only the (*E*)-isomer (**101**) was obtained from the acetoxycyclododecyl selenide (**100**; equation 39).[92]

The regioselectivity of selenoxide elimination is similar to that observed for sulfoxides in that it takes place preferentially towards allylic, propargylic and benzylic hydrogens to form conjugated alkenes with $CH_3 > CH_2 \gg CH$, *e.g.* the conjugated diene (**103**) was obtained from selenoxide (**102**; equation 40).[93]

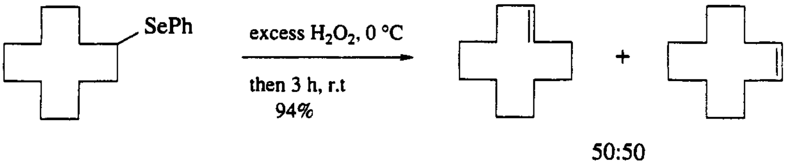
SePh
excess $H_2O_2$, 0 °C
then 3 h, r.t
94%
+
50:50

(38)

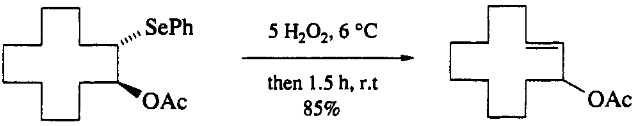
SePh
OAc
5 $H_2O_2$, 6 °C
then 1.5 h, r.t
85%
OAc

**(100)** **(101)**

(39)

However, the regioselectivity is also affected by statistical factors and if these two effects are in opposition, then the regioselectivity may not be very great, *e.g.* Scheme 22.[83] However, one extremely useful aspect of the regioselectivity of selenoxide elimination is the marked preference for elimination to take place away from an electronegative atom. β-Oxygen substituents in particular are very effective at directing the elimination away from themselves, as indicated in equations (41) and (42), and this forms the basis of a very useful allylic alcohol synthesis (Section 5.3.4.2.2).[85,94]

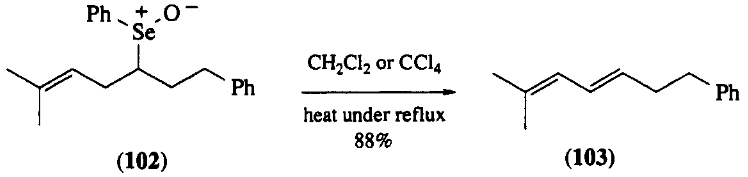
Ph
+
O⁻
Se
Ph
$CH_2Cl_2$ or $CCl_4$
heat under reflux
88%
Ph

**(102)** **(103)**

(40)

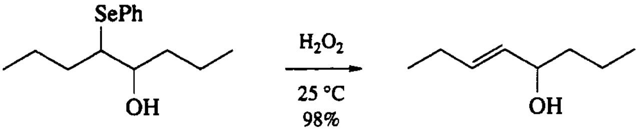
SePh
OH
$H_2O_2$
25 °C
98%
OH

(41)

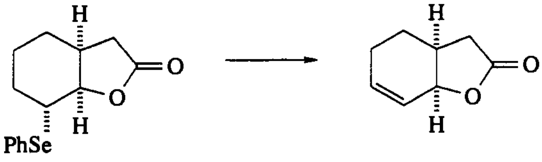
H
O
O
H
PhSe
H
O
O
H

(42)

Unlike sulfoxide elimination, selenoxide elimination can be used to prepare alkynes, providing the *syn* elimination process is sterically feasible, and has been used for the preparation of terminal alkynes (*e.g.* **104**; equation 43).[95,96]

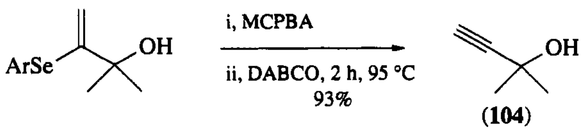
ArSe
OH
i, MCPBA
ii, DABCO, 2 h, 95 °C
93%
OH

**(104)**

(43)

### 5.3.4.2 Applications of Selenoxide Elimination

#### *5.3.4.2.1 Synthesis of α,β-unsaturated carbonyl compounds*

Several procedures have been developed for the preparation of α-arylselenocarbonyl compounds including phenylselenenylation of enol acetates,[97] enol ethers[98] and lithium and copper enolates.[99,100] Oxidative elimination then provides the α,β-unsaturated carbonyl compound (Schemes 24–26). Alternatively the α-phenylseleno compound can be alkylated prior to oxidative elimination (Scheme 26).[101]

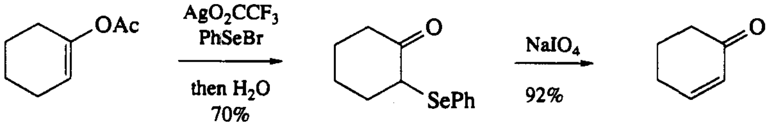
OAc
$AgO_2CCF_3$
PhSeBr
then $H_2O$
70%
O
SePh
$NaIO_4$
92%
O

Scheme 24

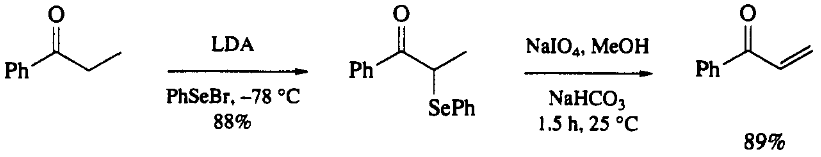
O
Ph
LDA
PhSeBr, -78 °C
88%
O
Ph
SePh
$NaIO_4$, MeOH
$NaHCO_3$
1.5 h, 25 °C
O
Ph
89%

Scheme 25

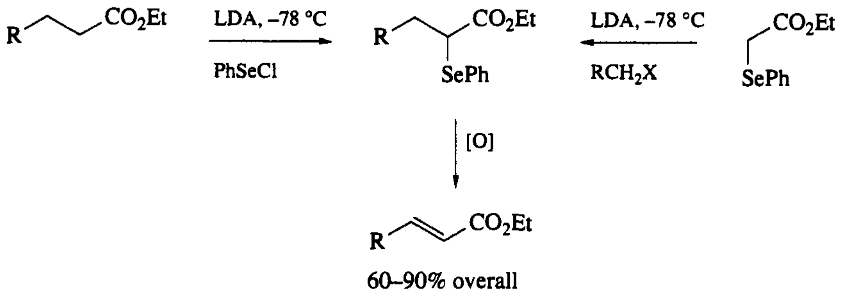
R
$CO_2Et$
LDA, -78 °C
PhSeCl
R
$CO_2Et$
SePh
LDA, -78 °C
$RCH_2X$
$CO_2Et$
SePh
[O]
R
$CO_2Et$
60–90% overall

Scheme 26

Although the selenoxide elimination when forming an α,β-unsaturated carbonyl compound is generally fast and efficient, the choice of conditions can be important if side reactions are to be avoided, especially if there is steric hindrance to the formation of the *syn* elimination transition state.[81,82] For example, an excess of oxidant is frequently used to remove the areneselenenic acid as it is formed in order to prevent the side reactions outlined in Scheme 23. However, in some cases the excess of oxidant can cause further oxidation. When the steroidal phenylseleno ketone (**105**) was oxidized using an excess of hydrogen peroxide, the major product was the unsaturated lactone (**108**). It appeared that the benzeneselenenic acid released during the elimination to form the unsaturated ketone (**106**) was being oxidized to benzene peroxyseleninic acid (**107**), which then effected a Baeyer–Villiger oxidation of the ketone (Scheme 27).[102,103] Moreover, Pummerer and other side reactions can interfere with the efficient oxidative elimination of α-phenylseleno ketones if the *syn* elimination is slow, because of the increased acidity

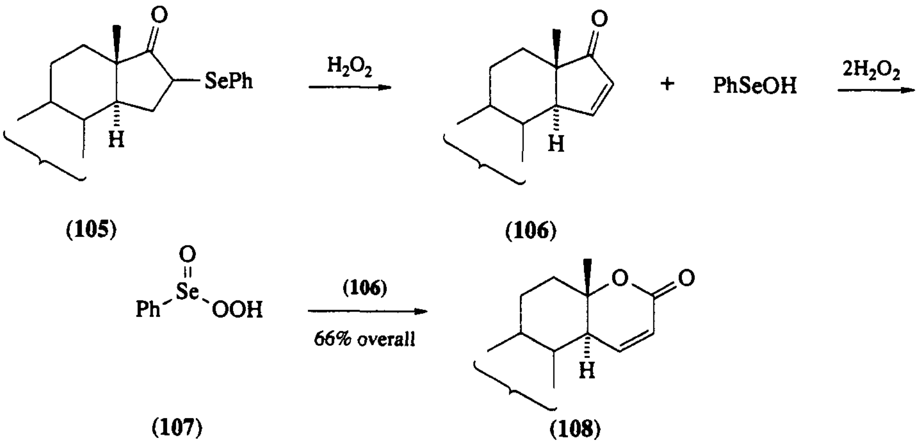
O
SePh
H
(105)
$H_2O_2$
O
H
(106)
+ PhSeOH
$2H_2O_2$
O
Se
Ph
OOH
(107)
(106)
66% overall
O
O
H
(108)

Scheme 27

of the α-hydrogen due to stabilization of the corresponding enolate anion by both the carbonyl and selenoxide groups. Oxidation of 6-methyl-2-phenylselenocyclohexanone (**109**) gave 6-methylcyclohex-2-enone (**111**), together with the phenylselenocyclohexenone (**112**) and diketone (**113**) formed by phenylselenenylation and Pummerer rearrangement of the intermediate selenoxide (**110**), respectively, as outlined in Scheme 28.[84,100] Low yields of enone were also obtained from 2-phenylselenocyclo-heptanone and -octanone due to competing Pummerer rearrangements.[100] The addition of a secondary amine to keep the reaction mixture basic has been recommended to prevent the Pummerer reaction, which is catalyzed by acids. Alternatively the ketone can be protected as a ketal prior to the oxidative elimination since this reduces the acidity of the α-hydrogens.[84] Recently better yields of the desired oxidative elimination product were obtained using 2-pyridinylseleno ketones.[104] However, notwithstanding these side reactions, the oxidative elimination of α-phenylselenocarbonyl compounds has been widely used in synthesis and generally gives very good results.[81]

With α-phenylselenolactones, endocyclic elimination is preferred if the *syn* elimination is possible (equation 44), perhaps because the conformation leading to the exocyclic product involves greater dipole–dipole interaction between the selenoxide and the carbonyl group. However, α-methylenelactones are obtained if *syn* elimination cannot be achieved (equation 45).[105] The conjugate addition of sodium phenylselenide has been recommended for the protection of α-methylenelactones, the double bond being reintroduced by selenoxide elimination.[106]

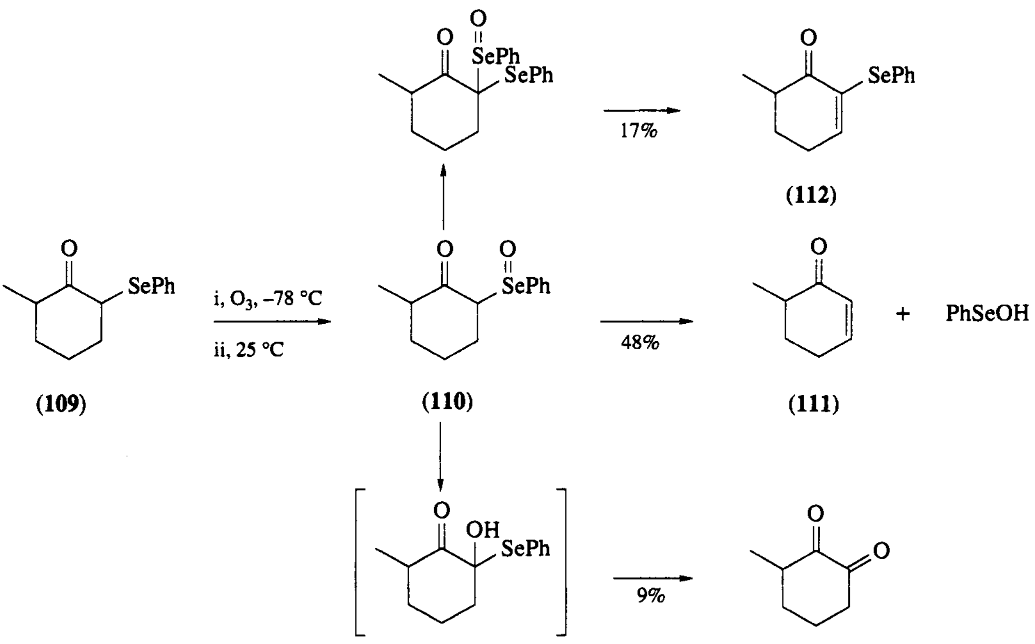

Scheme 28 **(113)**

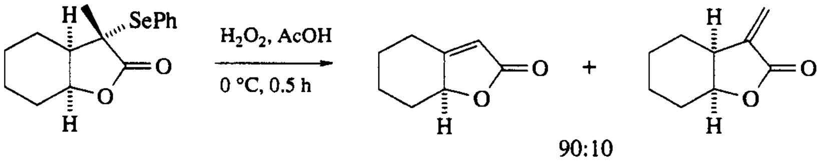

(44)

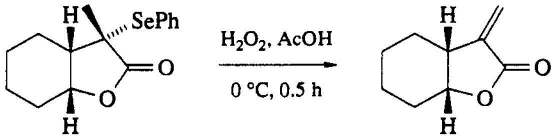

(45)

Procedures have been developed for the phenylselenenylation and oxidative elimination of β-formyl ketones[107] and aldehydes[108] to form the corresponding α,β-unsaturated aldehydes (Schemes 29 and 30). Other β-dicarbonyl compounds have also been oxidized to the corresponding α,β-unsaturated compounds by phenylselenenylation and oxidative elimination including 3-(1-oxotrienyl)pyrrolidinones, which give the corresponding pyrrol-2(5*H*)-one (*e.g.* **114**; Scheme 31). In this case the oxidative elimination was carried out using 1 mol equiv. of MCPBA at –50 °C, which selectively oxidized the selenide in the presence of the sensitive conjugated triene, with an excess of hydrogen peroxide present to trap the benzeneselenenic acid. The 3-(1-oxotrienyl)pyrrol-2(5*H*)-ones were unstable, undergoing intramolecular Diels–Alder cyclization, providing a route to the cytochalasans.[109]

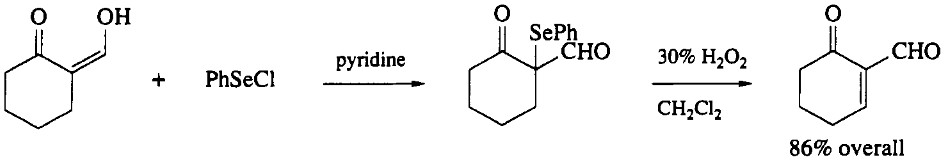
O
OH
+
PhSeCl
pyridine
O
SePh
CHO
30% $H_2O_2$
$CH_2Cl_2$
O
CHO
86% overall

**Scheme 29**

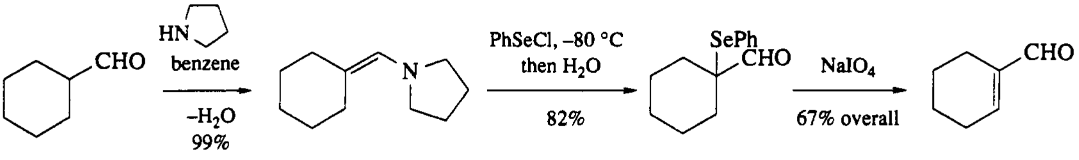
CHO
HN
benzene
$-H_2O$
99%
N
PhSeCl, –80 °C
then $H_2O$
82%
SePh
CHO
$NaIO_4$
67% overall
CHO

**Scheme 30**

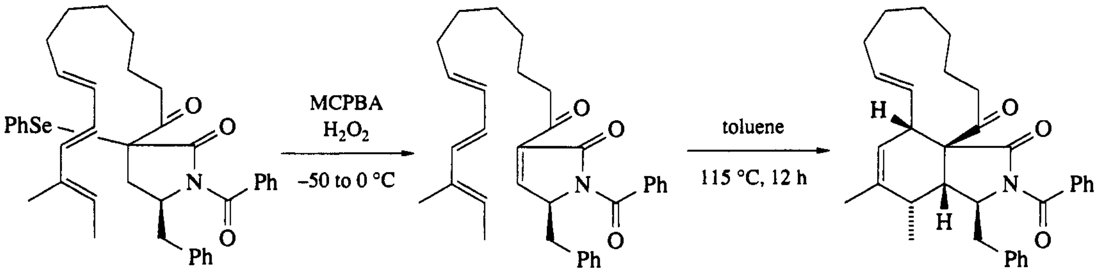
PhSe
O
O
N
Ph
O
Ph
MCPBA
$H_2O_2$
-50 to 0 °C
O
O
N
Ph
O
Ph
toluene
115 °C, 12 h
H
O
O
N
Ph
H
O
Ph

**(114)**

40% overall

**Scheme 31**

### *5.3.4.2.2 Synthesis of allylic alcohols, amines and derivatives*

The selenoxide elimination of β-hydroxy selenoxides, which takes place regioselectively away from the hydroxy group, *e.g.* as in equation (41), has been developed into a useful synthesis of allylic alcohols.[81] Similar regioselective elimination is also observed for β-acyloxy selenoxides, as shown in equations (39) and (42), and for β-acylamino selenoxides (*e.g.* **115**; equation 46).[110] However, the regioselectivity of elimination is less useful for β-chloro and β-amino selenoxides.[81,111]

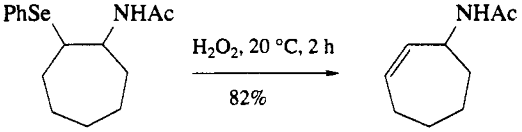
PhSe
NHAc
$H_2O_2$, 20 °C, 2 h
82%
NHAc

(46)

**(115)**

β-Hydroxy selenides are conveniently prepared from epoxides by treatment with sodium phenylselenide (Scheme 32)[85] and by the addition of benzeneselenenic acid and its derivatives to alkenes (Scheme 33),[86,87,112] although in some cases these reactions are not regioselective. Useful phenylseleno -etherification and -lactonization reactions have been developed which can be regioselective (equation 42 and Schemes 34 and 35).[94,113–115] Selenide- and selenoxide-stabilized carbanions have been used in addition reactions with aldehydes and ketones,[93,116] and the reduction of α-seleno ketones also provides a route to β-hydroxy selenides.[81]

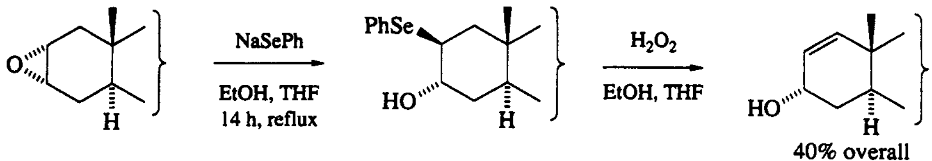
NaSePh
EtOH, THF
14 h, reflux
PhSe
HO
H
$H_2O_2$
EtOH, THF
HO
H
40% overall

Scheme 32

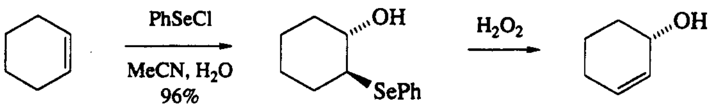
PhSeCl
MeCN, $H_2O$
96%
OH
SePh
$H_2O_2$
OH

Scheme 33

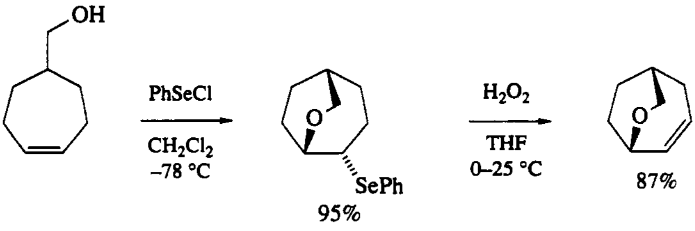
OH
PhSeCl
$CH_2Cl_2$
-78 °C
O
SePh
95%
$H_2O_2$
THF
0–25 °C
O
87%

Scheme 34

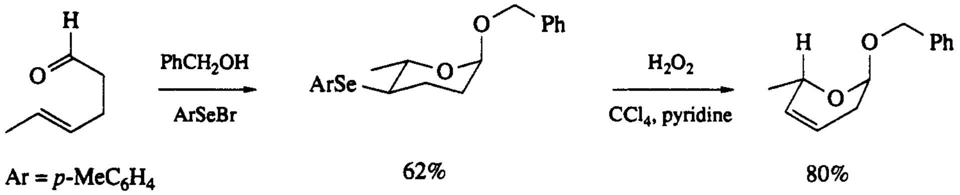
H
O
PhCH$_2$OH
ArSeBr
Ar = $p$-MeC$_6$H$_4$
O
Ph
ArSe
O
62%
$H_2O_2$
$CCl_4$, pyridine
H
O
Ph
O
80%

Scheme 35

Although the preference for selenoxide elimination to take place away from a β-oxygen substituent is very marked, the elimination will still occur towards the oxygen substituent if there is no alternative. This has been used in elegant syntheses of ketene acetals derived from allylic alcohols, which are useful Claisen rearrangement precursors (Scheme 36)[117] and for the synthesis of phenylseleno methyl ketones.[118]

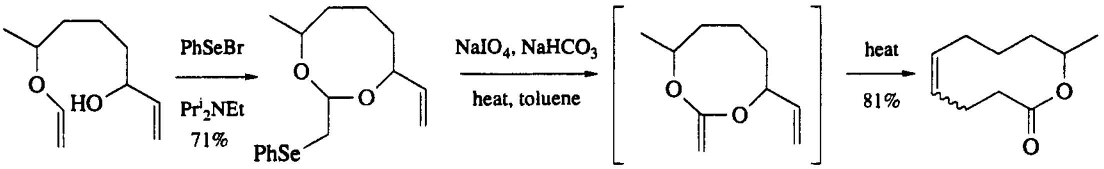
O
HO
PhSeBr
Pr$^i_2$NEt
71%
O
O
PhSe
NaIO$_4$, NaHCO$_3$
heat, toluene
O
O
heat
81%
O
O

Scheme 36

### 5.3.4.2.3 Synthesis of terminal alkenes

The oxidative elimination of primary selenides, readily available from the corresponding alcohol by treatment with an arylselenocyanate and tributylphosphine, is an attractive approach to the synthesis of terminal alkenes.[119] However these reactions are relatively slow when compared with other selenoxide eliminations allowing side reactions, in particular the addition of the areneselenenic acid to the newly formed double bond (Scheme 23), to compete. It has been found that arylselenides with electron-withdrawing substituents fragment more readily, giving improved yields of products,[120] in particular the use of *o*-nitrophenyl and 2-pyridyl selenides[121] has been recommended (Scheme 37). Often for the elimination of primary selenoxides, the solution containing the selenoxide is added to dichloromethane or carbon tetrachloride heated under reflux.[81]

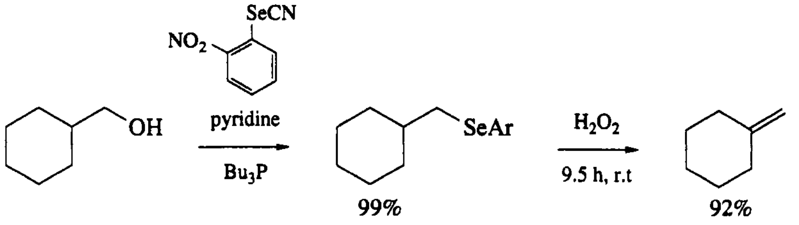

**Scheme 37**

Following these guidelines, the selenoxide elimination procedure has proved particularly useful for the synthesis of terminal double bonds, for example the introduction of vinyl groups during sesquiterpene synthesis as illustrated in equation (47).[122,123]

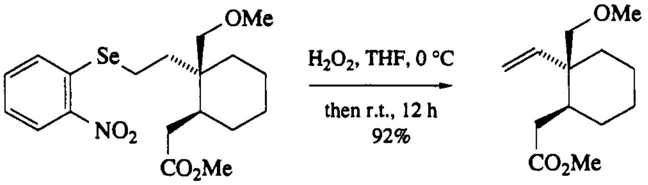

(47)

## 5.3.5 XANTHOGENATE AND ACETATE PYROLYSIS

### 5.3.5.1 Introduction

Useful procedures for the synthesis of alkenes by pyrolysis of acetates and xanthogenates have been developed, and have been extensively reviewed.[124–127]

Acetate pyrolysis is normally carried out using a flow apparatus at temperatures in the region of 300–600 °C. The *syn* elimination mechanism (equation 48) was established by pyrolysis of the stereospecifically deuterium-labeled acetates (**116**) and (**117**), which gave labeled and unlabeled products as shown in equations (49) and (50).[128] 1,2-Disubstituted acyclic alkenes are normally obtained with the (*E*)-stereochemistry, as for the other eliminations discussed in this chapter.[129] However, the regioselectivity of acetate pyrolysis can be rather modest. This is because the regioselectivity is affected by several factors, in particular the stability of the product alkene and the number of available β-hydrogens. If these two factors oppose each other only low regioselectivity is observed, *e.g.* a 50:50 mixture of alkenes (**119**) and (**120**) was obtained from the pyrolysis of acetate (**118**; equation 51).[130]

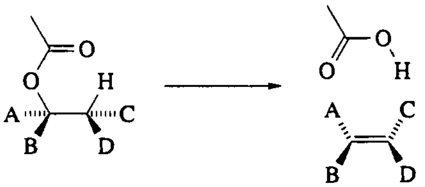

(48)

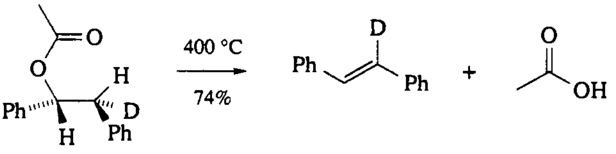

(**116**)

(49)

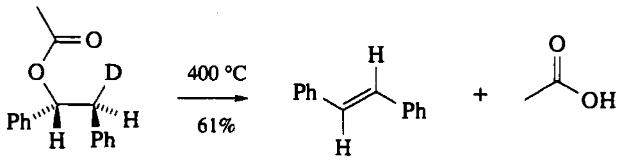

**(117)**

(50)

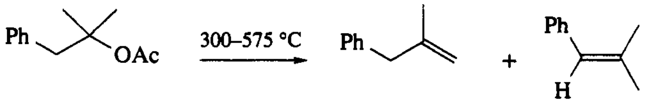

**(118)** **(119)** *ca.* 50:50 **(120)**

(51)

The rate of acetate fragmentation depends upon the nature of the alkyl group, with the relative rates of elimination of ethyl, isopropyl and *t*-butyl acetates being 1:26:1660, respectively, at 400 °C.[131] However, Hammett correlations for fragmentation of α- and β-aryl-substituted acetates show little sensitivity to aryl substituents.[124] The rates of fragmentation of esters derived from other carboxylic acids are dependent upon the p$K_a$ of the parent acid, but this does not appear to influence significantly the regioselectivity of their fragmentation.[124,132]

Xanthogenate pyrolyses are usually carried out by distillation at temperatures in the region of 150–250 °C, *i.e.* lower than those required for the corresponding acetate pyrolyses, with the stereochemistry of the elimination corresponding to that of the *syn* process outlined in equation (52).[133] In acyclic systems there is a modest preference for 1,2-disubstituted products to be obtained with (*E*)-stereochemistry, but the regioselectivity is often rather weak because of the conflicting demands of product stability and statistical factors. For these reasons simple xanthogenates derived from acyclic secondary alcohols, *e.g.* (**121**) and (**122**), often give mixtures of products, as illustrated in equations (53) and (54).[134]

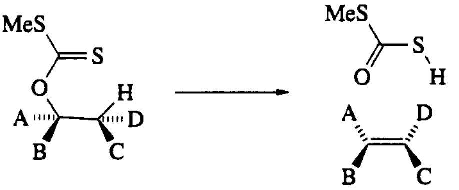

(52)

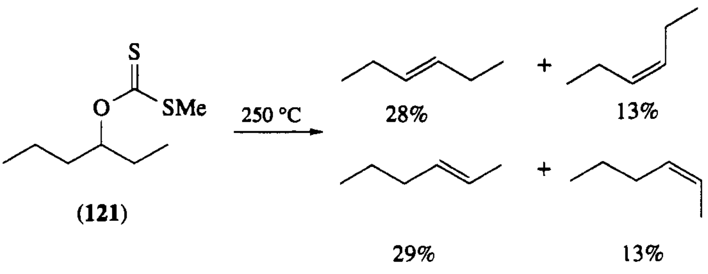

**(121)**

(53)

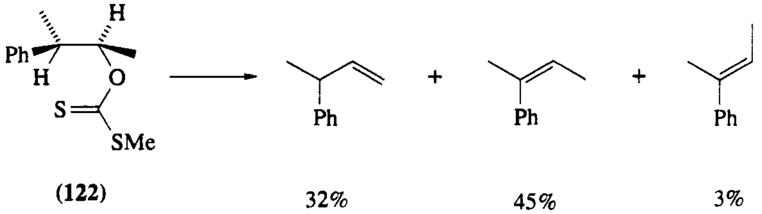

**(122)**

(54)

For xanthogenate and acetate elimination from cyclic systems, the regioselectivity is dependent upon the accessibility of the alternative *syn* elimination transition states. The *cis*-2-phenyl acetate (**123**; X = OAc) and xanthogenate (**123**; X = OCSSMe) both eliminate exclusively away from the phenyl substituent to give 3-phenylcyclohexene (**124**; equation 55), whereas the corresponding *trans*-2-phenyl compounds (**125**; equation 56) give mixtures of the 1- and 3-phenyl isomers (**126**) and (**124**).[124,127] The pyrolysis of 1-methylcyclohexyl acetate (**127**) differs from that of the corresponding amine oxide (**21**; *n* = 6) (Section 5.3.2.2) in that it gives predominantly the endocyclic alkene (equation 57).[135]

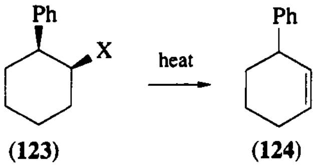
Ph
X
heat
Ph
(123)
(124)

(55)

X = OAc, 450 °C, 65%; X = OCSSMe, 435 °C, 100%

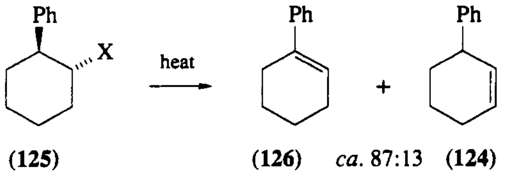
Ph
X
heat
Ph
Ph
+
(125)
(126)
*ca.* 87:13
(124)

(56)

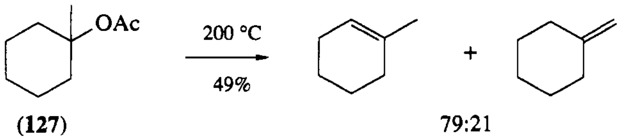
OAc
200 °C
49%
+
(127)
79:21

(57)

### 5.3.5.2 Applications in Synthesis

Despite the high temperatures required for acetate and xanthogenate pyrolysis, the accessibility of these compounds from the corresponding alcohols provides for a useful route to alkenes. One advantage is that as no acidic or basic reagents are required, rearrangement reactions, which can interfere with alcohol dehydration, are avoided. For example, pyrolysis of lactol acetates has been used to prepare 4,5-dihydrofurans, as illustrated in equation (58),[136,137] and pyrolysis of the corresponding thionocarbonate was used to dehydrate alcohol (**128**; Scheme 38).[138]

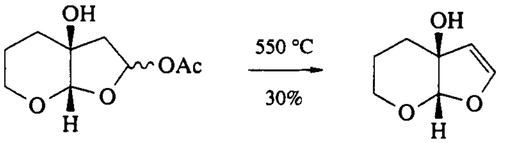
OH
OAc
O
O
H
550 °C
30%
OH
O
O
H

(58)

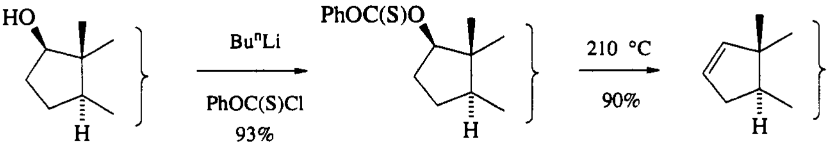
HO
H
Bu^nLi
PhOC(S)Cl
93%
PhOC(S)O
H
210 °C
90%
H

(128)

**Scheme 38**

Pyrolysis of peracetylated pyranose monosaccharides has been studied, and found to proceed *via* initial loss of the 1-acetoxy group followed in some cases by allylic rearrangement.[139] In contrast, peracetylated furanoses lose two acetoxy groups to give substituted furans, *e.g.* equation (59).[140]

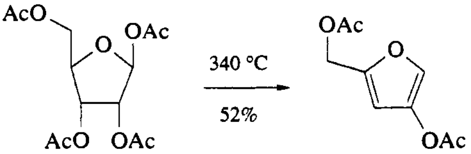
AcO
O
OAc
AcO
OAc
340 °C
52%
OAc
O
OAc

(59)

Thermolysis of acetates has been used to synthesize unstable bridgehead alkenes and dienes, which in some cases have been isolated by trapping at low temperatures. For example, the bicyclic acetate (**129**; equation 60) gave a mixture of bicyclo[3.3.1]non-1-ene (**130**) and its retro-Diels–Alder product (**131**) on pyrolysis at 375–400 °C,[141] and thermolysis of the 3-homoadamantyl acetate (**132**) gave a mixture of products whose formation may have been initiated by acetate elimination.[142,143] Bridgehead dienes are believed to be involved in the formation of products from the diacetate (**133**),[144] and novel dienes were isolated from pyrolysis of acetate (**134**).[145]

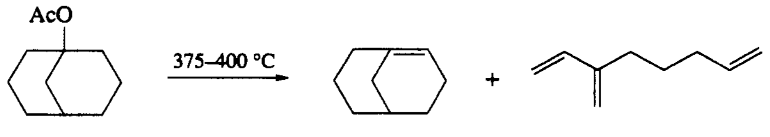

(**129**) (**130**) 66:34 (**131**) (60)

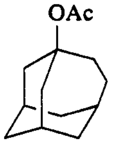

(**132**)

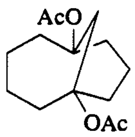

(**133**)

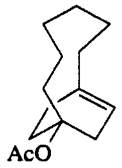

(**134**)

## 5.3.6 SUMMARY

The pyrolytic reactions discussed in this chapter play an important role in modern synthetic organic chemistry for the introduction of carbon–carbon double bonds into complex molecules. They are normally stereo- and regio-selective, and since they are carried out by simply heating the substrate to the required temperature, they avoid acid- and base-catalyzed rearrangements. The Cope elimination provides a useful alternative to the Hoffmann elimination, and the sulfoxide and selenoxide procedures are widely used, particularly for the synthesis of α,β-unsaturated carbonyl compounds, providing the preferred route to these compounds at the present time. The widespread use of xanthogenate, and more particularly acetate, pyrolyses, is limited by the high temperatures required; however, the ready availability of these compounds from alcohols, and the development of flash vacuum techniques, has encouraged their use in, for example, bridgehead alkene synthesis.

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# 5.4

# Fragmentation Reactions

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## 5.4.1 INTRODUCTION

### 5.4.1.1 Definition

Fragmentation reactions, according to the definition of Grob,[1,2] are processes (equation 1) where the reacting molecule breaks into three fragments.

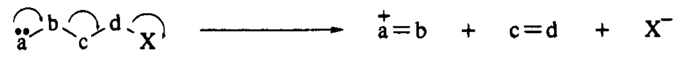

(1)

The electrofugal group a—b forms stable cations or neutral molecules depending on the initial charge. The middle group c—d gives an unsaturated fragment. The nucleofugal group X leaves the atom d with the bonding electron pair. There are many carbon or heteroatom groups containing electrofugal, middle, and nucleofugal groups which can be combined to give fragmentable systems.[1,2]

Fragmentation reactions have to be distinguished clearly from 1,2-elimination reactions (equations 2 and 3), where the electrofugal group is a single atom such as hydrogen or halogen, or an organometallic fragment such as MgBr.[1]

$$B^- + H{-}c{-}d{-}X \longrightarrow BH + c{=}d + X^- \qquad (2)$$

$$Y{-}c{-}d{-}X \longrightarrow Y^+ + c{=}d + X^- \qquad (3)$$

Furthermore, there is a class of reactions (retroaldol, retro-Claisen, *etc.*) which are similar to the fragmentations, but they are not to be considered as such. Here, the electron acceptor group X is double bonded to the atom d, and therefore two fragments rather than three are formed (equation 4).

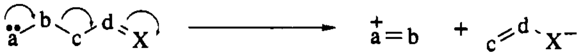

(4)

On the other hand, there are exceptions to the rule that a reaction must lead to three separate fragments when the potential fragments are ring members in cyclic reactants (equation 5).[1] This type is particularly useful in synthesis.

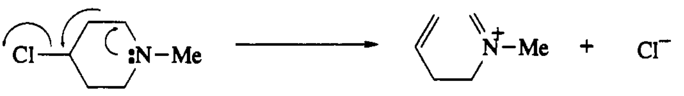

(5)

Finally, there are examples of a so-called seven center fragmentation (equation 6) which can lead to four fragments depending on the bonding situation.

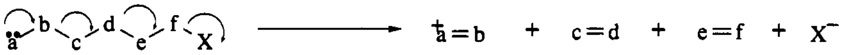

(6)

All the processes mentioned above are heterolytic fragmentations in solution. Homolytic fragmentations (preferably in the gas phase), by thermal energy or by electron impact (MS), will not be described. Unfortunately, the term 'fragmentation' is often confusingly used in the literature. Obviously, this is a semantic problem. Grob[2] first introduced 'Fragmentierung' in German language into the literature, employing this term in a well-defined sense. In English language 'fragmentation' is more or less synonymous with 'cleavage' or 'scission', and it is used in a broader sense. This chapter is limited to the 'real' fragmentations in the definition of Grob,[2] and some related reactions.

## 5.4.1.2 History

The first reactions of the type which we now call fragmentations had already been described in the last century, as Eschenmoser[3] realized in 1952 when he published the reaction of the β-mesyloxy ketone (**1**) with KOH or MeMgI to give the fragmentation products in over 80% yield (Scheme 1). He undoubtedly recognized the common principle, and gave the correct interpretation. It would therefore be justified for the fragmentation to bear his name. Coincidentally, he selected an appropriate educt, since even the next homolog of (**1**) with the six-membered ring yields mainly *S*Ni substitution products under comparable conditions.[4–7]

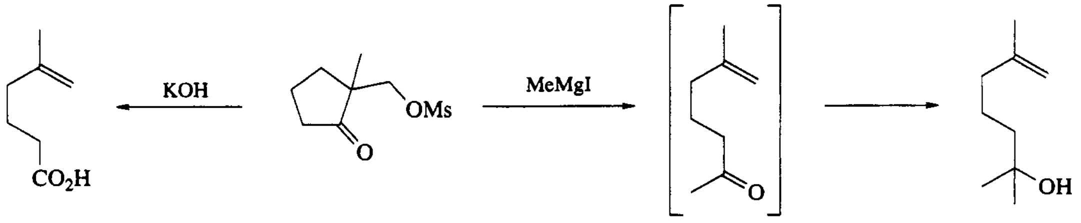

**(2)** **(1)** **(3)**

**Scheme 1**

Since the mid 1950s Grob has investigated these fragmentations in detail, and provided very much experimental material for the scope, mechanism and stereochemistry of this reaction type, summarized in some reviews.[1,2,8] Therefore, the term 'Grob fragmentation' is justified.

The great utility of fragmentations, especially those of 1,3-diol monosulfonates, for the construction of functionalized, medium-sized cycloalkenes was developed by Wharton,[9] by applying previous results.[10] In recognition of his important contributions to the chemistry of heterolytic fragmentations of cyclic 1,3-diol derivatives, this reaction type has been referred to in a recent review as the 'Wharton fragmentation'.[11]

Corey utilized the reaction of appropriately substituted 1,3-hydrindanediol monotosylates for the introduction of the cyclononene moiety in an elegant synthesis of caryophyllene and its isomers (Scheme 2).[12] Some further examples will be found in two recent reviews.[11,13]

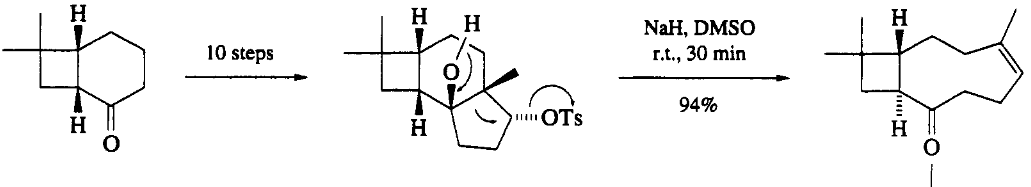

**Scheme 2**

Isocaryophyllene

A special reaction type involves the α,β-epoxy ketone to alkynone fragmentation, often cited as the 'Eschenmoser fragmentation'. First published by Eschenmoser,[14] and a little later and independently by Tanabe,[15] the utility of this fragmentation for the synthesis of open-chained or cyclic alkynones (Scheme 3) is obvious.

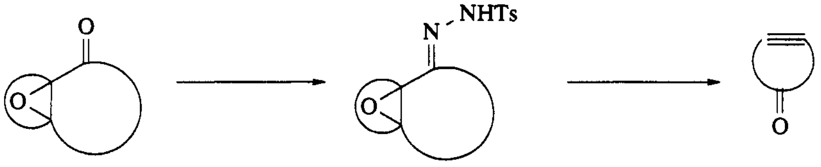

**Scheme 3**

### 5.4.1.3 Mechanism and Stereochemistry

Candidates appropriate for fragmentation (equation 1) in general can also react *via* other pathways. γ-Nucleofuge-substituted alcohols, for example, in nucleophilic solvents are able to undergo substitutions, eliminations and ring closure reactions (Scheme 4). The real result depends on both electronic and steric factors.

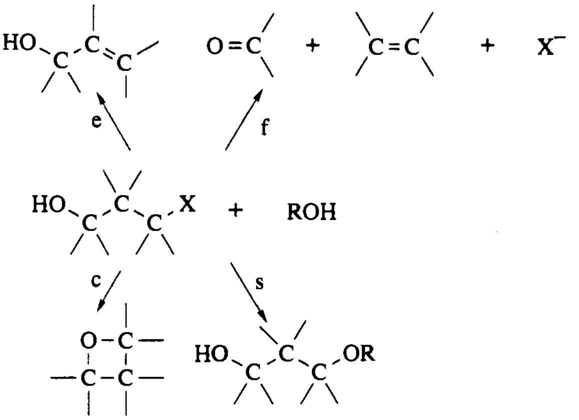

f = fragmentation, s = substitution, e = elimination, c = ring closure

**Scheme 4**

The basic mechanism of fragmentation (equation 1) is a concerted one, with a contribution from each of the five centers to the transition state. Two-step carbonium ion or, very rarely, carbanion mechanisms mean in all cases that substitution, elimination or ring closure can take place rather than fragmentation. However, the one-step synchronous fragmentation is allowed only when the compound can adopt a conformation where the leaving group X as well as the electron pair of the electrofuge Y are antiperiplanar to the C(2)—C(3) bond (Scheme 5).[8]

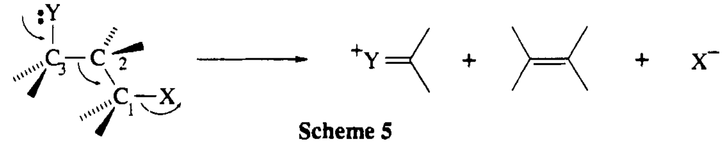

**Scheme 5**

When this stereochemical arrangement cannot be achieved, substitution of the leaving group and elimination reactions take place. This behaviour has also been shown convincingly by Wharton[9] for the four stereoisomeric tosylates (**4**; Scheme 6). (**4a**), (**4b**) and (**4d**) show the crucial bonds to be *anti*, and in these cases fragmentation to the cyclodecenones (**5**) occurs in over 90% yield. The stereochemistry of the C—C bond forming the double bond is strictly retained (**4a** and **4b** give **5a**; **4d** gives **5b**). The isomer (**4c**), having the bonds which may undergo cleavage in a *gauche* orientation remains largely unchanged.

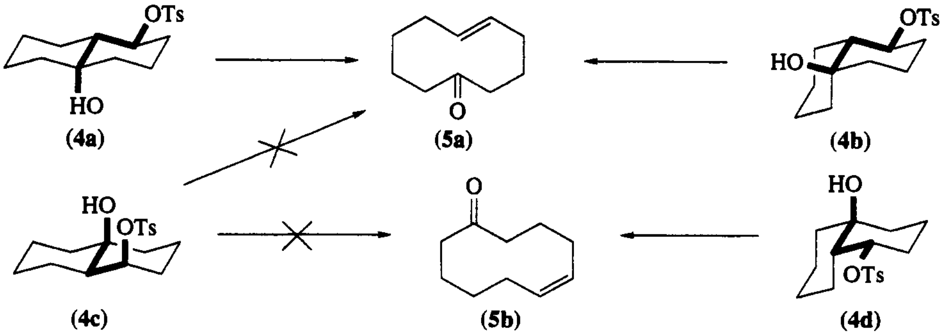

Scheme 6

However, there are some exceptions of this general rule[16a] if strained systems are involved. Together with the synthetic goals, mechanisms will be discussed where *syn* fragmentation apparently is concurrent[16b] or even preferred.[17]

The electronic requirements for the Grob fragmentation from a molecular orbital viewpoint have been described,[18] and in a recent investigation mechanisms of borderline cases of fragmentations have been discussed.[19]

## 5.4.2 SYNTHESIS BY GROB FRAGMENTATION

### 5.4.2.1 Open Chains and Normal Rings

The aim of this section is to show how cyclic precursors can serve as an appropriate starting material for the construction of open-chained or monocyclic intermediates with defined regio- and/or stereospecifity. The nucleofuge usually is halide or sulfonate and the electrofuge an alkoxide, generated from an alcohol by base or from a keto group by attack of a nucleophile.

Fencholene aldehyde (**7**), an interesting starting material for the synthesis of sandalwood fragrance compounds, has been prepared by $AgNO_3$-assisted fragmentation of bromoisofenchol (**6**). The acetals (**8**) of fencholene aldehyde (**7**) are directly available in a one-pot reaction under anhydrous conditions.[20] Also, these acetals are useful as fragrances (Scheme 7).

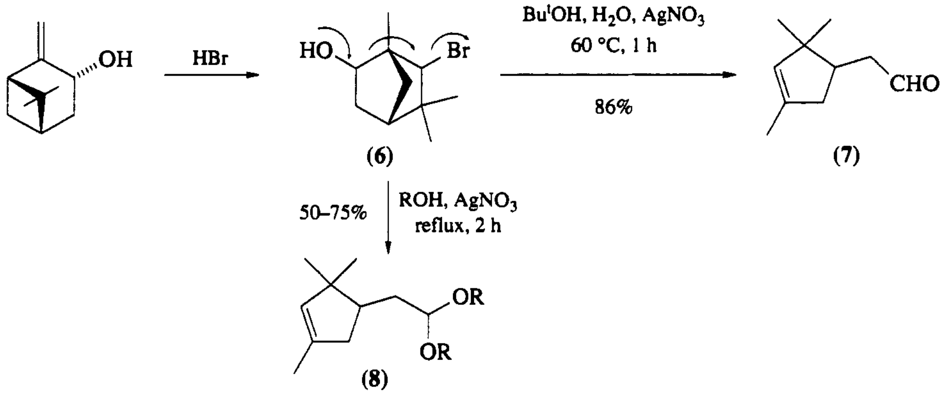

Scheme 7

For the stereoselective total synthesis of bazzanene (**12**; Scheme 8),[21] a sesquiterpene isolated from the liverwort *Bazzania pompeana*, the fragmentation of the monoprotected mesylate (**10**) was used. The mesylate (**10**) is obtained from the triol (**9**), an intermediate in the synthesis of gymnomitrane sesquiterpenes.[22] Treatment of (**10**) with KOBu$^t$ produces cleanly the expected cyclohexenone (**11**).

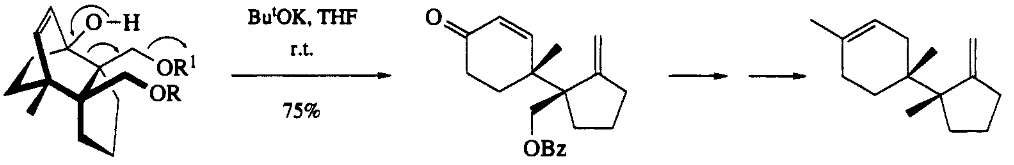

(**9**) R, R$^1$ = H
(**10**) R = Bz, R$^1$ = Ms

(**11**)

(**12**)

Scheme 8

The trichothecenes, *e.g.* (**15**), are a class of almost four dozen fungal metabolites that possess among them insecticidal, antifungal and cytotoxic activity. Related to the preceding fragmentation is a reaction sequence which was used by Still[23] in his trichodermol (**15**) synthesis, an outstanding piece of synthetic craftsmanship. Thirteen steps are necessary to obtain the tetracyclic triol derivative (**13**). Treatment with NaH under mild conditions gave stereoselectively the fragmentation product (**14**). After a further ten steps the target molecule (**15**) was obtained (Scheme 9).

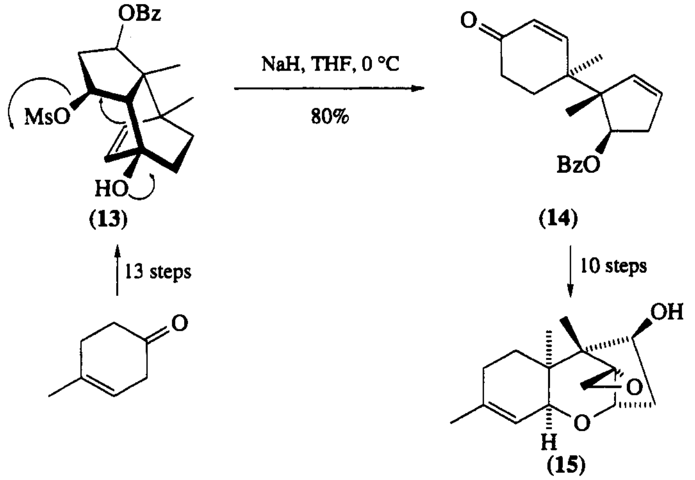

Scheme 9

The tricyclic ketone (**17**), a fragrant and volatile key compound of the zizaene (**19**) synthesis, results from a fragmentation of the tetracyclic mesylate (**16**).[24] This skeleton has also been formed by intramolecular photocycloaddition of the easily accessible enol acetate (**18**). Obviously, the ring strain of (**16**) is a strong driving force (Scheme 10).

The use of (+)- or (–)-camphor as a chiral starting material in natural product synthesis[25a] is dependent on the availability of methods for the regiospecific and stereoretentive functionalization of camphor at the C-8, C-9 or C-10 position.[25b] Money[26] has shown that (+)-camphor can easily be converted to (+)-9,10-dibromocamphor (**20**), and that the latter compound undergoes facile, efficient fragmentation with base to provide monocyclic bromo acid (+)-(**21a**), or its methyl ester (**21b**),[29b] in almost quantitative yield. This versatile chiral synthon has been used for an enantiospecific formal synthesis[27] of one of the sex pheromones of female California red scale (**22**), for a synthetic route to bicyclic enone (**23**), which could be used as a key intermediate in pseudoguaianolide synthesis,[28] for a new enantiospecific synthesis of (–)-estrone (**24**), providing ring D;[29a] and for the valuable chiral intermediate (**24a**) in steroid synthesis (Scheme 11).[29b]

The first naturally occurring member of the class of fenestranes is the diterpene lauren-1-ene (**27**), isolated in 1979 from the essential oil of *Dacrydium cupressinum*. The intermediate (**26**) for Wender's[30] stereocontrolled synthesis of (**27**) is readily accessible by attack of KOH on the tosyloxy ketone (**25**) to give, *via* fragmentation, a carboxylate anion which undergoes immediate ring closure to the lactone (**26**; Scheme 12).

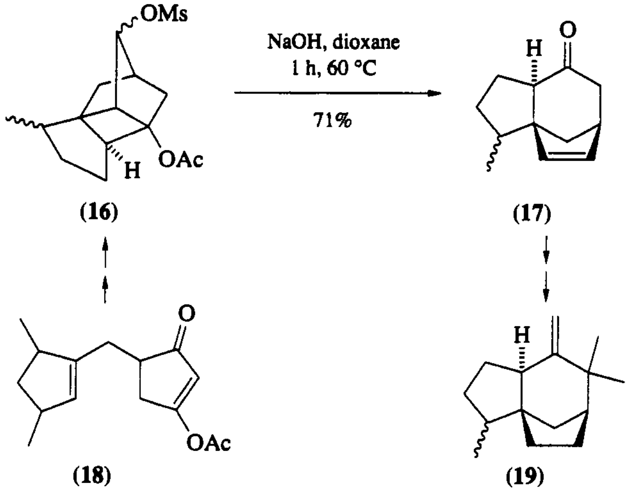
OMs
H
OAc
NaOH, dioxane
1 h, 60 °C
71%
H
O
O
OAc
H
(16)
(17)
(18)
(19)

**Scheme 10**

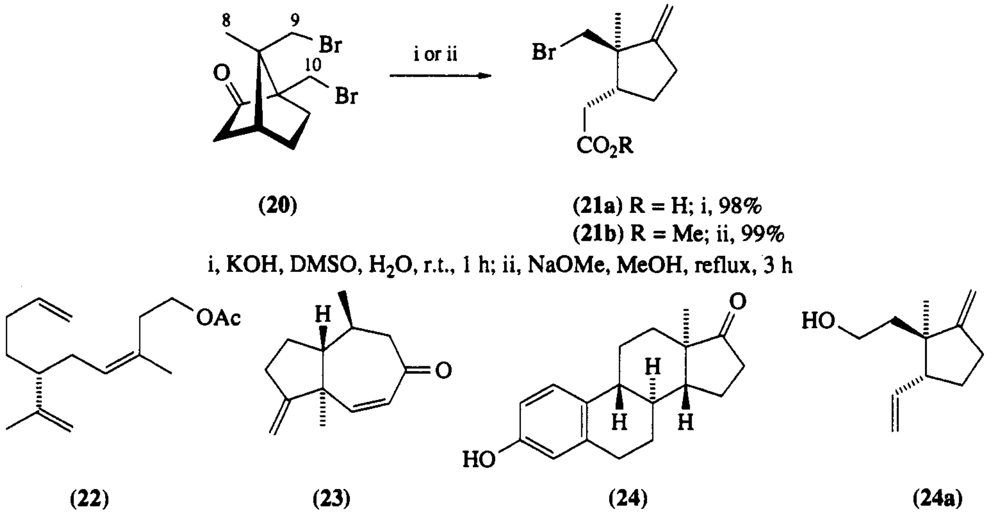
8
9
Br
10
Br
O
i or ii
Br
CO2R
(20)
OAc
H
O
O
H
H
H
HO
HO
(22)
(23)
(24)
(24a)

(**21a**) R = H; i, 98%
(**21b**) R = Me; ii, 99%
i, KOH, DMSO, $H_2O$, r.t., 1 h; ii, NaOMe, MeOH, reflux, 3 h

**Scheme 11**

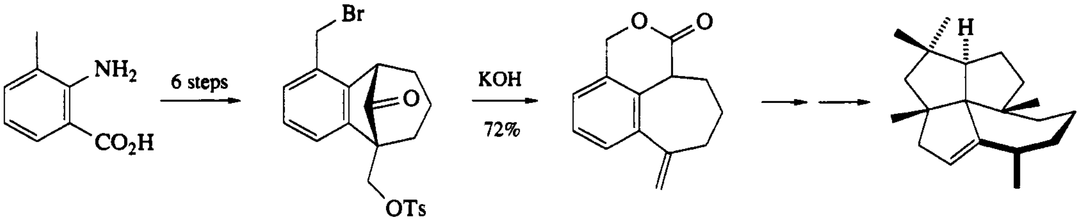
NH2
CO2H
6 steps
Br
O
OTs
KOH
72%
O
O
H
(25)
(26)
(27)

**Scheme 12**

Iwata's[31] synthesis of subergorgic acid (**30**), a silphiperfolane derivative isolated from a gorgonian coral, involved the reductive fragmentation of the cyclobutanone (**28**) to the alcohol (**29**) *via* an intermediate aldehyde (Scheme 13).

Two of the side chains of the geijerone (**35**) or γ-elemene (**36**) system have been introduced by Yoshikoshi[32a] by means of fragmentation of the appropriate bicyclus (**32**), synthesized from the Wieland–Miescher ketone (**31**). It is remarkable that reduction of ketone (**32**) under mild conditions allows the isolation of the hydroxy mesylate (**33**), which undergoes fragmentation to (**34**) at elevated temperatures (Scheme 14).

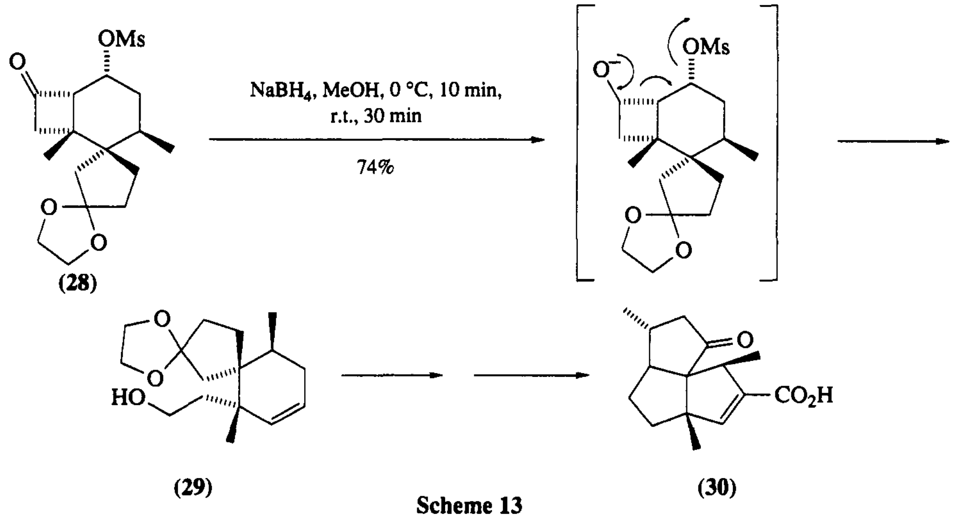
OMs
O
(28)
NaBH4, MeOH, 0 °C, 10 min, r.t., 30 min
74%
O⁻
OMs
O
HO
(29)
O
CO2H
(30)

**Scheme 13**

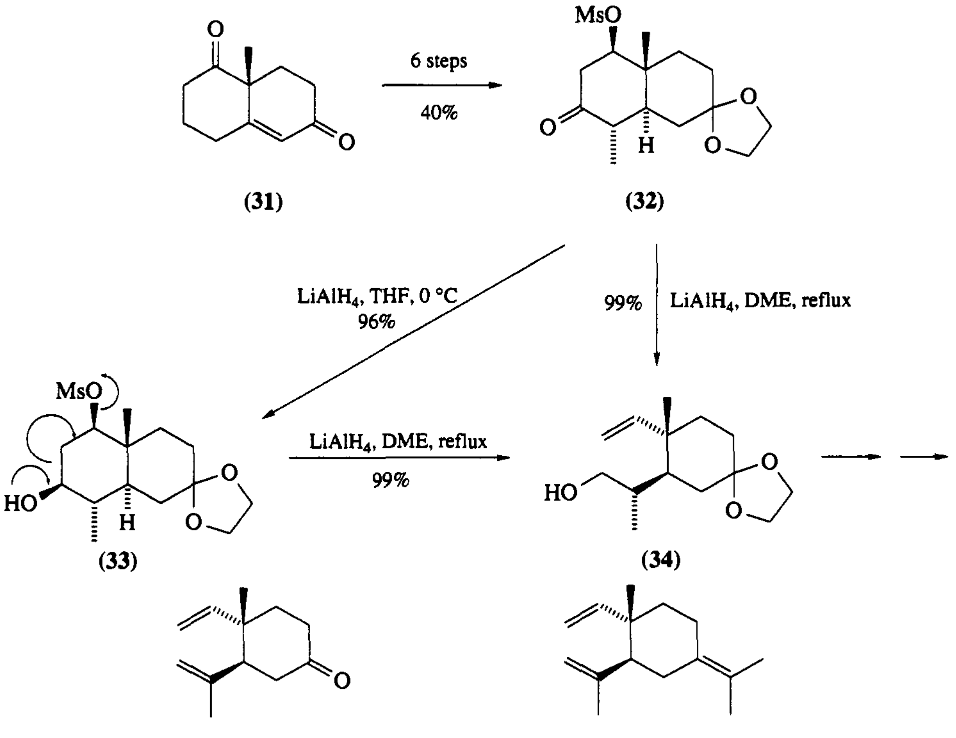
O
O
(31)
6 steps
40%
MsO
O
H
O
O
(32)
LiAlH4, THF, 0 °C
96%
99%
LiAlH4, DME, reflux
MsO
HO
H
O
O
(33)
LiAlH4, DME, reflux
99%
HO
O
O
(34)
O
(35)
(36)

**Scheme 14**

Yoshikoshi[32b] recently reported a 1,3-diol fragmentation (Scheme 14a) under mild conditions, where a benzylic hydroxy group activated by the 2,6-dimethoxy-4-methylphenyl group proved to be a remarkably reactive nucleofuge.

In a synthesis which correlates (–)-β-pinene with (+)-hinesol (**41**; Scheme 15), Magnus[33] started with (+)-nopinone (**37**) which provided, after several steps, the sulfone (**38**) as the key compound. Under alkaline conditions, (**38**) gives the β-keto sulfone (**40**) *via* intramolecular attack of the carbanion of (**38**) forming the alkoxide (**39**). Release of ring strain is responsible for the domination of the fragmentation rather than typical alternatives such as oxetane formation, substitution, or other reaction pathways. Traces of water in the fragmentation step give rise to the formation of carboxylic acid (**42**).

One of the very rare cases where a triple bond is formed by a normal Grob fragmentation is described by Corey[34] in the course of the synthesis of hybrida lactone (**45**), an eicosanoid, isolated from the marine alga *Laurencia hybrida*. The strained enol tosylate (**43**) yields the ethynyl ketone (**44**) under very mild

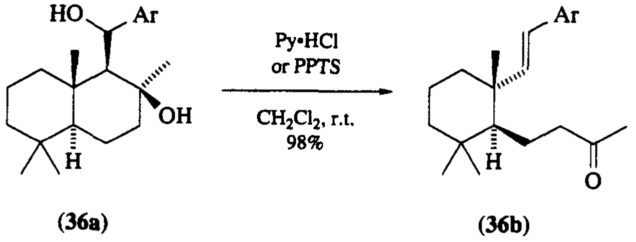
HO
Ar
OH
H
Py•HCl
or PPTS
$CH_2Cl_2$, r.t.
98%
Ar
H
O
(36a)
(36b)

Ar = 2,6-dimethoxy-4-methylphenyl

Scheme 14a

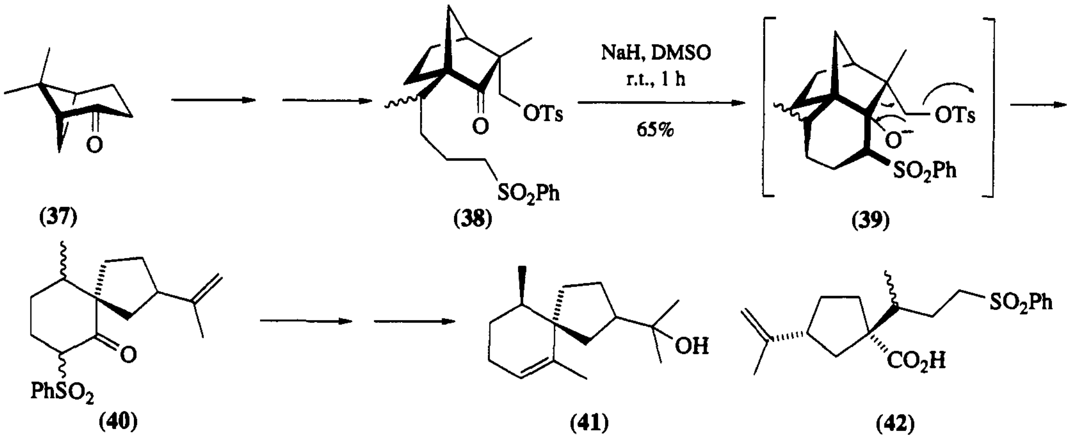
O
(37)
O
OTs
$SO_2Ph$
(38)
NaH, DMSO
r.t., 1 h
65%
OTs
$O^-$
$SO_2Ph$
(39)
O
$PhSO_2$
(40)
OH
(41)
$SO_2Ph$
$CO_2H$
(42)

Scheme 15

conditions. The initially formed *cis* isomer of (**44**) is equilibrated during the reaction time to a 9:1 *trans:cis* mixture (Scheme 16).

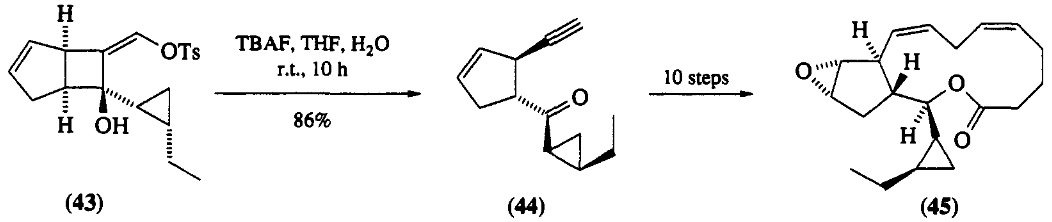
H
OTs
H
OH
(43)
TBAF, THF, $H_2O$
r.t., 10 h
86%
O
(44)
10 steps
H
O
H
O
H
O
(45)

Scheme 16

The introduction of cyclobutanone units into organic substrates has been combined with the Grob fragmentation by Trost,[16] giving a useful approach to chain extension. This procedure has been termed generally 'secoalkylation'. In the case shown in Scheme 17, since one of the ring atoms is oxygen, it is termed 'oxasecoalkylation'. Thus, epoxy ketone (**46**) when treated with NaOMe gives hydroxy ester (**47**) in almost quantitative yield. MeLi addition to (**46**) at −78 °C followed by addition of water and allowing to warm to room temperature yields hydroxy ketone (**49**; Scheme 18). Alternatively, the epoxycyclobutanol (**48**) can be isolated if the reaction mixture is worked up immediately after quenching with water at low temperatures. Treatment of (**48**) with NaOMe then gives smooth fragmentation to the same hydroxy ketone (**49**).

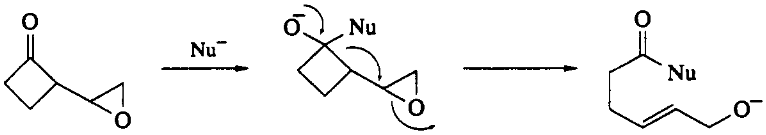
O
O
$Nu^-$
$O^-$
Nu
O
O
Nu
$O^-$

Scheme 17

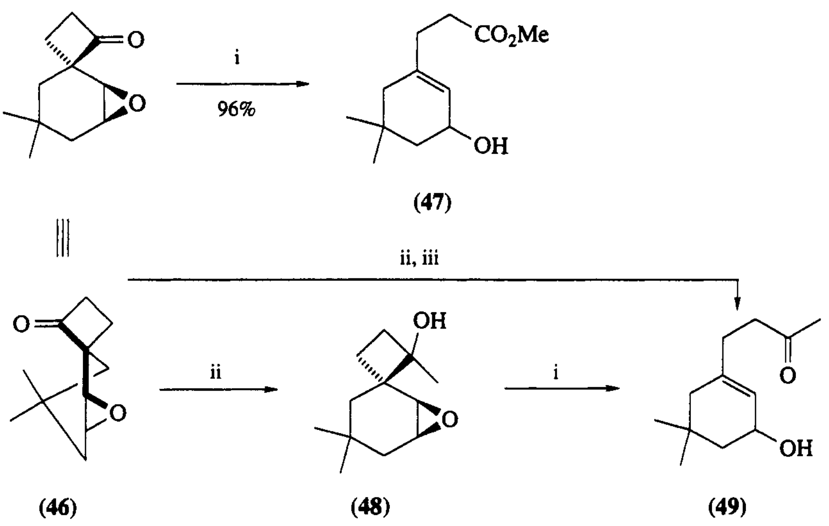

i, NaOMe, MeOH, r.t.; ii, MeLi, –78 °C; iii, $H_2O$, r.t.

**Scheme 18**

In the conformation of (**46**; Scheme 18), the cyclobutyl and epoxy bonds shown in bold bear an approximate *trans* diaxial relationship. Conversion of the carbonyl group into a good electron source by addition of nucleophiles should initiate fragmentation accompanied by the release of 54 kcal $mol^{-1}$ (1 cal = 4.2 J), the combined strain energies of the cyclobutyl and epoxide rings. However, Trost has pointed out that fragmentation of cyclobutanols does not appear to require the *trans* orientation, since even in cases where a *trans* elimination is not possible fragmentation is smooth in all cases of sterically rigid systems. To investigate unstrained systems, both isomers of epoxycyclobutanone (**50**) were converted with NaOMe to the hydroxy esters (**51**; Scheme 19). (**50a**) leads cleanly to a single (*Z*)-ester (**51a**), and similarly (**50b**) produces a single (*E*)-ester (**51b**). Although the fragmentation is stereospecifically *anti* under the above conditions, with stronger Lewis acids such as $Mg(OMe)_2$ chelation occurs to favour *syn* fragmentation with mixtures of (**51a**) and (**51b**) deriving from both pure (**50a**) and (**50b**). These findings reflect a mixed mechanism between the concerted *anti* and concerted *syn* fragmentation, but even the possibility of a carbonium ion mechanism cannot be rigorously excluded.

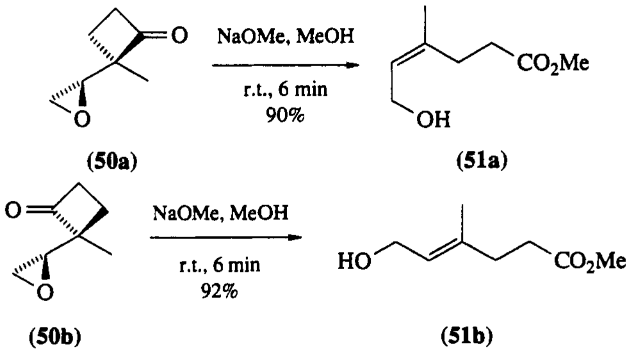

**Scheme 19**

Similarly, Trost[35] has also shown that carbon can function as a nucleofugal atom in Grob fragmentation. These fragmentations occur when two electron-withdrawing groups are present. Thus, the diester (**52**; Scheme 20) gives hydroxy diester (**53**) through reductive fragmentation. The monoester does not react at all in this sense.

The acid fragmentation of suitably substituted bicyclo[2.2.2]octanes to cyclohexenones and subsequent ring closure to spirovetivanes *via* π-cation cyclization has been used by Murai[36] for a highly stereoselective isolubimin (**56**) synthesis. (**56**) has been considered to play an important role in the biogenetic pathway of various spirovetivane phytoalexins in the Solanaceae family. Treatment of methyl

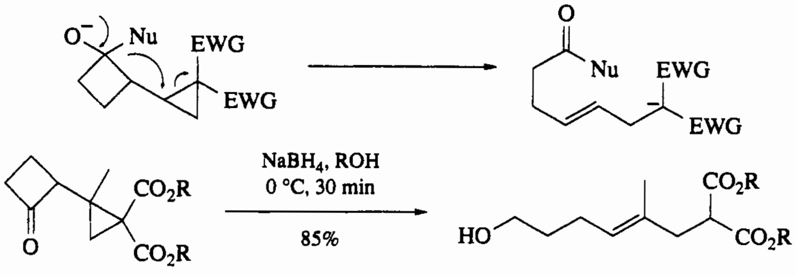

**(52)** **(53)**

**Scheme 20**

ether (**54**) with formic acid gives enone (**55**) by acid fragmentation. The crude (**55**) is immediately cyclized to the spiroketone (Scheme 21).

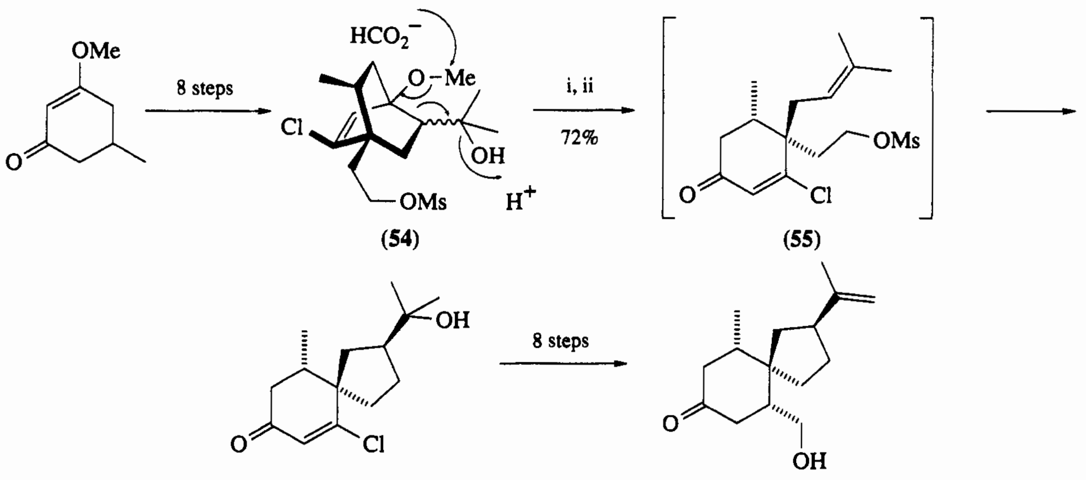

**(54)** **(55)** **(56)**

i, $HCO_2H$, r.t., 2 h; ii, $(CO_2H)_2$, $MeCOBu^i$, $H_2O$, reflux, 8 h

**Scheme 21**

### 5.4.2.2 Medium-sized and Large Rings

Fragmentation of appropriate bicyclic sulfonyloxy alcohols or ketones is a general route towards cycloalkene ketones or carboxylic acids. Thus, the hydroazulene alcohol (**59**; Scheme 22), precursor for the synthesis of daucene (**60**), jaeschkeana diol and others, has been synthesized[37] by a one-pot reaction (fragmentation and isopropylation) of the hydroxy tosylate (**57**) with $Pr^iLi$. The fragmentation of (**57**) to give the ketone (**58**) as the primary product can be achieved by treatment with pyridine.

The equatorial tosylate (**61**; Scheme 23) is smoothly converted to the half-ester (**62**) by treatment with KOH. Similarly, reaction of (**61**) with NaOEt furnishes the corresponding diester, whilst under these conditions the axial epimer (**63**) is recovered in high yield.[38] The inertness of (**63**) is not unexpected, for compounds of this type are stereoelectronically incapable of a facile fragmentation. It is therefore of interest that when again KOH is used, the axial tosylate affords the acid (**65**) in excellent yield. This product must arise *via* (**64**) by a synperiplanar fragmentation.

The bridged hydroazulene dehydrokessane (**70**; Scheme 24) has been synthesized from the methylene ketone (**69**). The precursor is the diol (**67**), obtained from the readily accessible photoadduct (**66**). Treatment of (**67**) with TsCl in pyridine furnishes directly the ketone (**69**) in high yield.[39] Obviously, fragmentation of the intermediate tosylate (**68**) proceeds very rapidly due to the ring strain of the tricyclus.

A fragmentation of a similar tricyclus has been used by Oppolzer[40] for the synthesis of the hydroazulene ketone (**74**; Scheme 25), precursor of the bulnesenes (**75**). The tricyclic ketone (**71**), obtained by intramolecular photoaddition, is converted to the diol (**72**). Fragmentation is accomplished in one

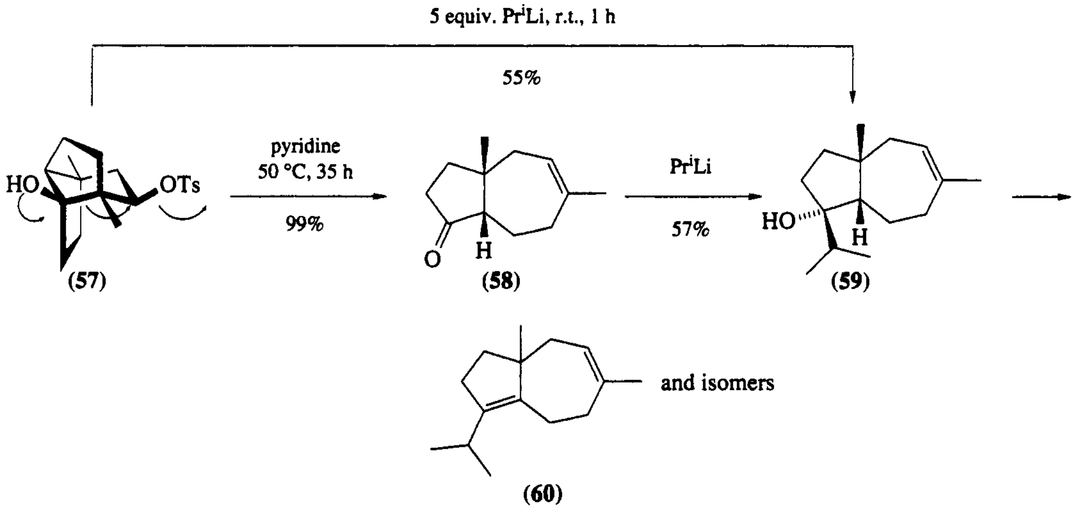
5 equiv. Pr$^i$Li, r.t., 1 h
55%
HO
OTs
(57)
pyridine
50 °C, 35 h
99%
O
H
(58)
Pr$^i$Li
57%
HO
H
(59)
and isomers
(60)

Scheme 22

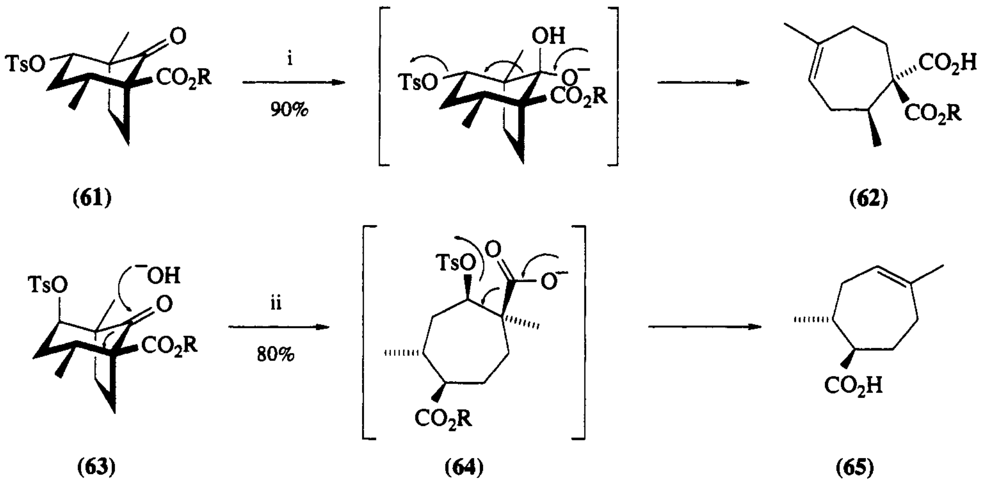
TsO
O
CO$_2$R
(61)
i
90%
OH
TsO
O$^-$
CO$_2$R
CO$_2$H
CO$_2$R
(62)
TsO
$^-$OH
O
CO$_2$R
(63)
ii
80%
TsO
O
O$^-$
CO$_2$R
(64)
CO$_2$H
(65)

i, KOH, dioxane, H$_2$O, reflux, 30 min; ii, KOH, EtOH, reflux, 16 h

Scheme 23

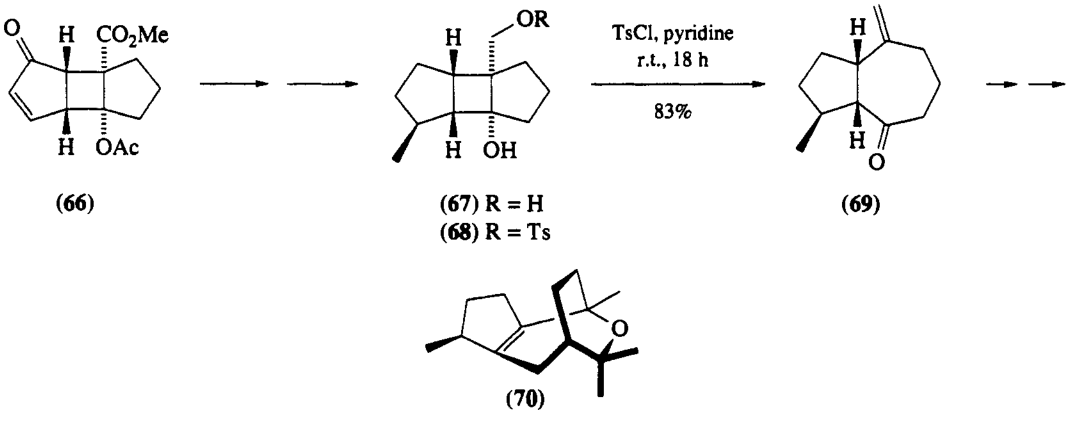
O
H
CO$_2$Me
H
OAc
(66)
H
OR
H
OH
(67) R = H
(68) R = Ts
TsCl, pyridine
r.t., 18 h
83%
H
H
O
(69)
O
(70)

Scheme 24

synthetic operation by reaction of (**72**) with MsCl, without isolation of the presumed intermediate mesylate (**73**), yielding (**74**).

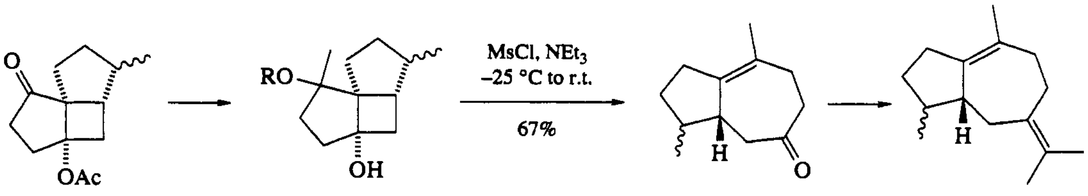

(**71**) (**72**) R = H (**73**) R = Ms (**74**) (**75**)

Scheme 25

Sakai[41] has reported that under acetalization conditions, cyclopentanones and cyclohexanones with carbonyl functions in an appropriate position in a side chain undergo facile ring cleavage to construct a new ring. Particularly useful is the reaction sequence starting from a cyclopentanone with the carbonyl function at the C-3 position of the α-position side chain (Scheme 26). After aldol condensation and acetalization, a fragmentation takes place which may be considered as one of the unusual cases of the Grob type.[42a] This ring expansion has been applied to the synthesis of bulnesol (**78**), with the sequence leading from (**76**) to (**77**) as the key step (Scheme 27). Similarly, bicyclo[*m*.*n*.0]alkanes are converted to spirocyclic skeletons.[42b]

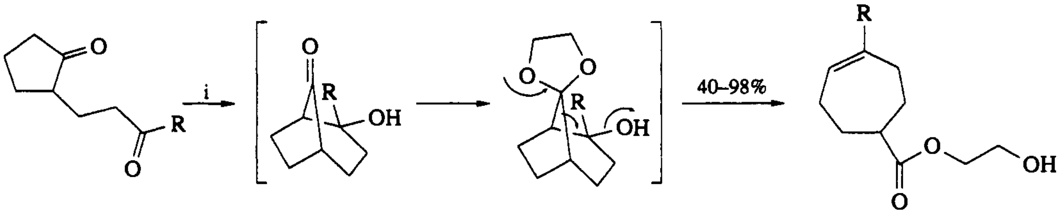

i, $BF_3 \cdot Et_2O$, $HOCH_2CH_2OH$, r.t., 2 h

Scheme 26

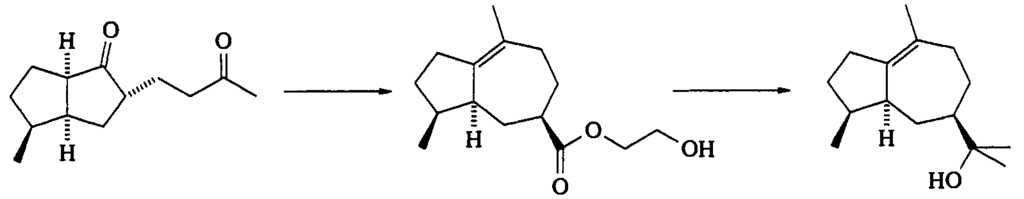

(**76**) (**77**) (**78**)

Scheme 27

Pleuromutilin (**81**; Scheme 28) an antibiotic isolated from several species of Basidiomycetes, *e.g. Pleurotus mutilis*, has been synthesized in a 30-step sequence.[43] One of the most important steps is the fragmentation of (**79**) to generate the required tricyclic skeleton of this diterpene. Direct retroaldol ring opening of (**79**) to the respective diketone is unsuccessful, but a two-step sequence *via* the ketoallyl bromide (**80**) results in the desired transformation.

The taxane family of diterpenes with a unique tricyclic ring system has attracted interest in both the biological and chemical communities. Particularly, taxol (**82**) exhibits singular biological activity through its ability to promote microtubule assembly. It is a most promising antitumor agent, now in phase II clinical trials, obtained from the bark of the pacific yew tree.

Holton's[44] plan for the synthesis of the AB ring system of taxanes (*e.g.* **83**) involves fragmentation of an easily accessible tricyclic compound derived from patchouli alcohol. Hydroxy-directed epoxidation of the tertiary alcohol (**84**) (from patchino **90**) gives an unstable substance which undergoes fragmentation *in situ* to provide the keto alcohol (**85**; Scheme 29).

Reactions similar to this type of fragmentation have been encountered by Sukh Dev[45] in longifolene chemistry. One noteworthy feature of the fragmentation leading to (**85**) is the synperiplanar orientation

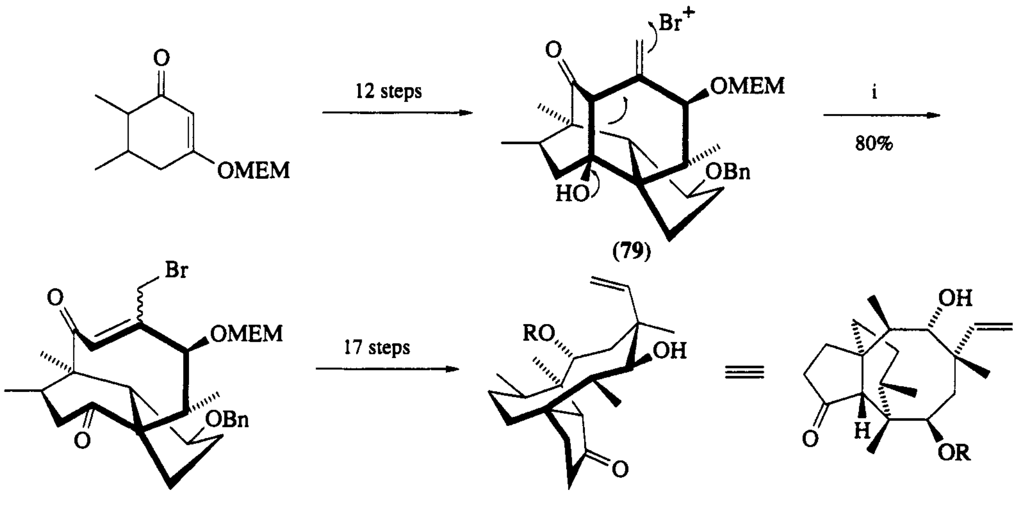
O
OMEM
12 steps
Br+
O
OMEM
OBn
HO
(79)
i
80%
Br
O
OMEM
OBn
O
(80)
17 steps
RO
OH
O
≡
OH
O
H
OR

(81) R = $COCH_2OH$

i, NBA, MeOH, $H_2O$, r.t., 8 h

Scheme 28

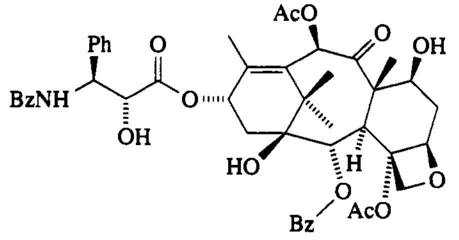
Ph
O
BzNH
O
OH
AcO
O
OH
HO
H
O
Bz
AcO
O

**(82)**

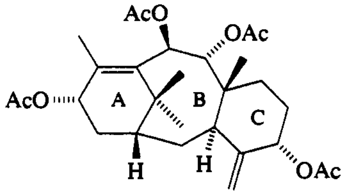
AcO
OAc
AcO
A
B
C
H
H
OAc

**(83)**

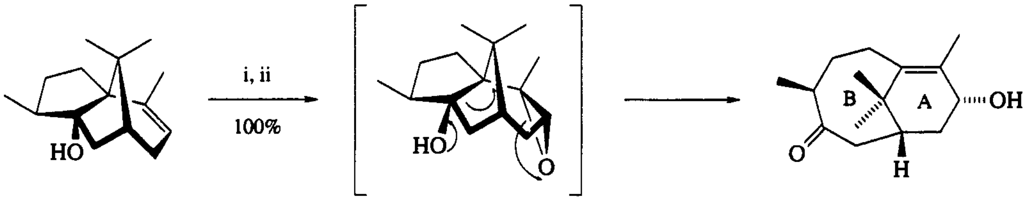
HO
i, ii
100%
HO
O
B
A
OH
O
H

**(84)** **(85)**

i, $Bu^tO_2H$, $Ti(OPr^i)_4$, $CH_2Cl_2$, 0 °C, 1 h; ii, $Me_2S$, reflux, 5–8 h

Scheme 29

of the breaking bonds. In ancillary studies it has been found that the synperiplanar relationship between breaking bonds is required for facile fragmentation in a related bridged bicyclic system.[17] Thus, the epoxy alcohol (**86**) with an antiperiplanar alignment of breaking bonds cyclizes to provide oxetane (**87**) in high yield. In contrast to this result, epoxide (**88**) reacts rapidly to provide a quantitative yield of lactol (**89**). These findings might be interpreted as a general preference for *syn* elimination of epoxides. However, the norbornane skeleton is constrained, so that the C(1)—C(2) bond and the C(6)—O bond are more nearly coplanar in *endo*-epoxide (**88**) than in *exo*-epoxide (**86**). This fact could be solely responsible for the above observations (Scheme 30).

The above results were again applied by Holton[46] in the even more challenging synthesis of taxusin (**83**). The cornerstone of the strategy is the fragmentation of the hydroxylated alkene (**91**) to the ketone (**92**) *via* the unstable epoxide (Scheme 31). This (–)-taxusin (**83**) synthesis requires more than 30

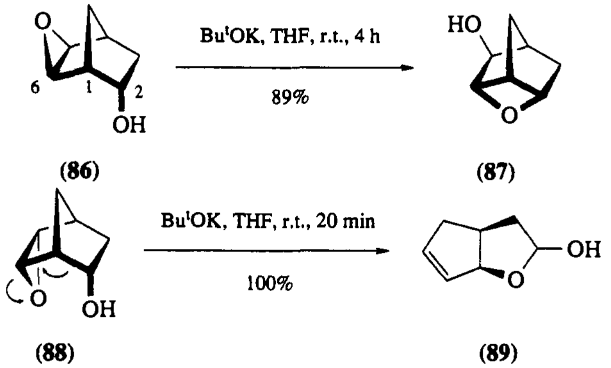

(86) (87) (88) (89)

Scheme 30

reactions; however, it is most efficiently performed in approximately 24 laboratory operations in more than 20% overall yield from (–)-patchino (**90**).

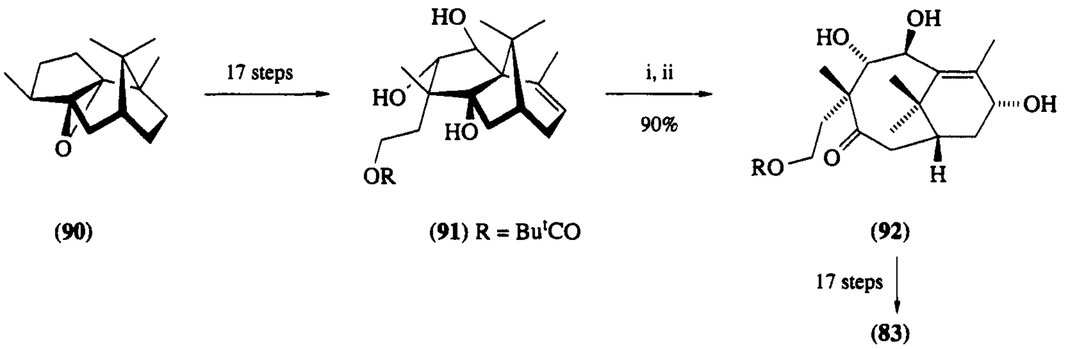

(**90**) (**91**) R = Bu$^t$CO (**92**) (**83**)

i, $MeCO_3H$ (large excess), $CH_2Cl_2$, r.t., 30 min; ii, $Ti(OPr^i)_4$, $CH_2Cl_2$, reflux, 45 min

Scheme 31

The fungus *Stereum purpureum*, the cause of the so-called silver leaf disease common on fruit trees, produces a new type of sesquiterpenoid (and derivatives) when grown in liquid culture, *viz.* sterpuric acid (**93**; Scheme 32). An undesired fragmentation reaction of a strained hydroxy tosylate (**95**) is observed during the synthesis of (**93**).[47] Attempts to transform the hydroxymethyl group of (**94**) to a methyl group have been unsuccessful, mainly because of the tendency of this system to undergo fragmentation. Tosylation of (**94**) provides (**95**) along with a small amount of the cyclooctenone (**96**). Several reactions designed to bring about replacement of the tosyloxy group with hydrogen (*e.g.* NaI/Zn) invariably lead to fragmentation.

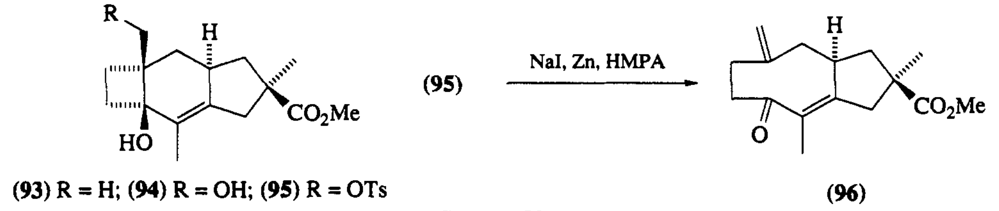

(**93**) R = H; (**94**) R = OH; (**95**) R = OTs (**96**)

Scheme 32

Wharton[48] has described the fragmentation of the fused bromochlorodecalin (**97**; Scheme 33) with zinc dust in the presence of EDTA in boiling aqueous ethanol which gives the cyclodecadiene system (**98**). Babler[49] has suggested the use of chromium(II) complexes for similar reactions, *e.g.* the reaction of (**99**) to give (**100**). If successful, chromium(II) may be advantageous over zinc since fragmentation reactions involving the latter are generally run at elevated temperatures, conditions under which a Cope rearrangement of the diene product can occur.

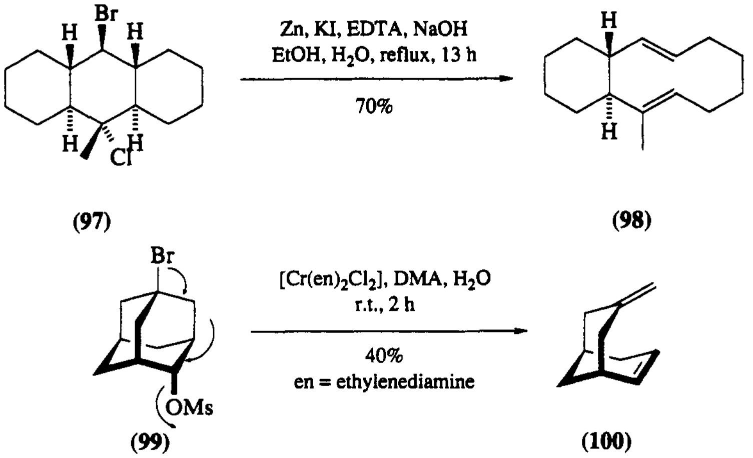
Br
H
H
H
H
Cl
(97)
Zn, KI, EDTA, NaOH
EtOH, $H_2O$, reflux, 13 h
70%
H
H
(98)
Br
OMs
(99)
$[Cr(en)_2Cl_2]$, DMA, $H_2O$
r.t., 2 h
40%
en = ethylenediamine
(100)

Scheme 33

Boronates are excellent starting points for a Grob fragmentation,[50] particularly in hydroazulene synthesis.[51] Another example is given by Wharton's synthesis of hedycaryol (**104**).[52a] The requisite boronate (**103**; Scheme 34) is prepared in a straightforward manner from (**101**), proceeding *via* hydroboration of the unsaturated tosylate (**102**) and subsequent hydrolysis of the monoalkylborane. The latter step also brings about the fragmentation to give (**104**).

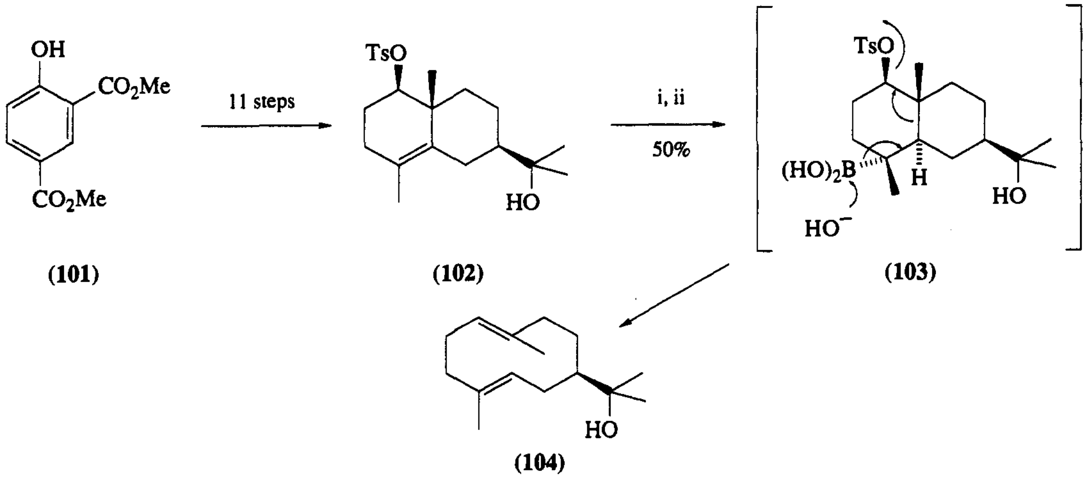
OH
$CO_2Me$
$CO_2Me$
(101)
11 steps
TsO
HO
(102)
i, ii
50%
TsO
$(HO)_2B$
H
HO
$HO^-$
(103)
HO
(104)

i, $B_2H_6$, THF, 0 °C, 2 h, r.t., 7 h; ii, 5 M NaOH, 65 °C, 13 h

Scheme 34

A very recent example of a Wharton-type fragmentation under modified conditions has been reported by De Clercq[52b] in an approach to the synthesis of periplanone B (**104c**) *via* diol (**104a**) and the 10-membered ketone (**104b**; Scheme 34a).

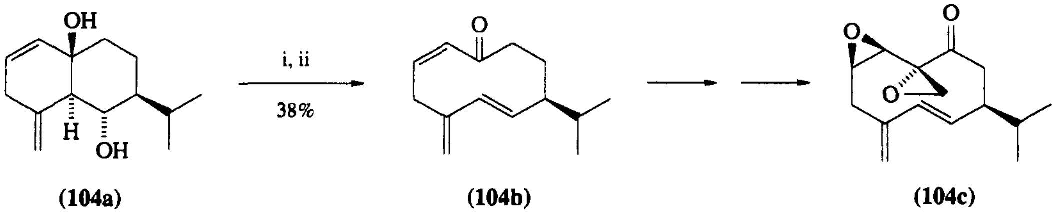
OH
H
OH
(104a)
i, ii
38%
O
(104b)
O
O
O
(104c)

i, 2 equiv. BuLi, –30 °C, 30 min; ii, 3 equiv. TFAA, ether, –20 °C, 15 min

Scheme 34a

Mander[53] has provided the first example of an enolate-assisted fragmentation reaction. It was shown that the ester enolate (**105**), in which the activating ester is exocyclic to the ring, clearly undergoes intraannular fragmentation to yield the 1,5-diene ester (**106**; Scheme 35).

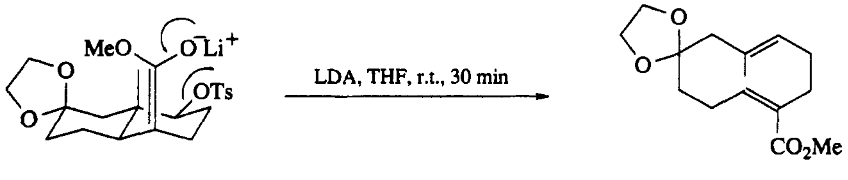

**(105)** **(106)**

Scheme 35

Another recent example for a similar enolate fragmentation to construct a 10-membered ring is represented by the last step of the sericenine (**108**; Scheme 36) synthesis.[54] (**108**) is a constituent of the essential oil of the leaves of *Neolitsea sericea* (Lauraceae), which grows in the southern parts of Japan and China. The tosyloxy ester (**107**) gives directly the furanogermacradiene (**108**), presumably *via* the neosericenine with the *cis*-α,β-unsaturated ester group, which isomerizes to the thermodynamically favored product.

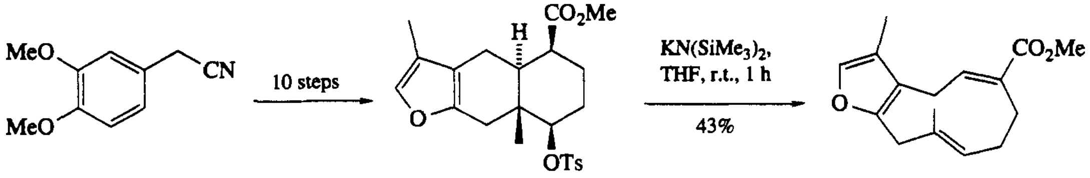

**(107)** **(108)**

Scheme 36

Fuchs[55] has used this reaction type for the construction of an 11-membered ring in the course of model studies for the [11]cytochalasin synthesis. These cytostatic compounds, *e.g.* cytochalasin C (**109**), are metabolites of microorganisms. Reductive fragmentation of the benzenesulfonates (**110**; Scheme 37) produces the dienols (**111**). In contrast, both the sulfonates (**112**) on treatment with LDA afford the tricyclic ketones (**113**), the products of internal alkylation. Less than 1% of (**111**) is formed. In conclusion, the author points out that the enolate conformation (Scheme 37, in parentheses) appears to be all important in determining the reaction products of the four diastereoisomers (**110**) and (**112**). Whenever the enolate can easily assume a folded conformation, the tricyclic cyclobutane (**113**) will result. Models of the enolates of (**110**), where the intraannular fragmentation successfully occurs, show that the folded conformations are more strained than are the extended conformations.

Unsaturated macrolides such as (**115**) or (**117**) (Scheme 38) have been synthesized by Eschenmoser using a fragmentation reaction as a key step. The tricyclic ketal carboxylate (**114**) can be cleaved as an amidinium salt to give (**115**) in excellent yield simply on heating.[56] Similarly, the macrolide (**117**) with (*E*,*E*)-configuration is obtained from (**116**).[57] This decarboxylative double fragmentation represents a nine-center Grob type.

Exaltone (cyclopentadecanone) (**118**; Scheme 39) and more so muscone (3-methylcyclopentadecanone) (**119**) are valuable musk fragrances of great commercial potential. Since the construction of a 15-membered ring by direct ring closure is quite difficult, ring extension methods possess particular

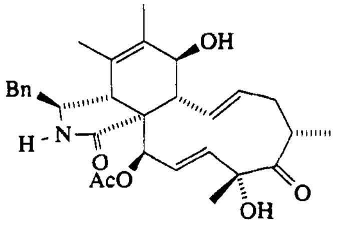

**(109)**

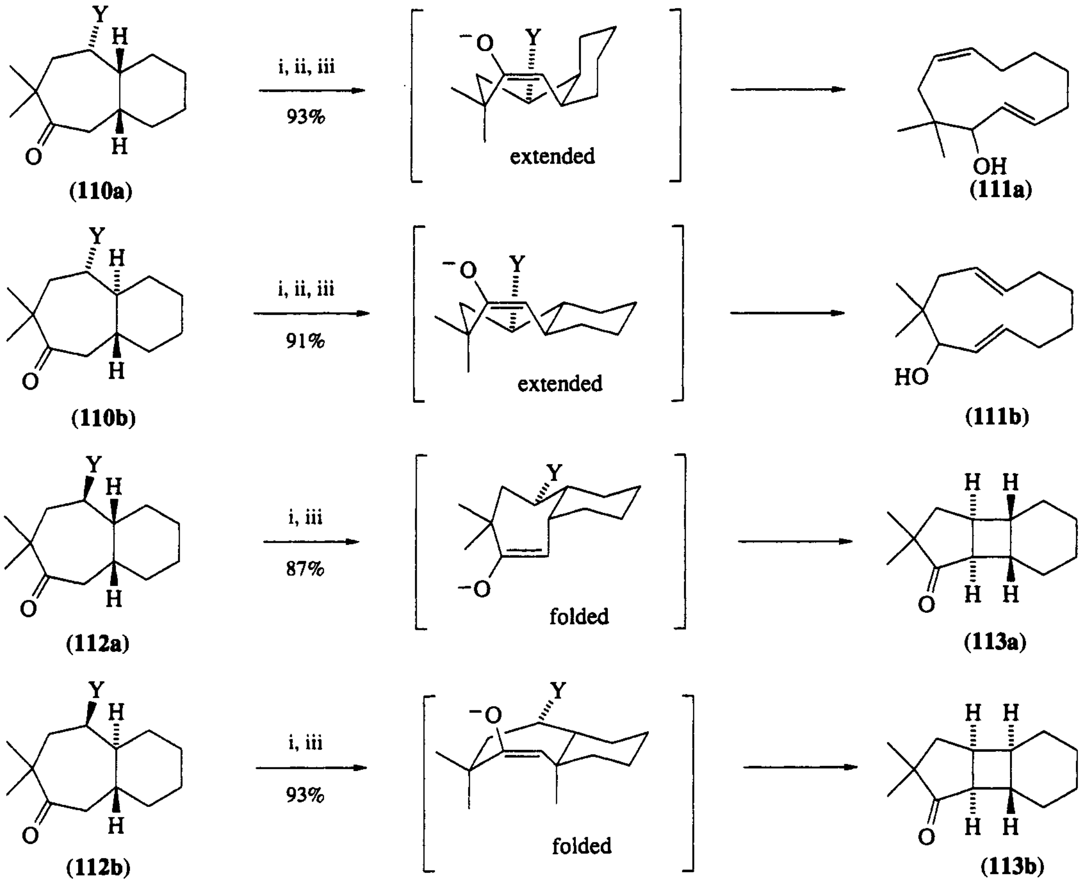
(110a)
i, ii, iii
93%
extended
(111a)
(110b)
i, ii, iii
91%
extended
(111b)
(112a)
i, iii
87%
folded
(113a)
(112b)
i, iii
93%
folded
(113b)

i, LDA, THF, –78 °C; ii, DIBAl-H, –78 °C; iii, warming to r.t., 2 h
Y = $OSO_2Ph$

**Scheme 37**

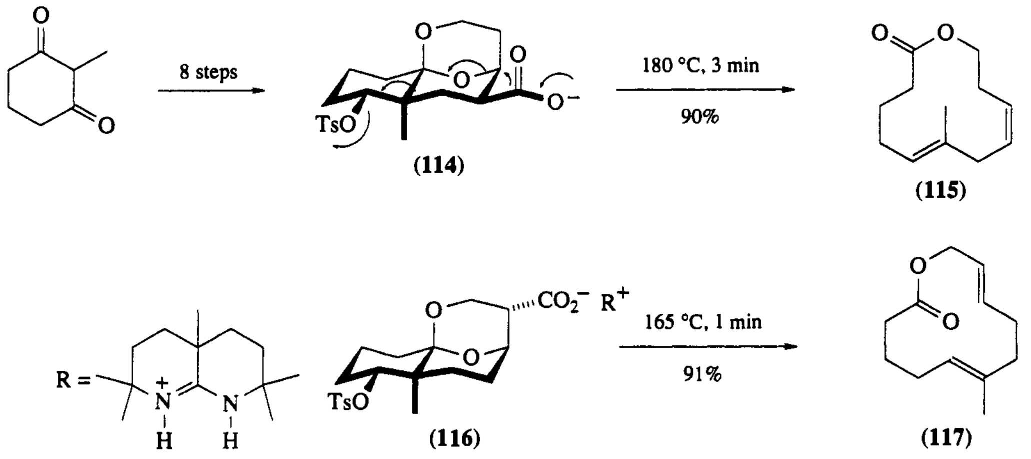
8 steps
(114)
180 °C, 3 min
90%
(115)
R =
(116)
165 °C, 1 min
91%
(117)

**Scheme 38**

interest. The most convenient and cheap starting material is cyclododecanone (**120**). There are numerous available syntheses of (**118**) and (**119**) and several of them use a fused 12-membered ring as the key compound in a fragmentation reaction.

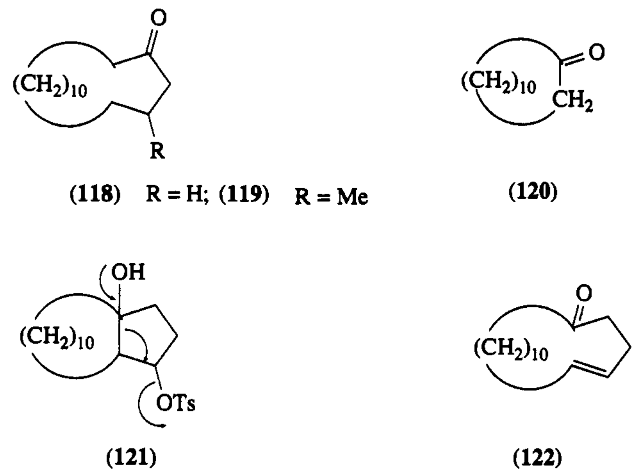

**(118)** R = H; **(119)** R = Me

**(120)**

**(121)**

**(122)**

**Scheme 39**

The pioneering work of Ohloff[58] in this field is shown by his historic paper on the synthesis of both (**118**) and (**119**). *Inter alia*, the bicyclic tosylate (**121**) provides, by Grob fragmentation, the unsaturated ketone (**122**), which also has a strong musk odour.

Fischli[59] has described a chiral, economic synthesis of (*S*)- and (*R*)-muscone (**119**) also starting from (**120**). The key step is the epoxysulfonyl cyclofragmentation of (**123**) to (*E,Z*)-dehydromuscone (**125**; Scheme 40) in a one-pot procedure. The sulfone moiety serves as a carbanion stabilizer for the epoxide cleavage as well as a leaving group.

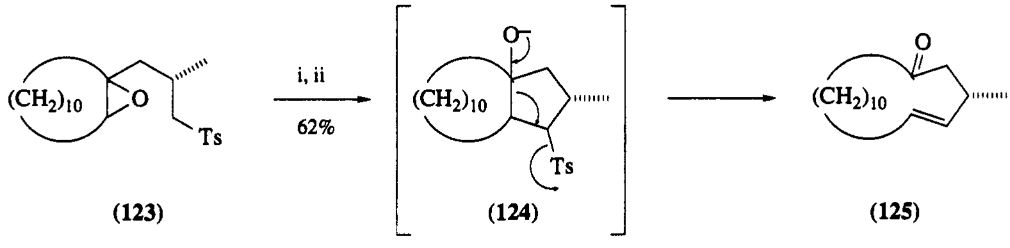

**(123)**

**(124)**

**(125)**

i, $NaNH_2$, toluene, reflux, 10 h; ii, $Bu^tOK$, $Bu^tOH$, HMPA, reflux, 16 h

**Scheme 40**

Another fragmentation on the way to muscone (**119**) has been used by Dreiding,[60] starting with epoxy tosylate (**126**; Scheme 41) to furnish dione (**129**). Possible mechanisms have been discussed in detail, with the most probable intermediates being (**127**) and (**128**) since the $^1H$ NMR data show that the C(1)—C(12) bond is almost antiperiplanar to the C(13)—OTs bond.

Hesse[61] has described an exaltolide (cyclopentadecanolide) (**134**; Scheme 42) synthesis starting from the readily available 2-cyanocyclododecanone (**130**). The latter is converted to the quaternary ammonium salt (**131**), which undergoes fragmentation under mild conditions to provide the lactone (**133**) *via* the lactole anion (**132**). The methylene compound (**133**) exhibits similar musk odor, as does (**134**).

### 5.4.2.3 Alkynones (Eschenmoser-type)

In his pioneering work, Eschenmoser[14] first described the epoxy ketone–alkynone fragmentation which now (usually) bears his name. Of course, this reaction is a special seven-center Grob-type reaction starting with the tosylhydrazone of an α,β-epoxy ketone (Scheme 43). Deprotonation leads to an alkoxide which immediately undergoes fragmentation to give four parts, a ketone, an alkyne, nitrogen and the leaving group toluenesulfinate. It is quite obvious that this reaction possesses synthetic value only if both the ketone and alkyne parts are connected to provide open-chained or cyclic alkynones (Scheme 43).

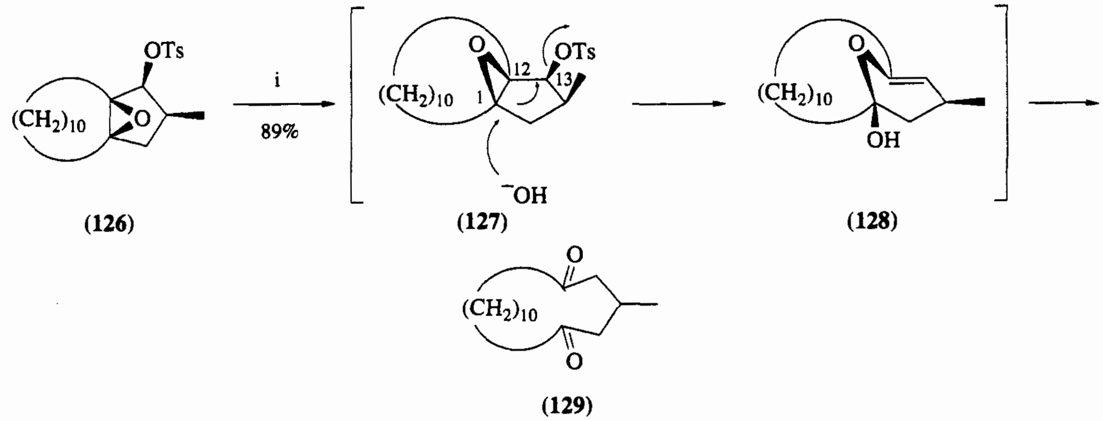
OTs
(CH2)10
O
i
89%
(126)
O
12
OTs
13
(CH2)10
1
⁻OH
(127)
O
(CH2)10
OH
(128)
O
(CH2)10
O
(129)

i, $CaCO_3$, dioxane, $H_2O$, reflux, 1 d

Scheme 41

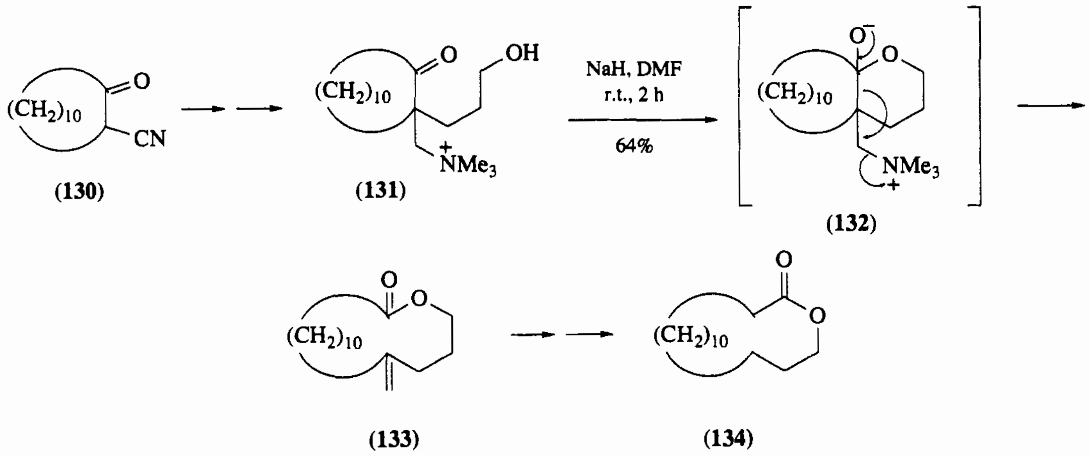
(CH2)10
O
CN
(130)
O
OH
(CH2)10
+
NMe3
(131)
NaH, DMF
r.t., 2 h
64%
O⁻
O
(CH2)10
NMe3
+
(132)
O
O
(CH2)10
(133)
O
O
(CH2)10
(134)

Scheme 42

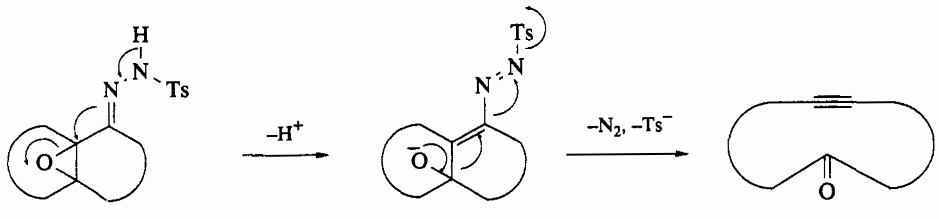
H
N
N
Ts
O
-H⁺
Ts
N
N
O
-N2, -Ts⁻
O

Scheme 43

The first examples to demonstrate the synthetic power of this method[62] were the preparations of exaltone (**118**) and muscone (**119**), starting from the α,β-unsaturated ketones (**135**) and proceeding *via* the epoxy ketones (**136**), the tosylhydrazones of which are cleaved to the cycloalkynones (**137**; Scheme 44). A little later, Tanabe[15] described the same reaction type starting from epoxydecalones, using this fragmentation for the synthesis of secosteroid alkynic ketones.[63]

Eschenmoser,[62,64] together with groups from Firmenich, Geneva, and CIBA, Basle, gave an extended scope to the synthesis of various alkynones. Some preparative variations and improvements have been introduced by the use of oximes,[65] *N*-aminoaziridines,[66] 2,4-dinitrobenzenesulfonohydrazides[67] and 1,3,4-oxadiazolin derivatives.[68]

Some examples of the synthetic value of the Eschenmoser fragmentation should be given. Kocienski's economical and highly stereoselective synthesis[69] of both *endo*- and *exo*-brevicomin (**140**) uses the alkynone (**139**) as an intermediate, easily accessible by fragmentation of the keto epoxide (**138**; Scheme 45). Stevens[70] used this fragmentation during the course of studies on the synthesis of vitamin $B_{12}$ precursors,

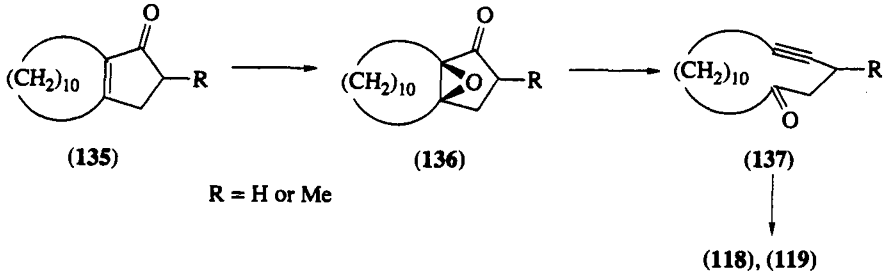
O
$(CH_2)_{10}$
R
(135)
O
$(CH_2)_{10}$
O
R
(136)
R = H or Me
$(CH_2)_{10}$
R
O
(137)
(118), (119)

Scheme 44

with various degrees of success. The precursor of ring C, the alkynic aldehyde (**143**), can be obtained from the epoxy ketone (**141**; Scheme 46); numerous experiments were required to find a set of special conditions. However, in the course of the synthesis of the B-ring all attempts to cleave (**142**) *via* the tosylhydrazone or similar intermediate failed. In each case reaction was observed, but the resulting complex mixtures were devoid of aldehyde or alkyne protons.

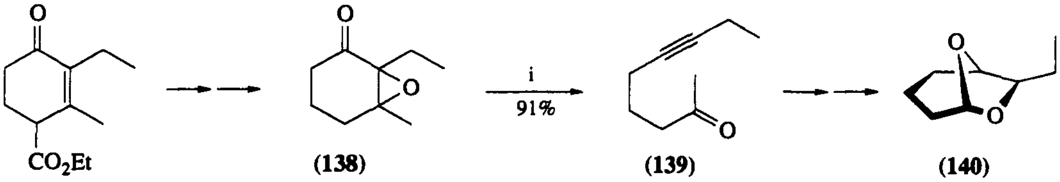
O
$CO_2Et$
O
O
i
91%
O
O
O
(138)
(139)
(140)

i, $TsNHNH_2$, 0 °C, 3 h, r.t., 3 h

Scheme 45

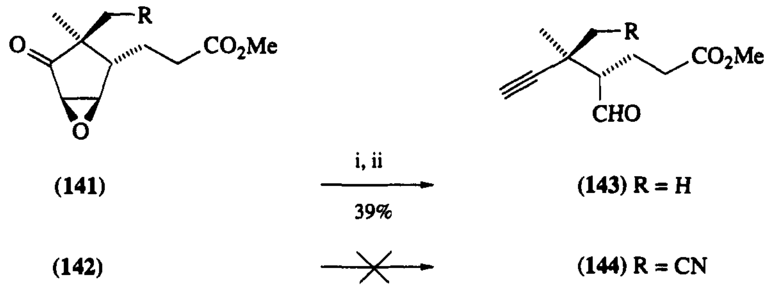
R
O
$CO_2Me$
O
R
$CO_2Me$
CHO
(141)
i, ii
39%
(143) R = H
(142)
(144) R = CN

i, $TsNHNH_2$, $CH_2Cl_2$, AcOH, 0 °C, 2 h; ii, $BF_3$•$Et_2O$, $CH_2Cl_2$, r.t.

Scheme 46

The formation of epoxy ketones from sterically crowded enones is often difficult. Avoiding the epoxidation step, fragmentation to give the alkynone (**137**; Scheme 47) occurs on treatment of the unsaturated hydrazones (**145**) (from **135**) with an excess of NBS in methanol. Ohloff and Büchi[71] used this sequence for a further synthesis of exaltone (**118**) and muscone (**119**).

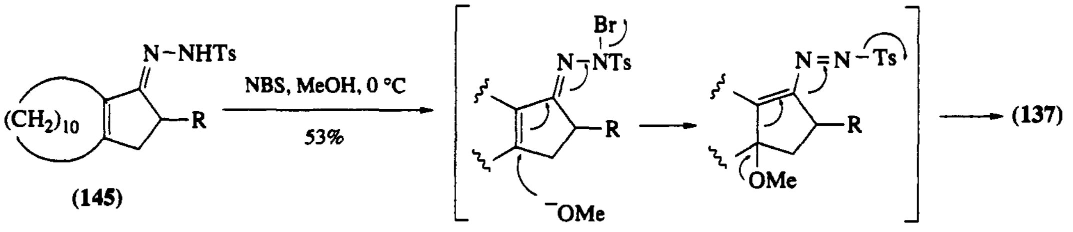
N–NHTs
$(CH_2)_{10}$
R
(145)
NBS, MeOH, 0 °C
53%
Br
N–NTs
R
$^-$OMe
N=N–Ts
R
OMe
(137)

Scheme 47

Treatment of the steroid (**146**; Scheme 48) with LTA and TMS-$N_3$ gives the 5,6-seco-5-oxo-7-carbonitrile steroid (**147**) useful for the synthesis of ring B homoazasteroids. Zbiral[72] explains the mechanism as an aza analog of the Eschenmoser fragmentation *via* formation of the azido epoxide.

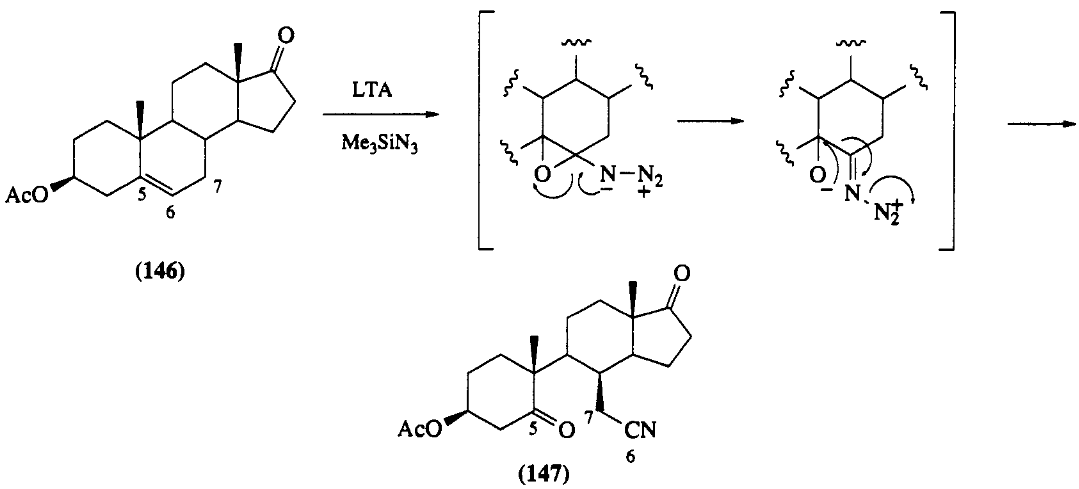

**(146)**

**(147)**

**Scheme 48**

α-Alkoxy tosylhydrazones without the ring strain of an epoxide react in a different way. Since there is insufficient driving force for immediate ring opening, these derivatives need two equivalents of strong base. Agosta[73] used this reaction for preparation of some allenes (**149**) from tosylhydrazones (**148**; Scheme 49).

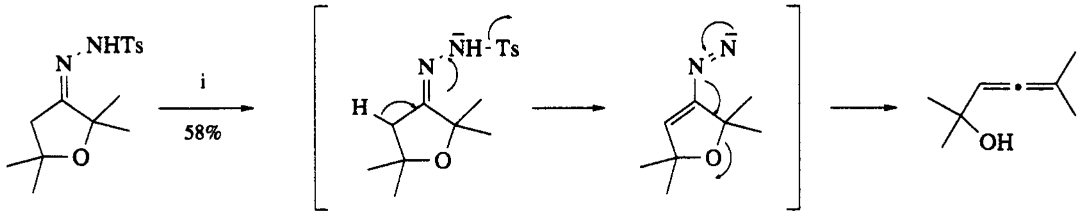

**(148)** **(149)**

i, 2.5 equiv. BuLi, ether, r.t., 30 min

**Scheme 49**

Occasionally, the fragmentation is unexpected and unwanted. For the synthesis of sesquicarene (**152**), Coates[74] heated the sodium salt of tosylhydrazone (**150**). However, the main reaction was the carbon analog of the Eschenmoser fragmentation leading to the alkyne (**151**; Scheme 50).

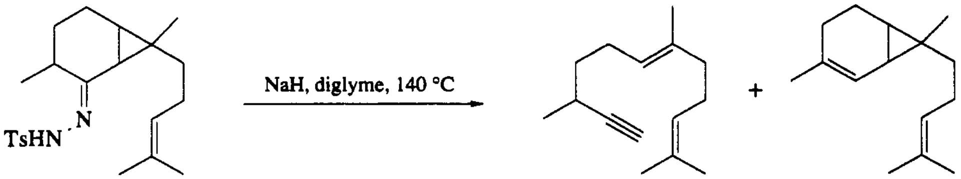

**(150)** **(151)** 53% **(152)** 15%

**Scheme 50**

### 5.4.2.4 Silicon- and Metal-assisted Fragmentations

There seems to be no compelling reason to discuss silicon- and metal-assisted fragmentations in a special chapter, since they are mostly ordinary Grob types leading to medium-sized ring systems. However, justification is given by the fact that these reactions use unusual reagents under mild conditions or involve subsequent reactions.

The bicyclo[6.3.0]undecenone (**155**) is elaborated from the silyl enol ether (**153**; Scheme 51) using a unique intramolecular [2 + 2] photocycloaddition–Grob fragmentation sequence.[75] When the silyl ether (**154**) is treated with aqueous hydrofluoric acid in THF, a smooth fragmentation ensues leading to the fused 5,8-ring enone (**155**) which is then converted to pentalenene (**156**), a triquinane isolated in 1980 from *Streptomyces griseochromogenes*. In the fragmentation step HF provides both the electrofugal and nucleofugal part by way of the F—Si affinity and by protonation of the hydroxy group.

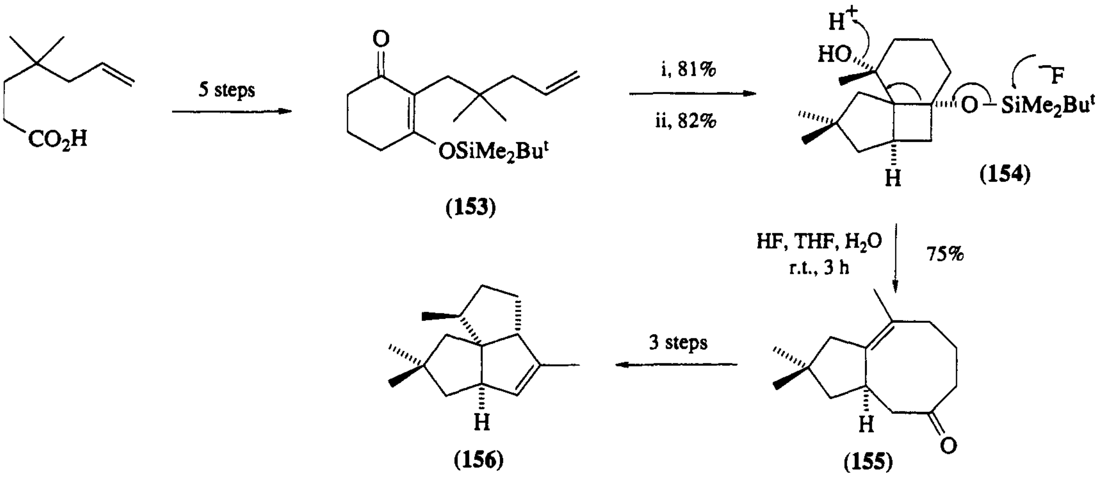

i, 450 W Hg lamp, heptane, 7 h; ii, $Me_3CuLi_2$, ether, –68 °C, 1 h

**Scheme 51**

Isoamijiol (**159**; Scheme 52), a linear 5,7,6-ring-fused member of the dolastane group of diterpenes, is the principal secondary metabolite in the brown seaweed *Dictyota linearis*. In the course of the synthesis of (**159**), Pattenden[76] also used a photocycloaddition–fragmentation sequence. Treatment of (**157**) with HF as mentioned above yields the hydroazulenone portion (**158**) of (**159**), which then was elaborated to isoamijiol. This is the first example of a C═C bond and an Si—O bond being used as 'push–pull' partners in a fragmentation.

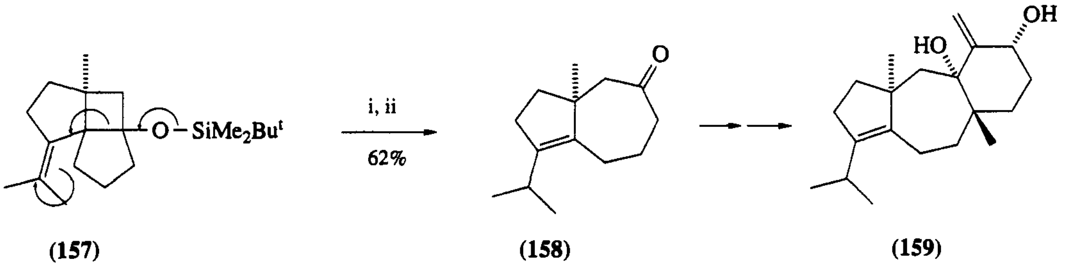

i, HF, THF, r.t., 1.5 h; ii, 60 °C, 2.5 h

**Scheme 52**

Whilst alkaline fragmentation of hydroxysulfonates such as (**160**; Scheme 53) is accompanied by isomerization to give *trans*-bicyclo[5.3.0]decenones, the fluoride-induced[77] fragmentation of the silyl ether (**161**) leads exclusively to the *cis* isomer (**162**). This reaction type is limited to strained systems. Thus, the silyl ether (**163**) does not react at all under similar conditions.

A mechanistically related and mild fragmentation is that of 2-trimethylsilylethyl esters (Tmse esters). The Tmse residue is a selectively cleavable carboxy-protecting group (see Volume 6, Chapter 3.2) Examples are known for the synthesis, *via* these esters, of peptides,[78] macrolides such as curvularin[79] and macrocyclic trichothecenes like verrucinol (Scheme 54).[80]

The reductive fragmentation with solvated electrons (metal in liquid ammonia) of strained rings bearing carbonyl groups in a 1,4-relationship leads to dicarbonyl systems with a lower number of fused rings (Scheme 55).

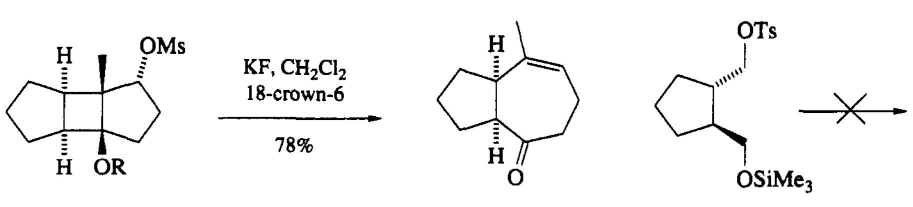

**(160)** R = H → **(161)** R = SiMe$_3$ **(162)** **(163)**

**Scheme 53**

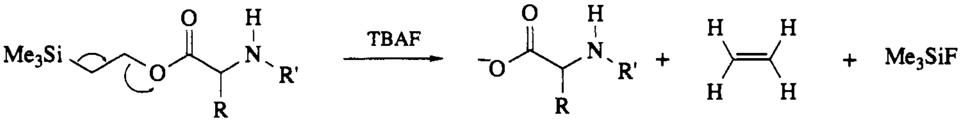

**Scheme 54**

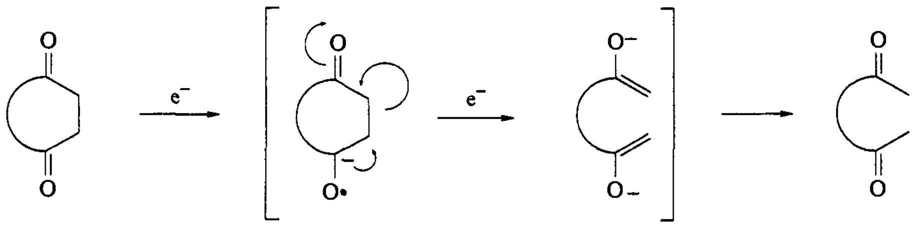

**Scheme 55**

Valuable applications of this principle have been described by Paquette[81] for the synthesis of topologically spherical molecules. Coates[82] used this reductive fragmentation for the synthesis of bicyclo[6.3.0]undecenecarboxylates, compounds which bear a structural resemblance to the A–B rings of the fusicoccin and ophiobolane natural products. Reduction of the unsaturated keto ester (**164**) affords an isomeric mixture of esters, the equilibration of which effects conversion to the single ester (**165**; Scheme 56).

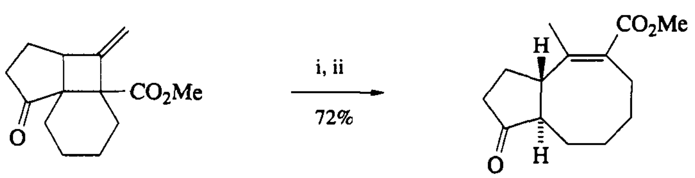

**(164)** **(165)**

i, Li, NH$_3$, THF, 5 min; ii, NaOMe, MeOH, reflux, 19 h

**Scheme 56**

The sequence of intramolecular photocycloaddition–cyclobutane fragmentation has been used by Crimmins in an excellent manner for the synthesis of pentalenenes[83] and the even more sophisticated lauren-1-ene (**27**). The latter synthesis[84] was accomplished in 27 steps from cyclopentenone (**166**). One of the key steps is the reductive cleavage of the tetracyclic cyclobutane (**167**), followed by hydrogenation of the resulting β,γ-unsaturated ester to give keto ester (**168**; Scheme 57).

Quite related to the above reaction type is the reductive α,β-fragmentation of γ-halocyclobutyl ketones (Scheme 58).[85] Oppolzer[86] used this reaction in a new approach to the acorane system, and the mechanism was discussed. It remains to be clarified as to what extent this type of reaction entails similar stereoelectronic constraints as the classical Grob fragmentation.

An elegant synthetic application of such a fragmentation has been described by Funk.[87] The ketone (**170**; Scheme 59) serves as a convenient precursor for 7,12-secoishwaran-12-ol (**171**), an antifertility

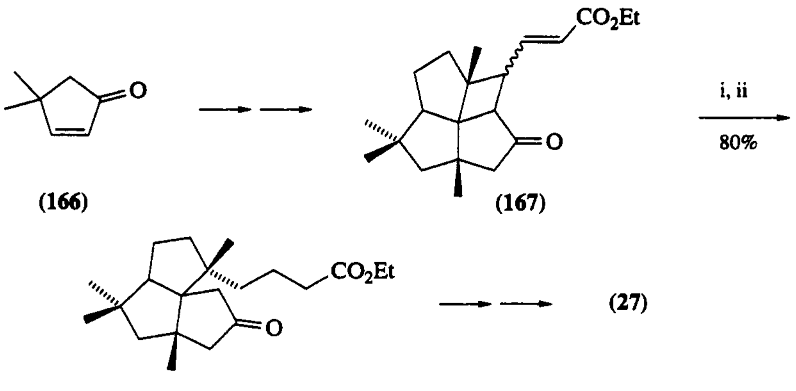

(166) (167) (168) (27)

i, Na, $NH_3$, ether, –33 °C, 5 min; ii, $H_2$, Pd–C, EtOH

**Scheme 57**

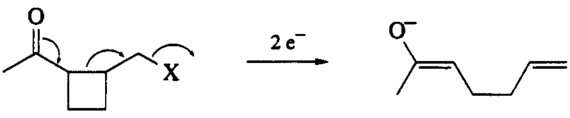

**Scheme 58**

agent isolated from *Aristolochia indica*. For the preparation of (**170**) the known ketone (**169**) requires only the formal addition of $H_2$ to the cyclobutane α-keto carbon–vinyl carbon σ-bond. To this end, anti-Markownikow addition of HBr to alkene (**169**) and treatment of the crude mixture of bromides with $Li/NH_3$ gives the allyl decalone (**170**).

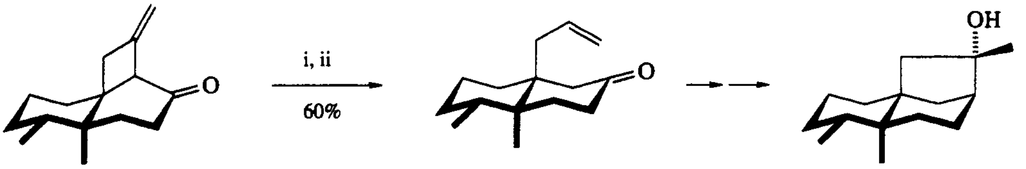

(**169**) (**170**) (**171**)

i, HBr, *hv*; ii, excess Li, $NH_3$, THF

**Scheme 59**

The stereospecific synthesis of some methyl (*E*)- and (*Z*)-alkenoates (**173**; Scheme 60) has been carried out using lead-assisted oxidative fragmentation.[88] Starting from trimethylsilyloxyalkenes, a mixture of *exo*-methylated (**172a**) and *endo*-methylated (**172b**) cyclopropanes has been prepared. Treatment with LTA, then with $CH_2N_2$ gives (**173a**) and (**173b**). The fact that (**172a**) gives only (**173a**) and (**172b**) gives only (**173b**) proves that the fragmentation is stereospecific. The most reasonable explanation for this process involves initial solvolysis by AcOH to give the corresponding cyclopropanol (**172c**; Scheme 61). This reacts with lead(IV) to give the alkenoic acid anhydride (**173c**) through a series of reactions including ring cleavage with inversion at the carbon bonded to Pb, followed by fragmentation with $Pb(OAc)_2$ as the leaving group. The antiperiplanar relationship of the C(1)—C(6) and the C(7)—Pb bonds of (**172d**) is ideal for a Grob fragmentation.

Treatment of patchoulol (**174**; Scheme 62), an olfactive component of patchouli oil, with LTA gives rise to a mixture from which the almost pure ketone (**175**) is distilled. Thomas[89] has postulated a free carbenium ion mechanism, but this reaction may be a regiospecific fragmentation facilitated by the fact that the proton on C(5) is oriented antiperiplanar to the C(1)—O bond.

The oxidative cleavage of γ-stannyl alcohols will be discussed in Volume 7, Chapter 4.2. Two recent examples of this so-called 'oxidative fragmentation' should be given. Posner[90a] has described a flexible and simple synthesis of macrolides involving this reaction to produce both ring enlargement and regio-

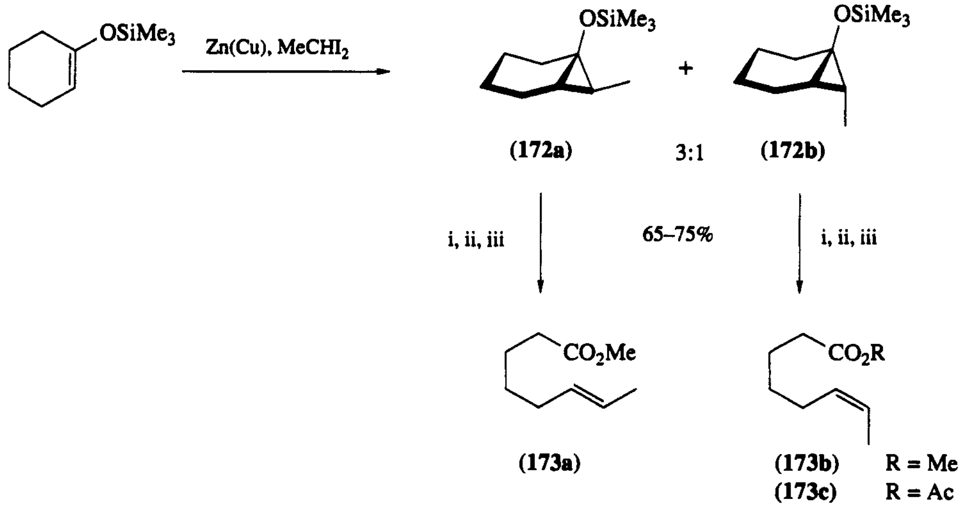
OSiMe3
Zn(Cu), MeCHI2
OSiMe3
+
OSiMe3
(172a)
3:1
(172b)
i, ii, iii
65–75%
i, ii, iii
CO2Me
CO2R
(173a)
(173b) R = Me
(173c) R = Ac

i, LTA, AcOH, r.t., 8 h; ii, $H_2O$, 20 min; iii, $CH_2N_2$

Scheme 60

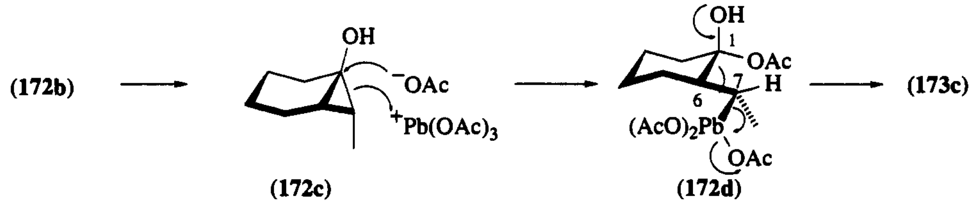
(172b)
OH
⁻OAc
⁺Pb(OAc)3
(172c)
OH
1
OAc
7
H
6
(AcO)2Pb
OAc
(172d)
(173c)

Scheme 61

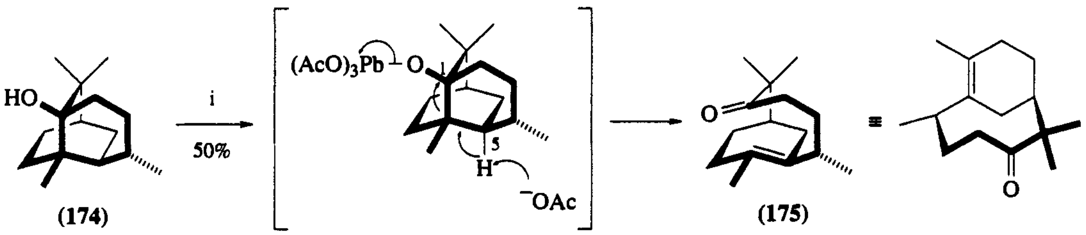
HO
(174)
i
50%
(AcO)3Pb
O
1
5
H
⁻OAc
O
(175)
≡
O

i, LTA, $CaCO_3$, benzene, reflux, 3 h

Scheme 62

specific formation of an alkenyl unit (Scheme 63). ω-Unsaturated carbonyl compounds have been obtained under modified Pfitzner—Moffatt (MOPMO) conditions (Scheme 63a).[90b]

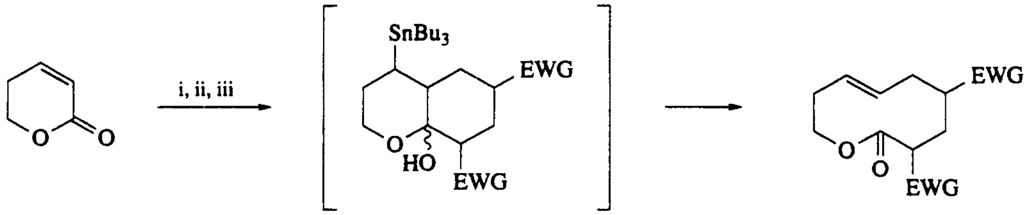
O
O
i, ii, iii
SnBu3
EWG
O
HO
EWG
EWG
O
O
EWG

i, $LiSnBu_3$; ii, $H_2C=CH\text{-}EWG$; iii, LTA, benzene, reflux

Scheme 63

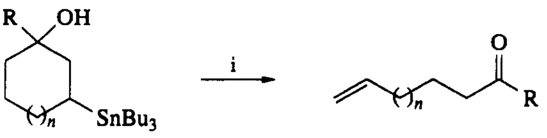

R = alkyl, phenyl; *n* = 0, 1, 2

i, $(PhIO)_n$, DCC, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 0 °C

**Scheme 63a**

### 5.4.3 BECKMANN FRAGMENTATION

The Beckmann fragmentation, as a special type of Beckmann rearrangement (see Volume 7, Chapter 5.2), occurs in particular when one of the alkyl groups attached to the oxime carbon is capable of stabilizing a positive charge, leading to a carbocation and a nitrile. Camphor oxime (**176**) is representative of the structural type which fragments to a tertiary carbocation, and its cleavage to α-campholenonitrile (**178**) with a variety of reagents was reported last century (Scheme 64). Hill[91] has done a historical review and investigated this reaction type in detail. With PPA, secondary reactions of the carbocation give rise to an array of novel products. Stevens has used the Beckmann fragmentation of the camphor derivative (**177**; Scheme 64) for an enantiospecific approach to the total synthesis of steroids[92] and precursors of vitamin $B_{12}$.[70] Under the reaction conditions the *endo*-alkene (**179**) is formed exclusively.

The key step in Ayer's[93] grandisol (**183**; Scheme 65) synthesis is the Beckmann fragmentation of oxime (**181**), which is prepared from eucarvone (**180**). Thus, nitrile (**182**) is readily accessible.

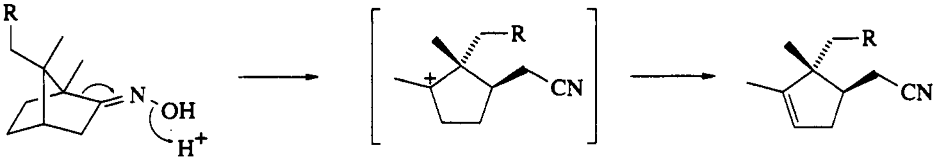

(**176**) R = H
(**177**) R = $CH_2CO_2Me$

$\xrightarrow[80\%]{\text{i, ii}}$

(**178**) R = H
(**179**) R = $CH_2CO_2Me$

i, TFAA, $CH_2Cl_2$, 0 °C to r.t., 4 h; ii, TFA, r.t., 24 h

**Scheme 64**

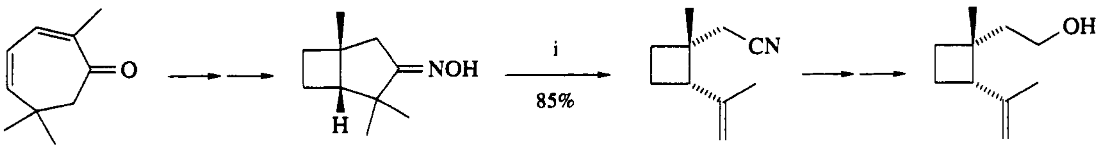

(**180**) (**181**) (**182**) (**183**)

i, $PCl_3$, lutidine, ether, 5 min

**Scheme 65**

Isatin oxime triflates (**184**; Scheme 66) undergo facile fragmentation promoted by DBU to form anthranilonitriles (**185**) after hydrolytic work-up.[94] The ketone (**187**; Scheme 67), key compound of Harding's[95] highly stereoselective, convergent synthesis of trichodiene (**190**), has been prepared by Nazarov cyclization from simple starting materials. Numerous reaction sequences have been investigated to find conditions to cleave the central five-membered ring. The only useful reaction is the Beckmann fragmentation of the oxime (**188**) to yield the cyanodienes (**189**). The silicon-directed Beckmann fragmentation is a valuable addition to the available synthetic methods. It leads to the regio- and stereo-specific formation of alkenes.[96,97] Most interesting is a variation which uses only catalytic amounts of TMS-OTf, since this reagent is recycled by the reaction itself.[98] This sequence has been utilized for the synthesis of the acetate (**193**; Scheme 68), a component of the sex pheromone of the potato tuberworm moth *Phthorimaea operculella*. Treatment of the key compound (**191**) with catalytic amounts of TMS-OTf cleaves the oxime under very mild conditions to give the nitrile (**192**).

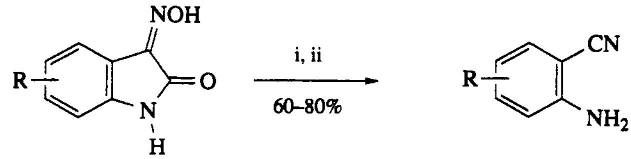

**(184)** **(185)**

i, TFAA, 2,6-lutidine, $CH_2Cl_2$, 0 °C, then 3 h reflux; ii, DBU, r.t., 1 h, then $NaHCO_3$

**Scheme 66**

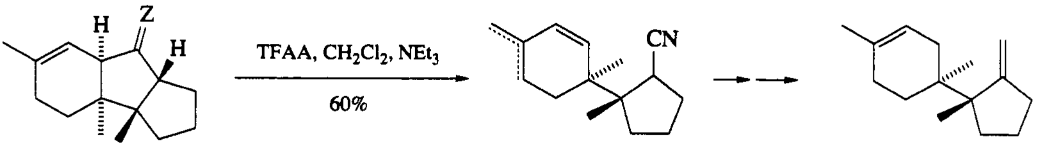

**(187)** Z = O
**(188)** Z = NOH

**(189)** **(190)**

**Scheme 67**

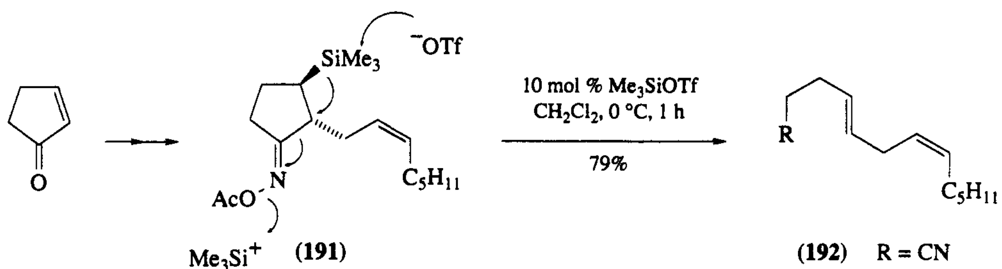

**(191)**

**(192)** R = CN
**(193)** R = $CH_2OAc$

**Scheme 68**

## 5.4.4 MISCELLANEOUS

The Polonovski reaction (see Volume 6, Chapter 4.7) — the action of an acid anhydride on an *N*-oxide — can give rise both to elimination or fragmentation reactions.[99] Potier[100] has modified the fragmentation by use of TFAA rather than $Ac_2O$ and has applied this version to a useful synthesis of compounds related to antitumor alkaloids of *Catharanthus roseus, e.g.* vinblastine and vincristine.

Treatment of catharanthine *N*-oxide (**194**; Scheme 69) with TFAA in $CH_2Cl_2$ at –78 °C in the presence of vindoline, and then with $NaBH_4$ in a one-pot reaction leads to anhydrovinblastine (**197**), in the natural (*S*)-configuration at C-16, in 50% yield. The reaction proceeds *via* the intermediate (**195**), its fragmentation to (**196**), and immediate attack of vindoline at the α-face of (**196**).

Despite that it is named as such quite often in the literature, the radical β-scission or β-cleavage is not a fragmentation in the sense considered in this chapter. The first example of a macrolide synthesis through such a reaction type was achieved by Ohloff[101] and resulted in an industrial synthesis of exaltolide (**134**; Scheme 70). Schreiber has described iron–copper-promoted fragmentation reactions of α-alkoxy hydroperoxides as a route to macrolides.[102,103] Two recent informative publications which cover the prior literature have been written by Suginome[104] and Macdonald.[105]

A short synthesis of ambrox (**202**; Scheme 71),[106] one of the most important ambergris fragrance compounds, has been performed, using natural sclareol (**198**) as starting material and involving β-cleavage as the key step. Iron(II) cleaves the hydroperoxide (**199**) to give the radical intermediate (**200**), which fragments into the alkyl radical (**201**) and methylvinyl ketone. Cyclization of (**201**) *via* the carbonium ion leads to ambrox (**202**). Similar results have been obtained by β-cleavage of other sclareol derivatives.[107]

Snowden has used the terminus fragmentation in his earlier papers for the β-cleavage of homoallylic alkoxides (Scheme 72). Such a reaction sequence (Scheme 73) has been used in particular for the synthesis of damascones (*e.g.* γ-damascone **203**) and related compounds.[108,109]

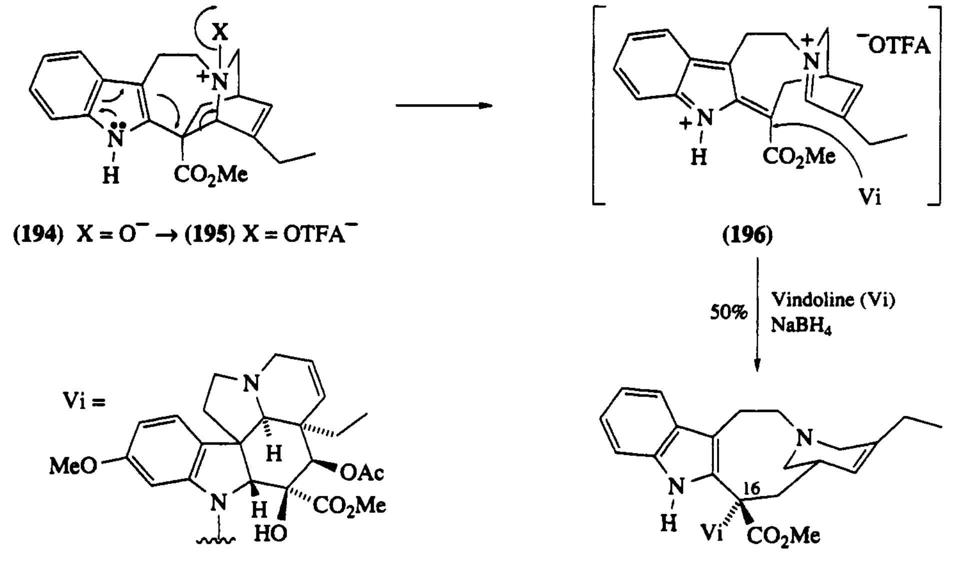
X
+N
N
H
CO2Me
(194) X = O− → (195) X = OTFA−
+
N
−OTFA
+N
H
CO2Me
Vi
(196)
50%
Vindoline (Vi)
NaBH4
Vi =
N
H
MeO
N
H
OAc
CO2Me
HO
N
N
H
16
Vi
CO2Me
(197)

Scheme 69

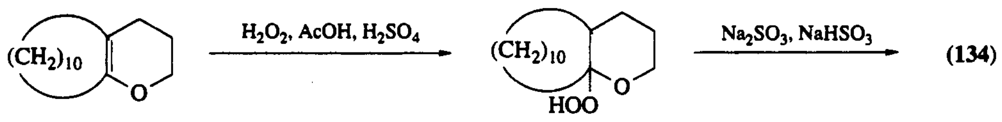
(CH2)10
O
H2O2, AcOH, H2SO4
(CH2)10
HOO
O
Na2SO3, NaHSO3
(134)

Scheme 70

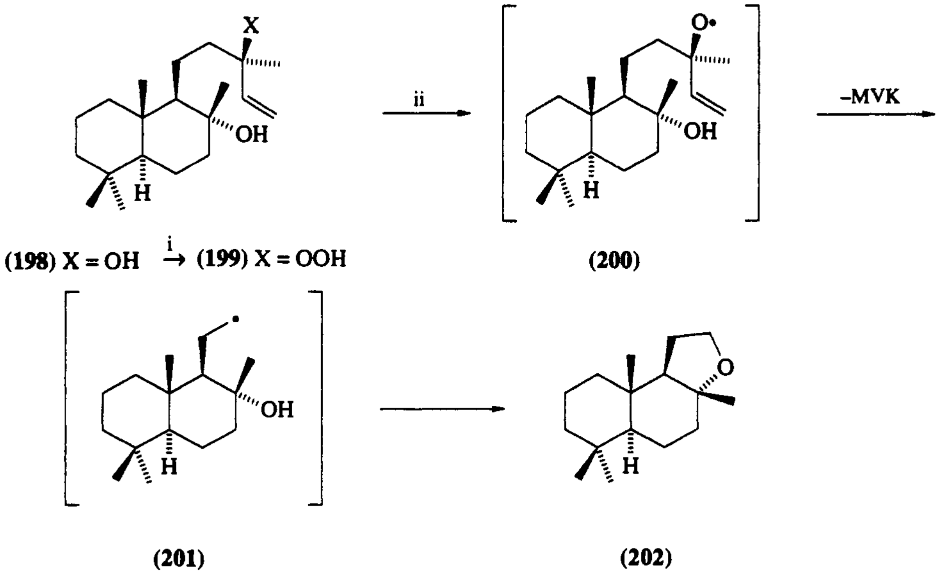
X
OH
H
(198) X = OH →i (199) X = OOH
ii
O•
OH
H
(200)
−MVK
OH
H
(201)
O
H
(202)

i, $H_2O_2$ (70%), $CH_2Cl_2$, r.t., 7 d; ii, $Cu(OAc)_2$, $FeSO_4$, MeOH, 50 °C, 2 h

Scheme 71

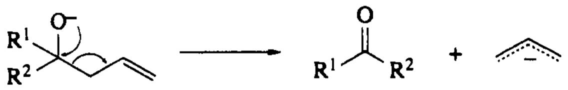
O−
R1
R2
O
R1
R2
+

Scheme 72

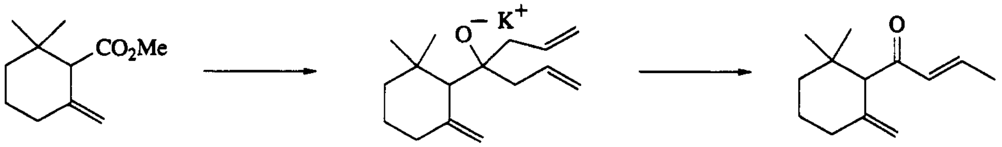

**(203)**

**Scheme 73**

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# Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

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The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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## Volume 7

## OXIDATION

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N,N′*-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1′-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| $E^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| $IpcBH_2$ | isopinocampheylborane |
| $Ipc_2BH$ | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1
# Oxidation by Chemical Methods

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## 1.1.1 INTRODUCTION

In this chapter, functionalization reactions are emphasized which are of genuine practical utility, but others that are noteworthy and of potential synthetic significance are also discussed. Apart from alkane reactions, some intermolecular functionalization reactions which operate on unactivated C—H bonds, *e.g.* the side chain of a steroid, are examined. Intramolecular cases are covered elsewhere, and general reviews of the area are available.[1,2]

### 1.1.2 ORGANIZATION OF SECTIONS

Examples of alkane functionalization reactions of the type shown in equation (1) are first considered, in which the atom X to which the new C—X bond is formed comes from metals in Group I, followed by subsequent groups in the Periodic Table. Within each section, radical, electrophilic and carbenoid mechanisms are discussed.

$$\text{R-H} + \text{X} \longrightarrow \text{R-X} \tag{1}$$

### 1.1.3 GENERAL PROBLEMS IN ALKANE FUNCTIONALIZATION

Alkanes have no lone pairs nor low-lying empty orbitals, but only the C—H and C—C $\sigma$- and $\sigma^*$-levels. It is therefore relatively hard either to attack the former with an oxidizing agent or to attack the latter with a reducing agent or base. This means that vigorous conditions and reactive reagents often have to be used. It will almost always be the case that the product of an alkane functionalization reaction is more reactive than the starting material and so reacts faster with the functionalizing reagent. This in turn means that overoxidation can be a severe problem. To take a simple case, it is very difficult to stop the air oxidation of methane at the methanol stage. This means that many of the reactions in this section can only be run to low or very low conversion in order to obtain a satisfactory selectivity. This may be tolerable if the substrate is methane, but not so with valuable substrates. Low conversions should be assumed in the cases discussed below unless specifically mentioned.

A second important selectivity issue arises when there are several different types of C—H bond in the molecule, typically, primary, secondary and tertiary C—H bonds. Since tertiary radicals and carbonium ions are more stable than their secondary or primary analogs, many functionalization processes have an intrinsic selectivity pattern: tertiary > secondary > primary. Steric effects favor attack at primary positions, which is seen for very bulky reagents or in reactions in which the C—H bond to be broken is brought side-on to the functionalizing group, and therefore makes the transition state very sensitive to steric effects. The best example is oxidative addition to a transition metal complex.

There are three general classes of mechanism most often encountered in alkane reactions: (i) radical; (ii) electrophilic;[3] and (iii) carbenoid. The C—H bond-breaking steps in (i) and (ii) are shown in equations (2) and (3). Carbenoid reactions can go either by direct insertion into the C—H bond (equation 4), which tends to happen when the carbene in question has singlet character, or by a two-step process (equations 5 and 6), in which H-atom abstraction precedes collapse of the radical pair, a pathway which is characteristic of triplet carbenes.

$$\text{C-H} + \text{Q}\bullet \longrightarrow \text{C}\bullet + \text{Q-H} \tag{2}$$

$$\text{C-H} + \text{E}^+ \longrightarrow \text{C}^+ + \text{E-H} \tag{3}$$

$$\text{:Q} + \text{C-H} \longrightarrow \text{C-Q-H} \tag{4}$$

$$\text{:Q} + \text{C-H} \longrightarrow \text{H-Q}\bullet + \text{C}\bullet \tag{5}$$

$$\text{H-Q}\bullet + \text{C}\bullet \longrightarrow \text{C-Q-H} \tag{6}$$

These three mechanistic pathways do not differ very markedly in selectivity. The usual pattern is tertiary > secondary > primary for C—H bonds, because this is the order of increasing stability both of the radical and of the carbonium ion. The concerted carbene route (equation 4) can show the reverse ordering (primary > secondary > tertiary) when the carbenoid in question is very bulky. This is notably the case for transition metal reagents undergoing oxidative addition of a C—H bond. The organometallic literature tends to look at this reaction from the point of view of the metal, as implied by the name 'oxidative addition', but from the point of view of alkane chemistry these reagents are carbenoids, perhaps having singlet character, which insert into an alkane C—H bond.

### 1.1.4 FORMATION OF R—M BONDS (M = GROUP I AND II METAL)

*s*-Butylpotassium (formed *in situ* from $R_2Hg$ and K) reacts with alkanes to give the terminally mono- and di-substituted organopotassium compounds. Treatment with $CO_2$ gives the terminal carboxylic acid and the corresponding *n*-alkylmalonic acid. This selectivity for primary attack is probably the result of deprotonation being the C—H activation step (equation 7).[4]

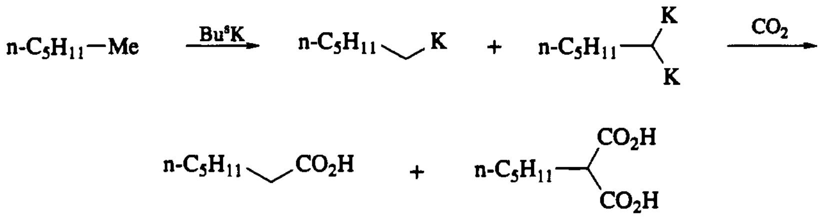

(7)

H/D exchange in alkanes is catalyzed by a number of heterogeneous catalysts, such as Ni/alumina.[5]

## 1.1.5 FORMATION OF R—M BONDS (M = GROUP III METAL AND THE LANTHANIDES AND ACTINIDES)

Watson[6] was the first to show that methane could be attacked by a Group III metal reagent, in a reaction termed '$\sigma$-bond metathesis'. This reaction probably proceeds *via* electrophilic attack on the C—H bond by the reagent (equation 8). Marks[7] described a nondegenerate example (equation 9) and Wolczanski[8] has shown that a zirconium imidate (Zr=NR) can also activate methane, the basic amine group receiving the proton released from methane (equation 10).

$$Cp^*_2LuMe + {}^{13}CH_4 \longrightarrow Cp^*_2Lu({}^{13}CH_3) + MeH \qquad (8)$$

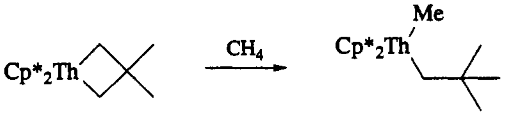

(9)

$$C_p^* = \eta^5\text{-}C_5Me_5$$

$$(R_3SiNH)_2Zr{=}NSiR_3 \;+\; CH_4 \xrightarrow[R\,=\,Bu^t]{} (R_3SiNH)_2Zr(Me)NHSiR_3 \qquad (10)$$

## 1.1.6 FORMATION OF R—M BONDS (M = TRANSITION METAL)

The area of alkane activation is of current interest in organometallic chemistry and several examples of electrophilic C—H bond activation and of insertion of a carbenoid metal fragment into an alkane C—H bond have now been observed.[1] The acetone complex (**1**) shown in Scheme 1 is extremely reactive thanks to facile loss of acetone. A number of cyclopentanes react to form cyclopentadienyl (Cp) complexes.[9] For example, cyclopentane itself gives (**2**). The hydrogen removed from the alkane is transferred to the hydrogen acceptor $Bu^tCH{=}CH_2$ to give $Bu^tCH_2Me$. If a quaternary center is present,[10] as in 1,1-dimethylcyclo-pentane or -hexane, then a diene complex can be formed, which in the cyclopentane case may undergo C—C cleavage by a Green–Eilbracht[11] migration of the methyl group to the metal to give (**4**). Other transformations are shown in Scheme 1. Evanescent intermediates containing M—C bonds are thought to be important in a variety of catalytic alkane conversions, *e.g.* dehydrogenation reactions, and are described in a later section.

Bergman,[12] Graham[13] and Jones[14] and their coworkers observed a series of reactions, of which the examples shown in equations (11) and (12) are typical. The alkyl groups could be functionalized successfully with mercury salts to give the corresponding organomercurial, but most reagents led to elimination of alkane from the metal. The interesting feature of the reaction from a synthetic perspective is that attack at the primary C—H bonds is favored both kinetically and thermodynamically. This is also the case for the catalytic alkane conversions, which are discussed in a later section, which use oxidative addition in the first step. Liquid Xe has been used as a reaction solvent for the iridium system (equation 11;

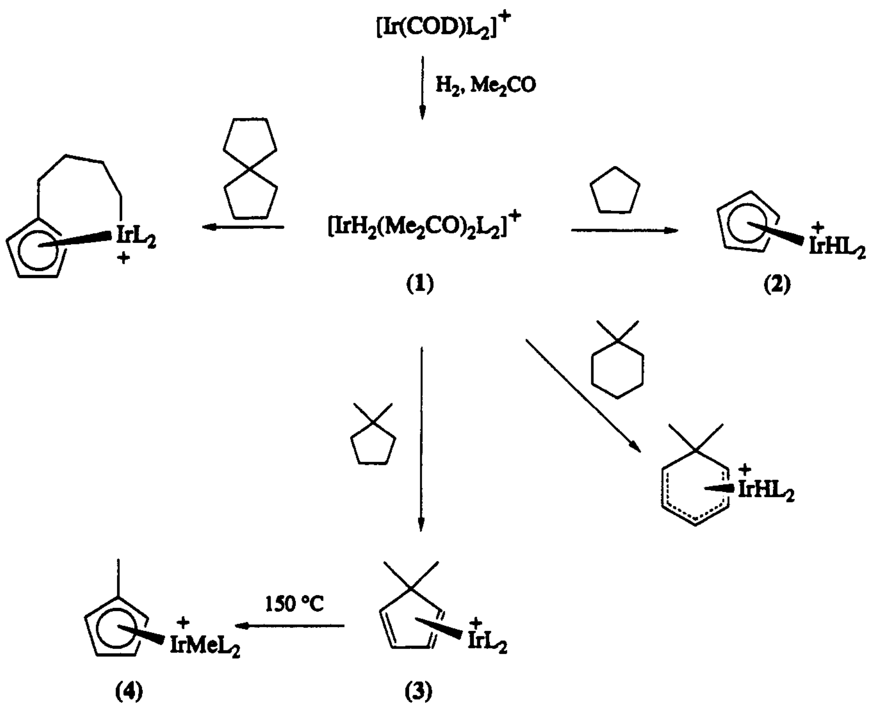

Scheme 1

L = PMe3) to allow the use of rare, gaseous and solid alkanes. These studies show that methane gives the methyl hydride, cubane the cubyl hydride (without C—C bond breaking) and adamantane the secondary adamantyl hydride.[15]

$$\mathrm{CpIrLH_2} \xrightarrow{h\nu,\ \mathrm{RH}} \mathrm{CpIrL(R)(H)} \qquad (11)$$

$$\mathrm{CpReL_3} \xrightarrow{h\nu,\ \mathrm{RH}} \mathrm{CpReL_2(R)(H)} \qquad (12)$$

$$(\mathrm{Cp} = \mathrm{C_5H_5};\ \mathrm{L} = \mathrm{PMe_3},\ \mathrm{R} = \mathrm{C_6H_{11}})$$

Strained alkanes, such as cyclopropane and cubane, react much more easily with transition metal compounds.[16] Bare metal atoms also react with alkanes under metal vapor synthesis conditions to give synthetically useful quantities of alkane derivatives. For example, W atoms, cyclopentane and $PMe_3$ give $[CpW(PMe_3)H_5]$,[17] while rhenium atoms react with benzene and propane to give $[(\eta^6\text{-}C_6H_6)_2Re_2(\mu\text{-}Me_2C)(\mu\text{-}H)_2]$.[18] Related transformations[1] in mass spectroscopic and ion cyclotron resonance experiments do not have preparative value.

Shilov[19] found that a methylplatinum complex, $[MePtCl_3(PPh_3)_2]$, was formed from methane and $H_2PtCl_6$ at 120 °C, followed by reaction with $PPh_3$.

## 1.1.7 FORMATION OF R—C BONDS

In this section, not only alkane isomerization and dehydrodimerization (equation 13) are considered, but also the dehydrogenation of alkanes to alkenes, as in this case, two adjacent C—H bonds are replaced by a π-type C—C bond. Other C—C bond-forming reactions are also mentioned.

$$2\ \mathrm{R{-}H} \longrightarrow \mathrm{R{-}R} + \mathrm{H_2} \qquad (13)$$

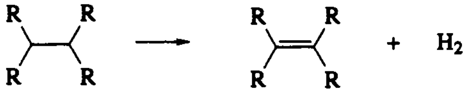

(14)

### 1.1.7.1 Alkane Isomerization

Acid catalysts are required for alkane isomerizations and all the reactions of this type probably involve carbonium ions.[20] Optically active tertiary alkanes can be racemized by sulfuric acid at room temperature or by fluorosulfonic acids at –80 °C.[21]

Skeletal isomerization also occurs readily with acid catalysts. If a tertiary C—H is present a less powerful acid (*e.g.* conc. $H_2SO_4$) is capable of catalyzing the reaction, otherwise something more powerful (*e.g.* aluminum halides or superacids) is used. More recent examples of acid catalysts are: $H_2SO_4/TiO_2$,[22] $SbF_5/Al_2O_3$[23] and $H_2SO_4–SbF_5/ZrO_2$.[24] The reactions are driven thermodynamically, so, for example, tetrahydrodicyclopentadiene gives adamantane while higher *n*-alkanes are subject to cracking, and cyclohexane gives both methylcyclopentane and *n*-hexane.[25]

### 1.1.7.2 Alkane Dehydrodimerization

The mercury-photosensitized dehydrodimerization reaction has been known for many years,[26] but it has only been made preparatively useful very recently.[27] The key feature of the process is that the system is only active in the vapor phase, so that after condensation the product is protected from further conversion. This implies that the reaction can be run to essentially quantitative conversion without a fall-off in yield. In order to run on a gram scale to tens of grams, all that is needed is a quartz flask and a low pressure mercury lamp. Heating the substrate or substrates in the quartz flask with a small drop of mercury leads to smooth formation of the products. Aspects of the process are shown in equations (15) to (18).

$$\mathrm{Hg} \xrightarrow{254\ \mathrm{nm}} \mathrm{Hg}^* \qquad (15)$$

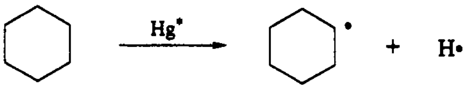

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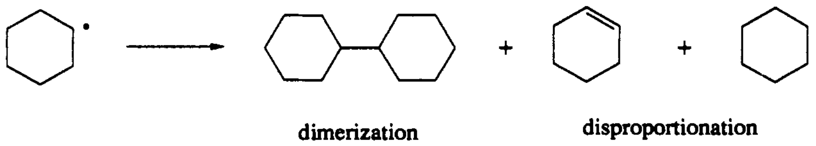

(17)

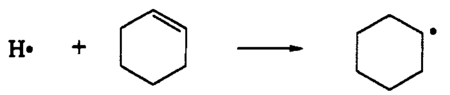

(18)

It might have been anticipated that this reaction would not work well because alkyl radicals tend to disproportionate to give alkenes (equation 17). In fact, the H-atoms produced in the initial homolysis rapidly readd to any alkene that forms to produce the alkyl radical (equation 18).

The reaction is also applicable to the dimerization of alcohols to glycols and amines to diamines (equation 19). The alcohol dimerization is important from the point of view of alkane functionalization because the cross dimerization of alkanes (RH) and alcohols (MeOH) gives the carbinol $RCH_2OH$ as the major product. This product is very easy to separate from the glycol by washing with water and from the alkane homodimer, $R_2$, using column chromatography. By altering the liquid phase ratio of the two reagents there is a corresponding change in the vapor phase ratio. This use of vapor pressure bias can give a different ratio of products. For example, if the alkane were expensive, then an excess of methanol

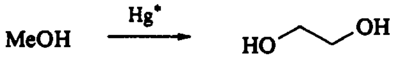

(19)

could be used in the vapor and only $RCH_2OH$ and $R_2$ would be formed. The yield based on alkane will exceed 90% and the mixture can be separated by solvent extraction.

Dehydrodimerization is also possible by an electrophilic route using superacids, but a substantial degree of rearrangement of the alkyl skeleton is often observed. For example, using $HSO_3F–SbF_5$ at 140 °C methane gives $Me_3C^+$, as does neopentane, the former *via* C—C bond formation, the latter by C—C cleavage.[28] The alkylation of alkenes by alkanes can also be brought about in a similar way, but alkene oligomerization is seen as a competing reaction (equations 20 to 23).

$$H_2C{=}CH_2 \ + \ H^+ \longrightarrow MeCH_2^+ \tag{20}$$

$$MeCH_2^+ \ + \ CH_4 \longrightarrow C_2H_6 \ + \ Me^+ \tag{21}$$

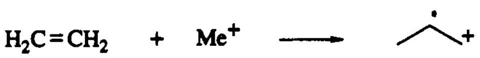

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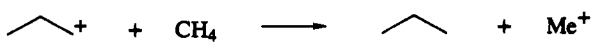

(23)

### 1.1.7.3 Transition Metal Catalyzed Alkane Dehydrogenation and Carbonylation

The groups of Felkin,[29] Crabtree[30] and Tanaka[31] have demonstrated that alkane dehydrogenation *via* oxidative addition is possible (equations 24 and 25). Attack at primary C—H bonds is favored, probably for steric reasons, but the stabilities of the catalysts are not yet sufficient for the reaction to be practically very useful. Tanaka's $[RhCl(CO)(PMe_3)_2]/h\nu$ system also carbonylates alkanes (equations 26 and 27). Lin[32] has applied the iridium system to more complex alkanes (equation 28).

$$C_6H_{12} \xrightarrow{IrH_2(O_2CCF_3)L_2,\ h\nu} C_6H_{10} \ + \ H_2 \tag{24}$$

$$\begin{aligned} n\text{-}C_8H_{18} \xrightarrow{ReH_7L_2} \ & (Bu^nCH{=}CHCH{=}CH_2)ReH_3L_2 \ + \ (Pr^nCH{=}CHCH{=}CHMe)ReH_3L_2 \ + \\ & (EtCH{=}CHCH{=}CHEt)ReH_3L_2 \xrightarrow{P(OMe)_3} 1\text{-Octene} \end{aligned} \tag{25}$$

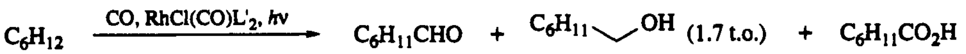

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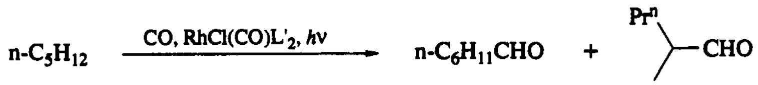

(27)

L = PPh₃; L' = PMe₃

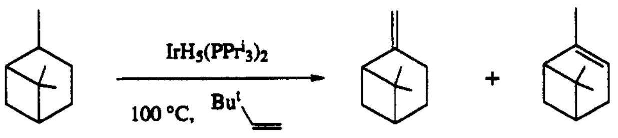

(28)

### 1.1.7.4 Dehydrogenation and Aromatization

The $[IrH_2(Me_2CO)_2(PPh_3)_2]PF_6/Bu^tCH{=}CH_2$ system, mentioned above, has also been used for the aromatization of cyclohexane.[33] Photolysis of pyridine *N*-oxide in an alkane leads to dehydrogenation of the alkane.[34] The formation of by-products in the reaction, as a result of photorearrangement of the *N*-oxide, can be partially suppressed by the addition of $BF_3$.[35] The classic reaction involving heating with elemental S or Te is a synthetically useful method of aromatization: for example, decalin is converted to naphthalene with Te at 200 °C.[36]

### 1.1.7.5 Cracking and Reforming

Thermolysis of alkanes at *ca.* 750–800 °C gives dehydrogenation, skeletal rearrangement, cracking and even aromatization in some cases.[37] Catalysts are available which favor one or other of these routes, which are all important in the petroleum-refining industry.[38] Pyrolysis of various alkanes in $H_2$ can lead to the epitaxial growth of a diamond phase on a suitable substrate.[39] Superacids bring about alkane rearrangements even at 25 °C.[40] Alkylation of alkanes with alkenes under acidic conditions is also well known (equation 29).

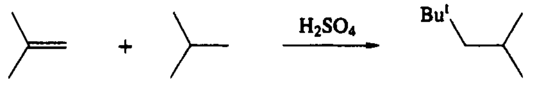

(29)

### 1.1.7.6 Other Reactions

Oxalyl chloride yields ·COCl radicals on photolysis and this reaction has been used to directly substitute alkanes with the chloroacyl group (equation 30).[41] Similarly, biacetyl reacts with alkanes in a benzoyl peroxide-initiated chain reaction to give ketones in *ca.* 60–70% yield (equation 31).[42,43] Cyanogen chloride affords nitriles under similar conditions with a strong tertiary > secondary > primary selectivity pattern in 50–95% yields (equation 32);[44] $MeO_2CCN$ is also reported to be an alternative reagent for the transformations.[45]

$$C_6H_{12} \quad + \quad (COCl)_2 \quad \xrightarrow[63\%]{h\nu} \quad C_6H_{11}COCl \qquad (30)$$

$$C_6H_{12} \quad + \quad (COMe)_2 \quad \xrightarrow[66\%]{\text{peroxide}} \quad C_6H_{11}COMe \qquad (31)$$

$$C_6H_{12} \quad + \quad ClCN \quad \xrightarrow[66\%]{\text{peroxide}} \quad C_6H_{11}CN \qquad (32)$$

A radical addition reaction has been used to functionalize cyclopentane. The chain carrier, Cl·, was generated and regenerated by a β-elimination process (equation 33).[46] Other activated alkenes, such as maleic anhydride, furanone and acrylonitrile, have also been added to cyclohexane in 15–45% yield in a reaction initiated by Bu$^t$OOH or light.[47]

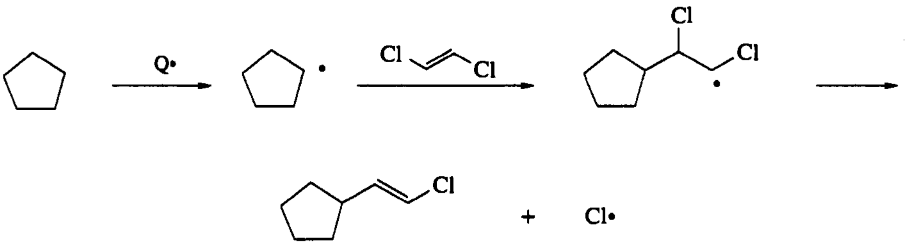

(33)

Alkane functionalization by electrophilic addition reactions is also possible; for example, the particularly stable tertiary adamantyl cation must be involved in equation (34), a reaction which gives an excellent 75% yield of adduct.[48] In a similar way, a variety of alkenes[49] and arenes[50] can be alkylated by alkanes, or alkanes acylated by $RCOCl/AlBr_3$.[51]

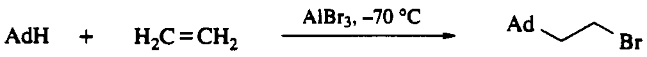

(34)

In the Koch–Haaf reaction, a superacid/CO mixture leads to carbonylation of the alkane.[52] A variety of products were obtained, *e.g.* $\mathrm{Bu^tCO_2H}$, $\mathrm{Pr^iCHCOMe}$ and $\mathrm{Pr^iCH_2COBu^t}$, from isobutane using this product. Usually the method is only useful for alkanes containing a tertiary C—H bond,[12] but Sommer has introduced a modification that allows secondary C—H bonds to be functionalized, although only with 4% conversion (equation 35).[53]

$$\mathrm{PrH + HF + SbF_5 + CO} \xrightarrow{\mathrm{Br^-, -10\,^\circ C}} \qquad (35)$$

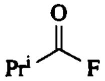

In the Benson process[54] $\mathrm{CH_4/Cl_2}$ mixtures are heated to 700–1700 °C and rapidly quenched. Ethylene, acetylene and benzene are formed by decomposition of the methyl chloride intermediate.

Several electrochemical methods for alkane oxidation have been used by Fleischmann and his coworkers.[55] These proceed *via* carbonium ion intermediates and, as expected, extensive rearrangement can be observed; for example, cyclohexane in $\mathrm{FSO_3H}$ gives 1-acetyl-2-methyl-1-cyclopentene as major product![56]

Carbene reagents also functionalize alkanes.[57] Triplet $\mathrm{:CH_2}$ adds unselectively to alkane C—H bonds. The product mixture obtained from *n*-pentane was found to be 48% *n*-hexane, 35% 2-methylpentane and 17% 3-methylpentane, so that addition to a primary C—H bond appears to be favored.[58] Monochloromethylcarbene, CHCl, is less reactive and more electrophilic and so the normal tertiary > secondary > primary selectivity pattern was observed.[59] Ethoxycarbonylcarbene, formed on photolysis of the corresponding diazo compound, inserts rather unselectively in to alkane C—H bonds to give the ethoxycarbonylmethyl derivatives in *ca.* 50% yield. Transition metals, such as copper(II)[60] or rhodium(I),[61] also usefully catalyze the insertion of carbenes into alkane C—H bonds.

## 1.1.8 FORMATION OF R—X BONDS (X = Si, Ge, Sn, Pb)

So far, only the mercury-photosensitized chemistry, discussed above, allows direct functionalization of alkanes with a Si substituent under mild conditions (equation 36).[19]

$$\mathrm{R_3Si{-}H + R{-}H \xrightarrow{Hg^*} R{-}SiR_3 + H_2} \qquad (36)$$

## 1.1.9 FORMATION OF R—N BONDS

Free radical nitration of alkanes has been carried out with nitric acid and related reagents at relatively high temperatures and has been used for the industrial synthesis of $\mathrm{MeNO_2}$ from methane. Hydrogen radical atom abstraction from the alkane is thought to be followed by trapping of the radical with $\mathrm{NO_2}$. A mixture of products tends to be formed in these cases, of which the nitroalkane and alkyl nitrite are most prominent.[62] Nitrogen oxides have been used for the same purpose.[63] Aminooxidation of cyclohexane with $\mathrm{NH_3/O_2}$ takes place at 180 °C and 30 atm with copper or cobalt naphthenoate catalysts to give good yields of adiponitrile.[64]

A recent radical-based system, shown in equations (37) to (40), has been developed by Hill *et al.*[65] The catalyst in this process is a manganese(III) porphyrin, which is oxidized by PhIO to give what is believed to be an oxomanganese(V) intermediate. This is thought to abstract an H-atom from the alkane to give the alkyl radical. The resultant R· radical can then abstract either OH or X from the Mn catalyst to give the two chiefly observed products, ROH and RX ($\mathrm{X = N_3}$, Cl, Br, I). In the case of $\mathrm{X = N_3}$, the azide $\mathrm{RN_3}$ is the major product, over 8 catalyst turnovers being observed (*i.e.* 800% yield based on Mn), accompanied by ROH (1.2 turnovers) and ketone (0.4 turnovers). The X = I example also works well, *ca.* 8 turnovers of RI being formed. The X = Cl and Br cases work less well and only *ca.* 1 turnover of RX and *ca.* 2 turnovers of ROH are formed, but an alternate approach is available.[66]

$$\mathrm{Mn(TPP)X + PhIO \longrightarrow O{=}Mn(TPP)X} \qquad (37)$$

$$\mathrm{RH + O{=}Mn(TPP)X \longrightarrow R\bullet + HO{-}Mn(TPP)X} \qquad (38)$$

$$\mathrm{R\bullet + HO{-}Mn(TPP)X \longrightarrow ROH + Mn(TPP)X} \qquad (39)$$

$$\mathrm{R\bullet + HO{-}Mn(TPP)X \longrightarrow RX + Mn(TPP)OH} \qquad (40)$$

Also developed by Hill[67] is a photochemical system (equations 41 to 48) based on a polyoxoacid, $H_3PW_{12}O_{40}$ (P). The excited state of the acid probably oxidizes the alkane in the first step. The radical can then either attack the solvent to give an iminium radical, which leads to ketone on hydrolysis, or it can be oxidized to the carbonium ion, in which case attack on the solvent leads instead to the *N*-alkylacetamide. If the substrate has two adjacent tertiary C—H bonds, then alkenes tend to be formed. The Barton reaction, normally known as an intramolecular C—H activation, can give some intermolecular reaction in some examples. Thus, when *n*-octyl nitrite is photolyzed in heptane, some nitrosoheptane is observed.[68]

$$P_{ox} + h\nu \longrightarrow P^*_{ox} \tag{41}$$

$$P^*_{ox} + 2\,RH \longrightarrow P_{red} + 2\,RH^{\bullet +} \tag{42}$$

$$RH^{\bullet +} \longrightarrow R^\bullet + H^+ \tag{43}$$

$$P_{red} + 2\,H^+ \longrightarrow P_{ox} + H_2 \tag{44}$$

$$C_6H_{11}^\bullet + MeCN \longrightarrow C_6H_{10}(C{=}NH)Me \tag{45}$$

$$C_6H_{10}(C{=}NH)Me + H_2O \longrightarrow C_6H_{10}COMe \tag{46}$$

$$C_6H_{11}^+ + MeCN \longrightarrow \left[C_6H_{11}{-}\overset{+}{N}{\equiv}{-}\right] \tag{47}$$

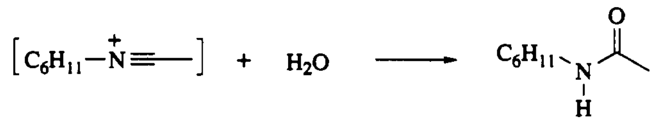
(48)

A mixture of hydrazine and zinc oxide aminates cyclohexane in *ca.* 40% yield on photolysis.[69] Possibly, the hydrazine is dissociated by ZnO photosensitization and $\cdot NH_2$ radicals both abstract an H-atom from the alkane and quench the resultant carbon radical.

A number of functionalization reactions in which C—N bonds are formed depend on the initial formation of a carbonium ion from the alkane. This cation is quenched by the acetonitrile solvent and an amide or related species is obtained after hydrolysis. In the example shown in equations (49) to (51) $Br_2$ was used to generate the carbonium ion. Adamantane is a particularly favorable substrate as the carbonium ion is so easily formed and resists elimination. A 92% yield of amide was obtained in this process.[70] In a related reaction, HCN gives amine products (equation 52).[71]

$$Ad{-}H + Br_2 \longrightarrow Ad^+ + HBr + Br^- \tag{49}$$

$$Ad^+ + MeCN \longrightarrow \left[Ad{-}\overset{+}{N}{\equiv}{-}\right] \tag{50}$$

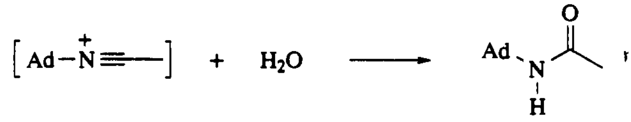
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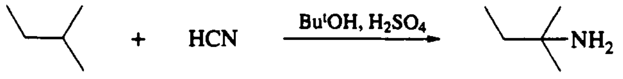

(52)

Another electrophilic reaction employs $AlCl_3/NCl_3$, in which case the aluminum reagent generates the carbonium ion which is then quenched by $NCl_2^-$. The amine is the final product of this reaction after hydrolysis. The system is selective for tertiary C—H bonds, *e.g.* methylcyclohexane gives an 82% yield of the tertiary amine compound. Arenes are also efficiently aminated.[72] $NO_2PF_6$ reacts with alkanes at 25 °C to give nitroalkanes, but skeletal rearrangements can occur and the yields are often poor.[73,74]

Carbenoid reagents can also introduce C—N bonds into alkanes. For example, cyanogen azide, $N_3CN$, decomposes at *ca.* 50 °C to give cyanonitrene, the ground state electronic structure of which is believed to be ·N═C═N·. Nevertheless, it reacts as :N—CN and gives insertion products with a variety of alkanes, selectively attacking the tertiary C—H bonds (equation 53). Reduction of the initial product can give the amine. Ethoxycarbonylnitrene reacts similarly.[75]

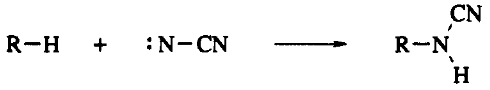

$$R{-}H + {:}N{-}CN \longrightarrow R{-}N(CN)H \qquad (53)$$

## 1.1.10 FORMATION OF R—X BONDS (X = P, As, Sb)

In the presence of $O_2$, $PCl_3$ reacts readily with alkanes even at 25 °C to give alkylphosphonyl chlorides in yields up to 60%.[76] Surprisingly little use of this reaction has been made in synthesis. No examples of similar reactions have been reported for the analogous As and Sb halides.

## 1.1.11 FORMATION OF R—O BONDS

### 1.1.11.1 Autoxidation[77]

Autoxidation, or air oxidation, is one of the simplest functionalization reactions of alkanes. In general, hydroperoxides are the first-formed products, but these can decompose under the conditions of the reaction to give the ketone and alcohol.[78] The reagents used to initiate the reaction are usually *O*-centered radicals or even $O_2$ itself. These can efficiently start a chain reaction of the sort shown in equations (54) to (56), because the O—H bond energy is usually greater than the C—H bond energy and so both the initiation (equation 54) and the chain-carrying steps (equations 55 and 56) are favorable. The selectivity observed in the liquid phase, tertiary > secondary > primary, is consistent with the radical mechanism proposed. For example, *n*-decane gives ketones formed by attack at all the secondary positions along the chain.[79] Alkyl hydroperoxides have been used as initiators.[80] The $RO_2$· radical appears to be a more selective abstractor than RO·, and good selectivity for the formation of the tertiary hydroperoxide can be obtained (equation 57).[81]

$$R{-}H + Q\bullet \longrightarrow R\bullet + Q{-}H \qquad (54)$$

$$R\bullet + O_2 \longrightarrow R{-}O{-}O\bullet \qquad (55)$$

$$R{-}O{-}O\bullet + R{-}H \longrightarrow R\bullet + R{-}O{-}O{-}H \qquad (56)$$

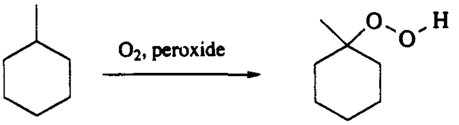

(57)

A special situation occurs if two tertiary centers are in a 1,3-relationship to each other. In this case, the intermediate peroxy radical tends to abstract an H-atom from the β-C—H bond to give the bis-1,3-hydroperoxide as the final product. The key steps are shown in equation (58).[82]

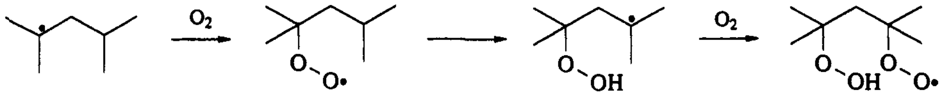

(58)

Air oxidation of *n*-butane to maleic anhydride is possible over vanadium phosphate and, remarkably, a 60% selectivity is obtained at 85% conversion.[83] In the gas phase oxidation, in contrast to the situation found in the liquid, *n*-alkanes are oxidized more rapidly than branched chain alkanes. This is because secondary radicals are more readily able to sustain a chain; for branched alkanes the relatively stable tertiary radical is preferentially formed but fails to continue the chain process. Vanadium(V)/manganese(II)/AcOH has been used as a catalyst for the autoxidation of cyclohexane to adipic acid, giving 25–30% yields after only 4 h.[84]

### 1.1.11.2 Hydroxylation and Related Reactions

The classical Fentons reagent,[85] $H_2O_2/Fe^{2+}$, hydroxylates alkanes by producing hydroxyl radicals in solution.[86] This reagent is relatively unselective and inefficient since much of the peroxide reagent is wasted by catalytic decomposition to $O_2$. Ferryl radicals, $FeO^{2+}$, have sometimes been invoked as intermediates by analogy with P-450 chemistry, but conclusive evidence is still lacking. Metal peroxide complexes are also known to hydroxylate alkanes.[87]

Alkane hydroxylation is carried out in nature by a variety of enzymes, but the ones that have attracted most attention are the cytochrome P-450 dependent systems[88] found, for example, in mammalian liver. In the liver they serve to detoxify lipid soluble species, such as drugs, by making them more water soluble and hence more easily eliminated. For some substrates, such as certain arenes, the hydroxylation in fact makes these substrates more toxic, by converting them to epoxides which then alkylate liver DNA. The ultimate source of the O-atom used in the hydroxylation is $O_2$, but only one of the two O-atoms of the $O_2$ is incorporated in the substrate, the other is reduced to $H_2O$. This means two reducing equivalents are also required. Because they introduce only one O-atom from $O_2$ into the substrate, these enzymes are called monooxygenases (equation 59).

$$\mathrm{R{-}H} \quad + \quad \mathrm{O_2} \quad + \quad 2e^- \quad + \quad 2\mathrm{H}^+ \longrightarrow \mathrm{R{-}OH} \quad + \quad \mathrm{H_2O} \qquad (59)$$

In cytochrome P-450, an iron(III) coordinated to protoporphyrin IX is bound at the active site of these enzymes by a cysteine thiolato group in the fifth coordination position. In the first step, the iron(III) is reduced to iron(II), which then binds $O_2$. By a process still not completely elucidated, the distal oxygen is lost as $H_2O$, leaving the active form of the cofactor, which is believed to be an oxoiron species, probably best described as $O{=}Fe^{IV}(P^{+}\cdot)$ (P = porphyrin). The oxo group has the reactivity of an oxene, and can either transfer oxygen to a double bond (*e.g.* forming an arene oxide from an arene) or insert into a C—H bond (*e.g.* to hydroxylate an alkane). In the case of alkane hydroxylation, the oxo group first abstracts an H-atom from the alkane, and the resulting alkyl radical abstracts an OH group from the metal (equations 60 and 61).

$$\mathrm{O{=}Fe^{IV}(P\overset{+}{\bullet})} \quad + \quad \mathrm{R{-}H} \longrightarrow \mathrm{HO{-}Fe^{IV}(P)} \quad + \quad \mathrm{R\bullet} \qquad (60)$$

$$\mathrm{HO{-}Fe^{IV}(P)} \quad + \quad \mathrm{R\bullet} \longrightarrow \mathrm{R{-}OH} \quad + \quad \mathrm{Fe^{III}(P)} \qquad (61)$$

The early functional models for this oxidation chemistry were rather simple: Udenfriend[89] used iron(II), EDTA, ascorbic acid (as the reducing agent) and $O_2$ to hydroxylate arenes, while Hamilton[90] showed that the same system hydroxylates unactivated C—H bonds (*e.g.* androsten-3-ol-17-one is converted to androsten-3,7-diol-17-one). Mimoun[91] developed the use of an iron(II)/PhNHNHPh/$PhCO_2H/O_2$ system which is also active for alkane hydroxylation. Curiously, other metals [copper(II), manganese(II), vanadium(II), cobalt(II)] are also active. In the hydroxylation of arenes, an arene oxide is believed to be the intermediate in P-450 dependent systems, because a 1,2-shift of a proton in the arene, the 'NIH shift' is often observed. Neither the Udenfriend nor Mimoun models show such a shift, however.

More physiologically relevant models have been studied by the groups of Groves and of Hill. [Fe(TPP)Cl] (TPP = tetraphenylporphyrin) was used as the catalyst, but instead of the $O_2$ and reducing agent, iodosobenzene was used as the O-transfer reagent. This reagent is also effective in the enzyme system itself, where it also obviates the need for $O_2$ and the reducing agent. Conversions are low because the alkane is always used in excess, but yields of 5–25% have been reported with respect to the oxidant.[92] In the presence of the bromine atom donor $BrCCl_3$, the radical intermediates could be converted in part to the corresponding bromide, RBr. The tertiary to secondary selectivity was found to be 10–40:1, depending on the substrate used.

Although less relevant as a model, [Mn(TPP)Cl] is a better reagent for alkane oxidation and up to 70% conversion has been reported for cyclohexane in $CH_2Cl_2$.[93] Rearrangements were observed for norcarane, which led to 7 products, including ones in which the $CH_2Cl_2$ solvent had been incorporated. Meunier was the first to show that the far cheaper reagent, hypochlorite, could also be used to oxidize the manganese system.[94]

The chief problem with these systems from the synthetic point of view is the relatively rapid oxidation of the catalyst. Traylor *et al.*[95] have introduced tetraphenylporphyrins bearing chloro substituents at the *ortho* positions, which make the system much more robust, and 440 turnovers have been observed with cyclohexane, for example. Unfortunately, these catalysts are not yet commercially available. A metal-catalyzed acetoxylation of cyclohexane has been reported which utilizes $Et_3NO$/iron(II)/$CF_3CO_2H$.[96]

In the chromate oxidation of (+)-3-methylheptane to the corresponding tertiary alcohol, there was 70–80% retention of configuration, which is a useful synthetic reaction.[97] Iridium and ruthenium salts also have been shown to catalyze this reaction.[98]

Hydroxylation is also induced in good yields by the photolysis of alkanes in nitrobenzene. Using a high pressure mercury lamp, the tertiary > secondary > primary selectivities observed have been 300:19:1 (pyrex filter) and 110:7:1 (vycor filter). No retention of configuration was observed in these reactions; consequently, a free radical mechanism was invoked.[99]

An interesting reagent, $CrO_2Cl_2/Me_2C{=}CHMe$, has been described, which is said to oxidize the methyl group of methylcyclohexane to CHO without affecting the tertiary C—H bond (equation 62).[100] This reaction is worth further investigation.

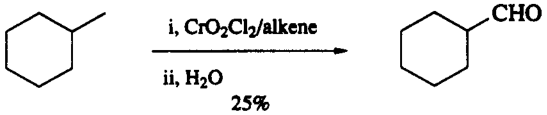

(62)

Other chromium(VI) reagents are known to attack at tertiary C—H bonds. For example, $CrO_3$/AcOH appears to be a general reagent for the introduction of an OH group at the 14-position of steroids (equation 63).[101] Yields depend critically upon the amount of water present, 1–2% being best. $CrO_2X_2$ (X = Cl or OAc) also reacts with alkanes to give oxidized products.[102]

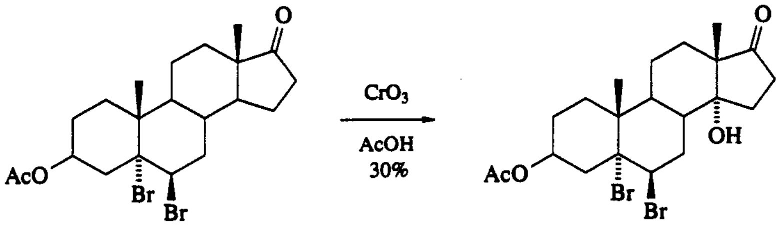

(63)

Basic $KMnO_4$ has been found to hydroxylate tertiary C—H bonds in certain cases (equation 64).[103] The tertiary alcohol functionality in the starting material seems to be essential in the reaction, and so an intramolecular reaction of a manganate ester is highly likely as an intermediate step. Alternatively, the hydroxy group may simply be required to improve the phase transfer into the aqueous medium, since the organic soluble reagent benzyltrimethylammonium permanganate readily attacks alkanes. *Trans*-decalin affords both the tertiary alcohol (37%) and *trans*-1-decalone (43%).[104] Overoxidation of the products with C—C bond cleavage can be a problem with manganese(VII) reagents, however.[105] $KMnO_4$ in trifluoroacetic acid reacts with alkanes at 25 °C with a tertiary > secondary > primary selectivity ratio of 2100:60:1; $k_H/k_D$ is 4.3 at 25 °C.[106]

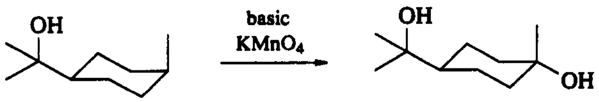

(64)

Cobalt(III) perchlorate in aqueous MeCN oxidizes alkanes at room temperature with an apparent secondary > primary > tertiary selectivity pattern. This pattern may not be real, however, because the product of tertiary attack may be much more sensitive to further oxidation. 2-Methylpentane was hydroxylated relatively selectively at the 4-position (74%); the minor products have OH groups at the 5- (13%), 1- (6%), 3- (2%) and 2-position (5%).[107] $Co(OCOCF_3)_3$ is a related reagent which has been reported to acetoxylate alkanes.[108]

Lead tetraacetate reacts poorly with acyclic alkanes, even 3-methylpentane,[109] although cyclohexane is readily converted to the corresponding acetate at 80 °C or with irradiation at room temperature.[110] The yield of acetate is increased 10-fold by the addition of $Bu^tOH$, under which conditions $Bu^tO\cdot$ is thought to act as H-atom abstractor.[111] The more reactive lead(IV) reagent $Pb(OCOCF_3)_4$ has been used to introduce the trifluoroacetate group. Hexafluorobenzene or $CF_3CO_2H$ are satisfactory solvents and hydrolysis to the alcohol is easily accomplished with NaOH, with an overall yield of *ca.* 45%. The secondary C—H bonds are attacked in *n*-alkanes and arenes also react under these conditions.[112]

A similar reagent is thought to be formed from $Ag_2O_2$ and trifluoroacetic acid. Here, the silver oxide reacts as $Ag^I[Ag^{III}O_2]$ and forms $Ag(OCOCF_3)$ *in situ*, which is believed to be the active oxidant. With adamantane, the normal tertiary substitution product, $AdOCOCF_3$, was obtained in 98% yield. This oxidation could be made catalytic using $NH_4NO_3$ as cooxidant and $AgOCOCF_3$ as catalyst.[113]

Alkyl peroxycarbonates, which give $\cdot CO_2R$ radicals on thermolysis, function in chain reactions to give good yields of the corresponding carbonates from alkanes (equation 65).[114]

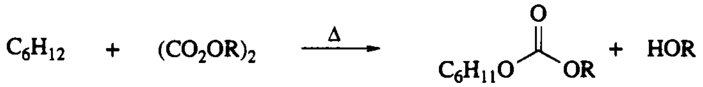

(65)

The 'Gif' system, discovered by Barton and coworkers at Gif-sur-Yvette,[115] consisting of air, iron powder, sulfide, organic solvent, acid and water, smoothly hydroxylates alkanes. The sulfide was found to be unnecessary if the reaction temperature exceeded 40 °C,[116] and the basic acetate $[Fe^{II}Fe^{III}{}_2O(OAc)_6py_3]$ was shown to be active in the presence of a reducing agent. Adamantane afforded up to 11% yield of adamantanone after 18 h. The system does not seem to fall into any of the usual mechanistic categories. Secondary C—H bonds appear to be attacked more readily than either primary or tertiary C—H bonds, but the selectivity is artificially elevated as a result of side reactions which the tertiary products undergo. The intrinsic secondary to tertiary selectivity of *ca.* 1:1 is still much higher than expected for radical or oxometal oxidations,[117] and is therefore of synthetic value. In addition, such species as diphenyl sulfide are not oxidized under the reaction conditions. Ketones, not alcohols, are the major products from cycloalkanes, but the ketones appear to be formed directly, not by oxidation of an alcohol intermediate. Nitrogenous bases, such as pyridine, are essential and Shilov[118] has suggested that the active oxidant may be pyridine-derived, *e.g.* $C_5H_4NO^{+\cdot}$. This suggestion is made more plausible by the fact that the iron can be replaced by other metals.[119] The same paper reports turnovers exceeding 3000 for the most recent version of the Gif system. A reagent which may operate by a related mechanism is iron(II)/$Et_3NO/CF_3CO_2H$, which gives trifluoroacetates from alkanes also without overoxidation.[120]

Peracids can react with alkanes to give hydroxylated products,[121] as shown in equation (66). This may be an electrophilic reaction because the rate increases with increasing acidity of the peracid. Radical side reactions were thought to be inhibited by added $I_2$.[122] $CF_3CO_3H$ is also an effective oxidant.[123] The reaction of *trans*-1,2-dimethylcyclohexane with $PhCO_3H$ is reported to be 97% stereoselective (retention) and 97% regioselective for tertiary hydroxylation.[95]

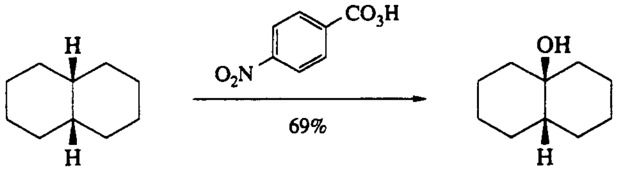

(66)

98% regioselectivity

Dioxiranes, generated by the oxidation of ketones with $KHSO_5$, insert an oxygen atom into alkane C—H bonds with retention of configuration by an oxenoid mechanism related to that found for peracids. Tertiary C—H bonds are hydroxylated and react faster than secondary $CH_2$ groups, which are completely oxidized to the ketone. Conversions of up to 50% have been observed.[124] $CF_3(Me)CO_2$ is a more recently developed reagent of the same type.[125] These easily prepared reagents have considerable promise for organic synthesis.

Ozone on silica gel has been used to hydroxylate alkanes and unactivated C—H bonds.[126] The example shown in equation (67) illustrates the application to a steroid, which was achieved in 51% yield at a respectable 11% conversion with regard to ozone.[127]

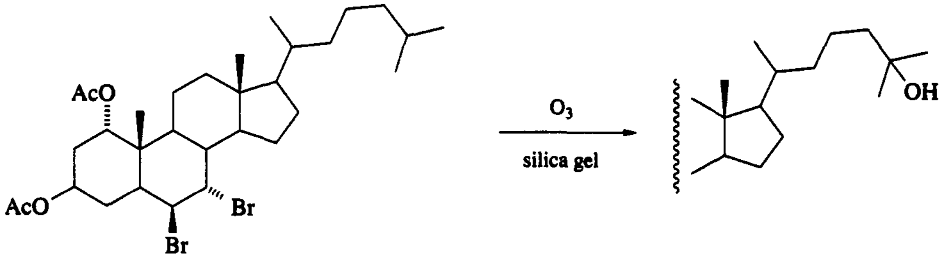

(67)

Ozone on silica gel at –78 °C is also a convenient form of the reagent and is especially useful for tertiary C—H bonds.[128] Ozone and $HSO_3F–SbF_6$ at –78 °C react with alkanes, but skeletal rearrangement often occurs; for example, methane gives acetone.[129] Oxygen atoms (in the $^3P$-state), formed from $CO_2$ in a microwave discharge at low pressure react with alkanes, to give, for example, the 1,2-epoxides and the tertiary alcohol from 2,3-dimethylbutane; $O_3$, in contrast, gives the tertiary alcohol and $Pr^iCOMe$.[130]

Methane may be oxidized to formaldehyde by $N_2O$ at 600 °C over $MoO_3$. At 5% conversion, 3.5% yield of $CH_2O$ and MeOH are also obtained.[131] These reactions are not especially useful for laboratory scale experiments.

## 1.1.12 FORMATION OF R—X BONDS (X = S, Se, Te)

Photolysis of $C_6F_5SCl$ in cyclohexane leads to formation of both arylthio- and chloro-cyclohexane by a radical pathway.[132] Sulfuryl chloride in pyridine can chlorosulfonate alkanes by a radical route under photolytic conditions, the chloride being a minor product (equation 68).[133] $SO_2$ and $Cl_2$ also gives the sulfonyl chloride by the route shown in equations (69) to (72).[134]

$$R{-}H + SO_2Cl_2 \longrightarrow R{-}SO_2Cl + R{-}Cl \quad , \qquad (68)$$

$$Cl_2 \xrightarrow{h\nu} 2Cl\bullet \qquad (69)$$

$$Cl\bullet + R{-}H \longrightarrow R\bullet + H{-}Cl \qquad (70)$$

$$R\bullet + SO_2 \longrightarrow RSO_2\bullet \qquad (71)$$

$$RSO_2\bullet + Cl\bullet \longrightarrow RSO_2Cl \qquad (72)$$

The synthesis of $MeSO_2Cl$ on an industrial scale has been achieved directly from methane by the Elf Aquitaine Company. This is notable not only in being a practical conversion of methane, but also in that it is a photochemical process.[135]

Lead tetraacetate in $CF_3CO_2H$, followed by RSH, affords the introduction of the SR group (R = $Bu^n$) into adamantane and bicyclo[3.3.1]nonane in high yields.[136]

Photolysis of alkane/$SO_2$ mixtures leads to the formation of alkylsulfonic acids,[137] the Hostapon process utilizing $SO_2/O_2/h\nu$.[138] It is curious that this reaction seems to be so efficient, given the low $\varepsilon$ for alkane and $SO_2$ at the wavelengths used, and an efficient chain reaction is presumably involved. The Reed reaction uses $SO_2/Cl_2/h\nu$ to convert alkanes to the corresponding sulfonyl chlorides.[139] Alkanes also react with $SO_3$ to give alkyl sulfonates, sulfones and sulfates.[140]

Methane reacts with elemental sulfur above 700 °C or at lower temperatures in the presence of a catalyst to give good yields of $CS_2$, a reaction that has been used for the commercial synthesis of the disulfide.[141] *n*-Butane, however, gives alkenes, dienes and thiophene under similar conditions.

The addition of $(PhSe)_2$ to the Gif system, mentioned above, leads to trapping of the radical intermediates with the formation of products with C—Se bonds, for example, 12% of 2-adamantyl phenyl selenide is formed from adamantane.[142]

## 1.1.13 FORMATION OF R—F BONDS

Fluorination is one of the few useful methods of preparing fluorocarbons. These materials have important physical and biological properties and are often high value chemicals. The problem with the reaction stems from the very large heat production in the overall process, thanks to the very weak bond strength of $F_2$, but the very high bond strengths of both H—F and C—F.[143] Nevertheless, by the use of diluted $F_2$ and appropriate choice of temperatures, a number of organic compounds can be successfully fluorinated (equation 73).[144]

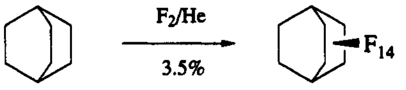

(73)

Barton and coworkers[145] have shown how elemental fluorine can be used in nitrobenzene to obtain a selective fluorination of a steroid, a reaction of importance in drug synthesis (equation 74). A variety of transition metal fluorides, such as $CoF_3$, are milder fluorinating agents for alkanes.[146]

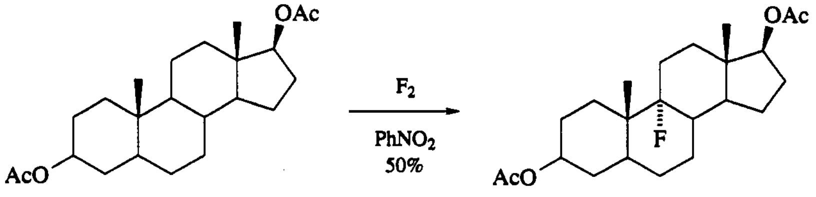

(74)

Another method that has proved useful involves photolysis of MeOF, which produces a methoxy radical and an F-atom. Substantial amounts of the fluoroalkane are produced *via* H-atom abstraction by MeO· and F·, and quenching the carbon radical with F·. This route was thought to be particularly useful for the synthesis of compounds with useful biological activity (equation 75).[147]

$$C_6H_{12} + MeOF \xrightarrow[44\%]{h\nu} C_6H_{11}F + MeOH \qquad (75)$$

## 1.1.14 FORMATION OF R—X BONDS (X = Cl, Br, I)

The radical chain halogenation of alkanes is a well-known process and is even commercially practised. The thermodynamics of this process are sufficient to allow the chain to progress for $Cl_2$ and $Br_2$, but not for iodine. These halogenations are easy to control and the selectivity of chlorination has been carefully studied.[148]

Photochlorination has been recommended for the preparation of choice of cyclodecene from cyclodecane *via* the intermediate chloride.[149] Bromine is a rather weak brominating agent for alkanes and only unusually favorable substrates, like adamantane, react at a reasonable rate. The mixture $HgO/Br_2$ is much more reactive than bromine itself, as shown by the facile bromination of 1,1,3,3-tetramethylbutane.[150] Silver hexafluoroantimonate has also been used to activate bromine for this type of reaction.[27] Iodine is normally ineffective in functionalizing alkanes, but use of γ-irradiation of a solution of $I_2$ in alkanes leads to unselective formation of all possible iodoalkanes.[151]

Rather than using the halogens themselves, other halogen radical donors are more commonly used in laboratory scale synthesis. One of the simplest of these is $CCl_4$, which can chlorinate alkanes by a free radical chain mechanism.[152] The chain lengths are not very long (equations 76–78), because of their slightly endothermic nature and in part because the reaction is also kinetically rather slow. Elevated temperatures are therefore normally required.[153] Nitrosylchloride at 100 °C has also been used for these reactions.[154]

Trichlorobromomethane appears to be an efficient bromination reagent because of kinetic rather than thermodynamic factors, and fairly long radical chain reactions result.[155] 1,2-Dibromotetrachloroethane is

$$Q\bullet + C_6H_{12} \longrightarrow QH + C_6H_{11}\bullet \qquad (76)$$

$$C_6H_{11}\bullet + CCl_4 \longrightarrow Cl_3C\bullet + C_6H_{11}Cl \qquad (77)$$

$$Cl_3C\cdot + C_6H_{12} \longrightarrow Cl_3CH + C_6H_{11}\cdot \qquad (78)$$

Q• = initiator

a useful reagent for the bromination of alkanes. The intermediate halocarbon radical spontaneously β-eliminates to afford a further bromine radical (equation 79).

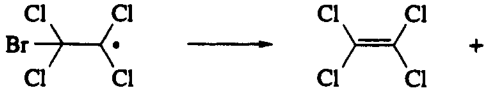

(79)

Trichloromethanesulfonyl chloride has also been used as a chlorination reagent for alkanes, but this reaction requires a peroxide initiation step (equation 80).[156]

$$Cl_3CSO_2Cl + R{-}H \longrightarrow R{-}Cl + SO_2 + HCCl_3 \qquad (80)$$

*N*-bromosuccinimide (NBS) is, however, one of the best known bromine donors. For example, it can brominate cyclohexane to give a 30% yield of the corresponding bromide.[157] NBS/dibenzoyl peroxide is not very selective, giving mixtures with methylcyclohexane,[158] although decalin gives tetrabromides in a reasonably well-defined manner (equation 81).[159]

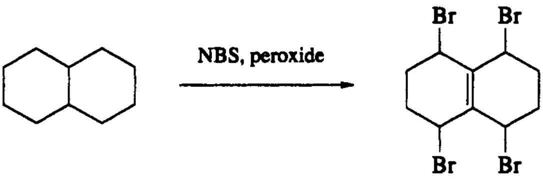

(81)

A useful degree of selectivity for attack at the ω-1 position has been reported in the photochlorination of a variety of linear alkyl compounds, such as *n*-hexyl chloride, with $Pr^i_2NCl$. The selectivity arises from the fact that many electron-withdrawing groups deactivate adjacent C—H bonds for abstraction by a chlorine radical. By the 'polar' effect, an electronegative atom, such as a chlorine radical, is better able to abstract a hydrogen atom from the most donor C—H bond available. The usual secondary > primary selectivity pattern prevents the terminal methyl group from being the preferred site of attack, hence the next methylene (*i.e.* at the ω-1 position) is attacked preferentially with selectivities of *ca.* 90% being reported.[160] Intramolecular versions of the reaction are also known.[161]

A similar reagent, benzeneiodonium chloride, is also effective under photolytic conditions. A 90% yield of the chloride has been reported for cyclohexane, for example, using this reagent.[162] A recent improvement to the use of $PhICl_2$ employs a trialkylboron as coreagent. *n*-Alkanes are converted to the chlorides in 99% yield under conditions which give no conversion in the absence of the borane catalyst.[163] In all these cases, the reaction is believed to go *via* chlorine radicals and PhICl radicals.

Iodine monochloride, ICl, is another reagent which is useful for the chlorination of alkanes. It was known in the 1950s that ICl was unstable in alkane solution,[164] but the use of irradiation to accelerate the reaction to useful rates was reported later.[165] The chain-carrying step is shown in equation (82).

$$R\cdot + ICl \longrightarrow R{-}Cl + I\cdot \qquad (82)$$

Similarly sulfuryl chloride, $SO_2Cl_2$, has been employed in this type of reaction, using a peroxide-initiated chain reaction to give chlorocarbons from alkanes. The reaction is rather unselective; for example, *n*-heptane gives 15% primary attack and 85% secondary attack. The hydrogen atom abstractor in this chain process is believed to be SOCl·, rather than the chlorine radical. The monochlorinated species is more reactive than the alkane and consequently multiple chlorination takes place. Electron-withdrawing groups destabilize a radical center and so subsequent chlorination events tend to take place at a site remote from the first point of attack.[166] In sulfolane, the same reagent apparently reacts by an electrophilic pathway, and adamantane gives almost exclusively the tertiary halide, compared to the mixture formed during radical reactions. Norbornane gives largely 2-*exo*-chloronorbornane, as the result of the steric bulk of the reagent leading to attack on the least-hindered site.[167] Sulfuryl chloride is also a useful halogenating agent for nonalkane substrates.[168]

*t*-Butylhypochlorite has been used to chlorinate alkanes with either peroxide or light initiation.[169] $Bu^tOI$, made from $Bu^tOCl$ and $HgI_2$, has also been used for iodination in $CCl_4$ under photolytic conditions. The secondary to primary selectivity in these reactions is good (*ca.* 30:1). Indeed the reaction is only preparatively useful for secondary iodides (yields 30–80%) since the tertiary iodides, although formed, decompose rapidly under the reaction conditions.[170] This process is an example of an apparent secondary > tertiary > primary selectivity pattern resulting from subsequent reaction, and may explain other anomalous selectivities occasionally reported by other workers.

A reagent which may operate by hydrogen atom abstraction from the alkane by the intermediate alkylammonium radical cation is iron(II)/$R_2NCl/CF_3CO_2H$, which affords secondary chlorides in good yield from *n*-alkanes without overoxidation.[171]

Chemistry reported by Shilov[2,172] allows chlorination of alkanes at the expense of a platinum(IV) halide as the chlorination reagent, but catalyzed by a platinum(II) species. Methane and ethane give the chlorides together with some of the corresponding alcohols. Propane gives a 3:1 mixture of $Pr^nCl$ and $Pr^iCl$, and *n*-pentane gives a ratio of normal to secondary halides of 56:44, while cyclohexane leads to benzene as the major product. The addition of copper(II) makes the reaction catalytic by reoxidizing the platinum with air as the ultimate oxidant system, although only 5 turnovers were obtained.[173]

$AgSbF_6/Cl_2/CH_2Cl_2$ at –15 to +35 °C is reported to be a convenient and effective reagent for the electrophilic chlorination of tertiary alkanes and cycloalkanes.[174] Adamantane was sufficiently reactive to undergo uncatalyzed electrophilic bromination at 80 °C.[175] Substrates with adjacent tertiary C—H bonds produce α,β,γ,δ-tetrabromides by a series of bromination/dehydrobromination reactions.[176] Alkanes also can be chlorinated by an electrophilic route using heterogeneous catalysts such as $TaOF_3/Al_2O_3$ at 180–250 °C: >90% yield is obtained at 10–50% conversion.[177] $Cl_2/SbF_5/SO_2ClF$ has been used for electrophilic chlorination, but, not surprisingly, skeletal rearrangements are often observed, and less than 20% of products are found from *n*-butane, for example.[178] Schwartz[179] has shown that $[Rh(allyl)_3]$ may be supported in molecular form on alumina, and that the resulting material can be used to chlorinate methane.[180]

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# 1.2

# Oxidation by Nitrene Insertion

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## 1.2.1 INTRODUCTION

Nitrenes are monovalent, neutral, electron deficient nitrogen species. Although a few nitrenes are sufficiently long lived to enable spectroscopic detection and measurements at low temperature, for synthetic purposes, nitrenes can be considered as highly reactive intermediates which have to be generated *in situ* in the presence of the substrate from a suitable stable precursor (see Section 1.2.2.1). The generation and reactivity of nitrenes are discussed in two books and in several reviews, and for general information on specific classes of nitrene, the reader is referred to the appropriate review: alkylnitrenes,[1,2] vinylnitrenes,[3,4] arylnitrenes,[5–7] acylnitrenes,[8–12] cyanonitrenes[13] and sulfonylnitrenes.[14] In addition there are relevant reviews on the nitrenes in heterocyclic synthesis,[15–17] photoaffinity labeling using nitrenes,[18] and on the decomposition and synthetic uses of azides.[19–21]

Although this chapter is primarily concerned with the functionalization of unactivated *sp*$^3$ C—H bonds by nitrene insertion, other relevant aspects of nitrene chemistry are included. Thus the brief section on nitrene reactivity highlights the rearrangement reactions which often compete with C—H insertion, and the final section covers insertion into *sp*$^2$ C—H bonds, since many of these reactions have found wide use in recent years in the synthesis of natural products.

## 1.2.2 NITRENE GENERATION AND REACTIVITY: A BRIEF OVERVIEW

### 1.2.2.1 Generation

The main methods of nitrene generation are summarized in Scheme 1, although it should be borne in mind that the isolation of nitrene-type products does not necessarily imply that the reaction involves a free nitrene. Azides are the most convenient precursors to nitrenes, since, for the most part they are easily prepared, and can be decomposed under 'reagent-free' conditions by the action of heat, light or a suitable catalyst to give the nitrene and molecular nitrogen. The thermal stability of azides varies greatly, with some such as cyanogen azide being notoriously unstable, whilst others require temperatures in excess of 200 °C to initiate decomposition. However, for handling purposes, all azides should be considered potentially explosive. Other reagent-free sources of nitrenes are isocyanates, ylides, small ring heterocycles such as aziridines and oxaziridines, and five-membered ring heterocycles such as 1,3,4-dioxazol-2-ones, *e.g.* (1), and 1,3,2,4-dioxathiazole 2-oxides which can eliminate $CO_2$ and $SO_2$ respectively, although none of these are widely used. More commonly used nitrene precursors are nitro compounds, which are deoxygenated by tervalent phosphorus reagents, and compounds which can undergo base-mediated α-elimination reactions such as *N*-chloro compounds and *N*-sulfonyloxy compounds, although of these only *N*-arenesulfonyloxy carbamates, *e.g.* (2), have found wide use as a source of ethoxycarbonylnitrenes. Finally amines can be oxidized using reagents such as lead(IV) acetate to give nitrene intermediates.

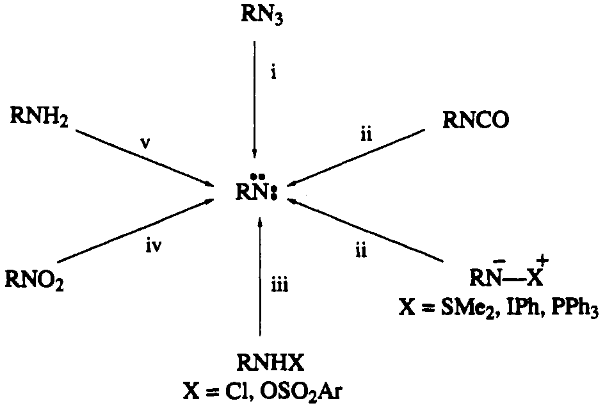

i, heat, *h*ν, or catalyst; ii, heat or *h*ν ; iii, base; iv, $P^{III}$ reagent; v, oxidant

Scheme 1

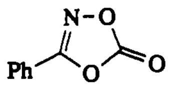

(1)

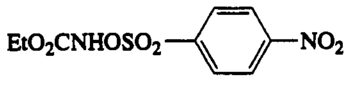

(2)

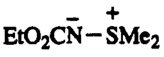

$EtO_2C\overset{-}{N}-\overset{+}{S}Me_2$

(3)

### 1.2.2.2 Reactivity

The high reactivity of nitrenes stems from the fact that the nitrogen has only six electrons in its outer shell. Of these, two are bonding electrons, two are the 'normal' nitrogen lone pair, and the remaining two can either be in the same orbital with their spins paired or in separate orbitals with unpaired spins, leading to the possibility of singlet and triplet (diradical) states. Although Hund's rule predicts that nitrenes should have a triplet ground state, many reactions of nitrenes are characteristic of the singlet state.

The four main characteristic reactions of nitrenes are summarized in Scheme 2. All of these reactions have parallels in carbene chemistry; for example, a full discussion of the C—H insertion reaction of carbenes is given in Volume 3, Chapter 4.2. The first reaction, the addition to an alkene to form an aziridine, is covered in detail in Volume 7, Chapter 3.5. The C—H insertion reaction, the subject of this chapter, can, in principle, occur by several mechanisms. However most of the reactions are believed to involve direct insertion of the singlet nitrene into the C—H bond, rather than a stepwise hydrogen abstraction–recombination mechanism involving the triplet, or stepwise ion pair mechanisms. On the other hand, some reactions of nitrenes which lead to products with a new C—N bond that are the result of a formal C—H insertion proceed by an entirely different mechanism. Therefore, although we are largely concerned with the preparative aspects of nitrene C—H insertions, the mechanistic detail cannot always be ignored since it may well impinge on other factors such as the stereoselectivity of the insertion process.

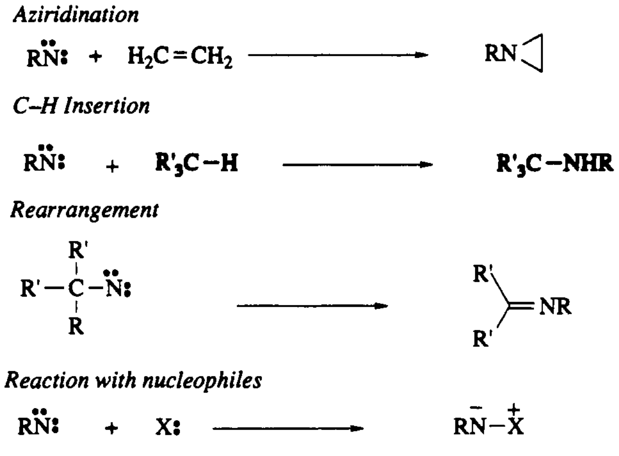

**Scheme 2**

Nitrenes in common with other electron deficient intermediates are prone to rearrangement by migration of an atom or group from the adjacent carbon to the electron poor center. This type of rearrangement, which often competes with C—H insertion reactions, is particularly favorable in two cases: the decomposition of alkyl azides to give imines, and of acyl azides to give isocyanates (the Curtius rearrangement). Indeed, in the first case, the rearrangement is so facile that the C—H insertion reaction of simple alkylnitrenes is not a synthetically useful process. The final characteristic reaction of nitrenes (Scheme 2) is that with nucleophiles containing a heteroatom lone pair such as sulfides and phosphines to give ylides. Although we are not concerned directly with this reaction, it does have important consequences for C—H insertion reactions that are carried out in heteroatom-containing solvents such as ethers.

## 1.2.3 INSERTION INTO $sp^3$ C—H BONDS

### 1.2.3.1 Intermolecular

The C—H insertion reaction of nitrenes is a potentially useful way of functionalizing unactivated C—H bonds, converting hydrocarbons into amine derivatives. In its intermolecular form the synthetic utility of the reaction is highly dependent on the substituents on the nitrene, and on the manner in which it is generated. To exemplify these effects, the results for the functionalization of cyclohexane by insertion of various nitrenes (equation 1) are summarized in Table 1.

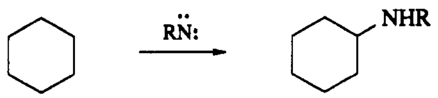

(1)

Several features are immediately apparent. The yields from simple alkylnitrenes are exceedingly poor because of the facile rearrangement by hydrogen migration. Polyfluorinated alkylnitrenes give higher yields, but the reaction is not generally useful. Intermolecular insertion reactions of arylnitrenes are rare, and generally give poor yields, the major reaction being formation of anilines by hydrogen abstraction by the triplet nitrene. Further evidence for triplet involvement in these cases comes from results of phenylnitrene insertion into the tertiary C—H bond of 2-methylpropane and its 2-deuterated analog.[24] The observed isotope effect of 4.1 was considered too large for a concerted C—H insertion reaction of the

**Table 1** Functionalization of Cyclohexane by Nitrene Insertion (equation 1)

| *R* | *Conditions of generation* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| Me | Azide, Δ | 0.4 | 22 |
| $CF_3CHFCF_2$ | Azide, *hν* | 18[a] | 23 |
| Ph | Azide, Δ | *b* | 24 |
| Tetrafluoropyrid-4-yl | Azide, Δ | 45 | 25 |
| $Bu^tCO$ | Azide, *hν* | 20 | 26 |
| PhCO | Azide, *hν* | 40–46 | 27, 28 |
| PhCO | (**1**), *hν* | 23 | 28 |
| $EtO_2C$ | Azide, Δ | 52–76[b] | 29, 30 |
| $EtO_2C$ | Azide, *hν* | 51, 78 | 31, 32 |
| $EtO_2C$ | (**2**), base | 13–20 | 33, 34 |
| $EtO_2C$ | (**3**), *hν* | 21 | 35 |
| $C_{18}H_{37}O_2C$ | Azide, Δ | 60–73[c] | 36 |
| Ms | Azide, *hν* | 18 | 37 |
| $C_5H_{11}SO_2$ | Azide, Δ | 54 | 38 |
| Ts | Azide, Δ | 58 | 38 |
| $(EtO)_2PO$ | Azide, *hν* | 88 | 39 |
| $(PhO)_2PO$ | Azide, *hν* | 67 | 39 |

[a] After hydrolysis to cyclo-$C_6H_{11}NHCOCHFCF_3$; GLC suggests yield is *ca.* 30%. [b] Gives mainly aniline; yield of cyclo-$C_6H_{11}NHPh$ not quoted. [c] Yield increased in presence of 'additives' such as 1,3-dinitrobenzene; see Section 1.2.3.1.

singlet. Relatively poor yields of C—H insertion products are also obtained from acyl azides; again the problem is a competing reaction, Curtius rearrangement to the isocyanate which in the case of photolysis of benzoyl azide was isolated in 57% yield.[27]

Ethoxycarbonylnitrene, however, gives a synthetically useful yield of the C—H insertion product, *N*-cyclohexylurethane, the carbamate group of which can subsequently be hydrolyzed or modified. The thermal reaction is carried out by simply heating a dilute solution of ethyl azidoformate in cyclohexane, although the yield can be improved by carrying out the reaction in the presence of 'additives' such as 1,3-dinitrobenzene, sulfur or hydroquinone.[29] The C—H insertion process is a singlet nitrene reaction, so the role of these additives, all of which are potential radical traps, is not completely clear. One possibility is that any radicals assist the singlet to triplet nitrene interconversion process, and since the triplet does not insert, yields are higher in the presence of radical traps. Likewise the yield of insertion product is increased in the presence of hexafluorobenzene.[30] Photochemical generation of ethoxycarbonylnitrene from ethyl azidoformate also gives a useful yield of the insertion product,[31,32] but the alternative nitrene precursors such as the *N*-arenesulfonyloxy carbamate (**2**) and the sulfimide (**3**) are less satisfactory,[33–35] the latter precursor giving largely triplet nitrene on irradiation. When the decomposition of the *N*-arenesulfonyloxy carbamate (**2**) was carried out in cyclohexane-$d_{12}$, an isotope effect of about 1.5 was observed.[33] This small effect is consistent with a concerted C—H insertion of the singlet nitrene. Octadecyl azidoformate also gives a good yield of the insertion product on heating in cyclohexane, although a small amount of intramolecular insertion occurs to give a mixture of five- and six-membered ring products.[36] Again, the yield of the *N*-cyclohexyl carbamate is improved in the presence of 1,3-dinitrobenzene. Finally, some sulfonyl- and phosphonyl-nitrenes give good yields of the corresponding cyclohexylamine derivatives.[37–39]

### *1.2.3.1.1 Chemoselectivity*

The insertion reactions into cyclohexane C–H bonds (Table 1) give some idea of which nitrenes give synthetically useful yields. However, since most other substrates will contain more than one sort of C—H bond, it is important to know the selectivity of nitrenes for different types of C—H bond. Several studies of nitrene selectivity towards tertiary, secondary and primary unactivated C—H bonds have been made, although attempts to study allylic C—H insertion reactions are complicated by the competing nitrene addition to the double bond. In cyclohexene it has been estimated that the allylic C—H bond is only about three times more reactive than the homoallylic C—H bond towards insertion of ethoxycarbonylnitrene.[31,33] However, the reaction is totally unsatisfactory as a means of allylic functionalization since, as shown in Scheme 3, the yields are so low.

The standard hydrocarbon substrate that has been used to determine the relative selectivities of nitrenes for tertiary, secondary and primary unactivated C—H bonds is 2-methylbutane, and the results of

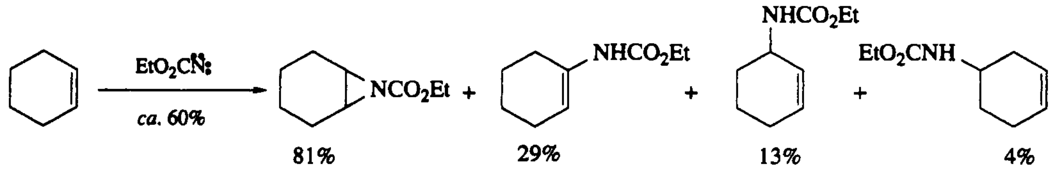

**Scheme 3**

several studies are summarized in Table 2. For all nitrenes, the order of reactivity is tertiary > secondary > primary C—H bonds, but there is a considerable variation in the degree of selectivity. Phenylnitrene is the most selective, although as has already been described, the overall yield of C—H insertion is very poor. The selectivity is thought to arise from stabilization of the nitrene by electron donation from the aromatic ring.[40] Pivaloylnitrene is also very selective in its insertion reactions, with benzoylnitrene being less so, although the yields are less than 25% because of the competing isocyanate formation.[26,41] In the latter case, the C—H insertion selectivity is apparently dependent on the nitrene precursor.[28]

**Table 2** Relative Reactivity of Tertiary, Secondary and Primary C—H Bonds in 2-Methylbutane towards Nitrene Insertion[a]

| *R* | *Conditions of generation* | *Tertiary* | *Secondary* | *Primary* | *Ref.* |
|---|---|---|---|---|---|
| Ph | Azide, Δ | 140–280 | >7 | 1 | 40 |
| $Bu^tCO$ | Azide, $h\nu$ | 120–200 | 9 | 1 | 26 |
| PhCO | Azide, $h\nu$ | 58 | 7 | 1 | 41 |
| $EtO_2C$ | Azide, $h\nu$ | 43 | 6.6 | 1 | 42 |
| $EtO_2C$ | Azide, $h\nu$ | 34 | 9 | 1 | 33 |
| $EtO_2C$ | Azide, Δ | 32 | 10 | 1 | 36 |
| $EtO_2C$ | (**2**), base | 27 | 11 | 1 | 33 |
| Ms | Azide, $h\nu$ | 9.6 | 4.2 | 1 | 37 |
| Ms | Azide, Δ | 5.8 | 2.2 | 1[b] | 43 |
| $(EtO)_2PO$ | Azide, $h\nu$ | 6.0 | 4.3 | 1 | 39 |
| $(PhO)_2PO$ | Azide, $h\nu$ | 3.4 | 1.2 | 1 | 39 |
| NC | Azide, Δ | 67 | | 1[c] | 46 |

[a] Statistically corrected for number of C—H bonds. [b] Substrate is 2,4-dimethylpentane. [c] Substrate is 2,3-dimethylbutane.

The much studied ethoxycarbonylnitrene is somewhat less selective, although tertiary C—H bonds are still about 30 times more reactive than primary ones towards the nitrene. The selectivity varies slightly according to which nitrene precursor is used, and is also influenced by the reaction solvent.[33,36] In the presence of dioxane, the selectivity for tertiary C—H insertion over primary decreases with increasing dioxane concentration.[44] The results are explained by formation of a complex (**4**) between dioxane and the singlet nitrene, hence the 'nitrene' is more sterically demanding and exhibits lower selectivity towards tertiary C—H bonds. The relative reactivity of axial and equatorial C—H bonds towards ethoxycarbonylnitrene has been determined using *cis*- and *trans*-1,4-dimethylcyclohexane as substrate. Results show that insertion into equatorial C—H bonds is favored over axial by a factor of about 1.3.[45] Sulfonyl- and phosphonyl-nitrenes are significantly less selective in their insertion reactions, although the reactions involving the phosphonylnitrenes are particularly high yielding.[37,39,43] The relative lack of selectivity compared to acylnitrenes is explained by the fact that both S═O and P═O bonds are considerably less effective than the C═O bond in stabilizing the electron deficient nitrogen. Cyanonitrene, which has been studied in a number of systems, is highly selective and high yielding, although the instability of the precursor, cyanogen azide, detracts from the synthetic utility.[46]

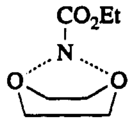

(**4**)

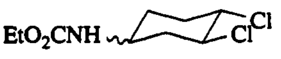

(**5**)

With polycyclic hydrocarbons such as norbornane, bicyclo[2.2.2]octane and adamantane, nitrene insertion can occur at a tertiary bridgehead C—H bond or at a $CH_2$ group. With the exception of norbornane, the tertiary C—H is more reactive; for example, in adamantane the selectivity of ethoxycarbonylnitrene for the tertiary C—H over the secondary is about 6:1.[47,48] Similarly, ethoxycarbonylnitrene inserts selectively at the ring junction tertiary C—H bond in bicyclic hydrocarbons such as decalin,[49] although in one experiment a CIDNP effect was observed, suggestive of triplet involvement.[50]

Two groups of insertion substrates that require special mention are ethers and chloroalkanes. In ethers, the nitrene inserts selectively α to the oxygen atom, and although the reaction has only been thoroughly investigated for ethoxycarbonylnitrene and cyclic ethers, the effect does seem to be general.[51–56] The chemoselective insertion α to the ring oxygen of cyclic ethers is synthetically useful, since the resulting insertion products can subsequently be transformed into α,ω-amino alcohol derivatives as shown in Scheme 4.[51]

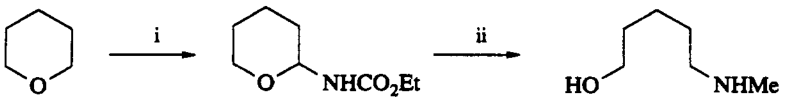

i, $EtO_2CN_3$, *hv*; ii, $LiAlH_4$

**Scheme 4**

The relative reactivity of C—H bonds α to ring oxygens have been estimated, and the results are summarized in Scheme 5. The results are rationalized by invoking stabilization of the nitrene by prior coordination to the ring oxygen. Dioxane with two oxygen atoms is particularly effective at stabilizing nitrenes, and the formation of complex (4) has been proposed to explain the pronounced solvent effect that dioxane has on a number of insertion reactions of ethoxycarbonylnitrene. Nitrene insertion reactions in chloroalkanes tend to occur away from the chlorine atom; with *trans*-1,2-dichlorocyclohexane as substrate, the insertion product (5) is formed in good yield.[57]

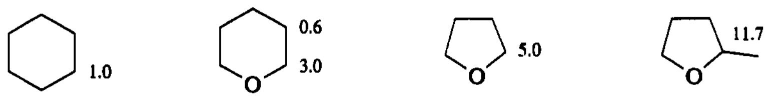

**Scheme 5**

In summary, most nitrenes exhibit some chemoselectivity in their intermolecular C—H insertion reactions, with the order of reactivity being tertiary > secondary > primary C—H bonds. Hence the ease of homolysis of the C—H bond in question would appear to be a good guide to its reactivity towards nitrene insertion, despite the fact that the reaction almost certainly involves a concerted reaction of the singlet nitrene and not a radical process.

### *1.2.3.1.2 Stereoselectivity*

The stereochemistry of nitrene insertion into unactivated C—H bonds has been studied using substituted cyclohexanes as substrates. For arylnitrenes which usually exhibit triplet reactivity, the reaction is nonspecific,[25] but most other nitrenes undergo stereospecific C—H insertion. For example, benzoylnitrene inserts selectively into the tertiary C—H bond of both *cis* and *trans*-1,4-dimethylcyclohexane with retention of configuration.[41,58] Similarly with *cis*- and *trans*-1,2-dimethylcyclohexane as substrate, ethoxycarbonyl-,[59] methanesulfonyl-[43] and cyano-nitrenes[46,60] all insert with retention of configuration at the tertiary C—H bond.

When optically active hydrocarbons have been used as substrates, a similar pattern of insertion reactivity emerges. Phenylnitrene inserts with a maximum of 30% retention into the tertiary C—H bond of optically active 2-phenylbutane implying a high degree of triplet involvement,[24] whereas ethoxycarbonylnitrene inserts stereoselectively with 98–100% retention into the tertiary C—H of (*S*)-(+)-3-methylhexane.[61] The result is independent of the method of nitrene generation, and of concentration, and lends support to the view that only singlet ethoxycarbonylnitrene inserts into unactivated C—H bonds.

### 1.2.3.2 Intramolecular

Although intermolecular nitrene insertion reactions can be a useful way of functionalizing unactivated C—H bonds, it is the intramolecular version of the reaction that has found the widest use in synthesis. Most types of nitrene will undergo intramolecular C—H insertion, and the following discussion is organized in terms of type of nitrene, scope and selectivity of the reaction, and, finally, specific uses in synthesis.

#### *1.2.3.2.1 Scope and selectivity*

Alkylnitrenes are very poor in functionalizing C—H bonds, even if the insertion is intramolecular. Earlier claims that pyrrolidines (**6**) could be formed by insertion of alkylnitrenes derived from simple alkyl azides have subsequently been disproved,[62] and the only apparently genuine example of a reaction of this type involves the azidosteroid 6β-azido-5α-pregnane (**7**), which leads to functionalization of the 19-methyl group upon irradiation, albeit in very poor yield.[63]

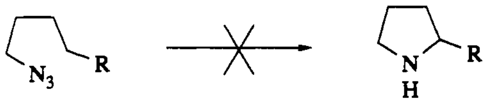

(**6**)

(2)

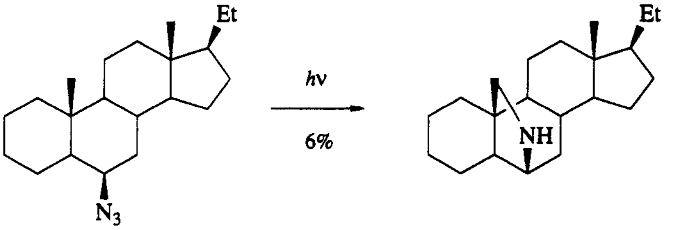

(**7**)

(3)

The decomposition of vinyl azides often leads to products of formal C—H insertion reactions, although in many cases the mechanism does not involve a genuine nitrene insertion. Some examples, which also include insertion into more activated C—H bonds, are shown in Scheme 6.[64–66] The yields of fused pyridines, formed by aromatization of the initial 'insertion' product, are variable, but the reaction is a useful way of constructing polycyclic systems such as the azafluoranthene (**8**) from, in this case, a relatively simple fluorene derivative. The formation of the azepinoindole (**9**) by 'insertion' into the unactivated methyl group of the ethyl substituent rather than into the activated CH$_2$ group is particularly interesting, although the reaction is solvent dependent with the alternative 'insertion product', ethyl 1-methyl-β-carboline-3-carboxylate being formed in competition in other solvents.[66]

Arylnitrenes, generated by thermolysis of aryl azides or by deoxygenation of the corresponding nitro compounds, readily undergo intramolecular insertion into the C—H bonds of *ortho* alkyl substituents. With azides as precursor, the reaction is often cleaner and higher yielding in the vapor phase than in solution. The reaction is a route to indolines, which may be dehydrogenated to indoles, and, in general, the formation of the five-membered ring indoline is preferred to the six-membered ring tetrahydroquinoline by a factor of about 4:1.[67–70] Some examples are shown in Scheme 7; again the reaction has been applied in the steroid field, the 1-azidoestrone (**10**) giving the C-11 functionalized product in good yield.[71]

The intramolecular insertion reaction of arylnitrenes proceeds with retention of configuration at carbon. For example, heating the (*S*)-aryl azide (**11**; X = N$_3$) in the vapor phase gives 2-ethyl-2-methylindoline in 50–60% yield in *ca.* 100% optical purity.[72] The optical purity of the product is lower if the azide is heated in solution, or if the nitrene is generated from the corresponding nitro compound (**11**; X = NO$_2$) with triethyl phosphite.[73]

The intramolecular reaction of acylnitrenes suffers from the same competing Curtius rearrangement as the intermolecular reaction, and therefore the yields of insertion product are often low. In general, the formation of δ-lactams is preferred to γ-lactams by a factor of about 2:1, where the possibility for competing intramolecular insertion into similar C—H bonds exists. Thus irradiation of the azides (**12**; R = Me, Pr) gives a mixture of δ- and γ-lactams in a ratio of 2:1 in lowish overall yield of 30–35% (Scheme 8).[8,74,75] The reaction proceeds stereoselectively at the C—H bond, the nitrene derived from the optically pure (*R*)-azide (**13**) inserting with *ca.* 98% retention of stereochemistry, although in poor chemical yield.[76]

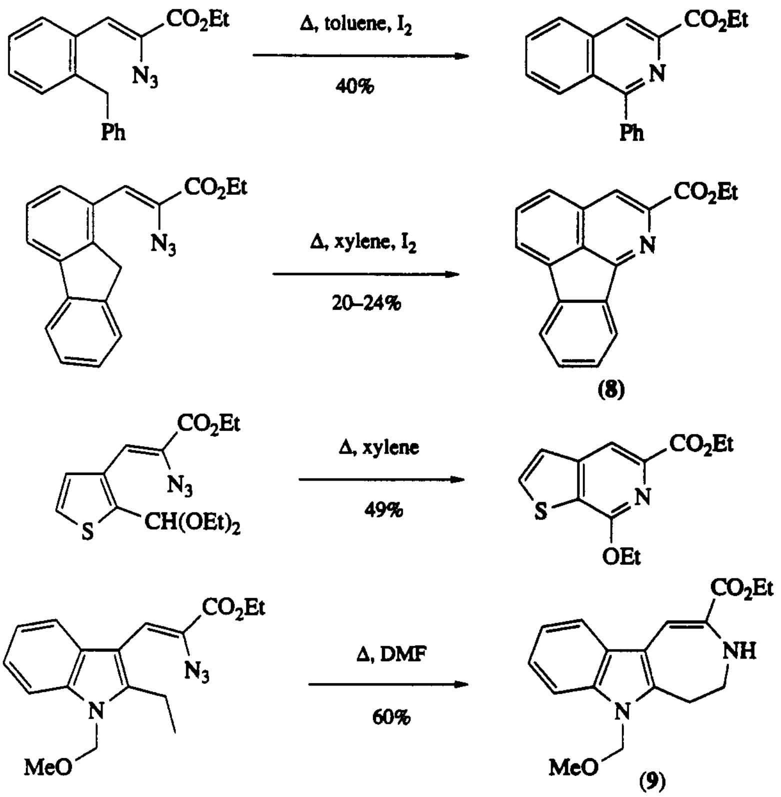

$CO_2Et$
$N_3$
Ph
Δ, toluene, $I_2$
40%
$CO_2Et$
N
Ph
$CO_2Et$
$N_3$
Δ, xylene, $I_2$
20–24%
$CO_2Et$
N
(8)
$CO_2Et$
$N_3$
S
$CH(OEt)_2$
Δ, xylene
49%
$CO_2Et$
S
N
OEt
$CO_2Et$
$N_3$
N
MeO
Δ, DMF
60%
$CO_2Et$
NH
N
MeO
(9)

Scheme 6

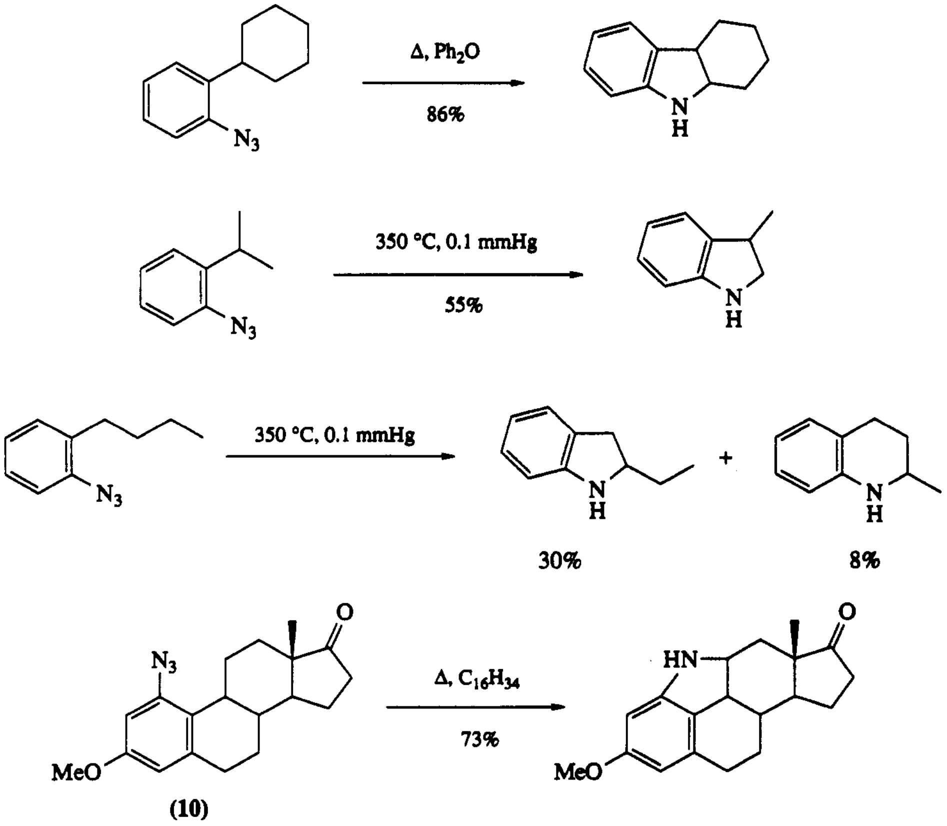

$N_3$
Δ, $Ph_2O$
86%
N
H
$N_3$
350 °C, 0.1 mmHg
55%
N
H
$N_3$
350 °C, 0.1 mmHg
N
H
+
N
H
30%
8%
$N_3$
O
MeO
(10)
Δ, $C_{16}H_{34}$
73%
HN
O
MeO

Scheme 7

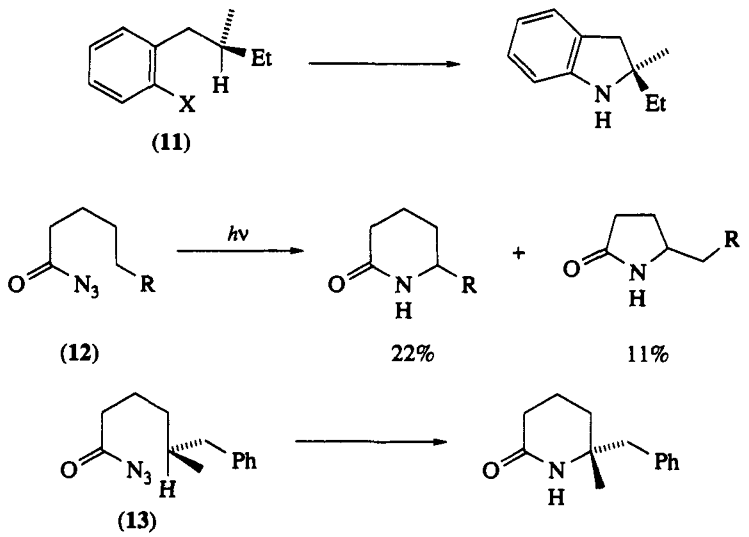

(11)

(4)

(12)

(13)

Scheme 8

Nitrenes derived from azidoformates, however, do not suffer from competing Curtius rearrangement, and undergo intramolecular C—H insertion in good yield. Thus irradiation of *t*-butyl azidoformate results in cyclization by insertion into the unactivated C—H bond of the methyl group to give the oxazolidinone (**14**) in good yield.[77] When the optically active (*S*)-azidoformates (**15**; R = Me, Ph) were irradiated, the corresponding oxazolidinones were formed with >97% retention of stereochemistry,[72,78] confirming once again that high stereoselectivity is a feature of nitrene insertion reactions.

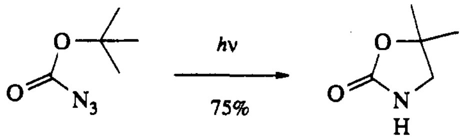

(5)

(14)

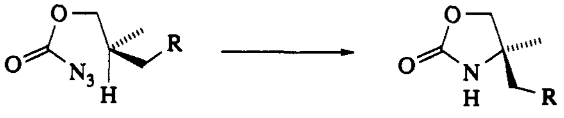

(6)

(15)

Sulfonylnitrenes also undergo intramolecular C—H insertion to give six-membered sultams.[79] In the series of sulfonyl azides (**16**; *n* = 0, 1), the sultams were formed in low yield; no five-membered sultams were observed.

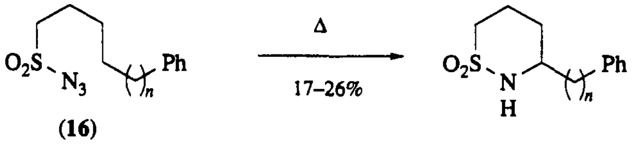

(7)

(16)

### *1.2.3.2.2 Use in synthesis*

Although the functionalization of unactivated C—H bonds by intramolecular nitrene insertion has been applied to the synthesis of diterpene alkaloids and in the modification of steroids as described below, it has also been used to good effect in simpler systems. For example, 1-adamantyl azidoformate, readily prepared from 1-adamantanol, gives the oxazolidinone (**17**) on irradiation in cyclohexane by intramolecular C—H insertion. Hydrolysis of **(17)** gives the otherwise inaccessible 2-amino-1-adamantanol (Scheme 9).[80]

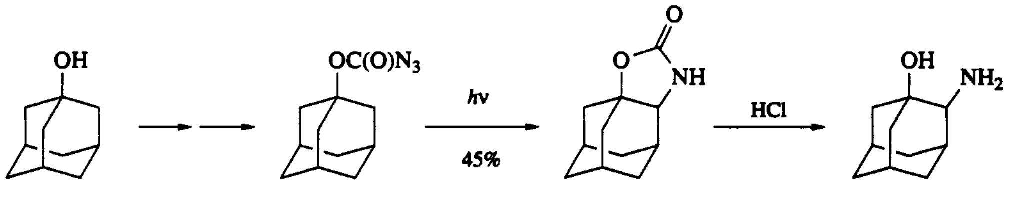

**(17)**

**Scheme 9**

A similar nitrene insertion reaction was used in the synthesis of 6″-aminogentamycin C2 by functionalization of the garosamine moiety of the antibiotic.[81] The key steps of the sequence are shown in Scheme 10; heating the azidoformate **(18)** to 130 °C in dichloromethane results in the desired intramolecular nitrene insertion and functionalization of the unactivated methyl group, although some cyclization to the five-position is also observed. The synthesis was completed by hydrogenolysis of the oxazolidinone and removal of the protecting groups.

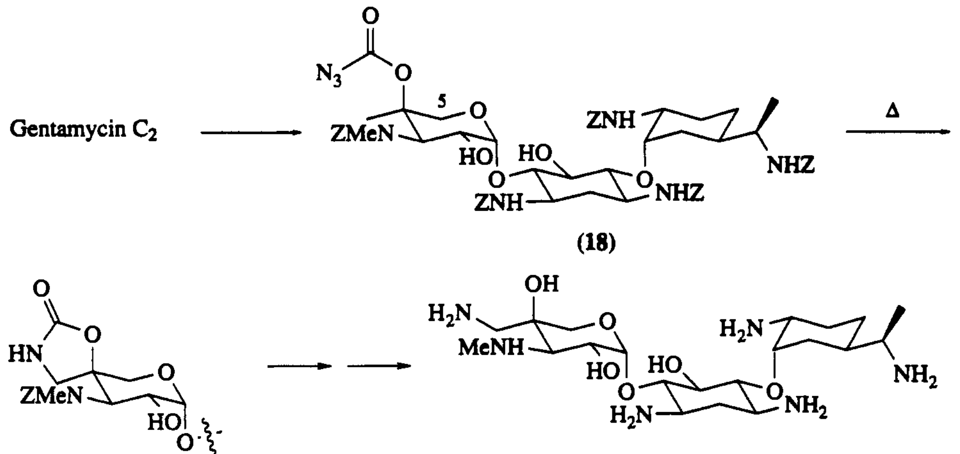

**(18)**

6″-Aminogentamycin C2

**Scheme 10**

The use of acylnitrene cyclizations in the synthesis of diterpene alkaloids goes back to the early 1960s, and although much of the early work has been reviewed,[10] selected examples are included here. The acyl azide **(19)**, readily prepared from podocarpic acid, was irradiated to give the δ-lactam (**20**; 20%), which has the azabicyclononane ring system of the diterpene alkaloids such as atisine.[82]

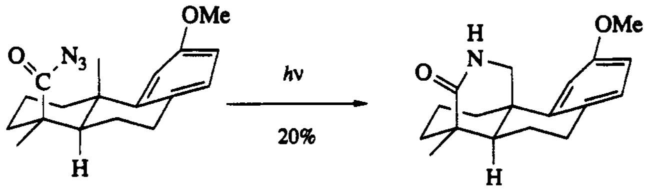

**(19)** **(20)** (8)

The azabicyclononane system is a common structural feature in diterpene alkaloids, and the nitrene insertion route to the ring system has been studied in detail in model decalins as well as in steroids (Scheme 11). Thus irradiation of the *trans*-acyl azide **(21)** gave, in addition to isocyanate (30–35%), a mixture of the γ- and δ-lactams **(22)** and **(23)**. The γ-lactam **(22)** predominated, although the overall yield was poor.[83,84] The corresponding *cis*-azide **(24)**, however, gave the δ-lactam **(25)** as the major product, again in low yield. One elegant application of this type of intramolecular nitrene insertion reaction was used as a key step (**26**) → (**27**) in Masamune's synthesis of the diterpene alkaloid garryine, although again the reaction was dogged by poor yields.[85]

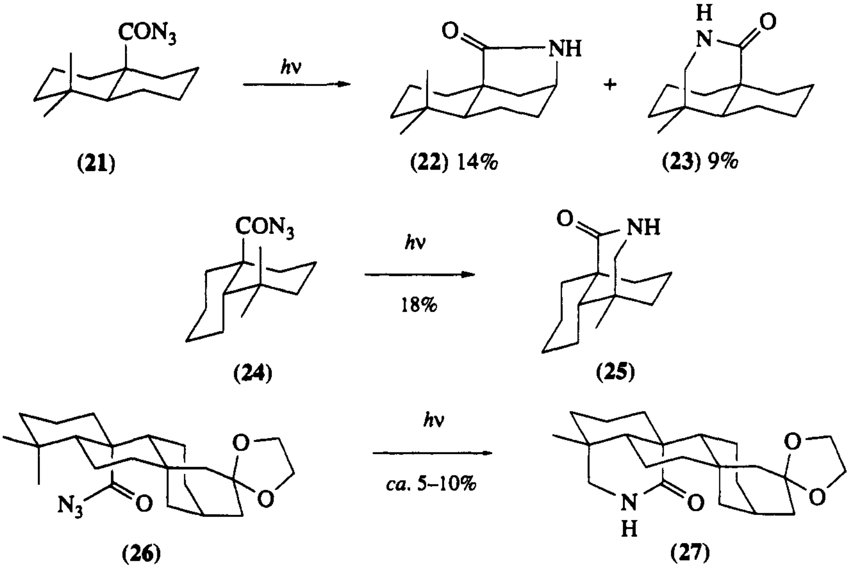

**Scheme 11**

Much of the remaining synthetic work in this area has been concerned with attempts to functionalize the 4,4-dimethyl groups in lanosterol, a process of considerable biosynthetic relevance and importance. For example, in a reaction that has also been studied in model *trans*-decalins,[86,87] thermal decomposition of 3β-lanost-8-enyl azidoformate (**28**) gives rise to a mixture of γ- and δ-lactams (**29**; 55%) and (**30**; 25%) resulting from nitrene insertion into the 2-$CH_2$ and the 4α-methyl group respectively.[88] Both insertions occur from the α-face of the steroid, and the overall yield of insertion products is excellent. The good yield of insertion products obtained from nitrenes derived from azidoformates is in contrast to the poor yields obtained from acylnitrenes derived from acyl azides. The nitrene derived from the related 7α-azidoformate derivative (**31**) of lanosterol undergoes selective C—H insertion at the 6α-C—H bond to give the modified steroid (**32**) in 52% yield.[89]

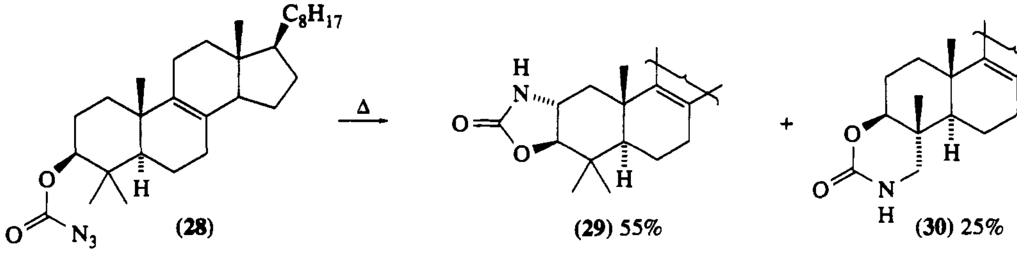

(**28**) (**29**) 55% (**30**) 25% (9)

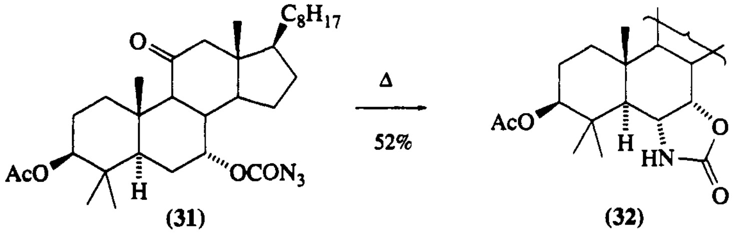

(**31**) (**32**) (10)

## 1.2.4 INTRAMOLECULAR INSERTION INTO $sp^2$ C—H BONDS

Intramolecular nitrene insertion reactions into $sp^2$ C—H bonds have found wide use in recent years in the synthesis of indole alkaloids and related natural products. In general, the reactions are of two types, and involve either vinylnitrenes or arylnitrenes inserting into an aromatic or vinylic $sp^2$ C—H bond to give an indole or a fused indole (Scheme 12). Although the indole is the product of a 'formal' C—H insertion reaction, the mechanism probably involves a six electron electrocyclic ring closure of the nitrene to give a 7a*H*-indole, followed by an aromatizing hydrogen shift.

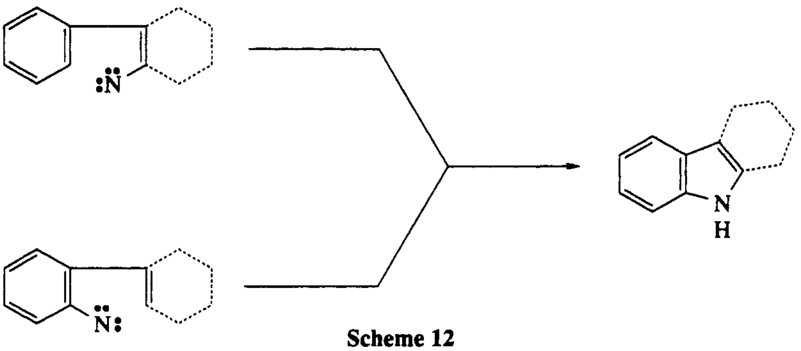

**Scheme 12**

Simple 3-substituted indoles can be formed in high yield by heating β-azidostyrenes in solution. Thus heating $Ph_2C{=}CHN_3$ in toluene gives 3-phenylindole in 82% yield.[90] The reaction has recently been extended to the preparation of 3,4-bridged indoles (Scheme 13),[91] and since the precursor azides are prepared from readily available cyclic ketones, the nitrene route represents a useful entry to these somewhat inaccessible bridged indoles.

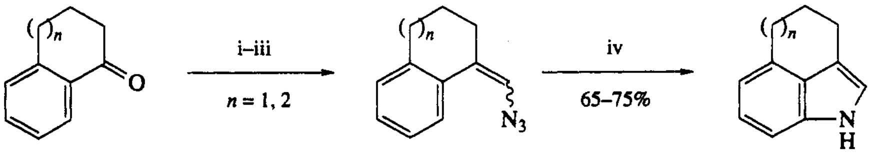

i, $Me_2\overset{+}{S}(O)CH_2^-$; ii, $NaN_3$; iii, MsCl, py; iv, Δ, mesitylene

**Scheme 13**

The formation of 2-substituted indoles from β-azidostyrenes can suffer from competing reactions of the azide and/or nitrene. However the discovery in 1970 that azidocinnamates (**33**; R = Me or Et) give indoles in excellent yield on heating in xylene,[92] together with further development in our own laboratories in collaboration with C. W. Rees (see below), has formed the basis of a versatile synthetic method. The azidocinnamates are readily prepared in a single step by base-mediated condensation of benzaldehydes with methyl (or ethyl) azidoacetate, and the reaction has been extended to heteroaromatic aldehydes to give the corresponding fused pyrroles.[93,94]

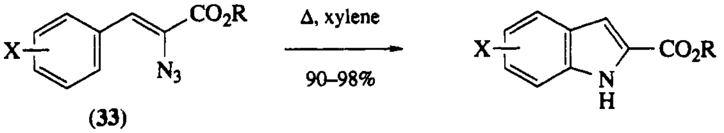

**(33)**

(11)

We have used the reaction extensively to prepare the indole moiety of several natural products. For example, the key step in the synthesis of the bacterial coenzyme methoxatin (**36**) is the formation of the indole (**35**) by intramolecular nitrene 'insertion' from the azide (**34**), readily prepared from commercially available 4-aminosalicyclic acid.[95] The third ring was annelated onto the indole (**35**) using conventional chemistry to give, after oxidation to the *ortho*-quinone, the natural product (**36**).

Similar nitrene-mediated cyclizations have been used in the synthesis of the indoles (**38**) and (**40**), key intermediates in the synthesis of the carbazole quinone alkaloid murrayaquinone B (**39**) and the unnatural cyclopropamitosene (**41**), an analog of the aziridinomitosene ring system, respectively.[96,97] In the first example, heating the azidocinnamate (**37**), prepared from 4-hydroxybenzaldehyde, in boiling toluene resulted in sequential indole formation and regioselective Claisen rearrangement to give the 7-isoprenylindole (**38**), the 2-ester group of which was elaborated to the third ring of the natural product.[96] The second example illustrates the value of the nitrene route to indoles, in that the polysubstituted indole (**40**), which

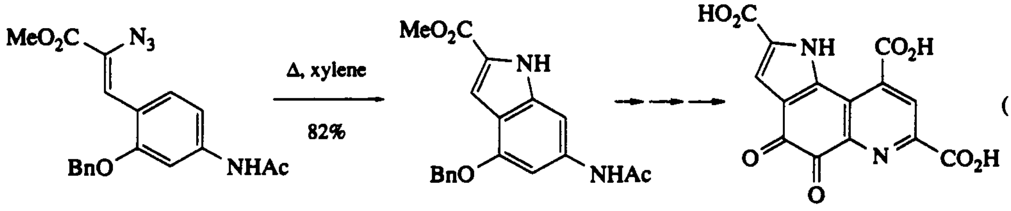

(34) (35) (36) (12)

contains all the functionality for the A-ring of the final product, is constructed from a relatively simple benzaldehyde in just two steps.[97]

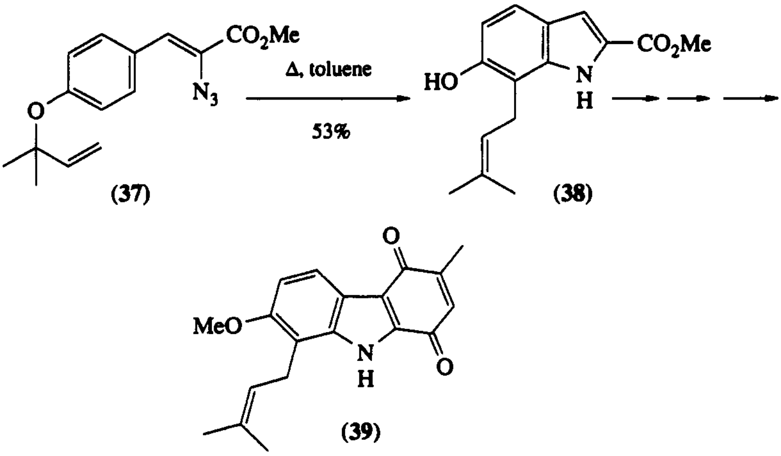

Δ, toluene
53%

(37) (38) (39) (13)

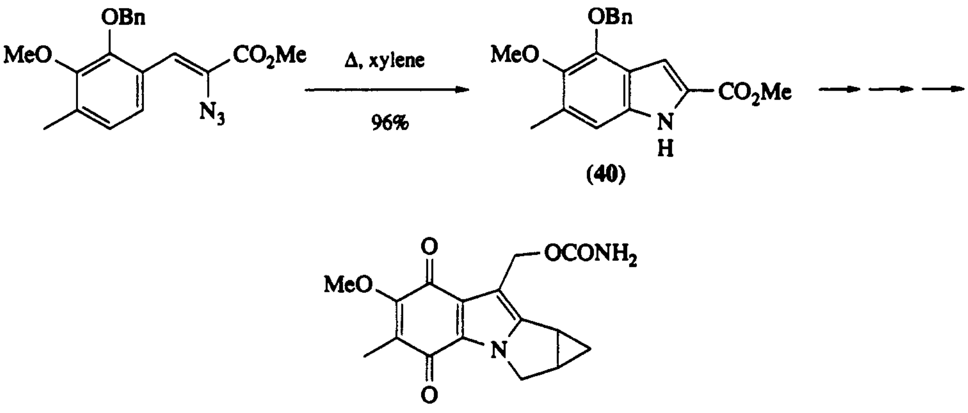

(40) (41) (14)

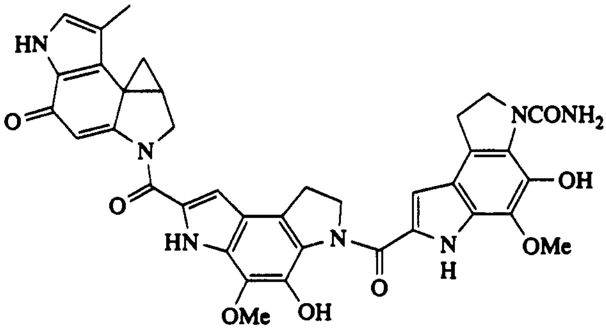

(42)

The most impressive example of the use of nitrene cyclizations in natural product synthesis is the Imperial College formal synthesis of the potent antitumor antibiotic CC-1065 (**42**).[98,99] In this synthesis, all six 'pyrrole' rings were formed using nitrene insertion. Thus *O*-benzylbromoisovanillin was converted into azidocinnamate (**43**), heating of which gave the indole (**44**) in essentially quantitative yield. After removal of the unwanted ester, the 4-bromoindole was converted into the aldehyde (**45**) and hence the azide (**46**). The second nitrene cyclization proceeded in 97% yield to give the key tricyclic indole (**47**), which was subsequently converted into the naturally occurring phosphodiesterase inhibitors PDE-I (**48**) and PDE-II (**49**), and by the coupling together of appropriate pyrroloindoles, into the 'dimer' (**50**), the combined central and right-hand unit of CC-1065. In a separate series of experiments, the left-hand unit of CC-1065 was also assembled using nitrene cyclization reactions. 5-Benzyloxy-2-bromoacetophenone was converted into the azide (**51**), heating of which in mesitylene, followed by reaction with benzenesulfonyl chloride, gave the indole (**52**; 53% over two steps). After introduction of the second azide (**53**), the tricyclic indole (**54**) was formed in 42% yield. Finally, following known chemistry, the indole (**54**) was converted into the cyclopropapyrroloindole (**55**). Since the left-hand unit (**55**) had previously been coupled with the 'dimer' (**50**) by workers at the Upjohn Company, this constituted a formal synthesis of CC-1065. A similar nitrene cyclization was also used by Boger in his total synthesis of CC-1065 to form the second pyrrole ring of the pyrroloindole subunits.[100]

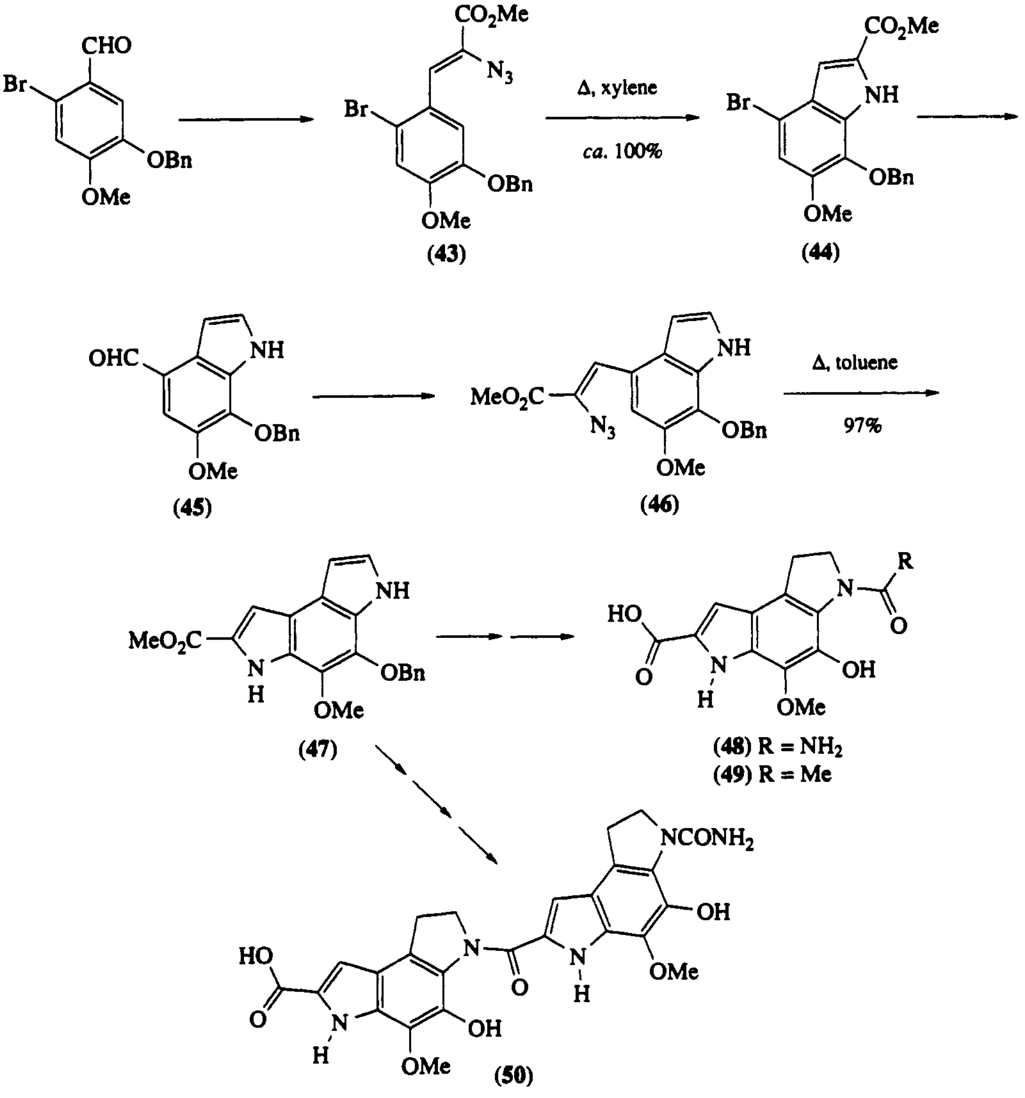
CHO
Br
OBn
OMe
CO2Me
N3
Br
OBn
OMe
(43)
Δ, xylene
ca. 100%
CO2Me
Br
NH
OBn
OMe
(44)
OHC
NH
OBn
OMe
(45)
MeO2C
N3
NH
OBn
OMe
(46)
Δ, toluene
97%
MeO2C
NH
N
H
OBn
OMe
(47)
HO
O
N
H
R
N
O
OH
OMe
(48) R = NH2
(49) R = Me
NCONH2
OH
OMe
N
H
HO
O
N
H
N
O
OH
OMe
(50)

**Scheme 14**

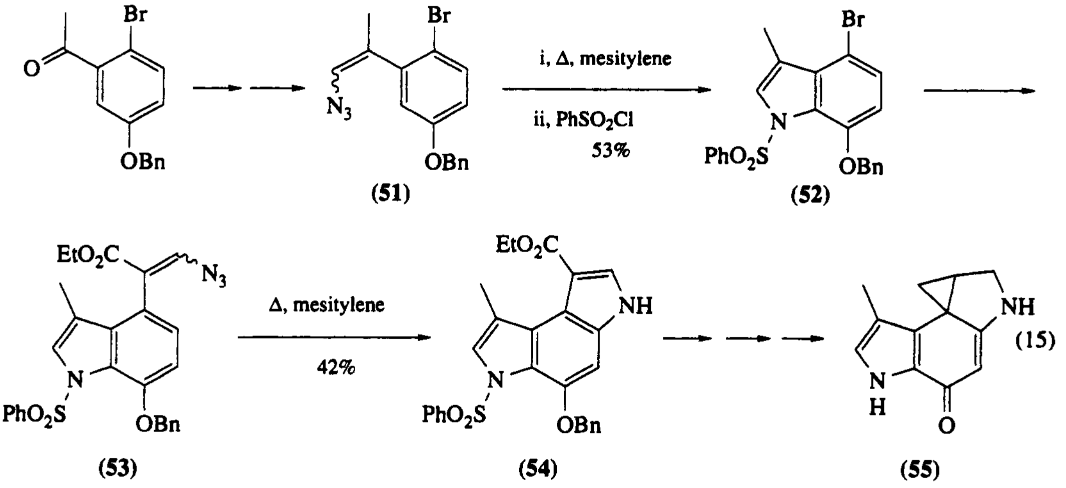

(51) (52)

(53) (54) (55) (15)

The intramolecular reaction of vinylnitrenes is not limited to formation of five-membered rings. For example, heating the azide (**56**) results in C—H insertion adjacent to the methoxy group to give (**57**), oxidation of which gave the tetracycle (**58**), a potential precursor to the marine alkaloid amphimedine.[101] Heating the azidocinnamate (**59**) results in formal intramolecular nitrene C—H insertion, followed by hydrogen shift, to give the benzazepine (**60**), a key intermediate in the synthesis of the alkaloid lennoxamine (**61**).[102]

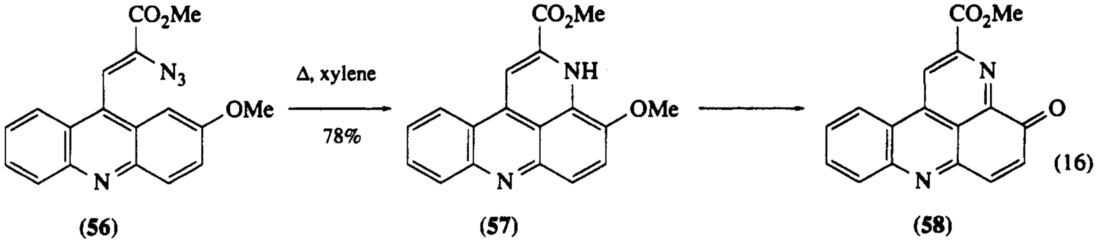

(56) (57) (58) (16)

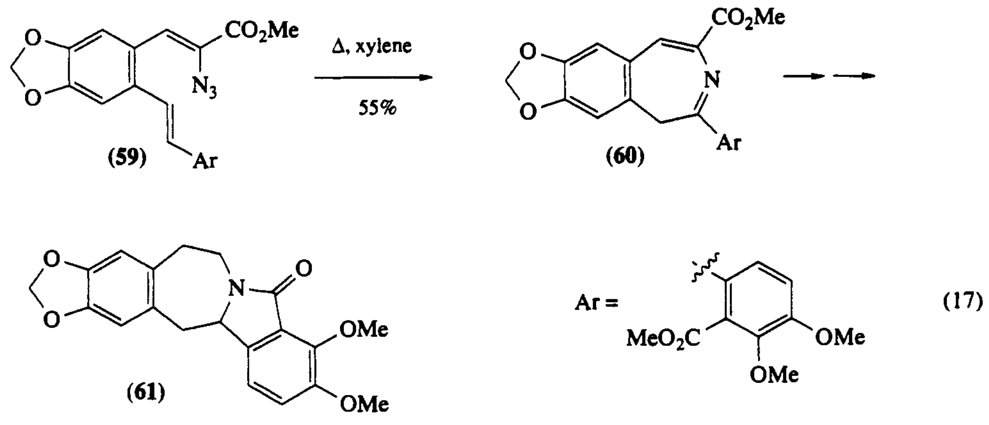

(59) (60) (61) (17)

Indoles can also be formed by arylnitrene cyclizations. Thus nitrenes derived by heating or irradiating 2′-azidostyrenes (**62**; $X = N_3$) or by deoxygenation of the corresponding nitro compounds (**62**; $X = NO_2$) cyclize to 2-substituted indoles in moderate to good yield (equation 18),[103,104] although a detailed study of the reaction has confirmed that the mechanism does not involve a genuine C—H insertion.[105] The corresponding reaction of the azidoquinone (**63**) has been used as a key step in the synthesis of the indolequinone (**64**), a precursor to the mitosene analog (**65**).[106]

The intramolecular cyclization of the arylnitrenes derived from azido- or nitro-biphenyls to the adjacent aromatic ring has been well reviewed.[5,7] The reaction is a useful route to carbazoles, two recent examples of which are shown in Scheme 15. In Raphael's elegant approach to the indolocarbazole fam-

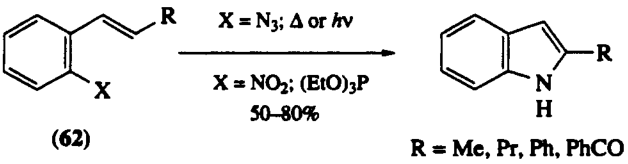
R
X
X = N3; Δ or hν
X = NO2; (EtO)3P
50–80%
R
N
H
R = Me, Pr, Ph, PhCO

(62)

(18)

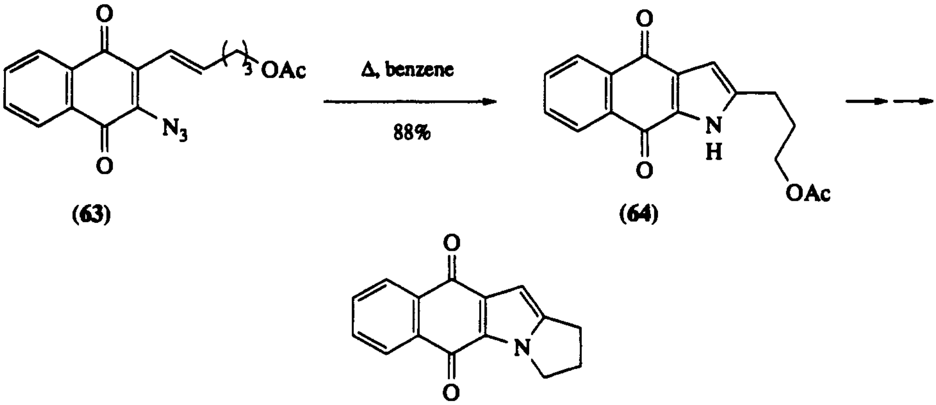
O
O
OAc
3
N3
Δ, benzene
88%
O
O
N
H
OAc
O
O
N

(63) (64) (65)

(19)

ily of antibiotics, the dinitro terphenyl (**66**), readily prepared by dehydrogenation of the Diels–Alder adduct of the appropriate 1,4-diarylbutadiene with maleimide, was deoxygenated with triphenylphosphine in collidine to give the 'double nitrene insertion' product, the indolocarbazole (**67**; 65%), demethylation of which gave arcyriaflavin B (**68**).[107] In the second example, the azide (**69**), constructed in 10 steps from 2,5-dimethylacetanilide, cyclized to the antitumor alkaloid ellipticine (**70**) in excellent yield on heating.[108]

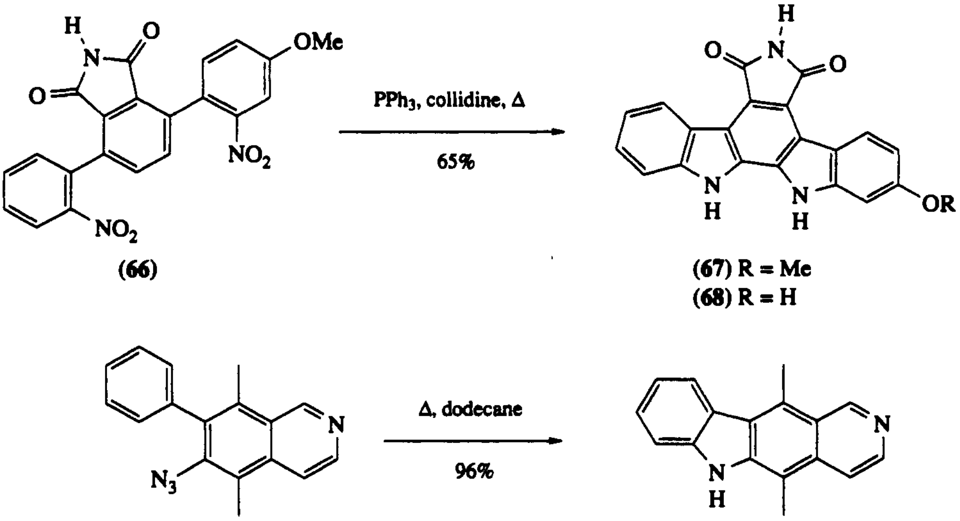
H
N
O
O
OMe
NO2
NO2
PPh3, collidine, Δ
65%
H
N
O
O
N
H
N
H
OR
N
N3
Δ, dodecane
96%
N
N
H

(66)

(67) R = Me
(68) R = H

(69) (70)

Scheme 15

Thus the intramolecular reaction of nitrenes with $sp^2$ C—H bonds, although it may not involve a genuine C—H insertion mechanism, is a useful synthetic method, which extends and complements the nitrene insertions into unactivated $sp^3$ C—H bonds discussed in earlier sections.

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# 1.3

# Oxidation by Remote Functionalization Methods

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## 1.3.1 INTRODUCTION

### 1.3.1.1 Topics Covered

'Oxidation' is not a well-defined concept in organic chemistry. It hardly ever involves simply the removal of electrons, and when covalent bonds are being made and broken some arbitrary choices must be made. When a C—H bond is converted to a C—OH bond, we say that the C—H bond has been oxidized. Similarly, the conversion of ethane to ethylene is generally considered to be an oxidation, and hydrogenation of an alkene is generally considered a reduction. However, if these conversions are indirect we must specify in which step the oxidation or reduction occurred.

As a simple case, the chlorination of a C—H bond, converting it to C—Cl, is certainly an oxidation. The chloride can be solvolyzed to an alcohol, which is an oxidation product of the original C—H bond, and no one would think of the solvolysis as the oxidation step. Thus we will consider as an oxidation any conversion of a C—H bond to a derivative in which the hydrogen has been replaced by a more electronegative element. Furthermore, conversion of a saturated carbon to an unsaturated one will be considered an oxidation of that carbon. In principle the double bond could be hydrated so as to leave the hydroxy group on that carbon, and addition of water to an alkene is not an oxidation step.

The insertion of a carbonyl group into a C—H bond is also an 'oxidation' by this reasoning. The resulting C—C—OH unit can in principle be dehydrated towards the original carbon, converting it to an unsaturated carbon, and dehydration of an alcohol is not an oxidation step. If the insertion was at a tertiary carbon such a simple dehydration would of course be impossible, but it is hard to imagine that carbonyl insertion into the C—H bond of a secondary carbon be considered an oxidation, but insertion at a tertiary carbon not be. Thus this chapter will discuss reactions that functionalize a C—H bond such that it is either directly oxidized or can be converted, by further nonoxidative steps, into an oxidized carbon.

The focus will largely be on cases in which the functionalization or oxidation is performed with geometric control, and in which that control permits selective attack at various predetermined positions remote from any functional groups of the substrate. Those methods in which oxidations, using geometric direction, occur in the near neighborhood of substrate functional groups will also be discussed briefly. Such methods were an important source of inspiration for the more remote functionalization procedures, and they perform many useful transformations.

Controlled functionalization of unactivated positions can also be achieved by putting the substrate into an inhomogeneous environment and then attacking it with an otherwise random reagent.[1] Good examples include hydroxylation with ozone on silica,[2-5] halogenation of substrates bound in zeolite cavities,[6] and reactions in solid inclusion complexes.[7] Some chemically selective reagents can also perform useful conversions of steroids, for instance, to more or less single products.[8-11] Methods that do not involve rationalizable geometric control will not be included in this review.

### 1.3.1.2 Biomimetic Chemistry

An important inspiration for this field also comes from a consideration of the selective oxidations commonly performed by enzymes. It is commonplace for an oxidative enzyme to convert an isolated methyl group to a carboxy group while leaving double bonds and carbinols alone;[12] this is done by geometric control within the enzyme–substrate complex. The outstanding regioselectivity and stereoselectivity of enzymatic processes led to the coining of the term 'biomimetic' to describe selective chemical functionalizations of unactivated positions similarly directed by geometric constraints.[13] In this chemistry the intrinsic reactivity of the substrate is overridden by the geometric preference of the reagent–substrate combination. The term 'biomimetic' has now been enlarged in scope, to refer to chemistry that mimics biochemical processes or pathways in any aspect.

## 1.3.2 INTRAMOLECULAR FUNCTIONALIZATIONS IN THE VICINITY OF EXISTING SUBSTRATE FUNCTIONAL GROUPS

Free radicals can undergo 1,5-hydrogen shifts. When the initial radical site is a heteroatom, the 1,5-shift leads to functionalization of the carbon four bonds away. There are many examples of such processes.

An early version was the Hofmann–Loffler–Freytag reaction (Scheme 1).[14] Irradiation of a chloramine in acid leads to formation of the aminium radical, which can abstract a hydrogen to generate a carbon radical. Then the resulting carbon radical abstracts chlorine from another protonated chloramine, producing a chlorinated carbon and regenerating the chain-carrying radical. On treatment with base, the product

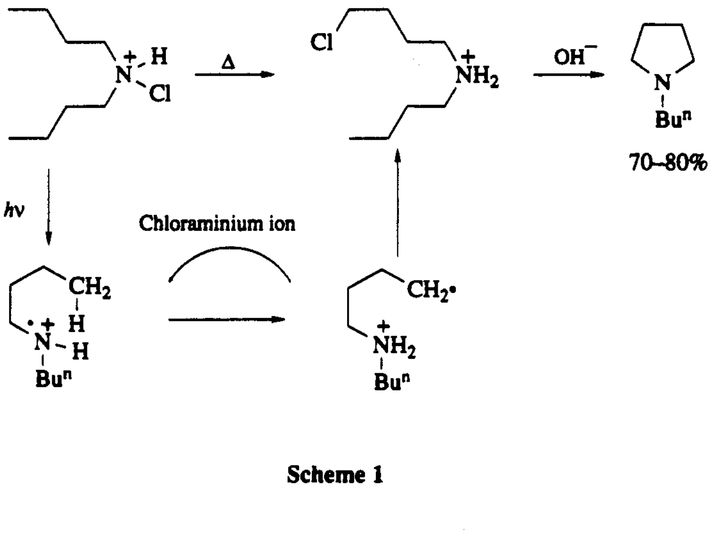

Scheme 1

δ-chloroamine can cyclize to form a pyrrolidine. More recently phosphoramidate radicals have been used to perform similar hydrogen abstractions.[15]

A related reaction occurs on irradiation of a hypochlorite (Scheme 2).[16] The alkoxyl radical can again abstract a hydrogen atom in a 1,5-shift, and the final chloro alcohol can be cyclized to form a tetrahydrofuran. Some processes lead directly to the cyclic product. For instance, an alcohol with an accessible δ-hydrogen can be directly converted to a tetrahydrofuran on refluxing with lead tetraacetate.[17] In a related reaction, treatment of an alcohol with silver carbonate and bromine can lead to the cyclic ether by initial formation of a hypohalite.[18] The cyclization occurs when the rearranged radical is converted to a cation, either by oxidation with $Pb(OAc)_4$ or by silver-assisted loss of halide ion. Hypoiodites are also frequently used, generated *in situ*.[19]

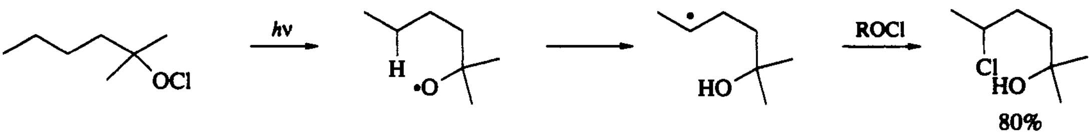

Scheme 2

A particularly nice conversion is the reaction of a cyanohydrin with $I_2$ and $Pb(OAc)_4$ (the Heusler–Kalvoda reaction; Scheme 3).[20] After the abstraction of a δ-hydrogen the cyano group migrates to the resulting radical. The final product has a ketone in place of the original cyanohydrin, which was of course formed from that ketone, and a cyano group on the carbon γ to the ketone.

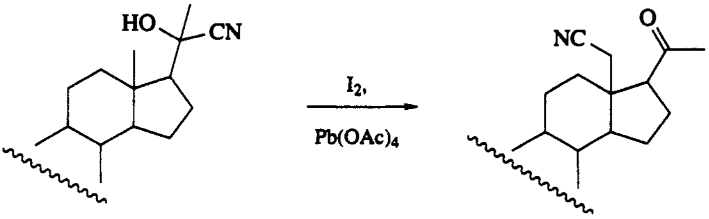

Scheme 3

A functionalization that converts C—H bonds to C—NO bonds occurs when nitrite esters are photolyzed (the Barton reaction; Scheme 4).[21] Again an alkoxyl radical abstracts a δ-hydrogen, and the resulting carbon radical picks up NO. The product nitroso compounds convert easily to oximes. Particularly valuable examples have been studied in the steroid field.[22] If the photolysis is performed in the presence of copper(II) acetate the intermediate carbon radical can be oxidized to an alkene, rather than capture NO.[23] If the alcohol whose nitrite ester is photolyzed is part of a cyanohydrin, then the Heusler–Kalvoda reaction occurs, and the product is a ketone with a migrated cyano group (Scheme 5).[24]

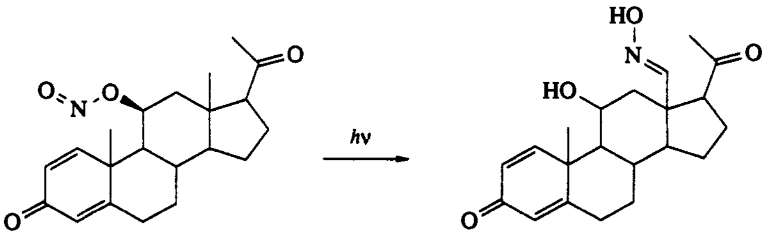

Scheme 4

Photolysis of ketones can also lead to 1,5-hydrogen shifts, resulting in functionalization of the γ-carbon. The resulting 1,4-diradical can then fragment or cyclize to form a cyclobutanol (Scheme 6).[25] Examples are also known in which hydrogen abstraction involves a seven-membered[26] or a five-membered ring transition state.[27] This photochemical Type II process has been shown to involve the intermediacy of an excited triplet state, with an electron promoted from an unshared pair into the π-system. Hydrogen abstraction occurs by attack of the half-vacant nonbonding orbital on the electrons of the nearby C—H

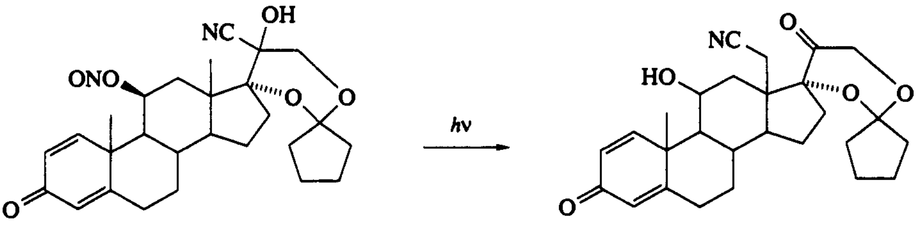

Scheme 5

bond. Thus the geometric requirement is accessibility of the hydrogen to the plane of the carbonyl group, not the π-system.

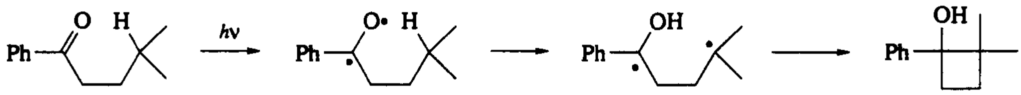

Scheme 6

Related photochemistry has also been examined with other functional groups such as phthalimides, which also abstract nearby hydrogens with the photoexcited carbonyl group.[28,29] Furthermore, since the hydrogen abstraction is performed by the half-vacant nonbonding orbital of a photoexcited ketone carbonyl, related chemistry is observed if the electron is removed electrochemically, not just photoexcited into a π*-orbital. Electrochemical functionalization of nearby carbons has been reported in which, after hydrogen atom abstraction by an oxidized ketone, the resulting radical is electrochemically oxidized further to the carbon cation, which reacts with solvent (Scheme 7).[30,31]

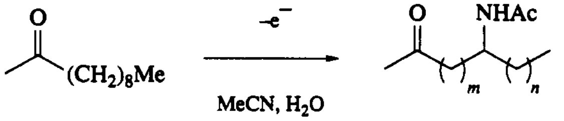

| m | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| % | 45 | 25 | 15 | 10 | 5 |

Scheme 7

In all these examples functionalization of unactivated carbons occurred, but at positions only a few carbons removed from a substrate functional group. The rest of this chapter shall consider cases in which this restriction is removed.

## 1.3.3 OXIDATIONS REMOTE FROM EXISTING SUBSTRATE FUNCTIONAL GROUPS

### 1.3.3.1 Remote Photochemical Functionalization

In 1969 the general principle of this field was enunciated in a paper[32] reporting the photochemical insertion of a benzophenone carbonyl group into the $CH_2$ groups of long alkyl chains (Scheme 8). It was pointed out that, as in biochemical reactions, the intrinsic reactivity of a substrate can be overridden by the geometric preferences imposed by a suitably oriented reagent. Specifically, the dodecyl ester of benzophenone-4-carboxylic acid (**1**) underwent photoinsertion into carbons 10 and 11 on irradiation; only minimal insertion occurred at carbon 9, and essentially none in carbons 1 to 8. The results were as expected for the geometry of (**1**) but the distribution of attack sites means that this is not a useful preparative method for a single product. Work with related compounds also gave a distribution of products, reflecting the flexibility of an alkyl chain.[33]

Good selectivity was seen with a flexible substrate immobilized by double ion-pair binding to a benzophenone dication (Scheme 9).[34] The insertion product could be dehydrated, and the resulting alkene fur-

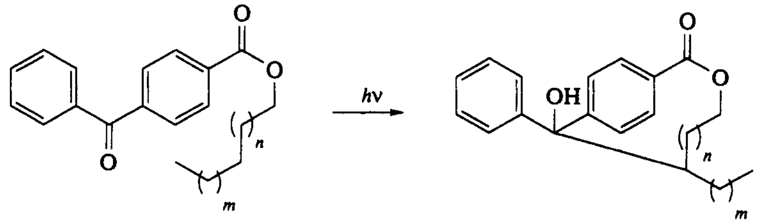

(1) $m + n = 9$  $m = 0$, 58%; $m = 1$, 30%; all others, 12%

**Scheme 8**

ther oxidized to furnish a keto diacid product with excellent selectivity. The high selectivity is restricted to substrates that are of the correct length to stretch out along the benzophenone reagent.

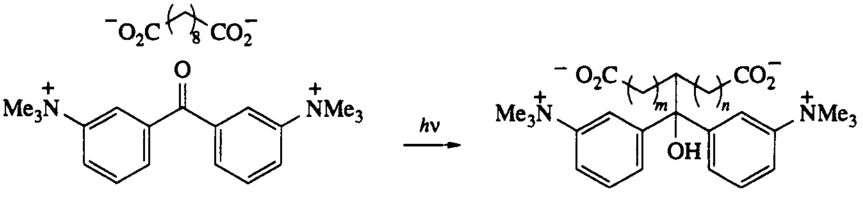

93% at C-5

**Scheme 9**

Photochemical functionalizations with synthetic potential have been achieved using benzophenone esters of steroids (Scheme 10). In some cases attack occurs on several hydrogens; for instance, a mixture of $\Delta^{14}$- and $\Delta^{16}$-alkenes is produced on irradiation of (**2**).[35] However, with compound (**3**) photolysis produces only (**4**) as a new steroid.[36] The yield of 55% involves some photoreduction of the benzophenone unit by solvent, so the other significant product is starting material with a reduced ketone group. Many other photolyses of benzophenone steroid esters have been studied;[37–39] they lead to useful information about conformations, but not the directed single-site functionalizations that would make them synthetically useful.

Irradiation of nitro aromatics produces excited states in which the nitro group oxygen can remove an accessible hydrogen. The resulting diradical can then undergo hydroxyl transfer to the substrate carbon. This process has been used to hydroxylate dammarane terpenes related to steroids, by preparing appropriate nitrophenyl esters of the substrates and then photolyzing (Scheme 11).[40,41] In the steroid series a related reaction led to remote dehydrogenation, not hydroxylation.[42] Oxygenation of C—H bonds can also be achieved by photolysis of nitroxides (Scheme 12),[43,44] but so far only at nearby carbons, not remote ones.[44]

### 1.3.3.2 Template-directed Epoxidation

Although epoxidation reactions are treated in detail elsewhere in these volumes, it should be mentioned here that a template ester attached to a steroid alkene can direct epoxidation to remote double bonds using the general concepts of remote functionalization.[45] Steroidal diene (**5**) underwent the epoxidation shown (Scheme 13) with excellent regiochemical and stereochemical control.[46] The product was formed in quantitative yield, although the reaction was carried through to only 25% conversion.

### 1.3.3.3 Directed Chlorinations

The major work to date on synthetic applications of remote functionalization has involved free radical chlorination. The earliest studies[8,47] involved the direct attachment of aryliodine dichloride units to the steroid substrates, then intramolecular free radical chain chlorination in benzene or chlorobenzene solution (Scheme 14). Yields were only in the 50% region, but fairly good selectivities were observed; compound (**6**) afforded chiefly the 9-chloro derivative, while compound (**7**) produced the 14-chloro steroid. The yields and selectivities were considerably improved when it was realized that aromatic solvents promote intermolecular random processes by forming complexes with Cl·, and when the radical relay method was developed.

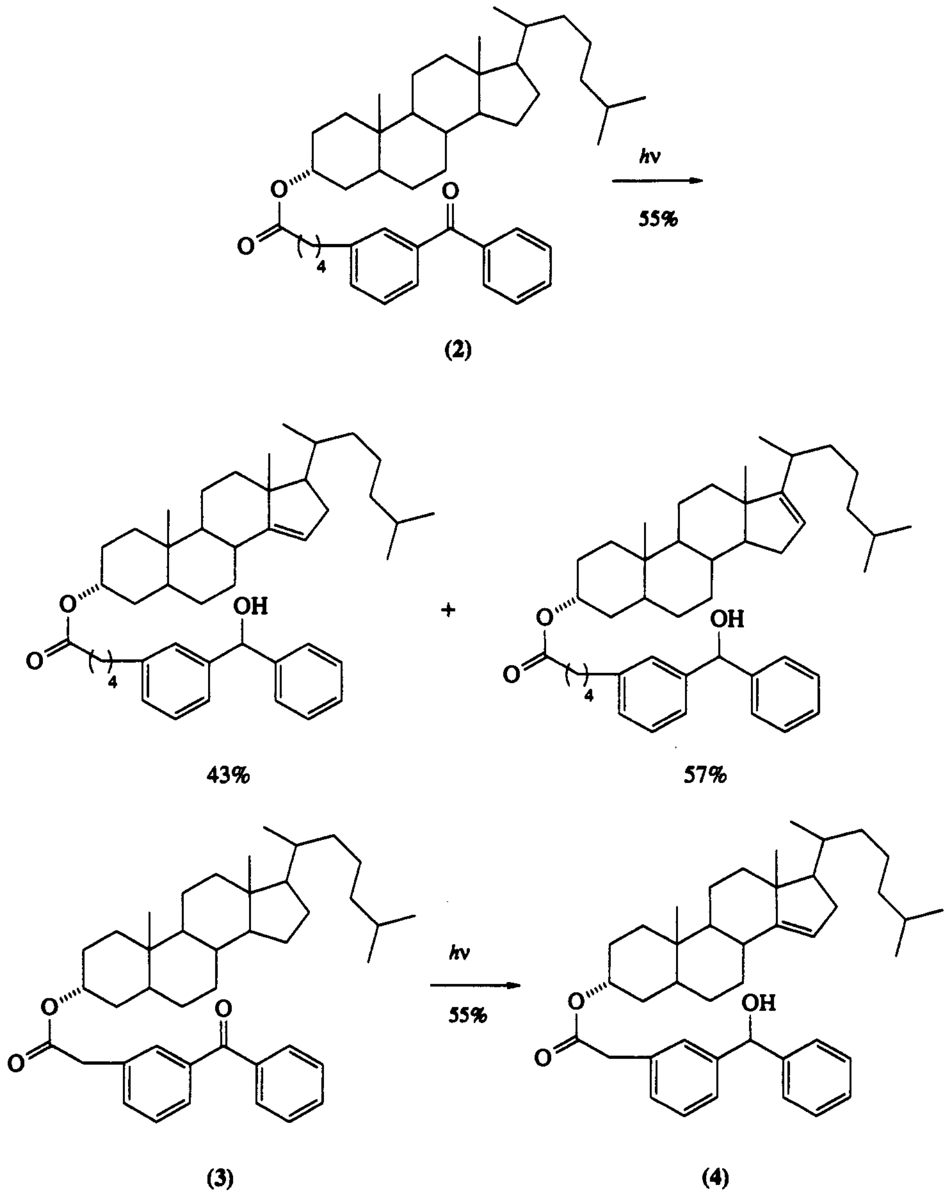
hν
55%
O
O
O
4
OH
+
OH
4
43%
57%
hν
55%
O
O
O
OH

(2)

(3)

(4)

only functionalized steroid

Scheme 10

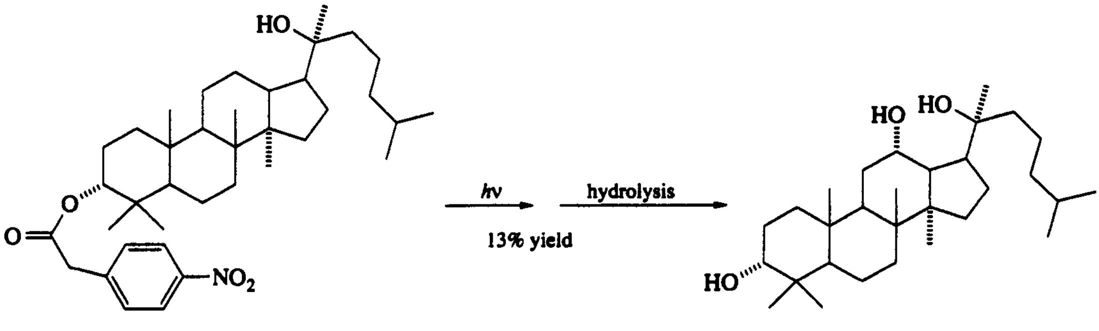
HO
O
O
$NO_2$
hν
hydrolysis
13% yield
HO
HO
HO

Scheme 11

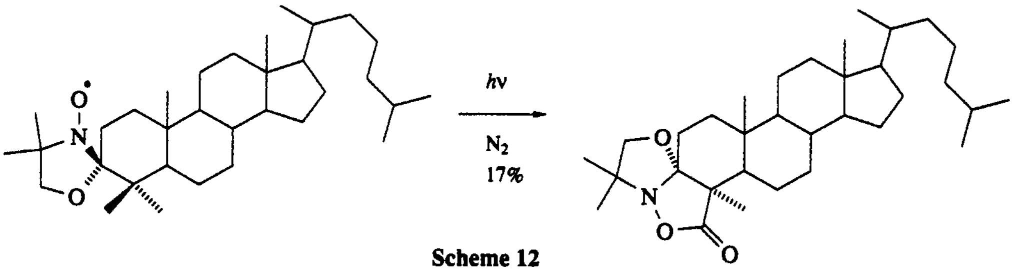

Scheme 12

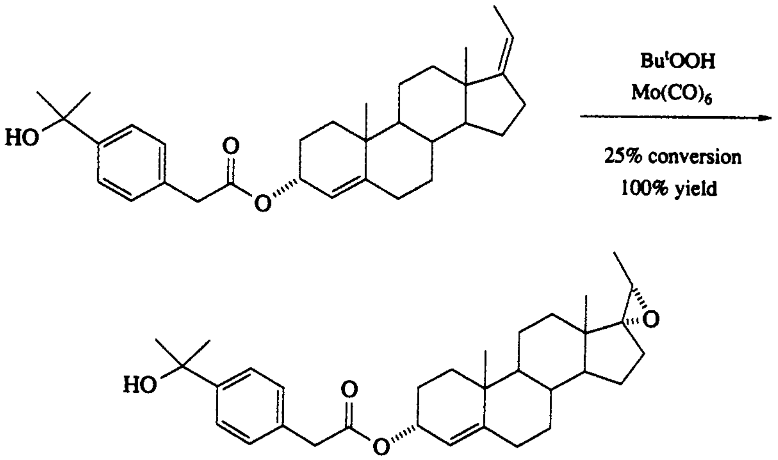

HO
Bu$^t$OOH
Mo(CO)$_6$
25% conversion
100% yield

Scheme 13

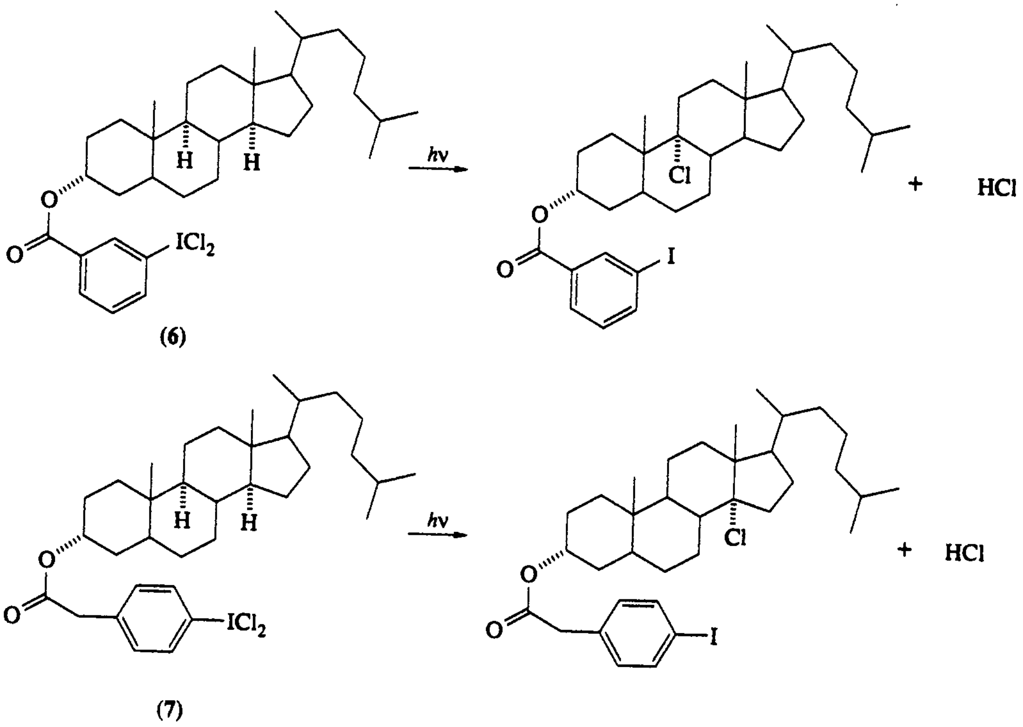

H
H
hν
Cl
+ HCl
ICl$_2$
I
(6)
hν
Cl
+ HCl
(7)

Scheme 14

In radical relay chlorination (Scheme 15), a substrate carries a template that can weakly bond to a chlorine atom and hold it near an appropriate substrate hydrogen.[48] A chlorine atom donor in solution, such as $PhCl\cdot$ or $SO_2Cl\cdot$ or $Cl\cdot$ itself, puts the chlorine atom on the bonding atom of the template. After the hydrogen atom is removed, under geometric control, the resulting substrate radical picks up a chlorine from the reagent ($PhICl_2$, $SO_2Cl_2$, or $Cl_2$) to produce a chlorinated substrate and regenerate the chlorine donor species. Under some conditions the resulting free radical chain process can have a chain length of 20 or so. With substrate concentrations of the order of $10^{-3}$ to $10^{-2}$ M there is normally little competition from intermolecular nondirected processes.

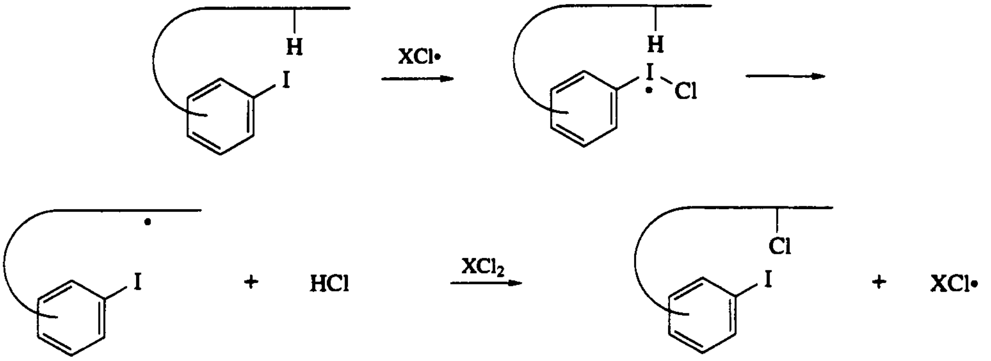

**Scheme 15** Radical relay chlorination

Iodoaryl esters of steroids can serve as templates for radical relay chlorination. For instance (Scheme 16), refluxing $10^{-2}$ M (**8**) in $CCl_4$ with 1.2 equiv. $SO_2Cl_2$ and 10 mol % benzoyl peroxide for 5 h, then basic hydrolysis and dehydrochlorination, afforded the $\Delta^{9(11)}$-alkene product (**9**) in 75% yield along with 15% of recovered cholestanol and only 10% of other products.[49,50] These are polar materials derived from further chlorination of alkenes formed *in situ*, and easily separated from the desired product. No isomeric alkenes were detected. As another example, the single template in compound (**10**) catalyzes and

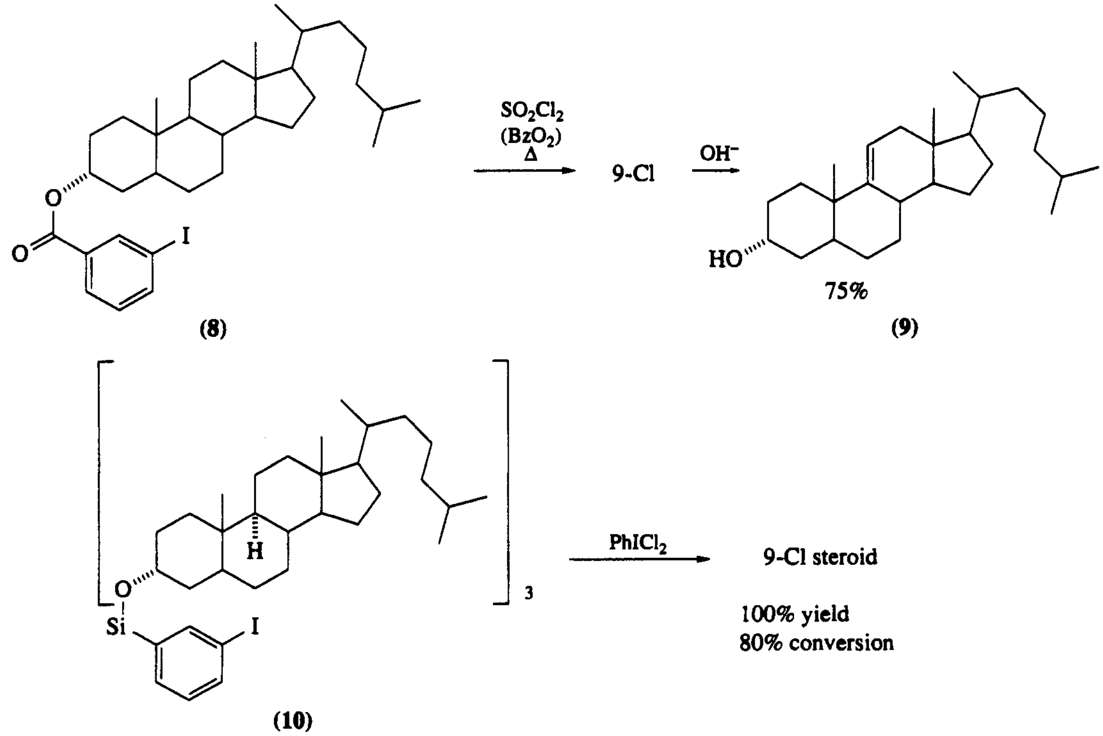

**Scheme 16**

directs the chlorination of three steroid substrates at C-9 under similar conditions, in quantitative yield and *ca.* 80% conversion.[51] This is possible since the template is regenerated after each functionalization, and the selectivity is so good that once a steroid is chlorinated it does not get attacked in another position.

Longer templates promote chlorination over greater distances. In compound (**11**; Scheme 17) the biphenyl template promotes chlorination of C-17 with good selectivity.[50,52] Dehydrochlorination forms the $\Delta^{16}$-alkene (**12**) in reasonable (66%) yield; this has been used in an indirect scheme to remove the side chain of cholesterol and of sitosterol to afford the 17-keto steroid. Under other conditions the 17-chloro steroids can be dehydrochlorinated toward C-20, and the resulting $\Delta^{17(20)}$-alkenes directly oxidized to afford the 17-keto steroid.[53,54]

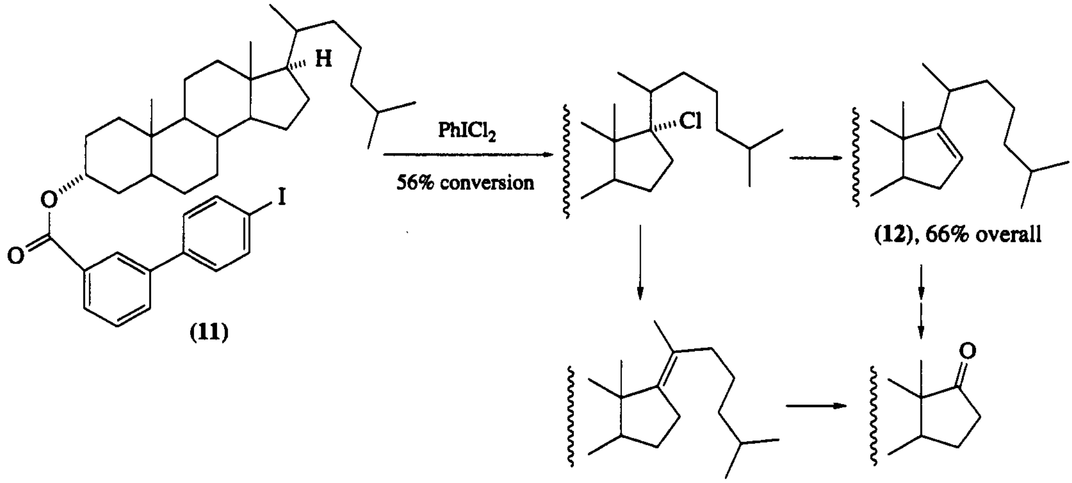

(**11**)

(**12**), 66% overall

**Scheme 17**

The selectivity of the radical relay chlorination is striking. In the case of the enone (**13**; Scheme 18), and in related compounds with A-ring dienones, the *m*-iodobenzoate template at C-17 directs chlorination to C-9 and not to the preexisting functional groups of (**13**).[50] The selective chlorination of C-9 seems to be quantitative, although in the first report[50] the $\Delta^{9(11)}$-alkene (**14**) was isolated in only 77% yield. Later work has shown that the overall introduction of this double bond can have yields in the 90–95% range, and good yields for this reaction have also been reported from another laboratory.[55] Template-directed radical relay chlorination on the α-face of steroids has also been successful in the A/B *cis*-coprostanol steroid series,[56] and in the cholestanol series with iodophenyl templates linked by amide, ether, or sulfonate functions rather than carboxylic esters.[57]

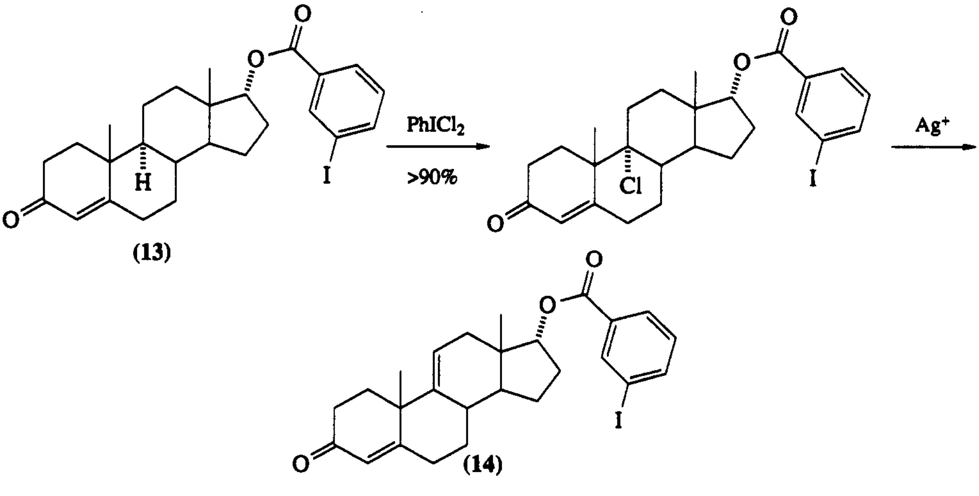

(**13**)

(**14**)

**Scheme 18**

Limited studies have been done on template-directed chlorination on the β-face of steroids. Compound (**15**; Scheme 19) was designed so that the template could curve around the angular C-18 methyl group and direct chlorination to C-20.[58] Reaction with an excess of $PhICl_2$ led to *ca.* 40% chlorination of C-20 with 25% unfunctionalized steroid. The 20-chloro steroid was converted in part to the $\Delta^{20(22)}$-alkene, which was ozonized to form the 17-acetyl steroid (**16**). A similar result was observed with the i-steroid derivative (**17**).[58] The selectivities and yields are not yet up to those of other examples of the radical relay reaction.

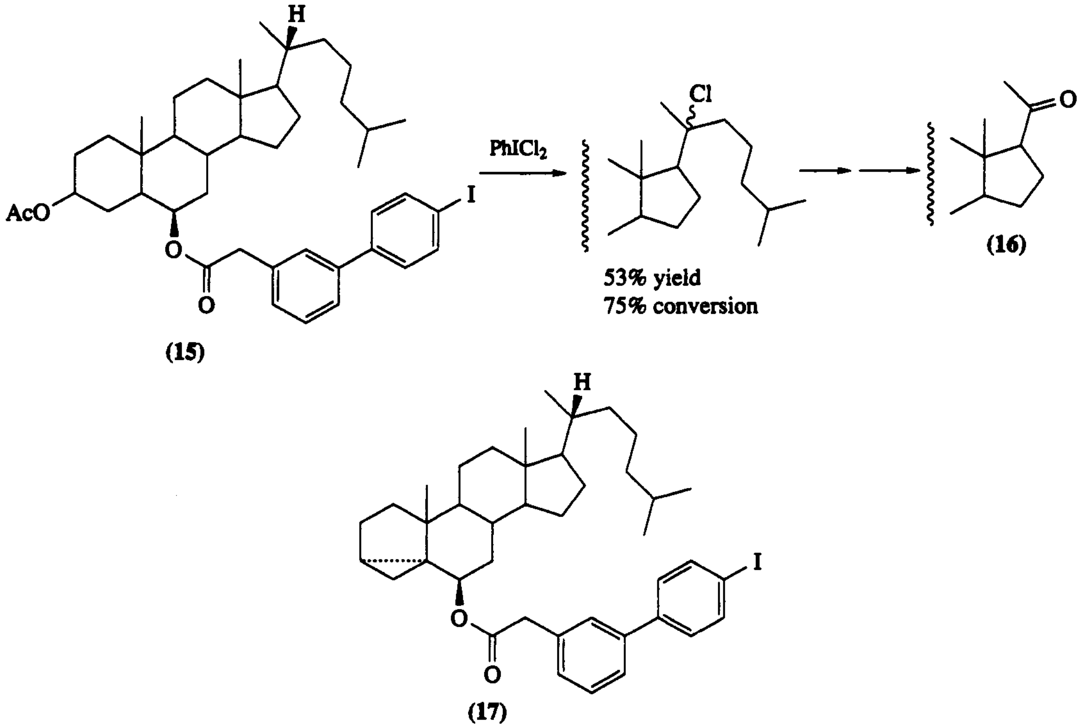

(**15**)

(**16**)

(**17**)

**Scheme 19**

Diaryl sulfide templates have also been used to direct chlorinations.[59] The selectivities indicate that the chlorine atom is bound to the sulfur, but the yields are not as good as those with aryl iodide templates. The problem is that the sulfur gets oxidized under the reaction conditions. As expected, a thiophene ring is more stable to oxidation and its sulfur atom can still bind chlorine in a radical relay process.[60] The best sulfur template so far examined is the thioxanthone system (Scheme 20).[61] Thus with 3 equiv. $PhICl_2$ compound (**18**) undergoes directed C-9 chlorination in 100% conversion, affording a 71% yield of the $\Delta^{9(11)}$-alkene after base treatment, along with some polar products from excessive chlorination. The thioxanthone template can be recovered unchanged.

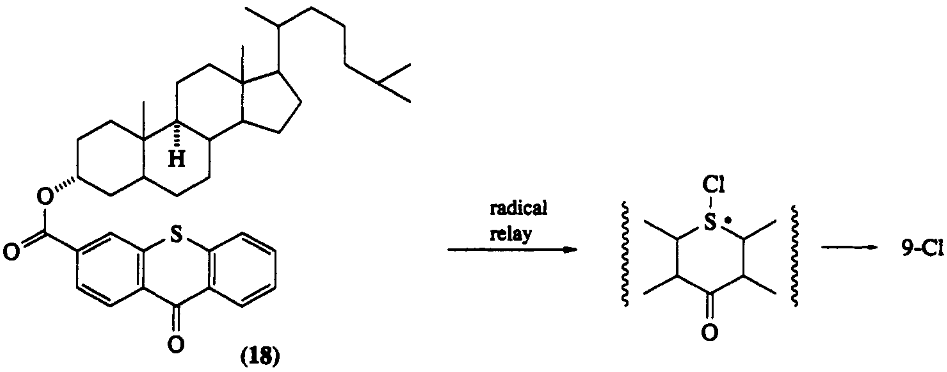

(**18**)

**Scheme 20**

Binding of Cl· to an aryl iodide may well involve $sp^3d$ hybridization at iodine to accommodate the ninth electron, but the involvement of a *d*-orbital in bonding at sulfur is more controversial. Recently it was discovered that even first row elements can form Cl· complexes; the evidence indicates that these complexes utilize three-electron bonds, not *d*-orbitals.[62] Best explored are templates for radical relay chlorination using nitrogen atoms.

As a striking example, photo-initiated chlorination (Scheme 21) of 3 mM (**19**) with 1.5 equiv. $PhICl_2$ led to the 9-chloro derivative (**20**) in >98% yield; with $Ag^+$ this was converted to the $\Delta^{9(11)}$-alkene.[63] Again the template-directed reaction overcomes the normal reactivity of the substrate, but at 21 mM (**19**) undirected reactions start to compete and some 6-chloro steroid is also formed. A pyridine *N*-oxide template, that can use three-electron bonding to complex a chlorine to the oxygen atom, seems to be almost as effective.[64] Furthermore, an imidazole template in compound (**21**) directs chlorination at C-9 with similar efficiency to the templates previously examined,[65] and (**21**) is particularly easily prepared using carbonyldiimidazole.

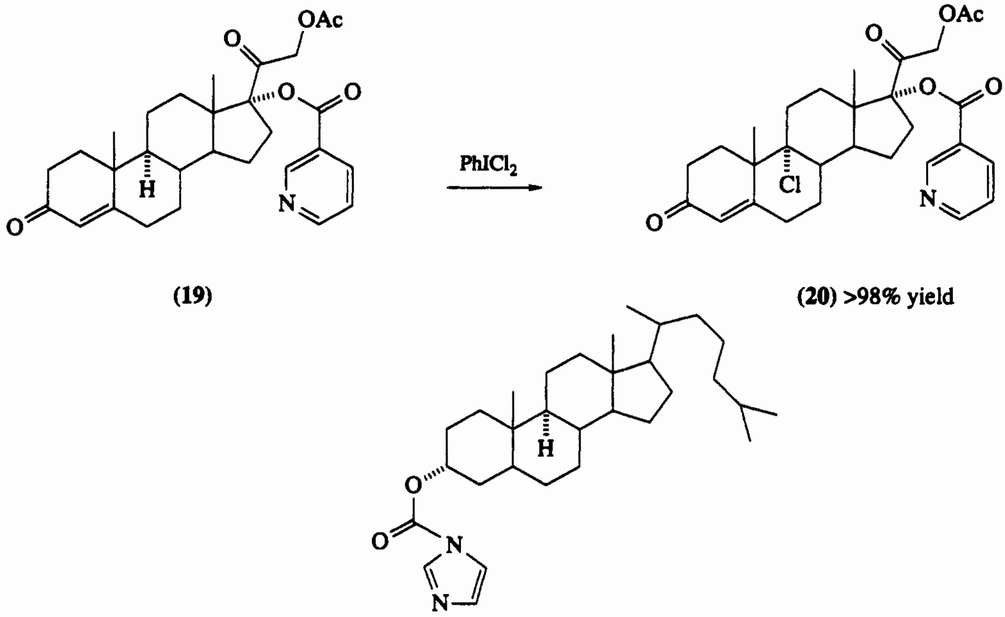

(**19**)

(**20**) >98% yield

(**21**)

Scheme 21

## 1.3.4 SELECTIVE REACTIONS IN MOLECULAR COMPLEXES

There is no good reason that a catalytic template, which directs remote functionalization reactions, need be covalently attached to the substrate. Indeed, it would be preferable to use catalytic amounts of such a template that could bind temporarily to a substrate, perform its reaction, and then move on.

A good example of such a process is the template-directed chlorination of an aromatic ring by β-cyclodextrin (Scheme 22).[66–68] Hydrophobic forces hold the complex together temporarily, and within the complex the chlorination is catalyzed and directed by a hydroxy group of the cyclodextrin. An electro-

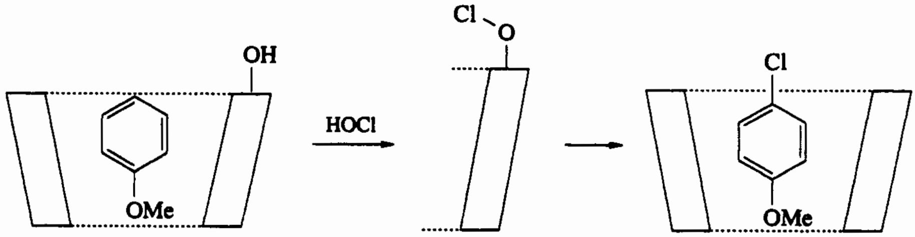

Scheme 22

chemical version of this has been devised, in which the cyclodextrin is chemically linked to an electrode and the chlorinating species is generated by anodic oxidation of chloride ion.[69] Other related reactions have also been observed in which cyclodextrin binding is used to direct functionalization chemistry.[70]

The shape-selective metalloporphyrin-catalyzed oxidations of hydrocarbons studied by Suslick are also relevant,[71,72] although the binding forces and geometry are less obvious. Groves' recent hydroxylation of steroids in a bilayer containing a metalloporphyrin (Scheme 23) is also clearly in the spirit of biomimetic chemistry.[73] In this case hydrophobic binding produces a complex with predictable geometry.

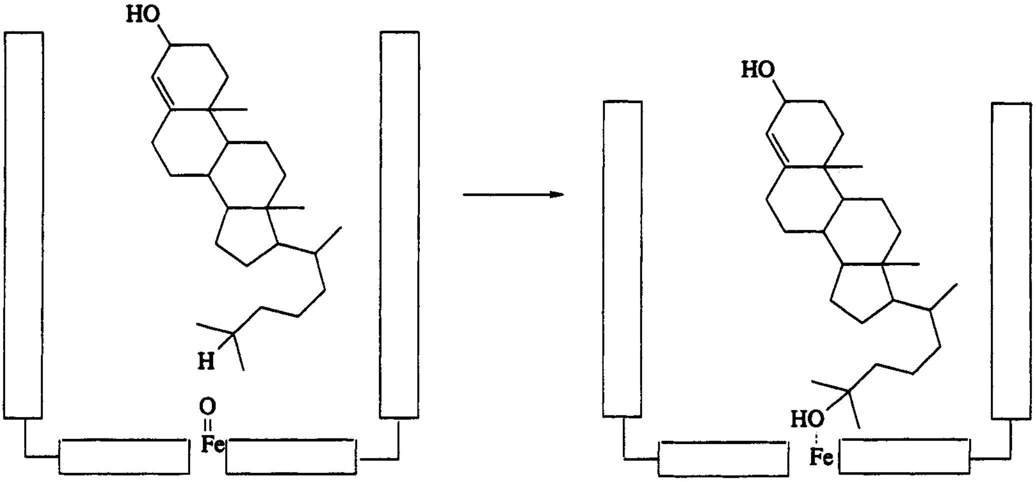

Scheme 23

Template-catalyzed remote chlorination reactions have also been examined in molecular complexes. In one early study (Scheme 24), ion pairing was used to hold a charged template near a charged substrate.[74] Selective catalyzed radical relay chlorination was observed, but the selectivity was not as good as has been seen when the template is covalently attached to the substrate. In more recent work better selectivity and some catalytic turnover has been observed.

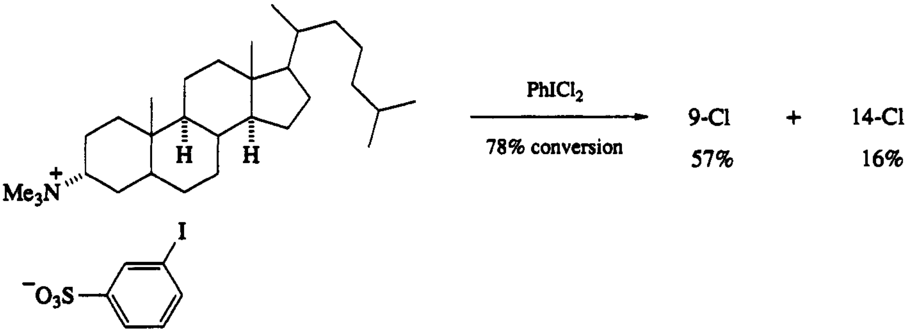

Scheme 24

Catalytic turnover has also been seen in radical relay chlorinations in which the template is temporarily linked to the substrate in a mixed metal complex. The steroid phosphate (**22**) and catalytic ligand (**23**) both bind to zinc in a mixed complex, and the iodine atom of (**23**) directs chlorination of (**22**) at C-9 with reasonable selectivity (Scheme 25). Five or more turnovers are seen, when only 10% of the catalyst (**23**) is used.[75]

## 1.3.5 FUTURE PROSPECTS FOR REMOTE OXIDATIONS

Most of the examples so far have utilized a single covalent bond, or an ionic or ligand bond, to hold the substrate to a catalytic template that can direct chlorination of a remote position. To achieve highly selective reactions several interactions are needed to impose strong geometric constraints, as in the

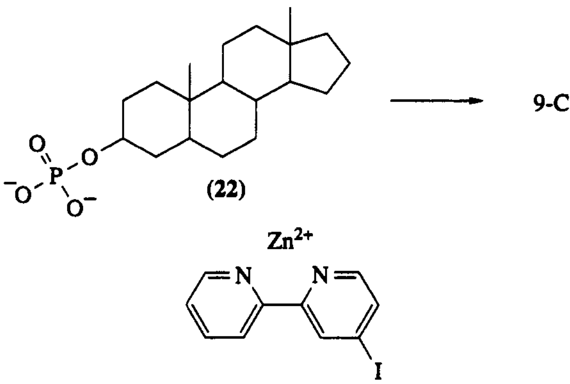

(22)

(23)

Scheme 25

double ion pair of Scheme 9. To justify the complex template catalyst that this implies, multiple turnovers are needed so the catalyst can be used in truly catalytic amounts. Furthermore, functionalizations other than radical relay chlorinations are of interest. As these techniques develop, the methods outlined here may become ever more useful in synthesis.

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# 1.4

# Oxidation by Microbial Methods

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## 1.4.1 INTRODUCTION

Microorganisms have the ability to effect chemical oxidations on a wide variety of substrates, many of which occur with chemo-, regio- or stereo-selectivities unattainable by conventional chemical methods. This is particularly true in the case of unactivated C—H oxidation. What chemical oxidation system, for example, would be capable of the stereoselective hydroxylation of the diol (**1**) to the 3β-hydroxy derivative (**2**)? This transformation has been reported to occur in 80% yield when a microbial oxidation is employed.[1]

Preparative microbial oxidations have long been practiced in organic synthesis, perhaps most prominently in the steroidal field, and a number of comprehensive and specialized reviews have appeared. The most recent review,[2] published in 1981, covers most aspects of biochemical oxidations, and gives an ex-

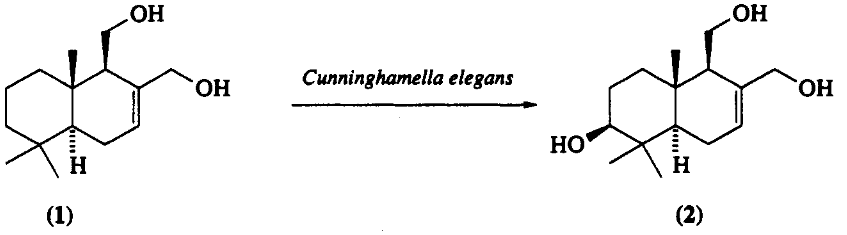

(1)

cellent bibliography of previous work and of books relevant to fermentation and microbial transformations in general. Other treatise giving comprehensive coverage of the scope and practical aspects of microbial oxidations (bacteria, fungi, yeasts and spores) alone have also appeared.[3–6]

Despite their well-researched and impressive capabilities, the use of microbial oxidations has not yet become commonplace in organic synthesis. Unfamiliarity and the difficulty in predicting when the use of a microorganism would be advantageous (except of course when there is no clear choice of chemical oxidant), and, if so, which one(s) should be used, are all impediments to wider use. However, with the advent of genetic engineering and increasing emphasis being placed upon the need for single enantiomers of chiral materials, microbial methods are likely to play an increasingly important role in organic synthesis.

A fundamental difficulty with microbial oxidations of unactivated C—H groups is that the dominant factors in controlling the site and extent of the reaction are often steric in nature, whereas in chemical oxidations electronic factors are often more important. Thus microbial and chemical oxidations can rarely be equated, and microbial oxidations cannot be treated directly on a functional group basis. Also, following from this, microbes cannot be considered as reagents; although some classes do show certain characteristics as to the type of hydroxylation effected, in many cases the site of hydroxylation, and even if hydroxylation will take place at all, is dependent upon the nature of the substrate and the strain of microbe used. Thus, unlike chemical oxidations where tens of oxidants are available (although fewer than this are useful for oxidation of unactivated C—H), literally hundreds of microorganisms have been employed, and many thousands are available.

However, the selection of a microorganism capable of bringing about a specific reaction on a new substrate is performed initially by seeking literature analogies. For example the conversion of cinerone (3) to the cinerolone (4) by *Aspergillus niger*[7] was used as the precedent which led to the stereospecific hydroxylation of the cyclopentenone (5) to the prostaglandin synthon (6) by the same microorganism (Scheme 1).[8]

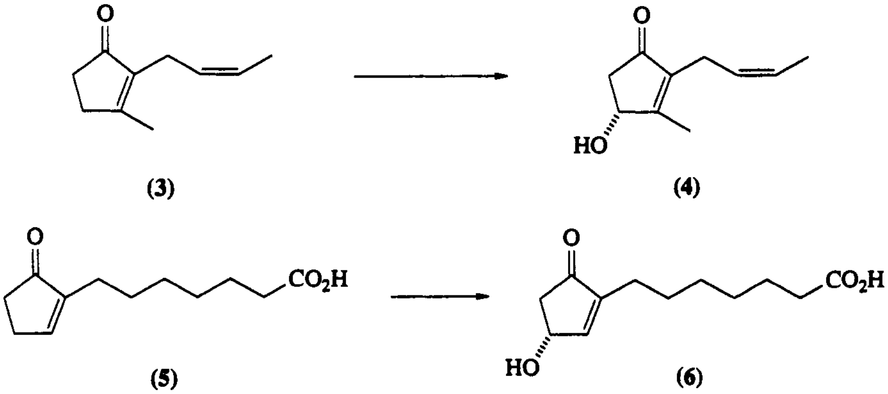

**Scheme 1**

In the following sections some of the general characteristics of microbes, and of oxidation of C—H bonds that can be effected by them, are discussed. Because microbes cannot be treated strictly as reagents, the organization of sections is largely on a substrate type basis, with the main division being between nonsteroidal and steroidal substrates.

## 1.4.2 GENERAL ASPECTS OF THE USE OF MICROORGANISMS

Few synthetic organic chemists are acquainted with the nomenclature or the use of microorganisms, and consequently there is a need to provide some guidance on where to start.

### 1.4.2.1 Taxonomy of Microorganisms

Microorganisms are classified according to genus and species. The first name of the microorganism is the genus, and the second is the species of that genus to which it belongs. Comprehensive lists of microorganisms have been published[5,9,10] and the detailed organization of genera into families, orders and classes has also been reviewed.[11]

### 1.4.2.2 Sources of Cultures

Microorganisms can be acquired from various sources and in many cases several strains or mutants will be available for each species of microorganism. In the more recent literature the precise identity (name, source and number) of the microorganisms used are normally stated, and Table 1 lists the more common reference collections. More extensive listings are available.[9] There may be considerable differences in the nature and yield of products from a given microbial oxidation if two different strains of the same species are used, and for this reason older work may be difficult to reproduce.

**Table 1** Sources of Supply of Microorganisms

| *Abbreviation* | *Source* |
|---|---|
| ATCC | American Type Culture Collection, Rockville, MD, USA |
| CBS | Centraalbureau voor Schimmelcultures, Baarn, The Netherlands. |
| CMI | Commonwealth Mycological Institute, Kew, Surrey, UK |
| DSM (or GCM) | German Collection of Microorganisms, Soc. Invest. Biotechnol., Gottingen, Germany |
| FERM | Fermentation Research Institute, Ibaraki, Japan |
| IAM | Institute of Applied Microbiology, University of Tokyo, Japan |
| IFO | Institute for Fermentation, Osaka, Japan |
| NCIB | National Collection of Industrial Bacteria, Torry Research Station, Aberdeen, UK |
| NCTC | National Collection of Type Cultures, Central Public Health Laboratory, London, UK |
| NCYC | National Collection of Yeast Cultures, Brewing Industry Research Foundation, Nutfield, Surrey, UK |
| NRRL | Culture Collection Unit, Northern Utilization Research Branch, (formerly Northern Regional Research Laboratories), US Department of Agriculture, Peoria 5, IL, USA |

In many cases microorganisms that will carry out a required transformation have been selected after screening many naturally occurring colonies. This approach is tedious and lengthy and needs to go hand in hand with the classification of those microorganisms giving the best results. For these reasons this approach is not to be recommended unless no precedents for the required transformation exist.

### 1.4.2.3 Use of Microorganisms

From many experiments with many different types of substrate and oxidation reaction, it is possible to compile a list of microorganisms that have shown considerable versatility and reliability, and which provide a good starting point for attempting a new oxidation, and these are given in Table 2. More extensive listings are available.[5,9] From this starting point, optimization of the yield and selectivity can be achieved by screening an ever broader range of strains and alternative microorganisms, and in the past it has not been unusual for many hundreds of these to have been assessed for a particularly rare or difficult transformation (one project reportedly screened 2000 strains of microorganisms). The ultimate objective is to identify a particular microorganism that can accomplish the desired oxidation in reasonable yield. If a low yield or selectivity is obtained (even at a few percent the yield may be far superior to that from the alternative chemical method) it may be possible to enhance this by selective mutation (for example by exposure of the organism to radiation or a chemical mutagenic agent). The mutation and selection of improved strains of microorganisms is a science in itself, and is beyond the scope of this work and has been discussed elsewhere.[12]

**Table 2** Some Microorganisms Commonly Used for Oxidation of Unactivated C—H Bonds

| *Microorganism* | *Class* | *Some applications* |
|---|---|---|
| *Beauveria sulfurescens*[a]<br>(ATCC 7159) | Fungi imperfecti | 11α-Hydroxylation of steroids, hydroxylation of cyclic and acyclic amides, tricyclic terpenes and aromatics |
| *Rhizopus nigricans*[b]<br>(ATCC 6227b) | Phycomycetes | 11α-Hydroxylation of steroids, hydroxylation of diterpenes |
| *Calonectria decora*<br>(ATCC 14767, NRRL 2380) | Ascomycetes | Steroid hydroxylation and dehydrogenation, hydroxylation of cyclic hydrocarbons |
| *Curvularia lunata*<br>(ATCC 12017) | Fungi imperfecti | Steroid 11β-hydroxylation |
| *Aspergillus niger* | Fungi imperfecti | Very general use |
| *Cunninghamella elegans*<br>(NRRL 1393) | Phycomycetes | Steroid hydroxylation and allylic hydroxylation |
| *Pseudomonas putida* | Schizomycetes | Unactivated C—H hydroxylation |

[a] This is the most commonly used name for this microorganism, but it has recently been reclassified as *Beauveria bassiana*. In earlier literature it is referred to as *Sporotrichum sulfurescens*. [b] This is the most commonly used name for this microorganism, but it has recently been reclassified as *Rhizopus stolonifer*.

By their very nature microbial oxidations require mild, usually near physiological, conditions; this can be both an advantage and a disadvantage. For example, the mild conditions often enable sensitive functional groups to remain unaltered during the oxidation (*e.g.* **1** above), but at the same time the use of mainly aqueous conditions precludes water sensitive substrates and can limit both the concentration of substrate and complicate the recovery of products. Experimental aspects of the use of microorganisms in oxidations have been discussed previously,[4,11–13] and these sources of information will provide all that is necessary to be able to carry out a laboratory microbial oxidation.

## 1.4.3 MICROBIAL OXIDATION OF NONSTEROIDAL SUBSTRATES

### 1.4.3.1 Acyclic Hydrocarbons and Their Functionalized Derivatives

Microbial oxidation of alkanes can take place at the terminal carbon, in which case an alcohol is the initial product, or at a subterminal position (often the β-position) to give either the secondary alcohol or a ketone. In both cases further oxidation[14] can take place to give carboxylic acids, themselves liable to β-oxidation and shortening of the carbon chain by successive two-carbon units (Scheme 2).

The mechanisms of these oxidations and the nature of the various enzyme systems involved have been discussed previously,[14] as have some examples of these types of microbial reactions.[15]

Mutation of the microorganism can lead to the blocking of undesirable secondary metabolism (a problem most serious for simple *n*-alkanes). For example a mutant of *Candida cloacae* (M-1) converted *n*-alkanes to α,ω-dicarboxylic acids, and up to 30 g $l^{-1}$ of the products could be accumulated in high yield.[16]

The fungi *Torulopsis gropengiesseri* and *Torulopsis apicola* have the ability to incorporate the primary oxidation products of alkanes and their derivatives into extracellular glycolipids, thus reducing secondary oxidation. Thus hydroxylation of long chain esters or amides can result in preparatively useful product yields (equation 2).[3] However simple alkanes, alcohols, halides or ethers as substrates can result in significant competitive α-oxidation at one or both ends of the carbon chain, to give primary alcohols and/or carboxylic acids.

β-Hydroxylation of short chain aliphatic carboxylic acids can be accomplished by a number of microorganisms[17] (see also Scheme 3) including *Endomyces reessii, Trichosporum fermentans, Torulopsis candida* and *Micrococcus flavus*. Longer chain carboxylic acids can also be satisfactorily hydroxylated.[18]

Many other microorganisms have been studied in relation to the degradation of environmental hydrocarbon pollutants; however the identification of metabolites and elucidation of metabolic pathways has often been the prime concern of these studies, rather than the development of synthetic methods. Methylotropic bacteria are noted for their ability to degrade hydrocarbons and in some cases intermediate hydroxylated products can be recovered. Patel and coworkers have done much of the work in this area[19] and systems capable of converting *n*-alkanes to secondary alcohols[20] or ketones[21] have been developed.

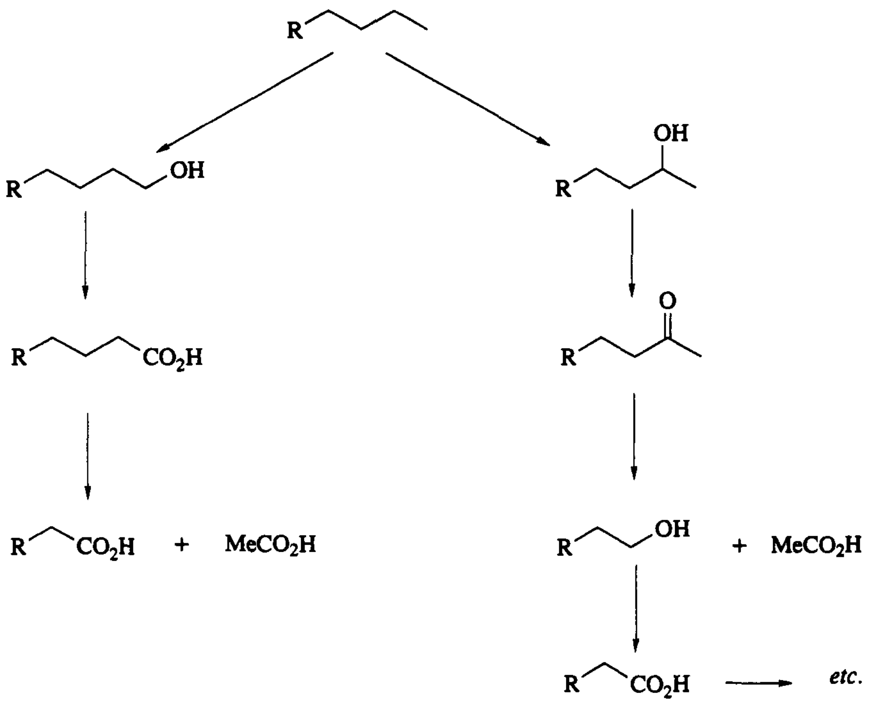

Scheme 2

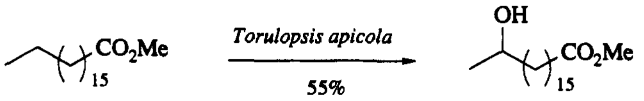

(2)

Species of the genera *Methylosinus* or *Methylococcus* are commonly used, and optically active derivatives can be produced in some cases.[22]

In many cases enantiospecific or enantioselective oxidation of acyclic hydrocarbons or their derivatives is possible using microorganisms, although in few cases has the extent of optical induction been accurately quantified. This is clearly an area where more work is required. In those cases studied so far hydroxylation has been found to occur with retention of configuration at the reacting carbon.

The enantiotopic discrimination of hydrogens during oxidation of unactivated C—H bonds by microorganisms is synthetically extremely useful, and some examples are shown in Scheme 3.[28–31] The resultant products are valuable chiral synthons. For example (*R*)-3-hydroxybutanoic acid (**7**) a versatile homochiral synthon, can be used in the synthesis of antibacterials.[23,24] (*S*)-2-Methyl-3-hydroxypropanoic acid (**8**) has been widely employed as a source of chirality, for example in the synthesis of maysine,[25] macrolide antibiotics[26] and both (*R*)- and (*S*)-muscone.[27] A variety of other optically active 3-hydroxy aliphatic carboxylic acids can be prepared by analogous methods.[18]

In the case of 2-arylpropanoic acids, although the (*S*)-enantiomer (**9**) is available by a terminal oxidation, the alternative (*R*)-enantiomer (**11**) can be prepared by the more extensive oxidative degradation of the alkylbenzene (**10**; equation 3) by *Rhodococcus* spp. (BPM 1613).[32] In this case the optical induction is due to oxidative kinetic resolution of intermediates; the recovered substrate is racemic.

This type of progressive chain shortening can be of general use, as higher homologs of hydrocarbon substrates are often more readily accepted by microbes than lower ones. The progress of the reaction needs to be carefully monitored, of course, to avoid overreaction. Another example of this approach is the synthesis of the homochiral antiulcer agent (**12**; equation 4) in near quantitative yield.[33]

In some cases the regioselectivity of a microbial oxidation is governed by the absolute configuration of the substrate. For example, the racemic amide (**13**; Scheme 4) gives two major products upon culturing with *Beauveria sulfurescens*, one from hydroxylation at C-5 (**14**; 29% yield, 44% *ee*) and derived from the (1*S*)-enantiomer of the substrate, and one from hydroxylation at C-4 (**15**; 22% yield, 53% *ee*) and derived from the (1*R*)-enantiomer.[34]

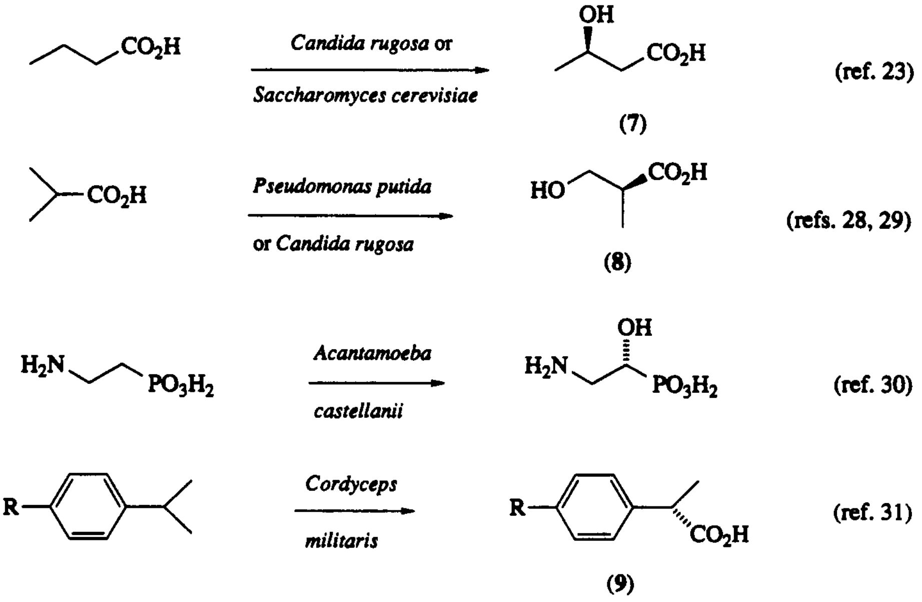
CO2H
Candida rugosa or
Saccharomyces cerevisiae
OH
CO2H
(7)
(ref. 23)
CO2H
Pseudomonas putida
or Candida rugosa
HO
CO2H
(8)
(refs. 28, 29)
H2N
PO3H2
Acantamoeba
castellanii
OH
H2N
PO3H2
(ref. 30)
R
Cordyceps
militaris
R
CO2H
(9)
(ref. 31)

Scheme 3

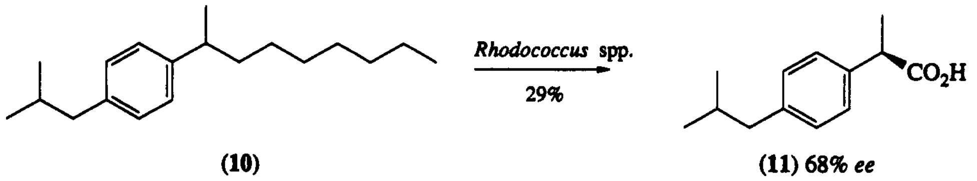
(10)
Rhodococcus spp.
29%
CO2H
(11) 68% ee

(3)

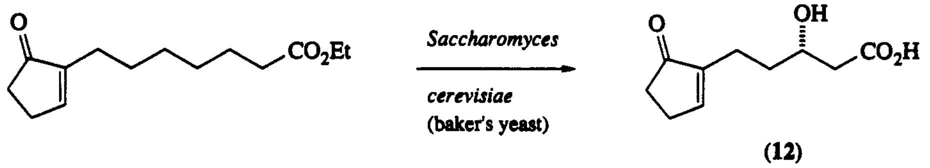
O
CO2Et
Saccharomyces
cerevisiae
(baker's yeast)
O
OH
CO2H
(12)

(4)

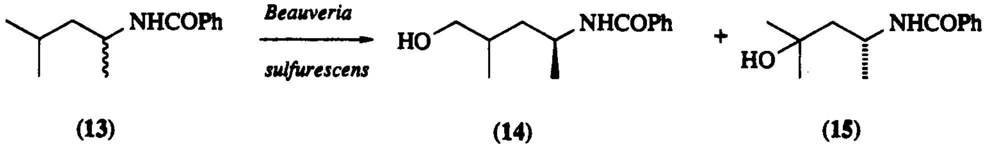
NHCOPh
(13)
Beauveria
sulfurescens
HO
NHCOPh
(14)
+
HO
NHCOPh
(15)

Scheme 4

### 1.4.3.2 Cyclic Hydrocarbons and Their Functionalized Derivatives

The literature in this area up until 1975 has been reviewed by Kieslich.[5] In common with acyclic hydrocarbons, simple unsubstituted cyclic hydrocarbons give poor yields of hydroxylated products with most microorganisms, either due to cascade degradation or volatilization of the product during the reaction.

*Beauveria sulfurescens* has repeatedly been shown to be particularly suitable for hydroxylations of a wide range of cyclic substrates, and much pioneering work was done by Fonken and coworkers, and is recorded in a number of patents held by Upjohn Co., two of which are particularly relevant.[35,36] Cyclohexylcyclohexane (16), for example, can be 4,4′-bishydroxylated by *Beauveria sulfurescens* to give a 30% yield of the 4,4′-dihydroxy derivative (17). More recent work employing *Beauveria sulfurescens* or *Cun-*

*ninghamella blakesleeana* gave the 4(e),4′(e) isomer, with some unspecified optical activity residing in the 3(e),4′(e) isomer also isolated.[37]

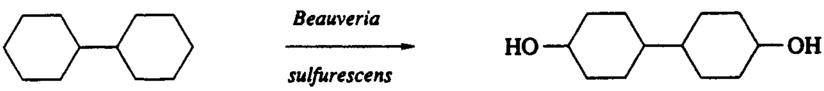

(5)

**(16)** **(17)**

Polar groups on the substrate molecule can facilitate hydroxylation of nonactivated positions, and the cyclohexane derivative (**18**) is regio- and stereo-selectively hydroxylated in 71% yield by *Penicillium concavo-rugulosum* (equation 6).[38]

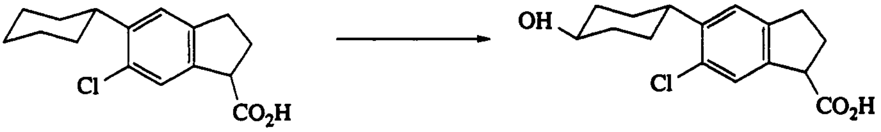

(6)

**(18)**

Hydroxylation of 7-carboxybicyclo[2.2.1]heptane (**19**) and the unsaturated analog (**20**) provide a good example of what can be achieved with microorganisms. Examination of 119 types of microorganism showed that most gave little or no regio- or stereo-selectivity, however *Aspergillus awamori* (FERM P-8052) showed excellent regio-, diastereo- and enantio-selectivity, resulting in the conversion of the acid (**19**) into the *endo*-alcohol (**21**) (84.7% *ee*)[39] This can then be oxidized to give the ketone (**22**; 92.2% *ee*; Scheme 5).

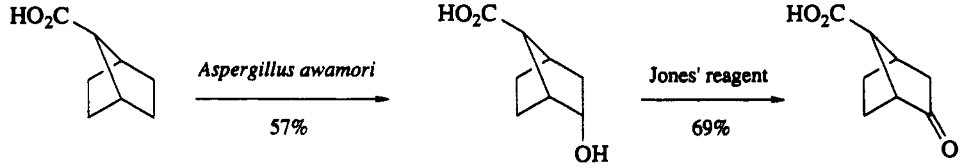

**(19)** **(21)** **(22)**

**Scheme 5**

The unsaturated ester (**20**) can be similarly converted to the *endo*-alcohol (**23**), which can be oxidized to the ketone (**24**; 81.9% ee) with an overall yield of 8% (Scheme 6). These products are potential intermediates for (–)-methyl jasmonate and natural prostaglandins.[40] Here the microorganism is showing good discrimination between the two enantiotopic *endo* hydrogens on C-2 and C-3.

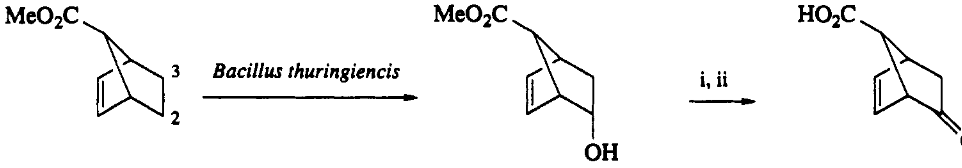

**(20)** **(23)** **(24)**

i, hydrolysis; ii, Jones' reagent

**Scheme 6**

Diastereoselective hydroxylations are more common, for example *Streptomyces rimosus* (NRRL 2234) will hydroxylate zearalenone (**25**) to give the (*S*)-8′-hydroxy derivative (**26**; equation 7).[41] Other microorganisms gave reduction of the 6′-ketone group in (**25**).

The presence of an amine or amide group in cyclic substrates greatly facilitates the hydroxylation by *Beauveria sulfurescens*. Numerous mono-, di- and tri-cyclic amides and saturated nitrogen heterocycles have been studied[5] and a rational basis for the position at which the hydroxy group is introduced into the substrate molecule has been put forward;[42,43] however, yet more work is required to define all the factors controlling the selectivity of hydroxylation. Nevertheless useful regio-, stereo- and in some cases

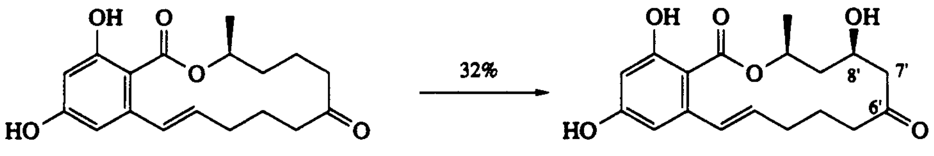

(25) (26) (7)

enantio-selectivities are possible, although as with other areas there is still a lack of detailed quantitative data, particularly on the optical purities of products.

Hydroxylation of the bridged piperid-2-one (27) can be accomplished with total stereocontrol[44] to give the *exo*-alcohol (28), a useful precursor to novel 2′-desoxynucleosides (equation 8). In other cases the regio- and stereo-chemical outcome of the reaction may be highly dependent upon the nature of the substrate; this seems particularly true for lactams such as (29). Here mixtures of regioisomers are obtained when using *Beauveria sulfurescens* and optical activity of these is usually low or absent.[45] For example the phenylacetyl amide of pyrollidin-3-one (30) gave the (*S*)-3-hydroxy derivative (31) with a 30% ee (equation 9).

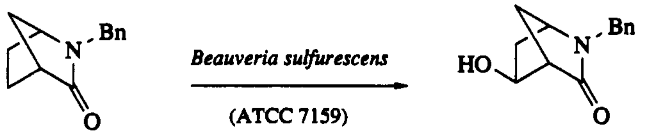

(±)-(27) (2*S*)-(28) (8)

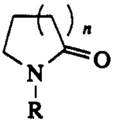

(29) $n = 1–3$

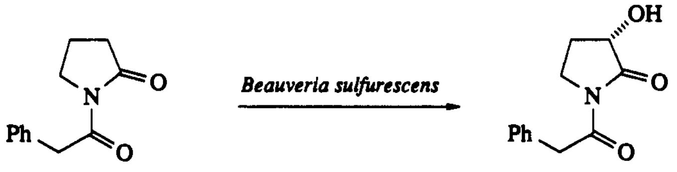

(30) (31) (9)

As with acyclic amides, enantiospecific discrimination of the enantiomers of a racemic substrate sometimes occurs. This phenomenon could prove useful in preparing new homochiral synthons. For example the two C-1 enantiomeric amides (32) and (33) are hydroxylated on different methyls (relative to the *t*-amide nitrogen) of the C-8 *gem*-dimethyl bridging group,[46a] as shown in Scheme 7. Hydroxylation of one methyl in a *gem*-dimethyl grouping by microorganisms is fairly common, and other examples are given later and elsewhere.[46b]

Thus the active site of the hydroxylating enzyme appears insensitive to the relative position of the amide group. This has also been observed for bicyclic amides, for example both *exo* and *endo* isomers of the amide (34) are hydroxylated to the *exo*-alcohol (35) with the same regio- and stereo-selectivity (equation 10).[43] Further, the hydroxylation can also be insensitive to the position of the carbonyl group. For example, bi-, tri- and tetra-cyclic amides, and the equivalent lactams, of which the amide (36a) and lactam (36b) are representative cases respectively, are both hydroxylated at the same position (Scheme 8a).[47a]

These observations have led to the development of a trajectory-based model to rationalize the selectivity of the monooxygenase enzyme in *Beauveria sulfurescens*,[47a] and this may allow the regio- and stereochemistry of transformations on new (related) substrates to be predicted. Also of some assistance in predicting the stereochemical outcome of the reactions is the study of the mechanism, and this has been investigated and shown, at least in some cases, to proceed with inversion of stereochemistry.[47b]

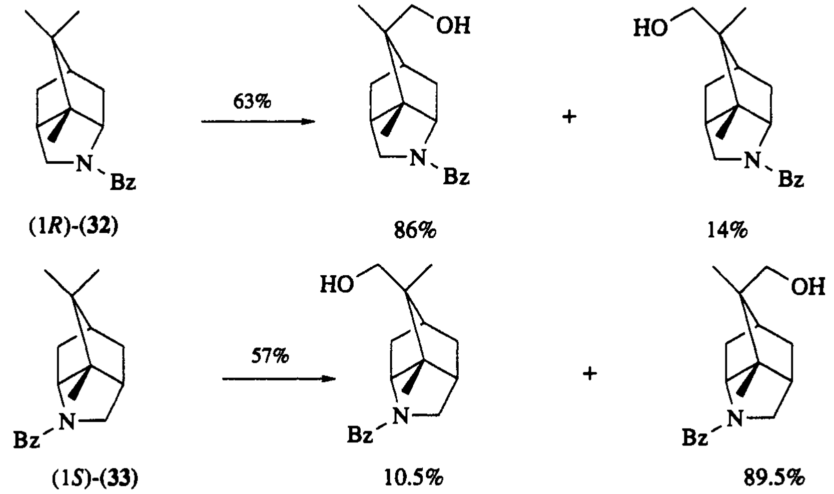
OH
HO
63%
+
N
Bz
(1*R*)-(32)
86%
14%
HO
OH
57%
+
Bz
N
(1*S*)-(33)
10.5%
89.5%

**Scheme 7**

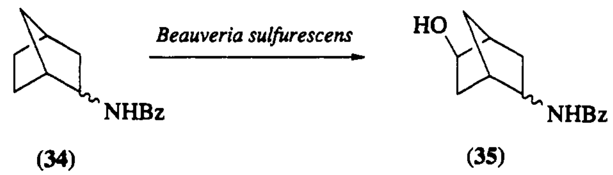
*Beauveria sulfurescens*
HO
NHBz
(34)
(35)

(10)

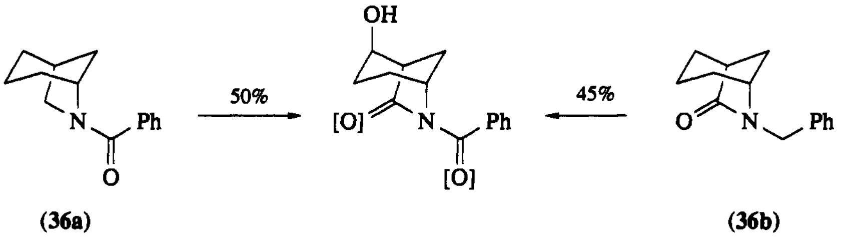
OH
50%
45%
N
Ph
O
[O]
(36a)
(36b)

**Scheme 8a**

Although much of the work on the microbial hydroxylation of amides has been directed at active-site mapping of the enzyme responsible, the products themselves are valuable building blocks for further synthesis, for example, for various optically active sesquiterpenes[48] or β-lactams. In this latter context regioselective hydroxylation of unactivated positions is particularly attractive as several β-lactam antibiotics, *e.g.* the carbapenem derivative thienamycin, have a free hydroxy group in their structure.

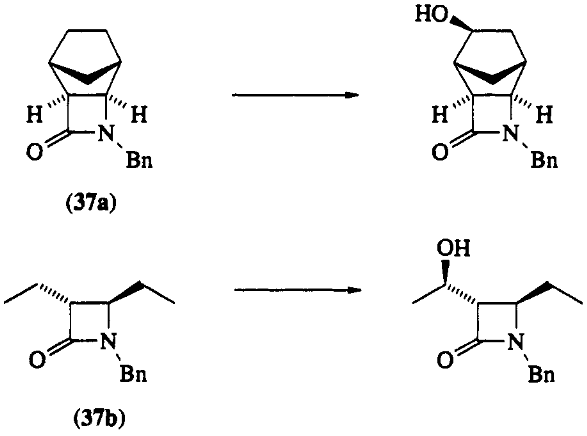
HO
H
H
N
O
Bn
(37a)
OH
(37b)

**Scheme 8b**

For example, monohydroxylation of the lactams (**37a**) and (**37b**) can be accomplished by *Beauveria sulfurescens* (ATCC 7159) in 65% and 10% yields respectively (Scheme 8b).[47c]

### 1.4.3.3 Isoprenoids

The hydroxylation of terpenes by microorganisms is of interest in the preparation of flavor and fragrance compounds

There have been a number of previous reviews on microbial oxidations of terpenes.[5,49,50a] Monoterpenes are often degraded progressively after an initial hydroxylation step, but di-, tri- and sesqui-terpenes can be converted more selectively, to accumulate useful quantities of hydroxylated products. Less systematic work on the microbial oxidation of terpenoids has been carried out than in the case of steroids, and therefore prediction of the regio- and stereo-chemistry is scarcely possible.

Acyclic triterpenes can be considered as aliphatic hydrocarbons and are α-hydroxylated by a number of microorganisms.[50b] The microbial oxidation of a variety of acyclic terpenoid hydrocarbons has been investigated by Nakajima,[51] and although terminal alcohols can be obtained, for example pristanol (**39**) from pristane (**38**; equation 11), further oxidation can also occur.

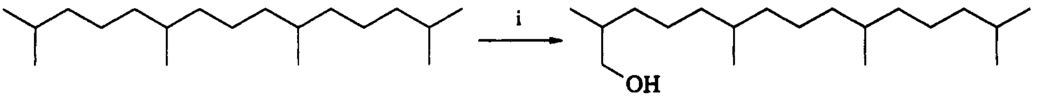

(11)

(**38**) (**39**)

i, *Rhodococcus* spp. (BPM 1613)

Citronellol, geraniol and linalool (as their acetates) can be regiospecifically hydroxylated at the terminal allylic carbon by a strain of *Aspergillus niger* (equation 12).[52a] Concurrent hydrolysis of the acetate groupings in these substrates also takes place to a certain extent. This hydroxylation is particularly interesting as previously a strain of *Aspergillus niger* has been reported[5] that rearranged geraniol (**40**) to linalool before oxidation to citral (**41**; Scheme 9). This difference could be due to acetylated *versus* unacetylated substrate or due to two different strains of microorganism being employed. Longer chain acyclic terpenoids can also be hydroxylated in allylic positions by *Aspergillus niger* (ATCC 9142).[52b]

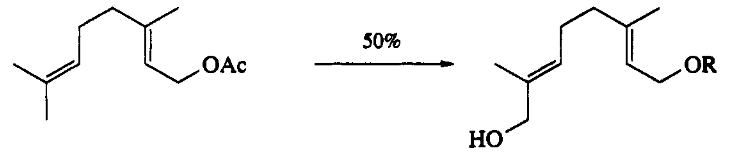

(12)

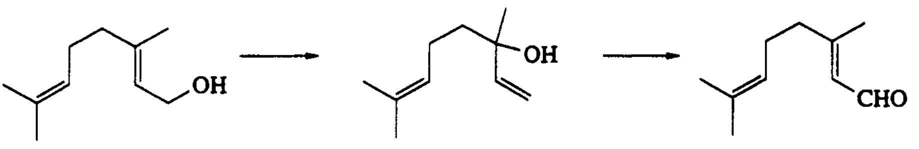

(**40**) (**41**)

**Scheme 9**

Mono- and bi-cyclic monoterpenes containing sites of unsaturation tend to be hydroxylated at the allylic position,[5] (more examples of allylic hydroxylation are discussed in Section 1.4.5.2) with regioisomers occurring if more than one allylic position is accessible. Some illustrative examples of reported hydroxylations are shown in Scheme 10.[53–57] The hydroxylation of 1,4-cineole (**42**)[53a] is illustrative of the enantioselectivity that may be achieved in such transformations. *Bacillus cereus* gives a 1:7 mixture of (2*R*)-*exo*- and (2*S*)-*endo*-monohydroxy-1,4-cineole, both with essentially 100% enantiomeric purity.[53b,53c]

In the case of the transformation of bornyl acetate (**43**) by *Fusarium culmorum* it is interesting to note that both enantiomers of the substrate yielded only the 5-*exo*-hydroxybornyl acetate as the major product.

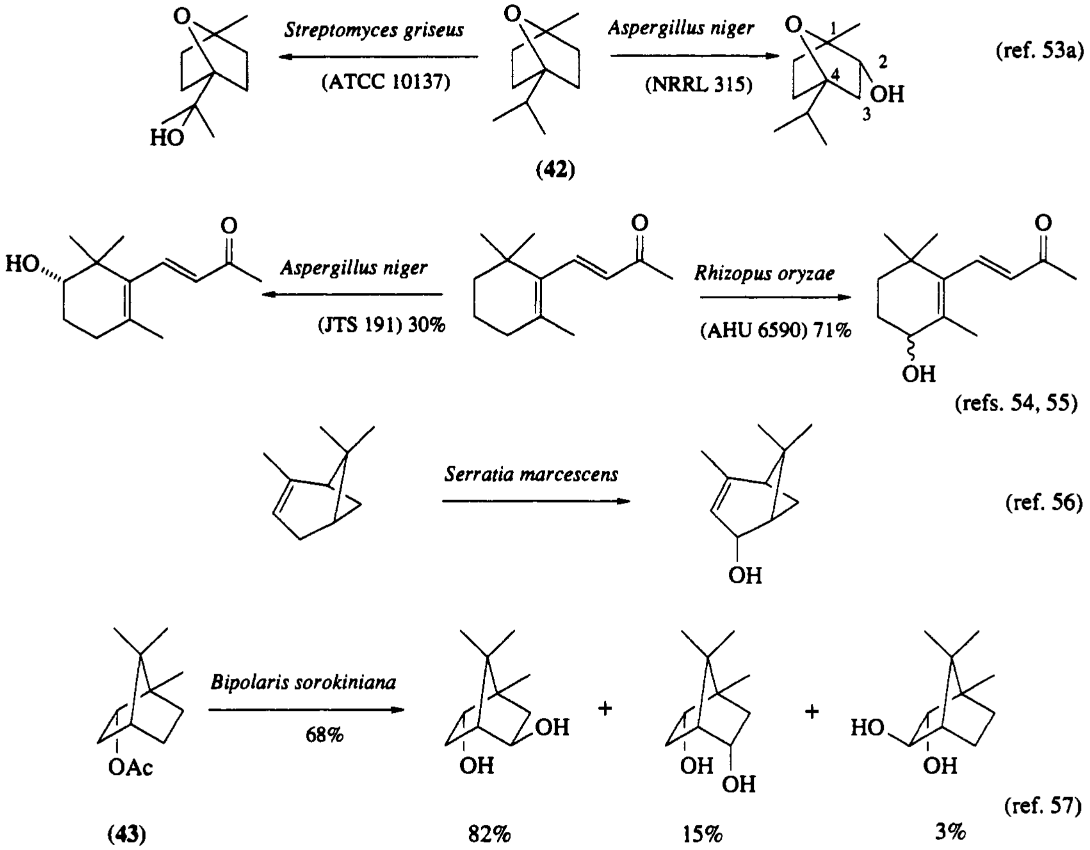
Streptomyces griseus
(ATCC 10137)
Aspergillus niger
(NRRL 315)
(ref. 53a)
(42)
Aspergillus niger
(JTS 191) 30%
Rhizopus oryzae
(AHU 6590) 71%
(refs. 54, 55)
Serratia marcescens
(ref. 56)
Bipolaris sorokiniana
68%
(43)
82%
15%
3%
(ref. 57)
HO
OH
OAc
O

**Scheme 10**

Also in this case the major product from microbial oxidation corresponded to that from chemical oxidation.[57]

Chemically difficult (or currently impossible) hydroxylations on more complex terpenes can be accomplished by microbial methods, but there is as yet no clear understanding of the factors affecting selectivity. As is often the case, microorganisms suitable for a required transformation have been selected largely on precedent or on an empirical basis. In some cases respectable yields of one stereoisomer may result.

Sesquiterpenes can also be hydroxylated and species of the genera *Aspergillus*, *Cunninghamella* and *Streptomyces* have all been used to accomplish miscellaneous hydroxylations.[5] Unfortunately prediction of the site of attack is not yet possible. To illustrate the difficulty in understanding the factors controlling the site of attack the sesquiterpene lactones (**44**) and (**45**) and the diol (**1**) serve as examples. Although the lactone (**44**) is hydroxylated predominantly at the reactive 8α-position (*Cunninghamella echinulata*, NRRL 3655),[58] the product from the hydroxylation of the lactone (**45**) (*Aspergillus niger*, MIL 5024) at the equivalent position is not obtained,[59] and the diol (**1**) is not hydroxylated at the expected (allylic) position (*Cunninghamella elegans*).[1]

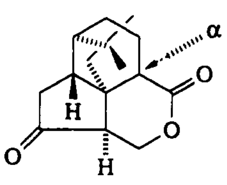

**(44)**

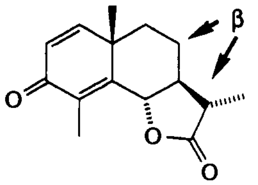

**(45)**

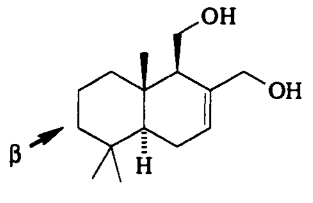

**(1)**

The sesquiterpene cedrol (**46**) can be hydroxylated regio- and stereo-selectively with *Beauveria sulfurescens* (equation 13).[60] This transformation serves to illustrate the general principle that substrates with an electron rich substituent, to serve as an anchor at, or close to, the active site of the hydroxylating enzyme system, generally are transformed with improved selectivity over those with no such anchor. For example, in the above system the unsaturated substrate cedrene (**47**) gives low yields of a mixture of products.[60]

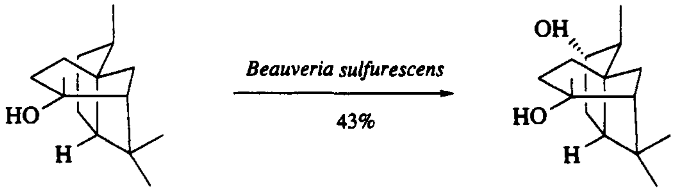

(**46**)

(13)

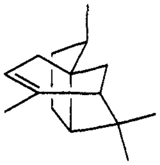

(**47**)

The related tricyclic sesquiterpene patchoulol (**48a**) is a good substrate for microorganisms[48] and hydroxylation at various sites can be accomplished, for example at C-5 by *Choanephora circinana* in 74% yield (equation 14). Hydroxylation of the methyl group on C-4 can be accomplished by *Penicillium rubrum* FX-318 in 75% yield,[61a] and of the C-14 methyl group in (1*R*)-caryolan-1-ol (**48b**) by *Aspergillus niger* (MMP 521) in 26% yield.[61b]

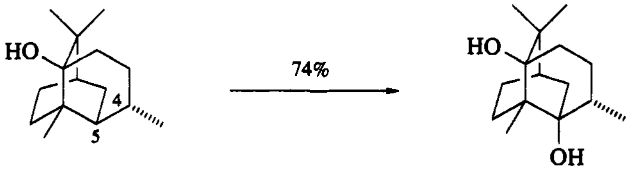

(**48a**)

(14)

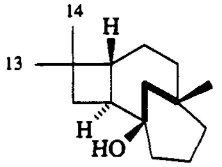

(**48b**)

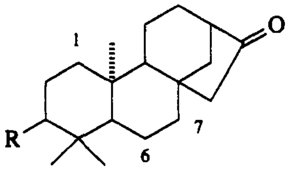

(**49**)

Because of their importance as precursors to gibberellins, diterpenes with the *ent*-kaurane skeleton have been subjected to microbial hydroxylation.[4] Favored microorganisms for these transformations have been *Calonectria decora, Rhizopus nigricans* and *Aspergillus ochraceus*. The hydroxylations are sometimes selective but often mixtures are obtained, made even more complex by di- as well as monohydroxylation. Some representative results illustrating regio- and diastereo-selectivities are shown in Table 3.[62] The same type of binding-site model can be used to rationalize the sites of hydroxylation in the ent-kaurene series as in the steroidal series *vide infra*.[63] Also, as in the case of steroids, better selectivity is obtained if two binding groups are present in the substrate rather than one.

Forskolin derivatives, for example (**50**), can be hydroxylated by, for example, *Neurospora crassa* (ATCC 10336), *Mortierella isabellina* (ATCC 160074) and *Aspergillus niger* (DSM 3210); 2α-, 2β-, 3α- or 3β-hydroxy derivatives can be obtained in this way (*e.g.* equation 15).[64]

**Table 3** Hydroxylation of *ent*-17-Norkauranones (**49**)

| *Substrate* (**49**) | *Microorganism* | *Yields (%)* *1α* | *7a* | *6β* |
|---|---|---|---|---|
| R = —OH | *Rhizopus nigricans* | 25 | 35 | |
| | *Calonectria decora* | | 40 | |
| | *Aspergillus ochraceus* | | 25 | 30 |
| R = ═O | *Calonectria decora* | | 40 | |

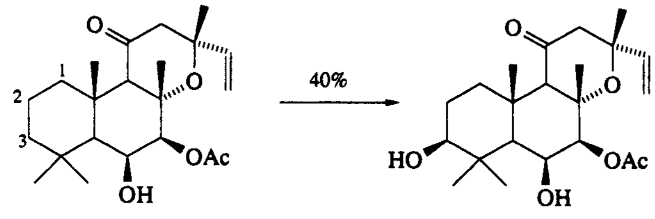

(**50**)

(15)

### 1.4.3.4 Alkaloids

Microbial oxidations are relatively common in the alkaloid field and a number of excellent reviews covering the literature up until 1984 have appeared.[13,65–67] Hydroxylation at both aliphatic and aromatic positions of alkaloid molecules can be accomplished, however the latter is favored and the site of hydroxylation in these cases is usually predictable based on the rules governing electrophilic aromatic substitution.[13]

The heteroyohimbine alkaloids can be effectively hydroxylated at the (aromatic) C-10 and C-11 positions.[68] For example ajmalcine (**51**) is 10-hydroxylated in 92% yield by *Cunninghamella elegans* (ATCC 9245) and tetrahydroalstonine (**52**) is 11-hydroxylated in 72% yield by a plant-derived mold. This latter transformation is particularly difficult to achieve by chemical methods.

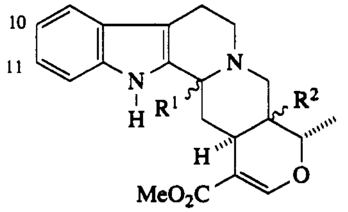

(**51**) $R^1$ = α-H , $R^2$ = β-H

(**52**) $R^1$ = α-H , $R^2$ = α-H

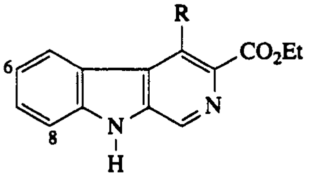

(**53**) R = H or alkyl

Carboline alkaloids (**53**) can be hydroxylated by *Beauveria sulfurescens* (ATCC 7195) at either the 6- or 8-position depending on the substituents on the substrate.[69] When R in the alkaloid (**53**) is methyl, then a mixture of products is obtained (20%, 6-hydroxy; 18%, 8-hydroxy) but if R is ethyl then only the 8-hydroxy product is obtained (70% yield).

Stereoselective dehydrogenation of some alkaloids can be carried out using microorganisms (see also steroids, Section 1.4.4.1). Glaucine derivatives (**54**) are dehydrogenated, in very high yield,[70] to dehydro derivatives by *Aspergillus flavipes* (ATCC 1030) and *Fusarium solani* (ATCC 12823) (equation 16). *Aspergillus flavipes* selectively dehydrogenates the *cis*-6a-(*R*)-enantiomer, whilst *Fusarium solani* selectively dehydrogenates only the *cis*-6a-(*S*)-enantiomer.

Hydroxylation of aliphatic carbon has rarely been accomplished in high yield in alkaloids, but some attempts have been made to produce an active site map for the hydroxylase of *Streptomyces roseochromogenes* which may be of predictive value.[71]

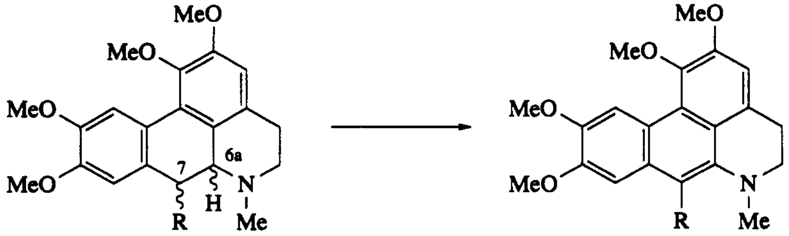

(16)

**(54)** R = H or Me

### 1.4.3.5 Prostaglandins and Cannabinoids

Hydroxylation of the side chain of prostaglandins is possible using microorganisms, but is often accompanied by reduction of double bonds, hydrolysis of esters or further oxidation of alcohols. Hydroxylation usually takes place at C-18, C-19 or C-20 [numbering with respect to prostanoic acid (**55**)]. *Streptomyces ruber* (NRRL B-1268), *Aspergillus niger* (ATCC 9142), *Cunninghamella blakesleeana* (ATCC 9245) or *Microascus trigonosporus* (NRRL 1199) can be employed with a wide range of prostaglandin substrates.[11,13] Little is known of the stereochemistry of these reactions.

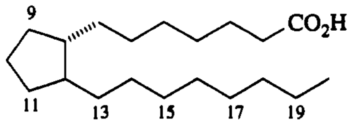

**(55)**

In cannabinoids, side chain hydroxylation is the most common step in microbial conversions, followed by hydroxylation of the terpenoid ring. Generally mixtures of products are obtained and yields are poor.[11] The following microorganisms can be employed for hydroxylation of unactivated C—H bonds in cannabinoids:[72] *Aspergillus niger* (ATCC 9142), *Botrytis allii* (ATCC 9435), *Cunninghamella elegans* (ATCC 9245), *Mycobacterium rhodochrous* (ATCC 19067) and *Streptomyces aureus* (ATCC 15437).

## 1.4.4 MICROBIAL OXIDATION OF STEROIDS

Of all the considerable research efforts expended on microbial oxidations, steroids have received the greatest share. The vast amount of work in this area has been stimulated by the medical importance of steroids, and the desire to develop new drugs with new or improved pharmacological properties.[73] The volume of work is so great that only an overview, with reference to the more interesting or higher yielding transformations, can be presented here. Many previous reviews on the subject have appeared, with a handbook by Charney and Herzog[10] being one of the most useful. Other publications of special importance as reviews and sources of references to the voluminous literature in this area have also appeared.[2–4,13,74] A discussion of practical aspects is also of great value to those unfamiliar with this area.[75a] The commercial relevance of steroid hydroxylation can also be appreciated from a recent extensive review on the subject.[75b]

Microbial oxidative transformations of steroids can be divided into a number of key categories:[13] (i) hydroxylation, (a) at all nuclear sites and angular methyl groups, mono-, poly-, carbonyl-activated, allylic, (b) at some side chain sites; (ii) alcohol dehydrogenation, (a) saturated alcohol to ketone, (b) allylic or homoallylic alcohol to $\alpha,\beta$-unsaturated ketone ($\Delta^1$- and/or $\Delta^4$-3-keto steroid formation); (iii) double bond formation, (a) introduction of a $\Delta^1$ double bond in 3-keto steroids, (b) introduction of a $\Delta^4$ double bond in 3-keto steroids, (c) A-ring aromatization; (iv) carbon–carbon bond oxidation, (a) side chain degradation, (b) ring cleavage; and (v) epoxidation.

Carbon–carbon bond oxidation is beyond the scope of this work, but is a consequence of initial hydroxylation followed by further metabolism involving other enzyme systems. Many examples of alcohol dehydrogenation and double bond epoxidation have been published previously,[76,77] and these will not be considered further here.

### 1.4.4.1 Dehydrogenation

The dehydrogenation of CH—CH, particularly to give α,β-unsaturation in 3-keto steroids can be readily accomplished using microorganisms, and an excellent review on this aspect of steroid oxidations has appeared.[2] Although many microorganisms possess the sterol 1-dehydrogenase enzyme, *Mycobacterium smegmatis* and *Arthrobacter simplex* (also known as *Corynebacterium simplex*), and various mutants thereof, have proved especially useful for 1,2-dehydrogenation. A more complete list is as follows: *Arthrobacter simplex* (ATCC 6946 and NRRL B-8055), *Bacillus lentus* (ATCC 13805), *Glomerella cingulata* (ATCC 10534), *Nocardia asteroides* (ATCC 3308), *Nocardia corallina* (ATCC 999) and *Nocardia restrictus* (ATCC 14887)

As an example, cortisone (**56**) can be converted to prednisone (**57**; equation 17) in up to 90% yield by *Arthrobacter simplex*.[2]

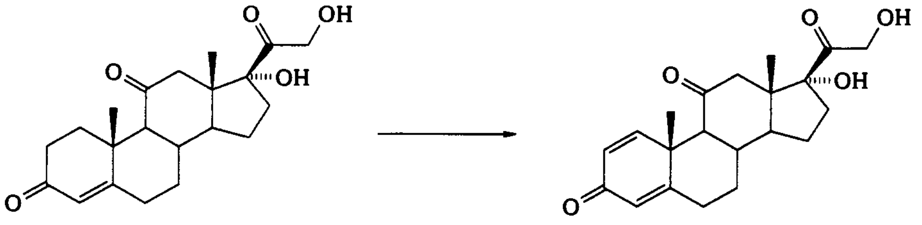

(17)

**(56)** **(57)**

In these transformations the microorganism will often accept a wide range of steroidal substrates and the conversion, or yield, can often be improved by the addition of an electron carrier such as 1,4-naphthoquinone.[78] The 1,2-dehydrogenation is reversible, but the forward reaction can be encouraged to go to completion by efficient aeration of the fermentation.[13] Existing alcohol groups present in the molecule generally remain unaltered, for example in the conversion of cortisol (**58**) to prednisolone (**59**; equation 18), although 3-ols can be oxidized to 3-keto steroids concomitant with 1,2-dehydrogenation. If the substrate contains a 20-keto group this may be reduced during the 1-dehydrogenation.

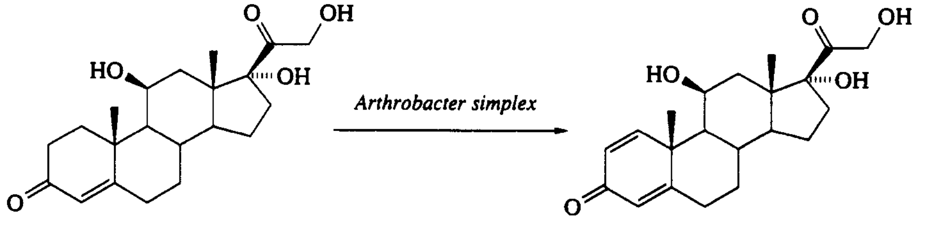

(18)

**(58)** **(59)**

The 1,2-dehydrogenation occurs by stereospecific removal of the 1α- and 2β-hydrogens, and, in addition, some microorganisms will differentiate between enantiomers of the substrate. For example, *Arthrobacter simplex* will usually dehydrogenate only the (*R*)-enantiomer of 10-substituted steroids; however, other microorganisms (*e.g. Corynebacterium hoagii*) having 1,2-dehydrogenase activity will accept both enantiomers.[2]

Double dehydrogenation and even complete aromatization of the A-ring of 3-hydroxy or 3-keto steroids can also be effected; the latter is of special interest in the preparation of estrogens, for example the conversion of the diene (**60**) to the α-estradiol derivative (**61**; equation 19) by *Proactinomyces globerula*.[79]

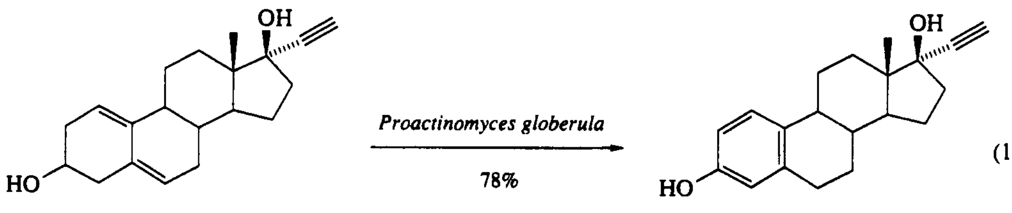

(19)

**(60)** **(61)**

Immobilized microorganisms, in particular *Arthrobacter simplex* and *Nocardia rhodocrous*, and fungal spores, in particular those from *Septomyxa affinis*, can also be used to effect dehydrogenations.[2,80] Dehydrogenations may also be advantageously carried out in the presence of hydrocarbon solvents, for example the conversion of 6α-methylhydrocortisone (**62**) to 6α-methylpredisolone (**63**; equation 20) with *Arthrobacter simplex*.[81]

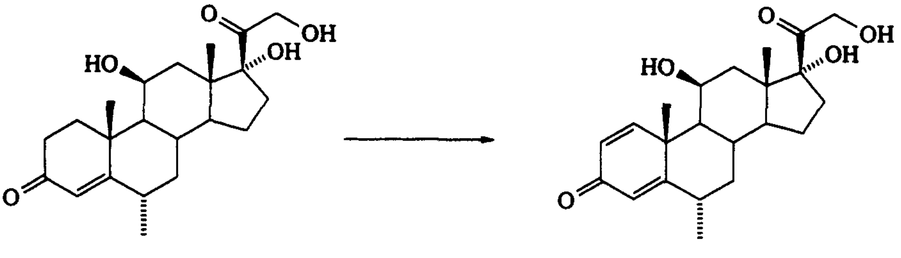

(20)

(**62**) (**63**)

### 1.4.4.2 Hydroxylation

Virtually every site in the steroid molecule is accessible for microbial hydroxylation, and almost all positions have been hydroxylated by various microbial strains. Of particular importance are hydroxylated products with the unnatural α-configuration, and of those the derived 11α- and the 16α-alcohols are of greatest synthetic interest.

Much of the fundamental work on the microbial hydroxylation of steroids, including selection of microorganisms and determination of specificities, was carried out in the 1950s and 1960s, following Peterson's original discovery of the 11α-hydroxylation of progesterone (**64**) by *Rhizopus nigricans* in 1952 (equation 21). A mutant strain of *Aspergillus ochraceus* has subsequently been found that will carry out this transformation in 91% yield at an initial substrate concentration of 40 g $L^{-1}$.[85]

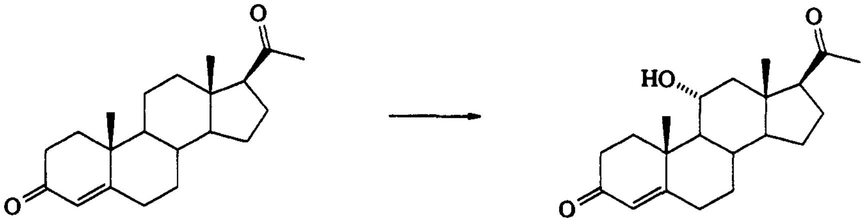

(21)

(**64**)

The basic work on steroid hydroxylation is recorded in the handbook by Charney and Herzog[10] published in 1967. Despite its age, this book still remains the most authoritative source of information on the microbial oxidation of steroids, with classification of hydroxylations given on the basis of site of attack, product formed and reaction shown by each genus of microorganism. Subsequent work has concentrated on developing a better understanding of the selectivity of different microorganisms,[82] on the mechanism of hydroxylation,[83a] and on improving the efficiency of synthetically important transformations.[83b]

Reviews consisting of a compilation of hydroxylations accomplished, along with the microorganisms employed, have been published to cover the period 1979 to 1988.[76,77,83b]

The greatest contribution towards understanding the structural features in the substrate that effect, or indeed control, the selectivity in microbial hydroxylation of steroids was carried out by Jones and Meakins and their work is recorded in a series of papers entitled 'Microbiological Hydroxylation'. Their last report was published in 1980, and serves as a source of references to earlier material.[84]

Generally speaking fungi are of greatest use in the hydroxylation of steroids, and five genera in particular have been found to be extremely useful; these are *Rhizopus*, *Calonectria*, *Aspergillus*, *Curvularia* and *Cunninghamella*.

As with other classes of substrate, hydroxylase enzymes are responsible for the hydroxylation reactions. A given microorganism may be capable of producing more than one steroid hydroxylase enzyme in response to a substrate, with certain features of the substrate inducing each enzyme. For example progesterone induces a 11α-hydroxylase enzyme in *Aspergillus ochraceus*, whilst a 11α-hydroxypregn-4-en-3-one structural feature induces an independently operating 6β-hydroxylase. For this reason whilst some generalizations are possible in discussing steroid hydroxylations, there is still an element of experimentation involved in developing new transformations.

Practical aspects are much as discussed earlier, and a good laboratory steroid hydroxylation procedure has been published.[86] Numerous additives (*e.g.* surfactants, antibiotics and fungicides) have been used to improve microbial hydroxylation of steroids, and some of these have been discussed previously.[87]

### *1.4.4.2.1 Chemoselectivity*[13]

The value of microbial hydroxylation of steroids has long been that they allow functionalization of positions not easily accessible by normal chemical methods. For this reason yields of a few percent have often been tolerated, but yields approaching quantitative can be achieved in many instances. The objective of much current work is to improve the selectivity of microbial hydroxylations. This can be achieved in a number of ways, for example by structural modifications of the substrate, optimization of fermentation conditions and by strain improvement. The latter is most likely to yield the most significant improvements in selectivity, and has previously been discussed at length.[88]

As in the case of nonsteroidal substrates, selectivity tends to be better with substrates containing more than one polar functional group, and functional group modification can be used to take advantage of this effect. Previous work has shown that steroid hydroxylation and epoxidation can be performed by the same enzyme,[89] and as a result those substrates containing double bonds may be epoxidized as well as hydroxylated. Similarly, steroid dehydrogenase enzymes may also be present or induced by some substrates, and as a consequence alcohol groups (already present in the substrate, or introduced by the microorganism) may be converted to ketones, and double bonds may also be introduced. The $\Delta^1$-dehydrogenation of $\Delta^4$-steroids by microorganisms can however be inhibited by the addition of metabolic poisons such as hydrazine, ammonia or some antibiotics.[90]

In some cases it is desirable to carry out a hydroxylation and a dehydrogenation concurrently, and the use of two microorganisms to take effect of the unique selectivity of each can be of great value. For example the fermentation of the steroid (**65**) with *Pellicularia filamentosa* (TFO 6675) and *Bacillus lentus* (ATCC 13805) gives simultaneous 11β-hydroxylation and $\Delta^1$-dehydrogenation.[91]

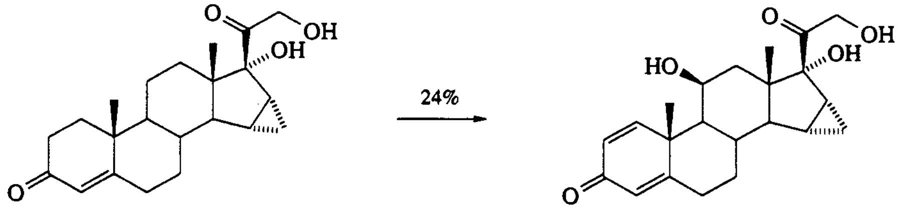

(22)

(**65**)

Microbial reduction of carbonyl groups is another possible side reaction, with a 3-keto group seemingly most susceptible to this reaction, but again the nature of the substrate and microorganism can have a major effect on the extent of this side reaction. In the hydroxylation of 5α-androstan-3-one (**66**) the results shown in Table 4 were obtained.[92]

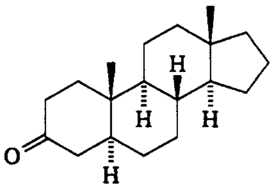

(**66**)

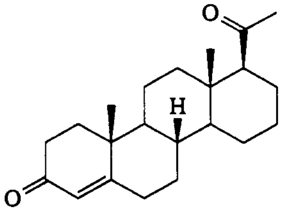

(**67**)

Multiple hydroxylation is one of the most frequently encountered problems in steroid hydroxylation, but this can be controlled to a certain extent by appropriate choice of fermentation conditions, usually involving low substrate concentrations and minimization of fermentation time. Some microorganisms are

**Table 4** Hydroxylation of 5α-Androstan-3-one (**66**)

| *Microorganism* | *Hydroxylation product* | *Yield (%)* | *Reduction of 3-C=O (%)* |
|---|---|---|---|
| *Calonectria decora* | 12β,15α | 47 | 65 |
| *Rhizopus nigricans* | 11α,16β | 35 | 30 |
| *Aspergillus ochraceus* | 6β,11α | 84 | 0 |

of value because they will accomplish di- rather than mono-hydroxylation, and again by appropriate selection of strain, isomeric mono- and/or di- hydroxylated products may be synthesized. For example D-homoprogesterone (**67**) can be converted to various mono- and di-hydroxylated products (Table 5).[91]

**Table 5** Hydroxylation of D-Homoprogesterone (**67**)

| *Microorganism* | *Main product* | *Yield (%)* |
|---|---|---|
| *Aspergillus ochraceus* | 11α-OH | 30 |
| *Calonectria decora* | 12β,15α-$(OH)_2$ | 23 |
| *Fusarium lini* | 15α-OH | 13 |
| *Glomeralla cingulata* | 11α,16β-$(OH)_2$ | 45 |
| *Pelliculariafilamentosa* | 11β,17α-$(OH)_2$ | 44 |
| *Rhizopus arrhizus* | 6β,11α-$(OH)_2$ | 51 |

After hydroxylation of a steroidal substrate has taken place, fission of carbon–carbon bonds may occur. Thus 9α-hydroxylation is the first stage in the fission of the B-ring. This process can be suppressed by restriction of metals (such as iron).[2] This has been accomplished using 2,2-bipyridyl,[93] either alone or in combination with an absorbent such as Amberlite XAD-7. Very substantial enhancements in yield are possible. For example 3-ketobisnorcholenol (**68**) gave <10% yield of the 7α-hydroxy derivative with *Botryodiploida theobromae* in the absence of these materials, but up to 45% when they were added together (equation 23).[94]

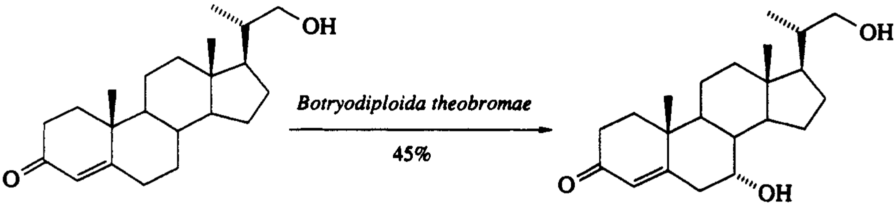

(**68**)

(23)

Side chain degradation is also a common problem, and those substrates with long chains at C-17 (*e.g.* cholesterol) are difficult to hydroxylate without loss or truncation of the hydrocarbon chain.

Chemoselectivity is indeed a very complex issue in the hydroxylation of steroids, but microorganisms capable of chemoselective transformations can often be selected on precedent.[10,13,74]

### *1.4.4.2.2 Regioselectivity*

Aspects of regioselectivity in the microbial hydroxylation of steroids have been reviewed most recently by Kieslich.[13]

The regioselectivity of hydroxylation with a given microorganism is largely dictated by the nature and position of substituents on the steroid substrate; however, a number of microorganisms do show a tendency to hydroxylate in certain positions irrespective of substituent patterns. For example *Rhizopus nigricans* and *Aspergillus ochraceus* have become known as efficient 11α-hydroxylators, *Curvularia lunata* as a 11β-hydroxylator (not as selective), *Calonectria decora* as a 12β,15α-dihydroxylator and *Rhizopus arrhizus* as a 6β-hydroxylator of 3-keto $\Delta^4$-steroids. *Cunninghamella elegans* is not as easy to categorize in this way, although it has been extensively used, but most frequently causes 7α- and 7β-hydroxylation.

Thus the site of hydroxylation may be influenced by the structure of the substrate or the type of microorganism used. The latter effect is evident in the hydroxylation of progesterone (**64**; Table 6).

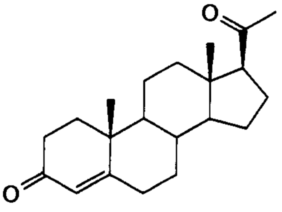

**(64)**

**Table 6** Hydroxylation of Progesterone (**64**)

| *Microorganism* | *Product(s)* | *Yield(s)(%)* | *Ref.* |
|---|---|---|---|
| *Aspergillus ochraceus* | 11α-OH | 91 | 85 |
| *Aspergillus ochraceus* (spores) | 11α-OH | | 95 |
| *Aspergillus phoenicis* | 11α-OH | | 10 |
| *Rhizopus nigricans* | 11α-OH | | 10 |
| *Cunninghamella echinulata* | 11α-OH | 29 | 96 |
| | 17α-OH | 54 | 96 |
| *Mucor* spp. | 14α-OH | | 98 |
| *Streptomyces coriofaciens* | 16α-OH | | 97 |

As in the case of nonsteroidal substrates, the regioselectivity can also be influenced by the stereochemistry of the reactant, for example hydroxylation of the 3α- and 3β-stereoisomers of the androstan-17-one (**69**) by *Calonectria decora* gave different regioisomeric products (Scheme 11).[4] In many cases mixtures of regioisomers are obtained.

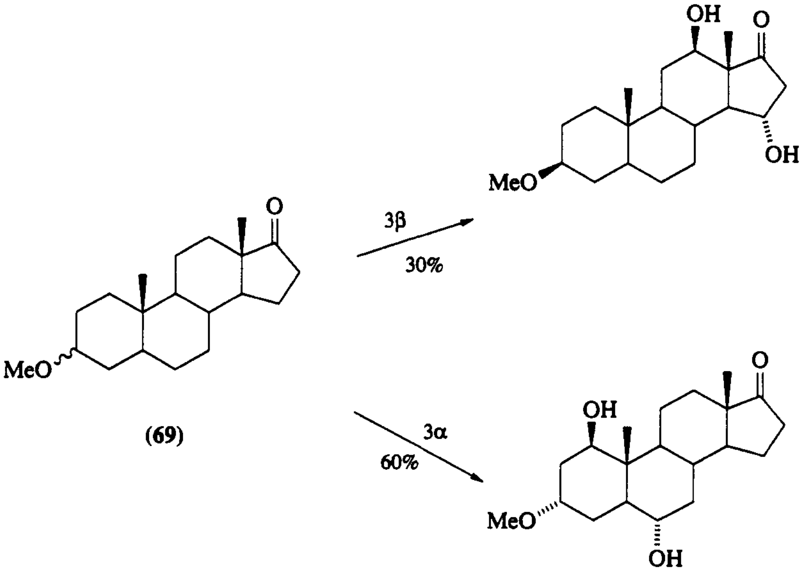

**Scheme 11**

In the case of keto androstanes some attempts have been made to rationalize the site of hydroxylation, particularly with *Calonectria decora* and *Rhizopus nigricans*[82] and a précis is presented elsewhere.[4] As with other substrates, binding of polar groups to the active site of a cytochrome *P*-450 dependent monooxygenase is thought, in most cases, to control both the regio- and stereo-chemistry of hydroxylation (although see 6β-hydroxylation of $\Delta^4$-steroids in Section 1.4.4.2.3). Thus binding of 16β-hydroxy-5α-androstan-3-one (**70**) to the hydroxylase of *Rhizopus nigricans* results in 11α-hydroxylation, but if the keto and alcohol groups are transposed, reversal of the binding orientation results in the 7α-hydroxylated product (**71**).[99] Similarly with *Rhizopus arrhizus*, whilst 9α,10β-androst-4-ene-3,17-dione (**72**) undergoes 11α- and 6β-hydroxylation, 9β,10α-androst-4-ene-3,17-dione (**73**) is 9β-hydroxylated, again due to the reversed binding orientation (Scheme 12).[100]

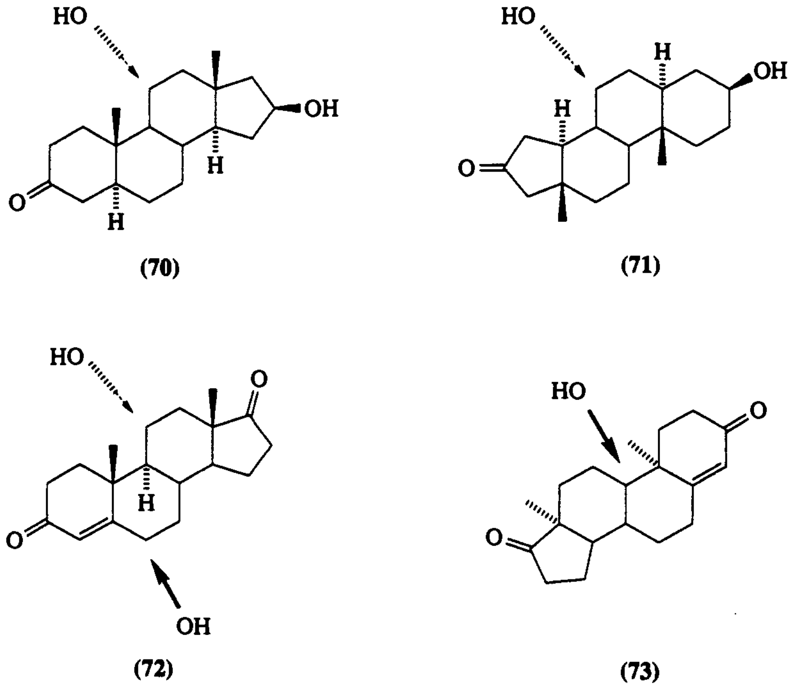

Scheme 12

### *1.4.4.2.3 Stereoselectivity*

Hydroxylation of steroids at unactivated positions occurs exclusively with net retention of configuration, and this is believed to be the case for all cytochrome *P*-450 dependent steroid hydroxylations, irrespective of the microorganism employed.[83a] As in the case of regioselectivity, certain microorganisms have become associated with introducing hydroxy groups with a preferred stereoselectivity irrespective of position hydroxylated. Thus *Calonectria decora* is associated with the introduction of equatorial —OH groups, *Curvularia lunata* an axial —OH group and *Rhizopus nigricans* largely an equatorial —OH group. *Cunninghamella* spp. are less stereospecific, giving both axial- and equatorial-substituted products.

Stereoselectivity will be dictated in most cases by the binding of the substrate to the hydroxylating enzyme. One exception to this occurs in the 6β-hydroxylation of 3-keto $\Delta^4$-steroids. In this case the stereochemistry of substitution at C-6 of the product is determined largely by conventional stereoelectronic processes, as the mechanism is believed to involve axial addition of oxidant to a conjugate of the substrate and the hydroxylating enzyme (equation 24).[83a]

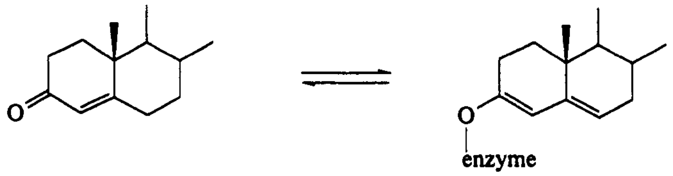

(24)

The principles alluded to above are exemplified by some further steroid hydroxylations in Sections 1.4.4.2.4 and 1.4.4.2.5.

### *1.4.4.2.4 Saturated substrates*

The hydroxylation of 5α-androstanes has previously been discussed on a microorganism basis,[4] and yields of from a few percent up to 50% or better can be achieved. The work has since been extended to cover the microorganism *Leptoporus fissilis* with oxygenated 5α-androstanes[84] and the microbial oxidation of A-nor- and A-homo-5α-androstanes by *Cunninghamella elegans*.[101] The chemically modified steroid (**74**) can be hydroxylated at the 11α-position by *Rhizopus nigricans* when R = H, but when R = Me hydroxylation occurs predominantly at the 1β-position[102] to give the steroid (**75**). Acid-catalyzed rearrangement of the steroid (**75**) can be used to give 1β,3β-dihydroxyandrost-5-en-17-one (**76**; Scheme 13).

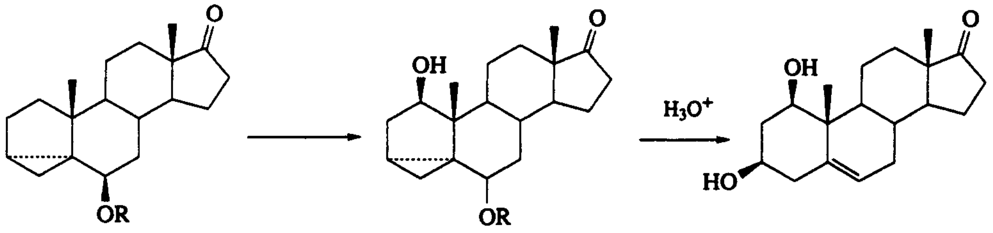

(**74**) (**75**) (**76**)

**Scheme 13**

Substitution on the steroid nucleus by fluorine leads to complicated changes in selectivity, but usually results in hydroxylation at sites remote from the fluorine substituent. Thus 5α-androstan-17-one (**77**) is primarily 7β,11α-dihydroxylated by *Aspergillus ochraceus*, but the 12,12-difluoro derivative (**78**) is 7β-monohydroxylated (Scheme 14).[92]

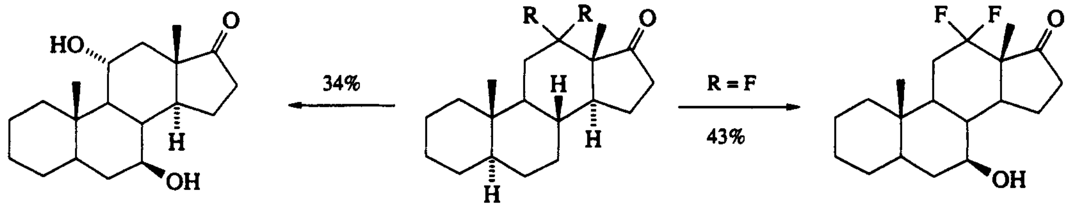

(**77**) R = H
(**78**) R = F

**Scheme 14**

### 1.4.4.2.5 *Unsaturated substrates*

*Aspergillus giganteus* (ATCC 10059) will dihydroxylate progesterone (**64**) to give the 11α,15β-dihydroxy derivative (**79**; equation 25), which is a precursor to the oogonial steroids.[103]

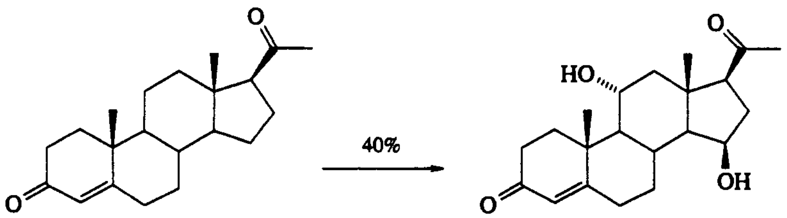

(**64**) (**79**) (25)

Bile acids have historically received much less attention than other steroids, for example the corticosteroids; however, now that useful therapeutic effects are being observed from some bile acids, there is fresh interest in this area. A strain of *Cunninghamella blakesleeana* has been isolated that will 15β-hydroxylate lithocholic acid (**80**; equation 26) in 31% yield.[104] Further reaction is possible[105] to give 3α,11β,15β-trihydroxy-5β-cholanic acid (15%), 3α,15β,18α-trihydroxy-5β-cholanic acid (4%) and 3α,11α,15β-trihydroxycholanic acid (9%). Taurolithocholic acid (**81**; equation 27) can be 7β-hydroxylated in virtually quantitative yield by *Mortierella ramanniana*.[106]

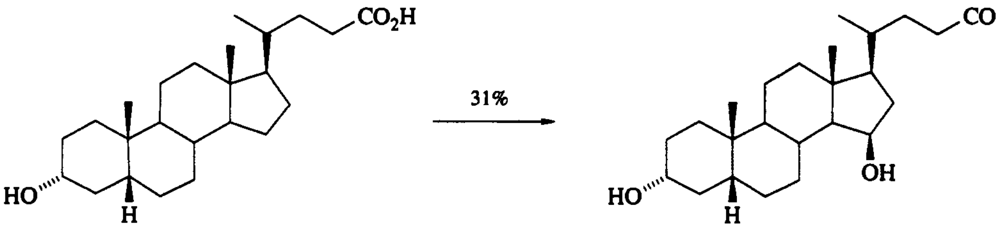

**(80)**

(26)

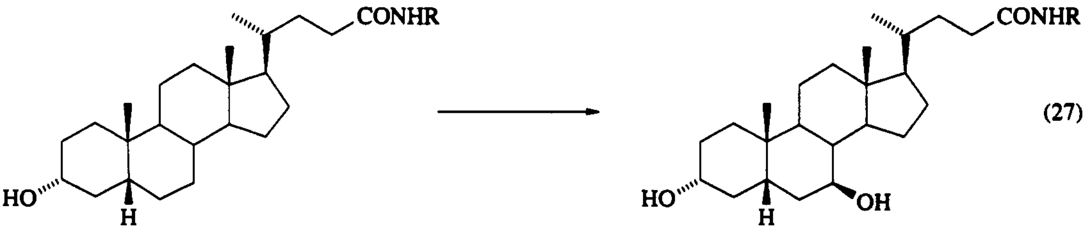

**(81)** $R = CH_2CH_2SO_3H$

(27)

Androst-4-ene-3,17-dione (**72**) can be hydroxylated readily and in high yield, and some examples are given in Table 7.

**Table 7** Hydroxylation of Androst-4-ene-3,17-dione (**72**)

| *Microorganism* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|
| *Neosaltria fisheri* (IFO-5866) | 11α-OH | 40 | 108 |
| *Nocardia canicruria* (ATCC 31548) | 9-OH | 45 | 90 |
| *Penicillium stoloniferum* (CBS P 102) | 15α-OH | 77 | 107 |

19-Hydroxy steroids are important as direct precursors to 19-norsteroids, but are not readily obtainable by microbial hydroxylation without additional nuclear substitution. However a strain of *Pellicularia filamentosa*[109] will 19-hydroxylate cortexolone (**82**; equation 28) successfully. 11β-Hydroxylation of cortexolone derivatives can be accomplished in up to 86% yield using a mutant strain of *Curvularia lunata* (FERM P-8515).[110]

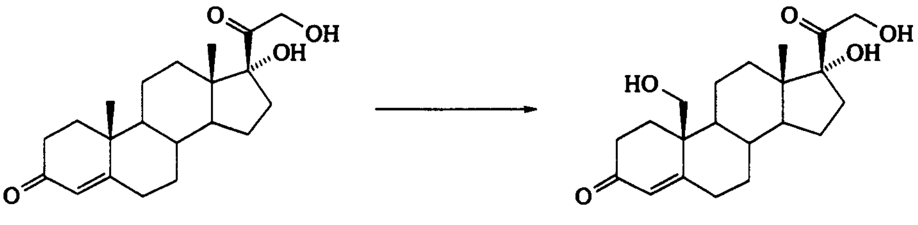

**(82)**

(28)

As a final example, hydroxylation of the $\Delta^5$-steroids (**83**) and (**84**) can be accomplished microbially, and the products are useful in the synthesis of the aldosterone antagonist, spirorenone (**85**; Scheme 15).[111,112]

## 1.4.5 SPECIAL METHODS

In the preceding sections oxidation of unactivated C—H bonds has been discussed, and this is the most useful category of oxidation facilitated by microorganisms. However, although not strictly in this ca-

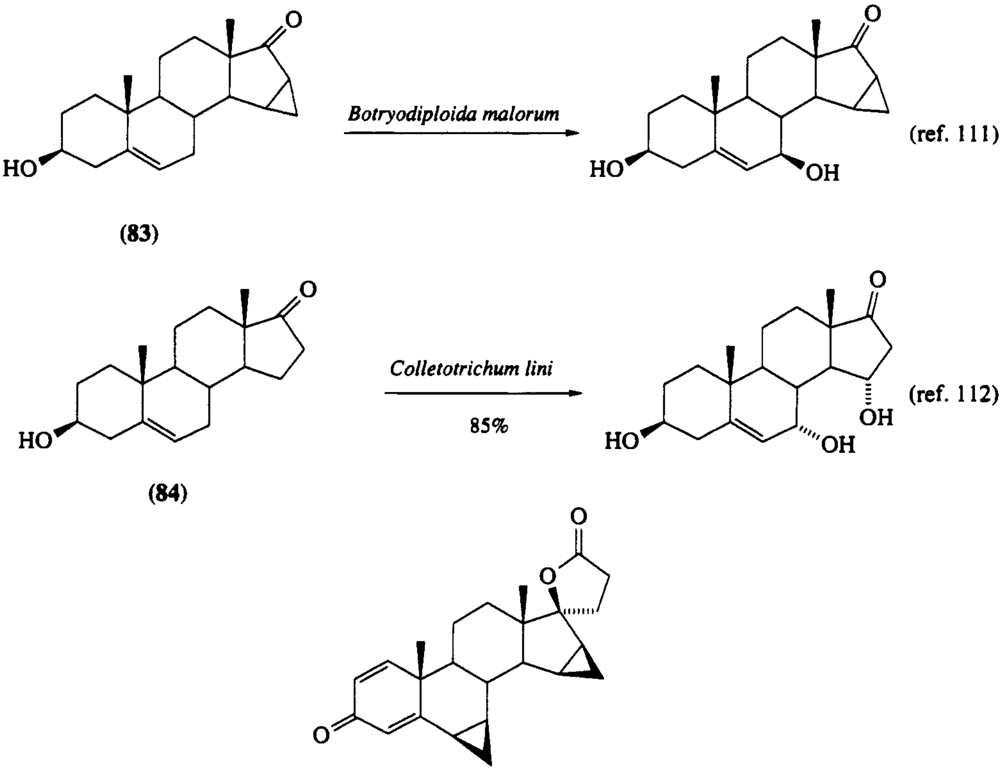

**(83)**

**(84)**

**(85)**

**Scheme 15**

tegory, some useful transformations of allylic, benzylic and aromatic substrates can also be accomplished in this way, and these are therefore considered in Sections 1.4.5.1 to 1.4.5.3.

### 1.4.5.1 Benzylic Substrates

In many cases benzylic oxidation by microorganisms does not stop at the alcohol but proceeds *via* the aldehyde through to the benzoic acid.[2] With some highly substituted substrates, however, good yields of the benzyl alcohol may be obtained. For example *Aspergillus selerotiorum* will convert the toluene derivative (**86**) into the benzyl alcohol (**87**; equation 29) in 66% yield.[113] The same microorganism (IMI 56673), along with *Aspergillus unifer* (NRRL 3228) and *Beauveria sulfurescens*, will convert methylpyridines to the corresponding alcohols, and some results are shown in Table 8.[114] *Penicillium adametzi* and a range of other microorganisms are also useful in benzylic hydroxylations in certain specific cases.[4]

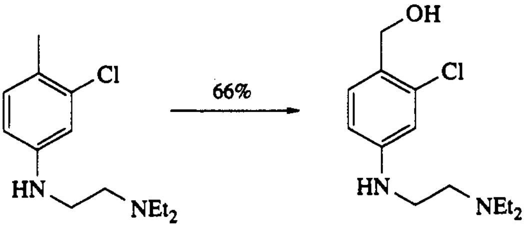

**(86)** **(87)** (29)

*Cunninghamella elegans* has shown a degree of generality in the oxidation of benzylic substrates. For example the tetrahydroquinoline (**88**) is converted to the derivative (**89**; equation 30), but the degree of enantioselectivity is not known.[115] Similarly triprolidine (**90**) is converted to the alcohol (**91**; equation 31) in respectable yield.[116]

**Table 8** Benzylic Hydroxylation of Methylpyridines

| *Substrate* | *Products* | *Yield (%)* |
|---|---|---|
| 2-Me | 2-$CH_2OH$ | 42.7 |
| 4-Me | 4-$CH_2OH$ | 44.4 |
| 2,6-$Me_2$ | 2-Me,6-$CH_2OH$ | 86.7 |
| 4,5-$Me_2$ | 4-Me,5-$CH_2OH$ | 81.7 |

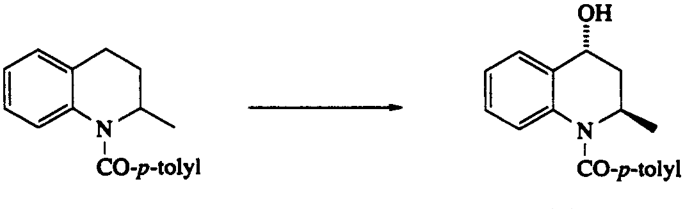

**(88)** **(89)**

(30)

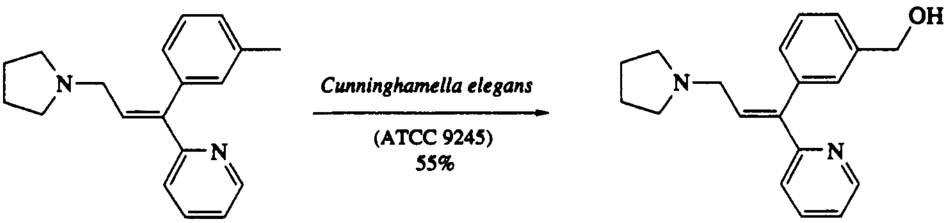

**(90)** **(91)**

(31)

The fungus *Mortierella isabellina* (NRRL 1757) hydroxylates the ethylbenzenes (**92**) to the 1-arylethanols (**93**; equation 32) with a degree of enantioselectivity as shown in Table 9. By-products resulting from terminal carbon hydroxylation and overoxidation (acetophenones) are also obtained.[117]

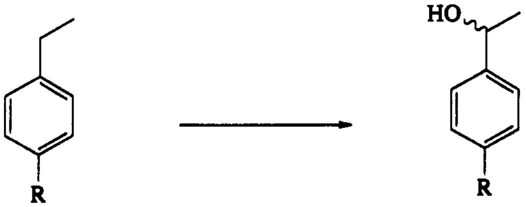

**(92)** **(93)**

(32)

**Table 9** Benzylic Hydroxylation of Ethylbenzenes by *Mortierella isabellina*

| *R* | *Yield (%)* | *ee (%)* | *Configuration* |
|---|---|---|---|
| H | 10 | 33 | (*R*) |
| CN | 60 | 39 | (*R*) |
| Cl | 30 | 34 | (*S*) |
| Pr | 45 | 25 | (*R*) |
| $NO_2$ | 40 | 9 | (*R*) |
| Me | 4 | 20 | (*R*) |

*Cunninghamella echinulata* (ATCC 26269) and *Helminthosporium* spp. (NRRL 4671) are also useful in the benzylic oxidation of ethylbenzenes, both exhibiting enantioselectivities similar to *Mortierella isabellina*.[117] The enzyme responsible for these transformations has the characteristics of a cytochrome *P*-

450 dependent monooxygenase and no contribution from an alcohol–carbonyl interconversion at C-1 is observed.

Benzylic oxidations to give aldehydes (rare) and carboxylic acids have been considered previously.[2]

### 1.4.5.2 Allylic Substrates

There are few examples of synthetically useful allylic hydroxylations except in the steroidal field (Section 1.4.4.2), although some others are shown in Sections 1.4.3.3 and 1.4.1. Previous reviews on microbial oxidation[3,4] have also included some examples of allylic oxidations.

Good regioselectivity is obtained in the allylic hydroxylation of β-damascone (**94**) by *Botryosphaeria rhodina* (equation 33),[118] with the allylic hydroxylation product (**95**) being preferred over the homoallylic one (**96**). Little work seems to have been done on comparing microbial and chemical allylic oxidation methods, although in at least some cases microbial oxidation shows better selectivity to the alcohol and less over oxidation to carbonyl compounds than chemical methods. For example oxidation of the terminal allylic methyl group in novobiocin (**97**; equation 34) and related antibiotics by *Sebekia benihana* (NRRL 11111) is superior to chemical methods.[119] A similar terminal methyl allylic oxidation on an acyclic terpene has also been affected by a *Nocardia* microorganism (FERM-P 1609).[120a]

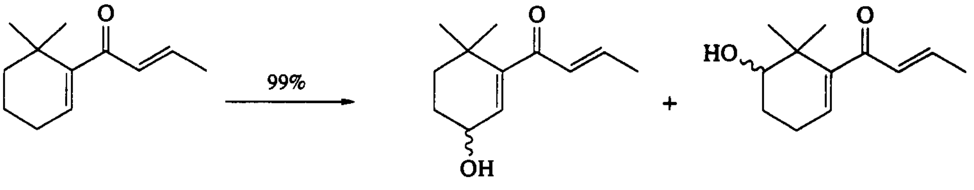

(33)

(**94**) (**95**) 98% (**96**) 2%

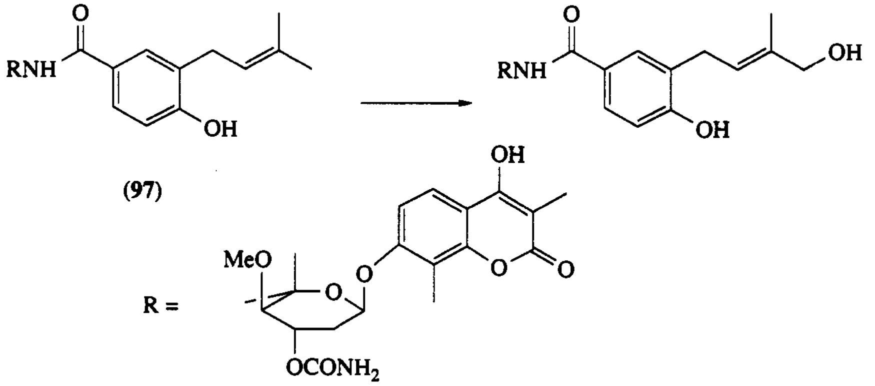

(34)

(**97**)

Allylic hydroxylation of Δ$^4$-steroids at the 6β-position and Δ$^5$-steroids at the 7-position is possible using a wide range of microorganisms,[2,10] including *Cunninghamella elegans* and *Rhizopus nigricans*.

Milbemycin derivatives can be stereoselectively hydroxylated at the allylic 13β-position by a variety of microorganisms including *Streptomyces violascens* (ATCC 31560), *Streptomyces carbophilus* (FERM BP-1145) or *Streptomyces diastatochromogenes* (ATCC 31561), and in preparatively useful yields.[120b]

In the general case of unsaturated substrates, double bond attack or migration may take place during microbial oxidation; numerous examples of the latter are to be found in the steroidal field,[2] and less commonly with other classes of substrate. Thus the antibiotics compactin (**98**) and monacolin-K (**99**) can be hydroxylated at the allylic 3- and 8a-positions by *Syncephalastrum nigricans* (SANK 42372) [3α, 26% from (**98**)],[121] *Mucor hiemaliis* (SANK 36372) [3β, 72% from (**98**)][122] or *Schizophyllum commune* [8a, 80% from (**98**)].[123] However hydroxylation of (**98**) with a *Nocardia* species gave rearrangement as well as hydroxylation to give the allyl alcohol[124a] (**100**; R = H), and the use of *Mucor heimaliis* with (**99**) gave the corresponding 6α-hydroxy derivative (**100**; R = Me) as shown in equation (35).[122]

In other examples of allylic hydroxylation, *Streptomyces roseosporus* A-5797 (FERM BP-1574), *Streptomyces sclerotialus* (FERM BP-1370) or *Nocardia autotrophica* (FERM BP-1573)[124b] and *Botrytic cincerea*[124c] have proved useful.

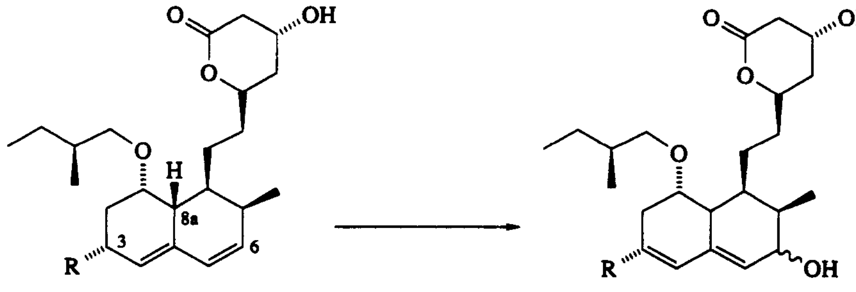

(98) R = H; (99) R = Me

(100)

(35)

### 1.4.5.3 Nuclear Hydroxylation of Aromatic Hydrocarbons

Much work has been devoted to this area but a large part of this has been on metabolic studies[5] and little can be truly said to be synthetically useful. As with chemical oxidations on aromatic rings, a fundamental problem with microbial oxidations is that once hydroxylated the aromatic ring becomes more susceptible to further degradation. Nevertheless some useful transformations have been accomplished, and many of these have been reviewed previously.[3,4] An impressive example is the conversion of L-tyrosine (**101**) into L-DOPA (**102**; equation 36).

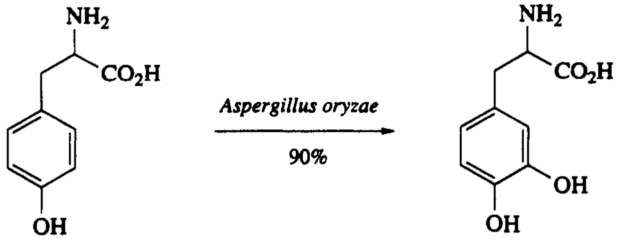

(101)

(102)

(36)

Microbial *ortho-* and *para*-hydroxylation reactions are considered to proceed *via* the arene oxide,[125] and a phenomenon known as the NIH shift is commonly found to occur (Scheme 16) with di- or polysubstituted substrates.

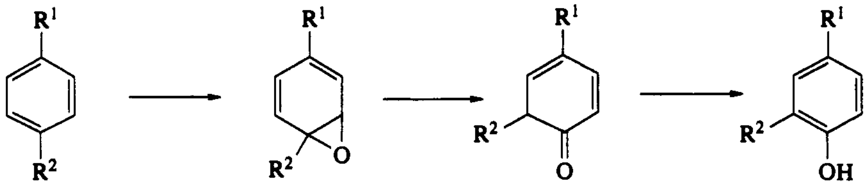

**Scheme 16**

Fungi appear to preferentially *ortho*-hydroxylate monosubstituted arenes,[125] however there are some exceptions. For example, the near ubiquitous fungus *Beauveria sulfurescens* (ATCC 7159) will hydroxylate the herbicide Propham (**103**) to give a 49% yield of *para*-substituted products (**104**; equation 37),[126] about half of which were *O*-glycosated.

Biphenyl (**105**) can be hydroxylated to either the mono- or di-hydroxylated derivatives. This is perhaps surprising considering the fungicidal properties of these materials; however, acclimatization of the microbe with monohydroxylated products allows a satisfactory rate of reaction. The 4,4′-dihydroxy isomer (**106**; equation 38) may be produced using *Absidia pseudocylindrospora* (NRRL 2770)[127] whilst *Pseudomonas* SG 1043 (FERM-P 4471) gives a mixture of 2- and 3-monohydroxy derivatives, in a ratio of 3:1.[128a]

Species of the *Aspergillus* genus (particularly various strains of *Aspergillus niger*) will also *p*-hydroxylate aromatics and accumulation of products can be good. Other substrates can be *p*-hydroxylated in

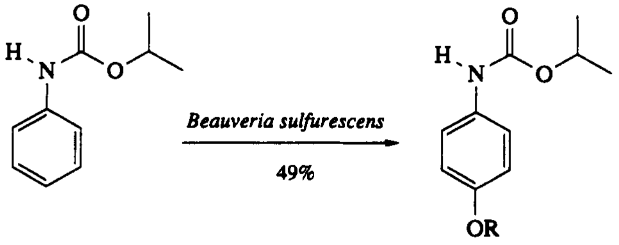

**(103)** **(104)** (37)

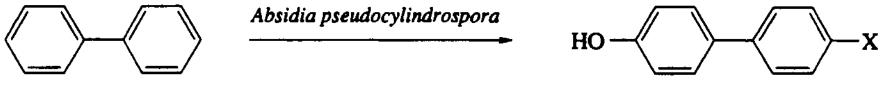

**(105)** **(106)** X = OH (38)

good yield by *Cunninghamella echinulata*,[128b] *Streptomyces rimosus* (ATCC 10970) or *Nocardia lyena* (ATCC 21430).[128c]

Methylotropic bacteria (for example *Methylomonas methanica*) will hydroxylate aromatics when methane or the like is also provided as a carbon source,[129] and as in the case of aliphatic hydrocarbons further developments are likely as new strains of these bacteria are isolated.

Little is known about the hydroxylation of heterocyclic substrates, and more experimental work is needed in this area. *Achromobacter xylosoxydans* (DSM 2783) and *Pseudomonas putida* (NCIB 8176 or 10521) are particularly effective in the hydroxylation of nicotinic acid (**107**) to 6-hydroxynicotinic acid (**108**; equation 39), and commercial processes capable of giving up to 97% yield have been developed.[130] It is interesting to note that in this case the product is precipitated as it forms by formation of its magnesium or barium salt, and this could serve to protect the product from further degradation as well as facilitating its recovery.

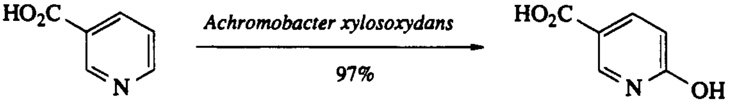

**(107)** **(108)** (39)

Benzimidazole can be hydroxylated in the 5-position by spores of *Absidia spinosa* and by microorganisms of the class micromycetes.[131]

## 1.4.6 ALTERNATIVES TO MICROORGANISMS

Microorganisms contain a multitude of enzyme systems, some of which are not directly involved in their use in chemical oxidations, but which are necessary for the cell to function in total. As discussed previously these ancillary enzymes can be harmful, and ways of reducing or avoiding their effects have been sought; two of these are considered in the following sections.

### 1.4.6.1 Oxidations with Isolated Enzymes

Isolated single enzymes have the potential advantage of totally specific transformations.[132,133] However this is often offset by disadvantages such as instability, the need to add or recycle cofactors, and the difficulty in obtaining suitable enzymes for oxidation of unactivated C—H systems.[132]

The nuclear hydroxylation of aromatics can be catalyzed by horseradish peroxidase, and with suitably activated substrates synthetically useful yields can be obtained.[134] The reactions are usually carried out at 0 °C in the presence of dihydroxyfumaric acid cofactor and a source of oxygen. Thus L-DOPA (**102**) has been prepared using this system.[135]

A general review on oxygenase-catalyzed hydroxylation of aromatic compounds has appeared, which discusses this area in greater detail.[136]

A bacterial methane monooxygenase that catalyzes the hydroxylation of saturated hydrocarbons[137] has been isolated, but there are severe limitations in practical use.[132] Similarly the enzymes involved in steroid hydroxylation have been isolated and used *in vitro*,[138,139] but this practice is not sufficiently well refined for general use in organic synthesis.

The cytochrome *P*-450 responsible for the hydroxylation of camphor by *Pseudomonas putida* has been isolated, and is, in contrast to most others, stable.[140] However this enzyme will only hydroxylate substrates closely related to camphor, and the site of hydroxylation may vary with substrate. Thus camphor gives the *exo*-5-hydroxy derivative but 5,5-difluorocamphor gives the 9-hydroxy derivative.[141]

### 1.4.6.2 Oxidation with Spores

In some cases improved selectivity in a microbial oxidation may be achieved by using spores rather than bacteria or fungal mycellium.[4] The technique has been largely restricted to the steroid area, with $\Delta^1$-dehydrogenation being the most common use.[2] In hydroxylation reactions the spores of *Aspergillus ochraceus* and *Cunninghamella elegans* have proved particularly useful,[142] and in general the spores produce the same hydroxylation product as the derived microorganism. A limitation of the technique is that not all microorganisms produce spores.

## 1.4.7 REFERENCES

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# 2.1

# Oxidation Adjacent to C=C Bonds

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## 2.1.1 INTRODUCTION

Allylic oxidation remains a reaction of considerable value in organic synthesis. Oxidation reactions in this section are divided into two types: reactions which produce allylic alcohols (equation 1) and those which produce α,β-unsaturated aldehydes or ketones directly (equation 2). Examples from the recent literature fall approximately equally into each type. Examples of allylic oxidations which occur with rearrangement (equation 3 and 4) or give mixtures are discussed individually within each reagent type; however, it is fair to say that many reagents and reaction conditions can give either direct oxidation or oxidative rearrangement, and almost no allylic oxidation system exclusively gives one course of reaction in all cases. In many examples the course of oxidation depends mostly upon substrate structure.

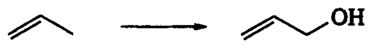

(1)

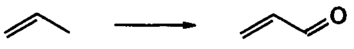

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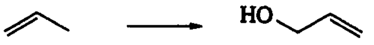

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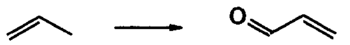

(4)

For most reagents this pattern is multiplied in cases where several similar possible sites of oxidation exist around a particular double bond. While chemoselectivity and stereoselectivity are often good, poor regioselectivity is a weakness afflicting many allylic oxidation methods.

Among oxidations producing allylic alcohols or their derivatives the modern variants of selenium dioxide oxidations are by far the most popular. Systems based on metal acetates, particularly palladium trifluoroacetate, can be very useful and are receiving increasing attention; but the Kharasch–Sosnovsky reaction, once very common for allylic oxidation, is now rarely used. Sensitized photooxidation with singlet oxygen, a very well-known procedure, is still somewhat unpredictable and has perhaps received less consideration than it deserves.

Fewer methods exist for direct allylic/benzylic oxidation to give α,β-unsaturated carbonyl compounds. Some of these occur by initial oxidation to the allylic alcohol, followed by a second oxidation or oxidative rearrangement step, and reagent systems often give mixtures of alcoholic and carbonylic products. The most valuable methods for direct oxidation to enones involve chromium(VI), palladium or selenium reagents, but none had proved particularly satisfactory in terms of predictability, selectivity and generality until the development of the chromium trioxide–3,5-dimethylpyrazole complex, no doubt the best system currently available.

It is interesting to note that few examples of propargylic oxidation were found for either type of oxidation reaction.

## 2.1.2 ALLYLIC OXIDATION REACTIONS WHICH PRODUCE ALLYLIC ALCOHOLS, ESTERS OR ETHERS

### 2.1.2.1 Selenium Dioxide Based Reagents

### *2.1.2.1.1 Stereochemistry and mechanism*

Selenium dioxide is still regarded as the most reliable and predictable reagent for this transformation, particularly for more substituted alkenes. A number of reviews of the reaction are available in the literature.[1] Selenium dioxide generally produces unrearranged (*E*)-allylic alcohols, an ene reaction–2,3-sigmatropic rearrangement sequence being the probable major pathway, and while several methods for the oxidation of allylic C—H bonds to produce alcohols are now available, the majority of recent synthetic examples have involved selenium methodology. Several studies of the stereochemistry and mechanism of selenium dioxide allylic oxidations have been carried out over the years and indeed a set of rules for predicting the outcome of such reactions appeared as early as 1939.[2] These studies serve to indicate the complexity of this reaction and the difficulties often observed in predicting its regio- and stereo-chemical outcome. Apart from allylic alcohols, other possible products are dienes, esters, ethers, enones, α-diketones and glycols. Following a number of less conclusive studies,[3] in 1970 Trachtenberg[4] examined the oxidation of a variety of substituted cyclohexene systems. Under conditions of refluxing wet dioxane solution and a deficiency of oxidant they obtained mostly unrearranged allylic alcohols, although enones were also observed in some cases. In contrast to earlier work they suggested that tertiary positions are preferentially oxidized over secondary, and secondary positions over primary ($CH > CH_2 > CH_3$). They further found the reactions to be stereoselective, pseudoaxial alcoholic products being favored in cyclic systems (*e.g.* equation 5).

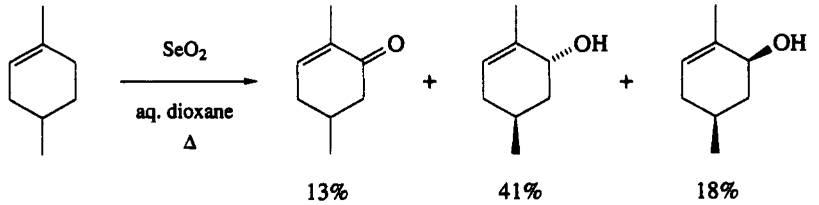

(5)

Early proposals concerning the mechanism of selenium dioxide allylic oxidations involved solvolysis of allylseleninic acid intermediates or free radical processes.[1,2,5,7,8] Trachtenberg[4] and Schaefer[7] discounted the involvement of allylseleninic acids on the grounds of inertness towards solvolysis, and subsequent work showed that radicals are not involved.[6,7] In order to explain his findings Trachtenberg[6] suggested a mechanism proceeding through an oxaselenocyclobutane intermediate (Scheme 1). This mechanism was preferred to those of Schaefer (Scheme 2)[7] and Wiberg[8] on stereochemical and other grounds.

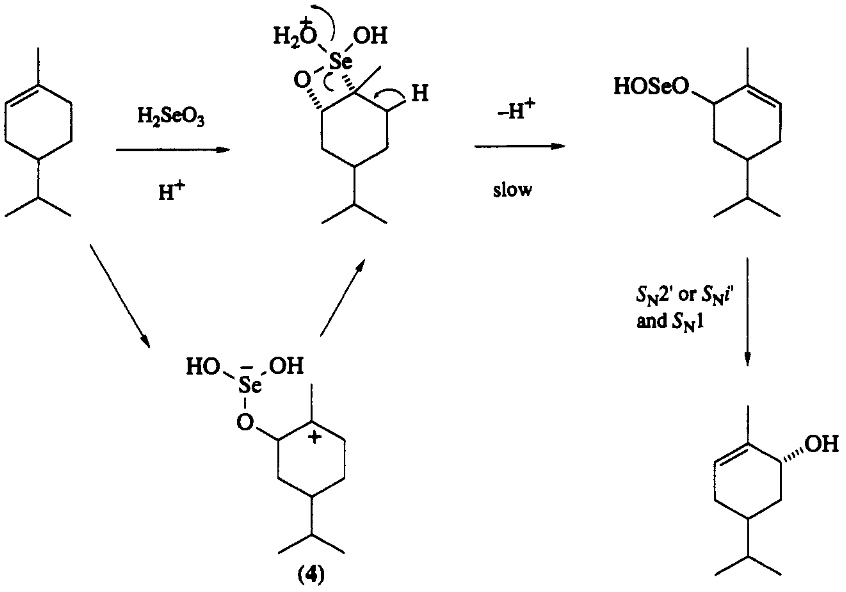

**Scheme 1**

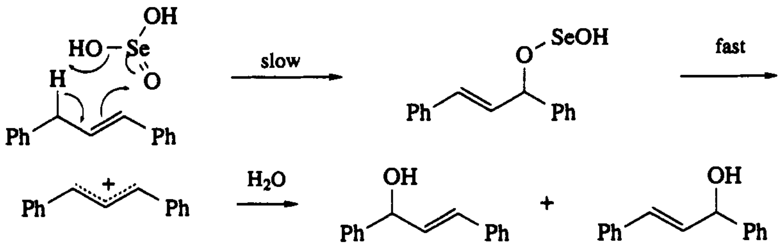

**Scheme 2**

A more complex picture was painted in a further study by Rapoport,[9] which indicated that both the mechanism and reactivity sequence are dependent upon the alkene structure and reaction conditions:[10] 1,2-disubstituted alkenes (**1**) reacting *via* an oxaselenocyclobutane intermediate with a reactivity sequence CH > CH$_2$ > CH$_3$; geminally disubstituted alkenes (**2**) with a reactivity sequence CH > CH$_2$ > CH$_3$; and trisubstituted alkenes (**3**) with a reactivity sequence CH$_2$ > CH$_3$ > CH, (*E*)-allylic alcohols being the preferred products as established by Büchi;[11] types (**2**) and (**3**) reacting *via* carbenium ion intermediates (**4**) without four-membered ring closure or by unspecified cyclic transition states. Rapoport's evidence also showed the final step to occur by $S_Ni'$ or $S_N1$ processes and not by $S_N2'$. Monosubstituted alkenes, particularly arylpropenes, commonly react with rearrangement.[2,12]

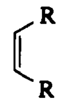

(1)

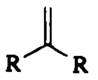

(2)

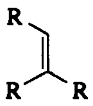

(3)

A new mechanism, now generally accepted, was proposed by Sharpless in 1972.[13] Following some elegant experimental work, Sharpless suggested that allylseleninic acids are indeed intermediates, but that they react by 2,3-sigmatropic rearrangement (well known for the analogous allylic sulfinates and sulfoxides) rather than by solvolysis. The fully regio- and stereo-specific sequence consists of two consecutive pericyclic reactions (an ene reaction followed by the sigmatropic rearrangement), and subsequent selenite ester hydrolysis (Scheme 3). Evidence for an initial ene reaction was provided by isolation from appropriate substrates of selenino ketones (5), presumed to be trapped forms of the allylseleninic acid intermediates (*e.g.* equation 6). However, while this mechanism does neatly explain the preference for (*E*)-allylic alcohol formation by invoking steric effects in the six-membered ring chair transition state of the sigmatropic rearrangement, it also implies a much higher level of stereo- and regio-control than is commonly observed. Stephenson[14] rationalized these facts on the basis of some careful kinetic isotope effect studies by proposing a mixture of the stereocontrolled Sharpless mechanism and a stereorandom ionic ene reaction equivalent, perhaps involving a carbon-bonded selenium-containing carbenium ion such as that shown in equation 7. Stephenson also comments that the ionic processes are suppressed in basic media, the Sharpless mechanism then being predominant. A similar ene reaction/2,3-sigmatropic rearrangement mechanism incorporating an alternative explanation for reduced regio- and stereo-selectivity was put forward in 1980 by Woggon[15] following a $^{13}$C-labeling study (Scheme 4).

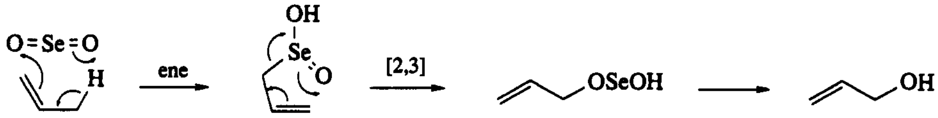

Scheme 3

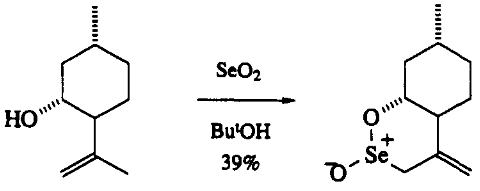

(5)

(6)

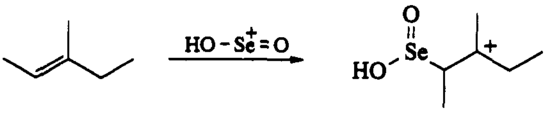

(7)

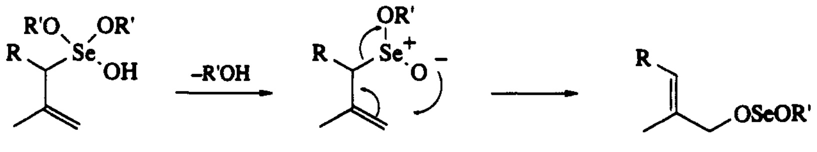

Scheme 4

### 2.1.2.1.2 Synthetic examples

Among early synthetic examples of selenium dioxide allylic oxidation[16a] is Rapoport's synthesis of sirenin (6).[16b] Oxidation of (7) with selenium dioxide in ethanol at 90 °C for 13 h gave a mixture of allylic alcohol (**8**) and aldehyde (**9**; equation 7a). The reaction was apparently regiospecific and it is valuable to note the survival of the three-membered ring under these conditions. Rapoport has also reported the oxidation of *cis–trans* mixtures of allylic alcohols to give all-*trans* $\alpha,\beta$-unsaturated aldehydes using the same reagent.[17] A mechanism proceeding through allylic selenite esters was proposed (Scheme 5) and the reaction applied to a synthesis of squalene.

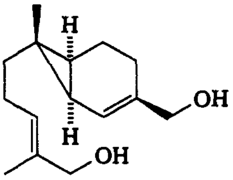

(**6**)

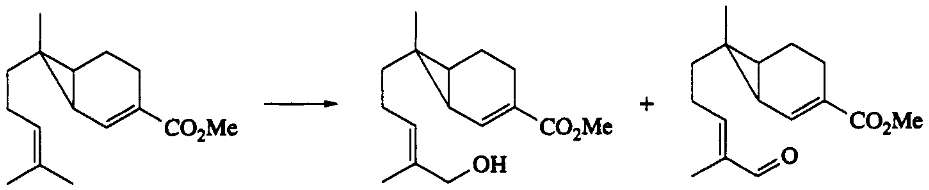

(**7**) (**8**) (**9**)

(7a)

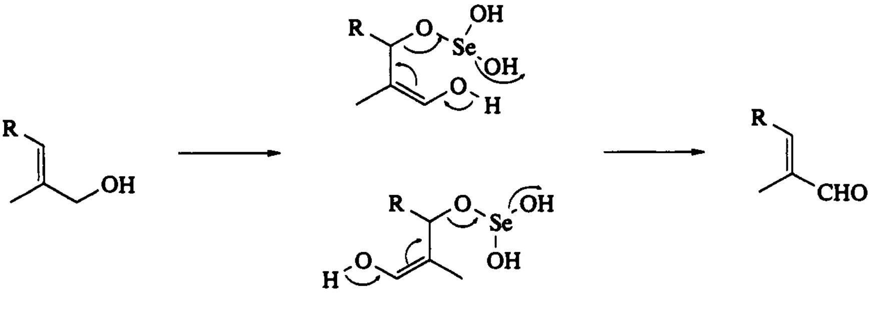

**Scheme 5**

While most synthetic examples of selenium dioxide allylic oxidation now involve more sophisticated systems (see below), use of the simple stoichiometric reagent alone is still popular.[12,18] One recent example which well illustrates the mildness and possible selectivity of the reaction is shown in equation (8).[18a]

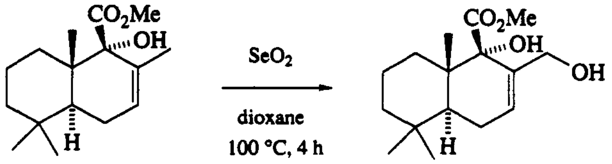

(8)

In this regiospecific oxidation, taken from a synthesis of (–)-warburganal (**10**) from glycyrrhetinic acid (**11**), only allylic methyl group oxidation occurred, no overoxidation or competing reactions at the tertiary alcohol or ester groups being reported. The reaction conditions, selenium dioxide in dioxane solution at 100 °C for 4 h, are typical, although one very recent example used *t*-butyl alcohol as solvent to produce the sensitive diol (**13**; equation 9).[19]

Selenium dioxide has also been used in combination with pyridine for the preparation of acid-sensitive materials.[20]

A useful modification of selenium dioxide allylic oxidation was introduced by Sharpless in 1977.[21] An inevitable complication of the normal reaction is the production of odoriferous low-valent selenium species which may be difficult to remove from the product mixtures and which can give rise to organoselenium by-products.[22] Sharpless provided a solution to this problem by the introduction into the re-

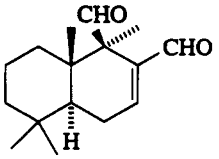

**(10)**

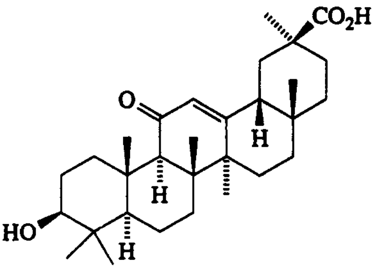

**(11)**

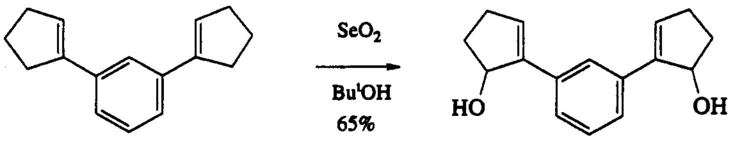

**(12)** **(13)** (9)

action of a selective reoxidant for selenium. While the use of hydrogen peroxide[23] tends to give rise to epoxide products, *t*-butyl hydroperoxide is successful and often results in higher yields and a cleaner reaction, although further oxidation of allylic alcohol competes in some cases. Propargyl substrates generally undergo α,α′-dioxygenation.[24] Oxidation of more substituted alkenes can also be carried out at room temperature under catalytic conditions (1.5–2% $SeO_2$) using *t*-butyl hydroperoxide as reoxidant, and is then most efficient in methylene chloride solution using 3 to 4 equiv. of reoxidant. Some alkenes require water or carboxylic acid catalysis, and indeed in the presence of a hydroxylic solvent the reagent may be selenious acid or an alkyl selenite. Less substituted and unreactive alkenes are not efficiently oxidized using the catalytic system or in the absence of reoxidant; but use of stoichiometric selenium dioxide in combination with 2 equiv. of *t*-butyl hydroperoxide in methylene chloride solution provides a very mild and general allylic and propargylic oxidation reagent. Indeed, this reagent combination is probably still the best currently available for selective allylic oxidation without rearrangement.

Under these conditions for 2 h at room temperature germacrane-type sesquiterpene lactones (**14**), (**15**) and (**16**) were all regio- and stereo-selectively oxidized at C-14 to give the corresponding allylic alcohols (**17**), (**18**) and (**19**), in which the double bond geometry within the 10-membered ring has been inverted.[25] Compound (**17**) was formed in 90% yield, the only observed by-product being aldehyde (**20**; 5%). The authors proposed an ene reaction–2,3-sigmatropic rearrangement pathway similar to those of Sharpless and Woggon but in which the initial reaction is the formation of an activated selenium *t*-butyl hydroperoxide species which undergoes the ene reaction (Scheme 6). The authors also comment that catalytic amounts of selenium dioxide suffice for the reaction.

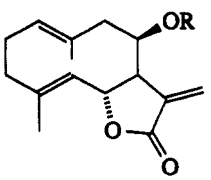

(**14**) R = Ac
(**15**) R = X
(**16**) R = $SO_2Me$

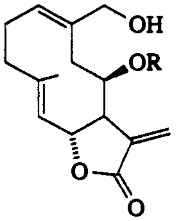

(**17**) R = Ac
(**18**) R = X
(**19**) R = $SO_2Me$

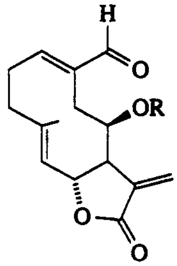

(**20**)

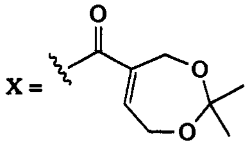

The selectivity of the reaction is nicely illustrated by the oxidation under similar conditions of 6-*N*-(3,3-dimethylallyl)adenosine (**21**), which regiospecifically gave (*E*)-zeatine β-D-ribofuranoside (**22**), none of the other functionality within the molecule being affected.[26]

The isomeric (*Z*)-zeatine riboside was obtained from (**22**) by UV irradiation induced equilibration.

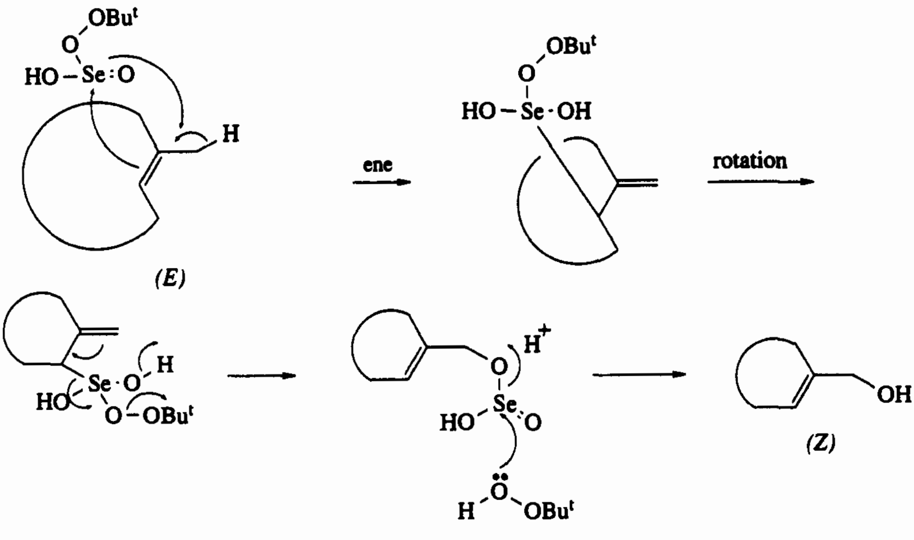
OBu$^t$
HO–Se:O
H
(E)
ene
HO–Se·OH
rotation
Se·O
HO
O–OBu$^t$
H$^+$
Se
HO
O
H
OBu$^t$
OH
(Z)

**Scheme 6**

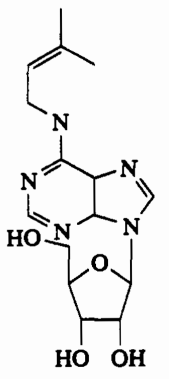

**(21)**

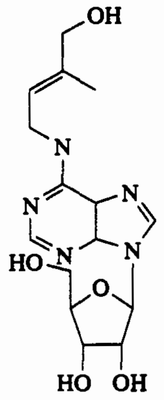

**(22)**

The possible regioselectivity and the preference for (*E*)-allylic alcohol production using the reoxidative modification are demonstrated in a projected synthesis of cembranolides (equation 10).[27] The substrate in this case contains two double bonds and several allylic positions. This oxidation is reported to be even more selective than the analogous oxidation of geranyl acetate originally reported by Sharpless.

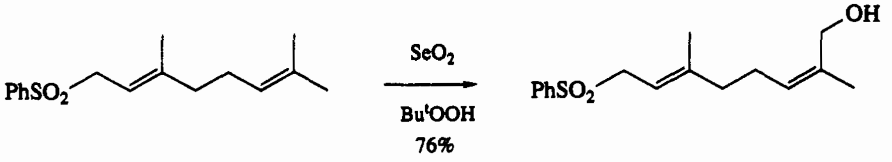
PhSO$_2$
SeO$_2$
Bu$^t$OOH
76%
PhSO$_2$
OH

(10)

An allylic oxidation of neryl acetate, apparently using partially catalytic conditions (0.25 equiv. $SeO_2$, 2 equiv. TBHP), has recently been reported (equation 11).[28] While this reaction is described as highly selective, it should perhaps be noted that the product was obtained in only 45% yield.

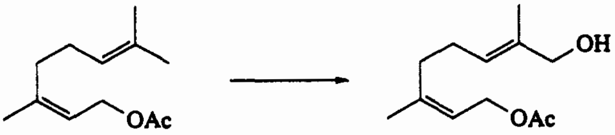

(11)

The method has also recently been used in a short synthesis of lipoic acid (Scheme 7)[29] and featured in MacMillan's conversion (equation 12a)[30] of gibberellin $A_3$ (**23**) into gibberellins $A_{67}$ (**24**) and $A_{68}$ (**25**), and in Mander's conversion of gibberellin $A_7$ (**26**) into antheridic acid (equation 12b).[31] In these last two examples the terminally disubstituted alkenes were oxidized with almost complete stereoselectivity to give the 15-hydroxy products consistent with sterically controlled approach of the reagent. The trisubstituted double bond in equation (12b) was unaffected, as was the remaining functionality in both substrate molecules.

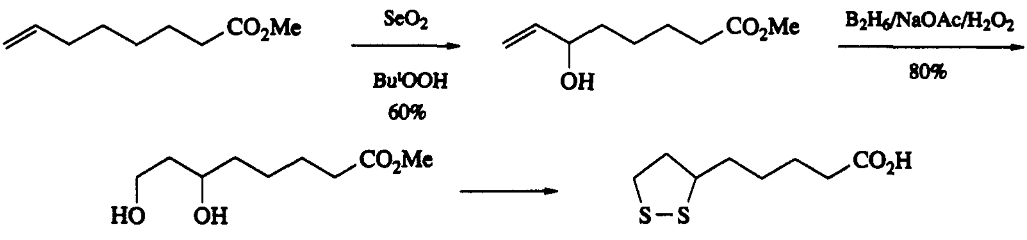

Scheme 7

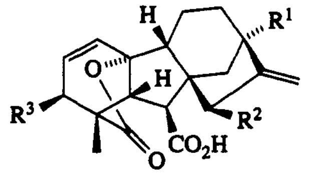

(**23**) $R^1$ = OH, $R^2$ = H, $R^3$ = OH

(**24**) $R^1$ = OH, $R^2$ = OH, $R^3$ = H

(**25**) $R^1$ = H, $R^2$ = OH, $R^3$ = OH

(**26**) $R^1$ = H, $R^2$ = H, $R^3$ = OH

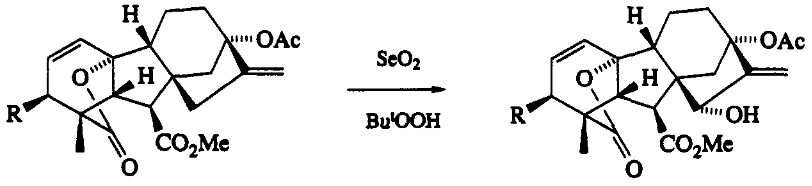

(12a)

R = H, OAc

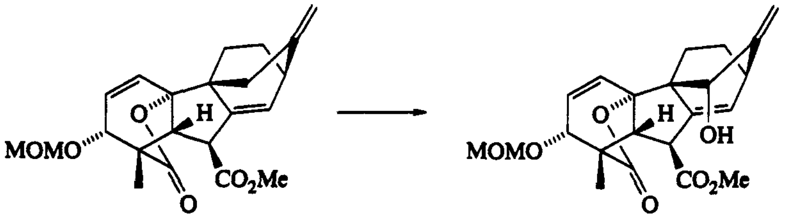

(12b)

A number of reoxidants for selenium dioxide have been examined. For example, while hydrogen peroxide is sometimes successful,[23] oxidation of cholecalciferol (**27**) or derivatives with selenium dioxide alone gave poor results not improved by addition of hydrogen peroxide. In this case, use of sodium periodate or tetra-*n*-butylammonium periodate gave increased yields.[32] The reaction was much improved when carried out under reflux in methanol or solvent mixtures containing methanol, and indeed selenous acid and dialkyl selenites, suggested as intermediates in the reaction, both accomplished a similar oxidation in nonalcoholic solvents in the presence of a reoxidant, *N*-methylmorpholine *N*-oxide proving superior.

Double allylic oxidation at the allylic methyl and methinyl positions of drimenyl acetate (**28**) was achieved[33] in boiling dioxane solution using 'catalytic amounts' of selenium dioxide in the presence of

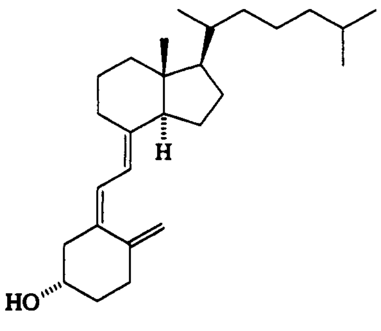

**(27)**

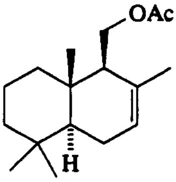

**(28)**

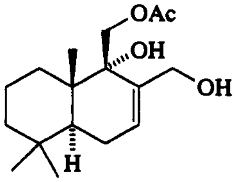

**(29)**

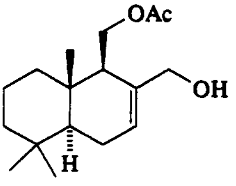

**(30)**

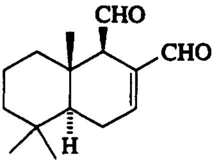

**(31)**

bis(4-methoxyphenyl) selenoxide (1.5 equiv.) as reoxidant.[34] Compounds (**29**; 60%) and (**30**; 30%) were both isolated from the reaction mixture. Compound (**30**) was used for a synthesis of (–)-polygodial (**31**).

Ethers (**32**) and peroxides (**33**) are seen as by-products in the catalytic selenium dioxide oxidation of cycloalkenes, and these materials can predominate in the case of small rings.[35] Addition of hydroquinone to the reaction mixtures suppresses their formation and consequently a free radical pathway has been proposed (Scheme 8).

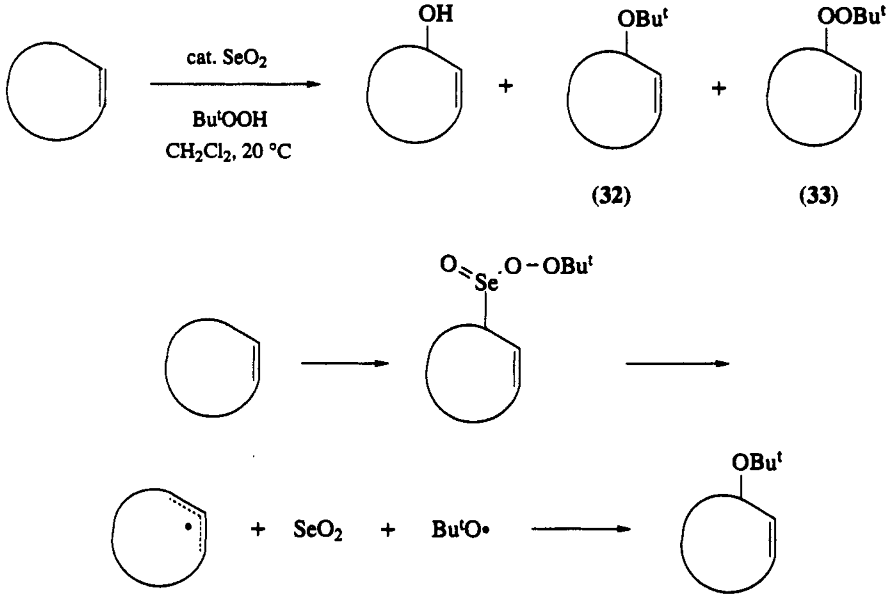
cat. SeO$_2$
Bu$^t$OOH
CH$_2$Cl$_2$, 20 °C
OH
+
OBu$^t$
+
OOBu$^t$
(32)
(33)
O=Se-O-OBu$^t$
+ SeO$_2$ + Bu$^t$O•
OBu$^t$

**Scheme 8**

Selenium dioxide has been used supported on silica gel in combination with *t*-butyl hydroperoxide in hexane or dichloromethane solution.[36]

Sharpless has achieved the allylic oxidation of alkenes using arylselenenic acids, generated *in situ* from the diselenide and *t*-butyl hydroperoxide, a reaction claimed to occur with exclusive allylic rearrangement.[37]

### 2.1.2.2 Metal Acetates and Related Reagents

#### 2.1.2.2.1 Mercury and related metals

Rappoport[38] and Muzart[39] have noted that the reaction of alkenes with metal acetates and related derivatives,[40,41] including those of mercury,[42] palladium (Section 2.1.2.2.2), thallium, manganese, silver and lead, can give rise to a variety of products including π-complexes, addition products, acetates, diacetates, rearrangement products and allylic esters. Lead tetraacetate in general gives mixtures of substitution, rearrangement and addition products, and is usually not a synthetically useful reagent for allylic oxidation.[40,41a] Thallium triacetate, while a more powerful oxidizing agent than mercury(II) acetate, normally gives allylic oxidation only as a minor side reaction.[40,41b] Manganese triacetate catalyzed by potassium bromide has been reported to convert toluene into benzyl acetate and alkenes into allylic acetates *via* a radical mechanism,[43] and cobalt triacetate can induce allylic oxidation or dihydroxylation of a double bond, depending upon substrate structure.[44]

While allylic oxidation products may arise by elimination of a metal hydride from an intermediate adduct or metal–alkene complex,[45] allylmercury species (**34**) are thought to be intermediates in the case of mercury(II) acetate.[42,46] A number of pathways have been suggested, for example involving radical[46] and carbenium ion[47] intermediates, and addition–elimination[48] and rearrangement processes.[49]

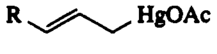

(**34**)

Winstein showed that the solvolysis of crotylmercury(II) acetate under kinetically controlled conditions gives >99.5% of α-methylallyl acetate (equation 13).[50] Subsequent work indicated that both the solvolysis of cinnamylmercury(II) acetate and the mercury(II) acetate oxidation of allylbenzene give *ca.* 60% cinnamyl acetate (**35**) and 40% α-phenylallyl acetate (**36**; equation 14).[38] An equilibrium exists between (**35**) and (**36**) favoring the primary ester which constitutes >99.5% of the equilibrium mixture at 75 °C. Oxidation of a range of both 1- and 2-alkenes under kinetically controlled conditions exclusively gave the secondary allylic esters.

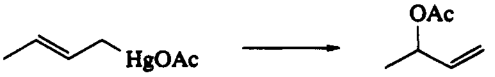

(13)

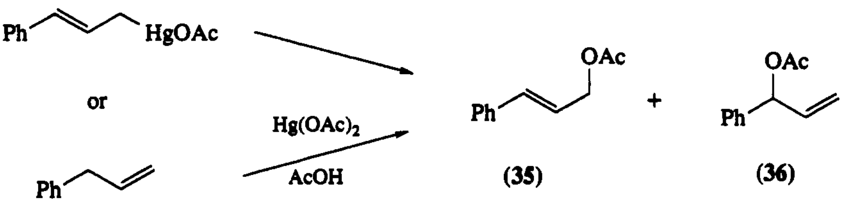

(14)

Similarly, both α- and β-pinene give the acetates of both myrtenol and *trans*-pinocarveol (and also the ring cleavage product) upon mercury(II) acetate oxidation (equation 15).[51]

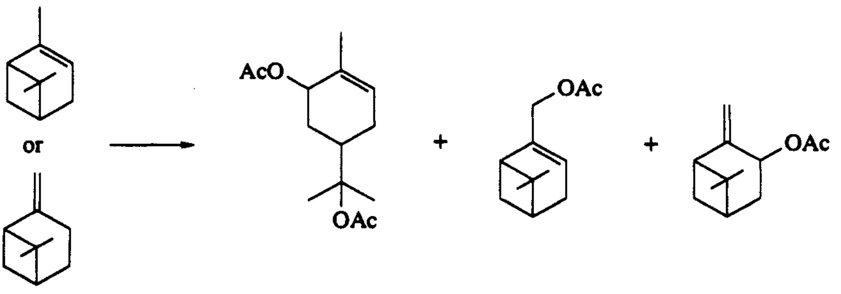

(15)

On the basis of this and other evidence allylic mercury(II) acetates are believed to be the reaction intermediates in all allylic oxidations with mercury(II) acetate. The isolation of the less stable secondary acetates from both 1- and 2-alkenes indicates that in the oxidation of 2-alkenes rearrangement of the secondary allylic mercury(II) acetate to the primary isomer is faster than solvolysis of the organomercurial (Scheme 9).

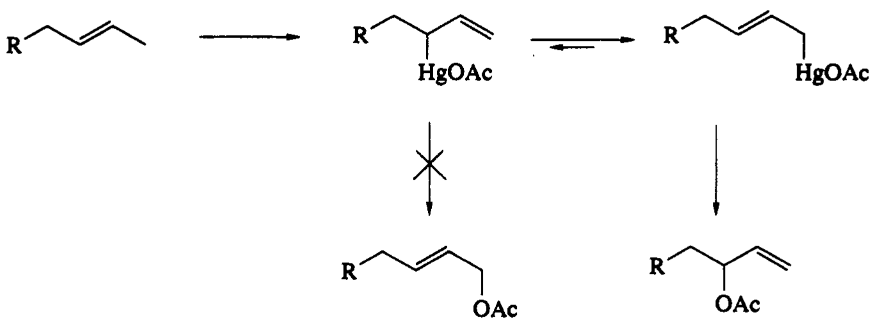

**Scheme 9**

In contrast to lead tetraacetate, simple addition to the double bond does not occur as a side reaction.[41b,42] While allylic rearrangement is common and mixtures of products are frequently obtained, the reaction often proceeds in very high yield and is simple to carry out; the alkene is simply heated in an appropriate solvent with mercury(II) acetate until reaction is complete. Mercury(II) acetate has also been used for dehydrogenation, particularly in the steroid field. One interesting example incorporating simultaneous dehydrogenation and allylic oxidative rearrangement is seen in the reaction of abietic acid (**37**; equation 16).[52]

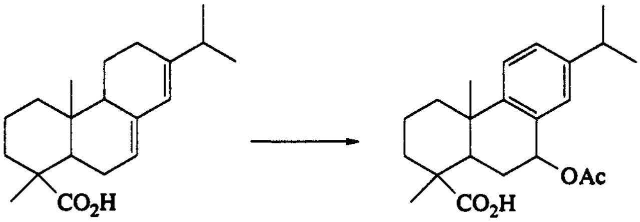

(**37**)

(16)

That mercury(II) acetate allylic oxidation can be a useful reaction in the case of complex and sensitive substrates is demonstrated by the oxidation of avermectin $A_{2a}$ (**38**).[53] The reaction, carried out in anhydrous toluene at 100 °C for 40 min, was remarkably selective, allylic oxidation occurring exclusively at the 3,4-double bond with rearrangement to give (**39**) in up to 73% yield (equation 17).

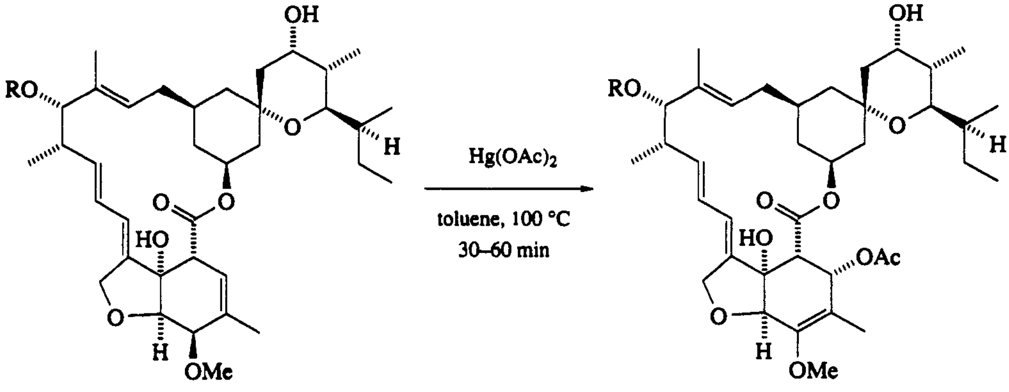

(**38**) (**39**)

(17)

Finally, mercury(II) oxide in combination with fluoroboric acid and ethanol in THF solution has been shown to convert allylbenzenes into the rearranged allylic ethyl ethers.[54]

### *2.1.2.2.2 Palladium and related metals*

Nucleophilic addition to π-allylpalladium complexes is known to take place with a range of nucleophiles, and the mechanism and stereochemistry of these reactions have been thoroughly investigated over the last few years.[39,41,55,60] For example, reaction with acetate anion occurs in the presence of benzoquinone at room temperature in acetic acid solution by initial *cis* attack at the metal atom and subsequent migration.[56] Alternatively, in the presence of chloride ions, a *trans* attack takes place to give the product of opposite stereochemistry (Scheme 10).[57] Intramolecular versions of the reaction are known.[58]

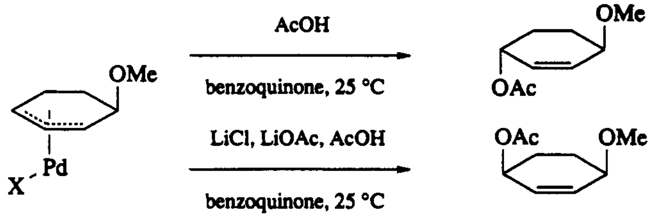

Scheme 10

A new and very highly selective catalytic method for allylic oxidation based on palladium acetate chemistry was discovered in 1984.[59] The alkene, palladium bis(trifluoroacetate) (5 mol %), 2-methoxyacetophenone (added ligand; 20 mol %), and benzoquinone (reoxidant; 1 equiv.) are dissolved in acetic acid and stirred for *ca.* 2 d at room temperature. Geranylacetone (**40**), which contains six allylic carbon atoms plus two carbon atoms adjacent to a carbonyl group, was oxidized using this procedure to give (**41**) and (**42**) in 85% yield and about 2:1 ratio (equation 18). No other available procedure proved as selective. The reaction presumably proceeds *via* formation of a π-allylpalladium complex[60] and attack by an oxygen nucleophile with expulsion of Pd$^0$, subsequently reoxidized to Pd$^{2+}$ by the oxidizing agent. A range of reoxidants and added ligands was examined. The reaction was used in a synthesis of helminthogermacrene (**43**) and β-elemene (**44**),[61] and then subsequently to prepare (**45**) in a synthetic approach to casbene (**46**);[62] however, despite its promise the method does not seem yet to have been widely adopted.

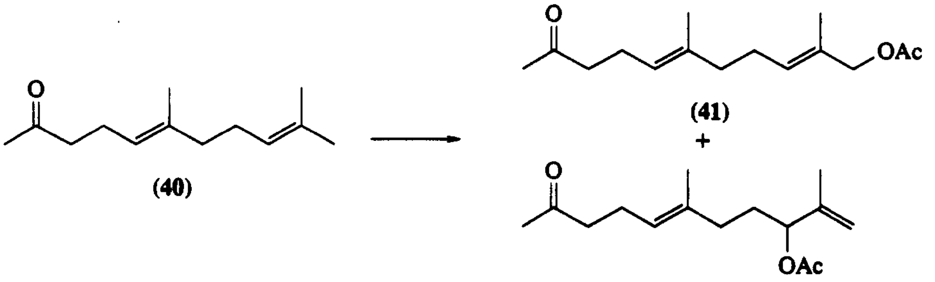

(**40**)

(**41**)

(**42**)

(18)

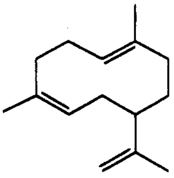

(**43**)

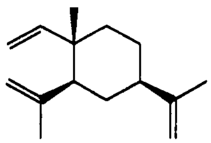

(**44**)

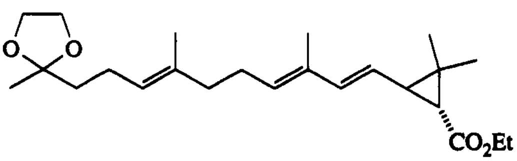

(**45**)

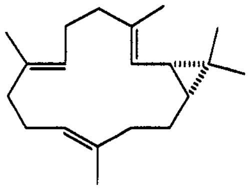

(**46**)

Palladium chloride in combination with potassium acetate, pentyl nitrite and oxygen,[63] and in combination with silver acetate, *t*-butyl hydroperoxide and tellurium dioxide in a 1:2:10:1 ratio,[64] has been shown to accomplish allylic oxidation, although in somewhat disappointing yields. Other reagent combinations with palladium chloride have also been used,[65] as has a palladium acetate–manganese dioxide–benzoquinone mixture.[66] Several other metal species,[39] among them rhodium(II) acetates,[67,172] rhodium(III)–copper(II) in combination,[68] vanadyl acetylacetonate,[69] rhodium(I)[70a] and iridium(I) chloride complexes,[70] and various iron-,[71,72] manganese-,[72] cobalt-[73a] and chromium-(III)[73b] complexes, catalyze allylic oxidation and epoxidation of alkenes with very limited selectivity in the presence of reoxidants such as molecular oxygen, *t*-butyl hydroperoxide, hydrogen peroxide and iodosylbenzene.

### 2.1.2.3 Miscellaneous Reagents

#### *2.1.2.3.1 Peroxy esters and peroxides*

Oxidation of C—H bonds by copper ion catalyzed reaction with an organic peroxy ester (the Kharasch–Sosnovsky reaction)[74] was at one time very popular for allylic oxidation and has been thoroughly reviewed.[39,75] The reaction is usually carried out by dropwise addition of peroxy ester (commonly *t*-butyl peracetate or *t*-butyl perbenzoate) to a stirred mixture of substrate and copper salt (0.1 mol %; commonly copper(I) chloride or bromide) in an inert solvent at mildly elevated temperature (60–120 °C). The mechanism involves three steps: (i) generation of an alkoxy radical; (ii) hydrogen atom abstraction; and (iii) radical oxidation and reaction with carboxylate anion (Scheme 11).

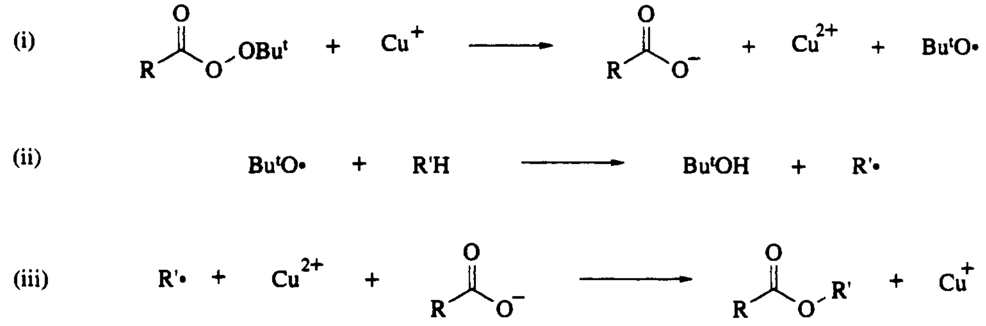

**Scheme 11**

With allylic substrates the intermediate is an allylic radical, and allylic oxidative rearrangement is therefore common; reaction of optically active bicyclo[3.2.1]oct-2-ene gave racemic *exo*-(47) after hydrolysis.[76] Benzylic oxidation is slow and proceeds in only moderate yield, but allylic oxidation is usually clean and can occur in high yield (*e.g.* equation 19).[75,77,78]

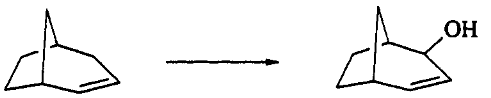

**(47)**

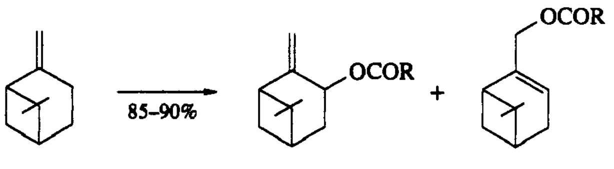

(19)

Terminal alkenes are oxidized with negligible rearrangement to give the 3-acyloxy species.[75,79] However, oxidation of internal alkenes, including cycloalkenes, may result in substantial or exclusive rearrangement.[75,80] Most notable is the reaction of 1-phenylpropene exclusively to give 3-acetoxy-3-phenylpropene, in which deconjugation of the double bond takes place (equation 20).[81]

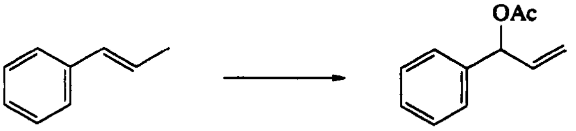

(20)

Unlike most other allylic oxidation systems, extensive rearrangement can take place with higher alkenes, and this limits the synthetic utility of the reaction. Nevertheless, some very selective allylic oxidations have been achieved in the steroid series;[82] for example treatment of progesterone with *t*-butyl perbenzoate in the presence of copper carbonate gave after hydrolysis and isomerization the 6α-hydroxylated product (**48**),[83] neither rearrangement nor competing reaction α to either carbonyl group being observed.

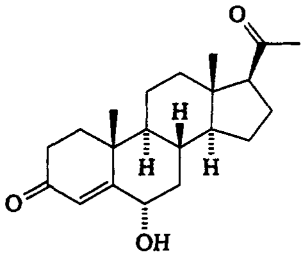

**(48)**

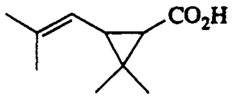

**(49)**

The reaction has also featured in a synthesis of chrysanthemic acid (**49**), exclusive rearrangement occurring to give the secondary allylic benzoate (equation 21).[84]

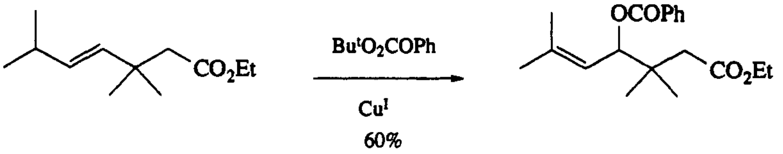

(21)

The Kharasch–Sosnovsky reaction may be carried out in the presence of carboxylic acids to introduce the acyloxy moiety of the acid used, and may also be conducted photochemically at room temperature using UV irradiation. Peroxy acids,[75] diacyl peroxides,[75] and peroxyphosphates and peroxyphosphonates[85] are alternative oxidants. *t*-Butyl hydroperoxide may also be used in place of peroxy esters with broadly similar results, although formations of mixed peroxides[75] and *t*-butyl ethers[86] can then compete with allyl ester production.

### *2.1.2.3.2 Singlet oxygen*

Photosensitized oxygenation of alkenes using singlet oxygen is a well-known reaction[87,199] and several comprehensive reviews have appeared.[39,88,89] The normal course of singlet oxygen reactions with monoalkenes is *via* an ene reaction to produce an allylically rearranged hydroperoxide, often in excellent yield, and this may be reduced to give allylic alcohol (Scheme 12). Other mechanisms, which may compete, have also been proposed, involving dioxetane (**50**) and perepoxide (**51**) intermediates,[88] and indeed perepoxides have been proposed as common intermediates for the formation of dioxetanes and other by-products.[90] Typical photosensitizers for singlet oxygen production in these reactions are rose bengal,

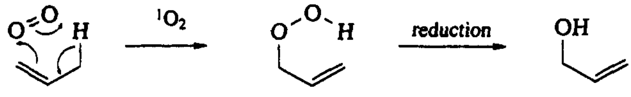

Scheme 12

hematoporphyrin, eosin, methylene blue, chlorophyll and fluorescein. 18-Crown-6 has been used to solubilize rose bengal and eosin in aprotic solvents.[91] Solvent effects are small, typical solvents being pyridine, methylene chloride, ether and methanol, although the lifetime of singlet oxygen in this last solvent is very much reduced.

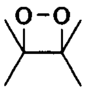

**(50)**

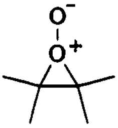

**(51)**

Oxidation with singlet oxygen is subject to steric effects[92] but can show poor regioselectivity.[88,89,93] For example, (+)-3-carene (**52**) is oxidized to produce a mixture of all three possible regioisomeric hydroperoxides with oxygenation occurring at the face of the allyl system opposite the *gem*-dimethylcyclopropane unit in each case (equation 22).[89,94]

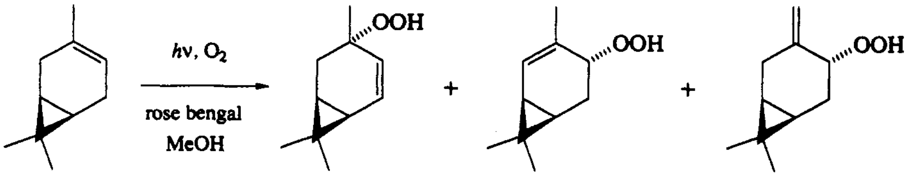

**(52)** (22)

The sensitivity to steric effects is nicely illustrated in the oxidation of dienes (**53**) and (**54**), where addition of a methyl group at a remote site is sufficient to change completely the course of the reaction (Scheme 13).[95]

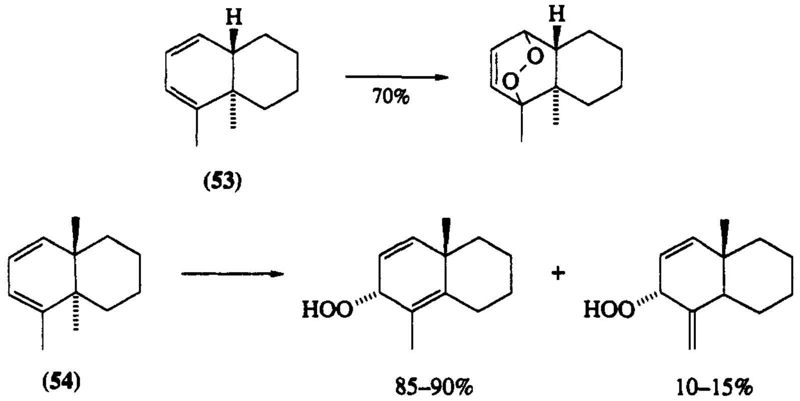

**Scheme 13**

Singlet oxygen is an electrophilic reagent and increasing substitution around a double bond therefore increases reactivity. Tetrasubstituted alkenes are around 20 times as reactive as trisubstituted alkenes, which are in turn about 150 times as reactive as disubstituted alkenes, which are some 15 times as reactive as monosubstituted alkenes.[88,89] This effect is illustrated in the oxidation of diene (**55**), in which oxidation occurred exclusively at the more substituted double bond.[96]

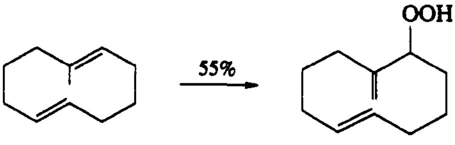

**(55)**

Furthermore, the presence of electron-withdrawing substituents, such as an allylic hydroxy group, is deactivating, an effect intensified by esterification to a degree such that acylation of an allylic alcohol may be sufficient to protect the double bond during photooxidation at another site.[88]

In some instances the primary product of alkene photooxidation is not the allylically rearranged hydroperoxide, but the dioxetane addition product, *e.g.* (**56**), which may or may not be formed by concerted [2 + 2] cycloaddition.[90] Some of these dioxetanes, *e.g.* (**57**), are relatively stable, although most suffer cleavage to produce carbonyl compounds or other materials.[97] For example, photooxidation of indene gives homophthaldehyde (**58**) which was not produced under identical reaction conditions from hydroperoxide (**59**).[98] Isomeric hydroperoxides (**60**) and (**61**) were also isolated when the oxidation was carried out in methanolic solution (Scheme 14).

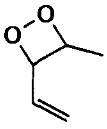

**(56)**

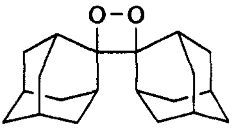

**(57)**

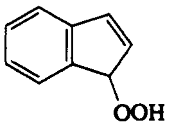

**(59)**

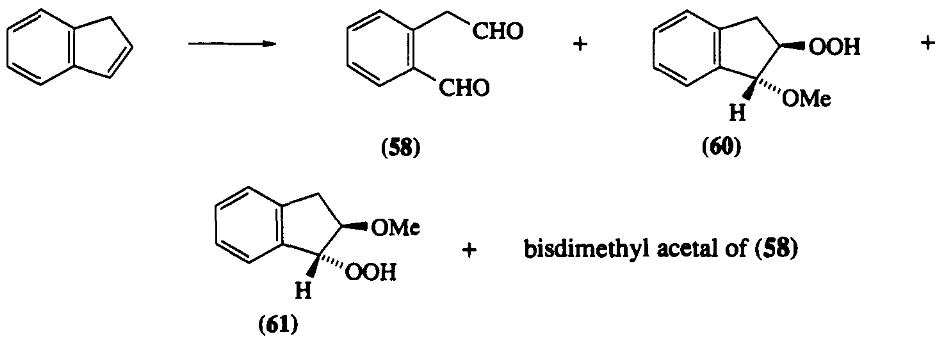

**Scheme 14**

The factors which control the reaction pathway followed in individual alkene photooxidations do not seem to be well understood,[99] although dipolar solvents such as acetonitrile seem to favor the dioxetane mode, while less polar solvents such as benzene favor the ene mode. A number of chemical methods for the production of singlet oxygen are known, including generation from triphenyl phosphite ozonide,[100] bromine–alkaline hydrogen peroxide,[101] sodium hypochlorite–hydrogen peroxide,[102] and anthracene endoperoxide;[103] however the potential for greater selectivity offered by such reagents has not yet been thoroughly investigated.

### *2.1.2.3.3 Electrochemical methods*

Torii has reported the electrochemical oxyselenation–deselenation of alkenes to give allylically rearranged allyloxy products.[104] A typical example is given below (equation 23).[105] Benzyl- or acetyl-(*S*)-citronellol was mixed in acetonitrile/water solution with diphenyl diselenide (0.5 mol equiv.) and a catalytic amount of tetraethylammonium bromide, and was electrolyzed at room temperature in an undivided cell using platinum electrodes and a constant current density of 10 mA $cm^{-2}$. The corresponding allylic alcohols were isolated in excellent yields. In methanolic solution, using a reduced amount of diphenyl diselenide (20 mol %), the methoxy compounds were obtained in slightly reduced yields.

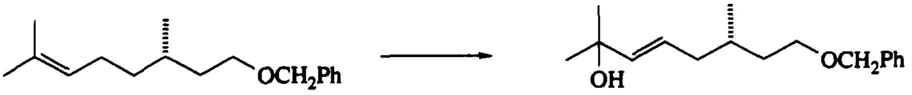

(23)

#### *2.1.2.3.4 Allylic oxidation* via *metallation*

Allylic alcohols may be derived from alkenes by metallation to give the allylpotassium species, followed by treatment with fluorodimethoxyborane. Oxidation of the resultant boronic ester with hydrogen peroxide gives the allylic alcohol (Scheme 15).[106,107] Some allylic rearrangement may be observed; for example, metallation of α-pinene with potassium *t*-butoxide in petroleum ether solution and subsequent boration and oxidation gave myrtenol (42%) and *trans*-pinocarveol (1%) (equation 24), while treatment of the allylpotassium with oxirane gave the alkylated products in a ratio of *ca.* 2:1.[106]

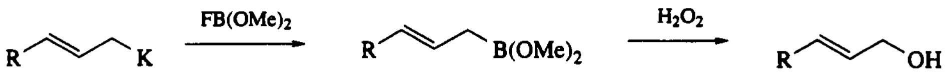

**Scheme 15**

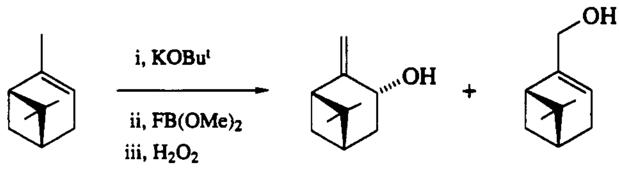

(24)

#### *2.1.2.3.5 Enzymatic methods*

The copper–protein dopamine β-monooxygenase (DBM), which catalyzes hydroxylation at the *pro*-(*R*) hydrogen atom of dopamine to form norepinephrine in mammalian tissues, has been used for enantioselective benzylic hydroxylation[108] and sulfoxidation.[109] Very recently enantioselective allylic oxygenation by DBM has also been reported.[110] 2-(1-Cyclohexenyl)ethylamine (**62**) was subjected to 'preparative scale' enzymatic reaction and the product (**63**) characterized as having the (*R*)-configuration by HPLC and $^1$H NMR analysis of a derivative using the Mosher model. No trace of the (*S*)-enantiomer was observed and neither allylic rearrangement nor epoxidation took place. The authors comment that DBM also catalyzes the allylic hydroxylation of (*Z*)-hex-2-enylamine with no detectable allylic rearrangement, and suggest that the reaction involves interaction of copper with the alkene moiety during catalysis, thus precluding double bond rearrangement.

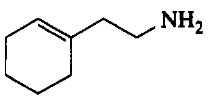

**(62)**

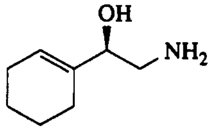

**(63)**

## 2.1.3 ALLYLIC OXIDATION REACTIONS WHICH PRODUCE α,β-UNSATURATED CARBONYL COMPOUNDS

### 2.1.3.1 Chromium(VI)-based Reagents

#### *2.1.3.1.1 Chromic acid and simple chromate esters*

Examples of the use of chromium(VI) reagents to effect the allylic oxidation of alkenes to give α,β-unsaturated carbonyl compounds are very common in the literature.[111,112] The reaction was first reported by Treibs and Schmidt[113] for the allylic oxidations of α-pinene to verbenone and verbenol, of dipentene to carvone and carveol, and of cyclohexene to cyclohexenol and cyclohexenone, using a solution of chromium trioxide in a mixture of acetic anhydride and carbon tetrachloride. However, yields were low and no synthetic use of this observation was made.

Chromic acid itself has been used in the oxidation of alkenes and in some cases allylic oxidation products were observed; for example, cyclohexene was converted to cyclohexenone in 37% yield and 1-methylcyclohexene was oxidized to a mixture of enones (Scheme 16).[114]

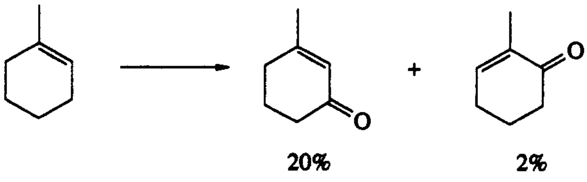

**Scheme 16**

Extension of this type of reagent[115] to the use of sodium dichromate in acetic acid[116] was found to furnish the allylic oxidation of 4,4,10-trimethyl-Δ$^5$-octalin into 7-keto-4,4,10-trimethyl-Δ$^5$-octalin (**64**)[117] in 65% yield (equation 25); this reaction was employed in the total syntheses of (±)-widdrol (**65**) and of (±)-thujopsene (**66**).[118]

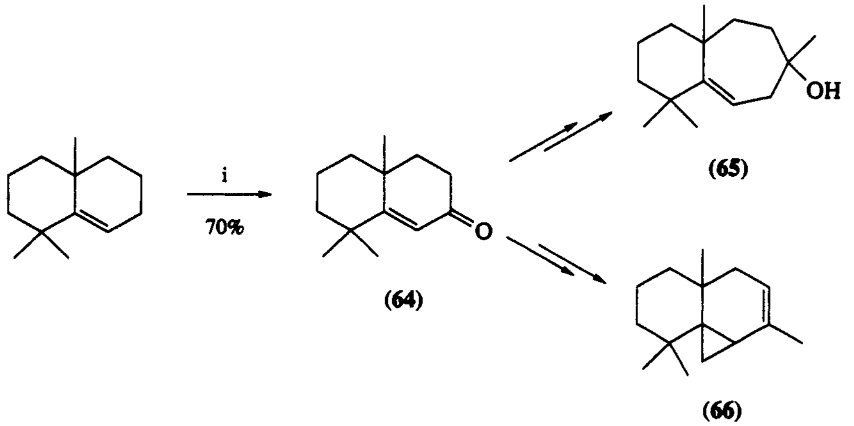

(25)

i, 1.4 equiv. $Na_2Cr_2O_7$, acetic acid, r.t./overnight, then 100 °C/2.5 h

Allylic oxidation of steroids, particularly at the 7-position, has evoked interest over many years. For example, chromium trioxide–acetic acid,[119] sodium dichromate,[120] and *t*-butyl chromate[121–128] have all been used in the oxidation of the 5-α-pregnane series (*e.g.* equation 26).

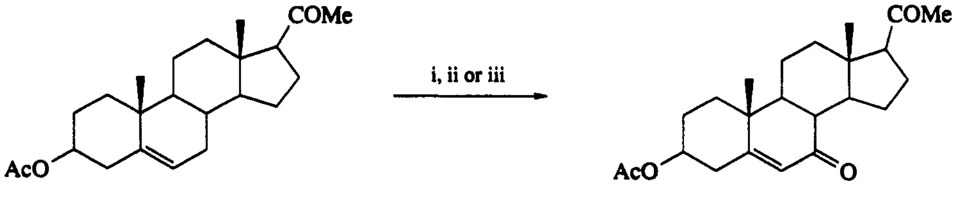

(26)

i, $CrO_3$, AcOH; 50%; ii, $Na_2Cr_2O_7$, AcOH, $Ac_2O$; 79%; iii, $(Bu^tO)_2CrO_2$; 62%

The overall mechanism of chromium(VI) allylic oxidation appears to consist of removal of a hydrogen atom or hydride ion from the alkene, forming a resonance-stabilized allylic radical or carbocation, which is ultimately converted into the unsaturated ketone (Scheme 17).[8]

An alternative mechanism has also been proposed in which oxidation at the double bond leads to a ketol derivative, elimination of water from which then gives the unsaturated ketone (Scheme 18a).[112] Limited kinetic data are available and suggest that Scheme 17 is obtained for chromic acid oxidations.[129]

The discovery of the chromium trioxide–pyridine complex led to the accessibility of allylic oxidation under much less harsh conditions, typically room temperature reaction in dichloromethane solution[130,131]

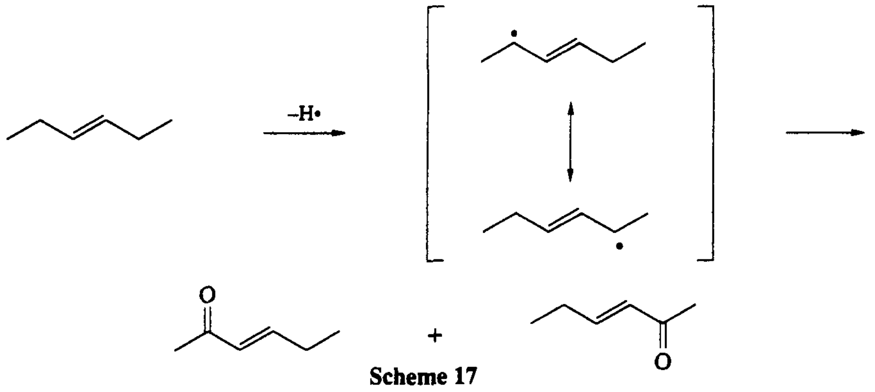

Scheme 17

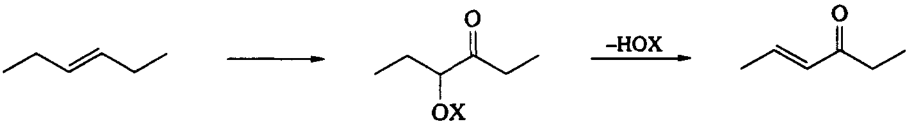

Scheme 18a

for a number of days, rather than high temperature conditions for extended periods. Dauben[132] proposed that the products of allylic oxidation using this reagent (according to Scheme 17) would be governed by a large number of factors, for example the steric accessibility of the allylic hydrogen atom towards abstraction, the relative stabilities of possible allylic intermediates, and the stereoelectronic control of the oxygen transfer step at competing sites.

Allylic oxidation in steroid systems provides a good illustration of the factors controlling the reaction pathway. In the oxidation of cholest-5-ene, which has a rigid structure with two allylic hydrogen atoms at C-4 and C-7, assuming axial preference of hydrogen atoms for abstraction,[133] an incoming chromium species should encounter steric hindrance from the methyl group above the plane and a less crowded approach from beneath. Indeed, allylic oxidation proceeds to yield only cholest-5-en-7-one in 52% yield (equation 27).

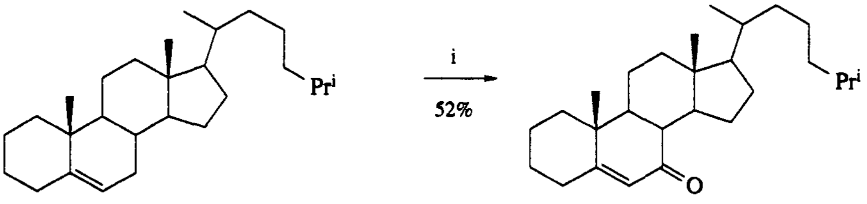

(27)

i, 20 equiv. $CrO_3$•2Py, $CH_2Cl_2$, r.t./24 h

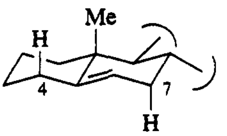

Dauben postulated that there is a preference for the abstraction of a tertiary allylic hydrogen atom and that this stems from the relative stability of the intermediate radical (or ionic) species rather than relative C—H bond strengths (Scheme 18b; the allylic oxidation of 1-methylcyclohex-2-ene).

From an extensive survey of this reagent system the following guidelines have been proposed: (i) allylic methyl groups are not readily oxidized; (ii) if more than one allylic methylene group is present in a conformationally flexible molecule, enones resulting from attack at all positions are formed, while if the molecule is conformationally rigid, as in a steroid, selectivity is observed; and (iii) attack at an allylic methinyl position yields a rearranged enone wherever possible; similar rearrangements may also occur in methylene systems possessing steric hindrance towards hydrogen atom abstraction.

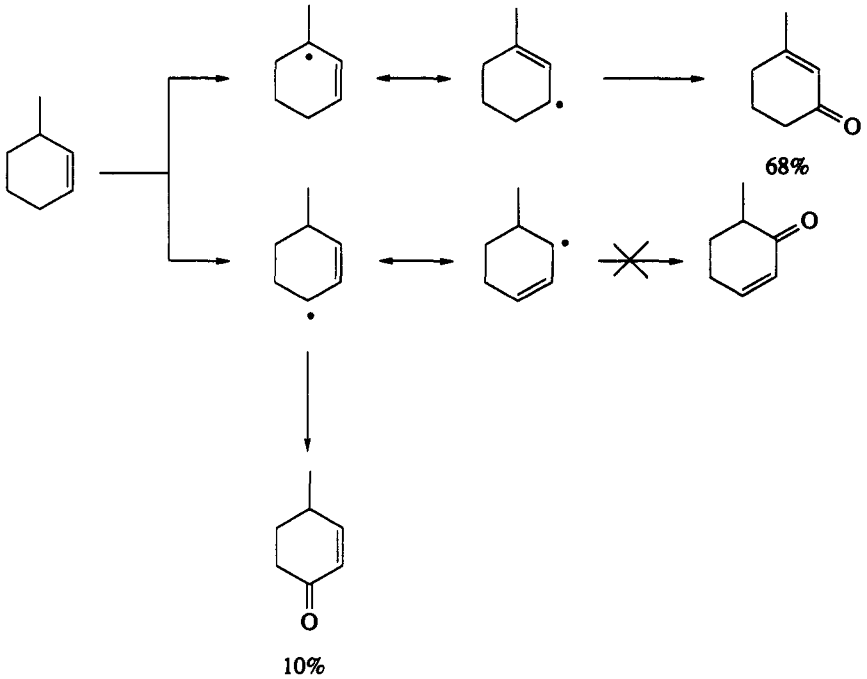

**Scheme 18b**

Allylic oxidation reactions employing chromium(VI) reagents therefore appear to be very much dependent upon the intrinsic nature of the substrate as to their regiochemical outcome. This is exemplified by the *t*-butyl chromate allylic oxidation of (+)-3-carene (**67**; equation 28)[134] where no great preference for either product exists.

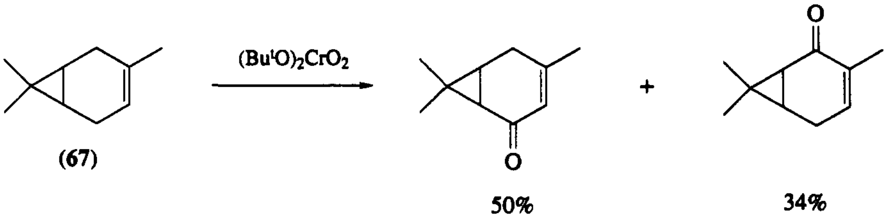

(28)

An attempted allylic oxidation of (**68**; equation 29) was found by Paquette[135] to be difficult to achieve using a range of reagents due to problems with polymerization and rearrangement. The chromium trioxide–pyridine complex was the only reagent combination found to be successful, albeit in low yield.

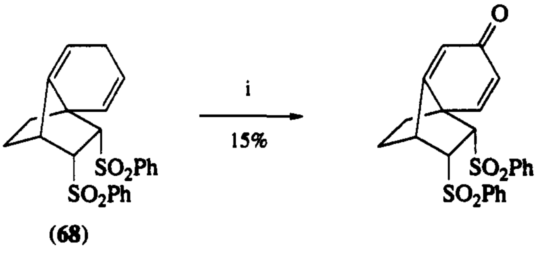

(29)

i, 20 equiv. $CrO_3{\bullet}2Py$, 25 °C/24h

The chromium trioxide–pyridine complex was also found to be the reagent of choice in a synthesis of α-methylene-γ-butyrolactones (equation 30).[136]

This method was found to be superior to others tested, including selenium dioxide, chromium trioxide–acetic acid, and *t*-butyl chromate.

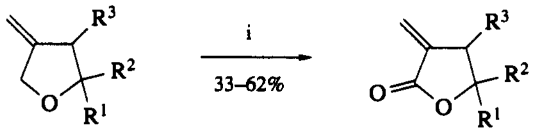

(30)

$R^1, R^2$ = H, Ph or alkyl
$R^3$ = H or alkyl
i, 20 equiv. $CrO_3 \cdot 2Py$, $CH_2Cl_2$, reflux, 1 h

### 2.1.3.1.2 Pyridinium chlorochromate and dichromate

An alternative to the chromium trioxide–pyridine complex is provided by pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC).[137] These reagents, now ubiquitous for chromate-based oxidation of alcohols, overcome the hygroscopic nature of the chromium trioxide–pyridine complex[138] and are prepared by a less hazardous procedure;[139] both are commercially available as are several other derivative reagents.

Pyridinium chlorochromate has been shown to be of particular value in the allylic oxidation of compounds containing an activated methylene group, such as 5,6-dihydropyrans (**69a** and **69b**; equations 31a and 31b).[140]

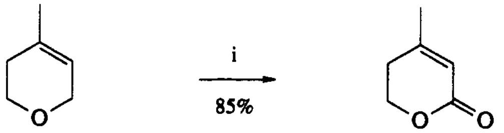

(31a)

**(69a)** i, 1 equiv. PCC, 60–70°C/9 h

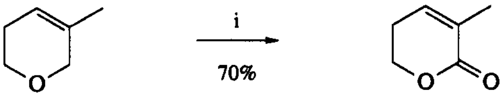

(31b)

**(69b)**

i, 1 equiv. PCC, 60–70 °C/12 h

Indeed, Parish[141] claims that PCC is the reagent of choice in the allylic oxidation of $\Delta^5$-steroids (*e.g.* equation 32). The reactions were carried out using PDC in pyridine solution at 100 °C, PCC in refluxing benzene solution, and PCC in DMSO solution at 100 °C. These solvent systems are claimed to be superior to the more usual methylene chloride.[138,142]

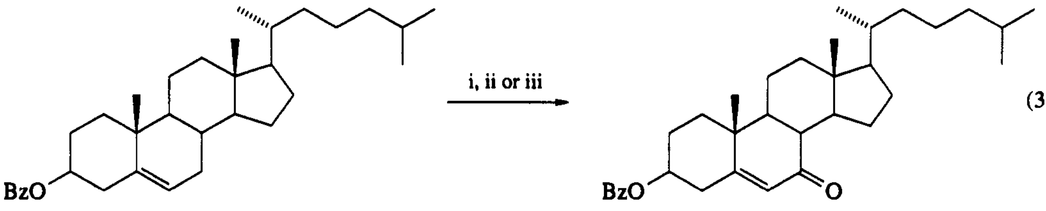

(32)

i, PCC, benzene, reflux, 89%; ii, PCC, DMSO, 100 °C, 78%; PDC, pyridine, 100 °C, 64%

One drawback associated with this type of chromium species is the frequent requirement for a large excess of reagent. Recent attempts to combat this problem have involved the use of a PCC–celite mixture in benzene solution under reflux[143] and more successfully a *t*-butyl hydroperoxide–pyridinium dichromate mixture (equation 33).[144]

While this latter modification appears to be efficient and highly regioselective for steroidal substrates which contain a rigid structure and provide a sterically crowded environment for the reacting double bond, the method can be rather poor in less hindered situations (*e.g.* equation 34).[144]

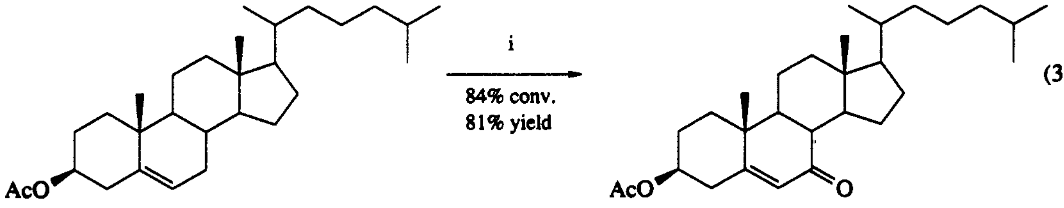
i
84% conv.
81% yield
AcO
AcO
O

(33)

i, 4 equiv. PDC, Bu$^t$OOH, celite, anhydr. benzene, r.t.

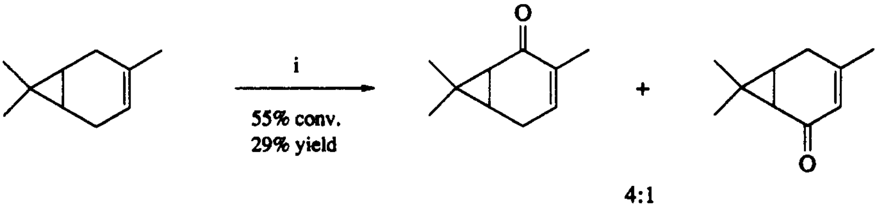
i
55% conv.
29% yield
O
+
O
4:1

(34)

i, 2 equiv. PDC, Bu$^t$OOH, celite, anhydr. benzene, r.t.

### *2.1.3.1.3 Chromium trioxide–3,5-dimethylpyrazole*

With the advent of the chromium trioxide–3,5-dimethylpyrazole complex as an oxidant[145,146] allylic oxidation has become far more valuable as a synthetic transformation. The reagent was applied by Salamond[129] to the allylic oxidation of cholesteryl benzoate to give the corresponding $\Delta^5$-7-ketone (equation 35). However, a 20 molar excess of reagent was still required to effect the reaction in less than 30 min at room temperature.

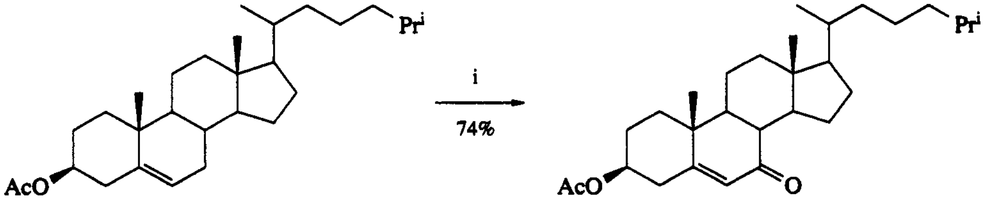
Pr$^i$
i
74%
AcO
Pr$^i$
AcO
O

(35)

i, 12 equiv. $CrO_3$•3,5-DMP, $CH_2Cl_2$, −15 °C, 4 h

The observed rate enhancement for this reagent over other chromium(VI) species has been rationalized as an effect of increased reagent solubility and by invoking the potential for acceleration by intramolecular participation by the pyrazole nucleus. Two mechanistic pathways have been proposed (Schemes 19a and 19b). The salient feature of both these pathways is that the chromium complex attacks first at the

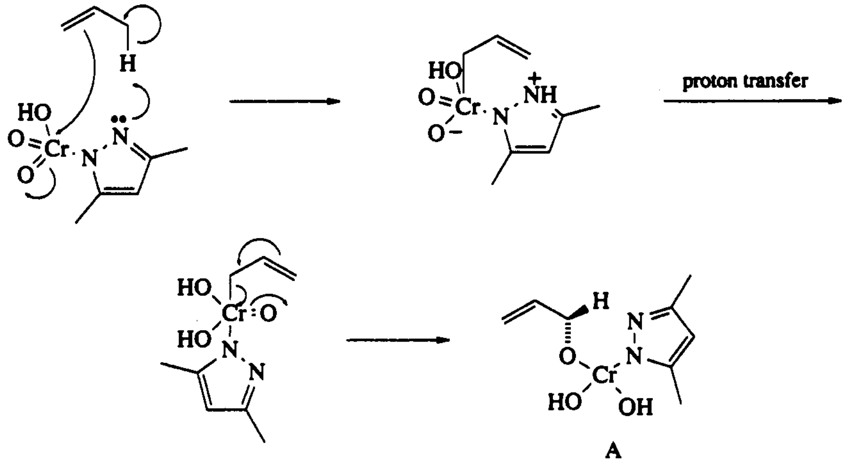
H
HO
O=Cr
O
N
N
HO
O=Cr
O−
N
NH
+
proton transfer
HO
HO
Cr=O
N
N
H
N
N
O
Cr
HO
OH
A

**Scheme 19a**

double bond and not at the allylic methylene group. This type of mechanism is not possible for chromium trioxide–pyridine, or for pyridinium chlorochromate or dichromate because: (i) no ligand sites are available for complexation with π-electrons unless pyridine is first displaced; and (ii) no basic nitrogen atom is available to assist in the removal of the allylic proton, other than by intermolecular deprotonation by a displaced pyridine molecule.

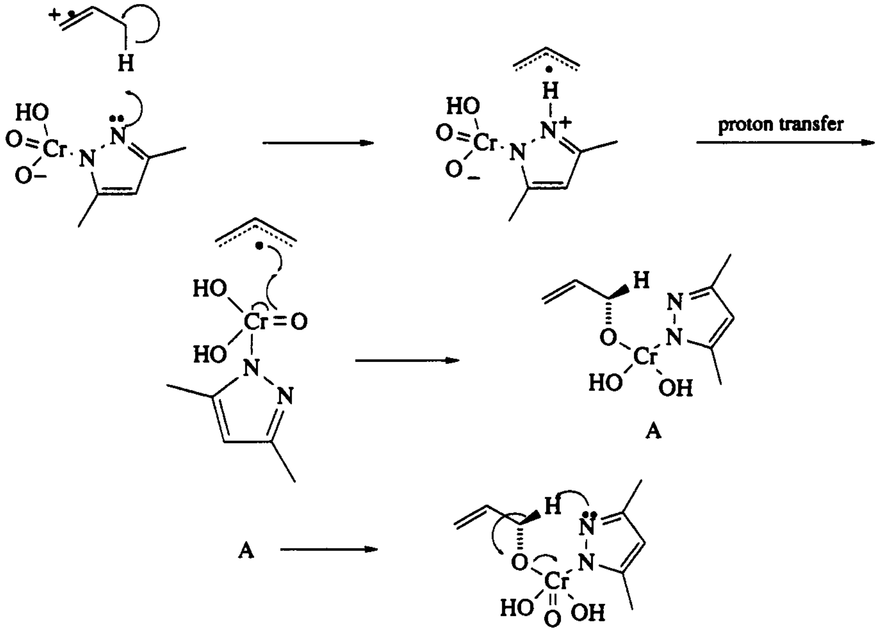

**Scheme 19b**

From a practical viewpoint the reagent is simple to make and use. It is prepared *in situ* at low temperature (*ca.* 20–25 °C), requiring about 15 min to form prior to the addition of substrate. It is important to note that the chromium trioxide should be thoroughly dried over phosphorus pentoxide before use.

Some fine examples of the synthetic use of this reagent are available in the literature;[147] for example in a total synthesis of vernolepin,[148] intermediate (**70**), containing a fairly sensitive lactol ether unit, was selectively prepared by the use of chromium trioxide–dimethylpyrazole with formation of only 5% of the allylically rearranged product (equation 36).

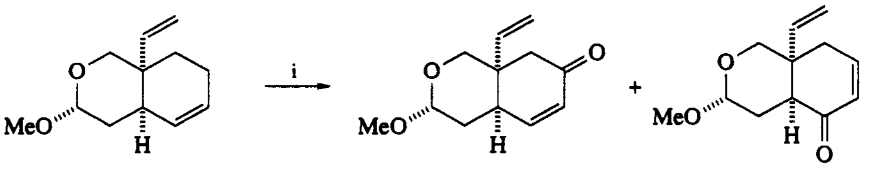

(36)

(**70**) 48% 5%

i, 20 equiv $CrO_3$•3,5-DMP, $CH_2Cl_2$, −20 °C/1 h then 0 °C/4 h

The reagent has been used by Magnus[149] in studies directed towards a synthesis of bachrachotoxin (**71**). A *cis*-decalin was oxidized selectively at the 7-position without the acetal or triple bond moieties present being affected (equation 37). The reagent has also found use in an approach to forskolin;[150] cyclohexadienone (**72**) was prepared by exclusive oxidation at the 7-position of (**73**; equation 38).

An interesting example of the incorporation of this oxidation into a synthetic strategy is seen in a route to quadrone (**74**) based on an intramolecular Diels–Alder reaction.[151] In this scheme highly selective allylic oxidative rearrangement of a *trans*-decalin (**75**) occurs to give a product (**76**) containing the double bond at a ring fusion position, allowing subsequent conversion to the desired *cis*-decalin system (Scheme 20). Neither of the other two possible ketonic oxidation products were observed.

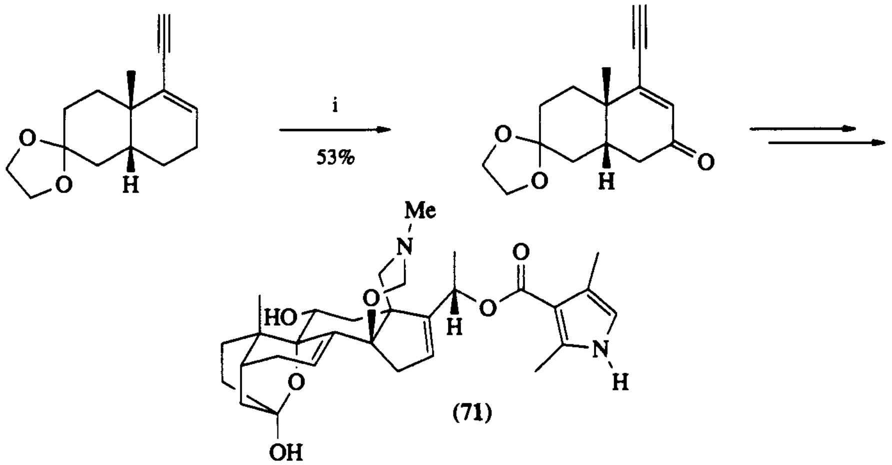
i
53%
Me
N
O
HO
O
H
O
N
H
O
OH
O
O
H
O
O
H
O

(71)

(37)

i, 30 equiv. $CrO_3$•3,5-DMP, $CH_2Cl_2$, r.t.

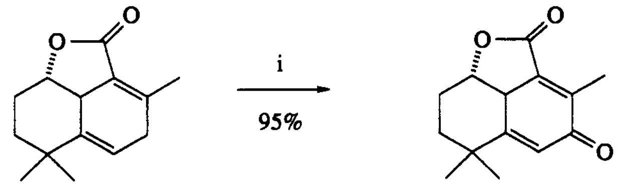

(73) (72)

(38)

i, 30 equiv. $CrO_3$•3,5-DMP, $CH_2Cl_2$, r.t.

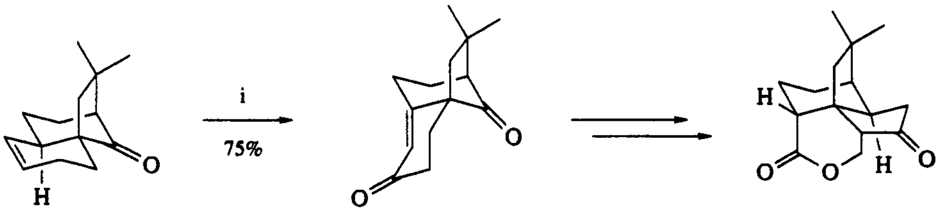
i
75%
O
H
O
O
H
O
O
H
O

(75) (76) (74)

i, $CrO_3$•3,5-DMP, $CH_2Cl_2$

Scheme 20

### *2.1.3.1.4 Other chromium-based reagents*

A number of other chromium-based reagents have been developed for allylic oxidation; for example that of steroids by *t*-butyl hydroperoxide in the presence of a catalytic amount (0.05–0.5 mol equiv.) of chromium trioxide[152] in dichloromethane solution at room temperature (equation 39). Yields vary from 32 to 69%. This modification is useful in terms of cost, operational simplicity and yields.

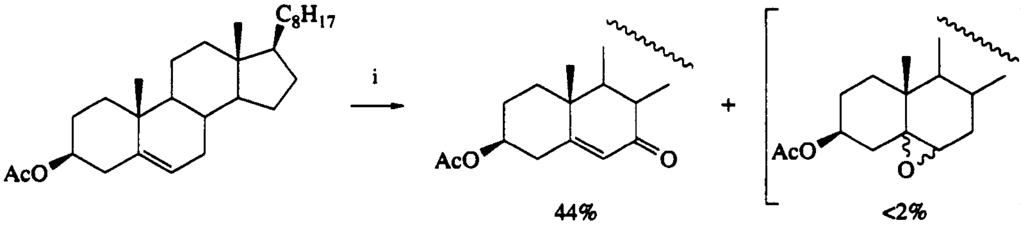
$C_8H_{17}$
AcO
i
AcO
O
44%
+
AcO
O
<2%

(39)

i, 0.4 equiv. $CrO_3$, $Bu^tOOH$, $CH_2Cl_2$, 5.5 h/r.t.

A chromium hexacarbonyl–*t*-butyl hydroperoxide system has also been developed with the remarkable chemoselective ability to effect allylic oxidation even in the presence of some secondary alcohols (equations 40 and 41).[153–155]

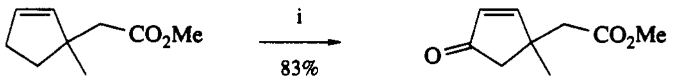

(40)

i, 0.5 equiv. $Cr(CO)_6$, 1.2 equiv. $Bu^tOOH$, MeCN, reflux/18 h

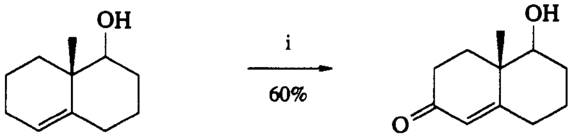

(41)

i, 0.25 equiv. $Cr(CO)_6$, 1.2 equiv. $Bu^tOOH$, MeCN, reflux/30 h

## 2.1.3.2 Other Transition Metal Catalyzed Allylic Oxidations

### *2.1.3.2.1 Palladium*

Palladium catalysts are best known for oxidizing alkenes to ketones or vinyl derivatives.[156] However, formation of α,β-unsaturated carbonyl compounds by UV irradiation of oxygenated solutions of alkenes in the presence of catalytic amounts of palladium salts has been observed by Muzart.[39,157,158] This reaction is believed to proceed through a π-allylpalladium trifluoroacetate complex, *e.g.* (77).

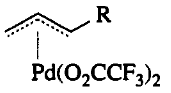

(77) R = alkyl

The process was later improved by the use of a *p*-toluenesulfonyl substituent[159] at the allylic carbon atom (equation 42). The authors claim that this modification has a powerful influence on both the selectivity and mechanism of the oxidation, exclusive oxidative rearrangement then being observed. Several other methods of achieving allylic oxidation using palladium catalysts have also been reported,[160–165] although these are generally of less importance.

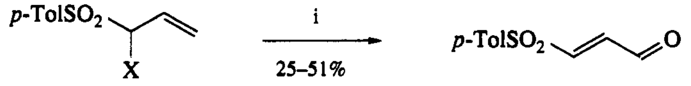

(42)

i, $Pd(O_2CCF_3)_2$, *h*ν, $O_2$, acetone

### *2.1.3.2.2 Rhodium*

Rhodium catalysis for effecting allylic oxidation has been developed and has led to considerable controversy over the operative mechanistic pathway.[166]

The first example of rhodium catalysis for this purpose utilized chlorotris(triphenylphosphine)rhodium(I) to catalyze the allylic oxidation of a range of alkenes.[167,168] This catalyst has also been shown to successfully oxidize cyclic allylsilanes[169] to afford β-silyl-2-cycloalkenones in very good yields and with exclusive rearrangement (equation 43).

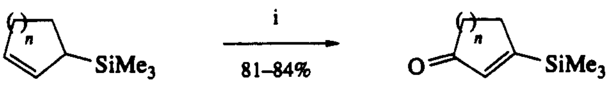

(43)

i, $O_2$, 0.01 equiv. $RhCl(PPh_3)_2$, 97 °C

A combination of rhodium(III) chloride with silver acetate,[170] and treatment of rhodium(II) acetate in acetic acid solution with ozone,[171] are two methods for generation of the $\mu_3$-oxotrimetal–acetato complex of rhodium $[Rh_3O(OAc)_6(H_2O)_3]OAc$. This '$Rh_3O$' complex was found to effect catalytic allylic oxidation of alkenes efficiently to give the corresponding α,β-unsaturated carbonyl compounds[172] in the presence of a reoxidant such as *t*-butyl hydroperoxide, although in disappointing yield (equation 44).

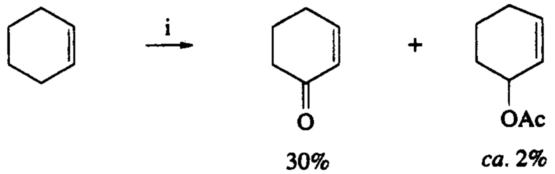

(44)

i, cat. $[Rh_3O(OAc)_6(H_2O)_3]OAc$, $Bu^tOOH$, AcOH

#### 2.1.3.2.3 Iridium

Iridium catalysts have not been widely developed for allylic oxidation; however a small number of examples of such use have been reported.[173,174] One example is given below (equation 45).

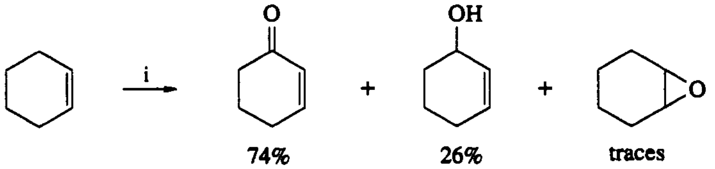

(45)

i, cat. $IrCO(PPh_3)_2Cl$, $O_2$

#### 2.1.3.2.4 Other transition metals

Overall, many transition metal complexes have been investigated. Among those not mentioned above which may carry out catalytic allylic oxidation to give enones under certain circumstances are $Co(PPh_3)Cl/O_2$,[175] $Mn(TPP)Cl/O_2$,[176] $[Fe(PPh_3)]_2O/UV$,[177] Ni(phthalocyanine)/$O_2$[178] and an unusual mercury(II) acetate example[179] in which the enone is formed rather than the expected acetate.

### 2.1.3.3 Selenium-based Reagents

#### 2.1.3.3.1 Selenium dioxide

Selenium-mediated allylic oxidations producing allylic alcohols have been discussed above; however, in some cases oxidation proceeds further to give the α,β-unsaturated carbonyl compounds directly, or mixtures of alcoholic and ketonic products.[180] That the regioselectivity observed in these allylic oxidation reactions closely resembles that found in classical selenium dioxide oxidations is in accord with initial formation of the intermediate allylic alcohol before *in situ* oxidation to the carbonyl compound.[1] This process was studied by Rapoport[17] and was explained mechanistically as an elimination of the intermediate allylic selenite ester *via* a cyclic transition state, analogous to $S_Ni'$ (rather than $S_N2'$) solvolysis (Scheme 21). Of the two possible transition states (**78**) and (**79**), the cyclic alternative (**78**) was preferred because oxidation exclusively yields *trans* aldehydes.

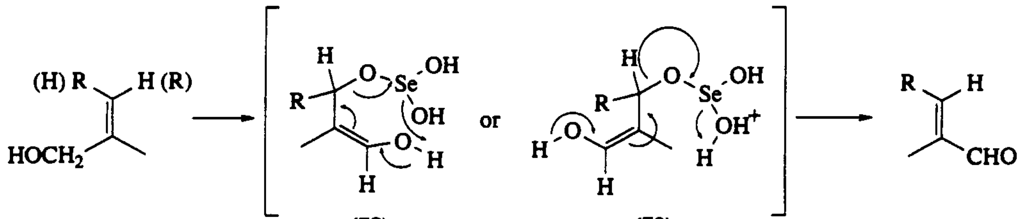

(78) (79)

Scheme 21

Oxidation reactions of this nature are common in the literature.[181] For example, selenium dioxide in refluxing ethanolic solution brought about the allylic oxidative rearrangement of geranyl acetate, which was further functionalized in a synthesis of the norsesquiterpenoid gyrinidal (equation 46).[182] This transformation was also used in a total synthesis of phytol.[183] Similarly, an α,β-unsaturated aldehyde was obtained under similar conditions in studies of a synthesis of pentalenic acid derivatives (equation 47).[184]

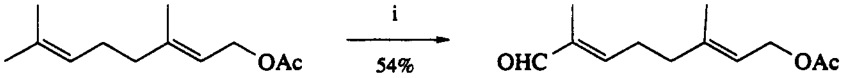

(46)

i, $SeO_2$, EtOH, reflux

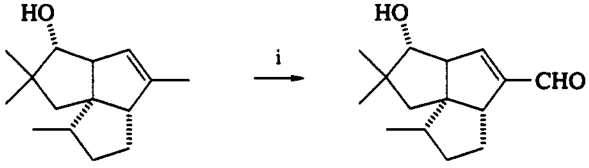

(47)

i, $SeO_2$, EtOH, reflux overnight

Evidence for the preferential formation of the *trans*-substituted product of selenium dioxide allylic oxidation[185] is seen in the synthesis of part of (13Z)-retinoic acid (equation 48). Reaction took place exclusively at the exocyclic double bond without rearrangement. Allylic oxidation of this nature has also been used in the synthesis of 6-conjugated 2-pyrones (equation 49).[186] This intermediate was employed in the total synthesis of natural pyrones such as yangonin.

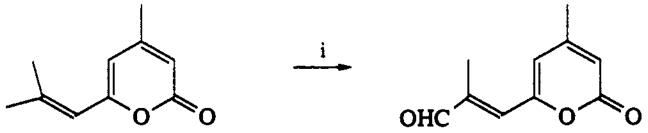

(48)

i, $SeO_2$, aq. dioxane, reflux/12 h

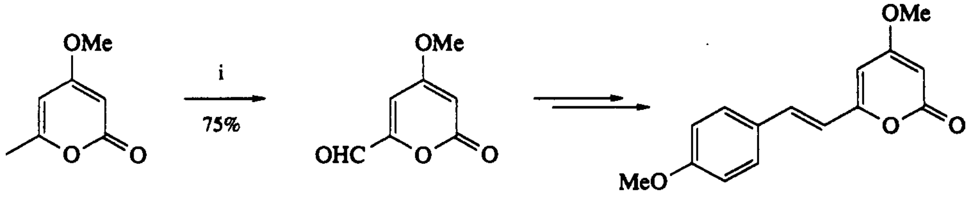

(49)

Yangonin

i, 5 equiv. $SeO_2$, dioxane, 180 °C, sealed tube, 3 h

### *2.1.3.3.2 Other selenium-based reagents*

More recently Barton and Crich[187] reported the use of 2-pyridineseleninic anhydride in the allylic oxidation of alkenes. This reagent is prepared *in situ* by the oxidation of the corresponding diselenide by iodylbenzene. It effects oxidation to α,β-unsaturated ketones with retention of the double bond regiochemistry (*e.g.* equation 50).

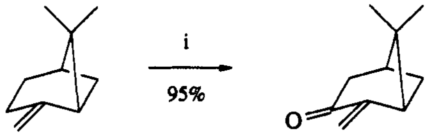

(50)

i, 0.1 equiv. 2,2'-dipyridyl diselenide, 3 equiv. iodylbenzene, chlorobenzene, 80 °C/1.5 h

Observation of the reaction by TLC indicated initial formation of the allylic alcohols which were oxidized *in situ* to give the enone. The following mechanism for allylic oxidation was proposed (Scheme 22).

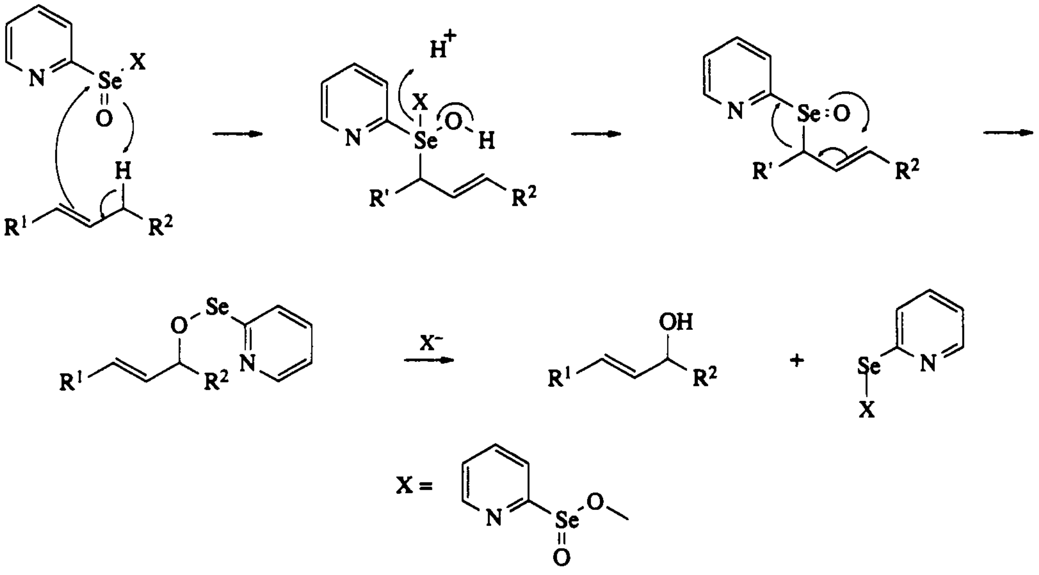

Scheme 22

2-Pyridineseleninic anhydride was also shown to be more reactive towards benzylic oxidation than the previously reported benzeneseleninic anhydride.[37,188,189] This was rationalized as an effect of the greater electron-withdrawing properties of the pyridine nucleus in rendering the Se═O bond a better enophile. Alternatively, the 2-pyridineseleninic anhydride may exist in equilibrium with a pyridinium salt which is the effective oxidant (equation 51).

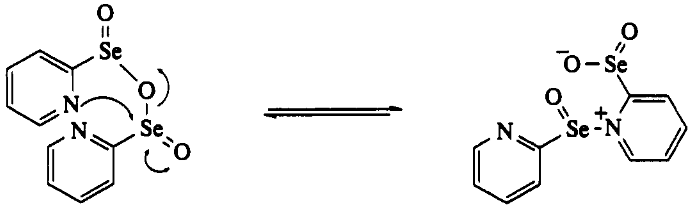

(51)

## 2.1.3.4 Singlet Oxygen

The ene reaction is by far the most widely investigated reaction of singlet oxygen,[88] involving the formation of an allylic hydroperoxide from an alkene by a process involving abstraction of an allylic proton with migration of the carbon–carbon double bond. Reduction of the resulting hydroperoxide, as discussed above, provides the corresponding allylic alcohol. Thus subsequent oxidation is required for formation of an α,β-unsaturated carbonyl compound.[190–192] A more direct route to the enone can also occur *via* β-elimination of water from the allylic hydroperoxide. Ireland,[190] in his investigation of α-methylene ketones, studied the photooxidation of some model systems and the subsequent reactions of the intermediate allylic hydroperoxides with acetic anhydride (Scheme 23).[88]

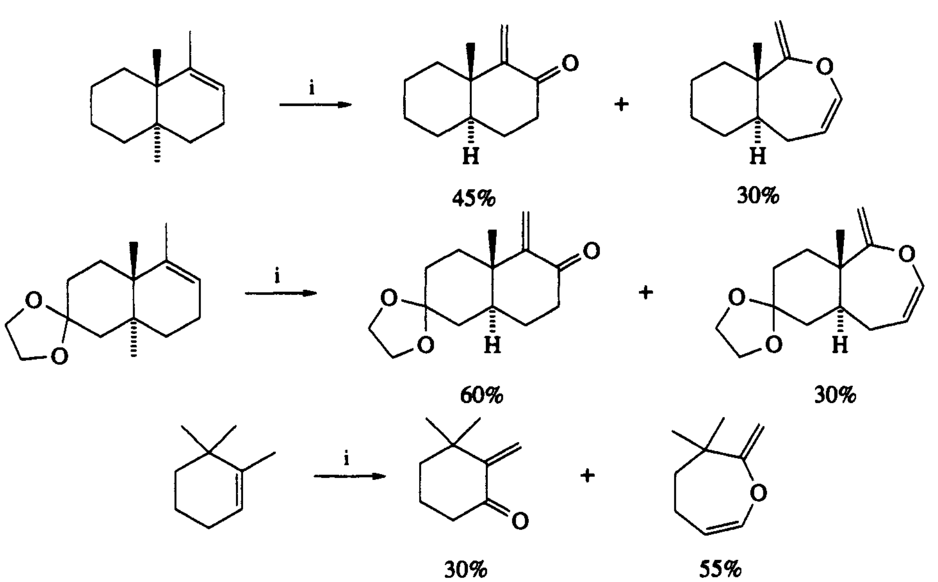

i, $^1O_2$, $Ac_2O$

**Scheme 23**

Decomposition of the intermediate allylic peracetates yielded the desired α-methylene ketones along with ring-expanded divinyl ethers, formed *via* a Hock fragmentation.[193] Direct formation of enones has also been reported by Mihelich[194] under similar conditions of photooxidation in the presence of acetic acid and a catalytic amount of base (Scheme 24).

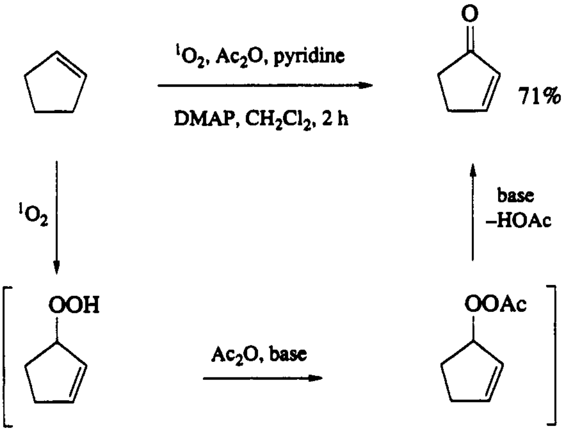

**Scheme 24**

For example, photooxidation of α-pinene led to formation of the desired product in 97% yield, whereas similar reaction of β-pinene was accomplished in only 58% yield (Scheme 25).

Interestingly, an anomalous result was obtained in the photooxidation of 1,3-cholestadiene and related compounds (equation 52).[195] Thus 1,4-cholestadien-3-one was obtained rather than the expected Diels–

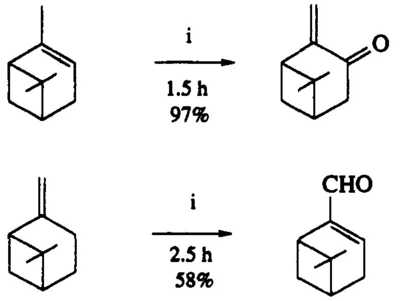

i, $^1O_2$, $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$

**Scheme 25**

Alder endoperoxide product. These results are discussed by the authors in terms of failure to meet the steric requirement for endoperoxide formation.[95,195]

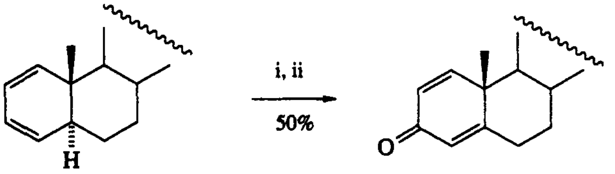

(52)

i, $^1O_2$, EtOH, 0 °C, *hv*, 18 h; ii, $Al_2O_3$

### 2.1.3.5 Miscellaneous Reagents

A few reagents have been reported for the allylic oxidation of particular substrates. These include *N*-bromosuccinimide oxidation of α-amyrin acetate in moist dioxane (equation 53),[196] a method later modified by Thomson.[197]

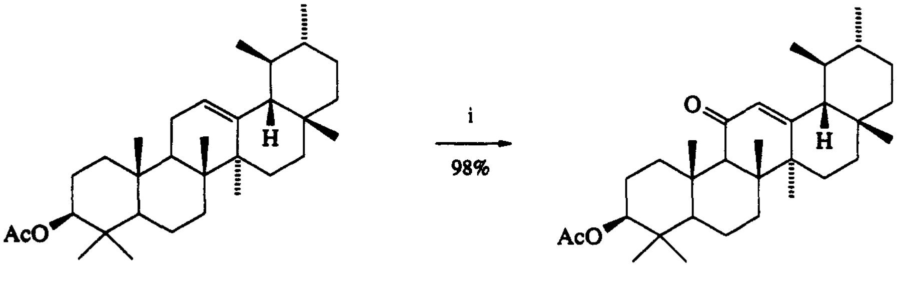

(53)

i, *N*-bromosuccinimide, aq. dioxane

A catalytic amount of palladium on charcoal (5 mol %) has been shown by Stoodley to effect allylic oxidation of cephem dioxides (**80**) and (**81**) in yields of about 60% in each case.[198]

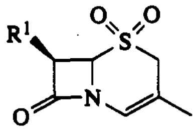

**(80)** a: $R^1 = H$
b: $R^1 = PhOCH_2CONH$

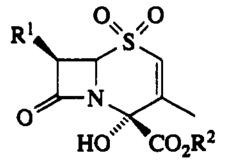

**(81)** a: $R^1 = H$, $R^2 = PhCH_2$
b: $R^1 = PhOCH_2CONH$, $R^2 = Ph_2CH$

The conversion of (**80b**) to (**81b**) and conversions of other compounds containing acidic allylic methine or methylene protons was found to proceed in the presence of activated carbon (Darco G-60; equations 54 and 55).

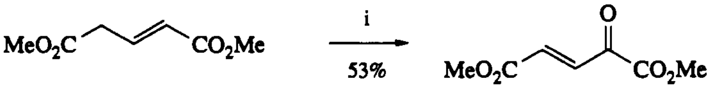

(54)

i, 4 equiv. Darco G-60, NEt$_3$, EtOAc, 24 h

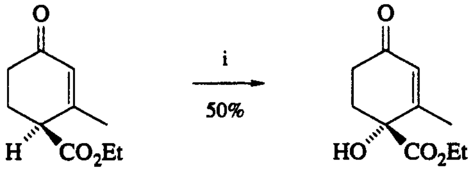

(55)

i, 4 equiv. Darco G-60, NEt$_3$, EtOAc, 24 h

Clearly, regio- and chemo-selectivities of this reagent are highly dependent on the substrate structure.

Allylic oxidation to give enones has also been reported at the 11-position of steroids upon treatment with nitrosyl fluoride solutions.[200]

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# 2.2

# Oxidation Adjacent to C=X Bonds by Dehydrogenation

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## 2.2.1 INTRODUCTION

The synthetic versatility of α,β-unsaturated carbonyl compounds has resulted in the development of a wide variety of methods for their synthesis. Many such procedures rely on the construction of the basic carbon framework from simpler fragments, and are typified by reactions of the Wittig, Knoevenagel, aldol and Reformatsky type.[1] To be able to introduce regioselective unsaturation into a previously established carbon skeleton is, however, an additional tool in the chemist's armamentarium. In this review we have attempted to bring together the main literature relating to dehydrogenation methodology. No attempt has been made to include similar reactions that would generate alkynes or reactions that would result in the formation of carbon atoms doubly bonded to heteroatoms. Several of the intermediates described, and especially those involving α-selenenyl or α-thio moieties, offer the opportunity for further elaboration prior to elimination, since such species are able to stabilize adjacent carbanions.[2–4] The synthetic applications arising from such intermediates are left to the ingenuity of the reader.

## 2.2.2 HALOGENATION–DEHYDROHALOGENATION REACTIONS

### 2.2.2.1 Halogenation

The traditional method for introducing α,β-unsaturation into compounds containing C═X groups is by a halogenation–dehydrohalogenation sequence. The halogen leaving group can be either α or β to C═X (Scheme 1), although base-mediated elimination is more facile in the latter instance. Since selective functionalization of the β-position is difficult, except where it is activated by other groups,[5,6] it is usual to introduce the halogen at the α-position.

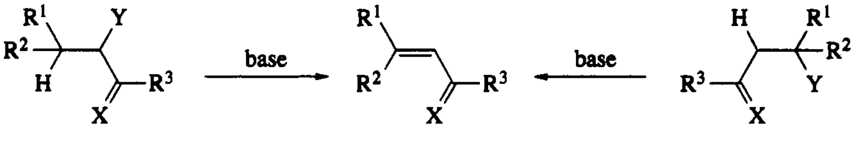

Y = halogen

Scheme 1

A variety of methods are available for the halogenation of aldehydes and ketones, and rely on the ease of enolization of such compounds. Copper(II) chloride[7] or bromide[8] in ethyl acetate at reflux have been shown to be effective reagents and rely on the promotion of enolization by the copper ion prior to the transfer of halogen. Since these conditions tend to favor the thermodynamic enol, unsymmetrical ketones preferentially halogenate at the more highly substituted α-carbon atom.[9] Similar selectivity is observed with NBS.[10,11]

While bromine itself can be used to effect α-bromination of ketones,[12,13] the hydrogen bromide produced can be detrimental.[10] The addition of acid scavengers such as 1,2-epoxycyclohexane (equation 1)[14] or potassium perchlorate[15] can, however, lead to good yields in the more difficult cases. As with copper(II) salts, the conditions for elemental bromine also favor substitution at the more highly substituted carbon atom.

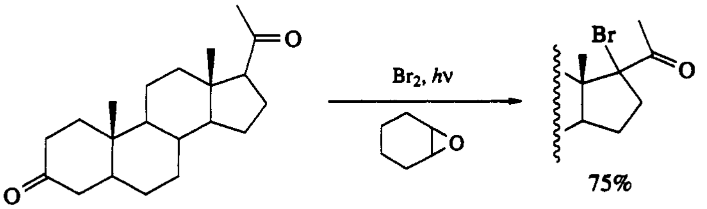

(1)

An alternative procedure to bromine itself is the use of complexed derivatives such as 2-pyrrolidone hydrotribromide (PHT), which is easier to handle. This reagent has been shown to brominate flavanones in THF, while the more vigorous conditions of hot DMSO result in concommitant dehydrohalogenation to give the flavone (Scheme 2).[16]

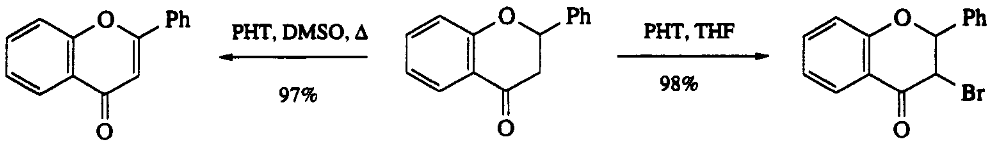

cis:trans 2:3

Scheme 2

A greater degree of regiocontrol over the above methods can be achieved by quenching the enolate of carbonyl compounds with either bromine[17] or iodine.[18,19] Thus, in the case of unsymmetrical ketones (Scheme 3), low temperature formation of the enolate allows exclusive bromination of the kinetic enolate to afford the haloketone (**1**), which on elimination gives the enone (**2**).[17] A similar procedure allows esters to be iodinated in excellent yields (Scheme 4).[18,19] Lactones (Scheme 5) also undergo bromination, and good yields have been obtained using 1,2-dibromoethane as the halogen source.[20,21]

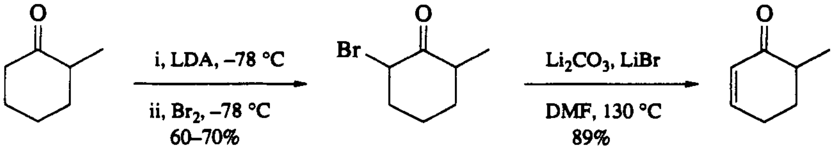
i, LDA, –78 °C
ii, $Br_2$, –78 °C
60–70%
Br
$Li_2CO_3$, LiBr
DMF, 130 °C
89%

(1) (2)

**Scheme 3**

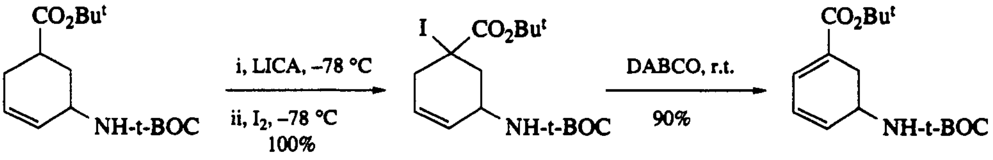
$CO_2Bu^t$
NH-t-BOC
i, LICA, –78 °C
ii, $I_2$, –78 °C
100%
I
$CO_2Bu^t$
NH-t-BOC
DABCO, r.t.
90%
$CO_2Bu^t$
NH-t-BOC

**Scheme 4**

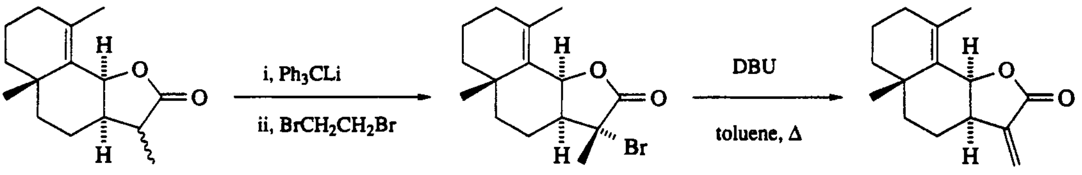
H
O
O
H
i, $Ph_3CLi$
ii, $BrCH_2CH_2Br$
H
O
O
H
Br
DBU
toluene, Δ
H
O
O
H

**Scheme 5**

Since enolate formation requires the use of strong base, compounds that are unstable to such conditions may be α-halogenated *via* the corresponding enol ether.[22,23] Thus, the iodination of enol acetates in the presence of thallium(I) acetate has been reported (entry 1, Table 1),[24] although the toxicity of this reagent limits its use to all but difficult cases. Silver acetate, although expensive, is an effective substitute (entry 2, Table 1).[25] The enol acetates of aldehydes undergo facile reaction with NBS and furnish good yields of the dehydrogenated derivatives on subsequent base treatment.[22,23] Fortunately, silyl enol ethers react well with elemental bromine or NBS under mild conditions[22,23,26,27] which makes this procedure one of the most synthetically useful alternatives (entry 3, Table 1).

Table 1 Reaction of Enol Ethers and Acetates with Halogens

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 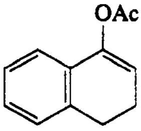 | 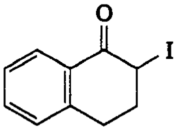 | TlOAc, $I_2$, $CH_2Cl_2$ | 75 | 24 |
| 2 | 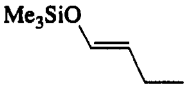 | 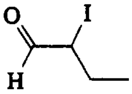 | i, AgOAc, $I_2$, $CH_2Cl_2$; ii, $Et_3N$•HF | 64 | 25 |
| 3 | 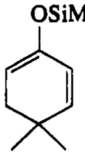 | 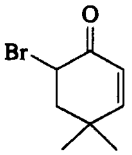 | $Br_2$, $CCl_4$, –20 °C | 90 | 26 |

The methods discussed so far are applicable to aldehydes, ketones, esters and lactones. The α-halogenation of acids has received relatively little attention, although the traditional Hell–Vollard–Zelinski conditions are adequate in most instances (equation 2).[28] Alternative conditions have been developed, however, in which the acyl halide may be halogenated using NBS.[29] Quenching the reaction with alcohols or amines offers the opportunity of forming carboxylate derivatives.

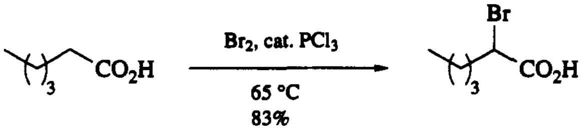

(2)

Tertiary amides can be converted into their α,β-unsaturated derivatives in good yield by the sequential treatment with phosgene then pyridine *N*-oxide and triethylamine (Scheme 6),[30] provided that only one hydrogen atom is present on the carbon atom adjacent to the amide group. In this instance, the intermediate chloroiminium salt (3) undergoes oxidation to the unsaturated amide. This method has the advantage that it does not involve the use of strong base and, with suitable protection of the amino group, furnishes a potential route to dehydro amino acids.[30]

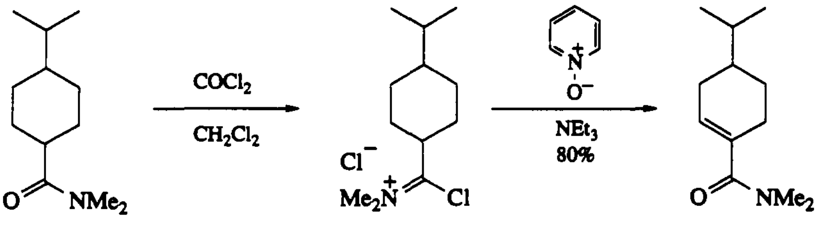

(3)

Scheme 6

### 2.2.2.2 Dehydrohalogenation

The second step in the dehydrogenation sequence involves the base-induced elimination of the α-halide. Depending on the nature of the substrate, it is possible to obtain both (*E*)- and (*Z*)-isomers since elimination usually proceeds *via* an antiperiplanar loss of the halogen acid (Scheme 7). For chiral compounds having only one β-hydrogen atom, the geometry of the resulting product is defined in the transition state (Scheme 7), although the strong thermodynamic preference for the formation of (*E*)-isomers may result in mixtures.

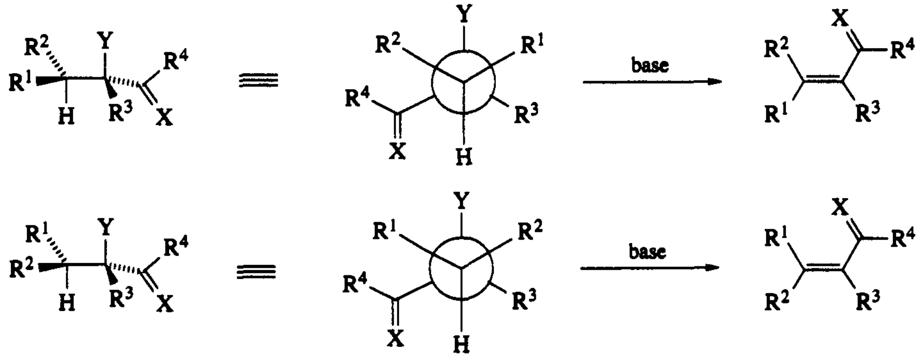

Scheme 7

In those cases where there are two hydrogen atoms on the β-carbon atom, two conformational preferences exist and, consequently, two isomers can result (Scheme 8). The relative ratio of isomers will be dependent on steric interactions in the transition state. Thus, if $R^1$ and $R^2$ are large formation of the alkene in which $R^1$ and $R^2$ are *trans* to one another will be preferred.

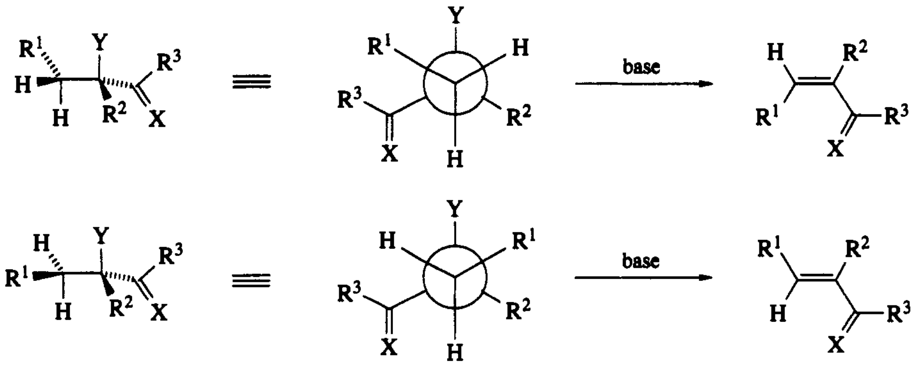

**Scheme 8**

A variety of bases have been used to effect the elimination of halogen acids from α-halo carbonyl compounds (Table 2). Among the more commonly used organic bases are DBN,[20] DABCO,[19] collidine[31] and triethylamine.[32] Yields tend to be variable with these reagents and reductive dehalogenation or double bond migration have been observed.[31] Inorganic bases such as lithium carbonate[12,17,27,33] or calcium carbonate[13] (Table 2) are usually preferred to organic bases since fewer side reactions are encountered. Stronger bases such as potassium hydroxide[34] and potassium *t*-butoxide[35] have been successfully employed, although with ketones the incidence of Favorskii rearrangement is increased.[36]

**Table 2** Base Elimination of α-Halides

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 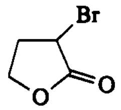 | 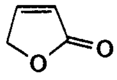 | $Et_3N$, ether, Δ | 60 | 32 |
| 2 | 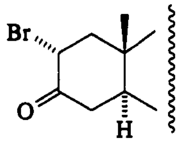<br>2α-Bromocholestan-3-one | 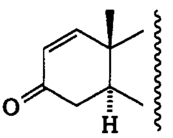 | γ-Collidine, Δ | 41 | 31 |
| 3 | 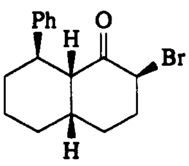 | 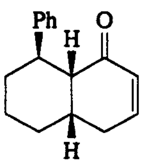 | $Li_2CO_3$, DMF, Δ | 51 | 12, 33 |
| 4 | 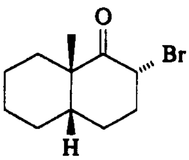 | 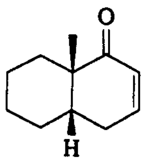 | $CaCO_3$, $MeCONMe_2$, Δ | 95 | 13 |
| 5 | 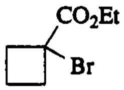 | 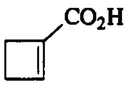 | KOH, toluene, Δ | >85 | 34 |

In general, although halogenation–dehydrohalogenation reactions are the classical method for the dehydrogenation of C=X compounds, there is little evidence that this method has been used where X is other than oxygen. Moreover, the development of more sophisticated methodology based on sulfur and selenium (see Sections 2.2.3 and 2.2.4) has placed halogenation–dehydrohalogenation low in the order of preferred alternatives. Nonetheless, it is possible to replace one α-substituent by another under nucleophilic conditions. While such processes appear to offer little advantage over the direct insertion methods, it is conceivable that the replacement of halogen atoms by thio[4] and selenenyl[37–39] groups may allow difficult eliminations to proceed under comparatively mild conditions. Such methods may be of particular value when the corresponding halo compounds are readily available.

## 2.2.3 SULFUR-BASED REAGENTS

Elemental sulfur has been used for many years to effect dehydrogenation reactions[40] and, provided that the substrate is thermally stable, it has the advantages of cheapness and simplicity. In a typical reaction, the carbonyl compound (4) and powdered sulfur are heated together to around 200 °C either neat[41] or using a high boiling solvent such as *p*-cymene,[42] as illustrated in equation (3).[41]

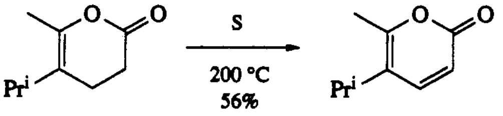

(4)

(3)

Although in some instances elemental sulfur is favorable to halogenation–dehydrohalogenation and quinone dehydrogenation reactions,[41] it has largely been superseded by organosulfur reagents. Like selenium (Section 2.2.4) the success of these reagents is dependent on the ease of the thermolytic *syn* elimination of sulfoxide from compounds bearing a suitably orientated hydrogen atom on the β-carbon atom (equation 4).[4] The temperature at which this elimination ensues varies with the nature of the substituent on sulfur, but aryl sulfoxides usually require temperatures of 25–80 °C compared to 110–130 °C for alkyl sulfoxides.[4] In general, exclusive formation of the (*E*)-geometric isomers is observed with the exception of those compounds having similar β,β-disubstitution or in those cases where this geometry is unattainable or otherwise disfavored.[4,43] Thus, in acyclic systems the regiochemistry for hydrogen abstraction is usually governed by the order $C{=}CCH_2 \approx C{\equiv}CCH_2 > ArCH_2 \approx CH_3 > CH_2 \gg C{-}H$, whereas in cyclic systems preference is for the formation of endocyclic alkenes.[4]

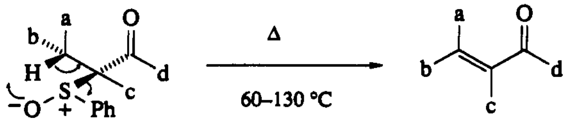

(4)

When the temperature needs to be kept as low as possible, elimination may be facilitated by incorporation of electron-withdrawing substituents in the *p*-position of the aromatic ring.[44] The 2-pyridylthio moiety has also been used to good effect in the synthesis of methyl dehydrojasmonate and tuberolactone.[45] Elimination may also be enhanced by conversion of the sulfide to the *N*-*p*-toluenesulfonylsulfilamine with Chloramine T prior to pyrolysis,[46] but the advantages, if any, of this modification have still to be shown. A further approach that assists the elimination of methylthio groups has been described by Vedejs and Engler.[47] Thus, alkylation of the thio compound (**5**) with ethyl trifluoromethylsulfonyloxyacetate generates the ylide (**6**) which spontaneously decomposes under the reaction conditions to give the corresponding α,β-unsaturated carbonyl compound (**7**; Scheme 9).[47]

Several methods are available for the introduction of sulfenyl groups α to carbonyl derivatives and these have been reviewed.[4,43] The most versatile procedure involves reaction of the enolate with an appropriate thiol derivative,[43,48] but the preferred method is largely dependent on the nature of the substrate employed (see below). In most instances, sulfur has been introduced in the divalent state and subsequently oxidized, although the oxidative step has been avoided by the direct introduction of sulfur at the $S^{IV}$ oxidation level.[49–51] The oxidation of sulfides to sulfoxides is a trivial procedure that can be effected by a variety of reagents. Sodium metaperiodate, *m*-chloroperbenzoic acid and hydrogen peroxide are the most common oxidants, but *t*-butyl hydroperoxide, *t*-butyl hypochlorite, *N*-chlorobenzotriazole,

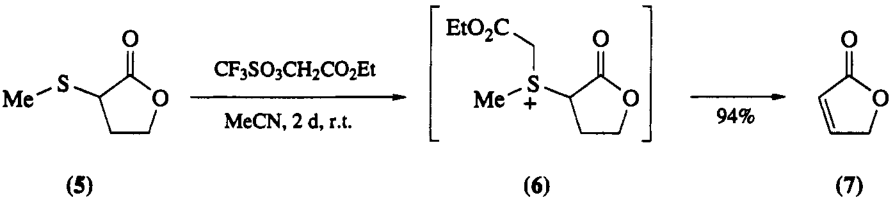

Scheme 9

chromic acid, dinitrogen tetroxide, iodosylbenzene, nitric acid, ozone and a host of other oxidizing agents have also been used.[43] Sodium metaperiodate is preferred in the absence of other determining factors and typical reaction conditions involve treatment of the sulfenyl compound in methanol at room temperature with 1 equiv. of the oxidant.[43]

Dehydrogenation reactions using sulfur reagents have been shown to tolerate a variety of other functional groups, including acetals, alkenes, epoxides and silyl ethers,[43,52] but the milder procedures available using selenenyl moieties may offer advantages in more sensitive molecules (see Section 2.2.4).

### 2.2.3.1 Sulfur(II) Reagents

The sulfenylation of esters,[43,52] lactones,[48,52,53] carboxylic acids,[48,54] amides[55] and lactams[55,56] may be effected by reaction of the corresponding lithium enolates in THF at –78 to 0 °C with dimethyl or diphenyl disulfides, or, less commonly, with methyl or phenyl sulfenyl halides.[48] The enolates of ketones, however, are insufficiently nucleophilic to react with dialkyl sulfides unless HMPA is added to the reaction mixture,[43] although they do react smoothly with diaryl sulfides.[43,48] This difference allows the selective sulfenylation of esters in the presence of ketones (entry 5, Table 3).[43]

In those instances where sulfenylation of ester enolates results in poor yields, use of the more stable *t*-butyl or silyl esters can offer advantages.[4] The sulfenylation of aldehyde enolates is only possible at –100 °C due to competing aldol condensation reactions.[48] Typical products made in this manner are illustrated in Table 3. The reaction of 2-methylcyclohexanone (**8**; entry 2) is of particular interest and clearly demonstrates the improved yield of kinetic enolate-derived product obtainable with more reactive sulfenylating agents.[43] Conformational studies indicate a slight axial preference for thiolate substitution in cyclohexanones, which is similar to that found on halogenation, although in condensed ring systems 1,3-diaxial interactions result in exclusive equatorial substitution.[43]

Dehydrogenation reactions involving sulfur have proved important in the formation of α-methylene-lactones such as (**9**; Scheme 10), but sulfenylation prior to alkylation is necessary for *cis*-fused systems in order to establish the correct geometry for exocyclic double bond formation.[53]

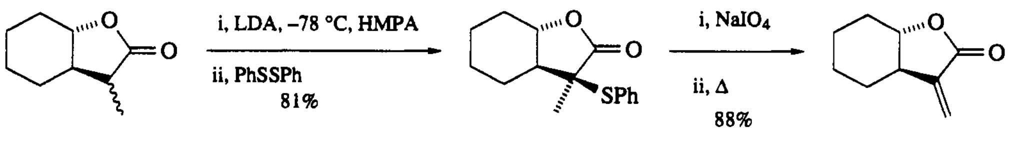

(**9**)

Scheme 10

Because of their tendency to undergo aldol reactions, various conditions have been investigated to develop methods for the sulfenylation of aldehydes. Indirect methods involving metallation of the corresponding imines (**10**; Scheme 11)[4] offer a preferred alternative to the low temperature direct sulfenylation described above, but better methods are still required. One possibility may be to exploit the rapid room temperature enolization of aldehydes observed on treatment with potassium hydride in THF.[57]

The sulfenylation of metalloimines is equally applicable to ketones, although using more reactive sulfur electrophiles it is possible to bring about reaction on the unmetallated enamine.[58,59] Sulfenylation of ketone enol silyl ethers also proceeds well with the more reactive sulfur species.[60] Sulfenamides and their derivatives (*e.g.* **11**) are particularly suited to the direct sulfenylation of ketones and active methylene compounds such as β-diketones, β-keto esters and malonates, which undergo facile reaction at room temperature (equation 5).[59] This procedure, however, does not appear to have been exploited for the dehydrogenation of active methylene compounds (*cf.* Section 2.2.4.1). By preparing the dianion (**13**)

**Table 3** Sulfenylation of Lithium Enolates

| *Entry* | *Substrate* | *Product* | *Reagent* | *Yield* (%)[a] | *Ref.* |
|---|---|---|---|---|---|
| 1 | 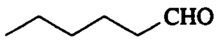 | 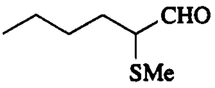 | MeSCl | 70[b] | 48 |
| 2 | 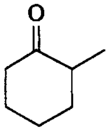<br>**(8)** | 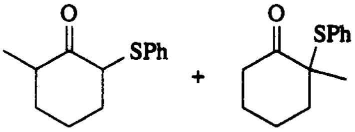<br>4:1 | PhSSPh | 87 | 43 |
|  |  | 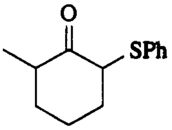 | $PhSSO_2Ph$ | 85 | 43 |
| 3 | 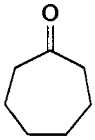 | 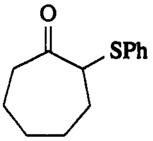 | PhSSPh | 87 | 43 |
| 4 | 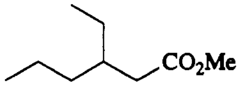 | 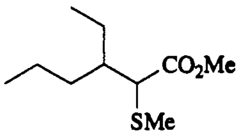 | MeSSMe | 88 | 52 |
| 5 | 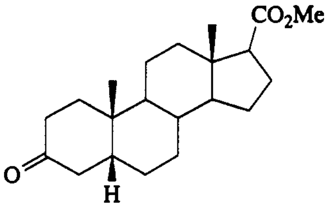 | 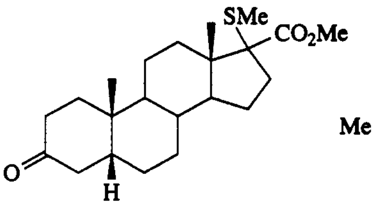 | MeSSMe | 100 | 52 |
| 6 | 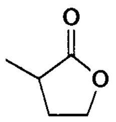 | 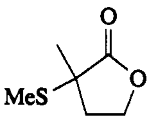 | MeSSMe | 79 | 53 |
| 7 | 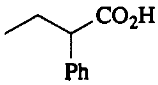 | 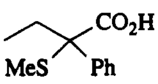 | MeSSMe | 96 | 48 |
| 8 | 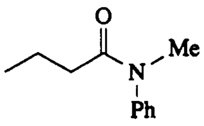 | 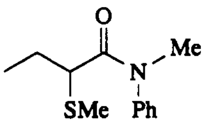 | MeSSMe | 80 | 55 |
| 9 | 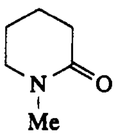 | 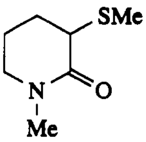 | MeSSMe | 69 | 55 |

[a] Reactions carried out at −78 to 0 °C in THF. [b] Reaction carried out at −100 °C.

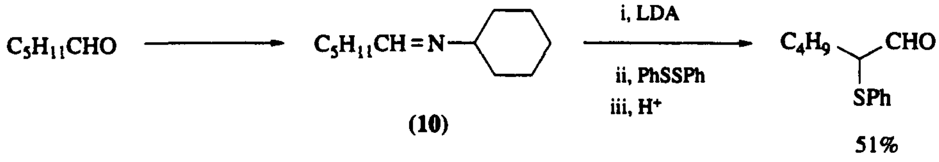
C5H11CHO
C5H11CH=N
(10)
i, LDA
ii, PhSSPh
iii, H+
C4H9
CHO
SPh
51%

**Scheme 11**

of the β-keto ester (**12**; Scheme 12) sulfur was incorporated at the more nucleophilic C-3 position on quenching with diphenyl disulfide.[61] This offers the opportunity to introduce unsaturation out of conjugation with the ester moiety.

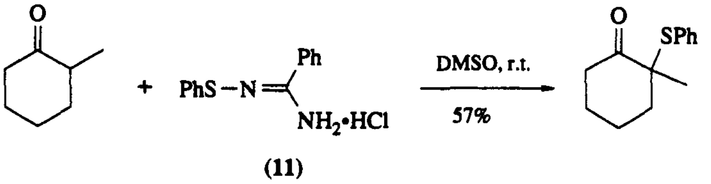
O
+
PhS−N
Ph
NH2•HCl
(11)
DMSO, r.t.
57%
O
SPh

(5)

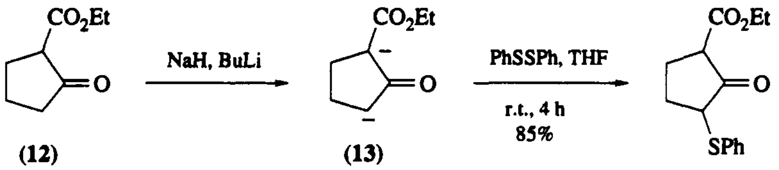
CO2Et
O
(12)
NaH, BuLi
CO2Et
O
(13)
PhSSPh, THF
r.t., 4 h
85%
CO2Et
O
SPh

**Scheme 12**

The direct sulfenylation of *N*,*N*-dimethylhydrazones *via* the reaction of the α-lithio derivative (**14**) with dimethyl disulfide (Scheme 13) has been reported, and the initially formed product (**15**) shown to isomerize to the more stable (*E*)-isomer (**16**).[62] While further transformations have been carried out on compound (**16**), attempts do not appear to have been made to introduce unsaturation by the elimination of the thiol group.

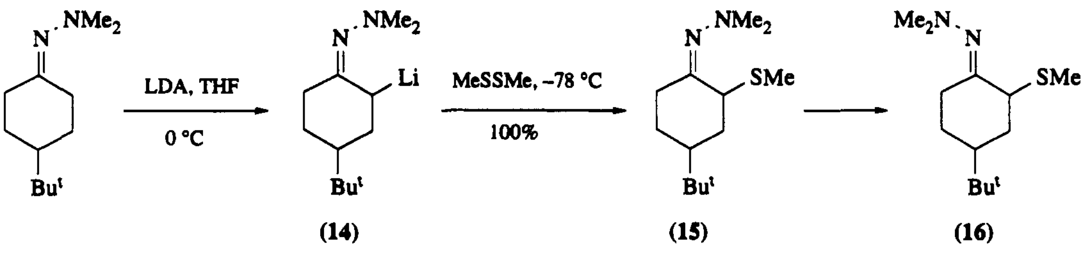
N
NMe2
Bu^t
LDA, THF
0 °C
N
NMe2
Li
Bu^t
(14)
MeSSMe, −78 °C
100%
N
NMe2
SMe
Bu^t
(15)
Me2N
N
SMe
Bu^t
(16)

**Scheme 13**

For a more comprehensive account of the methods available for the sulfenylation of carbonyl compounds the review by Trost is recommended.[4]

### 2.2.3.2 Sulfur(IV) Reagents

Methods for the sulfinylation of carbonyl species have not been extensively investigated, but are complementary to those used for sulfenylation and have the advantage of avoiding the oxidative step prior to elimination. Typically, ketones and esters have been sulfinylated in good yields by reaction of their enolates in ethereal solvents with methyl-, phenyl- or *p*-toluene-sulfinate at room temperature to reflux[49,50] (equation 6).[49] These bulky reagents have been used to good effect in distinguishing between two otherwise similar methylene groups in a complex asymmetric ketone.[51]

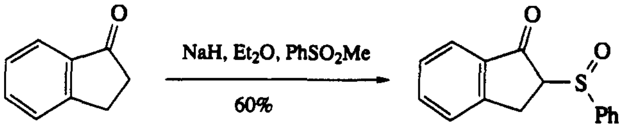

(6)

Little work has been carried out on sulfinylation reactions on those systems having thiocarbonyl and imino moieties. However, hydrazones are converted to α-sulfinyl derivatives on reaction of their anions (prepared from LDA in THF) at −78 °C with sulfinate esters,[63] although the full utility of this reaction remains to be explored. Furthermore, in an unusual reaction, *p*-toluenesulfinyl chloride has been shown to effect a facile one-step dehydrogenation of the thiolactam (**17**; equation 7) in good yield.[64] These reactions contrast with the oxidative removal of thiocarbonyl, hydrazonyl and similar functionalities with $Se^{IV}$ species (see Section 2.2.4.2).

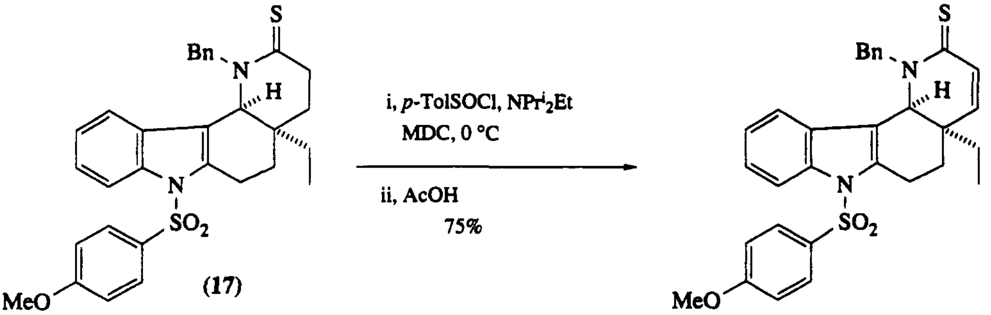

(**17**)

(7)

## 2.2.4 SELENIUM-BASED REAGENTS

Of all the methods currently used for the dehydrogenation of carbonyl and similar compounds, those utilizing selenium-based reagents have possibly received the greatest attention. Historically, selenium first found utility as its dioxide for the dehydrogenation of steroidal ketones (equation 8),[65,171] but the reagent lacks selectivity[37] and has proved problematical with more sensitive compounds.[66] As a consequence therefore, organoselenium reagents have virtually replaced selenium dioxide for effecting this transformation.

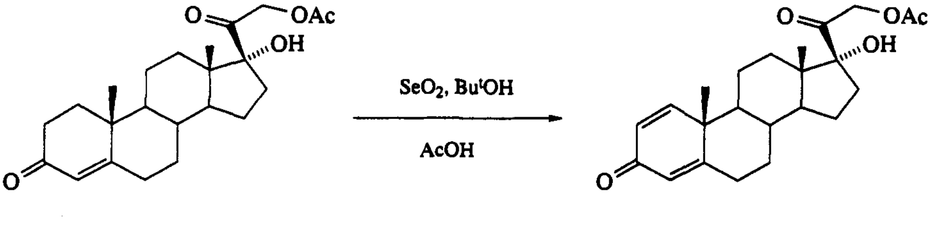

(8)

These newer reagents rely on the extremely facile *syn* elimination of selenoxides in which the β-carbon atom bears at least one hydrogen atom (equation 9).[37,67] In general, the elimination of selenoxides takes place at temperatures between 0 and 25 °C, except in those cases in which some factor renders the *syn* elimination unfavorable.[67] This contrasts with the stability of sulfoxides, which generally require heating to temperatures around 60 to 120 °C in order for elimination to occur.[4] As with sulfoxide eliminations, in those instances where geometric isomers are possible only the (*E*)-isomer is formed.[39] However, not all selenoxides collapse readily and difficulties have been found with primary alkyl selenoxides[38] and some ketones and aldehydes.[68] Since the rate of selenoxide elimination is enhanced by electron-withdrawing groups on the aromatic ring, the introduction of *o*- or *p*-nitro groups is particularly beneficial.[69] The use of 2-pyridylselenenyl bromide was found to be a useful alternative for the dehy-

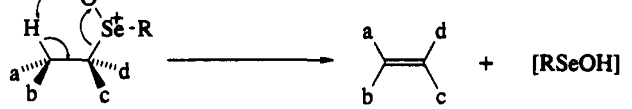

(9)

drogenation of ketones and aldehydes,[70] and Chloramine T under phase transfer conditions has also been found to facilitate the elimination of selenium in some difficult cases.[38]

The most versatile method for introduction of the selenenyl moiety is by low temperature reaction of the enolate anion or an enolic derivative with a suitable selenium species, the precise conditions being dependent on the reactivity of both the carbonyl compound and the selenium species.[37,71] Like sulfur, selenium may be introduced either in the divalent state and subsequently oxidized[37,71] or, more recently, as the selenoxide directly (Scheme 14).[72] The choice of method is determined by the subsequent reactions that need to be carried out.

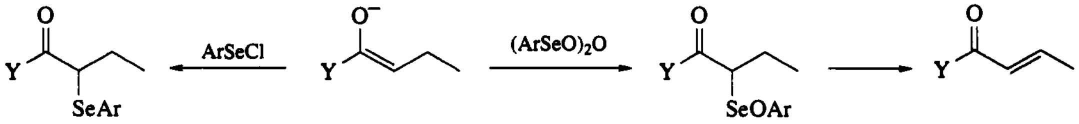

**Scheme 14**

Selenides are more readily oxidized to $Se^{IV}$ than the corresponding sulfur compounds and most oxidizing agents will effect this transformation.[3] The most commonly used reagents are hydrogen peroxide, sodium periodate, peracids and ozone,[37,67] although a number of more exotic reagents have also been used.[67] Ozone offers several advantages over the use of other oxidants. In particular, it reacts quantitatively with selenides in a variety of solvents at −10 to −50 °C and excess reagent is easy to remove.[37] Furthermore, whereas sulfides are oxidized more slowly than alkenes by ozone, selenides are oxidized considerably faster,[37,67] suggesting that selenium can be selectively oxidized in the presence of both sulfur and alkenes.

The drawbacks to the use of selenium-based reagents are their inherent toxicity, relative expense and the unpleasant odors frequently formed as a result of their use. The development of catalytic processes and polymer-bound systems should ultimately overcome these disadvantages.

### 2.2.4.1 Selenium(II) Reagents

Selenenylations of ketones,[71] esters,[2] lactones[2,71] and lactams[56] are usually effected by the reaction of the corresponding lithium enolates with PhSeCl, PhSeBr and PhSeSePh (with the exception of ketones) at low temperature.[71] Aldehydes have not been selenenylated in this manner. Table 4 illustrates some typical products that have been made in this way. Selenenylation has been especially useful in natural product synthesis for the formation of α-methylenelactones from the parent α-methyl compounds (Scheme 15 and Table 4),[73,74] and has significant advantages over the more traditional methods for ef-

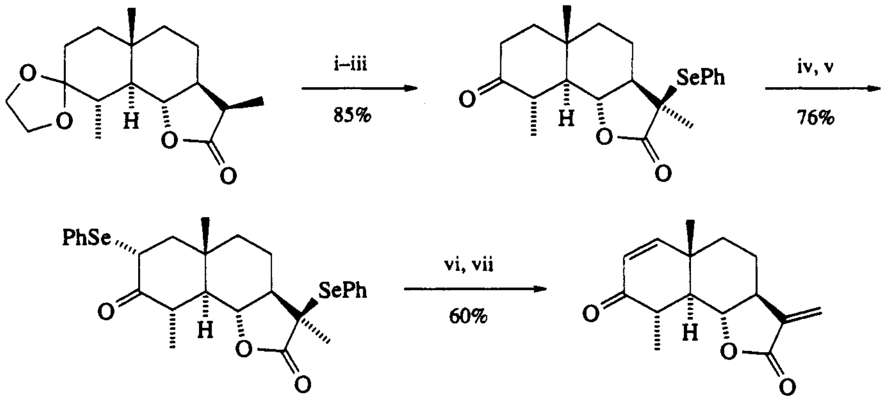

(±)-Tubiferine

i, LDA, THF; ii, $(PhSe)_2$, −20 °C; iii, HCl; iv, LDA, THF, −78 °C; v, PhSeCl, −78 °C; vi, $O_3$, −78 °C, $CH_2Cl_2$; vii, 25 °C

**Scheme 15**

fecting this transformation.[75] In order to ensure the formation of reasonable amounts of the *exo* isomers, however, it has often been found necessary to introduce the selenenyl moiety prior to alkylation, rather than the other way around.[73,74]

**Table 4** Dehydrogenation of Ketone, Ester, Lactone and Lactam Enolates[a]

| *Entry* | *Substrate* | *Product* | *Oxidant* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 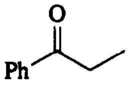 | 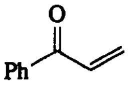 | $NaIO_4$ | 78 | 71 |
| 2 | 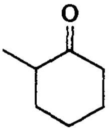 | 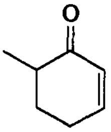 | $O_3$ | 65 | 71 |
| 3 | 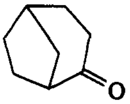 | 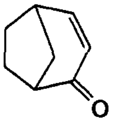 | $H_2O_2$ | 58 | 71 |
| 4 | 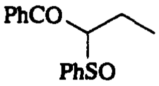 | 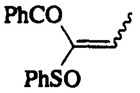 | $H_2O_2$ | 55 | 71 |
| 5 | 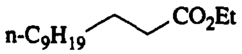 | 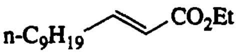 | $MeCO_3H$ | 79 | 39 |
| 6 | 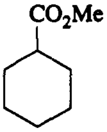 | 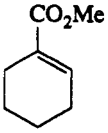 | $H_2O_2$ | 96 | 71 |
| 7 | 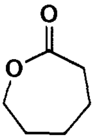 | 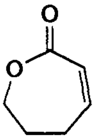 | $O_3$ | 46 | 71 |
| 8 | 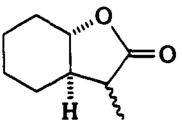 | 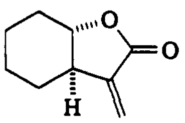 | $MeCO_3H$ | 82[b] | 74 |
| 9 | 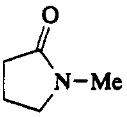 | 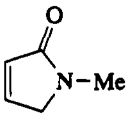 | $H_2O_2$ | 31 | 56 |

[a] Selenenylation of enolate, usually generated with LDA in THF, with PhSeCl or PhSeBr. [b] Reaction of enolate with $(PhSe)_2$ in HMPA.

Selenenylation of lithium enolates is particularly important in the case of unsymmetrical ketones, when the product of kinetic control is preferentially formed. The more-substituted isomeric derivative is prepared by the selenenylation of the corresponding enol acetate.[76] An interesting base-catalyzed transselenenylation reaction of α-alkyl-α-phenylseleneno ketones to the less-substituted α′-position has recently been reported[77] for which steric crowding at the α-position appears to be an essential requirement.

The selenenylation of aldehydes may be carried out in several ways, but most of the earlier methods involve prior formation of either the enol ether (**18**)[78] or the corresponding enamine (**19**; Scheme 16).[39,79] These stepwise procedures overcome the problems of slow incorporation and low yields of selenenyl moieties observed under acid-catalyzed conditions.[39] Selenium can be efficiently introduced in one step, however, using a combination of PhSeSePh and $SeO_2$ in the presence of a catalytic amount of sulfuric acid.[80]

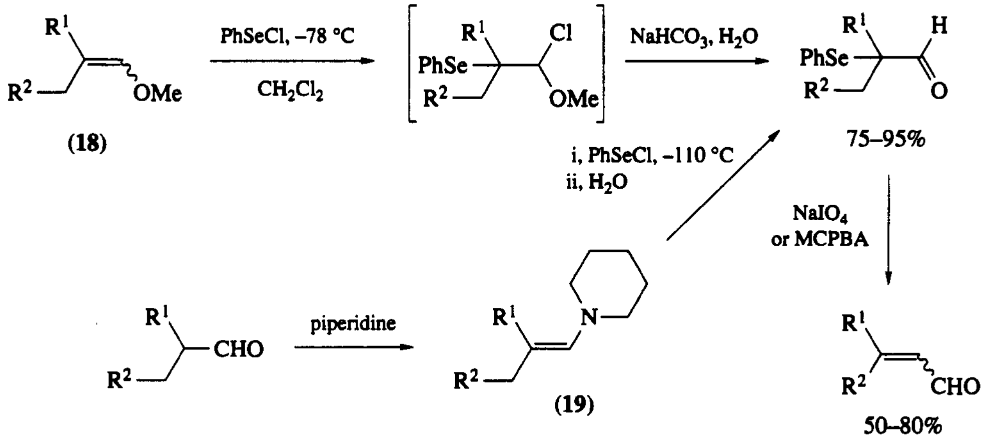

**Scheme 16**

An alternative one-step procedure using *N*,*N*-diethylbenzeneselenamide has been developed[81,82] and, as illustrated in equation (10), this reagent is particularly suitable for differentiating between aldehydic and ketonic moieties in the same molecule.[81] The analogous morpholinoselenamide has been shown to selenenylate the α-keto ester (**20**; equation 11) but no other examples have been reported.[67]

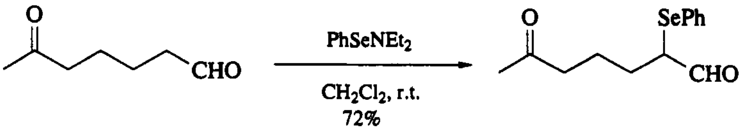

(10)

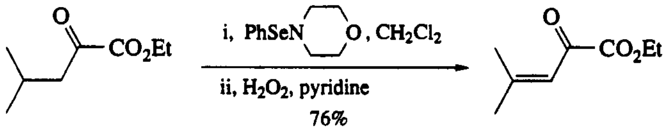

(11)

**(20)**

Using $PhSeNEt_2$, it is also possible to selenenylate β-dicarbonyl compounds, but this method has received little attention.[82] The enolates of β-dicarbonyl compounds are also selenenylated on treatment with PhSeCl or PhSeBr,[71] although such highly enolized compounds may be converted into their selenenylated derivatives in good yield under milder conditions using a 1:1 complex of PhSeCl and pyridine.[83] This latter method has the advantage that, by the avoidance of strong base, the reaction is compatible with a wide variety of other functional groups, without the need for prior protection. Nonenolized carbonyl compounds were shown not to react under these conditions.[83]

An interesting variation for the introduction of selenenyl species, which has the advantage of using cheaper elemental selenium, has been described by Liotta and coworkers (Scheme 17).[84–86] This reaction involves conversion of the lithium enolate (**21**) to the intermediate selenolate (**22**) which may be directly alkylated to give the selenenyl derivative (**23**) in high yield.[84–86] The reaction works well with ketones, esters and β-dicarbonyl compounds, but has the disadvantage of requiring the use of HMPA.[84,85]

The aromatization of cyclohexenones is an important process that can be easily accomplished by the use of selenium-based reagents using similar techniques to those previously discussed for other carbonyl species. Thus, enolates derived from α,β-enones readily undergo selenenylation at the α′-position and on oxidation and elimination afford the corresponding phenols.[87,88]

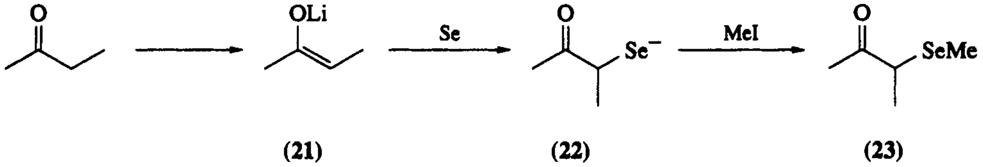

Scheme 17

A comprehensive review of the methods available for the introduction of selenenyl moieties has recently been published.[89]

### 2.2.4.2 Selenium(IV) Reagents

For those reactions in which the insertion of α,β-unsaturation is the immediate objective, the introduction of the selenenyl species as $Se^{IV}$, rather than as $Se^{II}$, may be expeditious since this obviates the need for a subsequent oxidative step. Selenium dioxide, benzeneseleninic acid and its anhydride act principally as oxidizing agents in their reaction with organic substrates and selenium tetrahalides are powerful halogenating agents.[89] Nevertheless, selenium dioxide effectively dehydrogenates 1,4-dicarbonyl compounds and has been useful for the dehydrogenation of steroidal and terpenoid ketones.[90] Benzeneseleninic anhydride has proved to be particularly suited to this transformation and has been used successfully for the dehydrogenation of steroidal ketones,[72,91] lactones[92] and lactams (Table 5).[93] Where comparisons have been made, this reagent is superior to selenium dioxide.[94] Typically the carbonyl compound is heated at 95 to 130 °C with the anhydride, in solvents such as chlorobenzene, to give high yields of the oxidized products.[72] At the higher temperatures (>120 °C) benzeneseleninic acid is converted to the anhydride and so forms a useful alternative reagent.[72] A feature of the reaction is that the PhSeSePh formed in the oxidation may be isolated and reoxidized to the anhydride with nitric acid if required.[72] The catalytic use of PhSeSePh with *t*-butyl peroxide,[72] iodosylbenzene,[95] or better *m*-iodosylbenzoic acid,[95] has also been described. It is interesting that all attempts to oxidize the γ-lactone (**24**; entry 3, Table 5) resulted only in dehydrogenation of the A-ring ketone.[92] Care must be taken to ensure minimum reaction times when effecting dehydrogenations with benzeneseleninic anhydride in order to avoid angular hydroxylation reactions resulting from further oxidation.[94] The addition of aluminum chloride to troublesome reactions appears to favor dehydrogenation.[96]

As a result of the powerful oxidizing potential of benzeneseleninic anhydride, it is incompatible with the presence of a number of functional groups, although many common moieties are well tolerated. Thus, it has been shown to convert thiocarbonyl compounds such as xanthates, thiocarbonates, thioamides and thiones,[97] and hydrazones, oximes, thiosemicarbazones and hydroxylamines,[98] into the corresponding carbonyl compounds under relatively mild conditions. Furthermore, hydrazo derivatives are converted to the azo compounds.[98]

Little work appears to have been carried out with benzeneseleninic anhydride on substrates other than steroidal or triterpenoid compounds, but it seems likely that the stronger conditions required to effect oxidation with this reagent makes it less attractive than the two-step procedure described above. Indeed, in the few instances reported it failed to convert hydrocinnamamide into cinnamamide,[93] and is said to be of no value for the dehydrogenation of acyclic esters.[99] There are, however, several reports in which either catalytic or stoichiometric benzeneseleninic anhydride has effectively dehydrogenated cyclic ketones in high yield,[94] a typical example being illustrated in equation (12).[95]

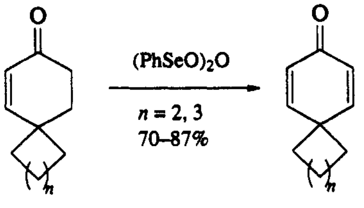

(12)

In an interesting extension of the use of benzeneseleninic anhydride, Barton and coworkers[100] have dehydrogenated steroidal and other oxazolines (*e.g.* **25**) in high yield (equation 13). This type of reaction has considerable potential for a wide variety of heterocyclic systems, due to the acidity of exocyclic

**Table 5** Dehydrogenation of Steroidal Ketones, Lactones and Lactams[a]

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 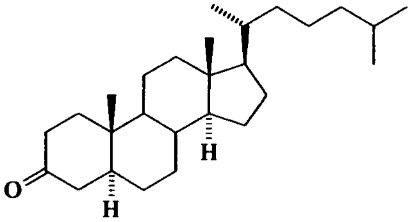 | 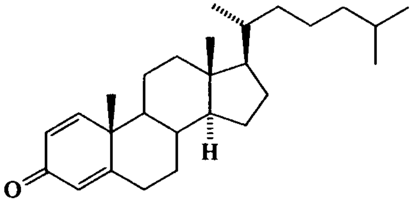 | 83[b] | 72 |
| 2 | 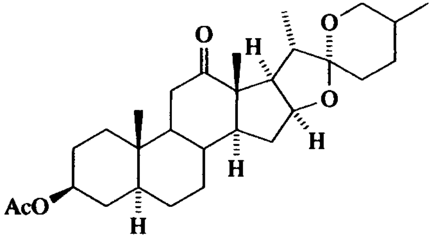 | 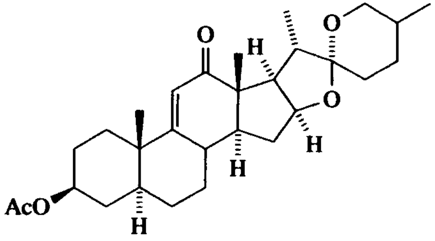 | 91 | 72 |
| 3 | 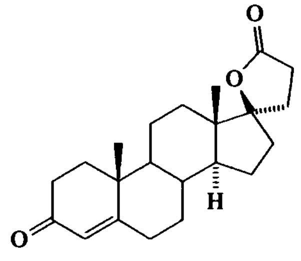<br>**(24)** | 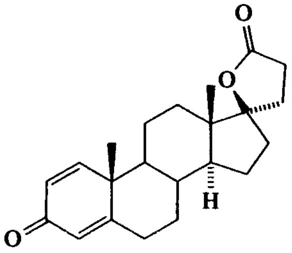 | 84 | 92 |

Table 5 *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 4 | 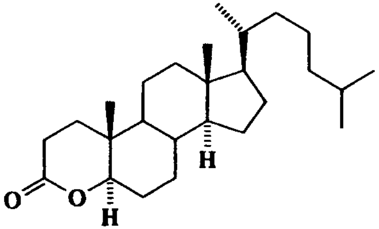 | 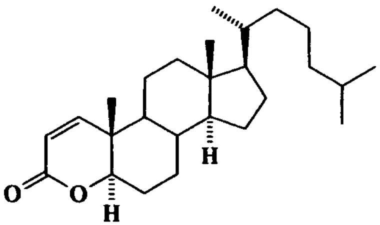 | 90 | 92 |
| 5 | 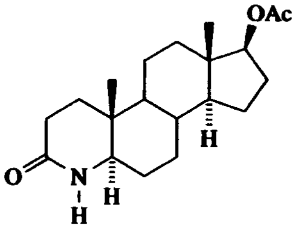 | 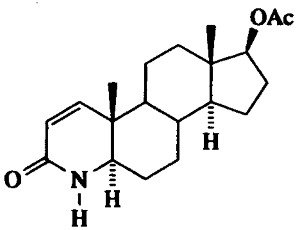 | 64 | 93 |

[a] Reaction with benzeneseleninic anhydride at 120–130 °C. [b] With 2 equiv. of anhydride.

methylene groups, but, apart from these few examples, it does not seem to have been explored. Possibly the greatest scope would result from the two-stage procedure using Se$^{II}$.

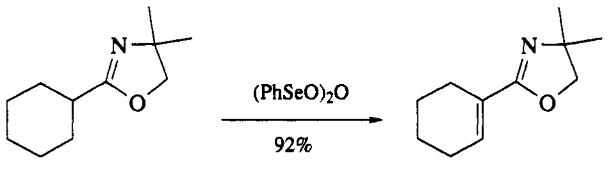

**(25)**

(13)

Benzeneseleninyl chloride is another example of a Se$^{IV}$ electrophile, but has found limited use for the dehydrogenation of ketones and esters[71] due to its hygroscopic nature. Thus, although a crystalline solid it is considerably more difficult to handle than the Se$^{II}$ halides. An alternative reagent, phenylselenium trichloride, offers a milder approach for the direct introduction of Se$^{IV}$, although its utility appears to be limited to ketones.[101] In a typical reaction cyclopentanone (**26**; Scheme 18) may be dehydrogenated *via* the intermediate (**27**) by reaction with phenylselenium trichloride in diethyl ether at 5 °C followed by mild aqueous hydrolysis.[101] The lower reactivity of aldehydes, acids, lactones and esters suggests that ketonic substrates may be selectively dehydrogenated in the presence of these functional groups (*cf.* equation 10).

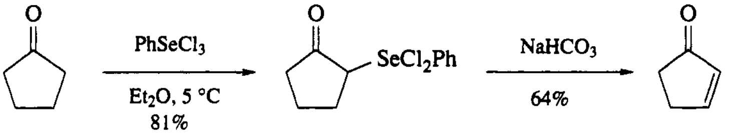

**(26)** **(27)**

Scheme 18

## 2.2.5 DICHLORODICYANOQUINONE AND RELATED REAGENTS

Although quinones have been recognized since the turn of the century, it was not until the mid 1950s that Braude and coworkers demonstrated their full potential as dehydrogenation reagents.[102,103] Those quinones bearing electron-withrawing groups showed the highest oxidation potentials, and therefore represented the most effective reagents,[104] which led to the development of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; **28**)[105] and chloranil (**29**)[106] as the most commonly used reagents.

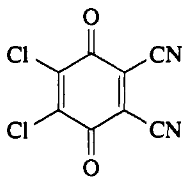

**(28)**

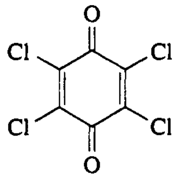

**(29)**

The dehydrogenation reaction is generally first order in both quinone and substrate and is enhanced in polar solvents. Together with other findings, these observations have suggested an ionic mechanism involving the initial formation of a charge-transfer complex (**30**) followed by hydride abstraction and rapid loss of a proton (Scheme 19).[102]

An alternative mechanism has been proposed to explain the rate enhancement seen in the presence of acids and which is particularly evident with quinones of low oxidation potential ($E_0$ = 600 mV, *cf.* DDQ, $E_0 \approx$ 1000 mV).[102] In this instance, formation of the quinone conjugate acid (**31**; Scheme 20) has been proposed, which might be expected to be a considerably more powerful hydride abstractor than the parent quinone.

$$\mathrm{RH_2 + Q} \xrightarrow{\text{complex}} \underset{(\mathbf{30})}{[\mathrm{RH_2Q}]} \xrightarrow{\text{slow}} \overset{+}{\mathrm{R}}\mathrm{H} + \overset{-}{\mathrm{Q}}\mathrm{H} \xrightarrow{\text{fast}} \mathrm{R + QH_2}$$

**Scheme 19**

$$\mathrm{Q + HX} \overset{\text{fast}}{\rightleftharpoons} \underset{(\mathbf{31})}{\overset{+}{\mathrm{Q}}\mathrm{H}} + \mathrm{X}^-$$

$$\mathrm{RH_2} + \overset{+}{\mathrm{Q}}\mathrm{H} \xrightarrow{\text{slow}} \overset{+}{\mathrm{R}}\mathrm{H} + \mathrm{QH_2}$$

$$\overset{+}{\mathrm{R}}\mathrm{H} + \mathrm{X}^- \xrightarrow{\text{fast}} \mathrm{R + HX}$$

**Scheme 20**

Quinones have been extensively used for aromatization reactions[107] in addition to the dehydrogenation of steroidal ketones and lactones.[105] Interestingly, whereas chloranil (**29**) and a number of other quinones oxidize steroidal 4-ene-3-ones (**32**) selectively to 4,6-dienones (**34**),[108] DDQ (**28**) results only in the formation of the 1,4-dienone (**36**; Scheme 21).[109] This divergent behavior is best explained by the intermediacy of the kinetic enolate (**35**) in the case of the higher potential DDQ, but of the thermodynamic enolate (**33**) in the case of the less reactive quinones.[110] Acidic conditions need to be avoided if the cross-conjugated ketone (**36**) is the desired product since under these conditions the 3,5-dienol (**33**) becomes both the kinetic and the thermodynamic enol, resulting only in the formation of the linear dienone.[110]

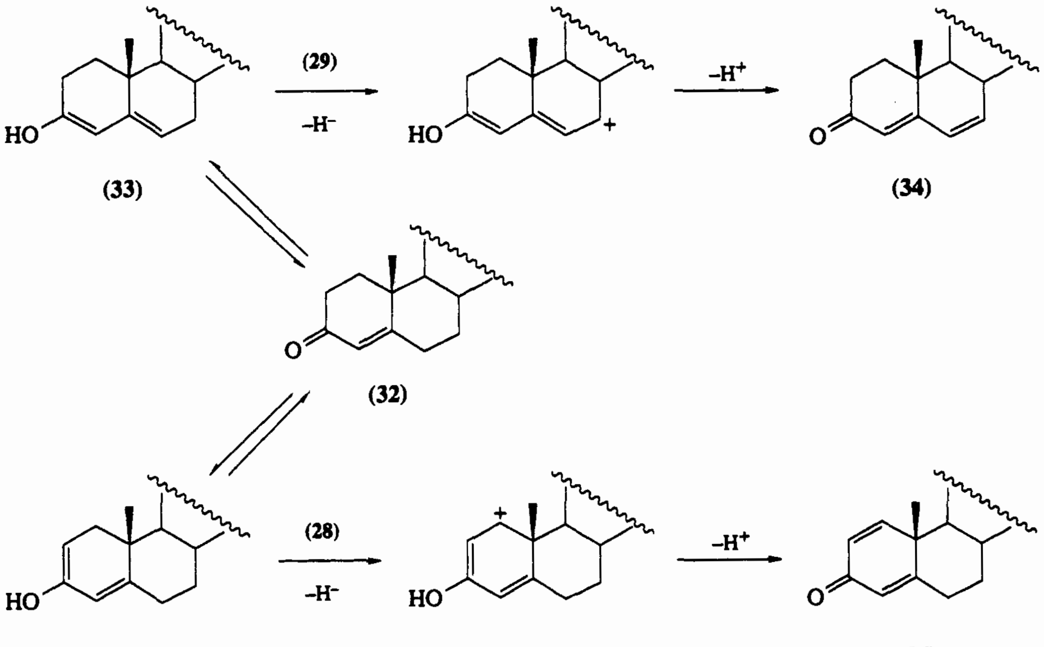

**Scheme 21**

In general, the dehydrogenation of steroidal ketones is carried out in dry benzene or dioxane at reflux with 1.1 to 2 equiv. of the quinone.[105] Similar conditions have also been used to prepare flavones,[111] chromones[112] and spirodienones[113] in good yields (Table 6). Consistent with the apparent requirement that enolization is a prerequisite to dehydrogenation with quinones,[114] reactants such as α-formyl ketones, *e.g.* (**37**) and (**38**), that have a high enol content, dehydrogenate rapidly at room temperature (Table 6).[115,116]

Steroidal enol ethers have also been shown to undergo facile dehydrogenation with DDQ, but the products formed are dependent on the reaction conditions.[117] Thus, whereas under anhydrous conditions the

**Table 6** Dehydrogenation of Ketones using DDQ

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 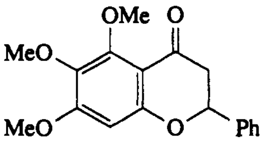 | 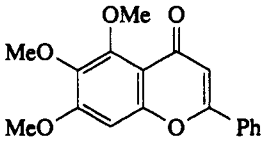 | DDQ, dioxane, Δ, 12 h | 100 | 111 |
| 2 | 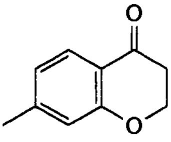 | 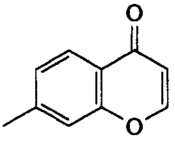 | DDQ, dioxane, Δ, 8 h | 75 | 112 |
| 3 | 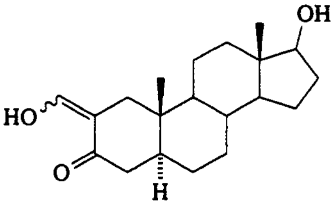 (37) | 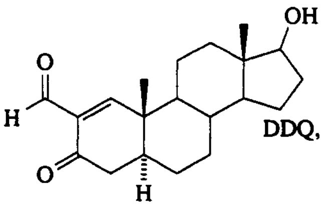 | DDQ, dioxane, r.t., 2 min | 50 | 116 |
| 4 | 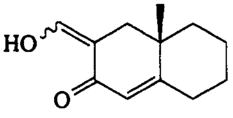 (38) | 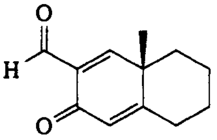 | DDQ, dioxane, r.t. | 76 | 115 |
| 5 | 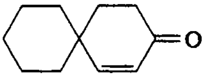 | 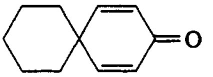 | DDQ, dioxane | — | 113 |

dienyl ether (**39**) furnished the trienone (**41**), in the presence of moist acetone the intermediate oxonium ion (**40**) was hydrolyzed to the dienone (**42**; Scheme 22).[117]

A more general approach involves the oxidation of silyl enol ethers with DDQ,[118–120] although for good yields care is needed to ensure removal of the acidic by-product $DDQH_2$. Usually this problem is overcome by the addition of bis(trimethylsilyl)acetamide[118] or bases such as collidine[119] or 2,6-lutidine (Table 7).[120] As with selenium, sulfur and palladium reagents (see Sections 2.2.3, 2.2.4 and 2.2.6) the use of silyl enol ethers allows the regioselective introduction of unsaturation (Table 7).[118] Typically, the dehydrogenation of silyl enol ethers is effected at ambient temperature using 1–1.5 equiv. of quinone in hydrocarbon solvents.

Most examples of quinone dehydrogenations adjacent to C=X have been carried out on steroidal ketones and are essentially limited to readily enolizable species. Reactions on esters and amides (Table 8) are far less common and, because of their relatively low ease of enolization, require harsh conditions.[121] Thus, unless stabilization of the intermediate carbonium ion is possible,[122,123] elevated temperatures and prolonged reaction times are required (Table 8), which increases the incidence of unwanted side reactions. Frequent by-products are those arising as a result of Diels–Alder reactions or Michael addition to the quinone.[105] Allylic alcohols may be rapidly oxidized to aldehydes or ketones under these conditions[105] and require prior protection.

The conversion of carboxylic acids to α,β-unsaturated acids is not a trivial transformation, although it can be effected by treatment of the α-anion of the carboxylate salt (**43**) with DDQ in THF containing HMPA at reflux (Scheme 23).[124,125] Using this procedure, a number of fatty acids have been successfully dehydrogenated, albeit only in around 30% yield. Only the (*E*)-isomers are isolated.

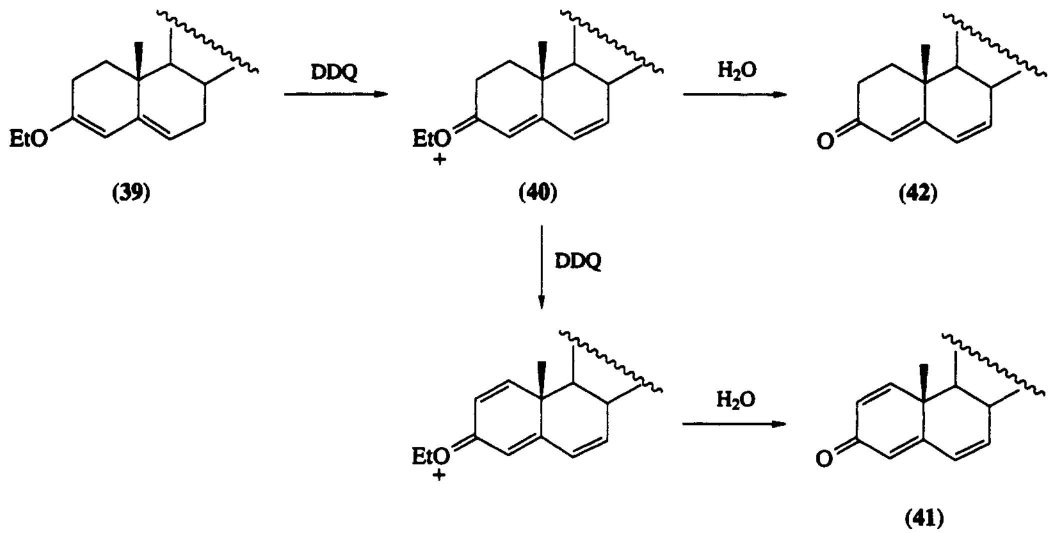
EtO
DDQ
EtO
+
H2O
O
(39)
(40)
(42)
DDQ
EtO
+
H2O
O
(41)

**Scheme 22**

**Table 7** Dehydrogenation of Trimethylsilyl Enol Ethers using DDQ

| *Entry* | *Substrate* | *Product* | *Conditions* [a] | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 1 | 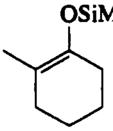 | 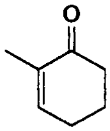 | BSA, 1 h | 50 | 118 |
| 2 | 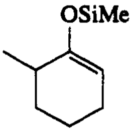 | 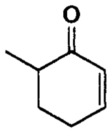 | BSA, 1 h | 53 | 118 |
| 3 | 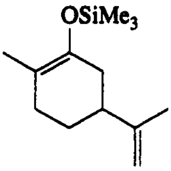 | 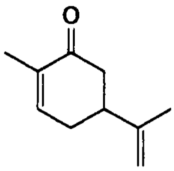 | Collidine, 1.5 h | 52 | 119 |

[a] Reactions carried out with DDQ in benzene at room temperature, BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

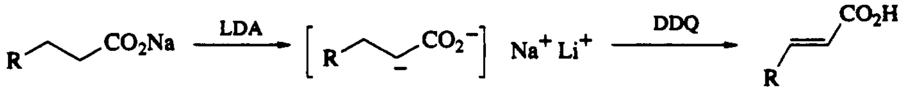
R
CO2Na
LDA
R
CO2−
Na+ Li+
DDQ
CO2H
R

**(43)**

**Scheme 23**

Quinones have also been used to dehydrogenate adjacent to C═N in a variety of substituted nitrogen heterocycles[125–127] with the ultimate generation of aromatic species (equation 14). In some instances DDQ has been claimed to be preferable to other reagents generally used for this purpose[125] but the eventual choice must be determined by the substituents present and the intrinsic stability of both product and starting material.

**Table 8** Dehydrogenation of Lactones and Lactams using DDQ

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 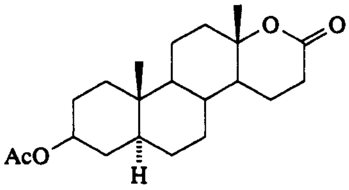 | 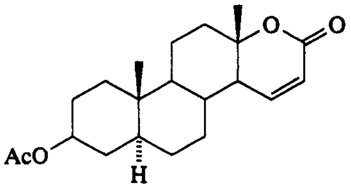 | 240 h[a] | 25 | 121 |
| 2 | 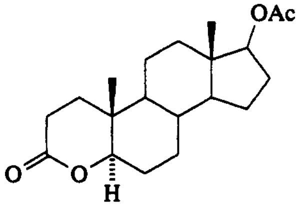 | 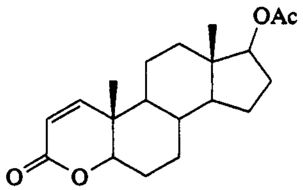 | 130 h[a] | 55 | 121 |
| 3 | 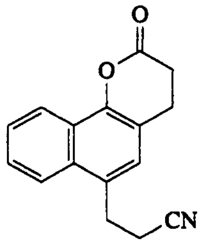 | 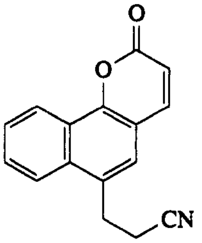 | 14 h[a] | 70 | 122 |
| 4 | 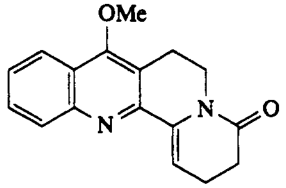 | 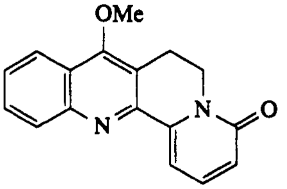 | Benzene | — | 123 |

[a] Reaction carried out in dioxane at reflux.

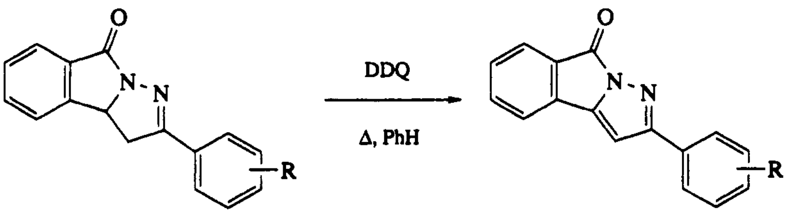

(14)

## 2.2.6 NOBLE METALS AND THEIR SALTS

The application of transition metals and their salts or complexes to dehydrogenation reactions adjacent to C=X compounds has received relatively scant attention compared to reagents such as selenium. In an early isolated example, however, 10% palladium on charcoal in refluxing *p*-cymene was shown to dehydrogenate the thermally stable steroidal lactone (**44**; equation 15) in good yield in instances where classical reagents such as selenium dioxide and halogenation–dehydrohalogenation failed.[128] Whereas these reaction conditions have proved to be successful for the aromatization of hydroaromatic compounds, newer transition metal based methodology has largely superseded this approach and led to increasing use of palladium salts and their complexes.

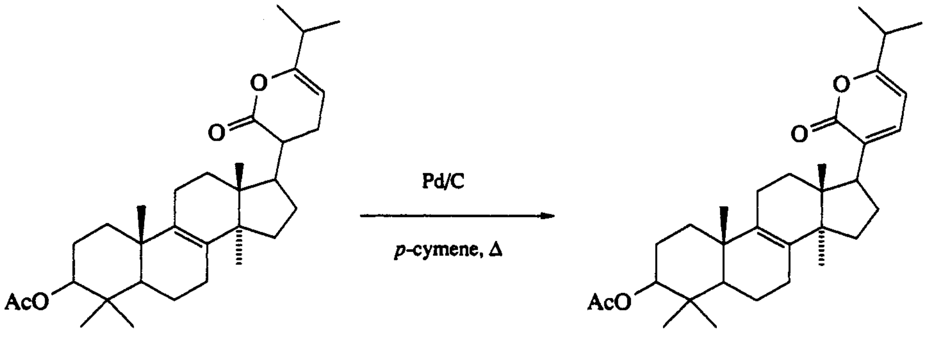

**(44)**

(15)

A detailed study of over 45 catalysts, primarily from Group VIII metal salts and complexes, showed palladium(II) compounds to be the most effective in the dehydrogenation of a variety of aldehydes and ketones.[129] Soluble palladium(II) salts and complexes such as dichloro(triphenylphosphine)palladium(II) and palladium(II) acetylacetonate have been shown to be optimal, with the salts of rhodium, osmium, iridium and platinum having reduced efficacy.[129] Since the dehydrogenation reaction is accompanied by reduction of the palladium(II) catalyst to palladium(0), oxygen and a cooxidant are required to effect reoxidation. Copper(II) salts are favored cooxidants, but quinones, and especially *p*-benzoquinone, are also effective (Scheme 24).[129,130]

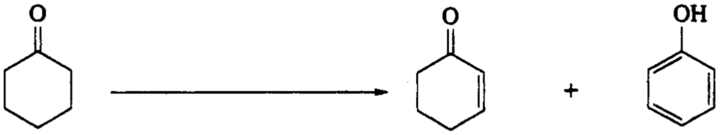

| | | |
|---|---|---|
| $Pd(acac)_2$, $Cu(OAc)_2$, $O_2$, AcOH, 100 °C<br>8% | 95% | 5% |
| $PdCl_2$, Bu$^t$OH, conc. HCl, 80 °C<br>90% | 90% | <5% |

**Scheme 24**

Improved conditions for dehydrogenation reactions have been developed using palladium(II) chloride in a mixture of *t*-butyl alcohol and concentrated hydrochloric acid,[130] although these conditions limit the utility of the method to compounds without acid sensitive groups. The yields of enones from readily enolizable carbonyl compounds are usually moderate, and reaction rates generally reflect the ease of enolization.[129,130] Thus, the method has been found to be particularly suitable for aldehydes and cyclic ketones, but acyclic ketones are less efficiently dehydrogenated.[129–131] Carboxylic acids, esters and amides are not dehydrogenated by palladium(II) derivatives,[129] which potentially offers the opportunity to selectively introduce double bonds into compounds possessing mixed functionality. In contrast to sulfur- and selenium-based dehydrogenations, unsymmetrical ketones generally afford a mixture of isomers (equations 16 and 17).[129,130] Like most other methods, however, acyclic aldehydes and ketones furnish *trans* enones exclusively.[129,130]

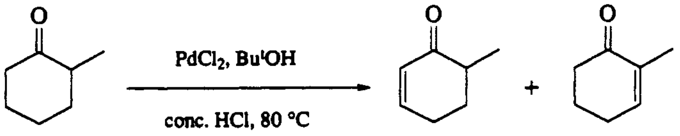

45% 46%

(16)

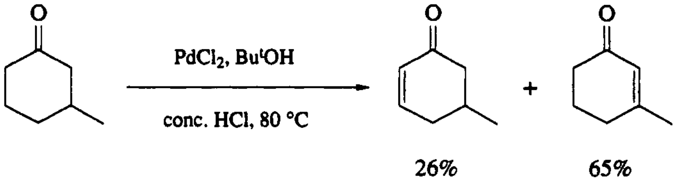

(17)

Mechanistically, palladium-catalyzed dehydrogenations have been shown to proceed according to Scheme 25, in which the initially formed π-complex (**45**) rearranges to a σ-complex (**46**) prior to the elimination of palladium hydride.[129,130]

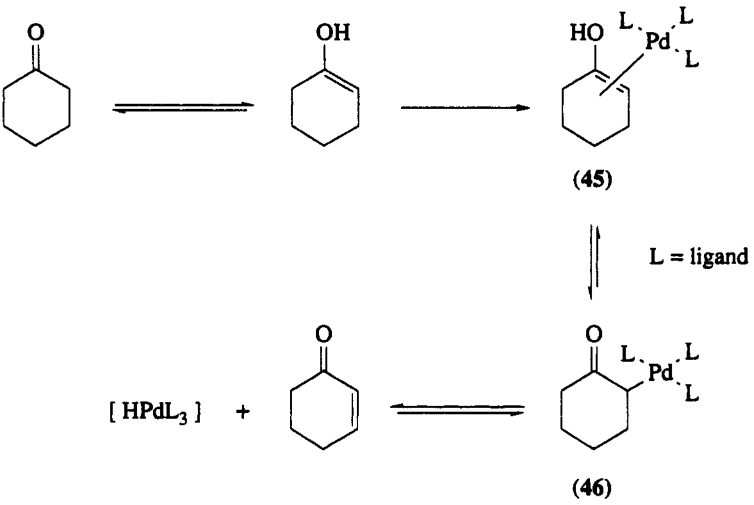

**Scheme 25**

Improved understanding of the mechanism of palladium-induced dehydrogenations has led to the development of significantly better catalysts and reaction conditions. In particular, mixtures of $PdCl_2(PhCN)_2$ and silver triflate in the presence of *N*-methylmorpholine have allowed the efficient dehydrogenation of aldehydes under ambient conditions and in nonacidic media (equation 18).[132] Ketones undergo a similar reaction, affording enones in 60–78% yield, but require prior formation of the tin enolate with tin(II) triflate.[132] Under these conditions, however, 2 equiv. of palladium(II) chloride were used to effect conversion, which severely limits the usefulness of the method.

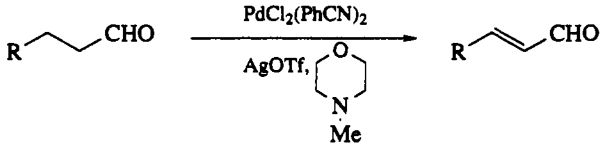

(18)

Probably the most widely applicable conditions developed for palladium catalysts utilize silyl enol ethers.[133,134] In one instance,[133] an excellent yield of enone was obtained using 0.5 equiv. each of palladium(II) acetate and *p*-benzoquinone in acetonitrile. The method has the advantage that the position of the double bond is determined by the geometry of the precursor silyl enol ether (Scheme 26). Palla-

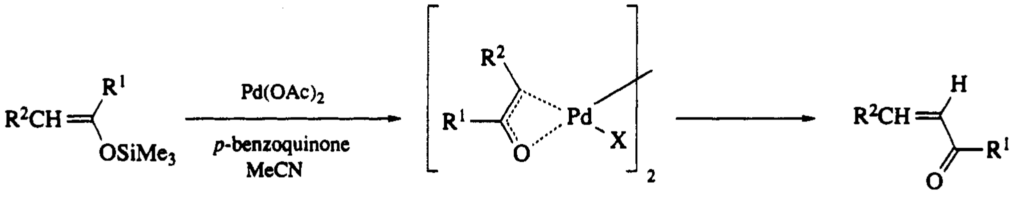

**Scheme 26**

**Table 9** Dehydrogenation of Trimethylsilyl Enol Ethers and Ketene Acetals with Pd$^0$

| *Entry* | *Substrate* | *Product* | *Conditions* [a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 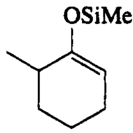 | 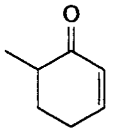 | A | 87 | 135 |
| 2 | 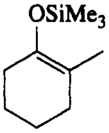 | 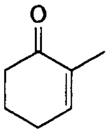 | A | 100 | 135 |
| 3 | 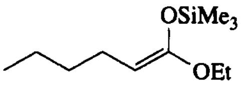 | 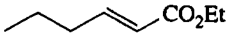 | B | 79 | 137 |
| 4 | 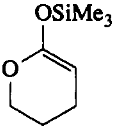 | 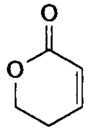 | B | 70 | 137 |

[a] Conditions. A: 5 mol % Pd(OAc)$_2$, 5 mol % DPPE, 2 equiv. dimethyl carbonate in acetonitrile at reflux. B: 10 mol % Pd(OAc)$_2$, 2 equiv. allyl methyl carbonate in acetonitrile at reflux.

dium(0) has also been used to effect a similar reaction with silyl enol ethers[134,135] and enol carbonates.[134,136] In these cases the palladium is present in truely catalytic quantities and the reaction proceeds with as little as 1 mol % of palladium(II) acetate (DPPE) in acetonitrile. It is also possible to oxidize esters *via* their corresponding silyl ketene acetals with Pd$^0$, although in this instance the yields are better in the absence of phosphine ligands.[137] Palladium(0) chemistry offers a mild, high yielding entry to α,β-unsaturated ketones and esters (Table 9), and should find a wide application as an alternative to selenium-based dehydrogenations.

A particularly interesting extension of this work is offered by the observed enantioselective hydrogen abstraction from the prochiral cyclohexanone (**47**) on treatment with chiral lithium amide bases (Scheme 27).[138] Thus, quenching the initially formed enolate afforded the asymmetric trimethylsilyl ether (**48**) which gave the chiral enone (**49**) in 65% enantiomeric excess on dehydrogenation.[138] Further work in this area should provide valuable methodology for the formation of chiral α,β-unsaturated carbonyl systems.

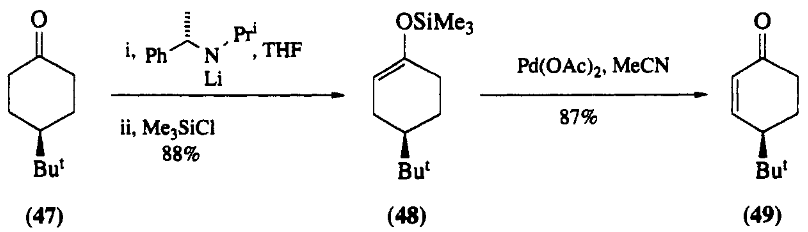

**Scheme 27**

## 2.2.7 MISCELLANEOUS CHEMICAL METHODS

Although the methods discussed in earlier sections generally constitute the preferred procedures by which to dehydrogenate carbonyl and similar compounds, a variety of other reagents will effect this transformation, and in some instances may offer certain advantages. Manganese dioxide is one reagent that has been extensively utilized, and is particularly suited to the dehydrogenation of heterocyclic compounds and the formation of quinones (Table 10, entries 1 and 2).[139–141] Where manganese dioxide oxidations have been compared with other methods they have frequently been found to give similar or better yields.[139,142] Typically, manganese dioxide oxidations are effected in aprotic solvents such as benzene or dioxane at reflux using approximately 5 equiv. of oxidant for each double bond.[139,141] The quality of the oxidant is important, with activated manganese dioxide[143] affording greatest efficiency.[139,141] Potassium nitrosodisulfonate (Fremy's salt) will also effect the oxidation of dihydroquinones to quinones,[144] in addition to effecting a wide variety of other oxidations.[145]

**Table 10** Miscellaneous Oxidations of Carbonyl Compounds and Heterocycles

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 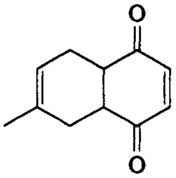 | 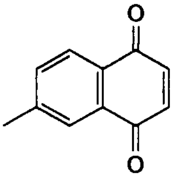 | $MnO_2$, Δ, PhH, 24 h | 62 | 139 |
| 2 | 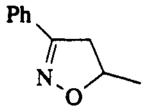 | 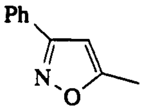 | $MnO_2$, Δ, PhH, 7 h | 98 | 141 |
| 3 | 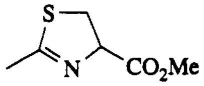 | 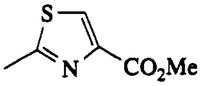 | $NiO_2$, $CHCl_3$, 25 °C, 3 d | 81 | 146 |
| 4 | 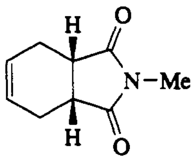 | 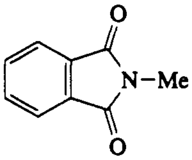 | $NiO_2$, PhH, Δ, 7 h | 62 | 146 |
| 5 | 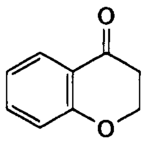 | 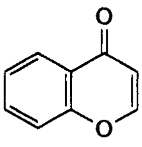 | $Tl(NO_3)_3$, MeOH, $HClO_3$, 5 h | 76 | 148 |
| 6 | 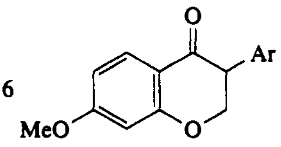 | 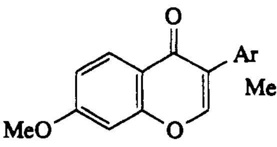 | $Me_3SiCl$, $Ac_2O$, 60–65 °C, 168 h | 55 | 150 |
| 7 | 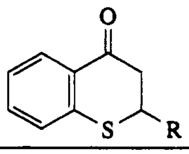 | 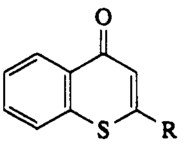 | *hv*, MeOH, 48 h | 50–55 | 151 |

Heterocyclic systems may also be conveniently dehydrogenated using nickel peroxide in aprotic solvents, and good yields may be obtained even in the presence of sensitive functional groups (Table 10, entries 3 and 4).[146] This reagent is not specific for the dehydrogenation of C=X compounds, however,[146] and may not be suitable for reactions requiring selective oxidation. A variety of other oxidants[147] have been shown to effect similar oxidations.

Thallium trinitrate has been shown to be an efficient reagent for the dehydrogenation of chromanones[148] and flavanones (Table 10, entry 5),[149] the reaction being carried out in methanol at room temperature. The addition of perchloric acid to chromanone oxidations enhances the yields and reaction rates by promotion of enolization,[148] but apparently was without effect on flavanones.[149] The ease with which chromanones and similar compounds may be dehydrogenated has also permitted unusual procedures such as trimethylsilyl chloride/acetic anhydride[150] and photolysis[151] to be used (Table 10, entries 6 and 7), but their generality is suspect.

The trityl carbonium ion has proved to be an interesting reagent for the dehydrogenation of ketones and esters *via* their silyl enol ethers (*e.g.* **50**; equation 19),[119,152] although major side reactions involving α-tritylation have been reported and yields are variable.[153] Nonetheless, this is a particularly suitable way to convert tetralones into naphthols (equation 20).[153] Both the perchlorate and tetrafluoroborate counterions are effective. Whether this procedure offers any advantages over the use of DDQ or chloranil, which effect the same transformations, is doubtful.[119,153] Palladium(II) acetate behaves similarly, but is expensive on catalyst.[133] Trityl tetrafluoroborate has also been shown to abstract hydrogen from enamines,[154] but whether this offers a useful alternative for the dehydrogenation of ketones remains to be proven. In common with many other reagents, trityl perchlorate will oxidize 4-chromanones and 4-thiochromanones to their corresponding α,β-unsaturated derivatives in excellent yields.[155]

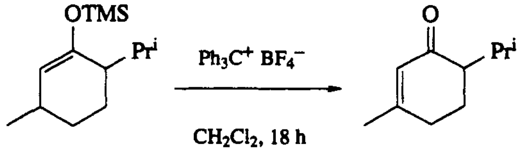

**(50)** 74%

(19)

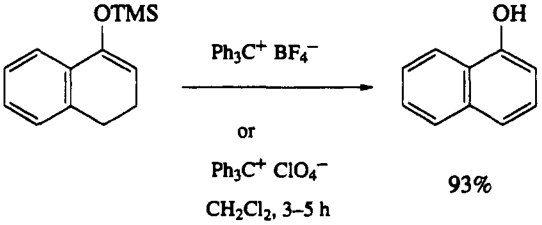

(20)

Pyridine *N*-oxide will dehydrogenate carboxylic acids in the presence of acetic anhydride,[156] but this does not represent an efficient method. Tertiary amides, however, may be smoothly oxidized in a two-step procedure *via* an intermediate chloriminium ion (see Section 2.2.2).[30]

Copper(II) bromide is another reagent that has been used successfully for the dehydrogenation of ketones and amides (equation 21).[157,158] This procedure, which presumably proceeds *via* the α-bromo compounds, (*cf.* Section 2.2.2) was found to have particular advantages over a number of alternative methods for the dehydrogenation of some dihydrouracils.[158]

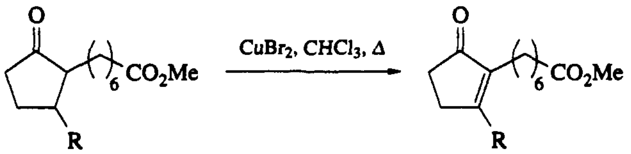

R = H, 66%
R = CHO, 38%

(21)

An interesting dehydrogenation of hydrazones (**51**) has been reported by Barton[35] which relies on the available oxygen of aromatic nitro groups (equation 22). In a detailed study, quantitative yields were obtained using 4-nitrobenzoic acid as the oxidant.[35] Whilst this unusual reaction affords some advantages over earlier methods it is unlikely to be the method of choice in most instances.

The introduction of hydroxy groups α to carbonyl-type functions is the subject of another chapter (Chapter 2.3, this volume), but clearly this represents an alternative, though seldom used, procedure for the dehydrogenation of such species. The direct insertion of other oxygen moieties is, however, com-

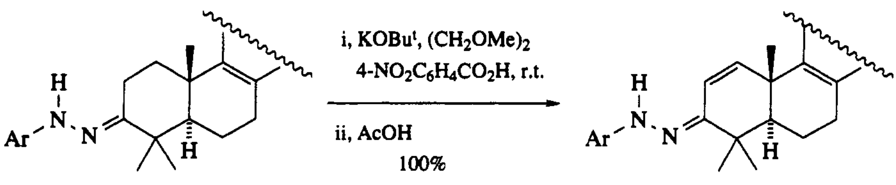

**(51)**

(22)

plementary to those methods already discussed. One method that has found use in terpenoid chemistry involves the incorporation of an α-benzoyloxy group *via* the enolate anion and thermolytic elimination at 450–550 °C to afford the enone.[20] Enolizable ketones will also react with lead tetraacetate and mercury(II) acetate[159] to give α-acetoxy derivatives that can be subsequently eliminated, but this method is unpopular.

More recently, work has been reported showing that silyl enol ethers of ketones, esters and lactones can be efficiently converted to α-sulfonyloxy carbonyl compounds on treatment with either [hydroxy(tosyloxy)iodo]benzene or [hydroxy(mesyloxy)iodo]benzene (equation 23).[160] This method is similar to that used by the same workers to introduce the trifluoromethylsulfonyloxy group α to ketone carbonyl groups *via* their silyl enol ethers.[161] While the major interest in these developments is the further functionalization of the α-position of carbonyl compounds the method clearly offers a route to α,β-unsaturated species.

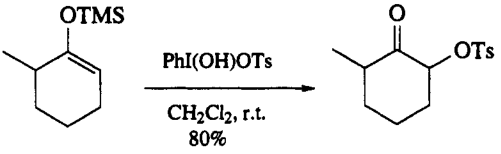

(23)

## 2.2.8 MICROBIAL AND ENZYMATIC METHODS

In addition to the chemically based methods described above, fermentation and enzymatic procedures are also available for the dehydrogenation of C=X compounds,[105,162–164] although this approach has found greatest favor for stereospecific reduction and regiospecific oxidation reactions.[165,166] The class of enzymes that effect dehydrogenation reactions are of the redox type and have been classified by the International Union of Biochemistry as oxidoreductases.[163] A number of such enzymes are now known.[163] Particular advantages of microbial and enzymatic methods are the versatility, efficiency and selectivity with which these reactions are carried out and the mild conditions that are employed. Thus, in contrast to most chemical methods, enzymes are often able to discriminate between enantiomers of racemic mixtures and to generate chiral products from prochiral substrates.[166] As a general rule, however, it seems unlikely that this approach would be favored over chemically based methods for dehydrogenation reactions, unless it was necessary to circumvent a particular synthetic problem.

The nature of oxidative processes requires the removal of electrons from the substrate and many enzymes of the redox class contain transition metals which act as an electron sink.[167] Those enzymes which do not satisfy this requirement need organic cofactors such as nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide 2′-phosphate to act as electron acceptors,[167] although simple quinones have been shown to suffice.[168]

Much of the work with microorganisms capable of effecting dehydrogenation reactions has been carried out using steroids, particularly those reactions introducing unsaturation at C-1 of 3-keto steroids. Those organisms most frequently used are *Bacillus sphaericus* and *Arthrobacter simplex*, but many others are claimed to be effective.[105] Yields of dehydro compounds formed by microbiological methods are somewhat variable, ranging from very little to 95%.[105] In a typical experiment, good yields of androstene-3,17-dione (**52**) have been obtained using *Bacillus sphaericus* and the mechanism established as proceeding *via* a *trans* diaxial (1α,2β) elimination (equation 24).[168] This result is consistent with the general observation that enzymatic oxidation of 3-keto steroids shows a preference for ring A.[164] Several other enzymes have been shown to dehydrogenate steroids,[163,166,169] but particularly interesting is the stereochemical preference shown by cortisone β-reductase for the 5β-hydrogen atom compared to the 5α-reductase, which shows a preference for the opposite enantiomer.[163]

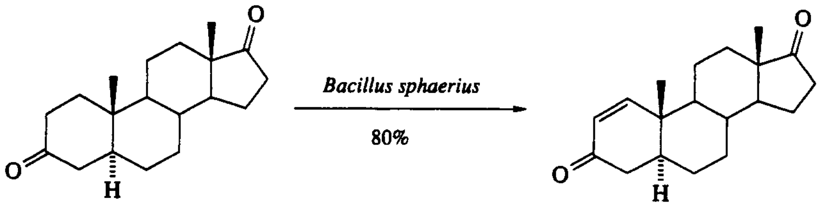

(24)

**(52)**

Specific enzymes have also been identified which convert 5,6-dihydrouracil into uracil, succinate into fumarate and acylated coenzyme A into 2,3-dehydroacyl derivatives.[163] While these are important biological processes, it is doubtful whether they will have general synthetic value. Of greater potential interest are those enzymes capable of converting 3-nitropropanoate to the corresponding acrylate and hexadecanal to its 2,3-unsaturated derivative,[163] although there is little evidence that these reactions can be advantageously exploited relative to alternative chemical methods.

## 2.2.9 SUMMARY

A wide diversity of reagents exists for effecting the dehydrogenation of C=X compounds. With a few exceptions, the most versatile methods are those based on selenium and sulfur, and there is little to choose between these two elements in most instances. Particular advantages of selenium pertain to the weaker σ-bonds that it forms with carbon, which results in the *syn* elimination of selenoxides being some 1000 times faster than that of sulfoxides.[3] Disadvantages of selenium, on the other hand, relate to its greater toxicity and expense. It is possible that dehydrogenations based on palladium chemistry will offer some advantages, especially in the light of newly developed methodology.

Throughout this review, elimination reactions have been restricted to the loss of an appropriate leaving group from the α-carbon atom, but both β-thio and β-selenenyl groups can be eliminated with ease from C=X compounds following oxidation.[170] As a rule, such derivatives are prepared by conjugate addition to α,β-unsaturated carbonyl compounds,[37] and therefore formation and elimination constitutes a formal protection of these compounds.

Most of the examples reviewed concentrate on instances in which the C=X heteroatom is oxygen, and this reflects the dearth of work that has been reported on other heteroatoms. Thus, although numerous examples of the aromatization of nitrogen heterocycles exist, there is very little pertaining to other systems. This is an area where more exploratory work is needed, especially on oxazolines and related heterocycles.[100] Reactions with C=S compounds are even more rare, presumably because of the ease with which such systems are oxidized under dehydrogenation conditions. Opportunities exist to develop the dehydrogenation of such systems, however, as demonstrated with thioamides which have served as suitable intermediates for the dehydrogenation of otherwise difficult amides.[64]

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# 2.3

# Oxidation Adjacent to C=X Bonds by Hydroxylation Methods

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## 2.3.1 INTRODUCTION

Many of the natural products of current biological importance and synthetic interest consist of highly oxygenated carbon skeletons. The desire to prepare these compounds and their analogs has led to many impressive advances in synthetic technology. The strategy of constructing the carbon skeleton in simplified form and subsequently installing the remainder of the functionality has many desirable attributes. Clearly the insertion of hydroxy groups (or protected hydroxy groups) α to preexisting functionality is valuable in this sense.

The earliest observations of α-hydroxylation relied on simple autoxidation of particularly susceptible compounds. In recent years the act of deliberate α-hydroxylation has been the subject of much attention and the area has grown to provide an abundance of expedient, rational approaches. This in turn has led to an increase in the use of these technologies in synthesis and a subsequent acceptance into basic synthetic planning.

It is the emergence and use of these techniques that this review is intended to cover and in such a way as to aid the selection of a successful procedure for any particular use.

## 2.3.2 HYDROXYLATION α TO C═O

### 2.3.2.1 Saturated Ketones

### *2.3.2.1.1 Directly from ketone/enol*

*(i) Transition metal salts*

One of the oldest methods for effecting the α-hydroxylation of ketones utilizes transition metal salts,[1] the most widely employed being lead tetraacetate (LTA).[2] Treatment of enolizable ketones with LTA (usually at reflux in acetic acid or benzene) affords the corresponding α-acetoxy derivatives. Originally a radical mechanism was proposed (Scheme 1),[3] but elsewhere it has been suggested that an incipient organolead species is involved prior to conversion to the α-acetoxy derivative by inter- or intra-molecular nucleophilic attack (Scheme 2).

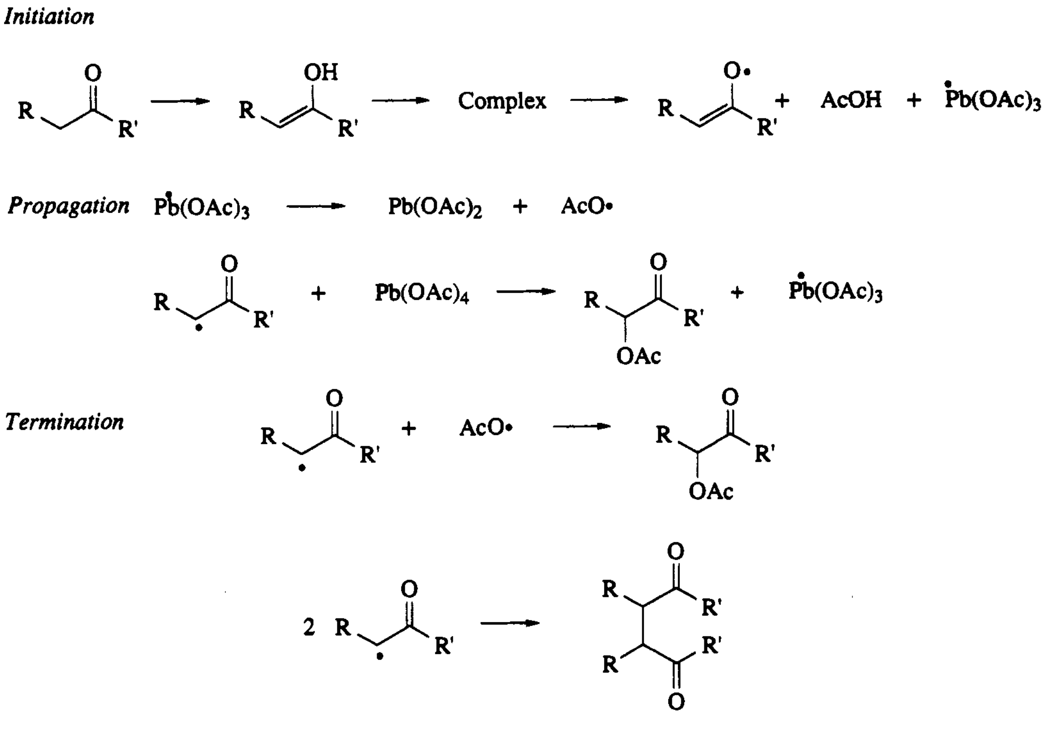

**Scheme 1**

Alternatively, the reaction may proceed through formation of a lead enolate derived from the enol[4] followed by intramolecular rearrangement[5] to the desired product (Scheme 2). It appears that the first and last mechanisms are operative, the product distribution reflecting a balance between the two dependent on temperature, solvent and substrate. In all three cases however the rate-determining step is the formation of the enol, a factor which heavily influences the choice of reaction conditions.

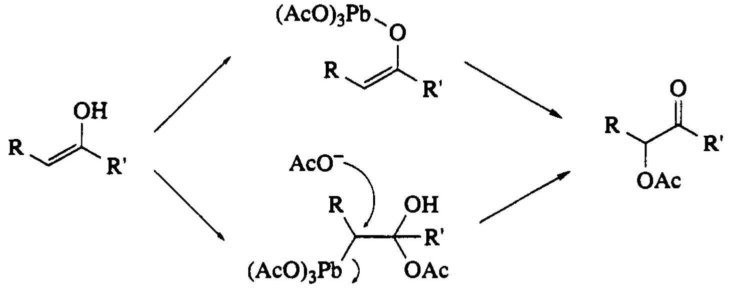

**Scheme 2**

Numerous examples are available that demonstrate the utility of the process. Sasaki and Eguchi[6] utilized LTA to effect α-acetoxylation of isodihydro-*O*-acetylisophotosantonic lactone (**1**). This oxidation is both chemoselective towards the ketone and regioselective towards the less substituted position (**2**). The opposite regioselectivity has been reported[2] and it does not seem that it can be reliably predicted. In the case of ketone (**1**) the oxidation was stereorandom. This is not an intrinsic problem with the process but rather a reflection of the steric similarity of the enol faces in these systems. Other examples do display stereoselectivity.[2] A recent report described angular acetoxylation of a highly functionalized octahydrobenzofuran[7] producing the stereoisomer indicated in good yield (**3** to **4**). β-Dicarbonyl substrates, α-aryl ketones and β,γ-unsaturated ketones may also be usefully oxidized with LTA.[8] α-Dicarbonyl compounds do not yield simple oxidation products.[9] It is quite possible to effect bisacetoxylation, the second residue being introduced regiospecifically at the α′-position (**5** to **6**).[10] The approach is successful for oxidation of primary, secondary and tertiary centers, but in most cases yields are only moderate.

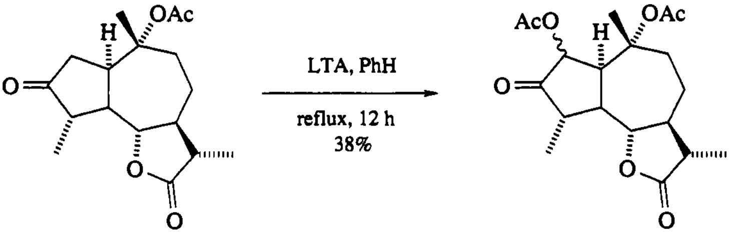

(**1**) (**2**)

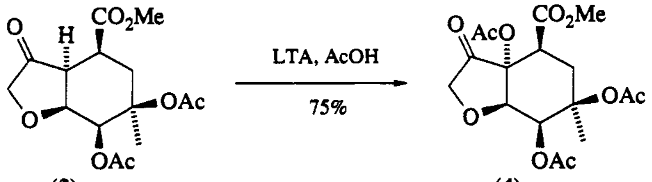

(**3**) (**4**)

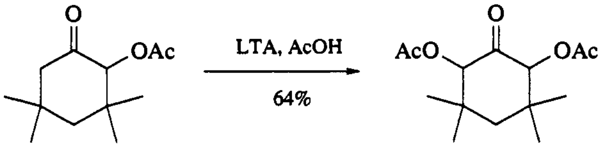

(**5**) (**6**)

In an attempt to ameliorate this situation Henbest reasoned[4] that introduction of a Lewis acid would facilitate the rate-determining enol formation. The whole reaction sequence would then be accelerated allowing the use of lower temperatures. This in turn would improve the chemo-, regio- and stereo-selectivity of the process. This proved to be a valid hypothesis.

Reaction of ketones with LTA in benzene in the presence of boron trifluoride etherate at or below room temperature effects rapid α-acetoxylation.[11] The yields are indeed improved in most cases, for example (**7**) to (**8**) and (**9**) to (**10**), although they remain generally moderate despite the remarkable example shown.[11b]

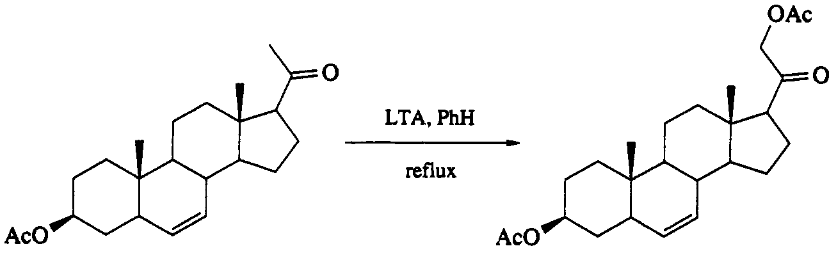

(**7**) (**8**)

with $BF_3{\bullet}OEt_2$ 71%
without $BF_3{\bullet}OEt_2$ 53%

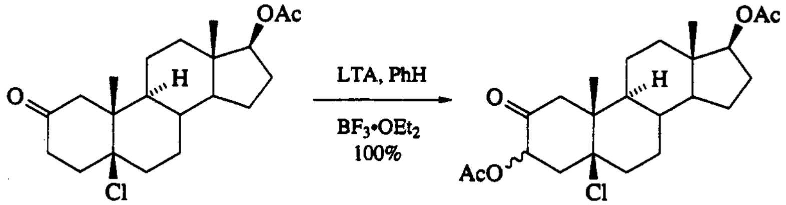

(**9**) (**10**)

The Lewis acid catalyzed process is not applicable to aryl ketones, where ester products have been observed through aryl migration.[12] Furthermore, anchimeric and solvent effects have been noted[13] during oxidation of a β-carboxy steroidal ketone. α-Oxygenation, although not inhibited, was altered. Despite the frequently disappointing yields the reagent has been widely used, particularly in the steroid field, and remains a useful, if not 'first choice', procedure.

Other transition metal salts mediate in similar oxidations. For example, mercury(II) acetate, a milder reagent than LTA, effects α-acetoxylation[2] through a comparable mechanism. However the corresponding yields for these processes are poor.[14] 3,3-Dimethylcyclohexanone, for example, is oxidized to the α-acetoxy derivative in only 14% yield.[15] The β,γ-unsaturated ketone, isopugelone, exhibits no oxidation at the α- or α′-positions, but affords a product derived from isomerization of the alkene and allylic oxidation.[16] Not surprisingly therefore the reagent has found little synthetic application for this transformation.

Thallium(III) salts also provide a means of α-oxidation. Thallium triacetate, which lies between LTA and mercury(II) acetate in oxidizing power, can induce α-acetoxylation of ketones[2] in hot acetic acid, although again the yields are low.[17] Thallium trinitrate has been shown to produce 2-hydroxycyclohexanone from cyclohexanone in 84% yield. In this case the sequence is thought to involve the intermediacy of the epoxy enol derivative generated through 'oxythallation' of the enol double bond.[19] Subsequent basic hydrolysis produces the required product. Despite the favorable yield, the process does not appear to be widely applicable.[18] Use of the reagent in acetonitrile produces α-nitrato ketones in high yield[20] for both aromatic and aliphatic ketone substrates, although with little or no regioselectivity. The process involves α-thallation of the enol and subsequent intramolecular rearrangement. The α-nitrato ketones can be readily reduced to the α-hydroxy ketones. This apparently efficient procedure has received little attention.

Thallium(III) sulfate can effect a similar α-hydroxylation of straight chain saturated ketones.[21] The vigorous conditions employed together with the apparently limited substrate effectiveness suggests that the procedure will find little synthetic application.

Salts of other transition metals including vanadium, cerium, chromium[22] and manganese[23] have been used for α-oxygenation, although rarely applied in synthesis. Manganese triacetate has been used for the efficient α′-oxidation of enones (Section 2.3.2.2.1.i), but appears not to have been used for the α-hydroxylation of saturated ketones despite its known ability to form the corresponding α-keto radicals.[24] Similarly the use of Lewis acid assisted enolization in the oxidative process appears to have been limited to the LTA-mediated examples.

### *(ii) Hypervalent iodine reagents*

In 1978 Mizukami and coworkers[25] showed that treatment of α-aryl ketones and β-dicarbonyl ketones with phenyliodosyldiacetate in strongly acidic media resulted in their α-acetoxylation (Scheme 3). The process was considered to rest on the coupling of the enol with the iodonium cation generated *in situ*, subsequent nucleophilic attack at the α-position effecting oxidation. The yields for the process were unremarkable. Later Moriarty introduced the use of iodosylbenzene or phenyliodosyldiacetate in basic media (KOH/MeOH) to effect an analogous transformation, yielding the α-hydroxydimethyl acetal.[26] Under these conditions oxidation involves nucleophilic attack of the enol on the iodosyl species.[27] Methoxide addition to the re-formed carbonyl unit results in generation of an epoxide, which is solvolyzed to the observed product (Scheme 4). Since the intermediacy of the reactive iodonium cation is avoided, the reaction can provide improved yields and stereoselectivity. A number of examples are displayed in Scheme 5.[28,29] Noteworthy is the compatibility with the tertiary amine (**11**) and the sulfide (**12**),[28] which are frequently difficult substrates for peroxide-based reagent systems (*vide infra*). Primary and secondary amines are similarly compatible.[28] 1,3-Dicarbonyl substrates are not oxygenated but produce stable iodonium ylides.[26] In some cases work-up is facilitated by the use of 2-iodosylbenzoic acid.[30] Yields are moderate or good.

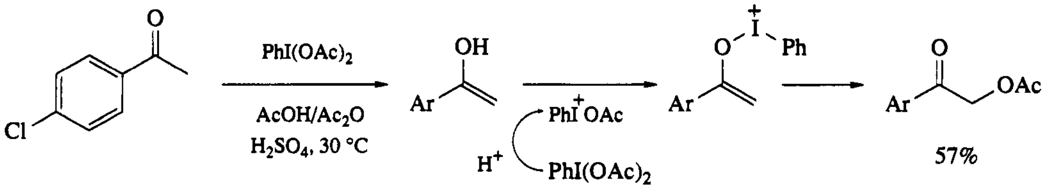

Scheme 3

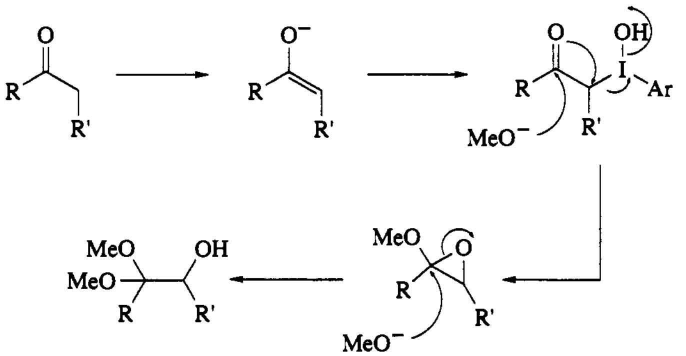

Scheme 4

Stereocontrolled oxidation with these reagents is possible. Thus α-hydroxydimethoxy acetal (**13**) was stereoselectively prepared from the precursor ketone in high yield during the synthesis of (±)-cephalotaxine.[29c] This also demonstrates a useful functional differentiation between ketone and amide carbonyl groups and an interesting although unobvious regioselectivity.

A similar reagent, [hydroxy(tosyloxy)iodo]benzene, has been used to prepare α-tosyloxy ketones, *e.g.* (**14**), from the corresponding ketones.[31a] A similar mechanism is thought to operate except that here the initially formed α-iodo species decomposes to the α-phenyliodonio ketone (the tosyloxy salt has been isolated in one case), which is displaced directly by tosyloxy anion. The yields are generally good for a range of substrates, including β-dicarbonyl systems.

The equivalent reagent for α-mesyloxylation has been reported.[31b] Again yields are high but little or no regioselectivity was observed. The question of stereoselection was not addressed. Most recently an analogous reagent for generating the α-ketophosphate has been reported.[31c]

These reagents provide efficient α-oxidation and their relatively recent emergence will, no doubt, be followed by the expansion of their use in synthesis.

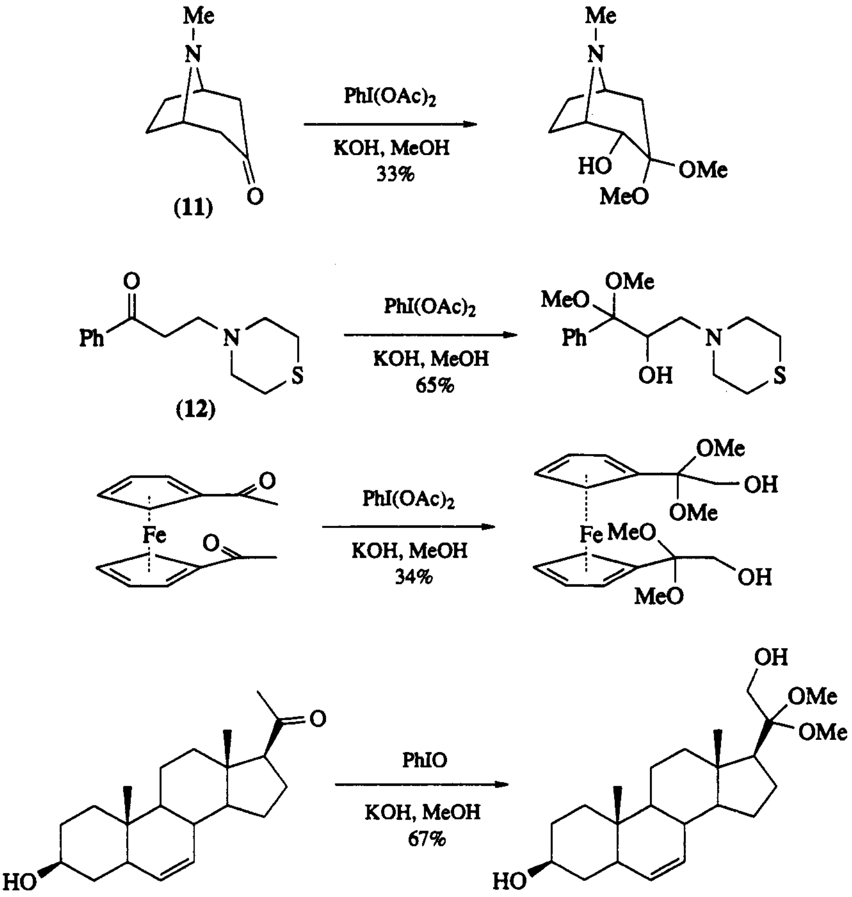
(11)
PhI(OAc)₂
KOH, MeOH
33%
(12)
PhI(OAc)₂
KOH, MeOH
65%
PhI(OAc)₂
KOH, MeOH
34%
PhIO
KOH, MeOH
67%

**Scheme 5**

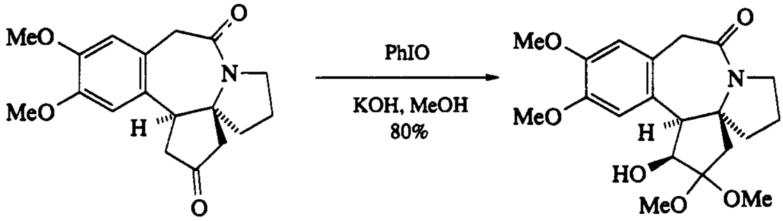
PhIO
KOH, MeOH
80%

**(13)**

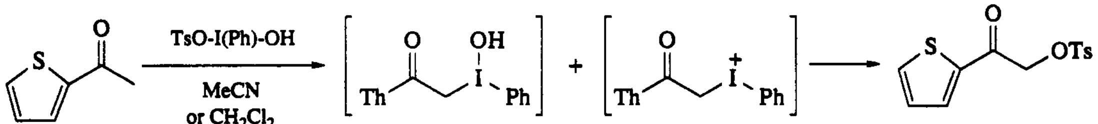
TsO-I(Ph)-OH
MeCN
or CH₂Cl₂

**(14)** 80%

*(iii) Molecular oxygen*

It has long been realized that the enol form of ketones can react with molecular oxygen to generate the α-hydroperoxy ketone[32] from which α-hydroxy ketones are readily obtained by reductive work-up. The oxidation was thought to arise either from direct attack of the enol on molecular oxygen or through a radical-mediated process (*vide infra*). Necessarily the oxidation is most efficient where the proportion of enol is enhanced, either as a result of substrate stabilization (for example in β-dicarbonyl or α-aryl ketones), or where the enol is generated as the product of a preceding reaction.

Enslin found that exposure to air of a crude mixture from the hydrogenation of a steroidal enone (**15**) provided an 80% yield of the corresponding α-hydroperoxy ketone (**16**).[32a] A relatively stable enol was formed in this case by the 1,4-addition of hydrogen across the enone. Similarly Crombie demonstrated that α-hydroxylation of an α-aryl ketone, (±)-isorotenone (**17**), could be achieved by simply passing air through an alkaline solution of the ketone.[32e] A number of similar oxygenations have been observed in the tetracycline system[33] involving highly enolized β-diketones. Thus, for example, exposure of ketone (**18**) to oxygen in the presence of platinum or palladium oxide resulted in the formation of the derived hydroxy ketone[33a] as a single stereoisomer. A recently described procedure[34] utilizing potassium superoxide/18-crown-6 and oxygen provides only low yields of the α-hydroperoxy ketones.

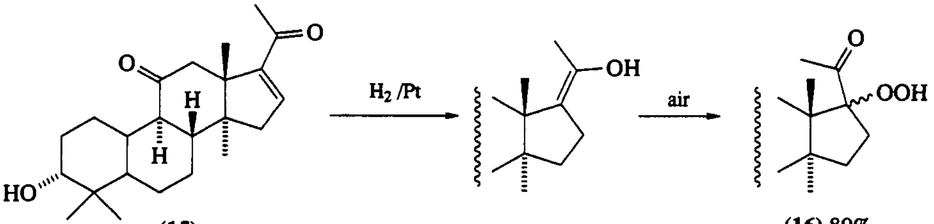

(**15**) (**16**) 80%

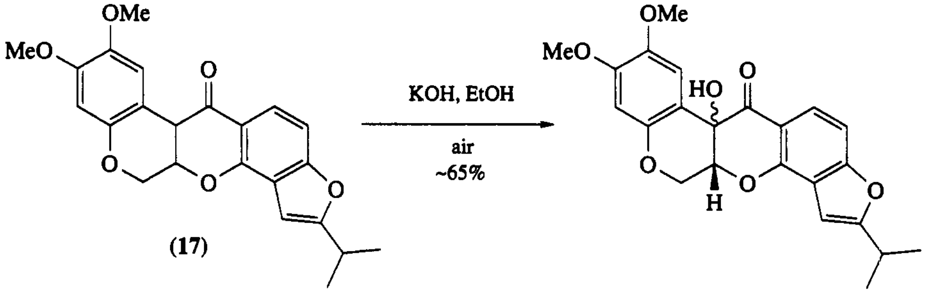

(**17**)

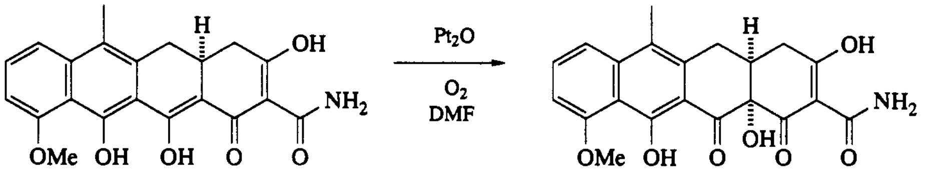

(**18**)

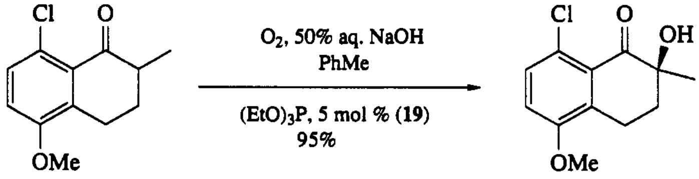

(*S*)-(**19a**) 79% *ee*

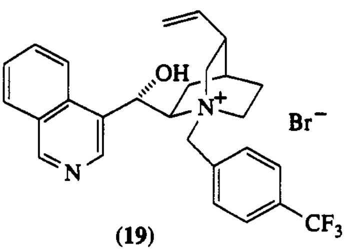

(**19**)

An excellent extension to these processes is the enantioselective, molecular oxygen mediated α-hydroxylation reported by Shiori.[35] Oxidation in a two-phase system using a chiral phase transfer catalyst (**19**) allowed preparation of α-hydroxy ketones, for example (**19a**), in high yield and with good enantioselectivity. This is the only currently available *catalytic* enantioselective α-hydroxylation process.

It is clear that such mild and efficient techniques can provide a synthetically economic procedure in appropriate cases.

### *(iv) Miscellaneous*

A number of additional methods are available. Among the most useful is the angular hydroxylation by benzeneseleninic anhydride. Oxidation of primary or secondary α-centers produces α,β-unsaturated ketones,[36a] but where the α-center is tertiary, stereoselective hydroxylation is possible, *e.g.* (**20**).[36b] The initially formed 'seleno enolate' undergoes 2,3-sigmatropic rearrangement and subsequent hydrolysis reveals the α-hydroxy ketone in good yield.

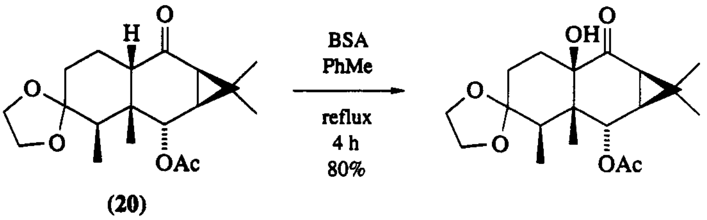

**(20)**

Treatment of a β-keto ester directly with peracid has been shown in one case (**21**)[37] to effect quantitative α-hydroxylation. Presumably this arises through epoxidation of the enol. Peracid reactions of this kind will be discussed in more detail in Section 2.3.2.1.3.i. Oxidations of the enols of β-keto esters to the α-hydroxy derivatives using singlet oxygen in the presence of fluoride ion occurs in moderate yield through an ene process (Section 2.3.2.1.3.ii).

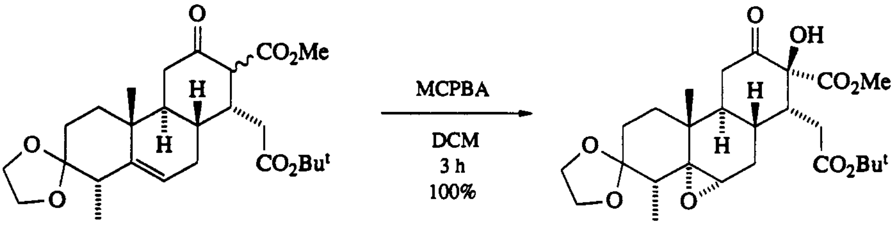

**(21)** (DCM = dichloromethane)

Hydroxylation using alkali metal based oxidants[32e,33b] (for example $KMnO_4$, $K_2Cr_2O_7$, *etc.*), is possible, although these somewhat harsh reagents frequently give rise to products of overoxidation and are limited with respect to substrate compatibility, particularly when one considers the complex nature of many natural products of current interest.

The peroxy ester reaction[38] provides a method for α-oxygenation, although it is of little synthetic value. The process hinges on the thermal or copper-catalyzed decomposition of a peroxy ester to initiate a radical sequence which ultimately generates and traps an α-keto radical. Yields are very low except for some β-dicarbonyl substrates where relatively efficient conversion is possible. DDQ has been used to effect α-oxygenation in a specific α-aryl case,[39] although the transformation is a reflection of the benzylic nature of the oxidation site. A ruthenium-based electrocatalytic system has been shown to cause α-hydroxylation of cyclohexanone in low yield[40] through a two-electron redox pathway involving hydride transfer. Finally microbial hydroxylation,[41] although usually effecting initial hydroxylation independent of the position of the ketone, has, in some cases, generated α-hydroxy ketones, either as the primary product[43] or through multiple hydroxylation.[42] Neither of these last two methods, although areas of expanding interest, are synthetically useful at the current time.

### *2.3.2.1.2* Via *preformed enolate*

All the procedures outlined in this section present no dilemma in regioselection, since they may take advantage of the well-documented regiocontrol of enolate formation.

#### *(i) Molecular oxygen*

Although autoxidation of enols can effect α-hydroxylation (*vide supra*), attempted oxygenation of ketones in basic media can result in skeletal fragmentation.[44] However the observation that even under strongly basic conditions oxygenation without skeletal alteration could be achieved in some cases[45] provided the basis for what has become a widely used procedure.

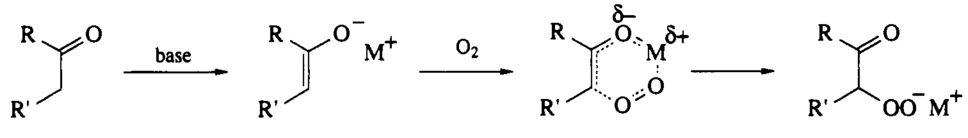

**Scheme 6**

Two mechanistic rationales have been proposed for this reaction. Electrophilic addition of molecular oxygen to the enolate, activated by counterion complexation in a six-membered transition state, could effect direct oxygenation (Scheme 6).[45] Alternatively oxidation may be thought to proceed through a radical chain mechanism involving single-electron transfer from the enolate to oxygen generating an α-keto radical (Scheme 7).[45] Presumably this process would only require an initiating quantity of the enolate.

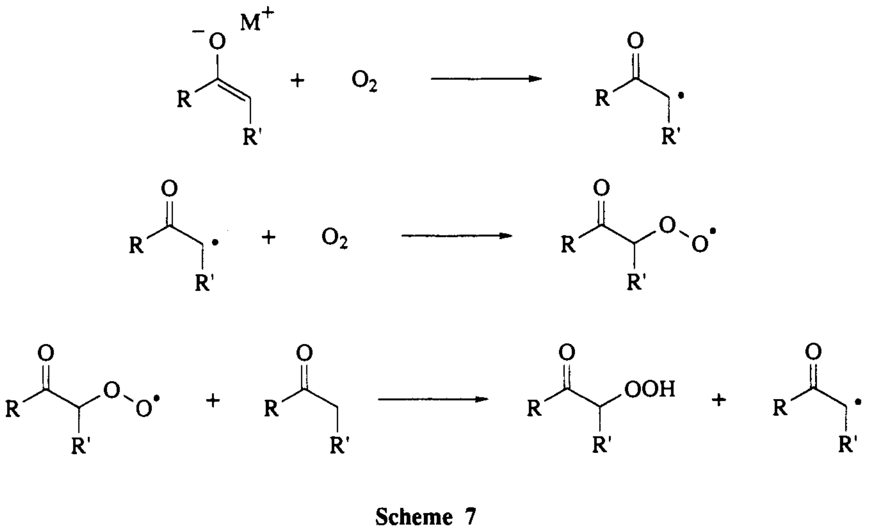

**Scheme 7**

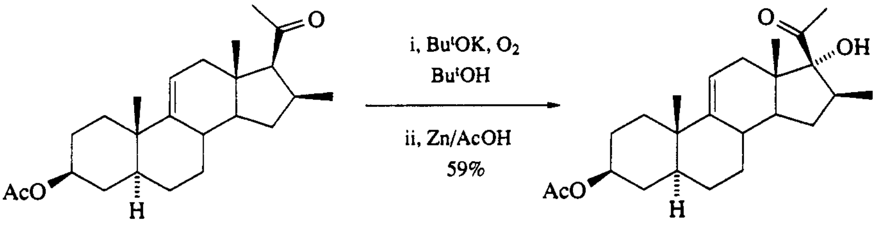

**(22)** **(23)**

The primary product is the α-hydroperoxy ketone. The corresponding alcohol is obtained after reductive work-up. Initially this was achieved using zinc dust in acetic acid, *e.g.* (**22**) to (**23**).[45] Potassium *t*-butoxide was used to generate the enolate in this case[46] and indeed is frequently the preferred base (*vide infra*). Subsequently it was found that the presence of triethyl phosphite in the reaction mixture provided an improved *in situ* reduction.[47] The combination of potassium *t*-butoxide, triethyl phosphite and oxygen in either DMF, *t*-butyl alcohol or monoglyme at temperatures between –30 °C and ambient may be regarded as standard conditions for the process. Where the α-center is primary or secondary, dehydrative overoxidation may occur and the method is generally only viable for the oxidation of tertiary centers, *e.g.* **(24)** to **(25)**.[48] Other potential sites of anion formation may also be susceptible, *e.g.* **(26)** to **(27)** and **(28)**.[49] Use of alternative combinations of reagents and solvents can promote efficient oxygenation, *e.g.* **(29)** to **(30)**, in this case producing a highly enolized β-dicarbonyl substrate used in the total synthesis of (±)-terramycin.[50] Clearly this method is of synthetic value.

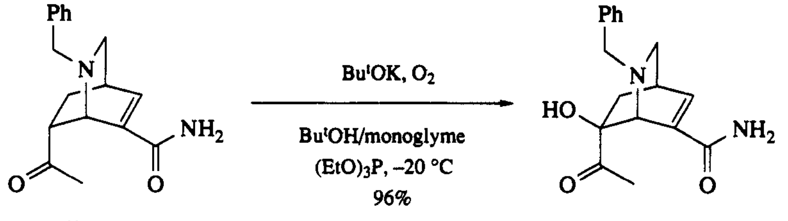

**(24)** **(25)**

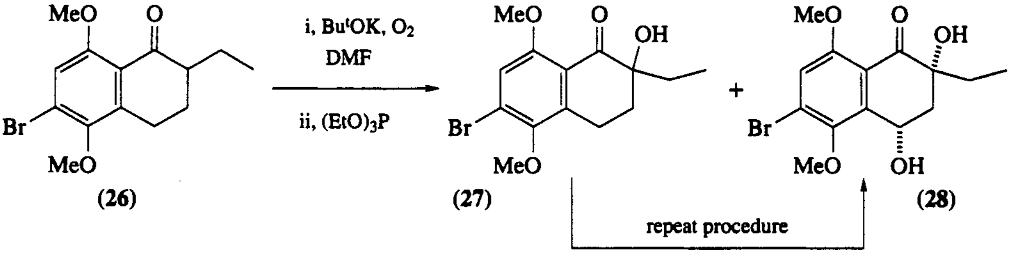

**(26)** **(27)** **(28)**

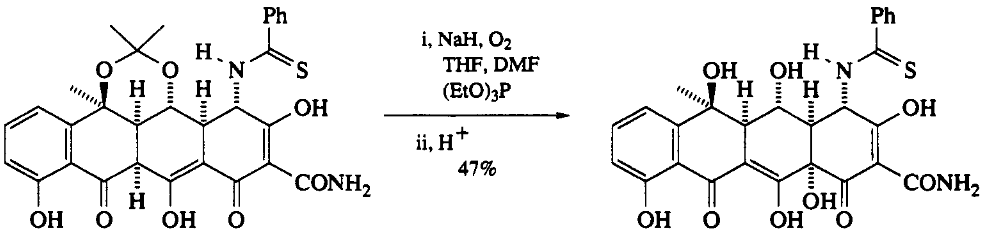

**(29)** **(30)**

### *(ii) Molybdenum peroxy complexes*

The first report of enolate hydroxylation by reaction with molybdenum peroxy complexes came in 1974 when Vedejs disclosed the use of MoOPH ($MoO_5$·py·HMPA complex).[51] A later more detailed publication[52] delineated the scope and limitations of the procedure and the advantages of the reagent over other molybdenum peroxy complexes. Molybdenum peroxy complexes, including MoOPH, had previously been prepared and studied with respect to their epoxidation of alkenes.[53–55] MoOPH **(31)** contains two electrophilic bridged peroxy ligands and a single oxo unit. α-Hydroxylation is effected by nucleophilic attack of the enolate at a peroxy oxygen atom. Two modes of attack are possible but the lack of α-hydroperoxy products suggests that the pathway involves only O—O cleavage (Scheme 8). The oxygenation has, in some cases, occurred using less than stoichiometric amounts of MoOPH, indicating that both peroxy bridges may be available for reaction.

In general the ketone enolate is formed and reacted at low temperature (between –50 °C and –30 °C). The preferred base is LDA and gives rise to the kinetic enolate under these conditions. The hydroxylation is frequently found to be sensitive to reaction variables (temperature, stoichiometry, concentration, *etc.*). This contrasts with the less sentient and more reactive ester enolates (Section 2.3.2.4.2.ii. The only noticeable competing reactions are overoxidation and aldol condensation of the product with unconsumed enolate. These processes rarely become noticeable and, where they do, are often significantly diminished by lowering the reaction temperature and/or increasing dilution. Aldol condensation is more

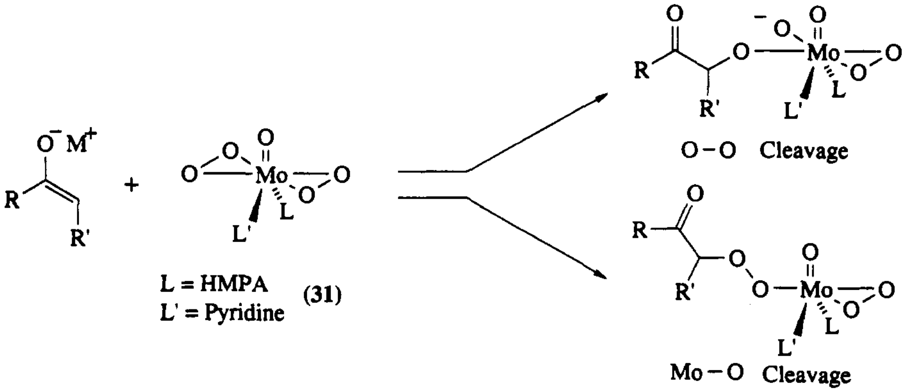
L = HMPA
L' = Pyridine
(31)
O–O Cleavage
Mo–O Cleavage

**Scheme 8**

of a problem where the enolate is unhindered and the process is generally inefficient for methyl ketones, although some improvement is possible by inverse addition of the enolate to MoOPH. β-Dicarbonyl compounds are not hydroxylated.[52]

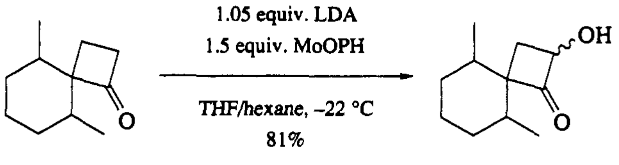
1.05 equiv. LDA
1.5 equiv. MoOPH
THF/hexane, –22 °C
81%

(32) (33)

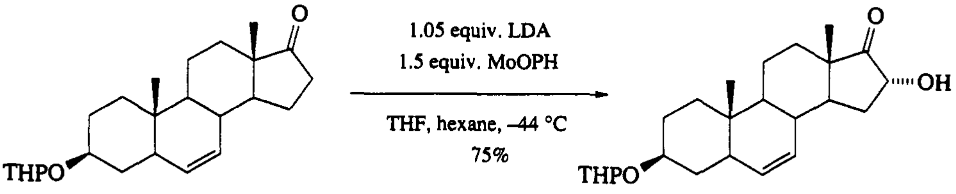
1.05 equiv. LDA
1.5 equiv. MoOPH
THF, hexane, –44 °C
75%

(34) (35)

Simple ketone substrates served to demonstrate the process. Thus bicyclic ketone (**32**) was oxidized at –22 °C to generate a mixture of diastereomers (**33**) in good yield. Good stereoselectivity was observed in the oxidation of steroidal ketone (**34**) to the hydroxy ketone (**35**). Application of the procedure in syn-

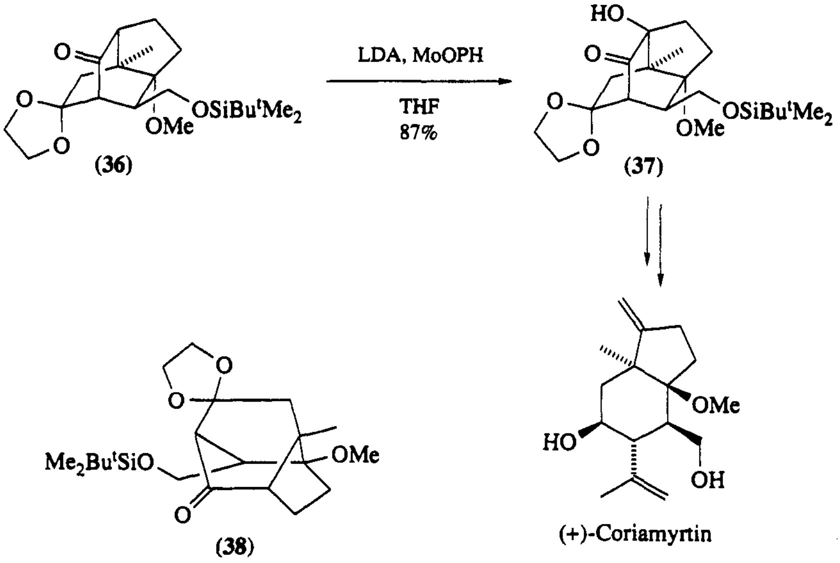
LDA, MoOPH
THF
87%
(36)
(37)
(38)
(+)-Coriamyrtin

thesis most often involves hydroxylation α to esters[56] or lactones[57] (Section 2.3.2.4.2.ii), although ketone hydroxylation has been applied. For example, bridgehead hydroxylation of ketone (**36**) provided (**37**), an intermediate used in the synthesis of (+)-coriamyrtin and (–)-picrotoxinin.[58] Interestingly, enolization in an anti-Bredt fashion is possible because the cyclohexane is locked in a boat conformation (**38**), with the result that the transoid enolate is effectively generated in a cycloheptane ring.

### *(iii) 2-Sulfonyloxaziridines*

In 1977 Davis reported the synthesis of 2-arylsulfonyl-3-phenyloxaziridines (**39**), the first stable oxaziridines heterosubstituted at nitrogen.[59] The highly electrophilic nature of the ring oxygen in these compounds was soon established.[60–63] That this was due at least in part to the powerfully electron-withdrawing phenylsulfonyl group was equally clear.[64] Reaction of ketone enolates with the reagents produces the α-hydroxy ketone by direct nucleophilic attack on the ring oxygen[61,65] and subsequent β-elimination (Scheme 9). The enolates are generated at –78 °C in THF by treatment with potassium hexamethyldisilazide (lithio bases are less successful) and are reacted and quenched at this temperature.[65] Products from condensation of the enolate with the generated sulfonimine (**40**) have been observed only where the corresponding base was potassium *t*-butoxide. Overoxidation is barely noticeable. The stereoselectivity of the oxidations is generally good and the yields of α-hydroxy ketones are frequently better than those available using MoOPH or molecular oxygen (*vide supra*); for example (**41**) to (**42**), and (**43**) to (**44**).[65] Oxidation of β-dicarbonyl compounds is possible (see Section 2.3.2.2.2.iii).

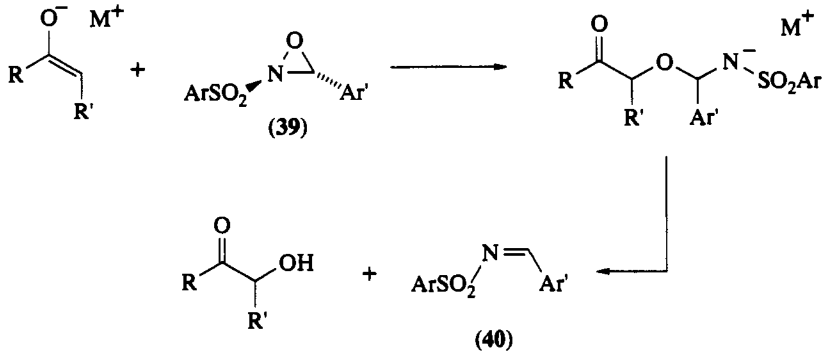

Scheme 9

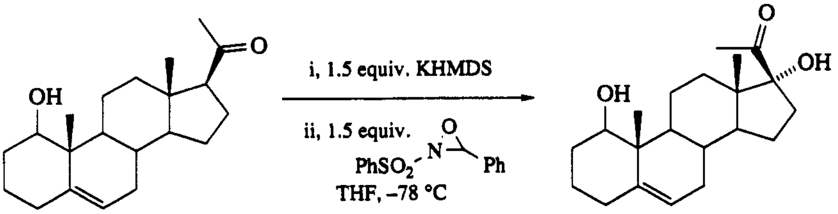

(**41**) (**42**) 78%

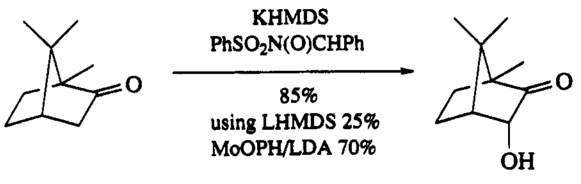

(**43**) (**44**)

Extension of this procedure to provide a means of asymmetric hydroxylation has been the subject of more recent attention. Initially oxaziridines bearing a camphor-derived residue at nitrogen, for example (**45**), were considered.[66,67] Relatively low levels of chiral induction were achieved[68] and a more rigid compressed system was sought. Camphorsulfonyloxaziridines (**46a** and **b**) were subsequently shown to provide variable although promising enantioselectivities, *e.g.* (**47**) to (**48**).[69] No convincing rationale is available, but it has been suggested that the principle determinant lies with the nonbonded, steric interactions in an open transition state.[69]

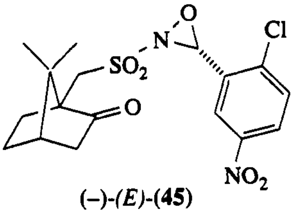

(–)-(*E*)-(**45**)
(also antipode)

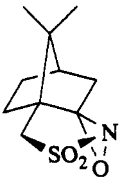

(**46a**)

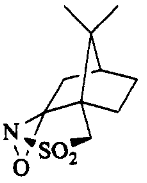

(**46b**)

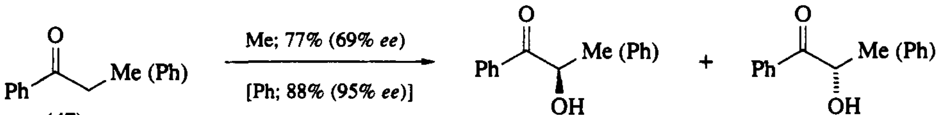

(**47**)

(*R*) minor (**48**) (*S*) major

The relatively recent emergence of this approach to hydroxylation will, no doubt, mature into a well-used facility.

*(iv) Miscellaneous*

Preformed enolates are susceptible to further methods of oxygenation. For example treatment with LTA in benzene effects α-acetoxylation[70] at lower temperature and more rapidly than the corresponding enol examples. Similarly α-benzoylation using benzoyl peroxide is possible for both lactones[71] and β-keto esters[72] and presumably could be used for less-activated ketones.

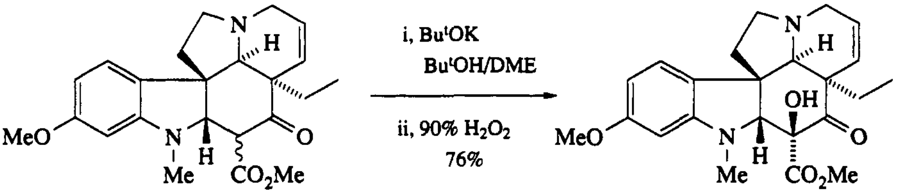

(**49**) (**50**)

In some cases, where enolate oxygenation with molecular oxygen failed, it has been reported that quenching with 90% hydrogen peroxide allows efficient conversion to the hydroxy ketone, *e.g.* (**49**) to (**50**).[73] Similarly enolate oxidation with organic peracids is possible (*vide infra*). α-Hydroxylation *via* preformed enolates comprises one of most synthetically expedient approaches for achieving this transformation.

### *2.3.2.1.3* Via *silyl enol ether*

*(i) Peracid*

Perhaps the most convenient and reliable α-hydroxylation procedure involves treatment of the silyl enol ether[74] of a ketone with organic peracids.[75] Initial epoxidation is followed by silyl migration and generation of the α-silyloxy ketone, which usually forms the hydroxy ketone directly, by rapid hydrolysis (Scheme 10). That epoxides are indeed the intermediates has been demonstrated by their isolation and X-ray characterization.[76,77] The silyl migration may occur by one of two processes involving either an oxacarbenium ion (**51**)[77] or a tight ion pair (**52**).[75] Recent work implicates the former.[76] The process is successful for a range of enol ethers derived from reaction of the enolate with various silylating agents[78] and for various peracid reagents. The synthetic usefulness is enhanced by the efficient regiocontrol arising from selective formation of the kinetic or thermodynamic enol ether.[74]

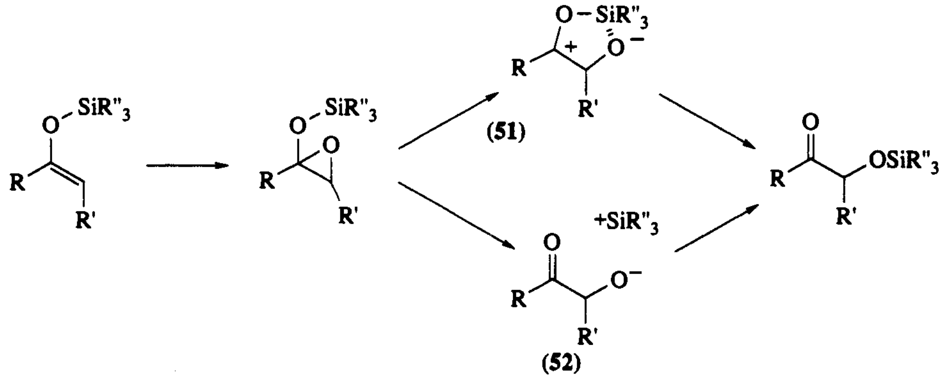

Scheme 10

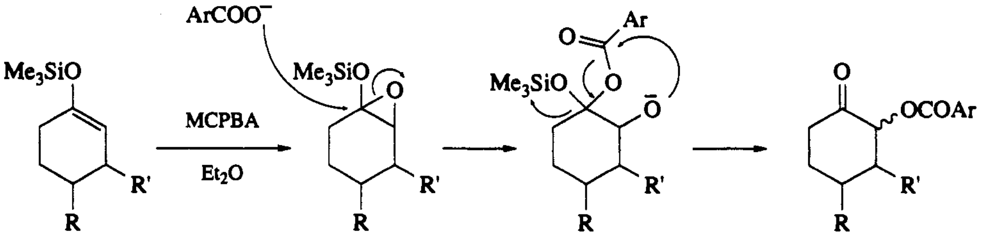

(53) (54)

Most frequently the reactions are performed by treating the crude silyl enol ether with MCPBA at 0–25 °C in dichloromethane. Solvent effects have been observed. Thus treatment of enol ether (**53**) with MCPBA in ether resulted in isolation of the benzoate (**54**).[79] This was considered to arise as a result of the increased nucleophilicity of the residual carboxylic acid in ether over that in dichloromethane. Isolation of the silyloxy epoxide by an analogous ethereal oxidation[77] suggests perhaps that the 1,4-silyl migration is intrinsically less facile in this solvent. Generally however the process is efficient and simple substrates are readily oxygenated (Scheme 11).

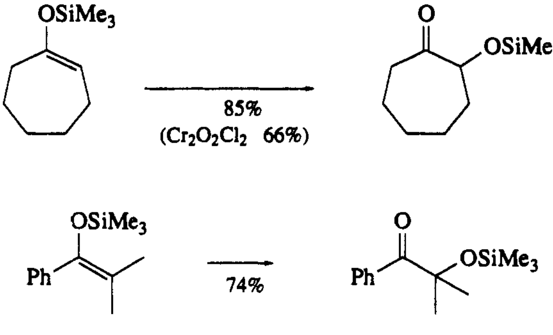

Scheme 11

Synthetic application includes Paquette's recent application in work directed toward the total synthesis of sterpuric acid.[76] Exposure of enol ether (**55**) to peracid provided a single diastereomer of the silyloxy compound (**56**) in good yield. It was from this substrate (**55**) that the first stable trimethylsilyloxy epoxide was obtained (**57**) and examined by X-ray crystallography. Similarly stereoselective oxygenation of β-keto ester (**49**) *via* the corresponding silyl enol ether provided (**50**), also in 76% yield.[80] Lastly efficient and highly stereoselective α-hydroxylation by this method was employed during studies towards the synthesis of helenanolides (**58** to **59**).[81]

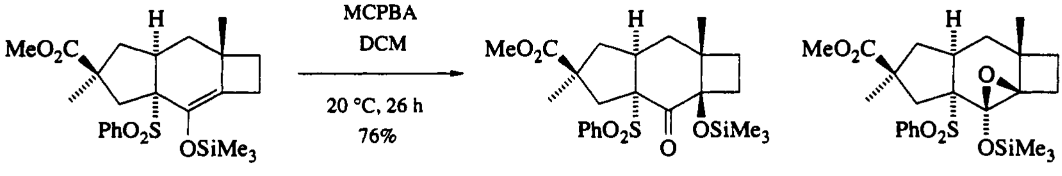
MeO2C
H
PhO2S
OSiMe3
MCPBA
DCM
20 °C, 26 h
76%
MeO2C
H
PhO2S
O
OSiMe3
MeO2C
H
O
PhO2S
OSiMe3

**(55)** **(56)** **(57)**

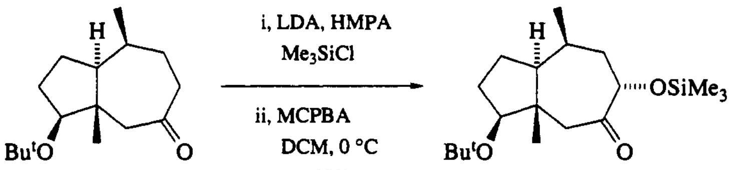
H
Bu<sup>t</sup>O
O
i, LDA, HMPA
Me3SiCl
ii, MCPBA
DCM, 0 °C
75%
H
OSiMe3
Bu<sup>t</sup>O
O

**(58)** **(59)**

*(ii) Singlet oxygen*

Singlet oxygen has been shown to react with silyl enol ethers in two ways (Scheme 12). Firstly a normal prototropic ene process may occur in a manner analogous to that with isolated alkenes.[82] Secondly a silatropic process cleaving the Si—O bond in a comparable fashion may occur. The latter process gives rise to α-oxygenated products. In general, however, where β-protons are available, the prototropic ene reaction takes precedence.[83,84] Clearly where β-protons are absent the silatropic process is free to run its course. Alternatively, where β-protons are present one could conceive of two situations where the silatropic mode would dominate. The ene process requires the reacting allylic proton to be orthogonal to the plane of the carbon–carbon double bond (coplanar with the π-system).[82] Consequently where allylic protons are not so arranged and are conformationally restricted from attaining such alignment, the silatropic process may be favored. Similarly, where the prototropic ene reaction is inhibited through an increase in strain associated with migration of the alkene the alternative process will again become favorable. That such restrictions are important is apparent from the outcome of the sensitized photooxygenation of silyl enol ether **(60)**.[85] The silatropic ene reaction dominates in the presence of an 'unavailable' β-proton.

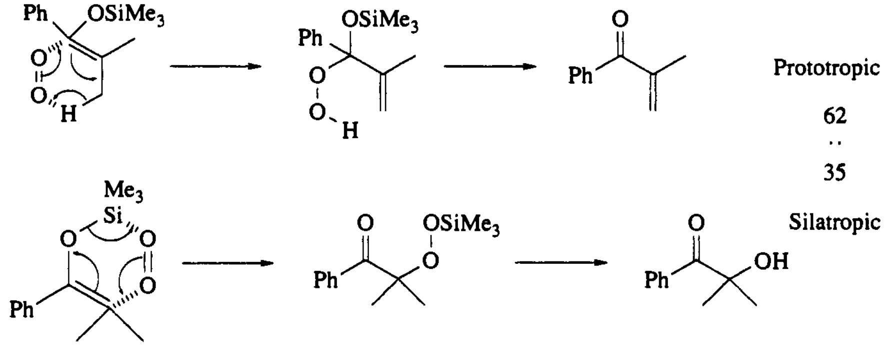
Ph
OSiMe3
O
O
H
Ph
OSiMe3
O
O
H
O
Ph
Prototropic
62
..
35
Silatropic
Me3
Si
O
O
O
Ph
O
OSiMe3
O
Ph
O
OH
Ph

**Scheme 12**

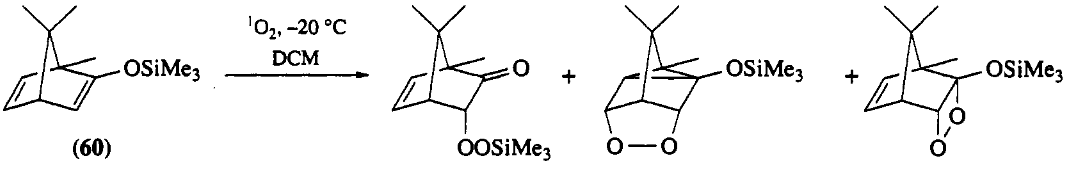
OSiMe3
¹O2, -20 °C
DCM
O
OOSiMe3
+
OSiMe3
O—O
+
OSiMe3
O
O
64%
30%
<5%

**(60)**

Clearly then, where examination of substrate conformation suggests poor alignment (or the absence) of allylic protons this mild process may well be viable.

### *(iii) Miscellaneous*

Heathcock has reported an anomalous case of ozonolysis of a silyl enol ether.[86a] Usually these substrates undergo facile oxidative cleavage in the same manner as alkenes. However, in this instance the α-silyloxy ketone (**61**) was obtained in quantitative yield. The intermediacy of a silyloxy epoxide was suggested. A more recent report[86b] has indicated that a similar process is competitive with the simple cleavage reaction, (**63a**) *versus* (**63b**), in the ozonolysis of the steroidal enol ether (**62**).

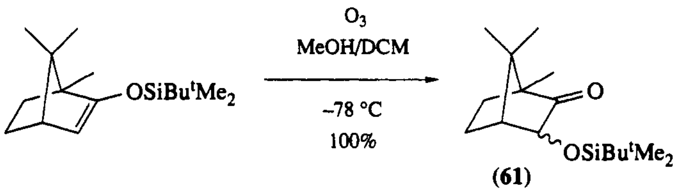

**(61)**

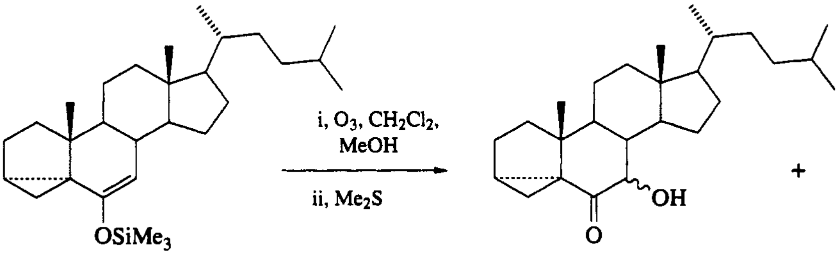

**(62)** **(63a)**

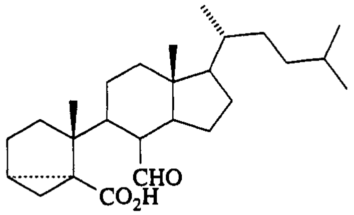

**(63b)**

Osmium tetroxide-mediated *cis* hydroxylation of a silyl enol ether has been demonstrated to produce the corresponding α-hydroxy ketone in moderate yield after exposure to an acidic work-up,[87] *e.g.* (**64**) to (**65**). The success of the catalytic procedure[88] bodes well for future application and furthermore bears some possibilities for asymmetric hydroxylation.[89]

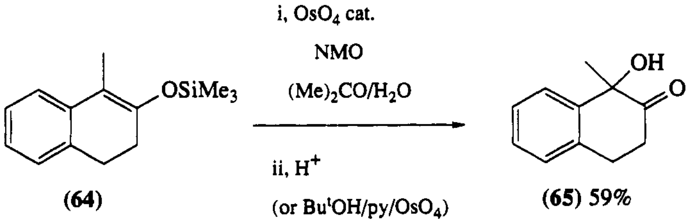

**(64)** **(65)** 59%

Lee has reported α-hydroxylation through the action of chromyl chloride, *e.g.* cycloheptanone (Scheme 11).[90] The yields were moderately good and no overoxidation was apparent, although the reagent may be of less synthetic value than more mild procedures.

The use of Moriarty's hypervalent iodine system (*vide supra*) has been extended to reaction with silyl enol ethers.[91] In this case a more activated electrophile is required and the reactions are carried out with iodosylbenzene in the presence of boron trifluoride etherate. However, yields are only moderate and the process seems less useful than the corresponding ketone/enol application.

One case has been reported[92] where simple photolysis of a crude silyl enol ether has generated the α-hydroxy derivative (**66** to **67**). This was considered to arise through coupling of the enol ether with photolytically generated silyloxy radicals derived from residual silicon-containing impurities. The presence of benzoyl peroxide, however, failed to provide useful quantities of the α-benzoyloxy ketone.

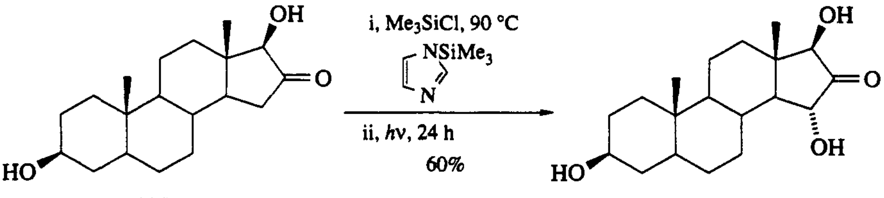

**(66)** **(67)**

Lead(IV) salts will α-oxygenate enol ethers as they do enols (*vide supra*), although in this case the process involves bisoxygenation of the unsaturated linkage and subsequent hydrolysis. For example, the combination of lead tetrabenzoate and triethylammonium fluoride at 0–25 °C effects efficient α-benzoyloxylation, *e.g.* **(68)** to **(69)**.[93] β,γ-Unsaturated ketones are also successfully oxidized, *e.g.* **(70)** to **(71)**.[94] The corresponding LTA α-acetoxylations are possible, but the benzoate salt remains the transition metal reagent of choice for these substrates.[74] These reactions appear to be uniformly efficient and perhaps deserve wider synthetic application.

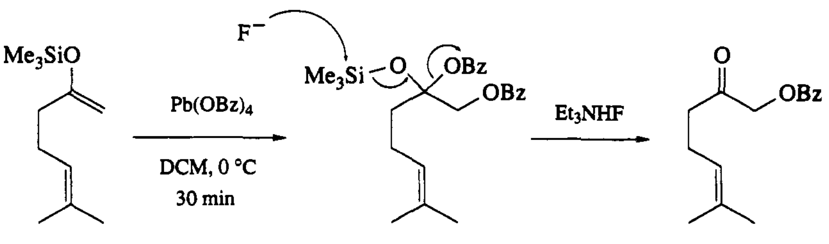

**(68)** **(69)** 92%

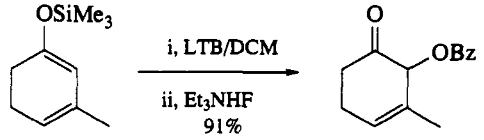

**(70)** **(71)**

Reagents which effect epoxidation of the enol ether unsaturation effect α-hydroxylation comparable to the peracid approach. Thus a combination of molybdenum hexacarbonyl and *t*-butyl hydroperoxide[95] converts the substrates to α-silyloxy derivatives.[78] The peroxide generated *in situ* from benzonitrile, potassium carbonate and hydrogen peroxide[96] can also perform the oxidation.[78] Molybdenum–peroxy complexes, including MoOPH, could presumably also effect this transformation. Lastly, dimethyldioxirane has been used to epoxidize alkenes and it is likely that application of this useful, debris free, organic peroxide to these reactions will soon emerge.[186]

### *2.3.2.1.4* Via *enol acetates and alkyl enol ethers*

#### *(i) Peracid*

Enol acetates and alkyl enol ethers can be α-hydroxylated through peracid epoxidation in a process analogous to that for silyl enol ethers (*vide supra*). In these cases however the epoxide intermediates are more readily isolable. Acetoxy epoxides, from enol acetates, may be rearranged by the action of heat or acid.[97] Where acid catalyzed, intramolecular rearrangement occurs with retention of configuration at the α-center of the acetoxy epoxide (Scheme 13).[97,98] The thermal rearrangement is thought to involve a slightly different mechanism.[97] Thus enol acetate **(72)** produces the α-acetoxy derivative **(73)** on treatment with perbenzoic acid in benzene.[99] Peracetic acid was less efficient. Numerous other examples are available.[100] Where dienol acetates are utilized, the product is derived from epoxidation of the more nucleophilic, remote unsaturation.[101] Both thermodynamic and kinetic enol acetates may be prepared[102] (although with less precision than the silyl equivalent), allowing a useful degree of regiocontrol.

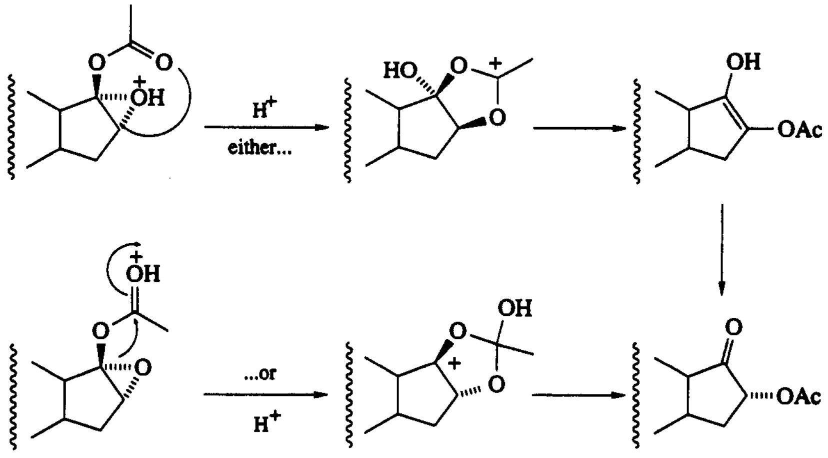
H+
either...
...or
H+
HO
O
+
OH
OAc
O

**Scheme 13**

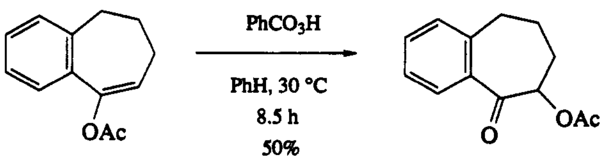
PhCO3H
PhH, 30 °C
8.5 h
50%
OAc
O

(72) (73)

The comparable process for alkyl enol ethers involves participation of solvent,[103] residual peracid[104] or water[105] in cleaving the initially formed epoxide.[106] Thus vinyl ether (74) produces the α-hydroxy derivative directly,[105] while (75) provides the dimethoxy acetal.[103b]

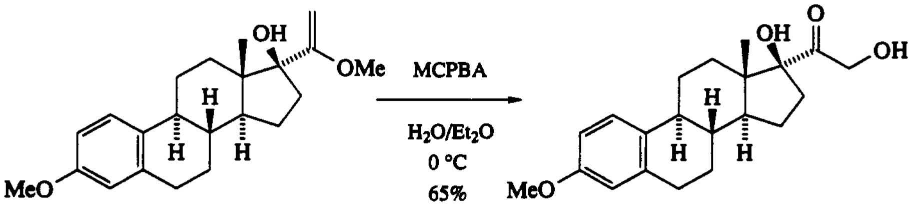
OH
OMe
MCPBA
H2O/Et2O
0 °C
65%
H
H
H
MeO
O
OH

(74)

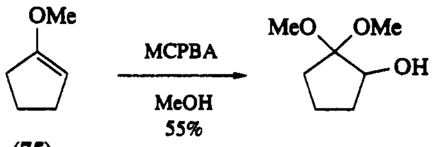
OMe
MCPBA
MeOH
55%
MeO
OMe
OH

(75)

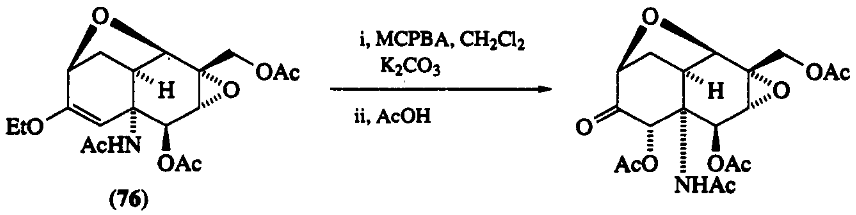
i, MCPBA, CH2Cl2
K2CO3
ii, AcOH
O
OAc
H
EtO
AcHN
AcO
NHAc

(76) (77)

A more complex example is seen in Kishi's tetrodotoxin synthesis.[107] Enol ether (76) provided the precursor to α-acetoxy ketone (77), which was obtained as a single stereoisomer by acetic acid opening of the initial ethoxy epoxide.

### *(ii) Singlet oxygen*

The discussion outlined above (Section 2.3.2.1.3.ii) for the interaction of singlet oxygen with silyl enol ethers is equally relevant here. Thus the oxygenation pathway competes with the normal ene reaction. The primary work with enol acetates[108] displayed solely the prototropic ene reaction generating the corresponding enones. Subsequent investigations into the reactions of enol acetates bearing less readily available allylic protons revealed the production of α-peroxy ester products derived from a novel acyl migration process (in this case an aldehyde-derived enol acetate was used).[109] Once again, where possible the normal ene process is dominant, although this in itself could provide an indirect oxygenation procedure. For example, if the dominant ene process pivoted on the acetoxy-bearing carbon (Scheme 14), the so-formed enol acetate (78)[109] would allow regeneration of the ketone.

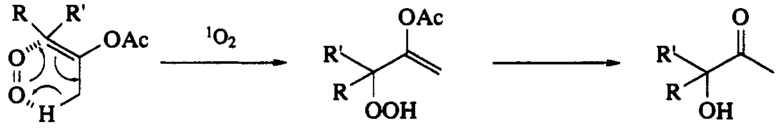

(78)

Scheme 14

In the case of alkyl enol ethers the normal ene process competes with solvent incorporated and 1,2-dioxetane products. Here however the ene process seems to be less inevitable when allylic protons are available and the product distribution may be effectively controlled by manipulation of solvent and temperature combinations.[110] Best results are nonetheless achieved where the competitive processes are restricted.[111] Thus enol ether (79) produces hydroxylated dimethoxy acetal (80) *via* direct incorporation of methanol or through reduction of the 1,2-dioxetane (81).

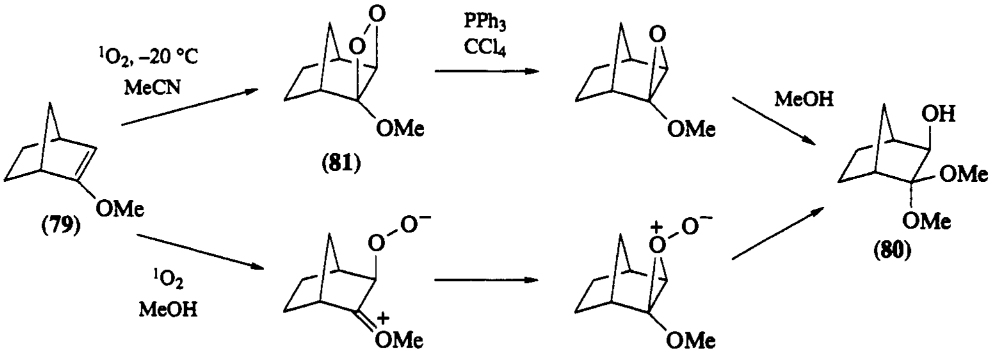

Although perhaps not widely applicable, these processes could find useful application in some instances.

### *(iii) Miscellaneous*

Treatment of enol acetates with LTA in acetic acid affords α-acetoxy ketones.[112,113] For example the tetracyclic substrate (82) is converted to the α-acetoxy derivative (83) in 95% yield and provides a step in the total synthesis of cycloneosamandione.[114] Vinyl ethers react similarly, suggesting that alkyl enol ethers should follow suit.

α-Arylsulfonyloxy ketones are formed from enol esters (and to a lesser extent from silyl enol ethers) by reaction with arylsulfonyl peroxides[115,116] in methanol at 0 °C. The process involves direct attack on the electrophilic peroxy oxygen atoms and the yields are high.

Reaction of enol acetates with hexamethyldisilyl peroxide in the presence of a Lewis acid (*e.g.* $FeCl_3$, $SnCl_4$ or $BF_3{\cdot}OEt_2$) gives moderate yields of α-acetoxy and α-hydroxy ketones.[117] A similar transforma-

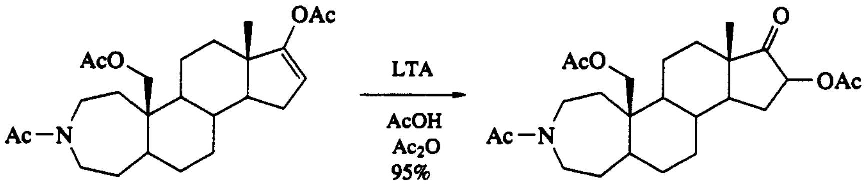

**(82)** **(83)**

tion is possible for some large ring enols. Osmium tetroxide in pyridine converts alkyl enol ethers to the corresponding α-hydroxy ketones[106] although the poor yield may be synthetically restrictive. Finally, electrochemical acetoxylation of enol acetates occurs in moderate yield.[118]

Although some of the procedures encountered in this section are efficient, in general they are less attractive than those using the silyl enol ethers.

### *2.3.2.1.5* Via *alternative derivatives*

#### *(i) Enamines and enamides*

Enamines are readily available ketone derivatives.[119] Exposure of these compounds to certain transition metal salts has been shown to produce α-oxygenated imines which are rapidly hydrolyzed to their ketone counterparts. Thus, for example, morpholino enamines, prepared *in situ*, are α-acetoxylated on treatment with thallium triacetate.[120] The process is thought to involve either direct nucleophilic extraction of an acetate unit or the intermediacy of an organothallium species which subsequently undergoes anchimerically assisted intramolecular acetoxy migration to generate the α-acetoxyimine (Scheme 15).

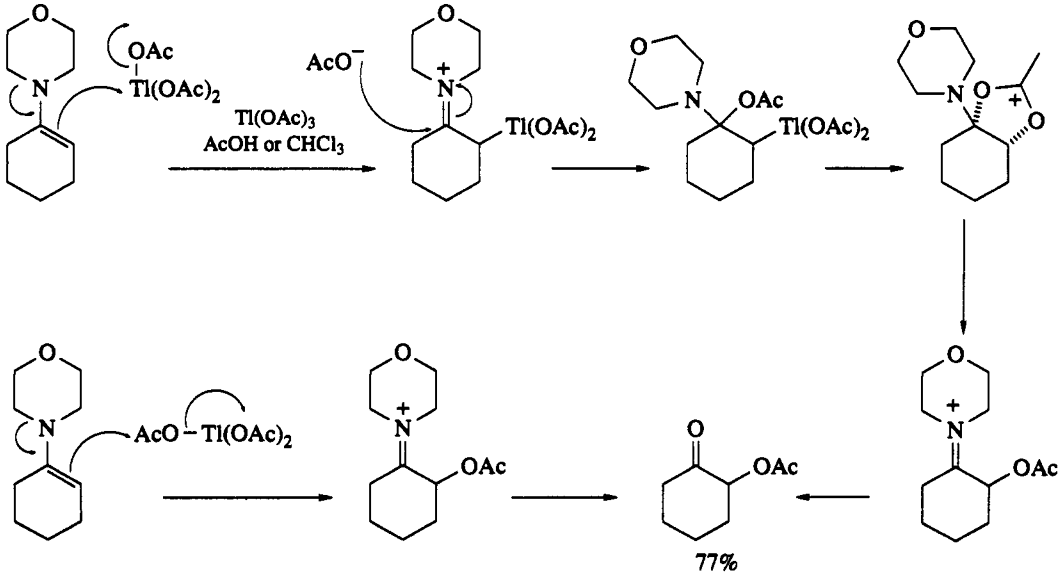

Scheme 15

Reaction with LTA in benzene generates the bisacetoxy derivative (84) analogous to the reaction with silyl enol ethers. Subsequent collapse of the intermediate is however somewhat dendritic (Scheme 16) and consequently of little synthetic value.[121] However it is clear from the nature of the alternative products that enamines possessing no protons at the a-positions could prove to be operable substrates.

Enamides, derived from ketoximes, provide more useful substrates for this procedure.[122] Thus exposure of the relatively stable enamide (86) to LTA in benzene affords the α-acetoxyimine (87), which can be used, if required, to regenerate the enamide and repeat the process. Alternatively, hydrolysis would re-

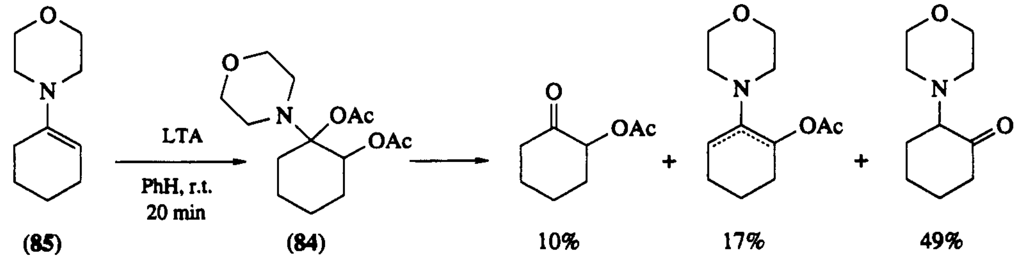
LTA
PhH, r.t.
20 min
OAc
OAc
(85)
(84)
10%
17%
49%

**Scheme 16**

veal the monoacetoxy ketone. The overall sequence from the ketone, although efficient, is dissuasively long.

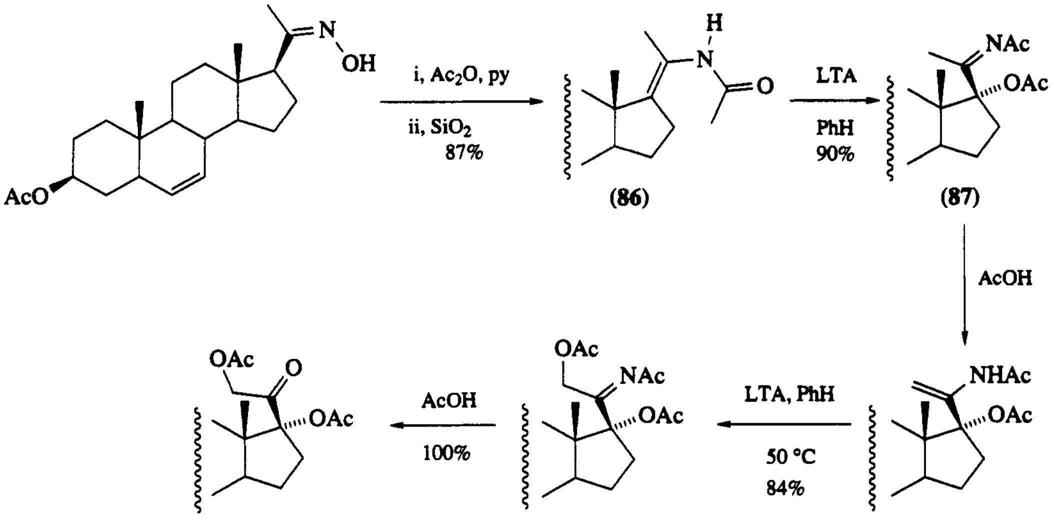
i, Ac$_2$O, py
ii, SiO$_2$
87%
LTA
PhH
90%
(86)
(87)
AcOH
LTA, PhH
50 °C
84%
AcOH
100%
NAc
OAc
NHAc
AcO

Enamines are susceptible to peracid oxidation, presumably through the epoxide, producing the α-hydroxy ketone after hydrolysis. Thus steroidal ketone (**88**) is converted *via* the pyrollidino enamine to the α-hydroxy derivative (**89**) in approximately 50% overall yield by treatment of the enamine with MCPBA followed by basic work-up.[123] Similar conversion of a steroidal enamide to the α-hydroxy ketone using monoperphthalic acid has been reported.

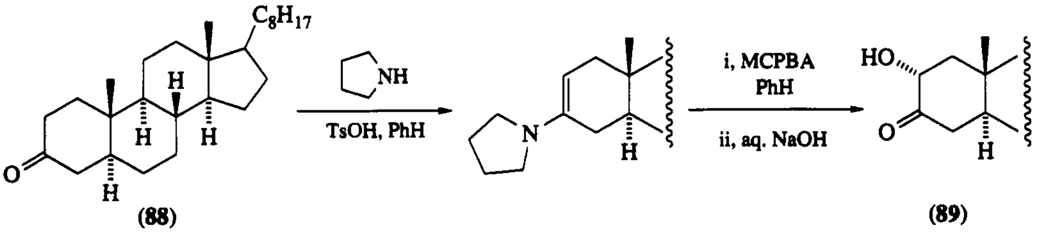
C$_8$H$_{17}$
TsOH, PhH
i, MCPBA
PhH
ii, aq. NaOH
(88)
(89)

The process used in the α-sulfonyloxylation of enol esters (Section 2.3.2.1.4.iii) may be used to regioselectively insert a sulfonyloxy group on morpholino and pyrrolidino enamines.[115,116] Yields of the corresponding ketones are high. Similarly reaction of morpholino enamines with benzoyl peroxide generates the α-benzoyloxy ketones after acidic work-up, although in variable yield (25–82%).[38] A single example describes α-hydroxylation of an enamide by ozonolysis and reductive work-up;[122] the steroidal conversion was achieved in remarkable 94% yield. The generality of the approach is unclear.

### *(ii) Vinyl cyanides*

Vinyl cyanides are readily prepared in single-pot reactions from the corresponding ketones.[124] The conversion is generally very efficient. Transformation of these substrates to the α-hydroxy ketones may be effected in a number of ways. Oxidation with potassium permanganate, although vigorous, provides the required hydroxy ketones, even in the presence of further unsaturation, *e.g.* (**90**) to (**91**).[125] A more recent permanganate-based approach utilizes triphenylmethylphosphonium permanganate at low temperature.[126] The yields are acceptable and conditions are such that a reasonable level of functional group compatibility is achieved, *e.g.* (**92**) to (**93**). Both processes involve initial formation of a cyclic permanganic ester analogous to that involved in the oxidation of isolated alkenes by the reagent. Osmium tetroxide reacts similarly to effect oxygenation.[125] Stoichiometric techniques work reasonably well, while the catalytic process requires the addition of a cyanide trap, in the form of a second transition metal salt (*e.g.* zinc(II) nitrate) to realize the same efficiency, *e.g.* (**94**) to (**95**).[130] Nonetheless the overall sequence provides a useful method.

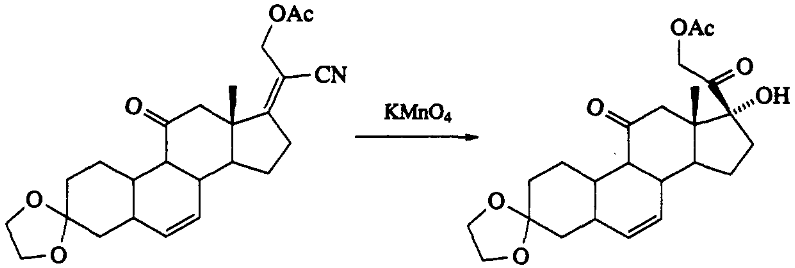

(**90**) (**91**)

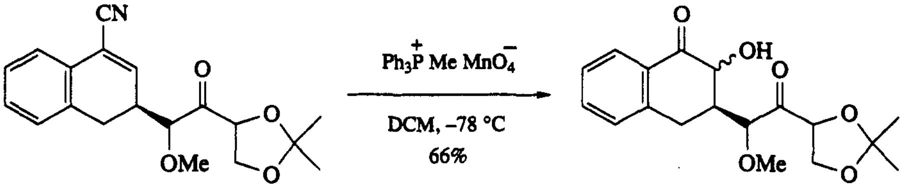

(**92**) (**93**)

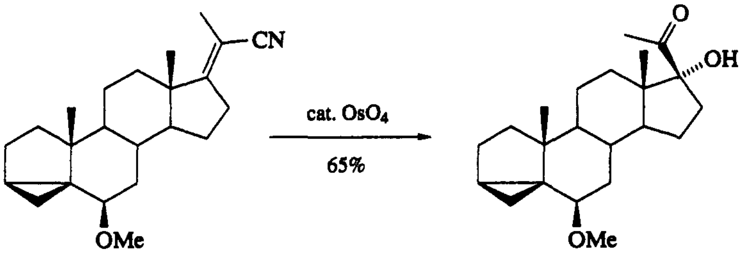

(**94**) (**95**)

### *(iii) Vinylsilanes*

Vinylsilanes may be prepared from the corresponding ketones by formation of the hydrazone followed by Shapiro reaction, quenching the vinylic anion with chlorosilanes.[127,128] An equally effective process derives the vinylsilane from the vinyl chloride, in turn prepared simply from the ketone.[128] The crucial oxidative transformation may be achieved in two ways. Firstly, ozonolysis in dichloromethane/methanol at approximately 0 °C followed by reductive work-up affords the α-hydroxy ketone, *e.g.* (**96**) to (**97**), *via* the intermediates (**98**) and (**99**). The outcome of the reaction varies with the solvent and work-up conditions, but using the combination indicated, good yields of the desired products are available.

Alternatively if an alkoxysilane is used, a second oxidation method is applicable.[129] Thus epoxidation of the vinylsilane (**100**) and oxidative cleavage of the crude silyl epoxide (**101**) provides a good yield of the product (**102**). The conversion (**101**) to (**102**) involves peroxidation of the silylalkoxy group and con-

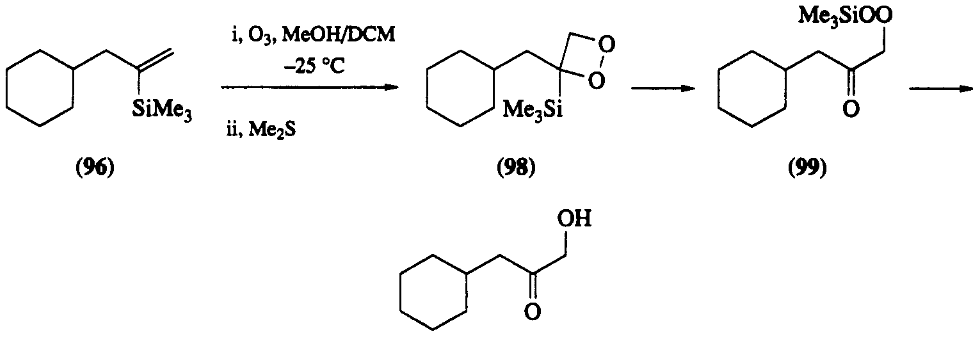
i, O3, MeOH/DCM
-25 °C
ii, Me2S
SiMe3
Me3Si
O
Me3SiOO
OH

**(96)** **(98)** **(99)**

**(97)** 73%

sequent oxiranyl migration. Fluoride-induced fragmentation then reveals (**102**). The process is ineffective for trialkylsilanes.

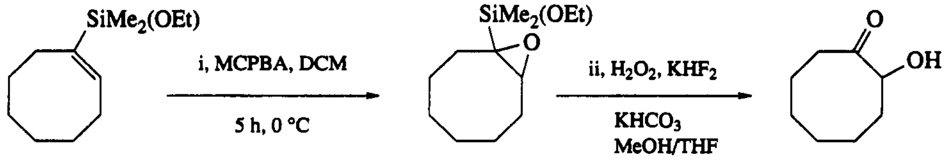
SiMe2(OEt)
i, MCPBA, DCM
5 h, 0 °C
O
ii, H2O2, KHF2
KHCO3
MeOH/THF
3 h, r.t.
OH

**(100)** **(101)** **(102)** 74%

### *(iv) Vinyl sulfides*

Vinyl sulfides are readily prepared directly from the ketone[130,131] in good yield. Exposure of these derivatives to a single equivalent of ozone provides the hydroxylated, alkene-migrated vinyl sulfide, (**103**) to (**104**), which may be hydrolyzed to the α-hydroxy ketone. Epoxy sulfide (**105**) is instrumental in the conversion, although alternative epoxidation methods fail to epoxidize without oxidizing at sulfur. It could prove possible however to α-oxygenate through the derived epoxy sulfones in a manner reported to occur to generate α-hydroxy aldehydes.[132]

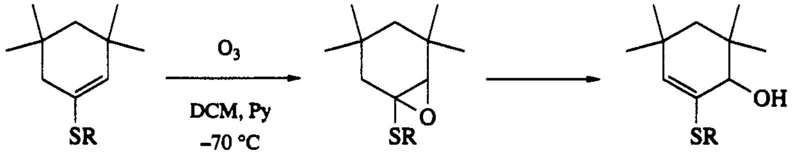
O3
DCM, Py
-70 °C
SR
O
OH

**(103)** **(105)** **(104)** 60%

LTA reacts with enol sulfides,[133] to produce thionium ions, *e.g.* (**106**), and thence allylic acetates (**107**) or bisacetoxylated products (**108**), in good yields. Presumably either of these compounds could be hydrolyzed to the α-acetoxy ketone.

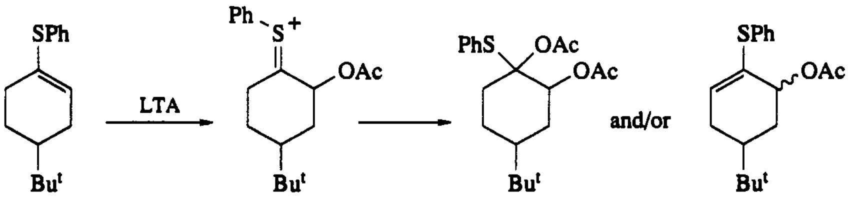
SPh
LTA
Ph
S+
OAc
PhS
and/or
Bu^t

**(106)** **(108)** **(107)**

### 2.3.2.2 α,β-Unsaturated Ketones: $sp^3$ Center

#### *2.3.2.2.1 Directly from ketone/enol*

*(i) Transition metal salts*

The majority of procedures outlined in Section 2.3.2.1 are applicable to these substrates through comparable mechanisms. Thus LTA played a dual role in the total synthesis of pyroangolensolide;[134] firstly α′-acetoxylation (**109**) and subsequently carbon–carbon bond cleavage (**110**). Numerous other examples of this process are available, *e.g.* (**111**)[81b] and (**112**).[135,140a] In some cases, however, α-oxidation (rather than α′-oxidation), occurs with alkene deconjugation, although this may in some cases be circumvented by using an alternative reagent (compare refs. 136 and 137). The α′-oxidation product is generally formed regardless of enol distribution.[138]

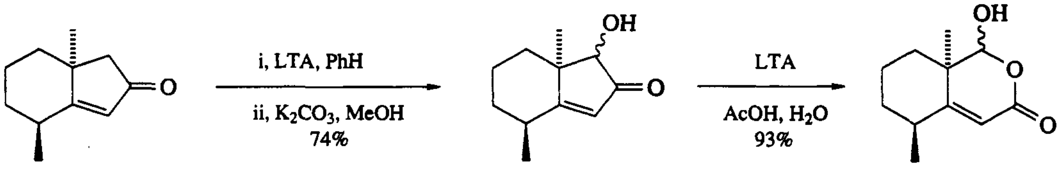
i, LTA, PhH
ii, $K_2CO_3$, MeOH
74%
OH
O
LTA
AcOH, $H_2O$
93%

**(109)** **(110)**

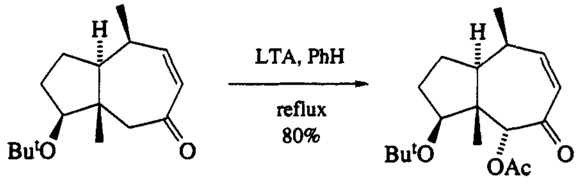
H
Bu$^t$O
O
LTA, PhH
reflux
80%
OAc

**(111)**

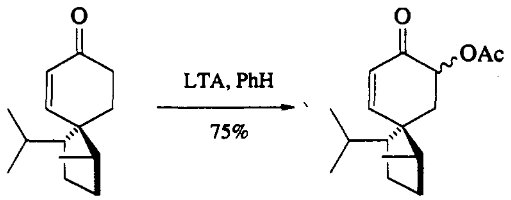
O
LTA, PhH
75%
OAc

**(112)**

Manganese triacetate has been specifically reported as a reagent for α′-oxidation.[139] Mechanistic dualism analogous to LTA (*vide supra*) is observed, although the radical process may be more dominant. Watt and coworkers used this technique during the synthesis of quassinoids.[140] Enone (**113**) was con-

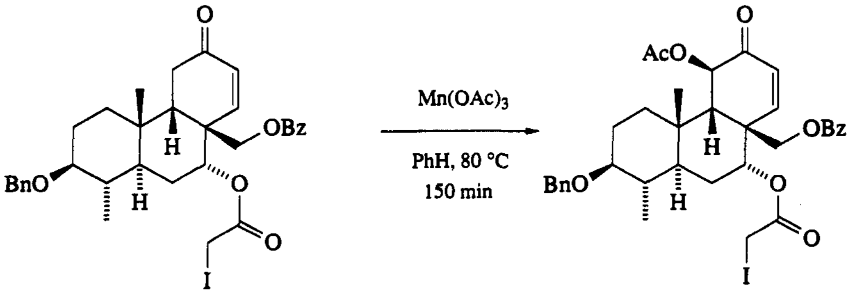
O
OBz
H
BnO
H
O
O
I
Mn(OAc)$_3$
PhH, 80 °C
150 min
AcO

**(113)** **(114)**

verted in high yield to the acetoxy derivative (**114**). Despite the potentially radical nature of the reaction, the alkyl iodide (primary, but α-keto) remained intact. That radicals were indeed involved was demonstrated in this system by intramolecular α′-oxygenation; a direct result of trapping of the α′-keto radical by a suitably positioned alcohol (**115** to **116**).

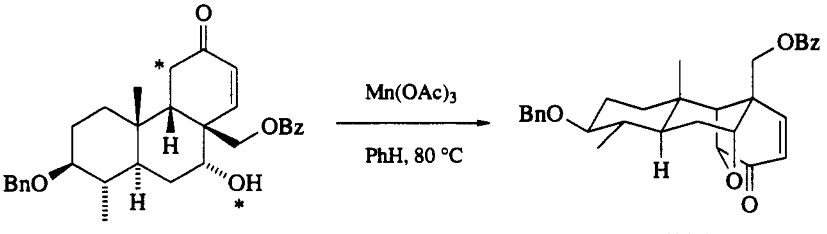

(**115**) (**116**)

α′-Acetoxylation of 2,3-dihydro-4-pyrones, *e.g.* (**117**), with this reagent proceeded in moderate yield under similar conditions to give stereochemically pure products.[141]

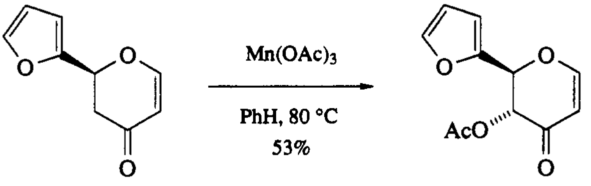

(**117**)

*(ii) Miscellaneous*

Where the dienol form of an α,β-unsaturated ketone is available, autoxidation giving the α′-hydroxy ketone through the α′-hydroperoxide is possible, as seen for saturated ketones (see Section 2.3.2.1.1.iii). Benzeneseleninic anhydride (see Section 2.3.2.1.1.iv) effects α′-hydroxylation at tertiary centers, *e.g.* (**118**) to (**119**), again in the same manner as for saturated ketones.[36b]

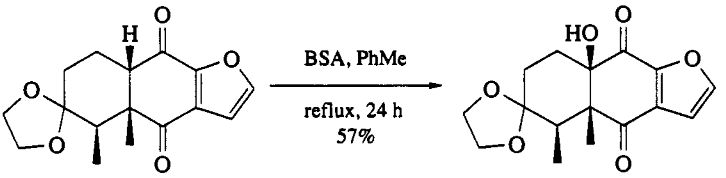

(**118**) (**119**)

### *2.3.2.2.2* Via *preformed enolate*

*(i) Molecular oxygen*

These substrates are as readily susceptible to hydroxylation as saturated ketones (Section 2.3.2.1.2.i). Thus enone (**120**) was oxygenated *via* the corresponding sodium enolate.[142] Exposure to oxygen and *in situ* reductive work-up provided (**121**) in moderate yield during the synthesis of (±)-deoxyaspidodispermine. Similarly (±)-kjellmanianone (**123**) was prepared through oxygenation of the potassium enolate of the corresponding deoxy substrate (**122**). The enolate was derived by the action of a less orthodox base.[143]

*(ii) Molybdenum peroxy complexes*

MoOPH may be used to α′-hydroxylate lithium enolates of α,β-unsaturated ketones (*cf.* Section 2.3.2.1.2.ii), although the conversion is less efficient than the equivalent process with saturated sub-

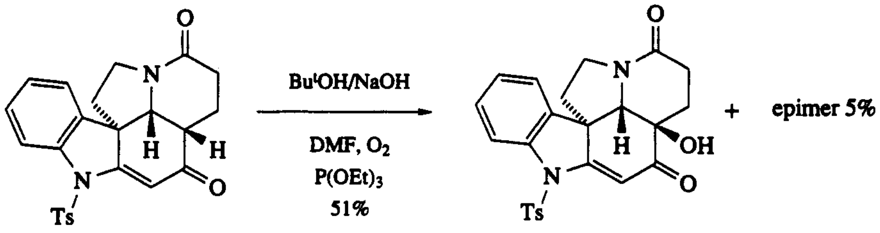
Bu'OH/NaOH
DMF, O2
P(OEt)3
51%
+ epimer 5%
H
H
OH
O
N
Ts

**(120)** **(121)**

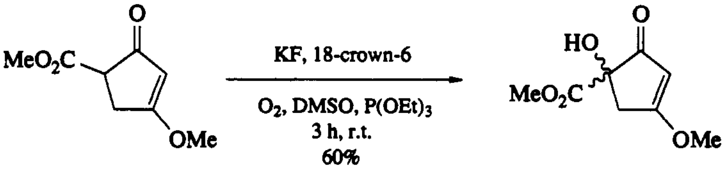
MeO2C
OMe
KF, 18-crown-6
O2, DMSO, P(OEt)3
3 h, r.t.
60%
HO
MeO2C
OMe

**(122)** **(123)**

strates. By-products formed by aldol condensation of the α′-hydroxy enone with unreacted enolate are more significant here and inverse addition of the enolate to MoOPH is required in order to achieve usable yields.[52] Thus enone (**124**) gives alcohol (**125**) in 52% yield. This particular example also suffers the handicap of being a less favorable methyl ketone substrate (*vide supra*) and the reasonable yield bears testimony to the ameliorating effects of inverse addition.

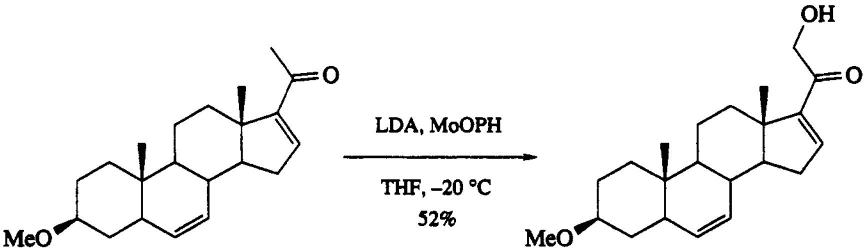
LDA, MoOPH
THF, -20 °C
52%
MeO
MeO
OH
O

**(124)** **(125)**

### (iii) 2-Sulfonyloxaziridines

Although few examples of the oxidation of α,β-unsaturated ketones with these recently established reagents (Section 2.3.2.1.2.iii) have been reported, the application is clearly plausible. The use of a chiral camphor-derived oxaziridine to effect this process has been reported.[67] Thus (+)-kjellmanionone (**123**) was prepared by treatment of the precursor (**122**) with oxaziridine (**45**) in THF at –78 °C. Although the yield in this case was only moderate, it would be unwise to generalize at this stage.

### (iv) Miscellaneous

Racemic kjellmanionone (**123**) has also been prepared by direct oxidation of the potassium enolate of the ketone (**122**) with MCPBA[67] and, if general, this would represent a convenient procedure. Oxidation of ketones with benzoyl peroxide is of no synthetic value (*vide supra*), but the process becomes useful if enolates are employed. Treatment of enone (**126**) with LDA in THF at 0 °C followed by quenching with

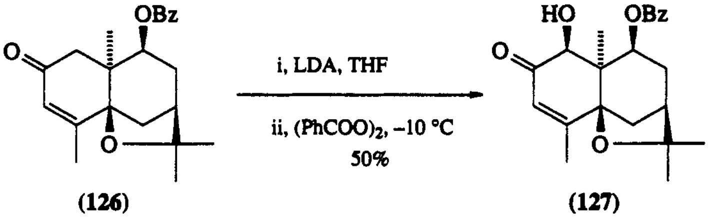
OBz
i, LDA, THF
ii, (PhCOO)2, -10 °C
50%
HO
OBz
O
O

**(126)** **(127)**

benzoyl peroxide at −10 °C produced hydroxy ketone (**127**).[144] The initial product, the α′-benzoyloxy ketone, is rapidly hydrolyzed. In this case the use of MoOPH was unsuccessful.

It has not been established whether enone-derived enolates are oxidized by LTA (*cf.* Section 2.3.2.1.2.iv), but the success of such a process seems likely.

### *2.3.2.2.3* Via *silyl dienol ethers*

#### *(i) Peracid*

Silyl dienol ethers are readily available.[74] α′-Hydroxylation through the action of peracids is facile (see Section 2.3.2.1.3.i).[145,146] Hence treatment of simple dienol ether (**128**) with MCPBA followed by fluoride-induced fragmentation of the unisolated epoxides gives α′-hydroxy ketone (**130**) or, in the case of (**129**), in the presence of acetylating agents, α′-acetoxy ketone (**131**). Oxidation of more adventurous substrates has been achieved. Thus, for example, dienol ether (**132**) gives the α′-hydroxy derivatives in 75% yield through the same process, although in this case with poor stereocontrol.[147] The tricyclic substrate (**133**) is similarly oxidized, albeit in surprisingly low yield.

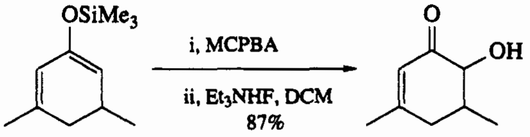
OSiMe$_3$
i, MCPBA
ii, Et$_3$NHF, DCM
87%
O
OH

(**128**) (**130**)

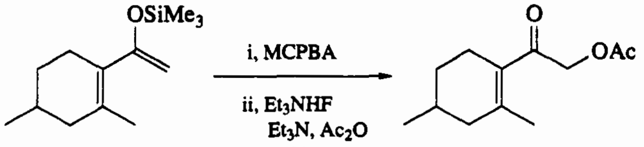
OSiMe$_3$
i, MCPBA
ii, Et$_3$NHF
Et$_3$N, Ac$_2$O
89%
O
OAc

(**129**) (**131**)

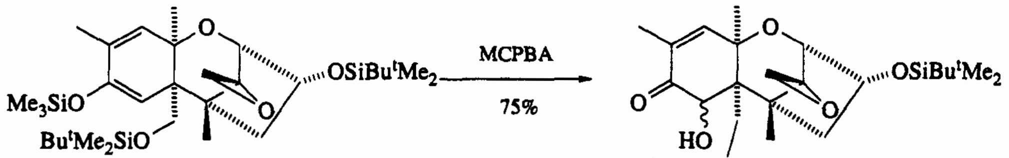
Me$_3$SiO
Bu$^t$Me$_2$SiO
O
O
OSiBu$^t$Me$_2$
MCPBA
75%
O
HO
Bu$^t$Me$_2$SiO
O
O
OSiBu$^t$Me$_2$

(**132**)

2:1 mixture of diastereoisomers; major isomer isolated as cyclic ether

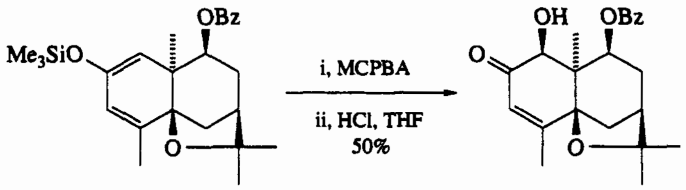
Me$_3$SiO
OBz
O
i, MCPBA
ii, HCl, THF
50%
OH
OBz
O
O

(**133**)

#### *(ii) Singlet oxygen*

While the reaction of singlet oxygen with silyl enol ethers was governed by competing prototropic and silatropic ene processes (see Section 2.3.2.1.3.ii), the interaction with dienol ethers displays a different mode of reactivity. Singlet oxygen generated from triphenyl phosphite ozonide at low temperature undergoes a [4 + 2] cycloaddition with the diene unit.[82] Reductive cleavage of the so-formed endoperoxide and dehydrative reconstitution of the enone generates the α′-hydroxy enone (Scheme 17).[148]

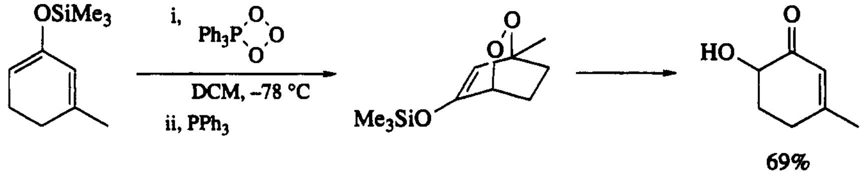
OSiMe3
i, Ph3P O O O
DCM, -78 °C
ii, PPh3
Me3SiO
HO
69%

**Scheme 17**

The technique has been applied to the total synthesis of (±)-oxylubimin (**134**) through hydroxylation of dienol ether (**135**).[148] The stereoselectivity is good, particularly when compared to the equivalent selectivities obtained using MCPBA, MoOPH or manganese triacetate.

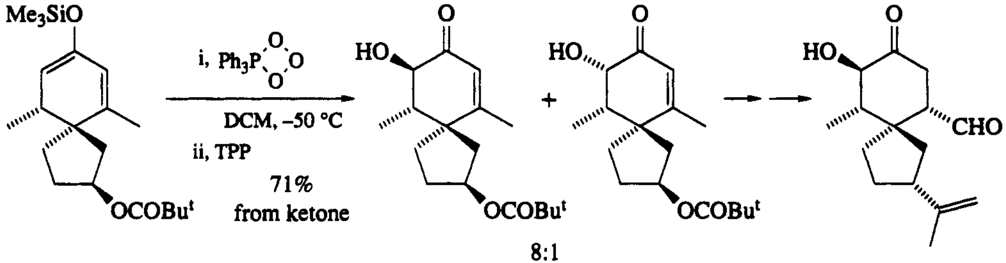
Me3SiO
OCOBu^t
i, Ph3P O O O
DCM, -50 °C
ii, TPP
71%
from ketone
HO
OCOBu^t
+
HO
OCOBu^t
8:1
HO
CHO

**(135)** **(134)**

The procedure is mild and reasonably efficient and may therefore find further synthetic use. One might also expect that photosensitized preparation of the singlet oxygen would be equally effective,[82] although this remains to be shown.

*(iii) Miscellaneous*

Other reagents have been utilized for this transformation. For example, lead tetrabenzoate (*cf.* Section 2.3.2.1.3.iii) provides the corresponding α′-benzoyloxy enones when combined with fluoride-induced hydrolysis of (**136**) and (**137**).[149] However, success is restricted to acyclic ketones. Where cyclic dienol ethers are employed, products derived from α-oxidation are obtained.[149]

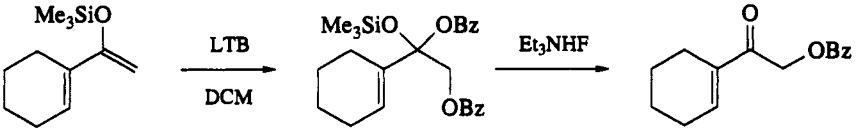
Me3SiO
LTB
DCM
Me3SiO
OBz
OBz
Et3NHF
O
OBz

**(136)** 54%

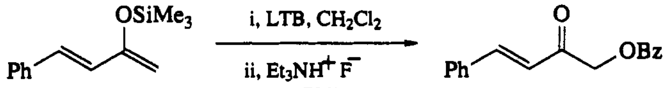
OSiMe3
Ph
i, LTB, CH2Cl2
ii, Et3NH+ F−
78%
O
Ph
OBz

**(137)**

Finally, a radical-induced α′-hydroxylation has been achieved using anhydrous *t*-butyl hydroperoxide in the presence of a copper(I) chloride catalyst at 50 °C in benzene,[150] but it is a relatively low yielding process.

### 2.3.2.2.4 Via *other derivatives*

While enol acetates from saturated ketones were useful α-oxygenation substrates, the corresponding dienol acetates are not. The relatively electron-deficient alkene bearing the acetoxy group is less attractive to electrophilic oxygenating agents than the unsubstituted double bond. Thus, for example, peracid treatment leads to epoxidation of the unfunctionalized alkene.[151] However, it would seem likely that reactions in basic media, which could initially hydrolyze the enol acetate, could be effective. Conversely the electron-rich alkyl enol ether should allow α′-oxidation of the dienol equivalent by electrophilic reagents (see Section 2.3.2.1.4 and *cf.* Section 2.3.2.1.3), although possibly complicated by skeletal cleavage.[151] By the same token enamine and ketoxime substrates should be effective (see Section 2.3.2.1.5).

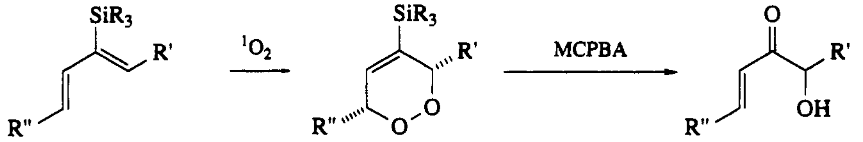

Scheme 18

Vinyl cyanides may be useful derivatives since permanganate-induced α-hydroxylation in the presence of alkenes has been demonstrated, *e.g.* (**90**) to (**91**). Oxygenation of α,β-unsaturated vinylsilanes and sulfides using the previously described procedures would not be successful (Sections 2.3.2.1.5.iii and 2.3.2.1.5.iv). However a singlet oxygen cycloaddition process (*cf.* Section 2.3.2.2.3.ii), followed by eliminative hydrolysis, could provide a usable, although lengthy, approach (Scheme 18).

### 2.3.2.3 α,β-Unsaturated Ketones: *sp*² Center

The overall sequence could be realized by 1,4-addition of a nucleophile to the enone and subsequent quenching at the α-position followed by β-elimination of the initial nucleophilic component.[152] Such multistep processes will not be discussed here. However direct hydroxylation methods are scarce. Moriarty has reported that α,β-unsaturated ketones are oxidized by phenyliodosyldiacetate at the α-site in preference to the α′-position, *e.g.* (**138**) to (**139**),[153] although no yield has been indicated. There is no available mechanistic rationale, although the intermediacy of the α,β-epoxide is precluded.

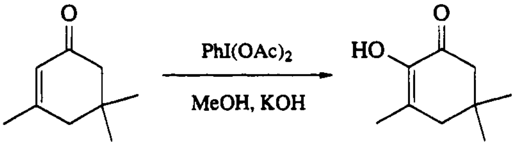

(**138**) (**139**)

Clearly there is little precedence for this *direct* procedure and the development of an efficient and reliable method is required.

### 2.3.2.4 Esters and Lactones

Much of the preceding discussion concerning the α-hydroxylation of ketones is relevant for ester and lactone substrates. Many examples have featured β-keto esters and these are clearly relevant. Reference should be made to these sections.

#### *2.3.2.4.1 Directly from enol form*

*(i) Hypervalent iodine reagents*

The procedure developed by Moriarty for the α-hydroxylation of ketones using iodosylbenzene or its diacetate has been extended for use with esters.[154] Thus treatment of methyl or ethyl esters with iodosylbenzene diacetate in a two-phase system (benzene/aqueous KOH) generates the α-hydroxy acid, while reaction in methanol in the presence of sodium methoxide provides the α-methoxy ester, (Scheme 19). Oxidation of the free acid was unsuccessful (Section 2.3.2.6). Both variations proceed in similar, moderately good yields, in a fashion mechanistically analogous to the reaction with ketones.

Similarly the α-mesyloxy esters are available by reaction with Koser's reagent.[31b] Neither of these studies addressed the question of stereoselectivity.

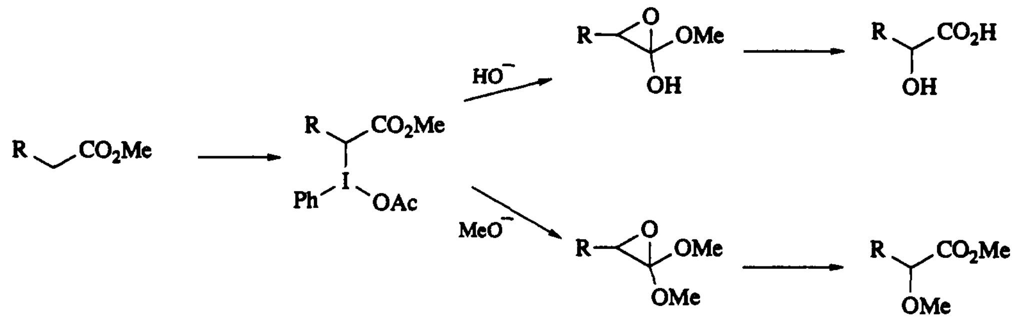

Scheme 19

### (ii) Miscellaneous

A number of enol oxidations of β-keto esters utilizing, for example, peracid, singlet oxygen or the peroxy ester reaction have been recorded (see Section 2.3.2.1.1.iv).

## 2.3.2.4.2 Via *preformed enolate*

### (i) Molecular oxygen

Electrophilic consumption of the enolates of esters and lactones is the most widely used process for effecting the α-hydroxylation. In analogy with the ketone series some of the earliest procedures employed molecular oxygen in combination with a suitable reducing agent. In this manner Corey produced hydroxy ester (**140**) during studies in the prostaglandin area.[155] Treatment of a lithio enolate with molecular oxygen at −78 °C and *in situ* reduction with triethyl phosphite gave a good yield of the required product, although with only minimal stereoselectivity. The oxidation of this substrate demonstrates a workable procedure but, as other studies have shown,[156] oxidation at nontertiary centers by a similar procedure are generally not useful. α-Hydroxylation of the extended enolates of enoate substrates, reducing with tin(II) chloride, has also been demonstrated.[157]

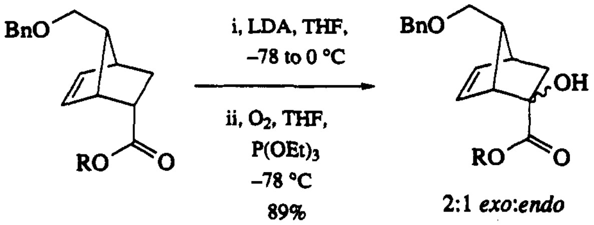

(**140**)

These methods have been somewhat superseded by the introduction of specific hydroxylating reagents (*vide infra*).

### (ii) Molybdenum peroxy complexes

Reaction of lactone or ester enolates with MoOPH (see Section 2.3.2.1.2.ii) produces the α-hydroxy derivative in high yield.[52] They appear to be better substrates than ketones, reacting at lower temperatures and with generally greater efficiency. The use of lower temperatures suggests an ameliorating effect on stereoselectivity. An interesting example (**141**) to (**142**)[158] cites interaction of the enolate counterion with a pendant trifluoromethyl group as providing the source of the stereochemical bias in a typically efficient oxidation. The benefit of this procedure over the simple molecular oxygen approach, in terms of stereoselectivity, is illustrated in the oxidation of the lactone (**143**).[159] A similar comparison of lactone enolate oxidation between MoOPH and 2-sulfonyloxaziridines has, however, suggested that better selectivity is achieved with the latter reagent (*vide infra*).

Taking stereoselectivity a stage further, MoOPH has been successfully employed in the enantioselective oxidation of esters bearing an enolate face discriminating chiral auxillary.[160] Thus exposure of the

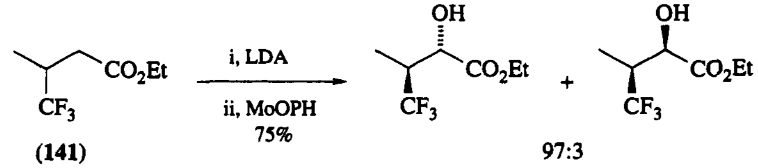

**(141)** **(142)**

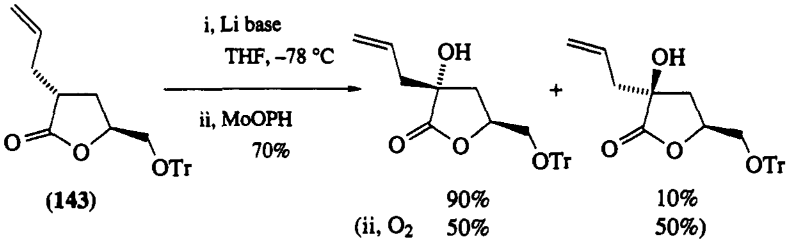

**(143)**

potassium enolate of ester (**144**) to MoOPH at *ca.* –50 °C delivers the α-hydroxy ester with a high level of diastereoselection. The process is independent of asymmetry at the adjacent carbon atom, but fails for oxidation of tertiary positions. Either diastereomer is available by appropriate selection of the (*E*)- or (*Z*)-enolate. Basic hydrolysis of the diastereomeric products produces the enantiomeric α-hydroxy acids without racemization.

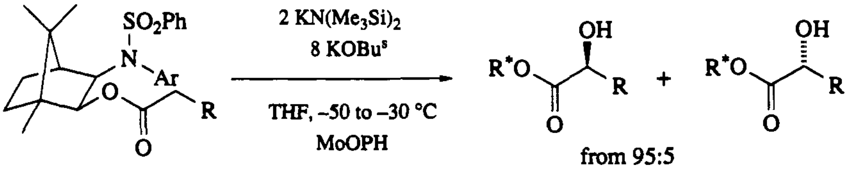

(**144**) Ar = 2,4,6-$Me_3C_6H_2$

*(iii) 2-Sulfonyloxaziridines*

Recent introduction of these reagents as a source of 'electrophilic oxygen' for a variety of oxidative processes was extended to the α-hydroxylation of ketone enolates (Section 2.4.2.1.2.iii), and, at the same time, to the analogous ester/lactone oxidations.

A comparative study,[65] contrasting this oxidation with that of MoOPH indicated a markedly improved yield and stereoselectivity (Scheme 20). Although undoubtedly a valid example, the distinction is unlikely to be so universally clear cut and both of these valuable reagents will be useful in synthetic application.

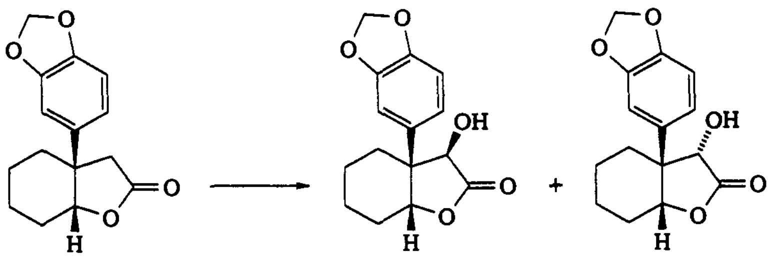

| | | | | |
|---|---|---|---|---|
| LDA/MoOPH | 15% | 75 | : | 25 |
| LHMDS/<br>oxaziridine | 62% | 100 | : | 0 |
| KHMDS/<br>oxaziridine | 91% | 100 | : | 0 |

**Scheme 20**

A recent display of such potential may be seen in Corey's excellent synthesis of (±)-Ginkgolide B.[161] Oxidation of the lithio enolate of lactone (**145**) provided the alcoholic derivative in, presumably, good yield and with a high degree of stereocontrol.

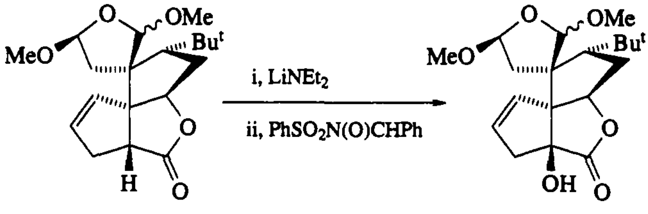

(**145**)

### *(iv) Miscellaneous*

α-Oxidation of the dienolate of dienoate systems through the intervention of benzoyl peroxide at low temperature has been demonstrated to be an efficient method for introducing an α-benzoyloxy substituent.[157] The procedure appears to have drawn little attention despite its obvious effectiveness.

## *2.3.2.4.3* Via *silyl ketene acetals*

### *(i) Peracid*

In a manner exactly analogous to the α-hydroxylation of ketone silyl enol ethers (Sections 2.3.2.1.3.i and 2.3.2.2.3.i) the corresponding ester silyl ketene acetals may be epoxidized by peracid and subsequently cleaved with fluoride to reveal the α-hydroxy ester.[162] Yields are good if hexanes are employed as solvent, while competing hydrolysis hampers the process in other media. The equivalent lactone hydroxylations are, however, not possible since hydrolysis is the dominant process even in hexane. This solvent limitation may prove restrictive to the widespread use of this technique.

### *(ii) Singlet oxygen*

One report has indicated the potential of this mild reagent for α-oxidation of silyl ketene acetals.[163] Once again the usefulness is restricted by competition between the required silatropic ene process and the prototropic ene reaction giving rise to the enoate. For substrates lacking β-protons the α-hydroperoxy ester is readily obtained in good yield. In one case where β-protons were present (methyl group) an 80% yield of the silatropic product was obtained by carefully optimizing the reaction conditions. This may not however always be possible.

### *(iii) Transition metal salts*

α-Acetoxylation and α-benzoylation of esters and lactones *via* their ketene acetals may be achieved using the appropriate lead(IV) salt.[164] Thus good yields of the acyloxy lactones (**146**) were obtained after fluoride treatment of the crude 'ortho ester' (*cf.* Section 2.3.2.1.3.iii). Although no information pertinent to the stereoselectivity was available here, subsequent studies have demonstrated that introduction of a steric bias can be fruitful. Oxidation of the ketene acetals of esters bearing camphor-derived auxiliaries produced the acetoxylated derivatives with a high degree of diastereoselectivity (Scheme 21).[165] Chemi-

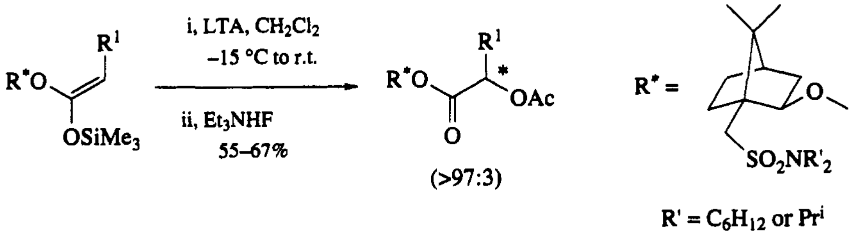

**Scheme 21**

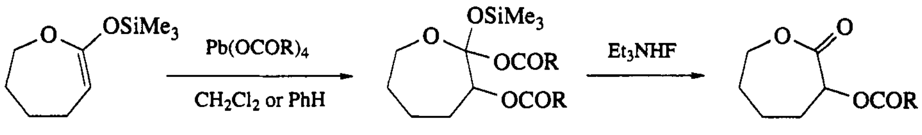
OSiMe3
Pb(OCOR)4
CH2Cl2 or PhH
OSiMe3
OCOR
OCOR
Et3NHF
O
OCOR

R = Me 82% **(146)**
R = Ph 78%

cal yields are somewhat lower than for simple substrates. Either antipode of the auxiliary may be used with equally good results and effective, nonracemizing hydrolysis procedures have been secured.

## 2.3.2.5 Amides and Lactams

### *2.3.2.5.1* Via *preformed enolates*

*(i) Molecular oxygen*

Just as ketones and esters may be derivatized by the action of molecular oxygen on the corresponding enolates, the same is true of amides. Generation of the lithio enolate (clearly not as facile as the previous substrates) and quenching with oxygen produce the α-hydroperoxyamide, which after *in situ* reduction, ($P(OEt)_3$),[166] or reductive work-up, ($NaHSO_3$),[156] gives good yields of the required material.

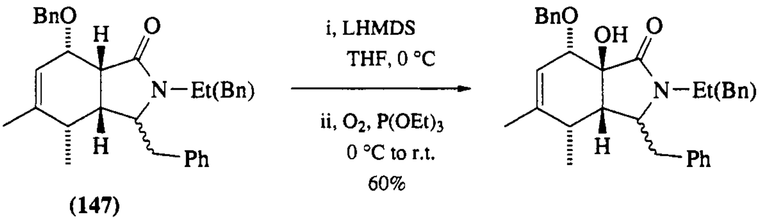
BnO
H
O
N−Et(Bn)
H
Ph
i, LHMDS
THF, 0 °C
ii, O2, P(OEt)3
0 °C to r.t.
60%
BnO
OH
O
N−Et(Bn)
H
Ph

**(147)**

Stereoselective oxidation is possible. A notable synthetic example involved hydroxylation of lactam (**147**) to produce a single diastereomer of the functionalized isoindoline — an intermediate required during work related to the cytochalasins.[166] It should be noted that in all the amide enolate examples the tertiary amide is utilized.

*(ii) Molybdenum peroxy complexes*

MoOPH (Section 2.3.2.1.2.ii)[52] may be a suitable reagent for lactam enolate hydroxylation. This is suggested by the oxidation of lactam (**148**).[167] Clearly the label 'enolate' is not strictly applicable to the bridgehead carbanion and it is likely that more forcing conditions would be necessary for genuine enolate hydroxylations. It is not clear whether *N*-oxidation would then emerge as a source of problems.

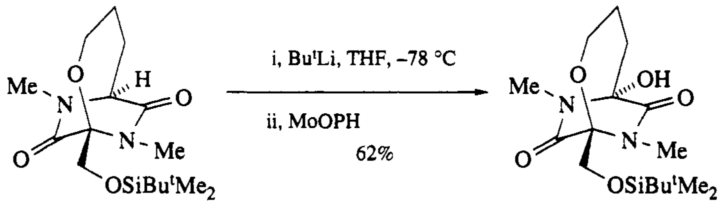
Me
O
N
H
O
O
N-Me
OSiBu^tMe2
i, Bu^tLi, THF, -78 °C
ii, MoOPH
62%
Me
O
N
OH
O
O
N-Me
OSiBu^tMe2

**(148)**

*(iii) 2-Sulfonyloxaziridines*

Hydroxylation of amide and lactam enolates using Davis' reagents (Section 2.3.2.1.2.iii) occurs readily at low temperature. The process can be highly stereoselective and is viable for oxidation of both secondary and tertiary positions (presumably also primary). Thus hydroxy lactam (**150**) is obtained as the sole diastereomer[168] after exposure of the lithio enolate of the lactam (**149**) to the oxidant at –78 °C.

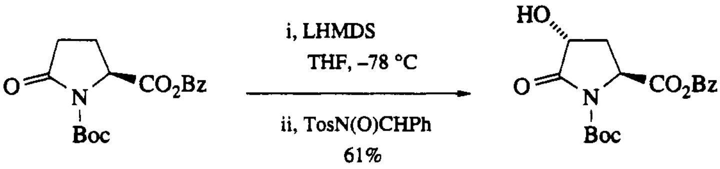
CO2Bz
Boc
i, LHMDS
THF, -78 °C
ii, TosN(O)CHPh
61%
HO
CO2Bz
Boc

**(149)** **(150)**

Futhermore the reagent has proven valuable for asymmetric hydroxylation of face-discriminating amide and oxazolidinone enolates. Davis has shown[169] that oxidation of secondary centers *via* the enolate derived from chiral pyrrolidinoamide (**151a**) provides the hydroxylated derivative in high yield (93–96%) and with excellent diastereoselection in either direction. The equivalent processes with methoxymethylpyrrolidine (**151b**) were of little value. This latter point contrasts with later studies concerning similar oxidations at tertiary centers.[170] Utilizing the chiral oxaziridines (**46a**) and (**46b**) and the methoxymethylpyrrolidinoamide (**152**), the corresponding tertiary alcohols were generated with good diastereoselection, although a little less efficiently than secondary alcohol products. Nonetheless the process represents the highest level of asymmetric induction of any electrophile from chiral, acyclic, tetrasubstituted enolates.

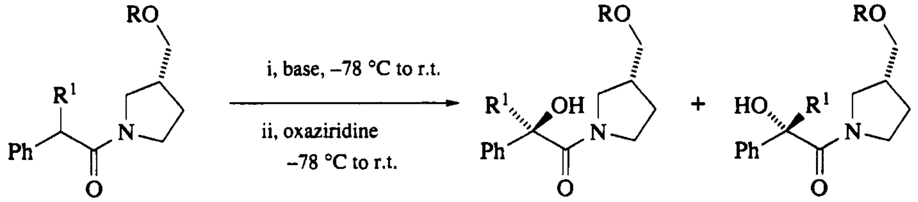
RO
R1
Ph
N
O
i, base, -78 °C to r.t.
ii, oxaziridine
-78 °C to r.t.
RO
R1
OH
Ph
N
O
+
RO
HO
R1
Ph
N
O

**(151)** a: R = H; $R^1$ = H
b: R = Me; $R^1$ = H
**(152)** R = Me; $R^1$ = Me

*(R)* **(151a)** *(S)*

| | | |
|---|---|---|
| LDA/THF | 96% | 2:98 |
| NaHMDS/THF | 93% | 96:4 |

Similar high levels of asymmetric induction using the oxazolidinone methodology developed by Evans have been observed.[171] In contrast to Davis' observations with amides[169,170] the sodium enolates were preferred in these cases, allowing diastereomeric ratios in the range 90:10–99:1 to be realized (Scheme 22).

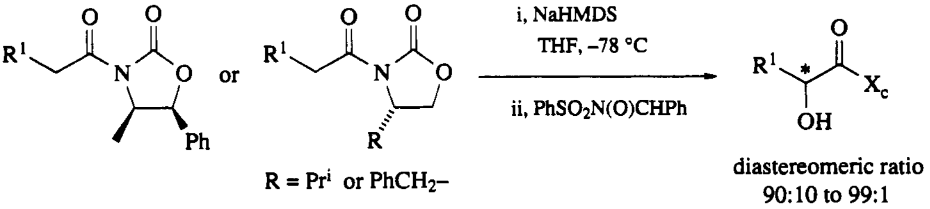
O
O
R1
N
O
Ph
or
O
O
R1
N
O
R
R = Pri or PhCH2–
i, NaHMDS
THF, -78 °C
ii, PhSO2N(O)CHPh
O
R1
*
Xc
OH
diastereomeric ratio
90:10 to 99:1

Scheme 22

The methodology was extended to show chemoselective hydroxylation (imide over ester) and α-hydroxylation of extended enolates. It also provided support for a stepwise mechanism (see Section 2.3.2.1.2.iii) involving a counterion dependent equilibrium.

### *(iv) Miscellaneous*

Hydroxylation of face-differentiated oxazolidinone enolates (*vide supra*) has also been enacted using dibenzoyl peroxydicarbonate as the electrophilic spouse.[172] Initial production of the α-benzyl carbonate (with analogously impressive diasereoselectivity) may be followed by facile hydrolysis to give essentially enantiomerically pure α-hydroxy esters.

## 2.3.2.6 Carboxylic Acids

### *2.3.2.6.1* Via *enol form*

Direct treatment of a free acid with thallium triacetate provides the α-acetoxy acids *via* intramolecular reductive rearrangement of the derived thallium enolate.[173] Only simple acids have been used and the necessity to use a large excess of the substrate acid limits the synthetic usefulness of the procedure.

### *2.3.2.6.2* Via *preformed enolate dianion*

A number of related procedures for this oxidation exist. Initially they were performed by bubbling air through solutions of the enolate,[174] but were subsequently improved by using oxygen or ethereal solutions of oxygen.[175] Reduction of the primary products (α-hydroperoxides) may be effected *in situ* or during work-up (see Section 2.3.2.5.1.i).

### *2.3.2.6.3* Via *bis-silyl ketene acetals*

*(i) Peracid*

These derivatives of carboxylic acids behave analogously to ester silyl ketene acetals (Section 2.3.2.4.3.i). Thus treatment with peracid in hexane followed by acidic work-up allows isolation of good yields of the α-hydroxy acids.[176]

*(ii) Singlet oxygen*

Bis-silyl ketene acetals devoid of β-protons undergo a clean silatropic ene reaction with singlet oxygen (see Sections 2.3.2.1.3.ii and 2.3.2.4.3.ii) to generate the α-silylperoxy silyl ester quantitatively.[177] Treatment with methanol affords the α-hydroperoxy acid, also quantitatively (Scheme 23). Hydrogenation over platinum reveals the α-hydroxy acid, once again, quantitatively. Despite this encouragement the substrate limitation is severe.

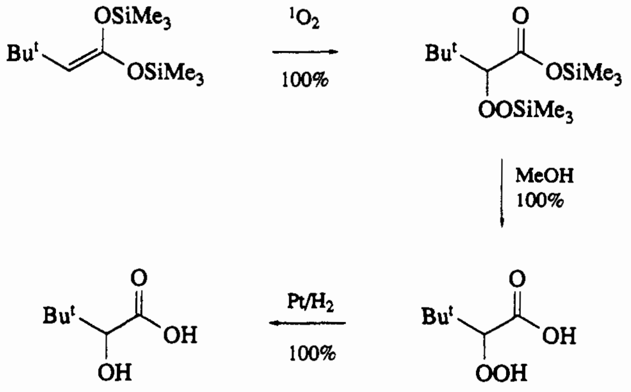

Scheme 23

#### 2.3.2.7 Aldehydes

Few methods for the α-hydroxylation of aldehydes are available. This is a reflection of their notorious instability towards polymerization and rearrangement to α-hydroxy ketones. All the useful procedures generate protected α-hydroxy aldehydes.

Exposure of the silyl enol ethers of aldehydes to peracid in dichloromethane, followed by treatment of the intermediate masked hydroxy aldehyde (*cf.* (**53**) to (**54**); Section 2.3.2.1.3.i) with acetic anhydride and triethylamine, allows isolation of the product α-acetoxy aldehydes in moderate yield.[178] Similarly treatment of the silyl enol ethers with LTA in acetic acid containing potassium acetate effects the same transformation.[179]

An indirect, although very valuable method provides a means of preparing optically active α-hydroxy aldehydes from the aldehyde-derived hydrazones (see Section 2.3.3.2).

## 2.3.3 HYDROXYLATION α TO C=N

### 2.3.3.1 Oxime Acetates and Nitrones

House has reported[180] that α-acetoxy ketones are available through 3,3-sigmatropic rearrangement of enamines derived from oxime acetates. Thus treatment of an oxime acetate with trimethyloxonium tetrafluoroborate generates the corresponding iminium salt (**153**) which, in the presence of triethylamine, rapidly isomerizes to the enamine. This in turn equally rapidly rearranges to the α-acetoxyimine (**154**) from which the corresponding ketone is recovered by acidic hydrolysis. The regioselectivity of the acetoxylation is dependent on the position of the enamine unsaturation rather than the original stereochemistry of the oxime.

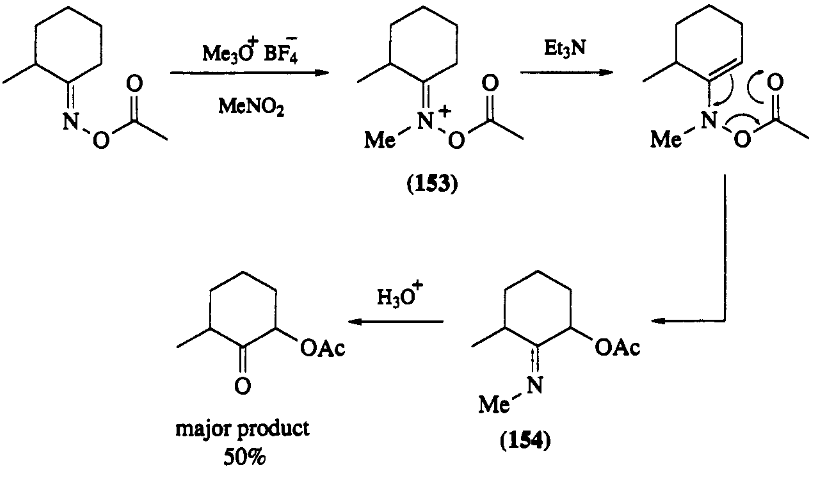

(**153**)

(**154**)

major product
50%

An identical rearrangement can be arrived at through acylation of *N*-methyl nitrones,[181] conveniently prepared from the ketone (**155** to **156**), although the process is apparently restricted to cyclic substrates. Finally a similar one-pot procedure for conversion of ketoximes to α-acetoxy ketones under the conditions shown (**157** to **158**), allows the transformation to be carried out simply and efficiently.[182] In this case rearrangement produces α-acyloxyenimides, whose hydrolysis provides the keto equivalent.

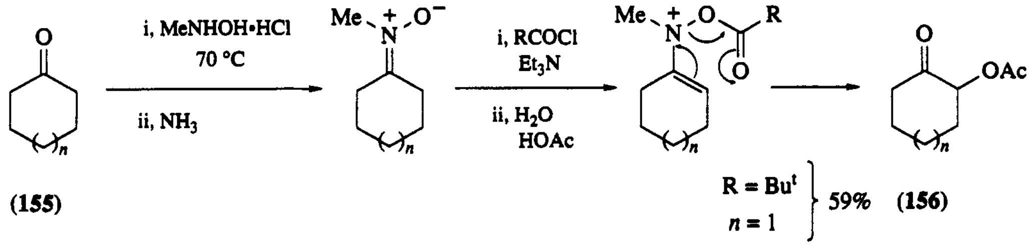

(**155**)

R = Bu$^t$, $n$ = 1 59% (**156**)

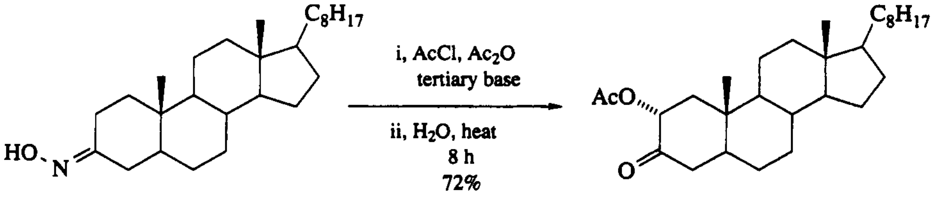

**(157)** **(158)**

### 2.3.3.2 Ketoximes and Hydrazones

Oxygenation of the dianion of a ketoxime[183,184] by MoOPH (*cf.* Section 2.3.2.1.2) provides α-hydroxy ketones after hydrolysis, albeit in relatively low yield. The equivalent process for hydrazones was unsuccessful,[52] although it appears that this was a problem associated with manipulation of the products rather than an intrinsic failure of reaction. Indeed subsequent work with hydrazone anions has shown that the process is viable.

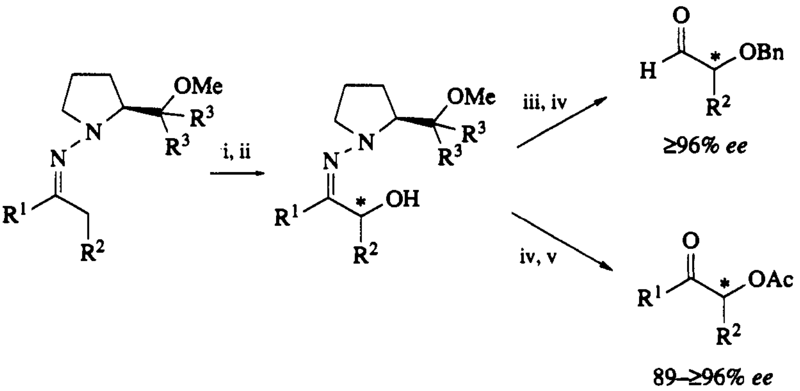

i, LDA, THF, 0 °C; ii. oxaziridine; iii, NaH, BnCl; iv, $O_3$ ; v, $Ac_2O$, DMAP

**Scheme 24**

Enders and coworkers have shown that deprotonation of chiral SAMP/RAMP hydrazones (or their substituted analogs) derived from ketones or aldehydes, followed by reaction with Davis' oxaziridine reagent provides the α-hydroxy hydrazones in moderate yield but with high diastereoselectivity.[185] Direct unmasking or protection followed by unmasking provides the corresponding α-hydroxy ketones or aldehydes respectively (Scheme 24). Both antipodes of the hydroxylated compounds are available by appropriate choice of (*S*)- or (*R*)-proline-derived auxiliaries. The direction of induction is predictable, if not wholly uniform ($R^3$ substitution alters the α-stereochemistry for aldehyde hydrazones). The process clearly provides a valuable approach to both systems.

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# 2.4
# Oxidation Adjacent to Sulfur

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## 2.4.1 INTRODUCTION

In this chapter oxidation of an activated C—H bond adjacent to a sulfur atom refers to any process whereby a C—H bond at the α-position of an alkyl sulfide is replaced by a C—X bond, where X is a halogen atom or an oxygen-, nitrogen-, carbon-, or sulfur-based substituent (equation 1). Processes in which a stabilized anion is generated adjacent to the sulfur atom of a sulfide, sulfoxide or sulfone and subsequently used as a nucleophile in addition or substitution reactions are excluded from this section. The use of such anions in organic synthesis is dealt with in Volume 1, Chapter 2.3.

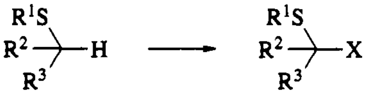

(1)

Conventional oxidants are little used for bringing about the functionalization reactions encompassed by equation (1), largely because of the ease with which oxidation occurs at the sulfur atom producing sulfoxides and sulfones. Nevertheless, the oxidation of sulfide to sulfoxide is very significant within the context of equation (1) since it provides the first stage of a valuable two-stage route from sulfides to α-functionalized sulfides. The second stage, involving reduction of the sulfoxide group with concomitant oxidation of the α-carbon atom, is often referred to as the Pummerer rearrangement. It is in fact one of two closely related processes by which the oxidation in equation (1) can most readily be accomplished. The second is ionic halogenation, in practice predominantly chlorination (Scheme 1). These two functionalization procedures have been in widespread use for many years, reflecting the very considerable utility of the reaction products as intermediates in organic synthesis (*vide infra*).

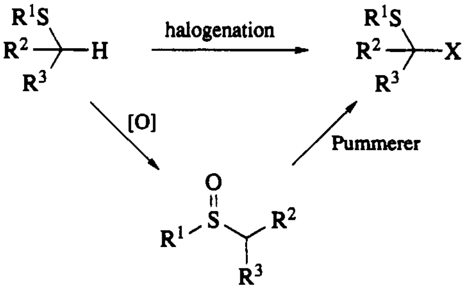

Scheme 1

## 2.4.2 THE PUMMERER REARRANGEMENT

In the early 1900s Pummerer observed that exposure of phenylsulfinylacetic acid (**1**) to either acetic acid or dilute sulfuric acid led to the formation of benzenethiol, glyoxylic acid and bis(thiophenoxy)acetic acid (equation 2).[1] Smythe, in the same year, found that dibenzyl sulfoxide in hot hydrochloric acid behaved rather similarly, producing phenylmethanethiol and benzaldehyde (equation 3).[2] Pummerer's study also contained the observation that exposure of the ethyl ester of acid (**1**) to hot acetic anhydride furnished the α-acetoxy sulfide shown in equation (4). These three reactions all contain the elements of a transformation which later was to become known as the Pummerer rearrangement. In equations (2) and (3) rearrangement produces unstable intermediates from which the products isolated are derived, whereas the rearrangement in equation (4) yields a stable product whose structure more clearly typifies the essential features of the reaction, namely reduction of the sulfoxide to sulfide with concomitant oxidation of the α-carbon atom. Originally, the term 'Pummerer rearrangement' was used to describe oxidation in the literal sense of replacement of an α-C—H bond by an oxygenated group. However, many later applications were to involve functionalization with carbon-, nitrogen-, sulfur- and halogen-based groups. Furthermore, the realization that Pummerer rearrangements can be brought about intramolecularly has proved especially effective in carbocyclic and heterocyclic synthesis.

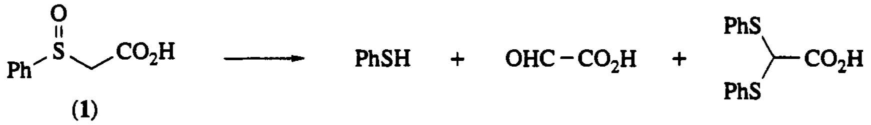

(1)

(2)

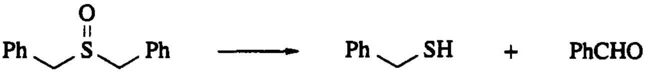

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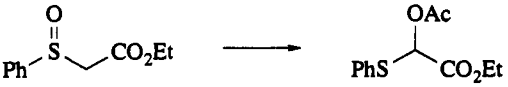

(4)

Use of the Pummerer rearrangement to produce α-functionalized sulfides presupposes access to sulfoxides from sulfides. Fortunately, many alkyl sulfides can be synthesized from readily available compounds and several reliable methods exist for their efficient conversion to sulfoxides. The latter include the use of (with respective examples in equations 5–9) *m*-chloroperbenzoic acid,[3] monoperphthalic acid magnesium salt,[4] sodium periodate,[5] hydrogen peroxide[6] and *t*-butyl hypochlorite.[7] Details of the use of these and other less common oxidants are available in Volume 7, Chapter 6.2. Madesclaire's recent extensive compilation of oxidants is also available.[8] Enzymic methods include the use of chloroperoxidase to catalyze oxygen transfer to sulfides.[9] β-Keto sulfoxides are particularly useful substrates for Pummerer rearrangement. Reaction can be brought about under very mild conditions and the presence of the β-keto group ensures the regioselectivity of the group transfer. β-Keto sulfoxides are readily available from methyl esters and dimethyl sulfoxide in the presence of base.[10]

Electrophilic reagents capable of bringing about Pummerer rearrangement include inorganic and organic acids, carboxylic anhydrides, acyl halides, isocyanates, carbodiimides, trimethylsilyl halides and triflate, sulfonyl and sulfenyl halides, phosphorus pentoxide and many typical Lewis acids such as boron

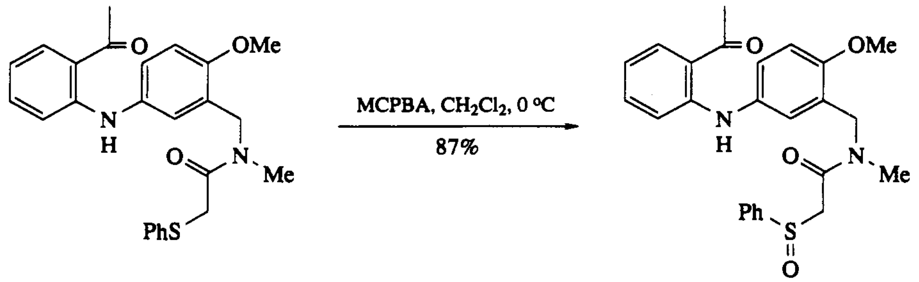

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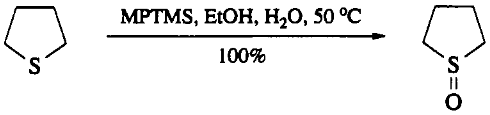

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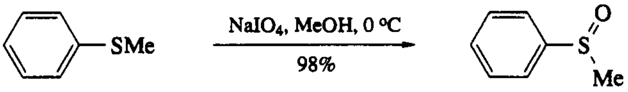

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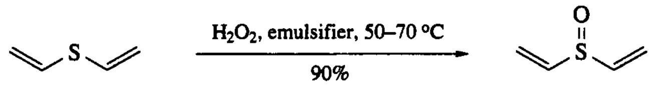

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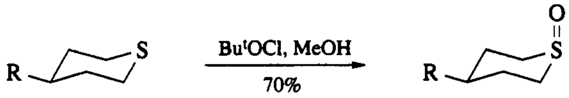

(9)

trifluoride, boron trichloride, silicon tetrachloride, phosphorus pentachloride and phosphorus oxychloride. Of these, carboxylic anhydrides are probably the most serviceable in synthetic procedures.

The generally accepted mechanism of the Pummerer rearrangement is one in which there is an initial attack on the sulfoxide oxygen atom by an electrophilic species, *e.g.* protonation or acylation. The latter process with methyl phenyl sulfoxide as the substrate is used in Scheme 2 to illustrate the likely mechanistic details. Acylation is followed by proton abstraction by a base (which in this case is the conjugate of the electrophile, though it need not be) from the α-carbon atom of the sulfoxide to form an ylide, which rapidly eliminates an acetate ion to form the α-thiocarbocation. Addition of acetate ion to the α-thiocarbocation completes the formation of the α-functionalized sulfide. The mechanism of ionic halogenation of alkyl sulfides can similarly be understood (*vide infra*). Ylide formation from sulfoxonium salts is well recognized and this aspect of the mechanism has received considerable experimental support. Although not definitive, there is also evidence to suggest that transfer of the acetoxy group from sulfur to carbon may be either intramolecular or may involve an intimate ion pair. Some of the evidence arises from the results of a study of Pummerer rearrangement of optically active sulfoxide where the asymmetry is transferred from sulfur to carbon with, in some instances, high enantioselectivity. For example, ethyl *p*-tolylsulfinylacetate with dicyclocarbodiimide in acetic anhydride furnishes the α-acetoxy sulfide shown in equation (10) with an *ee* of about 70%. Other examples of asymmetric synthesis in Pummerer rearrangement will be discussed later. $^{18}$O-Labeling studies have been interpreted in terms of both inter- and intramolecular mechanisms. For a much fuller account of mechanistic aspects of the rearrangement see the

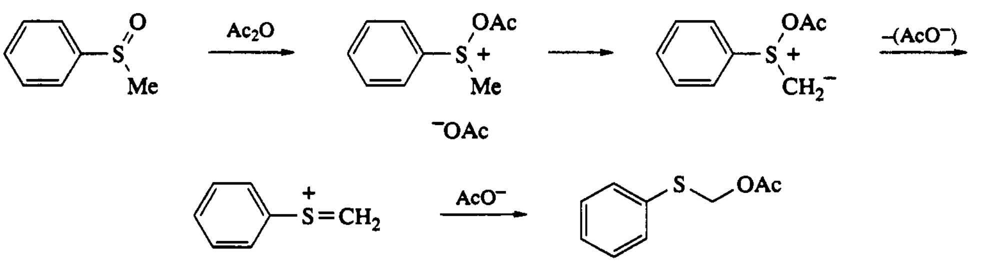

Scheme 2

analysis by Wolfe and his coworkers[11] and the review by Russell and Mikol.[12,13] The extension of the mechanism in Scheme 2 to include the intramolecular Pummerer rearrangement is shown in Scheme 3, the key feature being the capture of the α-thiocarbocation (or its equivalent) by an internal nucleophile thus completing the formation of a carbocyclic or heterocyclic ring. The discussion of the applications of the Pummerer rearrangement that follows has been organized according to the nature of the nucleophilic addition step which completes the functionalization sequence shown in Scheme 2.

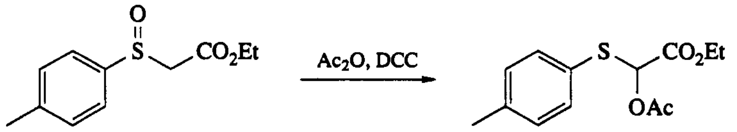

(10)

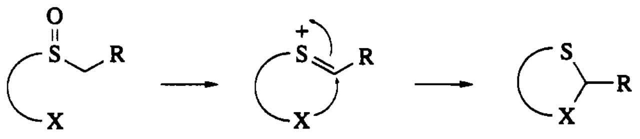

Scheme 3

## 2.4.3 THE PUMMERER REARRANGEMENT EXEMPLIFIED

### 2.4.3.1 Reaction with Carboxylic Anhydrides

α-Acetoxylation is probably the most commonly encountered form of the rearrangement. Acetic anhydride alone or accompanied by sodium acetate are popular reagents, though reaction usually requires elevated temperatures, often at reflux for several hours. Acetic anhydride containing dicyclohexylcarbodiimide has also been used. Convenient rearrangement rates can be realized at much lower temperatures (0–25 °C) if trifluoroacetic anhydride is employed as the reagent. Examples of the use of mixtures of acetic and trifluoroacetic anhydrides, with and without sodium acetate, are also available. Table 1 contains a selection of representative examples of the α-acetoxylation of alkyl sulfides *via* Pummerer rearrangement of sulfoxides.

Dimethyl sulfoxide in hot acetic anhydride (entry 1) furnishes acetoxymethyl methyl sulfide. Reaction of acetic anhydride with methyl alkyl sulfoxides not containing a β-keto or other acid strengthening substituent, *e.g.* entry 2, leads to functionalization of the methyl group. The reactivity series for alkyl substituents in the sulfoxide appears to be methyl > *n*-alkyl > vinyl. Entry 3 provides an example of a vinyl sulfoxide rearrangement in acetic anhydride. Entry 4 illustrates rearrangement in an amino acid substrate. The examples shown in entries 5 and 6 are part of an aldehyde synthesis; the yields quoted refer to the product obtained after hydrolysis of the α-acetoxy sulfide. Entry 7 contains a comparison of the use of acetic acid alone and admixed with trifluoroacetic anhydride. Entries 8 and 9 contain β-keto sulfoxides which are particularly popular substrates; where there is a choice, as in entry 9, rearrangement invariably occurs so as to replace the more acidic hydrogen atom between the keto and sulfide moieties. Other activated systems which undergo ready rearrangement are those containing the phosphoryl and cyano groups shown in entries 10 and 11. An additional feature of the former is that use of the sulfoxide in homochiral form yields α-acetoxy-α-(dimethylphosphoryl)methyl *p*-tolyl sulfide of 24% optical purity, a result used as evidence for an acetoxy migration *via* an intramolecular mechanism. Cyclic sulfoxides are also amenable to α-acetoxylation as shown by the examples in entries 12 and 13. Entry 14 is an example of the Pummerer rearrangement in the Sharpless–Masamune carbohydrate synthesis, the α-acetoxy sulfide being converted into a primary hydroxyl group by reduction with lithium aluminum hydride. Two other uses of the rearrangement are summarized in entries 15 and 16, the latter as part of side chain elaboration for cardenolide analogs.

These various intermolecular α-acetoxylation reactions have intramolecular counterparts. For example, treatment of the sulfinylbutanoic acid shown in equation (11) with acetic anhydride containing *p*-toluenesulfonic acid yields a sulfenylated butanolide, the carboxylic acid function having intercepted the α-thiocarbocation intermediate.[29] Yet another demonstration of the intramolecular process, due to Allenmark,[30] is the cyclization of *o*-carboxyphenyl benzyl sulfoxide with acetic anhydride to form the 1,3-benzoxathian-4-one shown in equation (12). This reaction was also conducted with one of the

**Table 1** Acetoxylation of Sulfides from Sulfoxides *via* the Pummerer Rearrangement

| *Entry* | *Substrate* | *Reagents* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | MeS(O)Me | $Ac_2O$, heat | $MeSCH_2OAc$ | — | 14 |
| 2 | $Bu^nS(O)Me$ | $Ac_2O$, heat | $Bu^nSCH_2OAc$ | — | 15 |
| 3 | PhCH=CHS(O)Me | $Ac_2O$, heat | $PhCH=CHSCH_2OAc$ | — | 16 |
| 4 | $HO_2CCH(NH_2)CH_2CH_2S(O)Me$ | $Ac_2O$, heat | $HO_2CCH(NHAc)CH_2CH_2SCH_2OAc$ | — | 15 |
| 5 | $PhCH_2S(O)Ph$ | $(CF_3CO)_2O$, 0 °C | $PhCH(OCOCF_3)SPh$ | — | 17 |
| 6 | 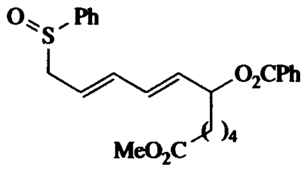 | $Ac_2O$, $(CF_3CO)_2O$, 2,6-lutidine | 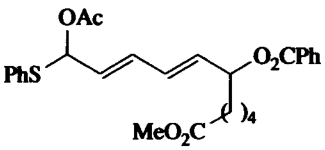 | >65 | 18 |
| 7a | $Me(CH_2)_4CH_2S(O)Ph$ | $Ac_2O$, heat | $Me(CH_2)_4CH(OAc)SPh$ | 62 | 19 |
| 7b | $Me(CH_2)_4CH_2S(O)Ph$ | $Ac_2O$, $(CF_3CO)_2O$, 0.5 h, 20 °C | $Me(CH_2)_4CH(OAc)SPh$ | 84 | 19 |
| 8 | $MeC_6H_4S(O)CH_2CO_2Et$ | $Ac_2O$, DCC, heat | $MeC_6H_4SCH(OAc)CO_2Et$ | 43 | 20 |
| 9 | $PhCOCH_2S(O)Me$ | $Ac_2O$, heat | PhCOCH(OAc)SMe | 95 | 21 |
| 10 | $(EtO)_2P(O)CH_2S(O)Me$ | $(CF_3CO)_2O$, –78 °C, 15 min | $(EtO)_2P(O)CH(OCOCF_3)SMe$ | 76 | 22 |
| 11 | $PhS(O)CH_2CN$ | $Ac_2O$, heat | PhSCH(OAc)CN | 85–90 | 23 |
| 12 | 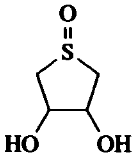 | $Ac_2O$, NaOAc, heat | 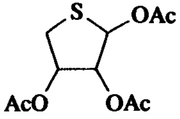 | 61 | 24 |
| 13a | 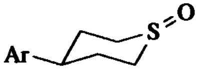 | $Ac_2O$, 100 °C | 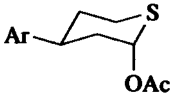 | 70<br>(from *cis* and *trans*) | 25 |
| 13b | 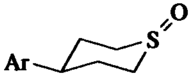 | $Ac_2O$, DCC | 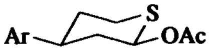 | 83 | |

**Table 1** *(continued)*

| *Entry* | *Substrate* | *Reagents* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 14 | 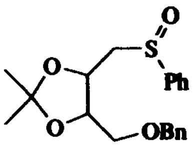 | $Ac_2O$, heat | 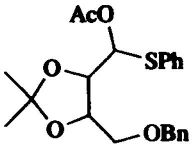 | 81 | 26 |
| 15 | 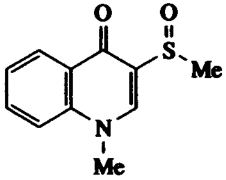 | $Ac_2O$, heat | 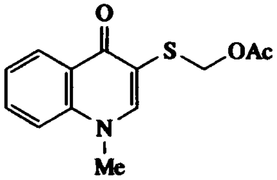 | 92 | 27 |
| 16 | 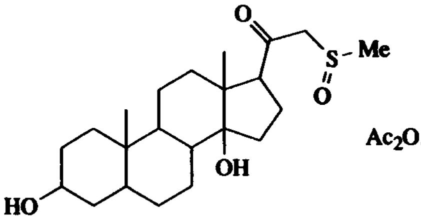 | $Ac_2O$, pyridine, 20 °C | 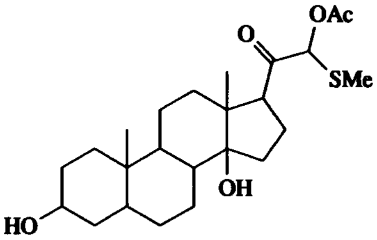 | 55<br>33 (3-OAc) | 28 |

enantiomers of the sulfoxide and asymmetry transfer to the extent of 11% was observed.[30] When the reaction was brought about by dicyclohexylcarbodiimide in dichloroethane, the optical purity increased to 30%.[11] This asymmetric synthesis has been interpreted as providing evidence for the formation of diastereoisomeric ylides as reaction intermediates.

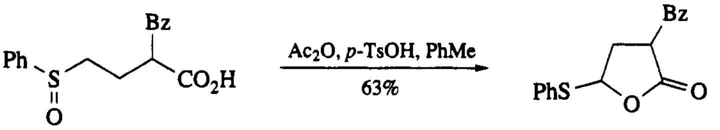

(11)

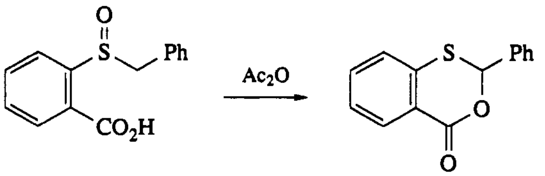

(12)

### 2.4.3.2 Pummerer Rearrangement with α-Alkylation and Arylation

Various kinds of α-alkyl and α-aryl substituted sulfides are accessible by Pummerer rearrangement where the α-thiocarbocation intermediate, or its equivalent, is intercepted, either intermolecularly or intramolecularly, by a nucleophilic carbon species. The most useful versions of this process involve interception by a carbon–carbon double bond. The transformation of the sulfoxide in equation (13) into the sulfide shown using 1-pentene in the presence of trifluoroacetic anhydride provides an illustrative example of the intermolecular process.[31] The nucleophilicity of silyl enol ethers has also been exploited for carbon–carbon bond formation with Pummerer intermediates, the example in equation (14) having been brought about at low temperature using trimethylsilyl triflate and diisopropylethylamine as the reagents.[32] A combination of trimethylsilyl triflate and Hunig's base in dichloromethane at –78 °C has been used to combine the silyl enol ether of cyclohexanone with the bifunctional reagent 3-phenylsulfinyl-2-(trimethylsilylmethyl) propene as shown in equation (15).[33] The intramolecular mode, which is in effect a π-route cyclization, has extended the usefulness of the Pummerer rearrangement very considerably. For example, the acyclic sulfoxide in equation (16) has been converted into the cyclic products shown by the action of trifluoroacetic anhydride.[34] The construction of a five-membered ring by the same approach is shown in equation (17) with the additional significant feature that use of the sulfoxide precursor in homochiral form produced the bicyclic sulfide with an enantiomeric excess of 75%.[35] Bridged-ring structures are also accessible, two notable successes in this area being the cyclization leading to bicyclo[3.2.1]octane derivatives in equation (18) reported by Mander and Mundill[36] and that in equation (19) due to Magnus and his coworkers, where the participating double bond is provided by the indole system.[37]

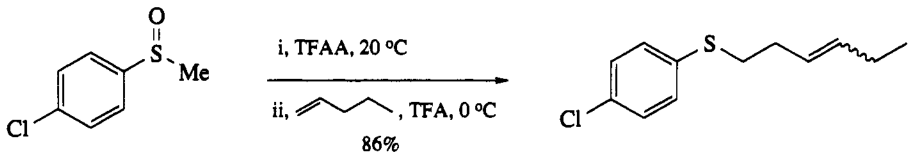

(13)

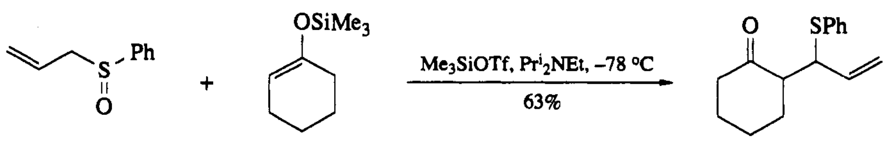

(14)

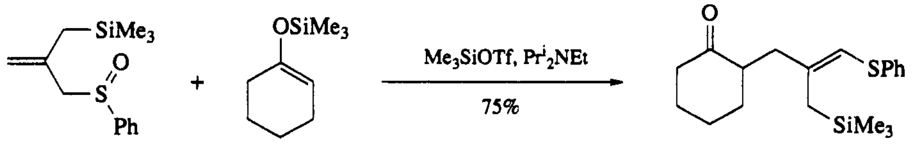

(15)

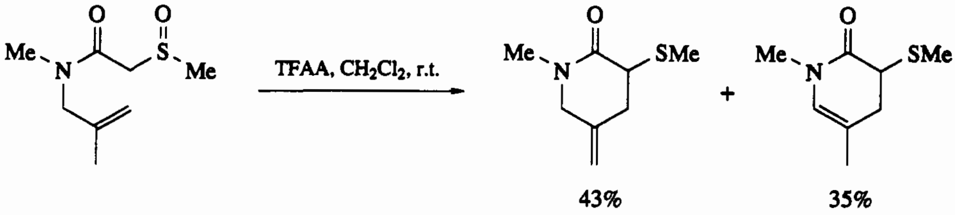

(16)

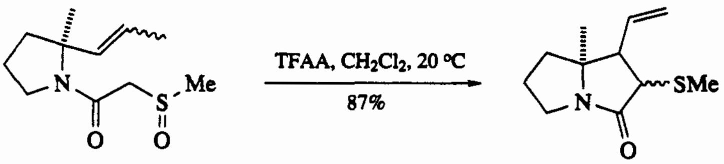

(17)

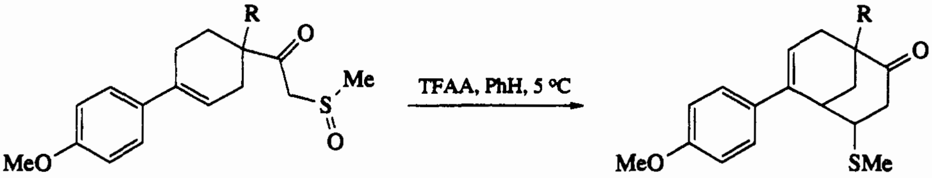

(18)

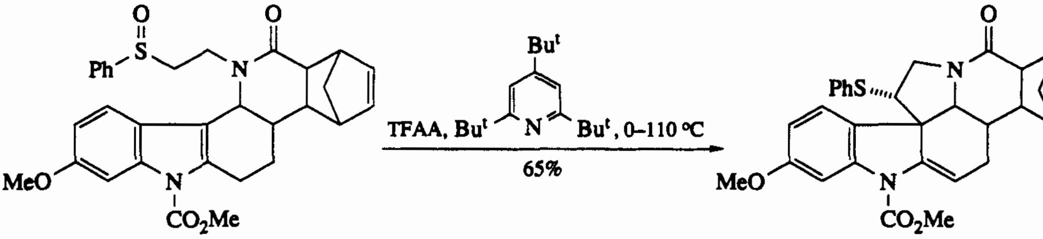

(19)

Participation by aromatic rings is also possible and there are now several examples of electrophilic aromatic substitution involving Pummerer intermediates. Equation (20), the alkylation of benzene with dimethyl sulfoxide in trifluoroacetic anhydride, illustrates the process in its simplest form.[38] As with alkenes, reaction with aromatics has been more widely exploited in intramolecular versions for the construction of carbocycles and heterocycles. In many cases the sulfoxide precursor is of the β-keto variety, thus ensuring regiospecificity in the point of cyclization. Equation (21) (formation of a six-membered carbocycle),[39] equation (22) (formation of a six-membered sulfur heterocycle),[41] equation (23) (formation of a six-membered nitrogen heterocycle)[40] and equation (24) (formation of a seven-membered nitrogen, sulfur heterocycle)[42] provide illustrations of the versatility of this form of intramolecular aromatic alkylation.

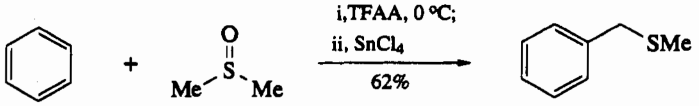

(20)

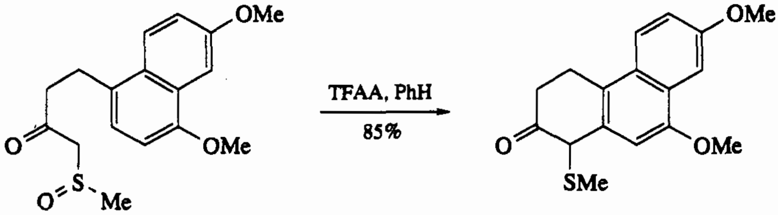

(21)

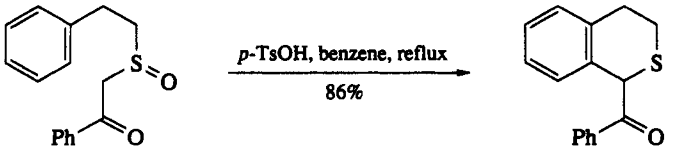
p-TsOH, benzene, reflux
86%
S
O
Ph
O
S
Ph
O

(22)

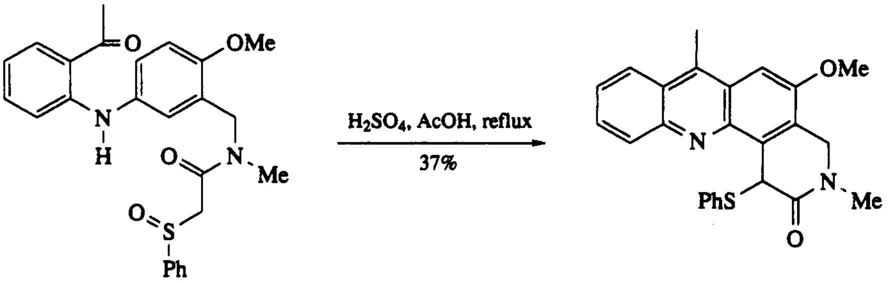
O
OMe
N
H
O
N
Me
O
S
Ph
H₂SO₄, AcOH, reflux
37%
OMe
N
PhS
N
Me
O

(23)

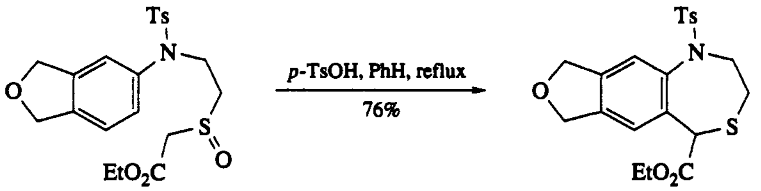
Ts
N
O
S
O
EtO₂C
p-TsOH, PhH, reflux
76%
Ts
N
O
S
EtO₂C

(24)

### 2.4.3.3 Pummerer Rearrangement with Participation by Nitrogen

A combination of the Pummerer rearrangement and the Ritter reaction occurs in the reaction of acetonitrile with methyl phenyl sulfoxide (equation 25) in a mixture of trifluoroacetic acid and its anhydride, although a substantial amount of the normal α-acetoxylation also occurs.[43] Participation by amido groups is also possible, the interest here being largely in the construction of lactams *via* the intramolecular cyclization mode. Whereas Wolfe and his coworkers were unable to find conditions for the cyclization of *S*-phenylcysteinamide sulfoxides under Pummerer conditions, Kaneko found that variously substituted 3-phenylsulfinylpropionamides (equation 26) were converted into 4-(phenylthio)-2-azetidinones in 14–50% yields by the combined action of trimethylsilyl triflate and triethylamine.[44] Kaneko has suggested that the sulfonium ion intermediate in this rearrangement may be considered as a chemical equivalent of an intermediate believed to be involved in the biosynthesis of β-lactam antibiotics. Keneko and his coworkers have extended this study to include the enantioselective Pummerer cyclization of homochiral

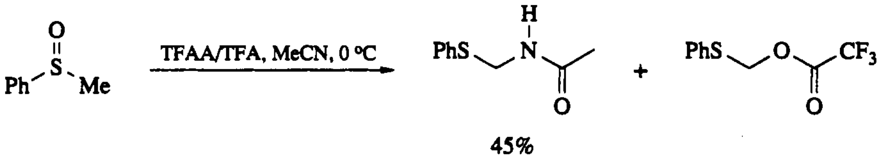
O
Ph
S
Me
TFAA/TFA, MeCN, 0 °C
H
PhS
N
O
45%
+
PhS
O
CF₃
O

(25)

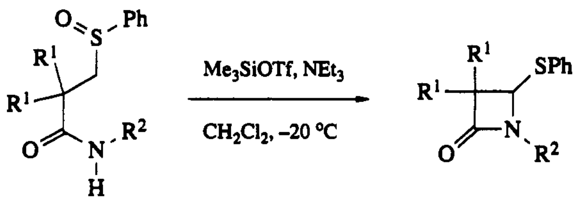
O
S
Ph
R¹
R¹
O
N
R²
H
Me₃SiOTf, NEt₃
CH₂Cl₂, -20 °C
R¹
R¹
SPh
O
N
R²

(26)

| *R¹* | *R²* | *Yield (%)* |
|---|---|---|
| R¹ = Me | R² = OBz | 51 |
| R¹ = H | R² = OBz | 14 |
| R¹ = H | R² = H | 41 |

3-phenylsulfinylpropionamide to produce the sulfenylated β-lactam with 67% *ee*. In this case the reagents employed were trimethylsilyl triflate and diisopropylethylamine.[45] An example of δ-lactam formation from an amide is shown in equation (27), the reaction being initiated by a ketone silyl acetal in the presence of zinc iodide in acetonitrile.[46] Equation (28) shows a variant of amide participation operating through the oxygen atom leading to the construction of a seven-membered heterocycle.

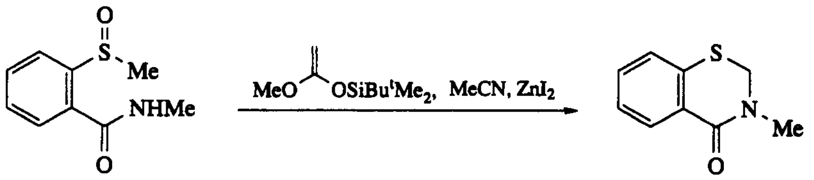

(27)

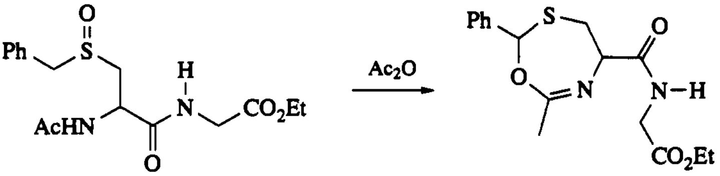

(28)

Use of trimethylsilyl triflate to bring about Pummerer rearrangement requires the presence of a base such as a tertiary amine (*vide supra* equations 15 and 26). In some instances, involving attempts to alkylate Pummerer intermediates with silyl enol ethers under such conditions, the base has been found to compete as a nucleophile.[33] In the absence of the silyl enol ether, amine addition can be very efficient. For example, treatment of methallyl phenyl sulfoxide with diisopropylethylamine and trimethylsilyl triflate in dichloromethane (equation 29) at 0 °C yields the ammonium triflate indicated in 91% yield.[33] Other tertiary amines which undergo this reaction include triethylamine and *N,N*-diethyltrimethylsilylamine. In the latter case with allyl phenyl sulfoxide as the substrate and a mildly acidic work-up, the Mannich derivative shown in equation (30) can be obtained in 90% yield.[33]

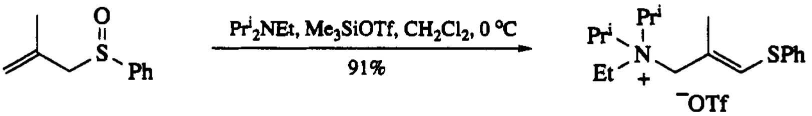

(29)

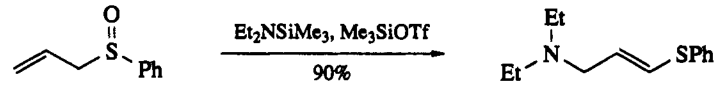

(30)

### 2.4.3.4 Pummerer Rearrangement in Hydroxylic Solvents

Pummerer[1] and Smythe[2] were the first to note that aqueous acids cause sulfoxides with an α-hydrogen atom to decompose to aldehydes, thiols and other products. In some cases, however, particularly those involving β-keto sulfoxides, stable mixed hemithioacetals, the primary Pummerer rearrangement products, may be isolated. Such a case is summarized in equation (31), where exposure of the phenothiazine sulfoxide shown to *p*-toluenesulfonic acid hydrate in tetrahydrofuran at 65 °C furnished the mixed hemithioacetal in 95% yield;[47] in this particular example aromatic participation in the Pummerer process did not occur. An indirect route to mixed hemithioacetals, shown in equation (32), involves Pummerer rearrangement in trifluoroacetic anhydride to bring about α-acetoxylation (*cf.* Section 2.4.3.1) followed by hydrolysis or solvolysis of the product. In this case an α-acetoxy intermediate is produced, which is cleaved to the hemithioacetal on treatment with sodium methoxide.[48] In another example addition of ethanol to the formyl group leads intramolecularly to attack on the α-acetoxy group with formation of the bridged product (equation 33).[49] Both intermolecular and intramolecular participation by hydroxy groups in Pummerer processes are known. Methylation of cyclopropyl phenyl sulfoxide (equation 34) with trimethyloxonium tetrafluoroborate, followed by treatment with methoxide ion in methanol produces the mixed thioacetal.[50] The conversion of 2-hydroxy-3-methoxy-1-methylsulfinylacetylbenzene (equation 35) into a benzofuranone on exposure to phosgene in pyridine illustrates the intramolecular version of hydroxy group participation.[51] Treatment of the vinyl sulfide shown in equation (36) with toluenesulfonic acid produces a tetrahydrofuran derivative whose formation probably also results from a thiocarbocation intermediate.[52]

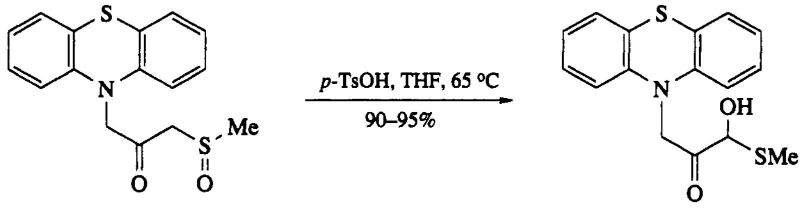
S
N
Me
S
O
O
p-TsOH, THF, 65 °C
90–95%
S
N
OH
SMe
O

(31)

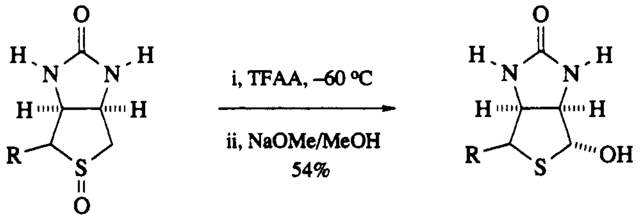
O
H
N
N
H
H
H
R
S
O
i, TFAA, –60 °C
ii, NaOMe/MeOH
54%
O
H
N
N
H
H
H
R
S
OH

(32)

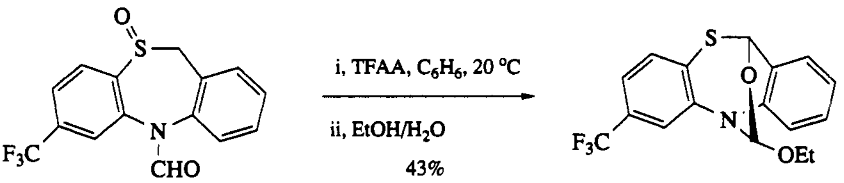
O
S
F3C
N
CHO
i, TFAA, C6H6, 20 °C
ii, EtOH/H2O
43%
S
O
F3C
N
OEt

(33)

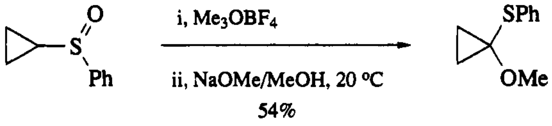
O
S
Ph
i, Me3OBF4
ii, NaOMe/MeOH, 20 °C
54%
SPh
OMe

(34)

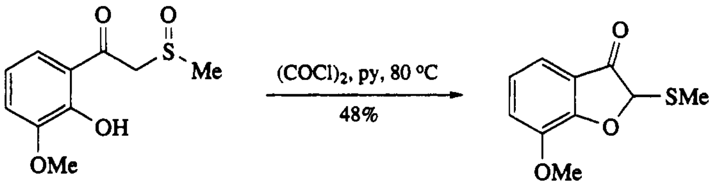
O
O
S
Me
OH
OMe
(COCl)2, py, 80 °C
48%
O
SMe
O
OMe

(35)

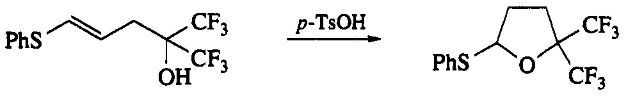
PhS
CF3
CF3
OH
p-TsOH
PhS
O
CF3
CF3

(36)

### 2.4.3.5 Miscellaneous and Abnormal Pummerer Rearrangements

Among other electrophilic reagents capable of bringing about the Pummerer rearrangement are halides of organic and inorganic acids. As these halides transform sulfoxides into α-chlorosulfides they complement the sulfide chlorination route to these compounds. Thionyl chloride reacts readily with sulfoxides and β-keto sulfoxides; methyl phenyl sulfoxide furnishes chloromethyl phenyl sulfide (equation 37).[53] Benzoyl chloride and acetyl chloride behave similarly.[53] Cyanuric chloride is transformed into cyanuric acid by dimethyl sulfoxide, which in turn is transformed into methyl chloromethyl sulfide (equation 38).[54,55]

In the examples of the Pummerer rearrangement presented above, the common feature has been the formation of an α-thiocarbocation, which is then captured either intermolecularly or intramolecularly by a nucleophilic species. There are of course other outlets through which the α-thiocarbocation can pro-

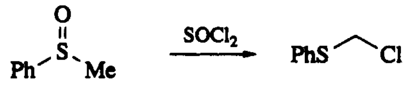
O
Ph
S
Me
SOCl₂
PhS
Cl

(37)

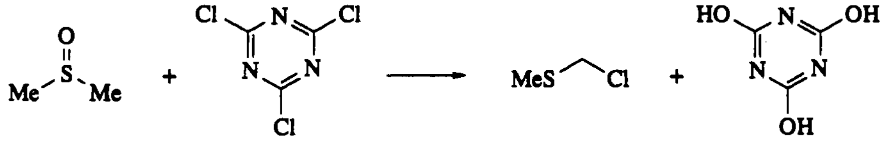
O
Me
S
Me
+
Cl
N
Cl
N
N
Cl
MeS
Cl
+
HO
N
OH
N
N
OH

(38)

gress to a stable neutral product, such as β-elimination. The reaction of cyclohexyl phenyl sulfoxide (equation 39) with trifluoroacetic anhydride and triethylamine to form 1-phenylthiocyclohexene is an illustrative example.[56] β-Elimination is also the main pathway of the Pummerer rearrangements summarized in equations (40) and (41). The reagents in these cases were trimethylsilyl chloride[7] and trifluoroacetic anhydride–lutidine,[57] respectively. The Pummerer process shown in equation (42) culminates in a δ-proton elimination.[58] A final example of the eliminative process is provided by the reaction shown in equation (43), which is brought about by heat alone and has been referred to as the 'sila-Pummerer' rearrangement.[59] A vinylogous Pummerer rearrangement has been observed in the reaction of the vinyl sulfoxide shown in equation (44) with acetic anhydride.[60]

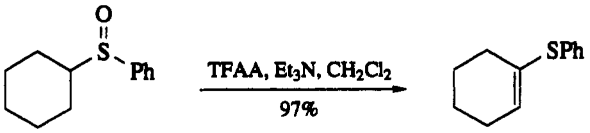
O
S
Ph
TFAA, Et₃N, CH₂Cl₂
97%
SPh

(39)

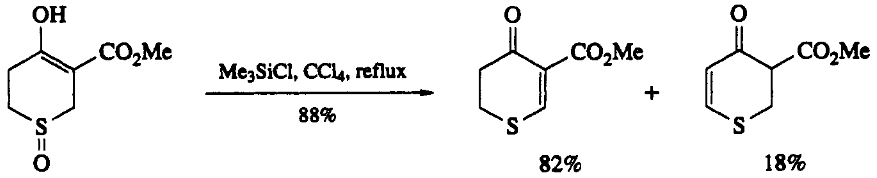
OH
CO₂Me
S
O
Me₃SiCl, CCl₄, reflux
88%
O
CO₂Me
S
+
O
CO₂Me
S
82%
18%

(40)

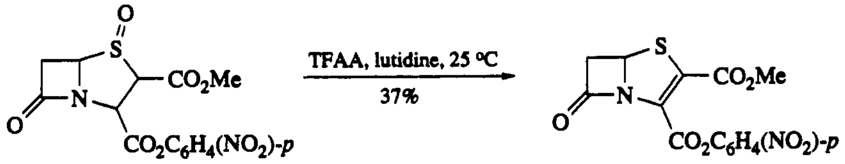
O
S
CO₂Me
N
O
CO₂C₆H₄(NO₂)-p
TFAA, lutidine, 25 °C
37%
S
CO₂Me
N
O
CO₂C₆H₄(NO₂)-p

(41)

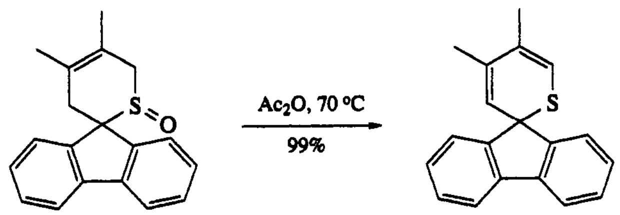
S
O
Ac₂O, 70 °C
99%
S

(42)

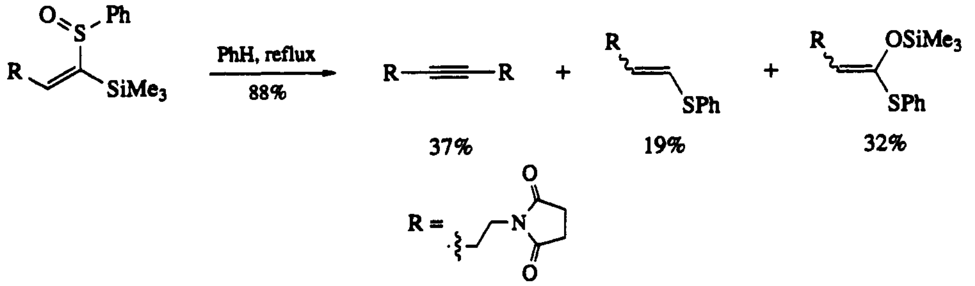
O
S
Ph
R
SiMe₃
PhH, reflux
88%
R
R
+
R
SPh
+
R
OSiMe₃
SPh
37%
19%
32%
R =
O
N
O

(43)

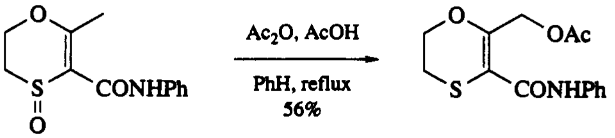
O
S
O
CONHPh
Ac$_2$O, AcOH
PhH, reflux
56%
O
OAc
S
CONHPh

(44)

This section concludes with a selection of reactions which are believed to follow the Pummerer pathway, but which lead to abnormal or unexpected products. For example, treatment of the sulfoxide shown in equation (45) with acetic anhydride produces two sulfides in a 5:1 ratio.[7] The major product is that of a ring contraction process which could involve a bicyclic episulfonium ion as an intermediate. Attack by acetate can occur at two sites yielding the products shown. C—S bond cleavage is also a feature of the Pummerer rearrangement of penicillin sulfoxide derivatives (equation 46)[61] and of the sulfoxide shown in equation (47).[61] Despite the absence of an α-hydrogen atom the sulfoxide shown in equation (48) does undergo a Pummerer rearrangement without C—S bond cleavage when exposed to hydrogen chloride in methanol.[62] A likely interpretation is that addition of methanol across the double bond precedes rearrangement during which a second molecule of methanol is added. A transannular Pummerer rearrangement involving sulfide participation and the formation of a dication intermediate has been proposed for the α-acetoxylation process shown in equation (49).[63]

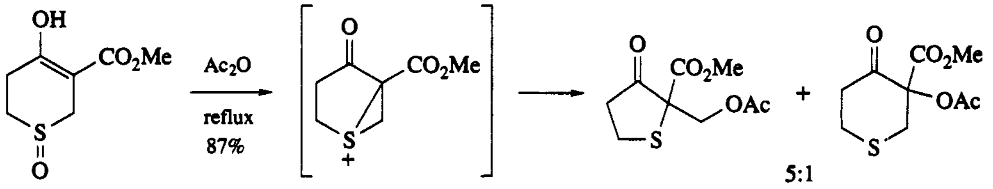
OH
CO$_2$Me
S
O
Ac$_2$O
reflux
87%
O
CO$_2$Me
S
+
O
CO$_2$Me
OAc
S
+
O
CO$_2$Me
OAc
S
5:1

(45)

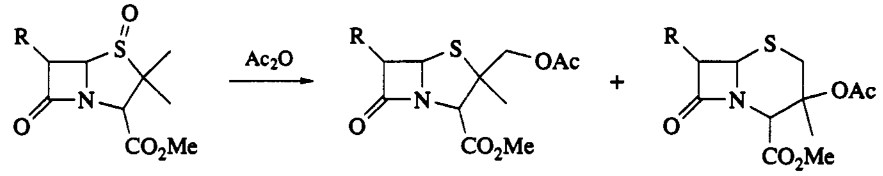
R
O
S
N
O
CO$_2$Me
Ac$_2$O
R
S
OAc
N
O
CO$_2$Me
+
R
S
N
OAc
O
CO$_2$Me

R = NHCOCH$_2$COPh

(46)

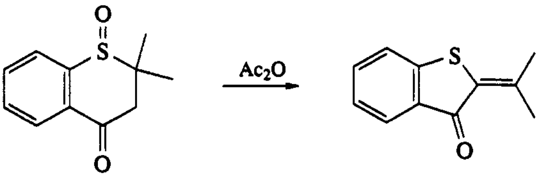

(47)

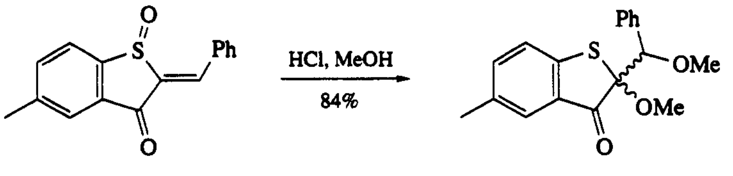
O
S
Ph
O
HCl, MeOH
84%
Ph
S
OMe
OMe
O

(48)

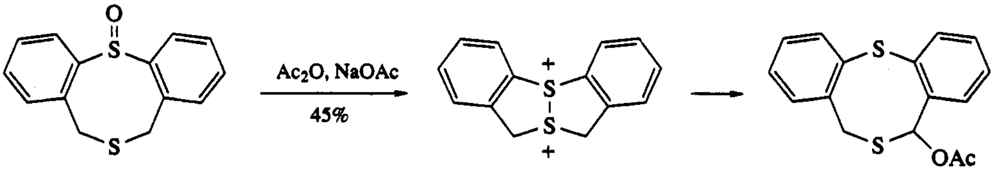
O
S
S
Ac$_2$O, NaOAc
45%
+
S
S
+
S
S
OAc

(49)

A few examples of additive Pummerer rearrangements are known involving direct conversion of α,β-unsaturated sulfoxides into α,β-disubstituted sulfides.[61,64,65] Scheme 4 illustrates two general pathways for such processes and specific examples of each are known. For example, alk-1-enyl phenyl sulfoxides on exposure to thionyl chloride at room temperature produce α,β-dichlorosulfides in excellent yield *via* a route which exemplifies pathway 1 of Scheme 4 (equation 50).[66] Pathway 2 is illustrated by the reaction of the cyclopentenone sulfoxide shown in equation (51) with dichloroketene to form a bicyclic product which was subsequently transformed into methyl jasmonate.[66] When the sulfoxide used in this sequence was enantiomerically pure, the product was assessed as being 20% optically pure.

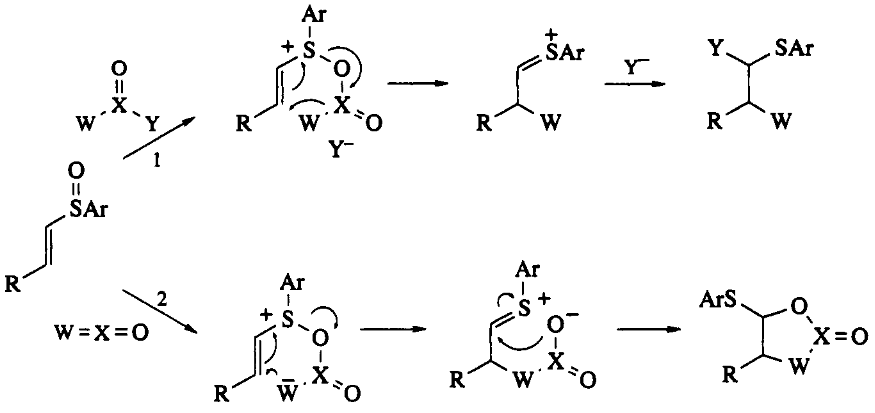

Scheme 4

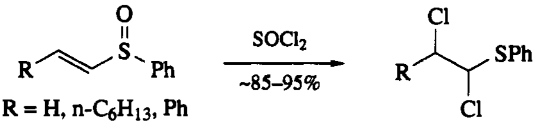

(50)

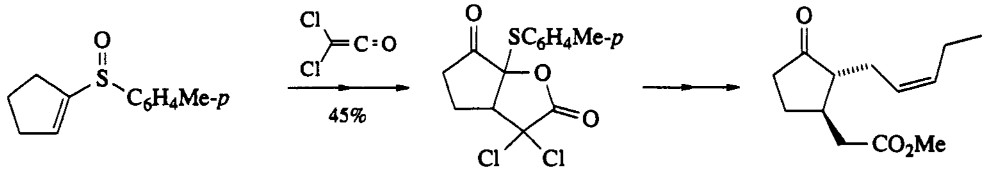

(51)

## 2.4.4 α-HALOGENATION OF SULFIDES

Whereas use of the Pummerer rearrangement to functionalize an alkyl sulfide normally requires prior preparation and isolation of the intermediate sulfoxide, α-halogenation may be accomplished in a single operation employing one of several readily available halogenation agents. The structural requirements for the two processes are very similar and their mechanisms undoubtedly have much in common. Although halogenation by all the halogens, with the exception of fluorine, does occur, chlorination is the most important. The earliest studies in this area were conducted using chlorine alone or in an inert solvent such as carbon tetrachloride.[67,68] However, molecular chlorine is no longer the reagent of choice for most sulfides, having been replaced by more convenient alternatives such as sulfuryl chloride, thionyl chloride, *N*-chlorosuccinimide (NCS), trichloroisocyanuric acid (chloreal), iodobenzene dichloride and benzenesulfenyl chloride. Of these, sulfuryl chloride and NCS are by far the most commonly used.

Sulfuryl chloride reacts vigorously with dimethyl sulfide at ambient temperatures, although at −15 °C it is possible to obtain a 45% yield of chloromethyl methyl sulfide (equation 52).[69] Bohme and Gran preferred the use of sulfuryl chloride in carbon tetrachloride for chlorination of dibenzyl sulfide (equation 53) and obtained the monochloride in 79% yield.[70] The same combination of reagent and solvent has been used to transform the isothiazolidine shown in equation (54) into the corresponding α-chlorosulfide.[71] Bordwell and Pitt employed sulfuryl chloride in pentane or dichloromethane to prepare α-chlorosulfides from several alkyl methyl sulfides and aryl methyl sulfides (equation 55).[72] However, complications often arise when sulfuryl chloride is used to chlorinate alkyl sulfides containing β-hydrogen atoms due to the ease of elimination of the products and subsequent further reactions. This is apparent during the chlorination of thiane and thiolane with sulfuryl chloride (equations 56 and 57), where only trace amounts of the normal products are obtained, the major products being 3,4-dihydro-2*H*-thiin and 2,3-dichlorothiolane, respectively.[72] On the other hand, Wilson and Albert have reported that addition of an equivalent amount of pyridine or triethylamine to solutions of sulfuryl chloride suppressed the elimination process to the extent that good yields of 2-chlorothiolane can be obtained from thiolane.[73] Controlled introduction of two chlorine atoms at the α-position of alkyl phenyl sulfides has been achieved using sulfuryl chloride–pyridine (1:1 molar ratio) in carbon tetrachloride at −5 °C.[74]

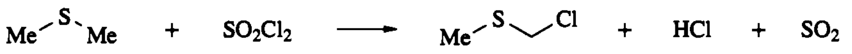
(52)

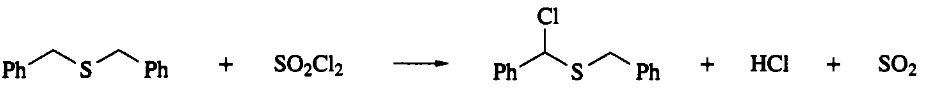
(53)

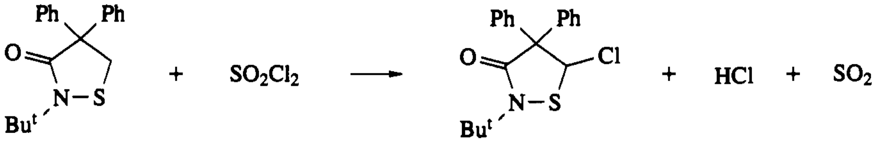
(54)

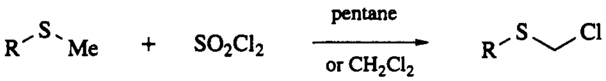

(55)

R = alkyl, aryl

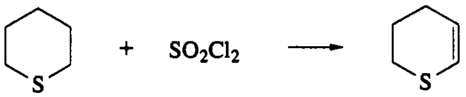
(56)

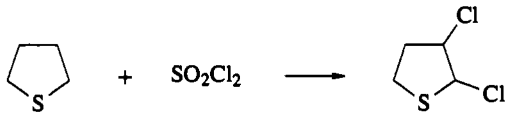
(57)

The introduction of NCS by Tuleen and Stevens, as a reagent for sulfide chlorination led to a major improvement in the preparation of α-chlorosulfides.[75] This crystalline reagent is easily handled and its reactivity is such that chlorination can be controlled to afford the monochlorination product selectively. Furthermore, NCS can be used for chlorination of acid-sensitive substrates. NCS is soluble in carbon tetrachloride at room temperature at ordinary concentrations, whereas its conjugate product, succinimide, is not. Solutions of α-chlorosulfides are therefore often prepared with NCS in $CCl_4$ and simply filtered prior to use without further purification. Other nonpolar solvents that have been used with NCS include chloroform, dichloromethane and benzene. Some of the very many examples of the use of NCS for sulfide chlorination from the recent literature are summarized in Table 2. For several of the entries yields were not recorded. This is almost always due to the fact that α-chlorosulfides are produced and treated as unstable reaction intermediates *en route* to more stable products.

The examples in Table 2 have been chosen so as to highlight significant features of the use of NCS. The isolation of α-chlorosulfides from substrates of diverse structural type in which β-elimination is possible is particularly noteworthy (entries 2–15). It is also apparent that functional groups such as alkenes, anhydrides, imides, esters, trimethylsilyls, acyl chlorides, amides, NBOC, acetals, β-lactams and ethers are all unaffected during the reaction (entries 12–23). However, allylic rearrangement does occur in some cases with allylic sulfides (entry 13 and equation 59). Small ring systems may be prone to ring-opening rearrangement as exemplified by the behavior of the bicyclo[3.2.0] system (entry 24). Highly reactive chlorosulfides such as 2-chloro-1,3-dithiane are also accessible (entry 25). This compound was also obtained using sulfuryl chloride as the reagent, provided very low temperatures were employed.

Although NCS continues to be the reagent of choice for sulfide chlorination, Cohen and his coworkers have advocated the use of trichloroisocyanuric acid as a less expensive alternative.[83] This substance, which is available commercially as an industrial deodorant and household cleaner under the trade name of Chloreal$^R$, is also useful for sulfide chlorination. Two examples of its use with sulfides are shown in

**Table 2** NCS Chlorination of Representative Sulfides

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | PhSMe | $PhSCH_2Cl$ | — | 75 |
| 2 | PhSEt | PhSCHClMe | — | 75 |
| 3 | $PhS(CH_2)_4Me$ | $PhSCHClBu^n$ | >90 | 76 |
| 4 | $Me_3SiO(CH_2)_2SPh$ | $Me_3SiOCH_2CHClSPh$ | >95 | 77 |
| 5 | $Me_3Sn(CH_2)_4SPh$ | $Me_3Sn(CH_2)_3CHClSPh$ | 100 | 78 |
| 6 | $PhS(CH_2)_4SPh$ | $PhSCHCl(CH_2)_2CHClSPh$ | >65 | 79 |
| 7 | 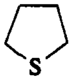 | 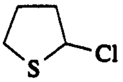 | — | 80 |
| 8 | 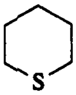 | 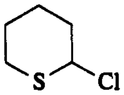 | — | 80 |
| 9 | 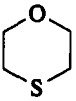 | 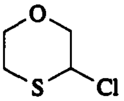 | — | 80 |
| 10 | 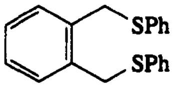 | 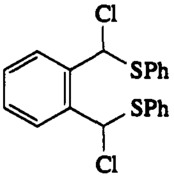 | >62 | 79 |
| 11 | 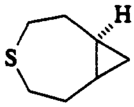 | 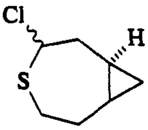 | 100 | 81 |
| 12 | 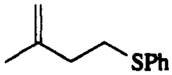 | 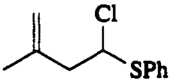 | >95 | 82 |
| 13 | 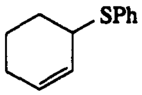 | 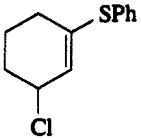 | — | 83 |
| 14 | 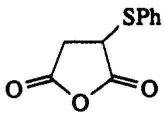 | 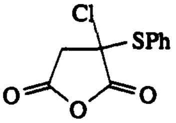 | 95 | 84 |
| 15 | 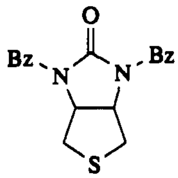 | 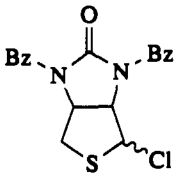 | 100 | 85 |
| 16 | $MeSCH_2CO_2Me$ | $MeSCHClCO_2Me$ | 78 | 86 |
| 17 | $PhSCH_2SiMe_3$ | $PhSCHClSiMe_3$ | 100 | 87 |
| 18 | $PhSCH_2COCl$ | PhSCHClCOCl | 86 | 88 |

**Table 2** *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 19 | 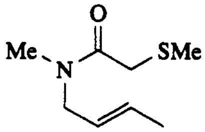 | 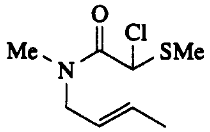 | ~100 | 89 |
| 20 | 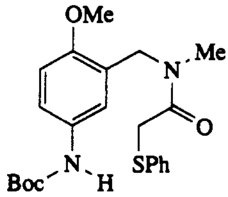 | 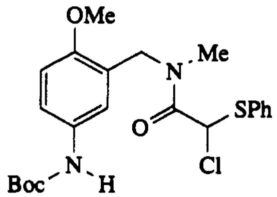 | 100 | 90 |
| 21 | 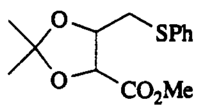 | 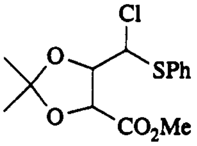 | — | 90 |
| 22 | 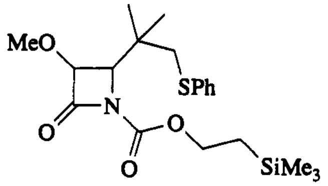 | 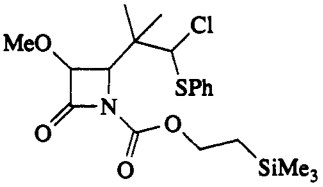 | — | 91 |
| 23 | 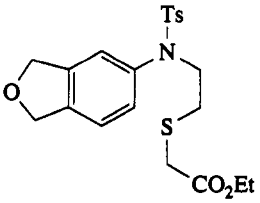 | 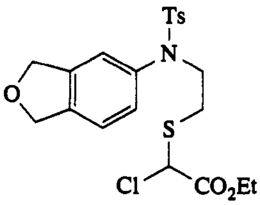 | — | 92 |
| 24 | 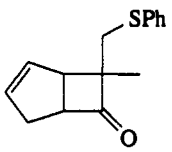 | 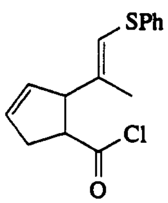 | — | 93 |
| 25 | 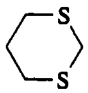 | 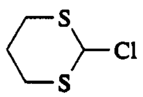 | — | 94 |

equations (58) and (59), the latter revealing that allylic rearrangement, as with NCS, is a feature of its reactivity. In a comparative study of the chlorination of allylic sulfides (equation 59) Cohen found that for substrates with $R^1$ = alkyl, Chloreal produced a much faster reaction at room temperature than did NCS.[83] Furthermore, chlorination of primary allylic phenyl sulfides (equation 59; $R^1$ = H) was also significantly faster with Chloreal than with NCS. Thus, phenyl crotyl sulfide (equation 59; $R^1$ = H, $R^2$ = Me) gave a 36% yield of chlorosulfide after 24 h at 5 °C with NCS, whereas the yield was quantitative with Chloreal; however, the amount of (*E*)-isomer in the product was greater with NCS.[83] Chloreal has also been used by Cohen to prepare the cyclopropyl chlorosulfide shown in equation (58).[95]

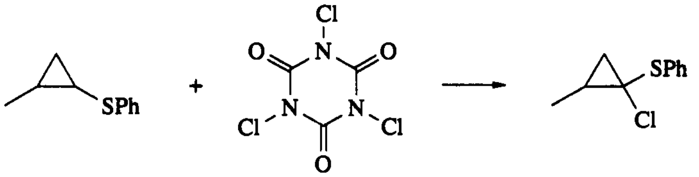

(58)

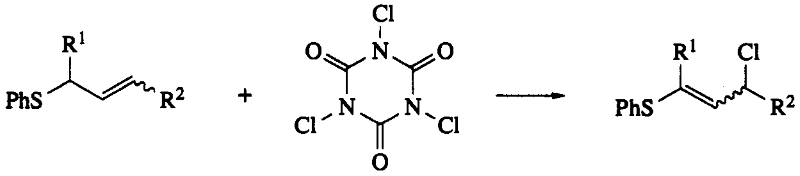

(59)

These various sulfide chlorinations are believed to follow ionic pathways similar to those summarized earlier for the Pummerer rearrangement of sulfoxides, the net result being the transfer of a chlorine atom from sulfur to carbon.[72] The broad outlines of the mechanism of action of NCS and of sulfuryl chloride are summarized in Scheme 5. The initiating step involves electrophilic attack by the reagent on the sulfur atom to form a sulfonium salt which, in some instances, can be isolated and converted into α-chlorosulfide on heating. Pathways A and B in Scheme 5 suggest two mechanistic extremes as to how this transformation may be brought about. The pathway favored for any particular substrate will reflect structural features, *e.g.* the acidity of the α-hydrogen atom(s) undergoing substitution and the extent of hyperconjugation. The choice of chlorinating agent may also be significant since the basicity of its conjugate anion is also implicated in the mechanism.

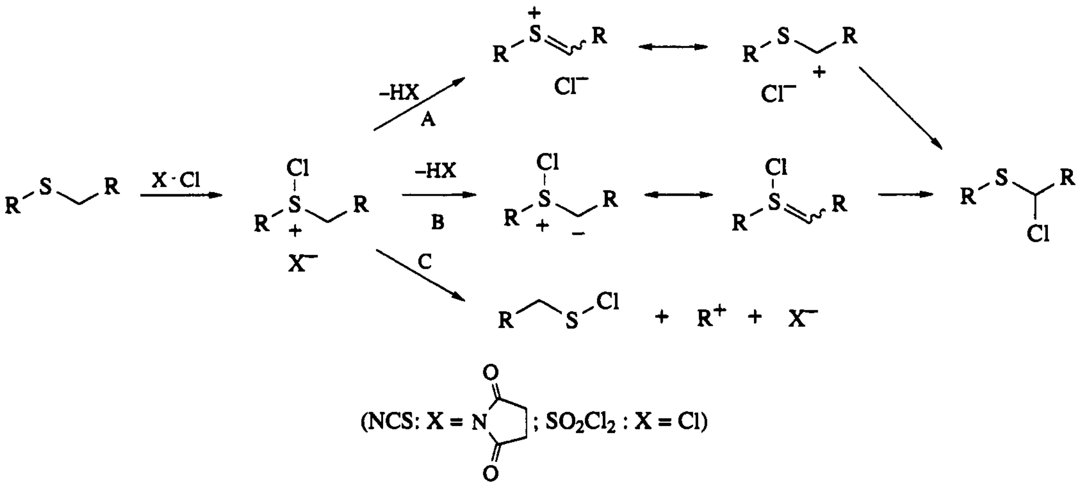

Scheme 5 Mechanisms of chlorination by NCS and $SO_2Cl_2$

The work of Tuleen and Stevens on the regioselectivity of chlorination of a series of unsymmetrically substituted dialkyl sulfides with NCS provides clues to the directive effects implicit in the mechanisms encompassed by Scheme 5.[96] These observations are collected in Scheme 6 where the preferred site of chlorination in each case is indicated with an arrow, the number over the arrow indicating the major:minor product ratio (minor = 1). In the first example, chlorination of benzyl methyl sulfide (**2**) produces chlorobenzyl methyl sulfide exclusively.[70] Secondly, chlorination of benzyl ethyl sulfide (**3**) and benzyl isopropyl sulfide (**4**) also shows a marked, though not exclusive, preference for the benzylic position.[96] In the latter case the extent of benzylic chlorination can be modulated by ring substitution. The directive effects in these internal competitions for *p*-methyl and *p*-chloro substituents are correlated by the Hammett relationship with a value of $\rho = 1.0$, which is consistent with a mechanism involving abstraction of the more acidic proton in the chlorosulfonium ion intermediate.[96] Further indications of the importance of proton acidity are shown by the behavior of alkyl sulfides (**5**)–(**8**) in Scheme 6, where the preferred site for chlorination is consistently that adjacent to the electron-withdrawing substituent.[96] The α-chlorosulfide carboxylate derived from (**6**) is a particularly notable (and useful) example of very high regioselectivity for the internal position.[86]

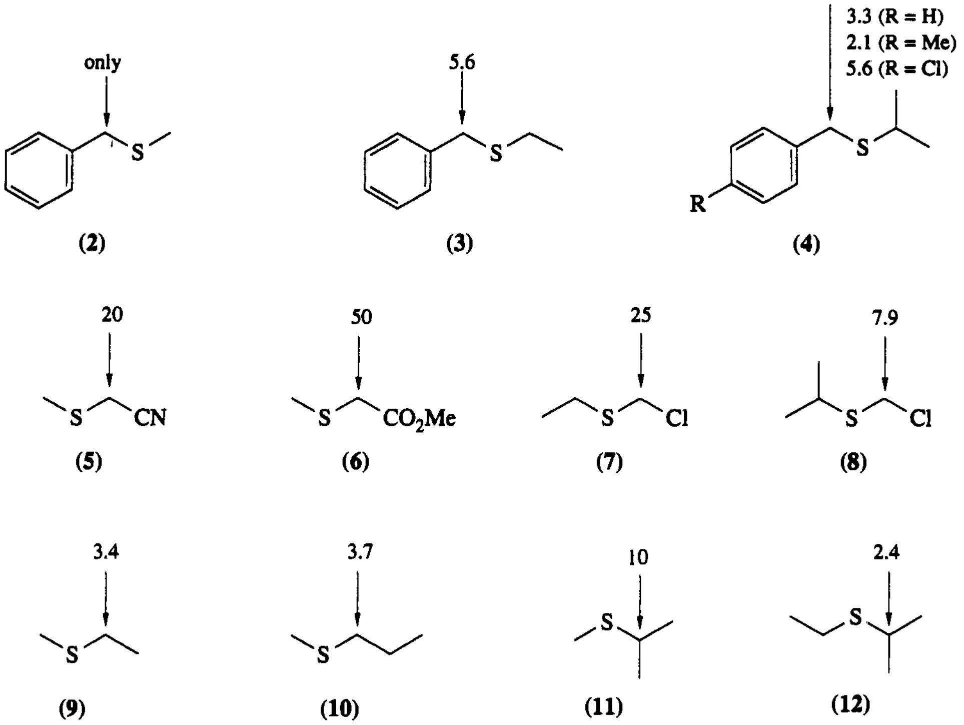

**Scheme 6**

While consideration of the relative acidities of the α-hydrogen atoms accounts satisfactorily for the dominant direction of chlorination of many alkyl sulfides, it does not explain the directive effects exhibited by the simple dialkyl sulfides (**9**)–(**12**) of which (**11**), with a 10:1 preference for the internal position, is the most notable. These substrates reveal an increasing susceptibility to chlorination of alkyl groups in the order methyl < ethyl ≈ *n*-propyl < isopropyl, which is also the order expected if in the course of the reaction the α-carbon atom assumes some degree of carbocation character in the transition state for α-hydrogen atom abstraction. This is consistent with pathway A in Scheme 5 in which concerted removal of hydrogen chloride from the chlorosulfonium ion generates a delocalized thiocarbocation. Pathways A and B are in fact variations on the *E*2 and *E*1cb mechanisms for 1,2-elimination, the latter leading to an ylide intermediate (*cf.* the Pummerer rearrangement), which should therefore become significant in sulfonium salts having an α-hydrogen atom of pronounced acidity.[97] The regiochemistry of further chlorination of chlorosulfides (**7**) and (**8**) demonstrates that a chloro substituent exerts a powerful directive effect in these systems. This effect is also apparent in the double chlorination of the tricyclic sulfide shown in equation (60), where formation of the geminal dichloride is favored over the 1,3-dichloride by a factor of 4:1 when the chlorinating agent is sulfuryl chloride.[98] On the other hand, NCS chlorination of the symmetrical bis-sulfide series in equation (61) produces symmetrical 1,X-dichlorides rather than geminal dichlorides.[79]

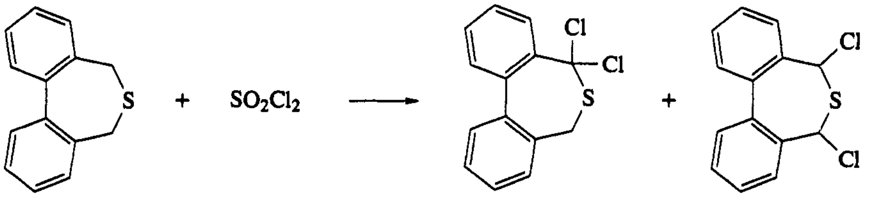

(60)

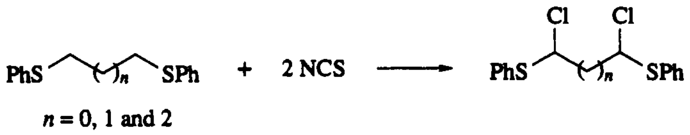

(61)

Tuleen and Stephens noted a regioselectivity difference during the chlorination of ethyl methyl sulfide by NCS and sulfuryl chloride, the latter being the more selective towards the internal position (ratio: 4.9 *versus*. 3.4).[96] In chlorination with sulfuryl chloride, proton abstraction from the chlorosulfonium ion is brought about by chloride ion, whereas with NCS the more basic succinimidyl ion is responsible. This difference suggests that of the two, the sulfuryl chloride reaction is more likely to follow the mechanism of pathway A in Scheme 5. Consequently, carbocation relative stabilities should have a greater influence in determining product composition with sulfuryl chloride than with NCS. Although pathway C in Scheme 5 does not lead to chlorosulfide, it is included here to highlight further differences between the reactivity of sulfuryl chloride and NCS. For example, while benzyl *t*-butyl sulfide and NCS give the expected chlorosulfide shown in equation (62), use of sulfuryl chloride affords predominantly the fragmentation products *t*-butyl chloride and dibenzyl disulfide (equation 63).[96] Similarly, benzyl *p*-methoxybenzyl sulfide behaves normally with NCS, but is cleaved to *p*-methoxybenzyl chloride and disulfide by sulfuryl chloride. Carbon–sulfur bond cleavage with sulfuryl chloride may be interpreted in terms of fragmentation of the chlorosulfonium cation (pathway C in Scheme 5), a process which should be facilitated by the release of a relatively stable carbocation, in this case *t*-butyl. That this does not happen with NCS suggests that the competition between pathway C leading to fragmentation and those leading to chlorosulfide is controlled by the relative basicities of chloride and succinimidyl ion.

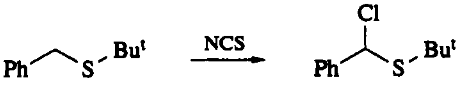

(62)

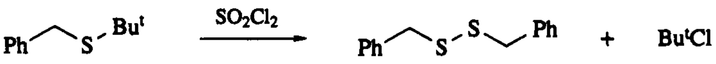

(63)

### 2.4.4.1 Miscellaneous Routes to α-Chloro Sulfides

Although this chapter is devoted primarily to methods of functionalizing alkyl sulfides at the α-position, it is appropriate to mention alternative routes to the same synthetic objective which do not involve direct functionalization of preformed sulfides. One such method, devised by Bohme and his coworkers, is based on the condensation of an aldehyde with a thiol in the presence of hydrogen chloride.[68,99] Use of formaldehyde in this way produces a primary chlorosulfide (equation 64). Higher aldehydes such as propanal yield secondary chlorosulfides (equation 65). The process is particularly useful in the synthesis of regiochemically pure chlorosulfides without danger of contamination by isomers in situations where the alternative of direct chlorination of a dialkyl sulfide would be nonregioselective. For example, NCS chlorination of benzyl *p*-methylbenzyl sulfide gives both possible monochlorides as shown in equation (66), whereas the condensation alternative of aldehyde, thiol and hydrogen chloride shown in equations (67) and (68) gives one or other of the individual monochlorides.[100]

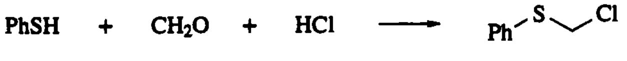

(64)

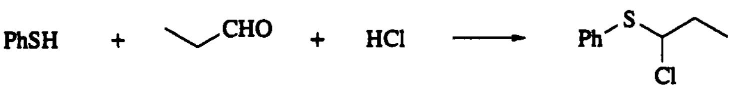

(65)

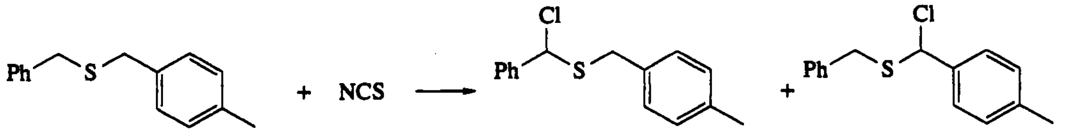

(66)

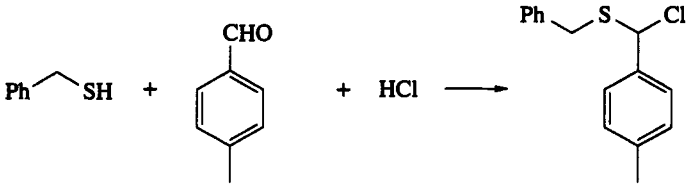

(67)

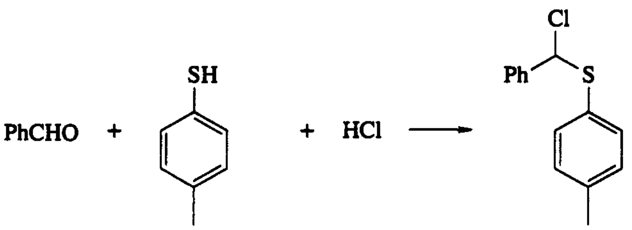

(68)

Yet another route to α-chlorosulfides which does not require the availability of sulfide is based on the reaction of diazo compounds, especially diazocarbonyls, with sulfenyl halides. Weygand and Bestmann found that α-diazo ketones and benzenesulfenyl chloride react smoothly together with loss of nitrogen at room temperature to furnish α-chloro-α-phenylthio ketones in excellent yield (equation 69).[101,102] This route, which features the simultaneous introduction of both chlorine and sulfur moieties, is particularly useful when one wishes to place the chlorosulfide unit adjacent to the carbonyl group of a ketone in a regiospecific manner. Since terminal α-diazo ketones may be obtained efficiently from acyl chloride and diazomethane, this route to α-chloro-α-phenylthio ketones is especially useful since it depends neither on the availability of the parent ketone nor on prior regiospecific introduction of the phenylthio group. More recent applications of this method to α-chlorosulfides include the reaction of benzenesulfenyl chloride with cyclic α-diazo ketones as summarized in equation (70).[103] The process is also applicable to α-diazo esters (equation 71) and 2-diazo-1,3-dicarbonyl compounds (equation 72).[102] Dimedone can be converted directly into an α-chlorosulfide without prior activation *via* the diazo intermediate (equation 73).[104]

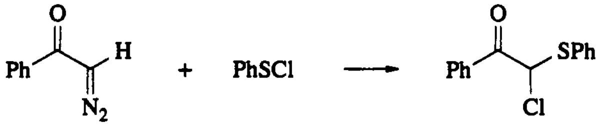

(69)

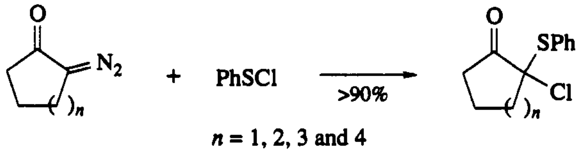

(70)

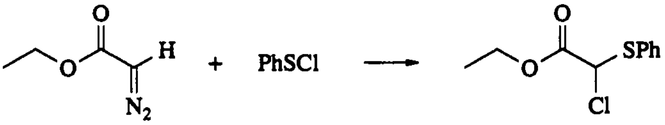

(71)

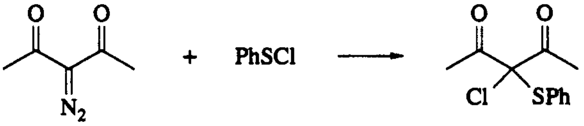

(72)

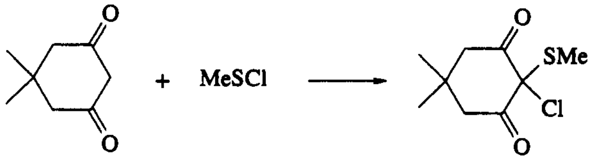

(73)

### 2.4.4.2 Summary of Uses of α-Chloro Sulfides in Organic Synthesis

α-Chlorosulfides exhibit a range of reactivity which makes them very useful as intermediates in organic synthesis.[105] We conclude this chapter with a schematic survey of their more important uses (see Scheme 7). In many ways they complement the uses of Pummerer products and intermediates.

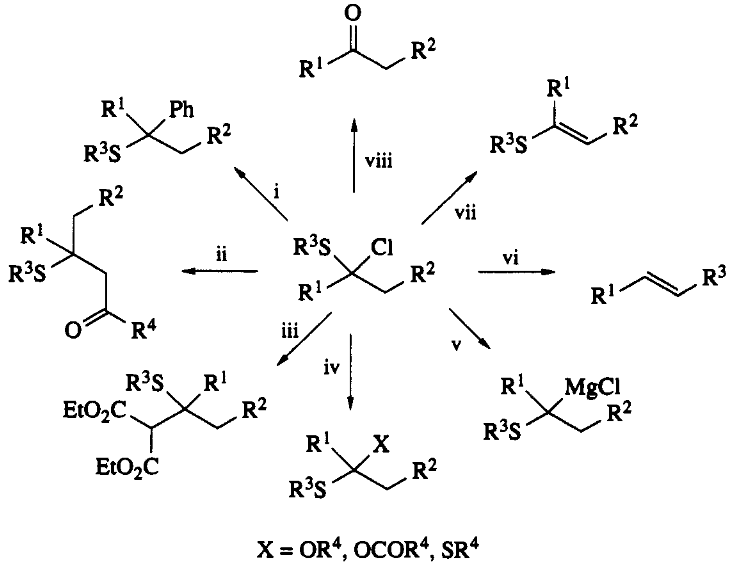

i, aromatic alkylation; ii, enol ether alkylation; iii, active methylene alkylation; iv, alcohol, thiol, carboxylate; v, Grignard formation; vi, Ramberg–Bäcklund rearrangement; vii, eliminate HCl; viii, hydrolysis

Scheme 7 Summary of α-chlorosulfide uses

α-Chlorosulfides are prone to solvolysis; in aqueous media they serve as aldehyde and ketone precursors. Exposure to alcohols or thiols leads to hemithioacetals or dithioacetals, which can serve as protecting groups. Under anhydrous conditions α-chlorosulfides are oxidized to α-chlorosulfones, which have been exploited extensively as alkene precursors in the Ramberg–Bäcklund synthesis. α-Chlorosulfides form and couple with Grignard reagents. Elimination of hydrogen chloride provides access to vinyl sulfides and thiocarbenoids. α-Chlorosulfides are also important sources of reactive electrophiles for alkylation reactions of aromatics, alkenes, alkynes, enolates and silyl enol ether derivatives of aldehydes, ketones, esters and lactones. As with Pummerer intermediates, intramolecular versions of α-chlorosulfide uses have also been developed.

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# 2.5

# Oxidation Adjacent to Nitrogen

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## 2.5.1 INTRODUCTION

Oxidation of carbon adjacent to nitrogen refers to the introduction of either an oxygen atom or a carbon atom next to a nitrogen atom, since either raises the oxidation state of the carbon atom attached to the nitrogen group. Sometimes, the nitrogen functionality is then lost on work-up or in a further hydrolysis step.

## 2.5.2 NITRO COMPOUNDS

### 2.5.2.1 The Nef Reaction

#### *2.5.2.1.1 Traditional Nef reactions*

Perhaps the most well-known example of this process is the Nef reaction.[1] This reaction was reported by the Swiss chemist Nef in 1894[2] and converts a primary or secondary nitro compound into an aldehyde or ketone (equation 1). The traditional base used in the reaction is sodium hydroxide and the acid is sulfuric acid. Side reactions sometimes are very significant. A study of pH dependence of the second step showed that the best results are obtained at a pH of 0.5.[3] At lower acidity, the starting nitro compound was recovered, in addition to some oxime and nitroso nitro compound (pseudonitrole).

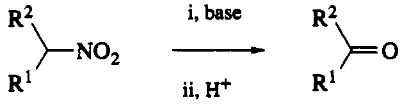

(1)

The popularity of the Nef reaction is due in part to the ready availability of nitro compounds.[4–7] Primary and secondary halides react with sodium nitrite in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) to give useful yields of nitro compounds.[4] Primary amines can be oxidized to nitro compounds with potassium permanganate, *m*-chloroperbenzoic acid[4] or ozone.[5] Chlorination of oximes with hypochlorous acid and reduction with magnesium, zinc or hydrogen/palladium gives secondary nitro compounds.[6] Stabilized carbanions can be nitrated by treatment with a nitrate ester,[4] and enol acetates are nitrated by acetyl nitrate to give nitro ketones.[7]

A wide array of compounds undergo the Nef reaction.[1] These include simple nitro compounds, as well as complex multifunctional species. For example, the carbohydrate in equation (2) was isolated as its hydrazone derivative in 72% yield.[8] Nitronate anions generated *in situ* can be acidified to give good yields of aldehydes and ketones. As an illustration, Michael addition of the dianion of hexanoic acid to 2-nitropropene gives the expected keto acid after acidification (equation 3).[9]

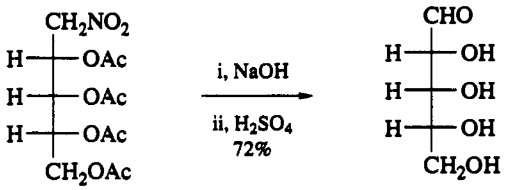

(2)

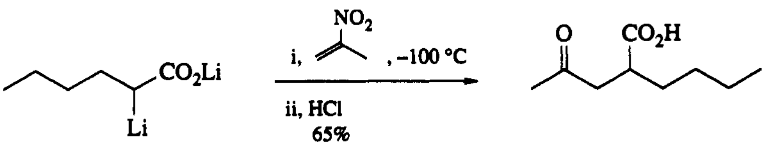

(3)

#### *2.5.2.1.2 Problems*

There are several problems and side reactions with the Nef reaction. The nitro compound or the anion is often insoluble in water; however, this shortcoming has been circumvented by running the reaction in a solvent such as methanol (equation 4).[10] An acetal may be formed if methanolic acid is used for the acidification stage (equation 5).[11] Interaction of neighboring groups leads to unexpected products in some cases such as with the nitro lactone in equation (6).[12] Systems which are prone to form carbocations may undergo rearrangement under Nef conditions. For example, attempts to prepare norcamphor derivatives led to an *N*-hydroxylactam as the product (equation 7).[13]

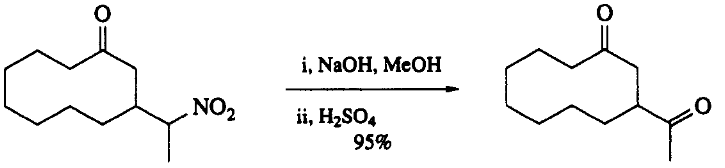

(4)

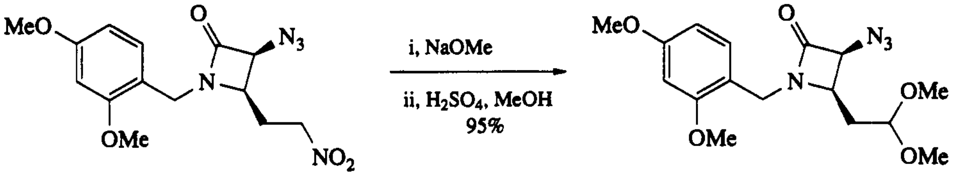

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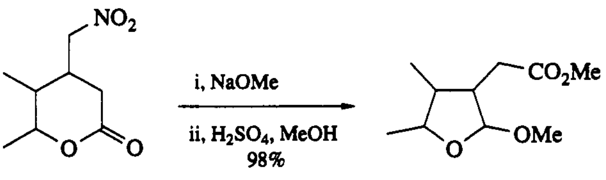

(6)

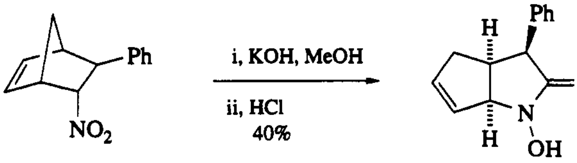

(7)

Many cyclic α-nitro ketones undergo ring opening when exposed to nucleophilic reagents. For example, 2-nitrocyclohexanone gives an 85% yield of 6-nitrohexanoic acid when stirred with aqueous sodium hydrogencarbonate at room temperature.[14] Interestingly, this strategy has been useful in the construction of macrocyclic nitro compounds (equation 8).[15]

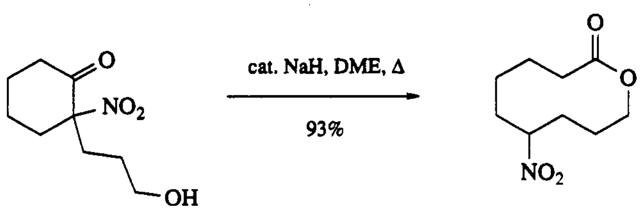

(8)

### *2.5.2.1.3 Modified Nef reactions*

The power of the Nef reaction as a tool in synthetic organic chemistry has been enhanced greatly by the development of modified reaction conditions. Many more polyfunctional compounds now can undergo one or more of these modified Nef reactions so that the scope of the original reaction is much greater. Many of these newer methods rely on oxidizing or reducing agents. Several of the more useful ones are outlined here, but a more comprehensive discussion is also available.[1]

Although discovered in the early 1900s, the oxidation of nitro compounds with potassium permanganate has become a truly useful reaction only within the last 25 years. An alkoxide base is used to form the nitronate salt, and aqueous potassium permanganate gives the oxidized product in excellent yield. Even aldehydes can be obtained as in equation (9) without loss of the pivaloyl group.[16] Cetyltrimethylammonium permanganate in dichloromethane also converts nitro compounds into aldehydes and ketones in synthetically useful yields.[17]

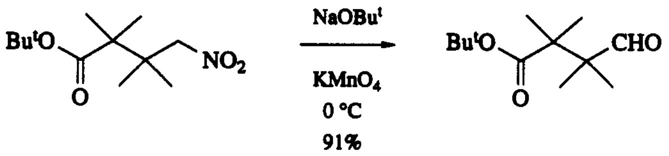
Bu$^t$O
NO$_2$
NaOBu$^t$
KMnO$_4$
0 °C
91%
Bu$^t$O
CHO
O
O

(9)

Titanium trichloride functions as an excellent reductive Nef alternative reagent. This aqueous reagent is very acidic, so that acid sensitive groups such as ketals and esters do not survive unless an acetate buffer is used.[18] Systems prone to acid-catalyzed rearrangements may then successfully undergo the reaction (equation 10).[19] Some very sensitive multifunctional compounds have been obtained using this modified Nef procedure (equation 11).[20] A related process is the formation of 1,4-diketones via *in situ* generation of a nitronate anion by the Lewis acid catalyzed addition of an enol silyl ether to a nitroalkene (equation 12).[21]

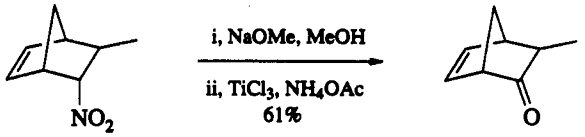
NO$_2$
i, NaOMe, MeOH
ii, TiCl$_3$, NH$_4$OAc
61%
O

(10)

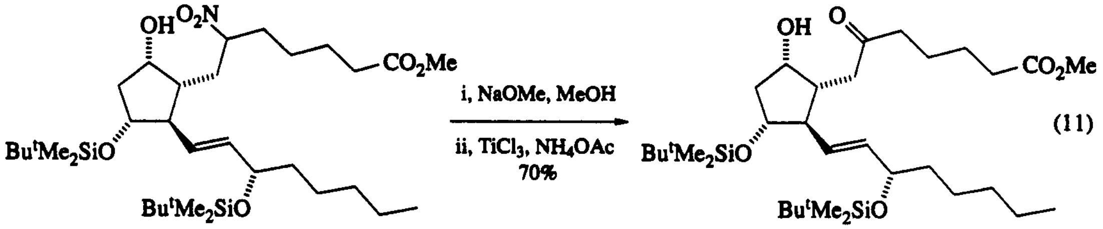
OH
O$_2$N
CO$_2$Me
Bu$^t$Me$_2$SiO
Bu$^t$Me$_2$SiO
i, NaOMe, MeOH
ii, TiCl$_3$, NH$_4$OAc
70%
OH
O
CO$_2$Me
Bu$^t$Me$_2$SiO
Bu$^t$Me$_2$SiO

(11)

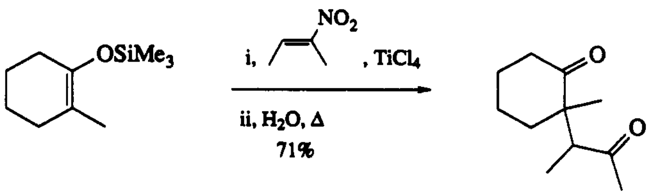
OSiMe$_3$
NO$_2$
i,
, TiCl$_4$
ii, H$_2$O, Δ
71%
O
O

(12)

Ozonolysis of intermediate nitronate anions also yields carbonyl compounds,[22] and, while unsaturation and acetal groups cannot be tolerated, other sensitive molecules have been prepared using this reaction (equation 13).[23]

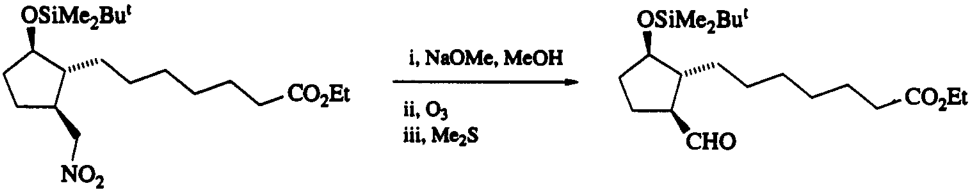
OSiMe$_2$Bu$^t$
CO$_2$Et
NO$_2$
i, NaOMe, MeOH
ii, O$_3$
iii, Me$_2$S
OSiMe$_2$Bu$^t$
CO$_2$Et
CHO

(13)

### 2.5.2.2 The Meyer Reaction

The Meyer reaction is generally not of major synthetic significance. It is observed when a nitro compound is exposed to strong acid. In this way, carboxylic acids are obtained from primary nitro compounds. The reaction is thought to involve nitrile oxides and hydroxamic acids (RCONHOH) as intermediates. The latter can be isolated by avoiding heat,[24] and the former have been trapped by 1,3-dipolar cycloaddition to alkenes and alkynes.[25]

## 2.5.3 TERTIARY AMINES

### 2.5.3.1 Mercury(II) Ion Oxidation

Tertiary amines form complexes with mercury(II) ion, which then give iminium ions by loss of a proton. Addition of perchloric acid permits isolation of the iminium ion as the perchlorate salt and generally the more-substituted ion is favored (equation 14).[26] Intramolecular trapping by a hydroxyalkyl group is also possible to form aminals (equation 15).[27] The lactam products result from over-oxidation, which is promoted by heat. Basification on the other hand usually allows the isolation of enamines[28] although hydroxyenamines have been obtained by reaction of enamines with mercury(II) acetate (equation 16),[29] while dihydroaromatic systems undergo aromatization (equation 17).[30]

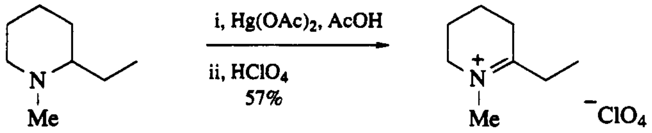

(14)

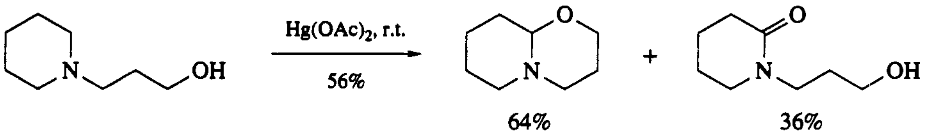

(15)

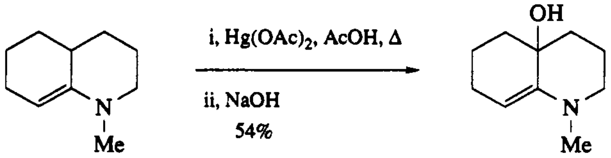

(16)

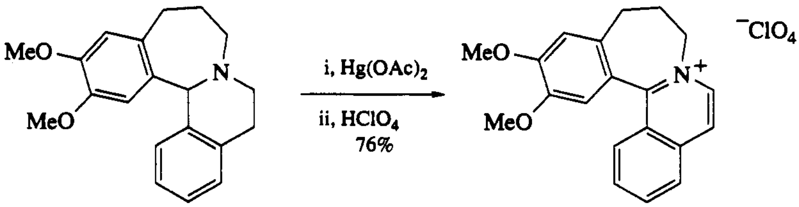

(17)

Lactams are obtained at higher pH by using $Hg^{II}$–ethylenediaminetetraacetic acid (EDTA) as the oxidizing agent (equation 18).[31] Nicotine gives an 88% yield of cotinine under these reaction conditions.

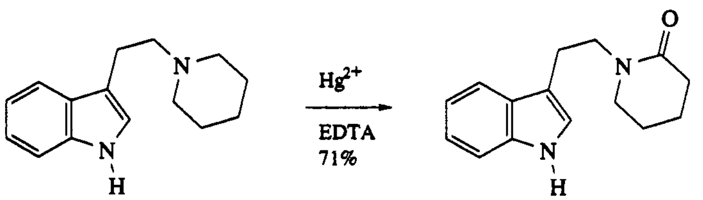

(18)

### 2.5.3.2 Chromium and Manganese Reagents

Chromium trioxide and pyridine have been used to form amides and lactams from tertiary amines. The yields are however only impressive for the preparation of formamides (equation 19).[32]

Manganese dioxide converts tertiary amines into amides. For example, *N*,*N*-dimethylaniline gives *N*-methyl-*N*-phenylformamide in 78% yield[33] and *N*-phenylpyrrolidine yields *N*-phenylformamide in 48% yield.[34] Dimethylaminocyclohexane on oxidation leads to cyclohexanone in 85% yield.[35] There is also

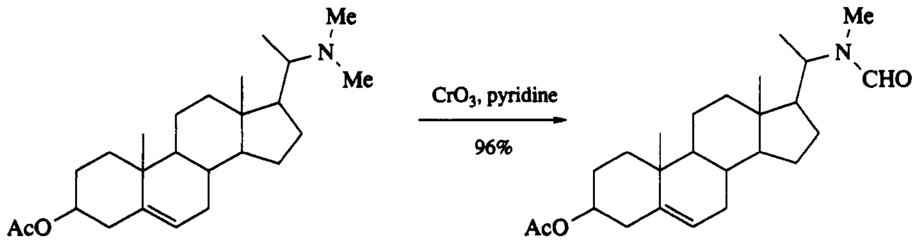

(19)

an isolated example of a lactam being isolated in about 5% yield using potassium permanganate as the oxidant (equation 20).[36]

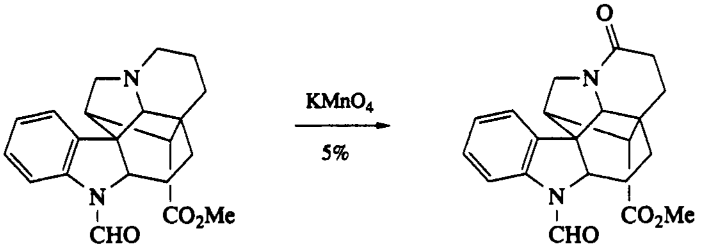

(20)

### 2.5.3.3 Hypervalent Iodine

Iodosylbenzene converts cyclic tertiary amines into lactams,[37] as indicated by nicotine affording a 20% yield of cotinine and *N*-methylpyrrolidine being converted into the corresponding lactam in 55% yield.

### 2.5.3.4 Platinum/Oxygen

Tertiary amines react with oxygen in the presence of platinum to give amides[38] showing a strong preference for reaction at methyl groups. For example, oxidation of trimethylamine gives *N*,*N*-dimethylformamide in 74% yield, and *N*-methylcyclohexylamine yields *N*-formylcyclohexylamine in quantitative yield.

### 2.5.3.5 Amine Oxides

#### *2.5.3.5.1 The Polonovski reaction*

The Polonovski reaction occurs when an amine oxide reacts with an acylating agent.[39] The accepted mechanism involves proton removal to give a nitrogen ylide which loses acetate (using acetic anhydride) which attacks the carbon adjacent to the nitrogen atom giving an α-acetoxyamine. These intermediates can be hydrolyzed to give aldehydes or eliminated to give enamines (equation 21).[40] This latter case was used to help determine the structure of the natural product nupharidine. A recent variant of the procedure occurred by silylation of amine *N*-oxides to give α-silyloxyamines which subsequently underwent elimination to give iminium ion intermediates which reacted with nucleophiles (equation 22).[41]

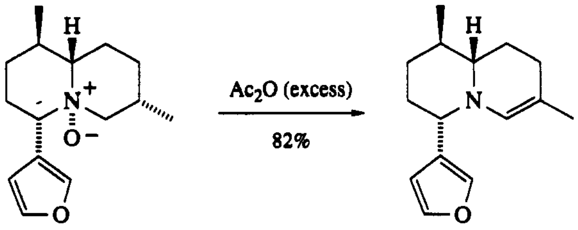

(21)

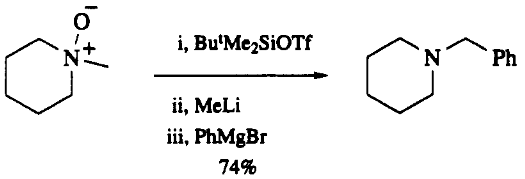

(22)

### *2.5.3.5.2 Pyridine* N*-oxides*

Pyridine *N*-oxides may be deprotonated to give ylides which react with electrophiles such as carbon dioxide and ketones. For example, 4-chloropyridine *N*-oxide reacts with butyllithium at −65 °C followed by quenching with carbon dioxide to give 4-chloropyridine *N*-oxide 2-carboxylic acid in 49% yield. Quinuclidine *N*-oxide can be deprotonated with *t*-butyllithium to give the anion which can be trapped with deuterium oxide or benzaldehyde.[42]

### 2.5.3.6 Miscellaneous Oxidation Reactions of Tertiary Amines

Irradiation of some amines in the presence of 1,4-dicyanonaphthalene causes the formation of radical cations, which give iminium ions by loss of a proton. Intramolecular addition of a hydroxylic nucleophile yields aminals (equation 23).[43]

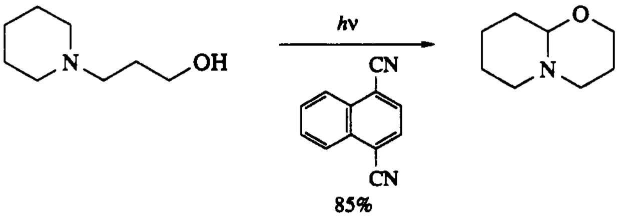

(23)

Benzylic quaternary salts react with hot dimethyl sulfoxide (DMSO) to give benzaldehyde.[44] For example, benzylammonium chloride gives 60% benzaldehyde plus 24% benzylmethylamine and 5% benzyldimethylamine.

Hydride abstraction from tertiary amines by arylmethyl cations leads to iminium ions which can be hydrolyzed or trapped with nucleophiles.[45] For example, *t*-butyldimethylamine reacts with triphenylmethyl perchlorate to give a 93% yield of the iminium salt. This can be trapped with acetophenone to give the Mannich product (Scheme 1).

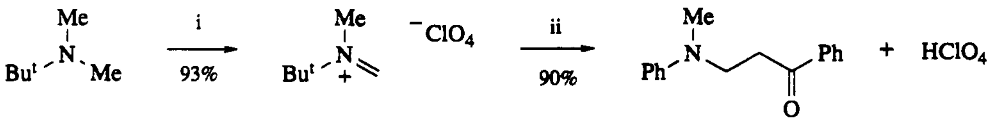

i, $Ph_3C^+ClO_4^-$; ii, PhCOMe

**Scheme 1**

Benzylic amines react with hydrogen peroxide to yield benzaldehydes.[46] For example, 4-bromobenzyldimethylamine gives a 60% yield of 4-bromobenzaldehyde. Only six cases were reported, with both dimethylamino and diethylamino groups undergoing the reaction.

## 2.5.4 SECONDARY AMINES

### 2.5.4.1 Formamidines

Secondary amines are easily converted into formamidines by reaction with amidines (equation 24).[47] Deprotonation and addition of electrophiles, including alkyl halides, acyl halides, aldehydes and diselenides, permit the introduction of various groups adjacent to the amino center, and therefore can be considered as an oxidation. Alkylation with dihalides gives intermediates which lead to new carbocyclic rings after removal of the formamidine group (equation 25).[48]

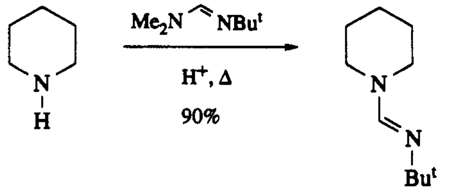
Me2N NBut
H+, Δ
90%
N
H
N
N
But

(24)

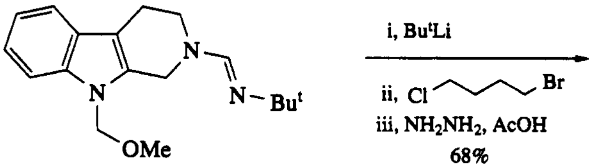
N
N
N—But
OMe
i, ButLi
ii, Cl Br
iii, NH2NH2, AcOH
68%
N
N
OMe

(25)

High enantioselectivity is also possible in these reactions by using an optically active amidine, readily available from (*S*)-valinol.[49] A recent synthesis of (+)-reticuline made elegant use of this chiral intermediate (equation 26).[50] Likewise, (–)-yohimbone was prepared in 98% enantiomeric excess using these reactions.[51]

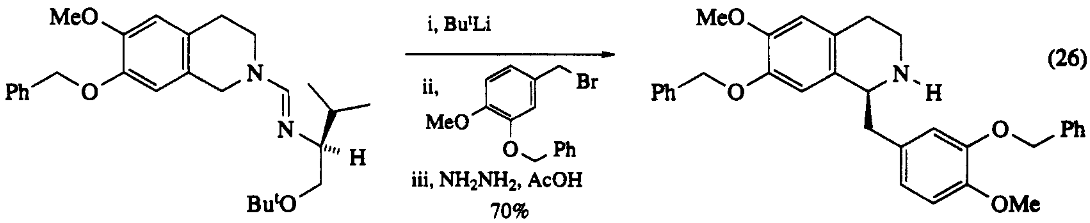
MeO
Ph O
N
N
H
ButO
i, ButLi
ii, Br
MeO
O Ph
iii, NH2NH2, AcOH
70%
MeO
Ph O
N
H
O Ph
OMe

(26)

Reticuline, 99% *ee*

Another formamidine which allows facile removal of hindered tertiary hydrogens has been recently introduced (equation 27).[52] The bridgehead position of a bicyclic amine has also been alkylated in good yields via the *t*-butylformamidine.[53]

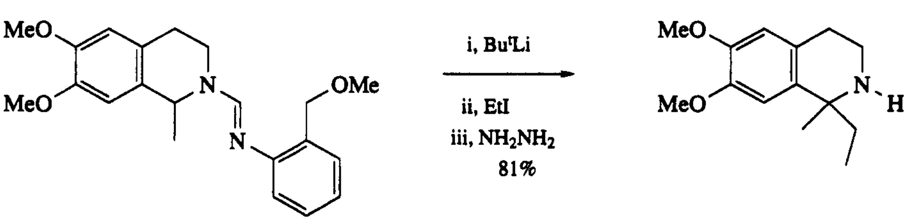
MeO
MeO
N
N
OMe
i, ButLi
ii, EtI
iii, NH2NH2
81%
MeO
MeO
N
H

(27)

### 2.5.4.2 *N*-Nitrosamines

The acidity of hydrogen atoms adjacent to the nitrogen substituent of *N*-nitrosamines has been known for many years,[54] although Seebach and coworkers played a major role in developing this into a useful synthetic process. For example, the anion of *N*-nitrosodimethylamine is formed by using LDA, and can be alkylated or condensed with carbonyl compounds or nitriles (Scheme 2).[55] 1-Bromo-3-iodopropane reacts with this anion, and formation of the kinetic anion of this intermediate gives *N*-nitrosopiperidine in 54% yield.[56] The key step in the total synthesis of macrostomine was accomplished using a nitrosamine alkylation (equation 28).[57] Many additional examples using *N*-nitrosamines are also available.[58,59]

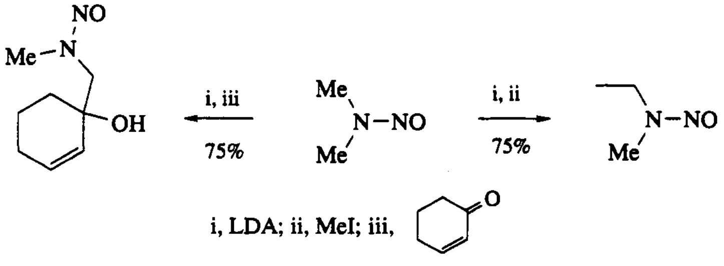

Scheme 2

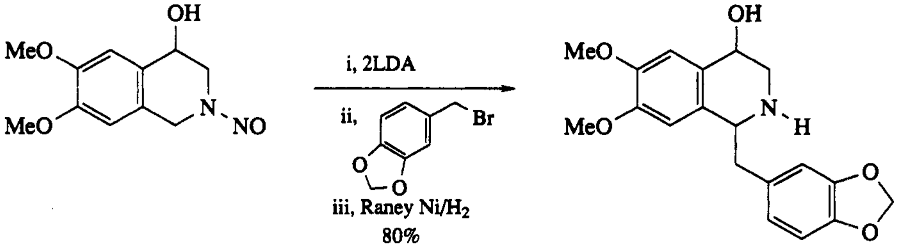

(28)

*N*-Nitroso-α-amino acids may be converted into α-acetoxynitrosamines.[60] For example, *N*-nitrosoproline gives a 40% yield of 2-acetoxy-1-nitrosopyrrolidine using lead tetraacetate in pyridine.

### 2.5.4.3 Amides

Secondary amines can be acylated with acyl groups bearing no α-hydrogens. Deprotonation next to the nitrogen atom and introduction of electrophiles allow the oxidation of that position. Early work showed that these anions underwent self-condensation. For example, *N*,*N*-dimethylbenzamide can be deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LITMP) to give *N*-methyl-*N*-phenacylbenzamide in 60% yield.[61] It is clear that lithium ion is crucial to the success of this reaction. Crown ethers prevent the reaction,[62] and recent kinetic studies show intermediate lithium complex formation.[63]

Simple benzamides undergo slow deprotonation with amide bases. Stronger base systems such as *s*-butyllithium in tetramethylethylenediamine (TMEDA) are too nucleophilic for simple benzamides but *N*,*N*-dimethyl-2,4,6-triisopropylbenzamide is deprotonated in only 5 min at –78 °C, and this anion is alkylated with methyl iodide to give a 77% yield of the expected product.[64]

Other amides have been alkylated by this method. For example, the system in equation (29) gives clean products even with secondary iodides.[65] Vinylogous amides behave in a similar manner (equation 30).[66] Thioamides also undergo alkylation without complications.[67]

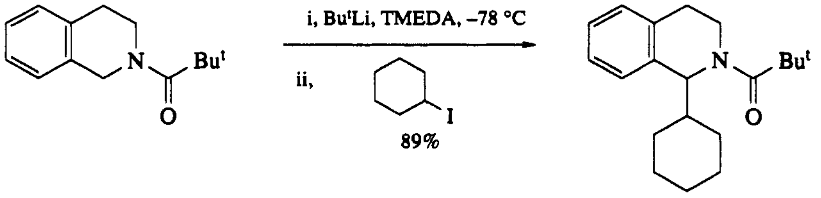

(29)

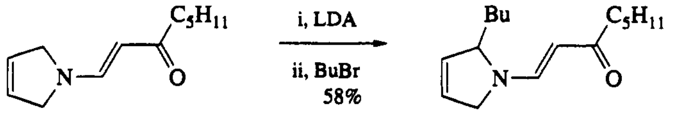

(30)

Trapping of these so-called dipole-stabilized anions with either oxygen or the complex of oxodiperoxymolybdenum with HMPA and pyridine gives hemiaminals which provide secondary amides.[68] The procedure can therefore be used as a method of benzyl deprotection of amides (equation 31).

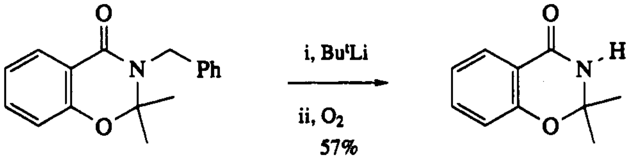
O
N
Ph
O
i, Bu$^t$Li
ii, $O_2$
57%
O
N
H
O

(31)

## 2.5.4.4 Urethanes

### *2.5.4.4.1 Anions*

Urethanes analogous to the amides of the previous section undergo similar deprotonation followed by alkylation and condensation reactions. For example, 2,4,6-tri-*t*-butylphenol may be converted into the corresponding urethane which can be further functionalized (equation 32).[69] *N*-Carbomethoxy-3-pyrroline has been converted into both the trail pheromone for the Pharaoh ant and gephyrotoxin 223 by using regiospecific alkylations (Scheme 3).[70] Similar approaches were used in the preparation of the natural product supinidine.[71] Piperidines also have been alkylated via the *t*-BOC-protected amines.[72]

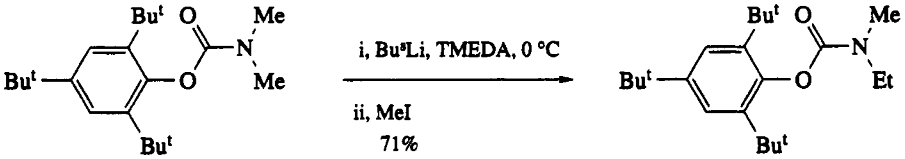
Bu$^t$
O
Me
N
Me
O
Bu$^t$
Bu$^t$
i, Bu$^s$Li, TMEDA, 0 °C
ii, MeI
71%
Bu$^t$
O
Me
N
Et
O
Bu$^t$
Bu$^t$

(32)

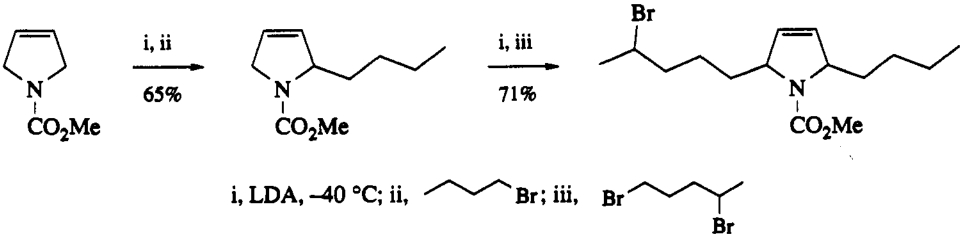
N
$CO_2Me$
i, ii
65%
N
$CO_2Me$
i, iii
71%
Br
N
$CO_2Me$
i, LDA, −40 °C; ii,
Br; iii,
Br
Br

Scheme 3

Carbamic acid dianions have also been reported and behave in the analogous manner (Scheme 4).[73]

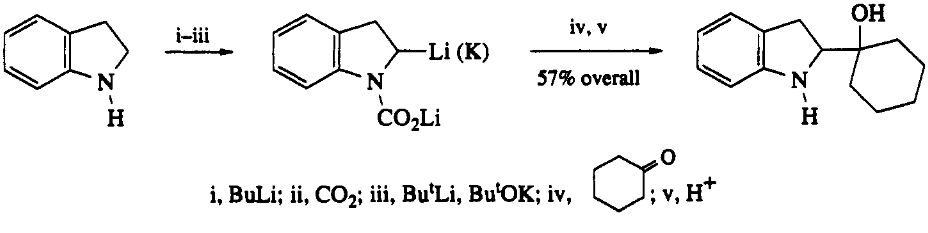
N
H
i–iii
Li (K)
N
$CO_2Li$
iv, v
57% overall
OH
N
H
i, BuLi; ii, $CO_2$; iii, Bu$^t$Li, Bu$^t$OK; iv,
O
; v, $H^+$

Scheme 4

### *2.5.4.4.2 Electrolysis*

Anodic electrolysis of urethanes in methanol gives α-methoxyurethanes, which have been used in reactions with nucleophiles or eliminated to give enamine derivatives. Yields from the electrolysis step are usually acceptable (typically 50%).[74] Several natural products have been prepared using this process as the key step.[75,76] For example, a simple synthesis of hygrine is possible (Scheme 5).[77] Only simple urethanes have been electrolyzed, which suggests a lack of functional group compatibility.

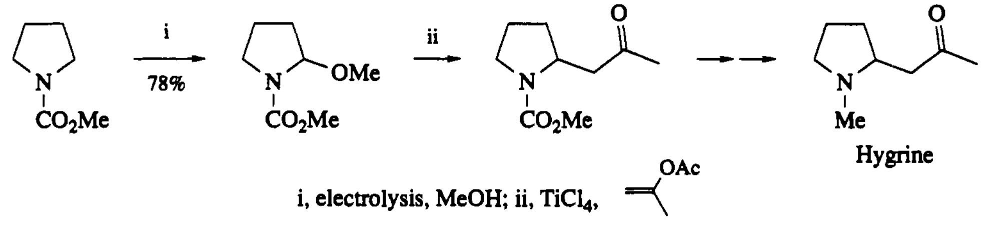

i, electrolysis, MeOH; ii, $TiCl_4$,

**Scheme 5**

### 2.5.4.5 Miscellaneous Methods

Secondary amines react with 2-ethoxy-4-isopropyloxazoline and acid to give oxazoline derivatives which may also be deprotonated. High enantiomeric excess is possible during alkylation by using chiral oxazolines,[78] as in the preparation of (+)-salsolidine (equation 33).[79] Likewise, isoindoline also has been alkylated by using a similar approach.[80]

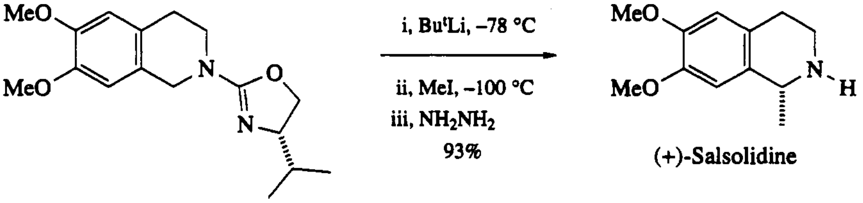

(33)

Iodosylbenzene oxidizes secondary amines to lactams in reasonable yields, much like the tertiary amines discussed in Section 2.5.3.3.[37] If only 1 equiv. of iodosylbenzene is used, the imine intermediates are isolated. Thus, 1,2,3,4-tetrahydroisoquinoline gives 3,4-dihydroisoquinoline in 61% yield.[81] This general reaction also has been reported with either iodosylbenzene or iodosylbenzene/$RuCl_2(PPh_3)_3$.[82]

Mercury(II) ion oxidizes secondary amines to imines when reacted in the presence of acetic acid.[83] For example, 2-*t*-butylpiperidine gives a 75% yield of the more substituted imine. Mercury(II) ion in EDTA gives lactams.[31] For example, 4-*t*-butylpiperidone is isolated in 81% yield from 4-*t*-butylpiperidine using mercury(II) ion in EDTA.

Photochemically induced oxidation of one secondary amine in the presence of 1,4-dicyanonaphthalene allows the introduction of oxygen into the position adjacent to the nitrogen atom (equation 34).[43]

Secondary amines have been oxidized to imines by several routes. The nitrogen atom can be halogenated and the *N*-chloramine eliminated with base. *N*-Chlorosuccinimide and potassium hydroxide are popular reagents[84] although *t*-butyl hypochlorite followed by potassium superoxide has also been used with some success.[85] The overall yields in these reactions are usually good. Diphenyl selenoxide and trifluoroacetic anhydride convert tetrahydroisoquinolines into dihydroisoquinolines.[86] Benzeneseleninic anhydride converts secondary amines into imines, which can be trapped by cyanide ion to give α-cyanoamines.[87] Tristriphenylphosphineruthenium dichloride and *t*-butyl hydroperoxide convert secondary amines into imines, although the products in all cases are conjugated with aromatic rings.[88] Finally, dehydrogenation of secondary amines into imines can be accomplished with a cobalt catalyst in the presence of oxygen at 60 °C.[89]

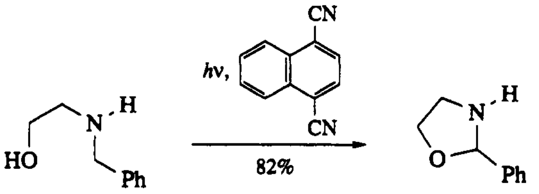

(34)

## 2.5.5 PRIMARY AMINES

### 2.5.5.1 Conversion into Aldehydes and Ketones

Primary amines have been transformed into imines which when metallated react with carbonyl compounds. Treatment with butyllithium, alkylation with allyl bromide and hydrolysis gives highly substituted aldehydes (Scheme 6).[90] Thus, in this example, the carbon adjacent to the original amino nitrogen atom becomes the carbonyl carbon. The technique has been used several times in the course of total synthesis, as with a recent approach to crinine[91] and as the key step in a recent highly regioselective preparation of α,β-unsaturated aldehydes (equation 35).[92]

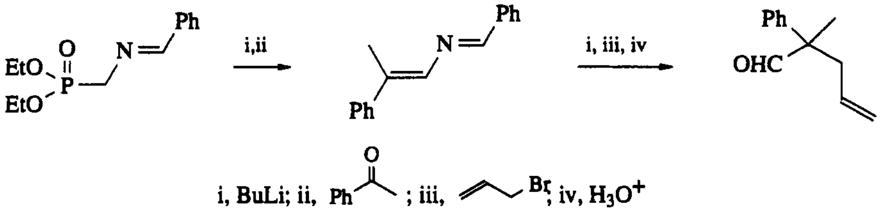

Scheme 6

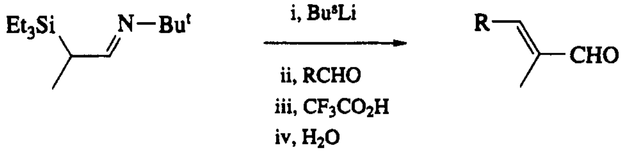

(35)

Many other methods have been developed for the conversion of primary amines into carbonyl groups *via* imines. Prostaglandin $E_1$ was prepared in over 25% yield from the corresponding amine with hydroxy groups protected as THP acetals. This was achieved by *N*-bromination (NBS) followed by loss of HBr and hydrolysis of the resulting imine.[93] The approach has been applied successfully to several primary amines having only one α-hydrogen atom using sodium hypochlorite under phase transfer conditions (nitriles are isolated from amines having two α-hydrogens). Cyclohexanone is obtained in 98% yield and norcamphor in 84% yield.[94] Another clever method for amine oxidation uses 3,5-di-*t*-butyl-1,2-benzoquinone to give an intermediate imine which is hydrolyzed to the carbonyl compound.[95] Camphor is isolated in 69% yield and cyclohexanone in 97% yield. The mechanism of these reactions has been examined in some detail recently.[96] The imines from reaction of primary amines with 2,6-di-*t*-butyl-1,4-benzoquinone react with oxygen and potassium *t*-butoxide or potassium hydroxide to give amides.[97] For example, benzylamine gives benzamide in 50% overall yield. Another method uses aromatic aldehydes to give imines which can be isomerized and then hydrolyzed, as with 2-pyridinecarboxaldehyde which converts undecylamine into the corresponding aldehyde in 94% yield.[98] In a similar manner, *N*-methyl-4-pyridinecarbaldehyde has been used for the oxidative deamination of primary amines (even lysine and lysine esters with the α-amino group protected).[99] Phenylselenyl chloride converts primary amines into imines.[100] 2-Adamantylamine gives adamantanone in 91% isolated yield using this method. Di-*t*-butyliminoxyl radical, from cerium(IV) ammonium nitrate oxidation of the oxime of di-*t*-butyl ketone, also oxidizes amines into imines.[101]

Primary amines *via* pyrilium salts react with 2-pyridone *N*-oxides and on decomposition give aldehydes in fair yields (equation 36).[102]

Various reagents will oxidize primary amines to intermediates, which are often hydrolyzed in acceptable yields *in situ* to give aldehydes and ketones. Hot potassium permanganate in a buffered (calcium sulfate) medium gives reasonable yields of carbonyl compounds, although of course double bonds and many other functional groups would not be compatible with this method.[103] Sodium persulfate and catalytic silver nitrate convert primary amines into aldehydes (43–96%).[104] Similarly, palladium(II) chloride or gold(III) chloride[105] as well as silver picolinate[106] have been used for this purpose also, although the latter reagent gives considerable amounts of nitrile as a side product and can be the major product in many cases depending upon the substituents present.

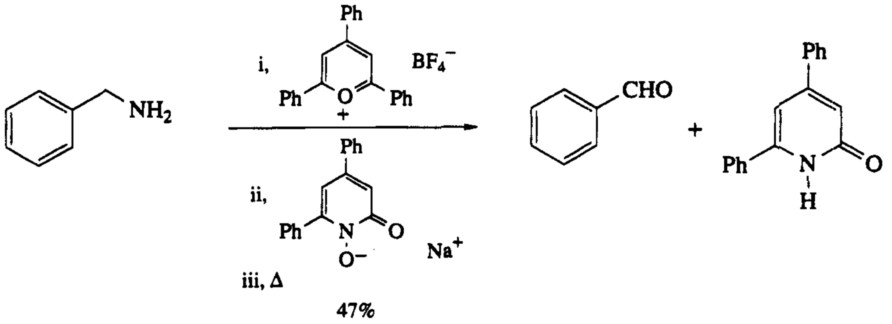

(36)

Aromatic aldehydes are obtained by reaction of primary amines with *p*-nitrobenzenesulfonyl peroxide followed by mild hydrolysis with dilute acid.[107]

*N,N*-Disulfonamides are decomposed with sodium hydrogencarbonate in DMSO to give ketones.[108]

Imines formed from the reaction of primary amines with carbonyl compounds can be oxidized to oxaziridines with MCPBA which hydrolyze to aldehydes or ketones with acid. When acetone is used, the final by-products are ammonia and acetone (equation 37).[109] The use of 2-pyridinecarbaldehyde is preferred since it gives an acid-soluble by-product which aids work-up (equation 38).[110]

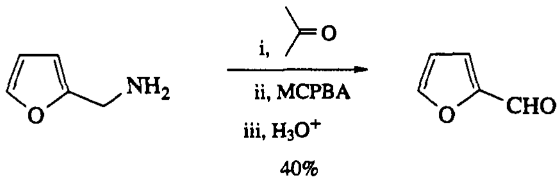

(37)

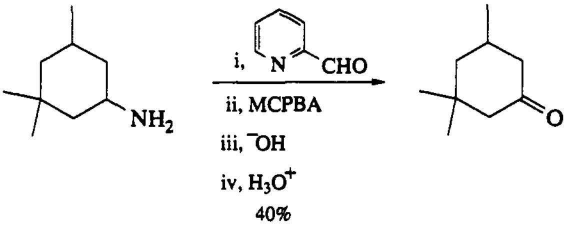

(38)

### 2.5.5.2 Conversion of Primary Amines into Nitriles

Many reagents convert primary amines into nitriles. Some of these have been mentioned above and represent serious limitations on methods for generating carbonyl compounds. Other ways of oxidizing amines to nitriles are the use of nickel peroxide,[111] lead tetraacetate,[112] copper(I) chloride plus oxygen and pyridine,[113] iodine pentafluoride[114] and benzeneseleninic anhydride.[115] A double bromination–dehydrobromination can be effected for the preparation of nitriles with 2 equiv. of NBS and trimethylamine.[116] Likewise, fluorination and elimination of HF gives nitriles.[117]

## 2.5.6 AMINO ACIDS

### 2.5.6.1 Alkylation

The introduction of alkyl groups at the α-carbon of amino acids has been accomplished most efficiently by formation of imine esters. For example, the benzaldehyde imine of ethyl glycinate can be deprotonated and alkylated (equation 39).[118] Other imines also have been used.[119] Optical activity has been introduced by using chiral palladium ligands during the alkylation step,[120] chiral alcohols to form the ester,[121] and chiral ketones to form the imine.[122] Alkylation of 2-pyrrole acetate esters has been accomplished in a similar fashion.[123]

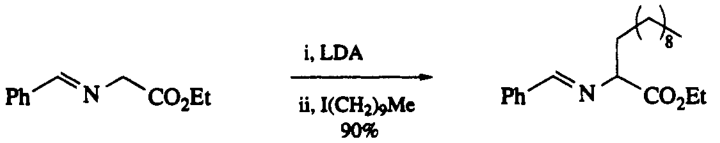
(39)

Alkylation of amino acids has also been achieved by first forming heterocyclic derivatives. For example, the oxazolidinone from CBZ-phenylalanine and formaldehyde reacts with potassium hexamethyldisilazide followed by allyl bromide to give the expected product in 76% yield.[124] Chiral tetrahydro-1,4-oxazin-2-ones have been used in a similar manner to give amino acids with a degree of diastereoselectivity.[125,126]

### 2.5.6.2 Degradation of Amino Acids

Amino acids are converted into aldehydes, the most popular method being the Strecker degradation.[127] The amino acid is simply mixed with reagents such as ninhydrin and heated to form ammonia and carbon dioxide as by-products. Sodium hypochlorite can be used in a process accelerated by UV irradiation.[128] A similar reaction is the Akabori reaction where the amino acid is heated with compounds such as glucose to give aldehydes, as in the Strecker process.[129]

*N*-Alkyl amino acids are decarboxylated to iminium salts by brief treatment with hot $POCl_3$.[130] These may be intercepted by internal nucleophiles to form cyclic compounds (equation 40).[131]

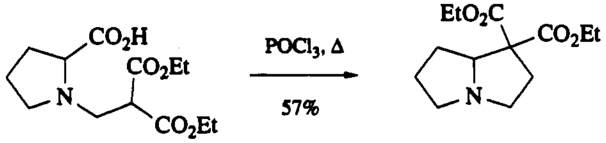
(40)

### 2.5.6.3 Miscellaneous

Oxidation with excess iodosylbenzene converts proline into 2-pyrrolidinone in up to 70% yield.[78] Use of only 1 equiv. of iodosylbenzene in this reaction gives 1-pyrroline, plus the corresponding trimer.

Oxygen substituents have been introduced into the α-position of amino acids by *N*-halogenation and elimination/addition in the presence of an alkoxide. For example, the methyl ester of BOC-phenylalanine reacts with *t*-butylhypochlorite followed by methoxide to give the α-methoxy amino acid derivative in 76% yield.[132] The intermediate halo compound reacts with Grignard reagents to give higher amino acids. *N*-BOC-glycinates react with NBS followed by 2 equiv. of a methyl Grignard reagent to give the protected alanine ester by a process which must involve an imino ester.[133] Similar intermediates may be obtained by alternative methods involving addition of alkoxides to imidates (equation 41).[134]

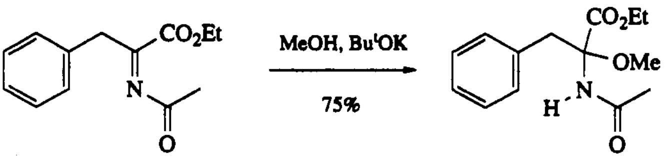
(41)

## 2.5.7 MISCELLANEOUS OXIDATIONS

### 2.5.7.1 Lactams/Amides

Lactams and amides are easily oxidized to imides with hydroperoxides in the presence of $Mn(acac)_2$ or $Co^{II}$ naphthenate.[135,136] For example, 2-piperidone is oxidized to glutarimide in 72% yield using $Mn(acac)_2$.

### 2.5.7.2 α-Cyanoamines

α-Cyanoamines can be deprotonated to allow the introduction of electrophiles at the α-position. The resulting adducts can be hydrolyzed to give ketones. These intermediate anions are therefore acyl anion equivalents. For example, aromatic ketones are efficiently prepared as illustrated in equation (42).[137] More recently, 1-benzyl-2,6-dicyanopiperidine was bisalkylated using sequential treatment with LDA and alkyl halides and the resulting product was hydrolyzed to give 1,5-diketones.[138]

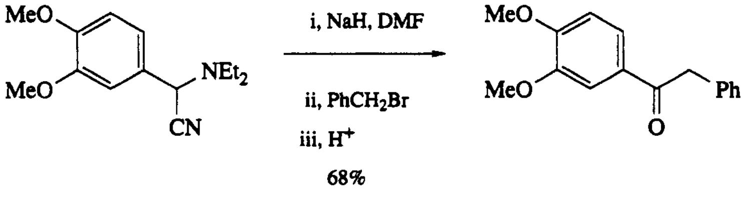

(42)

### 2.5.7.3 Pyridinium Salts

The classic Krohnke aldehyde synthesis results from the displacement of pyridinium salts by aromatic nitroso compounds to give nitrones which are hydrolyzed to aldehydes.[139] Phenacyl bromide reacts with pyridine and then nitrosobenzene to give phenylglyoxal in 76% yield after acid hydrolysis.[140] The pyridinium salts in these reactions must be activated in some way toward displacement to effect efficient conversions.

### 2.5.7.4 Hydrazones/Oximes

Lead tetraacetate converts hydrazones to carbonyl compounds plus the corresponding alcohols. For example, benzophenone hydrazone is converted into benzophenone in 36–67% yields plus lesser amounts of benzhydrol.[141,142] Substituted ketone hydrazones give α-acetoxyazo compounds with 1 equiv. of lead tetraacetate,[143] although 2 equiv. of lead tetraacetate results in ketones. This also has been observed with tosylhydrazones.[144] Arylhydrazones of aldehydes give diacylhydrazines (equation 43).[145,146]

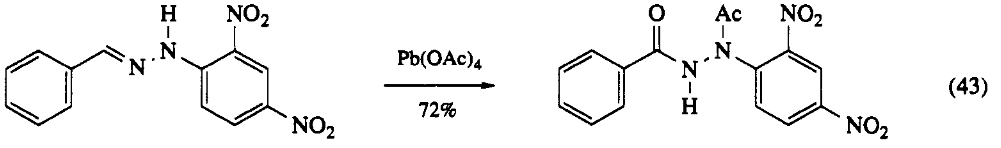

(43)

Lead tetraacetate oxidizes oximes to various products. For example, the oxime of cyclohexanone gives α-acetoxynitrosocyclohexane in 35% yield.[147] Aldoximes react with lead tetraacetate to give nitrile oxides which then yield acetyl hydroxamates by reaction with acetic acid.[148]

Miscellaneous derivatives are hydrolyzed back to the starting carbonyl compounds. Phenylhydrazones of ketones are converted into the parent ketones upon treatment with manganese dioxide.[149] Tosylhydrazones react with molybdenyl chloride[150] or tungsten tetrafluoride[151] to give both aldehydes and ketones. Sodium peroxide converts aldoximes into carboxylic acids.[152]

The anions of hindered hydrazones allow the introduction of electrophiles at the α-position, thus functioning as acyl anion equivalents after isomerization back to a hydrazone and hydrolysis.[153,154] For example, the *t*-butylhydrazone of acetaldehyde gives phenylacetone following the sequence of reactions shown in equation 44.

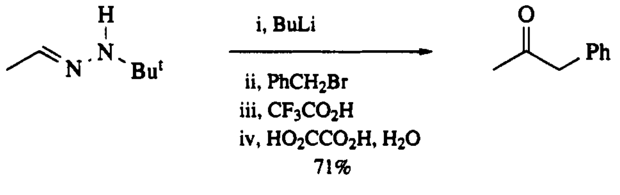

(44)

### 2.5.7.5 Isocyanides

Isocyanides similarly upon deprotonation and alkylation give amines or ketones after hydrolysis. For example, methyl isocyanide reacts with butyllithium, allyl bromide, and aqueous acid to give 3-butenamine.[155] Tosylmethyl isocyanide (TOSMIC) can be deprotonated with excess sodium hydride in DMSO, alkylated twice with benzyl bromide and hydrolyzed with acid and then base to give 1,3-diphenylpropanone.[156]

### 2.5.7.6 Nitrones

Certain nitrones react with acylating agents and then rearrange to give products having an oxygen group adjacent to the nitrogen of the original nitrone, somewhat reminiscent of the Polonovski reaction reported earlier.[157,158] An example is the reaction shown in equation (45).

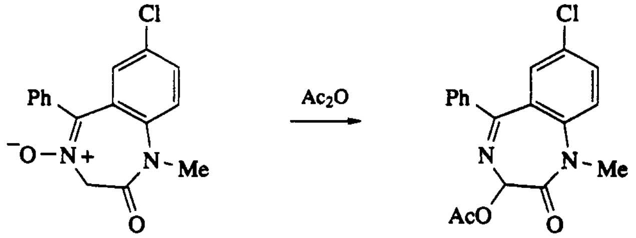

(45)

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# 2.6

# Oxidation Adjacent to Oxygen of Ethers

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## 2.6.1 INTRODUCTION

In the presence of certain oxidants, ethers possessing at least one C—H bond at the position adjacent to oxygen are susceptible to oxidation. The light-induced oxidation of diethyl ether in air is a well-known example of this phenomenon. In most instances, oxidative attack leads, *via* the intermediacy of carbonium ions or free radicals, to either esters (or lactones) or α-substituted ethers. Subsequent breakdown under the reaction conditions may then lead to mixtures of cleavage products, which can in turn suffer further oxidation. In principle, therefore, a wide range of products can result during the oxidation of an ether, depending on the nature of the substrate, the oxidant and the experimental conditions employed.

Although a number of different reagents have been discovered for the selective oxidation of ethers, *e.g.* halogens,[1] iodine tris(trifluoroacetate),[2] trichloroisocyanuric acid,[3] $UF_6$,[4] *N,N*-dibromobenzenesulfonamide[5] and lead tetraacetate,[6] few have assumed any synthetic importance. Of these, the most significant are the metallic oxidants chromic acid and ruthenium tetroxide. DDQ has also been widely used for the oxidative deprotection of benzyl ethers. It is the aim of this chapter to review the latest developments in ether oxidation by these, and other reagents, with particular emphasis on chemo- and regio-selectivity. Several reviews on the subject have appeared previously.[7–11] The related oxidation of acetals has been reviewed recently[11] and will not be dealt with here.

## 2.6.2 METALLIC OXIDANTS

### 2.6.2.1 Introduction

Most of the metallic oxidants which have been used for the oxidation of ethers have been based on oxides of the transition metals chromium, manganese and ruthenium, the latter being of greatest synthetic importance. The first reported example of the application of ruthenium tetroxide in the oxidation of ethers appeared over 30 years ago in 1958,[12] although an indication of its reactivity towards ethers had been obtained some years before.[13] In a systematic study which revealed the powerful oxidizing properties of the reagent, Berkowitz and Rylander demonstrated the quantitative conversion of tetrahydrofuran and *n*-butyl ether into γ-butyrolactone and butyl butyrate, respectively.[12] Significantly, no overoxidation was observed. Apart from an unsuccessful attempt to oxidize ethylene oxide, no further attempts were made by the authors to examine further the scope of this novel transformation. In a series of subsequent publications[14,15] and a patent,[16] Wolf and his coworkers went on to exploit the reaction in the preparation of aldosterone and related steroids (equation 1).

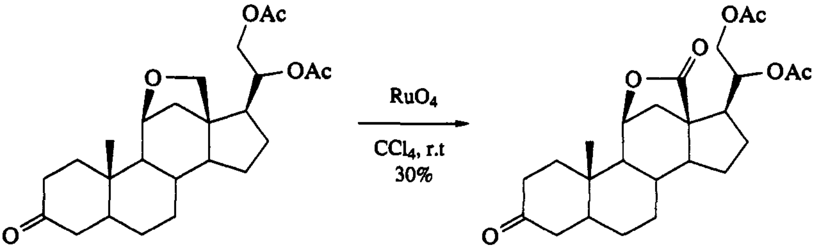

(1)

In 1959, Henbest and Nicholls reported the conversion of the ether (**1**) into the corresponding lactone (**2**), on treatment with chromic acid in acetone at room temperature (equation 2).[17] Mechanistic studies on the oxidation of ethers by both ruthenium tetroxide[18] and chromic acid[19] were duly carried out. A more detailed analysis of the mechanistic aspects of these reagents appears in a review published by Müller.[7]

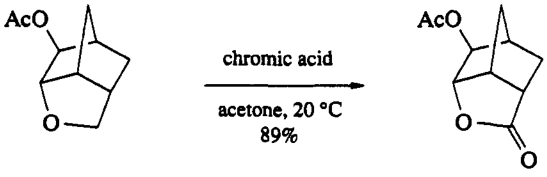

(2)

(**1**) (**2**)

Despite these early successes, few synthetic chemists appeared to recognize the potential of metallic oxidants for the oxidation of ethers to esters and lactones, and only a few further developments were published prior to 1980.[20–24] Since that time, as the chemistry of these reagents has become better understood, their use has increased dramatically to the stage where they are now the reagents of choice for many applications, including complex natural product synthesis.

Although most attention has been focused on ruthenium tetroxide and chromium trioxide, some other variants have appeared in the literature which are worthy of note. For example, a Merck group reported that *t*-butyl chromate was effective in the transformation of the spiro ether (**3**) into the corresponding lactone (**4**; equation 3).[25] The use of ruthenium tetroxide, on the other hand, led to extensive side reactions. Benzyltriethylammonium permanganate,[26] zinc dichromate[27] and zinc permanganate supported on silica gel[28] are all potent oxidants, which react readily with a wide range of substrates, including simple ethers. The full scope of these reagents, however, remains essentially unexplored. *cis*-$[Ru^{VI}(6,6'\text{-}Cl_2bpy)_2O_2][ClO_4]_2$ has recently been reported to oxidize a wide variety of substrates, including tetrahydrofuran, to butyrolactone.[29] Trömel and Russ have described the preparation and reactions of dimanganese heptoxide ($Mn_2O_7$) as dilute solutions in carbon tetrachloride or Freon 113.[30] This potentially explosive oxidant reacts within minutes with ethers at −45 °C to afford lactones or esters in high yield. However, even at this temperature, other functional groups, such as alkenes, alcohols and aromatic systems, are attacked.

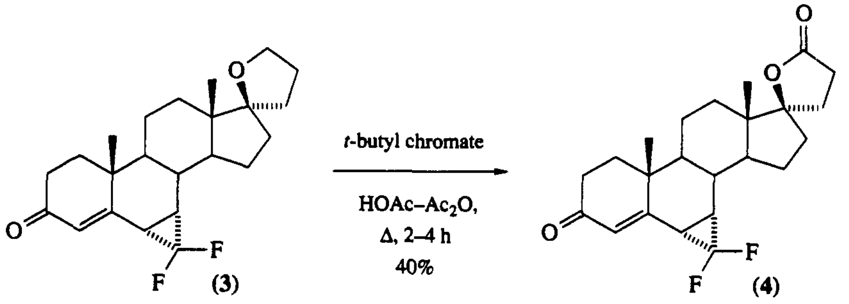

(3)

Cyclic ethers are oxidized to lactones in the presence of cerium(IV) salts.[31] Treatment of tetrahydrofuran with cerium(IV) ammonium nitrate in the presence of primary, secondary or tertiary alcohols leads to the formation of the corresponding tetrahydrofuranyl ethers in quantitative yield.[31] Furthermore, 4-methoxybenzyl ether derivatives of carbohydrates are selectively deprotected to the parent alcohols on reaction with cerium(IV) ammonium nitrate in aqueous acetonitrile.[32–34]

Finally, oxidative cyclization (HgO, I$_2$, *hν*) of appropriately substituted alcoholic ethers formed the basis of Kay's stereoselective syntheses of both 4-hydroxy-1,7-dioxaspiro[5.5]undecane, an olive fly pheromone component,[35] and (±)-talaromycin B (equations 4 and 5).[36] More recently, Danishefsky *et al.* have further extended the scope of this spiroketal-forming reaction in their elegant total synthesis of avermectin A$_{1a}$ (equation 6).[37]

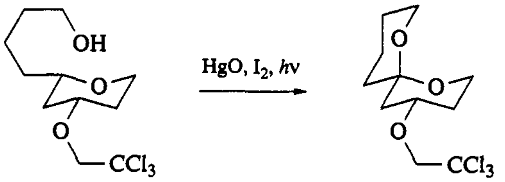

(4)

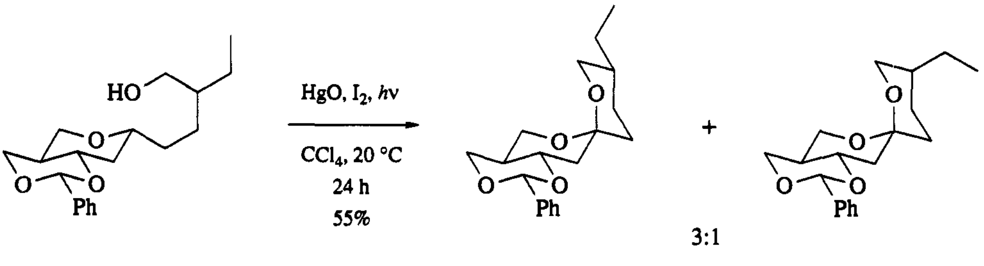

(5)

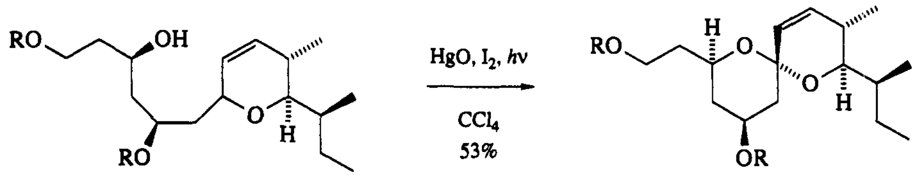

(6)

### 2.6.2.2 Reaction Conditions

The chromium-based reagents, particularly chromium trioxide, are commonly used in solution in acetic acid and/or acetic anhydride, or occasionally in a less polar organic solvent, such as dichloromethane. The high reactivity of zinc permanganate was effectively controlled by supporting the reagent on silica gel and carrying out its reactions in dichloromethane.[28] The reagents are used in stoichiometric quantities, or in excess, and reactions are generally carried out at room temperature or above.

Much of the early work with ruthenium tetroxide also made use of stoichiometric amounts of a solution of the reagent in an inert solvent, such as carbon tetrachloride. Reactions were carried out at room temperature. The general acceptance of the reagent as a powerful wide-ranging oxidant,[38] coupled with the expense of ruthenium metal, however, later provided the incentive to develop alternative catalytic procedures. In 1980, Smith and Scarborough published details of a systematic study of ether oxidation by ruthenium tetroxide in which they compared the relative merits of both the stoichiometric and the two-phase catalytic methods.[39] In the latter case, catalytic quantities of the reagent were generated by vigorously stirring a mixture of ruthenium dioxide in carbon tetrachloride with an aqueous solution of sodium periodate at room temperature. Good yields of esters and lactones were obtained from a series of simple ethers using the stoichiometric method (equations 7 and 8). When the two-phase catalytic method was employed, however, reaction times were long, and products unstable to aqueous conditions tended to undergo further oxidation to the corresponding carboxylic acids (equations 9 and 10). Similar results were obtained in a later study using catalytic ruthenium chloride and sodium or calcium hypochlorite as the stoichiometric oxidant under phase transfer conditions.[40] The use of sodium hypochlorite as cooxidant in the oxidation of the bicyclic ketone (**5**) led preferentially to the formation of the Baeyer–Villiger product (**6**), whereas sodium periodate gave the lactone (**7**; Scheme 1).[41]

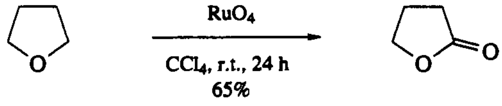

(7)

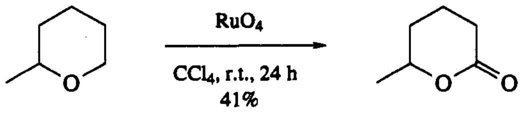

(8)

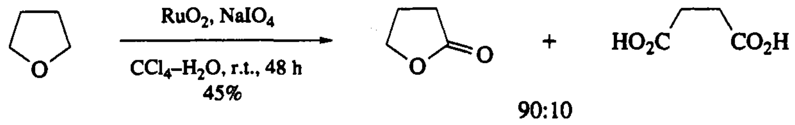

(9)

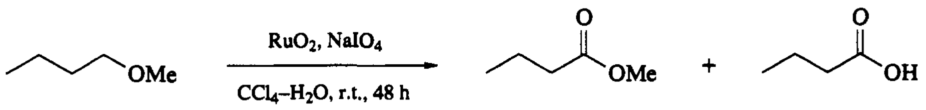

(10)

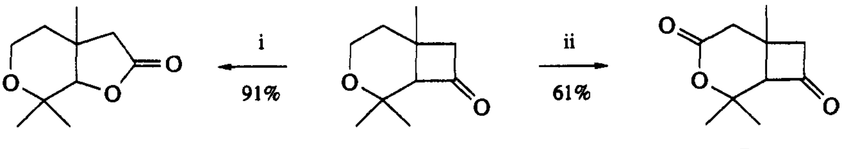

(**6**) (**5**) (**7**)

i, $RuCl_3$, NaOCl, $H_2O$–$CCl_4$, r.t., 5 h; ii, $RuCl_3$, $NaIO_4$, $H_2O$–$CCl_4$, r.t., 18 h

**Scheme 1**

In the acetonitrile modification reported by Sharpless and coworkers, hydrolysis apparently does not take place to any appreciable extent.[42] Consequently the yield of ester can be significantly increased (equation 11). This improved procedure, along with some minor variants,[43] therefore appears to be the method of choice for effecting the oxidation of ethers with ruthenium tetroxide, and has been widely adopted.

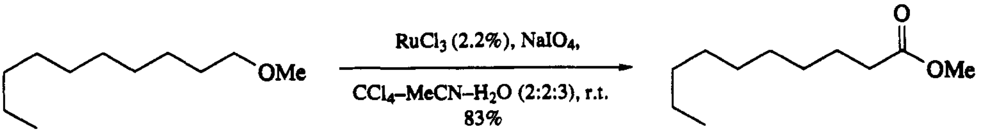

(11)

### 2.6.2.3 Selectivity of Reaction and Application in Synthesis

Since most of the synthetic applications described to date have involved the oxides of chromium and ruthenium, the discussion on reaction selectivity will be limited to these reagents. Even so, much work still remains to be done before the outcome of reactions on complex substrates can be predicted with absolute certainty.

Simple symmetrical ethers, such as tetrahydrofuran or *n*-butyl ether, and ethers possessing only one unsubstituted α-carbon atom and no other functional groups, clearly present no problems in terms of selectivity of reaction (*e.g.* equation 12).[44] In the absence of overriding steric effects, the reaction of simple unsymmetrical ethers with ruthenium and chromium oxidants generally proceeds with high regioselectivity. With complex substrates, however, mixtures of products are often produced.

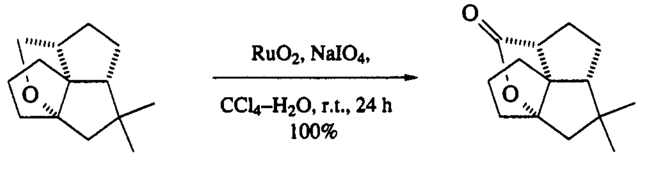

(12)

The relative reactivity of primary and secondary positions adjacent to oxygen can be strongly dependent on the nature of the oxidant. For example, treatment of the methyl ethers (**8**)[45] and (**10**)[46] with chromium trioxide in acetic acid leads to the formation of the formates (**9**) and (**11**), respectively (equations 13 and 14). In direct contrast, *n*-decyl methyl ether is oxidized exclusively to methyl *n*-decanoate (83% yield) by ruthenium tetroxide (equation 11).[42] Under similar reaction conditions, 3β-cholestanol methyl ether gives cholestan-3-one as the major product, together with traces of the corresponding formate.[42] Therefore, at least in the case of ruthenium tetroxide, primary positions appear to be more reactive than tertiary.

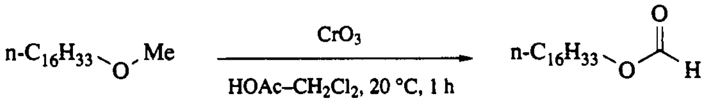

**(8)** **(9)** (13)

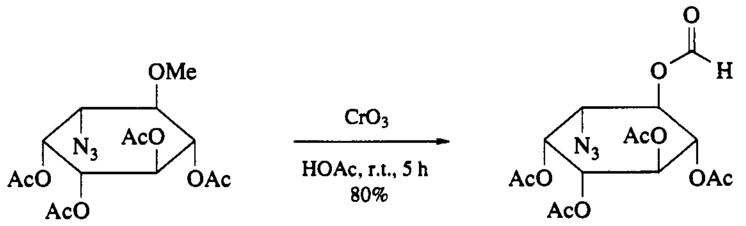

**(10)** **(11)** (14)

Secondary positions tend to be more reactive towards oxidation than tertiary positions, unless steric hindrance dictates otherwise. Good examples of this are the chromic acid oxidation of the ether (**12**)[47] and the ruthenium tetroxide oxidation of the ether (**13**),[48] both of which lead to lactone formation (Scheme 2). Oxidation of the quassinoid intermediate (**14**), on the other hand, is completely nonselective (equation 15).[49]

Salomon and coworkers observed high levels of selectivity in the oxidation of a series of polycyclic tetrahydrofuran derivatives.[50] Thus, reaction of the tricyclic ethers (**15**; $n = 2, 5$) with ruthenium tetroxide gave the corresponding lactones (Scheme 3). Conversely, the ether (**16**) afforded the lactol (**17**) as the major product of oxidation, together with small amounts of the corresponding lactone (**18**). Similarly, during the synthesis of both enantiomers of grandisol, Mori observed that the regioselectivity of ruthenium tetroxide oxidations was strongly dependent on steric factors (Scheme 4).[51] A further example is provided by Mori's work on the synthesis of both enantiomers of the spiroketal (**19**), a key intermediate in the synthesis of talaromycins A and B (equation 16).[52]

Predictably, when two secondary positions are available for reaction, mixtures of products ensue, with the reaction favoring the less hindered position.[50]

Allylic and benzylic ethers appear to be particularly susceptible to oxidation, and very high selectivities are often observed. For example, selective oxidation of the allylic ethers (**20**)[53] and (**21**)[54] has provided new methods for the synthesis of α-methylene-γ-butyrolactones (Scheme 5). Similarly, on

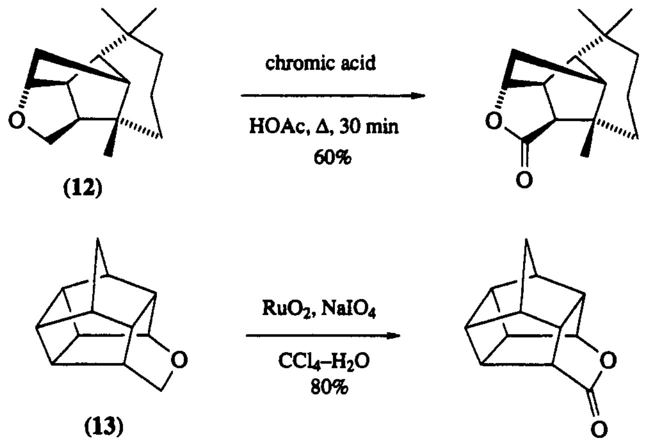
(12)
chromic acid
HOAc, Δ, 30 min
60%
(13)
RuO2, NaIO4
CCl4-H2O
80%

**Scheme 2**

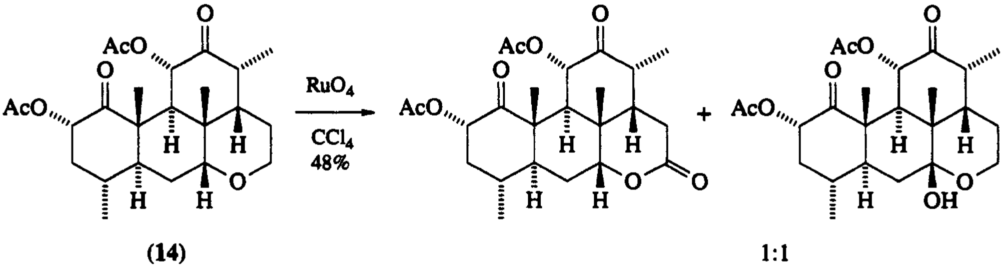
(14)
RuO4
CCl4
48%
1:1

(15)

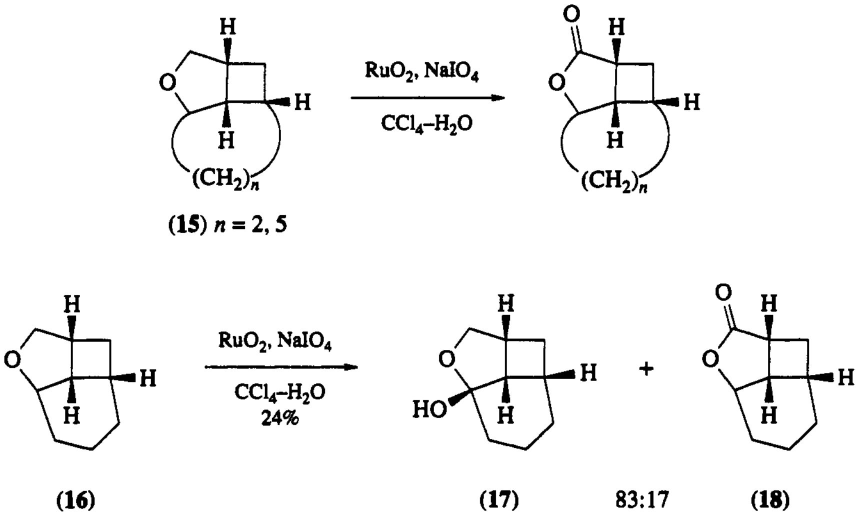
(15) n = 2, 5
RuO2, NaIO4
CCl4-H2O
(16)
RuO2, NaIO4
CCl4-H2O
24%
(17)
83:17
(18)

**Scheme 3**

treatment with pyridinium chlorochromate, the ether (22) afforded anhydromevalonolactone, an intermediate in the synthesis of pheromones and verrucarinic acid (equation 17).[55]

Benzylic oxidation using chromium reagents has been reviewed previously.[56] More recently, Pinnick's group has demonstrated that the Jones reagent readily oxidizes benzyl ethers.[57] However, selectivity is poor and mixtures of products result (equation 18). Collins reagent behaved similarly, whereas under the same conditions, pyridinium dichromate was ineffective. In contrast, catalytic oxidation of benzyl methyl ether with ruthenium tetroxide afforded methyl benzoate in excellent yield and none of the corresponding formate was detected.[42] Benzyl ethyl ether reacts similarly under these conditions.[58] During their work on the synthesis of coriolin, Schuda and coworkers carried out a systematic study of the ruthenium tetroxide oxidation of benzyl ethers of primary, secondary and tertiary alcohols to the corresponding ben-

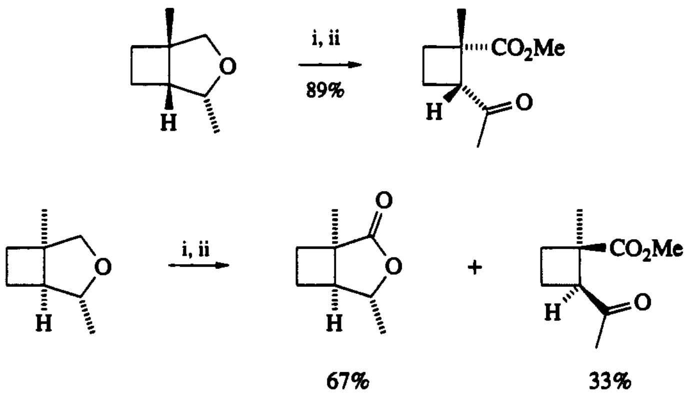
i, ii
89%
CO2Me
O
H
i, ii
H
67%
+
33%

i, $RuO_2$, $NaIO_4$, $CCl_4$–MeCN–phosphate buffer (pH 7), r.t., 12 h; ii, $CH_2N_2$, $Et_2O$

**Scheme 4**

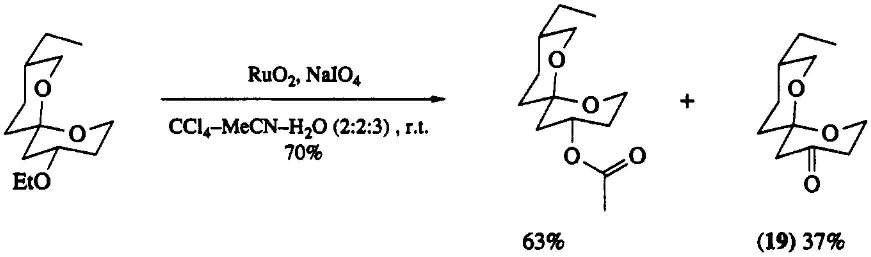
EtO
$RuO_2$, $NaIO_4$
$CCl_4$-MeCN-$H_2O$ (2:2:3), r.t.
70%
+
63%
(19) 37%

(16)

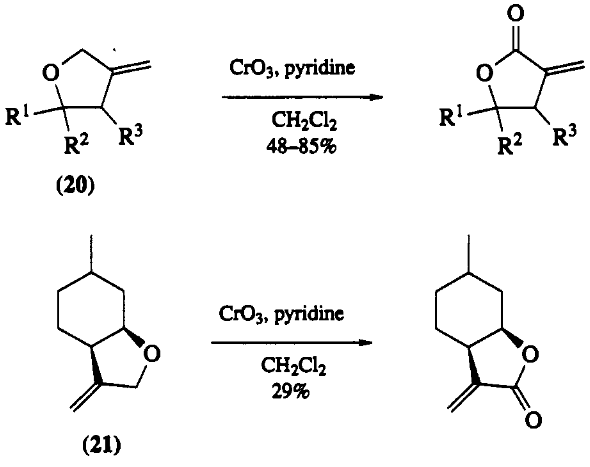
$R^1$
$R^2$
$R^3$
(20)
$CrO_3$, pyridine
$CH_2Cl_2$
48–85%
(21)
$CrO_3$, pyridine
$CH_2Cl_2$
29%

**Scheme 5**

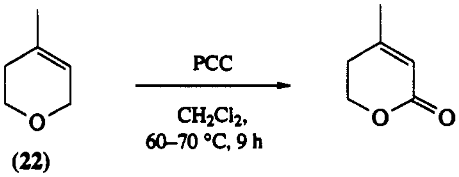
(22)
PCC
$CH_2Cl_2$,
60–70 °C, 9 h

(17)

zoates, in the presence of other functional groups.[59] They found that ethyleneketals, acetonides, benzoates and aromatic rings (including pyridine) were stable under the reaction conditions, but that other functional groups, such as alkenes and alcohols, were also oxidized. Interestingly, benzyl ethers of phenols appeared to resist oxidation.

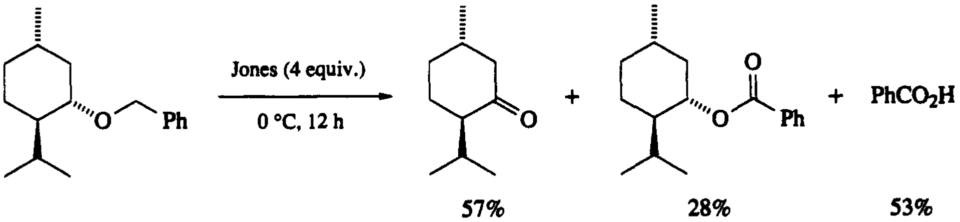
Ph
Jones (4 equiv.)
0 °C, 12 h
O
O
O
Ph
+
+ PhCO$_2$H
57%
28%
53%

(18)

Further examples of ether oxidation in natural product synthesis have been published recently which serve to illustrate the levels of selectivity which can be achieved with these reagents. For example, the high yielding oxidation of the ether (**23**) was a key step in model studies directed at the synthesis of taxane (equation 19).[60] In this case, stoichiometric amounts of ruthenium tetroxide were employed. In an alternative photochemical approach to the taxane skeleton, Berkowitz and coworkers achieved a 92% yield in the oxidation of the intermediate (**24**) with catalytic ruthenium tetroxide (equation 20).[61] During their work on the synthesis of the highly oxygenated sesquiterpene anisatin, Niwa's group was able to obtain the lactone (**25**) in 93% yield (equation 21).[62] As part of a programme aimed at the synthesis of known

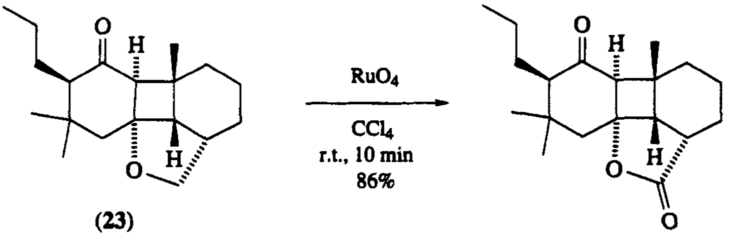
O
H
H
O
RuO$_4$
CCl$_4$
r.t., 10 min
86%
O
H
H
O
O

(**23**)

(19)

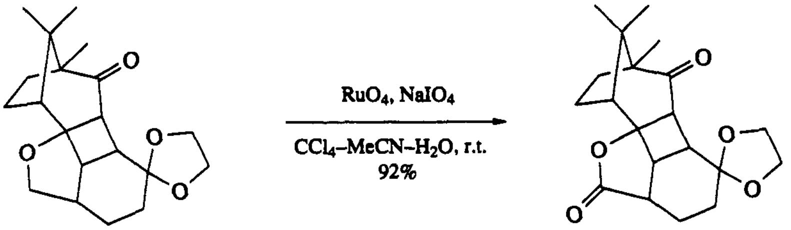
O
O
O
O
RuO$_4$, NaIO$_4$
CCl$_4$–MeCN–H$_2$O, r.t.
92%
O
O
O
O
O

(**24**)

(20)

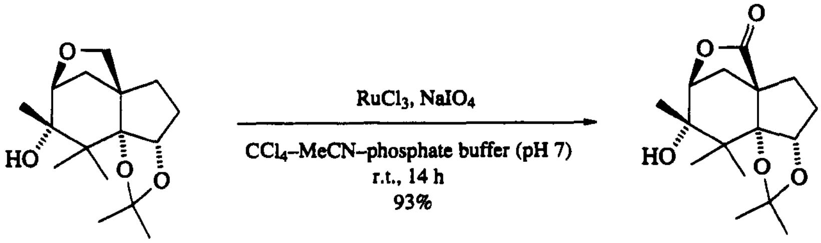
O
HO
O
O
RuCl$_3$, NaIO$_4$
CCl$_4$–MeCN–phosphate buffer (pH 7)
r.t., 14 h
93%
O
O
HO
O
O

(**25**)

(21)

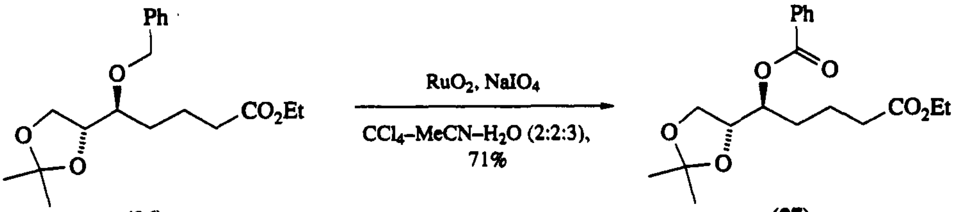
Ph
O
CO$_2$Et
O
O
RuO$_2$, NaIO$_4$
CCl$_4$–MeCN–H$_2$O (2:2:3),
71%
Ph
O
O
CO$_2$Et
O
O

(**26**)

(**27**)

(22)

intermediates to leukotrienes $B_4$ and $A_4$ from D-arabinose, the intermediate benzyl ether (**26**) was selectively converted into the corresponding benzoate (**27**) in 71% yield (equation 22).[63] Finally, on treatment with chromium trioxide in acetic acid–acetic anhydride, the enone (**28**) furnished the lactone (**29**), a key intermediate in the total synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A (equation 23).[64]

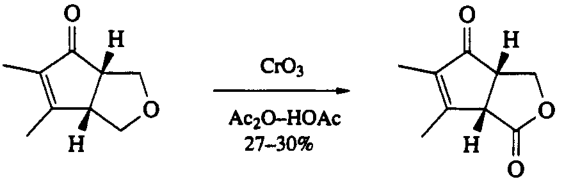

O
H
H
O
CrO3
Ac2O–HOAc
27–30%
O
H
H
O
O

(23)

**(28)** **(29)**

Where functional groups are present which are more readily oxidized than the ether group, multiple reactions can occur. For example, in their total synthesis of (+)-tutin and (+)-asteromurin A, Yamada *et al.* observed concomitant oxidation of a secondary alcohol function in the oxidation of the ether (**30**) with ruthenium tetroxide (equation 24).[65] The same group successfully achieved the simultaneous oxidation of both ether functions of the intermediate (**31**) in their related stereocontrolled syntheses of (–)-picrotoxinin and (+)-coriomyrtin (equation 25).[66] Treatment of karahana ether (**32**) with excess ruthenium tetroxide resulted in the formation of the ketonic lactone (**33**) *via* oxidation of both the methylene group adjacent to the ether function and the exocyclic alkenic group (equation 26).[67] In contrast, ruthenium tetroxide oxidation of the steroidal tetrahydrofuran (**34**) gave as a major product the lactone (**35**) in which the alkenic bond had been epoxidized.[68] A small amount of the 5,6-deoxylactone (17%) was also isolated (equation 27). This transformation formed the basis of a facile introduction of the ecdysone side chain into C-20 keto steroids.

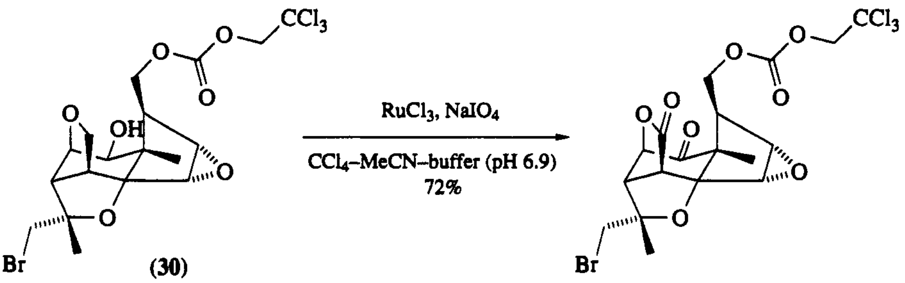

CCl3
O
O
O
O
OH
O
O
Br
RuCl3, NaIO4
CCl4–MeCN–buffer (pH 6.9)
72%
CCl3
O
O
O
O
O
O
O
O
Br

**(30)**

(24)

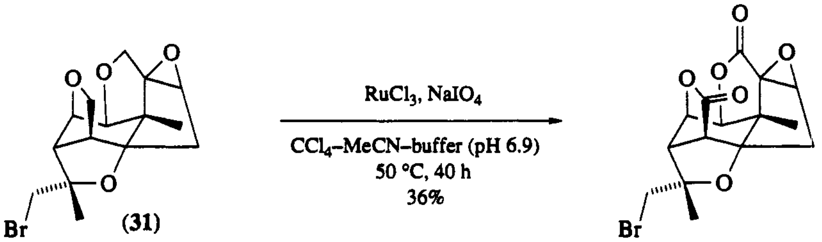

O
O
O
O
Br
RuCl3, NaIO4
CCl4–MeCN–buffer (pH 6.9)
50 °C, 40 h
36%
O
O
O
O
O
O
Br

**(31)**

(25)

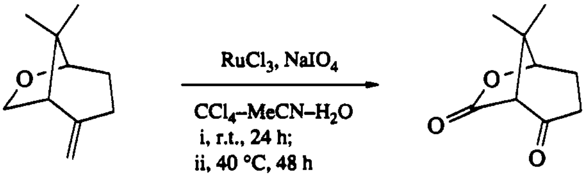

O
RuCl3, NaIO4
CCl4–MeCN–H2O
i, r.t., 24 h;
ii, 40 °C, 48 h
53%
O
O
O

(26)

**(32)** **(33)**

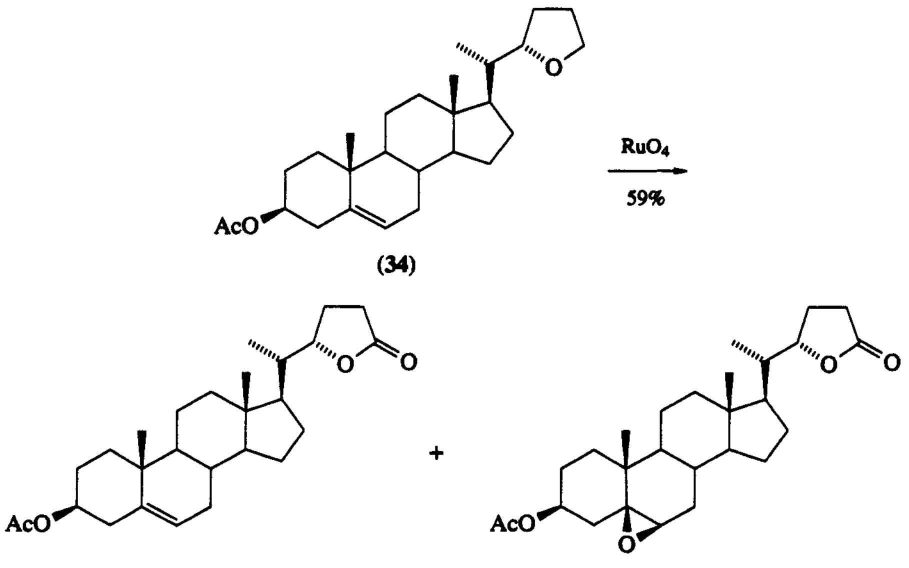

(34)

17%

(35) 83%

(27)

## 2.6.3 HYDRIDE TRANSFER REAGENTS

### 2.6.3.1 Introduction

In the early 1970s, Barton *et al.* published the results of their work on the oxidation of acetals and ethers by hydride transfer.[69,70] They observed that substituted benzyl ethers and benzyloxy carbonates, on brief exposure to trityl tetrafluoroborate in dichloromethane at 0 °C followed by aqueous work-up, afforded good yields of the parent alcohols together with the corresponding benzaldehydes. Under the same conditions, the tetrahydropyranyl ether of cholesterol was also efficiently deprotected. A mechanism was proposed which involved an initial hydrogen abstraction, followed by quenching of the resulting stabilized cation by water (Scheme 6).

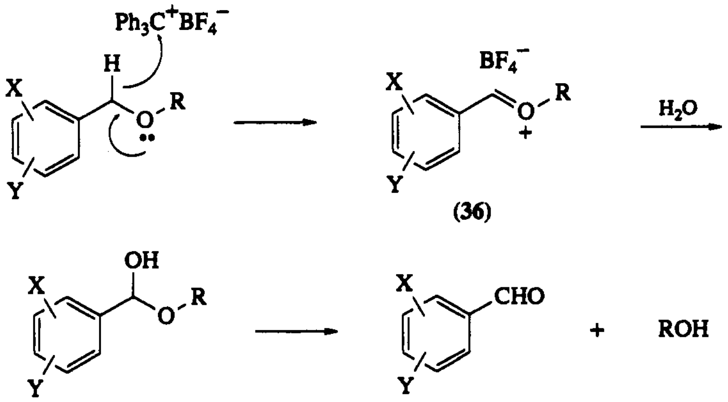

Scheme 6

Ten years later, a Japanese group led by Oikawa developed a mechanistically related method for the selective debenzylation of substituted benzyl ethers based on the reagent 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[71] In contrast to the trityl tetrafluoroborate reaction, the oxidation proceeds at room temperature in the presence of water. Furthermore, under these convenient and essentially neutral conditions, many functional groups, including other common protecting groups, such as isopropylidine, methoxymethyl, benzyloxymethyl, tetrahydropyranyl, acetyl, *t*-butyldimethylsilyl, benzyl, benzoyl and tosyl, are unaffected. As a result of the high levels of selectivity which can be achieved, this method for the deprotection of other derivatives of alcohols and related functional groups[72] has been widely used in the synthesis of complex molecules. In view of its importance, a more detailed analysis of this reaction will follow.

### 2.6.3.2 Reaction Conditions

Typically, the deprotection sequence involves treatment of the substrate with a 10% excess of DDQ at room temperature in an organic solvent containing traces of water.[73] Although the reaction can take place in aqueous methanol or tetrahydrofuran, reaction rates are slow, and dichloromethane containing approximately 5% water is vastly superior. Aqueous toluene is also occasionally employed. Under these conditions, the weakly acidic 2,3-dichloro-5,6-dicyanohydroquinone by-product is precipitated from solution as the reaction proceeds, and consequently the reaction medium is kept essentially neutral. Reaction times vary according to the reactivity of the benzyl ether function, unsubstituted benzyl groups requiring much longer reaction times than either 4-methoxybenzyl (MPM) or 3,4-dimethoxybenzyl (DMPM) groups. Aliphatic ethers are essentially unreactive.

### 2.6.3.3 Selectivity of Reaction and Application in Synthesis

The greater reactivity of MPM ethers with respect to unsubstituted benzyl ethers and aliphatic ethers can be attributed to the increased stabilization by the 4-methoxy substituent of a cationic intermediate of type (**36**; Scheme 6). The selectivity between these groups has been exploited in the synthesis of a variety of natural products, including octosyl acid A,[74] oligosaccharides,[75,76] inositol phosphates,[77,78] and the polyether antibiotics X-206[79] and salinomycin (equation 28).[80]

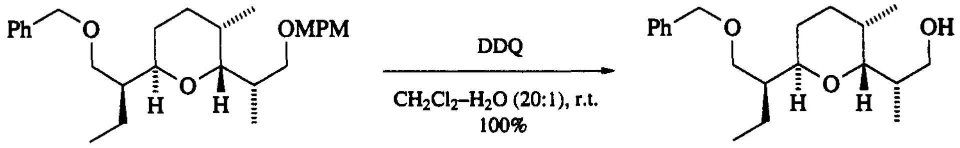

(28)

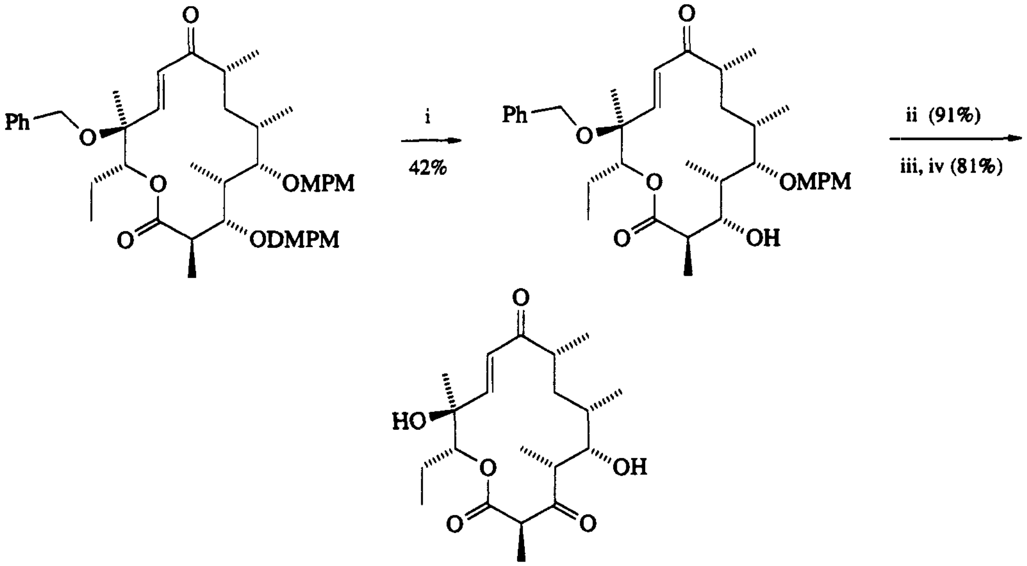

Pikronolide

i, DDQ, toluene–$H_2O$ (20:1), 0 °C, 4.5 h; ii, Swern; iii, DDQ, $CH_2Cl_2$–$H_2O$ (20:1), r.t., 5 min; iv, DDQ, $CH_2Cl_2$–$H_2O$ (20:1), r.t., 19 h

Scheme 7

The additional presence of a 3-methoxy substituent on the benzyl group confers greater stability on the intermediate cation, and consequently oxidation of DMPM ethers by DDQ is even more facile.[81,82] Yonemitsu and coworkers have used this differential reactivity of substituted benzyl ethers to great effect in the total synthesis of the macrolide antibiotics methynolide,[83] tylonolide,[84] (9*S*)-9-dihydroerythronolide A[85] and pikronolide.[86] The pikronolide synthesis provides an excellent example of the selective, sequential deprotection of DMPM, MPM and benzyl ether protecting groups (Scheme 7).

Recently, as part of their work on the biosynthesis of the ergot alkaloids, Kozikowski and Wu developed the use of (4-methoxybenzyloxy)methyl ethers as alcohol-protecting groups which can be removed oxidatively.[87] MPM ethers, however, are normally much more reactive towards oxidation than benzyloxymethyl (BOM) ethers. Thus, in the synthesis of aplysiatoxin and debromoaplysiatoxin, Kishi's group obtained the unstable diol (**38**) in 70% yield on treatment of the intermediate (**37**) with DDQ in dichloromethane–water at room temperature.[88] Following macrolactonization, the benzyloxymethyl groups were deprotected by hydrogenolysis. DDQ oxidation of a DMPM ether in the presence of an unprotected secondary alcohol and a benxyloxymethyl ether has also been used to selectively unmask the anomeric center of the zincophorin intermediate (**39**; equation 29).[89] Other examples of the selective deprotection at the anomeric center of carbohydrates have also been reported.[90,91] Allyl disaccharides containing MPM protecting groups are selectively deprotected on treatment with DDQ, whereas cerium(IV) ammonium nitrate leads to overoxidation.[92]

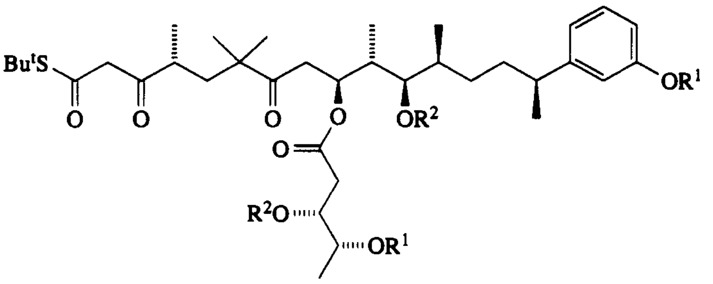

(**37**) $R^1$ = BOM, $R^2$ = MPM

(**38**) $R^1$ = BOM, $R^2$ = H

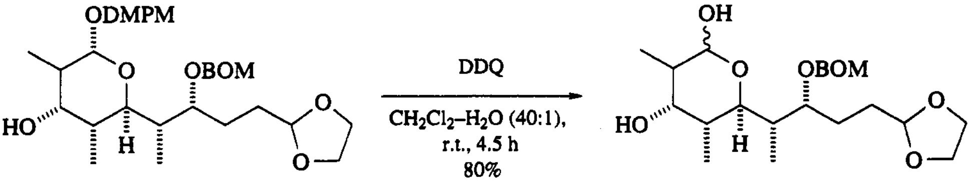

(**39**)

3:2 mixture of anomers

(29)

In cases where readily oxidized functional groups are also present in either the substrate or the product of the reaction, overoxidation can occur. However, this can sometimes be advantageous. For example, in the total synthesis of (±)-sterepolide Trost and Chung effected the deprotection of the MPM ether (**40**) with DDQ in moist dichloromethane.[93] Under the conditions of the reaction, further oxidation of the allylic alcohol took place to afford the final product (equation 30). However, separate treatment of the allylic alcohol with PDC in dichloromethane was found to be more effective. Similarly, treatment of the ether (**41**) with pyridinium tosylate followed by excess DDQ afforded the Ireland alcohol (**42**), a key intermediate for the synthesis of tirandamycin A (equation 31).[94] Propargylic alcohols, however, would appear to be less susceptible to oxidation.[95]

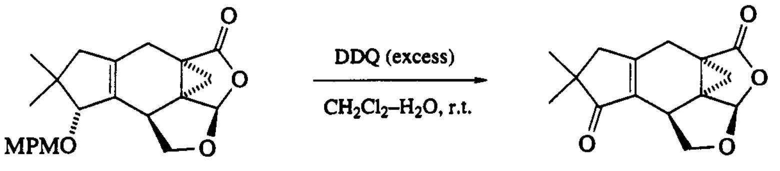

(**40**)

(±)-Sterepolide

(30)

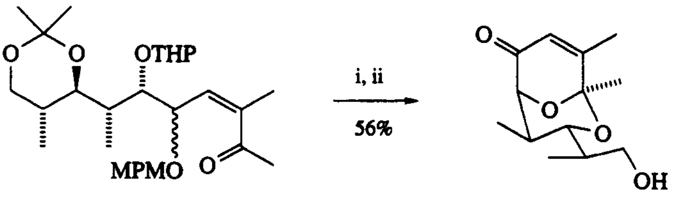

(41) (42)

(31)

i, pyridine–TsOH, MeOH; ii, DDQ, $CH_2Cl_2$–$H_2O$

## 2.6.4 OTHER METHODS

### 2.6.4.1 Oxygen and Ozone

Few synthetically useful examples of the oxidation of ethers by oxygen or ozone have been published.[7,96–100] In 1978, Ourisson and coworkers reported that ozonization of the natural product cedrane oxide (**43**) on silica gel at –78 °C led to the formation of the corresponding lactone (**44**) in 30% yield (equation 32).[101] A small amount of the tertiary alcohol (**45**) was also produced. Later, in the course of a chiral total synthesis of compactin, Hirama examined the ozonolysis of the alkene (**46**; equation 33).[102] Under carefully controlled conditions, selective ozonolysis of the double bond could be achieved in 88% yield. However, when excess ozone was employed, significant amounts of the benzoate (**47**) were obtained, even at –78 °C. In subsequent studies, benzyl ethers of primary and secondary alcohols,[103] and carbohydrates[104] were oxidized to the corresponding benzoates in excellent yields. Surprisingly, no further synthetic applications of this reaction have been reported.

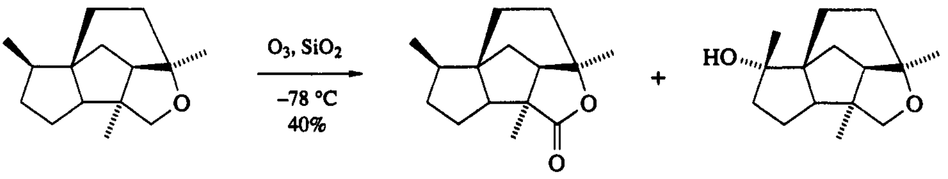

(43) (44) 75% (45) 25%

(32)

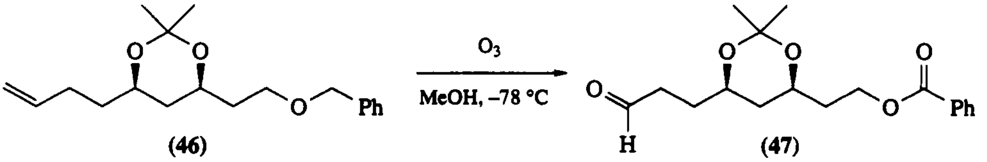

(46) (47)

(33)

### 2.6.4.2 Peracids and Related Reagents

During the course of a kinetic study on the oxidation of *trans*-stilbene with peroxyphosphoric acid ($H_3PO_5$), Ogata and coworkers observed the unexpected oxidation of the reaction solvent tetrahydrofuran to γ-butyrolactone.[105] However, although *n*-butyl ether was also oxidized by this reagent, tetrahydropyran and dioxane were apparently inert. Ethers undergo oxidation on treatment with 4-nitroperbenzoic acid in chloroform.[106] Moderate yields of esters and lactones are obtained when simple ethers are treated with calcium hypochlorite.[107] At room temperature, reaction times of 4–16 h are necessary. However, primary and secondary alcohols are readily oxidized under these conditions.

### 2.6.4.3 Electrochemical Oxidation

Several reports on the electrochemical oxidation of ethers have appeared in the literature within the last 10 years, although few have been of direct relevance to the synthetic chemist. The electrochemical α-hydroxylation of tetrahydrofuran in aqueous electrolytes has been investigated recently in some detail.[108] Shono *et al.* have shown that good yields of α-methoxylated products can be obtained *via* the anodic oxidation of aliphatic ethers in methanol and acetic acid.[109] Several groups have worked on the electrochemical oxidation of benzyl ethers.[110–112]

A novel procedure for the oxidative removal of benzyl protecting groups by catalytic homogeneous electron transfer has been developed by Schmidt and Steckhan (equation 34).[113] The selectivity of the reaction can be adjusted by altering the substitution on the aromatic rings of the cation radicals (**48**). Finally, a recent publication describes a photoinduced single electron transfer initiated oxidative cleavage of benzylic ethers.[114]

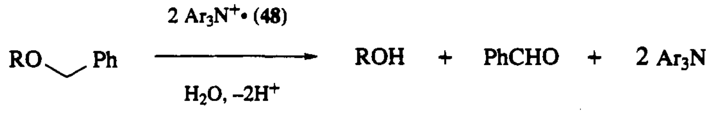

(34)

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# 2.7

# Oxidation Adjacent to Oxygen of Alcohols by Chromium Reagents

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## 2.7.1 INTRODUCTION

Chromium-based oxidants are probably the most widely used of all oxidizing agents. Over the years they have been continually developed and modified to overcome the typical problems that occur during oxidation and to accept wider ranges of substrates with improved selectivities. They have been accepted readily by synthesis chemists since they are easy to handle and are often 'off the shelf reagents'. However, they are not without their problems: work-up can be problematical; overoxidation can occur; and, at all times, removal of the product from toxic chromium contaminants is a concern, especially with respect to large scale preparations. In an attempt to circumvent these problems the trend has been to develop the use of catalytic and/or supported reagents. This review is concerned for the most part with the applications and limitations of more recent chromium(VI) oxidants. Several other comprehensive reviews have appeared in this area and should be consulted for more detailed descriptions of older methods, chromium(V) oxidants, mechanism of oxidation and for typical experimental procedures.[1–5]

## 2.7.2 CHROMIUM(VI) IN ACIDIC MEDIA

Many of the early methods devised around chromium oxidants have employed strongly acidic media. Although high yielding for some specific transformations, most methods require the use of harsh conditions that are often unsuited to modern approaches to the synthesis of complex, sensitive natural products and bioactive molecules.

### 2.7.2.1 In Aqueous Sulfuric Acid

Sodium dichromate in aqueous sulfuric acid has been used since the turn of the century.[6] It is a very strong oxidant; the use of this system to oxidize primary alcohols is severely limited by overoxidation, *via* the aldehyde hydrate, to the corresponding acid. This problem can be partially circumvented in the preparation of volatile aldehydes (in particular aromatic aldehydes[7]), by slow addition to excess alcohol and continuous removal of the aldehyde by distillation.[8] Oxidation of secondary alcohols that are reasonably soluble is acceptable, but milder methods are now available, and are discussed in detail later.

As may be expected, a totally aqueous system is also restricted by the low solubility of many potential substrates. Hence several variations have subsequently been developed from this basic technique.

### 2.7.2.2 In Aqueous Acetic Acid

The use of acetic acid increases the solubility of organic substrates and also increases the rate of oxidation *via* acid catalysis. Some water, however, is necessary to solubilize the chromium(VI) oxide.

Once again the selective preparation of aldehydes is problematical — oxidation generally proceeds rapidly to give the acid. Secondary alcohols give good yields of the corresponding ketones, but the use of excess oxidant should be avoided since yields may be lowered by cleavage of the desired products *via* the enol form; this becomes more prominent with increasing substitution α to the ketone. In addition to the use of minimum amounts of oxidant, degradation may also be retarded by the addition of manganese(II) or cerium(III) salts to the reaction.[9]

Substrates containing 1,2-diols will normally undergo oxidative cleavage with this oxidant, but again this may be inhibited by the addition of manganese(II) or cerium(III) salts.[10]

### 2.7.2.3 In DMF/DMSO with Catalytic Sulfuric Acid

Chromium(VI) oxide in DMF is a very poor oxidant. However, the reaction is catalyzed by the addition of concentrated sulfuric acid.[11] Acid sensitive functionalities such as acetonides and acetals were found to be stable to these milder conditions.

Similarly sodium dichromate dihydrate in DMSO is a poor oxidant, but the addition of catalytic quantities of sulfuric acid leads to the effective oxidation of a variety of alcohols to give aldehydes and ketones in good yield (80–90%).[12] Oxidations are normally complete within 90 min at 70 °C, and may be performed in commercial DMSO without the need for further purification.

The suitability of these methods for large scale preparations may be restricted by the problems of removal of large quantities of the polar solvents.

### 2.7.2.4 In Two-phase Systems

Two-phase oxidations have been developed to protect sensitive substrates from prolonged exposure to strongly acidic conditions, thus avoiding degradation of the product and/or epimerization of compounds containing α-chiral centres. Benzene and dichloromethane are commonly used for the organic phase, but diethyl ether is often found to be superior since it is less likely to form emulsions.

Brown *et al.* initially reported the use of two-phase oxidation for the preparation of a range of ketones;[13] the method has also recently been reported for the oxidation of a selection of primary alcohols.[14]

Phase transfer conditions can be used for substrates with only limited aqueous solubility. Phase transfer agents also facilitate the preparation of aldehydes under biphasic conditions.[15,16]

### 2.7.2.5 In Aqueous Sulfuric Acid/Acetone (Jones Oxidation[17])

This is one of the best-known and most widely used methods of oxidation using chromium(VI). The procedure, which is amenable to large scale preparations, uses a standard chromic acid/sulfuric acid solution which is simply titrated against a solution of the alcohol in acetone. Acetone performs a dual role: (i) it is an excellent solvent for a wide range of organic molecules; and (ii) it protects the substrate from overoxidation or undesired side reactions by reacting with the excess oxidant itself. Hence it is uncommon to observe substantial epimerization of α-chiral centres.[18,19]

Secondary alcohols give good yields of ketones, but the foremost use of the Jones oxidation has been for the conversion of saturated primary alcohols to the corresponding acid. In direct contrast, primary allylic and benzylic alcohols can be selectively oxidized to aldehydes; acids are obtained only after prolonged exposure to the oxidant. In rigid systems it has been found that axial alcohols are oxidized faster than equatorial alcohols.[20]

Isolated carbon–carbon multiple bonds are not normally attacked by Jones' reagent, but some double-bond isomerization may occur during the preparation of α,β-unsaturated aldehydes. Hydroxy-directed epoxidation (presumably *via* chromate ester formation, followed by oxygen transfer to the double bond) has also been observed in steroidal substrates for axial alcohols (equation 1).[21] Equatorial alcohols undergo oxidation to give the expected enone.

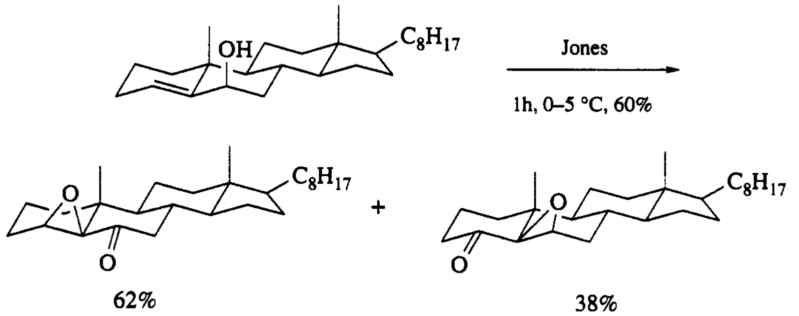

(1)

Care should be taken to avoid substrates containing either *cis* or *trans* 1,2-diols or α-hydroxy ketones since these groups are liable to be cleaved under the reaction conditions.[22]

Although acetonides and secondary THP groups are sometimes compatible with the Jones oxidation (Table 1), acid labile protecting groups are often removed during the reaction, thus effecting a convenient 'one-pot' deprotection–oxidation protocol. In a similar way nitrile groups may be 'deprotected' to reveal acids during Jones oxidations.[23]

**Table 1** Oxidation of Alcohols in Aqueous Sulfuric Acid/Acetone (Jones Oxidation)

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 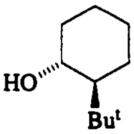 | 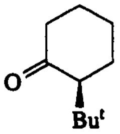 | 40 | 19 |
| 2 | 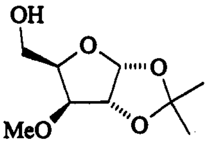 | 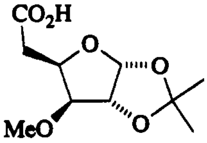 | 82 | 26 |
| 3 | 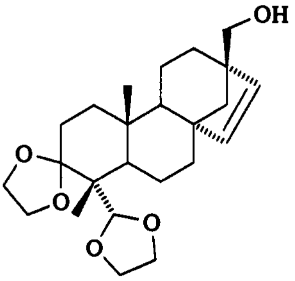 | 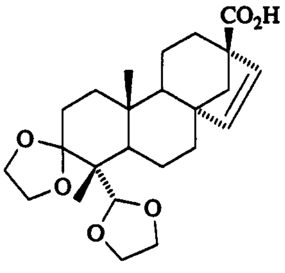 | 82 | 27 |
| 4 | 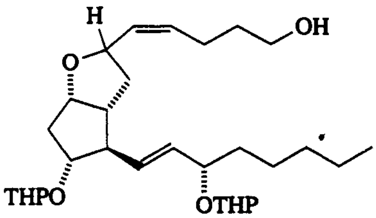 | 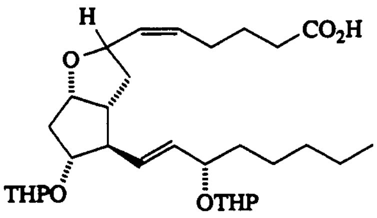 | 59 | 28 |
| 5 | 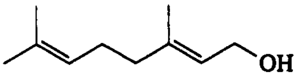 | 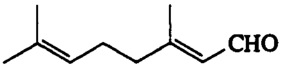 | 91<br>96:4 *(E)*:*(Z)* | 29 |
| 6 | 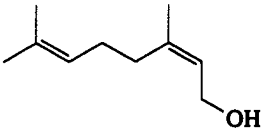 | 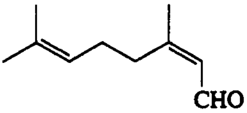 | 84<br>92:8 *(Z)*:*(E)* | 29 |
| 7 | 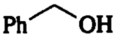 | 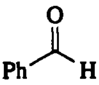 | 76 | 29 |
| 8 | 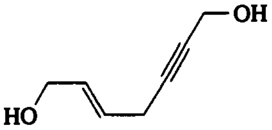 | 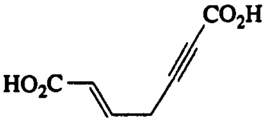 | 40 | 30 |
| 9 | 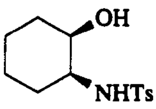 | 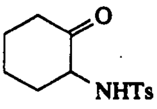 | 98 | 31 |

**Table 1** *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 10 | 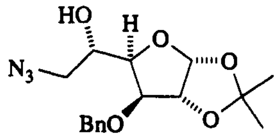 | 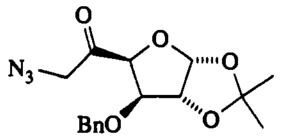 | 67 | 32 |
| 11 | 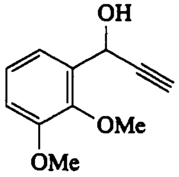 | 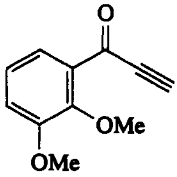 | 71 | 33 |
| 12 | 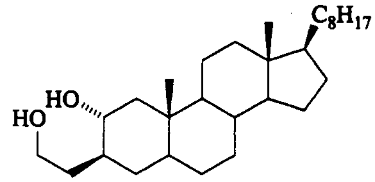 | 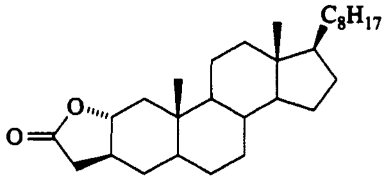 | 94 | 34 |
| 13 | 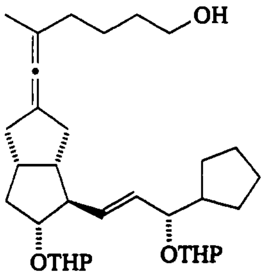 | 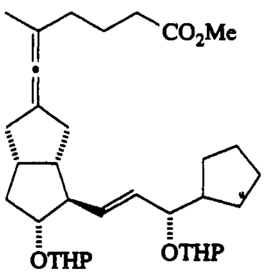 | 60<br>(over 2 steps) | 35 |
| 14 | 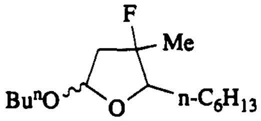 | 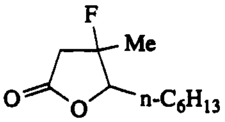 | 82 | 36 |
| 15 | 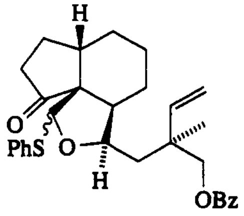 | 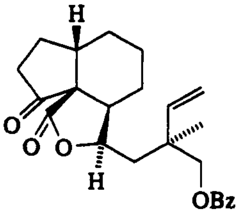 | 88 | 37 |
| 16 | 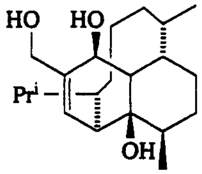 | 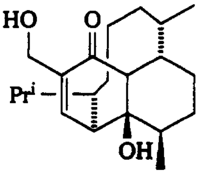 | 54 | 38 |

**Table 1** *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 17 | 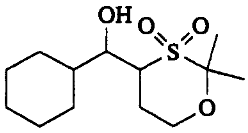 | 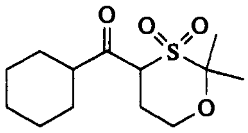 | 50–90 | 39 |
| 18 | 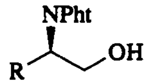 | 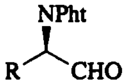 | 70–80 | 18 |

The oxidation of compounds with free N—H groups can be complicated by difficult product isolation.[24] However, conversion to the perchlorate salt prior to oxidation has been reported to alleviate this problem (equation 2).[25]

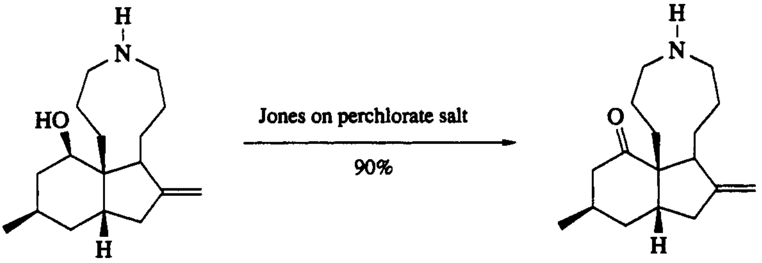

(2)

## 2.7.3 CHROMIUM(VI) WITH HETEROCYCLIC BASES

Chromium(VI) oxide is known to form complexes with several nitrogen heterocycles, many of which show oxidizing properties. They are milder, more selective oxidants than the acid-based reagent systems. Acid sensitive groups are tolerated much more, and the preparation of aldehydes is generally easier. However, oxidation may be difficult on substrates that contain basic nitrogens, since exchange may occur with the oxidant to give substrate–chromium complexes.

### 2.7.3.1 Chromium(VI) Oxide·(Pyridine)$_2$

Sarett and coworkers discovered that the complex (**1**) prepared by the addition of chromium(VI) oxide to pyridine (CAUTION—reverse order of addition may cause the mixture to inflame) is an efficient oxidizing agent for the preparation of ketones from secondary alcohols.[40] The reagent, as prepared by Sarett, is moderately soluble in pyridine, but is only sparingly soluble in standard organic solvents. Thus the normal procedure is to add a solution of the alcohol in pyridine to three equivalents of the complex, also in pyridine. This procedure is also useful for the preparation of aromatic and α,β-unsaturated aldehydes, but the use of pyridine as solvent prohibits the oxidation of volatile, saturated primary alcohols.[41]

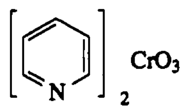

(**1**)

The practical problems encountered during the isolation of products from pyridine led Collins and coworkers to suggest an improved version of the Sarett oxidation, which has subsequently been widely adopted.[42] Collins and coworkers found that during the preparation of the dipyridine complex prolonged stirring gave a deep red macrocrystalline form, which could be isolated and stored (*n.b.* this reagent is very hygroscopic). This form of the complex exhibits moderate solubility in chlorinated solvents. Thus in

**Table 2** Oxidation of Alcohols with $CrO_3{\cdot}py_2$ (Collins Oxidation)

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 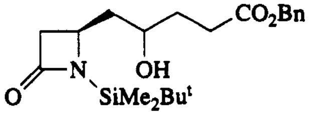 | 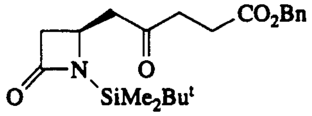 | 73 | 46 |
| 2 | 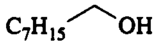 | 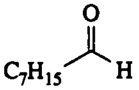 | 90 | 45 |
| 3 | 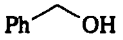 | 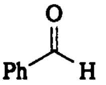 | 89 | 45 |
| 4 | 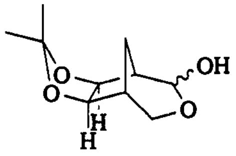 | 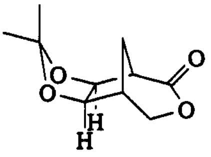 | 48<br>(over 3 steps) | 47 |
| 5 | 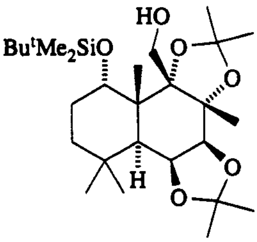 | 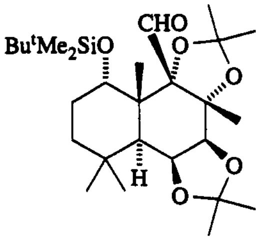 | 88 | 48 |
| 6 | 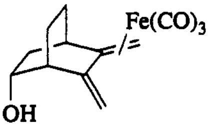 | 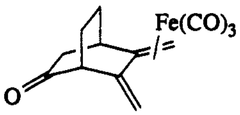 | 71 | 49 |
| 7 | 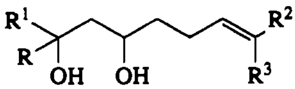 | 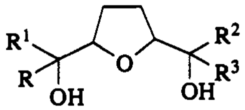 | ~50 | 50 |
| 8 | 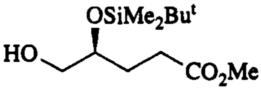 | 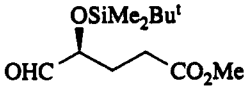 | 79<br>(over 2 steps) | 51 |
| 9 | 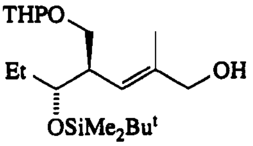 | 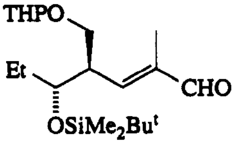 | 94 | 52 |
| 10 | 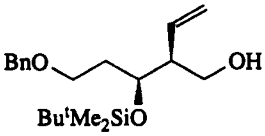 | 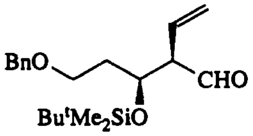 | 94 | 52 |

**Table 2** *(continued)*

| *Entry* | *Substrate* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 11 | 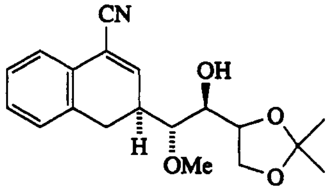 | 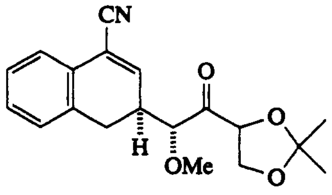 | 89 | 53 |
| 12 | 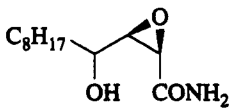 | 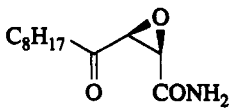 | 92 | 54 |
| 13 | 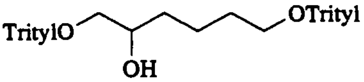 | 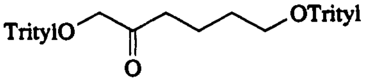 | 74 | 55 |
| 14 | 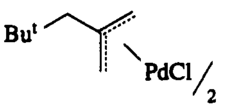 | 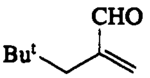 | 40 | 56 |

dichloromethane, the solvent of choice, oxidations of simple substrates are usually complete within 5–15 min at room temperature. Standard conditions employ six equivalents of oxidant in order to achieve quick, clean reactions. The excess oxidant can cause problems during work-up, but these may be eased by the addition of celite which adsorbs some of the chromium salts.[44]

This procedure for the oxidation of alcohols was further improved by Ratcliffe and Rodehorst:[45] *in situ* preparation of a dichloromethane solution of the complex immediately prior to use avoided the problems associated with the hygroscopic nature of the complex and the fire hazard endured during its preparation and isolation. (If desired, the dichloromethane solution may be stored for up to one month with little loss in activity.)

The Collins oxidation is efficient for the preparation of carbonyl compounds in the presence of a wide range of functionalities (Table 2); however, Dauben and coworkers observed that extended exposure to the complex (24 h at room temperature) can give moderate to excellent yields of allylic C—H oxidation products (equations 3 to 5).[57]

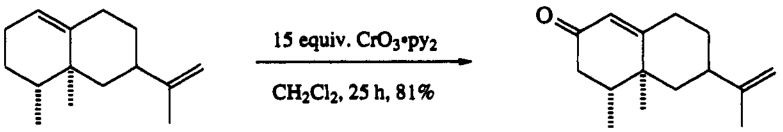

(3)

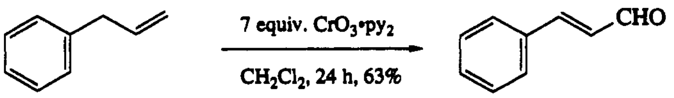

(4)

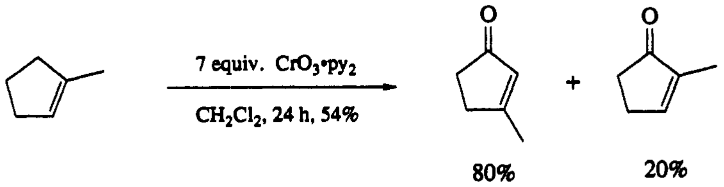

(5)

The chromium(VI) oxide–dipyridine complex also has been found to cause oxidative rearrangement of tertiary allylic alcohols to α,β-epoxy aldehydes and small amounts of α,β-unsaturated aldehydes (equation 6 and Table 3).[58] This is potentially useful as a homologation sequence since the starting materials are readily available from vinyl metal addition to ketones. Use of pyridinium chlorochromate (PCC) for this transformation gives mostly α,β-unsaturated aldehydes.

**Table 3** Rearrangement of Tertiary Allylic Alcohols with the Collins Reagent

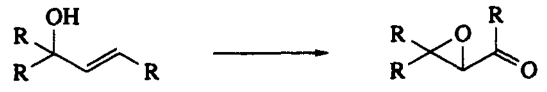

(6)

| *Entry* | *Substrate* | *Product(s)* | | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 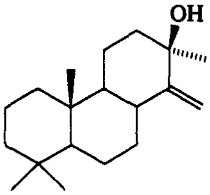 | 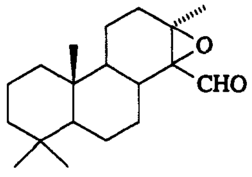<br>76% | 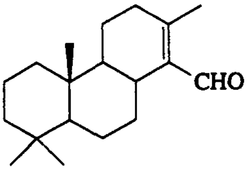<br>24% | 90 | 58 |
| 2 | 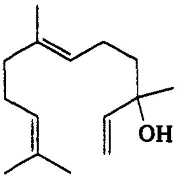 | 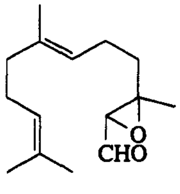<br>89% | 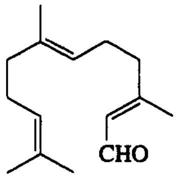<br>11% | 96 | 58 |
| 3 | 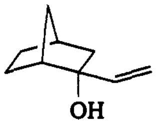 | 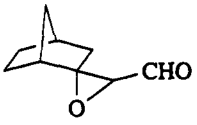<br>*ca.* 100% | 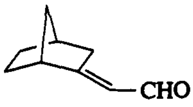<br>trace | 50 | 58 |
| 4 | 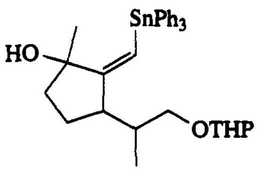 | 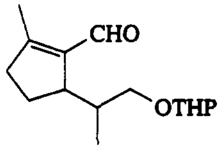 | | 54 | 62 |

Addition of acetic anhydride to the Collins reagent ($CrO_3$:pyridine:acetic anhydride 1:2:1) has been reported to be suitable for the oxidation of carbohydrates[59] and nucleoside substrates;[60] for example, 5′-*O*-acetylthymidine gives spontaneous elimination of thymine under Pfitzner–Moffat conditions. Similarly, 5′-*O*-tritylthymidine loses thymine when treated with $CrO_3 \cdot py_2$. However, under modified conditions ($CrO_3$:pyridine:acetic anhydride 1:2:1) good yields of the corresponding 3′-carbonyl compounds are regularly obtained (equation 7).[60]

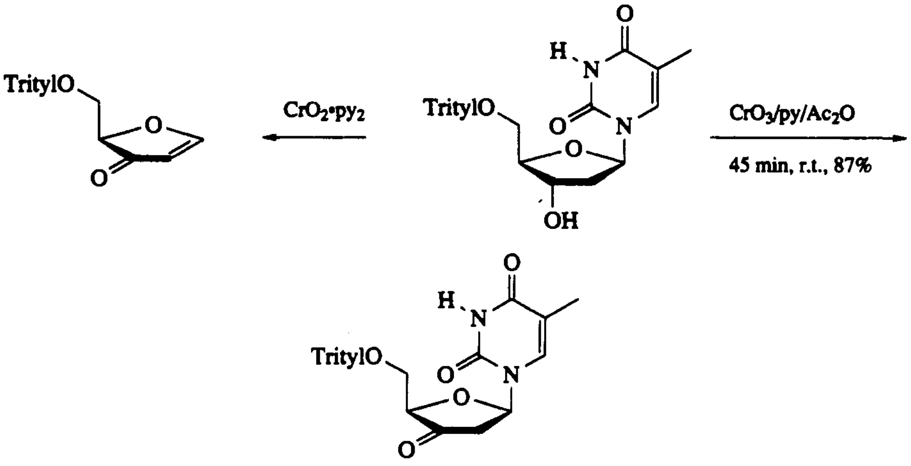

(7)

The complex formed by 2,2′-bipyridine with chromium(VI) oxide is a milder oxidant than the Collins reagent,[61] as indicated by the need for long reaction times (up to 48 h) and a larger excess of oxidant (8 equiv.).

### 2.7.3.2 Chromium(VI) Oxide·(3,5-Dimethylpyrazole)

In contrast to the Collins reagent, the complex formed by 3,5-dimethylpyrazole with chromium(VI) oxide (**2**) is very soluble in dichloromethane.[63] Hence, reactions (up to 0.1 mol scale) can be carried out in the minimum amount of solvent. Generally, 2.5 equiv. of complex, generated *in situ*, gives good yields of aldehydes and ketones. In addition, upon work-up most of the chromium salts may be precipitated by dilution with diethyl ether.

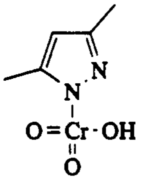

**(2)**

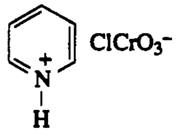

**(3)**

Although chromium(VI) oxide·(3,5-dimethylpyrazole) is also a good oxidant for allylic C—H bonds,[43] it is surprising that this reagent has not been more widely adopted.

### 2.7.3.3 Pyridinium Chlorochromate (PCC)

Pyridinium chlorochromate (**3**),[64] first developed by Corey and coworkers in 1977, is a commercially available, stable yellow solid, which may be stored in air.[65] With simple substrates, oxidations are normally performed in dichloromethane at room temperature with 1.5 equiv. of oxidant, and are usually complete within 2 h. (More polar solvents, in which PCC has higher solubility, unfortunately lead to prohibitively long reaction times.) Good yields of ketones and aldehydes are regularly obtained, but slight (*E*)/(*Z*)-isomerization is observed in allylic alcohol oxidations (Table 4). Significant overoxidation is rare, but if desired, acids may be prepared from aldehydes with stoichiometric sodium cyanide and PCC in THF at 45 °C.[84] The reaction is selective for aliphatic aldehydes; conjugated and α-oxygenated substrates are recovered unchanged. Oxidation direct from the alcohol is not as efficient.

The acidic properties of PCC, which if necessary may be buffered by the use of powdered sodium acetate, can be used to good advantage to effect oxidative cationic cyclizations.[85,86] Efficient cyclizations are limited to substrates that give tertiary carbonium ions as the initial cyclization product and to the formation of six-membered rings.

**Table 4** Oxidation of Alcohols with PCC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 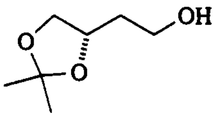 | 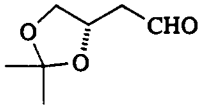 | 3 equiv., DCM, 1 h, r.t., 3Å sieves | 88 | 66 |
| 2 | 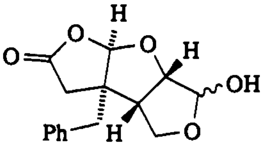 | 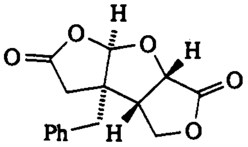 | 3 equiv., DCM, 4.5 h, r.t. | 65 | 67 |
| 3 | 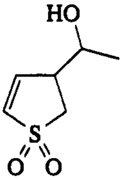 | 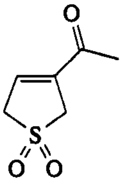 | 6.5 equiv., THF, 35 °C, 3Å sieves | 51 | 68 |
| 4 | 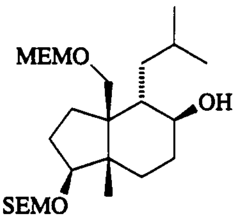 | 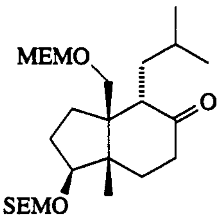 | 2 equiv., DCM, 3 h, r.t. | 74 | 69 |
| 5 | 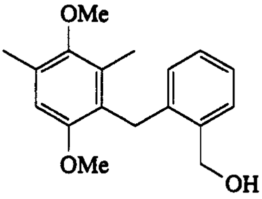 | 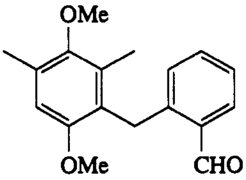 | DCM, 1 h, r.t. | 96 | 70 |
| 6 | 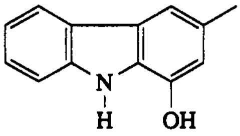 | 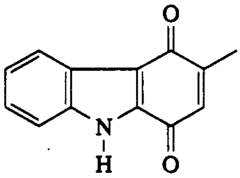 | DCM, r.t. | 40 | 71 |
| 7 | 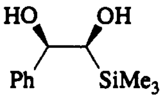 | 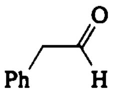 | DCM, r.t. | 90 | 72 |
| 8 | 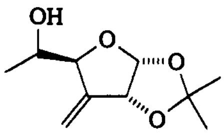 | 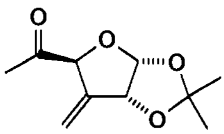 | 2.5 equiv., DCM, 3Å sieves, 3 h, reflux | 72 | 73 |

**Table 4** *(continued)*

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 9 | 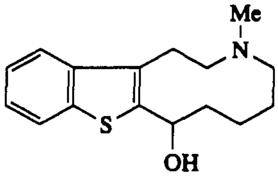 | 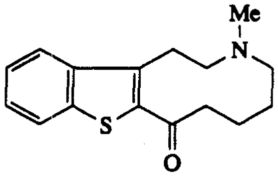 | 1.5 equiv., DCM, NaOAc, 17 h, r.t. | 71 | 74 |
| 10 | 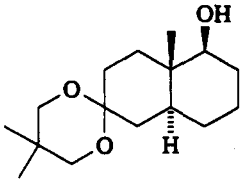 | 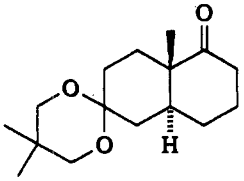 | 2 equiv., DCM, NaOAc, 3 h, r.t. | 88 | 75 |
| 11 | 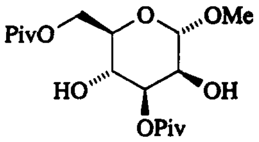 | 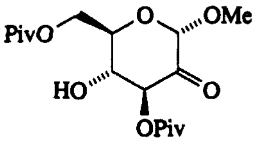 | 2 equiv., DCM, NaOAc, 24 h, reflux | 76 | 76 |
| 12 | 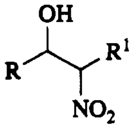 | 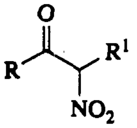 | DCM, 3Å sieves, 36 h, r.t. | 61–78 | 77 |
| 13 | 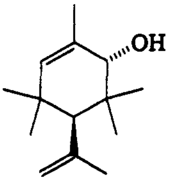 | 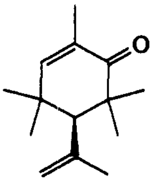 | 1.1 equiv., DCM, 2 h, r.t. | 85 | 78 |
| 14 | 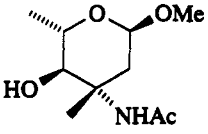 | 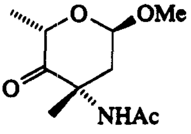 | 3 equiv., DCM, 3Å sieves, 3 h, r.t. | 66 | 79 |
| 15 | 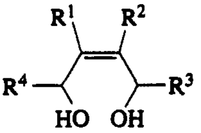 | 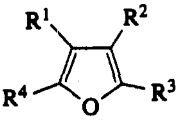 | 1.5 equiv., DCM, 0.5 h, r.t. | 35–89 | 80 |
| 16 | 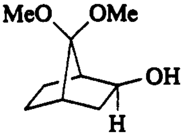 | 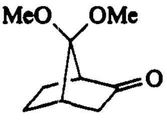 | 1.4 equiv., DCM, NaOAc, 2 *h*, r.t. | 95 | 81 |
| 17 | 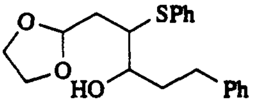 | 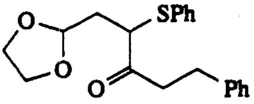 | 1.7 equiv., DCM, 40 h, reflux | 68 | 82 |

**Table 4** *(continued)*

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 18 | 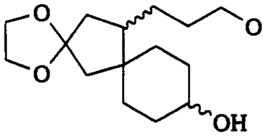 | 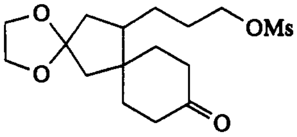 | 2 equiv., DCM, NaOAc, 2.5 h, r.t. | 98 | 83 |

In a similar fashion to the Collins reagent, PCC will also induce oxidative rearrangement of tertiary allylic alcohols (Table 5).[87,88] PCC, and several other chromium oxidants, will also cause tertiary cyclopropyl alcohols to rearrange to give β,γ-unsaturated carbonyl compounds (equation 8).[88]

**Table 5** Rearrangements of Tertiary Allylic Alcohols with PCC

| *Entry* | *Substrate* | *Product(s)* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 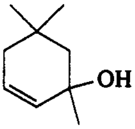 | 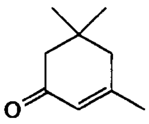 | 3 equiv. PCC, DCM, 16 h | 94 | 87 |
| 2 | 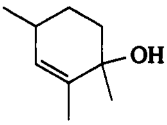 | 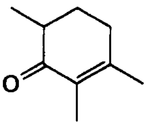 | 3 equiv. PCC, DCM, 16 h | 88 | 87 |
| 3 | 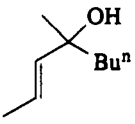 | 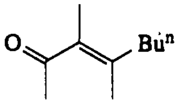 ~1:1 (*E*):(*Z*) | 3 equiv. PCC, DCM, 16 h | 50 | 87 |
| 4 | 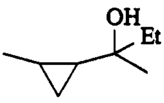 | 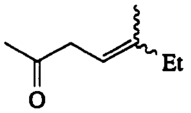 | 8 equiv. PCC, DCM, 6 h | 62 | 88 |
| 5 | 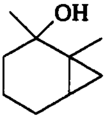 | 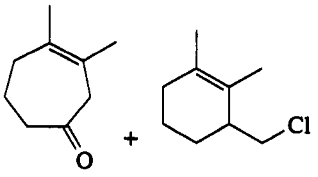 85% 15% | 8 equiv. PCC, DCM, 6 h | 36 | 88 |

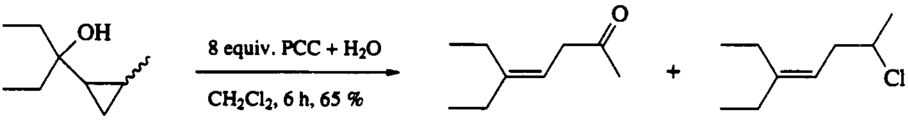

(8)

PCC can used for the oxidation of silyl-protected hydroquinones to quinones, except where there are electron-withdrawing substituents on the aromatic ring.[89] Interestingly, there was no evidence for cleavage of the silicon–oxygen bond as the first step, which might be expected under the acidic conditions of a PCC oxidation.

Organoboranes from hydroboration reactions can be oxidized directly to ketones with PCC, thus eliminating the need to isolate the intermediate alcohol.[90]

PCC can be modified to show selectivity for the oxidation of allylic alcohols in steroidal systems. A solution of PCC in dichloromethane with 2% pyridine at *ca.* 2 °C was found to be an effective and selective oxidant (Table 6).[91] In contrast to chromate oxidations of saturated alcohols in rigid systems, Parish and coworkers found that quasiequatorial allylic alcohols were oxidized faster than axial ones. Similar properties were also found for solutions of PCC and 3,5-dimethylpyrazole (2%) in dichloromethane.[92] In addition, Parish and coworkers also examined several other aromatic amines for the ability to promote allylic selectivity.[93] 2,2′-Bipyridine, pyrazine, pyridazine, *s*-triazine and 2,4,6-triphenylpyridine all had some effect, but their efficacy appeared to be substrate dependent. Most recently the combination of PCC

**Table 6** Oxidation of Allylic Alcohols with PCC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 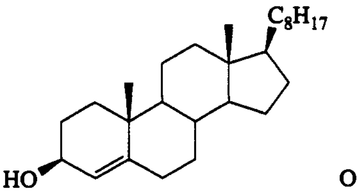 | 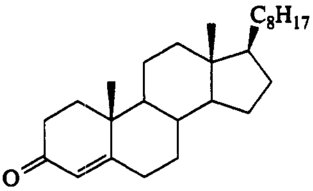 | 3.5 equiv. PCC, 2% BZT,[a] DCM, 2–3 °C, 30 min | 91 | 94 |
| 2 | 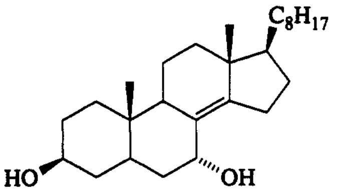 | 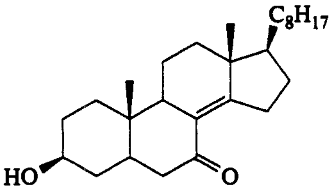 | 7 equiv. PCC, 2% Py, DCM, 2 °C, 30 min | 89 | 91 |
| 3 | 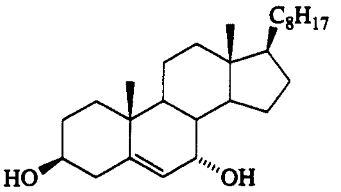 | 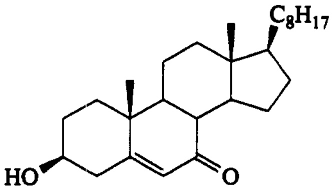 | 3 equiv. PCC, 2% DMP,[a] DCM, 2–3 °C, 30 min | 89 | 92 |
| 4 | 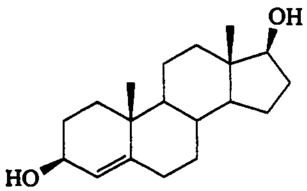 | 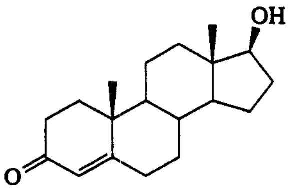 | 3 equiv. PCC, 2% DMP,[a] DCM, 2–3 °C, 30 min | 87 | 92 |
| | | | 3.5 equiv. PCC, 2% BZT,[a] DCM, 2–3 °C, 30 min | 92 | 94 |
| 5 | 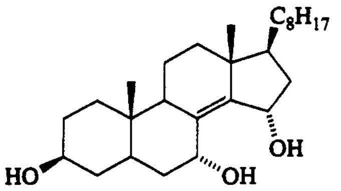 | 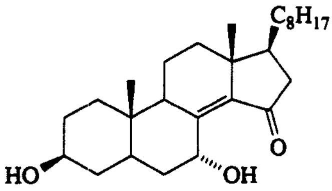 | 7 equiv. PCC, 2% Py, DCM, 2 °C, 30 min | 82 | 91 |

[a] BZT = benzotriazole; DMP = 3,5-dimethylpyrazole.

with benzotriazole (2%)[94] has been found to exhibit excellent selectivity for allylic alcohols (~90% allylic oxidation) (equation 9).

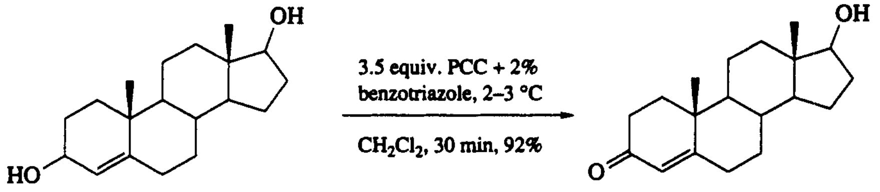

(9)

PCC becomes a much milder oxidant when it is adsorbed on alumina, e.g. added buffer is not required to prevent oxidative cationic cyclizations (see Section 2.7.5.1).[95]

Oxidation of carbohydrates with PCC *via* the standard procedure has been found to be slow, even with large excesses of oxidant. Use of boiling benzene instead of dichloromethane at room temperature can cause drastic reductions in reaction times.[96] Addition of molecular sieves to the oxidation of carbohydrates with PCC (or PDC) also gives dramatic rate enhancement.[97,98] (The use of molecular sieves in

**Table 7** Oxidation of Furans with PCC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 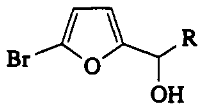 | 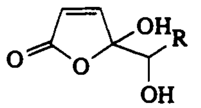 | 2 equiv. PCC, r.t., 1.5 h | 60–75 | 99 |
| 2 | 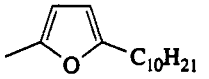 | 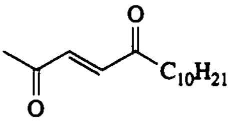 | PCC, DCM, reflux, 24 h, | 90 | 100 |
| 3 | 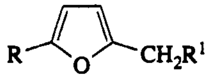 | 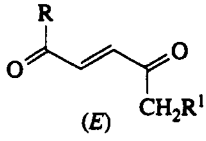 | 1.5 equiv. PCC, DCM, r.t., ~24 h, reflux, ~9 h | 50–80 | 101 |
| 4 | 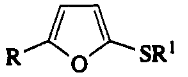 | 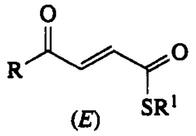 | 5 equiv. PCC, r.t., DCM, 2–24 h | 60–90 | 102 |
| 5 | 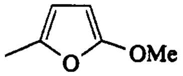 | 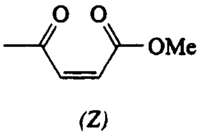 | 5 equiv. PCC, DCM, r.t., 10 min | 70 | 102 |
| 6 | 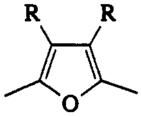 | 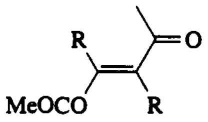 | 4 equiv. PCC, DCM, r.t., 10 h | 50–70 | 103 |
| 7 | 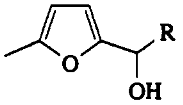 | 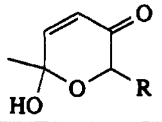 | 1.5 equiv. PCC, DCM, r.t., 1 h | 90 | 104 |

**Table 8** Alternative Oxidation Reactions of PCC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 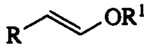 | 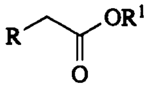 | 2 equiv. PCC, DCM, r.t., 1 h | 70–95 | 105 |
| 2 | 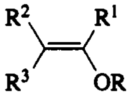 | 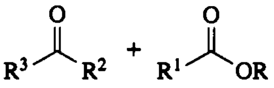  O<br>R$^3$<br>R$^2$<br>+<br>O<br>R$^1$<br>OR | 4 equiv. PCC/PDC, celite, r.t., 1 h, DCM or benzene | 60–90 | 106 |
| 3 | 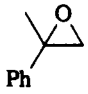 | 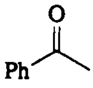 | 2 equiv. PCC, 4Å sieves, r.t., 1.5 h | 65 | 107 |
| 4 | 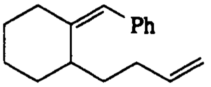 | 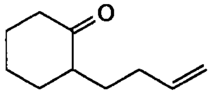 | 5 equiv. PCC, celite, reflux, 25 h | 82 | 108 |
| 5 | 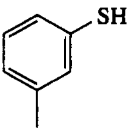 | 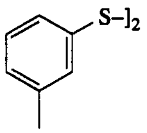 | 1 equiv. PCC, DCM, r.t., 2 min | 67 | 109 |
| 6 | 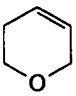 | 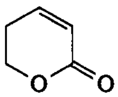 | 3 equiv. PCC, DCM, sealed vessel, 60 °C | 70 | 110 |
| 7 | 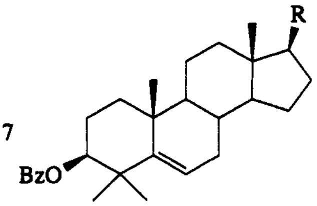 | 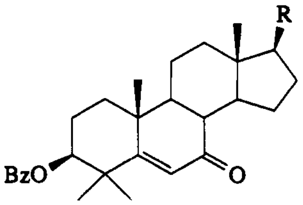 | 60 equiv. PCC, DCM, 3Å sieves, reflux, 48 h | 84 | 111 |
| 8 | 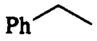 | 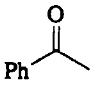 | 5 equiv. PCC, benzene, celite, r.t., 15 h | 71 | 112 |
| 9 | 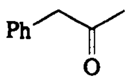 | 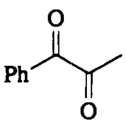 | 3 equiv. PCC, 3 equiv. Py, DCM, reflux, 25 h | 81 | 113 |
| 10 | 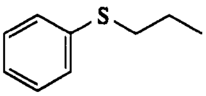 | 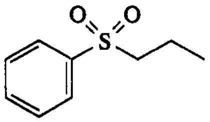 | 3 equiv. PCC, DCM, r.t., 3.5 h | 60 | 114 |
| 11 | 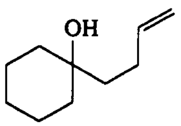 | 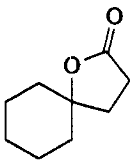 | 5 equiv. PCC, celite, DCM, reflux, 48 h | 53 | 115 |

many types of oxidations is now commonplace.) Comparative studies indicated that 3 Å sieves gave the best results [3 Å > 4 Å > 10 Å > 5 Å]. Celite, alumina and silica were found to have little or no effect upon the rate of oxidation of carbohydrates.

Mechanistic studies imply that there are specific sites in these zeolites that promote hydride transfer.

PCC is an excellent oxidant for the transformation of alcohol to carbonyl, but it is also a good general oxidant. Therefore it should be noted that with unreactive substrates that may require forcing conditions, there are a number of other possible oxidative (and degradative) pathways available: these are outlined below.

Furans appear readily to undergo a variety of oxidation reactions with PCC (Table 7).[99–104]

Simple mono- or di-substituted enol ethers may be oxidized to esters and lactones (Table 8, entries 1 and 2).[105] However, fully substituted enol ethers undergo oxidative cleavage, since the proposed mechanism for oxidation to an ester involves a hydride shift which can no longer take place.[106]

Phenyloxiranes are cleaved by PCC. The phenyl group appears to be essential for carbon–carbon bond scission (Table 8, entry 3).[107]

In general, PCC is inert towards isolated carbon–carbon multiple bonds, but it is possible to cleave aryl-substituted double bonds.[108] Once again, the aromatic group is necessary to impart sufficient reactivity for cleavage to occur (Table 8, entry 4). An exception has been reported by Chakraborty and Chandrasekaran.[115] It was found that γ- and δ-tertiary hydroxyalkenes give good yields of the corresponding spirolactones (Table 8, entry 11) upon treatment with $(bipyH_2)CrOCl_5$ and with PCC. Double-bond cleavage is well known with chromium(V) oxidants, but the use of PCC for this transformation is much less common.

It has been observed that PCC will rapidily dimerize aromatic, but not aliphatic, thiols to their corresponding disulfides in good yield (Table 8, entry 5).[109] Sulfides may undergo oxidation to give sulfones (Table 8, entry 10).[114]

Several chromium oxidants, including PCC, will oxidize activated methylene groups to carbonyl compounds, but much stronger conditions are usually required than for alcohol oxidation.

5,6-Dihydropyrans need only a moderate excess of PCC to be converted into unsaturated lactones (Table 8, entry 6).[110] However, the oxidation of normal allylic and benzylic C—H groups requires a large excess of PCC (Table 8, entries 7 to 9).[111] The amount of PCC needed is lower if benzene[112,116] or DMSO[116] are used as solvents for oxidation, but the reactions still need to be heated to obtain reasonable conversion.

## 2.7.3.4 Other Chromates

A number of different chromates have been developed for the oxidation of alcohols. Most changes have been made to create oxidants that are milder and more selective in comparison to PCC.

### *2.7.3.4.1 Pyridinium fluorochromate (PFC)*

Pyridinium fluorochromate is a stable solid, which can be stored for long periods.[117] It is as reactive as PCC, but slightly less acidic (pH of a 0.01 M solution = 2.45 compared to 1.75 for PCC), and thus substrates with acid labile groups can be oxidized without the need to add a buffer.[118] With 1.5 equiv. of oxidant in dichloromethane at room temperature, primary and secondary alcohols are oxidized to aldehydes and ketones in high yield (Table 9). Unfortunately, (*E*)/(*Z*)-isomerization has been observed during the oxidation of allylic alcohols.[118]

PFC is also a reasonable oxidant for activated C—H bonds. Allylic oxidation to a variety of ketonic products was observed upon treatment of $\Delta^3$-carene with PFC.[119] Benzylic C—H oxidation with PFC is also known.[117,120]

### *2.7.3.4.2 Bipyridinium chlorochromate (BPCC)*

Bipyridinium chlorochromate (**4**) is a mild, air stable nonhygroscopic oxidant.[61] It is weaker than PCC,[121] and thus 2–4 equiv. are required to obtain good yields of carbonyl compounds. The bipyridyl system acts as an internal buffer, permitting the ready oxidation of alcohols in substrates with acid labile groups. Bipyridinium chlorochromate will also oxidize sulfides to sulfoxides and sulfones.[114]

**Table 9** Oxidation of Alcohols with PFC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 1 | 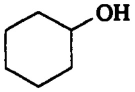 | 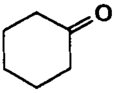 | 1.5 equiv., DCM, 3.5 h, r.t. | 89 | 117 |
| 2 | n-$C_7H_{15}OH$ | n-$C_6H_{13}CHO$ | 1.5 equiv., DCM, 1 h, r.t. | 84 | 117 |
| 3 | 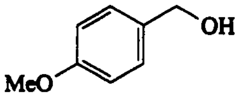 | 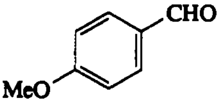 | 1.5 equiv., DCM, 1 h, r.t. | 90 | 117 |
| 4 | 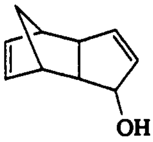 | 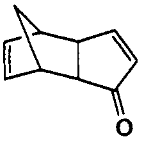 | 1.5 equiv., DCM, 1.5 h, r.t. | 92 | 117 |
| 5 | 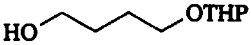 | 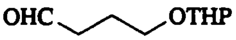 | 2 equiv., DCM, 4 h, r.t. | 78 | 118 |
| 6 | 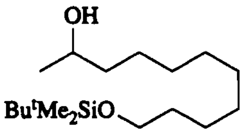 | 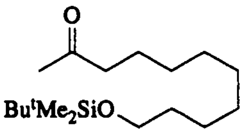 | 2 equiv., DCM, 3 h, r.t. | 89 | 118 |
| 7 | 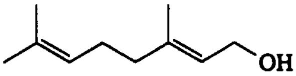 | 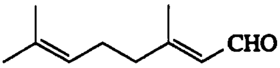 | 2 equiv., DCM, 2 h, r.t. | 80<br>85:15 *(E):(Z)* | 118 |
| 8 | 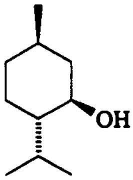 | 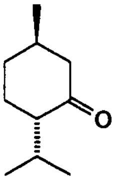 | 2 equiv., DCM, 2 h, r.t. | 97 | 118 |
| 9 | 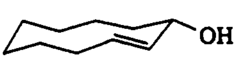 | 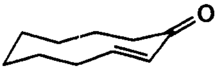 | 2 equiv., DCM, 4 h, r.t. | 87 | 118 |

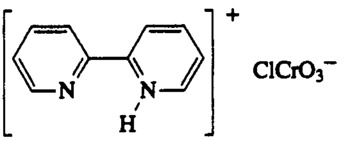

(4)

If necessary, bipyridinium chlorochromate may also be buffered with sodium acetate. In a system especially prone to epimerization (equation 10), bipyridinium chlorochromate/sodium acetate gave 90% of the ketone (**5**) with little isomerization,[122] whereas use of unbuffered PCC on a closely related substrate gave significant epimerization.[123]

Alumina (activity III) may also be used to create an even milder oxidant. Diol (**6**; equation 11) underwent cleavage to the aldehyde when treated with bipyridinium chlorochromate alone,[124] but bipyridinium chlorochromate/alumina (1:1) gave a good yield of the α-hydroxy ketone.[125]

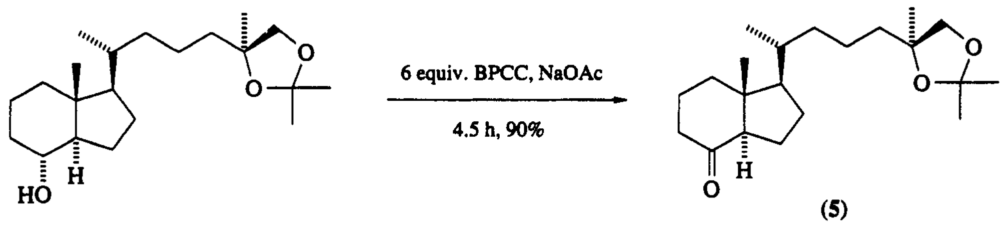

(10)

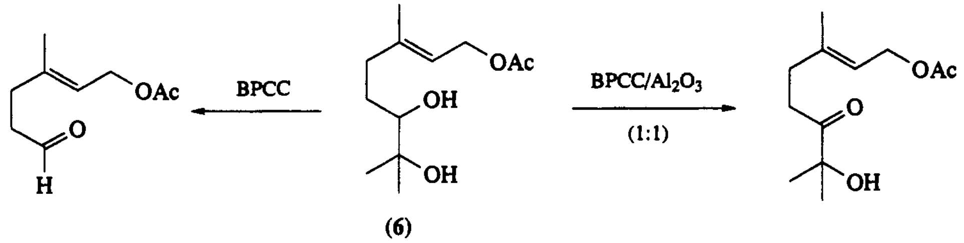

(11)

Other bipyridyl-related systems (**7** and **8**) have been found to be less effective for the oxidation of alcohols.[126] 2,2′:6′,2″-Terpyridinium hydrochloride chlorochromate (**9**) has also been prepared and found to be inert under standard conditions. It has been suggested that the steric bulk prevents effective electron transfer.[121]

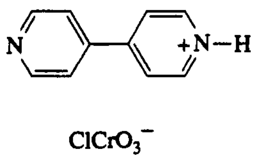

(7)

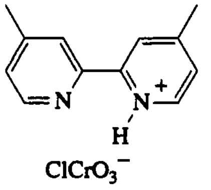

(8)

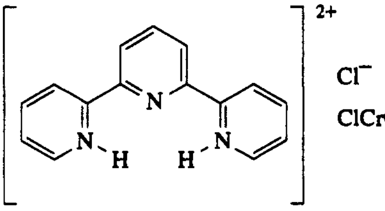

(9)

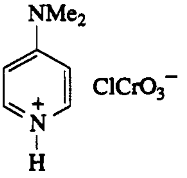

(10)

### *2.7.3.4.3 4-(Dimethylamino)pyridinium chlorochromate*

4-(Dimethylamino)pyridinium chlorochromate (**10**) is a commercially available, stable and nonhygroscopic solid, but it is light sensitive.[127] It is selective for allylic and benzylic alcohols. *n*-Heptanol gives only 5% aldehyde after 3 h with 4 equiv. The selectivity is greater over primary than secondary saturated alcohols. Between 4 and 6 equiv. of oxidant are normally required for good conversion, but this is often less than the amount of manganese(IV) oxide required for the same transformation, and reaction times are usually shorter. Unfortunately, (*Z*)-unsaturated aldehydes will isomerize to the (*E*)-isomers under the reaction conditions due to the acidic nature of this reagent (Table 10).

It should be noted that treatment of di-*n*-propylsulfide with 4-(dimethylamino)pyridinium chlorochromate (1 equiv.) in dichloromethane for 20 h gave only 5% oxidation, suggesting that this may be a useful oxidant for sulfur-containing compounds.[114]

**Table 10** Oxidation of Alcohols with DMAPCC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 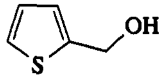 | 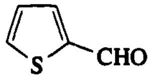 | 3 equiv., DCM, 4 h, r.t. | 73 | 127 |
| 2 | 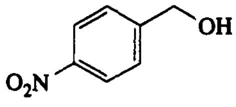 | 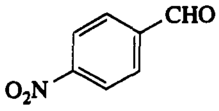 | 6 equiv., DCM, 20 h, r.t. | 43 | 127 |
| 3 | 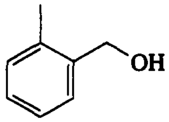 | 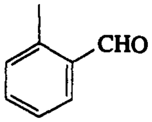 | 4 equiv., DCM, 15 h, r.t. | 78 | 127 |
| 4 | 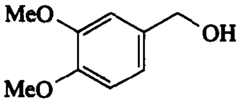 | 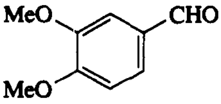 | 4 equiv., DCM, 14 h, r.t. | 91 | 127 |
| 5 | 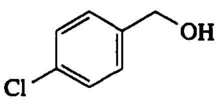 | 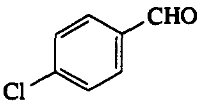 | 5 equiv., DCM, 21 h, r.t. | 91 | 127 |
| 6 | 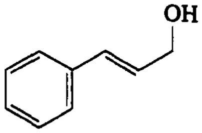 | 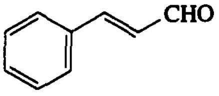 | 6 equiv., DCM, 15 h, r.t. | 62 | 127 |
| 7 | 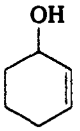 | 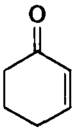 | 6 equiv., DCM, 7 h, r.t. | 74 | 127 |
| 8 | 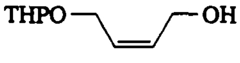<br>(*Z*) | 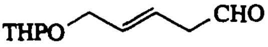<br>(*E*) | 5 equiv., DCM, 24 h, r.t. | 55 | 127 |
| 9 | 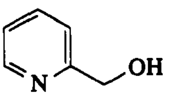 | 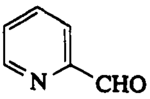 | 4 equiv., DCM, 6 h, r.t.[a] | 0 | 127 |
| 10 | 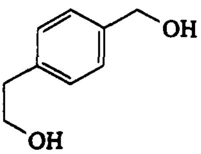 | 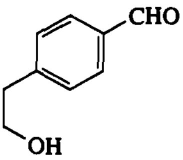 | 4 equiv., DCM, 2 h, r.t. | 62 | 127 |

[a] Note no reaction with this pyridine derivative.

### *2.7.3.4.4 1,8-Naphthyridinium chlorochromate (NapCC)*

NapCC[128] is much milder than PCC, and hence is less likely to cause overoxidation. It shows moderate selectivity for allylic and benzylic alcohols (Table 11). It has low solubility in solvents such as dichloromethane and diethyl ether, but is soluble in solvents with higher dielectric constants, such as DMSO or DMF.

**Table 11** Oxidation of Alcohols with Naphthyridinium Chlorochromate[128]

| *Entry* | *Substrate* | *Product* | $T_{50}$ (h)[a] |
|---|---|---|---|
| 1 | 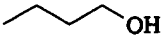 | 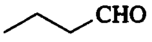 | 5.7 |
| 2 | 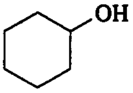 | 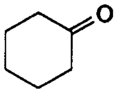 | 9.8 |
| 3 | 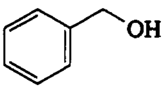 | 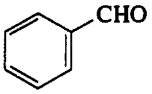 | 1.8 |
| 4 | 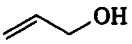 | 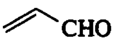 | 2.9 |

[a] $T_{50}$ = time taken for reaction to reach 50% completion.

### 2.7.3.4.5 *Quinolinium chlorochromate*

In a brief communication, it was reported that quinolinium chlorochromate is a selective oxidant for primary alcohols;[129] for example, this reagent is reported to oxidize the diol (**11**) selectively to the aldehyde (**12**; equation 12).

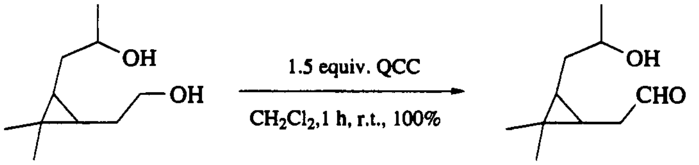

(**11**) (**12**) (12)

Secondary alcohols can be oxidized but require prolonged reaction times. The reagent is also reported to show sensitivity to substitution β to primary alcohols.

### 2.7.3.4.6 *Pyrazinium chlorochromate (PzCC)*

PzCC (**13**) is a much milder oxidant than PCC,[128,130] but is only moderately soluble in dichloromethane, carbon tetrachloride and diethyl ether. It is soluble in water and acetonitrile. In pyridine, exchange occurs freely to give PCC and pyrazine. Aldehydes and ketones are easily prepared, with no sign of overoxidation. However, PzCC displays no marked selectivity for any class of alcohols, so it is difficult to predict specific instances where it would be better to use this oxidant in place of the others available.

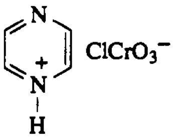

(**13**)

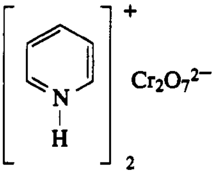

(**14**)

Preparation of pyrazinium *N*-oxide chlorochromate gives a reagent which is as reactive as PCC, but much less stable.[121] Again there is no apparent selectivity for a particular type of substrate.

### 2.7.3.5 Pyridinium Dichromate (PDC)

Pyridinium dichromate (**14**) is an isolable, stable orange solid that can be simply and safely prepared.[131] PDC had been used previously,[132,133] but it was Corey and coworkers who demonstrated the wide applicability of this mild and selective oxidant in organic synthesis. PDC is very soluble in solvents such as DMF, water and DMSO, but sparingly soluble in chlorinated hydrocarbons and acetone. It is normally used either as a solution in DMF or as a suspension in dichloromethane (Table 12).

Primary and secondary allylic alcohols and saturated secondary alcohols are oxidized to the corresponding carbonyl compounds quickly and in high yield at room temperature in DMF. There is no appreciable overoxidation of allylic alcohols in DMF, but primary saturated alcohols are readily oxidized to their corresponding acids. Recently, it has been reported that aldehydes may be converted to methyl esters by oxidation with PDC in the presence of methanol.[141] Preparation of other esters, or methyl esters direct from the alcohol, proved to be less efficient.

By using PDC as a suspension in dichloromethane it becomes a selective oxidant for the preparation of aldehydes, saturated or unsaturated. Allylic alcohols are oxidized faster than saturated alcohols, but some (*E*)/(*Z*)-isomerization has been observed during the preparation of α,β-unsaturated aldehydes with PDC in dichloromethane.

Initially, Corey and Schmidt found that by addition of pyridinium trifluoroacetate (0.4 equiv.) to their reactions,[131] there was an increase in rate and the amount of PDC needed for complete oxidation diminished. Subsequently, several other techniques have been devised to improve the rate and efficacy of PDC oxidations (most frequently in the field of carbohydrate research).

As mentioned for PCC,[98] the addition of molecular sieves causes a dramatic increase in the rate of oxidation of carbohydrates. Once again, molecular sieves have been used to improve the oxidations of a wide variety of substrates with PDC.

Addition of small quantities of anhydrous acetic acid and freshly activated sieves[142] to oxidations of carbohydrates has also been found to increase the rate of oxidation. In comparison to the addition of pyridinium trifluoroacetate, reaction times were reduced from days to minutes (Scheme 1). The acetic acid and sieves appear to have a synergistic effect, since both are required to give the dramatic rate enhancement.

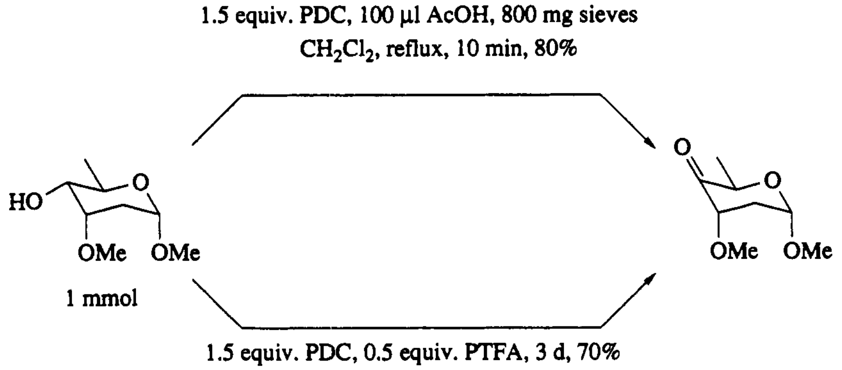
1.5 equiv. PDC, 100 μl AcOH, 800 mg sieves

$CH_2Cl_2$, reflux, 10 min, 80%

1 mmol

1.5 equiv. PDC, 0.5 equiv. PTFA, 3 d, 70%

Scheme 1

A combination of acetic acid and PDC has also been used to effect selective allylic oxidations on unprotected, unsaturated carbohydrates.[143] Interestingly, ethyl acetate was found to be the solvent of choice, and the reaction proceeded better if molecular sieves were omitted, since they appeared to cause unselective oxidation in this case (equation 13).

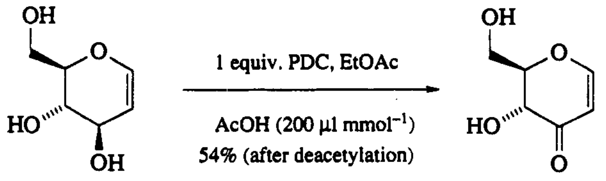
1 equiv. PDC, EtOAc

AcOH (200 μl $mmol^{-1}$)

54% (after deacetylation)

(13)

PDC with acetic anhydride gives a strong but mild, neutral oxidant.[144] It is normally used in dichloromethane at room temperature. Under these conditions secondary alcohols are oxidized to ketones in high yield with 0.6 equiv. of PDC and 3 equiv. of acetic anhydride. With only slightly more PDC (0.7 equiv.) primary alcohols are rapidly and selectively oxidized to aldehydes. (The extra oxidant serves to increase

**Table 12** Oxidation of Alcohols with PDC

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 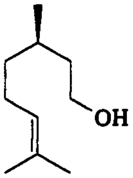 | 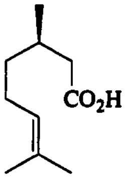 | 3.5 equiv. PDC, DMF, 7–9 h, r.t. | 83 | 131 |
| 2 | 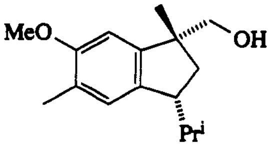 | 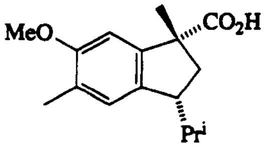 | 3.5 equiv. PDC, DMF, 7–9 h, r.t. | 85 | 131 |
| 3 | 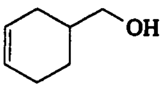 | 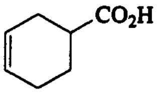 | 3.5 equiv. PDC, DMF, 7–9 h, r.t. | 92 | 131 |
| 4 | 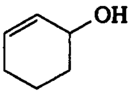 | 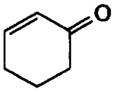 | 1.25 equiv. PDC, DMF, 4–5 h, 0 °C | 86 | 131 |
| 5 | 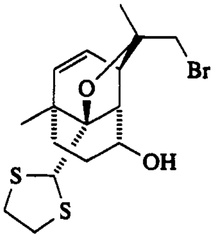 | 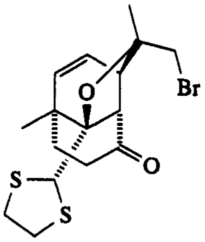 | 7 equiv. PDC, DMF, 6 h, 0 °C | 95 | 131 |
| 6 | 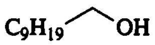 | 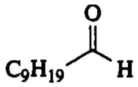 | 1.5 equiv. PDC, DCM, r.t., 20 h | 98 | 131 |
| 7 | 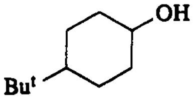 | 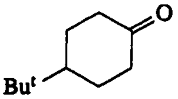 | 1.5 equiv. PDC, 0.4 equiv. PTFA, DCM, r.t., 3 h | 97 | 131 |
| 8 | 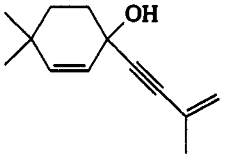 | 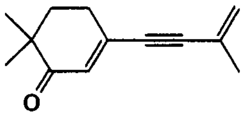 | 1.5 equiv. PDC, DCM, r.t., 16 h | 88 | 134 |
| 9 | 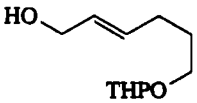 | 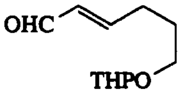 | 1.5 equiv. PDC, DMF, 2 h, 0 °C | 85 | 135 |

**Table 12** *(continued)*

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 10 | 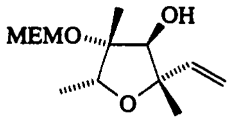 | 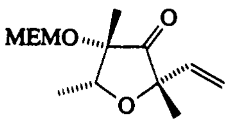 | 5 equiv. PDC, DCM, r.t., 16 h | 85 | 136 |
| 11 | 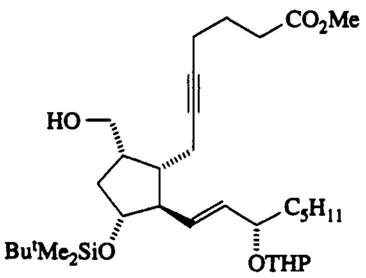 CO₂Me<br>HO<br>C₅H₁₁<br>Bu^tMe₂SiO<br>OTHP | 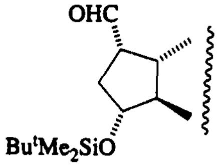 OHC<br>Bu^tMe₂SiO | 20 equiv. PDC, DCM, r.t., 11 h | 85 | 137 |
| 12 | 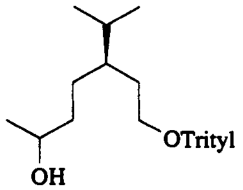 | 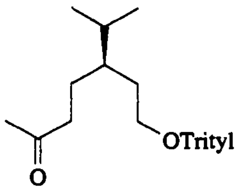 | 3 equiv. PDC, DCM, r.t., 48 h | 97 | 138 |
| 13 | 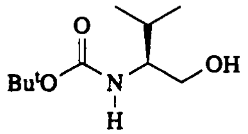 | 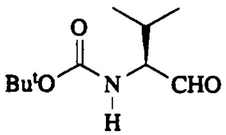 O<br>Bu^tO<br>N<br>H<br>CHO | 1.5 equiv. PDC, DCM, r.t., 16 h | 95 | 139 |
| 14 | 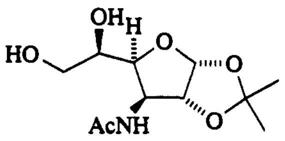 OH<br>H<br>HO<br>O<br>O<br>O<br>AcNH | 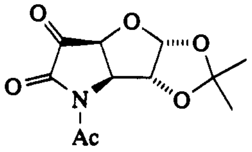 | 10 equiv. PDC, DMF, r.t., 24 h | 68 | 140 |

the rate and thus reduce side reactions.) Overoxidation can be a problem, but is conveniently avoided by the inclusion of *ca.* 20% DMF as cosolvent (equations 14 and 15).[144] In the absence of DMF, and with excess oxidant, this method may also be used to prepare acids in good yields.

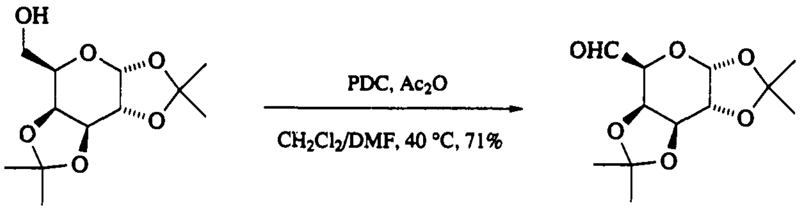
OH
O
O
O
O
O
PDC, Ac₂O
CH₂Cl₂/DMF, 40 °C, 71%
OHC
O
O
O
O
O

(14)

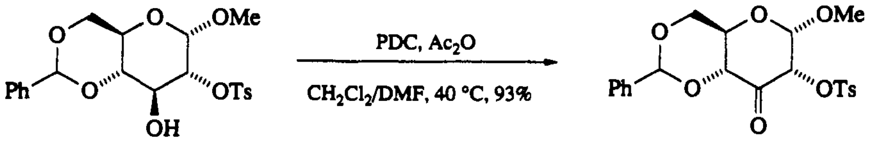
O
O
OMe
Ph
O
OTs
OH
PDC, Ac₂O
CH₂Cl₂/DMF, 40 °C, 93%
O
O
OMe
Ph
O
OTs
O

(15)

PDC with trimethylsilyl chloride[145] is not only a rapid oxidizing agent for alcohols, but will also effect a deprotection–oxidation sequence for silyl ethers. Both trimethylsilyl and *t*-butyldimethylsilyl ethers, which are normally stable to PDC, can be transformed directly into the corresponding carbonyl compounds in good yield (Table 13).

**Table 13** Oxidation of Alcohols and Silyl Ethers with PDC/$Me_3SiCl$

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 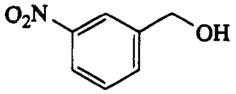 | 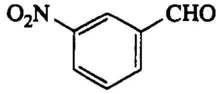 | 1.5 equiv., DCM, 2 h, r.t. | 90 | 145 |
| 2 | 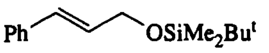 | 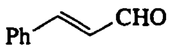 | 1.5 equiv., DCM, 1 h, r.t.[a] | 95 | 145 |
| 3 | 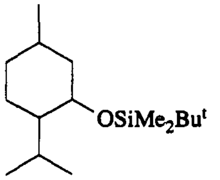 | 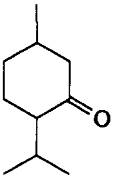 | 1.5 equiv., DCM, 1 h, r.t. | 95 | 145 |
| 4 | 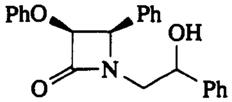 | 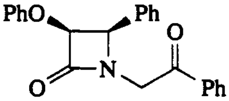 | 1.5 equiv., DCM, 25 min, r.t. | 88 | 145 |
| 5 | 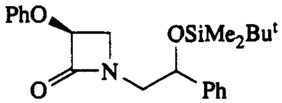 | 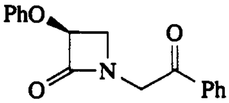 | 1.5 equiv., DCM, 1 h, r.t. | 85 | 145 |
| 6 | 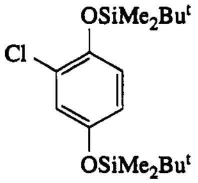 | 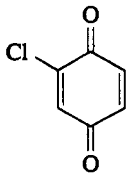 | 3 equiv., DCM, 20 min, r.t. | 70 | 145 |
| 7 | 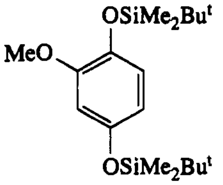 | 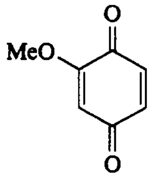 | 3 equiv., DCM, 15 min, r.t.[a] | 74 | 145 |

[a] Oxidation with preformed reagent.

This deprotection–oxidation can also be applied to the preparation of quinones from trialkylsilyl-protected hydroquinones. This method has wider applicability than that reported employing PCC,[89] since substrates with electron-releasing *and* those with electron-withdrawing groups are oxidized. Use of the reagent prepared *in situ* appears to be preferable to the preformed reagent.

It is possible to use PDC as a catalytic oxidant (10 mol %), with bis(trimethylsilyl) peroxide as the cooxidant, for the preparation of carbonyl compounds.[146,147] It is necessary to add the cooxidant slowly *via* syringe pump since the actual oxidizing agent (**15**) is unstable in solution. A range of primary and secondary alcohols were oxidized in good yields by this method (Table 14). Fortunately, isolated double bonds are inert under these conditions.

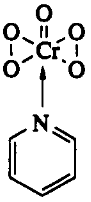

**(15)**

Table 14 Oxidation of Alcohols and Silyl Ethers with PDC and $(Me_3SiO)_2$

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 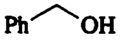 | 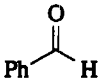 | 3 equiv. $(Me_3SiO)_2$, 10 mol % PDC | 91 | 147 |
| 2 | 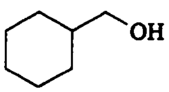 | 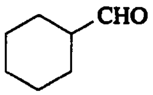 | 3 equiv. $(Me_3SiO)_2$, 10 mol % PDC | 71 | 147 |
| 3 | 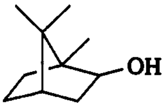 | 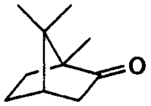 | 3 equiv. $(Me_3SiO)_2$, 10 mol % PDC | 98 | 147 |
| 4 | 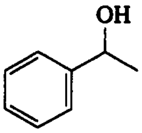 | 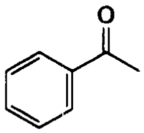 | 3 equiv. $(Me_3SiO)_2$, 10 mol % PDC | 97 | 147 |
| 5 | 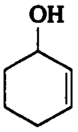 | 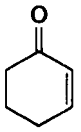 | 3 equiv. $(Me_3SiO)_2$, 10 mol % PDC | 90 | 147 |

Under similar conditions chromium(VI) oxide and PCC were found to be less effective. Other cooxidants were also examined: hydrogen peroxide gives unacceptable amounts of overoxidation of aldehydes, whilst *t*-butyl hydroperoxide, di-*t*-butyl peroxide and benzoyl peroxide all failed as cooxidants.

For substrates that will withstand it, Czernecki and coworkers have developed a work-up procedure for PDC reactions that should be applicable to other reagents.[143,148] Oxalate is known to be a very good ligand for chromium(III). Thus treatment of a reaction mixture with an aqueous solution of oxalic acid dihydrate and ammonium oxalate monohydrate readily removes residual chromium(III) salts. This procedure is particularly useful for large scale reactions.

Pyridinium dichromate will also undergo several other oxidation reactions, though not as many as PCC.

Aromatic oximes, for example, can be converted back to carbonyl compounds with only 2 equiv. of PDC in 1 h at room temperature.[149] PDC will also cleave enol ethers.[106,150]

Allylic C—H oxidation is known to occur if 1,4-dienes are treated with PDC in boiling chloroform[15] (equation 16).[151] In the presence of *t*-butyl hydroperoxide, PDC becomes an effective allylic and

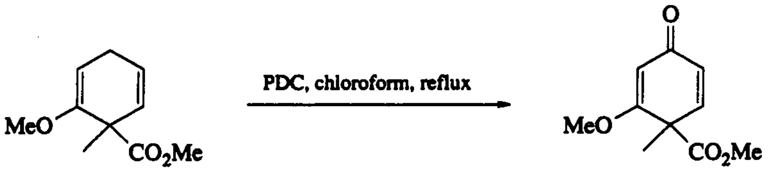

(16)

benzylic oxidant.[152] In steroidal systems reasonable amounts of allylic oxidation have been observed simply with excess PDC in benzene, DMSO or pyridine.[116]

### 2.7.3.6 Other Dichromates

#### *2.7.3.6.1 3-Carboxypyridinium dichromate (nicotinium dichromate)*

Nicotinium dichromate (**16**) is a stable, nonhygroscopic, nonphotosensitive, mild oxidant.[153,154] Nicotinium dichromate alone in dichloromethane gives moderate selectivity for benzylic and allylic over saturated alcohols. This selectivity is further increased by the use of benzene as solvent.

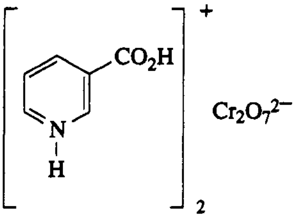

**(16)**

It was noted earlier that electron-withdrawing groups on aromatic rings tend to retard benzylic oxidation. However, addition of pyridine was found to improve these sluggish reactions. Indeed, pyridine appears to give good improvements in rates for the oxidation of many substrates. Use of 1:2.5:20 alcohol:nicotinium dichromate:pyridine generally gives quick oxidations, but there is an accompanying loss of selectivity with these faster reactions. Little (*E*)/(*Z*)-isomerization has been detected, but carbon–carbon bond cleavage is observed, especially in situations where there are electron-withdrawing groups β to the hydroxy group. This implies that the excess pyridine may promote formation of the enol, which may then be attacked by the remaining oxidant.

Nicotinium dichromate has been reported to be particularly useful for large scale carbohydrate oxidations where other modified chromium oxidants have failed.[155]

In the presence of pyridine, nicotinium dichromate is also a sufficiently strong oxidant for the preparation of quinones from hydroquinones.

Arenethiols may be dimerized to disulfides by nicotinium dichromate but aliphatic thiols are virtually inert.

4-Carboxypyridinium dichromate (isonicotinium dichromate) has also been prepared by Palomo and coworkers. It appears to have very similar properties to nicotinium dichromate,[154] and offers no further advantage for the oxidation of alcohols.

#### *2.7.3.6.2 Quinolinium dichromate*

Quinolinium dichromate (**17**)[156] shows the solubility profile common to most chromium based oxidants—sparingly soluble in chlorinated solvents, but more soluble in more polar solvents. It has been mainly used in dichloromethane at reflux, or in DMF at 30 °C to oxidize primary alcohols. Secondary alcohols are also oxidized reasonably well.

Quinolinium dichromate displays reverse selectivity to PDC: in dichloromethane primary alcohols can be oxidized directly to acids, but in DMF the oxidation is selective for the preparation of aldehydes.

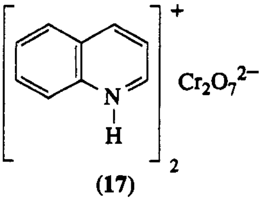

**(17)**

#### *2.7.3.6.3 Imidazolium Dichromate (IDC)*

Imidazolium dichromate is a selective oxidant for allylic and benzylic hydroxy groups.[157] (Allylic alcohols are oxidized faster than benzylic alcohols.) The selectivity over saturated alcohols is similar to that of 4-(dimethylamino)pyridinium chlorochromate. DMF is recommended as the solvent for oxidations, since it appears that the choice of solvent is critical to obtaining high yields. This reagent has also been observed to cause some (*E*)/(*Z*)-isomerization during the oxidation of allylic alcohols.

#### *2.7.3.6.4 1,8-Naphthyridinium dichromate*

This mild oxidant is stable in the absence of light, and is a weaker oxidant than PCC or BPCC; it is also less acidic, and displays good selectivity for benzylic alcohols.[121]

## 2.7.4 OTHER CHROMIUM(VI) OXIDE OXIDANTS

### 2.7.4.1 Chromium(VI) Oxide in Diethyl Ether

Fleet and coworkers discovered that chromium(VI) oxide in 3:1 dichloromethane/diethylether, in the presence of celite, acts as an efficient oxidant for a range of alcohols, and is tolerant of a wide range of acid labile functionalities.[158] In dichloromethane alone chromium(VI) oxide was reported to be inert due to low solubility. This oxidant is particularly effective for the preparation of ketones, but aldehydes, especially α,β-unsaturated, are found to be prone to overoxidation. The oxidizing species is unstable, and therefore it is better to add chromium(VI) oxide to a solution of the alcohol in 3:1 dichloromethane/diethylether. (*N.b.* Diethyl ether/chlorinated solvent mixtures have been reported elsewhere to inflame spontaneously in the presence of chromium(VI).[159])

### 2.7.4.2 Chromium(VI) Oxide and Crown Ethers

In contrast to earlier reports, Palomo and coworkers found that chromium(VI) oxide will effect the oxidation of alcohols in one day at room temperature.[159] They also found that the addition of semicatalytic amounts (0.3 equiv.) of crown ethers (either 18-crown-6 or 12-crown-4) led to significant rate enhancements. The crown ethers are thought to generate a soluble oxidizing agent, similar to the alkyl ammonium salts used for solid–liquid phase transfer with chromium(VI) oxide in dichloromethane (*vide infra*).

Chromium(VI) oxide will also oxidize hydroquinones to quinones, and thiols to disulfides.[160]

### 2.7.4.3 Catalytic Chromium(VI) Oxide Oxidations

#### *2.7.4.3.1 $CrO_3$ with t-butyl hydroperoxide*

Chromium(VI) oxide can be used as a catalytic oxidant for alcohols with *t*-butyl hydroperoxide as the cooxidant.[161] This reagent appears to be selective for allylic and benzylic over saturated alcohols, though (*E*)/(*Z*)-isomerization has been observed during the preparation of α,β-unsaturated aldehydes. This reagent is also a good oxidant for allylic and benzylic C—H bonds; these may be competing pathways in more sophisticated substrates.[162–164]

#### *2.7.4.3.2 $CrO_3$ complex with 2,4-dimethylpentane-2,4-diol*

Corey *et al.*[165] reported that the complex formed by chromium(VI) oxide and 2,4-dimethylpentane-2,4-diol can be used as a catalytic oxidant with peroxyacetic acid as a cooxidant. When used stoichiometrically, secondary alcohols are oxidized quickly even at –20 °C, but the oxidation of primary alcohols is slow and large amounts of ester coupling are observed.

With the catalytic system secondary alcohols are still oxidized quickly (Scheme 2) and in excellent yield with 2 equiv. of peracetic acid at 0 °C. Primary alcohols are also reported to be oxidized to aldehydes in good yields, but details have not been given.[165]

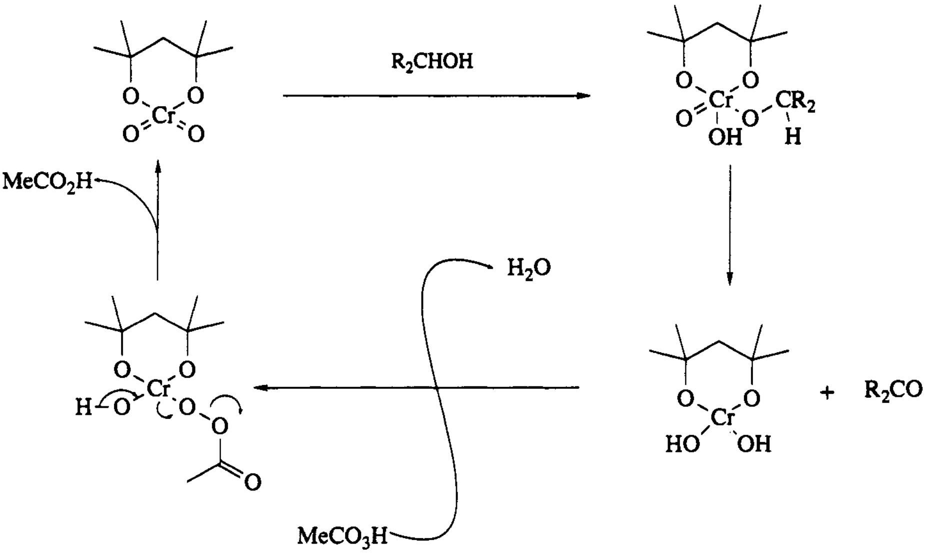

Scheme 2

The use of this oxidant is restricted by the sensitivity of potential substrates to the cooxidant (peracetic acid). *t*-Butyl hydroperoxide and hydrogen peroxide were found to be ineffective for the regeneration of the complex.

## 2.7.5 SUPPORTED OXIDANTS

Many oxidants, especially the older and stronger chromium oxidizing agents, may have their reactivity and selectivity modified by adsorption on to inert supports.[166] Reactions utilizing supported oxidants have the advantage that the residual chromium salts remain bound to the support and thus work-up often becomes reduced to a mere filtration. Many of these systems are discussed in detail later (Volume 7, Chapter 7.3).

Supported chromium oxidants fall in to three main categories: (i) adsorbed on alumina, silica or celite (Section 2.7.5.1); (ii) adsorbed on a polymer or resin (Section 2.7.5.2); and (iii) adsorbed on carbon (Section 2.7.5.3).

### 2.7.5.1 On Inert Inorganic Supports

Adsorbing PCC onto alumina not only eliminates the need to buffer reactions with sodium acetate, it also enhances its reactivity.[95] In addition, work-up requires only a filtration and then concentration. The reagent is stable for several weeks when stored under vacuum and in the absence of light (Table 15).

Pyridinium chromate on silica[170] is also a good general oxidant, even in the presence of acid labile groups. In contrast to PCC on alumina this oxidant may be stored at room temperature for one year, with no loss of activity. It is convenient to use it in the form of a column when performing small scale oxidations; the substrate is allowed to stand on the column for a few hours, and then the carbonyl compound is obtained simply by eluting the column with a suitable solvent.

Chromic acid is a very strong oxidizing agent, but its reactivity may be tempered by adsorption onto a support. Chromic acid on alumina was found to be inactive,[171] but on silica it gives instantaneous oxidation, in diethyl ether at room temperature, of primary and secondary alcohols to aldehydes and ketones in good to excellent yield. This reagent can also be conveniently used in the form of a column.[168–170]

In a similar fashion, chromyl chloride, normally a very vigorous oxidant, can be used to selectively prepare aldehydes and ketones once it has been adsorbed onto silica–alumina.[172] Unfortunately, double bonds are still cleaved under the reaction conditions.

Table 15 Oxidation of Alcohols with Chromium Reagents on Inert Inorganic Supports

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 1 | 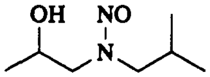 | 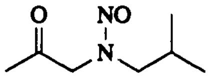 | 3 equiv. $CrO_3$ on celite, EtOAc, r.t., 15 min | 76 | 167 |
| 2 | 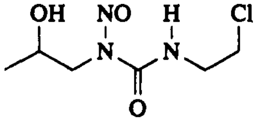 | 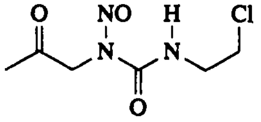 | 3 equiv. $CrO_3$ on florisil, EtOAc, r.t., 10 min | 79 | 167 |
| 3 | 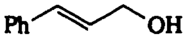 | 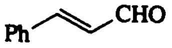 | $H_2CrO_4$, silica gel, $CCl_4$, r.t., 20 min | 78 | 168 |
| 4 | 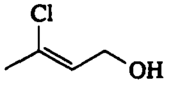 | 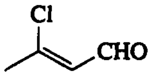 | $H_2CrO_4$, silica gel, $CCl_4$, r.t., 20 min | 69 | 168 |
| 5 | 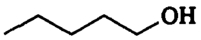 | 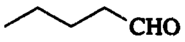 | $H_2CrO_4$, aluminum silicate, petroleum ether, 48 h | 74 | 169 |
| 6 | 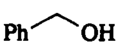 | 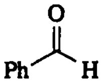 | $H_2CrO_4$, aluminum silicate, petroleum ether, 48 h | 90 | 169 |
| 7 | 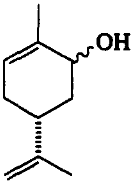 | 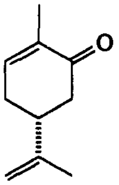 | 1.6 equiv. PCC/alumina, *n*-hexane, 2 h | 93 | 95 |
| 8 | 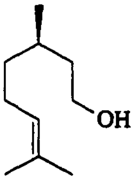 | 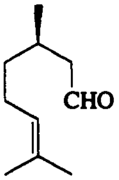 | 3 equiv. PCC/alumina, *n*-hexane, 4 h | 82 | 95 |
| 9 | 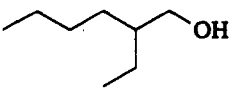 | 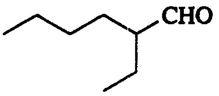 | 2.5 equiv. PCC/alumina, *n*-hexane, 2 h | 87 | 95 |

Chromium trioxide oxidations have also consistently been found to be enhanced by the addition of Florisil or celite.[167]

### 2.7.5.2 On Resins/Polymers

Chromic acid also becomes a selective oxidant for the preparation of aldehydes and ketones when it is supported on an anion exchange resin (Amberlyst A-26; Table 16).[177] The reaction appears to be general and highly tolerant of a wide range of solvents, unlike many resin-based oxidations where the availability of the oxidant is critically dependent upon the nature of the solvent.

Gelbard *et al.*[173] have prepared a number of neutral and acidic supported ammonium chromates. Neutral resins were found to be generally more effective than acidic resins. The large differences in reactivity between different unbound, soluble alkylammonium chromates (Section 2.7.6.1) are not so pronounced with the polymer-supported oxidants. Some comments about the reactivity of these supported oxidants were made: (i) quaternary ammonium salts are more reactive than the tertiary pyridinium chromates; (ii) the reactivity of a complex chromate $XCrO_3^-$ was found to increase as the basicity of $X^-$ decreases. Best

**Table 16** Oxidation of Alcohols with Chromium Reagents on Polymers/Resins

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield(%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 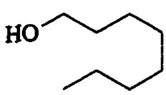 | 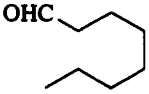 | 7 equiv. Cr on Amberlyst A-26, 12h$^{a}$ | 80 | 173 |
| 2 | 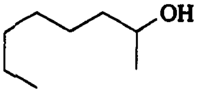 | 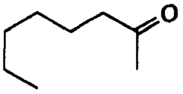 | 7 equiv. Cr on Amberlyst A-26, 12h$^{a}$ | 92 | 173 |
| 3 | 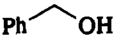 | 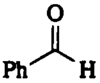 | 10 equiv. Cr on Amberlyst A-26, 12 h$^{a}$ | 73 | 173 |
| | | | 4 equiv. PVPCC, 0.25 h$^{b}$ | 95 | 174 |
| | | | 1.1 equiv. PVPDC, (wet), 2 h$^{c}$ | 96 | 175 |
| 4 | 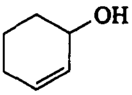 | 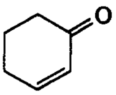 | 8 equiv. Cr on Amberlyst A-26, 8 h$^{a}$ | 2 | 173 |
| 5 | 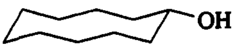 | 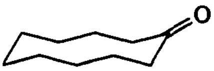 | Cr$^{III}$/NAFK with Bu$^{t}$OOH$^{d}$ | 86 | 176 |
| 6 | 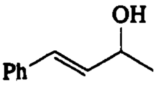 | 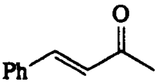 | Cr$^{III}$/NAFK with Bu$^{t}$OOH$^{d}$ | 81 | 176 |
| 7 | 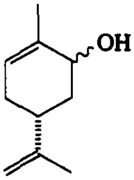 | 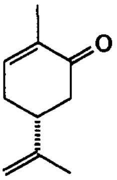 | Cr$^{III}$/NAFK with Bu$^{t}$OOH$^{d}$ | 82 | 176 |
| 8 | 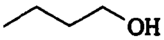 | 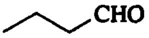 | 4 equiv. PVPCC, 4.5 h$^{b}$ | 90 | 174 |
| | | | 1.1 equiv. PVPDC, (wet), 68 h$^{c}$ | 81 | 175 |
| 9 | 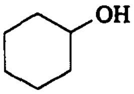 | 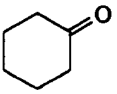 | 4 equiv. PVPCC, 24 h$^{b}$ | 94 | 174 |
| | | | 1.1 equiv. PVPDC, (wet), 68 h$^{c}$ | 66 | 175 |
| 10 | 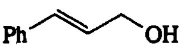 | 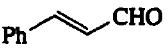 | 4 equiv. PVPCC, 0.5 h$^{b}$ | 100 | 174 |
| | | | 1.1 equiv. PVPDC, (wet), 4 h$^{c}$ | 98 | 175 |

[a] Reactions performed in cyclohexane at 70 °C. [b] Reaction performed at 70–80 °C in cyclohexane. [c] Reaction performed at 60 °C in cyclohexane. [d] Reactions performed in chlorobenzene at 85 °C for 6–8 h using 4 equiv. Bu$^{t}$OOH and 4 mol % of Cr$^{III}$ -impregnated NAFK.

results were obtained with trifluoroacetatochromates; and (iii) nonpolar solvents, such as cyclohexane, enhance reactivity by promoting the diffusion of substrates into the resin. For similar reasons, macroporous resins are preferred to gel types, even when well swollen.

The reagents prepared by Gelbard *et al.* were found to be selective for saturated alcohols, since the oxidation of allylic or benzylic alcohols requires either a vast excess of oxidant or prolonged reaction times.

To overcome the problems of toxicity and work-up associated with many inorganic oxidants, it would be advantageous to develop a catalytic supported oxidant. Towards this aim, chromium(III)-impregnated Nafion 511 (NAFK) has been used as a catalytic oxidant in the presence of *t*-butyl hydroperoxide.[176] This reagent gives good yields of ketones (80–100%), but unfortunately oxidation of primary alcohols leads to the formation of complex mixtures.

Poly(vinylpyridinium chlorochromate) (PVPCC)[174] is a mild oxidant for primary, secondary, allylic and benzylic alcohols. Unfortunately, optimum conditions require the use of very nonpolar solvents (best is cyclohexane) at 80 °C. More polar solvents (that would be more generally useful in synthesis) severely retard the rate of oxidation, thus necessitating an increase in the amount of oxidant used. Oxidations were found to have high inital rates, but were very slow to go to completion due to the inaccessibility of the chromium. This can be overcome by using a lower loading of oxidant or by an alternative preparation of the polymer,[175] where the addition of 1–5% divinylbenzene gives a much more porous resin.

Poly(vinylpyridinium dichromate) can be prepared in a similar way to PVPCC.[175] To be effective it must be used in the presence of water and in the most nonpolar solvent possible. It gives moderate to good yields, but long reaction times may be required for the reaction to proceed to completion. Even with the long reaction times, very little overoxidation is observed. Up to five oxidation–regeneration cycles may be completed without significant loss of activity.

### 2.7.5.3 On Carbon

Lalancette *et al.* described the preparation of chromium(VI) oxide intercalated in graphite[178] and its use as a selective oxidant for primary alcohols to aldehydes (Table 17). Secondary and tertiary alcohols are inert under the reaction conditions, but 1,2-diols are cleaved. However, Ebert and coworkers demonstrated that Lalancette probably used $Cr_2O_8$ rather than chromium(VI) oxide intercalated graphite for these oxidations.[179] This reagent does appear to show the properties described by Lalancette *et al.* Indeed, when Kagan and coworkers prepared fully characterized chromium(VI)-intercalated graphite it appeared to lack any oxidative properties.[180]

**Table 17** Oxidation of Alcohols with $CrO_3$ and Graphite

| *Entry* | *Substrate* | *Product* | *Conditions*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 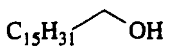 | 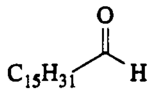 | 24 h | 95 | 178 |
| 2 | 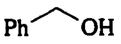 | 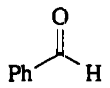 | 24 h | 98 | 178 |
| 3 | 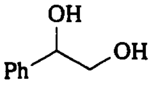 | 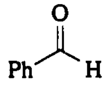 | 24 h | 80 | 178 |
| 4 | 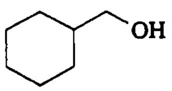 | 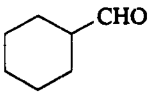 | 48 h | 52 | 178 |
| 5 | 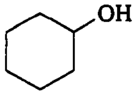 | 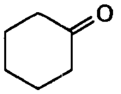 | 24 h | 2 | 178 |
| 6 | 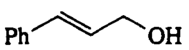 | 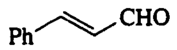 | 96 h | 100 | 178 |
| 7 | 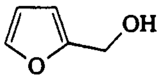 | 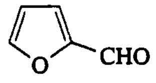 | 48 h | 72 | 178 |

[a] Oxidations in toluene at reflux with 4–10 equiv. of $CrO_3$.

## 2.7.6 MISCELLANEOUS CHROMATES AND DICHROMATES

### 2.7.6.1 Alkylammonium Chromates

Gelbard *et al.*[173,184] reported the use of tetraalkylammonium chromates (Table 18) for the oxidation of alcohols under mild, neutral conditions. They have the advantage of being much more soluble than PCC (and PDC) in standard organic solvents, and are readily prepared from chromium(VI) oxide and the appropriate tetraalkylammonium salt (equation 17).[188] They may be used stoichiometrically or catalytically. In the stoichiometric mode the oxidations are quick, but yields are low due to overoxidation. When used catalytically (Scheme 3 and Table 19), the reactions are much more efficient than the stoichiometric oxidations or oxidation with PCC. This intriguing observation led to the suggestion that there is actually a different oxidizing agent in solution—a complex polychromate (**18**). Overoxidation is not a problem, but the catalytic systems need longer reaction times and thus give rise to some (*E*)/(*Z*)-isomerization.[173]

$$\mathrm{CrO_3 \;+\; X^-NR_4^+ \longrightarrow XCrO_3^-NR_4^+} \qquad (17)$$

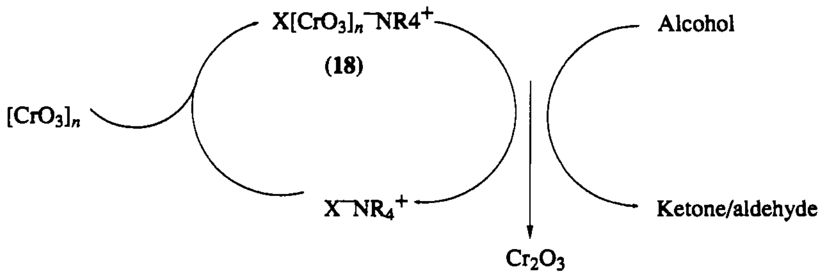

**Scheme 3**

The tetraalkylammonium chromates prepared by Gelbard and coworkers appeared to be equally effective for all types of alcohols, but under the conditions of Santaniello *et al.*,[181] tetra-*n*-butylammonium chlorochromate was found to be a selective benzylic and allylic oxidant. It also efficiently converts aliphatic and aromatic thiols to disulfides. Trimethylammonium chlorochromate has also been reported for the oxidation of allylic alcohols in DMF.[185]

Benzyltrimethylammonium chlorochromate is a neutral oxidant with similar selectivity to PFC.[118] However, it normally requires longer reaction times and higher temperatures (at reflux in 1,2-dichloroethane).

With only minor modifications it is possible to prepare a selective oxidant for benzylic alcohols: benzyltriethylammonium chlorochromate under phase transfer conditions exhibits such a preference.[182] The preparation of benzyltriethylammonium chlorochromate had been reported previously,[183] but was initially assigned as the dichromate. It was demonstrated that this reagent (chromate or dichromate) shows good selectivity for benzylic and allylic alcohols, but unfortunately it was necessary to perform the oxidation in HMPT.

### 2.7.6.2 Trimethylsilyl Chlorochromate (TMSCC)

Trimethylsilyl chlorochromate (**19**) must be formed *in situ* from trimethylsilyl chloride and moist, powdered chromium(VI) oxide,[186,187] since attempted isolation results in explosions.

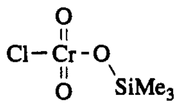

$$\mathrm{Cl-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{Cr}}-O-SiMe_3}$$

**(19)**

Trimethylsilyl chlorochromate gives good yields for secondary alcohols and benzylic alcohols, but saturated primary alcohols give complex mixtures. It will also oxidise thiols to disulfides, and cleave

**Table 18** Oxidation of Alcohols with Tetraalkylammonium Chromates

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 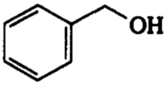 | 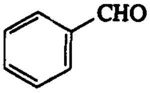 | 3 equiv., $Bu_4N^+$, 4 h, reflux[a]<br>1.5 equiv., $BnEt_3N^+$, 24 h, r.t.[b]<br>0.7 equiv., $BnEt_3N^+$, 4–6 h, HMPT[c] | 65<br>72<br>90 | 181<br>182<br>183 |
| 2 | 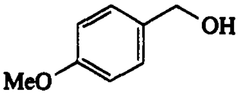 | 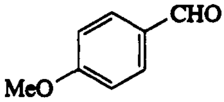 | 3 equiv., $Bu_4N^+$, 7 h, reflux[a]<br>0.7 equiv., $BnEt_3N^+$, 4–6 h, HMPT[c] | 85<br>95 | 181<br>183 |
| 3 | 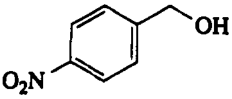 | 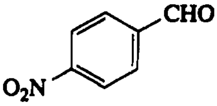 | 3 equiv., $Bu_4N^+$, 3 h, reflux[a] | 82 | 181 |
| 4 | 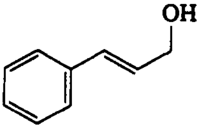 | 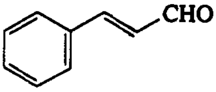 | 3 equiv., $Bu_4N^+$, 3 h, reflux[a] | 82 | 181 |
| 5 | 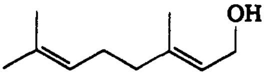 | 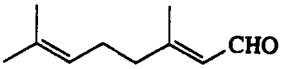 | 3 equiv., $Bu_4N^+$, 7 h, reflux[a]<br>3 equiv., $BnMe_3N^+$, 6 h, reflux[d] | 72<br>83<br>71:29 *(E):(Z)* | 181<br>118 |
| 6 | 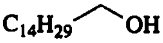 | 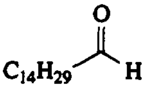 | 3 equiv., $Bu_4N^+$, 24 h, reflux[a] | 10 | 181 |
| 7 | 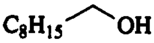 | 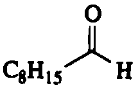 | 0.7 equiv., $BnEt_3N^+$, 4–6 h, HMPT[c] | 30 | 183 |
| 8 | 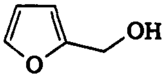 | 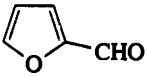 | 0.7 equiv., $BnEt_3N^+$, 4–6 h, HMPT[c] | 71 | 183 |
| 9 | 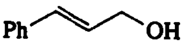 | 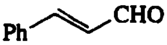 | 1.5 equiv., $BnEt_3N^+$, 24 h, r.t.[b]<br>0.7 equiv., $BnEt_3N^+$, 4–6 h, HMPT[c] | 72<br>90 | 182<br>183 |
| 10 | 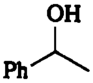 | 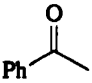 | 1.5 equiv., $BnEt_3N^+$, 24 h, r.t.[b] | 50 | 182 |
| 11 | 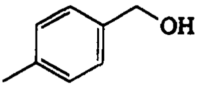 | 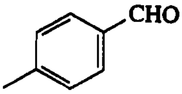 | 1.5 equiv., $BnEt_3N^+$, 24 h, r.t.[b] | 75 | 182 |
| 12 | 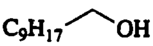 | 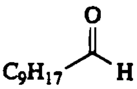 | 3 equiv., $BnMe_3N^+$, 10 h, reflux[d] | 92 | 118 |

**Table 18** *(continued)*

| *Entry* | *Substrate* | *Product* | *Conditions* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 13 | 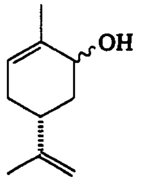 | 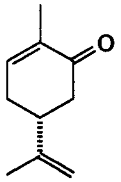 | 3 equiv., $BnMe_3N^+$, 4 h, reflux[d] | 87 | 118 |

[a] Reaction in chloroform. [b] Under phase transfer conditions. [c] Reactions performed at 60–80 °C. [d] Reaction in 1,2-dichloroethane.

**Table 19** Oxidation of Alcohols with $CrO_3$ and Catalytic *n*-Butylammonium Chloride

| *Entry* | *Substrate* | *Product* | *Conditions*[a] | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 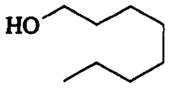 | 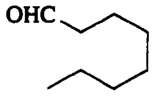 | 90 min | 60 | 173 |
| 2 | 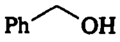 | 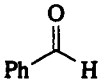 | 120 min | 70 | 173 |
| 3 | 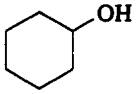 | 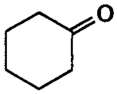 | 90 min | 63 | 173 |
| 4 | 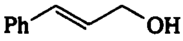 | 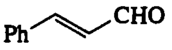 | 15 min | 85 | 173 |

[a] Reactions were carried out on a 50 mmol scale in DCM at r.t. using $CrO_3$ with 5 mol % of $Bu_4NCl$.

oximes and benzyl esters. Hence, it appears that trimethylsilyl chlorochromate does not offer any obvious advantage over other reagents available for the oxidation of alcohols.

### 2.7.6.3 Alkyl Metal Chromates

Oxidations with stoichiometric inorganic oxidants can generate large quantities of toxic waste and thus present potentially serious environmental problems. In part answer, several catalytic systems have been developed around different elements, but there still remains the problem of disposal of the cooxidant. Recently, Shapley and coworkers have reported the preparation of two alkyl metal complexes; *cis*-$[Bu^n{}_4N][Os(N)(CH_2SiMe_3)_2(CrO_4)]$ (**20**) and *cis*-$[PPh_4][Os(N)Me_2(CrO_4)]$ (**21**) (equation 18),[188] that are thermally stable and inert to most standard organic solvents. They act as catalysts (5 mol %) for the oxidation of primary and secondary alcohols, using air as cooxidant. Allylic and benzylic alcohols are oxidized faster than saturated secondary alcohols, which in turn are oxidized faster than saturated primary alcohols. No products of overoxidation could be detected. The chromates also appear to be inert towards

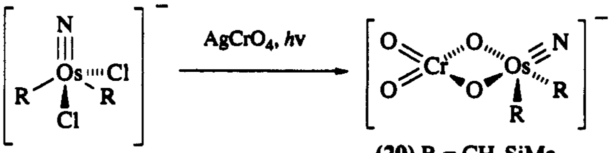

(18)

(**20**) R = $CH_2SiMe_3$
(**21**) R = Me

carbon–carbon double bonds. Chromate (**21**) was found to be more reactive than the more bulky chromate (**20**).

Turnovers for these oxidations range from moderate (57) to poor (2) but can be significantly improved by the addition of a copper(II) salt (10 mol %).

Even though the reactions are slow and the catalyst is degraded under the reaction conditions, the possibility of a ruthenium analog makes this a particularly promising area for further development.

### 2.7.6.4 Bis(tetrabutylammonium) Dichromate

Bis(tetrabutylammonium) dichromate is a neutral oxidant which at reflux in dichloromethane acts as a selective oxidant for allylic and benzylic alcohols.[189] Only 10% of oxidation products are obtained after treatment of *n*-decanol with bis(tetrabutylammonium) dichromate for 24 h.

### 2.7.6.5 Tetrakis(pyridine)silver Dichromate

Many chromium oxidants suffer from problems of stability, light sensitivity or acidity, but tetrakis(pyridine)silver dichromate[190] is stable, nonphotosensitive, nonhygroscopic and a neutral oxidant. It can be used to oxidize allylic and benzylic alcohols selectively in benzene. Unfortunately, it cannot be used in chlorinated solvents because it decomposes in these solvents.

A possible drawback for this oxidant is that the use of silver in a stoichiometric oxidant may render the reagent too expensive for large scale oxidations.

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# 2.8

# Oxidation Adjacent to Oxygen of Alcohols by Activated DMSO Methods

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## 2.8.1 INTRODUCTION

The nucleophilic nature of the sulfinyl oxygen of sulfoxides has been used to good effect in synthetic chemistry, most notably in the oxidation of primary and secondary alcohols to aldehydes and ketones using dimethyl sulfoxide (DMSO). The first report of the use of dimethyl sulfoxide in such an oxidation was due to Pfitzner and Moffatt,[1] although Kornblum had previously demonstrated the use of dimethyl sulfoxide as an oxidant for the conversion of alkyl halides to aldehydes.[2] There are now many examples of how advantageous the use of dimethyl sulfoxide can be, most notably in the oxidation of primary alcohols to aldehydes without overoxidation to carboxylic acids. Despite much activity in this area, resulting in a plethora of activated dimethyl sulfoxide reagents which behave as an oxidant, the method is still basically that originally described by Pfitzner and Moffatt. However, considerable practical improvements have been made by a number of groups, most notably that of Swern, who utilized oxalyl chloride as the activator, and the 'Swern oxidation' is now a well-established synthetic method.

To appreciate this important reaction requires a mechanistic understanding of how dimethyl sulfoxide can be activated for use as an oxidant. The following discussion therefore begins with the general mechanism of the reaction, followed by a description of the use of the more important activation methods, many of which are complementary. A description of the process from the viewpoint of the substrate then follows, emphasizing the advantages of using the activated dimethyl sulfoxide oxidation method. Earlier examples of the use of the method have been reviewed previously,[3–5] hence the present discussion concentrates on more recent applications.

## 2.8.2 GENERAL MECHANISM OF ACTIVATED DMSO OXIDATION

The key to successfully using dimethyl sulfoxide as an oxidant for alcohols is to activate the sulfur atom prior to reaction with a nucleophilic alcohol function. This activation involves electrophilic attack upon the sulfinyl oxygen by a variety of electrophiles. The initial product formed when an alcohol does attack the activated dimethyl sulfoxide is known to be the sulfonium salt (**1**; Scheme 1).

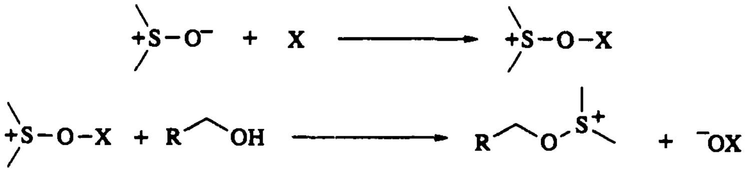

**(1)**

Scheme 1

Studies using $^{18}O$-labeled dimethyl sulfoxide have confirmed this pathway as opposed to an alternative in which the alcohol initially attacks the activator (Scheme 2) to form an ester which is subsequently attacked by dimethyl sulfoxide to give the same sulfonium species as above.[6]

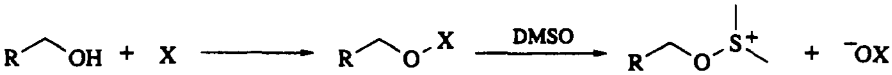

**(1)**

Scheme 2

The reaction requires the addition of base (commonly triethylamine) and results in the formation of an ylide (**2**; Scheme 3), which collapses intramolecularly to the carbonyl compound.[6,7–9] Further supportive evidence for ylide formation lies in the observation that sulfonium salts lacking a hydrogen α to the sulfur do not break down to form the carbonyl compound.[10]

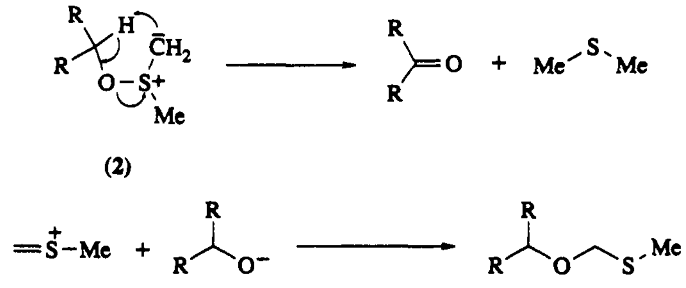

**(2)**

**(3)**

Scheme 3

Common by-products in these reactions are (methylthio)methyl ethers (**3**) formed by a Pummerer rearrangement which occurs *via* an alternative breakdown of (**2**), as shown in Scheme 3. The proportion of the Pummerer rearrangement derived product varies with the electrophilic activator used.

One of the major considerations in the choice of activator is the temperature at which the reaction can be performed. Most of the electrophilic activators used react rapidly with dimethyl sulfoxide, some of them violently; consequently temperatures of less than –30 °C are typically required. Another important consequence of these oxidations is that the initially acidic mixture becomes basic on completion of the oxidation, and highly sensitive substrates may undergo side reactions. An example of this is seen in the oxidation of the carbohydrate (**4**; equation 1) using sulfur trioxide/pyridine complex as the dimethyl sulfoxide activator, which causes spontaneous elimination of a β-acetoxy group.[11] As seen later, the use of the Swern variation overcomes these problems.

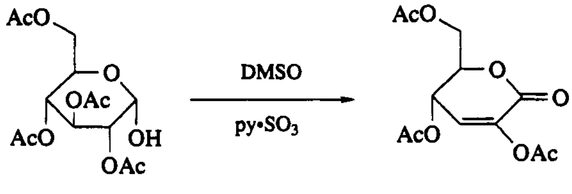

(4)

(1)

Oxidation of primary alcohols to aldehydes using these oxidants does not result in overoxidation to carboxylic acids, in contrast to many other oxidants. This arises since the aldehydes are formed under anhydrous conditions and are not capable of hydration, which is a necessary requirement for conversion to a carboxylic acid.

## 2.8.3 ACTIVATED DMSO REAGENTS

### 2.8.3.1 DMSO–Dicyclohexylcarbodiimide

The original Pfitzner–Moffatt procedure for alcohol oxidation by activated dimethyl sulfoxide utilized dicyclohexylcarbodiimide (DCC) and a source of protons such as polyphosphoric acid or pyridinium trifluoroacetate.[1] The use of strong acids such as the common mineral acids must be avoided since, although acidic conditions are initially required, the reaction must readily become basic in the later stages of the process. Mechanistically it is reasonable to suggest that the activation follows the pattern whereby initial attack of the nucleophilic sulfinyl oxygen of dimethyl sulfoxide, with the protonated carbodiimide, forms a sulfonium isourea. This is followed by displacement of dicyclohexylurea by the alcohol to form an alkoxysulfonium salt. Base treatment of this salt forms an ylide, which collapses *via* the proven cyclic mechanism to the carbonyl compound and dimethyl sulfide (Scheme 4).

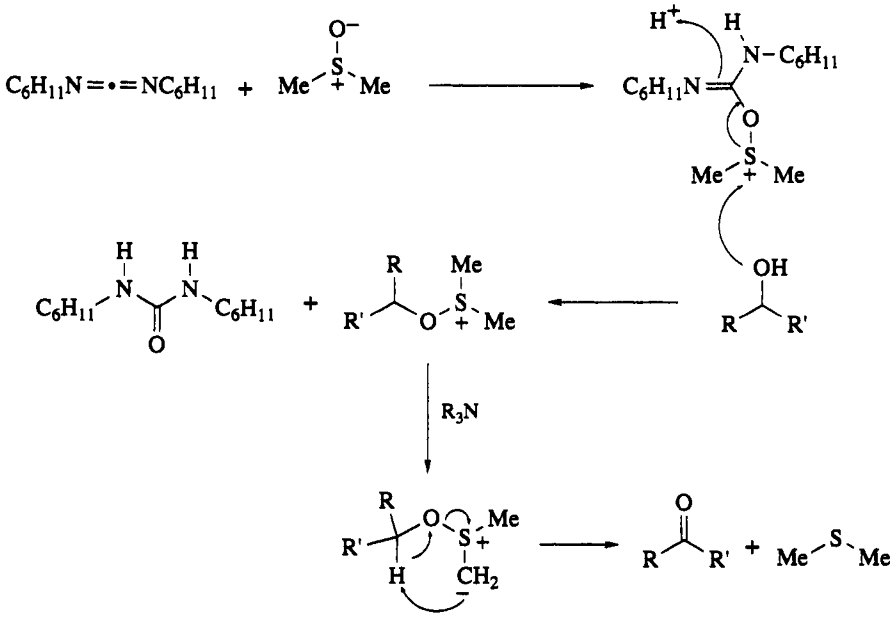

**Scheme 4**

One of the disadvantages of this procedure is that a large excess of DCC is required, the residue of which is difficult to remove during work-up, as is the dicyclohexylurea formed during oxidation. These problems provided the impetus behind the development of alternative activating agents. For example the water-soluble diimide 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide[12] should partially solve the work-up problem, and the use of polymer-bound DCC should permit the efficient removal of the urea by-product.[13] However, despite these limitations, much use has been made of the Pfitzner–Moffatt oxidation, especially during the oxidation of carbohydrate derivatives. For example the amino sugar derivative (**5**; equation 2) was converted in 86% yield to the corresponding ketone.[14]

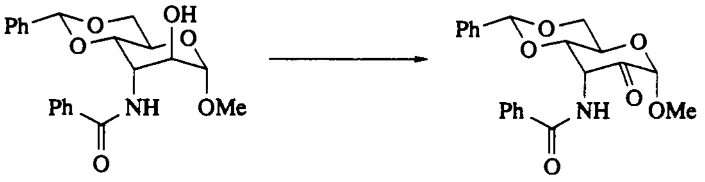

(**5**)

(2)

This combination was also suitable for the clean conversion of the alcohol (**6**; equation 3)[15] to the corresponding aldehyde, whereas all other attempts resulted in concurrent protiodesilylation or in the formation of the conjugated aldehyde (**7**).

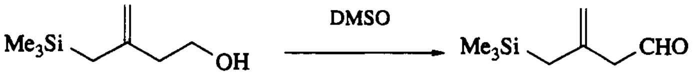

(**6**)

(3)

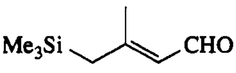

(**7**)

## 2.8.3.2 DMSO–Acetic Anhydride

Upon the addition of dimethyl sulfoxide to acetic anhydride the species (**8**; equation 4) is formed, which reacts with alcohols in the usual manner to give carbonyl products.

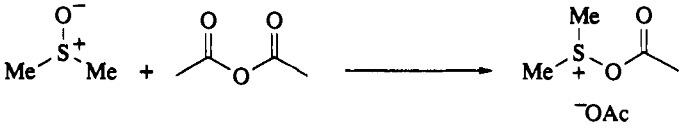

(**8**)

(4)

One of the advantages of using the acetic anhydride system is that the reaction can be performed at room temperature, which is in contrast to a report that trifluoroacetic anhydride is an unsatisfactory activator at this temperature.[16] Attempts have been made to use acylating activators such as benzoic anhydride, phosphorus pentoxide or polyphosphoric acid, although these tend to give lower yields of carbonyl compounds.[16]

In comparison to some of the other activation methods however, the dimethyl sulfoxide–acetic anhydride procedure has certain disadvantages. The method often requires the use of long reaction times (18–24 h), which can result in many side reactions, especially with sensitive substrates. Notable in this respect is that it is not uncommon for this procedure to result in the formation of substantial yields of the thiomethyl ethers obtained from the Pummerer rearrangement product as described above. In fact upon attempted oxidation of cholesterol with this system, the major product obtained was the corresponding (methylthio)methyl ether.[17] Acetates may also be formed if the alcohol is unhindered. For example the sugar derivative (**9**) reacts under these conditions to form an enol acetate (derived from the required carbonyl compound) in 40% yield contaminated with 30% of the acetate (**10**; equation 5).[18]

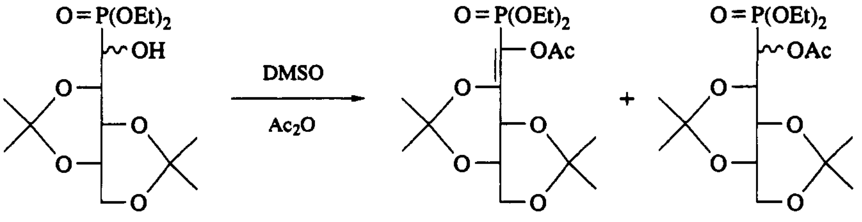

**(9)** **(10)**

(5)

Despite this, some useful oxidations have been achieved using the method, such as that of yohimbine to yohimbinone in 85% yield, which compares well with that achieved by using dimethyl sulfoxide activated with dicylohexylcarbodiimide.[19] The method has also been successfully applied to the oxidation of carbohydrates,[20] as shown by the formation of (**11**; equation 6), and aromatic α-diketones can be efficiently prepared using this method by oxidation of the corresponding acyloin products. Unfortunately this methodology cannot be extended to the more useful aliphatic diketones.[21]

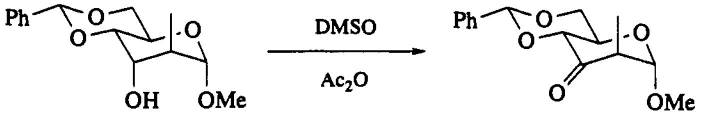

**(11)**

(6)

Amongst other less successful applications, however, are the oxidations of some steroidal systems such as testosterone, which afforded $\Delta^4$-androsterone-3,17-dione in only 34% yield and 11α-hydroxyprogesterone, in which the equatorial hydroxy group was oxidized to afford a poor yield of 11-oxoprogesterone (13%).[16]

### 2.8.3.3 DMSO–Trifluoroacetic Anhydride

Trifluoroacetic anhydride upon mixing with dimethyl sulfoxide can undergo a violent reaction at or just below room temperature. However, it is possible to moderate this behavior by working at temperatures below –60 °C in an inert solvent such as dichloromethane,[22] when dimethyl sulfoxide and trifluoroacetic anhydride react exothermically and instantly to form a white precipitate, which is most probably the species (**12**).

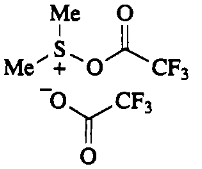

**(12)**

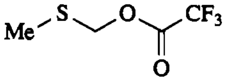

**(13)**

On warming above –30 °C the mixture clears and a Pummerer rearrangement occurs to form (methylthio)methyl trifluoracetate (**13**). However the extent of this by-product formation is minimized at the lower temperature, and the reaction with alcohols gives high yields of carbonyl products over short reaction times. This makes trifluoroacetic anhydride one of the better activators for dimethyl sulfoxide oxidations.

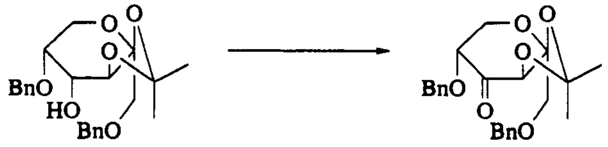

**(14)**

(7)

An oxidation where this system is superior is in the reaction of carbohydrate derivatives where it is notably better than the acetic anhydride method, mainly due to the shorter reaction times, *e.g.* the preparation of the ketone (**14**; equation 7).[23]

### 2.8.3.4 DMSO–Sulfur Trioxide/Pyridine

One of the best activators for dimethyl sulfoxide is the complex of sulfur trioxide/pyridine, which in the presence of triethylamine rapidly oxidizes primary and secondary alcohols to aldehydes and ketones in very good yields at ambient temperature.[24] This reagent also allows the very useful conversion of allylic alcohols to the corresponding α,β-unsaturated carbonyl compounds. A further advantage of this procedure over many of the others is the ease of work-up, especially over the dimethyl sulfoxide–dicyclohexylcarbodiimide method.

The precise intermediates formed in this version of the oxidation are not known, but it is possible that the necessary alkoxysulfonium intermediate is derived from a breakdown of the zwitterion (**15**; Scheme 5).

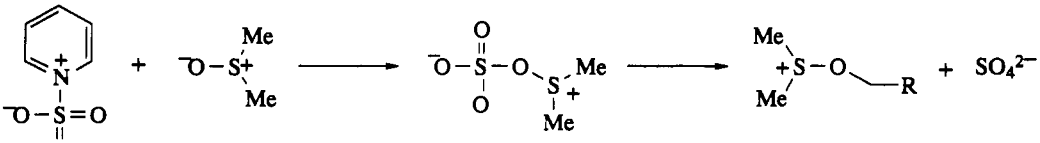

(**15**)

**Scheme 5**

In an example of the use of this activation method testosterone, with a 17β-hydroxy group, was oxidized to Δ$^4$-androstene-3,17-dione very rapidly in high yield, in contrast to the use of DMSO–acetic anhydride. During a reaction, when other oxidizing agents were found to be ineffective, sulfur trioxide/dimethyl sulfoxide led to smooth oxidation of the *cis*-diol (**16**; equation 8) to an *o*-quinone in 49% yield and the *cis*-diol (**17**) to (**18**; equation 9) in 98% yield.[25,26] The use of dimethyl sulfoxide–acetic anhydride for this oxidation gave large amounts of the diacetate as the by-product.

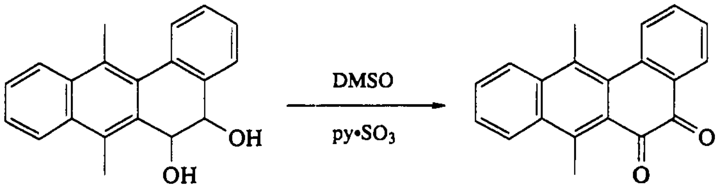

(8)

(**16**)

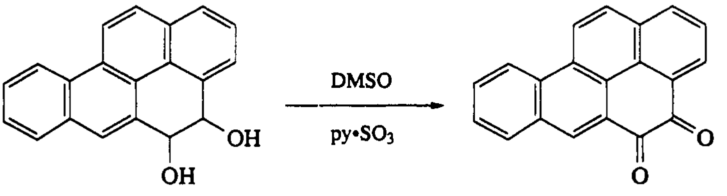

(9)

(**17**) (**18**)

### 2.8.3.5 DMSO–Oxalyl Chloride

Undoubtedly the most popular variation of these oxidations is the use of oxalyl chloride to activate the dimethyl sulfoxide, which is commonly referred to as the Swern oxidation. The advantages of the method are: the mild conditions; the ease of work-up, due to two of the main by-products being carbon monoxide and carbon dioxide; the low yields, if any, of Pummerer rearrangement products; and the fact that the reaction is usually very rapid. It is advantageous that freshly distilled oxalyl chloride is used in these reactions, and generally yields are excellent.[27,28]

Activation temperatures of about –60 °C are typically used to form the activated dimethyl sulfoxide intermediate (**19**), which arises by spontaneous loss of carbon dioxide and carbon monoxide from an initially formed salt (Scheme 6).

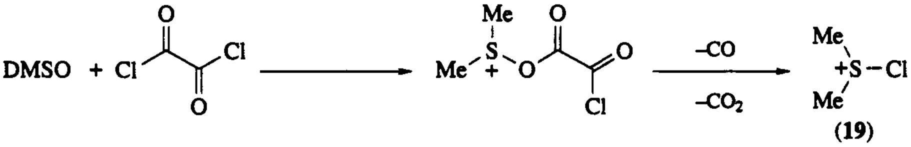

**(19)**

**Scheme 6**

Interestingly, this intermediate is identical to that formed in the reaction of dimethyl sulfide with chlorine, a mixture well known to be useful in the oxidation of alcohols to carbonyl compounds.[29]

The relatively mild conditions of this dimethyl sulfoxide activation method have been used to good effect to oxidize many sensitive substrates. For instance the alcohol (**20**; equation 10) was smoothly converted to the aldehyde without any racemization occurring, which can be a problem with other oxidizing systems.[30] Similar advantages were noted in the oxidation of the alcohol (**21**), thus demonstrating the compatibility of some sensitive protecting groups to the reaction conditions.[31]

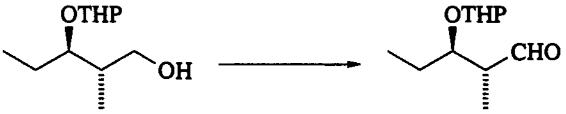

(10)

**(20)**

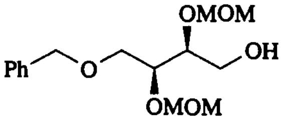

**(21)**

The unsaturated branched chain sugar (**22**; equation 11) was successfully converted to an enone under the Swern conditions[32] and the allylic alcohol (**23**), containing an α,β-unsaturated amide, was smoothly oxidized by this activated dimethyl sulfoxide reaction.[33]

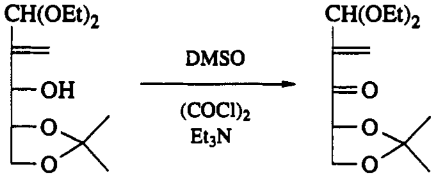

(11)

**(22)**

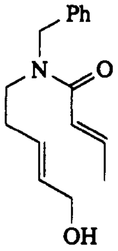

**(23)**

Amongst the more sensitive substrates which can be tolerated during the Swern oxidation is the formation of the aldehyde (**24**),[34] which normally undergoes very rapid epimerization in the presence of a trace of acid. Another example which serves to demonstrate the advantages of the Swern oxidation over other methods is the formation of the lactol (**25**), which is prepared in the presence of a sensitive vinylsilane group.[35]

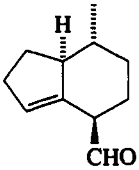

**(24)**

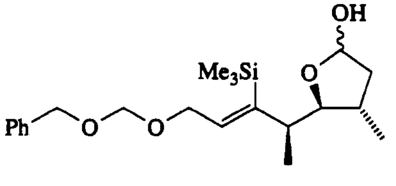

**(25)**

A very useful development of this reaction is the demonstration that trimethylsilyl-protected primary and secondary alcohols can be directly oxidized without prior deprotection,[36] but *t*-butyldimethylsilyl ethers do not similarly react.

The Swern procedure, however, is not without its problems; for instance, it has been shown that electrophilic chlorination can occur as a significant side reaction.[37] In these cases the use of trifluoroacetic or acetic anhydride as activators of dimethyl sulfoxide has been recommended.

### 2.8.3.6 DMSO–Thionyl Chloride

Thionyl chloride appears to be superior to trifluoroacetic anhydride as an activator of dimethyl sulfoxide during the oxidation of alcohols in terms of yields of carbonyl compounds,[27] although it has not been as widely used. The active species in this process, leading to an alkoxysulfonium species, is probably the ion pair (**26**).

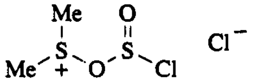

**(26)**

As with trifluoroacetic anhydride, activation of dimethyl sulfoxide with thionyl chloride must be carried out at low temperatures as the reaction is highly exothermic. Besides the higher yields, a further advantage of thionyl chloride to activate dimethyl sulfoxide over anhydrides is the lack of Pummerer rearrangement products or of esters formed as by-products (as long as the reactions are carried out below −60 °C). This is amply demonstrated by the oxidation of (−)-borneol which proceeds in an excellent 99% yield (equation 12).[27]

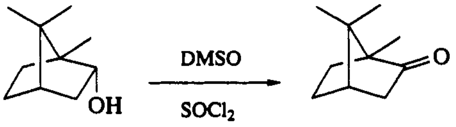

(12)

### 2.8.3.7 DMSO–Chlorine and Halogen Derivatives

Dimethyl sulfoxide and chlorine form highly reactive intermediates which are of some limited use as oxidants for alcohols. These intermediates are related to those derived from the reaction of the halogens with dimethyl sulfide and probably have a structure such as (**27**). When formed at −45 °C they allow the oxidation of primary and secondary alcohols to aldehydes and ketones[38] when used in a two-fold excess. For very simple alcohols the reaction proceeds in yields of greater than 90%, but there are considerable drawbacks if some types of additional functionality are present in the molecule, *e.g.* alkenes react very rapidly to form vicinal dichlorides.

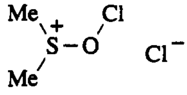

**(27)**

Attempted use of *N*-chlorosuccinimide or *N*-bromosuccinimide to activate dimethyl sulfoxide is limited, owing to the preferential formation of methylene acetals in good yields,[39] as illustrated in the preparation of the acetal (**28**; equation 13).

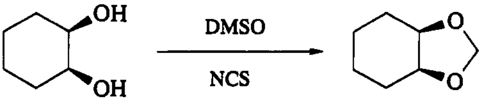

**(28)** (13)

### 2.8.3.8 DMSO–Miscellaneous Activators

A large number of other materials have been used to activate dimethyl sulfoxide for the oxidation of primary and secondary alcohols and new methods are still being introduced. The vast majority of these reactions proceed *via* an alkoxysulfonium salt and consequently are variants of the original Pfitzner–Moffatt procedure. Very few of these methods have been exhaustively tested and their advantages are often not apparent.

Despite this they should be considered as possible alternatives in cases where more familiar methods fail. Amongst this group of activators are *p*-toluenesulfonyl chloride,[40] trifluoromethanesulfonic anhydride,[40,41] silver tetrafluoroborate,[42] molybdenum oxide,[43] phosphorous pentoxide,[44] trichloromethyl chloroformate,[45] 2-fluoro-1-methylpyridiniumsulfonate,[46] chlorosulfonyl isocyanate,[47] antimony pentachloride (for which an X-ray structure of the DMSO–$SbCl_5$ complex was obtained)[48] and phenyl dichlorophosphate.[49]

One potential activator for dimethyl sulfoxide that in practice turns out to be very poor, is phosgene.[5] However, a related oxidation of alcohols using dimethyl sulfoxide does use phosgene for the preparation of a chloroformate (or carbonochloridate) such as (**29**).[50,51] This reacts with dimethyl sulfoxide to give, after spontaneous loss of carbon dioxide, an alkoxysulfonium salt (**30**) which upon treatment with triethylamine forms the carbonyl compound (Scheme 7). Relatively little use appears to have been made of this method.

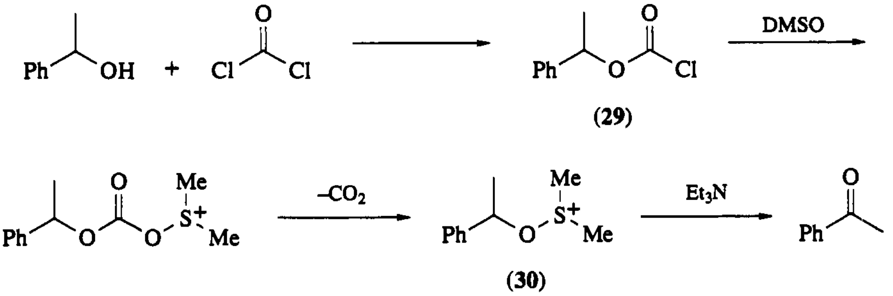

**Scheme 7**

### 2.8.4 OXIDATION OF ALCOHOLS

The above discussion has concentrated upon the reagents used, but it is equally of value to comment on the substrate, particularly in reactions for which other oxidation methods have been reported to fail. A good example is the oxidation of the iron–carbonyl complex (**31**) to the ketone (**32**; equation 14). The use of dimethyl sulfoxide activated with sulfur trioxide–pyridine complex gave a 70% yield of the product, in contrast to the use of the Pfitzner–Moffatt procedure (dimethyl sulfoxide–DCC) or the chromium trioxide/pyridine complex, both of which caused the alcohol (**31**) to fragment to benzaldehyde and benzene.[52]

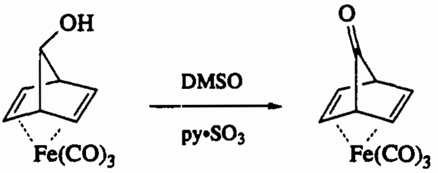

(**31**) (**32**)

(14)

The sulfur trioxide–pyridine activated dimethyl sulfoxide oxidation was also a key step in an excellent synthesis of the Prelog–Djerassi lactonic acid, being highly recommended as the best method to avoid epimerization of the C-2 center in the aldehyde (**33**).[53]

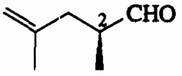

(**33**)

An area of recent intense synthetic endeavor has been in the synthesis of the avermectins and milbemycins, which contain a range of highly reactive functionalities such as the spiroacetal group, double bonds, and epimerizable centers. However, dimethyl sulfoxide activated oxidations, most notably the Swern variation, have been useful in this area of chemistry. For example, the sensitive spiroacetal (**34**) gave 92% of the derived aldehyde using dimethyl sulfoxide–oxalyl chloride–triethylamine at –50 °C (equation 15).[54]

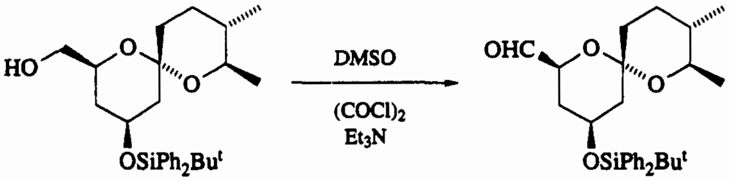

(**34**)

(15)

Additionally, in a carbohydrate-derived synthesis of the oxahydrindene portion of the avermectins, a Swern oxidation was performed on the alcohol (**35**), demonstrating further the range of functionality that can be accommodated under these conditions.[55]

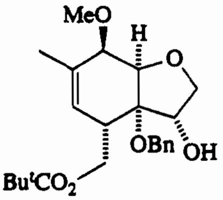

(**35**)

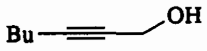

(**36**)

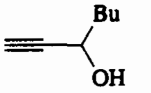

(**37**)

One class of compounds that does not react particularly well in activated dimethyl sulfoxide oxidations, however, is the alkynic alcohols, and only a few successful examples are known, *e.g.* (**36**) and (**37**).[5]

α-Diketones are also an important class of compounds which may be obtained very easily by using Swern oxidation of the sensitive α-hydroxy ketone precursors,[56] or vicinal diols.[57] Amongst such oxidations are the preparations of the α-diketones (**38**) and (**39**).

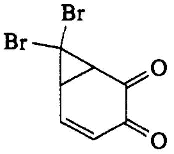

**(38)**

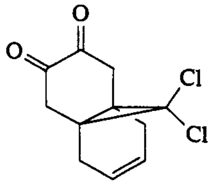

**(39)**

Activated dimethyl sulfoxide oxidations have been fairly well used in the synthesis of monoterpenes, as seen in the oxidation to an aldehyde of the alcohols (**40**), *en route* to loganin aglycone,[58] and (**41**), a precursor in a synthesis of specionin (equation 16).[59]

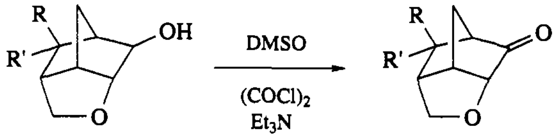

(16)

(**40**) R = H, R' = Me

(**41**) R = $CH_2OSiMe_2Bu^t$, R' = H

However, relatively less use of the reaction appears to have been made in the preparation of the higher terpenes, but some notable exceptions to this are the use of a Moffatt oxidation as a key step in an unusual approach to hydrazulene-based sesquiterpenes, (**42**) to (**43**; equation 17),[60] and the use of the Swern variation in the gibberellin synthesis (**44**) to (**45**; equation 18).

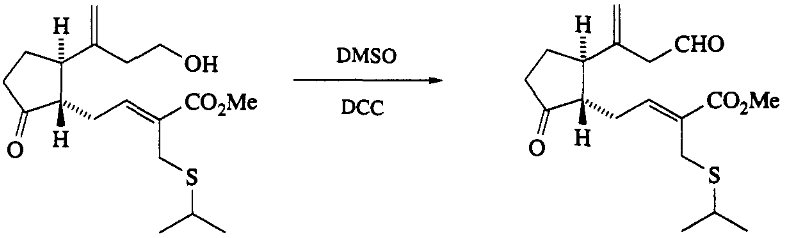

(17)

**(42)** **(43)**

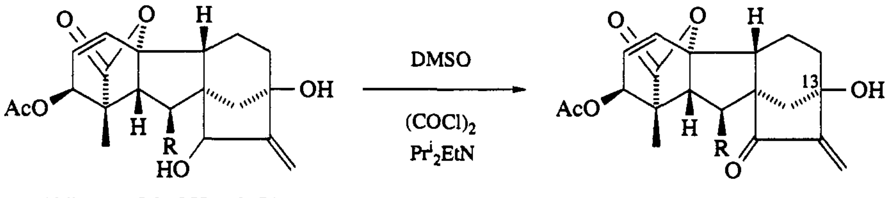

(18)

(**44**) R = $CO_2CH_2CO_2Ph$ **(45)**

Interestingly, this last case is one of the few reports which notes a dependence upon the base used in the oxidation. The use of diisopropylethylamine gives the ketone shown, whereas the usual triethylamine base forms the ketone containing the 13-chloro group, for reasons which are unclear.[61]

As seen above, activated dimethyl sulfoxide oxidations are often used to prepare carbonyl compounds which are highly sensitive and which do not withstand the more vigorous conditions of other, more traditional oxidants such as the $Cr^{VI}$-based reagents. A striking example of this comes from a series of studies aimed at preparing sensitive carbonyl compounds *in situ*, and subjecting them to further reaction such as a Wittig condensation.[62] The best oxidant for these systems is the dimethyl sulfoxide–oxalyl chloride–triethylamine mixture, *i.e.* the Swern oxidation. The fact that the carbonyl compounds could be used without purification to give high yields of products serves to emphasize that the by-products in these oxidations, carbon monoxide, carbon dioxide, dimethyl sulfide and triethylamine hydrochloride are relatively innocuous. In this study, for which other oxidation systems failed to give clean products, the ketone

(46) and the aldehydes (47) to (49) were prepared and used crude without the need for further purification.

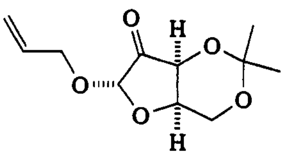

(46)

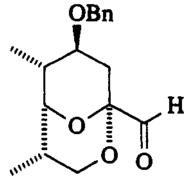

(47)

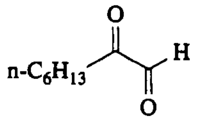

(48)

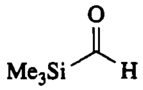

(49)

A further, extremely good demonstration of the advantages offered by these reactions is in the oxidation of the alcohol (50; equation 19), a precursor to some unusual prostaglandin analogs, which proceeds in 65% yield (with concurrent epimerization) using the Moffatt procedure (DMSO–DCC–$CF_3CO_2H$). In contrast, the use of $Ac_2O$–DMSO, DMS–$Cl_2$, PDC, $Ag_2CO_3$–celite, Collins reagent or Jones oxidation all failed.[63]

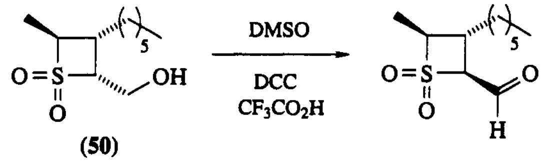

(50)

(19)

Very few reports of competitive reactions of alcohols have appeared in activated dimethyl sulfoxide oxidations, but the results obtained from these limited studies are interesting. It is known that dimethyl sulfoxide–trifluoroacetic anhydride oxidation is selective for primary or secondary alcohols in the presence of benzylic or allylic alcohols, due to the latter alcohols being preferentially converted to trifluoroacetates.[64] Additionally, secondary alcohols are known to be more reactive than primary alcohols in these oxidations, although the measured rate differences are not very high[65] and selectivity cannot be guaranteed.

## 2.8.5 CONCLUSIONS

The above discussion highlights the great synthetic utility of activated dimethyl sulfoxide oxidations in organic chemistry. The enormous amount of effort put into developing these procedures has resulted in a clear picture of their relative value, so enabling one to easily assess the method of choice for a particular oxidation. The popularity of the Swern oxidation reflects the very real advantages that it offers in terms of the mild conditions and high yields. However, there are many instances where alternative activators of dimethyl sulfoxide are better and it is wise to assess these in any synthetic scheme.

The range of substrates which have been oxidized by activated dimethyl sulfoxide covers a wide range of tolerant functional groups, and there are many reports of how these oxidations proved superior to others that were investigated.

Thus activated dimethyl sulfoxide oxidations are now well established as standard synthetic methods and are familiar to all organic chemists, and will continue into the future as new variations are developed.

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# 2.9

# Oxidation Adjacent to Oxygen of Alcohols by Other Methods

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## 2.9.1 INTRODUCTION

The oxidation of an alcohol to a carbonyl compound is a fundamental reaction which is encountered at all levels of organic synthesis. As might be expected there are numerous methods and reagents which are available for carrying out this transformation and two of the most important general types have been dealt with in the previous two chapters (2.7 and 2.8) of this volume. This chapter is concerned with the oxidation of alcohols using methods which are not based on chromium reagents or 'activated DMSO'. An attempt has been made to include reagents whose worth has already been demonstrated by their use in particular syntheses, or which appear to have some potential for use in organic synthesis by virtue of their selectivity. The usefulness of a reagent for organic synthesis is critically dependent upon its selectivity, mildness and availability *inter alia.* The organization of this chapter into specific synthetic transformations (rather than a classification based on reagent type) was chosen with the practising synthetic chemist in mind. In the author's experience the need to consider a range of possible reagents for a specific selective transformation arises more often than the need to know all about one specific reagent. This latter information is usually easy to obtain from reference sources or original literature.[1] In keeping with the aims of this work the main emphasis will be on reagents which exhibit selectivity of some kind.

## 2.9.2 OXIDATION OF PRIMARY ALCOHOLS

### 2.9.2.1 Selective Preparation of Aldehydes

The preparation of aldehydes by the oxidation of primary alcohols is often possible using reagents which also oxidize secondary alcohols to ketones, and some overlap with the section of this chapter dealing with the preparation of ketones is inevitable. Moreover some reagents which oxidize primary alcohols to aldehydes will also cleave 1,2-diols, and this will be pointed out where it is known. Notwithstanding these comments it is possible to carry out the oxidation of primary alcohols to aldehydes in the presence of other groups which themselves are easily oxidized. The extent of this chemoselectivity depends upon the reagent, for example some reagents will oxidize primary alcohols in the presence of other oxidizable hydroxy groups. On the whole, benzylic and allylic alcohols (and correspondingly 'activated' alcohols) are more easily oxidized than alcohols in which the hydroxy group is not 'activated' in this way. Not surprisingly there are many examples of chemoselective oxidation in which such an 'activated' alcohol is oxidized in the presence of other hydroxy groups. The first part of this section will cover some of the more recent examples of reagents which exhibit chemoselectivity.

As stated above the oxidation of allylic or benzylic alcohols is usually particularly easy, and the chemoselective oxidation of such an alcohol in the presence of other oxidizable hydroxy groups is one of the 'standard' examples of reagent selectivity in oxidation. The classical reagent is manganese dioxide in one form or another, and several reviews have appeared on this reagent.[2] Examples of the use of 'active' manganese dioxide are given in Scheme 1.[3–8] It must be emphasized that the success or otherwise of this reagent can depend critically on the method of preparation, and a comparison has been made of various samples of manganese dioxide for the oxidation of the allylic alcohols geraniol and nerol (**1**) to the corresponding aldehydes.[9]

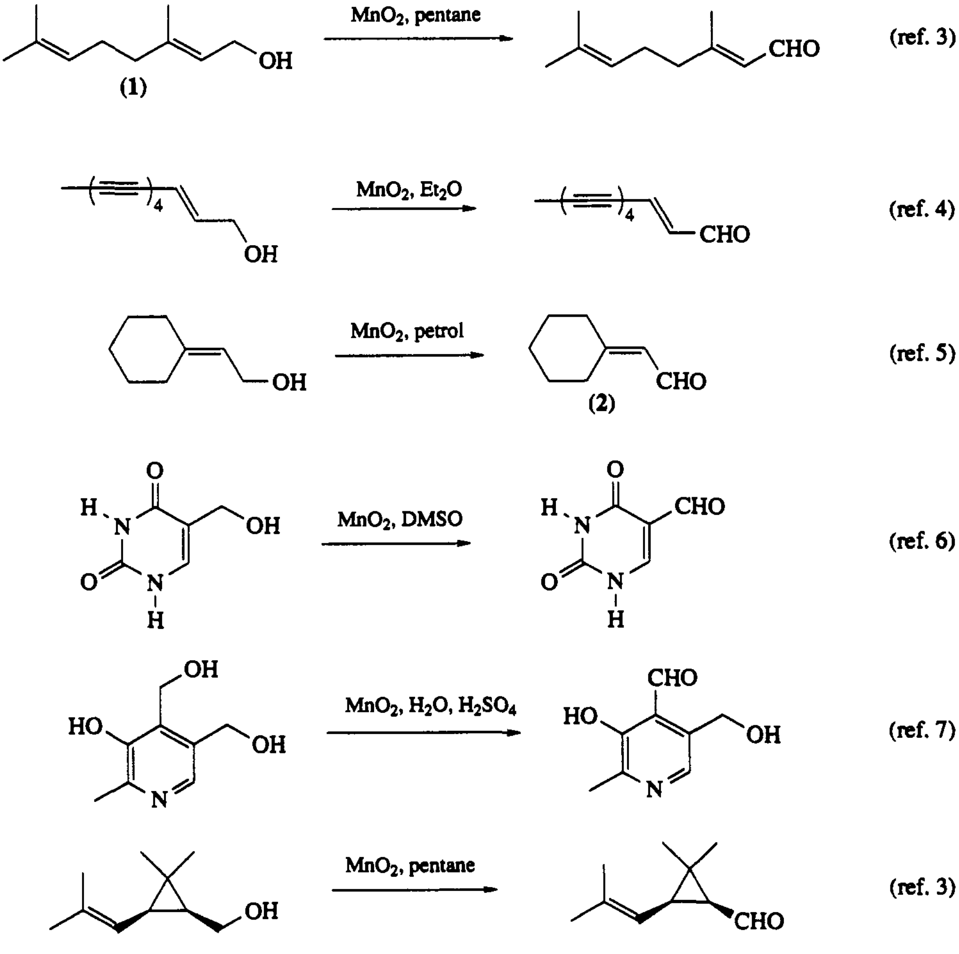

**Scheme 1**

This reagent can be of value not only for its inherent chemoselectivity, but also because of the mild conditions under which oxidation occurs. For example the cyclohexylideneacetaldehydes (**2**) can be produced by manganese dioxide oxidation of the allylic alcohols despite the instability of (**2**) to air, acids and bases.[5] Manganese dioxide is known to cleave 1,2-diols,[10] and can cause oxidative rearrangement to take place in some situations, for example the inositol derivative (**3**) is converted into the lactone (**4**; equation 1).[11]

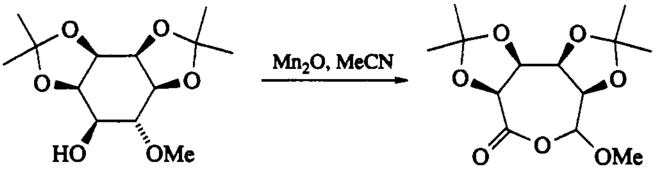

(**3**) (**4**)

(1)

Several other reagents will carry out similar chemoselective oxidations of allylic and benzylic alcohols, some of which are outlined here. Of the other manganese-based oxidants which will selectively oxidize allylic primary alcohols to aldehydes, barium manganate ($BaMnO_4$) is possibly the most useful.[12] Primary allylic alcohols can be oxidized by this reagent in dichloromethane at room temperature, and yields are equivalent to, or better than those obtained with manganese dioxide. Being easy to handle, and needing no activation, barium manganate can be particularly useful for large scale reactions.[12] It is of particular interest that barium manganate will give good yields of *vic*-dials (equation 2),[13] since these can be difficult to obtain by direct oxidation of the corresponding diol (however, if the hydroxy groups have sufficiently different reactivities, lactones can be produced in this reaction, see later). The selectivity of this reagent was used in studies on the synthesis of cinnamolide and polygodiol, in which the diol (**5**; equation 3) was selectively oxidized to the lactol (**6**), excess reagent giving the corresponding lactone.[14]

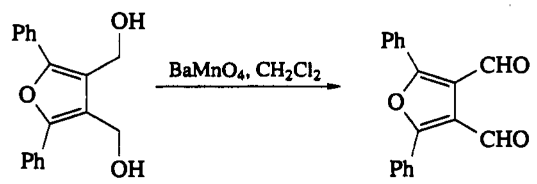

(2)

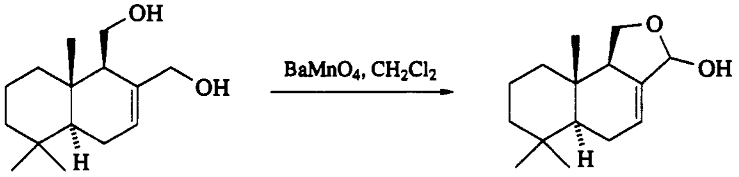

(**5**) (**6**)

(3)

Organoselenium reagents have been observed to exhibit selectivity for the oxidation of allylic alcohols, for example a catalytic amount of dimesityl diselenide with *t*-butyl hydroperoxide as cooxidant will oxidize benzylic and allylic alcohols in the presence of saturated alcohols, as in the case of the diol (**7**; equation 4).[15]

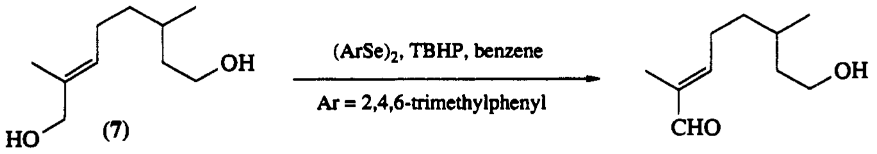

(**7**)

(4)

μ-Oxo-bis(chlorotriphenylbismuth) (**8**; equation 5) has also been used for this type of oxidation, and can exhibit very useful levels of chemoselectivity.[16]

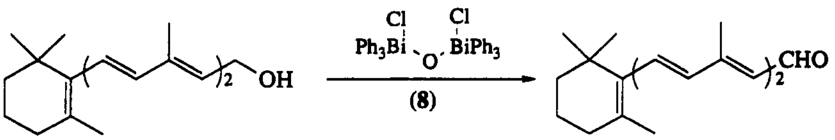

(5)

The selective oxidation of a primary allylic (**9**; equation 6) or benzylic (**10**; equation 7) alcohol in the presence of a secondary alcohol has been carried out using bis(trimethylsilyl) peroxide in the presence of bis(triphenylphosphine)ruthenium(II) chloride.[17]

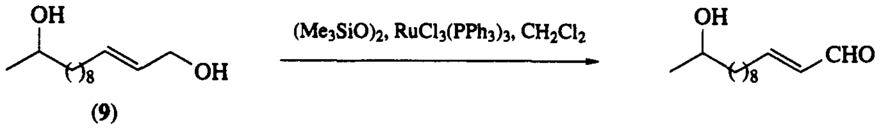

**(9)**

(6)

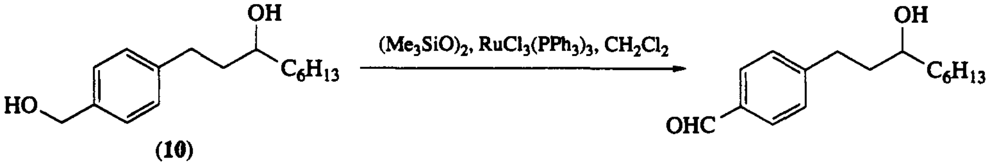

**(10)**

(7)

Hydrated ruthenium dioxide will act as a catalyst for the oxidation of primary allylic alcohols (equations 8 and 9) in an oxygen atmosphere (a trace of the antioxidant 2,6-di-*t*-butyl-4-methylphenol is required to prevent autoxidation of the aldehyde to the acid).[18] The oxidation is not accompanied by any loss in double bond stereochemistry, secondary allylic alcohols are oxidized but at a decreased rate, and saturated alcohols are scarcely oxidized at all. However, α-hydroxy ketones and α-hydroxylactones will oxidize under forcing conditions, so there is clearly likely to be some degree of substrate dependence.[18]

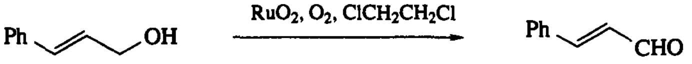

(8)

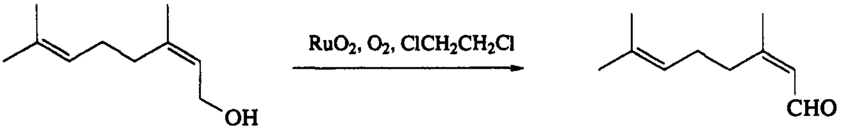

(9)

Primary benzylic alcohols (equation 10) can be oxidized in the presence of saturated primary alcohols using a catalyst derived from ammonium cerium(IV) nitrate supported on charcoal with air as the cooxidant (under these conditions α-hydroxy ketones are oxidized to α-diketones).[19]

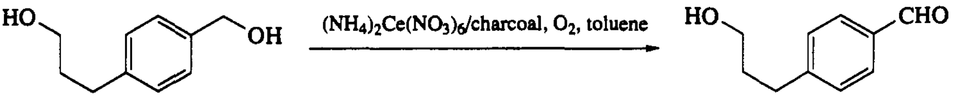

(10)

The chemoselective oxidation of a primary alcohol in the presence of a secondary alcohol is a somewhat more difficult task. Not only is the inherent difference in reactivity less than in the case of the selective oxidation of allylic alcohols discussed above, but most reagents will oxidize secondary alcohols somewhat more rapidly than primary alcohols. Nevertheless there are reagents which will carry out the selective oxidation of a primary alcohol to an aldehyde without oxidizing a secondary alcohol, some of which will be considered here.

This type of chemoselectivity has been observed in the oxidations of alcohols using copper(II) chloride and a catalytic quantity of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (**11**; equation 11).[20] The oxidizing species which is generated, in for example the oxidation of (**12**) to (**13**), is the cation (**14**), which may also be produced using electrochemical oxidation (in the presence of the weak base 2,6-lutidine). Allylic and benzylic alcohols are easily oxidized by this reagent, whereas secondary alcohols react slowly.

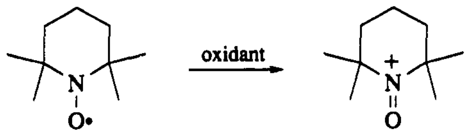

**(11)** **(14)**

(11)

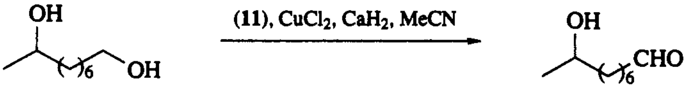

(12) (13)

(12)

An interesting example of this type of chemoselective oxidation has been reported with the reagent mixture derived from diisopropyl sulfide and *N*-chlorosuccinimide.[21] This reagent will oxidize selectively a primary alcohol to an aldehyde at 0 °C. Surprisingly, this same reagent at –78 °C will oxidize selectively a secondary alcohol to the corresponding ketone (Scheme 2). Allylic and benzylic alcohols are oxidized at both temperatures.

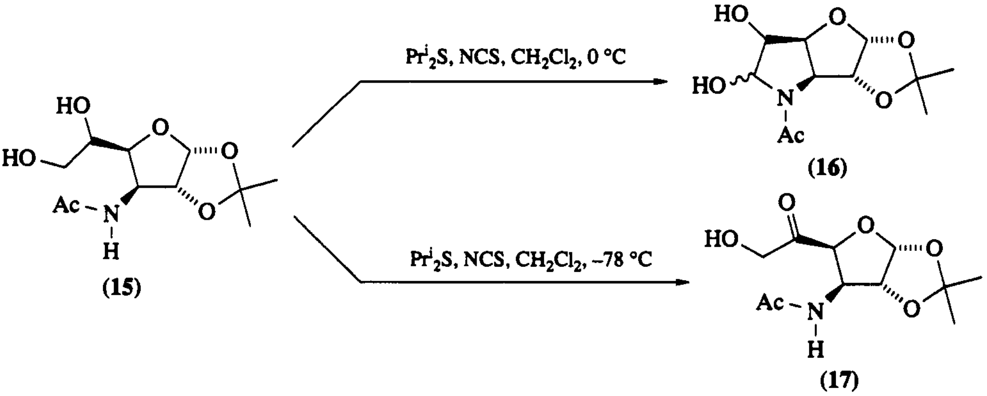
HO
HO
O
O
O
Ac
N
H
Pr$^i_2$S, NCS, CH$_2$Cl$_2$, 0 °C
Pr$^i_2$S, NCS, CH$_2$Cl$_2$, –78 °C
HO
HO
O
O
O
N
Ac
O
HO
O
O
O
Ac
N
H

(15) (16) (17)

| *Further examples* | 0 °C | -78 °C |
|---|---|---|
| Decan-1-ol | 90% | n.r. |
| Cyclohexylmethanol | 84% | n.r. |
| Heptan-2-ol | n.r. | 88% |
| 4-*t*-Butylcyclohexanol | n.r. | 83% |
| (15) → (16) | 70% | — |
| (15) → (17) | — | 65% |

**Scheme 2**

A number of derivatives of ruthenium(II) have the potential to oxidize a primary alcohol in the presence of a secondary alcohol; the original report of Sharpless *et al.*[22] has been followed by a number of modifications.[23] The ruthenium complex can be used as a catalyst in conjunction with a cooxidant, which in the original work was *N*-methylmorpholine *N*-oxide. In general benzylic and allylic alcohols react more readily than their saturated counterparts, and primary alcohols react more readily than secondary alcohols. Alkenes can interfere with this oxidation, probably by binding to the metal and inhibiting the catalytic process. The stoichiometric use of tris(triphenylphosphine)ruthenium(II) chloride will oxidize a primary/secondary diol to the corresponding hydroxy aldehyde in excellent yield (equation 13).[24]

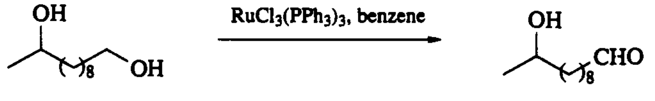

(13)

Zirconyl acetate [$ZrO(OAc)_2$] has been used as a catalyst for the oxidation of primary aliphatic alcohols to aldehydes, with *t*-butyl hydroperoxide as cooxidant. Under the reaction conditions benzylic and allylic alcohols are also oxidized, but the oxidation of saturated secondary alcohols is slow, and C—C double bonds are unaffected and some degree of chemoselectivity would appear to be feasible.[25]

A zirconium complex, bis(cyclopentadienyl)zirconium(IV) hydride will function as a catalyst for the chemoselective Oppenauer oxidation of primary alcohols in the presence of a hydrogen acceptor (cyclohexanone, benzaldehyde or benzophenone).[26] This method appears to be of some value, since it also allows for the selective monooxidation of primary (and secondary) diols (Scheme 3). 1,2-Diols are not cleaved under these conditions and retro-aldol reactions appear not to be a problem.

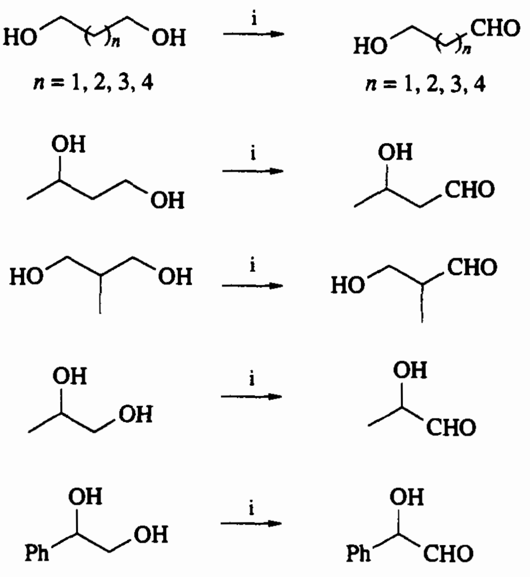

i, $Cp_2ZrH_2$ + H-acceptor (cyclohexanone, benzaldehyde or benzophenone)

**Scheme 3**

Under neutral or acidic conditions osmium tetroxide has been reported to exhibit selectivity for the oxidation of primary alcohols, although in the examples shown (equations 14 and 15) the yields appear to be lower than might be desirable (40–50%).[27]

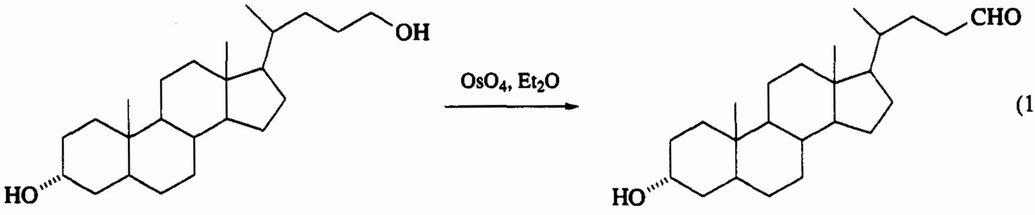

(14)

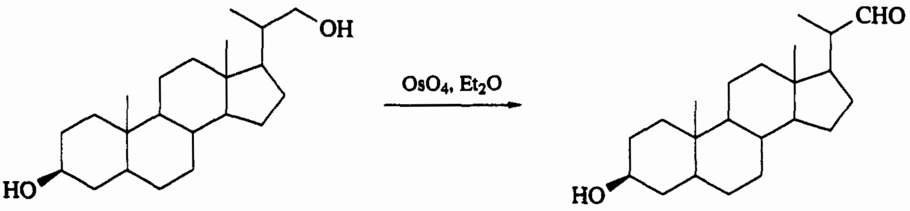

(15)

Clearly there are easily oxidizable groups other than alcohols which might be found within a particular structure, and which can interfere with the oxidative introduction of a carbonyl group. Not surprisingly reagents have been developed which will show chemoselectivity for the oxidation of the alcohol function in such systems. Triphenylbismuth carbonate and $\mu$-oxo-bis(chlorotriphenylbismuth) have been reported as such a chemoselective reagent, and will oxidize alcohols in the presence of other easily oxidized species such as benzenethiol, indole and pyrrole (Section 2.9.3).[16] This reagent also cleaves 1,2-diols.

It is possible to oxidize an alcohol in the presence of sulfur- or selenium-containing groups (equation 16) using *t*-butyl hydroperoxide and a diselenide as the oxidizing system (this also oxidizes secondary alcohols, see later).[15] Selenium chemistry can also be used to oxidize benzylic and related primary alcohols to the aldehydes without oxidizing pyridyl (**18**; equation 17) or thiophenyl (**19**; equation 18) groups.[28]

It is possible to oxidize sensitive allylic alcohols to aldehydes using catalytic tris(triphenylphosphine)ruthenium(II) chloride in an oxygen atmosphere, a thiophenyl group survives under these condi-

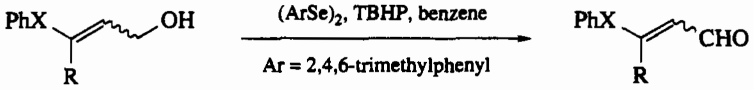
PhX
OH
R
(ArSe)2, TBHP, benzene
Ar = 2,4,6-trimethylphenyl
PhX
CHO
R
(16)

X = S, Se; R = H, Me, Ph

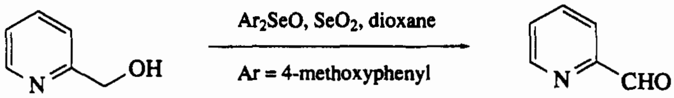
N
OH
Ar2SeO, SeO2, dioxane
Ar = 4-methoxyphenyl
N
CHO
(17)

**(18)**

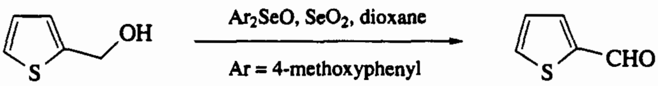
S
OH
Ar2SeO, SeO2, dioxane
Ar = 4-methoxyphenyl
S
CHO
(18)

**(19)**

tions (equation 19), and the polyene retinal is produced from retinol (equation 20) without loss of double bond geometry.[29]

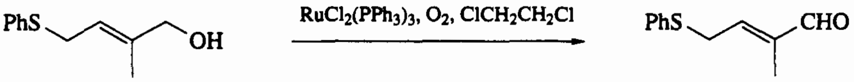
PhS
OH
RuCl2(PPh3)3, O2, ClCH2CH2Cl
PhS
CHO
(19)

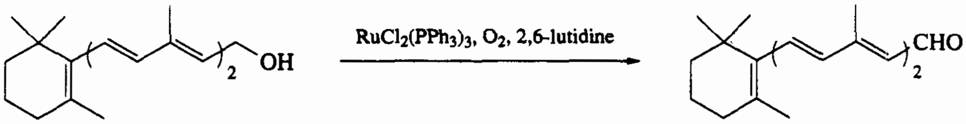
2
OH
RuCl2(PPh3)3, O2, 2,6-lutidine
CHO
2
(20)

A catalytic method which promises to find wide application in view of its mildness and ease of execution uses a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO) as the cooxidant.[30] Primary (and secondary) alcohols which contain a range of functional groups (alkenes, tetrahydropyran ethers, epoxides, lactones, silyl ethers and indoles *inter alia*) can be oxidized without interference by the other functional group (equations 21–23). The performance of the reagent is improved further by including molecular sieves in the reaction mixture.[31]

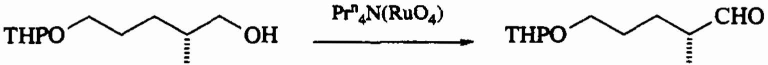
THPO
OH
Pr^n4N(RuO4)
NMO, CH2Cl2
THPO
CHO
(21)

(no racemization)

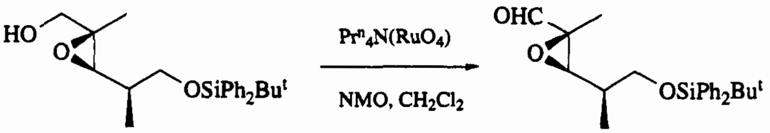
HO
O
OSiPh2Bu^t
Pr^n4N(RuO4)
NMO, CH2Cl2
OHC
O
OSiPh2Bu^t
(22)

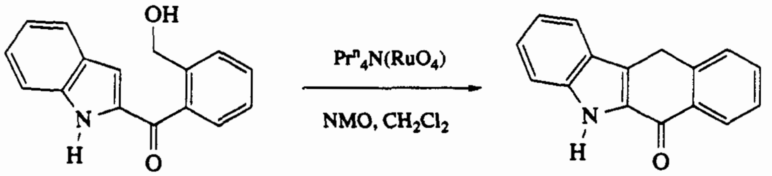
OH
N
H
O
Pr^n4N(RuO4)
NMO, CH2Cl2
N
H
O
(23)

Another reagent which undoubtedly will prove to be of real synthetic value is periodinane, which is an excellent, mild oxidant for primary (and secondary) alcohols.[32] This reagent is discussed further in Section 2.9.3.

The enzyme D-galactose oxidase has been reported to oxidize some racemic diols with kinetic resolution to provide the corresponding hydroxy aldehydes with high enantiomeric excesses.[33] A list of successful and unsuccessful substrates is given in Scheme 4.

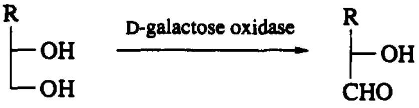

Successful substrates

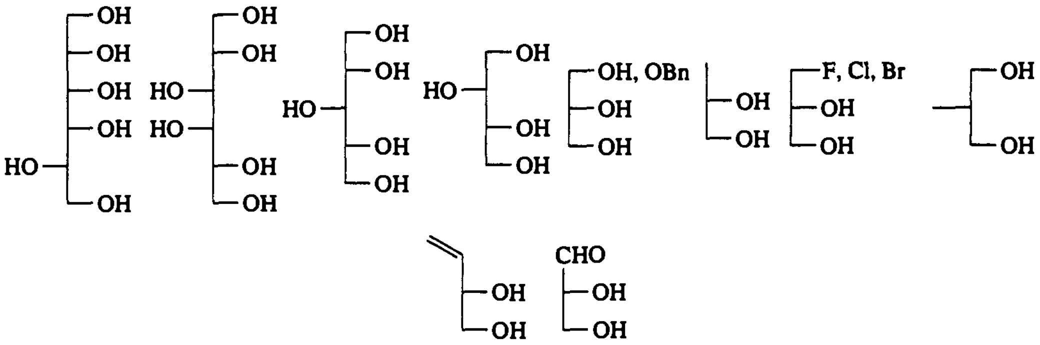

Unsuccessful substrates

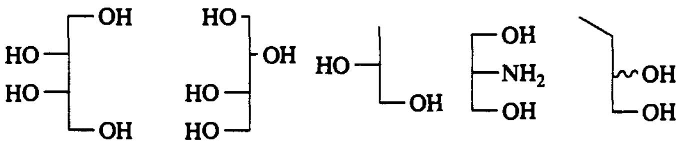

Scheme 4

## 2.9.2.2 Selective Preparation of Lactones from Diols

The oxidation of primary alcohols to the corresponding carboxylic acid or ester generally requires fairly powerful oxidants, and in most cases the issue of selectivity is dealt with by protection of other oxidizable functionality within the molecule. One important area in which this need not be the case is the oxidation of symmetrical and unsymmetrical diols to the corresponding lactone. The general scheme is presented in Scheme 5, and relies on an initial chemoselective oxidation to the hydroxy aldehyde, which is in equilibrium with the lactol. This lactol is then oxidized to the lactone. In some cases it is possible to halt the reaction at the lactol stage, but usually the lactone is the product. Most of this section will be concerned with this type of selective oxidation.

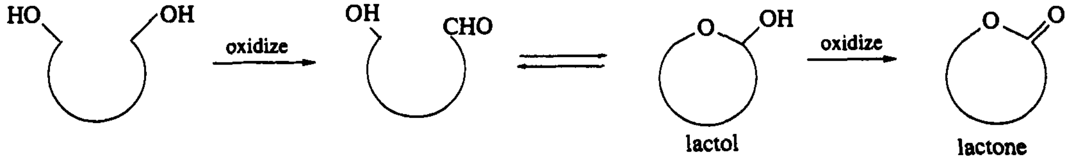

Scheme 5

The most widely known reagent for the oxidation of $\alpha,\omega$-diols to lactones is silver carbonate on Celite.[34] This reagent will oxidize primary 1,4-, 1,5- and 1,6-diols, to lactones. Primary–secondary diols can give the corresponding keto alcohol as a serious side product, but this can be overcome by a change in solvent.[30] As would be expected, primary–tertiary diols give the corresponding lactones in excellent yield. This oxidation was used as the key step in a simple synthesis of racemic mevalonolactone (**20**; Scheme 6).[34] Although this is often the first reagent to be tried in a given situation, this reagent is not free of problems, as often a large excess is required (10–26 equiv. in the original paper), which compounds the problem of the cost of silver salts, and sulfide groups appear to interfere.[34]

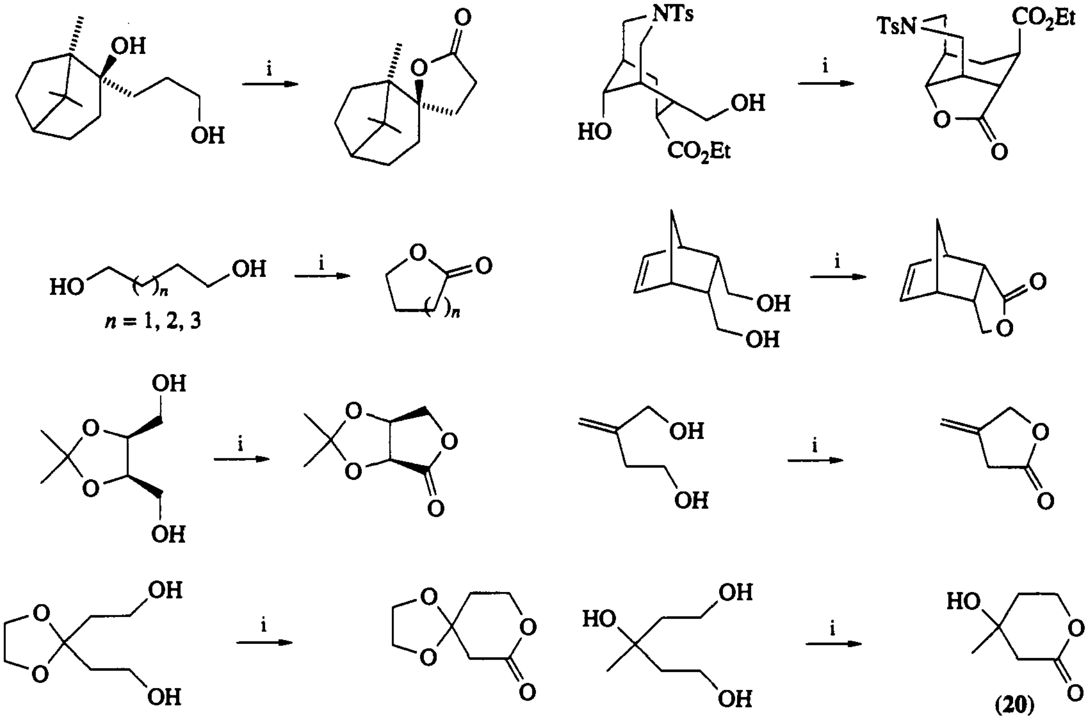

i, $Ag_2CO_3$/celite, benzene

**Scheme 6**

A mixture of potassium permanganate and copper sulfate will oxidize simple 1,4- and 1,5-diols to the corresponding lactones, and will oxidize selectively primary–secondary diols (**21**; equation 24) and (**22**; equation 25) to the corresponding lactones.[35]

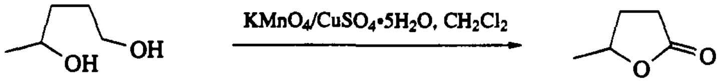

**(21)**

(24)

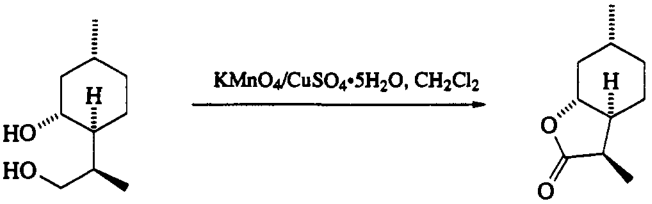

**(22)**

(25)

In work related to natural product synthesis the efficacy of silver carbonate on Celite was compared with a platinum-catalyzed oxidation using an oxygen atmosphere for the oxidation of (**23**; equation 26).[36] In some cases the $Pt/O_2$ system was superior, but in others the situation was reversed, with no obvious rationale. The $Pt/O_2$ reagent has been used in the total synthesis of the hydroazulene natural products damsin (**24**; Scheme 7),[37] aromatin (**25**)[38] and aromaticin (**26**; Scheme 8).[38]

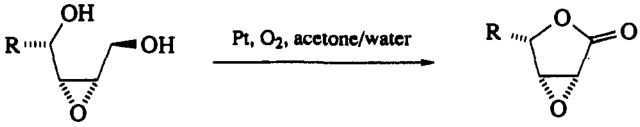

**(23)**

(26)

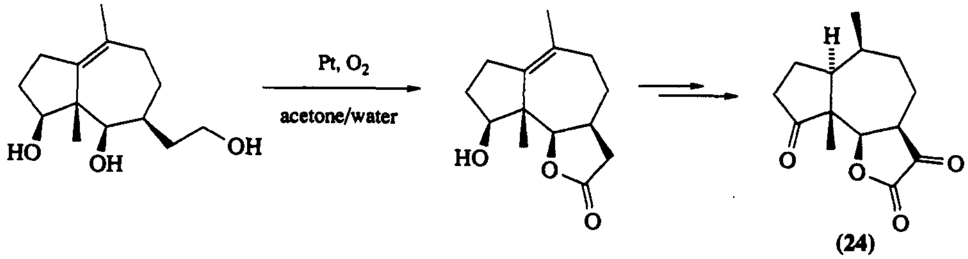
Pt, O2
acetone/water
HO
OH
OH
HO
O
O
H
O
O
O
O

**(24)**

**Scheme 7**

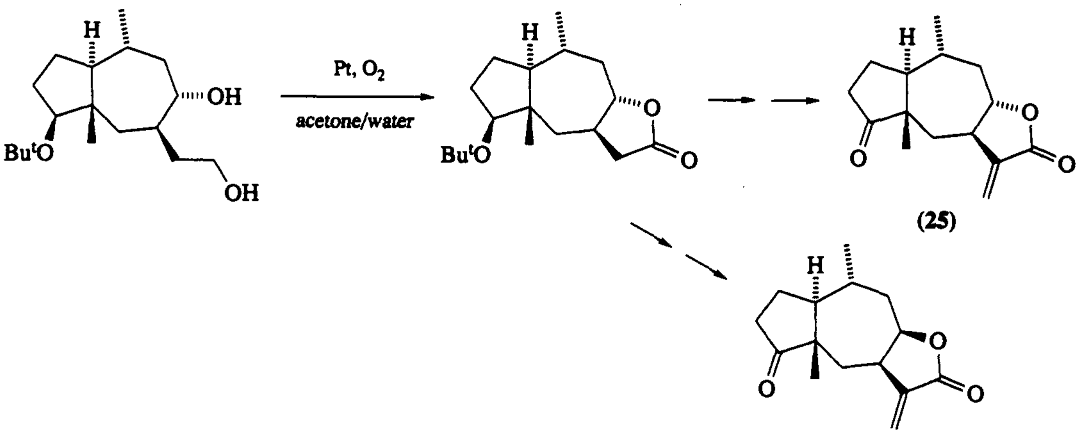
H
OH
Bu'O
OH
Pt, O2
acetone/water
H
O
Bu'O
O
H
O
O
O
H
O
O
O

**(25)**

**(26)**

**Scheme 8**

Reagent mixtures which utilize a catalytic metal complex, usually with a cooxidant (analogous to the $Pt/O_2$ reagent) for the selective oxidation of diols to lactones have been studied recently, with some interesting results.

Palladium acetate with bromobenzene as cooxidant will oxidize primary α,ω-diols (**27**; equation 27) and (**28**; equation 28) to lactones, but as can be seen from the examples given, the selectivity in unsymmetrical cases is rather low.[39]

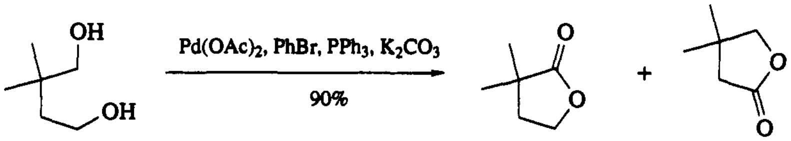
OH
OH
Pd(OAc)2, PhBr, PPh3, K2CO3
90%
O
O
+
O
O

**(27)** 70%:30% (27)

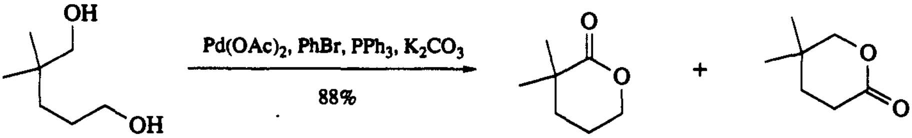
OH
OH
Pd(OAc)2, PhBr, PPh3, K2CO3
88%
O
O
+
O
O

**(28)** 62%:38% (28)

In contrast to this palladium reagent, several ruthenium complexes will catalyze this type of oxidation with high regioselectivity, but in the opposite sense. Tetrakis(triphenylphosphine)ruthenium(II) hydride has been used by two groups for the selective oxidation of symmetrical and unsymmetrical diols; some representative results are presented in Scheme 9.[40,41] In this case a hydrogen acceptor is useful in increasing the yield of the oxidation, although it is not always necessary. The use of an α,β-unsaturated ketone as hydrogen acceptor allows the reaction to be performed at room temperature, whereas the use of acetone for this purpose requires high temperatures (180°C).

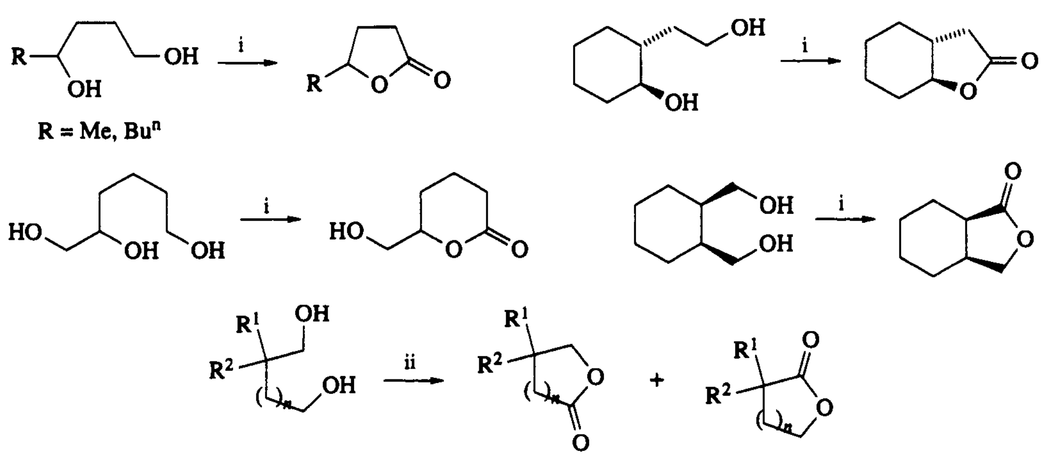

(29) (30)

i, $RuH_2(PPh_3)_4$, toluene, acetone, 180 °C (ref. 40); ii, $RuH_2(PPh_3)_4$, (*E*)-4-phenylbut-3-en-2-one, toluene, 20 °C (ref. 41)

| *R¹* | *R²* | *n* | *Yield (%)* | *(29):(30)* |
|---|---|---|---|---|
| Me | H | 1 | 94 | 93:7 |
| Pr$^i$ | H | 1 | 100 | 98:2 |
| Ph | H | 1 | 90 | 97:3 |
| MeO | H | 1 | 100 | 98:2 |
| Bu$^n$O | H | 1 | 100 | 98:2 |
| BnO | H | 1 | 100 | 96:4 |
| MOMO | H | 1 | 91 | 99:1 |
| Me | Me | 1 | 100 | 99.6:0.4 |
| Me | H | 2 | 100 | 84:16 |
| Ph | H | 2 | 93 | 98:2 |
| Me | H | 2 | 100 | 99.5:0.5 |

**Scheme 9**

A similar selective oxidation can be carried out with tetrakis(triphenylphosphine)rhodium(I) hydride and an α,β-unsaturated ketone as hydrogen acceptor, in this case the use of an optically active phosphine provided an enantioselective synthesis, although the levels of asymmetric induction were rather low (Scheme 10).[42]

An oxidizing system which uses bromine in the presence of carboxylate salts of nickel(II) has been studied in some detail,[43] and supersedes the analogous procedure which uses dibenzoyl peroxide in the presence of nickel(II) bromide. In some unsymmetrical cases the selectivity is somewhat dependent on

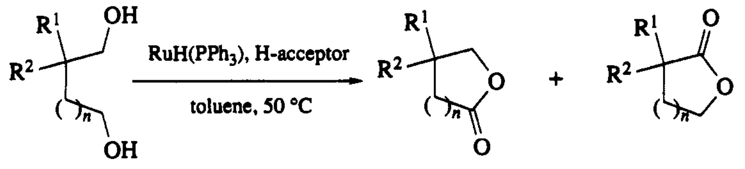

(31) (32)

| *R¹* | *R²* | *n* | *Yield (%)* | *(31):(32)* |
|---|---|---|---|---|
| Me | H | 1 | 82 | 86:14 |
| Pr$^i$ | H | 1 | 100 | 85:15 |
| Ph | H | 1 | 80 | 89:11 |
| MeO | H | 1 | 94 | 92:8 |
| Bu$^n$O | H | 1 | 90 | 90:10 |
| Me | Me | 1 | 95 | 98:2 |
| Me | H | 2 | 86 | 73:27 |
| Ph | H | 2 | 57 | 79:21 |
| Me | Me | 2 | 95 | 91:9 |

**Scheme 10**

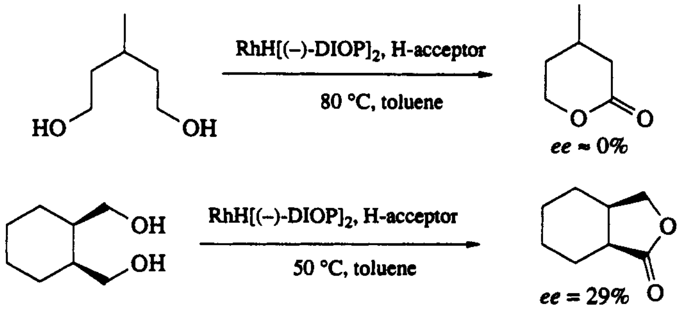

H-acceptor = (*E*)-4-phenylbut-3-en-2-one

**Scheme 10** *(continued)*

the carboxylate salt used, the catalyst of choice being nickel(II) 2-ethylhexanoate, although nickel(II) benzoate is often satisfactory. In Scheme 11 a limited comparison is made with triphenylmethyl tetrafluoroborate, a reagent which has also been used for the selective oxidation of unsymmetrical diols.[44]

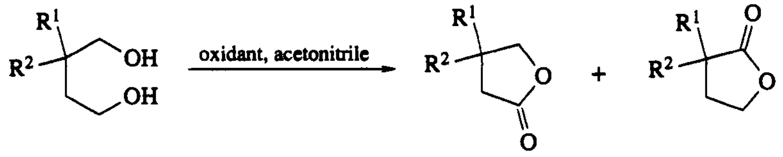

(33) (34)

| | $R^1, R^2 = Ph_2$ | | $R^1, R^2 = Me_2$ | | $R^1, R^2$ = Me, Et | |
|---|---|---|---|---|---|---|
| *Oxidant* | *Yield*[a] | *(33):(34)* | *Yield*[a] | *(33):(34)* | *Yield*[a] | *(33):(34)* |
| $Br_2$, $Ni(OBz)_2$ | 99 | 24:1 | 87 | 6.5:1 | 99 | 19:1 |
| $Br_2$, $Ni(Piv)_2$[b] | 99 | >100:1 | 99 | 6.6:1 | 88 | 23:1 |
| $Br_2$, $NiR_2$[c] | 99 | >100:1 | 82 | 14:1 | 93 | 35:1 |
| $Ph_3C^+BF_4^-$ | 77 | >100:1 | 47 | 24:1 | 59 | 24:1 |

[a] % Yield. [b] Piv = $Bu^tCO_2^-$. [c] R = 2-ethylhexanoate

**Scheme 11**

The use of enzymes for the enantioselective oxidation of prochiral (or racemic) diols has proved to be of significant synthetic interest. A range of simple racemic 1,2-diols proved to be good substrates for a system involving coimmobilized horse liver alcohol dehydrogenase (HLADH) and aldehyde dehydrogenase (AldDH) with NAD cofactor recycling.[45] This produced 'enantiomerically pure' α-hydroxycarboxylic acids (Scheme 12).

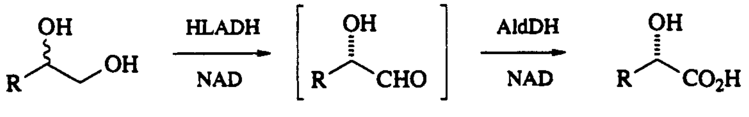

R = $HOCH_2$, $FCH_2$, $ClCH_2$, $BrCH_2$, $CH_2{=}CH$, Me, Et, $H_2NCH_2$

**Scheme 12**

Enzymes from *Gluconobacter roseus* organisms proved somewhat less versatile, but did allow a simple enantioselective synthesis of the unnatural enantiomer of mevalonolactone (**35**; Scheme 13) in reasonable optical purity.[46]

A thorough study of the use of HLADH for the enantioselective oxidation of *meso*-diols to lactones has provided a versatile and synthetically useful route to enantiomerically enriched lactones.[46–48] There are two major advantages of this system in that it appears to accept a fair amount of structural variation and full experimental details are available for preparative scale oxidations. A selection of results obtained with this enzyme system is presented in Scheme 14.

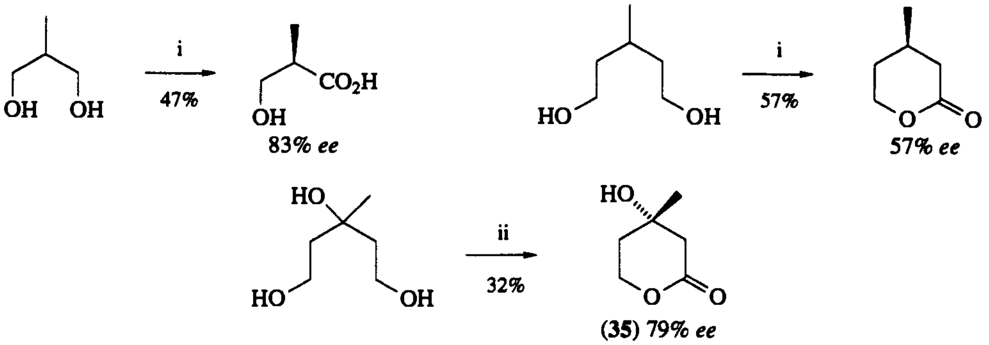
i
47%
$CO_2H$
OH
OH OH
83% *ee*
i
57%
HO
OH
O
O
57% *ee*
HO
HO
OH
ii
32%
HO
O
O
(35) 79% *ee*

i, *Gluconobacter roseus* IAM 1841; ii, *Gluconobacter scleroideus* IAM 1842

**Scheme 13**

General reaction

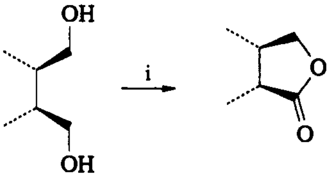

(ref. 46)

lactones prepared (100% *ee*):

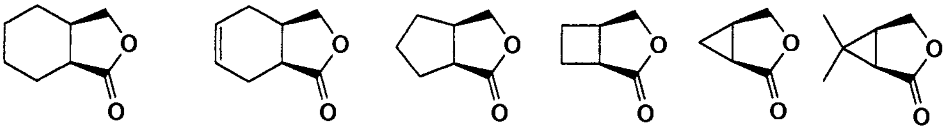

General reaction

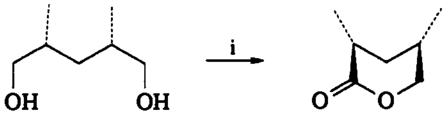

(ref. 47)

lactones prepared (100% *ee*):

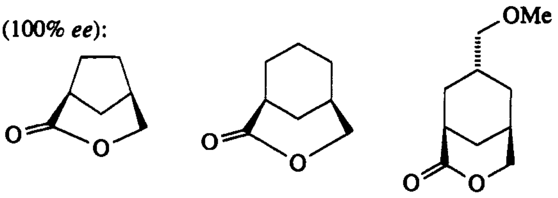

General reaction

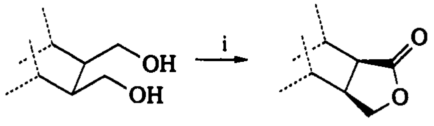

(ref. 48)

lactones prepared (>97% *ee*):

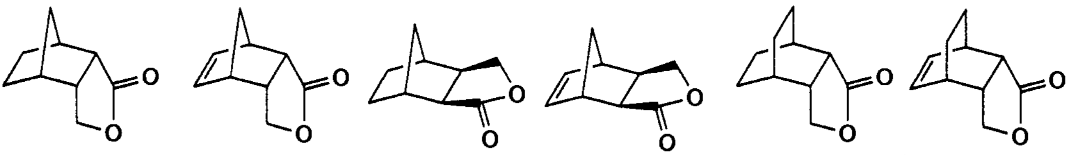

i, HLADH, pH 9, $NAD^+$, FMN, $H_2O$

**Scheme 14**

The selective oxidation of diols in which one or both hydroxy groups are allylic has been reported on a number of occasions. Reagents which have proved useful for this include silver carbonate on Celite,[48] barium manganate,[49] and manganese dioxide,[50] as illustrated in equations (29)–(31).

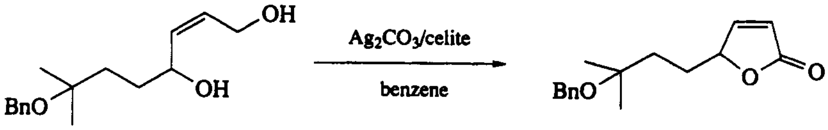

(29)

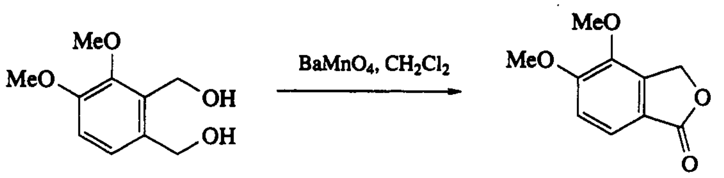

(30)

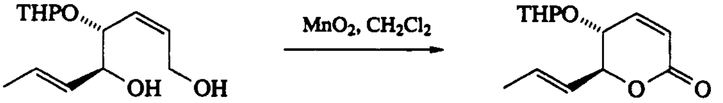

(31)

## 2.9.3 OXIDATION OF SECONDARY ALCOHOLS

### 2.9.3.1 Selective Preparation of Ketones

The oxidation of a secondary alcohol to the corresponding ketone is often a relatively straightforward task. There are several reasons for this. The product ketone is usually stable to the oxidating conditions and moreover with many reagents a secondary alcohol is oxidized more rapidly than a similar primary alcohol. Consequently there are more methods available for the chemoselective oxidation of secondary alcohols in the presence of primary alcohols. As might be expected from the preceding comments the selective oxidation of an allylic or benzylic secondary alcohol to the corresponding $\alpha,\beta$-unsaturated ketone is possible with a number of reagents. Essentially the same range of reagents can be used for this as is used for the equivalent oxidation of primary allylic alcohols (see Section 2.9.2.1). A selection of potentially useful reagents is given in Scheme 15.[16,51–58] The bismuth reagent is of particular interest in that it will also oxidize secondary allylic alcohols in preference to the corresponding saturated alcohols, and will not attack other sensitive functional groups (see later).[16]

The chemoselective oxidation of a saturated secondary alcohol in the presence of a saturated primary alcohol is possible with a number of reagents. *N*-Bromosuccinimide in an aqueous organic solvent has been used to carry out this type of selective oxidation and has found use in synthesis.[59,60] The value of this reagent is exemplified by its use in the synthesis of isocyanopupukeanane[59] and in work towards a total synthesis of gelsemine (equations (32) and (33) respectively).[60] Clearly this reagent would not be compatible with all functional groups, given the well-known reactivity of *N*-bromosuccinimide towards unsaturated compounds.

The use of *N*-chlorosuccinimide/diisopropyl sulfide for the selective oxidation of primary/secondary diols was outlined earlier in Section 2.9.2.1, where it was used for the selective oxidation of the primary alcohol. Remarkably, by carrying out the reaction at –78°C (as compared to 0°C in the previous case) this reagent system becomes selective for secondary alcohols in the presence of primary alcohols (see Scheme 2; Section 2.9.2.1).

Possibly the simplest reagent which has been reported to carry out the selective oxidation of a secondary alcohol is sodium hypochlorite in acetic acid.[61] Given the very low cost of the reagents, this system has obvious potential for large-scale operation. A modification of this procedure uses calcium hypochlorite, which has the advantage of being a stable solid and exhibits much the same reactivity as the original system.[62] Examples of these oxidations are given in equations (34) and (35).

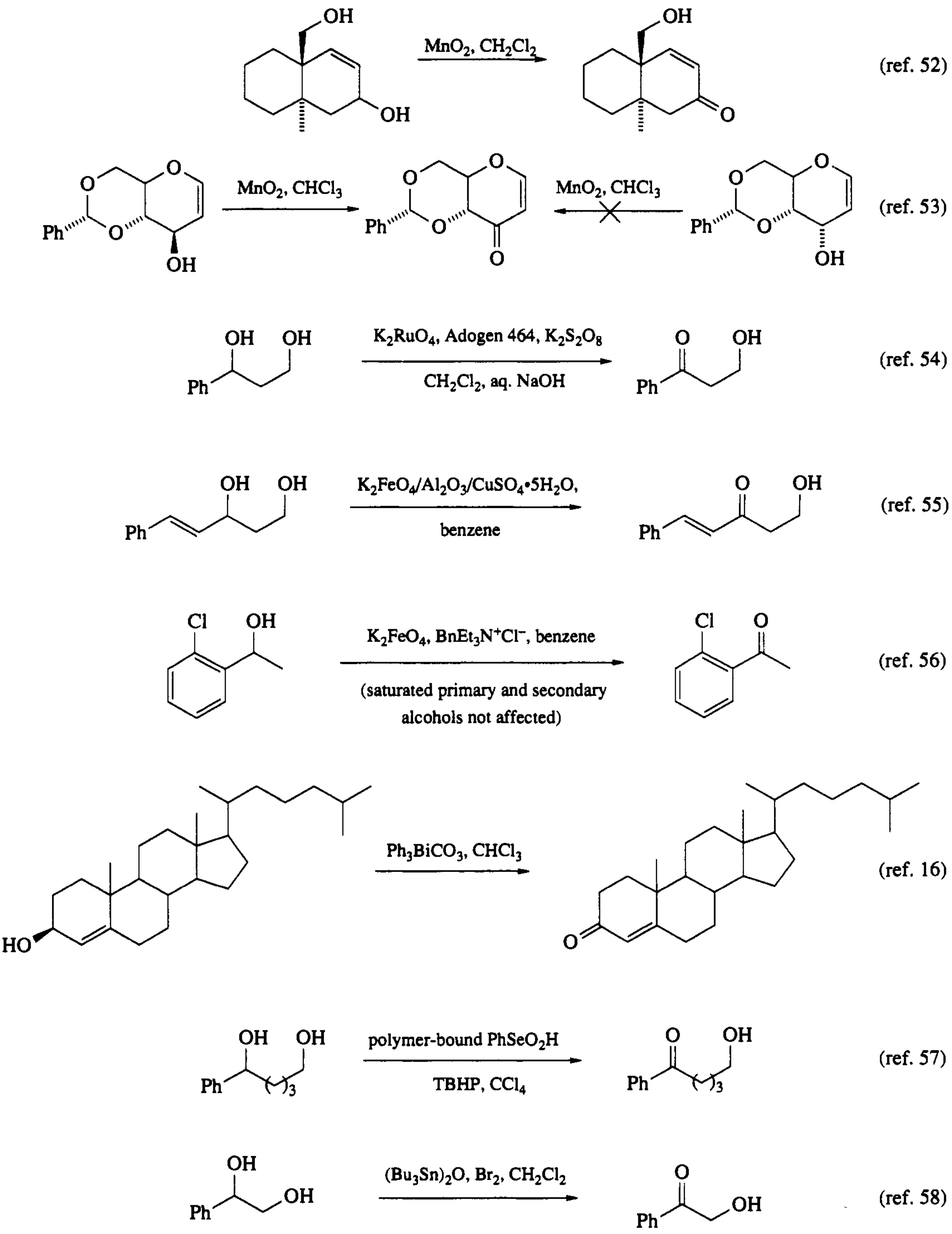
MnO2, CH2Cl2
(ref. 52)
MnO2, CHCl3
MnO2, CHCl3
(ref. 53)
K2RuO4, Adogen 464, K2S2O8
CH2Cl2, aq. NaOH
(ref. 54)
K2FeO4/Al2O3/CuSO4•5H2O,
benzene
(ref. 55)
K2FeO4, BnEt3N+Cl−, benzene
(saturated primary and secondary alcohols not affected)
(ref. 56)
Ph3BiCO3, CHCl3
(ref. 16)
polymer-bound PhSeO2H
TBHP, CCl4
(ref. 57)
(Bu3Sn)2O, Br2, CH2Cl2
(ref. 58)

**Scheme 15**

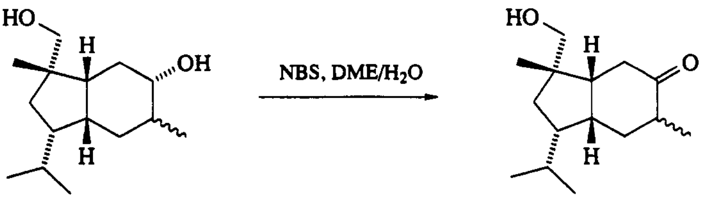
NBS, DME/H2O

(32)

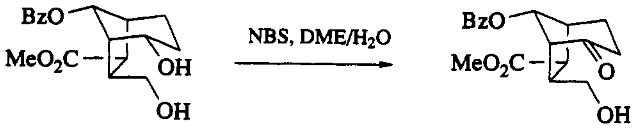

(33)

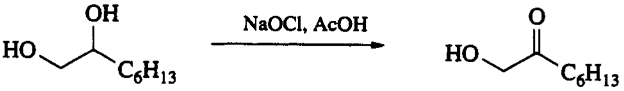

(34)

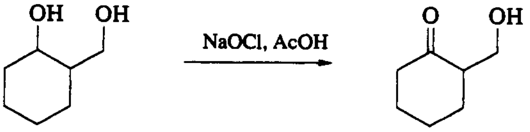

(35)

Examples of the highly chemoselective oxidation of a secondary hydroxy group have been reported using bromine in the presence of bis(tri-*n*-butyltin) oxide (equations 36 and 37), primary alcohols being essentially inert to this reagent mixture.[58]

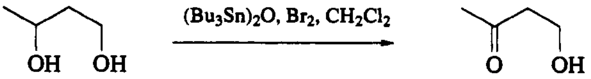

(36)

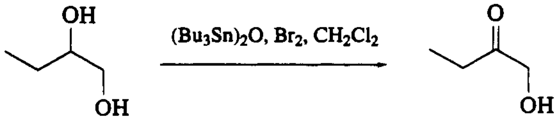

(37)

A modification of the Oppenauer oxidation which uses trichloroacetaldehyde on alumina provides a good, general oxidation of alcohols, and in particular will oxidize a secondary alcohol in the presence of a primary one, as shown by the examples given in Scheme 16.[63] This method is claimed to be superior to silver carbonate on Celite and much cheaper. Other advantages of this method are that it is neutral, nonaqueous, and halide, ester and lactone functionalities survive the reaction conditions.[63]

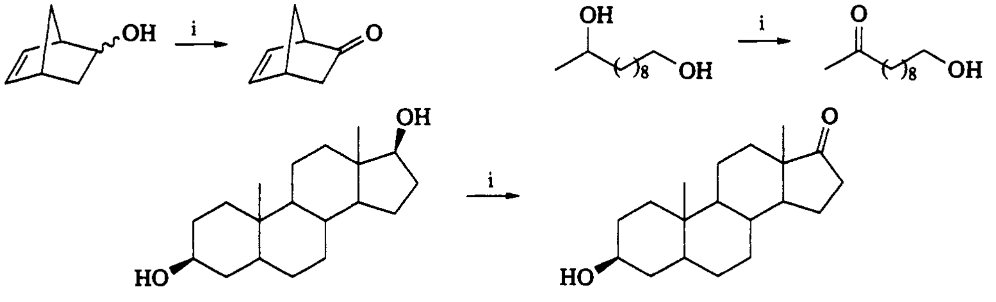

i, $Cl_3CCHO/Al_2O_3$, $CCl_4$

**Scheme 16**

Silver carbonate on Celite itself is a highly selective reagent for this type of chemoselective oxidation as can be seen from the examples in Scheme 17;[34] secondary diols can be oxidized to the hydroxy ketones, and primary diols are oxidized to lactones (see Section 2.9.2.2).

Several procedures for this chemoselective oxidation utilize molybdenum-based catalysts, with either hydrogen peroxide or *t*-butyl hydroperoxide as the stoichiometric oxidant. These include ammonium molybdate in the presence of a phase transfer reagent and hydrogen peroxide, which with pH control (potassium carbonate) will selectively oxidize a secondary alcohol in the presence of a primary alcohol without oxidizing alkenes.[64] In addition hindered alcohols are oxidized in preference to less hindered ones (Scheme 18).

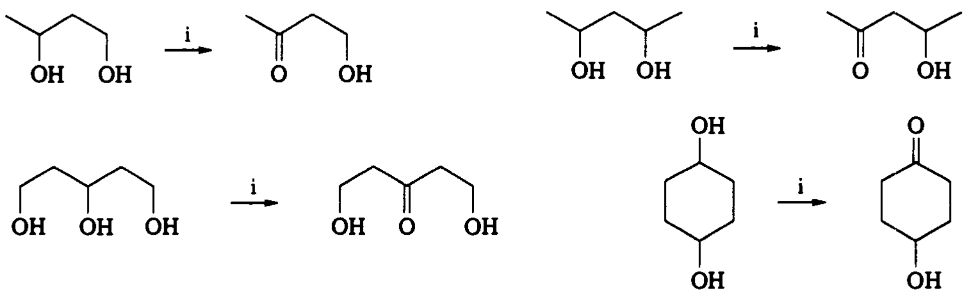

i, $Ag_2CO_3$/celite, benzene

**Scheme 17**

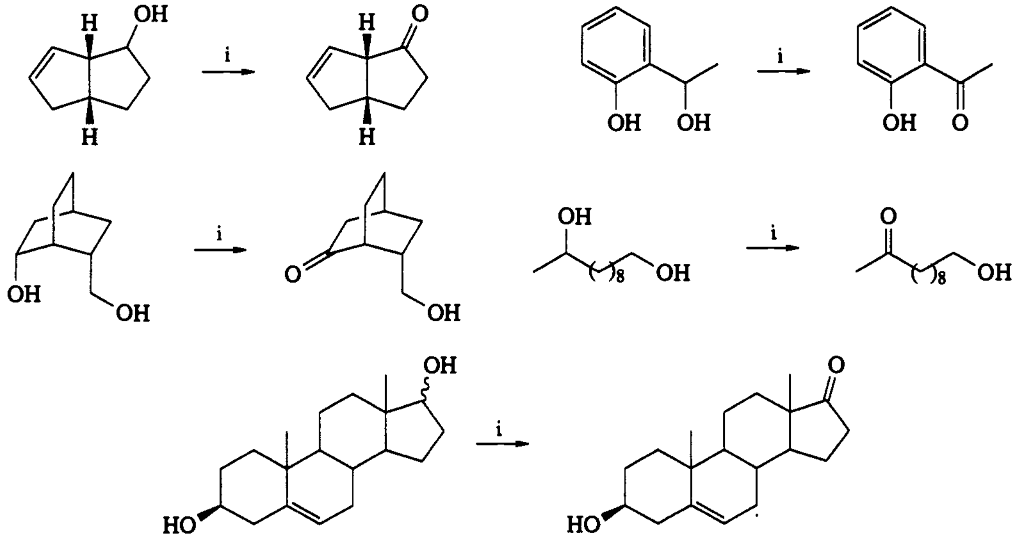

i, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, $H_2O_2$, $K_2CO_3$, $Bu_4N^+Cl^-$, THF

**Scheme 18**

Benzyltrimethylammonium tetrabromooxomolybdate will catalyze the chemoselective oxidation of secondary alcohols with *t*-butyl hydroperoxide as cooxidant.[65] Remote double bonds can interfere with this oxidation, and 1,2-diols are converted into 1,2-diketones (Scheme 19).

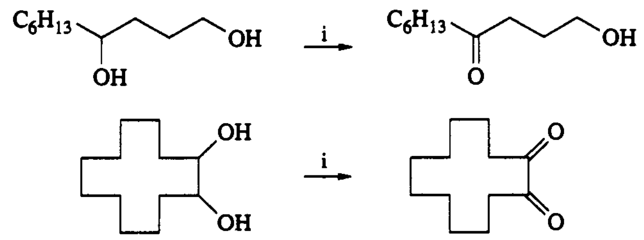

i, $BnMe_3N^+OMoBr_4^-$, TBHP, benzene

**Scheme 19**

The readily available catalyst vanadyl bisacetylacetonate when used with *t*-butyl hydroperoxide in benzene will oxidize secondary alcohols (Scheme 20) much more rapidly than primary ones (rate ratio > 100:1), but the other oxidizing properties of this system, in particular the epoxidation of allylic alcohols and the cleavage of 1,2-diols might well limit its uses somewhat.[66]

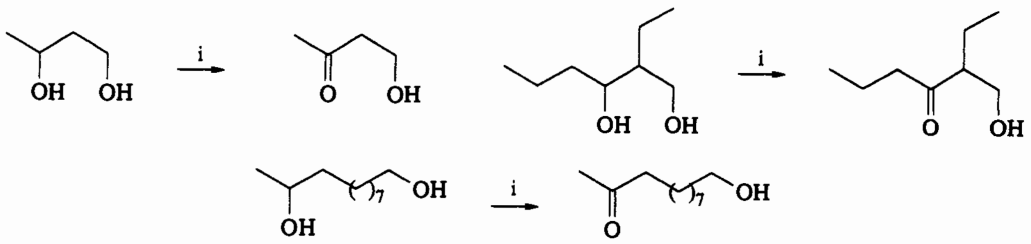

i, VO(acac)$_2$, TBHP, benzene

**Scheme 20**

Ammonium cerium(IV) nitrate or cerium(IV) sulfate will catalyze the selective oxidation of secondary alcohols with sodium bromate as cooxidant, in this case remote C—C double bonds interfere, but 1,2-diols are not cleaved.[67] It has been found that sodium bromite in aqueous acetic acid will act as a selective oxidant for secondary/primary diols without the need for other catalysts (Scheme 21).[68]

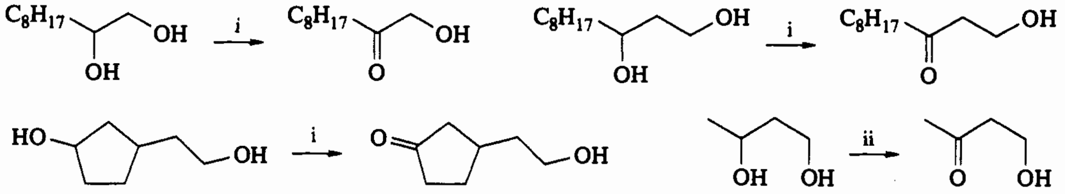

i, $(NH_4)_2Ce(NO_3)_6$, $NaBrO_3$, $MeCN/H_2O$; ii, $NaBrO_2$, $AcOH/H_2O$

**Scheme 21**

As referred to elsewhere μ-oxobis(chlorotriphenylbismuth) will carry out a number of interesting selective oxidations, amongst which is the selective oxidation of a secondary alcohol (equation 38), although this reagent will cleave 1,2-diols.[16]

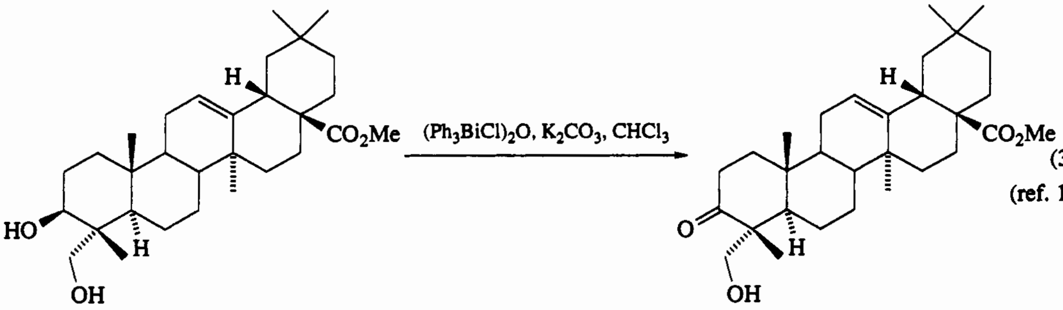

(38)
(ref. 16)

The preceding section dealt specifically with the chemoselective oxidation of secondary/primary diols. There is a clear interest in chemoselective oxidation of secondary alcohols in the presence of other sensitive functional groups, and some of the methods available will be described briefly in this section.

Remarkable chemoselectivity is exhibited by the pentavalent organobismuth reagents μ-oxo bis(triphenylbismuth) and triphenylbismuth carbonate referred to in the preceding sections.[16] The former reagent will oxidize a secondary alcohol without affecting a spiroacetal or an unsaturated carbonyl function. Triphenylbismuth carbonate is a highly selective, nonelectrophilic oxidant, which will oxidize α,β-unsaturated secondary alcohols without oxidizing thiols, pyrrolidine or indole. The selective oxidation of (**36**; Scheme 22) without oxidation of the selenium is also possible with this reagent. Other compounds/functional groups which are unaffected by this reagent include a range of carbonyl derivatives (dinitrophenylhydrazone, phenylhydrazone, semicarbazone, tosylhydrazone, excluding oximes), *O*-acetates, a vinyl ether, aniline, *N*,*N*-dimethylaniline, a dienamine, a thione, and a steroidal xanthate and *N*,*N*-diethyl thionocarbonate. Both these bismuth reagents will cleave 1,2-diols.

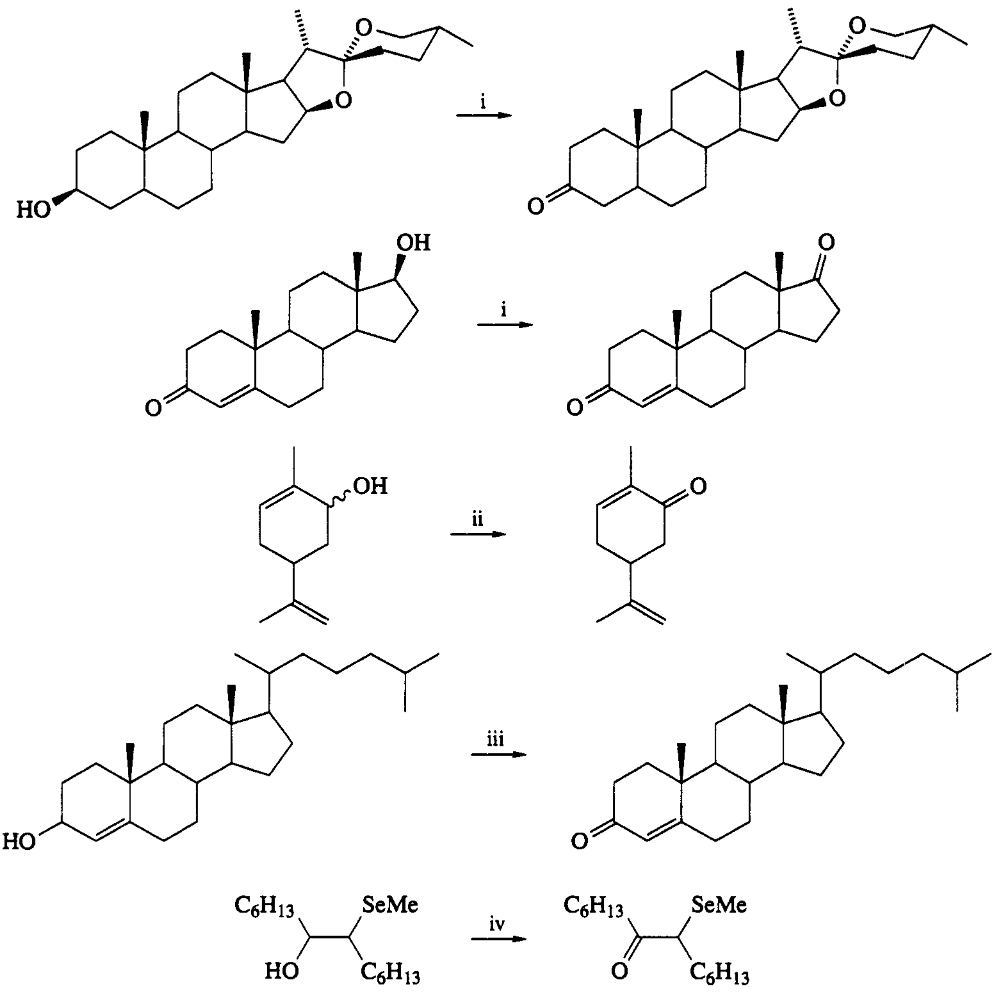
i
i
ii
iii
iv
HO
O
OH
C$_6$H$_{13}$
SeMe

**(36)**

i, $(Ph_3BiCl)_2O$, $CH_2Cl_2$ or $CHCl_3$, $NaHCO_3$ or $K_2CO_3$; ii, $Ph_3BiCO_3$, $CH_2Cl_2$, oxidation proceeds in the presence of either PhSH or Bu$^i$SH without oxidation of the thiol; iii $Ph_3BiCO_3$, $CH_2Cl_2$, oxidation proceeds in the presence of either indole or pyrrolidine without oxidation of either; iv $Ph_3BiCO_3$, $CH_2Cl_2$

**Scheme 22**

The selective oxidation of secondary alcohols which contain either a sulfide or selenide is also possible using either selenium-based oxidizing agents (equations 39 and 40),[69] or with a modified Oppenauer system involving trichloroacetaldehyde (equation 41).[15]

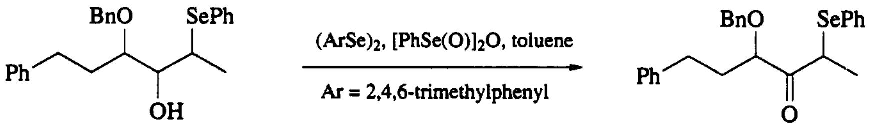
BnO
SePh
Ph
OH
(ArSe)$_2$, [PhSe(O)]$_2$O, toluene
Ar = 2,4,6-trimethylphenyl
BnO
SePh
Ph
O

(39)

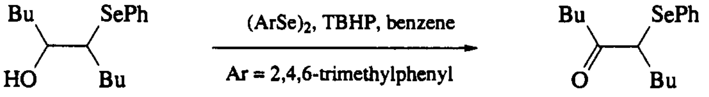
Bu
SePh
HO
Bu
(ArSe)$_2$, TBHP, benzene
Ar = 2,4,6-trimethylphenyl
Bu
SePh
O
Bu

(40)

*t*-Butyl hydroperoxide finds several applications as a stoichiometric oxidant in this area, when used with another reagent. Combination with aluminum tri-(*t*-butoxide) (equation 42) produces a mild, selec-

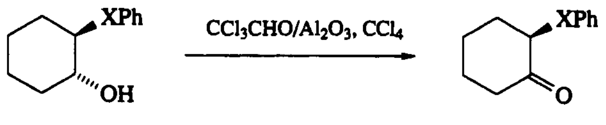
XPh
OH
$CCl_3CHO/Al_2O_3$, $CCl_4$
XPh
O

X = S, Se

(41)

tive oxidizing agent which tolerates other functional groups including, iodide, ester, terminal alkyne, aromatic ether and 1,3-dioxolane.[70] Various ruthenium complexes, including $RuCl_3$, $Ru(acac)_3$, $RuCl_2(PPh)_3$ and $[RuCl_2(CO)_3]_2$ in the presence of *t*-butyl hydroperoxide, will catalyze the selective oxidation of secondary alcohols containing styryl, furyl and thienyl groups (Scheme 23).[71]

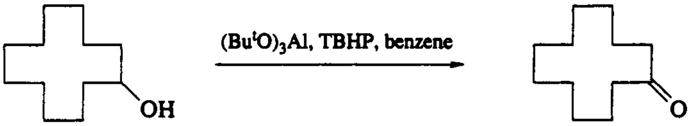
OH
$(Bu^tO)_3Al$, TBHP, benzene
O

(42)

1-iodododecane, methyl dodecanoate, phenylacetylene, anisole and dodecanal ethylene acetal were recovered unchanged under the reaction conditions

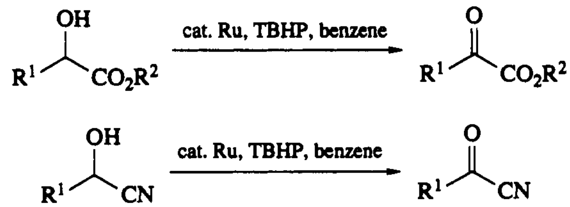
OH
$R^1$
$CO_2R^2$
cat. Ru, TBHP, benzene
O
$R^1$
$CO_2R^2$
OH
$R^1$
CN
cat. Ru, TBHP, benzene
O
$R^1$
CN

Ru catalysts include $RuCl_3$, $Ru(acac)_3$, $RuCl_2(PPh_3)_3$, $RuCl_2(CO)_3$
$R^1$ = methyl, styryl, phenyl, 2-furyl, 2-thienyl; $R^2$ = methyl, ethyl

Scheme 23

The selective oxidation of a secondary alcohol in the presence of a tertiary amine function has been carried out with manganese dioxide (equations 43 and 44) in the context of an alkaloid synthesis.[72]

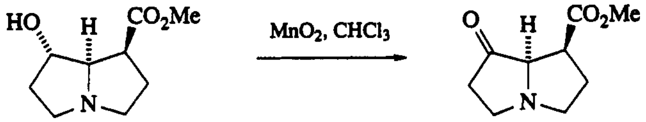
HO
H
$CO_2Me$
N
$MnO_2$, $CHCl_3$
O
H
$CO_2Me$
N

(43)

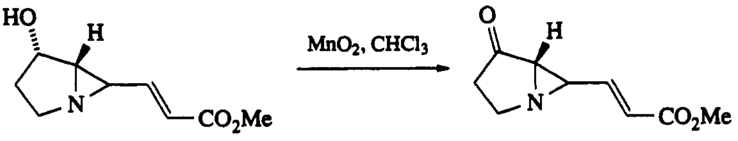
HO
H
N
$CO_2Me$
$MnO_2$, $CHCl_3$
O
H
N
$CO_2Me$

(44)

The versatile oxidizing agent 'periodinane', which functions as an excellent reagent for the oxidation of alcohols (see Section 2.9.2.1),[32] will oxidize a functionalized α-hydroxy ester to the corresponding α-keto ester in the amino acid derivatives (**37**) and (**38**; Scheme 24) without loss of stereochemical integrity or interference from the other highly polar groups in these molecules.[73]

## 2.9.4 CONCLUSION

There are numerous reagents available for the chemoselective oxidation of polyfunctional alcohols. The most promising general type of oxidant must be that in which a mild, clean oxidizing agent (*e.g.* *t*-butyl hydroperoxide, bromine, air or *N*-methylmorpholine *N*-oxide) is used in conjunction with a reagent which will catalyze the desired selective oxidation. Mild, stoichiometric oxidants (such as periodinane),

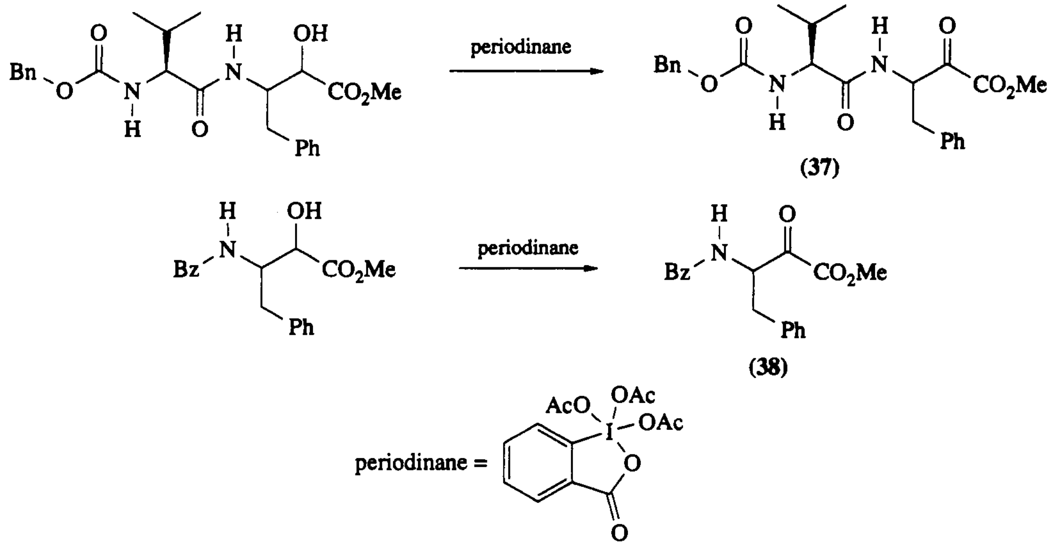

(37)

(38)

Scheme 24

which avoid the use of possibly toxic or expensive metals, and do not produce toxic or noxious by-products, provide an alternative of great value.

It is unlikely that any single reagent will prove to be a universal oxidant for a particular type of chemoselective oxidation. Many of the reagents considered in this chapter would need to be tested further, on more complicated substrates, before a 'reagent of choice' could be arrived at. Nevertheless, reagents which fall into the two general categories delineated in the preceding paragraph would be high on the list of potential reagents for a given selective oxidation.

Given the above it is rather surprising that chemoselective oxidation is encountered relatively rarely in the synthesis of complex molecules. The problem of selective oxidation is usually dealt with by careful choice of strategy, or by protection of the functional group which is not to be oxidized.

Why not use selective oxidants instead of protection or limiting the strategies considered? The usual response to this from those (including the author) involved in such complex syntheses is that the reagents are not proven in such a synthetic context. It is too risky, why take the chance? This is a perfectly reasonable response given the time and effort required to carry out such syntheses, but perhaps a little negative. No reagent is perfect, and in the area of selective oxidation much remains to be achieved, and no doubt new reagents will be discovered and developed in the future. Avoiding the use of relatively untried selective oxidants by protection of functional groups is far from perfect itself. While protecting group chemistry is certainly a more advanced art than selective oxidation, it can have its own problems. Selective deprotection, often a consequence of such protection, can prove far from trivial.

Perhaps organic chemists involved in the synthesis of complex organic compounds should have the courage to try this type of selective oxidant in new situations, especially where it might avoid difficult protection/deprotection, or where it would lead to a more direct synthetic route. Protection/deprotection is often cumbersome and far from elegant, and new or untried reagents can only be evaluated properly within the context of the synthesis of polyfunctional organic compounds. In this way the limitations of existing reagents are uncovered, and the requirements for new reagents may be determined, and the discovery and development of such new selective reagents is a worthy challenge for modern organic chemistry to meet.

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# 2.10
# Vinylic and Arylic C—H Oxidation

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## 2.10.1 INTRODUCTION

A comprehensive introduction to this subject will be found by consulting the excellent books by Haines[1] and Wakefield[2] and the reviews by Harvey[3] and Whiting.[4]

The replacement of an aromatic or vinylic hydrogen by any other element can formally be considered as an oxidative process.[5] In this review only replacement of hydrogen by oxygen and reactions that proceed by such a process have been considered. The subject matter has been divided into several sections covering oxidations that proceed *via* an organometallic species, and finally those that do not. In order to make comparisons or to highlight the uses of a particular reagent, this division of material has not been rigidly held to. With organometallic reagents, transmetallation is often used to obtain the desired intermediate, and these reactions have generally been classified according to the first metallation, as it is this process which controls the regioselectivity of the oxidation.

The bulk of material considered covers arylic C—H oxidation, since vinylic C—H oxidation is essentially covered elsewhere (Chapter 3.4, this volume).

The reaction of an arylorganometallic reagent with an oxygen species is a popular process for introducing oxygen functionality in organic synthesis. The main advantage of such a reaction is its regiospecificity; the oxygen is invariably introduced at the carbon–metal bond. The main difficulty with such a process is regioselective formation of the carbon–metal bond. This can be achieved by one of the following methods: (i) functional group directed metallation, such functionality must be either present in the product or subject to appropriate modification; (ii) halogen–metal exchange, this requires the presence of an appropriately positioned halogen; (iii) electronically directed metallation *e.g.* thallation; or (iv) incorporation of the metal in the synthesis, particularly applicable to silicon and tin. This process, along with (ii), is not formally an oxidation of a C—H bond, but is considered here because it helps to complete the picture for aryl C—O bond formation.

## 2.10.2 LITHIUM, MAGNESIUM AND BORON INTERMEDIATES

In addition to molecular oxygen, [6] a number of reagents have been developed for introduction of oxygen into a carbon–lithium or carbon–magnesium bond. These include peroxides,[7,8] molybdenum peroxide–pyridine–hexamethylphosphoramide (MoOPH),[9] sulfonyloxaziridines,[10] nitrobenzene[11] and oxidation of the boronate[12] after transmetallation.

### 2.10.2.1 Imidazolones

Taddei and Ricci[7] reported the use of bis(trimethylsilyl) peroxide for the electrophilic hydroxylation of aryllithiums. The aryllithiums were formed regiochemically pure by either halogen–metal exchange or *ortho*-directed lithiation (Scheme 1). The same authors also noted that when the carbanion is α to a heteroatom, as in the 2-lithiobenzthiazolone, the reaction afforded the trimethylsilyl derivative (**1**), with no trace of the siloxy product (Scheme 2). This is not the case with *N*-protected imidazoles, as shown by Lipshutz *et al.*[13] who reacted the 2-position and 5-position anions of *N*-SEM-protected imidazoles with either bis(trimethylsilyl) peroxide or benzoyl peroxide to give good yields of the imidazolone (**2**; Scheme 3) and the TMS-protected imidazolone (**3**; Scheme 3). The reason why an *N*-protected imidazole gives the siloxy derivative, while a benzthiazolone gives the trimethylsilyl adduct, is not immediately obvious.

$$\mathrm{RX} \xrightarrow{\mathrm{Bu^nLi}} \mathrm{RLi} \xrightarrow{(\mathrm{Me_3SiO})_2} \mathrm{ROSiMe_3} \xrightarrow{\mathrm{H^+}} \mathrm{ROH}$$

$$\mathrm{X = Br\ or\ H}$$

**Scheme 1**

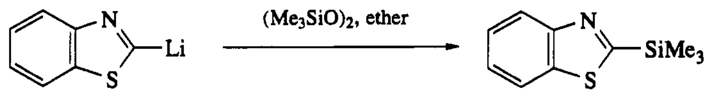

(**1**)

**Scheme 2**

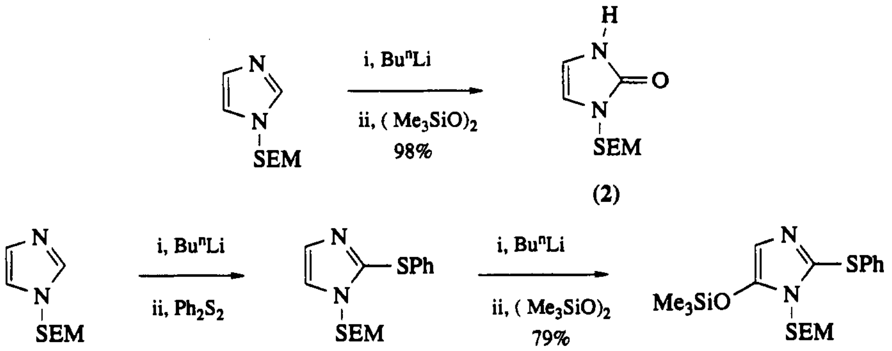

(**2**)

(**3**)

**Scheme 3**

### 2.10.2.2 Totarol Metabolites

In order to investigate the production of nagilactones from totarol by a route modeled on the suggested biogenetic pathway, Cambie *et al.*[14] needed to convert totarol (**4**) into 12-hydroxytotarol (**5**). Bromination of 13-methoxytotara-8,11,13-triene (**6**) with bromine and thallium(I) acetate in refluxing carbon tetrachloride gave the bromide (**7**) in 94% isolated yield. All attempts to form the Grignard reagent were unsuccessful, but treatment of the bromide with 1 equiv. of *n*-butyllithium resulted in a clean conversion to the aryllithium compound. Reaction of this intermediate with *t*-butyl perbenzoate gave back only starting material (**6**), but reaction with dry oxygen, MoOPH or lithium *t*-butyl hydroperoxide gave the natural product dispermol (**8**) in 47%, 40% and 36% yields respectively. It should be noted that higher yields of phenols were obtained with all these reagents in model studies. Dispermol (**8**) was then converted into the desired catechol (**5**) by pyridinium hydrochloride.

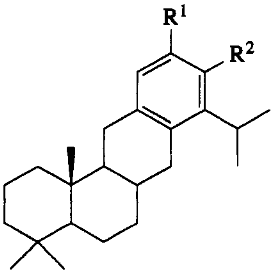

(**4**) $R^1$ =H, $R^2$ = OH
(**5**) $R^1$ = OH, $R^2$ = OH
(**6**) $R^1$ = H, $R^2$ = OMe
(**7**) $R^1$ = Br, $R^2$ = OMe
(**8**) $R^1$ = OH, $R^2$ = OMe
(**9**) $R^1$ = COMe, $R^2$ = OMe
(**10**) $R^1$ = OCOMe, $R^2$ = OMe

Alternative methods for the formation of the catechol (**5**) were examined, and these serve to show other methods for introduction of the hydroxy group. Nitration of triene (**6**) followed by reduction to the amine and diazotization in the presence of methanol gave the phenol (**8**), but only in poor yield. The best method developed appears to be acetylation of the triene (**6**) with titanium tetrachloride/acetyl chloride to give the ketone (**9**), followed by Baeyer–Villiger oxidation to the acetate (**10**), which on hydrolysis afforded the catechol (**8**) in 70% overall yield.

### 2.10.2.3 Tetralins

Whilst studying the metabolism of dopaminergic and serotonergic agonists, Wikström *et al.*[15] required the 5- and 8-hydroxy-2-(di-*n*-propylamino)tetralins. The synthesis of the 5-isomer (**11**) is shown in Scheme 4. The yield with nitrobenzene was poor, but this was the best reagent for the required conversion.

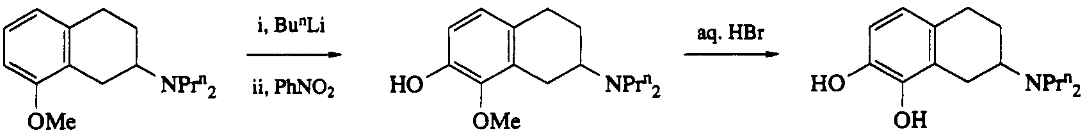

(**11**)

**Scheme 4**

Nitrobenzene has found little use as a source of an electrophilic hydroxy group, and the reader should be aware that other reactions can take place when it is reacted with organometallic reagents.[16]

### 2.10.2.4 Estrogens

A fine example demonstrating the use of an arylboron intermediate was reported by Santaniello *et al.*[17] As part of a project aimed at evaluating the biological activity of 2-and 4-substituted estrogens a convenient synthesis of 2-hydroxyestradiol was needed. Classical electrophilic oxidations usually lead to equimolar amounts of 2- and 4-isomers which are not easy to separate, and thus a method for regioselective hydroxylation was required. 3-Methoxyestra-1,3,5(10)-trien-17β-yl acetate (**12**) reacted with mercury(II) acetate in dry acetonitrile, and the reaction mixture was then treated with saturated aqueous sodium chloride to give the 2-chloromercurio derivative (**13**) in 80% yield. This intermediate was then exposed to diborane and the resulting organoboron complex directly oxidized to the 2-hydroxy estrogen which, after acetylation, gave the diacetate (**14**) in average yields of 48–50%. The methyl protecting group was removed and the triol stored as the triacetate (**15**; Scheme 5).

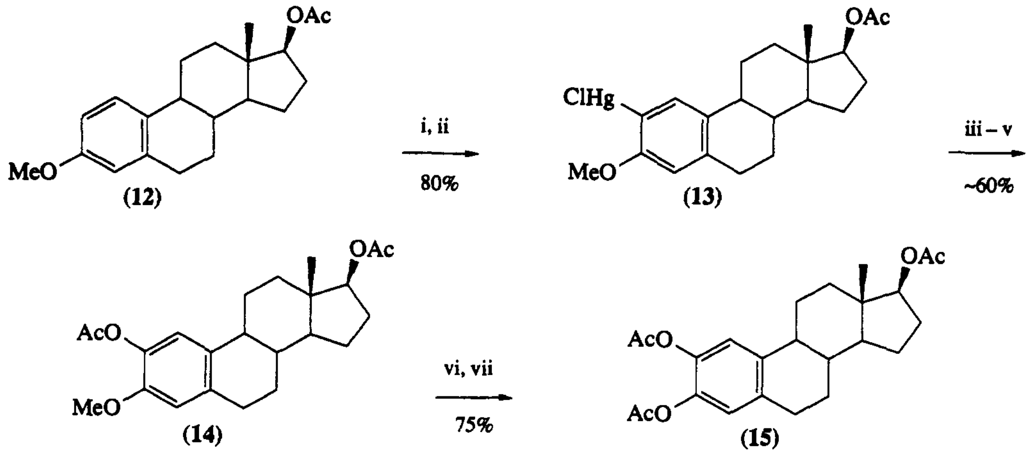

i, $Hg(OAc)_2$, MeCN; ii, aq. NaCl; iii, $B_2H_6$; iv, $H_2O_2$; v, $Ac_2O$; vi, pyridinium hydrobromide; vii, $Ac_2O$

**Scheme 5**

It is worthwhile here to put this work in context with related work in the field.[18] If the acetal-protected estrogen (**16**) was treated with *n*-butyllithium/TMEDA then metallation occurred at both the 2- and 4-positions. Conversion to the hydroxylated products (**17**) and (**18**) was then achieved *via* the boron complex using similar methodology to the above (Scheme 6). The same authors, Kirk and Slade,[19] did however report an efficient, regioselective synthesis of the 4-acetate isomer (**19**) by employing lead tetraacetate (LTA) as the oxidizing agent after initially forming the 4-mercurio intermediate (Scheme 7).

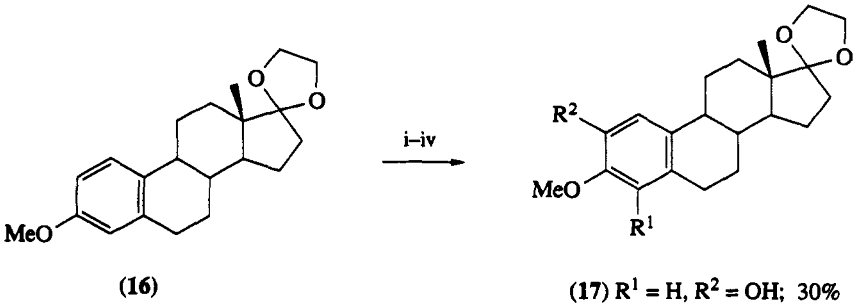

(**17**) $R^1$ = H, $R^2$ = OH; 30%

(**18**) $R^1$ = OH, $R^2$ = H; 15%

i, $Bu^nLi$; ii, $B_2H_6$, $B(OMe)_3$; iii, $H_2O_2$, NaOH; iv, $H^+$

**Scheme 6**

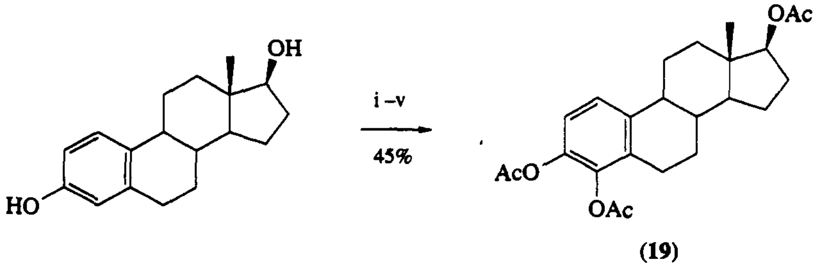

i, $Hg(OAc)_2$, AcOH, cat. $HClO_4$; ii, $Ac_2O$; iii, LTA, $CF_3CO_2H$; iv, $Ac_2O$; v, $H^+$

**Scheme 7**

In complete contrast to the above results is the oxidation of the estrone (**20**) by hydrogen peroxide in hydrogen fluoride/antimony tetrafluoride.[20] When subjected to hydroxylating conditions using this reagent, the estrone (**20**) gave a poor-yielding mixture of the oxidized products (**21–23**; Scheme 8).

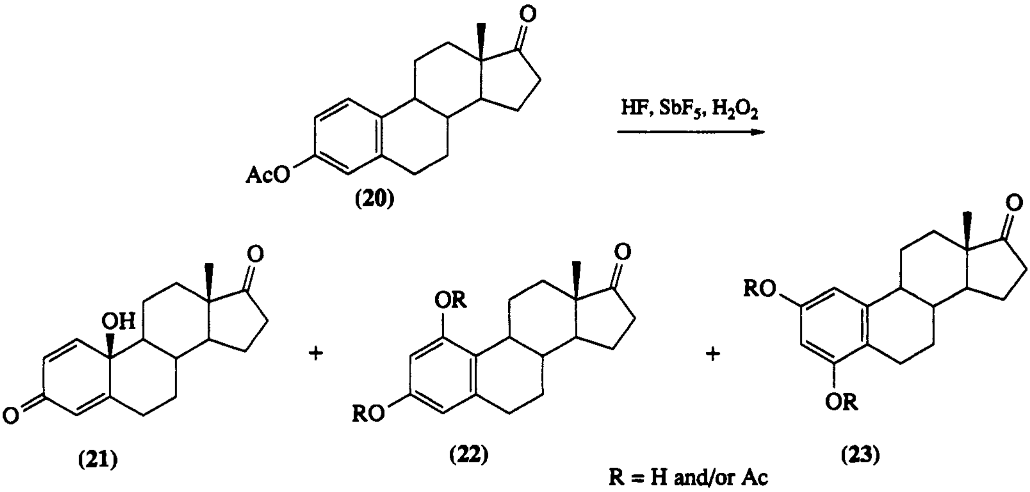

**Scheme 8**

These examples demonstrate that metal-directed hydroxylation is a powerful tool in organic synthesis.

### 2.10.2.5 Miscellaneous

A new method for the *ortho* hydroxylation of aromatic aldehydes *via* *ortho*-lithiated aromatic aminoalkoxides has recently been reported by Einhorn *et al.*[21] Formation of the aminoalkoxide serves two purposes. Firstly, the aldehyde group is protected and, secondly, the aminoalkoxide directs lithiation to the *ortho* position. Oxidation of the lithio species was effected by either MoOPH or molecular oxygen, albeit in poor yield. Alternatively, a two-step, one-pot condensation of the lithio intermediate with tributyl borate followed by oxidation with hydrogen peroxide gave the *ortho*-hydroxy aldehydes (**24**) in slightly better yields (Scheme 9).

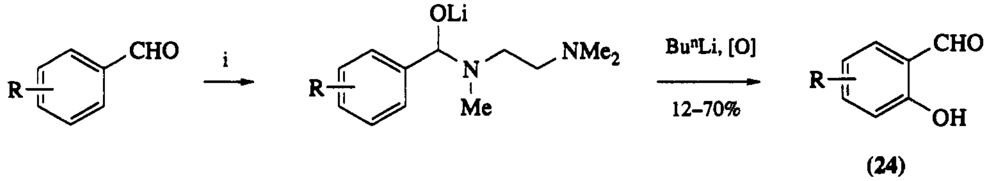

i, Bu$^n$Li, *N,N,N'*-trimethylethylenediamine

**Scheme 9**

Snieckus and coworkers[22] used the combination of a tertiary amide with a methylenedioxy group to direct lithiation to the *ortho* position, and then converted the lithiated intermediate to the 2-hydroxybenzamide (**25**), which was used as a starting material for the synthesis of acridones (Scheme 10).

A similar methodology was used by Borchardt and coworkers[23] in the synthesis of the phenol (**26**; Scheme 11). Here, the fact that 4-fluorophenol metallates next to fluorine when the phenol is protected as a TBDMS ether was put to good use for introduction of the hydroxy group. Likewise, oxidation of a boron complex was a key step in the synthesis of phenolic dihydrodiols of benzo[a]pyrene, (**27**) and (**28**),[24] and also in the synthesis of phenolic crown ethers (**29**).[25]

The use of thallium is covered later, but it is worthwhile mentioning here that in the hydroxylation of polystyrenes reported by Bullen *et al.*,[26] the mercury or thallium intermediates were converted to the boronic acid residue using diborane and the boronate then transformed into the phenol (**30**) using hydrogen peroxide or trimethylamine *N*-oxide.

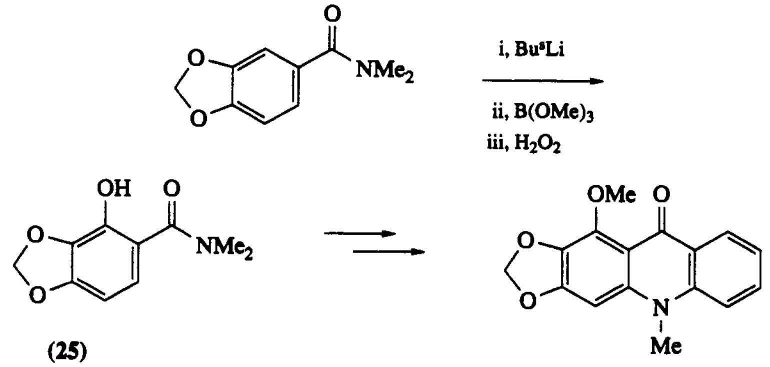
NMe2
i, BusLi
ii, B(OMe)3
iii, H2O2
OH
O
OMe
N
Me

(25)

Scheme 10

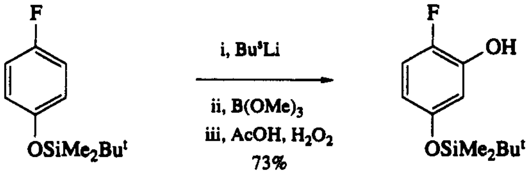
F
i, BusLi
ii, B(OMe)3
iii, AcOH, H2O2
73%
OSiMe2But
OH

(26)

Scheme 11

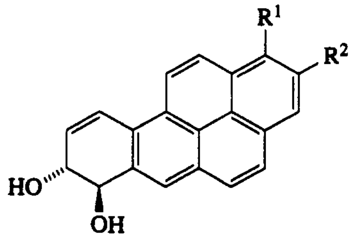

(27) $R^1 = H, R^2 = OH$

(28) $R^1 = OH, R^2 = H$

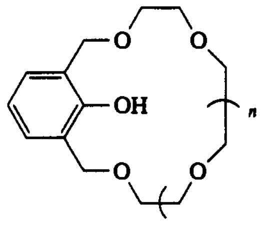

(29) $n = 1–7$

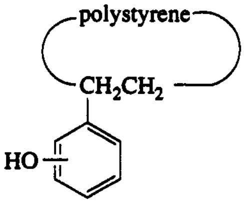
polystyrene
CH2CH2
HO

(30)

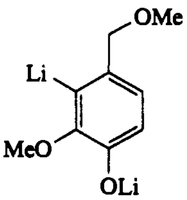
OMe
Li
MeO
OLi

(31)

It is only fair when reviewing syntheses to mention unsuccessful reactions so as to outline any shortcomings of a particular reagent, and this has been done throughout this review. Saà *et al.*[27] have recently reported that reaction of the metallated lithium phenolate (31) with either nitrobenzene or bis(trimethylsilyl) peroxide gave only starting material, while reaction with trimethyl borate followed by oxidation furnished a complex mixture.

## 2.10.3 THALLIUM INTERMEDIATES

The reactions of aromatic substrates with thallium reagents is a fascinating subject which has been reviewed by McKillop and Taylor,[28] two of the prime contributors to this field of chemistry. Two types of reaction are possible, both of which are important for the introduction of oxygen functionality. The first is electrophilic aromatic thallation, whilst the second involves one-electron oxidation.

Arylthallium compounds are very interesting species and so obviously different from their lithium/magnesium/boron counterparts. Formation of an aryllithium/magnesium/boron reagent involves either proton abstraction, halogen–metal exchange or metal–metal exchange, whereas arylthallium compounds are produced by a reversible electrophilic process. Subsequent reactions are also very different in that the thallium species can undergo electrophilic, nucleophilic or free radical reactions depending upon the choice of reagent. For an understanding of the factors controlling the regiochemistry of aromatic thallation the reader should consult McKillop's review; however, aromatic thallation will in general follow the basic rules governing electrophilic aromatic substitution. The following points, however, should be remembered: (i) the process is reversible and can lead in time to the thermodynamic product, (ii) any groups present capable of coordinating to thallium will direct the position of metallation, and (iii) aromatic moieties activated towards electrophilic substitution are likely to undergo one-electron oxidation.

Whilst direct electrophilic hydroxylation of the arylthallium species can be effected using peroxytrifluoroacetic acid, further oxidation of the phenol to a quinone accompanies this process. This over-oxidation can be avoided by initial transmetallation to a lead species with concomitant reduction of the thallium trifluoroacetate (TTFA) by triphenylphosphine, followed by displacement of the lead by trifluoroacetate to give the aryl trifluoroacetate.[28] This hydroxylation method has yet to find use in the synthesis of molecules which are more complex than simple arenes.

### 2.10.3.1 Indoles

The synthesis of compounds bearing the indole nucleus has received a lot of attention from Somei and coworkers. As part of this program they have developed methods for regioselectively introducing oxygen functionality into the 4- and 7-positions of indoles. Thus, subjecting indole-3-carbaldehyde to thallation with thallium trifluoroacetate, followed by reaction of the thallium intermediate with iodine/copper(I) iodide in DMF, gave the iodide (32), which was readily converted to the corresponding methoxyindole (33) with sodium methoxide. The overall yield was an excellent 86% (Scheme 12).[29]

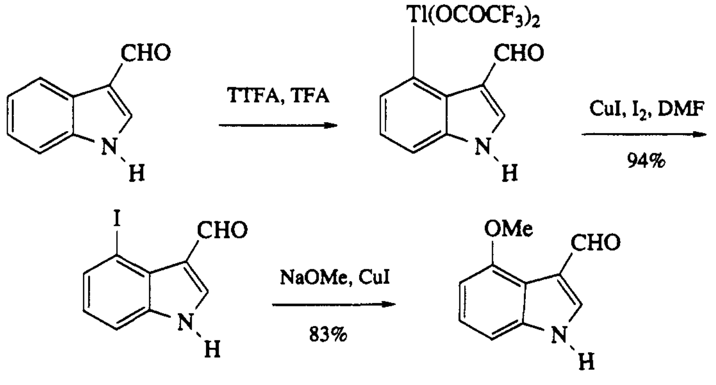

(32) (33)

Scheme 12

The synthesis of 7-methoxyindole was accomplished starting from 1-acetylindoline (34). Regioselective introduction of iodine was achieved using thallium trifluoroacetate, then potassium iodide. Deacetylation and oxidation to the indole (35), followed by reaction with sodium methoxide in DMF, gave the 7-methoxyindole (36) in 48% overall yield (Scheme 13).[30] More recently, Somei *et al.*[31] have reported that treating the intermediate thallium species with copper(II) sulfate pentahydrate gives directly the 1-acetyl-2,3-dihydro-7-hydroxyindole (37) in 42% yield (Scheme 14). It remains to be seen whether this is a general process.

A completely different approach to hydroxylation at the 5-position (indole numbering) in tryptophans was reported by Hino and coworkers.[32] Their synthesis involved either LTA or Fremy's salt oxidation of

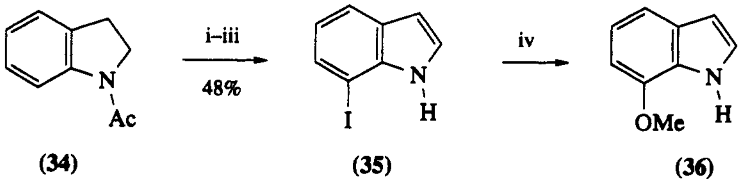
i–iii
48%
iv
N
Ac
N
H
I
N
H
OMe
(34)
(35)
(36)

i, TTFA, TFA; ii, KI; iii, $O_2$, salcomine; iv, NaOMe, CuI, DMF

Scheme 13

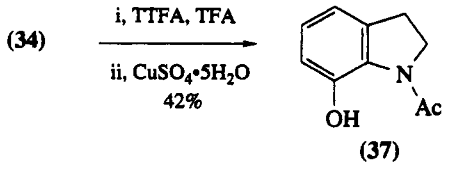
(34)
i, TTFA, TFA
ii, $CuSO_4 \cdot 5H_2O$
42%
N
OH
Ac
(37)

Scheme 14

the cyclic tautomer derived from tryptophan (**38**) to the *p*-quinoneimine (**39**), followed by sodium borohydride reduction and treatment with acetic acid, to give the hydroxytryptophan (**40**; Scheme 15).

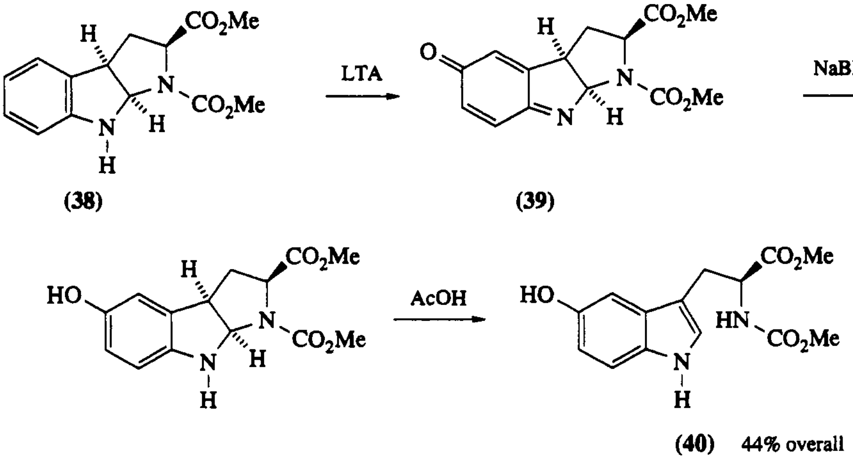
H
$CO_2Me$
N
$CO_2Me$
N
H
H
(38)
LTA
O
H
$CO_2Me$
N
$CO_2Me$
N
H
(39)
$NaBH_4$
HO
H
$CO_2Me$
N
$CO_2Me$
N
H
H
AcOH
HO
$CO_2Me$
HN
$CO_2Me$
N
H
(40) 44% overall

Scheme 15

### 2.10.3.2 Towards Lycorine Alkaloids

Although one-electron oxidation of arenes by thallium trifluoroacetate presumably does not proceed *via* formation of a discrete arylthallium bond, some examples involving oxidative cyclization mediated by thallium trifluoroacetate will be considered here. Schwartz and Hudec[33] employed thallium trifluoroacetate to effect an intramolecular cyclization of the amide (**41**) to give a key intermediate (**42**) in their projected synthesis of lycorine alkaloids (Scheme 16). Interestingly, when the bromine was replaced by a hydrogen the yield was poorer.

### 2.10.3.3 Dihydrocoumarins

Taylor and coworkers[34] have studied the intramolecular capture of radical cations from the thallium trifluoroacetate oxidation of arylalkanoic acids and arylalkanols. For example, 3-(3,4-dimethoxyphenyl)propionic acid (**43**) on treatment with thallium trifluoroacetate in trifluoroacetic acid containing a small amount of boron trifluoride etherate for a few seconds gave the oxidized products (**44**–**46**; Scheme 17), the exact yields dependent upon the reaction conditions and work-up. In analogous fashion, oxida-

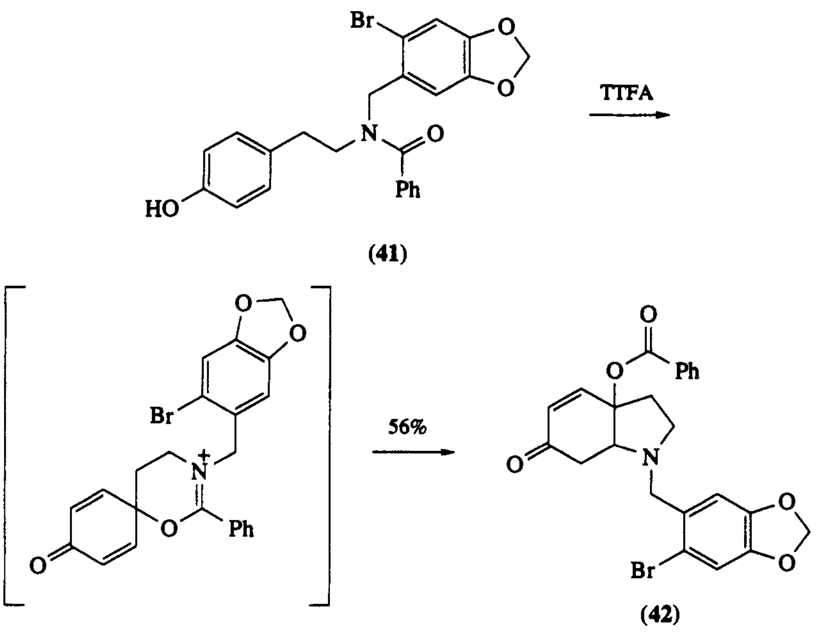

Br
O
O
N
O
Ph
HO
TTFA
(41)
O
O
Br
N+
O
Ph
O
56%
O
O
Ph
O
N
O
O
Br
(42)

**Scheme 16**

tion of 3-(2,3,4-trimethoxyphenyl)propionic acid (47) gave the dihydrocoumarin (48) in 53% yield (Scheme 18).

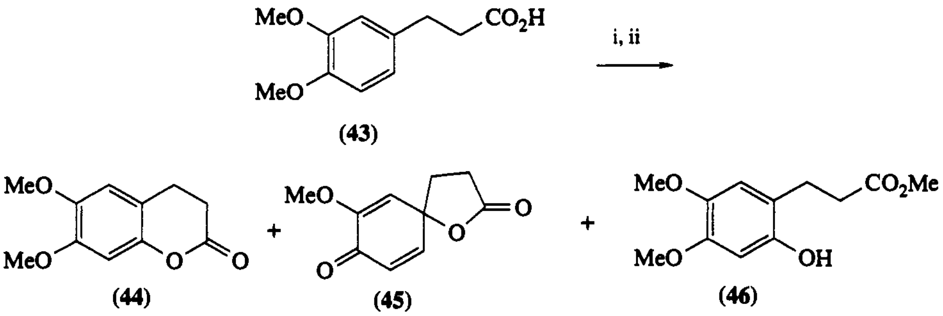

MeO
MeO
$CO_2H$
i, ii
(43)
MeO
MeO
O
O
(44)
+
MeO
O
O
O
(45)
+
MeO
MeO
$CO_2Me$
OH
(46)

i, TTFA, TFA, cat. $BF_3\cdot OEt_2$; ii, $\mathrm{Bu^tOH}$

**Scheme 17**

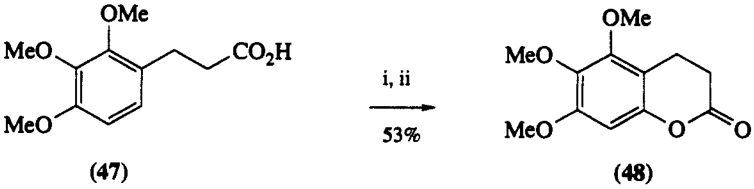

OMe
MeO
MeO
$CO_2H$
(47)
i, ii
53%
OMe
MeO
MeO
O
O
(48)

i, TTFA, TFA, cat. $BF_3\cdot OEt_2$; ii, $\mathrm{Bu^tOH}$

**Scheme 18**

Yamamura and coworkers have used a thallium trifluoroacetate mediated oxidative cyclization in their synthesis of aerothionin and related products[35] and also in the synthesis of bastadin-6,[36] a 28-membered ring lactone.

## 2.10.4 LEAD INTERMEDIATES

Lead tetraacetate (LTA) and lead tetrakisfluoroacetate (LTFA) are common oxidants for the introduction of the hydroxy group. It has been suggested that the oxidation proceeds *via* electrophilic attack directly onto oxygen,[37] but this seems unlikely in view of the fact that aryllead species are well characterized compounds,[38] and they are known to give the corresponding acetates on treatment with trifluoroacetic acid or acetic acid. Some examples of the use of LTA have already been described (see Sections 2.10.2.4 and 2.10.3).

### 2.10.4.1 Estrone

An impressive synthesis of estrone (**51**) was reported by Vollhardt and coworkers.[39] Cobalt-catalyzed cooligomerization of the diyne (**49**) with bis(trimethylsilyl)acetylene gave the estratrienone (**50**) in 71% yield. Introduction of the hydroxy substituent at C-3 was then cleverly achieved by selective protodesilylation at C-2, followed by oxidation of the carbon–silicon bond using LTFA (Scheme 19).

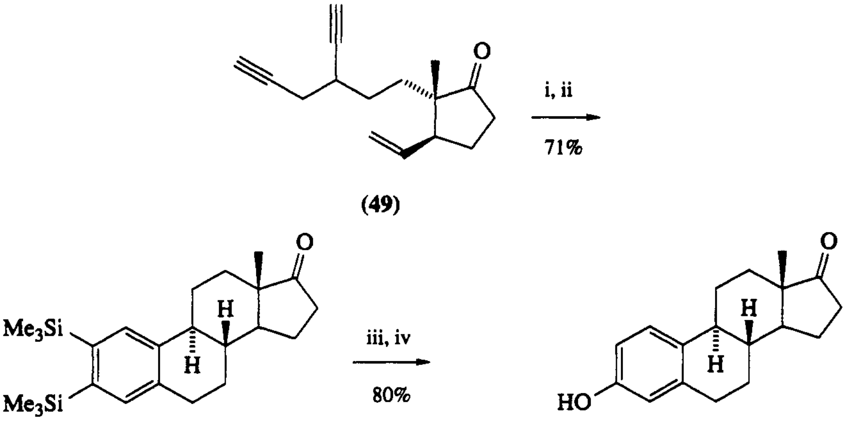

**(49)**

**(50)** **(51)**

i, $CpCo(CO)_2$, BTMSA; ii, xylene, reflux; iii, TFA, –30 °C; iv, LTFA

**Scheme 19**

### 2.10.4.2 Vitamin $B_6$

In a synthesis of vitamin $B_6$, which also employed a cobalt-mediated diyne cyclization, Vollhardt and coworkers[40] were unsuccessful in converting either the tin compound (**52**) or the corresponding silicon derivative to the hydroxylated material using LTA and trifluoroacetic acid. In fact, attempted hydroxylation of the tin compound (**52**) by transmetallation with *n*-butyllithium followed by reaction with molecular oxygen, nitrobenzene or trimethyl borate/hydrogen peroxide gave complex mixtures containing primarily destannylated material. A solution to the problem was eventually found by introduction of iodine, followed by displacement of iodide using a modification of the method developed by Tiecco (Scheme 20).[41]

### 2.10.4.3 Quinol Acetates

Pattenden and coworkers[42] have recently evaluated the relative merits of LTA and electrochemical oxidation of phenolic compounds with particular reference to synthesis of the antiallergic compounds sodium chromoglycate (INTAL; **53**) and proxicromil (**54**), which are used for the prophylactic treatment of asthma. The 2-carboxychromone moieties in the compounds (**53**) and (**54**) are synthesized from the appropriate 2′,6′-dihydroxyacetophenones. Oxidation of the 2′-hydroxyacetophenone (**55**) by LTA in dichloromethane gave almost exclusively the quinol acetate (**56**), which was subsequently converted to the 2′,6′-dihydroxyacetophenone (**57**), a precursor to proxicromil (**54**; Scheme 21). By contrast, electro-

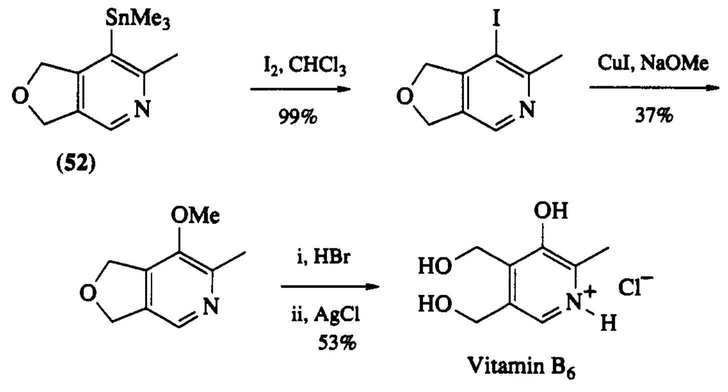
SnMe3
O
N
(52)
I2, CHCl3
99%
I
O
N
CuI, NaOMe
37%
OMe
O
N
i, HBr
ii, AgCl
53%
OH
HO
HO
N+
H
Cl−
Vitamin B6

**Scheme 20**

chemical oxidation of the acetophenone (**55**) gave four principal products, with the quinol acetate (**58**) as the major one. The acetate (**58**) was then converted to the 2′,6′-dihydroxyacetophenone (**57**; Scheme 22).

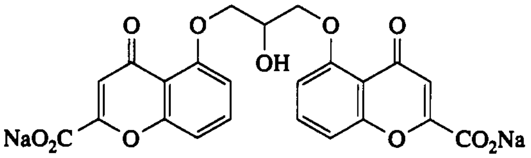
O
O
OH
O
O
NaO2C
O
O
CO2Na

**(53)**

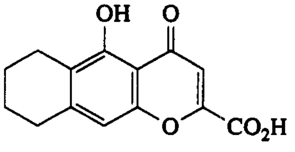

**(54)**

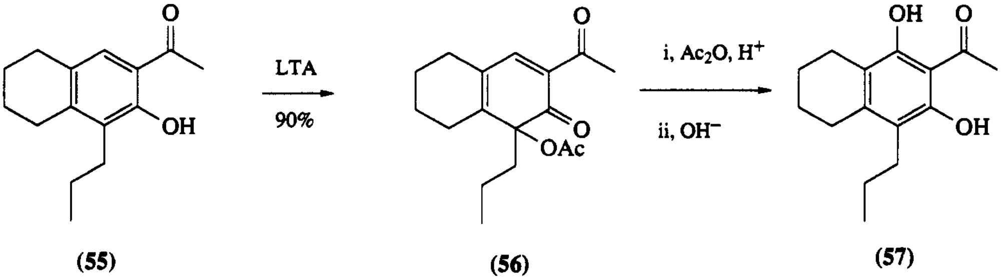
O
OH
LTA
90%
O
O
OAc
i, Ac2O, H+
ii, OH−
OH
O
OH
(55)
(56)
(57)

**Scheme 21**

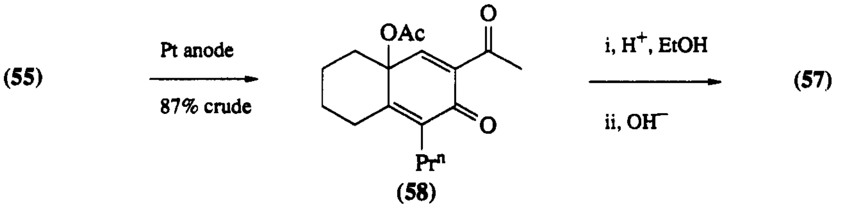
(55)
Pt anode
87% crude
OAc
O
O
Prn
(58)
i, H+, EtOH
ii, OH−
(57)

**Scheme 22**

Umezawa and coworkers[43] have extensively studied the LTA oxidation of hydroxytetrahydroisoquinolines, highlighting the range of products that can be obtained depending upon the reaction conditions and subsequent transformations.

## 2.10.5 NONMETALLATED INTERMEDIATES

Methods for the oxidation of arylic and vinylic C—H bonds which do not proceed *via* organometallic intermediates have already been referred to in the preceeding sections when it was appropriate to make comparisons.

Direct introduction of oxygen may be performed by a variety of reagents, but this type of oxidation does not normally extend beyond the preparation of simple phenols.[44] The oxidation of phenols to hydroquinones is occasionally encountered. Indirect oxidation may be effected in a number of ways. A reliable method is formation of either an aryl halide[45] or an aryldiazonium salt,[46] followed by attack with an oxygen nucleophile. The displacement of an aromatic halogen by alkoxides is a procedure which has been developed in particular by Testaferri and Tiecco.[41,47] Alternative procedures for indirect oxidation involve intramolecular delivery of oxygen, and encompass such reactions as the Baeyer–Villiger oxidation and the photochemical rearrangement of aromatic azoxy derivatives,[48] the latter process obviously being restricted to quite specific systems.

### 2.10.5.1 Hydroquinones

The Elbs persulfate oxidation procedure was used by Bach and coworkers[49] at an early stage of their synthesis of model compounds related to fredericamycin A. Thus the phenol (**59**) gave 2,5-dihydroxy-4-methoxybenzoic acid (**60**) in modest yield (30%). This was then transformed in several steps to the isobenzofuranone (**61**). Generation of the isobenzofuran (**62**) *in situ* and Diels–Alder reaction of this with the enedione (**63**) gave, after loss of the trimethylsilyl group, the desired compound (**64**; Scheme 23) in 62% yield from the isobenzofuranone (**61**).

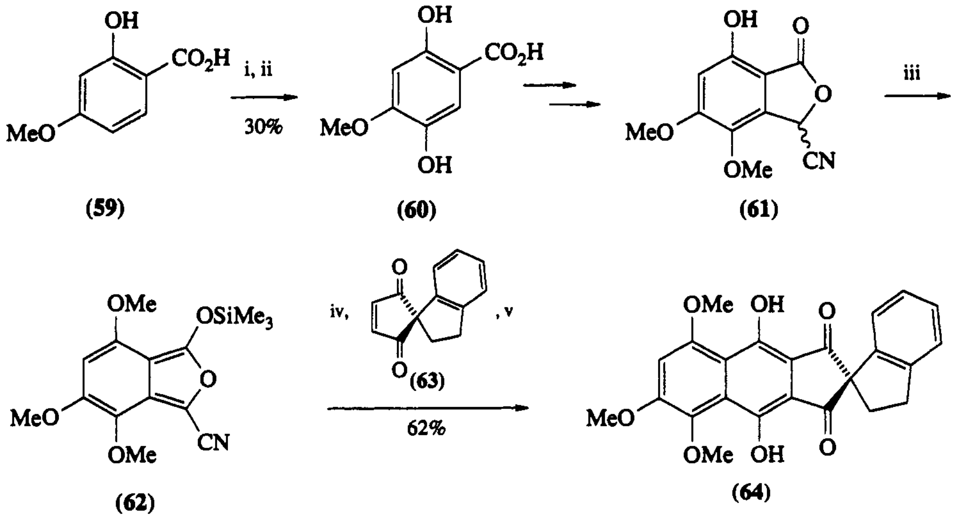
OH
CO2H
MeO
i, ii
30%
(59)
OH
CO2H
MeO
OH
(60)
OH
O
O
MeO
OMe
CN
(61)
iii
OMe
OSiMe3
O
MeO
OMe
CN
(62)
iv,
O
O
(63)
, v
62%
OMe
OH
O
MeO
OMe
OH
O
(64)

i, $K_2S_2O_8$, NaOH; ii, $H^+$; iii, $Bu^nLi$ then $Me_3SiCl$; iv, (**63**); v, silica gel

**Scheme 23**

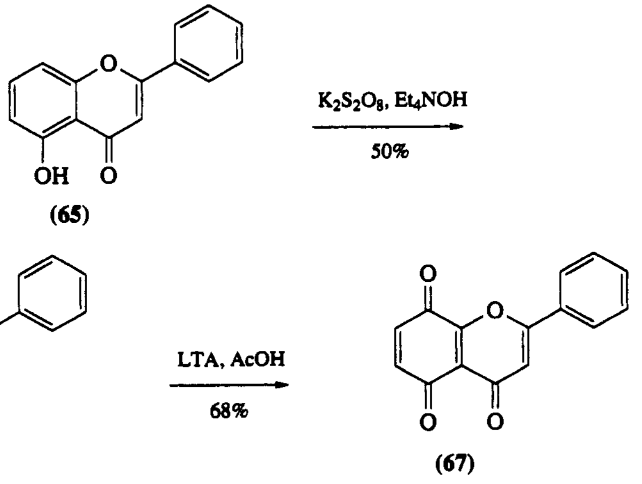
O
OH
O
(65)
K2S2O8, Et4NOH
50%
OH
O
OH
O
(66)
LTA, AcOH
68%
O
O
O
O
(67)

**Scheme 24**

Looker *et al.*[50] used a modification of the Elbs persulfate oxidation procedure in which tetraethylammonium hydroxide was used as the base in their synthesis of 5,8-quinoflavone. The phenol (**65**) was oxidized to the hydroquinone, primetin (**66**), which upon further oxidation with LTA afforded 5,8-flavoquinone (**67**) in 34% overall yield (Scheme 24).

### 2.10.5.2 Daunomycin and Adriamycin Analogs

One good example of the use of the Baeyer–Villager oxidation was reported by Mitscher and coworkers[51] in their approach to analogs of adriamycin and daunomycin, two important antitumor antibiotics. The anthracenone (**68**) was cyclized with hydrogen fluoride to give the unstable product (**69**), which upon treatment with hydrogen peroxide in acetic acid/sulfonic acid underwent oxidation to the quinone and also Baeyer–Villiger cleavage of the ketone moiety to give, after esterification, the anthraquinone (**70**), a key intermediate in their projected synthesis (Scheme 25). Unfortunately, problems in the latter stages of the synthesis and attractive routes to similar analogs from other workers led to this approach being abandoned. It is interesting to note that the same authors[52] had great difficulty in introducing a hydroxy group by displacement of a bromide in a similar system (Scheme 26). The desired transformation was finally effected in 65% yield using calcium hydroxide and copper powder in a sealed tube at 200 °C.

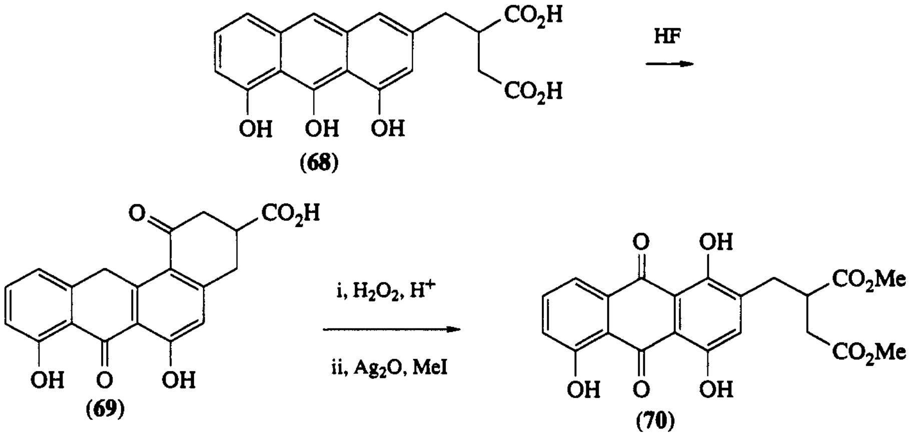

Scheme 25

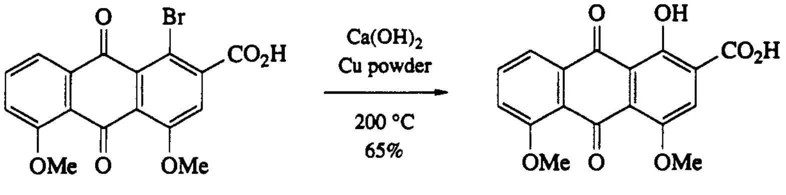

Scheme 26

### 2.10.5.3 Anthracycline Relatives

Lown and Sondhi[53] were interested in the synthesis of chromophores of the anthracycline antibiotics in which the quinone ring c was replaced by a $\gamma$-pyrone. The $\gamma$-pyrone ring was prepared by an oxidative cyclization mediated by DDQ, presumably proceeding *via* the quinone (Scheme 27).

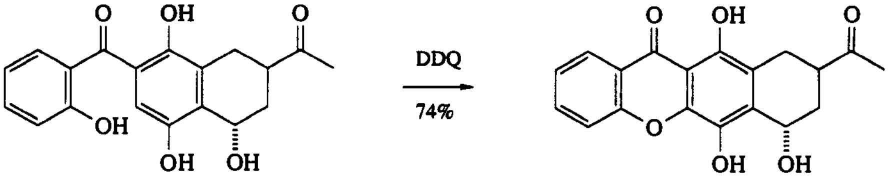

Scheme 27

### 2.10.5.4 Fervenulin Analogs

The synthesis of analogs of the antibiotic 2-methylfervenulone (MSD-92)[54] highlights an example of the displacement of a chloride by an oxygen nucleophile, although perhaps more interesting is the regioselective introduction of the chlorine by reacting the 4-deazafervenulin 2-oxide (**71**) with the Vilsmeier–Haack reagent to give the 3-chloro-4-deazafervenulin (**72**) in 45% yield. Senga and coworkers then converted this chloro compound (**72**) to the 4-hydroxy analog (**73**), which upon methylation gave 4-deaza-MSD-92 (**74**; Scheme 28).

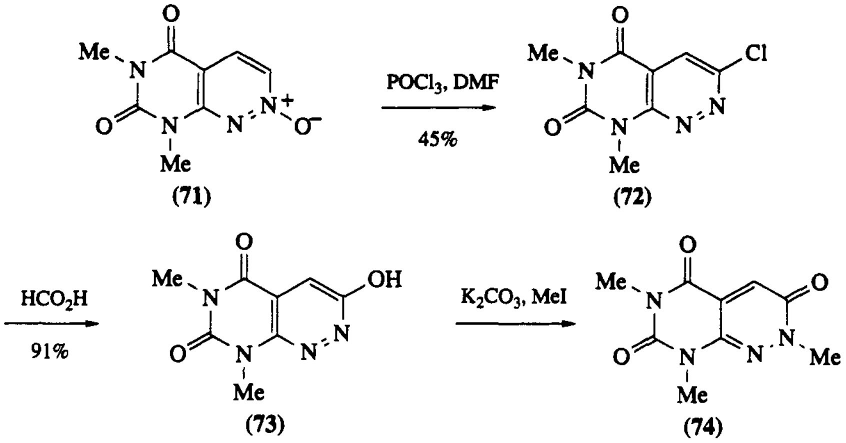

**Scheme 28**

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# 2.11

# Synthesis of Quinones

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## 2.11.1 INTRODUCTION

The synthesis of quinones,[1] including anthracyclinone antibiotics[2] and oxidized metabolites of polynuclear aromatic hydrocarbons,[3] has been reviewed.

The synthesis of quinones from arenes is an area which demands further research, despite the number of reagents presently available for this transformation. This is highlighted by the synthesis of the naphthoquinone (**3**).[4] Direct oxidation of the dibromoarene (**1**) was unsatisfactory, and therefore Bruce and coworkers had to resort to a multistep sequence involving nitration, reduction, diazotization, displacement by hydroxide and finally oxidation of the phenol (**2**) with Fremy's salt (Scheme 1). Although there are examples of the oxidation of polynuclear aromatic hydrocarbons to quinones, the direct oxidation of an arene to a quinone is a process not encountered in the synthesis of more complex molecules.

On the contrary, there are many examples of the synthesis of quinones from activated arenes, the activation normally arising from a hydroxy, alkoxy or amino group. It would be impossible here to cite every example from the last decade; however, it is hoped that the references expanded upon will give the reader a feel for the types of reagent which are most popular, the type of system that has employed this chemistry, and some of the problems involved. A number of reagents[5] are available for the oxidation of activated arenes to quinones, but there are only a few tried and tested reagents which are used again and again. The question posed by the reader who is looking to effect a particular oxidative transformation is

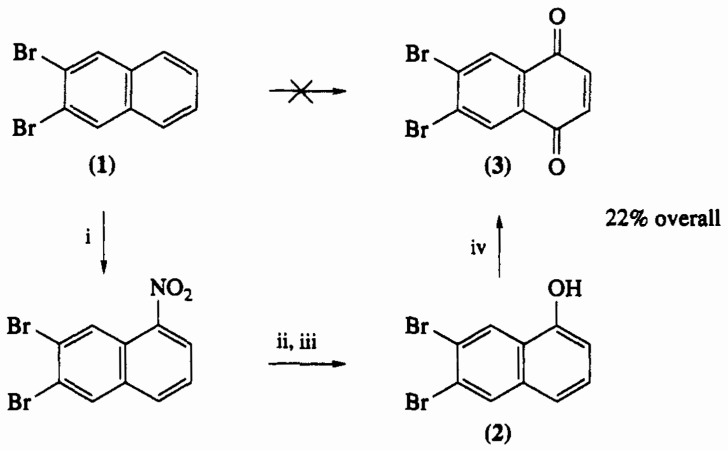

i, dil. $HNO_3$, $CH_2Cl_2$, conc. $H_2SO_4$; ii, $H_2NNH_2$, Pd–C; iii, $NaNO_2$, $H_2SO_4$ then $H_3O^+$; iv, Fremy's salt

**Scheme 1**

which reagent? Unfortunately in this area there is no simple answer. Although it could possibly be said that Fremy's salt is the reagent of choice for the synthesis of *p*-quinones from phenols, while cerium(IV) ammonium nitrate is often preferred for the oxidative demethylation of methoxyarenes, the following examples will serve to emphasize that experimentation is often necessary to find the best reagent for the transformation in question. Although this review is primarily concerned with synthesis it is most convenient to loosely categorize the syntheses according to the reagents that were utilized.

## 2.11.2 FREMY'S SALT

### 2.11.2.1 Towards Rubradirin

Fremy's salt (potassium nitrodisulfonate)[6] is a widely used reagent,[7–12] particularly in the synthesis of quinone antibiotics. One example has emerged from Kozikowski's group in their approach to the rubradirin antibiotics.[13] The MEM-protected 2-nitroresorcinol (4) was converted in several steps to the phenol

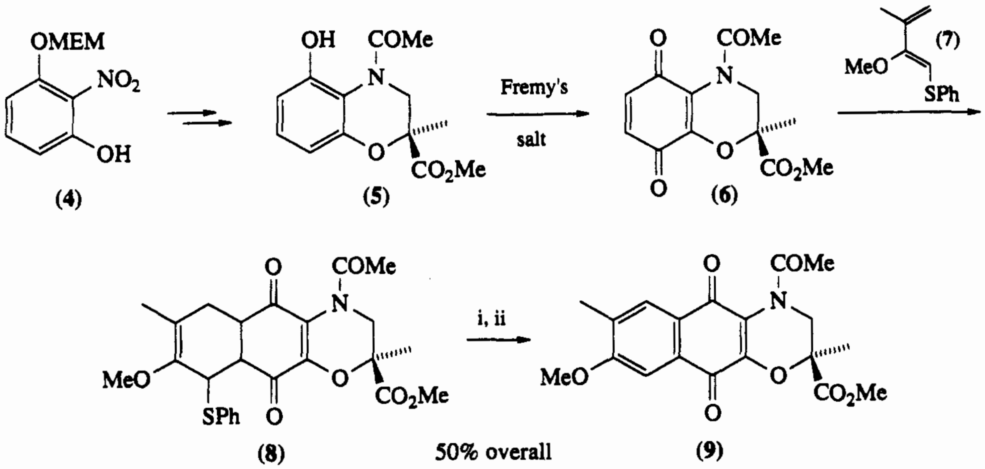

i, $KHCO_3$; ii, Fremy's salt

**Scheme 2**

(**5**), which was then oxidized with Fremy's salt to the quinone (**6**). It was imperative that the nitrogen was protected by an acyl group, otherwise none of the desired quinone was formed. Diels–Alder reaction with the diene (**7**) then gave the cyclohexenedione (**8**) which upon treatment with potassium hydrogencarbonate to eliminate thiophenol and oxidation with Fremy's salt gave the key intermediate quinone (**9**; Scheme 2).

### 2.11.2.2 Defucogilvocarcin V

A more recent example from McGee and Confalone[14] highlights the use of Fremy's salt in the oxidation of a latent phenol (**10**) to the quinone (**11**). The oxidation was initially problematic because Fremy's salt requires the free phenol and, although the lactone could be opened under basic conditions, the salt readily relactonized on acidification. The oxidation was finally accomplished by adding the initial hydrolysis mixture to a solution of Fremy's salt buffered to pH 7. The quinone (**11**) was then converted to the aglycone defucogilvocarcin V (**12**), an important compound for studying the mechanism of DNA damage by the antitumor gilvocarcins (Scheme 3).

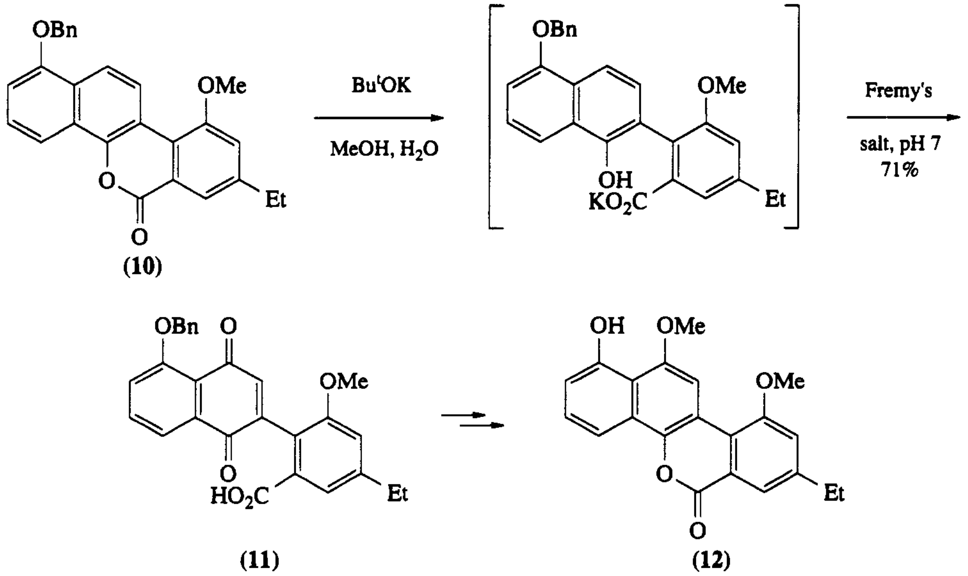

(**10**)

(**11**)

(**12**)

**Scheme 3**

### 2.11.2.3 α-Tocopherol

One complication that can arise when using Fremy's salt is that the substrate may be insoluble in the aqueous reaction medium, despite the use of organic cosolvents. Olson *et al.*[15] introduced an organic-soluble version of Fremy's salt in their synthesis of α-tocopherol. Hexahydrofarnesolacetone (**13**) was transformed to the phenol (**14**), which was oxidized in nearly quantitative yield to the tocopheryl quinone (**15**) using a mixture of Fremy's salt and tricaprylylmethylammonium chloride in a two-phase water/benzene solvent system. The oxidizing agent was presumed to be the bis(tricaprylylmethyl)ammonium nitrodisulfonate. The quinone (**15**) is a known precursor of α-tocopherol (**16**; Scheme 4).

### 2.11.2.4 Lavendamycin Pharmacophores

The idea of using a phase transfer procedure with Fremy's salt was further developed by Kende and Ebetino[16] who advanced tetra-*n*-butylammonium bisulfate as the phase transfer reagent in a dichloromethane/aq. bicarbonate two-phase system. Although Kende obtained disappointing results with this system in the synthesis of lavendamycin (**17**), Boger *et al.*[17] put these reagent conditions to good use in their synthesis of a similar quinoline-5,8-diene (**18**) which was designed to investigate the potential minimum, potent pharmacophores of lavendamycin (**17**) and the related streptonigrin, two powerful antitumor anti-

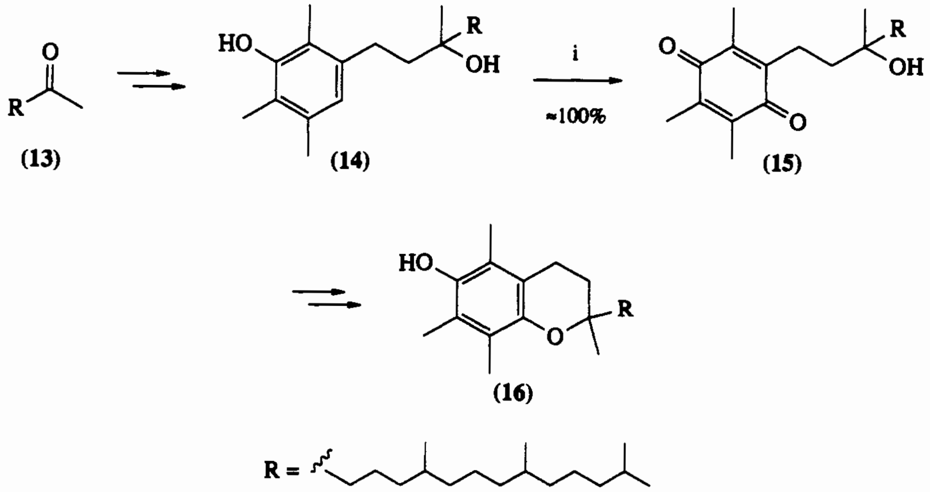

(13)
(14)
(15)
(16)
i
≈100%
R =

i, Fremy's salt, tricaprylylmethylammonium chloride

**Scheme 4**

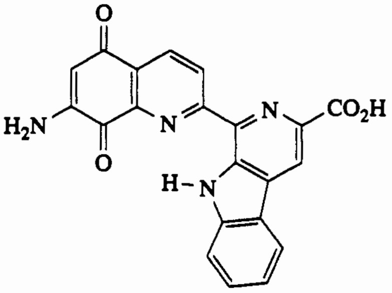

**(17)**

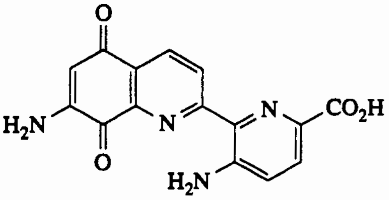

**(18)**

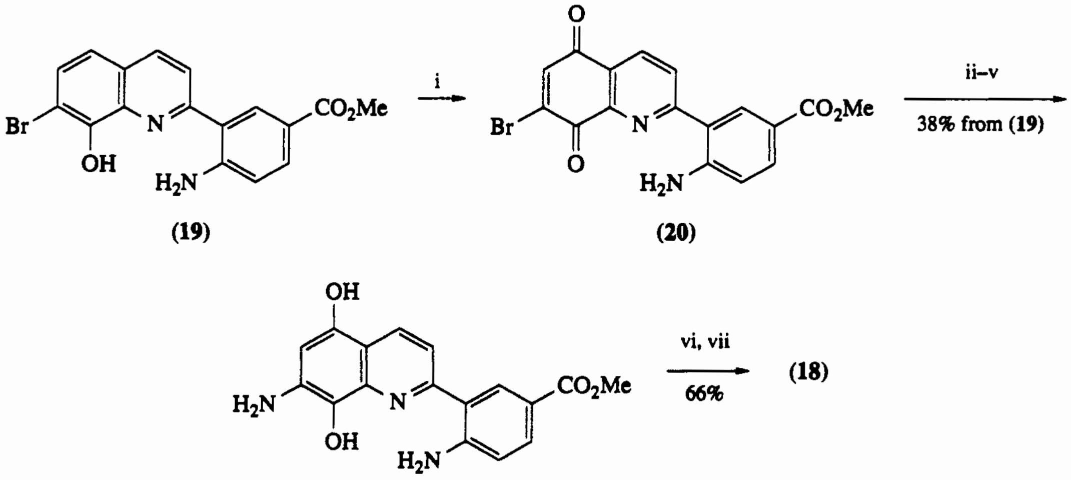

(19)
(20)
(21)
(18)
i
ii–v
38% from (19)
vi, vii
66%

i, Fremy's salt, $Bu^n{}_4NHSO_4$; ii, $NaN_3$; iii, $Ph_3P$; iv, $H^+$; v, $Na_2S_2O_4$; vi, LiOH; vii, air

**Scheme 5**

biotics. In Boger's synthesis, the phenol (**19**) was oxidized using the Kende conditions to give the quinone (**20**), which upon further manipulation afforded the hydroquinone (**21**). This upon exposure to lithium hydroxide, followed by air gave the desired quinone (**18**) (Scheme 5). Interestingly in the synthesis of a related quinone (**25**) by the Boger group, the phenol (**22**) gave only poor erratic yields of the quinone (**24**) using the above oxidation procedure. Cerium(IV) ammonium nitrate and ammonium nitrate/acetic anhydride/trifluoroacetic anhydride were equally unsuccessful. A satisfactory synthesis of the quinone (**24**) was accomplished by a three-step procedure involving nitration, reduction to the amine (**23**) and finally oxidation of the *p*-aminophenol to the quinone (**24**) using manganese dioxide.

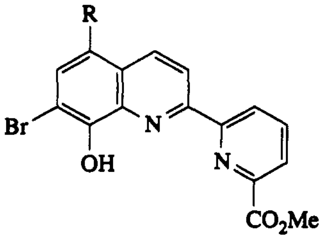

(**22**) R = H
(**23**) R = $NH_2$

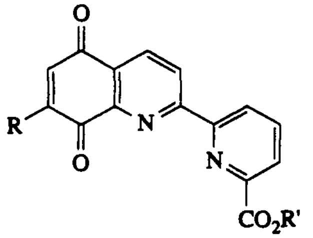

(**24**) R = Br, R' = Me
(**25**) R = $NH_2$, R' = H

### 2.11.2.5 Methoxatin

The insolubility of their substrate in the Fremy's salt reaction medium was a problem encountered by Rees and coworkers in their synthesis of the bacterial coenzyme methoxatin (**31**).[18] The methoxatin skeleton was rapidly assembled from the substituted benzaldehyde (**26**), using the nitrene insertion reaction to give the indole nucleus. Introduction of the *o*-quinone moiety, however, proved particularly troublesome. The methoxypyrroloquinoline (**27**) could not be oxidized directly to the quinone (**30**) and, although the oxidation could be effected indirectly by nitration, reduction and finally oxidation with manganese dioxide, the overall yield (29%) was disappointing. The problem was overcome by engaging an organic-soluble nitroxide equivalent of Fremy's salt, namely, benzoyl *t*-butyl nitroxide. Hydrogenolysis of the 4-benzyloxypyrroloquinoline (**28**) gave the phenol (**29**) in 89% yield. Attempted oxidation of this phenol with Fremy's salt was unsatisfactory, but using benzoyl *t*-butyl nitroxide in dichloromethane/methanol the required quinone (**30**) was prepared in excellent yield. Conversion to methoxatin (**31**) then followed a literature procedure (Scheme 6).

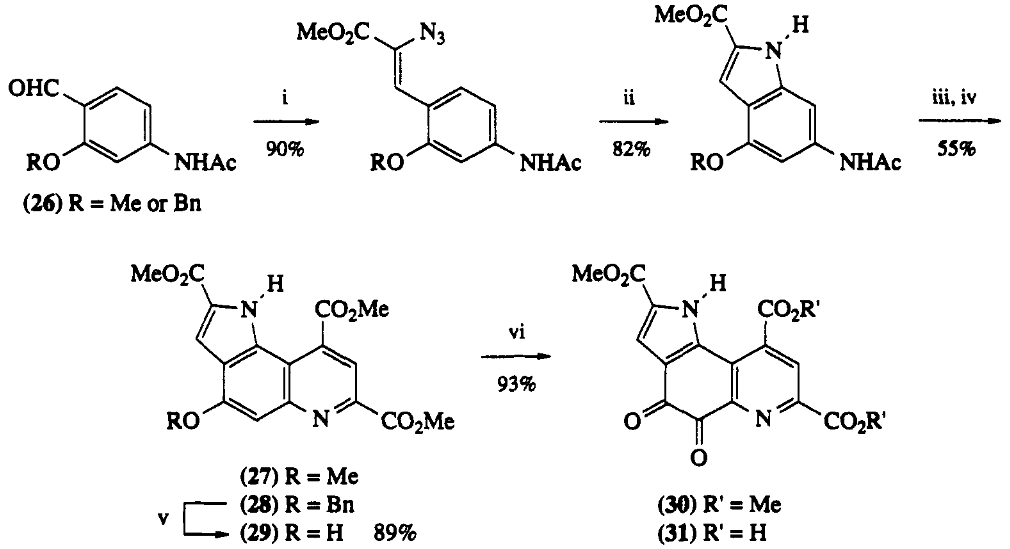

(**26**) R = Me or Bn

(**27**) R = Me
(**28**) R = Bn
(**29**) R = H 89%

(**30**) R' = Me
(**31**) R' = H

i, $MeO_2CCH_2N_3$, NaOMe, MeOH; ii, xylene, reflux; iii, $H^+$; iv, $MeO_2CCOCH{=}CHCO_2Me$ then $H^+$;
v, $H_2$, Pd–C; vi, $Bu^t(COPh)NO\bullet$; yields quoted for R = Bn

**Scheme 6**

These 'Fremy's salt variants' have so far found limited use in synthesis, but it is anticipated that they will become more prominent in the years to come.

## 2.11.3 CERIUM(IV) AMMONIUM NITRATE (CAN)

Cerium(IV) ammonium nitrate has been used increasingly during the last decade in the synthesis of quinones,[19–24] particularly as a means of effecting oxidative demethylation of methoxyarenes.

### 2.11.3.1 Quinone Derivatives of 2′-Deoxyuridine

The inhibition of thymidylate synthase is recognized as a viable approach to the control of cancer and DNA viral infections. Mertes and coworkers[25] proposed 5-quinone derivatives of 2′-deoxyuridine 5′-phosphate as potential irreversible inhibitors of this enzyme and prepared the quinones (**32a**) by oxidative demethylation of the appropriate dimethoxyarenes using CAN. Interestingly, the quinones (**32b**) were also prepared from the corresponding dimethoxyarenes but using silver(II) oxide and nitric acid in aqueous dioxane to effect this transformation. Cerium(IV) ammonium nitrate could not be used, due to precipitation.

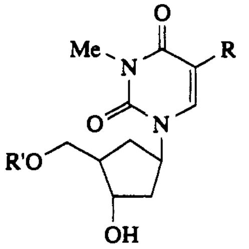

(**32a**) R′ = H
(**32b**) R′ = $PO_3H_2$

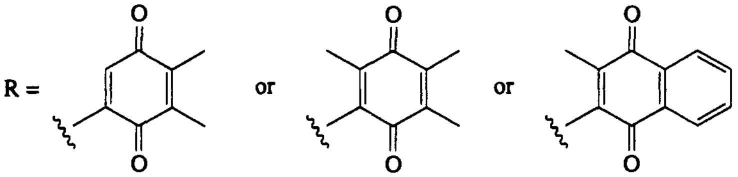

### 2.11.3.2 Pleurotin

Hart and Huang[26] employed CAN in the penultimate step in their synthesis of pleurotin (**38**), an antitumor antibiotic. Treatment of the β-keto ester (**33**) with the organometallic reagent derived from 2,5-dimethoxybenzylmagnesium chloride and cerium trichloride gave the alcohol (**34**; 92% yield), which was then transformed into the pentacycle (**35**). A carboxy group was then attached at C-8 and the dimethoxyarene (**36**) oxidized with CAN to give dihydropleurotin acid (**37**). The final step of the synthesis was accomplished using manganese dioxide and was based upon the known behavior of tetraalkyl-*p*-benzoquinones in the presence of nucleophiles. Although this synthesis was rather long, it represented the first total synthesis of the structurally complex pleurotin (Scheme 7).

### 2.11.3.3 Saframycin B

In the total synthesis of saframycin B (**40**) recently reported by Kubo *et al.*,[27] the final step, in which the polymethoxyarene (**39**) was converted to saframycin B, provided quite a challenge in itself and emphasizes how a seemingly straightforward transformation can prove difficult when incorporated into a natural product synthesis. The direct oxidative demethylation of the arene (**39**) could only be achieved using 10 M nitric acid, and this gave an unacceptable 1.5% yield of saframycin B. Other commonly employed reagents gave only starting material. Partial demethylation with boron tribromide followed by oxidation with CAN gave saframycin B (**40**) and the monoquinone (**41**) in 17% and 45% yields

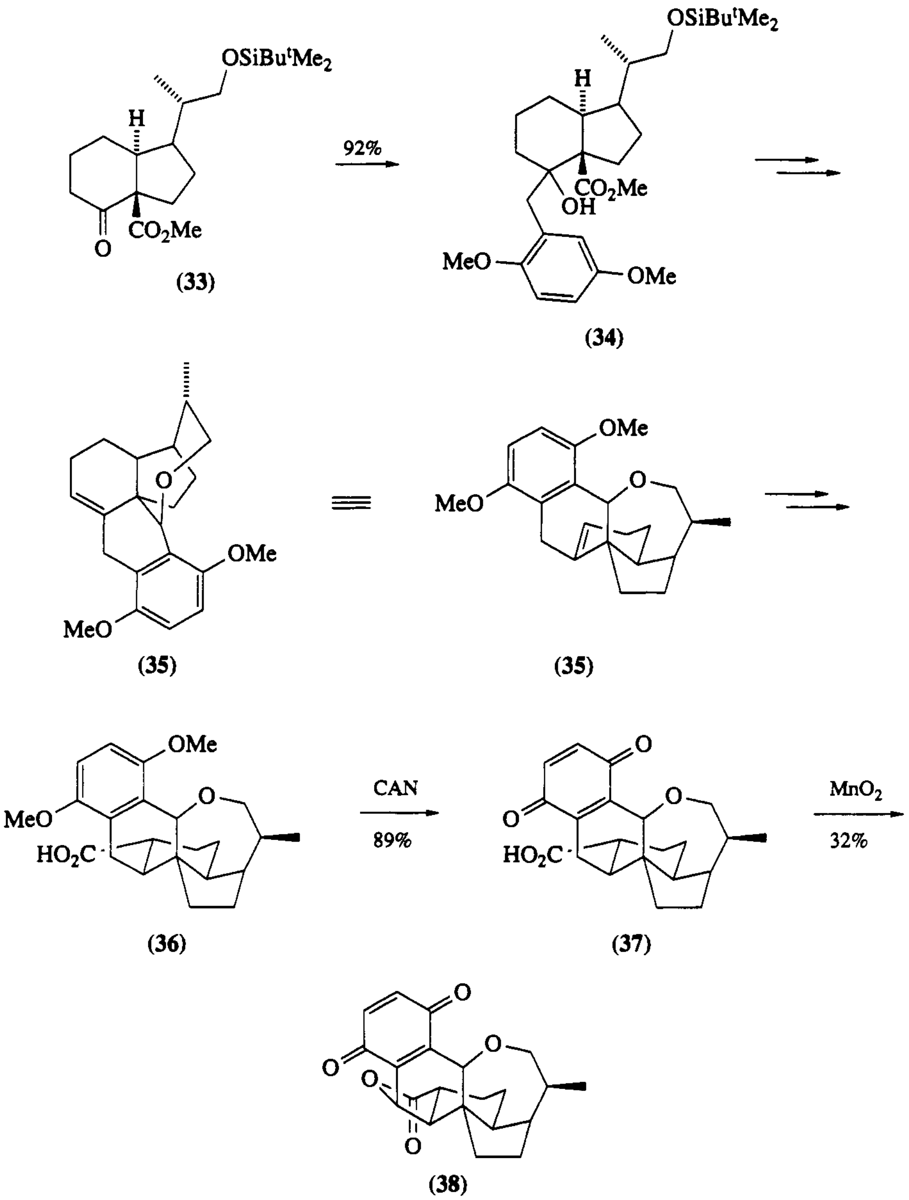
OSiBu'Me2
H
O
CO2Me
(33)
92%
OSiBu'Me2
H
CO2Me
OH
MeO
OMe
(34)
O
OMe
MeO
(35)
≡
OMe
MeO
O
(35)
OMe
MeO
HO2C
O
(36)
CAN
89%
O
O
HO2C
O
(37)
MnO2
32%
O
O
O
O
O
(38)

Scheme 7

respectively (Scheme 8). Finally, partial demethylation followed by oxidation with 10 M nitric acid gave saframycin B (**40**) in an acceptable 41% yield (Scheme 9).

## 2.11.3.4 Demethoxydaunomycinone

One final interesting application of CAN which exemplifies one of the many possible reactions of quinones comes from Hassall and coworkers[28] in their synthesis of 4-demethoxydaunomycinone (**47**). Thus, oxidation of the boronate (**42**) with CAN gave the crude quinone (**43**) which was reacted with *trans*-1,2-bis(acetoxy)-1,2-dihydrobenzocyclobutene (**44**) to give the tetracyclic quinone (**45**) in an impressive 79% overall yield. Deacetalization and reductive acetylation to the naphthacene (**46**), followed by oxidation with anhydrous chromium trioxide and deprotection with boron trichloride afforded the target compound (**47**; Scheme 10).

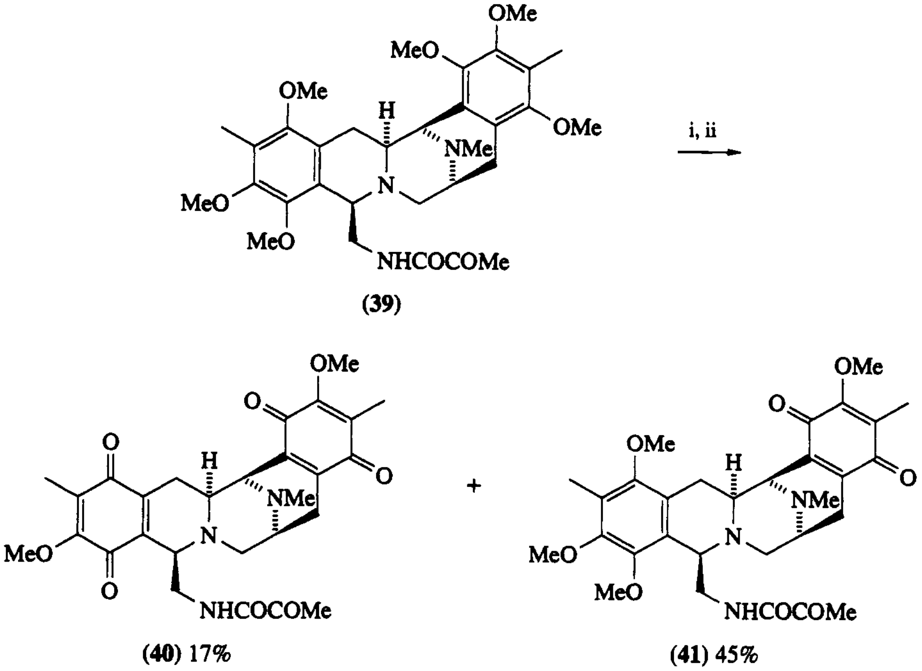

i, $BBr_3$, $CH_2Cl_2$, −78 to 0 °C; ii, CAN, MeCN, $H_2O$, 0 °C

Scheme 8

$$(39)\ \xrightarrow[\text{ii, 10 M HNO}_3\text{, r.t.}]{\text{i, BBr}_3\text{, CH}_2\text{Cl}_2\text{, −78 to 0 °C}}\ (40)$$

41%

Scheme 9

## 2.11.4 LEAD TETRAACETATE (LTA)

Lead tetraacetate is a versatile reagent which has many applications in organic synthesis, not least in the synthesis of quinones.[29–32]

### 2.11.4.1 Demethoxydaunomycinone

Lead tetraacetate was employed by Stoodley and coworkers[33] for an oxidative isomerization in their synthesis of 4-demethoxydaunomycinone (**47**). The diene (**48**) reacted with the oxirane dienophile (**49**) *via* the least hindered *endo* transition state to give the cycloadduct (**50**) in 86% yield. Hydrolysis of the silyl enol ether followed by reduction of the oxirane and introduction of the acetylene moiety gave the compound (**51**), which was oxidatively isomerized with LTA in acetic acid to give the quinone (**52**). All that remained now to complete the synthesis was conversion of the acetylene to a methyl ketone and dealkylation of the ether. The last two steps were accomplished in an overall yield of 38%, the low yield attributable to problems in formation of the hydroxy group from the ether (Scheme 11). Bulman-Page and Ley[34] employed LTA for a similar transformation in their synthesis of demethoxydaunomycinone and related anthracyclinones.

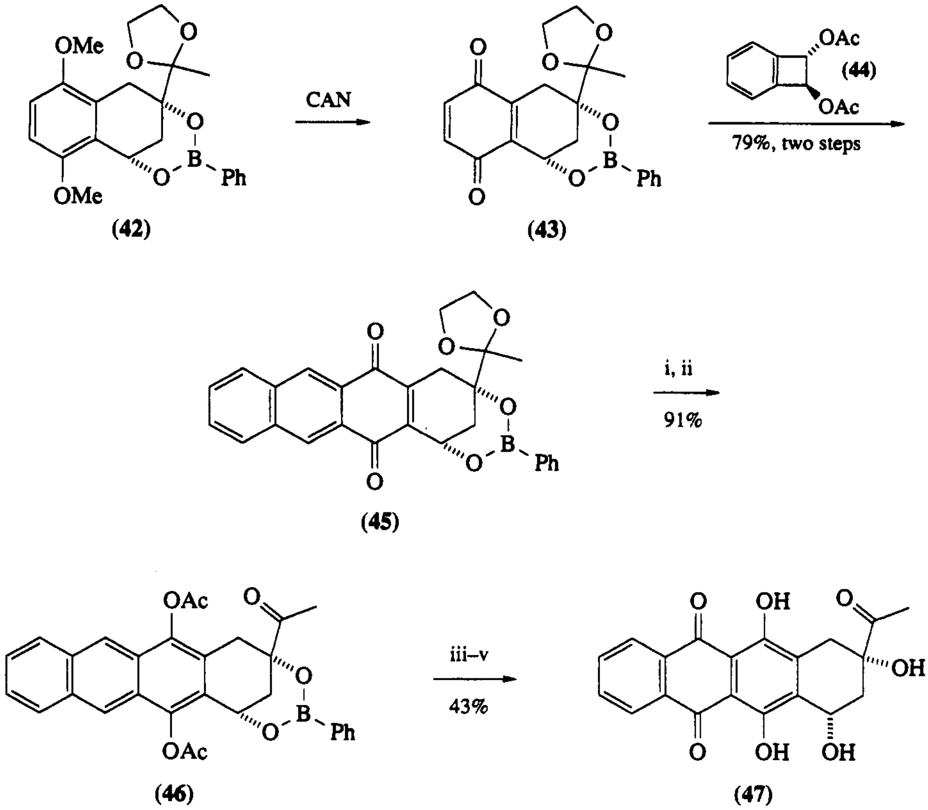
(42)
CAN
(43)
(44)
79%, two steps
(45)
i, ii
91%
(46)
iii–v
43%
(47)

i, $H^+$; ii, $H_2$, Pd–C, $Ac_2O$, pyridine; iii, $CrO_3$; iv, $BCl_3$; v, 2-methylpentane-2,4-diol

**Scheme 10**

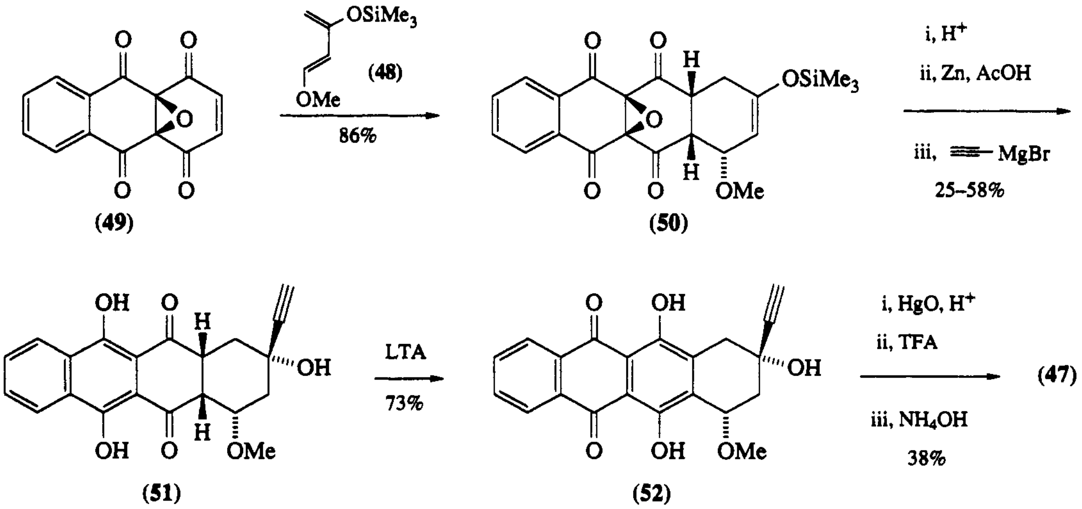
(49)
(48)
86%
(50)
i, H+
ii, Zn, AcOH
iii, ≡—MgBr
25–58%
(51)
LTA
73%
(52)
i, HgO, H+
ii, TFA
iii, NH4OH
38%
(47)

**Scheme 11**

### 2.11.4.2 Towards Mitomycin C

Another use of LTA was shown by Yoshida and coworkers[35] in studies directed towards the mitomycin family of antibiotics, *e.g.* mitomycin C (**58**). The aniline (**53**) was treated with LTA in dichloromethane to give the *o*-quinoneimide (**54**), which upon hydrolysis and then hydrogenation afforded the catechol (**55**) in reasonable overall yield. Further manipulation gave the phenol (**56**) which was oxidized using the cobalt(II) complex salcomine to give the *p*-quinone (**57**), a potential intermediate for mitomycin synthesis (Scheme 12).

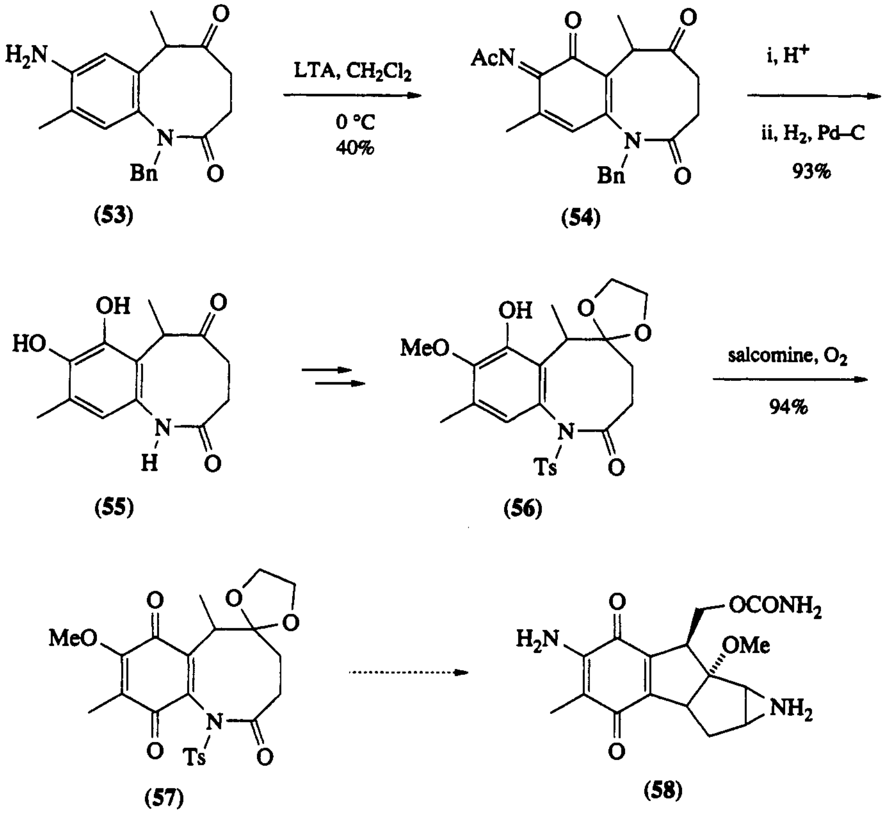

H$_2$N
O
N
Bn
O
(53)
LTA, CH$_2$Cl$_2$
0 °C
40%
AcN
O
O
N
Bn
O
(54)
i, H$^+$
ii, H$_2$, Pd–C
93%
OH
HO
O
N
H
O
(55)
OH
MeO
O
O
N
Ts
O
(56)
salcomine, O$_2$
94%
O
MeO
O
O
N
O
Ts
O
(57)
O
H$_2$N
OCONH$_2$
OMe
NH$_2$
O
(58)

Scheme 12

## 2.11.5 OTHER REAGENTS

### 2.11.5.1 Metacyclophanes

Thallium trifluoroacetate has not enjoyed widespread use as a reagent for quinone synthesis, possibly because it is still a relatively new reagent but more probably because of its toxicity. One example of its use lies in the synthesis of metacyclophanes and related compounds as reported by Tashiro *et al.*[36] Thus the *t*-butylphenol (**59**) gave the bisquinone (**61**), while the phenol (**60**) afforded the monoquinone (**62**). An alternative and more practical synthesis of the bisquinone (**61**) for large scale work involved dealkylation to afford the bisphenol (**63**) which was then treated with sodium nitrite to give the bisoxime (**64**). Hydrolysis of the bisoxime did not give the quinone (**61**), but it could be obtained by zinc/acetic acid reduction of the bisoxime followed by oxidation with nitric acid (Scheme 13).

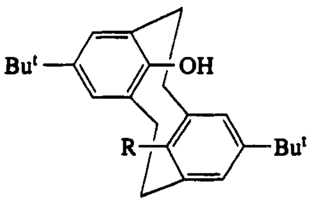

(**59**) R = OH
(**60**) R = OMe

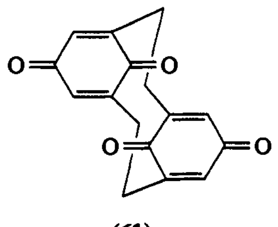

(**61**)

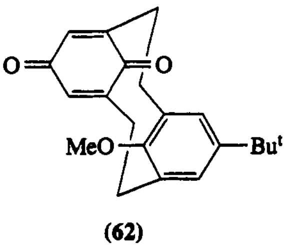

(**62**)

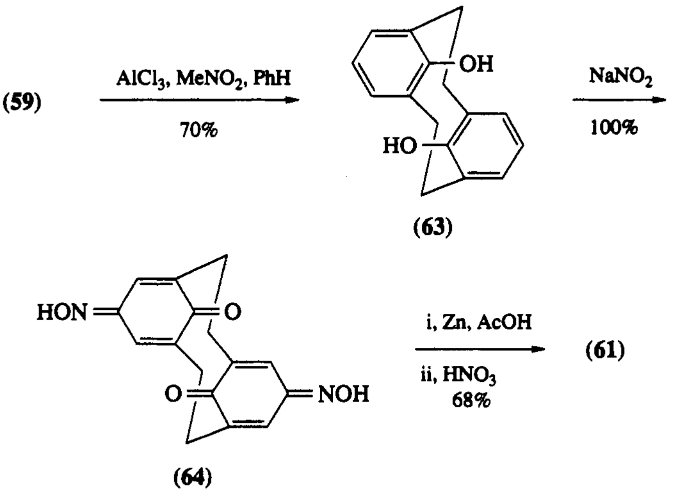
(59)
AlCl₃, MeNO₂, PhH
70%
OH
HO
(63)
NaNO₂
100%
HON
O
O
NOH
(64)
i, Zn, AcOH
ii, HNO₃
68%
(61)

Scheme 13

### 2.11.5.2 Diazaquinomycin A

The reader should always bear in mind that spontaneous oxidation in air can occur if a hydroquinone is sufficiently activated towards oxidation.[37] An example of this is exemplified by Kelly *et al.*[38] in a short synthesis of diazaquinomycin A (**68**). The synthesis incorporates the first reported use of a double Knorr cyclization. The key intermediate (**66**) was prepared in just two steps from the MOM-protected hydroquinone (**65**). Cyclization of the compound (**66**) then gave diazaquinomycin B (**67**), which either under the reaction conditions or by careful isolation prior to simply stirring the solution in an open flask afforded the antibiotic diazaquinomycin A (**68**), thereby confirming the structure of the only recorded example of the tricyclic 1,8-diazaanthraquinone ring system (Scheme 14).

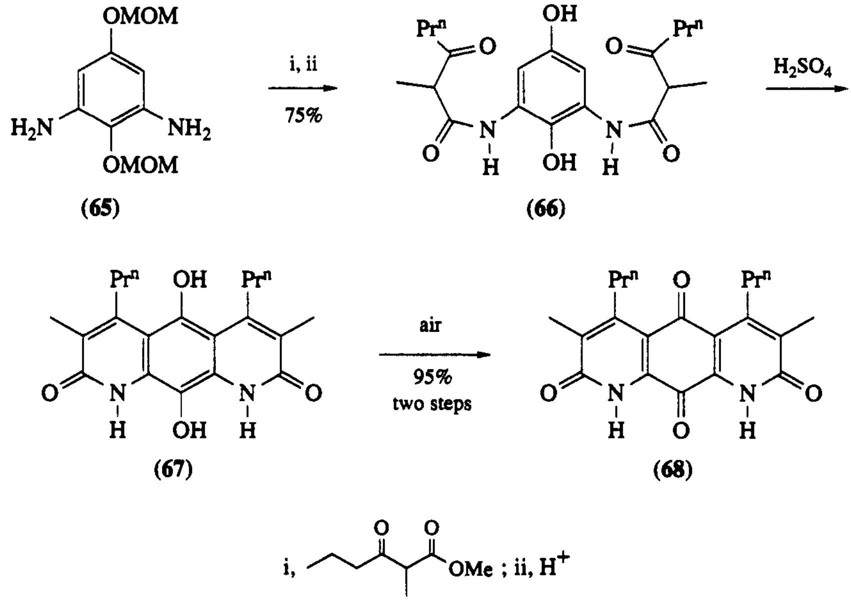
OMOM
H₂N
NH₂
OMOM
(65)
i, ii
75%
Prⁿ
O
OH
Prⁿ
O
N
H
OH
H
O
(66)
H₂SO₄
Prⁿ
OH
Prⁿ
O
N
H
OH
N
H
O
(67)
air
95%
two steps
Prⁿ
O
Prⁿ
O
N
H
O
N
H
O
(68)
i,
O
O
OMe ; ii, H⁺

Scheme 14

### 2.11.5.3 Miscellaneous

There are numerous other examples of the synthesis of quinones employing reagents such as nitric acid,[27,36] manganese dioxide,[17,18] salcomine/$O_2$,[24,35,39,40] silver oxide,[25,41–43] chromium oxidants,[16,28,44–47] benzene selenic anhydride[10,30,48–50] and DDQ,[51,52] some of which have already been referred to in the text.

No doubt, the next decade will see other reagents brought forward for the oxidative synthesis of quinones. The practicability of these and more recently introduced reagents will be shown by their efficacy in the synthesis of complex molecules.

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# 3.1

# Addition Reactions with Formation of Carbon–Oxygen Bonds: (i) General Methods of Epoxidation

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### 3.1.1 INTRODUCTION

Oxiranes (epoxides) are compounds which contain a saturated three-membered ring having one oxygen atom and two carbon atoms.[1] They are widely distributed in nature and are of industrial, mechanistic and biochemical interest.[1] Squalene 2,3-oxide is the biogenetic precursor of sterols. Leukotriene A (LTA) is the biogenetic precursor of the leukotrienes LTC, LTD and LTE which are important natural mediators of allergic asthma.[2] The ultimate carcinogenic metabolites of polycyclic aromatic hydrocarbons are the tetrahydrodiol epoxides.[3] An allene oxide is regarded as the precursor of preclavunone A.[4]

In their reports on oxiranes Lewars[1] and Rao *et al.*[2] have cited many of the earlier reviews. Recent work on oxiranes has been reviewed by Harvey,[3] Sharpless and Verhoeven,[5] Bartok and Lang,[6] Plesnicar,[7] Mimoun[8a] and Jorgensen.[8b] The various nomenclature systems are illustrated in the naming of (**1**) and (**2**). Cyclohexene oxide, 1,2-epoxycyclohexane and 7-oxabicyclo[4.1.0]heptane are the names used for (**1**) while (**2**) is 2,2-dimethyloxirane.

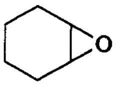

(**1**)

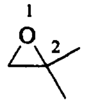

(**2**)

The ease of preparation of epoxides and their facile ring opening have made them important intermediates in organic synthesis for the past several decades. In the present decade the main objective in organic synthesis is to develop reactions which are enantio-, diastereo-, regio- and chemo-selective. With the discovery of enantioselective epoxidation of prochiral acyclic allyl alcohols by Katsuki and Sharpless[8a] and observation of high and predictable diastereoselectivity during (i) the epoxidation of several types of acyclic unsaturated chiral alcohols with MCPBA or TBHP/VO(acac)$_2$, and (ii) the preparation of epoxy alcohols *via* halolactonization, coupled with elegant routes for highly regioselective intramolecular ring opening of epoxides,[9] it may be noted that epoxides are versatile intermediates for organic synthesis in the present decade also. A number of complex compounds such as monensin,[10] maytansine[11] and prostaglandins[12] have been synthesized using epoxides as intermediates. Some of these developments are reviewed in this chapter, and enantioselective methods of epoxidation are presented in Chapter 3.2, this volume. There are also other chapters and sections which deal with the synthesis and reactions of epoxides.

## 3.1.2 EPOXIDATIONS WITH ORGANIC PEROXY ACIDS

### 3.1.2.1 General Survey of Reactivity

A large number of organic peroxycarboxylic acids having the general formula (**3**) readily epoxidize alkenes (equation 1).[7] The stereochemistry of the alkene is retained in the epoxide. There are a few apparent exceptions which will be presented later (see equation 38). The reaction is believed to take place *via* the transition state (**5**)[13] and involves the nucleophilic attack on the O—O bond by the π-electrons of the double bond.[5] The reaction rate increases when the groups R$^1$, R$^2$, R$^3$ and R$^4$, in (**4**), are electron releasing and also when R, in (**3**), is an electron-withdrawing group. In the case of polyunsaturated hydrocarbons, if the double bonds differ in their degree of substitution the regioselectivity can be easily predicted; the more substituted double bond is more reactive. The peroxy acid has a relatively low steric requirement. For example, epoxidation is the only addition reaction which has been carried out on the sterically hindered alkene (**6**).[14]

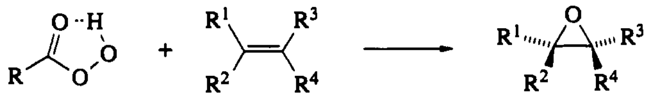

(**3**) (**4**) (1)

Epoxidation of an alkene containing one or more chiral centers can furnish two diastereoisomeric epoxides, depending on the face from which the reagent approaches the π-bond (equation 2). If the two faces of the π-bond are unequally shielded, and if polar and stereoelectronic factors are also involved, the two expected diastereomers will not be formed to the same extent, thus resulting in diastereoselectivity. An inspection of the molecular model may often reveal the face of the alkene which is more shielded, especially when the alkene has a rigid structure.

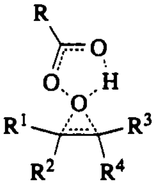

**(5)**

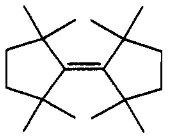

**(6)** 59%

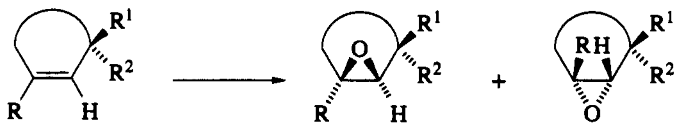

(2)

Data on diastereoselectivity are presented in two ways. When experimental conditions are different from the examples given earlier then an equation is given in full. When experimental conditions employed are similar to those used for earlier examples then two figures are given in brackets below the chemical structure, and after the structure number. The first figure gives the combined yield of both the diastereomers, the second figure gives the percentage of the major diastereomer. A solid arrow indicates that the major isomer was formed by attack on the β-face; a dashed arrow indicates that the preferred direction of attack is on the α-face, as shown in structures (**33**) and (**34**).

Since peroxides and peroxy acids are potentially explosive care is required while carrying out reactions and also during work-up of the reaction mixture.

### 3.1.2.2 Epoxidations with *m*-Chloroperbenzoic Acid (MCPBA)

#### *3.1.2.2.1 General comments*

MCPBA is a relatively stable solid which is soluble in many common organic solvents. It is the reagent of choice for laboratory scale experiments and is commercially available. Though reactions are carried out normally at 0–25 °C in $CH_2Cl_2$ or $CHCl_3$, one can use elevated temperatures (95 °C, ethylene dichloride) in conjunction with radical inhibitors if the alkene has low reactivity. The experimental conditions for the reaction and subsequent work-up depend on the stability of the epoxides. In the case of acid-sensitive epoxides the usual practice is to control the pH using $NaHCO_3$, aqueous $Na_2CO_3$, $Na_2HPO_4$ or KF.[15]

#### *3.1.2.2.2 MCPBA epoxidations of acyclic alkenes lacking directing groups*

The reactivity of an alkene depends on the degree of substitution; the least reactive are the monosubstituted (terminal) alkenes. Monosubstituted alkenes can be epoxidized by MCPBA (equation 3).[16] The diene (**7**) has been epoxidized regioselectively at the more electron-rich disubstituted double bond.[17] In the triene (**8**) all the double bonds are trialkylsubstituted; however the C(2)—C(3) double bond is strongly deactivated due to conjugation with electron-withdrawing $CO_2Me$. The C(10)—C(11) double bond is deactivated, but to a lesser extent due to the location of fluorine. Consequently the predicted reactivities are C(6)—C(7) > C(10)—C(11) > C(2)—C(3). Epoxidation of the triene (**8**) is highly regioselective at −20 °C (equation 4);[18] 30% of the starting material is recovered. However, the regioselectivity is very poor if epoxidation is carried out at 45 °C, when a 1:1 mixture of epoxides (**9**) and (**10**) is obtained.

The preparation of allylic epoxides from conjugated dienes requires careful control of pH, since allylic epoxides undergo ring opening by nucleophiles at acidic pH. The allylic epoxide (**12**) has been prepared from the diene (**11**; equation 5);[19] however, the ring opening of (**12**) cannot be totally suppressed.

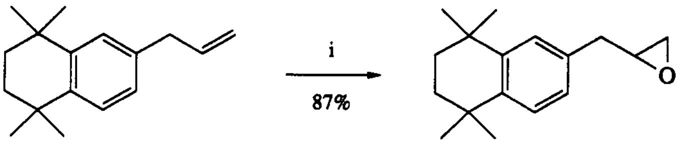

i, MCPBA, $CH_2Cl_2$, 20 °C, 8 h

(3)

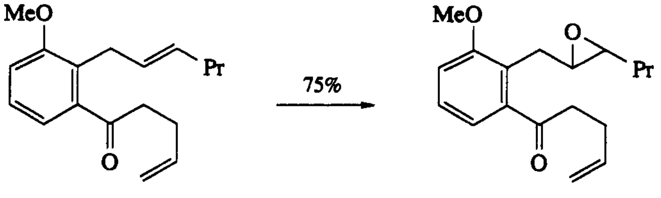
MeO
Pr
O
75%
MeO
O
Pr
O

(7)

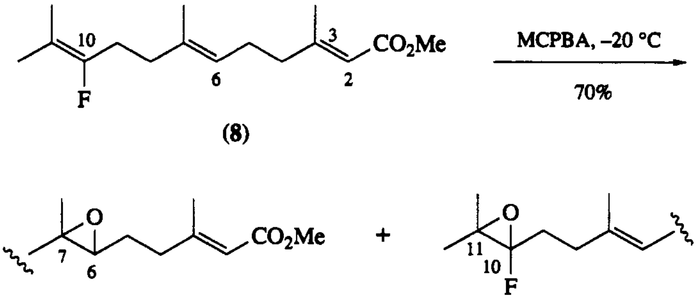
10
F
6
3
2
CO2Me
MCPBA, -20 °C
70%
O
7
6
CO2Me
+
O
11
10
F

(8)

(9) 100%

(10) 0%

(4)

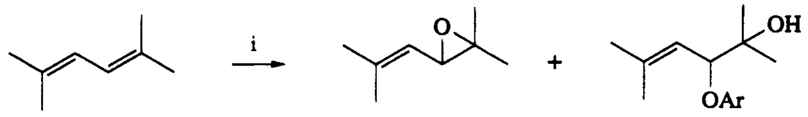

(11)

(12) 42%

(13) 28%

i, MCPBA, aq. $NaHCO_3$, $CH_2Cl_2$

Ar = 3-chlorobenzoyl

(5)

Epoxidation of the allylsilane (**14**) is diastereospecific (equation 6).[20] The favored conformation of (**14**) is (**14a**); the peroxy acid approaches the double bond from the face *anti* to the bulky silyl group. The epoxides (**16**) and (**17**) obtained from the acetonide (**15**; equation 7) can be readily separated in gram quantities using standard chromatographic techniques.[21] The presence of the conformationally rigid acetonide moiety in the epoxides (**16**) and (**17**) facilitates their separation; the corresponding epoxy diols cannot be separated by chromatography. The racemic epoxide (**19**), an intermediate for the synthesis of maytansine has been synthesized from (**18**; equation 8).[22]

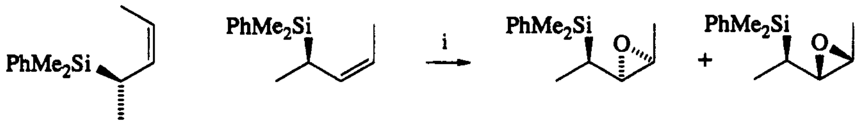
PhMe2Si
PhMe2Si
i
PhMe2Si
O
+
PhMe2Si
O

(14a)

(14)

95%

5%

i, MCPBA, $Na_2HPO_4$, $CH_2Cl_2$, 0 °C, 2 h

(6)

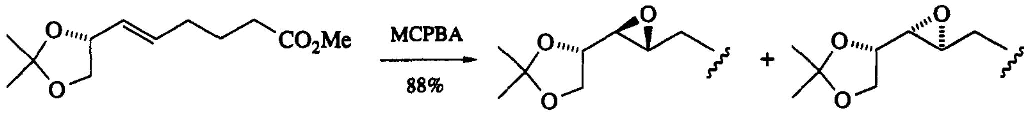

**(15)** **(16)** 33% **(17)** 67% (7)

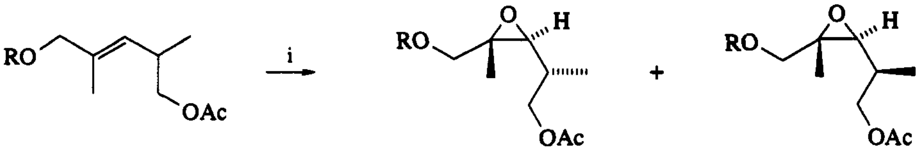

**(18)** R = $SiMe_2Bu^t$ **(19)** 53% **(20)** 47% (8)

i, MCPBA, $CH_2Cl_2$, 0 °C

### *3.1.2.2.3 MCPBA epoxidations of cyclic alkenes, methylenecycloalkanes and unsaturated macrocyclic lactones*

The conformational preferences and stereoselective reactions of a number of macrocyclic systems have been studied. The stereochemical results have been explained on the basis of the model of local conformer control. The epoxidation of a macrocyclic alkene containing the substitution pattern (**21**) provides a single epoxide having the stereochemistry (**22**).[23] A macrocycle containing a 1,5-diene system adopts the local conformation (**23**) that is free of torsional strain; epoxidation of (**23**) from the less hindered side furnishes the *syn*-diepoxide (**24**).[23] The MCPBA epoxidations of the unsaturated macrocyclic lactones (**25**) and (**26**) are stereoselective (equations 9 and 10).[23,24] In the epoxidation of (**26**) six new chiral centres are introduced; the reaction product is a 20:1:1 mixture of triepoxides. The triepoxide (**27**) is closely related to the C(9)–C(23) segment of monensin B.

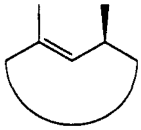

**(21)**

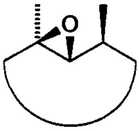

**(22)**

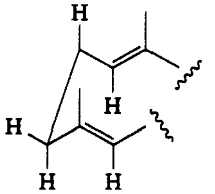

**(23)**

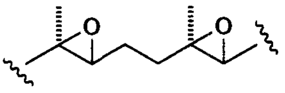

**(24)**

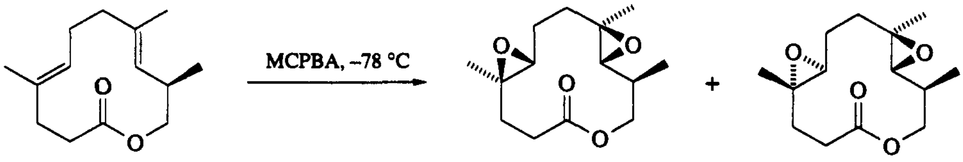

**(25)** 90% 10% (9)

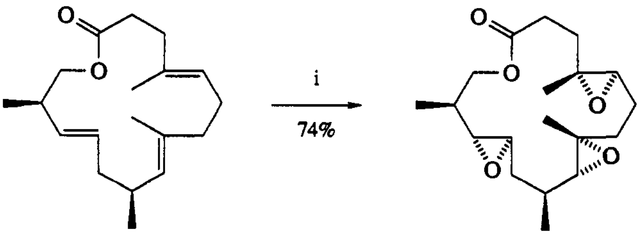

(10)

**(26)** **(27)**

i, MCPBA, $NaHCO_3$, $CH_2Cl_2$

In the peroxy acid epoxidation of cyclohexenes a substituent is more effective in blocking the approach of the reagent when it is pseudoaxial allylic or axial homoallylic than when it is pseudoequatorial allylic or equatorial homoallylic.[13] MCPBA epoxidation of tetramethyllimonene (**28**) is regio- and stereo-selective (equation 11);[25] approach of the reagent from the β-face is blocked by the pseudoaxial methyl at C-3 and the axial methyl at C-5. In contrast, epoxidation of limonene (**28**; R = H) furnishes an approximately 50:50 mixture of epoxides (**29a**; R = H) and (**29b**; R = H); the reaction is not stereoselective since there are no axially oriented bulky groups to selectively shield one face. The sensitive allylic epoxide (**31**) has been prepared stereoselectively employing a biphasic medium (equation 12);[26] the reaction proceeds from the α-face since the β-face is blocked by axial methyl at C-10. The epoxidation of (**32**) is stereoselective (equation 13);[27] (**32**) does not prefer the conformation with $CO_2Me$ equatorial since this leads to steric interference between $CO_2Me$ and hydrogen at C-11 ($A^{1,3}$ strain). In the preferred conformation, (**32**) has the $CO_2Me$ axial which leads to blocking of the β-face. MCPBA epoxidation (ethylene dichloride, 90 °C, 4 h) of (**33**) takes place selectively from the β-face since the α-face is blocked by the axial chlorovinyl group.[28] The more electron-rich trisubstituted double bond is selectively attacked. In the alkene (**34**), the β-methyl at C-10 being axial is more effective in shielding the double bond than the α-methyl at C-4 which is pseudoequatorial.[29] The diastereoselectivities in the epoxidation of the dienes (**35**), (**36**) and (**37**) have been studied (equations 14–16).[30] The selectivity depends on the nature of the groups at C-10 and also on the functional groups present on the double bond at C-8 and C-9. Epoxidation of vitamin $D_3$ (**38**) is regio- as well as stereo-selective (equation 17).[31] Though both C(5)—C(6) and C(7)—C(8) are trisubstituted double bonds reaction takes place selectively at C(7)—C(8), since only this route leads to the thermodynamically more stable conjugated diene derivative; attack is selectively from the α-face since the β-face is shielded by the axial methyl at C-13. Epoxidation of (**39a**) is stereoselective (equation 18).[32] The selectivity is higher in (**39a**) than in the reaction of (**39b**; R = MOM) due to stereoelectronic repulsive effects involving acetate and peroxy acid in the transition state leading to (**41**).

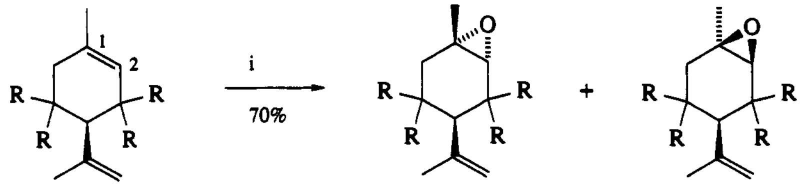

(11)

(**28**) R = Me (**29a**) 93% (**29b**) 7%

i, MCPBA, $CH_2Cl_2$, 5% aq. $NaHCO_3$, 24 h, r.t.

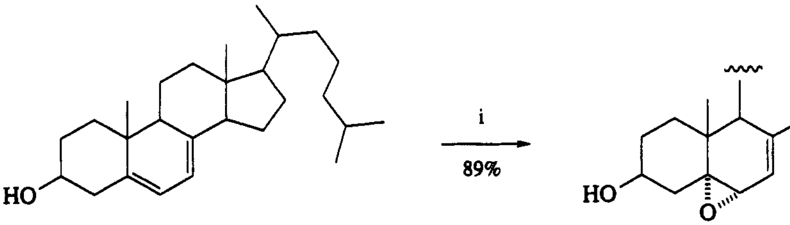

(12)

(**30**) (**31**)

i, MCPBA, aq. $Na_2CO_3$

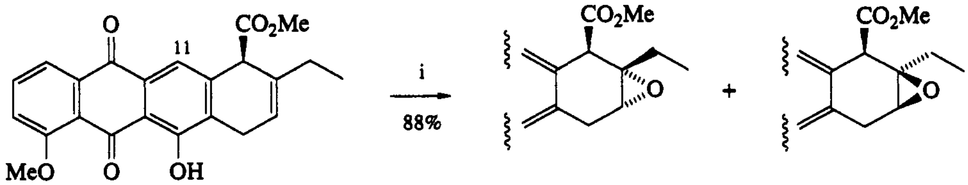

(13)

(**32**) 98% 2%

i, MCPBA, $CH_2Cl_2$, 17 h, r.t.

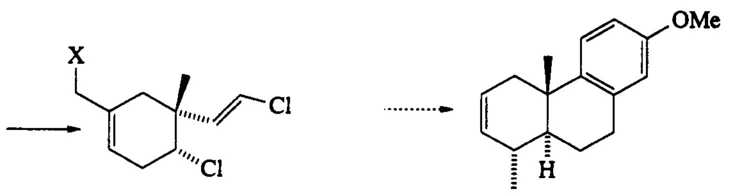

(33) (83, ≈100) X = Br

(34) (84)

—► indicates attack on β-face forms major isomer ·····► indicates attack on α-face

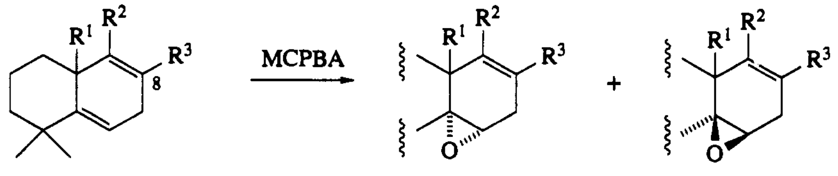

| | | *Yield* | | |
|---|---|---|---|---|
| (35) | $R^1 = Me, R^2 = H, R^3 = CO_2Et$ | 90% | 95:5 | (14) |
| (36) | $R^1 = H, R^2 = H, R^3 = CO_2Et$ | 77% | 33:67 | (15) |
| (37) | $R^1 = H, R^2 = CO_2Et, R^3 = H$ | 82% | 10:90 | (16) |

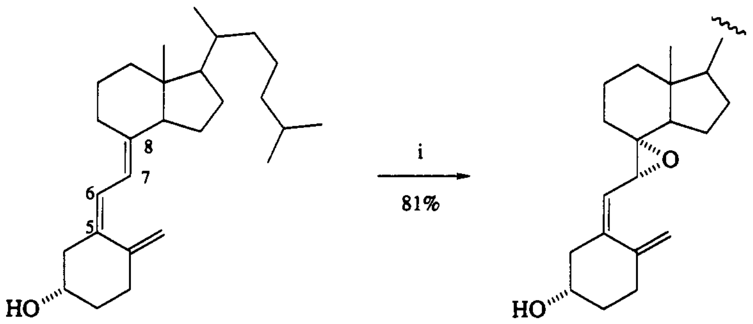

(17)

(38)

i, MCPBA, $CH_2Cl_2$ −70 °C to 0 °C

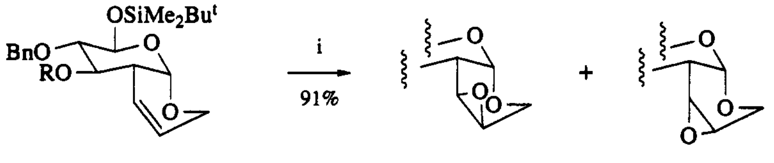

(18)

R = Ac (39a) (40) 95% (41) 5%

i, MCPBA, $CHCl_3$, $CCl_4$, 32 h, 25 °C

Folded molecules are epoxidized selectively from the less hindered convex side. This is illustrated by the reactions of (**42**; equation 19),[33] (**43**) and (**44**).[34,35] The electron-rich trisubstituted double bond of (**42**) is selectively attacked. The peroxy acid used for the epoxidation of (**44**) is peracetic acid. The compound (**45**) is attacked selectively from the more hindered concave side.[36]

Unhindered methylenecyclohexane derivatives undergo preferential axial epoxidation.[13] During the epoxidation of alkenes (**46**) and (**47**) the reagent approaches selectively from the axial side.[37,38] Probably in the epoxidation of (**47**) the selectivity is mainly due to the shielding of the α-face by the axial $CH_2OAc$ at C-5. The percentage of axial attack during the epoxidation of several 3-substituted methylenecyclohexanes (**48**) has been studied.[39] There is an increase in the proportion of axial attack with an increase in electronegativity of the remote 3-equatorial substituent; when R = $p$-$CF_3C_6H_4$ in (**48**), axial

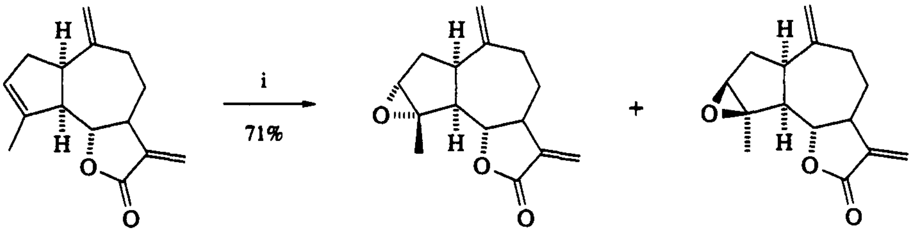

(19)

(42) 97% 3%

i, MCPBA, 3 h, 5 °C

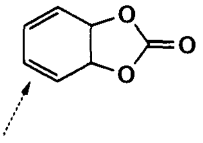

(43) (95, 82)

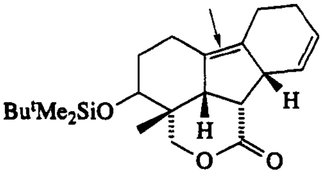

(44) (72, -)

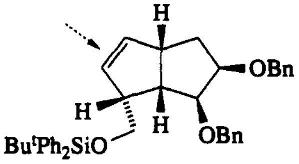

(45) (-, 75)

attack is 75%. In the alkene (**49**) the β-oriented siloxy group does not block the β-face since the C—O bond is in the plane of the π-bond; the epoxidation of (**49**) is not stereoselective.[40] The [10.10] betweenanene (**50a**) cannot be epoxidized since both faces of the π-bond are effectively blocked.[41a] Epoxidation of (**50b**) is highly stereoselective.[41b] The β-face of (**50b**) is sterically more shielded than the α-face, since the β-axial hydrogen at C-3 is closer to the π-system than the α-axial hydrogen at C-2a.

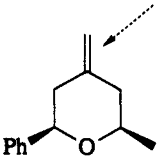

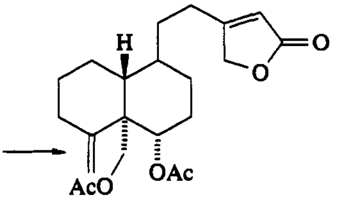

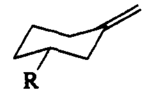

(46) (100, 86) (47) (-, 100) (48)

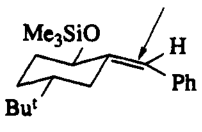

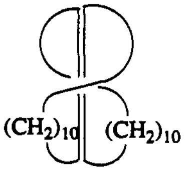

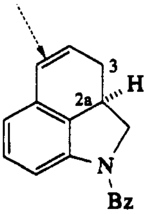

(49) (95, 50) (50a) (50b) (97, 98)

### *3.1.2.2.4 MCPBA epoxidations of cyclic alkenes and methylenecycloalkanes having directing groups*

Henbest *et al.* have shown that allylic cyclohexenols undergo epoxidation selectively *cis* to hydroxy if there is no severe steric interference.[13] It has been suggested that in the transition state for epoxidation, the hydroxy group is associated with the peroxy acid through hydrogen bonding. The ideal situation for the transition state is attained when the O—C—C=C dihedral angle is 120°.[5,42] The pseudoequatorial hydroxy is more effective than the pseudoaxial hydroxy in directing epoxidation. The rate of epoxidation of allylic cyclohexenol is about 10 times that of the corresponding allylic acetate and about one half that of cyclohexene.[13] The directive effect is rather weak and the stereoselectivity can be poor if the peroxy acid encounters severe steric interference. Homoallylic hydroxy can direct epoxidation if it can approach the double bond. In the cyclohexane system axial homoallylic hydroxy directs epoxidation. Besides the hydroxy, carbamates, ethers and ketones direct epoxidation.

In the *trans*-diol (**51**) both the hydroxys are equatorial. The homoallylic hydroxy, being equatorial, cannot direct epoxidation. Since only the allylic hydroxy can direct epoxidation (**51**) reacts with MCPBA stereoselectively (equation 20).[43] In the *trans*-diol (**52**) the hydroxys are diaxial. The β-oriented homoallylic hydroxy being axial can direct epoxidation from the β-face; the α-oriented allylic hydroxy also directs epoxidation but from the α-face. Hence the epoxidation of (**52**) is not stereoselective (equation 21).[44] The major diastereoisomer in the epoxidation of (**52**) is the β-epoxide showing that in this diol the directing effect of homoallylic hydroxy is stronger than that of allylic hydroxy. The allylic alcohols (**53**; equation 22),[45] and (**54**)–(**57**)[46–49] undergo stereoselective epoxidation due to the directing influence of hydroxy. Epoxidation of (**58**) furnishes almost exclusively the *trans*-epoxide (**59**; equation 23).[50] The moderate assistance provided by the allylic hydroxy for epoxidation from the β-face is not large enough to overcome steric interference with one of the geminal methyl groups.

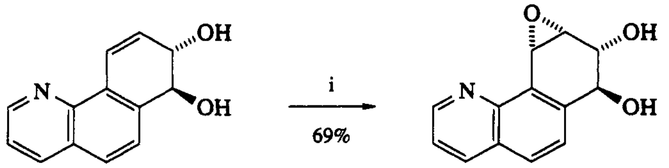

(20)

(**51**) i, MCPBA, dry THF, 48 h, r.t.

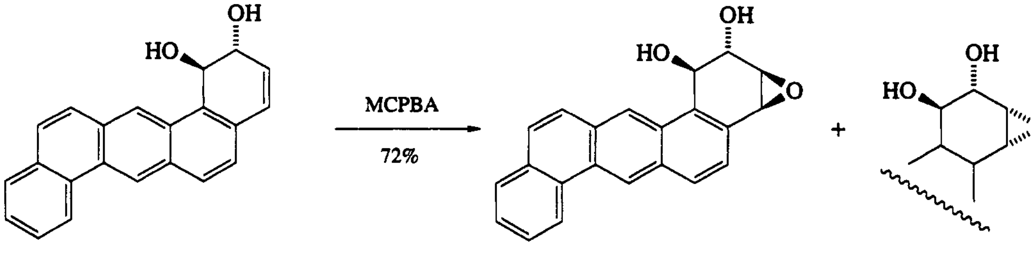

(21)

(**52**) 75% 25%

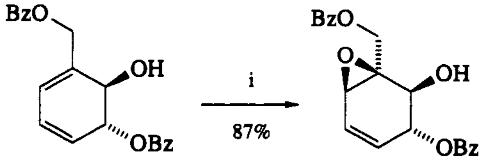

(22)

(**53**)

i, MCPBA, $CH_2Cl_2$, phosphate buffer, pH 8, 0 °C, 1 h

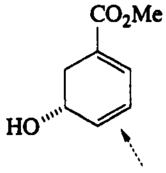

(**54**) (65, 95)

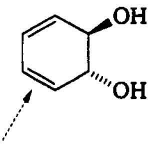

(**55**) (61, –)

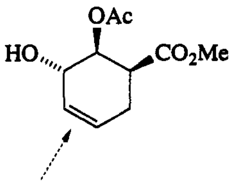

(**56**) (91, ~100)

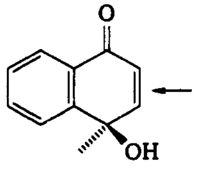

(**57**) (64, –)

When the allylic hydroxy in a methylenecyclohexane, *e.g.* (**61**), is equatorial then the C—O bond is in the plane of the π-bond and it does not direct epoxidation when it is reacted with peroxy acids (equation

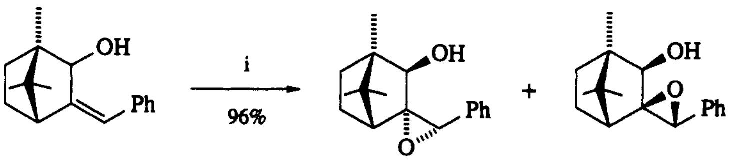

(23)

**(58)** **(59)** 97% **(60)** 3%

i, MCPBA, $CHCl_3$

24);[2,51] the stereochemistry of the product is determined by the steric hindrance exhibited by the axial methyl group at C-10. In the allylic alcohol (**62**) the secondary hydroxy is axial and is not in the plane of the C(5)—C(6) double bond. Hence it is able to direct epoxidation from the β-face; the directing effect is strong enough to overcome steric hindrance due to methyl at C-10, leading to the stereoselective formation of the product (**63**).[52]

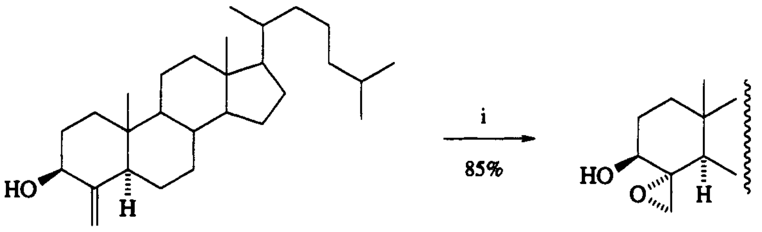

(24)

**(61)**

i, MCPBA, $CH_2Cl_2$, r.t., 1.5 h

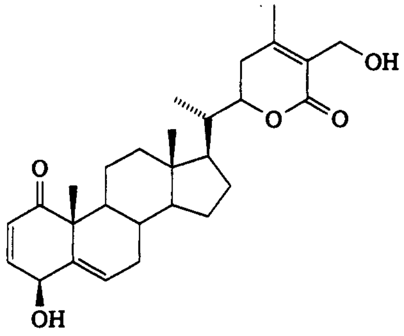

**(62)**

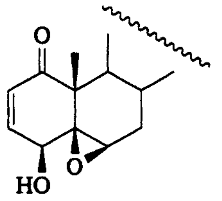

**(63)**

Moderate selectivity has been observed in the epoxidation of the homoallylic alcohol (**64**; equation 25).[53] In the nonsteroidal conformation of (**64**), the axial hydroxy is suitably oriented for forming a hydrogen bond with the peroxy acid in the transition state. That the epoxidation of (**64**; R = OH) is indeed hydroxy-directed is supported by the observation that the epoxidation of the acetate (**64**; R = OAc) furnishes exclusively the α-epoxide (**66**; R = OAc).

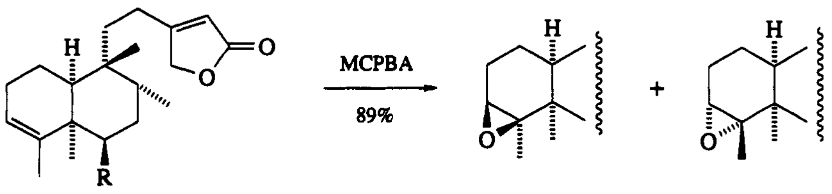

(25)

**(64)** R = OH **(65)** 63% **(66)** 37%

The epoxidation of the acid (**67a**; R = OH) furnishes exclusively the α-epoxide (**67b**; equation 26);[54] the corresponding methyl ester (**67a**; R = OMe) furnishes a 2:1 mixture of 9α,10α- and 9β,10β-epoxides. This shows that the hydroxy group of the acid (**67a**), which is attached to the bishomoallylic carbon, directs the epoxidation.

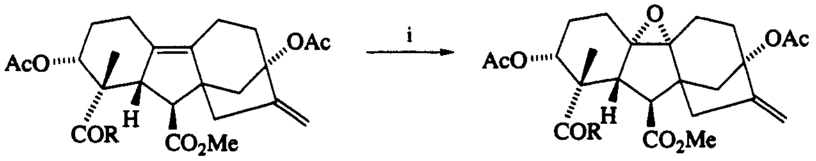

(26)

(**67a**) R = OH (**67b**) R = OH

i, MCPBA, $CH_2Cl_2$, reflux, 50 min

Alkene (**68**) undergoes carbamate-directed epoxidation (equation 27).[55] Epoxidation of the diketone (**69**) furnishes exclusively the *syn*-epoxide, probably due to hydrogen bonding between MCPBA and the carbonyl group (equation 28).[56] The epoxidation of the ketal (**70**) furnishes exclusively one epoxide (**71**), but the closely related ketone (**72**) furnishes a 70:30 mixture of 1α,2α- and 1β,2β-epoxides.[57] Comparison of the selectivities suggests that the α-oriented ketal oxygen of (**70**) directs epoxidation through hydrogen bonding to the peroxy acid. Ether-directed epoxidation has been observed in the reaction of alkene (**73**) with trifluoroperacetic acid (equation 29);[58] the selectivity is due to hydrogen bonding involving the hydroxy of the peroxy acid and the oxygen of the allyl ether.

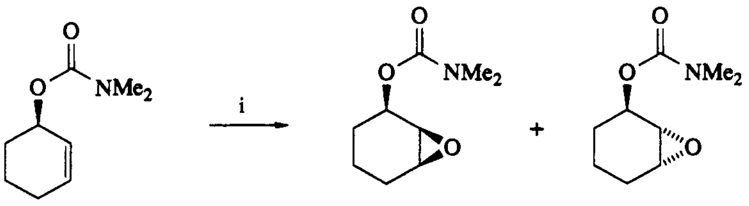

(27)

(**68**) 91% 9%

i, MCPBA, $CH_2Cl_2$, 0 °C

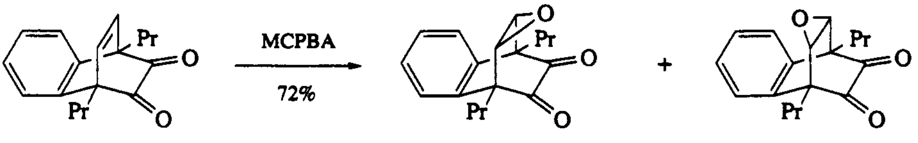

(28)

(**69**) 100% 0%

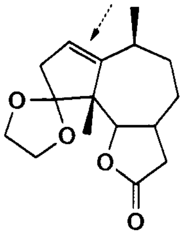

(**70**) (72, ~100)

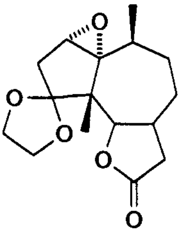

(**71**)

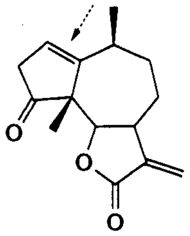

(**72**) (78, 70)

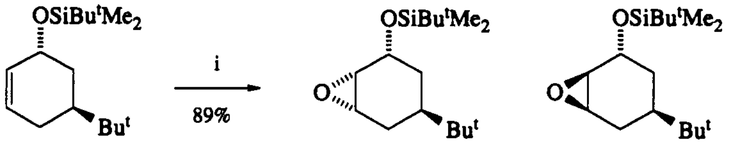

(73) (74) 93% (75) 7%

(29)

i, $CF_3CO_3H/CH_2Cl_2$ buffered with $Na_2HPO_4$, –40 °C

### *3.1.2.2.5 MCPBA epoxidations of acyclic alkenes having directing groups*

Several intermediates for the synthesis of macrolides and ionophore antibiotics have been prepared from epoxy alcohols, obtained through stereoselective epoxidation of acyclic allyl alcohols. One of the reagents studied extensively to effect stereoselective epoxidations is MCPBA. α,β-Epoxy alcohol (**77**) cannot be prepared through MCPBA epoxidation of geraniol (**76**) in an organic solvent. However, epoxide (**77**) has been prepared regioselectively from geraniol using an emulsion system (equation 30).[59] The emulsion system is prepared by stirring a mixture of geraniol, *n*-hexane, *n*-octanol, water, NaOH and dioctadecyldimethylammonium chloride.

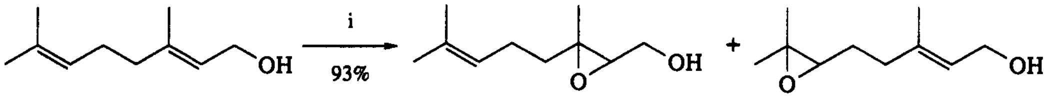

(76) (77) 100% (78) 0%

(30)

i, MCPBA in emulsion, 25 °C, 15 h

Epoxidation of the secondary allylic alcohol (**79**) can furnish the diastereoisomers, *threo*-epoxy alcohol (**80**) and *erythro*-epoxy alcohol (**81**). Epoxidation *via* the rotamer (**82**) leads to *threo*-(**80**) and epoxidation *via* the rotamer (**83**) leads to *erythro*-(**81**).[5,42] The steric interactions in the *threo* transition state[60] can be obtained by examining the rotamer (**82**) and the steric interactions in the *erythro* transition state can be obtained by examining the rotamer (**83**). During the epoxidation of (**79**), when both R$^c$ and R$^t$ are alkyl and also when R$^c$ is alkyl and R$^t$ is H, in the *erythro* transition state (see **83**) there is severe steric interference between R$^c$ and R which destabilizes the *erythro* transition state. High *threo* selectivity has been observed during the epoxidation of secondary allylic alcohols having trisubstituted (R$^t$ and R$^c$ are alkyl in **79**) or *cis*-disubstituted double bonds. During the epoxidation of secondary allylic alcohols having a *trans*-disubstituted double bond or a monosubstituted double bond (R$^t$ and R$^c$ are H in **79**) the *erythro* transition state is not sufficiently destabilized, since R interferes only with H; hence diastereoselectivity is poor.

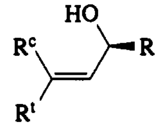

(**79**)

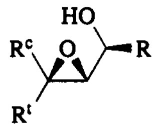

(**80**)

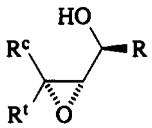

(**81**)

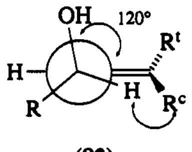

(**82**)

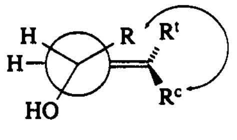

(**83**)

High stereoselectivity has been observed during the epoxidation of the allylic alcohol (**84**) having a trisubstituted double bond and the allylic alcohol (**85**) having a *cis*-disubstituted double bond (equations

31a and 31b).[61,62] In contrast, selectivity is poor during the epoxidation of the allylic alcohols (**86**) and (**87**) having *trans*-disubstituted double bonds.[61,62]

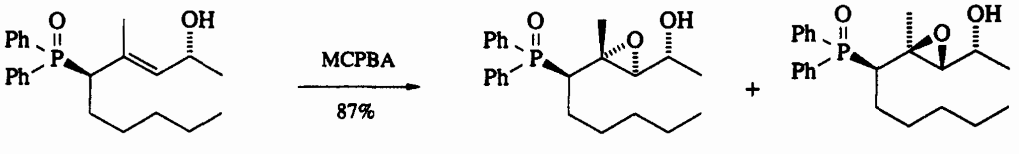

(**84**) 93% 7% (31a)

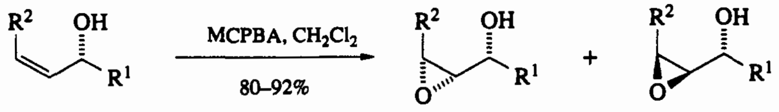

(**85**) 93% 7% (31b)

$R^1 = (CH_2)_6CO_2Me$, $R^2 = (CH_2)_5Me$

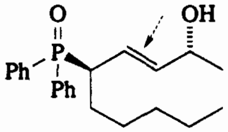

(**86**) (95, 73)

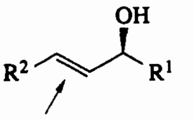

(**87**) (86, 50)

$R^1 = (CH_2)_6\ CO_2Me$, $R^2 = (CH_2)_5Me$

MCPBA epoxidation of the allylic alcohol (**88b**; R = H) is not a satisfactory route for the preparation of the *threo*-epoxy alcohol (**91**), as the stereoselectivity in this reaction is poor and a 61:39 mixture of (**91**) and (**92**) is obtained.[63] A convenient route has been developed for the synthesis of (**91**) employing reactions which are highly stereoselective (Scheme 1).[63] The epoxidation of (**88a**; R = TMS) is stereoselective since the *erythro* transition state is destabilized due to 1,3-steric interference between the bulky trimethylsilyl group and *n*-butyl group. The trimethylsilyl group of epoxide (**89**) can be replaced by hydrogen with retention of configuration by reacting it with F⁻. Several epoxy alcohols have been prepared stereoselectively starting from alkenes having a trimethylsilyl group on the double bond, following the route given in Scheme 1.

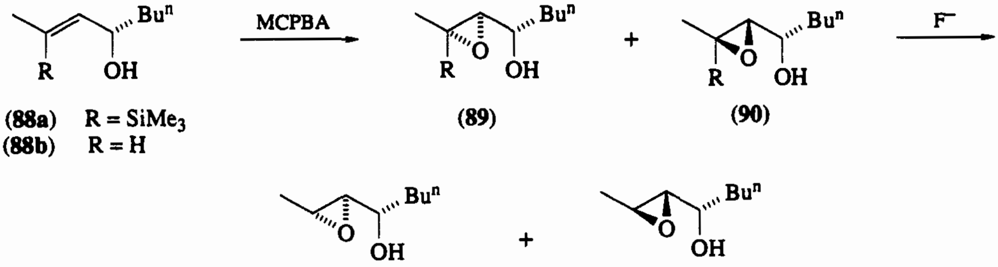

(**88a**) R = $SiMe_3$
(**88b**) R = H

(**89**) (**90**)

(**91**) 99% (**92**) 1%

Combined yield in two steps = 81%

**Scheme 1**

Kishi *et al.* have observed that the epoxidation of the allylic alcohol (**93**) which has a suitably located ether oxygen is stereoselective (equation 32).[64] In the transition state (**94**), which delivers oxygen from the β-face, MCPBA is complexed by two hydrogen bonds involving participation of ether oxygen as well as hydroxy. In the transition state (**94**) there is steric interference between allylic hydrogen at C-4 and methyl at C-2. In contrast, in the transition state which can deliver oxygen from the α-face, there is steric interaction between methyl at C-4 and methyl at C-2; this steric interaction is more severe than the corresponding interaction in (**94**). Hence epoxidation from the α-face of the alcohol (**93**) is not favored. The epoxidation of (**93**) presented above is an example of the cooperative effect of hydroxy and ether oxygen in directing epoxidation. High stereoselectivities have been observed in the epoxidations of the allylic alcohols (**95**; equation 33) and (**98**; equation 34);[65,66] the selectivities are due to a cooperative effect. Epoxidation of the allyl alcohol (**99**) is stereoselective (equation 35);[67] it is postulated that in the transition state the hydroxy of the allylic alcohol and the carbonyl oxygen form hydrogen bonds with the peroxy acid.

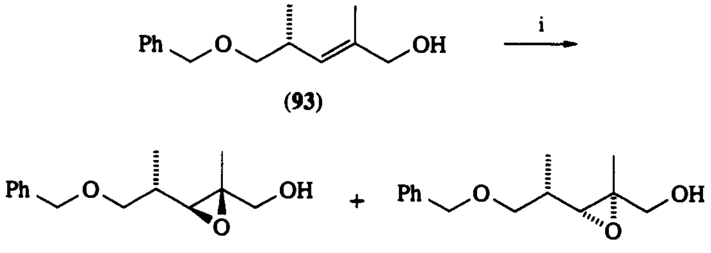
Ph
O
OH
i
(93)
Ph
O
OH
O
+
Ph
O
OH
O
96%
4%

(32)

i, MCPBA, $CH_2Cl_2$, 0 °C

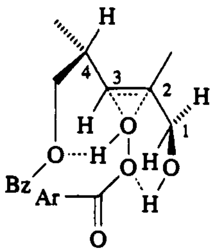
H
4
3
2
H
1
H
O
O
H
O
H
O
Bz
Ar
H
O

**(94)**

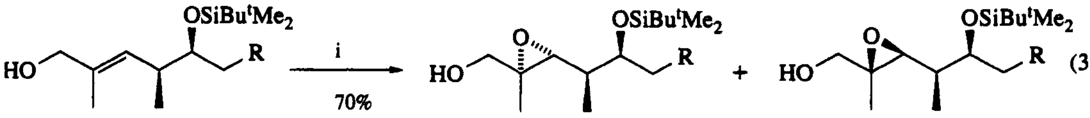
OSiBu$^t$Me$_2$
HO
R
i
70%
O
OSiBu$^t$Me$_2$
HO
R
+
O
OSiBu$^t$Me$_2$
HO
R

(33)

**(95)** **(96)** 98% **(97)** 2%

R = $C(OMe)_2CH(OMe)CH_2OAc$

i, MCPBA, $CH_2Cl_2$, –20 °C

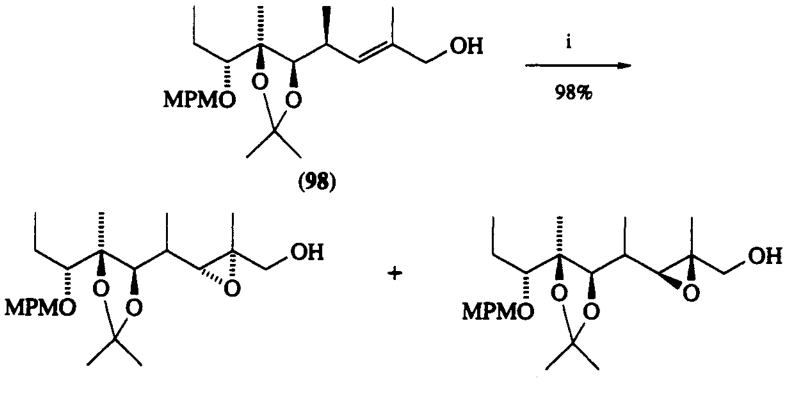
OH
MPMO
O
O
i
98%
(98)
OH
MPMO
O
O
O
+
OH
MPMO
O
O
O

(34)

100% 0%

i, MCPBA, $CH_2Cl_2$, –15 to –10 °C

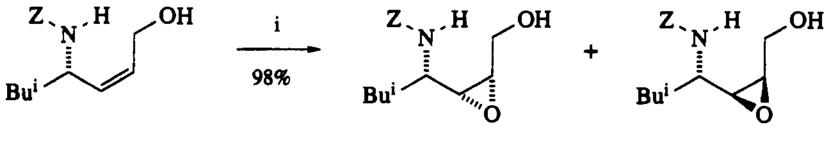

**(99)** 95% 5% (35)

Z = $PhCH_2OCO$

i, MCPBA, $CH_2Cl_2$, −10 °C

The epoxidation of the homoallylic alcohol (**100**) is regio- and stereo-selective (equation 36).[10] Epoxidation of (**100**) from the β-face involves a transition state which can be approximated by the conformer (**102**) complexed with MCPBA; in this conformation there is steric interference between the tertiary allylic hydrogen and ethyl group. Inspection of conformation (**103**) reveals that in the transition state leading to the α-epoxide there is steric interaction between the ethyl and allyl groups; the steric interaction in (**103**) is much larger than the interaction in (**102**).

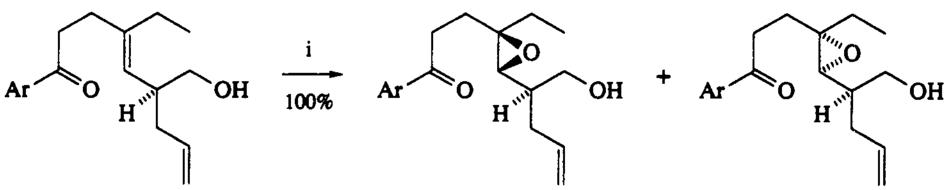

**(100)** **(101)** 95% <5% (36)

Ar = 4-$MeOC_6H_4$

i, MCPBA, $CH_2Cl_2$, aq. $NaHCO_3$, r.t.

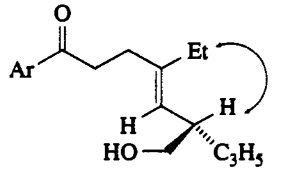

**(102)**

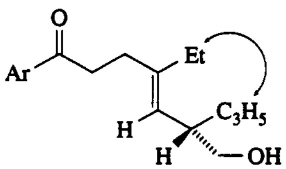

**(103)**

The stereoselectivities of the epoxidations of the homoallylic alcohols (**104**) and (**105**) and their benzoates (**106**) and (**107**) have been studied.[68] The amide-directed epoxidation of the *cis*-disubstituted alkene (**108**) is stereoselective (equation 37).[69]

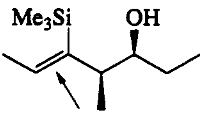

**(104)** (90, 80)

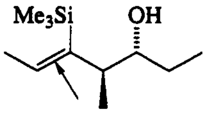

**(105)** (88, 75)

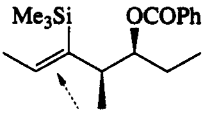

**(106)** (96, 86)

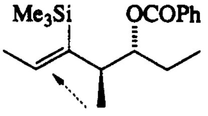

**(107)** (89, 75)

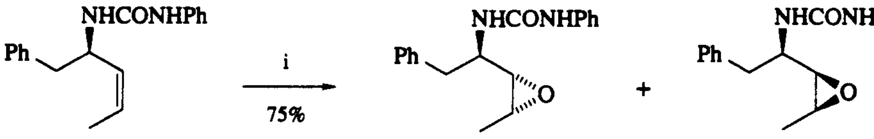

**(108)** 95% 5% (37)

i, MCPBA, $CH_2Cl_2$, 0 °C

#### *3.1.2.2.6 MCPBA epoxidations of electron-deficient alkenes*

Alkenes conjugated with C=O are electron-deficient and hence do not react readily with organic peroxy acids. The observation that the stereochemistry of the pyrazolinone (**109**) is not retained in the epoxidation product (**110**) is interesting (equation 38).[70] The epoxide (**110**) is not formed directly from (**109**). Since the double bond in (**109**) is electron-deficient its peroxy acid epoxidation to furnish (**111**) is a slow process. The isomerization of the (*Z*)-pyrazolinone (**109**) to the corresponding (*E*)-isomer is a comparatively fast process. MCPBA epoxidation of the (*E*)-isomer derived from (**109**) furnishes (**110**).

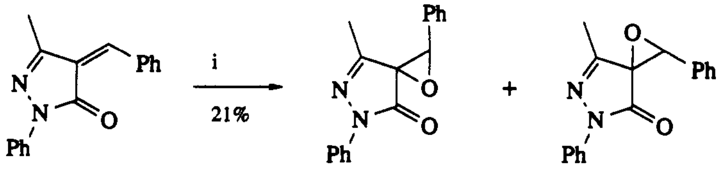

(38)

(**109**) (**110**) 85% (**111**) 15%

i, MCPBA, $CH_2Cl_2$, r.t., 7 d

Dienones with extended conjugation undergo peroxy acid epoxidation regioselectively at the γ,δ-double bond, even if it is less substituted than the α,β-double bond. The epoxidation of (**112**) is regio- and stereo-selective (equation 39).[71] Attempted epoxidation of (**113a**) using nucleophilic reagents furnishes polymeric materials. The epoxidation has been carried out with MCPBA (equation 40).[72a]

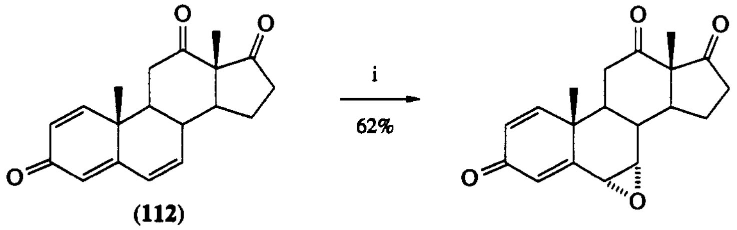

(39)

(**112**)

i, MCPBA, $CH_2Cl_2$, r.t., 5 d

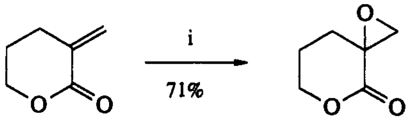

(40)

(**113a**)

i, MCPBA, dichloroethane, 2,6-di-t-butylphenol, reflux in dark, 5 h

### 3.1.2.3 Some of the Commonly Used Peroxy Acids and Related Reagents

For the large scale preparation of epoxides, reagents which are cheaper than MCPBA are available. Though many electron-deficient alkenes have been epoxidized with MCPBA at elevated temperatures, reagents which are more reactive than MCPBA have been used; when these reagents are employed the reactions can be carried out under comparatively mild conditions, leading to improvements in yields and selectivities.

#### *3.1.2.3.1 Peracetic acid and performic acid*

Peracetic acid is available commercially as a 40% solution in acetic acid. Both peracetic acid and performic acid prepared *in situ* are used industrially.[6,7]

### *3.1.2.3.2 Peroxycarboximidic acids*

Alkenes have been epoxidized with $H_2O_2$ in the presence of nitriles such as acetonitrile and benzonitrile. The actual epoxidizing agent is a peroxycarboximidic acid, $RC(=NH)CO_3H$, generated *in situ*.[13] The reagents are inexpensive and the method is convenient and safe for large scale preparations. Perbenzimidic acid epoxidation of (**113b**) takes place from the more hindered α-face.[72b] It has been suggested that the epoxidizing reagent complexes with the carbonyl group as well as the ether oxygen at C-3.

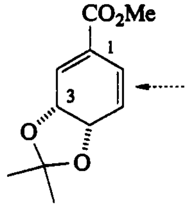

(**113b**) (90, ≈100)

### *3.1.2.3.3 Trifluoroperacetic acid*

The unsaturated ester (**114**) has been epoxidized with $CF_3CO_3H$ (equation 41).[73] Only one diastereoisomer is produced in the reaction (see also equation 29).

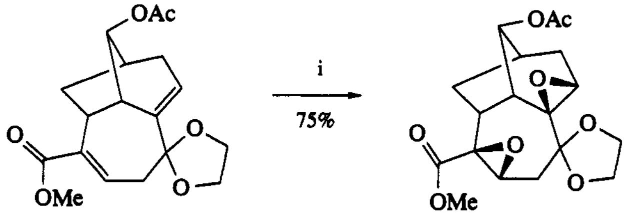

(41)

(**114**)

i, $K_2HPO_4$, $CF_3CO_3H$, $CH_2Cl_2$, 40 °C

### *3.1.2.3.4 4-Nitroperbenzoic acid*

4-Nitroperbenzoic acid has been used for the preparation of the epoxide (**116**; equation 42).[74] In the aldehyde (**115**), the tetrasubstituted C(1)—C(2) double bond is not epoxidized since it is deactivated by conjugation with the aldehyde group. The disubstituted double bond is not sufficiently reactive due to the inductive effect of the allyl ether moieties. The epoxidation takes place from the α-face since the β-face is blocked by the allylic substituents. The epoxide (**116**) cannot be prepared in satisfactory yields using MCPBA.

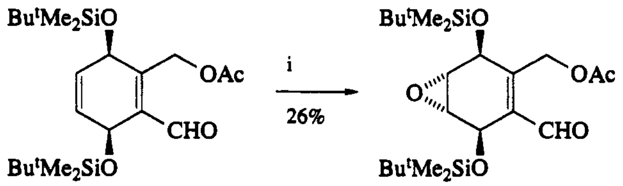

(42)

(**115**) (**116**)

i, 4-nitroperbenzoic acid, 4,4'-thiobis(6-*t*-butyl-3-methylphenol), $CHCl_3$, reflux, 3 d

### *3.1.2.3.5 3,5-Dinitroperbenzoic acid*

The diene (**117**) has been epoxidized with 3,5-dinitroperbenzoic acid (equation 43).[75] Attack at both the double bonds is stereoselective. Epoxides of enol ethers are normally difficult to isolate, but the epoxide (**118**) is quite stable. This stability is due to the attachment of the electron-withdrawing carboxylate substituent to the furan ring. When **(117)** is treated with the comparatively less reactive MCPBA, epoxidation takes place regioselectively at the trisubstituted double bond to furnish a monoepoxide.

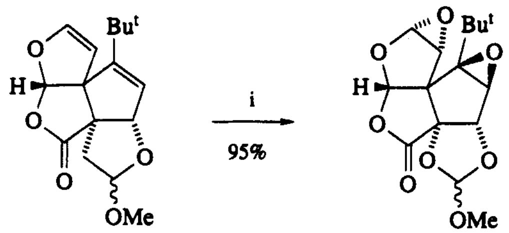

(43)

**(117)** **(118)**

i, 3,5-dinitroperbenzoic acid, $CH_2Cl_2$, $NaHCO_3$, 23 °C, 36 h

### *3.1.2.3.6 Dialkyldioxirane*

Murray *et al.* have shown that (≤0.1 M) solutions of dimethyldioxirane **(119)** in acetone can be obtained through low temperature distillation of caroate–acetone reaction mixtures. More recently it has been shown that solutions of methyl(trifluoromethyl)dioxirane **(120)**, a reagent which is more reactive than **(119)**, can be prepared starting from trifluoroacetone. A solution of dioxirane **(119)** in dry acetone reacts readily with disubstituted alkenes such as *cis*-3-hexene **(121)** and *trans*-3-hexene **(122)** to furnish corresponding epoxides in nearly quantitative yield. The *cis*-alkene **(121)** reacts about eight times faster than the *trans*-alkene **(122)**.[76] The dioxirane **(120)** is highly reactive. Reaction of **(120)** with phenanthrene at –20 °C for 5 min furnishes phenanthrene 9,10-oxide in 93% yield.[77a] Epoxidations with dimethyldioxirane **(119)** proceed under neutral and mild conditions in the absence of nucleophiles and electrophiles. It is the reagent of choice for synthesizing sensitive epoxides of enol esters, enol lactones and enol ethers.[77b] The epoxidations are carried out at –40 to 20 °C. The alkenes **(123a)**,[77c] **(123b)**, **(123c)**, **(123d)**[77d] and aflatoxin $B_1$[77e] have been epoxidized with the reagent **(119)**. For a recent review see Murray.[77f]

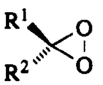

**(119)** $R^1 = R^2 = Me$

**(120)** $R^1 = CF_3$, $R^2 = Me$

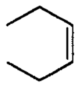

**(121)**

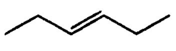

**(122)**

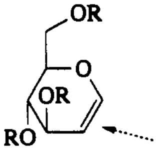

$R = SiMe_2Bu^t$

**(123a)** (100, 100)

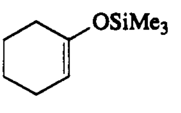

**(123b)** (99)

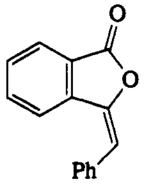

**(123c)** (85)

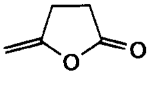

**(123d)** (96)

### *3.1.2.3.7 Magnesium monoperphthalate hexahydrate (MMPP)*

Pure MCPBA is shock sensitive and can deflagrate. Magnesium monoperphthalate is not shock sensitive and does not deflagrate. MMPP is cheaper than MCPBA and loses available oxygen at a slower rate than MCPBA. The reagent is water soluble and hence epoxidations are carried out in a water–isopropanol mixture. Epoxidation of cyclohexene with MMPP in isopropanol–water at 25 °C for 7 h furnishes the epoxidation product in 85% yield.[78]

#### 3.1.2.4 Intramolecular Epoxidations with Peroxy Acids

Treatment of the acid (**67a**) with carbonyldiimidazole and 90% $H_2O_2$ furnishes the epoxide (**67b**; equation 44).[54] This reaction is more than 100 times faster than the epoxidation of (**67a**) with MCPBA (see equation 26). It has been suggested that under the experimental conditions of equation (44) the acid (**67a**; R = OH) is transformed to the peroxy acid (**67a**; R = $O_2H$), which reacts regio- and stereo-selectively through an intramolecular reaction.

$$(\mathbf{67a}) \xrightarrow[75\%]{\text{i–iii}} (\mathbf{67b}) \qquad (44)$$

i, $CH_2Cl_2$, *N,N'*-carbonyldiimidazole, r.t., 30 min; ii, $H_2O_2$ (90%); iii, 0 °C, 5 min

### 3.1.3 EPOXIDATIONS WITH ALKYL HYDROPEROXIDES

#### 3.1.3.1 Epoxidations of Alkenes Lacking Directing Groups

One of the important developments in oxirane chemistry during the past 25 years is the use of alkyl hydroperoxides for the preparation of epoxides from alkenes, in the presence of high-valent $d^0$ transition metal complexes. *t*-Butyl hydroperoxide (TBHP) and ethylbenzene hydroperoxide (EBHP), in the presence of soluble compounds of Mo, are used for the manufacture of propylene oxide.[8] Alkenes can be epoxidized with TBHP using Mo, V, W or Ti complexes as catalyst; however, Mo is the catalyst of choice when the substrates lack directing groups such as hydroxy. Electron-rich alkenes react rapidly, but the reaction is sluggish when electron-deficient alkenes such as 1-decene are the substrates. Polar solvents, particularly alcohols and water, retard the epoxidation by competing with the hydroperoxide for coordination sites on the metal. Water reduces the selectivity by reacting with the epoxide to furnish the corresponding diol. Convenient procedures for the preparation of anhydrous solutions of TBHP in organic solvents and also the precautions that have to be taken while handling TBHP are given in a recent review.[5] The use of a solution of TBHP in toluene is preferred.[79] TBHP is one of the most stable organic peroxides known.[5]

In the synthesis of an epoxide from an alkene with TBHP/Mo, the stereochemistry of the alkene is retained in the epoxide.[8] It has been suggested that the reaction proceeds through the transition state (**124**).[80] 1-Decene and the alkene (**115**) (see equation 42) have been epoxidized with TBHP/Mo (equations 45 and 46).[5,74] The epoxidation of (**115**) is regio- as well as stereo-selective; the reagent approaches the electron-rich double bond from the less hindered face.

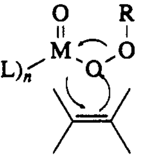

(**124**) L = ligand; M = Mo

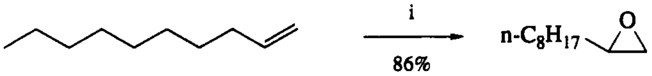

(45)

i, TBHP, 1,2-dichloroethane, $Mo(CO)_6$, $Na_2HPO_4$, reflux, 10 h

$$(\mathbf{115}) \xrightarrow[20\%]{\text{i}} (\mathbf{116}) \qquad (46)$$

i, TBHP, $Mo(CO)_6$, 4,4'-thiobis(6-*t*-butyl-3-methylphenol), benzene, reflux, 6 h

### 3.1.3.2 Epoxidations of Cyclic Alkenes Having Directing Groups

The rate of epoxidation of an allylic alcohol with TBHP in the presence of a vanadium catalyst is more than 1000 times the rate of epoxidation of the parent alkene.[5] An increase in reaction rate has also been observed in the vanadium-catalyzed epoxidation of homoallylic and bishomoallylic alcohols due to the location of the hydroxy group. Hence the epoxidation of polyunsaturated allylic and homoallylic alcohols with TBHP/V$^{5+}$ is regioselective; only those double bonds which come under the directing influence of hydroxy are epoxidized. For examples see compounds (**38**), (**131**), (**150**) and (**151**). The epoxidation of the cyclic allylic alcohol (**125**) is stereoselective and takes place from the face *cis* to hydroxy (equation 47).[5] Hydroxy-directed epoxidation of cyclic allylic alcohols employing TBHP/V has been used extensively in organic synthesis; high stereoselectivities have been observed during the epoxidations of the cyclic allylic alcohols (**128**)–(**131**).[81–84] The epoxidation of (**131**) is also regioselective; the disubstituted double bond, but not the trisubstituted double bond, is suitably located for hydroxy-directed epoxidation. The *cis*-directing effect of allylic hydroxy in the metal-catalyzed epoxidation is much stronger than the *cis*-directing effect observed in MCPBA epoxidation. When there is severe steric interference to the approach of the reagent *cis* to hydroxy then MCPBA epoxidations exhibit poor *cis* selectivity (see equation 23). In contrast high selectivity has been observed in the hydroxy-directed epoxidation of (**58**) with TBHP/V, even though one of the geminal methyl groups sterically interferes with the approach of the reagent from the face *cis* to the hydroxy (equation 48).[50] The primary allylic alcohol (**132**) undergoes hydroxy-assisted epoxidation, with high stereoselectivity from the less hindered side to furnish in 96% yield the epoxide (**133**), when it is reacted with trityl hydroperoxide/VO(acac)$_2$; there is a decrease in stereoselectivity if TBHP is used instead of trityl hydroperoxide.[85] TBHP epoxidation of the allylic alcohol (**134**) in which the C—O bond is in the plane of the double bond is not stereoselective.[86] The homoallylic alcohols (**135**), (**136**) and the bishomoallylic alcohol (**137**) undergo hydroxy-directed epoxidation stereoselectively.[87–89] Due to the directing effect of homoallylic hydroxy, vitamin D$_3$ (**38**) is epoxidized regio- and stereo-selectively at room temperature to furnish in 90% yield the (5*S*)-5,6-

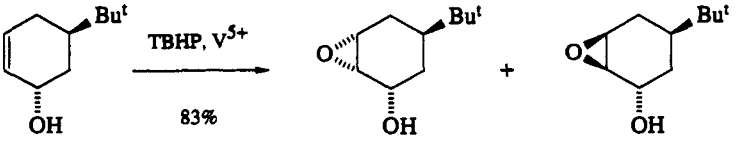

(47)

(**125**) (**126**) 100% (**127**) 0%

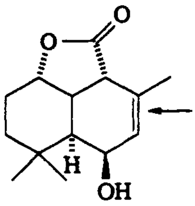

(**128**) (95, ≈100)

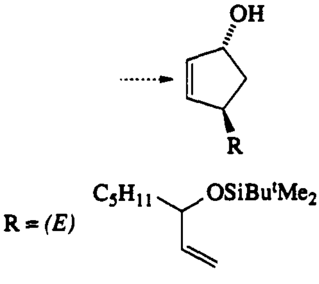

(**129**) (98, ≈100)

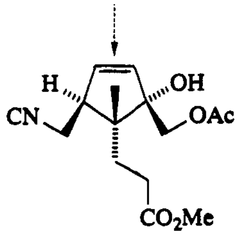

(**130**) (85, ≈100)

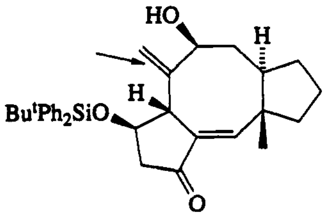

(**131**) (67)

monoepoxide when TBHP/VO(acac)$_2$ is employed.[31] The epoxidation of (**38**) does not take place at room temperature when the reaction is carried out with TBHP/Mo; when the reaction is carried out at higher temperature a complex mixture is obtained due to the instability of the substrate. Oxidations of some hindered allylic alcohols (*e.g.* **138a**) to the corresponding α,β-unsaturated ketones during attempted preparation of epoxy alcohols employing TBHP/V are reported.[90]

$$(\mathbf{58}) \xrightarrow[100\%]{\text{TBHP, VO(acac)}_2} \underset{>99\%}{(\mathbf{60})} + \underset{<1\%}{(\mathbf{59})} \qquad (48)$$

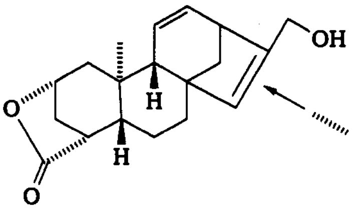

**(132)** (96, ≈100)

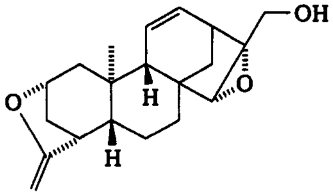

**(133)**

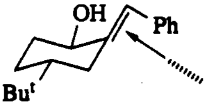

**(134)** (100, 55)

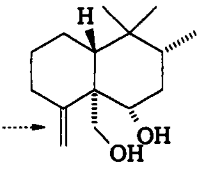

**(135)** (77, ≈100)

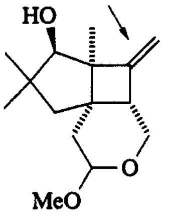

**(136)** (95, ≈100)

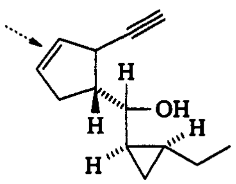

**(137)** (87, ≈100)

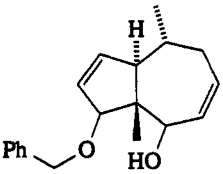

**(138a)**

Ester-directed epoxidations have been observed when Mo(CO)$_6$ is used as catalyst (equation 49).[91]

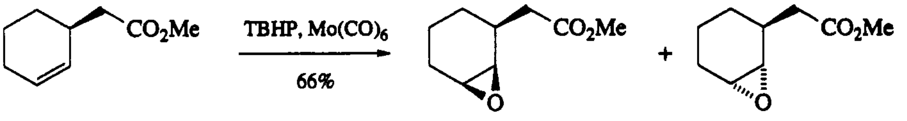
CO$_2$Me
TBHP, Mo(CO)$_6$
66%
CO$_2$Me
O
+
CO$_2$Me
O

(49)

**(138b)** 94% 6%

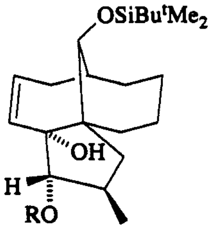
OSiBu$^t$Me$_2$
OH
H
RO

**(138c)** R = H

**(138d)** R = MeOCH$_2$

Hydroxy-directed epoxidation of (**138d**) with TBHP/Ti(OPr$^i$)$_4$ is complete in 2 h at −35 °C and gives in 87% yield the corresponding α-epoxide. In contrast, the epoxidation of the diol (**138c**) is extremely sluggish, probably due to the strong coordination of the Ti cation to the diol.[91b]

### 3.1.3.3 Epoxidations of Acyclic Alkenes Having Directing Groups

In the vanadium-catalyzed epoxidation of allylic alcohols the ideal geometry for the transition state is reached when the O—C—C═C dihedral angle is 50°.[5] To predict the stereochemistry of epoxidation of allylic alcohol (**139**) two conformers (**140**) and (**141**) have to be considered.[63] In the conformer (**140**) there is steric interference between TMS and H; in the conformer (**141**) there is steric interference between TMS and Me. Since the steric interference is less in (**140**), this conformer determines the stereochemistry of epoxidation and the epoxy alcohol (**142**) is anticipated as the major product. The direction of asymmetric induction during epoxidation of acyclic homoallylic alcohols can be predicted by considering steric interference in the transition state (**143**);[92] stereoselectivity is high when alkyl groups can be equatorially oriented (R$^2$ and R$^3$) in the transition state (**143**). The stereoselectivities observed during the epoxidation of several acyclic alcohols with TBHP/V have been given in a recent review.[2]

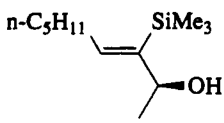

**(139)**

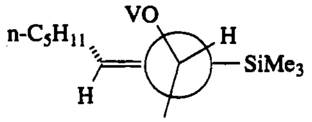

**(140)**

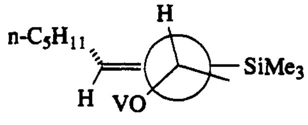

**(141)**

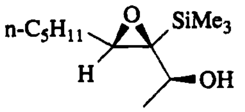

**(142)**

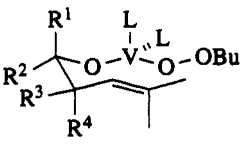

**(143)**

Epoxidations of the allylic alcohols (**144**),[93] (**145**),[94] (**146**; equation 50)[95] and (**148**; equation 51)[96] are highly stereoselective. The transformation of (**148**) to (**149**) is an example of the use of silyloxyalkenes in the stereoselective synthesis of *trans* α,β-epoxy alcohols. The epoxidation of the ester (**150**), which has a hydroxy allylic to a *trans*-disubstituted double bond, does not exhibit high stereoselectivity (equation 52);[97] the epoxidation is regioselective, involving only the C(13)—C(14) double bond.

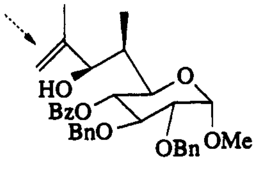

**(144)** (90, ≈100)

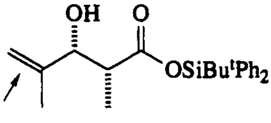

**(145)** (80, ≈100)

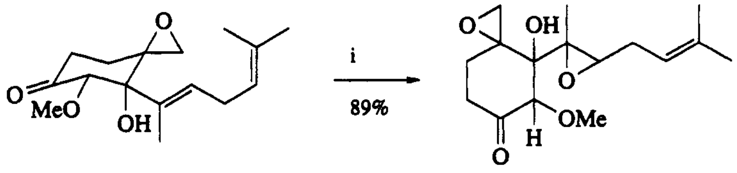

**(146)** **(147)** (50)

i, TBHP, VO(acac)$_2$, PhMe, r.t., 2 h

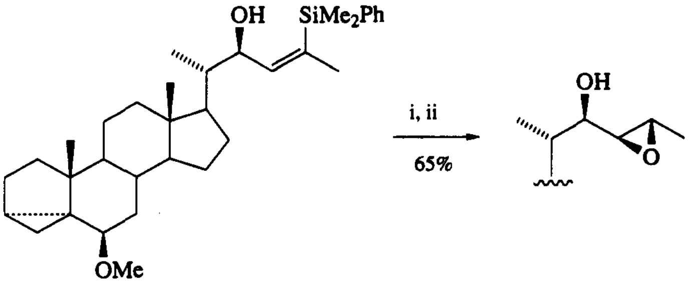

(148) (149)

(51)

i, TBHP, VO(acac)$_2$; ii, Bu$^n$$_4$NF

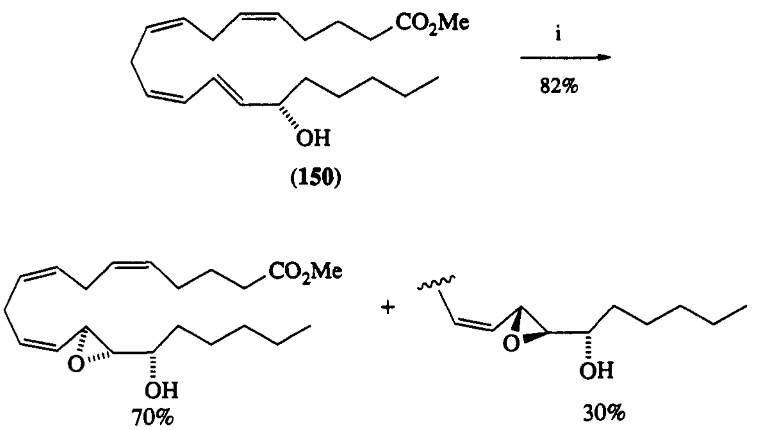

(150)

(52)

i, TBHP, VO(acac)$_2$

The acyclic homoallylic alcohol (**151**) is epoxidized regio- and stereo-selectively (equation 53).[98] High stereoselectivities have been observed in the epoxidations of the homoallylic alcohols (**152**) and (**153**) which have a *cis*-disubstituted double bond.[99] The stereoselectivity is excellent when the reactant is (**154**) but poor when the reactant is (**155**).[100]

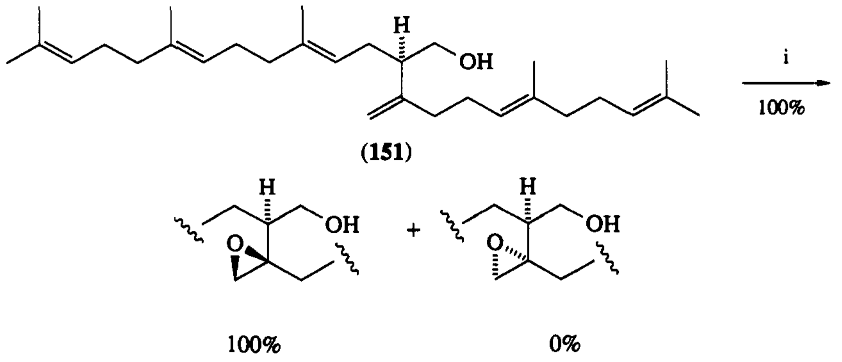

(151)

(53)

i, TBHP, VO(acac)$_2$, benzene, reflux, 45 min

Vanadium-catalyzed epoxidation of the diene (**156**) having hydroxy allylic to one double bond and homoallylic to the other double bond does not furnish exclusively (**157**; equation 54).[101] The epoxidation of (**156**) with dibutyltin oxyperoxide is regioselective, furnishing exclusively the regioisomer (**157**) as a 95:5 mixture of *erythro* and *threo* diastereoisomers.[101] Epoxidations of the diol (**159**) and its epimer (**160**) take place selectively from the α-face. On the basis of this observation and further studies it has been concluded that in (**159**) and (**160**) the epoxidation is directed by the homoallylic, but not the allylic,

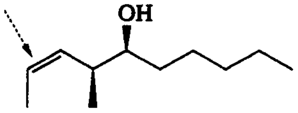

**(152)** (81, 97)

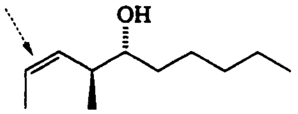

**(153)** (95, 97)

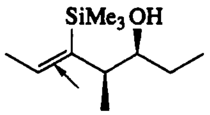

**(154)** (88, 99)

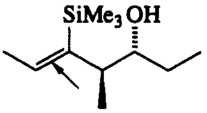

**(155)** (91, 67)

hydroxy.[102] Stereoselective epoxidations of some acyclic bishomoallylic alcohols have been reported (equation 55).[103]

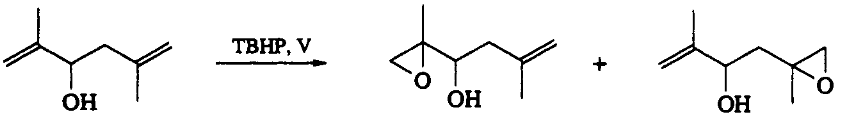

(54)

**(156)** **(157)** 87% **(158)** 13%

*erythro*:*threo* = 98:2

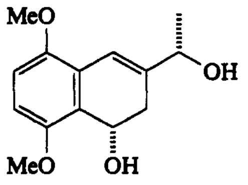

**(159)**

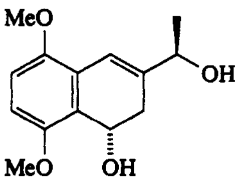

**(160)**

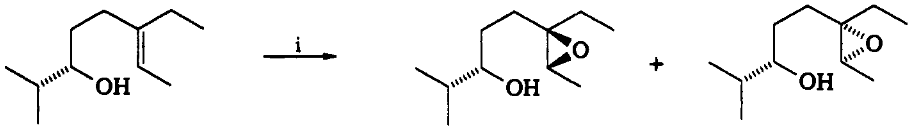

(55)

**(161)** 90% 10%

i, TBHP, VO(acac)$_2$, benzene, r.t.

The epoxy alcohol (**97**), a key intermediate in the synthesis of maytansine, has been prepared through Ti-catalyzed epoxidation of (**95**; equation 56).[65] The alcohol (**95**) exists predominantly in conformation (**162**), with the allylic hydrogen at C-4 and the π-bond very nearly eclipsed. The oxygens of the alcohol and silyl ether which are located below the plane of the π-bond complex with Ti; this complex blocks the approach of the epoxidizing reagent from the α-face and hence the β-epoxide is formed. It is of interest to note that the π-facial selectivity resulting from this route is the opposite of the π-facial selectivity observed in MCPBA epoxidation (see equation 33).

$$(\mathbf{95}) \xrightarrow[80\%]{\text{i}} \underset{99\%}{(\mathbf{97})} + \underset{1\%}{(\mathbf{96})} \qquad (56)$$

i, TBHP, Ti(OPr$^i$)$_4$, −20 °C, 11 h

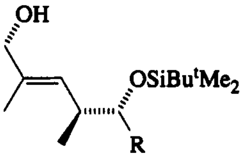

**(162)**

### 3.1.4 EPOXIDATIONS UTILIZING SILYL-PROTECTED PEROXY ESTERS

The regioselective intramolecular epoxidation of the peroxy ester (**163**), which can be prepared from farnesol, has been effected by treating it with $Cu(OCOCF_3)_2$ (equation 57).[104] This reaction provides a convenient route for the preparation of the 6,7-epoxide (**164**), which cannot be synthesized from farnesol by conventional methods or even by template-directed epoxidation using $Mo(CO)_6$/TBHP.

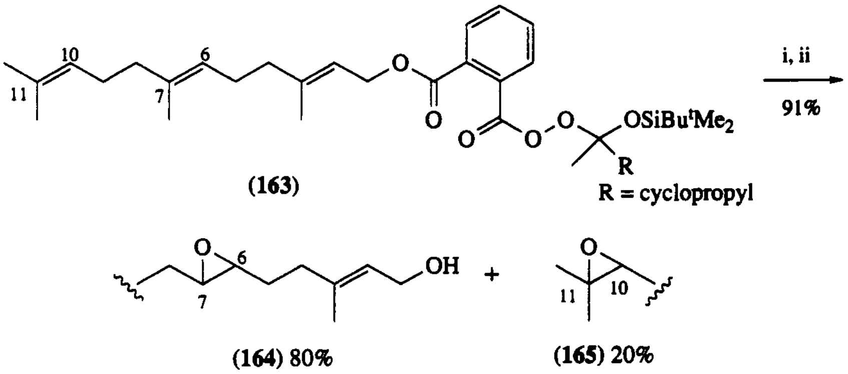

(57)

i, $Cu(OCOCF_3)_2$; ii, LiOH/aq. THF

### 3.1.5 EPOXIDATIONS WITH HYDROGEN PEROXIDE

Several acidic oxides such as $MoO_3$, $WO_3$ and compounds of selenium, arsenic and boron are effective catalysts for the epoxidation of alkenes by $H_2O_2$ through generation of inorganic peroxo acids, such as peroxoselenic and peroxoarsonic acids.[8]

When compared with Mo and V ions, tungsten ion induced $H_2O_2$ decomposition is very slow. Hence when peroxytungstic acid or peroxytungstates are employed as catalysts it is possible to carry out reactions on a large scale, employing strong $H_2O_2$ solutions and temperatures up to 70 °C. Allylic and *cis*-homoallylic alcohols can be efficiently epoxidized with $H_2O_2/WO_3$ as shown for the alcohol (**166**; equation 58).[105] The reaction is carried out in aqueous methanol at pH 4.5. The stereoselectivity of epoxidation is similar to that observed with TBHP/$V^{5+}$.

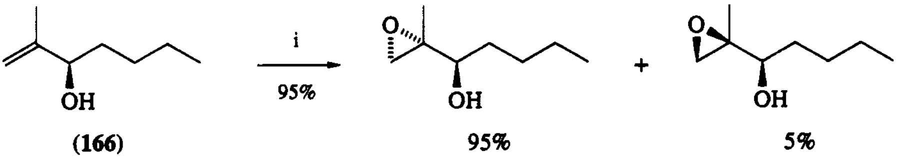

(58)

i, 30% $H_2O_2$, $H_2WO_4$, $Me_3NO$, r.t., 8 h

Under the experimental conditions used in the earlier epoxidation studies, $H_2O_2$ and the alkene to be oxidized are in the same phase. Since water reduces the rate of reaction and lowers the yield, it has to be removed continuously. Recently, it has been observed that epoxidations can be carried out, even with dilute $H_2O_2$, by employing a biphasic system. A quaternary phosphonium peroxotungstate catalyst has been used for the epoxidation of alkenes and allylic alcohols with 30% $H_2O_2$ (equation 59).[106] It has been observed that the pH of the reaction mixture remains close to 5–6 and there is no need to buffer the aqueous solution. The epoxidation proceeds in the organic phase where the phosphonium peroxotungstate enters because of the lipophilicity of the phosphonium moiety. Epoxidations have been carried out efficiently with 16% w/v $H_2O_2$ employing the (diperoxotungsto)phosphate catalyst (**168**) in a biphasic system (equation 60).[107]

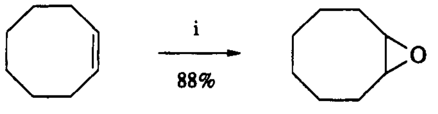

(59)

**(167)**

i, $(\mathrm{Ph_3\overset{+}{P}CH_2Ph})_2\,(\mathrm{W_2O_{11}})^{2-}$, 30% $H_2O_2$, 1,2-dichloroethane, 50 °C, 15 h

$[(\mathrm{C_8H_{17}})_3\overset{+}{\mathrm{N}}\mathrm{Me}]_3\,[\mathrm{PO_4\{W(O)(O_2)_2\}_4}]^{3-}$

**(168)**

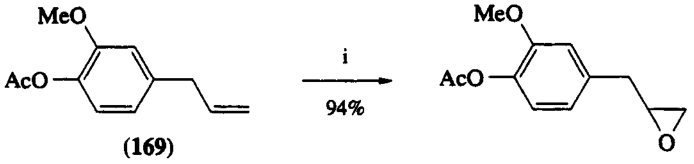

(60)

**(169)**

i, 1,2-dichloroethane, **(168)**, 16% $H_2O_2$, 60 °C, 150 min

### 3.1.6 STOICHIOMETRIC EPOXIDATIONS WITH Mo AND W PEROXO COMPLEXES

Epoxidations of triisopropylsilyl (TIS) ethers **(170)** and **(171)** with $WO_5$·HMPA in dichloroethane take place stereoselectively to furnish *syn*-epoxides;[99] these epoxidations, along with the vanadium-catalyzed epoxidations of **(152)** and **(153)** (described in Section 3.1.3.3), make available a group of all the four possible diastereoisomeric epoxides having four consecutive chiral centers in an acyclic carbon framework.

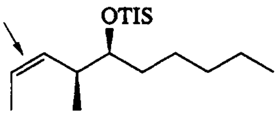

**(170)** (89, 94)

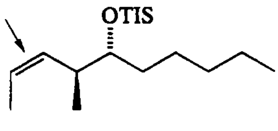

**(171)** (67, 88)

*cis*-2-Butene-1,4-diones are epoxidized by $MoO_5$·$H_2O$·HMPA. The diketone **(172)** furnishes the corresponding *cis*-epoxide when it is reacted with the molybdenum reagent in $CH_2Cl_2$ at room temperature for a week.[108] This is a rare example of epoxidation of an electron-deficient alkene by a $MoO_5$ complex.

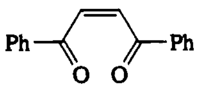

**(172)** (92)

### 3.1.7 EPOXIDATIONS *VIA* CATALYSIS BY FIRST-ROW TRANSITION METAL COMPLEXES

The observation that iron porphyrins can catalyze, under mild conditions, epoxidations of alkenes when iodosylbenzene is used as the oxidant has been followed up by a number of studies on metalloporphyrins as models for cytochrome *P*-450 enzymes. Cytochrome *P*-450 enzymes catalyze epoxidation of alkenes by molecular oxygen in the presence of a hydrogen donor, NADPH cofactor.[8] This has led to the study of a number of systems based on a metalloporphyrin/$O_2$/reducing agent, to bring about epoxidation of alkenes.

Cyclooctene has been epoxidized with oxygen using a manganese porphyrin as catalyst (equation 61).[109]

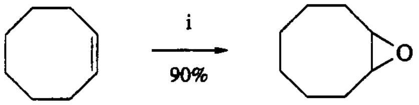

(61)

i, Mn(TPP)Cl, 1-methylimidazole, $O_2$, Zn, AcOH, 20 °C, 1 h
TPP = *meso*-tetraphenylporphyrin

Cobalt-catalyzed epoxidation of alkenes has been carried out with the cobalt derivative of (**174**), employing iodosylbenzene as the oxidant. Epoxidation of *cis*-β-methylstyrene furnishes exclusively the *cis*-epoxide (equation 62).[110] The reaction proceeds through an active oxo-cobalt(IV) species, and is more selective than reactions proceeding through oxo-chromium or oxo-manganese species. The catalyst can be recovered unchanged by simple filtration.

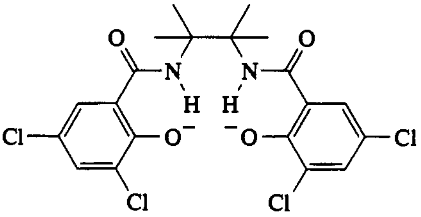

(**174**)

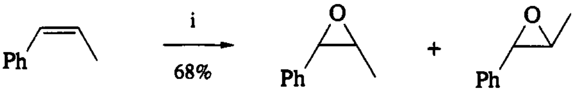

(62)

(**173**) 100% 0%

i, $Co^{II}(174)\cdot H_2O$, PhIO, $CH_2Cl_2$, r.t., 5 h

Epoxidation of the diene (**175**) with iodosylbenzene/$Fe^{II}$phthalocyanine is regio- and stereo-selective (equation 63).[111]

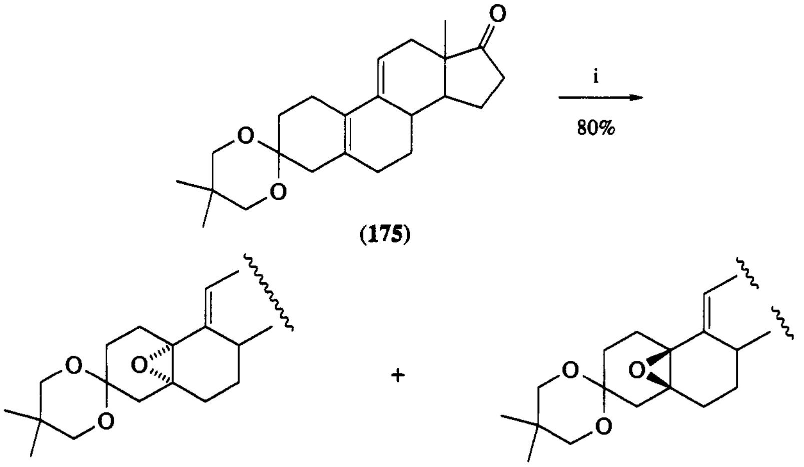

(**175**)

(63)

92% 8%

i, $Fe^{II}$ phthalocyanine, PhIO, MeCN

The applications of a wide variety of metal complexes in catalyzing the epoxidations of alkenes have been reviewed recently.[8]

### 3.1.8 EPOXIDATIONS USING OXYGEN

Ethylene oxide is manufactured by oxidizing ethylene with air or oxygen in the presence of a silver catalyst.[1] Alkenes furnish hydroperoxides when oxidized by oxygen in the presence of catalysts like salts of cobalt and manganese; the hydroperoxides are transformed to a number of products, including epoxides. Only in a few cases, such as oxidation of 1-phenylcyclooctene, have moderate yields of epoxides been obtained during autoxidation.[112]

Irradiation of an alkene in the presence of molecular oxygen and an α-diketone furnishes the corresponding oxirane in high yields. The reaction proceeds in the complete absence of nucleophiles, and thus can avoid formation of by-products arising from the reaction of nucleophiles with sensitive oxiranes.[2] The photoepoxidation proceeds *via* addition of an acylperoxy radical to the alkene.[113] Photochemical epoxidation of cholesteryl acetate (**176**) has been carried out (equation 64a);[114a] the major epoxidation product is the 5β,6β-epoxide (**177a**). In MCPBA epoxidation of (**176**) the major product is (**177b**).

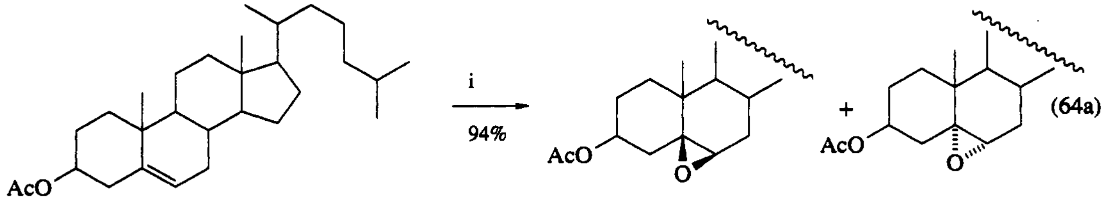

(64a)

(**176**) (**177a**) 70% (**177b**) 30%

i, biacetyl, $O_2$, *h*ν

The thermal rearrangement of unsaturated bicyclic 1,4-peroxides, readily available from the reaction of conjugated dienes with singlet oxygen, is a convenient route for the preparation of bisepoxides.[1]

Epoxidation of cholesteryl acetate (**176**) with air in the presence of a catalytic amount of dioxo(tetramesitylporphyrinato)ruthenium(VI) furnishes in 85% yield a 99:1 mixture of the epoxides (**177a**) and (**177b**).[114b]

Epoxy alcohols have been synthesized by carrying out the photooxygenation of alkenes in the presence of the transition metal complexes derived from Ti, V and Mo (for an example see equation 64b).[114c] The hydroperoxides formed from alkenes during the photooxygenation function as oxygen transfer reagents and precursors for the allylic alcohol intermediates.

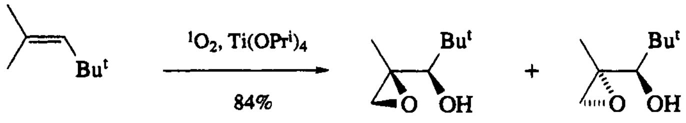

(64b)

(**178**) 5% 95%

### 3.1.9 CHEMOSELECTIVE EPOXIDATIONS

Chemoselective epoxidations of many alkenes carrying functional groups such as hydroxy, ether, ester, amide and ketone have been presented in this chapter. Chemoselective epoxidations of a few functionalized alkenes have proved difficult, but by using appropriate reagents and strategies the difficulties have been overcome. Some examples are given below.

When the unsaturated tertiary amine, pirprofen (**179**; R = H) is treated with MCPBA the reaction takes place selectively at the more nucleophilic nitrogen to furnish the corresponding amine oxide with the alkene moiety intact. In contrast, peroxycarboximidic acid, prepared *in situ* from acetonitrile/$H_2O_2$, reacts selectively with the alkene moiety of the ester (**179**; R = Me; equation 65).[115] The sterically hindered nitrogen of (**179**) is able to react with peroxy acids which have a low steric demand, but not with peroxycarboximidic acids which have a large steric demand.

To prevent *N*-oxide formation the tertiary nitrogen of (**181**) is blocked by protonation. The salt prepared from trifluoroacetic acid and (**181**) is epoxidized with $CF_3CO_3H$; work-up of the reaction mixture furnishes the epoxide (**182**; equation 66).[116]

Sulfides are readily oxidized by peroxy acids as well as TBHP/Mo. Hence the chemoselective epoxidation of the unsaturated sulfide (**183**) has been effected by an indirect method; the alkene is first trans-

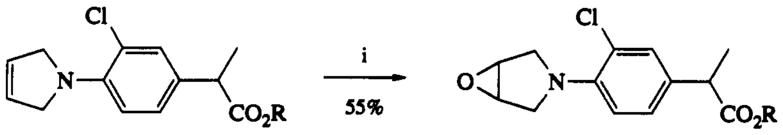

(65)

**(179)** R = Me **(180)**

i, $H_2O_2$, MeCN, MeOH, $KHCO_3$, pH 7.5–8.0

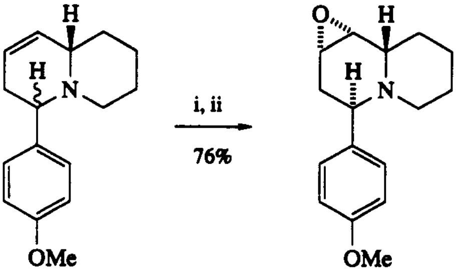

(66)

**(181)** **(182)**

i, $CF_3CO_2H$; ii, $CF_3CO_3H$

formed to a bromohydrin which is then treated with a base to furnish (**184**).[117] It has been suggested that unsaturated sulfides can be epoxidized chemoselectively using the photochemical epoxidation route, since under these experimental conditions sulfides remain unchanged.[113]

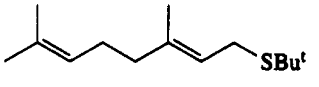

**(183)**

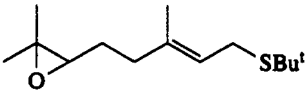

**(184)**

Cyclobutanones are susceptible to Baeyer–Villiger oxidation. The epoxide (**186**) cannot be prepared by reacting the ketoalkene (**185**; equation 67) with MCPBA. Moderate, chemoselective epoxidation has been observed in the reaction of (**185**; equation 68) with *O*-trichloroethylperoxycarbonic acid (**190**) prepared *in situ* from the triazole (**189**) and $H_2O_2$.[118]

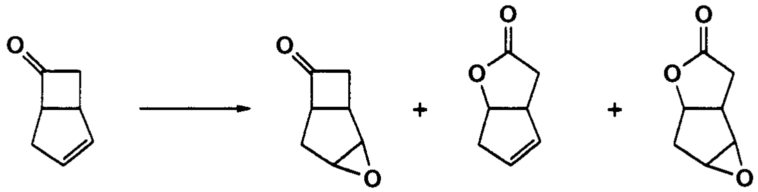

| **(185)** | **(186)** | **(187)** | **(188)** | |
|---|---|---|---|---|
| MCPBA | 1% | 96% | 3% | (67) |
| (189)/$H_2O_2$ | 31% | 28% | 41% | (68) |

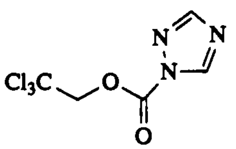

**(189)**

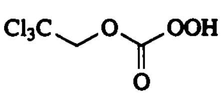

**(190)**

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# 3.2

# Addition Reactions with Formation of Carbon–Oxygen Bonds: (ii) Asymmetric Methods of Epoxidation

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## 3.2.1 INTRODUCTION

Alkenes are found in abundance in the realm of organic molecules, either derived from natural sources or generated as products of the chemical industry. Epoxidation is one of the most useful oxidative transformations of these alkenes and the reagents that have been developed for this process have a high degree of selectivity for the alkenic bond. Epoxidation functionalizes two adjacent carbon atoms while simultaneously activating either of these carbons towards attack by nucleophiles. If the epoxide is unsymmetrically substituted, regioselectivity in the attack of a nucleophile on the oxirane ring will be observed. Only when very similar substituents are present on the epoxide will selectivity of nucleophilic attack be difficult to achieve. A further advantage of an epoxide as an electrophilic intermediate is the fact that competing elimination reactions are rendered stereoelectronically unfavorable by the constraints of the cyclic structure. Whereas nucleophilic substitution at secondary carbon in larger cyclic or in acyclic systems is accompanied by significant elimination and is impossible at tertiary carbon, substitution at secondary or tertiary centers of epoxides is relatively free of competing elimination processes.

With chemoselectivity available in epoxidation reagents and regioselectivity inherent in the opening reactions of many epoxides, there remains the challenge of achieving epoxidation with asymmetric induction. The development of peracids as a standard method for epoxidation (see Volume 7, Chapter 3.1) led to an initial attempt in 1965 by Henbest to achieve asymmetric epoxidation using homochiral (enantiomerically pure) percamphoric acid.[1] Asymmetric induction was observed but the enantiomeric excess (*ee*) was a disappointing 8%. In retrospect, one can see that the stereogenic center of the peracid is far removed from the electrophilic peroxygen and that a low degree of asymmetric induction should not be surprising for this reaction. A brief, but thorough, review of the fitful progress over the following 15 years towards the goal of a synthetically useful asymmetric epoxidation has been recorded elsewhere,[2] while selected highlights of newer methods are described in a later section of this chapter.

In 1980, Katsuki and Sharpless reported that with the unique combination of a titanium(IV) alkoxide, an optically active tartrate ester, and *t*-butyl hydroperoxide, they were able to carry out the epoxidation of a variety of allylic alcohols in good yield and with an enantiomeric excess generally greater than 90%.[3] Subsequent improvements in the reaction have been described[4] and the frequent use of the process as reported in the literature attest to its wide generality and utility. Since, to date, this method provides the most successful general solution to the problem of asymmetric epoxidation, the present chapter deals primarily with this titanium-catalyzed process. A variety of other reagents which yield asymmetric epoxides are summarized briefly. A new approach to asymmetric epoxides proceeding *via* diols, currently at an early stage of development, is also outlined.

The literature has been reviewed through 1989 for the purposes of preparing this chapter but the documentation herein is not intended to be comprehensive. Other reviews have covered various aspects of asymmetric epoxidation including synthetic applications through 1984,[5,6] a thorough compilation of uses through early 1987[7] and an extensive discussion of the mechanism of the reaction.[2] Use of homochiral epoxy alcohols in the synthesis of polyhydroxylated compounds, *e.g.* sugars,[8,9] and for the preparation of various synthetic intermediates has been reviewed.[10] A personal account of the discovery of titanium-catalyzed asymmetric epoxidation has been recorded.[11] A comprehensive review of titanium-catalyzed asymmetric epoxidation is planned.[12]

## 3.2.2 FUNDAMENTAL ELEMENTS OF TITANIUM TARTRATE CATALYZED ASYMMETRIC EPOXIDATION

The essence of titanium-catalyzed asymmetric epoxidation is illustrated in Figure 1. As shown there, the four essential components of the reaction are the allylic alcohol substrate, a titanium(IV) alkoxide, a chiral tartrate ester and an alkyl hydroperoxide. The asymmetric complex formed from these reagents delivers the peroxy oxygen to one face or the other of the allylic alcohol depending on the absolute configuration of the tartrate used. If D-(−)-tartrate is used, oxygen delivery will be from the top face of the allylic alcohol, when drawn in the orientation shown in Figure 1, and if L-(+)-tartrate is used, oxygen delivery will be from the bottom face. The enantioselectivity of this reaction approaches 100% as measured by the optical purities (% *ee*) of the epoxy alcohol products. An enantiomeric excess of 94%, a degree of optical purity attained in many of the epoxide products, reflects an enantioselectivity of 97:3 for epoxidation of one face of the allylic alcohol over the other.

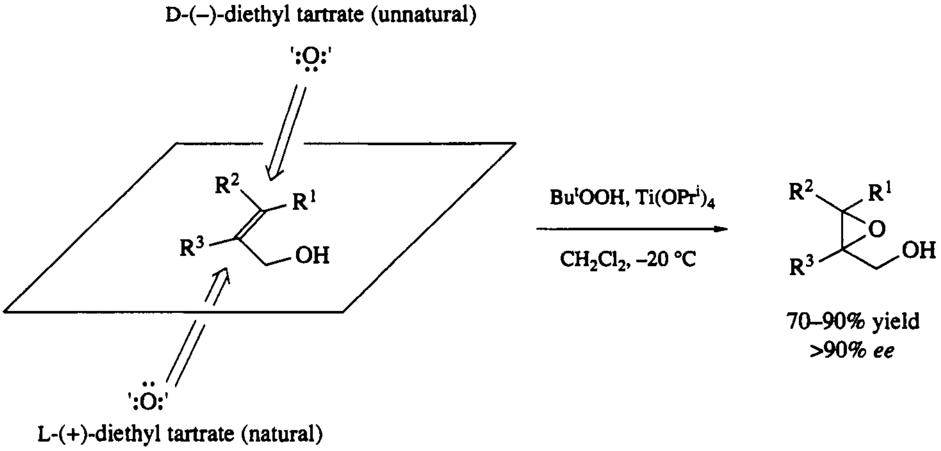

**Figure 1** Enantiofacial selectivity in the epoxidation of prochiral allylic alcohols with titanium/tartrate/TBHP

The enantioselectivity principles portrayed in Figure 1 have been followed without exception in all epoxidations of prochiral allylic alcohols reported to date. More than 300 prochiral allylic alcohols had been subjected to asymmetric epoxidation by the end of 1989. From this experience and a better understanding of the reaction mechanism, it is now safe to use the enantioselectivity principles portrayed in Figure 1 to assign absolute configurations to the epoxy alcohols prepared by the method. On the other hand, epoxidation of allylic alcohols with chiral substituents at C-1, C-2 and/or C-3 does not always follow these principles and assignment of absolute configuration to the products must be made with care. Even in the latter cases, reliable assignments can usually be made if the outcome (diastereomeric ratio) of epoxidation with both the (+)- and (−)-tartrate ester ligands is compared.

A structural variant of the allylic alcohol not shown in Figure 1 is encountered when a substituent is placed on the C-1 carbon, as illustrated in Figure 2. Such an allylic alcohol is a racemate (unless it has been previously resolved) in which one enantiomer will have the R group oriented in the direction of oxygen delivery, while the other enantiomer will have the R group oriented away from the direction of oxygen delivery. The enantioselective principles of asymmetric epoxidation remain in force for epoxidation of this type of substrate, but now oxygen is delivered at different rates to the two enantiomers depending on the orientation of the R group. Experimental results have shown that the difference in these rates is of sufficient magnitude that one enantiomer of the allylic alcohol will remain largely unoxidized while the other undergoes complete epoxidation, the net result being that a kinetic resolution of the enantiomers is achieved.[13] Experience has further shown that the slow-reacting enantiomer will always be the one having the R group oriented in the direction of oxygen delivery. For the example illustrated in Figure 2, the titanium/D-(−)-diethyl tartrate complex will deliver oxygen to the top face in preference to the bottom face of the substrate, in accordance with the rules implied in Figure 1, and this delivery will be more rapid when the R group is oriented toward the bottom face of the molecule. Opposite results will be obtained with the titanium/L-(+)-diethyl tartrate complex. Additional details for using this reaction in the kinetic resolution mode may be found in Section 3.2.5.9.

An important aspect of asymmetric epoxidation which is not apparent from Figures 1 and 2 is the fact that the allylic alcohol is coordinated to titanium as the alkoxide during the epoxidation process (see Section 3.2.6). Not only does this coordination play a key role in orientation of the allylic alcohol during the epoxidation process, but it also accounts for the selectivity of the process for allylic and homoallylic alcohols in preference to nearly all other alkenes. This effect is most clearly seen in comparison of allylic alcohols with the analogous allylic ethers. The latter are essentially unchanged by the $Ti(OR)_4$/tartrate/TBHP system during the same time required for epoxidation of the allylic alcohol. The $Ti(OR)_4$/tartrate/TBHP reagent thereby exhibits selectivity for allylic and homoallylic alcohols while being

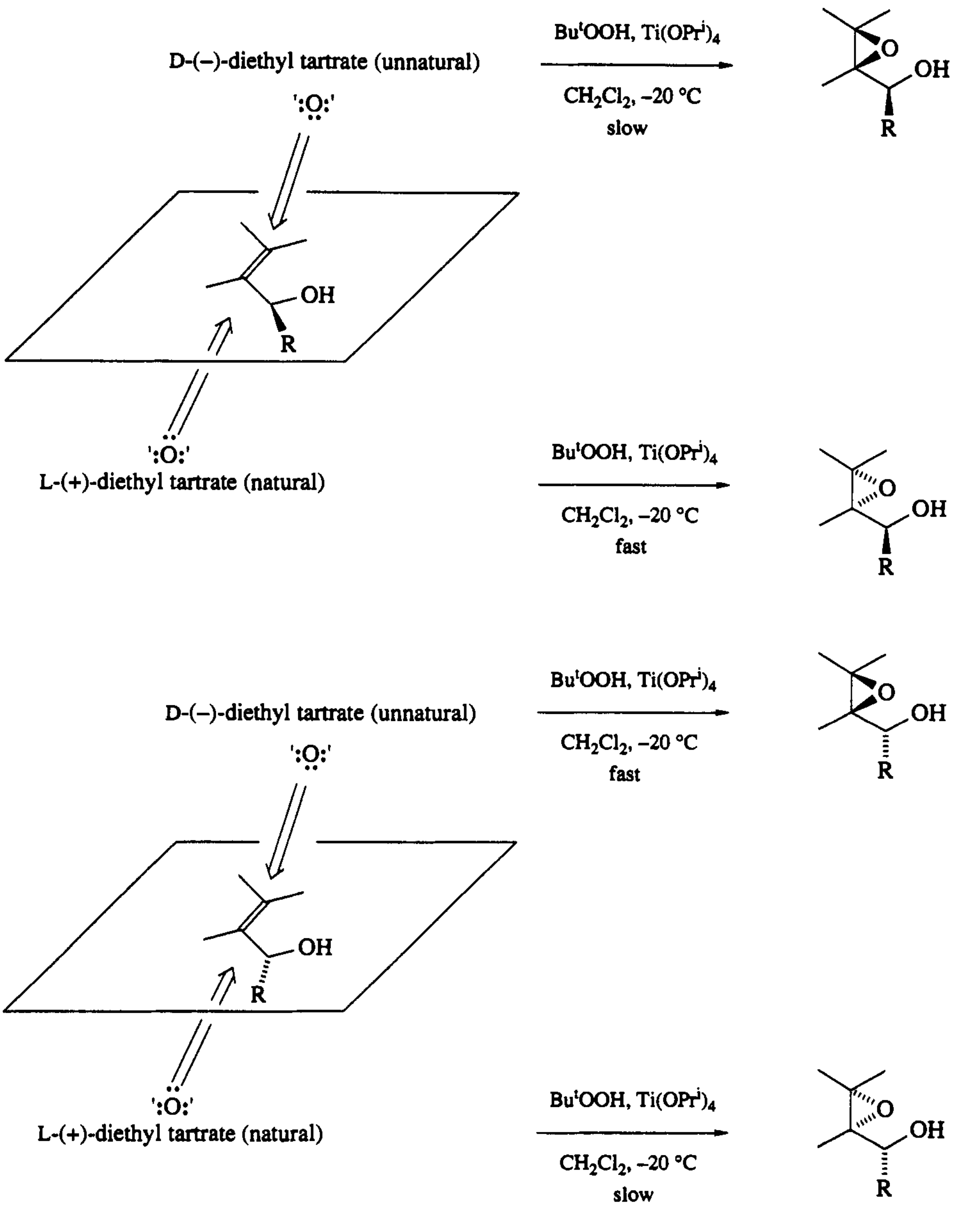
D-(−)-diethyl tartrate (unnatural)
':O:'
Bu$^t$OOH, Ti(OPr$^i$)$_4$
CH$_2$Cl$_2$, −20 °C
slow
O
OH
R
OH
R
':O:'
L-(+)-diethyl tartrate (natural)
Bu$^t$OOH, Ti(OPr$^i$)$_4$
CH$_2$Cl$_2$, −20 °C
fast
O
OH
R
D-(−)-diethyl tartrate (unnatural)
':O:'
Bu$^t$OOH, Ti(OPr$^i$)$_4$
CH$_2$Cl$_2$, −20 °C
fast
O
OH
R
OH
R
':O:'
L-(+)-diethyl tartrate (natural)
Bu$^t$OOH, Ti(OPr$^i$)$_4$
CH$_2$Cl$_2$, −20 °C
slow
O
OH
R

**Figure 2** Diastereofacial selectivity in the epoxidation of C-1—substituted allylic alcohols with titanium/tartrate/TBNP

**Table 1** Compatibility of Functional Groups with the Asymmetric Epoxidation Reaction

| *Compatible functional groups* | | *Incompatible groups* |
|---|---|---|
| Acetals, ketals | Ketones | Amines (most) |
| Alcohols (remote) | Nitriles | Carboxylic Acids |
| Aldehydes | Nitro | Thiols |
| Alkenes | Pyridines | Phenols (most) |
| Alkynes | Silyl ethers | Phosphines |
| Amides | Sulfones | |
| Azides | Sulfoxides | |
| Carboxylic esters | Tetrazoles | |
| Epoxides | Ureas | |
| Ethers | Urethanes | |
| Hydrazides | | |

compatible with other alkenic groups. Use of the reagent is compatible with many other functional groups as well (see Table 1).

An important improvement in the asymmetric epoxidation process is the finding, reported in 1986, that by adding molecular sieves to the reaction medium virtually all reactions can be performed with a catalytic amount (5–10 mol%) of the titanium tartrate complex.[14] Previously, only a few structural classes of allylic alcohols were efficiently epoxidized by less than stoichiometric amounts of the complex and most reactions were routinely performed with stoichiometric quantities of the reagent. The advantages of using a catalytic amount of complex include reagent economy, mildness of conditions, ease of isolation, increased yields and the potential for *in situ* derivatization of the product. However, there may be occasions where the use of stoichiometric quantities of the catalytic complex is necessary.

*In situ* derivatization of the crude epoxy alcohol product becomes a viable alternative to isolation when 5–10 mol % of catalyst is used for the epoxidation. This procedure is especially useful in those cases where the product is reactive or is difficult to isolate because of solubility in an aqueous extraction phase.[15,16] Low molecular weight epoxy alcohols, such as glycidol (see Section 3.2.5.1), are readily extracted from the reaction mixture after conversion to ester derivatives such as the 4-nitrobenzoate or 3-nitrobenzenesulfonate.[4,17] This derivatization not only facilitates isolation of the product but also preserves the epoxide in a synthetically useful form.

## 3.2.3 REACTION VARIABLES FOR TITANIUM TARTRATE CATALYZED ASYMMETRIC EPOXIDATION

This section presents a summary of the currently preferred conditions for performing titanium-catalyzed asymmetric epoxidations and is derived primarily from the detailed account of Gao *et al.*[4] We wish to draw the reader's attention to several aspects of the terminology used here and throughout this chapter. The terms titanium tartrate *complex* and titanium tartrate *catalyst* are used interchangeably. The term *stoichiometric reaction* refers to the use of the titanium tartrate complex in a stoichiometric ratio (100 mol %) relative to the substrate (allylic alcohol). The term *catalytic reaction* (or *quantity*) refers to the use of the titanium tartrate complex in a catalytic ratio (usually 5–10 mol %) relative to the substrate.

### 3.2.3.1 Stoichiometry

Two aspects of stoichiometry are important in an asymmetric epoxidation: one is the ratio of titanium to tartrate used for the catalyst and the other is the ratio of catalyst to substrate. With regard to the catalyst, it is crucial to obtaining the highest possible enantiomeric excess that at least a 10% excess of tartrate ester to titanium(IV) alkoxide be used in all asymmetric epoxidations. This is important when the reaction is being done with either a stoichiometric or a catalytic quantity of the complex. There appears to be no need to increase the excess of tartrate ester beyond 10–20% and, in fact, a larger excess has been shown to slow the epoxidation reaction unnecessarily.[4]

The second stoichiometry consideration is the ratio of catalyst to substrate. As noted in the previous section, virtually all asymmetric epoxidations can be performed with a catalytic amount of titanium tartrate complex if molecular sieves are added to the reaction milieu. A study of catalyst–substrate ratios in the epoxidation of cinnamyl alcohol revealed a significant loss in enantiomeric excess (Table 2) below the level of 5 mol % catalyst. At this catalyst level, the reaction rate also decreases with the consequence that incomplete epoxidation of the substrate may occur. Presently, the recommended catalyst stoichiometry is from 5% Ti/6% tartrate ester to 10% Ti/12% tartrate ester.[4]

**Table 2** Dependence of Enantiomeric Excess on Catalyst Stoichiometry

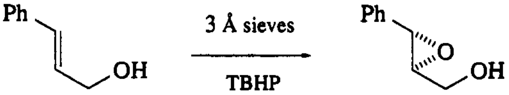

| *Entry* | *Ti(OPr$^i$)$_4$* (mol %) | *(+)-DIPT* (mol %) | *Enantiomeric excess* (%) |
|---|---|---|---|
| 1 | 5.0 | 6.0 | 92 |
| 2 | 4.0 | 5.2 | 87 |
| 3 | 2.0 | 2.5 | 69 |

### 3.2.3.2 Concentration

The concentration of substrate used in the asymmetric epoxidation must be given consideration because competing side reactions may increase with increased reagent concentration. The use of catalytic quantities of the titanium tartrate complex has greatly reduced this problem. The epoxidation of most substrates under catalytic conditions may be performed at a substrate concentration up to 1 M. By contrast, epoxidations using stoichiometric amounts of complex are best run at substrate concentrations of 0.1 M or lower. Even with catalytic amounts of the complex, a concentration of 0.1 M may be maximal for substrates, such as cinnamyl alcohol, which produce sensitive epoxy alcohol products.[4]

### 3.2.3.3 Preparation and Aging of the Catalyst

Proper preparation of the catalyst is essential for optimal reaction rates and enantioselectivity. The preparation and storage of stock solutions of the titanium tartrate catalyst should not be attempted as the complex is not sufficiently stable for long term storage. Best results are obtained when the catalyst is prepared by mixing the titanium(IV) alkoxide and the tartrate in a solvent at –20 °C, adding either TBHP *or* the allylic alcohol, and aging the system at this temperature for 20–30 min. This aging period is critical to the success of the reaction and must not be eliminated. On the rare occasion that a bulky titanium(IV) alkoxide such as the *t*-butoxide is used, the aging period should be increased to 1 h.[18] After the aging period, the temperature is adjusted to the desired level and the last reagent, either the allylic alcohol or the hydroperoxide, is added.

### 3.2.3.4 Oxidant and Epoxidation Solvent

*t*-Butyl hydroperoxide (TBHP) is used as the oxidant for nearly all titanium-catalyzed asymmetric epoxidations. Exceptions are for allyl alcohol and methallyl alcohol, where cumyl hydroperoxide is used to advantage for the epoxidation.[4] Cumyl hydroperoxide can be used for other epoxidations and is reported to result in slightly faster reaction rates than are observed with TBHP.[4] Trityl hydroperoxide also can serve as an effective replacement for TBHP.[2] TBHP is generally preferred, however, since product isolation is significantly easier when this oxidant is used. The most economical source of TBHP is the commercially available 70% solution in water, in which case steps must be taken to obtain anhydrous material. The detailed instructions for obtaining dry solutions of TBHP have been published elsewhere.[4,14] For smaller laboratory scale reactions, anhydrous solutions of TBHP in 2,2,4-trimethylpentane (isooctane) are available commercially. Storage of TBHP solutions over molecular sieves is not recommended, but brief drying over sieves (*ca.* 30 min) of the required amount of the solution just before use is good practice.

Since the preparation and storage of stock quantities of TBHP is a convenient way in which to deal with this reagent, compatibility with solvent is essential. Much care has gone into finding the optimum solvent for storage of TBHP and recommendations have changed as additional experience has been gained. The current solvent of choice is isooctane with the favored alternatives being dichloromethane or toluene.[4] Dichloroethane should not be used.[19] Dichloromethane solutions of TBHP require storage at 0 °C and toluene solutions occasionally develop a contaminant which inhibits the catalytic reaction. Due to safety considerations (chance of slight pressurization), high density polyethylene bottles are preferred over glass bottles for storage of TBHP solutions. However, both dichloromethane and toluene, but not isooctane, permeate through such bottles with the result that the concentration of the contents slowly changes with time. If the published instructions[4,14] for preparation of anhydrous TBHP in isooctane are followed, a relatively concentrated solution (5–6 M) is obtained. Aliquots of this solution are briefly dried over sieves and added directly to the epoxidation reaction without concern for removal of the isooctane. The use of dilute solutions of TBHP in isooctane (*e.g.* 3 M TBHP is too dilute) should be avoided since the additional isooctane involved in transfer will have an inhibitory effect on the rate of epoxidation and can lead to solubility problems with some substrates. Solutions of 5.5 M TBHP in isooctane now are available commercially.

For the asymmetric epoxidation reaction, dry, alcohol-free dichloromethane (the use of dichloromethane stabilized with methanol must be avoided) is usually the solvent of choice since it is inert to the reagents, has good solvent power for the components of the reaction and supports good epoxidation rates. A fortunate consequence of the asymmetric epoxidation process is that ligation of the allylic alcohol to the titanium center aids in solubilization of the substrate. Substrates that normally may only be modestly soluble in the above-mentioned solvents will be brought into solution as they complex with the titanium tartrate catalyst.

### 3.2.3.5 Tartrate Esters

Optically active tartrate esters are the source of chirality for the asymmetric epoxidation process. The esters used conventionally are dimethyl (DMT), diethyl (DET) and diisopropyl tartrate (DIPT), and, with a few subtle exceptions, all are equally effective at inducing asymmetry during the crucial epoxidation event. The minor exceptions that have been noted include: (i) a slight improvement in enantioselectivity (from 93% to 95% *ee*) when changing from DIPT to DET in the epoxidation of (*E*)-monosubstituted allylic alcohols such as (*E*)-2-hexen-1-ol (having only a primary alkyl chain at C-3); and (ii) a higher product yield (but no change in enantiomeric excess) when changing from DET to DIPT in the epoxidation of allyl alcohol.[4] Other subtle variations such as these may exist but their discovery awaits execution of the appropriate comparative experiments. If optimal conditions are desired for a specific asymmetric epoxidation, then variation of the tartrate ester is likely to be a useful exercise.

In the kinetic resolution of chiral 1-substituted allylic alcohols, there clearly is benefit to be gained in the choice of tartrate ester used for the reaction. In these reactions (see Section 3.2.5.9), the efficiency of kinetic resolution increases as the size of the tartrate alkyl ester group increases. Data for DMT, DET and DIPT are summarized in Table 8,[2] and the trend shown there continues with the use of the crystalline dicyclohexyl and dicyclododecyl tartrates.[4]

The nonconventional tartrate esters (1) to (3) have been used to probe the mechanism of the asymmetric epoxidation process.[20a] These chain-linked bis(tartrate) molecules when complexed with 2 equiv. of $Ti(OBu^t)_4$ catalyze asymmetric epoxidation with good enantiofacial selectivity. A number of tartrate-like ligands have been studied as potential chiral auxiliaries in the asymmetric epoxidation and kinetic resolution processes.[2,20b] Although on occasion a ligand has been found that has the capability to induce high enantioselectivity into selected substrates (see Section 3.2.7.3), none has exhibited the broad scope of effectiveness seen with the tartrate esters.

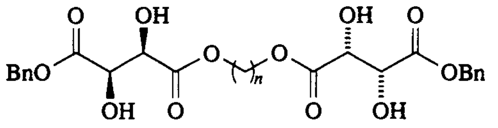

(1) $n = 3$
(2) $n = 4$
(3) $n = 5$

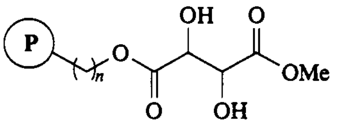

(4) $n = 1$
(5) $n = 2$

Polymer-linked tartrate esters have been prepared and used for asymmetric epoxidation in efforts to simplify reaction work-up procedures and to allow recycling of the chiral tartrate.[21] The tartrates are linked through an ester bond to either a hydroxymethyl or a hydroxyethyl group on the polymer backbone to form (4) or (5), respectively. Epoxidation catalysts were prepared from these polymer-linked tartrates by combination with 0.5 equiv. of $Ti(OPr^i)_4$, based on the weight of tartrate ester which had been added to the polymer. Epoxidation of geraniol with (4) or (5) gave the epoxy alcohol with enantiomeric excesses of 49% and 65%, respectively. Recycling of the polymer-linked tartrate was possible but the subsequent epoxidation suffered from significant loss in enantiomeric excess.[21]

### 3.2.3.6 Titanium Alkoxides

Titanium(IV) isopropoxide (*Chemical Abstracts* nomenclature: 2-propanol, titanium(4+) salt) is the titanium species of choice for preparation of the titanium tartrate complex in the asymmetric epoxidation process. The use of titanium(IV) *t*-butoxide has been recommended for those reactions in which the epoxy alcohol product is particularily sensitive to ring opening by the alkoxide.[18] The 2-substituted epoxy alcohols (Section 3.2.5.2) are one such class of compounds. Ring opening by *t*-butoxide is much slower than by isopropoxide. With the reduced amount of catalyst that now is needed for all asymmetric epoxidations, the use of $Ti(OBu^t)_4$ appears to be unnecessary in most cases, but the concept is worth noting.

### 3.2.3.7 Molecular Sieves

The addition of activated molecular sieves (zeolites) to the asymmetric epoxidation milieu has the beneficial effect that virtually all reactions can be carried out with only 5–10 mol % of the titanium tartrate catalyst.[4,14] Without molecular sieves, only a few of the more reactive allylic alcohols are epoxidized efficiently with less than an equivalent of the catalyst. The role of the molecular sieves is thought to be protection of the catalyst from adventitious water and water that may be generated in small amounts by side reactions during the epoxidation process.

There are several important guidelines to be followed in using activated molecular sieves for the asymmetric epoxidation process.[4] Stock solutions of TBHP should not be stored over molecular sieves (the sieves catalyze slow decomposition of TBHP), but the amount of TBHP solution required for a reaction should be placed over sieves briefly (10–60 min) before use. Likewise, neither the tartrate ester nor the titanium(IV) isopropoxide should be stored over sieves. Addition of the sieves at the time of mixing the tartrate ester with the $Ti(OPr^i)_4$ followed by the normal aging of the catalyst is sufficient to dry these reagents, provided they initially are of good quality (see ref. 4, p. 5771). The use of powdered, activated 4 Å molecular sieves is preferred and they are commercially available in preactivated form. Also effective are 3 Å, 4 Å and 5 Å molecular sieves in pellet form. In the case of allyl alcohol only 3 Å sieves are effective since this substrate is small enough to be sequestered by 4 Å or 5 Å sieves. Unactivated sieves can be activated by heating at 200 °C under high vacuum for at least 3 h.

## 3.2.4 SOURCES OF ALLYLIC ALCOHOLS

One of the amenities of present day organic synthesis is the availability of intermediates from the many chemical supply companies. Over 100 allylic alcohols (excluding extensive listings of phorbol esters and prostaglandin structures) are offered for sale from these sources. Two concerns about such supplies should be noted, the first being the desirability to check the (*E*)/(*Z*) composition of acyclic allylic alcohols when this is not specified, and the second is to check the optical purity of those allylic alcohols offered in optically active form.

When the allylic alcohol needed for asymmetric epoxidation is unavailable from a commercial source, reasonably general synthetic routes have been developed to allylic alcohols of several different substitution patterns. Good methods are available for the preparation of 3-substituted allylic alcohols, whereas synthesis of 2-substituted allylic alcohols is more problematic. 1-Substituted allylic alcohols, the substrates for kinetic resolution, frequently can be derived by addition of alkenyl or alkynyl organometallic reagents to aldehydes followed by modification of the resulting product as required.

The Horner–Emmons addition of dialkyl alkoxycarbonylmethylenephosphonates to aldehydes[22] has been widely used to generate α,β-unsaturated esters which, in turn, can be reduced to allylic alcohols. Under the original conditions of the Horner–Emmons reaction, the stereochemistry of the α,β-unsaturated ester is predominantly *trans*, and therefore the *trans*-allylic alcohol is obtained upon reduction. Still and Gennari have introduced an important modification of the Horner–Emmons reaction which shifts the stereochemistry of the α,β-unsaturated ester to predominantly *cis*.[23] Diisobutylaluminum hydride (DIBAL) has frequently been used for the reduction of the alkoxycarbonyl group to the primary alcohol functionality. The aldehyde needed for reaction with the Horner–Emmons reagent may be derived *via* Swern oxidation[24] of a primary alcohol. The net result is that one frequently sees the reaction sequence shown in equation (1) used for the preparation of (3*E*)- and (3*Z*)-allylic alcohols.

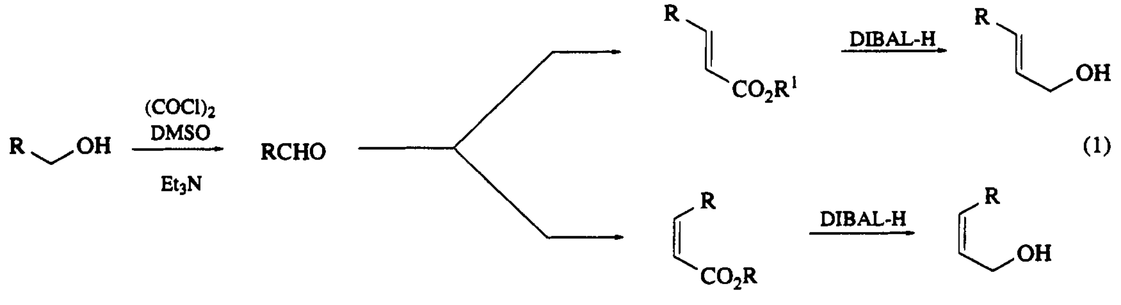

(1)

The propargylic alcohol group may be exploited as an allylic alcohol precursor (equation 2) and may be generated by nucleophilic addition to an electrophile[25] or by addition of a formaldehyde equivalent to a preexisting terminal alkyne group.[26] Once in place, reduction of the propargylic alcohol with lithium aluminum hydride or, preferably, with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[27] will produce the *trans*-allylic alcohol. Alternately, catalytic reduction over Lindlar catalyst can be used to obtain the *cis*-allylic alcohol.[28] The addition of other lithium alkynides to ketones produces chiral secondary alcohols which also can be reduced by the preceding methods to the *cis*- or *trans*-allylic alcohols. Additional synthetic approaches to allylic alcohols may be found in the various references cited in this chapter.

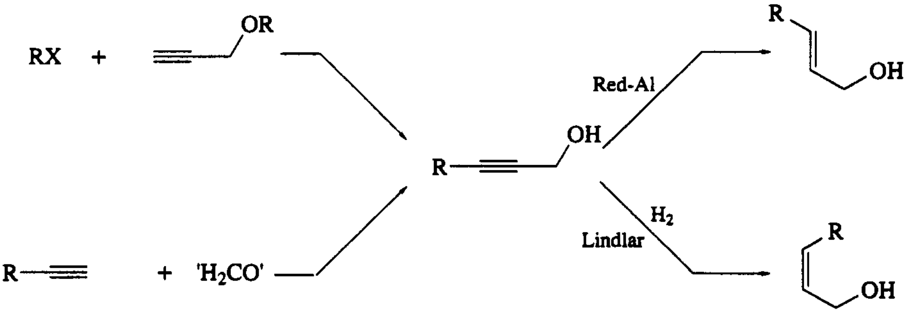

(2)

### 3.2.5 ASYMMETRIC EPOXIDATIONS BY SUBSTRATE STRUCTURE

The scope of allylic alcohol structures which are subject to asymmetric epoxidation was foreshadowed in the first report of this reaction. Examples of nearly all of the possible substitution patterns have been shown to be epoxidized in good yield and with high enantiofacial selectivity.[3] The numerous results that have appeared since the initial report have confirmed and extended the scope of the structures that have been epoxidized. This section of the chapter is intended to illustrate the structural scope without being exhaustive in coverage of the literature. Examples have been chosen as much as possible from those reports in the literature which provide experimentally determined yield and enantiomeric excess data. When there are limitations to the structural scope, as reflected by lower enantiofacial selectivity, these cases are noted. The results presented in this section are divided according to the substitution patterns of the allylic alcohol substrates. This organization is intended to provide easy access to precedent when the synthetic chemist is contemplating asymmetric epoxidation of a new substrate.

Before commencing, the attention of the reader is drawn to our usage of the terms enantiofacial selectivity and diastereoselectivity. The usage in this chapter does not conform to the strictest possible definitions of these terms. In particular, enantiofacial selectivity is used with reference to the selection and delivery of oxygen by the epoxidation catalyst to one face of the alkene in preference to the other. This usage extends to chiral allylic alcohols (primarily the 1-substituted allylic alcohols) when the focus of the discussion is on face selection in the epoxidation process. Diastereoselectivity is used in the discussion of kinetic resolution, when the generation of diastereomeric compounds is emphasized.

#### 3.2.5.1 Allyl Alcohol

Glyceraldehyde derivatives,[29] asymmetrically substituted glycerol[30] and glycidol[31] are three-carbon molecules which, especially in their optically active forms, find widespread use in organic synthesis. In the past, the source of these compounds in optically active form has been almost exclusively from the degradation of natural products such as mannitol. Efficient, multistep routes from the natural products provide access to either enantiomer of these three-carbon compounds. Since the discovery of asymmetric epoxidation in 1980, the potential has existed for a convenient one-step synthesis of optically active glycidol (7) from allyl alcohol (6).[3] However, because glycidol is one of the more sensitive epoxy alcohols to ring-opening reactions and also is a water soluble molecule, isolation from the stoichiometric asymmetric epoxidation is difficult and very little glycidol has been prepared in this way. Now with the use of catalytic epoxidation in the presence of molecular sieves, it is possible to isolate optically active glycidol of 88–92% *ee* in yields of 50–60%.[4] As a result of these improvements both enantiomers of glycidol are now available commercially.

An attractive alternative to isolation of glycidol is *in situ* derivatization of the crude product during work-up.[15] Two distinct applications of this method have been described. In the first, ring opening of glycidol (*R*)-(7) with a nucleophile such as sodium 1-naphthoxide produces an intermediate (8) that can be carried on to useful products, *e.g.* for the synthesis of β-adrenergic blocking agents,[15a] antidepress-

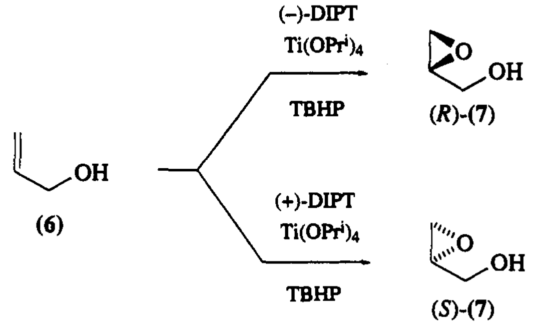

ants[32] and so on. In the second, esterification of the hydroxy group of glycidol improves the extraction of the glycidol moiety from the reaction mixture and at the same time generates a synthon in which all three carbon centers are differentiated for further reaction. Another benefit is that with certain derivatives, such as the 3-nitrobenzenesulfonate ester (**9**), recrystallization can be used to upgrade the optical purity to >99% *ee*.[4,16a]

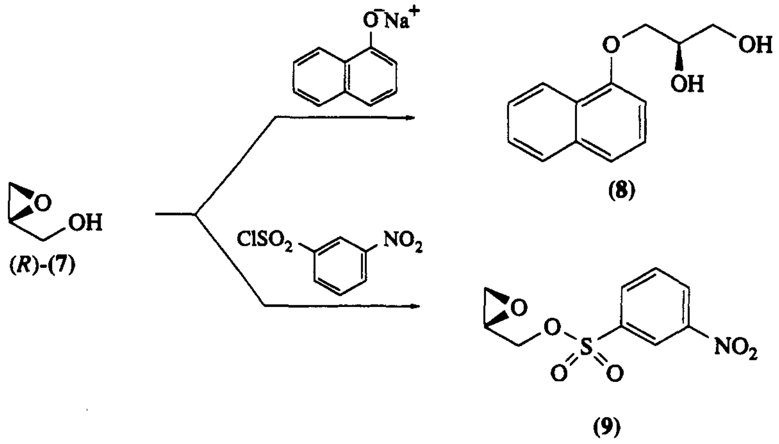

As an industrial process, production of optically active glycidol is at an early stage of development with additional improvements and economies certain to occur. As a chemical intermediate, optically active glycidol is the most versatile epoxy alcohol prepared by asymmetric epoxidation and is poised for exploitation in organic synthesis.[16]

### 3.2.5.2 2-Substituted Allyl Alcohols

The epoxides (**11**) derived from 2-substituted allylic alcohols (**10**) are particularly susceptible to nucleophilic attack at C-3, a reaction that is promoted by titanium(IV) species.[18] When stoichiometric amounts of titanium tartrate complex are used in these epoxidations considerable product is lost *via* opening of the epoxide before it can be isolated from the reaction. The primary nucleophilic culprit is the isopropoxide ligand of the $Ti(OPr^i)_4$. The use of $Ti(OBu^t)_4$ in place of $Ti(OPr^i)_4$ has been prescribed as a means to reduce this problem (the *t*-butoxide being a poorer nucleophile).[18] Fortunately, a better solution now exists in the form of the catalytic version of the reaction which uses only 5–10 mol % of titanium tartrate complex and greatly reduces the amount of epoxide ring opening. Some comparisons of results from reactions run under the two sets of conditions are possible from the epoxidations summarized in Table 3.

The prototype for this structural class is 2-methyl-2-propen-1-ol (methallyl alcohol) from which asymmetric epoxidation generates optically active 2-methyloxiranemethanol. Like glycidol, 2-methyloxiranemethanol has been difficult to obtain by stoichiometric asymmetric epoxidation, but with the use of the catalytic version reasonable quantities now are produced[4] and the compound has become commercially available. *In situ* derivatization also can be used to recover this epoxy alcohol from the epoxidation reaction. Progress in the isolation of 2-methyloxiranemethanol is reflected in entries 1–3 of Table 3, and

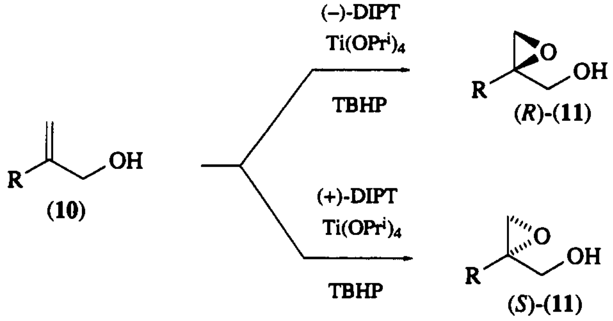

**Table 3** Epoxides from 2-Substituted Allylic Alcohols

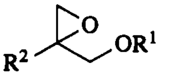

| *Entry* | *Epoxide* $R^1$ | $R^2$ | *Catalyst* (% Ti/% tartrate) | *Tartrate* | *Yield* (%) | *Enantiomeric excess* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | H | Me | 100/100[a] | (+)-DET | — | 85 | 33 |
| 2 | H | Me | 27/27 | (–)-DET | 32 | 94 | 34 |
| 3 | H | Me | 7.6/10[a] | (–)-DET | 47 | >95 | 35 |
| 4 | PNB | Me | 5/6 | (+)-DIPT | 78 | 92 (98)[b] | 4 |
| 5 | Tos | Me | 5/6 | (+)-DIPT | 69 | 95 | 4 |
| 6 | Nps[c] | Me | 5/6 | (+)-DIPT | 60 | (92)[b] | 4 |
| 7 | H | $Pr^n$ | 4.7/5.9 | (+)-DET | 88 | 95 | 4 |
| 8 | H | *n*-Nonyl | 100/110 | (+)-DET | 53 | >96 | 36 |
| 9 | H | *n*-Tetradecyl | 100/110[a] | (+)-DET | 51 | 95 | 18 |
| 10 | H | *n*-Tetradecyl | 10/13 | (+)-DET | 91 | 96 | 4 |
| 11 | H | $Pr^i$ | 65/120 | (+)-DET | 56 | 86 | 37 |
| 12 | H | $Bu^t$ | 120/150[a] | (+)-DET | 42 | 86 | 38 |
| 13 | H | Cyclohexyl | 100/100 | (+)-DET | 81 | >95 | 3 |
| 14 | H | —$CH_2OBn$ | 7.6/10[a] | (–)-DET | 74 | >95 | 35 |

[a] $Ti(OBu^t)_4$ used in this reaction. [b] Enantiomeric excess in parentheses is after recrystallization. [c] Nps = 2-Naphthalenesulfonyl.

the results of *in situ* derivatization are revealed by entries 4–6. The optical purity of 2-methyloxiranemethanol produced in this way is good (92–95%) and improvement to 98% *ee* is observed after recrystallization of the 4-nitrobenzoate derivative.

Several other allylic alcohols with primary C-2 substituents have been epoxidized with good results (Table 3, entries 7–10 and 14). Epoxy alcohols have been obtained with 95–96% *ee* and when the catalytic version of the reaction is used, as in Table 3, entry 10, the yield is excellent. When the C-2 substituent is more highly branched, as in entries 11–13, there may be some interference to high enantiofacial selectivity by the bulky group, since the *ee* in two cases (entries 11 and 12) is 86%. Another example which supports this possibility of steric interference to selective epoxidation is summarized in equation (3).[39] In this case, the optically active allylic alcohol (**12**) was subjected to epoxidation with both antipodes of the titanium tartrate catalyst. With (+)-DIPT enantiofacial selectivity was 96:4 ('matched pair'),[40a] but with (–)-DIPT selectivity fell to only 1:3 ('mismatched pair'), a further indication that a secondary C-2 substituent can perturb the fit of the substrate to the active catalyst species. In the epoxidation of the allylic alcohol shown in equation (4), the epoxy alcohol is obtained in 96% yield and with a 14:1 ratio of enantiofacial selectivity.[40b] An interesting alternate route to the epoxide of entry 12 (Table 3) has been described, in which 2-*t*-butylpropene is first converted to an allylic hydroperoxide *via* photooxygenation and then, in the presence of the titanium tartrate catalyst, undergoes asymmetric epoxidation (79%

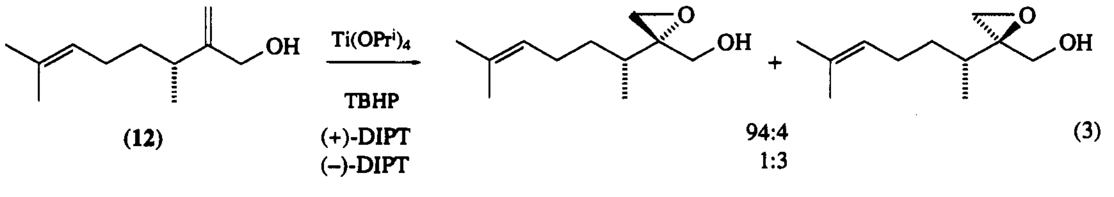

yield, 72% *ee*).[38b] The intermediate hydroperoxide serves as the source of oxygen for the epoxidation step.

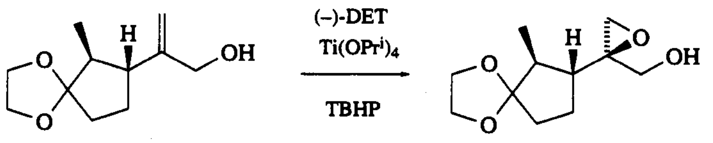

(4)

### 3.2.5.3 (3*E*)-Substituted Allyl Alcohols

Several factors contribute to the frequent use of (3*E*)-substituted allylic alcohols (**13**) for asymmetric epoxidation. The allylic alcohols are easily prepared, conversion to epoxy alcohol normally proceeding with good chemical yields and with >95% *ee*, and a large variety of functionality in the (3*E*)-position is tolerated by the epoxidation catalyst. Representative epoxy alcohols (**14**) are summarized in Table 4 and Figure 3, with results divided arbitrarily according to whether the (3*E*) substituent is a hydrocarbon

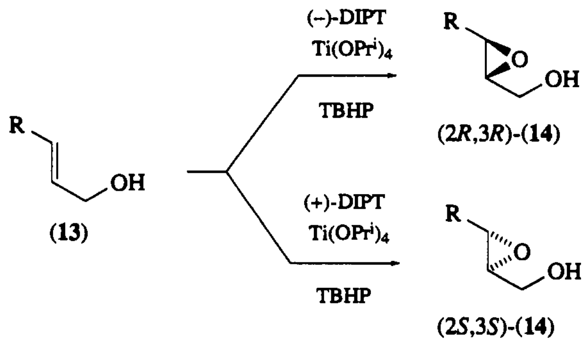

(**13**)

(2*R*,3*R*)-(**14**)

(2*S*,3*S*)-(**14**)

Table 4 Epoxides from (3*E*)-Substituted Allylic Alcohols (Hydrocarbon Substituents)

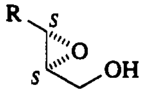

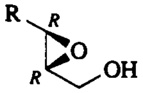

| Entry | Epoxide<br>R | Catalyst<br>(mol % Ti/% tartrate) | Tartrate | Epoxide configuration<br>(2,3) | Yield<br>(%) | Enantiomeric excess<br>(%) | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | Me | 100/100 | (–)-DIPT | (*R*,*R*) | 40–58 | 95 | 41–43 |
| 2 | Me | 5/6 | (+)-DIPT | (*S*,*S*) | 70 | 92 | 4 |
| 3 | Et | stoichiometric | (–)-DIPT | (*R*,*R*) | 80 | >95 | 44 |
| 4 | Pr$^n$ | 100/104 | (+)-DET | (*S*,*S*) | 64 | 93 | 45 |
| 5 | Pr$^i$ | 5/6 | (+)-DET | (*S*,*S*) | 85 | 94 | 4 |
| 6 | Pr$^i$ | 100/104 | (+)-DET | (*S*,*S*) | 66 | 98 | 45 |
| 7 | Bu$^s$ | — | (–)-DET | (*R*,*R*) | a | a | 46 |
| 8 | Bu$^t$ | 120/150 | (+)-DET | (*S*,*S*) | 52 | >95 | 38 |
| 9 | $CH_2{=}CH$ | 5/6 | (+)-DIPT | (*S*,*S*) | 56 | >91 | 47 |
| 10 | $MeCH{=}CHCH_2$ | 8/10 | (+)-DET | (*S*,*S*) | 81 | a | 48 |
| 11 | $n$-$C_5H_{11}$ | a | (+)-DET | (*S*,*S*) | 78 | 95 | 49 |
| 12 | $CH_2{=}CH(CH_2)_3$ | 100/100 | (+)-DET | (*S*,*S*) | 80 | >95 | 41 |
| 13 | $n$-$C_7H_{15}$ | 5/7.3 | (+)-DET | (*S*,*S*) | 99 | 96 | 4 |
| 14 | $n$-$C_8H_{17}$ | 5/6 | (+)-DET | (*S*,*S*) | 78 | 94 | 4 |
| 15 | $EtCH{=}CHCH_2CH{=}CHCH_2$ | a | (+)-DET | (*S*,*S*) | 82 | >95 | 46 |
| 16 | $EtC{\equiv}CCH_2C{\equiv}CCH_2$ | a | (–)-DET | (*R*,*R*) | 76 | a | 50 |
| 17 | $n$-$C_{10}H_{21}$ | 100/100 | (+)-DET | (*S*,*S*) | 79 | >95 | 3 |
| 18 | $n$-$C_{12}H_{25}$ | a | (+)-DET | (*S*,*S*) | a | a | 51 |
| 19 | $C_{14}H_{29}$ | a | (+)-DIPT | (*S*,*S*) | 77 | a | 52 |
| 20 | $C_{15}H_{31}$ | 120/160 | (–)-DET | (*R*,*R*) | 88 | >95 | 53 |

[a] Not reported.

(Table 4) or otherwise (Figure 3). The versatility of these and other 3-substituted epoxy alcohols for organic synthesis is illustrated with several examples in the following discussion.

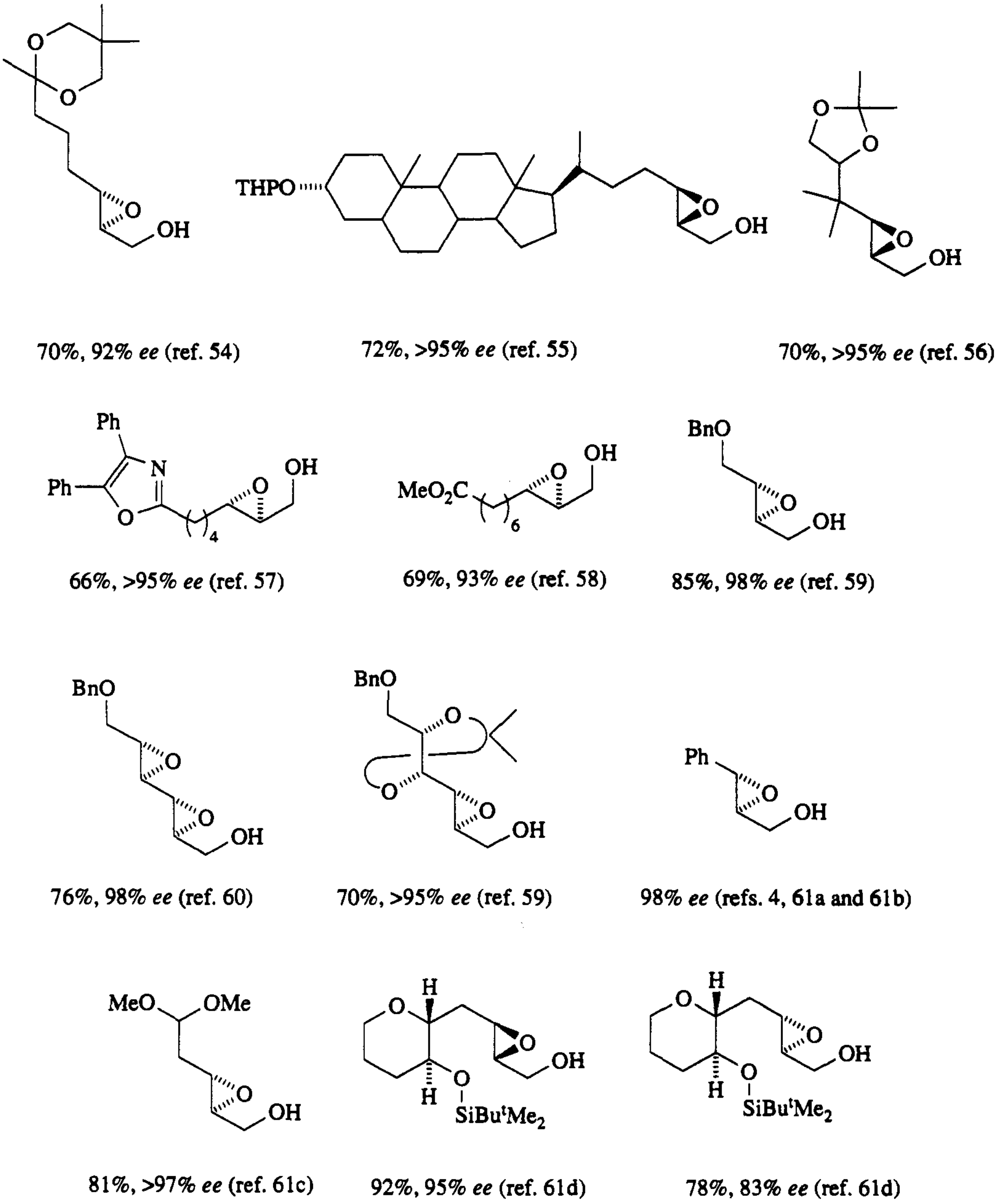

70%, 92% *ee* (ref. 54)
72%, >95% *ee* (ref. 55)
70%, >95% *ee* (ref. 56)
66%, >95% *ee* (ref. 57)
69%, 93% *ee* (ref. 58)
85%, 98% *ee* (ref. 59)
76%, 98% *ee* (ref. 60)
70%, >95% *ee* (ref. 59)
98% *ee* (refs. 4, 61a and 61b)
81%, >97% *ee* (ref. 61c)
92%, 95% *ee* (ref. 61d)
78%, 83% *ee* (ref. 61d)

**Figure 3** Epoxy alcohols from asymmetric epoxidation of (3*E*)-monosubstituted allylic alcohols

Compatibility of asymmetric epoxidation with acetals, ketals, ethers and esters has led to extensive use of allylic alcohols containing these groups in the synthesis of polyoxygenated natural products. An example which illustrates one such synthetic approach is the asymmetric epoxidation of (**15**), an allylic alcohol derived from (*S*)-glyceraldehyde acetonide.[59,62] In the epoxy alcohol (**16**) obtained from (**15**), each carbon of the five-carbon chain is oxygenated and all stereochemistry has been controlled. The structural relationship of (**16**) to the pentoses is evident, and methods leading to these carbohydrates have been described.[59,62a] This synthetic methodology has been extended by the development of an efficient series of reactions that can transform one allylic alcohol into a second which is two carbons longer than the first. Repetition of the reaction sequence can, in principle, be continued to any desired chain length.

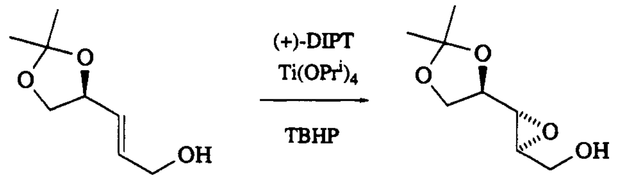

(15) (16)

The key steps in this ‘reiterative two-carbon extension cycle’ are illustrated in Scheme 1, which shows a synthetic route leading from an achiral alkoxyacetaldehyde (**17**) to L-allose, one of the eight possible L-hexoses.[63] In practice, all eight L-hexoses were synthesized by taking advantage of branch points in the sequence and by using both antipodes of the titanium tartrate catalyst to generate epimeric epoxides. The sequence of reactions begins with the two-carbon, benzyloxyacetaldeyde (**17**), which can be converted to the four-carbon intermediate (**18**) by means of a Wittig reaction. In the actual synthesis, intermediate (**18**) was the starting point and was obtained by an alternative method. The carboxylic acid ester of (**18**) is reduced with DIBAL to the (3*E*)-allylic alcohol (**19**) which, by asymmetric epoxidation, is converted to epoxy alcohol (**20**). Base-catalyzed rearrangement (Payne rearrangement) of (**20**) establishes the

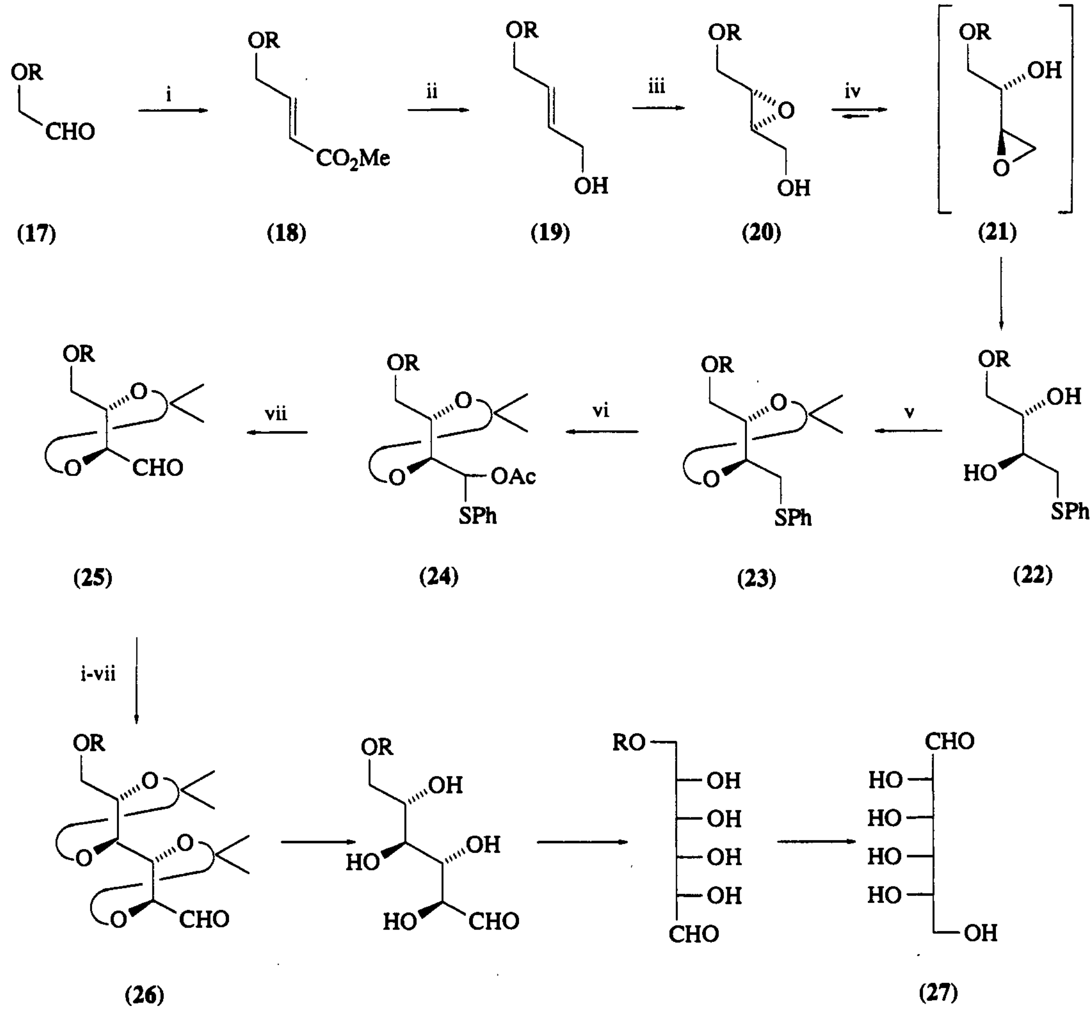

i, $(MeO)_3P(O)CHCO_2Me$; ii DIBAL; iii, (+)-DET/$Ti(OPr^i)_4$; iv, PhSH/$OH^-$; v, $MeC(=CH_2)OMe/H^+$;
vi, MCPBA, $Ac_2O/AcO^-$; vii, DIBAL (1 equiv.), $H_2O$

**Scheme 1**

equilibrium shown between (**20**) and the 1,2-epoxy alcohol (**21**). Benzenethiolate reacts regioselectively to open the 1,2-epoxide leading to the dihydroxy sulfide (**22**). The diol is protected by conversion to the acetonide (**23**) which, upon oxidation of the sulfide to a sulfoxide followed by Pummerer rearrangement, is converted to the acetoxythioacetal (**24**). Reduction of the latter (**24**) with one equivalent of DIBAL produces aldehyde (**25**). At this point the synthetic sequence can be branched by converting a portion of the aldehyde (**25**) to the epimeric aldehyde (not shown) by epimerization with potassium carbonate in methanol. Both of these new aldehydes can now be chain extended by repeating steps (i–vii), which in the case of (**25**) leads to the hexose derivative (**26**). In order to obtain all eight hexoses, a further branching during the second cycle is initiated at step (iii), with part of the material (an allylic alcohol) being subjected to asymmetric epoxidation with (–)-DET. Both of these branches are carried on through step (vi) or step (vii), thereby producing all eight L-hexose derivatives. Deprotection of the derivatives completes the synthesis, as shown for L-allose (**27**) in Scheme 1.

1,2-Epoxy-3-alcohols can be derived from 2,3-epoxy-1-alcohols by the base-catalyzed Payne rearrangement, as illustrated in step (iv) of Scheme 1.[59,64] The rearrangement is completely stereospecific but, since it is reversible, it usually results in an equilibrium mixture of the two epoxy alcohols for which the relative proportions are structure dependent. Practical synthetic applications of this rearrangement therefore depend on methods that will shift the equilibrium completely in the direction desired. Nucleophiles such as thiolates and amines are sufficiently selective to react preferentially at C-1 of the 1,2-epoxy-3-alcohol and thereby shift the equilibrium completely in that direction. However, many other nucleophiles are incompatible with the reaction conditions required for the Payne rearrangement and the approach of trapping the 1,2-epoxide cannot be used. To circumvent this problem and increase the scope of the Payne rearrangement/opening process, methods have been developed that lead to isolation of the terminal 1,2-epoxy-3-alcohols.[10,65]

One method uses the 2,3-diol-1-sulfide (**30**) produced by thiolate trapping of the 1,2-epoxide from the Payne rearrangement equilibrium between (**28**) and (**29**).[10,65] The sulfide is alkylated with $Me_3OBF_4$ in order to produce a good leaving group in (**31**). Then, base-promoted ring closure gives the 1,2-epoxide (**32**) in complete preference to formation of any 1,3-oxetane. The *erythro*-epoxy alcohol precursor (**31**) requires sodium hydride as the base in order to avoid reversal of the Payne rearrangement back to the starting 2,3-epoxy alcohol (**28**). The analogous *threo*-epoxy alcohol precursor can be closed with sodium hydroxide.

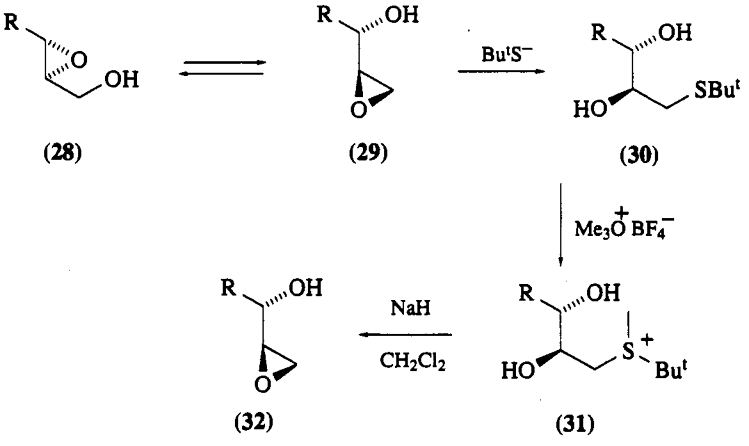

In a second method, the 2,3-epoxy-1-alcohol (**28**) is first converted to a mesylate (or a tosylate) and then the epoxide is opened hydrolytically with inversion at C-3 to give the dihydroxymesylate (**33**). A slight loss of optical purity has been observed in this process and is due to lack of complete regioselectivity for C-3 opening. Mild base is sufficient to effect ring closure of the dihydroxymesylate (**33**) to give the 1,2-epoxide (**34**).[10,65] The two methods are complementary in terms of stereochemistry such that if a 2,3-epoxy alcohol of the same absolute configuration is used to start each sequence, then the *erythro*-1,2-epoxy-3-ols produced will have opposite configurations at C-2 and C-3. This results from the fact that during the Payne rearrangement inversion occurs at C-2, while in the epoxymesylate opening, inversion occurs at C-3. Detailed discussions of these Payne rearrangement processes, as well as of further synthetic transformations of the 1,2-epoxy alcohols, have been presented elsewhere.[10,65]

When two allylic alcohols are contained in a symmetrical molecule, asymmetric epoxidation proceeds with interesting consequences for stereochemical purity. The results were first described for the asymme-

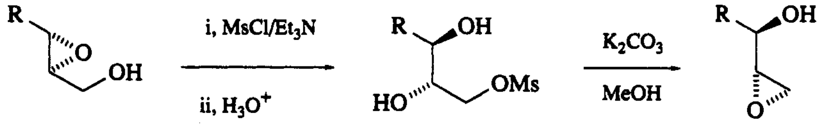

**(28)** **(33)** **(34)**

tric epoxidation of (2*Z*,6*E*,10*Z*)-dodeca-2,6,10-trien-1,12-diol (**35**).[66] The first epoxidation of (**35**) produces the major and minor enantiomers (**36**) and (**37**). Since the stereogenic centers in these compounds are remote from the second allylic alcohol, each enantiomer undergoes a second epoxidation with essentially the same enantiofacial selectivity as in the first epoxidation. Three bis(epoxide) products result; (**38a**), a *meso* compound (**39**) and (**38b**) (mirror image of **38a**). The overall consequence is that most of the epoxidation resulting from the undesired enantiofacial attack leads to the *meso* compound (**39**) which is in principle separable from the major product. Very little of the mirror image compound (**38b**) is formed and therefore the enantiomeric purity of the major product will be very high. In the example cited, enantiomeric purity could not be determined directly but was calculated according to the expression $(A_1 + B_1)(A_2 + B_2)$, where $A_1$ and $B_1$ are the enantiofacial selectivities of the first epoxidation and $A_2$ and $B_2$ are the enantiofacial selectivities of the second epoxidation. In the example being discussed an enantiofacial selectivity of 19:1 (90% *ee*) was assumed for both steps. The ratio of the three products therefore should be (19 + 1)(19 + 1), or 361:38:1, and the enantiomeric excess of (**38a**) should be 99.45%.

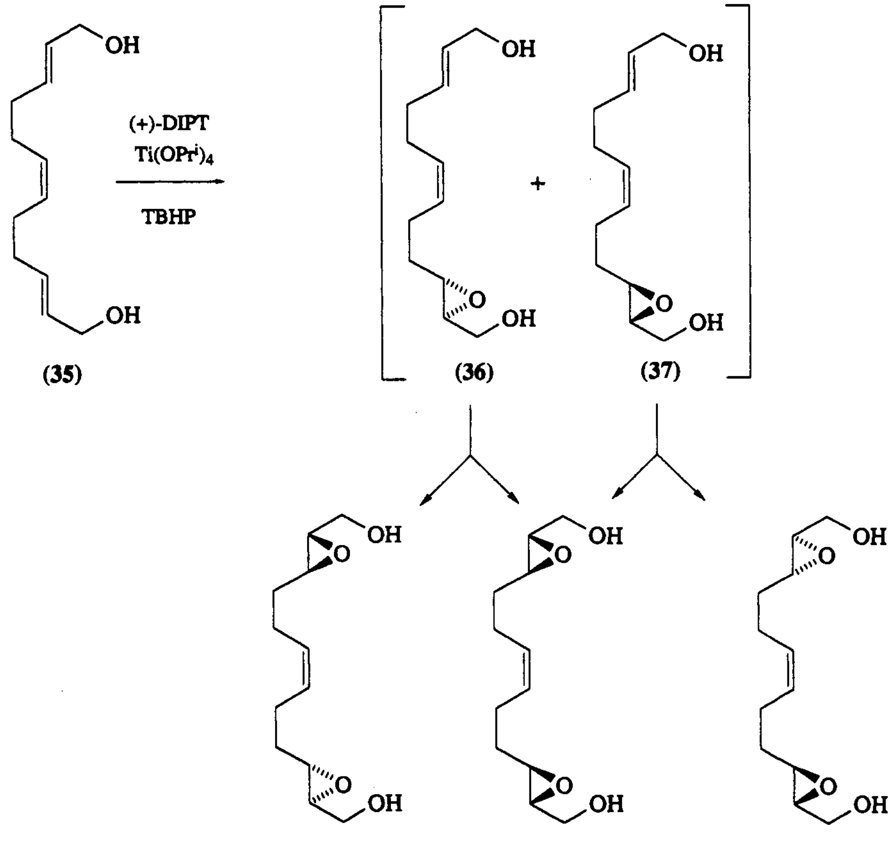

**(35)** **(36)** **(37)**

**(38a)** **(39)** **(38b)**

Fortunately, a wide variety of functionality is compatible with the titanium tartrate catalyst (see Table 1), but the judicious placement of functional groups relative to the allylic alcohol can lead to further desirable reactions following epoxidation. For example, in (**40**), asymmetric epoxidation of the allylic alcohol is followed by intramolecular cyclization under the reaction conditions to give the tetrahydrofuran (**41**).[67] Likewise, in the epoxidation of (**42**) cyclization of the intermediate epoxy alcohol occurs under the reaction conditions and leads to the cyclic urethane (**43**).[68] Titanium(IV) isopropoxide is an effective reagent for promoting the regioselective attack by nucleophiles at the 3-position of 2,3-epoxy alcohols,[69] 2,3-epoxy acids[70] and 2,3-epoxyamides.[70] This process has been proposed to involve coordination to the metal center in the bidentate manner shown for a 2,3-epoxy alcohol in structure (**44**). Such titanium-assisted nucleophilic opening of epoxides is thought to play a role in the *in situ* reactions leading to (**41**) and (**43**).

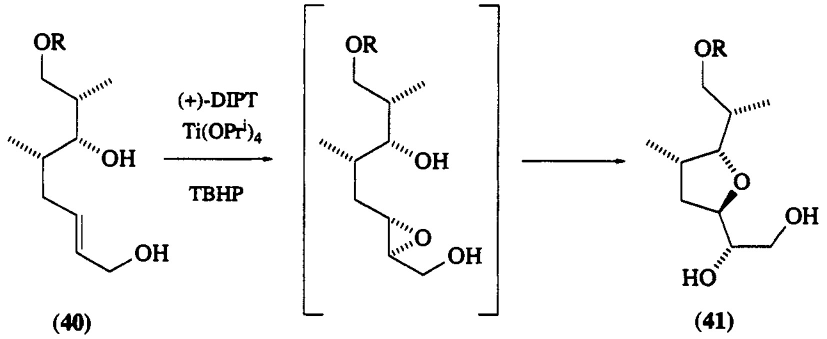

**(40)** **(41)**

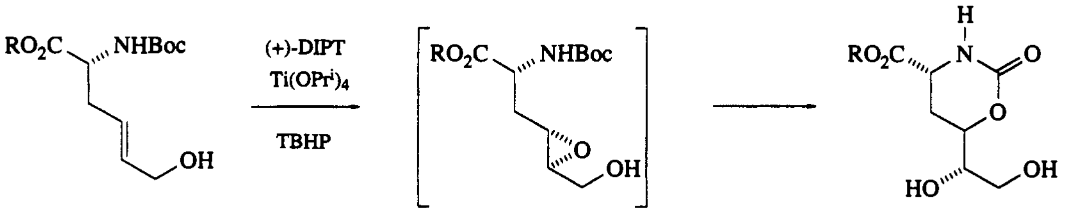

**(42)** **(43)**

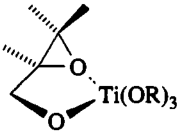

**(44)**

### 3.2.5.4 (3Z)-Monosubstituted Allyl Alcohols

Allylic alcohols having a *cis*-3-substituent (**45**) are the slowest to be epoxidized and give the most variable enantiofacial selectivities. Both of these characteristics suggest that allylic alcohols of this structure have the poorest fit to the requirements of the active epoxidation catalyst. Nevertheless, asymmetric epoxidation of these substrates is still effective and in most cases gives an optical purity of at least 80% *ee* and often as high as 95% *ee*. Patience with the slower reaction rate usually is rewarded with chemical yields of epoxy alcohols comparable to those obtained with other allylic alcohols. A number of representative examples are collected in Table 5.

There is a rough correlation between the enantiomeric excess observed for these epoxy alcohols and the steric complexity at the α-carbon of the C-3 substituent. When the C-3 substituent is a primary group (Table 5, entries 1, 2, 4, 6–12 and 19–21), enantiofacial selectivity is highest and enantiomeric excesses of 80–95% are observed for these compounds. When the substituent is secondary (entries 3 and 15–18) or tertiary (entry 5), enantiofacial selectivity is much more variable. When the substituent is asymmetric, enantiofacial selectivity depends on the absolute configuration, as is evident in comparison of entry 15 with 16 and of 17 with 18 in Table 5. Epoxidation of these chiral allylic alcohols with one antipode of catalyst yields moderate to good diastereoselectivity, while with the other antipode diastereoselectivity is virtually lacking.

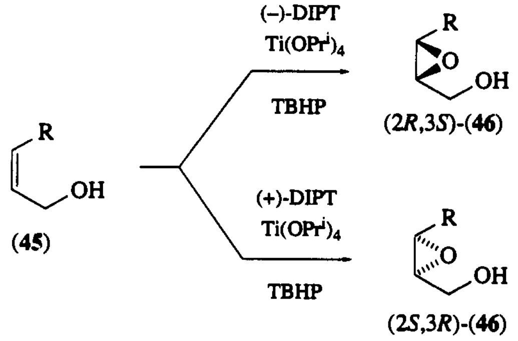

**Table 5** Epoxides from (3*Z*)-Substituted Allylic Alcohols

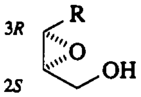

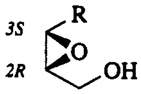

| *Entry* | *Epoxide* *R* | *Catalyst* (mol % Ti/% tartrate) | *Tartrate* | *Epoxide configuration* (2,3) | *Yield* (%) | *Enantiomeric excess* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Me | 5/6 | (+)-DIPT | (*S*,*R*) | 68 | 92 | 4 |
| 2 | Et | a | (+)-DET | (*S*,*R*) | 60 | 80 | 71 |
| 3 | Pr$^i$ | a | (+)-DET | (*S*,*R*) | 54 | 66 | 72 |
| 4 | Bu$^i$ | a | (+)-DET | (*S*,*R*) | 80 | 95 | 73 |
| 5 | Bu$^t$ | 120/150 | (+)-DET | (*S*,*R*) | 77 | 25 | 38 |
| 6 | n-$C_9H_{19}$ | 100/100 | (–)-DET | (*R*,*S*) | 80 | 91 | 3 |
| 7 | n-$C_7H_{15}$ | 10/14 | (+)-DET | (*S*,*R*) | 74 | 86 | 4 |
| 8 | n-$C_8H_{17}$ | 5/7.4 | (+)-DIPT | (*S*,*R*) | 63 | >80 | 4 |
| 9 | $CH_2CH{=}CHC_5H_{11}$ | 110/110 | (+)-DMT | (*S*,*R*) | 70 | 94 | 74 |
| 10 | $(CH_2)_3CO_2Me$ | a | (+)-DET | (*S*,*R*) | 57 | 95 | 75 |
| 11 | $CH_2OBn$ | 100/100 | (–)-DET | (*R*,*S*) | 84 | 92 | 59 |
| 12 | $CH_2OBn$ | 14/14 | b | — | — | 95 | 4 |
| 13 | Ph | 100/120 | (+)-DET | (*S*,*R*) | 61 | 78 | 76 |
| 14 | CHMePh | a | (+)-DIPT | (*S*,*R*) | a | a | 77 |
| 15 | 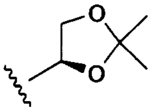 | 100/100 | (+)-DET | (*S*,*R*) | 55, 57 | 93, 84 | 59, 62a |
| 16 | as entry 15 | 100/100 | (–)-DET | (*R*,*S*) | a | 20 | 62a |
| 17 | $CHMeCH_2OBn$ | 100/100 | (+)-DET | (*S*,*R*) | a | 66 | 78a |
| 18 | as entry 17 | 100/100 | (–)-DET | (*R*,*S*) | a | 0 | 78a |
| 19 | $CH_2CH_2OBn$ | a | (+)-DIPT | (*S*,*R*) | 75 | 92 | 78b |
| 20 | n-$C_{11}H_{23}$ | 120/130 | (+)-DIPT | (*S*,*R*) | 83 | 92 | 78c |
| 21 | $(CH_2CH{=}CH)_2CH{=}CH_2$ | 100/148 | (+)-DET | (*S*,*R*) | 59 | 89 | 78d |

[a] Not reported. [b] See ref. 4, footnote 9, for this entry.

### 3.2.5.5 (2,3*E*)-Disubstituted Allyl Alcohols

Extensive use in synthesis has been made of the asymmetric epoxidation of (2,3*E*)-disubstituted allylic alcohols. With few exceptions enantiofacial selectivity is excellent as reflected by enantiomeric excesses in the range of 90–95%. The results for a number of epoxidations of allylic alcohols with smaller substituents are collected in Table 6, while a variety of other compounds with larger groups are illustrated by structures (**47**) to (**60**).

The epoxy alcohol (**47**) is a squalene oxide analog which has been used to examine substrate specificity in enzymatic cyclizations by baker's yeast.[85] The epoxy alcohol (**48**) provided an optically active intermediate used in the synthesis of 3,6-epoxyauraptene and marmine,[86] and epoxy alcohol (**49**) served as an intermediate in the synthesis of the antibiotic virantmycin.[87] In the synthesis of the three stilbene

Table 6 Epoxides from (2,3*E*)-Disubstituted Allylic Alcohols

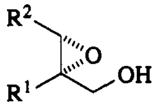

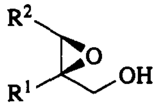

| | Epoxide | | | | | | |
|---|---|---|---|---|---|---|---|
| *Entry* | $R^1$ | $R^2$ | *Tartrate* | *Epoxide configuration* | *Yield (%)* | *Enantiomeric excess (%)* | *Ref.* |
| 1 | Me | Me | (+)-DET | (2*S*,3*S*) | 77 | 94 | 61b |
| 2 | Me | Et | (+)-DMT | (2*S*,3*S*) | 79 | 95 | 41, 78e |
| 3 | $—(CH_2)_3—$ | | (+)-DET | (2*S*,3*S*) | 38 | >95 | 79 |
| 4 | $—(CH_2)_4—$ | | (+)-DET | (2*S*,3*S*) | 77 | 93 | 4 |
| 5 | Me | $CH_2OBn$ | (–)-DIPT | (2*R*,3*R*) | 87 | 90 | 80 |
| 6 | Me | $CHMeCH_2OBn$ | — | — | 93 | >95 | 81 |
| 7 | Me | Ph | (+)-DIPT | (2*S*,3*S*) | 79 | >98[a] | 4 |
| 8 | Ph | Ph | (+)-DET | (2*S*,3*S*) | 70 | >95 | 3, 4 |
| 9 | Me | $CH_2CH_2CH{=}CH_2$ | (+)-DET | (2*S*,3*S*) | 71 | 96 | 82 |
| 10 | Me | 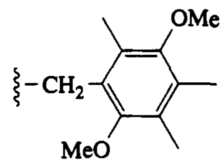 | (–)-DET | (2*R*,3*R*) | 87 | >95 | 83 |
| 11 | Me | $CH_2CH{=}CMe_2$ | (+)-DET | (2*S*,3*S*) | 64 | >90 | 84a |
| 12 | Me | $CH_2CH{=}CMe_2$ | (–)-DET | (2*R*,3*R*) | 59 | >91 | 84a |
| 13 | Me | $(CH_2)_3OSiMe_2Bu^t$ | (–)-DET | (2*R*,3*R*) | 89 | 93 | 84b |

[a] Enantiomeric excess after crystallization.

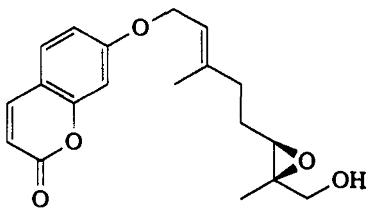

**(48)**

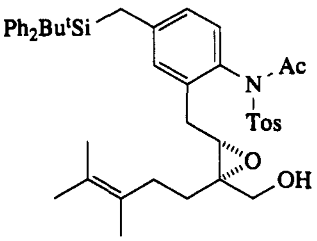

**(49)**

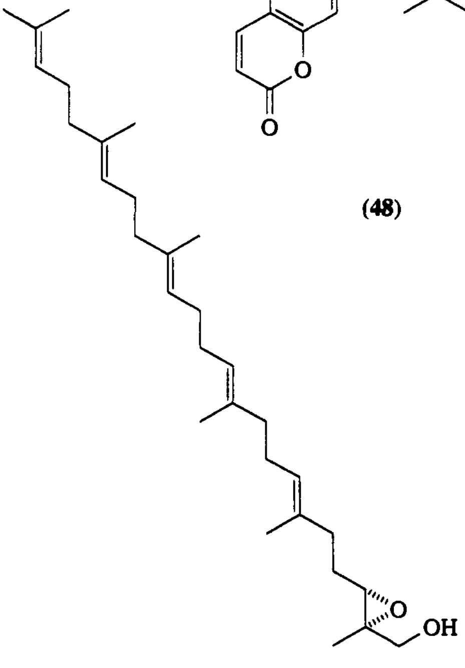

**(47)**

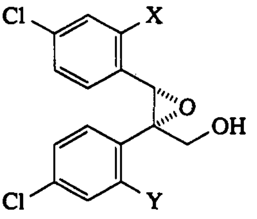

| | *X* | *Y* | *Enantiomeric excess (%)* |
|---|---|---|---|
| **(50)** | H | H | >90 |
| **(51)** | Cl | H | >90 |
| **(52)** | Cl | Cl | 70 |

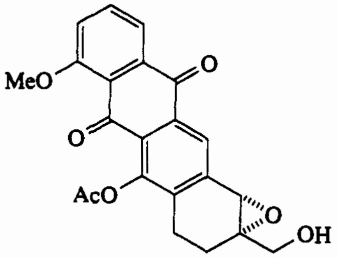

**(52a)**

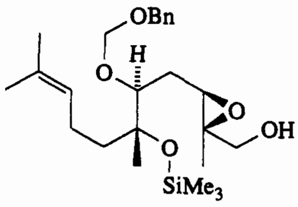

**(52b)**

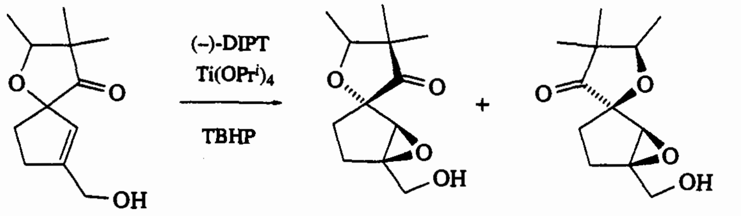

**(53)** **(54)** **(55)**

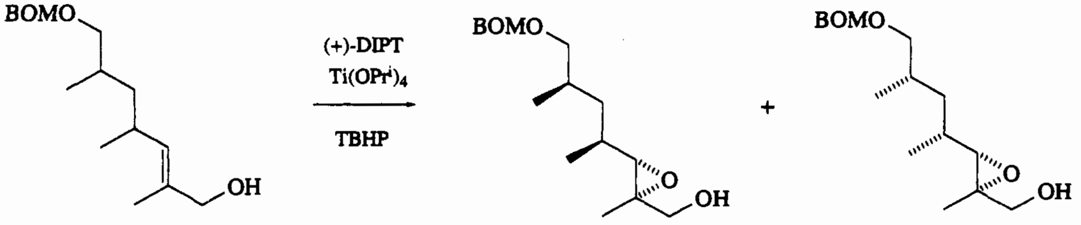

**(56)** **(57)** **(58)**

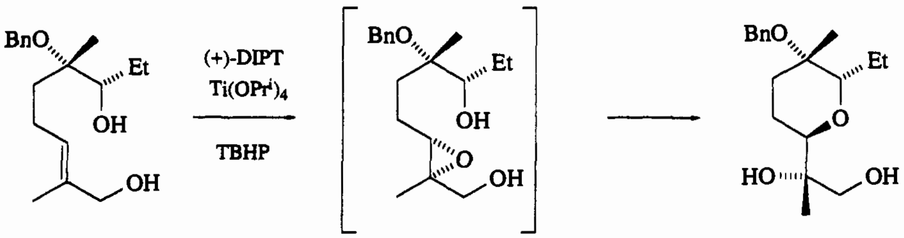

**(59)** **(60)**

oxides (**50**) to (**52**), the presence of an *ortho* chloro group in the 2-phenyl ring resulted in a lower enantiomeric excess (70%) when compared to the analogs without this chlorine substituent.[88a] The very efficient (80% yield, 96% *ee*) formation of (**52a**) by asymmetric epoxidation of the allylic alcohol precursor offers a synthetic entry to optically active 11-deoxyanthracyclinones,[88b] while epoxy alcohol (**52b**) is one of several examples of asymmetric epoxidation used in the synthesis of brevitoxin precursors.[88c] Diastereomeric epoxy alcohols (**54**) and (**55**) are obtained in combined 90% yield (>95% *ee* each) from epoxidation of the racemic alcohol (**53**).[89] Diastereomeric epoxy alcohols (**57**) and (**58**) also are obtained with high optical purity in the epoxidation of (**56**).[44] The epoxy alcohol obtained from substrate (**59**) undergoes further intramolecular cyclization with stereospecific formation of the cyclic ether (**60**).[90]

### 3.2.5.6 (2,3*Z*)-Disubstituted Allyl Alcohols

A limited number of allylic alcohols of this type have been subjected to asymmetric epoxidation. With one exception, the C-2 substituent in these substrates has been a methyl group, the exception being a *t*-butyl group.[38] The (3*Z*)-substituents have been more varied and are illustrated by structures (**61**) to (**64**), which show the epoxy alcohols derived from the corresponding allylic alcohol substrates. Epoxidation of (*Z*)-2-methyl-2-hepten-1-ol gave epoxy alcohol (**61**) in 80% yield, 89% *ee*,[3] while (*Z*)-2-methyl-4-phenyl-2-buten-1-ol gave (**62**) in 90% yield, 91% *ee*,[77] and (*Z*)-1-hydroxysqualene gave (**63**) in 93% yield, 78% *ee*.[85] The epoxy alcohol (**64**) was obtained with >95% *ee* after recrystallization.[91] In the epoxidation of (*Z*)-2-*t*-butyl-2-buten-1-ol, the allylic alcohol with a C-2 *t*-butyl group, the epoxy alcohol was obtained in 43% yield and with 60% *ee*.[38] These results lead one to expect that other (2,3*Z*)-disubstituted allylic alcohols will be epoxidized in good yield and with enantioselectivity similar to that observed for the (3*Z*)-monosubstituted allylic alcohols (*i.e.* 80–95% *ee*).

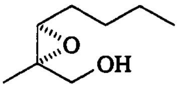

**(61)**

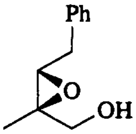

**(62)**

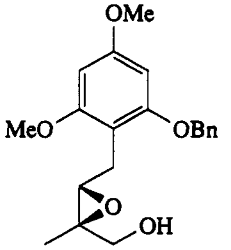

**(64)**

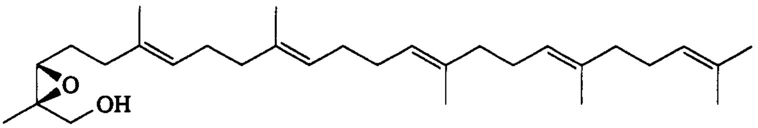

**(63)**

### 3.2.5.7 3,3-Disubstituted Allyl Alcohols

These substrates combine a (3*E*)-substituent with a (3*Z*)-substituent in the same molecule. Allylic alcohols with only a (3*E*)-substituent generally are epoxidized with excellent enantioselectivity, whereas those with only a (3*Z*)-substituent are epoxidized with enantioselectivity in the range of 80–95% *ee*. In the combination many of the reported examples have a methyl substituent at the (3*Z*)-position and all of these are epoxidized with an enantiomeric excess of 90–95% (Table 7, entries 1–4 and 6). Only a limited number of examples with larger groups at the (3*Z*)-position have been reported (entries 5 and 7–12) and in these the enantiomeric excesses are in the range 84–94%.

3,3-Dimethylallyl alcohol was epoxidized with >90% *ee* (Table 7, entry 1) but in low yield when a stoichiometric amount of the titanium tartrate complex was used. However, when a catalytic amount of the complex was used and *in situ* derivatization employed, the *p*-nitrobenzoate (>98% *ee* after recrystallization) and *p*-toluenesulfonate (93% *ee*) were isolated in yields of 70% and 55%, respectively. Likewise, the epoxidation of geraniol with a stoichiometric amount of the complex gave the epoxide (Table 7, entry 3) in 77% yield (95% *ee*) which was improved to 95% yield (91% *ee*) when a catalytic amount of complex was used (entry 4).

### 3.2.5.8 2,3,3-Trisubstituted Allyl Alcohols

Interesting structural diversity is present in the limited examples of trisubstituted allyl alcohols (equivalent to tetrasubstituted alkenes) to which asymmetric epoxidation has been applied. The epoxides (**65**) to (**70**) have been obtained from the corresponding allylic alcohols with yield and enantiomeric excess as indicated when such data have been reported. The lower enantiomeric excess observed for epoxy alcohol (**69**) may result from disruption of the catalyst structure by the phenolic groups or from alternate modes of binding of substrate to catalyst, again because of the phenolic groups.[102] Phenols bind strongly to titanium(IV), which may account for the fact that a large excess (six equivalents) of the titanium tartrate complex was required to achieve the yield and enantiomeric excess reported in the case of (**69**).

**Table 7** Epoxides from 3,3-Disubstituted Allylic Alcohols

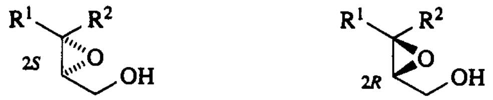

$R^1$
$R^2$
2*S*
O
OH
$R^1$
$R^2$
O
2*R*
OH

| *Entry* | *Epoxide* $R^1$ | $R^2$ | *Catalyst* (mol% Ti/% tartrate) | *Tartrate* | *Epoxide configuration* | *Yield* (%) | *ee* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | Me | 100/100 | (–)-DBT | (2*R*) | 25 | >90 | 92 |
| 2 | $CH_2CH{=}CMe_2$ | Me | 200/200 | (+)-DET | (2*S*,3*S*) | 67 | 95 | 93 |
| 3 | $(CH_2)_2CH{=}CMe_2$ | Me | 100/100 | (+)-DET | (2*S*,3*S*) | 77 | 95 | 3 |
| 4 | $(CH_2)_2CH{=}CMe_2$ | Me | 5/7.4 | (+)-DET | (2*S*,3*S*) | 95 | 91 | 4 |
| 5 | Me | $(CH_2)_2CH{=}CMe_2$ | 100/100 | (+)-DET | (2*S*,3*R*) | 79 | 94 | 3 |
| 6 | $(CH_2)_2OSiMe_2Bu^t$ | Me | 105/157 | (–)-DET | (2*R*,3*R*) | 81 | >95 | 94 |
| 7 | Me | $(CH_2)_2OSiMe_2Bu^t$ | a | (+)-DET | (2*S*,3*R*) | 98 | 90 | 95 |
| 8 | Me | $(CH_2)_2OSiMe_2Bu^t$ | a | (–)-DET | (2*R*,3*S*) | 98 | 86 | 95 |
| 9 | 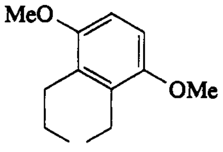 MeO OMe | | 10/15 | (+)-DET | (2*S*,3*R*) | 97 | 93 | 96 |
| 10 | 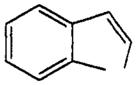 | | 100/110 | (+)-DET | (2*S*,3*S*) | a | 84 | 97a |
| 11 | 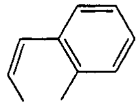 | | 100/110 | (+)-DET | (2*S*,3*R*) | a | 88 | 97a |
| 12 | $(CH_2)_4OBn$ | $CH_2CH(Me)CH_2OMEM$ | 10/12 | (–)-DIPT | (2*R*,3*S*) | 83 | 91 | 97b |

[a] Not reported.

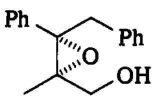

**(65)**

90%, 94% *ee* (ref. 98)

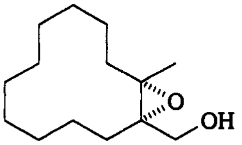

**(66)**

72%, 94% *ee* (ref. 99)

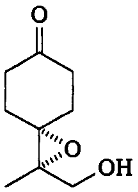

**(67)**

>90% *ee* (ref. 100)

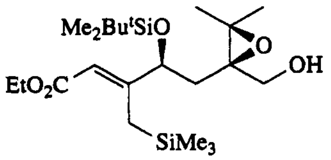

$Me_2Bu^tSiO$
O
OH
$EtO_2C$
$SiMe_3$

**(68)**

>90% *ee* (ref. 101)

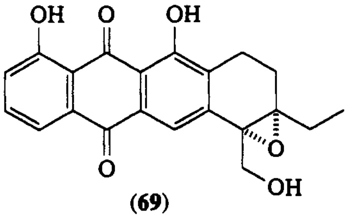

**(69)**

85%, 53% *ee* (ref. 102)

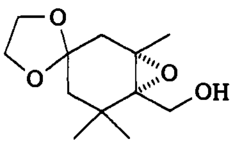

**(70)**

95%, 95% *ee* (ref. 103)

### 3.2.5.9 1-Substituted Allyl Alcohols: Kinetic Resolution

The presence of a stereogenic center at C-1 of an allylic alcohol introduces an additional factor into the asymmetric epoxidation process in that now both enantiofacial selectivity and diastereoselectivity must be considered. It is helpful in these cases to examine epoxidation of each enantiomer of the allylic alcohol separately. Epoxidation of one enantiomer proceeds normally and produces an *erythro*-epoxy alcohol in accord with the rules shown in Figure 1. Epoxidation of the other enantiomer proceeds at a reduced rate because contact between the C-1 substituent and the catalyst seriously impedes the necessary approach of alkene to oxidant (see Figure 2). The difference in epoxidation rates for the two enantiomers is usually of sufficient magnitude that either the epoxy alcohol or the recovered allylic alcohol can be produced with high optical purity. The net result is that a kinetic resolution is achieved.[13] In the case of a homochiral C-1-substituted allylic alcohol, asymmetric epoxidation will be fast and highly diastereoselective with one antipode of the titanium tartrate catalyst but not with the other, according to the guidelines of Figure 2. Although kinetic resolution is most frequently encountered and applied to chiral C-1-substituted allylic alcohols, the rationale also is applicable to allylic alcohols with chiral substituents at other positions, examples of which have been given in several preceding subsections.

The ratio of the rates of epoxidation of the two enantiomers, $k_{fast}/k_{slow}$, has been defined as the relative rate ($k_{rel}$) and is related to both the percentage conversion of allylic alcohol to epoxy alcohol and the enantiomeric excess of the remaining allylic alcohol. A mathematical relationship between these variables exists and can be represented graphically, as shown in Figure 4.[13] If values are known for two of the three variables, then the third can be predicted by use of this graph. Inspection of the graph reveals that relative rates of 25 or more are very effective for achieving kinetic resolution of 1-substituted allylic alcohols. With a relative rate of 25, the epoxidation need be carried to less than 60% conversion to achieve an enantiomeric excess of essentially 100% for the unreacted alcohol. A convenient method for limiting the extent of epoxidation to 60% is simply by controlling the amount of oxidant used in the reaction. However, for some substrates (see Table 8, entries 1, 9 or 10) even $k_{fast}$ is extremely slow and several days are needed for the epoxidation. To shorten the time needed for such reactions, an alternate practice is to use an excess of oxidant and to monitor the extent of epoxidation by an appropriate analytical method. If the optically active epoxy alcohol is the desired reaction product, then high enantiomeric excess can be insured by running the reaction to approximately 45% completion.

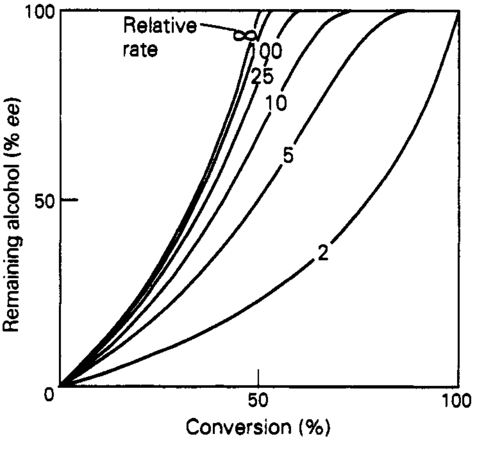

**Figure 4** Dependence of enantiomeric excess on relative rate in the epoxidation of C-1-substituted allylic alcohols

Relative rate data for the kinetic resolution/epoxidation of 1-substituted allylic alcohols of varying structure are summarized in Table 8. The $k_{rel}$ values at −20 °C for all entries in Table 8 were determined using DIPT as the chiral ligand. Additionally, for several entries (1–3, 10 and 11) the dependence of $k_{rel}$ on temperature, 0 °C *versus* −20 °C, and on steric bulk of the tartrate ester, DIPT *versus* DET *versus* DMT, has been measured. Lower reaction temperature and larger tartrate ester groups both are factors that clearly increase the magnitude of $k_{rel}$ and, therefore, improve the efficiency of the kinetic resolution process. While the results summarized in Table 8 are all from experiments in which stoichiometric quantities of titanium tartrate complex were used, the catalytic version of the reaction also may be used for kinetic resolution.[4] When comparing results with the same tartrate ester, a slight loss in enantioselectivity is seen in the catalytic mode relative to the stoichiometric reaction. The trend toward higher enantioselectivity with bulkier tartrate esters can be used to advantage in the catalytic reaction by using dicyclo-

**Table 8** Relative Rate ($k_{rel}$) Data for Kinetic Resolution of 1-Substituted Allylic Alcohols

| *Entry* | *Allylic alcohol* | *Reaction time* | *Relative rate at –20 °C* | *ee (%)* | *Relative rates at 0 °C* | | | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| | | | | | *DIPT* | *DET* | *DMT* | |
| 1 | 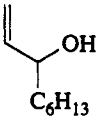 | 12 d | 83 | >96 | 60 | | | 2, 13 |
| 2 | 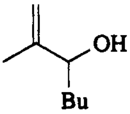 | 15 h | 138 | >96 | 96 | 52 | | 2, 13 |
| 3 | 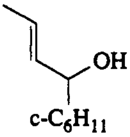 | 15 h | 104 | >96 | 74 | 28 | 15 | 2, 13 |
| 4 | 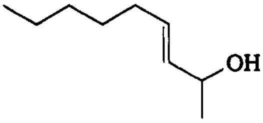 | | 160 | | | | | 104 |
| 5 | 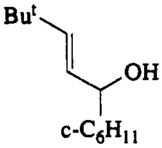 $Bu^t$<br>OH<br>c-$C_6H_{11}$ | | 300 | | | | | 104 |
| 6 | 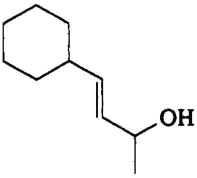 | | 330 | | | | | 104 |
| 7 | 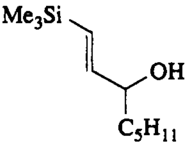 $Me_3Si$<br>OH<br>$C_5H_{11}$ | | 700 | | | | | 104–106 |
| 8 | 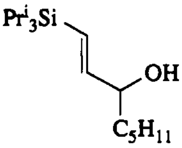 $Pr^i_3Si$<br>OH<br>$C_5H_{11}$ | | 300 | | | | | 104 |
| 9 | 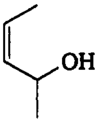 | 6 d | 20 | 91 | | | | 2, 13 |

**Table 8** *(continued)*

| *Entry* | *Allylic alcohol* | *Reaction time* | *Relative* rate at *-20 °C* | *ee (%)* | *Relative rates at 0 °C* *DIPT* | *DET* | *DMT* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 10 | 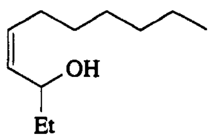 | 2 d | 16 | 82 | 13 | | | 2, 13 |
| 11 | 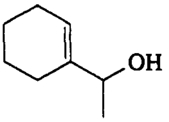 | 15 h | 83 | >96 | 60 | 38 | | 2, 13 |

hexyltartrate (DCT), which gives higher selectivity than DIPT, or dicyclododecyl tartrate, which gives yet higher selectivity than DCT.[4]

The efficiency of kinetic resolution is even greater when there is a silicon or iodo substituent in the (3*E*)-position of the C-1 chiral allylic alcohols. The compatibility of silyl substituents with asymmetric epoxidation conditions was first shown by the conversion of (3*E*)-3-trimethylsilylallyl alcohol into (2*R*,3*R*)-3-trimethylsilyloxiranemethanol in 60% yield with >95% *ee*,[107a] and further exploited by the conversion of (*E*)-3-(triphenylsilyl)-2-[2,3-$^2H_2$]propenol into (2*R*,3*R*)-3-triphenylsilyl[2,3-$^2H_2$]oxiranemethanol in 96% yield and with 94% *ee*.[107b,107c] With an *n*-pentyl group at C-1, the $k_{rel}$ for asymmetric epoxidation of the enantiomeric allylic alcohols is 700 (Table 8, entry 7), and both epoxy alcohol and optically active recovered allylic alcohol are obtained in 42% yield with >99% *ee* (see Table 9, entry 1). Equally good yields and optical purities are observed with other substituents in the C-1 position, as is shown by entries 2 to 9 in Table 9. Good yields with high enantiomeric excess also are reported in the kinetic resolution of (3*E*)-iodo analogs (entries 10–14) and of a (3*E*)-chloro analog (entry 15). (3*E*)-Stannyl substituents (entries 16–18) appear similar to carbon substituents in their effect on kinetic resolution.

The influence of both the steric and the electronic properties of the silyl group on the rate of epoxidation have been examined experimentally.[104] Two different rate effects were considered. First, the overall rate of epoxidation of the silyl allylic alcohols was found to be one-fifth to one-sixth that of the similar carbon analogs. This rate difference was attributed to electronic differences between the silicon and carbon substituents. Second, the increase in $k_{rel}$ to 700 for silyl allylic alcohols compared to carbon analogs (*e.g.* 104 for entry 3, Table 8) was attributed to the steric effect of the large trimethylsilyl group. As expected, when a bulky *t*-butyl group was placed at C-3, $k_{rel}$ increased to 300.[104]

At the end of 1989, over 75 1-substituted allylic alcohols had been used in kinetic resolution/asymmetric epoxidation experiments. In slightly over half of these experiments, the desired product was the kinetically resolved allylic alcohol, while in the remainder the epoxy alcohol was desired. In addition to the compounds in Table 8, experimental results for other kinetically resolved alcohols are summarized in Table 10. From these results, it appears that kinetic resolution is successful regardless of the nature of the (3*E*)-substituent and is successful with any except the most bulky substituents at C-2.

In those cases where the allylic alcohol is the desired product of the kinetic resolution process, the accompanying epoxy alcohol also may be converted to the desired allylic alcohol by the two-step sequence shown in Scheme 2. The epoxy alcohol, after separation from the allyl alcohol, is mesylated and then subjected to reaction with sodium telluride, which effects the transformation of epoxymesylate to the allylic alcohol with inversion at the asymmetric carbinol center.[115e] Preliminary results suggest that the rearrangement follows this pathway only when the epoxy alcohol is unsubstituted at the 3-position.

A small, structurally distinct class of 1-substituted allylic alcohols are those which are conformationally restricted by incorporation into a ring system. These allylic alcohols may be further subdivided into two types depending on whether the double bond is endocyclic or exocyclic. For allylic alcohols with endocyclic double bonds, kinetic resolution gives 2-cyclohexen-1-ol (**71**) with 30% *ee*,[13] (4a*S*,2*R*)-4a-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-ol (**72**) with 55% *ee*[116] and (*R*)-2-cyclohepten-1-ol (**73**) with 80% *ee*.[13] The epoxy alcohols, (1*S*,2*S*,3*R*)-2,3-epoxycyclopenten-1-ol (**74**),[117] (1*S*,2*S*,4a*R*)-4a-decahydronaphthalen-2-ol (**75**)[116] and (1*R*,2*S*,3*R*)-2,3-epoxy-6-cyclononen-1-ol (**76**)[118] are obtained with

**Table 9** Kinetic Resolution of 3-Silyl-, Halo- and Stannyl-substituted Allylic Alcohols

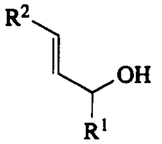

| Entry | Allylic alcohol $R^1$ | $R^2$ | Allylic alcohol Yield (%)[a] | Allylic alcohol Enantiomeric excess (%) | Epoxy alcohol Yield (%)[a] | Epoxy alcohol Enantiomeric excess (%) | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | n-$C_5H_{11}$ | $SiMe_3$ | 42 | >99 | 42 | >99 | 105 |
| 2 | $Pr^i$ | $SiMe_3$ | 40 | >99 | 41 | 99 | 105b |
| 3 | Ph | $SiMe_3$ | 44 | >99 | 42 | 97 | 105b |
| 4 | $CH_2OPh$ | $SiMe_3$ | 47 | >99 | 46 | >99 | 105b |
| 5 | $CH_2OCH_2Ph$ | $SiMe_3$ | 43 | >99 | 48 | >99 | 105b |
| 6 | $CH_2CH{=}CHC_5H_{11}$ | $SiMe_3$ | 44 | >99 | 43 | >99 | 105b |
| 7 | $CH_2CH_2OCH_2Ph$ | $SiMe_3$ | 43 | >99 | 45 | >99 | 105b |
| 8 | $CH_2CO_2Bu^n$ | $SiMe_3$ | 44 | >99 | | | 105c |
| 9 | $(CH_2)_3CO_2Me$ | $SiMe_3$ | 43 | >99 | 45 | >99 | 105b |
| 10 | n-$C_5H_{11}$ | I | 49 | >99 | 49 | >99 | 108 |
| 11 | Et | I | 40 | >98 | | | 108 |
| 12 | $CH_2$-c-$C_6H_{11}$ | I | 42 | >99 | | | 108 |
| 13 | c-$C_5H_9$ | I | 44 | >99 | | | 108 |
| 14 | Ph | I | 43 | >98 | | | 108 |
| 15 | n-$C_5H_{11}$ | Cl | 43 | >99 | | | 108 |
| 16 | n-$C_5H_{11}$ | $SnBu_3$ | 40 | >99 | b | 84 | 109 |
| 17 | c-$C_6H_{11}$ | $SnBu_3$ | 41 | >99 | | | 109 |
| 18 | $CH_2OPh$ | $SnBu_3$ | 40 | >99 | | | 109 |

[a] Maximum yield is 50%. [b] Not reported.

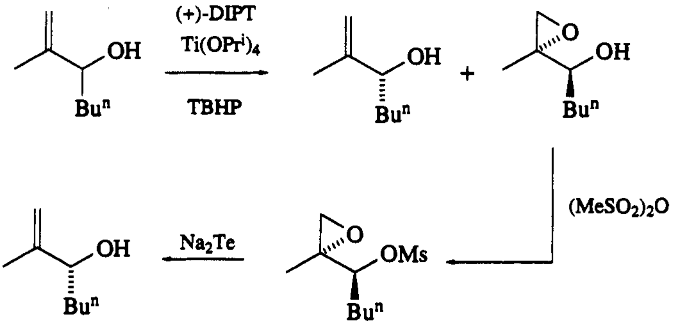

**Scheme 2**

60% *ee*, 61% *ee* and 90% *ee*, respectively. (*R*)-*trans*-Verbenol (**77**) is epoxidized five times as fast as is (*S*)-*trans*-verbenol when (+)-DIPT is used in the catalyst.[77] For allylic alcohols with an exocyclic double bond, kinetic resolution gives 2-methylenecyclohexanol (**78**) with 80% *ee* and a 46% yield when (–)-DIPT is used.[119] Epoxidation of the homochiral 4-methylene-5α-cholestan-3β-ol (**79**) is reported to be much faster with catalyst derived from (+)-DET than from (–)-DET.[120] The variable enantioselectivities seen in these results likely stem from conformational restraints imposed by the cyclic structures which prevent the allylic alcohols from attaining an ideal conformation for the epoxidation process (see Section 3.2.6 and Figure 5 for the proposed ideal conformation).

One especially interesting kinetic resolution/asymmetric epoxidation substrate is (*R*,*S*)-2,4-hexadien-3-ol (**80**).[77] The racemic diene has eight different alkene faces at which epoxidation can occur and thereby presents an interesting challenge to the selectivity of the epoxidation catalyst. The selectivity can be tested by using slightly less than 0.5 equiv. of oxidant (because the substrate is a racemate, the maximum yield of any one product is 50%). When the reaction was run under these conditions, the only product that was formed was the (1*R*,2*R*,3*R*)-epoxy alcohol (**81**). Three different principles of selectivity are required to achieve this result. First, the difference in rate of epoxidation by the catalyst of a disubstituted

**Table 10** Representative Kinetic Resolutions of 1-Substituted Allylic Alcohols

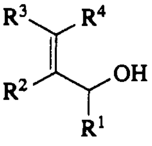

| *Entry* | *R*$^1$ | *Allylic alcohol* *R*$^2$ | *R*$^3$ | *R*$^4$ | *Yield* (%)[a] | *Enantiomeric excess* (%) | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | $CH_2CH{=}CH_2$ | H | 39 | 90 | 110 |
| 2 | c-$C_6H_{11}$ | H | H | H | 32 | >98 | 111 |
| 3 | Et | Me | H | H | b | >98 | 112 |
| 4 | Bu$^n$ | H | H | H | 43 | >90 | 113 |
| 5 | 2,4-$Cl_2C_6H_3$ | 2,4-$Cl_2C_6H_3$ | H | H | 42 | 90 | 114 |
| 6 | Et | H | Ph | H | b | 99 | 77 |
| 7 | $CH_2CH_2Ph$ | H | H | H | b | 99 | 77 |
| 8 | 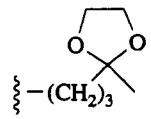 | H | H | H | b | 99 | 77 |
| 9 | $CH_2C({=}CH_2)CH{=}CH_2$ | H | Me | Me | 10 | >99 | 77 |
| 10 | n-$C_{12}H_{25}$ | H | Me | H | 44 | 97 | 115a |
| 11 | Me | Bu$^t$ | H | H | b | 30 | 38 |
| 12 | Bu$^t$ | H | Me | H | b | 5 | 38 |
| 13 | Bu$^n$ | H | $CH{=}CH_2$ | H | 40 | 90 | 115b |
| 14 | $CH_2CO_2Et$ | Me | H | H | 11 | >95 | 115c |
| 15 | $C{\equiv}C$-n-$C_6H_{13}$ | H | H | H | 35 | 95 | 115d |

[a]Maximum yield is 50%. [b]Not reported.

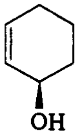

**(71)**

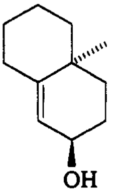

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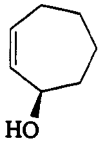

**(73)**

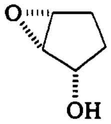

**(74)**

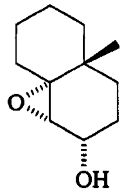

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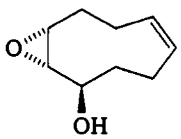

**(76)**

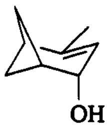

**(77)**

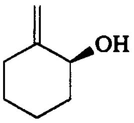

**(78)**

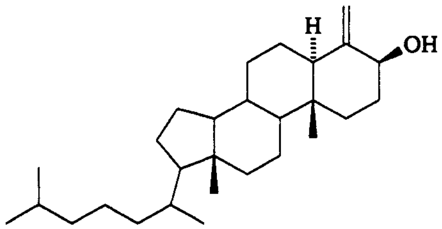

**(79)**

*versus* a monosubstituted alkene must be such that the propenyl group is epoxidized in complete preference to the vinyl group. The effect of this selectivity is to reduce the choice of alkene faces to the four in the propenyl groups. Second, the inherent enantiofacial selectivity of the catalyst as represented in Figure 1 narrows the choice of propenyl faces from four to two. Finally, the steric factor responsible for kinetic resolution of 1-substituted allylic alcohols (Figure 2) determines the choice between the propenyl groups in the enantiomers of (**80**). The net result is the formation of epoxy alcohol (**81**) and enrichment of the unreacted allylic alcohol in the (3*S*)-enantiomer.

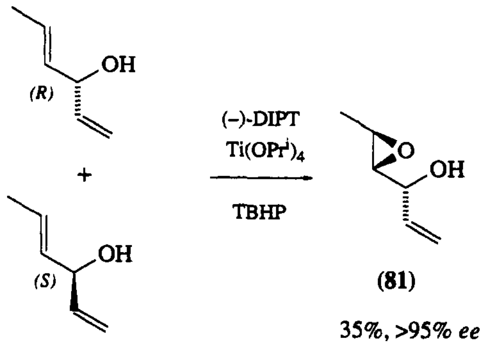

(*R*,*S*)-(**80**)

(**81**)

35%, >95% *ee*

*trans*-1,2-Dialkylcycloalkenes (**82**) have helical chirality and can be resolved if flipping of the ring from one face of the alkene to the other is restricted. These compounds, when appropriately substituted, also serve as synthetic precursors to the betweenanenes. The asymmetric epoxidation approach to kinetic resolution is ideally suited for the resolution of the cycloalkenes when a hydroxymethyl group is one of the substituents on the double bond, as shown for (**82**). The epoxidation of (**82**) with Ti(OPr$^i$)$_4$/(+)-DET and 0.6 equiv. of TBHP was complete within 10 min and gave resolved allylic alcohol (**83**) in 41% isolated yield with no detectable enantiomeric impurity and epoxy alcohol (**84**) in 50% yield (the maximum yield possible for both **83** and **84** is 50%).[121a] A variety of analogs of (**82**) including different ring sizes have been resolved by this method and have been used for the synthesis of optically active betweenanenes.[121b]

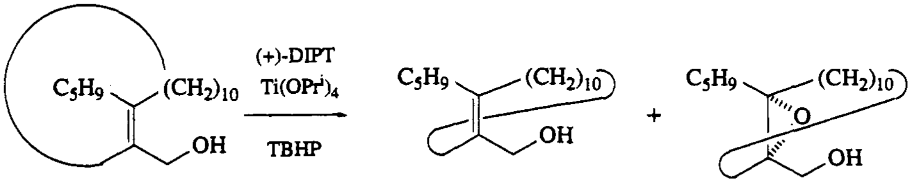

(**82**) (**83**) (**84**)

A final subclass of 1-substituted allylic alcohols is made up of carbinol derivatives having two identical alkenic substituents, the simplest example being 1,4-pentadien-3-ol or divinylcarbinol (**85**). Although these compounds *per se* are achiral, once they bind to the chiral titanium complex the two vinyl groups become stereochemically nonequivalent (diastereotopic). Asymmetric epoxidation now will occur selectively at one of the two vinyl groups, the choice being controlled by factors identical to those in effect during the kinetic resolution process. The similarity can be seen by comparison of the titanium–allylic alcohol complex portrayed in Scheme 3 with the kinetic resolution process depicted in Figure 2. The *pro-S* and *pro-R* conformations shown will be sterically favored and disfavored, respectively, for the same reasons that the enantiomers of chiral C-1 allylic alcohols are distinguished during kinetic resolution. Therefore, epoxidation of (**85**) produces (2*R*,3*S*)-epoxy alcohol (**86**).[122]

Further analysis of the asymmetric epoxidation of divinylcarbinol (**85**), including the minor products, has led to recognition of a second factor that influences the optical purity of the major product (**86**).[26,123] One of the minor epoxy alcohols is enantiomeric to (**86**) and therefore is responsible for lowering the optical purity of (**86**). However, in this minor isomer the configuration of the remaining allylic alcohol group favors a rapid second epoxidation and this isomer is quickly converted to a diepoxide. As a consequence, the optical purity of the major epoxy alcohol (**86**) increases as the reaction progresses. A mathematical equation relating optical purity to the various rates of epoxidation for these divinylcarbinols has been derived. This analysis can also be applied to asymmetric epoxidation of prochiral compounds such as (**87**).[124]

As noted earlier in this section on C-1-substituted compounds, preparation of the epoxy alcohol has been the synthetic objective nearly as often as has been the optically active allylic alcohol. The principles

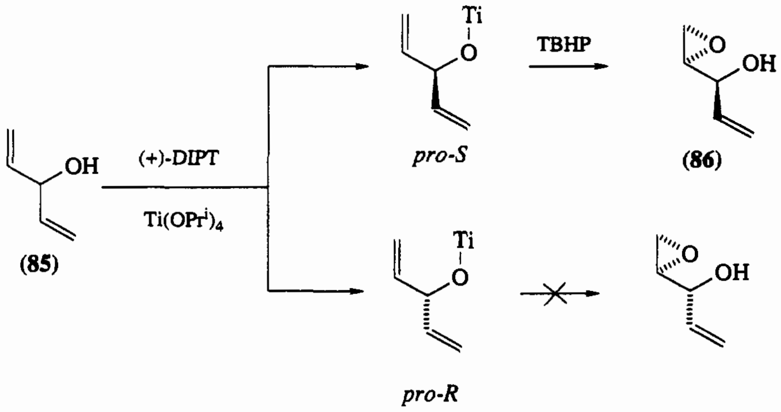

Scheme 3

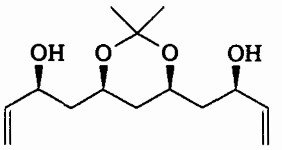

**(87)**

outlined in Figure 2 can again be used to guide the choice of tartrate ester needed in order to obtain the *erythro*-epoxy alcohol of desired absolute configuration. By limiting the amount of oxidant (TBHP) used for the epoxidation to 0.4 equiv. (relative to substrate), optimum optical purity of the epoxy alcohol can be assured and, in most cases, will be excellent. A few representative examples of epoxides prepared in this way are summarized in Table 11. In the special case where the substrate is already homochiral (as in Table 11, entry 5), it should be clear from Figure 2 that asymmetric epoxidation will be successful (with regard to diastereomeric purity) only when the choice of catalyst directs delivery of oxygen to the face of the alkene opposite that of the C-1 substituent. Such choice of catalyst is further illustrated in Scheme 4, wherein the two sequential epoxidations each proceed with >97% diastereoselectivity. The bis(epoxide) is obtained in an overall yield of 80%.[130c]

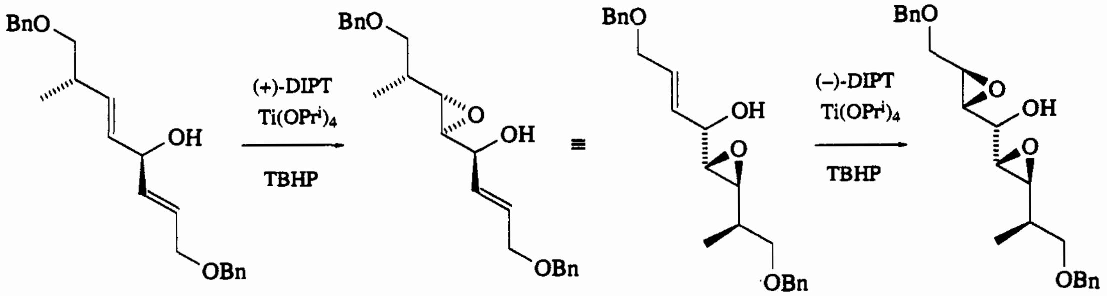

Scheme 4

### 3.2.5.10 1,1-Disubstituted Allyl Alcohols

The rationale that explains the kinetic resolution of the 1-monosubstituted allylic alcohols predicts that a 1,1-disubstituted allylic alcohol will be difficult to epoxidize with the titanium tartrate catalyst. In practice, the epoxidation of 1,1-dimethylallyl alcohol (**88**) with a stoichiometric quantity of the titanium tartrate complex is very slow and no epoxy alcohol is isolated.[131] Clearly, the rate of epoxidation of this substrate is slower than the subsequent reaction(s) of the epoxide.

**Table 11 Epoxides from 1-Substituted Allylic Alcohols**

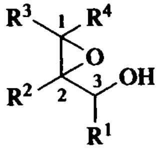

| *Entry* | *$R^1$* | *Epoxide* | | | | | | *Enantiomeric* | |
|---|---|---|---|---|---|---|---|---|---|
| | | *$R^2$* | *$R^3$* | *$R^4$* | *Tartrate* | *Configuration*[a] | *Yield (%)*[b] | *excess (%)* | *Ref.* |
| 1 | Et | H | H | H | (+)-DIPT | (2*R*,3*S*) | c | d | 125 |
| 2 | n-$C_5H_{11}$ | H | H | H | (–)-DIPT | (2*S*,3*R*) | 47 | 91 | 126 |
| 3 | $(CH_2)_6CO_2Me$ | H | H | H | (+)-DIPT | (2*R*,3*S*) | 36 | >95 | 127 |
| 4 | $CH_2C{\equiv}CSiPr^i_3$ | H | H | H | (–)-DIPT | (2*S*,3*R*) | 40 | >90 | 128 |
| 5[e] | Et | Me | H | H | (+)-DIPT | (2*R*,3*R*) | 82 | 92 | 90 |
| 6 | $CH_2CH{=}CH_2$ | H | Me | H | (–)-DIPT | (1*R*,2*R*,3*R*) | 27 | >95 | 129a–129c |
| 7 | $CH(OBn)CH{=}CHMe$ | H | Me | H | (+)-DIPT | (1*S*,2*S*,3*S*) | 35 | >95 | 130a |
| 8 | Me | H | $CH_2CH{=}CH_2$ | H | (–)-DIPT | (1*R*,2*R*,3*R*) | 40 | 90 | 129b |
| 9 | $C_5H_{11}$ | H | $SiMe_3$ | H | (+)-DIPT | (1*S*,2*S*,3*S*) | 40 | 99 | 105b |
| 10 | $CH_2CO_2Et$ | Me | Et | H | (–)-DET | (1*S*,2*S*,3*R*) | d | >95 | 115c |
| 11 | Me | $—CH_2CH{=}C(Me)CH_2—$ | | H | (+)-DIPT | (1*S*,2*S*,3*S*) | 37 | 95 | 130b |

[a] Note that the arbitrary numbering used here may not coincide in all cases (*e.g.* entries 7, 10, 11) with correct *Chemical Abstracts* numbering. [b] Maximum yield is 50%, except for entry 5. [c] The epoxy alcohol was converted without isolation to the ethoxyethyl derivative. [d] Not reported. [e] (3*S*)-2-Methylpent-1-en-3-ol was used as the substrate for this epoxidation.

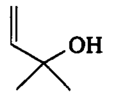

**(88)**

### 3.2.5.11 Homoallylic, Bis(homoallylic) and Tris(homoallylic) Alcohols

In contrast to allylic alcohols, the asymmetric epoxidation of homoallylic alcohols shows the following three general characteristics:[132] (i) the rates of epoxidation are slower; (ii) enantiofacial selectivity is reversed, *i.e.* oxygen is delivered to the opposite face of the alkene when the same tartrate ester is used; and (iii) the degree of enantiofacial selectivity is lower with enantiomeric excesses of the epoxy alcohols in the range 20–55%. A series of seven model homoallylic alcohols, including all but one of the possible substitution patterns, has been subjected to epoxidation using the stoichiometric version of the reaction with the results providing the basis for the preceding generalizations. An analogous complex composed of zirconium(IV) isopropoxide ($Zr(OPr^i)_4$) and (+)-dicyclohexyltartramide has been found to catalyze asymmetric epoxidation of homoallylic alcohols with the same sense of enantiofacial selectivity as the titanium tartrate ester complex. An improvement in enantiomeric excess was noted for epoxy alcohols derived from (*Z*)-homoallylic alcohols (to 77%), while other epoxy alcohols were obtained with enantiomeric excesses comparable to those achieved with titanium.[133]

The tris(homoallylic) alcohol (**89**) undergoes asymmetric epoxidation in a yield of 74% and with 'high' diastereofacial selectivity to give (**90**). Trityl hydroperoxide, which had been shown to be effective in the asymmetric epoxidation of allylic alcohols,[2] was required in order to attain enantiofacial selectivity in the epoxidation of (**89**).[134a] The titanium/tartrate/TBHP-catalyzed conversions of the bis(homoallylic) phenol (**90a**, *n* = 1, R = H) and the tris(homoallylic) analog (**90a**, *n* = 2, R = Me) into dihydrobenzofuran (**90b**, 22% yield, 29% *ee*) and dihydrobenzopyran (**90c**, 49%, 56% *ee*), respectively, is assumed to occur *via* the intermediate epoxides.[134b] The dihydrofuran (**90b**) is assigned the (2*S*,1'*R*)-configuration, whereas the configuration of the dihydropyran (**90c**) is unspecified.

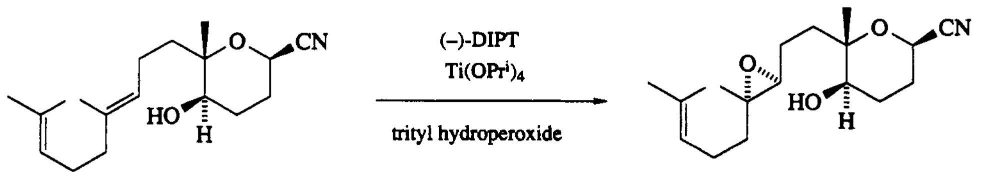

**(89)** **(90)**

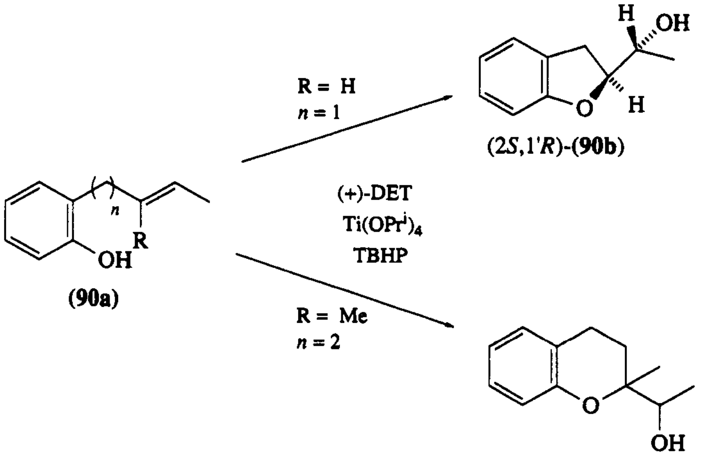

(2*S*,1'*R*)-(**90b**)

(**90a**)

(–)-(**90c**)

## 3.2.6 MECHANISM OF THE TITANIUM TARTRATE CATALYZED ASYMMETRIC EPOXIDATION

The hallmark of titanium tartrate catalyzed asymmetric epoxidation is the high degree of enantiofacial selectivity seen for a wide range of allylic alcohols. The question naturally arises as to what is the mechanism of this reaction and what are the structural features of the catalyst that produce these desirable results. These questions have been studied extensively and the results have been the subject of considerable previous discussion.[2,135,136] For the purpose of this chapter, we wish to review those aspects of the mechanistic–structural studies that may be helpful in devising synthetic applications of this reaction.

$$\mathrm{Ti(OR)_4} + \text{tartrate} \rightleftharpoons [\mathrm{Ti(tartrate)(OR)_2}] + 2\,\mathrm{ROH} \qquad (5)$$

Of fundamental importance to an understanding of the reaction and its mechanism is the fact that in solution there is rapid exchange of titanium ligands.[2] Thus, when equimolar solutions of a titanium alkoxide and a dialkyl tartrate are mixed, the equilibrium represented by equation (5) will be quickly reached with all but the most sterically demanding alkoxides. This equilibrium is shifted far to the right by virtue of the fact that a chelating diol (*i.e.* the tartrate) has a much higher binding constant for titanium than do monodentate alcohols. The binding of tartrate is also enhanced by the increased acidity of its hydroxy groups (due to the inductive effect of the esters). Spectroscopic evidence clearly reveals that two moles of free monodentate alcohol are present at equilibrium. Rapid ligand exchange continues as the hydroperoxide oxidant and the allylic alcohol substrate are added to the reaction medium. Pseudo-first-order kinetic experiments have shown a first order rate dependence on the titanium tartrate complex, the hydroperoxide and the allylic alcohol and an inverse second order dependence on the nonalkenic alcohol ligands (*i.e.* the isopropyl alcohol). The rate law derived from these results is expressed in equation (6).

$$\text{Rate} = k\,\frac{[\mathrm{Ti(tartrate)(OR)_2}][\mathrm{TBHP}][\text{allylic alcohol}]}{[\text{inhibitor alcohol}]^2} \qquad (6)$$

The mechanistic pathway outlined in Scheme 5 is consistent with equation (6) and clearly illustrates the ligand exchange processes essential for catalytic epoxidation. After formation of the [Ti(tartrate)(OR)$_2$] complex, the two remaining alkoxide ligands are replaced in reversible exchange reactions by the hydroperoxide (TBHP) and the allylic alcohol to give the 'loaded' complex [Ti(tartrate)(TBHP)(allylic alcohol)]. Now, in the rate-controlling step of the process, oxygen transfer from the coordinated hydroperoxide to the allylic alcohol gives the complex [Ti(tartrate)(OBu$^t$)(epoxy alcohol)]. The product alkoxides are replaced by more allylic alcohol and TBHP to regenerate the 'loaded' complex and complete the catalytic cycle.

$$\begin{tikzcd}[column sep=huge, row sep=large]
{[\mathrm{Ti(OR)_2(tartrate)}]} \arrow[r, shift left, "\mathrm{TBHP}"] \arrow[d, shift left, "\text{allylic alcohol}\ K'_2"] & {[\mathrm{Ti(OR)(TBHP)(tartrate)}]} \arrow[l, shift left, "\mathrm{ROH}\ K_1"] \arrow[d, shift left, "\text{allylic alcohol}\ K_2"] \\
{[\mathrm{Ti(OR)(allylic\ alcohol)(tartrate)}]} \arrow[u, shift left, "\mathrm{ROH}"] \arrow[r, shift left, "\mathrm{TBHP}"] & {[\mathrm{Ti(TBHP)(allylic\ alcohol)(tartrate)}]} \arrow[l, shift left, "\mathrm{ROH}\ K'_1"] \arrow[u, shift left, "\mathrm{ROH}"] \arrow[d, "k_e" ', "\text{epoxidation}"] \\
K_1K_2 = K'_1K'_2 & {[\mathrm{Ti(OBu^t)(epoxy\ alcohol)(tartrate)}]}
\end{tikzcd}$$

**Scheme 5**

An alternative mechanism invoking an ion-pair transition state assembly has been proposed to account for the enantioselectivity of the asymmetric epoxidation process.[137] In this proposal, two additional alcohol species are required in the transition state complex. This requirement is inconsistent with the kinetic studies of this reaction which have led to the rate law expressed in equation (5) and, therefore, this proposal must be considered incorrect.

Much of the experimental success of asymmetric epoxidation lies in exercising proper control of equation (5).[2] Both Ti(OR)$_4$ and [Ti(tartrate)(OR)$_2$] are active epoxidation catalysts and since the former is achiral, any contribution by that species to the epoxidation will result in loss of enantioselectivity. The addition to the reaction of more than one equivalent of tartrate, relative to titanium, will have the effect of minimizing the leftward component of the equilibrium and will suppress the amount of Ti(OR)$_4$ present in the reaction. The excess tartrate, however, forms Ti(tartrate)$_2$ which has been shown to be a catalytically inactive species and which will cause a decrease in reaction rate that is proportional to the excess tartrate added. The need to minimize Ti(OR)$_4$ concentration and, at the same time, to avoid a drastic reduction in rate of epoxidation is the basis for the recommendation of a 10–20 mol % excess of tartrate over titanium for formation of the catalytic complex. After the addition of hydroperoxide and allylic alcohol to the reaction, the concentration of ROH will increase accordingly and this will increase the leftward pressure on the equilibrium. Fortunately, in most situations this shift apparently is extremely slight and is effectively suppressed by the use of excess tartrate. One situation in which a shift in the equilibrium does begin to occur is when the reaction is run in the catalytic mode and the amount of catalyst used is less than about 5 mol % relative to allylic alcohol substrate. Loss in enantioselectivity then may be observed. This factor is the basis of the recommendation for use of 5–10 mol % of titanium tartrate complex when using the catalytic version of asymmetric epoxidation.

Comparison of the epoxidation rates of several *para*-substituted cinnamyl alcohols reveals that the alkene acts as a nucleophile towards the activated peroxide oxygen in the epoxidation reaction.[136] Relative to unsubstituted cinnamyl alcohol (relative rate = 1), an electron-withdrawing *p*-nitro group decreases the rate of epoxidation (0.42), while an electron-releasing group such as *p*-methoxy increases the rate (4.39). These results are consistent with the alkene acting as a nucleophile. Additional support for this conclusion arises from comparison of the rates for epoxidation of less-substituted allylic alcohols with those for more highly substituted analogs. A clear example of this substituent effect is seen in the epoxidation of (*R*,*S*)-2,4-hexadien-3-ol (**80**), described in the preceding section, where the propenyl group is epoxidized in nearly complete preference to the vinyl group.[77] Another example is seen with the allylic–homoallylic alcohol (**91**), where epoxidation occurs preferentially at the tetrasubstituted homoallylic alkene to give (**92**).[99] The preferential epoxidation of the more highly substituted alkene in these compounds is consistent with a nucleophilic role for the alkene.

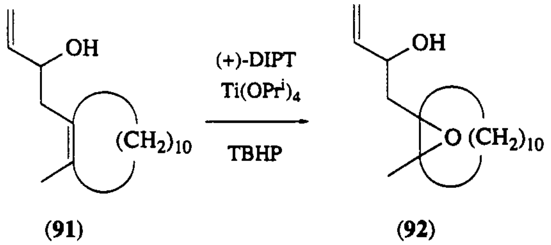

**(91)** **(92)**

While the mechanistic scheme portrayed in Scheme 5 provides important insight into the experimental aspects of asymmetric epoxidation, it sheds little light on the structure of the catalyst and on the features of the catalyst responsible for the concurrent high stereoselectivity and broad generality. The rapid ligand exchange, so crucial to the success of the reaction, makes characterization of the catalyst structure extremely difficult. Some reliable structural information has been obtained from spectroscopic measurements on the complex in solution.[2,136b] These data clearly support the conclusion that the major molecular species formed in solution is the dimeric composite [Ti$_2$(tartrate)$_2$(OR)$_4$]. Efforts to isolate this complex, ideally as a crystalline solid, have so far been fruitless. Therefore, assignment of a structure to the dimeric complex has depended on information provided by the X-ray crystallographic structure obtained for the closely related complex [Ti$_2$(dibenzyltartramide)$_2$(OR)$_4$].[138] The assumption of a similarity of structure for these two complexes receives some support from the fact that both catalyze the epoxidation of α-phenylcinnamyl alcohol with the same enantiofacial selectivity. From this analogy, the structure shown in equation (7) has been proposed for the [Ti$_2$(tartrate)$_2$(OR)$_4$] complex. This structure has a $C_2$ axis of symmetry with the two titanium atoms in identical stereochemical environments. To account for the fact that the tartrate ester groups all are identical in the room temperature NMR spectrum, a fluxional equilibrium between the two structurally degenerate complexes shown in equation (7) has been proposed. Catalysis of the epoxidation process is thought to involve only one of the two titanium atoms but the possibility that both are required has not yet been ruled out.

'Loading' of the catalyst with hydroperoxide and substrate can now be considered in terms of the proposed structure.[2] Orientation of these two ligands on the catalyst becomes a crucial issue. Three coordi-

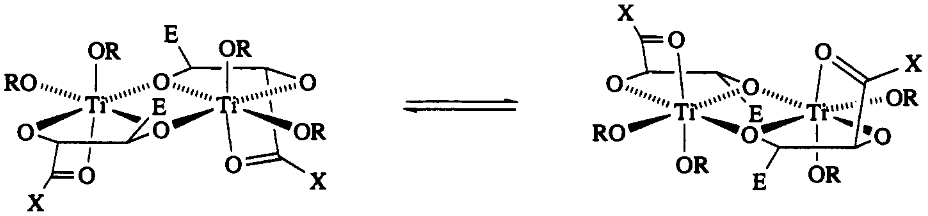
(7)

nation sites, two axial and one equatorial, become available by exchange of two isopropoxides and dissociation of the coordinated ester carbonyl group. These processes can occur with minimal perturbation of the remaining catalyst structure. The three coordination sites are in a semicircular (*i.e.* meridional) array around one edge of the catalyst surface. In the reactive mode, coordination of the hydroperoxide is assumed to be bidentate by analogy to the precedent of bidentate TBHP coordination to vanadium.[2,139] The hydroperoxide must occupy the equatorial and one of the two available axial coordination sites with the allylic alcohol in the remaining axial site. In order to achieve the necessary proximity for transfer of oxygen (the distal peroxide oxygen is assumed to be transferred) to the alkene, the distal oxygen is placed in the equatorial site (Figure 5) and the proximal oxygen is placed in the axial site. The axial site on the lower face of the complex (as drawn in Figure 5) is chosen for the peroxide because of the larger steric demands of the *t*-butyl group, or especially of the trityl group when trityl hydroperoxide is used, in comparison to the allylic alcohol.

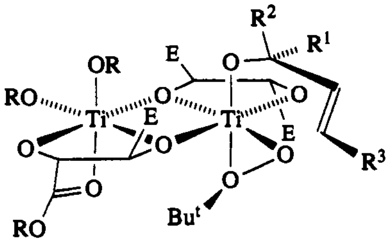

**Figure 5** Proposed structure of 'loaded' catalyst at the time of oxygen transfer

The allylic alcohol binds to the remaining axial coordination site where stereochemical and stereoelectronic effects dictate the conformation shown in Figure 5.[2] The structural model of catalyst, oxidant and substrate shown in Figure 5 illustrates a detailed version of the formalized rule presented in Figure 1. Ideally, all the observed stereochemistry of epoxy alcohol and kinetic resolution products can be rationalized according to the compatibility of their binding with the stereochemistry and stereoelectronic requirements imposed by this site.[2] A transition state model for the asymmetric epoxidation complex has been calculated by a frontier orbital approach and is consistent with the formulation portrayed in Figure 5.[140]

## 3.2.7 OTHER ASYMMETRIC EPOXIDATIONS AND OXIDATIONS CATALYZED BY TITANIUM TARTRATE COMPLEXES

### 3.2.7.1 $Ti_2$(tartrate)$_2$ Complex

The discussion to this point has focused entirely on the epoxidation of allylic (and homoallylic) alcohols catalyzed by the [$Ti(OR)_2$(tartrate)] complex. The role of the alkene as a nucleophile towards the activated peroxide oxygen in this reaction has been established (see Section 3.2.6). If the alkene of the allylic alcohol is replaced by another nucleophilic group then, in principle, oxidation of that group may occur (equation 8).[141] In practice, oxidations of this type have been observed and generally have been carried out with a substrate bearing a racemic secondary alcohol so that kinetic resolution is achieved. While these oxidations are not strictly within the scope of this chapter, they are summarized briefly in equations (9) to (11) in order to acquaint the reader with other potential uses for the titanium tartrate catalytic complex. In the kinetic resolutions shown in equations (9) and (10), the oxidations are controlled by limiting the amount of oxidant used to 0.6 equiv. Only modest resolution was attained for the alkynic alcohol (equation 9, 21% *ee*)[77] and the allenic alcohol (equation 10, 40% *ee*).[77] Resolutions of the furanols[142] or the thiophene alcohols[143] of equation (11) generally are excellent (*ca.* 90–98% *ee*, except when $R^1$ is a *t*-butyl group). Only in the kinetic resolution of the furanols has the oxidation product been identified and, in that case, is a dihydropyranone.

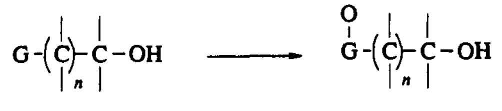
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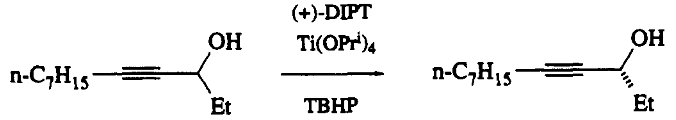

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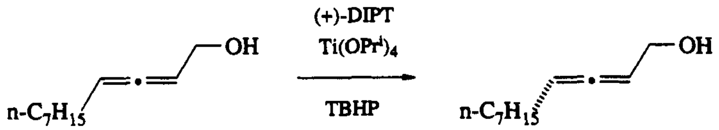

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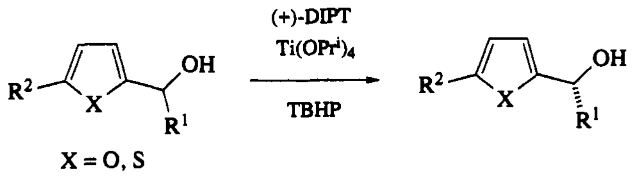

(11)

The asymmetric epoxidation of an allylic alcohol in which the carbinol has been replaced by a silanol has been described.[144] As shown in equation (12), (3*E*)-phenylethenyldimethylsilanol is converted to an epoxy silanol in 50% yield with 85–95% *ee*. Note that here the longer Si—C bonds appear to overcome the restriction to epoxidation associated with a fully substituted C-1 atom in the allylic alcohol series. Fluoride cleavage of the silanol group gives (*S*)-styrene oxide.

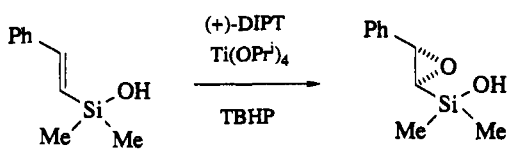

(12)

### 3.2.7.2 $Ti_2$(tartrate) Complex

The β-hydroxyamines are a class of compounds which fall within the generic definition of equation (8). When the alcohol is secondary, the possibility for kinetic resolution exists if the titanium tartrate complex is capable of catalyzing the enantioselective oxidation of the amine to an amine oxide (or other oxidation product). The use of the 'standard' asymmetric epoxidation complex, *i.e.* $Ti_2(tartrate)_2$, to achieve such an enantioselective oxidation was unsuccessful. However, modification of the complex so that the stoichiometry lies between $Ti_2(tartrate)_1$ and $Ti_2(tartrate)_{1.5}$ leads to very successful kinetic resolutions of β-hydroxyamines. A representative example is shown in equation (13).[141b,141c] The oxidation and kinetic resolution of more than 20 secondary β-hydroxyamines[141,145] provides an indication of the scope of the reaction and of some structural limitations to good kinetic resolution. These results also show a consistent correlation of absolute configuration of the resolved hydroxyamine with the configuration of tartrate used in the catalyst. This correlation is as shown in equation (13), where use of (+)-DIPT results in oxidation of the (*S*)-β-hydroxyamine and leaves unoxidized the (*R*)-enantiomer.

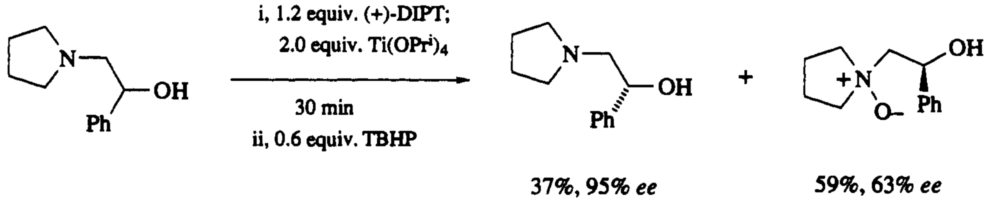

(13)

### 3.2.7.3 Ti(tartramide) Complexes

A number of derivatives of the tartaric acid structure have been examined as substitutes for the tartrate ester in the asymmetric epoxidation catalyst. These have included a variety of tartramides, some of which are effective in catalyzing asymmetric epoxidation (although none display the broad consistency of results typical of the esters). One notable example is the dibenzyltartramide which in a 1:1 ratio (in reality, a 2:2 complex as shown by an X-ray crystallographic structure determination[138]) with Ti(OPr$^i$)$_4$ catalyzes the epoxidation of allylic alcohols with the same enantiofacial selectivity as does the titanium tartrate ester complex.[18] Remarkably, when the ratio of dibenzyltartramide to titanium is changed to 1:2, epoxidation is catalyzed with *reversed* enantiofacial selectivity. These results are illustrated for the epoxidation of α-phenylcinnamyl alcohol (equation 14). α-Phenylcinnamyl alcohol is a particularly felicitous substrate for asymmetric epoxidation; epoxidation of other allylic alcohols with the 1:2 dibenzyltartramide–titanium complex does not give as high enantioselectivities but the reversed selectivity is consistent throughout.[18] An extensive listing of tartramides used in the epoxidation of α-phenylcinnamyl alcohol with both 1:1 and 1:2 catalysts has been tabulated elsewhere.[2]

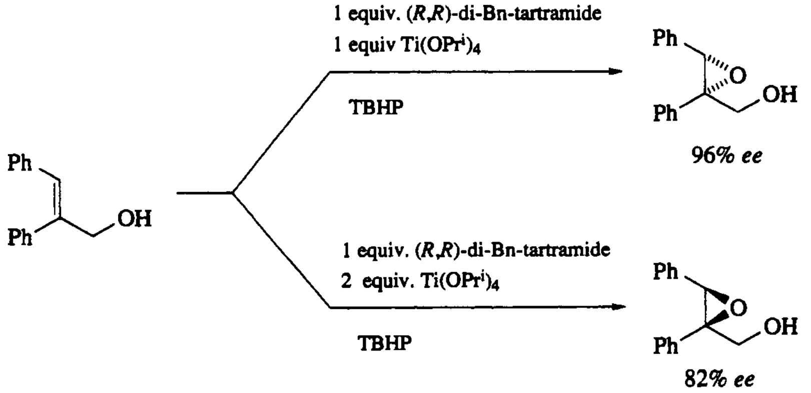

(14)

### 3.2.7.4 [Ti(OPr$^i$)$_2$Cl$_2$(tartrate)] Complexes

As described in earlier sections of this chapter, certain epoxy alcohols, *e.g.* the 2-monosubstituted epoxy alcohols, are particularly susceptible to ring-opening processes. With the intent of controlling the ring-opening reaction, the epoxidation catalyst was modified by the use of [Ti(OPr$^i$)$_2$Cl$_2$] in place of Ti(OPr$^i$)$_4$, the idea being to open the ring with chloride to produce a chlorodiol.[18] This modification was successful with 3-chloro-1,2-diols being formed in yields of 60–80% with good regioselectivity. Epoxy alcohols were assumed to be intermediates in these reactions and can be regenerated from the chlorodiols by base-promoted ring closure. Unfortunately, the enantioselectivity of the process varies from 20–70% *ee*. A point of interest concerning the chlorohydroxylation process is the fact that the enantiofacial selectivity is reversed from that of the normal asymmetric epoxidation process and is not altered by changing the [Ti(OPr$^i$)$_2$Cl$_2$]:tartrate ratio from 1:1 to 2:1. Chlorohydroxylation of 2-(6-chloropyridin-2-yl)-2-propen-1-ol (shown in equation 15) followed by closure of the epoxide ring has provided a useful route to the optically active epoxy alcohol in 50% yield and with 90% *ee*.[145b]

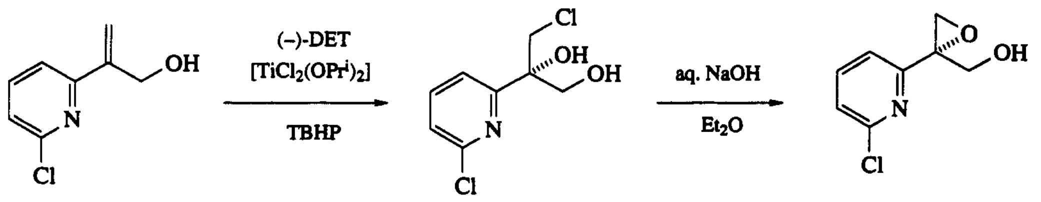

(15)

### 3.2.7.5 $[Ti(tartrate)_2(H_2O)]$ Complex

A complex of $Ti(OPr^i)_4$ and tartrate ester in a 1:2 ratio to which one equivalent of water is added has been found to oxidize prochiral sulfides to optically active sulfoxides.[146,147a] Yields of sulfoxides range from 50–95% and asymmetric inductions are in the range 75–95% *ee* for alkyl aryl sulfoxides and in the range 50–71% *ee* for dialkyl sulfoxides. The correlation between tartrate configuration and sulfoxide configuration shown in equation (16) has been found consistently when one of the sulfide substituents is an aryl group. As substrates, these sulfides differ from previously discussed substrates in one important respect: there is no adjacent hydroxy group by which the molecule may coordinate to titanium during the oxidation. This system appears to provide one of the first examples of effective asymmetric catalysis without the need for prior binding or tethering of the substrate to the catalyst (see Section 3.2.9 for another example of this presently rare phenomenon).[146]

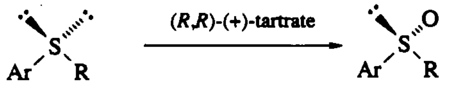

(16)

## 3.2.8 OTHER ASYMMETRIC EPOXIDATION METHODS

A review of nonenzymatic asymmetric epoxidations covering the literature through 1983 has been published elsewhere.[2] Improved enantioselectivity (to as high as 64% *ee*) for epoxidations of some alkenes with chiral oxaziridines has been described and results are included in a review of synthetic applications of oxaziridines.[147b] A summary of *catalytic* asymmetric epoxidations of alkenes is presented in Table 12, together with brief comments on each method.

Preliminary results for asymmetric epoxidations of (*E*)-cinnamyl alcohol and geraniol using (1*S*,2*S*)-1,2-di(2-methoxyphenyl)ethane-1,2-diol or (1*S*,2*S*)-1,2-di(4-methoxyphenyl)ethane-1,2-diol as chiral auxiliaries with titanium(IV) isopropoxide and TBHP have been described. High enantioselectivity (95% *ee*) is observed when the 2-methoxyphenyl compound is used, while somewhat lower enantioselectivity (64% *ee*) and *opposite face selectivity* is described for the catalyst comprised of the 4-methoxyphenyl analog.[149a] Further elaboration of the scope and generality of these observations will be of interest.

Sulfur ylides, derived from benzyl bromides and an optically active alkyl sulfide, undergo base-promoted reactions with aryl aldehydes to produce optically active 1,2-diaryl epoxides.[149b] The reaction is illustrated by equation (17) and produces epoxides with optical purities in the range of 28–47% *ee*. The bicyclic sulfide shown in equation (17) was derived from (+)-camphorsulfonic acid and produces the (*R*,*R*)-enantiomer of the epoxide in excess.

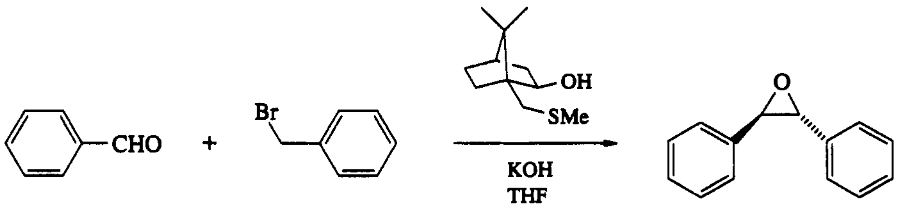

(17)

Asymmetric induction occurs during the alkylation of ketones with the α-sulfinyl carbanion derived from optically active 1-chloroalkyl-*p*-tolyl sulfoxides (equation 18).[149c] The resulting chloro alcohol may be converted to an optically active epoxide under alkaline conditions and the sulfinyl group is removed with n-butyllithium. While the process benefits from high asymmetric induction in the alkylation reaction, it must be recognized that, when either $R \neq H$ and/or $R^1 \neq R^2$, diastereomeric compounds are formed and require separation.

Asymmetric epoxidation of 2-alkylnaphthoquinones is achieved with TBHP in a buffered (pH 9) medium containing bovine serum albumin, but enantioselectivity is extremely sensitive to reaction condi-

**Table 12** Catalytic Asymmetric Epoxidation of Unfunctionalized Alkenes

| *Entry* | *Catalyst*[a] | *Oxidant* | *Substrate* | *ee (%)* | *Features and drawbacks* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | [MoO$_2$(acac)$_2$]/DIPT | TBHP | 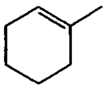 | 10 | 50 turnovers<br>All components commercially available and inexpensive<br>Very low selectivity<br>No subsequent promising results in catalysis with similar systems | 148a |
| 2 | A[a], M = FeCl, R = 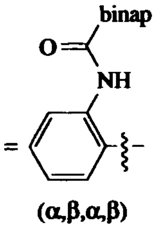 | 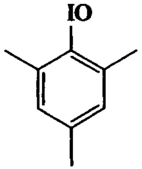 | 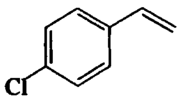 | 51 | First successful use of a chiral metal oxo-based system for catalytic asymmetric epoxidation<br>Ligand prepared in <<1% yield<br>Reactions taken to 30% conversion of alkene<br>Limited to terminal alkenes | 148b |
| 3 | B[a], M = FeCl RR = 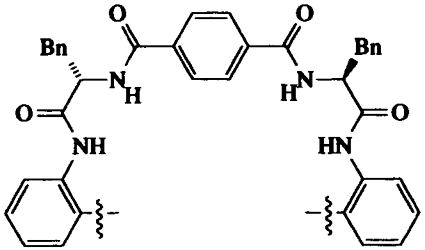 | 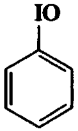 | 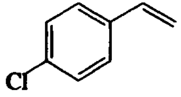 | 50 | First use of peptide/porphyrin complex<br>0.3% conversion of alkene<br>Difficult ligand synthesis (overall yield not reported) | 148c |
| 4 | [(chiraphos)Pt(CF$_3$)(CH$_2$Cl$_2$)]BF$_4$ | H$_2$O$_2$ | 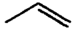 | 41 | High turnover numbers<br>Cheap oxidant<br>Tartrate-derived ligand<br>Reasonable success with difficult substrates<br>Only two substrates examined<br>Expensive metal | 148d |
|  |  |  | 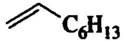 | 36 |  |  |

**Table 12** *(continued)*

| *Entry* | *Catalyst*[a] | *Oxidant* | *Substrate* | *ee* (%) | *Features and drawbacks* | *Ref.* |
|---|---|---|---|---|---|---|
| 5 | C[a], M = FeCl<br>R,R = 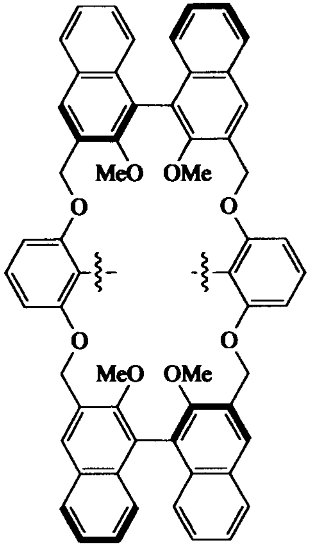 | 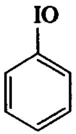 | 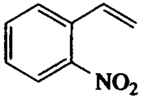 | 80 | High % *ee* reported for electron deficient styrenes<br><br>Ligand prepared in extremely low yield<br>Styrene gave only 14% *ee*<br>Reactions taken to only 20% conversion of alkene | 148e |
| 6 | A[a], M = MnCl<br>(α,β,α,β)<br>R = 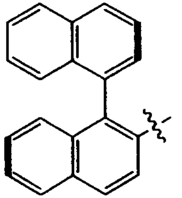 | NaOCl | 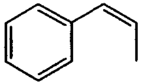 | 40 | Extremely sturdy catalyst (86% recovery after 2800 turnovers)<br>Good turnover rates<br>Cheap oxidant<br><br>Ligand prepared in low yield<br>Relatively low selectivity | 148f |

**Table 12** *(continued)*

| *Entry* | *Catalyst*[a] | *Oxidant* | *Substrate* | *ee* (%) | *Features and drawbacks* | *Ref.* |
|---|---|---|---|---|---|---|
| 7 | M = MnPF$_6$ 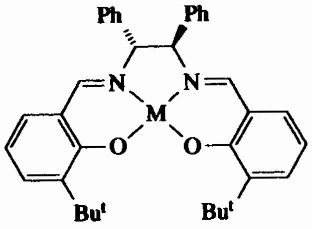  Ph<br>Ph<br>N<br>N<br>M<br>O<br>O<br>Bu$^t$<br>Bu$^t$ | 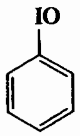 | 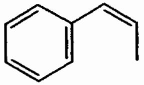 | 84 | Ligand synthesized in simple high yield steps<br>50 turnovers with NaOCl<br>Complete conversion of alkene<br>Structurally characterized catalyst precursor<br>*trans*-Disubstituted alkenes give only 20–34% *ee* | 148g |
| | | or | 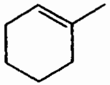 | 59 | | |
| | | NaOCl | 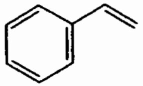 | 57 | | |

[a] A =

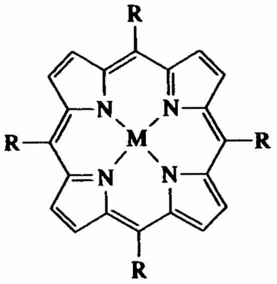

B =

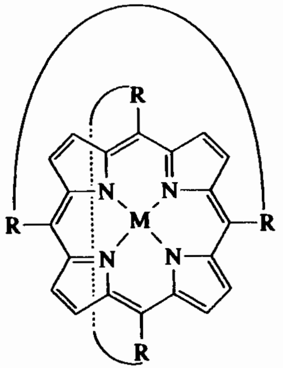

C =

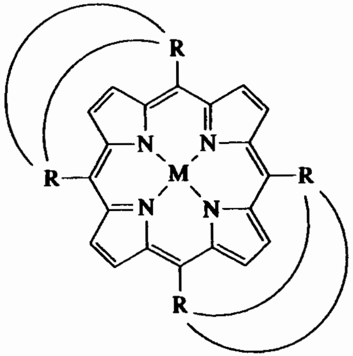

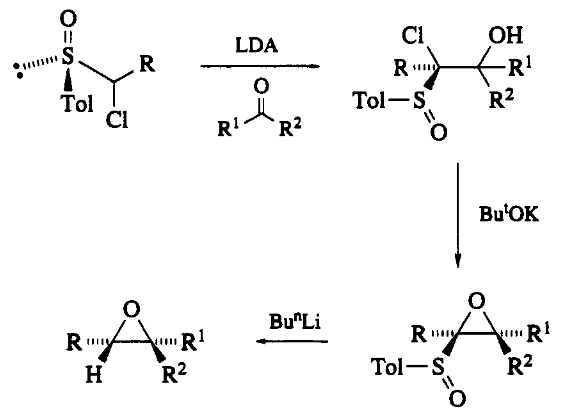

(18)

tions as well as to the nature of the alkyl substituent.[150a] Other routes to asymmetric epoxides have been described which employ enzymatic catalysis. The bacterium *Xanthobacter* Py2 has been used to resolve several 2,3-epoxyalkanes, such as *trans*-2,3-epoxypentane, by selective metabolism of one enantiomer of the substrate.[150b] In a similar vein, both hog pancreatic lipase and hog liver esterase have been used to selectively hydrolyze one enantiomer of 2,3-epoxy alcohol esters and thereby produce the optically active epoxy alcohol.[151]

A final method which has the potential for producing epoxides with high enantiomeric excess is biological epoxidation of alkenes. Microbial epoxidations have been known for at least 30 years[152] and find value as solutions to specific problems. Several examples illustrate the application of this method. Epoxidation of 1,7-octadiene by *Pseudomonas oleovorans* gives (*R*)-7,8-epoxy-1-octene (**93**) in 25% yield and with >80% *ee*.[153] 1-Hexadecene is epoxidized with >95% *ee* and in 41% yield to (*R*)-1,2-epoxyhexadecane (**94**) by *Corynebacterium equi*.[154] Similar epoxidations of terminal alkenes by *Nocardia corallina* yield epoxides with 76–90% *ee*.[155] The antibiotic fosfomycin (**95**) is produced in 90% yield by epoxidation of (*Z*)-2-methyl-1-vinylphosphonic acid with *Penicillium spinulosum*.[156] The optical purity of the epoxide was claimed to be high, based on an optical rotary dispersion measurement. Finally, several organisms useful for dihydroxylation of terpenes, presumably *via* intermediate epoxides, have been described and are the fungi *Corynespora cassicola*,[157a] *Diploda gossypina*[157a] and *Aspergillus niger*.[157b] The first of these is reported to oxidize 1300 g of (*R*)-(+)-limonene to 900 g of the (1*S*,2*S*)-diol (**96**) in 96 h at a level of 20 g $l^{-1}$ of fermentation medium.

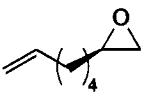

**(93)**

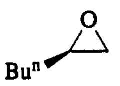

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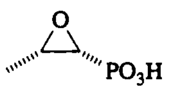

**(95)**

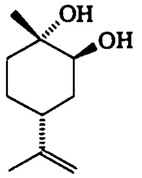

**(96)**

### 3.2.9 HOMOCHIRAL EPOXIDES *VIA* ASYMMETRIC DIHYDROXYLATION

Allylic alcohols represent a small fraction of the total population of alkenes found in organic molecules. Asymmetric epoxidation of allylic alcohols therefore taps only a small portion of the synthetic potential inherent in a completely general asymmetric epoxidation of isolated (nonfunctionalized) alkenes. A partial solution to this problem now exists. The recent development of a catalytic asymmetric process for the dihydroxylation of alkenes[158] provides an indirect route to epoxides or epoxide-like functionalization of alkenes. The stereochemistry of the process, the scope of enantioselectivity and chemical yield and a summary of key chemical transformations are presented in this section. Since this approach to alkene functionalization is at an early stage of development, the results summarized here are certain to benefit from extensions and improvements as research in this area progresses.

The essential components of the catalyst for the asymmetric dihydroxylation process are osmium tetroxide ($OsO_4$) and an ester of one or the other of the pseudoenantiomeric cinchona alkaloids dihydroquinidine (DHQD) and dihydroquinine (DHQ). An amine oxide, generally *N*-methylmorpholine *N*-oxide, serves as the oxidant for the reaction.[158] When an alkenic substrate is added very slowly to a mixture of the preceding reagents, asymmetric *cis*-dihydroxylation takes place in accord with the scheme shown in Figure 6.[158,159] When a DHQD ester is used as the asymmetric ligand, oxygen 'delivery' will occur from above the alkene plane when oriented as in Figure 6. When a DHQ ester is the ligand, oxygen delivery will be from below the plane of the alkene. A final ingredient of the reaction is water which is required for hydrolysis of the intermediate osmate ester to regenerate the catalyst and yield the vicinol diol product. The isolated yield of diol usually is in the range of 80–95%.

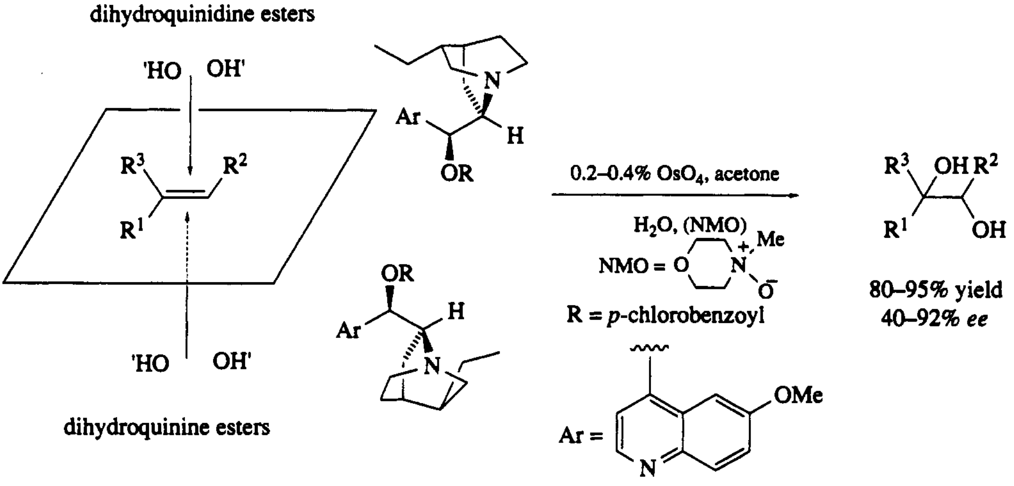
dihydroquinidine esters
'HO OH'
R3
R2
R1
'HO OH'
dihydroquinine esters
Ar
N
H
OR
0.2–0.4% OsO4, acetone
H2O, (NMO)
NMO =
Me
R = p-chlorobenzoyl
Ar =
OMe
R3 OH R2
R1 OH
80–95% yield
40–92% ee

**Figure 6** Enantiofacial selectivity in the dihydroxylation of alkenes with osmium tetroxide/alkaloid ester/NMO

The enantioselectivity of the process, as reflected by enantiomeric excesses, shows a rough correlation with the substitution pattern of the alkene, as shown in Figure 7. Highest enantiomeric excesses (70–90%) are obtained with *trans*-1,2-disubstituted alkenes. Trisubstituted (35–80% *ee*) and monosubstituted (25–60% *ee*) alkenes show greater variation in enantioselectivity while poorest enantioselectivity is observed with *cis*-1,2-disubstituted alkenes (<25% *ee*).

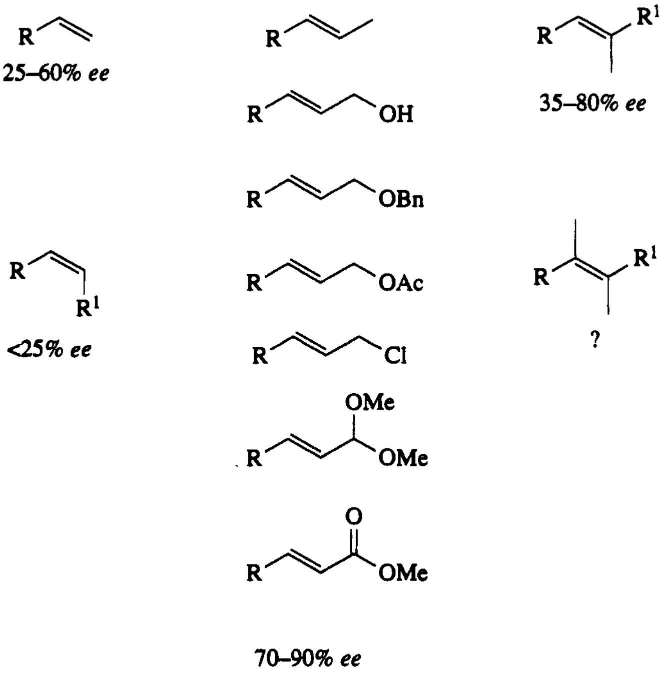
R
25–60% ee
R
R OH
R OBn
R OAc
R Cl
OMe
R OMe
O
R OMe
70–90% ee
R R1
35–80% ee
R R1
<25% ee
R R1
?

**Figure 7** Range of enantioselectivity (expressed as % *ee*) observed in the asymmetric dihydroxylation of alkenes with different substitution patterns

The asymmetric dihydroxylation is one of the simplest catalytic asymmetric processes to perform. The reaction is completely insensitive to water and oxygen and is performed in an open vessel in the range 0–25 °C. The activity of the catalyst is very good so that only 0.2–0.4% is commonly used. There is only weak product inhibition of the reaction so that high substrate concentrations (*e.g.* 2 M) give excellent results. The cinchona alkaloid ligand is easily recovered and reused.

The diols (**97**) from asymmetric dihydroxylation are easily converted to cyclic *sulfite* esters (**98**) and thence to cyclic *sulfate* esters (**99**).[160] This two-step process, reaction of the diol (**97**) with thionyl chloride followed by ruthenium tetroxide catalyzed oxidation, can be done in one pot if desired and transforms the relatively unreactive diol into an epoxide mimic, *i.e.* the 1,2-cyclic sulfate (**99**), which is an excellent electrophile. A survey of reactions shows that cyclic sulfates can be opened by hydride, azide, fluoride, thiocyanide, carboxylate and nitrate ions.[160] Benzylmagnesium chloride and the anion of dimethyl malonate can also be used to open the cyclic sulfates.[160] Opening by a nucleophile leads to formation of an intermediate β-sulfate anion (**100**) which is easily hydrolyzed to a β-hydroxy compound (**101**).[160] Conditions for catalytic acid hydrolysis have been developed that allow for selective removal of the sulfate ester in the presence of other acid sensitive groups such as acetals, ketals and silyl ethers.[161]

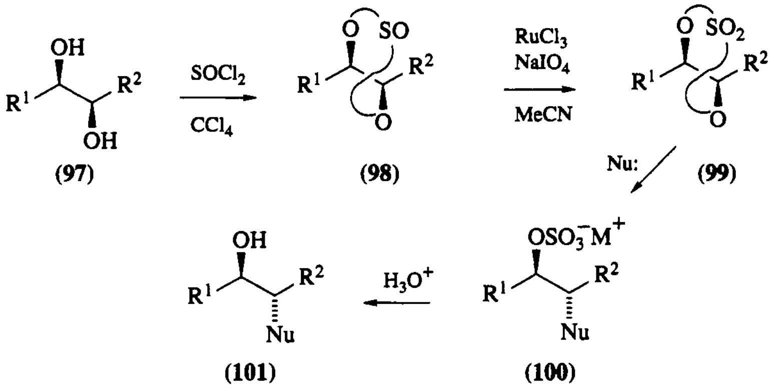

The β-sulfate need not be hydrolyzed and can instead be used as a leaving group for a second nucleophilic displacement reaction. For example, when the first-added nucleophile retains a nucleophilic capability, an intramolecular cyclization can be achieved *via* displacement of the sulfate group. The consequence of this sequence is illustrated by the reaction of cyclic sulfate (**102**) with malonate anion to generate the cyclopropane derivative (**103**).[160] This approach can also be used to prepare aziridines.[162] Opening of the cyclic sulfate (**99**) with azide gives an intermediate azidosulfate (**104**) which, after reduction of the azide to an amino group, undergoes intramolecular cyclization to form an aziridine (**105**). Alternately, opening with a primary amine leads to an aminosulfate (**106**) which can undergo hydrolysis to an amino alcohol (**107**) or cyclization to the *N*-substituted aziridine (**108**).

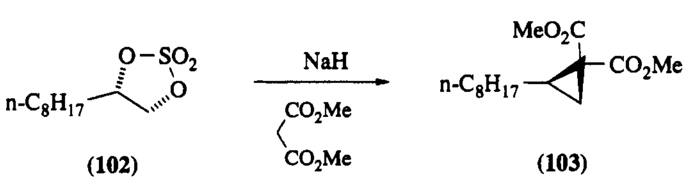

Not surprisingly, the regioselectivity in cyclic sulfate openings is strongly influenced by the nature of groups $R^1$ and $R^2$. Notable in this regard is the virtually complete (>100:1) regioselective attack by nucleophiles at the α-carbon of cyclic sulfates adjacent to carboxylic esters such as (**109**).[160] By contrast, analogous glycidic (α,β-epoxy) esters show no clear preference for C-2 *versus* C-3 opening by nucleophiles.

If desired, glycidic esters can be derived from α,β-dihydroxy esters, such as (**110**), by either of two methods. In one method, reaction of the diol with an arenesulfonyl chloride is regioselective, producing the α-arenesulfonate (**111**) in preference to the β-sulfonate. Treatment of (**111**) with an equivalent of base produces the *erythro*-glycidic ester (**112**) in good yield. In the second method, the diol is converted to a bromohydrin (**114**) *via* the acetoxy bromide (**113**). The bromohydrin (**114**) affords the *threo*-glycidic ester (**115**) on exposure to potassium carbonate in methanol.[163]

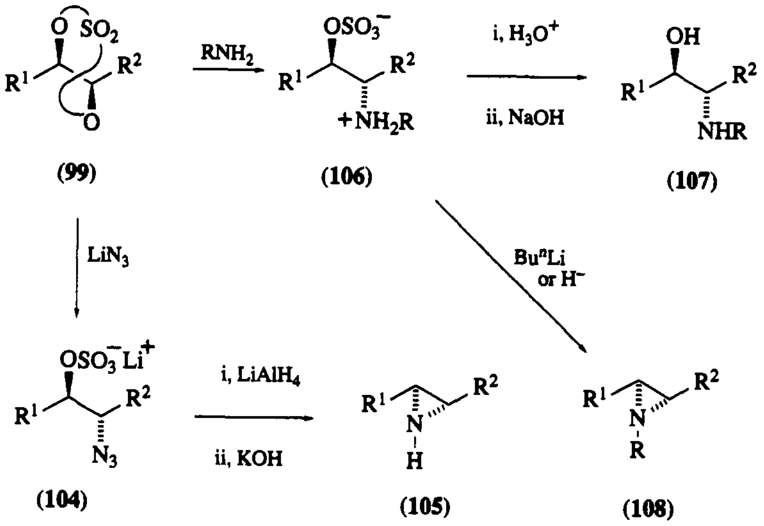
(99)
RNH2
(106)
i, H3O+
ii, NaOH
(107)
LiN3
Bu^nLi or H^-
(104)
i, LiAlH4
ii, KOH
(105)
(108)

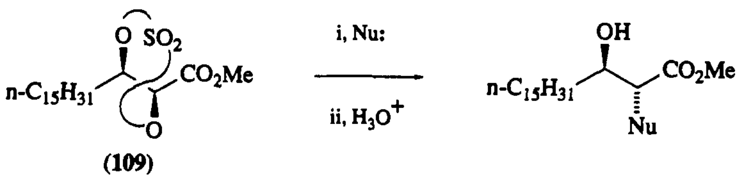
(109)
i, Nu:
ii, H3O+
n-C15H31
CO2Me
Nu

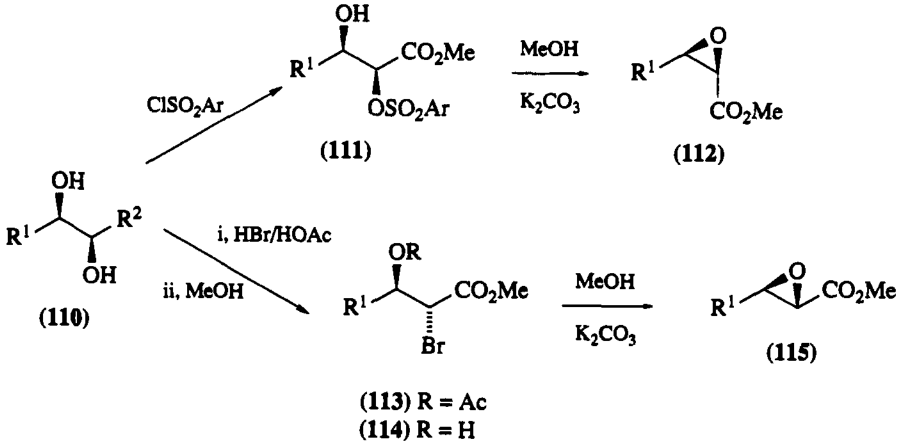
ClSO2Ar
(111)
MeOH
K2CO3
(112)
(110)
i, HBr/HOAc
ii, MeOH
(113) R = Ac
(114) R = H
MeOH
K2CO3
(115)

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# 3.3

# Addition Reactions with Formation of Carbon–Oxygen Bonds: (iii) Glycol Forming Reactions

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## 3.3.1 INTRODUCTION

The addition of hydroxy groups to the carbon–carbon double bond of an alkene (equation 1) is classed under the IUPAC nomenclature for transformations[1] as a dihydroxy addition. Many reagents can bring about this transformation,[2–9] which can proceed in a *syn* or *anti* manner, as shown in equation (2), and the type of addition which occurs depends on the reagent.

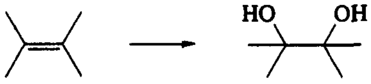

(1)

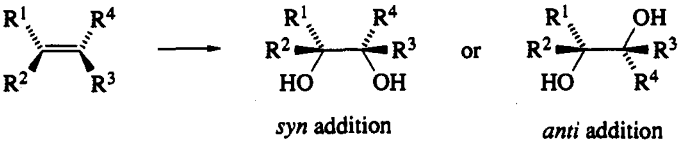

*syn* addition

*anti* addition

(2)

*Syn* hydroxylation is most commonly performed using osmium tetroxide or potassium permanganate, and addition usually occurs from the less hindered side of the double bond in the absence of other directing effects. With these reagents, the stereospecificity of *syn* addition results from formation of cyclic ester intermediates. Support for these arises from isolation of solid addition complexes (**1**) on reaction of alkenes with osmium tetroxide in the presence of tertiary amines (L),[6] and from spectral measurements during permanganate hydroxylations, which have been interpreted[9] in terms of the intermediate (**2**).

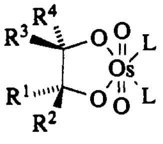

**(1)**

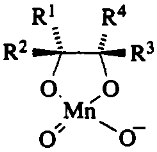

**(2)**

The oxidation of alkenes by osmium tetroxide has been thought, in general, to proceed by a direct oxygen attack at the unsaturated centers in a concerted [3 + 2] cycloaddition step, affording the six-electron transition state (**3**) in equation (3a). This type of transition state is supported by molecular orbital calculations.[10] An alternative mechanism[11,12] involves the intermediacy of the metallocycle (**4**; equation 3b), which might arise from an initially formed complex containing osmium π-bonded to the alkene or, possibly, by a direct [2 + 2] cycloaddition.[12] (A modified mechanism in which the initial π-complex reacts with a ligand to afford a complex like (**4**), but with the ligand attached to osmium, has been suggested.[12] This latter complex then reacts with a second molecule of the ligand, inducing formation of the complex **1**.) Evidence that (**4**) is a possible intermediate in alkene hydroxylation with the tetroxide comes from the enantioselective oxidation of (*E*)-stilbene in the presence of a chiral diamine[13] (see Section 3.3.2.1).

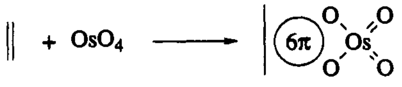

**(3)** (3a)

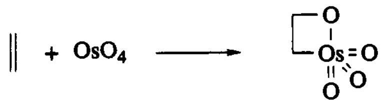

**(4)** (3b)

*Syn* hydroxylation from the more hindered face of a π-system can be effected using Woodward's procedure[2,4,5,14] in which an alkene is treated with iodine–silver acetate in acetic acid containing water. Variants of this method avoid the use of silver salts.[15–19] A versatile procedure by which *syn* hydroxylation can be performed on either the more hindered or less hindered face of an alkene relies on stereoselective formation of the appropriate *trans*-bromohydrin from the alkene.[20]

*Anti* hydroxylation of an alkene is readily achieved with peroxycarboxylic acids.[2,4,5] Acid-catalyzed ring opening of the initial product, an oxirane (epoxide), forms the monoester of a 1,2-diol, hydrolysis of which affords the parent diol. Alternative reagents which are often used for *anti* hydroxylation of alkenes are hydrogen peroxide with oxides of tungsten[2,4,5,21] or selenium,[2,4,5,21] and iodine–silver benzoate (Prévost reaction).[2,4,5]

With careful choice of reagent and reaction conditions, alkenes containing other functionalities can be selectively hydroxylated without complicating side reactions. For example, the oxidation may be carried out in the presence of ester, ether, sulfide, carboxylic acid, acetal, carbonyl, halo, alcohol and aryl groups. Regioselective hydroxylation is also possible in dienes in which one center is electron poor, and some selectivity is also found between isolated double bonds. For example, *syn* hydroxylation of diene (**5**) with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide as the secondary oxidant gives diol (**6**)[22] in 46% yield, and phase transfer catalyzed permanganate oxidation of diene (**7**) affords diol (**8**)[23] in 83% yield.

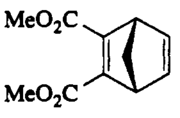

**(5)**

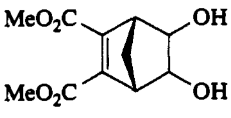

**(6)**

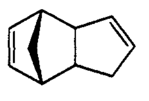

**(7)**

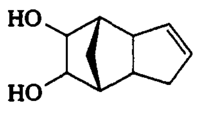

**(8)**

The diastereoselective and enantioselective oxidation of alkenes with osmium tetroxide is considered in Section 3.3.2.1.

## 3.3.2 *SYN* HYDROXYLATION METHODS

### 3.3.2.1 Osmium Tetroxide

Despite the development in recent years of new reagents for organic synthesis, osmium tetroxide, used either stoichiometrically or catalytically, remains the reagent of choice for *syn* hydroxylation of alkenes.[5–7] Surprisingly, the hydroxylation of alkynes to give[5–7,24,25] 1,2-dicarbonyl compounds has been much less studied, but it has considerable potential for use in the synthesis of complex molecules.

For the oxidation of alkenes, osmium tetroxide is used either stoichiometrically, when the alkene is precious or only small scale operation is required, or catalytically with a range of secondary oxidants which include metal chlorates, hydrogen peroxide, *t*-butyl hydroperoxide and *N*-methylmorpholine *N*-oxide. The osmium tetroxide/*N*-methylmorpholine *N*-oxide combination is probably the most general and effective procedure which is currently available for the *syn* hydroxylation of alkenes,[26,27] although tetrasubstituted alkenes may be resistant to oxidation.[28] For hindered alkenes, use of the related oxidant trimethylamine *N*-oxide in the presence of pyridine appears advantageous.[29] When *t*-butyl hydroperoxide is used as a cooxidant, problems of overoxidation are avoided which occasionally occur with the catalytic procedures using metal chlorates or hydrogen peroxide. Further, in the presence of tetraethylammonium hydroxide[30] hydroxylation of tetrasubstituted alkenes is possible, but the alkaline conditions clearly limit the application.

With osmium tetroxide, considerable diastereoselectivity may be achieved in the stoichiometric and catalytic hydroxylation of allylic alcohol systems in which the oxygen-containing group forms part of a chiral center (equation 4).[31–34]

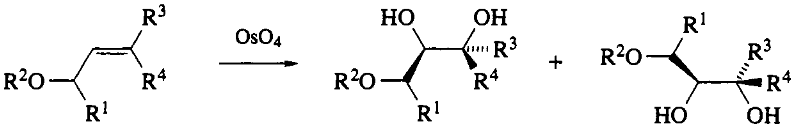

(4)

From a study embracing a large number of substrates, the following general observations were formulated: (i) the stoichiometric hydroxylation procedure provides a slightly higher diastereoselectivity than the catalytic procedure; (ii) protecting groups of the hydroxy at the chiral center, except acyl groups, have only a limited effect in determining the stereochemical course of the oxidation, while with acyl derivatives stereoselectivity is noticeably diminished or is absent; (iii) a hydroxy or alkoxy oxygen seems to play the important role in governing the high degree of stereoselectivity; (iv) the degree of selectivity observed with (*Z*)-alkenes is higher than that for the corresponding (*E*)-alkenes; (v) the relative stereochemistry between the preexisting hydroxy or alkoxy group and the adjacent, newly introduced hydroxy group of the major product is in all cases *erythro*.

A rationalization[31,34] of observations (iv) and (v) is based on conformational analysis of $sp^3$–$sp^2$ single bond systems, for which an eclipsed conformation seems to be preferred.[35] Of the three eclipsed conformations (**9a**), (**9b**) and (**9c**) of an allylic alcohol system $R^1(R^2O)CHCH{=}CR^3R^4$, conformation (**9a**) appears to be least sterically hindered and, therefore, most preferred. If this conformational preference is reflected in the transition state for hydroxylation, the major product can be seen to arise from the preferential approach of osmium tetroxide from the π-face opposite to that of the preexisting hydroxy or alkoxy group. An alternative rationalization, based[33] on observations on the hydroxylation of γ-hydroxy-α,β-unsaturated esters, suggests that conformation (**9b**) might be the preferred one, as a result of a favorable interaction between *p*-orbitals of the double bond and an unshared electron pair on the oxygen, and that attack would be directed from the side of the π-system opposite to that occupied by $R^1$. Interestingly, and in support of this idea, force-field calculations indicate[36] that the reactive conformer in the transition state for addition of a nitrile oxide to the allyl ether, 3-methoxy-1-butene, is one in which the alkoxy group is almost in the plane of the double bond in the 'inside' conformation shown in (**9b**), and a similar preference may apply in osmium tetroxide hydroxylations. A rationalization which focuses on the role of stereoelectronic factors in the transition state has also been proposed.[37] In the case of a (*Z*)-alkene (**9a–c**; $R^3$ = H) conformational preference for (**9a**) will be greater than that for the corresponding

($E$)-alkene (**9a–c**; $R^4$ = H), leading to an increased steric differentiation of the two π-faces in the case of the former alkene compared to the latter one.

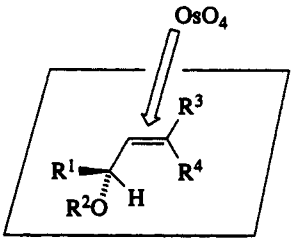

**(9a)**

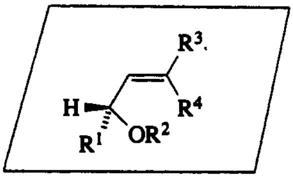

**(9b)**

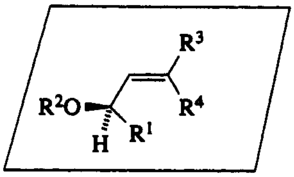

**(9c)**

Support for the empirical rule has been obtained, subsequently, during synthetic studies in carbohydrate chemistry.[37–39a,39b] For example, catalytic hydroxylation with osmium tetroxide of ($E$)-allylic alcohol (**10**) and ($E$)-allylic ether (**11**) gave the octose derivatives (**12**) and (**13**) as the major products, whereas the ($Z$)-allylic alcohol (**14**) gave (**15**) as the predominant product.[38] Similar steric control was apparent in the synthesis of decose derivatives in a related sequence of reactions,[39a] but some exceptions to the empirical rule are known for conjugated carbonyl compounds,[34,38,40] and it should be applied with caution to such compounds. It appears that the empirical rule may also predict, in general, the outcome of similar oxidations with potassium permanganate.[34]

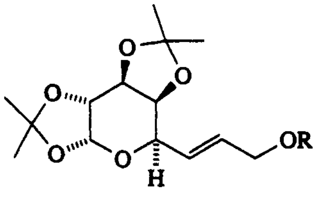

**(10)** R = H
**(11)** R = $CH_2Ph$

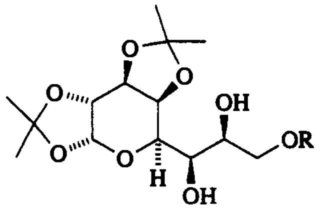

**(12)** R = H
**(13)** R = $CH_2Ph$

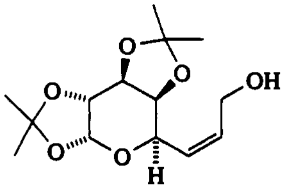

**(14)**

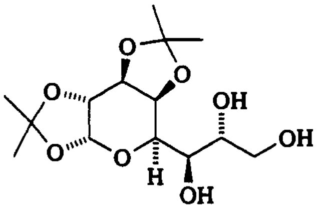

**(15)**

Substituents occupying sites more remote from the alkenic center than the allylic position may also influence the direction of attack on an alkene with diastereotopic π-faces. Thus, cyclic alkenes with a sulfoximine group attached to an exocyclic homoallylic carbon atom and a hydroxy group at the allylic position, for example (**16**) in equation (5), undergo *syn* hydroxylation with a very high degree of diastereoselectivity, diol (**17**) being produced as the sole diastereoisomer.[41]

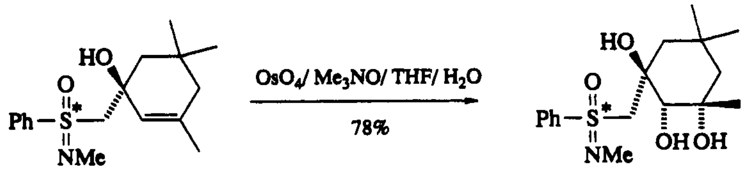

(5)

**(16)** *R* or *S* chiral center **(17)**

In contrast, the corresponding sulfone (**16**; O replacing NMe) gives, on similar reaction, a 2:1 mixture of diastereoisomeric *cis*-diols with (**17**) predominating.[41]

Diastereoselective hydroxylation has also been observed at an alkenic center in an acyclic system that is guided by a sulfoxide group that is more remote than the homoallylic position. Alkenes (**18**; equation 6) and (**20**; equation 7), were converted[42] by treatment with a catalytic amount of osmium tetroxide and trimethylamine *N*-oxide into diols, which on acetylation gave diacetates (**19**) and (**21**), respectively as the sole products of the individual reactions. Apparently, complexation occurs between the oxygen of the sulfoxide and the osmium reagent prior to hydroxylation of the alkenic center. Hydroxylation of the alkenic sulfone corresponding to (**18**) and (**20**) afforded, after acetylation of the product, diacetates (**19**) and (**21**) in a 3:2 ratio, indicating that it is not an intermediate in the oxidation and that the amide group exerts a relatively small influence in favor of the diol corresponding to (**19**).

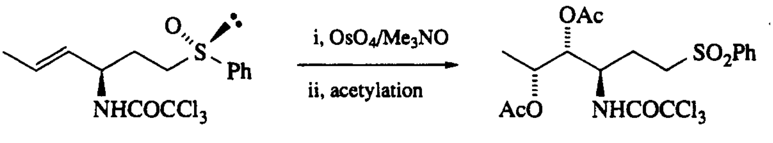

**(18)** **(19)** (6)

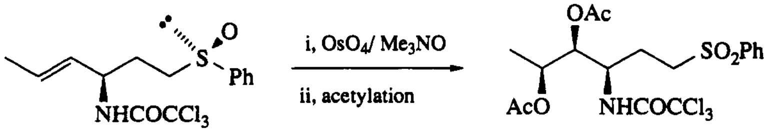

**(20)** **(21)** (7)

Enantioselective *syn* hydroxylation of alkenes with enantiotopic faces may be achieved if addition is performed under the influence of a chiral control element. In practice, the latter may take the form of a chiral grouping temporarily attached to the alkene if suitable functionality is present. (This description distinguishes this type of reaction from diastereoselective hydroxylations which are achieved when the chiral center is an integral part of the substrate such as in **9**.) This renders the π-faces diastereotopic and thus distinguishable by the nonchiral tetroxide. Alternatively, the hydroxylation may be conducted in the presence of a suitable chiral substance capable of coordination with osmium tetroxide, rendering the reagent chiral and able to differentiate, therefore, between the enantiotopic faces of the alkene. (This rationalization supposes a [3 + 2] cycloaddition mechanism.[10] In an alternative mechanism proposed by Sharpless,[11,12] enantioselectivity arises by steric differentiation of the initially formed enantiomeric alkene–osmium π-complexes upon reaction with a chiral reagent such as a chiral amine.[43]) An example of the first approach is the conversion of an ester derived from (*E*)-2-methylbut-2-enoic acid and a chiral alcohol to the corresponding ester of (2*S*,3*R*)- and (2*R*,3*S*)-2,3-dihydroxy-2-methylbut-2-enoic acid in an isomer ratio of 83:17, respectively (equation 8).[44] Chiral oxazolidines obtained by reaction of α,β-unsaturated aldehydes with L-*N*-benzyloxycarbonylnorephedrine have been used in a similar manner to prepare derivatives of chiral α,β-dihydroxy aldehydes.[45]

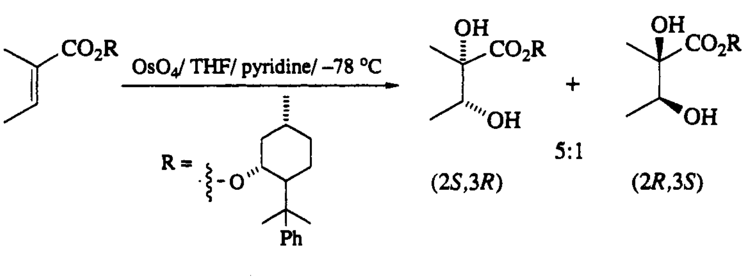

(8)

In the second approach, a chiral nitrogen-containing compound has most often been used as the ligand to achieve enantioselectivity. Thus, oxidation of (*E*)-stilbene (**22**; equation 9) with a stoichiometric quantity of osmium tetroxide in toluene at room temperature, in the presence of dihydroquinine acetate (**23**), yielded[12] *threo*-hydrobenzoins (**24**) after reductive hydrolysis, with an enantiomeric excess of 83.2% in favor of the (1*S*,2*S*)-(–)-isomer; performing the reaction at –78 °C increased the enantiomeric excess to 89.7%.

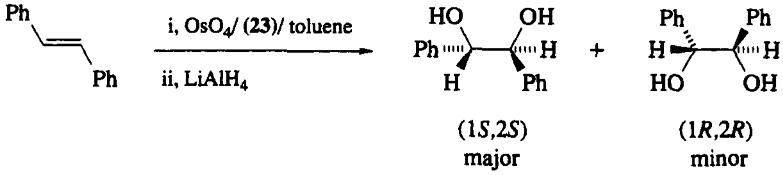

(9)

(22) (24)

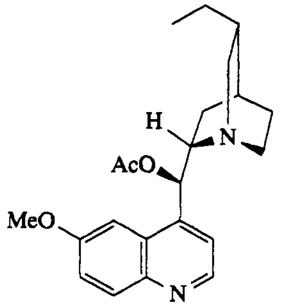

(23)

This procedure has been modified[46a] to become an effective catalytic procedure in which *N*-methylmorpholine *N*-oxide is used as the secondary oxidant. In this manner, (*E*)-stilbene has been converted[46a] into (+)-*threo*-hydrobenzoin (55% yield after two recrystallizations, >99% *ee*) on a one molar scale, by treatment with osmium tetroxide (0.002 mol equiv.) and *N*-methylmorpholine *N*-oxide (1.2 mol equiv.) in aqueous acetone in the presence of dihydroquinidine *p*-chlorobenzoate (0.134 mol equiv.). The latter compound can be recovered in 91% yield.

By the seemingly minor modification[46b,46c] to the original catalytic procedure[46a] of adding the alkene slowly to a stirred mixture of the alkaloid derivative, *N*-methylmorpholine *N*-oxide, and osmium tetroxide, nearly all alkenes react faster and give higher enantiomeric excesses in the product diols than with the earlier procedure[46a] in which all reactants, including the alkene, are present from the start of the reaction. This significant enhancement in enantioselectivity has been rationalized[46b] in terms of the existence of at least two diol-producing cycles as summarized in Scheme 1.[46b] The first cycle, which appears to give a high enantiomeric excess in the diol product, consists of reaction of the alkene with the alkaloid–osmium complex (**24a**) to give the monoglycolate ester (**24b**). This compound is oxidized to the key osmium(VIII) trioxoglycolate complex (**24c**), which is hydrolyzed to afford the 1,2-diol and complex (**24a**). By slow addition of the alkene, hydrolysis of (**24c**) can be made to dominate an alternative reaction with a second alkene molecule to give a bisglycolate ester (**24d**). Intrusion of the second cycle leads to reduced enantiomeric excess in the product since diol formation *via* the osmium(VIII) dioxobisglycolate complex (**24e**) proceeds with low enantioselectivity. Further, the rate of turnover in the secondary cycle is generally slower and involvement of this cycle in the reaction binds the catalyst in a relatively unproductive form.

Protected α,β-dihydroxy aldehydes have been prepared[47] by oxidation of acetals of α,β-unsaturated aldehydes with osmium tetroxide in the presence of (**23**), and a remarkable level of enantioselection (*ee* ≥ 90%) thereby achieved. Oxidation of chiral acetals of α,β-unsaturated aldehydes in which chirality resides in the noncarbonyl moiety with osmium tetroxide–dihydroquinine acetate (or dihydroquinidine acetate)[47] may be regarded as a process in which double stereoselection[48] is at work and a high diastereoisomeric ratio of products may be obtained.

Chiral diamines capable of chelating to a metal center, such as (–)-(*R*,*R*)–*N*,*N*,*N*′,*N*′-tetramethyl(*trans*-1,2-cyclohexanediamine (**25**),[43] the tartaric acid derived (–)-diamine (**26**),[49] and the (–)-1,2-dipyrrolidinylethane (**27**),[50] also lead to a high degree of asymmetric induction when alkene hydroxylation with osmium tetroxide is conducted in their presence.

With diamine (**25**), 1-heptene afforded[43] (*R*)-1,2-heptanediol as the major product (86% *ee*) in 75% yield by this procedure but, curiously, oxidation of (*E*)-stilbene proceeded with lower optical yield (34% *ee*). Particularly efficient enantioface differentiation was achieved in the reaction[50] of (*E*)-1-phenylpropene with a stoichiometric amount of osmium tetroxide in the presence of 1 mol equiv. of (–)-(**27**) when essentially optical pure (>99% *ee*) (1*S*,2*S*)-1-phenylpropane-1,2-diol was obtained in 73% yield. This procedure is effective for mono-, (*E*)-di- and tri-substituted alkenes, with enantioface selection being as shown in Scheme 2 but, notably, the oxidation of (*Z*)-alkenes does not give satisfactory optical yields.

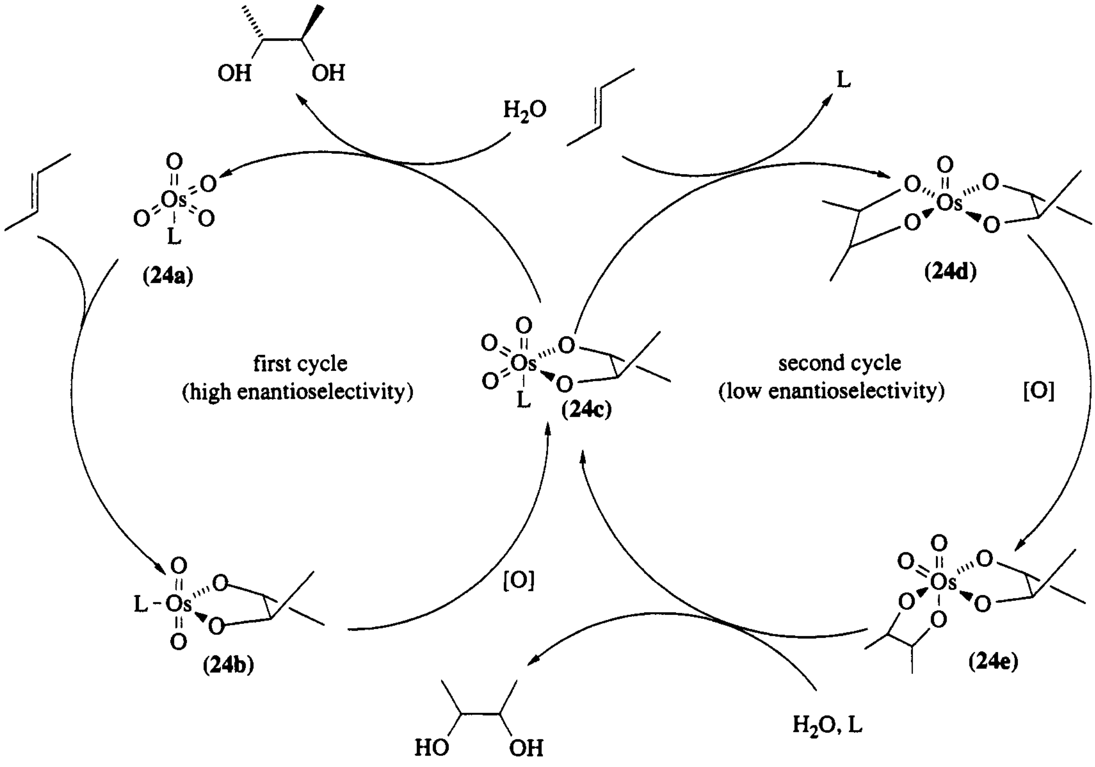

L = alkaloid ligand

Scheme 1 Proposed mechanism of the osmium-catalyzed asymmetric dihydroxylation of alkenes

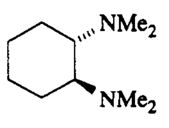

**(25)**

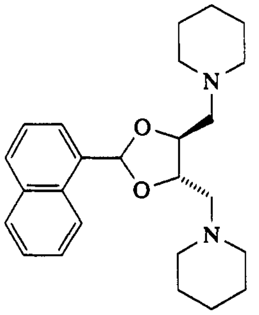

**(26)**

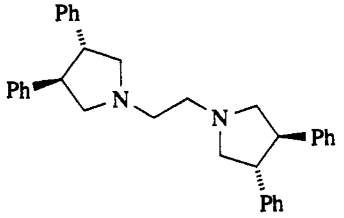

**(27)**

The structure of the osmate(VI) ester–(–)-(**27**) complex, which may be isolated from the reaction with (*E*)-stilbene, has been determined[13] by X-ray crystallography to be (**28**). Although (**28**) would reasonably seem to arise by a [3 + 2] cycloaddition pathway, it does not seem to account for the observed stereochemical outcome of the reaction since, on steric grounds, complex (**29**) would appear to be favored. On the other hand, the alternative pathway[11,12] *via* organometallocycle (**30**) seems to account more satisfactorily for the stereochemical result, since intramolecular attack by the nitrogen of the second pyrrolidine ring moiety places substituent $R^1$ in the least sterically demanding region and affords osmate ester (**28**) in accord with the observed enantioface differentiation. In the stereoisomeric organometallocycle (**31**), steric interactions between the phenyl group on the coordinated pyrrolidine ring and that on the four-membered metallocycle would disfavor formation of the osmate ester.

The 1:1 complex between bovine serum and an osmate ester is an enantioselective catalyst in the *syn* hydroxylation of certain alkenes,[51a] although synthetic applications appear to be limited. Asymmetric dihydroxylation of alkenes is considered in a review on catalytic asymmetric reactions.[51b]

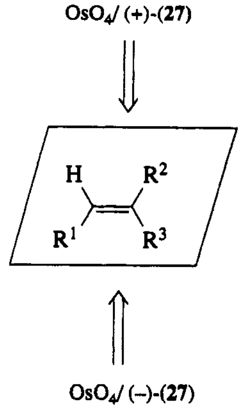

**Scheme 2** Enantioface selection on hydroxylation of an alkene with osmium tetroxide in the presence of (+)- and (–)-(27)

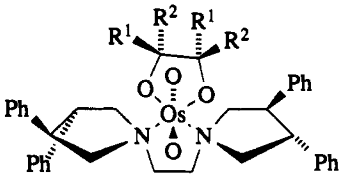

**(28)** $R^1 = Ph, R^2 = H$
**(29)** $R^1 = H, R^2 = Ph$

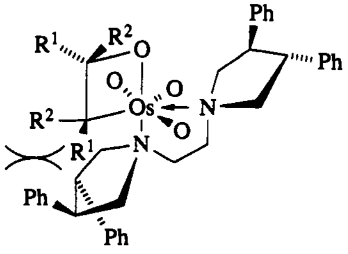

**(30)** $R^1 = Ph, R^2 = H$
**(31)** $R^1 = H, R^2 = Ph$

### 3.3.2.2 Potassium Permanganate

Alkaline aqueous potassium permanganate has long been used to achieve the *syn* hydroxylation of alkenes,[9] but overoxidation and alternative oxidation pathways often pose problems, and yields are rarely as high as those obtained with osmium tetroxide. Nevertheless, permanganate oxidation is less hazardous to perform and is much less expensive for large-scale operations. Improved yields of diols may sometimes be obtained by using phase transfer catalysis.[52–54] Typically, a solution of the alkene in dichloromethane is stirred vigorously with aqueous sodium hydroxide in the presence of a phase transfer agent such as benzyltriethylammonium chloride, while potassium permanganate is added portionwise. *cis*-1,2-Cyclooctanediol is prepared[53] from *cis*-cyclooctene in much higher yield by this method than with the conventional procedure employing basic, aqueous potassium permanganate. Solid–liquid phase transfer may be brought about under nonaqueous conditions, to bring potassium permanganate into solution in an organic solvent which contains the dissolved substrate.[54]

Turbulent stirring and the presence of low concentrations of sodium hydroxide are very beneficial in improving the yield of *cis*-1,2-cyclohexanediol from the hydroxylation of cyclohexene with potassium permanganate.[55–57] Presumably, hydroxylation of other alkenes with this reagent would also benefit by attention to these factors.

Recent evidence on the mechanism of permanganate oxidation of alkenes has been summarized;[9] the initial step probably involves a [3 + 2] cycloaddition between permanganate ion and the alkene to give a cyclic manganese(V) ester (**2**; see Section 3.3.1).

### 3.3.2.3 Methods Involving Halohydrin Esters as Intermediates

Several related procedures for *syn* hydroxylation of alkenes involve a halohydrin ester (**32**) as the key intermediate. In Woodward's procedure[14] an alkene in glacial acetic acid is treated with iodine and silver acetate. Acetyl hypoiodite, $MeCO_2I$, formed by reaction of the latter two reagents attacks the alkene, $R^1R^2C{=}CR^3R^4$, in an electrophilic manner, from the less hindered side to give, by overall *anti* addition, an iodoacetate (**32**; $R^5$ = Me, Hal = I), in which the acetoxy group is attached to the more hindered face of the alkene. After addition of water, the reaction mixture is heated, inducing silver(I)-assisted anchimeric displacement of the iodo group with formation of a 1,3-dioxolan-2-ylium ion (**33**). Addition of water to the cation affords orthoacetate (**34**) that rearranges to give a mixture of two diol monoacetates (**35a**) and (**35b**) that may be hydrolyzed to afford a diol having the hydroxy groups bonded to the more hindered side of the alkene. Some alkenes, however, particularly trisubstituted alkenes, can give other products in addition to the expected diol,[58] suggesting that the foregoing mechanism may be oversimplified. Further, hydroxylation of the tetrasubstituted alkene 1,2-dimethylcyclohexene by the Woodward procedure is not stereospecific, giving an approximately 3:2 ratio of *cis*- to *trans*-diol.[59]

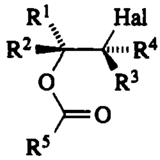
**(32)**

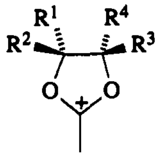
**(33)**

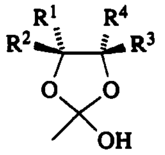
**(34)**

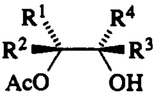
**(35a)**

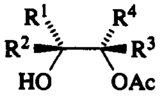
**(35b)**

Since silver salts are expensive, other cheaper reagents have been sought which can bring about the same type of conversion, and the iodine–potassium iodate–potassium acetate combination has been found to provide a useful alternative.[17–19] Thallium(I) acetate may be used[15,16] in place of silver acetate in the Woodward procedure, and *syn* hydroxylation of steroidal alkenes with thallium(III) acetate in acetic acid has been performed.[60]

In the 2-halocyanoacetate procedure,[20] a *trans*-bromohydrin (**36**; Scheme 3), prepared from an alkene, is esterified with cyanoacetic acid to give the 2-halocyanoacetate (**37**), and the latter is treated with sodium hydride to give, *via* the enolate anion, a cyanoketene acetal (**38**). Acid hydrolysis of the latter, followed by deesterification with base of the diol monocyanoacetate so-formed gives diol (**39**). Since the starting *trans*-bromohydrin may be prepared from a cyclohexene by two stereochemically complementary routes using hypobromous acid (oxygen added to the more hindered π-face) or peroxy acid epoxidation followed by cleavage with hydrogen bromide (oxygen added to the less hindered π-face) it is possible to achieve *syn* hydroxylation on either the more or less hindered π-face.

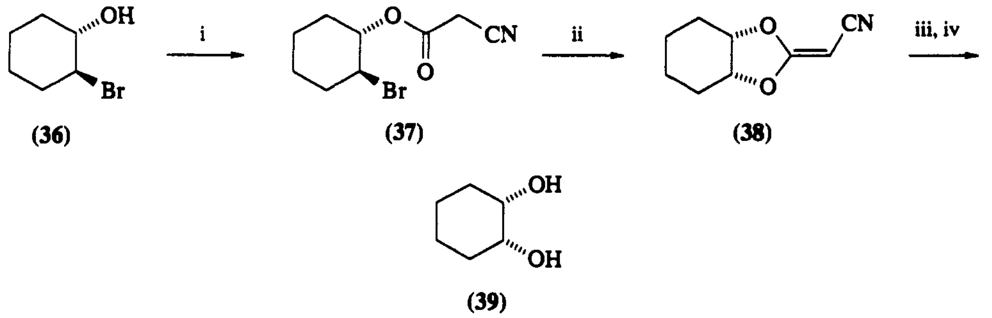

i, $NCCH_2CO_2H$/TsCl; ii, NaH; iii, $H_3O^+$; iv, base

**Scheme 3**

## 3.3.3 *ANTI* HYDROXYLATION METHODS

### 3.3.3.1 Peroxycarboxylic Acids

The hydroxylation of an alkene may be achieved by treatment with a suitable peroxycarboxylic acid, $RCO_3H$, the reaction proceeding (Scheme 4) by initial *syn* addition to give an epoxide (oxirane) (**40**), which undergoes acid-catalyzed ring scission in an *anti* manner through attack by the corresponding carboxylic acid, $RCO_2H$, normally present in the reaction medium, to give the monoesters (**41**) and (**42**). Hydrolysis of the ester mixture then affords a racemic mixture of the enantiomeric diols (**43a**) and (**43b**) with stereochemistry resulting from overall *anti* addition to the alkene.

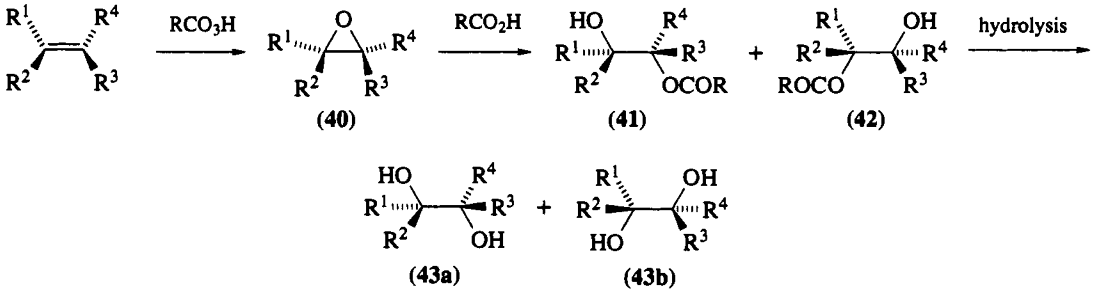

Scheme 4

Peroxyformic, peroxyacetic and peroxytrifluoroacetic acids are most commonly used to bring about this type of oxidation, but 2-sulfoperoxybenzoic acid,[61] monoperoxysuccinic acid[62] and disuccinoyl peroxide[63] (which is converted to monoperoxysuccinic acid by hydrolysis), also oxidize alkenes to diols with the advantage that the free diols are obtained directly.

In general, attack of the peroxycarboxylic acid on an alkene will occur from the less hindered π-face and ring opening of the oxirane usually occurs to place the acyloxy group on the more substituted carbon atom.

Sodium perborate ($NaBO_3{\cdot}nH_2O$; $n = 1$–$4$) is a cheap and widely used industrial chemical. If sulfuric acid is added to a mixture of the perborate and an alkene in acetic anhydride, an exothermic reaction occurs leading to *anti* addition to the double bond with formation of the corresponding 1-hydroxy-2-acetoxy derivative in moderate yield.[64] Peroxybis(diacetoxy)borane, $(AcO)_2BOOB(OAc)_2$, may be the reactive species in this oxidation and it seems likely that the epoxide is an intermediate.

### 3.3.3.2 Hydrogen Peroxide with an Oxide Catalyst

The oxidation of alkenes by hydrogen peroxide catalyzed by certain oxide catalysts, such as tungsten(VI) oxide ($WO_3$),[65] tungsten(VI) acid ($H_2WO_4$)[66] and selenium dioxide ($SeO_2$),[64,67–69] brings about *anti* hydroxylation with formation of 1,2-diols (equation 10). Tungsten(VI) oxide is a particularly effective catalyst and functions best at elevated temperatures (50–70 °C) in a purely aqueous medium. For oxidation of alkenes which are insoluble in water, a mixture of 30% hydrogen peroxide and acetic acid forms a suitable medium, and with the selenium dioxide–hydrogen peroxide system, *t*-butyl alcohol has been used as a solvent.

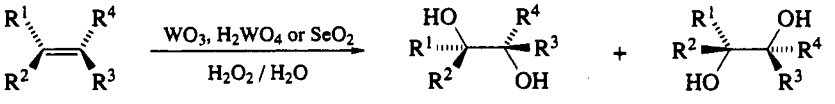

(10)

The observed stereochemistry of addition suggests that oxiranes (epoxides) may be intermediates. Oxiranes may, indeed, be isolated from the reaction of certain alkenes with hydrogen peroxide in the presence of sodium tungstate.[70]

Polystyrene-bound phenylseleninic acid has been used in catalytic amounts in a triphasic system consisting of the polymer, aqueous hydrogen peroxide, and dichloromethane, to catalyze the oxidation of alkenes to 1,2-diols;[71] cyclohexene gave *trans*-1,2-cyclohexanediol in high yield with no detectable amounts of the *cis*-diol.

### 3.3.3.3 Iodine–Silver Benzoate — the Prévost Reaction

In the Prévost reaction, an alkene is treated with 1 mol equiv. of iodine and 2 mol equiv. of silver carboxylate (most often silver benzoate) in an inert solvent (for example, benzene), leading to formation of a racemic mixture of 1,2-diesters (**46a** and **46b**; Scheme 5). Hydrolysis of the latter yields a mixture of the corresponding 1,2-diols with stereochemistry corresponding to *anti* hydroxylation of the alkene. The reaction proceeds through initial formation of a complex $RCO_2Ag/RCO_2I$ (the Simonini complex), which can itself be prepared and isolated separately, prior to use in such a reaction. *Anti* addition of the acyl hypoiodite ($RCO_2I$) to the alkene through a cyclic iodonium ion gives the 1-acyloxy-2-iodo compound (**44**), and displacement of iodide ion with anchimeric assistance by the neighboring acyloxy group affords the 1,3-dioxolan-2-ylium ion (**45**). Nucleophilic attack by carboxylate anion on (**45**) then leads to diesters (**46a**) and (**46b**).

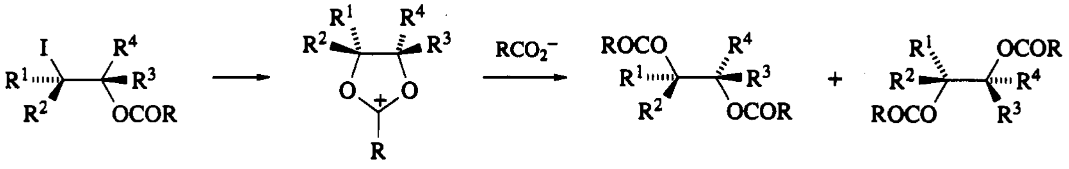

(**44**) (**45**) (**46a**) (**46b**)

**Scheme 5**

Thallium(I) acetate has been used in place of a silver carboxylate in a related procedure, for the preparation of *trans*-1,2-cyclohexanediol.[16]

### 3.3.3.4 Miscellaneous Procedures

Some mono- and di-substituted alkenes have been converted to 1,2-diacetoxy compounds by heating them in acetic acid solution with ammonium persulfate and a catalytic amount of iron(II) sulfate.[72] *Anti* addition is observed with 1,2-disubstituted alkenes; with trisubstituted alkenes complex mixtures are obtained.

Thallium(III) sulfate in water brings about the *anti* hydroxylation of 3-*t*-butyl- and 4-*t*-butyl-cyclohexene.[73] The reagent has been recommended[73] for the one-step preparation of *trans*-diols from conformationally rigid cycloalkenes.

## 3.3.4 REFERENCES

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# 3.4

# Addition Reactions with Formation of Carbon–Oxygen Bonds: (iv) The Wacker Oxidation and Related Reactions

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## 3.4.1 INTRODUCTION

The oxidation of ethylene to acetaldehyde using $PdCl_2$ and $CuCl_2$ as catalysts under an oxygen atmosphere is well known as the Wacker process (Scheme 1), and is one of the most important industrial processes employing transition metal catalysts.[1,2] This industrial oxidation reaction of ethylene involves the following three stoichiometric reactions. These sequential oxidation and reduction reactions constitute a catalytic cycle.

The Wacker process is carried out in an aqueous medium containing hydrochloric acid. In addition to ethylene, Smidt and coworkers carried out the oxidation of other alkenes in an acidic aqueous solution of $PdCl_2$ to prepare carbonyl compounds.[1,2] After this report, a few studies on the oxidation of higher alkenes were carried out in organic media.[3–6] In general, terminal alkenes are converted to methyl ketones rather than aldehydes (equation 1).

$$\begin{array}{rcl} H_2C{=}CH_2 + H_2O + PdCl_2 & \longrightarrow & MeCHO + Pd^0 + 2\,HCl \\ Pd^0 + 2\,CuCl_2 & \longrightarrow & PdCl_2 + 2\,CuCl \\ 2\,CuCl + 2\,HCl + 0.5\,O_2 & \longrightarrow & 2\,CuCl_2 + H_2O \\ \hline H_2C{=}CH_2 + 1/2\,O_2 & \longrightarrow & MeCHO \end{array}$$

**Scheme 1** Wacker process

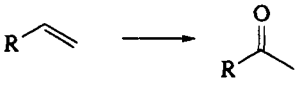

(1)

This reaction is a unique method for the one-step synthesis of ketones from alkenes. As such, alkenes can be regarded as masked ketones which are stable to acids, bases and nucleophiles. Thus, the reaction is potentially useful for organic synthesis, and has attracted the attention of synthetic organic chemists.[7] A considerable number of studies have been carried out on this oxidation and its synthetic applications. A number of review articles and books have been published on various palladium-catalyzed oxidative reactions of alkenes.[8–13] One comprehensive review on synthetic applications of the Wacker reaction was published in 1984.[14] In this chapter, the $Pd^{II}$-catalyzed oxidation of alkenes to carbonyl compounds is surveyed from a standpoint of organic synthesis by citing pertinent examples. Complete coverage of all related references is not the purpose of this review. Emphasis is placed on the oxidation of higher and functionalized alkenes, and many examples of the oxidation of lower simple alkenes are excluded. Oxidative conversion of alkenes to enol or allyl acetates with $Pd(OAc)_2$, although a closely related reaction, is not discussed. Repetition of material which has appeared in other reviews is avoided as far as possible. Also no mechanistic or kinetic discussion is given due to limited space.

## 3.4.2 REACTION CONDITIONS AND SCOPE OF THE REACTION

### 3.4.2.1 General Procedure

The oxidation on a laboratory scale can be carried out easily in a way similar to the hydrogenation of alkenes under atmospheric pressure of hydrogen using palladium black as a catalyst. Instead of palladium black and hydrogen, the oxidation is carried out with $PdCl_2$ and a copper salt under an oxygen atmosphere at room temperature using a similar apparatus. However, rates and yields of the oxidation are heavily dependent on the structure of alkenes. Also, the proper selection of solvents and reoxidants is crucial; this is surveyed in the following sections.

### 3.4.2.2 Solvents

The industrial Wacker process is carried out in aqueous hydrochloric acid using $PdCl_2/CuCl_2$ as the catalyst under oxygen pressure.[1,2] The oxidation of higher terminal alkenes under the same conditions is slow and sometimes accompanied by undesired by-products formed by the chlorination of carbonyl compounds by $CuCl_2$, and isomerization of double bonds. Earlier examples of oxidation of various alkenes, mainly in aqueous solutions, have been tabulated.[1,8] The pseudo-first-order rate constants for oxidation of various alkenes, relative to the value for cycloheptene, with $PdCl_2$ in the presence of benzoquinone in aqueous solution have been reported.[15] An accelerating effect of surfactants such as sodium lauryl sulfate on the stoichiometric oxidation of higher alkenes in an aqueous solution has been reported.[16]

The low rate of the reaction in the aqueous medium can be partly improved by the addition of suitable organic solvents which can mix alkenes with water. Several solvents have been tested, but the results are sometimes conflicting. At first, 1-dodecene and undecenoic acid were oxidized to the corresponding methyl ketones in good yields in aqueous DMF using $PdCl_2$ and $CuCl_2$ or benzoquinone.[3] However, the use of 3-methylsulfolane and NMP gave better results than DMF for the oxidation of 3,3-dimethyl-1-butene at 70–80 °C under 40–99 p.s.i. (1 p.s.i. = $6.9 \times 10^{-2}$ bar) of oxygen using 10 mol % of $PdCl_2$.[5] The following yields of the methyl ketone were obtained: 91% (in 3-methylsulfolane), 79% (in NMP) and 33% (in DMF). The oxidation in alcoholic solutions was carried out with terminal and internal alkenes and some cyclic alkenes.[4] The reaction in alcohols is faster than in DMF. Parallel oxidations of cyclohexene at 50 °C showed conversion of 30% in ethanol, 1.2% in 1,4-dioxane and less than 0.5% in DMF, DMSO, acetic acid and carbon tetrachloride.[4] Polyethylene glycol (PEG 400) is a good solvent for the oxidation of terminal and internal alkenes with $PdCl_2/CuCl_2$. *cis*-2-Butene was oxidized to 2-butanone in 82% yield.[17]

When the reaction is carried out in pure alcohol, the corresponding acetal is formed. Styrene was converted to the cyclic acetal of phenylacetaldehyde in 90% yield in ethylene glycol, whereas a mixture of products was obtained in ethanol. Interestingly, acrylonitrile was oxidized to 1,3-dioxolan-2-ylacetonitrile (**1**) in ethylene glycol (equation 2).[4,18] 2,2-Dimethoxypropionitrile was obtained in methanol.[4,19,20] Methyl acrylate behaves similarly.

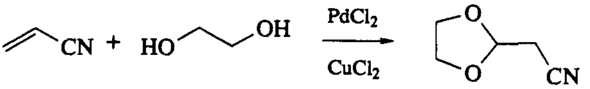

(**1**)

(2)

Another interesting example of the acetal formation is the synthesis of brevicomin (**2**), a cyclic acetal, by the palladium-catalyzed intramolecular oxidation and acetal formation of 6,7-dihydroxy-1-nonene (equation 3).[21,22]

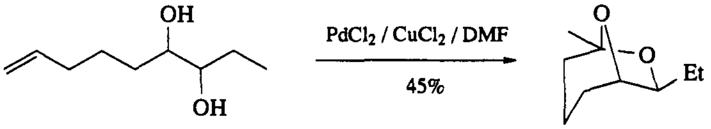

(**2**)

(3)

Similarly, frontalin,[23] and 2,9-dioxabicyclo[3.3.1]nonane[24] were prepared by the bicyclic acetal formation from terminal alkenes. γ-Butyrolactone is another solvent of choice.[25] A two-phase reaction was carried out using carbon tetrachloride and benzene.[26]

The oxidation and double bond isomerization are competitive reactions, and the extents of these reactions are influenced by solvents. DMF is good for the oxidation, whereas use of acetic acid facilitates the isomerization. Both reactions proceed in alcoholic solvents. Acetonitrile and DMSO retard oxidation by complex formation with the catalysts.[27] The double bond migration is facilitated by high temperatures. The oxidation of 1-octene in *n*-propyl alcohol yielded 2-octanone to the extent of 62% at 90 °C, 85% at 60 °C, and more than 97% at 30 °C. 4-Methyl-1-pentene isomerized to the 2- and 3-alkenes, which formed π-allylic complexes in ethanol, but normal oxidation to the methyl ketone took place in DMF and γ-butyrolactone.[25]

In some cases, ketones are obtained in high yields by the oxymercuration[28] or oxythallation[29] of alkenes, followed by treatment with $PdCl_2$ in aqueous THF.

Oxidation of terminal alkenes may be carried out in benzene–water in the presence of cetyltrimethylammonium bromide at 80 °C[30] although cyclodextrins are better phase-transfer agents. In the presence of a catalytic amount of β-cyclodextrin, 1-decene and *cis*-2-butene were oxidized at 65 °C to 2-decanone (61%) and 2-butanone (76%) respectively.[31] Selective oxidation of linear $C_8$–$C_{10}$ terminal alkenes took place at 75 °C in the presence of α-cyclodextrin in water,[32] but a low yield was obtained with 1-dodecene.

### 3.4.2.3 Reoxidants

The essence of the Wacker process is the invention of the reoxidation process for $Pd^0$ by using $CuCl_2$ as a cocatalyst. $Cu^{II}$ salts are good reoxidants, but chlorination of carbonyl compounds takes place with $CuCl_2$. For example, chloroacetaldehyde is a by-product of the Wacker process. Chlorohydrin is another by-product from the reaction of ethylene with $PdCl_2$ and $CuCl_2$.[33,34] Thus, a number of other reoxidants were introduced. When CuCl, pretreated with oxygen, is used, no chlorination of ketones takes place and the rate of the reaction is higher.[6,7] Also $Cu(NO_3)_2$[4,35] and $Cu(OAc)_2$[36] have been used. Oxidation of cyclopentene with $PdCl_2/Fe(ClO_4)_3$ combined with electrochemical oxidation was carried out.[37] Benzoquinone was used at first by Moiseev *et al.*[38] and later by many other researchers as a good reoxidant, but a stoichiometric amount is necessary. The oxidation of alkenes can be carried out smoothly with catalytic amounts of both $Pd(OAc)_2$ and benzoquinone by means of efficient electrochemical reoxidation of hydroquinone to benzoquinone.[39] A combination of $Pd(OAc)_2$/benzoquinone/Fe phthalocyanine in the presence of $HClO_4$ (5%) in aqueous DMF is an active catalyst.[40] A heterogeneous catalyst system of a $Pd^{II}$ salt and polymers containing quinone and sulfonic acid groups was used for ethylene oxidation.[41]

Alkyl nitrites (3) are good and unique reoxidants and used in industrial processes. 2,2-Dimethoxypropionitrile (4), an important intermediate for vitamin $B_1$ synthesis, is produced commercially by the oxidation of acrylonitrile in methanol (equation 4).[19] 3-Phenylpropene is oxidized to 1-phenyl-2,2-dialkoxypropane in a similar fashion.[20] Alkyl nitrites (3) are formed *in situ* from $O_2$, NO, and ROH, and can be recycled (equation 5).

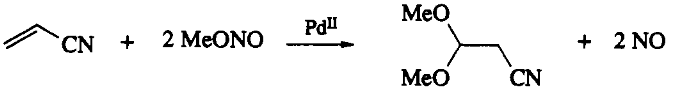

(3) (4)

(4)

$$2\,NO + 1/2\,O_2 + 2\,MeOH \longrightarrow \underset{(3)}{2\,MeONO} + H_2O \qquad (5)$$

Efficient catalytic oxidation of 1-octene (90–95% yields) was carried out in acetic acid or *t*-butyl alcohol at 80 °C in 3 h by using 5 equiv. of 30% hydrogen peroxide and 1/500 equiv. of $Pd(OAc)_2$.[42] Hydrogen peroxide was used for the styrene oxidation with $Na_2PdCl_4$ in NMP. Compared with $PdCl_2/CuCl$, the rate of the oxidation was very high.[43] However, extensive double bond migration of terminal alkenes occurred in the presence of hydrogen peroxide. *t*-Butyl hydroperoxide and hydrogen peroxide are efficient reoxidants for the oxidation of internal double bonds conjugated to carbonyl groups.[43] An *endo*-peroxide/$Pd(OAc)_2$[44] and *t*-butyl hydroperoxide/palladium trifluoroacetate[11,45] were used for the oxidation of 1-alkenes.

$PdCl_2$–cobalt–nitro complexes were found to be efficient catalysts for alkene oxidation.[46] Pd–nitro complexes catalyze the oxidation of l-alkenes under oxygen without using other reoxidants to give methyl ketones.[47–51] They are mechanistically different from $PdCl_2/CuCl_2$ catalysts.[50] Heteropolyacids such as $H_3PMo_6O_{40}$ are water soluble and good reoxidants when $PdSO_4$ is used rather than $PdCl_2$ to give methyl ketones with high selectivity.[52,53] The catalyst system $PdSO_4/H_3PMo_6W_6O_{40}$ was used for the oxidation of 1-butene, cyclohexene and cyclopentene in aqueous DMF.[54–57] Cyclohexanone was obtained in 85% yield.

Deactivation of the palladium catalyst is a serious problem. Sometimes, the reaction is stopped by the precipitation of black palladium metal. Furthermore, the deactivation occurs during the reaction even when no precipitation is observed. The formation of a bis(dimethylamine)–$PdCl_2$ complex deactivates the catalyst when DMF is used as a solvent.[5,6] Also, the formation of rather stable π-allylpalladium complexes (5) from alkenes may account for the deactivation of the catalyst (equation 6).[58–61]

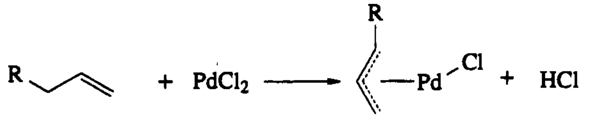

(5)

(6)

## 3.4.3 OXIDATION OF TERMINAL ALKENES TO METHYL KETONES

### 3.4.3.1 Oxidation of Terminal Alkenes Bearing Various Functional Groups

Terminal double bonds are selectively oxidized to methyl ketones. A typical procedure for the oxidation of l-decene to 2-decanone in 65–73% yield with $PdCl_2/CuCl$ is given in *Organic Synthesis*.[62] Although there are several known synthetic methods for methyl ketone preparation, the $PdCl_2$-catalyzed oxidation of terminal alkenes seems to be one of the best. In other words, terminal alkenes can be regarded as precursors of methyl ketones, or as masked methyl ketones based on this reaction. This reaction is useful because terminal alkenes are easily available, stable under acidic and basic conditions and inert to nucleophiles.

Various terminal alkenes with functional groups are oxidized to the corresponding methyl ketones. Since the oxidation proceeds under mild conditions, various functional groups, such as an aldehyde,[63] carboxylic acid,[3,64] ester,[65–68] alcohol,[69–71] MOM ether,[72] acetal,[73] bromide,[74] selenide,[75] sulfonyl ester[73] and amines,[76,77] which are located at suitable positions, remain intact. Though it is known that alcohols are oxidized to aldehydes or ketones with $PdCl_2$,[78–80] the oxidation of terminal alkenes is faster than that of alcohols under these conditions.

Since the rate of oxidation of terminal alkenes is much higher than that of internal alkenes, selective oxidation of terminal alkenic bonds is possible without attacking the internal alkenic bonds in various dienes (equation 7).[6,77,81–93]

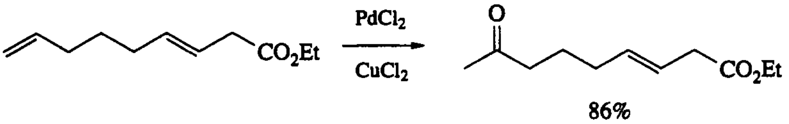

(7)

Steric hindrance considerably affects the rate of the oxidation. For example, one of the terminal double bonds in (**6**) was oxidized in 3 h, but it took 36 h to oxidize the other one (equation 8).[69]

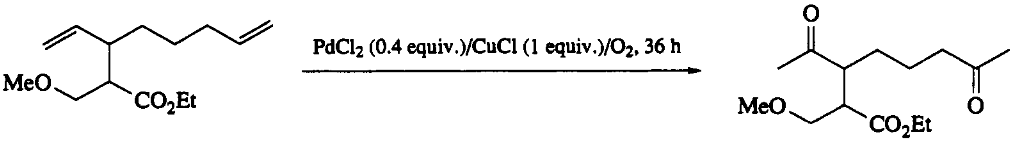

(**6**)

71%

(8)

Some allylic alcohols or acetates with terminal double bonds do not give methyl ketones cleanly. Oxidation of 1-undecen-3-ol (**7**) at room temperature gave the methyl ketone (**8**) in 60% yield and 1-hydroxy-3-undecanone (**9**) in 14% yield (equation 9).[69]

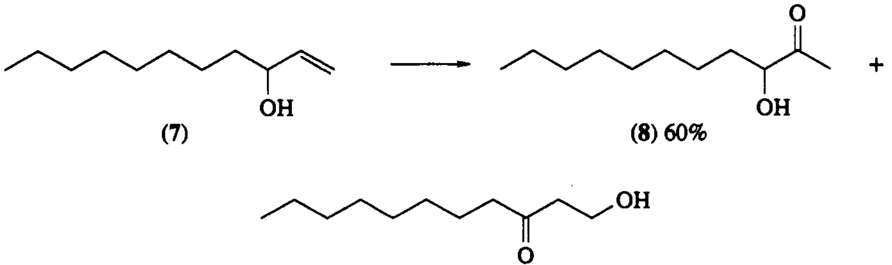

(**7**)

(**8**) 60%

(**9**) 14%

(9)

The acid sensitive 2-methyl-3-buten-2-ol (**10**) was oxidized to the corresponding methyl ketone (**11**) with a palladium–nitro complex (90% conversion, 90% selectivity) or $PdCl_2$–benzoquinone (98% conversion, 90% selectivity) (equation 10).[51]

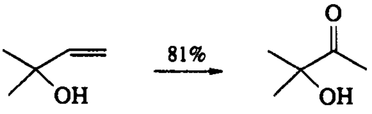

(**10**) (**11**)

(10)

1-Vinyl-1-cyclobutanols (**12**) undergo oxidative ring expansion to give cyclopentenones (**13**; Scheme 2).[94]

Oxidation of 3-acetoxy-1-nonene (**14**) at 50 °C gave a mixture of the methyl ketone (**15**) and 1-acetoxy-3-nonanone (**16**) in 33% and 17% yields.[69] The latter was formed by regioselective oxidation of 1-acetoxy-2-nonene, itself formed by the allylic rearrangement of (**14**) promoted by $Pd^{II}$ ions (equation 11).

2,2-Disubstituted ethylenes undergo oxidation with a skeletal rearrangement. Methylenecyclobutane (**17**) was oxidized to cyclopentanone *via* ring expansion (Scheme 3).[95]

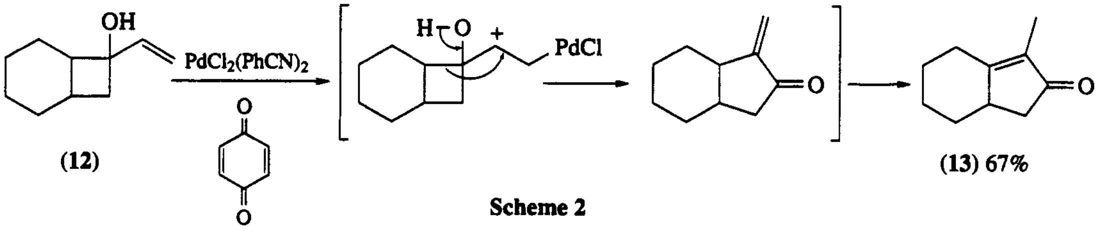
OH
PdCl2(PhCN)2
O
O
H
O
+
PdCl
O
O

(12) (13) 67%

Scheme 2

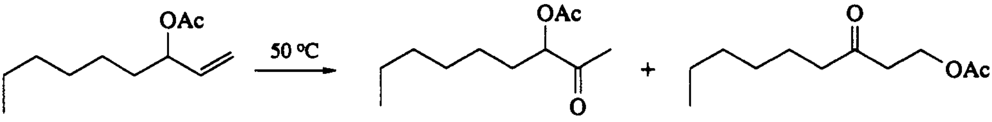
OAc
50 °C
OAc
O
+
O
OAc

(14) (15) 33% (16) 17% (11)

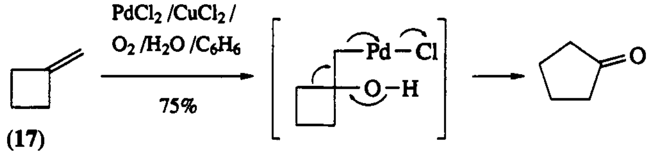
PdCl2 /CuCl2 /
O2 /H2O /C6H6
75%
Pd
Cl
O
H
O

(17)

Scheme 3

Some terminal alkenes are oxidized to aldehydes depending on their structure. As described before, acrylonitrile and acrylate are oxidized to acetals of aldehydes in alcohols or ethylene glycol.[18–20] Selective oxidation of terminal carbons in 4-hydroxy-1-alkenes (**18**) gave the five-membered hemiacetals (**19**), which can be converted to γ-butyrolactones by PCC oxidation (Scheme 4).[96] Formation of a tricyclic six-membered hemiacetal (62%) from a 5-hydroxy-1-alkene system was used for the synthesis of rosaramicin.[97] Formation of aldehydes as a major product from terminal alkenes using $(MeCN)_2Pd(Cl)(NO_2)$ and $CuCl_2$ in *t*-butyl alcohol under selected conditions was reported.[98] The vinyl group in the β-lactam was oxidized mainly to the aldehyde as shown below (equation 12).[99]

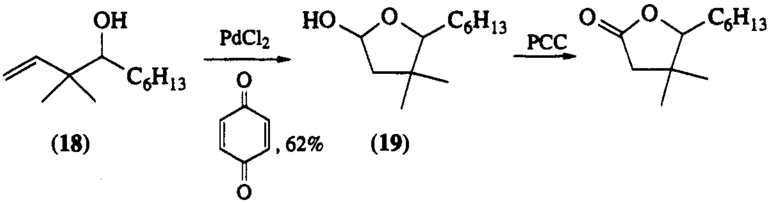
OH
C6H13
PdCl2
O
O
, 62%
HO
O
C6H13
PCC
O
O
C6H13

(18) (19)

Scheme 4

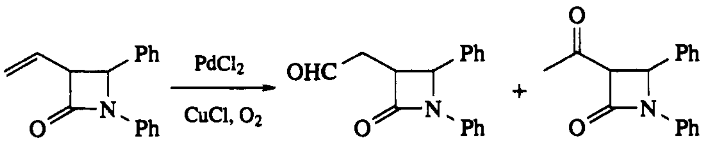
Ph
N
Ph
O
PdCl2
CuCl, O2
OHC
Ph
N
Ph
O
+
O
Ph
N
Ph
O

65% 5% (12)

### 3.4.3.2 Synthetic Applications

### *3.4.3.2.1 Synthesis of natural products*

Oxidation of terminal alkenes to methyl ketones is useful for the syntheses of natural products.[100–102] Based on this method, simple and efficient syntheses of prostaglandin intermediates,[64] Queen bee substance,[92] zearalenone,[73] dihydrojasmone, jasmone,[82] diplodialide B,[83] lasiodiplodin methyl ether,[84] curvularin,[86] resorcylide,[87] pyrethrolone,[88] muscone,[89,90] recifeiolide[93] and α-vetispirene[63] have been carried out. Syntheses of steroids based on this methodology are treated in Section 3.4.3.2.4.

### 3.4.3.2.2 Synthesis of 1,4-dicarbonyl compounds

#### (i) Synthesis via allylation of carbonyl compounds

A simple synthetic method for 1,4-dicarbonyl compounds was introduced, based on the allylation of carbonyl compounds with allyl halide as a $C_3$ component, followed by the palladium-catalyzed oxidation of the terminal alkenes (**20**) to methyl ketones (**21**).[7] In this method, the allyl group is a synthetic equivalent of the 2-oxopropyl group (Scheme 5). This is a good anellation method for cyclopentenones.

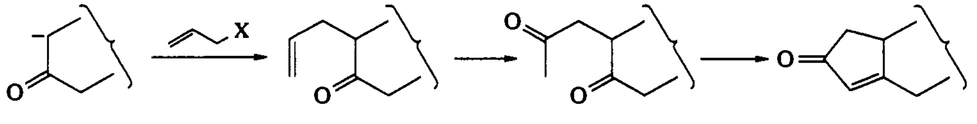

**(20)** **(21)**

**Scheme 5**

As a typical example, allylation of cyclohexanone *via* the pyrrolidine enamine with allyl bromide gave 2-allylcyclohexanone. Its terminal alkenic bond was oxidized with $PdCl_2/CuCl/O_2$ in aqueous DMF to give the 1,4-diketone (**21**) in 68% yield. The base-catalyzed cyclization of (**21**) gave the indenone (**22**) in 85% yield (Scheme 6).[7] This methodology was applied to the syntheses of pentalenene,[103] laurenene,[74] decarboxyquadrone,[104] and coriolin.[105]

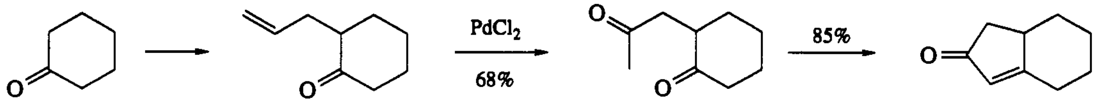

**(20)** **(21)** **(22)**

**Scheme 6**

Bicyclo[10.3.0]-$\Delta^{1,15}$-pentadecen-14-one (**25**) was prepared from cyclododecanone. Allylation of the β-keto ester (**23**) and the oxidation of the terminal alkenic bond afforded the 1,4-diketone (**24**) in 72% yield from the β-keto ester. Base-catalyzed cyclization and deethoxycarbonylation gave the bicycloketone (**25**), which was converted to muscone (**26**; Scheme 7).[106] Thus, this is a method for three-carbon ring expansion.

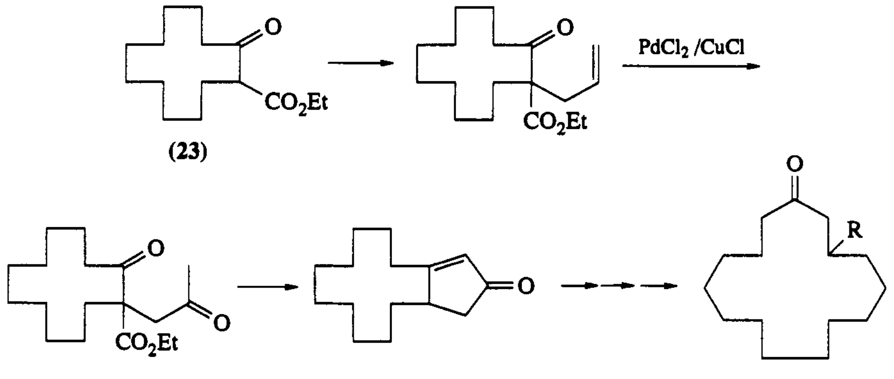

**(23)**

**(24)** 72% from (**23**) **(25)** **(26)**

**Scheme 7**

1,4-Keto aldehydes are prepared by the allylation of aldehydes. Reaction of 2-*p*-tolylpropanal (**27**) with allyl bromide gave 2-*p*-tolyl-2-methyl-4-pentenal (**28**) in 63% yield. The oxidation of the terminal alkenic bond to a methyl ketone gave the 4-oxopentanal (**29**) in 68% yield.[69] The keto aldehyde (**29**) was an intermediate for cuparanone (**30**) synthesis (Scheme 8).

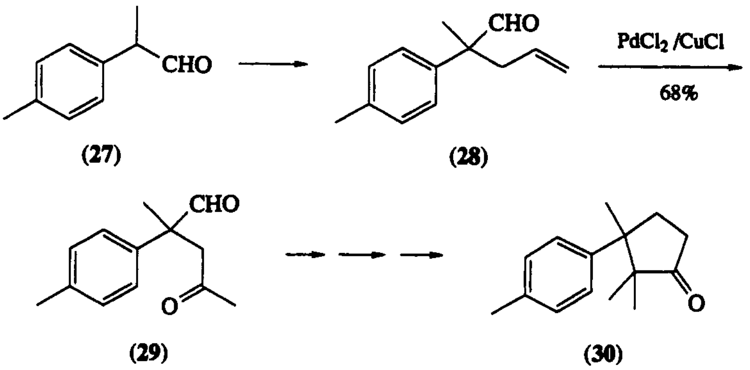

Scheme 8

The facile synthesis of 4,4-dimethyl-2-cyclopentenone by the allylation of isobutanal, followed by the oxidation and aldol condensation of the keto aldehyde is another example.[107]

### (ii) *Synthesis of 4-oxopentanals* via *Claisen rearrangement and oxidation*

4-Oxopentanals may be synthesized from allylic alcohols by 3,3-sigmatropic rearrangement of their vinyl ethers, and subsequent oxidation of the terminal double bond.[108] Cinnamyl alcohol (**31**) was converted to the allyl vinyl ether (**32**), which was subjected to Claisen rearrangement to give 3-phenyl-4-pentenal (**33**) in 50% yield. Oxidation of the terminal double bond of (**33**) gave 3-phenyl-4-oxopentanal (**34**) in 76% yield, which was converted to 2-methyl-3-phenylfuran (**35**) in quantitative yield (Scheme 9).

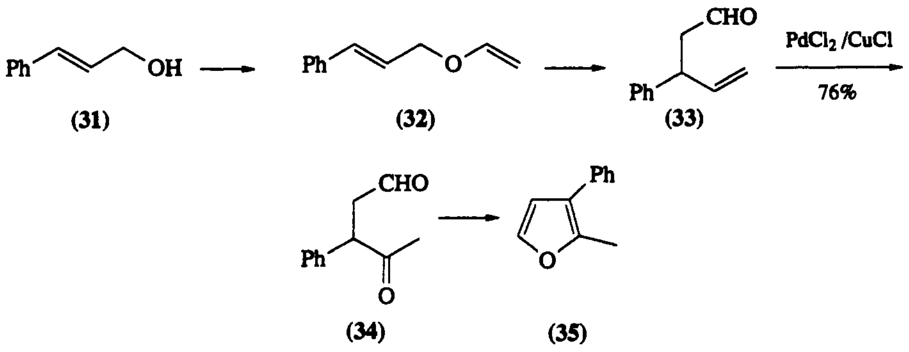

Scheme 9

3,3-Cyclohexano-4-oxopentanal (**37**) was synthesized from the allylic alcohol (**36**) by the same procedure, and the spiro compound (**38**) was obtained by intramolecular aldol condensation of (**37**; Scheme 10).

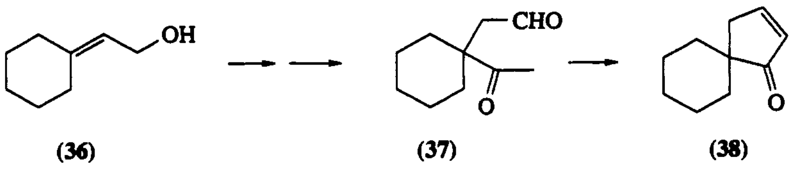

Scheme 10

The 3,3-sigmatropic rearrangement of 2-octenyl vinyl ether (**39**) afforded 3-pentyl-4-pentenal (**40**) in 79% yield. The terminal double bond was converted to the methyl ketone (**41**) in 90% yield. The keto aldehyde (**41**) was converted to 5-pentyl-2-cyclopentenone (**42**). The double bond migration gave 2-pentyl-2-cyclopentenone (dihydronorjasmone), which was converted to methyl dihydrojasmonate (**43**; Scheme 11).[108,109] Similarly, dihydrojasmone was synthesized from 2-octenyl allyl ether.

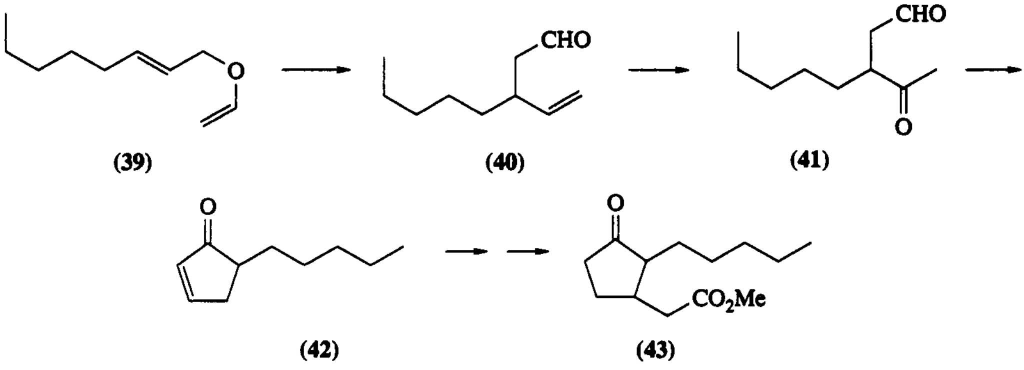

**Scheme 11**

*(iii) Other methods*

1,4-Addition of an acyl anion or its equivalent to $\alpha,\beta$-unsaturated ketones is an important synthetic method for 1,4-dicarbonyl compounds. In the palladium method for 1,4-dicarbonyl compounds, a vinyl Grignard or vinyllithium reagent is used as a synthetic equivalent of the acetyl anion. Reaction of lithium divinylcuprate with 2-cyclohexenone (**44**) afforded 3-vinylcyclohexanone (**45**), which was oxidized to the 1,4-diketone (**46**; Scheme 12).[108]

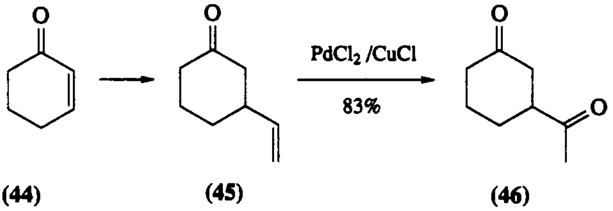

**Scheme 12**

The Lewis acid promoted addition of allylsilane (**48**) to nitroalkene (**47**) gave the unsaturated ketone (**49**) after hydrolysis of the nitro group. The palladium-catalyzed oxidation affords the 1,4-diketone (**50**; Scheme 13).[110]

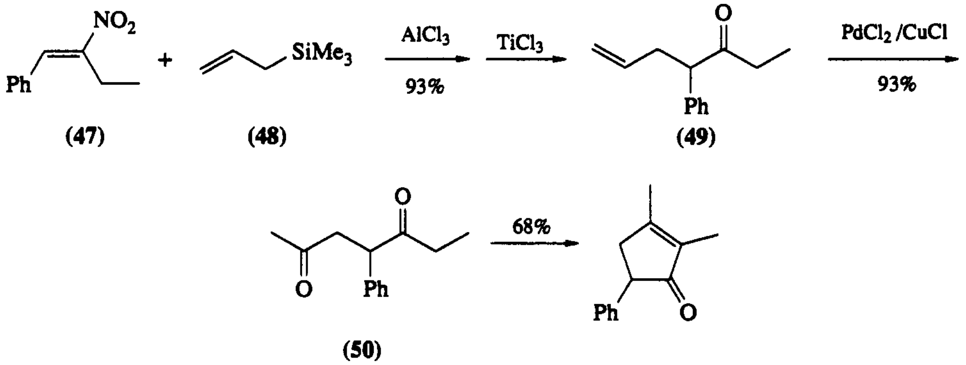

**Scheme 13**

The 1,4-diketone (**54**) was prepared by the titanium-catalyzed butenylation of the silylacetylene (**51**), followed by the oxidations of the terminal double bond in (**52**) to give (**53**) and the silylated double bond (Scheme 14).[111]

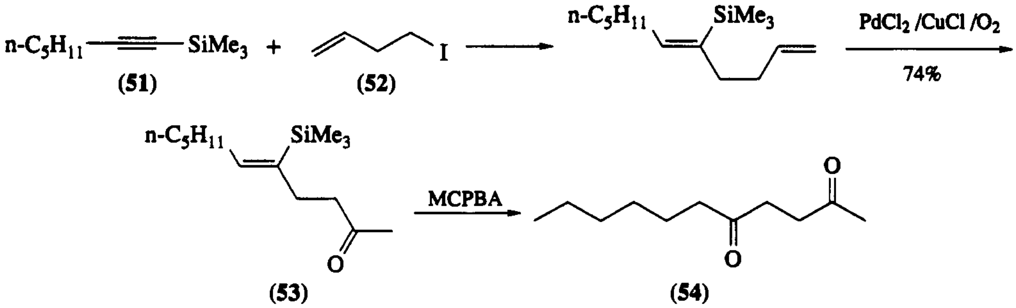

Scheme 14

### *3.4.3.2.3 Synthesis of 1,5-dicarbonyl compounds*

1,5-Dicarbonyl compounds can be prepared by the reaction of ketones with 3-butenyl halide as a $C_4$ component, following oxidation of the terminal double bond.[7] A modified method for 3-butenylation of ketones by the palladium-catalyzed reaction of 4-acetoxy-2-butenylmethyl carbonate with ketones, followed by the palladium-catalyzed reaction of ammonium formate was reported (Scheme 15).[112]

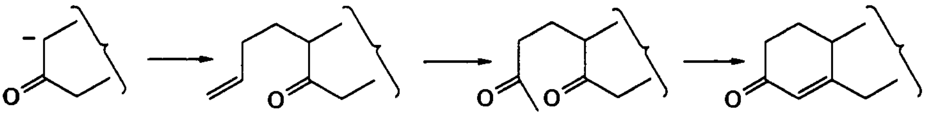

Scheme 15

Reaction of β-keto esters (**55a**) and (**55b**) with 3-butenyl bromide gave the alkenes (**56a**) and (**56b**) in 63% and 57% yields. Oxidation of the terminal double bonds gave the 1,5-diketones (**57a**) and (**57b**) in 61% and 58% yields (Scheme 16).

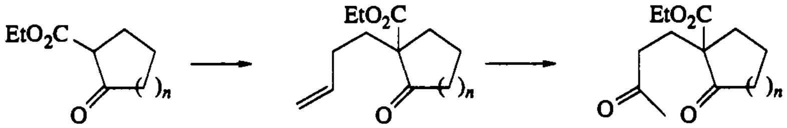

(**55a**) *n* = 1
(**55b**) *n* = 2

(**56a**)
(**56b**)

(**57a**)
(**57b**)

Scheme 16

In this synthesis of 1,5-dicarbonyl compounds, 3-butenyl halide is behaving as a masked 3-oxobutyl reagent, and can be used as an equivalent of methyl vinyl ketone. These reactions offer new anellation methods. Also 1,4-addition of the allyl group to enones, followed by oxidation, offers a convenient synthetic method for 1,5-diketone preparation. Lewis acid promoted Michael addition of allylsilane (**48**) to α,β-unsaturated ketones, followed by the palladium-catalyzed oxidation, affords 1,5-diketones (Scheme 17).[113]

The 1,5-diketone formation by the Michael addition of allylsilane (**48**) to α,β-unsaturated ketones was applied to the synthesis of (+)-nootkatone.[114] Reaction of the keto group of keto aldehyde (**58**) with allyl Grignard reagent and dehydration gave the diene aldehyde (**59**). The selective oxidation of the terminal double bond afforded the 1,5-dicarbonyl compound (**60**), which is not stable and converted directly to pyridines and phenols (Scheme 18).[115]

Synthesis of useful 5-oxohexanals can be carried out *via* the following three reactions: (1) 1,2-addition of allylmagnesium bromide to α,β-unsaturated aldehydes (**61**) to give 3-hydroxy-1,5-dienes (**62**); (2) conversion to 5-hexenals (**63**) by the oxy-Cope rearrangement; (3) the palladium-catalyzed oxidation of

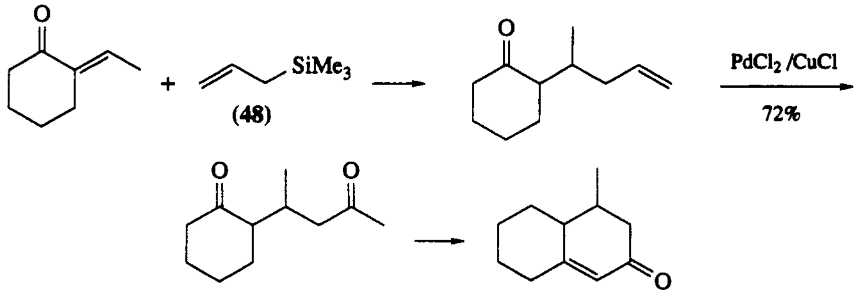
SiMe₃
PdCl₂ /CuCl
72%

(48)

Scheme 17

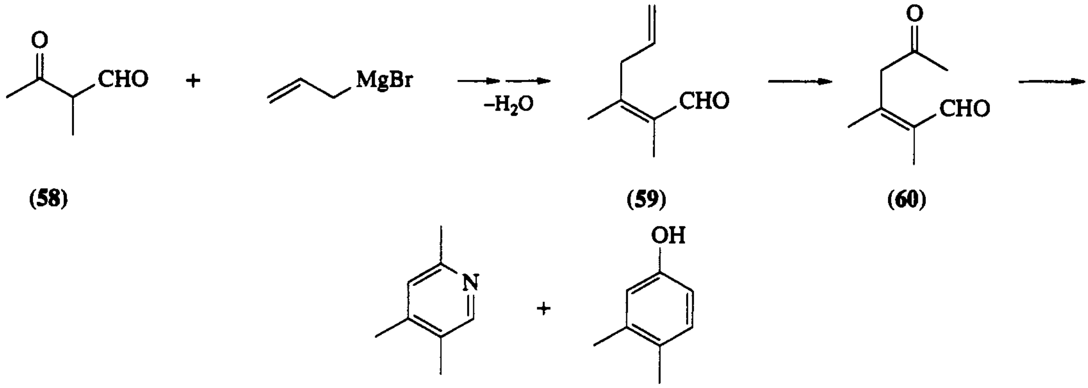
CHO
MgBr
-H₂O
CHO
CHO
OH
N

(58) (59) (60)

Scheme 18

the terminal alkene to give the 5-oxohexanals (**64**). In this method, α,β-unsaturated aldehydes are used directly without protection. Based on this process, formal Michael addition of the 2-oxopropyl anion to α,β-unsaturated aldehydes can be achieved (Scheme 19).[108]

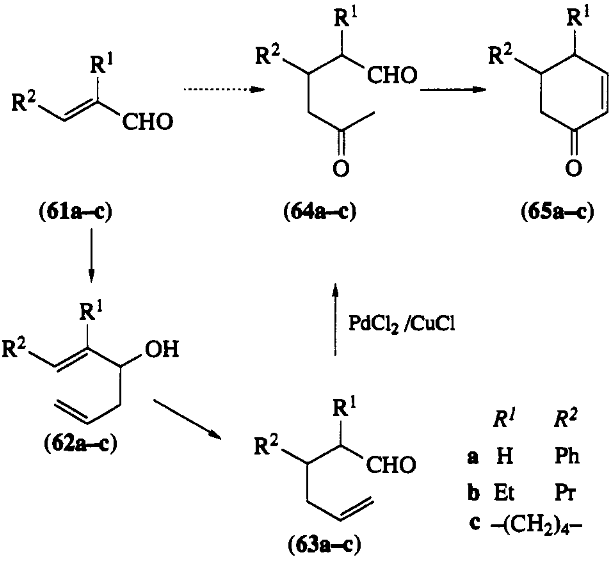
R¹
R²
CHO
OH
O
PdCl₂ /CuCl

(61a–c) (64a–c) (65a–c) (62a–c) (63a–c)

| | *R¹* | *R²* |
|---|---|---|
| a | H | Ph |
| b | Et | Pr |
| c | –(CH₂)₄– | |

Scheme 19

Reaction of allylmagnesium bromide with enals (**61a**)–(**61c**) gave allylvinyl methanols (**62a**)–(**62c**) in good yields. Oxy-Cope rearrangement using potassium hydride gave 5-hexenals (**63a**)–(**63c**) in 60–70%

yields. Terminal alkenes of the enals (**63a**)–(**63c**) were oxidized with $PdCl_2/CuCl$ to give 5-oxohexanals (**64a**)–(**64c**) in 66–68% yields. 5-Oxohexanals are converted to cyclohexenones (**65a**)–(**65c**). This synthetic method of 5-oxohexanals is useful for the anellation to convert cyclohexanone to $\Delta^{3,4}$-2-octalone (**65c**), which is difficult to obtain by common Robinson anellation. Acid-catalyzed cyclization of (**64c**) gave (**65c**) in 68% yield.

### *3.4.3.2.4 Application to steroid synthesis*

A new synthetic method for steroids has been developed using a butadiene dimer (**66**) as a building block and the palladium-catalyzed oxidation as the key reaction.[102,116] 3-Acetoxy-1,7-octadiene (**66**), prepared by the palladium-catalyzed reaction of butadiene with acetic acid, is hydrolyzed and oxidized to 1,7-octadien-3-one (**67**) in high yield. The enone (**67**) is a very useful reagent for bisanellation because its terminal double bond can be regarded as a masked ketone which can be readily unmasked by the palladium catalyst to form the 1,5-diketone (**68**) after Michael addition at the enone moiety of (**67**; Scheme 20). Thus, the enone (**67**) is the cheapest and most readily available bisanellation reagent, permitting a simple total synthesis of steroids.

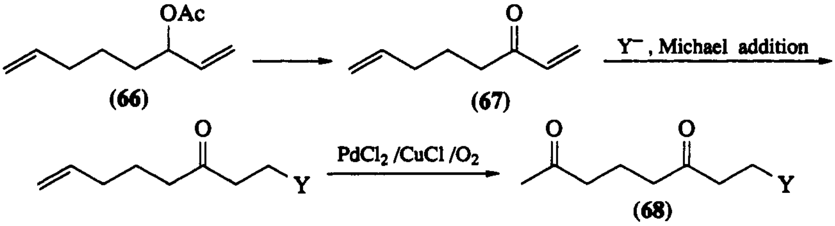

(**66**) (**67**) (**68**)

Scheme 20

In the simplest example, Michael addition to the enone (**67**) of the cyclohexanone enamine and aldol condensation yielded 4-(3-butenyl)-3-oxo-$\Delta^4$-octalin (**69**). The terminal double bond was oxidized to the ketone (**70**) by $PdCl_2/CuCl/O_2$, and subsequent aldol condensation leads to the tricyclic ketone (**71**; Scheme 21).

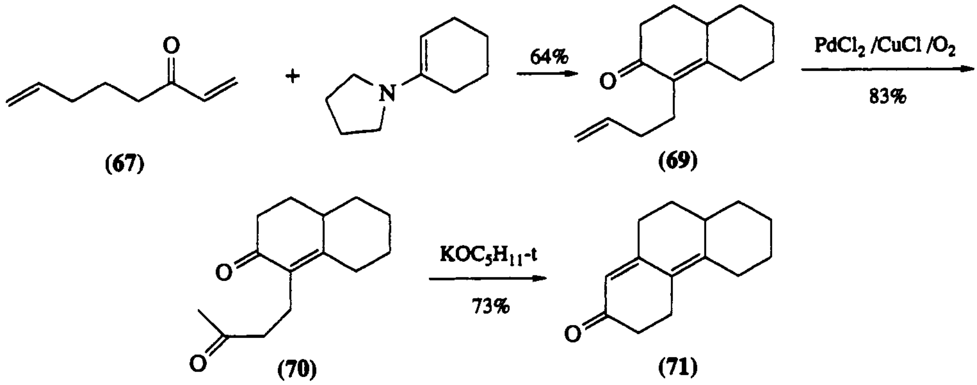

(**67**) (**69**) (**70**) (**71**)

Scheme 21

The synthesis of (+)-19-nortestosterone (**73**) was carried out starting from the optically active keto ester (**72**; equation 13).

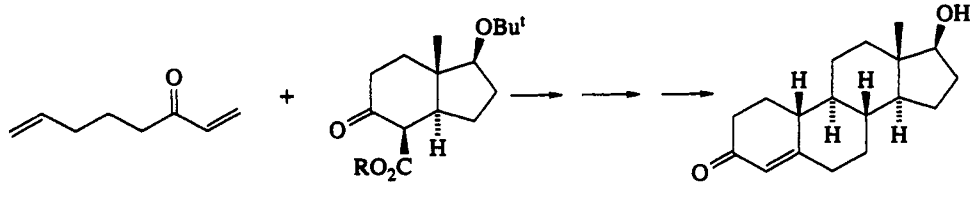

(13)

(**67**) (**72**) $[\alpha]^{25}_{D}$: +35.1° (**73**) $[\alpha]^{25}_{D}$: +57.8°

Another route to (+)-19-nortestosterone (**73**) started from 2-methyl-1,3-cyclopentanedione (**74**). The asymmetric aldol condensation of the Michael adduct using L-phenylalanine produced the optically active enone (**75**). The $PdCl_2$-catalyzed oxidation yielded crystalline trione (**76**) in 77% *ee*, which was recrystallized as an optically pure form. Reduction of the double bond and aldol condensation afforded the desired CD *trans*-fused ketone (**77**). The construction of the A-ring was carried out by alkylation with 4-bromo-1-butene to give (**78**), the palladium-catalyzed oxidation, and aldol condensation to give the optically active (+)-19-nortestosterone (**73**; Scheme 22).[117]

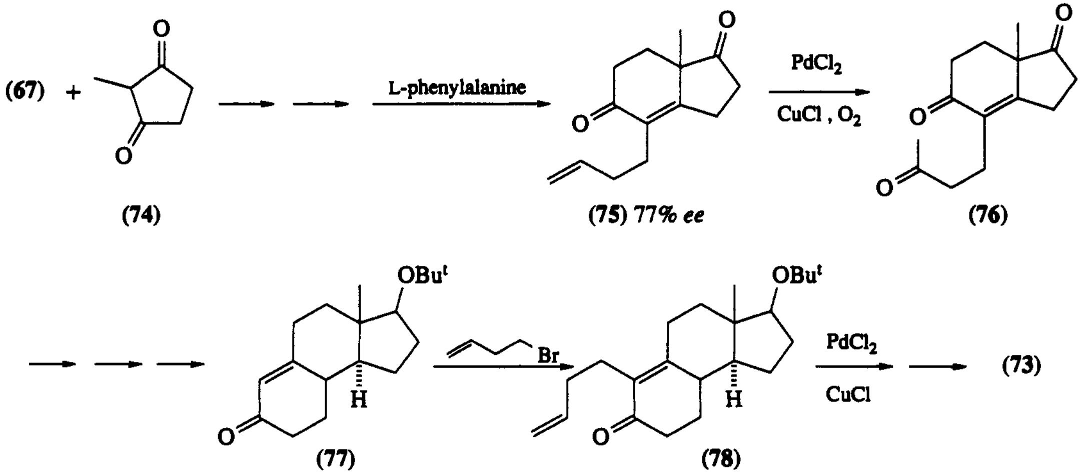
(67) +
O
O
(74)
L-phenylalanine
O
O
(75) 77% ee
PdCl2
CuCl, O2
O
O
O
(76)
OBu<sup>t</sup>
O
H
(77)
Br
OBu<sup>t</sup>
O
H
(78)
PdCl2
CuCl
(73)

Scheme 22

Subsequently the trisanellation reagent, 7-acetoxy-1,11-dodecadien-3-one (**80**) was prepared from the bisanellation reagent (**67**), and the synthesis of D-homo-19-norandrosta-4-en-3-one (**82**) was carried out from (**79**) as shown below.[118] For the A-ring formation, the unmasking of the terminal double bond and hydrogenation afforded the 1,5-diketone (**81**), which was subjected to intramolecular aldol condensation to give D-homo-4-androstene-3,17a-dione (**82**; Scheme 23).

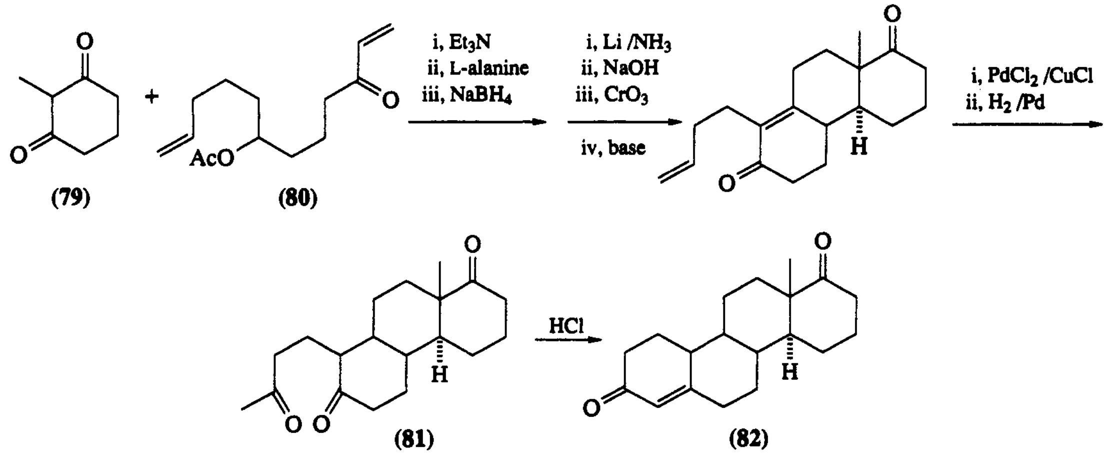
O
O
(79)
+
AcO
O
(80)
i, Et3N
ii, L-alanine
iii, NaBH4
i, Li/NH3
ii, NaOH
iii, CrO3
iv, base
O
O
H
i, PdCl2/CuCl
ii, H2/Pd
O
O O
H
(81)
HCl
O
O
H
(82)

Scheme 23

## 3.4.4 OXIDATION OF INTERNAL ALKENES

### 3.4.4.1 General Remarks

Compared with the facile oxidation of terminal alkenes, the oxidation of internal alkenes is extremely slow under the usual conditions. In addition, the reaction is not regioselective. The reaction would be very useful if cyclic alkenes could be oxidized to cyclic ketones. However, cyclic alkenes such as cyclopentene, cyclohexene and cyclooctene are not oxidized efficiently under the usual conditions. Good results so far reported are those with the use of heteropolyacids as the reoxidant.[54,55] Cyclohexene was oxidized by using $PdSO_4$ and heteropolyacid ($H_3PMo_6W_6O_{40}$) in aqueous DMF, giving cyclohexanone in 85% yield; the turnover of the catalyst was 90. For cyclopentanone, the turnover number was 30. Cyclopentene was oxidized smoothly by electrooxidation catalyzed by $Pd^{II}$ and benzoquinone.[39] Ethanol is a good solvent for the oxidation of cyclohexene and cyclopentene.[119–121] *cis*-2-Butene was oxidized to 2-butanone in 82% yield in polyethylene glycol.[17] The stoichiometric oxidation of 1-methylcyclobutene (**83**) gave cyclopropyl methyl ketone (Scheme 24).[122]

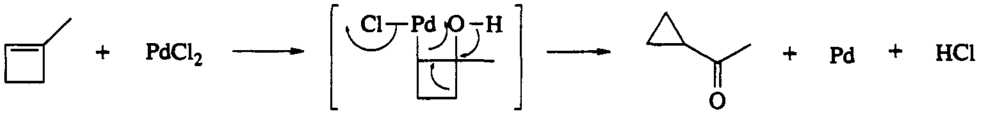

**(83)**

**Scheme 24**

The furan ring in khellin and cyclic ethers in sugars were oxidized to esters in methanol (Scheme 25).[35,123] Tricyclo [$4.2.2.0^{2,5}$]deca-3,7-diene-9,10-dicarboxylate (**84**) was oxidized to the monoketone in 7 h as a primary product, which was further oxidized to the diketone in 10 h in high yield with a stoichiometric amount of $Pd(NO_3)_2$ in refluxing methanol (equation 14).[124]

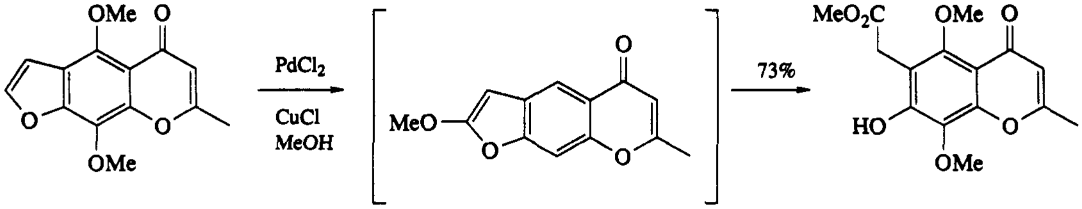

**Scheme 25**

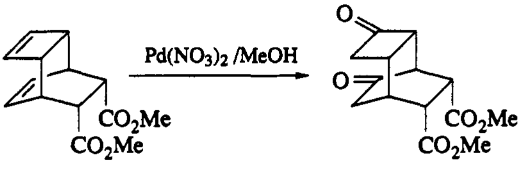

(14)

**(84)**

Thus, more improvement is still necessary for the oxidation of internal alkenes. However, internal alkenes with some functional groups at suitable positions are oxidized regioselectively by participation of the functional groups under proper conditions as surveyed in the following section.

### 3.4.4.2 Regioselective Oxidation of α,β- and β,γ-Unsaturated Carbonyl Compounds

The oxidation of α,β-unsaturated carbonyl compounds under the usual conditions in DMF using $PdCl_2/CuCl/O_2$ is very slow. However, regioselective oxidation of α,β-unsaturated esters to β-keto esters (equation 15), and α,β-unsaturated ketones to 1,3-diketones (equation 16) proceeds with $Na_2PdCl_4$ in solvents such as 50% acetic acid, isopropyl alcohol, and NMP.[43] *t*-Butyl hydroperoxide and hydrogen peroxide are used as the reoxidants of the reduced palladium. The reaction proceeds slowly at room temperature but smoothly between 50 and 80°C. Some typical examples of this process are shown in Table 1.

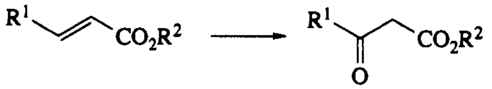

(15)

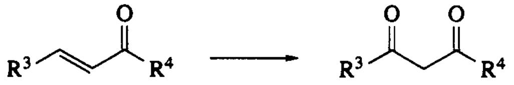

(16)

**Table 1** Oxidation of Various $\alpha,\beta$-Unsaturated Esters and Ketones

| *Alkene* | *Product* | *Yield (%)* |
|---|---|---|
| 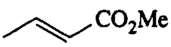 | 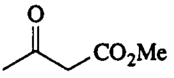 | 83 |
| 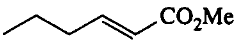 | 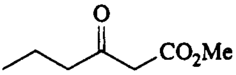 | 78 |
| 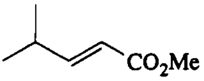 | 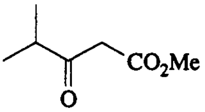 | 64 |
| 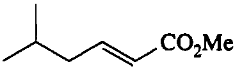 | 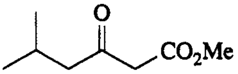 | 68 |
| 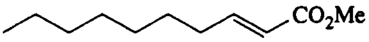 | 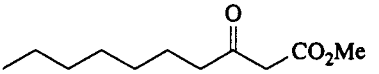 | 75 |
| 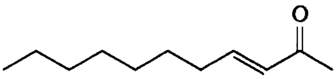 | 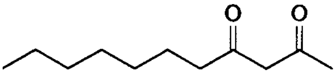 | 59 |
| 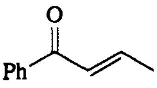 | 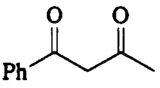 | 59 |

It is well known that π-allylpalladium complexes (**86**) are easily formed by the reaction of $PdCl_2$ with $\beta,\gamma$-unsaturated esters or ketones (**85**).[125] An attempted oxidation of $\beta,\gamma$-unsaturated esters and ketones with the $PdCl_2/CuCl/O_2$ catalyst system in aqueous DMF led to π-allylpalladium complex formation as the main reaction, and the oxidation of the alkenic bond was hardly observed to a significant extent. However, in aqueous dioxane or THF, the oxidation became the main reaction, giving γ-keto esters and 1,4-diketones (**87**), respectively, with high regioselectivity (Scheme 26).[126] Some results are shown in Table 2. In all cases, no β-keto ester or 1,3-diketone was detected. At the end of the reaction, formation of a considerable amount of the π-allylpalladium complex (**86**) was observed. γ-Keto esters and 1,4-diketones are useful intermediates for the preparation of cyclopentanedione and cyclopentenone, respectively, by base-catalyzed cyclization. This regioselective oxidation provides a unique and efficient synthetic method for γ-keto ester and 1,4-diketone synthesis.

1,4-Diketones were obtained mainly by the oxidation of $\gamma,\delta$-unsaturated ketones and used for cyclopentenone anellation.[127,128] One example is shown below (equation 17). However, the following $\gamma,\delta$-unsaturated lactone was oxidized regioselectively to give 1,5-ketolactone in 73% yield in one week (equation 18).[129]

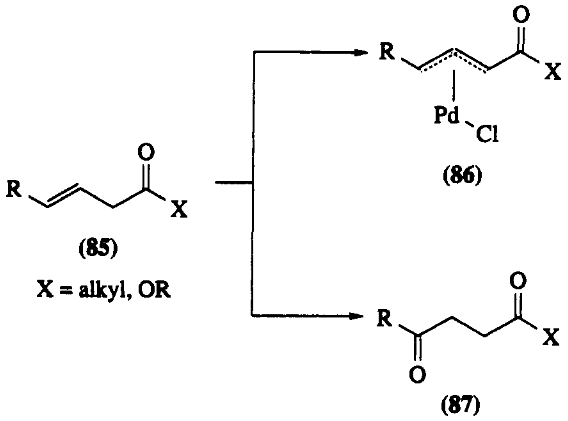
R
O
X
(85)
X = alkyl, OR
R
O
X
Pd
Cl
(86)
R
O
X
O
(87)

**Scheme 26**

**Table 2** Oxidation of Various β,γ-Unsaturated Esters and Ketones

| *Alkene* | *Product* | *Yield (%)* |
|---|---|---|
| 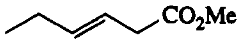 | 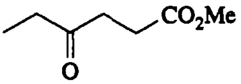 | 52 |
| 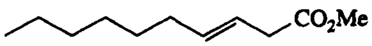 | 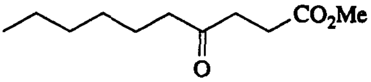 | 61 |
| 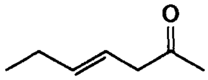 | 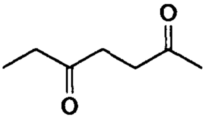 | 45 |
| 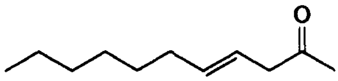 | 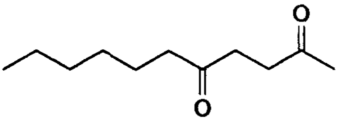 | 61 |

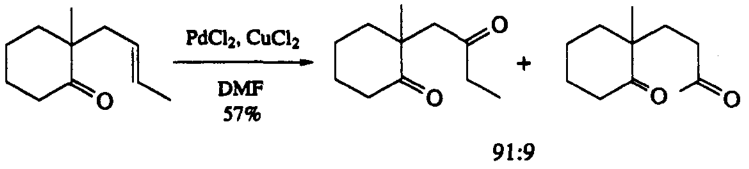
O
PdCl₂, CuCl₂
DMF
57%
O
O
+
O
O
91:9

(17)

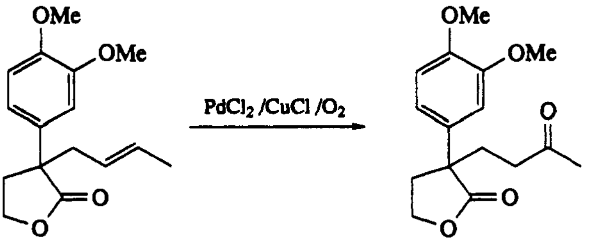
OMe
OMe
O
O
PdCl₂ /CuCl /O₂
OMe
OMe
O
O
O

(18)

### 3.4.4.3 Regioselective Oxidation of Allyl and Homoallyl Ethers and Esters

The oxidation of various allyl ethers and acetates with internal alkenes using $PdCl_2/CuCl/O_2$ or $PdCl_2$/*p*-benzoquinone catalyst systems gave the corresponding β-alkoxy ketones regioselectively (equation 19).[130] No α-alkoxy or α-acetoxy ketone was detected.

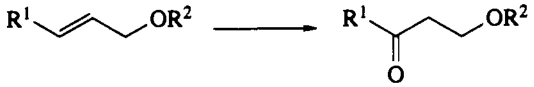

(19)

$R^1$ = alkyl; $R^2$ = alkyl, acetyl

In the oxidation of 2-octenyl acetate, in addition to the normal oxidation, palladium-catalyzed allylic rearrangement and subsequent oxidation took place to give a small amount of 3-acetoxy-2-octanone as a byproduct. Ethers of secondary allylic alcohols also underwent the regioselective oxidation to give the corresponding β-alkoxy ketones in 30–40% yields. But in this case too, by-products derived from the allylic rearrangement and subsequent oxidation were also detected. Results of the oxidation of some allyl ethers are shown in Table 3.[130]

**Table 3** Oxidation of Various Allyl Ethers

| *Substrate* | *Product* | *Yield (%)* |
|---|---|---|
| 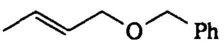 | 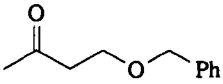 | 67 |
| 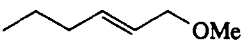 | 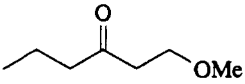 | 65 |
| 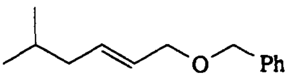 | 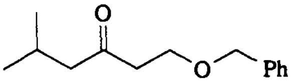 | 76 |
| 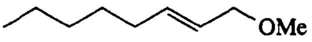 | 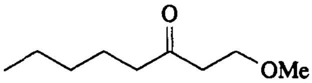 | 50–60 |
| 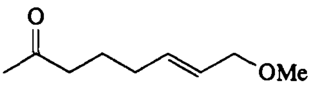 | 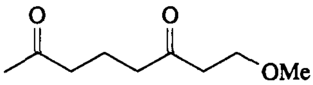 | 64 |

Homoallyl acetates were oxidized to form the corresponding γ-acetoxy ketones with high regioselectivity. The results are shown in Table 4. In this oxidation, small amounts of β-acetoxy ketones were sometimes formed (<10%).

In these oxidations of the internal alkenes, an oxygen atom was introduced at the alkenic carbon atom remote from the neighboring alkoxy or acetoxy group. The results suggest that there is definite influence of the alkoxy or acetoxy group, which may be explained by coordination of palladium with the oxygen function, to control the regioselection. As another example of this regioselection, β-tetrahydropyranylstyrene (**88**) was oxidized regioselectively to the phenyl ketone (**89**; equation 20). On the other hand, β-methylstyrene (**90**) was oxidized to give phenylacetone (**91**) and propiophenone (**92**) in a 3:1 ratio (equation 21).[131] The participation effect of the ether oxygen is clear.

The control of the regioselectivity by the neighboring oxygen function is effective only in the oxidation of internal alkenes. Terminal alkenes bearing a neighboring alkoxy or acetoxy group were oxidized to the corresponding methyl ketones, though the effect of the alkoxy or acetoxy group predicts the formation of the corresponding aldehydes (see equation 11).

β-Alkoxy ketones and γ-acetoxy ketones prepared by the oxidation of allyl ethers and homoallyl acetates, respectively, are synthetically useful intermediates. The reaction of (**93**) in the presence of excess sodium methoxide with 2-methylcyclohexanone afforded methyloctalone (**94**) in 42% yield (equation

**Table 4** Oxidation of Homoallyl Acetates

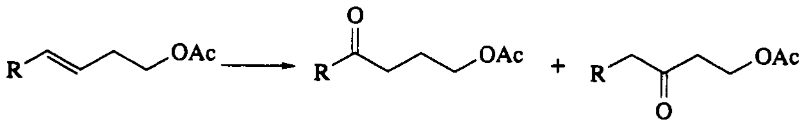
R
OAc
O
R
OAc
+
R
OAc
O

(A) (B)

| *Substrate* | *Catalyst* (%) | *Time* (h) | *Yield* (%) | *Ratio* (*A*):(*B*) |
|---|---|---|---|---|
| 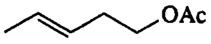 | 10 | 12 | 80 | 91:9 |
| 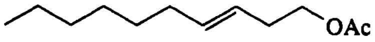 | 10 | 24 | 73 | 88:12 |
| 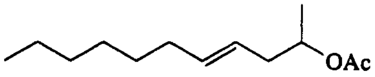 | 10 | 24 | 72 | 90:10 |
| 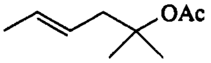 | 20 | 12 | 42 | 100:0 |

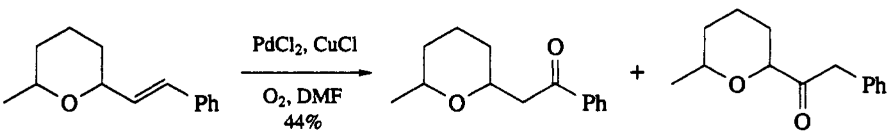
Ph
PdCl$_2$, CuCl
O$_2$, DMF
44%
O
O
Ph
+
O
Ph
O
O

(88) (89) 100:0 (20)

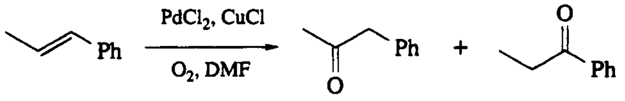
Ph
PdCl$_2$, CuCl
O$_2$, DMF
Ph
O
+
O
Ph

(90) (91) 75:25 (92) (21)

22). Thus, allyl ethers can be regarded as 'masked vinyl ketones' by means of this palladium-catalyzed oxidation.

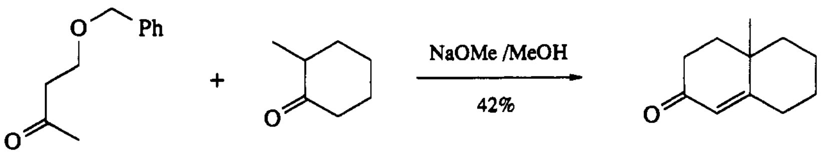
O
Ph
O
+
O
NaOMe /MeOH
42%
O

(93) (94) (22)

1,4-Diketones or γ-keto aldehydes (**95**) were prepared from γ-acetoxy ketones by saponification of the acetate with aqueous sodium hydroxide, followed by oxidation with PCC (equation 23).

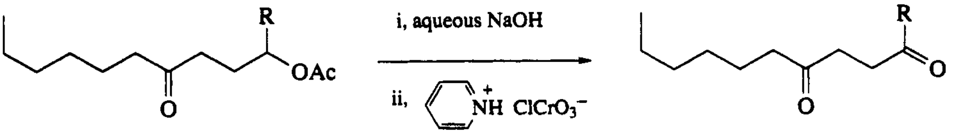
R
OAc
O
i, aqueous NaOH
ii, NH ClCrO$_3^-$
+
R
O
O

R = H, Me (95) (23)

## 3.4.5 REFERENCES

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23. B. Kongkathip, R. Sookkho and N. Kongkathip, *Chem. Lett.*, 1985, 1849.
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# 3.5

# Addition Reactions with Formation of Carbon–Nitrogen Bonds

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## 3.5.1 INTRODUCTION

This review is written to cover the needs of synthetic chemists with interests in oxidizing alkenes by addition of nitrogenous substituents. Whilst some aspects have been covered in previous reviews (noted in the text), most notably in the Tetrahedron Report No. 144, 'Amination of Alkenes'[1] and prior reviews on aziridines and nitrenes, the present review is the first compilation of references to the whole range of these particular bond-forming processes. A review by Whitham provides a useful general introduction to reaction mechanisms of additions to alkenes in greater detail than can be covered here.[2] The 'oxidation' requirement excludes from the scope the additions of N + H and most additions of N + Metal or N + C. Hence, unmodified Michael and Ritter reactions are excluded. These topics are mostly covered in Volume 4 of the present series.

Half this review is concerned with aziridination, but other cycloadditions are generally excluded, being reviewed elsewhere in this series (Volume 4, Part 4 and Volume 5, Part 4). The second half of this review covers additions of nitrogen and a chalcogen or halogen, or a second nitrogen. No examples of addition of N + P were found: this transformation can be achieved indirectly by opening aziridines with phosphorus nucleophiles.[3]

Surprisingly few of the reactions herein have been used widely, yet some have much to offer for synthesis. Many aziridinations, for example, occur under extremely mild conditions. The potential utility of aziridines as synthetic intermediates is enormous; for example, to make regiospecifically substituted diamines, but published examples to date are few. There is also much scope for wider usage of iodolactamizations and related cyclizations.

## 3.5.2 AZIRIDINE FORMATION FROM ALKENES

Aziridines are readily accessible, yet under used as synthetic intermediates.[4–7] There is an even greater variety of methods of preparation than for epoxides. Nitrene additions to congested alkenes (Section 3.5.2.3) often show stereoselectivity, and indirect syntheses, *e.g.* from amino alcohols, are stereospecific. Some success has already been achieved in chiral aziridine preparation (Section 3.5.2.5), though the generality, and enantiomeric excesses (except in a few specific cases) do not yet match those of, for example, the Sharpless epoxidation. The main utility of aziridines in synthesis lies in their ring-opening reactions analogous to those of epoxides, but more versatile owing to the varied exocyclic *N*-substituent which modulates the properties and reactivity of the three-membered ring.[4–9] It should be noted, however, that aziridines are toxic, and that the lower molecular weight compounds, particularly, can sometimes polymerize with a very vigorous exotherm, generally initiated by acid catalysis.[7]

### 3.5.2.1 Aziridines with Nitrogen Unsubstituted

Several reagents will effect the aziridination of alkenes directly, for example, electrophilic alkenes react with diphenylsulfilimine (**1**) in good yield, with the elimination of diphenyl sulfide (Scheme 1).[10–12] A similar reaction using the chiral sulfilimine (*R*)-(+)-(**3**) gives product (**2**; 96%) as the (2*R*,3*S*) form shown (64%), accompanied by the enantiomer (32%).[13] Cephalosporin substrates (**4**) react with achiral (**1**) to give products (**5**), as single diastereoisomers in 52–63% yields.[14]

Pentamethyleneoxaziridine (**6**) also acts as an aminating agent, giving quite good yield of aziridines (Scheme 2).[15,16] Remarkably, none of the corresponding epoxide was reported in this reaction. Cyclohexene yields instead the hydrazino alcohol (**8**), probably *via* the *N*-aminoaziridine (**7**). In view of the recent use of chiral oxaziridines for chiral oxidations, it will be interesting to see whether chiral aziridination is possible when chiral *N*-unsubstituted oxaziridines become available.[17]

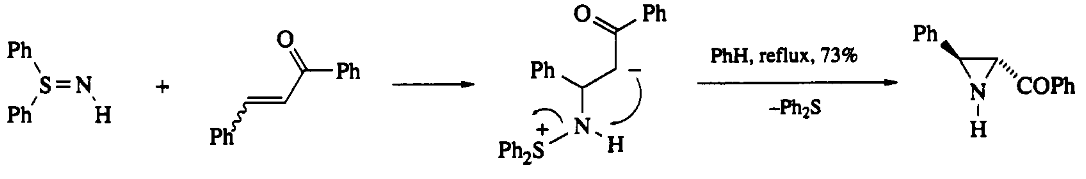

(**1**) (**2**)

**Scheme 1**

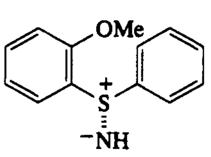

(3)

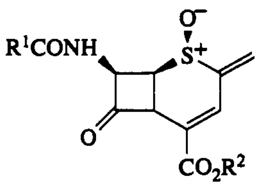

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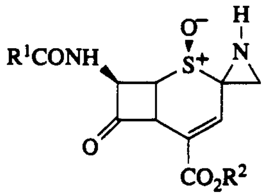

(5)

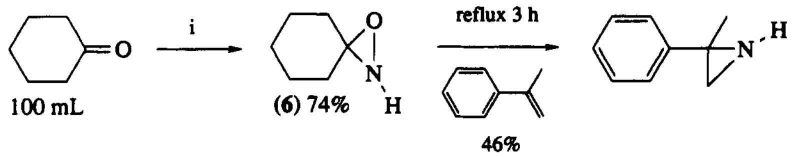
i
reflux 3 h
100 mL
(6) 74%
46%

i, NaOCl (200 mL 0.98 M), $NH_4OH$ (100 mL 2 M), PhMe (500 mL) ice/water (400 mL), shake 30 s, separate, wash $H_2O$, dry ($MgSO_4$)

**Scheme 2**

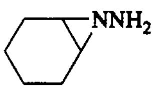

(7)

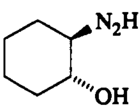

(8)

Electron deficient alkenes, *e.g.* $NCCH{=}C(CO_2Me)_2$, can be aziridinated with *O*-(arylsulfonyl)hydroxylamines. The reaction is believed to involve a Michael addition followed by cyclization with expulsion of a sulfonate anion (yields 30–90%).[18] Less electrophilic alkenes react in lower yield but with a high stereospecificity: a high degree of concertedness would appear to be present in this case (Scheme 3).[19] Related syntheses, where the leaving group is halide, alkoxide or trimethylamine, are discussed in Deyrup's[5] and Červinka's[20] reviews; some examples are given in Schemes 4[21] and 5;[22] reactions of haloamines, particularly with unactivated alkenes, are generally radical processes (Scheme 6).[23] An elegant one-pot aziridination of chalcones has been devised (Scheme 7).[24]

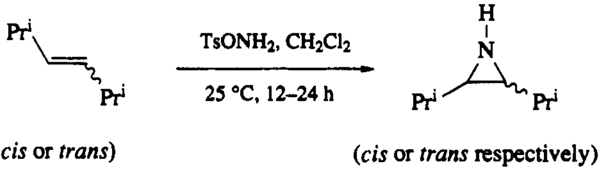
TsONH2, CH2Cl2
25 °C, 12–24 h
(cis or trans)
(cis or trans respectively)

**Scheme 3**

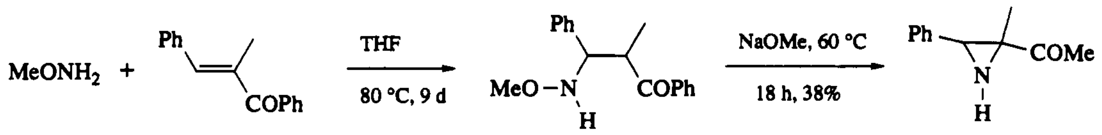
THF
80 °C, 9 d
NaOMe, 60 °C
18 h, 38%

**Scheme 4**

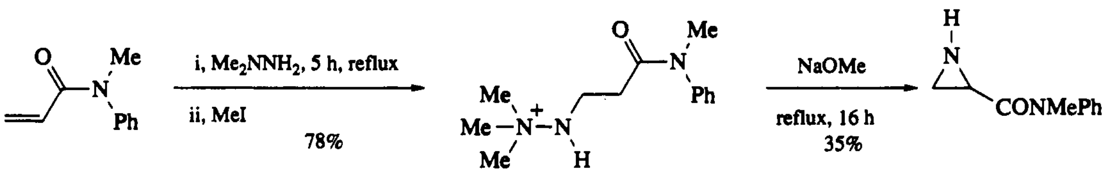
i, Me2NNH2, 5 h, reflux
ii, MeI
78%
NaOMe
reflux, 16 h
35%

**Scheme 5**

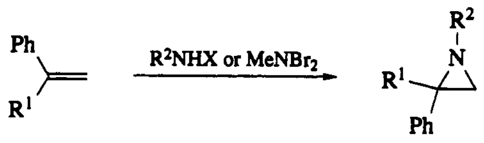
Ph
R¹
R²NHX or MeNBr₂
R²
N
R¹
Ph

$R^1 = H, Me; R^2 = H, alkyl; X = Cl, Br$

**Scheme 6**

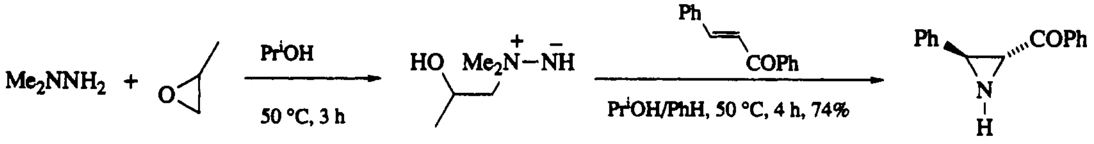
Me₂NNH₂ +
PriOH
50 °C, 3 h
HO Me₂N⁺–N⁻H
Ph
COPh
PriOH/PhH, 50 °C, 4 h, 74%
Ph
COPh
N
H

**Scheme 7**

Of the numerous other aziridine syntheses, there are several multistep procedures from alkenes. Though not strictly within the scope of this review, the practising chemist will wish to consider their merits alongside the direct syntheses, and the main possibilities are summarized in Scheme 8. There are several good recent reviews,[4,5] and two older compilations remain very useful.[6,7] Syntheses of those intermediates of Scheme 8 accessible from alkenes are described in later sections of the present review, and syntheses of epoxides (Volume 6, Chapter 1.1 and Volume 7, Chapters 3.1 and 3.2) and triazolines (Volume 5, Chapter 3.1) are described elsewhere in 'Comprehensive Organic Synthesis'. It is important to note that by careful choice of route one can either commence with alkene (**14**) and retain the *cis*/*trans* stereochemistry in the resulting aziridine (**16**), or start with alkene (**13**) and change the *cis*/*trans* relationships of the substituents.

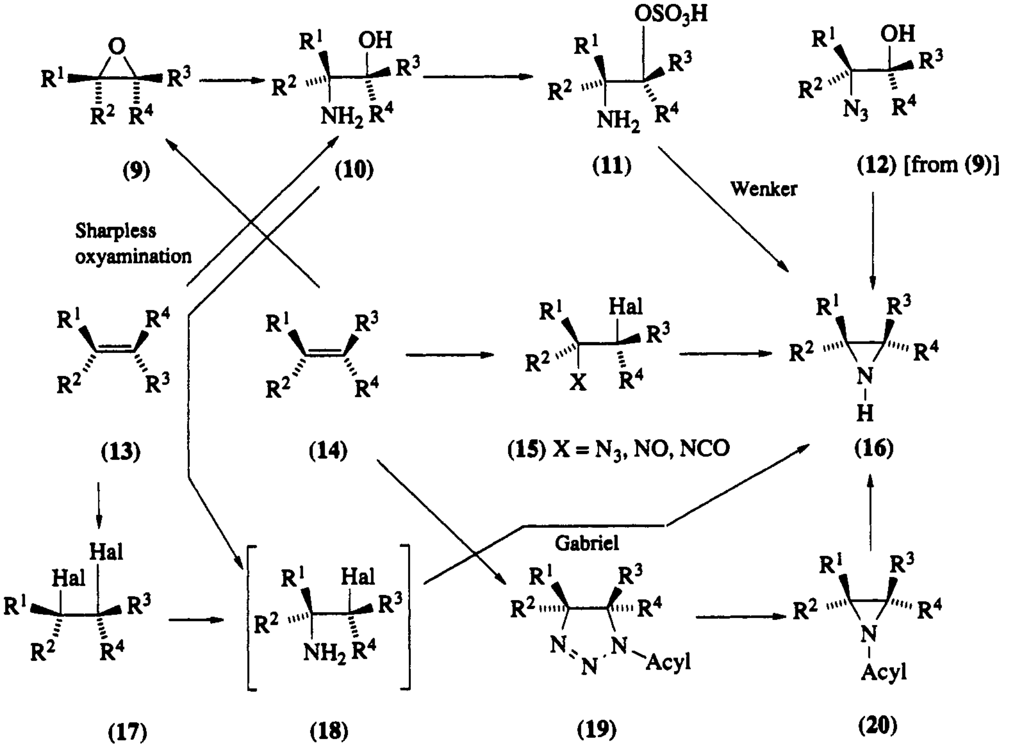
(9)
(10)
(11)
(12) [from (9)]
OSO₃H
OH
NH₂
N₃
Sharpless oxyamination
Wenker
(13)
(14)
(15) X = N₃, NO, NCO
(16)
Hal
X
Gabriel
(17)
(18)
(19)
(20)
N
N
N
Acyl
H

**Scheme 8** The major indirect aziridination routes

The Wenker and Gabriel syntheses have great scope and usually give good yields, however the routes *via* triazolines (*e.g.* **19**) are not good for *N*-unsubstituted aziridines or for *N*-alkylaziridines. The Gabriel synthesis is stereospecific, and by choice of appropriate precursor can yield stereospecific syntheses of the desired aziridines. The Wenker synthesis is also *generally* similarly stereospecific: a rare exception being when the sulfate leaving group is attached to a benzylic center.[6] In such systems the Gabriel synthesis remains stereospecific. Both syntheses require that the amine and leaving groups in (**11**) or (**18**) can adopt a *trans* coplanar, or nearly so, orientation. Several resolved amino alcohols are readily available by reduction of amino acids and can be utilized to make chiral aziridines, the Wenker synthesis of (*S*)-(–)-2-methylaziridine from L-alaninol being typical.[25] In certain cases, a resolved epoxide precursor may be available by the Sharpless procedure (Volume 7, Chapter 3.2) as in the PS5 synthesis (Scheme 9). This synthesis illustrates two further features of this utilization of epoxides: clean regiochemistry of the initial ring opening is not required to yield pure, resolved aziridines and, though *cis/trans* relationships are retained, this is by virtue of an inversion at each ring carbon atom.[26] This allows, in principle, the preparation of an *endo* aziridine *via* an *exo*-epoxide of, for example, a norbornene type of alkene, whereas direct aziridination, *e.g.* by nitrene addition to the double bond, would give the *exo*-aziridine.

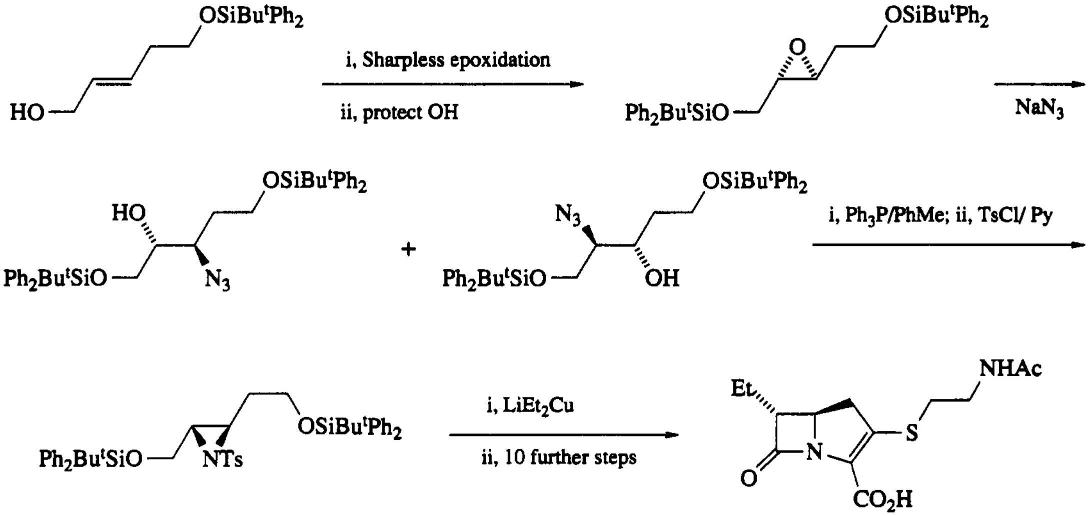

**Scheme 9**

The alkene pseudohalogen adducts (**15**) of Scheme 8 are also useful intermediates for aziridine synthesis. These adducts are discussed later in Sections 3.5.6.2–4. The iodine azide[27–29] and bromine azide[30] adducts may be reduced to aziridines with many reagents; recent references report use of lithium aluminum hydride[28,29] and dimethylamineborane.[27] The iodine isocyanate aziridination continues to prove useful, as in Scheme 10.[31–33] Since the recent reviews,[4,5] the mechanism of the triphenylphosphine-based cyclization of azido alcohols has appeared (Scheme 11); there are clear steric consequences.[34] Alkenes can be chlorinated in acetonitrile to give intermediates which can be worked up to yield aziridines (Scheme 12).[35]

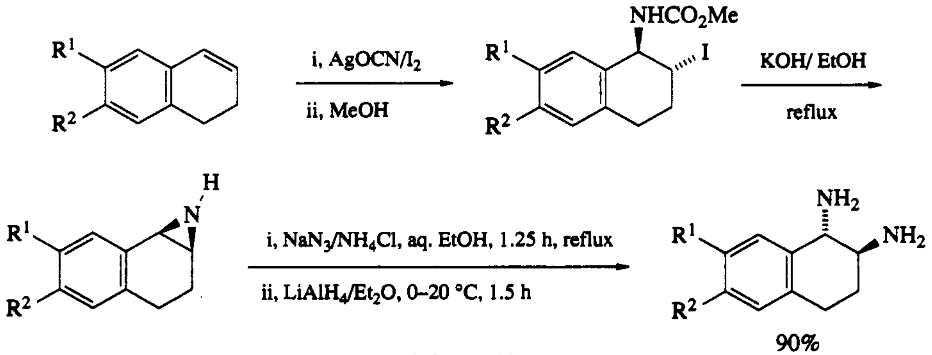
R$^1$
R$^2$
i, AgOCN/I$_2$
ii, MeOH
NHCO$_2$Me
I
KOH/ EtOH
reflux
H
N
i, NaN$_3$/NH$_4$Cl, aq. EtOH, 1.25 h, reflux
ii, LiAlH$_4$/Et$_2$O, 0–20 °C, 1.5 h
NH$_2$
NH$_2$
90%

**Scheme 10**

The regio- and stereo-chemical consequences of preparing an aziridine *via* IN$_3$, or INCO, or the above chlorination procedure are, in so far as they have been investigated, analogous to those of proceeding *via* an epoxidation, for the simple reason that all these last three reaction types appear to proceed *via* cyclic halonium ions, isosteric with epoxides.

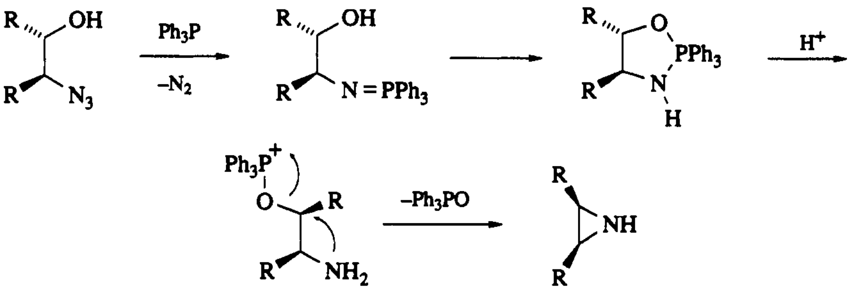

Scheme 11

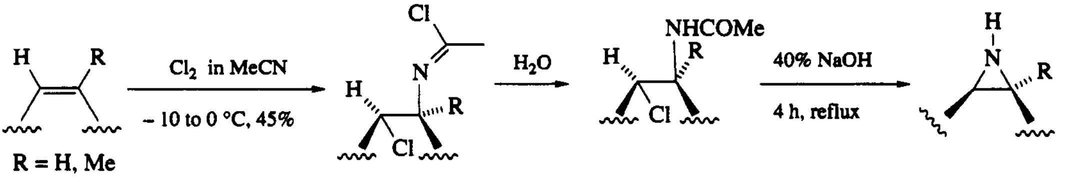

Scheme 12

Aziridines can be made in a sequence starting with the addition of NOCl to alkenes, Scheme 13. The sequence is probably limited to tetrasubstituted alkenes, owing to instability of the nitroso intermediates from less-substituted alkenes (Section 3.5.6.2).[36-38] Since the reagent reacts as $NO^+Cl^-$ and delivers the nitrogen, rather than the leaving group, to the exposed face of an alkene, one would expect an appropriate norbornene derivative to yield an *exo*-aziridine in contrast to the *endo* products obtained *via* epoxides, although this appears not to have been investigated yet.

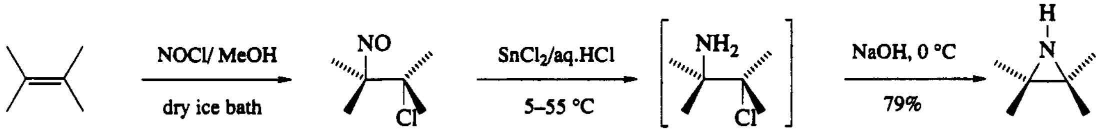

Scheme 13

*N*-Unsubstituted aziridines may be prepared by removal of *N*-substituents. Surprisingly vigorous reagents or conditions may be tolerated in these reactions: *N*-carbethoxy is cleavable with KOH as in Scheme 10, *N*-cyano[39] or acyl[40] by lithium aluminohydride, this last normally being considered an aldehyde synthesis.[40] An *N*-sulfenyl group (of under-used potential, Section 3.5.2.6) may be removed with sodium borohydride.[41] 1,2,3-Triphenylaziridine is quantitatively ozonolyzed to 2,3-diphenylaziridine.[42]

### 3.5.2.2 *N*-Alkyl- and *N*-Alkenyl-aziridines

There are no one-step syntheses of *N*-alkylaziridines direct from alkenes of proven generality, the most thoroughly investigated being the reactions of *N*-halo- and *N,N*-dihalo-alkylamines with alkenes referred to earlier (Scheme 6).[23] They are probably radical reactions and are not stereospecific; the *N*-haloamine reagents are difficult to prepare cleanly, and are rather dangerous. Representative examples (6 of 17) prepared from halogenated alkylamines are listed in Scheme 14.

A one-pot conversion of alkenes to *N*-methylaziridines has been achieved by aminopalladation followed by an oxidative work-up with bromine (Scheme 15).[43] The reaction is stereospecific, as shown by deuteration experiments, but has been little exploited.[43,44] 2-Aminopalladium compounds such as (**21**) are extremely versatile; depending on starting compounds and work-up reagents, they can be made to yield a wide variety of products (Scheme 16).[45]

Gabriel and Wenker type syntheses are thoroughly viable for *N*-alkylaziridines,[4-7] and there are examples of aziridination of alkenes, *via* *vic*-dihalides *etc.*, where by use of a chiral amine a kinetic induction of chirality in the aziridine nucleus has been achieved.[46,47] 2-Iodoalkyl azides react with alkyl and aryl dichloroboranes, forming aziridines (Scheme 17).[48] Sequences resembling the Wittig[49] and Wittig–Hor-

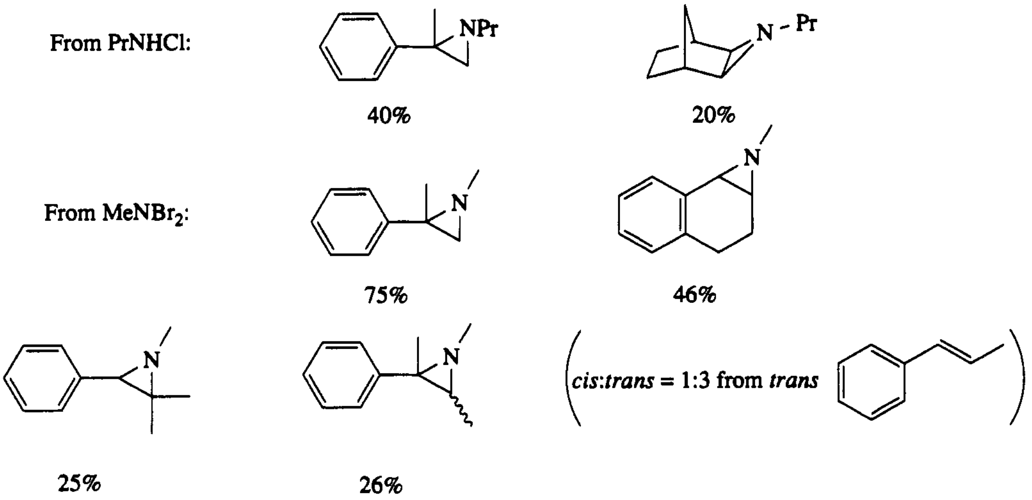
From PrNHCl:
NPr
40%
N - Pr
20%
From MeNBr2:
N
75%
46%
25%
26%
cis:trans = 1:3 from trans

Conditions: PhH, dioxane, PhMe, $CCl_4$ *etc.*; 20–110 °C; 10 min–3 d

**Scheme 14** *N*-Alkylaziridines from *N*-haloamines and alkenes

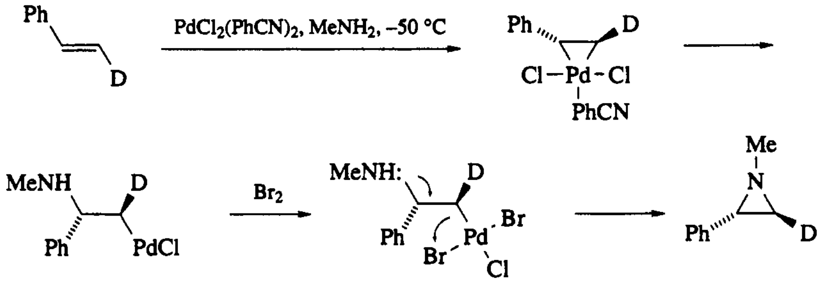
Ph
D
PdCl2(PhCN)2, MeNH2, -50 °C
Ph
D
Cl-Pd-Cl
PhCN
MeNH
D
Ph
PdCl
Br2
MeNH:
D
Ph
Pd
Br
Br
Cl
Me
N
Ph
D

**Scheme 15**

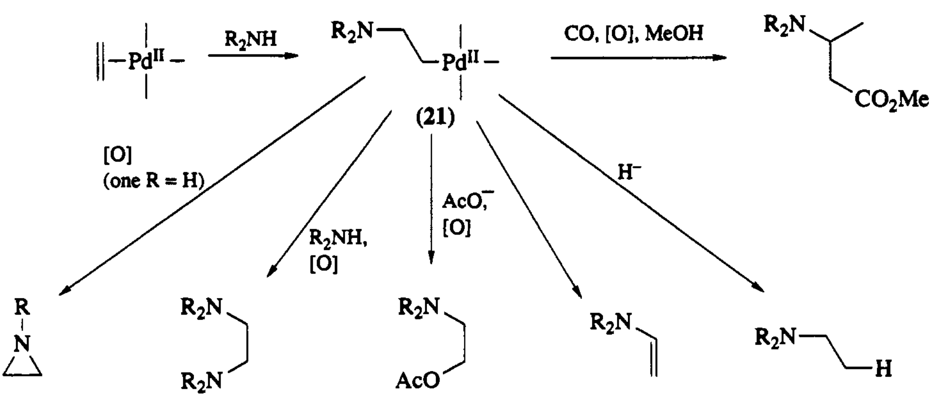
PdII
R2NH
R2N
PdII
(21)
CO, [O], MeOH
R2N
CO2Me
[O]
(one R = H)
R2NH,
[O]
AcO−,
[O]
H−
R
N
R2N
R2N
R2N
AcO
R2N
R2N
H

**Scheme 16**

ner[50] reactions can be carried out on epoxides, resulting in *N*-alkyl- or *N*-aryl-aziridines instead of imines.

Covalent azides add to alkenes in a [2 + 3] cycloaddition, giving triazolines (Volume 4, Chapter 4.10), and these in turn can be thermolyzed or photolyzed with loss of nitrogen to give aziridines. The addition obeys the complementarity principle for cycloadditions, which in this case means that electron-rich azides prefer to react with electron-poor alkenes and *vice versa*.[51] Thus, a few *N*-alkylaziridines have been prepared from electron-poor alkenes *via* triazolines.[52] The thermal stability of triazolines with respect to loss of nitrogen and aziridine formation varies with the electronegativity of the exocyclic *N*-substituent. Thus, *N*-vinyltriazolines decompose more readily than *N*-alkyltriazolines to give *N*-vinylaziridines in good yield, as in Scheme 18.[53–57] Several examples of intramolecular formation of

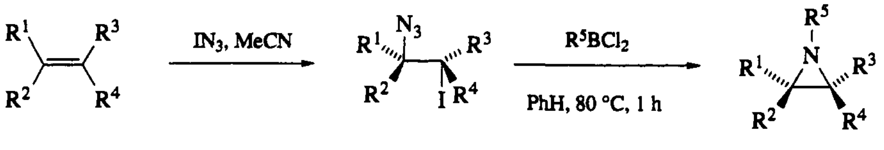

$R^5$ = alkyl, Ar

Scheme 17

vinyltriazolines, and subsequent pyrolysis to give fused-ring aziridines are known.[53] *N*-Alkylaziridines are accessible in good yield by intramolecular cyclization of suitable alkenic nitrenes, giving bridged ring systems (analogous intermolecular reactions are not useful).[58–60] This was put to good use in the synthesis of (**22**), a key intermediate in the synthesis of a tetracyclic alkaloid, ibogamine.[61]

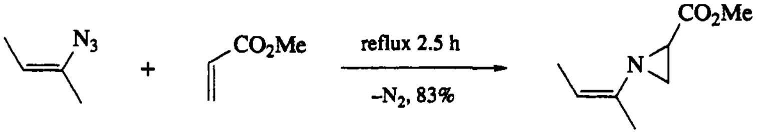

Scheme 18

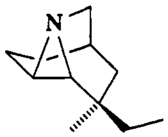

(**22**)

### 3.5.2.3 *N*-Aryl- and *N*-Heteroaryl-aziridines

The indirect routes: Gabriel and Wenker syntheses (Scheme 8),[4–7] the borane route (Scheme 17),[48] and Wittig-like syntheses[49,50] are all highly satisfactory for *N*-arylaziridines. It is, however, with the *N*-aryl compounds that the azide/triazoline route begins to be useful, though not, in general, preferable to the other routes: the explosive potential of azides limits their desirability. The preparation, thermolysis and photolysis of triazolines, including many *N*-aryl compounds, has been well reviewed recently.[53] A few key points of selectivity are worth noting. Norbornene-type systems form overwhelmingly the *exo*-triazolines, which on photolysis give *exo*-aziridines. Thermolysis of these systems occurs *via* a ring-opened intermediate and hence is not stereospecific (Scheme 19).[62] Complications are encountered when the thermal sequence is applied to very electron-poor alkenes: the thermolysis is slow, and the resulting aziridine ring opens with C—C cleavage to give an ylide, which then adds to the alkene to give a pyrrolidine (Scheme 20).[53,63]

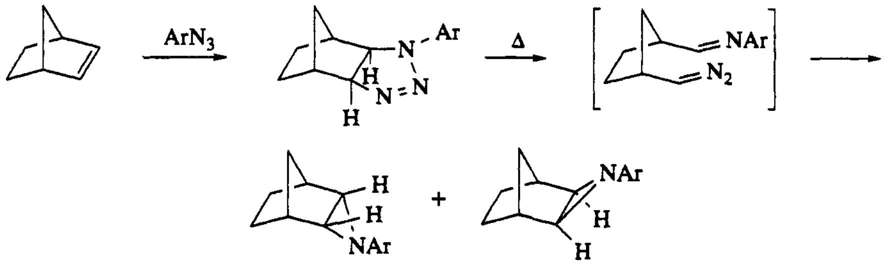

Scheme 19

Aziridine formation from arylnitrenes, rather than *via* triazolines, is known for highly fluorinated arenes.[64,65] Phenyl azide with trifluoroacetic acid generates a nitrenium ion which adds stereospecifically to alkenes to give aziridines. Yields are rather low, partly due to concurrent ring opening of the aziridine by addition of trifluoroacetic acid.[66] Similar reactions can be achieved with Lewis acids such as $AlCl_3$.[67] Enamines with aryl azides can yield either 2-aminoaziridines[68] or amidines.[53]

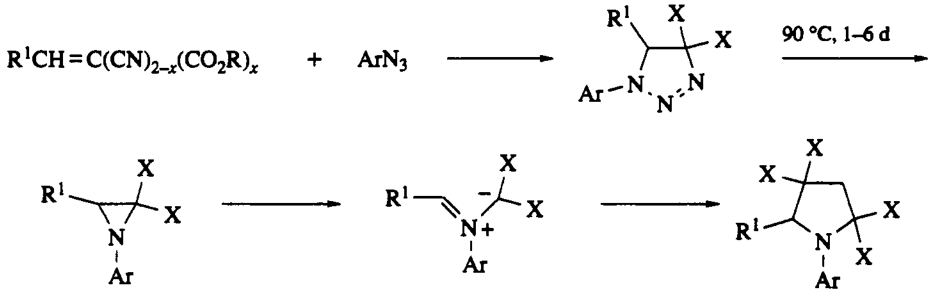

$R^1$ = alkyl, Ar; X = $CO_2R$, CN

Scheme 20

Heterocyclic azides can give good yields of aziridines (Scheme 21), but the reactions can give other products, depending on the precise combination of starting materials.[69] The reaction shown in Scheme 21 is believed to occur *via* a nitrene, not a triazoline, and is favored by electron-poor alkenes (in this case, electron-rich alkenes give much isomeric thiochroman).

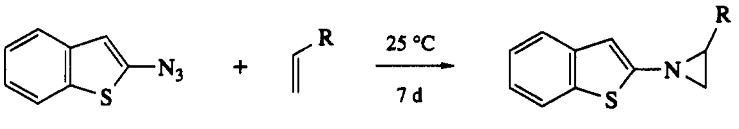

R = CN, 85%
R = $CO_2Me$, 90%

Scheme 21

### 3.5.2.4 *N*-Acyl- and *N*-Cyano-aziridines and Related Compounds

Acylaziridines are not freely available by the Gabriel or Wenker routes, oxazolines being the normal products of such reactions,[70] though *threo*-β-acylamino alcohols (from *trans* internal alkenes) can give aziridines.[71] Acyl azides undergo the Curtius rearrangement to isocyanates,[72] and additions to alkenes to yield triazolines and hence aziridines are rare.[73] Photolysis of acyl azides can yield acylaziridines,[74] though the reaction is only of potential preparative value when a strained ring increases alkene reactivity.[75] Pivaloyl azide, in particular, on photolysis yields a nitrene (50%) which is unusually slow to rearrange to the isocyanate. It adds to alkenes stereospecifically (as singlet) and stereoselectively (as triplet);[76,77] by use of as long a wavelength as possible (300–350 nm), and very pure solvents, especially dichloromethane which stabilizes singlet nitrenes, yields up to 45% are obtainable.

In a reaction modeled on the use of cytochrome *P*-450 to catalyze oxidations with iodosylbenzene, iron or manganese porphyrins have been used to catalyze aziridinations with iodinanes (Scheme 22).[78] In this early report *cis*- or *trans*-stilbene each gave the *trans*-aziridine, but stereoselectivity has since been achieved for the sulfonylaziridines (Section 3.5.2.6).

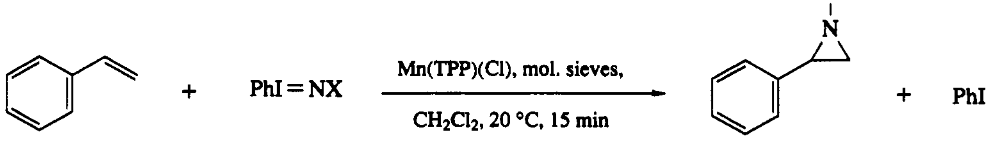

X = $COF_3$, 50%; $SO_2C_6H_4Me$-*p*, 80%

Scheme 22

Alkoxycarbonyl azides, which do not readily undergo the Curtius rearrangement, have a much richer triazoline and nitrene chemistry, the scope and theory of which are fully discussed by Lwowski.[72] Carbethoxynitrene may be generated by α-eliminations,[79,80] optionally assisted by ultrasound[79] or PTC (Scheme 23).[79,81]

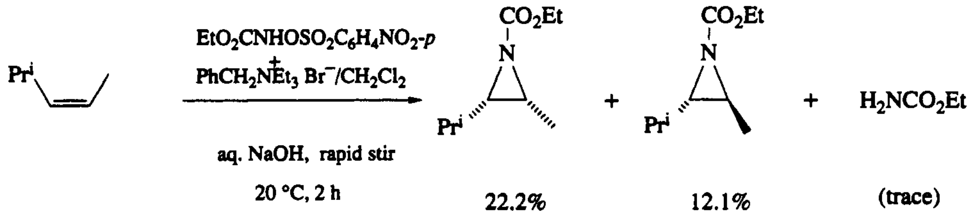
Pr$^i$
EtO$_2$CNHOSO$_2$C$_6$H$_4$NO$_2$-p
PhCH$_2\overset{+}{N}$Et$_3$ Br$^-$/CH$_2$Cl$_2$
aq. NaOH, rapid stir
20 °C, 2 h
CO$_2$Et
N
Pr$^i$
22.2%
+
CO$_2$Et
N
Pr$^i$
12.1%
+ H$_2$NCO$_2$Et
(trace)

Scheme 23

Results from *cis*- and *trans*-alkenes show that all the nitrene is generated in the singlet state (which adds stereospecifically) but concurrent decay to the triplet (1/30 as fast as addition) leads to loss of stereospecificity (Scheme 24).[80,82,83] However, by optimizing conditions, stereospecificities of 97.4% (from *trans*-alkene to *trans*-aziridine) and 98.2% (*cis* to *cis*) are obtainable by the α-elimination route. Thermolysis of ethoxycarbonyl azide also produces singlet nitrene,[84] however photolysis produces two-thirds singlet and one-third triplet, which sets an upper limit to the stereospecificity of the addition. Both reactions can be optimized to give about 70% yields of aziridines. The thermal reaction is complicated in those cases where the triazoline route competes with nitrene formation. This is the case with tetraalkylalkenes leading to increased proportions of, chiefly, imine by-products (Scheme 25).[85] Ethoxycarbonylnitrene can also be generated and trapped as an aziridine by thermolysis of a bis-silylated hydroxylamine (Scheme 26).[86]

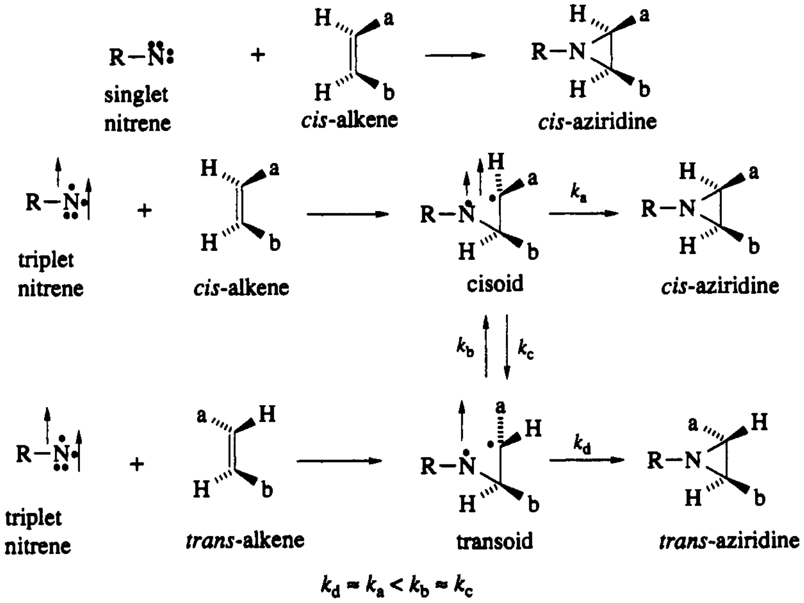
R–N:
singlet nitrene
+
cis-alkene
cis-aziridine
triplet nitrene
cis-alkene
cisoid
$k_a$
cis-aziridine
$k_b$
$k_c$
triplet nitrene
trans-alkene
transoid
$k_d$
trans-aziridine
$k_d \approx k_a < k_b \approx k_c$

Scheme 24

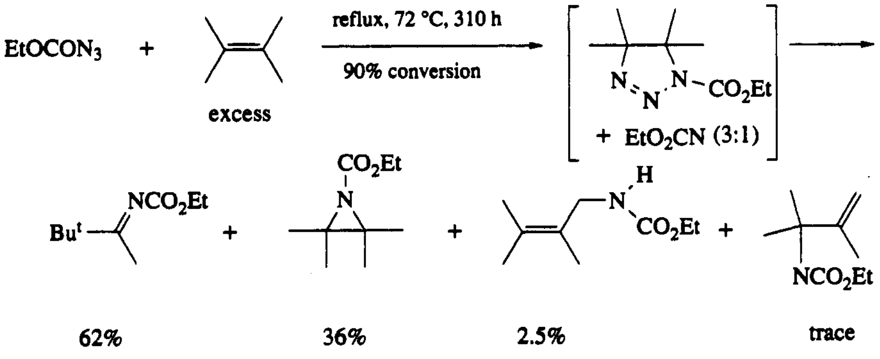
EtOCON$_3$
+
excess
reflux, 72 °C, 310 h
90% conversion
N N N–CO$_2$Et
+ EtO$_2$CN (3:1)
Bu$^t$
NCO$_2$Et
62%
CO$_2$Et
N
36%
H
N
CO$_2$Et
2.5%
NCO$_2$Et
trace

Scheme 25

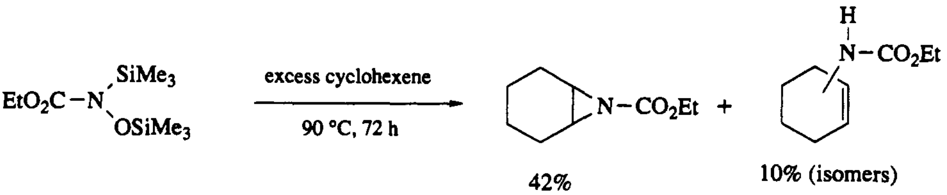
EtO2C–N(SiMe3)(OSiMe3)
excess cyclohexene
90 °C, 72 h
N–CO2Et
+
H
N–CO2Et
42%
10% (isomers)

**Scheme 26**

Norbornene adds to photolytically produced ethoxycarbonylnitrene specifically at the *exo* face;[87] the same aziridine is produced in the thermal addition of ethoxycarbonyl azide, but *via* the triazoline rather than the nitrene, with much imine by-product.[88] There can be problems of selectivity and rearrangements when one reacts ethoxycarbonylnitrene with more complex substrates, *e.g.* alkenic steroids.[89] Ethoxycarbonylnitrene (*via* $\alpha$-elimination) adds to vinyl chlorides to give 2-chloroaziridines,[90] which can be rearranged thermally to yield 2-chloroallyl carbamates. This nitrene also adds to enamines, giving an array of rearranged products.[91] A modern discussion of the reactivities of ethoxycarbonylnitrene (electrophilic) in comparison with phthalimidonitrene (nucleophilic) towards alkenes of different electronic properties has appeared.[92]

A procedure, primarily intended to yield diamines,[93] can be diverted to yield either imidoylaziridines or imidazolines, though rarely as well controlled as in the following example (Scheme 27). The initial step is regioselective (Markovnikov) and stereospecific. In a related procedure the $\beta$-bromocyanamide was reduced to a formamidine ($H_2$, 1% Pd/C, MeOH–AcOH, 20 °C, 1 atm) as an alternative intermediate.[94]

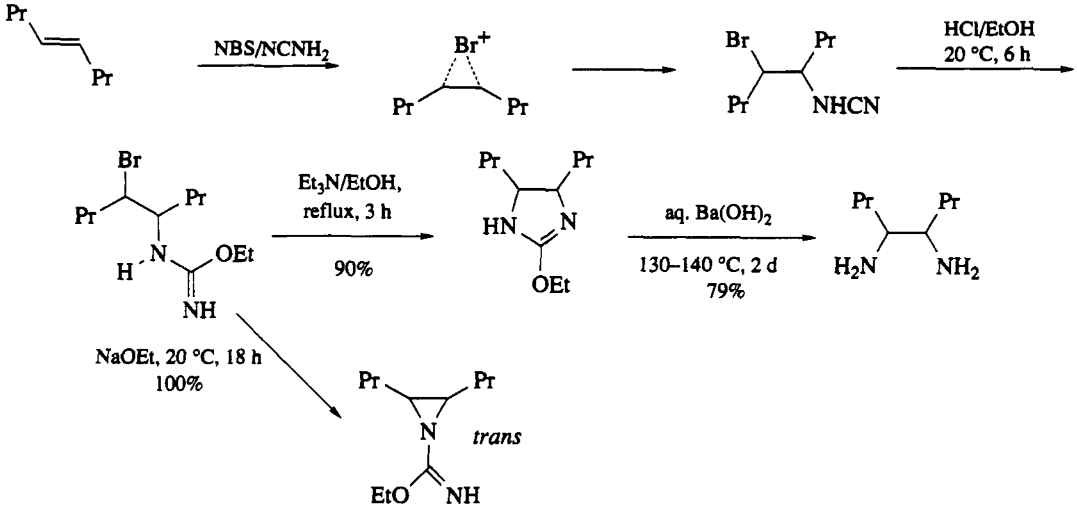
Pr
Pr
NBS/NCNH2
Br+
Pr
Pr
Br
Pr
Pr
NHCN
HCl/EtOH
20 °C, 6 h
Br
Pr
Pr
H
N
OEt
NH
Et3N/EtOH,
reflux, 3 h
90%
Pr
Pr
HN
N
OEt
aq. Ba(OH)2
130–140 °C, 2 d
79%
Pr
Pr
H2N
NH2
NaOEt, 20 °C, 18 h
100%
Pr
Pr
N
trans
EtO
NH

**Scheme 27**

*N*-Cyanoaziridines can be made from alkenes *via* either cyanogen azide or cyanonitrene. Cyanonitrene can be generated thermally and photolytically from cyanogen azide,[95] but the azide itself adds so readily to most alkenes to give a transient triazoline that this has prevented much study of the nitrene-mediated reactions from the azide. More recently, our own group oxidized cyanamide in the presence of various nitrene traps: alkenes, such as dicyclopentadiene (Scheme 28), and also phosphines, sulfoxides and sulfides (including penicillins), and obtained the products of formal cyanonitrene addition in each case, though this array of products remains the sole evidence of a nitrene mechanism for these reactions.[96] Cyanonitrene has also been generated by oxidation of sodium hydrogen cyanamide with $Bu^tOCl$, but was not, apparently, added to alkenes.[97]

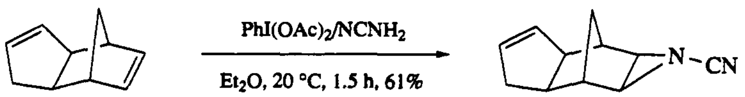
PhI(OAc)2/NCNH2
Et2O, 20 °C, 1.5 h, 61%
N–CN

**Scheme 28**

Cyanogen azide adds to alkenes at 0–35 °C giving transient triazolines, which decompose to alkylidenecyanamides, often with rearrangement (from simple alkenes), or to aziridines (cleanly only from polycyclic, strained or more highly alkylated alkenes).[98] A typically complex example is given in Scheme 29. The NBS/cyanamide addition to alkenes (Scheme 27) can also be modified to yield *N*-cyanoaziridines, by submitting the initial β-bromocyanamide adduct to a Gabriel cyclization (with NaOH/aq. acetone, reflux 30 min).[99]

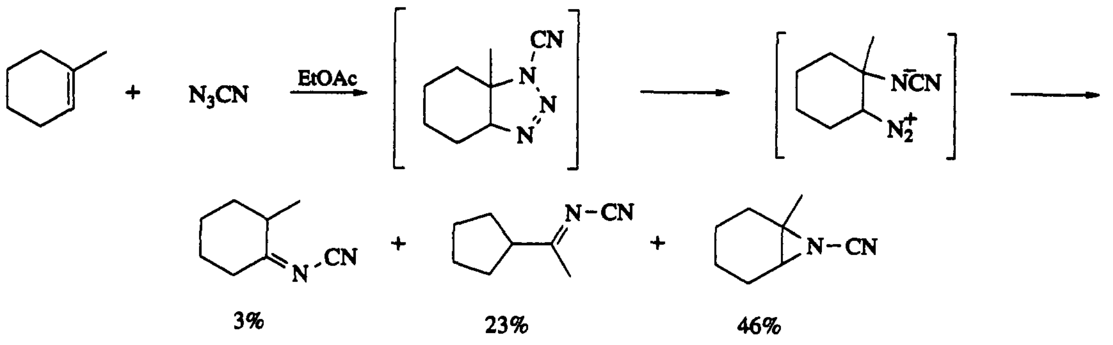

Scheme 29

### 3.5.2.5 *N*-Aminoaziridines, *N*-Phosphonylaziridines

Oxidation of the quinazoline (**23**) with lead tetraacetate gives an unstable intermediate (**24**) which shows a first order decomposition in $CH_2Cl_2$, $k = 3.68 \times 10^{-4}$ $s^{-1}$ at 10 °C.[100] The rate of disappearance of (**24**) increases on adding an alkene such as styrene (Scheme 30), with the formation of a metastable *cis* invertomer (**25**) of an aziridine (**26**), which last is the product eventually isolated.[101] It is suggested that the mechanism is analogous to the Bartlett mechanism for epoxidation.[100,102] Quinazoline (**23**) has an interesting chemistry, on oxidation adding to heterosubstituted alkenes to generate novel aziridines which show some previously unrecognized chemistry (Scheme 31).[103]

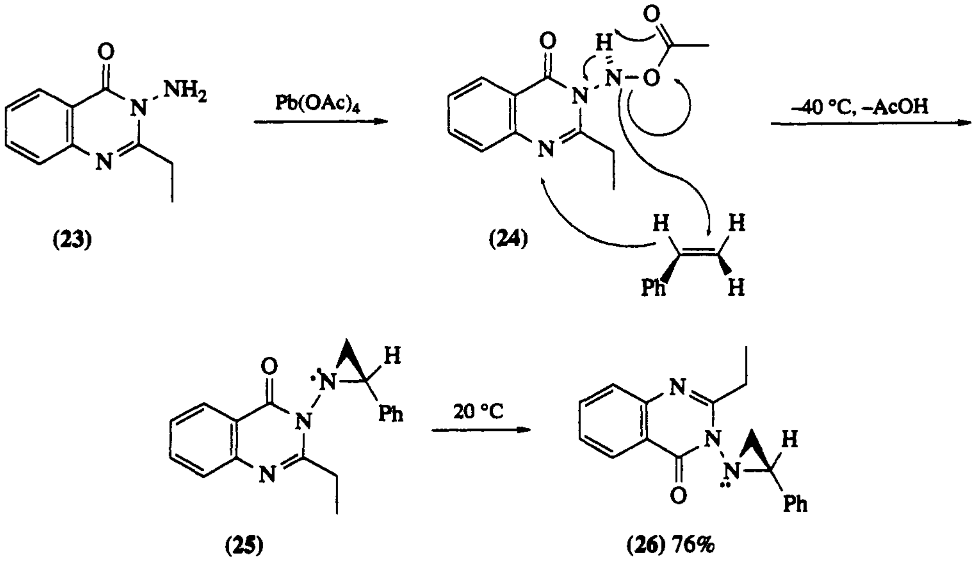

Scheme 30

It would appear that a similar mechanism probably applies to the many aziridinations of alkenes with lead tetraacetate and a wide variety of other *N*-aminoheterocycles. In any case, such reactions are now thought unlikely to occur *via* a nitrene: in competition experiments, *N*-aminophthalimide/lead tetraacetate reacts with styrene in preference to methyl acrylate (1.5:1), whereas with the supposed genuine nitrene (**27**) (whose nature is also in doubt[103]) prepared by pyrolysis (Scheme 32), the ratio is reversed (1:3).[100] Other sources of supposed (**27**) by pyrolysis include (**28**)[104] and (**29**).[105] Very recently, strong

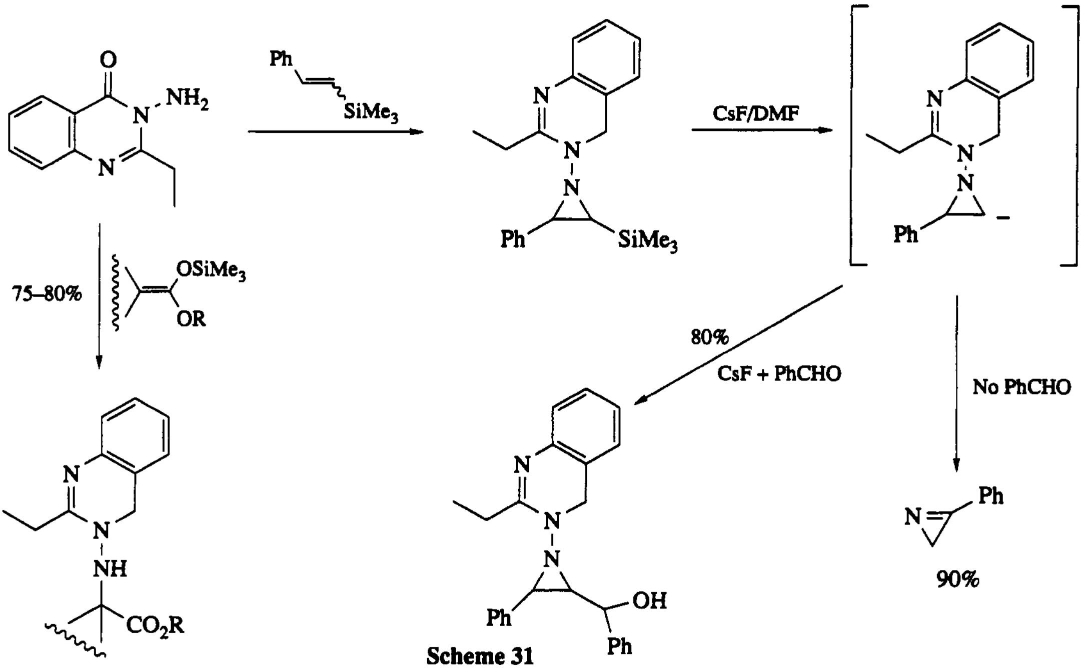

Scheme 31

evidence for an *N*-acetoxy intermediate has been obtained for the *N*-aminophthalimide/$Pb(OAc)_4$ reactions.[103,106]

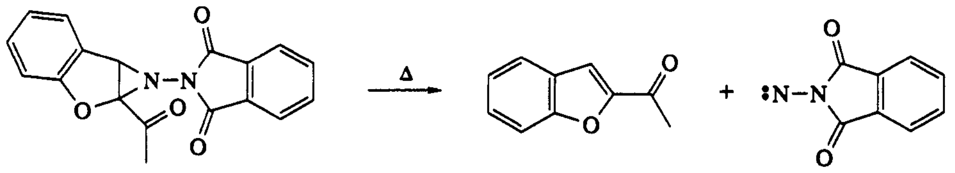

(27)

Scheme 32

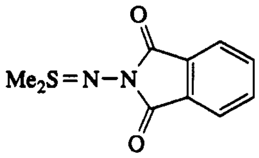

(28)

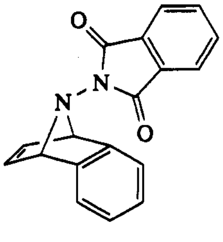

(29)

2-Cyclohexen-1-ol is aziridinated *syn* by (**24**); geraniol ($Me_2C{=}CHCH_2CH_2C(Me){=}CHCH_2OH$) is aziridinated at the 2,3-position due to hydrogen bonding, and geranyl chloride reacts at the 6,7-position.[107] These recent results also generally support the analogy with peroxy acid epoxidation, but there are some differences. Thus 3-chlorohexen-1-ol is also aziridinated *syn*, yet the corresponding epoxidation in this case is not stereoselective.[103]

The many *N*-aminoheterocycles convertible to aziridines by oxidation with lead tetraacetate, generally at ambient temperature in dichloromethane, are listed in Scheme 33.[5,58,108–111] The most frequently used is *N*-aminophthalimide, which gives good yields with a wide variety of alkenes, both electron-rich and electron-poor, most recently steroidal alkenes.[112] Prior to the appearance of ref. 100, these reactions were all assumed to occur *via* (singlet) nitrenes, and indeed all the early evidence was consistent with this suggestion, except perhaps, in retrospect, the absence of products of C—H insertion.

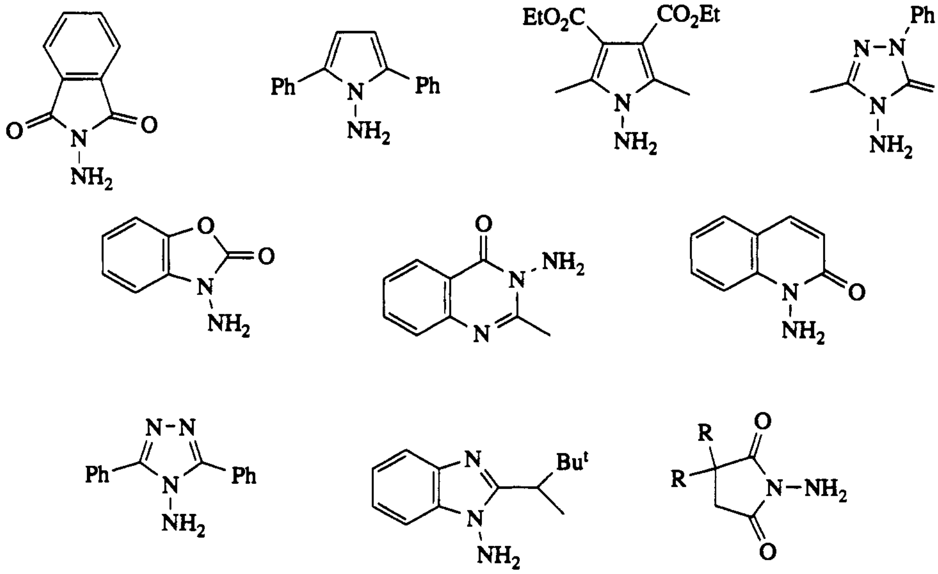

(30) R = H, alkyl, Ar

**Scheme 33** *N*-Amino heterocycles which yield aziridines from alkenes and $Pb(OAc)_4$

Some *N*-aminoheterocycles undergo other reaction modes on oxidation (perhaps *via* even less stable *N*-acetoxyamino compounds) and aziridines are not available from them, a well-known example being 1-aminobenzotriazole, which on oxidation yields benzyne and nitrogen.[113] An interesting case is (**30**; Scheme 33) which on oxidation in the presence of alkenes gives aziridines; in their absence, the intermediate fragments to nitrogen and two molecules of benzonitrile.[114]

A promising start has been made in applying the lead tetraacetate oxidation to chiral *N*-aminoheterocycles in the presence of achiral alkenes, leading to chiral aziridines *via* asymmetric induction, with compound (**31**) being obtained in 100% *de* from the appropriate precursors.[115] Similar reactions with the chiral quinazoline (**32**) give only modest face selectivities (stereoisomer ratios 1.2:1 to 2.4:1); however inclusion of trifluoroacetic acid in the reaction mixtures gives greatly improved purities (stereoisomer ratios 5.2:1 to 23:1) *via* a stabilized protonated intermediate originally formulated as the nitrene (**33**),[116] but which, in the light of later work would seem to be an *N*-acetoxyamino compound.[100] For wide utility of this potentially very useful reaction, a method for cleaving the N—N bond without destroying the aziridine ring would be needed. It would be most interesting to try some oxidations of achiral *N*-aminoheterocycles with lead(IV) salts of chiral acids: it could lead to a new chiral aziridination, but even in the absence of a preparatively useful *ee*, any significant *ee* would provide yet further evidence for (Het)—NHOCOR intermediates. Some resolved aziridines are also available in high optical purity by a kinetic resolution *via* carbonyl insertion with CO and a chiral rhodium complex.[117]

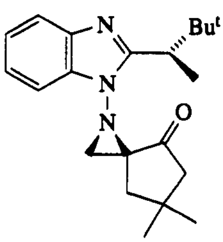

(**31**) racemic

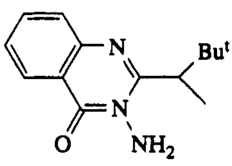

(**32**)

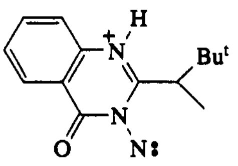

(**33**)

Phthalimidoaziridines can be cleaved by hydrazinolysis to give 1-aminoaziridines,[118,119] which decompose slowly at room temperature, and rapidly above 48 °C, regenerating the starting alkene with stereochemistry intact. There would appear to be some unexploited potential for phthalimidoaziridines to be used for alkene protection. Phthalimidoaziridines are stable to reflux in chlorobenzene (132 °C) for 24 h.[119] *N*-Aminoaziridines can be acylated to yield *N*-acylaminoaziridines of varying thermal stability:[105] (**34**; $t_{1/2}$ = 15 min at 37 °C) is a ready thermal source of benzamidonitrene from which new aziridines can be made by reaction with other alkenes, whereas the isomeric *cis*-aziridine is stable at 20 °C for at least 15 years. Two unusual intramolecular formations of *N*-aminoaziridines are given in Schemes 34 and 35.[120,121]

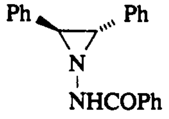

**(34)**

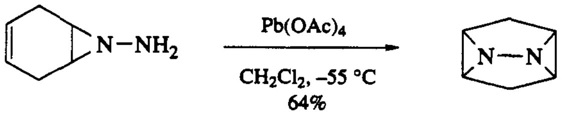

**Scheme 34**

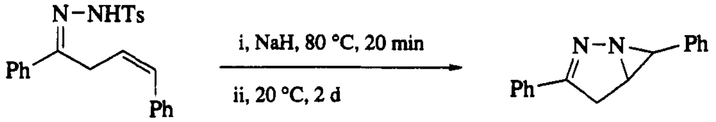

**Scheme 35**

Diethylphosphoryl azide gives an *exo*-triazoline with norbornene;[122] subsequent photolysis gives the phosphorylated aziridine, but pyrolysis gives the imine isomer. Markovnikov addition of diethyl dibromophosphoramidate to alkenes ($BF_3$ catalysis) occurs in high yield;[123] the initial adducts were converted to *N*-unsubstituted products but would be readily convertible to phosphorylated aziridines by the Gabriel method.[124] In any case, *N*-unsubstituted aziridines are readily phosphorylated.[5,125]

### 3.5.2.6 Aziridines *N*-Substituted with O or S

Treatment of *O*-alkylhydroxylamines with a mixture of an alkene and lead tetraacetate in dichloromethane gives aziridines in about 30% yields.[5,108] The products are mixtures of stable invertomers.[126] The reactions are not quite stereospecific.[127] Oxidation of certain nitroarylsulfenamides with lead tetraacetate in dichloromethane in the presence of alkenes gives *N*-sulfenylaziridines, 18–64%, together with some (identified) by-products.[41,108] The addition to *cis*-1-phenylpropene gives a mixture of *cis*- and *trans*-aziridines (3:1), and the unreacted alkene was partly isomerized (to *trans*) also.[128] Kinetic and ESR investigations have enabled these results to be rationalized in terms of a disproportionation of the (singlet) nitrene–sulfenamide mixture yielding amidyl radicals, which add reversibly to the alkene causing isomerization. The resulting *trans*-alkene is then, of course, the precursor of the *trans*-aziridine (Scheme 36). The investigation also concluded that a second aziridine-forming intermediate was involved, but that this was not the triplet nitrene. Mild thermolysis of *N*-arenesulfenylimino-1,4-dihydronaphthalenes also gives the sulfenylnitrenes which, in the presence of excess alkene, can be trapped quantitatively as the aziridines.[129] Though the thermal reaction is still not quite stereospecific, it has advantages over the lead tetraacetate procedure in giving higher yields, and also in working with electron-deficient alkenes. (It is also not dependent on nitro-substitution on the aromatic ring.) An *N*-sulfenyl group is readily removed by reduction ($NaBH_4$),[41] thus providing another overall route to *N*-unsubstituted aziridines from alkenes.

Fluorothiazyne (F—S≡N, not a nitrene) adds to perfluoropropene under photolysis[130] or *via* cesium fluoride catalysis[131] to give various abstruse derivatives of perfluoropropyleneimine. *N*-Arylsulfinylaziridines are available by acylation of the NH compounds.[125] Arenesulfonyl azides add to alkenes, forming unstable triazolines, which decompose spontaneously in a variety of ways, only rarely (norbornene) yielding aziridines as the main product.[72] *N*,*N*-Dibromosulfonamides were early on added to alkenes, a reaction that can give good yields, but has been little used.[132] The regiochemistry is interesting, and seems fairly well established (Scheme 37).

Compound (**35**) is also available in high yield by the porphyrin-catalyzed reaction described earlier (Scheme 22).[78,133] This reaction, originally reported as nonstereospecific, has recently been made stereo-

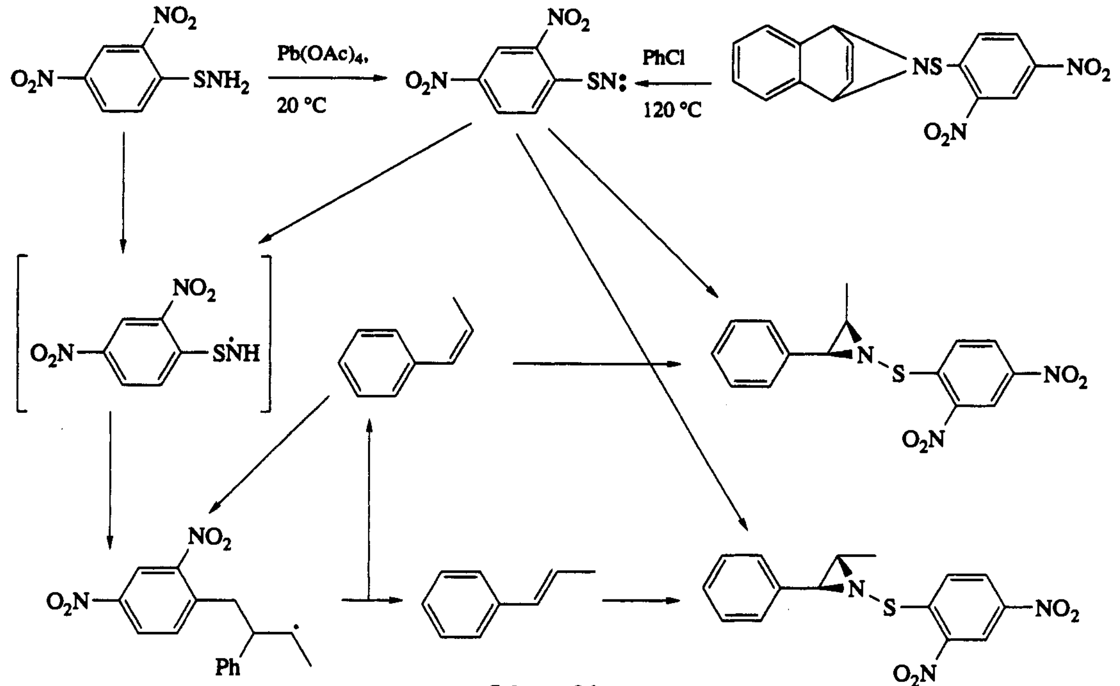

Scheme 36

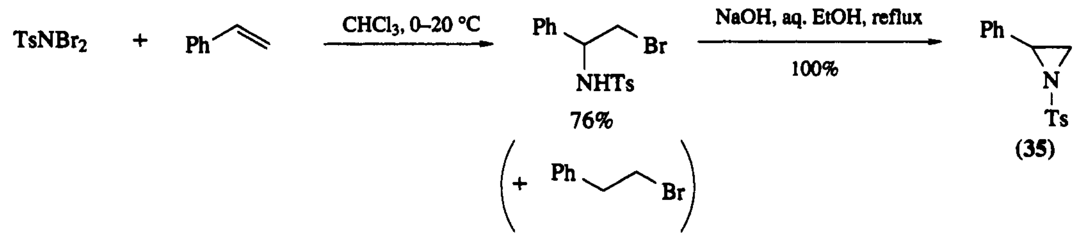

Scheme 37

specific for the tosylaziridination (the trifluoroacetylaziridination[78] appears not to have been followed up) by the adoption of tetrakis-2,6-dichlorophenylporphyriniron(III) perchlorate as catalyst.[133] Manganese porphyrins can also be used with terminal alkenes, but give allylic tosylamination with nonterminal alkenes.[134] Aryloxysulfonylaziridines can be made from the unsubstituted compounds or, in the case of norbornene derivatives, from norbornene and aryloxysulfonyl azides (65–98%).[135]

## 3.5.3 ADDITION OF TWO NITROGEN ATOMS TO ALKENES

### 3.5.3.1 Formation of Diamines

There is one direct method of preparing primary diamines from alkenes, in which the alkene is treated with nitric oxide and a cobalt complex, and the intermediate worked up reductively. The two-stage reduction gives better stereoselectivity (Scheme 38).[136] Typical yields from alkenes listed and *cis*:*trans* selectivities (expected product first) are: cyclopentene, 70%, 70:30; *trans*-3-hexene, 61%, 90:10; *cis*-3-hexene, 43%, 66:34; cyclohexene, 47%, 68:32; *trans*-1-phenylpropene, 90%, 85:15; *cis*-1-phenylpropene, 74%, 72:28. An alternative oxidative work-up with iodine gives, at least from the norbornene adduct, a dioxime.

The palladium-promoted vicinal diamination of alkenes can be achieved according to Scheme 39; the example chosen illustrates how the mechanism and stereochemistry were determined.[137] The independent synthesis of (36) from a quaternized aziridine is also noteworthy. Yields are 60–87% from ter-

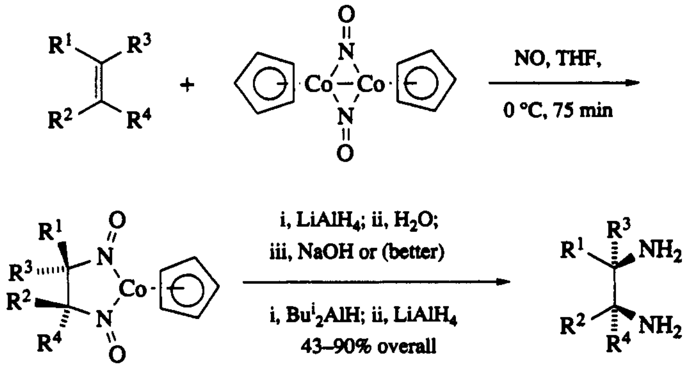
NO, THF,
0 °C, 75 min
i, LiAlH$_4$; ii, H$_2$O;
iii, NaOH or (better)
i, Bu$^i_2$AlH; ii, LiAlH$_4$
43–90% overall

Scheme 38

minal alkenes, 35–45% from internal alkenes. Tri- and tetra-substituted alkenes have not been reported, and the only amine used appears to be dimethylamine.

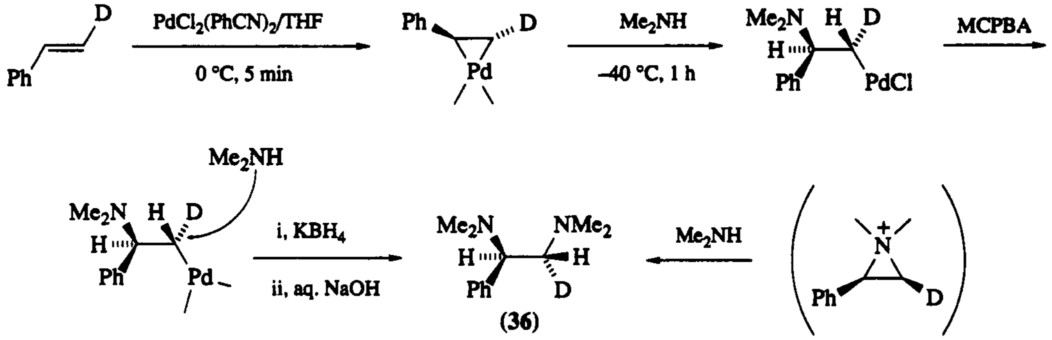
PdCl$_2$(PhCN)$_2$/THF
0 °C, 5 min
Me$_2$NH
−40 °C, 1 h
MCPBA
i, KBH$_4$
ii, aq. NaOH
Me$_2$NH
(36)

Scheme 39

Osmium *t*-alkylimides react with alkenes to give *cis*-diamines.[138] The reaction is limited to *t*-alkylamines, and further limited by the lack, so far, of a catalytic version. The problem would appear to be that whilst monoimides are readily made in aqueous solution, the bis- or tris-imides required to achieve diamination have to be prepared from phosphinimines (Scheme 40). The reactivities are modulated by steric and electronic factors; in being favored by electron-withdrawing substituents on the alkenes, the reactions resemble those of KMnO4 rather than OsO4. Unusually, *trans* double bonds are more reactive than *cis*, though this selectivity is shared by OsO4, KMnO4, RuO4 and Pd(II).

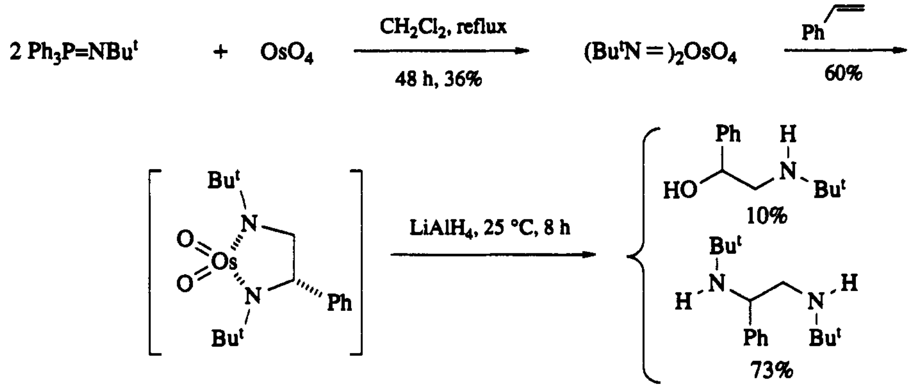
2 Ph$_3$P=NBu$^t$ + OsO$_4$
CH$_2$Cl$_2$, reflux
48 h, 36%
(Bu$^t$N=)$_2$OsO$_4$
60%
LiAlH$_4$, 25 °C, 8 h
10%
73%

Scheme 40

Two older direct methods are of limited scope. Tetrafluorohydrazine reacts thermally with alkenes at 50 °C, 6 h to give α,β-bis(difluoroamino) compounds in good yields.[139] Tetramethyltetrazene–zinc chloride complex, a source of dimethylamino radicals, adds to α-methylstyrene in 30–40% yield.[140] Barluenga's group have introduced two related methods for adding 2 equiv. of aniline across alkenic bonds, an earlier thallium procedure[141] being superseded by a better, mercury-mediated reaction (Scheme 41).[142]

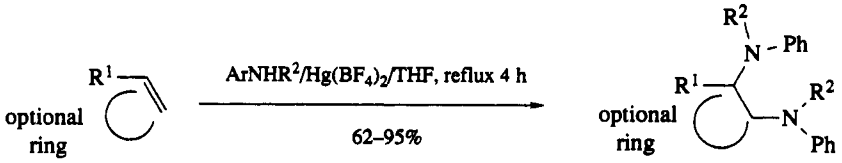
R¹
optional ring
ArNHR²/Hg(BF₄)₂/THF, reflux 4 h
62–95%
R²
N - Ph
R¹
R²
N
Ph
optional ring

$R^1$ = H, Me, Ph, $PhCH_2$; $R^2$ = H, Me

Scheme 41

Bisimides of sulfur dioxide undergo Diels–Alder additions to dienes (Scheme 42). The adducts can be processed to give the products of net 1,2-addition of amides to one of the double bonds.[143] The initial adducts (**37**) and (**38**) are mixtures of two diastereoisomers at sulfur. The S—C(6) *trans* and S—C(6) *cis* isomers have to be processed differently as shown; the *trans* isomers are cleaved with Grignard reagents to give sulfilimines (**39**) which undergo [2,3] sigmatropic rearrangement to sulfenylated diamides, *e.g.* (**40**), requiring only cleavage of the S—N bond [$(MeO)_3P$] to give the desired products (**41**). A similar sequence can be carried out on some of the S—C(6) *cis* isomers (**38**) but requires less sterically demanding organometallics (MeLi). However, these S—C(6) *cis* isomers are well set up for a novel [2,3] sigmatropic rearrangement to yield thiadiazolines (**42**), and these, on cleavage, ($NaBH_4$) happen to yield the same end product diamines. The full scope of this methodology is not yet known. Clearly, saturated diamides are available by reduction of the remaining double bond, and the methoxycarbonyl group (and, less conveniently, the tosyl group) can be modified or removed to give diamines.

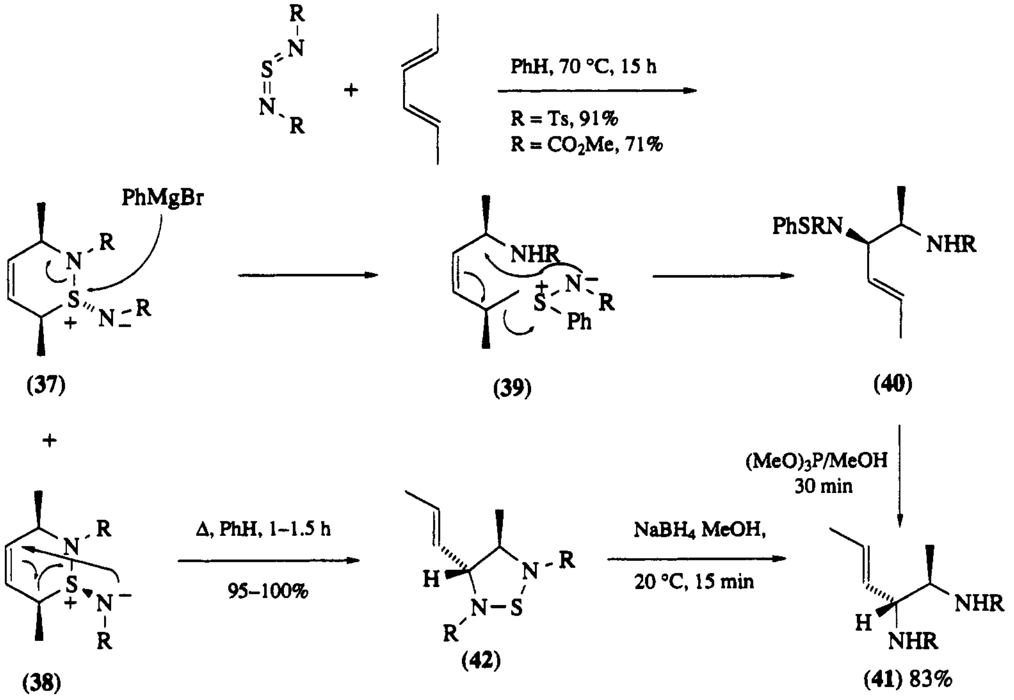
R
N
S
N
R
+
PhH, 70 °C, 15 h
R = Ts, 91%
R = CO₂Me, 71%
PhMgBr
N
R
S
N
R
+
(37)
NHR
N
S
R
Ph
+
(39)
PhSRN
NHR
(40)
+
(MeO)₃P/MeOH
30 min
R
N
S
N
R
+
(38)
Δ, PhH, 1–1.5 h
95–100%
H
N - R
N–S
R
(42)
NaBH₄ MeOH,
20 °C, 15 min
H
NHR
NHR
(41) 83%

Scheme 42

This sulfur work was preceded by a conceptually related selenium reaction (Scheme 43).[144] In accord with this mechanism, 1-vinylcyclohexene gives predominantly the isomer substituted at the more hindered endocyclic double bond.

A modified work up of the alkene–iodine isocyanate adducts (Section 3.5.6.4), yields imidazolinones (Scheme 44).[145]

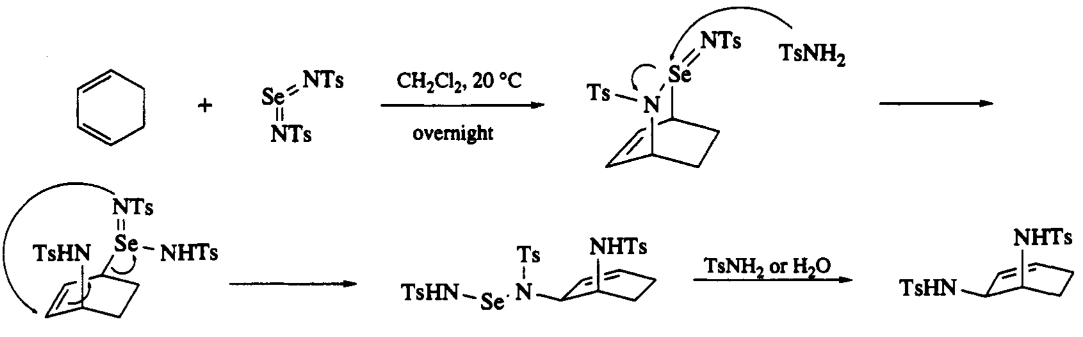

Scheme 43

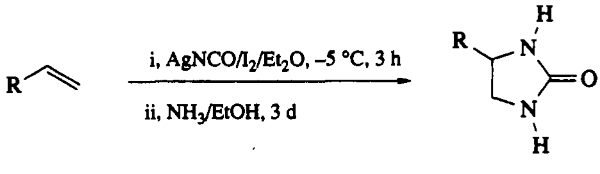

Scheme 44

Indirect methods of making diamines from alkenes include ring opening of aziridines or oxazolines with amines, amides or azides. Aziridines have received limited usage as yet, though there are many parallels with the ring opening of epoxides. In general, aziridines are less readily opened than epoxides unless strongly electron-withdrawing groups are present on the nitrogen. Examples include sulfonyl, but activation can also be achieved by quaternization (Scheme 39), by protonation or by Lewis acids.[9] Recent examples of ring openings with nitrogenous nucleophiles include chiral bisaziridines[146] and *N*-phthalimidoaziridines.[147] Oxazolines have been opened with primary and secondary amines to yield unsymmetrically substituted diamines.[148]

### 3.5.3.2 Formation of Diazides

Two recent high yielding processes for diazidation of alkenes have been reported.[60] In the first, Mn(OAc)3, NaN3 and the alkene are heated in glacial acetic acid until the brown colour is discharged (indicating complete conversion to $Mn^{II}$) (Scheme 45).[149] The paper also reviews the reduction of diazides, favoring Lindlar catalyst.

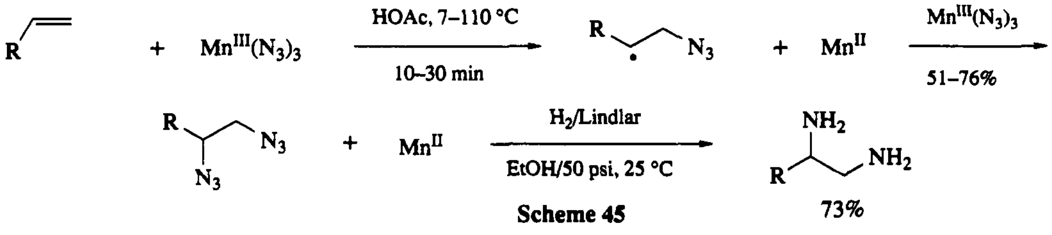

Scheme 45

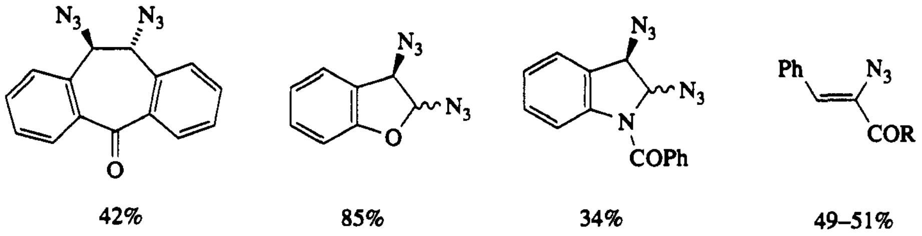

Scheme 46 Diazides and related compounds

A second paper achieves similar diazidations using iodosoylbenzene in acetic acid as oxidant, 2–3 h at 20–50 °C, yields were 34–70%.[150] Some of the more interesting products are listed in Scheme 46. The reactions are not stereospecific, but *trans* isomers predominate.

Earlier work using lead(IV) azide or persulfate mediated by iron as oxidant has been reviewed;[151,152] this last procedure, a radical redox one, can work very well (Scheme 47).[153] Dienes can undergo 1,4-addition with lead(IV) azide;[60] reactions with steroid alkenes are varied (refs. 152,154 and references cited therein, and Section 3.5.11) but can yield the 1,2-adducts.[154]

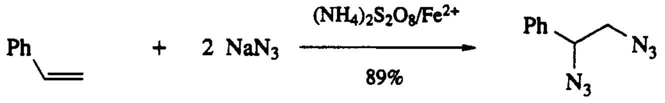

Scheme 47

### 3.5.3.3 Addition of Two Nitrogen Atoms, including a Nitroso or Nitro Group

Photoaddition of nitrosamines (carcinogens) to alkenes in the presence of oxygen gives quite good yields of 1:1 adducts as their oxime isomers.[155] Nitronium tetrafluoroborate in acetonitrile adds to alkenes in Markovnikov manner, giving acetamidonitro compounds, 38–84% (from arylalkenes) or 13–20% (from nonaromatic alkenes) (Scheme 48).[156]

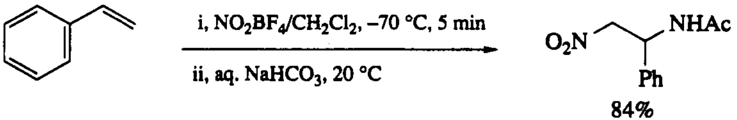

Scheme 48

The reaction is akin to the Ritter reaction, with activation achieved by nitration, rather than protonation, and the products accordingly retain the nitro group. Additions to 1-phenylcyclohexene (59%) and to *trans*-stilbene (72%) are stereospecific (*trans*); *cis*-stilbene gives the expected *threo* product (39%) plus some *erythro* (6%). Reactions of nitrogen dioxide with alkenes are very complex and rarely useful.[157] A recent mechanistic paper gives many key references.[158] Addition of $N_2O_3$ is occasionally useful, as with dicyclopentadiene (Scheme 49).[159]

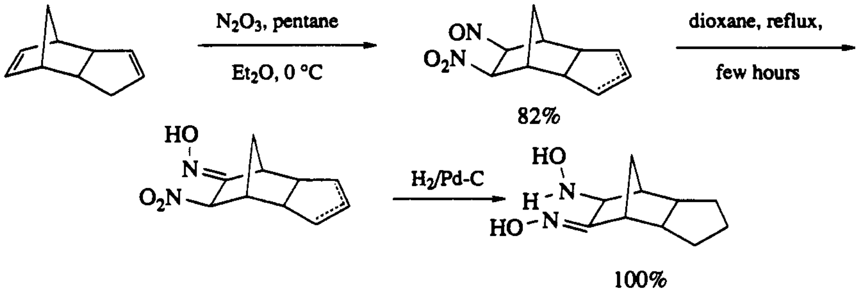

Scheme 49

Preparation of nitronitroso dimers from a variety of straight chain alkenes has been patented.[160] The reactions of nitric oxide with alkenes are extremely complex (*e.g.* isobutylene) and are rarely useful.[161] Perfluoroalkenes add nitric oxide at room temperature in the dark; tetrafluoroethylene gives $ONCF_2CF_2NO$ (68%);[162] the reaction with perfluoropropene is more complex.[163]

## 3.5.4 ADDITION OF NITROGEN AND OXYGEN TO ALKENES

### 3.5.4.1 Oxyamination and Oxyamidation

In an extension of the *cis* dihydroxylation of alkenes with osmium tetroxide, Sharpless has developed a series of reactions, reviewed by Gasc *et al.*,[1] in which an osmium imine species is added to an alkene, forming a cyclic amide ester, which on reductive work-up gives a *cis*-amino alcohol or derivative. The nitrogen is delivered to the least substituted end of the C═C bond. The original procedures were confined to *t*-alkylamines, and to stoichiometric usage of osmium tetroxide. In the definitive procedure, it was recommended that the imine be complexed with quinuclidine (Scheme 50).[164] It will be interesting to see if use of an optically active complexing base can yield asymmetric induction, in view of the high *ee* achieved recently in the related osmium-mediated dihydroxylations.[165] The imine reagent is a little milder than osmium tetroxide and appears to have as wide a functional group compatibility. Thus, the *N*-allylaniline yields an amino alcohol in 55% yield, whereas *cis* hydroxylation is achieved in only 10% yield.[166]

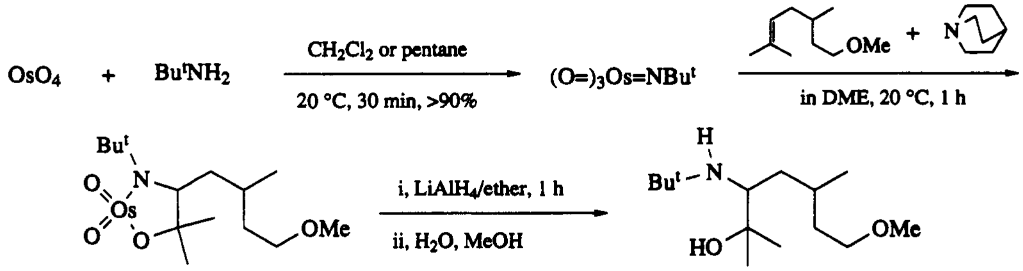
$OsO_4$
+
$Bu^tNH_2$
$CH_2Cl_2$ or pentane
20 °C, 30 min, >90%
$(O{=})_3Os{=}NBu^t$
OMe
+
N
in DME, 20 °C, 1 h
$Bu^t$
N
O
Os
O
O
OMe
i, $LiAlH_4$/ether, 1 h
ii, $H_2O$, MeOH
H
$Bu^t$
N
HO
OMe

**Scheme 50**

Two related procedures employing osmium in catalytic quantities, and providing, unlike the above, a removable nitrogen substituent, have been developed.[167,168] Scheme 51 represents a procedure suitable for mono- and 1,2-di-substituted alkenes,[167] but which is too vigorous for diethyl fumarate and enones; Scheme 52 is suitable for 1,1-di- and tri-substituted alkenes;[167] Scheme 53 is applicable to mono- and 1,2-di-substituted alkenes, especially electron-deficient alkenes,[168] and can be extended to trisubstituted alkenes by incorporation of $Et_4NOAc$ in the reaction mixture.[169]

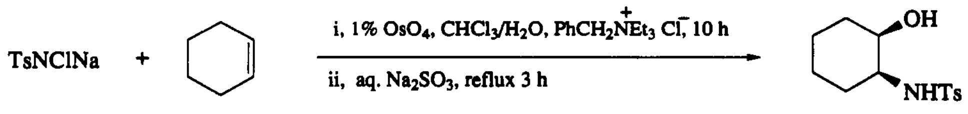
TsNClNa
+
i, 1% $OsO_4$, $CHCl_3/H_2O$, $PhCH_2\overset{+}{N}Et_3\ Cl^-$, 10 h
ii, aq. $Na_2SO_3$, reflux 3 h
OH
NHTs
74–81%

**Scheme 51**

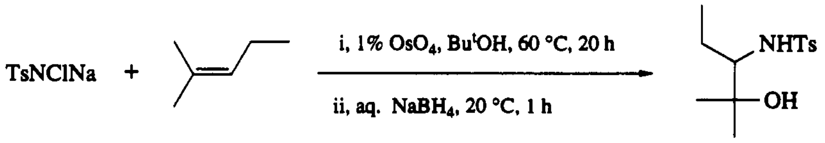
TsNClNa
+
i, 1% $OsO_4$, $Bu^tOH$, 60 °C, 20 h
ii, aq. $NaBH_4$, 20 °C, 1 h
NHTs
OH

**Scheme 52**

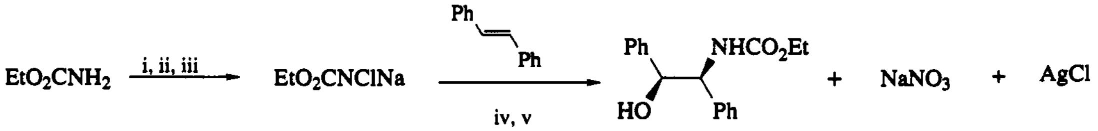
$EtO_2CNH_2$
i, ii, iii
$EtO_2CNClNa$
Ph
Ph
iv, v
Ph
$NHCO_2Et$
HO
Ph
+
$NaNO_3$
+
AgCl

i, $Bu^tOCl$/MeOH, 0 °C, 15 min; ii, NaOH/MeOH, 0 °C, 10 min; iii, evaporate to dryness;
iv, MeCN, $AgNO_3$, 20 °C, 5 min; v, 1% $OsO_4$, aq. $Bu^tOH$, 18 h, 20 °C, then aq. $Na_2SO_3$, reflux, 3 h

**Scheme 53**

Recent work has shown that the carbamate reaction shows no regioselectivity in the rather demanding case of 1,2,3,6-tetrahydropyridines; 1,2-dihydropyridines react at the 5,6 double bond, but with no selectivity in the N,O orientation.[170] The regioselectivities of the Sharpless oxyaminations have been rationalized,[171] and the reaction has recently been studied from the point of view of the inorganic chemist.[172] These procedures and other *cis* hydroxyaminations below produce stereochemistry complementary to that provided by ring opening of the epoxidized alkene.[173]

Alkenes can be palladated to yield a complex which can be opened *trans* by an amine nucleophile.[1,174] The resulting σ-palladium species can be worked up oxidatively to yield an amino alcohol (as its acetate ester). This depalladation occurs with inversion, yielding overall *cis* stereochemistry (Scheme 54). If the acetic acid in step iii is replaced with phenol, a β-phenoxyamine is produced.

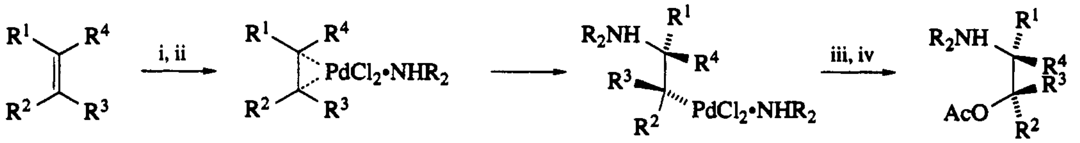
R1
R4
R2
R3
i, ii
PdCl2•NHR2
R2NH
iii, iv
AcO

i, $(PhCN)_2PdCl_2$, THF, $N_2$, 0 °C, 10 min; ii, $R_2NH$, –50 °C, 50 min;
iii, $Pb(OAc)_4$/AcOH, –50 °C, 5 min, then 20 °C, 2 h; iv, $KBH_4$, 20 °C, 20 min

**Scheme 54**

Use of resolved PhCHMeNHMe as complexing agent and nucleophile in this reaction causes asymmetric induction in the amino acetate, with *de* 20–60%;[175] alternatively, resolved $PhCHMeNMe_2$ can be used as complexing agent, followed by an achiral amine as nucleophile, but *ee* of only 3–12% was achieved.[175] Related transformations, but this time *trans* stereospecific, can be achieved using mercury activation; in these cases the mercury itself is the oxidant (Scheme 55).[176]

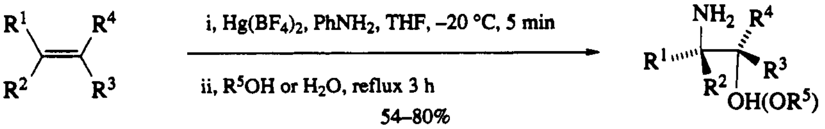
R1
R4
R2
R3
i, Hg(BF4)2, PhNH2, THF, –20 °C, 5 min
ii, R5OH or H2O, reflux 3 h
54–80%
NH2
OH(OR5)

**Scheme 55**

In its utilization of acetonitrile, the oxazoline synthesis shown in Scheme 56 resembles a Ritter reaction.[177] The procedure is convenient, but yields are variable; the pyrolysis gives starting alkene plus acetamide as by-products. Another oxazoline synthesis and subsequent conversion to a *cis*-amino alcohol is discussed later (Scheme 85). A recent γ-hydroxy-α-amino acid synthesis incorporates the following type of transformation (Scheme 57).[178] If a three-day equilibration with anhydrous HBr was introduced between stages i and ii, almost pure *trans* product was obtained. The paper has many useful references.[178] Yet another modified Ritter reaction is shown in Scheme 58.[179]

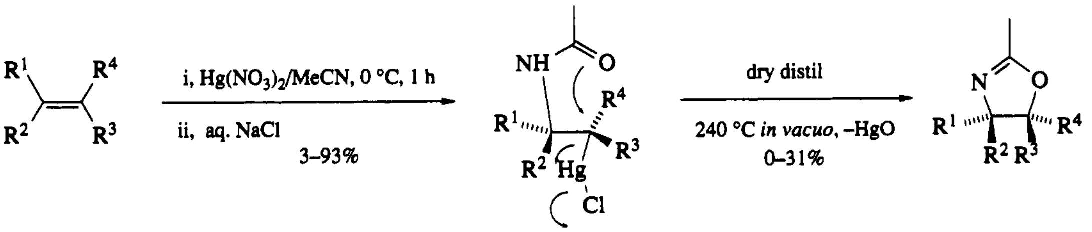
R1
R4
R2
R3
i, Hg(NO3)2/MeCN, 0 °C, 1 h
ii, aq. NaCl
3–93%
NH
O
Hg
Cl
dry distil
240 °C in vacuo, –HgO
0–31%
N
O

**Scheme 56**

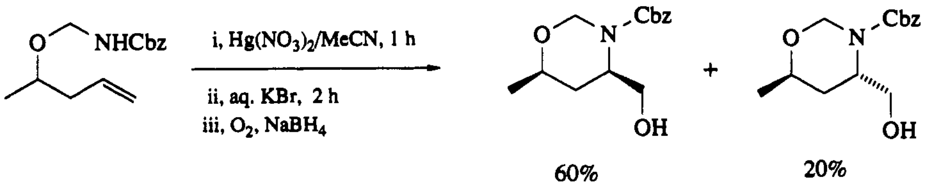
O
NHCbz
i, Hg(NO3)2/MeCN, 1 h
ii, aq. KBr, 2 h
iii, O2, NaBH4
O
N
Cbz
OH
+
60%
20%

**Scheme 57**

*N*-Nitrosopiperidine (carcinogen) with oxygen adds photolytically to alkenes to give *N*-(2-nitroalkyl)piperidines.[155] Indirect methods of preparing amino alcohols from alkenes include the well-known *trans* opening of epoxides with nitrogen nucleophiles and a recent, complementary, *cis* opening of

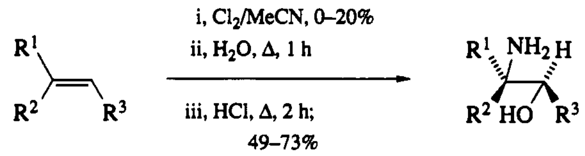
R1
R2
R3
i, Cl2/MeCN, 0–20%
ii, H2O, Δ, 1 h
iii, HCl, Δ, 2 h;
49–73%
R1 NH2 H
R2 HO R3

Scheme 58

acyclic or cyclic vinyl epoxides with tosyl or aryl isocyanates (Scheme 59).[180] Another indirect procedure, also requiring an auxiliary conjugated double bond, is shown in Scheme 60.[181] It is conceptually closely related to the diamination procedure of Scheme 42.

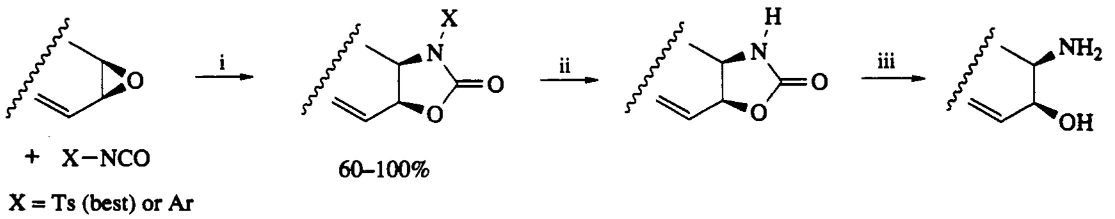
O
i
+ X–NCO
X = Ts (best) or Ar
X
N
O
O
60–100%
ii
H
N
O
O
iii
NH2
OH

i, $[(PhCH{=}CH)_2C{=}O]_3Pd_2$, $CHCl_3$, THF, $(Pr^iO)_3P$, 0–20 °C; ii, $C_{10}H_8^-Na^+$ (for X = Ts) or $Ce(NH_4)_2(NO_3)_6$, MeCN (for X = 4-$MeOC_6H_4$); iii, NaOH/aq. EtOH, reflux

Scheme 59

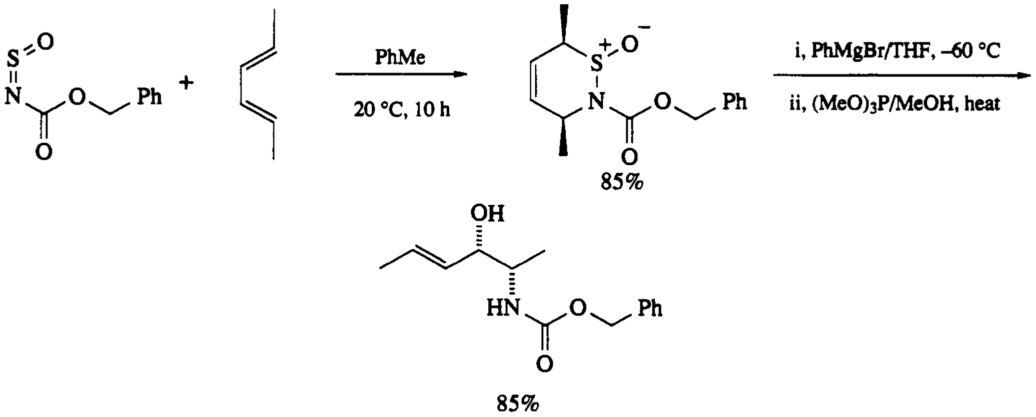
S=O
N
O
Ph
O
+
PhMe
20 °C, 10 h
S+ O−
N
O
Ph
O
85%
i, PhMgBr/THF, −60 °C
ii, (MeO)3P/MeOH, heat
OH
HN
O
Ph
O
85%

Scheme 60

Thallated aziridines can be opened with TFAA in high yield, giving *trans*-azido esters (Scheme 61).[182] A similar sequence with cyclohexene yields *trans*-1-azido-2-trifluoroacetoxycyclohexane (80%). Steroid alkenes yield azido alcohols with chromyl azide.[60]

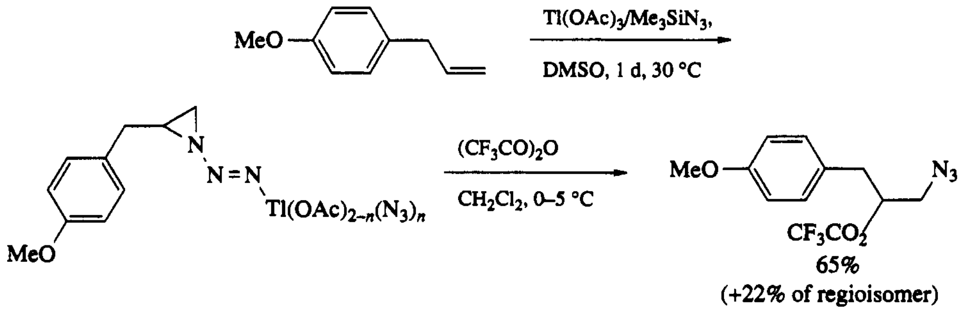
MeO
Tl(OAc)3/Me3SiN3,
DMSO, 1 d, 30 °C
N
N=N
Tl(OAc)2−n(N3)n
MeO
(CF3CO)2O
CH2Cl2, 0–5 °C
MeO
N3
CF3CO2
65%
(+22% of regioisomer)

Scheme 61

A tellurium reagent converts alkenes to oxazolidines in high yields (Scheme 62) with predictable regiospecificity.[183] For example, styrene derivatives give 5-phenyloxazolidines, and 1-hexene the 5- and 4-propyloxazolidines in a 3:1 ratio.

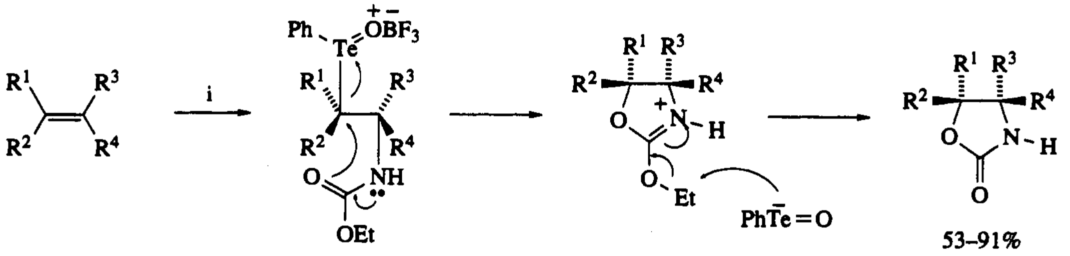

i, $PhTe(O)OCOCF_3$, $EtOCONH_2$, $BF_3{\bullet}OEt_2$, $CHCl_2CHCl_2$, reflux 6–20 h

Scheme 62

There are numerous examples of the intramolecular delivery of amide or imidate nitrogen to an alkene activated by halonium ion formation or by epoxidation leading, eventually, to stereo- and regio-specific

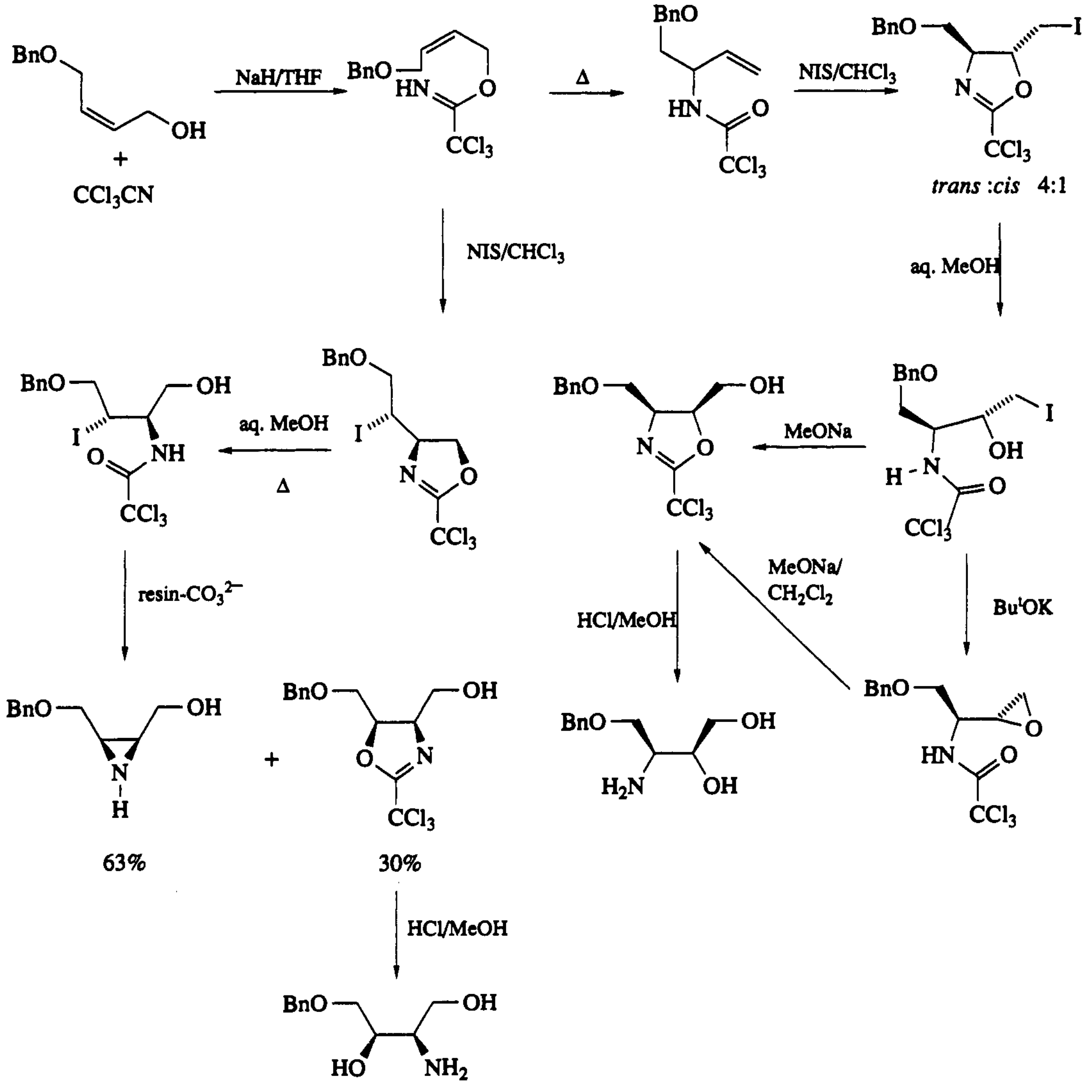
NaH/THF
Δ
NIS/CHCl3
trans :cis 4:1
NIS/CHCl3
aq. MeOH
aq. MeOH
Δ
MeONa
resin-CO3 2−
HCl/MeOH
MeONa/
CH2Cl2
ButOK
63%
30%
HCl/MeOH

Scheme 63

amino alcohols. An elegant series of reactions, including a Cope rearrangement, is given in Scheme 63.[184] Note that imidates give clean oxazolidinones, whereas with amides there is a tendency for aziridine formation to compete. Other examples are given in refs.185–188.

Whilst ring opening of epoxides (Volume 6, Chapter 1.3) is really beyond the scope of this review, two recent papers are noteworthy: poorly nucleophilic amines can be reacted very cleanly as their diethylaluminum derivatives,[189] and a start has been made on chiral induction of opening of epoxides (*e.g.* cyclohexene oxides).[190] Amino alcohols have been resolved by enantioselective enzymatic hydrolysis of their acetates.[191] Ring opening of phthalimidoaziridines has been achieved with water, phenol and tosic acid, amongst other nucleophiles,[147] giving products of formal N—O addition to the double bond.

### 3.5.4.2 Additions of Oxygen and a Nitroso or Nitro Group to Alkenes

Nitrosyl hydrogen sulfate adds to alkenes at –40 °C in liquid $SO_2$, in Markovnikov fashion giving 2-sulfato-oximes (37–84%).[192] Reactions of nitrogen oxides with alkenes are usually complex, yet some have limited industrial, rather than laboratory, importance.[193,194] Nitryl tetrafluoroborate in acetic anhydride at –65 to –45 °C adds Markovnikov fashion to alkenes, with only fair stereoselectivity, giving β-nitroacetates in 36–40% yields.[195] Nitryl fluorosulfonate adds to perfluoroalkenes in fluorosulfonic acid/freon-113 giving 63–92% β-nitroperfluoroalkyl fluorosulfonates.[196]

## 3.5.5 ADDITION OF NITROGEN AND SULFUR, SELENIUM OR TELLURIUM TO ALKENES

### 3.5.5.1 Addition of Nitrogen and Sulfur

There are several related reactions involving probable formation of episulfonium ions from alkenes, with subsequent addition of various nitrogen nucleophiles giving products of net *trans*-1,2-(N + S) addition (ref.197 and references cited therein). In a recent example (Scheme 64) the sulfur reagent also provides the nitrogen nucleophile; yields were best with styrene.[197] Related cyclizations are known in the β-lactam area,[198] *e.g.* Scheme 65; compounds (**43**) and (**44**) are also available by related but base-catalyzed cyclizations.[199]

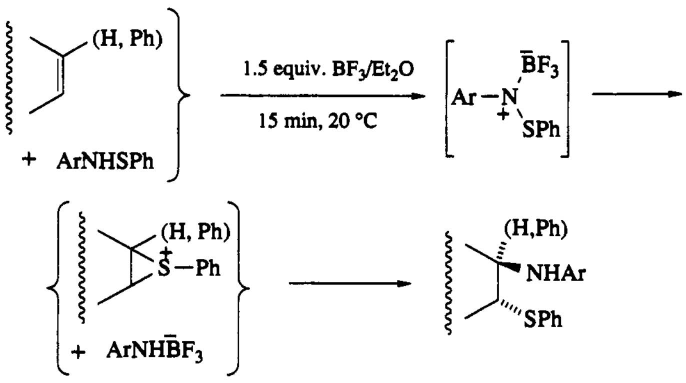

Ar = Ph, 4-$ClC_6H_4$, 3- or 4-$O_2NC_6H_4$, 4-$MeC_6H_4$, yields 25–88%;
Ar = 3- or 4-$MeOC_6H_4$, yields 4–9%

**Scheme 64**

Regiochemistry is generally Markovnikov in aminosulfenylations. However, *N*-phenylsulfenylpyrrolidine reacts with 1-octene ($TfOH/CH_2Cl_2$), to give products chiefly of anti-Markovnikov additions, probably for steric reasons.[200] Using dimethyl(methylthio)sulfonium fluoroborate as the source of $MeS^+$ permits a wide range of other nitrogen nucleophiles to be used (Scheme 66).[201] The authors draw attention to the versatility of these products, *e.g.* β-nitrosulfides are precursors of nitroalkenes, and oxazolines and *cis* amino alcohols are also available from *trans*-1-acetamido-2-methylthioalkenes.

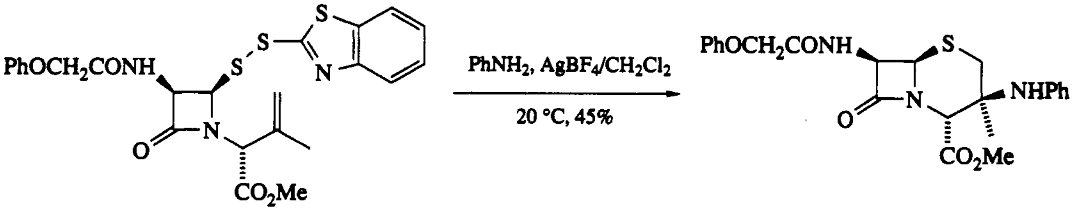
PhOCH2CONH
S
S
S
N
N
O
CO2Me
PhNH2, AgBF4/CH2Cl2
20 °C, 45%
PhOCH2CONH
S
N
NHPh
O
CO2Me

**Scheme 65**

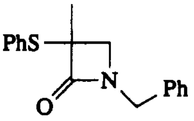

**(43)** 93%

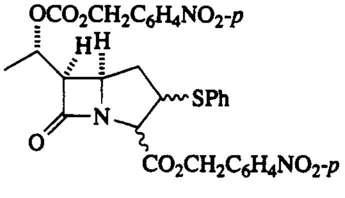
OCO2CH2C6H4NO2-p
HH
SPh
N
O
CO2CH2C6H4NO2-p

**(44)** 7%

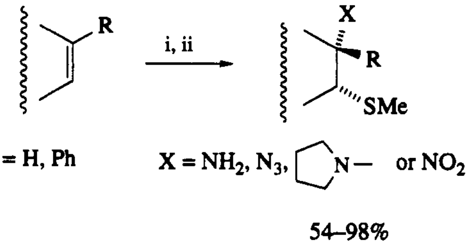
R
i, ii
X
R
SMe
R = H, Ph
X = NH2, N3, N— or NO2
54–98%

i, $Me_2\overset{+}{S}SMeBF_4^-/CH_2Cl_2$ or MeCN or $MeNO_2$, 0–20 °C, 1 h
ii, $NH_4OH$ or $NaN_3$ or piperidine or $NaNO_2$, 1–4 d, 20 °C

**Scheme 66**

If the reactions are carried out in a nitrile as solvent, rather than dichloromethane, using triflic acid as catalyst, a modified Ritter reaction takes place, and the intermediate nitrilium ion traps the liberated amine, forming an amidine (Scheme 67).[200] In an earlier reaction (*cf.* Scheme 67) the lithium perchlorate catalyzed reaction of sulfenyl chlorides with alkenes in the presence of nitriles had also given 1-amido-2-sulfenyl adducts.[202] Ritter products are also obtained in good yields by anodic oxidation (Pt or C, 1.2–1.4 V) of disulfides in acetonitrile, in the presence of excess alkene, using $Bu_4NBF_4$ as supporting electrolyte (Scheme 68).[203]

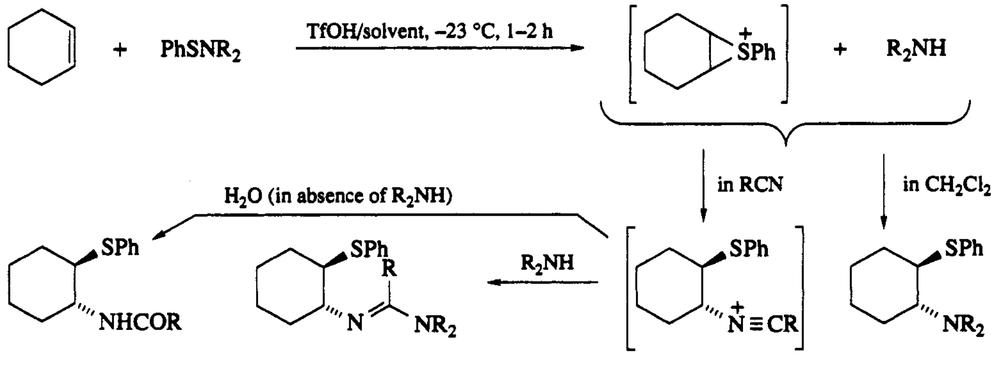
+ PhSNR2
TfOH/solvent, −23 °C, 1–2 h
SPh
+ R2NH
in RCN
in CH2Cl2
H2O (in absence of R2NH)
SPh
NHCOR
SPh
R
N
NR2
R2NH
SPh
N≡CR
SPh
NR2

**Scheme 67**

Similar products can be obtained in a two-step sequence using lead(IV) or manganese(III) acetate in $TFA/CH_2Cl_2$, 0 °C, giving an intermediate *trans*-ester sulfide which, after a simple work-up, is treated, crude, with sulfuric acid in acetonitrile, giving the acetamido sulfide product. Both the intermediate ester

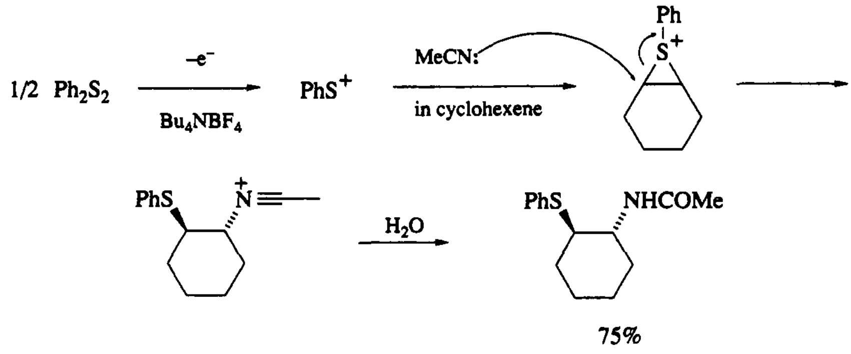

**Scheme 68**

and the final amide have *trans* Markovnikov orientation, suggesting that each is formed *via* the episulfonium ion (Scheme 69). The amides could be hydrolyzed to amino sulfides (KOH/glycol, reflux 4 h) and, in products from dibenzyl disulfide, the benzyl group removed (Na/$NH_3$) to give acetamidothiols, sometimes with partial epimerization.[203] Unfortunately, the requisite benzylthio compounds were among the worst yields, a major by-product in these cases[204] and in the electrochemical alternative[203] being benzylacetamide.

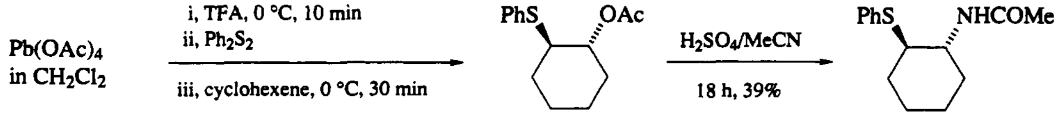

**Scheme 69**

Aziridines can be opened by thiols to give 2-amino sulfides.[146,147] The expected complete Walden inversion in this reaction has been confirmed recently, in the case of *cis*- and *trans*-stilbeneimine, whether the requisite prior activation of the aziridine is achieved by *N*-protonation or sulfonation or benzoylation.[205] Hexavalent sulfur can be introduced by yet another modified Ritter reaction (Scheme 70).[206]

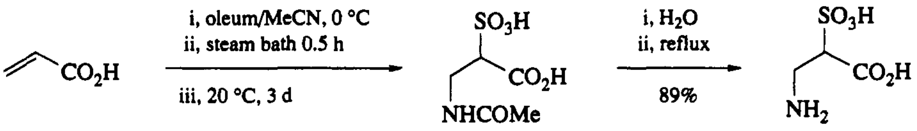

**Scheme 70**

### 3.5.5.2 Addition of Nitrogen and Selenium

In a modified Ritter reaction, terminal and 1,2-disubstituted alkenes are amidoselenated by treating with equimolar amounts of PhSeCl in a liquid nitrile solvent containing 5 equiv. of water, at 76–90 °C, for 1 h.[207] Yields are 72–98% with cyclohexene, poor (36%) with styrene. The selenides can be oxidized with $H_2O_2$ to give selenoxides which spontaneously eliminate PhSeOH to give allylic amides, though the selenoxide from cyclohexene is stabilized by an internal hydrogen bond and requires heating. Alternatively, the selenium can be removed reductively ($Ph_3SnH$) to give amides (Scheme 71). Terminal alkenes give predominantly (≈7:1) the terminal selenides, which yield stable selenoxides. Internal alkenes give products with the expected stereochemistry: *trans* to *erythro*, *cis* to *threo*. This chemistry has recently been extended to previously unusable alkenes by use of 2,2′-dipyridyl diselenide.[208] Anodic oxidation of diphenyl diselenide in acetonitrile in the presence of an alkene[209] gives acetamido selenides, in a procedure related to the acetamidosulfenylation of Scheme 68.[203]

β-Phenylselenocarbamates (20–95%) are obtained from alkenes with PhSeCl and carbamates with $AgBF_4$ in $CH_2Cl_2$ (4 h, 25 °C under Ar).[210] The intramolecular form of this reaction had been known previously;[211] indeed, selenocyclizations have been pursued rather more successfully than the related sulfur reactions. The reaction, introduced by Clive *et al.*,[211] has been developed by Toshimitsu's group, whose recent papers give many lead references;[212,213] typical products of selenocyclization include lactams

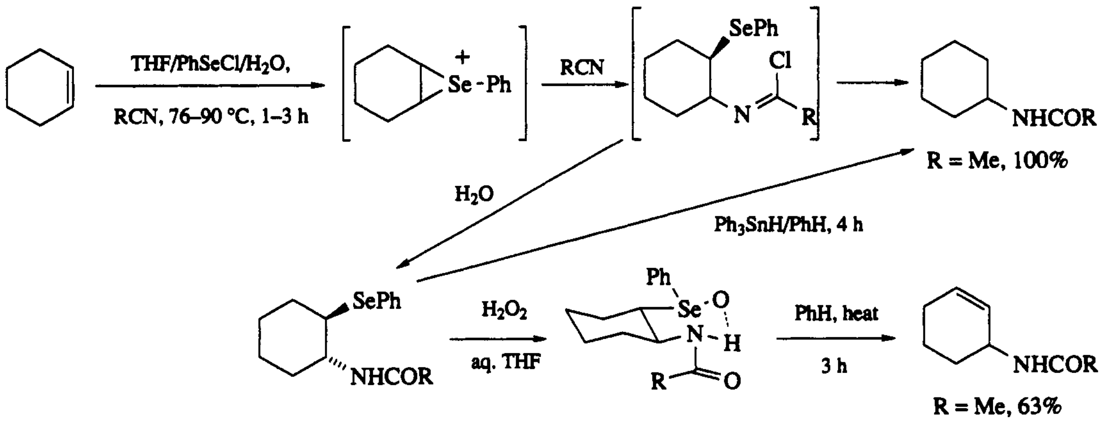
THF/PhSeCl/H2O,
RCN, 76–90 °C, 1–3 h
Se-Ph
RCN
SePh
Cl
N
R
NHCOR
R = Me, 100%
H2O
Ph3SnH/PhH, 4 h
SePh
NHCOR
H2O2
aq. THF
Ph
Se
O
N
H
R
O
PhH, heat
3 h
NHCOR
R = Me, 63%

Scheme 71

(47)–(50) and imidates (53) and (54). The reaction with amides can be very sensitive to ring size and substitution patterns: whereas compounds (45) and (46) give lactams, the closely related (51)[213] and also (52)[212] give cyclic imidates (Scheme 72). In some cases the problem is overcome by use of an imidate starting material.[213]

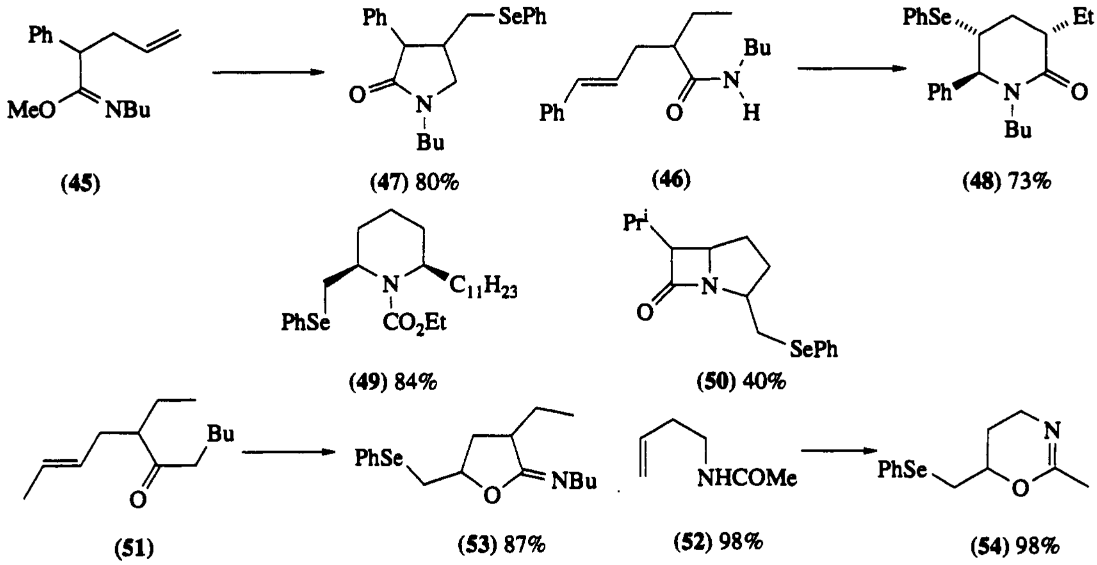
Ph
MeO
NBu
(45)
Ph
SePh
O
N
Bu
(47) 80%
Bu
N
H
Ph
O
(46)
PhSe
Et
Ph
N
O
Bu
(48) 73%
N
C11H23
PhSe
CO2Et
(49) 84%
Pr$^i$
O
N
SePh
(50) 40%
Bu
O
(51)
PhSe
O
NBu
(53) 87%
NHCOMe
(52) 98%
PhSe
N
O
(54) 98%

Reagent: PhSeCl/MeCN, 20 °C, 1–24 h

Scheme 72

Mono- and 1,2-di-substituted alkenes react with PhSeCl/Hg(SCN)$_2$ in benzene (0.5–96 h, at 20 °C), giving β-*trans*-phenylselenoalkyl isothiocyanates in 70–94% yields.[214] Terminal alkenes generally give the product with the selenium terminal (an exception is the product from Bu$^t$CH=CH$_2$); internal alkenes show the expected stereochemistry (*cis* to *threo*, *trans* to *erythro*). Oxidation to selenoxides could be achieved cleanly only with ozone, and the products *cis* eliminate in the usual manner to give predominantly the vinylic isothiocyanates (Scheme 73).

A similar two-step azidoselenation *via* (i) MeSeBr or PhSeBr, (ii) NaN$_3$/CF$_3$CH$_2$OH, and subsequent elimination (iii) (O$_3$) of selenium has been reported; unfortunately, selectivities in the second and third steps are poor.[215] Phenylselenyl azide (made *in situ* from PhSeCl/NaN$_3$/DMSO, room temperature) adds to alkenes (20 °C, overnight, 86–98%) stereospecifically;[216] regiospecificity is poor with terminal alkenes but good with highly polarized alkenes, typical products being (55) to (57); cyclohexadiene gives (58).

β-Nitroselenation of alkenes has been achieved using (i) PhSeBr, (ii) AgNO$_2$/HgCl$_2$ in MeCN/THF, −78 to +22 °C under argon,[217] and the products oxidized with hydrogen peroxide to give vinylic nitro

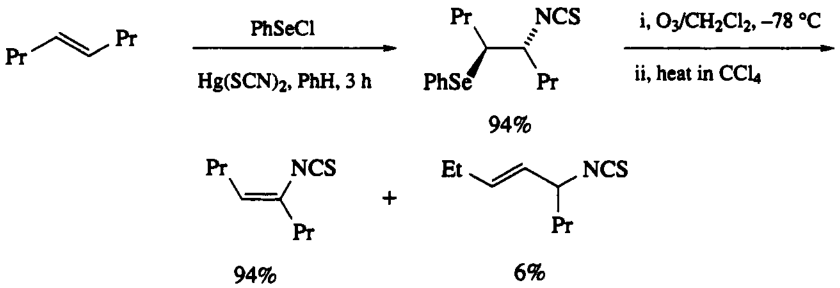
PhSeCl
Hg(SCN)2, PhH, 3 h
Pr
NCS
PhSe
Pr
94%
i, O3/CH2Cl2, –78 °C
ii, heat in CCl4
Pr
NCS
Pr
94%
+
Et
NCS
Pr
6%

Scheme 73

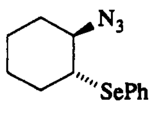

**(55)**

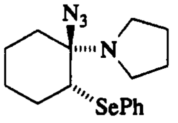

**(56)**

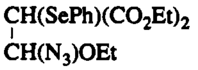

$$\begin{array}{l}\mathrm{CH(SePh)(CO_2Et)_2}\\ |\\ \mathrm{CH(N_3)OEt}\end{array}$$

**(57)**

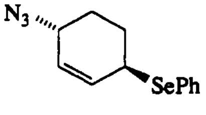

**(58)**

compounds in good yield. The reaction applied to 1-hexene again has only moderate regioselectivity, giving 78% (**59**) and 22% of the anti-Markovnikov product. However, alkenylsilanes react regiospecifically, giving (**60**), convertible in high yield on oxidation to (**61**).[218] Vinylsilanes (*i.e.* R = H) give (**62**), which are useful Diels–Alder dienophiles.[218]

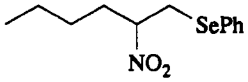

**(59)**

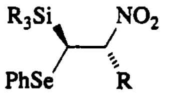

**(60)**

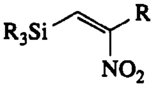

**(61)**

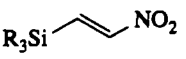

**(62)**

### 3.5.5.3 Addition of Nitrogen and Tellurium

Benzenetellurinyl acetate (or trifluoroacetate) reacts with alkenes and carbamates under $BF_3$ catalysis to give *trans*, predominantly Markovnikov, adducts, conveniently worked up *via* hydrazine reduction to give tellurides (Scheme 74).[219] The *trans* nature of (**63**) was confirmed by independent synthesis from PhTeNa and the appropriate aziridine. Alkenic carbamates undergo a much faster intramolecular telluro-lactamization (Scheme 75); yields are 49–97% over 15 varied examples.

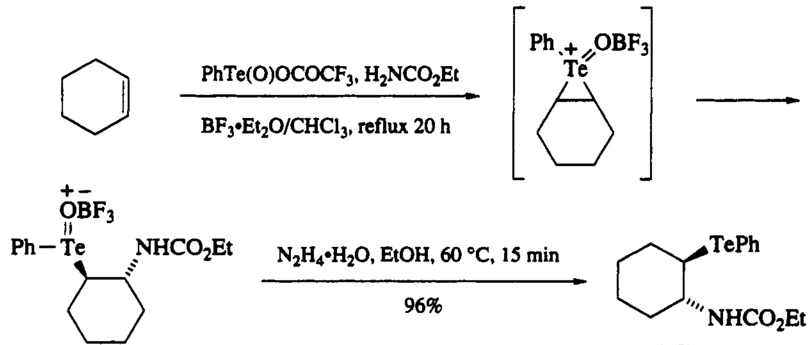
PhTe(O)OCOCF3, H2NCO2Et
BF3•Et2O/CHCl3, reflux 20 h
Ph
OBF3
Te
OBF3
Ph–Te
NHCO2Et
N2H4•H2O, EtOH, 60 °C, 15 min
96%
TePh
NHCO2Et

**(63)**

Scheme 74

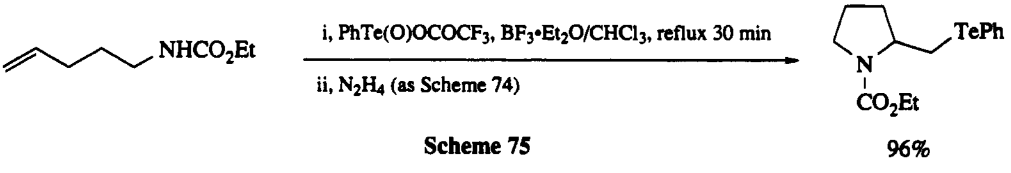
NHCO2Et
i, PhTe(O)OCOCF3, BF3•Et2O/CHCl3, reflux 30 min
ii, N2H4 (as Scheme 74)
TePh
N
CO2Et
96%

Scheme 75

## 3.5.6 ADDITION OF NITROGEN AND HALOGEN TO ALKENES

### 3.5.6.1 Addition of Nitrogen and Fluorine

There are few reports of these reactions. Anodic oxidation of styrene derivatives $PhCHR^1CHR^2$ in $HF/Et_4NF/MeCN$ gives 20–45% yields of fluorinated acetamides $PhC(NHAc)R^1CFR^2$ ($R^1$ = H, Me; $R^2$ = H, Me, Ph), generally with substantial quantities of by-products, chiefly isomers and 1,2-difluoro compounds.[220] Allylbenzene gives $PhCH(NHAc)CHFCH_2F$ (20%). Regioselectivity is high, but stereoselectivity low. 1-Fluoro-2-aminoalkanes are also obtained by the reaction of aziridines with pyridine–HF/benzene, generally at room temperature.[221,222] Yields are high, but again regio-, but not stereo-specific. 2-Phenylaziridine gives $PhCHFCH_2NH_2$ (78%) consistent with an $S_N1$ mechanism. Terminal alkenes react with $Tl(OAc)_3/TMSN_3$ to give thallated aziridines which, on treatment with 40% HF, give fluoro azides, sometimes with rearrangement and often with concomitant formation of hydroxy azides (Scheme 76).[223] Iodide or thiocyanate give the opposite regiochemistry $[ArCH(N_3)CH(I,SCN)]$; chloride or bromide give regioisomeric mixtures. Industrially satisfactory fluoronitrations have been reported, including a 93% conversion of vinylidene fluoride into $CF_3CH_2NO_2$ with HF and $HNO_3$ in fluorosulfonic acid at 0 °C.[224]

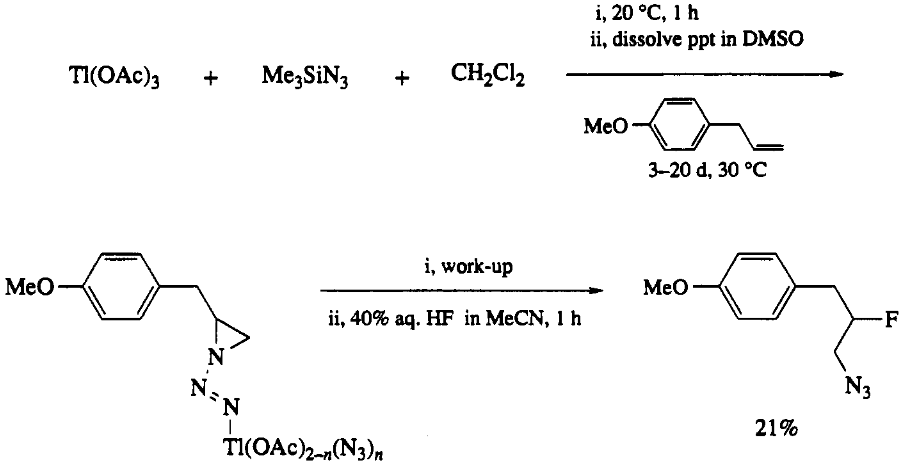

Scheme 76

### 3.5.6.2 Addition of Nitrogen and Chlorine

Surprisingly few heterolytic additions of nitrogen and chlorine to alkenes have been reported, and they are not (yet) synthetically useful. Chloramine-T in acetic acid, 50–60 °C, 2–3 h, gives low (6–25%) yields of adducts with alkenes[225] with regio- and stereo-chemistry consistent with a cyclic chloronium ion intermediate.[226] Chloramine and its alkyl derivatives react with alkenes in $CH_2Cl_2/Et_2O$ at −50 to −10 °C in the presence of $AlCl_3$, to give chloroamines non-regiospecifically.[227] Alkenes add $ClN(SO_2F)_2$ to give products consistent with formation from positive chlorine.[228]

Radical chloroaminations are known, using radical, transition metal ion or photochemical initiation. They also occur without overt initiation, thus anti-Markovnikov additions to terminal alkenes occur with *N,N*-dichlorourethane in benzene at 5–40 °C (yields ≈ 60%).[229] Similar reactions occur with *N,N*-dichloroarenesulfonamides in $CH_2Cl_2$ at or below room temperature (yields mostly 53–91%; 10% with isobutylene).[230a] The remaining N—Cl bond is readily reduced if desired with sodium sulfite. *N*-Halosulfoximines also add to alkenes thermally or photolytically.[230b]

Free radical additions to alkenes in the presence of redox systems, especially $Fe^{II}/Fe^{III}$, have been much investigated and reviewed by Minisci.[151] The redox approach may have many beneficial effects, *e.g.* in improving yields: the reaction of *N*-chloroamines with $Fe^{II}$ is faster than the competing electrophilic chlorination of the alkene; it favors 1,2-addition over polymerizations; it increases the scope of both adding groups, which can be provided by different reagents if necessary. The sequences of most relevance are given in Scheme 77, which may be an oversimplification (Minisci favors a complexed species $FeCl^{2+}(R_2N^+HCl)$ as the chlorinating agent in step 4). The reactions of Scheme 77 when applied to *N*-chloropiperidine and cyclohexene give a mixture of *cis* and *trans* adducts. However, an analogous sequence[151,231] can be achieved in a nonacidic medium also, providing in this case predominantly the *cis* isomer, ascribed to an intramolecular delivery of the chlorine atom (Scheme 78).

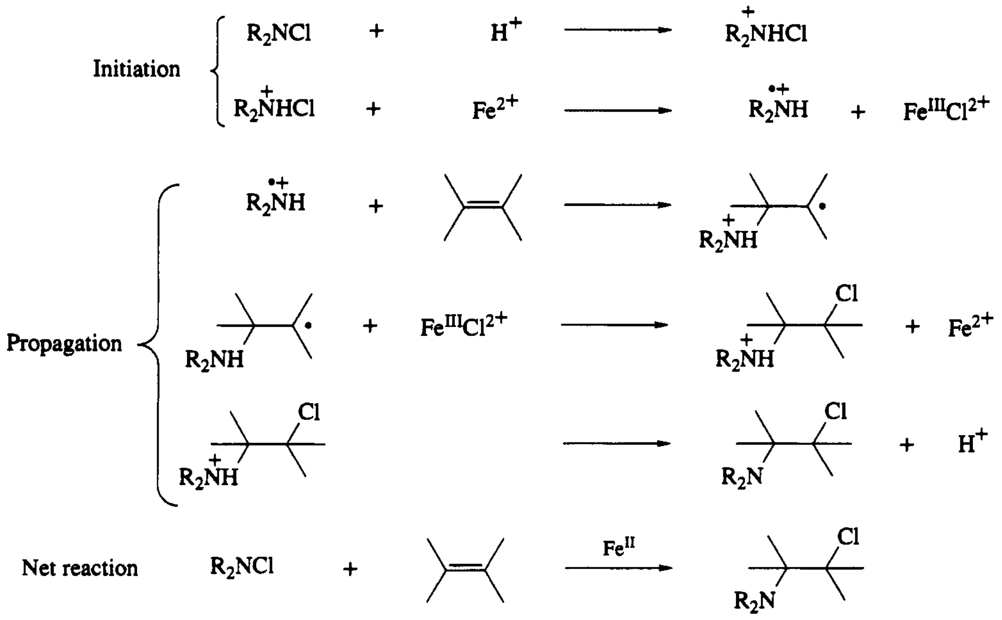

Scheme 77

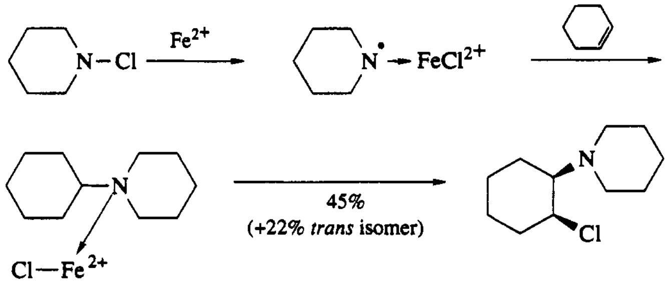

Scheme 78

This last reaction, and related sequences using $TiCl_3$ and $CrCl_2$ have been studied comparatively.[231] The overall yields are 75% with titanium, 14% with chromium. However, the chromium-based procedure can be applied to *N*-haloamides and to urethanes, when the yields are excellent, producing also a higher proportion of *cis* isomers from cyclohexenes. Furthermore, the amidic *N*-substituents are also more versatile. An example, illustrating also the anti-Markovnikov regiochemistry, is given in Scheme 79.[232] Such *cis*-haloamines are relatively inaccessible by other routes, most of which give *trans* products arising from cyclic intermediates (*e.g.* chloronium ions) or starting materials (aziridines), or from neighbouring group effects on attempted inversions (*e.g.* transient aziridinium ions). Intramolecular cyclizations have also been achieved with several different[151,231] metals, a recent example being given in Scheme 80.[233]

Additions of *N*-haloamides to alkenes can also be achieved photolytically, generally in $CH_2Cl_2$ (ref. 234 and references cited therein). Such additions are anti-Markovnikov. Both *cis* and *trans* internal alkenes give about 2:1 *threo* to *erythro* products. Yields vary widely but can be preparatively useful. Cyclohexene is substituted with predominantly *cis* orientation (2:1); this ratio is reversed in MeOH due to promotion of the competing electrophilic addition. Certain haloamides of electronegatively substituted acids (*e.g.* $CCl_3CONCl_2$) can give very high *cis* stereoselectivity. It would appear that as the electronegativity of the RCONH group is increased to approach that of halogen, homolytic cleavage is favored over heterolytic, thus decreasing the proportion of *trans* isomer in the product. In the case of *N,N*-dihalosulfonamides also the mechanism and hence the regiochemistry of the product is finely balanced, dibromo

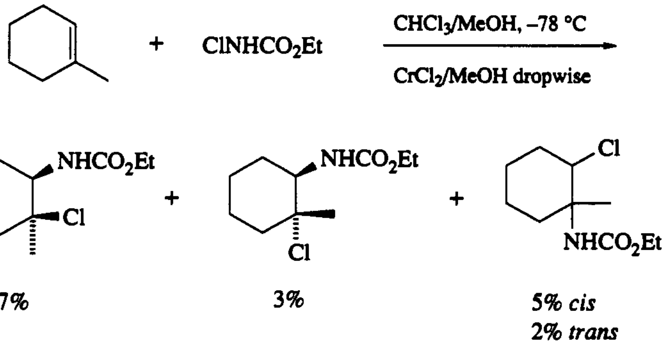

Scheme 79

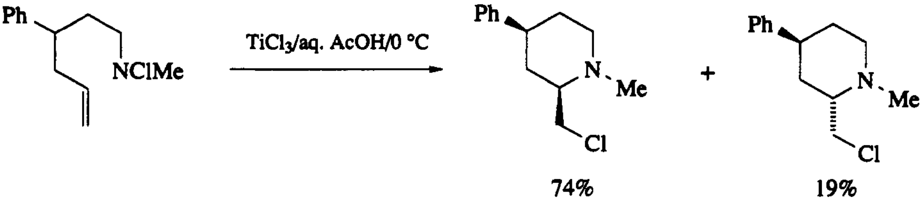

Scheme 80

reacting anti-Markovnikov (radical) and dichloro Markovnikov (ionic), and can switch between radical and ionic mechanisms according to catalyst and conditions.[235,236] A similar switching of mechanism occurs with chlorine azide[237] and with bromine azide additions (Section 3.5.6.3).

Nitrosyl halides add to alkenes: references are scattered through the literature back to 1875 (ref. 194 and references cited therein). The adducts vary enormously in their stability, but when their structures allow they, like nonhalogenated nitroso compounds, isomerize to oximes or dimerize. The orientation of the reaction is consistent with an electrophilic mechanism, in which the reagent is polarized as $NO^+Hal^-$. Bicyclic substrates and reaction media of low polarity favor *syn* addition, suggesting a four-center transition state (Scheme 81). Aziridine synthesis *via* NOCl/alkene adducts is discussed in Section 3.5.2.1.

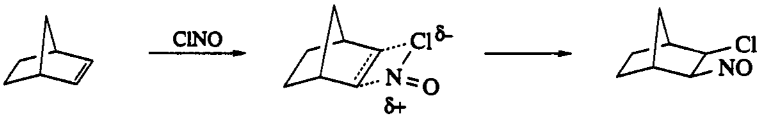

Scheme 81

With excess nitrosyl chloride, a chloronitro product is obtained in certain cases, a wide variety of steroid-5-enes giving 5α-chloro-6β-nitro derivatives in good yield ($CH_2Cl_2/CCl_4$, –60 to 0 °C, 2–24 h).[238] Nitryl chloride adds to terminal alkenes (56–80%) and to acrylic acid derivatives (refs. 239, 240 and references cited therein) at temperatures close to ambient. The reaction appears to be a radical one, the $NO_2$ entering the terminal position whatever the electronic requirement of the alkene.

### 3.5.6.3 Addition of Nitrogen and Bromine

There are several reports of homolytic addition of NBS[241] or *N*-bromophthalimide[242] to alkenes. Yields are moderate. The reaction can be promoted by conversion to a heterolytic mechanism with $BF_3$ catalysis: concurrent formation of the BrF adduct is of interest also (Scheme 82).[243]

Diethyl *N*,*N*-dibromophosphoramidate undergoes ready Markovnikov addition to styrene or cyclohexene (92%) in $CCl_4$ at –20 to +20 °C with $BF_3 \cdot Et_2O$ catalysis.[133,244] Alternatively, such reactions can be carried out in refluxing $CH_2Cl_2$ in the absence of catalyst, when anti-Markovnikov products (47–97%) are formed.[245] All these compounds are versatile intermediates (Scheme 83). A few *N*-bromoperfluoroamines have been added to alkenes, thermally or photolytically.[246]

Bromine azide reacts with alkenes by ionic or radical mechanisms according to conditions, adding to styrene in $MeNO_2/CH_2Cl_2$ to give $PhCH(N_3)CH_2Br$ (95%) or in $CHCl_3$ purged with $N_2$ (to remove $O_2$, a

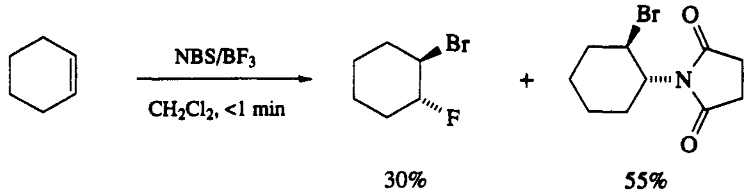
NBS/BF3
CH2Cl2, <1 min
Br
F
+
Br
O
N
O
30%
55%

Scheme 82

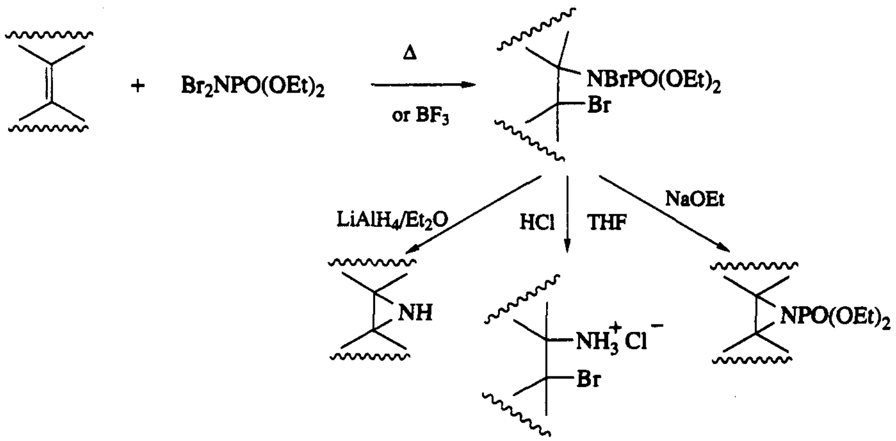
+ Br2NPO(OEt)2
Δ
or BF3
NBrPO(OEt)2
Br
LiAlH4/Et2O
HCl
THF
NaOEt
NH
NH3+ Cl−
Br
NPO(OEt)2

Scheme 83

radical inhibitor), $PhCHBrCH_2N_3$ (100%).[247] The two 2-butenes react stereospecifically in $MeNO_2/CH_2Cl_2$, *trans* to *erythro, cis* to *threo*.[248] The ionic reaction with deuterated styrene is regio- but not stereo-specific, indicating involvement of a benzylic cation.[248] If the reactions are done in acetonitrile, the initial product adds solvent, thus cyclohexene gives *trans*-1-(2-bromocyclohexyl)-2-methyl-tetrazole.[249]

Alkenes can be nitromercurated ($HgCl_2$/2 $NaNO_2/H_2O$, 30 h, 25 °C) and the products can be bromodemercurated, giving bromonitro compounds. An alternative work-up with base provides a valuable nitroalkene synthesis (Scheme 84).[250]

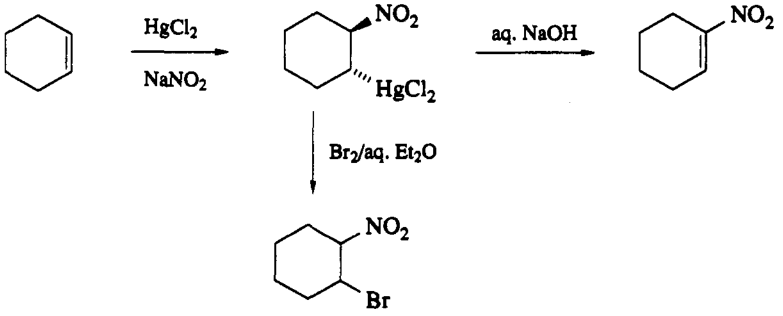
HgCl2
NaNO2
NO2
HgCl2
aq. NaOH
NO2
Br2/aq. Et2O
NO2
Br

Scheme 84

### 3.5.6.4 Addition of Nitrogen and Iodine

Iodine isocyanate, preformed or made *in situ* from AgNCO and $I_2$, adds to alkenes[31–33,251–255] with the regio- and stereo-chemistry expected of reactions proceeding *via* cyclic iodonium ions.[251] When the INCO is made *in situ*, a competing mechanism also occurs (except with the most reactive alkenes) in which the alkene complexes with the iodine, and the complex then reacts with the isocyanate ion to generate the same β-iodoisocyanate as obtained from INCO direct.[34] The reaction can be carried out at −35 to +20 °C in $Et_2O$, $CH_2Cl_2$, THF, pentane or excess alkene as solvent. Dichloromethane or ether are the solvents of choice: the reaction occurs faster in the more polar MeCN but with more side reactions.[253] Scheme 85 shows a sequence which illustrates a usage of this reaction to achieve an overall *cis* substitution (compare the *trans* substitution in Scheme 10).[33,253,254]

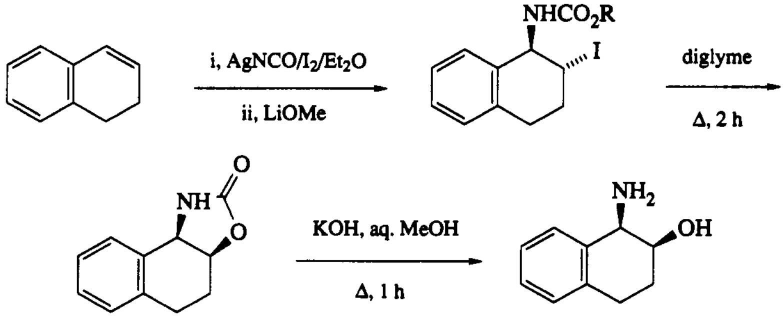

**Scheme 85**

Iodine azide, generally made *in situ* from ICl and $NaN_3$ in MeCN at 0 °C, adds readily to alkenes by a similar heterolytic mechanism to INCO. Whereas the *trans* stereochemistry is generally well established,[256,257] the regiochemistry of the adduct with 1-phenylcyclohexene[28] has been queried recently;[258] it was originally formulated as the 1-azido-2-iodo compound (Scheme 86), but base treatment was subsequently shown to yield what appeared to be 6-azido-1-phenylcyclohexene,[258] which would have arisen from the 1-iodo-2-azido isomer. However, it has very recently been shown by 300 MHz NMR that the elimination product is in fact 3-azido-1-phenylcyclohexene,[259] derived ultimately (Scheme 86) from the originally proposed 1-azido-2-iodo- structure.

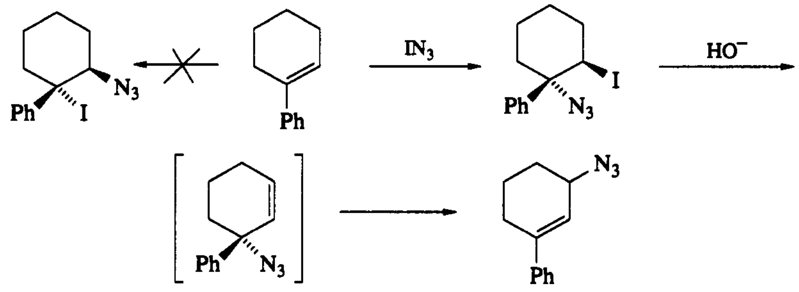

**Scheme 86**

There is one known exception to the *trans* nature of the addition: a hindered polycyclic alkene where a *cis* addition occurs.[260] More recently, small proportions of *cis* adducts have been detected as minor components in additions to cyclohexenes.[261] An interesting recent usage of the $IN_3$–alkene reaction is in the azirine synthesis of Scheme 87.[262]

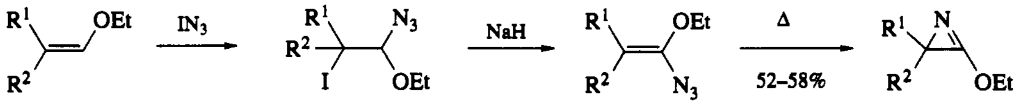

**Scheme 87**

Nitryl iodide, from iodine with silver nitrite[263,264] or from $NO_2$ and iodine,[265,266] adds to alkenes, generally in ether at room temperature, by a radical mechanism. Yields are 50–90%. The products yield nitroalkenes on treatment with base, a sequence used recently in the preparation of intermediates ($ArCH{=}CMeNO_2$) for amphetamine analogs.[264] The reaction is also a key step in the α-methylenebutyrolactone synthesis shown in Scheme 88.[266,267]

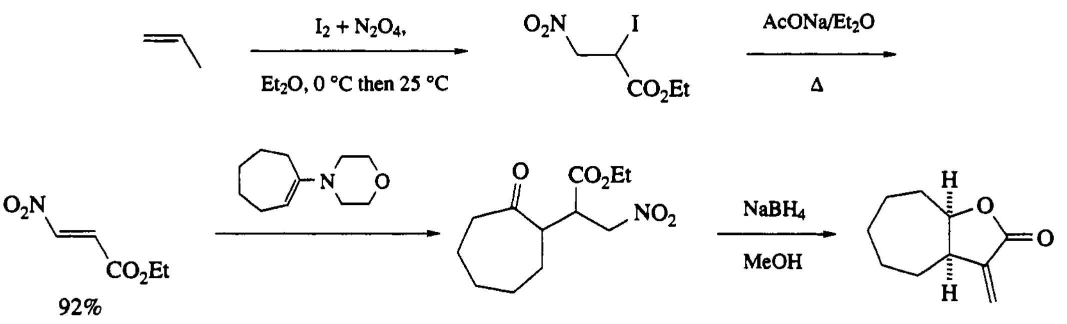
I2 + N2O4,
Et2O, 0 °C then 25 °C
O2N
I
CO2Et
AcONa/Et2O
Δ
O2N
CO2Et
92%
N
O
O
CO2Et
NO2
NaBH4
MeOH
H
O
O
H

Scheme 88

### 3.5.6.5 Iodolactamizations and Related Reactions

Early attempts to extend the halolactonization procedure to yield lactams gave cyclic imidates instead, but several approaches favor lactam products. These include: working with silyl imidates,[268] imidate esters[269] or oxazolines,[270] using sulfonylcarbamates[271] or other acidic amides;[272,273] or by using hydroxylamine derivatives with increased nucleophilicity due to the α-effect.[274] Lactams can also be favored as a consequence of steric requirements.[275] In a few cases, amines can be cyclized to cyclic amines: many lead references are given in a recent report on cyclic hydroxylamines such as (**64**).[276] Very recent work has provided a fairly general iodolactamization procedure from unsaturated amides, trimethylsilyl triflate and iodine (Scheme 89).[268]

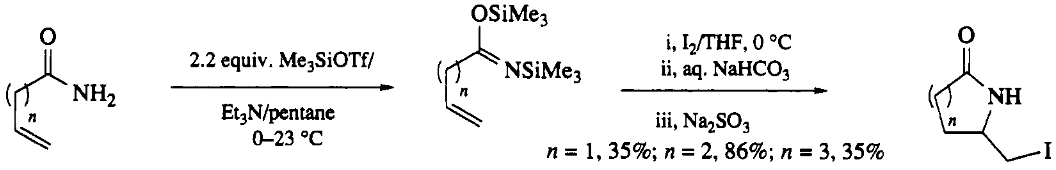
O
NH2
n
2.2 equiv. Me3SiOTf/
Et3N/pentane
0–23 °C
OSiMe3
NSiMe3
n
i, I2/THF, 0 °C
ii, aq. NaHCO3
iii, Na2SO3
n = 1, 35%; n = 2, 86%; n = 3, 35%
O
NH
n
I

Scheme 89

These products have a varied and useful chemistry, for example, the stereochemistry of substitution with azide can be manipulated by optional formation of an intermediate aziridine (Scheme 90).[268]

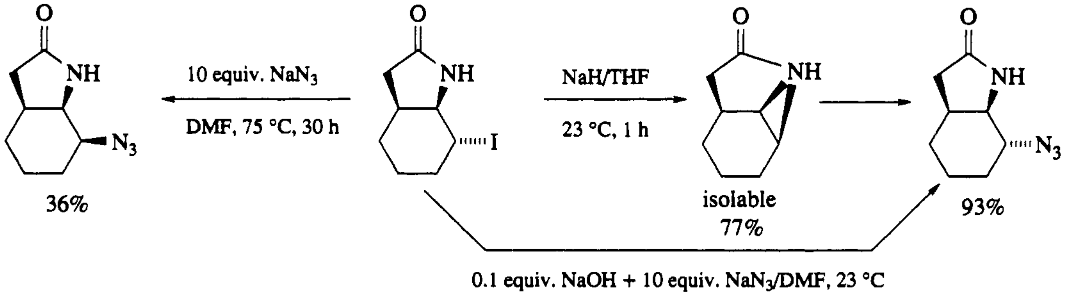
O
NH
N3
36%
10 equiv. NaN3
DMF, 75 °C, 30 h
O
NH
I
NaH/THF
23 °C, 1 h
O
NH
isolable
77%
O
NH
N3
93%
0.1 equiv. NaOH + 10 equiv. NaN3/DMF, 23 °C

Scheme 90

Alkenic oxazolines[270] undergo kinetically controlled[226] iodolactamizations in 52–91% yields ($I_2$ and $NaHCO_3$, aq. THF, 0–25 °C, 12 h). The extent and direction of steric induction vary widely and are not fully understood (Scheme 91). A 1989 paper contains many useful references.[270]

Other compounds prepared by halolactamization of alkenes (and preceding the above work[268]) include (**64**),[276] (**65**),[269] (**66**),[271] (**67**),[273] (**68**),[274] (**69**)[275] and (**70**).[277] Note that related sulfeno-, seleno- and telluro-cyclizations have been discussed earlier (Section 3.5.5). Finally, related products may be obtained by radical reactions of *N*-haloamides, giving the following (**71**–**73**) representative products in reactions promoted thermally (**71**),[278] photochemically (**72** and **73**),[279,280] with dibenzoyl peroxide (**73**)[280] or chromous chloride (**73**).[281]

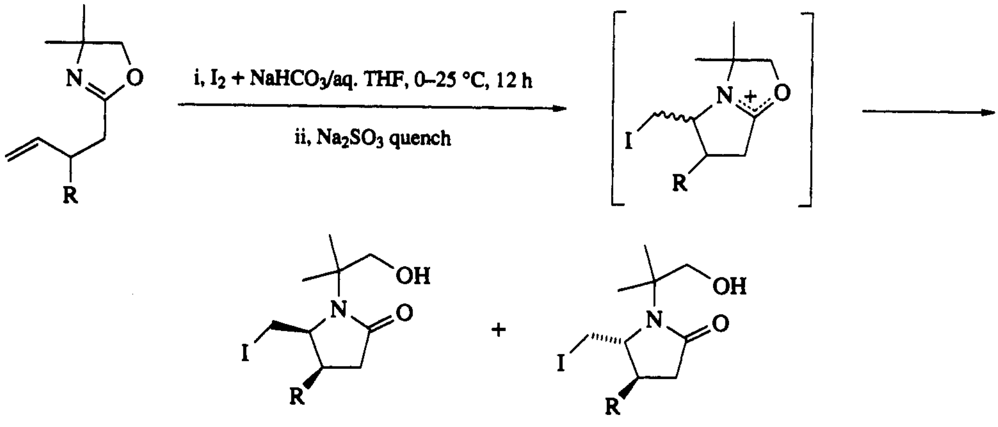

| R | *cis*:*trans* |
|---|---|
| Me | 2:1 |
| Bu$^t$ | 1:10 |

Scheme 91

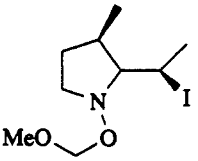

(64)
from *cis*-alkene

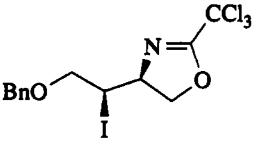

(65)

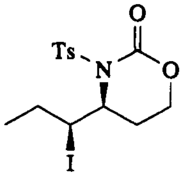

(66)

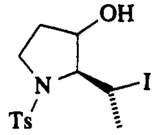

(67)
from a *trans*-allylic alcohol

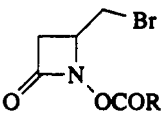

(68)

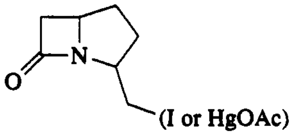

(69)

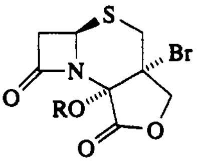

(70)

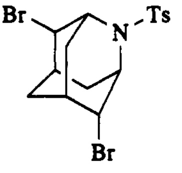

(71) 17%

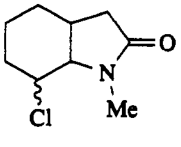

(72) 66%

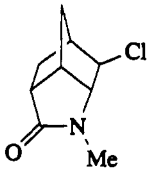

(73)

| *Induction* | *Yield (%)* |
|---|---|
| *hν* | 70 |
| $Bz_2O_2$ | 92 |
| $CrCl_2$ | 80 |

## 3.5.7 ADDITION TO POLYENES

### 3.5.7.1 Addition to Dienes

The palladium-promoted diamination of alkenes has been modified to yield *cis*-1,4-diamino-2-enes from dienes (Scheme 92).[282]

Lead(IV) azide yields 1,4-diazides from 1,3-dienes.[60,154] Whilst cycloadditions are beyond the scope of this review, the sequence of Scheme 93 is potentially important: 1,3-dienes undergo asymmetric Diels–Alder reactions with an α-chloronitroso derivative of epiandrosterone with high *ee*, and the N—O

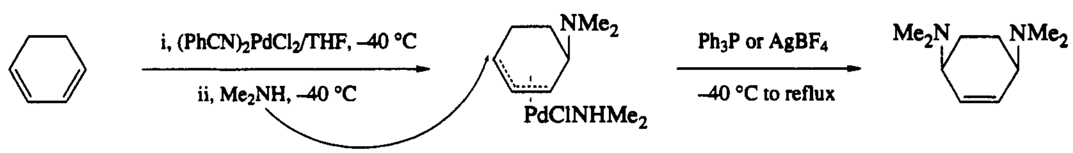
i, $(PhCN)_2PdCl_2$/THF, –40 °C
ii, $Me_2NH$, –40 °C
$NMe_2$
$PdClNHMe_2$
$Ph_3P$ or $AgBF_4$
–40 °C to reflux
$Me_2N$
$NMe_2$

Scheme 92

bond of the adduct can be cleaved to yield a resolved 1-amino-4-hydroxy-2-alkene derivative.[283] In the example shown,[283] the configuration was established as (1*R*,4*S*) by degradation to an L-glutamic acid derivative.[284]

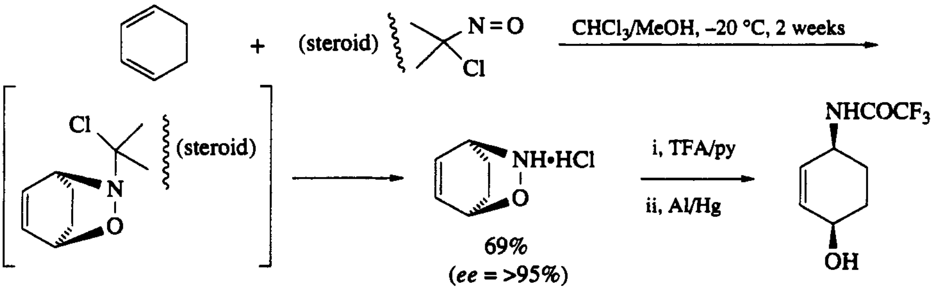
+
(steroid)
N=O
Cl
$CHCl_3$/MeOH, –20 °C, 2 weeks
Cl
(steroid)
N
O
NH•HCl
O
69%
(*ee* = >95%)
i, TFA/py
ii, Al/Hg
$NHCOCF_3$
OH

Scheme 93

1,3-Butadiene, in 0.1% water in MeCN, treated with $HBF_4$ and $I(py)_2BF_4$ in $CH_2Cl_2$ at –5 °C, 15 min, undergoes a vinylogous Ritter reaction to yield *trans*-$ICH_2CH{=}CHCH_2NHCOMe$ (72%).[285] Conjugated dienes react with arylsulfonyl azides to give enamines rather than either sulfimides or aziridines.[286] 1,3-Dienes react with trifluoroacetyl nitrate in refluxing $CH_2Cl_2$ and trace $HBF_4$ to give a mixture of 1,2- and 1,4-nitrotrifluoroacetates; base and NaOAc or NaH then gives 1-nitro-1,3-dienes (35–89%).[287] Benzeneselenenyl iodide ($Ph_2Se_2$, $I_2$) adds to dienes in acetonitrile (18 h, 20 °C); the solvent participates and a cyclization, sometimes transannular, takes place, giving acetamido selenides in good yield but moderate stereochemical purity. The precise product depends on the stereochemical opportunity, *e.g.* (**74**) gives (**75**); (**76**) gives (**77**).[288]

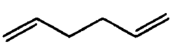

**(74)**

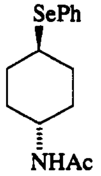

**(75)**

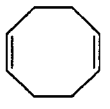

**(76)**

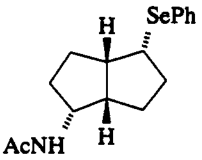
H
SePh
AcNH
H

**(77)**

Halogenation of (**78**) in excess of tertiary amine solvents yields quaternary adamantane salts (**79**).[289] Nitryl iodide ($N_2O_4$, $I_2$) in ether at –15 °C adds to isoprene and to chloroprene to give good yield of $O_2NCH_2CX{=}CHCH_2I$ (X = Me or Cl).[290] *N*-Chlorodibutylamine adds photolytically to butadiene, in 4M $H_2SO_4$, 1.5M HOAc aq., giving $Bu_2NCH_2CH{=}CHCH_2Cl$ (60%).[291] *N*-Halocarbamates add (5 °C,

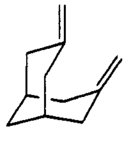

**(78)**

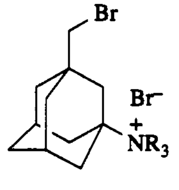

**(79)**

$CHCl_3$) to conjugated alkenynes, with the nitrogen on the terminal carbon, to give a variety of alkynic and allenic adducts, often in good yield.[292] A 1,4-azidoselenation of cyclohexadiene was discussed earlier (Section 3.5.5.2).

### 3.5.7.2 Addition to Cumulenes

Certain congested alkenes add $N_2O_4$ giving 1,2-dinitro compounds ($Et_2O$, –10 °C, 27–78%) which can be isolated at 0 °C, but which at room temperature convert to azetines, *e.g.* (**80**; 35–77%).[293] Iodine azide adds to allenes to give $RCH{=}CHICHRN_3$ or, from allene itself, $(N_3)_2C(CH_2I)_2$.[294] Cyclonona-1,2-diene gives the *cis* adduct; cycloundeca-1,2-diene gives the *trans* adduct.[295]

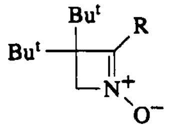

R = H, Me, Cl, $CONH_2$ *etc.*

**(80)**

## 3.5.8 ADDITIONS YIELDING MORE HIGHLY OXIDIZED COMPOUNDS

Introduction of oxygen into a Minisci-type reaction mixture leads to formation of amino ketones (Scheme 94).[296] The mixed acetate/azide of lead(IV) with styrene in acetonitrile at –20 °C yields phenacyl azide (60%).[152] One example of azirine formation has already been discussed (Scheme 87). Other related syntheses from vinyl azides are included in a recent review.[297]

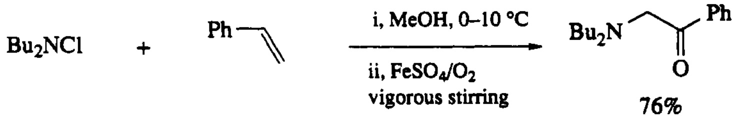

**Scheme 94**

## 3.5.9 ADDITIONS LEADING TO REARRANGEMENTS

The examples of aziridination with strongly electronegatively substituted azides cited earlier (Section 3.5.2) were, as indicated, special cases. More typically, imines are formed, and rearrangements are frequent: the key to understanding these reactions is given in Scheme 95, the final product being determined by the chemistry of the ion (**81**). Typical reactions (a–d) are given in Scheme 96 (refs. 298–301 respectively). The C=N bonds of (**82–86**) are readily hydrolyzed, yielding lactones, ketones or acids: hydrolysis of (**86**) provides an efficient synthesis of the antiinflammatory drug, naproxen. The diphenyl phosphorazidate procedure has recently been extended to enamines of $ArCH_2COAr$.[302]

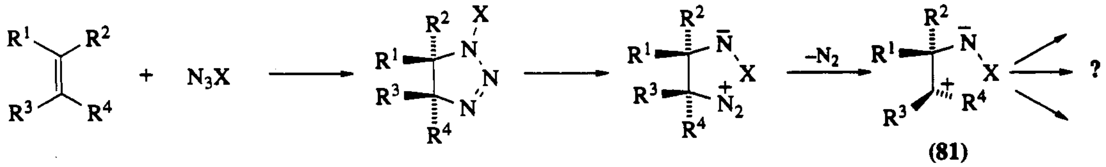

**(81)**

**Scheme 95**

## 3.5.10 ADDITIONS CLEAVING THE C=C BOND

Styrenes and stilbenes are cleaved by sodium hydrazide in boiling ether,[303] $PhCH{=}CMe_2$ giving $Me_2C{=}NNH_2$ (53%) and toluene (74%) after 6 h reflux. A wide variety of alkenes, dienes and aralkenes are also cleaved by diazonium salts (Scheme 97).[304] Yields and reaction rates vary widely.

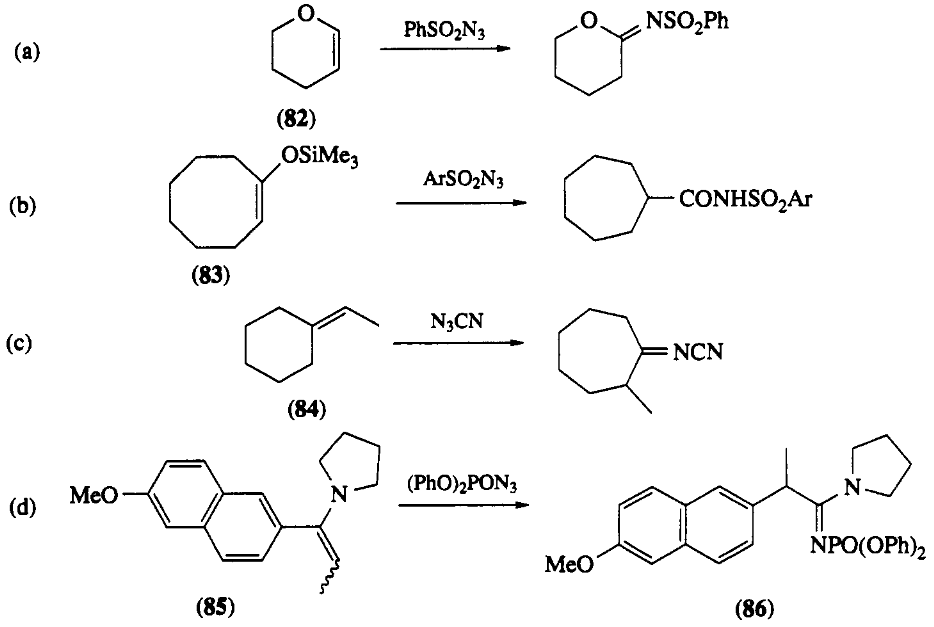
(a)
PhSO2N3
NSO2Ph
(82)
(b)
OSiMe3
ArSO2N3
CONHSO2Ar
(83)
(c)
N3CN
NCN
(84)
(d)
MeO
N
(PhO)2PON3
N
NPO(OPh)2
MeO
(85)
(86)

Scheme 96

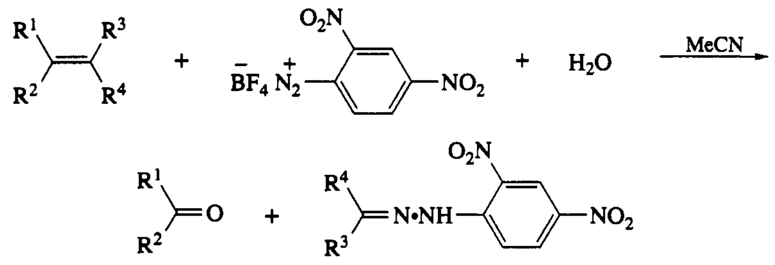
R1
R3
R2
R4
+
O2N
BF4 N2
NO2
+
H2O
MeCN
R1
O
R2
+
R4
R3
N•NH
O2N
NO2

Scheme 97

Ozonolysis of cyclic alkenes in aqueous ammonia yields a variety of products, depending on starting material;[305] for example, indene yields isoquinoline (62%). Other less general reactions include conversion of 1,4-cyclohexadiene to *N*-(methoxycarbonyl)azepine in four steps (INCO, NaOMe, $Br_2$, NaOMe);[306] a somewhat similar cleavage has been reported in a [3.8.3] fused ring system.[307] In both cases, the key concept is, in effect, aziridination of the central bond of an (incipient) 1,3,5-triene, and the resulting adduct is then set up to lose the second of the original alkenic bonds in a Cope rearrangement. Enamine aldehydes and ketones are cleaved by reactive azides, *e.g*. Scheme 98, which depicts the first synthesis of a diazoaldehyde.[308]

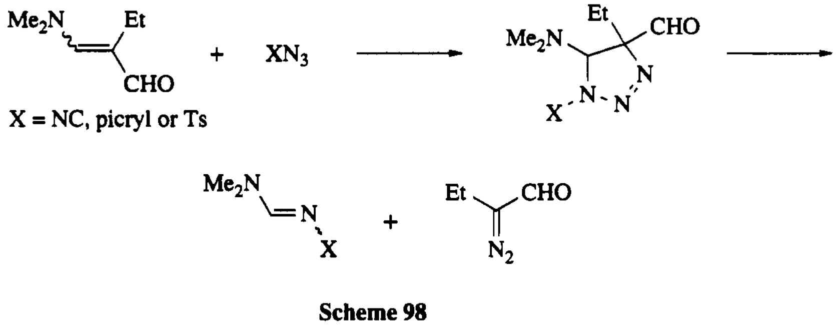
Me2N
Et
CHO
X = NC, picryl or Ts
+
XN3
Et
Me2N
CHO
N
X
N
N
Me2N
N
X
+
Et
CHO
N2

Scheme 98

Cyclic enol ethers are cleaved by butyl nitrite in acidic ethanol, providing a useful synthesis of oximinomacrolides (Scheme 99).[309] 1,2-Dichloroazides, from addition of chlorine azide to 1,2-dichloroalkenes (Scheme 100) (and also from addition of chlorine to vinyl azides), are unstable, and fragment to yield alkyl halides, cyanides and nitrogen.[310]

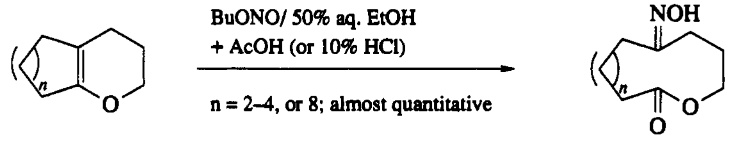

Scheme 99

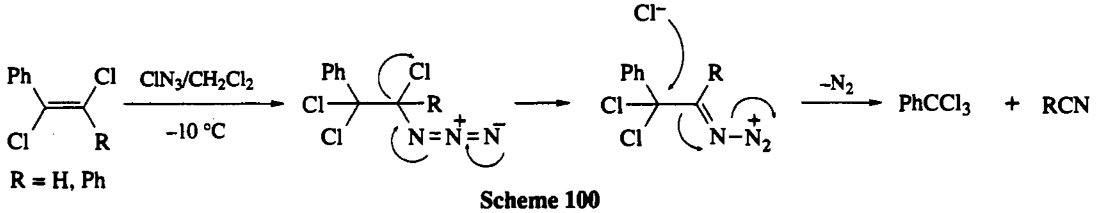

Scheme 100

Steroidal alkenes, with lead(IV) azide/acetate, can yield cleaved derivatives such as (**87**),[311] or its des-azido analog, or the uncleaved azido ketone,[154] or the allylic azide,[311] according to conditions, as well as the 1,2-diazides mentioned earlier (Section 3.5.3.2).

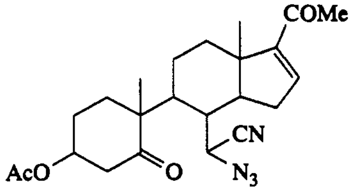

(**87**) 35%

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# 3.6

# Addition Reactions with Formation of Carbon–Sulfur or Carbon–Selenium Bonds

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## 3.6.1 INTRODUCTION

Organosulfur and organoselenium reagents offer many advantages over their first row counterparts for effecting a wide range of important synthetic transformations. These materials can be introduced into substrates either as nucleophiles, radicals or electrophiles. Once introduced, they can facilitate a variety of different processes by stabilizing adjacent positive or negative charges. Finally, after serving their purpose, they can be removed either oxidatively or reductively, thereby introducing either unsaturation or saturation, respectively.

In this chapter addition reactions involving organosulfur and organoselenium reagents are discussed. The examples to be discussed here emphasize those processes which appear to be relatively general and efficient. Although exceptions exist, organoselenium derivatives have generally proven to be more effective than comparable organosulfur derivatives.[1]

## 3.6.2 THE FORMATION OF CARBON–SULFUR BONDS FROM ADDITIONS TO $\pi$-BONDS

### 3.6.2.1 Formation of Thiiranes

Thiiranes are prepared by two major pathways. The first pathway is the conversion of alkenes to intermediates, such as dihalides, halohydrins or epoxides, followed by nucleophilic attack and subsequent closure of the thiirane sulfur.[2] The other pathway, discussed here, involves the reaction of the alkenes with electrophilic sulfur reagents to produce α-halo-β-sulfur intermediates, which can then be induced to cyclize to thiiranes. There are two methods of introducing sulfur oxidatively to alkenes; these involve the use of either sulfur monochloride or arenethiosulfenyl chloride. In both these methods, the sulfur is introduced stereoselectively (*e.g.* with *trans*-alkenes, *trans*-substituted thiiranes are produced; Scheme 1).

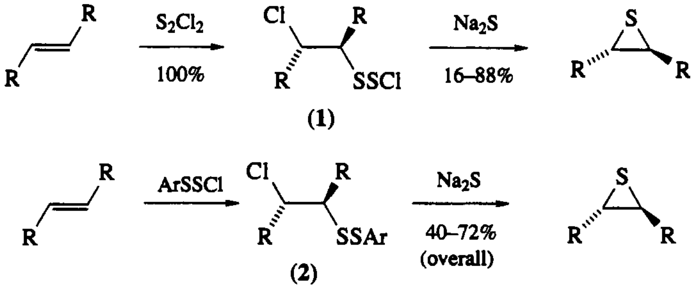

**Scheme 1**

The first method involves sulfur monochloride addition to alkenes forming an α-chloro-β-disulfide (**1**), which can be reduced with sodium sulfide or aluminum amalgam. Unfortunately this procedure suffers from three drawbacks: (i) low yields are realized on reduction of the disulfide; (ii) an excess of alkene (2–3 equiv.) is required to produce good yields; and (iii) the reactions occur poorly with acyclic molecules in general.[3]

A more promising method involves the use of arenethiosulfenyl chlorides. These reagents oxidize alkenes to α-chloro-β-disulfidearenes (*i.e.* **2**) in high yields. The intermediates are then reduced by sodium sulfide and cyclized to thiiranes in good to moderate yield. Unfortunately these arenethiosulfenyl chlorides must be prepared from arenethiols and sulfur dichloride; nevertheless, the yields of acyclic adducts are reliably moderate. In addition, the arene substituents may be changed to modify the nucleophilicity and reducibility of the reagent.[4]

For the formation of thiiranes from alkenes, it seems best to use the arenethiosulfenyl chloride method since this appears to result in the highest yields. While the sulfur monochloride method can be used, the yields are typically poor to moderate over a wide range of substrates. For both methods there are some common problems which include competing group reactivity (other alkenes or electron-rich groups) and, of course, the stench associated with many sulfides.

### 3.6.2.2 Electrophilic Sulfur Additions

Electrophilic sulfur reagents have been little used in organic synthesis. The reasons include sluggish reactivity, low stability and good alternative methods, such as organoselenium electrophiles. The additions of electrophilic sulfur reagents to alkenes occur in good to excellent yield. Some good examples of electrophile-induced cyclizations are known. Although the electrophilic sulfur reagents are usually divalent, a few reports of hexavalent sulfur electrophiles are also known. These organosulfur reagents offer some synthetic utility, but have seen limited use.

Several types of sulfenyl chlorides are known. Sulfur monochloride and dichloride can add to dienes forming sulfur bridges.[5,6] The most commonly used sulfenyl halides are benzenesulfenyl chlorides and methanesulfenyl chloride. Other sulfenyl halides, such as acetylthiosulfenyl chloride and thiocyanogen chloride, have been added to alkenes, but few subsequent transformations have been carried out with those intermediates.[7,8]

The regiochemistry of additions of alkenes with sulfenyl chlorides exhibits some unusual trends. 2,4-Dinitrobenzenesulfenyl chloride reacts with alkenes, only forming Markovnikov addition products. These results suggest the transition structure possesses little thiiranium character and a large amount of carbonium character.[9] However, methanesulfenyl chloride typically gives anti-Markovnikov addition products (80–95% anti-Markovnikov) with alkyl-substituted terminal alkenes under kinetic control. These initially formed products can be equilibrated to Markovnikov products (all 88% Markovnikov) by trace acid (equation 1). Methanesulfenyl chloride reacts with phenyl-substituted terminal alkenes producing a high preponderance of Markovnikov addition (90–98%). With sterically encumbered terminal alkenes (4-methylbut-1-ene), the degree of anti-Markovnikov addition increases to 95%. Benzenesulfenyl chloride also gives mixtures of regioisomers (63–87%), with anti-Markovnikov products predominating.

These addition products may also be equilibrated to Markovnikov products.[10] The regiochemistry of the addition of sulfenyl chlorides to alkenes is determined by the polarity of the sulfenyl chloride, the relative stability of the carbonium ion intermediates and the steric bulk at or around the alkene.

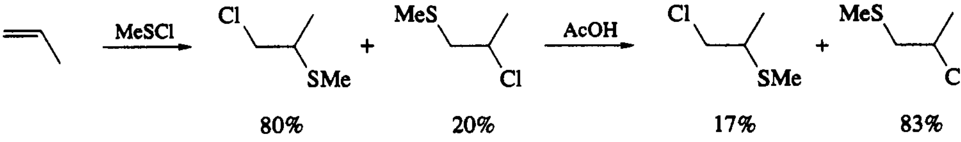

(1)

Benzenesulfenyl chloride alkene adducts may be transformed to many useful molecules. Intermediates, such as (**3**), can be treated with base to produce vinyl or allyl sulfides (equation 2). Alternatively, the adducts can be oxidized and treated with base to yield vinyl sulfones in high overall yield (equation 3).[11] The thiirane intermediates or adducts, *i.e.* (**3**), may be alkylated with alkyl-titanium and -aluminum reagents which replace the chloride substituent with retention of configuration.[12]

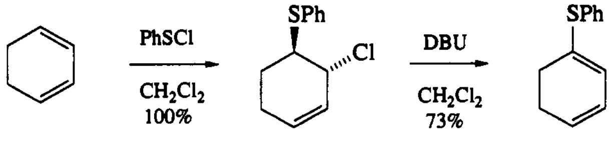

(**3**)

(2)

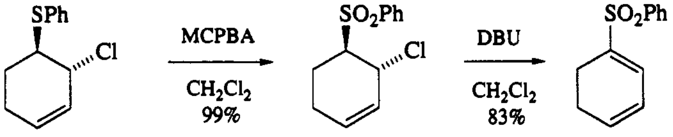

(**3**)

(3)

Cyclizations involving sulfenyl chlorides must be designed carefully, since these reagents can also react with alcohols, amines and other nucleophiles.[13] Benzenesulfenyl chloride has been used to cyclize a 1,4-diene. For example, diene (**4**) cyclizes in good yield to tricyclic heptane product (**5**). This material was then further elaborated to a cyclosativene precursor (**6**; equation 4).[14]

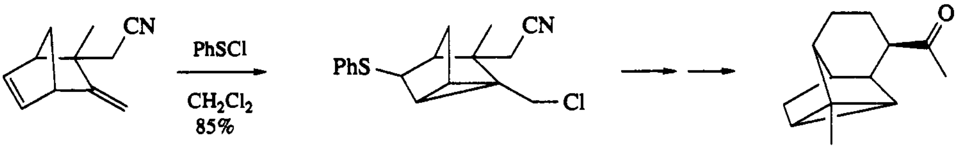

(**4**) (**5**) (**6**)

(4)

Another useful cyclization results in the stereoselective synthesis of β-lactams from thiiranium ions derived from α,β-unsaturated amides. Unsaturated amides are treated with benzenesulfenyl chloride and the product is subsequently treated with base under phase transfer conditions. The reaction regenerates a thiiranium ion in the presence of amide anion, which then cyclizes to form β-lactams. The regiochemistry of the alkene addition determines the eventual stereochemical outcome (*e.g. cis*-alkenes produce *cis*-β-lactams; Scheme 2). The yields of the cyclization products are quite sensitive to the amide-protecting group which was employed. With 4-anisyl amide the yield is moderate (73%), but with 4-nitrophenyl amide the yield is excellent (97%), suggesting that the amide must be deprotonated before cyclization can occur.[15]

Benzenesulfenyl chloride can convert unsaturated acids to lactones. The unsaturated acid (**7**) is treated with benzenesulfenyl chloride, followed by Raney nickel, to afford the γ-lactone (**8**) in excellent overall yield (equation 5). Another acid (**9**) has been lactonized to produce the spiro-β-lactone (**10**) which rearranges on silica gel to γ-lactone (**11**; equation 6). δ-Lactones have been also prepared using this approach. An additional advantage of this approach is that the phenyl sulfide moiety can be manipulated into a variety of functional groups to facilitate cyclization.[16] In summary, successful cyclization reactions

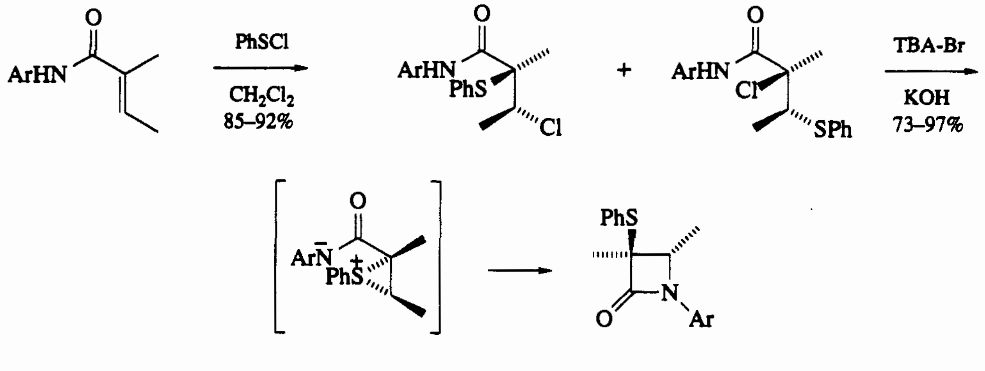
ArHN
PhSCl
CH2Cl2
85–92%
PhS
Cl
+
SPh
TBA-Br
KOH
73–97%
ArN
PhS
N
Ar

Scheme 2

can be achieved, provided the precursors lack functionality which can react competitively with sulfenyl halides.

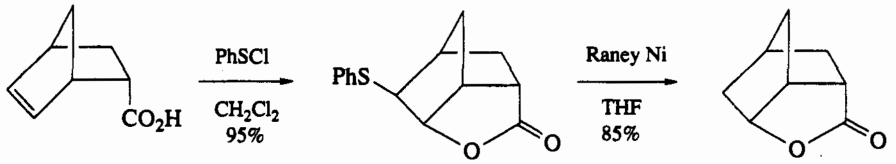
CO2H
PhSCl
CH2Cl2
95%
PhS
Raney Ni
THF
85%

(7) (8) (5)

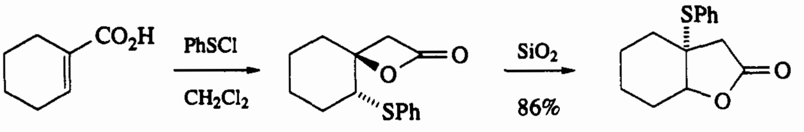
CO2H
PhSCl
CH2Cl2
SPh
SiO2
86%
SPh

(9) (10) (11) (6)

Arylsulfenyl trifluoroacetates have been generated *in situ* and used for the hydroxysulfenylation of alkenes. These reagents are prepared from diaryl disulfides and LTA in trifluoroacetic acid. Yields for the addition are generally good (42–95%). The hydroxysulfenate intermediate can be oxidatively cleaved by LTA (provided the groups can achieve an antiperiplanar arrangement) to form an α-aldehyde-ω-acetoxy sulfide in good yield (40–88%; Scheme 3).[17]

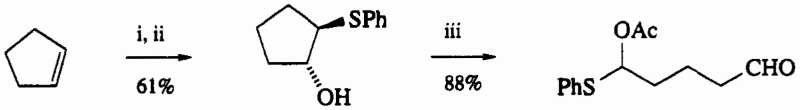
i, ii
61%
SPh
OH
iii
88%
OAc
PhS
CHO

i, LTA, PhSSPh, TFA; ii, $H_2O$, $NaHCO_3$; iii, LTA, pyridine, AcOH

Scheme 3

Arenesulfonyl halides can add to alkenes with the assistance of a metal catalyst. Several types of catalysts have been employed with varying degrees of success. Substituted phenyl vinyl sulfones, although only the (*E*)-isomers have been prepared from styrenes, benzenesulfonyl chlorides and a ruthenium catalyst in good yield.[18] This same reaction has been tried with chiral ruthenium catalysts with modest success (20–40% *ee*).[19]

### 3.6.2.3 Radical Sulfur Additions

The number of reported additions of sulfur radicals to π-bonds, while very limited, is growing fast. In general, the major problem which must be overcome in these reactions is the recombination of thiyl radicals to form stable disulfide bonds. This has been partially achieved by the use of dilution techniques and by the use of selenosulfur reagents.

The early work with thiyl radicals primarily involved the intramolecular cyclization of alkenes. The reaction appears to be useful since high yields and stereoselective formation of products are observed (equation 7). Under a variety of conditions the diallyl diester (**12**) produces a 6:1 mixture of stereoisomeric cyclopentanes (**13**) and (**14**) in high yield.[20] When enynes are treated with thiyl radicals, low to moderate yields of addition products are observed (equation 8).[21]

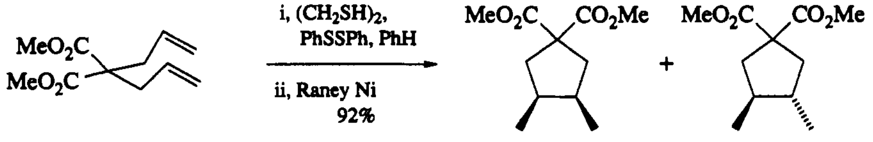
MeO2C
MeO2C
i, (CH2SH)2, PhSSPh, PhH
ii, Raney Ni
92%
MeO2C
CO2Me
+
MeO2C
CO2Me

(7)

(**12**) (**13**) 86% (**14**) 14%

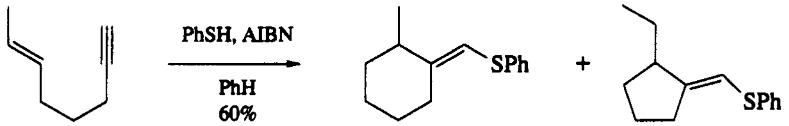
PhSH, AIBN
PhH
60%
SPh
+
SPh

(8)

87% 13%

A large amount of work has been accomplished using mixed sulfur/selenium reagents, such as selenosulfides and selenosulfones. One example of selenosulfide addition *via* radicals is selenothiolactonization. When selenosulfide (**15**) is treated with AIBN, a mixture of γ-seleno-substituted thiolactones is produced (equation 9). Although these lactonizations result in mixtures of stereoisomers, they usually can be separated.[22] In addition to these reports, selenosulfones have been used to form allenic sulfones, alkynic sulfones and (phenylsulfonyl)dienes (Scheme 4).[23]

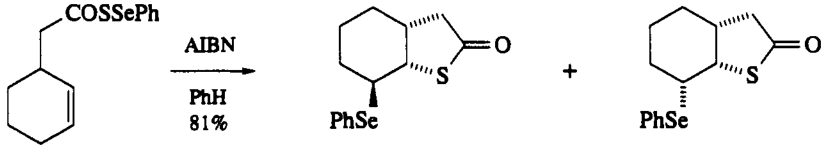
COSSePh
AIBN
PhH
81%
O
S
PhSe
+
O
S
PhSe

(9)

(**15**) 92% 8%

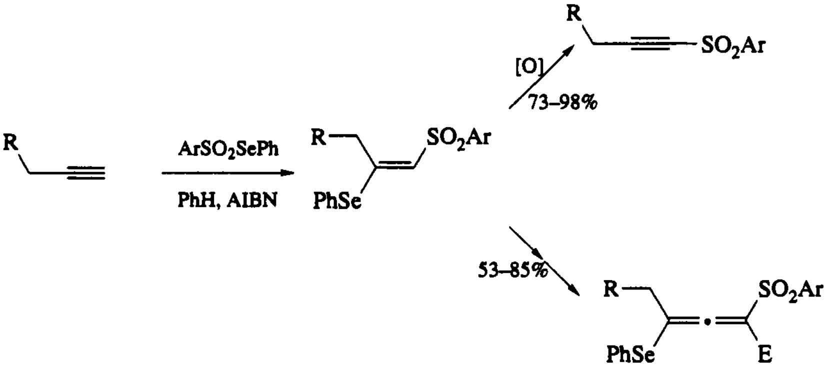
R
SO2Ar
[O]
73–98%
R
ArSO2SePh
PhH, AIBN
R
SO2Ar
PhSe
53–85%
R
SO2Ar
PhSe
E

Scheme 4

In summary, much work has been accomplished with selenosulfur radicals, while little has been done with thiyl radicals.

## 3.6.3 FORMATION OF CARBON–SELENIUM BONDS FROM ADDITIONS TO π-BONDS

### 3.6.3.1 Regiochemistry of Additions

Selenium electrophiles add to a wide range of π-bonds, usually with good regiochemical and stereochemical results, to form a variety of selenium-containing intermediates.[24] These intermediates can be further elaborated to desired products.

Selenium electrophiles, such as benzeneselenenyl chloride, add to unactivated monosubstituted alkenes, forming Markovnikov or anti-Markovnikov addition intermediates depending on conditions employed. Markovnikov addition products (thermodynamic control) are observed using polar solvents or ambient temperature. Anti-Markovnikov (kinetic control) adducts are initially formed at low temperature and in nonpolar solvents. These adducts can be isolated directly or isomerized to Markovnikov adducts upon warming (equation 10).[25] The isomerization is caused by a reversible seleniranium ion formation and subsequent halide reopening, a process which is accelerated by polar solvents and higher reaction temperatures. Under these conditions 1,2-disubstituted alkenes provide mixtures of regiochemical adducts, while trisubstituted alkenes only give Markovnikov adducts.[24,25]

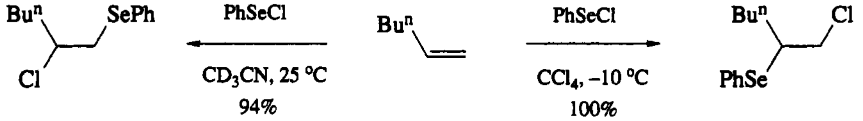

(10)

Benzeneselenenyl chloride adds to allylic alcohols and acetates in a highly regio- and stereo-selective fashion. Substituted cyclohexenyl acetates and benzoates react with benzeneselenenyl chloride, only forming one diastereomer (equation 11). The adduct (**16**) can then be elaborated to an enone. The proposed mechanism for explaining the observed regio- and stereo-selectivity involves the formation of a seleniranium ion *syn* to the ester. The seleniranium ion is then opened by an axial attack of halide ion. With noncyclic allylic acetates, good yields of products possessing the same regio- (>96%) and stereo-chemistry are seen. In additions to allylic alcohols, the *syn* stereochemistry is preserved, but mixtures of regioisomers are observed (70:30).[26]

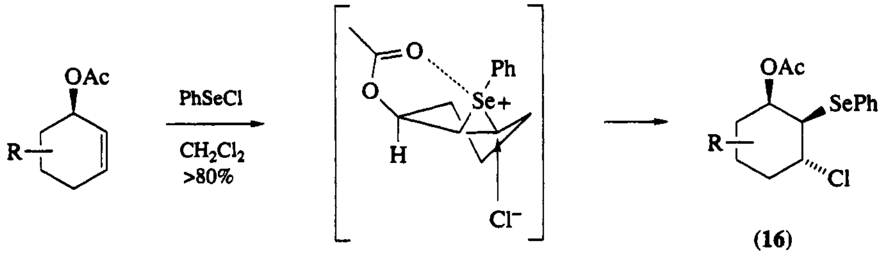

(**16**)

(11)

Selenium electrophiles add to conjugated dienes, only forming 1,2-adducts. Although Markovnikov addition is seen, only a few examples have been reported.[27] With allenes the additions are regiospecific, with the phenylseleno group usually adding to the *sp*-carbon. Unfortunately, all four stereoisomers of halide attack are seen with unsymmetrically substituted allenes.[28]

The addition of selenium electrophiles to activated π-bonds (*i.e.* enol ethers) occurs readily. Enol ethers react with benzeneselenenyl chloride to produce *cis*- and *trans*-α-chloro-β-phenylseleno adducts. These adducts can be transformed into α,β-dichlorides or allylic chlorides.[29] If the reaction is carried out in the presence of alcohols, stereoisomers of β-seleno mixed ketals are isolated (equation 12).[30]

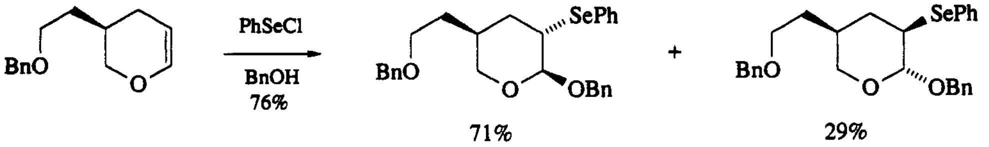

(12)

It has been found that selenium electrophiles add to electron-deficient alkenes to form mixtures of adducts. Benzeneselenenyl chloride adds to chlorocyclohexene (**17**), producing a mixture of adducts (equation 13).[31] 1,1-Difluoroethylene furnishes only one regioisomer (equation 14).[32] Benzeneselenenyl chloride adds to several acrylates (*i.e.* ethyl acrylate, acrolein and others) to produce good yields of regioisomeric adducts. The mixture always favors Markovnikov addition (73–95%), presumably due to electronic effects.[33] However, the pyridine–benzeneselenenyl chloride complex adds to cyclic enones to produce 2-(phenylseleno)enones in good yields. The mechanism is thought to involve a Michael reaction between the enone and pyridine. The enolate is subsequently attacked by the benzeneselenenyl moiety, followed by elimination of pyridine forming the product (equation 15).[34]

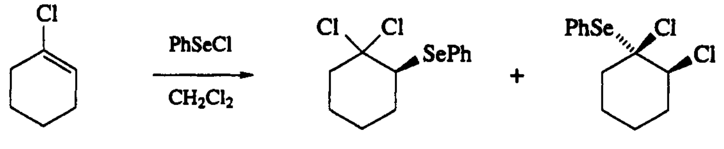
Cl
PhSeCl
$CH_2Cl_2$
Cl
Cl
SePh
+
PhSe
Cl
Cl

**(17)** 75% 25%

(13)

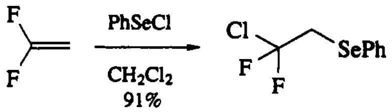
F
F
PhSeCl
$CH_2Cl_2$
91%
Cl
F
F
SePh

(14)

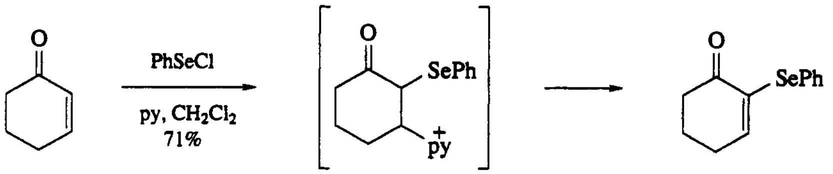
O
PhSeCl
py, $CH_2Cl_2$
71%
O
SePh
$\overset{+}{py}$
O
SePh

(15)

Benzeneselenenyl chloride adds to alkynes to produce mixtures of *trans*-alkene adducts. For example, the addition of benzeneselenenyl chloride to the alkyne (**18**) produces the alkene (**19**), which can be transformed to yield the unusual diene (**20**; equation 16).[35] Alkynic alcohols give anti-Markovnikov addition products under kinetic control. The reaction is thought to proceed through the selenirenium ion (**21**; equation 17).[36] Selenium electrophiles add to α,β-alkynic carbonyl moieties to produce *cis* adducts in good yield (equation 18).[37]

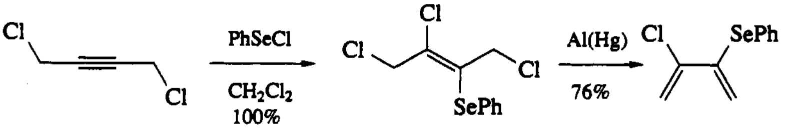
Cl
Cl
PhSeCl
$CH_2Cl_2$
100%
Cl
Cl
Cl
SePh
Al(Hg)
76%
Cl
SePh

**(18)** **(19)** **(20)**

(16)

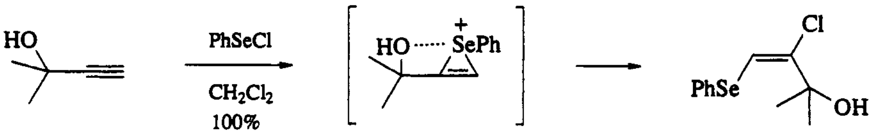
HO
PhSeCl
$CH_2Cl_2$
100%
HO
$\overset{+}{SePh}$
Cl
PhSe
OH

**(21)**

(17)

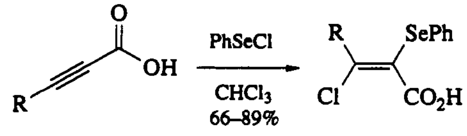
O
OH
R
PhSeCl
$CHCl_3$
66–89%
R
SePh
Cl
$CO_2H$

(18)

In summary, several types of carbon π-bonds react with benzeneselenenyl halides producing usually one or more regioisomers. Several of these regioisomers may be equilibrated *via* their seleniranium ions.

### 3.6.3.2 Seleno–Heteroatom Additions

Several different functional groups can be introduced by selenenylation. The benzeneselenenyl ion tolerates a wide range of anionic groups. However, with differing anionic moieties the reactivity of the benzeneselenenyl ion varies greatly. All adducts can be subsequently converted to either allylic or vinylic moieties by the *syn* elimination of the corresponding selenoxide (oxidized selenide).

Benzeneselenenyl azide adds to alkenes readily. The addition of the selenenyl azide always occurs with *trans* stereochemistry. The yield of adducts is reliably high with several different alkenes. Unlike benzeneselenenyl chloride, mixtures of regioisomers are found with simple primary alkenes. No addition occurs between benzeneselenenyl azide and ethyl crotonate. The reagent adds to conjugated dienes in a *trans* 1,4-fashion which is thought to be due to an initial *trans* 1,2-addition, followed by a facile 1,3-allylic azide shift (equation 19). Unfortunately, this reagent must be prepared and used *in situ*.[38]

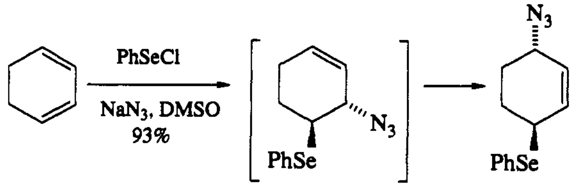

(19)

Cyanoselenenation of unactivated alkenes occurs only under harsh conditions, such as strong Lewis acid catalysis (*e.g.* tin(IV) chloride). The yields are usually good and only *trans* stereoisomers are observed. Unfortunately, unsymmetrical (terminal and trisubstituted) alkenes yield regioisomeric mixtures. This method provides easy access to unusual trisubstituted carbonitriles starting from relatively simple alkenes (equation 20). Several different cyanoselenates are readily available.[39]

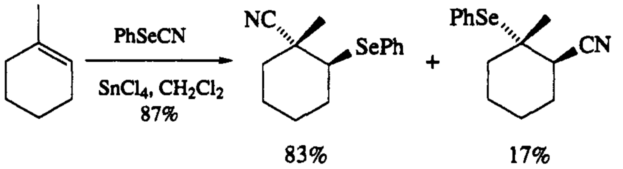

(20)

Hydroxyselenenations can be accomplished in good yields by using phenylselenenyl trifluoroacetate. Although the product stereochemistry is consistently *trans*, the observed regioselectivity is poor for unsymmetrical alkenes. The reagent adds to ethyl acrylate, but again the adducts are a mixture of regioisomers. This reagent also adds to alkynes to produce, after hydrolysis, α-phenylseleno ketones (equation 21). This procedure represents an efficient method for the preparation of rearranged allylic alcohols from alkenes similar to allylic oxidations with singlet oxygen but complementary to those obtained from selenium dioxide. The reagent must be prepared *in situ*.[40]

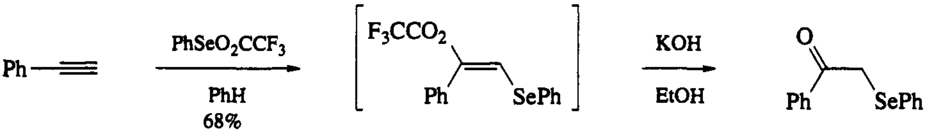

(21)

Another method of hydroxyselenenation involves trapping the seleniranium ion by water. The use of *N*-phenylseleno-succinimide (N-PSS) or -phthalimide (N-PSP) as the selenium electrophile facilitates the reaction, since the succinimide or phthalimide anion is not as nucleophilic as water. With dienes, transannular cyclizations can occur, forming bis(phenylseleno) ethers in good yields (equation 22).[41]

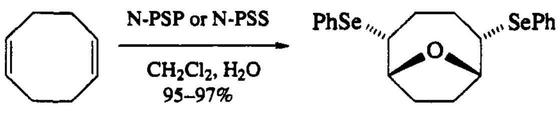

(22)

A method for the conversion of alkenes to α-phenylseleno carbonyl compounds involves the use of benzeneselenenic anhydride. This reagent, which has a relatively short lifetime, is prepared *in situ* from diphenyl diselenide and *t*-butyl hydroperoxide. The alkene is converted to a phenylseleniranium ion which is opened by benzeneselenenic acid. The adduct then loses benzeneselenol, forming the desired product. Unfortunately, high temperatures are required for reaction and all of the adducts from unsymmetrical alkenes are mixtures of regioisomers (equation 23).[42]

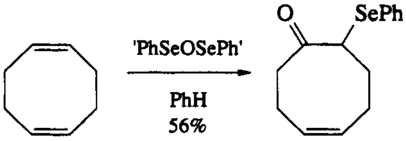

(23)

Another interesting sequence is the amidoselenenation of alkenes for the synthesis of allylic amides. The seleniranium ion is trapped by a nitrile group which is first converted to an iminium chloride and then hydrolyzed to the amide (similar to the Ritter amide synthesis). Several differing nitriles (*e.g.* methyl to phenyl) have been utilized and all provide good yields of amides. The stereochemistry of addition is always *trans* but mixtures of regioisomers occur with terminal and unsymmetrically substituted olefins (equation 24). The β-seleno amide is easily converted to the allylic amide by oxidation of the phenyl selenide using the standard conditions.[43]

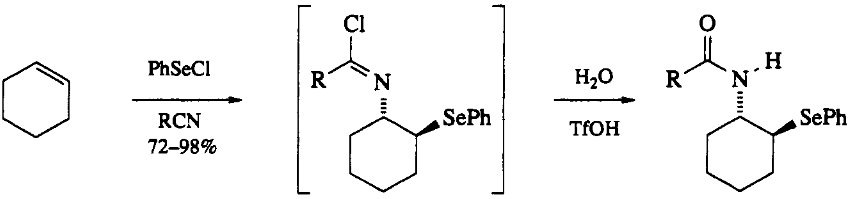

(24)

Selenosulfonates (see also Section 3.6.2.3) add to alkenes when catalyzed by Lewis acids. These adducts are transformed *via* oxidative elimination to vinyl sulfones in good overall yields. Similar to other methods only *trans* addition is observed. Mixtures of regioisomers are often produced with unsymmetrical unactivated alkenes. All other alkenes (*i.e.* styrene and acrylonitrile) provide Markovnikov additions. Radical processes yield anti-Markovnikov adducts. Thus, either regioisomeric vinyl sulfone may be prepared from almost any activated alkene by simply varying the mode of addition.[44]

### 3.6.3.3 Selenium-induced Cyclizations

Several electrophilic selenium-induced cyclizations are known.[1] They include etherifications, lactonizations and lactamidation. Some reasons why selenium electrophiles are used extensively in cyclizations include consistently good yields, few by-products and mild reaction conditions, as well as the ability to further manipulate the seleno group in a variety of straightforward fashions.

Electrophile-induced alkenol cyclizations are well known with many electrophiles.[45] Benzeneselenenyl electrophiles are effective cyclization agents, forming cyclic ethers in high yield. In cyclizations which can involve either a 5-*exo* or a 6-*endo* transition state, the 5-*exo* is highly favored (*i.e.*, tetrahydrofurans, THFs, are produced instead of tetrahydropyrans, THPs). Two examples (equations 25 and 26) illustrate the methodology. When alkenol (**22**; equation 25) is allowed to react with benzeneselenenyl chloride, the allylic ether (**23**) is produced as the only THF.[46] A particularly useful cyclization agent is *N*-phenylselenophthalimide (N-PSP), which possesses a strong selenenylating agent and a very weak nucleophile (phthalimide ion). Using this reagent, ketone alcohol (**24**; equation 26) is transformed to the spiroketal (**25**), a functional group which is often found in ionophore antibiotics.[47] Cyclization can also involve ketones instead of alcohols. For example, ketone (**26**; equation 27) could be cyclized to a mixture of stereoisomeric tetrahydrofurans (**27**) and (**28**). These adducts could be further functionalized *via* both the enol and the phenylseleno group.[48]

Several lactones are ubiquitous in nature. Early workers found that iodine cyclizes unsaturated acids to lactones (iodolactonization). However, since the regiochemistry of selenoxide eliminations is often complementary to the regiochemistry of dehydrohalogenations, selenolactonizations possess obvious synthetic utility. With this methodology several lactones containing five-, six- and seven-membered rings have been prepared in good yield. Also a large macrocyclic lactone (16-membered ring) has been prepared using similar methodology.[41] The first example depicts the conversion of the unsaturated acid (**29**) to the bicyclic lactone (**30**; equation 28).

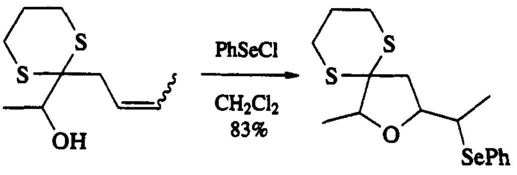
PhSeCl
CH$_2$Cl$_2$
83%
S
S
OH
O
SePh

(22) (23)

(25)

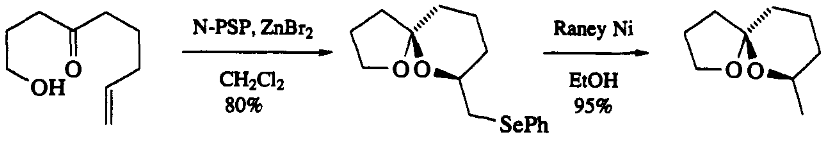
N-PSP, ZnBr$_2$
CH$_2$Cl$_2$
80%
Raney Ni
EtOH
95%
OH
O
O O
SePh

(24) (25)

(26)

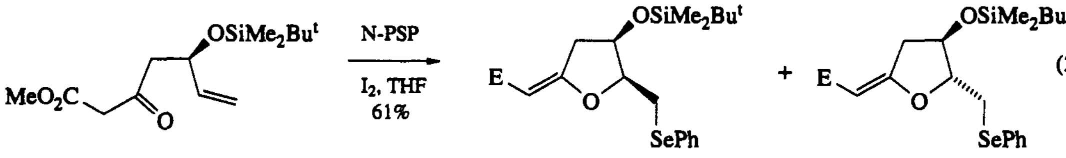
OSiMe$_2$Bu$^t$
MeO$_2$C
O
N-PSP
I$_2$, THF
61%
E
O
SePh
+

(26) (27) 30% (28) 70%

(27)

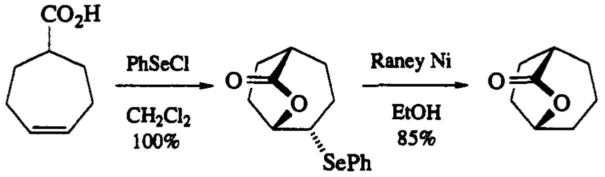
CO$_2$H
PhSeCl
CH$_2$Cl$_2$
100%
Raney Ni
EtOH
85%
O
O
SePh

(29) (30)

(28)

Several other transannular lactonizations and reductions have been reported to proceed in high overall yields.[49] Also other acid derivatives, such as amides and esters, cyclize to form lactones.[50] Alkynoic acids have been lactonized to γ-alkylidene-γ-lactones in good yield, *e.g.* the conversion of (**31**) to (**32**; equation 29). Unfortunately the vinyl selenide product can isomerize from (*E*) to (*Z*) in a secondary process.[51] Analogous lactam formation is also known. Unsaturated amides, when cyclized with benzeneselenenyl halides, produce good yields of lactams or iminolactones depending upon the alkene utilized.[52] The amide (**33**) cyclizes to the iminolactone (**34**), producing a mixture of stereoisomers (65:35; Scheme 5). The amide (**35**) is cyclized to lactam (**36**) in moderate yield.

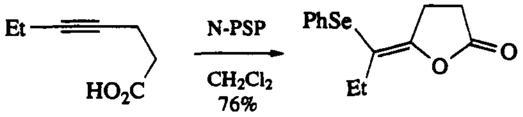
Et
HO$_2$C
N-PSP
CH$_2$Cl$_2$
76%
PhSe
Et
O
O

(31) (32)

(29)

Heterocycles can be prepared from selenium-induced cyclizations of urethanes, thioesters and alkenes. These cyclizations are seen infrequently, but have much potential in heterocyclic synthesis. The aniline (**37**) was treated with benzeneselenenyl chloride and silica gel (to facilitate the ring closure) to produce the hexahydrocarbazole (**38**) in good yield (equation 30).[53] Sulfur heterocycles are prepared similarly to nitrogen heterocycles.[54]

Selenium reagents can be used to form carbocycles. A good example of the formation of carbocycles is the elegant synthesis of hirsutene (equation 31). The key step involves the attack of an enol on a seleniranium ion. This type of carbocyclization proceeds very nicely and in high yield.[55]

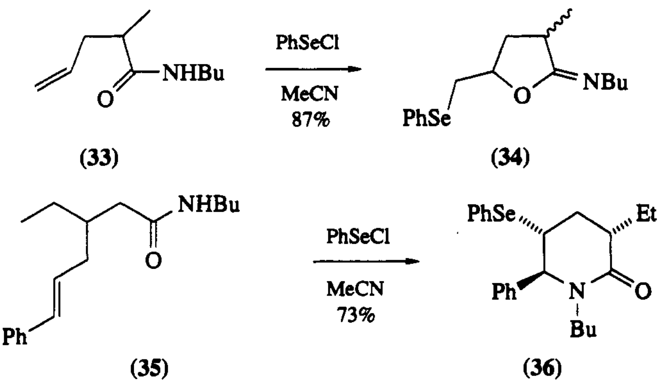

(33) (34) (35) (36)

**Scheme 5**

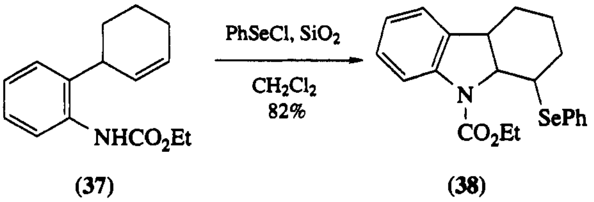

(37) (38) (30)

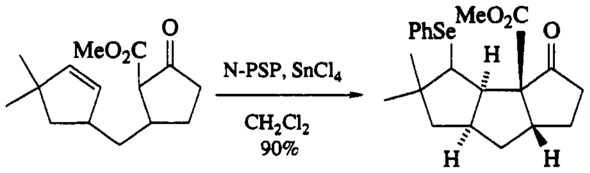

(31)

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# 3.7

# Addition Reactions with Formation of Carbon–Halogen Bonds

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## 3.7.1 OXIDATIVE HALOGENATION WITH HALOMETALLIC REAGENTS

Transition metal species play an important role in oxidative halogenation of alkenes, leading to halogenated compounds.[1] Certain oxo-metal compounds, *e.g.* $CrO_2Cl_2$, $VOCl_3$, $MoCl_5$ and $SbCl_5$, are advantageous for this type of halogenation. Chromyl chloride ($CrO_2Cl_2$), especially, reacts in unique ways with alkenes, to which its oxygen and halogen atoms transfer. The reaction proceeds *via* initial attack at the metal center. On the other hand, molecular halogens and halide salts, when combined with oxidizing agents such as $CrO_3$, $Cu(OAc)_2$ and $Pb(OAc)_4$, are capable of converting alkenes to halohydrins and α-halo ketones. Manganese(III) and iron(III) reagents are also beneficial for oxidative halogenation of alkenes through a radical process.

The oxidation of alkenes with $CrO_2Cl_2$ (1.3 equiv.) in $CH_2Cl_2$ at –78 °C proceeds in a *cis* stereospecific manner to produce the corresponding chlorohydrin and epoxide. Typically, (*E*)-cyclododecene (**1**; equation 1) gives the corresponding *cis*-chlorohydrin (**2**; 60%), epoxide (**3**; 20%), α-chloro ketone (**4**; 8%) and others (7%).[2] In contrast, the reaction with 2 equiv. of $CrO_2Cl_2$ in acetone gives preferentially the α-chloro ketones (**5**) and (**6**; equation 2).[4] *cis*-Chlorohydrin acetate (**7**) is formed similarly in a

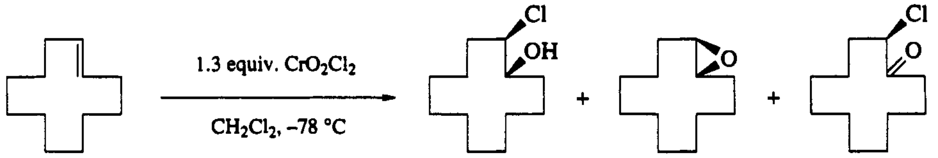

(1)

**(1)** **(2)** 60% **(3)** 20% **(4)** 8%

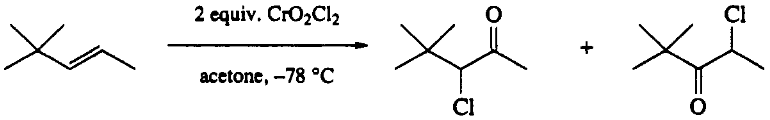

(2)

**(5)** 54% **(6)** 6%

$CH_2Cl_2/AcCl$ (2:1) system as shown in equation (3).[3] This procedure provides a method which may avoid the over-oxidation of products. Sharpless has proposed a chromyl chloride–alkene π-complex as an intermediate in terms of its *cis* addition. A coordinated alkene (**8**) probably adds to a chlorine–chromium bond to produce an alkylchromium intermediate (**9**; *cis* chlorination), which gives chlorohydrin (**12**) by migration of the alkyl group from chromium to oxygen *via* a chromium derivative (**11**) together with dichloride (**10**) by reductive elimination, as shown in Scheme 1.[2] Migration of the O—Cr bond of the C—Cr complex (**13**) occurs with retention of configuration, giving the epoxide (**15**). *trans*-Chlorohydrin and a ketone are produced by an acid-catalyzed ring opening of the epoxide with either HCl or Lewis acidic chromium species.[5,6]

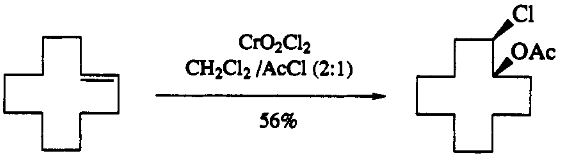

(7) (3)

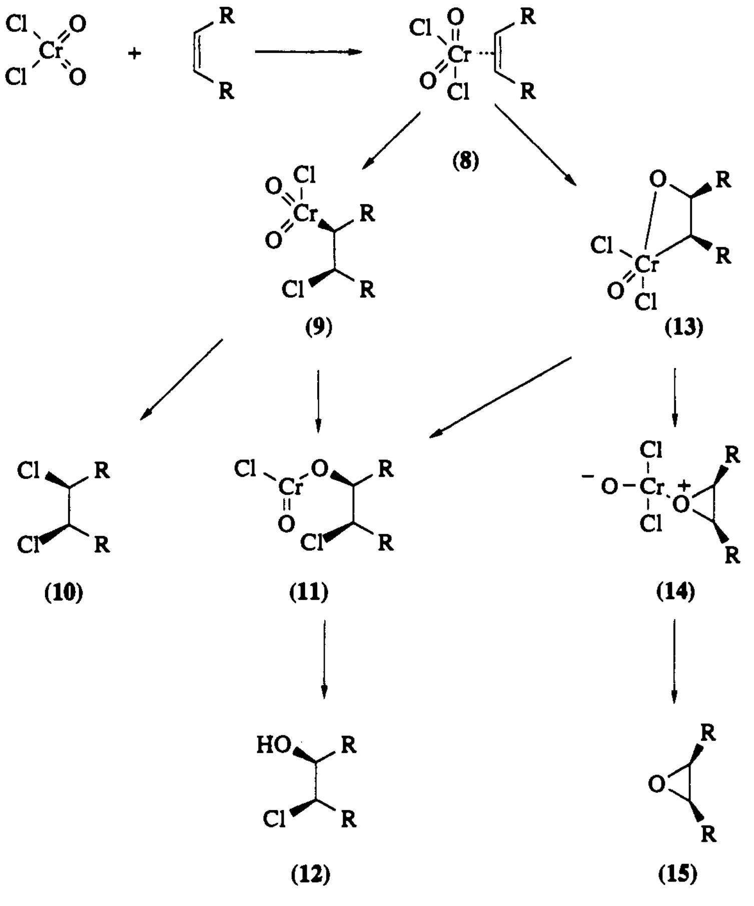

**Scheme 1**

Norbornadiene can be oxidized with chromyl chloride to give *cis*-1,2-chlorohydrin (**16**; 50%) and rearrangement product (**17**; 37%; equation 4). Thus, chromyl chloride oxidation of norbornadiene generates partially a species of sufficient carbenium ion character to promote the Wagner–Meerwein rearrangement.[7] Similarly, the oxidation of norbornene at –80 °C affords the corresponding *exo-cis*-chlorohydrin (63%), 3-*exo*-chloronorcamphor (11%) and norcamphor (3.1%; equation 5).[8] The chromyl chloride oxidation procedure can be successfully applied to the formation of aldehydes from *exo*-alkenes in monoterpenoid synthesis, *e.g.* the conversion of (**18**) to (**19**) in good yield, by the combination of zinc dust reduction (equation 6).[9] Chromyl fluoride, prepared from $CrO_3$ and cobalt(III) fluoride at 450 °C,[10] can react with ergosteryl acetate (**20**) to give 5α-hydroxy-6α-fluoro derivatives (**21**) in 43% yield (equation 7).[11] However, the oxidation of other steroid alkenes with $CrO_2X_2$ (X = Cl, F) is affected by the structure of substrates. For example, cholesteryl acetate (**22**), when treated at –70 to –30 °C, produces 3β-acetoxy-5α-chlorocholestan-6-one (**23**; 12%), a mixture of α- and β-cholesteryl acetate epoxides (**24**; 4%), 3β-acetoxy-6β-chlorocholestan-6α-ol (**25**; 9%) and 3β-acetoxy-5α-chlorocholestan-6β-ol (**26**; 18%; equation 8).[11]

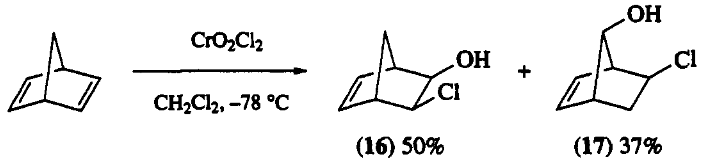

$CrO_2Cl_2$
$CH_2Cl_2$, –78 °C
OH
Cl
+
OH
Cl
(**16**) 50%
(**17**) 37%

(4)

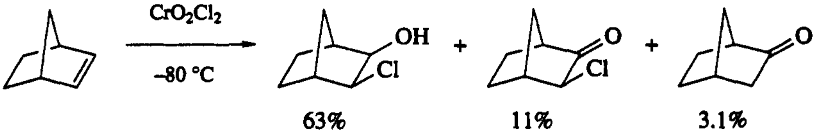

$CrO_2Cl_2$
–80 °C
OH
Cl
+
O
Cl
+
O
63%
11%
3.1%

(5)

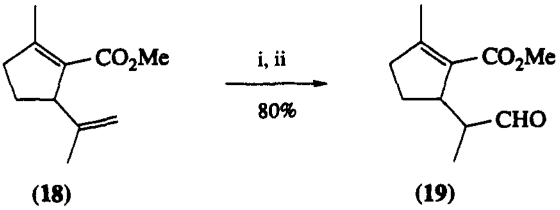

$CO_2Me$
i, ii
80%
$CO_2Me$
CHO
(**18**)
(**19**)

(6)

i, $CrO_2Cl_2$; ii, Zn, $H_2O$

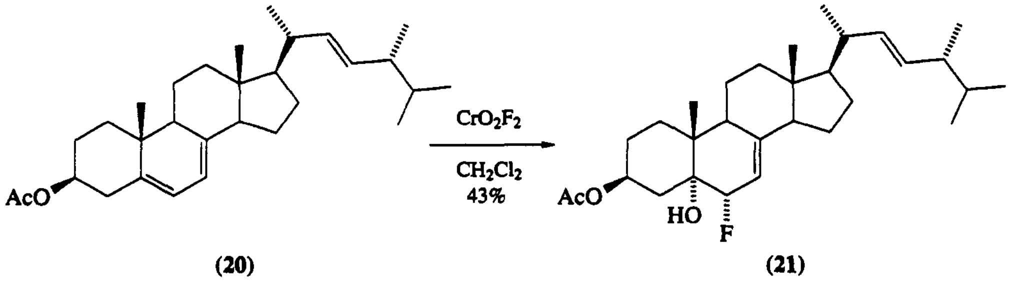

AcO
$CrO_2F_2$
$CH_2Cl_2$
43%
AcO
HO
F
(**20**)
(**21**)

(7)

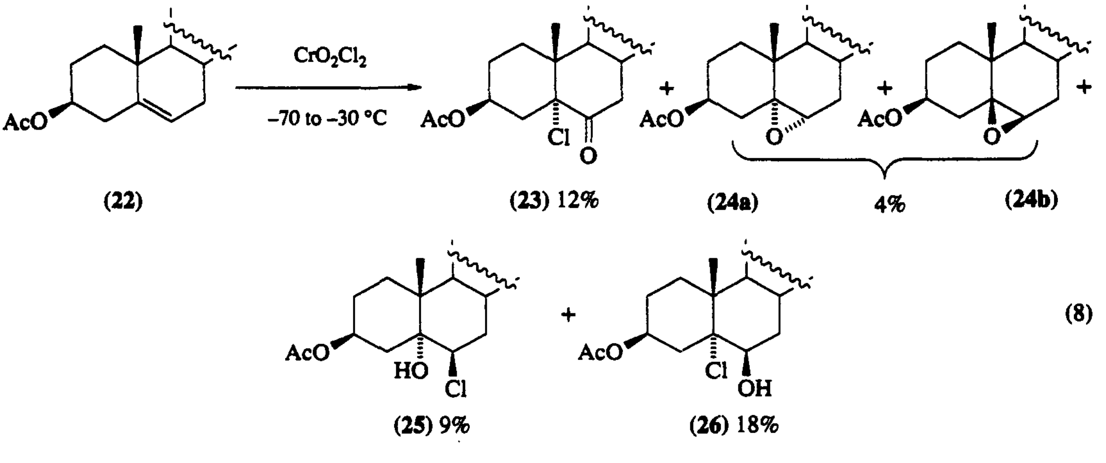

AcO
$CrO_2Cl_2$
–70 to –30 °C
AcO
Cl
O
+
AcO
O
+
AcO
O
+
(**22**)
(**23**) 12%
(**24a**)
4%
(**24b**)
AcO
HO
Cl
+
AcO
Cl
OH
(**25**) 9%
(**26**) 18%

(8)

Perrhenyl chloride ($ReO_3Cl$) can react with alkenes to produce *cis*-chlorohydrins, while $CrOCl_3$,[2] $MnOCl_3$[2] and $VOCl_3/POCl_3$[12] result in chlorination.

The silver chromate–iodine[13] or pyridinium chlorochromate–iodine[14] reagents can be used for the oxidation of double bonds, leading to the corresponding α-iodo ketones. In the case of the former reagent, the nucleophilic addition of a hypoiodous chromic acid mixed anhydride (**27**) probably produces α-iodo ketones (**28**) in an analogy to a Prevost reaction (Scheme 2). The oxidation of trisubstituted alkenes by use of iodine and pyridinium dichromate (PDC) produces the corresponding iodohydrin (**29**) in a regioselective and stereospecific manner (equation 9).[15] α-Chloro ketones (**30**) are also obtained in 60–90% yields by the oxidation of di- and tri-alkyl-substituted alkenes with a $CrO_3$/TMS-Cl/$CCl_4$ system, whose selectivity and yields are superior to those in the chromyl chloride system (equation 10). In this conversion, polyoxochromium dichloride $[Cl(CrO_2)_nCl]$ is postulated as an active oxidizing species.[16]

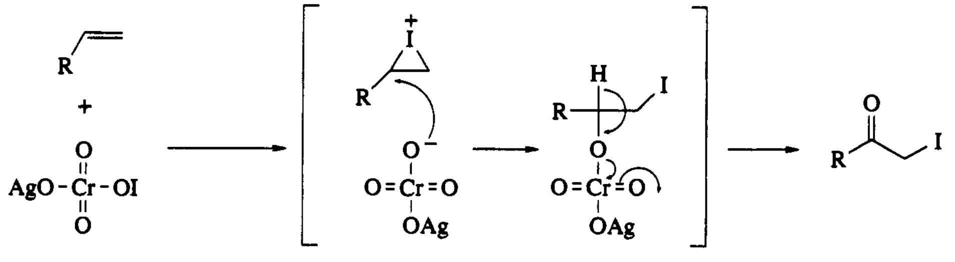

**(27)** **(28)** 60–80%

**Scheme 2**

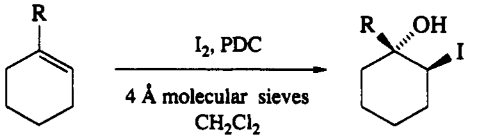

**(29)** 50–60%

(9)

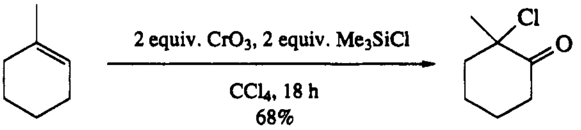

**(30)**

(10)

Halogenation of enol ethers and enol esters, leading directly to α-halo ketones is realized by use of molecular halogen or halide salts and metal oxidants. Pyridinium chlorochromate $(PCC)/I_2$,[17] $CrO_3$/TMS-Cl/$I_2$,[18] $AgOAc/I_2$,[19] $TlOAc/I_2$,[20] $Pb(OAc)_4$ and metal halides[21] and $Cu(OAc)_2/I_2$[22] are useful classes of reagents for this conversion, and some examples are listed in Table 1.

Antimony(V) chloride ($SbCl_5$)[23,24] and molybdenum(V) chloride ($MoCl_5$)[25,26] can react spontaneously with alkenes to give predominantly the corresponding *cis*-1,2-dichlorides (equation 11). The reaction probably proceeds through a successive insertion and reductive elimination sequence. The chlorination of butadiene with $SbCl_5$[24] and copper(II) chloride[27] results preferentially in the formation of (*Z*)- and (*E*)-1,4-dichloro adducts,[24] while the reaction with chlorine gives an 1:1 mixture of 1,2- and 1,4-adducts, as shown in Table 2 and equation (12).[28] The formation of (*Z*)-1,4-dichloro-2-butene may be ascribed to a transition state as shown in Scheme 3.

Enol silyl ethers can lead to α-chloro ketones on treatment with anhydrous copper(II) chloride in DMF or iron(III) chloride in acetonitrile (equation 13, Table 1).[29] The chlorination of (**36**; equation 14) proceeds through a cation radical intermediate formed by an electron-transfer process with metal halides.

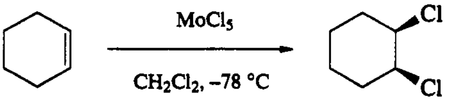

**(31)**

(11)

**Table 1** Halogenation of Enol Ethers and Esters with Metallic Reagents

| *Alkene* | *Reagents and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 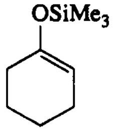 | | 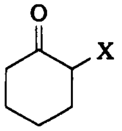 | | |
| | 2 equiv. PCC, 1 equiv. $I_2$, $CH_2Cl_2$ | X = I | 76 | 17 |
| | 2 equiv. $CrO_3$/ClSiMe$_3$, 1.5 equiv. $I_2$ | X = I | 83 | 18 |
| | 1 equiv. AgOAc, 1 equiv. $I_2$, $CH_2Cl_2$ | X = I | 84 | 19 |
| | 1 equiv. TlOAc, 1 equiv. $I_2$, AcOH | X = I | 46 (11) | 20 |
| | 3.3 equiv. $Pb(OAc)_4$, 2.2 equiv. NaBr, MeOH | X = Br | 47 | 21 |
| | 3.3 equiv. $Pb(OAc)_4$, 2.2 equiv. NaI, MeOH | X = I | 87 | 21 |
| | 3 equiv. $CuCl_2$, DMF | X = Cl | 58 | 22 |
| | 5 equiv. $FeCl_3$, DMF | X = Cl | 52 | 22 |
| 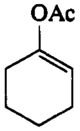 | | 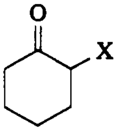 | | |
| | 3.3 equiv. $Pb(OAc)_4$, 2.2 equiv. NaBr, MeOH | X = Br | 82 | 21 |
| | 3.3 equiv. $Pb(OAc)_4$, 2.2 equiv. $CuCl_2$, MeOH | X = Cl | 99 | 21 |
| 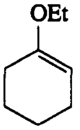 | | 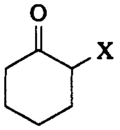 | | |
| | 3.3 equiv. $Pb(OAc)_4$, 2.2 equiv. NaBr, MeOH | X = Br | 90 | 21 |
| 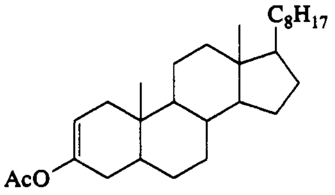 | | 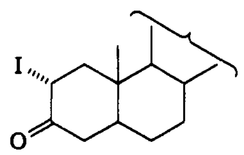 | | |
| | 1.1 equiv. $Cu(OAc)_2$, 1.1 equiv. $I_2$, AcOH | | 71 | 22 |

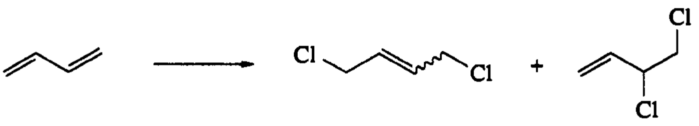

(32) (33)

(12)

**Table 2** Halogenation of 1,3-butadiene

| *Reagent* | *Solvent* | *1,4-Adduct:1,2-Adduct* | *Ref.* |
|---|---|---|---|
| $Cl_2$ | $CH_2Cl_2$ | 43.5:56.5 | 28 |
| $SbCl_5$ | $CH_2Cl_2$ | 62:38 | 24 |
| $CuCl_2$ | MeCN | 85:15 | 27 |

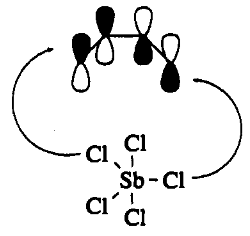
Cl
Cl
Sb - Cl
Cl
Cl

**Scheme 3**

The reaction of indole (**38**) with copper(II) chloride also proceeds through a cation radical intermediate (**39**) to give mainly 2-chloroindole (**40**), together with a dimeric by-product (**41**), as shown in equation (15).[30]

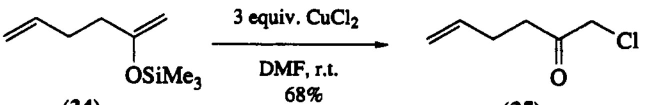
OSiMe3
3 equiv. CuCl2
DMF, r.t.
68%
Cl
O

(**34**) (**35**) (13)

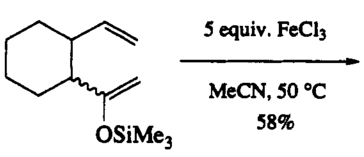
OSiMe3
5 equiv. FeCl3
MeCN, 50 °C
58%
Cl
O

(**36**) (**37**) (14)

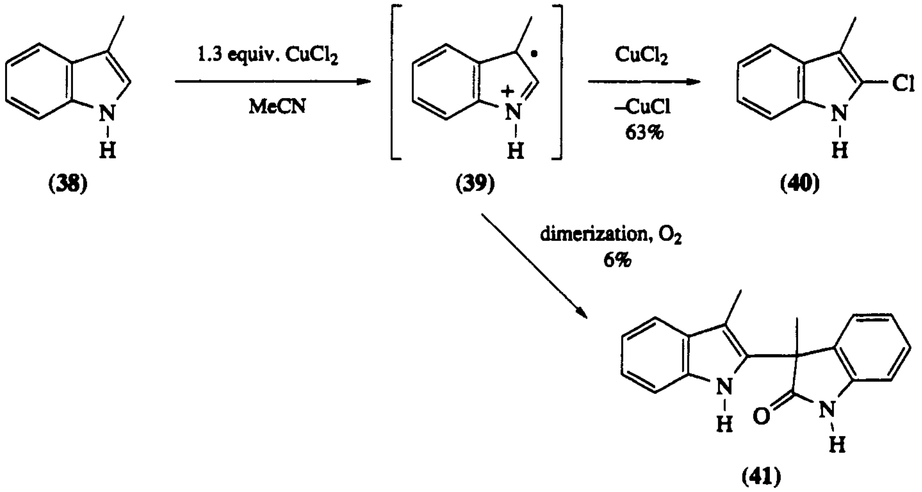
N
H
1.3 equiv. CuCl2
MeCN
+
N
H
CuCl2
–CuCl
63%
Cl
N
H
dimerization, O2
6%
N
H
O
N
H

(**38**) (**39**) (**40**) (**41**) (15)

Manganese(III) acetate or chloride salts [$Mn_3O(OAc)_7HOAc$, $MnCl_3$] can react with alkenes to afford 1,2-dichlorides and chlorohydrin acetates (equation 16).[31] The manganese(III) reagent promotes the chlorination of 1,6-heptadiene (**42**) to afford almost equal amount of open chain and cyclized dichlorides

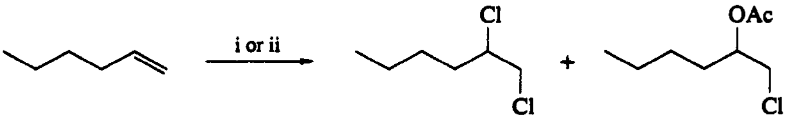
i or ii
Cl
Cl
+
OAc
Cl

(16)

| | | |
|---|---|---|
| i, [$Mn_3O$]/$CaCl_2$, AcOH, 110 °C | 81% | - |
| ii, $MnCl_3$, AcOH, 25 °C | 52% | 11% |

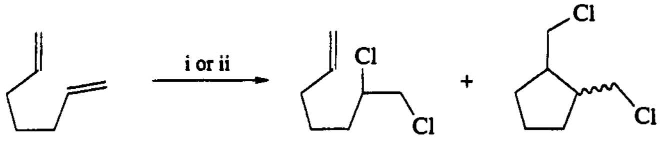

(17)

**(42)** **(43)** **(44)**

i, $[Mn_3O]/CaCl_2$, AcOH, 110 °C 40.9:1

ii, $MnCl_3$, AcOH, 25 °C 1.12:1

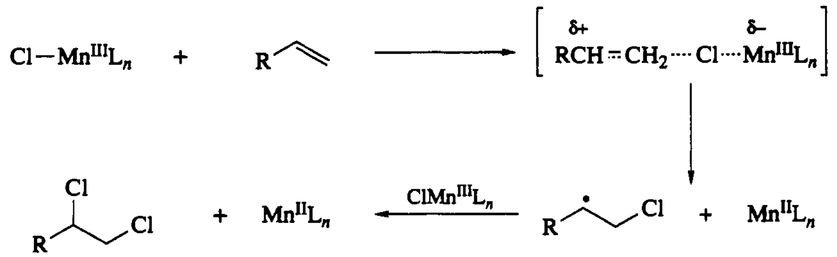

Scheme 4

(43) and (44; equation 17), depending on reaction conditions, which suggests the mechanism involving the radical intermediate as shown in Scheme 4.

Oxidation of pregnenolene (45) with Bornstein's reagent $[PbF_2(OAc)_2]$ or $Pb(OAc)_4$–HF (1:4) produces an organolead complex (46), and the subsequent treatment with bromine gives a 6β-bromo-5α-fluoro derivative (47), a reversed regiochemical bromofluoro isomer which can be obtained by a usual FBr-releasing reagent (equation 18).[32]

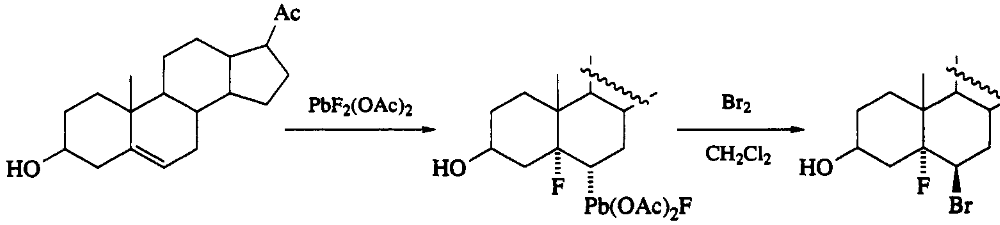

(18)

**(45)** **(46)** **(47)** 95%

Direct synthesis of α-bromo ketones from alkenes is carried out by use of sodium bromite ($NaBrO_2$).[33] The reaction proceeds *via* the bromohydrin (48) as intermediate (equation 19).

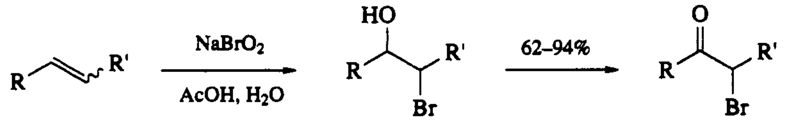

(19)

**(48)**

## 3.7.2 HALOFUNCTIONALIZATIONS WITH $Hg^{II}$, $Tl^{III}$ AND $Te^{IV}$ REAGENTS

1,2-Bifunctionalization of alkenes has been performed by the reaction of mercury(II) salts (chloride, fluoride, nitrate, *etc.*) and halogens ($Br_2$ or $I_2$) with alkenes, through the addition of halogen and mercury(II) salt anion.[34–36] The mercury(II) salt–halogen combination method provides a potential method for the preparation of a variety of 1,2-bifunctionalized organic halides. For instance, the reaction of alkenes with bromine or iodine and different mercury(II) salts ($HgX_2$; X = F, Cl, Br, $HCO_2$, AcO, $CF_3CO_2$, $EtCO_2$, $PhCO_2$, $NO_3$, $MeSO_3$, $4\text{-}MeC_6H_4SO_3$, SCN or $4\text{-}MeC_6H_4SO_2$) in $CH_2Cl_2$ affords the corresponding 1,2-bifunctionalized products (49) as shown in equation (20). β-Bromoalkyl nitrates (50) are formed by treating alkenes with mercury(II) nitrate and bromine, in which the alkenes react rapidly and reversibly with mercury(II) nitrate to give β-nitratoalkylmercury(II) nitrates which undergo brominolysis to give the product (**50**; equation 21).[35,37] Nitromercuration of alkenes followed by demercuration of the resulting (**51**) produces nitroalkenes as shown in equation (22).[38] This nitration of alkenes is improved by using nitryl iodide prepared from $AgNO_2$ and $I_2$ (equation 23).[39]

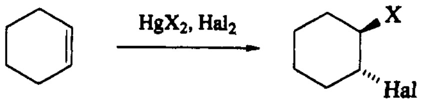
HgX2, Hal2
X
Hal

(**49**)

(20)

$X = F, Cl, Br, RCO_2, NO_3, RSO_3, SCN$, *etc.*; Hal = Br, I

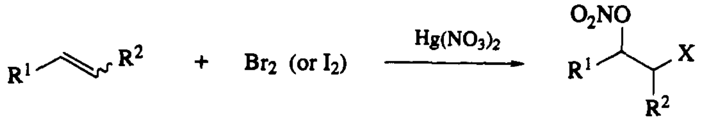
R1
R2
+
Br2 (or I2)
Hg(NO3)2
O2NO
R1
X
R2

(**50**) X = Br, I

(21)

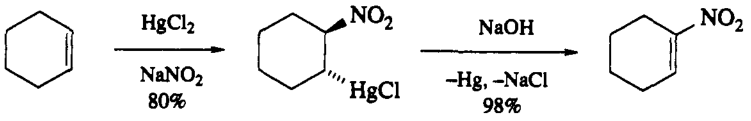
HgCl2
NaNO2
80%
NO2
HgCl
NaOH
-Hg, -NaCl
98%
NO2

(**51**)

(22)

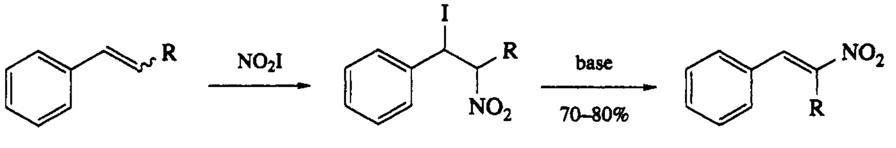
R
NO2I
I
R
NO2
base
70–80%
NO2
R

(23)

The reaction of alkenes with thallium(III) acetate (TTA) forms oxythallium adducts (**52**) in a similar manner to the case of oxymercuration. The thallium moiety of adducts can be replaced by a halogen atom by heating with copper(I) salts (CuX–KX; X = I, Br, Cl) in acetonitrile (equation 24).[40,41]

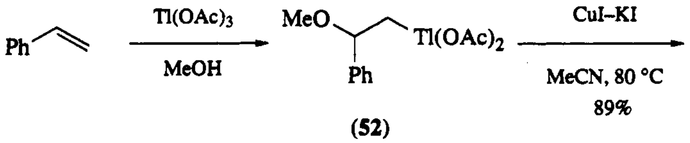
Ph
Tl(OAc)3
MeOH
MeO
Tl(OAc)2
Ph
CuI–KI
MeCN, 80 °C
89%
MeO
I
Ph

(**52**)

(24)

Selenium and tellurium reagents have been used for stereoselective halogenations of alkenes. For example, *trans* addition of benzeneselenenyl chloride to alkenes followed by the displacement of the seleno moiety with chloride can lead to *cis*-1,2-dichlorides (equation 25).[42] The addition of 2-naphthyltellurium trichloride proceeds in an *anti* stereospecific manner (equation 26), whereas tellurium tetrachloride gives a mixture of *syn* and *anti* adducts.[43] The reaction of allyl esters with tellurium tetrachloride accompanies acyl migration to give the 1-(trichlorotelluro)-3-chloro adduct (**54**; equation 27).[44]

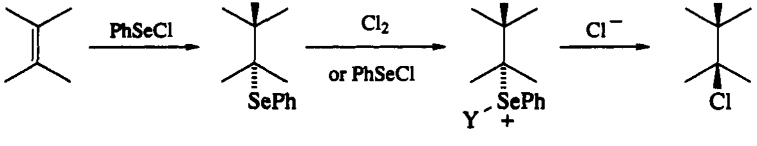
PhSeCl
Cl
SePh
Cl2
or PhSeCl
Cl
Y-
SePh
+
Cl−
Cl
Cl

Y = Cl, PhSe

(25)

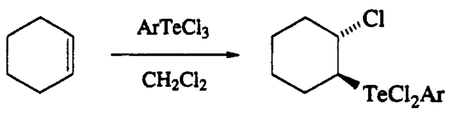
ArTeCl3
CH2Cl2
Cl
TeCl2Ar

**(53)** >97% *anti*

(26)

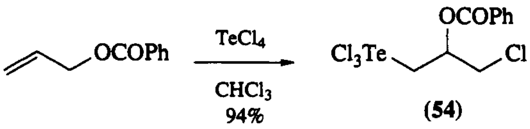
OCOPh
TeCl4
CHCl3
94%
OCOPh
Cl3Te
Cl

**(54)**

(27)

### 3.7.3 OXIDATIVE HALOGENATION WITH NONMETALLIC REAGENTS

Generation of positive-like halogen species *in situ* has been realized by the oxidation of halide salts with *m*-chloroperbenzoic acid (MCPBA). The procedure can be used for haloetherification and lactonization (equation 28).[45] Oxidation of potassium bromide with MCPBA in the presence of 18-crown-6 (10 mol %) produces *m*-chlorobenzoylhypobromite, which adds across the double bond to furnish *trans*-1,2-bromocarboxylates (**55**; equation 29).[46]

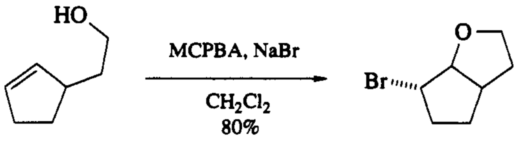
HO
MCPBA, NaBr
CH2Cl2
80%
O
Br

(28)

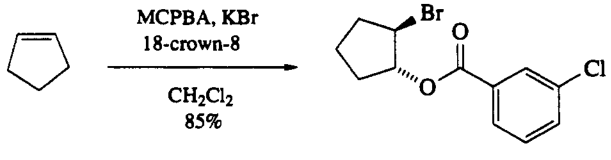
MCPBA, KBr
18-crown-8
CH2Cl2
85%
Br
O
O
Cl

**(55)**

(29)

The fluorination of uracil (**56**) and cytosine (**57**) in a $F_2$/AcOF/aq. AcOH system has been performed *via* a radical cation fluoride complex (**58**). This radical cation intermediate (**58**) is probably formed by an electron transfer due to the action of hypofluorite (AcOF) as shown in Scheme 5.[47]

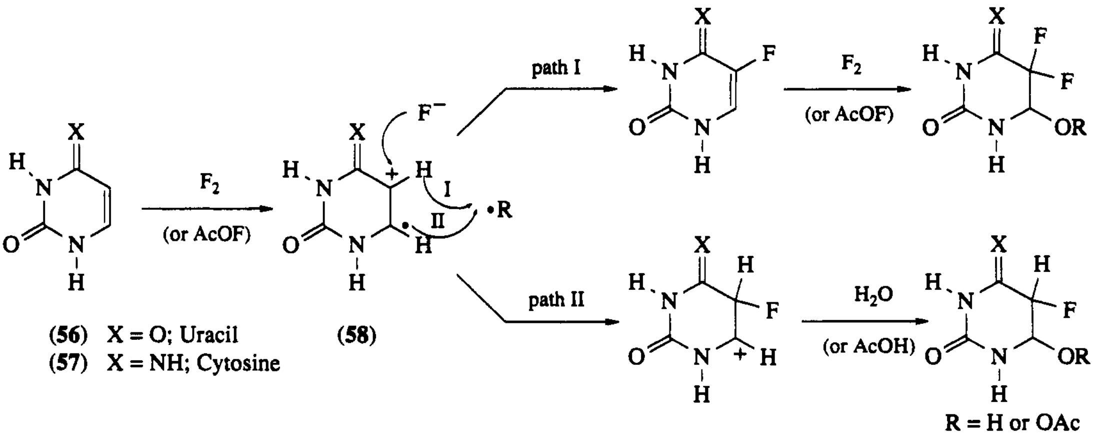
F2
(or AcOF)
F⁻
I
II
•R
path I
path II
F2
(or AcOF)
H2O
(or AcOH)
X
H
N
O
F
OR

**(56)** X = O; Uracil
**(57)** X = NH; Cytosine
**(58)**
R = H or OAc

Scheme 5

Positive halogen complexes with pyridine bases are known as versatile halogenating reagents.[48] Bis(*sym*-collidine)iodine(I) tetrafluoroborate (**59**) in dimethyl sulfoxide is a potential reagent for the direct conversion of alkenes to α-iodo carbonyl compounds (Scheme 6).[49] The oxidation involves the transfer of an iodo cation species to the carbon–carbon double bond, forming a three-membered iodonium ring intermediate. Subsequent nucleophilic addition of DMSO, forming a dimethyloxosulfonium salt, followed by proton abstraction with collidine gives the α-iodo carbonyl compound (Scheme 6). Glycals (**60**) can be converted into the corresponding α-iodo-α,β-unsaturated lactones (**61**) with this reagent (equation 30). On the other hand, the reaction of alkenes with this reagent (**59**) in $CH_2Cl_2$ results in the formation of 1,2-iodofluorides.[50]

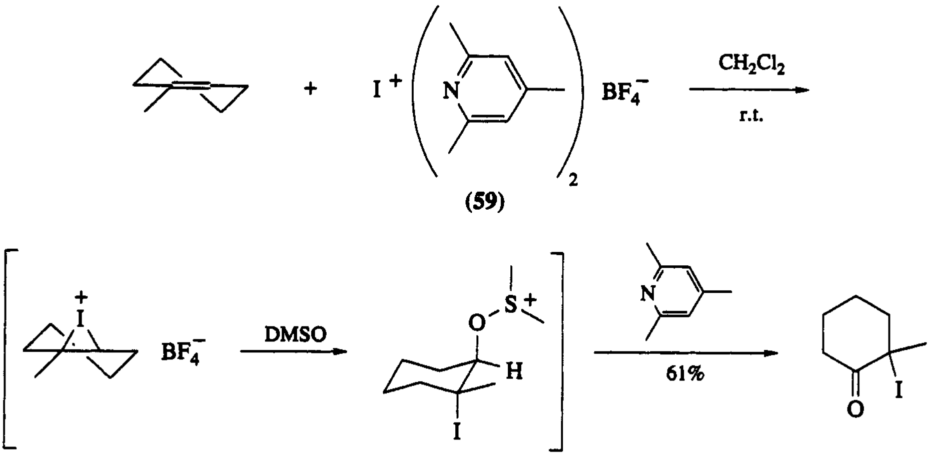
I⁺
N
2
BF₄⁻
CH₂Cl₂
r.t.
(59)
I
BF₄⁻
DMSO
O
S
H
I
N
61%
O
I

**Scheme 6**

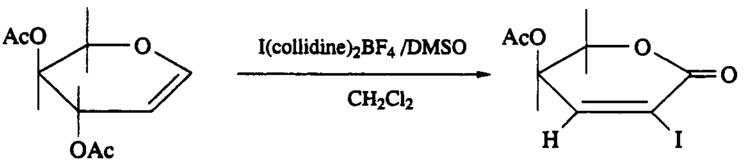
AcO
O
OAc
I(collidine)₂BF₄ /DMSO
CH₂Cl₂
AcO
O
O
H
I

**(60)** **(61)** (30)

Intramolecular bromoalkylamine addition to alkenes has been performed by using bis(*sym*-collidine)bromine(I) perchlorate (**62**; equation 31).[51] The method plays an important role in the key step of (±)-sporamine synthesis (**63**) → (**65**). The reaction of $I(py)_2BF_4$ and alkenes in the presence of nucleophiles produces 1,2-bifunctionalized iodo compounds (equation 32).[52] The reaction of 1,3-dienes with $I(py)_2BF_4$ allows the regiospecific 1,2-addition of iodine and a nucleophile to terminal dienes to give (**69**; equation 33) and the 1,4-addition to internal 1,3-dienes to give (**70**; equation 34).[53] 1,4-Addition with this reagent is enhanced by the addition of tetrafluoroboric acid. Iodine-induced cyclization of arylalkene system (**71**) occurs with this reagent as shown in equation (35).[54,55]

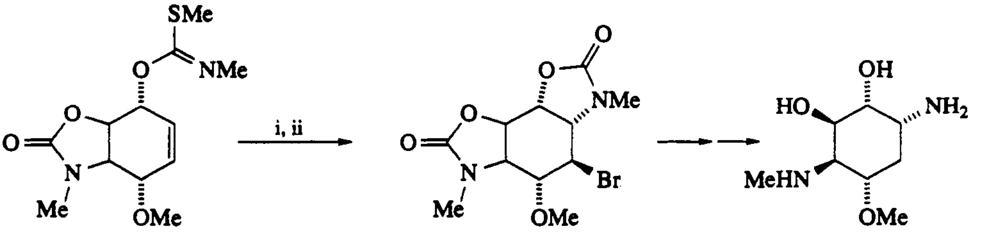
SMe
O
NMe
O
O
N
Me
OMe
i, ii
O
O
NMe
O
O
N
Me
Br
OMe
OH
HO
NH₂
MeHN
OMe

**(63)** **(64)** **(65)** (31)

i, $Br(collidine)_2ClO_4$ (**62**); ii, $Na_2CO_3$, $H_2O$

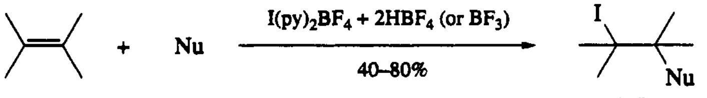
+
Nu
I(py)₂BF₄ + 2HBF₄ (or BF₃)
40–80%
I
Nu

**(66)** **(67)** (32)

Nu = $F^-$, $Cl^-$, $Br^-$, $NO_2^-$, $OCN^-$, MeOH, AcOH, MeCN

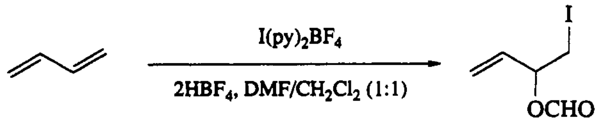
I(py)2BF4
2HBF4, DMF/CH2Cl2 (1:1)
I
OCHO

(68) (69) 30% (33)

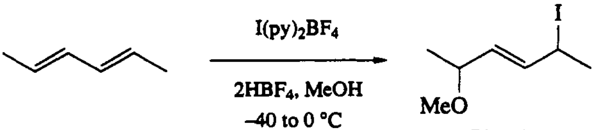
I(py)2BF4
2HBF4, MeOH
–40 to 0 °C
I
MeO

(70) 90% (34)

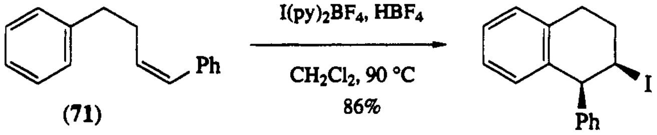
Ph
I(py)2BF4, HBF4
CH2Cl2, 90 °C
86%
I
Ph

(71) (72) (35)

Chloramine T (CT) is a powerful positive chlorine releasing reagent toward alkenes in acetic acid, giving mainly a *trans*-chlorohydrin acetate (**73**) as shown in Scheme 7. The similar reaction in an acetone/$H_2O$(1:1)/$H_2SO_4$ system under reflux produces chlorohydrins in moderate yields.[56,57]

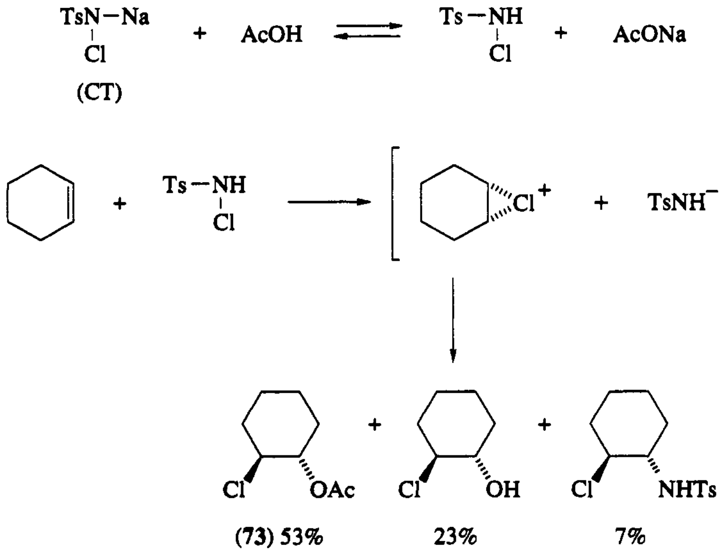
TsN–Na
Cl
(CT)
+
AcOH
Ts–NH
Cl
+
AcONa
+
Ts–NH
Cl
Cl+
+
TsNH−
+
+
Cl
OAc
Cl
OH
Cl
NHTs
(73) 53%
23%
7%

Scheme 7

The ene-type chlorination, specific with this halogen atom, of alkenes would account for a somewhat different mode of halogen addition, giving useful allylic chlorides. Efficient and convenient reagents and methods developed are dichlorine monoxide ($Cl_2O$; equation 36),[58] *t*-butyl hypochlorite,[59] and electrochemical reactions with chloride ion (equation 37).[60] The ene-type chlorination proceeds smoothly with 1,1-disubstituted alkenes (**74**) and (**76**) to give (**75**) and (**77**). Especially, dichlorine monoxide is a potential reagent for complex molecules such as penicillin and cephalosporin derivatives.[58]

Electrooxidation of halide salts is quite useful for the generation of reactive species of halogen atoms under mild conditions.[61] Functionalization of alkenes involving the formation of halohydrins, 1,2-halides, α-halo ketones, epoxides, allylic halides and others has been achieved by electrochemical reactions and is well documented in the literature.[62] On the other hand, electrogenerated carbenium ions can be captured by nucleophilic halide anions, providing a new route to halogenated compounds

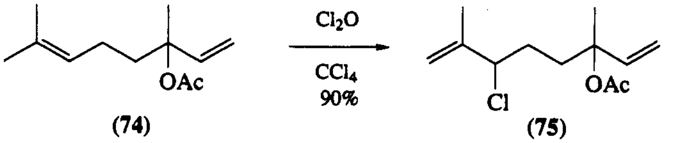
OAc
(74)
$Cl_2O$
$CCl_4$
90%
Cl
OAc
(75)

(36)

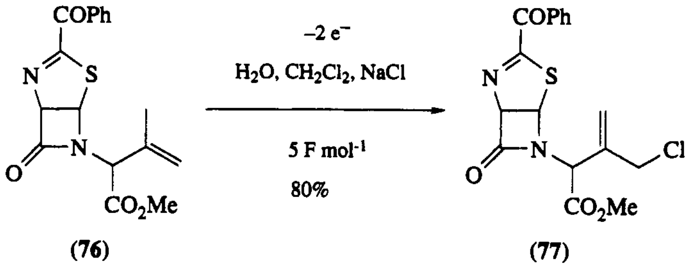
COPh
N
S
O
N
$CO_2Me$
(76)
–2 e⁻
$H_2O$, $CH_2Cl_2$, NaCl
5 F mol⁻¹
80%
COPh
N
S
O
N
Cl
$CO_2Me$
(77)

(37)

(Scheme 8). For instance, the fluorination at the position α of ketones has been realized by the anodic oxidation of enol acetates (**78**) in an MeCN/$Et_3N{\cdot}3HF$/(Pt) system under potential control, giving α-fluoro ketone (**79**; equation 38).[63]

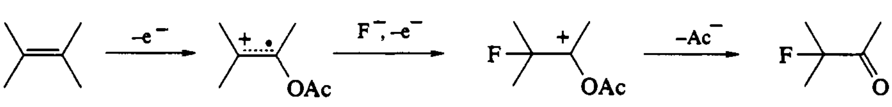
–e⁻
+
OAc
F⁻, –e⁻
F
+
OAc
–Ac⁻
F
O

**Scheme 8**

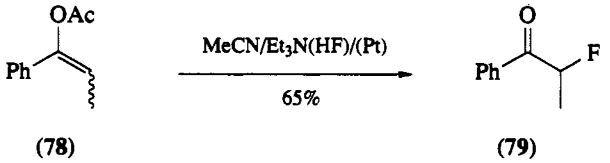
OAc
Ph
(78)
MeCN/$Et_3N(HF)$/(Pt)
65%
O
Ph
F
(79)

(38)

## 3.7.4 MISCELLANEOUS (PHOTOCHEMICAL AND ENZYMATIC REACTIONS)

Photochemically induced oxidative halogenation of alkenes has been carried out in the presence of metal halide/oxygen complexes. The photooxidative halogenation of disubstituted alkenes (**80**; R = H) in a $FeCl_3/O_2$ system can lead to α-chloro ketones (**82**).[64] The initial step of the reaction involves a photoinduced interligand electron transfer from the chlorine ligand to molecular oxygen through the metal ion and alkene molecule. The chlorine radical then adds to the alkene, and successive coupling of the resulting carbon radical with an oxygen radical anion and protonation completes the process (Scheme 9). The

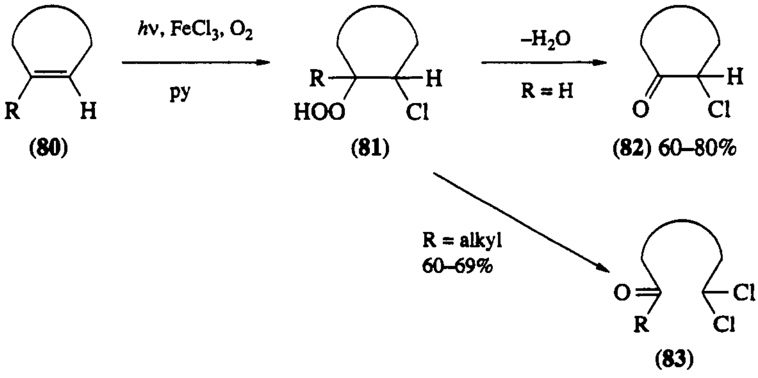
R
H
(80)
hv, $FeCl_3$, $O_2$
py
R
H
HOO
Cl
(81)
–$H_2O$
R = H
H
O
Cl
(82) 60–80%
R = alkyl
60–69%
O
R
Cl
Cl
(83)

**Scheme 9**

hydroperoxides (**81**) further decompose into α-chloro ketones. The metal-catalyzed photooxidation of alkenes is operated with uranyl acetate (1 equiv.) in the presence of bromotrichloromethane (equation 39).[65]

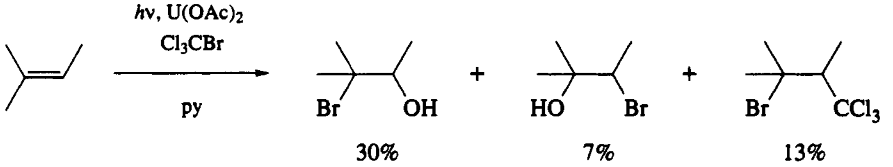

(39)

Semiconductor-mediated photoelectrochemical oxidation of halide salts provides a procedure for the halogenation of alkenes *via* excitated halide species.[66] For example, bromination of cyclohexene has been performed in a $TiO_2/Bu_4NBr$ (or $Ph_3PMeBr$) /$O_2$ system. The reactive bromine species probably arise from a one-electron oxidation of adsorbed bromide ions on the semiconductor by photoirradiation, which produces surface-bound bromine atoms (equation 40).

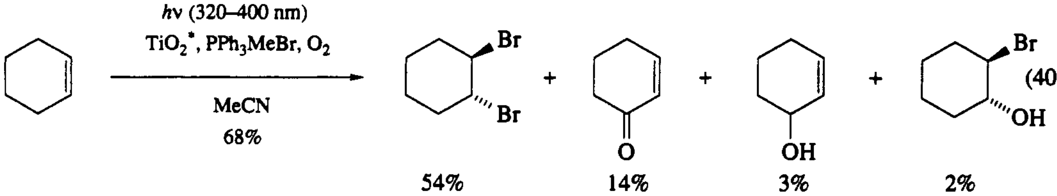

(40)

Enzyme-catalyzed halogenation has been found in biological processes. In the haloperoxidase reaction, halide ions are converted to positive halogen species by hydrogen peroxide. For example, haloperoxidase catalyzes the chlorination, bromination and iodination of cytosine, uracil, *etc.*, to give the corresponding halogenated compounds (**84**; equation 41).[67] The reaction is carried out in a phosphate buffer at pH 3 in the presence of KCl, KBr, or KI by gradually adding $H_2O_2$.

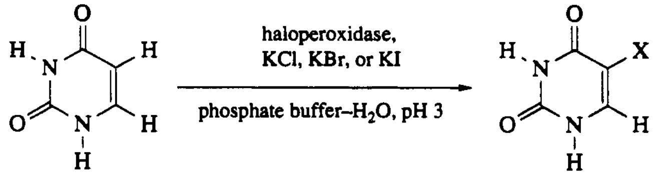

(**84**) X = Cl, Br, I

(41)

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# 3.8

# Cleavage Reactions

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## 3.8.1 INTRODUCTION

Oxidative cleavage is a procedure often employed to degrade large compounds or to introduce different functionality into complex molecules. A number of reagents have been used for this purpose with generally good success.[1–4]

The nature of the products obtained is dependent on the choice of oxidant, the structure surrounding the double bond, the reaction conditions, and the work-up procedures. In general, if the double-bonded carbon is tertiary, then ketones or secondary alcohols can be easily obtained. However, if the carbon is secondary, the products will be primary alcohols, aldehydes or, most likely, carboxylic acids. Because they are very susceptible to further oxidation, the most difficult of these products to obtain are the aldehydes. Selective oxidants and mild conditions are required to produce good yields.

Some procedures result in the introduction of nonoxygen functionalities when cleavage occurs. For example, both nitriles and sulfides can be obtained by the use of appropriate reagents and conditions.

Equations (1)–(5) summarize the types of reactions that will be discussed in this chapter.

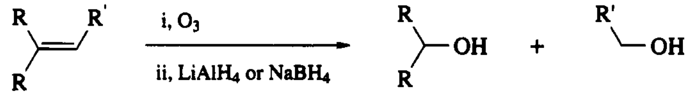
(1)

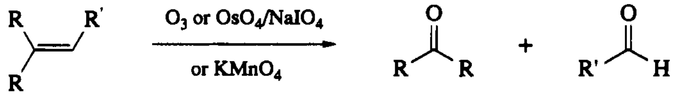
(2)

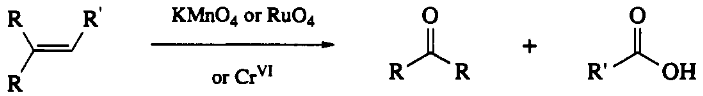
(3)

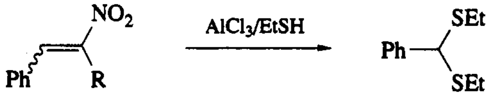
(4)

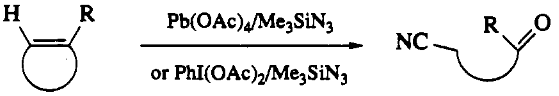
(5)

Transition metal oxidants such as permanganate, ruthenium tetroxide and chromium(VI) oxide are convenient and efficient reagents for routine cleavage reactions. The use of phase transfer catalysts (quaternary ammonium and phosphonium ions, primarily) has made it possible to solubilize transition metal oxides such as permanganate and chromate in nonaqueous solvents, and to thereby increase the scope of these reactions substantially.[5]

Sodium periodate, used along with catalytic amounts of osmium tetroxide, ruthenium dioxide or potassium permanganate, can also be employed to cleave carbon–carbon double bonds. When used with osmium tetroxide, carbonyls are produced; however, the presence of permanganate results in the formation of more highly oxidized products (carboxylic acids) from secondary carbons.

Ozone, while somewhat inconvenient to use, is very specific in its reactions with alkenes.[6–8] It is widely employed for selective synthesis, for qualitative and quantitative analysis of unsaturated compounds, and for studying the position of double bonds in macromolecules. The nature of the products obtained from ozonolysis reactions is determined by the way in which the reaction is carried out. Different work-up procedures (hydrolytic, reductive or oxidative) can be used to produce alcohols, aldehydes, ketones, carboxylic acids or esters.

Oxidative cleavages have been categorized in this chapter according to the products that are produced. Section 3.8.2 describes methods for the cleavage of double bonds to primary or secondary alcohols. Section 3.8.3 describes the formation of carbonyl compounds and Section 3.8.4 those reactions that result in the formation of carboxylic acids, esters, or lactones. Cleavage reactions that give other (nonoxygen containing) functional groups are described in Section 3.8.5. The approach will be to describe sequentially the use of various reagents for these purposes. Each section is followed by a table of representative reactions and a list of references that can be consulted for exact experimental details.

Wherever practical, reaction mechanisms have been used to indicate why the products of a particular reaction can be altered by using different conditions.

## 3.8.2 CLEAVAGE OF CARBON–CARBON DOUBLE BONDS WITH THE FORMATION OF PRIMARY OR SECONDARY ALCOHOLS

In practice, alcohols can always be obtained from the reduction (in a second step) of the products obtained from oxidative cleavage reactions. However, when ozone is used as the cleavage reagent it is possible to obtain alcohols directly without the need to isolate intermediate products.

### 3.8.2.1 Ozone

The use of ozone in organic synthesis has been reviewed by Haines,[1] Below,[6] Razumovskii and Zaikov,[7] Bailey,[8] Kuczkowski,[9] Criegee[10] and Carruthers.[11] Although the details of the reaction of ozone with carbon–carbon double bonds are not all completely understood, there is good evidence that the mechanism proposed by Criegee[10] is fundamentally correct.

The first step, a 1,3-dipolar addition, results in the formation of a 'primary' ozonide (**1**; equation 6). This intermediate then opens to give a carbonyl and a zwitterion that can recombine to give the more stable 'normal' ozonide (**2**; equation 7). Reduction of (**2**), without isolation, by lithium aluminum hydride, diborane or sodium borohydride then gives either primary or secondary alcohols, depending on the nature of starting alkene (equation 8).

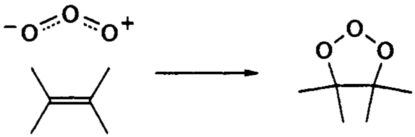

**(1)**

(6)

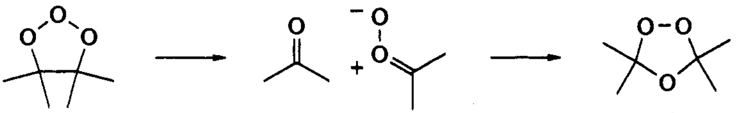

**(2)**

(7)

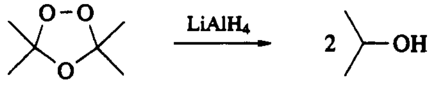

(8)

The cleavage reaction, commonly referred to as 'ozonolysis', is carried out by bubbling ozonized oxygen through a solution of the alkene in various solvents, including methanol,[12] dichloromethane,[13] carbon tetrachloride[14] and ethyl acetate.[15] Other solvents (ethanol, tetrahydrofuran, acetic acid, or a combination of ethyl acetate and hexane) have also been reported for use in individual reactions.[16–20] The reaction is usually performed at low temperatures (about 0 °C), and, since ozonides are potentially explosive compounds, the intermediates are not isolated.

For example, Magari *et al.*[21] have described the preparation of alcohol (**3**) in 90% yield from the corresponding alkene (equation 9). It was found that each mole of ozonide required at least one mole of sodium borohydride for complete reduction to the desired alcohol.

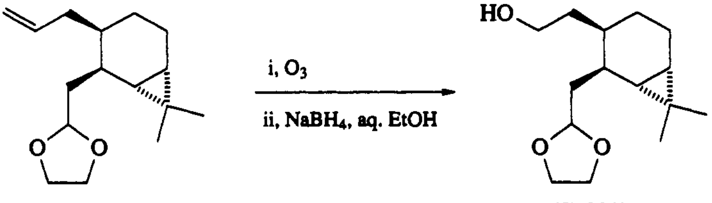

**(3)** 90%

(9)

The reaction can also accommodate other reducible functional groups, such as esters, when sodium borohydride is used as the reducing agent. For example, Dyke *et al.*[22] obtained alcohol (**4**) from the corresponding alkene in 57% yield when using this procedure (equation 10).

Low temperature is required for most reactions, as for example in the preparation of (**5**) recently reported by Boger and Coleman (equation 11).[23]

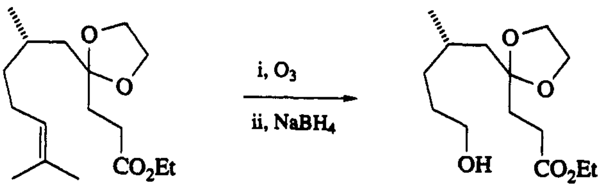

(4) 57%

(10)

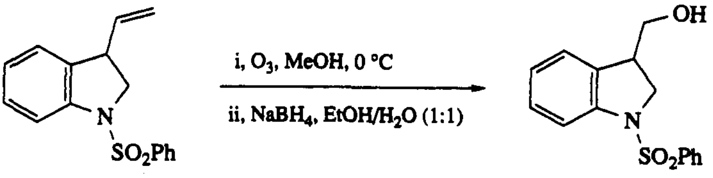

(5)

(11)

In a typical procedure,[23] a solution of 3-vinylindoline (65 mg, 0.23 mmol) in 2.0 mL of methanol was cooled to 0 °C and treated with a stream of 3–8% ozone in oxygen (300 mL min$^{-1}$, 20 min). The reaction mixture was then stirred for an additional 20 min (0 °C) before the excess ozone was removed by passing a stream of nitrogen through the reaction mixture (10 min). Fifty percent aqueous ethanol (1.0 mL) was added at 0 °C, followed by the careful addition of excess sodium borohydride (20 mg, 2.1 mmol). The mixture was allowed to warm up and stirred for 1 h at 23 °C. It was then poured into 10 mL of 10% aqueous HCl and extracted with EtOAc (30 mL). The organic extract was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* and flash chromatography (1 × 15 cm $SiO_2$, 30–100% $Et_2O$/hexane gradient elution) afforded the hydroxymethylindoline (5) in 59% yield (38.6 mg). Other examples of the formation of alcohols from the cleavage of carbon–carbon double bonds by ozone are summarized in Table 1.

## 3.8.3 CLEAVAGE TO CARBONYL COMPOUNDS

The conversion of tetrasubstituted double bonds to the corresponding ketones is easily achieved using a number of oxidants. However, if one or more of the alkenic carbons is secondary, the product will be either an aldehyde or a carboxylic acid. Ozone and a combination of osmium tetroxide and sodium metaperiodate are recommended if the desired product is an aldehyde. Under carefully controlled conditions it is also possible to obtain good yields of the aldehyde when permanganate is used as the oxidant. All methods that give aldehydes from secondary carbons can also be used to prepare ketones from tertiary carbons.

### 3.8.3.1 Ozone

Hydrolysis of ozonides produces carbonyl compounds and hydrogen peroxide, as in equation (12).

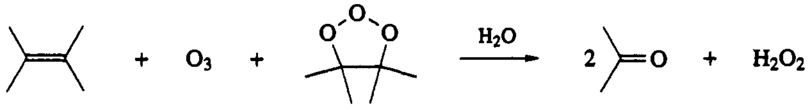

(12)

Since the formation of peroxides is highly undesirable, a mild reductant is usually added to the reaction medium. Many reducing agents including hydrogen and a catalyst, zinc and acetic acid, potassium iodide and acetic acid, sulfides, disulfites, and phosphenes have been used for this purpose.[34–39] However, the most convenient and efficient reagent is dimethyl sulfide (DMS). It is effective under neutral conditions and highly selective for peroxides, but it does have a low boiling point (37 °C) and a rather obnoxious odor. These disadvantages can be overcome by using thiourea instead of DMS as the reducing agent.[40] Yields of aldehydes and ketones are comparable with both reagents.

In a typical experiment,[40] ozonized oxygen (1.22% w/w $O_3$ in $O_2$) was bubbled through a solution of (+)-3-carene (2.74 g, 0.02 mol) in anhydrous methanol (30 mL) at −10 to −15 °C until the required quan-

**Table 1** Cleavage of Carbon–Carbon Double Bonds with the Formation of Alcohols

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 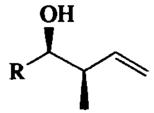 | i, $O_3$, THF, –78 °C, DMS; ii, $LiAlH_4$ | 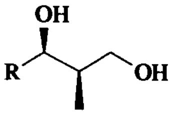 | 79 | 24 |
| 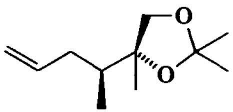 | i, $O_3$, EtOH, –78 °C; ii, DMS, $NaBH_4$, –40 to 25 °C | 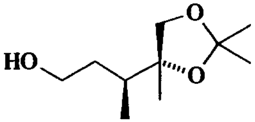 | 87 | 25 |
| 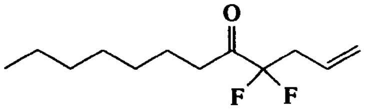 | i, $O_3$, MeOH, –70 °C; ii, $NaBH_4$ | 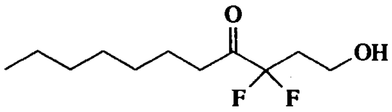 | 90 | 26 |
| 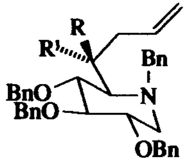 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, $NaBH_4$, EtOH | 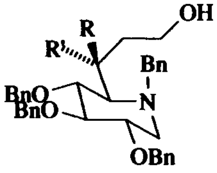 | >55 | 27 |
| 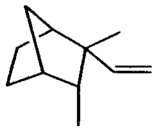 | i, $O_3$; ii, $LiAlH_4$ | 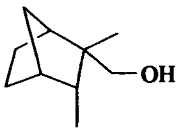 |  | 28 |
| 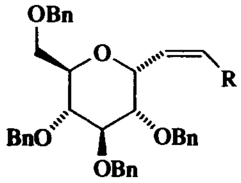 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, $NaBH_4$ | 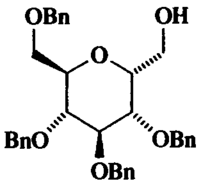 |  | 29 |

Table 1 *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 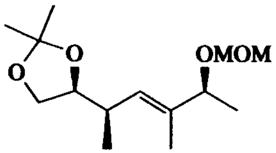 | i, $O_3$, MeOH; ii, $NaBH_4$ | 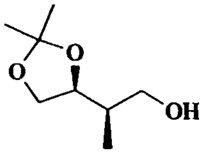 |  | 30 |
| 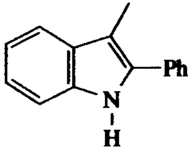 | i, $O_3$; ii, $NaBH_4$, EtOH, 0 °C | 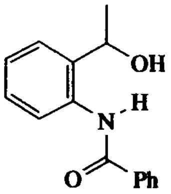 | 75 | 31 |
| 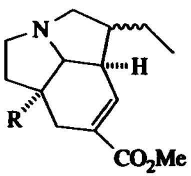 | i, $O_3$, MeOH; ii, $NaBH_4$ | 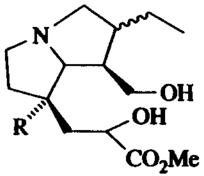 | 63 | 32 |
| 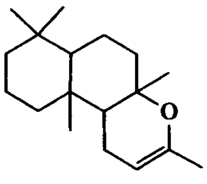 | i, $O_3$, *n*-hexane, −30 °C; ii, $LiAlH_4$ | 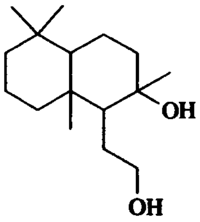 | 75 | 19 |

**Table 1** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 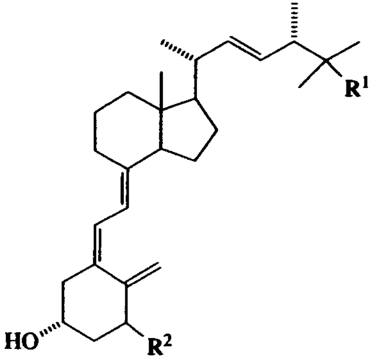 | i, $O_3$, MeOH–Py; ii, $NaBH_4$ | 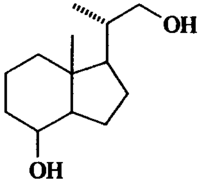 | 85 | 33 |

tity of $O_3$ had been passed (65 min). Nitrogen was then bubbled through the solution for about 10 min and thiourea (0.767 g. 0.01 mol) in dried methanol (3 mL) was added at 0 °C with stirring. Thiourea *S*-dioxide deposited as white crystals. After continued stirring for another 40 min, the mixture was filtered and the filtrate evaporated under reduced pressure (150 mmHg). The residue was dissolved in light petroleum (b.p. 60–80 °C, 60 mL), washed with 1% sodium bicarbonate (10 mL) and water (3 × 10 mL), and dried ($Na_2SO_4$). Distillation of the dried solution gave 2,2-dimethyl-3-(2′-oxo)propylcyclopropane-1-acetaldehyde dimethylacetal. Other examples of this reaction are summarized in Table 2.

Selective cleavage of compounds containing two or more sites of unsaturation can also be achieved by the use of ozone. Some examples are given in Table 3. Optimum yields in these selective cleavages requires use of an appropriate amount of oxidant. Addition of too much ozone with subsequent attack on the second site of unsaturation can be avoided by careful monitoring[9,10] or by use of an appropriate dye as an internal standard. Compounds (**6**) and (**7**) have been used for this purpose by Veysoglu *et al.*[68]

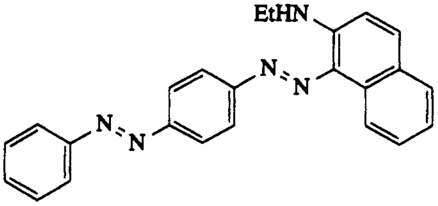

(**6**)

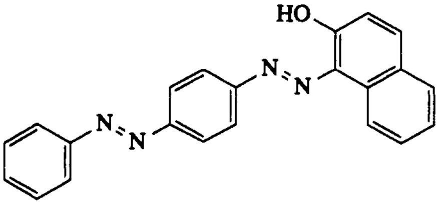

(**7**)

Pyridine has also been used to enhance selectivity.[61,62] When present, reaction occurs at exocyclic rather than at endocyclic double bonds of steroid derivatives, as in equation (13).

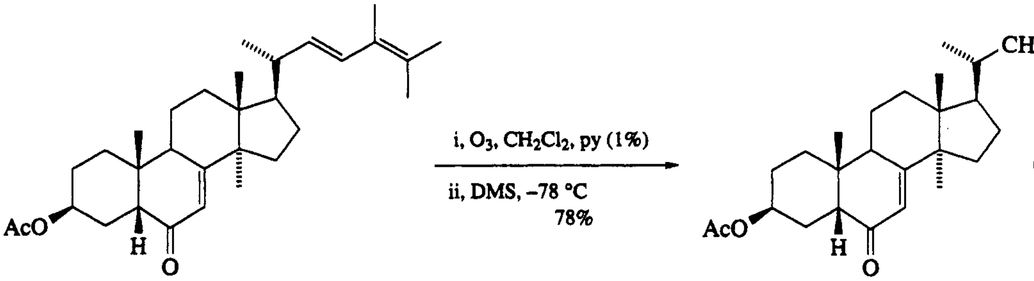

(13)

These reactions are known to benefit from the addition of phase transfer agents under certain conditions. For example, 3,5,5-trimethylcyclohex-2-enone was cleaved, with loss of one carbon atom as illustrated in equation (14), when Adogen 464 (a quaternary ammonium chloride) was present.

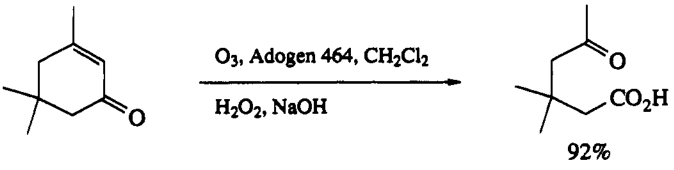

(14)

Ozone adsorbed on silica gel has also been found to be an effective cleavage reagent.[56,76] For example, compound (**8**), which is normally very difficult to cleave, underwent the reaction indicated in equation (15) without loss of chirality.

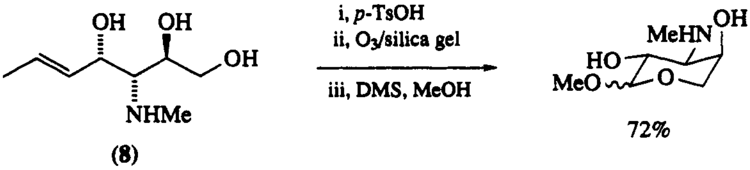

(15)

The product distribution and mechanism of ozonolysis differ when the oxidant is adsorbed on silica gel. When dried silica gel was used, Besten and Kinstle[76] found that the products were similiar to those

**Table 2** Cleavage of Double Bonds with Ozone to give Carbonyl Compounds

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 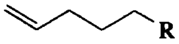 | i, $O_3$, $CH_2Cl_2$, −78 °C; ii, DMS | 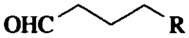 | 80 | 41 |
| 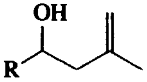 | i, $O_3$, $CH_2Cl_2$, −60 °C; ii, DMS | 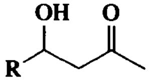 |  | 42 |
| 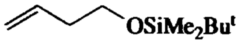 | i, $O_3$, $CH_2Cl_2$; ii, DMS | 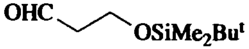 | 73 | 43 |
| 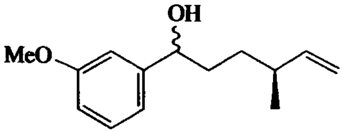 | i, $O_3$, MeOH; ii, DMS | 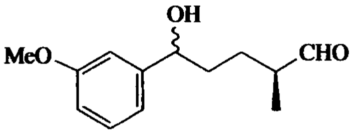 | >42 | 44 |
| 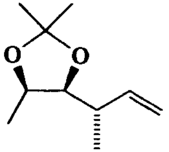 | i, $O_3$, MeOH, −78 °C; ii, $PPh_3$ | 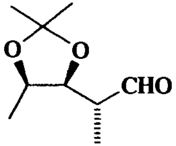 | 85 | 45 |
| 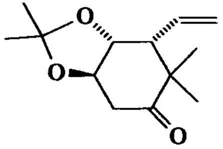 | i, $O_3$, MeOH; ii, DMS | 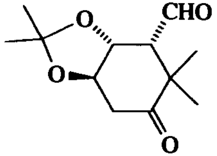 |  | 46 |
| 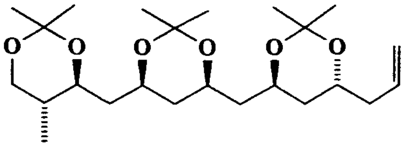 | i, $O_3$, MeOH, −78 °C; ii, DMS, r.t. | 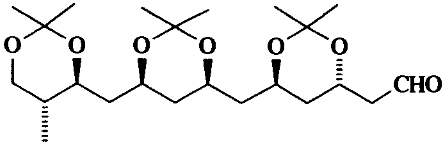 | >84 | 47 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 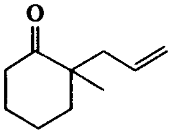 | i, $O_3$, $CH_2Cl_2$; ii, $Et_3N$ | 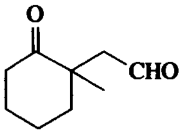 |  | 48 |
| 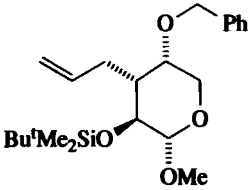 | i, $O_3$, $CH_2Cl_2$, −78°C; ii, $Et_3N$, r.t., 4 h | 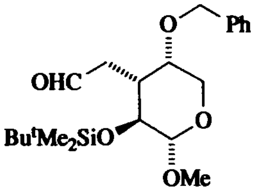 | 93 | 49 |
| 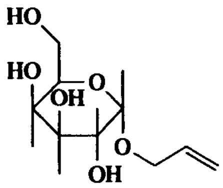 | i, $O_3$; ii, DMS | 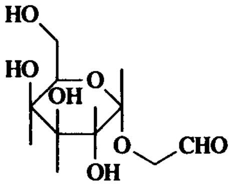 | 70–90 | 50 |
| 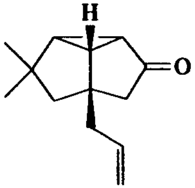 | i, $O_3$, MeOH, −78 °C; ii, DMS, 25 °C | 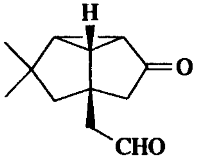 | >55 | 51 |
| 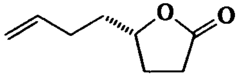 | i, $O_3$, $CH_2Cl_2$/MeOH, −78 °C; ii, DMS, −78 °C, 1 h | 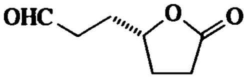 | >57 | 52 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 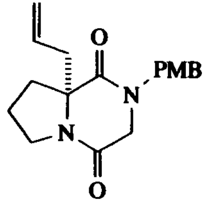 | i, $O_3$, MeOH; ii, DMS | 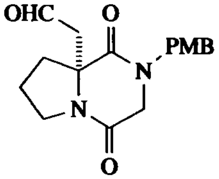 | 99 | 53 |
| 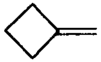 | i, $O_3$, $CH_2Cl_2$/MeOH, –78 °C; ii, S=C($NH_2$)$_2$, $NaHCO_3$, $CH_2Cl_2$, 0 °C | 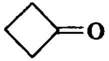 | 71 | 17 |
| 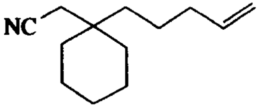 | i, $O_3$, MeOH, –78 °C; ii, DMS, –78 to 25 °C | 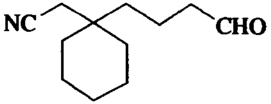 | 63 | 12 |
| 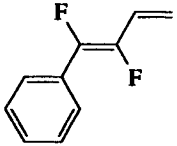 | i, $O_3$, $CH_2Cl_2$, –70 °C; ii, DMS, r.t., overnight | 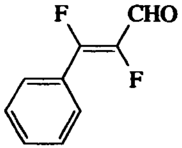 | 64 | 54 |
| 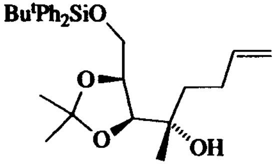 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, $PPh_3$ | 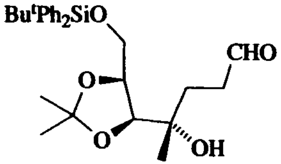 | 90 | 38 |
| 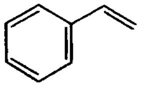 | i, $O_3$, MeOH, –10 to –15 °C; ii, S=C($NH_2$)$_2$ | 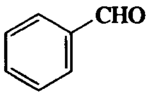 | 81 | 40 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 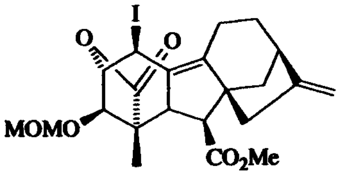 | i, $O_3$, $CH_2Cl_2$–Py, –78 °C, 5 s; ii, DMS | 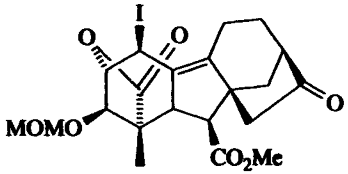 | 68 | 55 |
| 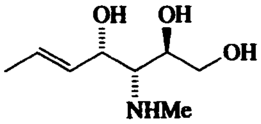 | i, *p*-TsOH; ii, $O_3$/silica gel; iii, DMS, MeOH | 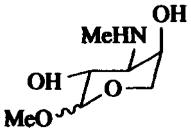 | 72 | 56 |
| 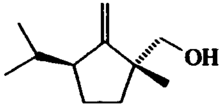 | i, $O_3$, MeOH, –78 °C; ii, DMS, –78 °C, 2 h and r.t., overnight | 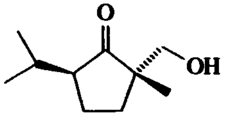 | 70 | 57 |
| 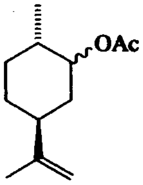 | i, $O_3$, $CH_2Cl_2$, –78 °C, 1 h; ii, Zn–AcOH, r.t., 30 min | 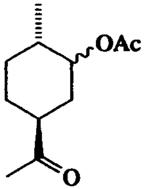 | 95 | 58 |
| 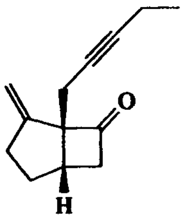 | i, $O_3$, MeOH, –78 °C; ii, DMS | 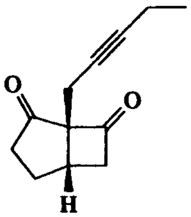 |  | 59 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 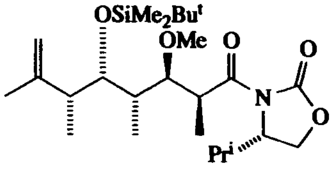 | i, $O_3$, $CH_2Cl_2$/MeOH/$NaHCO_3$, –78 °C; ii, DMS, 0 °C to r.t., 10 h | 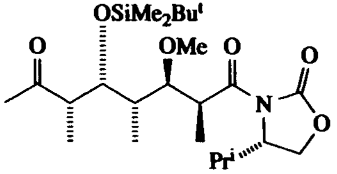 | 92 | 60 |
| 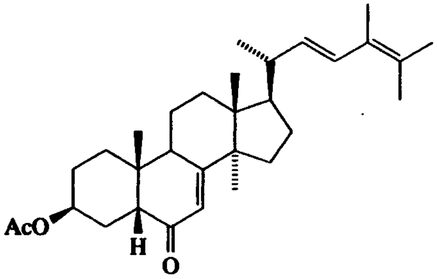 | i, $O_3$, $CH_2Cl_2$–Py (1%), –78 °C; ii, DMS, –78 °C | 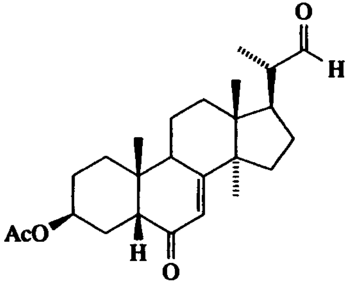 | 78 | 61 |
| 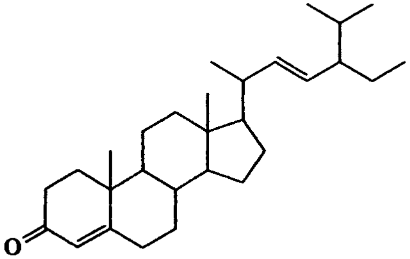 | i, $O_3$, $CH_2Cl_2$–Py, –78 °C | 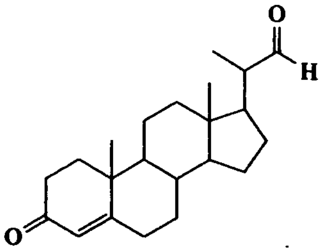 | 94 | 62 |
| 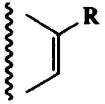 | i, $O_3$, EtOAc; ii, S=C($NH_2$)$_2$, MeOH | 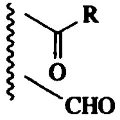 |  | 39 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 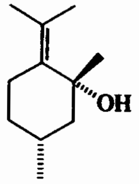 | i, $O_3$, $CH_2Cl_2$, EtOH, red dye, –60 °C; ii, DMS, r.t., overnight | 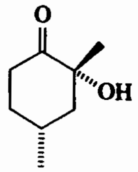 | 80 | 63 |
| 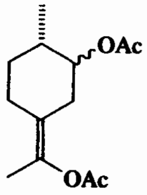 | i, $O_3$, $CH_2Cl_2$/MeOH, –78 °C, 1 h; ii, Zn–AcOH r.t., 30 min | 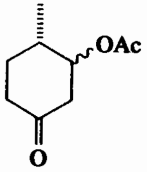 | 85 | 58 |
| 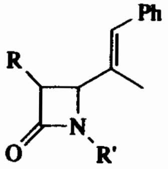 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, DMS | 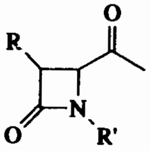 | 70 | 64, 65 |
| 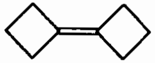 | i, $O_3$, $CH_2Cl_2$/MeOH, –20 °C; ii, S=C(NH$_2$)$_2$ NaHCO$_3$, $CH_2Cl_2$, 0 °C | 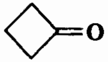 | 67 | 17 |
| 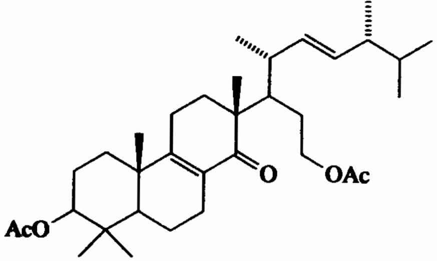 | i, 1.1 equiv $O_3$, $CH_2Cl_2$, –78 °C; ii, DMS | 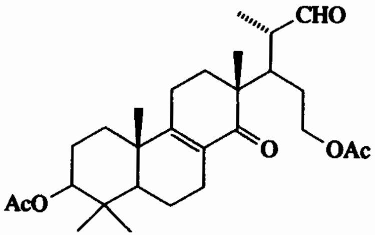 | 76 | 67 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 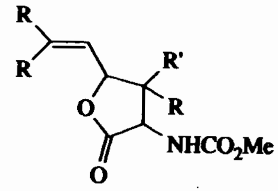 | i, $O_3$, MeOH; ii, DMS | 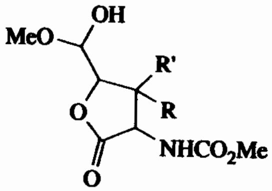 | 93 | 66 |
| 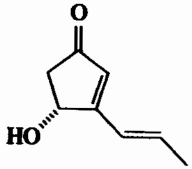 | i, $O_3$, EtOH; ii, DMS | 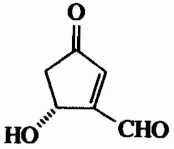 | 90 | 68 |
| 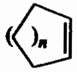<br>$n = 1–3$ | i, $O_3$, $CH_2Cl_2$/MeOH, –78 °C; ii, $Et_3N$, AcOH/MeOH | 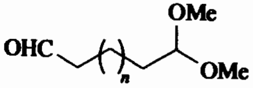<br>$n = 1–3$ |  | 69 |
| 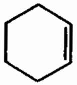 | i, $O_3$, EtOAc, –20 to –30 °C; ii, $Pd/CaCO_3/H_2$ | 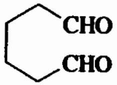 | 61 | 70 |
| 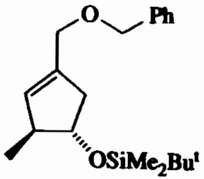 | i, $O_3$; ii, $PPh_3$ | 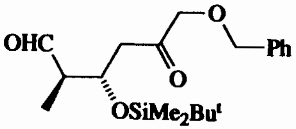 | 43 | 71 |

**Table 2** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 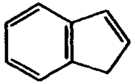 | i, $O_3$, MeOH; ii, $(MeO)_3P$ | 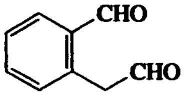 | 65 | 72 |
| 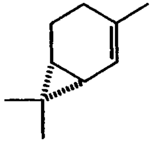 | i, $O_3$, $CH_2Cl_2$/MeOH, –78 °C, 32 min; ii, DMS, r.t., 3 h | 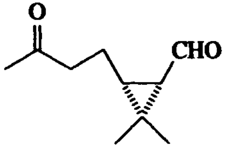 | 99 | 73 |
| 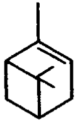 | i, $O_3$, MeOH, –10 to –15 °C; ii, $S{=}C(NH_2)_2$ | 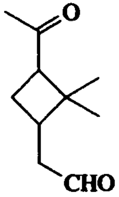 | 75 | 40 |
| 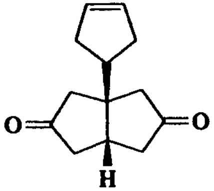 | i, $O_3$, EtOAc, –50 °C; ii, DMS, MeOH | 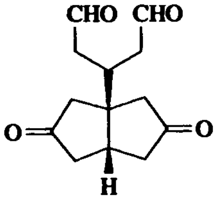 |  | 39 |
| 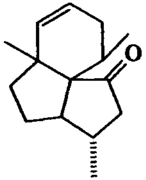 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, Zn–AcOH, 0 °C, 5 h | 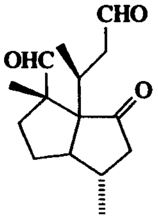 | 68 | 35 |

**Table 3** Selective Cleavages by Ozone

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 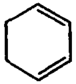 | i, $O_3$ (1.5 mol), $CH_2Cl_2$ | 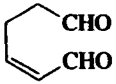 | 70 | 74 |
| 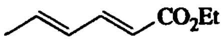 | i, $O_3$, EtOH; ii, DMS | 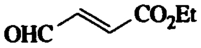 | 85 | 68 |
| 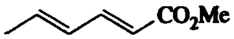 | i, $O_3$, $CH_2Cl_2$; ii, DMS | 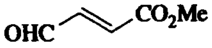 | 90 | 75 |
| 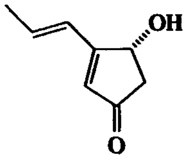 | i, $O_3$, EtOH; ii, DMS | 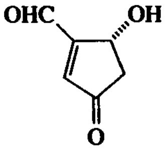 | 90 | 68 |
| 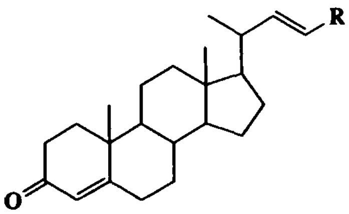 | i, $O_3$, $CH_2Cl_2$/EtOH (2:1); ii, DMS | 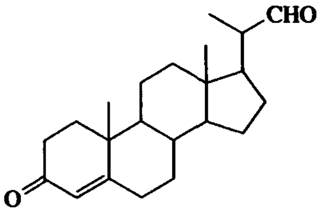 | 85 | 68 |
| 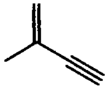 | i, $O_3$, MeOH/$Et_2O$ (1:1); ii, DMS | 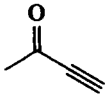 | 64 | 68 |

obtained in aprotic and nonparticipating solvents.[9,10] However, when the silica gel was wet, double bond cleavage resulted in the formation of equimolar amounts of aldehyde and carboxylic acid. For example, the oxidative cleavage of cyclopentene by ozone on silica gel containing 5% water gave 5-oxopentanoic acid in 80% yield (equation 16).[76]

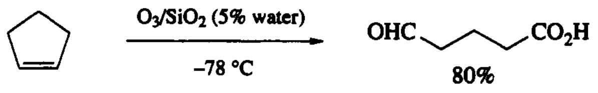

(16)

### 3.8.3.2 Permanganate

### *3.8.3.2.1 Aqueous potassium permanganate oxidations*

It is difficult to prepare aldehydes by the cleavage of carbon–carbon double bonds with permanganate under aqueous conditions. In water, aldehydes exist at least partly as the corresponding hydrates, $RCH(OH)_2$, and are therefore very susceptible to further oxidation by permanganate. Consequently the products obtained are usually carboxylic acids. Aldehydes have been obtained in good yields only when the products are deactivated, as in equation (17).[77]

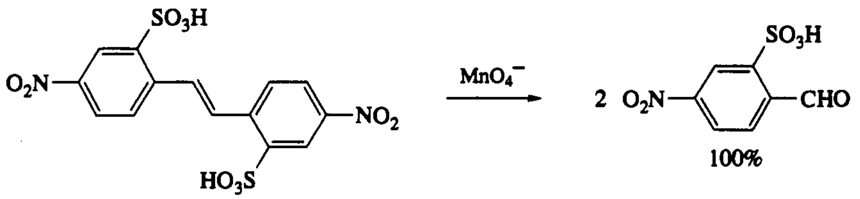

(17)

Wiberg and Saegebarth[78] also obtained fair yields of cyclopentane-1,3-dialdehyde from the oxidation of bicyclo[2.2.1]hept-2-ene under mild conditions (equation 18). However, the oxidation of unsaturated tertiary carbons to the corresponding ketones is much more typical. The reaction depicted in equation (19), where a trisubstituted double bond is cleaved to a ketone and a carboxylic acid, is exemplary of the products that are normally produced when alkenes react with aqueous permanganate.[79]

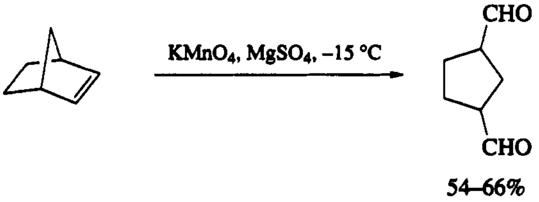

(18)

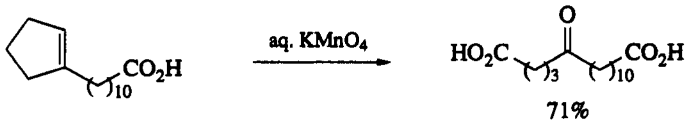

(19)

### *3.8.3.2.2 Mixed solvent systems*

Since organic compounds are often not sufficiently soluble in water to permit oxidation in completely aqueous systems, several authors have reported the use of mixed solvent systems (such as acetone and water or alcohol and water) in which the oxidant and reductant are mutually soluble.[3,5] Recent work has shown that the best solvent system to use for the preparation of aldehydes from permanganate cleavages is THF and water. Simandi and coworkers[80] have reported that the treatment of a concentrated aqueous solution of permanganate with a dilute solution of alkene in THF affords the desired aldehydes in good yields. The authors have suggested that the solvent, under these conditions, acts as a quenching reagent that prevents over-oxidation.

In a typical experiment,[80] a solution of 4-formyl-2,2-dimethy-1*H*-1,5-benzodiazepine (0.036 mol) in THF (300 mL) was added in small portions to a solution of potassium permanganate (0.063 mol) in water (100 mL) over a period of 3.5 h. (Addition of solid $KMnO_4$ to neat THF could produce an explosive mixture, and should therefore be avoided.) During the addition, the mixture was allowed to warm to about 40 °C. The mixture was then filtered to remove manganese dioxide and the filtrate was concentrated and extracted with diethyl ether. After drying, the extract was concentrated and the resulting product crystallized from diisopropyl ether. The overall yield was 7 g (79%).

### *3.8.3.2.3 Phase transfer assisted oxidative cleavages*

As depicted in equation (20), the addition of a phase transfer agent, $Q^+$ (*eg*. quaternary ammonium or phosphonium ions), brings permanganate into solution in nonaqueous solvents.[5] Once solubilized, it reacts with alkenes to produce an intermediate that has been characterized by Ogino *et al.*[81] as a cyclic manganate(V) diester (**9**), that can be decomposed by acidic solutions to yield aldehydes or by mild base to give the corresponding α-diol, as in Scheme 1.

$$Q^+\,(\text{aq.}) \quad + \quad MnO_4^-\,(\text{aq.}) \quad \rightleftharpoons \quad Q^+MnO_4^-\,(\text{org.}) \qquad (20)$$

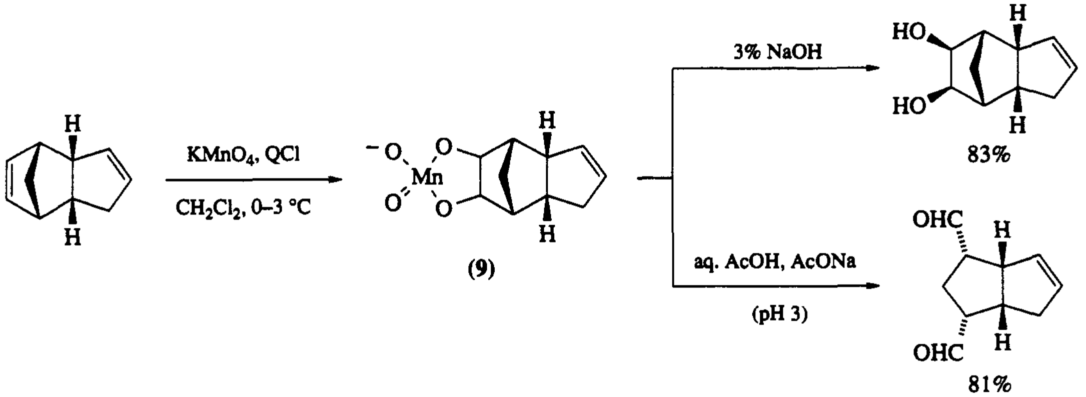

**Scheme 1**

Under phase transfer conditions Rathore and Chandrasekaran[82] have shown that permanganate selectively cleaves aryl-substituted double bonds in the presence of alkyl-substituted double bonds (equation 21), and that oxidative cleavage can be effected in the presence of other oxidizable functional groups (equation 22).

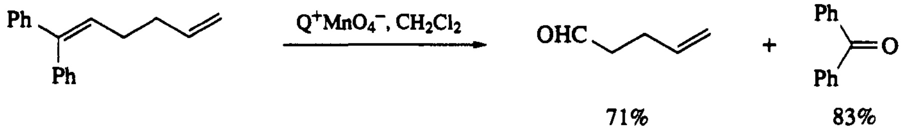

(21)

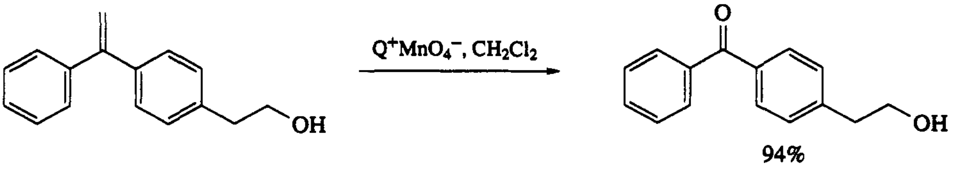

(22)

A typical procedure is provided by the oxidative cleavage of *endo*-dicyclopentadiene to the corresponding dialdehyde (Scheme 1).[81] A solution of potassium permanganate (3.41 mmol) and triethylbenzylammonium chloride (3.41 mmol) in dichloromethane (40 mL) was added dropwise to a solution of *endo*-dicyclopentadiene (2.27 mmol) in 20 mL of the same solvent maintained at 0–3 °C. After the addition, which took 40–50 min, stirring was continued for an additional 30–40 min by which

**Table 4** The Oxidative Cleavage of Double Bonds to Carbonyl Compounds by Permanganate

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 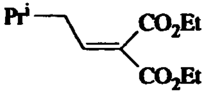 | $KMnO_4$, $THF/H_2O$ | 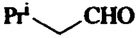 | 14 | 80 |
| 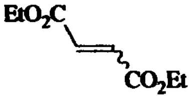 | $KMnO_4$, $THF/H_2O$ | $EtO_2C-CHO$ | 48–51 | 80 |
| 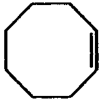 | i, $KMnO_4/Et_3\overset{+}{N}CH_2Ph\ Cl^-$, $CH_2Cl_2$<br>ii, 1 M $HClO_4$ | 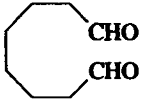 | 74 | 81 |
| 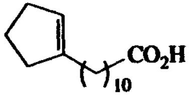 | aq. $KMnO_4$ | 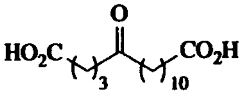 | 71 | 79 |
| 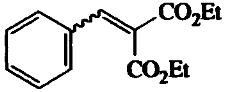 | $KMnO_4$, $THF/H_2O$ | 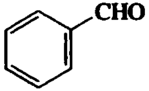 | 38 | 80 |
| 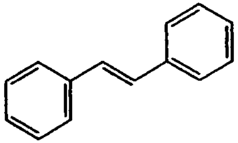 | $KMnO_4$, $THF/H_2O$ | 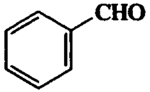 | 71 | 80 |
| | i, $KMnO_4/Et_3\overset{+}{N}CH_2Ph\ Cl^-$, $CH_2Cl_2$; ii, AcOH/NaOAc (pH 5) | | 74 | 81 |
| | Cetyltrimethylammonium permanganate, $CH_2Cl_2$, 25 °C, 2 h | | 92 | 82 |

**Table 4** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 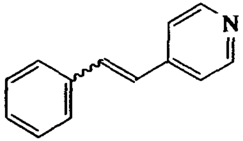 | $KMnO_4/MgSO_4$, $H_2O$/acetone, 0 °C, 2 h<br>or $KMnO_4$, $H_2O$/NaOH–acetone, 0–5 °C, 2 h | 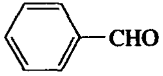 | 63–72 | 84 |
| | | 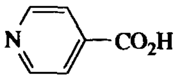 | ≈40–70 | 84 |
| 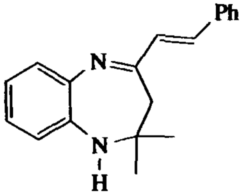 | $KMnO_4$, THF, $H_2O$ | 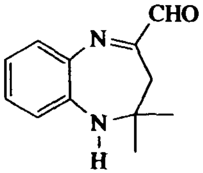 | 79 | 80 |
| 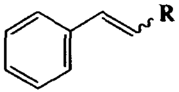 | Bis(2,2'-bipyridyl)copper(II) permanganate, acetone | 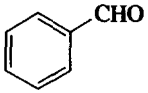 | 80–90 | 85 |
| 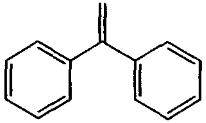 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 2 h | 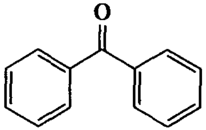 | 94 | 82 |
| 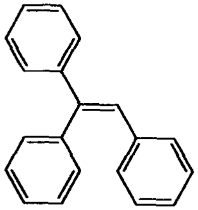 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 2 h | 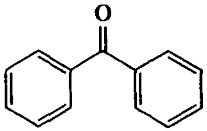 | 96 | 82 |
| | | 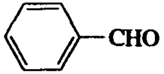 | 86 | 82 |

**Table 4** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 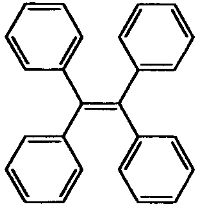 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 2 h | 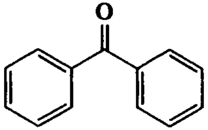 | 90 | 82 |
| 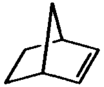 | $KMnO_4$, $MgSO_4$, acetone | 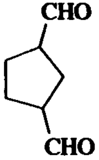 | 54–66 | 78 |
| 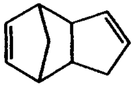 | i, $KMnO_4$, $Et_3\overset{+}{N}CH_2Ph\ Cl^-$, $CH_2Cl_2$<br>ii, AcOH–NaOAc (pH 3) | 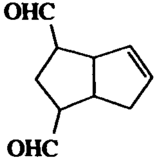 | 81 | 81 |
| 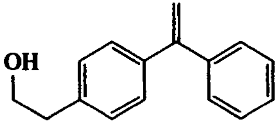 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 2.5 h | 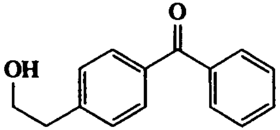 | 94 | 82 |
| 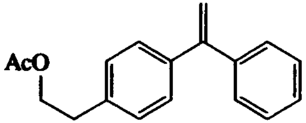 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 2.5 h | 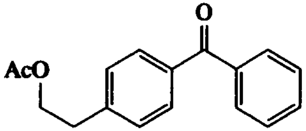 | 92 | 82 |

**Table 4** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 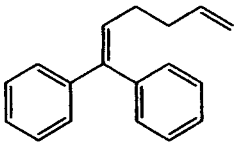 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 5 h | 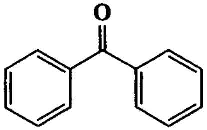 | 83 | 82 |
| | | 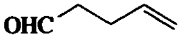 | 71 | 82 |
| 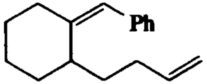 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 4.5 h | 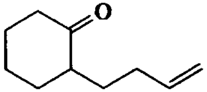 | 86 | 82 |
| 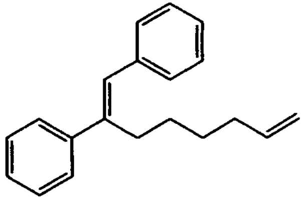 | $QMnO_4$, $CH_2Cl_2$, 25 °C, 4.0 h | 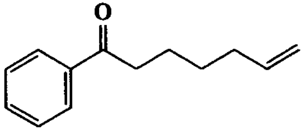 | 86 | 82 |

time the permanganate had been completely consumed with the formation of a dark brown solution. Treatment of this solution with 30 mL of water, buffered at pH 3, produced an 81% yield of dialdehyde.

Additional examples of the oxidative cleavage of double bonds by permanganate to produce aldehydes and ketones are summarized in Table 4. A detailed study of the reaction mechanism has also been reported.[83]

### 3.8.3.3 Osmium Tetroxide and Sodium Periodate

Osmium tetroxide reacts with double bonds to form cyclic osmate(VI) diesters (**10**), which can then be hydrolyzed to provide vicinal diols in good yields.[1,86] If, however, sodium periodate is also present, the diol is cleaved, as in Scheme 2, and carbonyl compounds are the final products. Periodate serves the additional purpose of regenerating osmium tetroxide, thus permitting the use of this expensive and toxic reagent in minimum amounts.

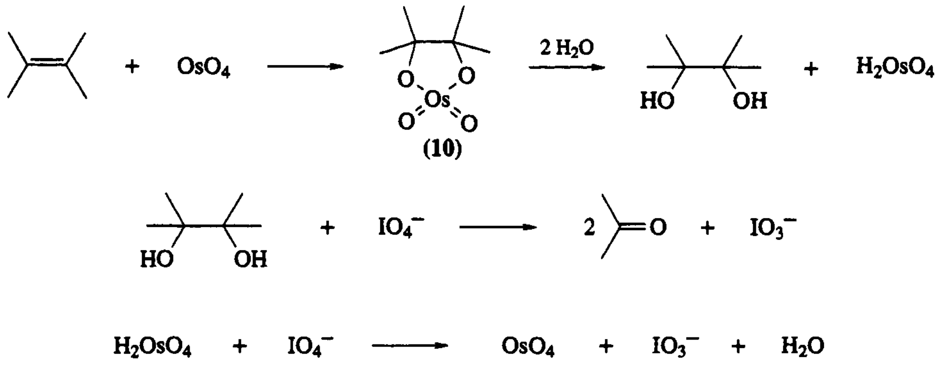

**Scheme 2**

The reaction is usually carried out in a mixed solvent containing water and dioxane, acetone, acetic acid or tetrahydrofuran.[71,87–93] Nonaqueous solvents can also be used if a phase transfer agent is added to bring the periodate ion into solution[94,95] or, alternatively, by use of periodic acid in THF.[96]

In a typical example,[91] sodium periodate (18.2 g, 85 mmol) was added in small portions over a 45 min period to 1,4-dioxa-6-acetyl-6-allylspiro[4.5]decane (8.9 g, 40 mmol) and osmium tetroxide (0.10 g, 0.39 mmol) in a solution of THF (126 mL) and water (42 mL) at room temperature. The mixture was stirred for 2 h at this temperature during which time the black slurry turned brown. Water (600 mL) was introduced, and the mixture was extracted with ether. The extract was dried over anhydrous magnesium sulfate and stripped of solvent to give 7.4 g of crude aldehyde. (Because osmium tetroxide is a toxic and volatile irritant, all preparations should be carried out in a fume hood with use of adequate personal protection, gloves and safety glasses.) Other examples of the use of this reagent have been summarized in Table 5.

### 3.8.3.4 Ruthenium Tetroxide

The physical properties, preparation and reactions of ruthenium tetroxide have been reviewed by Lee and van den Engh,[109] Rylander,[110] Haines[1] and Henry and Lange.[4] A more vigorous oxidant than osmium tetroxide, its reaction with double bonds produces only cleavage products.[111] Under neutral conditions aldehydes are formed from unsaturated secondary carbons while carboxylic acids are obtained under alkaline or acidic conditions. For example, Shalon and Elliott[112] found that ruthenium tetroxide reacted with compound (**11**) to give the corresponding aldehyde under neutral conditions, but that a carboxylic acid was formed in acidic or alkaline solvents (equation 23).

When used in stoichiometric amounts, ruthenium tetroxide is usually prepared by oxidation of hydrated ruthenium dioxide or trichloride with aqueous periodate or hypochlorite and then extracted into carbon tetrachloride.[86,109] However, since ruthenium compounds are expensive it is more common to use only catalytic amounts of $RuO_2{\cdot}2H_2O$ or $RuCl_3{\cdot}H_2O$ in the presence of a cooxidant that continuously regenerates ruthenium tetroxide.

**Table 5** Cleavages to Carbonyl Componds by use of Osmium Tetroxide with Periodate as a Cooxidant

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 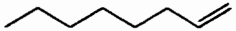 | $OsO_4/H_5IO_6$, THF, r.t. | 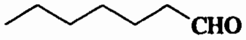 | 86 | 96 |
| 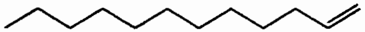 | $OsO_4/NaIO_4$, dioxane/$H_2O$, 24–26 °C, 2 h | 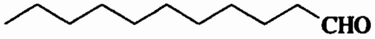 | 68 | 93 |
| 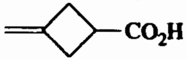 | $OsO_4/NaIO_4$, $Et_2O$, $H_2O$, 12 h | 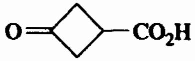 | 70 | 90 |
| 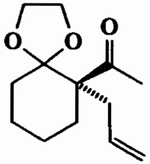 | $OsO_4/NaIO_4$, THF/$H_2O$ | 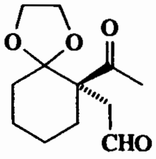 | 80 | 91 |
| 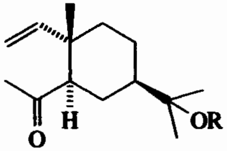 | $OsO_4/NaIO_4$, aq. dioxane | 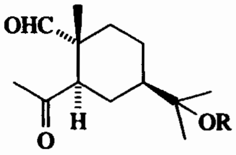 | 75 | 87 |
| 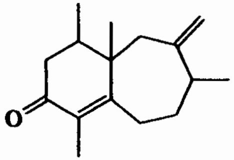 | $OsO_4/NaIO_4$, aq. dioxane | 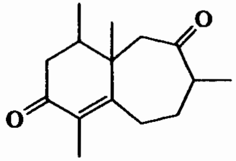 | 83 | 97 |
| 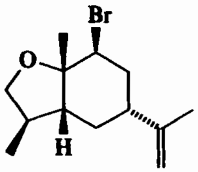 | $OsO_4/NaIO_4$, THF/$H_2O$ | 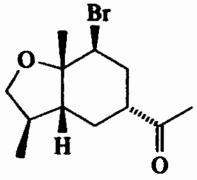 | 90 | 98 |

**Table 5** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 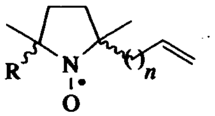 | $OsO_4/KIO_4$ | 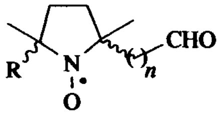 | 39–59 | 99 |
| 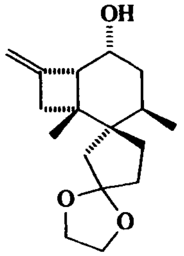 | $OsO_4/NaIO_4$, dioxane/$H_2O$/Py | 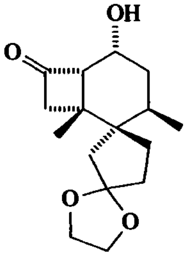 | 87 | 35 |
| 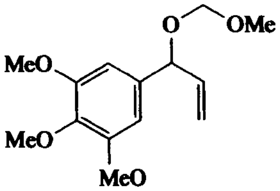 | $OsO_4/KIO_4$, dibenzo-18-crown-6 | 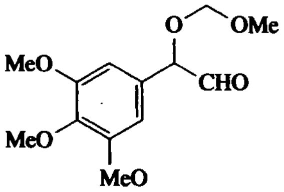 | 70 | 94 |
| 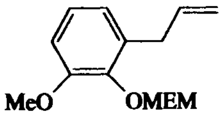 | $OsO_4/NaIO_4$ | 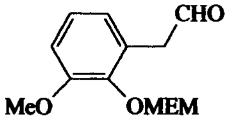 | >74 | 100 |
| 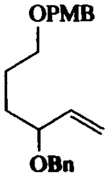 | $OsO_4/NaIO_4$, dioxane/$H_2O$/AcOH, r.t. overnight | 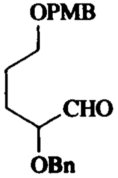 | 86 | 101 |

**Table 5** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 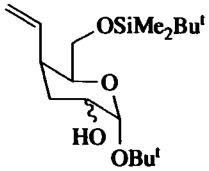 | $OsO_4/NaIO_4/NMO$, acetone | 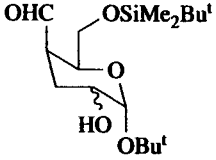 | 71 | 102 |
| 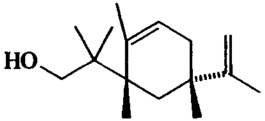 | $OsO_4/NaIO_4$, $THF/H_2O$ | 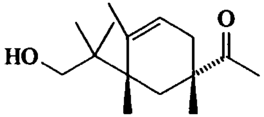 | 90 | 98 |
| 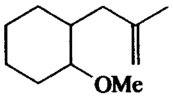 | $OsO_4/NaIO_4$, dioxane, $H_2O$, 6.5 h | 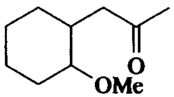 | 60 | 103 |
| 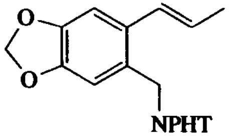 | i, $OsO_4/NMO$, acetone/$H_2O$ (8:5), 0–25 °C, 3 h<br>ii, $NaIO_4$, acetone/$H_2O$ (1:1), r.t., 1 h | 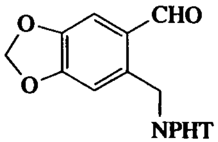 |  | 104 |
| 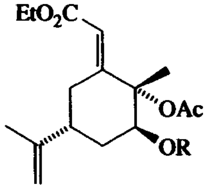 | $OsO_4/KIO_4$, $THF/H_2O$ | 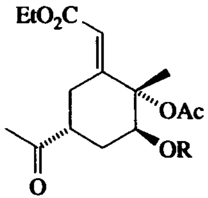 | 97 | 92 |

**Table 5** *(continued)*

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| 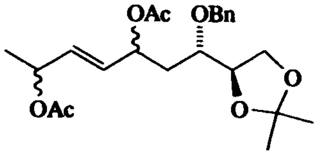  OAc OBn OAc O O | $OsO_4/NaIO_4$, dioxane/$H_2O$, r.t. | 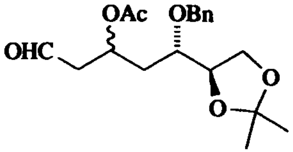  OAc OBn OHC O O | | 105 |
| 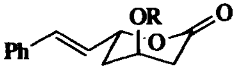 | $OsO_4/NaIO_4$, MeOH | 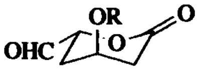 | 53 | 88 |
| 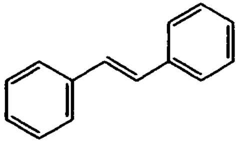 | $OsO_4/R_4NIO_4$ | 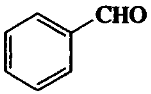 | 95 | 95 |
| | $OsO_4/H_5IO_6$, THF, r.t. | | 92 | 96 |
| 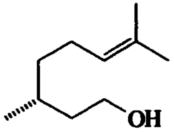 | $OsO_4/NaIO_4$, dioxane/$H_2O$ | 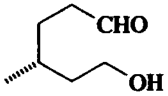 | >68 | 106 |
| 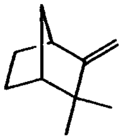 | $OsO_4/H_5IO_6$, THF, r.t. | 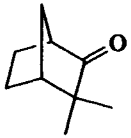 | 91 | 96 |
| 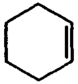 | $OsO_4$, $NaIO_4$, $Et_2O/H_2O$, 2 h | 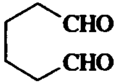 | 77 | 93 |

Table 5 *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
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| 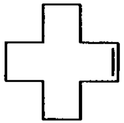 | $OsO_4/H_5IO_6/THF$, r.t. | 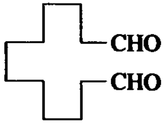 | 92 | 96 |
| 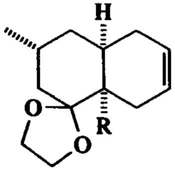 | $OsO_4/H_5IO_6$, NMO | 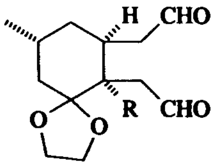 | 92 | 108 |
| 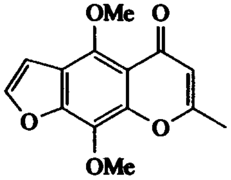 | $OsO_4/NaIO_4$, THF, 50 °C | 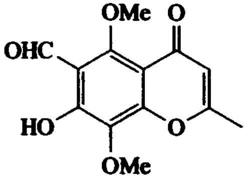 | 73 | 106 |
| 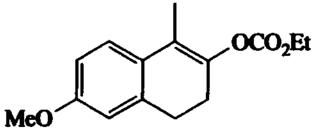 | $OsO_4/NaIO_4$, $Et_2O/H_2O$ | 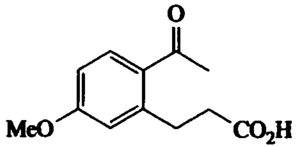 | 65 | 89 |
| 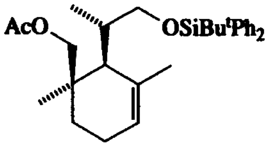 | i, $OsO_4$, Py; ii, $NaIO_4$, MeOH/THF; iii, $CH(OMe)_3$<br>MeOH, $CeCl_3 \cdot xH_2O$ | 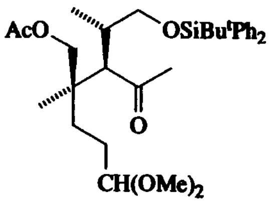 | 70 | 107 |

**Table 5** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
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| 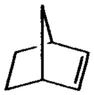 | $OsO_4/H_5IO_6$/THF, r.t. | 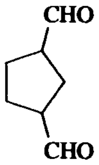 | 94 | 96 |

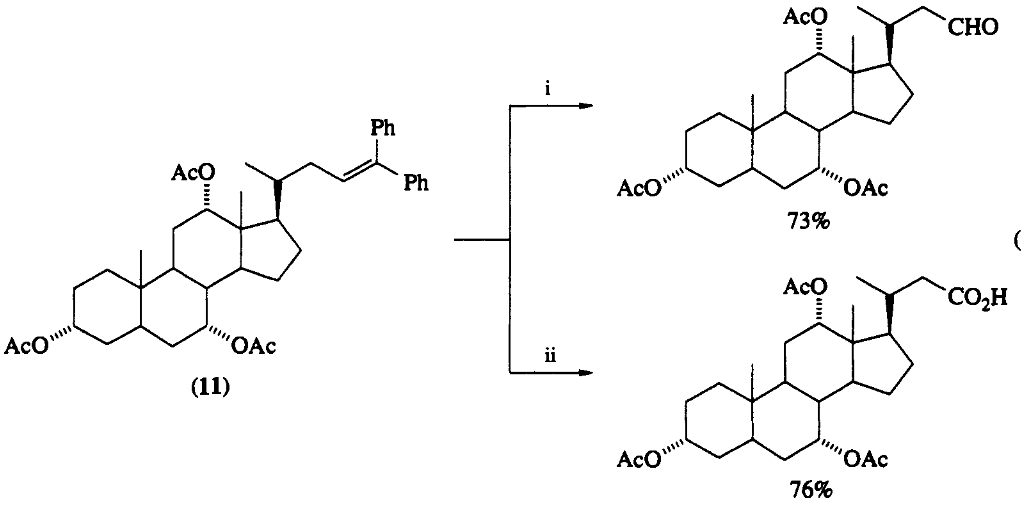

(23)

i, $RuO_4$, $CCl_4$, acetone/$H_2O$; ii, $RuO_4$, $CCl_4$, AcOH/$H_2O$

A two-phase system (carbon tetrachloride and water) is often used for these reactions. It appears that contact between ruthenium tetroxide and the alkene takes place in the organic phase where they are both most soluble. The ruthenium dioxide produced when oxidation occurs is insoluble in all solvents and migrates to the interphase where it contacts the cooxidant (in the aqueous phase) and is reoxidized, as summarized in Scheme 3. Because good contact between all components is essential, best results are obtained when the mixture is shaken or stirred vigorously throughout the course of the reaction. Sharpless and his coworkers[115] have also found that the addition of acetonitrile to the two-phase mixture improves yields.

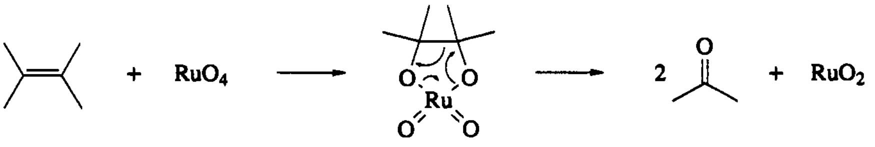

$$RuO_2 + 2\,NaIO_4 \longrightarrow RuO_4 + 2\,NaIO_3$$

**Scheme 3**

In a typical experiment,[113] a flask was charged with carbon tetrachloride (2 mL), acetonitrile (2 mL), water (3 mL), alkene (1.0 mmol), sodium periodate (877 mg, 4.1 equiv.) and $RuCl_3{\cdot}H_2O$ (5 mg, 2.2 mol %), and the entire mixture was stirred vigorously for 2 h at room temperature. Then dichloromethane (10 mL) was added to assist in the separation of the phases and the aqueous phase was extracted three times with additional volumes of $CH_2Cl_2$. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in 20 mL of ether, filtered through a Celite pad to remove traces of ruthenium dioxide and concentrated again to give the crude carbonyl products. A few typical examples of this reaction have been summarized in Table 6.

### 3.8.3.5 Hexavalent Chromium Compounds

The reactions of alkenes with chromate or dichromate ions usually leads to an array of products arising from oxidative attack at the double bond and the allylic positions.[3] Only in special cases where the double bond bears one or more phenyl[118] or alkoxy[119] substituents have good yields of the corresponding carbonyl compounds been reported.

Chromium trioxide adsorbed on silica or alumina has been used for the oxidative cleavage[120] of alkenes to aldehydes or ketones with little or no formation of carboxylic acids. A solution of bis(triphenylsilyl) chromate has also been used for the selective cleavage of double bonds to carbonyl compounds.[121]

**Table 6** Cleavage of Double Bonds to Carbonyl Compounds by Ruthenium Tetroxide

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 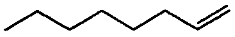 | $RuO_4$, $CCl_4$ | 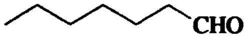 | 12 | 114 |
| 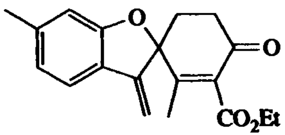 | $RuO_4$, $CCl_4$ | 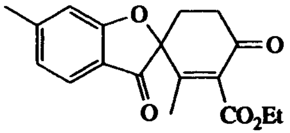 | 3–32 | 111 |
| 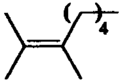 | $RuCl_3{\cdot}H_2O/NaIO_4$, $CCl_4/MeCN/H_2O$ | 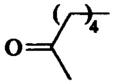 | >95 | 113 |
| 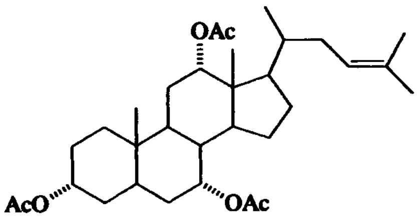 | $RuO_4$, $CCl_4$/acetone/$H_2O$ | 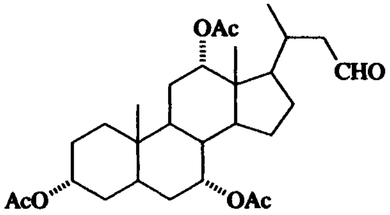 | 73 | 112 |
| 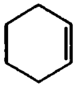 | $RuO_4$, $CCl_4$ | 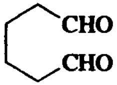 | 10 | 114 |
| | $RuCl_3$, 4.0 equiv. $NaClO_4$ | | 25–30 | 115 |
| 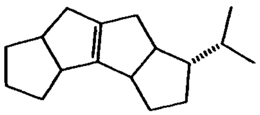 | $RuO_2/NaIO_4$, $CCl_4/MeCN/H_2O$ | 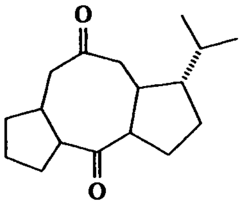 | 82 | 116 |

Table 6 *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 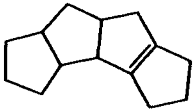 | $RuO_2/NaIO_4$, $CCl_4/MeCN/H_2O$ | 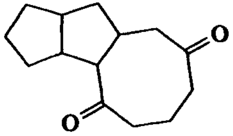 | 92 | 116 |
| 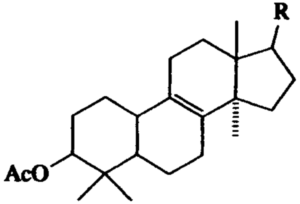 | $RuO_4$, $CCl_4$ | 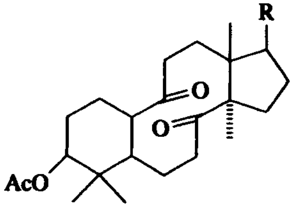 | 60 | 117 |

Finally, a compound formed by dissolving chromium trioxide and 2,2-bipyridyl in glacial acetic acid saturated with dry hydrogen chloride has been reported to cleave double bonds without complicating side reactions.[122] Unfortunately this oxidant, which is reported to have the formula of (bipy)$H_2CrOCl_5$, is effective only with phenyl-substituted double bonds.

Some examples of the use of hexavalent chromium compounds for oxidative cleavages are given in Table 7.

## 3.8.4 CLEAVAGE OF DOUBLE BONDS TO YIELD CARBOXYLIC ACIDS, ESTERS OR LACTONES

Oxidative cleavage of a carbon–carbon double bond produces ketones from tertiary carbons with almost all oxidants. If, however, one or both of the carbons are secondary, either aldehydes or, more generally, carboxylic acids are obtained. In some cases these latter products undergo subsequent reactions to form either esters or lactones.

If carboxylic acids are the desired products, the double bonds should be oxidized by potassium permanganate, ruthenium tetroxide, hexavalent chromium, or ozone followed by an oxidative work-up.

### 3.8.4.1 Ozone Followed by an Oxidative Work-up

Carboxylic acids are produced in good yields if the ozonide, formed when ozone reacts with a double bond as in equation (6), is subjected to oxidative hydrolysis. Although a variety of oxidants (*e.g.* chromic acid, permanganate ion and peroxy acids) have been used for this purpose, hydrogen peroxide is most commonly employed.

Two typical examples are illustrated in equations (24)[125] and (25).[126]

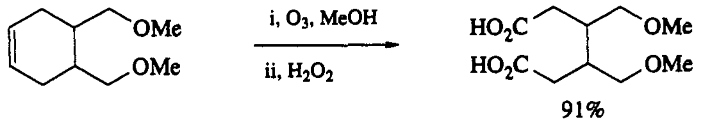

(24)

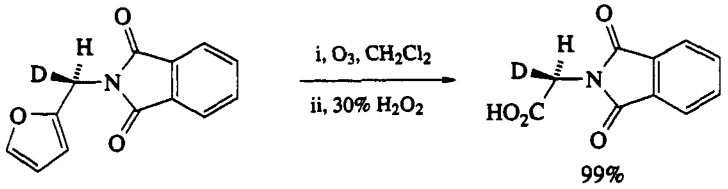

(25)

If the reaction is carried out in an emulsion of sodium hydroxide and hydrogen peroxide, the ozonide intermediates are converted to carboxylic acids directly, with a consequent increase in yields.[127]

Oxidative cleavage of γ-hydroxyalkenes results in the formation of lactones in good yields (equation 26).[128]

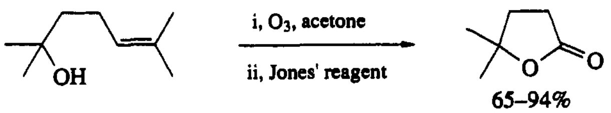

(26)

Ozonolysis of 1,2-dichloroalkenes in methanol affords the corresponding methyl esters in good yield (equation 27).[140] It has been suggested that the intermediates in these reactions must be either the corresponding acid chlorides or α-chloro-α-methoxyalkyl hydroperoxides, as in Scheme 4.

When the alkene bears an oxygen or nitrogen substituent in the allylic position, oxidation often proceeds with the loss of one carbon atom, as in equation (28).[127]

In a typical experiment,[126] ozone was bubbled into a solution of alkene (8.8 mmol) dissolved in dichloromethane (120 mL) at reduced temperatures (–78 °C) until TLC analysis indicated no starting material remained (about 2 h). Then 30% hydrogen peroxide (2 mL) was added and the reaction mixture stirred at room temperature for 18 h. The product mixture was washed with water, dried over anhydrous sodium

**Table 7** Cleavage of Double Bonds to Carbonyl Compounds by Hexavalent Chromium Compounds

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| $H_2C{=}CH_2$ | $CrO_3/SiO_2/Al_2O_3$, cyclohexane | HCHO | | 120 |
| 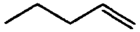 | $(Ph_3SiO)_2CrO_2$, heptane or $CCl_4$ | 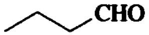 | | 121 |
| 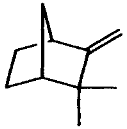 | $(bipy)H_2CrOCl_5$ (2 equiv.), $CH_2Cl_2$, r.t., 0.5 h | 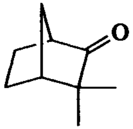 | 80 | 122 |
| 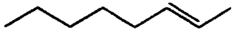 | $(Ph_3SiO)_2CrO_2$, heptane or $CCl_4$ | 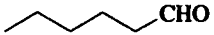 | | 121 |
| 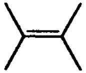 | $CrO_3/SiO_2/Al_2O_3$, cyclohexane | 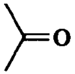 | | 120 |
| 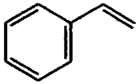 | $(bipy)H_2CrOCl_5$ (4 equiv.), $CH_2Cl_2$, r.t., 4.5 h | 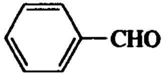 | | 122 |
| | $CrO_3/SiO_2/Al_2O_3$, cyclohexane | | | 120 |
| 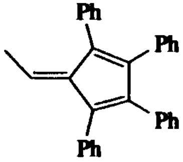 | $(bipy)H_2CrOCl_5$ (2 equiv.), $CH_2Cl_2$, r.t., 2 h | 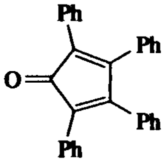 | 70 | 122 |
| 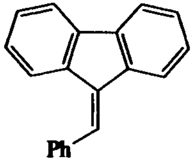 | $(bipy)H_2CrOCl_5$ (2 equiv.), $CH_2Cl_2$, r.t., 0.75 h | 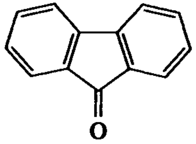 | 90 | 122 |

**Table 7** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 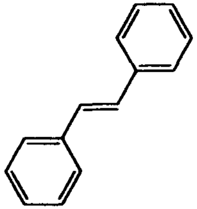 | $CrO_3/SiO_2/Al_2O_3$, cyclohexane | 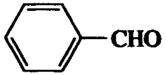 | ≈100 | 120 |
| | (bipy)$H_2CrOCl_5$ (4 equiv.), $CH_2Cl_2$, r.t., 4 h | | 96 | 122 |
| 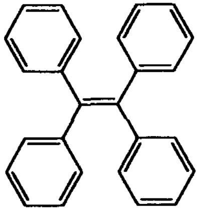 | $CrO_3$, $AcOH/H_2O$, 90–95 °C | 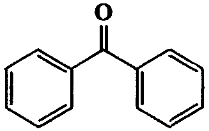 | 26–44 | 123 |
| 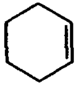 | $(Ph_3SiO)_2CrO_2$, heptane or $CCl_4$ | 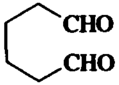 | | 121 |
| 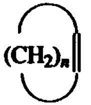 <br>$n = 3–6$ | $CrO_2(OCOCCl_3)_2$, acetone | 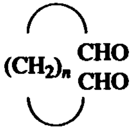 $(CH_2)_n$<br>CHO<br>CHO<br>$n = 3–6$ | 43–70 | 124 |
| 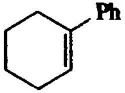 | $CrO_3$, 30 °C | 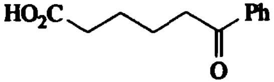 | | 118 |

Table 7 *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 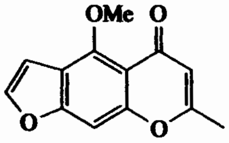 | $CrO_3$ | 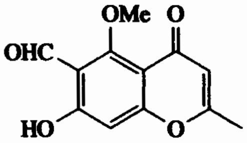 |  | 119 |

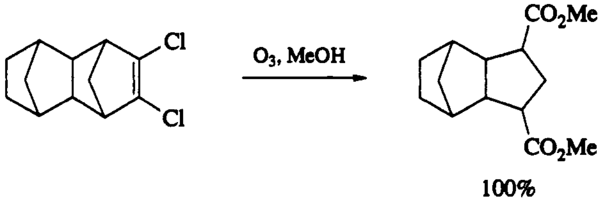
Cl
Cl
O3, MeOH
CO2Me
CO2Me
100%

(27)

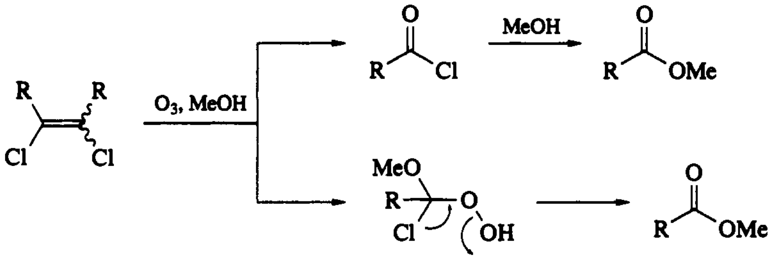
R
R
Cl
Cl
O3, MeOH
O
R
Cl
MeOH
O
R
OMe
MeO
R
O
Cl
OH
O
R
OMe

Scheme 4

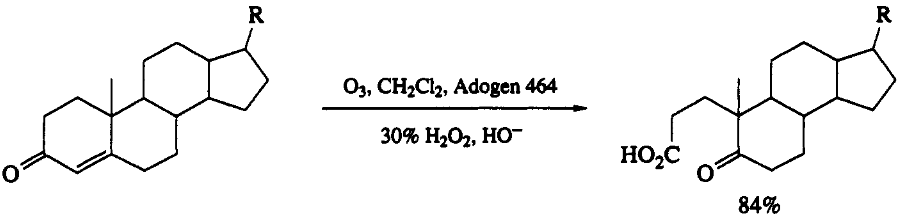
R
O
O3, CH2Cl2, Adogen 464
30% H2O2, HO−
R
HO2C
O
84%

(28)

sulfate, and concentrated to give crude product (99% yield). Other examples of this reaction are summarized in Table 8.

### 3.8.4.2 Permanganate Reactions

#### *3.8.4.2.1 Aqueous potassium permanganate oxidations*

The oxidative cleavage of carbon–carbon double bonds has been reviewed by Stewart.[150] In general, carboxylic acids are produced under acidic conditions. However, since many alkenes lack sufficient solubility in water, cosolvents such as pyridine, acetone or acetic acid have often been used to bring the oxidant and reductant into contact. For example, a good yield of 2,6-diphenyl-4-pyridinecarboxylic acid was obtained from the reaction depicted in equation (29).[151] Table 9 contains additional examples.

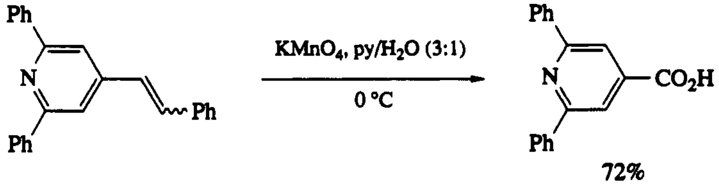
Ph
N
Ph
Ph
KMnO4, py/H2O (3:1)
0 °C
Ph
N
CO2H
Ph
72%

(29)

#### *3.8.4.2.2 Phase transfer assisted permanganate oxidations*

The ability to dissolve permanganate in nonaqueous solvents by use of phase transfer agents (as previously discussed in Section 3.8.2.3.3) extends its use for oxidative cleavages to compounds that are not soluble in aqueous solutions. It has been reported, for example, that 1-eicosene and other long-chain alkenes can be converted into the corresponding carboxylic acids in good yields by use of the following procedure.[154]

**Table 8** Cleavage of Double Bonds to give Carboxylic Acids or Esters using Ozone

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 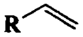 | i, $O_3$, THF; ii, $H_2$/Pd, $CaCO_3$, PbO | R−$CO_2$H | 85 | 18 |
| 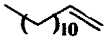 | i, $O_3$, $CHCl_3$, −5 °C; ii, $Ag_2O$, NaOH | 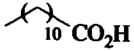 | 94 | 130 |
| 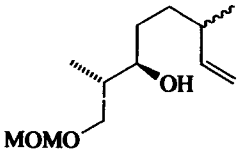 | i, $O_3$ (excess), $CH_2Cl_2$, −78 °C, 15 min; ii, DMS, MeOH −78 to 25 °C, 20 min | 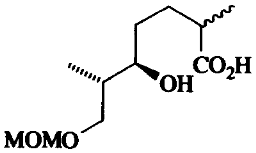 CO2H<br>OH<br>MOMO | >47 | 131 |
| 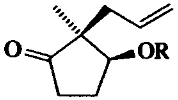 | $O_3$, $CH_2Cl_2$, Py, −78 °C | 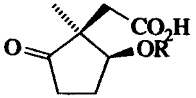 | >60 | 132 |
| 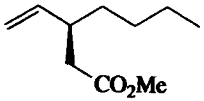 | i, $O_3$; ii, $H_2O_2$, 1 M NaOH | 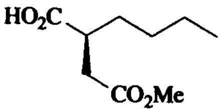 | >95 | 133 |
| 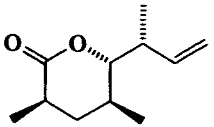 | i, $O_3$, EtOAc; ii, $H_2O_2$ | 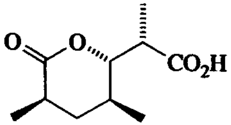 | 85 | 134 |
| 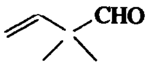 | $O_3$ | 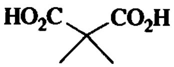 |  | 135 |
| 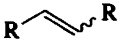 | $O_3$, HCl, MeOH | R−$CO_2$Me | 62–85 | 136 |
| 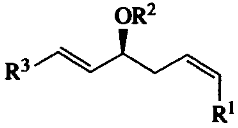 | i, $O_3$, $CH_2Cl_2$, −78 °C; ii, 12% $H_2O_2$, AcOH, 60 °C, 30 min | 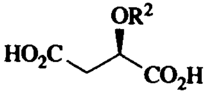 OR2<br>HO2C<br>CO2H | >30 | 137 |

**Table 8** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 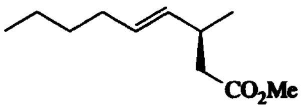 | i, $O_3$; ii, $H_2O_2$; iii, $CH_2N_2$ | 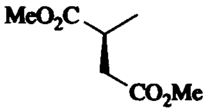 | >95 | 133 |
| 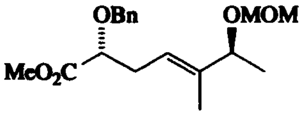 | i, $O_3$, MeOH; ii, $CrO_3$, $H^+$; iii, $CH_2N_2$ | 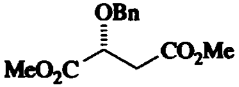 |  | 30 |
| 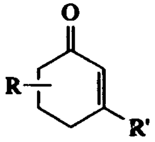 | $O_3$, 30% $H_2O_2$–NaOH, Adogen 464 | 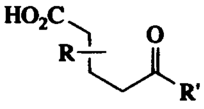 | 92 | 127 |
| 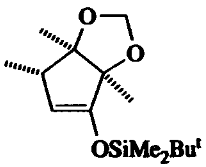 | i, $O_3$; ii, $H_2O_2$–$HCO_2H$ | 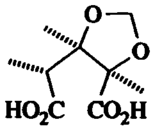 | 78 | 144 |
| 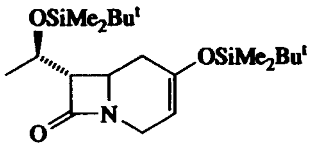 | i, $O_3$, MeOH, benzyl alcohol; ii, $(PyS)_2$–$PPh_3$ | 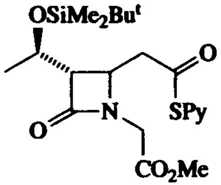 | 85 | 145 |
| 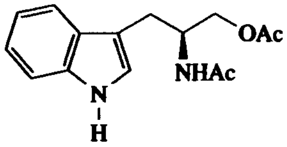 | i, $O_3$, AcOH; ii, $H_2O_2$, HCl, Δ | 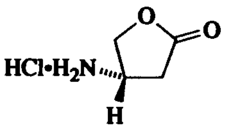 |  | 146 |

**Table 8** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 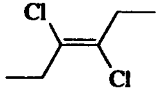 | $O_3$, MeOH | 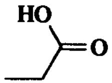 | 92 | 140 |
| 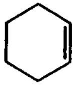 | i, $O_3$, MeOH, –70 °C; ii, $H_2O_2$, AcOH | 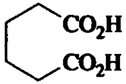 | 85 | 141 |
| | i, $O_3$, AcOH, 0 °C; ii, AcOOH, AcOH | | 86 | 142 |
| | i, $O_3$, AcOH, 0 °C; ii, $H_2CrO_4$, 50 °C, 12 h | | 71 | 142 |
| 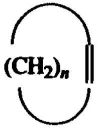 <br>$n = 4–10$ | i, $O_3$, THF; ii, $H_2$/Pd, $CaCO_3$, PbO | 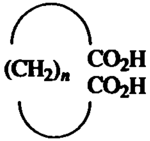 $(CH_2)_n$<br>$CO_2H$<br>$CO_2H$<br>$n = 4–10$ | 78–99 | 18 |
| 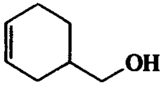 | i, $O_3$, MeOH; ii, $H_2O_2$, $HCO_2H$, 90 °C | 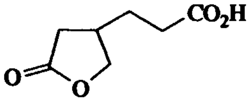 | 83 | 129, 139 |
| 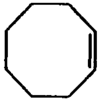 | $O_3$, $H_2O$, emulsifier, NaOH, $H_2O_2$, 10 °C | 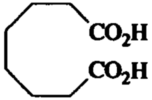 | 63 | 143 |
| 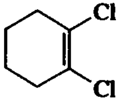 | $O_3$, MeOH | 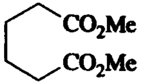 $CO_2Me$<br>$CO_2Me$ | 84 | 140 |

**Table 8** *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 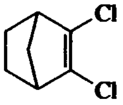 | $O_3$, MeOH | 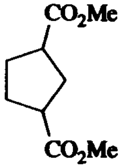 | ≈100 | 147 |
| 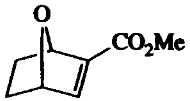 | i, $O_3$, $CH_2Cl_2$, –78 °C; ii, $H_2$, Pd–C, MeOH | 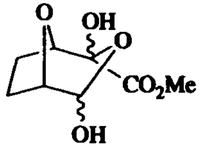 | >50 | 148 |
| 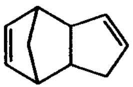 | $O_3$, $H_2O$, emulsifier, NaOH, $H_2O_2$, 10 °C | 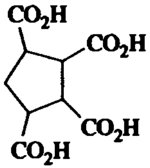 | 66 | 149 |
| 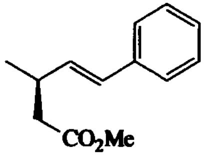 | i, $O_3$; ii, $H_2O_2$; iii, $CH_2N_2$ | 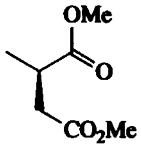 | 42 | 138 |
| 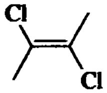 | $O_3$, MeOH | 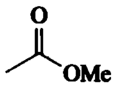 | 90 | 140 |

**Table 9** Cleavage of Double Bonds by Permanganate Solutions

| *Substrate* | *Oxidant and Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 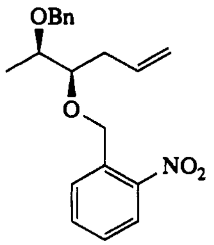 | $KMnO_4$, $NaIO_4$, $Bu^tOH/H_2O$ | 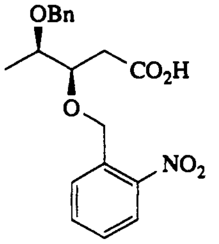 | 81 | 44 |
| 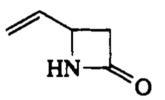 | $KMnO_4$, $H_2SO_4$ | 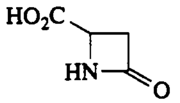 | 54 | 152 |
| 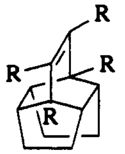 | $KMnO_4$, acetone, reflux | 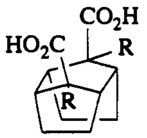 |  | 153 |

A 5 L three-necked round-bottomed flask fitted with a mechanical stirrer is placed in an ice bath and charged with 1000 mL of distilled water, 120 mL of 9 M sulfuric acid, 3.0 g of Adogen 464, 20 mL of glacial acetic acid, 1000 mL of dichloromethane, and 0.2 mol of alkene. The solution is rapidly stirred and 80 g (0.544 mol) of potassium permanganate is added in small portions over a 3 h period. Stirring is continued for an additional 18 h at room temperature. The mixture is cooled in an ice bath, and 60 g of sodium hydrogensulfite is added in small portions to reduce any precipitated manganese dioxide. The solution is acidified, if basic, with sulfuric acid and separated. The aqueous layer is extracted with two 400 mL portions of dichloromethane. The organic extracts are combined, washed with two 400 mL portions of water, washed once with brine, and concentrated to 400 mL on a rotary evaporator. The resulting mixture is heated to dissolve any precipitated product, a small amount of amorphous solid is removed by filtration, and the filtrate is cooled to 0 °C. A first crop of white crystals is collected by suction filtration and washed with a minimum amount of ice-cold dichloromethane. Concentration of the mother liquor to 150 mL, and cooling to 0 °C yields a second crop of crystals. The yield is 55–90%.[154,158]

Acetic acid is used in these procedures to neutralize the base that is produced whenever permanganate is reduced (equation 30).

$$MnO_4^- + 2\,H_2O + 3\,e^- \longrightarrow MnO_2 + 4\,OH^- \qquad (30)$$

Over-oxidation occurs if the solution is permitted to become basic. For example, 3-phenylpropene gives approximately equal amounts of phenylacetic acid and benzoic acid when oxidized under phase transfer conditions using a two-phase benzene/water solvent system. However, when acetic acid is added, the yield of phenylacetic acid increases to 80%.[155]

Best results are usually obtained for these reactions when permanganate is transferred into the organic phase from an aqueous solution rather than from a solid ($KMnO_4$) phase. When it is necessary to use solid $KMnO_4$ as the oxidant, care should be taken to add the phase transfer agent to the organic phase before the alkene. When the reverse procedure is followed, the alkene may occasionally form an unreactive complex on the surface of the solid $KMnO_4$.[156] Several examples of preparations using these procedures have been summarized in Table 10.

**Table 10** Phase Transfer Assisted Permanganate Oxidations

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 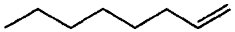 | $KMnO_4$, Aliquat 336, benzene/$H_2O$/glacial acetic acid | 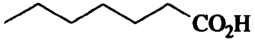 | 80 | 155 |
| 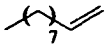 | $KMnO_4$ (s), dicyclohexano-18-crown-6, benzene | 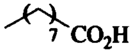 | 86 | 157 |
| 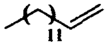 | $KMnO_4$, Aliquat 336, benzene/$H_2O$/AcOH | 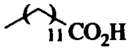 | 83 | 155 |
| 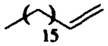 | $KMnO_4$, Adogen 464, $CH_2Cl_2/H_2SO_4$/AcOH/$H_2O$ | 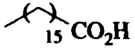 | 81 | 154 |
| 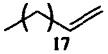 | $KMnO_4$, Aliquat 336, benzene/$H_2O$/AcOH | 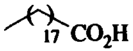 | 90 | 155 |
| 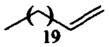 | $KMnO_4$, Adogen 464, $CH_2Cl_2/H_2SO_4$/AcOH/$H_2O$ | 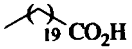 | 84 | 154 |
| 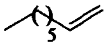 | $KMnO_4$, Adogen 464, $CH_2Cl_2/H_2SO_4$/AcOH/$H_2O$ | 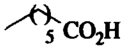 | 88 | 158 |
| 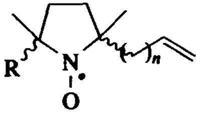 | $KMnO_4$, 18-crown-6 | 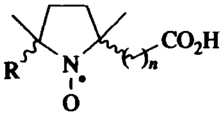 |  | 102 |
| 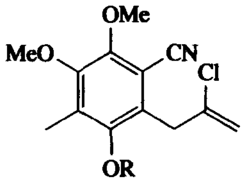 | $KMnO_4$, Adogen 464, $CH_2Cl_2/H_2SO_4$/AcOH/$H_2O$ | 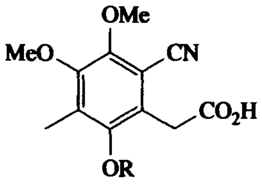 | >70 | 159 |
| 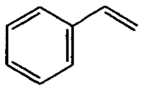 | $KMnO_4$, Adogen 464, $CH_2Cl_2/H_2SO_4$/AcOH/$H_2O$ | 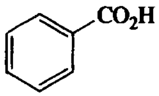 | 96 | 154 |

Table 10 *(continued)*

| *Substrate* | *Oxidant and conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 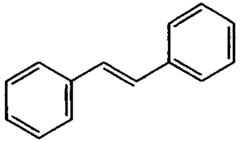 | $KMnO_4$, crown ether, benzene | 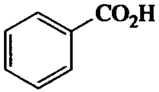 | 97 | 160 |
| 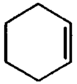 | $KMnO_4$, crown ether, benzene | 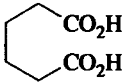 | ≈100 | 160 |
| 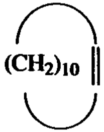 | $KMnO_4$, $MeO(CH_2CH_2O)_nMe/CH_2Cl_2/AcOH/H_2O$ | 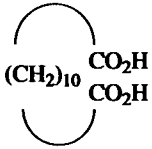 | 82 | 161 |
| 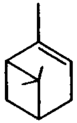 | $KMnO_4$, crown ether, benzene | 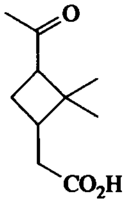 | 90 | 160 |

### *3.8.4.2.3 Heterogeneous permanganate oxidations*

Potassium permanganate adsorbed on either silica or alumina can also be used to cleave double bonds under mild conditions and in good yields. In one procedure the alkene, dissolved in benzene, is passed through a column packed with $KMnO_4$ on a silica gel support.[162] The reaction occurs rapidly at room temperature and is equally effective for the cleavage of all types of double bonds, even some that are inert to other traditional methods.[162]

It has also been found that it is not necessary to pack the oxidant into a column.[163] The alkene, dissolved in dichloromethane, can be cleaved by adding it to a flask containing $KMnO_4$ and silica gel that have been mixed mechanically. After shaking or stirring the mixture for an appropriate time, the product can be isolated by filtration and evaporation of the solvent. Alumina can also be used equally well as the solid support.[163] Additional examples are summarized in Table 11.

**Table 11** Oxidative Cleavages by Permanganate on Solid Supports

| *Substrate* | *Oxidant and Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 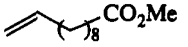 | $KMnO_4$, $SiO_2$ (support), benzene | 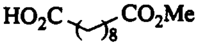 | 85 | 162 |
| 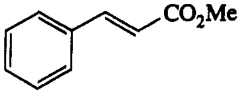 | $KMnO_4$, $SiO_2$ (support), $CH_2Cl_2$<br>or $KMnO_4$, $Al_2O_3$ (support), $CH_2Cl_2$ | 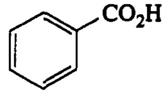 | 50–70 | 163 |
| 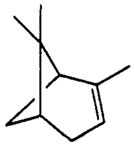 | $KMnO_4$, $SiO_2$ (support), benzene | 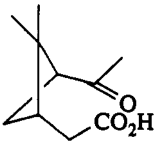 | 84 | 162 |
| 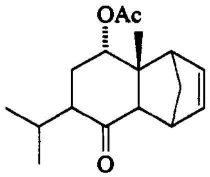 | $KMnO_4$, $SiO_2$ (support), benzene | 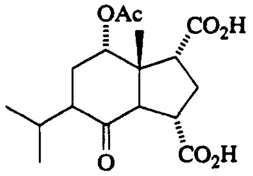 | 62 | 162 |
| 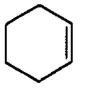 | $KMnO_4$, $SiO_2$ (support), benzene | 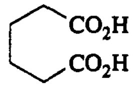 | 74 | 162 |

### *3.8.4.2.4 Permanganate/periodate*

A mixture of potassium permanganate and sodium periodate has also been used to cleave double bonds. This procedure, usually referred to as the Lemieux–von Rudloff reaction,[164] can be carried out in several mixed solvent systems such as butanol and water,[144] dioxane and water[165] or acetone and water.[166] It has also been claimed that the addition of phase transfer agents improves yields.[167]

In a typical procedure,[44] a solution of $KMnO_4$ (7 mg), $NaIO_4$ (225 mg) and $K_2CO_3$ (29 mg) in 29 mL of 7:3 *t*-butyl alcohol/water was added to a solution of alkene (0.213 mmol) in 2 mL of *t*-butyl alcohol. After 2.5 h the reaction mixture was poured into 50 mL of ether and 30 mL of water acidified to pH 2 with 1 M HCl. The aqueous phase was drawn off and extracted with 50 mL of ether. The combined organic layers were washed with 60 mL of 0.1 M HCl, dried ($Na_2SO_4$) and concentrated under reduced pressure to furnish the expected product.

### 3.8.4.3 Ruthenium Tetroxide

Although aldehydes are obtained from the cleavage of double bonds by ruthenium tetroxide under neutral conditions (Section 3.8.3.4), carboxylic acids are produced under alkaline or acidic conditions.[112] For example, the oxidation of cyclohexene by $RuO_4$ under alkaline conditions has been reported to give adipic acid in yields of 86–95%.[168]

Mechanistic studies have indicated that this reaction proceeds as in equations (31) and (32), with the initial step being a direct electron transfer that results in the formation of a radical cation–perruthenate complex.[169]

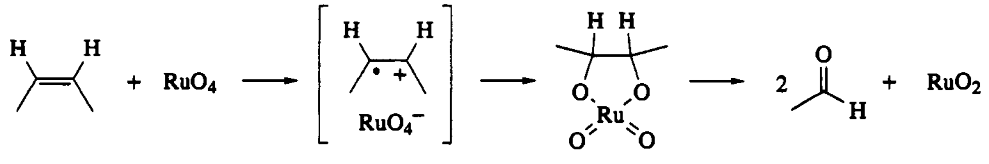
(31)

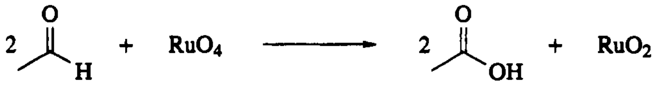
(32)

When ruthenium dioxide or ruthenium trichloride is used to catalyze periodate cleavages, it is likely that $RuO_4$ is first formed (equation 33) and then reacts with the double bond as depicted in equations (31) and (32). Sharpless and coworkers[113] have demonstrated that the best solvent system for this reaction is a mixture of carbon tetrachloride, acetonitrile and water, in a volume ratio of 2:2:3.

$$RuO_2 + 2\,NaIO_4 \longrightarrow RuO_4 + 2\,NaIO_3 \qquad (33)$$

### 3.8.4.4 Chromium Trioxide

Under acidic conditions $CrO_3$ will cleave double bonds to give the corresponding carboxylic acids. When the alkene also contains a hydroxy group lactones are readily formed, especially when acetic anhydride is used as a cosolvent (equation 34).[170]

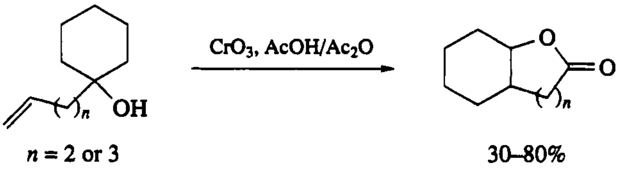

(34)

### 3.8.4.5 *t*-Butyl Peroxide and Molybdenum Dioxide Diacetylacetonate

$MoO_2(acac)_2$ and *t*-butyl peroxide when dissolved in benzene form a reagent that can be used for the specific cleavage of silyl enol ethers.[171] For example, the silyl ether of β-ionine is selectively cleaved as indicated in equation (35), to give β-(2,6,6-trimethylcyclohexyl)acrylic acid.

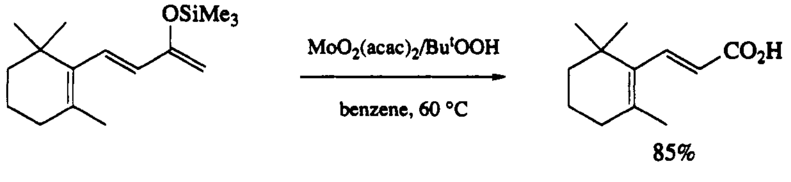

(35)

Since the formation of silyl enol ethers from the corresponding ketones is subject to either thermodynamic or kinetic control, this reagent can be used (as demonstrated in equation 36) to achieve useful regiospecific cleavages.

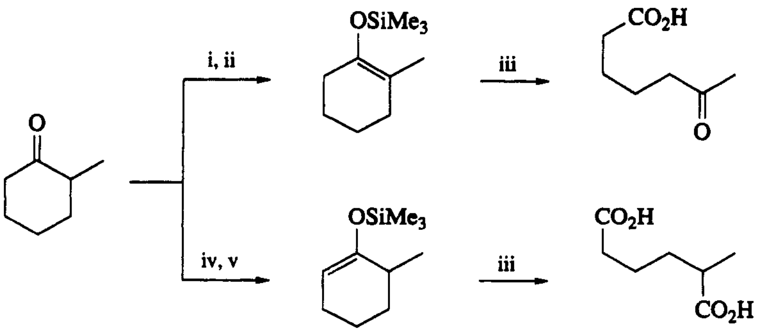

(36)

i, $Me_3SiCl$, DMF, $Et_3N$, Δ; ii, $NaHCO_3$, $H_2O$; iii, $MoO_2(acac)_2$, $Bu^tOOH$; iv, LDA, DME; v, $Me_3SiCl$

## 3.8.5 CLEAVAGE WITH THE INTRODUCTION OF NITROGEN AND SULFUR FUNCTIONAL GROUPS

### 3.8.5.1 Trimethylsilyl Azide and Lead Tetraacetate

Trimethylsilyl azide, ($TMSN_3$) reacts with carbon–carbon double bonds to form a compound which can be cleaved by lead tetraacetate (or phenyliododiacetate) to yield a carbonyl and a nitrile, as in equation (37).[172,173] The reagent has been applied extensively to the cleavage of unsaturated steroids, as illustrated in equation (38).

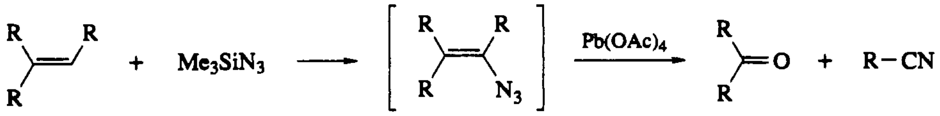

(37)

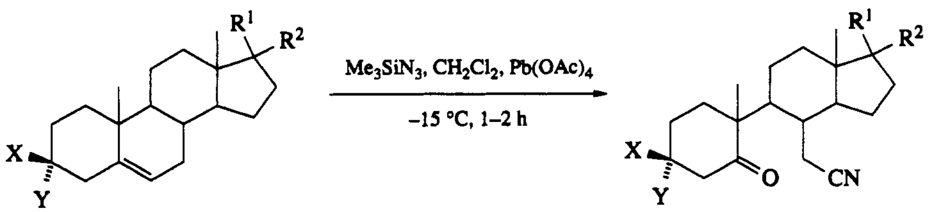

30%

(38)

In a typical procedure,[172] lead tetraacetate (2 mmol) in 50 mL of absolute dichloromethane was slowly added (over a period of 1.5 h) while stirring to a cold (−15 °C) solution of the steroid (2 mmol) and trimethylsilyl azide (8 mmol) in 250 mL of absolute $CH_2Cl_2$. After cooling for an additional 15 h, the red heterogeneous solution was slowly warmed to room temperature. Water was added and the precipitate removed by filtration through glass wool. The filtrate was washed with saturated $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum and the residue separated by use of silica gel column chromatography.

### 3.8.5.2 Ethanethiol and Aluminum Chloride

Double bonds activated by the presence of electron withdrawing groups ($NO_2$, $CO_2Et$, COMe, CN) can be cleaved by use of ethanethiol and a hard Lewis acid such as $AlCl_3$, $AlBr_3$, $FeCl_3$ or $ZnCl_2$ to give dithioacetals in good yields.[174,175] For example, dicyanostyrene (**12**) can be converted into the corresponding dithioacetal (**13**) in quantitative yields when treated with aluminum chloride and ethanethiol (equation 39).

The general procedure reported by Fuji *et al.*[175] involves addition of a solution of the alkene (0.5 mmol) in dichloromethane (1 mL) to a mixture of Lewis acid (1.5 mmol) in ethanethiol (1 mL) with ice cooling and under argon. After stirring for an appropriate time, the reaction mixture is poured into

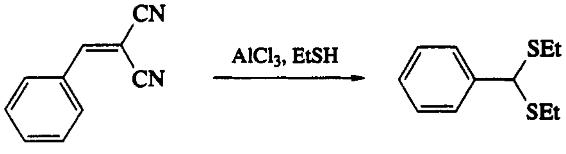

(12) (13) 100%

(39)

ice/water and extracted with dichloromethane. The organic layer is washed with brine, dried over $Na_2SO_4$ and evaporated to give the dithioacetal.

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# 4.1

# Oxidation of Carbon–Boron Bonds

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## 4.1.1 INTRODUCTION

Carbon–boron bonds are generally rather easily oxidized and indeed volatile trialkylboranes such as trimethylborane and triethylborane are spontaneously inflammable when exposed to air. Less volatile organylboranes do not spontaneously inflame but are nevertheless readily oxidized by oxygen and a variety of other reagents. Consequently, it is normally necessary to carry out organoborane reactions in an inert atmosphere.

The high reactivity of organoboranes to oxidizing agents can be ascribed to the availability of a vacant *p*-orbital on boron, which provides the opportunity for a kinetically favorable attack, and to the thermodynamic stability of the B—O bond (111–120 kcal $mol^{-1}$; 1 cal = 4.18 J) compared with the B—C bond (81–88 kcal $mol^{-1}$).[1]

Although oxidation of R—B bonds may be defined very generally, for the purposes of this review only processes leading from R—B to R—X, where X is a group bonded *via* an atom more electronegative than carbon (in particular OR, $NR_2$, SR, SeR, halogen), and processes leading to alkenes [R(–H)], are included.

Oxidations of organoboranes involve numerous reagents and several different general mechanisms, most of which parallel those which occur for other types of organoborane reactions. The mechanisms fall under three broad headings: (i) ionic, with a 1,2-shift from boron to a heteroatom (equations 1–3); (ii) radical; and (iii) electrocyclic.

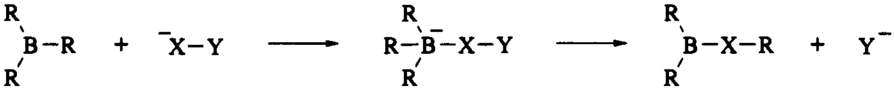
(1)

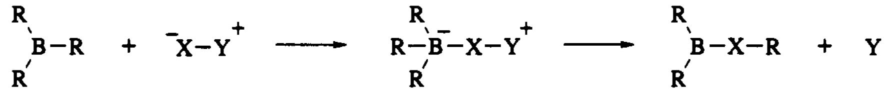
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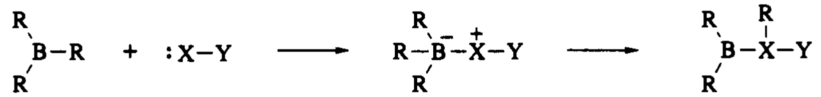
(3)

In general, the ionic reactions of equations (1) to (3) proceed with retention of configuration of the migrating organyl group.

There are two common types of radical reactions of organoboranes: bimolecular homolytic substitution ($S_H2$; equation 4); and α-abstraction processes (equation 5). Both of these can lead to final products by chain processes, as illustrated for the α-abstraction reaction by the continuation shown in equation (6). The radicals produced in these reactions are unlikely to retain complete stereochemical integrity except in special circumstances. The nature of the further reactions, such as equation (6), determines whether or not the products are such as to be included in this section.[2]

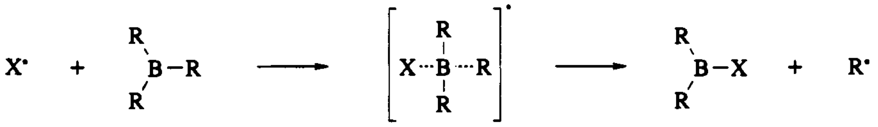
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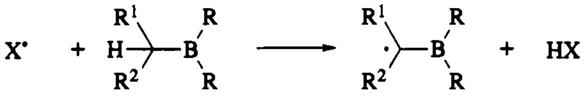
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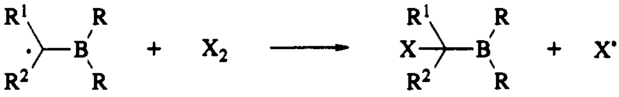
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Electrocyclic reactions (equation 7) may also lead to oxidation of organoboranes, usually with retention of configuration of the organyl group.

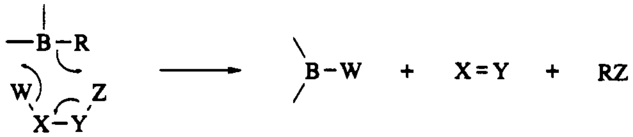
(7)

Oxidation reactions of organoboranes have been extensively reviewed as subsections of general accounts of boron chemistry,[3–7] of which reference 3 is the latest and most complete. In the remaining sections of this review, the essential features of the more synthetically useful oxidation reactions are considered in detail.

### 4.1.2 OXIDATION WITH ALKALINE HYDROGEN PEROXIDE

The reaction of organoboranes with alkaline hydrogen peroxide (equation 8) is one of the oldest[8,9] and most widely used methods for the release of organyl residues from organoboranes. The reaction proceeds with retention of configuration for all three alkyl groups.[10,11] This property is proving invaluable for the production of alcohols of high optical purity. Thus, enantiomerically pure (+)-$Ipc_2BH$ gives (*S*)-(+)-butan-2-ol of 98.4% enantiomeric purity by hydroboration of *cis*-but-2-ene followed by alkaline hydrogen peroxide oxidation of the intermediate organoborane.[12] Similarly, 3-methylbutan-2-ol of 99.6% optical purity has been prepared by the oxidation of diethoxysiamylborane with alkaline hydrogen peroxide.[13,127]

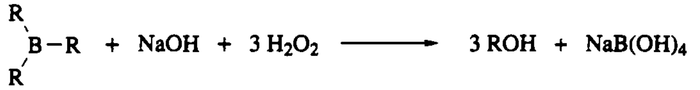

$$R_3B + NaOH + 3\,H_2O_2 \longrightarrow 3\,ROH + NaB(OH)_4 \qquad (8)$$

The mechanism of the reaction[14,15] is believed to be that shown in equation (9), this being a specific example of equation (1), with hydroperoxide anion being the reactive species. Detailed study[14] has led to the proposal of various transition states at different pH values.[16] However, the reaction may be carried out satisfactorily over a wide range of concentrations of base and hydrogen peroxide[17] providing that the reaction mixture is kept alkaline, as otherwise radical reactions may intervene with deleterious stereochemical consequences.

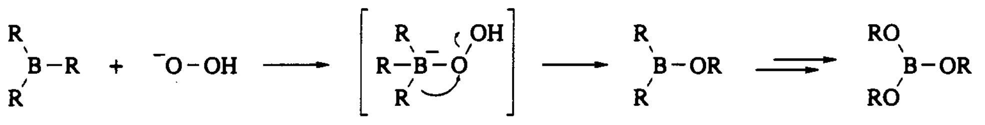

(9)

In general, oxidation is carried out in the medium used for hydroboration (THF, glyme, diglyme). Immiscibility is generally not a problem, though sometimes ethanol may be added to aid miscibility. Aqueous alkali is added first to the organoborane and then hydrogen peroxide, with caution.[3] Isolation of products is simple, though when 1,2- or 1,3-diols are produced, it is an advantage to add mannitol to liberate them.[18] The reaction mixture is frequently opened to air during the oxidation. However, this may lead to radical oxidation by oxygen competing with alkaline hydrogen peroxide oxidation. Hence, when retention of stereochemistry is important, it is sensible to maintain an inert atmosphere until oxidation is complete.

Oxidation with alkaline hydrogen peroxide is remarkably specific for cleavage of the C—B bond and, in the usual conditions, will tolerate acetal, aldehyde, alkene, alkyne, carboxylic acid, ester, ether, ketone, halogeno, nitrile, silyl and sulfonyl groups.[17] Cyclopropylboranes may need special conditions,[19] though not always.[20,21] In certain cases, such as readily hydrolyzed phenolic esters, the use of acetate or phosphate buffers at pH $\approx$ 8 is advantageous.[22,23] It is even possible to selectively oxidize an organoborane containing a sulfide group as long as 3 mol equiv. or more of sodium hydroxide to 1 of trialkylborane are used.[24,25]

Alkaline hydrogen peroxide easily oxidizes practically all alkyl- and cycloalkyl-boranes in a rapid and quantitative fashion.[17] There is a reactivity trend of $R_3B > R_2BX > RBX_2$ (X = halogen, OH, OR; note that boron halides will anyway be hydrolyzed to hydroxides under the oxidation conditions), which is consistent with reduced acceptor ability of the boron atom when an electron pair of an adjacent group interacts with the vacant boron orbital.[7,8] Increasing the steric hindrance around the boron atom may inhibit the reaction to the point at which it ceases altogether.[26,27]

Although hydroboration of alkenes is the most widely used method for the production of organoboranes, some alkylboranes as well as allyl- and aryl-boranes cannot be made by this method. Another general process that can then be used, and that proceeds in reasonable yields, is the reaction of a boron compound such as diborane[28,29] or, more commonly, an alkoxyborane[30] with an organometallic compound. The organometallic compound may be an organolithium,[5] organomagnesium[28] or organomercury(II) compound.[31] Thus, the overall process of reaction of the organometallic with the boron reagent followed by alkaline hydrogen peroxide allows 'one pot' oxidation of many organometallic compounds (equation 10).

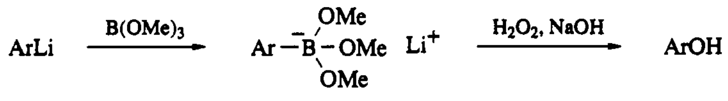

$$ArLi \xrightarrow{B(OMe)_3} Ar\!-\!\overset{-}{B}(OMe)_3\ Li^+ \xrightarrow{H_2O_2,\ NaOH} ArOH \qquad (10)$$

Many aromatic boron compounds are readily oxidized to phenols, as illustrated in equation (11) for the oxidation of aryldihydroxyboranes (arylboronic acids). This is a useful synthetic pathway as arylboronic acids can resist both alkaline permanganate and nitric acid, so that many derivatives are available.[32]

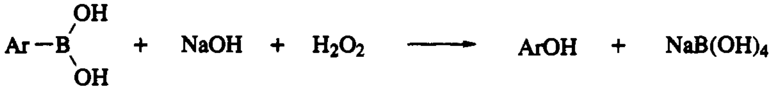

$$\mathrm{Ar{-}B(OH)_2} + \mathrm{NaOH} + \mathrm{H_2O_2} \longrightarrow \mathrm{ArOH} + \mathrm{NaB(OH)_4} \qquad (11)$$

The process has been used with heteroaromatics, examples being the production of 2- and 3-thiolenones (equation 12),[33a] thienylmethacrylates[33b] and butenolides.[34]

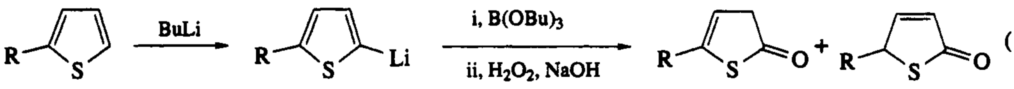

(12)

Oxidation of alkenylboranes with alkaline hydrogen peroxide is an important pathway to aldehydes and ketones (equation 13). Care must be taken to inhibit hydrolysis of the alkenylborane to the corresponding alkene and hence buffered conditions are frequently used.[35–37] The reaction tolerates the same wide range of functionality as the oxidation of alkylboranes.

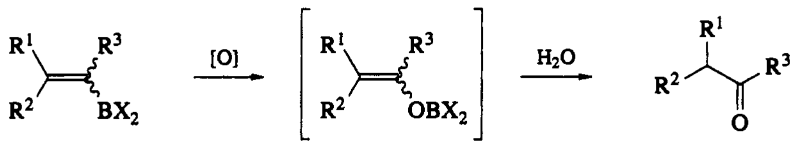

(13)

Allylboranes, which are available from organometallics or by hydroboration, undergo oxidation without allylic transposition and with retention of stereochemistry. This applies both to regio- and stereochemically defined allylic dialkylboryl[38] and allylic dialkoxyboryl[39] compounds (equations 14 and 15).

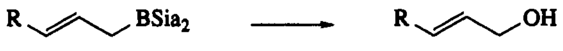

(14)

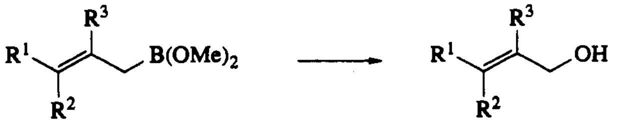

(15)

1,1-Diboryl compounds do not yield aldehydes with alkaline hydrogen peroxide. Instead there is rapid hydrolysis, presumably *via* a boron-stabilized carbanion (see Volume 1, Chapter 2.6) which is protonated and then oxidized to the alcohol (equation 16).[35]

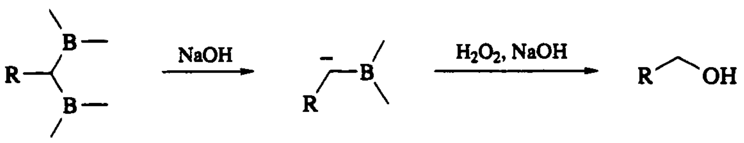

(16)

Boracyclanes are oxidized in the usual fashion to yield either diols or triols (*e.g.* equations 17[40] and 18[41]), as are compounds containing two or more independent boryl groups.

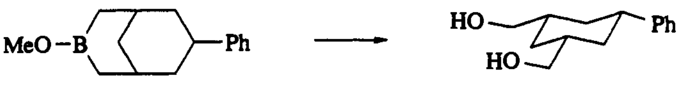

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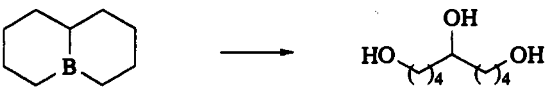

(18)

### 4.1.3 OXIDATION WITH HYDROGEN PEROXIDE IN AN ACIDIC MEDIUM

Organoboranes may be oxidized by hydrogen peroxide in an acidic medium. The mechanism of oxidation of alkyldihydroxyboranes in such conditions has been studied and the protonated transition state (**1**) proposed, as compared with transition state (**2**) for the reaction in an alkaline medium.[14]

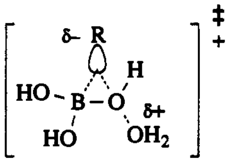

**(1)**

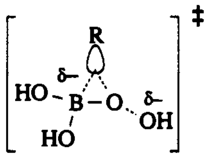

**(2)**

The acid reaction has been used in cases in which complications have been noted with the alkaline hydrogen peroxide reaction. Thus, 1,1-bis(boronates) smoothly yield aldehydes and 1,2-bis(boronates) give 1,2-diols (equations 19 and 20) when oxidized with acidic hydrogen peroxide.[42,43]

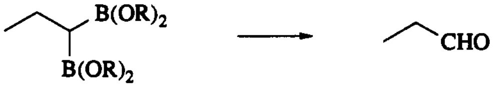

(19)

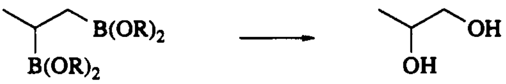

(20)

Vinylboranes react with acidic hydrogen peroxide to give aldehydes,[44] whilst the oxidation of α-haloboronic acids in the presence of DNP/$H_2SO_4$ to give aldehyde-2,4-DNPs in good yields was used as a proof of structure (equation 21).[45]

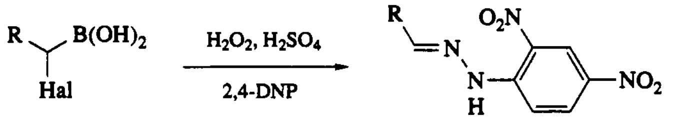

(21)

Though oxidation with acidic hydrogen peroxide is rarely used, alkyl- and aryl-boronic acids are readily attacked with a migratory order of $Bu^t \approx PhCH_2 > Bu^s > Bu^n > Ph >$ vinyl >> Me. It appears, therefore, that the reaction might be useful for selective oxidations as well as for oxidations of base labile organoboranes.[14]

### 4.1.4 OXIDATION WITH TRIMETHYLAMINE *N*-OXIDE

Trimethylamine *N*-oxide, either anhydrous[46] or as its readily available dihydrate,[47] smoothly oxidizes a wide variety of alkyl, cycloalkyl, aryl and heterocyclic boron derivatives to the corresponding organyloxyboranes (equation 22) which, in the case of the dihydrate, are hydrolyzed in the reaction mixture. Anhydrous trimethylamine *N*-oxide is simply prepared[48] and this reagent must be used for the oxidation of alkenylboranes if prior hydrolysis is not to compete with oxidation.[48,49] Alkynylboranes are not oxidized by trimethylamine *N*-oxide.[46]

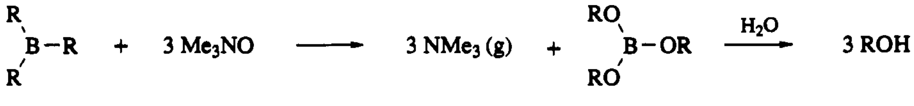

$$R_3B + 3\,Me_3NO \longrightarrow 3\,NMe_3\,(g) + (RO)_3B \xrightarrow{H_2O} 3\,ROH \qquad (22)$$

Oxidation with trimethylamine *N*-oxide is not complicated by side reactions and proceeds in a stepwise fashion such that one primary alkyl group is oxidized at 25 °C, the second at 65 °C and the third at 120 °C.[50] The trimethylamine evolved can be estimated and thus the method can be used for the quantitative estimation of organoboranes.[46] The rates of oxidation are not markedly solvent dependent and there is a clear cut ease of oxidation in the order tertiary alkyl > secondary cycloalkyl > secondary alkyl > primary alkyl > branched primary alkyl > vinyl. Some examples of useful differentiation are shown in equations (23)[51] and (24).[52]

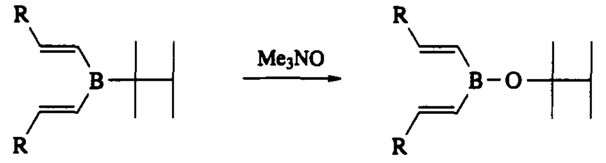
(23)

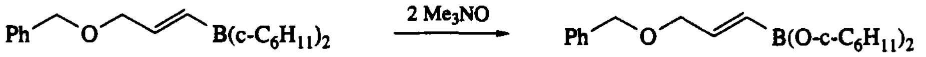
(24)

The oxidation tolerates many functional groups, including alkyl sulfide,[25] and has been used for the oxidation of cyclopropylboranes[53] (see references 19 and 54); however, it has also been used to produce acylsilanes (equation 25)[55] which are particularly sensitive to alkaline hydrogen peroxide.

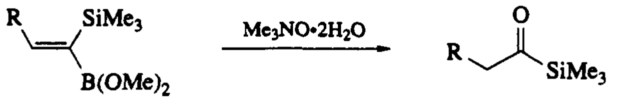
(25)

The reaction proceeds with retention of configuration, as illustrated for the oxidation of a chiral organoborane in equation (26), which goes in good yield to give product of 98% optical purity.[56] The mechanism is expressed by equation (27) and is an example of general equation (2). Certain betaines (3), particularly those derived from tripropynylborane,[57] triphenylborane[58] and $BF_3$,[59] are reasonably stable and can be characterized.

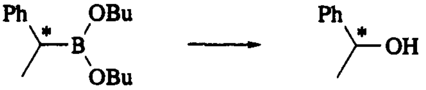
(26)

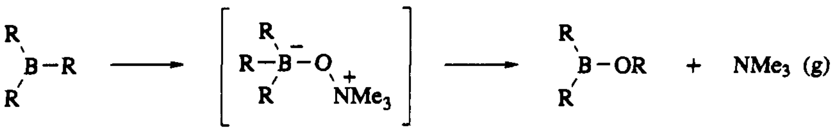
(3)

(27)

The action of *N*-oxides of α-dimethylaminocarboxylic acids on dihydroxyphenylborane produces the internal chelates of the oxidation products.[60] Various pyridine and quinoline *N*-oxides may be used to oxidize organylboranes, but there can be some alkylation of the heteroaromatic rings.[61]

## 4.1.5 AUTOXIDATION

The autoxidation of organoboranes has been extensively studied and there are many reviews of the topic.[3-7]

Autoxidation of organoboranes generally proceeds to give dialkoxyboranes (equation 28) but by use of pure oxygen and in the presence of THF the reaction may be taken to completion (equation 29).[68]

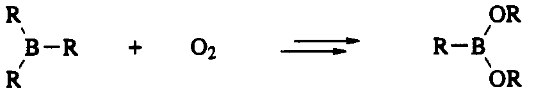
(28)

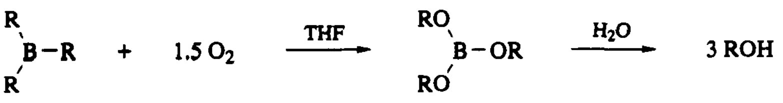
(29)

It is generally agreed,[6,7] on the following grounds, that autoxidation is a radical chain process: (a) reactive radical scavengers (galvinoxyl or iodine) exhibit a measurable inhibiting effect; (b) the reaction can be initiated by radical generators such as Bu$^t$OCl; and (c) stereodefined alkyl groups lose their stereointegrity in forming the intermediate alkylperoxyboron compounds. The kinetic behavior is reminiscent of hydrocarbon oxidation, but the $S_H2$ step is up to $10^7$ times faster than for the corresponding reaction of hydrocarbons.

The initiation step remains in doubt. It may involve a transient $O_2BR_3$ complex which rearranges, followed by homolytic cleavage to give a supply of radicals. Alternatively, a displacement reaction (equation 30) might occur. The initiation step is first order in borane and also in oxygen and there is a large steric effect on both its induction period and rate.[62,63] Thus, tri(primary alkyl)boranes generally undergo initiation more readily than tri(secondary alkyl)boranes but an order of tricyclohexylborane > $Bu^s{}_3B$ > $Bu^i{}_3B$ suggests that steric factors cannot be considered alone.[62,63]

For the overall reaction the first B—C bond oxidizes faster than the second and this, in turn, much faster than the third. The observed trends are $R_3B > R_2BX > RBX_2$ (X = OR, OH, Cl), and $R^t$—B > $R^s$—B > $R^n$—B > Me—B > vinyl—B. The overall process has been expressed[7] as in equations (30)–(33).

$$R_3B + O_2 \longrightarrow R^\bullet + R_2BO_2{}^\bullet \qquad (30)$$

$$R^\bullet + O_2 \longrightarrow RO_2{}^\bullet \qquad (31)$$

$$RO_2{}^\bullet + R_3B \longrightarrow RO_2BR_2 + R^\bullet \qquad (32)$$

$$2\,RO_2{}^\bullet \text{ or } 2\,R^\bullet \longrightarrow \text{stable products} \qquad (33)$$

Although this is the mechanism which is generally written, it has not been rigorously verified and is incomplete. It does not indicate how $R_2BO_2R$ is converted into $RB(OR)_2$ and it may be that this step is not radical in nature. Further evidence for this is that boron peroxides $(RO_2)_3B$ and $(RO)_2BOOR^1$ decompose only above 100 °C,[64] whereas reaction of $Pr_3B$ with $Bu^tO_2B(OBu)_2$ proceeds rapidly at room temperature.[65] Studies on $BuO_2BBu_2$ and its analog indicate that their decomposition does not proceed by a radical mechanism.[66] Furthermore, although simple chiral boranes autoxidize with racemization,[67,68] this loss of steric integrity need not be total, as shown in equation (34).[69]

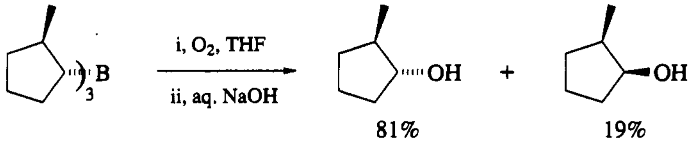

(34)

Whereas the use of 1.5 equiv. of oxygen to 1 of trialkylborane leads to quantitative yield of alcohol, as in equation (29), use of 2 equiv. of oxygen followed by addition of hydrogen peroxide (to prevent internal redox reactions) proceeds according to equation (35) to give 2 mol equiv. of alkyl hydroperoxide per mol of trialkylborane.[70]

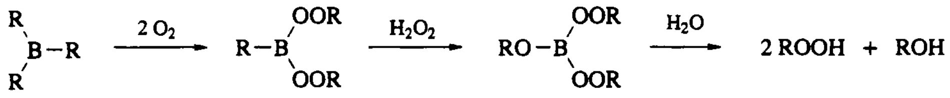

$$R_3B \xrightarrow{2\,O_2} RB(OOR)_2 \xrightarrow{H_2O_2} ROB(OOR)_2 \xrightarrow{H_2O} 2\,ROOH + ROH \qquad (35)$$

This reaction wastes one of the three alkyl groups, a limitation overcome by use of alkyldichloroborane etherates (equation 36), which are the precursors of choice for the preparation of alkylhydroperoxides.[71]

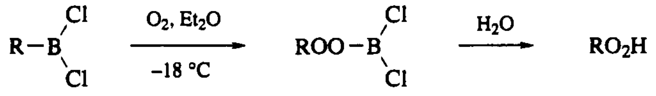

$$RBCl_2 \xrightarrow[-18\ ^\circ C]{O_2,\ Et_2O} ROOBCl_2 \xrightarrow{H_2O} RO_2H \qquad (36)$$

## 4.1.6 OXIDATION BY PERACIDS

It was early reported[8a] that perbenzoic acid in chloroform at room temperature quantitatively oxidizes tri-*n*-butylborane as in equation (37). The reaction with peroxytrifluoroacetic acid has been used analytically[72] but very little in synthesis.

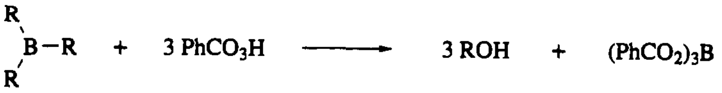

$$R_3B + 3\,PhCO_3H \longrightarrow 3\,ROH + (PhCO_2)_3B \qquad (37)$$

The mechanism of the reaction is not certain, but it appears to have analogies with the protonolysis of organoboranes by carboxylic acids and on that basis could be formulated as in equation (38), which is an example of general equation (7).

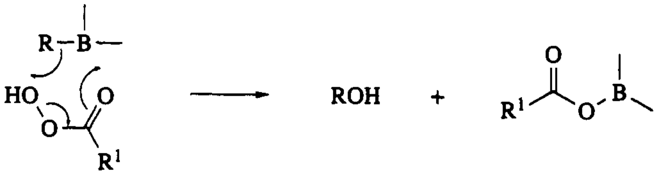

(38)

Although oxidation of 1,1-bis(dialkylboryl) compounds with alkaline hydrogen peroxide proceeds with initial hydrolysis rather than oxidation (equation 16), oxidation with excess MCPBA yields carboxylic acids in good yields. The overall process is an excellent route from 1-alkynes to carboxylic acids (equation 39).[73]

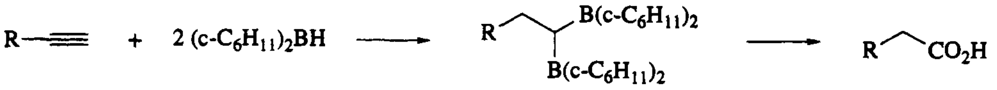

(39)

Oxidation of 1,1-bis(dialkoxyboryl)alkanes with MCPBA gives aldehydes, and similar oxidation of 2,2-bis(dialkoxyboryl)alkanes yields ketones.[74]

Oxidation by MCPBA offers advantages when other methods give problems. Thus, a series of alkenylboranes containing malonate or acetoacetate units could not be converted directly to the corresponding ketones using alkaline hydrogen peroxide due to complications arising from ester hydrolysis. However, MCPBA oxidation gave the ketones in excellent yields (*e.g.* equation 40).[23]

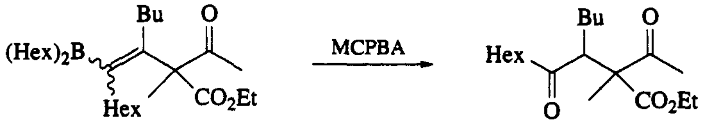

(40)

Similarly, an acetoxyphenyl-substituted boron heterocyclic compound, resulting from a cyanoborate reaction, lost the phenolic acetate group even when buffered hydrogen peroxide was used. However, MCPBA gave the required ketone retaining the labile ester group (equation 41).[75]

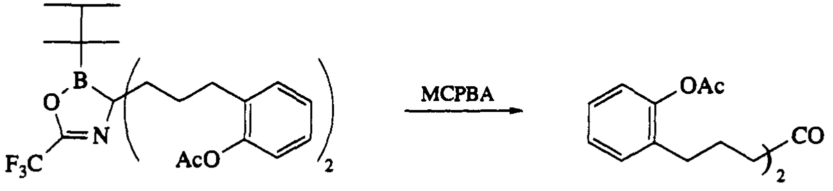

(41)

Peracid oxidation of organylboranes is a smooth and operationally simple procedure that proceeds in mildly acidic conditions in anhydrous solvents. Yields are generally high and the method, though infrequently used at present, should always be considered as an alternative to oxidation with alkaline hydrogen peroxide.

## 4.1.7 OXIDATION WITH CHROMIUM REAGENTS

### 4.1.7.1 Chromic Acid

The oxidation of (secondary alkyl)boranes with chromic acid leads to ketones,[76–78] and in combination with hydroboration provides a high-yielding route from alkenes to ketones. The reaction gives ketones at pH < 3, whereas at pH 3–7 secondary alcohols are produced.[78] Therefore, 4M $H_2Cr_2O_7$ in a water–ether two-phase system has been recommended for conversion of cycloalkylboranes to cycloalkanones.[77] The method has been used widely in synthesis,[3,7] an example being given in equation (42) in which a chiral ketone is produced.[79,80]

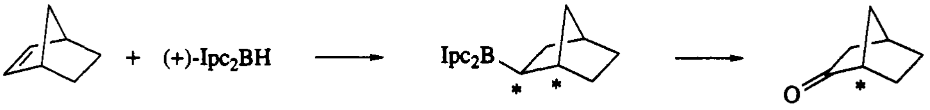

(1*S*)-norbornan-2-one

(42)

The ketone produced is generally that to be expected, but occasionally the strong acid conditions may lead to unexpected products, as shown in equations (43)[81] and (44).[82]

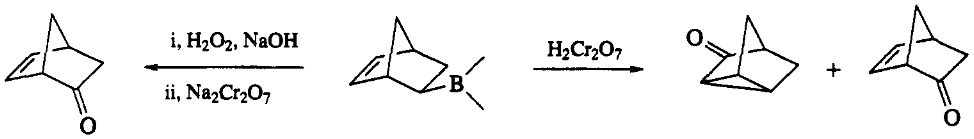

(43)

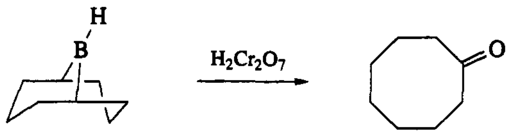

(44)

1,2-Diboryl compounds yield alkenes on reaction with chromic acid (equation 45),[83] a reaction also noted in a peracid oxidation[73] and oxidation with pyridinium chlorochromate.[84]

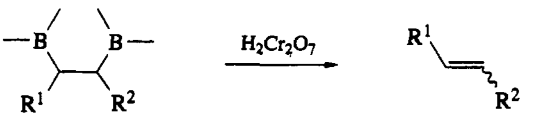

(45)

Chromic acid is particularly useful for the oxidation of heterocyclic boranes[85–87] which are resistant to oxidation by the usual oxidants ($NaOH/H_2O_2$; $R_3NO$; $O_2$), *e.g.* equation (46).[85]

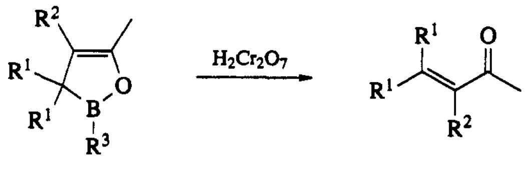

(46)

### 4.1.7.2 Chromyl Trichloroacetate

Some 2,5-diboradihydropyrazines have been successfully oxidized with chromyl trichloroacetate,[88] but the reagent has not been widely used.

### 4.1.7.3 Pyridinium Chlorochromate

Pyridinium chlorochromate (PCC) is a very useful reagent for the oxidation of organoboranes to carbonyl compounds in mildly alkaline and anhydrous conditions.[89] As well as oxidizing (secondary alkyl)boranes to ketones,[90,91] PCC oxidizes (primary alkyl)boranes to aldehydes in excellent yields (equation 47).[89] The latter transformation cannot be accomplished with chromic acid. The reagent tolerates the presence of alkene, ester and acetal groups.[90]

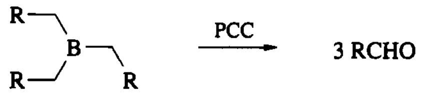

(47)

The observation[92] that trialkylboranes are oxidized to aldehydes as fast as the free alcohols and much faster than acetates prompted the introduction of an efficient one-pot procedure for the conversion of acids to aldehydes (equation 48) in 69–82% isolated overall yields.[93]

PCC oxidizes *gem*-diboryl compounds to ketones.[84]

$$\mathrm{RCO_2H} \xrightarrow{\mathrm{H_3B{\bullet}SMe_2}} \mathrm{(RCH_2O)_3B} \xrightarrow{\mathrm{PCC,\ CH_2Cl_2}} 3\ \mathrm{RCHO} \qquad (48)$$

## 4.1.8 MISCELLANEOUS CHEMICAL OXIDIZING AGENTS

Almost any oxidizing agent might be expected to oxidize an organoborane, but few have received systematic investigation. Moreover, aryldihydroxyboranes are relatively resistant to oxidation and nitration of the ring,[94] and oxidation of a methyl group to a carboxy group with potassium permanganate[95] has been achieved without breaking the Ar—B bond.

The reagent $MoO_5$–pyridine–HMPA (MOPH) was introduced for the anhydrous, ambient temperature oxidation of intermediates in aldol reactions of alkenyloxyboranes.[96] It also oxidizes simple organoboranes, the oxidation proceeding with retention of configuration of the alkyl groups.[97]

A mixture of ruthenium tetroxide, sodium periodate and sodium acetate was effective for the conversion shown in equation (49).[98]

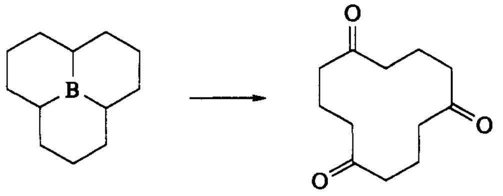

(49)

The action of lead tetraacetate on trialkylboranes produces alkyl acetates.[99]

Although aryldihydroxyboranes appear to resist alkaline permanganate,[94,95] butyldihydroxyborane is oxidized to butanol with this reagent.[100]

Dialkoxy(α-phenylthio)alkylboranes are readily converted to monothioacetals by *N*-chlorosuccinimide in methanol (equation 50).[101]

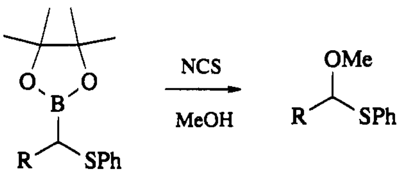

(50)

Sodium hypochlorite oxidizes aryldihydroxyboranes to phenols[102] and trialkylboranes to the corresponding alcohols.[103] Use of sodium hypobromite for the oxidation of phenyldihydroxyborane gave 2,4,6-tribromophenol, regardless of the ratio of the reactants.[102]

Sodium perborate has been recommended for the oxidation of alkenyldialkoxyboranes to aldehydes.[104] In particular, the reagent avoids the formation of possibly hazardous 2:1 aldehyde–hydrogen peroxide adducts as well as C—C bond cleavage.[104a] Sodium percarbonate is an air-stable solid, inexpensive and self-buffered, that appears to be a promising oxidant.[104b]

Alkyl- and phenyl-dihydroxyboranes, their anhydrides and dialkoxy derivatives are oxidized with alkyl hydroperoxides to the corresponding alcohols and phenols.[105–107]

## 4.1.9 ELECTROCHEMICAL OXIDATION

Electrochemical oxidation of organoboranes can lead to a variety of products, depending on the natures of the electrodes, solvents and electrolytes. It appears that radicals, R·, are generated and that these may couple to give dimeric alkanes, react with other species present or be further oxidized to cations, $R^+$, which then react. Thus, when trialkylboranes, $R_3B$, are subjected to electrolysis in methanolic KOH solution between platinum electrodes, the alkyl residues couple to each other to give dimeric alkanes R—R.[108] However, when a graphite anode is used in a methanolic solution containing NaOMe and $NaClO_4$, then trialkylboranes yield alkyl methyl ethers (ROMe) in 84–100% yield.[109] This reaction is thought to pass through $R^+$, as isomerization occurs to an appreciable extent. Thus the oxidation of tri-*n*-octylborane gives a mixture of 1-, 2-, 3- and 4-methoxyoctanes with a ratio of 8:66:25:1. In the presence of sodium acetate, electrolysis of $R_3B$ gives alkyl acetates.[109] When acetonitrile is used as the medium then $RCH_2CN$ is obtained[110] and if nitromethane is used then $RCH_2NO_2$ results.[111]

Sodium tetraphenylborate[112] and diphenylhydroxyborane[113] both yield biphenyl on anodic oxidation. Similar results can be obtained using a variety of chemical oxidants.[114]

## 4.1.10 OXIDATION BY CARBONYL COMPOUNDS TO PRODUCE ALKENES

Trialkylboranes reduce carbonyl compounds by utilizing a β-hydrogen atom, as in equation (51).[115]

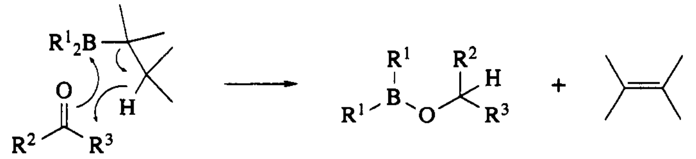

(51)

The reaction was first explored with triethylborane[116] and then extended to higher alkylboranes.[117] Only two unbranched alkyl groups participate and even then prolonged heating at 150–200 °C is required.[117] Only the exocyclic alkyl groups of *B*-alkyl-9-BBN compounds participate in the reaction and hence such compounds may be used as a probe of the intrinsic ease of oxidizability of different alkyl groups.[118] The results show that branching at the β-position strongly enhances the ease of oxidation. The relative rates of oxidation of the *trans*-2-methylcyclopentyl, siamyl, cyclopentyl, isobutyl and ethyl derivatives are 1000:364:267:50:0.72, respectively.[118] Since *B*-alkyl-9-BBN derivatives are mostly prepared from alkenes by hydroboration with 9-BBN-H, the process has little preparative value for the synthesis of alkenes. Instead, the reaction is useful as a very specific method for the reduction of the carbonyl compound, and for this purpose *B*-siamyl-9-BBN has been used for the reduction of aldehydes.[119] α,β-Unsaturated aldehydes yield only allylic alcohols.[119] The rates of reaction of aldehydes vary very little but ketones react at least two orders of magnitude more slowly, thus allowing highly selective reductions to be carried out. The process has been shown to tolerate alkene, amino, aryl, ether, halogen and nitro groups.[119]

3-Pinanyl-9-BBN (Alpine borane; **4**) is a chiral borane that is readily oxidized by aldehydes. Aliphatic deuterioaldehydes undergo chiral reduction to give alcohols with 84–98% *e.e.*[120] The chiral alkene is regenerated in the process, only the hydrogen at the 2-position having been utilized, and can be reused. Equation (52) serves as an illustration of the stereochemistry of the process.

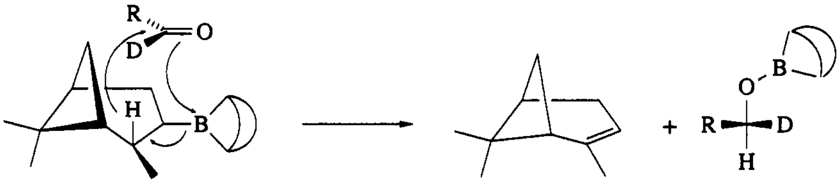

(52)

α,β-Alkynyl ketones are excellent substrates for chiral reduction by Alpine borane.[121] The stereochemistry of the product alcohol is predicted by replacement of the deuterium atom in equation (52) by the alkynyl group.[122] Use of neat reagents[123] and/or pressure[124] allows the reduction of simple ketones, α-halo ketones, α-keto esters and α-ketonitriles.

The nopol derivative (**5**) has advantages in some cases[125] but the most striking advance has been the introduction of commercially available chloroborane (**6**). Compound (**6**) is a stronger Lewis acid than (**4**) or (**5**) and also less subject to steric hindrance.[126] It readily reduces acetophenone (98% *ee*), 2,2-dimethylcyclopentanone (98% *ee*) and pinacolone (95% *ee*).[126]

Another important application of the alkene displacement process is in the synthesis of a whole series of alkyldiethoxyboranes of very high optical purity by displacement of α-pinene from 3-pinanylalkyl-

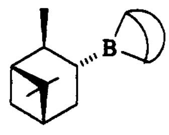

**(4)**

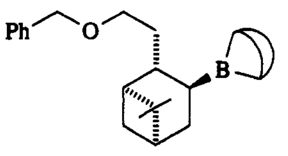

**(5)**

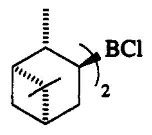

**(6)**

ethoxyboranes, as in equation (53).[127] The chiral alkyldiethoxyborane products are certain to have enormous influence on the field of chiral synthesis.[127]

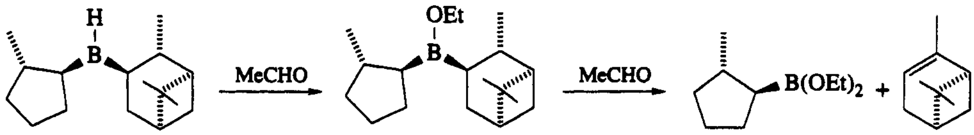

## 4.1.11 CHLORINOLYSIS OF C—B BONDS

The chlorination of trialkylboranes has not been well studied. The chlorination of $Me_3B$ at –95 °C yields $ClCH_2BMe_2$.[128] The oxidation of dialkoxy(α-phenylthio)alkylboranes with NCS has been referred to in Section 4.1.8 (equation 50). The reaction of thionyl chloride with $PhSCH_2B(OR)_2$ yields $PhSCH_2Cl$.[101]

Direct chlorination has not been used for the production of organyl chlorides from trialkyl- or triarylboranes. Chlorinolysis has been achieved by the reactions of organoboranes with aqueous copper(II) chloride[129] and iron(III) chloride.[130] However, only two of the three alkyl residues on boron are utilized (equation 54). Arylboranes are also converted to aryl chlorides with copper(II) chloride.[131]

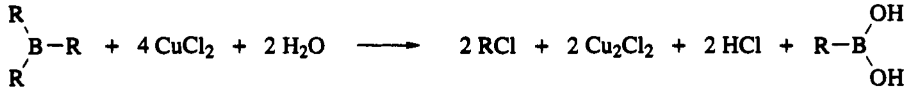

$$\mathrm{R_2B{-}R} + 4\,\mathrm{CuCl_2} + 2\,\mathrm{H_2O} \longrightarrow 2\,\mathrm{RCl} + 2\,\mathrm{Cu_2Cl_2} + 2\,\mathrm{HCl} + \mathrm{R{-}B(OH)_2} \qquad (54)$$

Nitrogen trichloride converts all three alkyl groups of $R_3B$ into alkyl chlorides, but 3 equiv. of a hazardous and not readily available reagent must be used.[132] Chlorodimethylamine[133] or dichloramine-T (equation 55)[134] may be used, but here too there is poor utilization of alkyl groups, a problem eased, but not completely overcome, by the use of *B*-alkyl-9-BBN derivatives.[134]

$$\mathrm{R_3B} + \mathrm{Cl_2NSO_2C_6H_4Me} \longrightarrow \mathrm{RCl} + \mathrm{R_2BNClSO_2C_6H_4Me} \qquad (55)$$

## 4.1.12 BROMINOLYSIS OF C—B BONDS

All three organyl groups of trialkylboranes[135] or triphenylborane[136] can be cleaved by reaction with bromine in the presence of sodium methoxide. High yields of bromoalkanes (equation 56) or bromobenzene are obtained.[148]

$$\mathrm{R_3B} + 3\,\mathrm{Br_2} + 4\,\mathrm{NaOMe} \longrightarrow 3\,\mathrm{RBr} + 3\,\mathrm{NaBr} + \mathrm{NaB(OMe)_4} \qquad (56)$$

The brominolysis of trialkylboranes is unusual among the reactions of organoboranes in that it proceeds mainly with inversion. Thus, tris-*exo*-2-norbornylborane gives 75% of *endo*-2-bromonorbornane and 25% of the *exo* isomer.[137] Over 95% inversion has been observed in the bromination of the *threo* and *erythro* isomers of tris(3,3-dimethyl-1-butyl-1,2-$d_2$)borane in the presence of NaOMe (equation 57).[138]

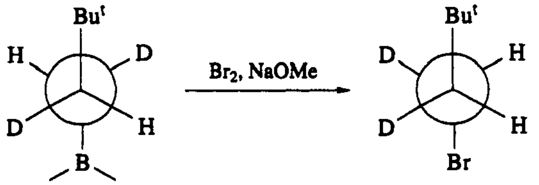

*erythro* *threo*

(57)

A modification involving the use of sodium bromide in the presence of chloramine-T has been devised to allow optimum incorporation of radioisotopic bromine.[139]

In neutral conditions bromine reacts with triorganylboranes to convert one organyl group into the corresponding bromoalkane.[140] The reaction involves a free radical α-bromination (see equations 5 and 6), followed by cleavage with hydrogen bromide, and therefore the product bromide does not retain the configuration of the original organoborane.[140] Although there is normally a strong preference for reaction with secondary rather than primary alkyl groups,[141] *B*-alkyl-9-BBN derivatives react with complete conversion of the primary *B*-alkyl group into the alkyl bromide.[142] The overall process is an efficient anti-Markovnikov addition of HBr to a terminal alkene (equation 58).

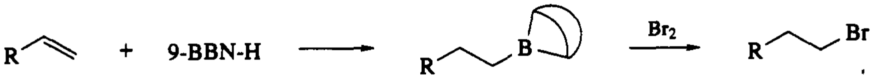

(58)

An alternative indirect but efficient method for the bromination of all three groups of tri(primary alkyl)boranes involves initial reaction with mercury(II) acetate followed by *in situ* bromination.[143]

Alkenyldialkylboranes react with bromine to give bromoalkenes *via* an addition–elimination mechanism.[144] The method of elimination controls the stereochemistry of the product bromoalkenes (Scheme 1). For reasons which are not clear, exactly opposite stereochemical results are obtained from (arylethenyl)dialkylboranes as compared with (alkylethenyl)dialkylboranes (Scheme 1).[144]

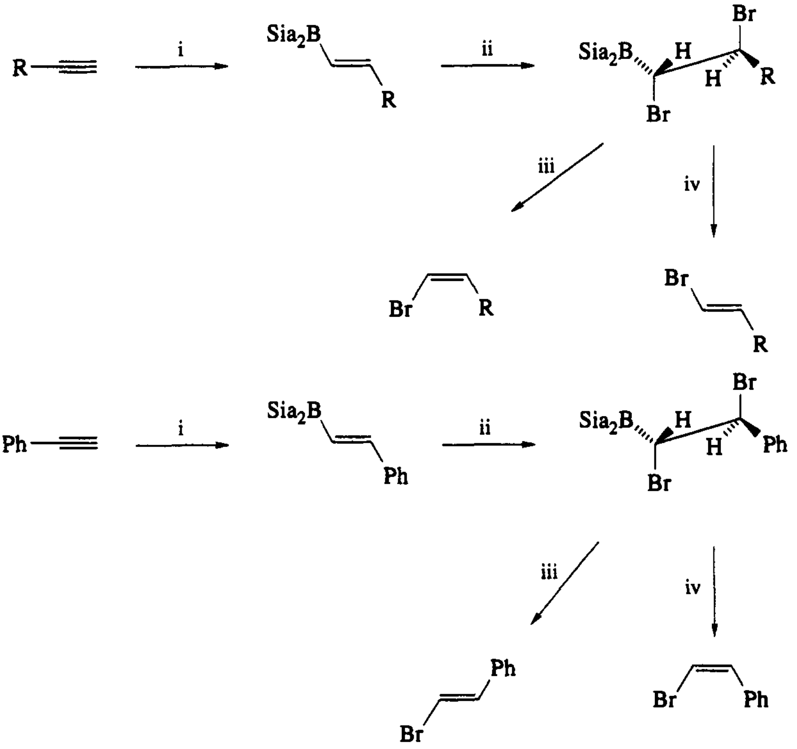

i, $Sia_2BH$, THF; ii, $Br_2$, $CCl_4$, 0 °C; iii, NaOH, 0 °C; iv, 76 °C

**Scheme 1**

Alkenyldihydroxyboranes react with bromine and base with inversion of configuration irrespective of the nature of the alkenyl group (equation 59).[145] Use of excess bromine allows utilization of catecholborane derivatives.[145]

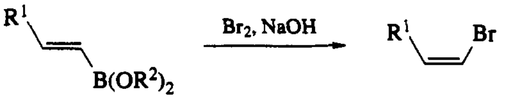

(59)

## 4.1.13 IODINOLYSIS OF C—B BONDS

In the presence of sodium methoxide, tri(primary alkyl)boranes react smoothly to yield 3 mol equiv. of iodoalkane.[146] In the presence of sodium hydroxide, two C—B bonds of tri(primary alkyl)boranes are cleaved to the corresponding iodides.[147] In the same conditions tri(secondary alkyl)boranes react significantly more slowly and only one C—B bond is broken.[147,148] For anti-Markovnikov addition of HI to terminal alkenes the process shown in equation (60) is therefore applicable.[147]

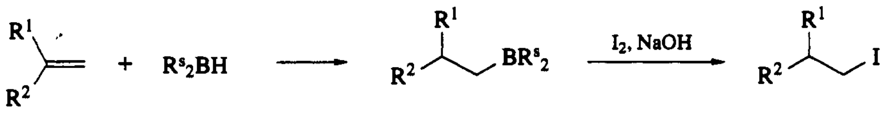

(60)

Like brominolysis, iodinolysis of trialkylboranes occurs with inversion of stereochemistry of the displaced carbon atom.[149,150]

Sodium iodide and chloramine-T can be used for the production of iodides,[150] a process that has particular application to the introduction of radioactive iodine.[151]

The reactions of alkenyldialkylboranes with iodine lead to rearrangements rather than iodinolysis. However, alkenyldihydroxyboranes undergo iodinolysis with *retention* of configuration, in contrast to the corresponding reaction with bromine, to give high yields of the corresponding iodoalkenes (equation 61).[152]

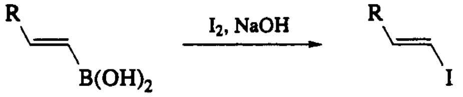

(61)

## 4.1.14 REPLACEMENT OF BORON BY NITROGEN

### 4.1.14.1 Synthesis of Primary Amines

Amines containing good leaving groups, such as hydroxylamine-*O*-sulfonic acid[153–155] and chloramine,[153] yield alkylamines on reaction with organoboranes (equation 62). Mesitylenesulfonylhydroxylamine is more soluble in THF than are the other reagents and reacts faster.[156] Chloramine may be formed *in situ* from ammonium hydroxide and sodium hypochlorite in a reaction designed for the incorporation of $^{15}N$.[157] Two of three alkyl groups on boron are displaced and hindered organoboranes may require forcing conditions.[154] The reactions proceed with strict retention of configuration at carbon and probably by an ionic 1,2-migration process,[158] an example of general equation (3).

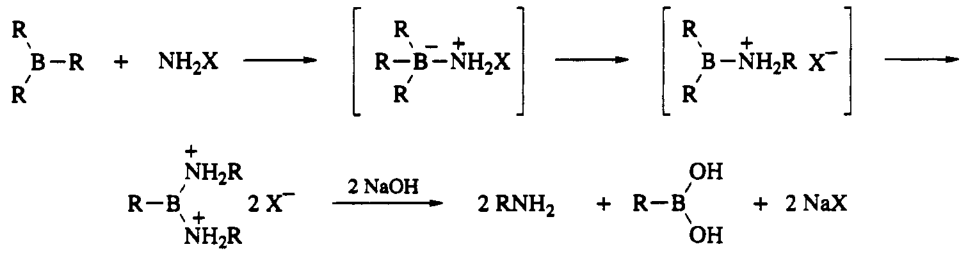

(62)

Primary amines of high optical purity can be obtained with full utilization of the organyl group through the intermediate formation of alkylmethylalkoxyboranes (equation 63).[159]

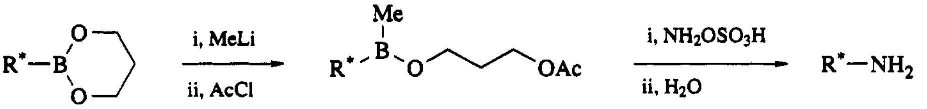

(63)

For the replacement of boron by an amino group in aryl-, styryl- and ferrocenyl-dihydroxyboranes, the reaction of copper(II) phthalimide followed by hydrazinolysis or hydrolysis, has been used (equation 64).[160,161]

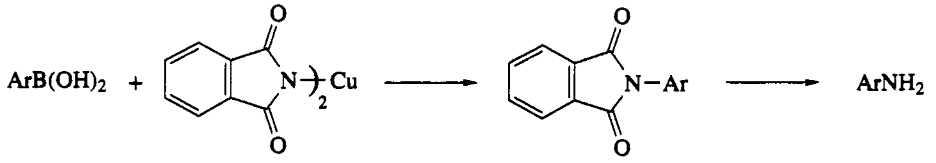

(64)

### 4.1.14.2 Synthesis of Secondary Amines

Trialkylboranes and triphenylborane react with alkyl, cycloalkyl and aryl azides with the evolution of nitrogen and the formation of dialkyl(dialkylamino)boranes, which yield secondary amines on solvolysis.[162] As only one of the organyl groups is utilized it is advantageous to use organyldichloroboranes (equation 65), which have the further advantage of requiring milder conditions.[163] The reactions proceed with retention of configuration.[164] 2-Iodoalkyl azides react at room temperature with phenyl- and alkyldichloroboranes to give products that on treatment with base give aziridines (equation 66).[165]

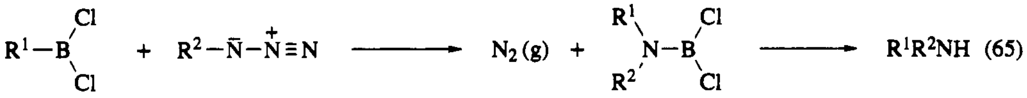

$$R^1BCl_2 + R^2{-}\bar{N}{-}\overset{+}{N}{\equiv}N \longrightarrow N_2(g) + R^1R^2N{-}BCl_2 \longrightarrow R^1R^2NH \quad (65)$$

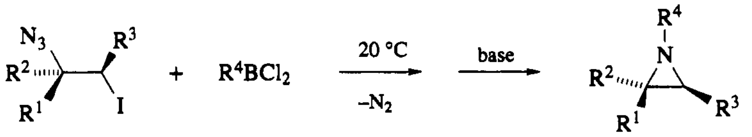

(66)

In one instance a secondary amine has been produced by two migrations from boron to nitrogen using a reagent with two good leaving groups attached to nitrogen.[166]

### 4.1.14.3 Synthesis of Tertiary Amines and Other Derivatives

*N*-Chlorodimethylamine reacts with trialkylboranes to give alkyldimethylamines, so long as the alternative radical reaction leading to alkyl chlorides is suppressed by use of the radical scavenger, galvinoxyl (equation 67).[133]

$$R_3B + ClNMe_2 \xrightarrow{\text{galvinoxyl}} R_2BCl + RNMe_2 \quad (67)$$

Trialkylboranes react with chloramine-T to give alkyl toluenesulfonamides in good yields based upon the transfer of one alkyl group (equation 68).[167]

$$R_3B + NaNClSO_2Ar \longrightarrow R_2BNRSO_2Ar \xrightarrow{\text{NaOH}} RNHSO_2Ar \quad (68)$$

Trialkylboranes react with sodium azide in the presence of hydrogen peroxide and iron compounds to give azidoalkanes ($RN_3$) in fair yields based upon the transfer of one alkyl group.[168]

## 4.1.15 REPLACEMENT OF BORON BY SULFUR OR SELENIUM

Dialkyl or diaryl disulfides react with trialkylboranes in the presence of oxygen or light to give dialkyl or alkyl aryl sulfides in good yields based upon the transfer of one alkyl group (equation 69).[169] If it is

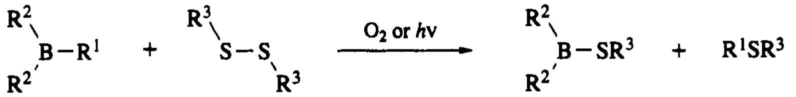

$$R^2_2B{-}R^1 + R^3S{-}SR^3 \xrightarrow{O_2 \text{ or } h\nu} R^2_2B{-}SR^3 + R^1SR^3 \quad (69)$$

necessary to conserve alkyl groups then *B*-alkylborinanes may be used, as only the *B*-alkyl group is utilized in excellent yield.[169]

Alkyl thiocyanates are obtained by the reaction of iron(III) thiocyanate on trialkylboranes in a fashion reminiscent of the reactions of iron(III) chloride (Section 4.1.11). It is not clear whether there is 60% usage of three alkyl groups or whether only two groups are in fact utilized.[170] Equation (70) shows the reaction based on the assumption of usage of three groups.

$$R_3B + 6\,Fe(SCN)_3 + 3\,H_2O \longrightarrow 3\,RSCN + B(OH)_3 + 6\,Fe(SCN)_2 + 3\,HSCN \qquad (70)$$

A similar reaction yielding alkyl selenocyanates occurs between trialkylboranes and sodium selenoisocyanate in the presence of iron(III) ions.[171] There is a strong preference for the transfer of secondary or tertiary as compared to primary alkyl groups. This allows selective transfer reactions to be carried out in yields of 57–68% (equation 71) and 67–78% (equation 72).[171]

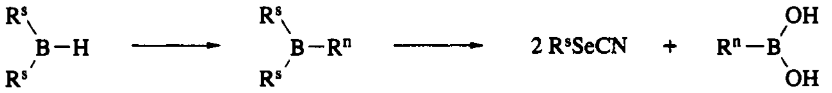

(71)

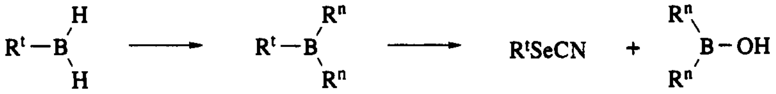

(72)

In the presence of base, phenylselenenyl bromide reacts with alkenyldihydroxyboranes to give alkenyl phenyl selenides with retention of configuration at the double bond (equation 73).[172]

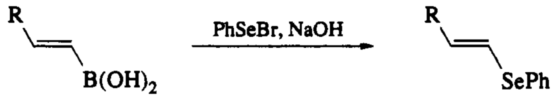

(73)

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# 4.2
# Oxidation of Carbon–Metal Bonds

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## 4.2.1 INTRODUCTION

Organometallic compounds based on very electropositive elements such as lithium and magnesium have long served as carbanion sources, but far less frequently in tactical oxidations. Oxidation of Grignard reagents and organolithium compounds to form alcohols has been employed, particularly when the direct halide to alcohol conversion is unattractive, for example because of β-branching.[1] Although organometallics may be formed in a wide variety of ways, their value in synthesis depends on the ease with which the carbon–metal bond may be transformed into some other desired functionality. Thus, in principle there should exist a range of synthetic applications for the oxidation of relatively weak carbon–metal bonds provided some (or most) of the following criteria are met: (a) the metal-containing moiety can be introduced easily and preferably in a number of ways which exhibit high levels of regio- and stereocontrol; (b) the method of introduction shows good functional group tolerance and hence minimizes protection–deprotection sequences; (c) the resulting organometallic is stable enough to withstand standard manipulations if necessary; (d) subsequent oxidation proceeds under suitably mild conditions with reagents that are chemoselective for the carbon–metal system; and (e) the oxidation pathway exhibits a high level of regio- and even stereo-control and is synthetically efficient.

The carbon–metal systems considered appropriate for this section (and not covered elsewhere in this series) are carbon–tin, carbon–mercury and, to a restricted extent, carbon–palladium bonds. Although organomercurials and organostannanes have been studied for over a century, the former continue to attract attention because of their controlled formation by the Markovnikov oxymercuration reaction (OM) and its variants,[2] and the latter because of newer and regiospecific methods for forming C—Sn bonds and oxidatively cleaving them. In both cases, significant examples of synthetically useful oxidations have appeared in recent years and form the substance of this chapter. Organothallium compounds, sometimes usefully compared with the isoelectronic organomercury systems, also exhibit synthetic utility but in general are less stable, less generally acquired and more prone than the mercurials to rearranging (carbocationic), dethallation reactions *etc*. The synthetic aspects of organothallium chemistry have been reviewed recently.[3]

## 4.2.2 OXIDATION OF CARBON–TIN BONDS

### 4.2.2.1 Introduction

Although organotin compounds (*i.e*. with at least one carbon–tin bond) date back to 1849, only relatively recently has there been general recognition of the many roles organostannanes have in synthesis. For example, organostannanes find important applications in the free radical based generation of C—H and C—C bonds, transmetallation reactions providing a range of organolithium reagents, and a number of transition metal catalyzed reactions. Much of this chemistry has been nicely organized and discussed elsewhere.[4] A newer and expanding role is related to their entry into oxidation reactions and this aspect is discussed below.

Most organostannanes are relatively stable liquids or solids, which are easily handled in air and are, by and large, insensitive to moisture. The toxicity of organostannanes has been extensively investigated, and as a rule these compounds should be regarded as hazardous and use of gloves and operating in an efficient fume hood are strongly recommended.[5] Methyl- or ethyl-tin derivatives have the highest mammalian toxicity, whereas *n*-butyl derivatives are significantly less toxic. This factor, coupled with the commercial availability of the cheaper *n*-butyl derivatives, indicates that unless methyl derivatives have special advantages, the *n*-butyl derivatives should be preferred. Reactions involving trialkylstannanes ($R_3SnR'$; R = Me, $Bu^n$) produce one equivalent of 'trialkyltin salt' ($R_3SnX$), which is generally removed by thorough washing with aqueous fluoride solution, forming the sparingly soluble $R_3SnF$ derivatives. This procedure works well for $Me_3SnX$, but less well for $Bu^n{}_3SnX$. Washing the organic phase with aqueous ammonia may be advantageous in those cases.

Two general categories of oxidation may be recognized: (a) 'direct' oxidation of the C—Sn bond to C—O groupings as in alcohols or ketones; and (b) 'oxidative fragmentations' of certain specifically functionalized organostannanes, usually under free radical conditions. With respect to cleavage of the C—Sn bond, the large covalent radius of tin (0.14 nm), the long C—Sn bond (0.22 nm), the relatively low mean C—Sn bond dissociation energy (~50 kcal $mol^{-1}$; 1 kcal = 4.18 kJ) and the polarizable but essentially covalent C—Sn bond should be noted. Thus it is no surprise that the C—Sn bond exhibits convenient reactivity under both free radical and polar conditions.

### 4.2.2.2 Unactivated Carbon–Tin Bonds

That unactivated carbon–tin bonds could be oxidized directly in a potentially useful synthetic way was demonstrated in 1964. Symmetrical tetraalkylstannanes reacted with chromic anhydride ($CrO_3$) in acetic acid to yield aldehydes and acids depending on the conditions (equation 1). Using a large excess of oxidant (12-fold excess) and long reaction times (360 h at 20 °C) a near quantitative yield of *n*-butanoic acid was obtained from $Bu^n{}_4Sn$.[6]

$$Bu^n{}_4Sn \xrightarrow[AcOH]{CrO_3} PrCHO + PrCO_2H + \text{other products} \qquad (1)$$

Development of this approach to a synthetically useful level was reported by Still, who employed large excesses of the $CrO_3$–pyridine oxidant.[7] The trimethylstannyl group was introduced either by bromide displacement or conjugate addition to enones (using $Me_3SnLi$) to provide a range of secondary or tertiary stannanes. Oxidation with $CrO_3 \cdot 2py$ (py ≡ pyridine) led to ketones, ketols or alcohols depending on the system (Scheme 1).

In the case of tertiary stannanes, oxidation leads to mixtures of alcohols and alkenes and some allylic oxidation, although 1-adamantyltrimethylstannane, incapable of elimination, provided the tertiary alcohol in good yield (Scheme 2).

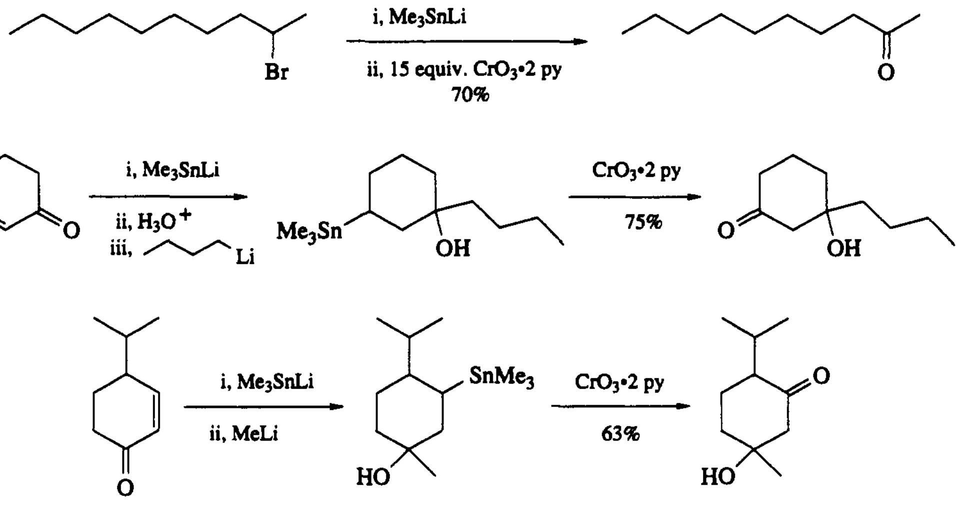
i, Me3SnLi
ii, 15 equiv. CrO3•2 py
70%
Br
O
i, Me3SnLi
ii, H3O+
iii, Li
Me3Sn
OH
CrO3•2 py
75%
O
i, Me3SnLi
ii, MeLi
SnMe3
HO
CrO3•2 py
63%

**Scheme 1**

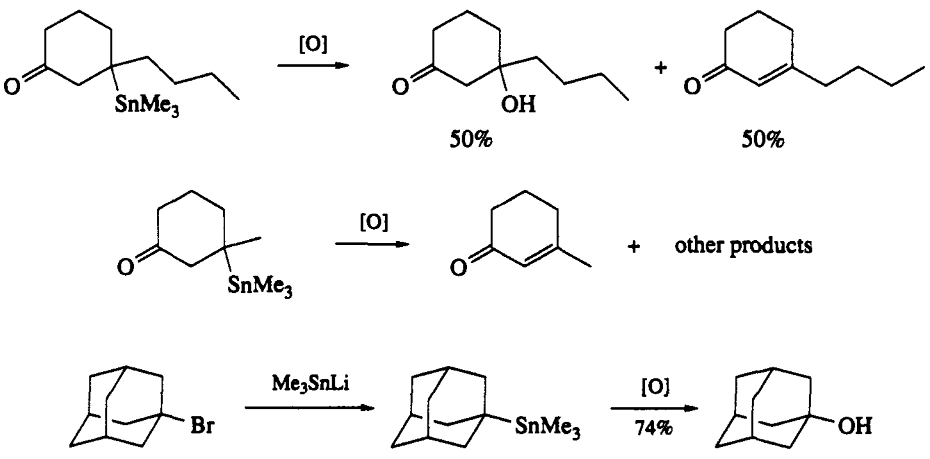
[O]
SnMe3
OH
50%
50%
+
+ other products
Me3SnLi
Br
[O]
74%
OH

**Scheme 2**

The examples shown in Scheme 2 illustrate: (a) a method for $R_3C—Br \rightarrow R_2C{=}O$ or $R_3C—OH$; and (b) dialkylative enone transposition as shown in essence in equation (2). The sequence $R_2CH—Cl \rightarrow R_2CH—Sn \rightarrow R_2C{=}O$ was crucial in a synthesis of the troponoid nezukone (**1**), as other methods of functionalizing the $R_2CH—Cl$ system in this ring failed (equation 3).[8] The dialkylative enone transposition (equation 2) was illustrated by a short synthesis of dihydrojasmone (equation 4).[7]

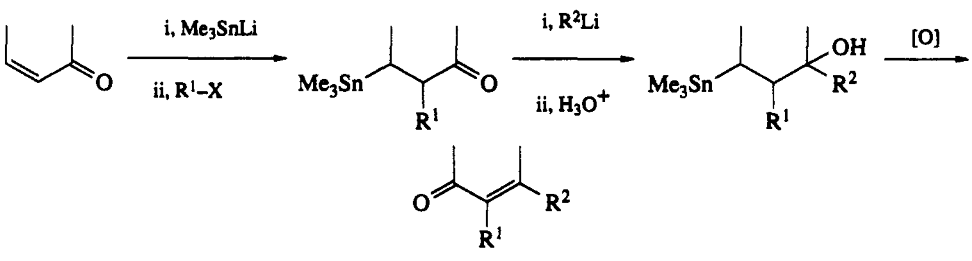
i, Me3SnLi
ii, R1-X
Me3Sn
R1
i, R2Li
ii, H3O+
OH
R2
[O]

(2)

Oxidation of dimethylhalotin groups to hydroxy groups with retention of configuration can be achieved under relatively mild conditions using alkaline hydrogen peroxide,[9] a procedure of importance for the oxidation of carbon–silicon bonds (see Volume 7, Chapter 4.3). Thus the iodine(III)-mediated cleavage of $Me_3SnR$ to $Me_2SnClR$, followed by oxidation, provides an efficient route for $R_2CH—SnMe_3$

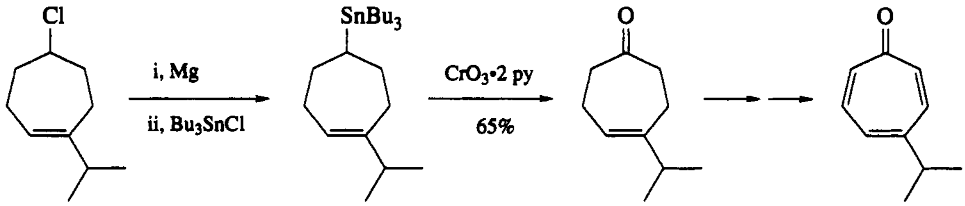

(1)

(3)

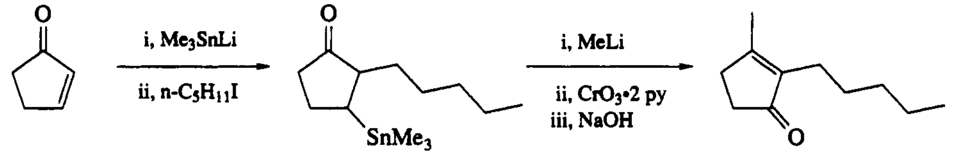

(4)

→ $R_2CH—OH$ with configurational retention (equation 5). This finding may have applications in the synthesis of various hydroxylated natural products based on organotin intermediates.

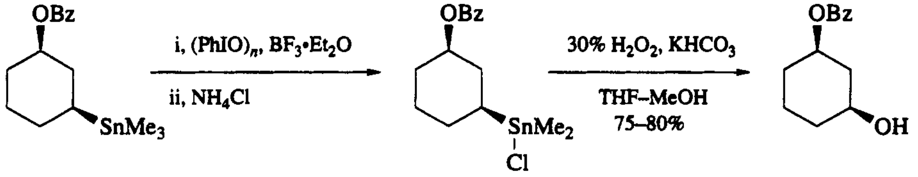

(5)

### 4.2.2.3 Allylic Stannanes

In contrast to the oxidation of unactivated stannanes, allylic derivatives are expected to be more reactive, and mild conditions and oxidizing agents can be employed successfully. A particularly useful reaction involves the conversion of an allylstannane to the allylic alcohol, and the commercially available, solid, easily handled *m*-chloroperbenzoic acid (MCPBA) is the reagent of choice for oxidations employing organic solvents such as dichloromethane. Under these conditions epoxystannanes cannot be isolated and allylic alcohols form directly (equation 6).[10,11]

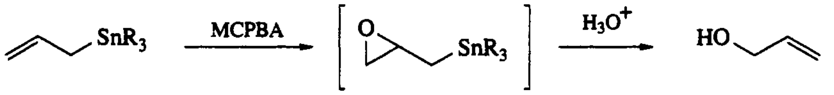

(6)

However, given the periodicity of the Group XIV congeners, and that epoxysilanes can be isolated from reactions of allylsilanes and MCPBA,[12,13] it is reasonable that epoxystannanes are intermediates in the overall conversion. Just as the 'β-silicon effect' may be regarded as dominating the chemistry of allylsilanes with electrophilic reagents,[14] the influence of the $SnR_3$ group in allylstannanes is similarly dominant. Thus epoxidation of allylstannanes may be viewed as electrophilic addition to the double bond (probably *anti* to the tin moiety), followed by rapid acid-promoted ring opening and destannylation. This yields the allyl alcohol in a regiospecific manner with allylic transposition.

It is possible to write a cyclic destannylation mechanism for allyl alcohol formation as shown in Scheme 3, but this implies hydroxylation *syn* to the departing tin group, and there is evidence that this concerted route (**2**) is not dominant (Scheme 3).[15]

There thus exists a preference for *anti* (or *antara*) hydroxylation in these cyclohexenylstannanes, where electrophilic substitutions are known to proceed faithfully with allylic rearrangement.[16,17] A more likely pathway is shown in Scheme 4, which is supported by results with optically active allylsilanes,[18] which require *anti* attack by MCPBA on the silane conformation maximizing C—Si σ–π interaction.

This chemistry forms the basis of a general method for 1,3-hydroxy transposition in allylic alcohols (equation 7).[19] The starting alcohol is converted by 3,3-sigmatropic rearrangement of the *O*-allyl-*S*-methyldithiocarbonate followed by hydrostannolysis to the allylic stannane, which is oxidized by MCPBA in a completely regiospecific manner. A similar sequence has been reported for allylsilanes.[20]

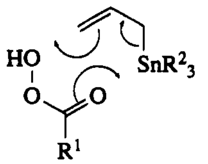
HO
O
O
SnR$^2_3$
R$^1$

**(2)**

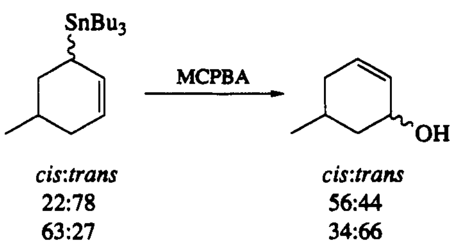
SnBu$_3$
MCPBA
OH
*cis:trans*
22:78
63:27
*cis:trans*
56:44
34:66

**Scheme 3**

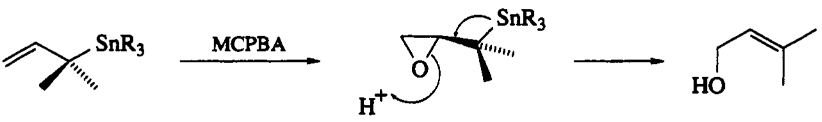
SnR$_3$
MCPBA
SnR$_3$
O
H$^+$
HO

**Scheme 4**

Some typical results are shown in Scheme 5, and other oxidants such as LTA and bisacetoxyphenyliodine were unsatisfactory.

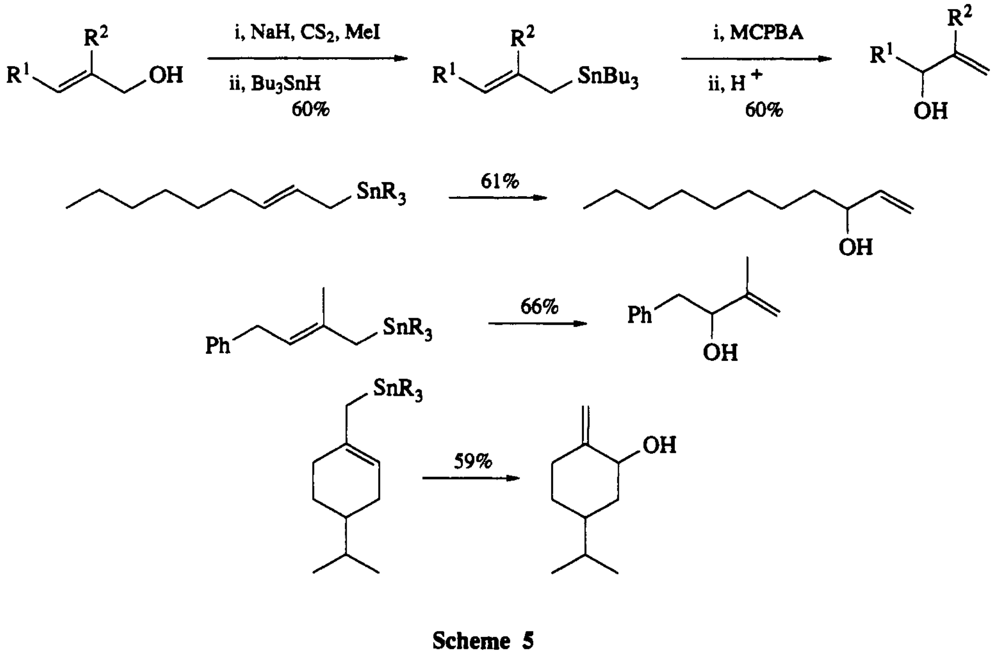
R$^2$
R$^1$
OH
i, NaH, CS$_2$, MeI
ii, Bu$_3$SnH
60%
R$^2$
R$^1$
SnBu$_3$
i, MCPBA
ii, H$^+$
60%
R$^2$
R$^1$
OH
SnR$_3$
61%
OH
Ph
SnR$_3$
66%
Ph
OH
SnR$_3$
59%
OH

(7)

**Scheme 5**

MCPBA oxidation of an allylic stannane is a key step in the overall conversion of an α,β-unsaturated aldehyde to an (*E*)-β-bromo-α-enone, as shown in equation (8).[21]

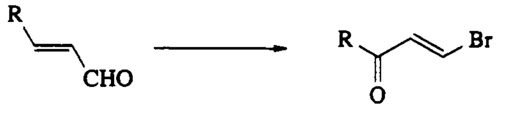

(8)

Addition of $Bu^n_3SnLi$ to the α,β-enal provides the sensitive α-hydroxyallylstannane, which is converted directly to the α-bromoallylstannane without allylic rearrangement. Subsequent oxidative destannylation with MCPBA is accompanied by allylic rearrangement, and further oxidation yields the β-bromoenone (Scheme 6).

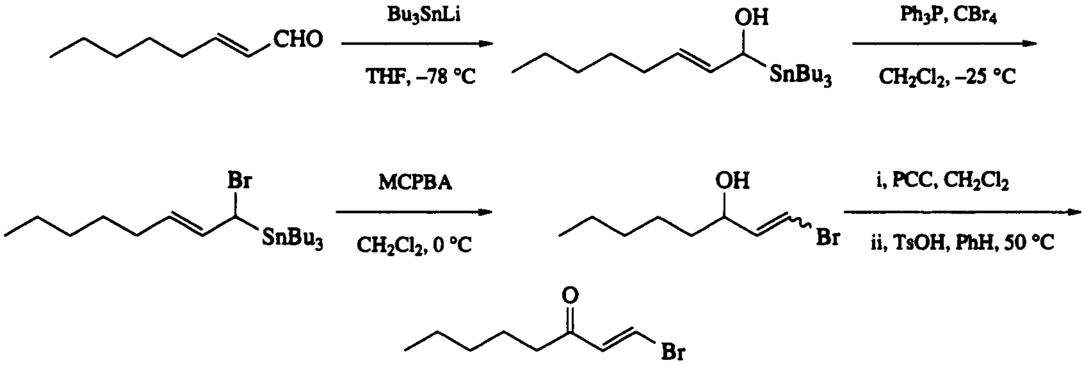
CHO
Bu3SnLi
THF, –78 °C
OH
SnBu3
Ph3P, CBr4
CH2Cl2, –25 °C
Br
SnBu3
MCPBA
CH2Cl2, 0 °C
OH
Br
i, PCC, CH2Cl2
ii, TsOH, PhH, 50 °C
O
Br

Scheme 6

Replacement of a trialkyltin group with the acetoxy group using LTA in $CH_2Cl_2$ proceeds with acceptable yields for *O*-activated, allylic and vinylic C—Sn bonds. These sequences may involve intermediate organolead triacetates ($RPbOAc_3$), which demetallate to yield carbonium ions (Scheme 7).[22]

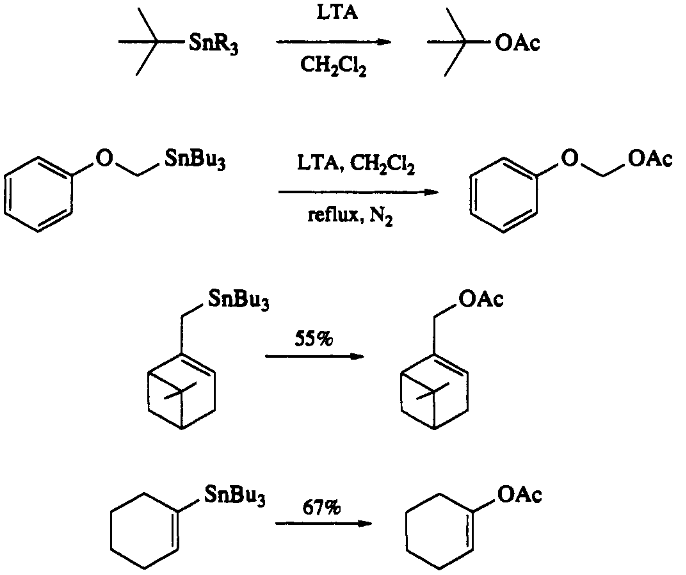
SnR3
LTA
CH2Cl2
OAc
O
SnBu3
LTA, CH2Cl2
reflux, N2
O
OAc
SnBu3
55%
OAc
SnBu3
67%
OAc

Scheme 7

Heterocyclic stannanes were also employed and yielded 5-acetoxyfuran-2(5*H*)-ones and 5-acetoxy-1-methyl-3-pyrrolin-2-one from 2-stannylfurans and 2-stannyl-*N*-methylpyrrole, respectively (Scheme 8).[22a] In the furan system, it appears initial oxidation of the stannane provides the 2-furyl acetate, which is known to undergo further oxidation with LTA (Scheme 8).[23]

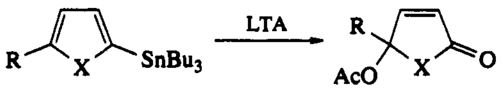
R
X
SnBu3
LTA
R
AcO
X
O

| | | | |
|---|---|---|---|
| | R = H | X = O | 60% |
| (3) | R = Me | X = O | 91% |
| (4) | R = $PhCH_2CH_2$ | X = O | 55% |
| | R = H | X = NMe | 20% |

Scheme 8

Compound (**3**; Scheme 9) on elimination of AcOH provided (**5**), which dimerized to the natural product anemonin (**6**). This approach provides access to 4-ylidenebutenolides, an arrangement frequently found in biologically active natural products (Scheme 9).

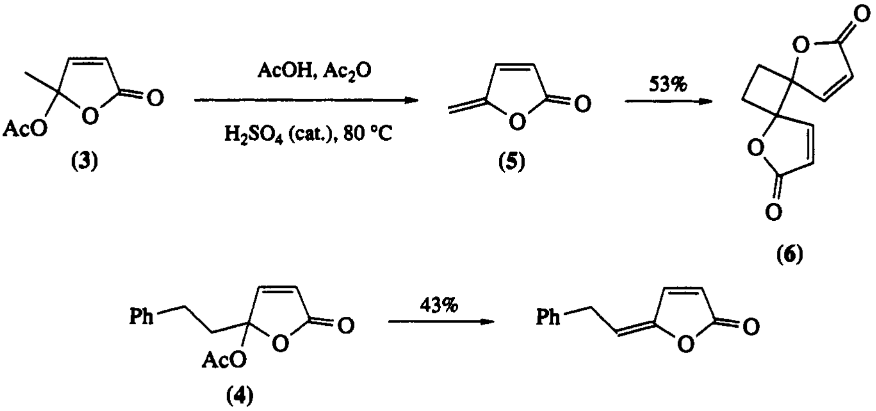
AcO
O
O
(3)
AcOH, $Ac_2O$
$H_2SO_4$ (cat.), 80 °C
O
O
(5)
53%
O
O
O
O
(6)
Ph
AcO
O
O
(4)
43%
Ph
O
O

**Scheme 9**

The β-stannyl silylenol ether is a useful protection device for α,β-enones, as the ethers are relatively unreactive towards most nucleophiles and are reconverted to the enone on mild oxidation. This form of protection was developed and employed in the acquisition of a crucial disubstituted cyclohex-2-enone (**7**) required in the synthesis of (±)-periplanone-B, a sex pheromone of the American cockroach.[24] Similarly, this sequence was successful in effecting (*Z,E*) to (*E,E*) isomerization of isoacoragermacrone (**8**) to acoragermacrone (**9**), when other methods (*e.g.* photoisomerization) failed (Scheme 10).[25]

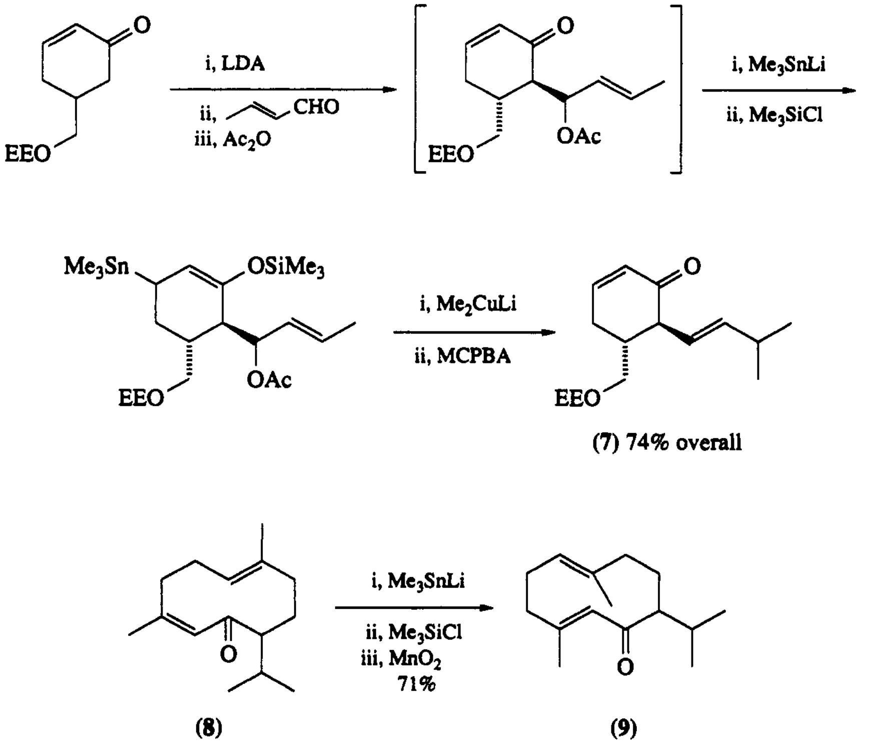
O
EEO
i, LDA
ii, CHO
iii, $Ac_2O$
O
EEO
OAc
i, $Me_3SnLi$
ii, $Me_3SiCl$
$Me_3Sn$
$OSiMe_3$
EEO
OAc
i, $Me_2CuLi$
ii, MCPBA
O
EEO
(7) 74% overall
O
i, $Me_3SnLi$
ii, $Me_3SiCl$
iii, $MnO_2$
71%
O
(8)
(9)

**Scheme 10**

### 4.2.2.4 Vinylstannanes

In 1973, it was demonstrated that 1,2-epoxystannanes, produced from vinylstannanes and MCPBA, could be isolated and characterized,[10] in comparison with 2,3-epoxystannanes (from allylstannanes), which are extremely reactive and have not been isolated (see Section 4.2.2.3). Subsequently, useful applications of 1,2-epoxystannanes have been reported, including the internal alkyne → ketone conversion, in the carbapenem and carbacephem (β-lactam antibiotic) skeletons. Ketone (**10**) should be of value in the construction of the biologically interesting 1-carbapen-2-ene ring system. Synthesis of ketoacetates of potential use in the carbacephem system (*e.g.* **11** and **12**) was also achieved by similar sequences shown in Scheme 11.[26]

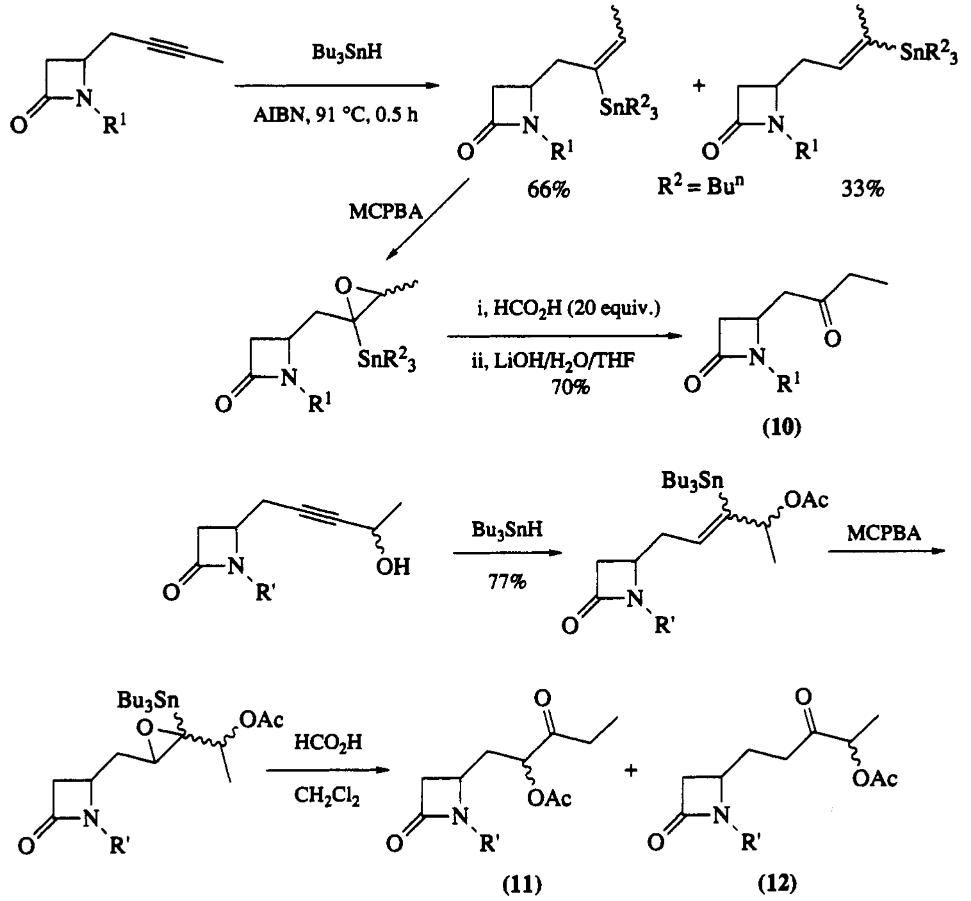

**Scheme 11**

Oxidation of vinylstannanes with LTA is a critical aspect of the introduction of angular ethynyl groups, for which the $Cu^I$-based methodology, so useful for angular vinyl groups, is precluded because of the efficient binding of ethynyl ligands by copper. Treatment of a range of alkenylstannanes with LTA in acetonitrile resulted in conversion to terminal alkynes,[27] and this novel transformation was rationalized as involving a 'Pb for Sn' substitution to produce (**13**) and (cationic) deplumbation. The approach is shown in Scheme 12 in general terms and then for the bicyclic ketone (**14**).

α-Alkenylation of β-dicarbonyl compounds has been achieved in a similar reaction by generation of what are presumed to be 'alk-1-enyllead triacetates', by treating dialk-1-enylmercurials or alk-1-enyltrialkylstannanes with LTA in $CHCl_3$ in the presence of the β-dicarbonyl compounds.[28]

It should be noted from Schemes 12 and 13 that the mode of decomposition of the presumed 'alk-1-enyllead triacetate' varies depending on the circumstances of its generation, *i.e.* from a mercury or stannane precursor. Similarly, alk-1-ynyltrialkylstannanes (**15**) are oxidized by LTA in $CHCl_3$ to form a species capable of α-alk-1-ynylation of β-dicarbonyl compounds (Scheme 13).[29]

The chemistry outlined in Schemes 12 and 13 has been developed to provide a mild method for the conversion of aldehydes to alkynes *via* vinylstannanes as intermediates, and moderately complex

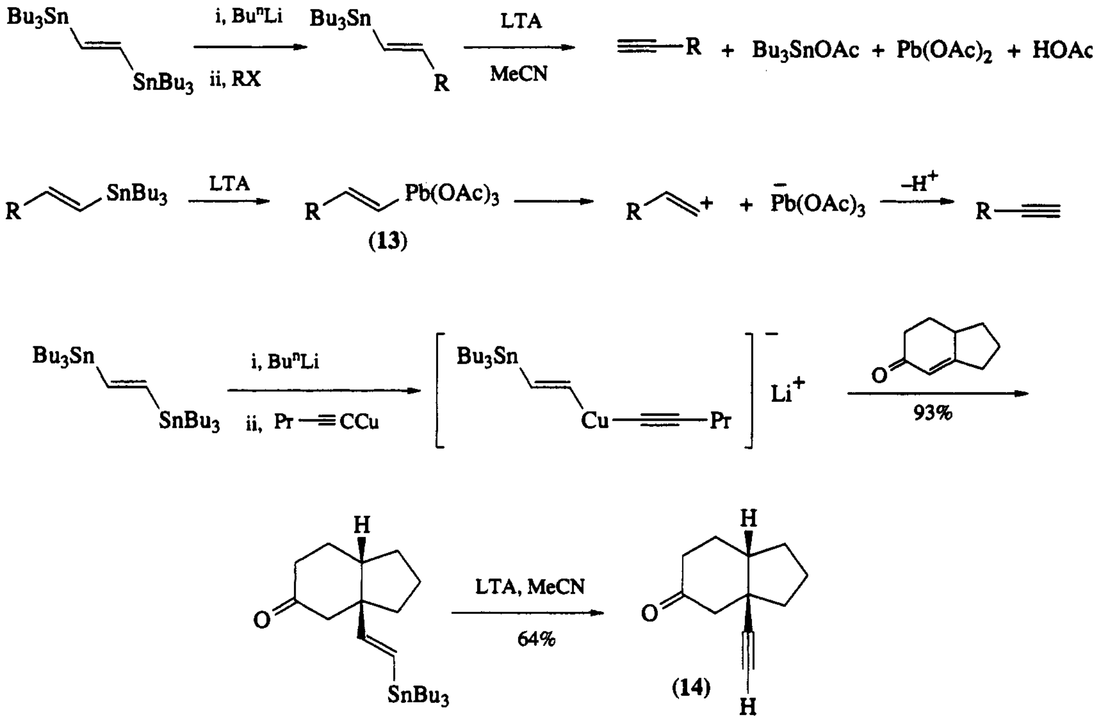
Bu3Sn
SnBu3
i, BunLi
ii, RX
Bu3Sn
R
LTA
MeCN
R + Bu3SnOAc + Pb(OAc)2 + HOAc
SnBu3
LTA
Pb(OAc)3
(13)
R+ + Pb(OAc)3
-H+
R
i, BunLi
ii, Pr—≡CCu
Bu3Sn
Cu—≡—Pr
Li+
93%
H
O
SnBu3
LTA, MeCN
64%
(14)
H

**Scheme 12**

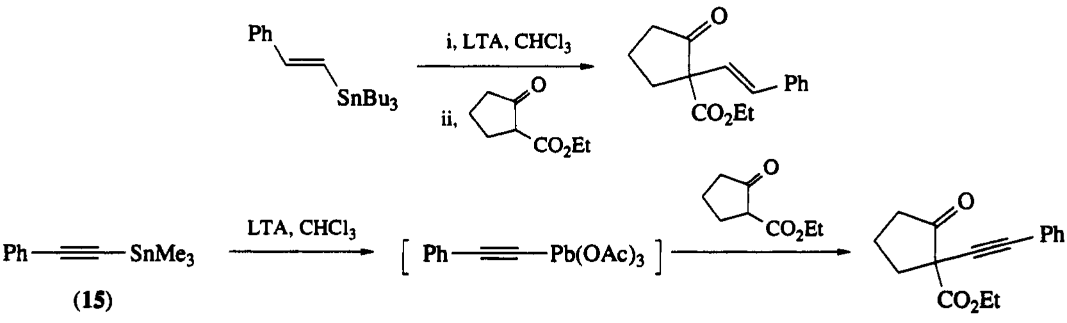
Ph
SnBu3
i, LTA, CHCl3
ii,
O
CO2Et
Ph
CO2Et
Ph—≡—SnMe3
(15)
LTA, CHCl3
[ Ph—≡—Pb(OAc)3 ]
O
CO2Et
O
Ph
CO2Et

**Scheme 13**

systems are amenable to the general procedure as shown in Scheme 14.[30] This aldehyde → alkyne transformation was applied in the synthesis of 9(O)-thia-$\Delta^6$-PGI$_1$ (as shown in Scheme 15)[30] and a PGA$_2$ ethynyl derivative has been obtained using this method of ethynyl group introduction.[31] It should be mentioned that the intermediate alkenylstannanes provide a route to alkenyllithium reagents from the starting aldehydes.[4]

### 4.2.2.5 γ-Trialkylstannyl Alcohols; Oxidative 1,4-Fragmentation

γ-Stannyl alcohols display considerable potential for use in organic synthesis, and mention has been made of the chromic anhydride oxidation of certain such alcohols and its role in dialkylative enone transposition (Section 4.2.2.2, equation 2).[7] Two other reactions which have been developed recently into attractive sequences are: (a) 1,3-eliminative cyclization of γ-stannyl alcohols to cyclopropanes;[4,32,33] and (b) 1,4-fragmentation of (cyclic) γ-stannyl alcohols to yield an unsaturated carbonyl compound, which proceeds in a stereospecific manner. 1,4-Fragmentation under Grob conditions utilizes electron-attracting groups, whereas cation or radical induced fragmentations are rarer. Thus oxidation of γ-stannyl alcohols with a hypervalent organoiodine compound (in the presence of DCC)[34] proceeds differently from the chromic anhydride reaction (equation 9).[7]

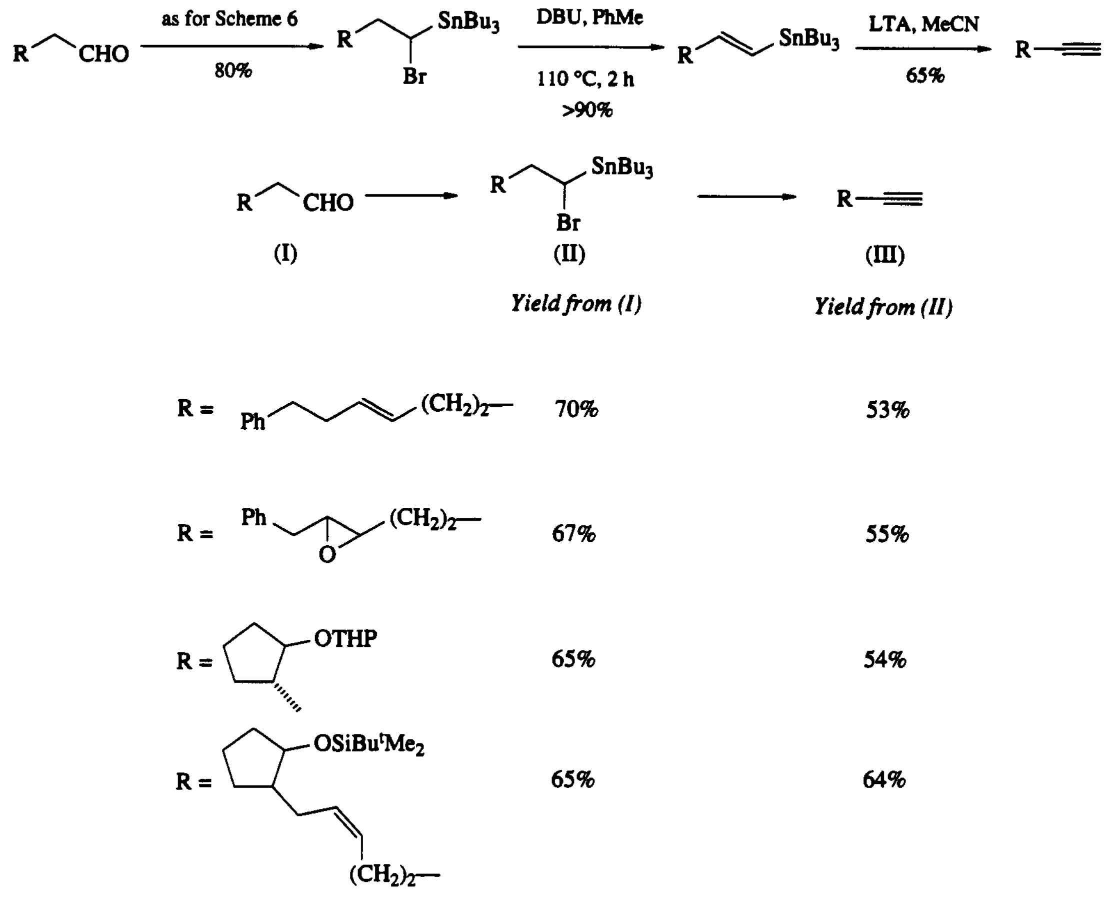
as for Scheme 6
80%
SnBu3
Br
DBU, PhMe
110 °C, 2 h
>90%
SnBu3
LTA, MeCN
65%
R
CHO
(I)
(II)
(III)
Yield from (I)
Yield from (II)
R =
Ph
(CH2)2—
70%
53%
67%
55%
O
OTHP
65%
54%
OSiBu^tMe2
65%
64%

Scheme 14

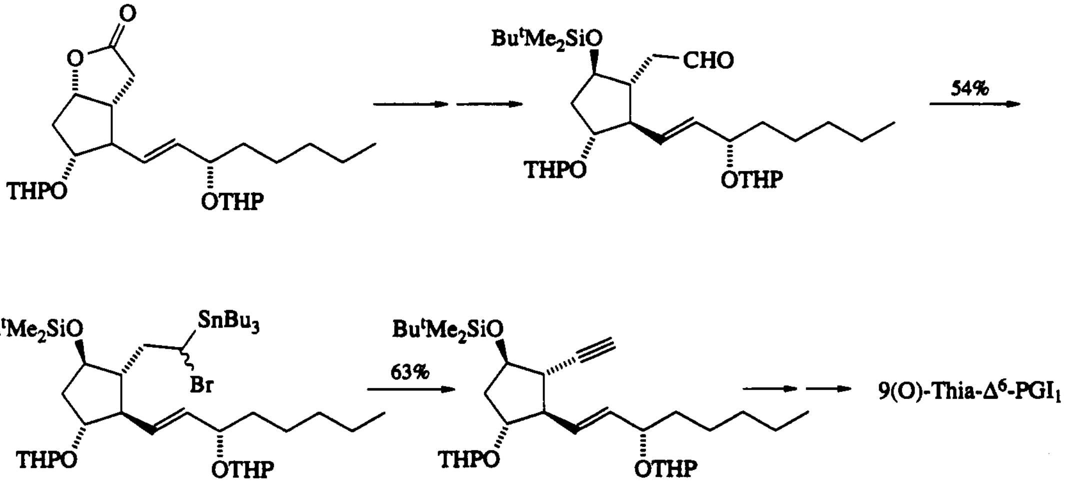
O
THPO
OTHP
Bu^tMe2SiO
CHO
54%
SnBu3
Br
63%
9(O)-Thia-Δ^6-PGI1

Scheme 15

The required organostannanes are accessible by conjugate addition of trialkyltinlithium reagents to cyclic enones,[7] followed by treatment with the appropriate RLi or RMgX reagent, as shown in Scheme 16.

Fragmentation of the isomeric mixtures of γ-stannyl alcohols was achieved by adding a preformed solution (stir for 1 h at room temperature) of $BF_3 \cdot Et_2O$ and DCC to the stannane and iodosylbenzene at 0 °C, under a $N_2$ atmosphere. Fragmentation of five-, six- and seven-membered ring stannanes proceeded

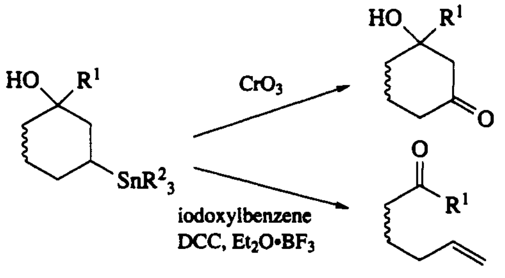

(9)

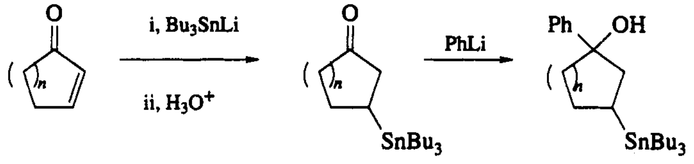

$n = 1$, 58%
$n = 2$, 78%
$n = 3$, 76%

**Scheme 16**

efficiently, and secondary alcohols (from $NaBH_4$ reduction of the stannyl ketones) provided the unstable enals. These results are listed in Table 1.

**Table 1** Iodine(III)-mediated 1,4-Fragmentation of γ-Stannyl Alcohols[a]

| *System* | *Reaction time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|
| 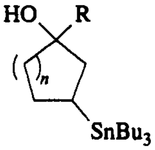 | | 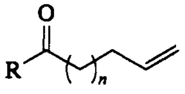 | |
| $n = 1$, R = Ph | 5 | $n = 1$ | 63 |
| $n = 2$, R = Ph | 4 | $n = 2$ | 81 |
| $n = 3$, R = Ph | 2.5 | $n = 3$ | 86 |
| 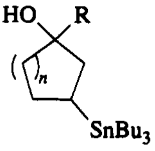 | | 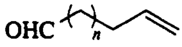 | |
| $n = 2$, R = H | 2 | $n = 2$ | 74 |
| $n = 3$, R = H | 3 | $n = 3$ | 55 |

[a] Conditions: add preformed solution (stir for 1 h at room temperature) of $BF_3$•$OEt_2$ and DCC to the stannane and iodosylbenzene at 0 °C with $N_2$ atmosphere.

Addition of $Bu_3SnLi$ to cyclohex-2-enone followed by enolate trapping with *n*-decyl iodide proceeded with high diastereoselectivity to provide the 2,3-*trans*-stannyl ketone (**16**), which could be equilibrated with the *cis* diastereomer (**17**) upon treatment with base.[35] LAH reduction, followed by separation of the diastereomers, afforded samples of the 2-alkyl-3-stannylcyclohexanols as shown in Scheme 17. Iodine(III)-mediated fragmentation was shown to proceed in a stereospecific *anti* manner, with either of the *trans*-2,3-cyclohexanols affording (*E*)-enal (**18**), and the *cis*-2,3-alcohol the (*Z*)-enal (**19**; Scheme 17). Enal (**18**) was then utilized in a stereoselective synthesis of the mosquito pheromone, *erythro*-6-acetoxyhexadecan-5-olide (**20**; Scheme 18).[35]

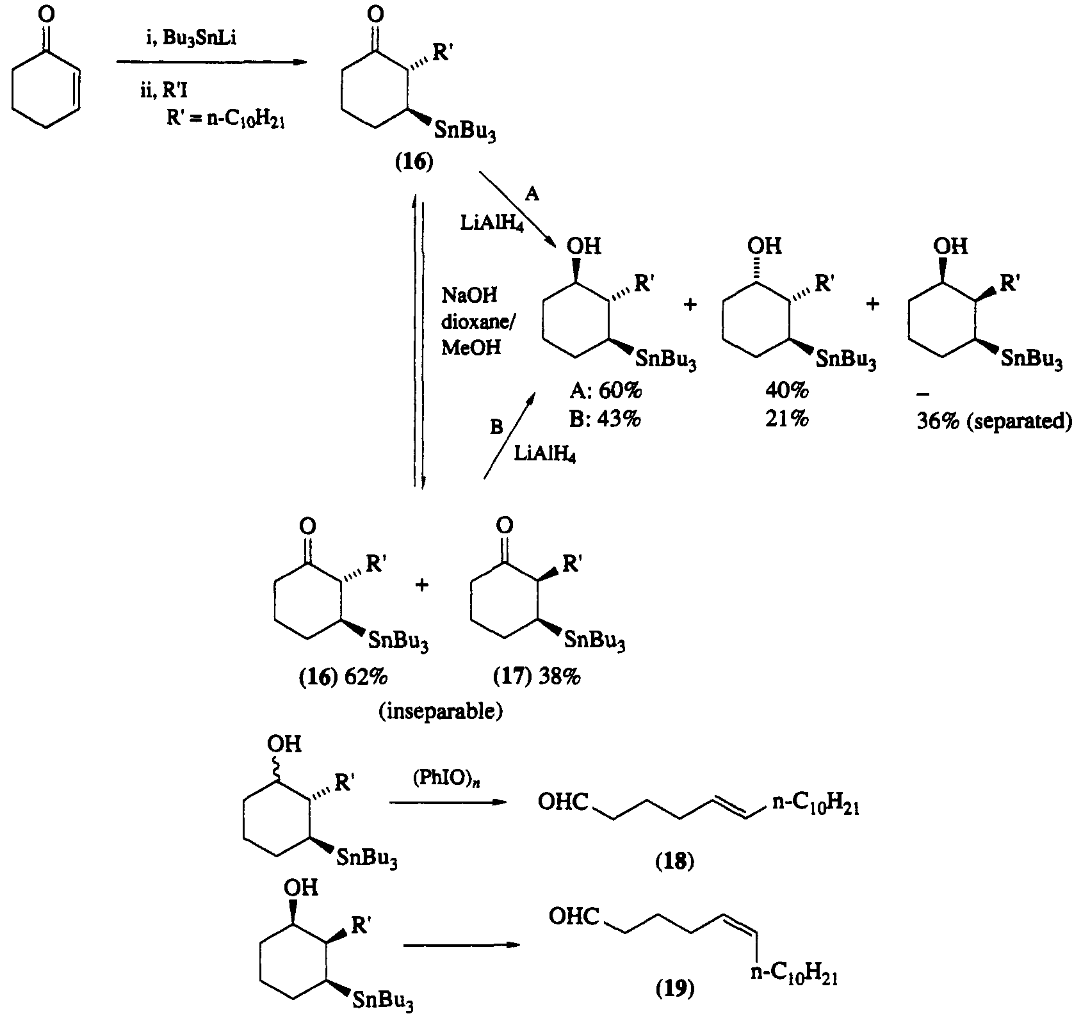

i, Bu3SnLi
ii, R'I
R' = n-C10H21
R'
SnBu3
(16)
A
LiAlH4
NaOH
dioxane/
MeOH
OH
A: 60%
B: 43%
40%
21%
36% (separated)
B
LiAlH4
(16) 62%
(17) 38%
(inseparable)
(PhIO)n
OHC
n-C10H21
(18)
(19)

Scheme 17

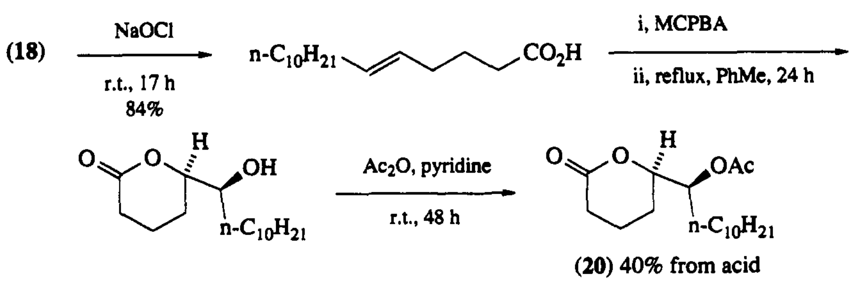

(18)
NaOCl
r.t., 17 h
84%
n-C10H21
CO2H
i, MCPBA
ii, reflux, PhMe, 24 h
H
OH
Ac2O, pyridine
r.t., 48 h
OAc
(20) 40% from acid

Scheme 18

This iodine(III) oxidative fragmentation has been exploited to generate unsaturated medium ring lactones in good yields and with complete control of double bond stereochemistry as shown in Scheme 19.[36] Use of diacetoxyiodobenzene (DAIB) instead of iodosylbenzene–$BF_3$–$Et_2O$–DCC resulted in much enhanced yields (~80%).

LTA in refluxing benzene will also effect fragmentation of γ-stannyl alcohols to (*E*)- and (*Z*)-ketoalkenes in a stereospecific manner depending on the *cis* or *trans* nature of the 2,3-groups, and, for overall synthetic ease, the use of LTA may be more attractive.[37] The fragmentation may be viewed as a trialkyltin-triggered radical cleavage as shown in Scheme 20. Under the conditions for this cleavage of the γ-stannyl alcohols, the corresponding silanes do not react, but there are methods for such silane re-

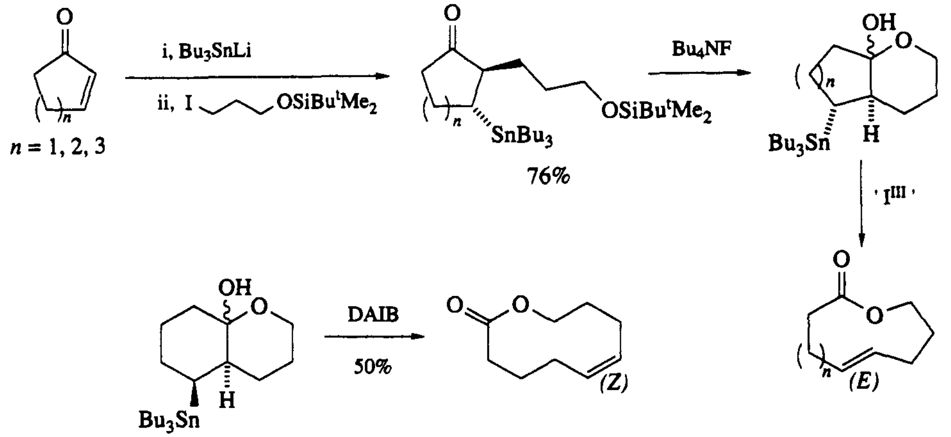

Scheme 19

actions.[38] The LTA-based cleavage has been elegantly applied to part of the sequence leading to brefeldin A seco acid (**21**)[39] and has found application also in the synthesis of dienones[40] capable of ready elaboration to various spiroacetal systems, for example (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**22**; Scheme 21).

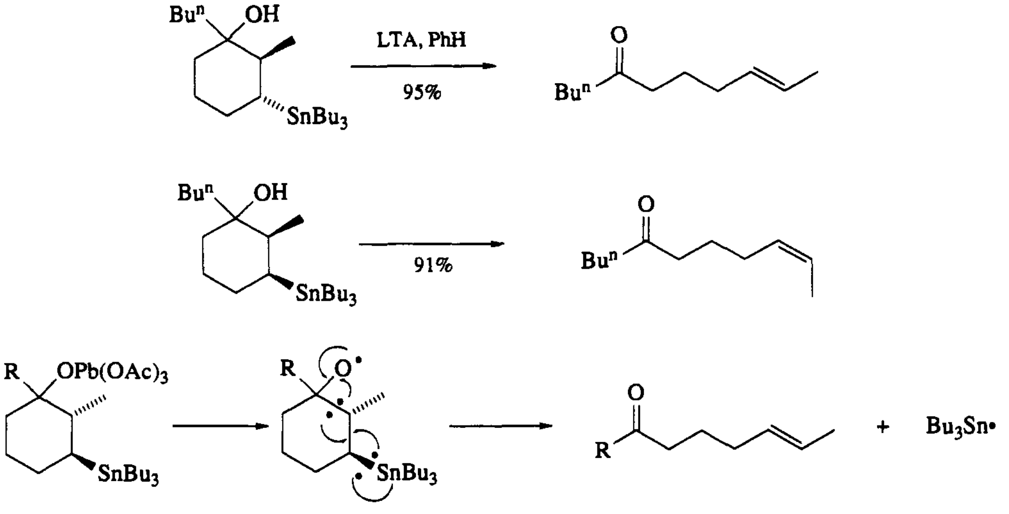

Scheme 20

Oxidative fragmentation (and oxidation) of carbon–tin bonds are part of an overall sequence based on Michael–Michael ring closure reactions (MIMIRC) which represent extraordinarily easy, high yielding, one-pot, four-component coupling reactions, which may lead finally to functionalized cyclohexenes, cyclohexanols, cyclodecenones and aromatic systems, as shown in Scheme 22.[41] Quenching of the trialkyltin enolate with 2 equiv. of methyl acrylate or methyl α-bromoacrylate provides ester enolates which spontaneously execute intramolecular aldol cyclizations to form polyfunctionalized cyclohexanols (**23**) and (**24**), each as a mixture of two diastereomers only. LTA cleavage (of each separated diastereomer) resulted in a stereodefined richly functionalized cyclodecene system (**25**) related to the germacrane class of sesquiterpenes, whereas oxidation–dehydrobromination formed regiospecifically tetrasubstituted aromatics (**26**; Scheme 22).

This general strategy was extended to include five- and seven-membered ring α,β-enones, which also underwent 'one-pot' Michael reactions with $Bu_3SnLi$, followed by enolate 1,4-addition to vinyl ketones and aldol reactions with aldehydes to provide cyclic hemiketals (MIMIARC).[42] LTA fragmentation results in four-atom enlarged, vicinally disubstituted, regio- and stereo-specifically unsaturated macrolides as summarized in Scheme 23. Yields of chromatographically pure macrolides were in the 30–47% range. Exclusive formation of the (*E*)-alkenolides (Scheme 23) is due to the *trans* nature of bonds a and b in the

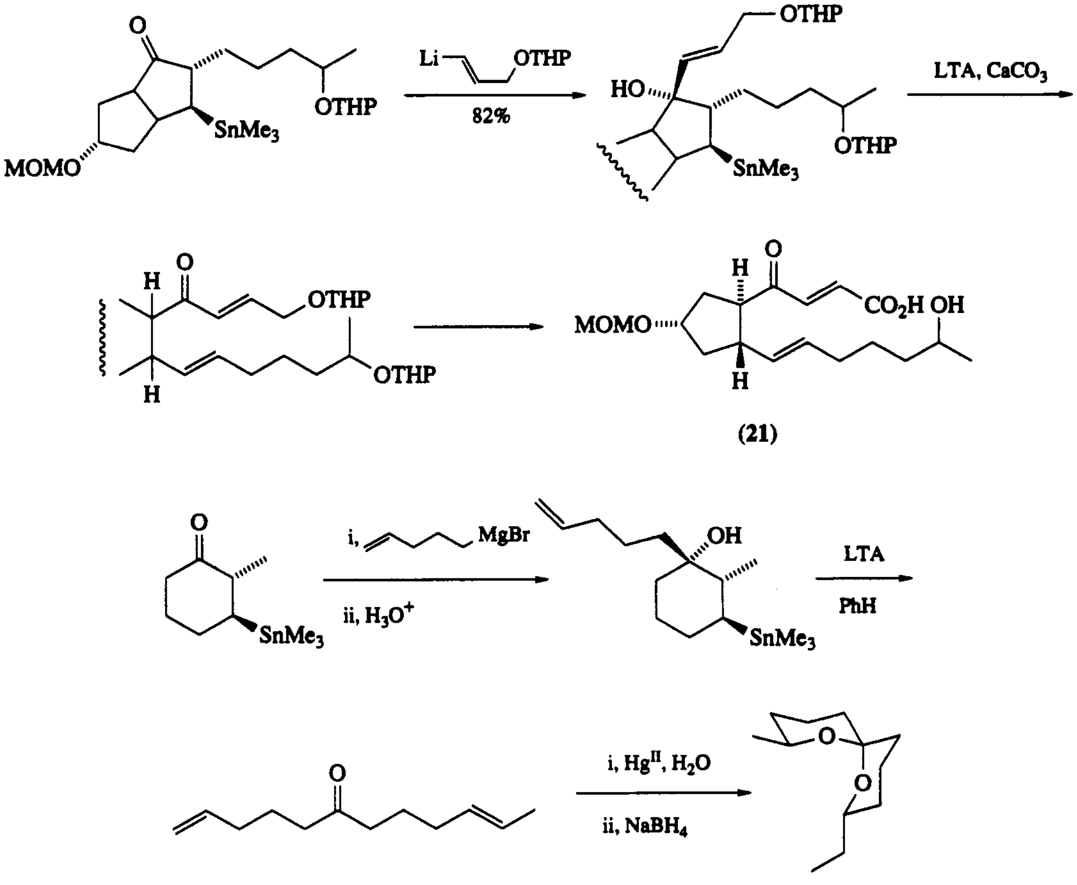
MOMO
SnMe₃
OTHP
Li
OTHP
82%
HO
OTHP
OTHP
SnMe₃
LTA, CaCO₃
H
H
OTHP
OTHP
MOMO
H
H
CO₂H OH
i, MgBr
ii, H₃O⁺
SnMe₃
OH
SnMe₃
LTA
PhH
i, Hg^II, H₂O
ii, NaBH₄
O
O

(21)

(22)

**Scheme 21**

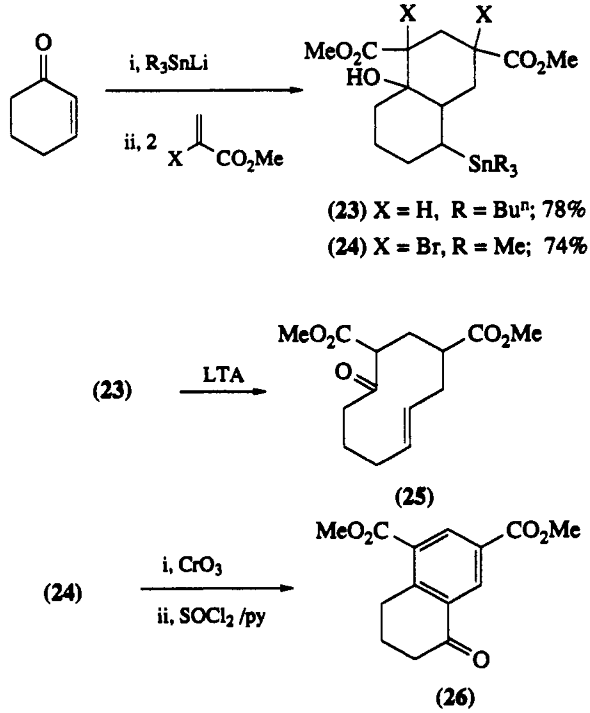
i, R₃SnLi
ii, 2 X CO₂Me
X
X
MeO₂C
HO
CO₂Me
SnR₃
LTA
MeO₂C
CO₂Me
i, CrO₃
ii, SOCl₂ /py
MeO₂C
CO₂Me

(23) X = H, R = $\mathrm{Bu^n}$; 78%
(24) X = Br, R = Me; 74%

(23)

(25)

(24)

(26)

**Scheme 22**

hemiketals, and the *anti* elimination involved in the oxidative cleavage of the γ-stannyl–hydroxy arrangement.

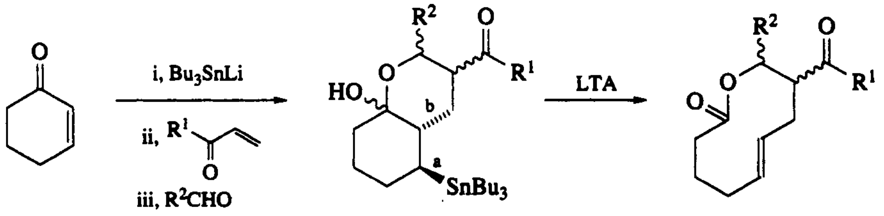
i, Bu3SnLi
ii, R1 (enone)
iii, R2CHO
R2
O
R1
HO
b
a
SnBu3
LTA

| | | |
|---|---|---|
| $R^2 = Me$ | $R^1 = Et$ | 47% |
| $R^2 = H_2C{=}CH$ | $R^1 = Et$ | 39.5% |
| $R^2 = o\text{-}IC_6H_4$ | $R^1 = Et$ | 37% |

Scheme 23

The general attractiveness and flexibility were illustrated by acquisition of 2,3-disubstituted quinolines (**27**) and also phorocantholide (**28**), a natural 10-membered ring lactone constituent of an insect secretion.[42] The use of α,β-unsaturated ketones as initial receptors lends extra scope to the overall sequence, and permits preparation of substituted 9-, 10- and 11-membered unsaturated macrolides (**29**) bearing double bonds of fixed geometry at specific positions in lactone rings (Scheme 24).[43] As illustrated in Scheme 24, intramolecular cyclizations of the *vic* groups may also lead to regiospecifically substituted

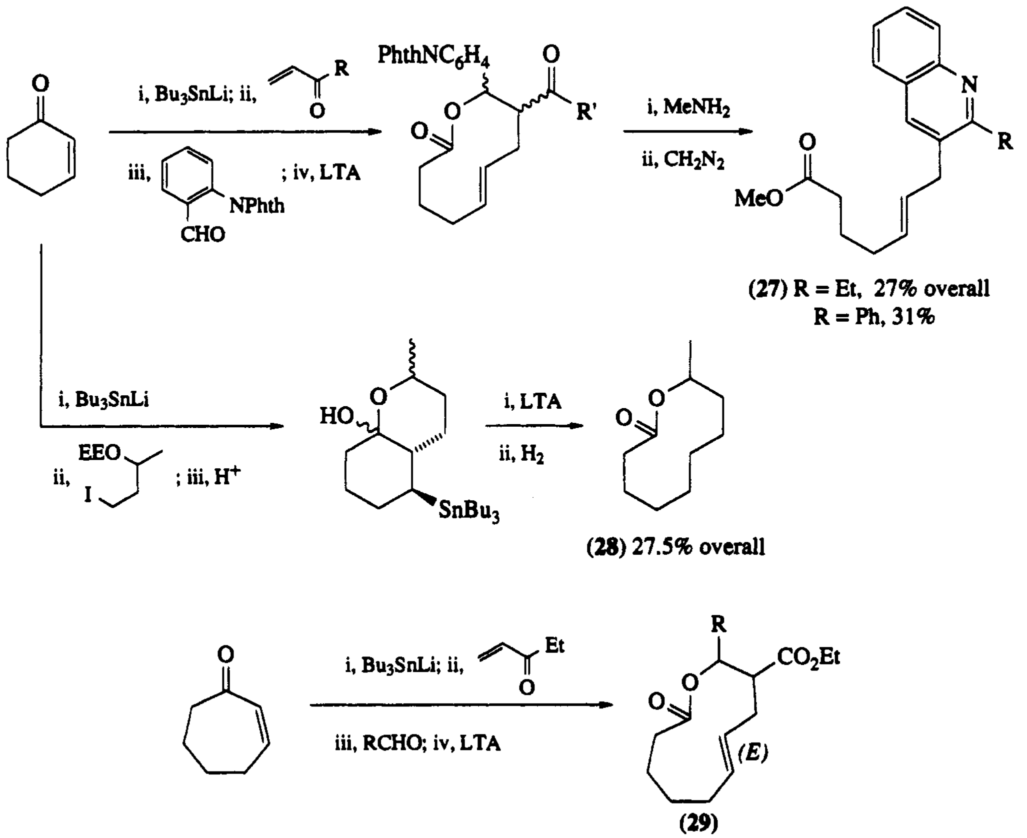
i, Bu3SnLi; ii,
R
iii,
NPhth
CHO
; iv, LTA
PhthNC6H4
R'
i, MeNH2
ii, CH2N2
MeO
N
R
i, Bu3SnLi
ii, EEO, I
; iii, H+
HO
SnBu3
i, LTA
ii, H2
i, Bu3SnLi; ii,
Et
iii, RCHO; iv, LTA
R
CO2Et
(E)

(**27**) R = Et, 27% overall
R = Ph, 31%

(**28**) 27.5% overall

(**29**)

| | |
|---|---|
| $R = c\text{-}C_3H_5$ | 44% overall |
| $R = Me$ | 36% |
| $R = 3\text{-}MeOC_6H_4$ | 42% |

Scheme 24

naphthalenes, quinolines, benzofurans and benzothiophenes. This great versatility and flexibility coupled with regio- and stereo-control make the MIMIRC and MIMIARC reactions very attractive, but control is due to the stereochemistry of enolate alkylation and the *anti* fragmentation of the γ-stannyl alcohols.

### 4.2.2.6 β-Stannyl Hydrazones, Oximes and Carboxylic Acids

Trialkyltin-triggered oxidative fragmentations of hydrazones, oximes and carboxylic acids have been reported, and may develop into very useful procedures. β-Stannyl phenylhydrazones[44] on oxidation with NBS provided the interesting azocyclopropanes (**30**), which could be transformed to the pyrazolines (**31**) by treatment with $SnCl_2$ in refluxing benzene. DDQ and LTA were also efficient oxidants. Homolytic cyclopropanation was suggested (Scheme 25) and shown to proceed with inversion of the C—Sn configuration, eventually yielding pyrazolines, regio- and stereo-specifically (Scheme 25).

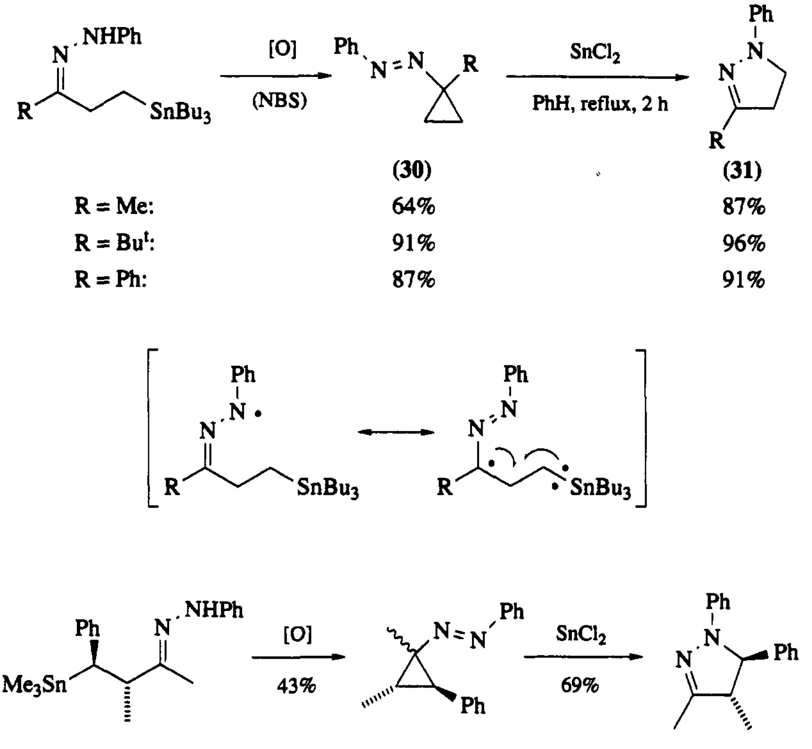

**Scheme 25**

$\Delta^2$-Isoxazolines exhibit considerable versatility in synthesis and one-pot oxidative ring contraction of stannyl oximes to $\Delta^2$-isoxazolines with stereocontrol results from the strong directing effect of the tin group, followed by 1,3-dipolar cycloaddition (Scheme 26).[45] In conjunction with other results, it was suggested that oximes with the stannyl group too far removed from the iminoxyl group (3-electron σ-radical) for direct interaction react by fragmentation–recombination, whereas sufficient proximity leads to direct C—O bond formation.

β-Stannyl- (and β-silyl-) carboxylic acids undergo oxidative decarboxylation with LTA under mild conditions to provide the corresponding alkenes.[46] This represents an improvement on the well-known alkene-forming decarboxylation of acids with LTA, which requires thermal or photochemical conditions, for example.[47] The directing metal effect leads to improved yields and regioselectivity. However, stereospecific alkene formation did not occur and this could imply free radical involvement or transmetallation (Pb for Sn) (stereochemistry?) followed by cation formation, see for example Scheme 27.

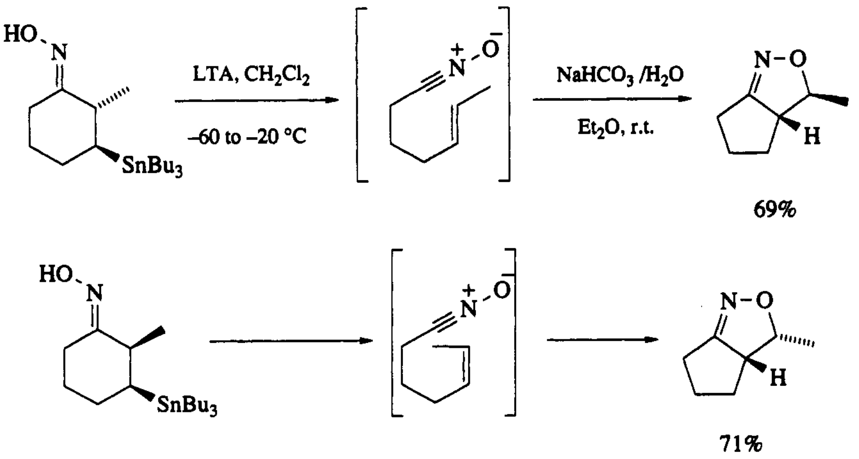

Scheme 26

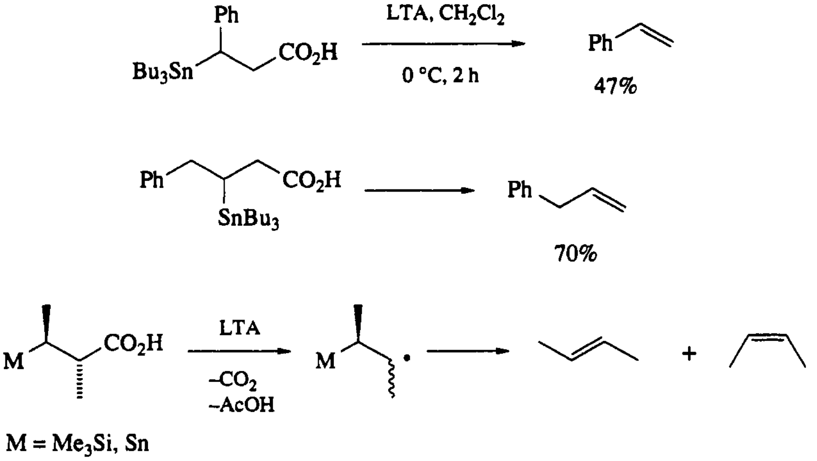

Scheme 27

## 4.2.3 OXIDATION OF CARBON–PALLADIUM BONDS

The oxidative cleavage of the bond between carbon and palladium is often a key step in Pd-catalyzed reactions, in which transiently formed organopalladium systems are implicated. These latter aspects are covered elsewhere (Volume 7 Chapter 3.4) and the present discussion is restricted to oxidation of preformed, stable organopalladium compounds.

### 4.2.3.1 π-Allylpalladium Complexes

Despite the existence of a formidable literature on systems in which transitory π-allylpalladium complexes are involved,[48] only a few papers describe the oxidation of preformed π-allylpalladium complexes to alcohols, rather than to carbonyl compounds. Nevertheless, these reports suggest that the procedure has considerable potential, in view of the stereoselectivities reported. In the steroid area, it was established that π-allyl–Pd complexes were oxidized regiospecifically and with high stereoselectivity to allylic alcohols by MCPBA, using pentane–pyridine as solvent.[49] The hydroxy group was delivered preferentially to the same diastereotopic face of the allyl system as that originally occupied by palladium. These oxidations have severe solvent effects, with pyridine appearing to suppress carbonyl compound formation, and enhancing the regio- and stereo-selectivity of the oxidations (Scheme 28). Some studies of the oxidation of organopalladium compounds with $Cr^{VI}$ reagents have also been reported, and only

Collins reagent ($Cr^{VI}$ oxide–2py) appears to provide acceptable yields (40–60%) of aldehydes and ketones (Scheme 28).[50]

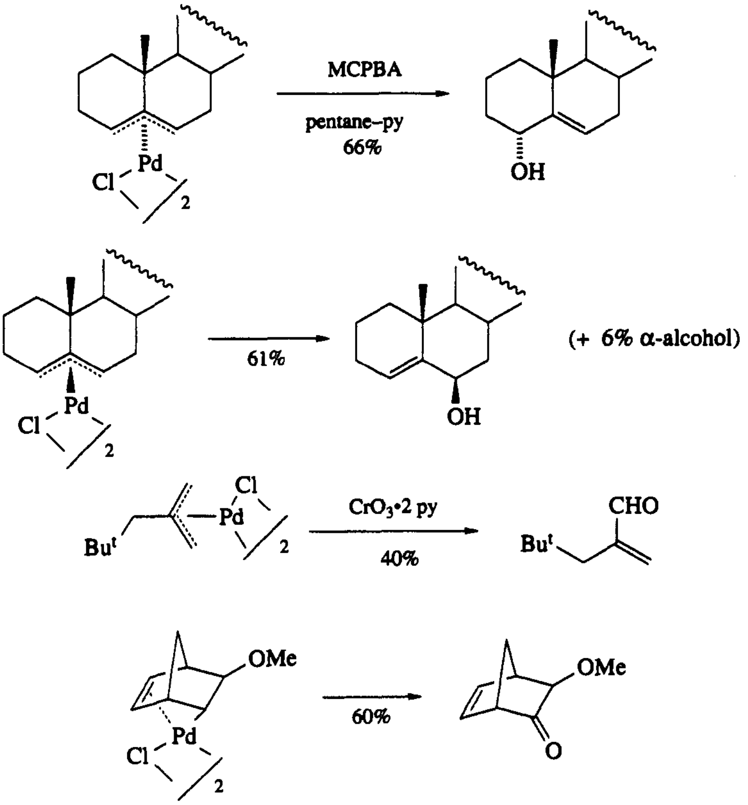

Scheme 28

### 4.2.3.2 Cyclopalladation–Oxidation

The Shaw cyclopalladation reaction (equation 10), reported in 1978, has been developed sufficiently to conclude that it has considerable potential for functionalization of unactivated methyl groups in the vicinity of a ketone, *via* the oxime.[51] This was demonstrated with lanost-8-en-3-one, which furnished a cyclopalladated derivative (**32**), which allowed functionalization of the 4-Me group to $CH_2D$ ($NaBD_4$) and $CH_2I$ ($I_2/CHCl_3$).[52] Attempted oxidation of the cyclohexanone derivative (**33**) with MCPBA unexpectedly provided the chloromethyl compound (Scheme 29).

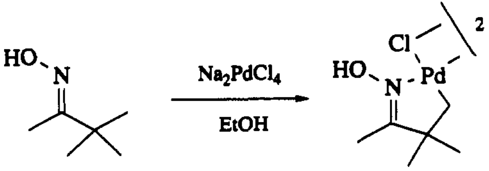

(10)

However, smooth conversion in the sense C—Pd → C—O was achieved when LTA–Py was employed as oxidant, and very high yields (80–100%) of *O*-functionalized methyl compounds were obtained (Scheme 30).[53] Notice that the second palladation to form (**34**) occurs regiospecifically on the second methyl group in 2,2-dimethylcyclohexanone. Hindered ketones, such as 2,2,6,6-tetramethylcyclohexanone also behaved in excellent fashion. An argument based on conformational control has been presented to account for the regiospecificity of the second palladation step.[54] Lupanone oxime (**35**) was successfully converted in high yield to the expected 23-acetoxy derivative (**36**) by this sequence (Scheme 30).[54] Cyclopalladation–oxidation has found interesting applications in the synthesis of carbohydrate-derived, equatorially functionalized *gem*-di-*C*-alkyl derivatives, which are important for certain enantioselective syntheses.[55] Thus (**37**; Scheme 30) provided a single acetoxy oxime (**38**) in nearly quantitative yield, and the stereospecific functionalization is attributed to the necessity for a nearly coplanar arrange-

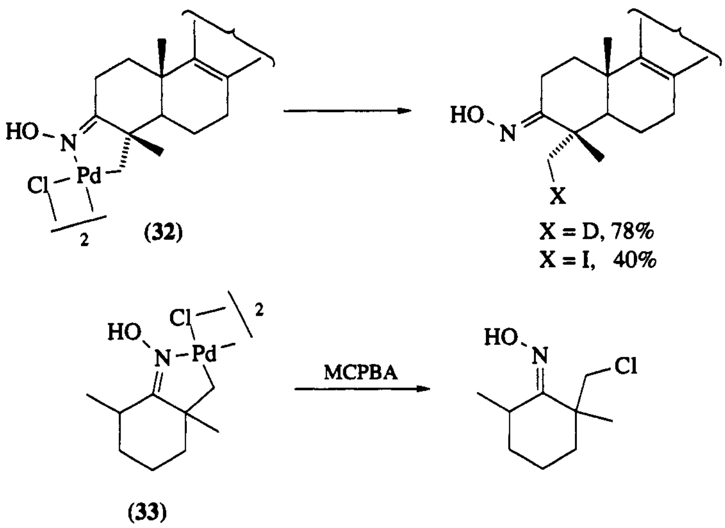
HO
N
Cl
Pd
2
(32)
HO
N
X
X = D, 78%
X = I, 40%
HO
Cl
N
Pd
2
MCPBA
HO
N
Cl
(33)

Scheme 29

ment of the oxime carrying Pd and the methyl group. The use of $NaBH_4$ as the final step in the synthetic sequence prevents trapping of $Pd^{II}$ by the oxime, by reduction to $Pd^0$.

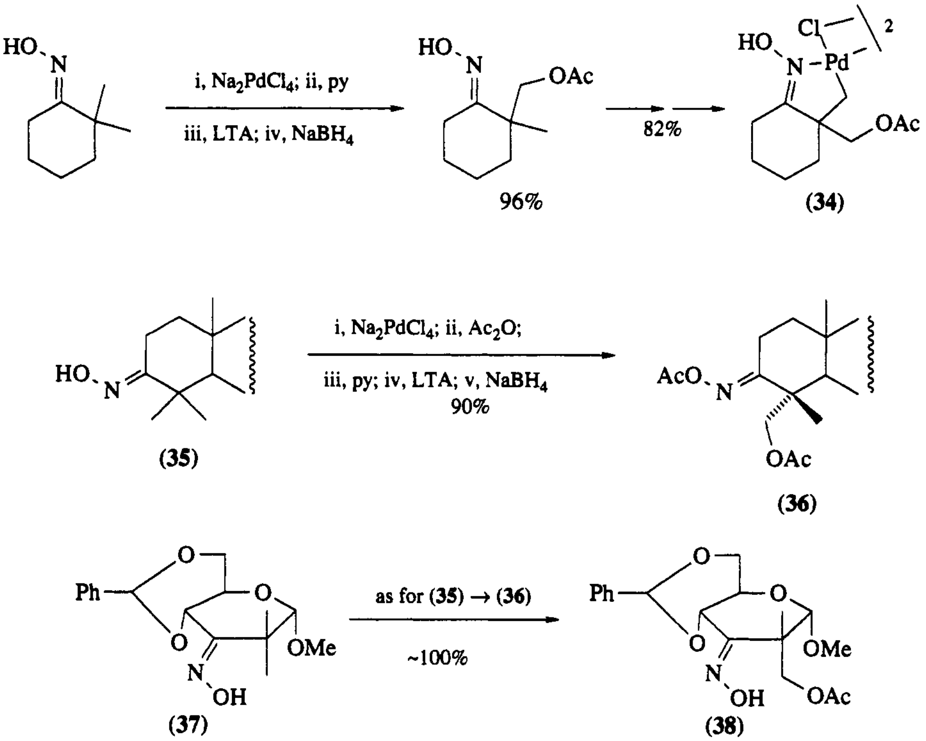
HO
N
i, Na₂PdCl₄; ii, py
iii, LTA; iv, NaBH₄
HO
N
OAc
96%
82%
HO
Cl
N
Pd
2
OAc
(34)
HO
N
(35)
i, Na₂PdCl₄; ii, Ac₂O;
iii, py; iv, LTA; v, NaBH₄
90%
AcO
N
OAc
(36)
Ph
O
O
O
OMe
N
OH
(37)
as for (35) → (36)
~100%
Ph
O
O
O
OMe
N
OH
OAc
(38)

Scheme 30

## 4.2.4 OXIDATION OF CARBON–MERCURY BONDS

### 4.2.4.1 Introduction

Applications of organomercury compounds in synthesis[2,56] overwhelmingly concern Markovnikov conversion of alkenes, allenes and cyclopropanes to alcohols, ethers, amines, peroxides and azides by oxy-, alkoxy-, amino-, peroxy- or azido-mercuration of the unsaturated group, followed by reductive demercuration.[2,57] Sodium borohydride is routinely used to effect reductive demercuration and there has been considerable interest in the mechanism of this step. This sequence is shown in equation (11) for the more common oxymercuration–reductive demercuration. Full details and discussion of these procedures have been presented elsewhere.[2]

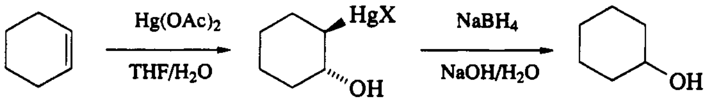

(11)

There is persuasive evidence that reductive demercuration involves a noncage free radical chain mechanism with a common hydrogen source (RHgH) irrespective of the hydride employed ($NaBH_4$, $Bu_3SnH$, LAH) (equations 12–14).[58–60]

$$\mathrm{RHgX} \xrightarrow{[\mathrm{H}]} \mathrm{RHgH} \qquad (12)$$

$$\mathrm{RHgH} \longrightarrow \mathrm{R}\bullet \qquad (13)$$

$$\mathrm{R}\bullet + \mathrm{RHgH} \longrightarrow \mathrm{RH} + \mathrm{R}\bullet + \mathrm{Hg} \qquad (14)$$

Hill and Whitesides demonstrated that reduction of organomercurials with $NaBH_4$ in the presence of oxygen gave a spectrum of products in line with free noncaged alkyl radicals as intermediates, and suggested that efficient oxygen-trapping of such radicals would provide a useful method of carbon–oxygen bond formation, and generally of adding functionality to alkene moieties (equations 15 and 16).[58]

$$\mathrm{R}\bullet + \mathrm{O_2} \longrightarrow \mathrm{ROO}\bullet \qquad (15)$$

$$\mathrm{ROO}\bullet \xrightarrow{\mathrm{HX}} \mathrm{ROOH} \xrightarrow{\text{reduce}} \mathrm{ROH} \qquad (16)$$

## 4.2.4.2 Oxymercuration–Oxidative Demercuration

Oxymercuration–oxidative demercuration (OM–OD) has considerably broadened the utility of organomercurial applications in synthesis.[56] Typically, a solution of the mercurial in DMF (room temperature) was added to a DMF solution of $NaBH_4$, through which oxygen was rapidly passed.[58] Generally 1.2–1.3 mol of borohydride was required to effect complete demercuration. In addition to the expected alcohols and hydrocarbons, other products presumed to be alkoxyboron compounds were also formed, but these could be hydrolyzed to alcohols. A typical result is shown in equation (17), with yields after the hydrolysis step.

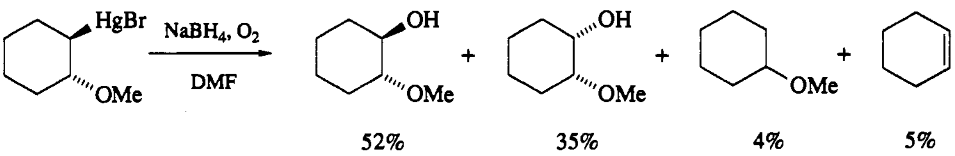

(17)

Thus good yields of β-alkoxy alcohols can be obtained, albeit as diastereomeric mixtures, but unfortunately hydroxymercurated alkenes under similar conditions do not lead to useful products.[58] Despite this apparent limitation, alkoxymercuration–oxidative demercuration has been very effective in a number of systems described below, and there is no doubt it is a procedure worth consideration for hydroxy group introduction.

The first general application of this procedure was to the synthesis of tetrahydrofurfuryl alcohols, the precursor mercurials of which resulted from an intramolecular reaction of alkenic alcohols (Scheme 31).[61,62] Both mercurials and alcohols were formed as diastereomeric mixtures, the latter in moderate yields (Table 2).

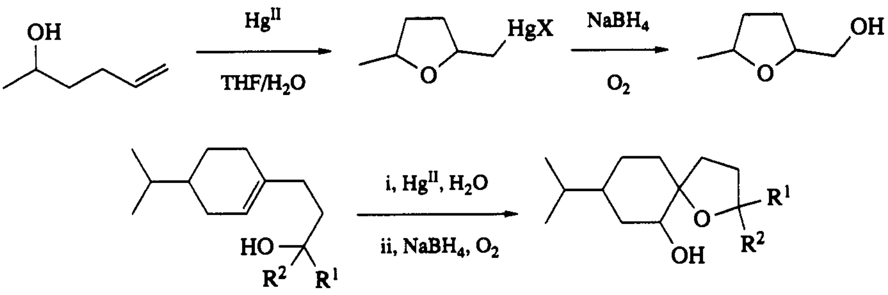

Scheme 31

Table 2

| *Mercurial* | *Hydroxy derivative* | *Yield (%)* |
|---|---|---|
| 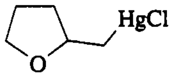 | 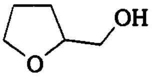 | 10 |
| 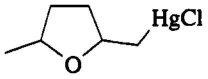 | 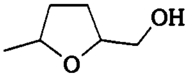 | 20 |
| 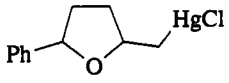 | 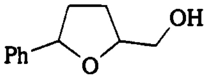 | 25 |
| 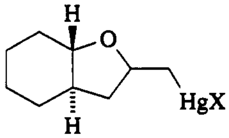 | 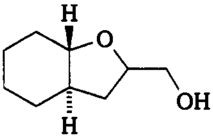 | 60 |
| 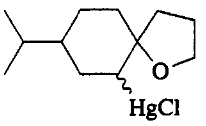 | 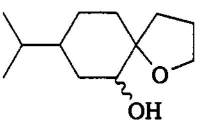 | 45 |
| 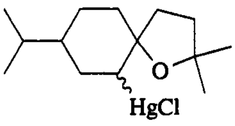 | 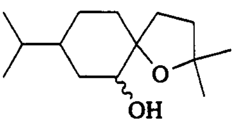 | 60 |

Oxidative replacement of HgX by hydroxy is straightforward in more complex systems. For example, this conversion was an important step in the total synthesis of the potent antiviral agent aphidicolin (**39**), shown in Scheme 32.[63] The 6,11α-oxygen ring system was introduced by a (cyclization) oxymercuration–oxidative demercuration sequence in the synthesis of 5(*E*)- and 5(*Z*)-11-deoxy-6,11-α-epoxy-$\Delta^5$-prostaglandin $F_{1\alpha}$ in a most efficient manner (Scheme 33).[64] A number of other cyclization methods ($I_2$, selenium reagents) were tried but were unsuccessful. Thus oxymercuration–cyclization provided the bicyclo[3.2.1] system in good yield, which was then acetylated (for subsequent differentiation of the C-15 and C-5 hydroxy groups) and oxidatively demercurated to provide a separable diastereomeric set of C-5 alcohols. This type of approach has also been employed in the synthesis of 5-hydroxy-$PGI_2$.[65]

Mercuricyclization–oxidation has been utilized in a short stereoselective approach to the *trans*-fused pyranopyran ring system (**40**), which is found in some squalene-derived tetracyclic ethers such as thyrsiferol and venustatriol.[66] Unsaturated hydroxy nitrile (**41**) on $Hg^{II}$ cyclization (with $Hg(OCOCF_3)_2$ in DMF), followed by metathesis to the chloride afforded the tetrahydropyranylmercurial, which on oxidative demercuration provided an easily separated alcohol mixture, with the desired axial alcohol (**42**)

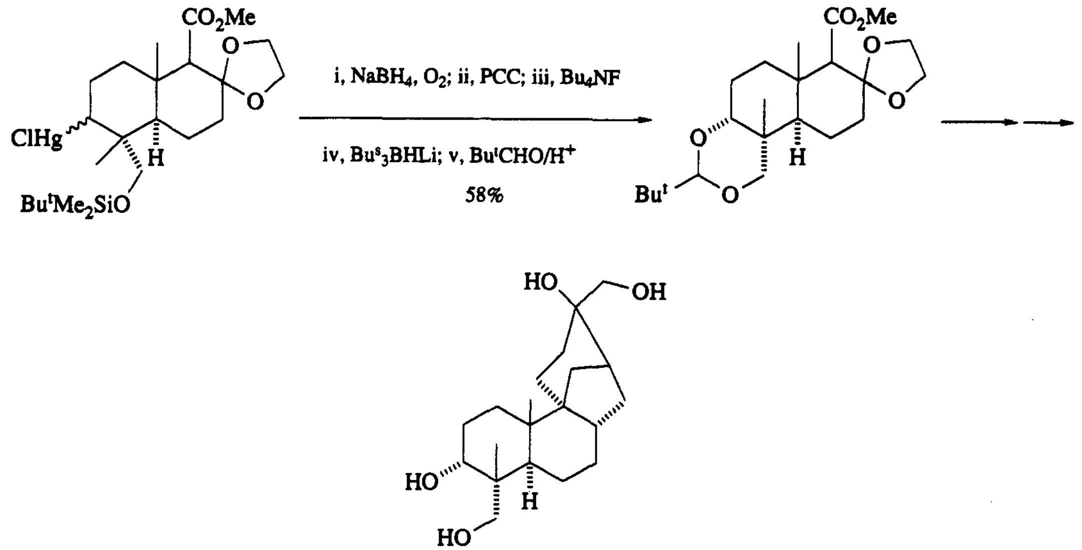
CO2Me
ClHg
H
ButMe2SiO
i, NaBH4, O2; ii, PCC; iii, Bu4NF
iv, Bus3BHLi; v, ButCHO/H+
58%
CO2Me
But
H
HO
OH
HO
H
HO

(39)

Scheme 32

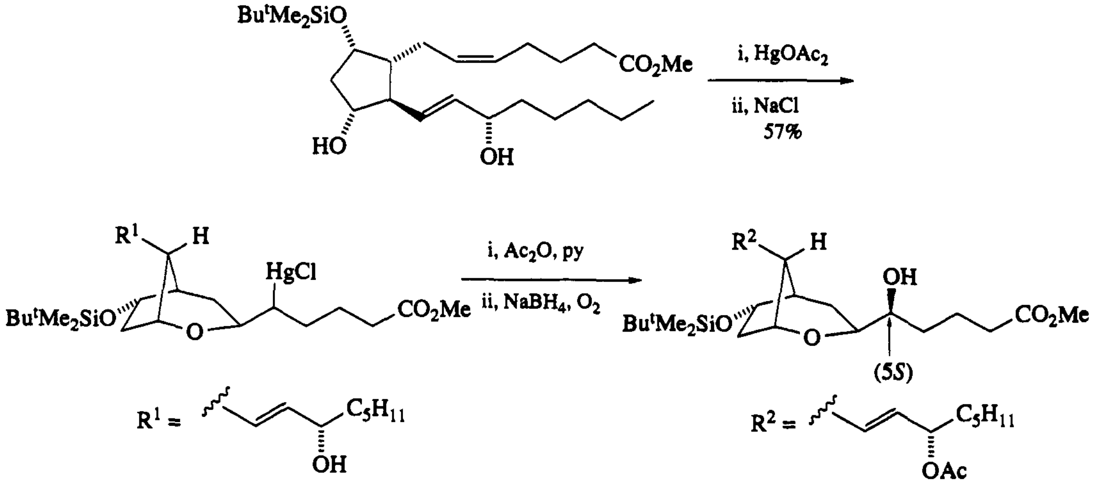
ButMe2SiO
CO2Me
i, HgOAc2
ii, NaCl
57%
HO
OH
R1
H
HgCl
ButMe2SiO
O
CO2Me
i, Ac2O, py
ii, NaBH4, O2
R2
H
OH
ButMe2SiO
O
CO2Me
(5S)
R1 =
C5H11
OH
R2 =
C5H11
OAc

Scheme 33

predominating. Alcohol (**42**) was converted to the chair-boat pyrano–pyran system (**43**), again utilizing mercuricyclization–oxidation (Scheme 34).

The synthesis of the limonoid azadiradione, utilizing a Hg$^{II}$ cyclization–oxidative demercuration sequence with an enol phosphate derived from *trans,trans*-farnesol has been reported.[67] Azadiradione, a tetracarbocyclic member of the limonoid group isolated from the neem tree, *Azadirachta indica*, has been converted to other tetracyclic limonoids, and is thus a key intermediate. The sequence is shown in Scheme 35.

Organomercurial intermediates have also been utilized in the biomimetic conversion of communic acids to the pimarane system, during which the radical involved in the $NaBH_4$-demercuration step was captured by oxygen.[68] Treatment of *trans*-communic acid with $Hg(OAc)_2$ (2 equiv.), followed by reduction, led to (**44**) and (**45**) and other products. These results are consistent with the intervention of the radical formed from the dimercurial (**46**) and, indeed, separate reduction in the presence of oxygen provided the peroxy compound (**45**) directly (Scheme 36).

In the area of pheromone synthesis, oxymercuration–oxidative demercuration has also proven valuable. For example, all four stereoisomers of tetrahydro-2,2,6-trimethyl-2*H*-pyran-3-ol, from the elm bark beetle *Pteleobius vittatus* have been acquired by a sequence from (*R*)- and (*S*)-sulcatol, which incorporates this mercury chemistry.[69] The epimeric alcohols (**47**) and (**48**; Scheme 37) were separable (MPLC)

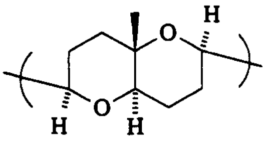

**(40)**

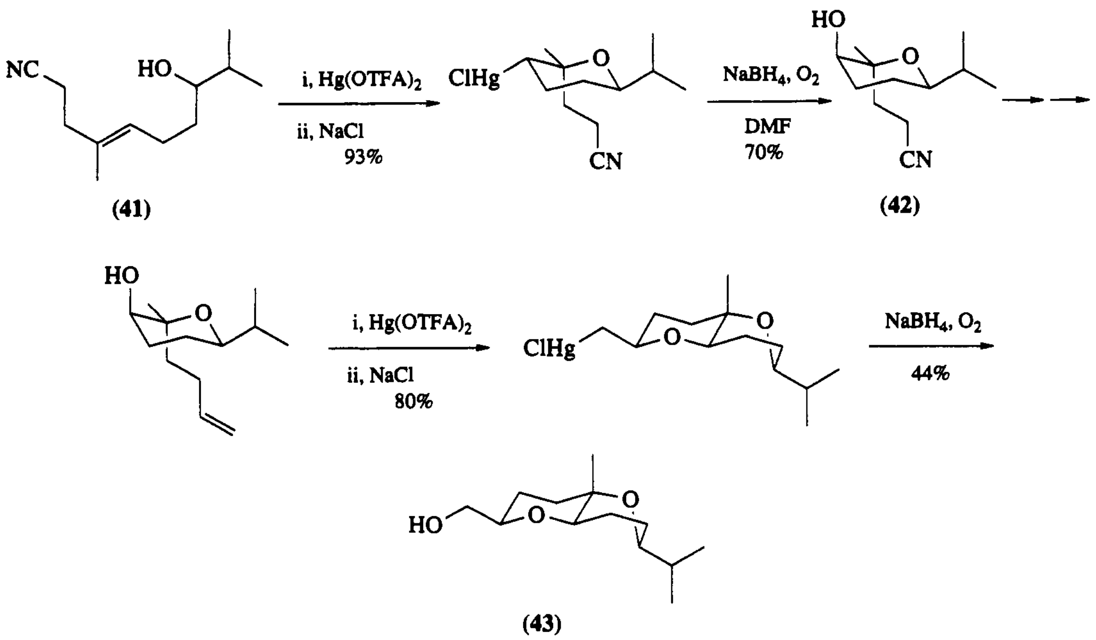
NC
HO
(41)
i, Hg(OTFA)2
ii, NaCl
93%
ClHg
CN
NaBH4, O2
DMF
70%
HO
CN
(42)
HO
i, Hg(OTFA)2
ii, NaCl
80%
ClHg
NaBH4, O2
44%
HO
(43)

**Scheme 34**

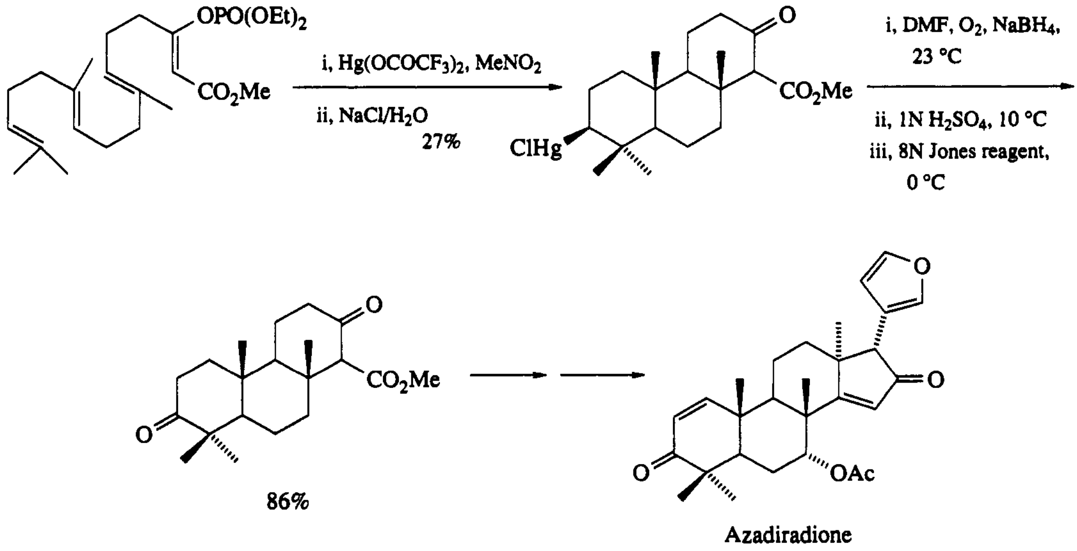
OPO(OEt)2
CO2Me
i, Hg(OCOCF3)2, MeNO2
ii, NaCl/H2O
27%
ClHg
O
CO2Me
i, DMF, O2, NaBH4, 23 °C
ii, 1N H2SO4, 10 °C
iii, 8N Jones reagent, 0 °C
O
CO2Me
O
86%
O
O
O
OAc
Azadiradione

**Scheme 35**

and shown to possess *ca.* 100% *ee*. In the same manner, the (3*R*,6*S*)- and (3*S*,6*S*)-stereoisomers were obtained. A number of naturally occurring spiroacetals bearing hydroxy substituents have been described and mercury chemistry was employed to obtain (*E*,*E*)-2-hydroxymethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**49**), a component of the rectal gland secretion of the cucumber fly *D. cucumis* (Scheme 37).[70]

Useful transformations in the carbohydrate field have also been reported.[71] Wittig reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose provided alkene (**50**), which on $Hg^{II}$-mediated cyclization provided

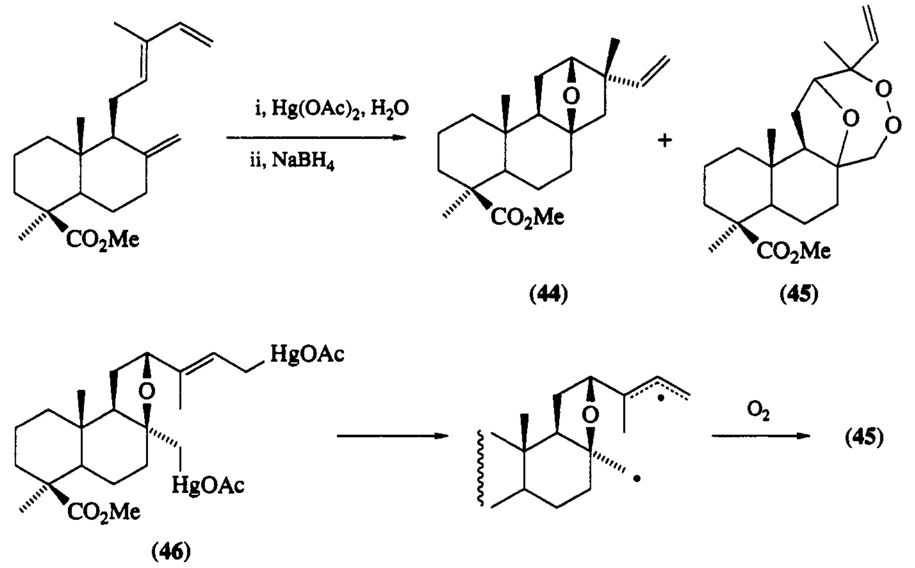

CO2Me
i, Hg(OAc)2, H2O
ii, NaBH4
O
CO2Me
+
O
O
O
CO2Me
(44)
(45)
HgOAc
O
HgOAc
CO2Me
(46)
O
O2
(45)

**Scheme 36**

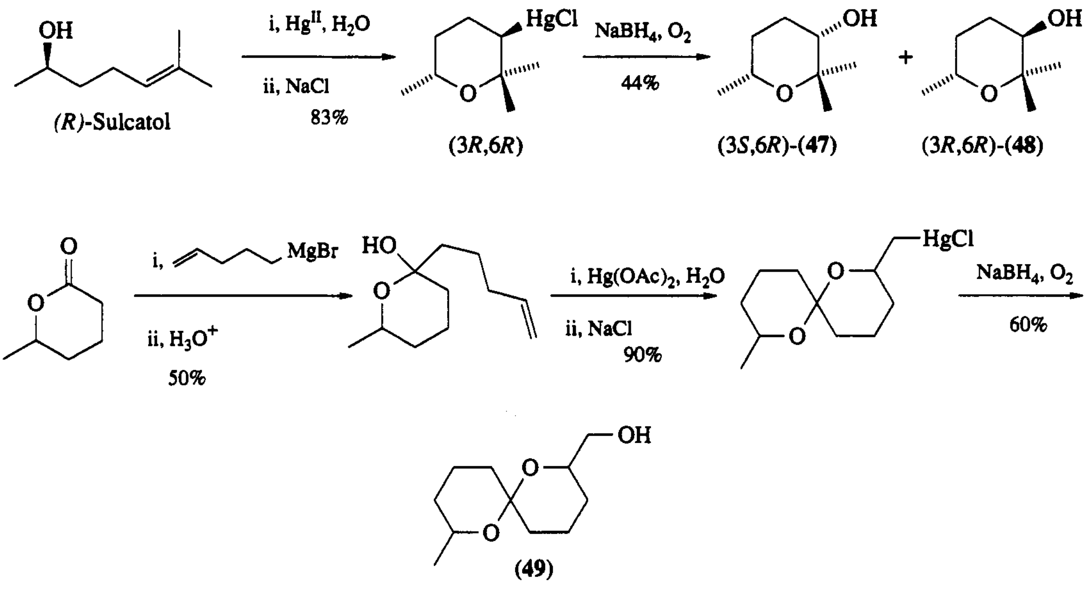

OH
(R)-Sulcatol
i, Hg^II, H2O
ii, NaCl
83%
HgCl
O
(3R,6R)
NaBH4, O2
44%
OH
O
(3S,6R)-(47)
+
OH
O
(3R,6R)-(48)
O
O
i, MgBr
ii, H3O+
50%
HO
O
i, Hg(OAc)2, H2O
ii, NaCl
90%
HgCl
O
O
NaBH4, O2
60%
OH
O
O
(49)

**Scheme 37**

essentially pure α-chloromercurial product (**51**) in high yield. Thus the axially oriented mercury group was well equipped for a range of further transformations and this cyclization provides an entry to 1,5-*trans* (*e.g.* α-D) *C*-glucopyranosyl derivatives (Scheme 38).

An especially important example of ring-forming aminomercuration–oxidation has been outlined in the synthesis of 1-deoxynojirimycin (**52**) and 1-deoxymannojirimycin (**53**), which are an interesting class of glycosidase inhibitors.[72] The reported method (Scheme 39) allows the conversion of a natural sugar into an azaalditol possessing the same relative and absolute configuration. Thus aminoalkene (**54**) (from tri-*O*-benzyl-6-bromopyranoside) on cyclizing aminomercuration *etc.* provided bromomercurials (**55**) and (**56**). Oxidation provided (**57**), which on hydrogenolysis *etc.* led to (**52**). The minor mercurial (**56**) after oxidative demercuration could be oxidized (Swern) to the aldehyde, followed by epimerization (DBU) and reduction ($NaBH_4$) to afford additional (**57**). Use of methyl-α-D-mannopyroside provided the epimeric aminoalkene (**58**), which was then transformed as described for (**52**) to (**53**) in 15% overall yield, although the mercuricyclization provided predominantly the unwanted isomer, which was epimerized as outlined (Scheme 39).

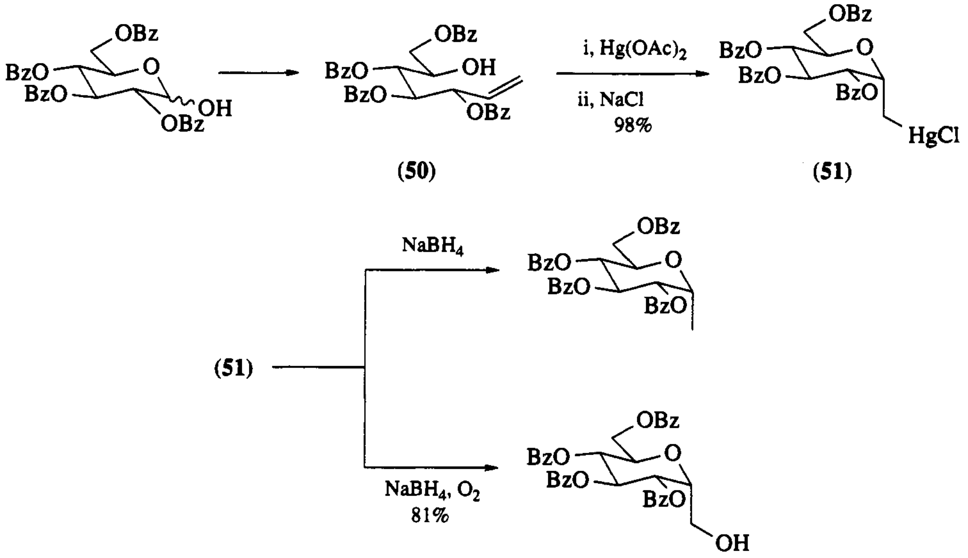
OBz
BzO
BzO
O
OH
OBz
OBz
BzO
BzO
OH
OBz
(50)
i, Hg(OAc)2
ii, NaCl
98%
OBz
BzO
BzO
O
BzO
HgCl
(51)
(51)
NaBH4
OBz
BzO
BzO
O
BzO
NaBH4, O2
81%
OBz
BzO
BzO
O
BzO
OH

**Scheme 38**

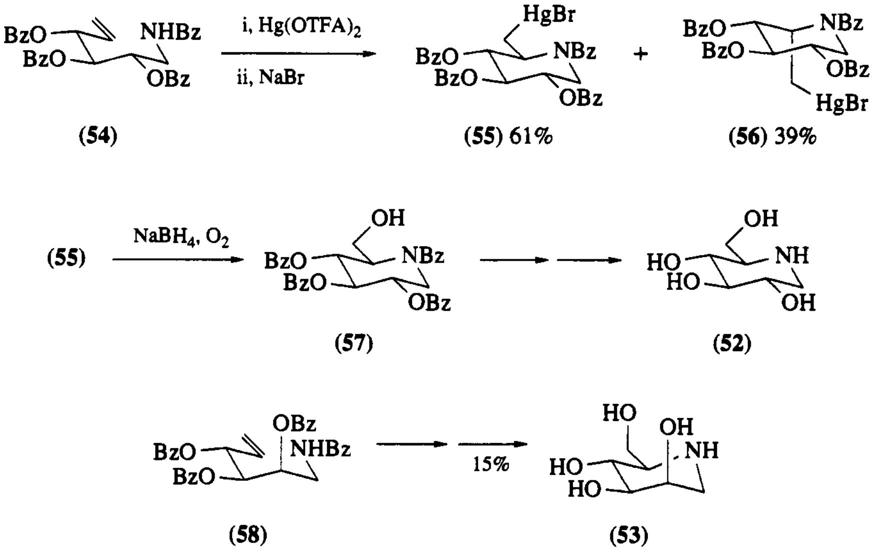
BzO
BzO
NHBz
OBz
(54)
i, Hg(OTFA)2
ii, NaBr
HgBr
BzO
BzO
NBz
OBz
(55) 61%
+
BzO
BzO
NBz
OBz
HgBr
(56) 39%
(55)
NaBH4, O2
OH
BzO
BzO
NBz
OBz
(57)
OH
HO
HO
NH
OH
(52)
OBz
BzO
BzO
NHBz
(58)
15%
HO
OH
HO
HO
NH
(53)

**Scheme 39**

### 4.2.4.3 Miscellaneous Oxidations

Some other reactions involving oxidation of the C—Hg bond have been known for some time, but these are either of limited synthetic appeal or have experienced no significant development in recent years. Thus ozonolysis of the C—Hg bond to form carboxylic acids or ketones falls into the first category,[58] whereas allylic acetoxylation of alkenes by $Hg(OAc)_2$ falls into the second category. Nevertheless, this allylic oxidation (Treibe's reaction) has considerable synthetic utility, and has been reviewed quite recently.[56,73]

It is worth noting at this point that palladium(II) salts intervene in a synthetically useful way when alkenes are reacted with $Hg^{II}$ salts in either water or alcohols.[74,75] Thus oxymercuration–palladation–depalladation ensues and results in alkene → ketone conversions (equation 18).[56] The reaction can be catalytic in $Pd^{II}$, if a reoxidant such as $Cu^{II}$ is employed.

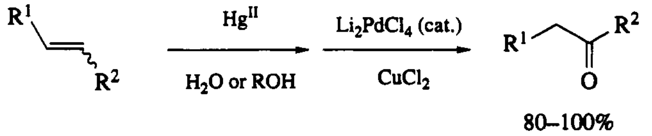

(18)

## 4.2.5 REFERENCES

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# 4.3
# Oxidation of Carbon–Silicon Bonds

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## 4.3.1 INTRODUCTION

This chapter concentrates on those processes in which oxidative cleavage of a carbon–silicon bond results in production of the alkyl/aryl fragment as an alcohol/phenol. Other cleavage processes are dealt with, but more briefly.

The first example of such cleavage was reported in 1958 by Buncel and Davies, in a pioneering study[1] of the rearrangement of triorganosilyl perbenzoates to yield alkoxy- or aryloxy-silanes (Scheme 1). Hydrogen peroxide can also be employed as oxidant, in a sequence which illustrates the migratory preference of the phenyl group. Later kinetic studies[2] confirmed that the rearrangement was intramolecular.

Until recently, little attention has been paid to the synthetic potential of this oxidative cleavage. Due largely to the studies[3] of Tamao and Kumada and, independently, those of Fleming,[4] and their coworkers, such potential has now been revealed. It is the purpose of this chapter to highlight some of its applications. Since the emphasis is on synthetic utility, only high-yielding reactions have been selected for inclusion. Unless otherwise stated, all compounds shown are racemic; only one enantiomer is shown for clarity.

For successful cleavage, the silane must carry at least one electronegative substituent, such as alkoxy or fluorine. This requirement can be fulfilled either at an early stage by hydrosilylation of alkenes or alkynes using suitably functionalized hydridosilanes, or by late-stage electrophilic desilylation of phenyldimethylsilyl or allyldimethylsilyl moieties in the presence of a source of fluoride ion. Either excess hydrogen peroxide or MCPBA may be used as oxidant, and the alcohol is produced with ***retention of configuration***. Fluoride ion is normally a mandatory additive in what is believed to be an assisted rearrangement of a silyl peroxide, as shown in Scheme 2.

Anhydrous trimethylamine *N*-oxide[5] has been suggested[6] as an alternative, neutral oxidant, although with dialkoxysilanes relatively high reaction temperatures are required. Alkyltrifluorosilanes, on the other hand, undergo cleavage with this oxidant at room temperature.[7]

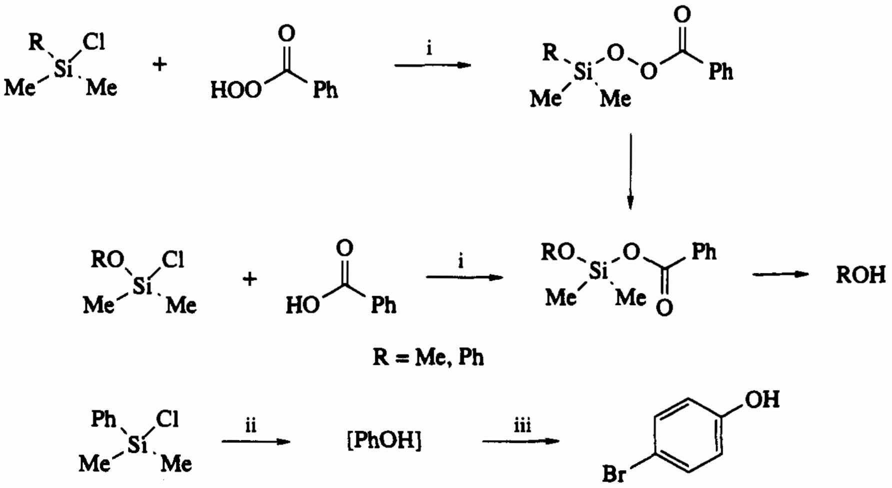

i, $NH_3$; ii, $H_2O_2$, AcOH, $H_2SO_4$ cat.; iii, $Br_2$

Scheme 1

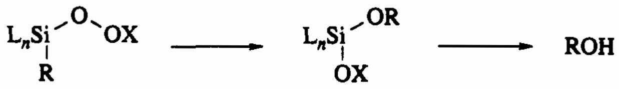

$L_n$ = F, R

Scheme 2

## 4.3.2 GENERATION OF ORGANOFLUOROSILICATES

### 4.3.2.1 By Hydrosilylation

#### *4.3.2.1.1 Hydrosilylation of alkenes with $Cl_3SiH$*

Catalyzed addition of trichlorosilane to terminal alkenes and alkynes, followed by the addition of an aqueous solution of potassium fluoride, produces highly reactive organopentafluorosilicates[8] (Scheme 3).

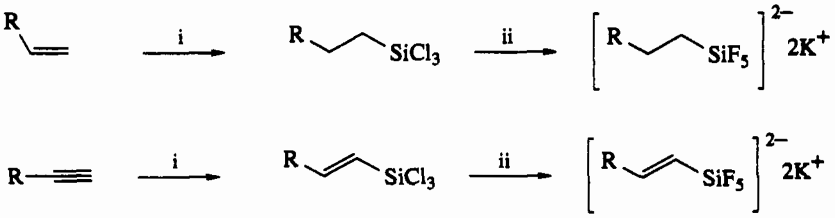

i, $Cl_3SiH$, $H_2PtCl_6$ cat.; ii, KF

Scheme 3

Alkylpentafluorosilicates react, in some cases exothermically, with a wide range of electrophilic reagents such as MCPBA,[8] and halogens and halogenoids.[9] Careful stereochemical investigation has shown that oxidative cleavage using MCPBA produces an alcohol with predominant *retention*[8] of stereochemistry, whereas cleavage using NBS gives an alkyl bromide with predominant *inversion* (Scheme 4).[10] Single-electron transfer processes have been implicated.[11] When combined with asymmetric hydrosilylation using a chiral catalyst, optically active alcohols can be generated.[12]

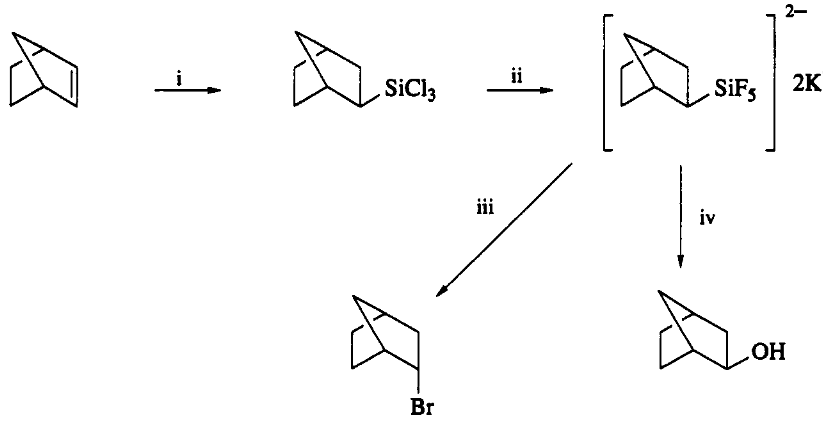

i, $Cl_3SiH$, chiral $Pd^{II}$ cat.; ii, KF; iii, NBS; iv, MCPBA

**Scheme 4**

#### *4.3.2.1.2 Hydrosilylation of alkynes with $Me_2SiClH$ and $MeSiCl_2H$*

Reaction of $H_2C{=}CHSiMeCl_2$ (obtained from the catalyzed hydrosilylation of acetylene with $MeSiCl_2H$) with an ephedrine-derived lithium dialkylamide produces the chiral vinylsilane (**1**). Addition of BuLi to this vinylsilane followed by treatment with $MgBr_2$ gives the corresponding Grignard reagent (**2**). This latter species can be transformed as shown in Scheme 5 into chiral alcohols in reasonable enantiomeric excess (*ee*).[13]

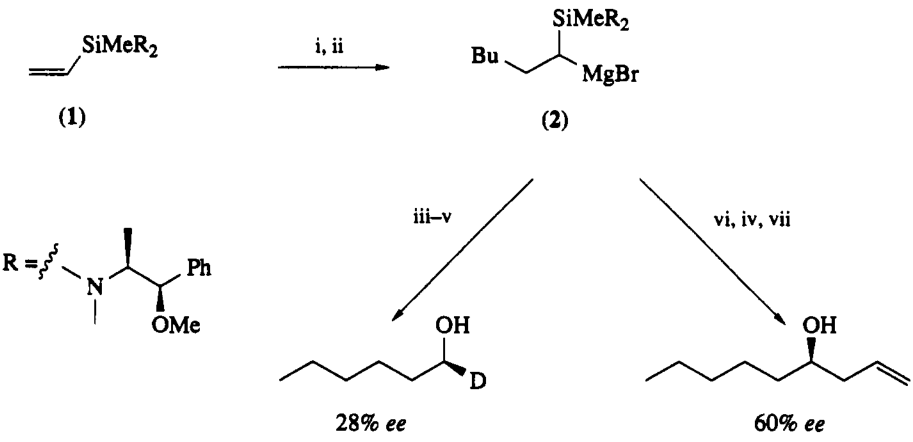

i, $Bu^nLi$; ii, $MgBr_2$; iii, $D_2O$; iv, $H_3O^+$; v, $H_2O_2$; vi, $H_2C{=}CHCH_2Br$, CuI; vii, $KHF_2$, $H_2O_2$

**Scheme 5**

The isomeric epoxysilanes (**3**) and (**4**), prepared as shown in Scheme 6, undergo a copper-catalyzed Grignard ring-opening[14] to give β-hydroxysilanes. Oxidative cleavage then completes this selective route to either *syn* (**5**) or *anti* (**6**) 1,2-diols. Such methodology has been utilized in a synthesis of (±)-*exo*-brevicomin.

#### *4.3.2.1.3 Hydrosilylation of Alkynes with $(EtO)_2MeSiH$*

Hydrosilylation of terminal alkenes using the air-stable silane $(EtO)_2MeSiH$ in the presence of either $H_2PtCl_6$ or $(Ph_3P)_3RhCl$ results in the introduction of silicon exclusively at the terminal carbon atom. When coupled with oxidative cleavage, this protocol[15] provides a simple one-pot synthesis of anti-Markovnikov alcohols from terminal alkenes (Scheme 7).

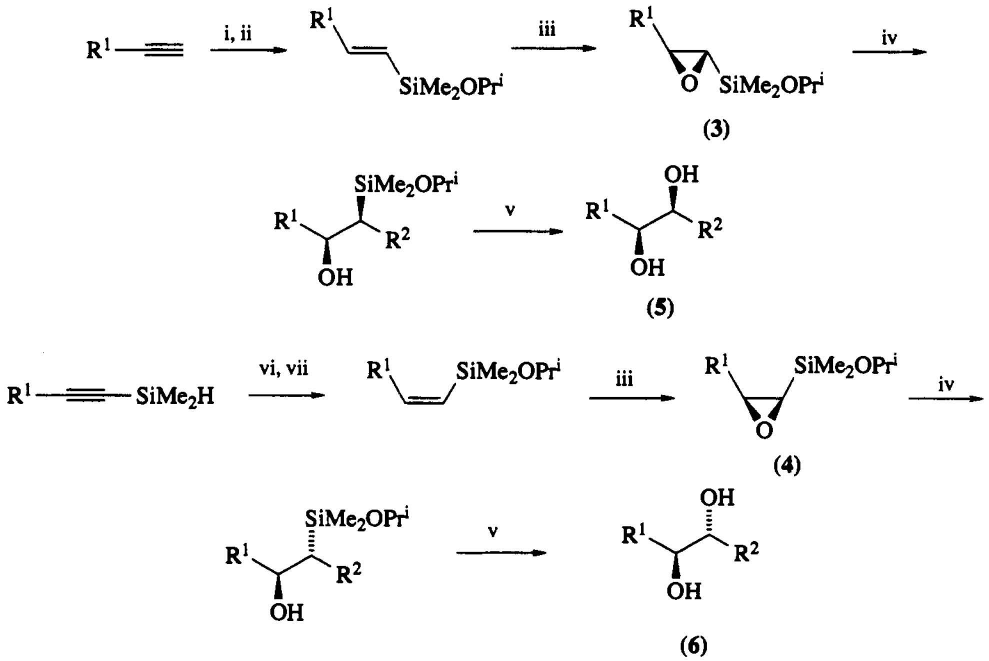
i, ii
iii
iv
(3)
v
(5)
vi, vii
iii
iv
(4)
v
(6)

i, $Me_2SiClH$, $H_2PtCl_6$ cat.; ii, $Pr^iOH$, $Et_3N$; iii, MCPBA; iv, $R^2MgX$, CuCN; v, $H_2O_2$, KF, $KHCO_3$, MeOH, THF; vi, hydroalumination then hydrolysis; vii, $Pr^iOH$, $H_2PtCl_6$ cat.

Scheme 6

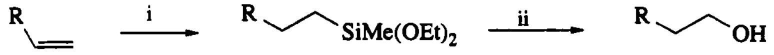

i, $(EtO)_2MeSiH$, cat.; ii, $H_2O_2$, $KHF_2$, DMF or MCPBA, $KHF_2$, DMF

Scheme 7

A related sequence involving alkynes, with the intermediacy of vinyl(alkoxy)silanes, has been described in detail;[16] the various oxidation conditions are summarized in Scheme 8.

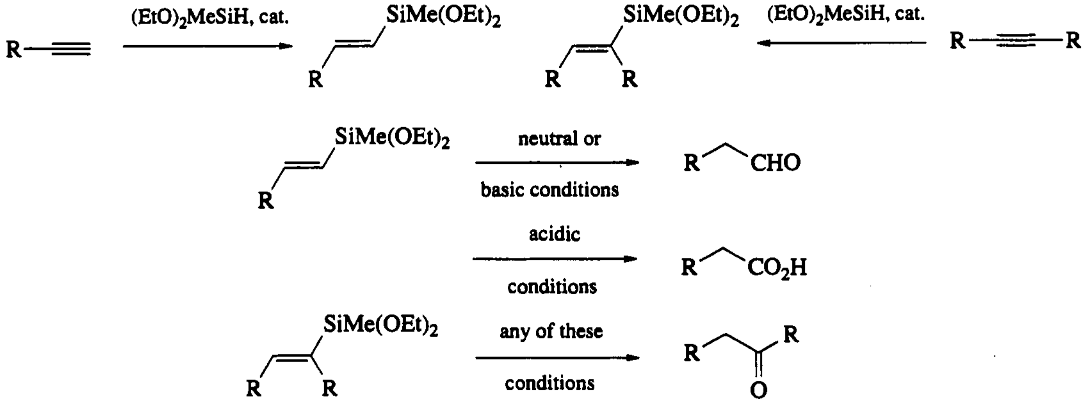
(EtO)2MeSiH, cat.
(EtO)2MeSiH, cat.
neutral or
basic conditions
acidic
conditions
any of these
conditions

Neutral conditions = 30% $H_2O_2$, $KHF_2$, DMF, r.t. to 60 °C
Acidic conditions = 30% $H_2O_2$, $Ac_2O$, $KHF_2$, DMF, r.t.
Basic conditions = 30% $H_2O_2$, $KHCO_3$, MeOH, THF, 60 °C

Scheme 8

Addition[17] of organolithium and organomagnesium reagents to such vinyl(alkoxy)silanes, followed by catalyzed coupling of the new organometallic with either vinyl or allyl bromide, leads,[18] after oxidative cleavage, to allylic or homoallylic alcohols, respectively (Scheme 9).

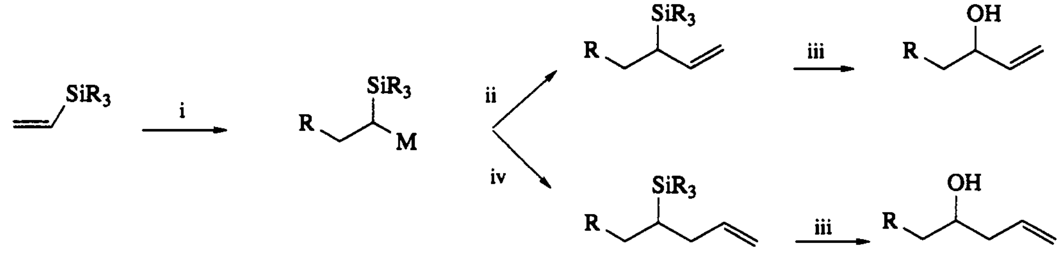

$SiR_3 = SiMe(OEt)_2$, *etc.*

i, RM; ii, $H_2C{=}CHBr$, cat.; iii, MCPBA, KF; iv, $H_2C{=}CHCH_2Br$, cat. [catalyst either $NiCl_2$ or $PdCl_2(DPPF)$]

**Scheme 9**

#### *4.3.2.1.4 Intramolecular hydrosilylation of allylic and homoallylic alcohols*

Intramolecular hydrosilylation of allyl and homoallyl alcohols, with subsequent oxidative cleavage of the resultant C—Si bond, has provided[19] a new approach to the regiocontrolled synthesis of 1,2-and/or 1,3-diols (see also Section 4.3.2.2.3). The example shown[20] (Scheme 10) illustrates nicely the use of *syn* stereoselection in a reiterative manner.

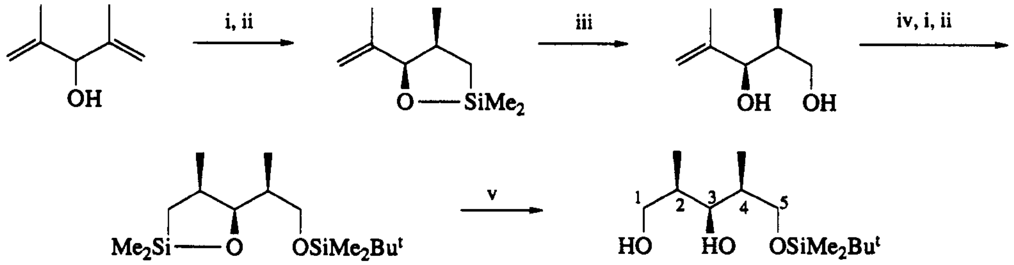

2,3 *syn*:*anti* 10:1
3,4 *syn*:*anti* 13:1

i, $(HMe_2Si)_2NH$, r.t. to 60 °C; ii, $H_2PtCl_6$ cat., 60 °C; iii, $H_2O_2$, $NaHCO_3$, MeOH, THF;
iv, $Bu^tMe_2SiCl$, $Et_3N$, DMAP; v, $H_2O_2$, KF, $KHCO_3$, MeOH, THF

**Scheme 10**

In an extension of this process, the intramolecular hydrosilylation of α-hydroxy enol ethers has been presented[21] as a new, *syn* selective route to 1,2,3-triols (Scheme 11). With such sensitive substrates, a neutral hydrosilylation catalyst, $Pt\{[(CH_2{=}CH)Me_2Si]_2O\}_2$,[22] must be used. The utility of this method has been demonstrated in a synthesis of the pentitols, D-arabinol and xylitol (as their pentaacetates), in optically pure form.

In a related study[23] of the Lewis acid catalyzed intramolecular hydrosilylation of β-silyloxy ketones, *anti* selective hydrosilylation has been observed.

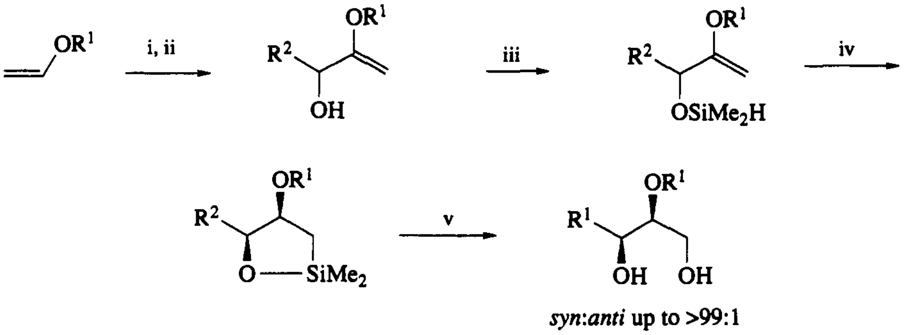

i, BuLi; ii, $R^2CHO$; iii, $(HMeSi)_2NH$, $NH_4Cl$ cat.; iv, $Pt^0$ cat.; v, $H_2O_2$, KOH, MeOH, THF

Scheme 11

### 4.3.2.2 From Functionalized Silanes

#### *4.3.2.2.1 Use of $PhMe_2Si$ moieties*

Extensive studies[4] by Fleming and his group have elegantly demonstrated the utility of lithium bis(phenyldimethylsilyl)cuprate, $(PhMe_2Si)_2CuLi$, for the stereocontrolled nucleophilic introduction of hydroxy groups. Conjugate addition of this reagent to an α,β-unsaturated ester[24] (or an α,β-unsaturated δ-lactone[25]) produces an intermediate β-silyl enolate, which can be trapped with electrophiles such as iodomethane to produce the *anti* diastereoisomer selectively. Access to the *syn* diastereoisomer is provided by similar conjugate addition to the α-methyl-α,β-unsaturated ester followed by protonation (Scheme 12). In either case, the $PhMe_2Si$ group can be converted[26] in two steps into a hydroxy group with retention ofconfiguration, by protiodesilylation using either $HBF_4$ or $BF_3.2AcOH$ to generate the required fluorosilane (and benzene), followed by a peracid-mediated rearrangement. It can also be applied to the synthesis of chiral β-hydroxy esters[27,28] and amides, in those cases where the α,β-unsaturated carbonyl is functionalized by a chiral alcohol or amine auxiliary.

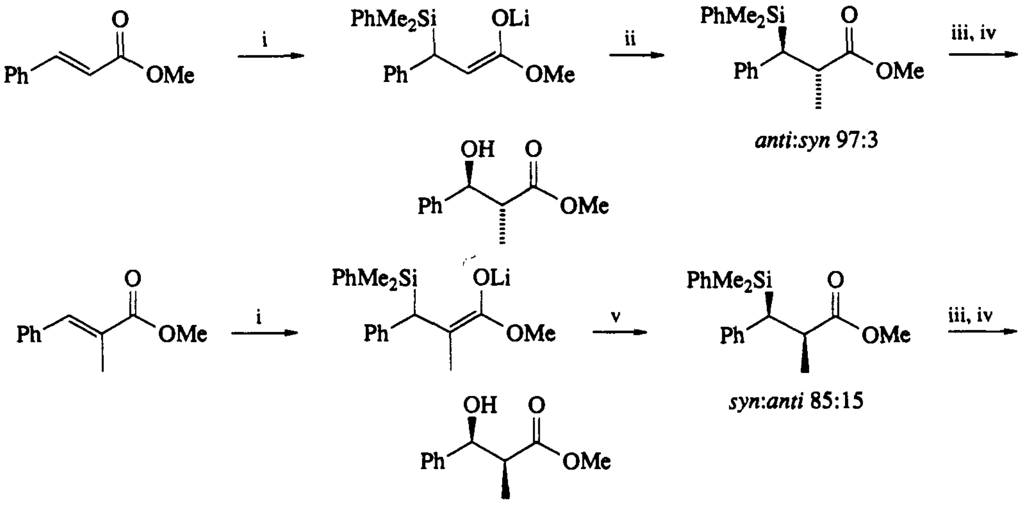

i, $(PhMe_2Si)_2CuLi$; ii, MeI; iii, $HBF_4$; iv, MCPBA, $Et_3N$; v, $NH_4Cl$

Scheme 12

Such β-silyl enolate intermediates also react with aldehydes[29] with high diastereoselectivity with respect to both new chiral centers being created, the relative stereochemistry in the aldol reaction being dependent upon the original geometry of the enolate double bond (Scheme 13). This aldol reaction has been applied to a formal synthesis of thienamycin,[30] and, with imines as the electrophilic partners, to a stereocontrolled route[31] to 3-(1-hydroxyethyl)azetidin-2-ones.

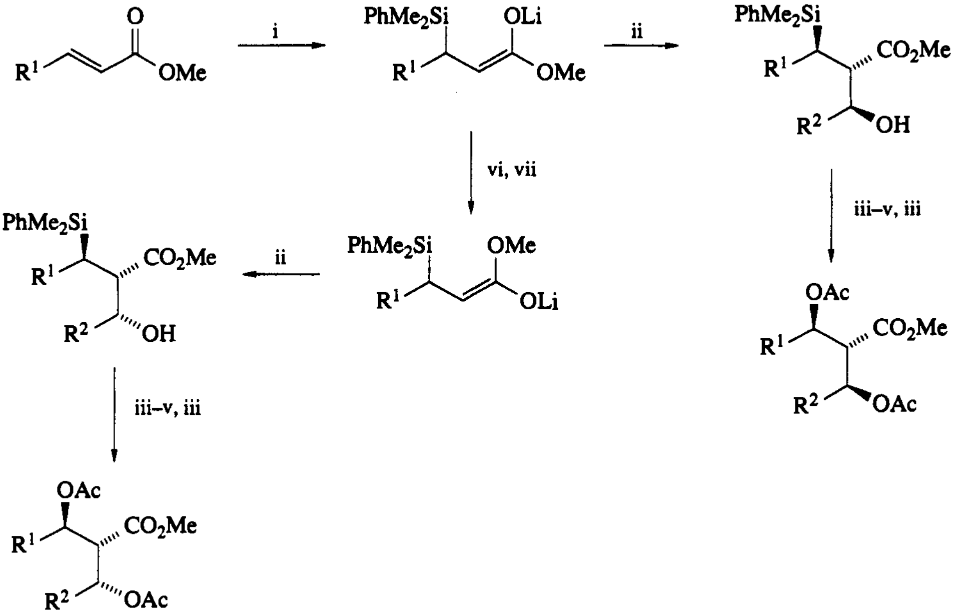

i, $(PhMe_2Si)_2CuLi$; ii, $R^2CHO$, –78 °C, iii, $Ac_2O$, $Et_3N$; iv, $BF_3 \cdot AcOH$; v, MCPBA, $Et_3N$; vi, $NH_4Cl$; vii, LDA, –78 °C

**Scheme 13**

This two-step protiodesilylation/oxidative cleavage, converting a $PhMe_2Si$ function into a hydroxy group, can be carried out in one pot,[32] using either $Br_2$ or mercury(II) in an acetic acid solution of peracetic acid. The bromine may be generated by adding the peracid solution to KBr, making it unnecessary to handle bromine itself, and sodium acetate may be used to buffer the sulfuric acid present in commercial peracetic acid. However, the latter device, useful when acid-sensitive groups are present, only works in those reactions using bromine. When using mercury(II), acid is needed to catalyze the mercuration of the benzene ring.

In a synthesis of (–)-reserpine, Stork[33] was unable to effect selective protiodesilylation, using $HBF_4$, of a $PhMe_2Si$ group in the presence of a benzyl ether. However, alternative use of a 2-furyldimethylsilyl group obviated this difficulty, due to the enhanced reactivity of the furan ring towards fluoride displacement under neutral conditions.

#### *4.3.2.2.2 Nucleophilic hydroxymethylating agents, $d^1$-methanol synthons*

The Grignard reagent $(Pr^iO)_2MeSiCH_2MgCl$ takes part in a metal-catalyzed coupling reaction[34] with alkyl, vinyl (stereochemistry retained), allyl (stereochemistry and regiochemistry retained), aryl and heteroaryl chlorides and bromides. With functionally substituted aryl or heteroaryl halides, conversion into the corresponding organozinc reagent confers increased chemoselectivity. Reaction of the adducts with KF or $KHF_2$, followed by oxidative cleavage using either $H_2O_2$ or peracetic acid results in the overall nucleophilic introduction of a hydroxymethyl group, as exemplified in Scheme 14. One application of its use can be seen in a synthesis[35] of (–)-asperdiol, in this case with copper-catalyzed coupling with an alkyl mesylate.

Later studies have shown that a single isopropoxy group suffices for successful oxidative cleavage. The Grignard reagent $Pr^iOMe_2SiCH_2MgCl$ adds[36] to ketones and aldehydes to give adducts which, upon oxidative cleavage, yield 1,2-diols, as shown in Scheme 15. This reagent also effects a copper-catalyzed coupling with allylic chlorides, as demonstrated in a synthesis of (+)-casbene.[37]

The latter reagent undergoes 1,2-addition to α,β-unsaturated aldehydes; 1,4-addition, with copper catalysis, is observed with cyclohexenone alone. A more satisfactory reagent[38] for the conjugate introduction of the hydroxymethyl group is the allyldimethylsilylmethyl Grignard reagent

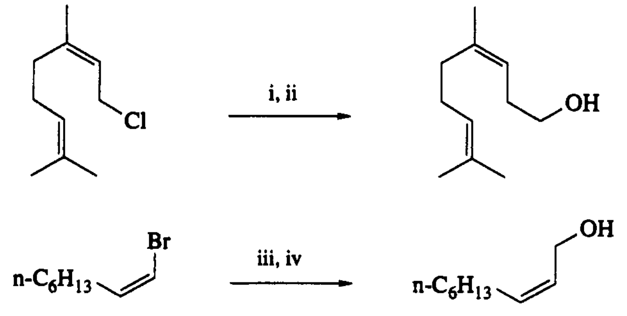

i, $(Pr^iO)_2MeSiCH_2MgCl$, CuI cat. ; ii, 90% $H_2O_2$; iii, $(Pr^iO)_2MeSiCH_2MgCl$, $NiCl_2(DPPP)$ cat.; iv, 30% $H_2O_2$

**Scheme 14**

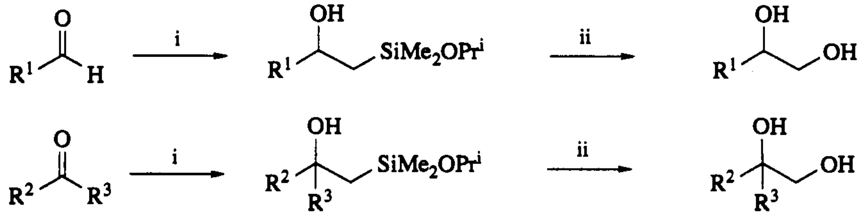

i, $Pr^iOMe_2SiCH_2MgCl$; ii, $H_2O_2$, $NaHCO_3$, MeOH, THF

**Scheme 15**

$(CH_2{=}CHCH_2)Me_2SiCH_2MgCl$. Protiodesilylation of the intermediate adduct from isophorone in the presence of fluoride ion generates the fluorosilane (7), which then undergoes oxidative cleavage under the normal conditions (Scheme 16). One limitation of this sequence is that it cannot be applied to cyclopentenone nor to $\Delta^{1,9}$-2-octalone systems.

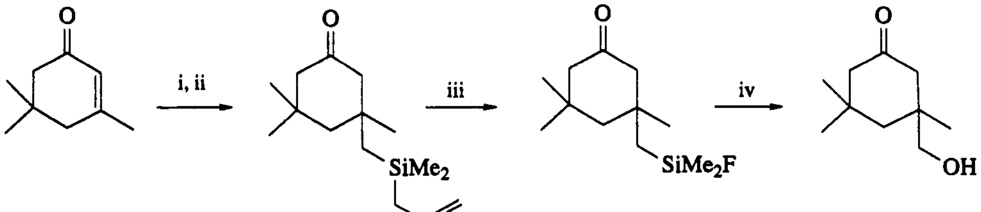

(7)

i, $(H_2C{=}CHCH_2)Me_2SiCH_2MgCl$, CuI cat.; ii, $NH_4Cl$; iii, $KHF_2$, TFA; iv, $H_2O_2$, $NaHCO_3$, MeOH, THF

**Scheme 16**

#### *4.3.2.2.3 Radical cyclization of halomethylsilyl ethers of allylic alcohols*

Silylmethyl radicals,[39,40] generated for halomethylsilyl ethers of allylic alcohols, can provide an indirect method of achieving acyclic stereocontrol. Depending on the substrate substitution pattern, either 6-*endo*- or 5-*exo-trig* cyclization can predominate. Stork and coworkers have developed an excellent method[41] for the control of ring junction stereochemistry using such radicals (Scheme 17). In such a 5-*exo-trig* process, transition state geometry dictates a *cis* fusion of the new five-membered ring. The resulting radical, being cup shaped, allows ready access to tributylstannane only from the convex face, resulting, after oxidative cleavage, in the effective overall *anti* addition of a hydroxymethyl group and a hydrogen to the original double bond.

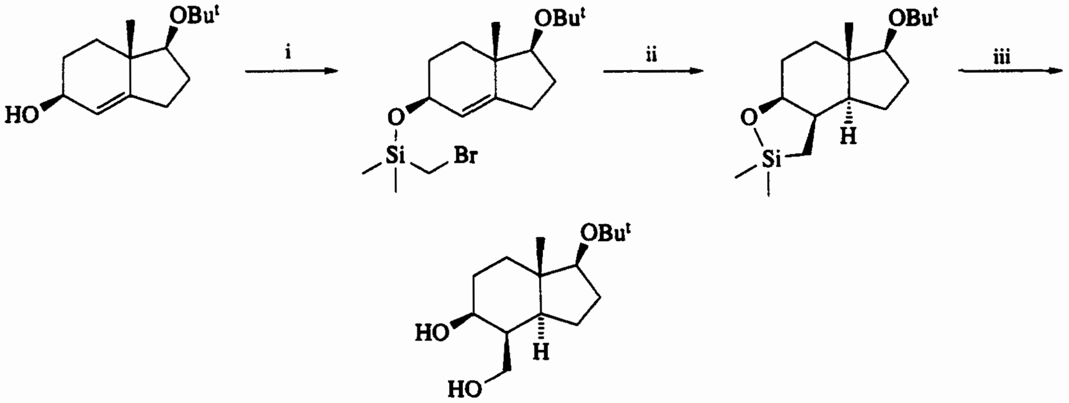

i, $Me_2Si(Cl)CH_2Br$, $Et_3N$, DMAP; ii, $Bu_3SnH$, AIBN cat., PhH or $NaCNBH_3$, $Bu_3SnCl$ cat., AIBN cat., $Bu^tOH$; iii, $H_2O_2$, KF, DMF

**Scheme 17**

Similar methodology can be used in acyclic systems[42] for the diastereoselective, and sometimes diastereoselective (Scheme 18), formation of 1,3-diols. With some substrates, the proportion of products arising from 6-*endo-trig* cyclization can be significant.

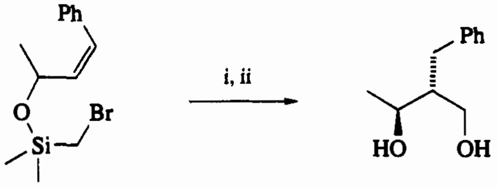

i, $Bu_3SnH$, AIBN cat., PhH; ii, $H_2O_2$, KF, DMF

**Scheme 18**

Indeed, in certain steroidal systems, 6-*endo-trig* cyclization becomes preferred, with ultimate regio- and stereo-controlled production[43] of 1,4-diols (Scheme 19). However, other steroidal systems which react by 5-*exo-trig* cyclization have been described.[44]

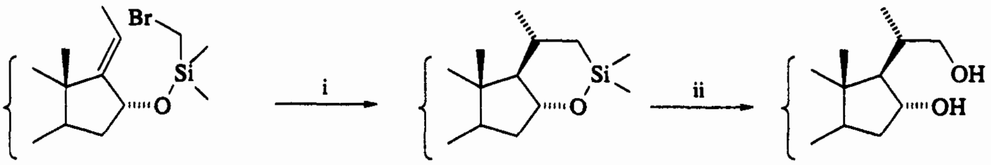

i, $Bu_3SnH$, AIBN cat., PhH; ii, $H_2O_2$, $KHCO_3$, MeOH, THF

**Scheme 19**

### 4.3.3 MISCELLANEOUS

Aryltrimethylsilanes undergo a facile metal/metal exchange[45] with lead(IV) trifluoroacetate; the intermediate aryllead species then eliminate lead(II) acetate to form the corresponding aryl trifluoroacetates in almost quantitative yield (Scheme 20).

Benzyltrimethylsilanes, on the other hand, give products of C–Si cleavage, *i.e.* benzyl nitrate and acetate, on treatment with cerium(IV) ammonium nitrate in AcOH; based on ring substituent effects, a one-electron transfer mechanism[46] seems to be in operation.

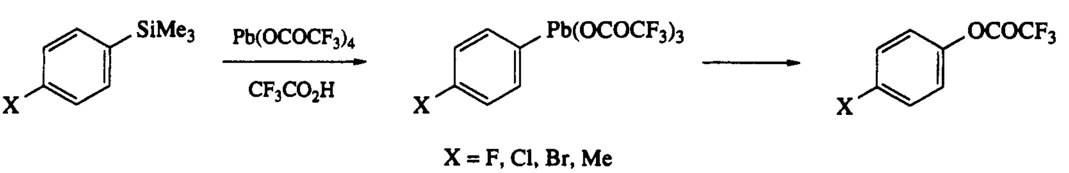

Scheme 20

Methoxy(trimethylsilyl)methane and methoxybis(trimethylsilyl)methane have been proposed[47] as new synthons for the formyl anion and the methoxycarbonyl anion, respectively; after alkylation, C–Si cleavage is achieved by anodic oxidation. Similar electrochemical oxidative cleavage[48] of acylsilanes reveals their potential as acyl cation synthons. Anodic oxidation[49] of *N*-silylmethyl carbamates in methanol produces *N*-methoxymethyl carbamates in high yield.

Treatment of tetramethylsilane with TfOH yields[50] trimethylsilyl triflate (Scheme 21). Although not a direct oxidation, this is an excellent, simple method for the preparation of a most useful reagent.[51]

$$Me_4Si + CF_3COOH \longrightarrow Me_3SiOCOCF_3 + CH_4$$

Scheme 21

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# 4.4

# Oxidation of Carbon–Halogen Bonds

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## 4.4.1 INTRODUCTION

Halides are extremely versatile intermediates. One of their more valuable and interesting transformations is their oxidation to carbonyl compounds, thus providing straightforward routes to relatively inaccessible compounds such as 1,2-diketones and heterocyclic aldehydes. As will be seen below, there are many, often complementary, synthetic methods for the oxidation of organic halides. The oxidation of halomethyl compounds has been reviewed recently.[1]

## 4.4.2 KORNBLUM OXIDATION AND RELATED METHODS

### 4.4.2.1 Oxidation with Dimethyl Sulfoxide

Known as the Kornblum oxidation, this is perhaps the most widely used and best-known method for the oxidation of halides.[2,3] It works best with activated halides such as benzyl halides, α-halocarbonyl compounds and iodides, though unactivated bromides also work reasonably well. Experimentally, the method consists of heating the halide in DMSO, usually in the presence of a base such as sodium bicarbonate to scavenge the HX. The reaction proceeds by an $S_N2$ displacement by the oxygen atom of the dimethyl sulfoxide, followed by proton loss and 3,2-sigmatropic rearrangement of the resulting sulfur ylide. The mechanistic analogy with the Swern oxidation is clear, since only the route to the sulfonium ion intermediate differs (Scheme 1).[4]

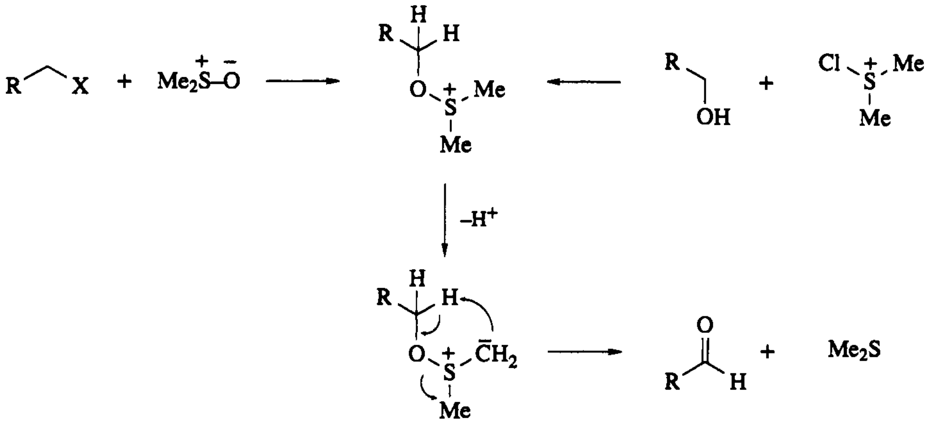

Scheme 1

However, as shown in Scheme 2, a different mechanism intervenes when R is a carbonyl group, since the protons adjacent to it are now more acidic than those of the methyl groups of the sulfonium ion.[5]

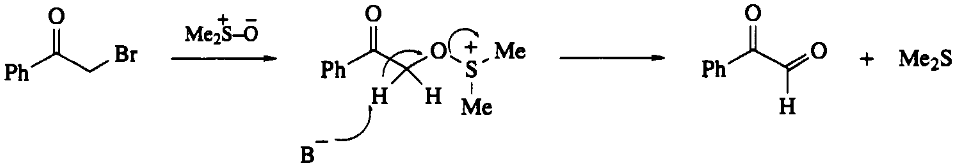

Scheme 2

As can be seen from Table 1 the method is general for a wide variety of activated halides, and provides an excellent alternative to selenium dioxide for the synthesis of 1,2-diketones and keto aldehydes. It constitutes, perhaps, the definitive synthesis of glyoxylates. It is not necessary to heat many α-bromo ketones since the reaction often proceeds smoothly at room temperature.

There are some important limitations on the Kornblum oxidation, however, as would be expected for a reaction relying on an $S_N2$ displacement as the first step. Secondary halides are prone to elimination under these conditions.[6] Similarly, if the approach of the DMSO is hindered, *e.g.* by a 1,3-diaxial interaction, the oxidation proceeds poorly (equation 1).[7] Overoxidation can also occur, at least in steroidal α-bromo ketones (Scheme 3).[8]

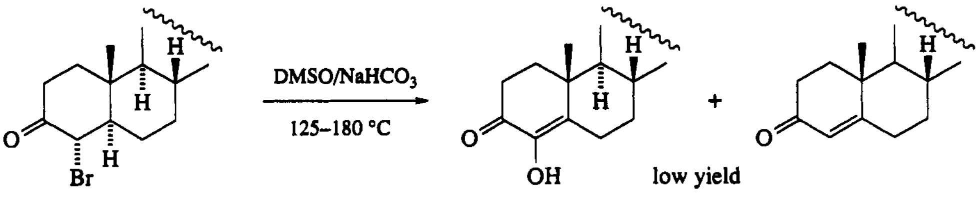

(1)

Kornblum *et al.* had asserted[9] that it was necessary to convert primary iodides to tosylates for the oxidation to proceed. However, Johnson and Pelter[10] have claimed that primary iodides can be oxidized directly. They observed that ketonic substrates failed, undergoing aldol condensation under the reaction conditions, but that hydroxy-containing halides reacted normally. For substrates insoluble in DMSO such as 1-bromododecane, they found that DME worked well as a cosolvent. The most interesting example

**Table 1**

| *Halide* | *Conditions* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 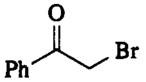 | DMSO, 25 °C | 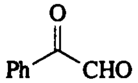 | 71 | 18 |
| 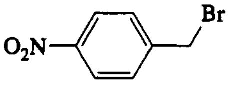 | DMSO, MeCN, 25 °C | 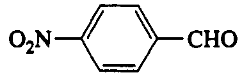 | 48 | 18 |
| 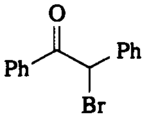 | DMSO, 45 °C | 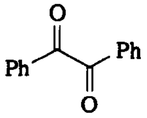 | 95 | 18 |
| $BrCH_2CO_2Et$ | 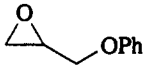 , DMSO | $OHCCO_2Et$ | 70 | 19 |
| 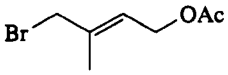 | DMSO, $NaHCO_3$, 25 °C | 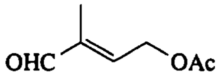 | 81 | 20 |

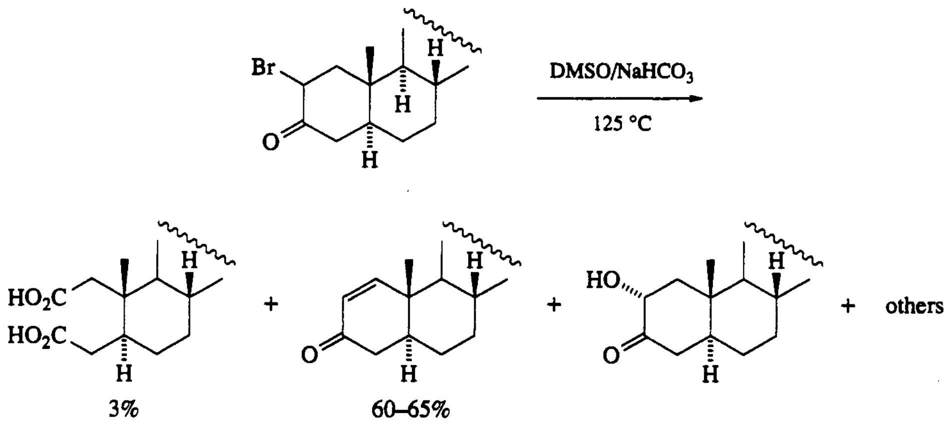

**Scheme 3**

was the oxidation of 2-iodooctane to the ketone, albeit in a yield of 32%, showing that secondary substrates are sometimes feasible.

Omission of the base in the Kornblum oxidation can have interesting consequences. Bromine, produced by the oxidation of the liberated HBr by DMSO,[11] may lead to bromination of the primary oxidation product in good yield (equation 2).[12] Note the use of epichlorohydrin as an HBr scavenger (equation 3).

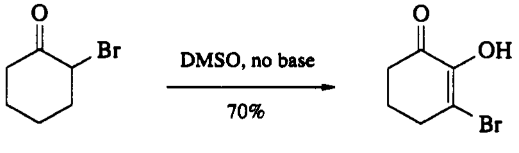

(2)

One way to increase the nucleofugacity of halides is to introduce silver ion. Kornblum reported that primary unactivated chlorides, bromides and iodides could be oxidized by prior conversion to the tosylate with silver tosylate, followed by reaction in DMSO (Scheme 4).[9]

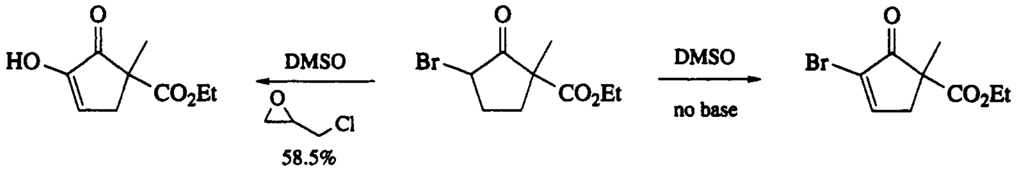

(3)

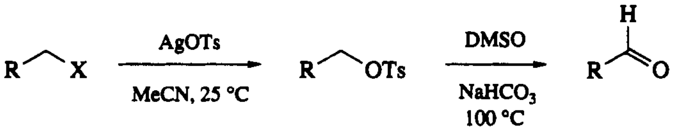

| *R* | *X* | *Yield* (%) |
|---|---|---|
| n-$C_7H_{15}$ | Cl | 71 |
| $C_6H_{13}$ | I | 70 |
| 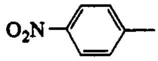 | Br | 76 |

**Scheme 4**

However, the neopentyl example still failed. Later it was found that addition of a silver salt to the DMSO solution was equally effective (Table 2). In two of the three reports[13,14] triethylamine was added as a base after formation of the sulfonium salt. Silver perchlorate is claimed to be superior to silver nitrate.[15] The method fails for unactivated chlorides, for deactivated bromides, and for substrates where solvolytic reactions are possible.

**Table 2**

| *Halide* | *Conditions* | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|
| 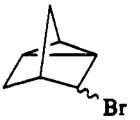 | i, $AgBF_4$, DMSO, 25 °C; ii, $Et_3N$ | 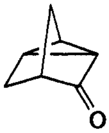 | 68.5 | 14 |
| 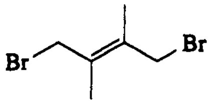 | i, $AgBF_4$, DMSO, 25 °C; ii, $Et_3N$ | 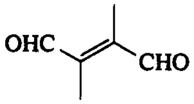 | 60 | 13 |
| 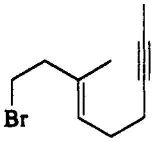 | i, $AgBF_4$, DMSO, 25 °C; ii, $Et_3N$ | — | 0 | 13 |

The Kornblum oxidation can be combined with halogenation to provide a very convenient synthesis of 2- and 4-pyridinecarbaldehydes from the corresponding picolines (equation 4).[16]

The procedure could also be used to synthesize 2,4- and 2,6-pyridinedicarbaldehydes from the lutidines.

Reaction of cyclic 1,3-diones with DMSO containing catalytic bromine gives 1,2,3-triones *via* the 2-bromodione (equation 5).[17] Unfortunately, the reaction gives only poor yields with acyclic diones.

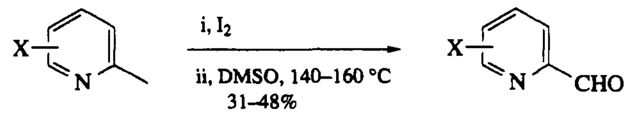

(4)

X = Me, Et, $CO_2Me$, CHNOH

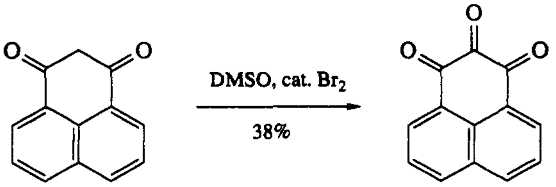

(5)

### 4.4.2.2 Oxidation with Selenoxides

Use of dimethyl selenoxide[21] or di(4-anisyl) selenoxide[22] in place of DMSO is claimed to offer some advantages in terms of mildness for polysubstituted or base sensitive benzyl halides. Problems of cost, accessibility and toxicity are not addressed.

## 4.4.3 THE KRÖHNKE OXIDATION

One of the oldest and most popular methods for oxidizing activated halides is the three-step Kröhnke oxidation.[23] The individual steps are: (i) quaternization of the halide with pyridine; (ii) deprotonation in base and reaction of the resulting pyridinium ylide with *N,N*-dimethyl-4-nitrosoaniline; and (iii) acid hydrolysis of the nitrone to the carbonyl compound (Scheme 5).

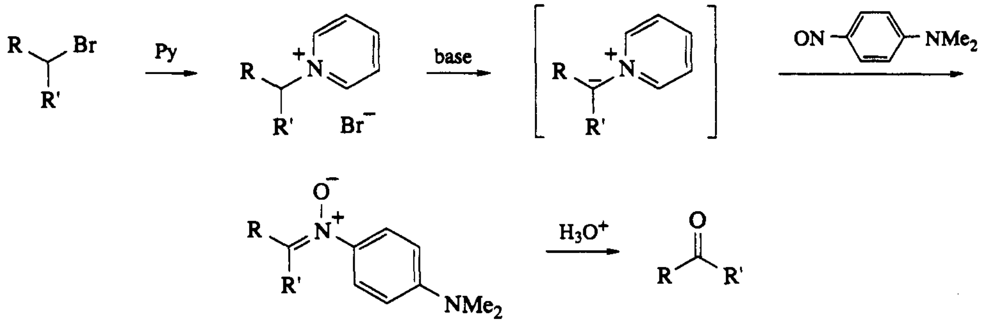

Scheme 5

The method is limited to activated halides which are stable to alkoxide bases and aqueous acids. According to the discoverer,[23] the Kröhnke oxidation is inferior to the Sommelet reaction for benzyl halides, especially those bearing electron-withdrawing groups, such as nitro. Some representative examples are shown in Scheme 6[27] and equations (6)–(12).[28–34] As can be seen, the Kröhnke oxidation is an excellent method for the preparation of heterocyclic aldehydes which would otherwise be difficult to synthesize. The preparations of a phthalimidoketo aldehyde (equation 11) and benzene-1,3,5-tricarbaldehyde (equation 12) are also noteworthy.

The Kröhnke oxidation often gives good results when other methods fail. In the example given (equation 13)[35] neither the Sommelet or the Hass–Bender method gave any aldehyde.

Similarly, in the preparation of 2-acetoxy-5-nitrobenzaldehyde from the benzyl bromide, the Sommelet reaction affords only 7% of the product, whereas the Kröhnke method worked in good, but unspecified yield.[24]

For acid sensitive substrates, the nitrone can be removed by hydrazinolysis followed by diazotization.[25] In the example given (equation 14),[25] direct acid hydrolysis of the nitrone with 1 M HCl gave only a 4% yield.

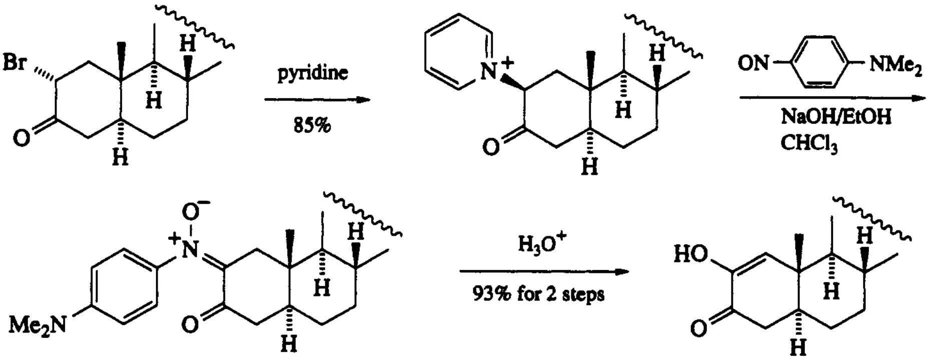
pyridine
85%
ON—C6H4—NMe2
NaOH/EtOH
CHCl3
H3O+
93% for 2 steps

**Scheme 6**

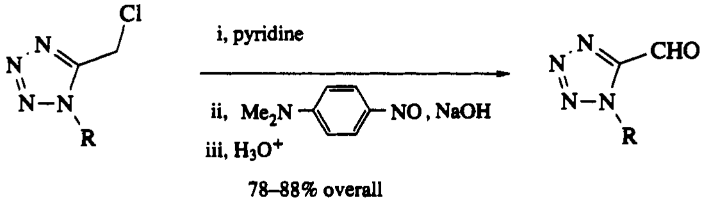
i, pyridine
ii, Me2N—C6H4—NO, NaOH
iii, H3O+
78–88% overall

(6)

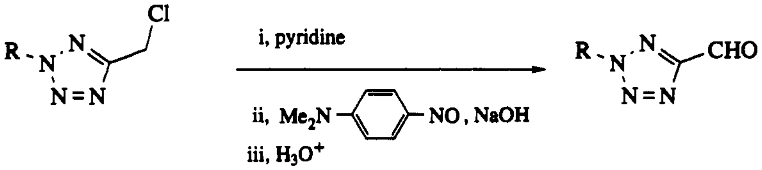
i, pyridine
ii, Me2N—C6H4—NO, NaOH
iii, H3O+

(7)

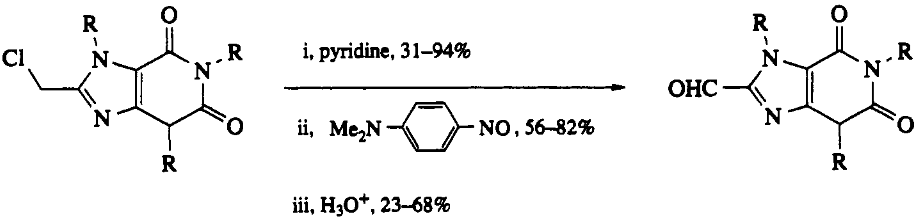
i, pyridine, 31–94%
ii, Me2N—C6H4—NO, 56–82%
iii, H3O+, 23–68%

(8)

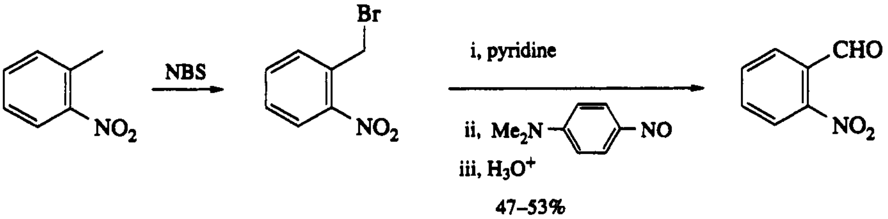
NBS
i, pyridine
ii, Me2N—C6H4—NO
iii, H3O+
47–53%

(9)

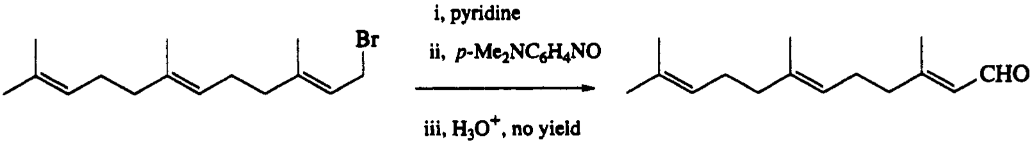
i, pyridine
ii, p-Me2NC6H4NO
iii, H3O+, no yield

(10)

By combination of the King–Ortoleva reaction and Kröhnke oxidation, activated methyl groups have been transformed directly into carbaldehydes (Scheme 7).[26]

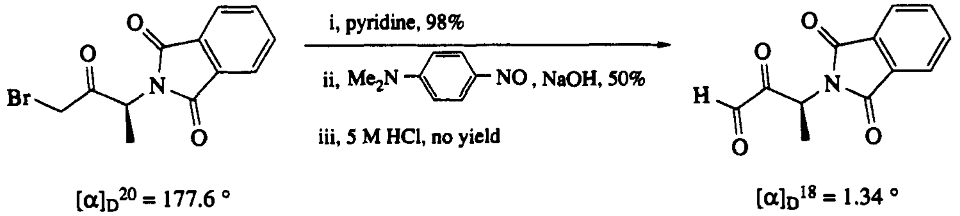
Br
O
O
N
O
i, pyridine, 98%
ii, Me2N–⟨⟩–NO, NaOH, 50%
iii, 5 M HCl, no yield
H
O
O
N
O
O
[α]D20 = 177.6 °
[α]D18 = 1.34 °

(11)

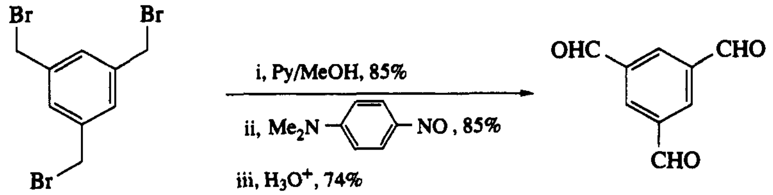
Br
Br
Br
i, Py/MeOH, 85%
ii, Me2N–⟨⟩–NO, 85%
iii, H3O+, 74%
OHC
CHO
CHO

(12)

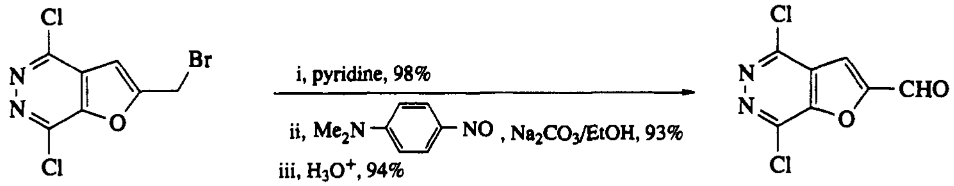
Cl
N
N
Cl
O
Br
i, pyridine, 98%
ii, Me2N–⟨⟩–NO, Na2CO3/EtOH, 93%
iii, H3O+, 94%
Cl
N
N
Cl
O
CHO

(13)

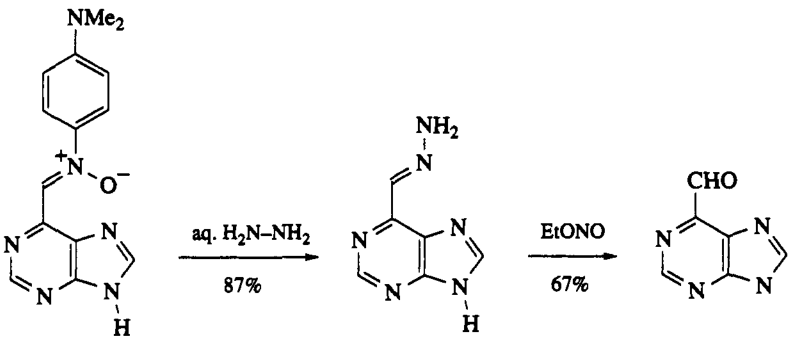
NMe2
+N
O−
N
N
N
N
H
aq. H2N-NH2
87%
NH2
N
N
N
N
N
H
EtONO
67%
CHO
N
N
N
N

(14)

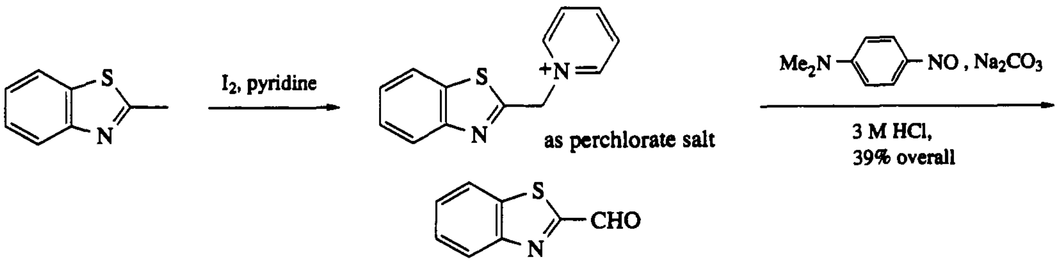
S
N
I2, pyridine
S
N
+N
as perchlorate salt
Me2N–⟨⟩–NO, Na2CO3
3 M HCl,
39% overall
S
N
CHO

**Scheme 7**

### 4.4.4 THE HASS–BENDER REACTION

Reaction of a disubstituted nitronate anion with an allylic or benzylic halide leads not to the expected *C*-alkylated nitro compound, but rather to the carbonyl product.[36] Presumably this reaction, known by the names of its discoverers, proceeds by the displacement of the halide ion by nitronate oxygen followed by loss of the oxime (equation 15).

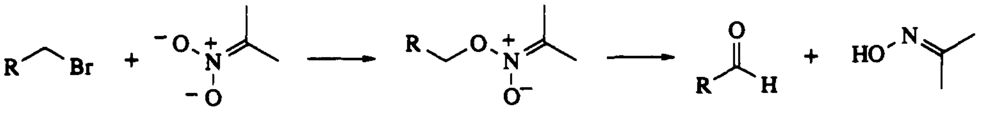
R
Br
+
−O
N+
−O
R
O
N+
O−
O
R
H
+
HO
N

(15)

Representative examples of the reaction are shown in equations (16)–(20).[37–41] The method works well for primary allylic and benzylic chlorides and bromides. There appear to be no examples of the oxidation of secondary halides to ketones by this method, presumably for reasons of lower reactivity. Neither are there any reports of the oxidation of α-halocarbonyl compounds, which is curious since these would be expected to be good substrates.

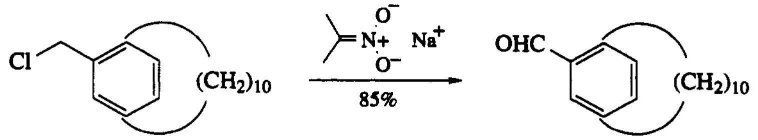
Cl
$(CH_2)_{10}$
$O^-$
N+
$Na^+$
$O^-$
85%
OHC
$(CH_2)_{10}$

(16)

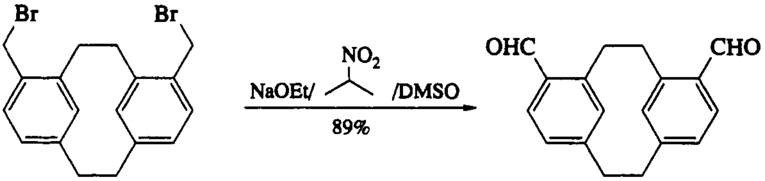
Br
Br
$NO_2$
NaOEt/
/DMSO
89%
OHC
CHO

(17)

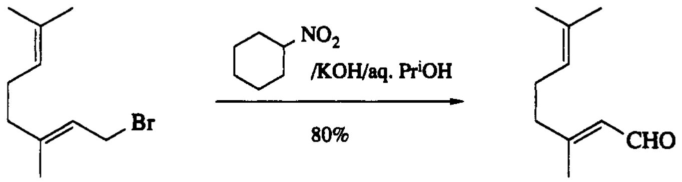
Br
$NO_2$
/KOH/aq. $Pr^iOH$
80%
CHO

(18)

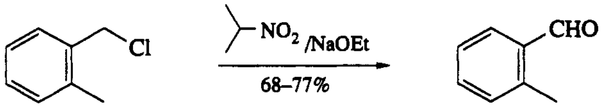
Cl
$NO_2$ /NaOEt
68–77%
CHO

(19)

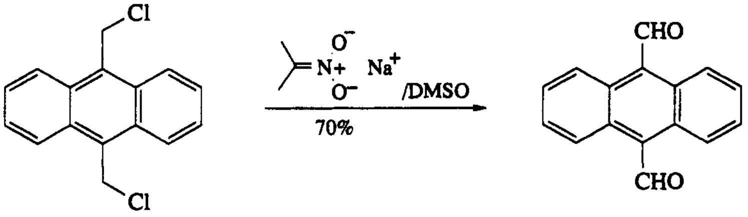
Cl
$O^-$
N+
$Na^+$
$O^-$
/DMSO
70%
CHO
CHO
Cl

(20)

The Hass–Bender oxidation is often competitive with other methods: in equation (16)[37] the Sommelet reaction gave only 20% of the aldehyde, whereas in equation (20)[41] DMSO and sodium hydrogen carbonate failed to furnish any of the desired product.

There is an interesting limitation to the method: 4-nitrobenzyl chloride gives only 1% of the aldehyde, the major product being the result of single-electron transfer and radical coupling (equation 21).[42]

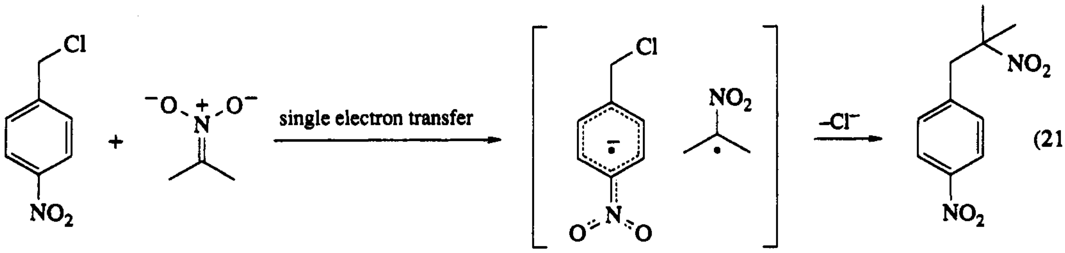
Cl
$NO_2$
+
$^-O$
+
N
$O^-$
single electron transfer
Cl
$NO_2$
O
N
O
$-Cl^-$
$NO_2$
$NO_2$

(21)

A Pd$^0$ catalyst has been used *in situ* to isomerize a secondary allylic halide prior to oxidation (equation 22).[43] In this case it is possible that reaction is occurring by attack of the nitronate anion on the π-allyl–palladium complex rather than on the chloride itself.

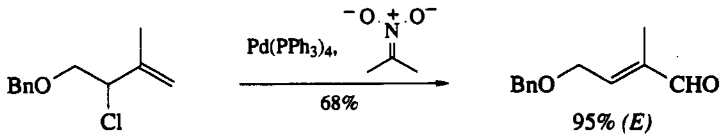
BnO
Cl
Pd(PPh3)4,
68%
BnO
CHO
95% (E)

(22)

## 4.4.5 OXIDATION WITH *N*-OXIDES, *N*-HYDROXYPYRIDONES AND HYDROXYLAMINES

### 4.4.5.1 Pyridine *N*-Oxides and Derivatives

The oxidation of alkyl halides to carbonyl compounds with pyridine or 2-picoline *N*-oxide is a popular and general method, applicable even to unactivated substrates. The reaction may be performed in two ways. In the first, the halide is heated with the *N*-oxide in the presence of a base such as sodium hydrogen carbonate. In the second, the intermediate *N*-alkoxypyridinium salt is isolated before base treatment. The reaction has been shown by labeling to proceed *via* the pyridinium ylide,[44] or, in the case of picoline *N*-oxide, *via* the anhydrobase (Scheme 8).[45] Some typical examples are shown in equations (23)–(25).[46–48]

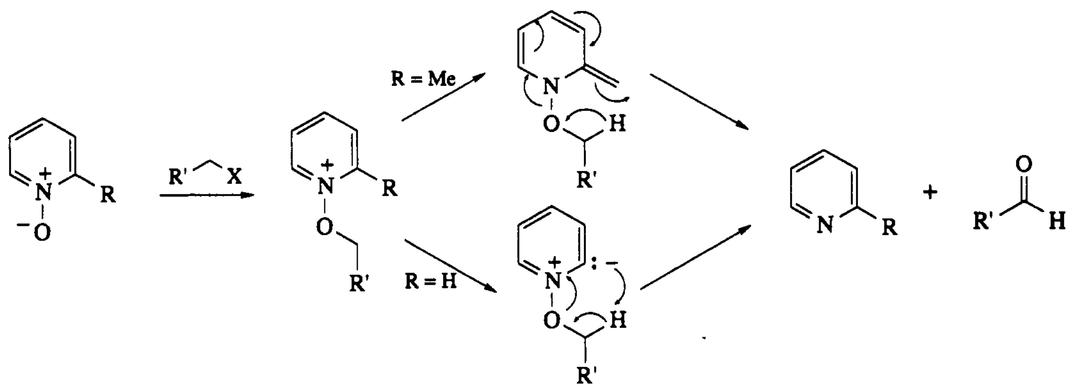
R
R' X
R
R'
R = Me
R = H
H
R'
H
R'
R
R'
H

Scheme 8

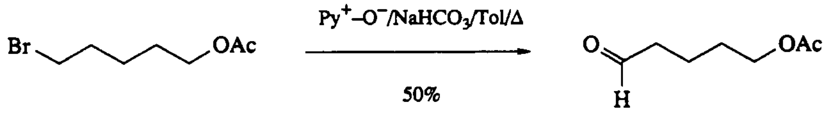
Br
OAc
Py+-O−/NaHCO3/Tol/Δ
50%
O
OAc
H

(23)

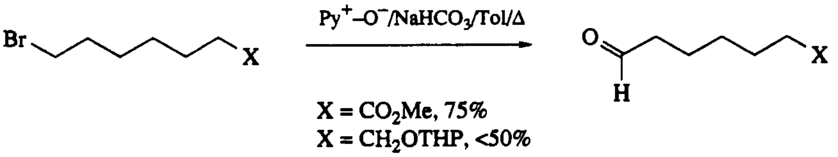
Br
X
Py+-O−/NaHCO3/Tol/Δ
X = CO2Me, 75%
X = CH2OTHP, <50%
O
X
H

(24)

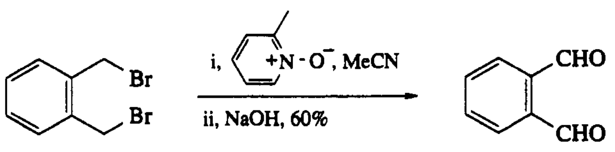
Br
Br
i, +N-O−, MeCN
ii, NaOH, 60%
CHO
CHO

(25)

The example in equation (24) demonstrates how the yield of these oxidations is sensitive to remote substituents, possibly due to cleavage of the THP ether under the reaction conditions.

The method is excellent for the preparation of α-keto esters and α-keto acids. In the examples given (equations 26–28) the α-bromo ester or acid was treated with pyridine *N*-oxide and silver nitrate at 0 °C. Decomposition of the isolated salt with base gave the dicarbonyl compounds in high yield.[49]

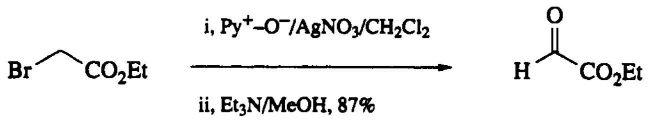
Br
CO2Et
i, Py+-O−/AgNO3/CH2Cl2
ii, Et3N/MeOH, 87%
O
H
CO2Et

(26)

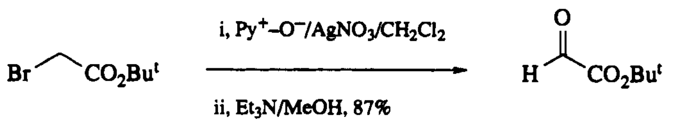
Br
CO2Bu^t
i, Py+-O−/AgNO3/CH2Cl2
ii, Et3N/MeOH, 87%
O
H
CO2Bu^t

(27)

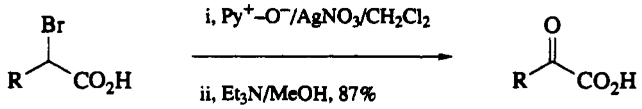
Br
R
CO2H
i, Py+-O−/AgNO3/CH2Cl2
ii, Et3N/MeOH, 87%
O
R
CO2H

(28)

The transformation shown in equation (27) is impressive since DMSO had previously been tried and shown to fail for this substrate.[50] The reaction was also performed as a one-pot procedure, with pyridine *N*-oxide and silver nitrate in acetonitrile followed by addition of triethylamine. This is the preferred method of these authors for these substrates.

It is curious that under thermal conditions α-bromo acids preferentially undergo oxidative decarboxylation rather than oxidation to the α-keto acid (equation 29).[51]

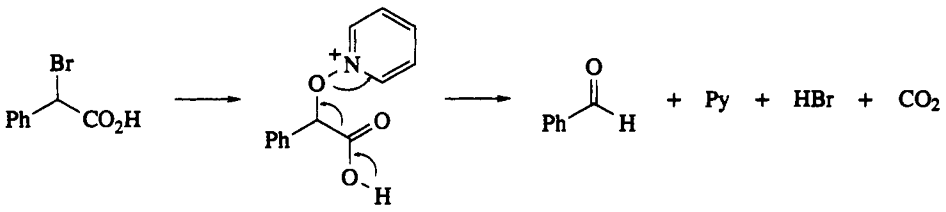
Br
Ph
CO2H
+N
O
Ph
O
O
H
O
Ph
H
+ Py + HBr + CO2

(29)

The 1-*N*-oxide of 4-dimethylaminopyridine would be expected to be a more powerful nucleophile than the parent compound. This is indeed the case (equations 30–32), and DMAP 1-oxide is able to displace bromide even from secondary unactivated substrates, *e.g.* equation (31). However, the method still fails due to elimination with cyclohexyl bromide.[52]

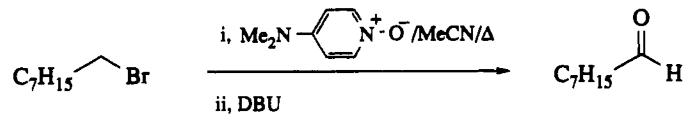
C7H15
Br
i, Me2N N+-O− /MeCN/Δ
ii, DBU
O
C7H15
H

(30)

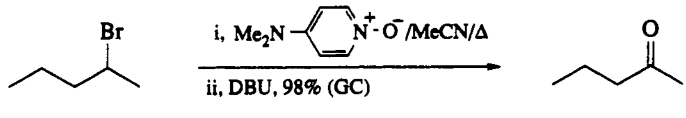
Br
i, Me2N N+-O− /MeCN/Δ
ii, DBU, 98% (GC)
O

(31)

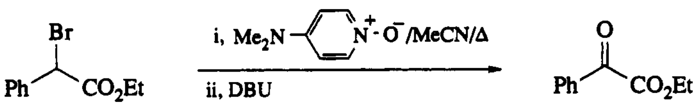
Br
Ph
CO2Et
i, Me2N N+-O− /MeCN/Δ
ii, DBU
O
Ph
CO2Et

(32)

### 4.4.5.2 *N*-Hydroxypyridones

The use of *N*-hydroxypyridone salts offers some advantages over the procedures above in that the second step can be done under nonhydrolytic conditions either thermally or photochemically (equation 33).[53] This could be advantageous for base sensitive substrates. However, these methods are unsuitable for aliphatic halides (alcohols are the major product), and there appear to be no α-halocarbonyl examples. For photochemical cleavage, the *N*-oxides (**1**) and (**2**) offer some advantages.[54,55] However, the need to prepare these rather elaborate and high molecular weight reagents would seem to be a disadvantage.

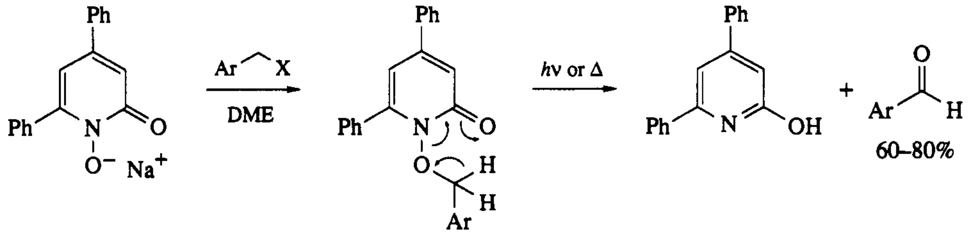

(33)

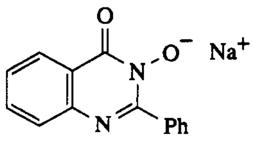

**(1)**

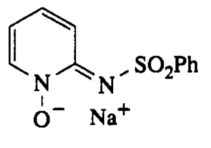

**(2)**

### 4.4.5.3 Amine Oxides and Hydroxylamines

Amine oxides can be used in place of pyridine *N*-oxide for the oxidation of activated and unactivated bromides and iodides (equation 34).[56,57] Scope and limitations are similar, though the yields appear to be somewhat lower.

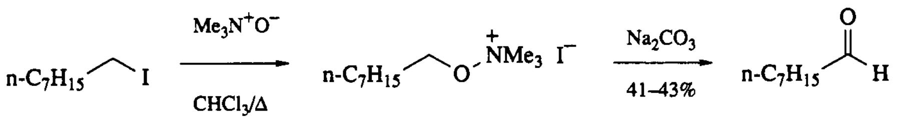

(34)

However, more recently the use of a polymer amine oxide for the oxidation of an alkyl iodide has been reported (equation 35).[58] The yield and experimental simplicity are impressive. The polymer may be regenerated.

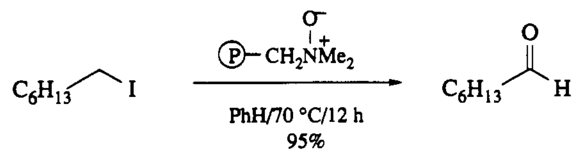

(35)

There is one report of the use of *N*,*N*-dialkylhydroxylamines to oxidize phenacyl bromides (equation 36).[59]

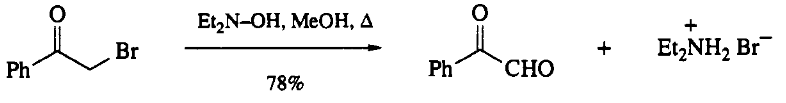

(36)

Advantages over the other methods are not obvious, and the method is not applicable to other α-halocarbonyl compounds such as 2-chlorocyclohexanone and α-bromopropiophenone.

## 4.4.6 CHROMIUM-BASED METHODS

Chromate and dichromate are capable of displacing halide from benzylic and allylic halides. Oxidation with dichromate has been performed under 'traditional' conditions (equation 37)[60] with the aqueous sodium salt, or with a quaternary ammonium salt in an aprotic solvent (equation 38).[61] Of the two procedures the first would seem to be preferable from the point of view of simplicity and safety.

Two procedures exist for the oxidation of allylic and benzylic halides with chromate ion. In the first,[62] the halide is heated with potassium dichromate in dry HMPA in the presence of 18-crown-6 (equation

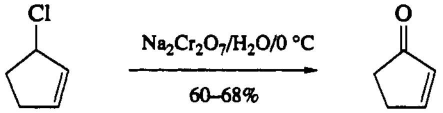
Cl
$Na_2Cr_2O_7/H_2O/0$ °C
60–68%
O

(37)

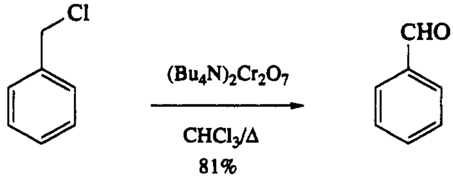
Cl
$(Bu_4N)_2Cr_2O_7$
$CHCl_3/\Delta$
81%
CHO

(38)

39). Fortunately the same authors report a far more pleasant and less hazardous procedure utilizing a polymer-supported hydrogen chromate ion (equation 40).[63] The yields are all in excess of 95%, and the experimental simplicity is commendable.

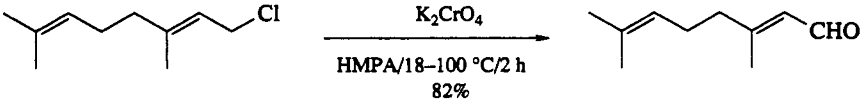
Cl
$K_2CrO_4$
HMPA/18-100 °C/2 h
82%
CHO

(39)

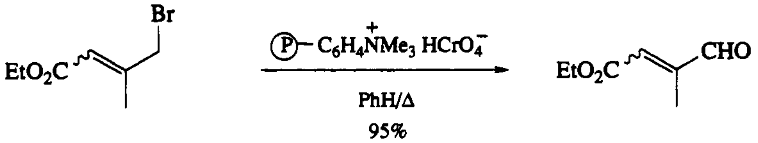
Br
$EtO_2C$
Ⓟ $-C_6H_4\overset{+}{N}Me_3\ HCrO_4^-$
$PhH/\Delta$
95%
$EtO_2C$
CHO

(40)

## 4.4.7 METAL NITRITES AND NITRATES

### 4.4.7.1 Silver Nitrate

Reaction of halides with silver nitrate to give nitrate esters has been known for years, but its synthetic application is more recent. Kornblum showed that the nitrate esters derived from α-bromo ketones and esters decompose smoothly with catalytic sodium acetate in DMSO to give the α-dicarbonyl compounds in high yield.[64] It was found unnecessary to isolate the nitrate ester; after reaction of the halide with silver nitrate the solution was filtered to remove AgBr, concentrated, and added to DMSO containing catalytic sodium acetate. The method complements the others for the synthesis of α-dicarbonyl compounds since it employs nonacidic, nonbasic conditions. Unfortunately, the method gave variable results with benzyl halides. The application of the method to bromo esters other than bromoacetates was not reported. Some related oxidations are shown in equations (41) and (42), and Schemes 9 and 10.[65,66] The oxidation of an iminium salt is notable.

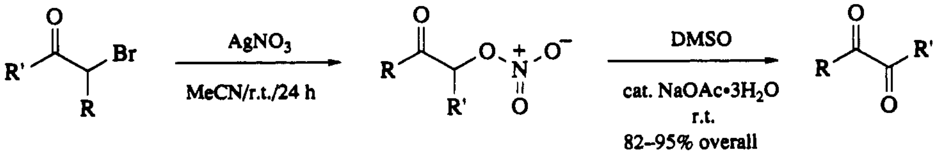
O
R'
Br
R
$AgNO_3$
MeCN/r.t./24 h
O
R
R'
$O\overset{+}{N}O^-$
O
DMSO
cat. $NaOAc{\cdot}3H_2O$
r.t.
82–95% overall
O
R
R'
O

(41)

R = Ph, $p$-$C_6H_4Cl$, Br, $NO_2$; R' = H, Me, Ph

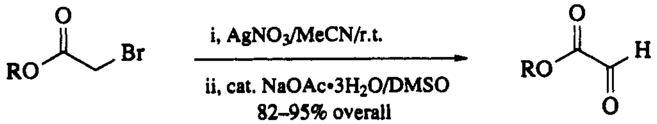
O
RO
Br
i, $AgNO_3/MeCN/r.t.$
ii, cat. $NaOAc{\cdot}3H_2O/DMSO$
82–95% overall
O
RO
H
O

(42)

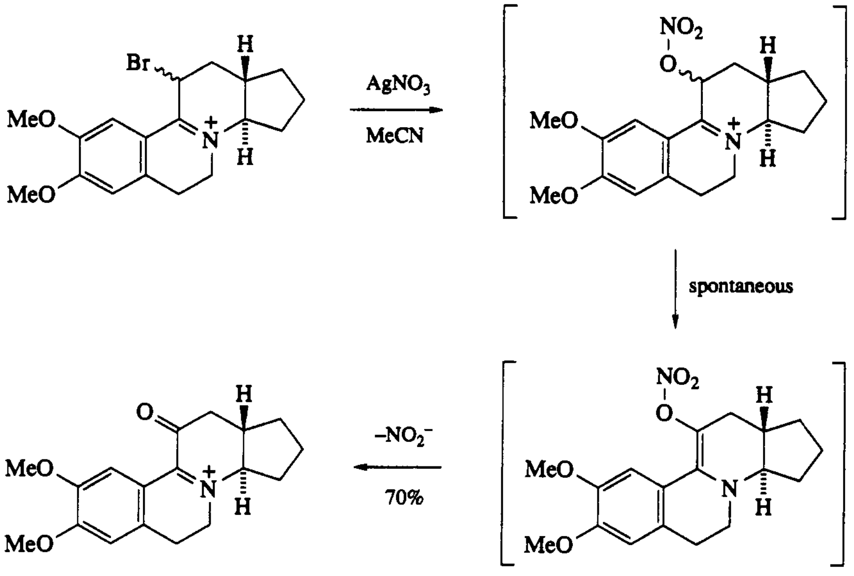
Br
H
MeO
MeO
N
H
AgNO3
MeCN
NO2
O
spontaneous
-NO2-
70%
O

**Scheme 9**

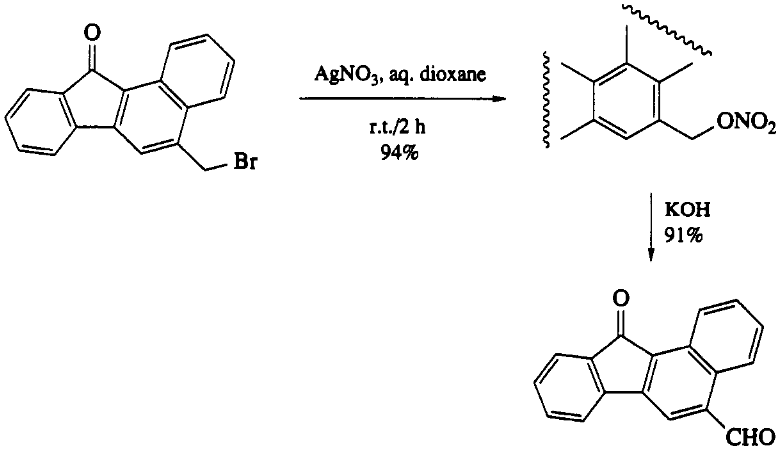
O
Br
AgNO3, aq. dioxane
r.t./2 h
94%
ONO2
KOH
91%
CHO

**Scheme 10**

### 4.4.7.2 Other Metal Nitrates and Nitrites

The difficulty experienced by Kornblum in the oxidation of benzylic halides (*vide supra*) was solved by McKillop and Ford[67] who found that mercury(II) nitrate gave the requisite nitrate esters in high yield with a wide variety of benzylic substrates (equation 43). However, problems were encountered at the hydrolysis stage. If the phenyl ring is substituted at positions 2 or 4 by an alkoxy group, the benzyl alcohol results rather than the aldehyde, due to expulsion of a nitrate ion. No recognizable products resulted when the ring bore a 4-nitro group. The successful oxidation of 2,6-dichlorobenzyl bromide is interesting.

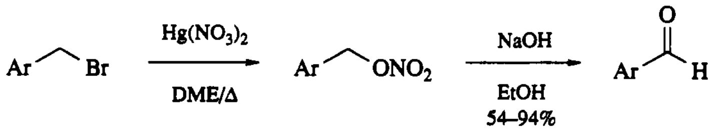
Ar
Br
Hg(NO3)2
DME/Δ
ONO2
NaOH
EtOH
54–94%
O
H

(43)

Ar = Ph, 3- and 4-$MeC_6H_4$, 3-$MeOC_6H_4$, 2- and 4-$BrC_6H_4$, 2,6-$Cl_2C_6H_3$, 1-naphthyl

Sodium nitrite in DMSO is a powerful nitrogen nucleophile,[68] and this property has been used in a very mild, nonhydrolytic method for the oxidation of activated and unactivated bromides.[69] A particularly impressive feature is the successful oxidation of secondary unactivated bromides prone to elimination (equations 44 and 45).

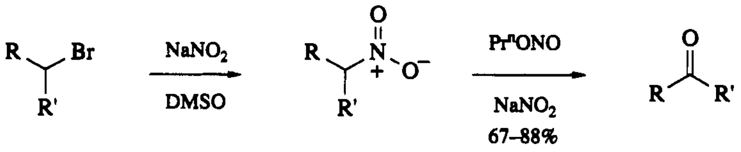

(44)

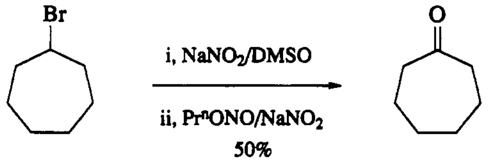

(45)

For the sake of completeness, examples of benzylic halide oxidation with copper(II) nitrate[70] and lead(II) nitrate[71] are shown in equations (46) and (47). It is probable that the more modern methods would give better yields.

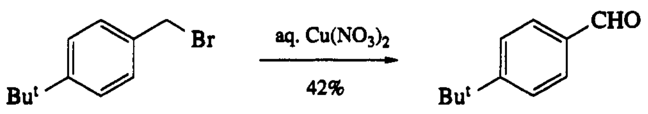

(46)

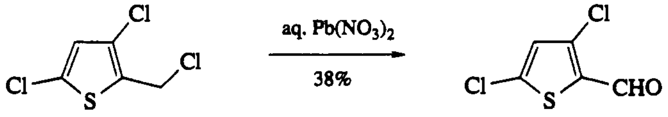

(47)

## 4.4.8 THE SOMMELET OXIDATION

This is one of the oldest methods for the oxidation of halides,[72] and has been used quite widely for the preparation of benzaldehydes and heteroaromatic aldehydes from the halomethyl compounds. Unactivated aliphatic halides give reduced yields.

The reaction is experimentally simple: either the halide is heated with hexamethylenetetraamine (HMTA) in a polar solvent such as aqueous acetic acid, or, with unreactive halides, the quaternary salt is first prepared in chloroform and then decomposed in a protic medium. The reaction is believed to proceed as shown in Scheme 11.

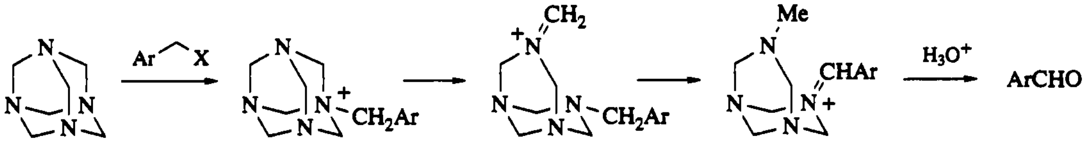

Scheme 11

At the end of the reaction it is normal to add hydrochloric acid to ensure the hydrolysis of the Schiff base. In some cases isolation was performed by steam distillation. As can be seen in equations (48)–(52), the yields are variable but often reasonable.[73–77]

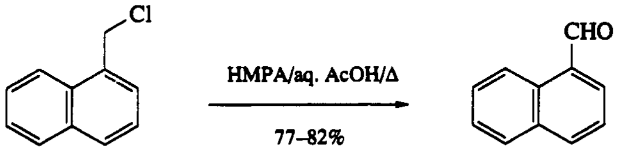

(48)

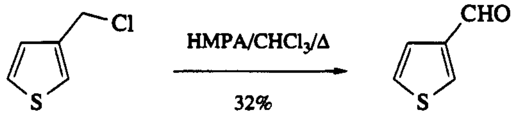
HMPA/CHCl3/Δ
32%

(49)

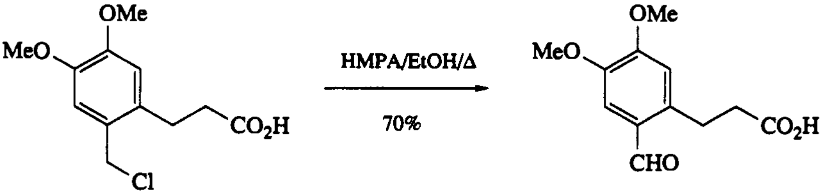
HMPA/EtOH/Δ
70%

(50)

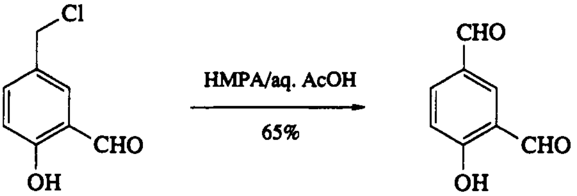
HMPA/aq. AcOH
65%

(51)

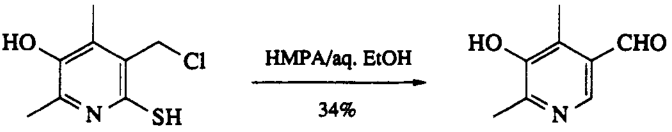
HMPA/aq. EtOH
34%

(52)

The method has an advantage over those involving base since it is applicable to phenolic substrates. The limitations are as one would expect; highly hindered substrates such as 2,6-disubstituted benzyl halides are unreactive, though mononitro-substituted substrates are oxidized.

## 4.4.9 MISCELLANEOUS METHODS

### 4.4.9.1 Oxidation *via* the Pummerer Rearrangement

A Japanese group has reported a general oxidation method for activated and unactivated bromides in which the key step is the Pummerer rearrangement of a pyrazinyl sulfoxide (Scheme 12).[78]

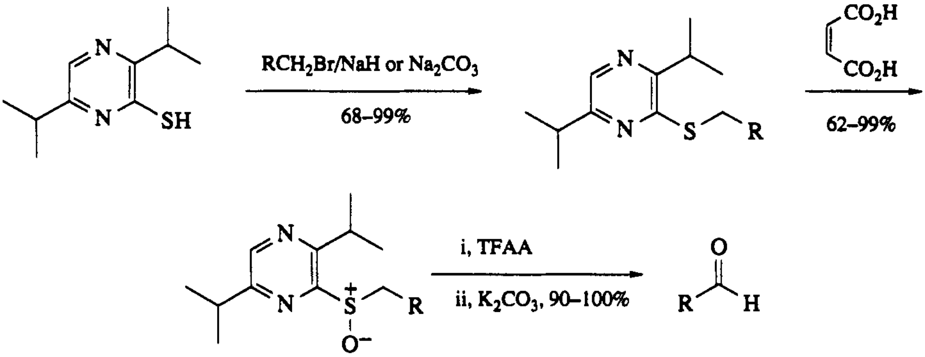
RCH2Br/NaH or Na2CO3
68–99%
62–99%
i, TFAA
ii, K2CO3, 90–100%

**Scheme 12**

This is an improvement of an earlier procedure[79] in which benzenethiol was used as the precursor. The method gives high yields, but several steps are involved and the pyrazinethiol must be prepared separately.

Paquette has reported a related method based on the chlorination of sulfides (Scheme 13).[80]

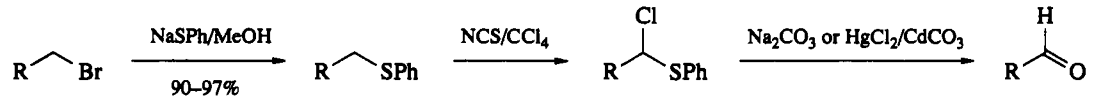

NaSPh/MeOH
90–97%
NCS/CCl4
Na2CO3 or HgCl2/CdCO3
R
Br
SPh
Cl
H
O

Scheme 13

Problems can arise at the last stage due to difficulties in the isolation of the aldehyde and/or preferential vinyl sulfide formation. Nonetheless, the method has some potential. Sulfoxides are prone to thermal elimination, and this has been used by Trost in his method,[81] which can also be used for the oxidation of primary amines (Scheme 14). The procedure is limited to benzylic and allylic bromides.

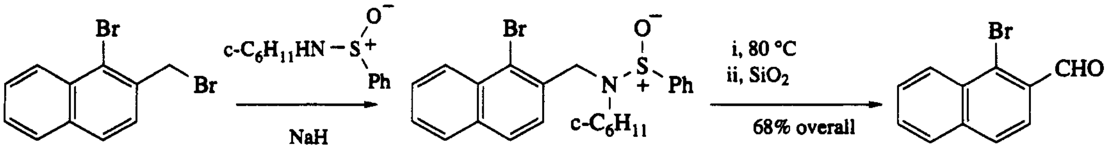

Br
Br
c-C6H11HN–S+
O−
Ph
NaH
N
S
Ph
c-C6H11
i, 80 °C
ii, SiO2
68% overall
CHO

Scheme 14

### 4.4.9.2 Triflamides and Triflic Hydrazides

The anion of *N*-phenyltriflamide is nucleophilic enough to react with activated and unactivated halides under mild conditions. Base treatment of the adduct eliminates triflinate (trifluoromethanesulfinate, $CF_3SO_2$–) to give the anil, which is then hydrolyzed in acid to the aldehyde (Scheme 15).[82] The method works quite well with α-bromocarbonyl compounds (Scheme 16).[83]

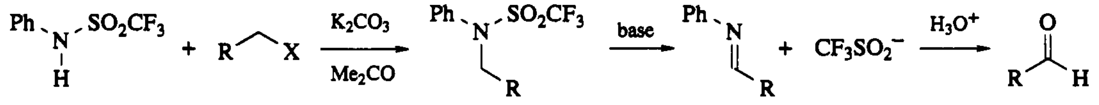

Ph
N
SO2CF3
H
+
R
X
K2CO3
Me2CO
base
+ CF3SO2−
H3O+
O
R
H

Scheme 15

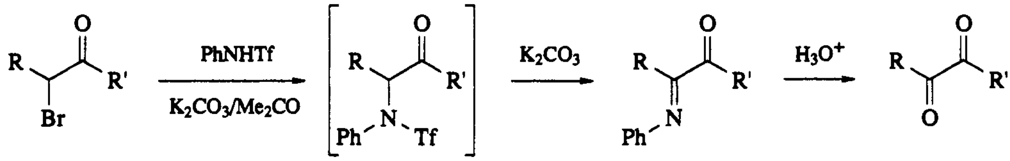

PhNHTf
K2CO3/Me2CO
K2CO3
H3O+
R
R'
Br
O
N
Ph
Tf

| *R* | *R'* | *Yield* (%) |
|---|---|---|
| Me | Ph | 73 |
| Me | $C_8H_{17}$ | 79 |
| Pr | OEt | 67 |
| $C_6H_{13}$ | OEt | 62 |

Scheme 16

With benzylic halides, the elimination requires sodium hydride in hot DMF, whereas aliphatic substrates do not undergo elimination at all. This drawback was surmounted by the use of *N*-4-acetoxyphenyltriflamide.[83] Elimination now occurs *via* the quinoneimines under mild conditions, even with aliphatic substrates (Scheme 17). Despite the ingenious chemistry, there appear to be few advantages over other methods. A procedure exists for the synthesis of hydrazones from halides (Scheme 18).[84]

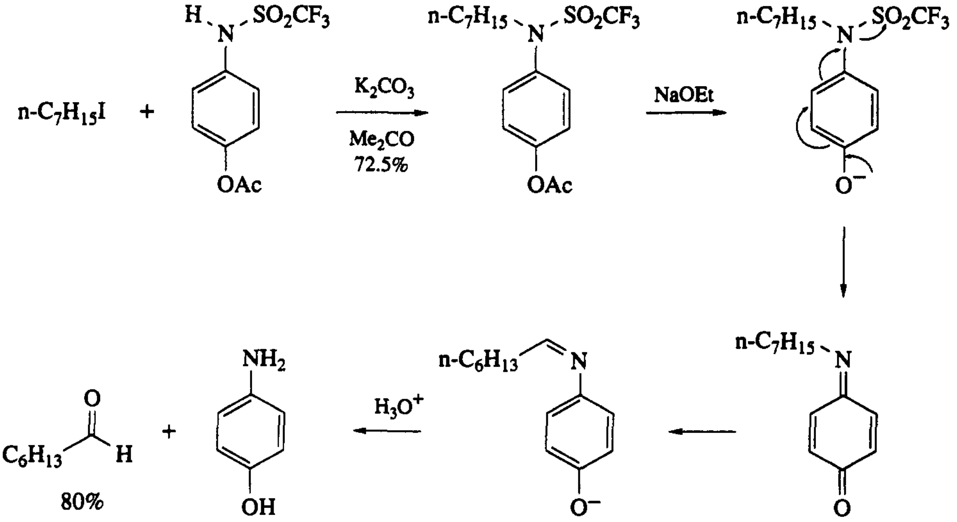
n-C7H15I
H
SO2CF3
N
OAc
K2CO3
Me2CO
72.5%
n-C7H15
NaOEt
O−
n-C6H13
H3O+
NH2
OH
O
C6H13
H
80%

Scheme 17

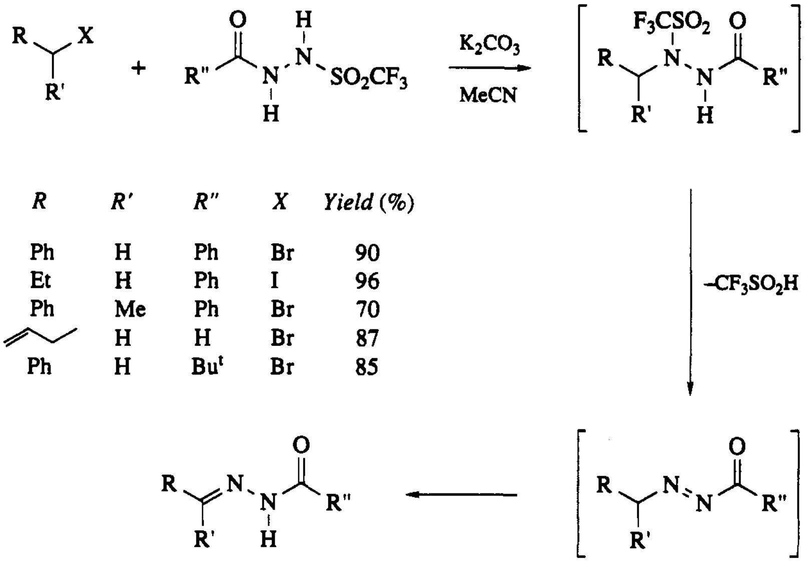
R
X
R'
O
H
R''
N
SO2CF3
K2CO3
MeCN
F3CSO2
−CF3SO2H

| *R* | *R'* | *R''* | *X* | *Yield (%)* |
|---|---|---|---|---|
| Ph | H | Ph | Br | 90 |
| Et | H | Ph | I | 96 |
| Ph | Me | Ph | Br | 70 |
| $CH_2{=}CHCH_2$ | H | H | Br | 87 |
| Ph | H | Bu$^t$ | Br | 85 |

Scheme 18

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# 5.1
# The Baeyer–Villiger Reaction

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## 5.1.1 INTRODUCTION

The oxidation of ketones with organic peroxy acids, hydrogen peroxide or alkyl hydroperoxides to give esters/lactones or derived alcohols and acids is known as the Baeyer–Villiger reaction.[1–15] Similar oxidations of aldehydes to the corresponding formate esters or their hydrolysis products also belong to this class of reactions.[1,2,16] The Baeyer–Villiger reaction is of considerable synthetic use as a component of methods for shortening carbon chains, hydroxylating aromatic rings, converting carbocycles to heterocycles and opening cyclic arrays to prepare functionalized chains and/or rings.

## 5.1.2 MECHANISM

### 5.1.2.1 General

The accepted two-step mechanism (Scheme 1) for the Baeyer–Villiger reaction is based upon kinetic, isotopic substitution, stereochemical and substituent effect studies.[2] In step 1 of the reaction, addition of peroxy acid to the ketone carbonyl gives a Criegee intermediate (**1**). In step 2, which is usually rate determining, (**1**) rearranges to product (**2**). Migration of the $R_M$ group from carbon to oxygen in step 2 is normally concerted with O—O bond breaking, although stepwise processes have been noted.[9] Acid catalysts facilitate breaking of the O—O bond by protonation of the carbonyl oxygen. Bases aid the rearrangement by removal of the hydroxy proton. Either electron-donating groups on $R_M$ and $R_R$ or electron-withdrawing groups on $R_L$ facilitate migration.[2]

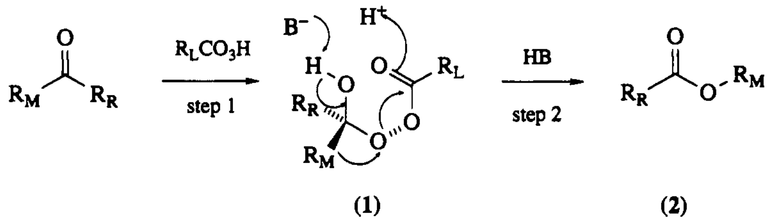

Scheme 1

The stereoelectronic requirements proposed for the migration step are an antiperiplanar arrangement of the C—$R_M$ bond and the breaking O—O bond. It has been further suggested that one of the hydroxy nonbonding electron pairs must be antiperiplanar to the migrating carbon atom, as in (**3**).[9]

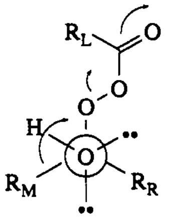

(**3**)

### 5.1.2.2 Stereochemistry

The Baeyer–Villiger reaction occurs with retention of stereochemistry at the migrating center.[1] This stereoselectivity has been utilized in a practical method for the preparation of isotopically chiral methyl acetic acid (**5**) from [2-$^3$H]cyclohexanone (**4**) prepared by enzyme-catalyzed stereoselective exchange of the *pro-R* α′-proton and enantioconvergent exchange of the α-proton with deuterium (Scheme 2).[17] As a cautionary note, prior epimerization of an acyl group prior to oxidation has been observed.[18]

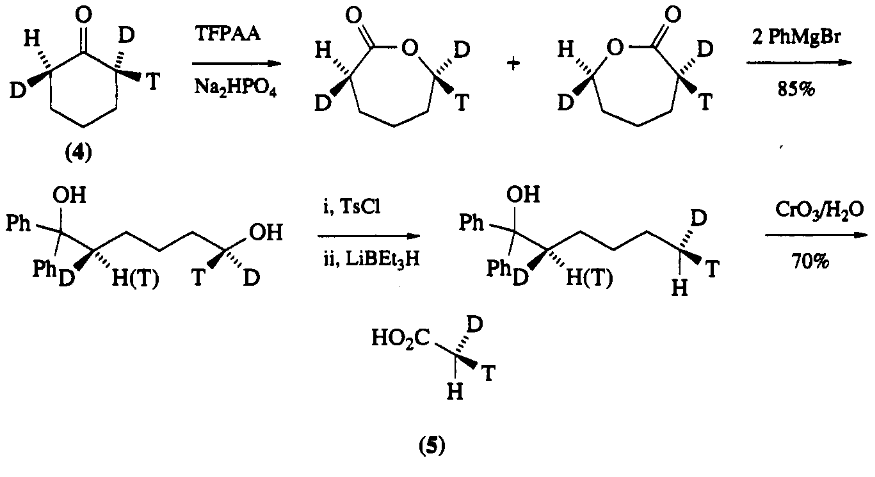

Scheme 2

### 5.1.2.3 Regiochemistry

The usual migratory preference of alkyl groups in the Baeyer–Villiger reaction is tertiary > secondary > primary > methyl.[2,19] This order has been attributed to the greater electron-releasing power[10] of, or to steric acceleration of migration by, the larger group.[19] Conformational, steric and electronic factors can alter the normal migratory preference.[9] Allyl[20] and alkenyl[21] migrations occur in preference to that of a primary alkyl group. Phenyl alkyl ketones with trifluoroperoxyacetic acid (TFPAA) undergo migration of the phenyl group if the alkyl group is primary, but secondary alkyl group rearrangement is favored over phenyl.[19] Aryl substituents may alter this preference (equation 1).[22] Cyclopropyl migration is favored over methyl migration,[2] but not over migration of other primary alkyl substituents.[23]

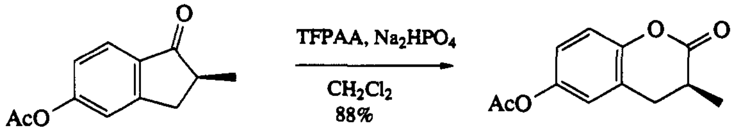
O
AcO
TFPAA, $Na_2HPO_4$
$CH_2Cl_2$
88%
O
O
AcO

(1)

An α-acyloxy or -ether substituent facilitates migration, even in competition with a secondary carbon (equation 2),[24] while an α-halogen substituent retards migration.[25] Despite its electron-withdrawing capability, an α-ethoxycarbonyl group in (6) is not sufficient to deter migration of the attached carbon (equation 3).[26]

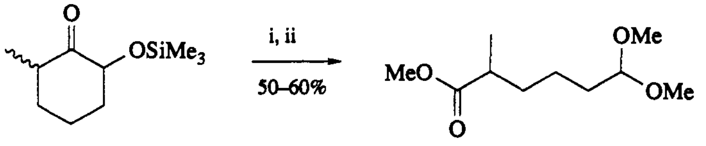
O
$OSiMe_3$
i, ii
50–60%
MeO
O
OMe
OMe

(2)

i, MCPBA, ether; ii, MeOH/$H^+$

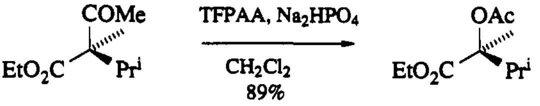
COMe
$EtO_2C$
$Pr^i$
TFPAA, $Na_2HPO_4$
$CH_2Cl_2$
89%
OAc
$EtO_2C$
$Pr^i$

(3)

**(6)**

A β-silicon atom directs migration of the proximate carbon (equation 4).[27] Conversely, electron-withdrawing β-substituents retard migration of the carbon near to these groups even, as in (7), in competition with a methyl group (equation 5).[28]

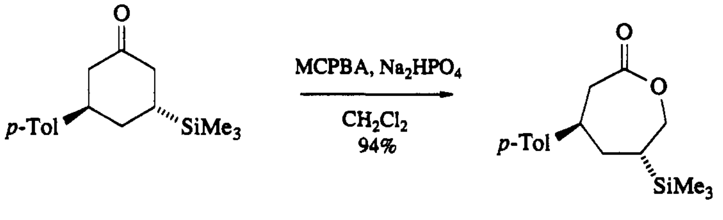
O
*p*-Tol
$SiMe_3$
MCPBA, $Na_2HPO_4$
$CH_2Cl_2$
94%
O
O
*p*-Tol
$SiMe_3$

(4)

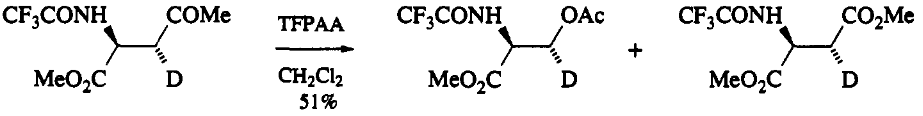
$CF_3CONH$
COMe
$MeO_2C$
D
TFPAA
$CH_2Cl_2$
51%
$CF_3CONH$
OAc
$MeO_2C$
D
+
$CF_3CONH$
$CO_2Me$
$MeO_2C$
D

(5)

(7) 37% 63%

Substituent effects can be catalyst[29] and peroxy acid dependent (equation 6).[30] Occasionally, when regioisomeric lactones are formed, preferential base hydrolysis of one of them may facilitate isolation of a pure product.[9,31]

A reaction sequence which complements the Baeyer–Villiger reaction has been described (equation 7).[32] Regioselective silylenol ether formation allows for introduction of oxygen away from the more highly alkylated side of a ketone.

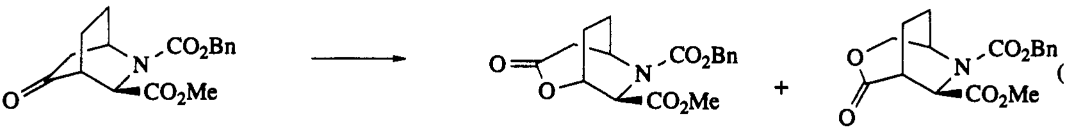

(6)

| | | | |
|---|---|---|---|
| i, 38% | 100 | : | 0 |
| ii, 59% | 18 | : | 82 |

i, PAA, NaOAc, AcOH, 72 h; ii, MCPBA, NaHCO$_3$, CH$_2$Cl$_2$, 72 h

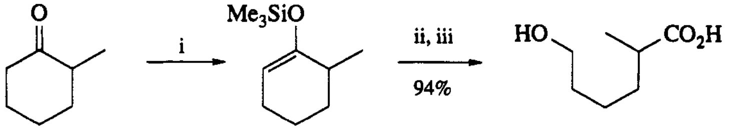

(7)

i, LDA, Me$_3$SiCl; ii, O$_3$, CH$_2$Cl$_2$, MeOH; iii, NaBH$_4$

## 5.1.3 REACTION METHODS

The oxidizing power of a Baeyer–Villiger reagent is related to the strength of the conjugate acid of the leaving group; thus, the reactivity order is Bu$^t$OOH < HOOH << peracetic acid (PAA) < perbenzoic acid (PBA) < MCPBA = HCO$_3$H[33] < *p*-nitroperbenzoic acid[34] (PNPBA) < mono-*o*-peroxyphthalic acid (MPPA) < monoperoxymaleic acid (PMA)[33] < TFPAA.[3] Among this group, commercial availability, ease of handling or oxidizing power make peracetic acid (40%), *m*-chloroperbenzoic acid (85%) (MCPBA) and TFPAA (90%) the most commonly reported organic peroxy acid reagents used in Baeyer–Villiger oxidations.

PAA solutions of differing strengths can be prepared by adding hydrogen peroxide of varying power to acetic anhydride,[35] glacial acetic acid[36] or aqueous acetic acid[37] containing a catalytic quantity of sulfuric acid. Sodium acetate is the most commonly used buffering agent. Reaction times of one to several days at room temperature are common.

Commercially available 85% MCPBA is generally employed in chlorinated hydrocarbon solvents at room temperature. Reaction times are typically a few hours to several days. Buffers utilized include disodium hydrogen phosphate, sodium acetate and sodium bicarbonate, the catalytic effect of which has been occasionally noted.[38] Acid catalysis with sulfuric acid or Nafion-H are alternatives.[39] Oxidations have been performed at elevated temperature with the aid of radical scavengers.[40]

TFPAA, a remarkably powerful reagent, is prepared prior to use by adding trifluoroacetic anhydride to a suspension of the appropriate strength hydrogen peroxide in dichloromethane at 0 °C.[2,3] Reactions are generally performed in dichloromethane in the presence of dibasic hydrogen phosphate buffer, and are carried out at between 0 °C to reflux temperature for several hours.

Because of safety considerations, 90% hydrogen peroxide, used in most TFPAA oxidations, and 85% MCPBA may soon become commercially unavailable. Possible alternatives are magnesium monoperoxyphthalate for MCPBA[41] and the easily handled acid catalyst Nafion-H which facilitates oxidations with 30% H$_2$O$_2$.[39] Weaker strength TFPAA acid solutions are effective,[42] and the strength of MCPBA is easily increased by washing with buffer solution.[43]

Peroxysulfuric acid, PBA and MPPA, common reagents of the past,[1] appear less frequently in the current literature. Basic 30% hydrogen peroxide[44] or *t*-butylhydroperoxide[45] have special utility for oxidation of cyclobutanones and strained, bridged cycloalkanones to lactones. Basic 3–6% hydrogen peroxide is used in the Dakin oxidation of aryl aldehydes to phenols,[1,3] while peroxymonophosphoric acid oxidizes aryl ketones to phenolic acetates.[46]

Rarely used oxidants with potential advantages as chemoselective or regioselective reagents include silylated forms of HOOH and peroxysulfuric acid,[47,48] and the safe and inexpensive weak oxidant sodium perborate.[49] Benzeneseleninic acid/30% hydrogen peroxide has been reported as a polystyrene-bound version,[50] as has peroxyarsenic acid.[51]

## 5.1.4 CHEMOSELECTIVITY

### 5.1.4.1 Competitive Reactions with Other Functional Groups

Many of the oxidizing agents used in Baeyer–Villiger oxidations of ketones will also react with alkenes, amines, sulfides and selenides. Reagents have been developed which allow selective oxidations in the presence of some of these functional groups. The reactivities of alkenes and ketones with organic peroxy acids are comparable and are reagent sensitive. Thus, it is possible to either ring expand (equation 8) or epoxidize (equation 9) 2-allylcyclohexanone (**8**).[52] Basic hydrogen peroxide, which does not epoxidize isolated alkenes, will effect Baeyer–Villiger oxidation of strained cyclic ketones (equation 10).[2,53] If alkene epoxidation cannot be avoided, protection as a dibromide prior to oxidation may be necessary.[54] Baeyer–Villiger oxidations with[55] and without[56] *N*-oxide formation have been reported. Only heteroatom oxidations of α-thiophenyl[57] and α-selenenylphenyl[58] ketones have been reported with MCPBA.

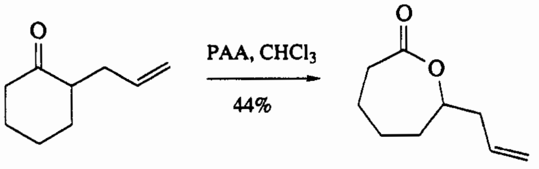

(**8**)

(8)

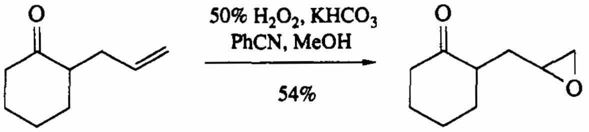

(**8**)

(9)

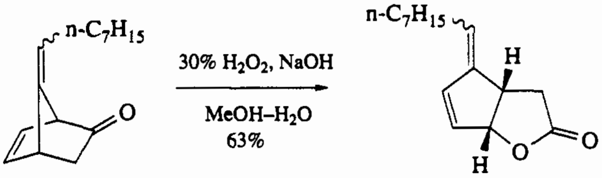

(10)

### 5.1.4.2 Competitive Baeyer–Villiger Reactions

Molecules containing multiple carbonyl groups may be oxidized with group selectivity. For example, cyclobutanones are highly reactive and ring expand even with basic HOOH.[2] Relative reactivities of steroidal ketones depend upon the position of the carbonyl group (equations 11 to 13).[21,59,60] Cyclohexa-

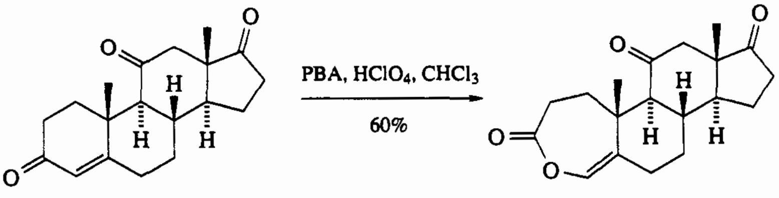

(11)

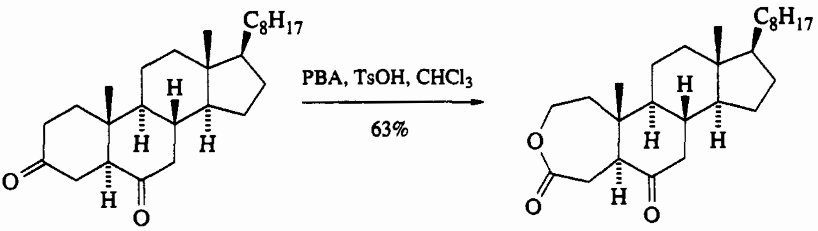

(12)

nones are normally oxidized faster than acyl side chains;[61] however, steric effects may alter this reactivity pattern (equation 14).[62]

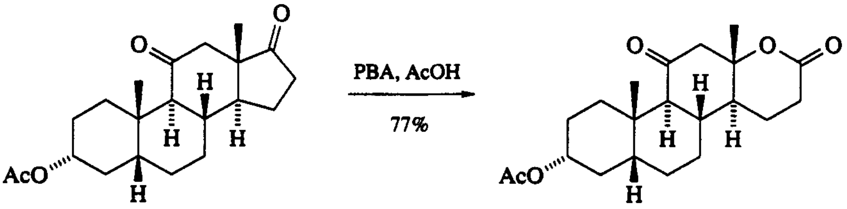
PBA, AcOH
77%
AcO
H
O

(13)

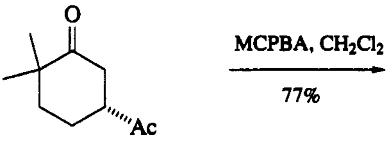
MCPBA, $CH_2Cl_2$
77%
Ac
OAc
O

(14)

## 5.1.5 REGIOSELECTIVITY

### 5.1.5.1 Acyclic Aliphatic Ketones

The regioselective Baeyer–Villiger oxidation of acyclic aliphatic ketones normally results in the insertion of oxygen next to the bulkier alkyl chain. Since methyl is a poor migrating group, a common use of this reaction is to reduce the chain length of methyl ketones by two carbons to provide alcohols, after hydrolysis. The ability to synthesize methyl ketones from acids[63] and methyl-substituted alkenes (equation 15)[64] extends the utility of this method. Complementary to this chain cleavage is the formation of carboxylic acids, following migration of the larger alkyl group attached to the carbonyl group (equation 16).[65]

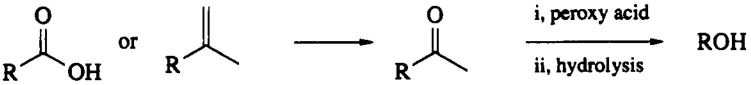
O
R
OH
or
R
i, peroxy acid
ii, hydrolysis
ROH

(15)

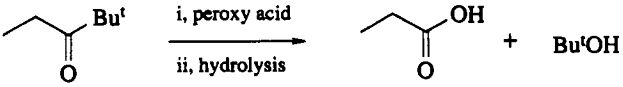
Bu$^t$
O
i, peroxy acid
ii, hydrolysis
OH
+
Bu$^t$OH

(16)

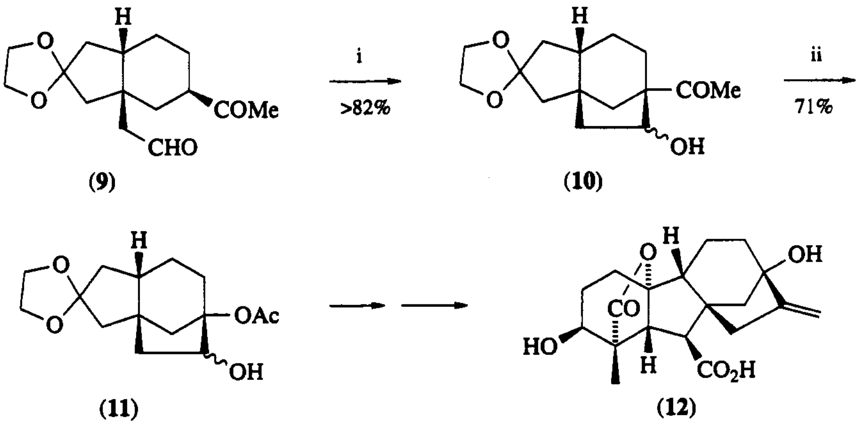
H
O
COMe
CHO
(9)
i
>82%
(10)
ii
71%
OH
OAc
(11)
HO
CO
$CO_2H$
(12)

i, NaOH, EtOH; ii, 3,5-$(O_2N)_2$PBA, $Na_2CO_3$, $ClCH_2CH_2Cl$, 4,4-thiobis(6-*t*-butyl-3-methylphenol), 54 °C

**Scheme 3**

Corey and Smith,[66] as part of a total synthesis of gibberellic acid (**12**), required the hydroxylated bicyclo[3.2.1]octane (**11**) shown in Scheme 3. An acyl group was first used as the nucleophilic partner in an intramolecular aldol condensation of the keto aldehyde (**9**). The acyl group in (**10**) was subsequently oxidized to become the precursor of the required bridgehead oxygen functionality of (**12**).

During the synthesis of the Woodward reserpine precursor (**17**; Scheme 4), Pearlman[67] used the protected acylacetal (**13**) to control the stereochemistry of an intramolecular photochemical cycloaddition to (**14**). The strategy for opening the cyclobutane ring employed the Baeyer–Villiger reaction to convert the γ-keto ester (**15**) to a β-hydroxy ester (**16**), which underwent retroaldolization to (**17**).

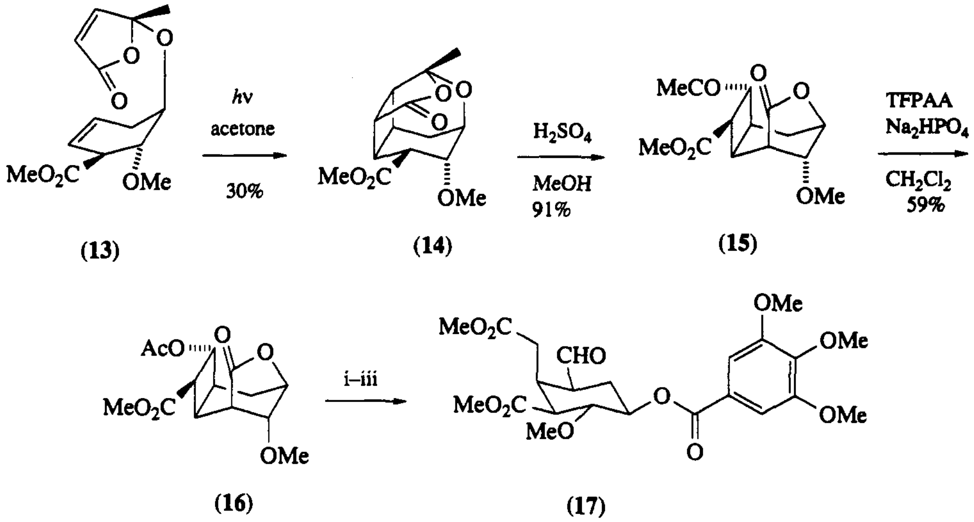
MeO2C
OMe
(13)
hν
acetone
30%
(14)
H2SO4
MeOH
91%
MeCO
(15)
TFPAA
Na2HPO4
CH2Cl2
59%
AcO
(16)
i–iii
MeO2C
CHO
MeO
OMe
(17)

i, MeOH, $H_2SO_4$; ii, $[3,4,5\text{-}(MeO)_3C_6H_2CO]_2O$, $p\text{-}Me_2NC_6H_4N$; iii, $H_3O^+$

**Scheme 4**

Hart and Tsai[68] have found that the allylic acetate (**18**) undergoes directed radical cyclization to afford the pyrrolizidinone (**19**) with good stereoselectivity (Scheme 5). The adduct (**19**) was converted to isoretronecanol (**21**) following conversion of the side chain to methyl ketone (**20**), which was oxidized with TFPAA.

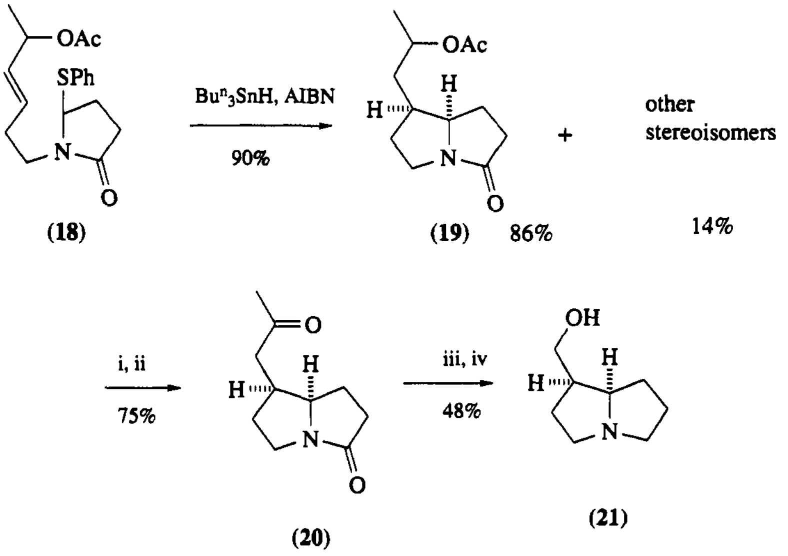
OAc
SPh
N
O
(18)
Bun3SnH, AIBN
90%
H
H
(19) 86%
+
other stereoisomers
14%
i, ii
75%
(20)
iii, iv
48%
OH
(21)

i, NaOH, MeOH, $H_2O$; ii, $(COCl)_2$, DMSO, $Et_3N$; iii, TFPAA; iv, $LiAlH_4$

**Scheme 5**

### 5.1.5.2 Acyclic Diaryl and Aryl Alkyl Ketones

A two-step procedure consisting of Friedel–Crafts acetylation followed by Baeyer–Villiger oxidation is a useful method for the introduction of oxygen onto an aromatic ring. A conversion of L-tyrosine (**22**) to L-dopa (**23**) utilized this procedure (Scheme 6).[69] An attempt to use this method to introduce a hydroxy group into the 6-position of 1-methylindole-3-carboxylate by oxidation of the 6-acetyl derivative with MCPBA failed.[70] By using a chloro substituent to discourage migration of the attached alkyl carbon atom, the chloroacetylated indole (**24**) was selectively converted to the desired phenol precursor (**25**; equation 17).

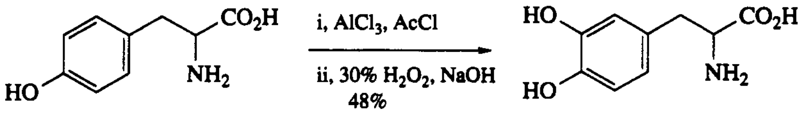

(L)-(**22**) (L)-(**23**)

Scheme 6

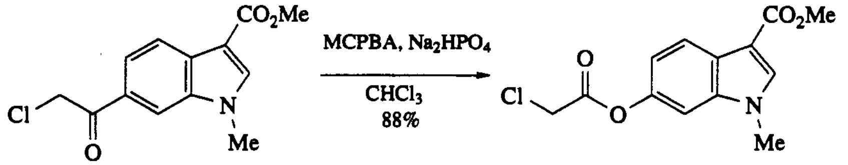

(17)

(**24**) (**25**)

A procedure to introduce a C-11 methoxy group into the aryl ring of (**26**; Scheme 7) also used a Baeyer–Villiger reaction.[71] Ring opening and subsequent Friedel–Crafts ring closure at a free aryl position afforded the dimethoxypodocarpic acid derivative (**27**).

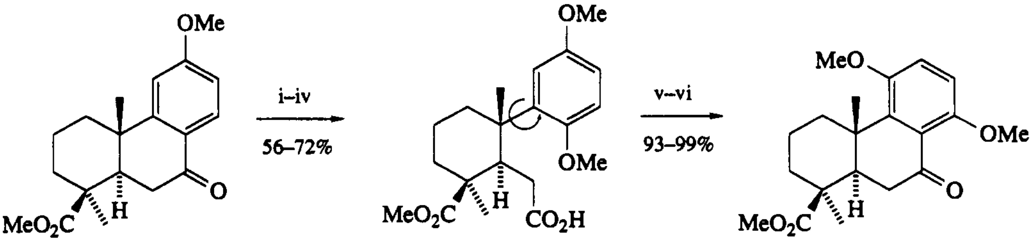

(**26**) (**27**)

i, MCPBA; ii, MeOH; iii, $Me_2SO_4$; iv, 10% $K_2CO_3$; v, TFAA; vi, KOH, MeOH

Scheme 7

### 5.1.5.3 Monocyclic and Spirocyclic Ketones

Because it is often possible to control the stereochemical orientation of substituents on a cyclic array, Baeyer–Villiger cleavages of substituted cyclic ketones have been used extensively in the stereocontrolled syntheses of substituted carbon chains. An asymmetric synthesis of L-daunosamine intermediate (**30**) from a noncarbohydrate precursor employed the cyclopentenol (**28**), prepared in optically pure form (95% *ee*) from 2-methylcyclopentadiene using asymmetric hydroboration (Scheme 8).[72] Stereoselective epoxidation, conversion to the ketone and regioselective Baeyer–Villiger oxidation afforded lactone (**29**).

The total synthesis of erythronolide B, the biosynthetic progenitor of all the erythromycins, employed a Baeyer–Villiger oxidation of the substituted cyclohexanone (**31**; equation 18). The oxidation was surprisingly slow using customary procedures, but Corey *et al.*[73] found that forcing conditions provided the required lactone (**32**).

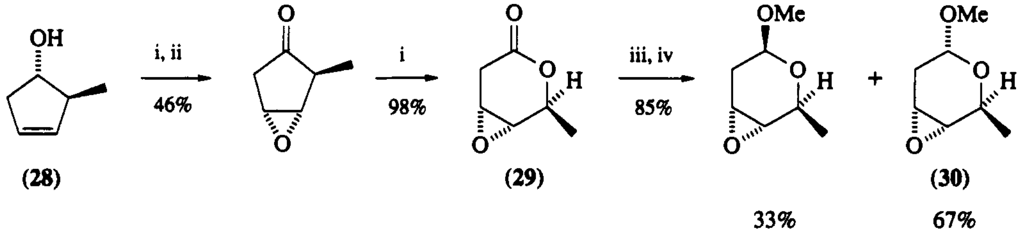
i, ii
46%
i
98%
iii, iv
85%
(28)
(29)
(30)
33%
67%

i, MCPBA, $Na_2CO_3$; ii, $CrO_3$; iii, DIBAL-H; iv, MeOH, $BF_3$

Scheme 8

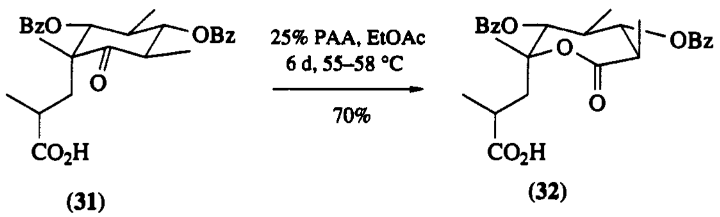
25% PAA, EtOAc
6 d, 55–58 °C
70%
(31)
(32)

(18)

Integerrinecic acid (**36**), which occurs as the dilactone in the pyrrolizidine alkaloid integerrimine (**33**; Scheme 9), was obtained from ketone (**34**). The observed regioselectivity in the oxidation leading to (**35**) presumably results from steric and dipolar effects.[74]

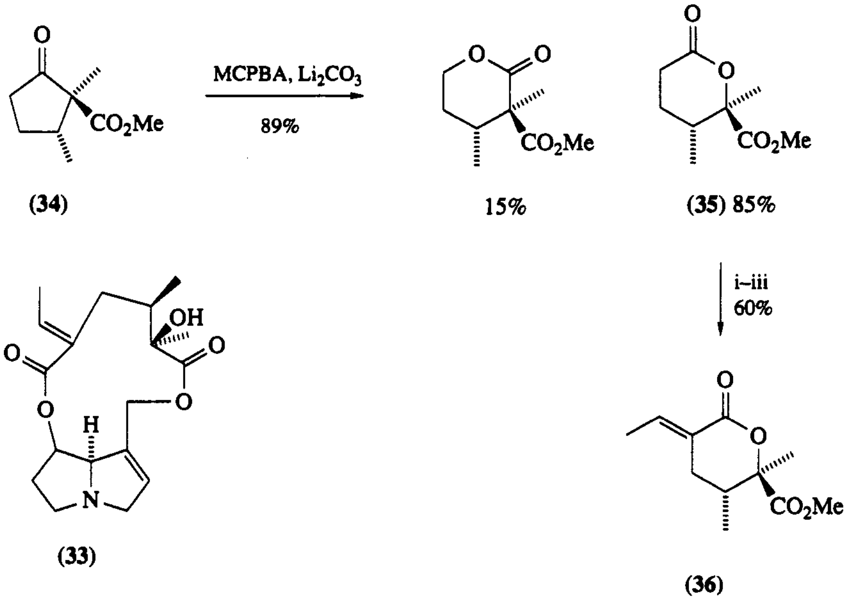
MCPBA, $Li_2CO_3$
89%
(34)
15%
(35) 85%
i–iii
60%
(33)
(36)

i, LDA; ii, MeCHO; iii, 2-F-1-$MeC_5H_3N^+OTos^-$

Scheme 9

The Baeyer–Villiger oxidation can be used to convert large ring cyclic ketones to macrocyclic lactones.[74b] Lactones can be precursors of cyclic ethers. Chiral ketone (**37**) was oxidized to lactone (**38**) and subsequently stereoselectively converted to the *cis*-2,8-disubstituted oxocane (**39**; Scheme 10).[75]

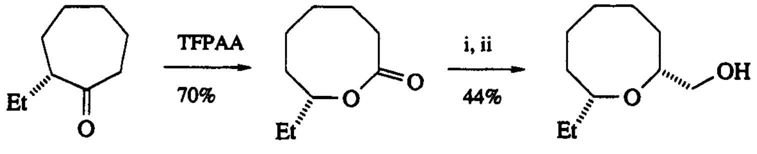

(37) (38) (39)

i, $Cp_2(CH_2)(Cl)AlMe_2$, $Me_2NC_5H_4N$; ii, $Sia_2BH$, 30% $H_2O_2$, NaOH

Scheme 10

### 5.1.5.4 Fused Ring Bicyclic and Polycyclic Ketones

The Baeyer–Villiger reaction has been used to synthesize naturally occurring lactones, such as brassinolide (**41**), a plant growth promoter (equation 19).[76] The usual secondary > primary migratory preference observed during TFPAA oxidation of acyclic ketones is not followed in the oxidation of the B-ring of (**40**) under buffered conditions. Similarly unusual is the completely regioselective oxidation of the cyclobutanone (**42**), observed by Corey *et al.*,[77] during an early stage in the synthesis of the trilactone ginkgolide B (**43**), the platelet-activating factor in ginkgo extract (Scheme 11). Introduction of oxygen into a steroidal A-ring of (**44**), however, follows with the usual regioselectivity, giving an intermediate which leads to a steroidal 3-oxo-4-ene (**45**; Scheme 12).[78]

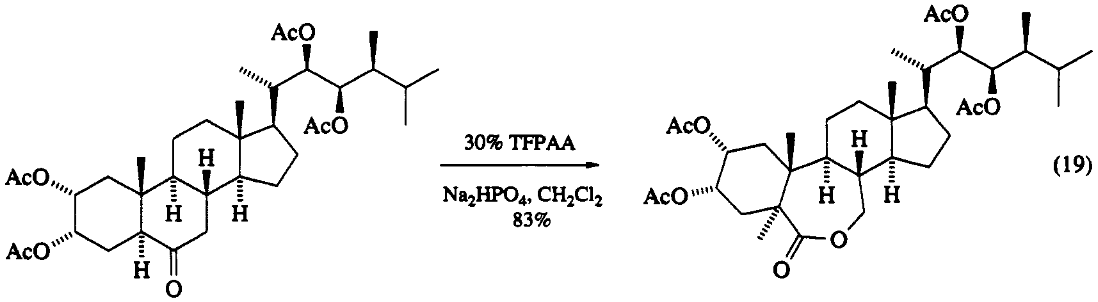

(40) (41) (19)

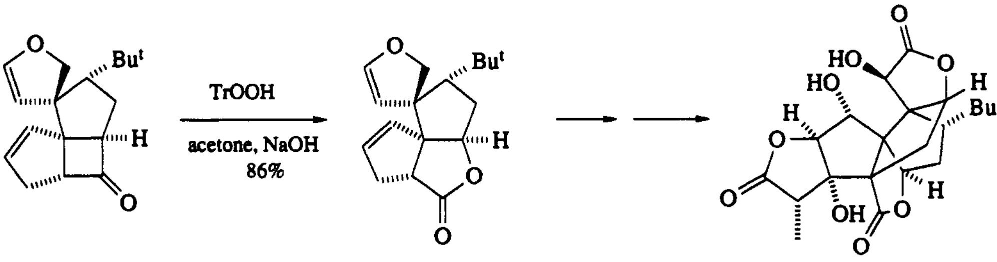

(42) (43)

Scheme 11

Fused ring ketones have been utilized as templates for stereocontrolled elaboration of substituents fused to smaller rings. Ohno and coworkers[79] have described a regio- and stereo-controlled process for the preparation of the thienamycin intermediate (**48**; Scheme 13). Oxidation of ketone (**46**) provided lactone (**47**), which has three of the required chiral centers of thienamycin.

Murai *et al.*,[80] in their total synthesis of glycinoeclepin A (**53**), exploited the chirality of (*R*)-(–)-carvone (**49**) in the preparation of the functionalized *cis*-decalin (**50**; Scheme 14). Removal of the stereocontrolling isopropenyl side chain from (**50**) involved Baeyer–Villiger methodology. Likewise, a second Baeyer–Villiger oxidation revealed the four contiguous chiral centers of the C–D rings of glycinoeclepin A in (**52**).

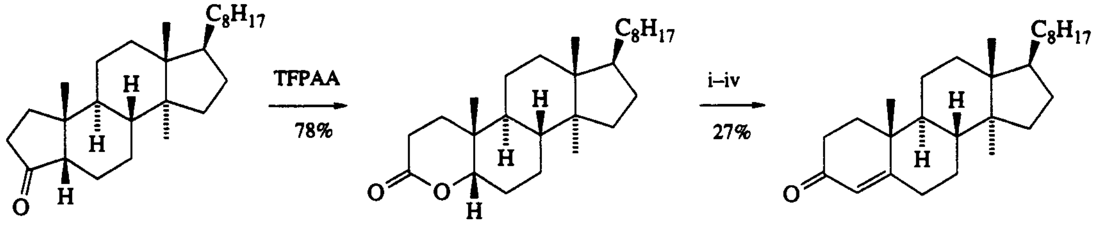
C8H17
H
H
O
H
TFPAA
78%
i–iv
27%

(44) (45)

i, $CrO_3$; ii, $Ac_2O$, EtOAc; iii, MeMgI; iv, MeOH, NaOH

Scheme 12

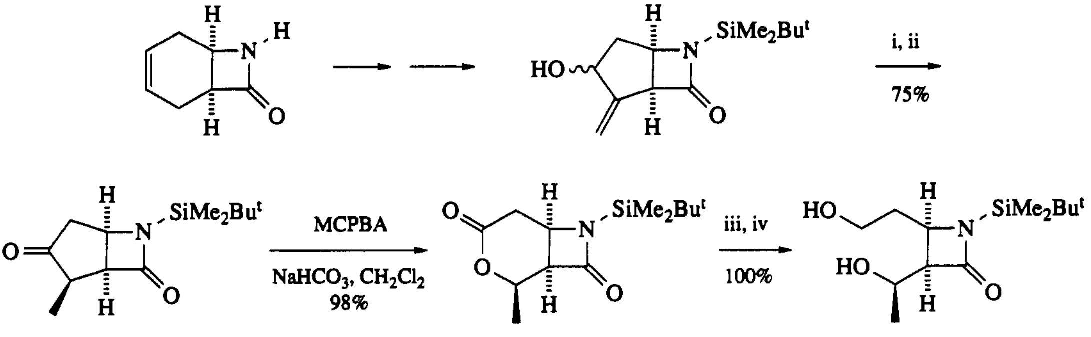
H
N
O
HO
SiMe2But
i, ii
75%
MCPBA
NaHCO3, CH2Cl2
98%
iii, iv
100%

(46) (47) (48)

i, $H_2$, Pd/C; ii, $CrO_3$, $C_5H_5N$; iii, DIBAL-H, $Bu^nLi$; iv, $NaBH_4$

Scheme 13

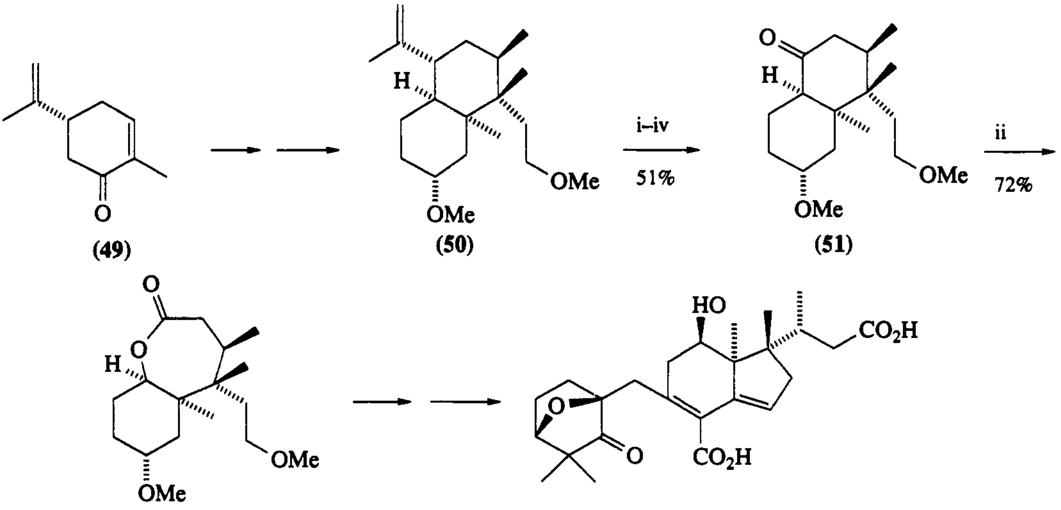
O
H
OMe
i–iv
51%
ii
72%
HO
CO2H

(49) (50) (51)

(52) (53)

i, $O_3$, $Me_2S$; ii, TFPAA; iii, $LiAlH_4$; iv, $CrO_3$

Scheme 14

### 5.1.5.5 Bridged Bicyclic and Polycyclic Ketones

The ability to control substituent stereochemistry and regiochemistry during formation and elaboration of bridged bicyclic ketones combined with regioselective Baeyer–Villiger oxidations provides a useful route to stereoselectively functionalized cycloalkanes. The lactone (**55**), which is available from norcamphor,[81] has been used by Takano *et al.*[82] for the preparation of a number of alkaloids, of which antirhine (**56**; Scheme 15) is one example. Norbornenone (**57**), disubstituted at C-7, has been exploited by Grieco *et al.*[83] in a stereocontrolled synthesis of estrone (**58**; Scheme 16). Both norbornanes and norbornenes have also been used extensively in prostaglandin synthesis.[84,85]

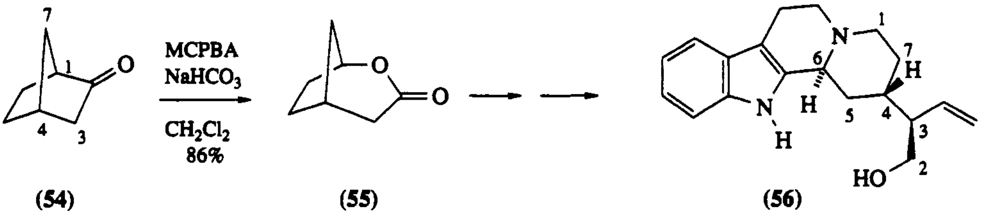
7
1
O
4
3
MCPBA
NaHCO3
CH2Cl2
86%
O
O
N
1
7
H
6
N
H
H
5
4
3
HO
2
(54)
(55)
(56)

Scheme 15

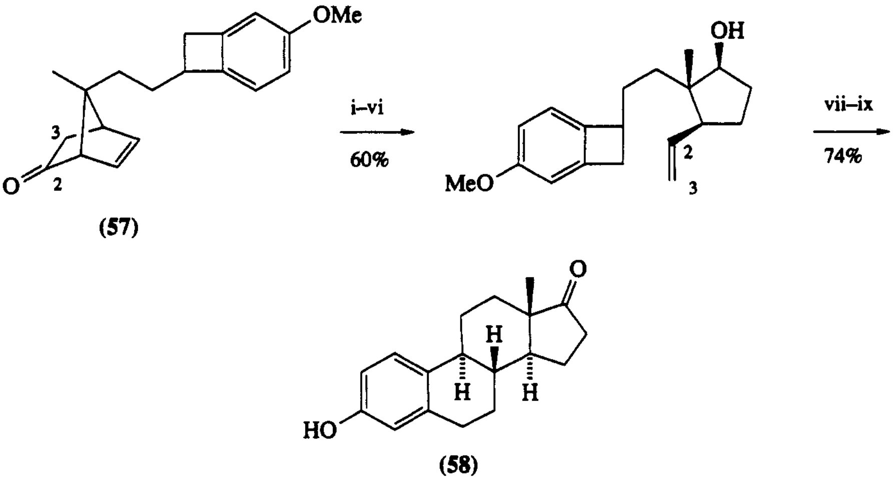
OMe
3
O
2
(57)
i–vi
60%
OH
MeO
2
3
vii–ix
74%
O
H
H
H
HO
(58)

i, 30% $H_2O_2$, NaOH; ii, $CH_2N_2$; iii, $H_2/PtO_2$; iv, $LiAlH_4$; v, $p\text{-}NO_2C_6H_4SeCN$, $Bu_3P$; vi, 50% $H_2O_2$; vii, $o\text{-}Cl_2C_6H_4$, 200 °C; viii, $CrO_3$; ix, $BBr_3$

Scheme 16

Stereocontrolled approaches to natural *C*-nucleosides have been based upon Baeyer–Villiger ring opening of bridged oxygen heterocycles. Noyori *et al.*[86] have successfully converted lactone (**59**) to pseudocytidine (**60**; Scheme 17).

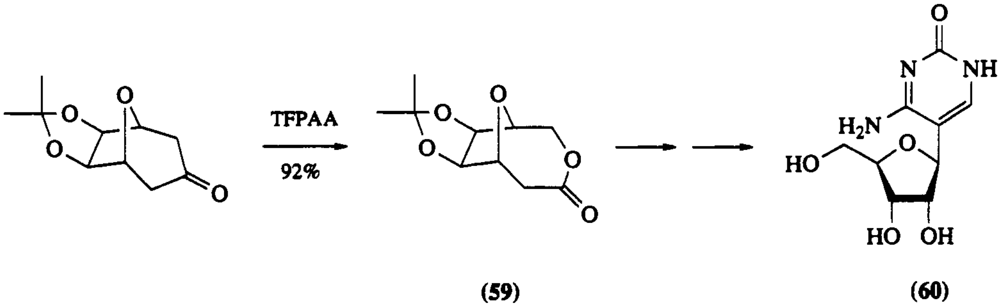
O
O
O
O
TFPAA
92%
O
O
O
O
O
O
N
NH
H2N
O
HO
HO
OH
(59)
(60)

Scheme 17

An example of the utilization of a bridged bicyclic ketone for preparation of an acyclic moiety is the stereoselective synthesis of the C-21 to C-27 segment of rifamycin-S, a member of the ansamycin family of antibiotics (Scheme 18). Rao *et al.*[87] used ketone (**61**), derived from furan, to prepare lactone (**62**). Exhaustive reduction of (**62**) provided the segment (**63**), which contains five chiral centers of rifamycin-S.

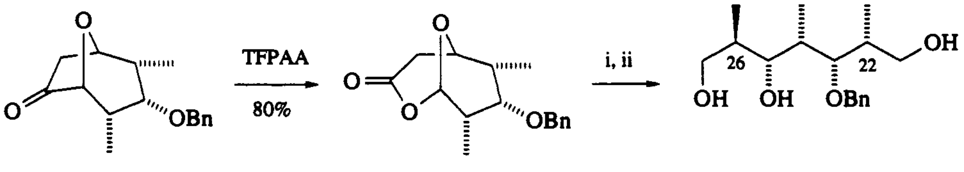

(**61**) (**62**) (**63**)

i,LDA, MeI; ii, LiAlH$_4$

**Scheme 18**

The Baeyer–Villiger oxidation has been utilized as an element of several novel functional group manipulations. Suginome and Yamada[88] converted adamantanone (**64**) to 2-thiaadamantane (**66**) *via* the lactone (**65**; Scheme 19). Eaton *et al.*,[89] in the synthesis of pentaprismane (**70**) from homopentaprismanone (**67**; Scheme 20), required that a leaving group be introduced α to the carbonyl group in order to carry out a Favorskii ring contraction. Oxidation of (**67**) afforded lactone (**68**), which was converted in several steps to the requisite hydroxy ketone (**69**).

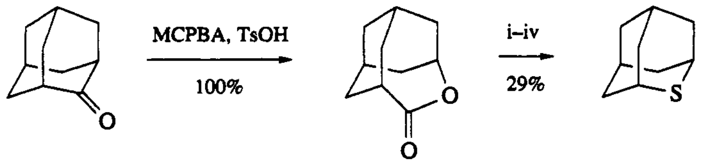

(**64**) (**65**) (**66**)

i, MeLi; ii, HgO, I$_2$, *hv*; iii, Me$_3$SiI ; iv, Na$_2$S, EtOH

**Scheme 19**

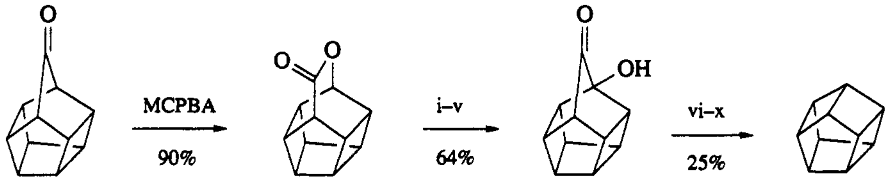

(**67**) (**68**) (**69**) (**70**)

i, KOH; ii, RuO$_2$, NaIO$_4$; iii, CH$_2$N$_2$; iv, Na/NH$_3$; v, Cl$_2$/Me$_2$S, Et$_3$N; vi, TsCl;
vii, KOH; vii, ClCOCOCl; ix, Bu$^t$OOH; x, heat

**Scheme 20**

A 4,4-disubstituted cyclohexenone synthesis has been developed by Holmes and Madge.[90] The procedure is based upon PAA oxidation of anisole-derived bicyclo[2.2.2]oct-5-en-2-ones, followed by acid-catalyzed isomerization of the products (Scheme 21).

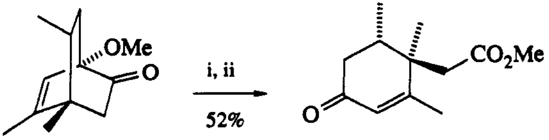

i, PAA, NaOAc, AcOH; ii, Me$_2$SO$_4$, NaOH

**Scheme 21**

### 5.1.5.6 α,β-Unsaturated Ketones

Montury and Gore[91] have developed a 1,2-ketone transposition method (Scheme 22). Baeyer–Villiger oxidation of conjugated ketone (71) afforded an enol acetate and subsequent hydrolysis revealed a carbonyl group, one carbon removed from the original position.

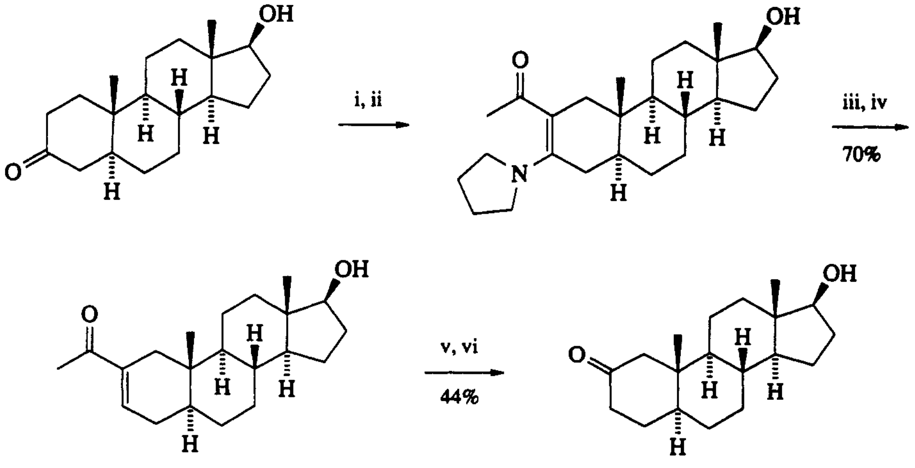

(71)

i, $C_4H_9N/H^+$; ii, AcCl; iii, $BH_3$; iv, AcOH; v, MCPBA; vi, hydrolysis

Scheme 22

Silverstein and coworkers[92] have used the peroxy acid oxidation of *exo*-alkylidene cycloalkanones as a route to keto acids (Scheme 23). Oxidation of pulegone (72) and hydrolysis of the derived enol lactone led to the keto acid (73).

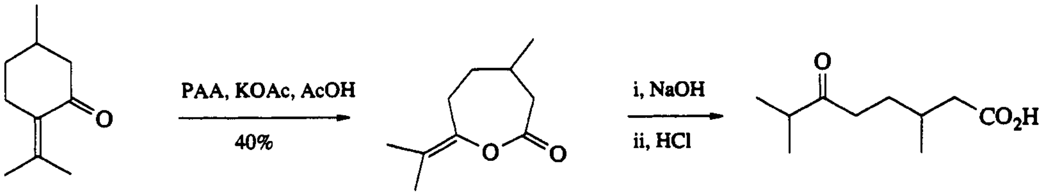

(72) (73)

Scheme 23

### 5.1.5.7 1,2-Dicarbonyl Compounds

Peroxy acids normally form anhydrides when reacted with 1,2-dicarbonyl compounds in inert solvents or acids in alkaline or acidic media.[1] An exception to this generality is the oxidation of the keto ester (74; Scheme 24), in which the ring oxygen facilitates tetrahydrofuran ring migration. Ohno and coworkers[93a] have exploited this reaction to develop a chemicoenzymatic approach from furan to the protected L-ribofuranoside (75).

### 5.1.5.8 Aryl- and Alkyl-carbaldehydes

A convenient and inexpensive method to transform electron rich aromatic aldehydes to phenols,[93b] or α,β-unsaturated aldehydes to vinyl formates, utilizes 30% hydrogen peroxide catalyzed by bis(*o*-nitrophenyl) diselenide.[93c] A two-step formylation/MCPBA oxidation procedure (Scheme 25) was utilized by Kishi and coworkers[94] in the 100 g scale conversion of 2,6-dimethoxytoluene to the mitomycin precursor (76). An organic peroxy acid was not required for the conversion of 9-formyl-6-methylellipticine (77) to 9-hydroxyellipticine (78; Scheme 26).[95] Under these conditions, the pyridine nitrogen was not oxidized.

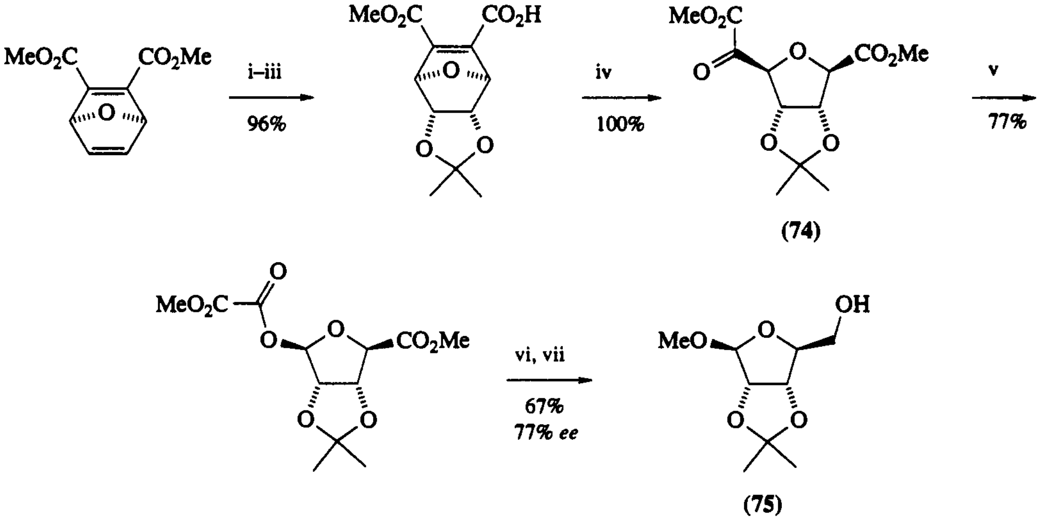
i–iii
96%
iv
100%
v
77%
vi, vii
67%
77% ee
(74)
(75)

i, $OsO_4$, NMO; ii, 2,2-dimethoxypropane, TsOH; iii, pig liver esterase; iv, $O_3$, MeOH; v, MCPBA; vi, HCl, MeOH; vii, $LiAlH_4$

Scheme 24

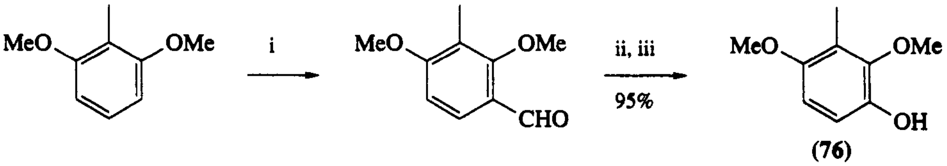
i
ii, iii
95%
(76)

i, $Cl_2CHOMe$, $TiCl_4$; ii, MCPBA; iii, NaOMe, MeOH

Scheme 25

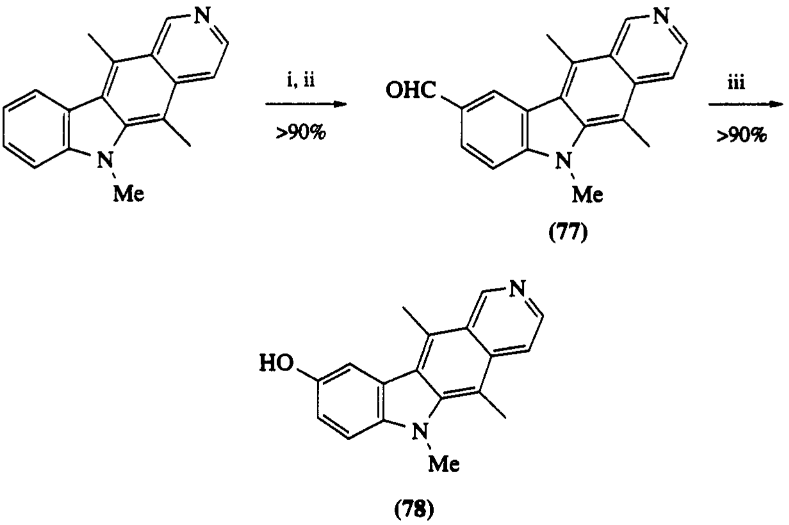
i, ii
>90%
iii
>90%
(77)
(78)

i, $ClCH_2OCHCl_2$, $AlCl_3$; ii, hydrolysis; iii, 35% $H_2O_2$, $H_2SO_4$, MeOH

Scheme 26

### 5.1.6 SIDE REACTIONS

While Baeyer–Villiger oxidations of saturated ketones generally occur without skeletal rearrangements, heterolytic cleavages may occur if cations are readily accessible. For example, ring A of triterpenoid (**79**; Scheme 27) can be converted into the lactone (**80**) by exhaustive Baeyer–Villiger oxidation using an acid catalyst. The lactone (**80**) can be converted to the steroidal enone (**81**).[96]

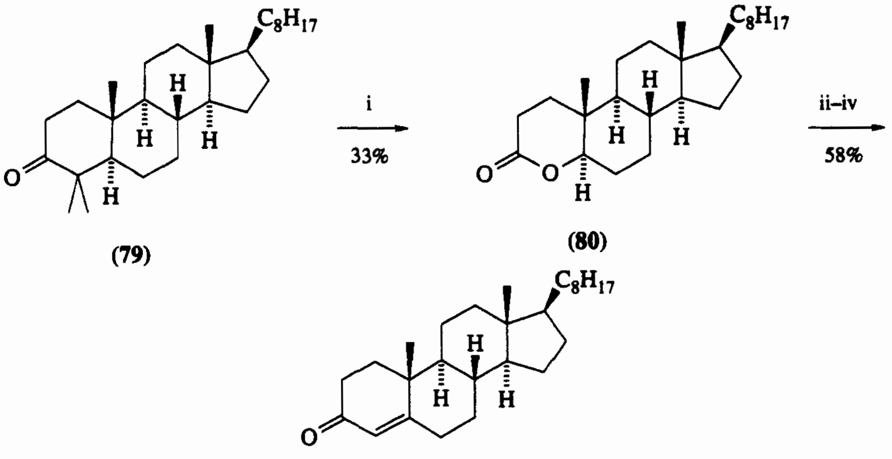

$C_8H_{17}$
H
H
H
O
H
i
33%
$C_8H_{17}$
H
H
H
O
O
H
ii–iv
58%
$C_8H_{17}$
H
H
H
O

(**79**) (**80**) (**81**)

i, 40% PAA, $BF_3$ etherate; ii, MeLi; iii, PDC; iv, MeOH, NaOH

**Scheme 27**

Rearrangements can provide access to novel ring structures; The strained 1,3-bishomocubanone (**82**) led to significant amounts of rearranged lactone (**83**; equation 20).[97] Galteri *et al.*[98] have found synthetically useful ring contractions of α-acyldecalones (equation 21). Peroxy acid attacks the exocyclic ketone of (**84**) and the bond between this carbonyl group and the ring cleaves during rearrangement to (**85**).

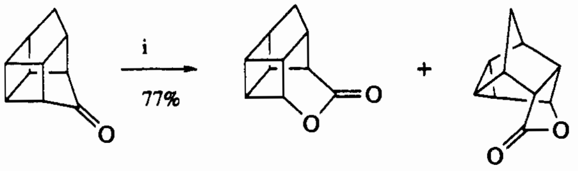

60% 40%

(**82**) (**83**)

(20)

i, MCPBA, 1:1 dioxane:$H_2O$, 1 h

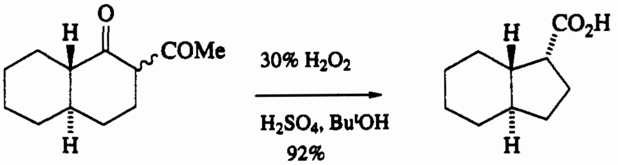

O
H
COMe
H
30% $H_2O_2$
$H_2SO_4$, $Bu^tOH$
92%
H
$CO_2H$
H

(**84**) (**85**)

(21)

Cationic rearrangement of the bridged bicyclic lactone (**86**) provides a less-strained fused lactone (**87**; equation 22).[99] This rearrangement has proven useful in prostaglandin synthesis.[99,100] Other oxidative rearrangements are discussed in more detail in Chapter 7.2 of this volume.

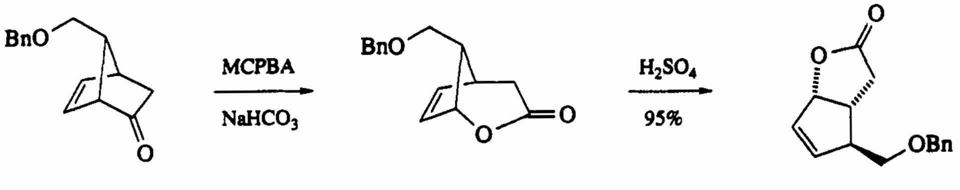

BnO
O
MCPBA
$NaHCO_3$
BnO
O
O
$H_2SO_4$
95%
O
O
OBn

(**86**) (**87**)

(22)

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# 5.2

# The Beckmann and Related Reactions

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## 5.2.1 INTRODUCTION

The preeminence of the Beckmann reaction among oxidative synthetic transformations since its discovery[1] over a century ago is borne witness by its frequent review.[2–11] The reaction has found most widespread use in the rearrangement mode, and may be regarded as the nitrogen analog of the Baeyer–Villiger reaction. Thus, nitrogen may be inserted into carbonyl carbon–α-carbon bonds of aldehydes and ketones *via* rearrangement of the derived oximes. The stereoselectivity of the rearrangement allows distinction to be made between the α- and α′-carbon atoms flanking a ketone group (Scheme 1).

Only in relatively recent times has the potential for Beckmann-type reactions other than rearrangements been exploited fully. Reactive Beckmann intermediates have been intercepted successfully both inter- and intra-molecularly, with both carbon and heteroatomic nucleophiles. Reactions in the presence of reducing agents give the products of redox processes insofar as the migrating carbon atom undergoes oxidation whilst the ex-carbonyl carbon is reduced. In certain circumstances fragmentation, rather than rearrangement, becomes dominant, and such reactions have found particular application in ring-cleavage processes.

This chapter is divided into the three broad categories described above, namely rearrangement, addition and fragmentation. Although it is beyond the scope of this account to provide exhaustive coverage of this active area, close attention has been paid to work published since the last major review.[11] Neither

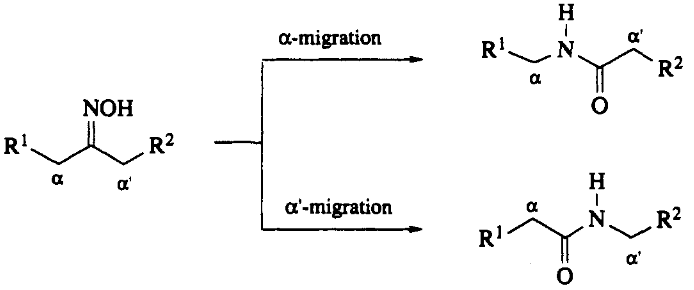
NOH
R1
R2
α
α'
α-migration
α'-migration
H
N
O

**Scheme 1**

the photochemically induced Beckmann rearrangement[12] nor the Schmidt reaction of ketones[13] has been covered.

Throughout this chapter, (*E*)- and (*Z*)-nomenclature refers to oxime geometry, and has been indicated whenever specified in the original work.

## 5.2.2 REARRANGEMENT REACTIONS

### 5.2.2.1 Mechanism and Stereochemistry

The generally accepted mechanism for the Beckmann rearrangement is presented in Scheme 2. The *N*-hydroxy group of the oxime is rendered more nucleofugal either by protonation or esterification. Migration of hydrogen, alkyl or aryl groups from carbon to nitrogen may be followed by attack of an oxygen nucleophile at the incipiently cationic ex-carbonyl carbon to yield an imidate; this may then undergo Chapman rearrangement[14] to give an *N*-substituted amide. Alternatively, in some instances, free nitrilium species have been implicated. It has also been suggested that nitrenium ions and tetrahedral intermediates may be involved in certain cases.

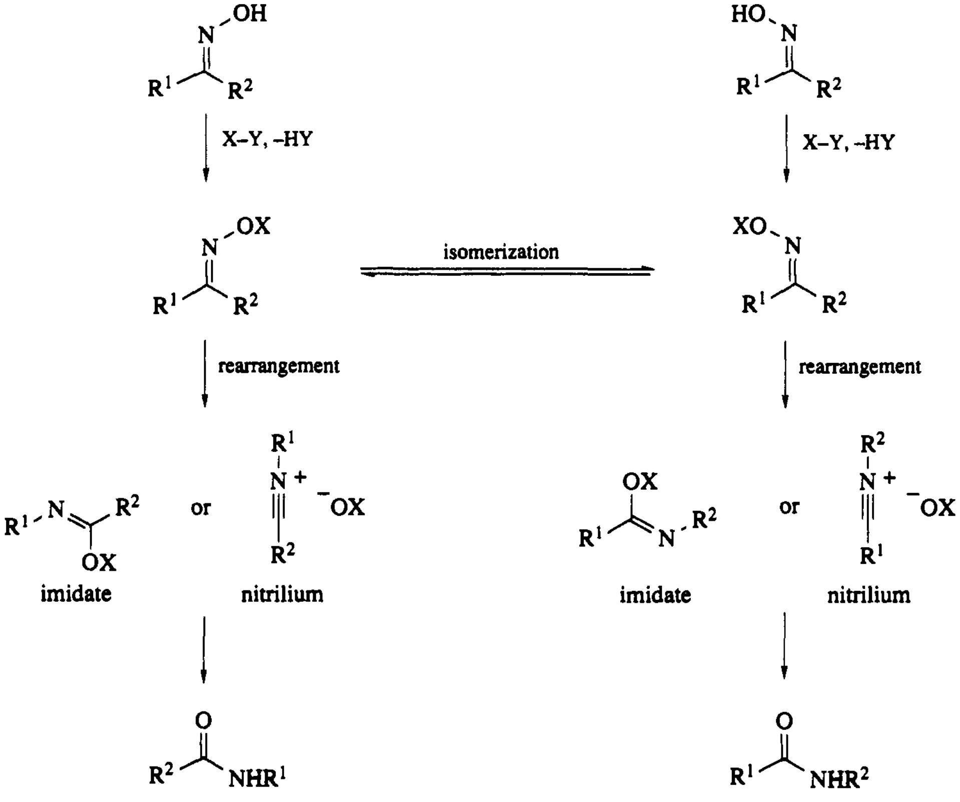
X-Y, -HY
X-Y, -HY
isomerization
rearrangement
rearrangement
or
or
imidate
nitrilium
imidate
nitrilium
OH
OX
HO
XO
R1
R2
NHR1
NHR2

**Scheme 2**

It has long been considered that migration of the substituent *anti* to the leaving group on nitrogen predominates to the extent that product identity may serve as a reliable indicator of oxime geometry. However, the tendency for oxime isomerization to occur under certain reaction conditions, and the differing migratory aptitudes of oxime substituents are such that this 'rule' should be used with caution. The dependence of product composition upon the rearrangement conditions employed further suggests that varying mechanisms may be operative. Mechanisms are discussed in greater depth in the context of the specific examples presented below.

### 5.2.2.2 Ketoximes

#### *5.2.2.2.1 O-Unsubstituted ketoximes*

Ketoximes may be rearranged directly to amides under a wide variety of conditions. Phosphorus pentachloride, phosphorus oxychloride, thionyl chloride, trimethylsilyl iodide (TMS-I), formic acid, polyphosphoric acid, trimethylsilyl polyphosphate and mineral acids have all been successfully employed. Representative procedures using these and other reagent systems have been documented previously.[5,11]

Compelling evidence for the isomerization of oximes prior to rearrangement was provided by studies on the menthone-derived oxime (**1**) shown in equation (1).[15] The use of strong anhydrous acid in these reactions resulted in amides formed *via* rearrangement of ostensibly the less thermodynamically stable (*Z*)-oxime. This was also observed in the acid-mediated reaction of the (*E*)-polycyclic oxime (**2**),[16] which rearranged with migration of the *syn*-alkyl rather than the *anti*-aryl group (equation 2). It was argued that whilst the (*Z*)-isomer would be thermodynamically disfavored due to steric interactions between the oxime oxygen and the *ortho* hydrogen atom, it would be more reactive for the same reason, and apparent *syn* migration would result.

Under conditions where oxime isomerization is facile, product distribution is clearly the result of a subtle combination of factors, including relative migratory aptitudes of substituents as well as the thermodynamic stability of oxime isomers. Both geometric isomers of (**3**) gave the lactam (**4**) upon treatment with hot polyphosphoric acid (equations 3 and 4).[17] In contrast, identical processing of tetralone oxime (**5**) gave exclusively ε-lactam (**6**),[18] the product of aryl rather than alkyl migration (equation 5).

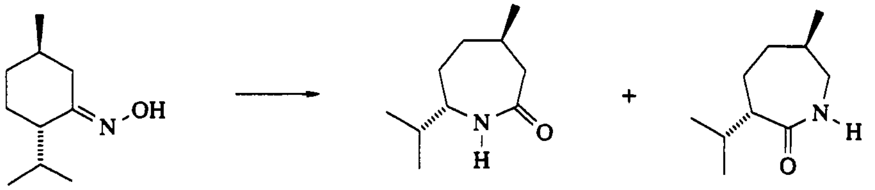

(1)

(**1**)

| | | |
|---|---|---|
| $POCl_3$, pyridine | 98% | 2% |
| $SOCl_2$, pyridine | 90% | 10% |
| 20% aq. $H_2SO_4$ | 43% | 57% |
| $HCl/Et_2O$ | 5% | 95% |

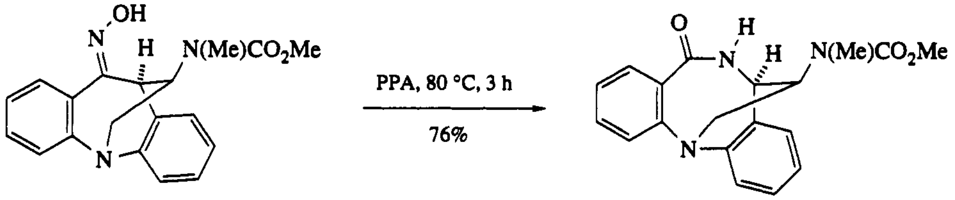

(2)

(**2**) (**3**)

The indanone oximes (**7**) gave the aryl- and alkyl-migrated products (**8**) and (**9**) (equation 6), with the proportion of (**9**) increasing with increasing steric demand of arene substituents at the 4- and 7-positions.[18] Exposure of the (*E*)-oxime (**10**) to phosphorus pentoxide and methanesulfonic acid[19] gave the product (**11**) of migration of the *syn*-alkyl group,[20] presumably *via* the (*Z*)-isomer (equation 7).

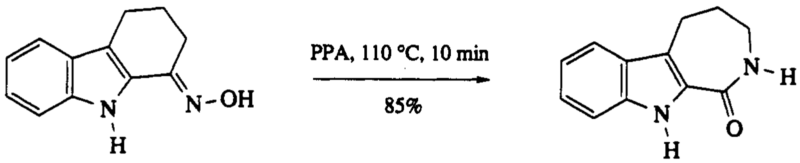
PPA, 110 °C, 10 min
85%

*(E)*-**(3)** → **(4)** (3)

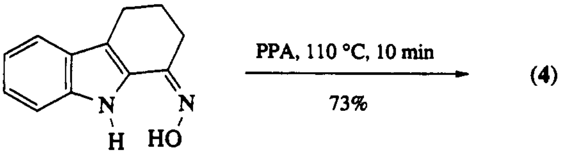
PPA, 110 °C, 10 min
73%
(4)

*(Z)*-**(3)** (4)

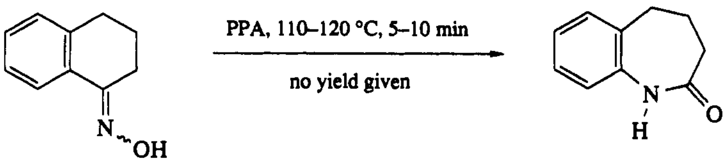
PPA, 110–120 °C, 5–10 min
no yield given

**(5)** → **(6)** (5)

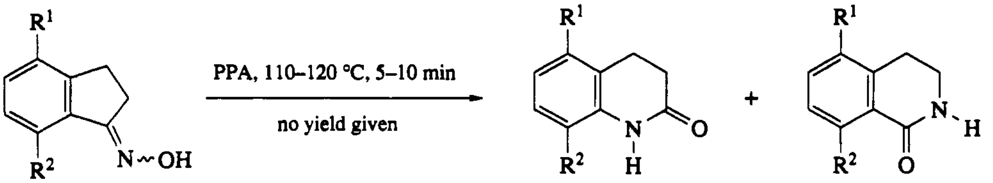
PPA, 110–120 °C, 5–10 min
no yield given
+

**(7)** → **(8)** + **(9)** (6)

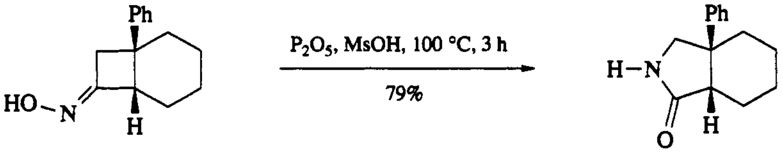
$P_2O_5$, MsOH, 100 °C, 3 h
79%

**(10)** → **(11)** (7)

*O*-Unsubstituted ketoximes undergo rearrangement in nonacidic media also. Thus, both geometric isomers of cholest-4-en-3-one oxime (**12**) rearranged to (**13**) in the presence of triphenylphosphine in refluxing tetrachloromethane (equation 8);[21] the apparent reluctance to migrate of endocyclic unsaturated substituents has also been observed for *O*-substituted oximes (*vide infra*).

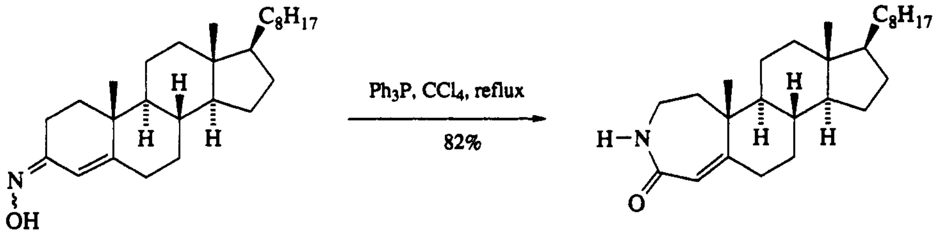
$Ph_3P$, $CCl_4$, reflux
82%

**(12)** → **(13)** (8)

When treated with benzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate, benzophenone oxime gave a high yield of *N*-benzoylbenzanilide (**14**), formed *via* rearrangement of the intermediate *O*-benzoyloxime (**15**).[22] Reaction of *p*-methoxyacetophenone oxime with 1,1′-carbonyldiimidazole (**16**) gave the *O*-substituted derivative (**17**),[23] whereas in the presence of allyl bromide efficient Beckmann rearrangement was observed (equation 9). Bentonite clay has been effectively employed as a rearrangement promoter.[24]

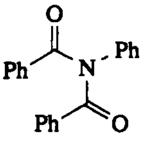

**(14)**

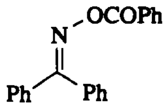
OCOPh
N
Ph
Ph

**(15)**

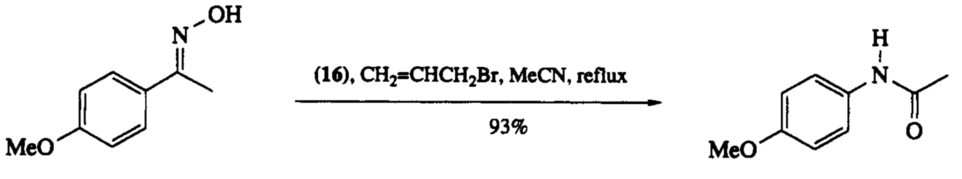
OH
N
MeO
(16), CH$_2$=CHCH$_2$Br, MeCN, reflux
93%
H
N
O
MeO

(9)

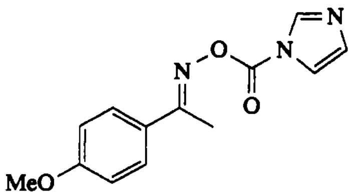

**(17)**

### *5.2.2.2.2 O-Substituted ketoximes*

*O*-Tosyl ketoximes generally rearrange smoothly and with exclusive *anti* migration when dissolved in polar media; a typical example is depicted in equation (10).[25] The tosyl derivatives frequently rearrange under the conditions of their formation (equation 11),[26] and the mildness and specificity of this procedure recommend it for use with acid-sensitive substrates (equation 12).[27]

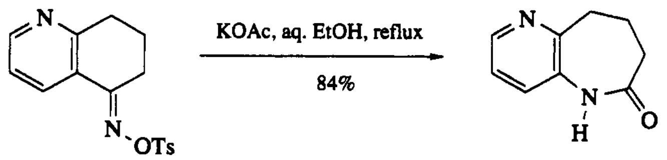
N
N
OTs
KOAc, aq. EtOH, reflux
84%
N
N
H
O

(10)

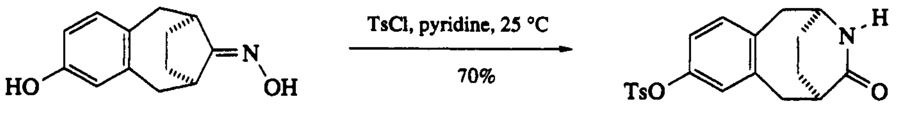
HO
N
OH
TsCl, pyridine, 25 °C
70%
TsO
N
H
O

(11)

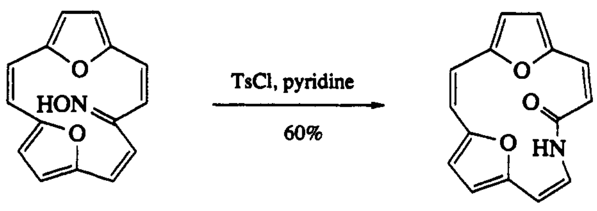
O
HON
O
TsCl, pyridine
60%
O
O
O
HN

(12)

Oxime methanesulfonates are also suitable rearrangement substrates. Thus, the azetidinone oxime methanesulfonate (**18**) underwent smooth rearrangement[28] upon exposure to basic alumina (equation 13);[29] more conventional mineral and organic acid based reagents were ineffective in promoting this transformation.

A striking example of the differing migratory aptitudes of saturated and unsaturated endocyclic groups is represented in equation (14). Under identical conditions, (*E*)-(**19**) was unreactive.[30]

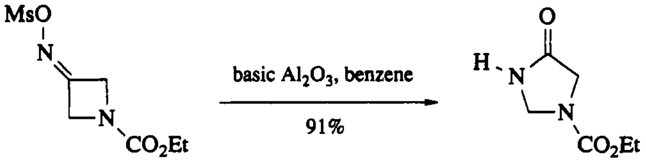
MsO
N
N
$CO_2Et$
basic $Al_2O_3$, benzene
91%
O
H
N
N
$CO_2Et$

**(18)**

(13)

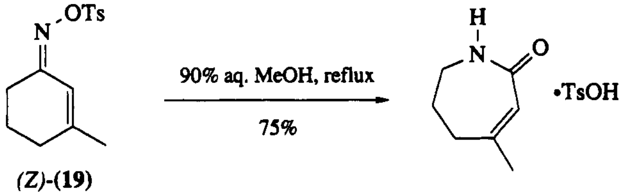
N
OTs
90% aq. MeOH, reflux
75%
H
N
O
•TsOH

*(Z)*-**(19)**

(14)

In contrast, exocyclic vinylic groups migrate readily. (*E*)-α-Benzylidenecyclohexanone oxime (**20**) formed a stable, crystalline addition product (**21**) upon tosylation in pyridine; dilute acidolysis gave the caprolactam derivative (**22**) in high overall yield (Scheme 3).[30]

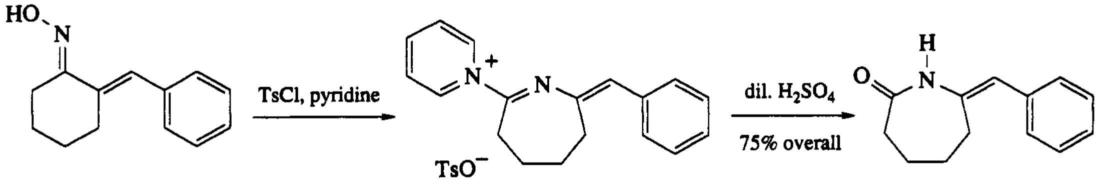
HO
N
TsCl, pyridine
N
+
N
TsO⁻
dil. $H_2SO_4$
75% overall
H
N
O

**(20)** **(21)** **(22)**

**Scheme 3**

Grob and coworkers have presented evidence for π-participation by migrating acyclic vinylic groups: the 2,4-dinitrophenol derivative (**23**) rearranged more than 2000 times faster than the saturated analog (**24**).[31]

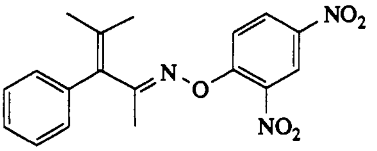

**(23)**

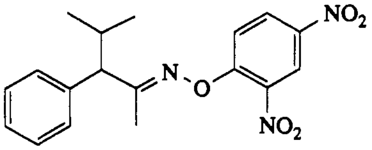

**(24)**

### *5.2.2.2.3 Direct conversion of ketones to amides*

Under appropriate conditions, ketones may be converted directly to amides. The facility of ketoxime formation from ketones strongly suggests that the former are reactive intermediates in these processes. Treatment of the strained bicyclic ketone (**25**) with *O*-(mesitylsulfonyl)hydroxylamine gave a mixture of the isomeric lactams (**26**) and (**27**) in good yield, and with moderate stereoselectivity (equation 15).[32]

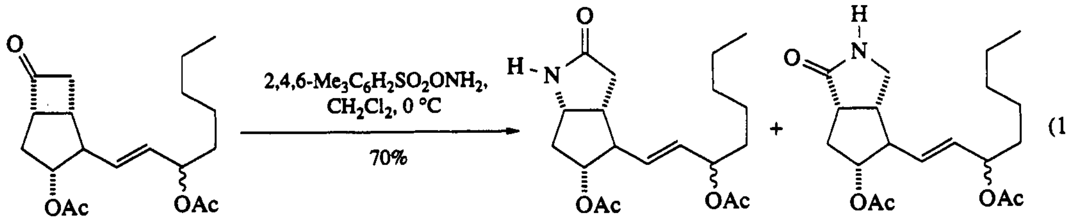
O
OAc
OAc
2,4,6-$Me_3C_6H_2SO_2ONH_2$,
$CH_2Cl_2$, 0 °C
70%
O
H
N
OAc
OAc
+
H
N
O
OAc
OAc

**(25)** **(26)** 79% **(27)** 21%

(15)

Bicyclo[3.2.1]octan-2-one underwent a highly selective Beckmann rearrangement in the presence of hydroxylamine *O*-hydrogensulfate and formic acid (equation 16).[33] A modification of this procedure using catalytic trifluoromethanesulfonic acid has been reported.[34]

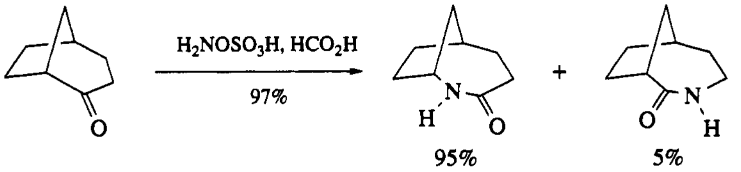

(16)

### *5.2.2.2.4 Miscellaneous reactions*

Migration of an acyl substituent was observed during rearrangement of the α-diketone monooxime (**28**),[35] with formation of the tetrasubstituted isoquinoline (**29**) presumably occurring *via* a cyclic imide intermediate (equation 17).

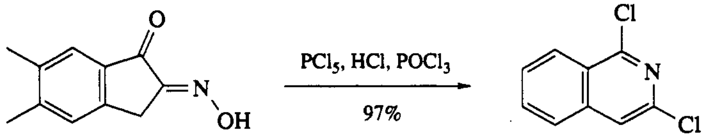

(**28**) (**29**)

(17)

A diastereomeric mixture of heterocyclic ketones (**30**) formed a single bicyclic ketolactam (**31**) when heated in refluxing trifluoroacetic acid (equation 18).[36] Ring contraction similarly occurred on thermolysis of (**32**; equation 19).[37]

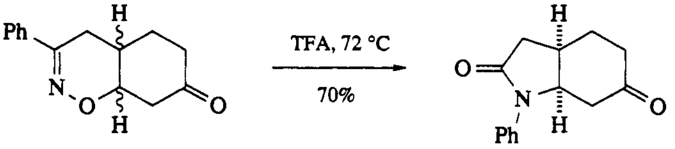

(**30**) (**31**)

(18)

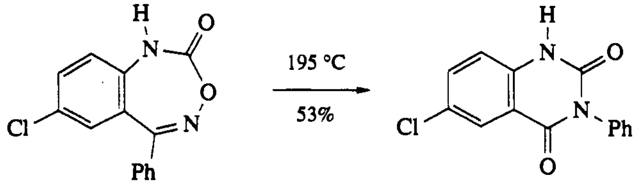

(**32**)

(19)

### 5.2.2.3 Aldoximes

Under a variety of conditions, aldoximes almost invariably rearrange in a nonstereospecific manner to give primary amides. Reagents which have been used to effect this transformation include boron trifluoride, phosphorus pentoxide and methanesulfonic acid, transition metal complexes and silica gel. Certain reagents may promote stereospecific *anti* migration in (*E*)-benzaldoximes to give formanilides. A comprehensive bibliography is provided in ref. 11.

## 5.2.3 ADDITION REACTIONS

One of the most useful variants of the Beckmann reaction is that in which the intermediate is trapped with a nucleophile other than water. Both carbon and heteroatomic nucleophiles have been used in this context. Intramolecular interception gives cyclized products.

### 5.2.3.1 Intermolecular Reactions

Treatment of the carbonate derivative (**33**) of acetophenone oxime with TMS-I gave a quantitative yield of the imidoyl iodide (**34**), as determined by $^1$H NMR (equation 20). The reactive product could be reacted further with a range of nucleophiles giving substituted imines in high yields.[38] Interestingly, exposure of acetophenone oxime itself to similar conditions gave the aryl-migrated Beckmann rearrangement product in moderate yield.[39]

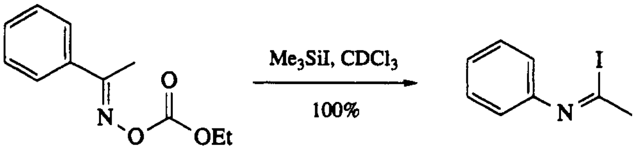

(**33**) (**34**)

(20)

Intermediates have been trapped by distal attack of halide ion. Reaction of the α,β-unsaturated oxime (**35**) with $PCl_5$ gave a good yield of *N*-phenyl-3-chloropropionamide (equation 21).[40] Similar reactivity was observed with the alkynic oxime (**36**; equation 22).[41]

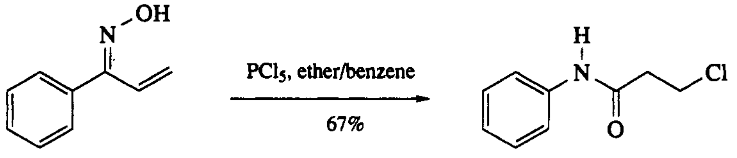

(**35**)

(21)

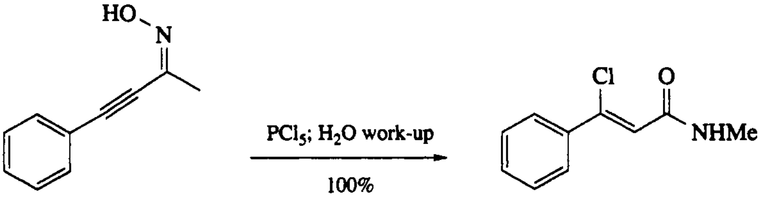

(**36**)

(22)

Azide ion has been shown to be an effective trap for a Beckmann intermediate. Treatment of acetophenone oxime with thionyl cloride in the presence of hydrazoic acid gave tetrazole (**37**), as shown in equation (23).[42] Thiolates participate efficiently in Beckmann reactions, and the sulfur nucleophile may be incorporated into a Lewis acidic reagent, as demonstrated in equation (24).[43]

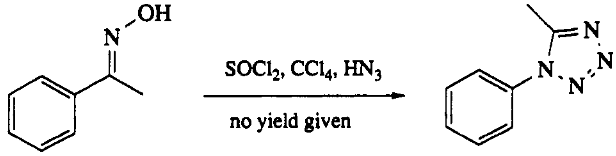

(**37**)

(23)

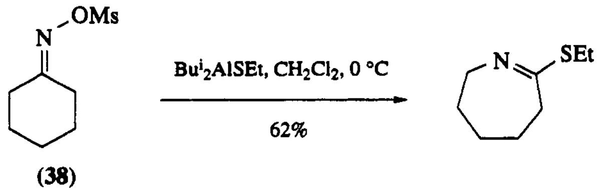

(**38**)

(24)

This general strategy has also successfully been exploited for the formation of carbon–carbon bonds. Compound (**38**) underwent ring expansion with concomitant formation of two new carbon–carbon bonds when treated sequentially with Grignard reagents as depicted in equation (25).[44] Similarly, treatment of cyclic ketoxime methanesulfonates with trimethylaluminum in dichloromethane gave cyclic imines, the products of formation of a single new carbon–carbon bond.[43,45] *In situ* treatment of the imines with DIBAL-H gave cyclic amines in good yields, as represented in equation (26).[43,46]

(38)

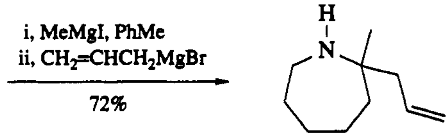
i, MeMgI, PhMe
ii, CH₂=CHCH₂MgBr
72%
H
N

(25)

(38)

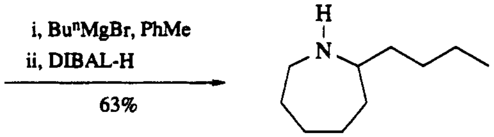
i, BuⁿMgBr, PhMe
ii, DIBAL-H
63%
H
N

(26)

Lewis acid induced Beckmann reaction in the presence of silyl enol ethers has been used to prepare vinylogous amides (equation 27).[47]

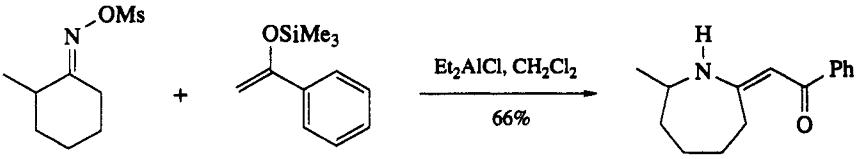
OMs
N
+
OSiMe₃
Et₂AlCl, CH₂Cl₂
66%
H
N
Ph
O

(27)

### 5.2.3.2 Intramolecular Reactions

The use of internal nucleophiles in the Beckmann reaction has been demonstrated to be an effective method for the synthesis of N-heterocycles. Substituted pyrrolines are readily available *via* this approach, as exemplified in equation (28).[48]

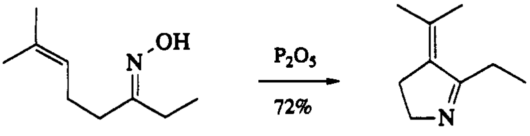
OH
N
P₂O₅
72%
N

(28)

Endocyclic cyclization of double bonds onto Beckmann intermediates gives doubly unsaturated N-heterocycles, which may be oxidized under mild conditions to give aromatic products (Scheme 4).[49]

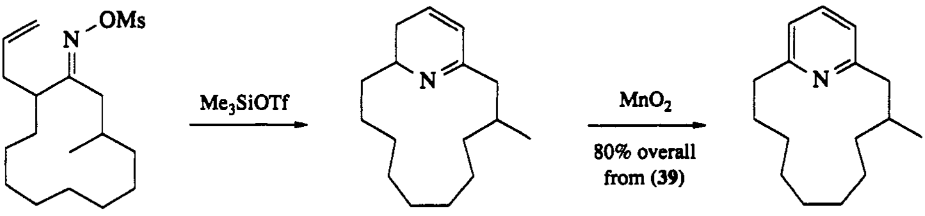
OMs
N
Me₃SiOTf
N
MnO₂
80% overall
from (39)
N

(39)

**Scheme 4**

The imines formed in the cyclization reactions may be trapped reductively (*vide supra*).[49] Reaction of the intermediate formed by ring-closure with trimethylaluminum to give a *gem*-dimethyl group as in equation (29)[49] further increases the scope of this transformation.

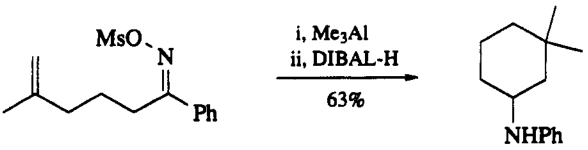
MsO
N
Ph
i, Me₃Al
ii, DIBAL-H
63%
NHPh

(29)

Benzoxazoles have been prepared by intramolecular reaction of a phenolic —OH group with a Beckmann intermediate (equation 30).[50] A cyclic imidate was isolated in high yield from tosylation and *in situ* Beckmann reaction of the erythromycin-derived oxime (**40**; equation 31).[51]

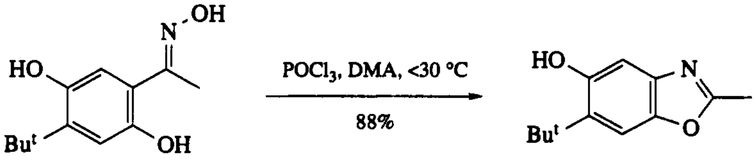

(30)

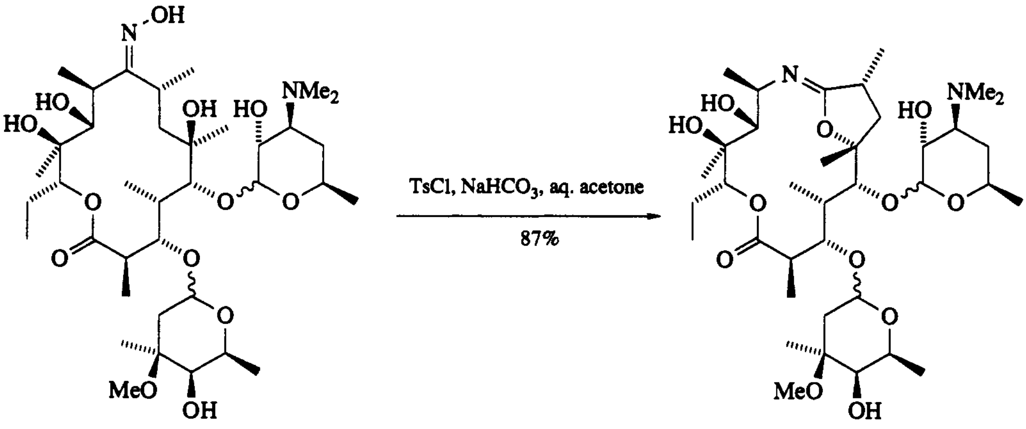

(**40**)

(31)

## 5.2.4 FRAGMENTATION REACTIONS

Fragmentation reactions, in which the α-carbon–carbon bond breaks, rather than migrates, may compete significantly with rearrangement processes when there is assistance from a neighboring center. Such assistance may be provided in the form of hyperconjugation (in the case of quaternary carbon atoms), or by mesomerically electron-donating heteroatoms. These processes may be stepwise, with the aforementioned assistance taking place during the break-down of the intermediate imidate. Substrates may undergo both rearrangement and fragmentation, depending on the reagents and reaction conditions employed. The fragmentation of aldoximes to give nitriles has been extensively reviewed elsewhere[11] and will not be considered here.

### 5.2.4.1 Carbon-assisted Fragmentations

Reaction *via* the fragmentation pathway increases with the ability of the α-carbon atom to support positive charge. Fragmentation of *cis*-1-methylbicyclo[4.3.0]nonan-2-one oxime (**41**) competed with normal Beckmann rearrangement to the extent shown in equation (32). The 1-unsubstituted analog gave exclusively the δ-lactam corresponding to (**42**).[52] Analogously, bicyclic oxime (**43**; R = Ph) gave only the fragmentation product (**44**; equation 33), whilst Beckmann rearrangement product (**45**) was the sole compound isolated when (**43**; R = H) was subjected to the same conditions.[53]

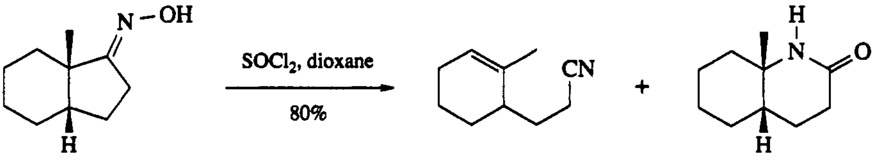

(**41**) 50% (**42**) 50%

(32)

The reactivity of spirooxime (**46**) was found to depend on the reagent system employed. In the absence of water, ring cleavage occurred to give unsaturated nitrile (**47**) as the only product. Reaction of (**46**)

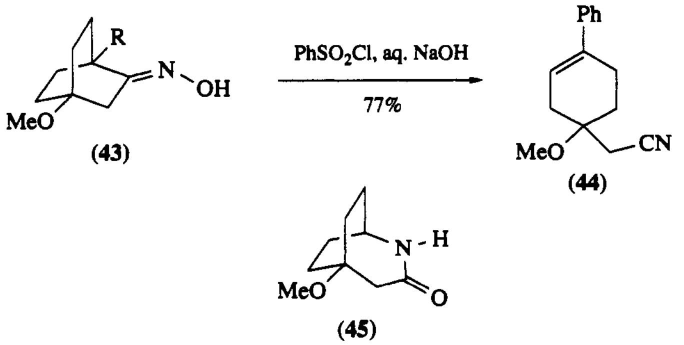
R
N
OH
MeO
PhSO2Cl, aq. NaOH
77%
Ph
MeO
CN
N-H
MeO
O

(43) (44) (45)

(33)

with benzenesulfonyl chloride in aqueous acetone gave exclusively the Beckmann rearranged spirolactam (**48**).[54]

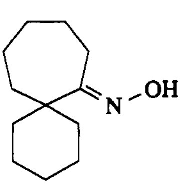

(**46**)

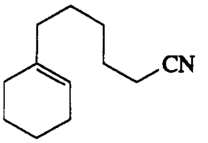

(**47**)

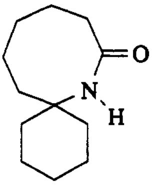

(**48**)

Under forcing conditions, the presumed intermediate (**49**) of fragmentation of oxime (**50**) underwent recyclization to give the product (**51**) of overall ring contraction, albeit in low yield (Scheme 5).[55]

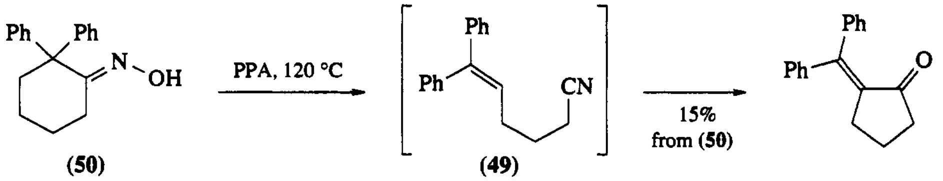
Ph
Ph
N
OH
PPA, 120 °C
Ph
Ph
CN
15%
from (50)
Ph
Ph
O

(**50**) (**49**)

**Scheme 5**

Fragmentations may be governed by stereoelectronic factors.[11] The steroidal oxime (**52**; equation 34) fragmented with loss of a deuteron from the 4α-methyl group, whereas the $\Delta^{5,6}$ analog (**53**; equation 35) fragmented with proton abstraction from the 4β-methyl group.[56,57]

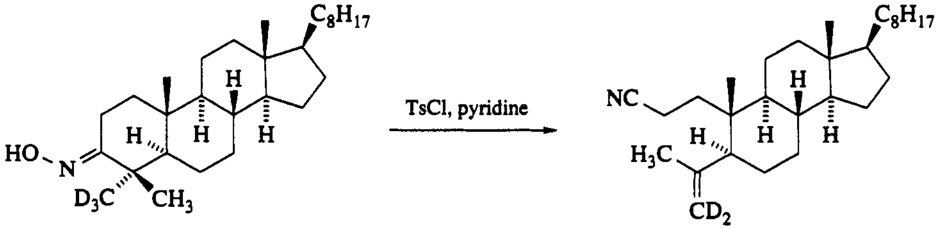
C8H17
H
H
H
H
HO
N
D3C
CH3
TsCl, pyridine
NC
C8H17
H
H
H
H
H3C
CD2

(**52**)

(34)

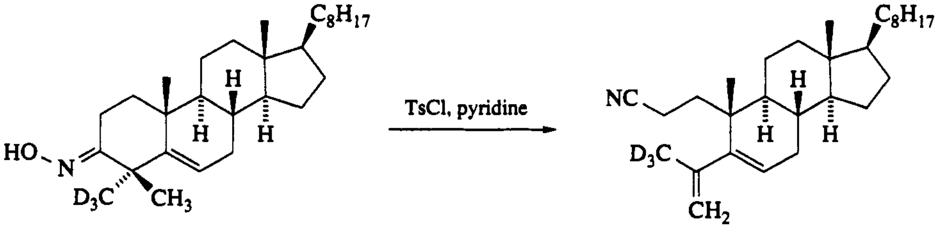
C8H17
H
H
H
HO
N
D3C
CH3
TsCl, pyridine
NC
C8H17
H
H
H
D3C
CH2

(**53**)

(35)

### 5.2.4.2 Heteroatom-assisted Fragmentations

The oxime (**54**), derived from dihydrocamphorquinone, fragmented under phase transfer conditions, with oxime —OH activation presumably taking place *via* nucleophilic attack on dichlorocarbene (equation 36).[58] Carbonyl oxygen assisted ring opening was observed in the fragmentation of the cyclic α-diketone monooxime (**55**),[59] probably *via* a tetrahedral intermediate (equation 37).[11] Fragmentation of oxime orthoester (**56**) using catalytic MsOH gave a quantitative yield of methyl acetate, trimethyl orthoformate and acetonitrile.[60]

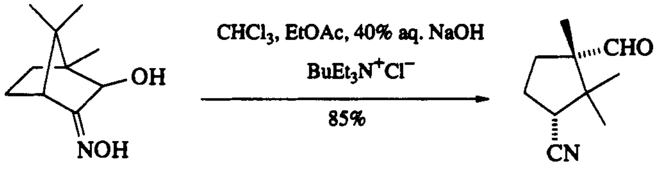
OH
NOH
CHCl₃, EtOAc, 40% aq. NaOH
BuEt₃N⁺Cl⁻
85%
CHO
CN

(**54**)

(36)

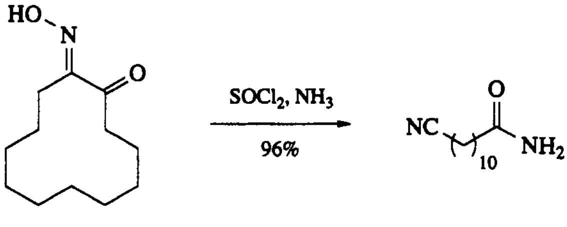
HO
N
O
SOCl₂, NH₃
96%
O
NC
10
NH₂

(**55**)

(37)

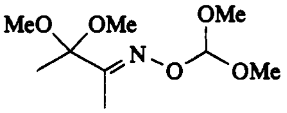
MeO
OMe
OMe
N
O
OMe

(**56**)

Distal oxygen functionality may assist fragmentation. Basic ethanolysis of the bicyclic ketoxime (**57**) gave the acyclic unsaturated nitrile ester (**58**) as a single geometric isomer (equation 38).[61]

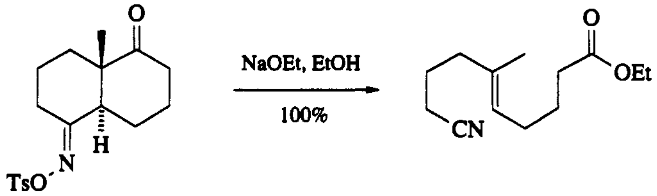
O
H
N
TsO
NaOEt, EtOH
100%
O
OEt
CN

(**57**) (**58**)

(38)

Analogously with the reaction depicted in equation (37), α-*N*-morpholino oxime (**59**) underwent oxidative ring cleavage under standard Beckmann conditions (equation 39).[62] Azide nitrogen assisted cleavage of the steroidal azido oxime (**60**) gave a dinitrile (equation 40).[63]

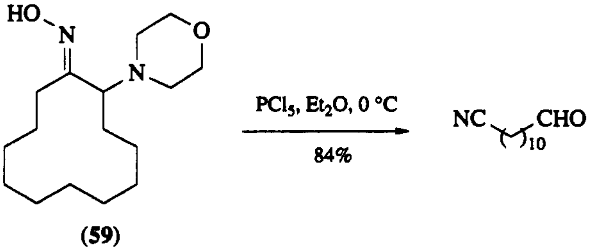
HO
N
N
O
PCl₅, Et₂O, 0 °C
84%
NC
CHO
10

(**59**)

(39)

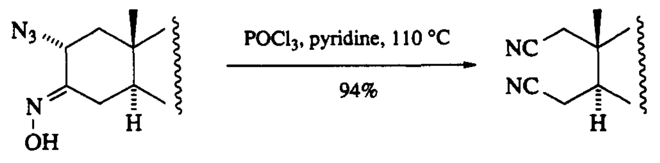

(60)

(40)

The ability of silicon to stabilize positive charge β to itself has been exploited in silicon-directed fragmentations of β-silyl oximes. Oxime *O*-acetate (**61**) fragmented stereospecifically to the (*E*)-alkenic product in the presence of catalytic TMSOTf (equation 41).[64]

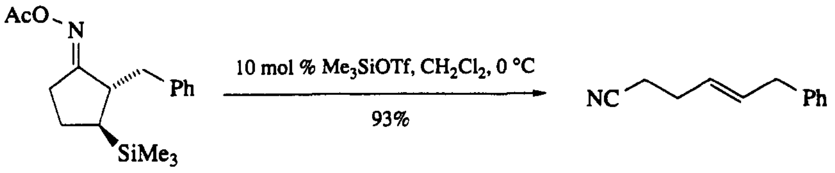

(61)

(41)

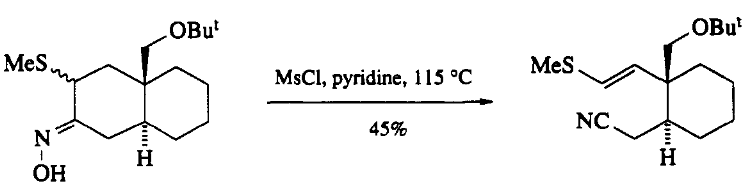

(62)

(42)

Adjacent sulfur substituents have been observed to promote fragmentation of oximes under Beckmann conditions. The bicyclic α-methylthio ketoxime (**62**) gave a thio enol ether on mesylation in pyridine (equation 42).[65] Anchimeric, rather than mesomeric assistance was observed for the fused tetrahydrothiophene derivative (**63**) (Scheme 6);[66] the involvement of sulfur was strongly implicated by the resistance to fragmentation of the corresponding sulfoxide under similar conditions.

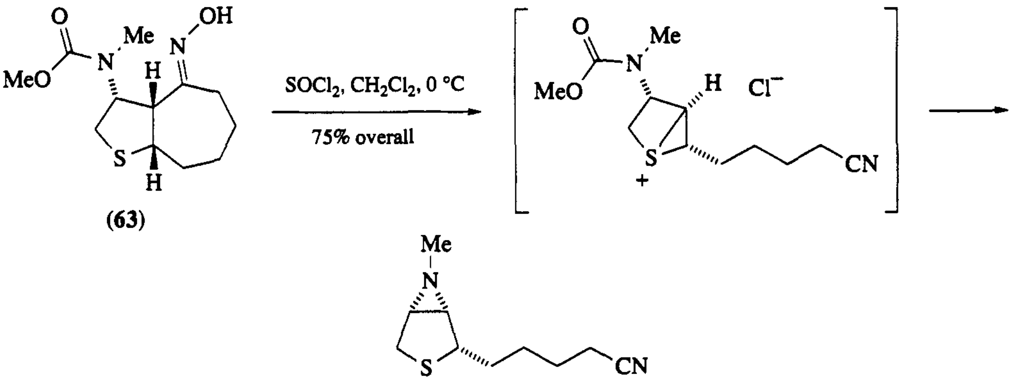

(63)

**Scheme 6**

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# 5.3
# Glycol Cleavage Reactions

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## 5.3.1 INTRODUCTION

This chapter discusses the oxidative carbon–carbon bond cleavage of vicinal diols (α- or 1,2-glycols) and related functional groups. There are many oxidants which can effect this transformation; however, the classical oxidants LTA, periodic acid and its salts are still the reagents of choice. The glycol fission reactions by these oxidants are usually very rapid, clean, quantitative and specific. Sodium periodate is particularly popular, attributable to the neutral and mild conditions used which are compatible with a wide range of functionalities. The studies of other reagents have been mainly exploratory or mechanistic. Some have shown promise for a specific application which is indicated in each section, but none has demonstrated the versatility exhibited by LTA and periodate in natural product synthesis. Several reviews of glycol cleavage reactions have appeared.[1–5]

## 5.3.2 SODIUM BISMUTHATE

Sodium bismuthate ($NaBiO_3$) was first used by Rigby[6,7] as an oxidant for α-glycol cleavage reactions to give carbonyl compounds (equation 1), and was found to be similar in scope to lead tetraacetate and periodic acid. Like lead tetraacetate but unlike periodic acid, it readily cleaves α-hydroxycarboxylic acids and α-hydroxy ketones. Aldehydic products, except formaldehyde,[8] are not oxidized further by the reagent which also oxidizes phenols and alkenes. The rate of alkene oxidation is slow compared with that of glycol cleavage.[9] Sodium bismuthate is generally used in combination with acetic or phosphoric acid in aqueous alcohol and the relatively harsh conditions required limit its synthetic applications. The mechanism of glycol cleavage by sodium bismuthate is still obscure. Since oxidation of *trans*-cyclopentane-1,2-diol with sodium bismuthate gives glutardialdehyde (equation 2),[10] and no difference in reaction rate is observed for the oxidation of *cis*- or *trans*-cyclohexane-1,2-diol, the proposed[7] mechanism involving a bismuth diester intermediate is not justified.

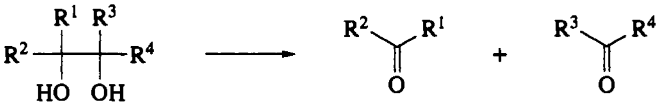
(1)

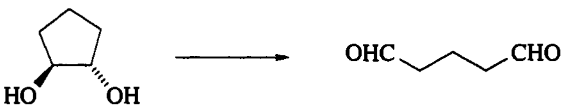
(2)

Selective oxidative cleavage of the corticosteroid side chain by sodium bismuthate was used as an analytical technique for the determination of urinary corticosteroids.[11] Sodium bismuthate was chosen since it cleaves α-hydroxy acids readily (unlike periodic acid) and tolerates the water in urine samples (in contrast to LTA).

## 5.3.3 PENTAVALENT ORGANOBISMUTH REAGENTS

Pentavalent derivatives of triphenylbismuth such as μ-oxobis(chlorotriphenylbismuth) (**1**) and triphenylbismuth carbonate (**2**) have been developed[12] recently as oxidizing agents which cleave α-glycols into the corresponding carbonyl derivatives (equation 1). Aldehydic products do not undergo further oxidation. Reagent (**1**) also oxidizes saturated alcohols as well as allylic and benzylic alcohols, whereas (**2**) selectively oxidizes allylic alcohols in the presence of saturated alcohols.[12]

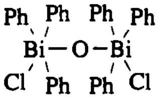
$\mathrm{ClPh_2Bi{-}O{-}BiPh_2Cl}$

(**1**)

$Ph_3BiCO_3$

(**2**)

Triphenylbismuth carbonate (**2**) displays remarkable chemoselectivity, allowing alcohol oxidation in the presence of benzenethiol, pyrrolidine, indole, aniline, dimethyl aniline and 3-pyrolidinocholesta-3,5-diene. The diol moiety in (**3**) is cleaved selectively without oxidizing the dithioacetal function (equation 3).[13] The rate of the stoichiometric oxidative cleavage of *cis*-cyclohexane-1,2-diol to adipic aldehyde with $Ph_3BiCO_3$ is faster than that of the *trans* isomer, suggesting the formation of a cyclic organobismuth intermediate (**4**; Scheme 1).[12]

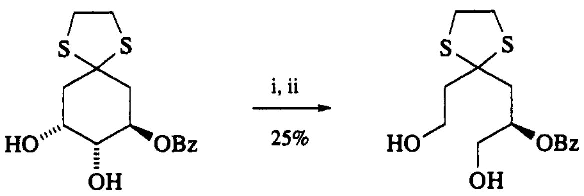
(3)

i, $PH_3BiCO_3$; ii, $NaBH_4$

A catalytic bismuth system ($Ph_3Bi$–NBS–$K_2CO_3$–MeCN with 1% water) has been reported[14] to cleave a range of 1,2-glycols efficiently and is shown to have a different mechanism from the cyclic process observed with the stoichiometric bismuth reagent (**2**). The catalytic system cleaves *cis*- and *trans*-decalin-9,10-diols at nearly the same rate, whereas the stoichiometric reagent (**2**) does not cleave the *trans*

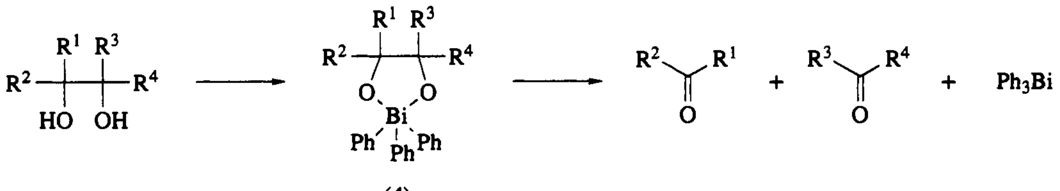
R¹ R³
R² R⁴
HO OH
O O
Bi
Ph Ph Ph
R² R¹
O
+
R³ R⁴
O
+ Ph₃Bi

(4)

Scheme 1

isomer. The mechanism involves the formation of a hypobromite which oxidizes Ph$_3$Bi to give a pentavalent alkoxy intermediate (5). Base-induced reductive elimination of (5) then gives the carbonyl derivatives and triphenylbismuth (Scheme 2).[14]

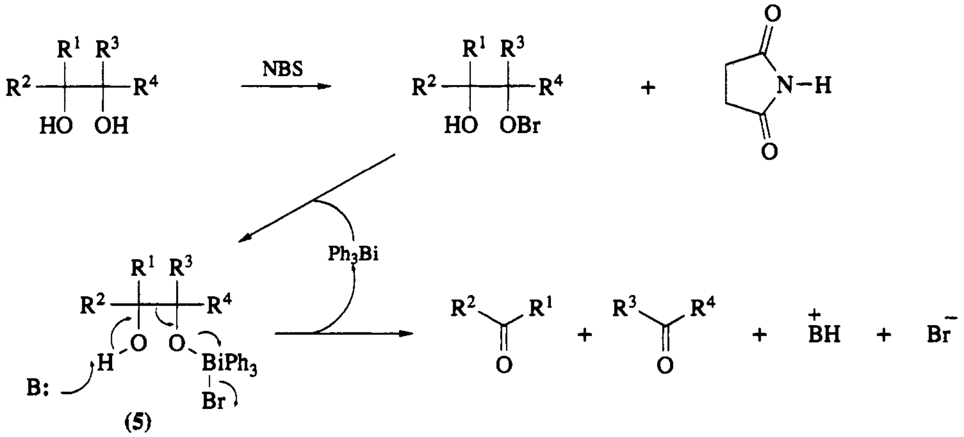
R¹ R³
R² R⁴
HO OH
NBS
HO OBr
+
O
N–H
O
Ph₃Bi
B:
H
O O
BiPh₃
Br
R² R¹
O
+
R³ R⁴
O
+ BH + Br⁻

(5)

Scheme 2

### 5.3.4 CERIUM(IV) REAGENTS

Cerium(IV) is an efficient reagent for α-glycol cleavage (equation 1). Vicinal and polyhydric alcohols are quantitatively broken down by the cerium(IV) ion.[15] There are no large differences in the overall oxidation rates of *cis*- and *trans*-cyclohexane-1,2-diols and of *cis*- and *trans*-cyclopentane-1,2-diols. However, the effect of ring size is considerable, cyclopentanediols reacting more rapidly than cyclohexanediols. It is noteworthy that cerium(IV) also cleaves 2-methoxycycloalkanols to give the corresponding dialdehydes.[16] The mechanism for the 1,2-glycol cleavage by cerium(IV) involves the formation of a monodentate complex followed by a one-electron cleavage to give an intermediate radical which is then further oxidized (Scheme 3). The main support for this mechanism comes from the similar rates of oxidation of glycols (6) and (7) and the monomethyl ether (8),[16] radical-trapping experiments[17] and parallel studies of lead(IV) and cerium(IV) glycol cleavage oxidations.[18] However, the synthetic aspects of cerium(IV) oxidation require further investigation.

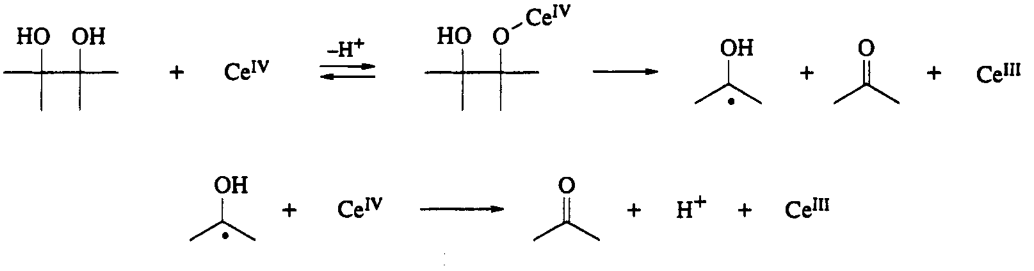
HO OH
+ Ce^IV
-H⁺
HO O
Ce^IV
OH
+
O
+ Ce^III
OH
+ Ce^IV
O
+ H⁺ + Ce^III

Scheme 3

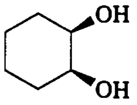

**(6)**

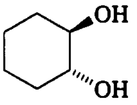

**(7)**

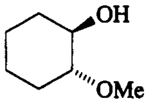

**(8)**

## 5.3.5 CALCIUM HYPOCHLORITE

Calcium hypochlorite, $Ca(OCl)_2$, an inexpensive and easily stored oxidant, can be used to cleave α-glycols to the corresponding carbonyl compounds. α-Diones, α-hydroxy ketones and α-hydroxy and α-keto acids are also oxidatively fragmented.[19] Aldehydic products are further oxidized to acids with an excess of the reagent. Consequently, this reaction is more suitable to produce carboxylic acids from 1,2-diols on a preparative scale. α,β-Unsaturated aldehydes and aromatic aldehydes with electron-donating groups undergo a competing nuclear chlorination, whereas aliphatic aldehydes and aromatic aldehydes with electron-withdrawing groups give the expected acids.[20] Reactions are carried out at room temperature in aqueous acetonitrile/acetic acid solution.

## 5.3.6 CHROMIUM(VI) REAGENTS

Glycol cleavage oxidation by chromic acid usually affords ketones and acids since the first formed aldehydes undergo rapid oxidation.[21] The synthetic aspects of these oxidations have received little attention, probably owing to the relatively harsh conditions used. Recently, PCC has been employed to effect the fission of simple vicinal diols under very mild conditions (a few hours at room temperature in dichloromethane solution) to give aldehydes and ketones in good yields.[22] The oxidative cleavage seems to involve an intermediate chromate ester (**9**). However, the reaction is sensitive to steric crowding: benzpinacol failed to react even after prolonged heating with a large excess of oxidizing agent.[22]

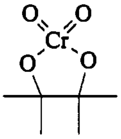

**(9)**

## 5.3.7 COBALT(II) REAGENTS

Cobalt(II) salts are effective catalysts for the oxidation of 1,2-glycols with molecular oxygen in aprotic polar solvents such as pyridine, 4-cyanopyridine, benzonitrile, DMF, anisole, chlorobenzene and sulfolane.[23] Water, primary alcohols, fatty acids and nitrobenzene are not suitable as solvents. Aldehydic products are further oxidized under the reaction conditions. Thus, the oxidative fission of *trans*-cyclohexane-1,2-diol gives a mixture of aldehydes and acids. However, the method is of value in the preparation of carboxylic acids from vicinal diols on an industrial scale; for example, decane-1,2-diol is cleaved by oxygen, catalyzed by cobalt(II) laurate, to produce nonanoic acid in 70% yield.[23,24]

## 5.3.8 IODO REAGENTS

Alicyclic, aromatic, aliphatic, steroidal and triterpenoid 1,2-diols are cleaved by iodine triacetate and iodine(I) acetate to generate carbonyl compounds. Aldehydic products are not further oxidized.[25] Iodine triacetate is prepared from iodine trichloride and silver(I) acetate, whereas iodine(I) acetate is prepared from iodine and silver(I) acetate. Reactions occur in acetic acid at room temperature under nitrogen, and a radical pathway involving a hypoiodite is suggested. The cost and the availability of these reagents are probable reasons for their unpopularity.

Five simple α-diols have been successfully cleaved by *N*-iodosuccinimide (NIS) in THF at ambient temperature.[26] Products from the oxidation are aldehydes, ketones, iodine and succinimide. Irradiation of the reaction increases the cleavage rate, indicating a radical pathway. Its attractiveness is its simplicity of operation and easy availability of the reagent. However, the generation of iodine during the reaction may pose complications with substrates containing sensitive functional groups.

## 5.3.9 VANADIUM REAGENTS

Although the dioxovanadium cation, $VO_2^+$, is a useful oxidant for the cleavage of simple ditertiary and secondary–tertiary glycols,[27] the strong acid conditions required for the reaction ($H_2SO_4$ or $HClO_4$) limit its synthetic application.

Recently, bis(acetylacetonato)oxovanadium [VO(acac)$_2$] has been shown to be a selective oxidant for the quantitative cleavage of ditertiary glycols to ketones under mild conditions.[28] Reactions proceed at room or higher temperatures (up to 70 °C) in aprotic solvents (dichloromethane, benzene or mixtures thereof). The selectivity of the reagent towards ditertiary glycols is demonstrated by the fact that pinacol and benzpinacol are smoothly cleaved to acetone and benzophenone, respectively, whereas butane-2,3-diol and cyclohexane-1,2-diol (*cis–trans* mixture) are inert under the reaction conditions. The reagent also shows excellent chemoselectivity, permitting glycol cleavage of substrates possessing a variety of functional groups (equation 4).

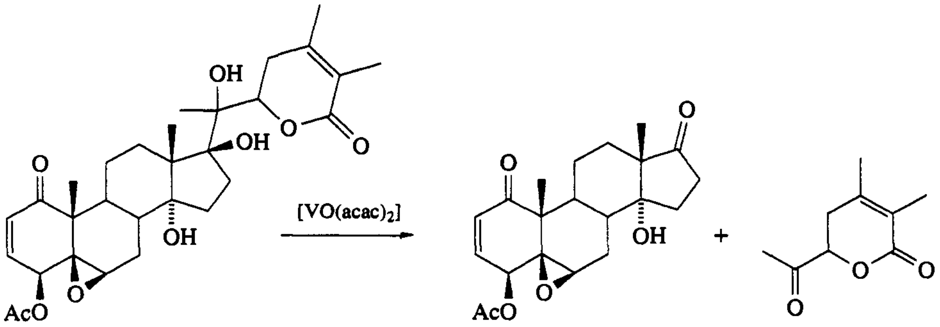

(4)

The reaction proceeds also with catalytic amounts of [VO(acac)$_2$], in the presence of *t*-butyl hydroperoxide or *m*-chloroperoxybenzoic acid.[28]

## 5.3.10 ANODIC OXIDATION

The anodic oxidation of 1,2-diols and their ether derivatives is a simple and clean method for the fission of glycols to the corresponding carbonyl compounds (equation 1). The reaction is carried out using carbon electrodes in methanol containing tetraethylammonium *p*-toluenesulfonate as a supporting electrolyte.[29]

In contrast to other cleavage reagents, this anodic oxidation does not show stereochemical preference. In addition, ether derivatives are oxidized in similar current efficiencies to those of the parent 1,2-diols. Cyclohexene oxide is oxidized *via* the corresponding hydroxy ether.

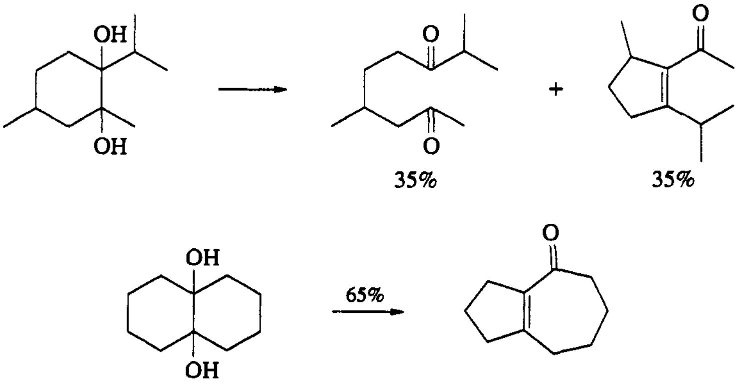

**Scheme 4**

Aldehydic products are usually isolated as their corresponding acetals. The ketones formed from the oxidation may undergo intramolecular aldol condensation to give enones (Scheme 4).[29]

## 5.3.11 HYDROGEN PEROXIDE

Aqueous hydrogen peroxide in conjunction with catalytic amounts of tungstate and phosphate (or arsenate) ions, under acidic conditions (pH 2), provides a synthetically useful procedure for the oxidative fission of water soluble 1,2-diols to carboxylic acids.[30] This method, which employs an inexpensive catalyst and a cheap, nonpolluting oxidant, is particularly suitable for large scale operations. Primary–secondary, secondary–secondary and secondary–tertiary 1,2-diols (open chain and cyclic) can be satisfactorily oxidized. Thus, *trans*-1,2-cyclopentanediol, *cis*- and *trans*-1,2-cyclohexanediol, *trans*-1-methyl-1,2-cyclohexanediol and 1,2-hexanediol react with $H_2O_2$, $Na_2WO_4{\cdot}2H_2O$ and $H_3PO_4$ at 90 °C for 5 h to give glutaric, adipic, 6-oxoheptanoic and valeric acid, respectively, in 87–96% yield.[30] This method has been applied to water insoluble diols by the use of a phase transfer agent. Thus, 1,2-octanediol gives 78% of heptanoic acid.[30]

A related hydrogen peroxide oxidation of α-glycols catalyzed by tris(cetylpyridinium) 12-tungstophosphate, $[\pi\text{-}C_5H_5N(CH_2)_{15}Me]_3^+(PW_{12}O_{40})_3^-$, (CWP) has also been reported.[31] This catalyst–oxidant system also epoxidizes alkenes and allylic alcohols and converts secondary alcohols to ketones. 1,2-Glycols react with three equivalents of $H_2O_2$ mediated by CWP in refluxing *t*-butanol to give carboxylic acids in good yields. The oxidation of 4-vinyl-1,2-cyclohexanediol gives 3-vinyladipic acid in 55% yield (equation 5), indicating that the reaction is chemoselective. The cleavage reaction involves the formation of an α-ketol which subsequently undergoes C—C bond fission.[30,31] This CWP–$H_2O_2$ system, which is also efficient for the oxidative cleavage of carbon–carbon double bonds of alkenes, provides a new way of converting alkenes into carboxylic acids.[31]

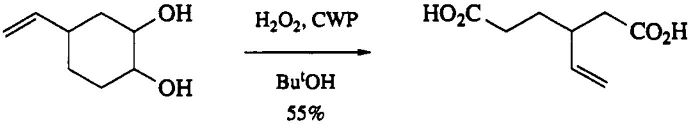

(5)

## 5.3.12 MANGANESE DIOXIDE

Vicinal diols can be cleaved smoothly under neutral conditions to give carbonyl compounds using an excess of activated manganese dioxide.[32] The reaction proceeds under very mild conditions (stirring in $CH_2Cl_2$ at room temperature). Only 1,2-*cis*-diols and the analogous *trans* compounds with a flexible arrangement of their hydroxy groups can be oxidized. Even diols subject to extensive steric hindrance undergo oxidative fission (Scheme 5). 9,10-*cis*-Decalindiol is easily cleaved, whereas the 9,10-*trans* isomer remains inert. Reactions work well with glycols containing at least one tertiary hydroxy group. If the hydroxy groups are secondary, ketonization is observed instead of complete oxidative fission. For example, dodecanedial, the oxidation product of 1,2-*cis*-cyclododecanediol, is accompanied by 1,2-cyclododecanedione (14%) and traces of 2-hydroxycyclododecanone.[32] The mild conditions and the ease of work-up of the manganese dioxide oxidation is a valuable method for the fission of 1,2-glycols containing at least one tertiary hydroxy group.

## 5.3.13 LTA AND PERIODATE

### 5.3.13.1 General Characteristics

In 1928, Malaprade[33] discovered that periodic acid and its salts cleaved the carbon–carbon bond of 1,2-diols efficiently to give carbonyl compounds. Subsequently, Criegee[34] found that LTA could also effect such transformations. The glycol cleavage reactions of these two reagents are usually very rapid, clean, quantitative and specific. The reactions are usually stoichiometric, with one mole of oxidant being consumed for each carbon–carbon bond cleaved. The carbonyl compounds generated are inert towards further oxidation under the reaction conditions. For many applications, periodate and LTA complement each other. LTA is generally used in acetic acid or aprotic solvents such as benzene, ethyl acetate and

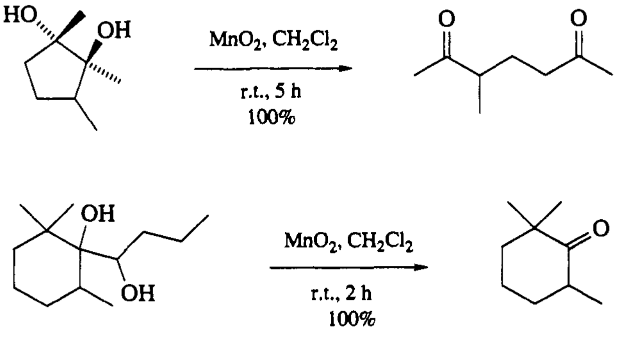

**Scheme 5**

dichloromethane. Sodium and potassium periodate can be used only in water or aqueous organic solvents owing to their solubility properties, whereas periodic acid can be used in water or aprotic solvents (diethyl ether or THF).[35] In order to carry out periodate oxidation in nonaqueous media, sodium periodate supported silica[36] and quaternary ammonium periodates[37] have been developed. Recently, polymer-supported quaternary ammonium periodate, which was used for glycol cleavage reactions in dichloromethane, has been reported as a practically useful alternative.[38]

The fact that periodate fission functions best in aqueous media[39] and LTA in organic solvents makes glycol scission oxidations possible with all types of substrates. These reagents were used extensively for structural elucidation of carbohydrates before the advent of modern spectral instrumentation.[40,41] Now, they are generally used in synthetic work.

## 5.3.13.2 Reaction Mechanism

The mechanism of cleavage by periodate is consistent with a cyclic, five-membered ring intermediate (**10**) shown in Scheme 6. Support comes from the fact that the *cis* isomers of cyclic diols are more reactive than the *trans* isomers, *threo*-1,2-diols undergo oxidation faster than the *erythro* isomers[42] and the inert behavior of diaxial *trans*-1,2-diols which cannot form a cyclic periodate ester.[43]

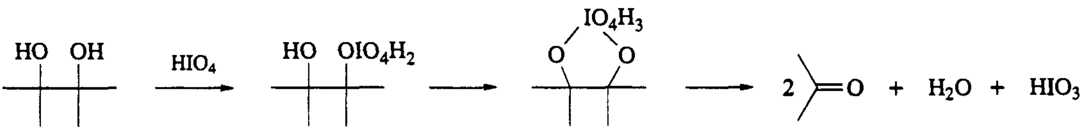

**(10)**

**Scheme 6**

The mechanistic aspects of LTA oxidation are more complicated and the results indicate several pathways dependent on the steric environment of the glycols. In cases where geometry is favorable, oxidative scission *via* a cyclic intermediate (**11**) proceeds by a two-electron transfer (path a, Scheme 7).[44] With *trans*-diols possessing antiperiplanar hydroxy groups, which for steric reasons cannot form the lead(IV) cyclic intermediate (**11**), an alternative cyclic pathway consisting of an intramolecular proton transfer in (**12**) becomes important (path b).[45] In addition, the role of both base[45] and acid[46] in enhancing the fission of these *trans*-diols has been rationalized by involving two noncyclic transition states, such as (**13**) and (**14**) (paths c and d).

## 5.3.13.3 Applications in Organic Synthesis

In addition to the oxidative scission of 1,2-diols, the reaction can be extended to related 1,2-bifunctional compounds such as oxiranes,[47] 1,2-dicarbonyl compounds, 2-hydroxy aldehydes, ketones and acids, α-amino alcohols, 1,2-diamines and also to polyols.[1,2] LTA cleaves α-hydroxy acids much more readily than do periodates and both reagents oxidize 2-hydroxy aldehydes and 1,2-dicarbonyl compounds relatively slowly.[1,2] Only periodic acid[47] in water reacts with oxiranes *via* the corresponding diols.

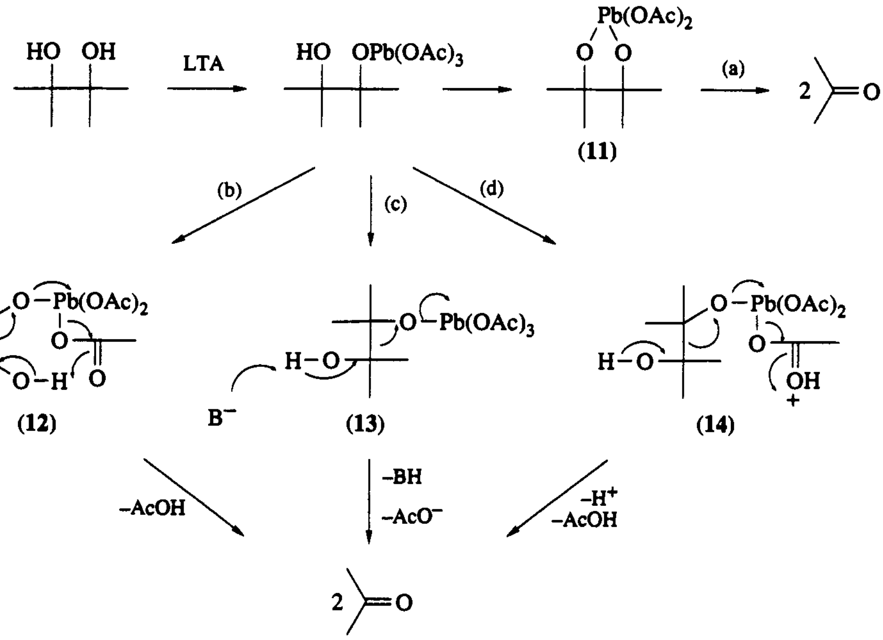

Scheme 7

Although periodates also oxidize polycyclic aromatic hydrocarbons, phenols, hydrazines, active methylene compounds and sulfides,[3] chemoselectivity can usually be achieved and glycol cleavage oxidation takes precedence. For example, the diol moiety in the diethyl dithioacetal derivative of D-glucose can be selectively oxidized in good yield (equation 6).[48] In contrast, LTA is less selective than periodate and oxidizes a far greater variety of organic compounds.[5] Consequently, in order to minimize undesired reactions, it is customary to add LTA slowly to avoid contact of the initially formed products with an excess of the oxidant (equation 7).[49]

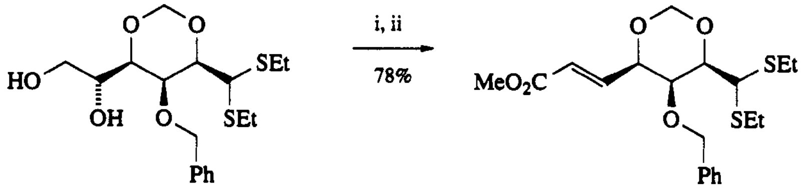

(6)

i, $NaIO_4$, aq. MeOH; ii, $Ph_3P=CHCO_2Me$

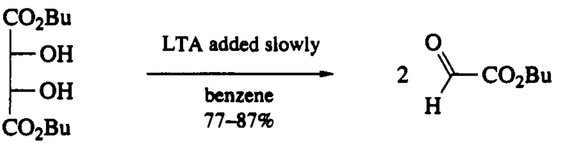

(7)

Periodate oxidation is sensitive to the stereochemistry[42,43] of the substrates: cyclic *trans*-1,2-glycols containing a tertiary hydroxy group and conformationally biased *trans*-diaxial 1,2-diols[1] are generally unreactive. Being a more powerful oxidizing agent, LTA complements periodates in the cleavage of diols which are inert to periodates.[1,2] An interesting application of this type of LTA cleavage is the fission of angular *trans*-diols which allows entry into medium or large rings, illustrated by equations (8)[50] and (9).[51] In cases where the angular diols are *cis*-disposed, oxidative cleavage with periodate occurs readily and thus fragmentation into medium or large rings can be achieved from *trans*-angular alkenes *via* the periodate–ruthenium tetroxide oxidation;[52] an example is provided in the synthesis of the 5-8-5 carbon skeleton of fusicoccins and ophiobolins (equation 10).[53] Trisubstituted alkenes yield keto acids (equation 11).[54] A related reaction, known as the Lemieux–von Rudloff (periodate–permanganate) oxidation,[55] is also used to oxidize alkenes to acids or ketones (equation 12).[56] If aldehydes are required from alkenes, the Lemieux–Johnson (periodate–osmium tetroxide) oxidation[57] is appropriate and equation (13)[58] shows that a free hydroxy group is not oxidized under the reaction conditions. If LTA is used as the oxidant, the dicarbonyl compounds are obtained in two separate steps from cyclic alkenes. Treatment of the dicarbonyl compounds with base causes aldol condensation and hence provides a general method for the preparation of cyclic enones (equation 14)[59] or enals (equation 15).[60]

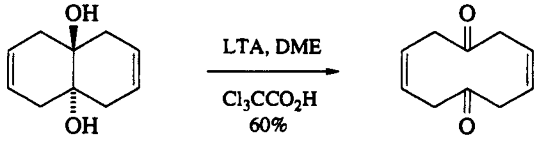
OH
OH
LTA, DME
$Cl_3CCO_2H$
60%
O
O

(8)

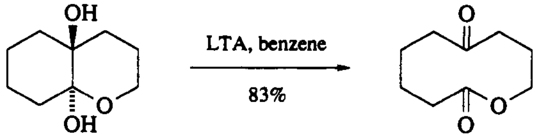
OH
O
OH
LTA, benzene
83%
O
O
O

(9)

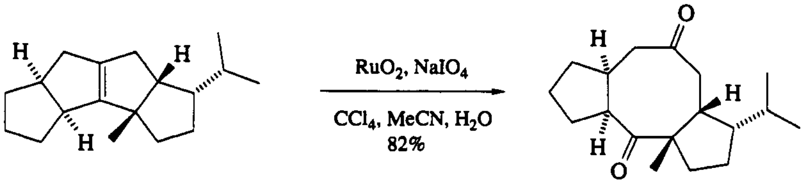
H
H
H
$RuO_2$, $NaIO_4$
$CCl_4$, MeCN, $H_2O$
82%
O
H
H
H
O

(10)

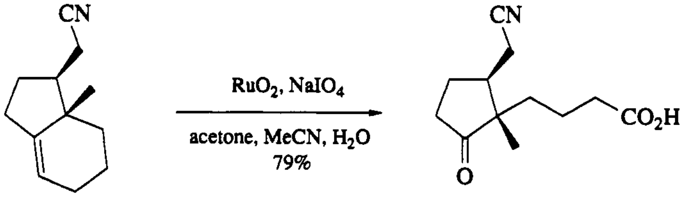
CN
$RuO_2$, $NaIO_4$
acetone, MeCN, $H_2O$
79%
CN
$CO_2H$
O

(11)

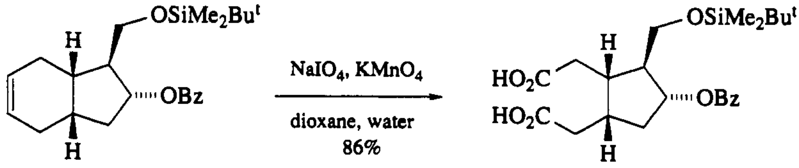
$OSiMe_2Bu^t$
H
OBz
H
$NaIO_4$, $KMnO_4$
dioxane, water
86%
$OSiMe_2Bu^t$
H
$HO_2C$
$HO_2C$
OBz
H

(12)

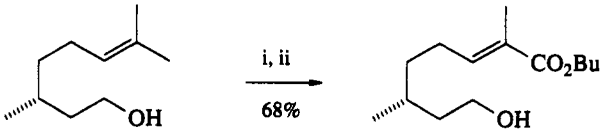
OH
i, ii
68%
$CO_2Bu^t$
OH

(13)

i, catalytic $OsO_4$, $NaIO_4$; ii, $Ph_3P{=}CMeCO_2Bu^t$

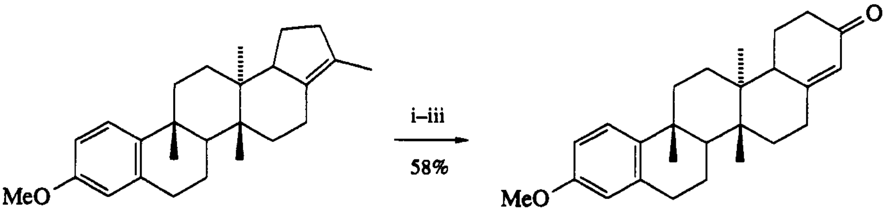
MeO
i–iii
58%
O
MeO

(14)

i, $OsO_4$; ii, LTA, THF; iii, KOH, $H_2O$

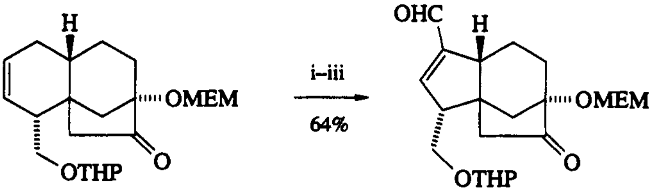

(15)

i, $OsO_4$; ii, LTA, benzene; iii, $Bn_2NH_2^+CF_3CO_2^-$, benzene

Aldol-type cyclization of dialdehydes with nitroalkanes is a valuable synthetic route to amino sugars, amino cyclitols and nucleosides of amino sugars.[61] Recently, the cyclization of the di- and tetra-aldehydes derived from sucrose (**15**) with nitroalkanes has appeared. It is noteworthy that the oxidative cleavage of sucrose with LTA affords the dialdehyde selectively (Scheme 8).[62]

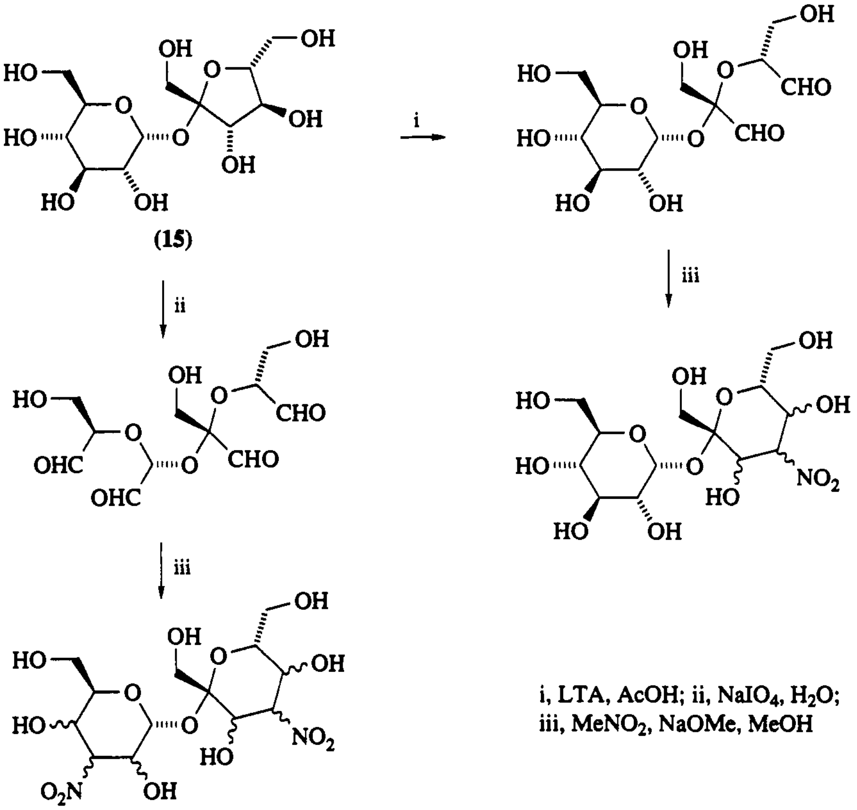

i, LTA, AcOH; ii, $NaIO_4$, $H_2O$; iii, $MeNO_2$, NaOMe, MeOH

**Scheme 8**

Generation of aldehydes from oxidative fission of diols for further synthetic elaboration is generally more efficient than that from oxidation of the corresponding primary alcohols. The sequence involving a glycol cleavage followed by a Wittig-type homologation, illustrated in equation (16),[63] is particularly attractive and finds wide application in the syntheses of arachidonic acid metabolites. Recently, a series of hydroxylated aldehydes which are useful intermediates in the synthesis of lipoxygenase metabolites of arachidonic acid have been prepared from the corresponding acetonides (equation 17).[64] The use of periodic acid permits the transformation (hydrolysis followed by glycol scission) to proceed in one pot. In a similar way, periodic acid is useful for the hydrolysis of resistant 1,3-dioxolane protecting groups (equation 18).[65] The glycol cleavage–Wittig condensation sequence has also been employed in the total synthesis of other natural products, *e.g.* altholactones (equation 19),[66] and (*S*)-homolaudanosine and (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (equation 20).[67]

The extensive use of periodate, frequently sodium periodate, as oxidants for water insoluble glycols in contemporary organic synthesis contradicts the recommendation made earlier[2] that LTA is the preferred reagent. Hydrophobicity of the substrates does not appear to pose problems since they are readily soluble in aqueous solvents. In addition, periodate cleavage can proceed in a two-phase mixture, indicated in

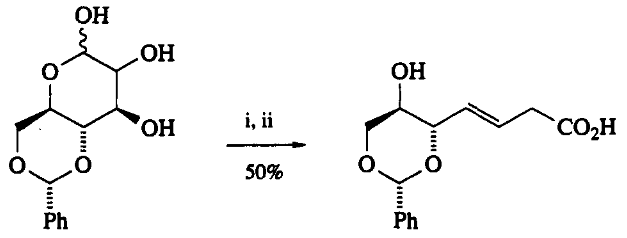

(16)

i, $NaIO_4$, $NaHCO_3$, $CH_2Cl_2$, $H_2O$; ii, $HO_2CCH_2CH{=}PPh_3$, THF, DMSO

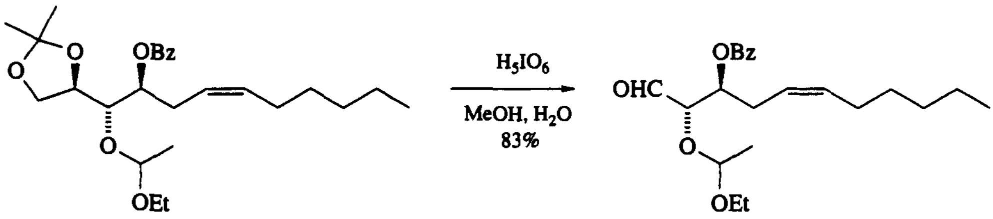

(17)

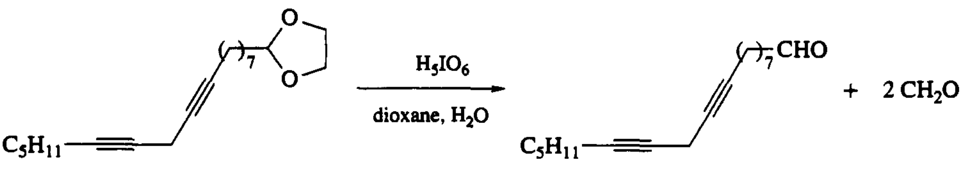

(18)

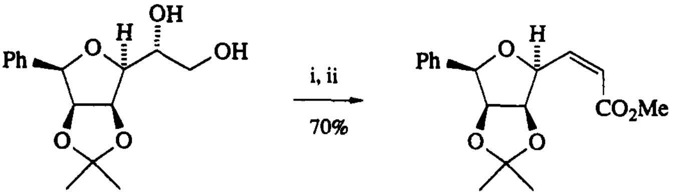

(19)

i, $NaIO_4$, MeOH, $H_2O$; ii, $Ph_3P{=}CHCO_2Me$, MeOH

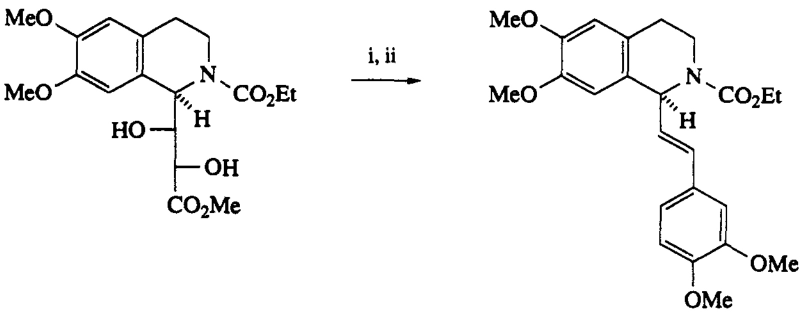

(20)

i, $NaIO_4$, MeOH, $H_2O$; ii, ylide derived from 3,4-dimethoxybenzyltriphenylphosphonium chloride, THF

equation (16). More examples of the application of sodium periodate mediated glycol fission reactions in synthesis are illustrated in equations (21)–(25).[68–72] The attractiveness of sodium periodate is attributable to its unique features, such as: (i) it has an indefinite shelf life and can be handled easily; (ii) it is used under mild and neutral conditions; (iii) it is highly specific; and (iv) isolation of the reaction products is by extraction into organic solvents. However, if the reaction products are highly water soluble or prone to hydrate formation, LTA is the preferred reagent, as used in the preparation of 2,3-*O*-isopropylidene-D-glyceraldehyde (**16**),[73] a versatile homochiral building block. A convenient synthesis of enal (**17**) results from a simplified work-up procedure for (**16**).[74] The procedure involves filtration of the glycol cleavage reaction mixture in EtOAc through a celite/silica pad followed by neutralization of the filtrate with solid

$NaHCO_3$; the resultant mixture is filtered and $Ph_3P{=}CHCHO$ added to the filtrate to give enal (**17**) in 75% overall yield from the diol (Scheme 9).

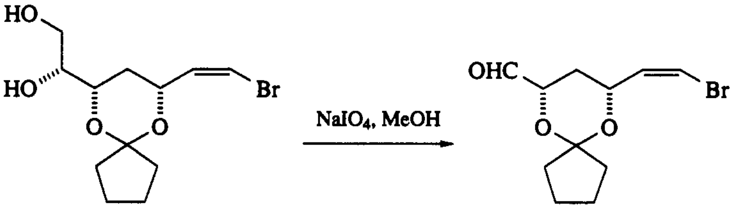
HO
HO
O
O
Br
NaIO4, MeOH
OHC
O
O
Br

(21)

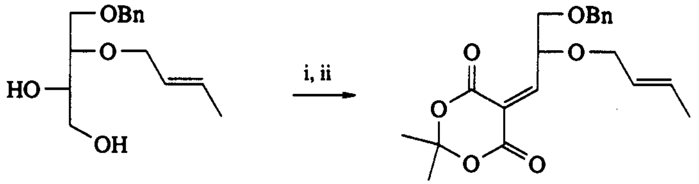
OBn
O
HO
OH
i, ii
O
O
O
O
OBn
O

(22)

i, $NaIO_4$, aq. MeOH, 0 °C to r.t.; ii, Meldrum's acid, $(CH_2NH_3)^+{}_2(AcO^-)_2$, MeOH

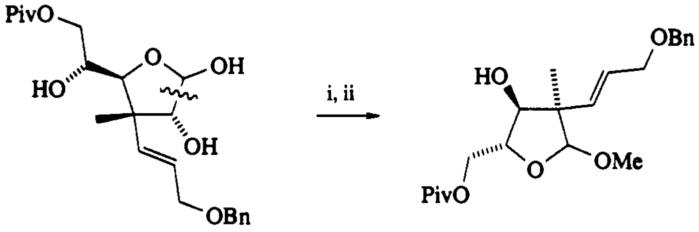
PivO
HO
O
OH
OH
OBn
i, ii
OBn
HO
O
OMe
PivO

(23)

i, $NaIO_4$, aq. MeOH; ii, MeOH, acid resin

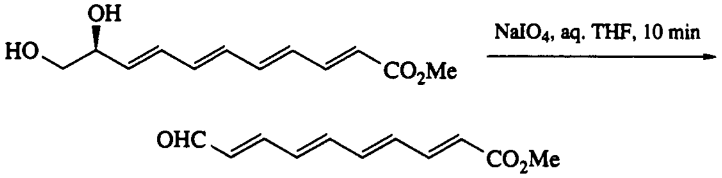
OH
HO
CO2Me
NaIO4, aq. THF, 10 min
OHC
CO2Me

(24)

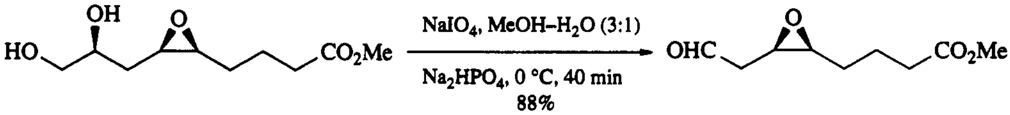
OH
HO
O
CO2Me
NaIO4, MeOH-H2O (3:1)
Na2HPO4, 0 °C, 40 min
88%
OHC
O
CO2Me

(25)

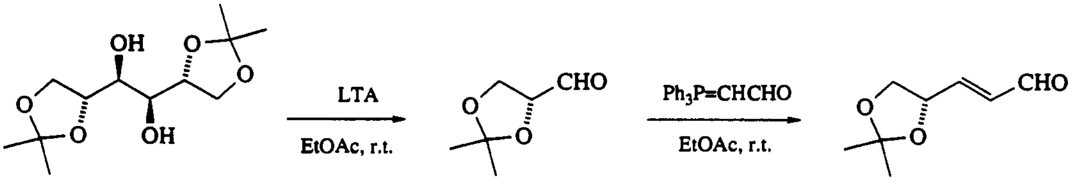
OH
O
O
O
O
OH
LTA
EtOAc, r.t.
CHO
O
O
Ph3P=CHCHO
EtOAc, r.t.
CHO
O
O

(**16**)

(**17**)
75% overall

**Scheme 9**

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# 5.4
# The Hunsdiecker and Related Reactions

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## 5.4.1 INTRODUCTION

The main theme of this chapter is the cleavage of alkyl–, aryl– and vinyl–carboxyl single bonds by means of the fragmentation (decarboxylation) of carboxyl radicals (equation 1). The fragmentation of acyl radicals (decarbonylation) (equation 2), although much less efficient, is also considered where appropriate.

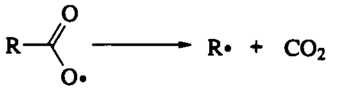
(1)

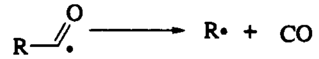
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Methods for the generation of carboxyl radicals are considered first. The trapping of the ensuing alkyl radicals by various radical-trapping agents allowing the overall transformation of carboxylic acids into a range of diverse functional groups of the first lower homolog is then discussed.

The majority of reactions discussed are readily applicable to simple primary, secondary and tertiary aliphatic acids. The decarboxylation of aryl- and vinyl-carboxyl radicals is a much more difficult process which limits the application of many of the methods described to aliphatic acids. As such, particular attention is drawn in the text to examples of aryl and vinyl decarboxylations.

This chapter does not include electrochemical decarboxylation processes (the Kolbe reaction, Volume 3, Chapter 2.9) and transition metal catalyzed decarbonylation reactions.

## 5.4.2 GENERATION OF CARBOXYL RADICALS: FUNCTIONAL GROUP COMPATABILITY

The generation of carboxyl radicals requires the preparation of suitable precursors containing a weak carboxyl–X bond susceptible to homolytic cleavage. In the classical Hunsdiecker reaction, the precursor is an acyl hypohalite (X is halogen). More recently, methods have been developed in which X is a lead(IV) salt or a nitrogen atom. These more recent methods tolerate a much wider range of functional groups as they operate under much milder conditions. Throughout the text examples are chosen to illustrate the degrees of functionality and complexity compatible with the various methods. Methods with relatively limited applications, such as the pyrolysis of peroxy esters and the silver-catalyzed oxidation of carboxylate salts by the persulfate anion, are discussed at appropriate points in the text.

### 5.4.2.1 Acyl Hypohalites

Acyl hypohalites are usually prepared *in situ* by reaction of a metal salt of the carboxylic acid with a halogen (equation 3). Classically the silver salt[1] is used, but problems associated with the preparation of dry silver carboxylates, as well as the more obvious economic factor, have led to the development of methods using mercury[2] and thallium[3] salts. Evidently, those functional groups which react readily with halogens are not compatible with this approach. A major limitation of the acyl hypohalites is the readiness with which they transfer halogen atoms to alkyl radicals; this property essentially limits their use to decarboxylative halogenation reactions.

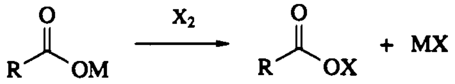
(3)

### 5.4.2.2 Lead(IV) Carboxylates

The generation of lead(IV) carboxylates involves exchange of an acetate of LTA for the acid to be decarboxylated (equation 4). The weak bond cleaved to generate the carboxyl radical is a carboxyl–lead(IV) bond. The higher activation energy for decarboxylation of acetoxyl radicals ensures preferential decarboxylation of most other alkanoic acids. On the other hand, attempts at the decarboxylation of aryl acids fail due to competing acetoxyl decarboxylation. Evidently, those functional groups which undergo

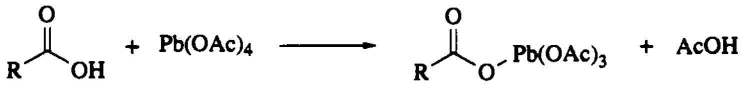
(4)

facile oxidation with LTA are not compatible. An excellent review[4] provides further information on functional group compatability and experimental details.

### 5.4.2.3 *O*-Acyl Oximes and *O*-Acyl Thiohydroxamates

Recently, methods have been devised for carboxyl radical generation by homolytic cleavage of weak carboxyl—N single bonds. Such methods have great potential in organic synthesis as precursor generation requires neither strong oxidants nor strongly electrophilic species. Such precursors are hence compatible with a wide range of functional groups. One such precursor type is composed of the *O*-acyl benzophenone oximes, prepared[5] by the reaction of activated acyl derivatives with benzophenone (equation 5). Carboxyl radical generation is achieved by simple UV photolysis in ordinary pyrex glassware. The inevitable by-product from this method is benzophenone azine.

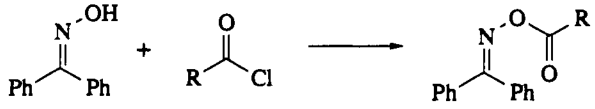

(5)

A second, more versatile, method involves the *O*-acyl thiohydroxamates.[6] These compounds are generally prepared[7] by reaction of acyl chlorides with the commercial sodium salt (1) of 2-mercaptopyridine *N*-oxide (equation 6; X = Cl). Use of mixed anhydrides formed by reaction of the carboxylic acid with isobutyl chloroformate (equation 6; X = $OCO_2CH_2CHMe_2$) renders the procedure compatible with unprotected indoles, phenols, secondary and, presumably, tertiary alcohols. An alternative mode of preparation[7] of the *O*-acyl thiohydroxamates involves the salt (2) in reaction with the carboxylic acid (equation 7).

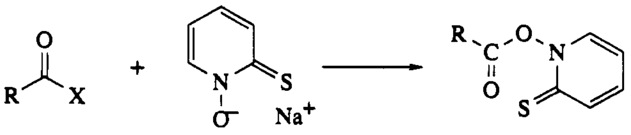

(6)

(1)

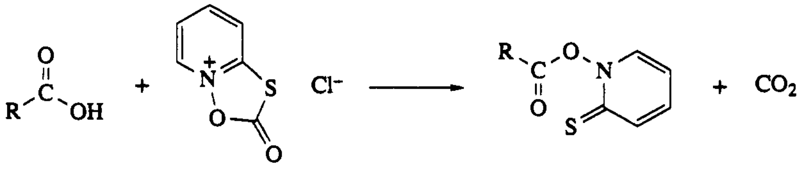

(7)

(2)

A wide variety of thiophilic radicals induce fragmentation of *O*-acyl thiohydroxamates by addition to the thiocarbonyl group, and in doing so generate carboxyl radicals (Scheme 1). After decarboxylation the

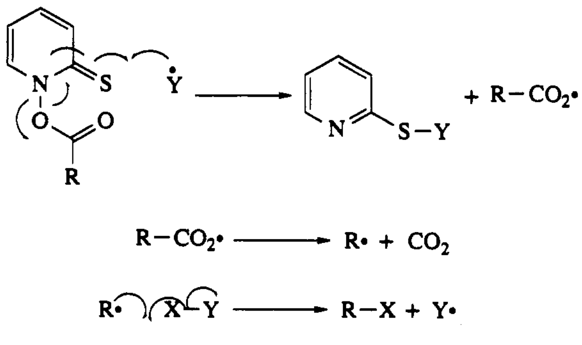

Scheme 1

alkyl radical can be trapped with a variety of radical-trapping reagents. The most efficient reactions occur when the radical trap X—Y (Scheme 1) is designed to release a new thiophilic chain-carrying radical (Y·) on trapping the alkyl radical, so setting up a chain mechanism. The reactions are initiated thermally in benzene or other appropriate solvents, or by simple white light photolysis.

## 5.4.3 REDUCTIVE DECARBOXYLATION

Reductive decarboxylation requires the generation of the carboxyl and hence the alkyl radical in the presence of a suitable hydrogen donor. Some modifications use the reaction solvent as hydrogen donor (cumene, *p*-cymene, *etc.*), others use added thiols or stannanes. This most basic of reactions has, until recently, been very little used in organic synthesis, owing perhaps to a shortage of suitable methodology for all but simple aliphatic compounds. The discovery of the *O*-acyl thiohydroxamates by the Barton[6] group has made reductive decarboxylation a much more practicable possibility.

Reductive decarboxylation of aryl and vinyl acids, not readily achieved by any of the methods described here, is best brought about by the classical copper/quinoline procedure.[8]

### 5.4.3.1 Peroxy Esters and Hydrogen Donor Solvents

The pyrolysis of *t*-butyl peroxy esters in suitable hydrogen donor solvents has been reviewed by Rüchardt.[9] The method involves the reaction of an acyl chloride with *t*-butyl hydroperoxide followed by thermolysis of the resulting peroxy ester in cumene or *p*-cymene. Yields are moderate, but the pyrolysis step tolerates a certain degree of functionality as illustrated in equation (8).[10] More recently, the use of ethyl phenylacetate as the pyrolysis solvent and hydrogen donor has been advocated.[11]

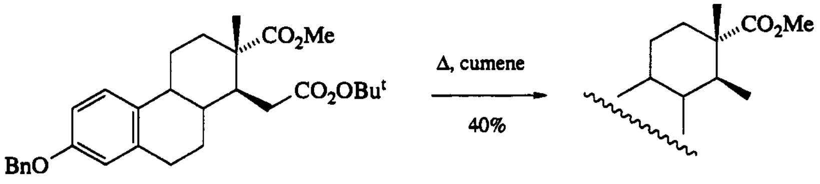

(8)

### 5.4.3.2 LTA and Hydrogen Donor Solvents

Reductive decarboxylation has been achieved by heating the acid with LTA in chloroform as solvent and hydrogen donor. Only a moderate number of examples are known.[12] The more facile oxidation of secondary and tertiary radicals by LTA effectively limits the method to primary carboxylic acids. It should be noted that stoichiometric quantities of trichloromethyl radicals are generated in the course of this reaction.

### 5.4.3.3 Persulfate Oxidation in Chloroform

Silver-catalyzed persulfate decarboxylation of carboxylic acids in chloroform provides the noralkane in modest to good yields.[13] Only a limited number of examples with simple aliphatic carboxylic acids are known.

### 5.4.3.4 *O*-Acyl Benzophenone Oximes and *t*-Butyl Thiol

The photolysis of *O*-acyl benzophenone oximes in isopropyl alcohol in the presence of *t*-butyl thiol leads to overall reductive decarboxylation. Yields for simple aliphatic and amino acids are reported to be good.[14] It is especially noteworthy that reductive decarboxylation of 2- and 4-quinolinecarboxylic acids (although not of the 3-isomer, nor 1- or 2-naphthalenecarboxylic acids) was achieved in moderate yield by this method (equation 9).

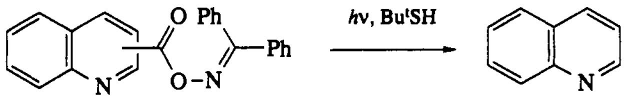

(9)

*ortho* 60%, *para* 40%

### 5.4.3.5 *O*-Acyl Thiohydroxamates and Tertiary Thiols

The free radical chain reaction of *O*-acyl thiohydroxamates with a tertiary thiol (*t*-butyl, triethylmethyl or more recently *t*-dodecyl) is by far the most wide-ranging reductive decarboxylation method described to date.[7] A wide variety of functional groups, including aldehydes, ketones, esters, amides, isolated and conjugated double bonds, are tolerated. Representative examples are given in equations (10)[7] and (11).[15]

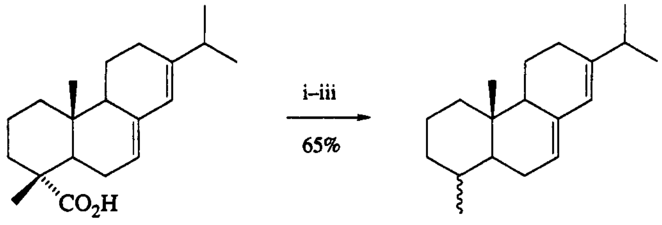

(10)

i, $(COCl)_2$; ii, (**1**); iii, $Bu_3SnH$, 80 °C

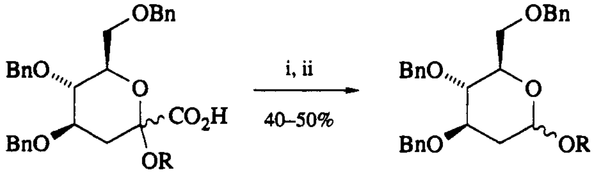

(11)

i, (**2**); ii, $R^1SH$, *hv*

### 5.4.3.6 Decarbonylation Methods

Overall reductive decarboxylation of a carboxylic acid may be achieved[16] by the reaction of the derived acyl chloride with triisopropylsilane (equation 12). Relatively high temperatures are required to bring about efficient decarbonylation of the intermediate acyl radical. A related method[17] involves the reaction of acyl phenyl selenides with tri-*n*-butyltin hydride. Here again relatively high temperatures are required for primary and secondary, although not for tertiary, acids (equation 13).

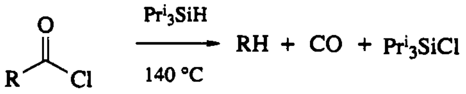

$$RCOCl \xrightarrow[140\ ^\circ C]{Pr^i_3SiH} RH + CO + Pr^i_3SiCl \qquad (12)$$

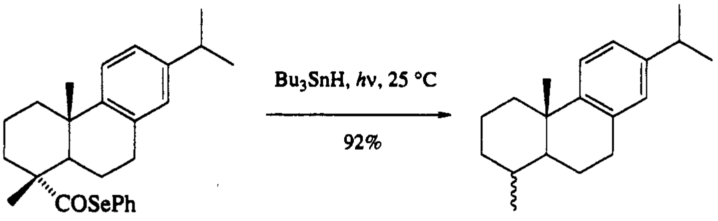

(13)

## 5.4.4 OXIDATIVE DECARBOXYLATION

### 5.4.4.1 LTA/Copper(II) Acetate and Carboxylic Acids

The oxidative decarboxylation of aliphatic carboxylic acids is best achieved by treatment of the acid with LTA in benzene, in the presence of a catalytic amount of copper(II) acetate. The latter serves to trap the radical intermediate and so bring about elimination, possibly through a six-membered transition state. Primary carboxylic acids lead to terminal alkenes, indicating that carbocations are probably not involved. The reaction has been reviewed.[4] The synthesis[18] of an optically pure derivative of L-vinylglycine from L-aspartic acid (equation 14) is illustrative. The same transformation has also been effected[13] with sodium persulfate and catalytic quantities of silver nitrate and copper(II) sulfate, and with the combination of iodosylbenzene diacetate and copper(II) acetate.[19]

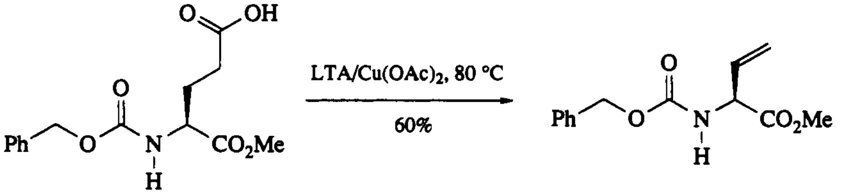

(14)

A mild, but indirect, approach to oxidative decarboxylation involves a modification[20] of the *O*-acyl thiohydroxamate decarboxylative rearrangement (Section 5.4.6.1). An *O*-acyl selenohydroxamate is photolyzed to give a noralkyl-2-pyridyl selenide which, after ozonolysis to the selenoxide, undergoes *syn* elimination to the alkene (equation 15).

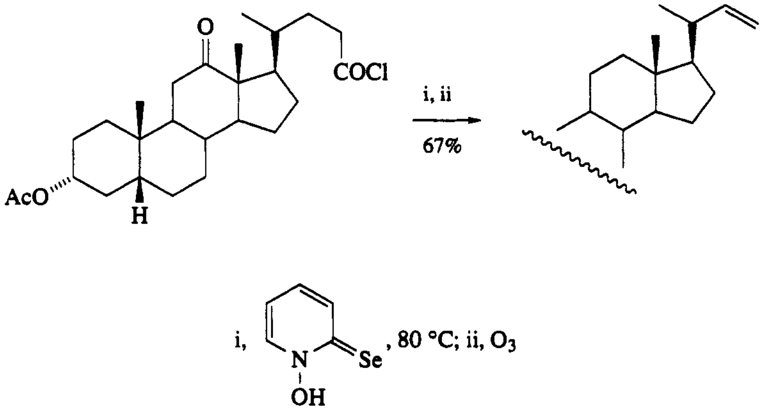

(15)

### 5.4.4.2 1,4-Dicarboxylic Acids

The oxidation of 1,4-dicarboxylic acids with LTA in benzene results in double decarboxylation with the formation of a double bond (equation 16).[4] Similarly, the pyrolysis of the di-*t*-butyl peroxy esters of 1,4-dicarboxylic acids in high boiling solvents leads to the formation of double bonds (equation 17).[21] The method is especially useful in so far as 1,4-diacids are readily available from Diels–Alder reactions using derivatives of maleic and fumaric acid as the dienophile. Apparently, application of the *O*-acyl thiohydroxamate method to 1,4-diacids does not result in the formation of double bonds but rather in the product of double decarboxylative rearrangement (Section 5.4.6.1).[22]

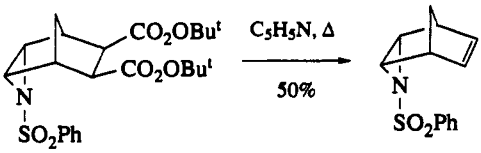

(16)

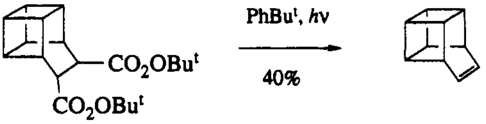

(17)

## 5.4.5 DECARBOXYLATIVE HALOGENATION

### 5.4.5.1 Acyl Hypohalites and Related Species

The classical Hunsdiecker reaction (equation 18), involving the reaction of silver carboxylates with halogens, and the various associated side reactions, has been reviewed several times. Optimum yields are obtained with bromine, followed by chlorine. Iodine gives acceptable yields provided that the correct stoichiometry of 1:1 is used. The reaction is most frequently carried out in tetrachloromethane at reflux. From a practical point of view, one drawback is the difficulty encountered in the preparation of dry silver carboxylates; the reaction of silver oxide on the acyl chloride in tetrachloromethane at reflux has been employed to circumvent this problem.[23] Evidently the use of molecular bromine limits the range of functional groups compatible with the reaction; the different reaction pathways followed by the silver salts of electron poor (equation 19) and electron rich (equation 20) aryl carboxylates illustrate this point well.

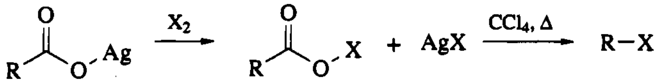

(18)

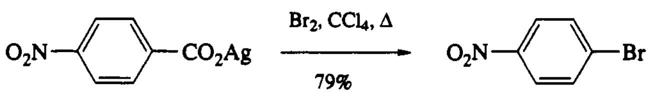

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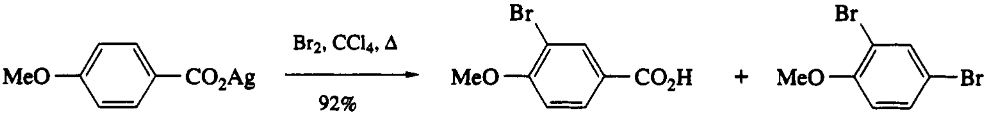

(20)

79 : 21

An alternative method for the formation of acyl hypoiodites, developed by Barton,[24] involves the treatment of the acid with *t*-butyl hypoiodite. Subsequent white light photolysis in benzene at room temperature gave good yields of iodides from primary, secondary and tertiary acids (equation 21). The method was not applicable in the presence of alcohols. A more recent technique[19] involving hypervalent iodine is due to Suarez: primary, secondary or tertiary aliphatic acids are heated to reflux in tetrachloromethane with iodosylbenzene diacetate and iodine resulting in good yields of iodides. The method is mild and, with obvious exceptions such as unprotected alcohols, is tolerant of many functional groups, as illustrated in equation (22).[25]

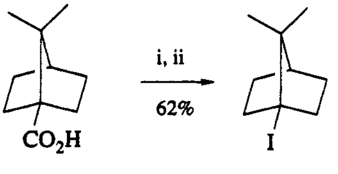

(21)

i, $Bu^tOI$; ii, $C_6H_6$, *h*ν

Decarboxylative fluorination, presumably *via* intermediate acyl hypofluorites, has been achieved[26] in low yield by passing a dilute stream of fluorine in nitrogen into aqueous solutions of sodium carboxylates. A somewhat more promising method, tolerant of aryl groups, ketones and ethers, involves reaction of a dichloromethane solution of the acid with xenon difluoride and hydrogen fluoride (equation 23).[27]

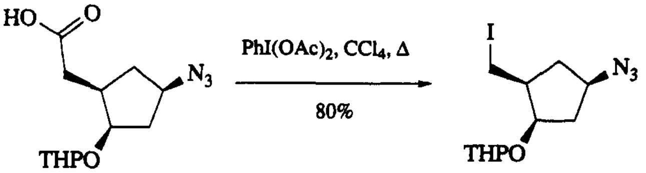

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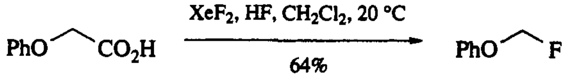

(23)

### 5.4.5.2 Mercury(II), Thallium(I) and Lead(IV) Salts

The difficulties and expense associated with the use of silver salts have led to the development of methods using other metal carboxylates. The modification of Cristol[2] involves the action of bromine on a mixture of the acid and red mercury(II) oxide in tetrachloromethane (equation 24). The procedure is easy to carry out and gives good yields with simple aliphatic carboxylic acids. However, concomitant formation of alkyl chlorides, particularly with highly reactive radicals from bridgehead acids, led several groups[28] to prefer bromotrichloromethane as reaction solvent. Iodine has been substituted for bromine leading to overall decarboxylative iodination (equation 25);[29] however, yields are no better than with the corresponding silver salt.

$$2RCO_2H + HgO + 2Br_2 \longrightarrow 2RBr + HgBr_2 + H_2O + 2CO_2 \qquad (24)$$

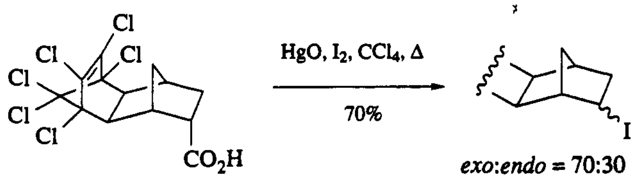

(25)

The use of stable, crystallizable thallium(I) carboxylates with bromine in tetrachloromethane at reflux has also been demonstrated[3] to be effective in bringing about overall decarboxylative halogenation, provided the correct stoichiometry (equation 26) is adhered to.

$$2RCO_2Tl + 3Br_2 \longrightarrow 2RBr + 2CO_2 + Tl_2Br_4 \qquad (26)$$

Two procedures exist for decarboxylative halogenation with LTA. In the first, reported by Barton,[24] the acid is treated with a combination of LTA and iodine in tetrachloromethane, providing good yields of iodides (equation 27). The second, complementary technique, uses a combination of LTA and a lithium halide in a solution of the acid in benzene at reflux.[4] Both lithium chloride and bromide have been employed to good effect leading, respectively, to alkyl chlorides and bromides. Carbocations are not involved; *t*-butylacetic acid gives neopentyl chloride free from *t*-amyl chloride. It is thought that the radical is trapped by halogen abstraction from a lead(IV) halogen complex. LTA can also be used in conjunction with NCS as the chlorine atom donor.[30]

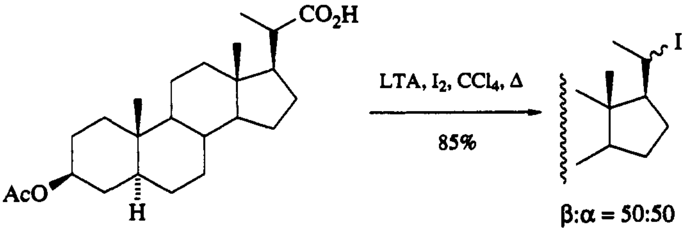

(27)

### 5.4.5.3 *O*-Acyl Thiohydroxamates and Halogen Donor Solvents

The photolytic or thermal decomposition of *O*-acyl thiohydroxamates in halogen donor solvents such as tetrachloromethane or bromotrichloromethane constitutes the most wide-ranging and generally applicable Hunsdiecker system currently available.[7] Decarboxylative iodination by this method uses iodoform as an iodine donor in benzene or, better, cyclohexene. The reactions proceed by chain mechanisms (Scheme 1; X—Y = Cl—$CCl_3$; Br—$CCl_3$; I—$CHI_2$) under very mild conditions; no free halogens or other strongly electrophilic species or oxidants and toxic metal salts are required. A wide variety of primary, secondary and tertiary acids, ranging from steroids[7] through terpenoids[7] to amino acids[19,31] (equation 28), have been subjected successfully to this variant of the Hunsdiecker reaction. The synthesis[32] of an α-chlorooxetane, albeit in low yield, by this method is worthy of particular note (equation 29).

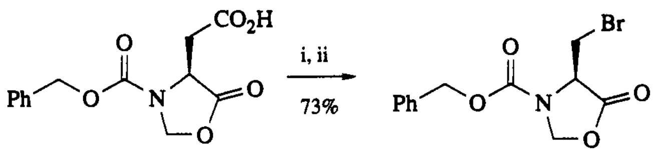

(28)

i, $ClCO_2CH_2CHMe_2$; ii, (1), $BrCCl_3$, *hν*

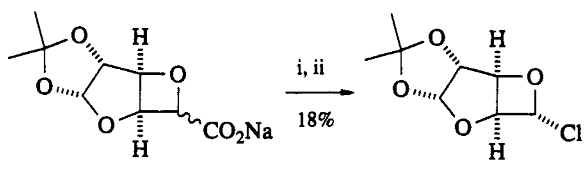

(29)

i, $(COCl)_2$, ii, (1), $CCl_4$, Δ

A variety of aromatic and vinylcarboxylic acids have also been decarboxylated by an adaptation[33] of this method involving the use of AIBN as chain initiator (equations 30 and 31). Unlike the classical Hunsdiecker reaction this variant is applicable to both electron poor and electron rich aryl acids without the risk of electrophilic aromatic halogenation.

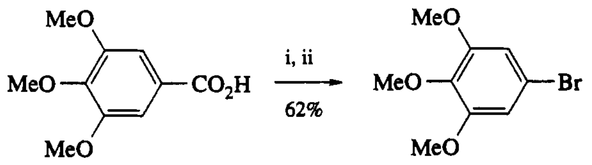

(30)

i, $(COCl)_2$; ii, (1), AIBN, $BrCCl_3$, Δ

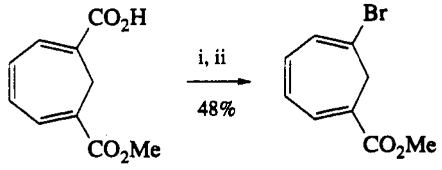

(31)

i, DCC, (1); ii, $BrCCl_3$, Δ

## 5.4.6 DECARBOXYLATIVE CHALCOGENATION AND PHOSPHORYLATION

With the exception of an isolated report[34] on the decomposition of diacyl peroxides in acetonitrile in the presence of copper(II) isothiocyanate and potassium thiocyanate (equation 32), the only preparative methods available for decarboxylative chalcogenation and phosphorylation make use of the *O*-acyl thiohydroxamates.

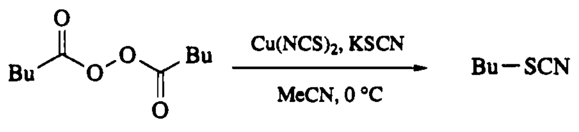

(32)

### 5.4.6.1 Sulfuration

Alkyl 2-pyridyl sulfides are formed on simple photolytic or thermal decomposition of *O*-acyl thiohydroxamates in the absence of other radical-trapping agents (equation 33).[7] Other mixed alkyl or alkyl aryl sulfides can be prepared[35] in good yield by irradiation of *O*-acyl thiohydroxamates in the presence of the appropriate dialkyl or diaryl disulfide at low temperature (equation 34).

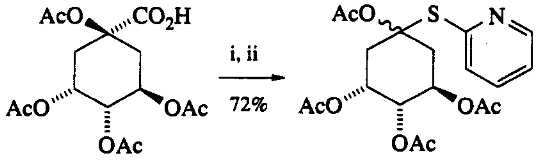
AcO
CO2H
AcO
OAc
OAc
i, ii
72%
AcO
S
N
AcO
OAc
OAc

(33)

i, $(COCl)_2$; ii, (1), 110 °C

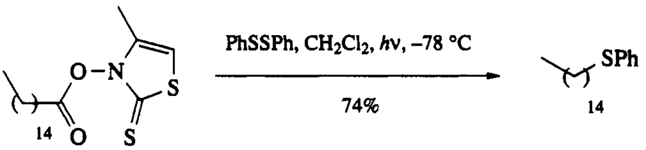
O–N
S
14
O
S
PhSSPh, CH2Cl2, hv, –78 °C
74%
SPh
14

(34)

Thiosulfonates can be synthesized[36] by photolysis of *O*-acyl thiohydroxamates in a 1:1 mixture of dichloromethane and sulfur dioxide at –10 °C (equation 35). For simple primary, secondary and tertiary carboxylic acids yields vary between 30% and 90%.

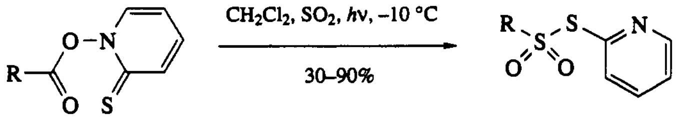
O–N
R
O
S
CH2Cl2, SO2, hv, –10 °C
30–90%
R
S
S
N
O
O

(35)

### 5.4.6.2 Selenation and Telluration

*O*-Acyl selenohydroxamates[6,20] decompose analogously to *O*-acyl thiohydroxamates (Section 5.4.6.1) to give alkyl 2-pyridyl selenides (equation 15). A more general method[35] for decarboxylative selenation or telluration makes use of the photolytic or thermal reaction of *O*-acyl thiohydroxamates with dialkyl or diaryl diselenides or ditellurides (equations 36 and 37). It is reported that under photolytic conditions at low temperature only a slight excess of diselenide or ditelluride is required in order to obtain high yields of mixed diselenides and ditellurides, respectively. A somewhat related method,[37] using dicyanogen triselenide as the radical trap, leads to alkyl selenocyanates.

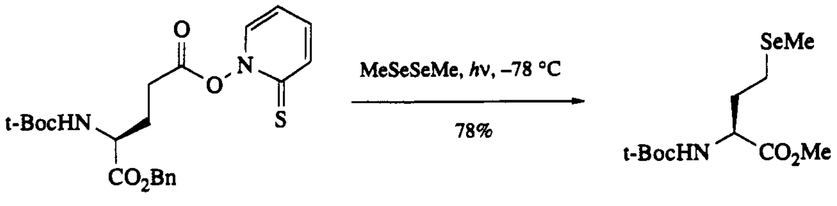
O
O
N
S
t-BocHN
CO2Bn
MeSeSeMe, hv, –78 °C
78%
SeMe
t-BocHN
CO2Me

(36)

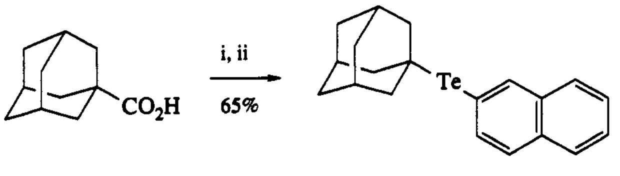
CO2H
i, ii
65%
Te

(37)

i, $(COCl)_2$; ii, (1), 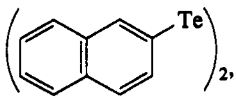 $_2$, 50–60 °C

### 5.4.6.3 Phosphorylation

The reaction of *O*-acyl thiohydroxamates with tris(phenylthio)phosphorus, initiated by adventitious oxygen at room temperature, leads in the first instance to alkylbis(phenylthio)phosphines (Scheme 2) by a chain mechanism. Combination of the latter with the disulfide by-product affords a phosphorus(V) species which on work-up gives alkylbis(phenylthio)phosphonates (Scheme 2 and equation 38) with moderate to good yields.[38] This reaction sequence provides a convenient method for the overall transformation of a carboxylic acid into a readily hydrolyzable ester of the analogous phosphonic acid.

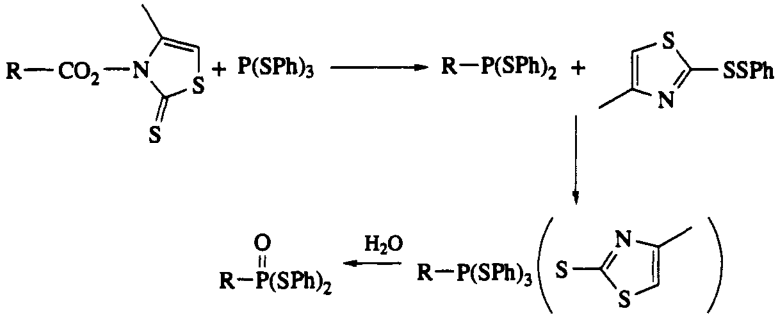

Scheme 2

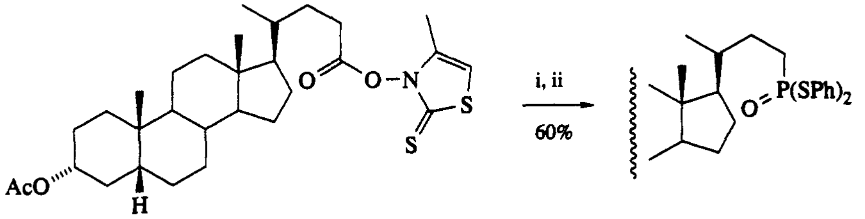

(38)

i, (PhS)$_3$P; ii, H$_2$O

## 5.4.7 DECARBOXYLATIVE OXYGENATION

Acetate esters are common by-products of LTA decarboxylation procedures.[4] The yield of these products, derived from further oxidation of the alkyl radical and quenching of the subsequent carbocation by acetate ions, can be improved by working in acetic acid in the presence of potassium acetate. Selective monodecarboxylation of 1,3- and 1,4-dicarboxylic acids leads, *via* an analogous mechanism, to γ- and δ-lactones in moderate to good yields, as illustrated in equation (39).

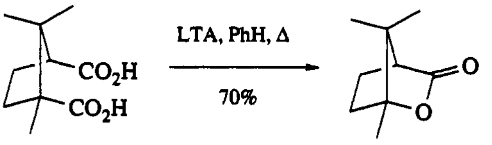

(39)

Simple alcohols can be obtained from the decomposition of peroxy acids in cyclohexane or benzene at reflux. This chain reaction, which is efficient for adamantane-1-carboxylic acid (equation 40), is unfortunately usually complicated by side reactions involving hydrogen abstraction from the substrate or solvent.[39]

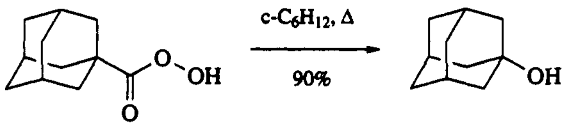

(40)

A more efficient and general procedure once again involves the *O*-acyl thiohydroxamates. Decomposition in the presence of triplet oxygen, and *t*-butyl thiol as hydrogen donor, provides noralkyl hydroperoxides. In the original procedure,[7] hydroperoxides obtained in this manner were not normally isolated but immediately reduced *in situ* with trimethyl phosphite to the corresponding alcohols (equation 41). An alternative work-up (equation 42)[7] involves *in situ* treatment of the hydroperoxide with *p*-toluenesulfonyl chloride and pyridine resulting in the isolation of carbonyl compounds. One problem associated with this system is the difficulty encountered in maintaining a suitable concentration of *t*-butyl thiol in the solution during the passage of oxygen. A solution involves the replacement of *t*-butyl thiol with the less volatile triethylmethyl thiol. In this manner,[40] it is possible to prepare and isolate hydroperoxycyclooct-4-ene from cyclooctene-5-carboxylic acid (equation 43).

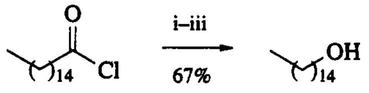

(41)

i, (1); ii, $O_2$, Bu$^t$SH, *hν*; iii, $(MeO)_3P$

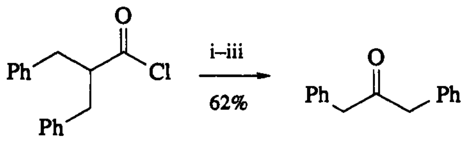

(42)

i, (1); ii, $O_2$, Bu$^t$SH, *hν*; iii, TsCl, $C_5H_5N$

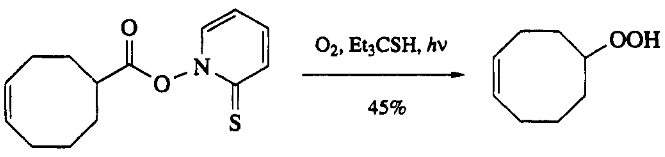

(43)

In an alternative sequence,[41] *O*-acyl thiohydroxamates are reacted with tris(phenylthio)antimony to give the corresponding alkylbis(phenylthio)antimony compound. On admission of air this latter species undergoes oxygen insertion and rearrangement. Finally, hydrolysis provides the alcohol (Scheme 3 and equation 44).

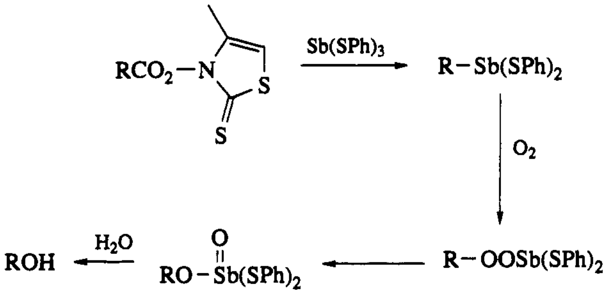

**Scheme 3**

Finally, a useful, although not strictly a radical, method of effecting decarboxylative oxygenation is the so-called carboxy inversion reaction. The activated acid is transformed into a mixed alkyl aryl diacyl peroxide which suffers decarboxylative rearrangement to the alkyl ester of the aryl acid. This reaction is particularly useful as it takes place with retention of configuration at the migrating center (equation 45).[42]

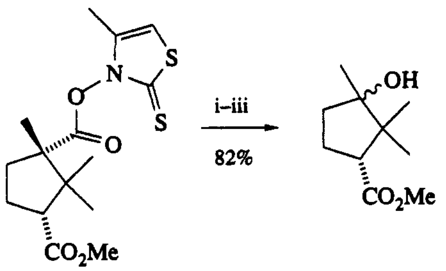

(44)

i, $Sb(SPh)_3$; ii, $O_2$; iii, $H_2O$

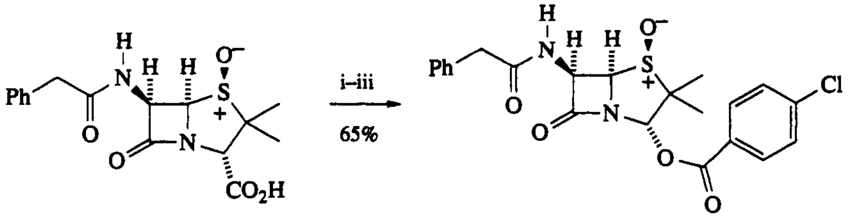

(45)

i, EtOCOCl; ii, MCPBA, −10 °C; iii, −10 °C to 0 °C

### 5.4.8 DECARBOXYLATIVE AMINATION

The overall transformation of a carboxylic acid into an amide or carbamate or similar nitrogen-containing function is best achieved by one or other of the Hofmann, Curtius, Schmidt, Lössen and related reactions.

Efficient preparative sequences involving radical decarboxylation followed by carbon–nitrogen bond formation are rare. Acyl nitrates decompose at elevated temperatures to give nitroalkanes (equation 46),[43] but are unfortunately explosive and have to be prepared *in situ* and stored in solution. A noteworthy exception[44] is found in the thermal or photochemical decarboxylation of tetrahydro-1,2-oxazine-3,6-diones leading to β-lactams (equation 47). Doubtless a key factor in this reaction, considered to proceed *via* a radical cage mechanism, is the intramolecular nature of the carbon–nitrogen bond formation.

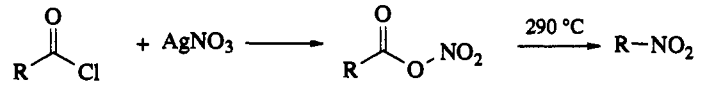

(46)

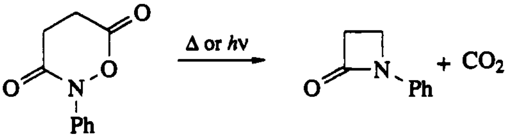

(47)

### 5.4.9 DECARBOXYLATION WITH SUBSEQUENT C—C BOND FORMATION

Alkyl radicals derived by decarboxylation of carboxyl radicals may be added to carbon–carbon multiple bonds resulting in an overall homologation of the starting acid. This reaction type is not strictly a C—C bond oxidation; nevertheless, one of the key steps is C—C bond cleavage by decarboxylation and it is appropriate to briefly consider the scope of such reactions here. A more complete description of inter- and intra-molecular radical C—C bond-forming reactions is given in Volume 4, Chapters 4.1 and 4.2.

### 5.4.9.1 Addition to C—C Multiple Bonds

Decarboxylation of aliphatic acids by means of their derived *O*-acyl thiohydroxamates in the presence of an electron deficient terminal alkene results in the overall addition of an alkyl radical and a 2-pyridylthiyl radical across the double bond (equation 48).

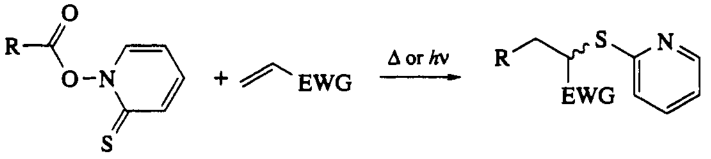

(48)

The alkyl radical, R·, may be any primary, secondary or tertiary radical compatible with the formation of the *O*-acyl thiohydroxamate. The alkene is activated towards radical addition by any strongly electron-withdrawing group, commonly esters, ketones, nitriles and nitro[45,46] groups but also sulfones and phosphonium[47] groups. A recent report[48] has shown that the use of chiral electron-withdrawing groups in this reaction gives moderate levels of asymmetric induction at the newly formed chiral center. With the exception of 1-nitro-1-propene,[46] examples of addition to singly activated internal alkenes are very rare. Doubly activated alkenes such as maleic anhydride undergo the standard addition reaction but suffer *in situ* elimination of the sulfide moiety, thereby providing[45] an excellent route to diversely alkylated maleic anhydrides (Scheme 4). Under thermal conditions, 1,4-benzoquinone behaves in a similar manner to give moderate yields of 2-alkyl-1,4-benzoquinone;[45] however, if the reaction is carried out photochemically at low temperature the main product is the 2-alkyl-3-(2-pyridylthio)-1,4-benzoquinone.[49] Evidently, the primary addition product evolves along different pathways depending on the reaction conditions. Radical alkylation of 1,4-quinones[50] may also be achieved in moderate yield by LTA decarboxylation of alkanoic acids in the presence of the quinone.

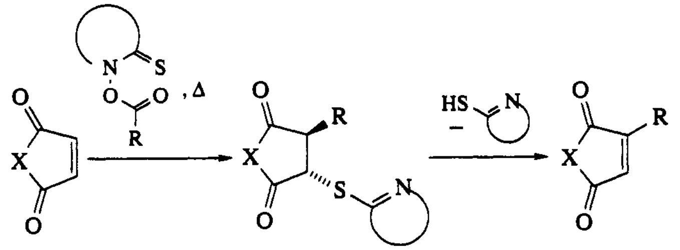

X = O, CMe$_2$, CH=CH

Scheme 4

Electron deficient terminal alkenes substituted with an alkyl- or aryl-thiomethylene group at the 2-position react efficiently with *O*-acyl thiohydroxamates by a distal addition/elimination sequence,[46,51] as illustrated in equation (49). Alkene polymerization is not a competing side reaction in this process.

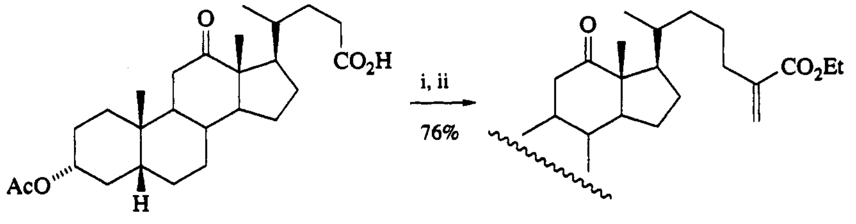

(49)

i, (COCl)$_2$; ii, (1), 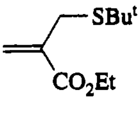 , 130 ° C

$CH_2{=}C(SBu^t)CO_2Et$

The decarboxylation of perfluoroalkanoic acids may also be achieved *via* the *O*-acyl thiohydroxamates. When carried out in the presence of electron rich alkenes such as ethyl vinyl ether the perfluoroalkyl radical adds to the terminal position of the double bond in moderate to good yields (equation 50).[52] This method provides an attractive alternative to the addition of perfluoroalkyl iodides to alkenes.

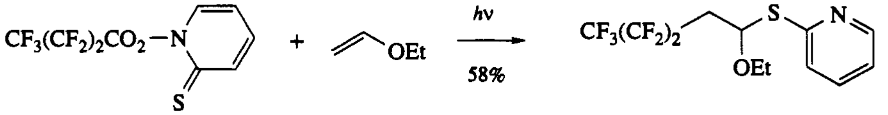

(50)

5-Hexenyl radicals cyclize to cyclopentylmethyl radicals (see Volume 4, Chapter 4.2). Thus radical decarboxylation of 6-heptenoic acids, by whatever means, usually results in the formation of five-membered rings. Although this fact had been appreciated previously[1] it is only recently,[45] with the advent of the *O*-acyl thiohydroxamates, that it has been exploited from a synthetic point of view. An example is provided by the synthesis[53] of bicyclo[4.3.0]proline derivatives from aspartic acid carried out by the Barton group (equation 51). It will be noted that activation of the C—C double bond acting as a radical trap is not necessary in these intramolecular reactions.

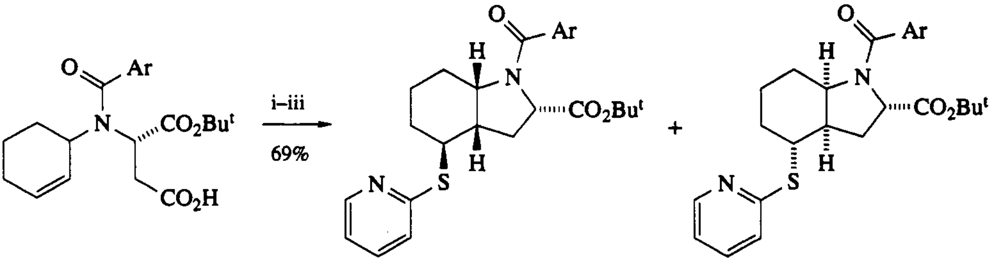

(51)

i, $Me_2CHCH_2OCOCl$; ii, (1); iii, hν

Radical addition to C—C triple bonds is also possible with the *O*-acyl thiohydroxamate methodology. As with addition to C—C double bonds (*vide supra*), the triple bond must be either terminal and activated with an electron-withdrawing group (equation 52) or doubly activated if internal.[45]

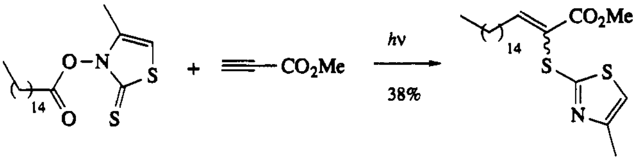

(52)

### 5.4.9.2 Addition to C–Heteroatom Multiple Bonds

The one-carbon homologation of alkyl radicals by trapping with C–heteroatom multiple bonds is at present extremely rare. Preparative procedures, using *t*-butyl isocyanide and formaldehyde oximes as one-carbon radical traps, have only recently appeared.[54] Application of such procedures to radicals obtained by decarboxylation methods provides a means of reforming the original acid. This is a potentially important reaction sequence as the use of a $^{13}C$- or $^{14}C$-labeled trap will afford the isotopically labeled acid. The methodology for such a sequence has recently been published by the Barton group.[55] Thus photolysis of *O*-acyl thiohydroxamates in the presence of an isocyanide in which the electron density of carbon is reduced by an electron-withdrawing substituent, as for example in 4-nitrophenyl isocyanide and protonated 3-pyridyl isocyanide, leads after aqueous work-up to the amide of the original acid. Hydrolysis to the acid can then be achieved by various methods. The application of this sequence to arachidonic acid (equation 53) provides a further illustration of the mildness and applicability of the *O*-acyl thiohydroxamate chemistry.

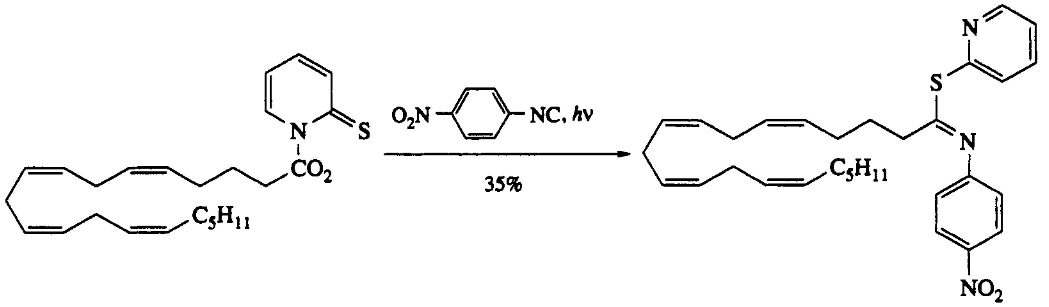

(53)

### 5.4.9.3 Addition to Aromatic Systems

Decarboxylation of alkanoic acids by means of LTA in benzene as solvent is hindered by the formation of alkylbenzenes as by-products. This side reaction is especially pronounced with radicals derived from primary acids or other acids from which the radical is not easily oxidized by LTA. In some cases, such as that of apocamphane-1-carboxylic acid (equation 54),[56] good yields of alkylbenzene can be obtained. Intramolecular versions of this reaction in which the radical cyclizes onto an aromatic nucleus at the appropriate position in the chain have also been observed.

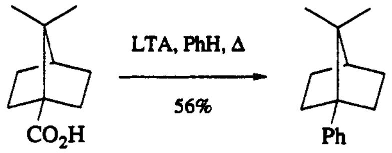

(54)

In an analogous manner, the generation of alkyl radicals in benzene solution by the *O*-acyl oxime method results in the formation of alkylbenzenes with moderate to good yields for simple acids (equation 55).[57] Use of pyridine as solvent leads to the formation of alkylpyridines as mixtures of *ortho*, *meta* and *para* isomers in which the *para* isomer predominates. The *O*-acyl benzophenone oxime chemistry can also be applied to aryl acids in benzene or pyridine, resulting in the formation of mixed biaryls.[5] A closely related method[58] involves photolysis of mixed anhydrides of arenecarboxylic acids with the hydroxamic acid *N*-hydroxy-2-pyridone in benzene solution (equation 56).

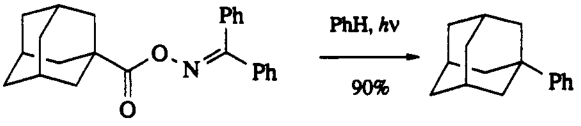

(55)

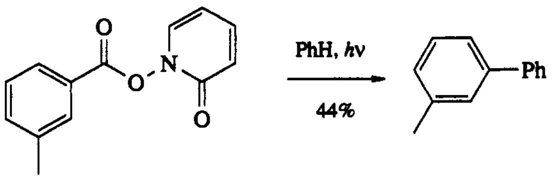

(56)

The simple photolytic or thermal decomposition of *O*-acyl thiohydroxamates in benzene or pyridine as solvent yields the product of decarboxylative rearrangement, and not alkylbenzenes or alkylpyridines. However, photolysis in dichloromethane in the presence of *protonated* heteroaromatic bases results in the formation of alkylated heterocycles in good yield, as illustrated in equation (57).[59] The great advantage of this latter method lies in the fact that the base to be alkylated is not used as the reaction solvent, which evidently permits the use of a much wider range of bases as trapping agents.

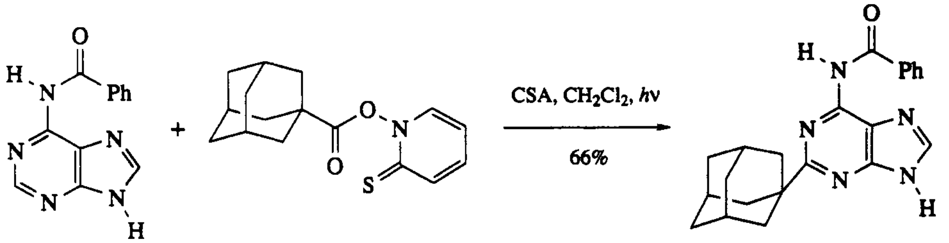

(57)

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# 6.1
# Oxidation of Nitrogen and Phosphorus

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## 6.1.1 INTRODUCTION

The aim of this chapter is to describe the main types of functional group interconversion which involve oxidation at nitrogen or phosphorus. 'Oxidation' has been interpreted as including nitrosation, amination, halogenation and other reactions in which attack by an electrophilic heteroatom takes place. The material has been organized on the basis of the nature of the starting materials and the products, rather than on the mechanism of oxidation or the type of oxidant. For example, no attempt has been made to cover comprehensively the chemistry of aminium cation radicals[1] or of aminyl radicals[2] which can occur as intermediates in the oxidation of amines (Scheme 1). Also, oxidation which results in reaction at carbon, such as radical coupling through carbon or reaction at a C—H bond adjacent to nitrogen, is not covered in any detail here, even if the initial oxidation occurs at nitrogen. Reactions of C—H bonds activated by nitrogen are described in Chapter 2.5 of this volume. The biological oxidation of amines and other organic nitrogen compounds has also been reviewed elsewhere.[3]

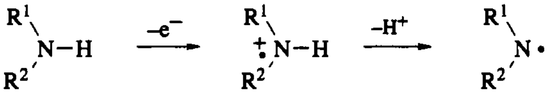

Scheme 1

Of the many reviews on oxidation which are available, two in particular provide detailed coverage of the literature up to the early 1980s on aspects of oxidation at nitrogen. One of these, by Boyer, is a comprehensive survey of oxidation reactions of nitrogen compounds in which the number of oxygen atoms attached to nitrogen is increased.[4] The other, by Rosenblatt and Burrows, deals with oxidation of amines.[5] References to the primary literature have not always been included here if they are available from these two reviews.

## 6.1.2 OXIDATION OF THE $NH_2$ GROUP

### 6.1.2.1 Primary Amines

### *6.1.2.1.1 Oxidation to hydroxylamines, nitroso compounds and nitro compounds*

Aromatic and aliphatic primary amines can be oxidized to the corresponding nitro compounds by peroxy acids and by a number of other reagents.[5,6] The peroxy acid oxidations probably go by way of intermediate hydroxylamines and nitroso compounds (Scheme 2). Various side reactions can therefore take place, the nature of which depends upon the structure of the starting amine and the reaction conditions. For example, aromatic amines can give azoxy compounds by reaction of nitroso compounds with hydroxylamine intermediates; aliphatic amines can give nitroso dimers or oximes formed by acid-catalyzed rearrangement of the intermediate nitrosoalkanes (Scheme 3).

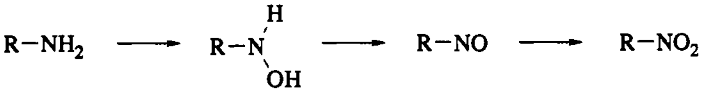

$$R{-}NH_2 \longrightarrow R{-}N(H)OH \longrightarrow R{-}NO \longrightarrow R{-}NO_2$$

Scheme 2

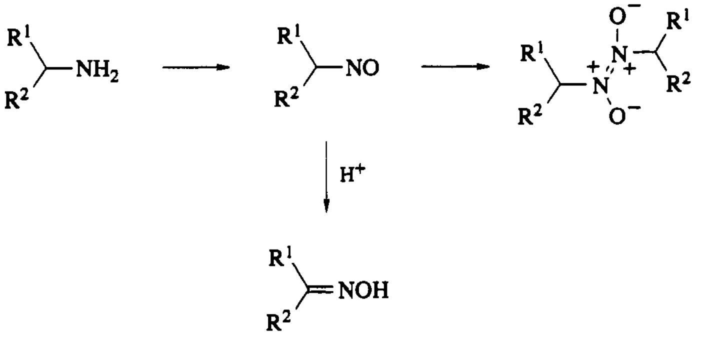

Scheme 3

MCPBA has been regarded as the reagent of choice for the conversion of primary aliphatic amines into the corresponding nitro compounds.[5] The peroxy acid must be used in excess to minimize formation of dimers of the intermediate nitroso compounds. The yield of nitroalkane is also increased if the reaction is carried out at elevated temperature, since this favors the monomeric rather than the dimeric form of the intermediate nitrosoalkane and allows it to be oxidized further.[7] For example, cyclohexylamine gave the dimer of nitrosocyclohexane (43%) when oxidized by MCPBA at 23 °C, but at 83 °C (in boiling 1,2-dichloroethane) the only product was nitrocyclohexane (86%).

Ozone is an alternative oxidant for aliphatic primary amines.[8] The yields are generally not as good as with MCPBA, although a technique of 'dry ozonation' on silica at low temperature has been described which results in good conversions of cyclohexylamine and other aliphatic primary amines into the corresponding nitro compounds.[9] Solid sodium permanganate has been used to prepare 2-methyl-2-nitropropane from *t*-butylamine in good yield.[10] An oxidant which has given excellent yields of both aromatic and aliphatic nitro compounds from the corresponding amines is dimethyldioxirane (**1**).[11] The reagent is readily prepared *in situ* from acetone and a commercial oxidant, Oxone. When used under phase transfer conditions it is a mild, nonacidic oxidant which allows the selective oxidation of aromatic amines in the presence of indoles and furans. This reagent has also been used for the selective oxidation of primary amines to hydroxylamines.[12]

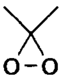
(1)

Aromatic primary amines have also been converted into the corresponding nitro compounds with peroxy acids: trifluoroperacetic acid, peroxymaleic acid and peracetic acid have all been used. A good alternative reagent for aromatic amines bearing electron-withdrawing substituents is sodium perborate in acetic acid. 4-Nitrobenzonitrile was prepared (91%) from 4-aminobenzonitrile with this reagent.[13] Hindered aromatic amines are oxidized only to the nitroso compounds: MCPBA[14] and perbenzoic acid[15] in stoichiometric amounts give the nitroso compounds in good yield. Thus, 2,6-difluoroaniline is oxidized to 2,6-difluoronitrosobenzene (85%) by perbenzoic acid, and other 2,6-disubstituted anilines react in a similar way. Fremy's salt can also oxidize hindered arylamines to the nitroso compounds.[4] Partial oxidation of *o*-phenylenediamine to 2-nitrosoaniline was achieved by dropwise addition of peracetic acid to the diamine.[4]

Corey and Gross have made use of the peracetic acid oxidation of *t*-butylamine and other tertiary amines to nitrosoalkanes in a synthesis of di-tertiary alkylamines.[16] This is illustrated in Scheme 4 by the synthesis of di-*t*-butylamine. Cyclohexylamine and other alkylamines have been oxidized to the nitroso compounds in high yield by a reagent consisting of sodium percarbonate, sodium hydrogen carbonate and tetraacetylethylenediamine in aqueous dichloromethane.[17] Several nitrosoalkanes have also been obtained from the corresponding amines by oxidation with aqueous hydrogen peroxide and sodium tungstate;[4] various other metal catalysts, including titanium(IV) and vanadium(V) species, have been used in combination with *t*-butyl hydroperoxide.[18] A procedure has been described for the low temperature oxidation of trimethylsilylamines to oximes, by way of the nitroso compounds (Scheme 5): the oxidant is

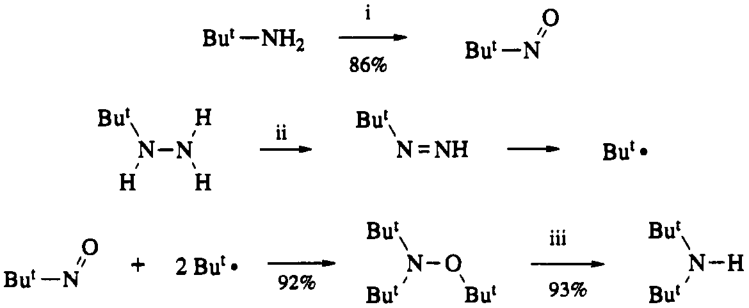

i, $MeCO_3H$, ii, $PbO_2$; iii, sodium naphthalenide

**Scheme 4**

dry air, which reacts with the lithium salts of the amines.[19] This reaction is tolerant of phosphines, sulfides and other functional groups which are susceptible to oxidation.

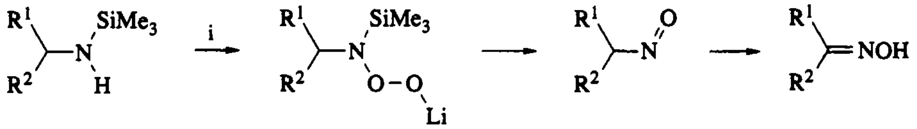

i, BuLi, dry air, –60 to –40 °C

Scheme 5

Hydroxylamines are commonly postulated as intermediates in these oxidations, but they are rarely isolated or detected. Two examples of reactions in which products at the hydroxylamine oxidation level can be isolated both involve peroxides. Oxidation of alkylamines (**2**; R = Bu$^t$, Me and $PhCH_2$) with arenesulfonyl peroxides bearing an electron-withdrawing group gave the arenesulfonyloxyamines in good yields (Scheme 6).[20] A similar reaction of primary amines with dibenzoyl peroxide gave benzoyloxyamines.[21]

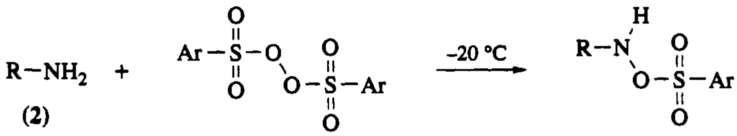

Scheme 6

### 6.1.2.1.2 Oxidation to azo compounds and related dehydrogenation

Aromatic azo compounds can be obtained by the oxidation of primary arylamines. The reagent most widely used for this purpose is activated manganese dioxide.[22] This converts aniline and substituted anilines into the corresponding azo compounds in moderate to good yield.[23] At room temperature the products are the *cis*-azobenzenes, which are isomerized to the *trans* compounds on heating.[24] It is probable that hydrazobenzenes are intermediates in the reaction, but these are more easily oxidized than the starting anilines (Scheme 7). These oxidations are inhibited by electron-withdrawing substituents and some nitro-substituted anilines fail to react.

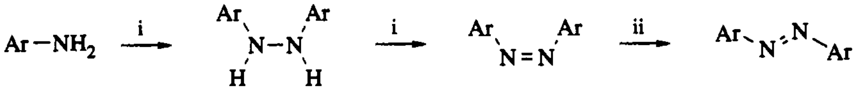

i, $MnO_2$; ii, heat

Scheme 7

Nickel peroxide also oxidizes anilines to azoarenes.[25] Yields are moderate, although nitroanilines can also be oxidized with this reagent. Other reagents which have been used are silver oxide on Celite,[26] lead(IV) acetate[27] and barium manganate (which is claimed to give azo compounds in higher yield than manganese dioxide).[28] Bispyridinesilver permanganate, $py_2Ag^+MnO_4^-$, which is soluble in polar organic solvents, is also a good alternative to manganese dioxide.[29] Sodium perborate is a convenient oxidant for the conversion of *para*-substituted anilines into azo compounds.[30] Sodium hypochlorite has been used for the oxidation of pentachloroaniline and other chlorinated anilines,[31] while potassium superoxide is capable of selectively oxidizing *ortho*- and *para*-substituted diamines and aminophenols to the corresponding azo compounds in good yield.[32] Thus, 2-aminophenol gave the azo compound (**3**; 70%),

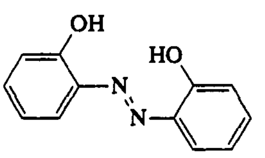

(**3**)

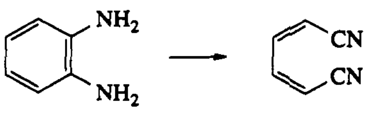

(**4**)

whereas *meta*-substituted anilines failed to react. Oxidation of the anilines to aminyl radicals, followed by their combination to hydrazobenzenes, can account for the observed selectivity.

Manganese dioxide and potassium superoxide both oxidize *o*-phenylenediamine to the azo compound, but the more powerful oxidants nickel peroxide and lead(IV) acetate cause ring cleavage; the product, which can be isolated in low to moderate yield, is the (*Z*,*Z*)-dinitrile (**4**). This oxidative cleavage can be brought about in high yield with oxygen in the presence of copper(I) chloride and pyridine.[33] Some five-membered heteroaromatic amines can be cleaved to nitriles on oxidation: an example is the amine (**5**; Scheme 8) which undergoes ring opening on oxidation by lead(IV) acetate.[34]

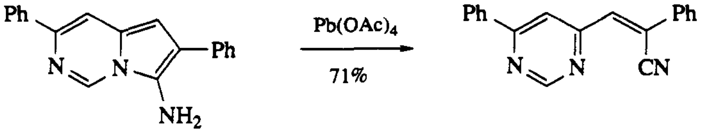

(**5**)

**Scheme 8**

Nitriles are also the usual products of oxidation of aliphatic amines $RCH_2NH_2$ by nickel peroxide and lead(IV) acetate. Aliphatic azo compounds can be prepared from these primary amines by first converting them into sulfamides (**6**), these then being oxidized with sodium hypochlorite or (better) *t*-butyl hypochlorite (Scheme 9).[35] A few aliphatic azo compounds can be formed in good yield by direct oxidation of *t*-alkylamines; for example, AIBN was formed (86%) by oxidation of the amine $Me_2C(CN)NH_2$ with sodium hypochlorite. A special case of azoalkane formation is the synthesis of chlorodiazirines (**7**) from amidines $RC({=}NH)NH_2$ by oxidation with sodium hypochlorite.[36]

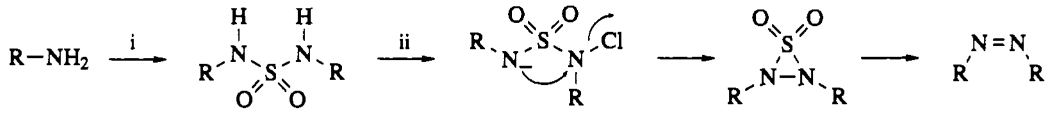

(**6**)

i, $SO_2Cl_2$, pyridine; ii, Bu$^t$OCl, Bu$^t$OK

**Scheme 9**

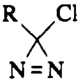

(**7**)

Oxidation of primary aromatic amines bearing a nucleophilic substituent at the *ortho* position can provide a useful route to some heterocyclic compounds. Some examples, shown in Scheme 10, are syntheses of benzofuroxans,[37] benzotriazoles[38] and benzisoxazoles.[39]

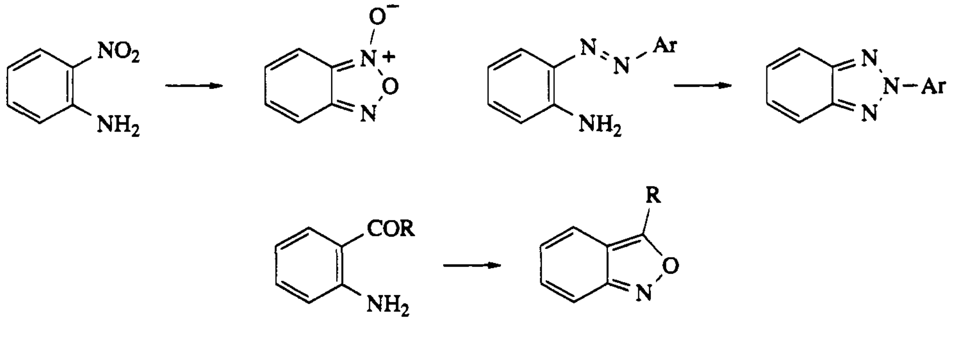

**Scheme 10**

### *6.1.2.1.3 Diazotization*

The formation of aromatic diazonium salts from aromatic primary amines is one of the oldest synthetic procedures in organic chemistry. Methods based on nitrosation of the amine with nitrous acid in aqueous solution are the best known, but there are variants which are of particular use with weakly basic amines and for the isolation of diazonium salts from nonaqueous media. General reviews include a book by Saunders and Allen[40] and a survey of preparative methods by Schank.[41] There are also reviews on the diazotization of heteroaromatic primary amines[42] and on the diazotization of weakly basic amines in strongly acidic media.[43] The diazotization process (Scheme 11) goes by way of a primary nitrosamine.

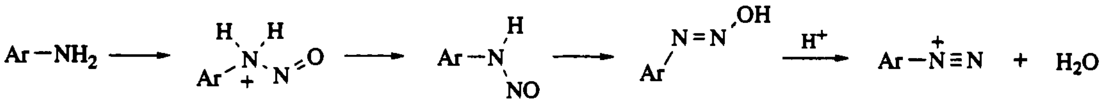

**Scheme 11**

If the amine is basic enough to form a salt with dilute mineral acids in aqueous solution, the normal diazotization method of adding sodium nitrite in aqueous solution to a solution or suspension of the amine salt is satisfactory. Variations in the order of addition of the reagents are sometimes used, for example, when there is another functional group present which is sensitive to nitrous acid, or if the amine salt is very insoluble.[40] Weakly basic amines can often be diazotized successfully either in concentrated sulfuric acid or in a mixture of sulfuric acid with acetic or phosphoric acid.[43] It is likely that nitrosylsulfuric acid is formed on addition of sodium nitrite to concentrated sulfuric acid, and that this is the nitrosating agent when the amine is subsequently added.

Diazotization in organic solvents allows solid diazonium salts to be isolated. Diazotization can be carried out using an ester of nitrous acid, such as pentyl nitrite, in a solvent such as acetic acid or methanol. A procedure has also been described for isolating diazonium tetrafluoroborates, in excellent yield, by carrying out the diazotization with boron trifluoride etherate and *t*-butyl nitrite in ether or dichloromethane at low temperature.[44] Another method for the preparation of a variety of diazonium salts in a nonaqueous medium makes use of the chemistry of bis(trimethylsilyl)amines (**8**).[45] These compounds react in dichloromethane with nitrosyl chloride and other nitrosating agents which are generated *in situ*. Thus, benzenediazonium chloride was isolated (96%) from bis(trimethylsilyl)aniline.

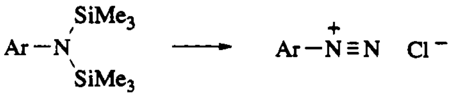

$Ar-N(SiMe_3)_2 \longrightarrow Ar-\overset{+}{N}\equiv N\ Cl^-$

**(8)**

The diazotization of aromatic amines with a nucleophilic substituent at the *ortho* position is a common method of synthesis of benzo-fused heterocyclic compounds with two or more contiguous nitrogen atoms. Benzotriazoles (**9**), benzotriazinones (**10**), and benzothiadiazoles (**11**) are examples of heterocyclic ring systems that can be prepared in this way.

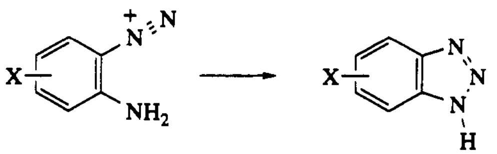

**(9)**

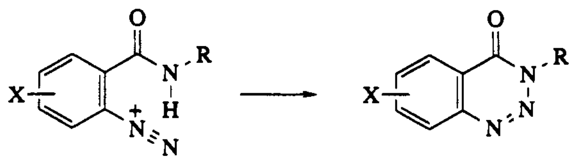

**(10)**

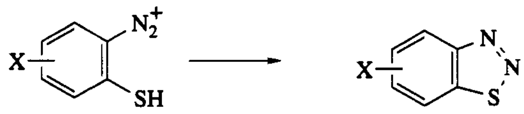

**(11)**

### 6.1.2.1.4 Amination

Simple primary alkylamines can be converted into the corresponding monoalkylhydrazines in moderate yield by amination with chloramine or with hydroxylamine-*O*-sulfonic acid.[46] The method is tolerant of the presence of double bonds: allylhydrazine was prepared (52%) by reaction of chloramine with allylamine. The method is not generally applicable to the preparation of 1,2-disubstituted hydrazines from primary alkylamines and *N*-chloroalkylamines although intramolecular examples are known.[47] Tetrahydropyrazole was prepared in moderate yield in this way (Scheme 12) and piperazine was prepared in low yield by the same type of reaction.

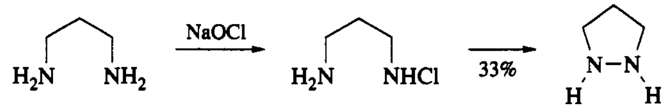

**Scheme 12**

### 6.1.2.1.5 Halogenation, sulfenylation and related reactions

Methods for the *N*-chlorination and *N*-bromination of amines have been reviewed.[48] Alkylamines are chlorinated by aqueous sodium hypochlorite, chlorine in aqueous sodium bicarbonate, *N*-chlorosuccinimide, or *t*-butyl hypochlorite at low temperature. By using the appropriate amount of chlorinating agent, selective mono- and di-chlorination can be achieved. Although some of these compounds, especially those derived from *t*-alkylamines, are stable enough to be isolated, the majority are unstable since they can undergo further reaction associated with the loss of a proton from the α-carbon atom. *N*-Chloroanilines are also unstable unless the ring is substituted by an electron-withdrawing group, because of the tendency of the chlorine to migrate to a ring carbon atom. Reagents which have been used for *N*-bromination include bromine and aqueous sodium hypobromite. *N*-Haloamines have also been prepared by the action of the appropriate halogens on *N*-trimethylsilylamines. An indirect method of *N*,*N*-difluorination of *t*-alkylamines is illustrated in Scheme 13.[49]

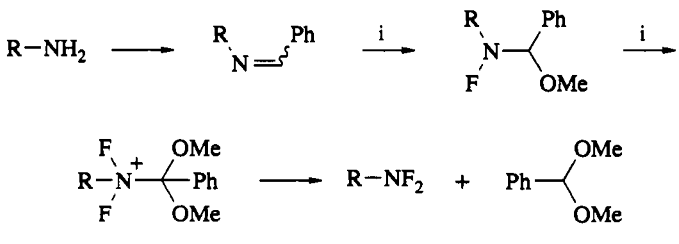

i, $CF_3OF$, MeOH

**Scheme 13**

The reaction of primary amines with arenesulfenyl halides leads to the formation of sulfenamides (**12**).[50] These compounds are most stable when the aryl group has electron-withdrawing substituents at the 2- and 4-positions. Selenamides are formed in an analogous manner but are somewhat less stable: aliphatic amines give isolable compounds, but most anilines react with selenyl halides to give products of ring substitution.[51] An example of an isolable selenamide is compound (**13**), which was prepared (79%) from the amine and 2-nitrobenzeneselenyl chloride.[52] This compound was used as an intermediate in the preparation of 7α-methoxycephalosporins.

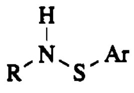

**(12)**

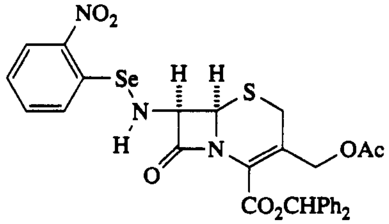

**(13)**

### 6.1.2.2 Hydrazones, Hydrazines and Hydroxylamines

#### *6.1.2.2.1 Dehydrogenation*

This section includes synthetically useful oxidative reactions of substrates of the general types $R^1R^2C{=}NNH_2$, $R^1R^2NH_2$ and $RONH_2$, where the groups $R^1$, $R^2$ and R can be alkyl, aryl or acyl.

The oxidation of many hydrazones provides a method of preparation of the corresponding diazo compounds $R^1R^2C{=}N_2$.[53] The oxidant most commonly used for this purpose is mercury(II) oxide.[54] Fluorenone hydrazone is converted in high yield into diazofluorene and many other diaryldiazomethanes can be prepared in the same way. Diazo ketones of relatively high stability, such as phenylbenzoyldiazomethane, can also be obtained by the oxidation of 1,2-diketone monohydrazones. Silver oxide reacts more rapidly with hydrazones than does mercury(II) oxide, and it is better for the preparation of monoaryldiazomethanes.[53] Activated manganese dioxide has also been used. The usual side products in these oxidations are azines $R^1R^2C{=}NN{=}CR^1R^2$, which are derived from the less stable diazo compounds by decomposition if the contact time with the oxidant is prolonged. Bishydrazones of 1,2-diketones are oxidized by mercury(II) oxide to alkynes (Scheme 14). This reaction provides a good method of synthesis of cycloalkynes such as cyclooctyne.[53]

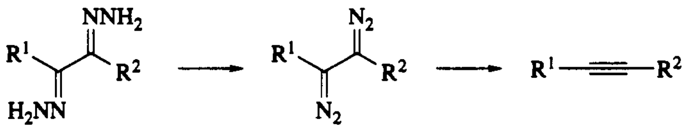

Scheme 14

The oxidation of 1,1-disubstituted hydrazines can be achieved by a wide range of oxidants. The oxidative removal of hydrogen formally leads to the production of aminonitrene, or 1,1-diazene, intermediates and many products of such reactions have been interpreted as being derived from aminonitrene intermediates.[55] Indeed, several of these species, derived from sterically hindered hydrazines by oxidation with nickel peroxide or *t*-butyl hypochlorite, have been detected and characterized in solution at low temperature. Examples include the diazenes (**14**)[56] and (**15**)[57]. The diazene (**16**) is stable enough to persist in solution at room temperature for several days.[58]

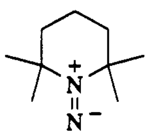

**(14)**

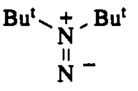

**(15)**

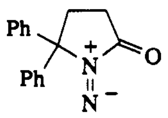

**(16)**

With many oxidants the most common products derived from 1,1-disubstituted hydrazines are the tetrazenes $R^1R^2NN{=}NNR^1R^2$. Benzeneselenic acid appears to a good reagent for their preparation[59] although several others, including mercury(II) oxide and nickel peroxide, have been widely used. These tetrazenes are formally the dimers of aminonitrenes and indeed are formed from long-lived species such as (**14**) by dimerization. Another possible mode of formation of tetrazenes, which is illustrated in Scheme 15, is the reaction of an aminonitrene, or its precursor, with the starting hydrazine to give a tetrazane, followed by further oxidation. This sequence was established for the oxidation of *N*-aminophthalimide by iodosylbenzene diacetate: the tetrazane (**17**) was isolated and gave the corresponding tetrazene with an excess of the oxidant.[60]

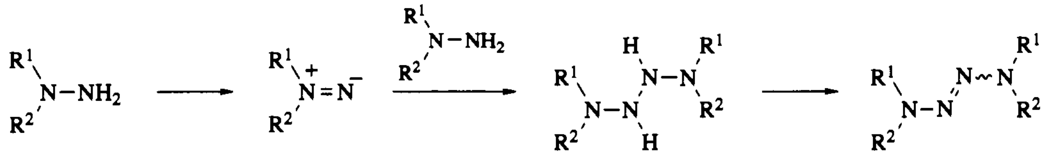

**Scheme 15**

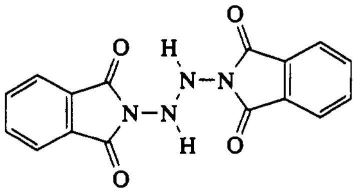

**(17)**

Lead(IV) acetate has proved to be a most efficient oxidant for these hydrazines. The oxidation of *N*-aminoheterocyclic compounds by lead(IV) acetate has, in particular, provided several very useful preparative procedures.[55,61] 1-Aminobenzotriazole (**18**; Scheme 16) is oxidized to 1,2-didehydrobenzene (benzyne) in high yield at low temperature.[62] This reaction has been widely exploited not only for the generation of benzyne but for the formation of cycloalkynes and of other arynes. For example, oxidation of the bisaminotriazole (**19**) gave products derived from 1,2,4,5-tetradehydrobenzene (**20**).[63] Campbell and Rees considered the possibility that benzyne was generated from 1-aminobenzotriazole by way of an aminonitrene and an unstable 1,2,3,4-benzotetrazine (Scheme 16).[62] A similar oxidation, of compound (**21**), did yield an isolable but unstable tetrazine (**22**) as the product.[64] 2-Aminobenzotriazole (**23**) clearly does not give the same intermediates as its isomer (**18**) on oxidation because it is oxidized cleanly to the dinitrile (**4**). On the other hand both 1- and 2-amino-3-phenylindazole give the same product of ring expansion, the benzotriazine (**24**), on oxidation (Scheme 17).[65]

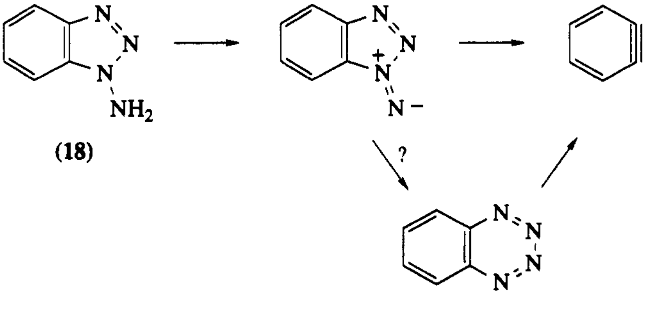

**(18)**

**Scheme 16**

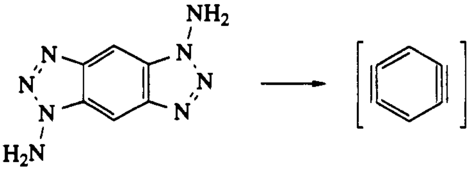

**(19)** **(20)**

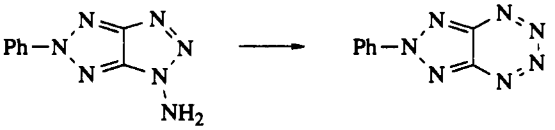

**(21)** **(22)**

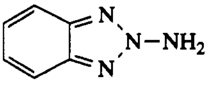

**(23)**

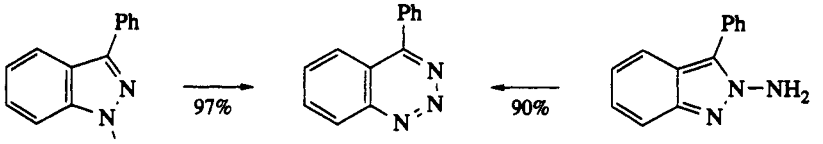

**(24)**

**Scheme 17**

The oxidation by lead(IV) acetate of *N*-aminophthalimide and of several *N*-aminolactams leads to the formation of intermediates which do not undergo fragmentation or rearrangement, but which can be intercepted by alkenes, alkynes, sulfoxides and other nucleophiles. The reactions have proved particularly useful for the synthesis of aziridines from a variety of alkenes.[55] The mechanism of these reactions has commonly been assumed to require the intermediacy of aminonitrenes, but this is probably not the case. Atkinson and Kelly have shown that oxidation of the aminolactam (**25**) by lead(IV) acetate at –20 °C leads to the formation of an unstable *N*-acetoxy compound.[66] This is the species which can form aziridines with alkenes. The mechanism shown in Scheme 18, which is analogous to that for the epoxidation of alkenes by peroxy acids, has been proposed for the aziridination process.

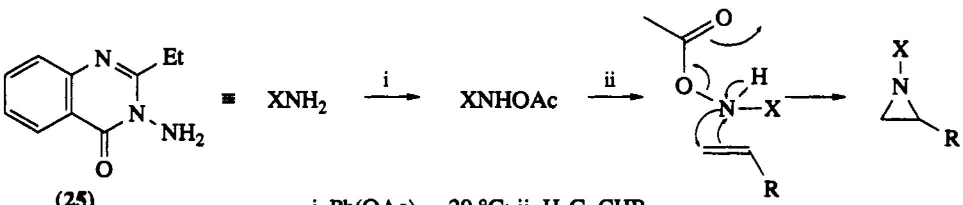

(**25**)

i, Pb(OAc)$_4$, –20 °C; ii, H$_2$C=CHR

**Scheme 18**

Oxidation of methoxylamine and some other *O*-substituted hydroxylamines by lead tetraacetate in the presence of alkenes can also lead to the formation of aziridines. The oxidation of 2,4-dinitrobenzenesulfenamide is analogous.[67] In view of the results reported with aminolactams, these reactions do not necessarily establish the intermediacy of nitrenes in the oxidations.

### *6.1.2.2.2 Other oxidations*

1,1-Diphenylhydrazine is oxidized to diphenylnitrosamine (50%) by potassium superoxide.[68] The same reagent also oxidizes 1-methyl-1-phenylhydrazine, but here the nitrosamine is a minor product; the major reaction is deamination. A better method of oxidative deamination of some 1,1-disubstituted hydrazines and hydrazinium salts is reaction with nitrous acid. Thus, several hydrazinium salts $Me_2RN^+NH_2\ X^-$ were deaminated to the tertiary amine by treatment with nitrous acid.[69] The method has also been used to deaminate *N*-aminoheterocyclic compounds; for example, some 1,2,3-triazoles are conveniently prepared by deamination of the corresponding 1-aminotriazoles with nitrous acid.[70]

Monosubstituted hydrazines and hydrazides are converted into azides by a variety of nitrosating agents. The mildest reagent appears to be dinitrogen tetroxide, which can be used below 0 °C in acetonitrile to convert benzoylhydrazine, *p*-toluenesulfonylhydrazine and 4-nitrobenzoylhydrazine, among others, into the corresponding azides in high yield.[71] Another mild method involves the use of iron(III) nitrate supported on clay.[72] These reactions probably proceed by way of transient *N*-nitroso compounds (Scheme 19).

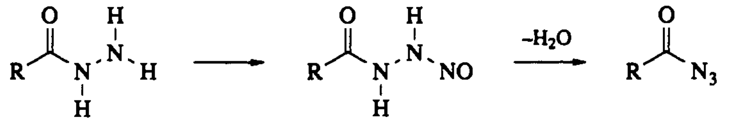

**Scheme 19**

Katritzky and coworkers have nitrated hydrazinium salts and 1,1-disubstituted hydrazines with nitronium tetrafluoroborate and other nitrating agents.[73] Thus, nitrimides $R_3N^+N^-NO_2$ were prepared in good yield from hydrazinium salts derived from tertiary amines such as trimethylamine and 2-methylpyridine; 1-aminobenzotriazole was also nitrated at the amino group.

## 6.1.3 OXIDATION OF THE NH GROUP

### 6.1.3.1 Secondary Amines

### *6.1.3.1.1 Oxidation to nitroxides and hydroxylamines*

The conversion of secondary amines $R_2NH$ into nitroxides $R_2NO\cdot$[74] has been carried out using hydrogen peroxide, MCPBA and metal oxides, including silver oxide, mercury(II) oxide and lead(IV) oxide. Secondary amines which have low solubility in water have been oxidized by sodium tungstate and hydrogen peroxide in a mixture of methanol and acetonitrile.[5] Dimethyldioxirane (**1**) is also a good reagent for the oxidation of hindered secondary amines to nitroxides.[75] As illustrated in Scheme 20, such oxidations probably go by way of the hydroxylamines as intermediates. When the secondary amine has a hydrogen atom attached to an α-carbon atom, the hydroxylamine formed by oxidation with sodium tungstate and hydrogen peroxide reacts further by losing this hydrogen atom. For example, tetrahydroisoquinoline was oxidized to the nitrone (**26**; 85%).[76] The reaction has been modified to provide a method of synthesis of *N*-hydroxy amino acids from secondary amines. Thus, *N*-hydroxyproline was prepared from pyrrolidine by oxidation with hydrogen peroxide and sodium tungstate, the intermediate being intercepted by cyanide. This gave the hydroxylamine (**27**) which could then be converted into *N*-hydroxyproline by hydrolysis.[77] A related oxidation has been used for the conversion of tetrahydroquinolines into the corresponding 3,4-dihydro-1-hydroxy-2-quinolones.[78]

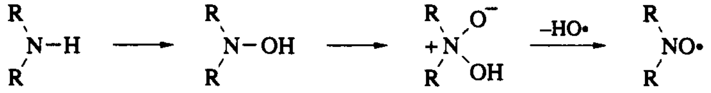

**Scheme 20**

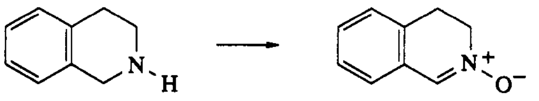

**(26)**

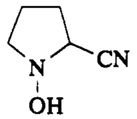

**(27)**

Dibenzoyl peroxide oxidizes morpholine, piperidine and other simple secondary amines in good yield to the corresponding benzoyloxyamines; these compounds can then be hydrolyzed in basic conditions to the free hydroxylamines.[79] An analogous reaction takes place between secondary amines and bis(diphenylphosphinyl) peroxide; for example, diethylamine is converted into the hydroxylamine derivative $Et_2NOPOPh_2$ (97%) by this reagent.[80] The products are easily hydrolyzed to the free hydroxylamines, and they can also be used as aminating agents.

### *6.1.3.1.2 Oxidation to aminium ions, aminyl radicals and hydrazines*

The one-electron oxidation of a secondary amine results in the formation of a secondary aminium ion[1] which on deprotonation gives an aminyl radical (Scheme 1).[2] The nature of the final products derived from these intermediates depends very much on the structure of the substrate and the reaction conditions. If the amine has a hydrogen atom on the α-carbon atom the major products usually result from deprotonation at this α-position. With aromatic secondary amines, products can result from coupling of the delocalized radicals at a ring carbon atom. The formal dimerization of aminyl radicals shown in Scheme 21 is therefore not often a useful method of preparation of hydrazines. Nickel peroxide has been used to oxidize diphenylamine to tetraphenylhydrazine in moderate yield, and other secondary arylamines also give mixtures of products in which the corresponding hydrazines are the major components.[25] The reagent formed by the addition of oxygen to copper(I) chloride in pyridine can also oxidize secondary arylamines. Diphenylamine was oxidized to tetraphenylhydrazine in 83% yield, and *N*-methylaniline gave the corresponding hydrazine in 52% yield.[81] Lithium piperidide and lithium salts of other secondary amines have also been oxidized to the hydrazines with copper(I) chloride and oxygen.[82] Intramolecular coupling of the diamines (**28**) to the pyrazolines (**29**) has also been achieved, using activated manganese dioxide (Scheme 21).[5,83]

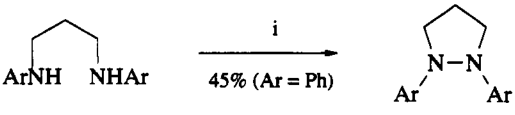

(**28**) (**29**)

i, $MnO_2$, –20 °C

**Scheme 21**

### *6.1.3.1.3 Nitrosation and nitration*

Methods of formation of *N*-nitrosamines from secondary amines have been reviewed.[84] The most widely used reagent is sodium nitrite in an aqueous acidic medium; others include nitrosyl chloride, nitrogen oxides and nitrite esters. Fremy's salt [$2K^+$ $(SO_3^-)_2NO\cdot$] reacts with hydroxylamine in the presence of secondary amines to give *N*-nitrosamines, or, in the presence of an excess of hydroxylamine, tetrazenes $R_2NN{=}NNR_2$. The nitrosating agent derived from hydroxylamine and Fremy's salt is suggested to be the anion $(SO_3^-)_2NONO$.[85]

Direct *N*-nitration of secondary amines by nitric acid is possible only for weakly basic amines.[86] The more basic amines can be nitrated under neutral conditions with reagents such as dinitrogen pentoxide and nitronium tetrafluoroborate, but nitrosamines are significant by-products. The nitrate ester $CF_3CMe_2ONO_2$ has been recommended as a nonacidic nitrating agent for secondary amines which avoids the problem of contamination of the products by *N*-nitrosamines: piperidine and pyrrolidine were nitrated in yields of 75% and 72%, respectively.[87] Amides and imides are efficiently *N*-nitrated using ammonium nitrate in trifluoroacetic anhydride.[88]

### *6.1.3.1.4 Amination*

The conversion of secondary amines into 1,1-disubstituted hydrazines requires the use of an electrophilic aminating agent. Several such reagents are available, and their use has been reviewed.[46,89–91] Chloramine and hydroxylamine-*O*-sulfonic acid are the commonest reagents of this type. Secondary amines have been aminated by chloramine in moderate yield in aqueous solution, and in good yield by passing gaseous chloramine into methanolic solutions of the amines.[46] Hydroxylamine-*O*-sulfonic acid is a more powerful aminating agent and has been used to aminate heterocyclic compounds such as benzotriazole in good yield. Its disadvantage is its low solubility in nonpolar organic solvents. To overcome this problem several soluble *O*-substituted hydroxylamines have been introduced as aminating agents. These include *O*-mesitylhydroxylamine (**30**), *O*-2,4-dinitrophenylhydroxylamine (**31**), and *O*-mesitylenesulfonylhydroxylamine (MSH; **32**). MSH is a particularly good aminating agent, but it is rather tedious to prepare.[90] A promising, and much more accessible, reagent is *O*-diphenylphosphinylhydroxylamine (**33**).[92] This reagent has been used to aminate imides such as phthalimide in high yield. The oxaziridine (**34**) can act as an aminating agent for amino acids and peptides.[93]

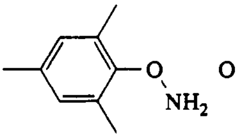

(**30**)

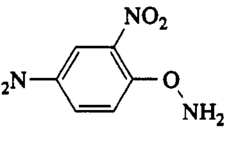

(**31**)

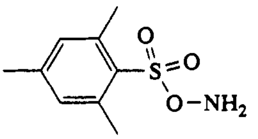

(**32**)

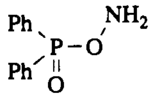

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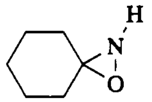

(34)

### 6.1.3.1.5 *Halogenation and other reactions*

Methods for the chlorination of secondary amines, secondary amides and imides have been reviewed.[48] Secondary alkylamines can be chlorinated by *t*-butyl hypochlorite at low temperature, or by sodium hypochlorite or *N*-chlorosuccinimide. *N*-Bromination and *N*-iodination can be brought about by using the appropriate halogen, but these *N*-halodialkylamines are unstable and are rarely isolated. *N*-Fluoroamines and *N*-fluoroamides are also rare.[94] The *N*-fluoroimide $(CF_3SO_2)_2NF$, has, however, been prepared by direct fluorination with fluorine. It is a stable liquid which shows promise as a fluorinating agent for aromatic compounds.[95]

*N*-Chloroaziridines (**35**) are configurationally stable, and there have been attempts to prepare them in optically active form by carrying out the chlorination with *t*-butyl hypochlorite or with *N*-chlorosuccinimide in the presence of the optically active alcohol (*S*)-(+)-PhCH(OH)$CF_3$.[96] Optical yields were, however, low (less than 10% *ee*).

Secondary amines can be converted into sulfenamides by reaction of the lithium dialkylamides with disulfides.[50,97] Perchlorylamines (**36**) have been prepared in good yields from piperidine and other secondary amines by reaction with chlorine(VII) oxide.[98]

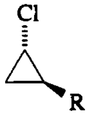

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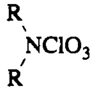

(36)

## 6.1.3.2 Hydrazines and Hydroxylamines

Methods of oxidation of hydrazo to azo compounds[99] and hydroxylamino to nitroso compounds[100] have been reviewed. Reagents which oxidize aromatic primary amines to azo compounds are also suitable for the oxidation of aromatic hydrazo compounds, since the hydrazo compounds are intermediates in the oxidation of the amines. Thus, manganese dioxide, mercury(II) oxide and lead tetraacetate are all suitable oxidants. Silver carbonate on Celite rapidly oxidizes both diarylhydrazines and acylhydrazines to the corresponding azo compounds in good yield.[26] Another supported oxidant which can convert hydrazobenzene into azobenzene in high yield is sodium periodate on silica gel.[101]

Two-phase oxidation systems are useful for the selective oxidation of the hydrazo to the azo group in the presence of other functional groups. For example, the hydrazotriazine (**37**) was oxidized by chlorine to the azo compound in high yield, without hydrolysis of the delicate ring chloride, in a two-phase system of chloroform and aqueous sodium bicarbonate.[102] Aqueous potassium ferricyanide has also been used in a two-phase system to oxidize hydrazo compounds. A coreagent is required, which is either a hindered phenol[103] or carbon black.[104] In either case the active oxidant is believed to be an aryloxy radical. This type of reagent has been used to produce AIBN and acylazo compounds such as PhN═NCOPh from the corresponding hydrazo compounds in high yield. Oxygen can also oxidize such hydrazo compounds in the presence of a palladium catalyst at room temperature.[105] Benzeneseleninic anhydride has been used to convert arylhydrazones of aldehydes into α-carbonylazo compounds: for example, furfural phenylhydrazone gave the azo compound (**38**) in 92% yield (Scheme 22).[106] Arylhydrazones

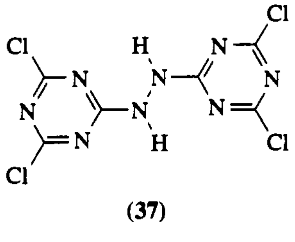

(37)

$R_2C{=}NNHAr$ are also oxidized to α-acetoxyalkylazo compounds $R_2C(OAc)N{=}NAr$ by lead tetraacetate.[99]

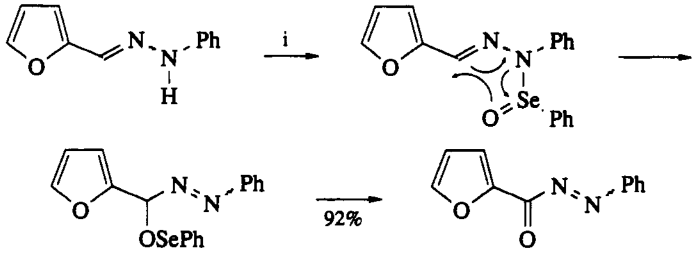

(38)

i, $(PhSeO)_2O$

Scheme 22

Several oxidants have been used to produce the highly reactive cyclic azocarbonyl compounds (39) from the corresponding hydrazides.[107] These include *t*-butyl hypochlorite, dinitrogen tetroxide and *N*-bromosuccinimide. Anodic oxidation[108] and oxidation by iodosylbenzene diacetate[109] are also effective for preparing these and related azocarbonyl compounds.

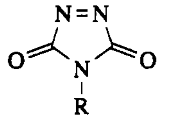

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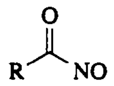

(40)

Aliphatic nitroso compounds can be prepared from *N*-alkylhydroxylamines by oxidation with bromine, chlorine or sodium hypochlorite in weakly acidic solution, by reaction with potassium dichromate in acetic or sulfuric acid, and by oxidation with yellow mercury(II) oxide in suspension in an organic solvent.[100] Silver carbonate on Celite has also been used to prepare aliphatic nitroso compounds, such as nitrosocyclohexane, in high yield from the corresponding hydroxylamines.[110] Aqueous sodium periodate and tetraalkylammonium periodates, which are soluble in organic solvents, are the reagents most commonly used for the oxidation of hydroxamic acids and *N*-acylhydroxylamines to acylnitroso compounds (40).[111] These compounds are rarely isolated, but are useful as highly reactive dienophiles in the Diels–Alder reaction.[112]

## 6.1.4 OXIDATION OF TERTIARY ($sp^3$) NITROGEN

### 6.1.4.1 Formation of *N*-Oxides

Tertiary alkylamines can be converted into the corresponding *N*-oxides with hydrogen peroxide or with peroxy acids.[113] *t*-Butyl hydroperoxide has also been used in the presence of a catalyst such as $VO(acac)_2$. Sharpless and coworkers have carried out the oxidative kinetic resolution of several β-hydroxy tertiary amines such as (41) with *t*-butyl hydroperoxide, titanium(IV) isopropoxide and (+)-diisopropyl tartrate, the titanium(IV):tartrate ratio being about 2:1.[114] After 60% conversion, one enantiomer was selectively oxidized, and the other enantiomer could be recovered in good optical purity (Scheme 23).

Tertiary alkylamines are normally autoxidized and dealkylated by oxygen, but it has been shown that they can slowly be converted into the *N*-oxides by heating at 90–130 °C with oxygen under pressure in a polar solvent.[115] The reaction is thought to involve electron transfer from the amine to oxygen as the rate-determining step. Pyridine does not react with oxygen under these conditions. The cyclic hydrazine *N*-oxide (42) has been prepared from the corresponding hydrazine by oxidation with 30% hydrogen peroxide at room temperature.[116]

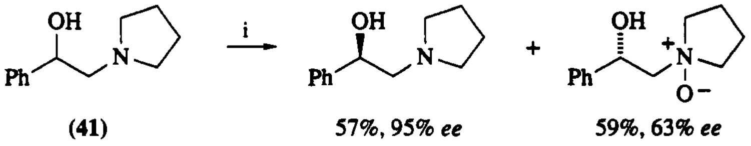

i, $Bu^tOOH$, $Ti(OPr^i)_4$, (+)-diisopropyl tartrate; 60% conversion

Scheme 23

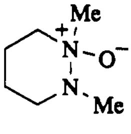

**(42)**

#### 6.1.4.2 Other Reactions

One-electron oxidants convert tertiary amines into aminium ions.[1] Chlorine dioxide[5] is an example of such a reagent; this converts triethylamine and other tertiary alkylamines into aminium ions, which normally react further by the loss of hydrogen from an α-carbon atom. An example of a synthetic application of this reaction sequence is shown in Scheme 24, the intermediate iminium ion being intercepted intramolecularly.[117] Nitrosonium tetrafluoroborate and dioxygenyl hexafluoroantimonate, $O_2^+SbF_6^-$, are also good one-electron oxidants which can be used at low temperature.[118]

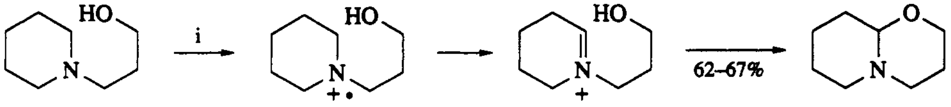

i, $ClO_2$, pH 9–11

Scheme 24

Reagents for amination, nitrosation and nitration of tertiary alkylamines are discussed in the appropriate reviews listed in Sections 6.1.3.1.4 and 6.1.3.1.5. Tertiary amines can be nitrosated with dealkylation by dinitrogen tetroxide: for example, 1-methylpiperidine gave 1-nitrosopiperidine (80%).[119] This reaction probably starts by one-electron oxidation of the amine, the aminium ion then undergoing dealkylation. Other oxidative deacylations and dealkylations include the formation of *N*-nitrosodibenzylamine in high yield from the acid chloride $(PhCH_2)_2NCOCl$ and sodium nitrite[120] and the conversion of the amine **(43)** into the nitramine **(44)** with nitric acid.[121]

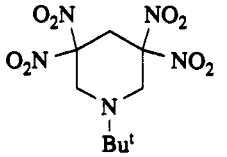

**(43)**

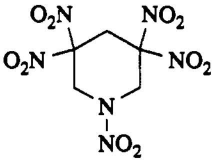

**(44)**

## 6.1.5 OXIDATION OF TRIGONAL ($sp^2$) NITROGEN

### 6.1.5.1 *N*-Oxidation of Heteroaromatic Amines

The standard methods of oxidation of pyridines and other heteroaromatic nitrogen compounds make use of peroxy acids or hydrogen peroxide in carboxylic acid solution.[122] Peracetic acid, peroxymonophthalic acid and MCPBA can all convert simple pyridines to the *N*-oxides. For example, the pyridine **(45)** was oxidized at nitrogen by MCPBA without attack on the vinyl group.[123] Peroxymaleic acid has been used to convert deactivated heteroaromatics, such as 2-chloroquinoline, into the *N*-oxides.[122] Trifluoroperacetic acid, or hydrogen peroxide in trifluoroacetic acid can also oxidize deactivated and hindered heteroaromatic compounds; for example, 2,6-dibromopyridine was oxidized in good yield by 30% hydrogen peroxide in trifluoroacetic acid.

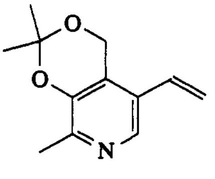

**(45)**

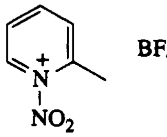

**(46)**

These and more powerful oxidants are often required for the oxidation of diazines and triazines.[124] Chivers and Suschitzky succeeded in oxidizing pentafluoropyridine, tetrachloropyrazine and other polyhalogenated azines with 90% hydrogen peroxide in acetic and sulfuric acids or in trifluoroacetic and sulfuric acids.[125] The hazards of handling 90% hydrogen peroxide solutions can be avoided if the commercially available solid adduct formed between urea and hydrogen peroxide is used instead.[126] Diazines and diazanaphthalenes which are sensitive to peroxy acids can be oxidized by hydrogen peroxide in the presence of a sodium tungstate catalyst.[127] Sodium perborate in acetic acid is an especially useful oxidant for water-soluble pyrazine *N*-oxides.[128]

Dimethyldioxirane (**1**) is a mild and efficient oxidant for pyridine; pyridines and quinolines have also been oxidized in good yield by *t*-pentylhydroperoxide in the presence of molybdenum(V) chloride.[129]

*N*-Halogenation and other oxidative reactions of pyridines and related heterocycles have been reviewed.[130] Thus, pyridines and some diazines[124] can be aminated by mesitylenesulfonylhydroxylamine (**32**) and similar reagents. *N*-Nitration of 2-picoline by nitronium tetrafluoroborate gives the salt (**46**) which is itself a nitrating agent.

### 6.1.5.2 *N*-Oxidation of Imines

Imines are oxidized by peroxy acids to oxaziridines, with the formation of nitrones as a competing process (Scheme 25).[131] Oxaziridines are probably formed by a two-step process involving nucleophilic addition of the peroxy acid to the C=N bond, followed by elimination, as illustrated; nitrones are formed by competing *N*-oxidation.[4] The oxidation of chiral imines to oxaziridines by MCPBA proceeds with good, but not complete, diastereoselectivity.[132]

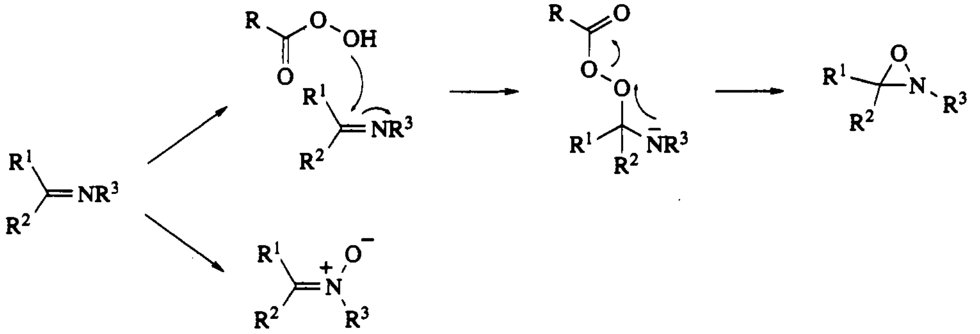

Scheme 25

### 6.1.5.3 Oxidation of Azo to Azoxy Compounds

Methods for the oxidation of azo to azoxy compounds have been reviewed.[133] Typical oxidants are MCPBA and other peroxy acids and hydrogen peroxide. *t*-Butyl hydroperoxide is also an effective oxidant for azobenzenes in the presence of molybdenum hexacarbonyl.[134] Trifluoroperacetic acid has been used to oxidize perfluoroazobenzene and other fluorinated azobenzenes to the azoxy compounds in high yield;[135] It is also capable of oxidizing azoxyarenes, such as compound (**47**), to the di-*N*-oxides.[136]

Bridgehead azoalkenes (**48**) can be oxidized to the azoxy compounds and to the di-*N*-oxides with MCPBA.[137]

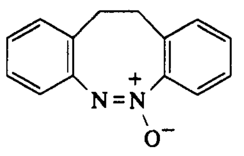

(**47**)

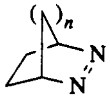

(**48**)

### 6.1.5.4 Oxidation of Oximes and Nitroso Compounds

The *N*-oxidation of oximes leads to the formation of *aci*-nitro compounds. In a polar organic solvent such as acetonitrile these compounds are isomerized to nitro compounds (Scheme 26) and are thus protected from further oxidation. The reagent of choice is trifluoroperacetic acid.[138] The oxidation of oximes derived from α-epoxy ketones results in the formation of a nitroalkene with opening of the epoxide, as illustrated in Scheme 27.[139]

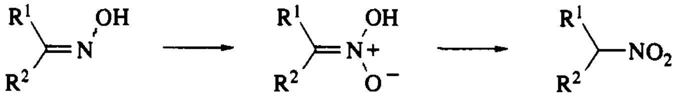

Scheme 26

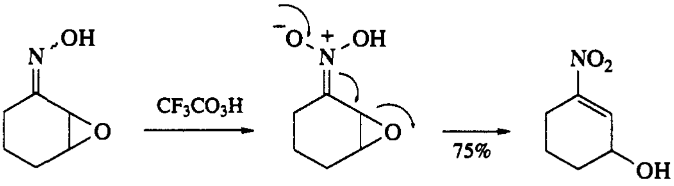

Scheme 27

*N*-Nitrosation of oximes by nitrosyl halides or nitrite esters often results in the formation of *N*-nitrimines, $R^1R^2C{=}NNO_2$, these compounds being formed by rearrangement of the initial adducts.[140] *N*-Amination of oximes by chloramine or by hydroxylamine-*O*-sulfonic acid can result in the formation of diazo compounds (Scheme 28). The reaction, known as the Forster reaction,[53] has been used for the preparation of aryldiazoalkanes, although better methods are usually available. Diazo ketones of the general formula (**49**) have also been prepared by this method from the oximes.[141]

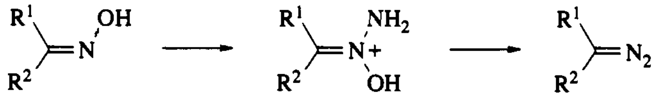

Scheme 28

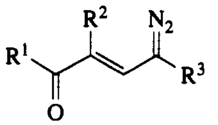

(**49**)

The oxidation of oximes by lead(IV) acetate, chlorine and other oxidants results in the formation of α-substituted nitroso compounds $R^1R^2C(X)NO$ by attack of the oxidant at carbon. This is also the reaction commonly observed with dinitrogen tetroxide (the Ponzio reaction), the products being *gem*-

dinitro compounds or α-nitronitroso compounds.[142] It has, however, been claimed that many alkyl ketoximes can be converted into the corresponding ketones in good yields by reaction with dinitrogen tetroxide at low temperature.[143] Other oxidative methods of deprotection of oximes exist.[143,144]

Nitroso compounds are readily oxidized to the corresponding nitro compounds by peroxides, peroxy acids, oxygen, ozone and dinitrogen tetroxide.[4]

### 6.1.5.5 Other Reactions

Reactions which formally involve the oxidation of azides have been reviewed by Boyer.[4] Other oxidations with useful synthetic applications include two which start from nitrogen ylides. Sulfimides (**50**) derived from electron-deficient aromatic and heterocyclic amines are oxidized to the corresponding nitroso compounds by MCPBA.[4,145] This is a very useful method of preparation of some otherwise inaccessible nitroso compounds such as 2-nitrosopyridine and 1-nitrosoisoquinoline. They can be further oxidized, for example by ozone, to the nitro compounds. Phosphimides (**51**) are oxidized directly by ozone to the nitro compounds, although the nitroso compounds are intermediates.[146] Isocyanates can also be oxidized to the corresponding nitro compounds, by dimethyldioxirane (**1**).[147]

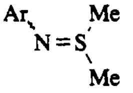

**(50)**

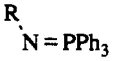

**(51)**

## 6.1.6 OXIDATION OF PHOSPHORUS

A comprehensive survey of the chemistry of organophosphorus compounds was published in 1982.[148] This provides descriptions of many of the oxidation methods in phosphorus chemistry, and primary literature references to them. Primary references are not given here if they are available from this source.

Tertiary phosphines (phosphanes) are normally very easily oxidized to the corresponding phosphine oxides.[149] The reaction can be brought about by oxygen alone or with hydrogen peroxide. Bis(trimethylsilyl) peroxide has been recommended as a selective oxygenating agent for phosphines and phosphites.[150] Oxidation of the chiral phosphine (*R*)-(–)-methylpropylphenylphosphine proceeded with 95% retention of configuration and the chlorodioxaphosphorinane (**52**) gave the oxide (**53**) with complete retention of stereochemistry. Diaryl selenoxides[151] and sulfur trioxide[152] have also been used for the oxidation of phosphines. Electrochemical oxidation of phosphines and phosphites proceeds in the presence of diethyl disulfide, which is effectively a catalyst for the reaction.[153]

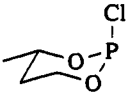

**(52)**

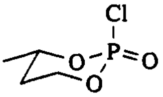

**(53)**

Tertiary phosphine sulfides and selenides are readily obtained from the phosphines and elementary sulfur or selenium. Potassium selenocyanate provides a convenient alternative to selenium for preparing selenides.[149] Phosphinimides (iminophosphoranes), $R_3P{=}NR'$, are prepared by the reaction of phosphines with azides or with *N*-chloroamines, among other methods. Phosphines can be aminated by reaction with *O*-diphenylphosphinylhydroxylamine.[92] The reaction of triphenylphosphine with diethyl azodicarboxylate results in rapid conjugate addition of the phosphine to the N=N bond. The resulting betaine has been used as a method of activation of alcohols (the Mitsunobu reaction), allowing displacement by nucleophiles and conversion of the alcohols into esters and other derivatives (Scheme 29).[154]

Many reagents, including the halogens themselves, are suitable for the conversion of trisubstituted phosphines into dihalides $R_3PX_2$ (X = F, Cl, Br or I).[155] These compounds can exist either in the pentacovalent form, or in an ionic form $R_3PX^+\ R_3PX_3^-$, the covalent structure being favored in the order F > Cl > Br > I and by solvents of low polarity.

Secondary phosphines, $R_2PH$, can be chlorinated under controlled conditions to give the corresponding chlorophosphines.[156] These compounds can be further oxidized in a number of ways (Scheme 30).[157] The reaction of chlorodiphenylphosphine with dibenzoyl peroxide gives diphenylphosphinic acid

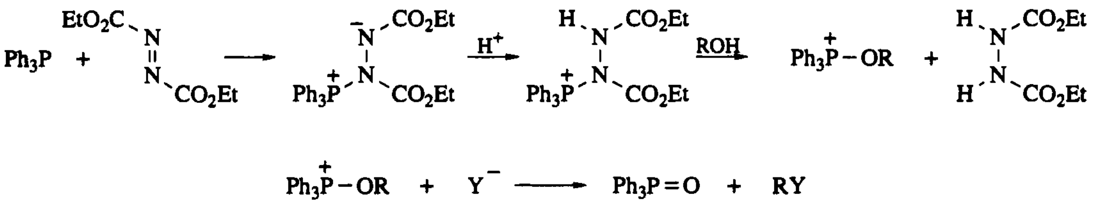

**Scheme 29**

anhydride in 82% yield. With sulfur dioxide, diphenylphosphinyl chloride is formed in high yield. Oxidation with oxygen, or with sodium hydride and oxygen in the presence of a secondary alcohol such as diphenylmethanol, gives diphenylphosphinic acid after hydrolysis. Diphenylphosphinic anhydride can also be obtained by oxidation of the bisoxide $(Ph_2PO)_2$ with perbenzoic acid.

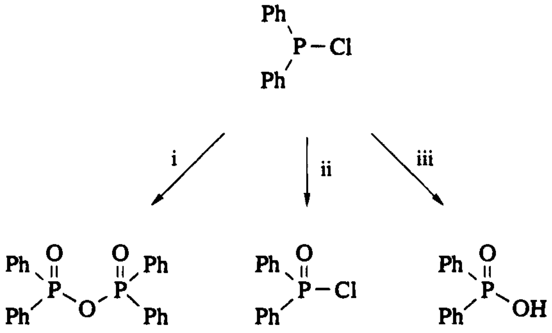

i, $(PhCO_2)_2$; ii, $SO_2$; iii, NaH, $Ph_2CHOH$, $O_2$

**Scheme 30**

Derivatives of phosphonic acids, $RP{=}O(OH)_2$, can be prepared by several different oxidative methods.[158] Primary phosphines $RPH_2$ are oxidized to phosphonic acids by hydrogen peroxide or by sulfur dioxide: thus, phenylphosphine gave benzenephosphonic acid (96%) on reaction with sulfur dioxide at room temperature in a sealed tube. Phosphinic acids, $RP{=}O(OH)H$, can also be oxidized to the corresponding phosphonic acids with hydrogen peroxide. Ozone oxidized the dioxaphosphorane (**54**) to the phosphonic ester in 73% yield. Ozone is also capable of stereospecific oxidation of phosphite esters to phosphates.[159] For example, the cyclic phosphite (**55**) was oxidized to the phosphate (**56**) with retention of configuration. Peroxy acids and selenium dioxide are other common oxidants for phosphite esters.[160]

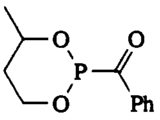

**(54)**

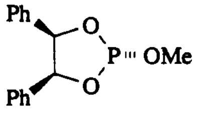

**(55)**

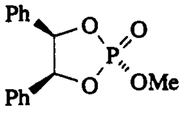

**(56)**

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# 6.2

# Oxidation of Sulfur, Selenium and Tellurium

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## 6.2.1 INTRODUCTION

A variety of organo-sulfur, -selenium and -tellurium compounds can be oxidized to their corresponding higher oxidation state species. Thiols are reasonably stable in air and are oxidized by various reagents to disulfides (equation 1), while selenols, although isolable, are unstable in air and are oxidized readily to diselenides (equation 2). Tellurols are very sensitive to air and are normally present as ditellurides (equation 3). These disulfides, diselenides and ditellurides are further oxidized to various higher oxidation products depending on the specific reaction conditions. Sulfides (**1**; M = S), selenides (**1**; M = Se) and tellurides (**1**; M = Te) are generally oxidized to the corresponding sulfoxides (**2**; M = S), selenoxides (**2**; M = Se) and telluroxides (**2**; M = Te), which in turn are further oxidized to sulfones (**3**; M = S), selenones (**3**; M = Se) and tellurones (**3**; M = Te), respectively (Scheme 1). These oxidized species are also written in the alternative formats of (**4**) and (**5**), and syntheses of chiral sulfoxides and selenoxides by direct oxidation are known. A variety of chemical oxidizing agents can be employed for these transformations and some electrochemical, photochemical and enzymatic oxidations are also known.

$$\mathrm{R{-}SH} \xrightarrow{[\mathrm{O}]} \mathrm{RS{-}SR} \qquad (1)$$

$$\mathrm{R{-}SeH} \xrightarrow{[\mathrm{O}]} \mathrm{RSe{-}SeR} \qquad (2)$$

$$\left[\mathrm{R{-}TeH}\right] \xrightarrow{[\mathrm{O}]} \mathrm{RTe{-}TeR} \qquad (3)$$

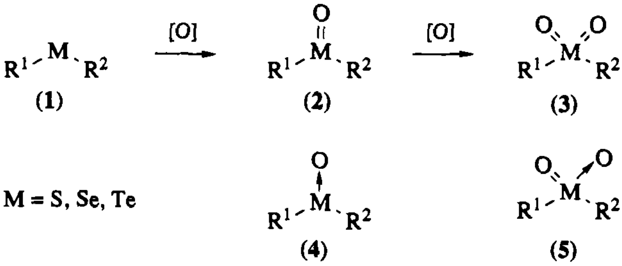

**Scheme 1**

Disulfides, diselenides and ditellurides are useful compounds in their own right for introducing organic sulfur, selenium and tellurium moieties to other organic molecules. Oxidized species such as $R^1M(O)R^2$ and $R^1M(O)_2R^2$ also find much use in organic synthesis. Many of these applications can be seen in the relevant chapters of this series and the reader is referred to these reviews: (i) stabilization of carbanions by sulfur and selenium moieties [$RSO$, $RSO_2$, $RSeO$ and $RSeO_2$] resulting in a favorable carbon–carbon bond formation (Volume 1, Chapters 2.3 and 2.6 and Volume 3, Chapter 1.3); (ii) selenoxide and telluroxide elimination reactions giving alkenes (Volume 6); (iii) 2,3-sigmatropic rearrangement of allylic sulfoxides and selenoxides affording allylic alcohols (Volume 6); (iv) Diels–Alder reaction of heterodienophiles such as alkynyl and alkenyl sulfoxides (Volume 5); and (v) substitution of $RMO$ and $RMO_2$ moieties by other functional groups (Volume 8). This chapter however deals with oxidation of representative organic sulfur, selenium and tellurium compounds shown in equations (1)–(3) and Scheme 1, concentrating mainly on highly selective methods using chemical oxidizing agents, and covering the literature up to the end of 1989.

## 6.2.2 OXIDATION OF ORGANIC SULFUR COMPOUNDS

### 6.2.2.1 Oxidation of Thiols to Disulfides by Molecular Oxygen and Chemical Reagents

The oxidation of thiols to disulfides is a very facile process and many reagents function as oxidants.[1-4] Ease of oxidation usually decreases in the following order: ArSH > *n*-RSH > *s*-RSH > *t*-RSH. The use of vigorous conditions such as strong oxidants, excess oxidants, higher temperatures and longer reaction times *etc.* usually results in further oxidation of initially produced disulfides to give a mixture of several higher oxidation products (Scheme 2). It is normally difficult to synthesize these compounds selectively, although a few methods for obtaining sulfinic acids ($RSO_2H$) or sulfonic acids ($RSO_3H$) directly from thiols have been reported. For the selective synthesis of disulfides the recommended oxidants are oxygen or air in the presence of metal catalysts, bromine under phase-transfer conditions, iodine, and various metal salts such as Fe$^{III}$, Mn$^{IV}$ and Tl$^{III}$.

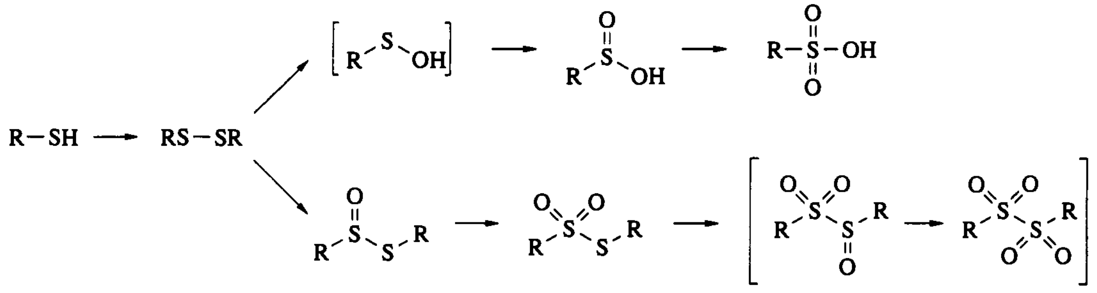

Scheme 2

### 6.2.2.1.1 *By molecular oxygen*

The oxidation of thiols to disulfides by molecular oxygen or air is believed to proceed *via* two routes as shown in Scheme 3.[5] Thus, the reaction may be enhanced under basic conditions but more stable anions react at a slower rate, while aliphatic thiols are oxidized faster than aromatic ones.[6,7]

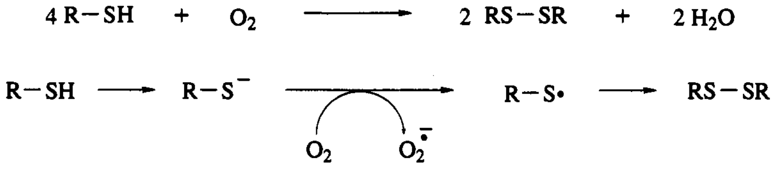

Scheme 3

The oxidation is catalyzed by various heavy metal ions such as Cu$^{II}$, Fe$^{III}$ (hemin complex), Ni$^{II}$ and Co$^{II}$ and their complexes,[1,8–10] and more importantly, the addition of these ions leads to the selective formation of disulfides without any overoxidized products. The cluster $(Bu^n_4N)_2[Fe_4S_4(SR)_4]$, the analog of the active site of nonheme iron–sulfur proteins, catalyzed extremely smooth oxidation of thiols by oxygen to disulfides in acetonitrile at 0 °C (equation 4), while in the case of $FeCl_2$ or $FeCl_3$ catalysts oxygen uptake was very slow.[11] The catalysis by $Al_2O_3$ for aerobic oxidation is also common.[12] Thus, by stirring thiols in benzene with exposure to air at room temperature for 4–6 h disulfides were obtained almost quantitatively except in the hindered case of Bu$^t$SH.

$$4\,R^1{-}SH \;+\; O_2 \xrightarrow[\substack{100\% \\ R^1 = Ph,\ PhCH_2,\ Et}]{[Fe_4S_4(SR^2)_4]^{2-},\ MeCN} 2R^1S{-}SR^1 \;+\; 2\,H_2O \qquad (4)$$

The use of a large excess of base and/or prolonged reaction times results in the absorption of excess oxygen leading to overoxidation.[6,13] The type of product also varies, $RSO_3H$ in the case of KOH/HMPA[13] and a mixture of $RSO_2H$ (major) and $RSO_3H$ (minor) in the case of Bu$^t$OK/Bu$^t$OH.[14] More detailed investigations[15] indicated that the main product is $RSO_2H$ which is in accord with the latter result. Similar overoxidation is also known in benzenethiol oxidation by the superoxide anion ($O_2^{\cdot -}$) generated from $KO_2$ and 18-crown-6.[15] Thus, at room temperature diphenyl disulfide was formed quantitatively, while both $PhSO_2H$ and $PhSO_3H$ were produced by heating with excess $O_2^{\cdot -}$ at 60 °C. In the cases of benzylic thiols desulfurization occurred unexpectedly to give benzoic acids and alkenes by aerobic oxidation in DMSO in the presence of a basic catalyst.[16]

#### *6.2.2.1.2 By metal ions, oxides and carboxylates*

Metal ions of higher oxidation states, such as Fe$^{III}$,[17] Ce$^{IV}$, Co$^{III}$ and V$^{V}$,[18,19] oxidize thiols effectively to disulfides in the absence of oxygen. A large variety of metal oxides such as $MnO_2$, $CrO_3$, $PbO_2$, $FeO_3$, $Co_2O_3$ and CuO are also useful for this transformation at low temperatures in chloroform or xylene solutions.[20,21] Various modified chromium compounds such as bis(benzyltriethylammonium) dichromate,[22] bis[trinitratocerium(IV)] chromate,[23] pyridinium chlorochromate[23] and a combination of $CrO_3$ with chlorosilane[24] are reported to be effective oxidizing agents. Bentonite-supported iron(III) nitrate,[25] CAN[26] and bis(2,2′-bipyridyl)copper(II) permanganate[27] are also selective oxidants to produce disulfides. LTA[28–31] and thallium triacetate (TTA)[32] readily effect the oxidation of thiols to disulfides (equation 5). The use of excess LTA in alcoholic solvents resulted in a selective overoxidation of the initially formed diaryl disulfides to aromatic sulfinic esters ($ArSO_2R$).[30]

$$\mathrm{Bu^t{-}SH} \;+\; \mathrm{Tl(OAc)_3} \;\xrightarrow[100\%]{\mathrm{CHCl_3,\ r.t.,\ 5\ h}}\; \mathrm{Bu^tS{-}SBu^t} \;+\; \mathrm{TlOAc} \;+\; 2\,\mathrm{AcOH} \qquad (5)$$

#### *6.2.2.1.3 By organic oxides, hydrogen peroxide and organic peroxy acids*

Dialkyl sulfoxides such as DMSO work as oxidants for the selective preparation of disulfides.[33–35] The order of thiol reactivity is ArSH > $ArCH_2SH$ > RSH.[34] Several amine oxides, such as pyridine *N*-oxides[36,37] and triethylamine oxide,[38] also oxidize sulfides to sulfoxides, but the reaction generally requires higher temperatures.

The oxidation of thiols by $H_2O_2$, dialkyl peroxides and peroxy acids is known to give disulfides as the initial products, which are further oxidized by excess oxidant.[2,39–41] Because of easy overoxidation these reactions are rarely used for preparative purposes of disulfides, but the method is often useful for obtaining some overoxidized compounds. Thus, $RSO_3H$ is produced from tertiary thiols in high yields,[2] and mercaptoimidazole (6) was oxidized by alkaline $H_2O_2$ to the corresponding sulfonic acid (7) in a moderate yield (equation 6).[40] Selective and effective oxidation of alkane thiols to the corresponding $RSO_2H$ occurs by treatment with 2 equiv. MCPBA (equation 7).[42]

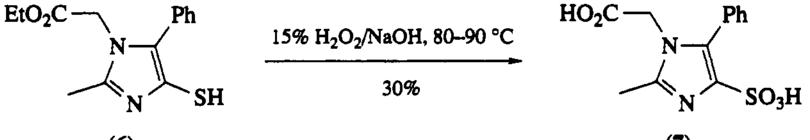

(6) (7)

(6)

$$\mathrm{R{-}SH} \;\xrightarrow[80\text{–}85\%]{2\ \mathrm{equiv.\ MCPBA,\ CH_2Cl_2,\ -30\ ^\circ C}}\; \mathrm{R{-}SO_2H} \qquad (7)$$

#### *6.2.2.1.4 By halogens and halogen compounds*

In aqueous solvents chlorine and bromine react with thiols to give sulfonyl halides or sulfonic acids (equations 8 and 9), while under anhydrous conditions various reactions occur to give sulfenyl halides (RSX), $RSX_3$ and/or disulfides.[1,2] On the contrary, oxidation with iodine is prone to give disulfides (equation 10) typically using a solution of $I_2$ in acetic acid, alcohol, ether or aqueous KI.[2,3,43,44] Under two-phase conditions of aq. $KHCO_3/CH_2Cl_2$ bromine works at room temperature as an excellent oxidant of general utility for the preparation of various disulfides (Scheme 4).[45] 2-Polyvinylpyridine–bromine complex[46] and bromodimethylsulfonium bromide ($Me_2S^+BrBr^-$)[47] are also useful reagents for obtaining disulfides from thiols.

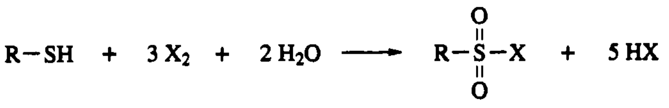

$$\mathrm{R{-}SH} \;+\; 3\,\mathrm{X_2} \;+\; 2\,\mathrm{H_2O} \;\longrightarrow\; \mathrm{R{-}}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{\mathrm{S}}}\mathrm{{-}X} \;+\; 5\,\mathrm{HX} \qquad (8)$$

Several ‘positive halogen’ compounds such as NBS, NCS, (dichloroiodo)benzene ($PhICl_2$), sulfuryl chloride, thionyl chloride, 2,4,4,6-tetrabromocyclohexa-2,5-dienone[48,49] and diethyl bromomalonate[50] *etc.* react with thiols to produce initially RSX, which then reacts with excess thiol to give disulfides.[2] Tri-

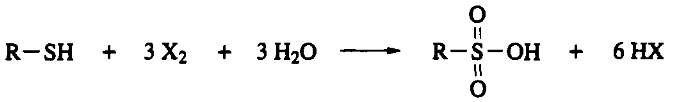

$$\mathrm{R{-}SH} + 3\,\mathrm{X_2} + 3\,\mathrm{H_2O} \longrightarrow \mathrm{R{-}\overset{\overset{\large O}{\|}}{\underset{\underset{\large O}{\|}}{S}}{-}OH} + 6\,\mathrm{HX} \tag{9}$$

$$2\ \mathrm{R{-}SH} + \mathrm{I_2} \longrightarrow \mathrm{RS{-}SR} + 2\,\mathrm{HI} \tag{10}$$

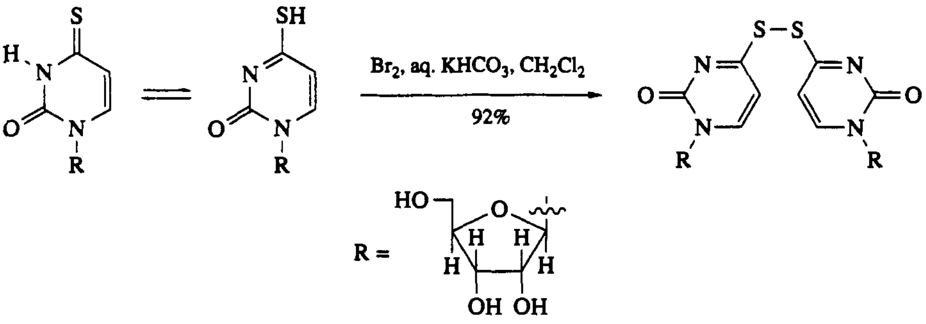

**Scheme 4**

chloromethanesulfonyl chloride is a very good reagent for selective disulfide formation in pyridine (equation 11).[51]

$$\mathrm{R{-}SH} \xrightarrow[\text{93–98\%}]{\mathrm{Cl_3CSO_2Cl},\ \text{pyridine}} \mathrm{RS{-}SR} \tag{11}$$

$\mathrm{R = Bu, Bu^t, Ph, PhCH_2}$

### *6.2.2.1.5 By other chemical reagents and other methods*

A variety of other oxidants are known for thiol oxidation, including diethyl azodicarboxylate,[52] azodicarbonamide,[53] nitrosobenzene and nitrobenzene,[36,37,53] maleic anhydride,[53] nitrogen oxide (NO),[54] iodosylbenzene (PhIO)[55] and nickel peroxide.[56] Excess dinitrogen tetroxide ($N_2O_4$) reacted with thiols to give either disulfides, thiolsulfonates ($RSSO_2R$) or sulfonic acids selectively by controlling carefully the concentration of $N_2O_4$ and other reaction conditions (Scheme 5).[57,58] Bis(4-methoxyphenyl) telluroxide[59] and selenoxide[60] as well as their polymer-bound compounds[61] are mild oxidizing agents for preparing disulfides, the ability of the telluroxides being stronger than the selenoxides. The oxidation with powerful oxidants like $HNO_3$ and $KMnO_4$ has long been known to give overoxidized sulfonic acid products.[2]

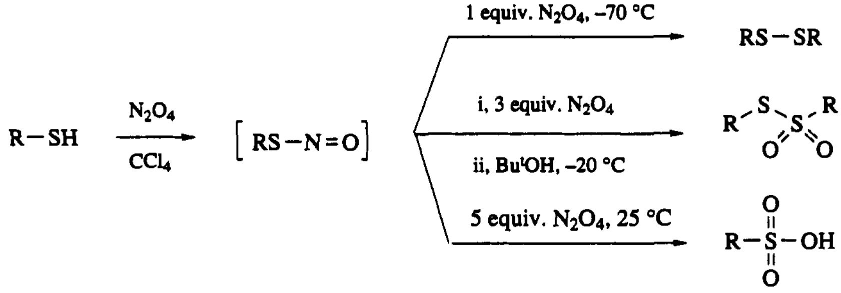

**Scheme 5**

Flavins (**8**),[62,63] 8-azaflavin (**9**)[64] and their analogs are characteristic oxidants toward thiols under anaerobic and other specific conditions (equation 12).[62–64] 5-Arylidene-1,3-dimethylbarbituric acid derivatives (**10**) also work as the oxidant in dioxane at 120–150 °C, and the method was applied to synthesis of unsymmetrical disulfides.[65] Electrochemical oxidation[66] and photolysis[67] of thiols to disulfides are also known.

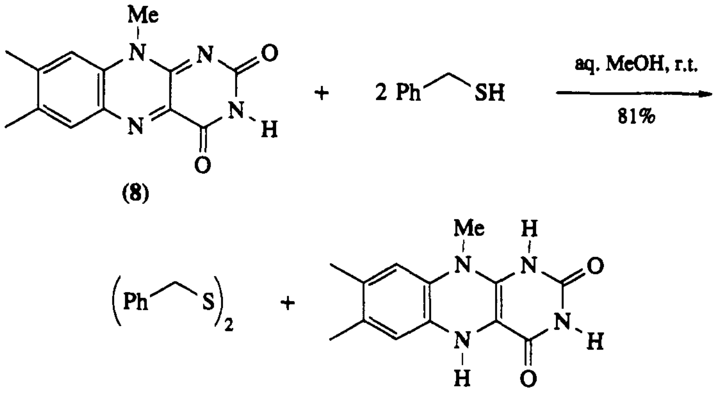

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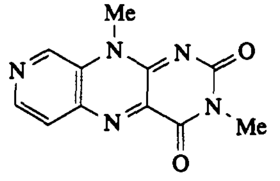

**(9)**

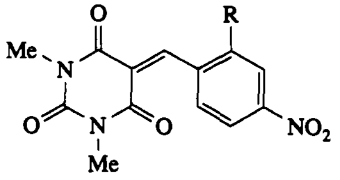

**(10)** R = $NO_2$, H

### 6.2.2.2 Oxidation of Sulfides to Sulfoxides by Chemical Reagents

The oxidation of sulfides (thioethers) gives the corresponding sulfoxides or sulfones or both, depending on the reaction conditions employed (equation 13).[68-70] In order to obtain sulfoxides selectively it is necessary to add equimolar or slightly excess amounts of oxidants to the sulfides under mild conditions. Among a variety of oxidants so far employed for this reaction are: MCPBA, TBHP, $PhICl_2$, PhIO and sodium metaperiodate ($NaIO_4$). All appear to be particularly useful for obtaining sulfoxides selectively in good yields.

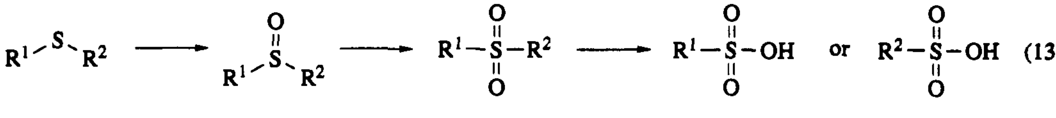

$$R^1{-}S{-}R^2 \longrightarrow R^1{-}\overset{O}{\overset{\|}{S}}{-}R^2 \longrightarrow R^1{-}\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}{-}R^2 \longrightarrow R^1{-}\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}{-}OH \text{ or } R^2{-}\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}{-}OH \quad (13)$$

#### *6.2.2.2.1 By hydrogen peroxide and organic peroxides and peroxy acids*

One of the simplest methods of oxidation of sulfides to sulfoxides is the use of $H_2O_2$ in acetone[71-73] or preferably in methanol.[74] The oxidation normally proceeds highly selectively under very mild conditions and can be applied to the preparation of various acid-sensitive sulfoxides such as allylic sulfoxides (**11**),[73] silyl-substituted vinyl sulfoxides (**12**)[75] and thietane sulfoxides (**13**).[76] The oxidation is accelerated in the presence of acetic acid although selective oxidation for *S*-monoxides is possible as shown in equations (14),[77] (15)[78,79] and (16).[80] However, the use of excess $H_2O_2$ often leads to overoxidation to give sulfones. Many metal salts such as $SeO_2$,[81] $V_2O_5$,[82] $TiCl_3$[83] and $VO(acac)_2$[84] also function as good catalysts.

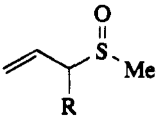

**(11)**

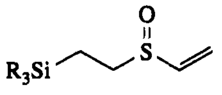

**(12)**

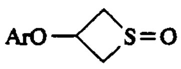

**(13)**

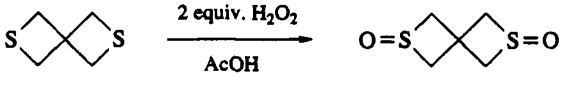

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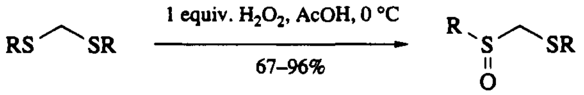

(15)

R = Me, Et, Pr$^i$, Bu$^t$, Ph

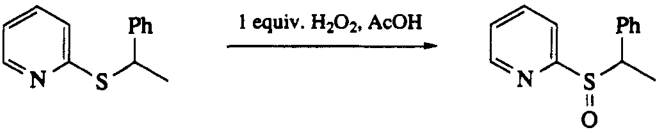

(16)

Organic peroxides such as cyclohexyl or *t*-butyl hydroperoxide[85] and benzoyl peroxides[86] can oxidize various sulfides to the corresponding sulfoxides where oxidation with TBHP in alcohols or benzene appears to be synthetically useful.[85,87,88] 2-Hydroperoxyhexafluoro-2-propanol [$(CF_3)_2C(OH)OOH$], formed *in situ* from hexafluoroacetone and $H_2O_2$, is also a very effective and convenient reagent for this purpose.[89] 4a-Hydroperoxylumiflavin (**14**) oxidizes sulfides to sulfoxides in organic solvents such as Bu$^t$OH or dioxane at 30 °C much more effectively than $H_2O_2$.[90–92] The reactivity of the flavins was shown to be $10^3$–$10^6$ more reactive than TBHP and ~$10^3$ less reactive than MCPBA.[91]

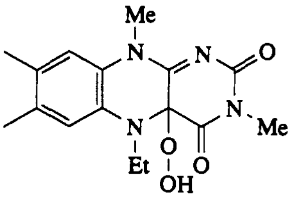

(**14**)

A variety of organic peroxy acids such as perbenzoic acid,[93,94] MCPBA,[95,96] monoperoxyphthalic acid,[97] peracetic acid[98] and trifluoroperacetic acid[99] are much stronger oxidants than $H_2O_2$, and oxidize sulfides to sulfoxides under very mild conditions. Usually 1 equiv. of peroxy acid to sulfide is employed, otherwise overoxidation easily occurs to give sulfones.[99] Among these, MCPBA has the advantage of being convenient to use and the oxidation is normally carried out at 0 °C or lower temperatures, in dichloromethane. The preparations of the base-sensitive sulfoxide (**15**),[100] a new dienophile alkynyl sulfoxide (**16**),[101] and thiiraneradialene *S*-oxide (**17**)[102] are typical examples. Selective oxidation of the sulfur atom of penicillins by polymer-supported peroxy acids in DMF or acetone is also known (equation 17).[103]

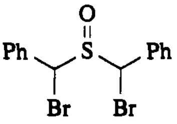

(**15**)

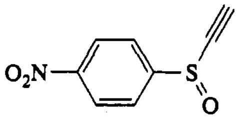

(**16**)

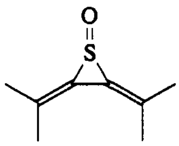

(**17**)

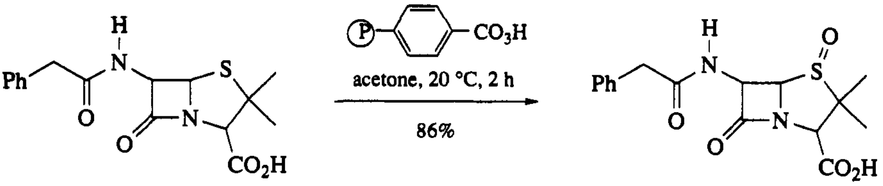

(17)

#### 6.2.2.2.2 By halogens and halogen compounds

Molecular halogens have been known to form some addition compounds (**18**) with organic sulfides which are readily hydrolyzed to sulfoxides (Scheme 6). However, undesired side reactions sometimes occur, such as cleavage of a C—S bond giving a C–halogen bond and halogenation or alkoxylation at various positions.[104–106] The formation of by-products can be prevented by carrying out the reaction in the presence of amines[107] or under two-phase conditions ($CH_2Cl_2/H_2O$) using $KHCO_3$ as a base.[108] The treatment of sulfides with bromine and then with hexabutyldistannoxane gives sulfoxides in high yields without sulfone by-product contamination (equation 18).[109] The sulfoxide formation by iodine oxidation is relatively slow, but can be accelerated by certain nucleophiles such as phthalate ion[110] or β-cyclodextrin phosphate ion.[111] Sulfides react with the stoichiometric quantity of $PhICl_2$ in aqueous pyridine between −40 and 20 °C to give high yields of the corresponding sulfoxides completely free from sulfones, and use of $^{18}O$-enriched water readily gives $^{18}O$-labeled sulfoxides (equation 19).[112] PhIO,[55,113] $PhIO_2$ with $VO(acac)_2$ catalyst[114] and (diacetoxyiodo)benzene $[PhI(OAc)_2]$[115] can also be used for oxidation of some sulfides.

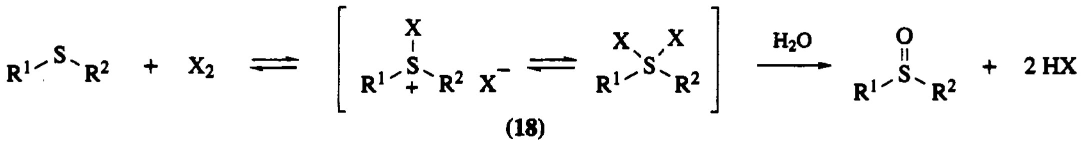

**(18)**

**Scheme 6**

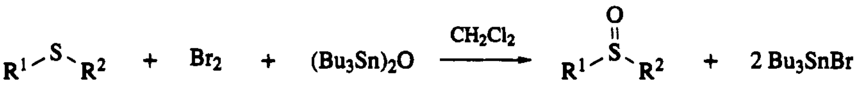

(18)

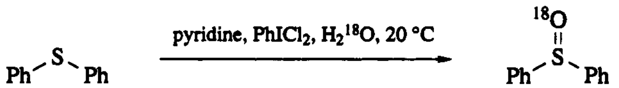

(19)

Many 'positive halogen' compounds such as NBS,[116–118] NCS,[118] 1-chlorobenzotriazole,[119] and chloramine-T and bromamine-T[120–122] oxidize sulfides to sulfoxides. Sulfides may also be oxidized efficiently to sulfoxides uncontaminated by sulfones using 2,4,4,6-tetrabromocyclohexa-2,5-dienone in aqueous dioxane or THF (equation 20)[49] and also using sulfuryl chloride at room or lower temperature.[123,124] Hypochlorites such as sodium hypochlorite (NaOCl),[125,126] hypochlorous acid (HOCl)[125] and Bu$^t$OCl[127–129] are sometimes used as stereo- and chemo-selective oxidants for obtaining sulfoxides from sulfides, as shown in equations (21)[126] and (22).[127] However, application to sulfides bearing an ethynyl or a methoxycarbonyl group α to sulfur resulted in sole formation of the corresponding α-alkoxy sulfides, rather than the expected sulfoxides (equation 23).[128] Oxidation of sulfides by $NaIO_4$ in water, aqueous methanol or other organic solvents at 0 °C results in a selective formation of sulfoxides.[130] This reaction was applied to the preparation of various sulfoxides including 1-butadienyl phenyl sulfoxide (**21**),[131] α-phos-

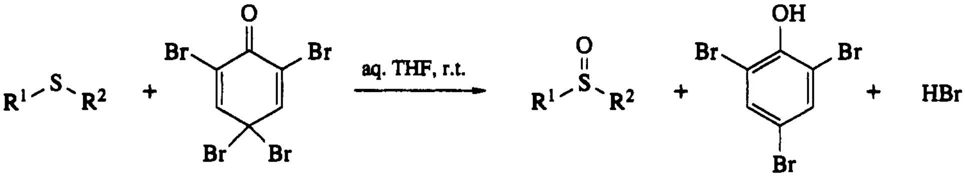

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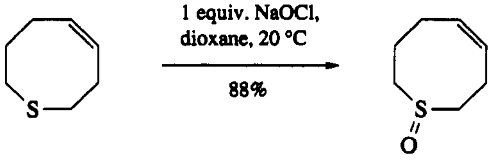

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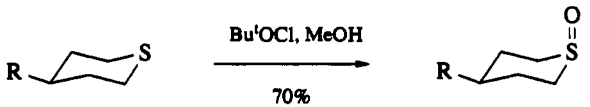

**(19)** **(20)** *cis* > 89%

(22)

phoryl sulfoxides (**22**),[132] and sulfoxides containing a disulfide moiety (**23**).[133] Various modifications have been made to this method, such as the use of tetrabutylammonium periodate[134] and the use of alumina-[135] and silica gel-supported NaIO$_4$.[136] Sodium bromite (NaBrO$_2$) is also used as an oxidant for sulfoxides in aqueous dioxane.[137]

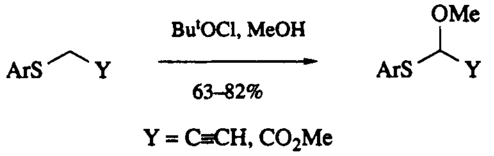

(23)

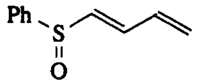

**(21)**

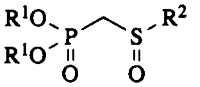

**(22)**

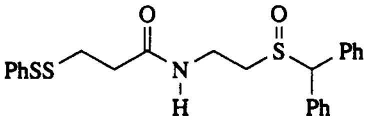

**(23)**

### *6.2.2.2.3 By other chemical reagents and other methods*

A variety of other oxidants that produce sulfoxides from sulfides are known, such as nitric acid,[138,139] acyl nitrates,[140] nitronium salts,[141] N$_2$O$_4$,[142,143] oxygen with ruthenium complex catalysts,[144,145] pressurized oxygen with CAN as a catalyst,[146] ozone,[147,148] TTN,[149] Ce$^{IV}$ salts,[150,151] LTA[152,153] and potassium peroxodisulfate (K$_2$S$_2$O$_8$).[154] Potassium hydrogen persulfate (KHSO$_5$; Oxone) is a very efficient and chemoselective oxidant to produce sulfoxides from sulfides under phase-transfer conditions[155] and also in a catalytic cycle involving *N*-sulfonyloxaziridines (**24**), as shown in Scheme 7.[156] Selenium compounds such as dialkyl[157] or diaryl selenoxides,[60] areneselenonic acids (ArSeO$_3$H)[158,159] and areneseleninic acids (ArSeO$_2$H)[159] are also useful reagents for the sulfoxidation of various sulfides. Sulfides may be oxidized to sulfoxides highly selectively and almost quantitatively by sulfinylperoxy intermediates (ArSO$_3$· or ArSO$_3^-$; Ar = 2-NO$_2$C$_6$H$_4$) generated *in situ* from 2-nitrobenzenesulfinyl chloride (ArSOCl) and superoxide (O$_2^-$) in acetonitrile at –25 °C.[160]

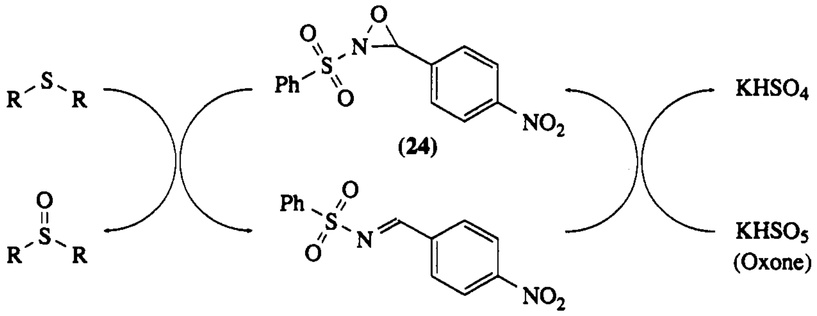

Scheme 7

Sulfides are also oxidized to sulfoxides under electrochemical[161–165] and photochemical[166–168] conditions. Electrochemical oxidation has remained rather unselective, giving mixtures of sulfoxides and sulfones, but a highly selective electrolytic oxidation is now known where the electric current passes through a bath of 4-polyvinylpyridine hydrobromide (PVP·HBr) and sulfide (equation 24).[163]

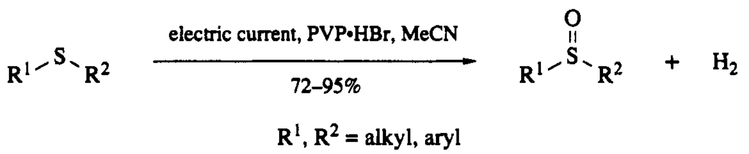

(24)

### 6.2.2.3 Oxidation of Sulfoxides to Sulfones by Chemical Reagents

Oxidation of sulfoxides usually results in the formation of sulfones, although under extremely vigorous conditions $RSO_3H$ may be produced.[169] Sulfones are also obtained by direct oxidation of sulfides *via* sulfoxides (equation 13). A variety of oxidants have been utilized to effect these transformations, among which $H_2O_2$ in acetic acid, NaOCl, $PhICl_2$, $CrO_3$, $KMnO_4$ and $KHSO_5$ (Oxone) appear to be most useful from the synthetic viewpoint. With peroxy acids and peroxides the oxidation of sulfoxides to sulfones generally proceeds more slowly than that of sulfides to sulfoxides because of the reduced nucleophilicity of the sulfoxide sulfur atom compared to that of the sulfide. Completely the reverse is normally observed with oxidants of a nucleophilic nature such as periodates or transition metal salts such as $CrO_3$ and $KMnO_4$.

#### *6.2.2.3.1 By hydrogen peroxide and organic peroxy acids and peroxides*

Hydrogen peroxide has long been known to oxidize sulfoxides to sulfones either alone or in the presence of metal catalysts such as $Fe^{III}$ salts,[170,171] $Na_2WO_4$,[172,173] $WO_3{\cdot}H_2O$[173] and $Na_2VO_4$.[173] The use of $H_2O_2$ in acetic acid is also most effective for obtaining sulfones, the reactive species most probably being peracetic acid. The oxidation is catalyzed by $Mn(acac)_3$.[174] The oxidation of diaryl sulfoxides to diaryl sulfones has been shown to proceed several hundred times slower than that of diaryl sulfides to the sulfoxides,[175] in accordance with the result shown (for dialkyl compounds) in equation (14). Probably as an exception, the oxidation of 1,4-dithiadiene monosulfoxide (**25**) is reported to give the corresponding monosulfone instead of the expected bis-sulfoxide (equation 25).[176]

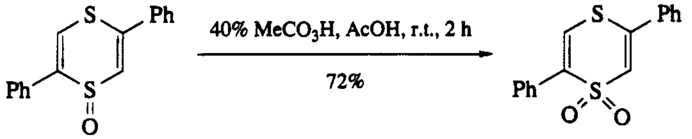

(**25**)

(25)

Many other peroxy acids, such as trifluoroperacetic acid (equation 26),[99,177] peroxydodecanoic acid (equation 27)[178] and various perbenzoic acids[100,179–182] are also useful oxidants to give a high yield of sulfones from sulfoxides or directly from sulfides under suitable conditions.

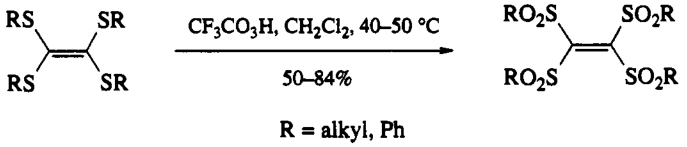

(26)

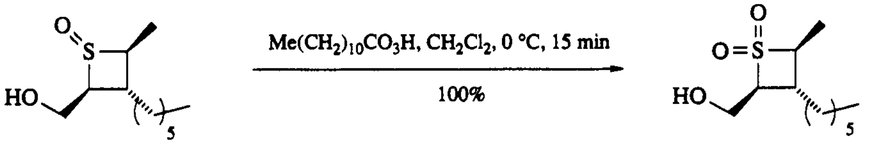

(27)

Organic hydroperoxides are generally used for the preparation of sulfoxides from sulfides,[85,87,88] while sulfones can be obtained in neutral organic solvents in the presence of metal catalysts such as V, Mo and Ti oxides at 50–70 °C.[183] Two polymer-supported reagents which involve peroxy acid groups[184] and bound hypervalent vanadium(V)[185] and molybdenum(VI)[186] compounds have been developed for facile oxidation of sulfoxides to sulfones.

Solutions of $KO_2$ and 18-crown-6 in DMSO cause oxidation of the solvent to the sulfone.[187] The phosphorus-containing peroxy anion $(EtO)_2PO_3^-$ obtained on reaction of $KO_2$ with diethyl chlorophosphate $[(EtO)_2POCl]$ in acetonitrile has been used to prepare sulfones from sulfoxides at 20 °C.[188] Similarly, various sulfoxides are readily oxidized chemoselectively to the sulfones in high yields by 2-nitrobenzene peroxysulfur intermediate (**26**) generated *in situ* from 2-nitrobenzenesulfonyl chloride and $KO_2$ (Scheme 8; Ar = $2\text{-}NO_2C_6H_4$).[189]

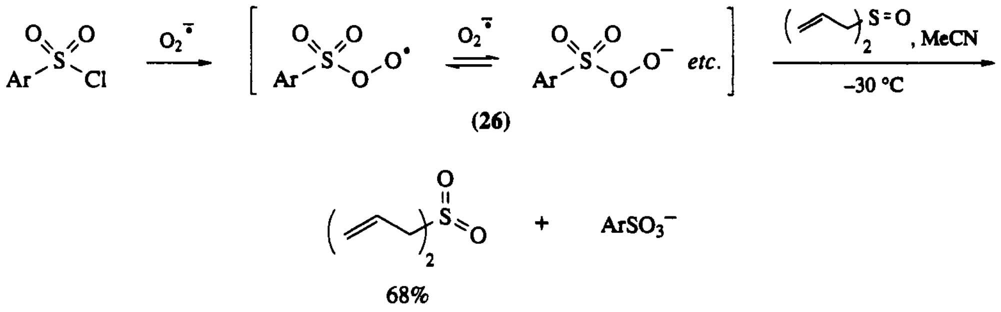

Scheme 8

### 6.2.2.3.2 By halogens and halogen compounds

A number of halogen compounds are capable of oxidizing sulfoxides to sulfones, although synthetically useful procedures are rather limited. Chlorine and sulfuryl chloride oxidize sulfoxides to sulfones in aqueous solvents, but the oxidation is often accompanied by many side reactions as shown in equations (28)[190] and (29).[191] NaOCl seems to be a general oxidant to generate sulfones from either sulfides[192] or sulfoxides.[126] At low temperature 1-chlorobenzotriazole converts sulfoxides to sulfones in high yields.[119] In aqueous pyridine solution excess $PhICl_2$ oxidizes most diaryl sulfides and sulfoxides to the corresponding sulfones, except those bearing electron-withdrawing substituents on the aryl ring (equations 30 and 31).[112,193] PhIO with ruthenium(II) complex as a catalyst[194] as well as $PhI(OAc)_2$[195] work as oxidants for producing sulfones either from sulfoxides or sulfides, the products depending on the amount of the oxidant used (Scheme 9).[194] Bromine and hypobromite ($OBr^-$) oxidize sulfoxides to sulfones in alkaline solutions, but multihalogenated products are usually produced (equation 32).[196]

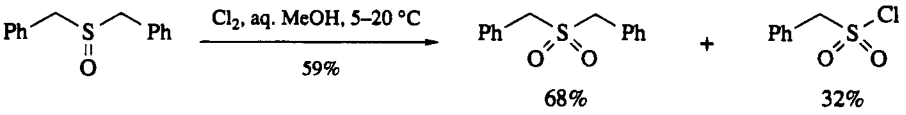

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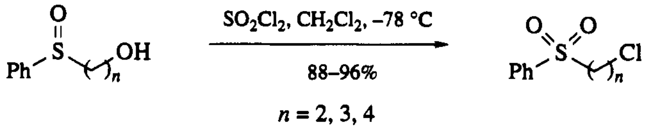

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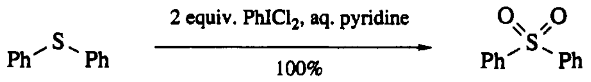

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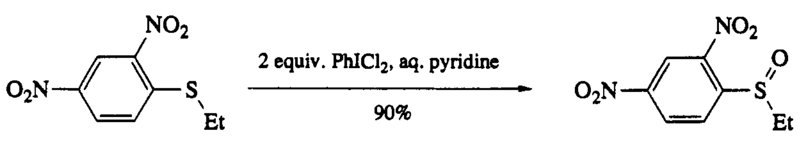

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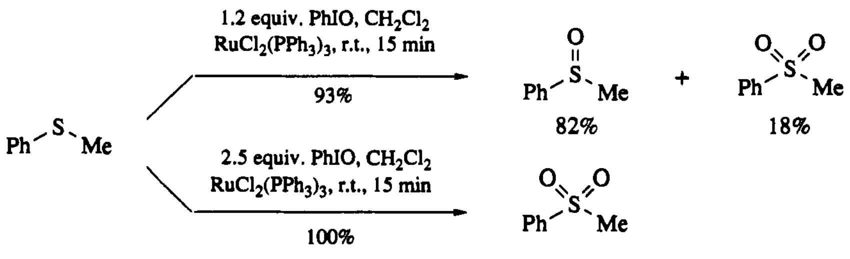

Scheme 9

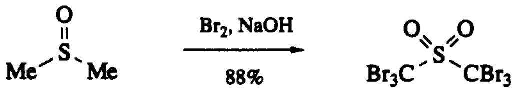

(32)

### 6.2.2.3.3 By transition metal salts

In sharp contrast to peroxy acid oxidation[175] the oxidation of sulfoxides to sulfones with various transition metal salts proceeds much faster than that of sulfides to sulfoxides and consequently sulfoxides may be selectively oxidized to sulfones in the presence of sulfides.

Chromium trioxide is a very effective oxidant in aqueous $H_2SO_4$,[197] aqueous acetic acid[198] or water[199] where many other functional groups are tolerated (equation 33).[199] Potassium permanganate, though slightly less reactive than $CrO_3$, can also be used for oxidation of sulfoxides to sulfones in aqueous acid media (equations 34–36).[197,200–202] In the presence of $MgSO_4$ and in acetone, $KMnO_4$ becomes a chemoselective oxidant which reacts faster with sulfoxides than with sulfides, as exemplified in Scheme 10 for the preparation of 1,3-dithietane 1,1-dioxide (27).[203] Comparison with other oxidants highlights the selectivity in this reaction.[203]

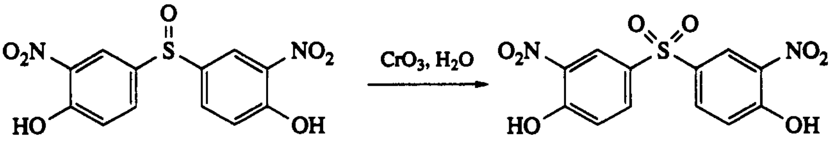

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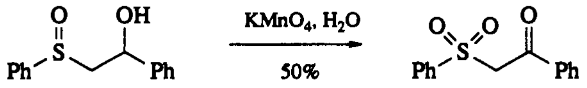

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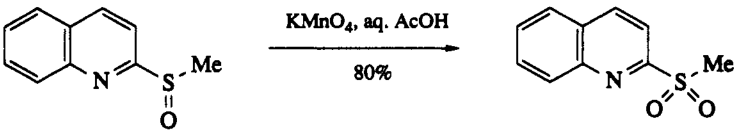

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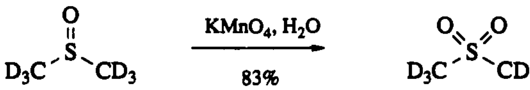

(36)

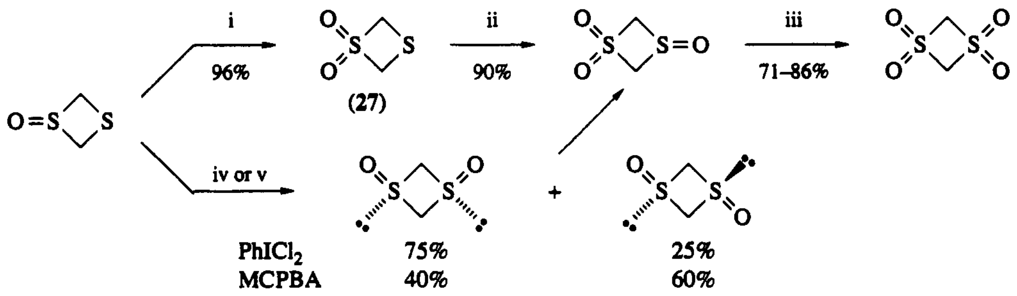

i, $KMnO_4$, $MgSO_4$, acetone, –20 °C; ii, $MeCO_3H$, $CHCl_3$, 0 °C; iii, 30 equiv. $MeCO_3H$, 100 °C, 4 h;
iv, $PhICl_2$, aq. pyridine, –30 °C; v, MCPBA, $CH_2Cl_2$, 0 °C

Scheme 10

Permanganates of zinc,[204] sodium[205] and benzyltriethylammonium[206] have also been shown to be effective and selective oxidants to obtain sulfones from sulfides. The method of sulfoxide oxidation under phase-transfer conditions has also been developed using $KMnO_4$[207] and $Cu(MnO_4)_2$.[208]

Osmium tetroxide is another chemoselective oxidant reported to yield sulfones from sulfoxides. Thus, treatment of a mixture of diphenyl sulfide and sulfoxide with $OsO_4$ in boiling ether for 48 h affords diphenyl sulfone in 96% yield without any change of the sulfide component.[205] Other transition metal salts such as Ce$^{IV}$, Ni$^{IV}$ and Ru$^{VIII}$ may be used for sulfoxide oxidation.

#### *6.2.2.3.4 By other chemical reagents and other methods*

A number of other oxidants which produce sulfones from sulfoxides are known, such as $HNO_3$,[209] $NO_2BF_4$,[210] oxygen with Ir or Rh catalysts,[211] ozone,[147] $KHSO_5$ (Oxone)[212] and $K_2S_2O_8$.[213] Oxone is a highly chemoselective oxidant for the conversion of sulfides to sulfones without affecting hydroxy or alkenic groups (equation 37).[212] Similarly flavin (**14**) oxidizes aryl methyl sulfoxides to sulfones fairly selectively.[91]

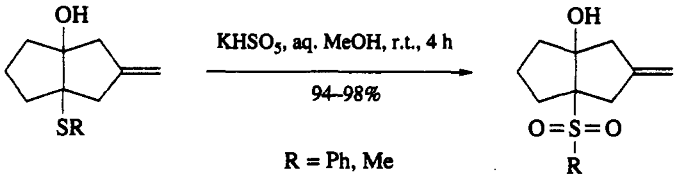

(37)

It is worthy of note that oxidation of thiolsulfinate (**28**) with sodium periodate in aqueous acetonitrile or dioxane gives thiolsulfonate (**29**) by attack on the sulfur atom of the S=O moiety and not the S atom, as shown in equation (38).[214] These data clearly indicate the nucleophilic nature of the periodate ion.

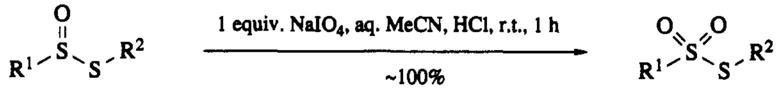

(**28**) (**29**)

(38)

Diphenyl sulfoxide[215] and dimethyl sulfoxide[216] are oxidized electrochemically to the corresponding sulfones in acetonitrile and 1 M $H_2SO_4$, respectively. The product yields are enhanced by the presence of transition metal salts or oxides of W, V, Mo or Se.[217] In some cases sulfonic acid salts are formed with C—S cleavage.[218] Sulfoxides react with oxygen under photochemical conditions to give sulfones in good yields.[219–222]

## 6.2.3 OXIDATION OF ORGANIC SELENIUM COMPOUNDS[223,224]

### 6.2.3.1 Oxidation of Selenols to Diselenides and Further Oxidized Species by Chemical Reagents

As compared with thiols, selenols are readily oxidized to diselenides (equation 39). Although aryl selenols are more stable than alkyl selenols, both must be stored under inert gas in order to preserve the selenol form.[225] Consequently they are normally prepared *in situ* and used directly as a source of RSe moiety or as a reducing agent. Diselenides can be prepared merely by bubbling air or oxygen through a selenol solution.[226–228] Other oxidizing agents employed are $H_2O_2$,[229,230] $Br_2$,[231] $R_2NCl$[232] and $K_3Fe(CN)_6$.[233]

$$4\,R{-}SeH + O_2 \longrightarrow 2\,RSe{-}SeR + 2\,H_2O \qquad (39)$$

Oxidation of diselenides with $Br_2$,[234] $H_2O_2$,[235–239] $HNO_3$,[239–241] ozone,[242] TBHP[243,244] and MCPBA[235] affords seleninic acids (**30**) and/or their anhydrides (**31**; equation 40), both of which are known as useful oxidants of various organic compounds.[245] The oxidation has been suggested to proceed as shown in Scheme 11[242] and as evidence intermediate compounds were isolated from the MCPBA oxidation of

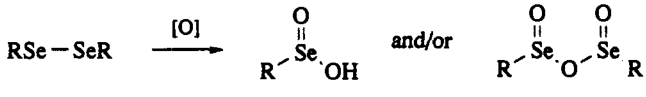

(**30**) (**31**)

(40)

naphtho[1,8-*cd*]-1,2-diselenole (**33**; Scheme 12).[246] In some cases, however, selenenic acids (RSeOH) are isolated which readily disproportionate into selenols and seleninic acids (**30**).[234] Only a few RSeOH compounds have so far been isolated,[235,247,248] and many compounds previously claimed as RSeOH are in fact anhydrides (**32**).[249,250] The seleninic acids are also synthesized by oxidation of selenocyanates (RSeCN) with $HNO_3$,[239,251-253] peracetic acid[238] and $KMnO_4$.[234]

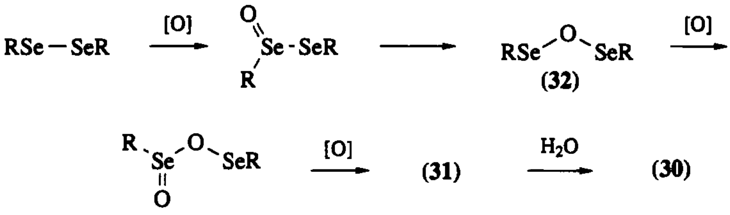

**Scheme 11**

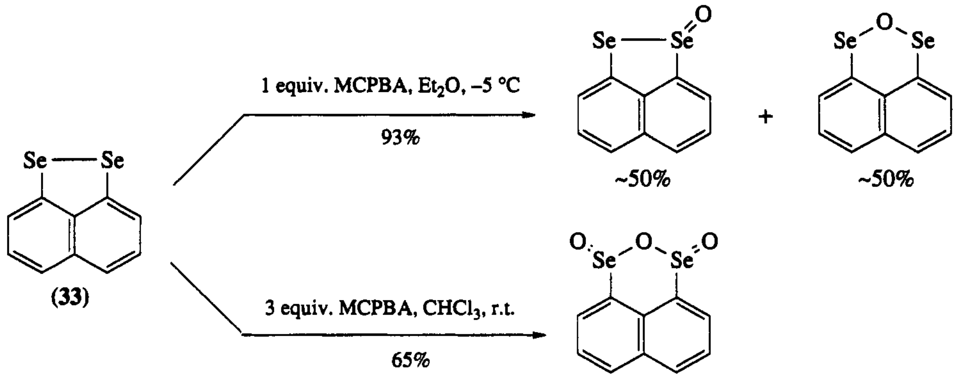
Se—Se
(33)
1 equiv. MCPBA, $Et_2O$, -5 °C
93%
Se—Se
O
~50%
+
Se
O
Se
~50%
3 equiv. MCPBA, $CHCl_3$, r.t.
65%
O
Se
O
Se
O

**Scheme 12**

Permanganate oxidation of seleninic acids has been reported to give selenonic acids ($RSeO_3H$).[240,254,255] The oxidation product of benzeneseleninic acid seems to be the selenonate (**34**).[256a] Selenonic acids or their K or Na salts may be isolated by ion exchange chromatography[255,256a] and are generally very hygroscopic substances having strong oxidizing properties.

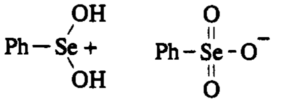

$$\mathrm{Ph{-}\overset{OH}{\underset{OH}{Se^{+}}}}\qquad \mathrm{Ph{-}\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{Se}}}}{-}O^{-}}$$

(**34**)

Oxidation of diphenyl diselenide with $(NH_4)_2S_2O_8$ gives phenylselenenyl cation ($PhSe^+$) which effects the oxyselenenylation of alkenes.[256b] Similar oxidation has also been effected electrochemically.[256c]

### 6.2.3.2 Oxidation of Selenides to Selenoxides by Chemical Reagents

Selenides may be oxidized by various reagents to selenoxides. When the resulting selenoxides bear a β-hydrogen atom *syn* elimination giving alkenes occurs readily at room temperature with formation of selenenic acid by-products (Scheme 13). For allylic selenides, the oxidation does not lead to conjugated

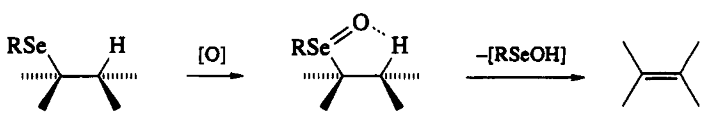

**Scheme 13**

dienes, rather a facile formation of allylic alcohols *via* selenenic esters (**35**) by 2,3-sigmatropic rearrangement occurs (Scheme 14). These two reactions are very useful in synthetic organic chemistry and described in detail in Volume 6 of this series.

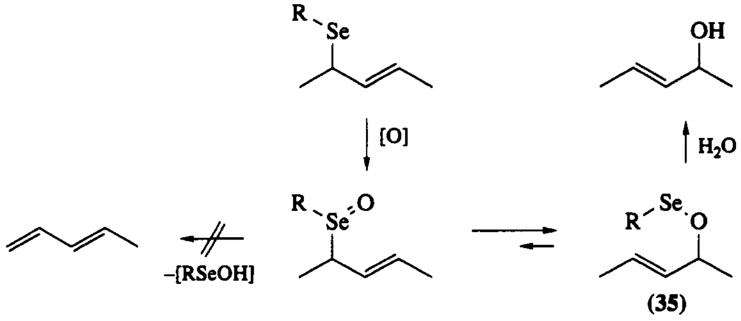

**Scheme 14**

The isolable and thermally stable selenoxides are, therefore, rather limited. Stable examples are as follows: those derived from selenides which have no hydrogen atoms on the β-carbon, such as dimethyl selenide,[256,257] aryl methyl selenides,[256,257] diaryl selenides[258,259] and benzyl phenyl selenides,[260,261] those with an intramolecular hydrogen bonding, such as (**36**)[262,263] and (**37**),[264] and those leading to an unfavorable double bond such as (**38**).[265] Vinylic selenoxides (**39**)[266] and (**40**)[267] are also generally isolable.

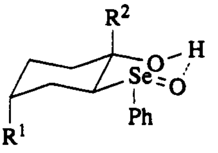

(**36**) R = 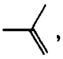, $R^2$ = Me; $R^1$ = $R^2$ = H

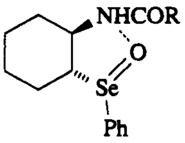

(**37**)

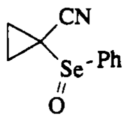

(**38**)

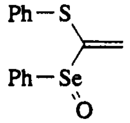

(**39**)

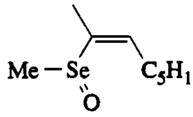

(**40**)

### *6.2.3.2.1 By hydrogen peroxide and organic peroxides and peroxy acids*

The most commonly used oxidant for selenium compounds is $H_2O_2$.[227,228,268–272] The oxidation procedure normally involves addition of 30% $H_2O_2$ to a THF or preferably dichloromethane solution of the selenide at 0 °C. The oxidation proceeds chemoselectively and, thus, many potentially oxidizable functional groups such as alkenes, sulfides, amines, sulfoxides, tertiary alcohols, esters, lactones, nitriles and carboxylic acids remain intact. Several selenoxides including (**36**) and (**37**) were isolated by this method.[259,263,264,273]

MCPBA and peracetic acid are also effective oxidants,[272,274] particularly at low temperature (–78 °C) where the selenoxides are stable.[275–277] These reagents may be used in the presence of a double bond, a triple bond[278] or an amino group.[272] Various selenoxides, especially vinylic selenoxides such as (**40**), have been isolated using this route.[267,279–282] *t*-Butyl hydroperoxide is an especially mild oxidant which can be used in excess as a replacement for $H_2O_2$ without undesirable overoxidation side-reactions taking place.[283]

### *6.2.3.2.2 By other chemical reagents*

Ozone is an effective chemoselective oxidant at low temperatures affording selenoxides without affecting alkenic or sulfide groups in the same molecule.[231,242,260,261,276,284,285] For example diastereoisomeric selenoxides (**41**) and (**42**) were prepared by oxidation of the corresponding selenide with ozone.[284] The β-elimination process affording the alkene (**43**) proceeds much faster with (**41**) than with (**42**).

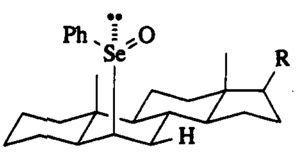

**(41)**

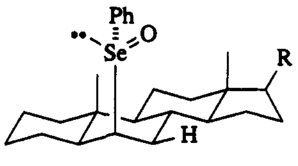

**(42)**

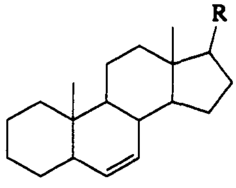

**(43)**

Sodium periodate is also frequently used as an oxidant for selenides, the reaction proceeds slowly in aqueous methanol.[272] Various selenoxides such as methyl phenyl and benzyl phenyl selenoxides,[286] (**38**),[265] (**39**),[266] (**40**)[267] and 2-azidocyclohexyl phenyl selenoxide[287] have been isolated in this way. Other solvents and reaction conditions may also be employed.[231,267,268,272,288–290]

*N*-Sulfonyloxaziridine (**24**) oxidizes selenides to selenoxides in aprotic solvents at 0–5 °C, sometimes giving quantitative yields.[291] Also halogenation of selenides with $Cl_2$ or $Br_2$ followed by alkaline hydrolysis or treatment with silver oxide gives selenoxides in good yields (equation 41).[292–295] The corresponding hydrates (**44**) can be isolated when the aromatic nucleus bears donor groups such as methoxy and ethoxy.[296] A similar hydrate (**45**) was also isolated during $H_2O_2$ oxidation of the corresponding selenide.[268] It has also been proposed that benzyl phenyl selenoxide is in equilibrium with its hydrate in aqueous DMSO.[260] This halogenation–hydrolysis method has recently been applied to alkyl phenyl selenides for the syntheses of vinylic and allylic chlorides,[297] enones[297] and *cis*-1,2-substituted cyclohexanes.[298] Isolation of the selenoxide (**38**) was achieved by treatment of the selenide with $(Bu^n{}_3Sn)_2O/Br_2$ in dichloromethane.[265] Similarly $PhICl_2$ oxidizes diaryl and aryl benzyl selenides to the corresponding stable selenoxides in aqueous pyridine.[286]

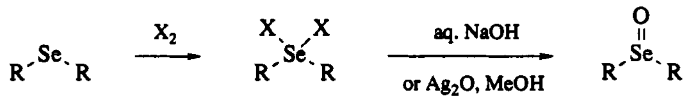

(41)

R = Me, PhCH₂, aryl

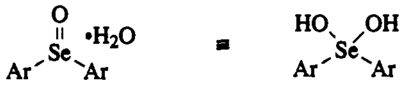

**(44)**

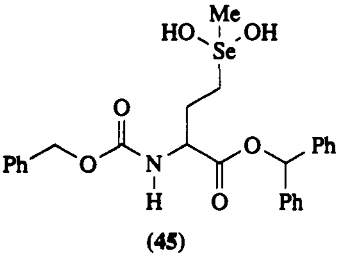

**(45)**

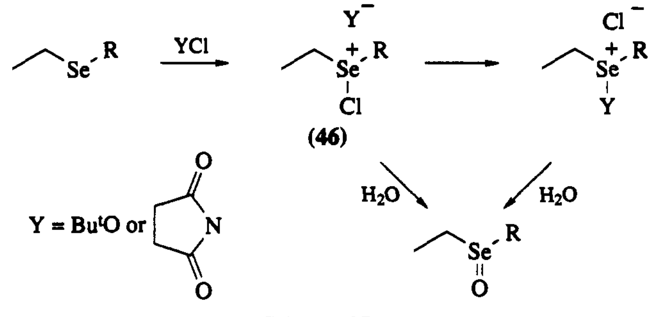

**Scheme 15**

Treatment of selenides with NBS,[265] NCS[262,265] or $Bu^tOCl$[262,299] followed by hydrolysis gives selenoxides or elimination products in good yields (Scheme 15). The intermediate (**46**) can oxidize alcohols to ketones.[300] Other oxidants such as $N_2O_4$,[294] TTN[149,301] and $CrO_3$[302] have been reported to be effective for oxidation of selenides.

### 6.2.3.3 Oxidation of Selenides and Selenoxides to Selenones

The oxidation of selenoxides to selenones is slow requiring drastic conditions to be used. Diaryl, aryl methyl and dimethyl selenones are prepared by the oxidation of the corresponding selenoxides with prolonged exposure to $KMnO_4$[293,303] or ozone.[295] The direct oxidation of selenides to selenones by PhIO with ruthenium(II) complex catalyst,[194] $H_2O_2$[304] and $Cu(MnO_4)_2$[208] has also been described. Aryl trifluoromethyl selenides, selenoxides and selenium dichlorides are oxidized with a mixture of trifluoroacetic anhydride and 85% $H_2O_2$ at low temperature to give the corresponding selenones in good yields (equation 42).[304] However MCPBA appears to be the most effective oxidant of selenides and selenoxides to selenones,[242,279,305] several vinyl selenones being prepared by this method (equation 43)[279] and used for many useful organic transformations.[279,280,306] Recent detailed studies on oxidation of various dialkyl and alkyl aryl selenides to the corresponding selenones revealed that MCPBA, $CF_3CO_3H$ and $KMnO_4$ are the reagents of choice, while oxidation with $H_2O_2$, TBHP and $NaIO_4$ often stops at the selenoxide stage (Scheme 16).[307]

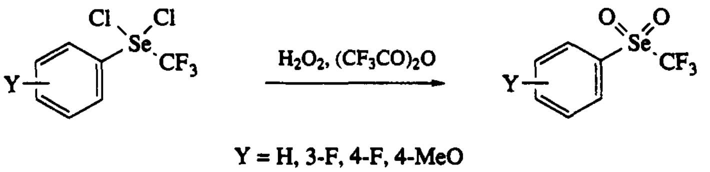
Cl
Cl
Se
CF3
Y
H2O2, (CF3CO)2O
O
O
Se
CF3
Y
Y = H, 3-F, 4-F, 4-MeO

(42)

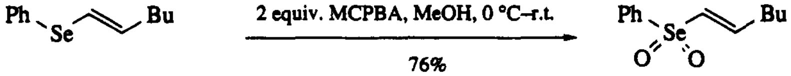
Ph
Se
Bu
2 equiv. MCPBA, MeOH, 0 °C–r.t.
76%
Ph
Se
O
O
Bu

(43)

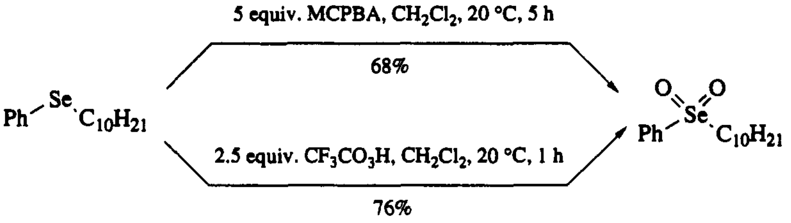
5 equiv. MCPBA, CH2Cl2, 20 °C, 5 h
68%
Ph
Se
C10H21
2.5 equiv. CF3CO3H, CH2Cl2, 20 °C, 1 h
76%
O
O
Ph
Se
C10H21

Scheme 16

Oxidation of alkyl phenyl selenides with excess MCPBA in alcohols results in a facile substitution of a selenone moiety by an alkoxy group (Scheme 17).[308,309] The intermediate addition compound (**47**) be-

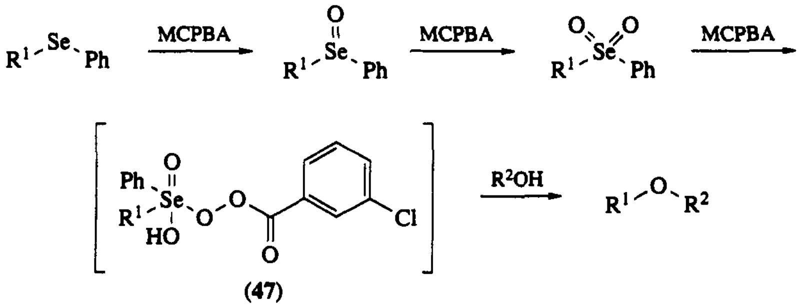
R1
Se
Ph
MCPBA
O
R1
Se
Ph
MCPBA
O
O
R1
Se
Ph
MCPBA
Ph
O
R1
Se
HO
O
O
O
Cl
O
R2OH
R1
O
R2

(**47**)

Scheme 17

tween the selenones and MCPBA is thought to be the reason why a phenylselenonyl group works as a very good leaving group. MCPBA is the oxidant of choice for this transformation, since the use of other oxidants such as $H_2O_2$, TBHP and $NaIO_4$ leads to normal selenoxide *syn* elimination providing the corresponding alkenes.

Few examples of photooxidation of selenides are known. Photolysis of dilute aerated solutions of dibenzyl diselenide in benzene resulted in the formation of benzaldehyde and elemental selenium.[310] Without oxygen present during the photolysis only decomposition to dibenzyl selenide and selenium was observed.[310,311] Photolysis in $CDCl_3$ in an NMR tube in the presence of oxygen gave complex mixtures of products derived from benzyl radicals.[312] It appears that monoselenides are more stable than the corresponding sulfides and tellurides to photooxidation.[313]

## 6.2.4 OXIDATION OF ORGANIC TELLURIUM COMPOUNDS

### 6.2.4.1 Oxidation of Tellurols to Ditellurides and Further Oxidized Species by Chemical Reagents

Tellurols are extremely air sensitive and are normally not isolated as they are converted to ditellurides (equation 44).[314–319] Nevertheless there are two reports on the isolation of alkanetellurols.[320,321] Benzenetellurol may be prepared *in situ* by treatment of trimethylsilyl phenyl telluride ($PhTeSiMe_3$) with methanol[322] or $CF_3CO_2H$[323] and also by reduction of diphenyl ditelluride with $H_3PO_2$ or $NaBH_4$[322,324–326] and used as a reducing agent.[322,323]

$$2\,[\mathrm{R{-}TeH}] + \mathrm{O_2} \longrightarrow 2\,\mathrm{RTe{-}TeR} + 2\,\mathrm{H_2O} \qquad (44)$$

Treatment of ditellurides with $H_2O_2$[327] or air[327–329] gave white products which were not further characterized. Oxidation of diphenyl ditelluride with conc. $HNO_3$ has been reported to give benzenetellurinic acid nitrate $[PhTe(O)ONO_2]$.[330,331] *t*-Butyl hydroperoxide oxidizes diaryl ditellurides to the corresponding tellurenic esters (**48**) and/or tellurinic esters (**49**) in the presence of carboxylic acids (equation 45).[332] For an exceptional example, the formation of benzotellurophene derivatives (**52**) by $SeO_2$ oxidation of 1-tellurochromenes (**50**) *via* ditellurides (**51**) was reported (Scheme 18).[333] Halogenation of ditellurides ($R_2Te_2$) with excess bromine or sulfuryl chloride gives tellurinyl halides ($RTeX_3$).[334,335] With an equimolar amount of bromine an unstable tellurenyl halide (RTeX) was isolated when R is 2-nitrophenyl,[334] while the reaction of di-2-naphthyl ditelluride with iodine produced a stable 2-naphthalenetellurenyl iodide.[336] Oxidation of diphenyl ditelluride with lead tetraacetate gives phenyltellurium triacetate, the hydrolysis of which occurs readily to give a mixture of tellurinic acid and anhydride, (**53**) and (**54**; Scheme 19).[337]

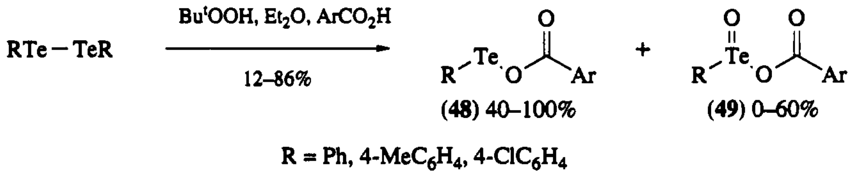
RTe−TeR
Bu$^t$OOH, Et$_2$O, ArCO$_2$H
12–86%
(48) 40–100%
(49) 0–60%
R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$

(45)

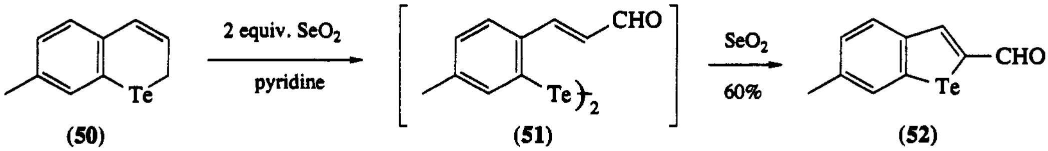

**Scheme 18**

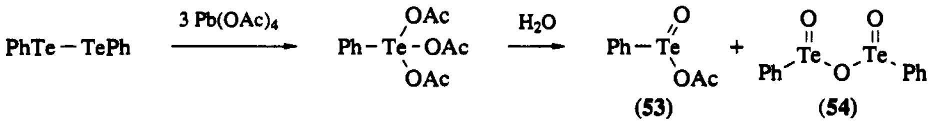

**Scheme 19**

### 6.2.4.2 Oxidation of Tellurides to Telluroxides

Diaryl and dibenzyl tellurides are oxidized slowly by atmospheric oxygen to the corresponding telluroxides.[338–340] There are also reports of the formation of tellurinic acid ($RTeO_2H$) derivatives by air or alkaline $H_2O_2$ oxidation of dialkyl tellurides.[341] Treatment of the telluride (**55**) with chloramine-T followed by hydrolysis gives the telluroxide (**57**) *via* *N*-tellurosulfonamide (**56**; Scheme 20).[342] However telluroxides are more generally prepared by alkaline hydrolysis of diorganyltellurium dihalides[343–345] which can be formed by halogenation of tellurides by various halogenating agents such as $Br_2$, $Cl_2$, $I_2$, $SOCl_2$, $SO_2Cl_2$, $FeCl_3$, $CuCl_2$, vicinal bromides,[345] ICl and IBr.[346] Treatment of tellurides with NCS or $Bu^tOCl$ followed by hydrolysis with 10% NaOH or saturated $NaHCO_3$ produces telluroxides in 90–95% yield.[262] The isolable telluroxides are thermally stable, but hygroscopic, white solids, and appear to be often present in their hydrated forms (equation 46).[262,341,347,348] The telluroxide (**58**), however, decomposes in boiling toluene to give alkenes (equation 47).[349]

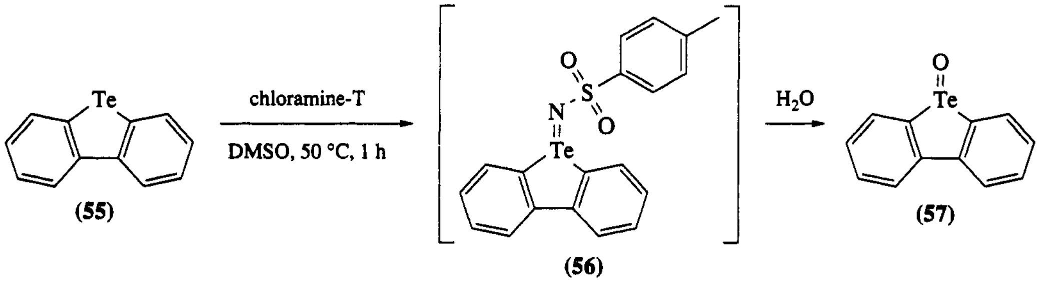

Scheme 20

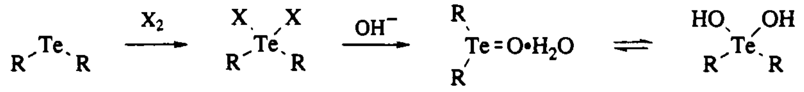

$$R_2Te \xrightarrow{X_2} R_2TeX_2 \xrightarrow{OH^-} R_2Te{=}O\cdot H_2O \rightleftharpoons R_2Te(OH)_2 \qquad (46)$$

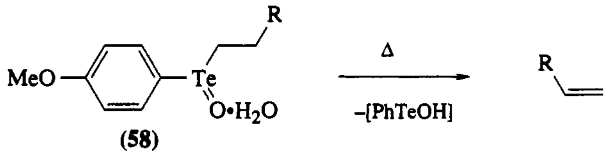

(47)

On the contrary, in the cases of benzylic, allylic and *s*-alkyl tellurides the corresponding telluroxides are very unstable and cannot be isolated by either a direct oxidation method or a halogenation–hydrolysis method. Thus, dibenzyl telluride[350,351] and benzyl phenyl telluride[352a,b] decompose quickly when exposed to air. Allylic phenyl tellurides are oxidized readily by various oxidants including air to the corresponding allylic alcohols presumably *via* 2,3-sigmatropic rearrangement of the intermediate allylic telluroxides.[352b,c] Further, direct oxidation of various *s*-alkyl phenyl tellurides by MCPBA, $H_2O_2$ or TBHP in organic solvents[353,354] and bromination of the tellurides followed by alkaline hydrolysis gave a mixture of alkenes, respectively, by telluroxide elimination (Scheme 21).[355] The double bond geometry

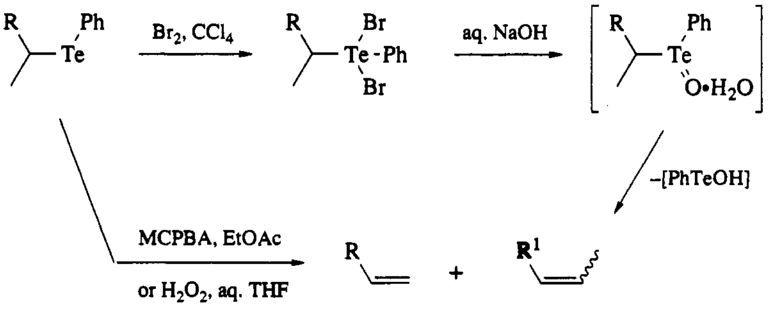

Scheme 21

of the internal alkenes produced by direct oxidation depends upon the amount of oxidant present. Also it should be noticed that the behavior of telluroxides differs from the corresponding selenoxides.[356]

LTA' oxidizes diaryl tellurides to diaryltellurium diacetates,[337] while the treatment of diaryl, divinyl, alkyl aryl and dialkyl tellurides with $Pd(OAc)_2$[357] or $Li_2PdCl_4$[358] results in a new carbon–carbon bond being formed (equations 48 and 49).

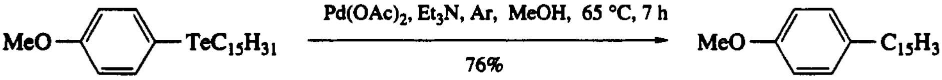

(48)

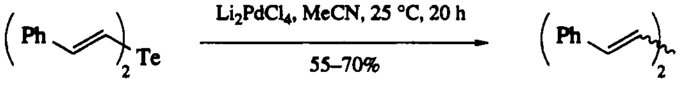

(49)

### 6.2.4.3 Oxidation of Tellurides to Tellurones

Little has so far been reported on the chemistry of tellurones. The preparation of several dialkyl tellurones by $H_2O_2$ or air oxidation of the corresponding tellurides or telluroxides has been claimed,[341,347,359,360] but it is doubtful whether those compounds were isolated in a pure tellurone form. In 1982 the first definitely characterized tellurone, bis(4-methoxyphenyl) tellurone (**60**), was prepared by periodate oxidation of the corresponding telluroxide (**59**; equation 50).[361] Both (**59**)[59,362] and (**60**)[361] work as mild useful oxidants which show some chemoselectivities and readily oxidize thiols to disulfides. The preparation of dodecyl 4-methoxyphenyl tellurone by a similar method has also been claimed.[349]

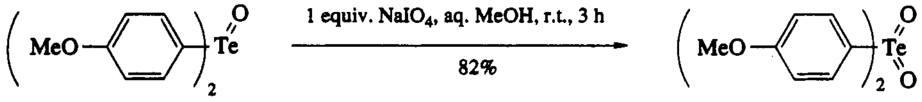

(50)

**(59)** **(60)**

As in the selenium case (Scheme 17) the oxidation of alkyl phenyl telluride with excess MCPBA in the presence of alcohols results in a facile substitution of a PhTe moiety by an alkoxy group. The reaction is assumed to proceed *via* a similar tellurone–MCPBA adduct intermediate. Oxidation of cycloalkyl telluride (**61**) was accompanied by ring contraction to produce an acetal (**62**),[308,309] while the bromination–hydrolysis method affords the allylic ether by telluroxide elimination (Scheme 22).[355]

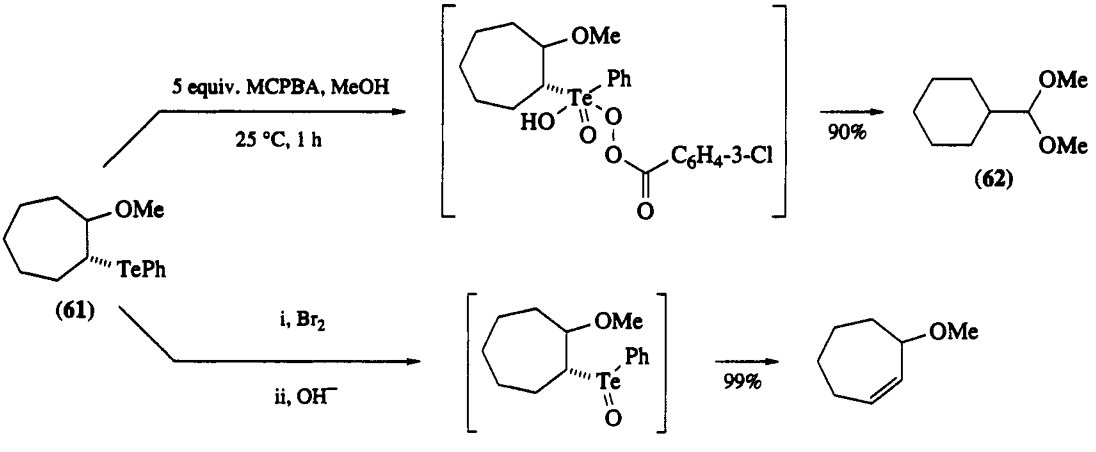

Scheme 22

Oxidative α-elimination occurs with organotellurium(IV) halides when treated with some oxidants, preferably TBHP, in organic solvents to give the corresponding organic halides in good yields with retention of configuration and by *ipso* replacement. A 1,2-halogen shift of the unstable organotellurium(VI) oxyhalide (**63**) was proposed to account for these reactions (Scheme 23).[363]

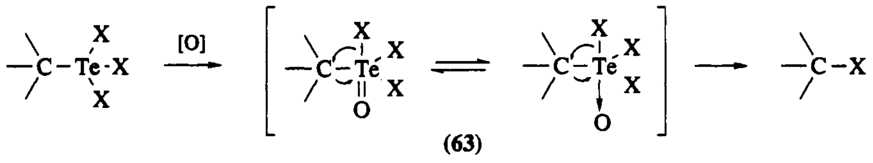

Scheme 23

#### 6.2.4.4 Photooxidation of Organic Tellurium Compounds

Dibenzyl ditelluride and dibenzyl telluride photodecompose in the presence of oxygen in $CDCl_3$ to give a mixture of oxidation products such as benzaldehyde, benzyl alcohol and diphenylethane thought to be derived from a benzyl radical.[312] Although benzyl tellurocyanate ($PhCH_2TeCN$) is photochemically stable in the absence of oxygen, it rapidly suffers photooxidation in oxygen to give elemental tellurium and a mixture of 60% benzaldehyde and 40% benzyl alcohol.[313]

The tellurophenopyridazine (**64**) decomposed under the influence of light and oxygen to 4,5-dibenzoylpyridazine (**66**) *via* the peroxide (**65**) derived from Diels–Alder reaction of singlet oxygen with (**64**; Scheme 24).[364] Tellurapyrylium dyes such as (**67**) react with singlet oxygen within a few seconds to give dihydroxides (**68**; Scheme 25).[365]

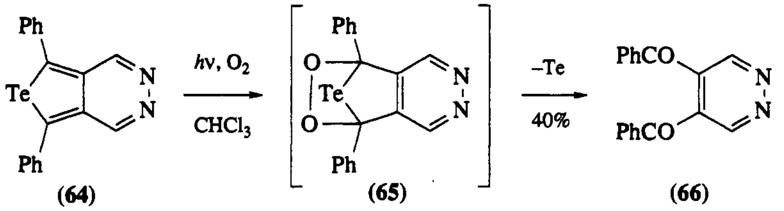

Scheme 24

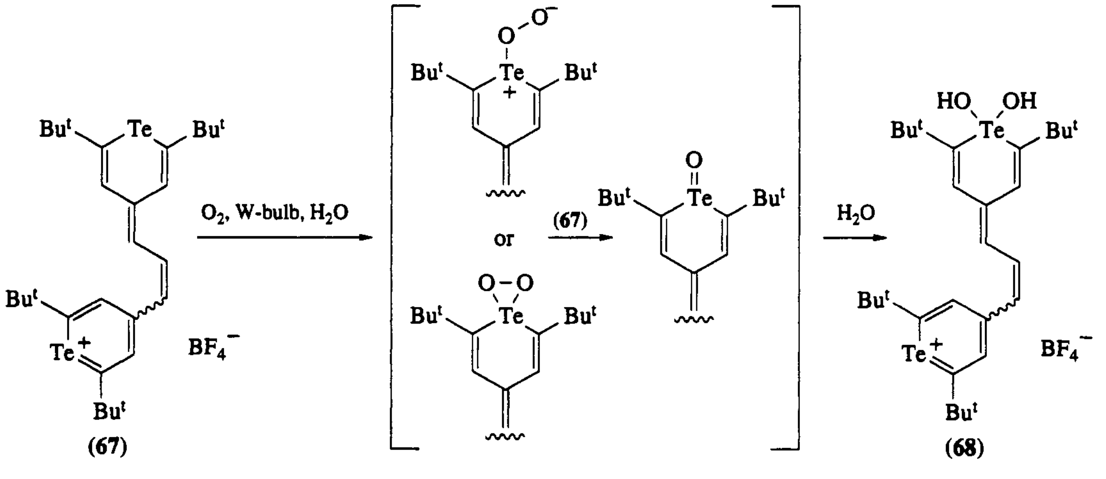

Scheme 25

## 6.2.5 SYNTHESIS OF OPTICALLY ACTIVE SULFOXIDES AND SELENOXIDES BY CHEMICAL AND BIOLOGICAL OXIDATION

### 6.2.5.1 Synthesis of Optically Active Sulfoxides by Chemical Oxidation

Since the first report in 1960,[366,367] many procedures have been reported for the synthesis of optically pure sulfoxides by chemical oxidation of sulfides.[68,69a,b] Typical examples are as follows: (i) the oxidation of achiral sulfides by chiral peroxy acids,[368–375] (ii) oxidation by TBHP in chiral solvents[376] or in the presence of chiral catalysts,[376–382] and (iii) diastereoselective oxidation of sulfides containing another chiral center.[80,383–389] Similar methodologies have been reported using other oxidants such as organic halogen compounds,[390–394] $Bu^tOCl$,[395] $NaIO_4$,[135,396,397] 2-sulfonyl- and 2-sulfamyl-oxaziridine derivatives,[398–402] organic hydroperoxides[403,404] and electrochemical oxidations.[405,406] Oxidation in the presence of asymmetric 'host' molecules such as cyclodextrins,[407,408] bovine serum albumin[409–411] and chiral clay-chelates[412] has also been reported. As a method of homo-chiral sulfoxide preparation most are less successful than the procedures using chiral sulfenic acid derivatives which are prepared by resolution methods.[413] Some examples of chemical oxidations for obtaining optically active sulfoxides are useful, for example using modified Sharpless reagent [$Ti(OPr^i)_4$/(*R*,*R*)-diethyl tartrate (DET)/TBHP/$H_2O$ (1:2:1:1.1)] was found to oxidize various alkyl aryl sulfides and dialkyl sulfides to the chiral sulfoxides with *ee* in the range of 80–90% (equation 51).[377–379] 2-Aryl-3-sulfamyloxaziridines (**69**)[401a] and (–)-α,α-dichlorocamphorsulfonyloxaziridine (**70**)[401b] were recently described as being equally effective chiral oxidizing agents for nonfunctionalized sulfides to optically active sulfoxides (equation 52).[401]

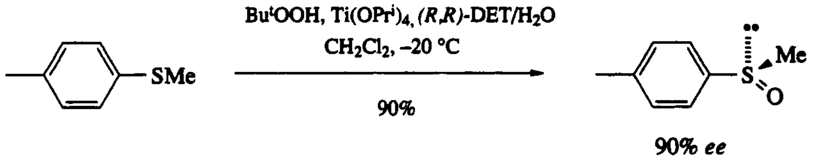

(51)

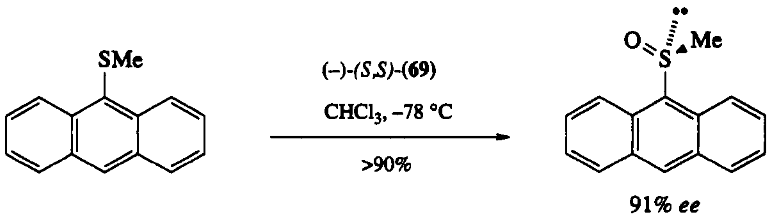

(52)

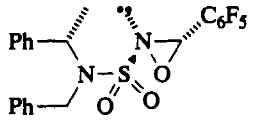

(–)-(*S*,*S*)-(**69**)

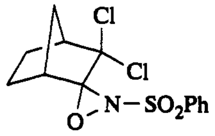

(**70**)

### 6.2.5.2 Synthesis of Optically Active Sulfoxides by Biological Oxidation

Microbiological oxidation of achiral sulfides to homo-chiral sulfoxides has been studied longer than have chemical methods and often gives better results.[68,69,414] It was reported that *Mortierella isabellina* NRRL 1757 converted methyl *p*-tolyl sulfide into (+)-(*R*)-sulfoxide with 100% *ee*, whereas *Helminthosporium sp.* NRRL 4671 oxidized the same sulfide to (–)-(*S*)-sulfoxide with 100% *ee* (Scheme 26).[415] Oxidation of similar sulfides by *Corynebacterium equi* IFO 3730 was also reported to proceed with high enantioselectivities (equation 53).[416]

Similar to biological oxidation, enzymatic oxidation of drugs[417–419] opened a way to studies on the preparation of optically active sulfoxides by enzymatic procedures. Among numerous reports[68,69] a typical example is the oxidation of aryl aminoalkyl sulfides by dopamine β-hydoxylase (DBH) in the presence of some electron donors to afford the sulfoxide with high enantioselectivity (equation 54).[420]

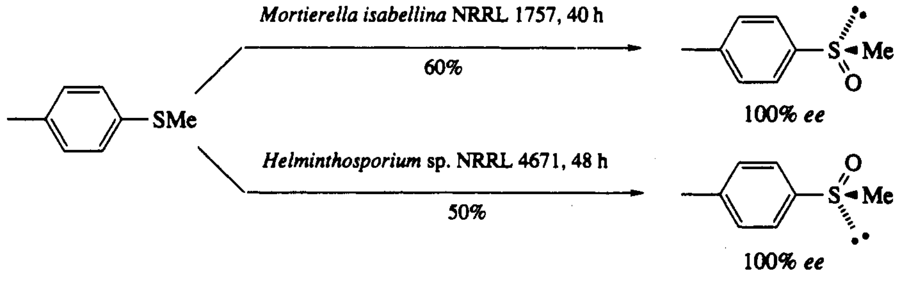

*Mortierella isabellina* NRRL 1757, 40 h
60%
SMe
S
Me
O
100% *ee*
*Helminthosporium* sp. NRRL 4671, 48 h
50%
O
S
Me
100% *ee*

**Scheme 26**

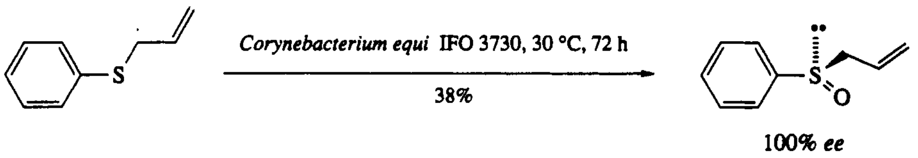

S
*Corynebacterium equi* IFO 3730, 30 °C, 72 h
38%
S
O
100% *ee*

(53)

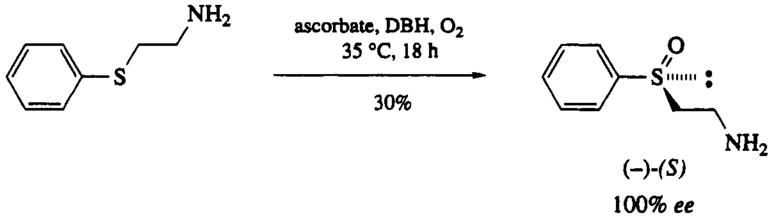

$NH_2$
S
ascorbate, DBH, $O_2$
35 °C, 18 h
30%
O
S
$NH_2$
(–)-(*S*)
100% *ee*

(54)

### 6.2.5.3 Synthesis of Optically Active Selenoxides by Chemical Oxidation

Until quite recently the isolation of optically active selenoxides has been limited to those contained in steroids (isolated as diastereoisomers).[421,422] The difficulty in obtaining these compounds was attributed to the racemization through the achiral hydrated intermediates.[260,269,423–425] Simple optically active selenoxides (5–11% *ee*) were first prepared by kinetic resolution.[425] Direct oxidation of selenides to selenoxides was first reported using optically active oxaziridine derivatives under anhydrous conditions, but the extent of the asymmetric induction was somewhat unsatisfactory with methyl phenyl selenide as substrate (8–9% *ee*).[426] Recently much improved enantiomeric excesses (45–73%) were achieved with new oxaziridine reagents such as (**70**).[401b] An attempt at the asymmetric oxidation of more bulky selenides was independently carried out using $\mathrm{Bu^tOCl}$ in the presence of (–)-2-octanol (equation 55),[299] but resulted in unsatisfactory enantioselectivities (*ee* 1%). Much better results were obtained by the oxidation of β-oxyalkyl aryl selenides (*ee* 18–40%; equation 56)[427] and alkyl aryl selenides (*ee* 1–28%)[428] using TBHP in the presence of (+)- or (–)-diisopropyl tartarate (DIPT) and titanium(IV) alkoxide.

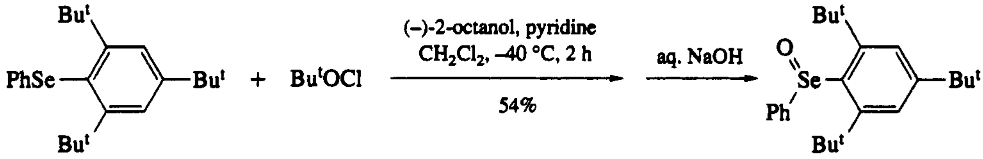

$Bu^t$
PhSe
$Bu^t$
$Bu^t$
+ $Bu^tOCl$
(–)-2-octanol, pyridine
$CH_2Cl_2$, –40 °C, 2 h
54%
aq. NaOH
O
Se
Ph
$Bu^t$
$Bu^t$
$Bu^t$

(55)

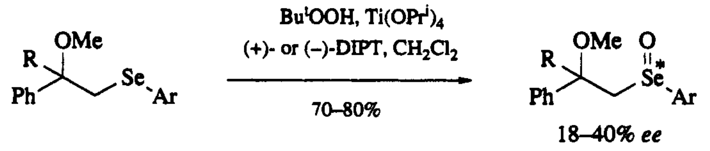

R
OMe
Ph
Se
Ar
$Bu^tOOH$, $Ti(OPr^i)_4$
(+)- or (–)-DIPT, $CH_2Cl_2$
70–80%
R
OMe
O
Ph
Se
Ar
18–40% *ee*

(56)

An attempt to prepare optically active selenoxides by microbial oxidation of achiral selenides gave poor results.[429] For the preparation of optically pure selenoxides therefore, methodology based on the separation of racemic[430] or diastereoisomeric[431] selenoxides gives the best results, although future developments of asymmetric reagents will undoubtedly become competitive.

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# 7.1
# Oxidation by Electrochemical Methods

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## 7.1.1 INTRODUCTION

The chemistry of reactions promoted by electrochemical oxidation or reduction of organic substrates is called electroorganic chemistry. This term is often used along with organic electrochemistry. The difference between these two terms is not always clearly determined, the latter emphasizing electrochemistry rather than organic chemistry and involving electrochemical and electrotheoretical studies, while the former is more concerned with organic chemistry which is beneficial to synthesis, and it is these methods which are surveyed below.

### 7.1.1.1 Inversion of Polarity of Substrates

In electroorganic reactions, the active species is generated on the electrode surface by electron transfer between a substrate molecule and the electrode, as shown in equation (1). The substrate molecule is transformed to a cation radical or an anion radical, depending on the direction of electron transfer. When the substrate molecule is a radical or ionic species, the transformation of the substrate is as shown in equation (2).

$$A^{2-} \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{\bullet-} \underset{+e}{\overset{-e}{\rightleftharpoons}} A \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{\bullet+} \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{2+} \qquad (1)$$

$$A^{-} \underset{+e}{\overset{-e}{\rightleftharpoons}} A\bullet \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{+} \qquad (2)$$

Generally, an organic reaction between two substrate molecules is not achievable when the polarity of the reaction site is the same in both substrates. In other words, the reaction usually takes place between a nucleophile (Nu) and an electrophilic site (E). In organic synthesis, however, it is not uncommon that reaction between two groups of the same polarity is required to synthesize the target compound. As a result, inversion of the polarity of one of the groups is necessary to achieve reaction, although this inversion (Umpolung) is not always easy. As equations (1) and (2) clearly show, in an electroorganic reaction the generation of active species through electron transfer between a substrate and an electrode always involves inversion of polarity of the substrate. Thus, this facile inversion of polarity makes electroorganic chemistry a unique tool in organic synthesis.

### 7.1.1.2 Interface Reactions

As the active species is formed on the electrode surface at an interface between solid and solution, unique characteristics in reactivity can occur that are useful to the organic chemist.

#### *7.1.1.2.1 Stereochemistry*

One of these useful characteristics is that of stereoselectivity. The stereoselectivities observed in the acetoxylation of methylcyclohexenes are good examples of reactions taking place at the interface (see Section 7.1.3.2.1). Further examples of this selectivity have been observed in the anodic acetoxylation of some cyclic dienol acetates carried out in acetic acid containing potassium acetate as the supporting electrolyte (equation 3).

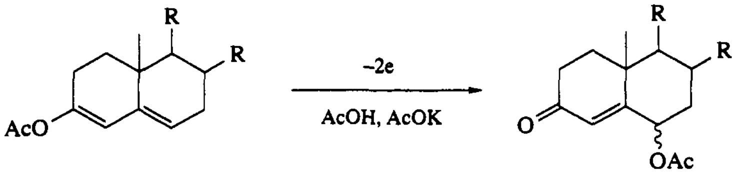

(3)

α- and β-isomers

The same products are also obtained by oxidation of the dienol acetates with peroxybenzoic acid or by oxidation of the corresponding enones with the liver microsomal oxidation systems.

The configuration of the products obtained by the anodic method ($\beta/\alpha = 13.9$) shows a remarkable similarity with the microsomal oxidation products ($\beta/\alpha = 14.1$), whereas peroxybenzoic acid oxidation exhibits poor stereospecificity ($\beta/\alpha = 3$).[1]

The similarity of anodic and microsomal oxidations may be explained by the fact that both types of oxidation take place at interfaces.

#### *7.1.1.2.2 Distribution of the active species*

The active species generated on the electrode surface usually reacts with other reagents before it diffuses into the solution, whereas in the usual organic homogeneous reactions the distribution of active species is uniform in solution. Due to this difference the electrogenerated active species displays unique characteristics.

The famous Kolbe electrolysis is a typical example showing the uniqueness of the distribution of the electrogenerated active species. Thus, the free radical species, formed at rather high concentration on the anode surface through anodic oxidation of a carboxylate anion, dimerizes before it is diffused into solution. The same radical species generated in a homogeneous solution by chemical methods forms the dimer as a minor product, the major product being that derived by hydrogen abstraction from the solvent.

## 7.1.2 APPARATUS AND TECHNIQUES

### 7.1.2.1 Apparatus

#### *7.1.2.1.1 Electrolysis cell*

The simplest and most convenient cell is a cylindrical glass cell with a capacity less than several hundred milliliters, although those of approximately one milliliter may be less appropriate for synthetic reaction studies (Figure 1).

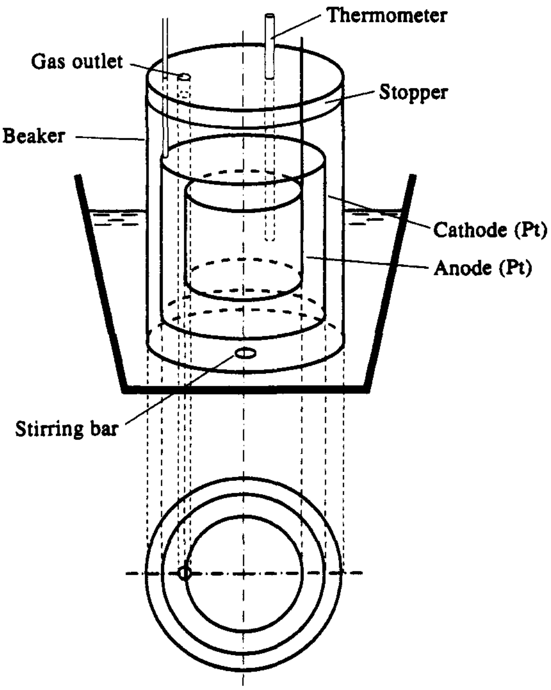

**Figure 1 Undivided cell**

The cell shown in Figure 1 is usually used for the reaction carried out under constant current conditions. For carrying out the reaction under a constant potential condition a cell equipped with three electrodes is required.

These cells are usually equipped with anode, cathode, stirrer, thermometer and gas inlet and outlet. In the case of a divided cell, a diaphragm is also used.

#### *7.1.2.1.2 Electrode*

Generally, the material of the electrode must be stable toward electrochemical oxidation and reduction and also to the chemicals such as substrates, solvents, supporting electrolytes and products.

The materials which are commonly used for the anode are graphite (carbon), Pt, Au, Ti coated by Pt (Pt/Ti), Rh/Ti, $TiO_2$/Ti, $RuO_2$/Ti, $PbO_2$/Pb, some types of alloy of Pb (Pb–Ag, Pb–Sb) and titanium suboxide.

On the other hand, the material of the cathode is generally not limited. Almost any type of metal and graphite may be used as the cathode, though the material of the cathode greatly influences the pattern of the reaction in some cases.

### 7.1.2.2 Techniques

#### *7.1.2.2.1 Constant current or controlled potential method*

In the constant current method, the current is kept constant throughout the reaction and hence the total amount of electricity (F $mol^{-1}$) is easily calculated by the equation

$$\text{relative amount of electricity (F mol}^{-1}) = (60^2 \times HA)/(96500 \times M)$$

where $H$ = time (h), $A$ = current (A), $M$ = mole (substrate), F = faraday

The correlation between the amount of electricity passed and the extent of the reaction is followed conveniently by this method. The electrode potential is, however, not kept constant in this method and hence it is not always possible to achieve reaction selectively.

On the other hand, the electrode potential is kept constant against a reference electrode in the controlled potential method. The fact that potential is constant throughout the reaction often leads to better regio- and chemo-selectivity than in the constant current method.

#### *7.1.2.2.2 Method with or without a diaphragm*

It is not an exceptional case in the electroorganic reaction that a substrate is reactive to both anode and cathode. Also, the product obtained by anodic oxidation or cathodic reduction is often further reduced or oxidized at the counter electrode.

The primary role of the diaphragm, therefore, is to separate the anolyte and catholyte to avoid undesirable side reactions. The diaphragm is also essential in the cases where the anolyte and catholyte are different.

The method using a diaphragm is suitable to the basic research for small-scale reactions, whereas it is not always convenient for synthetic chemistry. Anodic oxidation is often carried out without using the diaphragm, while it is generally necessary for cathodic reduction.

#### *7.1.2.2.3 Selection of solvent*

The following characteristics are required for solvents used in electroorganic reactions, namely: (i) good solubility of supporting electrolytes and substrates to the solvent; (ii) high electroconductivity; (iii) high electrochemical stability; and (iv) suitable chemical reactivity.

The commonly used solvents other than water are as follows. For the anolyte: MeOH, $MeCO_2H$, MeCN, $CH_2Cl_2$, $MeNO_2$, tetramethylene sulfone, pyridine, THF, $MeOCH_2CH_2OMe$ and propylene carbonate. For the catholyte: MeCN, DMF, $Me_2$ NCOMe, $Me_2SO$, HMPA, *N*-methylpyrrolidone, THF, dioxane, propylene carbonate, $MeOCH_2CH_2OMe$, MeOH, $MeCO_2H$ and $NH_3$.

The solvent is used alone or as a mixture with other solvents, including water.

#### 7.1.2.2.4 *Selection of supporting electrolytes*

The supporting electrolyte is essential for the electroorganic reaction. The following points are important for the selection of the supporting electrolyte: (i) solubility to the solvent commonly used for electrolysis; (ii) electrochemical stability; (iii) interaction with reaction intermediate; and (iv) relative difficulty of preparation.

Solvents such as water, methanol, MeCN or DMF dissolve a variety of inorganic supporting electrolytes, while only organic supporting electrolytes are used for organic solvents. The anion part of the commonly used supporting electrolyte is $X^-$ (halide anion), $ClO_4^-$, $BF_4^-$, $PF_6^-$, $OTs^-$ or $RO^-$, whereas the cation is $M^+$ (alkali metal cation) or $R_4N^+$.

#### 7.1.2.2.5 *Amount of electricity passed through the cell*

The amount of electricity needed corresponds to the quantity of the reagents in the chemical reaction. The theoretical amount of the electricity can be calculated on the basis of numbers of electrons which are required to promote the reaction. The unit usually used is the coulomb or the Faraday per mole (F $mol^{-1}$) as previously shown.

Since the electricity needed corresponds to a reagent, the yield is often calculated on two different bases. Namely, one is the usual material yield and the other is the current yield (or current efficiency), calculated on the basis of the amount of electricity used from the equation

$$\text{current yield (\%)} = (P/T) \times 100$$

where P = amount of product (mol) obtained at the stage where a certain amount of electricity is passed and T = theoretical amount of product (mol) at the stage where the same certain amount of electricity is passed.

In the electroorganic synthesis an excess amount of electricity is often required to achieve the synthesis with a high material yield, and the current yield is often determined at an early stage of reaction.

## 7.1.3 DIRECT OXIDATION

### 7.1.3.1 Oxidation of Carbon–Hydrogen and Carbon–Carbon Single Bonds

Direct anodic oxidation of alkanes may be performed if they have ionization potentials lower than about 10 eV.[2] Such oxidations can be classified into two types of reactions, cleavage of C—H bonds (equation 4) and cleavage of C—C bonds (equation 5).

$$RH \xrightarrow{-2e} R^+ + H^+ \qquad (4)$$

$$R{-}R \xrightarrow{-2e} 2\,R^+ \qquad (5)$$

The high oxidation potentials of alkanes, however, make it difficult to carry out the oxidation in solvents such as acetonitrile since the first intermediates generated in these oxidations are carbonium ions, as illustrated by equations (4) and (5). Their stabilization with strongly acidic solvents like anhydrous fluorosulfonic acid often lowers the oxidation potentials of these hydrocarbons.[3]

#### 7.1.3.1.1 *Cleavage of carbon–hydrogen bonds*

The controlled potential electrolysis of cyclohexane carried out at 1.85 V in fluorosulfonic acid containing 1.15 M acetic acid yields an α,β-unsaturated ketone as a single product in 30% current yield.

In the anodic oxidation, adamantane is a unique compound among alkanes. It has a rather low oxidation potential, and its anodic oxidation in acetonitrile affords acetamidoadamantane (**1**; equation 6) in 90% yield.[4]

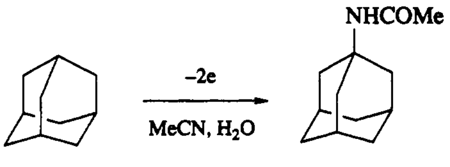

(6)

**(1)**

### *7.1.3.1.2 Cleavage of carbon–carbon single bonds*

The direct anodic cleavage of saturated aliphatic carbon–carbon bonds is only possible if an electron is removed from the highest occupied molecular orbital (HOMO) of the C—C bond, *e.g.* due to the presence of strain in the bond.[5]

Tetramethylcyclopropane (**2**; equation 7) is the simplest strained hydrocarbon which is easily oxidized by the anodic method in methanol to give two products with a total yield of 71%.[6]

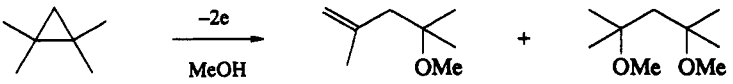

(7)

**(2)** 47% 24%

## 7.1.3.2 Oxidation of Unsaturated Systems

As the oxidation potentials of simple alkenes clearly show, carbon–carbon double bonds are usually anodically oxidized unless electron-withdrawing groups located on the alkene carbon atoms attract electrons from the unsaturated systems to shift the oxidation potentials beyond those accessible by anodic oxidation. On the other hand, electron-donating groups on the unsaturated bonds facilitate oxidation.

The initiation step of the anodic oxidation involves removal of an electron from the double bond leading to a cation radical as the first reactive intermediate. Depending on the structure of the unsaturated compounds, a variety of reactions will take place after the formation of the first intermediate. Thus, typical reactions are addition of nucleophiles (equation 8), allylic substitution (equation 9) and dimerization (equation 10).

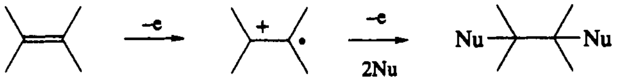

(8)

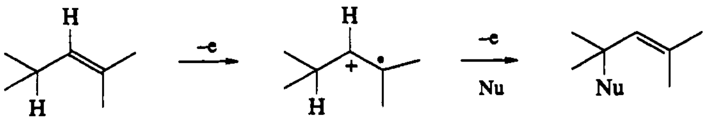

(9)

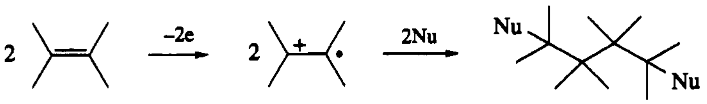

(10)

### *7.1.3.2.1 Aliphatic systems*

In general, the anodic oxidation of simple alkenes in nucleophilic solvents yields products resulting from both allylic substitution and oxidative addition of nucleophiles. Cyclohexene has been studied extensively as the starting compound.[7a–7e] The anodic oxidation of cyclohexene in methanol or acetic acid gives three types of products, those from allylic substitution (**3**), oxidative addition (**4**) and rearrangement (**5**; equation 11).

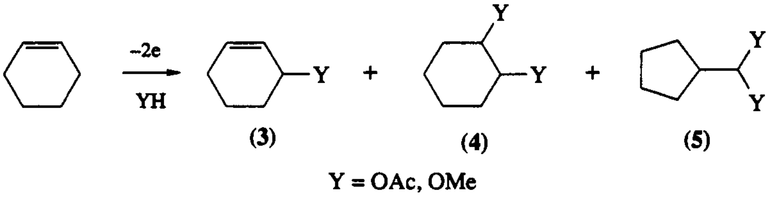

(11)

The mechanism of oxidation of cyclohexene has been shown to involve direct removal of one electron from the double bond to generate a cation radical intermediate (**6**; equation 12).[8]

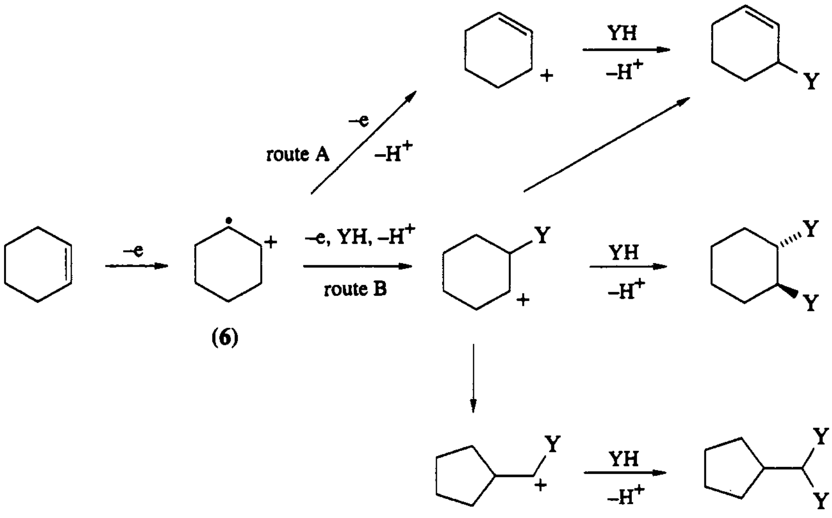

(12)

The relative ratio of routes A and B in equation (12) is controlled by the nucleophilicity of YH. Conjugated dienes are generally more susceptible to oxidation than simple alkenes.[9]

When using a carbon electrode, the anodic oxidation of conjugated dienes (**7**) such as isoprene, piperylene, cyclopentadiene and 1,3-cyclohexadiene in methanol or acetic acid mainly gives oxidative 1,4-addition products (**8**; equation 13). For example, 1,3-cyclohexadiene gives 1,4-dimethoxycyclohex-2-ene (**9**) in 47% yield (equation 14).[10] 1,3-Cyclooctadiene, in a similar experiment, yields a considerable amount of the allylically substituted product.

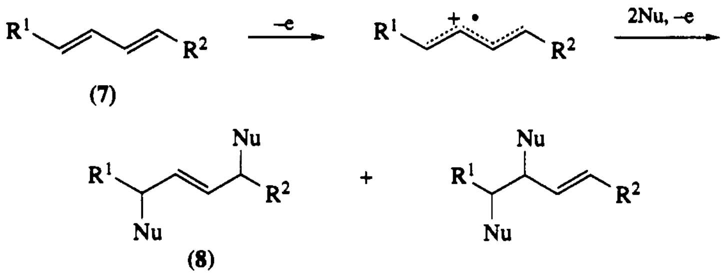

(13)

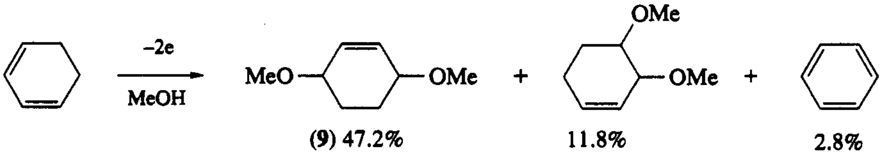

(14)

The oxidation of conjugated dienes has been successfully applied to the synthesis of allethrolone.[11]

Compared with simple aliphatic alkenes and conjugated dienes, the behavior of nonconjugated dienes in anodic oxidation is unique.[12] The possible reaction pathway of the oxidation of nonconjugated dienes (**10**) can be classified into two categories (equation 15).

In route A, one electron is removed from one double bond to generate a cation radical, and subsequent transannular reaction of the cation radical with the other double bond forms a new carbon–carbon bond. On the other hand, in route B, allylic substitution or oxidative addition at one double bond takes place without intramolecular interaction between the double bonds. As exemplified by the anodic oxidation of 4-vinylcyclohexene (**11**) in methanol (equation 16), such dienes as 4-vinylcyclohexene, limonene and 1,5-cyclooctadiene yield only products *via* route B.

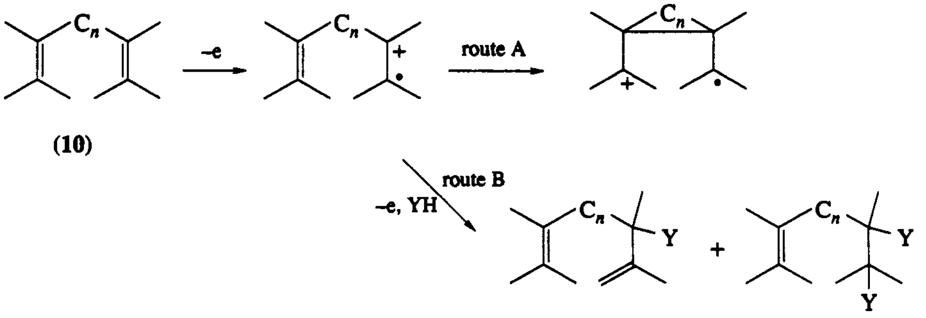

(15)

(**10**)

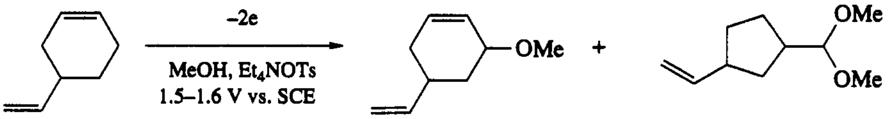

(16)

(**11**) 32% 21%

On the other hand, the electrooxidation of norbornadiene (**12**), in which two double bonds are suitably arranged for the transannular interaction to take place, products *via* route A are seen (equation 17).

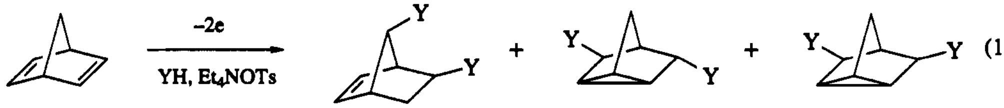

(17)

(**12**)

| | | | |
|---|---|---|---|
| Y = OAc | 6.2% | 14.1% | 15.4% |
| Y = OMe | 8.8% | 16.5% | 18.4% |

Cycloheptatriene gives 7-methoxycycloheptatriene (**13**) (7-MCHT) by anodic oxidation in methanol (equation 18).[13]

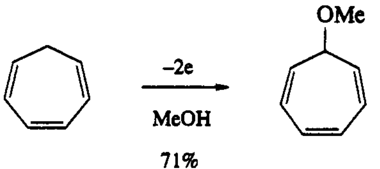

(18)

(**13**)

Although (**13**) gives benzaldehyde dimethyl acetal (63%) upon further anodic oxidation, 3-methoxycycloheptatriene (**14**) (3-MCHT) and 1-methoxycycloheptatriene (**15**) (1-MCHT) afford 7,7-dimethoxycycloheptatriene (**16**), which is a good precursor of tropone (equation 19).

Although the oxidative addition of nucleophiles to the double bond of arylalkenes has long been known,[14] the most interesting reaction from the synthetic point of view is oxidative dimerization. Using a graphite electrode, the anodic oxidation of styrene in methanol containing NaOMe and NaClO$_4$ as supporting electrolytes yields 1,4-dimethoxy-1,4-diphenylbutane (**17**) in 64% yield (equation 20).[15]

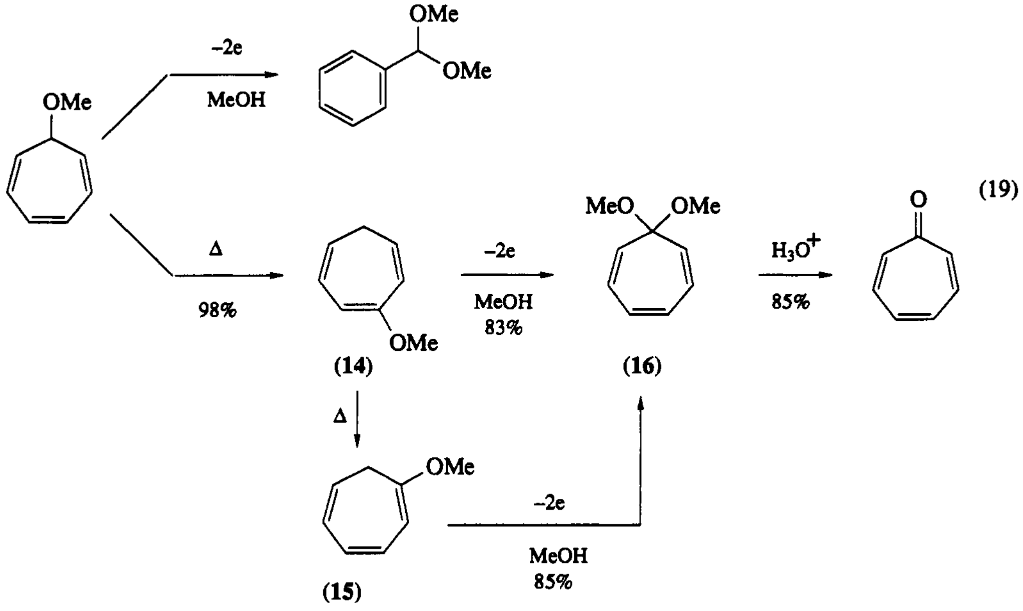

(14) (15) (16)

(19)

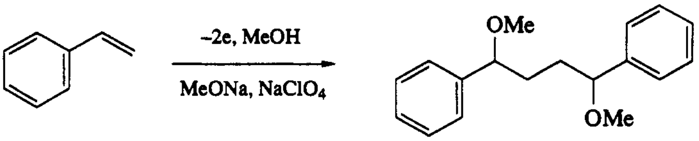

(17)

(20)

Enolic alkenes, *i.e.* alkenes bearing electron-donating substituents such as alkoxy, acyloxy and dialkylamino groups, are easily oxidizable by the anodic method.[16,17]

The addition of methoxy groups to an unsaturated carbon takes place by anodic oxidation of enol ethers in methanol containing sodium methoxide; yields are generally satisfactory (equation 21).[18,19]

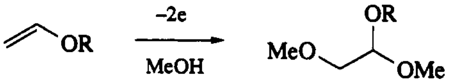

(21)

The anodic oxidation of enol ethers at a graphite anode in methanol containing 2,6-lutidine and sodium perchlorate results in the dimerization of the enol ethers to acetals of 1,4-dicarbonyl compounds (equation 22).[17] The mechanism of dimerization is thought to involve a tail–tail coupling of the cation radicals generated by the one-electron oxidation of the enol ethers.

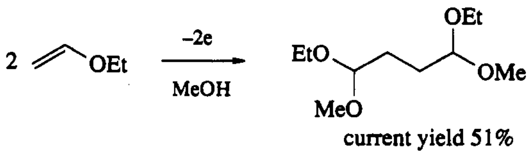

(22)

The oxidation of enol acetates in acetic acid containing tetraethylammonium *p*-toluenesulfonate gives four types of compounds (equation 23): conjugated enones (A), α-acetoxycarbonyl compounds (B), geminal diacetoxy compounds (C) and triacetoxy compounds (D).[16] Similar to enol ethers, the first reactive intermediates are cation radicals generated from enol acetates by one-electron oxidation. The yields and the distribution of products A, B, C and D depend on the structure of the starting enol acetates and the reaction conditions.[20]

The formation of α,β-unsaturated enones from enol acetates has been applied to the synthesis of 2,3-disubstituted 2-cyclopentenones, including jasmone homologs. The yields of the anodic oxidation are usually in the range of 80–90%.

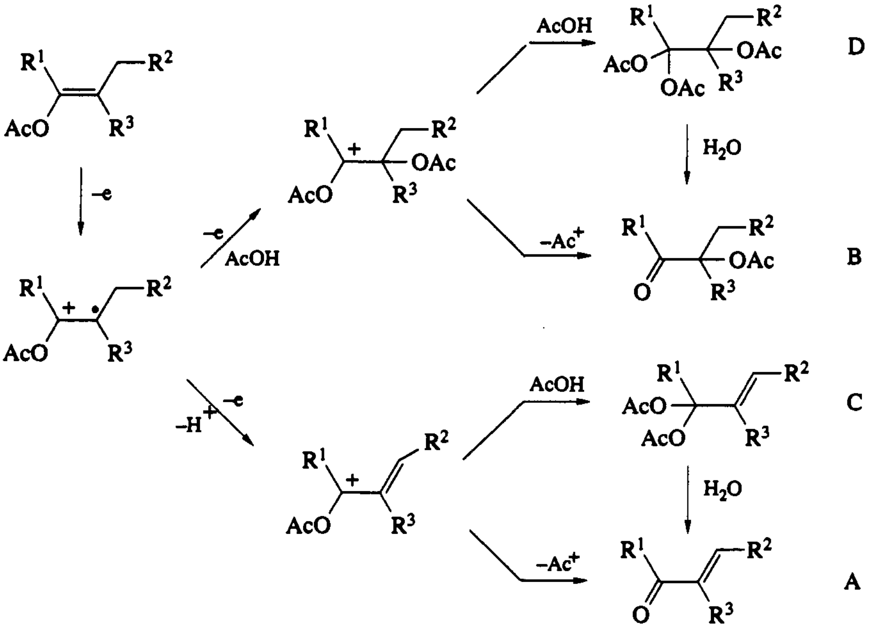

(23)

The anodic α-acetoxylation or α-methoxylation of ketones has been shown to be a powerful tool for the 1,2-transposition of the carbonyl group. The overall process is described by equation (24).[21]

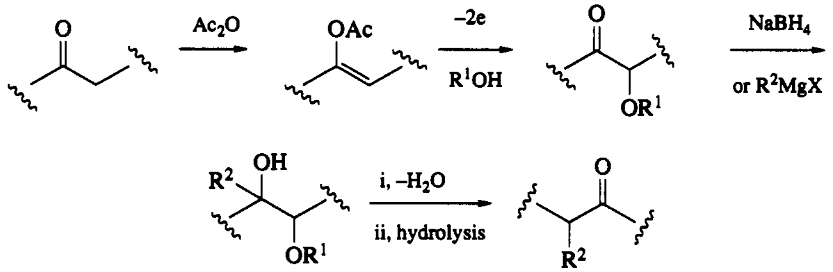

(24)

$R^1$ = COMe  $R^1$ = Me

$R^2$ = H  $R^2$ = alkyl or aryl

The concept of this 1,2-transposition can be extended to 1,4-transposition by using enones as the starting compounds. The anodic methoxylation of dienol acetates prepared from enones in a mixed solvent of acetic acid and methanol (1:9) yields γ-methoxylated enones regioselectively (equation 25). Reduction of the γ-methoxylated enones with $NaBH_4$ to the corresponding alcohols followed by solvolysis of the derived tosylates in aqueous acetone gives products in which the carbonyl group is transposed to the γ-position of the starting enones.[22]

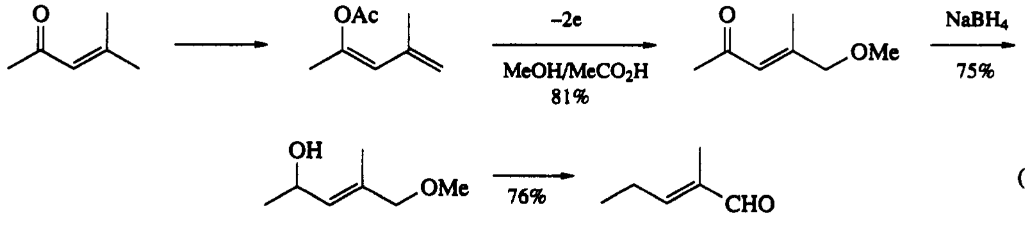

(25)

The anodic oxidation of enamines in methanol containing sodium methoxide as the supporting electrolyte shows a reaction pattern different from that of enol ethers or enol acetates. The main products are mixtures of isomeric methoxylated enamines, (**18**) and (**19**), with yields in the range 74–76% (equation 26).[18b,23]

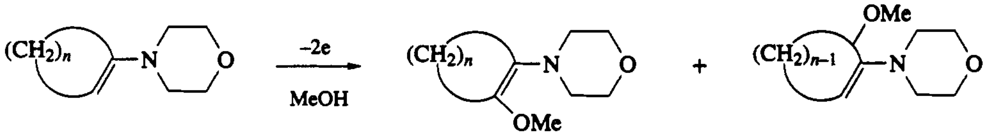

(18) $n = 3, 4$ (19) (26)

### 7.1.3.2.2 Aromatic systems

Removal of electrons from aromatic π-electron systems may be achieved by electrochemical oxidation, and the resulting aromatic cation radical or other aromatic cationic species undergoes interesting and important reactions, such as aromatic substitution (equation 27) and coupling (equation 28).

$$\mathrm{ArH} \xrightarrow[\mathrm{Nu}^-]{-2e} \mathrm{Ar{-}Nu} + \mathrm{H}^+ \qquad (27)$$

$$2\ \mathrm{ArH} \xrightarrow{-2e} \mathrm{Ar{-}Ar} + 2\ \mathrm{H}^+ \qquad (28)$$

#### (i) Aromatic substitution

*(a) Acetoxylation.* Although a variety of mechanisms including radical substitution and EE mechanisms have been proposed, an ECEC mechanism (equation 29) is now believed to be most probable for the acetoxylation.[24]

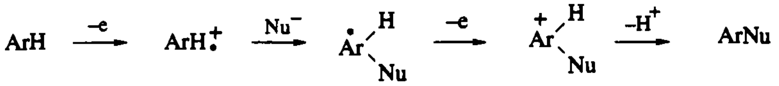

(29)

When the aromatic substrates contain benzylic hydrogens, anodic benzylic substitution always competes with ring substitution.

The yields of ring acyloxylation products are improved by carrying out the reaction in $CF_3CO_2H/CF_3CO_2Na$, since the first products, namely trifluoroacetoxylated compounds, are generally stable under the conditions of anodic substitution.[25]

*(b) Methoxylation.* Ring methoxylation of substrates possessing high oxidation potentials is only achieved with difficulty, although naphthalene[26] and anthracene[27] are readily methoxylated (equation 30).

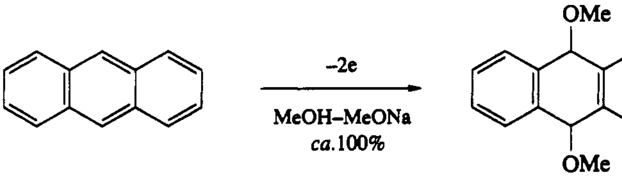

(*cis*:*trans* = 1:1) (30)

The transformation of easily oxidizable substrates such as 1,4-dimethoxybenzene to the corresponding quinone diacetals occurs in high yields, as shown in equation (31).[28] These quinone diacetals have been used as starting materials in a variety of organic syntheses.

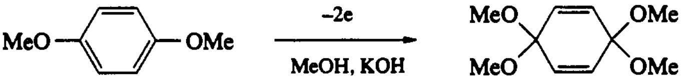

(31)

Quinone monoacetal, which is obtained by careful hydrolysis of quinone diacetal, can also be prepared directly by anodic oxidation under modified reaction conditions.[29]

*(c) Formation of quinones.* Quinones can be prepared directly by anodic oxidation of aromatic compounds.[28a,30] An example is shown in equation (32).[30a,30b]

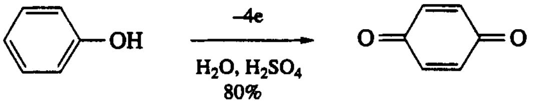

(32)

*(d) Oxidation of benzene.* Owing to the high oxidation potential of benzene, the direct anodic transformation of benzene to phenol and hydroquinone, and their derivatives, is not always successful. Hence, some modifications are essential to achieve conversion of benzene into phenolic compounds. The anodic oxidation of benzene in trifluoroacetic acid containing sodium trifluoroacetate and subsequent hydrolysis of the reaction product affords phenol in 65% yield.[25a,31]

The hydroxylation of the aromatic nucleus by hydroxyl radicals, generated by decomposition of hydrogen peroxide in the presence of iron(II) ions, may be applied to the electrochemical synthesis of phenol from benzene, since the concentration of the iron(II) ions can be controlled by the cathodic reduction of iron(III) ions formed by oxidation of iron(II) ions with $H_2O_2$.

*(e) Acetamidation and nitration.* The anodic oxidation of aromatic compounds in the presence of acetonitrile leads to nuclear acetamidation (equation 33).[32]

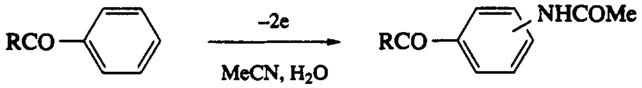

(33)

| | *ortho* | *para* |
|---|---|---|
| R = Me | 70% | 24% |
| R = Pr | 52% | 23% |
| R = OH | 54% | 11% |

The electrochemical oxidation of aromatic compounds in the presence of ammonium nitrate or $N_2O_4$ results in the nuclear nitration shown in equation (34).[33]

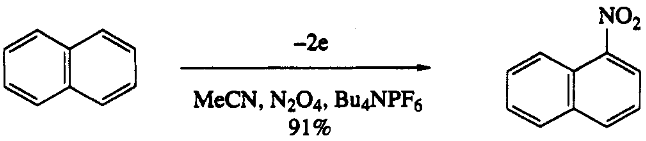

(34)

*(f) Halogenation.* The mechanism of the halogenation depends on the relative values of the oxidation potentials of the halogen and aromatic substrate. When the oxidation potential of the halogen is lower than that of the aromatic compounds, halogenation is initiated by the oxidation of halogen. Hence, this section is mainly concerned with the fluorination of aromatic compounds. One of the most important points in the anodic fluorination is the choice of the fluoride ion source. The use of anhydrous hydrofluoric acid usually leads to low yields.[34] Higher yields are obtained when a combination of tetraalkylammonium fluoride and hydrofluoric acid are employed, as shown in equation (35).[35]

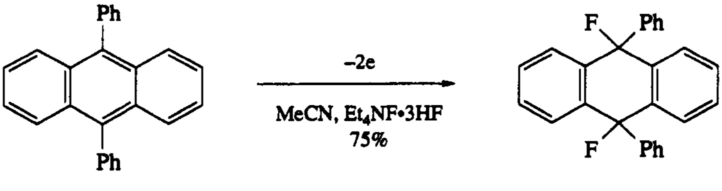

(35)

*(g) Cyanation.* The direct cyanation of the aromatic nucleus usually affords poor yields of cyanated products. However, considerably higher yields are obtained when one of the alkoxy groups of the starting alkoxyanisole or 4,4′-dialkoxybiphenyl is electrochemically substituted by a cyano group.[36]

### *(ii) Coupling*

*(a) Intramolecular coupling.* When the structure of the substrate is suitable for coupling, the intramolecular coupling takes place rather easily.[37]

Coupling of the substrates $Ar(CH_2)_nAr'$ (**20**) is controlled by a variety of factors,[38] including solvent and supporting electrolyte, molecular geometry, anode potential and difference in the oxidation potentials of Ar and Ar′ (equation 36). The presence of trifluoroacetic acid or $HBF_4$ in the reaction system leads to satisfactory yields of coupled products.[39] Intramolecular coupling is readily achieved if *n* is 1, 2, 3 or 4, whereas with longer chain lengths intermolecular coupling predominates.[40]

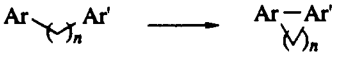

**(20)**

(36)

The skeleton of morphine alkaloids has been synthesized by intramolecular coupling (equation 37).[41]

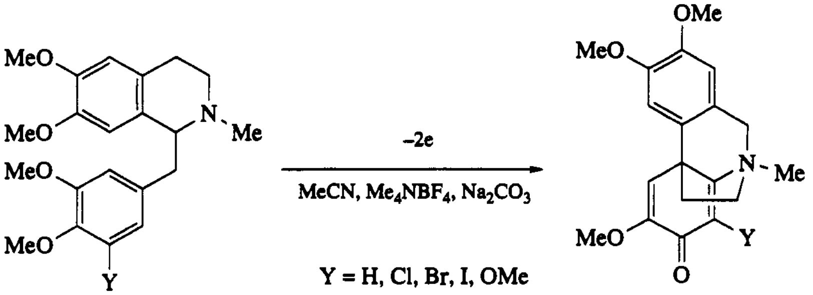

(37)

*(b) Intermolecular coupling.* When suitable aromatic compounds are oxidized in the absence of nucleophiles, the aromatic compounds themselves behave as nucleophiles to yield dimers. Equation (38) shows a typical reaction.[42]

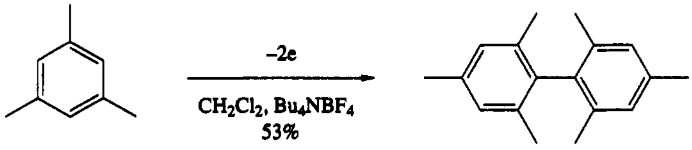

(38)

### *(iii) Oxidation at the benzylic position*

As described in the previous section, substitution at the benzylic position always takes place together with nuclear substitution if the aromatic substrates possess replaceable benzylic hydrogens (equation 39).[43] Benzylic alcohols, esters and ethers can all be oxidized at the benzylic position to yield the corresponding carbonyl compounds.[44]

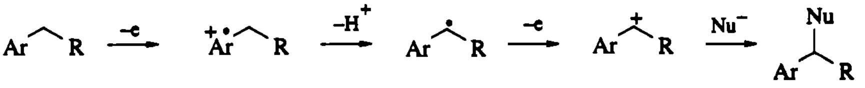

(39)

Carbon–carbon bond cleavage can also take place at the benzylic position if the intermediate cationic species is sufficiently stabilized by suitable substituents (equation 40).[45]

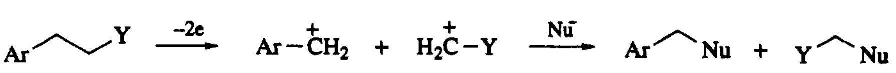

Y = cation-stabilizing group

(40)

#### 7.1.3.2.3 *Heterocyclic systems*

##### *(i) Furans*

The anodic oxidation of furans is one of the most extensively studied reactions because electrooxidation of furans in methanol yields 2,5-dimethoxy-2,5-dihydrofurans (21; equation 41), which are useful starting materials in organic synthesis.[46]

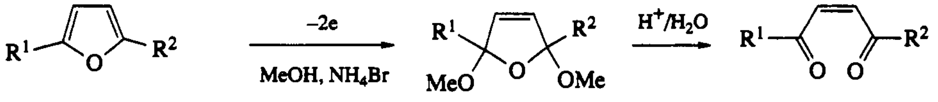

(21)

(41)

2,5-Dimethoxy-2,5-dihydrofuran derivatives have been used extensively for the synthesis of aromatic and aliphatic ring systems, as shown in equations (42)[47] and (43).[48]

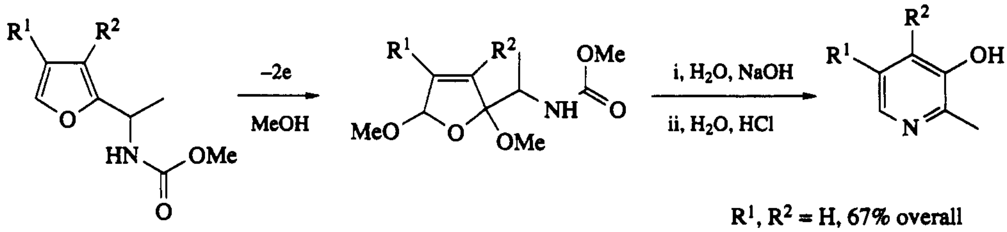

(42)

R$^1$, R$^2$ = H, 67% overall

R$^1$, R$^2$ = CH$_2$OH, 76% overall

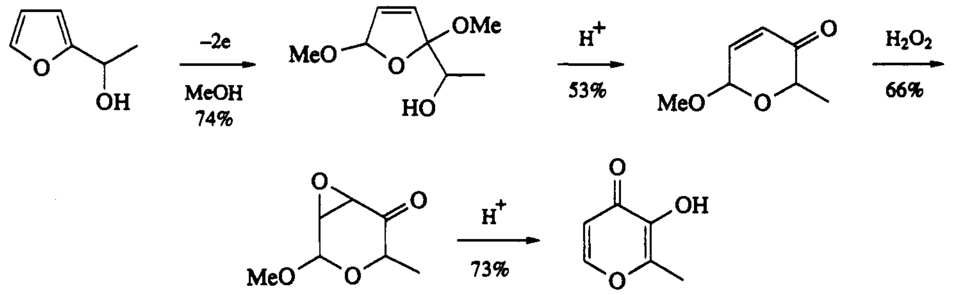

(43)

A variety of cyclopentenone derivatives have been synthesized using the anodic oxidation of furans as a key step.[49]

### 7.1.3.3 Oxidation of Systems Bearing Lone Pairs of Electrons

#### 7.1.3.3.1 *Systems containing oxygen*

The direct anodic oxidation of aliphatic saturated alcohols to the corresponding carbonyl compounds is not always effective, because the high oxidation potentials of these alcohols make difficult the direct removal of an electron from the lone pair electrons on the oxygen atom.

The direct electrochemical oxidation of alcohols has been surveyed by Scholl *et al.*,[50] and their conclusions are that this oxidation is best achieved in the neat liquid substrate. Where this is not possible acetonitrile is the best solvent. A fluoroborate as the supporting electrolyte is recommended to obtain higher yields and oxidation with a controlled potential is not effective.

### *(i) Oxidation of glycols*

The anodic oxidation method is highly efficient for the oxidative cleavage of glycols (**22**) and related compounds. The oxidation of glycols and glycol ethers in methanol results in a clean cleavage to the corresponding carbonyl compounds (equation 44).[51]

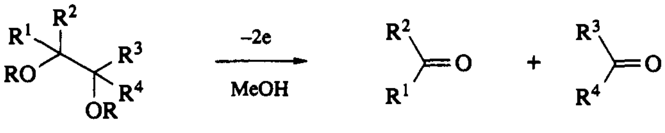

(44)

(**22**)

R = H, Me

This anodic oxidation does not show any of the stereochemical limitations usually observed in cleavage reactions by chemical oxidizing reagents.[52] Furthermore, 1,2-dimethoxy- and 1-hydroxy-2-methoxyalkanes are also oxidized with similar current efficiencies.

The initiation step of this anodic oxidation of glycols may be the electron transfer from the lone pair electrons of the oxygen atom to the anode. This anodic cleavage of 1,2-glycols has been utilized for a variety of organic syntheses.[53]

The anodic oxidation of enol ethers in methanol yields α-methoxylated carbonyl compounds, which are useful intermediates for the synthesis of carbonyl compounds utilizing the technique of oxidative cleavage of glycols (equation 45).[54]

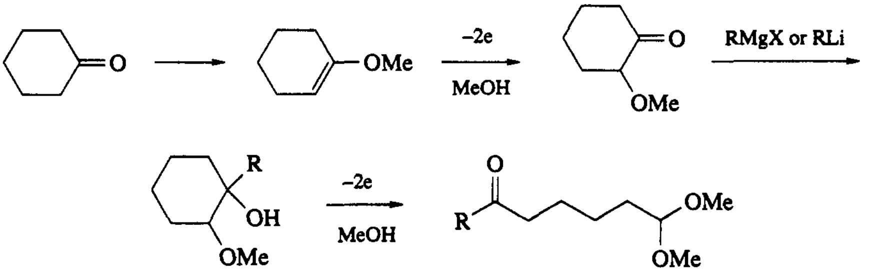

(45)

| *R* | *Yield (%)* |
|---|---|
| Me | 75 |
| Bu | 72 |
| $CH_2CN$ | 40 |
| $CH_2CO_2Et$ | 44 |

Saturated aliphatic ethers are oxidized in AcOH/MeOH containing $Et_4NOTs$ or $Bu_4NBF_4$.[55]

## *7.1.3.3.2 Systems containing nitrogen*

### *(i) Oxidation of aliphatic amines*

The relatively low oxidation potentials of simple aliphatic amines indicate that they should be easily oxidized by the anodic method.[56]

In the presence of an adequate amount of water, aliphatic amines are generally dealkylated by anodic oxidation.[57] Thus, a tertiary amine is successively dealkylated to a secondary amine, a primary amine and finally to ammonia. The mechanism involves initial removal of one electron from the lone pair electrons of nitrogen leading to a cation radical, though a variety of mechanisms have been proposed depending on the structures of the amines and the reaction conditions.

### (ii) Oxidation of aromatic amines

In contrast to aliphatic amines, the anodic oxidation of aromatic amines shows a rather complex reaction pattern. Although extensive studies on the electrochemical reaction mechanism have been carried out, there are very few examples for the application of the anodic oxidation of aromatic amines to organic synthesis.

Methoxylation of *N,N*-dimethyl- or *N*-methyl-*N*-alkyl-anilines occurs predominantly at the methyl group (equation 46).[58]

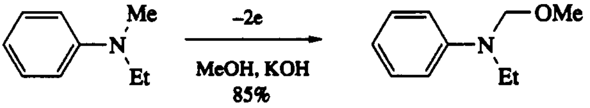

(46)

### (iii) Oxidation of amides and carbamates

As described in the previous section, the anodic oxidation of aliphatic amines is utilized only rarely in organic synthesis due to the instability of the generated intermediates, whereas amides and carbamates of aliphatic amines yield relatively stable intermediates which are sufficiently promising as starting materials in organic synthesis (equations 47 and 48).[59,60]

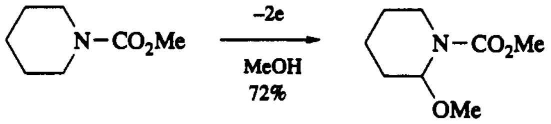

(47)

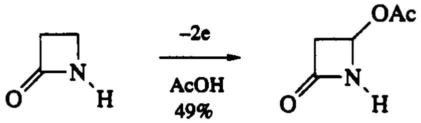

(48)

The reaction mechanism of the α-methoxylation or α-acetoxylation of amides[61] and carbamates[59] has been shown to involve direct one-electron removal from the lone pair electrons of the nitrogen atom in the initial step when inert supporting electrolytes are used.

The anodic oxidation of piperidine derivatives in acetic acid gives α,β-disubstituted products in good yields (equation 49).[62]

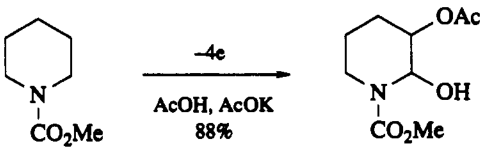

(49)

The products obtained by the anodic oxidation of amides or carbamates in methanol have the same structures as the compounds which can be synthesized from amides (carbamates), aldehydes and methanol (equation 50). The regeneration of iminium cations from these α-methoxyamides and subsequent reactions of the iminium cations with nucleophiles such as active methylene compounds or nucleophilic aromatic nuclei is well known under the term amidoalkylation (equation 50).[63]

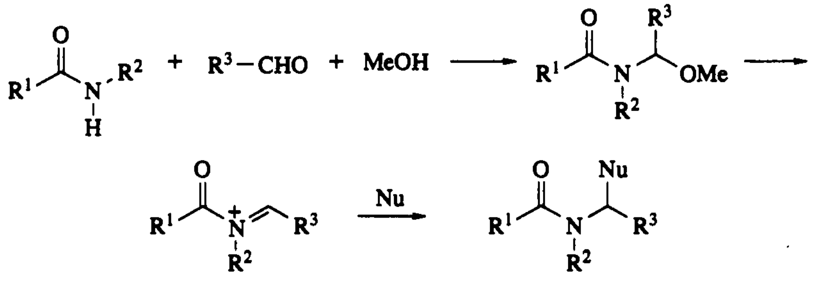

(50)

In the amidoalkylation, however, the preparation of the starting α-methoxyamides is often difficult since the reaction of aldehydes higher than formaldehyde is not necessarily successful, and even when formaldehyde is employed the yields and purities of the α-methoxyamides are not always satisfactory. On the other hand, the anodic α-methoxylation of amides and carbamates generally allows the synthesis of α-methoxyamides (carbamates) which cannot be prepared by the method described by equation (50).

Since anodically prepared α-formyloxy-*N*,*N*-dimethylformamide has successfully been used as an electrophilic reagent,[64] and it has been found that the α-methoxylation of the carbamates of a variety of higher aliphatic amines and alicyclic amines can be readily performed,[59] extensive studies have been carried out to utilize the anodically synthesized α-methoxy- or α-acyloxy-amides and -carbamates as electrophiles in organic synthesis. One example is shown in equation (51).[65]

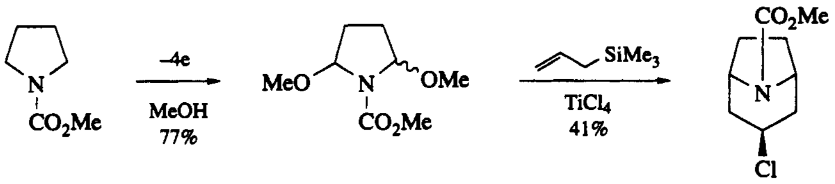

(51)

### 7.1.3.4 Oxidation of Anions

#### *7.1.3.4.1 Carbanions*

As the oxidation potential clearly shows, carbanions may easily be oxidized by the anodic method.[66] The most typical process of the anodic oxidation of carbanions is the formation of radical species (equation 52).

$$R^- \xrightarrow{-e} R\bullet \qquad (52)$$

Although generally dimerization is one of the typical reactions of radical species, the yields of the dimers are not always high. Thus the anodic oxidation of anions of monoalkylated malonic esters in acetonitrile gives the corresponding dimers in 20–55% yield.[67] However, Grignard reagents give satisfactory results in anodic dimerization (equation 53).[68]

$$2\,\mathrm{RMgBr} \xrightarrow{-2e} \mathrm{R{-}R} \qquad (53)$$

| *R* | *Yield (%)* |
|---|---|
| $C_5H_{11}$ | 55–60 |
| $C_{18}H_{37}$ | 54 |
| Ph | 55 |

#### *7.1.3.4.2 Carboxylate anions*

Oxidation of carboxylic acids can be classified into two major categories, formation of radical intermediates followed by dimerization and generation of cation intermediates followed by reaction with nucleophiles (equation 54). The reaction is controlled by a variety of factors including anode material, anode potential, current density, solvent, supporting electrolyte, structure of R and temperature.

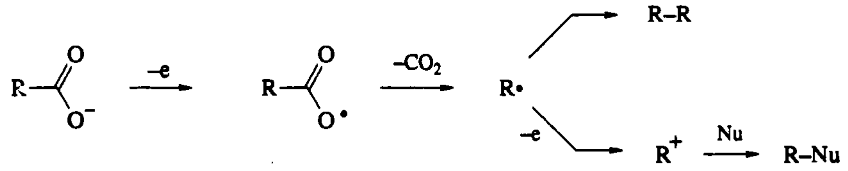

(54)

### *(i) Formation of radicals: Kolbe-type reactions*

The Kolbe dimerization is believed to be favored by the following reaction conditions: high concentration of carboxylic acid, low pH value, absence of foreign anions, high current density and use of a platinum anode.

Since the Kolbe dimerization has already been reviewed,[69] only a few examples of its application are given in equations (55)[70] and (56).[71]

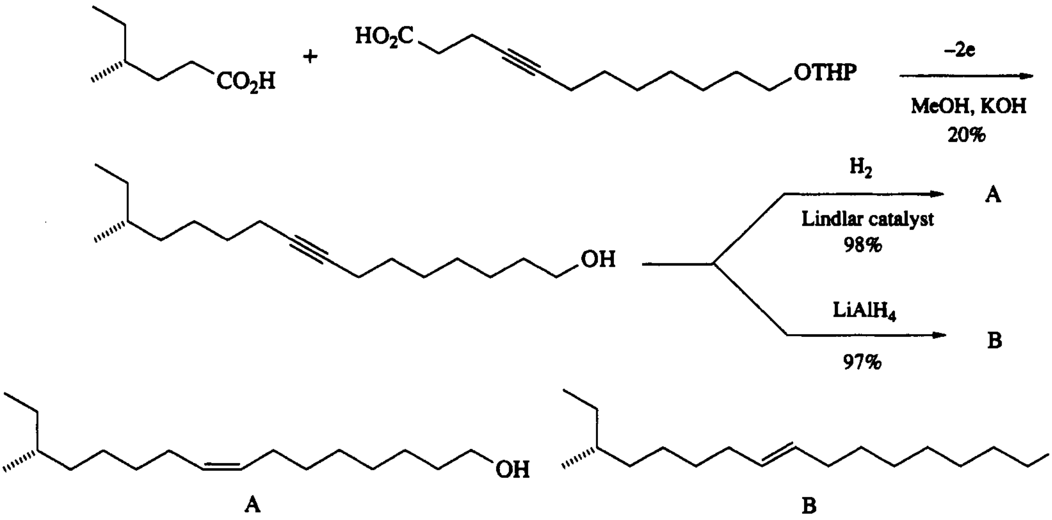

$CO_2H$
+
$HO_2C$
OTHP
−2e
MeOH, KOH
20%
OH
$H_2$
Lindlar catalyst
98%
A
$LiAlH_4$
97%
B
OH
A
OH
B

(55)

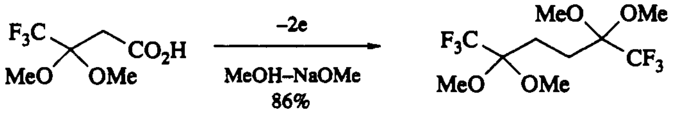

$F_3C$
$CO_2H$
MeO
OMe
−2e
MeOH–NaOMe
86%
MeO
OMe
$F_3C$
$CF_3$
MeO
OMe

(56)

Intermolecular addition of the radical and mixed coupling with the radical of a coacid gives 3-alkyl-substituted pyrrolidine (23; equation 57).[72]

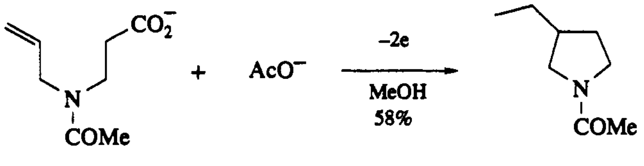

$CO_2^-$
N
COMe
+
$AcO^-$
−2e
MeOH
58%
N
COMe

(57)

(23)

### *(ii) Formation of cations*

When the cation $R^+$ is adequately stable and the reaction conditions are favorable for its formation, the radical R· formed from the carboxylic acid $RCO_2H$ is further oxidized to the cation $R^+$ which is then trapped by a nucleophile, $Nu^-$.[73] This reaction has been applied to the transformation of a carboxy group to a hydroxy group (equation 58).[74]

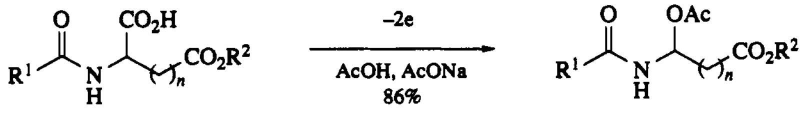

O
$CO_2H$
$R^1$
N
H
$CO_2R^2$
n
−2e
AcOH, AcONa
86%
O
OAc
$R^1$
N
H
$CO_2R^2$
n

(58)

$n = 2$, $R^1 = Ph$, $R^2 = CH_2Ph$

A Wagner–Meerwein-type rearrangement of the cation has been often observed in the oxidation of carboxylic acids (equation 59). The relative migratory aptitude of $R^1$ and $R^2$ has been studied, and this type of rearrangement has been applied to the synthesis of (±)-muscone (equation 60).[75]

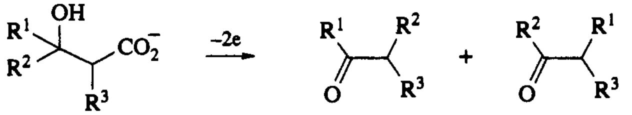

(59)

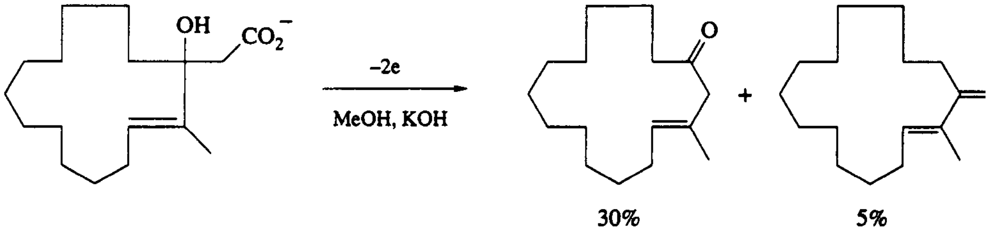

(60)

## 7.1.4 INDIRECT OXIDATIONS

### 7.1.4.1 Oxidation Using Mediators

### *7.1.4.1.1 Principles*

As described in the previous sections, the active species are generally generated by direct electron transfer between substrate and electrode in the electroorganic reactions. Hence, the formation of active species is highly controlled by the oxidation and reduction potentials of the substrates. When these potentials are beyond the range accessible by the usual electrochemical technique, the direct electron transfer between the substrate and electrode hardly takes place as described in the direct oxidation of aliphatic saturated alcohols. Therefore, it is necessary to devise some other methods to oxidize or reduce the substrates. Also, even if the oxidation and reduction potentials of the substrates are in the accessible range of the electrochemical method, it is more desirable to oxidize or reduce them at much lower potentials than those applied in the direct method. This is achieved by the electroorganic synthesis using mediators. The oxidative reaction system using a mediator is schematically represented in Figure 2.

The oxidation potential of the substrate S in Figure 2 is beyond the range accessible by the electrochemical method so that direct electron transfer from S to the anode hardly occurs, and also the high oxidation potential necessary for the direct oxidation of S causes unexpected side reactions involving oxidation of the solvent or supporting electrolyte. However, when a compound $M_{red}$ (a reduced form of M) which may be oxidized at a sufficiently lower potential than S is added to the reaction system, the oxidation of $M_{red}$ to $M_{ox}$ (an oxidized form of M) will take place prior to the oxidation of S. Provided that $M_{ox}$ is able to oxidize S to product P, the oxidation of S will be achieved at a potential lower than that necessary for its direct oxidation. Oxidation of S with $M_{ox}$ may be effected in two ways, namely by direct electron transfer (homogeneous electron transfer) from S to $M_{ox}$ in solution or by chemical oxidation of S with $M_{ox}$. The former system is called a homomediatory system and the latter a heteromediatory (or chemomediatory) system. The compound M is called a mediator or an electron carrier, since M mediates electron transfer between S and the anode. When $M_{ox}$ oxidizes S in solution, $M_{ox}$ is reduced to $M_{red}$

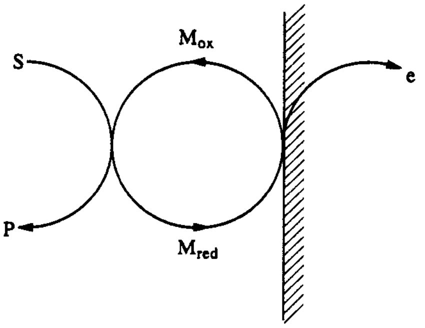

**Figure 2** Mediatory system

which is again oxidized at the anode to regenerate $M_{ox}$. Thus, if the lifetime of the redox system $M_{ox} \leftrightarrow M_{red}$ is sufficiently long, only a catalytic amount of the mediator is required to initiate the entire reaction. As a matter of course, the concept of the mediatory system is not only applicable to oxidations, as illustrated by Figure 2, but also to reductions. Although the term mediator or electron carrier has been introduced rather recently, many types of reaction systems involving a compound which behaves as a mediator were already known.

### *7.1.4.1.2 Homomediatory systems*

The homomediatory system is represented by equations (61) to (63), in which the mediator M is first oxidized to the cation radical $M^{+}\cdot$ at a relatively low oxidation potential. The next step involves a homogeneous electron transfer from S to $M^{+}\cdot$ to form $S^{+}\cdot$; this step is a reversible reaction. In the final step, $S^{+}\cdot$ is transformed to the products $P_1{}^{+}$ and $P_2\cdot$ by an irreversible reaction.

$$M \xrightarrow{-e} \overset{+}{M\cdot} \qquad (61)$$

$$\overset{+}{M\cdot} + S \rightleftharpoons M + \overset{+}{S\cdot} \qquad (62)$$

$$\overset{+}{S\cdot} \longrightarrow P_1^{+} + P_2^{\bullet} \qquad (63)$$

Since the oxidation potential of S is more positive than that of M, the equilibrium in equation (62) is largely shifted to the left hand side. Hence, the rate of the whole reaction greatly depends on the rate of the irreversible reaction in equation (63). In fact, the oxidation described by equation (61) proceeds effectively only when $S^{+}\cdot$ is transformed sufficiently fast to products $P_1{}^{+}$ and $P_2\cdot$.

When the oxidation potential of S is much more positive than that of M the oxidation illustrated by equation (61) is almost impossible, even though the irreversible reaction of $S^{+}\cdot$ is fast. In such a case, some further activation of $M^{+}\cdot$ is necessary to make the oxidation possible.[76]

### *7.1.4.1.3 Heteromediatory systems*

In the heteromediatory system, the substrate S is not oxidized by direct electron transfer from S to $M_{ox}$ but by chemical reaction between S and $M_{ox}$. Many of the mediatory systems which are useful in organic synthesis may be classified into this category. Among a variety of mediators, the redox system consisting of a halide anion and a positive halogen species is one of the most interesting mediators used in organic synthesis.

One of the earliest synthetic reactions in which the halide anion was used as a mediator is the anodic methoxylation of furan in the presence of 0.05 equiv. of ammonium bromide, though the reaction has not been termed a mediated oxidation (equation 64).[77]

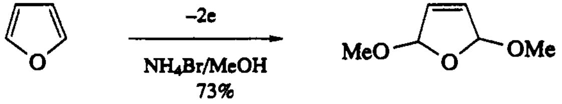

(64)

After this early investigation, a variety of oxidations using the redox system halide anion/positive halogen species as the mediator have been studied. Some of these oxidation systems are shown below in equations (65),[78] (66)[79] and (67).[80]

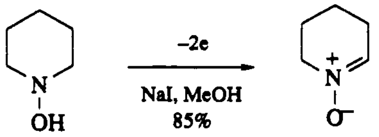

(65)

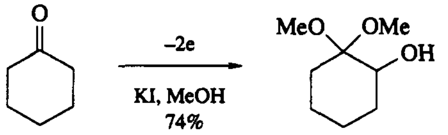

(66)

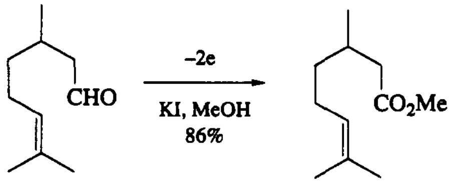

(67)

Besides halide ions organic sulfides are also efficient mediators. The oxidation of secondary alcohols to ketones has been successfully achieved by using methyl phenyl sulfide (**24**) as the mediator (equation 68).[81]

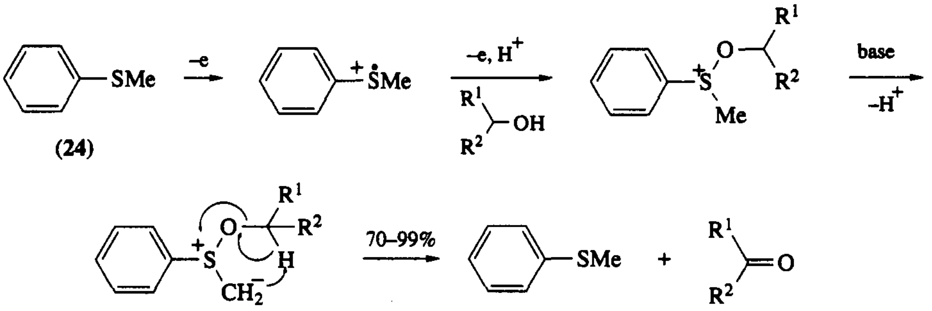

(24)

(68)

It is remarkable that carbon–carbon double bonds are completely inert in these oxidations. Some organic mediators, *e.g.* (**25**),[82] (**26**)[83] and (**27**),[84] have been exploited for the oxidation of alcohols.

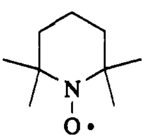

(**25**)

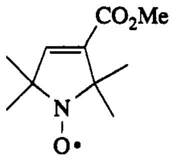

(**26**)

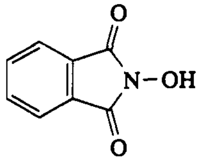

(**27**)

### *7.1.4.1.4 Double mediatory systems*

As described above, the mediatory system is an effective tool to oxidize the substrates that cannot be readily oxidized by the direct method. Further development of this concept has led to the combination of two types of mediators (Figure 3). As a result, the oxidation of substrates is achieved at a potential which is far lower than that required when the system contains only one type of mediator.[85]

In this system, the potential ($E_p$ = 1.1 V *versus* SCE) of the oxidation of $Br^-$ to $Br^+$ is the lowest, and the oxidation of $R'_2S$ to $R'_2S^{+\cdot}$ does not take place at this potential. As described above, alcohols such as $R^1R^2CHOH$ are oxidized by $R'_2S^{+\cdot}$, whereas $Br^+$ itself is not sufficiently reactive to oxidize alcohols to ketones in satisfactory yields. When both mediators are combined as depicted in Figure 3, however, the oxidation of alcohols may be achieved at a considerably lower potential than that necessary for the oxidation of $R'_2S$ to $R'_2S^{+\cdot}$.

The yields of the obtained ketones are in the range of 80–94%. The mediatory system shown in Figure 3 can be called a double mediatory system. A double mediatory system containing the redox systems $Pd^0 \leftrightarrow Pd^{2+}$ and quinone ↔ hydroquinone has been reported.[86]

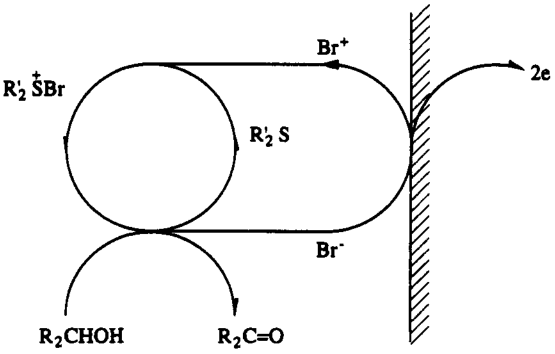

$R'_2\overset{+}{S}Br$
$R'_2S$
$Br^+$
2e
$Br^-$
$R_2CHOH$
$R_2C=O$

**Figure 3** Double mediatory system

## 7.1.4.2 Formation of Active Species

### *7.1.4.2.1 Halogenation*

The cationic species formed by the anodic oxidation of halide anions add to alkenes in the presence of suitable nucleophiles (equation 69).[87]

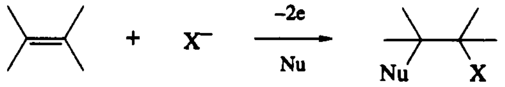

(69)

Early investigations on the oxidative addition of halogens to alkenes have mainly been focused on the preparation of epoxides from lower alkenes such as ethylene and propene.[88]

Halogenation of aromatic nuclei may also be achieved by halogen or positively charged species of halogen formed in solution by anodic oxidation of halide anions (equation 70).[89]

$$\text{ArH} + X^- \xrightarrow{-2e} \text{ArX} + H^+ \qquad (70)$$

The anodic oxidation of a mixture of iodine and aromatic compounds in acetonitrile gives aryl iodides in rather low yields. This iodination is improved by using a stepwise method (equation 71).[90]

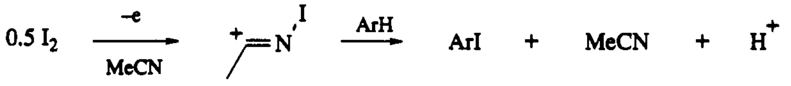

$0.5\,I_2$
−e
MeCN
I
+
N
ArH
ArI
+
MeCN
+
$H^+$

(71)

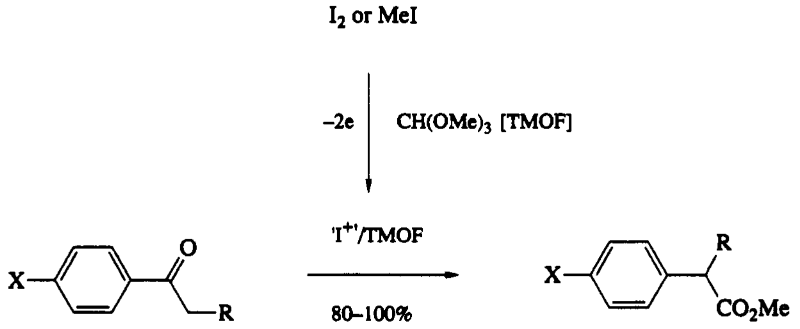

$I_2$ or MeI
−2e
$CH(OMe)_3$ [TMOF]
'$I^+$'/TMOF
80–100%
X
O
R
X
R
$CO_2Me$

(28) (29) (72)

X = H, $Bu^i$, Cl, Br, $Bu^tCO_2$; R = alkyl

Anodic oxidation of iodine or MeI in trimethyl orthoformate (TMOF) gives a new positive iodine active species ('$I^+$'/TMOF), which makes possible a unique rearrangement of aryl alkyl ketones (**28**) to methyl arylalkanoates (**29**; equation 72).[91]

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# 7.2

# Oxidative Rearrangement Reactions

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## 7.2.1 INTRODUCTION

Oxidative rearrangements comprise a highly diverse group of reactions, some of which enjoy broad usage in synthesis, while others remain curiosities. This chapter necessarily reflects this heterogeneity. The designation 'oxidative rearrangement' is not used uniformly in the literature; the discussion in this chapter is limited to reactions which alter the connectivity in one or more carbon–carbon π- or σ-bonds in the substrate, and in which the molecule undergoes a net oxidation. Most often these changes will occur simultaneously, forming part of a single transformation, and the rearrangement is frequently driven by the oxidation. For the sake of brevity, the scope is further narrowed by excluding oxidative rearrangements of heterocyclic rings such as furans, pyrans, pyrroles and indoles; these reactions in themselves are numerous enough to fill a chapter. The overall emphasis is on selectivity and synthetic utility.

The organization is by type of reacting bond. The first section deals with functional group rearrangements — connectivity changes in carbon–carbon π-bonds and of bonds to heteroatoms which do not alter the carbon skeleton. The second section covers the skeletal rearrangements — connectivity changes in the carbon–carbon σ-bond framework with the concomitant functional group changes. Within each of these sections the discussion is divided according to the functional group undergoing oxidation.[1,2] The strained rings of cyclopropanes[3] and cyclobutanes[4] are treated as functional groups, and the oxidative rearrangements of these small rings which have no counterpart in the chemistry of larger rings are covered separately. Perhaps arbitrarily, oxidative cleavages of small rings are considered with the functional group rearrangements, while other structural reorganizations are covered with the skeletal rearrangements.

Several factors may cause an oxidation to take place with rearrangement. Conformational features of the substrate play an important role; steric crowding at the reaction site may favor strain relief through rearrangement over the normal mode of oxidation, or favorable overlap of the reacting bond with an allylic or an isolated but proximate double bond may cause a rearrangement. The first-formed products or intermediates of oxidation, such as an epoxide[5] or an alkylthallium(III) adduct,[6a] may be unstable and the pathway to a more stable species will involve a rearrangement. Many oxidative rearrangements follow a predictable pattern, and thus constitute reliable synthetic methods. Others are highly substrate dependent, and their utility in synthesis requires a careful conformational analysis of the substrate, or a good measure of luck.[7]

The examples presented here were selected to represent the variety of transformations which have been uncovered, from the heavily used to the seemingly unique cases. The aim is to acquaint practitioners with the more established methods, and to pique the interest in some reactions which could become useful tools with further development.

## 7.2.2 OXIDATIVE REARRANGEMENT OF FUNCTIONAL GROUPS

The discussion in this section is divided according to the functional group undergoing oxidative rearrangement: alkenes and enols, allylic alcohols, cyclopropanes and cyclobutanes, and miscellaneous functional group rearrangements. For the cyclopropanes and cyclobutanes, the scope is limited to the oxidative cleavages of the small rings which do not have counterparts in the chemistry of larger ring compounds. The major oxidants used commonly for these reactions include chromium(VI),[1,2b,8] lead(IV),[1,2c,9] and singlet oxygen ($^1O_2$).[10] From among the functional group rearrangements, the strongest contributors to synthetic methodology are the allylic oxidations of alkenes (including the singlet oxygen ene reaction), and the 1,3-ketone transposition resulting from the oxidative rearrangement of allylic tertiary carbinols.

### 7.2.2.1 Alkenes and Enols

The reaction of oxygen with vinyl halides gives acyl derivatives,[11] as shown in equation (1). These reactions proceed in moderate to good yield, and follow a radical chain mechanism. The migratory preference is Br > Cl > F when mixed polyhaloalkenes are used. This reaction has found particular utility in the preparation of functionalized fluorocarbons, as shown in Scheme 1 for the example of perfluoroacrylic acid (**1**). Vinyl sulfides also undergo this oxidative rearrangement to give α-thio acyl derivatives.

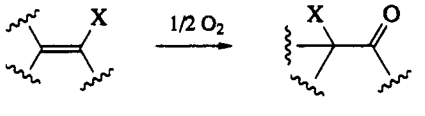

(1)

X = halogen

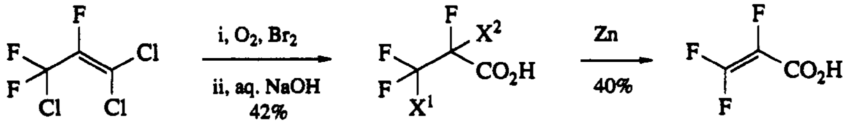

(**1**)

X$^1$, X$^2$ = Br, Cl; Cl, Br

**Scheme 1**

Vinylsilanes follow a similar course on oxidation with peroxy acid or with ozone.[6b,12] Depending upon the conditions of oxidation they can be converted either to a carbonyl compound (**2**) or to the α-hydroxycarbonyl compound (**3**), as in Scheme 2.[12,13] Vinyl silanes are useful synthetic intermediates, and this oxidation rearrangement procedure is an important component in their spectrum of reactivity.

Enol ethers, and in particular silylated enols (see Volume 2, Chapter 2.3), react with peroxy acid reagents to give initially a silyloxy epoxide, which rearranges with silyl migration to yield an α-silyloxy ketone,[12,14] as in Scheme 3. The net result is that a ketone is converted to a protected α-hydroxy ketone, and the stereochemistry is determined by the least hindered approach of the peroxy acid to the enol.

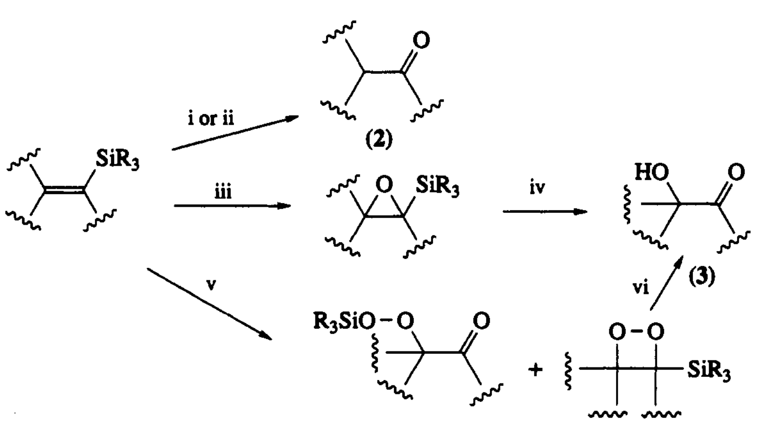

i, MCPBA, $KHF_2$, DMF; ii, 30% $H_2O_2$, $NaHCO_3$, MeOH, THF; iii, MCPBA, $CH_2Cl_2$;
iv, 30% $H_2O_2$, $KHF_2$, $KHCO_3$, MeOH, THF; v, $O_3$; vi, [H]

**Scheme 2**

Although peroxy acid is the reagent of choice, under the proper conditions simple double bonds survive this reaction.

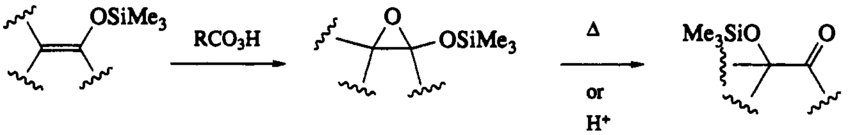

**Scheme 3**

Allylic oxidation (which is discussed in Chapter 2.1, this volume) takes place with rearrangement in certain substrates, the driving force being either a lower activation energy barrier for the chromate insertion into the C—H bond with rearrangement and/or a greater stability for the transposed enone product. Moderate selectivity is obtained in the case of 4,4-dimethylcyclohexene which serves to demonstrate,[8] as seen in equation (2). The oxidant shows a three-fold preference for hydrogen abstraction at C-3 over C-6 in order to avoid a 1,3-diaxial interaction with one of the methyl groups. The abstraction at C-3 leads mainly to the rearranged enone (4) for either steric or stereoelectronic reasons.

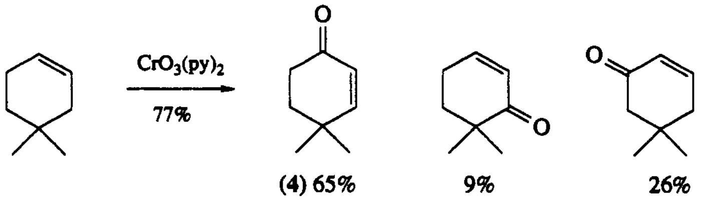

(2)

Two independent syntheses of quadrone employed an allylic oxidation with rearrangement, as shown in equation (3),[8] where the chromium trioxide·(3,5-dimethylpyrazole) reagent ($CrO_3$·DMP) was used. In some cases, the success of the reaction strongly depends on the nature of the oxidant, as shown in an approach to (–)-upial (equation 4). Here the chromium trioxide–heterocycle reagents, which are weaker oxidants, are quite inferior compared to the Fieser reagent.[15]

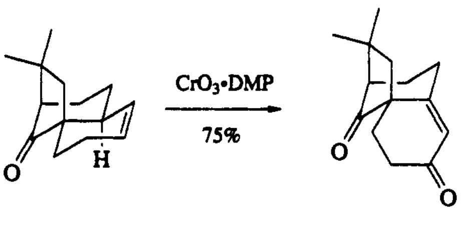

(3)

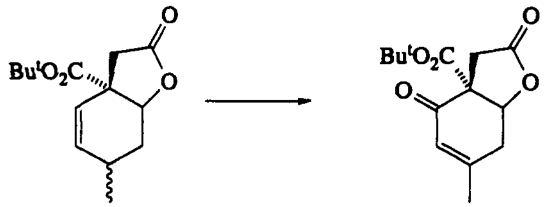

(4)

| | |
|---|---|
| $CrO_3(py)_2$ | 0% |
| $CrO_3$•DMP | 18% |
| $CrO_3$/HOAc/$Ac_2O$ | 67% |

The allylic oxidation of alkenes by $^1O_2$ involves an ene reaction, and proceeds with rearrangement[10] as in Scheme 4. The intermediate allylic hydroperoxide (5) can be reduced to yield an allylic alcohol (6), or be treated with base to give an unsaturated carbonyl compound (7). The reaction works best on tri- or tetra-substituted alkenes, and the relative preference for attack is Me ≈ $CH_2$ >> CH. The $^1O_2$ allylic oxidation has been used in the synthesis of a large number of natural products, including some naturally occurring allylic hydroperoxides. It is possible that $^1O_2$ reactions of this type are involved in biosynthetic processes.

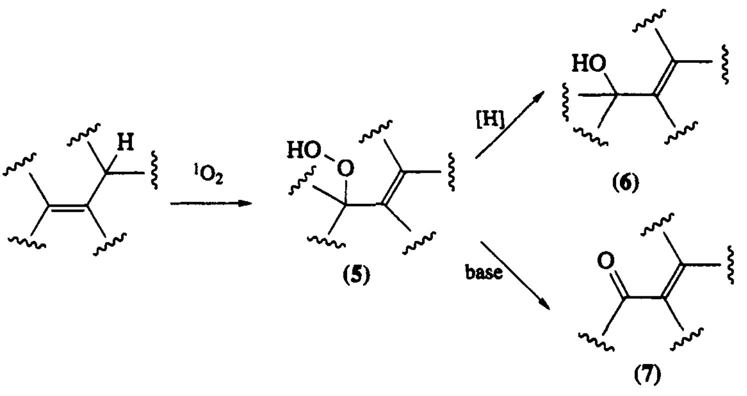

Scheme 4

This oxidation is applicable to a wide variety of both electron-rich and electron-poor alkenes; for example a number of tiglic acid derivatives undergo this reaction in moderate to excellent yield,[16] as in equation (5). In cases where there are several nonequivalent allylic sites the course of this reaction is highly substrate dependent, and the yields and selectivity vary from excellent to mediocre. In trisubstituted alkenes (except for most 1-alkylcyclohexenes), a reactivity pattern has emerged which has been termed a preference for *syn* ene attack (or 'PSEA').[17] This means that $^1O_2$ will preferentially attack one of the two allylic carbons which are *cis* to each other. In practical terms, this still translates into relatively low product selectivity in most cases such as in equation (6), although some notable exceptions are known (equations 7 and 8).

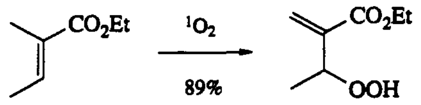

(5)

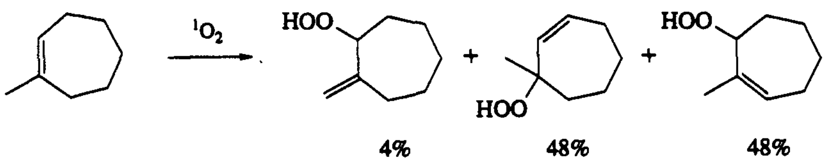

(6)

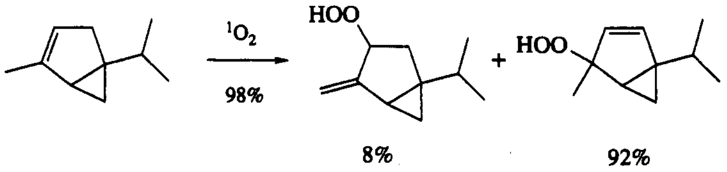

(7)

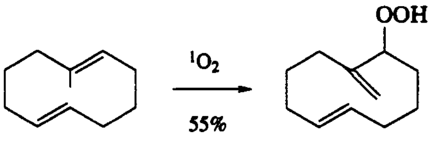

(8)

A procedure for the large-scale conversion of alkenes to unsaturated carbonyl compounds using singlet oxygen has been published,[18] whereby the conversion of cyclopentene to cyclopentenone can be carried out on a molar scale in 60% yield.

Another variant on this chemistry is the use of triphenyl phosphite ozonide as a source of singlet oxygen.[19] This reagent mimics singlet oxygen in many of its reactions, and is easier to quantify.

A further alternative to the singlet oxygen allylic oxidation method involves selenium chemistry.[20] This route involves epoxidation of the alkene, followed by nucleophilic opening of the epoxide with phenyl selenide anion, and finally oxidation to the selenoxide, which eliminates spontaneously to produce an allylic alcohol,[21] as described in Scheme 5. The β-hydroxy phenyl selenide (**8**) need not be isolated but can be oxidized *in situ*. The regioselectivity of this conversion depends on the degree of substitution on the alkene and the conformation of the β-hydrogens. The phenyl selenide anion will attack the least hindered carbon of the corresponding epoxide, and the geometry of the resulting double bond depends on the alignment of the hydrogens allylic to the original double bond; the elimination of the selenoxide is *syn*, and the transition state for elimination may require a rotation. If a ring fusion or conformational restrictions prevent the proper orbital overlap, the elimination may fail, or may give an enol if the hydroxy-bearing carbon is secondary.

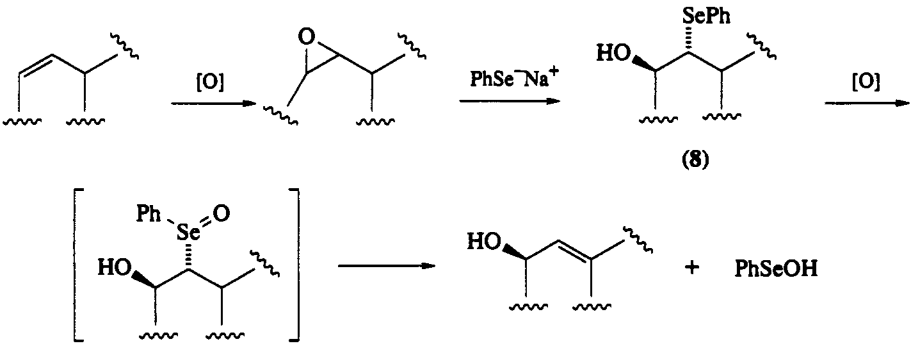

**Scheme 5**

An electrochemical synthetic process (see Chapter 7.1, this volume) has been reported which requires only a catalytic amount of the selenating agent, and converts an alkene to the allylic alcohol in an aqueous cell, or to the allylic methyl ether if the electrolysis is run in methanol, as in equation (9).[22]

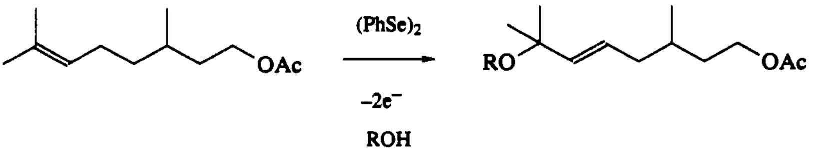

(9)

R = Me, 82%; R = H, 80%

A special case of allylic oxidation with rearrangement occurs in the action of chromium(VI) agents on 3,4-unsaturated ketones (**9**), and this is shown in Scheme 6. Hydrogen abstraction by the oxidant takes place at the doubly activated C-2 position of (**9**), and ultimate oxidation occurs at C-4 to give an enedione (**10**). This reaction is driven by the lability of the C-2 hydrogen, and by conjugation of the double bond with the carbonyl group; oxidation of the 3,4-unsaturated ketones is far more rapid than oxidation of their 2,3-unsaturated isomers. This reaction may have a broad scope, but the only examples to date involve six-membered ring-fused polycyclic and acyclic substrates.

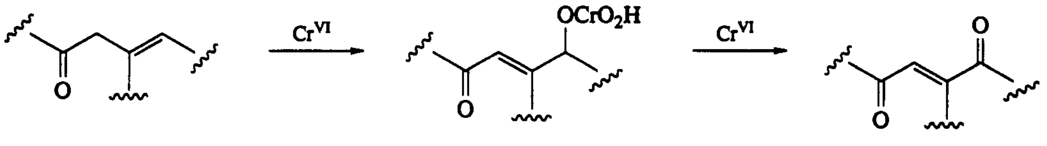

**(9)** **(10)**

**Scheme 6**

The formation of a second carbonyl is not required, and where C-4 is fully substituted a 4-hydroxy-2-en-1-one is obtained.[23] The original carbonyl group may arise by oxidation of an alcohol, the classic example being the oxidation of cholesterol (**11**) to cholest-4-en-3,6-dione (**12**) with chromium(VI) reagents, in which a yield as high as 85% can be obtained, as in equation (10).[24] In degradation work on isopimarenes isolated from the mollusc *Aplysia kurodai*, Jones reagent serves to convert a β-hydroxyalkene (**13**) into the enedione (**14**) in moderate yield, as shown in equation (11).[25]

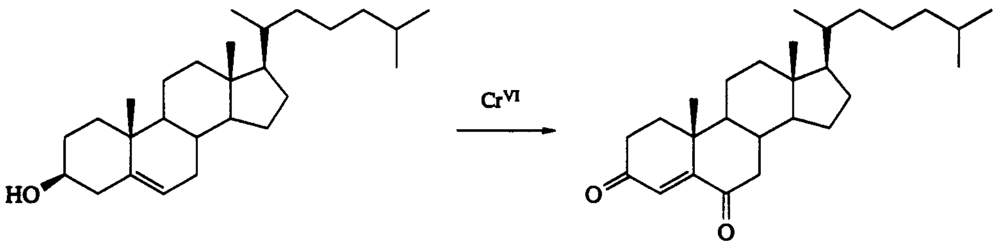

**(11)** **(12)** (10)

$Na_2Cr_2O_7$, AcOH, 40%; $CrO_3(py)_2$, AcOH, 85%

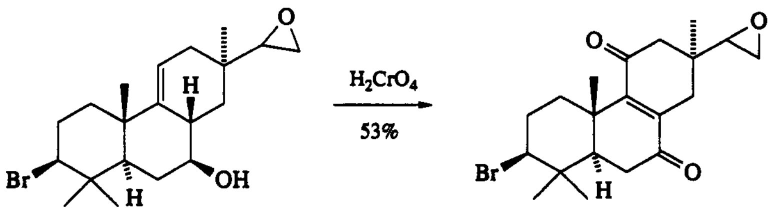

**(13)** **(14)** (11)

A related oxidative rearrangement of cephem dioxides has been reported[26] in which an alkene is oxidized stereospecifically with rearrangement to the allylic alcohol in good yield by simple exposure to a palladium/carbon catalyst, as depicted in equation (12). Adventitious oxygen preadsorbed on the catalyst seems the likely oxidant. The reaction fails on the parent cephem or its monoxide, or on the free acid of the dioxide. This reaction would seem to hold some promise for further utility in the cephem field and other related systems.

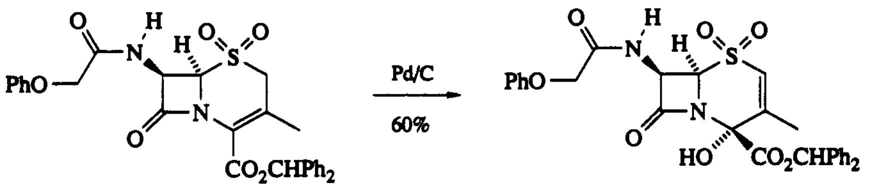

(12)

### 7.2.2.2 Allylic Alcohols

The oxidative rearrangement of allylic alcohols to α,β-unsaturated ketones or aldehydes is one of the most widely used synthetic reactions in this group, and forms part of a 1,3-carbonyl transposition sequence.[8] Scheme 7 shows this reaction and the related conversion of the allylic alcohol to an α,β-epoxy carbonyl compound. Chromate reagents induce some allylic alcohol substrates to undergo a directed epoxidation of the alkene without rearrangement, but this reaction is beyond the scope of the present discussion.

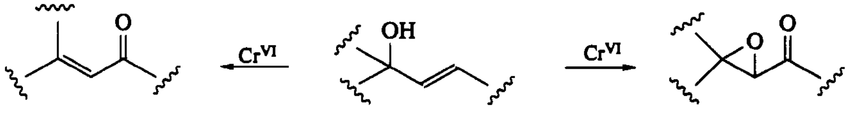

Scheme 7

The mechanism for this transformation, and the partitioning between unsaturated carbonyl and epoxycarbonyl products has been the subject of several studies.[27] The production of epoxycarbonyl compounds seems to be correlated with the nature of the chromate reagents used, although substrate structure also helps to determine this preference.

However, the conversion to the transposed α,β-unsaturated carbonyl compound is by far the more useful reaction. The full sequence serves both to form carbon–carbon bonds as well as to adjust the functional group array in the synthetic intermediate. Thus, starting with the enone (**15**), organometallic addition generates a tertiary allylic alcohol (**16**) and oxidative rearrangement yields a β-alkyl-α,β-enone (**17**), as shown in Scheme 8.

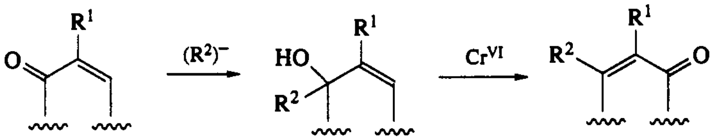

**(15)** **(16)** **(17)**

Scheme 8

Applications are found in acyclic as well as five-, six-, seven- and eight-membered ring cyclic substrates, and yields are generally in the range of 50–90%. The best substrate is one in which the C—O bond of the alcohol is (or can easily become) parallel with the *p*-orbitals of the alkene double bond, as the transition state is believed to involve a 3,3-sigmatropic rearrangement of the chromate ester. Isolated double bonds, esters, lactones and silyl ethers, and a number of other functional groups, survive these conditions. Protected carbohydrates undergo degradation which limits the application to such substrates. Examples are found in equations (13)–(15).[28–30]

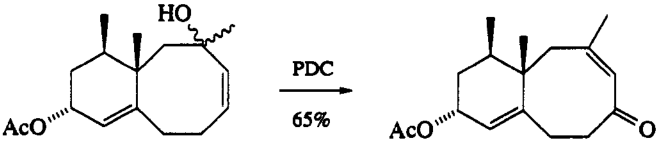

(13)

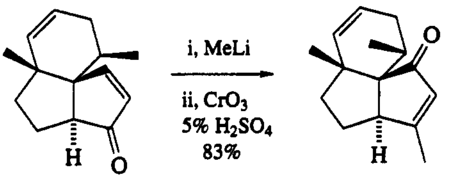

(14)

Ketones can be homologated to unsaturated ketones or aldehydes by addition of the appropriate vinyl nucleophile followed by oxidative rearrangement, as shown in Scheme 9. The use of this transformation in a synthetic approach to steroids with unsaturated side chains is shown in equation (16).[31]

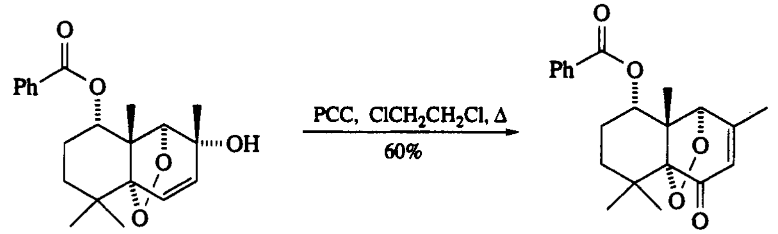

(15)

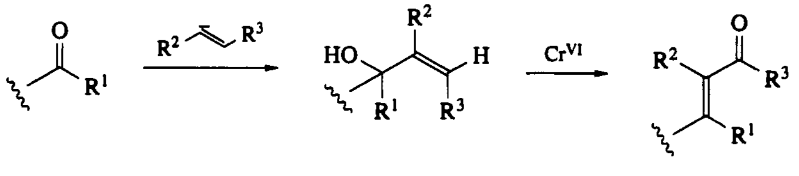

**Scheme 9**

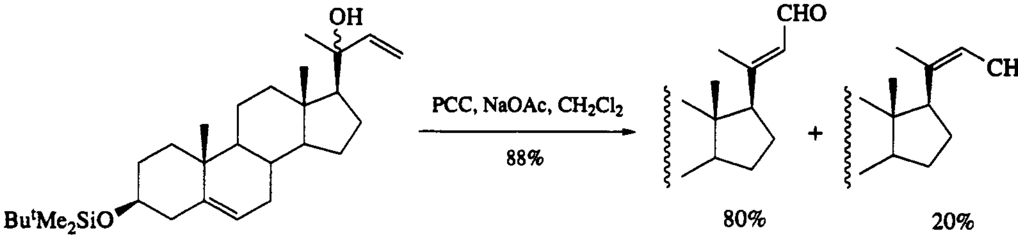

(16)

The regioselectivity of these reactions has been studied in cases where two allylic rearrangements would be possible. In one report tertiary alcohols which were both allylic and propargylic were found to rearrange solely over the allylic system where the alkene is contained in a five- or six-membered ring.[32] In a cyclic system where the alcohol is equatorial, and in acyclic systems, the yield of rearrangement is poor and oxidative cleavage becomes important. In a particularly interesting study a series of bis-allylic alcohols were examined.[33] Vinylic cyclohexenols and cyclopentenols rearrange exclusively within the ring to give 57–80% yields of the β-vinylic cyclohexenone or cyclopentenone, as shown in equation (17). The bis-allylic alcohol (**18**; equation 18), which contains an allylsilane substituent, undergoes clean oxidative rearrangement to the dienone (**19**). This example helps to clarify the mechanism of the rearrangement, since a discreet carbonium ion intermediate would doubtless be trapped through cyclization with the allylsilane moiety; the absence of such cyclization products argues against a cationic intermediate and in favor of the 3,3-sigmatropic mechanism. The fact that the mildly nucleophilic allylsilanes (see Volume 2, Chapter 2.2) survive this reaction is important for its synthetic utility.

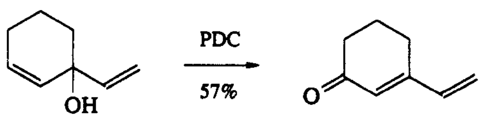

(17)

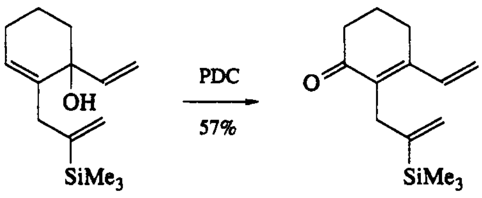

(18)

**(18)** **(19)**

Where the allylic alcohol is in a secondary position, conformational effects or the character of the oxidant can still favor an oxidative rearrangement over simple oxidation to the ketone (equation 19).[34]

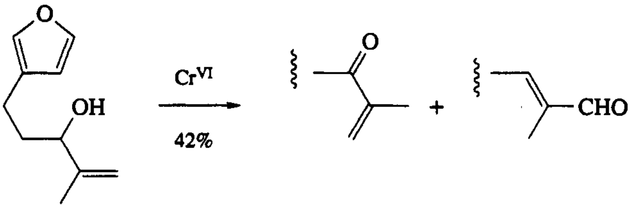

(19)

| | | |
|---|---|---|
| PCC | 100% | |
| PCC, TsOH | 17% | 83% |

An oxidative rearrangement took place during the MCPBA epoxidation of the secondary allylic alcohol auraptenol, leading to the enal shown in equation (20). This reaction has been used in an approach to casegravol and in a synthesis of arnottinin.[35] The reason why the intermediate epoxy alcohol undergoes rearrangement in this case is not known beyond the possibility that the *m*-chlorobenzoic acid by-product could act as an acidic catalyst.

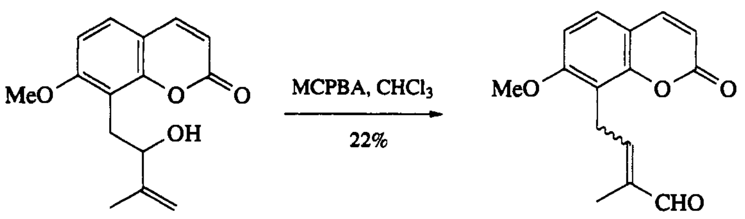

(20)

The peculiar oxidative rearrangement of cycloocta-2,4-dien-1-ol (**20**) shown in equation (21), involves a highly selective *cis* epoxidation (*cis*:*trans* = 20:1) followed by transannular $S_N2'$ attack by the hydroxy group on the allylic epoxide to give the *exo*-β-hydroxy cyclic ether (**21**).[36] This rearrangement is stereospecific in that the *trans*-epoxy alcohol, available by treatment of the cyclooctadienol with MCPBA, does not give a rearranged product. A similar example with a cycloheptadienol was also reported. The pure *cis*-epoxy alcohol rearranges to the bicyclic alcohol at 156 °C, but does so far more rapidly in the presence of the vanadium catalyst at 60 °C.

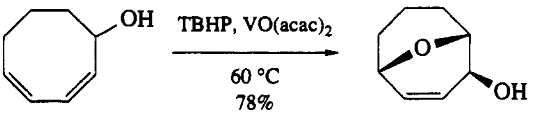

**(20)** **(21)**

(21)

The cyclodecenol substrate (**22**; equation 22), undergoes a transannular oxidative rearrangement to yield the decalone (**23**) in moderate yield.[37] Although not strictly a simple functional group rearrangement, this reaction can be thought of as the through-space version of the oxidative rearrangement of allylic alcohols. In this case it is quite likely that the reaction proceeds through attack by the alkene on the carbon bearing a preformed chromate ester, which behaves as a leaving group. The intermediate decalinyl carbonium ion is captured by additional chromate and eliminates to the observed product (**23**).

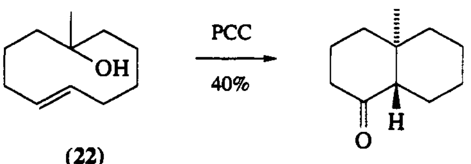

**(22)** **(23)**

(22)

A related example occurs in the adamantane field, as seen in equation (23).[38] It is surprising that a primary alcohol undergoes ring closure instead of the standard oxidation to an aldehyde or acid under the influence of chromate. The chromate ester of this *endo*-oriented alcohol would undoubtedly experience severe crowding, and direct oxidation is probably inhibited for steric reasons.[39] In both of these cases the proximity of the alkene to the carbinol carbon seems to drive the rearrangement, and there is precedent for a related type of oxidative cyclization.[8] In a further example, the norbornadienol (**25**; equation 24) is oxidized by $MnO_2$ with rearrangement to give the hemiacetal (**26**).[40] This reaction is believed to involve a displacement of the Mn$^{4+}$ ester by the alkene, followed by oxidation of the resulting carbonium ion and cleavage.

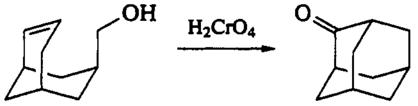

(**24**)

(23)

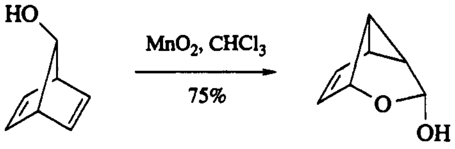

(**25**) (**26**)

(24)

### 7.2.2.3 Cyclopropanes and Cyclobutanes

The strained rings of cyclopropanes[3] and cyclobutanes[4] can be considered as functional groups, since these molecules react in ways which are not characteristic of other cycloalkanes. The chemical behavior of cyclopropanes in particular has many analogies to that of alkenes. For the purposes of this discussion the oxidative ring cleavage reactions of cyclopropanes and cyclobutanes which do not have counterparts in the chemistry of larger rings are considered as functional group rearrangements.

Oxidative cleavage of cyclopropanes has been studied mostly with lead(IV),[2c,9] thallium(III)[6] and chromium(VI) reagents.[2b,8] The oxidative cleavage of cyclobutanols has been explored mainly with chromium(VI) reagents,[2b,8] although other oxidants have been studied.[4]

Cyclopropanols undergo oxidative cleavage with a variety of oxidants to give β-functionalized propanal derivatives. Even secondary cyclopropanols give moderate yields of ring-opened products. The activation barrier on the pathway to cyclopropanone is steep, and the alternative pathway of rearrangement is driven by relief of ring strain. The example given in equation (25) shows the use of chromic acid.[8] These oxidations are much faster than the oxidation of a normal secondary alcohol.

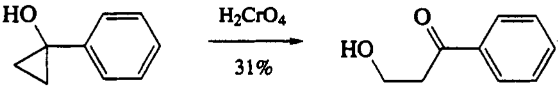

(25)

An approach to a prostaglandin intermediate employed a cyclopropanol oxidation with a mixed chromate/cerate reagent shown in equation (26), but the yield was unacceptably low.[41] Although no information on the selectivity is available, the *trans* stereochemistry of oxidative cleavage in the reported product is of note. In these more complex substrates, side reactions and low yields plague the reaction, which will see only limited use in synthesis unless a better reagent system is developed.

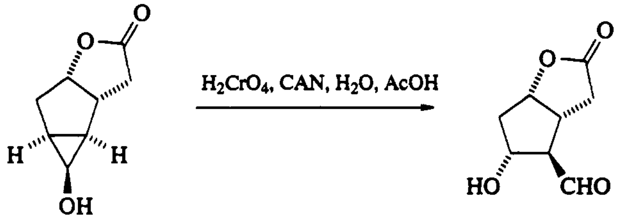

(26)

The lead tetraacetate oxidation of tertiary cyclopropanol silyl ethers does show some promise.[42] As shown in Scheme 10, a two-bond oxidative cleavage of the three-membered ring takes place in acetic acid solvent to yield the alkenoic acid (**27**); a carboxy group is produced from the original carbinol carbon and the alkene is derived from the other two ring carbons. The yields for this transformation are from 65–88%, and with a substituent on the methylene bridge the fragmentation is highly stereoselective for alkene geometries. In methylene chloride, a one-bond cleavage takes place to give the acetoxymethylcycloalkanone (**28**). Both types of reaction are useful, and as the starting cyclopropanols are available through Simmons–Smith methylenation of the corresponding silylated enol (see Volume 4, Chapter 4.7), these methods have good synthetic potential.

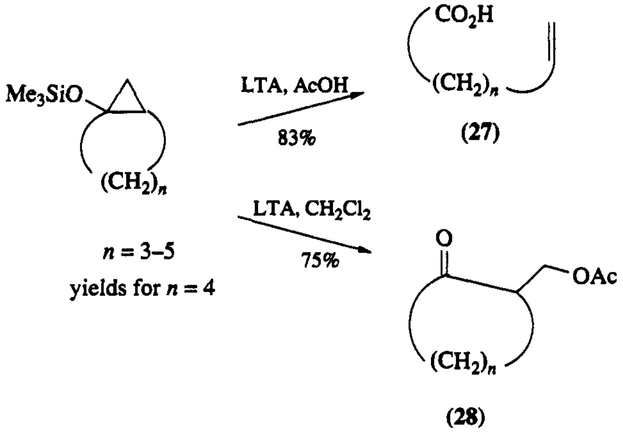

**Scheme 10**

Cyclopropenes undergo an oxidative cleavage to yield substituted enones, as shown in equation (27).[43] The reaction is believed to proceed through the unstable epoxide. The regioselectivity is generally low if $R^1 \neq R^2$, but if one of the substituents is trimethylsilyl a highly selective conversion to the α-silyl enone takes place. There is one report of a similar oxidative cleavage that takes place with thallium(III).[6]

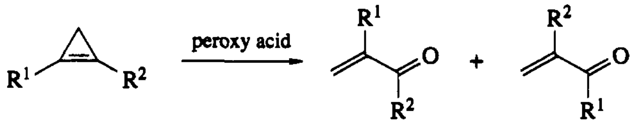

(27)

Methylenecyclopropane undergoes oxidative cleavage and ring expansion with thallium trinitrate in methanol to furnish in quantitative yield a mixture of the ring cleavage product 1-methoxybutan-3-one and cyclobutanone in the ratio of 4:1, as in equation (28).[44]

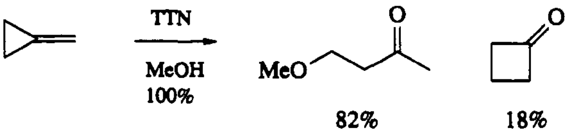

(28)

The oxidative rearrangement of tertiary cyclopropylcarbinols to 3,4-unsaturated carbonyl compounds is analogous (or homologous) to the reaction of allylic alcohols, and is shown in the example in equation (29).[8] This reaction has been shown to proceed stereospecifically in the conversion of the *cis*-substituted cyclopropylcarbinol (**29**) to the (*Z*)-enynone (**30**) shown in equation (30).[45] The substrates with R = H, Me and TMS all gave comparable yields.

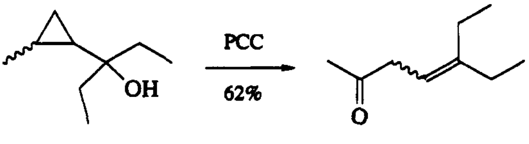

(29)

Cyclobutanols oxidize with ring cleavage to 4-hydroxy ketones, 4-hydroxy acids, or 1,4-diones under the influence of chromium(VI) reagents (Scheme 11).[8] The first formed product is a 4-hydroxycarbonyl compound (**31**) which exists as the five-membered ring hemiacetal (**32**). This form will persist in the absence of excess reagent under nonforcing conditions; otherwise further oxidation takes place to give a

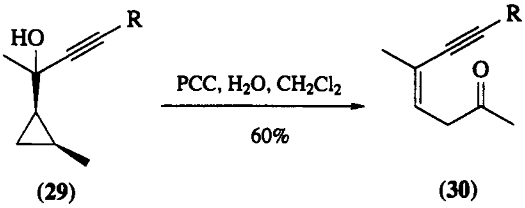

(30)

4-hydroxy acid (**33**; if $R^1$ = H) or a 1,4-dione (**34**; if $R^3$ = H). In unsymmetrical cyclobutanes the bond cleaved is the one between the carbinol carbon and the more highly substituted β-carbon, and the yields are generally good. With a quaternary β-carbon ($R^2$ and $R^3$ = alkyl) some of the 3,4- or 4,5-unsaturated carbonyl product arises.

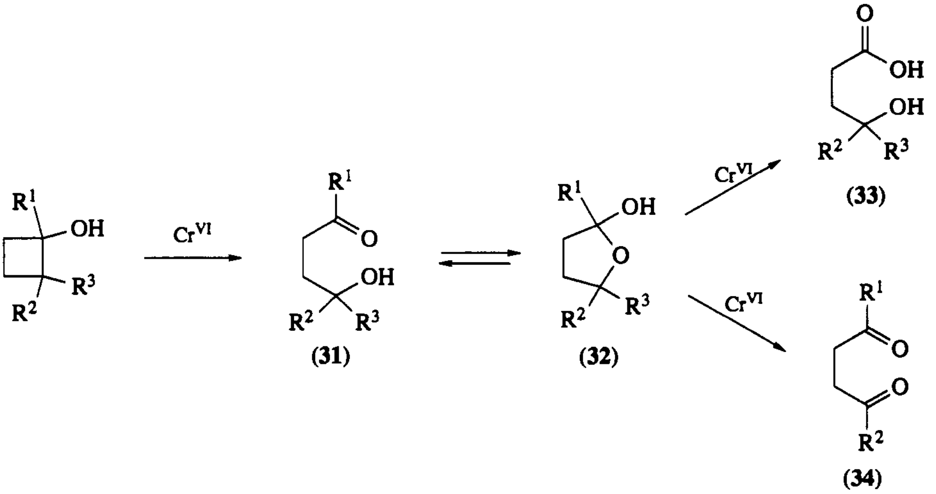

**Scheme 11**

### 7.2.2.4 Miscellaneous Functional Group Rearrangements

Treatment of 1,1-disubstituted epoxides of the gibberellin family with sulfuryl chloride results in the formation of the corresponding α,β-enal in good yield, as shown in equation (31).[46] Four examples were reported in which alcohols, esters, lactones and alkenes survive. The postulated mechanism involves an electrophilic opening of the epoxide with elimination, followed by oxidation of the primary chlorosulfate ester. A steroidal 3-spirooxirane also undergoes this reaction, but the yield is poor and several products are obtained, suggesting that the overall scope of this reaction may be limited.

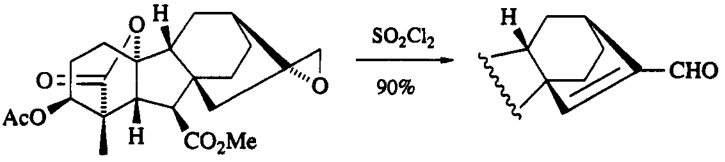

(31)

The Pummerer rearrangement (which is discussed in Volume 6, Chapter 4.7) is a type of oxidative rearrangement, as is the related 2,3-sigmatropic rearrangement of 2,3-unsaturated sulfoxides. Two related examples are presented here from selenium chemistry.[20] These reactions enhance the attractiveness of sulfur- and selenium-based synthetic methods, in that after being used to forge new carbon–carbon bonds, the heteroatom moiety can be exploited for a further functional group interchange.

Propargyl phenyl selenide is a versatile multifunctional acrylate synthon, as shown in Scheme 12.[47] The dianion is prepared and reacted successively with an alkylating agent (R—X) and an electrophile ($E^+$). The oxidative rearrangement of the propargylic selenoxide (**35**) to an allenic selenenate (**36**), and thence to the α-phenylselenoenone (**37**), forms the keystone of this synthetic method, and overall yields from propargyl phenyl selenide are in the range of 38–68%. Further elaboration of (**37**) is possible through conjugate additions, deselenation or another oxidative rearrangement. This method was used in a synthesis of 7-hydroxymyoporone.[47]

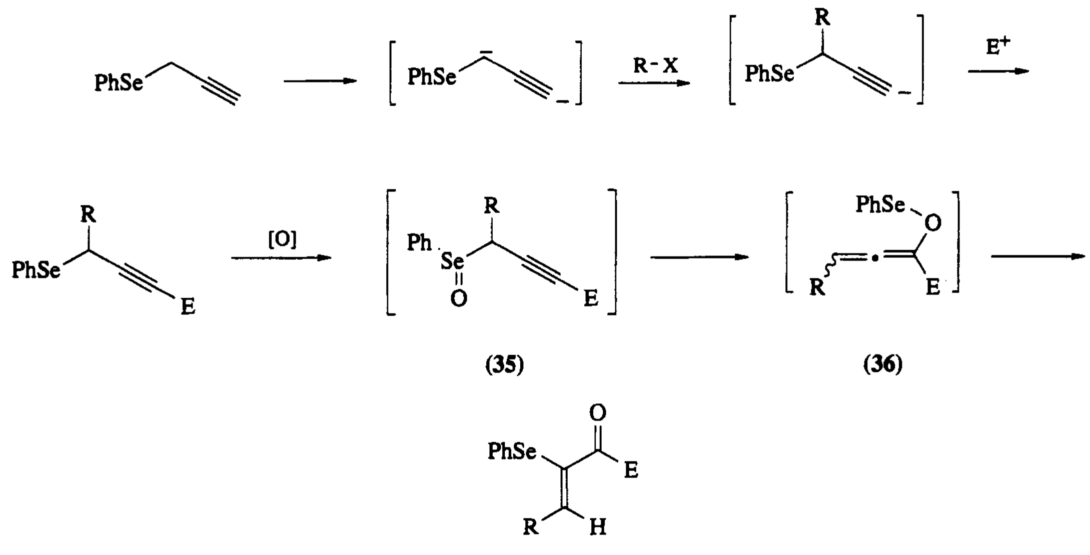

(35) (36)

(37)

Scheme 12

Equation (32) shows another example of this type of rearrangement, in which a phenylselenoallenic ester is converted to an α-keto alkynic ester in quantitative yield.[48]

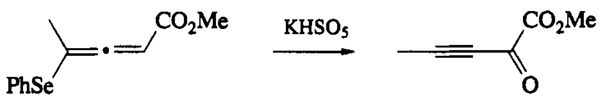

(32)

## 7.2.3 OXIDATIVE SKELETAL REARRANGEMENT

The discussion in this section is divided according to the functional group undergoing oxidative rearrangement: alkenes and enols, dienes, alkynes, cyclopropanes and cyclobutanes, and miscellaneous skeletal rearrangements. In view of the voluminous body of work on alkenes and enols, this area has been subdivided according to particular substrates: arylalkenes, aryl ketones, chalcones and cinnamyl compounds, and cyclic alkenes and ketones. Chalcones and cinnamyl compounds are treated as a special case of arylalkenes because of the extensive synthetic use of the chalcone to isoflavone transformation. In order to focus on the application to ring expansion and ring contraction reactions, cyclic alkenes and ketones are treated as a separate case, and methylenecycloalkanes are discussed with cycloalkenes. For the cyclopropanes and cyclobutanes, the scope is limited to the skeletal rearrangements of the small rings which do not have counterparts in the chemistry of larger ring compounds. The oxidants which have played the largest role in these transformations are thallium(III),[6a] lead(IV)[2c,9] and iodine.[49] The best reagents appear to be lead tetraacetate and thallium trinitrate, although on a larger scale cost is a concern for the latter, and toxicity is a problem for both. The newer hypervalent iodine reagents may prove more amenable in view of these factors.

Three highly useful synthetic transformations are presented in this section: the synthesis of isoflavones from chalcones, the synthesis of α-arylalkanones from arylalkenes, and the synthesis of α-arylalkanoic acids from aryl ketones. Two others are potentially useful methods, but are not as yet widely used: the preparation of α-branched carboxylic acids from alkynes, and the ring expansion and ring contraction of cyclic alkenes and ketones.

### 7.2.3.1 Alkenes and Enols

The oxidative rearrangement most widely used in synthesis is the oxidative 1,2-shift of an alkene or enol, which is shown in the formal sense in equation (33). The alkene may be electron deficient such as an unsaturated ketone, or electron rich such as an enol, enol ether or enamine.

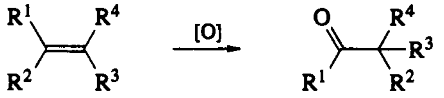

(33)

If $R^2$ and $R^3$ are connected then a ring contraction results. If $R^1$ and $R^2$ are connected, a ring expansion takes place. The reagents used to carry out this transformation are strongly electrophilic oxidants, or an oxidant used together with a Lewis acid. Hypervalent main group oxidants such as thallium(III), lead(IV) and iodine(III) have played the largest role in this area. The substrates have been divided into four major groups by compound class: arylalkenes, aryl ketones, chalcones and cinnamyl compounds, and cyclic alkenes and ketones in ring expansion and ring contraction reactions.

#### *7.2.3.1.1 Arylalkenes*

Arylalkenes undergo oxidation with 1,2-rearrangement of the aryl group to give α-arylcarbonyl compounds, and this reaction is shown in the formal sense in equation (34). Useful reagents for this transformation include lead(IV),[50] thallium(III),[51] iodine(III),[52] and palladium.[53] The yields for this reaction are moderate to excellent, and there is a reasonable tolerance of functional groups on the aromatic ring ($R^1$) such as halogen, methyl or methoxy. At least one *ortho* substituent is permissible with no loss in yield. If $R^2$ = H, the product is an α-aryl aldehyde, and if $R^2$ = alkyl an α-aryl ketone is obtained. The rearrangement of 2-propenylbenzenes to the 1-arylpropan-2-ones is important due to the interest in the latter compounds as pharmaceutical intermediates, as in equation (35).[50b]

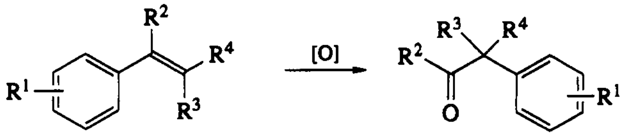

(34)

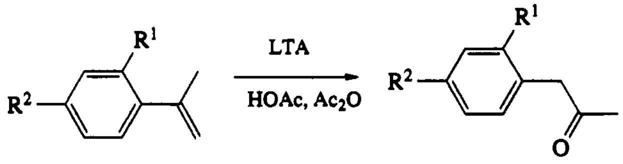

(35)

$R^1$ = OMe; $R^2$ = Me; 52%

$R^1$ = H; $R^2$ = OMe; 80%

The interesting sequence depicted in Scheme 13 for a sequential oxidative rearrangement and hydroxylation of citral shows some potential for this reaction in nonaromatic alkenes. This transformation affords an elegant, single-step approach to the 6,8-dioxabicyclo[3.2.1]octane skeleton, although the stereoselectivity for the two induced centers is poor.[54]

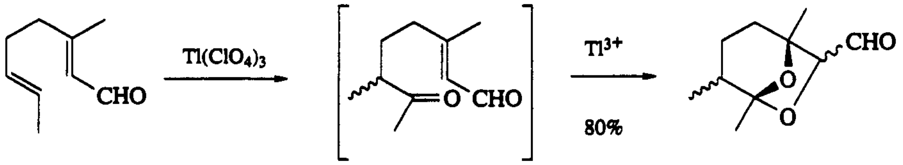

Scheme 13

#### 7.2.3.1.2 Aryl ketones

Aryl ketones undergo oxidative rearrangement with hypervalent main group oxidants such as thallium(III), lead(IV) and iodine(III) to give α-arylalkanoic acids in good to excellent yield,[55] and the general transformation is shown in equation (36).[6a,56] This reaction is related to the Willgerodt–Kindler reaction,[57] and has drawn considerable attention due to the antiinflammatory properties of the product α-arylalkanoic acids. A Friedel–Crafts acylation of an aromatic precursor followed by this oxidative rearrangement forms the synthetic sequence of choice for these compounds. At least a dozen patents have been issued on applications of this method, including one which describes a process catalytic in thallium.

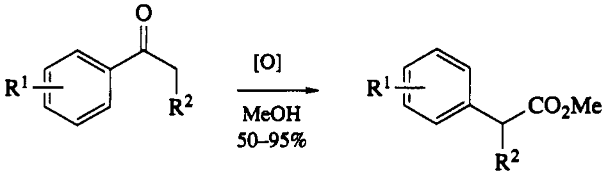

(36)

The best results are obtained with the above-named oxidants in a mixed solvent of methanol and trimethyl orthoformate in the presence of a strong acid; these conditions presumably ensure rapid acetalization of the carbonyl to prevent α-oxidation. This side reaction is more serious when $R^2$ is alkyl and the orthoformate is omitted, or if ethyl carbonate or acetonitrile is used as solvent. Preformed enol ethers and enamines give the desired oxidative rearrangement in high yield.

A wide variety of substituents are tolerated. The group $R^1$ can be alkyl, halogen, alkoxy, *N*-amido, azidomethyl, ester, aryl, aryloxy and aryloyl, and at least one *ortho* substituent is permissible with no loss in yield. The aromatic ring can also be 2-naphthyl, 9,10-dihydro-2-phenanthryl, 3-pyridyl, thiophen-2-yl or pyrrol-3-yl. The group $R^2$ can be hydrogen, alkyl, acyl or acetic acid. Beyond the antiinflammatory targets, successful reaction substrates include the methyl ketones of a binaphthyl crown ether, a morphinane and a polyaromatic hydrocarbon. The preparation of ibuprofen methyl ester (**38**) is shown in equation (37) as a typical example.[56c]

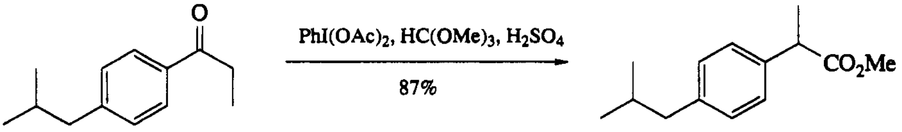

(37)

**(38)**

Dialkyl ketones have been little studied as precursors in this reaction. Selenium dioxide with hydrogen peroxide and *t*-butyl alcohol effects a similar reaction with these substrates to give 35–40% yield of the corresponding carboxylic acid. In methyl alkyl ketones, the regioselectivity is of the order of 5:1 in favor of methyl migration.[58]

#### 7.2.3.1.3 Chalcones and cinnamyl compounds

While following the reactivity patterns of arylalkenes, the extensive use in synthesis that has been made of the chalcone to isoflavone conversion and related sequences warrants a separate treatment. Chalcones (**39**) oxidize with thallium(III)[6a,59] and iodine(III)[52a] under rearrangement of the aromatic B-ring to give 3,3-dimethoxy-1,2-diarylpropan-1-ones (**40**) in yields from 30–90%, as shown in Scheme 14. This intermediate can be hydrolyzed in aqueous acid, and will cyclize to give an isoflavone (**41**) if a hydroxy group is present at C-2′ in the A-ring, or to give a benzoyl benzofuran (**42**) if a hydroxy group is present at C-2 in the B-ring. If the oxidation is carried out in acidic aqueous glyme, deformylation of this intermediate takes place *in situ* to furnish a substituted benzyl phenyl ketone (**43**), which undergoes further oxidation to the benzil (**44**). The isolated dimethyl acetal can be hydrolyzed, deformylated and cyclized to the corresponding phenylbenzofuran (**45**).[60] A preformed chalcone acetal (**46**) undergoes oxidation with migration of the A-ring phenyl to give 3-methoxy-1,2-diarylpropionates (**47**).

By far the most used pathway is that leading to the isoflavones, and literally scores of natural products have been prepared in this way. The yields for these cyclizations vary from 10–90%. Good solubility in methanol is the key to a successful reaction. The oxidation may be carried out with an unprotected C-2′ hydroxy with TTN/methanol, as long as the C-5′ position is unsubstituted; substrates of the latter type

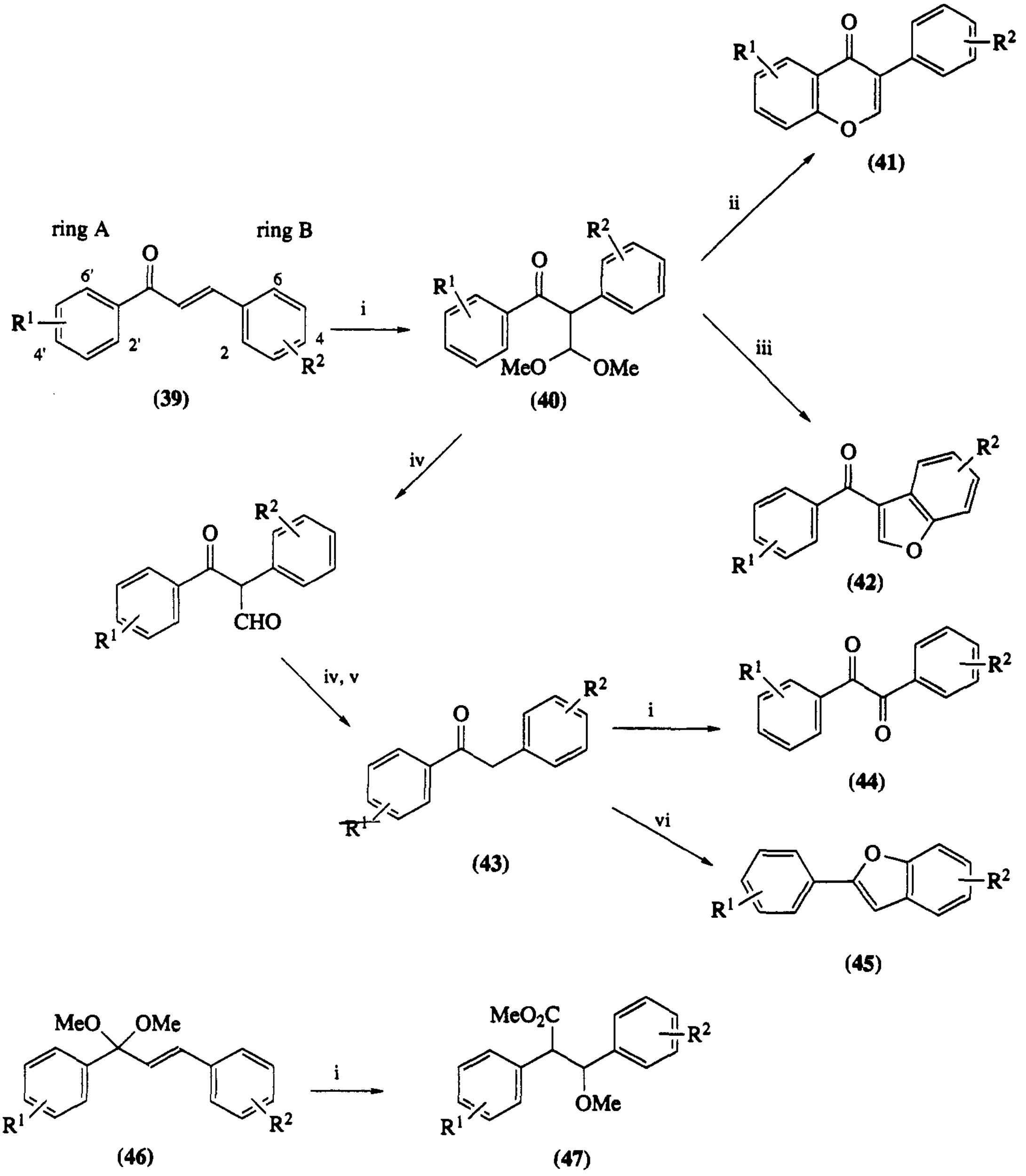

i, TTN, MeOH; ii, HCl (2'-hydroxy); iii, HCl (2-hydroxy); iv, HCl, $H_2O$; v, heat; vi, heat (2-hydroxy);
$R^1$ and $R^2$ can be alkyl, alkoxy, single or multiple

**Scheme 14**

will oxidize to quinone-type products. Aside from this exception, the tolerance for substitution in both rings is rather broad. $R^1$ and $R^2$ can be alkyl, alkoxy, halogen, acetoxy, methylenedioxy and pentaacetyl-β-glycosyl. Attempted oxidative rearrangement of a unprotected C-3′-β-glucosyl chalcone in a synthesis of 7,4′-di-*O*-methylpuerarin gave a low yield, but this was attributed to low solubility and separation problems; the protected glucosyl derivative gave a 90% yield of the target.[61] A dihydropyran ring may be fused to either of the aromatic rings, but some degradation does occur with a similarly fused pyran ring. A free hydroxy group in the B-ring has been used, as in the example found in equation (38), but yields are somewhat better if it is protected as the acetate or the methoxymethyl ether. Ring B can tolerate at least one *ortho* substituent, but ring A can be fully substituted with little loss in yield.

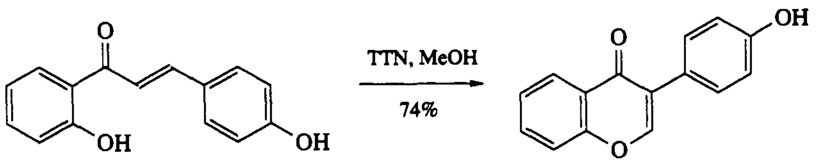

(38)

The ready availability of chalcones, from aldol condensation of acetophenones and benzaldehydes, makes this oxidative rearrangement a useful synthetic entry to isoflavone targets. The isoflavone products may be further elaborated to isoflavanones, isoflavans, pterocarpans and coumestones, broadening the scope of this method.

Cinnamyl compounds rearrange in a similar fashion under the influence of thallium(III), as shown in equation (39); this reaction was used in a synthetic approach to the polystachins.[62] Cinnamaldehydes and cinnamate esters react likewise to give the corresponding α-aryl-substituted malondialdehyde bisacetals and β,β-dimethoxypropionates, respectively.

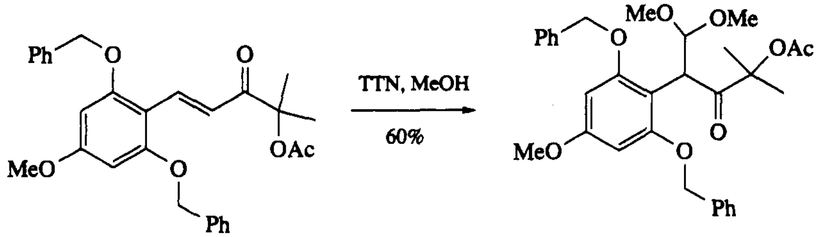

(39)

### 7.2.3.1.4 Cyclic alkenes and cyclic ketones: ring expansion and ring contraction

The oxidative rearrangement of cyclic alkenes and ketones often leads to ring expansion[63] or ring contraction reactions. The reagents generally used for this purpose are hypervalent main group oxidants such as thallium(III), lead(IV), iodine(III) and selenium(IV), although palladium(II) has been used as well.

Methylenecycloalkanes undergo ring expansion to the next higher homologous cycloalkanone, as shown in equation (40). The yields are good to excellent for four- and five-membered rings, and for six-membered rings if fused to an aromatic ring. The example given in equation (41) comes from a synthetic route to dopamine receptor stimulating compounds.[64] Simple methylenecyclohexanes give hydroxylation products, and the reaction does not appear to have been tried in larger rings. Thallium(III),[6a] lead(IV)[65] and palladium(II)[66] reagents have been used for this transformation, which is related to the pinacol rearrangement and the Demjanov rearrangement (Volume 3, Chapters 3.2 and 3.3 respectively).

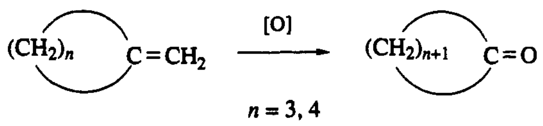

(40)

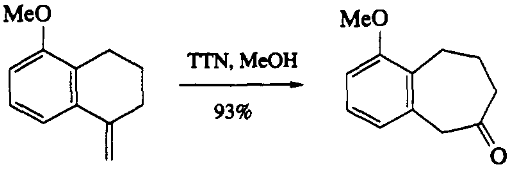

(41)

Cycloalkenes give ring contraction products, as shown in equation (42). This reaction is related to the Favorskii rearrangement and the Wolff rearrangement of ketones (Volume 3, Chapters 3.7 and 3.9, respectively). Moderate to good yields are obtained from four- to seven-membered ring cycloalkene substrates, although cyclopentenes give lower yields in favor of hydroxylation. Dihydropyrans yield the corresponding tetrahydrofuranyl aldehydes. This type of reaction was used in the stereospecific preparation of a key prostaglandin intermediate, as shown in equation (43).[67] Thallium(III)[6a] and lead(IV)/$BF_3 \cdot Et_2O$[68] are the reagents of choice for this transformation.

Cycloalkanones of ring size from four to six oxidize with ring contraction to give the cycloalkanecarboxylic acid of the next smaller ring size with thallium(III), as shown in equation (44). This reaction

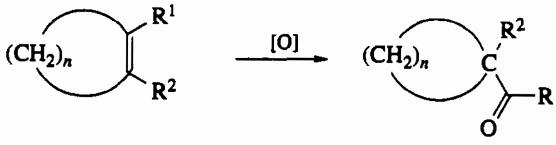

(42)

R$^1$ = H, alkyl, amino; R$^2$ = H, alkyl; $n$ = 2–5

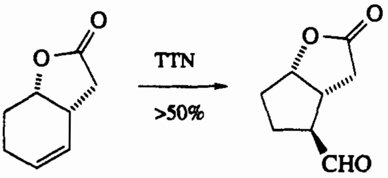

(43)

goes through the enol form, and requires acid, since in base cycloalkanones undergo α-hydroxylation. Cyclohexenones are converted in moderate to good yield to the cyclopentene-3-carboxylic esters by TTN/methanol.[69] Good yields of ring contraction products are obtained from 3-keto steroids, as shown in equation (45),[6a] but ketones at other positions are much less selective in this reaction. Selenium dioxide has been used in this reaction with five-, six-, seven- and twelve-membered ring ketones.[70] This reagent does not tolerate α-branching in the substrate, which leads to Baeyer–Villiger-type reaction.

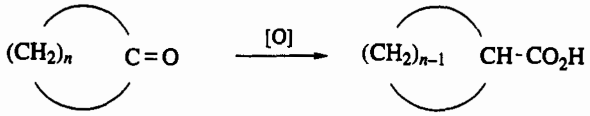

(44)

$n$ = 3–5

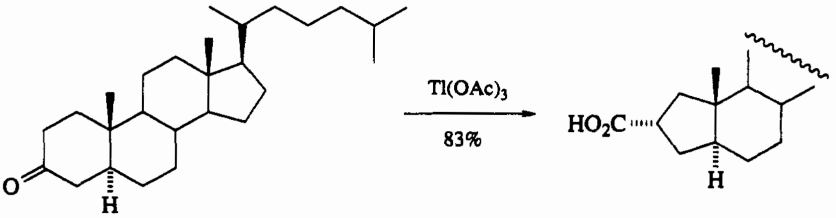

(45)

With some polycyclic substrates, a tandem ring expansion and ring contraction can take place under conditions of oxidative rearrangement. The 11-oxolanostanyl acetate (**48**; equation 46) undergoes such a reaction, in which ring C is contracted and ring D is expanded and aromatized.[71] The yield is poor though, and such a transformation would seem to have limited synthetic potential.

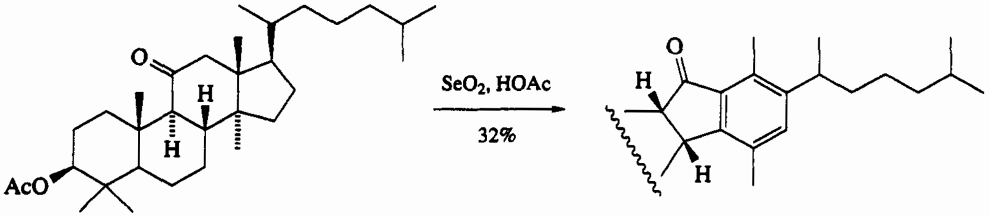

(46)

(**48**)

### 7.2.3.2 Dienes

Oxidative rearrangements of dienes are related to the dienone/phenol rearrangement, which is discussed in Volume 3, Chapter 3.5. The examples discussed here are limited to cyclohexadienes, and the driving force for the rearrangement is aromatization.

A novel route to the ring B aromatic anthrasteroids (**49**) from 5,7-dienes (**50**) proceeds in two steps and uses 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) as the oxidant, as is shown in equation (47).[72] Addition of PTAD to the steroidal 5,7-diene gives an adduct which, when treated with boron trifluoride etherate, rearranges to the anthrasteroid in generally greater than 90% yield. This reaction presumably proceeds through a spirocyclohexa-1,4-diene.

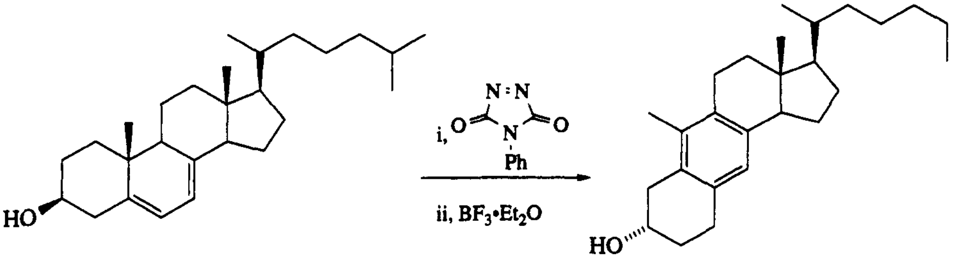

(47)

**(50)** **(49)**

Scheme 15 depicts a high yield, general method for specific *ortho* alkylation of polycyclic aromatic hydrocarbons.[73] In this example, biphenyl is subjected to reductive methylation followed by oxidative rearrangement with trityl tetrafluoroborate to give 2-methylbiphenyl. In unsymmetrical substrates the regioselectivity is poor; phenanthrene gives a 3:2 mixture of 4-methyl- and 1-methyl-phenanthrene.

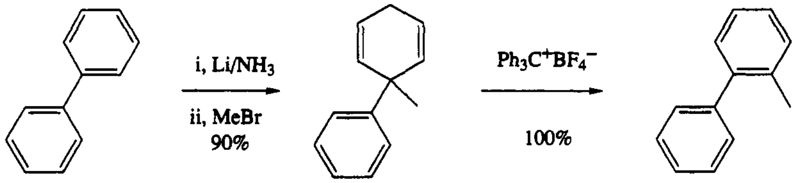

**Scheme 15**

### 7.2.3.3 Alkynes

Disubstituted alkynes will undergo oxidation with a concomitant 1,2-alkyl shift under the right conditions, to yield α-branched carboxylic acid derivatives. A variety of oxidants will effect this transformation, including nitrous oxide,[74] peracetic acid,[75] thallium trinitrate (TTN)[6a] and [hydroxy (tosyloxy)iodo]benzene (HTIB).[76] Yields are moderate to good, as shown in equation (48) for the use of HTIB, where $R^1$ is alkyl and $R^2$ may be alkyl or aromatic. The TTN procedure is limited to arylalkylalkynes, as diarylalkynes will oxidize to α-diones and dialkylalkynes yield α-methoxy ketones. The TTN and HTIB reactions proceed through a solvometallation intermediate. The peroxy acid and $N_2O$ reactions are believed to proceed through cycloaddition and rearrangement to a ketene; diphenylacetylene is converted to methyl diphenylacetate by $N_2O$ in methanol.

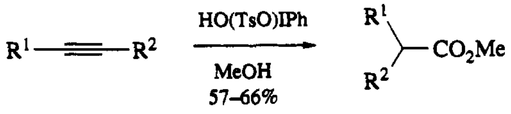

(48)

### 7.2.3.4 Cyclopropanes and Cyclobutanes

As was discussed in Section 7.2.2.3, cyclopropanes[3] and cyclobutanes[4] form a special group, with behavior distinct in many ways from that of other cycloalkanes. Several examples of oxidative skeletal rearrangements of these strained ring compounds are presented here.

Methylenecyclopropanes undergo oxidative ring expansion in a two-step sequence; peroxy acid oxidation to an oxaspiropentane followed by lithium iodide induced rearrangement yields a cyclobutanone in moderate yield, as illustrated in equation (49).[77] Cyclobutanone is a minor product from the reaction of methylenecyclopropane with thallium trinitrate, in contrast to the analogous reaction of the larger methylenecycloalkanes.

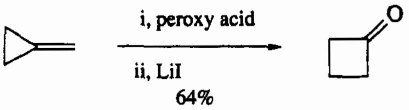

(49)

Spiro-fused cyclopropyl carbinols undergo solvolysis with hydrogen peroxide to give the corresponding hydroperoxides (**51**), which rearrange to the two carbon ring-expanded bicyclic hydroperoxy hemiacetals (**52**) in good yield, as in equation (50).[78] Yields range from 72–91% for a variety of ring size substrates, and the rearrangement is stereospecific in that the stereochemistry of the initial alcohol is reflected in the stereochemistry of the bridgehead carbon in those rings large enough to accommodate this feature.

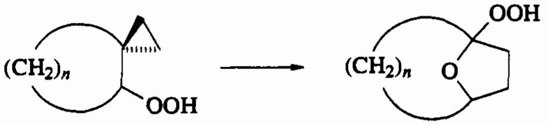

(50)

(**51**) (**52**)

Ring D norsteroidal carboxylic acid chlorides do not follow the normal carboxy inversion reaction on treatment with MCPBA, as shown in Scheme 16.[79] The β-acid chloride (**53**) undergoes rearrangement to the allylic cyclopropane (**54**) in good yield, while the α-acid chloride (**55**) gives mostly the intended alcohol (**57**) and a lesser amount of the product of elimination with methyl migration (**56**). Conformational analysis of these substrates suggests that the stereochemistry of the acid chloride group guides the course of rearrangement, since the bond to the migrating group must be suitably disposed to participate in the decarboxylation.

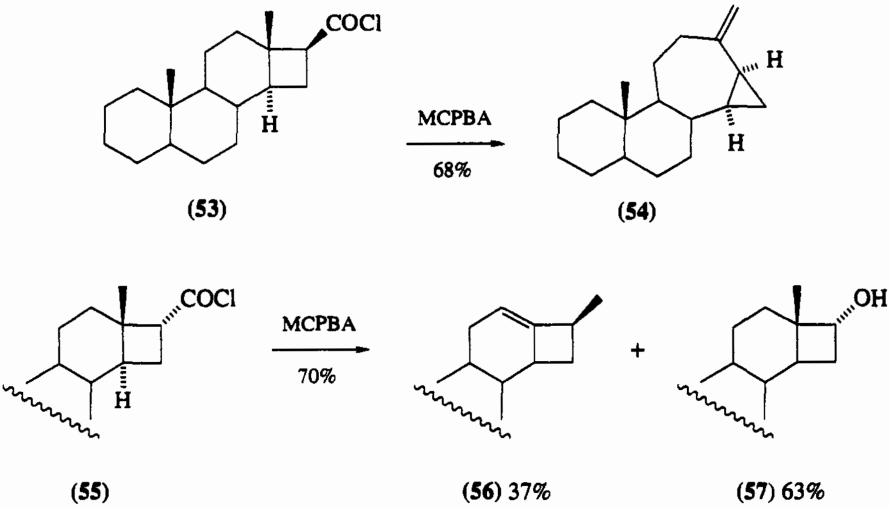

(**53**) (**54**)

(**55**) (**56**) 37% (**57**) 63%

**Scheme 16**

Bicyclo[2.2.0]hexan-2-ols oxidize with rearrangement to the isomeric bicyclo[2.1.1]hexan-2-ones. This takes place under Oppenauer oxidation conditions,[80] as well as with chromic acid,[81] and is illustrated for photolevopimarate and chromic acid in equation (51). The yield for this transformation is excellent, although the scope and synthetic potential are probably quite limited. The reaction is highly dependent on the nature of the oxidant, as the chromate/pyridine reagent gave only 15% of the product after several days, and most of the starting alcohol was recovered.

The oxidation of the cyclobutylcarbinol in equation (52) with buffered PCC proceeds with partial rearrangement; a 1:2 ratio of the expected aldehyde (**58**) to the ring-expanded cyclic enol ether (**59**) is ob-

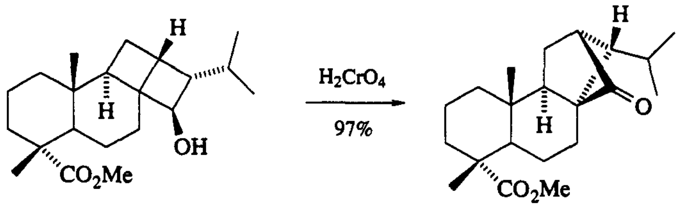

(51)

tained.[82] This latter product is suggested to arise through a 1,3-rearrangement of the first-formed aldehyde, driven by relief of strain; the rearrangement of (**58**) to (**59**) goes to completion on standing.

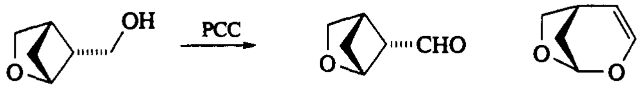

(**58**) 33% (**59**) 67%

(52)

### 7.2.3.5 Miscellaneous Skeletal Rearrangements

Into this group fall the named oxidation rearrangement reactions which proceed with carbon–carbon bond cleavage and 1,2-transfer of an alkyl group to a heteroatom, such as the Baeyer–Villiger reaction (discussed in Chapter 5.1, this volume) and the Beckmann reaction (found in Chapter 5.2, this volume) of ketones, as well as the Hofmann reaction/Schmidt reaction/Curtius rearrangement of carboxylic acid derivatives. The two examples discussed here involve related reactions of alcohols.

The oxidative cleavage of the alcohol (**60**; equation 53) by mercury(II) oxide and iodine leads to the iodoacetal (**61**) in good yield.[83] If cholesterol (**11**) is treated with lead tetraacetate and iodine under irradiation, the lactol acetate (**62**) is obtained in moderate yield, as seen in equation (54).[84] These reactions are both believed to go through the hypoiodite, which cleaves heterolytically to an oxygen radical. This intermediate fragments to an aldehyde and an allylic radical, and it is at this point that the mechanisms seem to diverge. In the mercury(II) cyclization the aldehyde adds IO·, and the resulting oxygen radical adds to the terminus of the allyl radical. The second oxygen of the acetal adds to the remaining alkene, and the penultimate intermediate carbon radical is trapped by iodine to give the observed product. In the lead(IV) cyclization the intermediate allyl radical is believed to add to the oxygen of the aldehyde to give an oxepanyl radical, which oxidizes to the lactol acetate. The scope of these reactions seems limited, since other similar substrates give poor selectivity and low yields in these reactions.

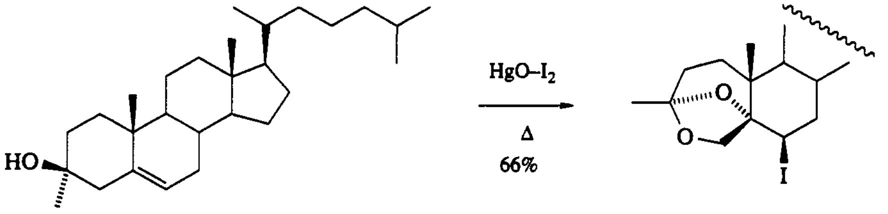

(**60**) (**61**)

(53)

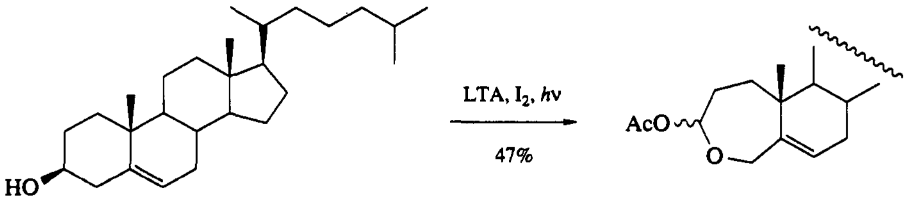

(**11**) (**62**)

(54)

Sodium periodate is known to oxidize 2-alkylphenols to the corresponding 2-hydroxycyclohexadienones. Phenolic benzhydrol-type compounds (**63**) follow a rearrangement pathway under these conditions, and the results are shown in Scheme 17.[85] The benzylic hydroxy group participates in the periodate oxidation to give an intermediate spiroepoxycyclohexadienone (**64**), which suffers intramolecular attack with carbon–carbon bond cleavage by the ketone carbonyl to yield the benzaldehyde acetal (**65**). Yields for this reaction are in the range of 40–60%.

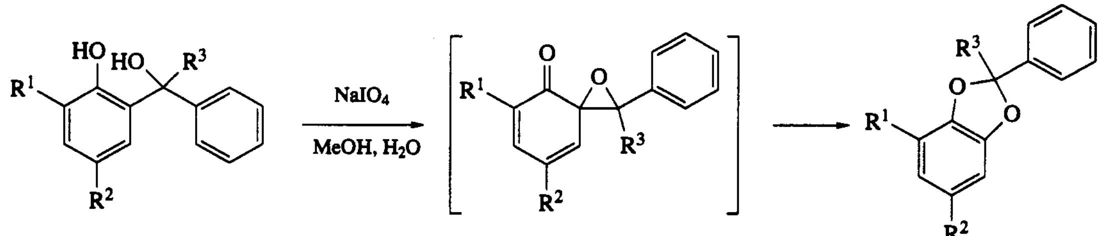

**(63)** **(64)** **(65)**

Scheme 17

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# 7.3
# Solid-supported Oxidants

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## 7.3.1 INTRODUCTION

The benefits of using supported reagents[1] for organic synthesis are considerable, especially as they offer remarkable ease of handling and use; often one can simply weigh the amount of reagent to be used. At the end of the reaction a filtration suffices to remove the contaminating by-products. Solvent evaporation from the filtrate is often sufficient to provide the product in pure form. Likewise, reagent recovery or regeneration can also be very easy. Another advantage is the reduction in product contamination assured by having the reagent fully bound to a solid support. This is very important for oxidation reactions so that overoxidation reactions can be minimized. Solid-supported oxidants are relatively safe to handle owing to full chemisorption of the toxic chemicals. Two examples of toxic oxidants whose contamination is considerably reduced by adsorption to solid supports are thallium(III) salts and chromium salts[2] in all the various oxidation states. Such supported reagents also reduce environmental problems upon work-up. Many inorganic species are powerful oxidants of organic matter and can cause explosions. However they can be tamed by prior adsorption onto the solid supports. These oxidants also enjoy good thermal and mechanical stabilities, allowing higher stirring rates if necessary. High reagent activity and, more importantly, high reagent selectivity are frequent features of supported reagents. The high activity stems from physical factors, such as vastly enhanced collision rates between reactants, due to either the reduced dimensionality on the solid reaction sites or the boost in their local concentration due to trapping in the interstitical spaces of microporous solids.[3] Chemisorption generally activates adsorbates, with respect to bond breaking. The high selectivity is easily understood in terms of shape selectivity (reactant, transition state or product) when, for example, zeolites are involved.

Other more specific advantages of supported reagents exist for oxidants such as chromium(III) anhydride complexes where there are many problems associated with solubility, the ligand and stoichiometry.[4] For example in procedures using pyridine or polar aprotic solvents, the ligand doubles up as solvent, causing complication in work-up with soluble metal species. However, these are avoided by the supported oxidants.

By measurement of aqueous redox potentials an overall impression of the metallic species most often used in the empirical Edinsonian or the rational design of solid-supported oxidants can be obtained (Table 1).

**Table 1** Electroreduction Potentials (V)

| *Metallic species* | *Electroreductive potentials (V)* |
|---|---|
| $MnO_2 + 4 H^+ + 2 e^- = Mn^{2+}$ | 1.23 |
| $IO_3^- + 6 H^+ + 5 e^- = I_2$ | 1.195 |
| $OsO_4 + 8 H^+ + 8 e^- = Os$ | 0.85 |
| $Ag^+ + e^- = Ag$ | 0.799 |
| $Fe^{3+} + e^- = Fe^{2+}$ | 0.771 |
| $Cu^+ + e^- = Cu$ | 0.521 |
| $Cu^{2+} + e^- = Cu$ | 0.337 |
| $CrO_4^{2-} + 3 e^- = Cr(OH)_3 + 5 OH^-$ | 0.13 |
| $MnO_4^- + 4H^+ + 3 e^- = MnO_2$ | 1.695 |
| $Ce^{4+} + e^- = Ce^{3+}$ | 1.61 |
| $MnO_4^- + 8 H^+ + 5 e^- = Mn^{2+}$ | 1.51 |
| $Mn^{3+} = e^- = Mn^{2+}$ | 1.51 |
| $Cr_2O_7^{2-} + 14 H^+ + 6 e^- = 2Cr^{3+}$ | 1.33 |
| $Tl^{3+} + 2 e^- = Tl^+$ | 1.25 |

Typically the supports most widely used are alumina, silica and aluminosilicates (clays and zeolites). These inorganic solids all contain surface hydroxy groups and it can be valuable to examine activation of these surfaces by dehydration.

Amorphous $SiO_2$ contains tetrahedral silicate units whereby each oxygen atom bridges two silicon atoms, together with silanol (Si—OH) groups covering the surface. The vicinal silanol groups may be characterized by lower frequency IR absorptions as compared to isolated silanol groups, owing to their hydrogen-bonding patterns (3550 *versus* 3750 $cm^{-1}$). Upon dehydration, such vicinal silanol groups give surface Si—O—Si linkages.

Alumina, on the other hand, exists in various forms, of which $\alpha$-$Al_2O_3$ is the stable and crystalline form. So-called transition aluminas, $\eta$- and $\gamma$-$Al_2O_3$, are defective, metastable solids arising from the heating of aluminum hydroxide gels. Both have spinel structures, with a disordered aluminum lattice interlocked with a cubic close-packed oxygen sublattice. Surface layers are occupied by Al—OH alanol groups. Both the IR[5] spectra and modeling of the alumina surfaces[6] suggest five types of environments for these surface hydroxy groups. Dehydrative activation is performed by heating above 200 °C. The attendant dehydroxylation creates coordinatively unsaturated oxide $O^{2-}$ ions and an adjacent surface anion vacancy. This void in the upper layer exposes, if one considers the case of a close-packed (III) surface plane, either two five-coordinate $Al^{3+}$ ions or one three-coordinate $Al^{3+}$ ion.[7] In a similar manner, silicate and aluminosilicate minerals, such as clays, pillared clays and zeolites, bear surface hydroxy groups whose dehydrative thermal activation creates Lewis and Brønsted acidic and basic sites on the surface. Recent attention has focused[8] on these resulting $O^-$ centers. Such $O^-$ groups with an unpaired electron can dimerize to form peroxo links (Si—O—O—Si), which are relevant to oxidation by these surfaces. Dissociation of peroxy linkages will regenerate two $O^-$ states. Physically, such $O^-$ states are defect electrons or positive holes. They are paramagnetic and they are delocalized over the surface oxygens. For instance, the mineral obsidian suddenly develops positive charge carriers when heated above 450 °C. These $O^-$ states, resulting from dehydrative thermal activation, are also responsible for the yellowing of magnesia, MgO, upon heating. These $O^-$ states are powerful oxidation centers and, accordingly, such minerals serve as supports for solid oxidants.

Historically, the first supported oxidizing reagent, reported by Fétizon and Golfier, was silver carbonate on celite (another diatomaceous earth).[9] This was obtained by precipitation of the reagent onto its support. $Ag_2CO_3$ on celite smoothly oxidizes primary and secondary alcohols, α,ω-diols, hydroquinones and amines. The main practical asset of the reagent is that it avoids the need to filter off finely divided silver salts after reaction.

## 7.3.2 ALUMINA-SUPPORTED OXIDANTS

### 7.3.2.1 Chloral

Chloral, when adsorbed on activated Woelm-200 neutral alumina, is a mild, chemoselective oxidant of secondary alcohols over primary alcohols.[10–12] It oxidizes vinyl alcohols to vinyl ketones without the usual polymerization or oxidation of the ethylenic double bond. Also of importance is that it effects high yield conversion of cyclobutanol into cyclobutanone, without ring cleavage. β-Hydroxy sulfides and selenides are oxidized to the corresponding β-keto sulfides and selenides. Typically, the reaction is run in carbon tetrachloride at room temperature or at reflux with yields being normally in the range of 60–75%. The one drawback of the reagent is the necessity for the vacuum drying at 400 °C of commercial alumina immediately before use. However, the advantage is its selectivity in that other functional groups, such as primary iodides, benzylic chlorides, methyl esters, ethers, lactones and nitro groups,[10] all remain intact.

### 7.3.2.2 Pyridinium Chlorochromate

Another supported chemoselective alcohol oxidant in common use is pyridinium chlorochromate on alumina[13] which transforms alcohols to carbonyls even in the presence of THP acetals (equation 1).[14] That such acid-sensitive groups resist the reaction conditions derives from the neutralization by the alumina support of the acidity of the PCC. Examples of alcohols which have been oxidized in good yields using this reagent include carveol, 2-ethylhexanol, menthol, tetrahydrogeraniol, citronellol, 2-methylcyclohexanol, cinnamyl alcohol, isopulegol and cholesterol. In typical experiments methylene chloride is used as solvent at room temperature.

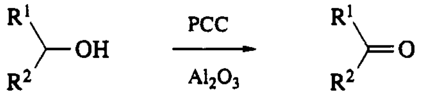

(1)

### 7.3.2.3 Periodic Acid

Periodic acid is a versatile oxidant since, depending on pH, the redox potential for the periodate–iodate couple varies from 0.7 V in aqueous basic media to 1.6 V in aqueous acidic media.[15] Based on this observation, Villemin and Ricard devised an oxidative cleavage of glycols,[16] in which *meso*-1,2-diphenyl-1,2-ethanediol was oxidized by periodic acid on alumina to benzaldehyde in 82% yield in aqueous ethanol (90% ethanol) at room temperature in 26 h. The same supported oxidant converted aromatics into quinones. In the presence of transition metal complexes ($Mn^{II}$), α-arylalkenes suffer oxidative cleavage to aldehydes. For example, *trans*-stilbene gives benzaldehyde at room temperature.

### 7.3.2.4 Potassium Dichromate and Epoxidizing Agents

Potassium dichromate is another inorganic oxidant that can be supported on alumina and used to convert alcohols into carbonyl compounds.[17] Its chief merit is its selectivity for allylic and benzylic alcohols.[18,19] For instance, 1-phenylpropane-1,3-diol is oxidized selectively to the benzylic oxidation product.

Alumina also serves as the support for reagents effecting the epoxidation of alkenes efficiently under mild conditions. This is the case with triphenylsilyl hydroperoxide; even aryl-substituted alkenes are easily oxidized.[20] The reactions are run in methylene chloride at room temperature and are stereospecific. In a similar manner, alkenes *gem*-disubstituted by two electron-withdrawing groups, dispersed on alumina, are conveniently epoxidized by sodium hypochlorite.[21] Often the reaction, run in acetonitrile at room temperature, is stereospecific and yields are excellent (80–98%). Hydration of the alkene, which is one of the drawbacks of aqueous hypochlorite as an epoxidizing agent is thus avoided.

### 7.3.2.5 Sodium Metaperiodate

Sodium metaperiodate, $NaIO_4$, is a two-electron chemoselective oxidant and when absorbed on alumina oxidizes alcohols[16] to carbonyl compounds and sulfides to sulfoxides without overoxidation to sulfones.[22] Alkenic double bonds in the substrate remain intact during this oxidation. Typically reactions are performed in 95% ethanol at room temperature for a few hours and with good (85–90%) yields.

## 7.3.3 SILICA-SUPPORTED OXIDANTS

### 7.3.3.1 Ozone

Mazur's oxidation method consists of ozone combined with adsorption of the organic substrate on silica gel to effect the clean oxidation of tertiary carbon–hydrogen bonds, in the absence of any solvent (dry medium).[23] Adamantane, for instance, gives a better than 80% yield of 1-adamantanol (equation 2).[24,25] This hydroxylation method has been applied successfully to a number of natural products,[26–28] but does not always work as well with aliphatic substrates[24,29–31] or for the oxidation of secondary carbon–hydrogen bonds.[32] Nevertheless, it converts quantitatively 2-adamantanol to 2-adamantanone (equation 3).[24] This ozonization resembles some biological oxidation processes in its ability to oxidize methylene groups at a distance from other functional groups and is exemplified by transformations of acetates into keto acetates.[32] Dry ozonization is a choice method for oxidizing methylene groups adjacent to cyclopropane rings to carbonyl compounds.[33,34]

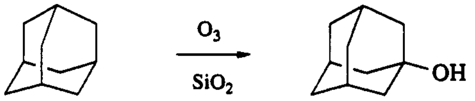

(2)

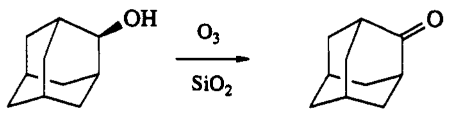

(3)

Dry ozonization of alkenes and alkynes has also been explored. Sometimes these results resemble those of the homogeneous ozonization in an aprotic solvent.[35]

Dry ozonization is also an efficient procedure for oxidation of aliphatic primary amines into nitro groups, with yields of about 70%. Arylamines are also oxidized to nitro aromatics, albeit with low yields.[36,37] Ozone on silica gel has also been shown to oxidize arenes in some cases.[38]

### 7.3.3.2 Sodium Methoxide

Sodium methoxide on silica gel (2 mol equiv. Na per g reagent), is an excellent reagent for effecting the Nef reaction by converting nitro compounds to aldehydes and ketones.[37] The reactions are run either at room temperature or at 80 °C, for a short reaction time. The success of these reactions depends on the neutralization of the normally weakly acidic silica gel by treatment with methoxide in methanol, followed by evaporation to dryness and activation by heating to 400 °C. The nitro substrate is then impregnated onto this methoxide-doped silica gel to effect reaction.

### 7.3.3.3 Iron(III) Chloride

Two slightly different reagents may be made by adsorption of iron(III) chloride onto silica gel under dehydrating conditions. If anhydrous iron(III) chloride is used, this provides a pale yellow-green powder. This reagent,[39,40] sometimes referred to as the Salaün reagent, dehydrates tertiary alcohols and deprotects THP ethers. Also in dry media Salaün reagent promotes the Wagner–Meerwein ring expansion of tertiary cyclobutanols into cyclopentenes. By similar carbocationic mechanisms, the Salaün reagent will induce the cyclization of alkenic alcohols.[39,40] If iron(III) chloride hexahydrate is used as the starting material, a dry yellow-brown powder results from its deposition onto silica gel under high vacuum (0.1 Torr; 1 Torr ≈ 33 Pa) for 3 h at 60 °C.[41] This reagent performs the dehydration of allylic and tertiary alcohols. In special cases it will dehydrate secondary alcohols in sterically hindered positions. In the steroid series, use of this reagent induces the cholestane–diacholestene and backbone rearrangements under relatively mild conditions.[42] This $FeCl_3$–$SiO_2$ reagent achieves the oxidative coupling of phenol ethers or the cleavage of the ether function into phenols.[43,44] The latter process is much faster if the solvent is removed.[44] Oxidative desilylation reactions and cleavage of benzyl esters are also possible, all with commendable ease of work-up.

### 7.3.3.4 Selenium Dioxide

Allylic methyl groups are oxidized to allylic alcohols by the combination of selenium dioxide adsorbed on $SiO_2$ together with *t*-butyl hydroperoxide (TBHP) in nonpolar solvents such as hexane or methylene chloride. This procedure has been applied to a number of medium-ring sesquiterpenes.[44]

### 7.3.3.5 Cerium(IV)

Catechols and hydroquinones can be converted (91–98%) into quinones by cerium(IV) salts coated onto silica as free-flowing yellow powder from impregnation with cerium(IV) ammonium nitrate. This reaction is usually performed in the presence of magnesium sulfate.[45] The same $(NH_4)_2Ce(NO_3)_6 \cdot SiO_2$ reagent in the dry state effects oxidative nitrations of arenes. For example α-naphthol is converted to the *ortho* (42%) and the *para* (38%) nitro compounds, while its methyl or ethyl ethers give exclusively the *para* nitration product (equation 4).[46] In solution, the products are contaminated with the products of dinitration and of oxidation into quinones.[47,48]

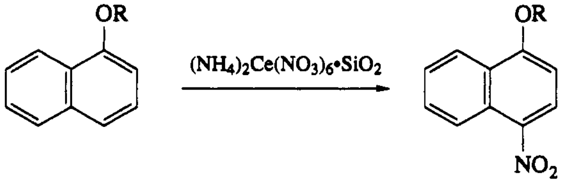

(4)

### 7.3.3.6 Periodates

The periodate oxidations (see the above Section 7.3.2)[15] can also occur with dimesoperiodate, $K_4I_2O_9$, supported on silica gel. Poorer loadings of reagent on this support are observed when compared with alumina-based reagents. Nevertheless periodates supported on silica gel, in solvents such as methylene chloride or benzene, at room temperature, are good oxidants of hydroquinones into quinones, or hydrazarenes into azoarenes, and of glycols into dialdehydes.[49] X-Ray and Raman spectroscopy show that the $NaIO_4$ reagent consists of a monomolecular layer of the salt bound to the surface through the silanol groups.

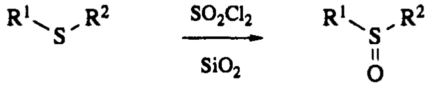

(5)

This $IO_4^-$–$SiO_2$ reagent is not very effective in the oxidation of sulfides into sulfoxides.[49] However, sulfuryl chloride adsorbed on wet silica gel is an excellent reagent for this transformation (equation 5).[50] High yields of methyl aryl, diaryl, allylic, benzylic and dialkyl sulfoxides are thus obtainable. The procedure commends itself by its simplicity and its extension to thioacetals provides a good, quantitative regeneration of the carbonyl groups by oxidative cleavage.[51] This supported sulfuryl chloride oxidation has been used as a method for partial $^{18}O$ enrichment of sulfoxides and of carbonyl compounds from $^{18}O$-enriched water.[52]

### 7.3.3.7 Permanganates

The seminal observation that a number of solid supports, such as aluminosilicates (clays and zeolites) and silica gel, activate potassium permanganate[53] led to the use of this reagent for synthesis. Oxidation of an alcohol in benzene normally does not proceed, due to the insolubility of the oxidant.[54] However, using $KMnO_4$ adsorbed onto silica gel at 70 °C, the quantitative conversion of benzyl alcohol to benzaldehyde is effected without overoxidation to benzoic acid.[54] The optimized reagent was also applied successfully to the Nef reaction, converting nitro groups into carbonyls.[55] Thus 1-nitro 4-ketones are turned into 1,4-diketones in boiling benzene, in variable yields (4–55%). The poor yields are probably due to the difficulty in product recovery arising from adsorption of the 1,4-diketones to the surface covered with the silanol hydrogen-bond donors.

Potassium permanganate impregnated on silica gel is the reagent of choice for the cleavage of ethylenic double bonds.[56] The reaction requires only mild conditions, such as room temperature, for 20–30 min. The process can be applied to terminal, secondary, tertiary and also electron withdrawing substituted double bonds and provides good to excellent yields of cleavage products.

Another very active permanganate is the zinc salt, which functions as an oxidant *via* a three-electron conversion of $Mn^{VII}$ to $Mn^{IV}$. The advantage of $Zn(MnO_4)_2$ is that it is a neutral oxidant. However, it strongly complexes organic substrates.[57] The oxidizing power is reported to be 13% that of TNT, *i.e.* about twice that of potassium permanganate. Use of a silica gel support permits the safe handling of this strong oxidant.[57] Halogenated solvents (methylene chloride, chloroform) are best for the oxidation reactions, which are best conducted at room temperature or at reflux. For instance, thioanisole is oxidized in 92% isolated yield into the corresponding methyl phenyl sulfone by 1.2 equiv. of $Zn(MnO_4)_2$ in methylene chloride at 20 °C for 2.5 h. Alkynes are oxidized to diketones, ethers lactones, cyclic ketones to diacids, cyclic ketals to ketones and acylated amines into acylimides.[57]

It has also been found that addition of a catalytic amount of calcium hydride and silica gel to the Sharpless reagent can greatly reduce the reaction time for asymmetric epoxidation of an allylic alcohol. The time saving is often a factor of 10 or 15, and always at least a factor of 3.[58]

### 7.3.3.8 Chromium(VI)

The general scheme for $Cr^{VI}$ oxidation of organic compounds[59] makes use of the $Cr^{V}$, $Cr^{IV}$ and $Cr^{III}$ oxidation states.

$$\begin{array}{llllll} H_2A + Cr^{VI} & \rightleftharpoons & A + Cr^{IV} & \text{slow} \\ Cr^{IV} + Cr^{VI} & \rightleftharpoons & 2\,Cr^{V} & \\ Cr^{V} + H_2A & \rightleftharpoons & Cr^{III} + A & \end{array}$$

Chromic acid, $H_2CrO_4$, is a well-known powerful oxidant, with an electroreduction potential determined by the process:

$$CrO_4^{2-} + 4\,H_2O + 3\,e^- \rightleftharpoons Cr(OH)_3\,(s) + 5\,OH^- \qquad E^\circ = -0.13\ V$$

Chromic acid deposited on silica gel from the anhydride $CrO_3$ in aqueous (or in aqueous acidified) solutions[60] affords a useful oxidant.

Other preparations of this reagent are known[61] but the reagent has only a limited shelf life of less than a week. Oxidations with the reagent are conducted in diethyl ether, using 3 g of reagent per mmol of alcohol substrate. Generally they are rapid at ambient temperature, giving good yields (60–98%) of ketone products.[60,61] It is interesting to note that impregnation of chromium(IV) anhydride on alumina provides only an inactive reagent.[62] Conversely, chromium(IV) anhydride can be adsorbed on resins, such as polyvinylpyridines, polyacrylates, *etc.* (typically 6 mmol $CrO_3$ per g resin).[4,63] These reagents oxidize primary and secondary alcohols and may be used in nonpolar solvents. The ratio Cr:alcohol is usually in the range 1–4. Yields are, however, very variable (10–80%).[4] The procedure is improved by the use of catalytic amounts of quaternary ammonium salts, such as $(NBu^n{}_4)^+$, and by recourse to trifluoroacetato chromate as the $Cr^{VI}$ impregnated species.[63]

The procedure is commendable for its simplicity, reduced toxicity (chromium in all its oxidation states is carcinogenic) and achieves good yields of ketones from alcohol, for example, octan-2-ol is oxidized into octan-2-one (92%), cyclohexanol into cyclohexanone (90%) and menthol into menthone (98%).[63] Pyridinium chromate is also a well-known oxidant for allylic oxidations.[64] As a silica gel supported reagent, this is turned into an efficient alcohol oxidant that will leave acid-labile functions unscathed.[61] Another advantage of the reagent is the long shelf-life of more than a year. These solid-supported oxidants also greatly facilitate product work-up, when compared with their solution counterparts.

Oxidation of alcohols typically proceeds in 4–12 h giving excellent yields of carbonyl products.[61]

Chromyl chloride, $CrO_2Cl_2$, like other $Cr^{VI}$ species, is a vigorous oxidant of organic compounds. It may be, however, tamed as a silica gel adsorbate.[65] This reagent combination is also a good oxidant of alcohols, alkenes and alkynes, that will tolerate halides, esters, lactones, ethers and nitriles. The shelf life of the reagent appears to be indefinite in the dry state.

Potassium dichromate, $K_2Cr_2O_7$, adsorbed on silica gel (or on alumina, magnesia or Florisil) is a selective oxidant of allylic and benzylic alcohols and halides in neutral media.[66]

Similarly, supported ammonium dichromate is an effective reagent for hydroquinone to quinone oxidation.[67]

## 7.3.4 CLAY-SUPPORTED OXIDANTS

Firstly it should be recognized that clays will oxidize organic matter. One of the most effective means for detoxification of 1,4-dioxin is oxidation into the radical cation and subsequent polymerization on $Cu^{II}$–smectites.[68] Transition metal centers in phyllosilicate clays, such as $Fe^{III}$, are known to oxidize aromatic molecules by such single-electron transfers.[69–76] Some radical-coupling products have also been obtained.[73,75] A study of the oxidation of hydrocortisone by the two fibrous clay minerals sepiolite and palygorskite (a commercial variety of attalpugite)[77] has been reported. The former clay has the lower $Fe^{III}$ content and accordingly has lower oxidizing power. The latter oxidizes the steroid due to surface-adsorbed iron oxides and to octahedral $Fe^{III}$, present in 2–3% amounts.

### 7.3.4.1 Permanganate

Clay-supported potassium permanganate oxidizes secondary alcohols into ketones.[78] A great asset is the ability of this reagent to selectively oxidize an allylic alcohol into the α,β-unsaturated ketone without any double bond oxidation. The procedure is extremely simple, involving grinding of the inorganic salt with a bentonite clay, prior to heating the alcohol and reagent in methylene chloride. Although reaction times are rather long (days), good yields are obtained (80–100%). Note that with a very large excess of oxidant and prolonged reaction times, alkenic bonds may be cleaved. The advantage of this method, as compared with the use of manganese dioxide,[79] is that prior activation of the reagent is not necessary.

### 7.3.4.2 Thallium Trinitrate

The oxidative potential of thallium(III) trinitrate was discovered by Taylor and McKillop.[80] The reagent was supported on the K10 acidic montmorillonite ($H_0 = -6$ to $-8$) by stirring the clay suspended in a methanol–trimethyl orthoformate solution of the thallium salt, followed by evaporation to dryness. In this way a colorless, free-flowing solid is obtained. Oxidations are very easily performed in inert solvents such as toluene, heptane, methylene chloride or carbon tetrachloride. A first application of this reagent was to the oxidative rearrangement of alkyl aryl ketones, leading to alkyl arylcarboxylates in *ca.* 90% yields.[80–82] Acetophenones are converted into methyl arylacetates. Likewise, propiophenone and butyrophenone are cleanly oxidized into methyl α-methyl- and α-ethyl phenylacetate, respectively. The thallium trinitrate–K10 system effects the rapid and effective oxidative rearrangement of alkenes into acetals. Cyclohexene is converted in less than a minute into the dimethylacetal of cyclopentanecarbaldehyde, and styrene and 1-phenyl-1-propene also give clean rearrangement into the corresponding aryl acetal propionaldehyde dimethylacetals, all in 85–92% yield. Likewise, cinnamaldehydes and cinnamic esters undergo such oxidative rearrangements in 85–90% yields. The Princeton–East Anglia coworkers also demonstrated the superiority of lamellar K10 montmorillonite support to microporous supports for thallium trinitrate.[80] Another good application of this system was the oxidative rearrangement of 3-acetylpyrroles into the corresponding methoxycarbonylpyrroles.[83]

### 7.3.4.3 Iron(III) and Copper(II) Nitrates

An asset of lamellar clays as supports for oxidants is their effective surface dimensionality. This leads to fast diffusional kinetics on the clay surfaces, which translate through the Smoluchowsky–Debye equation into high collision rates and, in turn, through the preexponential term, into high kinetic rates.[3,84]

Dehydrative activation of surface $O^-$ centers has already been mentioned (Section 7.3.1) and produces powerful oxidation centers. Doping by transition metal ions is best performed under strong dehydration conditions such that the metal atoms are associated with resulting new anionic sites.

Addison in the 1960s prepared covalent metallic nitrates under anhydrous conditions and gave vibrational spectroscopic criteria to ascertain if the nitrato group is coordinated as a unidentate, a bidentate or a bridging ligand. This group showed that metallic nitrates were powerful oxidants if: (i) there is covalent bonding of the nitrato group, as a bidentate ligand; and (ii) the metal can fall back on lower oxidation states.[85] The oxidizing power of such covalent metallic nitrates is such that copper(II) nitrate effects both these coupled transformations, at liquid nitrogen temperature (equations 6 and 7).[86]

$$\mathrm{Et_2O + Cu(NO_3)_2 \longrightarrow EtONO + MeCHO + Cu(NO_3)OH} \tag{6}$$

$$\mathrm{MeCHO + Cu(NO_3)_2 \rightarrow Cu(NO_3)OAc + HONO} \tag{7}$$

Although it is possible to obtain the acetone solvate of anhydrous iron(III) nitrate, this oil decomposes in a vigorous exothermic reaction. However, it is possible to stabilize the oil by impregnation on the K10 acidic montmorillonite. The name 'clayfen' has been given to the resulting reagent.[87–89]

This reagent was first applied to the oxidation of alcohols where use of this 'clayfen' system gave satisfactory yields (65–90%), avoided overoxidation of aromatic aldehydes and required only inexpensive reagents.[87] A great practical advantage of this and other 'clayfen' oxidations is the opportunity for visual monitoring of the reactions. The start of the reaction is signalled by the evolution of reddish nitrous fumes and their cessation indicates completion. 'Clayfen' smoothly oxidizes benzoins into benzils,[90] with better isolated yields (85–95%) than the ytterbium(III) nitrate catalyzed Kagan procedure.[91] The alcohol oxidation proceeds through intermediate nitrous esters.[88] Likewise, oxidative coupling of thiols into disulfides is effected by 'clayfen' *via* thionitrite intermediates.[92] 'Clayfen' also converts *N,N*-dimethylhydrazones into the parent carbonyl compounds in 67–91% isolated yield.[93]

Regeneration of the carbonyl group from various protecting groups may be achieved by 'clayfen', for example from imine-protecting groups, tosylhydrazones, phenylhydrazones, 2,4-dinitrophenylhydrazones and semicarbazones.[94] 'Clayfen', because it is an inexpensive and mild source of nitrosonium ions, $NO^+$,[89] can be used to convert hydrazines into azides which in turn are transformed into iminophosphoranes.[95]

'Claycop' is a related reagent to 'clayfen'. This reagent is based on anhydrous copper(II) nitrate and is somewhat less reactive but enjoys much greater stability than 'clayfen'.[86,96,97] Clay-supported copper(II) nitrate ('claycop') is prepared in a process similar to the preparation of 'clayfen', by adding K10 clay to a solution of copper(II) nitrate trihydrate in acetone. This reagent has been applied to the aromatization of dihydropyridines, with consistently better isolated yields (40–93%) than with 'clayfen'.[97] It is also the reagent of choice for quantitative regeneration of carbonyl groups from protective bisthioacetals.[98] 'Claycop' also regenerates carbonyls from selenoacetals[99] and from thiocarbonyls[100] with very good isolated yields, although 'clayfen' is superior to 'claycop' for this last application.

## 7.3.5 CONCLUSIONS

Owing to the limited format, this review has not discussed the use of enzyme-supported materials or catalytic oxidants with industrial applications, even though both these are of current interest. The illustrative examples of solid oxidants that have been discussed display considerable differences in reactivity and selectivity from solution chemistry using the same or similar reagents. The choice of which support to use is still very much a matter of trial and error, although progress is being made rapidly. The single most useful asset of supported oxidants is their ease of use, offering cleanliness, safety and simplicity. These reagents now have a secure future in organic synthesis.

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# 7.4
# Electron-transfer Oxidation

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## 7.4.1 SCOPE AND DEFINITIONS

Electron-transfer oxidation of the vast majority of organic compounds involves multiple steps with transient radicals as key reactive intermediates. Since stable organic compounds are mostly diamagnetic donors with even numbers of electrons, the electron transfer must perforce generate an odd-electron species. In the case of a neutral organic donor (generically represented hereafter as RH), electron-transfer oxidation produces a radical cation (equation 1a),[1–3] which is constrained to undergo a second electron transfer before it ultimately yields the diamagnetic product. It is the unique properties of organic radical cations that lead to the rich menu of organic transformations exploitable for organic synthesis.

$$\mathrm{RH} \xrightarrow{-e^-} \mathrm{RH}^{+\bullet} \tag{1a}$$

$$\mathrm{RH} \xrightarrow{+e^-} \mathrm{RH}^{-\bullet} \tag{1b}$$

Oxidation is the microscopic reverse of reduction, and electron transfer in equation (1a) has its counterpart in reduction, *i.e.* equation (1b). Accordingly, for every organic oxidation there is a conjugate process involving reduction, as simply illustrated by the electron-transfer equilibria among carbenium ions, free radicals and carbanions (equation 2).[4,5]

$$\mathrm{R}^+ \overset{e^-}{\rightleftharpoons} \mathrm{R}\bullet \overset{e^-}{\rightleftharpoons} \mathrm{R}\!:^- \tag{2}$$

Indeed the combination of the reactive intermediates in equations (1a) and (2) forms the chemical basis of electron-transfer oxidation (reduction) of organic compounds in both stoichiometric and catalytic processes.[6]

The energetic basis for electron-transfer oxidation includes the thermodynamic potential $E^\circ_{\mathrm{ox}}$ for the initial act of electron transfer from RH in equation (1a).[7,8] Such an electron detachment is commonly effected: (a) at an electrode; (b) by an oxidant; or (c) with light. Thus the organic oxidation in equation (1a) is driven electrochemically by the anodic electrode potential (*E*) to match the value of $E^\circ_{\mathrm{ox}}$,[9] *i.e.* equation (3a). Likewise, the driving force in the chemical oxidation of RH is provided by the redox potential $E^\circ_{\mathrm{red}}$ of the electron acceptor or oxidant (hereinafter referred to as A; equation 3b).[10]

$$\mathrm{RH} \xrightarrow{[E]} \mathrm{RH}^{+\bullet} \tag{3a}$$

$$\mathrm{RH} + \mathrm{A} \longrightarrow \mathrm{RH}^{+\bullet} + \mathrm{A}^{-\bullet} \tag{3b}$$

Photochemical electron transfer proceeds either by the prior actinic activation of the organic donor RH followed by quenching by the electron acceptor (equation 4), or by the reverse sequence involving the prior acceptor activation and quenching with donor.[11] Photochemical electron transfer can also be effected by the irradiation of the charge-transfer (CT) absorption band of the precursor electron donor–acceptor (EDA) complex (equation 5).[12]

$$\mathrm{RH} \xrightarrow{h\nu} \mathrm{RH}^{*} \xrightarrow{\mathrm{A}} \mathrm{RH}^{\overset{+}{\bullet}} + \mathrm{A}^{\overset{-}{\bullet}} \qquad (4)$$

$$\mathrm{RH} + \mathrm{A} \rightleftharpoons [\mathrm{RH,A}] \xrightarrow{h\nu_{\mathrm{CT}}} \mathrm{RH}^{\overset{+}{\bullet}} + \mathrm{A}^{\overset{-}{\bullet}} \qquad (5)$$

The actinic irradiation of the charge-transfer band of the EDA complex in equation (5) is the most direct method for the photoactivation of electron-transfer oxidation, since the absorbed energy $h\nu_{\mathrm{CT}}$ is directly applied to the conversion of a bonding electron in the HOMO of the donor RH to an antibonding electron in the LUMO of the acceptor A. Such a spontaneous generation of $[\mathrm{RH}^{+\bullet},\mathrm{A}^{-\bullet}]$ represents the contact ion pair (CIP)[13] in Figure 1 with an interionic separation that is essentially that originally present in the EDA precursor [RH,A].[14] However in the alternative mode of photoactivation (equation 4) the excitation of only RH (see $h\nu_{\mathrm{RH}}$ in Figure 1) is followed by electron transfer to A in a subsequent step. Since the latter takes place by a diffusional process,[15] $[\mathrm{RH}^{+\bullet},\mathrm{A}^{-\bullet}]$ is not necessarily the same contact ion pair formed by the direct charge-transfer activation. Indeed, there are examples of diffusional quenching by electron transfer over long distances to form initially a less intimate, solvent-separated ion pair (SSIP).[16] The same situation pertains to the photoinduced electron-transfer oxidation by the prior excitation of the acceptor (see $h\nu_{\mathrm{A}}$ in Figure 1). The modulating effect of varying ion-pair structures lies at the core of electron-transfer oxidation, as will be elaborated in the following sections. Finally, in the electron-transfer oxidation of a particular organic donor RH, the thermal process in equation (3b) invariably requires a stronger oxidant (*i.e.* A with more positive $E^{\circ}_{\mathrm{red}}$) than its photochemical counterparts in equations (4) and (5) owing to the contribution from the actinic input (see Figure 1).

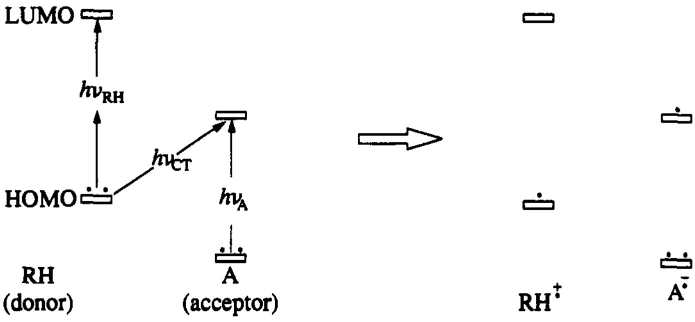

**Figure 1** Energy level diagram (qualitative) for the charge-transfer excitation ($h\nu_{\mathrm{CT}}$) of the electron donor-acceptor complex (RH, A) in comparison with that for the excitation of either the donor ($h\nu_{\mathrm{RH}}$) followed by quenching of RH* with the acceptor or the acceptor ($h\nu_{\mathrm{A}}$) followed by quenching of A* with the donor

Since electrochemical methods are described in Volume 7, Chapter 7.1, emphasis will be placed on the thermal and photochemical activation of electron-transfer oxidation. Even with this restriction the scope of electron-transfer oxidation is too extensive to be covered completely in a single chapter. Therefore the approach here is to present those fundamental aspects that allow electron-transfer oxidations to be developed for synthetic transformations. Hopefully this format will encourage the creative chemist to devise myriad oxidative syntheses from a limited number of principles. Fortunately, there are already available a variety of recent monographs with each presenting a restricted coverage to permit the inclusion of detailed and useful examples. For the convenience of the reader these articles are listed as references 17 to 32, with the chapter titles included where appropriate. Taken all together they offer the reader an interesting panoply of electron-transfer oxidations that are intertwined by the principles outlined herein.

It is important to emphasize the anodic, chemical and actinic activations of electron-transfer oxidation to be complementary methods that all commonly involve the reactive intermediates like those presented in equations (1a) and (2). As such, cognizance must always be taken of the subtle differences of concentration, temperature, solvent polarity, *etc.* that affect the behavior of the transient radicals and ion radicals sufficient to alter the unique complexion of products obtainable in the course of electrochemical, chemical or photochemical oxidation of a given organic substrate. For this reason it is helpful to define first the features that are critical to electron-transfer oxidation, independent of the methodology to be employed. These include the consideration of: (a) the driving force for electron transfer in terms of the oxidation potential $E^{\circ}_{ox}$ of the organic substrate and the reduction potential $E^{\circ}_{red}$ of the oxidant; and (b) the chemical properties of the oxidized donor ($RH^{+\bullet}$) as well as those of the reduced acceptor ($A^{-\bullet}$).

## 7.4.2 THE FORMULATION OF ELECTRON-TRANSFER OXIDATION

Electron-transfer oxidation in equation (3b) can be considered to consist of a series of preequilibria, in the limit where the radical cation of the organic donor and radical anion of the acceptor are both persistent species (equation 6a).[33] The first set of brackets encloses the electron donor–acceptor or EDA precursor complex, and the second set the contact ion pair or CIP successor complex that is constrained by the solvent cage.[34] Intermolecular reactions of $RH^{+\bullet}$ that lead to the oxidation products largely occur subsequent to cage escape ($k_3$).

$$\mathrm{RH} + \mathrm{A} \rightleftharpoons [\mathrm{RH}, \mathrm{A}] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [\overset{+}{\mathrm{RH}}\bullet, \overset{-}{\mathrm{A}}\bullet] \overset{k_3}{\rightleftharpoons} \overset{+}{\mathrm{RH}}\bullet + \overset{-}{\mathrm{A}}\bullet \qquad (6a)$$

Electron-transfer oxidation of an organic substrate in equation (6a) derives from a driving force given as $-\Delta G = F(E^{\circ}_{ox} + E^{\circ}_{red})$, where $F$ is the Faraday constant and the conversion factor is 1 V ≈ 23 kcal mol$^{-1}$ (1 cal = 4.18 J).[8] In the simplest cases of anionic donors (*e.g.* carbanions) reacting with cationic oxidants, the ion-pair annihilation will proceed by electron transfer even when the driving force is endergonic by as much as 0.7 V (*i.e.* uphill by ~15 kcal mol$^{-1}$).[35] Moreover electron transfer between uncharged donors and acceptors may occur with as little as −0.4 V of driving force. These qualitative estimates are of course strongly tempered by solvent effects and inherent factors that are intrinsic to the donor and acceptor. The latter in outer-sphere electron transfer is represented by the reorganization energy ($\lambda$) as described by Marcus.[36] (For an excellent account of the use of Marcus theory in organic chemistry the reader is referred to the recent monograph by Eberson.[37]) Suffice it to mention here that most organic reactions proceed *via* inner-sphere electron transfer in which the intermolecular interactions in the first-formed contact ion pair $[RH^{+\bullet}, A^{-\bullet}]$ must be explicitly taken into account.[38] As such, the facility with which electron transfer occurs is not so readily predicted from only a knowledge of the measurable quantities $E^{\circ}_{ox}$, $E^{\circ}_{red}$, $\lambda(RH)$, $\lambda(A)$ and $\Delta G_s$. In other words, simply a knowledge of $E^{\circ}_{ox}$ and $E^{\circ}_{red}$ alone is insufficient to predict whether electron transfer will or will not be a viable process in the oxidation of the organic donor RH. This caveat must be underscored, since the thermodynamic driving force is often and erroneously taken as a predictor of electron-transfer oxidation. At best, the driving force ($E^{\circ}_{ox} + E^{\circ}_{red}$) relates only to the electron-transfer equilibrium. The critical element in oxidation efficiency is the behavior of the contact ion pair, as determined by the competition between its formation ($k_1$) and further reaction ($k_3$) relative to the energy-wasting, back electron transfer ($k_2$) in equation (6a).[32]

### 7.4.2.1 Oxidation Potentials of Organic Compounds

Except for very electron-rich organic donors that yield stable, persistent radical cations, the values of the one-electron potential $E^{\circ}_{ox}$ for equation (1a) are not generally available for organic compounds. Thus the radical cations $RH^{+\bullet}$ that are derived from most organic donors are too reactive to allow the measurement of their reversible potentials $E^{\circ}_{ox}$ in either aqueous or organic solvents by the standard techniques. This problem is partially alleviated by the measurement of the irreversible anodic peak potentials $E_a$ that are readily obtained from the linear-sweep or cyclic voltammograms (CV) of RH.[39] Since the values of $E_a$ contain contributions from kinetic terms, a comparison with the values of the thermodynamic $E^{\circ}_{ox}$ is restricted to a series of related donors, *i.e.* $E^{\circ}_{ox} = \beta E_a$ + constant, where $\beta \approx 1.0$, as illustrated in Figure 2(a).[40] It is important to emphasize this limitation when values of $E_a$ (at a constant CV sweep rate) are employed as measures of the electron-donor properties of various organic donors, as in Table 1.[41,42] Alternatively, the energetics of electron detachment from RH are obtained in the gas-phase measurements of the ionization potential *IP*. The ionization potentials of many organic donors have been determined experimentally, most conveniently from the photoelectron spectra (PES) obtained by the photoionization of RH.[43] The values of *IP* measured in the gas phase differ from the values $E^{\circ}_{ox}$ in solution largely by solvation, *i.e.* $E^{\circ}_{ox} = IP + \Delta G_s$ + constant, where $\Delta G_s$ is the solvation energy of the radical cation, owing to a negligible contribution from the solvation of the uncharged donor RH. Since the variations in $\Delta G_s$ are usually minor, the values of *IP* such as those listed in Table 1 can be adequate measures of the electron-donor abilities of organic compounds applicable to a particular solvent. This generalization is especially tenable for a series of related compounds, as illustrated in Figure 2(b). Independently of whether the electron-donor properties are evaluated by such indirect measures as $E_p$ and *IP*, note must always be taken of the approximations that relate them to the thermodynamic values of $E^{\circ}_{ox}$.

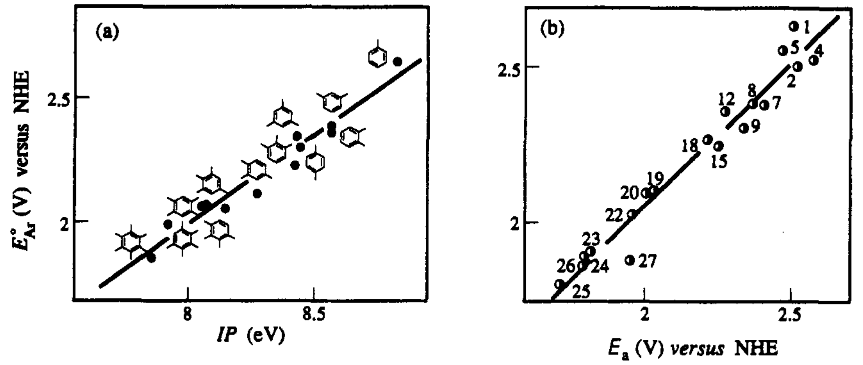

**Figure 2** (a) Correlation of the reversible oxidation potentials and the vertical ionization potentials of methylarenes; (b) the correlation of the standard oxidation potentials $E^{\circ}_{Ar}$ of various alkylbenzenes with the irreversible CV peak potentials $E_a$. Numbers refer to the aromatic hydrocarbons identified in ref. 40

**Table 1** Some Representative Values of the Oxidation Potentials and Ionization Potentials of Organic Electron Donors[a]

| *Donor (RH)* | *IP* | $E^{\circ}_{ox}$ | *Donor (RH)* | *IP* | $E^{\circ}_{ox}$ |
|---|---|---|---|---|---|
| 2-Methylpentane | 10.11 | 3.01 | Benzene | 9.24 | 2.04 |
| 2,2-Dimethylbutane | 10.05 | 3.28 | Toluene | 8.82 | 1.96 |
| Ethylene | 10.51 | 2.90 | *o*-Xylene | 8.56 | 1.58 |
| 1-Butene | 9.58 | 2.78 | *m*-Xylene | 8.56 | 1.60 |
| 1-Octene | 9.52 | 2.70 | *p*-Xylene | 8.45 | 1.54 |
| 2-Methylpropene | 9.23 | 2.65 | *p*-Bromotoluene | 8.67 | 1.72 |
| 2-Butene | 9.13 | 2.21 | Iodobenzene | 8.73 | 1.77 |
| 1,4-Cyclohexadiene | 8.40 | 1.60 | Anisaldehyde | 8.86 | 1.64 |
| 1,3-Butadiene | 9.07 | 2.03 | *p*-Chlorotoluene | 8.69 | 1.76 |
| Cyclohexene | 8.95 | 1.98 | Chlorobenzene | 9.07 | 2.07 |
| 2-Methyl-1-butene | 9.12 | 1.97 | Bromobenzene | 8.89 | 1.98 |
| 2,3-Dimethyl-1,3-butadiene | 8.27 | 1.84 | Biphenyl | 8.27 | 1.48 |
| 2-Iodopropane | 9.17 | 2.04 | 1-Propylbenzene | 8.72 | 1.97 |
| Methyl iodide | 9.54 | 2.12 | 2-Propylbenzene | 8.69 | 1.88 |
| *n*-Butanethiol | 9.14 | 1.34 | Pentamethylbenzene | 7.92 | 1.28 |
| Dimethyl sulfide | 8.69 | 1.26 | 1,2,4,5-Tetramethylbenzene | 8.03 | 1.29 |
| Diethyl sulfide | 8.43 | 1.35 | 1,2,3-Trimethylbenzene | 8.48 | 1.58 |
| Dimethyl sulfoxide | 8.84 | 1.73 | 1,2,4-Trimethylbenzene | 8.27 | 1.41 |
| Diphenylamine | 7.40 | 0.53 | Mesitylene | 8.39 | 1.53 |
| 1-Naphthylamine | 7.30 | 0.34 | Indene | 8.81 | 1.25 |
| 2-Naphthylamine | 7.25 | 0.44 | Hexamethylbenzene | 7.85 | 1.20 |
| Dimethylaniline | 7.14 | 0.45 | 1,4-Dimethoxybenzene | 7.90 | 1.04 |
| Triethylamine | 7.50 | 0.79 | Naphthalene | 8.12 | 1.34 |
| Trimethylamine | 7.82 | 0.82 | 1-Methylnaphthalene | 7.96 | 1.24 |
| Aniline | 7.70 | 0.70 | 2-Methylnaphthalene | 7.96 | 1.22 |
| *n*-Butylamine | 8.71 | 1.87 | Phenanthrene | 7.80 | 1.23 |
| *N,N*-Dimethylacetamide | 8.81 | 1.82 | Anthracene | 7.23 | 0.84 |
| Pyridine | 9.27 | 1.82 | Tetracene | 6.88 | 0.53 |
| Quinoline | 8.30 | 1.73 | Fluorene | 8.63 | 1.25 |
| Phenol | 8.50 | 1.04 | Triphenylene | 7.80 | 1.35 |
| 1,4-Dioxane | 9.13 | 1.97 | Coronene | 7.60 | 0.93 |
| Anisole | 8.22 | 1.40 | Perylene | 7.15 | 0.55 |
| Thiophene | 8.86 | 1.70 | Azulene | 7.43 | 0.61 |
| *t*-Butyl alcohol | 9.71 | 2.94 | Chrysene | 7.75 | 1.22 |

[a] *IP* in eV; $E^{\circ}_{ox}$ in V *versus* $Ag^+/AgNO_3$, in MeCN (consult the text in ref. 41 for the reliability).

### 7.4.2.2 Reduction Potentials of Oxidants (Electron Acceptors)

The electron-acceptor properties of oxidants are most readily evaluated by the reversible potentials $E^\circ_{red}$ for the one-electron reduction, *i.e.* equation (6b). Values of $E^\circ_{red}$ for many types of oxidants, particularly those based on transition metal cations, have been tabulated, and some of the more common ones in water are listed in Table 2.[44] However there are a number of useful oxidants that undergo a multiple electron change, *e.g.* $Tl^{3+} + 2e^- \rightarrow Tl^+$, $O_2Cr^{2+} + 3e^- \rightarrow Cr^{3+}$, *etc.*, and $E^\circ_{red}$ is known only for the overall change. With these oxidants, the one-electron potential of relevance to electron-transfer oxidation must be evaluated separately by such transient electrochemical techniques as linear-sweep microvoltammetry.[45] Reduction potentials are also highly dependent on the solvent, particularly in those oxidants undergoing a pronounced change in charge. Since the values of $E^\circ_{red}$ are generally unattainable in organic solvents, an alternative measure of the electron-acceptor properties of A can be evaluated from the irreversible cathodic peak potential $E_c$. For a series of related compounds the values of $E_c$ can parallel the gas-phase electron affinities ($E_A$).[46] (Note the same limitations apply to the use of $E_c$ as those described above for the anodic counterpart.) Moreover, there are a number of stable organic and nonmetallic radicals that are useful in electron-transfer oxidations. Table 3 also includes several varieties of organic acceptors that afford persistent radical anions. Owing to their use as photochemical quenchers, the enhanced values of the reduction potentials $E_S$ and $E_T$ for the excited singlet and triplet acceptor species, respectively (see $h\nu_A$ in Figure 1), are also included in Table 3.[47–59]

$$A + e^- \xrightleftharpoons{E^\circ_{red}} A^{\bullet-} \qquad (6b)$$

Table 2 Reduction Potentials of Some Common Metal Oxidants[a]

| *Oxidant (A)* | $E^\circ_{red}$ | *Oxidant (A)* | $E^\circ_{red}$ |
|---|---|---|---|
| $Ag^{II}$ | 2.00 | $Ru^{IV}$ | 0.86 |
| $Co^{III}$ | 1.81 | $Ag^{I}$ | 0.80 |
| $O_4Bi_2^{IV}$ | 1.59[b] | $Tl^{III}$ | 1.26[b] |
| $Ce^{IV}$ | 1.61 | $O_4Re^{VII}$ | 0.77 |
| (5-NOphen)$Fe^{III}$ | 1.53[c] | $Fe^{III}$ | 0.77 |
| $ORh^{IV}$ | 1.43 | $(phen)_2Fe^{III}$ | 1.33[c] |
| $Hg^{II}$ | 0.91[b] | $O_4Ru^{VII}$ | 0.59 |
| $Ru^{IV}$ | 1.01 | $O_4Mn^{VII}$ | 0.57 |
| $Au^{III}$ | 1.4[b] | $(NC)_6Fe^{III}$ | 0.55 |
| $O_2V^{V}$ | 1.00 | $Cu^{I}$ | 0.52 |
| $O_4Ru^{VIII}$ | 1.00 | $(NC)_8W^{V}$ | 0.46 |
| $Pb^{IV}$ | 1.65[b] | $W^{VI}$ | 0.26 |
| $Pu^{VI}$ | 0.92 | $O_4Os^{VIII}$ | 0.18[c] |
| $Cl_6Ir^{IV}$ | 0.87 | $Cu^{II}$ | 0.17 |
| $XeF_2$ | 2.2[b] | $OTi^{IV}$ | 0.1 |
| $Pd^{II}$ | 0.92[b] | $O_2Cl^{IV}$ | 0.06 |

[a] One-electron potential (NHE) in water with oxo and aquo ligands, unless indicated otherwise.[44] [b] Two-electron potential. [c] MeCN.

## 7.4.3 GENERIC BEHAVIOR OF RADICAL IONS AS REACTIVE INTERMEDIATES IN ELECTRON-TRANSFER OXIDATION

The fate of the contact ion pair $[RH^{\bullet+}, A^{\bullet-}]$ is critical to electron-transfer oxidation. Oxidative efficiency is the highest with those organic donors that yield unstable radical cations, such as hexamethyl(Dewar benzene), which undergoes spontaneous rearrangement (equation 7).[60,61]

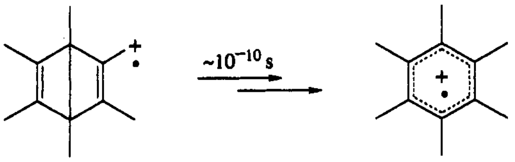

(7)

When such a unimolecular process occurs faster than back electron transfer ($k_2$ in equation 6a), electron-transfer oxidation in Scheme 1 proceeds rapidly despite an unfavorable driving force ($E^\circ_{ox} + E^\circ_{red} \approx$ 30 kcal mol$^{-1}$) for electron transfer.[62]

**Table 3** Reduction Potentials of Organic Electron Acceptors[a]

| *Acceptor (A)* | $E^\circ_{red}$ | *Ref.* |
|---|---|---|
| Thianthrenium $ClO_4^-$ | 1.28 | 47 |
| 2,4,6-Triphenylpyrilium $ClO_4^-$ | −0.29 (2.8) | 48 |
| Tropylium $BF_4^-$ | −0.18 | 49 |
| Nitrosonium $BF_4^-$ | 1.28 | 50 |
| Tris-*p*-bromophenylaminum $BF_4^-$ ($BA^{+\cdot}$) | 0.80 | 51 |
| 2-Phenylpyrrolinium $ClO_4^-$ | — (2.9) | 52 |
| Nitronium $BF_4^-$ | 1.27 | 50 |
| 1,2,4,5-Tetracyanobenzene (TCB) | −0.65 (3.83) | 53 |
| 9,10-Dicyancyanoanthracene (DCA) | −0.98 (2.88) | 53 |
| 2,6,9,10-Tetracyanoanthracene (TCA) | −0.45 (2.82) | 53 |
| 1,4-Dicyanonaphthalene (DCN) | −1.28 (3.45) | 53 |
| 9-Cyanoanthracene | −1.39 (2.96) | 53 |
| 1-Cyanonaphthalene (CN) | −1.98 (3.75) | 54 |
| 1,4-Dicyanobenzene (DCB) | −1.60 (4.2) | 53 |
| Chloranil (CA) | 0.02 [2.70] | 55 |
| Dioxygenyl ($O_2^{+\cdot}$) $SbF_6^-$ | 5.3 | 56 |
| 2,4,4,6-Tetrabromocyclohexa-2,5-dienone | 0.29 | 57 |
| Tetracyanoethylene (TCNE) | 0.24 | 58 |
| Tetracyanoquinodimethane (ICNQ) | 0.19 | 53 |
| Tetranitromethane (TNM) | ~0.0 | 59 |
| Dioxygen ($O_2$) | −0.78 (0.98) | 55 |
| 1,2-Benzoquinone | 0.12 [2.3] | 53 |
| Dichlorodicyano-1,4-benzoquinone (DDQ) | 0.52 | 55 |
| 1,4-Dinitrobenzene | −0.69 [2.6] | 55 |
| Nitrobenzene | −1.15 | 55 |
| N,N′-Dimethyl-4-bipyridinium ($MV^{2+}$) $ClO_4^-$ | −0.45 [3.1] | 53 |

[a] In V *versus* SCE in MeCN solution; $E_S$ (parentheses) and $E_T$ [brackets] in eV.

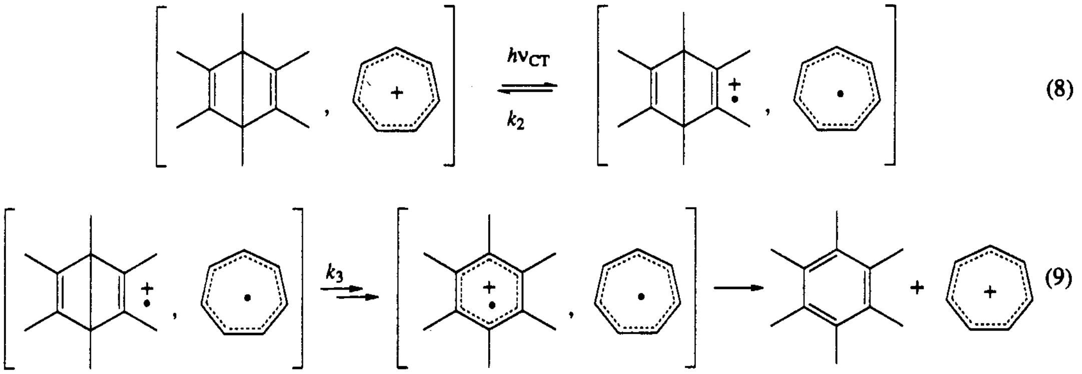

**Scheme 1**

Analogously, those oxidants that produce unstable radical anions, *e.g.* tetranitromethane, which suffers spontaneous fragmentation (equation 10),[63] similarly facilitate electron-transfer oxidation by pulling the redox equilibria in equation (6a) to the right. As a result, the alkene addition of tetranitromethane (Scheme 2) occurs despite an unfavorable redox equilibrium.[64]

$$\mathrm{C(NO_2)_4^{\bullet-}} \xrightarrow{\sim 10^{-12}\,\mathrm{s}} \mathrm{C(NO_2)_3^{-}} + \mathrm{NO_2^{\bullet}} \qquad (10)$$

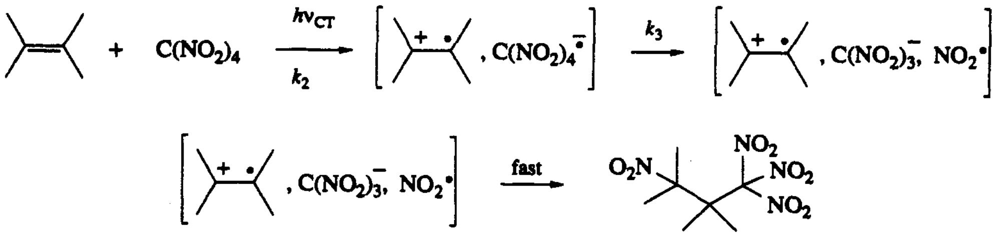

(11)

(12)

Scheme 2

Moreover, the facile bimolecular reactions of the cationic donor RH$^{+}$ and/or the anionic acceptor A$^{\bullet-}$, especially with additives that are present during oxidation, can accomplish the same displacement of the redox equilibria in measure with the competition from back electron transfer. For example, the arene activation with nitrosonium ion merely reaches a low steady-state concentration of the radical pair, which persists indefinitely in equation (13). However, oxygen rapidly traps even small amounts of nitric oxide to render back electron transfer ineffective, and successfully effects aromatic nitration (Scheme 3).[65]

$$\mathrm{ArH} + \mathrm{NO^+} \underset{k_2}{\rightleftharpoons} [\mathrm{ArH^{\overset{+}{\bullet}}}, \mathrm{NO}] \qquad (13)$$

$$[\mathrm{ArH^{\overset{+}{\bullet}}}, \mathrm{NO}] + 1/2\,\mathrm{O_2} \xrightarrow{\text{fast}} [\mathrm{ArH^{\overset{+}{\bullet}}}, \mathrm{NO_2}] \longrightarrow \mathrm{ArNO_2} + \mathrm{H^+} \qquad (14)$$

Scheme 3

In the related photochemical context, the EDA complex of hexamethylbenzene and maleic anhydride merely reaches a photostationary state (equation 15; Scheme 4) with no productive photochemistry, except when acid is present to trap the acceptor anion on its way to the photoadduct in equation (16).[66]

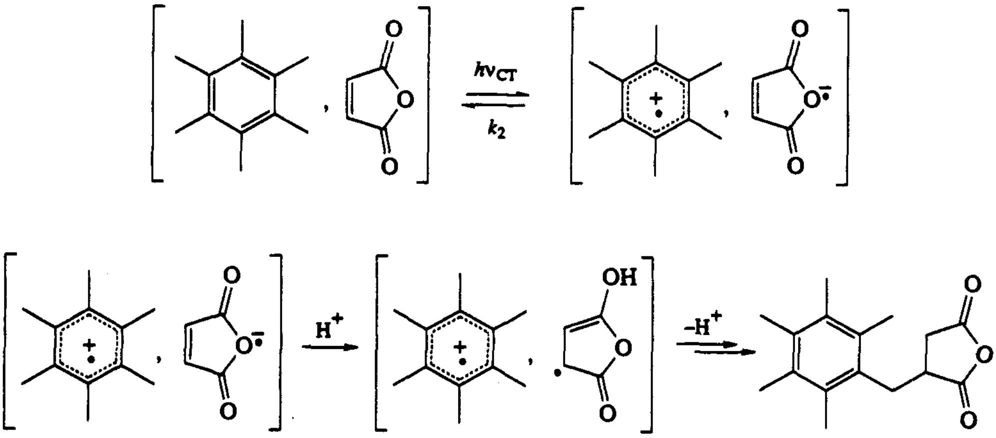

(16)

Scheme 4

Owing to the central role of radical cations and radical anions, any general description of electron-transfer oxidation must rely on their individual behavior, as described in the next section.[67,68]

### 7.4.3.1 Chemistry of Organic Radical Cations

With few exceptions the removal of a bonding electron from the HOMO generates a radical cation of greatly enhanced reactivity in both fragmentation and rearrangement as well as homolytic and electrophilic activity. For purposes of organization the reactions of organic radical cations can be broadly classified according to their kinetic behavior, unimolecular reactions occurring optimally within the contact ion pair [$RH^{+\bullet}$,$A^{-\bullet}$] and the bimolecular reactions of $RH^{+\bullet}$ taking place largely after diffusive separation as in equation (6a).

Unimolecular reactions of organic radical cations are fragmentation, rearrangement and cyclization, as illustrated by the following generic examples. The specific details of each of these transformations are included in Section 7.4.6. (Note Ar and R represent aryl and alkyl groups, respectively.)

#### *7.4.3.1.1 α-Fragmentation*

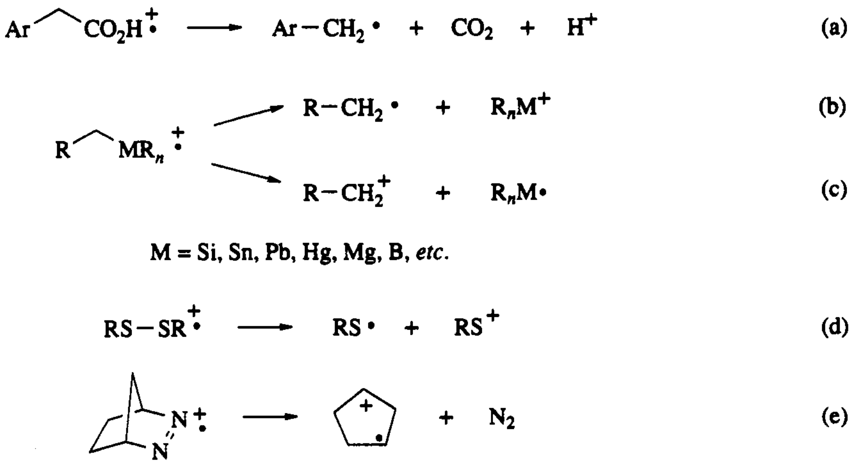

Ar CO2H+•
Ar–CH2• + CO2 + H+
(a)
R–CH2• + RnM+
(b)
R MRn+•
R–CH2+ + RnM•
(c)
M = Si, Sn, Pb, Hg, Mg, B, etc.
RS–SR+•
RS• + RS+
(d)
N+•
N
+ N2
(e)

#### *7.4.3.1.2 β-Fragmentation*

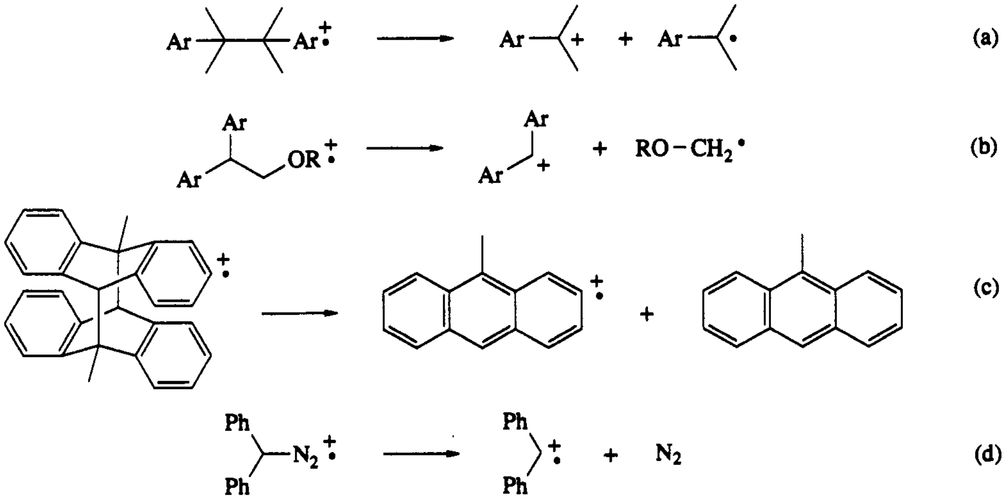

Ar Ar+•
Ar + Ar
(a)
Ar
Ar OR+•
Ar
Ar +
+ RO–CH2•
(b)
+•
(c)
Ph
Ph N2+•
Ph
Ph +•
+ N2
(d)

### *7.4.3.1.3 Rearrangement*

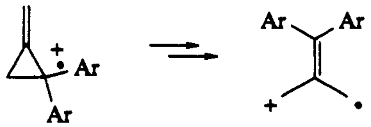

(a)

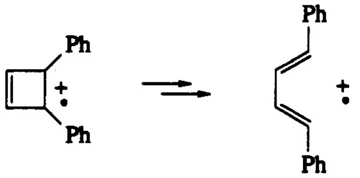

(b)

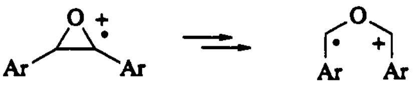

O
Ar
Ar
O
Ar
Ar

(c)

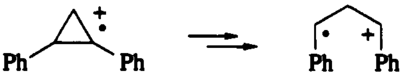

(d)

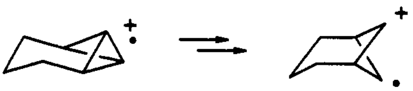

(e)

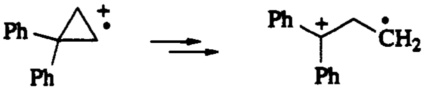

Ph
Ph
Ph
CH2
Ph

(f)

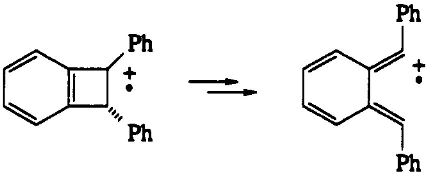

(g)

### *7.4.3.1.4 Cyclization*

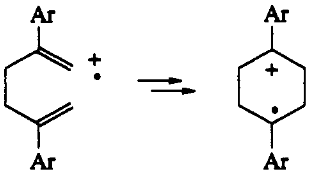

(a)

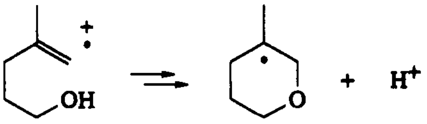

(b)

Bimolecular reactions of organic radical cations relating to their ambivalent character involve the reactions with bases, nucleophiles and radicals.

### 7.4.3.1.5 Deprotonation

$$ArCH_3^{+\bullet} + Py \longrightarrow ArCH_2\bullet + PyH^+ \qquad (a)$$

Py = pyridine

$$Me_3CH^{+\bullet} + H_2O \longrightarrow Me_3C\bullet + H_3O^+ \qquad (b)$$

(Note hydrocarbon radical cations are conjugate acids of the hydrocarbyl radical.)

$$Et_3N^{+\bullet} + MeOH \longrightarrow Et_2N\dot{C}HMe + MeOH_2^+ \qquad (c)$$

### 7.4.3.1.6 Nucleophilic addition

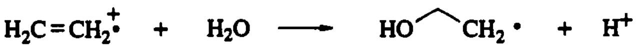

(a)

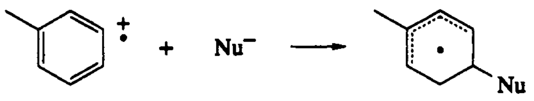

(b)

Nu = amine, OAc⁻, OH⁻, CN⁻, MeOH, *etc.*

### 7.4.3.1.7 Dimerization

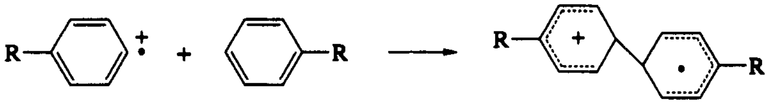

(a)

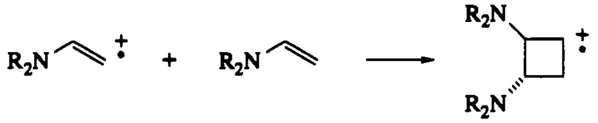

(b)

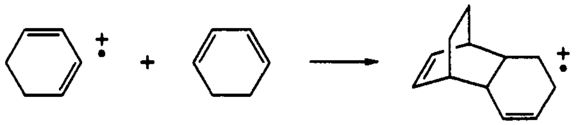

(c)

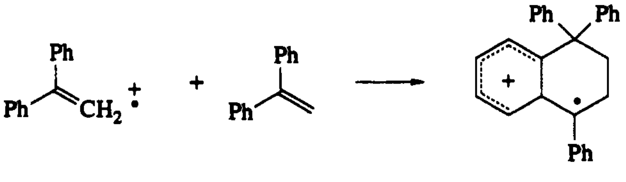

(d)

### 7.4.3.1.8 Cycloaddition

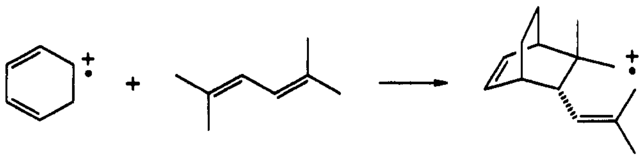

(a)

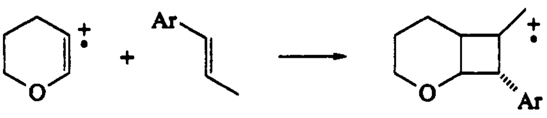

(b)

#### *7.4.3.1.9 Homolytic addition*

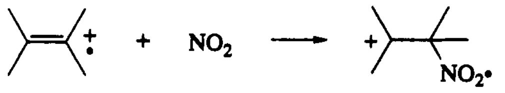

(a)

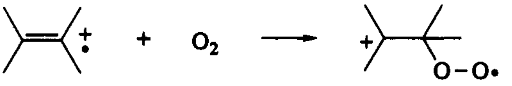

(b)

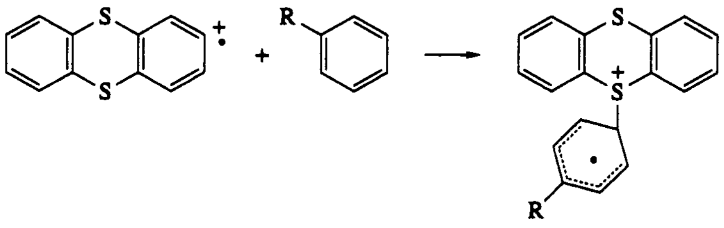

(c)

#### *7.4.3.1.10 Electron transfer*

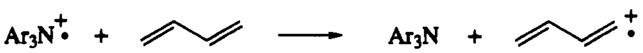

(a)

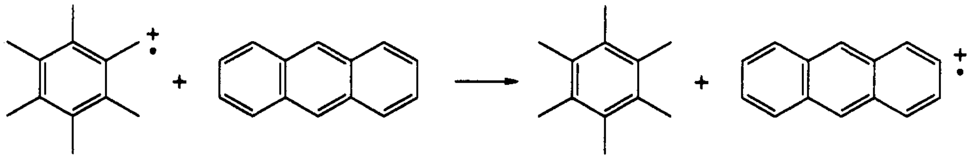

(b)

$$O_2^{+\bullet} + R_3N \longrightarrow O_2 + R_3N^{+\bullet} \qquad \text{(c)}$$

### 7.4.3.2 The Follow-up Reactions of Organic Radical Cations

Each of the generic reactions of organic radical cations (as presented in Sections 7.4.3.1.1–7.4.3.1.10) generates a new radical and cation center. In the dissociative processes (such as $\alpha$-fragmentation and deprotonation) the radical and cation centers become separated; the further follow-up oxidations of the uncharged organic radical by electron transfer and ligand transfer are already well described,[69] and the reader is referred to several monographs on free radical chemistry.[70,71] Suffice it to mention two examples here to illustrate this point with the electron-transfer oxidation of acids by LTA (equations 17 and 18).[72]

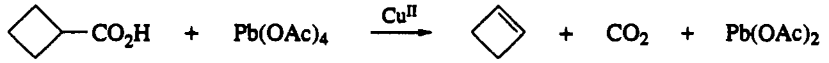

(17)

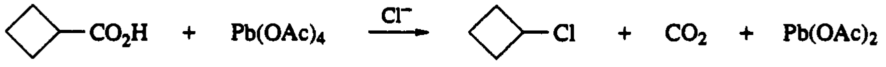

(18)

Thus the first electron transfer to $Pb^{IV}$ relates to the reaction (a) in Section 7.4.3.1.1, and the second involves the oxidation of the cyclobutyl radicals either by electron transfer/deprotonation with $Cu^{II}$ in equation (17) or by ligand transfer of chlorine with $Pb^{IV}Cl$ in equation (18). When the product of a generic reaction is itself a radical cation (such as in Sections 7.4.3.1.8 and 7.4.3.1.9), an electron-transfer chain or ETC process[73] can ensue, as in the hole-catalyzed cycloadditions and autoxidations of dienes.[74,75] The electron-transfer propagation sequence for the latter is simply given as in equations (19) and (20).

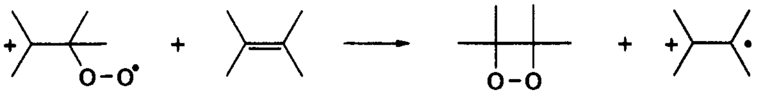

(19)

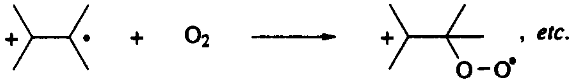

(20)

### 7.4.3.3 Chemistry of Organic Radical Anions

Electron attachment to the LUMO of an organic acceptor can produce a radical anion that is subject to ready unimolecular decomposition, as given by the following generic examples.[76,77]

#### 7.4.3.3.1 *Fragmentation*

$$\mathrm{ArX}^{\bullet-} \longrightarrow \mathrm{Ar}^{\bullet} + \mathrm{X}^{-} \qquad \text{(a)}$$

$$\mathrm{RX}^{\bullet-} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{X}^{-} \qquad \text{(b)}$$

X = I > Br > Cl

$$\mathrm{Ar_2O}^{\bullet-} \longrightarrow \mathrm{Ar}^{\bullet} + \mathrm{ArO}^{-} \qquad \text{(c)}$$

$$\mathrm{RO{-}OR}^{\bullet-} \longrightarrow \mathrm{RO}^{-} + \mathrm{RO}^{\bullet} \qquad \text{(d)}$$

$$\mathrm{RS{-}SR}^{\bullet-} \longrightarrow \mathrm{RS}^{\bullet} + \mathrm{RS}^{-} \qquad \text{(e)}$$

R = alkyl, H

Bimolecular reactions of radical anions are largely restricted to arene acceptors owing to their generally more persistent character. The ambivalence of arene radical anions generally relates to the reactivity towards acids, electrophiles and electron acceptors.

#### 7.4.3.3.2 *Protonation*

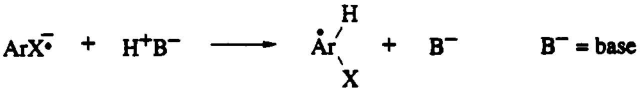

$$\mathrm{ArX}^{\bullet-} + \mathrm{H^{+}B^{-}} \longrightarrow \overset{\bullet}{\mathrm{Ar}}(\mathrm{H})(\mathrm{X}) + \mathrm{B}^{-} \qquad \mathrm{B}^{-} = \text{base} \qquad \text{(a)}$$

#### 7.4.3.3.3 *Electrophilic addition*

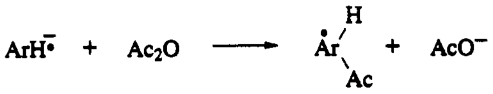

$$\mathrm{ArH}^{\bullet-} + \mathrm{Ac_2O} \longrightarrow \overset{\bullet}{\mathrm{Ar}}(\mathrm{H})(\mathrm{Ac}) + \mathrm{AcO}^{-} \qquad \text{(a)}$$

#### 7.4.3.3.4 *Electron transfer*

$$\mathrm{ArH}^{\bullet-} + \mathrm{ArX} \longrightarrow \mathrm{ArH} + \mathrm{ArX}^{\bullet-} \qquad \text{(a)}$$

$$\mathrm{ArH}^{\bullet-} + \mathrm{RX} \longrightarrow \mathrm{ArH} + \mathrm{R}^{\bullet} + \mathrm{X}^{-} \qquad \text{(b)}$$

(See nucleophilic aromatic substitution ($S_{\mathrm{RN}}$) in Volume 4, Chapter 2.1)

$$\mathrm{ArH}^{\bullet-} + \mathrm{O_2} \longrightarrow \mathrm{ArH} + \mathrm{O_2}^{\bullet-} \qquad \text{(c)}$$

### *7.4.3.3.5 Dimerization/disproportionation*

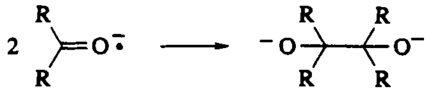

(a)

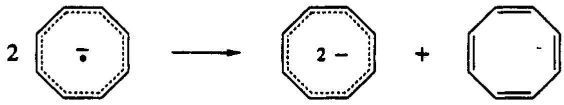

(b)

Although it may appear that the collapse of the contact ion pair [RH$^{+}$,A$^{-}$] with bond formation would frequently be the most favored pathway for its annihilation, only a few examples are presently available. These include the osmylation of arenes to be described in Section 7.4.4.8 (equation 24), as well as the following examples.

### *7.4.3.3.6 C—C bond formation*[78,79]

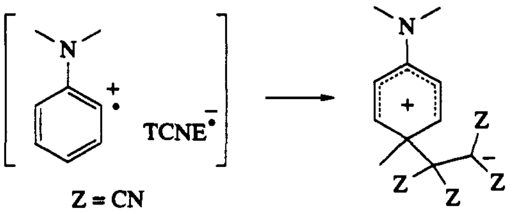

(a)

### *7.4.3.3.7 [3 + 2] cycloaddition*[80]

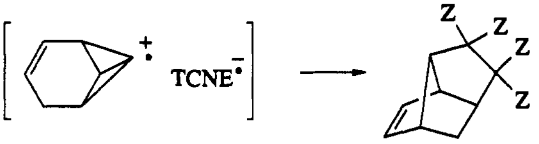

(b)

### *7.4.3.3.8 [4 + 2] cycloaddition*[81]

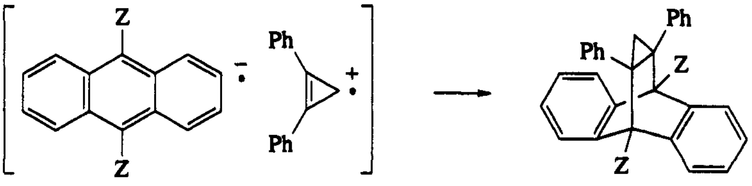

(c)

In each case the formation of the σ-bond(s) between RH$^{+}$ and A$^{-}$ must compete with back electron transfer.

## 7.4.4 THERMAL AND PHOTOCHEMICAL ACTIVATION OF ELECTRON-TRANSFER OXIDATION

When the oxidation–reduction equilibria in equation (6a) are included, the thermal activation of electron-transfer oxidation in equation (3b) follows a course that is akin to the charge-transfer activation in equation (5). In both, the EDA complex [RH,A] is the important precursor which is directly converted into the critical contact ion pair [RH$^{+}$,A$^{-}$]. Such an involvement of reactive intermediates in common does widen the scope of electron-transfer oxidations to include both thermal and photochemical processes in related contexts. The latter is especially useful in organic synthesis since a much wider range of organic acceptors become employable as oxidants that are otherwise too weak to effect the thermal oxidation of many organic donors. Accordingly, it is necessary to delineate the intimate relationship between charge-transfer activation and thermal activation, especially with regard to the reactive intermediates.

The osmylation of arenes (Ar) with osmium tetroxide is a particularly informative system with which to illustrate the close interrelationship between the thermal and photochemical activation of electron-transfer oxidation. For example, a colorless solution of osmium tetroxide in *n*-hexane or dichloromethane upon exposure to benzene turns yellow instantaneously.[82] With durene an orange coloration develops and a clear bright red solution results from hexamethylbenzene. The quantitative effects of the dramatic color changes are illustrated in Figure 3 by the spectral shifts of the electronic absorption bands that accompany the variations in aromatic conjugation and substituents. The progressive bathochromic shift parallels the decrease in the arene ionization potentials (*IP*) in the order: benzene 9.23 eV; naphthalene 8.12 eV; anthracene 7.55 eV. Such spectral behaviors are diagnostic of electron donor–acceptor complexes [Ar,$OsO_4^-$]. According to Mulliken,[83] the new absorption bands derive from charge-transfer excitation with the energetics defined by[84] $h\nu_{CT} = IP - E_A - \omega$, where $E_A$ is the electron affinity of the $OsO_4$ acceptor and $\omega$ is the dissociation energy of the CT excited ion-pair state [$Ar^{+\cdot}$,$OsO_4^-$].

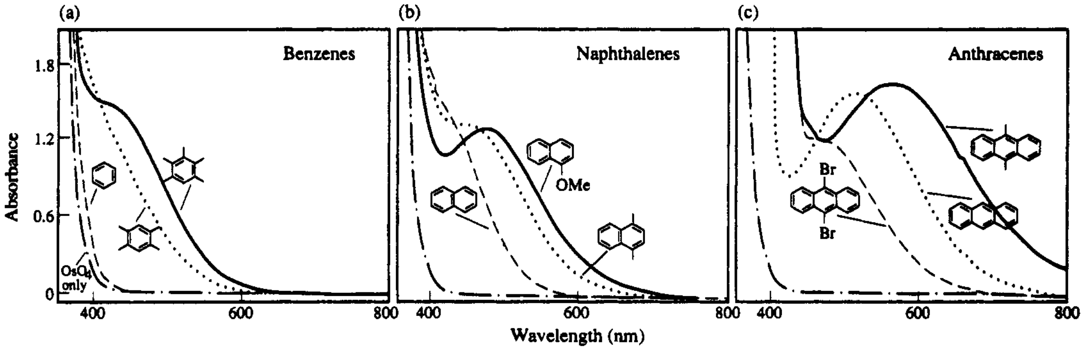

**Figure 3** Charge-transfer absorption bands from $OsO_4$ and: (a) benzene, durene and pentamethylbenzene; (b) naphthalene, 1,4-dimethylnaphthalene, and 1-methoxynaphthalene; (c) 9,10-dibromoanthracene, anthracene and 9,10-dimethylanthracene. Solution of $OsO_4$ only ( —— · —— )

### 7.4.4.1 Thermal Osmylation of Naphthalene, Anthracene and Phenanthrene

Benzene shows no signs of osmylation in the absence of light, as indicated by the persistence of the yellow color of the [$C_6H_6$,$OsO_4$] complex in *n*-hexane even upon prolonged standing. On the other hand, the orange CT color of the phenanthrene complex [$C_{14}H_{10}$,$OsO_4$] slowly diminishes over a period of weeks, accompanied by the formation of a dark brown precipitate of composition $C_{14}H_{10}OsO_4$. Dissolution of the solid in pyridine yields the 1:1 adduct (**1**; $C_{14}H_{10}OsO_4Py_2$) as the sole product in very low conversion. Anthracene behaves similarly to afford the 2:1 adduct in 10% conversion only after two months. The thermal osmylation can be expedited in a purple solution of refluxing *n*-heptane (100 °C) to effect a 68% conversion in 30 h. However even at these relatively elevated temperatures naphthalene is converted to the corresponding 2:1 adduct to only a limited extent. In every case the dark brown primary adducts are easily collected from the reaction mixture as insoluble solids, and then immediately ligated with pyridine for structural characterization. Indeed the characteristic IR and $^1H$ NMR spectra of the anthracene, phenanthrene and naphthalene adducts (**2**), (**1**) and (**3**) respectively, allow the ready analysis of the osmylated adducts. Since these adducts are derived from the arenes with only $OsO_4$ present, the chemical transformation is hereinafter designated as the direct thermal or DT osmylation. For comparison, the same polynuclear arenes can be osmylated in the presence of promoter bases, typically pyridine. Under these conditions the adducts (**2**), (**1**) and (**3**) are formed directly in the reaction mixture and at substantially increased rates of reaction, as previously established with the related family of alkene substrates.[85] Such a procedure differs visually from the DT osmylation described above in that the charge-transfer colors are not observed as transients, owing to the preferential complexation of $OsO_4$ with pyridine. Accordingly, this promoted thermal or PT osmylation is to be distinguished by the enhanced reactivity of the pyridine complex relative to the free $OsO_4$ in the DT osmylation. The corresponding increase in the yields of adducts such as (**2**), (**1**) and (**3**) within a shorter span of reaction times is apparent from the comparison of the results of DT and PT osmylations.

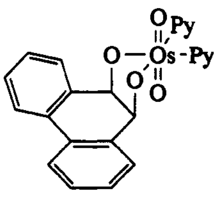

**(1)**

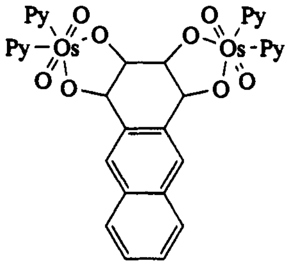

**(2)**

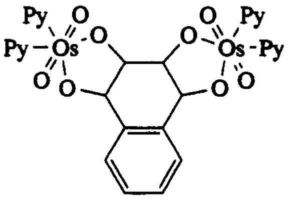

**(3)**

### 7.4.4.2 Charge-transfer Osmylation of Benzene, Naphthalene and Anthracene

The various charge-transfer colors for the different arene complexes with $OsO_4$ are persistent for days. However when the colored solutions are deliberately exposed to visible light with energy sufficient to excite only the charge-transfer band, they always deposit a highly insoluble, dark brown solid of the $OsO_4$ adducts obtained from the direct thermal osmylation of arenes (*vide supra*). Since this actinic process must have arisen *via* the electronic excitation of the EDA complex, it is referred to hereafter as charge-transfer or CT osmylation for individual arenes. For example, the irradiation of the charge-transfer bands (see Figure 3) of the $OsO_4$ complexes with various benzenes, naphthalenes and phenanthracene yields the same osmylated adducts such as (**3**) and (**2**) described above.[86] Anthracene is unique in that it affords two entirely different types of products upon the photoexcitation of the EDA complex $[C_{14}H_{10},OsO_4]$ in dichloromethane and hexane, despite only minor solvent effects on the charge-transfer bands. Irradiation of the purple solution of anthracene and $OsO_4$ in dichloromethane at $\lambda > 480$ nm yields the 2:1 adduct (**2**) together with its *syn* isomer as the sole products. On the other hand, irradiation of the same purple-colored solution in *n*-hexane under otherwise identical conditions leads to a small amount of polymeric osmium dioxide $(OsO_2)_x$. Work-up of the hexane solution yields anthraquinone as the major product contaminated with only traces (<1%) of the 2:1 adduct (**2**). Interestingly, even higher yields of anthraquinone are obtained from 9-bromo-, 9-nitro- and 9,10-dibromo-anthracene when the CT osmylation is carried out in *n*-hexane. Such an accompanying loss of the electronegative substituents (X = Br, $NO_2$) probably occurs *via* osmylation at the *meso* (9,10) positions followed by oxidative decomposition of the unstable adduct with the stoichiometry shown in equation (21).

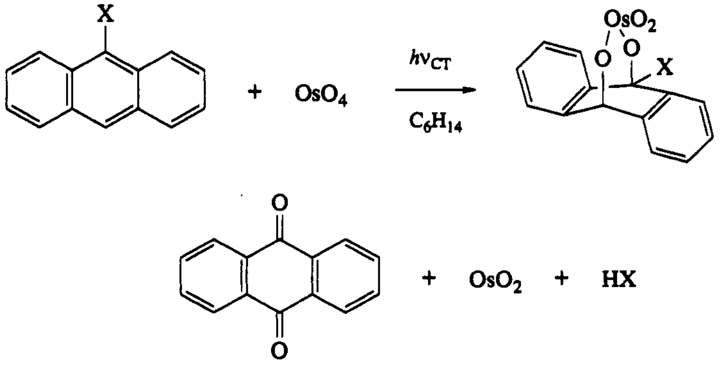

(21)

### 7.4.4.3 Time-resolved Spectra of Arene Radical Cations in Charge-transfer Osmylation

In order to identify the reactive intermediates in the charge-transfer excitation of arene–$OsO_4$ complexes, the time-resolved spectra are measured immediately following the application of a 30 ps pulse consisting of the second harmonic at 532 nm of a mode-locked Nd:YAG laser. The wavelength of this excitation source corresponds to the maxima (or near maxima) of the charge-transfer absorption bands of the series of anthracene complexes with osmium tetroxide illustrated in Figure 3(c). Accordingly, the time-resolved spectra from the anthracene–$OsO_4$ system relate directly to the CT osmylation since there is no ambiguity about either the adventitious local excitation[83] of complexed (or uncomplexed) chromophores, or the photogeneration of intermediates that did not arise from the photoexcitation of the EDA complex. Indeed, intense absorptions are observed in the visible region between 700 and 800 nm from the excitation of the anthracene–$OsO_4$ complex, as shown in Figure 4(a). This time-resolved absorption spectrum from anthracene is obtained in the time interval of ~30 ps following the application of the 532 nm laser pulse. Comparison with the steady-state absorption spectrum of the anthracene radical cation (see inset Figure 4(a) generated by the spectroelectrochemical technique,[87] thus establishes the identity of the charge-transfer transient. Similar time-resolved spectra of arene radical cations are obtained from various anthracene and naphthalene EDA complexes despite the excitation of only the low-energy tails of the CT bands in Figure 3 with the 532 nm laser pulse. The evolution of the anthracene radical cation is followed by measuring the absorbance change at $\lambda_{max}$ = 742 nm upon the charge-transfer excitation of the EDA complex with a single laser shot of ~10 mJ. The time evolution of the absorbance shown in Figure 4(b) includes the initial onset for ~20 ps owing to the rise time of the 30 ps (fwhm) laser pulse. The first-order plot of the decay portion is shown in the inset to the figure. Decay curves similar to those shown in Figure 4(b) are also observed for the disappearances of the radical cations derived from all of the other arene–$OsO_4$ complexes. In each case the highest concentration can be obtained of the arene radical cation, the decays of which are all first-order processes. The magnitudes of the rate constant $k_1$ are applicable to the complete disappearance of $Ar^{+\cdot}$, as indicated by the return of the radical cation absorbances to the baseline.

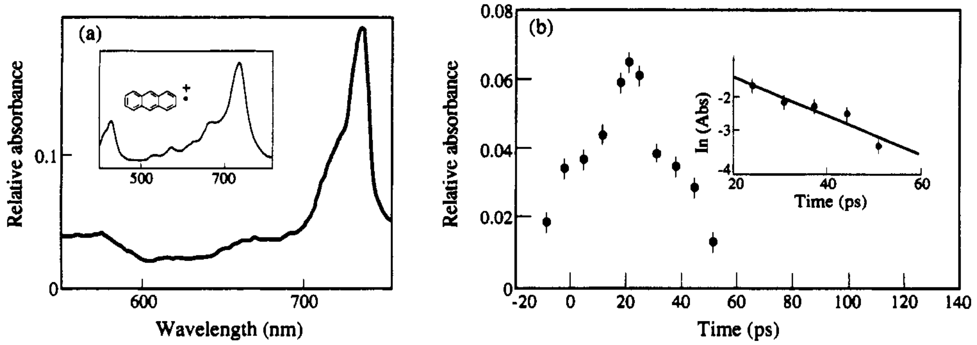

Figure 4 (a) Transient absorption spectrum of the cation radical from anthracene at ~40 ps following the 532 nm CT excitation of the $OsO_4$ complex with a 30 ps (fwhm) laser pulse. The inset is the steady-state spectrum of $Ar^{+\cdot}$ obtained by spectroelectrochemical generation. (b) Appearance and decay of the radical cation from anthracene by following the change of the absorbance at $\lambda_{max}$ = 742 nm. The inset shows the first-order plot of the absorbance decay subsequent to the maximum at ~20 ps

### 7.4.4.4 Common Features in Thermal and Charge-transfer Osmylations

The [Ar,$OsO_4$] complexes are involved as the common precursors in the oxidative addition of osmium tetroxide to various arenes by the three independent procedures designated as direct thermal (DT), promoted thermal (PT) and charge-transfer (CT) osmylation. For example, the anthracenes react rather slowly with osmium tetroxide *via* the EDA complex to effect DT osmylation in nonpolar solvents and afford 2:1 adducts that are then converted to the more tractable pyridine derivatives such as (**2**). Alternatively, the same ternary product (**2**) is directly formed at a significantly enhanced rate by the PT osmylation of anthracene with a mixture of $OsO_4$ and pyridine. Finally, the $OsO_4$ adduct to anthracene is instantly produced by CT osmylation involving actinic excitation of the [Ar,$OsO_4$] precursor complex. As such, the three procedures represent different activation mechanisms for arene oxidation. Thus DT and PT osmylations are adiabatic processes in which the transition states are attained *via* the collapse of an arene donor with the $OsO_4$ and the base-coordinated $OsO_4$(Py) electrophile, respectively. On the other hand, CT osmylation is a nonadiabatic process resulting from the vertical excitation of the [Ar,$OsO_4$] complex. For the latter, time-resolved picosecond spectroscopy can define the relevant photophysical and photochemical events associated with the charge-transfer excitation of an arene EDA complex, as previously established with arene complexes involving other electron acceptors. Accordingly, the CT osmylation is delineated first and then related to DT and PT osmylation. Before proceeding, however, it is important to emphasize that the DT, PT and CT osmylations all share in common the formation of the 1:1 osmium(VI) cycloadduct $ArOsO_4$ in the initial rate-limiting step, since the concomitant loss of aromaticity produces a reactive alicyclic diene that is highly susceptible to the further thermal osmylation.[88] The universal adherence to the 2:1 adduct $Ar(OsO_4)_2$ (except phenanthrene), irrespective of the molar ratios of arene/$OsO_4$ and the particular procedure employed, accords with the rapid addition of a second mole of $OsO_4$ in DT, PT and CT osmylations. This allows the focus on the formation of a single intermediate $ArOsO_4$ in order to delineate the unifying activation processes for DT, PT and CT osmylations.

### 7.4.4.5 Electron Transfer in the Charge-transfer Osmylation of Arenes

The direct observation of the reactive intermediates by the use of time-resolved picosecond spectroscopy and fast kinetics (Figure 4) enables the course of CT osmylation to be charted in some detail. The analysis proceeds from the mechanistic context involving the evolution and metamorphosis of the CT ion pair, as summarized in Scheme 5 (the brackets denote solvent-caged pairs) for the critical initial step (equation 24) to form the 1:1 adduct to a benzene donor.

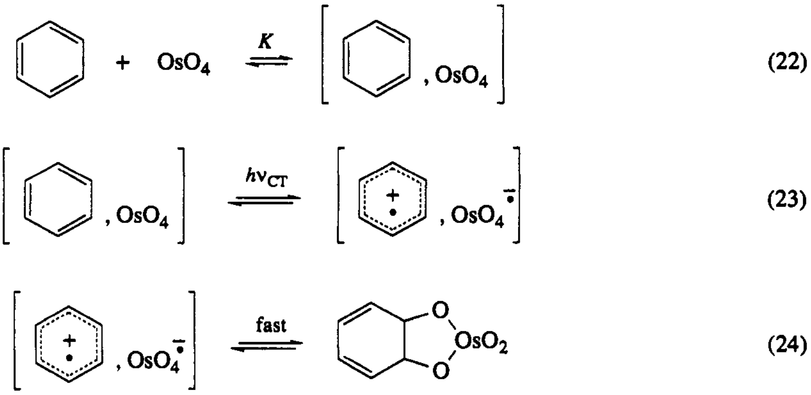

Scheme 5

All the experimental observations on CT osmylation indeed coincide with the formulation in Scheme 5. Thus the exposure of arene to osmium tetroxide leads immediately to new absorption bands (Figure 3) that are readily associated with the formation of the EDA complex in equation (22). These binary complexes are always present in low steady-state concentrations owing to the limited magnitudes of *K* determined by the Benesi–Hildebrand method. The complexes are so weak that every attempt at isolation, including the freezing of various mixtures of $OsO_4$ in neat aromatic donors, merely leads to phase separation. The absorption bands are thus properly ascribed to contact charge transfer, as formulated by Orgel and Mulliken,[89] who predicted the CT absorption bands in these EDA complexes to be associated with the electronic excitation to the ion-pair state (equation 23). As such, the time-resolved spectrum in Figure 4(a) indicates that the formation of the arene radical cation occurs within the rise time of the 30ps laser pulse. (The accompanying presence of the perosmate(VII) ($OsO_4^-$) counteranion is obscured by the arene absorptions.) The electron transfer from the arene donor to the $OsO_4$ acceptor in the EDA complex in equation (23) effectively occurs with the absorption of the excitation photon ($h\nu_{CT}$), in accord with Mulliken's theory. Furthermore the appearance at <30 ps demands that $Ar^{+\cdot}$ and $OsO_4^{-\cdot}$ are born as an intimate ion pair with a mean separation essentially that of the precursor complex [Ar,$OsO_4$] since this timescale obviates significant competition from diffusional processes. The seminal role of the ion pair [$Ar^+$,$OsO_4^-$] as the obligatory intermediate from the photoexcitation of the EDA complex must be included in any formulation of CT osmylation, by taking particular note of how it decays. The spontaneous collapse of the CT ion pair in equation (24) represents the most direct pathway to arene cycloaddition—the measured half-life of $\tau \approx 35$ ps for the disappearance of the anthracene radical cations in Figure 4(b) largely precluding diffusive separation of such ion pairs. However the magnitudes of the product quantum yield, $\phi_p \approx 10^{-2}$, indicate that the primary route for ion-pair decay is the back electron transfer ($k_2$) as the reverse step of equation (23). Such an energy-wasting process with an estimated rate constant of $k_2 \approx 10^{11}\ s^{-1}$, derives from a highly exergonic driving force that is estimated to be $\Delta G \approx -30$ kcal $mol^{-1}$, based solely on the standard redox potentials of $E^\circ = +1.30$ and $-0.06$ V for anthracene and the perosmate(VII) anion, respectively. More relevant to this issue is an estimated first-order rate constant for cycloaddition of $k_c = 10^9$ s$^{-1}$ for the ion-pair collapse to the arene cycloadduct in Scheme 5. Such a relatively large rate constant also points to a highly exergonic (bond-making) process for the cycloaddition in equation (24). Therefore the selectivity in adduct formation can be considered for various polynuclear arenes in which the initial addition of $OsO_4$ is possible at several sites. The regiospecificity observed in the CT osmylation of phenanthrene and 1,4-dimethylnaphthalene to produce only one isomeric adduct, (**1**) and (**3**), respectively, accords with the reactive site centered on the arene HOMO.[90] However in the extended polynuclear anthracenes the separation of the HOMO and subjacent SHOMO (*i.e.* HOMO-1) is not so well delineated,[91] and the regiospecificity is strikingly modulated by solvent polarity. Ion-pair annihilation is known to occur with the greatest ease in highly nonpolar alkanes.[92] Accordingly in *n*-hexane as solvent, the immediate collapse of the first-formed ion pair (**4**) centered at the anthracene HOMO is expected to occur at the *meso* (9,10) positions. Such an ion-pair collapse would produce anthraquinone in a manner similar to that presented in equation (21). On the other hand, the formation of only adduct (**2**) from the initial addition of $OsO_4$ to the terminal ring (**5**) represents a very unusual regiospecificity insofar as other addition (and substitution) reactions of anthracene are concerned. It suggests that the initially formed HOMO ion pair (HIP) has time to relax in the more polar dichloromethane medium to the isomeric SHOMO ion pair (SIP) that rapidly leads to adduct (**2**). This proposal receives support from the observation of adducts related to (**2**) from the CT osmylation of both 9-methyl- and 9,10-dimethyl-anthracene in hexane. The enhanced stability of the radical cations from these relatively electron-rich anthracenes will optimize the opportunity to convert the HIP to the more reactive SIP even in the nonpolar hexane medium, particularly if the collapse of the former is reversible.

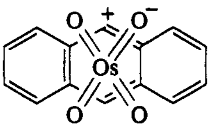

(**4**)

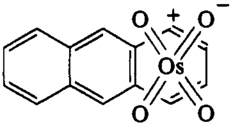

(**5**)

### 7.4.4.6 Electron Transfer as the Common Theme in Arene Osmylation

The wide-ranging reactivity of various aromatic hydrocarbons to $OsO_4$ offers the unique opportunity to probe the activation process for oxidative osmylation, especially with regard to the role of the EDA complex and the reactive intermediates. In particular, the deliberate photoexcitation ($h\nu_{CT}$) of the EDA complex in hexane or dichloromethane effectively activates various arenes including benzenes, naphthalenes and anthracenes to CT osmylation. This photoactivated process is readily associated with the charge-transfer ion pair, *i.e.* equation (25), as established by the growth and decay of arene radical cations with the aid of time-resolved picosecond spectroscopy. When kept in the dark, the same solutions of the EDA complexes slowly afford arene–$OsO_4$ adducts that are identical to those derived by CT osmylation. Indeed the close kinship between the thermal and charge-transfer activation of osmylation is underscored by the unique adduct (**2**) in which $OsO_4$ addition occurs exclusively to the terminal ring and not to the usual *meso* (9,10) positions of anthracene. The activation process to form the kindred adiabatic ion pair $[Ar^+, OsO_4^-]_s$ in the thermal osmylation provides the unifying theme in arene oxidation. Furthermore the promoted thermal osmylation of arenes *via* the five-coordinate pyridine analog $OsO_4Py$ is related to the widely used procedure for alkene bishydroxylation[88] and the same regiochemistry is observed, especially with anthracene donors, indicating that the activated complex for PT osmylation is strongly related to that for DT osmylation.

$$[Ar, OsO_4] \xrightarrow{h\nu_{CT}} [Ar^{+\bullet}, OsO_4^{-\bullet}] \xrightarrow{\text{fast}} ArOsO_4, \textit{etc.} \tag{25}$$

The variable regiochemistry observed in the collapse of $[Ar^{+\bullet}, OsO_4^{-\bullet}]$ to the cycloadduct $ArOsO_4$ underscores the importance of CIP structures in determining the course of electron-transfer oxidation. Since CIP structures are not readily determined as yet, the structural effects induced by qualitative changes in solvent polarity, salts, additives and temperature are reaction variables that must always be optimized in the synthetic utilization of electron-transfer oxidation by either thermal or photochemical activation.

### 7.4.5 ELECTRON-TRANSFER OXIDATION *VERSUS* ELECTROPHILIC OXIDATION

With oxidants such as $Mn^{VII}$, $Cr^{VI}$, $Bi^{V}$, $Pb^{IV}$, $Tl^{III}$, $Pd^{II}$, *etc.* (as well as most organic electron acceptors) that are capable of several electron changes, the multistep electron-transfer oxidation of an organic donor must be distinguished from the one-step electrophilic process. Thus a series of one-electron transformations will always have a concerted counterpart. This dichotomy can be considered in the oxidative thallation and mercuration of arenes with thallium(III) and mercury(II) trifluoroacetates, in which kinetic studies establish the principal active forms of the electrophile to be the cationic $Tl(O_2CCF_3)_2^+$ and the neutral $Hg(O_2CCF_3)_2$, respectively.[93] Thus the ionic dissociation of mercury(II) trifluoroacetate to the cation is not important, even in the polar trifluoroacetic acid with a dielectric constant of $\varepsilon_{CF_3CO_2H} = 42.1$. On the other hand, the uncharged form of thallium(III) trifluoroacetate is an inactive electrophile. As such, thallation requires prior dissociation primarily to the monocation for activation even in the nonpolar dichloromethane ($\varepsilon_{CH_2Cl_2} = 9.08$). The second dissociation to the dication (equation 26) can also be relevant (*vide infra*). Although the active electrophiles $Hg(O_2CCF_3)_3$ and $Tl(O_2CCF_3)_2^+$ are isoelectronic (and probably isostructural) species, they basically differ in the charge they bear. Accordingly, the activation processes for mercuration and thallation show strong similarities, although at the same time they exhibit some striking differences.

$$Tl(O_2CCF_3)_3 \rightleftharpoons Tl(O_2CCF_3)_2^+ + CF_3CO_2^- \rightleftharpoons TlO_2CCF_3^{2+} + 2\,CF_3CO_2^- \qquad (26)$$

#### 7.4.5.1 EDA Complexes as Intermediates in Mercuration and Thallation. Comparison of Their Ground and CT Excited States

Quantitative spectrophotometric analysis establishes the transient charge-transfer absorption spectra observed during mercuration and thallation to derive from the same electrophilic species involved in the kinetics, *viz.* $Hg(O_2CCF_3)_2$ and $Tl(O_2CCF_3)_2^+$, respectively. Indeed these species form two series of arene–EDA complexes, $[ArH,Hg(O_2CCF_3)_2]$ and $[ArH,Tl(O_2CCF_3)_2^+]$, which bear strong resemblances to each other, both in the ground state and in the CT excited state (CIP). Ground state similarities of the mercury(II) and thallium(III) EDA complexes are reflected in the linear relationship of the association constants (log *K*) in Figure 5(a), which indicates that the stabilization of both series of EDA complexes is affected in the same way with changes in the arene structure. The correlation with a slope of 1.4 indicates that the cationic complexes $[ArH,Tl(O_2CCF_3)_2^+]$ are stabilized about 40% more than their neutral counterparts $[ArH,Hg(O_2CCF_3)_2]$. CT excited state similarities of the arene complexes of $Hg(O_2CCF_3)_2$ and $Tl(O_2CCF_3)_2^+$ are revealed in the parallel trend in their absorption bands in Figure 5(b). Thus for weak electron donor–acceptor complexes of the type described as EDA complexes, the spectral transition $h\nu_{CT}$ represents an electronic excitation of the arene moiety from the neutral ground state to the contact ion pair, *i.e.* its photoionization to an electrophilic acceptor.[83] For the mercury(II) complexes the relevant CT transition corresponds to equation (27), and for the thallium(III) complexes it is as shown in equation (28).

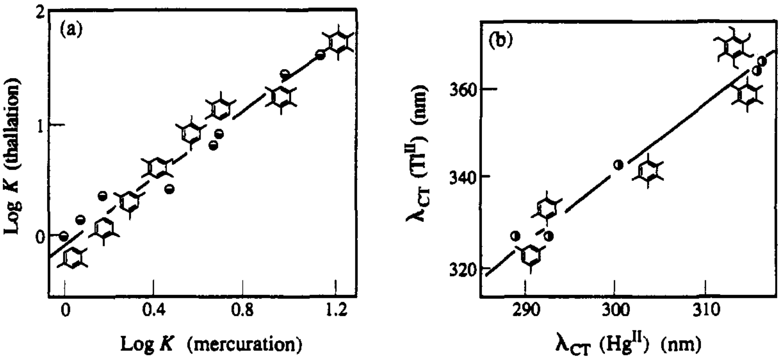

**Figure 5** Ground-state and excited-state similarities of the arene π-complex of mercury(II) and thallium(III), as shown by (a) association constants (*K*) and (b) CT absorption spectra ($\lambda_{CT}$)

$$[ArH,\ Hg^{II}(O_2CCF_3)_2] \xrightarrow{h\nu_{CT}} [ArH^{\bullet+},\ Hg^{I}(O_2CCF_3)_2^{\bullet-}\ ] \qquad (27)$$

$$[\mathrm{ArH}, \mathrm{Tl^{III}(O_2CCF_3)_2^+}] \xrightarrow{h\nu_{CT}} [\overset{+}{\mathrm{ArH}\bullet}, \mathrm{Tl^{II}(O_2CCF_3)_2\bullet}] \quad (28)$$

Both series of EDA complexes share the arene cation in the form of the radical pair shown in the brackets in equations (27) and (28), as the CT excited state according to expectations of Mulliken theory. The slope of 1.3 in the linear correlation (Figure 5b) indicates that the energy of the CT excitation of the cationic EDA complex from $Tl(O_2CCF_3)_2^+$ is merely ~30% more sensitive to changes in arene structure compared to that derived from $Hg(O_2CCF_3)_2$. Otherwise both series of EDA complexes show parallel behavior in the transformation to the CT excited state. The similarity in the EDA complexes of $Hg(O_2CCF_3)_2$ and $Tl(O_2CCF_3)_2^+$ with the series of sterically crowded 1,3,5-trialkylbenzenes indicates that the CT interaction occurs at relatively long range. The latter is confirmed by the pair of long Hg—C bond distances in the $\eta^2$-bonding of the electrophilic mercury(II) to the hexamethylbenzene donor as determined by X-ray crystallography.[94] As a result, any minor difference which may exist in the steric properties of $Hg(O_2CCF_3)_2$ and $Tl(O_2CCF_3)_2^+$ is expected to be obscured in the EDA complexes, both in the ground state and in the CT excited state.

### 7.4.5.2 Comparison of the Activation Barriers for Mercuration and Thallation

The kinetic studies also establish the neutral $Hg(O_2CCF_3)_2$ and the cationic $Tl(O_2CCF_3)_2^+$ to be the principal electrophiles in mercuration and thallation,[95] respectively. The reactivity trends in the two types of metallations are quantitatively compared with a graded series of arene ranging from the electron-rich mesitylene at one end to the least reactive arene chlorobenzene at the other extreme. The relative reactivity of an arene to electrophilic metallation is represented by the activation free energy difference: $\Delta G_r^\ddagger = -2.3RT \log k_{rel}$, where $k_{rel} = k/k_0$ represents the second-order rate constant relative to that of benzene ($k_0$) arbitrarily chosen as the reference arene. The direct comparison between mercuration and thallation is shown in Figure 6, in which the logarithms of the ratio of second-order rate constants for mercuration are plotted against those for thallation in trifluoroacetic acid. The striking linear free energy correlation spans more than six orders of magnitude in rate with a 1:1 relationship, as shown by the fit of the data to the line drawn with a slope of unity. In other words, those factors relevant to surmounting the activation barrier for mercuration are mirrored in exactly the same way during thallation as a consequence of systematic changes in the arene donor.

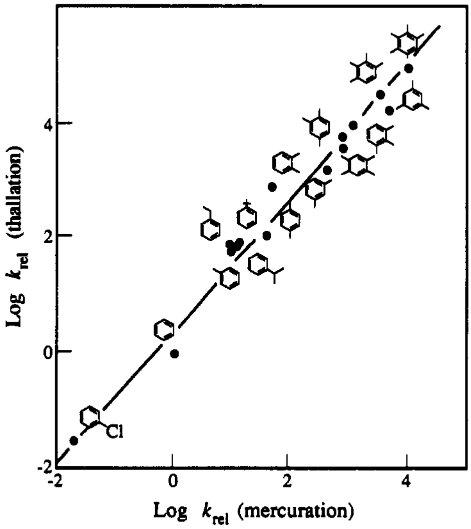

**Figure 6** Direct relationship of the relative reactivities ($k_{rel}$) of arenes in mercuration and thallation

### 7.4.5.3 Correlation of the Rates of Mercuration and Thallation with the CT Excitation Energies of the EDA Complexes

The relative reactivities of arenes to metallation are represented by the activation free energy difference $\Delta G_r^\ddagger$ (*vide supra*). In the same way, the transition energy $h\nu_{CT}$ associated with the charge-transfer excitation of the EDA complex can be evaluated from the absorption spectrum ($\lambda_{CT}$) by a similar comparative method, *i.e.* $\Delta h\nu_{CT} = h\nu_{CT} - h\nu^0_{CT}$, where $h\nu^0_{CT}$ is the CT transition energy of the benzene–EDA complex. In the comparative method the values of $\Delta h\nu_{CT}$ focus primarily on the contribution from the arene moiety, since the electrophile component largely cancels out in the difference procedure. In the correlation of the activation barriers with the CT excitation energies, a linear plot is observed for the CT transition energy with a slope of close to unity. In other words these mercuration rates relate to the CT excited state of the EDA complex with a free energy relationship described as: $\log k/k_0 = -\Delta h\nu_{CT}/2.3\,RT + \text{constant}$.

### 7.4.5.4 The Relevance of Arene Radical Cations in Electrophilic Aromatic Substitution

The linear free energy relationship observed for arene donors relates the activation barrier $\Delta G^\ddagger$ for aromatic substitution directly to the CT transition energy $h\nu_{CT}$ of the EDA complex. Since $h\nu_{CT}$ pertains to the energetics of the photoionizations in equations (27) and (28), the correlation suggests that these arene contact ion pairs are reasonable approximations to the transition states for both mercuration and thallation, *e.g.* Scheme 6.

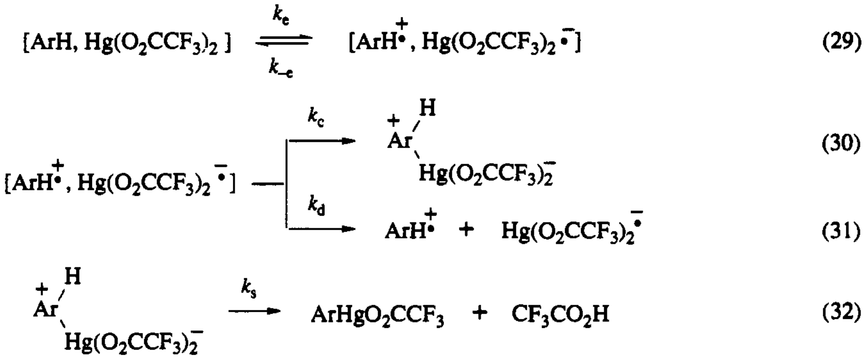

$$[\mathrm{ArH, Hg(O_2CCF_3)_2}] \underset{k_{-e}}{\overset{k_e}{\rightleftharpoons}} [\mathrm{Ar\overset{+}{H}^{\bullet}, Hg(O_2CCF_3)_2{}^{\bullet}{}^{-}}] \qquad (29)$$

$$[\mathrm{Ar\overset{+}{H}^{\bullet}, Hg(O_2CCF_3)_2{}^{\bullet}{}^{-}}] \xrightarrow{k_c} \mathrm{\overset{+}{Ar}(H)Hg(O_2CCF_3)_2^-} \qquad (30)$$

$$[\mathrm{Ar\overset{+}{H}^{\bullet}, Hg(O_2CCF_3)_2{}^{\bullet}{}^{-}}] \xrightarrow{k_d} \mathrm{Ar\overset{+}{H}^{\bullet}} + \mathrm{Hg(O_2CCF_3)_2{}^{\bullet}{}^{-}} \qquad (31)$$

$$\mathrm{\overset{+}{Ar}(H)Hg(O_2CCF_3)_2^-} \xrightarrow{k_s} \mathrm{ArHgO_2CCF_3} + \mathrm{CF_3CO_2H} \qquad (32)$$

Scheme 6

In Scheme 6 the activation step for electrophilic substitution proceeds by electron transfer ($k_e$) to the arene ion pair, which is to be likened to the photoactivation of the EDA complex in equations (27) and (28). The substitution product determining process ($k_s$) is then dependent on the rate constants $k_c$ and $k_d$ for collapse to the Wheland intermediate and diffusive separation to free ions, respectively. Since the rate constant $k_d$ is likely to be invariant between a given electrophile and a series of structurally related arenes, the rate of aromatic substitution will be strongly mediated by the value of $k_c$. As the rate of arene ion pair collapse is retarded, the competition from back electron transfer ($k_{-e}$) will become increasingly important. Under these circumstances the reaction rate will no longer follow the linear free energy relationship (*vide supra*). Indeed at some point back electron transfer will dominate (*i.e.* $k_{-e} >> k_c$), and it is conceivable that little or no thermal reaction will take place. The experimental variables pertaining to electronic effects, steric effects, solvent effects, and product studies can be reconciled with Scheme 6 in terms of the facility with which such an arene ion pair collapses. For example, electronic effects in the collapse of the arene ion pair can be viewed as the influence of substituents on the spin density in the singly occupied orbital (SOMO) requisite to bond formation in equation (30). With mesitylene as the donor, the pair collapse at any of the three unsubstituted nuclear positions is unimpeded since the SOMO is degenerate. Similarly the SOMOs in the cations of *p*-xylene, *m*-xylene, and pseudocumene are conducive to pair collapse at the free positions owing to the available spin densities. By contrast, the SOMOs of the cations of durene and pentamethylbenzene have nodes at the free 3- and 6-positions and collapse therefore is not favored at these positions. Indeed the lack of spin density at these positions of durene and pentamethylbenzene cations accords with the observed magnitudes of the $^1$H hyperfine splittings in the ESR spectra,[96] *i.e.* (6) and (7) respectively.

Thus the pair collapse of durene and pentamethylbenzene cations is only favored at the already substituted *ipso* positions, and is probably a reversible process. Product studies provide a divergent view of

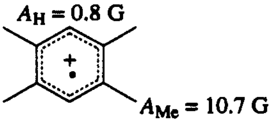

**(6)**

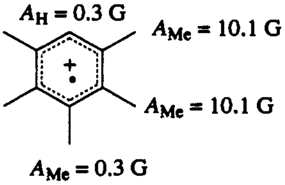

**(7)**

the arene ion pair collapse during mercuration and thallation. The dichotomy is most pronounced in pentamethylbenzene. Thus the treatment of pentamethylbenzene with $Hg(O_2CCF_3)_2$ affords the substitution product pentamethylphenylmercury trifluoroacetate in high yields (equation 33).

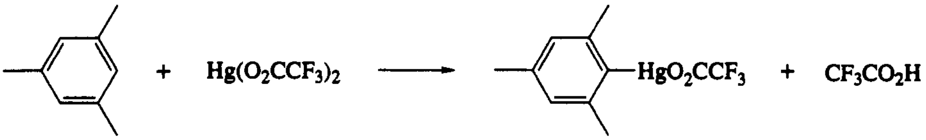

(33)

No transient intermediates other than the π-complex are observed in either the UV–visible or ESR spectra. On the other hand, the thallation of pentamethylbenzene proceeds only 26% to nuclear substitution, the remainder being accounted for by side products resulting from side chain substitution and dimer formation (equation 34).

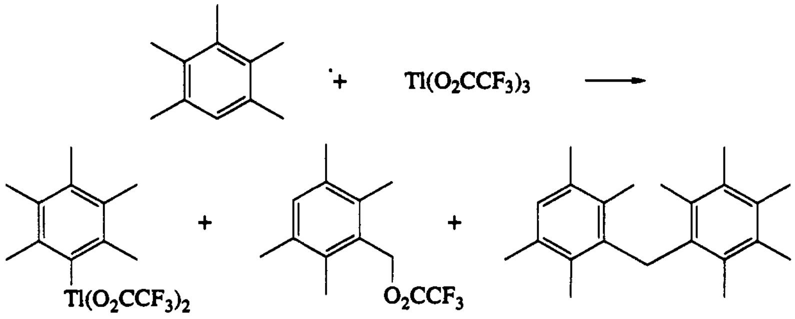

(34)

Such side products are known to derive from the radical cation of pentamethylbenzene,[9] *i.e.* equations (35) and (36).

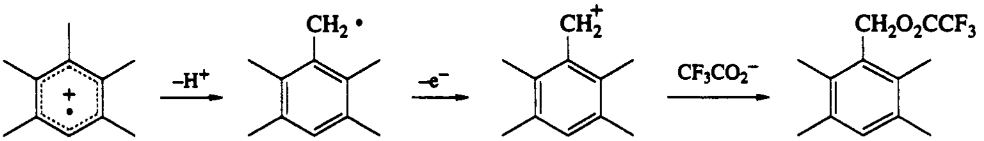

(35)

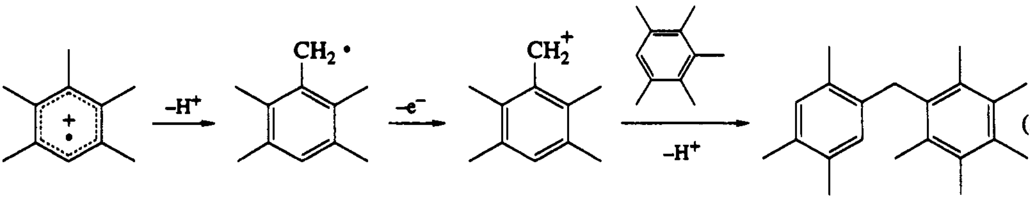

(36)

Indeed the diversion to side products during thallation coincides with the direct observation of the arene radical cation as a transient intermediate both by UV–visible and ESR spectroscopy. A similar dichotomy between the products of mercuration and thallation exists with durene, albeit to a lesser degree. Finally no discrepancy is observed with mesitylene, nuclear substitution occurring exclusively in both mercuration and thallation. Such a divergence between mercuration and thallation can be reconciled by the formulation in Scheme 6 if they differ by the extent to which diffusive separation ($k_d$) occurs in equation (31). All factors being the same, diffusive separation of the radical pair from thallium(III) should occur more readily than that from mercury(II) owing to a significant difference in the coulombic interactions, the arene ion being paired with the anionic $\text{Hg}^{\text{I}}(\text{O}_2\text{CCF}_3)_2^-$ in mercuration and with the neutral $\text{Tl}^{\text{II}}(\text{O}_2\text{CCF}_3)_2$ in thallation, as described in equations (27) and (28). Moreover the same electrostatic argument provides a ready rationalization for the ability of Lewis acids as additives to promote arene radical cation formation (leading to biaryls) during both mercuration and thallation of even unexceptional arenes.[97] Thus the addition of boron trifluoride (as the etherate) will foster ionic dissociation of mercury(II) trifluoroacetate, *i.e.* equation (37), as well as thallium(II) trifluoroacetate cation, *i.e.* equation (38).

$$\text{Hg}(\text{O}_2\text{CCF}_3)_2 + \text{BF}_3 \rightleftharpoons \text{HgO}_2\text{CCF}_3^{\,+} + \text{CF}_3\text{CO}_2\text{BF}_3^{\,-} \qquad (37)$$

$$\text{Tl}(\text{O}_2\text{CCF}_3)_2^{\,+} + \text{BF}_3 \rightleftharpoons \text{TlO}_2\text{CCF}_3^{\,2+} + \text{CF}_3\text{CO}_2\text{BF}_3^{\,-} \qquad (38)$$

The results lead to a diminution in the coulombic interaction in the radical pair $[\text{ArH}^{+\bullet},\text{Hg}^{\text{I}}\text{O}_2\text{CCF}_3]$ during mercuration, and enhancement of the coulombic repulsion in the radical pair $[\text{ArH}^{+\bullet},\text{Tl}^{\text{II}}\text{O}_2\text{CCF}_3^{\,+}]$ during thallation. In both cases the increased amounts of cage escape will lead to a higher component of electron transfer derived products (such as biaryls). Attractive as such a simple electrostatic explanation may seem, cognizance must also be taken of the attendant change in the driving force for back electron transfer $k_{-e}$ in equation (29).

### 7.4.5.5 Electron Transfer *versus* Electrophilic Pathways for Aromatic Substitution

The study of mercuration and thallation provides a sharp focus on the experimental delineation of stepwise and concerted mechanisms for arene activation. Thus the unequivocal demonstration of arene radical cations as key intermediates in thallation, particularly of durene and pentamethylbenzene, is consistent with a stepwise (electron-transfer) mechanism for arene activation (compare Scheme 6[98] and equation 39).

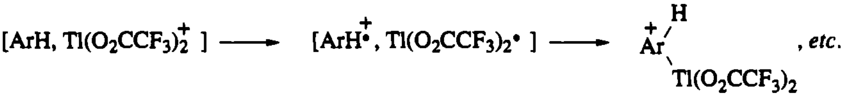

$$[\text{ArH}, \text{Tl}(\text{O}_2\text{CCF}_3)_2^{\,+}] \longrightarrow [\overset{+}{\text{ArH}^{\bullet}}, \text{Tl}(\text{O}_2\text{CCF}_3)_2^{\bullet}] \longrightarrow \overset{+}{\text{Ar}}\begin{matrix}\text{H}\\ \text{Tl}(\text{O}_2\text{CCF}_3)_2\end{matrix}, \textit{etc.} \qquad (39)$$

By the same token, the singular absence of any experimental evidence for such intermediates during mercuration is directly accommodated by a concerted (electrophilic) mechanism for arene activation, *i.e.* equation (40).

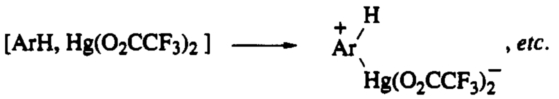

$$[\text{ArH}, \text{Hg}(\text{O}_2\text{CCF}_3)_2] \longrightarrow \overset{+}{\text{Ar}}\begin{matrix}\text{H}\\ \text{Hg}(\text{O}_2\text{CCF}_3)_2^{\,-}\end{matrix}, \textit{etc.} \qquad (40)$$

The difficulty with two separate mechanisms for arene activation by mercury(II) and thallium(III) is underscored by the striking correlation in Figure 6 which establishes the activation barriers to follow identical trends. In other words the rate-determining processes for mercuration and thallation are similar yet they distinctly differ in the products derived for the electron-rich arenes (durene and pentamethylbenzene in equation 35). Such a kinetics situation commonly demands that there exists at least one intermediate which separates the activation process from the products, as in Scheme 6. This paradox can be resolved in one of two ways. Firstly, the formulation in Scheme 6 merges stepwise and concerted processes by the modulation of a pair of rate constants. According to Scheme 6, the two principal pathways are differentiated during the competition between cage collapse ($k_c$) and diffusive separation ($k_d$) of the arene ion pair. The inability to observe the arene cation (*e.g.* from mesitylene) could be attributed to a rate of cage collapse to the Wheland intermediate occurring substantially faster than diffusive separation (*i.e.* $k_c >> k_d$), which is tantamount to a concerted process. Likewise the ESR observation of the arene cation would derive from a diffusive process occurring faster than collapse (*i.e.* $k_c << k_d$), which could appear as a stepwise process. Some of the structural and environmental factors which influence both rate constants have been presented in the discussion above. However this mechanism is not without its problems since it does not as yet address the observed kinetic isotope effects in a quantitative way (*vide supra*). Secondly, the stepwise and concerted processes for arene activation may simply represent competing pathways, namely equations (41) and (42), where the superscript ‡ represents the activated complex. If so those factors related to the donor properties of arenes, such as EDA complex formation, CT excitation, activation barriers, *etc.*, are too common to both to allow any distinction between these pathways. Moreover the common dependence on isoelectronic electrophiles, independent of charge, further obscures any difference in their transition states. This formulation thus recognizes two such dissimilar mechanisms as electron transfer and electrophilic processes in mercuration and thallation to be remarkably alike. Crucial to the resolution of this dilemma is the understanding of the stepwise process for arene activation. Particularly germane are the microdynamics of the contact ion pairs in Scheme 6, especially as they collapse or evolve to 'loose' (solvent-separated) ion pairs and finally to 'free' (separate) pairs of radicals, as described in Section 7.4.4.

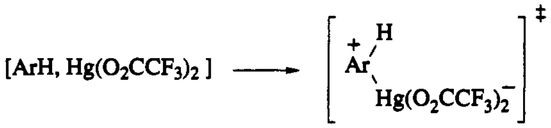

$$[\mathrm{ArH}, \mathrm{Hg(O_2CCF_3)_2}] \longrightarrow \left[\overset{+}{\mathrm{Ar}}\genfrac{}{}{0pt}{}{\diagup\mathrm{H}}{\diagdown\mathrm{Hg(O_2CCF_3)_2^-}}\right]^{\ddagger} \tag{41}$$

$$[\mathrm{ArH}, \mathrm{Tl(O_2CCF_3)_2^+}] \longrightarrow [\overset{+}{\mathrm{ArH}}{}^{\bullet}, \mathrm{Tl(O_2CCF_3)_2}]^{\ddagger} \tag{42}$$

## 7.4.6 SYNTHETIC TRANSFORMATIONS *VIA* ELECTRON-TRANSFER OXIDATION

The foregoing elements of electron-transfer oxidation presented in terms of the energetics (Section 7.4.2) of contact ion-pair $[\mathrm{RH}^{+\bullet},\mathrm{A}^{-\bullet}]$ formation (Section 7.4.1) and the generic reactions of the individual organic radical cations (Section 7.4.3.1) and acceptor radical anions (Section 7.4.3.3), allow a variety of thermal and photochemical processes (Section 7.4.4) to be predicted in terms of CIP behavior (Section 7.4.5). The following examples are from the chemical literature and only the reactants, principal products and predominant methodologies are included. They are deliberately chosen to illustrate how electron-transfer oxidations can be utilized in various types of synthetic transformations. Representative citations to the original literature are included to facilitate the delineation of the roles of radical cations and anions in sometimes complex pathways. Accordingly, the examples in Section 7.4.6.1 and Section 7.4.6.2 are presented in the same sequence as the generic reactions are listed in Section 7.4.3.1 for organic radical cations ($\mathrm{RH}^{+\bullet}$) and in Section 7.4.3.3 for acceptor radical anions ($\mathrm{A}^{-\bullet}$), respectively. For conciseness and generality the complete structures are avoided, and the following abbreviations employed: Ar (aromatic moiety); R (aliphatic moiety); Z (CN); E ($\mathrm{CO_2Et}$); M ($\mathrm{CO_2Me}$); Py (pyridine); $\mathrm{BA}^{+\bullet}$ [tris(*p*-bromophenyl)aminium]; $h\nu_{\mathrm{CT}}$ (charge-transfer activation); $h\nu_{\mathrm{A}}$ (acceptor (sensitizer not specified) activation); $h\nu$ (general photochemical activation unspecified). A blank space over the arrow represents thermal activation, and only the principal products are given.

### 7.4.6.1 Donor Radical Cations

#### *7.4.6.1.1 α-Fragmentation*

(a)

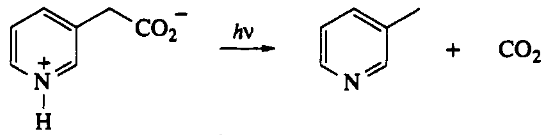

(ref. 99)

(b)

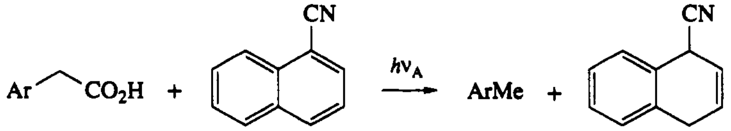

(ref. 100)

(c)

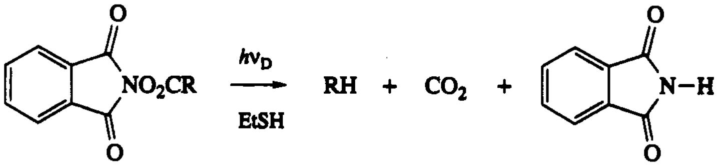
NO2CR
hνD
EtSH
RH + CO2 +
N–H

(ref. 101)

(d)

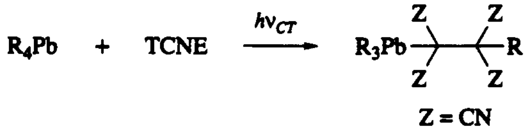
R4Pb + TCNE
hνCT
R3Pb
R
Z
Z = CN

(ref. 102)

(e)

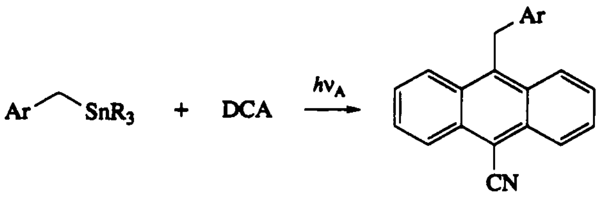
Ar
SnR3
+ DCA
hνA
Ar
CN

(ref. 103)

(f)

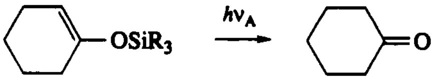

(ref. 104)

(g)

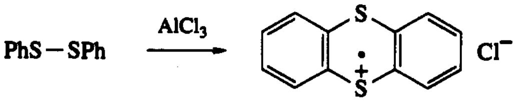
PhS – SPh
AlCl3
S
S
Cl⁻

(ref. 105)

(h)

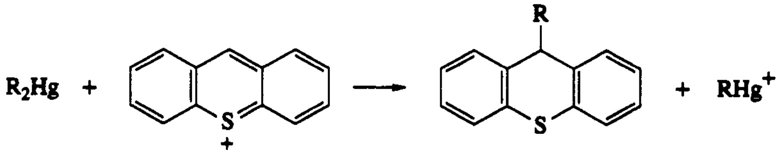
R2Hg +
S
R
S
+ RHg+

(ref. 106)

### 7.4.6.1.2 β-Fragmentation

(a)

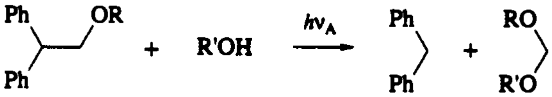
Ph
OR
Ph
+ R'OH
hνA
Ph
Ph
+
RO
R'O

(ref. 107)

(b)

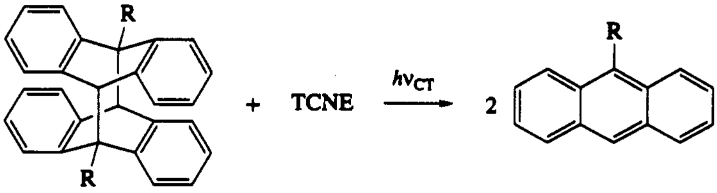
R
R
+ TCNE
hνCT
2
R

(ref. 108)

(c)

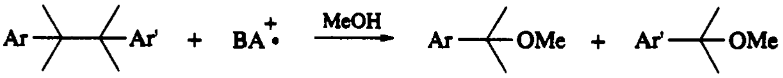
Ar
Ar'
+ BA+•
MeOH
Ar
OMe
+ Ar'
OMe

(ref. 109)

(d)

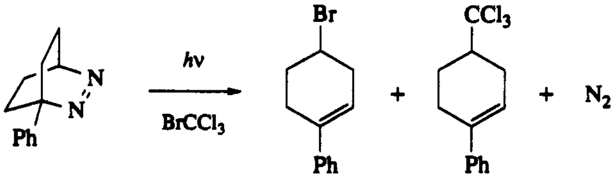
N
N
Ph
hν
BrCCl3
Br
Ph
+
CCl3
Ph
+ N2

(ref. 110)

### 7.4.6.1.3 Rearrangement

(a)

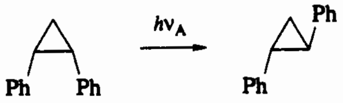
Ph
Ph
$h\nu_A$
Ph
Ph

(ref. 111)

(b)

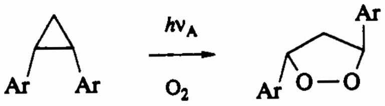
Ar
Ar
$h\nu_A$
$O_2$
Ar
Ar
O—O

(ref. 112)

(c)

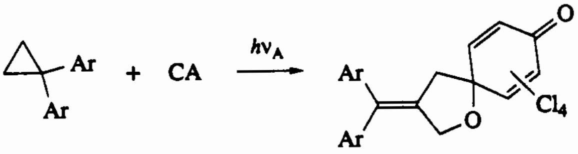
Ar
Ar
+ CA
$h\nu_A$
O
Ar
Ar
O
$Cl_4$

(ref. 113)

(d)

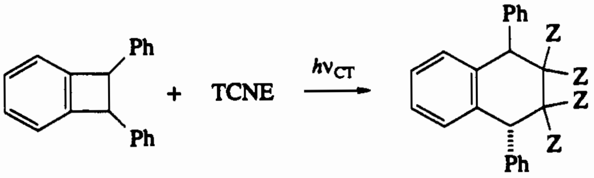
Ph
Ph
+ TCNE
$h\nu_{CT}$
Ph
Z
Z
Z
Z
Ph

Z = CN

(ref. 114)

(e)

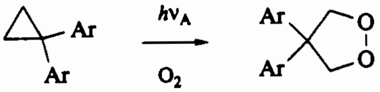
Ar
Ar
$h\nu_A$
$O_2$
Ar
Ar
O
O

(ref. 115)

(f)

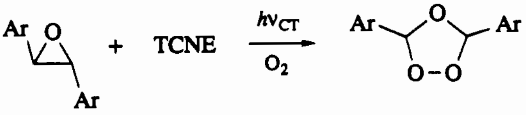
Ar
O
Ar
+ TCNE
$h\nu_{CT}$
$O_2$
Ar
O
Ar
O–O

(ref. 116)

(g)

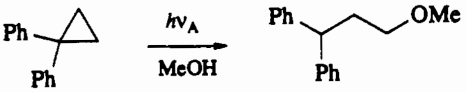
Ph
Ph
$h\nu_A$
MeOH
Ph
OMe
Ph

(ref. 117)

(h)

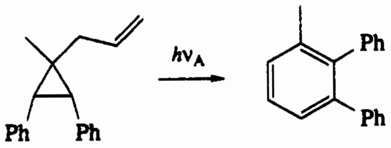
Ph
Ph
$h\nu_A$
Ph
Ph

(ref. 118)

(i)

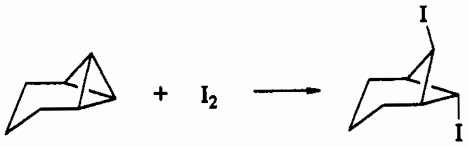

(ref. 119)

### *7.4.6.1.4 Cyclization*

(a)

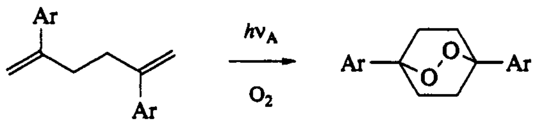
Ar
Ar
$h\nu_A$
$O_2$
Ar
O
O
Ar

(ref. 120)

(b)

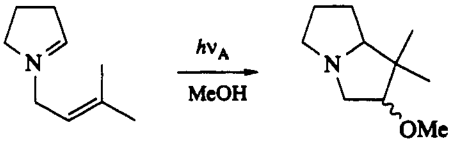
N
$h\nu_A$
MeOH
N
OMe

(ref. 121)

(c)

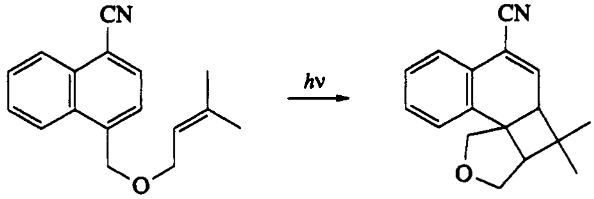

(ref. 122)

(d)

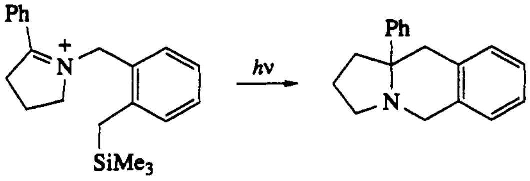
Ph
+
N
SiMe₃
$h\nu$
Ph
N

(ref. 123)

(e)

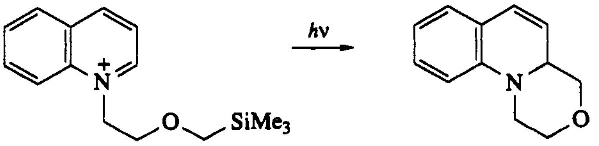
+
N
O
SiMe₃
$h\nu$
N
O

(ref. 124)

(f)

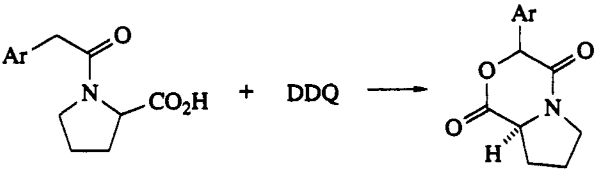
Ar
O
N
CO₂H
+
DDQ
Ar
O
O
N
O
H

(2*S*,5*S*)

(ref. 125)

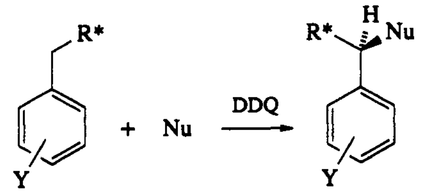
R*
Y
+
Nu
DDQ
H
R*
Nu
Y

R* = chiral

(ref. 125)

(g)

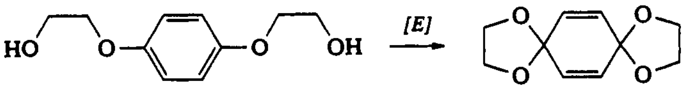
HO
O
O
OH
[E]
O
O
O
O

(ref. 126)

### 7.4.6.1.5 Deprotonation

(a)

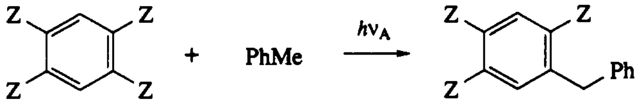
Z
Z
Z
Z
+ PhMe
hν_A
Z
Z
Z
Ph

(ref. 127)

(b)

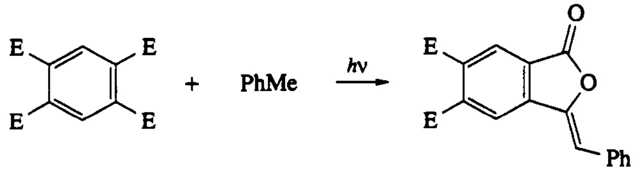
E
E
E
E
+ PhMe
hν
E
E
O
O
Ph

(ref. 128)

(c)

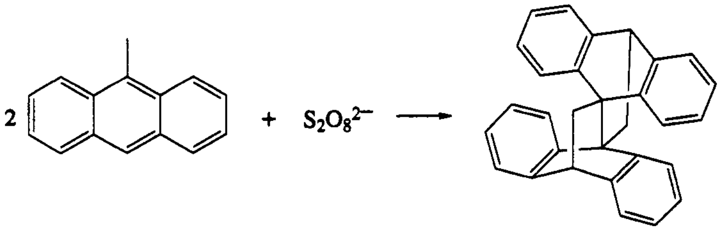

(ref. 129)

(d)

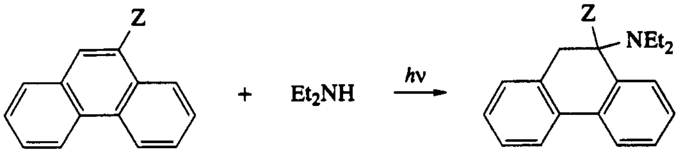
Z
+ Et2NH
hν
Z
NEt2

(ref. 130)

(e)

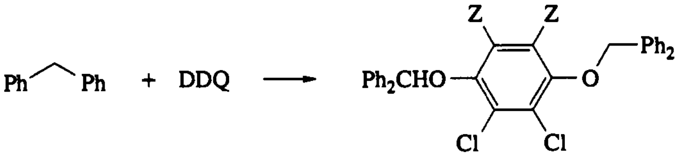
Ph
Ph
+ DDQ
Z
Z
Ph2CHO
O
Ph2
Cl
Cl

(ref. 131)

(f)

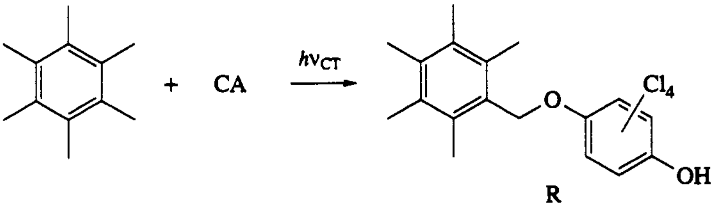
+ CA
hν_CT
O
Cl4
OH

(ref. 132)

(g)

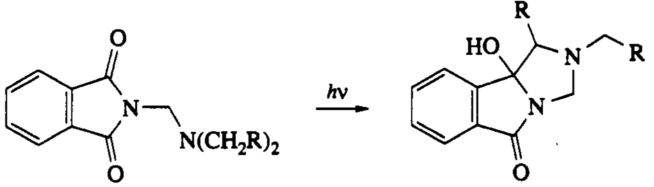
O
N
N(CH2R)2
O
hν
R
HO
N
R
N
O

(ref. 133)

(h)

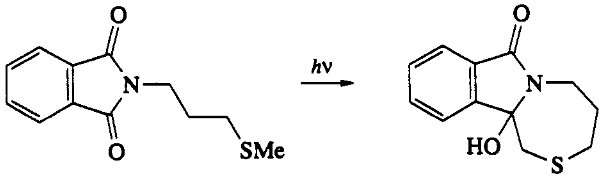
O
N
SMe
O
hν
O
N
HO
S

(ref. 134)

(i) $PhNMe_2 + PyO \xrightarrow{h\nu_{CT}} PhNHMe + H_2CO + Py$ (ref. 135)

### *7.4.6.1.6 Nucleophilic addition*

(a) $\mathrm{ArH} + \mathrm{C(NO_2)_4} \xrightarrow{h\nu_{CT}} \mathrm{ArC(NO_2)_3} + \mathrm{HONO}$ (ref. 136)

(b)

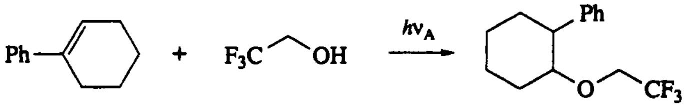
Ph
F₃C
OH
hν_A
Ph
O
CF₃

(ref. 137)

(c)

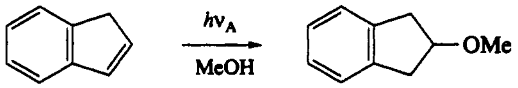
hν_A
MeOH
OMe

(ref. 138)

(d) $\mathrm{ArF} + \mathrm{AcO^-} \xrightarrow{[E]} \mathrm{ArOAc} + \mathrm{F^-}$ (ref. 139)

(e)

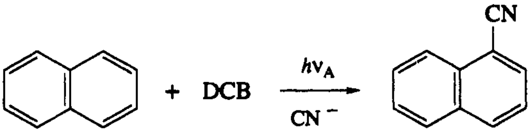
DCB
hν_A
CN⁻
CN

(ref. 140)

(f) $\mathrm{ArH} + \mathrm{XeF_2} \longrightarrow \mathrm{ArF} + \mathrm{HF} + \mathrm{Xe}$ (ref. 141)

(g) $\mathrm{ArH} + \mathrm{WCl_6} \longrightarrow \mathrm{ArCl}$ (ref. 142)

(h)

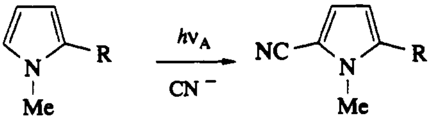
N
Me
R
hν_A
CN⁻
NC
N
Me
R

(ref. 143)

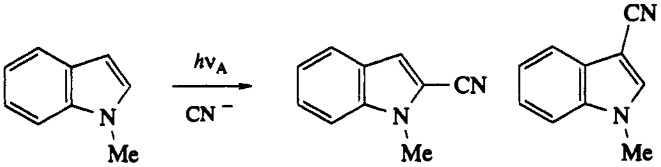
N
Me
hν_A
CN⁻
CN
N
Me
CN
N
Me

(ref. 143)

(i)

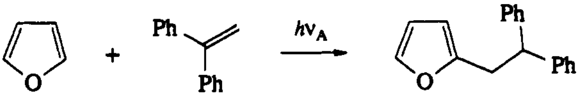
O
Ph
Ph
hν_A
Ph
O
Ph

(ref. 144)

(j)

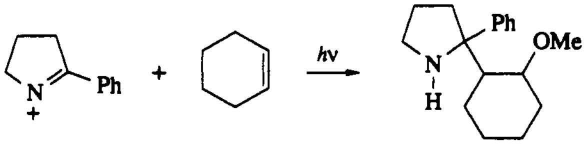
N
+
Ph
hν
Ph
N
H
OMe

(ref. 121)

(k)

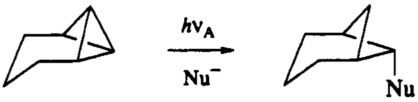

(ref. 145)

### 7.4.6.1.7 Dimerization

(a)

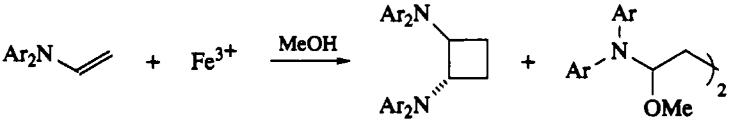
Ar$_2$N
+
Fe$^{3+}$
MeOH
Ar$_2$N
Ar$_2$N
+
Ar
N
Ar
OMe
2

(ref. 146)

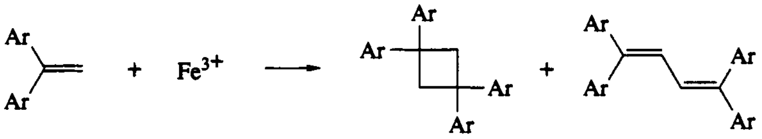
Ar
Ar
+
Fe$^{3+}$
Ar
Ar
Ar
Ar
+
Ar
Ar
Ar
Ar

(ref. 146)

(b)

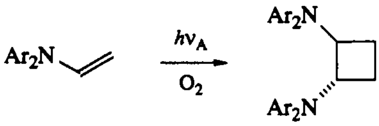
Ar$_2$N
$h\nu_A$
O$_2$
Ar$_2$N
Ar$_2$N

(ref. 147)

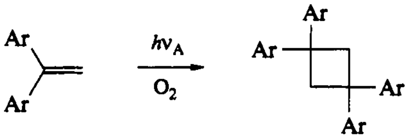
Ar
Ar
$h\nu_A$
O$_2$
Ar
Ar
Ar
Ar

(ref. 147)

(c)

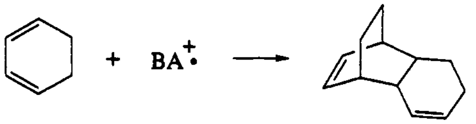

(ref. 148)

(d)

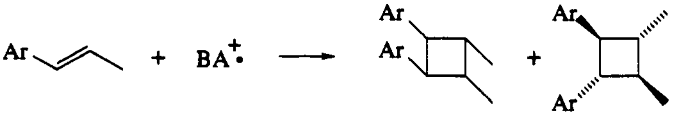
Ar
+
BA$^{+\bullet}$
Ar
Ar
+
Ar
Ar

(ref. 149)

(e)

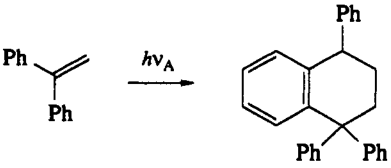
Ph
Ph
$h\nu_A$
Ph
Ph
Ph

(ref. 150)

(f) $\mathrm{ArH} + \mathrm{NO_2}^+ \longrightarrow \mathrm{Ar{-}Ar} + \mathrm{NO_2}$ (ref. 151)

### *7.4.6.1.8 Cycloaddition*

(a)

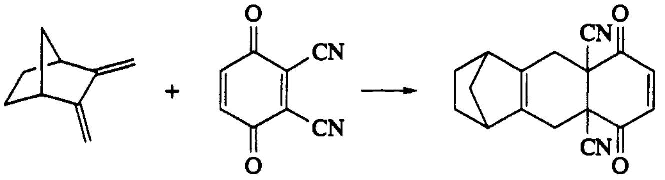
O
CN
CN
O
O
CN
CN
O

(ref. 152)

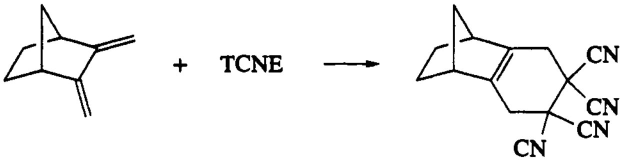
TCNE
CN
CN
CN
CN

(ref. 152)

(b)

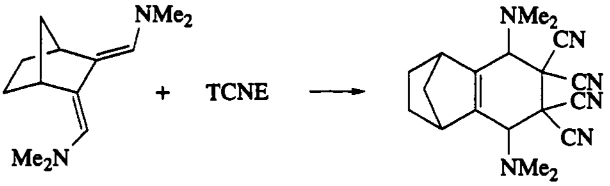
NMe$_2$
Me$_2$N
TCNE
NMe$_2$
CN
CN
CN
CN
NMe$_2$

(ref. 153)

(c)

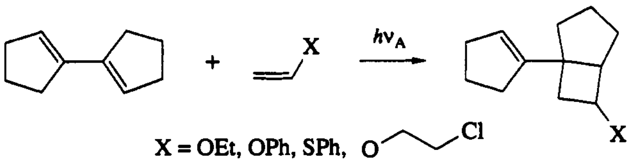
X
$h\nu_A$
X
X = OEt, OPh, SPh, O⌒⌒Cl

(ref. 154)

(d)

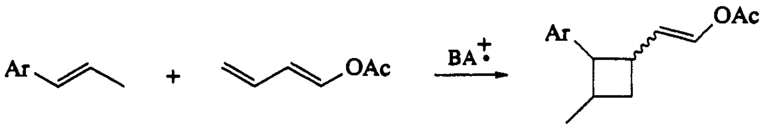
Ar
OAc
BA$^{+\bullet}$
Ar
OAc

(ref. 154)

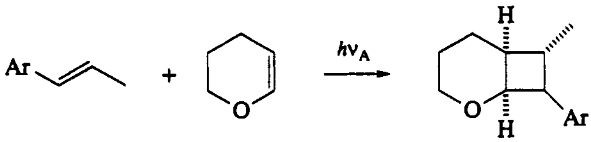
Ar
O
$h\nu_A$
H
O
H
Ar

(ref. 149)

(e)

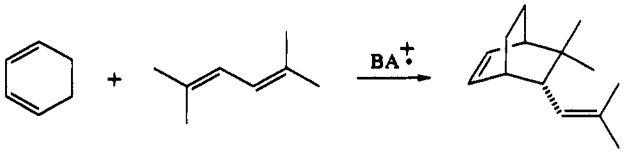

(ref. 148)

(f)

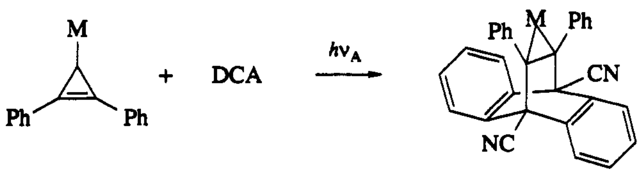
M
Ph
Ph
DCA
$h\nu_A$
Ph
M
Ph
CN
NC

(ref. 155)

### 7.4.6.1.9 Homolytic addition

(a)

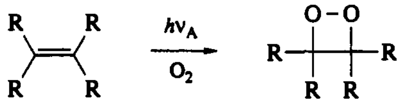
R
R
R
R
hν_A
O₂
O–O
R
R
R R

(ref. 156)

(b)

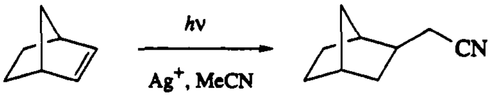
hν
Ag⁺, MeCN
CN

(ref. 157)

(c)

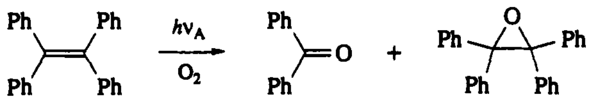
Ph Ph Ph Ph
hν_A
O₂
Ph Ph O
+
O Ph Ph Ph Ph

(ref. 158)

(d)

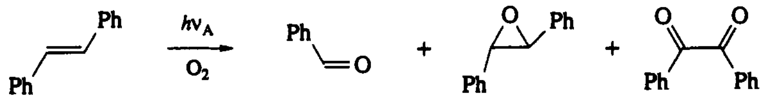
Ph Ph
hν_A
O₂
Ph O
+
O Ph Ph
+
O O Ph Ph

(ref. 159)

(e)

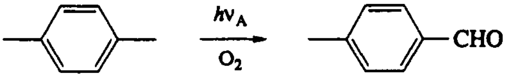

(ref. 160)

(f)

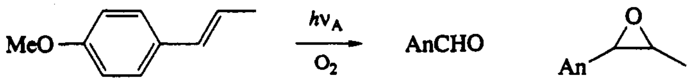
MeO
hν_A
O₂
AnCHO
O
An

(ref. 161)

(g) $ArH + C(NO_2)_4 \xrightarrow{h\nu_{CT}} ArNO_2 + HC(NO_2)_3$ (ref. 162)

(h)

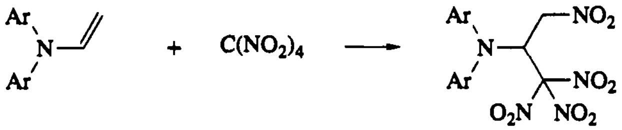
Ar N Ar
+
C(NO₂)₄
Ar N Ar
NO₂
NO₂
O₂N NO₂

(ref. 163)

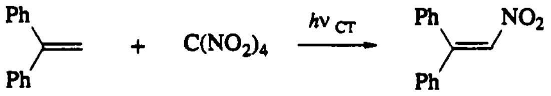
Ph Ph
+
C(NO₂)₄
hν_CT
Ph NO₂ Ph

(ref. 163)

(i)

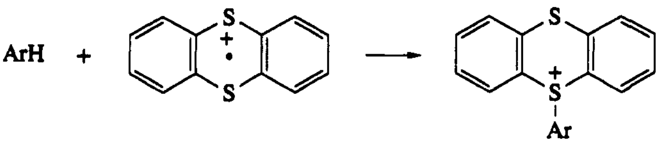

(ref. 164)

#### *7.4.6.1.10 Electron transfer*

(a)

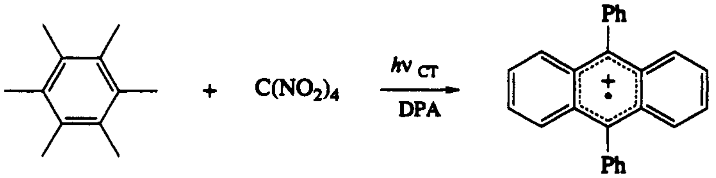
+
C(NO2)4
hν CT
DPA
Ph
Ph

(ref. 165)

(b)

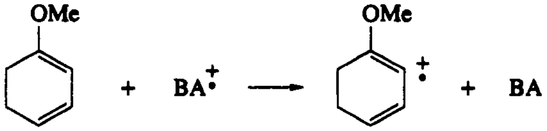
OMe
+ BA•+
OMe
+ BA

(ref. 166)

(c)

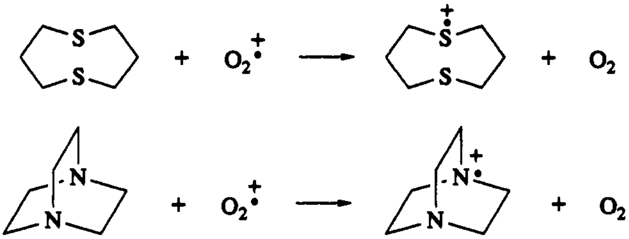
S
S
+ O2•+
S
S
+ O2
N
N
+ O2•+
N
N
+ O2

(ref. 167)

(ref. 167)

(d) $C_6F_6 + O_2^{\bullet +} \longrightarrow C_6F_6^{\bullet +} + O_2$ (ref. 168)

### 7.4.6.2 Acceptor Radical Anions

#### *7.4.6.2.1 Fragmentation*

(a)

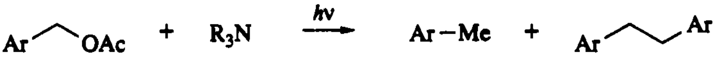
Ar
OAc
+ R3N
hν
Ar−Me
+
Ar
Ar

(ref. 169)

(b)

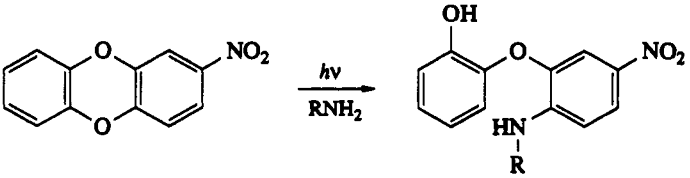
O
O
NO2
hν
RNH2
OH
O
NO2
HN
R

(ref. 170)

(c)

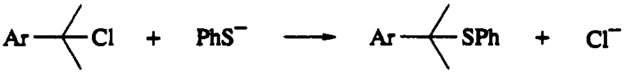
Ar
Cl
+ PhS−
Ar
SPh
+ Cl−

(ref. 171)

(d)

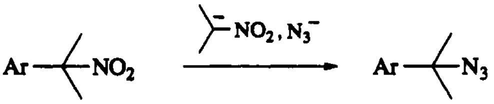
Ar
NO2
NO2, N3−
Ar
N3

(ref. 172)

(e)

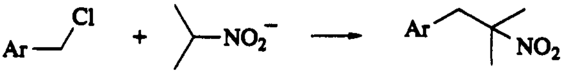
Cl
Ar
+
NO2−
Ar
NO2

(ref. 173)

(f) $RNO_2 + Bu_3SnH \longrightarrow RH + NO_2^-$ (ref. 174)

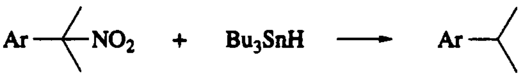
Ar
NO2
+ Bu3SnH
Ar

(ref. 175)

(g)

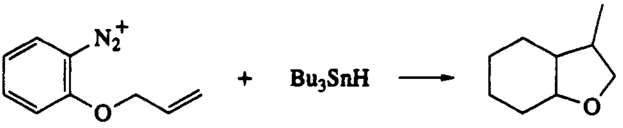
N2+
O
+ Bu3SnH
O

(ref. 176)

(h)

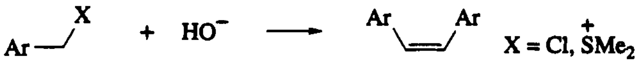
Ar
X
+ HO−
Ar
Ar
X = Cl, S+Me2

(ref. 177)

(i)

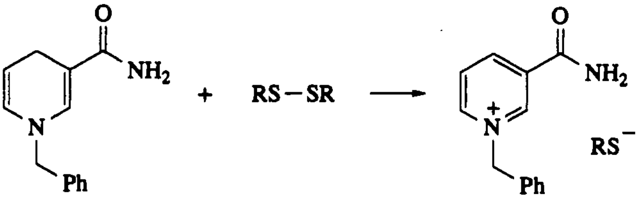
O
NH2
N
Ph
+ RS−SR
O
NH2
N+
RS−
Ph

(ref. 178)

(j)

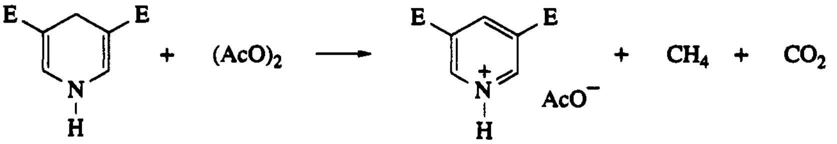
E
E
N
H
+ (AcO)2
E
E
N+
H
AcO−
+ CH4 + CO2

(ref. 179)

(k)

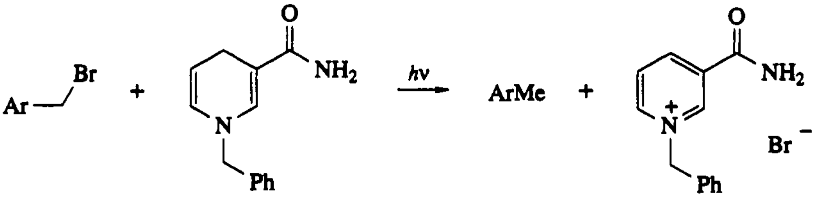
Br
Ar
+
O
NH2
N
Ph
hν
ArMe
+
O
NH2
N+
Br−
Ph

(ref. 180)

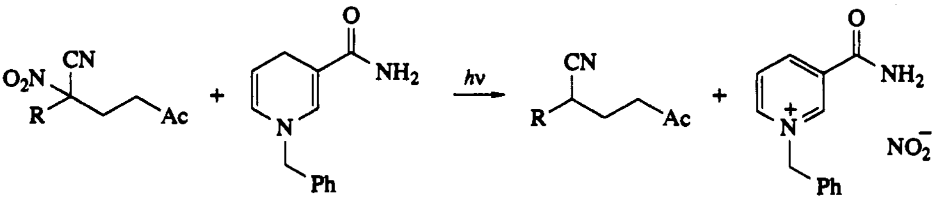
O2N
CN
R
Ac
+
O
NH2
N
Ph
hν
CN
R
Ac
+
O
NH2
N+
NO2−
Ph

(l) 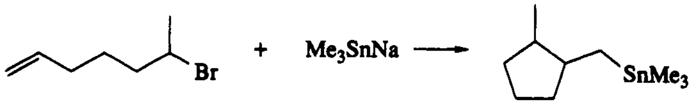 (ref. 181)

### 7.4.6.2.2 Protonation

(a) 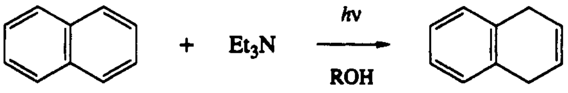 (ref. 182)

(b) 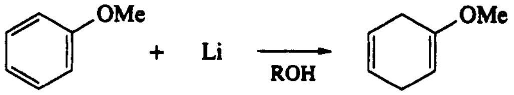 (ref. 183)

### 7.4.6.2.3 Electrophilic addition

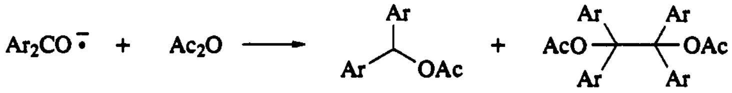 (ref. 184)

### 7.4.6.2.4 Electron transfer

(a) 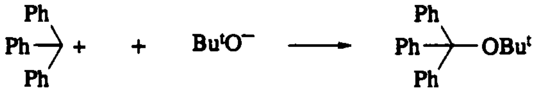 (ref. 185)

(b) $ArN_2^+ + PhO^- \longrightarrow Ar{-}O{-}Ph + N_2$ (ref. 186)

(c) $O_2 \xrightarrow[D]{h\nu_A} O_2^{\bullet -}$ (ref. 187)

### 7.4.6.2.5 Dimerization/disproportionation

(a) 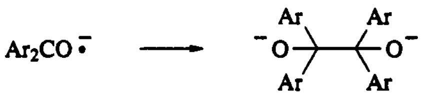 (ref. 188)

(b) 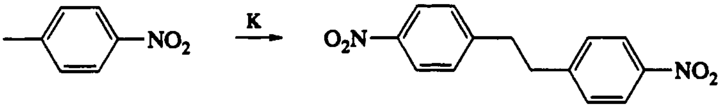 (ref. 189)

(c) $ArN_2^+ + I^- \longrightarrow Ar{-}Ar + N_2$ (ref. 190)

(d) 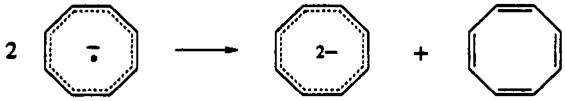 (ref. 191)

## ACKNOWLEDGMENTS

I thank S. Sankararaman and T. M. Bockman for their invaluable help and illuminating discussions in the preparation of this chapter.

## 7.4.7 REFERENCES

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2. A. Ledwith, *Acc. Chem. Res.*, 1972, **5**, 133.
3. A. J. Bard, A. Ledwith and H. J. Shine, *Adv. Phys. Org. Chem.*, 1976, **13**, 156.
4. D. J. Mackinnon and W. A. Waters, *J. Chem. Soc.*, 1953, 323.
5. I. V. Khudyakov and V. A. Kuz'min, *Russ. Chem. Rev. (Engl. Transl.)*, 1978, **47**, 22.
6. J. K. Kochi, 'Free Radicals', Wiley, New York, 1973, vol. 1, p. 591.
7. By convention, the electrode potentials for redox are referred to only in terms of reduction ($E^\circ_{red}$). For electron-transfer oxidation, however, the values of $E^\circ_{ox}$ are employed for RH donors here with the understanding that $E^\circ_{ox} = -E^\circ_{red}$ of the radical cation.
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11. R. S. Davidson, *Adv. Phys. Org. Chem.*, 1983, **19**, 1; *Molecular Association*, 1975, **1**, 216.
12. G. Jones, II, 'Photochemistry and Photophysics of Organic Charge-Transfer Complexes,' in 'Photoinduced Electron Transfer', ed. M. A. Fox and M. Chanon, Elsevier, Amsterdam, 1988, p. 245.
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15. G. J. Kavarnos and N. J. Turro, *Chem. Rev.*, 1986, **86**, 401.
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# Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

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The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# COMPREHENSIVE ORGANIC SYNTHESIS

***Selectivity, Strategy & Efficiency in Modern Organic Chemistry***

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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# Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

***Techniques***

| | |
|---|---|
| CD | circular dichroism |
| CIDNP | chemically induced dynamic nuclear polarization |
| CNDO | complete neglect of differential overlap |
| CT | charge transfer |
| GLC | gas–liquid chromatography |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICR | ion cyclotron resonance |
| INDO | incomplete neglect of differential overlap |
| IR | infrared |
| LCAO | linear combination of atomic orbitals |
| LUMO | lowest unoccupied molecular orbital |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| PE | photoelectron |
| SCF | self-consistent field |
| TLC | thin layer chromatography |
| UV | ultraviolet |

***Reagents, solvents,* etc.**

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonyl |
| 9-BBN-H | 9-borabicyclo[3.3.1]nonane |
| BHT | 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene) |
| bipy | 2,2′-bipyridyl |
| Bn | benzyl |
| t-BOC | *t*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| BSTFA | *N*,*O*-bis(trimethylsilyl)trifluoroacetamide |
| BTAF | benzyltrimethylammonium fluoride |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| COD | 1,5-cyclooctadiene |
| COT | cyclooctatetraene |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| CSA | camphorsulfonic acid |
| CSI | chlorosulfonyl isocyanate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBA | dibenzylideneacetone |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAC | diethylaluminum chloride |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate (+ or –) |
| DHP | dihydropyran |
| DIBAL-H | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| dimsyl Na | sodium methylsulfinylmethide |
| DIOP | 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DIPT | diisopropyl tartrate (+ or –) |
| DMA | dimethylacetamide |
| DMAC | dimethylaluminum chloride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMI | *N*,*N*′-dimethylimidazolone |
| DMSO | dimethyl sulfoxide |
| DMTSF | dimethyl(methylthio)sulfonium fluoroborate |
| DPPB | 1,4-bis(diphenylphosphino)butane |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1′-bis(diphenylphosphino)ferrocene |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| E$^+$ | electrophile |
| EADC | ethylaluminum dichloride |
| EDG | electron-donating group |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline |
| EWG | electron-withdrawing group |
| HMPA | hexamethylphosphoric triamide |
| HOBT | hydroxybenzotriazole |
| IpcBH$_2$ | isopinocampheylborane |
| Ipc$_2$BH | diisopinocampheylborane |
| KAPA | potassium 3-aminopropylamide |
| K-selectride | potassium tri-*s*-butylborohydride |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LITMP | lithium tetramethylpiperidide |
| L-selectride | lithium tri-*s*-butylborohydride |
| LTA | lead tetraacetate |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MEM-Cl | β-methoxyethoxymethyl chloride |
| MMA | methyl methacrylate |
| MMC | methylmagnesium carbonate |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| MSA | methanesulfonic acid |
| MsCl | methanesulfonyl chloride |
| MVK | methyl vinyl ketone |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |

| | |
|---|---|
| NMO | *N*-methylmorpholine *N*-oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| $Nu^-$ | nucleophile |
| PPA | polyphosphoric acid |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| phen | 1,10-phenanthroline |
| Phth | phthaloyl |
| PPE | polyphosphate ester |
| PPTS | pyridinium *p*-toluenesulfonate |
| Red-Al | sodium bis(methoxyethoxy)aluminum dihydride |
| SEM | β-trimethylsilylethoxymethyl |
| $Sia_2BH$ | disiamylborane |
| TAS | tris(diethylamino)sulfonium |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDMS-Cl | *t*-butyldimethylsilyl chloride |
| TBHP | *t*-butyl hydroperoxide |
| TCE | 2,2,2-trichloroethanol |
| TCNE | tetracyanoethylene |
| TES | triethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPBS-Cl | 2,4,6-triisopropylbenzenesulfonyl chloride |
| TIPS-Cl | 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane |
| TMEDA | tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-CN | trimethylsilyl cyanide |
| Tol | tolyl |
| TosMIC | tosylmethyl isocyanide |
| TPP | *meso*-tetraphenylporphyrin |
| Tr | trityl (triphenylmethyl) |
| Ts | tosyl (*p*-toluenesulfonyl) |
| TTFA | thallium trifluoroacetate |
| TTN | thallium(III) nitrate |

# 1.1

# Reduction of C=O to CHOH by Metal Hydrides

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## 1.1.1 INTRODUCTION

The reduction of the carbonyl group of aldehydes and ketones to the corresponding alcohol is ubiquitous in organic synthesis. Since the first report of reduction by diborane more than half a century ago,[1] metal hydride reagents have achieved preeminence as the reagents of choice for performing this synthetic transformation. The opportunities for variation in the metal, ligands, counterion and reaction conditions have enabled most problems of stereo-, regio- or chemo-selectivity in synthesis to be overcome satisfactorily. The majority of the complex metal hydrides described in this chapter that exhibit useful reducing properties are readily available from commercial sources, which has contributed enormously to their widespread acceptance and application.

The state of the art of reductions with metal hydrides a decade ago was the subject of comprehensive reviews. A detailed survey of reductions of carbonyl compounds with alkali and alkaline earth metal hydrides, borane and derivatives, alane and derivatives, metal borohydrides, metal aluminohydrides, silanes, stannanes and transition metal hydrides was compiled.[2] The properties, preparation and applications of each reagent were discussed together with methods for their determination, handling techniques and mechanistic aspects. The functional group selectivity of selected reagents was assessed,[3] and Brown described a 40-year odyssey in the development of a range of complex nucleophilic alumino- and borohydrides from their electrophilic counterparts, borane and alane.[4] Reductions by metal alkoxyaluminum hydrides were the subject of an exhaustive *Organic Reactions* review which emphasized the mechanism, scope, limitations and synthetic utility of the reagents.[5]

It is not the intention of this chapter to reiterate the conclusions of these compilations, but rather to concentrate on important synthetic developments that have appeared subsequently.

### 1.1.1.1 Kinetics and Mechanism

In spite of four decades of investigation, the full details of the mechanism of reduction of ketones by sodium borohydride and lithium aluminum hydride remain to be established.[6] Sodium borohydride reacts with first-order kinetics involving a rate-determining hydride attack on the carbonyl carbon, but the nature of the interaction of the metal cation or boron atom with the carbonyl oxygen is unknown. An *ab initio* theoretical study of borohydride addition to formaldehyde concluded that the traditional [2 + 2] four-center transition state, with simultaneous CH and BO bond formation and BH bond breaking, was not the optimum representation. The preferred alternative was a single-step mechanism with a nonsynchronous four-center transition state with a product-like geometry involving transfer of $BH_3$ from the hydride, already bonded to carbon, to the carbonyl oxygen atom.[7] The energy of this pathway was further reduced by the incorporation of a water molecule, an OH substituent on boron or a metal counterion. The importance of a metal counterion was demonstrated experimentally in a series of ketone reductions with lithium and sodium alumino- and boro-hydrides. In ethereal solvents reduction proceeded uneventfully, but, when macrocyclic cryptands, specific to either metal ion, were added, no reduction was observed.[8] The details of the effect of the metal counterion and reaction medium on the reduction of carbonyl compounds with alkali metal alumino- or boro-hydrides has been reviewed recently.[9]

The reduction of a series of chiral acyclic ketones, lacking polar functional groups, with a range of lithium, sodium and potassium alumino- and boro-hydrides was investigated in various solvents under different reaction conditions. The changes in steric bulk of the reagents and reaction medium enabled a semiempirical scale for the effective size of the reagent to be applied to the stereochemical analysis of the observed diastereoselectivity.[10]

The reduction kinetics of mesityl phenyl ketone, selected for its convenient rate, with lithium and sodium aluminum hydrides in THF were studied in detail.[11] In the presence of excess hydride, the reaction was first-order in hydride and ketone. A lithium counterion was worth a 10-fold increase in rate over sodium, indicating the influence of the cation on the mechanism. The observed deuterium kinetic isotope effect ($k_H/k_D = 1.27$) was consistent with a rate-determining transfer of hydride to the carbonyl carbon. Further evidence for the association of the counterion with the carbonyl oxygen during reduction was obtained from comparison of entropies of activation of both reactions. The results were rationalized by considering the metal hydrides as solvent-separated ion pairs and/or free ions, prior to coordination of the metal cation to the carbonyl oxygen and hydride delivery *via* a cyclic transition state. Analogous experiments on the reduction of camphor led to the same kinetic conclusions. Significantly, lithium *t*-butoxy- and methoxy-aluminohydrides were observed to follow kinetics consistent with disproportionation of the alkoxide species to give LAH which was the predominant reducing agent.[12]

The kinetics of reduction of 15 cyclohexanones by $Li(Bu^tO)_3AlH$ were investigated and found to follow a simple second-order process.[13] The rate constants were determined at various temperatures and were found to exceed the corresponding values for sodium borohydride. Activation parameters were derived for the reduction, which was nearly isoenthalpic, and rate differences were attributed to the entropic contribution. The results were consistent with a simple four-centred transition state, but additional work is required for a definitive conclusion.

First-order kinetic behavior was observed in the reduction of aldehydes and reactive ketones with 9-BBN-H dimer, but with hindered ketones intermediate or three-halves order kinetics were observed.[14] Monomeric 9-BBN-H was the active intermediate, as in the case of the hydroboration of alkenes and alkynes by this reagent. 9-BBN-H was less sensitive to steric effects than sodium borohydride; hindrance on one side of the ketone caused a moderate rate decrease, while a significant drop was observed with bulky groups on either side of the carbonyl group. The rate was also sensitive to electronic factors; electron-releasing substituents increased the rate of reduction, and electron-withdrawing groups retarded it. These data strongly suggested that the boron atom was coordinated to the carbonyl oxygen during reduction, but it was not established if this was in advance of hydride transfer or simply in the transition state.

Although a polar mechanism is generally accepted for hydride reduction, evidence for an electron transfer mechanism in the reduction of hindered aromatic ketones by main group hydrides has been presented.[15] Dimesityl ketone formed deeply colored, electron paramagnetic resonance active solutions with neutral hydrides of aluminum, boron and magnesium in THF. The kinetic analysis for alane reduction, which produced a long-lived paramagnetic intermediate, suggested a radical cation–radical anion pair as a relatively stable intermediate. The contribution of this pathway in the reduction of dialkyl ketones remains to be established.

## 1.1.2 THEORY OF STEREOSELECTIVITY

### 1.1.2.1 Acyclic Carbonyl Compounds

The origin and magnitude of the stereoselectivity observed in the reduction of chiral carbonyl compounds has long been an area of intense theoretical and practical study. Efforts have concentrated largely on the 1,2-asymmetric induction that occurs in the hydride addition to a carbonyl group flanked by an asymmetric center (Scheme 1). Cram's rule was formulated to rationalize the results of nucleophilic addition to aldehydes and ketones containing nonpolar groups.[16] The most stable conformation (**1**) was assumed to arise by minimization of the interaction between the largest group ($R^l$) and the carbonyl group, which was coordinated to the incoming reagent. Addition then occurred preferentially on the side of the smallest substituent ($R^s$) rather than the larger medium sized group ($R^m$). The outcome of Cram reduction of ketone (**2**) to alcohol (**3**) is illustrated. This rule enabled a large body of experimental results to be correlated, but its theoretical basis was subsequently shown to be flawed.

The results for reduction of α-halo aldehydes and ketones were anomalous and led to Cornforth's dipolar model (**4**), in which the dipoles due to the carbonyl group and the carbon–halogen bond were in an antiperiplanar arrangement. Reduction then proceeded from the less-hindered side of ketone (**5**), leading to alcohol (**6**).[17] The possibility of chelation when the α-substituent was an alcohol, alkoxy or amino group (X) was covered by Cram's cyclic or chelate model (**7**).[18] The chelating group (X) and the carbonyl group were eclipsed, coordinating to the metal (M), and reduction occurred from the less-hindered side. This model has been widely used to rationalize diastereoselectivity in reduction of ketones (**8**) when chelation is important, depending on the nature of the substituent (X) and the metal ion.

Information about the ground state conformations of carbonyl compounds that demonstrated that conformations with one bond eclipsing the carbonyl group were energetically favored led Karabatsos to propose an alternative model.[19] Calculations suggested that the most favored conformation (**9**) would have the medium-sized group ($R^m$) of ketone (**10**) eclipsing the carbonyl group, and addition of hydride would occur from the side of the less bulky substituent ($R^s$) to give alcohol (**11**). Comparison of the calculated energies of the other possible transition states with this conformation allowed the magnitude of diastereoselectivity to be correlated with experimental results.

The most influential contribution to the interpretation of 1,2-asymmetric induction in carbonyl group reduction was that of Felkin.[20] Attention was directed for the first time to the structure of the transition state, which was assumed to be very similar to that of the substrate. Torsional strain caused by interactions between the partially formed hydride–carbonyl bond and the full bonds at the adjacent center was of paramount importance. The nucleophile was assumed to attack perpendicular to the carbonyl group plane and staggered to the largest or most electronegative group ($R^l$). This angle of approach was later revised to the Bürgi–Dunitz trajectory,[21] derived from crystallographic studies, which placed the incoming hydride much closer to the substituent ($R^s$). This interaction was the decisive influence on the selection of the transition state illustrated (**12**) over the alternative which would have the positions of the small ($R^s$) and medium ($R^m$) groups exchanged. This model was successfully applied to acyclic and cyclic ketones and allowed crude quantitative rationalization of experimental diastereoisomeric ratios.[22]

Support for the Felkin model was provided by *ab initio* calculations of a range of transition state geometries for reductions of carbonyl compounds with and without an adjacent polar substituent.[23] The transition state energies were found to be minimized in the Felkin conformation as a consequence of the *anti* disposition of the bond forming to the incoming hydride and the bond between the adjacent carbon and the largest or most electronegative group ($R^l$). Other models that correctly predicted the stereochemical outcome required transition states of significantly higher energy.

Further refinement of the model by calculated trajectory analysis enabled the steric influence of the group (R) attached directly to the carbonyl to be assessed. Increasing the size of R was known to enhance the reduction diastereoselectivity.[22] This may be understood by the perturbation of the trajectory of the

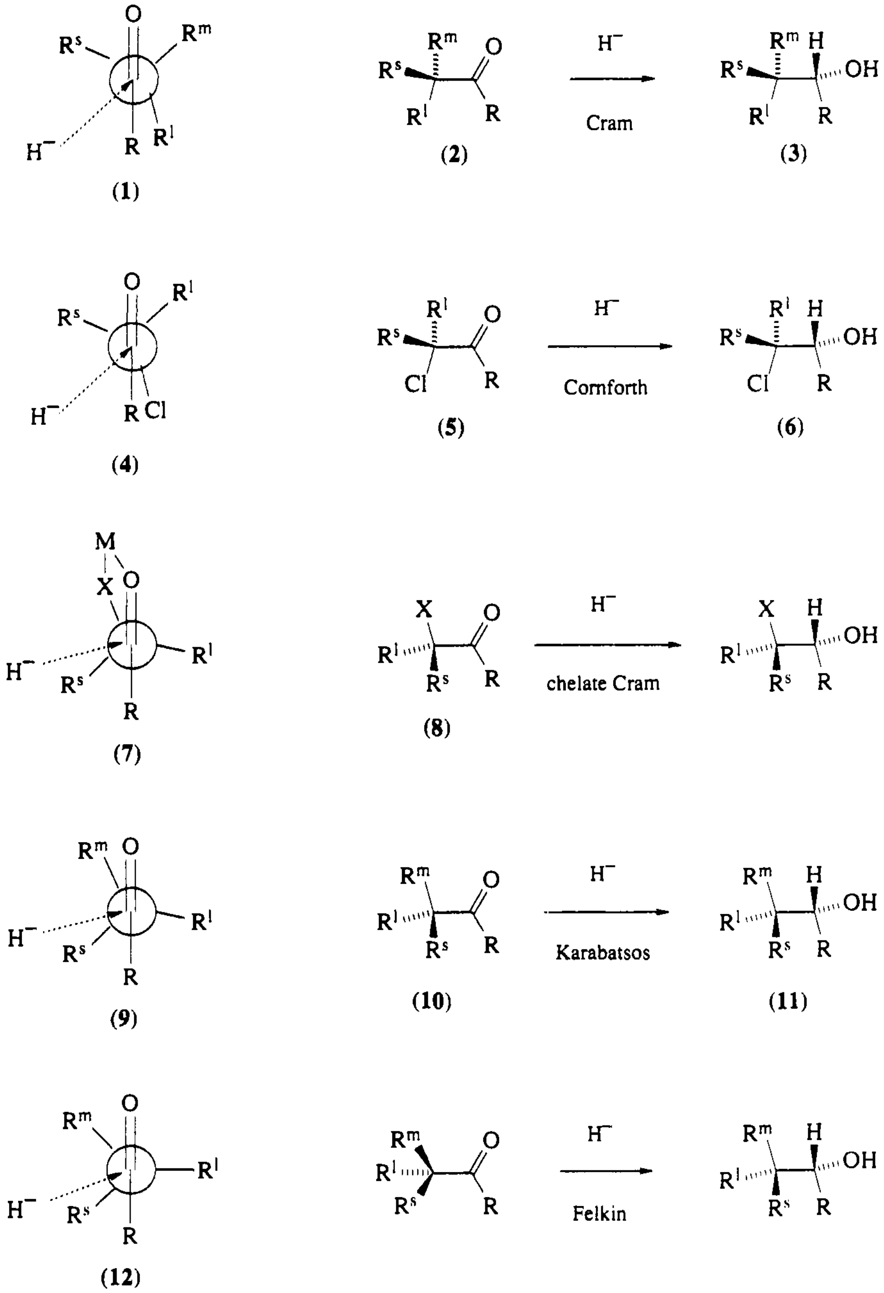

**Scheme 1**

nucleophile from perpendicular to the carbonyl plane away from the bulky group; the interactions of the nucleophile with the α-center would thus become more decisive. Quantitative support for such deviations from normal approach was provided by calculations on hydride addition to pivaldehyde.[24]

*Ab initio* calculations of transition state geometries for additions of lithium and sodium hydrides to formaldehyde, acetaldehyde, propionaldehyde and acetone indicated that nucleophilic attack *anti* to a methyl group was disfavored over attack *anti* to a hydrogen by 1–2 kcal $\mathrm{mol}^{-1}$ (1 kcal = 4.18 kJ). The combination of the torsional effects identified by Felkin, steric influences and the tendency to avoid attack *anti* to an alkyl group controlled the observed stereoselectivities. Importantly, in agreement with the Felkin model, when two alkyl substituents were present, the most stable conformation had the larger group perpendicular to the carbonyl group and the remaining alkyl group away from the incoming nucleophile. The alternative conformation with an *anti* carbon–hydrogen bond was disfavored because the alkyl groups were unable to attain their preferred dihedral angles. The incorporation of these effects into an MM2 force field enabled good qualitative rationalization of $LiAlH_4$ reductions of a wide range of alkyl ketones.[25]

The computational support for Felkin's torsional strain model and its success in interpretation of experimental diastereoselectivities has led to its widespread adoption. It appears to be the preeminent open transition state involved in reductions when chelation is not important. Complementary selectivity observed in reductions that do involve chelation may be understood in terms of Cram's cyclic model.

### 1.1.2.2 Cyclic Carbonyl Compounds

The stereochemistry and mechanism of reduction of cyclic ketones by metal hydride reagents provided a unique opportunity for comparison of experimental results with theoretical expectation. The models proposed by Cram, Cornforth and Karabatsos described above were inadequate to explain the stereochemical outcome, and so a wide range of models was developed to explain the dichotomy between cyclic and acyclic results.[26] The theoretical basis, applications and limitations of these models have been critically reviewed.[6] The effect of steric influences, torsional and electronic factors, and the nature of the cation on the rate of reduction, stereochemical outcome and position of the transition state have also been surveyed.[27]

The stereochemical characteristics of lithium trimethoxyaluminohydride and lithium aluminum hydride in the reduction of cyclic ketones were analyzed by a linear combination of steric strain and product stability control. Qualitative and quantitative explanation of the experimental observations was possible using this approach.[28]

Consideration of the stabilizing interaction between the low-lying $\sigma^*$-orbital associated with the bond forming between the incoming hydride and the carbonyl carbon, and remote electron-donor $\sigma$-orbitals led Cieplak to an explanation for many kinetic and stereochemical effects in cyclohexanones that were previously unexplained.[29] The normal preference for axial attack in simple cyclohexanones was attributed to the improved electron-donor ability of carbon–hydrogen bonds over carbon–carbon bonds that would be antiperiplanar to the incoming nucleophile in the transition state.

The electronic contribution to reduction stereoselectivity was assessed with a series of substituted 9-benzonorbornenones (**13**) with a range of reducing agents.[30] The observed selectivity, increasing *anti* attack with electron-rich benzene rings, paralleled the homoconjugation sequence. Analogous results were observed in the reduction of a series of 5-substituted adamantanones (**14**) with electronically varied substituents (X), providing strong support for the importance of $\sigma$-participation in diastereoselectivity.[31] The unexpected preference for axial reduction of 2-methoxy-4-pyranones (equation 1) with an equatorial methoxy group, even with L-selectride, was explained by the electronic effects of the two conformationally defined carbon–oxygen bonds.[32]

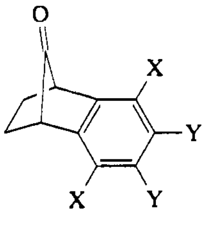

X = F, Cl, H, OMe
Y = F, Cl, H, OMe

**(13)**

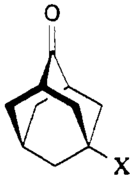

X = Ar, Bu$^t$, F, Cl, OH, CF$_3$

**(14)**

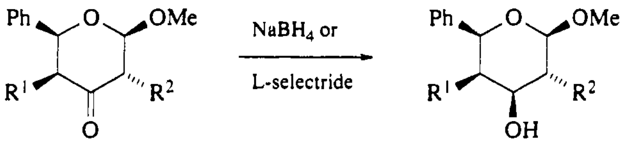

(1)

Felkin identified torsional effects in cyclohexanone reductions that accounted for the observed stereoselectivity. Minimization of these torsional effects, in the absence of steric hindrance, led to the predominance of axial attack (equation 2).[33] Recently, a computational approach has provided quantitative support for this model.[25] The eclipsing interactions between the incoming nucleophile and the bonds $\alpha$ to the carbonyl group are more serious, for any given trajectory, from the equatorial direction. The differences are clearly illustrated in the Newman projection of cyclohexanone (**15**). Differences in bond lengths and thus torsional bond energies were used to explain observed stereoselectivity in hetero-substituted cyclohexanones.

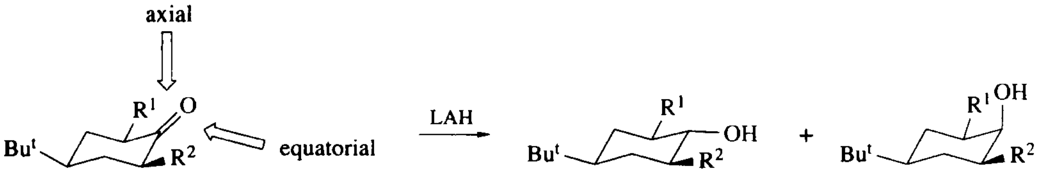

(2)

| | | | |
|---|---|---|---|
| $R^1 = R^2 = H$ | 92 | : | 8 |
| $R^1 = Me, R^2 = H$ | 83 | : | 17 |
| $R^1 = R^2 = Me$ | 53 | : | 47 |

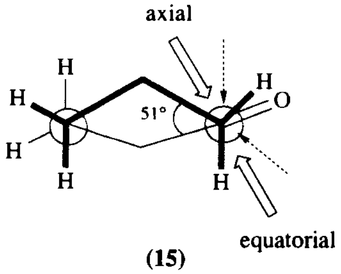

**(15)**

The dramatically enhanced axial selectivity demonstrated in the addition of sterically undemanding nucleophiles, such as lithium aluminum hydride, to conjugated cyclohexenones was explained by the application of the modified MM2 model.[34] The important difference between cyclohexanones and their unsaturated counterparts was the flattening of the ring. The internal dihedral angle was reduced from 51° in cyclohexanone to 22° in cyclohexenone. This in turn produced a dramatic change in the torsional interactions corresponding to axial and equatorial attack, illustrated on the Newman projection (**16**). Calculated energies of transition states for axial and equatorial addition were used to calculate diastereoisomeric ratios that showed good agreement with experimental results.

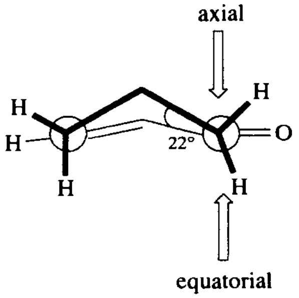

**(16)**

The accuracy and applicability of the model was tested further on the lithium aluminum hydride reduction of a series of benzocycloheptenones (**17**; equation 3). Dynamic NMR studies and MM2 calculations demonstrated that the chair conformation shown was the most stable. Since the substrates were sterically unhindered most models predicted that axial attack would be favored. Conversely, MM2 calculations indicated that the transition state for equatorial approach was of lower energy than its axial counterpart. In fact equatorial reduction to give the axial alcohol predominated (60:40) with a single methyl substituent (**17**; $R^1$ = Me), and was the exclusive outcome in the more hindered case with two methyl groups (**17**; $R^1$

= $R^2$ = Me).[35] Felkin's torsional strain approach was considered to be the only model consistent with these results, but an alternative interpretation based on participation of the aromatic ring, consistent with Cieplak's model, has recently been advanced.[36] The significance of torsional interactions was related to the degree of puckering in the cyclic ketone according to the 'flattening rule'.[37]

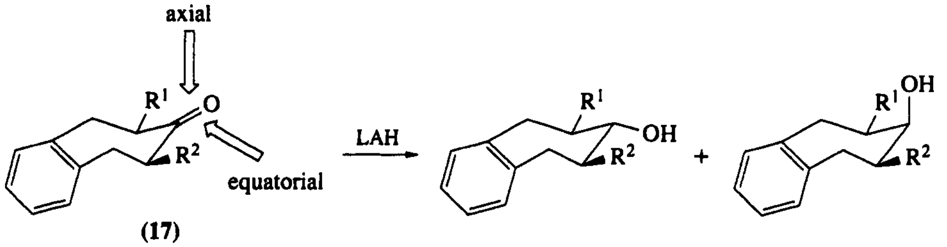

(17)

(3)

$R^1$ = Me, $R^2$ = H 40 : 60

$R^1$ = $R^2$ = Me 0 : 100

The success of this method for calculating quantitative stereoselectivities of reductions of substituted five-, six- and seven-membered ring and bicyclic ketones was impressive, but additional examples are required to demonstrate its generality.

## 1.1.3 DIASTEREOSELECTIVITY

### 1.1.3.1 Acyclic Carbonyl Compounds

The development of reliable methods for the diastereoselective reduction of carbonyl compounds in a wide range of acyclic systems has been an area of explosive growth in recent years.[38] This was prompted by the requirements of modern total synthesis in which redundant diastereoisomers are avoided,[39] together with enhanced theoretical understanding of stereoselectivity which allows rationalization of the results.

An exhaustive compilation of examples of reduction of acyclic ketones with an adjacent chiral center appeared recently and is not reproduced here.[40] Those methods that give excellent levels of asymmetric induction likely to be useful in synthesis are highlighted here. The results are collected according to the substrate being reduced rather than the reducing agent. Most of the examples can be rationalized by consideration of the Felkin transition state or, where appropriate, the chelated transition state (Section 1.1.2.1).

α-Hydroxy ketones (**18**) were reduced to the corresponding *anti*-diols (**19**) by zinc borohydride with good selectivity (77:23–99:1) *via* a chelated transition state (equation 4). Silylation with the bulky TBDMS group gave the protected derivatives (**20**) which were reduced by Red-Al at –78 °C preferentially to the *syn* products (**21**) according to a Felkin transition state with the silyl ether in the perpendicular position (equation 5).[41] Selectivity was good (76:24–98:2), except when $R^1$ was a branched or long chain alkyl group, presumably due to an unfavorable interaction with the silyl ether. These complementary methods were used to synthesize various diastereoisomers of a possible fragment of polyoxygenated antibiotics.[42] Analogous results were observed when a range of reducing agents were screened for reduction of α-benzyloxy alkynic ketone (**22**; Scheme 2).[43] The *anti* isomer (**23**) was produced by zinc borohydride (95:5) *via* chelation control, and K-selectride gave the *syn* Felkin product (**24**; 90:10). The generality of these results was demonstrated on five additional substrates. Significantly, Red-Al was *anti* selective, due to coordination to the benzyloxy group, which was not as effective as TBDMS at suppressing chelation. The dramatic difference between these two protecting groups was again manifested in the

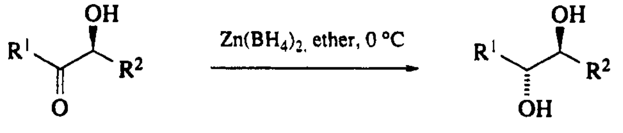

**(18)** **(19)**

(4)

LAH reduction of α-alkoxy enone (**25**; equation 6). Chelation to the benzyloxy group favored formation of the *anti* product (**26**; 98:2) while the TBDMS ether prevented chelation so that reduction occurred *via* an open transition state to give the *syn*-alcohol (**27**; 95:5).[44]

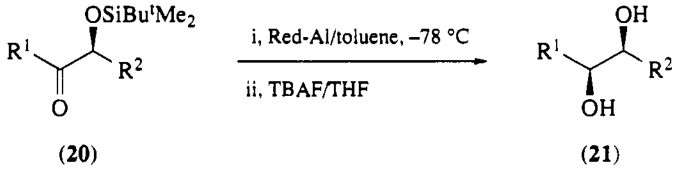
OSiBu$^t$Me$_2$
R$^1$
R$^2$
O
i, Red-Al/toluene, –78 °C
ii, TBAF/THF
OH
R$^1$
R$^2$
OH
(20)
(21)

(5)

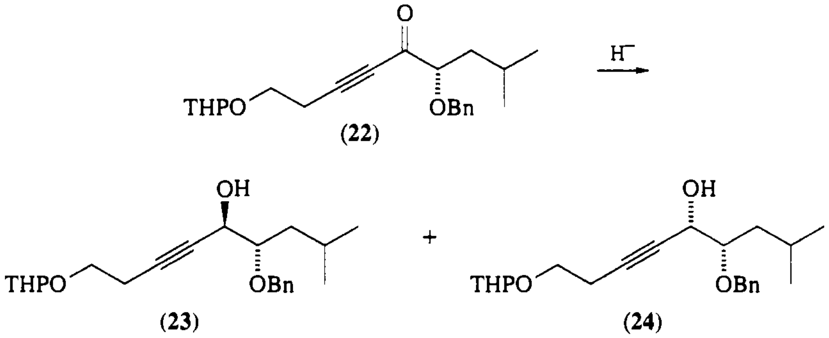
O
THPO
OBn
(22)
H$^-$
OH
THPO
OBn
(23)
+
OH
THPO
OBn
(24)

| | |
|---|---|
| Zn(BH$_4$)$_2$, ether, –30 °C | 95 : 5 |
| K-selectride, THF, –95 °C | 10 : 90 |

Scheme 2

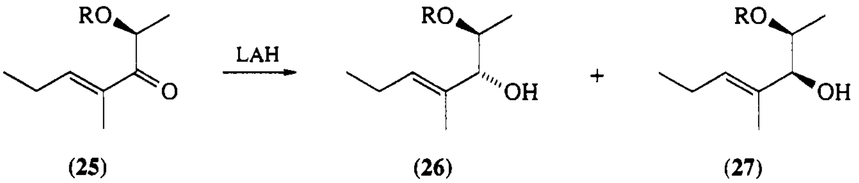
RO
O
LAH
RO
OH
+
RO
OH
(25)
(26)
(27)

(6)

| | |
|---|---|
| R = Bn, ether, –10 °C | 98:2 |
| R = Bu$^t$Me$_2$Si, THF, –20 °C | 5:95 |

Hydrosilylation provided a novel alternative reduction of α-oxy ketones (**29**) with tunable diastereoselectivity (Scheme 3). Fluoride-catalyzed reduction with phenyldimethylsilane in HMPA provided the *syn*-alcohols (**28**) with high selectivity (87:13–96:4).[45] The absence of a coordinating cation and the bulkiness of the reducing species combined to favor the Felkin model for these reductions. Conversely, reduction in trifluoroacetic acid proceeded *via* a proton-bridged cyclic transition state to give the *anti* products (**30**; 84:16–99:1).[46] These complementary methods constitute a powerful tool in stereoselective synthesis.

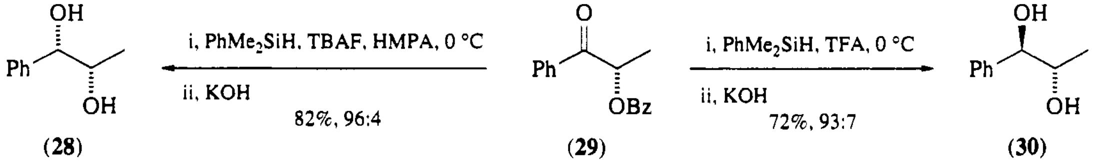
OH
Ph
OH
(28)
i, PhMe$_2$SiH, TBAF, HMPA, 0 °C
ii, KOH
82%, 96:4
O
Ph
OBz
(29)
i, PhMe$_2$SiH, TFA, 0 °C
ii, KOH
72%, 93:7
OH
Ph
OH
(30)

Scheme 3

The 1,3-diol unit is an important constituent of many highly oxygenated natural products. Consequently, highly diastereoselective methods for reducing β-hydroxy ketones to either of the possible diastereoisomers have been developed. The *syn* isomer was produced by attack of an external hydride reagent on a six-membered chelate such as (**31**), the conformation of which was governed by the substituent at the alcohol center. Conversely, intramolecular delivery of hydride from a group bound to the alcohol *via* a chair transition state (**32**) gave the *anti* diastereoisomer.

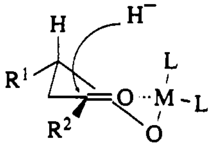

(**31**)

M = B; L = Bu, Et

M = Li; L = THF

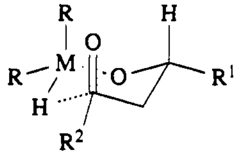

(**32**)

M = Si; R = $Pr^i$

M = B; R = OAc

The combination of trialkylboranes and sodium borohydride in THF at –100 °C was the first highly *syn* selective method of this type.[47] This was later refined by using alkoxydialkylboranes to chelate the β-hydroxy ketones (**33**) and conducting the reduction at –70 °C in THF–methanol (4:1).[48] The *syn*-1,3-diols (**34**) predominated by at least 98:2 (equation 7). Reduction of β,δ-diketo esters to the corresponding *syn*-β,δ-dihydroxy esters was accomplished with excellent diastereoselectivity.[49] A comparative study of hydrogenation with iron(II) chloride to enhance carbonyl reduction, alkylborane-mediated $NaBH_4$ reduction and zinc borohydride alone, demonstrated the generality of useful *syn* selectivity.[50] DIBAL-H has also been used to reduce β-hydroxy ketones to *syn*-1,3-diols with high diastereofacial selectivity (≥92:8) at –78 °C in THF.[51] Tributyltin hydride with both Lewis acid and radical catalysis exhibited lower levels of selectivity.

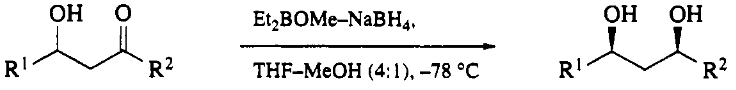

(**33**) (**34**) (7)

Lithium iodide apparently was chelated by β-alkoxy ketones to form a similar six-membered transition state, allowing LAH to reduce the carbonyl group at –100 °C in ether with high *syn* selectivity (≥95:5) (Scheme 4).[52]

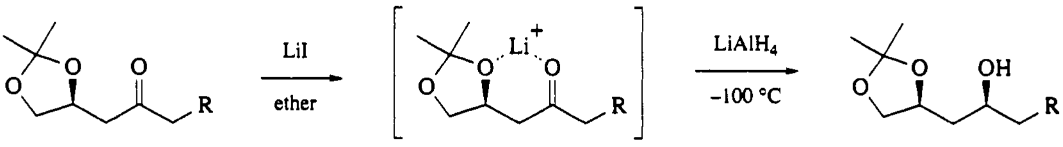

**Scheme 4**

Intramolecular hydrosilylation of the carbonyl group of β-silyloxy ketones (**35**) induced by tin(IV) chloride catalysis at –80 °C in dichloromethane generated the *anti*-1,3-diols (**36**) after desilylation with excellent stereoselectivity (>95%).[53] Unfortunately, the overall yield (60–69%) of the process was reduced by inefficient initial silylation (Scheme 5). Tetramethylammonium triacetoxyborohydride in acetic acid–acetonitrile, a mild reducing agent, reduced acyclic β-hydroxy ketones to the *anti*-1,3-diols with high diastereoselectivity (>92:8), independent of α-alkyl group stereochemistry.[54] The reducing agent requires coordination to an adjacent hydroxy group to allow intramolecular delivery of the hydride and so is highly chemoselective. Internal stereopropagation allowed sequential diastereoselective reductions of hydroxy diketone (**37**) to give *anti,anti*-triol (**38**) in 50% isolated yield (equation 8). Most of the β-hydroxy ketones screened had a bulky isopropyl group at the β-position; it is not clear if this is a requirement for high diastereoselectivity.

Reduction of TBDMS ethers of α-substituted-β-hydroxy ketones (**39** and **41**) with LAH in ether at – 78 °C proceeded with high 1,2-*anti* diastereoselectivity (>96:4) to give the corresponding *syn,anti*- (**40**) or *anti,anti*-1,3-diols (**42**) after acidic hydrolysis.[55] The stereochemistry results from a chelation-free Felkin transition state with the bulky alkylsilyloxy group in the perpendicular position. The result was independent of the configuration of the silyloxy substituent (equations 9 and 10).

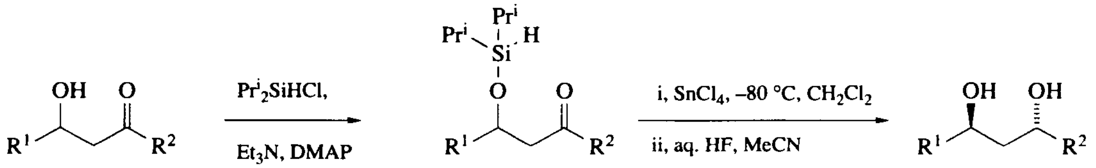
$Pr^i_2SiHCl$, $Et_3N$, DMAP
i, $SnCl_4$, −80 °C, $CH_2Cl_2$
ii, aq. HF, MeCN

(33) (35) (36)

Scheme 5

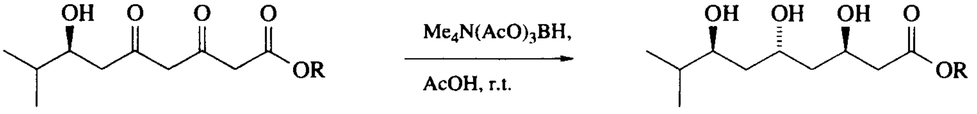
$Me_4N(AcO)_3BH$,
AcOH, r.t.

(8)

(37) (38) 50% isolated yield

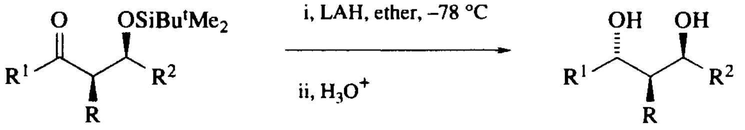
i, LAH, ether, −78 °C
ii, $H_3O^+$

(9)

(39) (40)

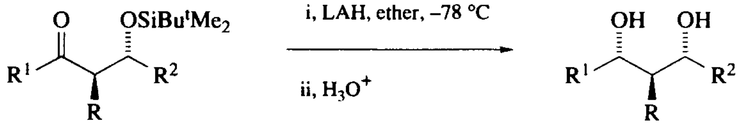
i, LAH, ether, −78 °C
ii, $H_3O^+$

(10)

(41) (42)

Examples of asymmetric induction from more remote hydroxy groups in the reduction of hydroxy ketones are rare. However the correct choice of reducing agent allowed complete diastereoselectivity to be achieved in the reduction of γ-hydroxy ketone (**43**) in a synthesis of ancistrofuran.[56] 2 equiv. of $LiEt_3BH$ in THF, one presumably coordinating the γ-hydroxy ketone in a fixed conformation, gave the diol (**44**) as the sole product in 88% yield (equation 11).

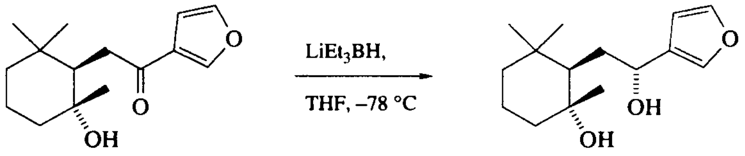
$LiEt_3BH$,
THF, −78 °C

(11)

(43) (44)

The unsaturated linkage in enantiomerically pure α-methyl-β,γ-unsaturated ketones (**45**) exerted a powerful stereochemical influence on their reduction with L-selectride, particularly when $R^1$ is a trimethylsilyl group.[57] The *anti* homoallylic alcohols (**46**) were produced with uniformly excellent stereoselectivity (>93:7) *via* a Felkin transition state in which the double bond occupied the perpendicular position (equation 12). This Felkin selectivity was sufficient to overcome any chelation-mediated contribution in the reduction of α-vinyl-β-hydroxy ketones (**47**) to the 1,2-*syn* diols (**48**) with $LiEt_3BH$ in THF at −78 °C (equation 13).[58]

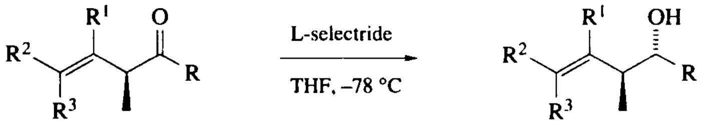
L-selectride
THF, −78 °C

(12)

(45) (46)

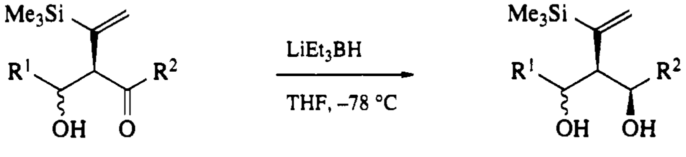

**(47)** **(48)** (13)

Zinc borohydride was effective for the reduction of α,β-epoxy ketones (**49**) to the corresponding *anti*-α,β-epoxy alcohols (**50**) in ether at 0 °C irrespective of the substituents on the epoxide (equation 14).[59] The selectivity was rationalized by intramolecular hydride delivery from a five-membered zinc chelate avoiding the epoxide ring. In a limited study of the stereoselective reduction of γ,δ-epoxy ketones (**51**), LAH and di-2-(*o*-toluidinomethyl)pyrrolidine in ether at −78 °C gave the desired *cis*-epoxy alcohols (**52**) required for ionophore synthesis with good selectivity (>10:1) (equation 15).[60]

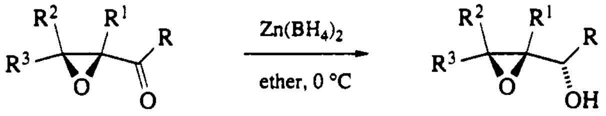

**(49)** **(50)** (14)

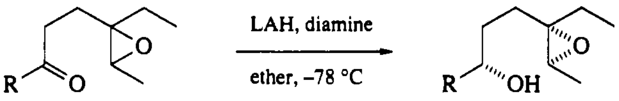

**(51)** **(52)** (15)

Stereoselective reduction of α-alkyl-β-keto acid derivatives represents an attractive alternative to stereoselective aldol condensation. Complementary methods for production of either diastereoisomer of α-alkyl-β-hydroxy amides from the corresponding α-alkyl-β-keto amides (**53**) have been developed. Zinc borohydride in ether at −78 °C gave the *syn* isomer (**54**) with excellent selectivity (≥97:3) in high yield *via* a chelated transition state.[61] A Felkin transition state with the amide in the perpendicular position accounted for reduction with potassium triethylborohydride in ether at 0 °C to give the stereochemically pure *anti* diastereoisomer (**55**). The combination of these methods with asymmetric acylation provided an effective solution to the asymmetric aldol problem (Scheme 6).[62] In contrast, the reduction of α-methyl-β-keto esters with zinc borohydride was highly *syn* selective when the ketone was aromatic or α,β-unsaturated, but less reliable in aliphatic cases.[38] Hydrosilylation also provided complete diastereocontrol (Scheme 7). The fluoride-mediated reaction was *anti* selective (≥98:2) while reduction in trifluoroacetic acid favored production of the *syn* isomer (≥98:2).[63] No loss of optical purity was observed under these mild conditions.

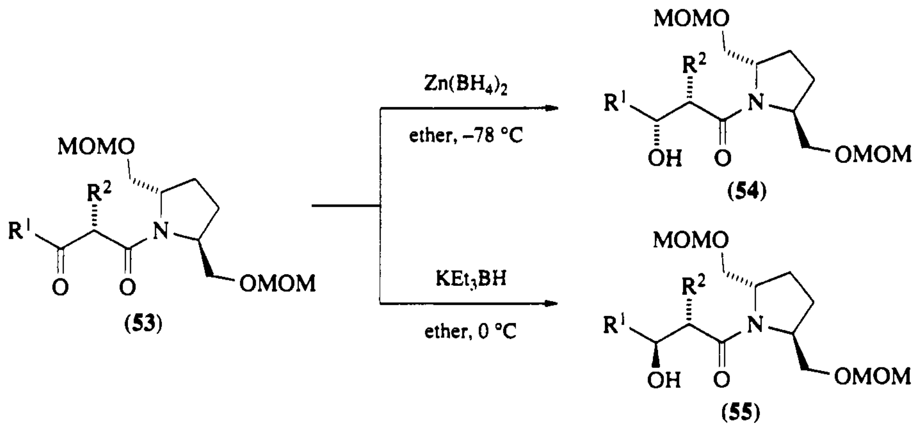

**Scheme 6**

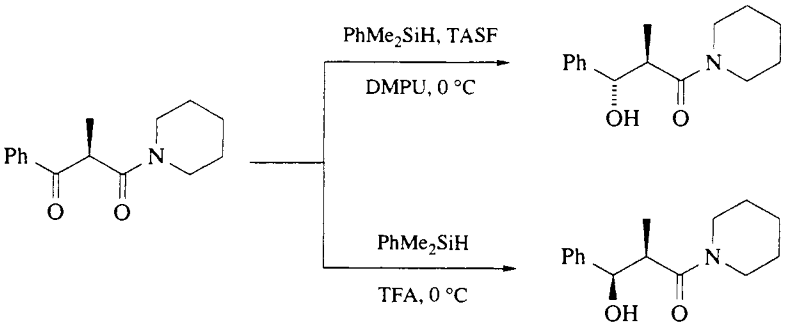

**Scheme 7**

Diastereoisomerically pure β-hydroxy sulfides are useful synthetic intermediates for the preparation of geometrically pure alkenes or single diastereoisomers of epoxides. Reduction of β-keto sulfides (**56**) with L-selectride in THF gave the *syn*-β-hydroxy sulfides (**57**) *via* a Felkin transition state.[64] The selectivity was good (≥92:8) unless the acyl group was branched. Chelation-controlled reduction with zinc borohydride was successful in favorable situations, but a more general solution to the production of the *anti* diastereoisomers (**59**) and ultimately *trans*-epoxides was reduction of the sulfonium salts (**58**), prepared by methylation of the β-keto sulfides (**56**), with sodium borohydride in dichloromethane (Scheme 8). The selectivity was excellent (≥95:5) when $R^2$ was a branched alkyl group, but declined when it was not. This is consistent with a cyclic charge-controlled transition state analogous to a chelated conformation without a metal ion.[65]

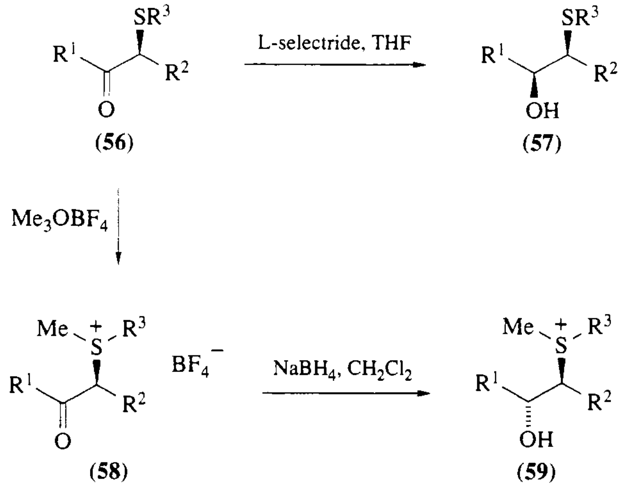

**Scheme 8**

The stereocontrolled reduction of optically pure β-keto sulfoxides (**60**) with DIBAL-H (*anti* selective, ≥93:7) or DIBAL-H in the presence of zinc chloride (*syn* selective, >95:5) provided an entry to enantiomerically pure alcohols after desulfurization (Scheme 9).[66] The stereoselectivity may be rationalized by consideration of transition states analogous to those described for β-hydroxy ketone reduction (**31** and **32**), cyclic chelation by zinc chloride and external hydride delivery giving the *syn* isomer, and coordination of the DIBAL-H to the sulfoxide and internal hydride delivery giving the *anti* product.

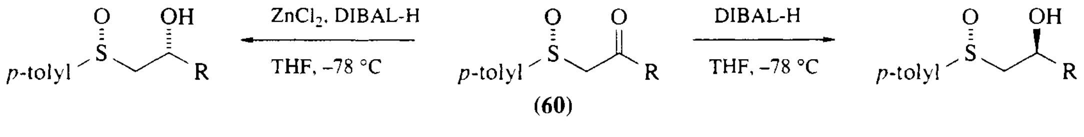

**Scheme 9**

Geometrically pure alkenes were generated by Horner–Wittig elimination of stereochemically pure β-hydroxy diphenylphosphine oxides available from reduction of the corresponding β-keto phosphine oxides.[67] Reduction with a range of reagents was generally *syn* selective according to the Felkin model, but the success of the method depended on the ease of separation of diastereoisomers rather than intrinsically high stereoselectivity. However, in the presence of cerium chloride, sodium borohydride reduced sterically hindered α′-diphenylphosphinoyl ketones and enones (**61**) to the *anti*-alcohols (**62**) exclusively, presumably *via* a chelated transition state (equation 16).[68]

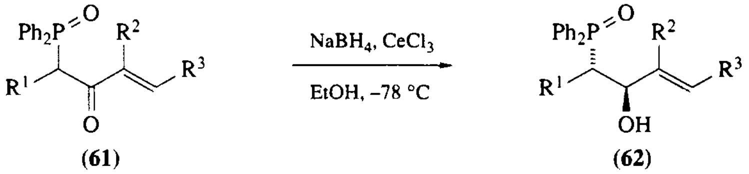

(16)

Diastereocontrolled reduction of amino ketones represents an attractive route to amino alcohols, many of which are pharmacologically important, and has been exhaustively reviewed.[69] Even in the case of α-amino ketones, examples of high stereoselectivity were rare[70] with conventional metal hydride reagents,[71] and mixtures were common as the amino group became more distant.[72] In contrast, α-triazolyl ketones (**64**) were reduced with high stereoselectivity by tetraalkylammonium borohydrides to the *syn*-alcohols (**63**) in dichloromethane or to the *anti* isomers (**65**) when titanium tetrachloride was added (Scheme 10).[73]

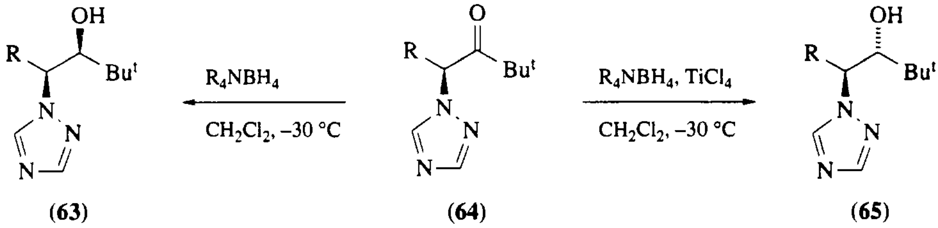

Scheme 10

Hydrosilylation of α-amino ketones (**66** and **68**) exhibited extremely high levels of selectivity in either direction depending on the reaction conditions (equations 17 and 18). The *syn*-alcohol (**67**) was the exclusive product of the fluoride-catalyzed reduction,[45] while trifluoroacetic acid catalysis generated the *anti* isomer (**69**).[46] Both these examples of highly diastereocontrolled reduction depended on the selection of either an open Felkin or a proton- or metal-bridged transition state.

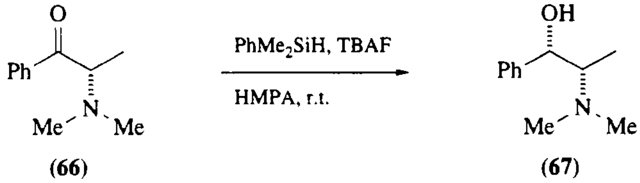

(17)

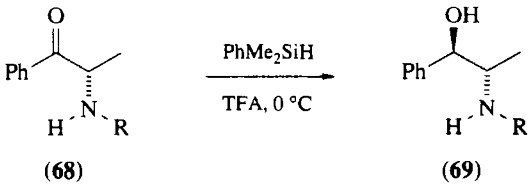

(18)

The diastereoselectivity of reduction of a series of symmetrical diketones to the corresponding diols revealed an intriguing dependance on the separation of the carbonyl groups, but the selectivity was not generally useful.[74] However, in the case of 1,3-diketone (**71**) lithium borohydride alone produced the *anti* isomer (**70**) with 91% diastereoselectivity, but prior addition of titanium tetrachloride gave the *syn*-diol (**72**) with 96% diastereoselectivity *via* a chelated intermediate analogous to the crystalline complex between the diketone and $TiCl_4$ (Scheme 11).[75]

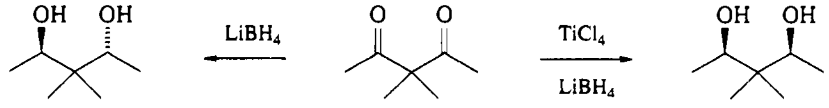

(70) (71) (72)

Scheme 11

### 1.1.3.2 Cyclic Carbonyl Compounds

The stereoselective reduction of cyclic ketones is profoundly influenced by conformational effects and is an area of intense theoretical study (Section 1.1.2.2). From a practical perspective, impressive diastereoselectivity in the required direction is possible by the correct choice of reagent (Table 1). Conformational homogeneity has been recognized as an important factor in achieving high diastereoselectivity. Temperature control is extremely important as at –78 °C a methyl group has almost the same conformational biasing effect as a *t*-butyl group at 0 °C.[76]

Table 1 Comparison of Selectivity for Equatorial Attack in Reductions of Alkyl Substituted Cyclic Ketones

| *Substituent(s)* *Reagent* | *2-Me* $C_6$[a] | *3-Me* $C_6$ | *4-Me* $C_6$ | *4-Bu*$^t$ $C_6$ | *3,3,5-Me*$_3$ $C_6$ | *2-Me* $C_5$[b] | *Ref.* |
|---|---|---|---|---|---|---|---|
| $LiBu^s_3BH$ | 99.3 | 95 | 90 | 96.5 | 99.8 | 99.3 | 27 |
| $LiMes_2BH_2$ | 99 | 99 | 94 | 94 | — | 98 | 80 |
| $Li(MeCp)_3BH$ | 99.5 | 99 | 98 | 99.4 | — | — | 79 |
| $LiSia_3BH$ | 99.7 | 99.6 | 99 | 99.4 | — | 99.5 | 79 |
| K9-OThx-9-BBN-H | 98.5 | 90 | 85.5 | 87 | 99.9 | — | 84 |
| K9-Bu$^t$-9-BBN-H | 99.5 | 98 | 94 | 98.5 | 99 | — | 83 |
| $LiBuBH_3$ | — | 8 | 6 | 2 | — | — | 77 |
| $LiMeBH_3$ | 13 | 5.7 | 4.5 | 1.7 | 66 | — | 77 |
| NiCRA | 7 | — | 5 | 6 | 1 | — | 86 |
| $LiAlH_4THF$ | 24 | 16 | — | 10 | 80 | 23 | 27 |
| $NaBH_4$ | 30 | 14 | — | 14 | 52 | 26 | 27 |

[a] $C_6$, cyclohexanone. [b] $C_5$, cyclopentanone.

Unhindered cyclohexanones exhibited an intrinsic preference for axial attack by small hydride reagents ($NaBH_4$, $LiAlH_4$) leading to the equatorial alcohol. Monoalkylborohydrides, prepared from borane–dimethyl sulfide and the corresponding alkyllithium, proved to be superior to the traditional reagents, but the selectivity declined as the ketone became more hindered.[77] Axial alcohols, *via* equatorial attack, were produced from both hindered and unhindered ketones with bulky hydride reducing agents. The most successful were highly branched alkylborohydrides generally with a lithium counterion.[78] Lithium trisiamylborohydride[79] demonstrated exceptional stereoselectivity, better than the tris(*trans*-methylcyclopentyl)borohydride ($Li(MeCp)_3BH$), L-selectride or lithium dimesitylborohydride ($LiMes_2BH_2$).[80] In contrast, the analogous ate complex formed from *t*-butyllithium and DIBAL-H, which was expected to be highly hindered and hence stereoselective, reduced 4-*t*-butylcyclohexanone without any preference.[81] Potassium trisiamylborohydride, prepared from potassium hydride and trisiamylborane with triisopropoxyborane catalysis, exhibited stereoselectivity comparable with the lithium analog.[82]

Two new classes of bulky reducing agents generated from potassium hydride and *B*-alkyl-[83] or *B*-alkoxy-9-boratabicyclo[3.3.1]nonanes[84] have been investigated. The optimum stereoselectivity was obtained with maximum branching in the alkyl group and *t*-butyl was significantly better than 2,4-dimethyl-2-pentyloxy (OThx). Various reagents based on magnesium hydride with a variety of ligands on magnesium (hydridomagnesium alkoxides, dialkylaminomagnesium hydrides, and lithium alkoxy- and dialkoxy-magnesium hydrides) have been prepared and some bulky examples provided useful selectivity in ketone reduction.[85]

Complex reducing agents containing sodium hydride, a metallic salt and an alcohol were screened against six representative cyclic ketones for stereoselectivity. Cadmium, cobalt and manganese chlorides gave rise to reagents that favored formation of the axial alkoxides, but the selectivity was not outstanding. Those derived from zinc chloride and particularly nickel acetate 2,5-dimethylhexanediol (NiCRA) provided the more stable equatorial alkoxides in very good yield with high selectivity.[86] The proposed equilibration to the more stable product parallels the classical solution to the production of equatorial alcohols from hindered cyclohexanones based on equilibration with Raney nickel.[87]

Correct reagent selection allowed reduction of steroidal enone (**74**) to either diastereoisomeric allylic alcohol, uncontaminated by its isomer. Sodium borohydride/cerium chloride in methanol–THF gave the equatorial alcohol (**73**), while L-selectride produced the axial isomer (**75**) *via* equatorial attack (Scheme 12).[88] Unexpected axial attack on diketone (**76**) to give equatorial alcohol (**77**; equation 19) led to the proposition that for hydride additions to decalones two 1,3-diaxial interactions override one *peri* interaction which in turn takes precedence over a single 1,3-diaxial interaction.[89]

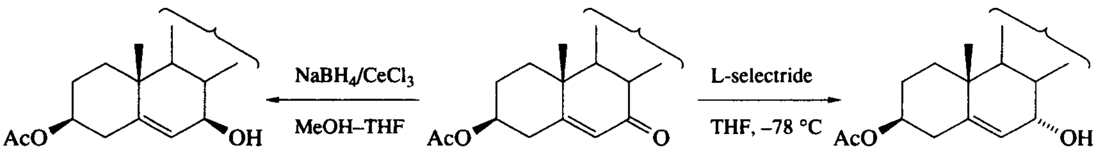

(**73**) (**74**) (**75**)

**Scheme 12**

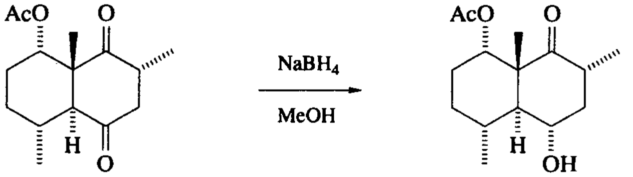

(**76**) (**77**) (19)

The influence of polar substituents on the stereoselectivity of reduction of cyclic ketones has not been widely studied. A series of cyclohexanones with hydroxy groups in differing positions on the ring and on alkyl chains attached to the ring was reduced with a selection of reducing agents to investigate the selectivity, but, although some examples of high stereoselectivity were observed, no clear pattern emerged.[90] Conformationally flexible and conformationally locked 2-methylthio- and 2-methylsulfonyl-cyclohexanones were studied with a range of reducing agents. Exclusive axial approach, even with bulky hydrides, was observed when the sulfur adopted the axial disposition, but diastereoisomeric mixtures resulted when the sulfur was equatorial.[91] The selectivity was rationalized by a combination of steric and stereoelectronic factors. The effect of ring size on reduction selectivity for a series of α-phenylthio ketones was investigated.[92] Small rings (five- and six-membered) exhibited reasonable selectivity (>7:1), consistent with the preceding results, but medium sized (seven- and eight-membered) and large rings produced low selectivity (<2:1). The reversal was explained by a conformational change in the ring position in the transition state.

## 1.1.4 CHEMOSELECTIVITY

### 1.1.4.1 Reduction of Enones

Reduction of α,β-unsaturated ketones by metal hydrides can follow two pathways; addition to the carbonyl group (1,2-addition, charge control) to give the allylic alcohol, or addition to the conjugated double bond (1,4-addition, frontier orbital control) to give the saturated ketone. The concept of hard and soft acids and bases has been used to explain observed selectivities.[93] The hard metal hydrides attack the carbonyl group while the softer metal hydrides, with a more covalent M—H bond, favor conjugate addition. Borohydrides are softer than their aluminum counterparts due to the more covalent hydride bond and both can be hardened by incorporating alkoxy groups on the metal. The counterion is also important, sequestration of lithium by a [2.1.1]cryptand causes conjugate reduction of cyclohexenone by $LiAlH_4$ and $LiBH_4$ to predominate[94] while added hard lanthanide salts enhance reduction to the allylic alcohols (*vide infra*).

In spite of substantial evidence, the tendency for sodium borohydride to reduce enones in a conjugate sense is often ignored,[95] but the need for reduction to the corresponding allylic alcohols has led to the development of several new specific reagent combinations. The most widely accepted of these involves sodium borohydride in the presence of cerium chloride, which has been optimized to give excellent selectivity under mild and experimentally convenient conditions.[96] The success of this reagent may be explained by considering the active species as an alkoxy borohydride in combination with a hard cerium cation which coordinates to the carbonyl to enhance 1,2-selectivity. Other lanthanoid-mediated processes include sodium borohydride with $LnCpCl_2(THF)_3$ (Ln = Sm and Er) in methanol[97] and LAH with a lanthanoid salt,[98] particularly cerium chloride, in THF.

DIBAL-H has often proved effective in 1,2-reduction of enones[99] and the ate complex generated with *n*-butyllithium is a powerful and selective reducing agent, which has been used in toluene–hexane to reduce cyclic enones and in toluene–THF to reduce acyclic examples.[100] 1-Pyrrolylborane–THF complex, which may be prepared from pyrrole and borane–THF, is a reactive aminoborane and has been used to reduce enones and enals to the corresponding allylic alcohols, but its scope remains to be established.[101]

Complex reducing agents prepared from sodium hydride, in combination with sodium alkoxides and metal salts to moderate its basicity, have proved effective for highly regioselective 1,4- and 1,2-reductions of enones depending on the choice of metal salt.[102] The reagent based on nickel acetate was selective for conjugate reduction while that derived from zinc chloride produced allylic alcohols both in good yields.[103] This method has been extended to hydrosilylation of the carbonyl group of enones by incorporation of trimethylsilyl chloride into the reagent.

Molecular orbital calculations have suggested that cyclopentenone is intrinsically more prone to conjugate reduction than cyclohexenone[104] and thus is a good substrate on which to test new 1,2-selective reagents. The selectivity of reduction of both these enones with the best of the new reagents together with the results for 9-BBN-H, the previous reagent of choice,[105] are tabulated for comparison (Table 2).

**Table 2** Comparison of Selective Reagents for Allylic Alcohol Formation over Saturated Ketone or Alcohol in Cyclic Ketone Reduction

| *Reagent* | *Cyclopentenone* | | *Cyclohexenone* | | *Ref.* |
|---|---|---|---|---|---|
| | *Yield (%)* | *Selectivity* | *Yield (%)* | *Selectivity* | |
| $LiAlH_4$ | 100 | 85:15 | 97 | 94:6 | 95 |
| $NaBH_4$ | 100 | 0:100 | 90 | 59:41 | 95 |
| $NaBH_4/CeCl_3$ | 100 | 97:3 | 100 | >99:1 | 96 |
| $NaBH_4/SmCpCl_2$ | 95 | 98.8:1.2 | 99 | 97.9:2.1 | 97 |
| $NaBH_4/ErCpCl_2$ | 83 | 100:0 | 99 | 97.8:2.2 | 97 |
| $LiAlH_4/CeCl_3$ | 99 | 64:36 | 100 | 98:2 | 98 |
| DIBAL-H | 81 | 98:2 | 94 | 98:2 | 100 |
| DIBAL-H/BuLi | 83 | 99:1 | 96 | 94:6 | 100 |
| 9-BBN-H | 85 | >99:1 | 85 | >99:1 | 105 |

### 1.1.4.2 Aldehydes *versus* Ketones

The selective reduction of the more reactive and sterically less hindered aldehyde functionality in the presence of a ketone is a problem often encountered in synthesis. Moderation of the reactivity of the reagent by changes in its structure or to the nature of the reaction medium have been the aims of recent solutions to this problem. An exhaustive listing of 30 modern methods has appeared recently and will not be duplicated here.[106] Those methods that are likely to prove successful in synthesis have been selected for consideration (Table 3).

The reactivity of sodium borohydride has been controlled by employing a mixed solvent system (ethanol/$CH_2Cl_2$ 3:7) and performing the reduction at –78 °C. Under these conditions most aldehydes were reduced in the presence of ketones with >95% selectivity.[106] The comparison between benzaldehyde and 4-methylcyclohexanone revealed the limitation of this method, as substantial reduction of the ketone occurred during the long reaction time that was required. Borohydride exchange resin, prepared from anionic exchange resin and sodium borohydride, reduced aldehydes in preference to ketones in ethanol at 25 °C.[107] The polymeric nature of this reagent facilitates isolation of the products and regeneration of the polymer is possible. Remarkably, at –10 °C in methanol, selectivity between aldehydes was observed. Aromatic aldehydes were reduced in the presence of aliphatic compounds and the reaction was sensitive to the electronic effects of aromatic substituents. Cyclohexanone was reduced much more rapidly than acyclic or bicyclic ketones.

Tetra-*n*-butylammonium triacetoxyborohydride in refluxing benzene reduced aldehydes but not acyclic ketones, the selectivity was demonstrated in competition experiments and keto aldehyde reductions.[108] The more reactive cyclohexanones were reduced only slowly under the same conditions. The limitation of this convenient method is that proximal hydroxy groups activated the reagent enabling the

**Table 3** Comparison of Chemoselectivity in Reductions of Aldehydes in the Presence of Reactive Ketones

| *Reagent* | *Aldehyde/Ketone* | *Yield of Alcohol (%)* | *Ref.* |
|---|---|---|---|
| $NaBH_4EtOH/CH_2Cl_2$ | Hexanal | 97 | 106 |
| | 4-Me-Cyclohexanone | 5 | |
| Borohydride exchange resin | Benzaldehyde | 99 | 107 |
| | Acetophenone | 1.0 | |
| $Bu_4NBH(OAc)_3$ | Benzaldehyde | 95 | 108 |
| | Acetophenone | <4 | |
| 9-BBN-H–py | Benzaldehyde | 93 | 109 |
| | Cyclohexanone | 1.5 | |
| *B*-Siamyl-9-BBN | Benzaldehyde | >95 | 110 |
| | Acetophenone | 0 | |
| 8-Oxyquinoline dihydroboronite/$BF_3$ | Nonanal | 90 | 111 |
| | 4-Me-Cyclohexanone | 28 | |
| $Li(Et_3CO)_3AlH$ | Hexanal | 99.6 | 112 |
| | Cyclohexanone | 0.4 | |
| $Et_4N[\mu\text{-}HMo_2(CO)_{10}]/HOAc$ | Hydrocinnamaldehyde | 100 | 113 |
| | 4-Bu$^t$-Cyclohexanone | 0 | |
| $Bu_3SnH/SiO_2$ | *n*-Octanal | 99 | 114 |
| | Cyclohexanone | 13 | |
| $NaBH_4/CeCl_3/EtOH/H_2O$ | Hexanal | 2 | 116 |
| | Cyclohexanone | 100 | |

stereoselective reduction of ketones (Section 1.1.3.1). Thus a β-keto aldehyde was reduced to the corresponding diol in high yield.

The complex formed from 9-BBN-H and pyridine is a readily prepared stable crystalline solid, which is a mild highly selective reducing agent.[109] Even unhindered ketones were not significantly reduced under conditions that led to complete reduction of aldehydes to the corresponding alcohols. Various representative functional groups were inert to this reagent. 9-BBN-H has also been modified by hydroborating 2-methyl-2-butene to give *B*-siamyl-9-BBN which reduced a wide range of aldehydes at rates at least 100–200 times faster than all ketones tested.[110] 8-Hydroxyquinoline has been used to moderate the reactivity of borane–dimethyl sulfide, the resulting complex could be stored for several weeks under nitrogen at low temperature. In the presence of catalytic boron trifluoride etherate the 8-oxyquinoline dihydroboronite selectively reduced aldehydes rather than ketones.[111] The selectivity was good for alkyl ketones over alkyl aldehydes and two ketoaldehydes were reduced exclusively to the corresponding hydroxy ketones. Cyclohexanones proved to be rather reactive and competed with the aldehydes. As a result 4-methylcyclohexanone could be selectively reduced in preference to 3-pentanone.

A comparison of four tri-*t*-alkoxyaluminum hydrides revealed that lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride, prepared from LAH and 3-ethyl-3-pentanol, was the most selective for reduction of aldehydes over ketones of all types.[112] Even the less reactive benzaldehyde was reduced in THF at –78 °C faster than cyclohexanone (97.7:2.3). A good correlation between the steric demands of the reducing agent and the observed chemoselectivity was observed.

Highly selective reduction of aldehydes rather than ketones, even 4-*t*-butylcyclohexanone, has been achieved by a binuclear hydrido molybdenum anion ($Et_4N[\mu\text{-}HMo_2(CO)_{10}]$) and acetic acid in refluxing THF.[113] The stable complex is readily prepared from molybdenum hexacarbonyl, which can be recovered after reduction. The full value of this reagent in synthesis remains to be established. Tributyltin hydride has been shown to be effective for the selective reduction of aldehydes in the presence of dried silica gel which acts as a mild acid catalyst.[114] The reaction proceeded at room temperature in cyclohexane, many common functional groups were inert under these conditions.

Investigations into the selective hydration and ketalization of various classes of aldehydes and ketones with lanthanoid chlorides have revealed interesting opportunities for selective reductions of less reactive or more hindered carbonyl groups. Ketalization with methanol catalyzed by cerium, erbium or neodymium chlorides protected the aldehydes *in situ*, while sodium borohydride reduced the unreacted ketones; on work-up the aldehydes were released.[115] The selectivity of this method declined with easily ketalized ketones, but conducting the reaction in aqueous ethanol with $NaBH_4/CeCl_3$ provided a more useful alternative.[116] Selective hydration discriminated between ketones and aldehydes and between conjugated and nonconjugated aldehydes.[117] Similarly, selective imine formation with *t*-butylamine and 4Å sieves, reduction with $Li(Bu^tO)_3AlH$, and mild acidic hydrolysis allowed aldehydes to remain unchanged while ketones were reduced.[118]

### 1.1.4.3 Ketones *versus* other Carbonyl Groups

The requirement for a powerful nucleophilic hydride reagent able to reduce even very hindered ketones rapidly and quantitatively has been satisfied by lithium triethylborohydride which was screened against selected representative functional groups.[119] The quest for increased chemoselectivity in total synthesis has led to the development of reducing agents that will discriminate between various classes of ketone or between ketones and other carbonyl groups.

Potassium triisopropoxyborohydride, a mild selective reducing agent, rapidly converted ketones and aldehydes to the corresponding alcohols, while many common functional groups were inert.[120] The reaction of potassium hydride with triphenylborane produced the triphenylborohydride, which is highly hindered and which exhibited excellent chemoselectivity between ketones.[121] Cyclohexanone was reduced in preference to cyclopentanone (97:3) and 4-heptanone (99.4:0.6), while methyl ketones were more reactive than 4-heptanone (2-heptanone, 94:6; acetophenone, 97.8:2.2).

Zinc-modified cyanoborohydride, prepared from anhydrous zinc chloride and sodium cyanoborohydride in the ratio 1:2 in ether, selectively reduced aldehydes and ketones but not acids, anhydrides, esters and tertiary amides.[122] In methanol the reactivity paralleled the unmodified reagent. Zinc and cadmium borohydrides form solid complexes with DMF, which may prove to be convenient sources of the reducing agents.[123] Aromatic and α,β-unsaturated ketones were reduced much more slowly than saturated ketones, so chemoselective reduction should be possible.

Sodium borohydride in methanol/dichloromethane (1:1) at –78 °C reduced ketones in the presence of conjugated enones with excellent selectivity.[124] Competition experiments were complemented by reductions of diones to illustrate the synthetic value of the method. The Wieland–Miescher ketone was reduced to the 1-β-alcohol contaminated by less than 3% diol in quantitative yield. The same reagent in acetic acid was shown to be effective at reducing aromatic ketones with *ortho* hydroxy or *ortho* amino substituents rapidly.[125] Other aromatic ketones were relatively inert under the same conditions. Presumably the success of this procedure relies on activation and intramolecular delivery of the acetoxyborohydride by the *ortho* substituent.

Borane was modified by reaction with half a molar equivalent of 2-aminoethanol to give a reagent that reduced aldehydes and ketones rapidly at room temperature in THF, but did not reduce esters, oxime esters, tetiary amides, nitriles, halides and acid chlorides.[126] Complete chemoselectivity between acetophenone and ethyl benzoate was demonstrated. The combination of polymer-bound amino alcohols and borane was also investigated to take advantage of simplification in work-up and the possibility of enhanced selectivity. Various amines were combined with borane to produce reagents of moderated reactivity. The most promising was *t*-butylamine borane, which exhibited dramatic rate differences between different types of ketone, suggesting that chemoselective reduction of certain diketones would be possible with this reagent.[127] The reducing power of LAH has been tempered by pretreatment with dry silica gel in ether to enable reductions of keto esters to hydroxy esters in nonpolar solvents.[128] Diphenylstibine has been used, for the first time, in combination with Lewis acids, particularly aluminum trichloride, to reduce aldehydes and ketones in THF at room temperature in excellent yields.[129] Esters, acid chlorides, alkyl halides and alkenes were unreactive under these conditions, so this new reagent holds promise as a mild chemoselective reducing agent.

The concept of *in situ* protection of the less hindered or more Lewis basic of two ketones to enable selective reduction of the usually less reactive groups has been successfully developed.[130] The sterically hindered Lewis acid MAD (**78**) derived from BHT and trimethylaluminum was used to coordinate preferentially to the less hindered ketone and DIBAL-H reduced the more hindered ketone that remained uncomplexed. An approximate order of comparative reactivity for various classes of ketones has been established. The selectivity was improved by using the more hindered Lewis acid MAB (**79**) and/or dibromoalane as the reducing agent. The discrimination between aromatic ketones is good but less successful between two dialkyl ketones. The chemoselectivity was demonstrated in the reduction of diketone (**80**) to keto alcohol (**81**) in 87% yield and excellent selectivity (equation 20).

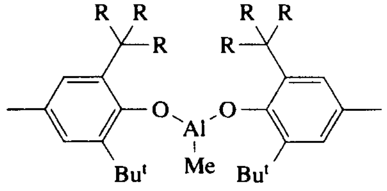

(**78**) MAD, R = Me
(**79**) MAB, R = Et

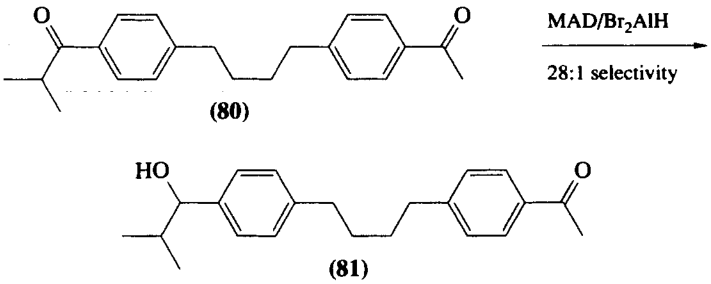

**(80)**

**(81)**

(20)

### 1.1.4.4 Quinones to Hydroquinones

The reduction of quinones to the corresponding hydroquinones is an important synthetic transformation that has been accomplished with various conventional reducing agents.[131] Complex metal hydride reagents have not tended to be the method of choice, as competitive formation of the dihydrodiols is frequently a problem. These two possible outcomes are illustrated for anthraquinone (**83**) giving the hydroquinone (**82**) and dihydrodiol (**84**), respectively (Scheme 13). Route 1, to the hydroquinone, diverges from route 2 after the first hydride equivalent has been added, as the remaining carbonyl group is enolized rather than reduced; hydrogen is liberated as a result.

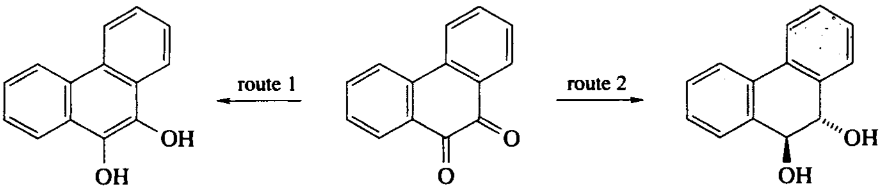

**(82)** **(83)** **(84)**

**Scheme 13**

Alkoxyaluminum hydrides including Red-Al, Li(Bu$^t$O)$_3$AlH and Li(MeO)$_3$AlH have been used extensively, particularly for the reduction of *o*-quinones to the corresponding *o*-hydroquinones.[5] It appears that the use of more soluble reagents and powerful ethereal solvents also favors reduction to the hydroquinone.[132]

Hydrosilylation to give bis(trimethylsilyloxy)benzenes has proved an attractive alternative.[133] The most convenient and high yielding method used 1,1,3,3-tetramethyldisiloxane (TMDS) and a catalytic quantity of iodine or trimethylsilyl iodide[134] in refluxing dichloromethane. A range of *p*-quinones (**85**), including 1,4-naphthoquinone, was reduced and the resulting silyl ethers were hydrolyzed to give uniformly good yields (85–98%) of the corresponding hydroquinones (**86**; equation 21).

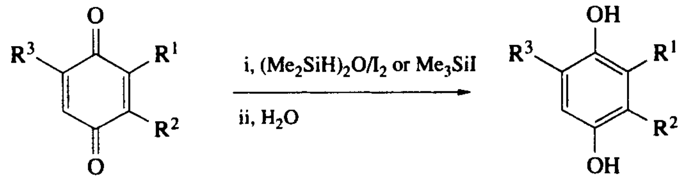

**(85)** **(86)**

(21)

Hydrides of tin and germanium also reduce quinones, ultimately to the hydroquinones. The detailed mechanism of hydrogen transfer between four stannanes and four quinones has been studied which suggested a radical mechanism in which hydrogen transfer was the first step.[135]

### 1.1.4.5 α-Halo Ketones

α-Halocarbonyl compounds can be reduced at the carbonyl group to give the chlorohydrins or at the carbon–halogen bond to give the saturated ketones or alcohols. Hydrogenolysis of the carbon–halogen bond is often a severe limitation on the value of this route to chlorohydrins, particularly when nucleophilic reducing reagents are used.

A detailed study of a series of α,α-halo ketones demonstrated that electrophilic reducing agents, notably borane, DIBAL-H and $BH_3$·DMS, provided excellent yields of the alcohols without reduction of the halogen bond.[136] In contrast, nucleophilic reagents ($NaBH_4$, $Li(Bu^tO)_3AlH$ and K-selectride) were unsatisfactory. The results for a representative α,α-dibromo ketone (**87**) being reduced to the mono- (**89**) and di-bromohydrin (**88**; equation 22) are shown in Table 4.

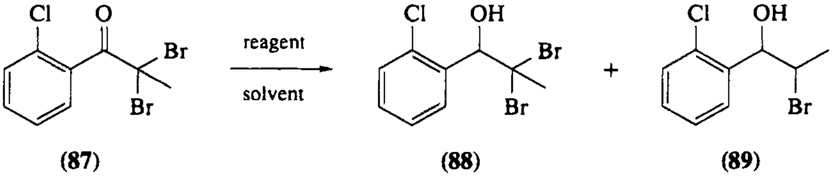

(22)

**Table 4** Comparison of Reducing Agents for the Reduction of α,α-Dibromoketone (**87**)

| *Reagent* | *Solvent* | *Yield of* (**88**) *(%)* | *Yield of* (**89**) *(%)* |
|---|---|---|---|
| $NaBH_4$ | MeOH | 50 | 50 |
| $Li(Bu^tO)_3AlH$ | THF | 55 | 45 |
| K-Selectride | Ether | 25 | 75 |
| DIBAL-H | Hexane | 90 | 0 |
| $BH_3$·DMS | Ether | 87 | 0 |
| Borane | THF | 90 | 0 |

Under radical conditions tributyltin hydride reduced α-chlorocarbonyl compounds to the corresponding saturated carbonyl derivatives but in the presence of phosphine oxides (HMPA or $Bu_3PO$) chemoselective reduction of the carbonyl group was observed. α-Chloro ketones and aldehydes were reduced with this reagent combination to give good yields of the chlorohydrins.[137] The choice of ligand was important as neither phosphines nor amines were effective substitutes for the phosphine oxides.

## 1.1.5 OTHER METAL HYDRIDES

### 1.1.5.1 Silicon

Silicon hydrides are an interesting class of carbonyl reducing agents as they are reasonably stable under normal conditions requiring activation with a transition metal complex,[138] fluoride ion[45] or Lewis acid.[46] The correct choice of reaction conditions allows highly chemo- and stereo-selective reduction of particular classes of carbonyl compounds with these convenient reagents.

Tris(triphenylphosphine)chlororhodium promoted hydrosilylation of α,β-unsaturated carbonyl compounds and the resulting adducts gave the corresponding alcohols on methanolysis.[139] The regioselectivity of addition depended on the silane; monohydrosilanes ($Et_3SiH$,$EtMe_2SiH$) favor conjugate reduction to give the silyl enol ether, but dihydrosilanes ($Ph_2SiH_2$, $Et_2SiH_2$) reduced the carbonyl group directly, generating allylic alcohol derivatives. The yields were uniformly high and the regioselectivity in the substrates screened was impressive.

Aldehydes and ketones were reduced chemoselectively under mild conditions by hydrosilanes (generally $PhMe_2SiH$) in dipolar aprotic solvents with TBAF or tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) as catalytic fluoride source. The reduction of α-substituted ketones is highly *syn* selective (Section 1.1.3.1). The mechanism of this reaction has been investigated and involves rate-determining hydride transfer from a hexavalent silicate $[HSiR_3F(HMPA)]^-$ (**90**) and not prior coordination of the fluorosilane with the carbonyl group (Scheme 14).[45] Minor amounts of radical-derived reduction products due to single-electron transfer processes, together with predominant hydride transfer, have been observed in certain mechanistic probe systems.[140]

An analogous pentacoordinate hydridosilicate reagent (**91**), prepared from trichlorosilane and catechol or 2,2′-dihydroxybiphenyl with butyllithium (equation 23), reduced aldehydes and ketones in THF under mild conditions in high yield to the corresponding alcohols without any added catalyst (equation 24).[141]

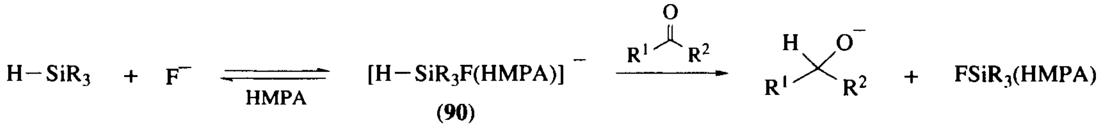

**Scheme 14**

The chemo- and stereo-selectivity of this reagent was briefly examined, as was the mechanism indicating that rate-determining hydride transfer was involved.

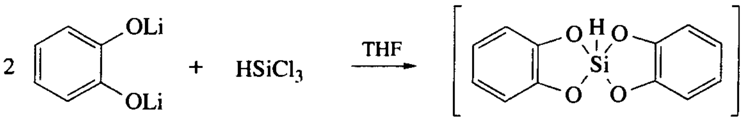

(91)

(23)

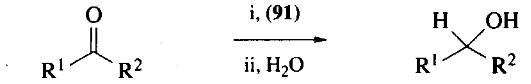

(24)

Although hydrosilanes reduce ketones, in trifluoroacetic acid, to the corresponding methylene compounds or dimeric ethers *via* ionic hydrogenation, the reduction of α-amino and α-oxy ketones and β-keto acid derivatives with hydrosilanes, particularly $PhMe_2SiH$, under these conditions proceeded with high *anti* selectivity to the alcohols.[46] No racemization was observed at the carbon α to the carbonyl group. Intramolecular hydrosilylation catalyzed by Lewis acids provided a highly stereoselective route to *anti*-1,3-diols from β-hydroxy ketones (Section 1.1.3.1).[53]

### 1.1.5.2 Tin

Hydrostannation of carbonyl compounds with tributyltin hydride is promoted by radical initiation and Lewis or protic acid catalysis.[142] The activation of the carbonyl group by the acidic species allows the weakly nucleophilic tin hydride to react *via* a polar mechanism. Silica gel was a suitable catalyst allowing chemoselective reduction of carbonyl groups under conditions that left many functional groups unchanged.[114] Tributyltin triflate generated *in situ* from the tin hydride and triflic acid was a particularly efficient catalyst for the reduction of aldehydes and ketones with tributyltin hydride in benzene or 1,2-dichloromethane at room temperature.[143] Esters and ketals were not affected under these conditions and certain aldehydes were reduced selectively in preference to ketones.

Sterically hindered ketones were more difficult to reduce with tin hydrides but reduction at high pressure (1 GPa) without radical or Lewis acid catalyst in methanol at 55 °C was effective.[144] Reduction of the very hindered ketone (**92**) did not occur at atmospheric pressure but proceeded usefully at high pressure (equation 25). The absence of radical intermediates allowed even α,β-epoxy and cyclopropyl ketones such as (**93**) to be reduced in high yield, largely without cleavage of the strained ring (equation 26). Under conventional AIBN-initiated conditions radical-mediated processes predominated.

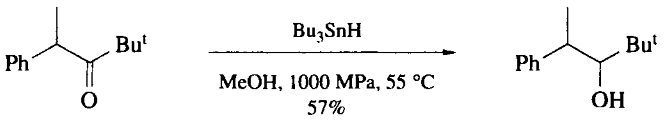

(25)

(**92**)

*anti*/*syn* = 0.14

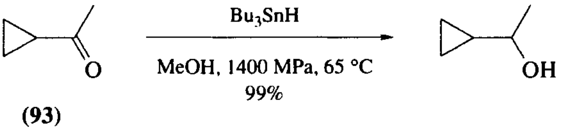

(26)

(**93**)

### 1.1.5.3 Transition Metals

Transition metal hydrides have also been investigated as potential reducing agents for aldehydes and ketones. A preliminary study of the reaction of neutral metal hydrides with acetone and trifluoroacetone indicated that complexes of metals on the left of the transition series were more likely to reduce the ketones.[145] Anionic Group VI transition metal hydrides [$HM(CO)_5^-$ and *cis*-$HM(CO)_4P(OMe)_3^-$, M = Cr, W] were screened against a range of aldehydes and ketones.[146] The former complex required acid activation for all aldehydes except formaldehyde, but the latter was more nucleophilic and reduced all the aldehydes to the corresponding alcohols in good yield. Ketone reduction was possible in the presence of acetic acid, but competitive destruction of the metal complex was a problem. Useful chemoselectivity allowing reduction of aldehydes but not ketones was noted with an anionic molybdenum hydride complex.[113]

Lithium hydride, prepared by hydrogenolysis of *t*-butyllithium under pressure, was observed to reduce aldehydes and cyclohexanones to the corresponding alcohols in the presence of transition metal halides.[147] An equimolar quantity of vanadium trichloride was found to be the most effective catalyst, but the identity of the active reducing species was not established.

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# 1.2

# Reduction of C=N to CHNH by Metal Hydrides

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## 1.2.1 INTRODUCTION

The reduction of various carbon–nitrogen π-systems to saturated derivatives with metal hydrides, principally aluminum- and boron-based reagents, provides highly useful processes for the preparation of amines and related functionalities.

Since their introduction in the 1940s, lithium aluminum hydride ($LiAlH_4$, LAH)[1] and sodium borohydride ($NaBH_4$)[2] have, of course, enjoyed enormous popularity for reduction of organic groups including nitrogen-containing double bonds. In addition, systematic alterations of these reagents, usually by replacement of one or more hydrogens with other functionalities or by combination with other reagents, have provided a great number of useful, modified hydrides, many of which have found significant utility for the manipulation of carbon–nitrogen π-systems, as well as other organic functional types.

The dominance of various metal hydrides for reductions of organic functionalities has led to several reviews, monographs and books devoted to discussions of their utility (including this volume), embedded in which are often included applications to carbon–nitrogen π-systems. Thus, LAH and modified derivatives,[3–10] $NaBH_4$ (in alcohol, ether,[4–13] and carboxylic acid[10–12,14] solvents) and altered derivatives,[7–9,11–13,17] sodium cyanoborohydride ($NaBH_3CN$),[7,9,11,12,15,16] borane ($BH_3$)/THF,[4,5,7,11–13,17,18] $BH_3SMe_2$[19] and amine·$BH_3$[20] complexes, as well as less-utilized hydride reagents,[7,9–11] have received considerable coverage, and much general information concerning carbon–nitrogen π-reductions may be extracted from the above, as well as from most recent advanced texts and discussions of imine chemistry.[21,22] However, no extensive reviews have appeared which focus primarily on imino π-reductions, offer comparisons between hydride reagents and present an overview of synthetic possibilities. Thus, coverage in this chapter will survey metal hydride reductions of the various carbon–nitrogen π-systems with an eye toward identifying superior choices for a given functionality and to augment, not duplicate, the above discussions, although some overlap is inevitable. Other, complementary, reducing systems, not involving metal hydrides, as well as asymmetric conversions are discussed elsewhere in this volume (*i.e.* Chapters 1.3–1.8). Likewise, reductions of nitriles (Chapters 1.10–1.12), most heterocyclic C=N systems (Chapters 3.6–3.8) and C=N reductions which proceed further to products devoid of nitrogen (*e.g.* sulfonylhydrazone reductions to hydrocarbons, see Chapter 1.14) are not included.

## 1.2.2 REDUCTION OF IMINES AND IMINIUM SALTS OF AMMONIA AND AMINES

### 1.2.2.1 General Considerations and Comparisons to Carbonyl Reductions

In a general sense, reductions of imine-type π-bonds with metal hydrides broadly parallel the corresponding reductions of carbonyls to alcohols, and many of the same reagents are routinely utilized (*e.g.* LAH, $NaBH_4$, $NaBH_3CN$, $BH_3$, *etc.*, see also Section 1.2.2.2). However, as expected, the type of *N*-substitution present in imino π-systems does alter, often substantially, the electrophilicity of the carbon under attack, and this in turn provides wide variations in reduction rates or, in some cases, prevention of reduction altogether. Thus, for example, while trialkylborohydrides rapidly reduce most carbonyls (even at –78 °C),[23] oximes and oxime ethers are essentially inert at 65 °C.[24,25] As with carbonyls, protonation or complexation of imino nitrogens enhances the electrophilicity of the resulting iminium salts and increases reduction rates. This has led to the development of highly successful reducing systems conducted under mildly acidic conditions (pH *ca.* 3–6) using reagents (*e.g.* $NaBH_3CN$,[15,16,26] $NaBH_4/RCO_2H$,[14] amineboranes[20]) which tolerate acidic media and a substantial portion of imino group reductions presently utilize such systems. Furthermore, the relatively enhanced reduction rates of imines compared to carbonyls under acidic conditions, presumably because of the higher basicity of the former, permits the *in situ* generation of the requisite iminium ions from carbonyls and amines, and eliminates the need to preform the imino derivatives.[26] This has led to direct reductive amination processes, particularly with $NaBH_3CN$,[26] which are presently the most successful and often used procedures for this important transformation.

The stereochemical outcomes of the reductions of cyclic imino derivatives often display surprisingly great differences from those obtained with cycloalkanones[7,27] and, in fact, attenuations or even reversals in stereoselectivity are common.[28]

Mechanistic details involved in imine and carbonyl[27,29] reductions are undoubtedly similar, although thorough investigations of the former are lacking. Certainly, hydride transfer to the electrophilic carbon, with or without prior activation by protonation or complexation is essential for both types of π-systems (Scheme 1). Whether or not alcohol solvents participate in imine reductions by borohydride (in the absence of added acid) to furnish the amine proton (as is the case with carbonyls)[29] is not known and must await detailed kinetic study and analysis of the initial intermediates formed before hydrolysis. Direct, *in situ*, reductive amination with $NaBH_3CN$ has been attributed to initial, reversible formation (*via* an intermediate hydroxyamine, (**1**) of an iminium ion (**2**) from carbonyls and amines followed by rapid attack by hydride (Scheme 2).[26] However, the inertness of an imine (partial structure **3**) to the usual reductive amination conditions ($NaBH_3CN$, MeOH, $H^+$) coupled with successful reductive amination of the corresponding ketone of (**3**) suggests that, at least in some cases, direct reduction of the hydroxy amine (**1**) occurs.[30] This possibility is supported by the successful reduction of bis(methoxymethyl)amines to dimethylamines[31] and methylols (*e.g.* **4**) to *N*-methylamides[32] with $NaBH_3CN$ in acidic media. Further investigation of this question appears warranted.

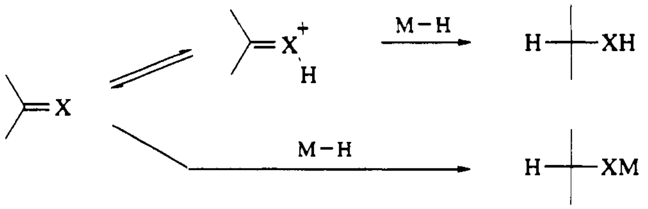

**Scheme 1**

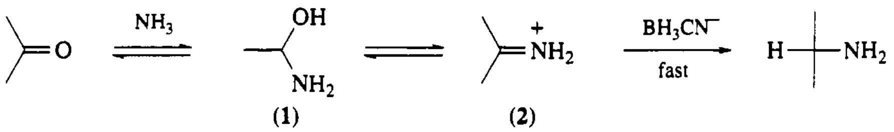

**Scheme 2**

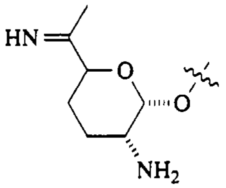

(**3**)

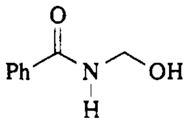

(**4**)

The sections which follow present an overview of of the most effective and convenient reagent(s), and the chemo- and stereo-selectivities (where known) expected with them. Of course, the choice of reagents and conditions is often dictated by a combination of these considerations, so that structural types and functional group complexity play key roles in reagent selection. A wide selection of examples are presented, chosen to illustrate the range of successful structural types and potential pitfalls. Further examples may be obtained from reviews and monographs.[3–20]

## 1.2.2.2 Reduction of Preformed Imines and Iminium Salts of Ammonia, Primary and Secondary Amines

### *1.2.2.2.1 Choice of hydride reagent and solvent*

As mentioned above, a variety of metal hydrides have been employed for successful imine and iminium ion reductions, particularly LAH and its derivatives[3–10] and $NaBH_4$ and derived reagents.[4–20] For discussion here, iminium ions imply those derived from secondary amines, although protonated ammonia derivatives and primary imines are actually the intermediates involved in reductions in acidic media. The most popular reagents for imine reductions, especially in recent years and with complex synthetic targets, include $NaBH_4$ in alcohol or carboxylic acid [usually acetic acid in which the actual reducing species is $NaBH(OAc)_3$][14] solvents and $NaBH_3CN$ in acidic media (usually methanol/HCl or acetic acid). To illustrate the versatility of $NaBH_4$ and $NaBH_3CN$ for imine reductions, collections of successful conversions, chosen to represent varieties of structural types, are presented in Tables 1 and 2.

Table 1 demonstrates that $NaBH_4$ may be used in the presence of heterocyclic rings (entries 8–10, 13–17), esters (entries 8–10, 17), amides (entries 1, 9), conjugated double bonds (entry 7), alkynes (entry 5) and acetals (entry 4). The process can also be used to methylate an amine with formaldehyde as the carbonyl (entry 13). With certain structures, further reactions may occur subsequent to reduction (*e.g.* entry 6). Entry 15 illustrates a synthetically useful amine alkylation reaction which may occur in acetic acid. This remarkable reaction is attributed to self-reduction of an acyloxyborohydride to an aldehyde

**Table 1** Reduction of Imines with $NaBH_4$

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 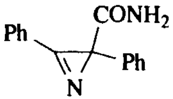 | MeOH | 65 | 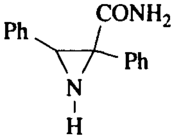 | 73 | 33 |
| 2 | 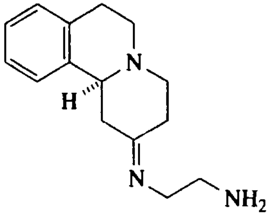 | MeOH | 35 | 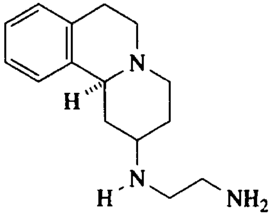 | 86 | 34 |
| 3 | 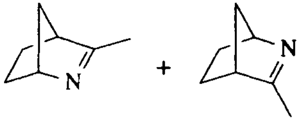 | MeOH | — | 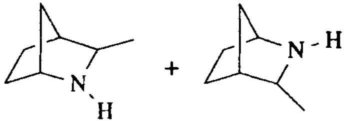 | — | 35 |
| 4 | 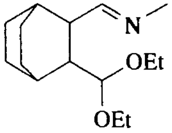 | MeOH | 0 | 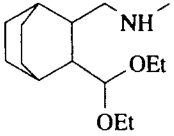 | — | 36 |
| 5 | 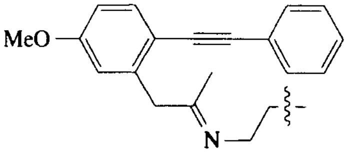 | MeOH | 25 | 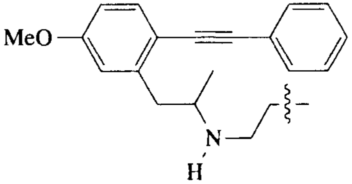 | 56 | 37 |

**Table 1** *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 6 | 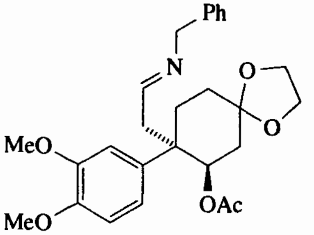 | MeOH | 25 | 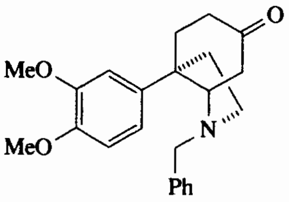 | 75 | 38 |
| 7 | 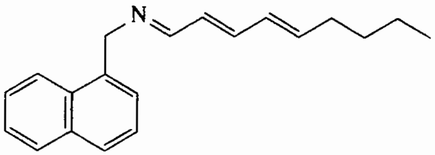 | MeOH[a] | 40 | 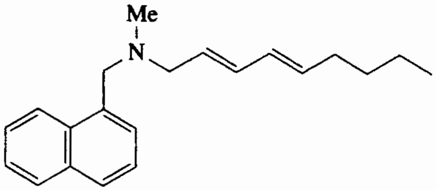 | 67 | 39 |
| 8 | 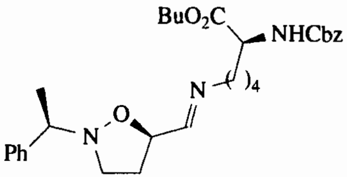 | MeOH | 5 | 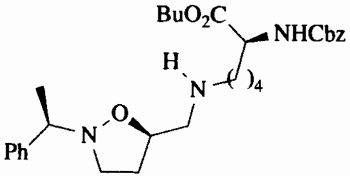 | 68 | 40 |
| 9 | 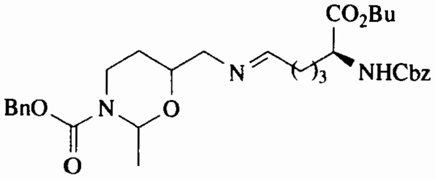 | THF/MeOH | 5 | 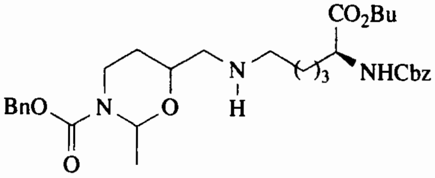 | 46 | 41 |

**Table 1** *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 10 | 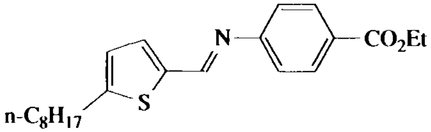 | EtOH | 78 | 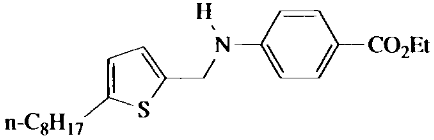 | 75 | 42 |
| 11 | 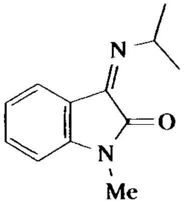 | MeOH | — | 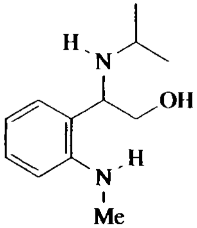 | — | 43 |
| 12 | 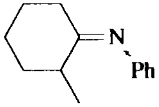 | $Pr^iOH$ | 25 | 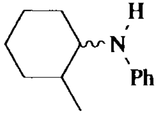 | $93^b$ | 28 |
| 13 | 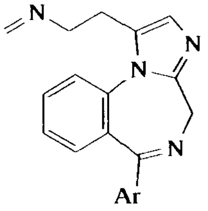 | MeOH | 25 | 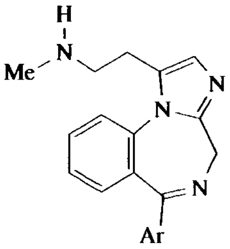 | 43 | 44 |

**Table 1** *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 14 | 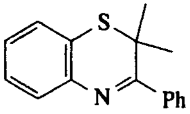 | AcOH | 80 | 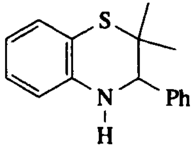 | 60 | 45 |
| 15 | 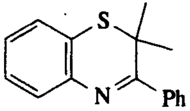 | AcOH | 80 | 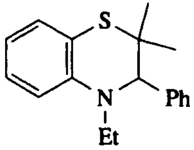 | 75 | 45 |
| 16 | 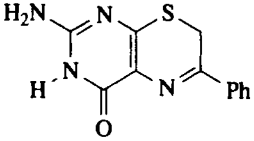 | $CF_3CO_2H$ | 80 | 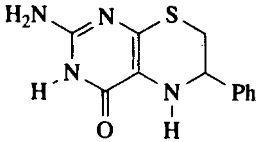 | 51 | 46 |
| 17 | 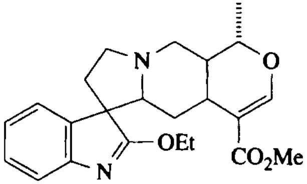 | AcOH | 25 | 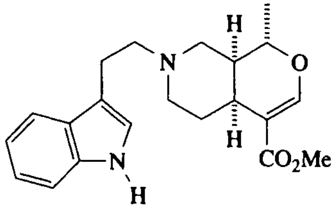 | 55 | 47 |

[a] Reduction was followed by reductive *N*-methylation with $CH_2O/NaBH_4$. [b] *Cis/trans* ratio 75:25.

**Table 2** Reduction of Imines with $NaBH_3CN$

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 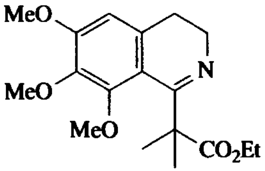 | AcOH | 25–30 | 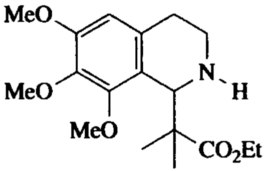 | 94 | 53 |
| 2 | 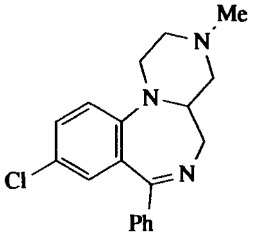 | $CF_3CO_2H$ | 25 | 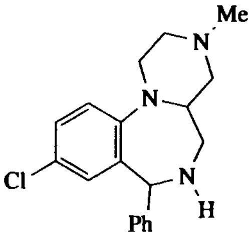 | 95 | 54 |
| 3 | 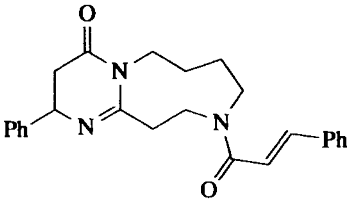 | AcOH | 25 | 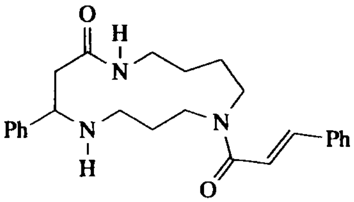 | 93 | 55 |

**Table 2** *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 4 | 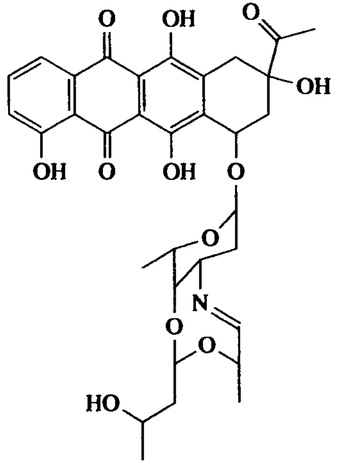 | AcOH/MeOH | 0 | 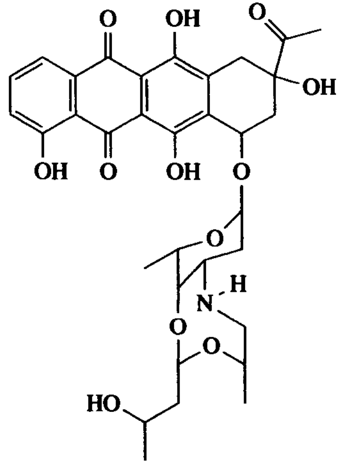 | — | 56 |
| 5 | 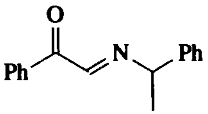 | AcOH/MeCN | –10 | 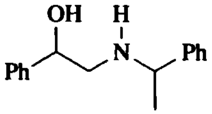 | 62 | 57 |
| 6 | 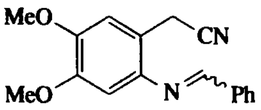 | MeOH/HCl | 25 | 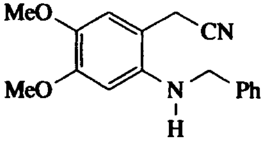 | 76 | 58 |
| 7 | 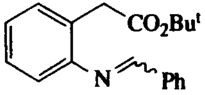 | MeOH/HCl | 25 | 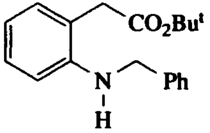 | 75 | 58 |

Table 2 *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 8 | 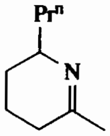 | THF/$H_2O$ | — | 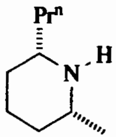 | 81 | 59 |
| 9 | 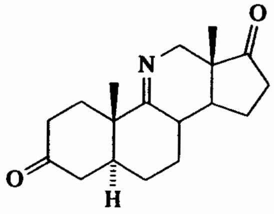 | MeOH/HCl | 25 | 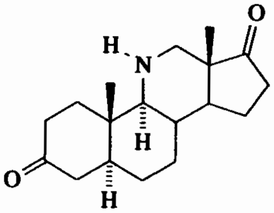 | 65[a] | 60 |
| 10 | 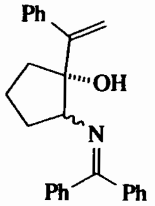 | — | — | 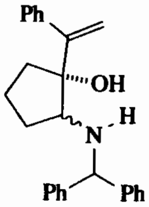 | 63 | 61 |
| 11 | 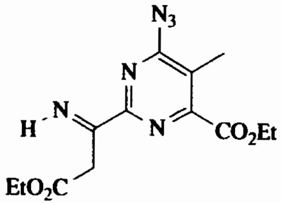 | MeOH/HCl | 25 | 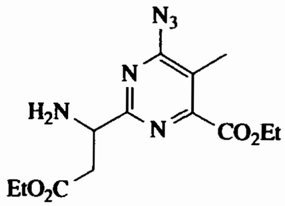 | 80 | 62 |

**Table 2** *(continued)*

| *Entry* | *Imine* | *Solvent* | *Temp.* (°C) | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|---|
| 12 | 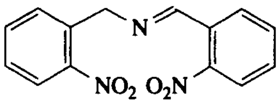 | MeOH/THF/HCl | 25 | 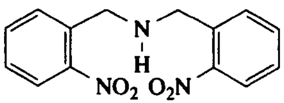 | 92 | 63 |
| 13 | 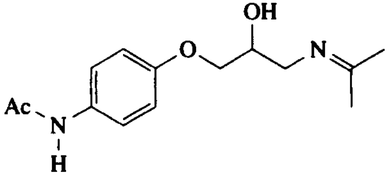 | MeOH | — | 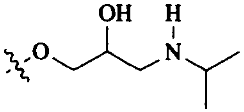 | — | 64 |
| 14 | 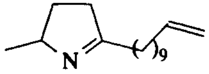 | MeOH/HCl | — | 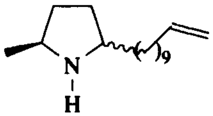 | >93 | 65 |
| 15 | 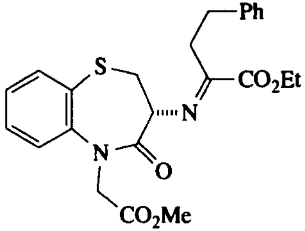 | MeOH/AcOH | 25 | 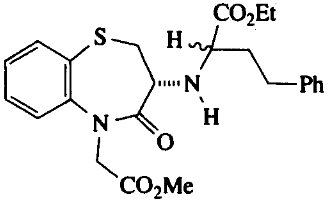 | 48 | 66 |

[a] After reoxidation with Jones reagent.

followed by condensation with an amine and subsequent reduction of the resulting imine.[11,14,45,48] Imine reductions with $NaBH_4$ have also been employed in the biochemical arena, for example, to couple drugs (*e.g.* digoxin) to polydimethylsiloxanes (in methanol),[49] to attach immunoglobulins to liposomes *via* glycosphingolipids (in water, pH 9.5),[50] to attach spin labels (for ESR studies) to adenylic acid and tRNA,[51] and to affinity label (and introduce tritium *via* $NaBH_3T$) diphtheria toxin with ADP-ribose (in aqueous phosphate buffer, pH 8).[52] It should be noted that the even milder reagent $NaBH_3CN$ is more commonly used in biological applications, as will be addressed below.

A variety of imine reductions using $NaBH_3CN$ in acidic media (where the actual species reduced are protonated iminium ion intermediates) are presented in Table 2 and illustrate the versatility of this mild reagent for synthetic applications. Thus, esters (entries 1, 7, 11, 15), amides (entries 3, 13, 15), cyano (entry 6), nitro (entry 12) and even such normally sensitive moieties as ketones (entry 4; however, see entry 5) and azide (entry 11) remain immune to this exceptionally tolerant reagent.

As mentioned, the mildness of $NaBH_3CN$ (coupled with its effectiveness and stability in aqueous media) has attracted considerable interest for applications in biochemical areas. Examples include the trapping of suspected imine intermediates produced in enzyme (mitochondrial monoamine oxidase) inactivation by amines,[67] the establishment by reduction of the positions of imine-forming amines in 2-keto-3-deoxy-6-phosphogluconate aldolase,[68] and the transfer labeling of methionyl-tRNA synthetase[69] and methionyl-tRNA transformalase[70] by treatment with periodate-treated tRNA. In fact, most biochemical applications of $NaBH_3CN$ have utilized *in situ* imine formation–reduction (*i.e.* reductive amination) conditions and will be further discussed in Section 1.2.2.3.1.

Although $NaBH_4$ and $NaBH_3CN$ usually attract the most attention, many other reagents reduce imines to amines and have been utilized in synthetic applications. These include the previously mentioned LAH,[3–10,71–74] borane[18,19,75] and amineborane complexes,[20,24,28] as well as various substituted derivatives such as $KBH_4$,[33] $NaAlH_4$,[76] $NaAlH_2(OCH_2CH_2OMe)_2$,[28,33] diisobutylaluminum hydride (DIBAL-H),[77] lithium triethyl-[24,78] and tri-*s*-butyl-borohydride[24,28,72,75,78] ('Superhydride' and 'L-Selectride,' respectively), alkyl- and dialkyl-cyanoborohydrides,[78] sodium dithionite,[79] hydridoferrates [*e.g.* $KFeH(CO)_4$,[80,81] and $Fe_3H(CO)_{11}$[82]], silanes [*e.g.* $Et_3SiH/CF_3CO_2H$,[83] $Et_3SiH/(Ph_3P)RhCl$[84]] and selenophenol (PhSeH).[85] A brief selection of representative examples of imine reductions with various hydride reagents listed above is presented in Table 3. Entry 2 illustrates a side reaction with LAH, in which initial reduction is followed by an internal displacement to afford an aziridine.[73] Furthermore, reduction of imines with trimethylamineborane in acetic acid gives *N*-acylation concomitant with C═N reduction (*e.g.* entry 5).[87] This result is probably distantly related to the previously described alkylation of amines with $NaBH_4/AcOH$[14,45,48] except that in this case the amine is acylated by attack on an acetoxyborane. As with ketones, bulky reagents (*e.g.* $LiBHEt_3$ and, particularly, $LiBHBu^{s}_{3}$) find utility in imine reductions where stereocontrol of cyclic systems is desired (*e.g.* entries 6–8, see also Section 1.2.2.2.3).

With certain structural types, the reduction course and subsequent reactions exhibited with hydride reagents may depend on the relative reduction rates of groups present. Thus, for example, reduction of the keto imine (**5**) with LAH (THF, reflux) afforded a mixture of the amino alcohol (**6**; 29%) and the *O*-bridged derivative (**7**; 10%), while $NaBH_4$ (THF/MeOH) gave (**7**; 49%) and $NaBH_3CN$ (EtOH/AcOH) afforded only the *N*-bridged compound (**8**). This suggests that LAH reduced the imine and ketone at comparable rates, while $NaBH_4$ and $NaBH_3CN$ selected the ketone and the imine (*via* the iminium ion) groups, respectively.[88]

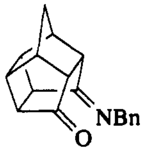

(**5**)

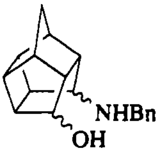

(**6**)

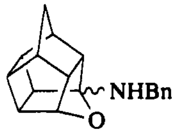

(**7**)

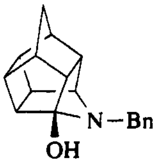

(**8**)

As described above, the reduction of imines often proceeds *via* iminium ions particularly in acidic media, since protonation enhances the electrophilicity of the imine carbon. Thus, as expected, preformed iminium salts generated from carbonyls and secondary amines are also readily reduced by most hydride reagents. Several examples of synthetic applications with a variety of reagents are illustrated in Table 4. Entries 9–12 illustrate the use of iminium intermediates for the reductive removal of amide carbonyls. Thus, treatment of amides with $POCl_3$ affords the iminium derivatives (*e.g.* **9**; Scheme 3), which are reduced by $NaBH_4$ to the corresponding amines (Table 4, entries 9, 10).[96–98] Likewise, reaction of amides with trialkyloxonium salts to give imidic esters (entry 12) or thioamides with methyl iodide to give thioiminium salts (*e.g.* entry 11) followed by reduction with $NaBH_4/SnCl_4$[100] (or $NaBH_4$)[101] or $NaBH_4$ (also $NaBH_3CN$),[99] respectively, affords amines.

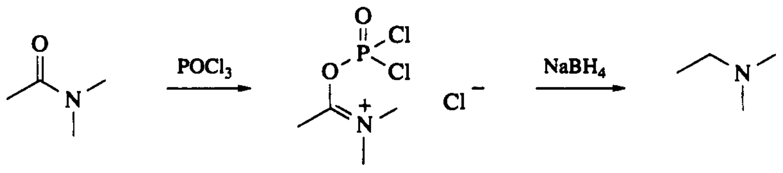

**(9)**

**Scheme 3**

### 1.2.2.2.2 *Chemoselectivity of hydride reagents*

An important consideration in the selection of a metal hydride reagent for C=N reductions is, of course, that other functionalities present are not affected. Summaries and tables of the chemoselectivities of various hydride reagents are available,[8,102] (*e.g.* also ref. 9, p. 177; ref. 11, p. 129) and can be consulted for particular situations. However, in general, the principal reason that $NaBH_4$ and, particularly, $NaBH_3CN$ have enjoyed extensive popularity is directly related to the selectivity available with these reagents, since both are essentially inert toward most common functional groups except aldehydes and ketones, and even these latter are resistant toward $NaBH_3CN$ in neutral or basic conditions.[16,26] As previously mentioned, this tolerance has been exploited to allow imine reductions in the presence of esters, amides, alkenes, ethers, nitriles, nitro groups, ketones, a variety of heterocyclic rings (see Tables 1 and 2), and with sensitive biological systems. Other functional groups such as aryl and alkyl halides (*e.g.* entry 8, Table 4), sulfoxides, sulfones and even some epoxides also remain intact under conditions used for imine reductions.[103]

### 1.2.2.2.3 *Stereoselectivity with cyclic derivatives*

Another consideration which often must be addressed in reductions of cycloalkanone imines involves the control of stereochemistry, so that proper diastereorelationships can be installed in complex molecules. Although considerably less investigation of this topic has occurred compared to the immense efforts devoted to corresponding ketone reductions,[27,29,104] (see also ref. 7, chap. 12; ref. 11, p. 141 and references cited therein) several features have emerged which allow some degree of prediction and control of stereochemical outcomes.[24,28,72,75,78,91] Thus, in general, and in analogy to ketones, 'small' unsubstituted metal hydrides (*e.g.* LAH,[72,91] $NaBH_4$,[28] $NaBH_3CN$[28,72,78]) prefer to approach from the axial direction of unhindered cyclohexyl imines and iminium ions (*i.e.* **10**; equation 1) to afford predominantly the corresponding equatorial amines (*i.e.* **11**; equation 1). Likewise, results with very bulky reagents (*e.g.* $LiBHBu^s_3$) also correspond with those obtained with ketones[22] in that equatorial attack of (**10**) to give **12**) is highly favored.[24,28,72,78] On the other hand, major differences between ketones and imines are observed with even moderately bulky reagents [*e.g.* $BH(OAc)_3$,[28] $NaAlH_2(OCH_2CH_2OMe)_2$,[28] $(alkyl)_2BHCN$[78]]. Thus, such reagents normally afford principally axial attack with ketones but equatorial approach with imines and, in many cases, the difference is substantial.[28] Thus, for example, the imine (**10a**; R = $Bu^t$) afforded a 16:84 *trans*:*cis* mixture of amines (**11a**; *trans*) and (**12a**; *cis*) with $Bu^tNH_2{\cdot}BH(OAc)_2$, while the analogous ketone, 4-*t*-butylcyclohexanone, gave an 84:16 *trans*:*cis* mixture of the corresponding alcohols.[28] This divergent behavior has been attributed to increased steric impedance toward axial approach induced by substituents on nitrogen (*i.e.* as indicated in **13** and **14**).[28] Table 5 presents stereochemical results for several 4-substituted cycloalkyl imines with a variety of hydride reagents, along with comparisons to the analogous ketones (see also entries 3 and 5, Table 4), and illustrates the similarities and differences described above.

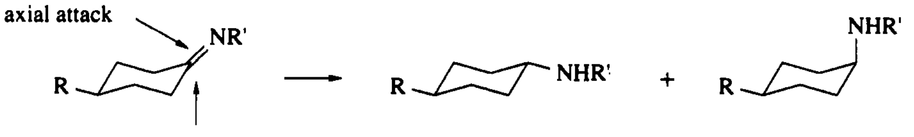

**(10)** **(11)** **(12)**

**Table 3** Reduction of Imines with Various Hydride Reagents

| *Entry* | *Imine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 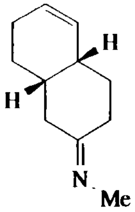 | $LiAlH_4$ | THF | 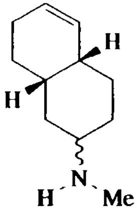 | a | 72 |
| 2 | 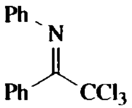 | $LiAlH_4$ | $Et_2O$ | 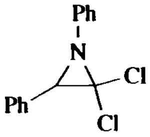 | 66 | 73 |
| 3 | 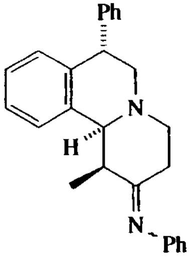 | $BH_3$•THF | PhMe/THF | 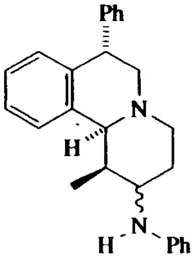 | 99[b] | 75 |
| 4 | 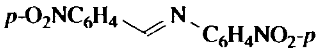 | $Me_2NHBH_3$ | AcOH | 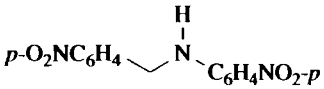 | 71 | 86 |
| 5 | 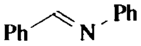 | $Me_3NBH_3$ | AcOH | 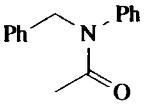 | 61 | 87 |

**Table 3** *(continued)*

| *Entry* | *Imine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 6 | 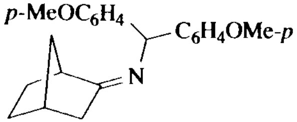 | $LiBHEt_3$ | THF | 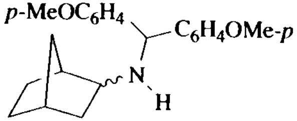 | 72[c] | 24 |
| 7 | 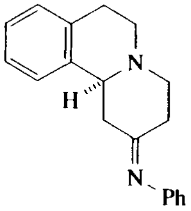 | $LiBHBu^s_3$ | THF/PhMe | 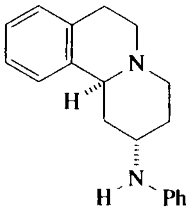 | 86 | 75 |
| 8 | 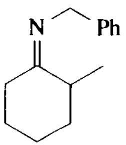 | Na 9-BBN | MeOH/THF | 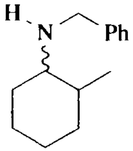 | 80[d] | 78 |
| 9 | 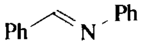 | $Fe_3H(CO)_{11}$ | — | 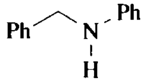 | 88 | 82 |
| 10 | 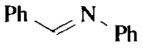 | $Et_3SiH/(Ph_3P)_3RhCl$ | PhH | 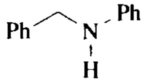 | 91 | 84 |
| 11 | 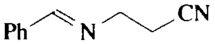 | $(Ph_3P)SeH$ | $CHCl_3$ | 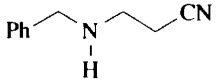 | 80 | 85 |

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[a] 1:1 mixture of diastereomers. [b] Mixture of diastereomers. [c] *Endo/exo* ratio 94:6. [d] *Cis/trans* ratio 84:16.

**Table 4** Reduction of Iminium Salts with Various Hydride Reagents

| *Entry* | *Iminium Salt* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 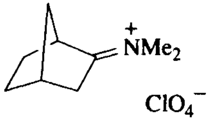 | LiAlH$_4$ | — | 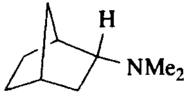 | 85[a] | 89 |
| 2 | 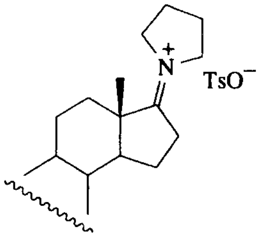 | LiAlH$_4$ | Et$_2$O | 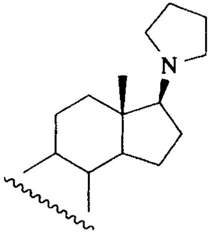 | 93[a] | 90 |
| 3 | 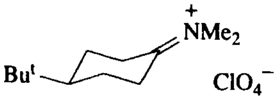 +<br>NMe$_2$<br>Bu$^t$<br>ClO$_4^-$ | LiAlH$_4$ | Et$_2$O | 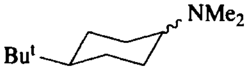 | b | 91 |
| 4 | 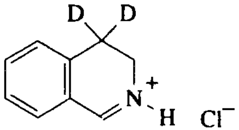 | NaBH$_4$ | MeOH | 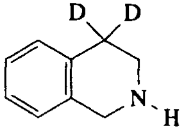 | 88 | 92 |
| 5 | 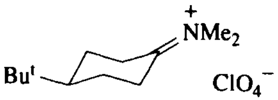 +<br>NMe$_2$<br>Bu$^t$<br>ClO$_4^-$ | NaBH$_4$ | Pr$^i$OH | 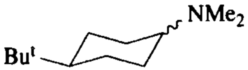 | 97[c] | 28 |

**Table 4** *(continued)*

| *Entry* | *Iminium Salt* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 6 | 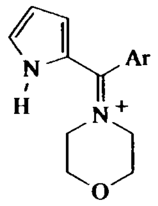 | LiBH$_4$ | THF | 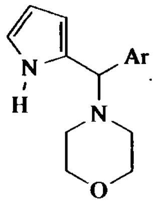 | 99 | 93 |
| 7 | 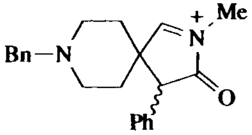 | NaBH$_3$CN | HMPA | 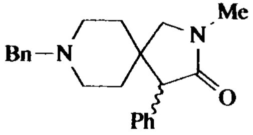 | 90 | 94 |
| 8 | 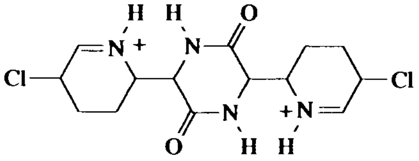 | NaBH$_3$CN | MeOH/AcOH | 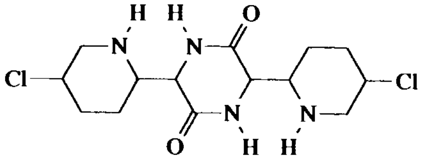 | 62 | 95 |
| 9 | 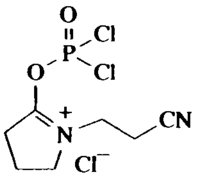 | NaBH$_4$ | DME | 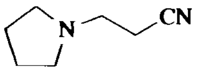 | 66 | 96 |

**Table 4** *(Continued)*

| *Entry* | *Iminium Salt* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 10 | 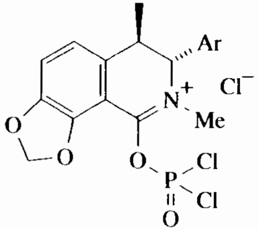 | $NaBH_4$ | DME/EtOH | 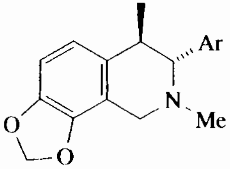 | 57–66 | 97, 98 |
| 11 | 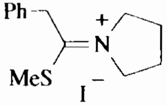 | $NaBH_4$ | MeOH | 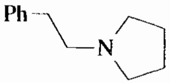 | 96 | 99 |
| 12 | 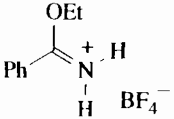 | $NaBH_4/SnCl_4$ | DME | 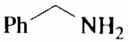 | 51 | 100 |

[a] Only product detected. [b] *Cis/trans* ratio 36:64. [c] *Cis/trans* ratio 14:86.

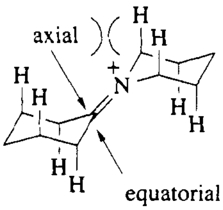

**(13)**

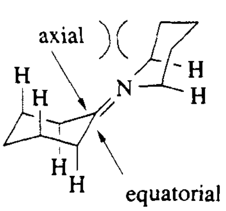

**(14)**

The reduction of 2-alkylcyclohexyl imines is even more dramatic with regard to differences compared to the corresponding 2-alkylcyclohexanones. As illustrated in Table 6, all studied reagents prefer equatorial approach to give the *cis*-amines (**12**). This is strikingly divergent from results with 2-methylcyclohexanone, and even from other substituted cyclohexyl imines (*e.g.* entries 1, 2, 9, 10, Table 5). These enhanced differences are attributed to a combination of the decreased axial attack on the equatorial methyl conformer (**15**), coupled with an augmentation of the axial methyl conformer (**16**) induced by 1,3-allylic strain[106] in (**15**; Scheme 4). In this latter conformer (**16**), the axial methyl apparently retards equatorial approach thus favoring axial attack. The combination of favored equatorial approach to (**15**) and axial approach to (**16**) results in the observed high proportion of *cis* isomers.[28] The reluctance of equatorial approach to axial 2-methyl systems was demonstrated by the nondiscriminatory attack of 2-methylcyclohexyl iminium derivatives (*e.g.* entry 11, Table 6) by LiBHBu$^s_3$[28] in contrast to the usual extreme stereoselectivity for equatorial approach observed with ketones[23] and unhindered imines (see Tables 5 and 6).

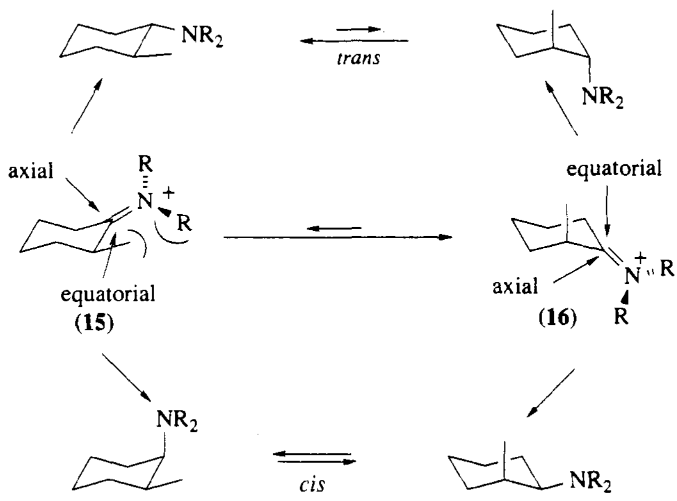

**Scheme 4**

Other cyclic imines also show enhanced stereoselectivities compared to ketones. Thus, 3,3,5-trimethylcyclohexyl imine (**17**) afforded a 94:6 *trans*:*cis* ratio with NaBH$_4$[28] compared to 58:42 with 3,3,5-trimethylcyclohexanone,[107] again suggesting increased steric interference from *N*-substituents.

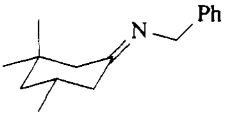

**(17)**

Reductions of substituted rings containing internal imines with hydrides display varying stereoselectivity dependent on the reagent. Thus, the 2,6-dialkylpiperideine (**18a**; equation 2, R$^1$ = Me, R$^2$ = *n*-undecyl, *n* = 2) afforded predominantly (>99%) the *cis*-piperidine (**19a**) with DIBAL-H or LAH/NaOMe, but the *trans* isomer (**20**) with LAH/Me$_3$Al.[108] The difference in stereoselectivity has been attributed to a change in conformation stemming from Me$_3$Al complexation with nitrogen forcing the 2-methyl group into an axial orientation, which reverses the normal direction of attack caused by preferred

**Table 5** Stereochemistry of Reduction of 4-*t*-Butylcyclohexyliminium Salts and other Cyclohexyl Imines with Hydride Reagents

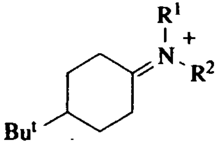

| *Entry* | *$R^1$* | *$R^2$* | *Hydride* | *Solvent* | *Yield (%)* | *Product cis:trans ratio* | *Ketone reduction cis:trans ratio (ref.)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Bn | — | $NaBH_4$ | $Pr^iOH$ | 82 | 30:70 | 17:83 (21) | 28 |
| 2 | Bn | — | $NaBH_3CN$ | MeOH/HCl | 87–97 | 35:65–46:54 | 16:84 (27) | 28, 78 |
| 3 | Bn | — | $Me_2NHBH_3$ | $MeCO_2H$ | 74 | 66:34 | — | 28 |
| 4 | Bn | — | $NaAlH_2[O(CH_2)_2OMe]_2$ | THF | 94 | 64:36 | 8:92 (28) | 28 |
| 5 | Bn | — | $LiBHEt_3$ | THF | 89 | 67:33 | — | 78 |
| 6 | Bn | — | $LiBHBu^s_3$ | THF | 77–95 | 97:3–98:2 | 93:7 (23) | 28, 78 |
| 7 | Me | — | $LiAlH_4$ | THF | — | 25:75 | 10:90 (27) | 72 |
| 8 | Me | — | $NaBH_3CN$ | MeOH, $H^+$ | — | 40:60 | 16:84 (28) | 72 |
| 9 | Me | Me | $NaBH_4$ | $Pr^iOH$ | 70 | 16:84 | 17:83 (23) | 28 |
| 10 | Me | Me | $LiAlH_4$ | — | — | 35:65 | 10:90 (27) | 91 |
| 11 | Me | Me | $NaAlH_2[O(CH_2)_2OMe]_2$ | — | 74 | 72:28 | 8:92 (28) | 28 |
| 12 | $CH(C_6H_4\text{-}p\text{-}OMe)_2$ | — | $LiBHBu^s_3$ | — | 59 | 99:1 | 93:7 (23) | 24 |
| 13 | 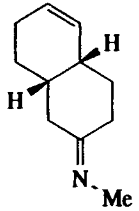 |  | $LiBHBu^s_3$ | THF |  | 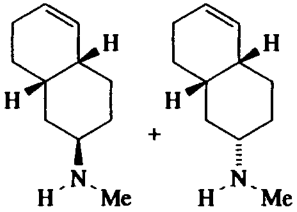<br>92:8 | — | 105 |

**Table 5** *(continued)*

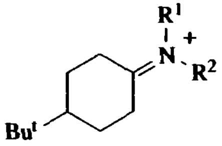

| *Entry* | *R¹* | *R²* | *Hydride* | *Solvent* | *Yield (%)* | *Product cis:trans ratio* | *Ketone reduction cis:trans ratio (ref.)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 14 | 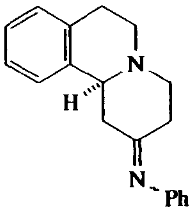 |  | $LiBHBu^s_3$ | THF | 86 | 0:100 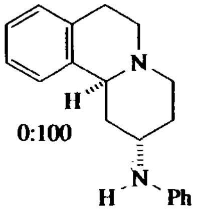 | — | 75 |

**Table 6** Stereochemistry of Reduction of 2-Methylcyclohexyl Imines and Iminium Salts with Hydride Reagents

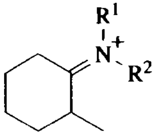

| *Entry* | *R*$^1$ | *R*$^2$ | *Hydride* | *Solvent* | *Yield (%)* | *Product cis:trans ratio* | *Ketone reduction cis:trans ratio (Ref.)* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| 1 | Bn | — | $NaBH_4$ | $Pr^iOH$ | 90 | 85:15 | 25:75 (27) | 28 |
| 2 | Bn | — | $NaBH_3CN$ | MeOH/HCl | 82–92 | 64:36–76:24 | 28:72 (28) | 28,78 |
| 3 | Bn | — | Na 9-BBNCN | MeOH/THF/HCl | 80 | 84:16 | — | 78 |
| 4 | Bn | — | Na disiamylBHCN | MeOH/THF/HCl | 73 | 81:19 | — | 78 |
| 5 | Bn | — | 9-BBN | MeOH/THF/HCl | 70 | 83:17 | — | 78 |
| 6 | Bn | — | $Bu^tNH_2BH_3$ | THF | 78 | 90:10 | — | 78 |
| 7 | Bn | — | $LiBHEt_3$ | THF | 84 | 97:3 | — | 78 |
| 8 | Bn | — | $LiBHBu^s_3$ | THF | 78 | 99:1 | 99.3:0.7 (23) | 28 |
| 9 | Bn | — | $NaAlH_2[O(CH_2)_2OMe]$ | THF | 81 | 78:22 | — | 28 |
| 10 | $CH(C_6H_4\text{-}p\text{-}OMe)_2$ | — | $LiBHBu^s_3$ | THF | <10 | — | 99.3:0.7 (23) | 24 |
| 11 | $—(CH_2)_4—$ | | $LiBHBu^s_3$ | THF | 60 | 48:52 | 99.3:0.7 (23) | 28 |

orbital overlap stabilization.[108] Likewise, 2,5-dialkylpyrrolines (*e.g.* **18b**; $n = 1$, $R^1 = Me$, $R^2 = n$-nonyl) gave the *cis*-pyrrolidine (**19b**) with DIBAL-H ($CH_2Cl_2$), while (**18c**; $n = 1$, $R^1 = Me$, $R^2 = n$-undecyl) provided a 95:5 *trans:cis* (**20c**:**19c**) mixture with LAH/$Me_3Al$ (THF).[65] Other hydride reagents (*e.g.* $NaBH_4$, $NaBH_3CN$) afforded much less stereoselectivity with analogs of (**18**; *e.g.* entry 14, Table 2).[65]

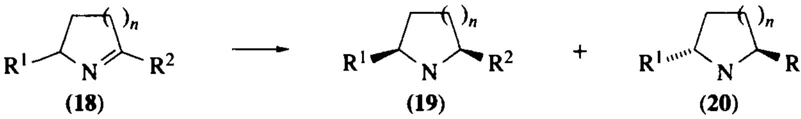

(2)

## 1.2.2.3 Reduction of *In Situ* Generated Imines and Iminium Salts of Ammonia, Primary and Secondary Amines; Reductive Amination

### *1.2.2.3.1 Reductive aminations with sodium cyanoborohydride*

As described in the sections above, imines and iminium salts are effectively reduced by a number of reagents. However, most hydride reducing agents require preformation of the carbon–nitrogen π-system, since reduction of aldehydes and ketones is very facile with most of them. As mentioned previously, the introduction of $NaBH_3CN$ into the arsenal of reducing agents altered this situation, primarily because of the exceptional functional group tolerance exhibited by this reagent. Thus, under neutral or slightly acidic (*i.e.* pH > 5) conditions, reductions of nearly all common functionalities, including aldehydes and ketones, are slow.[15,16,26] The principal exceptions to this are iminium ions, which are rapidly attacked by cyanoborohydride. These properties, then, allow the sequence depicted in Scheme 2 to be accomplished *in situ* without prior formation and isolation of the intermediate imines. Thus, reductive amination of carbonyls may be accomplished directly by reaction of an aldehyde or ketone with ammonia, primary or secondary amines at pH *ca.* 5–7 in the presence of $BH_3CN^-$ (usually in MeOH, but occasionally in other solvents, *e.g.* $H_2O$, EtOH, MeCN, THF, DMF) at room temperature, leading directly to primary, secondary or tertiary amines. Since the process relies on successful iminium ion generation (*i.e.* **1**; Scheme 2), the use of molecular sieves (and presumably other drying agents) to absorb water produced in the initial equilibrium (Scheme 2) is beneficial, especially with carbonyls which form imines slowly (*e.g.* norbornanone).[26] As expected, hindered ketones (*e.g.* phenyl *t*-butyl ketone) which resist imine formation are not successfully reduced using the standard procedure,[26] and require more forcing conditions to preform the imines. Nevertheless, the overall reliability and convenience of reductive amination with $NaBH_3CN$, coupled with the reagent's stability in most solvents, including acidic media, and its compatibility with other functional groups, have combined to provide enormous popularity for the process. Indeed, several hundred reports have appeared describing diverse applications to synthetic endeavors requiring the insertion of amino groups, and this popularity continues unabated. At present, then, this methodology must be regarded as the protocol of choice for reductive amination.

The utility of reductive amination with $NaBH_3CN$ in synthesis is contained in reviews[15,16] and successful applications have been compiled through 1978.[16] Table 7 provides a variety of examples taken from more recent accounts and chosen to illustrate the versatility and compatibility of the process with diverse structural types and chemoselectivity demands. Thus, esters (entries 2–4, 8–12), amides (entries 3, 6–9, 12), nitro groups (entry 13), alkenes (entry 2), cyclopropyl groups (entry 2), organometallics (entry 5), amine oxides (entry 14) and various heterocyclic rings (entries 1, 3, 5–10) all survive intact. Entry 6 illustrates that deuterium can be conveniently inserted *via* the readily available $NaBD_3CN$,[15,16] and entry 15 demonstrates that double reductive amination with diones can be utilized to afford cyclic amines.

The functional group tolerance possible with $NaBH_3CN$ is even more amply illustrated by the successful reductive amination of the C-20 aldehyde in tylosin (**21**) with several amines,[124] of the C-3a aldehyde of the chlorophyll derivative Chl b (**22**) with $NH_3$ (80% yield),[125] and the C-11 aldehyde of the modified tetrodotoxin derivative (**23**) with several amino acids.[126]

The usefulness of reductive amination is augmented by the facile methylation of amines with formaldehyde (usually in MeCN),[127] which provides a convenient, mild alternative to Clark–Eschweiler and other methylation procedures. Table 8 presents a selection of successful methylation applications with various amines, and further illustrates the chemoselectivity and versatility of the process.

As described previously, $NaBH_3CN$ has found wide usage in the biochemical arena where mildness and compatibility with aqueous media are essential, and reductive amination has been utilized especially

**Table 7** Reductive Amination of Carbonyls with NaBH$_3$CN

| *Entry* | *Carbonyl* | *Amine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 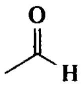 | 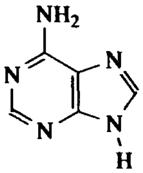 | 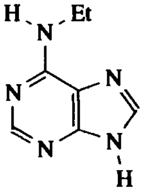 | 80 | 109 |
| 2 | 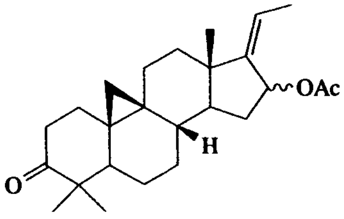 | MeNH$_2$ | 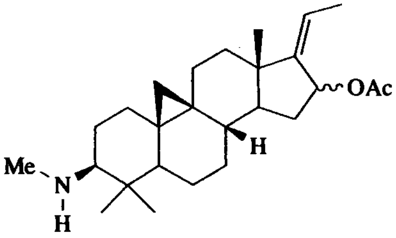 | 67 | 110 |
| 3 | 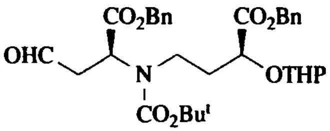 | 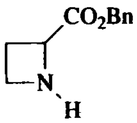 | 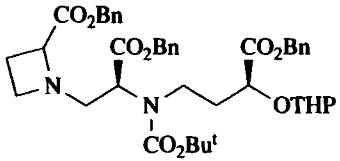 | 59 | 111 |
| 4 | 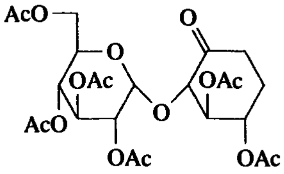 | NH$_3$ | 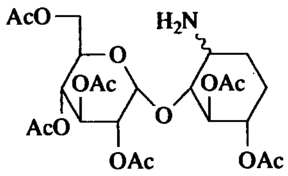 | 41 | 112 |

**Table 7** *(continued)*

| *Entry* | *Carbonyl* | *Amine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 5 | 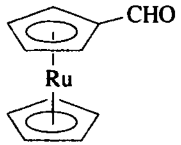 | 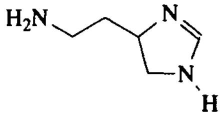 | 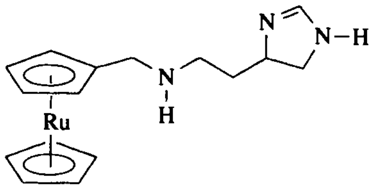 | 55 | 113 |
| 6 | 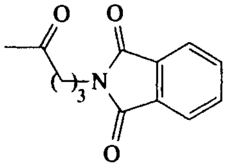 | 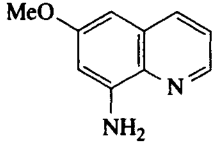 | 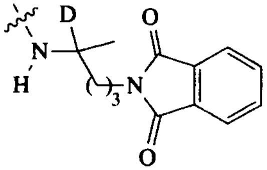 | 46[a] | 114 |
| 7 | 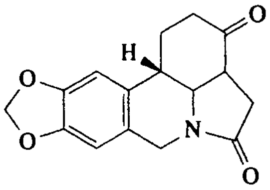 | HNMe$_2$ | 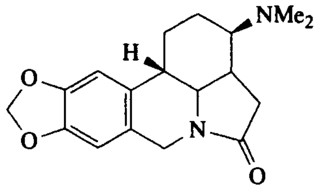 | 43 | 115 |
| 8 | 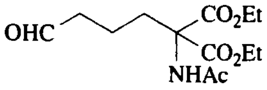 | 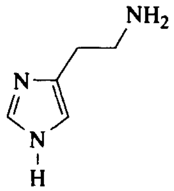 | 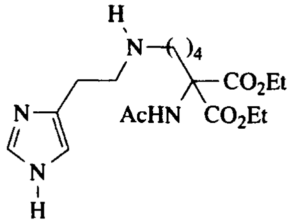 | 87 | 116 |

**Table 7** *(continued)*

| *Entry* | *Carbonyl* | *Amine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 9 | 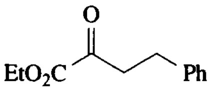 | 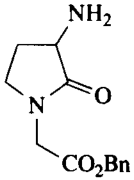 | 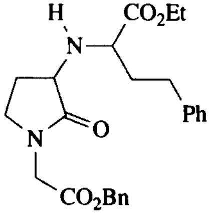 | $68^{b,c}$ | 117 |
| 10 | 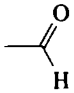 | 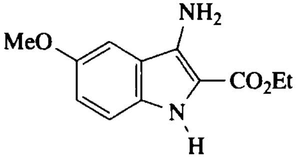 | 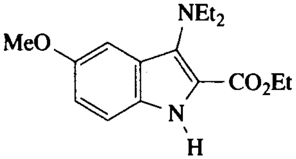 | $76^{d}$ | 118 |
| 11 | 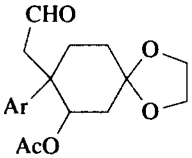 | $HNMe_2$ | 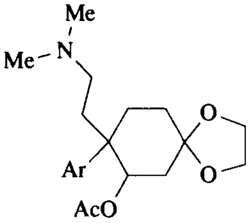 | 84 | 119 |
| 12 | 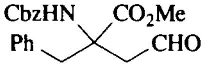 | 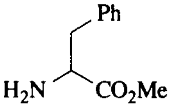 | 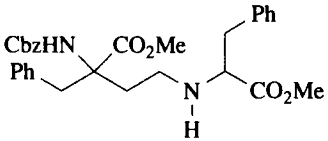 | 78 | 120 |

**Table 7** *(continued)*

| *Entry* | *Carbonyl* | *Amine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 13 | 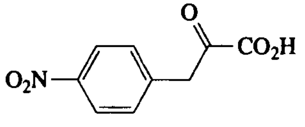 | 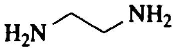 | 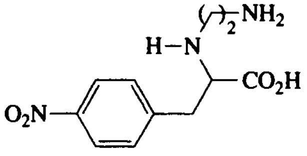 | 23 | 121 |
| 14 | 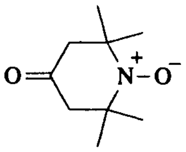 | $H_2NMe$ | 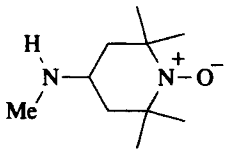 | 73 | 122 |
| 15 | 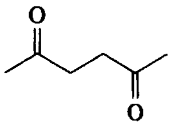 | $NH_3$ | 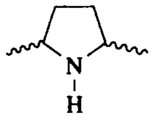 | 62 | 123 |

[a] $NaBD_3CN$ used. [b] Ethanol solvent. [c] Mixture of diastereomers. [d] MeCN solvent.

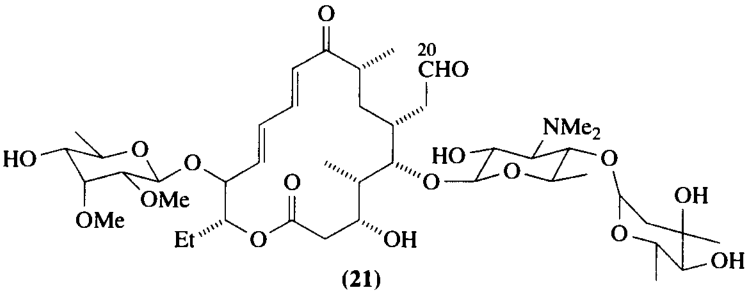

**(21)**

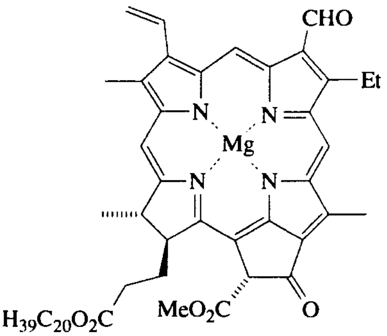

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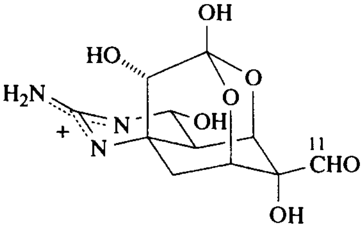

**(23)**

in linking proteins and related polypeptides to various supports. Examples include the coupling of aldehyde-bearing glycosides to amino groups of proteins (*e.g.* bovine serum albumin,[134,135] human fibrinogen,[135] bovine pancreatic ribonuclease-A,[135] low density lipoprotein,[136] invertase,[137] collagen,[138] and polylysine,[139] to name a few), the binding of the globular protein concanavalin A to silica,[140] of a number of enzymes to alumina (*via* pyridoxyl 5′-phosphate),[141] and the reductive alkylation of the opioid peptide methionine-enkephalin.[142] Other applications encompass the labeling of oligosaccharides with UV-absorbing aromatic amines,[143] specific methylation of amino acid residues in enzymes and proteins (*e.g.* aspartate aminotransferase,[144] concanavalin A,[145] and the L-subparticles of rabbit cytoplasmic ribosomes[146]) and the spin labeling of AMP and $NaD^+$.[147] It must be noted that the above represent only a small portion of the extensive applications of reductive amination to biochemical problems, further discussion of which is beyond the scope of this chapter.

Although reductive amination with $NaBH_3CN$ has been successfully utilized for numerous synthetic applications, side reactions and failures have been noted. Thus, reductive amination (with ammonia) of the keto sugar (**24**) afforded a mixture of products including two isomeric cyanohydrins and alcohols (partial structures **25** and **26**, respectively), in addition to the expected diaminated product.[148] Also, the diketone corresponding to (**5**) gave a diol (resulting from reduction of both carbonyls) and the cyclic amino alcohol (**8**), in addition to the diamine resulting from reductive amination with ammonia, all in low yields.[149] Likewise, carbohydrate derivatives (**27**)[150] and retinal (**28**)[151] failed to give satisfactory yields of amine products upon reductive amination.

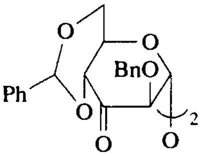

**(24)**

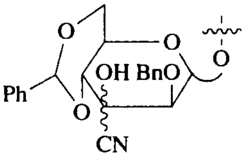

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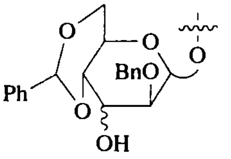

**(26)**

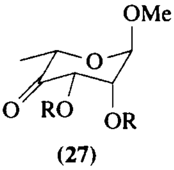

**(27)**

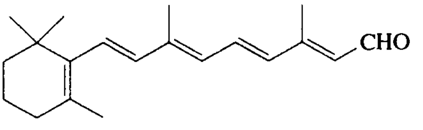

**(28)**

**Table 8** Reductive Methylation with $NaBH_3CN$/Formaldehyde

| *Entry* | *Amine* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 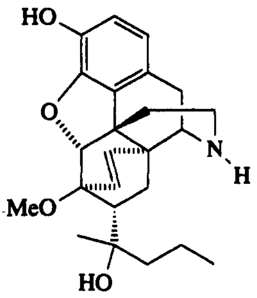 | 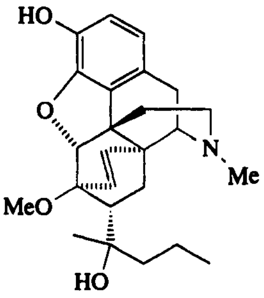 | — | 128 |
| 2 | 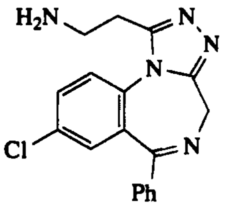 | 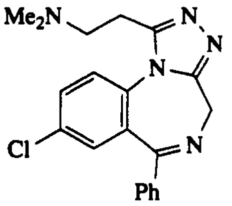 | 68 | 129 |
| 3 | 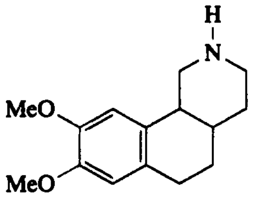 | 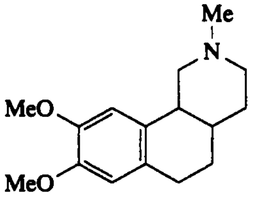 | 83 | 130 |
| 4 | 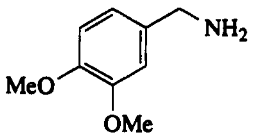 | 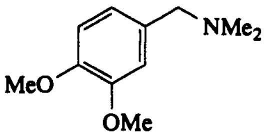 | — | 131 |
| 5 | 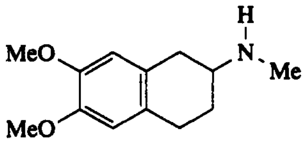 | 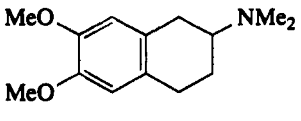 | — | 132 |
| 6 | 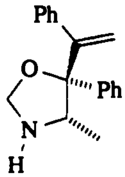 | 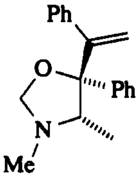 | 84 | 133 |

### *1.2.2.3.2 Reductive aminations with other hydride reagents*

Although the use of $NaBH_3CN$ alone for reductive amination has thus far dominated applications in synthesis, modified cyanoborohydride derivatives and other reagents, which offer viable alternatives and potential improvements, have recently been introduced. Thus, $Zn(BH_3CN)_2$ (methanol solvent) is apparently equally effective for reductive aminations and amine methylations and, in most cases, requires short reaction times (*ca.* 1–6 h).[152] In addition, the combination of $NaBH_3CN$ and $Ti(OPr^i)_4$ is reported to afford superior results with difficult carbonyls and those sensitive to acidic conditions,[153] and other Lewis acids (*i.e.* $MgCl_2$) have also been employed with $NaBH_3CN$.[154] Alkylammonium cyanoborohydrides allow reductive aminations to be conducted in nonpolar solvents.[155] One study reports the use of Na-9-BBNCN-H for the reductive amination of 2-methylcyclohexanone with ammonia, but the yield was low (31%).[78] Other boron-based mild reducing reagents also provide alternative reductive amination processes. These include $BH_3$·THF,[156] pyridine·$BH_3$,[20,157,158] $NaBH_4$ (or $NaBD_4$) in liquid or aqueous ammonia,[159] and $NaBH(OAc)_3$ in THF or $ClCH_2CH_2Cl$.[160] The previously mentioned $KFeH(CO)_4$[80,81] reductively aminates carbonyls in ethanol with best results obtained under a CO atmosphere. The reagent also provides methodology for the methylation of amines using formaldehyde as the carbonyl partner.[161]

### *1.2.2.3.3 Stereoselectivity with cyclic derivatives*

Investigations of stereochemical outcomes of *in situ* reductive aminations have been sparse and the few reports generally indicate relatively poor diastereoselection with cyclohexyl systems. Table 9 presents a selection of available stereochemical results with the reagents which successfully reductively aminate ketones and indicate that selectivities generally parallel those obtained with preformed imines where comparisons are available (see Table 5, entries 2, 3, 8; Table 6, entries 2–4). Thus, 4-substituted cyclohexanones display no or low selectivity with 'small' reagents (*i.e.* $BH_3CN^-$, entries 1, 7) while moderately bulky reagents [*i.e.* $NaBH(OAc)_3$, entries 2, 3] afford a predominance of *cis* (*i.e.* axial amine) diastereomers. Likewise, 2-methylcyclohexanone gives principally *cis* isomers with $NaBH_3CN$, as well as with the more hindered Na-9-BBNCN-H. In contrast to this, electrolytic reductive amination (Hg cathode, aqueous ethanol, pH 10–11) of 2-methylcyclohexanone (with $MeNH_2$) provided a 2:1 *trans*:*cis* mixture of amines, while 4-*t*-butylcyclohexanone gave high *trans* diastereoselectivities with $MeNH_2$ and $Me_2CHNH_2$ (*trans*:*cis* 14:1 and 20:1, respectively).[163]

**Table 9** Stereochemistry of Reductive Amination of Cyclohexanones with Amines and Hydride Reagents

| *Entry* | *Cyclohexanone* | *Amine* | *Reagent* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| | | | | | *cis*:*trans* | |
| 1 | 4-*t*-butyl | 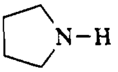 | $Bu_4NBH_3CN$ | 73 | 33:67 | 155 |
| 2 | 4-*t*-butyl | 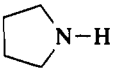 | $NaBH(OAc)_3$ | 96 | 71:29 | 160 |
| 3 | 4-*t*-butyl | $Me_2CHNH_2$ | $NaBH(OAc)_3$ | 91 | 79:21 | 160 |
| 4 | 2-methyl | $PhCH(Me)NH_2$ | $NaBH_3CN$ | 63 | 65:35 | 162 |
| 5 | 2-methyl | $NH_3$ | Na-9-BBNCN-H | 31 | 70:30 | 78 |
| 6 | 2-carboethoxy | $Me_2NH$ | $NaBH_3CN$ | 53 | 40:60 | 26 |
| 7 | 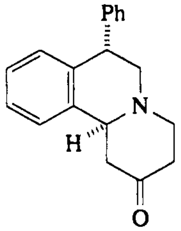 | $PhNH_2$ | $NaBH_3CN$ | 96 | 50:50 | 75 |

### 1.2.2.4 Reduction of Enamines *via* Iminium Ion Intermediates

#### *1.2.2.4.1 Choice of hydride reagent and solvent*

Although enamines are normally resistant to reduction by hydride reagents, rapid and reversible protonation on carbon in acidic media generates iminium ions, which, as presented above, are rapidly attacked by hydride reagents (Scheme 5). Thus, reagents which tolerate acidic conditions [*e.g.* $NaBH_3CN$,[15,16,26] $NaBH(OAc)_3$,[14] $BH(OAc)_2$[20,28], $BH(O_2CCF_3)_2$[164,165]] provide effective systems for enamine reductions to amines. Normally the latter three reagents are generated *in situ* from $NaBH_4$, $BH_3$ or amine·$BH_3$ complexes and the corresponding carboxylic acid as solvent, followed by addition of the enamine substrate. For this reason, the exact reducing species are not accurately known and therefore may be mixes of variously substituted acyloxyboranes. The reviews and reports listed above for acid-stable reagents provide collections of successful enamine reductions. Table 10 presents further examples with a variety of reducing systems and illustrates the versatility of the methodology and, again, the chemoselectivity possible with such mild reagents as $NaBH_3CN$ and acetoxyboranes. Thus, esters (entries 5, 6, 9, 10, 12), lactones (entry 2), certain heterocycles (entry 4), phosphites (entry 8), and even sensitive ketones (entry 7) and epoxides (entry 10) remain intact. Other types of enamines including vinylogous amides (entries 5–7, 9, 10, 12, 13) and indoles (entries 14, 15) are also effectively reduced. Occasionally, elimination of appropriately placed groups has been observed (*e.g.* a β-amino ketone, entry 13).

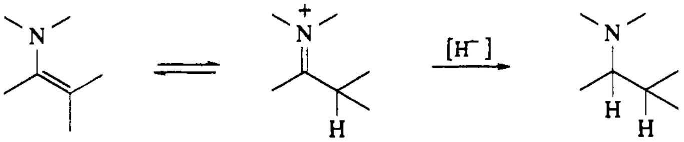

**Scheme 5**

Other reagent systems not listed in Table 10 which successfully reduce enamines (*i.e.* indoles) include $BH_3$·pyridine in AcOH[179] or TFA,[164] catecholborane/TFA,[164] $NaBH_3CN$/TFA,[164] and $KFeH(CO)_4$/CO/ethanol.[180]

#### *1.2.2.4.2 Stereoselectivity with cyclic derivatives*

Since enamine reductions proceed through iminium ion intermediates, stereochemical features with cyclic examples should parallel results with preformed derivatives, and this is generally the case, at least with the acid-stable systems described above.[28] Furthermore, since the successful reagents are usually the moderately bulky acetoxyborane or acetoxyborohydride derivatives, a preponderance of *cis* diastereomers (from equatorial attack on cyclohexyl systems, equation 1 and Scheme 4) is obtained with 2- and 4-substituted derivatives.[28] In addition, 2-methylcyclopentenylamines are reduced in high stereoselectivity to the corresponding *cis*-2-methylcyclopentylamines with borane and borohydride reagents in AcOH (Scheme 6). This result is attributed to 1,3-allylic strain in the iminium ion: the methyl group is pushed into a pseudoaxial orientation which blocks the approaching reagent and forces attack from the opposite side.[28]

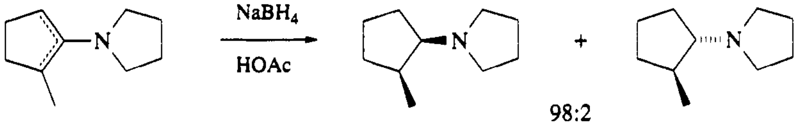

**Scheme 6**

Table 10 Reduction of Enamines with Hydride Reagents in Acidic Media

| *Entry* | *Enamine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 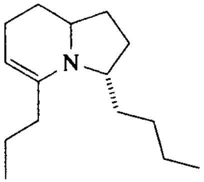 | $NaBH_3CN/HCl$ | MeOH | 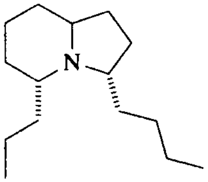 | 62 | 166 |
| 2 | 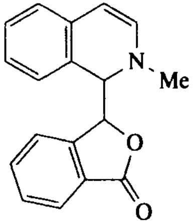 | $NaBH_3CN/HCl$ | MeOH | 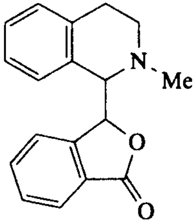 | 45 | 167 |
| 3 | 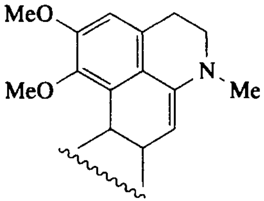 | $NaBH_3CN/HCl$ | EtOH | 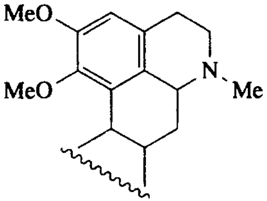 | — | 168 |
| 4 | 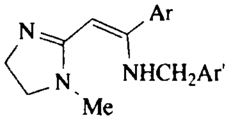 Ar<br>N<br>N<br>Me<br>NHCH2Ar' | $NaBH_3CN/HCl$ | THF/MeOH | 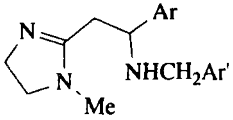 Ar<br>N<br>N<br>Me<br>NHCH2Ar' | 70–77 | 169 |
| 5 | 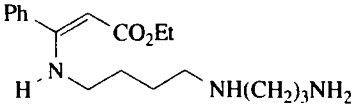 Ph<br>CO2Et<br>H<br>N<br>NH(CH2)3NH2 | $NaBH_3CN$ | — | 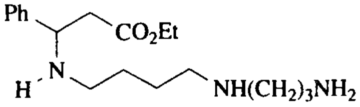 Ph<br>CO2Et<br>H<br>N<br>NH(CH2)3NH2 | 43 | 170 |

**Table 10** *(continued)*

| *Entry* | *Enamine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 6 | 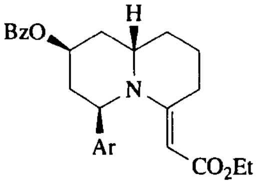 | NaBH$_3$CN/HCl | THF/MeOH | 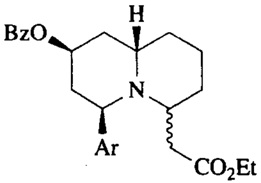 | 98[a] | 171 |
| 7 | 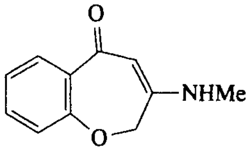 | NaBH$_3$CN/AcOH | *p*-Dioxane | 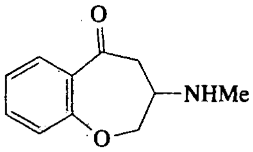 | 79 | 172 |
| 8 | 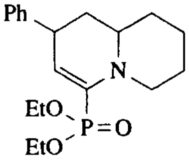 | NaBH$_3$CN/HCl | — | 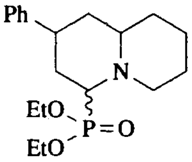 | 50 | 173 |
| 9 | 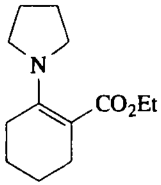 | NaBH$_3$CN/H$^+$ | MeOH | 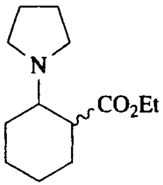 | 50 | 26 |

**Table 10** *(continued)*

| *Entry* | *Enamine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 10 | 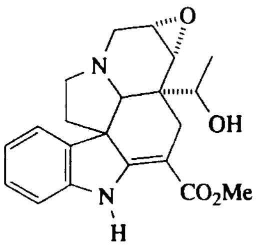 | NaBH$_3$CN | AcOH | 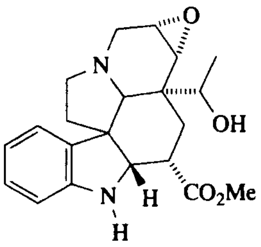 | 43[b] | 174 |
| 11 | 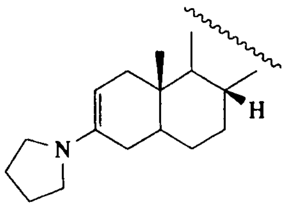 | NaBH$_4$/AcOH | THF | 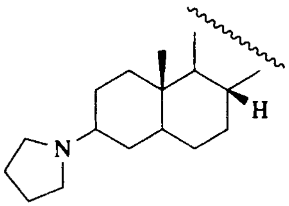 | 70 | 175 |
| 12 | 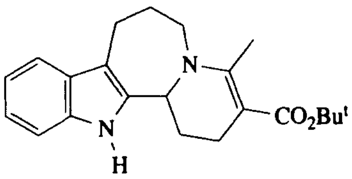 | NaBH$_4$ | AcOH | 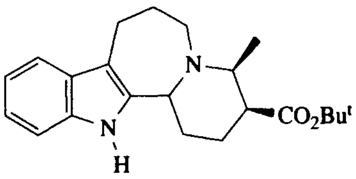 | 80 | 176 |
| 13 | 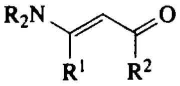 | NaBH$_4$/AcOH | Pr$^i$OH | 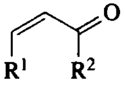 | 60–80 | 177 |

**Table 10** *(continued)*

| *Entry* | *Enamine* | *Reagent* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 14 | 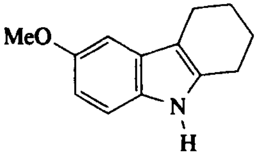 | $BH_3$ | $CF_3CO_2H$ | 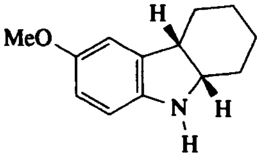 | 90 | 164 |
| 15 | 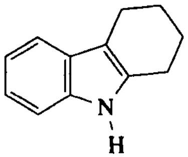 | $Me_3N{\bullet}BH_3/HCl$ | *p*-Dioxane | 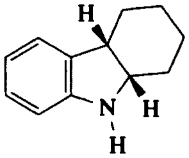 | 87 | 178 |

[a] *Cis*/*trans* = 9:1. [b] Plus 28% lactone side product.

## 1.2.3 REDUCTIONS OF *N*-HETEROATOM-SUBSTITUTED IMINES

### 1.2.3.1 Reduction of Oximes, Oxime Ethers and Oxime Esters to Hydroxylamines and Derivatives

### *1.2.3.1.1 Reduction of oximes to hydroxylamines*

Aldoximes and ketoximes are reduced to hydroxylamines with an assortment of mild reducing reagents including $BH_3$/THF (at moderate temperatures),[181] $BH_3$·pyridine/HCl,[20,182,183] $BH_3·NMe_3$/7 M HCl,[20,183] $LiBH_4$,[184] $NaBH_4$ in basic[185] or acidic (*e.g.* carboxylic acid)[14] media and $NaBH_3CN$ with HCl[15,16,26] or AcOH.[20,186] The products obtained with the latter two reagents depend somewhat upon the reaction conditions. Thus, $NaBH_4$/AcOH at 25°C affords *N*-monoalkylhydroxylamines while *N,N*-dialkylhydroxylamines are obtained at higher temperatures *via* reduction of imines generated *in situ* from aldehydes (Scheme 7).[20,186] In addition, aldoximes may also give *N,N*-dialkylhydroxylamines *via* condensation of an initially produced hydroxylamine (**29**) with the aldoxime and subsequent reduction.[20,186] This latter side reaction is also observed in reductions with $NaBH_3CN/H^+$ at pH *ca.* 4 but not at pH 3 (Scheme 8).[16,26] Table 11 presents a selection of successful oxime reductions with various reagents, and illustrates the chemoselectivity toward acetals (entry 1), alkenes (entries 2, 3), esters (entries 4, 7) and nitro groups (entry 6) Reduction may be followed by cyclization to *N*-hydroxyamides, as is the case in entry 4.

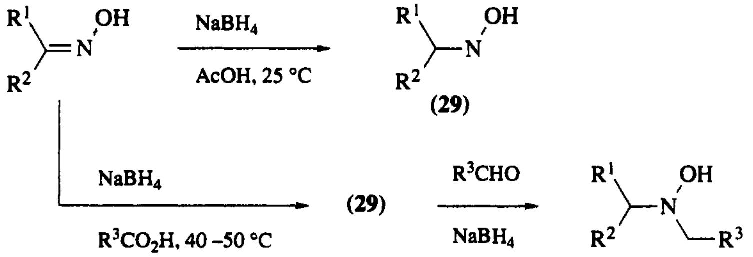

Scheme 7

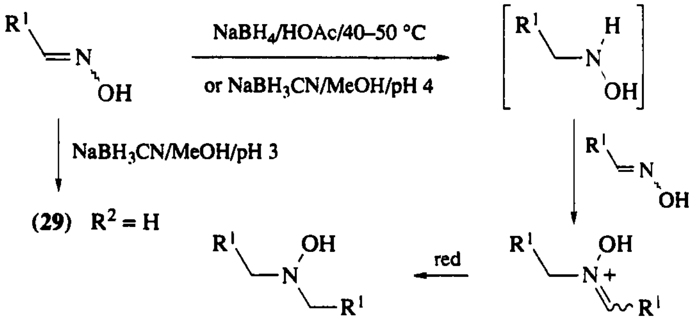

Scheme 8

### *1.2.3.1.2 Reduction of oxime ethers and esters to hydroxylamine ethers and esters*

Many of the same reagents which reduce oximes to hydroxylamines are also effective for the conversion of *O*-alkyl, *O*-aryl and/or *O*-acyl oximes to the corresponding *O*-alkyl-, *O*-aryl- and *O*-acyl-hydroxylamines, respectively. Thus, $BH_3$,[181] $BH_3$·pyridine/HCl,[20,182,183] $BH_3·NMe_3$/HCl,[20,183] $NaBH_3CN$ with HCl[192,193] or AcOH,[194] all reduce *O*-alkyl (or *O*-aryl)[193] derivatives, a selection of which are presented in Table 12. Again, the chemoselectivity available with the reagents is displayed by the inertness of cyano, carbohydrate, amide and ester groups (entries 1, 2, 5 and 7, respectively). An interesting synthesis of *N*-alkoxyazetidines is illustrated (entry 4) in which the initially produced *O*-alkylhydroxylamine underwent an intramolecular substitution to give the four-membered ring.[194] Reduction of the oxime corre-

**Table 11** Reduction of Oximes to Hydroxylamines

| *Entry* | *Oxime* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 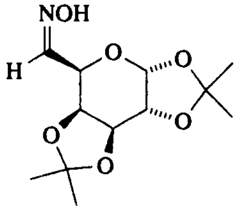 | $NaBH_3CN/HCl$ | 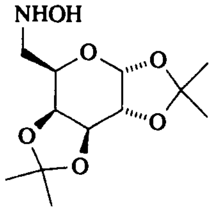 | 73 | 187 |
| 2 | 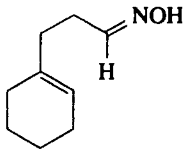 | $NaBH_3CN/HCl$ | 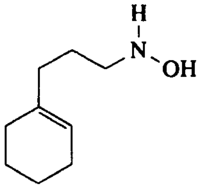 | 95 | 188 |
| 3 | 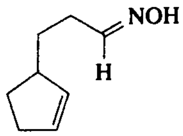 | $NaBH_3CN/HCl$ | 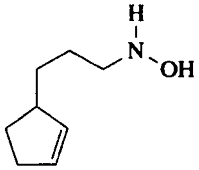 | 95 | 189 |
| 4 | 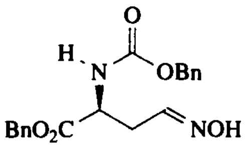 | $NaBH_3CN/HCl$ | 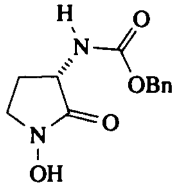 | 29 | 190 |
| 5 | 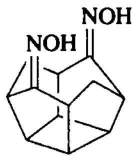 | $NaBH_3CN/AcOH$ | 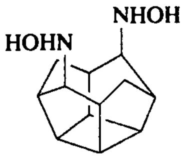 | 85 | 191 |
| 6 | 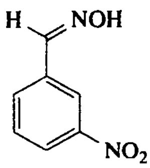 | $Py{\bullet}BH_3/HCl$ | 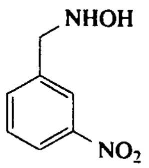 | 91 | 182 |
| 7 | 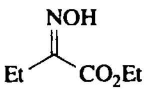 | $Et_3N{\bullet}BH_3/HCl$ | 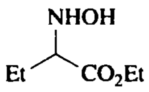 | 92 | 183 |
| 8 | 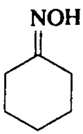 | $LiBH_4$ | 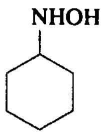 | 93 | 184[a] |

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[a] Ref. 186 reported 81% yield with $NaBH_3CN/AcOH$.

**Table 12** Reduction of *O*-Alkyl, *O*-Aryl and *O*-Acyl Oximes to *O*-Substituted Hydroxylamines

| *Entry* | *Oxime* | *Reagent* | *Product* | *Yield* (%) | *Ref.* |
|---|---|---|---|---|---|
| 1 | 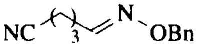 | $NaBH_3CN/HCl$ | 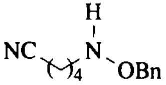 | 84 | 195 |
| 2 | 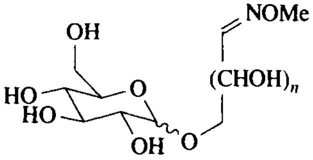 | $NaBH_3CN/HCl$ | 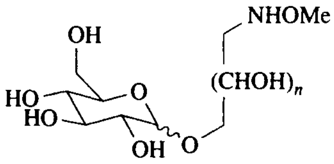 | — | 196 |
| 3 | 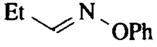 | $NaBH_3CN/HCl$ | 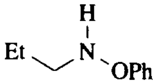 | — | 193 |
| 4 | 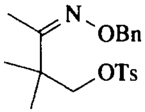 | $NaBH_3CN/AcOH$ | 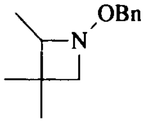 | 63 | 194 |
| 5 | 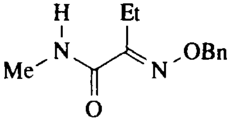 | $Py•BH_3/HCl$ | 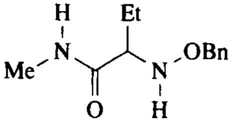 | 70 | 183 |
| 6 | 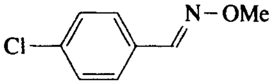 | $Py•BH_3/HCl$ | 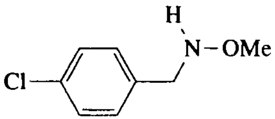 | 92 | 182 |
| 7 | 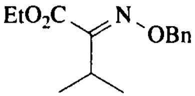 | $Me_3N•BH_3/HCl$ | 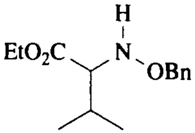 | 82 | 183 |

Table 12 (continued)

| *Entry* | *Oxime* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 8 | 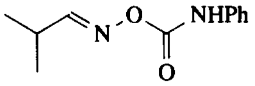 | $NaBH_3CN/HCl$ | 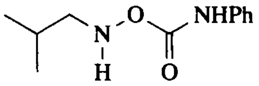 | — | 197 |
| 9 | 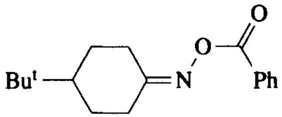 | $NaBH_3CN/AcOH$ | 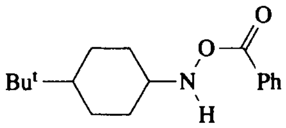 | 90[a] | 198 |
| 10 | 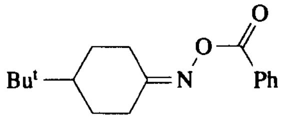 | $Et_3SiH/TFA$ | 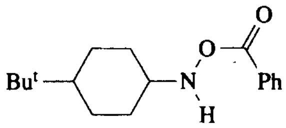 | 85[b] | 198 |

[a] *Cis:trans* = 1:4. [b] *Cis:trans* = 5:1.

sponding to entry 4 afforded the five-membered isoxazolidine resulting from displacement of tosyl by the hydroxylamine oxygen.[194]

The reduction of *O*-acyl oximes to *O*-acylhydroxylamines also is accomplished under mild conditions with pyridine·$BH_3$/HCl,[182] $NaBH_3CN$/HCl,[197] and $NaBH_3CN$/AcOH[198] in a similar fashion as with other oxime derivatives. In addition, $BH_3$ (1 equiv.)[199] and the combination of $Et_3SiH$/TFA[198] also effects efficient reduction. With the former reagent, rearrangement to *N*-acylhydroxylamines has been observed (equation 3).[199] Representative examples of *O*-acyl oxime reductions are presented in Table 12. The related derivatives nitrones are also reduced by LAH,[200,201] or $NaBH_3CN/H^+$[202] to hydroxylamines (equation 4).[202]

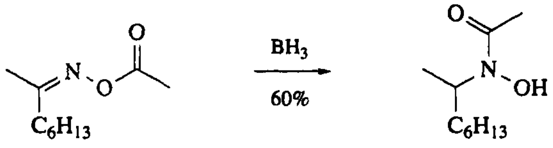

(3)

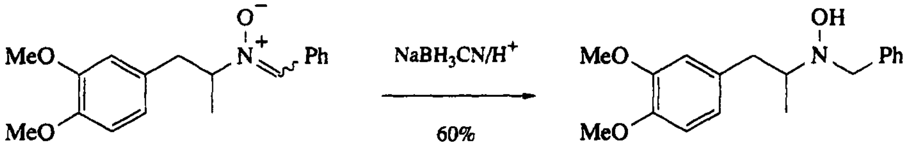

(4)

### 1.2.3.2 Reduction of Oximes, Oxime Ethers and Oxime Esters to Amines

The reduction of oximes and subsequent cleavage of the N—O bond to afford primary amines occurs with a variety of potent hydride reagents including LAH,[7,9,201,203] $NaAlH_2(OCH_2CH_2OMe)_2$,[7,204] $BH_3$ (at 105–110 °C),[205] $NaBH_2S_3$,[206] and $NaBH_4$ in combination with a variety of transition metal salts including $TiCl_3$,[207a,b] (also with $NaBH_3CN$[207c]), $ZrCl_4$,[208] $NiCl_2$,[209] and $MoO_3$.[209] Several representative examples of oxime reductions to amines with a variety of reagents are presented in Table 13. Although thorough chemoselectivity studies with the transition metal salts/$NaBH_4$ systems have not been conducted, several functionalities do survive, including $NO_2$ (entry 3), cyclopropyl (entry 5), ketal, amide and certain heterocycles (entry 8). With $NiCl_2/NaBH_4$, conjugated oximes afford saturated amines (entry 6) while $MoO_3/NaBH_4$ gives mostly the allylic amine (entry 7). Alternate pathways are obtained with DIBAL-H which efficiently affords rearranged secondary amines as the only product (entry 9), presumably *via* Beckmann-type rearrangement and subsequent reduction of the resulting imine. This result also sometimes occurs as a side reaction with LAH. Ketoximes and aldoximines bearing a β-phenyl and ketoximes with an α-phenyl generally afford aziridines with LAH in ether solvents although yields are usually moderate (entry 10). Likewise, $NaAlH_2(OCH_2CH_2OMe)_2$ affords mixtures of amines and aziridines with oximes.[204]

Treatment of oximes with LAH in HMPA does not afford the expected amine products, but rather gives ketones from ketoximes and nitriles and/or aldehydes from aldoximes. These unusual results are attributed to the formation of imine intermediates which are hydrolyzed to carbonyls or undergo elimination to nitriles (which may be further reduced and hydrolyzed to aldehydes).[215]

Oxime ethers yield amines from reduction with $BH_3$ (25 °C),[205] $NaBH_4$ in combination with $ZrCl_4$[208] or $CF_3CO_2H$ ($NaBH_3O_2CCF_3$),[216,217] LAH/NaOMe,[218] and $NaAlH_2(OCH_2CH_2OMe)_2$.[204] This latter reagent affords aziridines in addition to primary amines.[204] Likewise, *O*-acyl oximes afford amines upon reduction with $BH_3$,[205,219] or $NaBH_4$ in combination with $NiCl_2$ or $MoO_3$,[212] while oxime sulfonate esters undergo Beckmann rearrangement and reduction to secondary amines with DIBAL-H[220] in a similar fashion as observed with oximes (Table 13, entry 9).[213] A selection of reductions of *O*-substituted oximes is presented in Table 14.

### 1.2.3.3 Stereoselectivity of Reductions of Cyclic Oximes and Oxime Derivatives

Systematic investigations of the stereochemical outcomes of reductions of cyclic oximes and their derivatives have been sparse; the available information suggests that results sometimes parallel those obtained in other imine reductions (Sections 1.2.2.2.3, 1.2.2.3.3 and 1.2.2.4.2), but differences are also noted. A collection of examples in which the stereochemistry was determined is presented in Table 15. Thus, with cyclohexyl systems enhanced equatorial attack (compared to ketones) leading to axial amines

**Table 13** Reduction of Oximes to Amines

| *Entry* | *Oxime* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 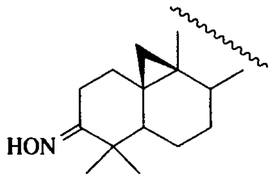 | $LiAlH_4$ | 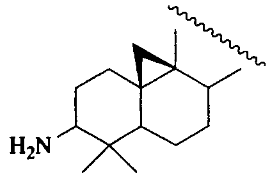 | — | 210 |
| 2 | 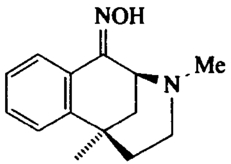 | $LiAlH_4$ | 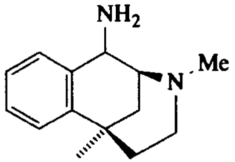 | 80 | 211 |
| 3 | 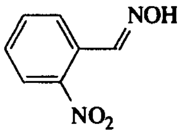 | $NaBH_4/TiCl_4$ | 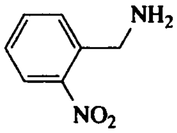 | 82 | 207 |
| 4 | 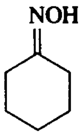 | $NaBH_4/ZrCl_4$ | 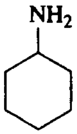 | 85 | 208 |
| 5 | 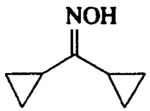 | $NaBH_4/NiCl_2$ | 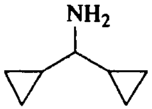 | 70 | 209 |
| 6 | 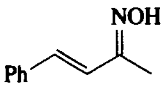 | $NaBH_4/NiCl_2$ | 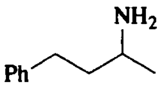 | 95 | 209 |

**Table 13** *(continued)*

| *Entry* | *Oxime* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 7 | 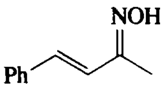 | $NaBH_4/MoO_3$ | 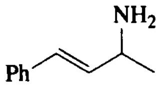 | 66[a] | 209 |
| 8 | 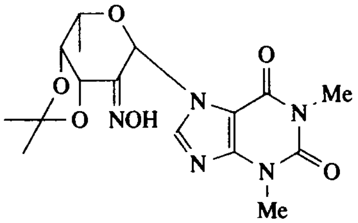 | $NaBH_4/MoO_3$ | 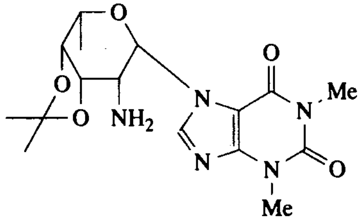 | 60 | 212 |
| 9 | 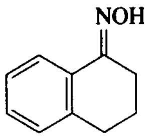 | $Bu^i_2AlH$ | 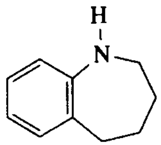 | 92 | 213 |
| 10 | 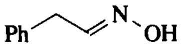 | $LiAlH_4$ | 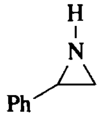 | 34 | 214 |

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[a] *ca.* 29% of the saturated amine also obtained.

**Table 14** Reduction of Oxime Derivatives to Amines

| *Entry* | *Oxime derivative* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 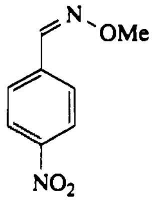 | $BH_3$/THF | 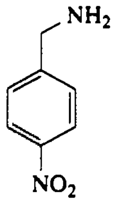 | 82 | 205 |
| 2 | 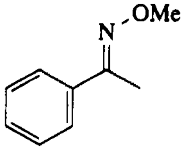 | $NaBH_4/ZrCl_4$ | 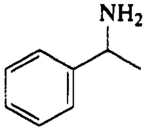 | 95 | 208 |
| 3 | 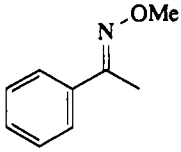 | $NaBH_3O_2CCF_3$ | 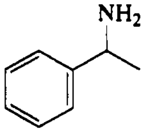 | 90 | 216 |
| 4 | 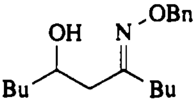 | $LiAlH_4$/NaOMe | 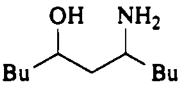 | 92[a] | 218 |
| 5 | 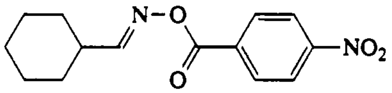 | $BH_3$/THF | 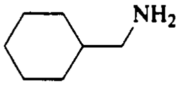 | 68[b] | 205 |
| 6 | 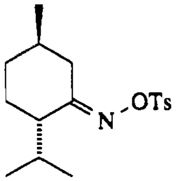 | DIBAL-H/$Et_2O$ | 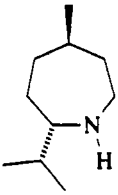 | 82 | 220 |
| 7 | 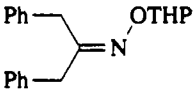 | $NaAlH_2[O(CH_2)_2OMe]$ | 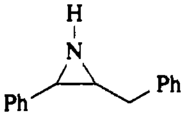 | 88[c] | 204 |

[a] *Syn*/*anti* = 96:4. [b] Also, 81% *p*-nitrobenzyl alcohol. [c] Also, 12% primary amine.

(or derivatives) is observed with $NaBH_4/NiCl_2$ (entries 2–4)[209] while $NaBH_4/MoO_3$ gives predominatly axial attack (compare entries 4 and 5).[209] However, with more substituted rings this latter reagent gives almost entirely equatorial approach (*e.g.* entry 6; also entry 8, Table 13),[212] possibly induced by the *syn*-axial alkoxy. Since the actual reducing species with these transition metal modified reagents is not known, speculation as to the origin of these differences is not warranted without additional study. The combination of $Et_3SiH$/TFA also gives predominately axial amine derivatives, while $NaBH_3CN$/HOAc affords mostly (80%) axial attack to give the equatorial amine (entries 7, 8).[198] Unfortunately, as mentioned previously, the use of bulky trialkylborohydrides to obtain highly stereoselective reductions of oximes and oxime ethers (as occurs with imines, Section 1.2.2.2.3) is prevented by the inertness of these derivatives toward the reagents.[24,25]

**Table 15** Stereochemistry of Reduction of Oximes and their Derivatives

| *Entry* | *Oxime derivative* | *Reagent* | *Product* | *Ratio of isomers* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 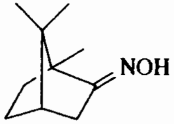 | $NaBH_4/NiCl_2$ | 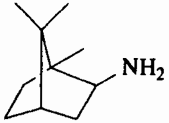 | | 92 | 209 |
| 2 | 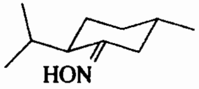 | $NaBH_4/NiCl_2$ | 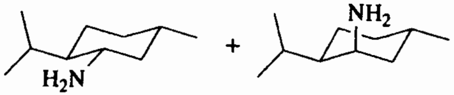 | 33:67 | 92 | 209 |
| 3 | 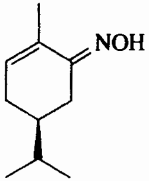 | $NaBH_4/NiCl_2$ | 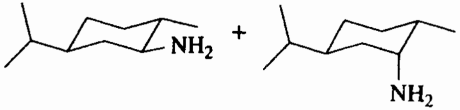 | 50:50 | 90 | 209 |
| 4 | 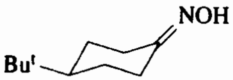 | $NaBH_4/NiCl_2$ | 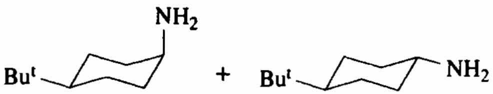 | 62:38 | 95 | 209 |
| 5 | 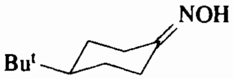 | $NaBH_4/MoO_3$ | 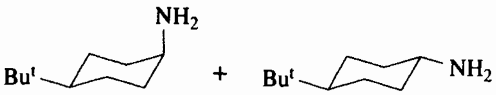 | 25:75 | 87 | 209 |
| 6 | 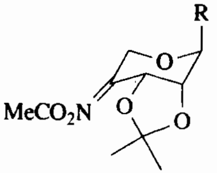 | $NaBH_4/MoO_3$ | 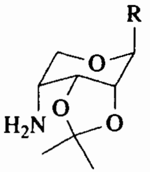 | | 70 | 212 |

**Table 15** *(continued)*

| *Entry* | *Oxime derivative* | *Reagent* | *Product* | *Ratio of isomers* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 7 | 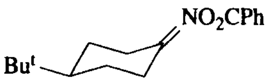 | $NaBH_3CN/AcOH$ | 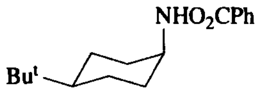 + 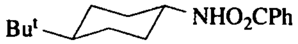 | 20:80 | 90 | 198 |
| 8 | 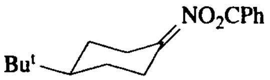 | $Et_3SiH/TFA$ | 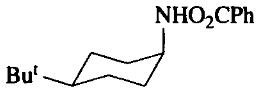 + 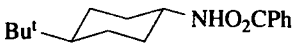 | 83:17 | 85 | 198 |
| 9 | 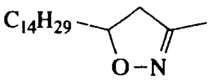 | $LiAlH_4$ | 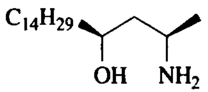 + 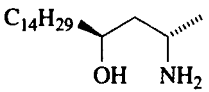 | 88:12 | 95 | 221 |

Entry 9 in Table 15 illustrates another synthetically useful stereocontrolled reduction of cyclic oxime ethers (isoxazolines) to alicyclic amino alcohols using LAH. The stereoselectivity obtained is further enhanced by the incorporation of a 4α-hydroxy group which, upon reduction, affords almost entirely the *erythro* isomer (equation 5).[221–223] High diastereoselectivity in the reductive cleavage of isoxazolines has also been obtained using $LiBH_4$ (equation 6).[224]

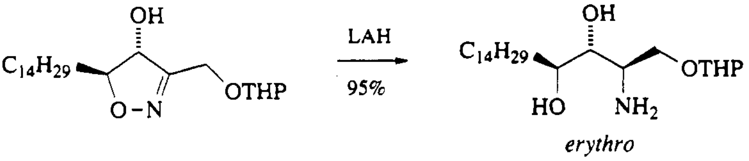

(5)

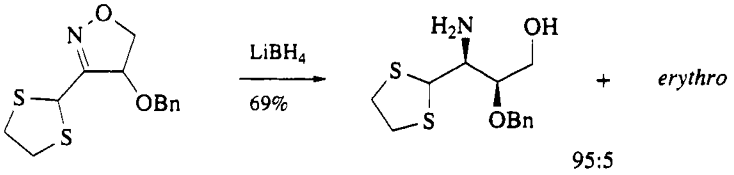

(6)

## 1.2.3.4 Reduction of Hydrazone Derivatives to Hydrazine Derivatives

As expected, many of the same hydride reagents which convert other imine derivatives to the saturated analogs also reduce hydrazones, although extensive surveys have not been conducted. Successful reagents with varying types of hydrazones include LAH,[4,7,9,225] $BH_3$,[7,226] $NaBH_4$,[227,228] catechol borane,[229] pyridine·$BH_3$/HCl,[20,230] and $NaBH_3CN$/HCl.[16,231–233] Representative examples of hydrazone reductions are presented in Table 16 along with conversions of other *N*-heteroatom-substituted derivatives.

Probably the most synthetically important conversion in the hydrazone category involves reduction of *N*-arylsulfonyl hydrazones to arylsulfonyl hydrazine intermediates which undergo further decomposition to give hydrocarbons, a topic covered in Chapter 1.14, this volume. Under mild conditions (*e.g.* pyridine·$BH_3$/HCl,[20,230] $NaBH_3CN$/HCl[16,231,234]), the arylsulfonylhydrazines survive, providing preparative methods for these derivatives (entries 3, 4).

Aldehydes and ketones undergo *in situ* reductive amination with hydrazine (*via* hydrazone intermediates) using $NaBH_3CN$/HCl in an analogous fashion, as previously described for amines (Section 1.2.2.3), to afford alkyl-substituted hydrazines, and the process can be utilized to synthesize nitrogen heterocyclic rings with dialdehydes (entries 5, 6).[235] Reductions of hydrazones with $NaBH_3CN$ have also been used in the biochemical area to attach fluorescent chromophores to gangliosides.[233]

Reductions of hydrazones with LAH may, as expected, proceed further if carbonyls or other susceptible groups are present. Thus, *N*-acyl hydrazones (*e.g.* **30**) give *N*-alkylhydrazines along with the *N*-acyl derivative (equation 7),[236] while the phenylosazone (**31**) gave further rearrangements of the intermediate dihydrazine to afford (**32**; equation 8).[237]

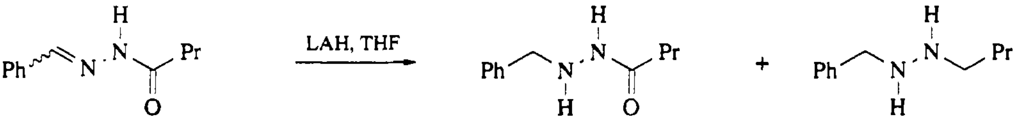

(7)

(**30**)

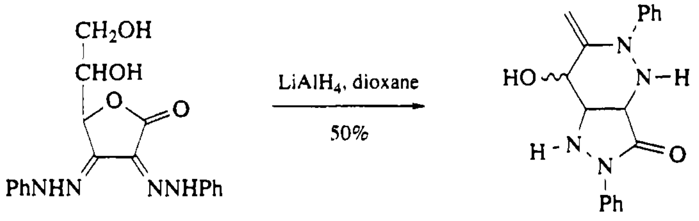

(8)

(**31**) (**32**)

**Table 16** Reduction of Various *N*-Heterosubstituted Imines to *N*-Heterosubstituted Amines

| *Entry* | *N-Heteroimine* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 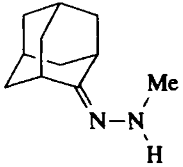 | $LiAlH_4/Et_2O$ | 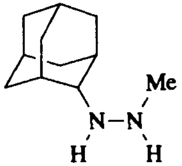 | 80 | 225 |
| 2 | 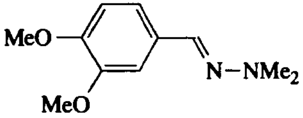 | $NaBH_4/MeOH$ | 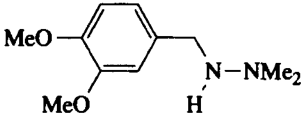 | 56 | 227 |
| 3 | 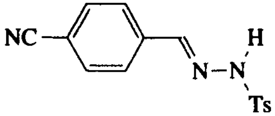 | Py•$BH_3$ | 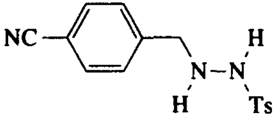 | 94 | 230 |
| 4 | 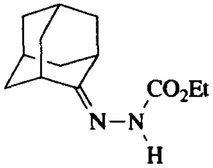 | $NaBH_3CN/HCl$ | 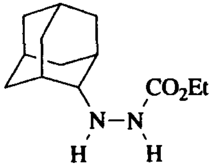 | 83 | 225 |
| 5 | 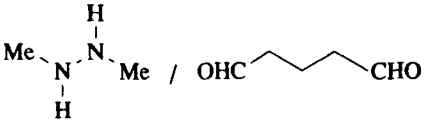 | $NaBH_3CN/HCl$ | 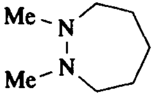 | 27 | 235 |
| 6 | 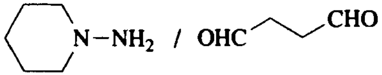 | $NaBH_3CN/HCl$ | 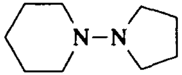 | 36 | 235 |

**Table 16** *(continued)*

| *Entry* | *N-Heteroimine* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 7 | 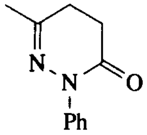 | $NaBH_3CN$/HCl | 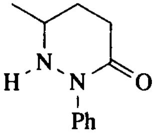 | 40 | 232 |
| 8 | 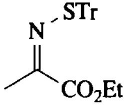 | $NaBH_3CN$/TFA | 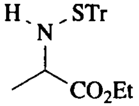 | 91–96 | 238 |
| 9 | 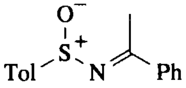 | $NaBH_4$/EtOH | 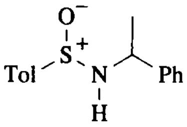 | 90–100 | 239 |
| 10 | 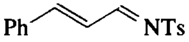 | $NaBH_4$/MeOH | 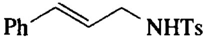 | 82 | 240 |
| 11 | 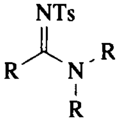 | $LiAlH_4$ | 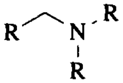 | — | 241 |
| 12 | 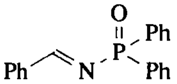 | $NaBH_4$/THF | 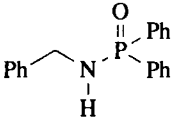 | 65 | 242 |
| 13 | 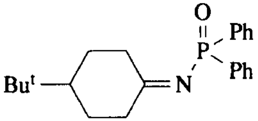 | $LiBHBu^s_3$/THF | 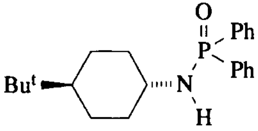 | 93[a] | 243 |

**Table 16** *(continued)*

| *Entry* | *N-Heteroimine* | *Reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 14 | 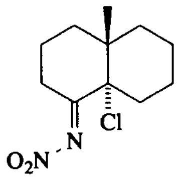 | NaBH$_4$/AcOH | 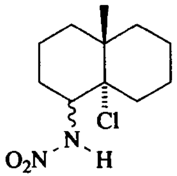 | 70 | 247 |
| 15 | 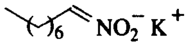 | NaBH$_4$/dioxane/EtOH/AcOH | 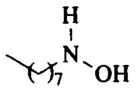 | 32 | 248 |

[a] 99% *cis*.

### 1.2.3.5 Reduction of *N*-Sulfur-substituted Imines to *N*-Sulfur-substituted Amines

Relatively little investigation of the reduction of sulfur-substituted imines has appeared. Tritylsulfenimines are reduced with $NaBH_3CN/CF_3CO_2H$ to the corresponding tritylsulfenamides, but are resistant toward $NaBH_4$/THF/EtOH.[238] The more highly activated sulfinyl imines (i.e. *N*-alkylidenesulfinamides) are reduced by LAH/$Et_2O$ (and various alkoxy-modified reagents) and $NaBH_4$/EtOH to sulfinylamides (*e.g.* Table 16, entry 9).[239] With optically active derivatives, significant diastereoselectivities (20–80%) are obtained in the reductions and are enhanced by reduction of racemic derivatives with optically active LAH-derived reagents.[239] More thorough examination of such asymmetric reductions are found in Chapter 1.7, this volume. The product sulfinamides may be cleaved with TFA to the corresponding primary amine or oxidized to sulfonamides.[239] The activated imine linkage in *N*-sulfonyl imines is reduced under mild conditions with $NaBH_4$/MeOH (entry 10)[240] or LAH (entry 11)[241] and probably many other reagents, although the range has not been explored. Entry 11 illustrates an unusual reductive removal of a sulfonyl imine with LAH.[241]

### 1.2.3.6 Reduction of *N*-Phosphorus-substituted Imines to *N*-Phosphorus-substituted Amines

The attachment of the strongly electronegative phosphinyl (P—O) group to an imine, usually *via* reaction of an oxime with a chlorophosphine,[242] also gives highly electrophilic imines which are reduced by $NaBH_4$/THF[242,243] and various modified borohydride and LAH derivatives[243–245] under mild conditions. The product *N*-phosphinylamines are protected forms of primary amines since removal of the phosphorus substituent is accomplished under mild acidic conditions.[242,246] Entries 12 and 13 (Table 16) present representative reductions and illustrate (entry 13) that highly diastereoselective reductions of cyclic systems to axial amine derivatives are accomplished with $LiBHBu^s_3$.[243] Enantioselective reductions of *N*-diphenylphosphinyl imines to optically active amine derivatives have also been reported (Chapter 1.7, this volume).[244,245]

### 1.2.3.7 Reduction of other *N*-Heteroatom-substituted Imines to *N*-Heteroatom-substituted Amines

A few other *N*-substituted imines have occasionally been reduced to amine derivatives. Thus, *N*-nitro imines (nitrimines) are reduced by $NaBH_4$/dioxane/EtOH/AcOH[247] to *N*-nitroamines (Table 16, entry 14), and nitronate salts are reduced by $BH_3$/THF to hydroxylamines (entry 15) *via* oximes.[248] Isocyanates are reduced by $LiBHEt_3$,[25] $LiAlH(OBu^t)_3$ (at low temperature),[249] or $Ph_3SnH$[250] to formamides, which may be hydrolyzed in acidic workup to amines,[25] while reduction with LAH affords *N*-methylamines.[251]

## 1.2.4 REFERENCES

1. A. E. Finholt, A. C. Bond, Jr. and H. I. Schlesinger, *J. Am. Chem. Soc.*, 1947, **69**, 1199.
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# 1.3

# Reduction of C=X to CHXH by Hydride Delivery from Carbon

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## 1.3.1 INTRODUCTION

Unanticipated developments help to put known facts into place. Results from biochemistry drove home to organic chemists the message that it was not a chemical rarity for carbon–hydrogen bonds to be sources of hydride equivalents. Westheimer, Vennesland *et al.*[1] established beyond doubt that in a redox reaction mediated by the coenzyme couple NAD(P)$^+$/NAD(P)H the carbon–hydrogen bond of ethanol could serve directly as a hydride donor to an electron-deficient carbon of a pyridinium ion, and that this hydride equivalent could in turn be donated directly to the electropositive carbon of a carbonyl group. Thus the hydride donor capacities of carbon are also part and parcel of life. All this can occur under physiological conditions with the help of an enzyme, which somehow activates these reactants. The sequence is illustrated schematically in equation (1). In either direction hydride is transferred from carbon to carbon.

The organic ground on which these observations fell was fertile. The reducing power of aldehydes was well known, for example the use of formaldehyde (together with zinc dithionite) in the dye industry.[2]

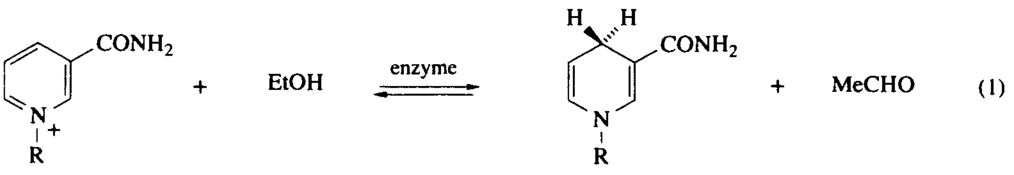

(1) R = ribose-OPOP-ribose-adenine (2a)

(1)

The Cannizzaro reaction (Section 1.3.3.2), the Leuckart reaction (Section 1.3.3.1), wherein formic acid is used as a reductant, and the Meerwein–Ponndorf–Verley (MPV) reaction (Section 1.3.3.3), wherein alcohols serve as reducing agents, had been used and studied widely by the organic community. The results from biochemistry underscored the kindredness of these different processes.

Another development also had an effect, but in this case a delaying one, on the development of carbon–hydrogen bonds as hydride donors; the advent of highly reactive but safe metal hydrides as reducing agents tempered interest for a time in the less potent organic reducing agents. In recent years, however, interest in some new synthetic and mechanistic aspects of 'hydride transfer' from carbon has been rekindled.

The quotation marks of the foregoing sentence refer to a convention that will be adopted here, namely that the descriptors 'hydride' and 'hydride transfer' will represent an end result, not a mechanistic implication. The mechanistic aspects will be discussed when relevant to the material of this chapter. Indeed the majority of more recent work is more mechanistically than synthetically oriented.

## 1.3.2 STRUCTURE AND REACTIVITY

### 1.3.2.1 Structural Types that may donate Hydride

Some representative examples of hydride donor couples are triarylmethanes (**3a,b**), cycloheptatrienes (**4a,b**), α-heterosubstituted methanes (**5a,b**), and heterocycles such as 1,4-dihydropyridines (**6a,b**).

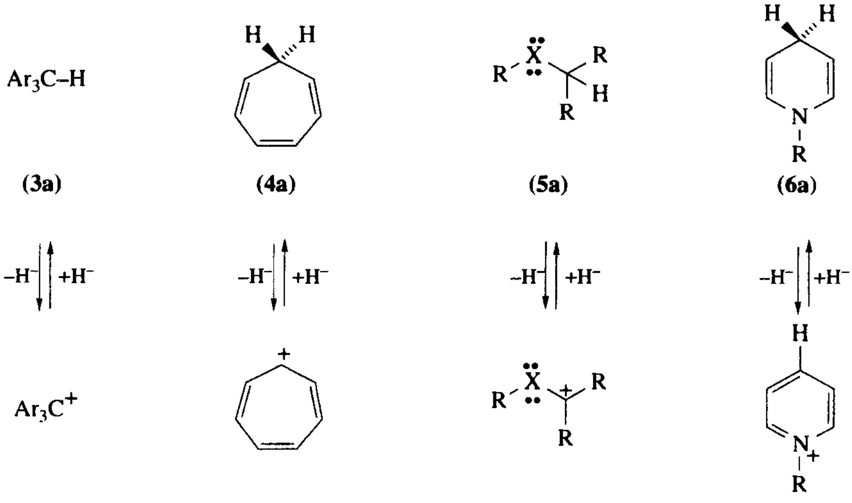

**(3a)** **(4a)** **(5a)** **(6a)**

**(3b)** **(4b)** **(5b)** **(6b)**

Primary and secondary alcohols or alkoxides may serve as hydride sources; the generation of a strong carbonyl bond serves as a driving force (equation 2). Other atoms can replace oxygen; an analogous process whereby a carbon–carbon double bond is formed *via* loss of hydride from a carbanion has much synthetic potential (equation 3). In some cases the metal remains bonded to the alkene (Section 1.3.3.7). Some relatively isolated examples wherein bonds other than double bonds are formed will be discussed later. Most of these reactions will be seen to proceed often (but not obligatorily) through six-membered ring transition states.

Examples of transpositions of hydride *via* sigmatropic reactions (equation 4)[3] will be restricted to one special example, which will be discussed in Section 1.3.3.5.3.

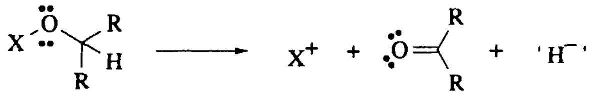

(2)

X = H, metal ion

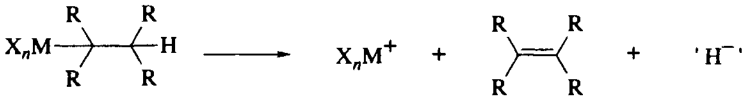

(3)

X = ligand; M = B, Al, Zn, Mg, Mo, *etc.*

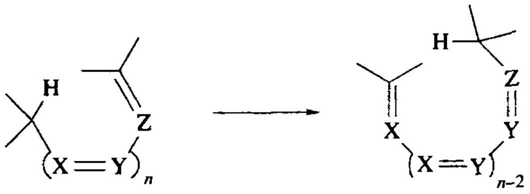

(4)

*n* = 1, 3, 5,...

Some cases of hydride donation from carbon will not be treated here, including various industrial catalyzed cracking processes.[4]

### 1.3.2.2 Some Mechanisms for Hydride Donation

Proper kinetic and thermodynamic meshing of the reactants is necessary for hydride transfer from a donor to an acceptor. There are at least three obviously different mechanisms by which hydride equivalents can be transferred. These are: (i) concerted transfer of the proton and two electrons (equation 5); (ii) homolytic cleavage of the carbon–hydrogen bond followed by subsequent transfer of an electron (equation 6); and (iii) initial loss of a proton followed by transfer of two electrons, either together or stepwise (equation 7). Fusion of pathways is imaginable, dependent on the structures of the participating molecules and possibilities for catalysis.

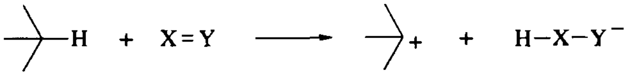

(5)

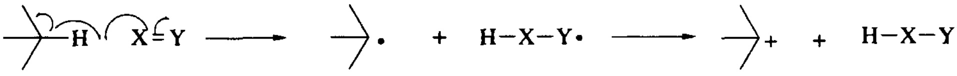

(6)

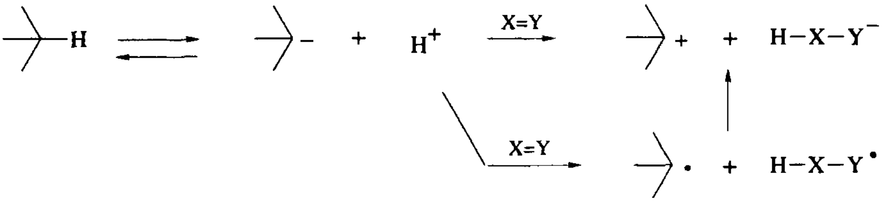

(7)

The concerted mechanism (equation 5) is often encountered (or experimental techniques are not sensitive enough to detect very rapid consecutive steps). Unless otherwise stated a concerted mechanism will be presumed. In a number of examples to be cited, however, the final word is doubtless not yet in.

### 1.3.2.3 Catalysis

Catalysis and activation are not the same. In Friedel–Crafts acylations of aromatics, aluminum chloride is used in more than stoichiometric amounts as an activator and coreagent. A similar approach is often used on a stoichiometric basis to activate carbon–hydrogen bonds toward hydride donation. This chemical approach stands in sharp contrast to the enzyme alcohol dehydrogenase, which works catalytically *via* a complex mechanism wherein activation is achieved but not at the expense of irreversible consumption of a coreagent.[1b]

A brief discussion of some aspects of alcohol dehydrogenase will be used to illustrate the potential for catalysis. This system is chosen for illustration because it has been studied so extensively. Lessons drawn can be applied in a broader context. The 1,4-dihydropyridine (**2a**) is the reductant and this affords a nicotinium ion (**1**) on transfer of hydride, as illustrated in equation (1). This process is mimicked in many abiotic systems by derivatives of (**2**; R = alkyl or benzyl), by Hantzsch esters (**7**), which are synthetically readily accessible, and 1,4-dihydro derivatives (**8**) of pyridine-3,5-dicarboxylic acid. A typical abiotic reaction is the reduction of the activated carbonyl group of an alkyl phenylglyoxylate (**9**), activated by a stoichiometric amount of the powerful electrophile $Mg(ClO_4)_2$, by, for example, (**2b**; equation 8). After acrimonious debate the consensus seems to be that such reactions involve a one-step mechanism (*i.e.* equation 5), unless the reaction partner strongly demands a radical intermediate, as in the reduction of iron(II) to iron(III).

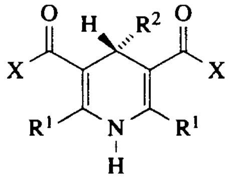

(**7**) $R^1$ = alkyl, aryl; X = OR, $NR_2$, $CR^2$; $R^2$ = alkyl, aryl

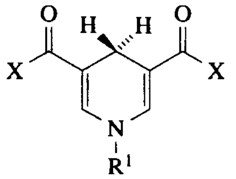

(**8**) $R^1$ = alkyl, benzyl; X = OR, $NR^2$

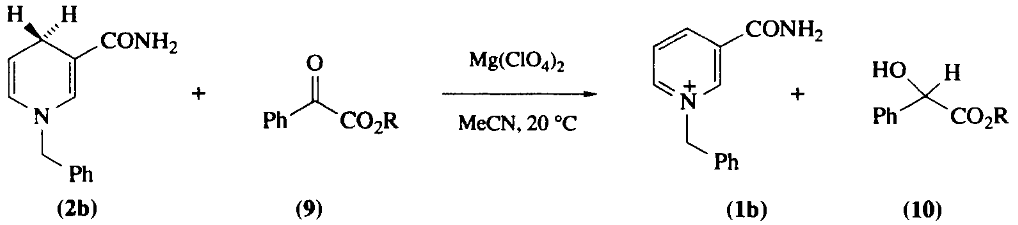

(8)

How may the kinetic barriers to hydride transfer be lowered? The following arguments pertain to both biotic and abiotic systems. Activation is possible. Most likely magnesium ion activates the carbonyl group *via* complexation as depicted in equation (9). The hydride-donating potential can be modified by structural change. Using (**7**) and (**8**) as examples, it is known that introduction of carboxamide groups (X = $NR_2$) increases the redox potential relative to X = OR(see **8a** and **8b**), and introduction of substituents at the 2,6-positions of the 1,4-dihydropyridine ring also has the same effect (see **7a** and **8a**). As a marker NADH (**2a**) has $E^0 = -361$ mV.[5]

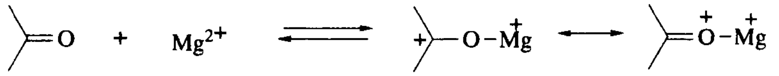

(9)

Hard electrophiles like $Mg(ClO_4)_2$ are used to activate abiotic systems. In the enzyme liver alcohol dehydrogenase (LAD) a considerably different catalytic apparatus is present; a zinc ion coordinated to two cysteines and a histidine serves as a coordinating site for the carbonyl compound/alcoholate, as illustrated in equation (10). This zinc ion has amphoteric properties consistent with the capacity to activate the reaction in both directions without being consumed, in other words to act as a catalyst. Synthetic models of this catalytically active zinc have been shown to possess some catalytic activity in analogy to the enzyme (see Section 1.3.3.5.1iii).

Various experimental and theoretical approaches suggest that in the transition state only slight, if any, negative charge is present on the hydrogen atom being transferred; B in Scheme 1 rather than A.[6] In fact argument on the basis of precedent suggests that the transition state may actually involve a positively charged hydrogen atom (C in Scheme 1). For example, the bridged 1,5-hydridocyclodecyl carbocation

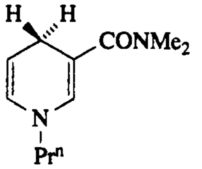

**(2c)** $E° = -434\text{mV}$

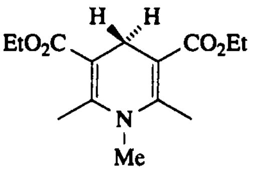

**(7a)** $E° = -363$ mV

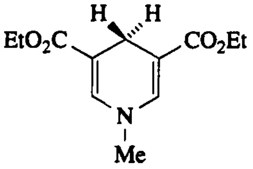

**(8a)** $E° = -260$ mV

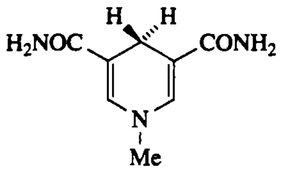

**(8b)** $E° = -365$ mV

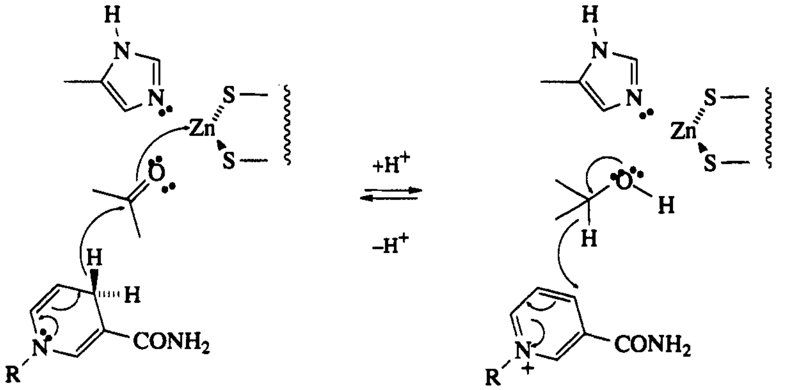

(10)

(A) is a model for the transition state for hydride transfer.[7] The situation in (A) is a particularly good model for hydride transfer from an $sp^3$ carbon to an $sp^2$ carbonium ion center. NMR investigations of (A) indicate that the hydrogen undergoing transfer has indeed only about 0.1 electron.

A $\quad \mathrm{C{-}H} + \mathrm{C}^{+} \longrightarrow \left[\overset{+}{\mathrm{C}}\cdots\overset{-}{\mathrm{H}}\cdots\overset{+}{\mathrm{C}}\right]^{\ddagger}$

B $\quad \mathrm{C{-}H} + \mathrm{C}^{+} \longrightarrow \left[\overset{1/2+}{\mathrm{C}}\cdots\mathrm{H}\cdots\overset{1/2+}{\mathrm{C}}\right]^{\ddagger}$

C $\quad \mathrm{C{-}H} + \mathrm{C}^{+} \longrightarrow \left[\mathrm{C}\cdots\overset{+}{\mathrm{H}}\cdots\mathrm{C}\right]^{\ddagger}$

**Scheme 1**

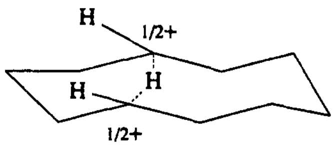

(A)

Simple frontier orbital arguments have been made on how a transition state analogous to C (Scheme 1) could be stabilized by the carboxamide of nicotinamide or amide units from the peptide chain. This is, of course, the essence of complementarity in an enzyme.[6] More rigorous calculations (Section 1.3.3.5.1i) indeed indicate participation of the carboxamide in stabilization of the transition state for hydride transfer. These simple schemes can be put in even more primitive acid/base terms. The hydrogen being transferred has the character of an acid and as such will be stabilized by interaction with bases like carbonyl oxygen. One may expect acceleration of hydride transfer when such opportunities for stabilization are present.

## 1.3.3 COMPOUND CLASSES

### 1.3.3.1 Hydride Transfer from Formic Acid

Formic acid is an exception among organic acids in having reducing capacity because of its combined acid/aldehyde character and the possibility for exothermic release of carbon dioxide on hydride donation. Ammonium formate, $NH_4CO_2H$, has long been used for reductive alkylation of amines. This is the Leuckart reaction, which has been reviewed.[8] In this process aldehydes or ketones are used to alkylate ammonia and form a primary amine (**11**), as depicted in equation (11). The reductive step is the reaction of formate with an iminium ion or its equivalent (equation 12).[9]

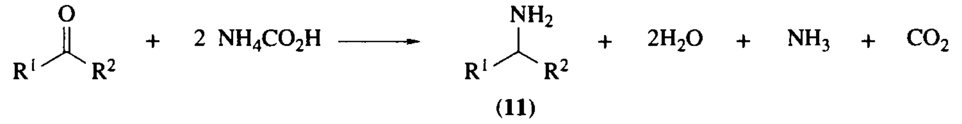

(11)

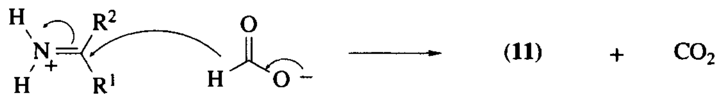

(12)

Formic acid also reduces stable iminium functionalities (but not in general carbonyl groups). Acridinium ions are also readily reduced. This process bears some outward resemblance to the enzymatic transformation of formate to carbon dioxide by formate dehydrogenase, although a molybdenum/sulfur cluster is probably the hydride acceptor in the enzyme.[10]

Probably the most use has been made of the Eschweiler–Clarke modification wherein formaldehyde is used together with formic acid to methylate amines.[11] This procedure is especially useful for the clean preparation of *N*,*N*-dimethylamines, a particularly useful example being the *N*,*N*-dimethylation of amino acids.[12]

#### *1.3.3.1.1 Catalysis*

The synthetic potential of reductions by formate has been extended considerably by the use of ammonium formate with transition metal catalysts like palladium and rhodium. This forms a safe alternative to use of hydrogen. In this fashion it is possible to reduce hydrazones to hydrazines, azides and nitro groups to amines, to dehalogenate chloro-substituted aromatics, and to carry out various reductive removals of functional groups. For example, phenol triflates are selectively deoxygenated to the aromatic derivatives using triethylammonium formate as reductant and a palladium catalyst.[13] These recent applications have been reviewed.[14]

Catalyzed reductions with ammonium formate proceed with retention of configuration, at least for the case of nitro compounds. Treatment of steroid derivative (**12**) with ammonium formate in methanolic solution and a catalytic amount of palladium on charcoal gave exclusively amino steroid (**13**), as shown in equation (13).[15] A similar technique has been used to produce members of the ephedrine family.

Hydrogenation of itaconic acid (**14**) with $Rh(COD)Cl_2$ catalyst and commercially available triethylammonium formate as hydrogen source delivers (*S*)-(**15**) in good enantiomeric excess (equation 14); with hydrogen as reductant instead of ammonium formate a 94% *ee* is obtained.[16]

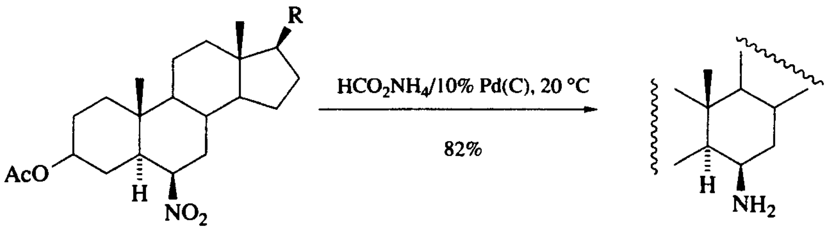
R
AcO
H
NO2
HCO2NH4/10% Pd(C), 20 °C
82%
H
NH2

**(12)** **(13)**

(13)

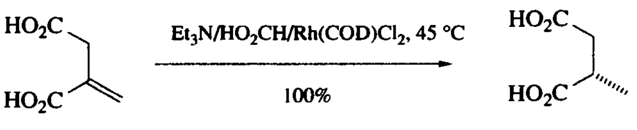
HO2C
HO2C
Et3N/HO2CH/Rh(COD)Cl2, 45 °C
100%
HO2C
HO2C

**(14)** **(15)** 84% *ee*

(14)

An attractive method for the regeneration of NAD(P)H (see also Section 1.3.3.5.1) is *via* regioselective reduction of NAD(P)$^+$ by formate ion, catalyzed by a rhodium derivative.[17]

Ortho esters or amides or mixed ortho derivatives of formic acid might also be expected to be fairly good hydride donors. The absence of proton acidity is attractive for potential application in catalyzed reactions. This type of reaction is, however, rather uncommon, owing to ready loss of a heteroatom and formation of a stabilized carbocation.[18] Compound (**16**) represents an interesting case that has been examined by Wuest *et al.*[19] In the indicated conformation the lone pairs on the nitrogen atoms are antiperiplanar to the carbon–hydrogen bond; at first sight good stereoelectronic activation of the hydride-donating potential would be expected. Although (**16**) will generate molecular hydrogen in the presence of a strong acid like $HBF_4$ (equation 15) with generation of (**17**), reduction of ethyl phenylglyoxylate (**9a**) to ethyl mandelate (**10a**) in the presence of $Mg^{2+}$ occurs with hydride donation from a methylene carbon (Scheme 2), as evidenced by the formation of (**19**). On the other hand (**20**) does provide under analogous conditions (**10a**) and ion (**21**; equation 16).

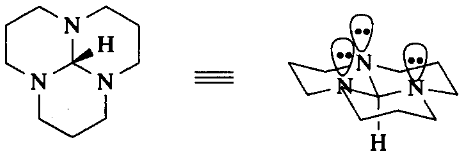

**(16)** **(16)**

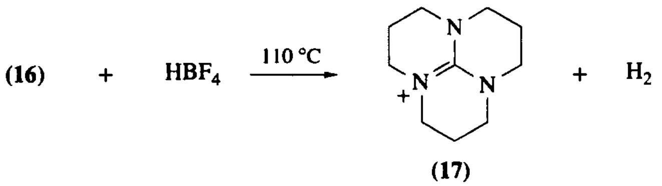
(16)
+
HBF4
110 °C
N
N
N
+
+
H2

**(17)**

(15)

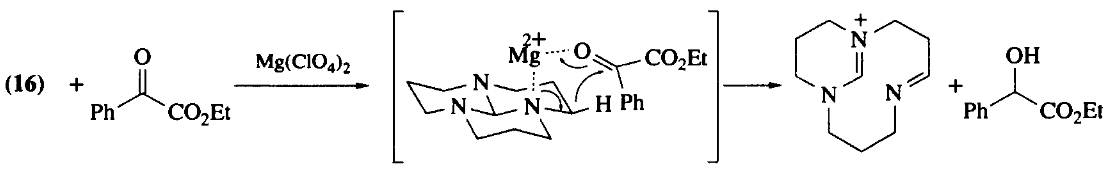
(16)
+
O
Ph
CO2Et
Mg(ClO4)2
2+
Mg
O
CO2Et
N
N
N
H Ph
+
N
N
N
+
OH
Ph
CO2Et

**(9a)** **(18)** **(19)** **(10a)**

**Scheme 2**

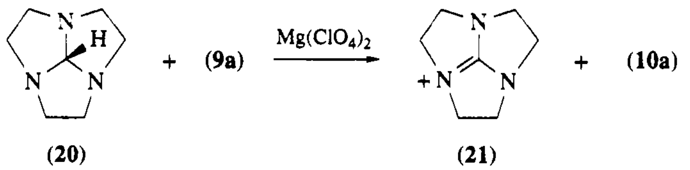

(16)

### 1.3.3.2 Hydride Transfer from Aldehydes

The Cannizzaro reaction (Scheme 3), in which a nonenolizable aldehyde (**22**) disproportionates in the presence of strong base, usually NaOH, to an acid (**25**) and alcohol (**26**), is one of the longest known organic reactions. The crossed version wherein excess formaldehyde is used as the reductant is especially popular. Geissman has adequately reviewed these variations.[20] Current mechanistic thinking entails hydride transfer from a tetracoordinate intermediate (**23**) formed on addition of hydroxide to the aldehyde. The most straightforward course of reaction is rate-determining transfer of hydride *via* a linear or bent transition state (**24**) to a second molecule of aldehyde.[21] MNDO-SCF calculations support a linear geometry for transition state (**24**) with only 0.11 electron on the hydrogen atom.[22]

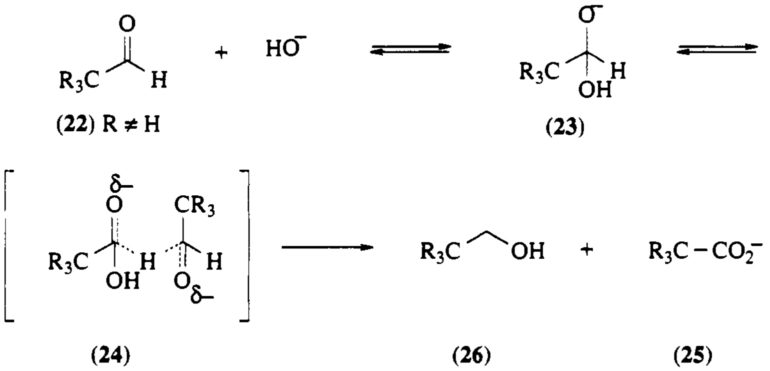

**Scheme 3**

Intermediate (**23**) could also react *via* a ketyl radical (**27**) and hydrogen atom (equation 17). Ketyl radical intermediates have been detected, isotopic exchange experiments suggest radical pathways, and calculations indicate that a radical pathway could well be followed, particularly in the case of aromatic aldehydes.[23,24]

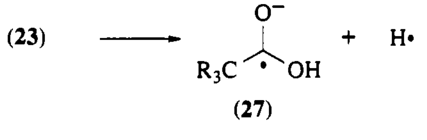

(17)

An additional complication in mechanistic interpretation is the fact that methoxide (reactions are often run in methanol) serves also as an effective hydride donor towards aldehydes and the derived formaldehyde may participate in a crossed Cannizzaro reaction.[21] The conditions of the Cannizzaro reaction are fairly extreme (strong base, reasonably high temperatures) and complex mechanistic behavior is therefore not surprising.

#### *1.3.3.2.1 Catalysis*

Various methods, many with an eye towards industrial application, have been examined to accelerate Cannizzaro reactions. For example copper–silica catalysts,[25] $Na_2S$, $Na_2S_2O_3$ or $Na_2SO_3$ supported on $Al_2O_3$, and ultrasound all have been reported to accelerate certain Cannizzaro processes.[26] An extremely promising development is the use of transition metal catalysts, which may be employed under neutral conditions in the absence of strong base. This permits the use of enolizable aldehydes like (**28**), which under basic conditions would immediately be consumed *via* aldol reactions. For example, in the presence of $H_4Ru(CO)_8(PBu_3)_3$ or $Ru_2(CO)_4(MeCO_2)_2(PBu_3)_2$, the disproportionation of (**28**) to (**29**)/(**30**) indicated in equation (18) occurs readily. Small enantiomeric excesses of acid have been obtained when an optically active ruthenium complex is used as catalyst.[27]

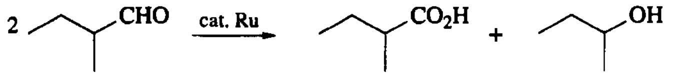

(**28**) (**29**) (**30**) (18)

In view of the hydride-donating potential of (**23**), one might anticipate similar reactivity for adducts derived from, for example, amines and thiols. Intermolecular demonstrations of such reactivity are scarce; on the other hand intramolecular examples are well known, although they may be mechanistically ambiguous. The prototype reaction is the intramolecular disproportionation of glyoxal (**31**) to glycolic acid (**32**), shown in equation (19). This reaction may be induced by hydroxide.[28] With the aid of *ab initio* and MNDO-SCF-MO calculations a highly bent transition state has been calculated for hydride transfer.[29]

$$\underset{(\mathbf{31})}{(CHO)_2} + HO^- \rightleftharpoons \underset{(\mathbf{32})}{HOCH_2-CO_2^-} \qquad (19)$$

Chemically analogous transformations occur enzymatically. For example, in the glycolase system glutathione (**34**; GSH, Glu-Cys-Gly) catalyzes the conversion of methylglyoxal (**33**) to lactic acid (**35**), as shown in equation (20). This transformation is initiated not by hydroxide, but by the addition of thiolate from GSH to the aldehyde carbonyl group.[30]

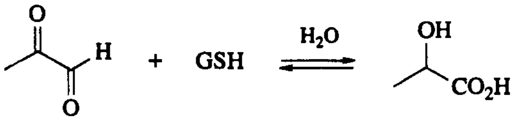

(**33**) (**34**) (**35**) (20)

The enzyme systems are complex; two reactions are catalyzed, namely formation of a thioester and its subsequent hydrolysis to free acid. Because little or no tritium or deuterium from solution is incorporated into the rearranged product, a hydride shift was assumed.[31] With optically pure thiols like (**36**) the rearrangement of (**37**) to (**10b**) can be catalyzed (equation 21). The methyl mandelate formed has a very modest enantiomeric excess.[32]

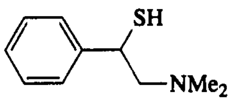

(**36**)

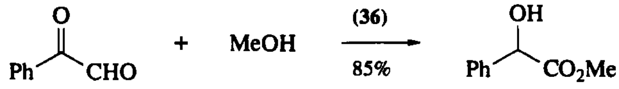

(**37**) (**10b**) (21)

Evidence later became available that indicated that the lack of isotope incorporation from solvent in enzymic experiments is misleading.[33] Trapping experiments have established quite conclusively that an enediol (**38**) is a kinetically competent intermediate. Hydride transfer occurring through a transition state like (**39**; equation 22) is therefore not required.[34]

The glyoxalase system bound on a solid phase has been used for the asymmetric synthesis of α-hydroxy acids (equation 23). Aldehyde (**40**; R = $Pr^n$) provides the acid (**42**) in 79% yield and in >99% *ee*.[35] The enzyme system GX-I/GX-II is not especially stable when isolated on a matrix and scale-up is difficult because large quantities of GSH are required.

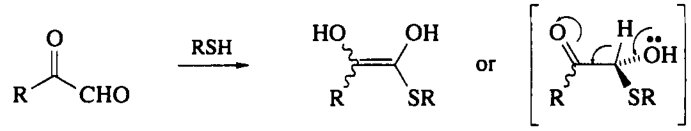

(38) (39) (22)

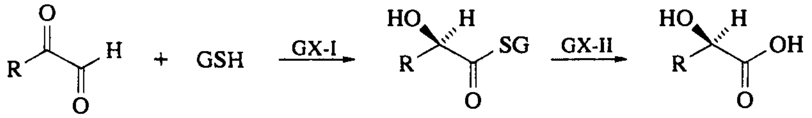

(40) R = $p$-ClC$_6$H$_4$, Ph, $p$-MeOC$_6$H$_4$, Me, Pr$^n$ (41) (42) (23)

Intramolecular redox reactions *via* enediol chemistry are, of course, well known. Ascorbic acid and the multitude of known related structures which readily form enediols have even been coined 'reductones' by von Euler and Eistert.[36]

### 1.3.3.3 Hydride Transfer from Alcohols and Amines

The classical Meerwein–Ponndorf–Verley (MPV) process, named after the independent originators, can be illustrated by the reduction of crotonaldehyde (**43**) by aluminum isopropoxide (**44**) in isopropyl alcohol (equation 24). Aluminum isopropoxide transfers hydride reversibly to a carbonyl acceptor. Acetone is formed as a volatile side product, which can be removed during reaction. The reaction of equation (24) is forced even further to the right by the use of excess isopropyl alcohol. MPV reactions have been reviewed.[37] In the Oppenauer variant of this reaction an alcohol is oxidized to a ketone, and acetone is used as hydride acceptor in the presence of a strong base like *t*-butoxide. This reaction was originally developed for the selective oxidation of sterols. The synthetic aspects of this procedure have also been reviewed.[38]

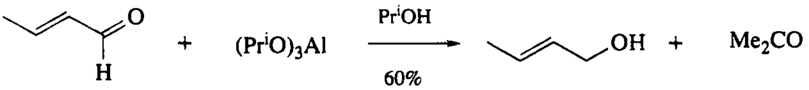

(43) (44) (45) (24)

Examples of amines serving as hydride donors are scarce (for a special case, see Section 1.3.3.5.3). That this reaction is possible is exemplified by a side reaction that occurs when simple aldehydes are treated with lithium diisopropylamide (**46**); reduction of the aldehyde with formation of an imine (**47**) occurs (equation 25).[39]

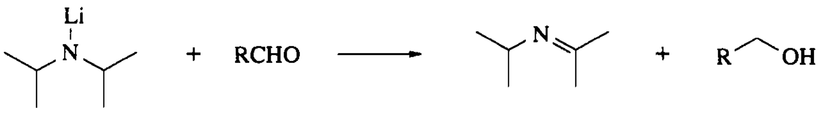

(46) (47) (25)

A mass of experimental evidence on MPV reactions, much of which has been summarized by Morrison and Mosher,[40,41] points to hydride transfer through a six-membered Lewis salt (**50**; equation 26). No account of aggregation is taken in this model.[42] The observation (equation 26) that the major enantiomer obtained from reductions with optically pure aluminum alkoxides is correctly predicted by (**50**) provides additional support for the six-membered intermediate postulate. Examples of reductions by alkoxides wherein this geometry is unattainable will shortly be discussed, however.

Calculational results also support a transition state formed from the six-membered Lewis salt (**50**). As calculated at the 3-21G level the transition state for the reaction of lithium methoxide with formaldehyde

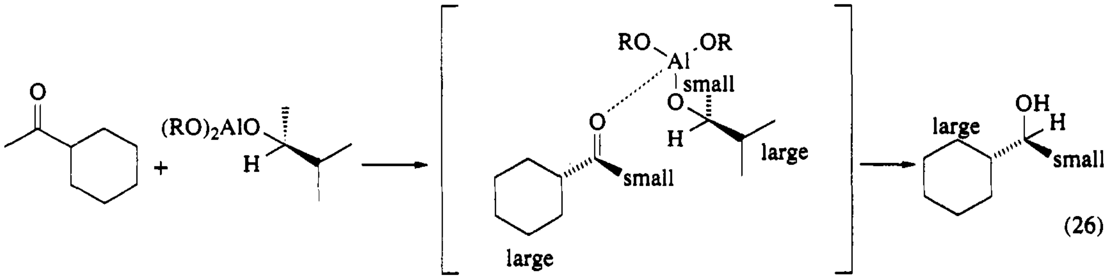
(RO)2AlO
H
+
RO
OR
Al
small
O
H
large
small
large
OH
H
large
small

(26)

**(48)** **(49)** **(50)** *(S)*-**(51)** 22% *ee*

involves a bent C—H—C bond with rather low bending energies.[43] Moreover, the hydrogen atom being transferred is calculated to bear little negative charge.

Assessment of the role of the cation in MPV reduction is difficult. Conversion of alcohol to alkoxide certainly enhances the reactivity towards hydride donation, and aluminum ions aid *via* chelation in arranging alkoxide and carbonyl compound properly for reaction. However, alkoxides bearing cations other than aluminum may also exhibit good hydride-donating tendencies. Lithium isopropoxide reduces steroidal ketones efficiently[44] and magnesium alkoxides derived from chiral alcohols have been used extensively in chiral syntheses. Isobornyloxy magnesium bromide (**52**) has been used widely for this purpose (equation 27).[41]

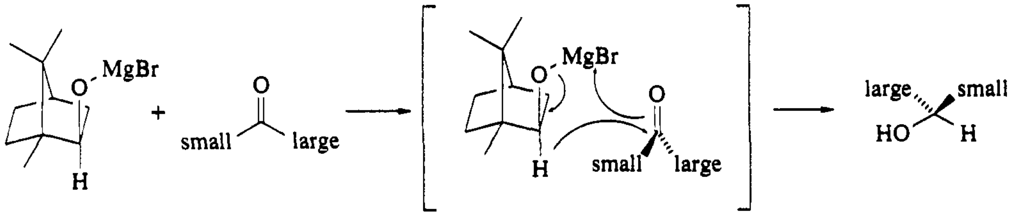
MgBr
O
H
+
O
small
large
MgBr
O
O
H
small
large
large
small
HO
H

(27)

**(52)** **(53)**

Proper orientation plays a large role. For example (**54**) rearranges cleanly to (**55**) merely with sodium sulfite or dilute sodium hydroxide (pH 10.5), an equilibrium mixture of 75% (**55**) and 25% (**54**) being formed (equation 28).[45]

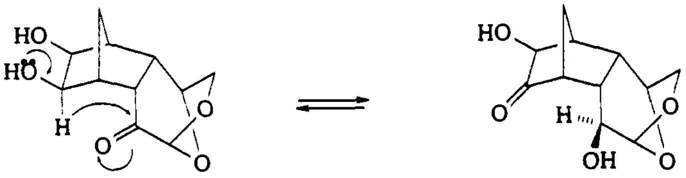
HO
HO
H
O
O
O
HO
O
H
O
OH
O

(28)

**(54)** **(55)**

The rather complex conversion of (**56**) to (**58**) depicted in Scheme 4 doubtless involves an intramolecular hydride shift through a boat conformation (**57**). Benzaldehyde generated by this process undergoes

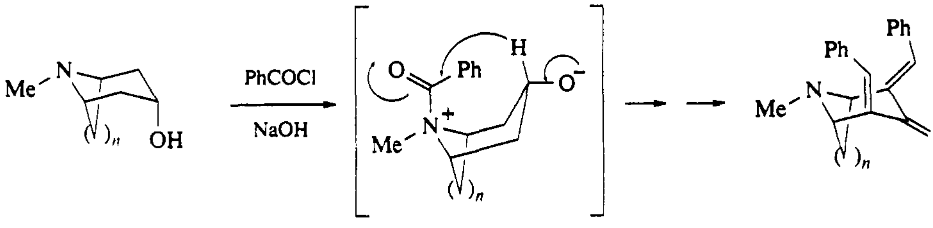
Me
N
OH
n
PhCOCl
NaOH
O
Ph
H
O−
N+
Me
n
Ph
Ph
N
Me
O
n

**(56)** **(57)** **(58)**

**Scheme 4**

subsequent aldol condensation to give (**58**). This entire sequence occurs under mildly basic Schotten–Baumann conditions.[46]

Thus intramolecular hydride transfers occur quite readily if the conformation is suitable for the efficient interaction of acceptor, usually carbonyl, and hydride donor carbon atom. In the transformation of (**59**) to (**62**; Scheme 5) intramolecular hydride transfer occurs from an amine (**59**) rather than an alcohol.[47] This reaction is probably mechanistically akin to the chemistry discussed in Section 1.3.3.5.3.

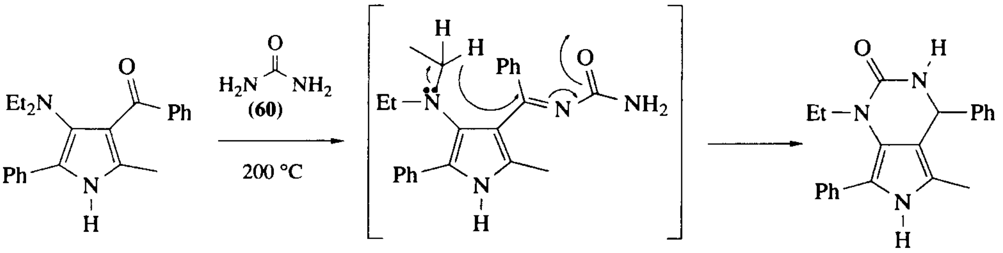

**(59)** **(61)** **(62)**

**Scheme 5**

In the presence of a metal isopropoxide (**63**) undergoes either intermolecular reduction to form (**66**), or reacts intramolecularly to form (**65**). The latter appears to be the product expected from transition state (**64**), derived from a boat conformation (Scheme 6). The intramolecular reaction is much faster than its intermolecular competitor with $Ba^{2+}$ or $K^+$ as cation but when $Al^{3+}$ is the cation, *i.e.* classical MPV conditions, then only intermolecular reduction occurs.[48]

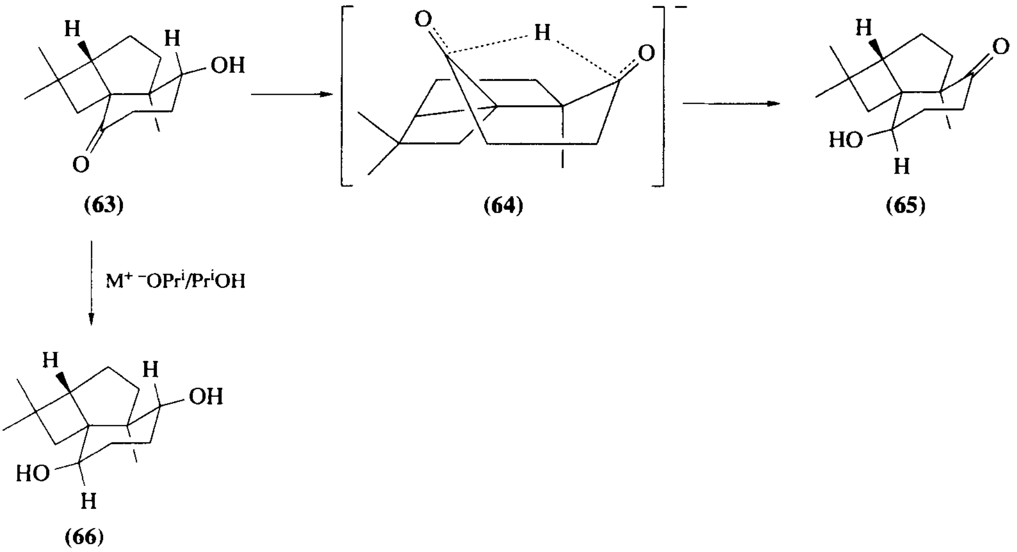

**(63)** **(64)** **(65)**

**(66)**

**Scheme 6**

Hydride is transferred intramolecularly in (**67**; equation 29) in a degenerate process.[49] Clearly the six-membered transition state characteristic of the MPV reaction cannot be achieved here because the orientation of hydroxy and carbonyl is incompatible with simultaneous coordination to a metal ion. The rates depend on the cation; if the alkoxide is a solvent-separated ion pair the hydride-donating potential in the intramolecular reaction is increased, consistent with the greater charge localized on alkoxide oxygen.

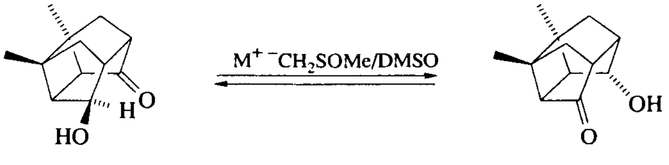

(29)

*(R)*-(**67**) *(S)*-(**68**)

Alcohols also transfer hydride to carbonium ions.[50] In seminal experiments Bartlett[51] demonstrated that isopropyl alcohol as well as other alcohols readily transferred hydride to various triaryl carbonium ions; oxidation of the alcohol and reduction of the carbonium ion is the result.

In a similar fashion ethers, acetals[52] and formic acid may serve as efficient hydride donors towards carbonium ions, aryldiazonium salts (reduction with loss of nitrogen occurs) and pyrylium salts. A review of this chemistry is available.[53]

### *1.3.3.3.1 Catalysis*

Promise is held in MPV reactions carried out under catalytic conditions. Instead of, for example, stoichiometric amounts of aluminum as the metal ion activator, catalytic quantities of complexes of rhodium and iridium can sometimes be used to bring about the same reactions. Although the catalytic mechanisms have not been established, postulation of the usual six-membered transition state in the critical step of hydride transfer appears reasonable. The strongly basic conditions of the MPV reaction are avoided. Reductions of aryl ketones (**69**; equation 30) using (excess) isopropyl alcohol as hydrogen donor and at partial conversions have led to the formation of alcohol (**70**) in modest enantiomeric excesses with various chiral ligands.[54–57]

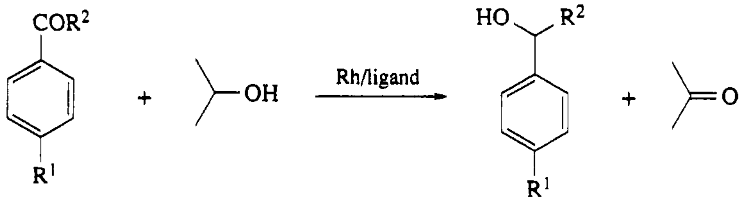

(30)

**(69)** **(70)**

Metal carbonyls like $Mo(CO)_6$ or $Mn_2(CO)_{10}$ will catalyze the reduction of carbon tetrachloride to chloroform by isopropyl alcohol. Apparently these are radical reactions initiated by abstraction of a chloride from carbon tetrachloride by the metal complex.[58]

Homogeneous (or heterogeneous) catalyst systems offer the exciting perspective of high efficiency, optimal use of (chiral) ligands in enantioselective reactions, and the possibility of taking many different compounds as 'hydride' sources. The use of isopropyl alcohol has been illustrated in this regard, but dioxane, dihydrofuran, aldehydes, formic acid, cyclohexene or *N*-benzylaniline are some of the other compounds that already have been employed as alternatives.[4]

### *1.3.3.3.2 Photochemical reactions*

Alcohols (as well as amines, sulfides and many hydrocarbons) may act as overall hydride donors towards excited nonbonding–π* states of carbonyl compounds and heterocycles. The synthetic as well as the photophysical aspects of these processes have been discussed extensively.[59] These reactions will not be dealt with further here. Singlet oxygen also accepts hydride from alkoxides in the gas phase; the mechanisms of such reactions have received considerable study.[60]

## 1.3.3.4 Hydride Transfer from Hydrocarbons

Cycloheptatriene and derivatives thereof donate hydride readily to a variety of carbonium ion acceptors. The position of the end equilibrium depends on the thermodynamics of the exchange.[61–63] These reactions are prototypes of a broad area of carbonium ion chemistry wherein carbonium ions equilibrate *via* intra- and inter-molecular hydride shifts between a donor C—H bond, usually $sp^3$ hybridized, and a carbonium ion acceptor. This chemistry is often achieved with heterogeneous catalysts and is of great industrial significance; it lies outside the emphasis of this review, however. Excellent treatises are available,[4,64] and a review has appeared on the use of carriers like adamantane to promote hydride transfer in hydrocarbons under strongly acidic conditions.[65]

Although not many examples are known, properly constrained organic compounds can transfer the elements of hydrogen in what appears to be a concerted process akin to reductions by diimide, HN═NH. The reduction of 1,2-dimethylcyclohexene (**72**) by *cis*-9,10-dihydronaphthalene (**71**) is an example (equation 31). Yields are only moderate, but the stereospecificity is consistent with a concerted process.[66]

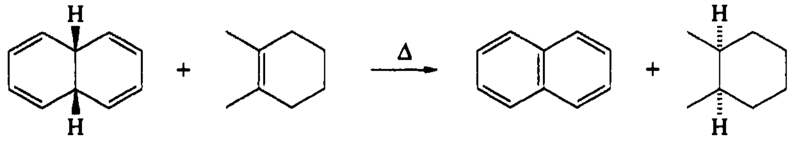

(31)

**(71)** **(72)** **(73)** **(74)**

### 1.3.3.5 Hydride Transfer from Heterocycles

Heterocyclic redox couples do not differ in any profound chemical sense from other hydride donors discussed here. Practical aspects such as reasonable stability of both partners of the redox pair as well as synthetic accessibility, do play a major role, however. In the majority of cases a (hetero)aromatic cation is formed, the developing aromaticity being the driving force for the loss of hydride. By far the most used couple is the dihydropyridine/pyridinium salt (or pyridine) combination already discussed.

#### *1.3.3.5.1 1,4-Dihydropyridines*

The hydride-donating potential of 1,4-dihydropyridines has already been discussed in a mechanistic context in Section 1.3.2.3. Commonly available 1,4-dihydropyridines are the 'Hantzsch esters' (**7**; X = OR), obtained from condensation of a β-keto ester with ammonia and an aldehyde.[67] By far the simplest syntheses of Hantzsch esters involve condensation of ammonia (substituted amines react in general poorly) and an aldehyde if a hydride equivalent at the 4-position is desired. The Hantzsch synthesis has been used in many guises, also to produce nonsymmetrical systems. The interest in these compounds as calcium antagonists has doubtless stimulated the extensive synthetic effort.[68]

Hantzsch esters like (**7b**) react with appropriate acceptors to provide reduced product and pyridine (**75**), as shown in equation (32). The elements of hydrogen are transferred, but there are no effective ways to transform (**75**) cleanly back to (**7b**) so that a catalytic cycle may be established.

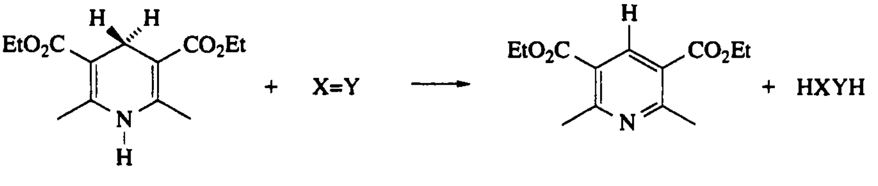

(32)

**(7b)** **(75)**

Derivatives of 1,4-dihydronicotinamide (**2**) and 1,4-dihydropyridine-3,5-dicarboxylic acid (**8**) are obtained from the corresponding pyridines by alkylation followed by reduction with sodium dithionite, as illustrated for (**76**) in equation (33). The absolutely regioselective reduction by dithionite of pyridinium salts to 1,4-dihydropyridines is true synthetic good fortune; most other reducing agents reduce pyridinium salts nonregioselectively and often with reduction beyond the dihydro stage.

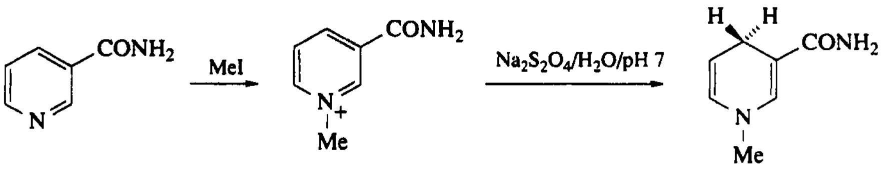

(33)

**(76)** **(1c)** **(2c)**

In general only very electron-deficient double bonds will react spontaneously with 1,4-dihydropyridines. (This statement applies to nonenzymic chemistry; enzymatically, as in LAD, NAD(P)H, with a lesser reduction potential than many of the 1,4-dihydropyridines used in abiotic reactions, reduces unactivated carbonyl groups.) Thiobenzophenone, quinone, maleic acid, and hexachloroacetone react spontaneously with simple dihydropyridines and undergo reduction (the carbon–carbon double bond of maleic anhydride is reduced).[69] Trifluoroacetophenone will also often react spontaneously with 1,4-dihydropyridines.

Reduction of iminium salt (**77**) is illustrated in equation (34). On hydrolysis (**78**) is obtained in good yield.[70]

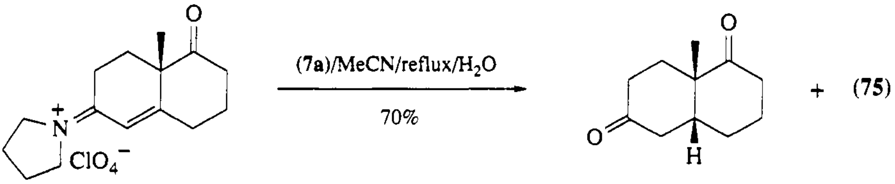

(**77**) (**78**) (34)

More complex pathways can be followed dependent on the structure of the hydride acceptor. For example, dihydroacridine reacts cleanly with 2,3,5,6-tetracyanobenzoquinone to generate a pyridinium/radical anion pair.[71]

The acceptors thus far discussed react spontaneously. By far the greatest amount of work has been done by use of an electrophilic activator, present in stoichiometric amounts, to activate the receptor, usually carbonyl. Dry $Mg(ClO_4)_2$ is particularly effective;[72] zinc ions are sometimes used although their effectiveness is often lower. Presumably the magnesium ion polarizes the carbonyl group making it more electrophilic and a better hydride acceptor (equation 9). Ethyl phenylglyoxylate (**9a**) is not reactive enough to react spontaneously with (**2b**); however, on addition of a stoichiometric amount of $Mg(ClO_4)_2$ spontaneous reduction occurs at room temperature in the dark (equation 8).

### *(i) Enantioselective reductions*

In a timely experiment Ohno demonstrated that 1,4-dihydropyridine (*R*)-(**79**) in the presence of $Mg(ClO_4)_2$ reduced (**9a**) to (**10a**) with modest (18%) enantiomeric excess.[73] This observation gave rise to an enormous amount of work on the design, synthesis and reactions of optically active 1,4-dihydropyridines.

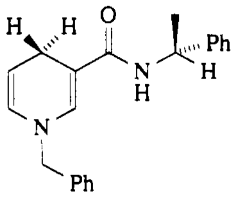

(*R*)-(**79**)

Before further discussion some consideration of the structure and reactivity of 1,4-dihydropyridines is in order. A pyridinium salt is almost certainly capable of accepting a hydride from a 1,4-dihydropyridine. As long as hydride transfer occurs between the 4-positions of structurally analogous 1,4-dihydropyridine and pyridinium salts, the reaction is thermoneutral and leads to no net change. An example is given in equation (35).[74] At 25 °C only 'blind' exchange between the 4-positions occurs and this can only be made visible by isotopic labeling. This '4,4-exchange' reaction can be used to establish the relative redox potentials of 1,4-dihydropyridines (Section 1.3.2.3). But at 67 °C irreversible competitive hydride transfer to the 2(6)-position occurs to form the 1,2-dihydropyridine; all the dihydropyridine present eventually falls into this thermodynamic pit. In any reaction whereby pyridinium salt is generated during the reaction in the presence of unconsumed 1,4-dihydropyridine, exchange and isomerization may be complicating factors especially in the case that the substrates to be reduced are only sluggishly reactive. Additional mechanistic and synthetic aspects of these types of hydride transfers have been considered.[75-77]

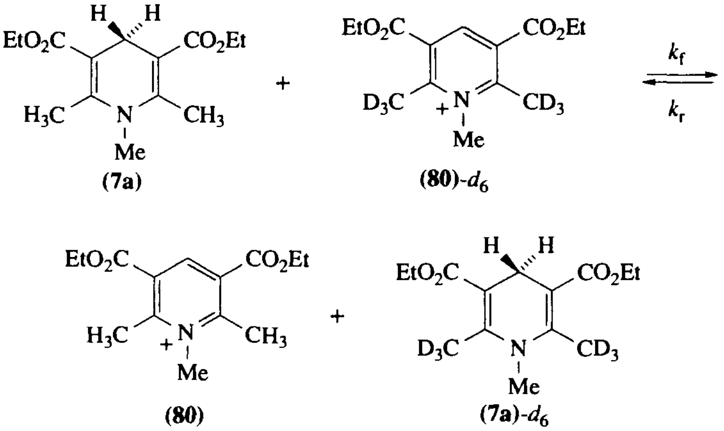

(7a) (80)-$d_6$

(80) (7a)-$d_6$

$K_{eq}$(25 °C) = 0.84

(35)

An additional complication peculiar to derivatives of 1,4-dihydronicotinamide (**2**) is the pronounced sensitivity of the enaminic 5-position to electrophilic attack.[77,78] The (reversible) addition of water to 1,4-dihydronicotinamides (protonation at the 5-position and addition of hydroxide to the 6-position) has caused difficulties in kinetic measurements[79] and the instability of NADH towards acid is doubtless also the result of chemistry initiated at the enaminic 5-carbon.[69] This problem is not, or only barely, present in 1,4-dihydropyridines like (**7**) and (**8**) which bear electron-withdrawing substituents at the 5- as well as 3-positions.

With this knowledge in mind, enantioselective reductions by chiral 1,4-dihydropyridines can be considered in more detail. Two types will be used to illustrate cogent points: 1,4-dihydropyridines wherein C-4 of the heterocyclic ring is stereogenic, and 1,4-dihydropyridines incorporated into a macrocyclic framework that contains stereogenic centers.

It has been found that (4*R*,9*R*)-(**81**) in the presence of a stoichiometric amount of $Mg(ClO_4)_2$ affords (**10b**) in virtually enantiomerically pure (*R*)-form (equation 36).[80] Similar reductions of 2-benzoylpyridine, 2-acetylpyridine, and 4-chlorotrifluoromethylacetophenone proceeded with enantiomeric excesses ranging from 60–100%.

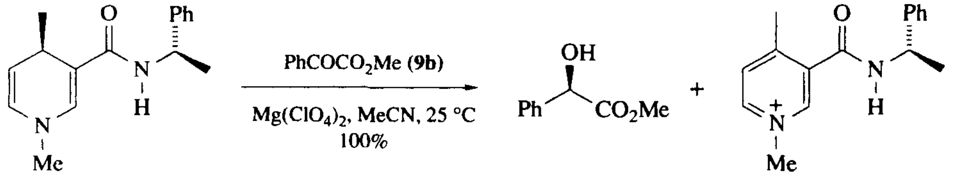

(4*R*,9*R*)-(**81**) (**10b**) 97.6% *ee* (9*R*)-(**82**)

(36)

The stereochemical situation in these experiments may be more involved than one would anticipate at first sight. Buck *et al.*[81] have succeeded in resolving (**83**). These enantiomers can only be the result of axial chirality caused by a torsional barrier to rotation about the aromatic–carbonyl bond being high enough to freeze the amide groups out of plane in the pyridinium salt.

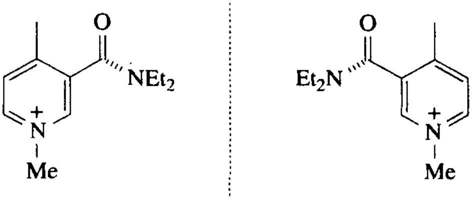

(**83**)

Buck and Donkersloot[82] had suggested on the basis of MINDO/3 calculations that the carbonyl dipole of the amide group will be oriented in the direction of a hydride approaching C-4 of (**83**) (or departing from the corresponding 1,4-dihydropyridine). This hypothesis is supported by several lines of experimental evidence. In the crystal structure the carboxamide group of (4*R*,9*R*)-(**81**) is 65° out of plane and the oxygen is indeed oriented along the line of the carbon–hydrogen bond at C-4.[83] Circumstantial evidence has also been accumulated that nicotinamidium salts with locked conformations about the carboxamide group are reduced on the oxygen side of the carboxamide.[84]

A model for reduction (**84**) proposed by Ohno[85] entails folding the carbonyl back over the dihydropyridine ring; magnesium is complexed simultaneously to both the heterocyclic nitrogen and carbonyl oxygen. It is not clear how axial chirality should be incorporated in this model.

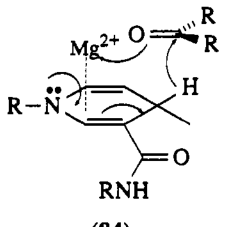

**(84)**

More potent electrophilic activators can be used with 1,4-dihydropyridines more stable to acid conditions. Considerable stabilization is achieved by fusion of an aromatic ring to the 5,6-positions. For example (**85**) will reduce benzaldehyde to benzyl alcohol in moderate yield in the presence of benzenesulfonic acid (equation 37).[86] An optically active variant analogous to (**81**) has also been studied.[87] In addition to proton sources, electrophiles like $AlCl_3$ and $TiCl_4$ may also be used.[88,89]

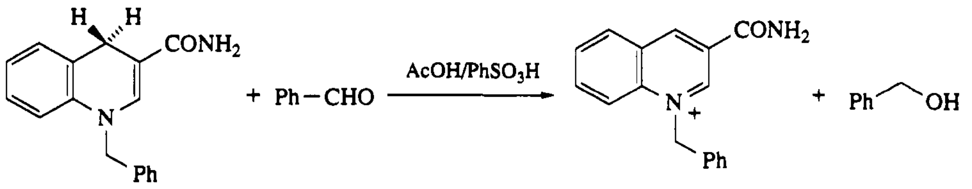

(37)

**(85)** **(86)**

The presence of axial chirality embodied in the carboxamide linkage is certainly no prerequisite to high enantioselectivities. In a very rapid intramolecular reaction the carbonyl group of glyoxylate is reduced in >99% *ee*, as shown in equation (38).[90] The carbonyl group is assumed to be oriented back over the dihydropyridine ring during reduction.

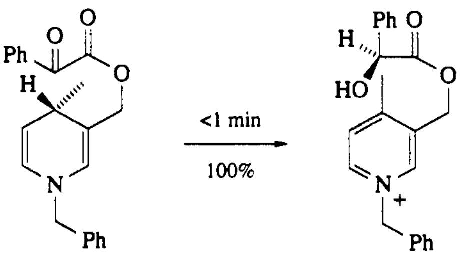

(38)

**(87)** **(88)** >99% *ee*

A considerably different approach to enantioselective reductions is represented by chiral 1,4-dihydropyridine (**89**).[91] The anticipation was that a structured ternary complex could be formed (equation 39).

As in other experiments with 1,4-dihydropyridines only activated carbonyl compounds like (**9**) could be reduced; (**9a**) is reduced to (*S*)-(**10a**) in 80% yield and 86% *ee* at room temperature in the presence of a stoichiometric amount of $Mg(ClO_4)_2$ (equation 40). This agrees entirely with the prediction embodied in equation (39) if the phenyl group is regarded as the larger and the ester as the smaller substituent.

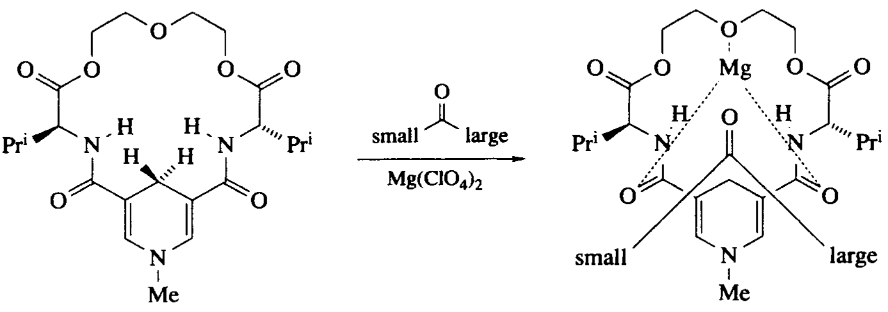

**(89)** **(89)**-complex

(39)

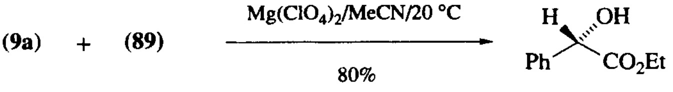

(**10a**) 86% *ee*

(40)

Macrocycles related to (**89**) but derived from alanine, phenylalanine, *t*-leucine,[92] proline and phenylglycine have been prepared. The enantioselectivities for the reduction of (**9a**) increase with the size of the amino acid substituent (proline 0% *ee*, methyl 65% *ee*, benzyl 87% *ee*, isopropyl 86% *ee*). In all cases the natural amino acids of (*S*)-configuration always deliver an excess of the (*S*)-enantiomer of the alcohol.

The bridge that holds the two amino acid carboxylate groups can be varied in shape and length. For bridges five atoms long, *i.e.*—$(CH_2)_2O(CH_2)_2$— or —$(CH_2)_5$—, up to eight atoms long the enantioselectivities remain high. For longer bridges considerable loss of enantioselection occurs, apparently because of the greater conformational flexibility.

From the body of experimental data available a model fairly close to that initially postulated (equation 39) has been developed, except that the carbonyl group is skewed relative to this model about 120°.

It is conceivable that all the various geometries suggested for arrangement of dihydropyridine and carbonyl during the transition state for hydride transfer may be correct. Hydride transfer could occur *via* various orientations analogous to alkoxides; the classical six-membered transition state of the MPV reductions is not mandatory (Section 1.3.3.3). MINDO calculations on the transition state for thermoneutral hydride transfer between a 1,4-dihydropyridine and a pyridinium salt indicate virtually no energy barrier to rotation of the participants, *i.e.* (**90**) is as stable as (**91**).[93]

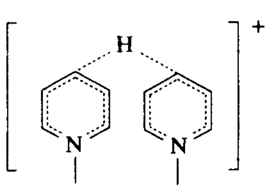

**(90)**

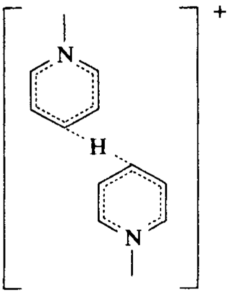

**(91)**

In other words the relative orientations of hydride donor and double bond acceptor may not be as crucial as once thought.

*(ii) Oxidative reactions*

The oxidation of primary and secondary alcohols by pyridinium salts, *i.e.* the reverse of the reactions just discussed, is seldom seen. An experimental difficulty is that MPV conditions, that is formation of metal alkoxides, must be used to obtain any reaction at all. Under these strongly basic conditions most pyridinium salts are unstable. There is a dearth of processes of obvious synthetic usefulness based on this approach.[94]

A notable exception is catalytic oxidation wherein a pyridodipyrimidine is used as a shuttle in the oxidation of alcohols by molecular oxygen. Pyridodipyrimidine (**92**) oxidizes cyclohexanol to cyclohexanone and the dihydro form (**93**) is oxidized *in situ* back to (**92**) by oxygen (equation 41). The yield of cyclohexanone is >22 000% based on (**92**).[95]

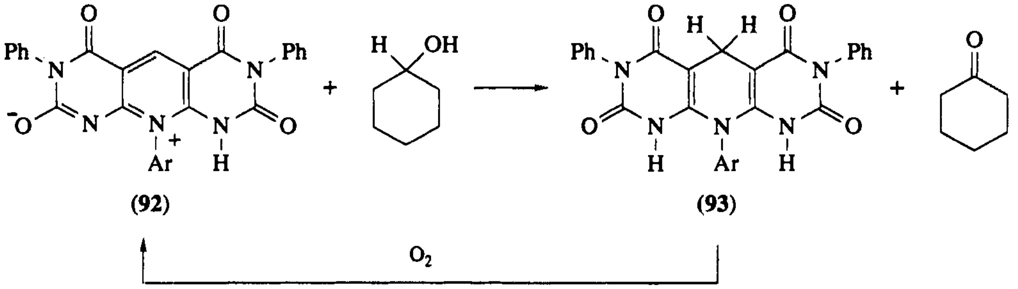

(41)

*(iii) Catalyzed hydride transfer*

Few truly catalytic systems have been reported. An *N*-alkylated 1,4-dihydropyridine forms a pyridinium salt on hydride loss. In principle the pyridinium salt may be recovered and reduced regioselectively with sodium dithionite (equation 33). This reaction is very general and fails only when the 1,4-dihydropyridines are excessively strained or too reactive to be isolated.

Attempts to design systems wherein $Na_2S_2O_4$ is used as a continuous electron source *via* an *in situ* reduction of the pyridinium salt formed have met with little success. In principle one would expect a two-phase system consisting of $Na_2S_2O_4$ in the aqueous layer and 1,4-dihydropyridine/substrate in the organic layer to be effective. The charged pyridinium salt will have some solubility in water so that it can be reduced. Unfortunately the electrophilic activators tend to remain in the aqueous rather than organic layer and $Na_2S_2O_4$ has a pronounced tendency to reduce directly most potential ketonic substrates. These problems can be circumvented, at least on a small scale, by using a water/toluene two-phase system, zinc metal as electron source, the bis-*N*-methylpyridinium salt of 4,4′-bipyridine as electron carrier, and a 1,4-dihydronicotinamide/nicotinamidium salt couple as reductor. Reasonable rates of reduction of (**9a**) to (**10a**) can be obtained.[96] Attachment of the 1,4-dihydropyridine to a polymer or other solid matrix is another potential solution to the problem of regeneration.

Certain transition metal complexes exhibit activating properties and act with turnover on the metal center analogously to the catalytically active zinc ion in the active center of liver alcohol dehydrogenase. Various chiral europium shift reagents, for example Eu(hfc)$_3$, induce reduction of (**9b**) by 1,4-dihydronicotinamides. Turnovers of about 100 are obtained on the metal complexes and methyl mandelate is formed with enantiomeric excesses of 25–44%.[97]

Complex (**94**) (the corresponding $Zn^{2+}$ complex is insoluble) will induce the same reduction with turnovers of about 100 on the complex. This complex approximates the coordination about zinc in the active site of liver alcohol dehydrogenase.[98]

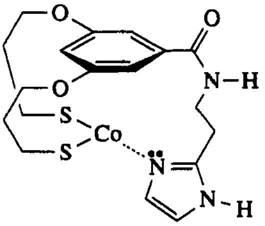

(**94**)

### 1.3.3.5.2 Other heterocyclic hydride donors

The 1,4-dihydropyridine/pyridinium salt couple is by far the most common six-membered heterocyclic ring redox couple. Other combinations are possible, for example pyrimidines and pyrazines. However, the dihydro forms tend often to be poorly defined, consist of more than one regioisomer, and/or are too reactive to be readily handled.

Five-membered heterocyclic ring systems can also act as redox shuttles. An example using an uncharged form of the reduced heterocycle is shown in equation (42).[99,100] The *N*-alkylated derivatives of (**95**), which provide positively charged ions on hydride loss, seem to be somewhat more reactive.[101,102]

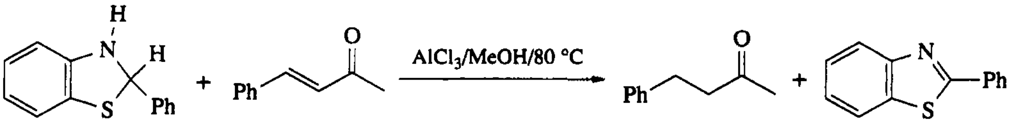

(42)

(**95**) (**96**) (**97**) 87% (**98**) 98%

### 1.3.3.5.3 *Tertiary anilines as hydride donors*

Although also a special case of a MPV reduction (Section 1.3.3.3) some unusual reactions of practical import will be considered here because of the heterocyclic characteristics. Donation in an intramolecular reaction of a hydride from a tertiary aniline derivative to generate an iminium ion initiates the reaction. An example is given in Scheme 7. Tertiary aniline derivative (**99**) rearranges thermally apparently *via* intermediate (**100**) to pyrrolo[1,2-*a*]quinoline (**101**).[103] The highly electron-deficient double bond is clearly the hydride acceptor; in this case exclusively the most substituted iminium salt is formed. Subsequent ring closure provides the end product (**101**). Formation of the more substituted iminium ion is not always the case.[104,105]

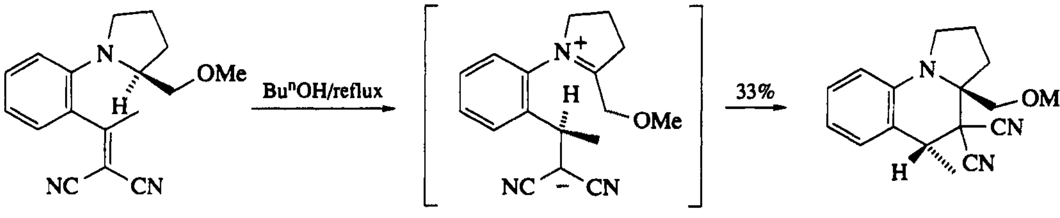

(**99**) (**100**) (**101**)

**Scheme 7**

Extensive use of this process for synthesis of various heterocycles has been made. The cited examples are probably the best studied of a broad set of unusual reactions of tertiary aniline derivatives wherein the aromatic ring bears an *ortho* substituent. These examples have been compiled in a remarkably prescient review by Meth-Cohn and Suschitzky.[106]

## 1.3.3.6 Hydride Transfer from Organometallics

Hydrogens located on a carbon adjacent to a negatively charged atom (*i.e.* β) are always potential sources of hydride; the possibility of formation of a double bond (equation 43) is an effective driving force. As seen with MPV reductions (X = O) the success of the hydride transfer depends also on the thermodynamics of the reaction, the possibility of finding a proper orientation of the reacting partners, the cation and the nature of ion pairing. The possibilities for carbanions are in general greater since the carbanionic character is profoundly affected by the choice of metal counterions. Covalency, back donation possibilities from the metal, as well as ligation of the carbanion acceptor to the metal with concomitant increase of effective molarity are some of the additional factors to be considered.

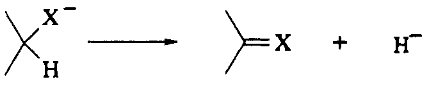

(43)

The additional stereochemical control available in carbanions relative to alkoxides arises both from the extra ligation about carbon and the contributions of the metal. The stereochemistry of hydride transfer from organostannanes has been particularly well investigated. Coordinatively saturated metals like tin function less well as Lewis acids in a cyclic mechanism, and tend to induce hydride loss through an antiperiplanar conformation.[107] The hydride transfer reactions of organometallics have long been known and are in many cases chiefly an annoying complication to C—C bond formation, especially in the reactions of Grignard reagents.

### *1.3.3.6.1 Divalent metals: Grignard reagents and organozinc compounds*

An example of reduction of a ketone by a Grignard reagent is given in equation (44).[108] The combination of a hindered ketone (**103**) and branched Grignard reagent (**102**) inhibits carbanionic addition to the carbonyl group (<3% occurs) and promotes reduction. On the basis of extensive work ably reviewed by Morrison and Mosher,[109] it appears that a MPV-like transition state (**106**) is involved. Not an antiperiplanar but a *syn* arrangement of metal and departing hydride is involved in this case. Stereochemical analyses are complicated by the complex nature of Grignard reagents and the complexation of ether molecules to the magnesium. The scope and limitations and the possibilities for enantioselective synthesis have been discussed in detail.[109] The use of chiral Grignard reagents for enantioselective syntheses has been largely supplanted by boron reagents (Section 1.3.3.6.2ii).

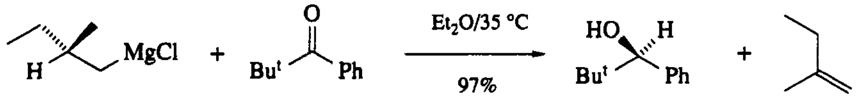

(44)

(*S*)-(**102**) (**103**) (*R*)-(**104**) 36% *ee* (**105**)

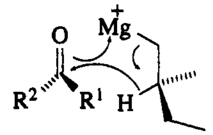

(**106**)

Dialkylzincs are on the whole less reactive towards addition to carbonyl groups.[110] Diethylzinc reduces benzophenone without significant formation of a tertiary alcohol by addition.[111] Reaction of phenyl isopropyl ketone (**107**) with (+)-bis[(*S*)-2-methylbutyl]zinc (**108**) affords a modest enantiomeric excess of alcohol (**109**) and alkene (**110**; equation 45).[112] The kinetics of the reaction are second order; a six-membered transition state analogous to the Grignard reduction seems probable. Reaction is clearly sluggish compared to the corresponding Grignard reagents. The enantiomeric excesses obtained are not high and the factors that lead to enantioselection are not readily identified. As in the case of the Grignard reagents, the coordination about zinc is uncertain. This latter point is no triviality; the reactivity and potential for enantiomeric recognition are profoundly affected by the nature of the ligation.[113]

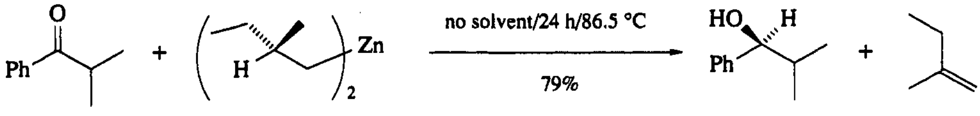

(45)

(**107**) (**108**) (**109**) 15.2% *ee* (**110**)

### *1.3.3.6.2 Trivalent metals: alkyl-aluminum and -boron compounds*

#### *(i) Alkylaluminums*

Trialkylaluminum compounds and trialkylboranes seem to reduce carbonyls in the same fashion as Grignard reagents and dialkylzincs. The reactivity towards carbonyl groups is greater than that of dialkylzincs, despite the third substituent, which does provide, however, additional opportunities for recognition. The compounds are well defined and can encompass a fairly wide range of alkyl substituents. This is especially true of the trialkylboranes.

Triisobutylaluminum (racemic) is commercially available in toluene solution. Triethylaluminum and related compounds are used, of course, commercially in Ziegler–Natta polymerization.[114] These solutions can be handled safely in contrast to the pure materials, which are violently reactive. The applications of triisobutylaluminum have been reviewed.[115] Its use is difficult to divorce from its chemical relative, diisobutylaluminum hydride, which is probably more often used for reductions of carbonyl groups. This latter reagent reduces, of course, *via* the reactive aluminum–hydride bond. The thought that the dialkylaluminum is less bulky than the trimer is misleading; there is a greater tendency of the former towards aggregation.[116]

Triisobutylaluminum (**111**), of the trialkylaluminums, is probably used most often for reductions. The reducing capacity of only one of the isobutyl groups is used. Reduction of carbonyl groups apparently occurs by the now familar MPV six-membered ring mechanism found with Grignard reagents and dialkylzincs (equation 46). Alkynes and nitriles (benzonitrile has been studied) are also reduced by triisobutylaluminum *via* analogous six-membered ring transition states. The very bulky reagent (**115**), prepared from diisobutylaluminum hydride and 2,6-di-*t*-butyl-4-methylphenol is useful for the stereoselective reduction of the α,β-unsaturated carbonyl functionality of prostaglandins; reduction of (**114**) affords a ratio of (15*S*):(15*R*)-alcohols of 92:8 (equation 47).[117] The (15*S*)-diastereomer is the desired product and also the more difficult to obtain.

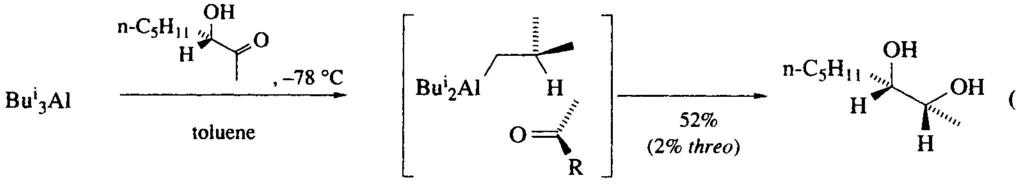

(46)

(**111**) (**112**) R = (*S*)-C(OH)(n-C$_5$H$_{11}$)H (**113**)

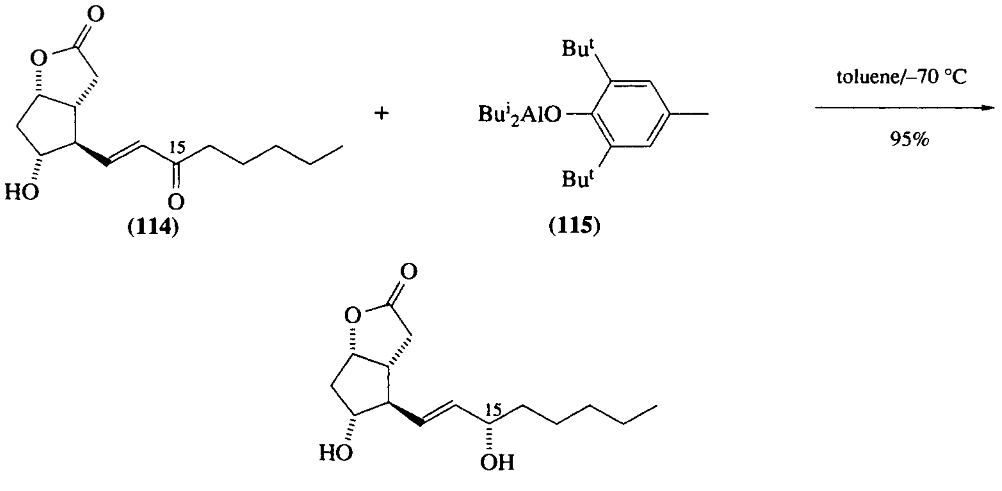

(**114**) (**115**)

(47)

(**116**) 92:8 *de*

Quite extensive studies of the reduction of (chiefly phenyl) ketones have been carried out with optically active trialkylaluminum (**117**). Enantiomeric excesses are at best only moderate. Again it is difficult to develop a model that rationalizes the interactions between groups that determine the enantiomeric recognition capacities of the reagent. Comparisons of reactivity and recognition capacities of RMgCl, $R_3Al$, and $R_2Be$ reagents with the same R-groups have been made.[118]

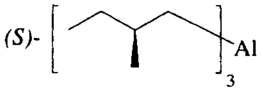

(**117**)

Much better results in enantioselective reductions have been obtained with reagent (**118**) derived from β-pinene.[118e] For example, reduction of (**119**) affords the corresponding alcohol (**120**) in excellent enantiomeric excess (equation 48). Good results have also been obtained in the reductions of a number of other carbonyls.

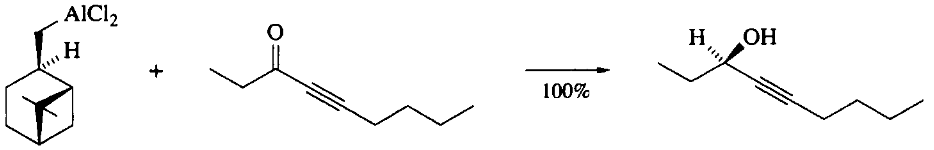

(48)

**(118)** **(119)** **(120)** 78% *ee*

*(ii) Reductions by trialkylborons*

Quite practical reagents, although of relatively high molecular weight per hydride equivalent, have been developed from sterically crowded trialkylboranes, derived from addition of a dialkylborane to an alkene (equation 49).[119] That trialkylboranes can react with carbonyl groups *via* donation of hydride and freeing of an alkene was apparent from the reaction of tributylborane (**121**) with formaldehyde (equation 50).[120]

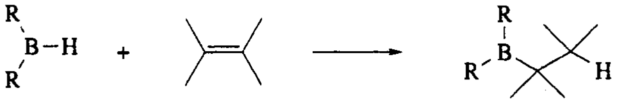

(49)

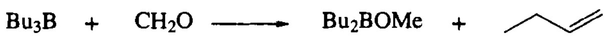

(50)

**(121)** **(122)**

The trialkylborane (**123**) derived from addition of 9-borobicyclo[3.3.1]nonane to α-pinene reduces benzaldehyde-α-*d* (**124**) in nearly 100% *ee* (equation 51) after correction for optical purity of (**123**) (commercial α-pinene is only about 92% enantiomerically pure).[121] Only a single hydride equivalent, the tertiary hydrogen of pinene, is transferred. Under analogous conditions simple aldehydes are reduced to α-*d*-alcohols in 81–100% *ee*.[122]

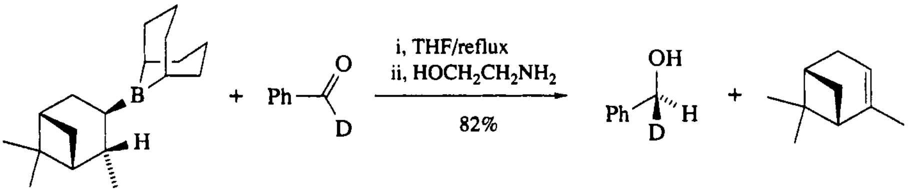

(51)

**(123)** **(124)** **(125)** 100% *ee* **(126)**

Again rationalization of the stereochemical course of reaction is not easy. The Lewis salt (**127**), formed by complexation of oxygen with boron (equation 52), may be the actual reactive species. To explain the stereochemistry of reduction observed in equation (51), (**128**) has been suggested, with the R-group oriented over the pinane ring in what seems at first glance an abuse of stereochemical logic. The explanation may lie in the formation of a 'pocket' in which the alkyl group can fit in hydrophobic surroundings.

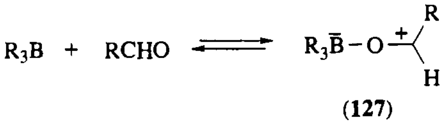

$$R_3B + RCHO \rightleftharpoons R_3\bar{B}{-}\overset{+}{O}{=}C(R)H \qquad (52)$$

**(127)**

The rates of hydride transfer with (**123**) are only moderate with aldehydes in THF solution. However if no solvent is used and reaction times of several days are tolerated both aliphatic and aryl ketones can be reduced to the corresponding secondary alcohols (equation 53).[123] Although reactions are sluggish,

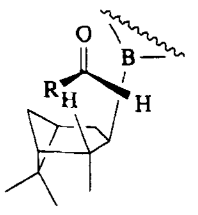

**(128)**

several hours in THF solution at room temperature being required for reaction, alkynic ketones (**131**) are reduced by (**123**) in quite reasonable enantiomeric excesses (equation 54).[124]

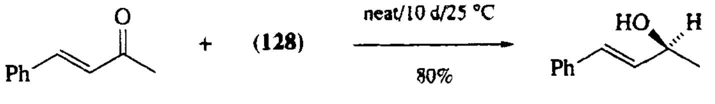
O
Ph
+ (128)
neat/10 d/25 °C
80%
HO
H
Ph

**(129)** **(130)** 97% *ee* (53)

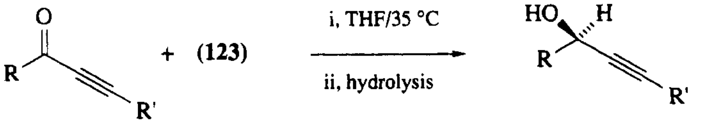
O
R
R'
+ (123)
i, THF/35 °C
ii, hydrolysis
HO
H
R
R'

**(131)** **(132)** (54)

| *R* | *R'* | *yield* (%) | *ee* (%) |
|---|---|---|---|
| Ph | Bu$^n$ | 72 | 89 |
| Pr$^i$ | H | 78 | 91 |
| 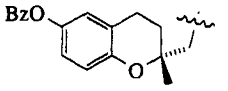 BzO | Me | 77 | 85:15 *de* |
| Ph | $CO_2Et$ | 64 | 92 |

Synthetic applications of this methodology have been made[125] and mechanistic investigations have been carried out.[126] Reagents (**133**) and (**134**), derived, respectively, from addition of 9-borobicyclo[3.3.1]nonane to β-pinene and nopol benzyl ether, are also capable of delivering a single hydride equivalent with good enantioselectivity.[127,128]

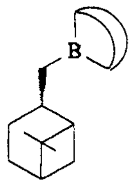

**(133)**

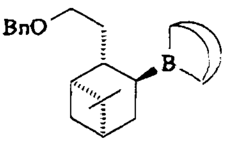

**(134)**

The boroadamantane (**135**), formed by addition of methyllithium to the corresponding trialkylborane, transfers a bridgehead hydride to acetyl chloride to form (**136**), as shown in equation (55).[129]

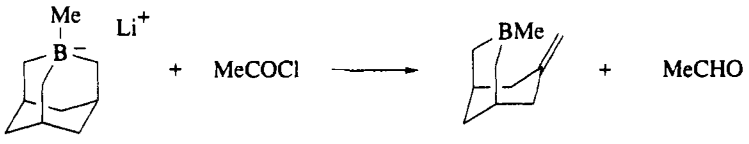
Me
B
Li+
+ MeCOCl
BMe
+ MeCHO

**(135)** **(136)** (55)

### 1.3.3.7 Hydride Transfer from Transition Metal Alkyls

Considerable mechanistic examination of hydride transfer from transition metal alkyls where M is, for example, $C_5H_5Fe(CO)_2$ or $C_5H_5Re(NO)PPh_3$ has been carried out. Hydride transfer may occur either from an α- or β-position on the alkyl framework, dependent on structural features and the identity of the transition metal. Stereoelectronic effects, kinetic factors, and electronegativity considerations have been considered in recent review articles.[130,131] Because of the excellent coverage already available, no detailed discussion will be given here.

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# 1.4

# Reduction of C=X to CHXH by Dissolving Metals and Related Methods

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## 1.4.1 INTRODUCTION

Dissolving metals have been used as reducing agents in organic synthesis for well over a century and for many years metal–alcohol or metal amalgam–water systems were the principal methods employed for the reduction of aldehydes and ketones to primary and secondary alcohols, respectively. The same reagents were employed for the reduction of imines and oximes to the corresponding amines. Catalytic hydrogenation was the only viable alternative to dissolving metal reductions until the development of the Meerwein–Pondorff–Verley reduction in the mid 1920s and the introduction of complex metal hydrides in the years following World War II.

Although complex metal hydrides have, to a large extent, replaced dissolving metal systems for the reduction of carbonyl compounds and their derivatives, dissolving metal reductions frequently offer advantages for the control of stereochemistry. In particular, the dissolving metal reduction of hindered cyclic ketones provides a highly stereoselective method for the preparation of equatorial alcohols, which are difficult to prepare by other methods. The prototype for this synthetic methodology was the nearly simultaneous observation that Li–$NH_3$–alcohol[1] or Na–propanol[2] reduction of 11-keto steroids gives exclusively the equatorial 11α-alcohol, while metal hydride reduction of these hindered ketones gives the axial 11β-alcohol.

The stereochemical course of these, and other similar reductions, led Barton to suggest that dissolving metal reductions of ketones and oximes to secondary alcohols and primary amines would lead to mixtures of products rich in the thermodynamically more stable product.[3] However, in the early 1960s a number of reports appeared in which the reduction of ketones gave primarily the thermodynamically less stable epimeric alcohol. These observations have prompted a continuing series of investigations into the mechanism of these reductions.

In contemporary organic synthesis, dissolving metal reductions still provide the most effective method for reducing hindered cyclic ketones steroselectively to the more stable secondary alcohol, and in many cases are more stereoselective than complex metal hydrides for the reduction of unhindered cyclic ketones. These procedures also continue to be useful for the reduction of oximes and imines to the corresponding amines. Although many of the dissolving metal reductions employed in organic synthesis are carried out using either active metals (Li, Na, K) in liquid $NH_3$, or the same metals in alcohols, a number of variations on these precedures have been developed, and several low-valent metal ions, most notably $Sm^{2+}$, have been found to give improved chemoselectively. However, all of these reactions are mechanistically similar in that they proceed by initial addition of a single electron to the substrate to form a radical anion, the fate of which is determined by a complex set of variables. Among the more important of these variables are the structure of the substrate, the metal or metal ion used as reducing agent, and the solvent system.

## 1.4.2 MECHANISM OF CARBONYL REDUCTION

### 1.4.2.1 Early Mechanistic Studies

The overall transformation effected in the reduction of an aldehyde or a ketone to the corresponding alcohol by a dissolving metal is conceptually simple; however, the reaction is actually quite complex, and an evolving series of mechanisms has been suggested to explain the experimental observations. Historically, the reducing properties of dissolving metals were attributed to 'nascent hydrogen', but it is now recognized that these reactions proceed *via* single electron transfer (SET) reaction paths.

It was suggested in the 1950s that the reduction of aliphatic ketones by dissolving metals proceeded by two sequential one-electron additions to provide a dianion (equation 1). This mechanism was based on the observation that benzophenone affords a dianion on reaction with excess Na in liquid $NH_3$, and it was inferred that aliphatic ketones would behave similarly. A number of workers presented mechanistic rationalizations for the stereochemical course of the dissolving metal reductions of cyclic aliphatic ketones based on this dianion concept. However, in a 1972 review, it was noted that the reduction potentials of alkali metals were not sufficient to effect the addition of two electrons to an aliphatic carbonyl group, and an alternative mechanism was suggested which with some modification is now generally accepted.[4]

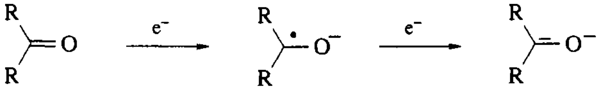

(1)

The contemporary view of these reductions recognizes that the reactions of carbonyl compounds with dissolving metals follow one of two general reaction paths. One of these prevails in reductions carried out in the absence of proton donors, the other in reductions in the presence of an alcohol or other proton source, frequently $NH_4Cl$. Two recent reviews present rather different mechanistic explanations for these reactions, particularly those in liquid $NH_3$ in the absence of added proton donors.[5,6]

### 1.4.2.2 Reduction in the Absence of Proton Donors

For reductions carried out in the absence of an added proton donor the usual solvents are liquid $NH_3$, usually with an ethereal cosolvent, or less commonly an ether (THF, DME or diethyl ether). The reducing agent is usually one of the common alkali metals (Li, Na, K), although Rb, Cs and alkaline earth metals have also been used.[4–6] At least in the case of camphor both types of solvent systems give similar ratios of epimeric alcohols; however, product ratios may vary as a function of the metal used as reducing agent.[4–7] In reductions carried out in ethereal solvents the use of ultrasound increases the rate of the reaction, but does not affect the product distribution.[7]

A number of experimental details have contributed to an understanding of the mechanism of reductions carried out under these conditions. Among the more important observations are the facts that ketones react with one and only one equivalent of alkali metal in $NH_3$; enolizable ketones afford equal amounts of enolate and alcohol, while nonenolizable ketones give metal ketyls which are stable at low temperature.[5,7–9] Also, pinacol formation is a major reaction path with Li, but K affords little or no pinacol.[5,10] Finally, α-deuterio ketones afford product alcohols in which deuterium has been transferred to the carbinol carbon of the product alcohol or alcohols.[9,10]

The substrate ketone which has been investigated most extensively is camphor (**1**; equation 2), both as one optical antipode (usually the (+)-enantiomer) and as the racemate. In addition to borneol (**2**) and isoborneol (**3**), reduction using Li–$NH_3$ or Li–THF gives up to 70% yield of dimeric reduction products, while Na–$NH_3$ gives 20%.[11] Pinacols are not usually obtained when K is used as the reducing agent. Although (+)-camphor can, in theory, afford three pinacols, only two, which correspond to *exo–endo* and *endo–endo* coupling have been isolated.[10,12,13] A third dimeric reduction product which apparently arises by β-cleavage of an intermediate alkoxyl radical has also been observed.[13] Although the relative proportions of isomeric pinacols varies as a function of reaction conditions, the ratios of epimeric alcohols are apparently independent of the composition of the pinacol mixtures.[13] For a detailed discussion of pinacol formation see Volume 3, Chapter 2.6.

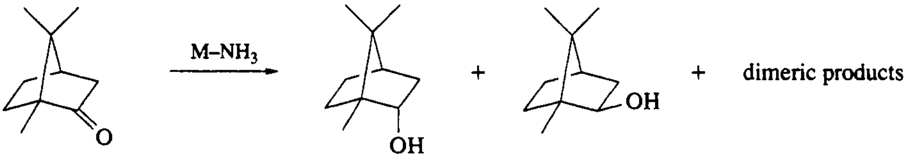

(2)

**(1)** **(2)** **(3)**

It has been long known that different ratios of product alcohols (**2** and **3**) are obtained in the reduction of (+)-camphor with various metals in liquid ammonia. On the other hand, reduction of (±)-camphor with Li, Na or K in liquid $NH_3$ affords, within experimental error, the same 82:18 ratio of (**2**):(**3**). An explanation in terms of diastereomeric bimolecular reactions has been presented.[14]

On the basis of these observations and a variety of other experimental data, a mechanism has been suggested which in modified form is presented in equations (3) to (5).[5] The first step (equation 3) is the reversible transfer of an electron to a carbonyl group, generating a metal ketyl, which may be in equilibrium with a dimer or higher aggregate, although not necessarily of the structure depicted. The position of the equilibrium for the addition of an electron to a carbonyl group is a function of the difference in reduction potential of the carbonyl group and the oxidation potential of the metal. Unfortunately the reduction potentials of aldehydes and ketones in liquid $NH_3$ are not known, but for the reaction of camphor with an alkali metal $K_{eq}$ has been estimated, using reduction potentials in other solvents, to be $3.4 \times 10^2$ based on $\Delta V = 0.15$ V.[7] The intervention of ketyl aggregates in these reactions was inferred from studies carried out on aromatic and nonenolizable aliphatic ketones.[5] Regardless of the exact nature of the intermediate at this stage, it must be formed at a considerably greater rate than its subsequent irreversible conversion to products, because it has been observed that in reductions of (+)-camphor carried out with mixtures of alkali metals and the salt of a second metal, the products reflect a weighted average of that predicted assuming a mixture of metals.[11]

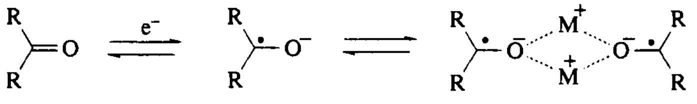

(3)

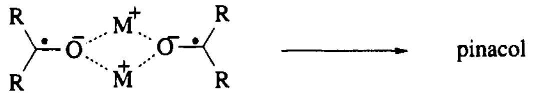

(4)

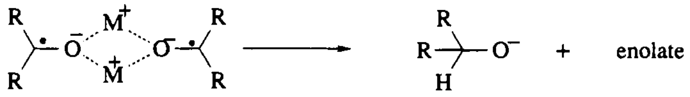

(5)

Pinacol formation (equation 4) is considered to occur *via* coupling of two ketyl units, either within a higher aggregate as depicted or by direct coupling of two ketyls. Production of alcohols by hydrogen transfer (equation 5) probably occurs either within a ketyl aggregate or by the direct interaction of two metal ketyls.[5,9,10]

In a recent review it was once again suggested that these reductions proceed by way of the vicinal dianion path.[6] This argument has again been refuted on the basis of reduction potentials and stoichiometry[7] and most convincingly by a consideration of the relative acidities of the various species present in the reaction medium.[15]

### 1.4.2.3 Reduction in the Presence of Proton Donors

In terms of synthetic utility, the reduction of carbonyl compounds by a dissolving metal in liquid $NH_3$ in the presence of an alcohol, water or $NH_4Cl$ is far more common and usually far more efficient than reduction in the absence of a proton donor. Historically these reductions were carried out using active metals, usually Na, in alcohols and the experimental results are similar in both systems.[4–6]

Although reductions under these conditions are more common than those carried out in the absence of a proton donor, relatively few mechanistic studies have been carried out. It is known that in the presence of $NH_4Cl$ the reduction of (+)–[3,3–$^2H_2$]camphor by Li, Na or K in liquid $NH_3$ gives very little product resulting from deuterium transfer.[10] In the presence of water or ethanol–water mixtures some deuterium transfer occurs, but to a lesser extent than is observed in the absence of an added proton donor, which indicates that the disproportionation path presented in equation (5) is attenuated in the presence of strongly acidic proton donors.[10] The generally accepted alternative mechanism is that suggested by House,[4] in which a ketyl is protonated to give a carbon radical which is subsequently reduced to a carbanion (equation 6) which on protonation provides the product alcohol. Although the details of the mechanism are not certain, it appears that the stereochemical course of the reaction is relatively insensitive to the nature of the metal used for reduction since (+)-camphor gives a borneol:isoborneol ratio of 9.0–9.5:1 using Li, Na or K in $NH_3$ with $NH_4Cl$ present.[10] With less acidic proton donors there is competition by reduction *via* protonation and hydrogen transfer.[5,10]

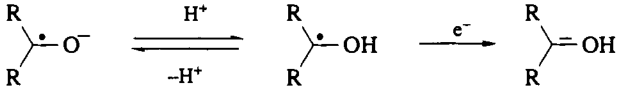

(6)

Although it was once believed that reductions by dissolving metals in alcohols or liquid $NH_3$ would invariably provide the thermodynamically more stable alcohol as the major product,[3] it has been known for many years that the thermodynamically less stable epimeric alcohol is sometimes the major product on either metal–alcohol or metal–$NH_3$–proton donor reduction.[4–6] A detailed explanation for the stereochemistry of these reductions based on a combination of steric and frontier molecular orbital interactions has been presented.[6]

It must be emphasized that reduction of carbonyl compounds by dissolving metals, either in the presence or absence of an added proton donor is a kinetically controlled process. This was tacitly stated in 1972,[4] and has been repeated or implied in more recent reviews of this topic.[5,6] A recent study of the reduction of several bicyclo[2.2.1]heptanones using alkali metal–$NH_3$–$NH_4Cl$ systems emphasizes that these reductions are kinetically controlled.[16]

A variety of other less common reaction conditions, which employ a variety of either dissolving metals or low-valence metal cations, have been used to effect the reduction of carbonyl groups to primary or secondary alcohols. Although the mechanisms of these reactions have not been explored in detail, they almost certainly proceed by mechanisms similar to those outlined above.

## 1.4.3 SYNTHETIC UTILITY OF CARBONYL REDUCTION

### 1.4.3.1 Reaction Medium

#### *1.4.3.1.1 Alcohols and water*

The reduction of various substrates by dissolving metals in alcoholic and aqueous media is a very old procedure in synthetic organic chemistry. In addition to aldehydes, ketones, imines and other unsaturated nitrogen compounds, many other functional groups are reduced under these conditions. Historically, the most common reduction conditions were Na in ethanol, and the reductions were carried out by adding the metal to a solution of the substrate in alcohol and the reaction mixture was heated at reflux for varying periods of time. Other reduction systems included Na–Hg amalgam in water or alcohols and, for easily reduced compounds such as aldehydes and aromatic ketones, Zn–NaOH or Fe–acetic acid have been used.[4]

Although reductions of ketones by active metals in alcohols have been largely supplanted by other procedures in modern synthetic chemistry, these methods still find occasional use. A modification employing K in *t*-butyl or *t*-pentyl alcohol has been used for the stereoselective reduction of 7-keto steroids in high yield,[17,18] and the Li–ethanol and Na–ethanol reductions of 16-keto steroids have been investigated.[19] Both traditional Na–ethanol[20–22] reductions and a variation using Na–propan-2-ol in toluene[4,23] have also been used recently in selected systems.

In terms of product distribution, reductions in these protic media are similar to those obtained using metal–$NH_3$–proton donor systems and it is generally accepted that they proceed by similar mechanisms.[4–6] However, in terms of synthetic utility, metal/alcohol systems suffer from two inherent liabilities. The first, which has been commented upon in various reviews, is the possibility of equilibration of epimeric product alcohols as their alkoxide *via* a Meerwein–Pondorff–Verley-type mechanism.[4,6] Thus, although the initial product distribution is the result of a kinetically controlled reduction, prolonged heating of the reaction mixture will lead to mixtures approaching the composition predicted on the basis of thermodynamic control. It has been suggested that equilibration *via* hydrogen transfer from the solvent alcohol may be alleviated by carrying out metal–alcohol reductions in *t*-butyl alcohol,[6] other tertiary alcohols appear to be equally effective.[18]

The second inherent problem is encountered in the reduction of ketones with a proton-bearing chiral center adjacent to the carbonyl group. In this case, enolate formation may lead to equilibration before reduction. For example, reduction of a 98.6:1.4 mixture of menthone (**4**) and its epimer isomenthone (**5**) with Na or K in ethanol gave approximately 15% of a mixture of alcohols (**8**) and (**9**), in addition to 82% of menthol (**6**) and a small amount of neomenthol (**7**),[22] because of partial isomerization.

Enolization is an inherent problem with any metal–alcohol reducing system, and cannot be avoided due to the inevitable formation of metal alkoxides. This side reaction also occurs, although to a somewhat lesser extent, in the reduction of (**4**) with Na in moist ether.[22]

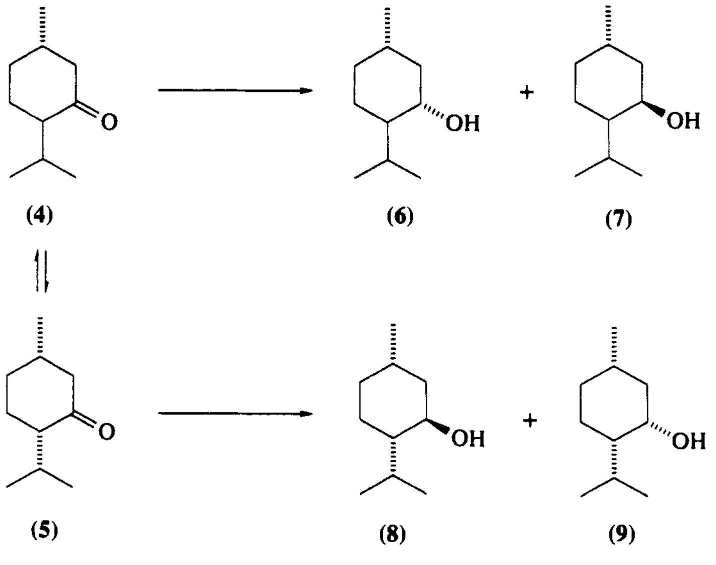

(7)

### *1.4.3.1.2 Ammonia, added proton source*

In terms of mechanism and stereochemical consequences, reductions by dissolving metals in liquid $NH_3$ are very similar to reductions by the same metals in alcoholic media.[4–6] However, reductions carried out in liquid ammonia do not suffer from the same inherent problems as those by metals in alcohols. There is no evidence for equilibration of the product alcohols, and ketones which undergo epimerization prior to reduction with metals in alcohols are reduced cleanly by metals in $NH_3$. For example, menthone (**4**) on reduction with Li–$NH_3$–ethanol gives a mixture of alcohols (**6**) and (**7**), with no trace of alcohols (**8**) and (**9**).[22]

The conventional method for carrying out reductions under these conditions consists of adding the appropriate metal to a solution of the compound to be reduced in a mixture of liquid $NH_3$ and an ethereal cosolvent, usually ether or THF, plus the proton donor, commonly $NH_4Cl$ or an alcohol. The use of $NH_4Cl$ has been advocated due to the observation that reduction by hydrogen transfer (Section 1.4.2.2) is effectively suppressed under these conditions.[10] However, $NH_4Cl$ is a very strong acid which is only sparingly soluble in $NH_3$–ether mixtures and in preparative scale work a large excess of metal must be used to ensure complete reduction.[24] A suitable alternative is the use of an excess of a primary alcohol (methanol or ethanol) which affords little of the product obtained by hydrogen transfer.[25] This procedure results in a homogeneous reaction mixture, and complete reduction is obtained with only a modest excess of metal.[22] Tertiary alcohols and relatively small amounts of primary alcohols lead to product mixtures resulting from reduction by a combination of hydrogen transfer and protonation.[5,26]

Reductions carried out under these procedures do not lead to bimolecular products and usually afford excellent yields of reduction products. Dissolving metal reductions in liquid $NH_3$ in the presence of a proton donor are usually the method of choice for effecting the reduction of a substrate by a dissolving metal.

### *1.4.3.1.3 Ammonia, no added proton source*

As noted above (Section 1.4.2.2) reduction of carbonyl compounds under these conditions proceeds with hydrogen transfer to afford an equimolar mixture of alkoxide and enolate, plus varying quantities of dimeric reduction products. As a consequence, at least in theory, this procedure should afford an equimolar mixture of recovered ketone and reduction product. This appears to be the case if less than one equivalent of metal is used; however, with excess metal, camphor,[10,11] some 12-keto steroids[25] and several 1-decalones[24] afforded 70–99% yields of secondary alcohols. The explanation which has been offered is that the product enolate is protonated by $NH_3$ to regenerate the starting ketone, which is recycled through the reduction process.[10]

The usual experimental procedure for carrying out reductions in the absence of an added proton donor entails the addition of a metal (Li, Na, K) to a solution of the substrate ketone in a mixture of $NH_3$ and an ethereal cosolvent, usually ether or THF at the reflux temperature of liquid $NH_3$. The metal is added until a permanent blue color is obtained and the reaction is stirred for 10 to 30 min. The excess Li is decomposed, traditionally with $NH_4Cl$ or an alcohol; however, sodium benzoate is probably superior.[6]

Reductions by dissolving metals in liquid $NH_3$ in the absence of proton donors, are, in general, inferior in terms of general synthetic utility to reductions carried out under other conditions. In many cases, particularly when Li is used as a reducing agent, bimolecular reduction is difficult to predict and the ratios of epimeric alcohols may vary as a function of the metal used as the reducing agent.[4–6]

### *1.4.3.1.4 Other solvents*

The vast majority of the dissolving metal reductions of carbonyl compounds which have been carried out synthetically have used either alcohols or liquid $NH_3$ as the solvent.[4–6] However, a variety of other solvents have been employed, frequently in connection with studies of the mechanism of the reductions or in exploratory synthetic studies.

Ethereal solvents, principally THF, either with or without sonication, have been reported to give results similar to those obtained on reductions in $NH_3$ with no added proton donor, and pinacol formation as a major reaction path.[7,27] A potentially useful selective reduction of unhindered cyclohexanones in the presence of other ketones using Al amalgam in aqueous THF has been described and will be discussed in detail subsequently (Section 1.4.3.3.2).[28] In this procedure aliphatic ketones give no pinacols; however, aromatic ketones give only the corresponding pinacol.[28]

A number of steroidal and triterpenoid ketones have been reduced with Li–ethylenediamine to give results consistent with those anticipated by analogy with $NH_3$.[29–31] In addition to $NH_3$ and aliphatic amines, a number of other solvents provide relatively stable solutions of solvated electrons, usually using Na as the metal. These solvents, which include HMPA, *N,N*-diethylacetamide and *N*-ethylpyrrolidone, provide a medium for producing Na ketyls, which have been reacted with alkenes both inter- and intramolecularly.[32] In these reactions, secondary alcohols are by-products, and presumably conditions could be found which would provide a viable synthetic method for the reduction of ketones to secondary alcohols. These solvents, however, would appear to offer no advantages compared to $NH_3$.

The reduction of a number of ketones by alkali metals in HMPA has been carried out, both in the presence and absence of added proton donors.[27,33] The results are qualitatively similar to those obtained using the corresponding metal in $NH_3$ under similar conditions. If deuterated *t*-butyl alcohol is used as the proton donor, high levels of deuterium incorporation at the carbinol position are obtained.[27] Due to the carcinogenicity of HMPA it cannot be considered as a viable solvent for preparative chemistry and it also offers no advantage over other solvents.

### 1.4.3.2 Metal

In reductions carried out by dissolving metals in alcohols, Na in primary alcohols or K in tertiary alcohols are the most common systems. Somewhat different epimeric mixtures are occasionally obtained with these systems[18] and it has been reported that Li–ethanol does not reduce a menthone/isomenthone mixture.[22]

All five Group I metals (Li, Na, K, Rb and Cs) and three Group II metals (Ca, Sr, Ba) have been used in $NH_3$ to effect the reduction of ketones to secondary alcohols.[4–6,11] In addition, it has been reported that Yb–$NH_3$ reduction of α,β-unsaturated ketones affords the saturated alcohol as the major product, which presumably arises *via* reduction of the intermediate saturated ketone.[34] Reduction of (+)-camphor with Yb–$NH_3$ both in the absence and presence of $NH_4Cl$ affords the same 86:14 ratio of borneol (**2**) to isoborneol (**3**). In the presence of $NH_4Cl$, the ketone is completely consumed and dimeric reduction products are not observed.[35] Excess Yb–THF–HMPA effects bimolecular reduction of aromatic ketones,[36] but aliphatic ketones are apparently inert to Yb–THF.[35,36]

A variety of other electron transfer reagents have been employed in reactions which appear to be mechanistically similar to the more common metal–$NH_3$ or metal–alcohol systems. These include K–graphite,[37,38] Zn–KOH–DMSO[39] and both Li[40] and Al[28] amalgams. The amalgams from Zn, Mg, Ni, Cu, Sn and Pb have been found not to be effective in the reduction of cyclohexanone in aqueous THF.[41] Also, several low-valent metal cations have been employed in the reduction of carbonyl compounds to alcohols. Among these reagents are low-valence salts of Ti,[42–46] Ce[47] and Sm.[48,49]

Some of these procedures have considerable potential as chemoselective reagents for the reduction of different types of carbonyl groups as will be discussed below. However, others, in particular $CeI_2$[45] and low-valence Ti salts,[42–45] are primarily of interest as reagents for dimeric reduction and are of little synthetic utility in reductions to form alcohols (see Volume 3, Chapter 2.6).

### 1.4.3.3 Chemoselectivity

#### *1.4.3.3.1 Metal–ammonia and metal–alcohol systems*

Under the usual reaction conditions alkali metal–$NH_3$ and alkali metal–alcohol systems are very powerful reducing systems. As noted above (Section 1.4.2.2) the reduction potentials of various functional groups in liquid $NH_3$ are not known. However, if it is assumed that the same relative order of reduction potentials is maintained in aqueous and nonaqueous systems, then it is apparent that in polyfunctional molecules the functional group with the least negative reduction potential should be reduced most readily. The reduction potentials (*versus* saturated calomel electrode) for aliphatic ketones range from –2.3 to –2.7 V and aromatic carbonyl compounds are considerably less negative (approximately –1.5 V).[50] Many common functional groups, including conjugated dienes, aromatic hydrocarbons, unsaturated carbonyl, halo, nitro and nitroso compounds all have reduction potentials less negative than those of aliphatic ketones and do not survive dissolving metal reductions using alkali metals in $NH_3$ or alcohols. Although carboxylic acids are stable to metal–$NH_3$ reductions,[4,5] they are reduced to aldehydes by Li in methylamine (see Chapter 1.12, this volume).[4] The reduction of esters to primary alcohols with Na in alcohol is the classical Bouveault–Blanc reduction (see Chapter 1.10, this volume).[4]

Both disubstituted alkynes (Chapter 3.3, this volume) and isolated terminal double bonds may be reduced by alkali metals in $NH_3$, but isolated double bonds are usually stable to these conditions. However, 16,17-secopregnanes (**10**; equation 8) afford mixtures of cyclization products (**11**) and (**12**) in 61% to 80% yield with Na naphthalenide–THF, Na–$NH_3$–THF, Na–THF or Li–$NH_3$–THF. With Na–$NH_3$–THF–*t*-butyl alcohol, a 91% yield of a 72:28 mixture of (**11**):(**12**) (R = Me) is obtained.[51] This type of radical cyclization of alkenes and alkynes under dissolving metal reduction conditions to form cyclopentanols in the absence of added proton donors is a general reaction, and in other cases it competes with reduction of the carbonyl group.[6,51,52] Under the conditions of these reactions which involve brief reaction times, neither competitive reduction of a terminal double bond nor an alkyne was observed.[51,52] However, allenic aldehydes and ketones (**13**) with Li–$NH_3$–*t*-butyl alcohol afford no reduction products in which the diene system survives.[53]

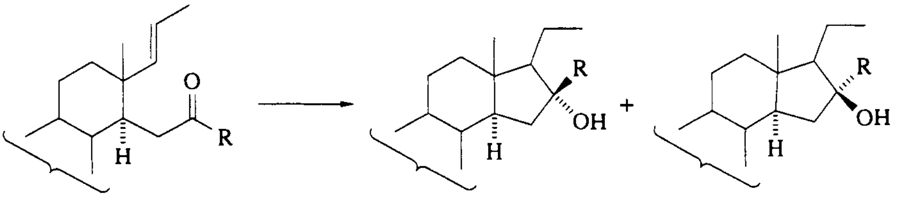

(8)

(**10**) R = H, Me (**11**) (**12**)

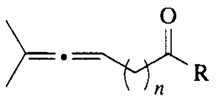

(**13**) *n* = 2, 3; R = H, Me

In addition to the inherent problems associated with easily reduced functional groups in dissolving metal reductions, ketones with an α-hetero substituent suffer removal of the α-substituent rather than reduction of the carbonyl group (Chapter 4.8, this volume). Cyclopropyl ketones constitute a special example of reduction of α-substituted ketones in which the ketyl formed by addition of one electron to the carbonyl group behaves as a cyclopropyl carbinyl radical, providing ketonic products arising from cleavage of the cyclopropane ring.[54–56]

The metal–$NH_3$ reductions of carbonyl groups are exceedingly fast reactions; for the reaction of acetone with an ammoniated electron the rate is $9 \times 10^7$ $M^{-1}$ $s^{-1}$.[57] Although many, particularly older, published experimental procedures for the metal–$NH_3$ reduction of ketones employ prolonged reaction times with excess metal, these conditions are unnecessarily harsh. The reactions of carbonyl compounds with metals in $NH_3$ are effectively instantaneous and by using short reaction times it appears that reduction of terminal alkenes and disubstituted alkynes can be avoided.[52] In addition to the functional groups mentioned above, alcohols, amines and ethers, other than epoxides, are usually stable to reductions of aldehydes and ketones by dissolving metals.[4–6]

Aromatic ketones represent a rather special case in dissolving metal reductions. Under many conditions pinacol formation is the predominent reaction path (see Volume 3, Chapter 2.6). Also, the reduction potentials of aromatic carbonyl compounds are approximately 1 V less negative than their aliphatic counterparts.[50] The reductions of aromatic ketones by metals in ammonia are further complicated by the fact that hydrogenolysis of the carbon–oxygen bond can take place (Chapter 1.13, this volume) and Birch reduction may intervene (Chapter 3.4, this volume).

The course of reductions of aromatic ketones is far more dependent on the exact reaction conditions than those of aliphatic ketones. A series of aromatic ketones, of which 1-tetralone (**14**; Scheme 1) is typical, on reduction with excess Li–$NH_3$ in the presence of a trace of Co or Al and quenching with $NH_4Cl$ gave almost exclusively tetralin (**15**).[58,59] However, quenching with sodium benzoate[58] or inverse quenching into aqueous $NH_4Cl$ gave 1-tetralol (**16**) as the major product.[59] Reduction at –78 °C with Li gave significant amounts of dimeric reduction products. Up to 31% of a Birch reduction product was obtained when Li or Na was added to a solution of (**14**) in THF–$NH_3$.[59]

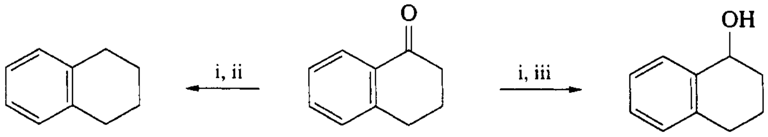

**(15)** **(14)** **(16)**

i, Li–$NH_3$–THF, -33 °C; ii, $NH_4Cl$; iii, NaOBz

**Scheme 1**

The metal–$NH_3$ and metal–amine reductions of acetophenone and acetyl derivatives of polycyclic aromatics are complex and afford primarily mixtures of Birch reduction products. In some cases a ketonic carbonyl survives the reduction, and in some cases it is reduced to the corresponding alcohol.[60–63]

### *1.4.3.3.2 Other systems*

Reduction of aromatic ketones using dissolving metal systems other than alkali metals–$NH_3$ in the absence of proton donors usually provide good yields of pinacols (see Volume 3, Chapter 2.6) with only small amounts of the secondary alcohol as by-product. A detailed study of the reduction of acetophenone by Li amalgam in several solvents using a variety of proton donors has been carried out.[40] In benzene the ratio of carbinol to pinacol was found not to vary in a regular way with the $pK_a$ of the proton donor. Using ethanol as a proton donor and a variety of solvents the carbinol:pinacol ratio was greatest in solvents which coordinate poorly with Li (cyclohexane, benzene, ether). In polar solvents which coordinate well with Li ions (propan-2-ol, acetonitrile, THF) the pinacol was the major product. In the presence of optically active quaternary ammonium salts some asymmetric induction was observed, but the optical purity of the 1-phenylethanol did not exceed 8.9%.[40]

A potentially useful chemoselective dissolving metal reagent for the reduction of aromatic ketones in the presence of other functional groups is the combination Zn–DMSO and aqueous potassium hydroxide.[39] In three examples (benzophenone, fluorenone and 4-benzoylpyridine), the yields of secondary alcohols were over 90%. Two other ketones (xanthone and thioxanthone) gave mixtures of alcohol and the hydrocarbon obtained by hydrogenolysis of a carbon–oxygen bond.[39]

In general, the reduction of aromatic carbonyl compounds to the corresponding alcohols by dissolving metals is not a particularly valuable synthetic procedure. Better yields and chemoselectivity are usually obtained using complex metal hydrides.

In contrast to traditional dissolving metal systems, low-valence metal cations, particularly $Sm^{2+}$, show considerable chemoselectivity in carbonyl reductions. In some cases these reagents can effect transformations which are difficult using metal hydrides or other traditional reducing agents. It has been suggested, and is almost certain, that these reductions are mechanistically similar to alkali metal reductions.[49]

Samarium diiodide is usually prepared *in situ* by the reaction of Sm metal with 1,2-diiodoethane in THF,[48,64] but a more convenient method appears to be the direct interaction of a slight excess of the metal with iodine in THF.[65] Although this reagent has found its principal utility as a reagent for effecting Barbier-type coupling reactions, in the presence of a proton donor it is an effective reagent for the reduction of aldehydes and ketones to the corresponding alcohols.[48,49] With methanol as a proton donor, aldehydes and aromatic ketones are reduced efficiently to the corresponding alcohol. Aliphatic ketones are, however, only partially reduced at room temperatures in THF solution. This provides an effective and experimentally simple method of effecting the selective reduction of an aldehyde in the presence of an aliphatic ketone.[48] This procedure appears to be at least as efficient as other procedures for the selective reduction of aldehydes.[66] With water as the proton donor, 2-octanone is reduced to the corresponding alcohol in 64% yield; in the absence of proton donors pinacols are the major product in the reaction of carbonyl compounds with $SmI_2$.[64] Ytterbium diiodide behaves similarly, but is not as effective a reducing agent.[48]

Although $SmI_2$ is more chemoselective than traditional dissolving metal reagents, it does react with sulfoxides, epoxides, the conjugated double bonds of unsaturated ketones, aldehydes and esters, alkyl bromides, iodides and *p*-toluenesulfonates.[48] It does not, however, reduce carboxylic acids, esters, phosphine oxides or alkyl chlorides.[48] In common with most dissolving metal systems, ketones with an α-hetero substituent suffer loss of the substituent rather than reduction of the carbonyl group.[67]

Other low-valence metal ions which can effect selective reductions are $VCl_2$ and $TiCl_3$, both in aqueous THF, which selectively reduce benzils (**17**; equation 9) to the corresponding benzoin (**18**).[46] A similar chemo- and enantio-selective reduction of benzil employs the combination $SmI_2$–HMPA–quinidine, which affords the (*R*)-enantiomer of benzoin (56% *ee*). Other chiral reagents are not as effective.[68] In basic media (methanol–$NH_4OH$ or NaOH), $TiCl_3$ reduces both benzil (**17**) and benzoin (**18**) to the corresponding diol in 98% yield, with a (±):*meso* ratio of approximately 3:1.[43] Acetophenones and substituted acetophenones with alkaline $TiCl_3$ usually give pinacols; however, *p*-amino- and *p*-hydroxyacetophenone afford the corresponding alcohols in good yield.[43]

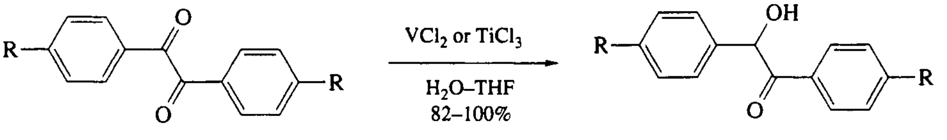

(9)

(**17**) R = H, Me, OMe, Ph (**18**)

Aluminum amalgam in aqueous THF is a reagent which shows some promise for the selective reduction of unhindered cyclohexanones in the presence of a variety of other aliphatic ketones.[28,41] Reduction of cyclohexanone and 3- and 4-methylcyclohexanone gave, respectively, 94%, 71% and 70% yields (GLC) of the corresponding secondary alcohols; however, cyclooctanone, cyclononanone, cyclododecanone, norcamphor, menthone, and 2-, 3- and 4-heptanone gave at most traces of reduction products. Cyclobutanone, cyclopentanone and cycloheptanone gave 12–33% yields of the corresponding alcohols.[28] Aromatic ketones gave good yields of pinacol under these conditions.[28] Based on preliminary competitive rate studies cyclohexanones are reduced approximately 10 times faster than cyclopentanones by Al amalgam–aqueous THF.[41]

### 1.4.3.4 Stereoselectivity

#### *1.4.3.4.1 Generalizations*

It was originally believed that the dissolving metal reduction of cyclic ketones would invariably afford the more stable of a pair of epimeric ketones as the major product.[3] Although it has since been established beyond reasonable doubt that these reactions are kinetically controlled and that the less stable epimeric alcohol frequently predominates,[4–6,16] the belief persists that these reductions are under thermodynamic control.[29,69]

Reductions of cyclic ketones by dissolving metals are frequently highly stereoselective and these reductions have been used to obtain secondary alcohols which are difficult or impossible to prepare by metal hydride reduction. In terms of yield, the best results are usually obtained either by reductions with alkali metals (commonly Li) in liquid $NH_3$ in the presence of proton donors[4–6,10] or with active metals in an alcohol.[4,6] Although a number of explanations have been advanced for the stereoselectivity of these reductions, they are all rationalizations with dubious predictive value.[4–6] There are, however, a number of empirical generalizations which are based on a considerable body of experimental data, specifically: (i) cyclohexanones with one or no α-alkyl substituents afford almost exclusively the equatorial alcohol; (ii) very hindered cyclic ketones afford almost exclusively the thermodynamically more stable alcohol; (iii) 2,2- or 2,6-disubstituted cyclohexanones may afford the less stable epimeric alcohol as the major product; and (iv) bicyclo[2.2.1]heptanones afford the *endo*-alcohol without regard to the relative stability of the *exo*- and *endo*-alcohols.

In reductions carried out in the absence of an added proton donor, it is difficult to predict the stereochemical consequences of a given reduction. The details of reductions under various conditions are discussed in Sections 1.4.3.4.2 through 1.4.3.4.6.

#### *1.4.3.4.2 Cyclohexanones with one or no α-substituents*

Reduction of a series of cyclohexanones (2- and 4-methyl, 4-isopropyl, 4-*t*-butyl and 3,3,5-trimethyl), both in the presence and absence of proton donors gave a 99:1 ratio of equatorial to axial alcohol. For 3-methylcyclohexanone the ratio was 94:6.[70] Also, reduction of menthone (**4**) affords a 97:3 ratio of equatorial alcohol to axial alcohol at –30 °C[22] These are somewhat larger ratios of equatorial to axial alcohol than can be obtained by equilibration and considerably greater than can be obtained by conventional complex metal hydride reduction. Although LAH reduction of 4-*t*-butylcyclohexanone affords an equatorial:axial ratio (90:10) which is comparable to that obtained using dissolving metals, reduction of 3,3,5-trimethylcyclohexanone by either LAH or sodium borohydride gives the axial alcohol as the major product.[71]

Although the metal–$NH_3$ reduction of unhindered cyclohexanones usually affords equatorial alcohols with greater stereoselectivity then metal hydride reductions, this method has not been used frequently in synthesis. An exception is the highly stereoselective reduction of ketoxime (**19**; equation 10), an intermediate in the synthesis of (±)-perhydrohistrionicotoxin, which gave an excellent yield of equatorial alcohol (**20**) on reduction with Na–$NH_3$. This reduction is noteworthy in that the oxime survives the reduction, which was carried out below the boiling point of liquid $NH_3$ for a relatively short period of time (30 min).[72]

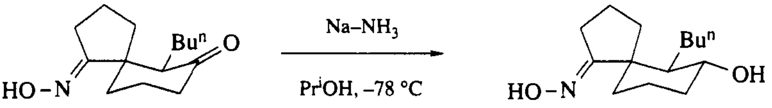

**(19)** **(20)** (10)

An unhindered keto triterpene, friedelan-3-one (**21**), with a large excess of Li in refluxing ethylenediamine has been reported to give a good (85–90%) yield of equatorial alcohol (**22**).[29,30] Reduction of a second 3-ketofriedelane which also contained a sterically hindered lactone afforded the 3α-ol with concomitant hydrogenolysis of the lactone.[73] The hydrogenolysis of esters by alkali metals in amines is a general method for the conversion of alcohols to the corresponding alkane.[74]

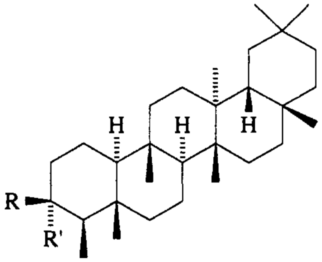

**(21)** R, R' = O
**(22)** R = H, R' = OH

Although metal–alcohol reductions of ketones suffer from possible epimerization of the product alcohol as well as isomerization of the substrate ketone (see Section 1.4.3.1.1), it was found possible to employ the latter type of epimerization to advantage in the preparation of an alcohol used as a chiral director in asymmetric synthesis.[23] In this preparation an 85:15 mixture of ketones (**23**) and (**24**; equation 11) was reduced with Na–isopropyl alcohol in toluene to afford alcohol (**25**) as the only isolated product in good yield.[23]

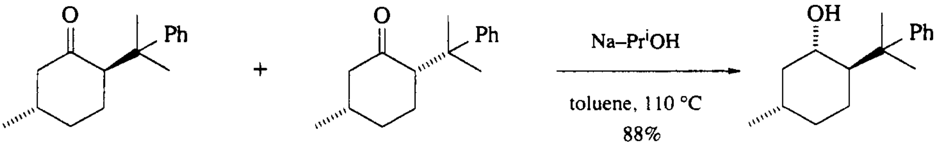

**(23)** **(24)** **(25)** (11)

Metal–alcohol reductions have also been used in the stereoselective reduction of 3α-hydroxy-7-ketocholanic acid (**26**) to the commercially important equatorial 7β-ol (**27**).[17,18] These reductions have been carried out with several alkali metals in secondary and tertiary alcohols, where reduction with K in tertiary alcohols is more stereoselective than Na–isopropyl alcohol.[17,18] These reductions afford the equatorial alcohol as the major product in good yield, in contrast to sodium borohydride reduction, which provides the axial alcohol (**28**) almost exclusively.

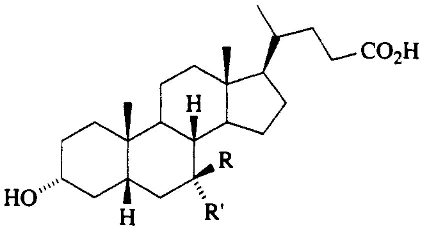

**(26)** R, R' = O
**(27)** R = OH, R' = H
**(28)** R = H, R' = OH

### *1.4.3.4.3 Sterically hindered cyclohexanones*

Dissolving metal reductions remain the method of choice, and are frequently the only viable method, for the reduction of sterically hindered cyclohexanones to equatorial alcohols. In the early 1950s it was found that reduction of 11-keto steroids using either Na–propan-1-ol[2] or Li–$NH_3$–dioxane–ethanol[1] gave good yields of the equatorial 11α-alcohol. 11-Keto steroids, such as androstan-11-one (**29**; equation 12) have two axial methyl groups in a 1,3-relationship to the carbonyl group and afford exclusively the axial 11β-ol (**30**) on reduction with metal hydrides.

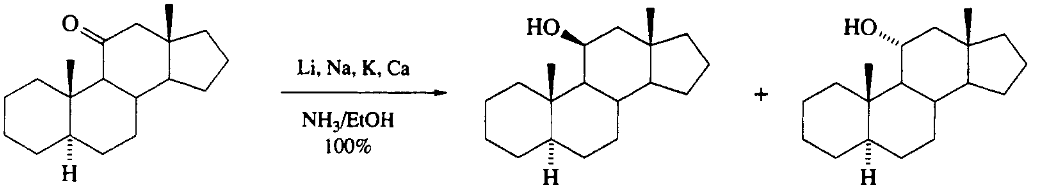

(12)

**(29)** **(30)** 5:95 **(31)**

Reduction of the ketone (**29**) in $NH_3$–ethanol gave a quantitative yield of a mixture in which the equatorial 11α-ol (**31**) predominated.[75] With Li–$NH_3$–$NH_4Cl$ a quantitative yield of alcohols was also obtained, but quite surprisingly the ratio of (**31**):(**30**) was 55:45, which is similar to that obtained using alkali and alkaline earth metals (Li, Na, K, Cs, Sr) in the absence of a proton donor. Under these conditions Ca and Ba gave 79:21 and 65:35 ratios of (**31**):(**30**), respectively. In none of these reductions is there any evidence for pinacol formation.[75] Reduction of 19-keto-α-agarofuran (**32**; equation 13) using excess Li–$NH_3$–ethanol gave almost exclusively the equatorial 9α-ol (**34**), while LAH gave the axial 9β-ol (**33**) as the only isolable product.[26] As expected with a severely hindered ketone, no pinacols were obtained with any alkali metal–proton donor combination.[26]

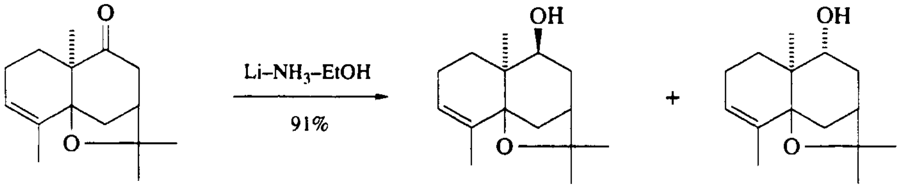

(13)

**(32)** **(33)** **(34)**

Although alkali metal–$NH_3$ reductions are usually preferable to Na–alcohol reductions in terms of yield and convenience, the stereochemical consequences of both systems are similar, at least for all sterically hindered systems studied thus far. Illustrative examples are the reductions of bicyclo[3.3.1]nonanones (**35**; equation 14) and (**36**; equation 15).[20] In both cases the equatorial alcohols (**37**) and (**38**) were obtained in excellent yield and with complete stereoselectivity. LAH reduction of ketone (**35**) gave only the epimeric axial alcohol, while (**36**) gave a mixture of (**38**) and its epimer.[20]

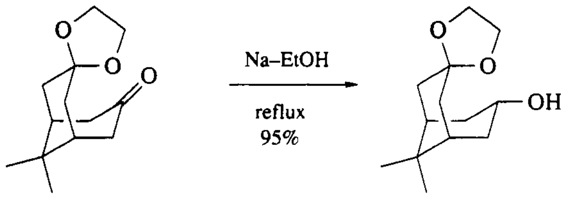

(35) (37)

(14)

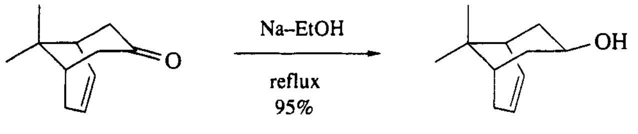

(36) (38)

(15)

Several sterically hindered keto triterpenes, including friedelan-7-one (**39**; equation 16), were reduced with a large excess of Li in refluxing ethylenediamine.[29] This exceedingly hindered ketone (three axial methyl groups with a 1,3-diaxial relationship to the carbonyl) affords only the equatorial 7α-ol (**40**) in good yield. Other ketones which were reduced under these conditions are considerably less hindered than ketone (**39**), but all gave the equatorial alcohol in good yield.[29]

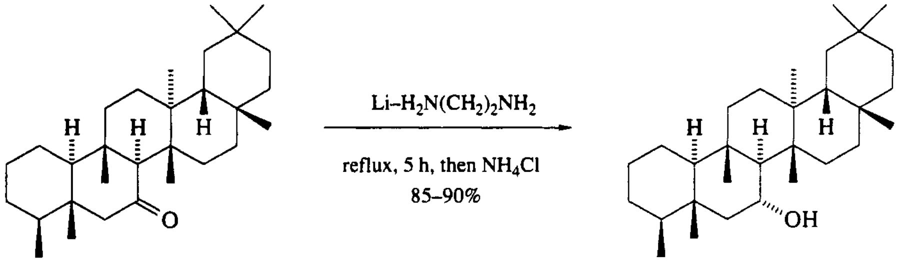

(39) (40)

(16)

### *1.4.3.4.4 Moderately hindered cyclohexanones*

A group of moderately hindered cyclohexanones which has been thoroughly studied is the 12-keto steroids, in which the stereochemical course of the reduction is governed by the structure of the C-17 alkyl group.[5,6,25] Reduction of 12-keto steroids which have a secondary substituent on C-17, (**41**), (**42**) and (**43**), gave mixtures of alcohols with Li–NH$_3$–methanol in which the axial 12α-ol, (**45**), (**46**) and (**47**), was the major product (70–80%).[5,25] However, reduction of 5β-pregnan-12-one (**44**) under the same conditions gave a mixture containing only 11% of the axial alcohol. Similar results were obtained using Na–propan-1-ol.[6] Reduction of ketones (**41**) and (**42**) with Li–NH$_3$ in the absence of an added proton donor gave mixtures of epimeric alcohols containing from 10–20% of axial alcohols (**45**) and (**46**). Considerable quantities of pinacol were obtained under these conditions and pinacol was the major product from the reduction of ketone (**44**) in the absence of a proton donor.[25] Sodium borohydride reductions of ketones (**41**), (**42**) and (**43**) were comparable in terms of yield and stereoselectivity to reduction by Li–NH$_3$–alcohol. However, borohydride reduction of ketone (**44**) gave an approximately 1:1 mixture of alcohol (**48**) and the equatorial 12β-ol.[25]

Although they have apparently not been studied in detail, dissolving metal reductions of 1-keto steroids appear similar to those of the 12-keto steroids. In one report, cholestan-1-one (**49**; equation 17) on reduction with Na in either ethanol or 1-pentanol gave the axial alcohol, cholestan-1α-ol (**50**), as the major reduction product in unspecified yield.[76] The equatorial 1β-ol was detected by TLC, but could not be isolated.

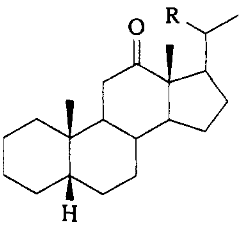

(41) R = Pr
(42) R = Et
(43) R = Me
(44) R = H

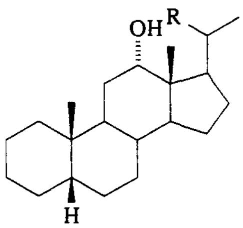

(45) R = Pr
(46) R = Et
(47) R = Me
(48) R = H

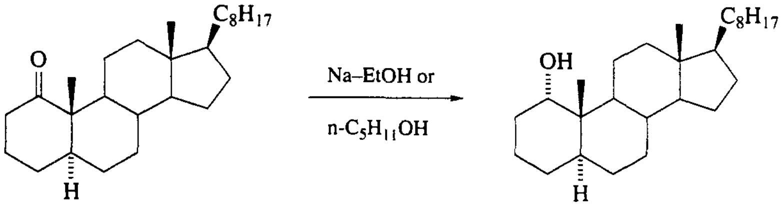

(49) (50) (17)

The other group of moderately hindered cyclohexanones which has been examined in detailed is a group of substituted 1-decalones, which gave results similar to those of the 12-keto steroids on Li–$NH_3$ reduction.[24] These decalones were all derived from protected diketone (**51**) and included two different 2-monosubstituted derivatives (**52**) and (**53**). These decalones were reduced both in the presence of a proton donor ($NH_4Cl$) and under anhydrous conditions in yields of 69–99%. The axial alcohol was the major product in the presence of a proton donor, while the equatorial alcohol was predominant in its absence.[24]

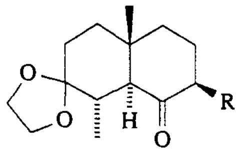

(**51**) R = H
(**52**) R = $CH_2CH{=}CMe_2$
(**53**) R = $CH_2CO_2H$

The reductions of 1- and 12-keto steroids and their 1-decalone derivatives graphically illustrate the fact that dissolving metal reductions of ketones do not necessarily afford the more stable of a pair of epimeric alcohols. As a corollary, while the reduction of cyclic ketones is a synthetically useful procedure for the stereoselective preparation of secondary alcohols, it cannot be assumed that the thermodynamically stable alcohol will be the product which is obtained stereoselectively.

### *1.4.3.4.5 Bicyclo[2.2.1]heptan-2-ones*

The dissolving metal reductions of bicyclo[2.2.1]heptanones have been studied extensively, and it has been established that both metal–alcohol and metal–$NH_3$–proton donor systems provide the *endo*-alcohol regardless of its stability relative to the *exo* isomer.[4–6,10,16,70] In the case of camphor (**1**) which has been studied in the most detail, the ratio of *endo*-alcohol (borneol; **2**) to *exo*-alcohol (isoborneol; **3**) is very close to 90:10 for all metal–$NH_3$ conditions employed. The variables include temperature (–33 and –78 °C),[16] cosolvent (ether and THF),[16] metal (Li, Na, K, Rb)[16,70] and proton donor ($NH_4Cl$ and ethanol).[16,70] The same results are obtained with both (+)- and (±)-camphor.[16] These results are, coincidentally, almost identical to the equilibrium ratio for alcohols (**2**) and (**3**).[16]

In addition to camphor (**1**), the metal–$NH_3$–proton donor reduction of four other bicyclo[2.2.1]heptan-2-ones and bicyclo[2.2.1]hept-5-en-2-one (**54**) have been studied systematically.[16,70] The other ketones include the parent bicyclo[2.2.1]heptan-2-one (**55**), fenchone (**56**), 1-methylbicyclo[2.2.1]heptan-2-one (**57**) and 7,7-dimethylbicycloheptan-2-one (**58**). The results of these reductions and, where known, the equilibrium ratio of the alcohols are summarized in Table 1. In all cases and under the conditions noted, the *endo*-alcohol is produced stereoselectively.

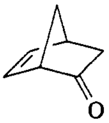

**(54)**

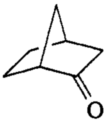

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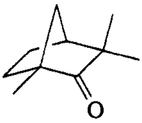

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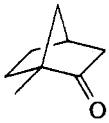

**(57)**

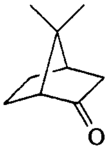

**(58)**

**Table 1** Metal–Ammonia Reductions of Bicyclo[2.2.1]heptanones and Equilibrium Ratios of the Corresponding Alcohols

| *Ketone* | *Metal* | *Cosolvent* | *Proton donor* | *Endo:exo (reduction)* | *Endo:exo (equilibrium)* | *Ref* |
|---|---|---|---|---|---|---|
| (**54**) | Li | THF | $NH_4Cl$ | 99:1 | 50:50 | 16 |
| (**55**) | Li | $Et_2O$ | $NH_4Cl$ | 89:11 | 5:95 | 16, 70 |
| (**55**) | Li | $Et_2O$ | EtOH | 85:15 | — | 69 |
| (**55**) | Na | $Et_2O$ | $NH_4Cl$ | 89:11 | — | 16, 70 |
| (**55**) | Na | $Et_2O$ | EtOH | 85:15 | — | 69 |
| (**55**) | K | $Et_2O$ | $NH_4Cl$ | 90:10 | — | 16, 70 |
| (**55**) | K | $Et_2O$ | EtOH | 90:10 | — | 70 |
| (**56**) | Li | THF | $NH_4Cl$ | >99:1 | 72:28 | 16 |
| (**57**) | Li | $Et_2O$ | $NH_4Cl$ | 91:9 | 40:60 | 16 |
| (**58**) | Li | $Et_2O$ | $NH_4Cl$ | 83:17 | Unknown | 16 |

The reduction of bicycloheptanones, particularly camphor (**1**) in the absence of added proton donors has been studied extensively in connection with the mechanism of the dissolving metal reductions and are discussed in Section 1.4.2.2. As previously noted, reductions under these conditions are of considerably less utility in synthesis than those carried out in the presence of a relatively acidic proton donor ($NH_4Cl$ or ethanol).

The stereoselective dissolving metal reduction of bicycloheptanones has been applied to the synthesis of two tricyclic sesquiterpenes, longiborneol (**59**; equation 18) and ylangoborneol (**60**; equation 19). Alcohol (**59**) was originally prepared by metal–alcohol reduction of longicamphor (**61**)[77] and in improved yield using a metal–$NH_3$–alcohol procedure.[78] Using a similar procedure, ylangocamphor (**62**) gave alcohol (**60**) in excellent yield.[79] Reduction of ketone (**62**) using LAH afforded exclusively the *exo* isomer of alcohol (**60**).

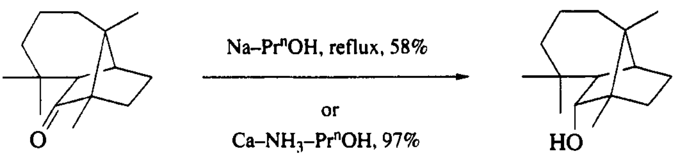

**(61)** **(59)** (18)

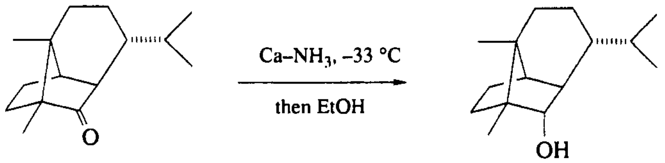

**(62)** **(60)** (19)

### *1.4.3.4.6 Cyclopentanones*

The stereochemistry of the reduction of substituted cyclopentanones has not been studied in great detail and it is not possible to make detailed generalizations regarding their course. Based on limited experimental data, it appears that metal–alcohol and metal–$NH_3$–proton donor reductions of alkyl-substituted cyclopentanones will usually afford a greater than equilibrium ratio of the thermodynamically more stable alcohol. In the absence of an added proton donor, pinacol formation may be a problem and different metals may give different ratios of epimeric alcohols.

The reductions of two steroidal ketones, androstan-17-one (**63**)[75] and androst-5-en-16-one (**64**)[19] under various conditions have been studied in some detail. In the case of 17-ketone (**63**) the β-ol (**65**) is the stable epimer and for the 16-ol (**66**), the α-isomer is more stable. Dissolving metal reductions of both ketones in the presence of proton donors gave the more stable alcohol as the major product; however, reduction of 17-keto steroid (**63**) is considerably more stereoselective as noted in Table 2. Although pinacols are not usually obtained in dissolving metal reductions carried out in the presence of proton donors, ketone (**63**) gave from 6 to 34% of dimeric products under these conditions (Li, 6%; Na, 34%; K, 13%).[75]

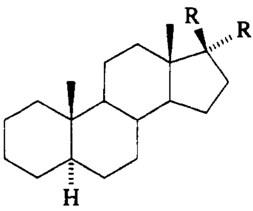

(**63**) R, R' = O
(**65**) R = OH, R' = H

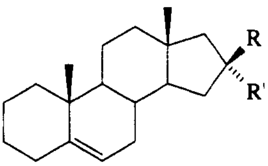

(**64**) R, R' = O
(**66**) R = H, R' = OH

**Table 2** Dissolving Metal Reductions of Androstan-17-one (**63**) and Androst-5-en-16-one (**64**)

| *Ketone* | *Reduction conditions* | *α-ol:β-ol (Reduction)* | *α-ol:β-ol (Equilibrium)* | *Ref.* |
|---|---|---|---|---|
| (**63**) | Li–$NH_3$–EtOH | 3:97 | 42:58 | 75 |
| (**63**) | Na–$NH_3$–EtOH | 0:100 | — | 75 |
| (**63**) | K–$NH_3$–EtOH | 0:100 | — | 75 |
| (**64**) | Li–EtOH | 63:37 | 82:18 | 19 |
| (**64**) | Na–EtOH | 85:15 | — | 19 |
| (**64**) | Li–$NH_3$–THF | 55:45 | — | 19 |
| (**64**) | Na–$NH_3$–THF | 42:58 | — | 19 |
| (**64**) | K–$NH_3$–THF | 22:78 | — | 19 |

In the absence of an added proton donor, the 17-keto steroid again gave the 17β-ol (**65**) as the predominant or exclusive product with seven metals (Li, Na, K, Cs, Ca, Ba, Sr) in $NH_3$. All the alkali metals gave the 17β-ol (**65**) exclusively and the alkaline earth metals gave only 2–5% of the α-ol. With the exception of Ca, all of the metals gave pinacols in yields of 3% (Cs) to 28% (Li).[75] Reduction of 16-keto steroid (**64**) with alkali metals–$NH_3$ in the absence of an added proton donor gave less 16α-ol with Na than with Li and still less with K (Table 2).[19] Pinacols were not reported in the reductions of ketone (**64**).

A series of dialkylcyclopentenones (**67**) has been reduced with Li–$NH_3$ in the presence of various proton donors (phenol and methyl, ethyl, isopropyl and *t*-butyl alcohols).[80] These reductions gave complex mixtures of products, most of which were cyclopentanols (**68**), arising from sequential conjugate reduction to the cyclopentanone followed by reduction to the saturated secondary alcohol. In all cases, and regardless of the relative stereochemistry of R, R′ and X, the major product was a secondary alcohol in which the hydroxy group was *trans* to the adjacent alkyl group (**68**).[80]

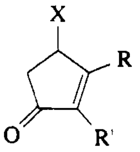

(**67**)

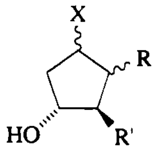

(**68**)

X = H or OH; R = R' = Me; R = Me, R' = $Bu^t$; R = Me, R' = $Pr^i$

A stereoselective Li–NH$_3$ reduction of a cyclopentenone has been employed in two different syntheses of the cytotoxic sesquiterpene coriolin (**69**; Scheme 2). In one synthesis, tricyclic ketone (**70**) was reduced stereoselectively to alcohol (**71**) using Li–NH$_3$–methanol.[81] In the second synthesis, tetracyclic enone (**72**) was converted in a single step to (**71**).[82] This reduction proceeds by initial cleavage of the cyclopropyl ketone unit of (**72**) to give ketone (**70**), which is then reduced to (**71**).

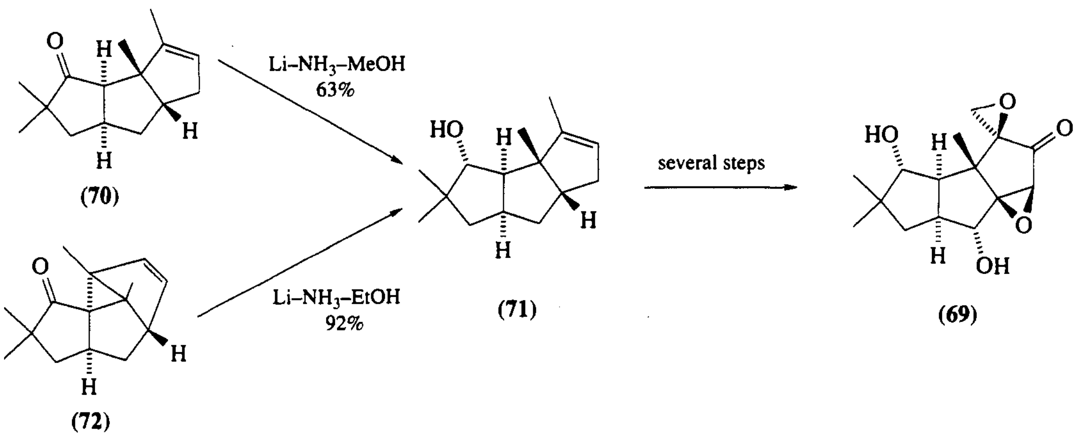

**Scheme 2**

Metal–alcohol reductions of substituted indanone (**73**; equation 20) which afford mixtures of alcohols (**74**) and (**75**) have been described.[21] Although alcohol (**75**) is the more stable isomer, Li and Na both afford alcohol (**74**) as the major reduction product (**74**:**75** = 60:40). Aluminum gives a (**74**):(**75**) ratio of 90:10, but with K it is 30:70. Prolonged (12 h) heating of the Al and K reactions changes the ratios to (**70**):(**30**) and (**10**):(**90**), respectively.[21] It is apparent that some equilibration is occurring under these conditions, but it is not clear if the results after 3 h represent partial equilibration or if they are truly the result of kinetically controlled reductions.

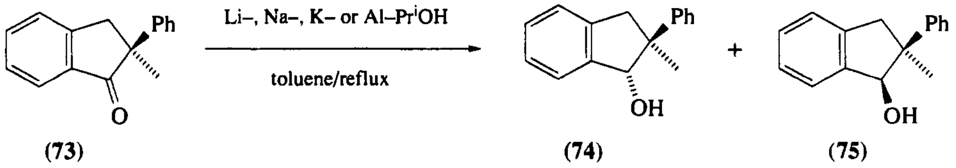

(20)

## 1.4.4 REDUCTION OF C═N AND C═S

### 1.4.4.1 Reduction of Imines and Oximes

#### *1.4.4.1.1 Reduction of imines*

The reduction of imines to amines (equation 21) by dissolving metals is usually carried out using active metals in a protic solvent, typically Na–alcohol, Zn–NaOH and Al or Mg in alcohols.[83-85] Although the mechanism of these reductions has not been investigated in detail it is almost certainly analogous to that of the reduction of ketones (Section 1.4.2). It has been established that radical anions are intermediates in these reductions and in the absence of a proton donor reductive dimerization is the principal reaction path.[86]

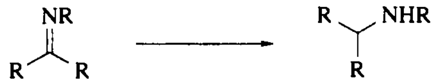

(21)

The reduction of a series of 1,3-diimines (**76**) has been investigated in which the dissolving metal reductions have been carried out both in the presence[87] and absence[88] of proton donors. These compounds exist as a tautomeric mixture of two enaminoimines (**77**) and (**78**) and the diimine (**76**). Reduction by Na–propan-2-ol of five examples (Ar = Ph, β-tolyl; R = Me; R′ = Ph, β-tolyl, cyclohexyl) gave excellent (90–99%) yields of diastereomeric mixtures of three of the four possible fully reduced diamines in which no isomer comprised more than 50% of the reaction mixture. Diamines (**79**) were not observed, and their absence was attributed to steric factors.[87] On reduction with Li–THF for several hours, followed by quenching with methanol, ethanol or water a number of these tautomeric mixtures (**76**, Ar = Ph, β-tolyl; R = H, Me, $PhCH_2$, $CH_2{=}CH{-}CH_2$; R′ = Ph, β-tolyl, Me, cyclohexyl) gave saturated ketones, (**80**) in 70 to 93% yield.[88]

The metal–alcohol reduction of imines usually produces the reduced amine in good yield; however, the reduction of some allylic imines (**81**, R = $Pr^n$,$Bu^n$) with Na–alcohol proceeds with hydrogenolysis to give alkene (**82**).[89]

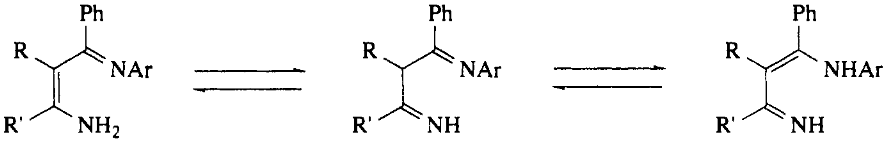

**(78)** **(76)** **(77)**

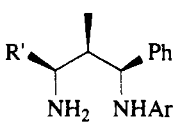

**(79)**

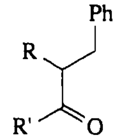

**(80)**

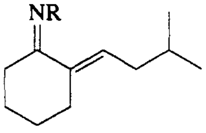

**(81)**

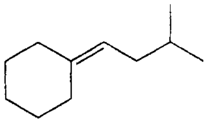

**(82)**

Although by far the most usual method for the dissolving metal reduction of imines is metal–alcohols, a few other systems have been explored with mixed results. In one of these, the reduction of three imines (**83**)–(**85**) with potassium graphite ($C_8K$) in anhydrous THF gave the corresponding amines in 83–90% yields at room temperature in 30 min.[90] Much less favorable results were found in the reduction of benzalaniline (**86**) with $SmI_2$ in methanolic THF which gave *N*-benzylaniline in 50% yield, with much recovered starting material. An attempted Barbier-type coupling reaction employing (**86**), 1-iodobutane and $SmI_2$–THF gave a mixture of products of which *N*-benzylaniline constituted 60%.[64]

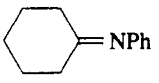

**(83)**

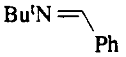

**(84)**

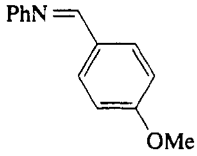

**(85)**

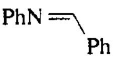

**(86)**

### *1.4.4.1.2 Reduction of oximes*

The reduction of oximes to primary amines by dissolving metals, usually Na–alcohol, is an established synthetic procedure which has been employed for many years.[83,84] Although in some cases LAH reduction is superior, the reduction of many oximes with LAH leads either to aziridines or Beckman-type rearrangements.[91]

The reduction of a series of bicyclic and tricyclic ketoximes using both Na–ethanol and LAH has been carried out and the product mixtures analyzed in detail.[92] In this investigation it was found that reduction of the oximes derived from two tricyclo[2.2.1.$0^{2,6}$]heptan-3-ones (**87**) and (**88**) with either LAH–THF or Na–ethanol gave mixtures of *exo* (**89**) and (**90**) and *endo* (**91**) and (**92**) amines. Neither method of reduction was particularly stereoselective and the yields were somewhat better with LAH (**87**; 76% *versus* 67% and **88**; 67% *versus* 44%). In contrast, reduction of the oximes of three bicyclo[2.2.1]heptan-2-ones (**93**)–(**95**) with LAH–THF gave significant quantities of azabicyclo[3.2.1]octanes (**96**)–(**98**) in addition to mixtures of *exo* and *endo* primary amines. Reduction of oximes (**93**)–(**95**) with Na–alcohol gave only mixtures of epimeric amines.[92] These results, outlined in Table 3, show that the *endo*-amine is the major stereoisomer, although the unsubstituted oxime (**93**) had previously been reported to give an *exo*:*endo* ratio of 75:25 on Na–alcohol reduction and exclusively the *endo*-amine on LAH reduction.[93]

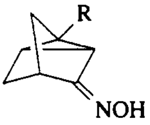

(**87**) R = Me
(**88**) R = Et

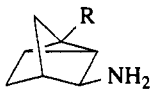

(**89**) R = Me
(**90**) R = Et

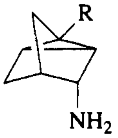

(**91**) R = Me
(**92**) R = Et

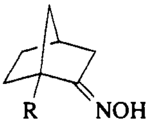

(**93**) R = H
(**94**) R = Me
(**95**) R = Et

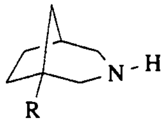

(**96**) R = H
(**97**) R = Me
(**98**) R = Et

**Table 3** Reduction of Oximes of Bicyclo[2.2.1]heptan-2-ones[91]

| *Oxime* | *Conditions* | *Yield (%)* | *Rearrangement (rel. %)* | *Amine (rel. %)* | *Exo:endo* |
|---|---|---|---|---|---|
| (**93**) | Na–EtOH, 80 °C | 67 | 0 | 100 | 27:73 |
| (**93**) | LAH–THF, 65 °C | 79 | 36 | 64 | 36:64 |
| (**94**) | Na–EtOH, 80 °C | 52 | 0 | 100 | 32:68 |
| (**94**) | LAH–THF, 65 °C | 87 | 60 | 40 | 10:90 |
| (**95**) | Na–EtOH, 80 °C | 50 | 0 | 100 | 14:86 |
| (**95**) | LAH–THF, 65 °C | 59 | 52 | 48 | 10:90 |

The chemoselective reduction of a series of 2-oximo-1-tetralones (**99**–**103**; equation 22) to the corresponding aminotetralones has been carried out using Zn–HOAc–$Ac_2O$ in 55–65% yield. The amino group is acetylated under these conditions and the 2-acetamidotetralone is the product which is isolated.[94]

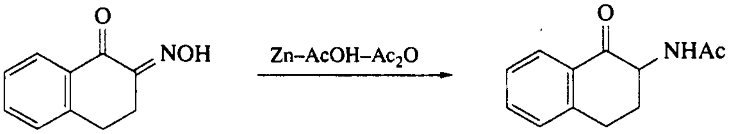

(22)

(**99**) unsubstituted; 65%
(**100**) 5-OMe; 62%
(**101**) 6-OBn; 65%
(**102**) 7-OBn; 60%
(**103**) 5,8-di-OMe; 55%

The reduction of oximes by $SmI_2$ has been attempted, but complex mixtures of products are obtained.[64] In the case of benzaldehyde oxime (**104**; equation 23) two dimeric reduction products (**105**) and (**106**) were isolated, apparently in good yield.[64]

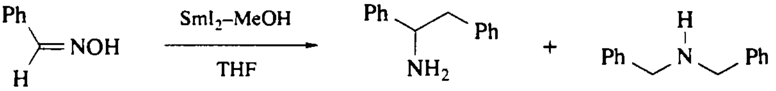

(23)

(**104**) (**105**) (**106**)

### 1.4.4.2 Reduction of Thioketones

There is apparently only one report of the dissolving metal reduction of thioketones; thiobenzophenone (**107**) has been reduced with excess Na–THF to give dianion (**108**), which on acidification gave thiol (**109**). The thiol was not isolated, but was oxidized with iodine to give the corresponding disulfide in 65% overall yield.[95] The mechanism of the reduction is suggested to be the sequential addition of two electrons to the thiocarbonyl, which was confirmed by electron spin resonance spectroscopy studies of the intermediate thioketyl, and trapping dianion (**108**) with a variety of electrophiles.[95]

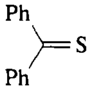

**(107)**

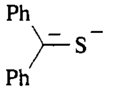

**(108)**

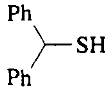

**(109)**

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# 1.5

# Reduction of C=X to CHXH Electrolytically

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## 1.5.1 INTRODUCTION

Electrochemical methodology has proven to be a useful tool for carrying out certain redox reactions which normally require stoichiometric amounts of (organo)metallic reagents.[1] The reagent in this case is an electrode which, when negatively charged (cathode), can transfer an electron onto a substrate molecule in solution (*i.e.* reduction), or, when positively charged (anode), can abstract an electron from it (*i.e.* oxidation). In this chapter a review will be presented dealing with the cathodic reduction of C=O and C=N groups. In order to make the text more intelligible for the synthetic chemist who may not be familiar with electrochemical jargon, a short review of the basic principles of electrosynthesis is presented here.

In a cathodic reduction process electrons are transferred from the electrode surface onto the substrate molecules only if the former possess enough potential energy, *i.e.* if the electrode potential is negative enough. Each organic compound has its own reduction potential (expressed in volts) at which it is reduced but the value depends greatly on the solvent, supporting electrolyte and the presence of other compounds that may interact with the substrate or electrode surface. In anodic oxidations the term 'oxidation potential' is used, referring to the electrode potential at which electrons will be transferred from the substrate to the positively charged anode surface. Thus, the higher the oxidation potential of a compound, the more difficult it is to oxidize it. In an electrochemical reaction electrons will only flow in a closed circuit (Figure 1) which includes a 'counter electrode' (sometimes called 'auxiliary electrode'). The cathode receives electrons from the counter electrode, which becomes positive (anode) with the help of a power supply (potentiostat), which serves as an 'electron pump'. As a result an oxidation process needs to take place near the anode surface to maintain the current flow. The electrode at which the desired reaction occurs is called the 'working electrode'. The term 'electrode potential' is in reality a potential difference measured relative to a reference electrode, such as the 'saturated calomel electrode' (SCE) or the silver–silver halide electrode. Whenever a potential value is reported for a compound, the type of reference electrode must be indicated. When the reduction is carried out at a constant potential (see Figure 1), the potentiostat uses the reference electrode as a zero point against which it will maintain the negative potential value required at the cathode surface. In order to maintain electroneutrality in the solution during the electrolysis it is necessary to add a so-called 'supporting electrolyte' which makes the medium electrically conductive. The most popular are the tetraalkylammonium salts (*e.g.* $Bu_4NBr$) and alkali metal salts (*e.g.* $LiClO_4$), although virtually any soluble salt can be used. The solvent required for dissolving these salts must be very polar (high dielectric constant) and, therefore, electrosynthetic reactions are usually carried out in dimethylformamide, acetonitrile, dimethyl sulfoxide, alcohols, water and sometimes even ethers (*e.g.* tetrahydrofuran).

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*This chapter is dedicated to the memory of Dr. Manuel M. Baizer

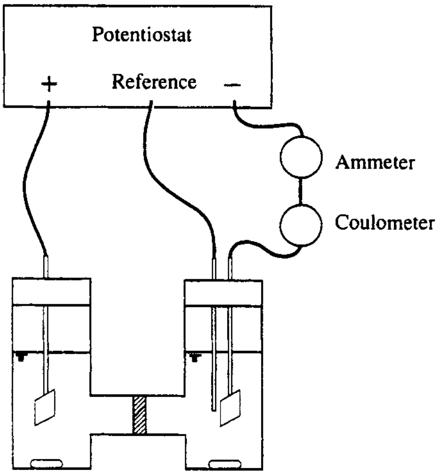

**Figure 1** Controlled potential electroreduction in H–cell

The cell shown in Figure 1 (also called an H-cell because of its shape) is a divided cell, wherein a porous glass frit or polymer (*e.g.* Nafion) prevents the anolyte and catholyte solutions from mixing with each other. In some cases, however, a simple beaker can be used (undivided cell).

Once the potential is dialed on the potentiostat and the electrodes are activated, a current flows through the cell but decreases gradually until all the substrate at the working electrode is converted into products. The current is monitored with an ammeter (Figure 1) and it is also common to include a coulometer so that at the end of the electrolysis the total charge that has passed through the cell can be measured. For instance, in a 'one-electron' process a total charge of 96 487 C will be consumed by 1 mol of substrate knowing that 1 mol of electrons (each carrying a charge of $1.6 \times 10^{-19}$ C) is required. That total charge of 1 mol of electrons is commonly referred to as one Faraday (1 F = 96 487 C) and the electron consumption is expressed in Faraday per mol of substrate (F $mol^{-1}$). Suppose that one deals with a well-established one-electron process and at the end of the experiment the coulometer indicates the consumption of 2 F $mol^{-1}$, then it is obvious that 1 F $mol^{-1}$ of electricity must have been consumed by impurities or secondary electron transfer reactions. While it is theoretically possible to obtain 100% chemical yield in such an electrolysis, the 'current efficiency' or 'current yield' is 50%: only 50% of the current is used for the desired reaction.

In the electrochemical literature one often encounters reports dealing with electrolyses carried out under a constant current (*i.e.* galvanostatic), expressed as 'current density' (*e.g.* A $cm^{-2}$), instead of a constant potential. Such experiments do not require the use of a reference electrode and may also take less time, but a major drawback is that the potential value of the working electrode increases gradually as the substrate in the solution is consumed. For a reduction it means that the cathode potential becomes more negative and consequently the product selectivity may suffer if the composition of the reaction mixture is not carefully monitored during the electrolysis.

There are many electrochemical reactions known that involve the use of so-called 'mediators', which are basically redox catalysts. The active form acts as an electron transfer agent to convert the substrate into products. The catalyst is then regenerated at the electrode surface and the cycle can be repeated until all the substrate is consumed. Such an 'indirect' electrode reaction is schematically shown in Figure 2 for the case of an electroreduction. The mediator is reduced to its active form at potentials that can be up to 600 mV more positive than the potential required for direct reduction of the substrate.

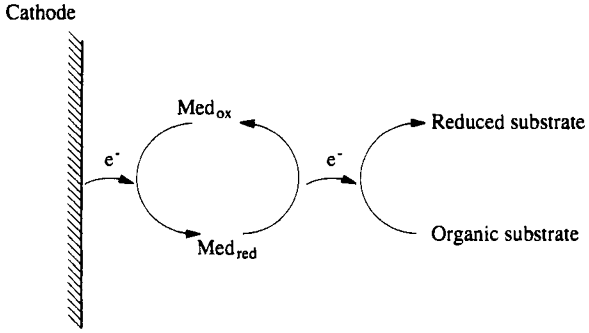

**Figure 2** Indirect electroreduction

Before embarking on an electrosynthesis it is desirable to know the potential at which the desired reaction is expected to occur. That information can be obtained from electroanalytical techniques, such as polarography and cyclic voltammetry.[2,3]

These basic principles will hopefully clarify some data presented in the following review that covers the literature from 1979 until the present, dealing with the electroreduction of a carbonyl group to an alcohol, and of an imino group to the corresponding amine. Earlier literature on this topic has been reviewed elsewhere.[1]

## 1.5.2 KETONES AND ALDEHYDES

### 1.5.2.1 Nonalkenic Ketones and Aldehydes

#### *1.5.2.1.1 General mechanism and products*

The product distribution obtained in the cathodic reduction of ketones and aldehydes depends strongly on the right choice of the solvent (aqueous or nonaqueous), the supporting electrolyte, the electrode material and additives. Scheme 1 shows a simplified overview of the reduction pathways that lead to alcohols (pinacols **2** and methanols **3**) or deoxygenated products (**4**). In solutions containing aqueous acid the carbonyl group exists partly in the protonated form, which is more electrophilic and thus easier to reduce to the neutral radical (**1**). In some cases complete reduction of the carbonyl group to a methylene group (as in **4**) can be observed.

Van Tilborg and coworkers have reported synthetically useful data that support this mechanistic scheme.[4,5] They found that the reduction of acetophenones often leads to nearly quantitative yields of pinacols in aprotic media, as shown in equation (1).

Presumably a layer of tetraalkylammonium ions is formed at the mercury surface from which the radical anion of acetophenone is quickly expelled into the bulk solution, where pinacolization can take place. An increased bulk of the alkyl chain of the ketone caused a lower selectivity: reduction of isobutyrophenone afforded, besides 68% pinacol, 17% of the corresponding alcohol. Reduction of isobutyrophenone under protic conditions gave predominantly alcohol and only 13% of the pinacol. Aryl alkyl ketones also undergo pinacolization in excellent yields when lithium ions are added to the aprotic medium.[6] However,

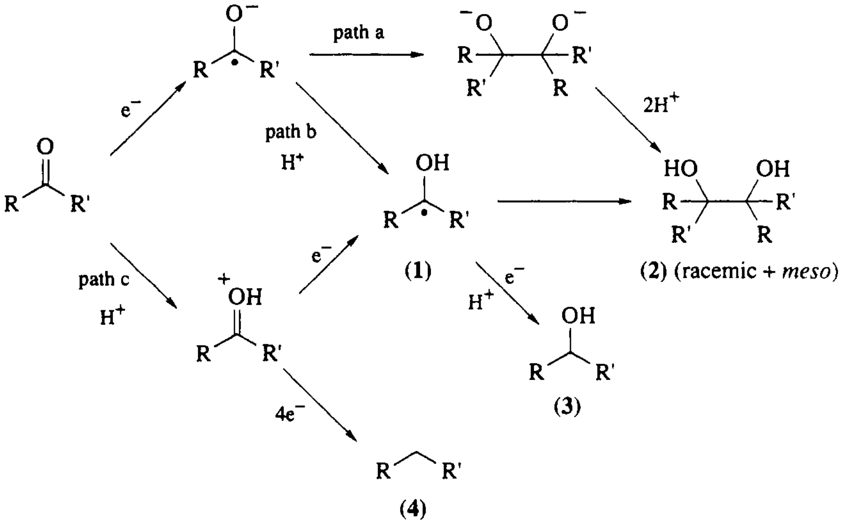

**Scheme 1**

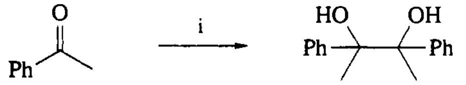

(racemic:*meso* = 6:1)

(1)

i, Hg, −2.0 V (SCE), 1.3 F $mol^{-1}$, $Et_4NClO_4$, MeCN, 98%

in the case of diaryl ketones a disproportionation of the radical anion has been observed in the presence of lithium ions, affording the corresponding alcohols.[7] Dialkyl ketones have received much less attention in such reduction studies, mainly because they can undergo aldol-type reactions when enolizable protons are present within the molecule.[4]

Pletcher and Razaq studied the four-electron reduction of acetophenone to ethylbenzene in strongly acidic media.[8] Such an electroreduction is analogous to the classical Clemmensen reaction, which is carried out with amalgamated zinc in concentrated hydrochloric acid.

The pathway for the cathodic reduction of acetophenone can be profoundly altered when the aromatic ring is complexed inside the hydrophobic cavity of β-cyclodextrin.[9] Products resulting from *ortho* and *para* coupling to the carbonyl carbon are isolated in excellent yield, as shown in equation (2).

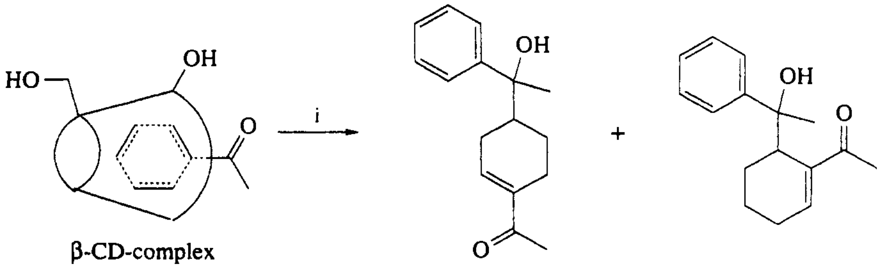

(1:1)

(2)

i, Hg, −1.34 V(Ag/AgI), 1.5 F $mol^{-1}$, $Bu_4NBF_4$, DMF, 90%

### *1.5.2.1.2 Indirect electroreduction*

The reduction potential of an unactivated carbonyl group in aprotic media lies so close to the reduction potential of the supporting electrolyte that the latter is often reduced first. Kariv-Miller and coworkers recently exploited this seemingly undesirable effect in the development of extremely powerful electroreductions.[10–14] They showed that the tetraalkylammonium cation can act as a mediator, which accepts an electron from the cathode and transfers it onto the carbonyl group. The reduction of cyclohexanone (**5**) shown in Scheme 2 serves as an example of the high yields and high selectivities that can be obtained by this method. Addition of dimethylpyrrolidinium ions (DMP$^+$) causes the reduction to occur at less negative potentials (compared to $Bu_4N^+$ ions) and at the same time favors pinacolization (*i.e.* the one-electron process). The DMP$^+$ ion is reduced by one electron to generate a radical species that reacts with the mercury cathode, forming a black solid material characterized as $DMPHg_5$. The latter is believed to be the active reducing agent in these indirect electroreductions.

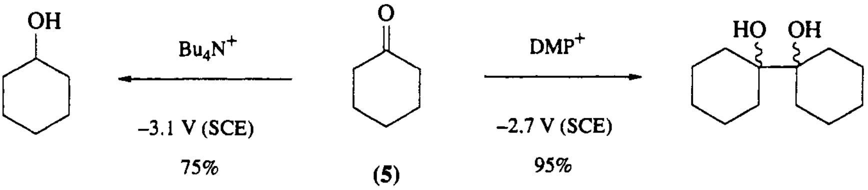

**Scheme 2**

### *1.5.2.1.3 Electroreduction in the presence of transition metal ions*

Several studies have been done on the product distribution resulting from electroreduction of ketones and aldehydes in the presence of transition metal ions.[15–22] The complexation of such ions with the carbonyl group causes the latter to be reduced at less negative potentials and also determines the regio- and stereo-chemical outcome of the reduction. Sopher and Utley showed that $CrCl_3$ favors the pinacolization of ketones and aldehydes.[15,16] Controlled potential electrolysis of benzophenone (Hg cathode, DMF, $NaClO_4$) required a potential of −1.3 V (*versus* Ag/AgI) to afford 80% alcohol, while addition of 1 equiv. of $CrCl_3$ resulted in the formation of the pinacol (70%) and alcohol (10%) at only −1.0 V. The cathodic reduction of sterically hindered aromatic ketones and aldehydes in the presence of $Cr^{3+}$, $Mn^{2+}$, $Fe^{2+}$, $Co^{2+}$, $Ni^{2+}$ and $Zn^{2+}$ also gave good yields of the corresponding pinacols with predominantly the racemic diastereoisomer.[19–21] A stereoselective pinacolization (100% racemic diastereoisomer) of acetophenone (**6**) was observed when the electroreduction was carried out in the presence of $Eu^{3+}$ ions (equation 3).[22]

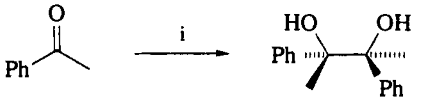

(3)

(**6**) 100% racemic isomer

i, $EuCl_3 \cdot 6H_2O$, Hg, −1.4 V (Ag/AgI), $Bu_4NClO_4$, DMF, 97%

### *1.5.2.1.4 Stereocontrol in the electroreduction of ketones*

An important issue in the reduction of a carbonyl group is the degree of stereocontrol that can be obtained by using a particular set of conditions. A few systematic studies dealing with stereocontrol in cathodic reductions of cyclic ketones were reported independently by Utley[23–25] and Shono[26] in the early 1970s. More recently, Le Guillanton reported a study on the electroreduction of 2-ethoxycarbonyl cycloalkanones (**7**) in aqueous media, as shown in equation (4).[27] Both *cis*- and *trans*-2-hydroxy esters (**8a**) and (**8b**) were isolated in a ratio depending strongly on the nature of the supporting electrolyte and the cathode material.

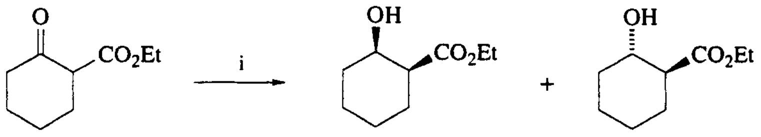

(4)

(**7**) (**8a**) (**8b**)

i, Hg, −2.2 V (SCE), $Et_4NI$, $H_2O$, EtOH, 90%

The most important parameter was the temperature: at −6 °C *cis* isomer (**8a**) predominated (*cis*:*trans* = 65:35), while at 80 °C the thermodynamically more stable *trans* isomer (**8b**) was the major compound (*cis:trans* = 15:85), suggesting that the isomers result from an equilibrium of an intermediate radical or anionic species. The electroreduction of acyclic ketones with a chiral center (optically inactive) at the α- and β-positions has been studied by Nonaka and coworkers.[28,29] Unfortunately the yields were generally very low for aliphatic ketones, probably because the reactions were carried out under extreme pH conditions. Tetraols are formed stereoselectively in the coupling of 2-substituted indan-1-ones.[30,31]

#### *1.5.2.1.5 Asymmetric electroreduction of a carbonyl group*

The development of asymmetric electroreductions remains a major challenge in spite of the many different approaches that have been tested during the last two decades. The literature on this topic prior to 1979 has been reviewed.[1,4,32] Chirality can be induced during electropinacolization of acetophenones by using chiral supporting electrolyte salts.[4] The enantiomeric excess (*ee*) in the (*RS,RS*)-pinacols varied between 3 and 25%, depending on the nature of the chiral supporting electrolyte, the applied potential and the solvent. Anhydrous media gave the highest optical yield.[32] Chemically modified electrodes, such as poly-L-valine coated graphite electrodes have been tested but they gave less than 7% optical yield in the reduction of phenylglyoxylic acid.[33] A very intriguing method reported by Takahashi deals with the electrolytic reduction of phenylglyoxylic acid in a magnetic field of 1680 G (1 G = $10^{-4}$ T), affording dextrorotatory mandelic acid with 21% *ee*.[34]

### 1.5.2.2 Alkenic and Alkynic Ketones and Aldehydes

#### *1.5.2.2.1 Nonconjugated alkenic ketones*

Kariv-Miller and coworkers have developed indirect electroreductive cyclizations with the dimethylpyrrolidinium ion ($DMP^+$) as a mediator. Preparative electrolysis of 6-hepten-2-one (**9**) at a graphite cathode afforded *cis*-dimethylcyclopentanol (**10**) in 90% yield (equation 5).[13] The reduction is believed to occur *via* the ketyl radical anion, which cyclizes onto the alkenic bond.[10] In the absence of $DMP^+$ simple reduction to 6-hepten-2-ol takes place.[13] Very recently it was shown that instead of $DMP^+$ several aromatic hydrocarbons can be used as mediators to initiate the cyclization reaction.[10] The carbonyl group can also be cyclized onto an alkynic bond[12] and even an aromatic ring.[12,35]

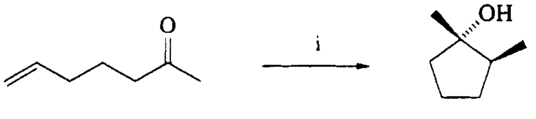

(5)

**(9)** **(10)**

i, C, –2.75 V (SCE), DMF, $DMP^+ BF_4^-$, $Bu_4NBF_4$, 90%

#### *1.5.2.2.2 α,β-Unsaturated ketones and aldehydes*

When an alkenic bond is conjugated with the carbonyl group, the carbonyl carbon and the β-carbon become the two reactive centers and a variety of products can be obtained depending on the medium.[1] Presence of water in the reduction of 4-methyl-2-cyclohexenones results in a mixture of products.[36] However, when the β-position is substituted such as in retinal (**11**), pinacolization takes place to form the pinacol (**12**) in 89% yield, provided that the electroreduction is carried out in an aprotic medium in the presence of a mild proton donor, such as diethyl malonate (equation 6).[37]

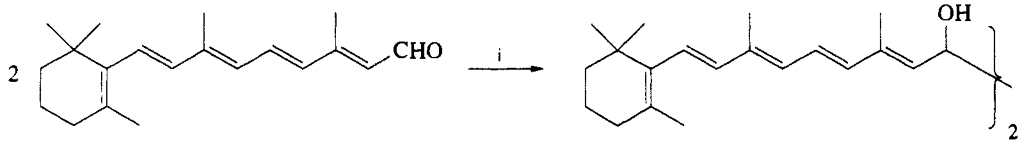

(6)

**(11)** **(12)**

i, Hg, 1.09 F $mol^{-1}$, $Bu_4NClO_4$, MeCN, $CH_2(CO_2Et)_2$, 89%

Similarly, the pinacols of β-ionone could be obtained in 75% yield by carrying out the electrolysis in the presence of chromium(III) chloride.[16] Touboul and Dana observed a unique case of enantiomeric recognition when they reduced a series of racemic 1,9,10,10a-tetrahydro-3(2*H*)-phenanthrones (**13**). Pinacolization occurred with formation of a new carbon–carbon bond preferentially between identical enantiomers, as shown in equation (7).[38].

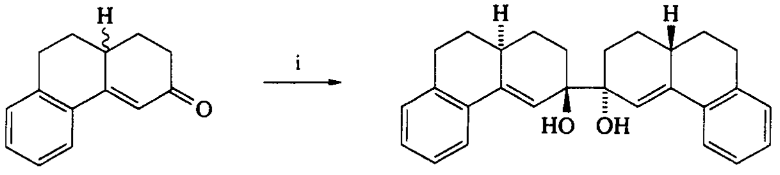

(7)

(**13**)

i, Hg, –1.4 V (SCE), 0.96 F mol$^{-1}$, EtOH, AcOH, 79%

### 1.5.2.3 Electrocatalytic Hydrogenation

A different type of electroreduction is the catalytic hydrogenation of organic compounds at an activated electrode surface in an aqueous medium. The water is cathodically reduced to hydrogen gas, which reacts immediately with the dissolved organic substrate. Lessard and coworkers found that benzophenone can be reduced to benzhydrol in nearly quantitative yields using a Raney nickel cathode.[39] Other catalytic electrode materials, such as palladium black[40] and platinized platinum,[41] have also been used. Chiba and coworkers showed that a series of aromatic and aliphatic ketones and aldehydes can be reduced to the corresponding alcohols with Raney nickel electrodes in a methanolic medium.[42] Under certain conditions the ketone can be reduced directly to the hydrocarbon.[43,44]

## 1.5.3 IMINES AND OXIMES

### 1.5.3.1 Electroreduction of Acyclic and Cyclic Compounds with a C=N Bond

#### *1.5.3.1.1 General mechanism and products*

The mechanism of the cathodic reduction of carbon–nitrogen double bonds is not very different from that of a carbonyl group. As shown in Scheme 3, an initial one-electron reduction leads to a radical anion (**14**), which in most cases is quickly protonated due to its high basicity.[45] The resulting neutral radical (**15**) can dimerize to form vicinal diamines (**16**)[46,47] or can be further reduced to lead to the amine (**17**) after a second protonation. Reversibility has been observed with several imines for the first and second electron transfer step.[48,49]

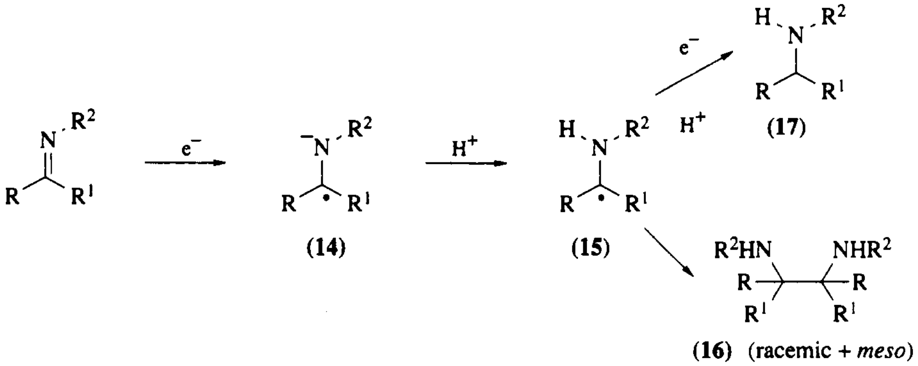

**Scheme 3**

The equilibrium existing in an aqueous medium between a Schiff base and its corresponding aldehyde or ketone can be exploited in reductive aminations, as shown recently by Pienemann and Schäfer.[50] Because of its slightly more positive reduction potential compared to a carbonyl group, the Schiff base can be selectively reduced in a controlled potential electrolysis, to yield an amine in high yields, as shown in equation (8). This method is applicable to a variety of ketones and aldehydes.

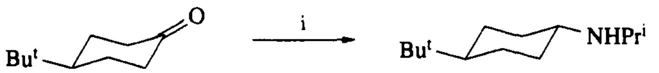

(8)

i, Pr$^i$NH$_2$, Hg, −1.68 V (SCE), H$_2$O, EtOH, 81%

A nice example of regioselectivity that can be obtained with controlled potential electrolyses has been reported by Tallec.[47] Electroreduction of the 2-phenyl-6*H*-1,3-thiazine (**18**) in aqueous ethanol with an acetate buffer and a mercury pool cathode afforded the dimer (**19**; 80%) at a working potential of −0.80 V (SCE) or the 2,3-dihydro compound (**20**: 75%) at −1.40 V (SCE) (Scheme 4).

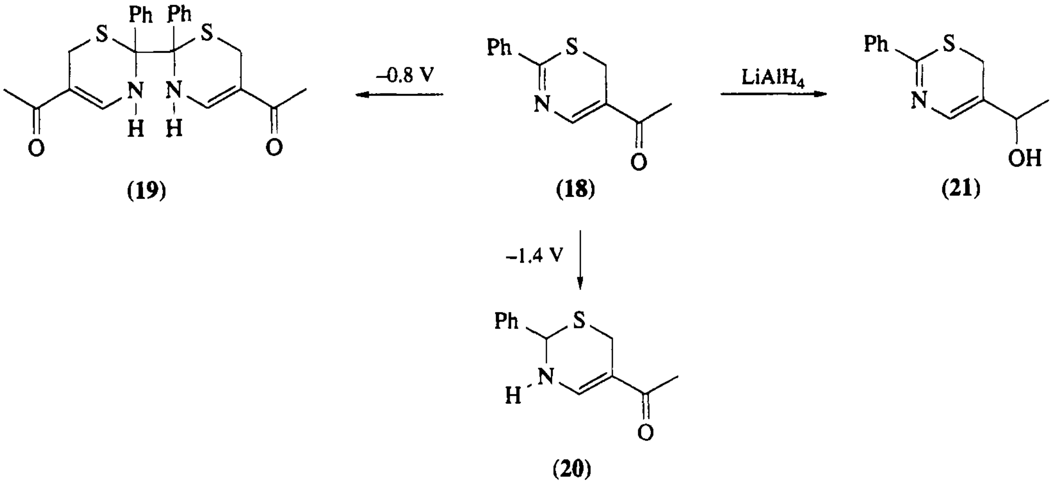

**Scheme 4**

In contrast, sodium borohydride or lithium aluminum hydride reduced the carbonyl group to the alcohol (**21**) leaving the C═N double bond intact.

Imino lactones, such as (**22**), can be reduced cleanly to the morpholinone (**23**) in an aprotic medium using diethyl malonate as a mild proton donor (equation 9).[51] The electroreductive behavior of this class of activated imines is presently under study.

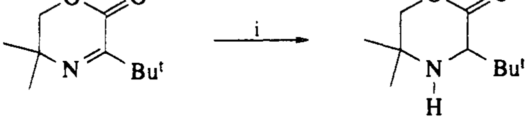

(9)

**(22)** **(23)**

i, Hg, −1.83 V (SCE), 1.9 F mol$^{-1}$, Bu$_4$NBr, DMF, CH$_2$(CO$_2$Et)$_2$, 81%

### *1.5.3.1.2 Electroreductive cyclization*

Schiff bases have been used in electroreductive cyclizations, leading to heterocyclic compounds. The bisimine (**24**), when reduced in glyme, affords the piperazine (**25**) in 42% yield after quenching with methyl iodide (equation 10).[52] When the solvent is changed to dimethylformamide, saturation of the imino bonds takes place without ring closure. Transannular ring closure of diazocine (**26**) led to indolo-indole (**27**) with a *cis* ring junction in 94% yield, as shown in equation (11). The radical anion generated from an imino bond can also act as a nitrogen base and consequently intramolecular deprotonation reactions may compete with the cyclization process if acidic protons are present in the chain.[53]

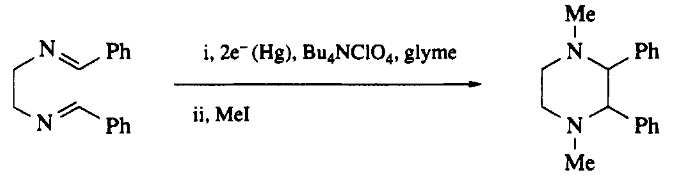

(**24**) (**25**)

(10)

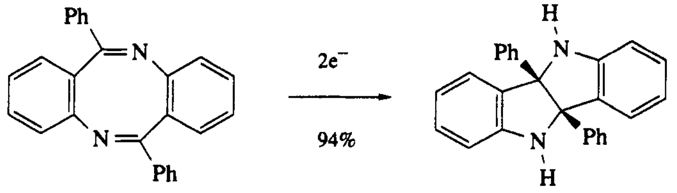

(**26**) (**27**)

(11)

### 1.5.3.2 Electroreduction of Oximes

Another method for reductive amination of carbonyl compounds is based on the electroreduction of oximes in aqueous media. Thus, sugar oximes were reduced to their corresponding glycamines in good yields (Hg, KCl, acetate buffer).[54] Similar reductions of oximes derived from furfural, salicylaldehyde, benzophenone and cyclohexanone have also been described,[55–58] but reports of preparative electrolyses in strictly aprotic media seem to be absent in the literature.

### 1.5.3.3 Asymmetric Electroreduction of a C=N Bond

The asymmetric electroreduction of an imino group has also been the subject of several studies. The use of modified electrodes,[33] or chiral additives that supposedly create a chiral environment close to the electrode surface, give only low optical yields.[32,59,60] Other strategies will have to be explored in order to obtain high optical purities useful for synthetic work.

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# 1.6

# Reduction of C═X to CHXH by Catalytic Hydrogenation

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## 1.6.1 INTRODUCTION

This chapter deals with heterogeneous and homogeneous catalytic hydrogenation of the C═X bond, mainly compounds containing carbon–oxygen and carbon–nitrogen double bonds.[1–8] Various catalysts are employed for the hydrogenation reaction, the most widely used for heterogeneous catalytic hydrogenation being based on Fe, Ni, Co, Ru, Rh, Pd, Os, Ir and Pt, with the most popular catalysts based on Pt, Pd and Ni. The so-called copper chromite has also been used for hydrogenation of C═X double bonds.

Heterogeneous catalytic hydrogenation is a classical method of hydrogenation for preparative organic chemistry. Recently various reducing reagents of the metal hydride type have become popular in synthetic organic chemistry; however, classical heterogeneous hydrogenation is still an important and convenient method for the preparation of organic compounds both on the macro and the micro scale.

Some metallic elements such as rhodium have been used for homogeneous catalytic hydrogenation in a properly designed complex. However, most homogeneous catalytic hydrogenations, including asymmetric reactions, have been applied to substrates containing a carbon–carbon double bond, and few have been applied to the reduction of carbon–oxygen double bonds.

Heterogeneous catalytic hydrogenations using chirally modified metal catalysts have been carried out successfully. This method is interesting chemically and could be a useful production method for chiral organic compounds. However, the application of this type of modified catalyst is, for the present, rather limited.

## 1.6.2 HETEROGENEOUS CATALYTIC HYDROGENATION OF THE C=O BOND

### 1.6.2.1 Hydrogenation of Aldehydes

Saturated aliphatic aldehydes are easily reduced to the corresponding alcohols in high yield by heterogeneous catalytic hydrogenation. Saturated aliphatic aldehydes are converted to the corresponding alcohols quantitatively using Raney nickel,[9–11] and hydrogenation of glucose over nickel to produce sorbitol has been used on an industrial scale.[12] Platinum oxide is also an efficient catalyst.[13]

Unsaturated aliphatic aldehydes can be selectively hydrogenated in three ways: reduction of (a) the aldehyde group, (b) the carbon–carbon double bond, or (c) both the aldehyde and carbon–carbon double bond. A rhenium catalyst was suitable for selective hydrogenation of the carbonyl group;[14] crotonaldehyde (**1**) was hydrogenated, using osmium on charcoal, to crotyl alcohol in high yield.[15] In contrast, crotonaldehyde was converted to butyraldehyde using a palladium catalyst prepared by reduction of Pd salts with sodium borohydride.[16] Finally, using a nickel catalyst, crotonaldehyde was reduced to *n*-butanol (Scheme 1), indicating that the palladium or osmium catalyst is more selective than the nickel catalyst. Similar catalytic hydrogenations of cinnamaldehyde were also carried out. The substrate was reduced to cinnamyl alcohol by osmium on charcoal,[15] to hydrocinnamaldehyde using a palladium catalyst[16] and to hydrocinnamyl alcohol by Raney nickel.[9] Palladium[17] and platinum[18] catalysts, modified with iron(II) ion and zinc acetate, were also effective for selective hydrogenation of the carbonyl group of unsaturated aldehydes.[14]

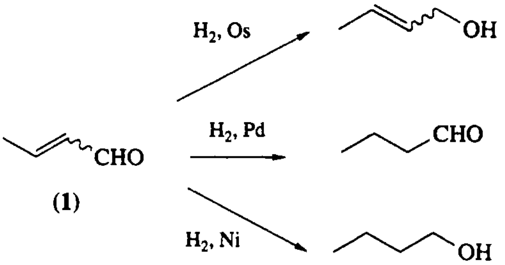

(**1**)

**Scheme 1**

2,2-Dimethyl-4-pentenal was hydrogenated to form 2,2-dimethylpentanal using 5% palladium on alumina.[16] On the other hand, the substrate was converted to 2,2-dimethylpentanol using Raney nickel under stronger conditions.[19] Similar hydrogenation of citral (**2**) to geraniol (**3**) has been carried out using a modified platinum oxide catalyst (equation 1).[20]

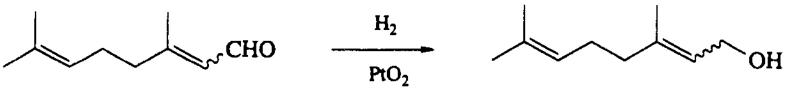

(1)

(**2**) (**3**)

The catalytic hydrogenation of benzaldehyde to benzyl alcohol has been carried out using various catalysts. Prolonged hydrogenation results in the formation of toluene, and hydrogenation must be stopped when the uptake of hydrogen reaches the theoretical value.[13,21–23] Further hydrogenolysis of the resulting benzyl alcohol tends to proceed to a larger extent when a platinum catalyst is employed as compared to palladium. Nickel,[10,24] Raney nickel[9] and copper chromite[25] are suitable for hydrogenation of benzaldehyde to benzyl alcohol practically without any hydrogenolysis. The use of platinum oxide modified by the addition of iron(II) chloride is also a good catalyst for hydrogenation, preventing further hydrogenolysis.[13] Benzaldehyde is hydrogenated to benzyl alcohol using a platinum catalyst in ethanol,[22] but in acetic acid it is further hydrogenolyzed to toluene.[22] Benzaldehyde is similarly converted to toluene with a palladium catalyst in acetic acid,[26] and fluorene-1-carbaldehyde and furfural are converted to 1-methylfluorene and methylfuran, respectively.[26,27]

### 1.6.2.2 Hydrogenation of Ketones

Heterogeneous catalytic hydrogenation of saturated ketones proceeds easily to form secondary alcohols using various metal catalysts such as platinum, palladium, nickel, copper chromite and rhodium. However, the rate of hydrogenation of ketones is generally lower than that of the corresponding aldehydes. Catalytic hydrogenation over platinum oxide,[28] rhodium, ruthenium[28–30] and Raney nickel[10] gives the corresponding alcohols under mild conditions. On the other hand, hydrogenation over nickel[24] and copper chromite[25] requires stronger reaction conditions, although it still proceeds almost quantitatively. For example, hydrogenation of acetone over Raney nickel (25 °C, 1 atm) or copper chromite (150 °C, 100 atm) gives isopropyl alcohol in almost 100% yield.

Heterogeneous catalytic hydrogenation of aromatic ketones takes place easily to form the corresponding alcohols using various metal catalysts. Special care should be taken to avoid further hydrogenolysis if the products are of the benzyl alcohol type. Acetophenone was hydrogenated over palladium oxide in ethanol to form the secondary alcohol in good yield without hydrogenolysis. However, the same reaction in acetic acid gave the hydrogenated and hydrogenolyzed product ethylcyclohexane,[28,29] and nitroacetophenone was converted to ethylaniline over a palladium catalyst at room temperature in acetic acid.[31] Noble metal catalysts tend to hydrogenate the aromatic ring and also hydrogenolyze the resulting benzylic alcohol. The hydrogenation of acetophenone over rhodium–platinum oxide in ethanol gave 1-cyclohexylethanol in good yield, whereas hydrogenation of the same substrate over palladium or platinum oxide in acetic acid in the presence of hydrochloric acid gave ethylbenzene.[28] The same hydrogenation reaction using nickel and copper chromite gave 1-phenylethanol without hydrogenolysis.[9,10,24,25]

Hydrogenations of acetylpyridines were carried out similarly, and yielded various products depending on the reaction conditions and especially on the catalyst used.[32] Thus 4-acetylpyridine was hydrogenated over palladium oxide to form the corresponding alcohol, 4-(1-hydroxyethyl)pyridine, with a small amount of the pinacol (**4**), but it was converted mainly to the pinacol using palladium on charcoal or rhodium on alumina. However, under different conditions, the pyridyl ring of 3-acetylpyridine was reduced to a mixture of 3-acetyl-1,4,5,6-tetrahydropyridine and 3-acetylpiperidine.

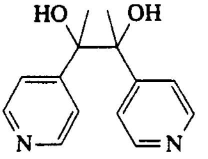

(**4**)

Hydrogenation of cyclic ketones yields secondary alcohols. In these reactions, the stereochemistry of the products depends on the reaction conditions.[33]

Heterogeneous catalytic hydrogenation generally takes place with *syn* addition to the double bond. An empirical rule for heterogeneous hydrogenation of cyclohexanones over Pt or Ni catalysts has been proposed by von Auwers and Skita.[34–36] According to this rule, when Pt is employed as a catalyst, *cis* compounds are obtained under acidic conditions, while the reaction tends to favor the *trans* isomer in neutral or basic conditions. Barton has also expressed the rule of hydrogenation in terms of the conformations of the product; the catalytic hydrogenation of a derivative of cyclohexanone should yield the axial alcohol predominantly in acidic conditions, while in neutral conditions the equatorial alcohol is obtained predominantly.[37] Table 1 shows the results of catalytic hydrogenation of cyclohexanone derivatives under various conditions.[38–43]

In the reactions (a) and (b), the percentage of the *cis* products depended on the catalysts and the solvent, hydrogenation over platinum or platinum oxide giving the *cis* isomer, but giving the *trans* isomer with a basic catalyst (Raney Ni).[44] Hydrogenation in acidic media favors the formation of axial hydroxy products, and alkaline conditions gave alcohols with an equatorial hydroxy group.[38] In reaction (c), a higher proportion of the *cis* product was obtained.

Several factors such as the structure of the substrate, the catalyst, the solvent, the reaction temperature, the pressure of hydrogen and other reaction conditions determine the stereochemistry of the catalytic hydrogenation of cyclic ketones,[36] and it is sometimes difficult to predict the major product of catalytic hydrogenation. One reason for the complexity of the stereochemistry of the hydrogenation of cyclic ketones, at least in part, is related to the isomerization of the products under the reaction conditions. Some cyclohexanols were isomerized in the presence of platinum or nickel catalysts at room temperature or at higher temperature under a hydrogen atmosphere, and the isomerization reached a *cis–trans* equilibrium.[45] For example, *trans*-3,3,5-trimethylcyclohexanol isomerized in the presence of a nickel catalyst,

Table 1 Catalytic Hydrogenation of Cyclic Ketones

| *Substrate* | *Solvent* | *Catalyst* | *Percentage of cis-product* |
|---|---|---|---|
| (a) 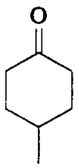 | AcOH, HCl | $PtO_2$ | 80 |
| | AcOH | $PtO_2$ | 47 |
| | MeOH | $PtO_2$ | 26 |
| (b) 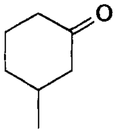 | AcOH | Pt | 73 |
| | AcOH | $PtO_2$ | 38 |
| | EtOH | R, Ni | 23 |
| (c) 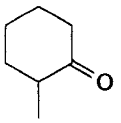 | AcOH, HCl | Pt | 93 |
| | AcOH | $PtO_2$ | 70 |
| | MeOH | R, Ni | 70 |

and reached equilibrium (*cis*:*trans* = 73:27). The presence of alkali accelerates the isomerization[39] and, therefore, isomerization of cyclohexanol takes place in the presence of basic catalysts such as Raney nickel or Adams' platinum oxide.[46] However, isomerization occurred to a much lower extent when an acid-washed platinum catalysts was used.[47] The mechanism of the isomerization has been considered in two ways as shown in equation (2).[39,48] Reaction (a) is an equilibrium between the *cis* and *trans* isomers by dehydrogenation and subsequent hydrogenation.[39] A kinetic study of the isomerization suggests that the racemization reaction takes place directly following adsorption of the alkohol on the catalyst (reaction b).[47,48]

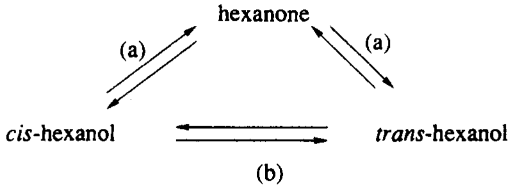

(2)

Unsaturated ketones can be hydrogenated to saturated alcohols, or to saturated ketones by controlled catalytic hydrogenation. The latter is not the subject of this article and hydrogenation to saturated alcohols will be discussed. Hydrogenation of a ketone group to a secondary alcohol was achieved for chalcone (benzylideneacetophenone) and phenylbutan-2-one using platinum oxide[49] or copper chromite,[25] and a nickel catalyst was also used for the hydrogenation.[10] Chalcone was converted to the unsaturated alcohol using a modified colloidal palladium.[50] A temperature effect in the catalytic hydrogenation of unsaturated aromatic ketones was observed using nickel catalyst.[51] The carbon–carbon double bond was hydrogenated at room temperature, while the carbonyl group was reduced to an alcohol at 120 °C; at even higher temperatures (260 °C) the phenyl group was hydrogenated to a cyclohexyl group.

α-Keto alcohols (acyloins) were hydrogenated to the mixture of glycols (**5**) over copper chromite under relatively strong conditions (150 °C, 100 atm; equation 3).[52] Benzoquinone was converted to hydroquinone easily over a palladium catalyst under mild conditions,[53] and 1,4-cyclohexanedione was hydrogenated to 4-hydroxycyclohexanone using ruthenium on silica.[54]

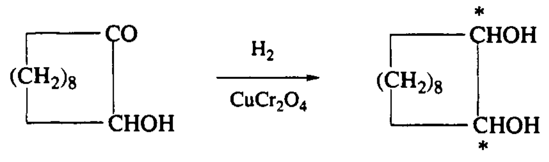

$$\begin{matrix} (CH_2)_8 \left[ \begin{matrix} CO \\ CHOH \end{matrix} \right. \end{matrix} \xrightarrow[CuCr_2O_4]{H_2} \begin{matrix} (CH_2)_8 \left[ \begin{matrix} \overset{*}{C}HOH \\ \underset{*}{C}HOH \end{matrix} \right. \end{matrix} \qquad (3)$$

(**5**)

## 1.6.3 HETEROGENEOUS CATALYTIC HYDROGENATION OF THE C=N BOND

### 1.6.3.1 Hydrogenation of Oximes and Hydrazones

The carbon–nitrogen double bonds of oximes and hydrazones are hydrogenated to form the corresponding amines by heterogeneous catalytic hydrogenation.

The oximes of cyclohexanone and cycloheptanone were converted to cyclohexylamine[9] and cycloheptylamine[55] in good yield over Raney nickel or rhodium on alumina, respectively. Benzaldehyde oxime was converted to benzylamine over a nickel catalyst in good yield.[56] The stereochemistry of the hydrogenation is different depending on the catalyst and the reaction conditions. The catalytic hydrogenation of 2-alkylcyclohexanone oxime (**6**) over platinum yielded *cis*-2-alkylcyclohexylamine as the major product,[57] and hydrogenation over Raney nickel gave the *trans* product (Scheme 2).[58] Other stereochemically interesting results are obtained by heterogeneous catalytic hydrogenation of the monooximes of diketones such as compounds (**7**)[59,60] and (**8**).[61] These were both hydrogenated to form *erythro*-amino alcohols over platinum oxide and palladium catalysts.[62,63] The stereochemistry of the catalytic hydrogenation will be discussed later along with studies on asymmetric syntheses using heterogeneous catalytic hydrogenation (Section 1.6.4).

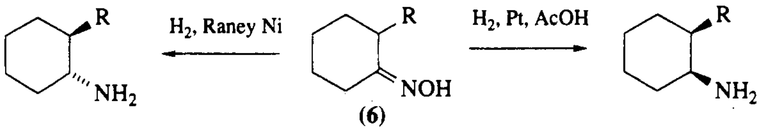

**(6)**

**Scheme 2**

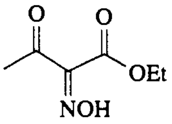

(**7**)

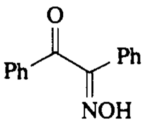

(**8**)

The phenylhydrazone of acetone was hydrogenated to form *N*-isopropyl-*N*-phenylhydrazine over colloidal platinum.[64] However, a similar hydrazone, 1-(*N*-acetyl-2-piperidyl)acetone phenylhydrazone, was hydrogenated and hydrogenolyzed to form 1-(*N*-acetyl-2-piperidyl)-2-aminopropane in good yield.[65]

### 1.6.3.2 Hydrogenation of Schiff's Bases (Aldimines and Ketimines)

Hydrogenation of a mixture of amines and aldehydes or ketones results in the formation of unsymmetrical secondary amines. The hydrogenation of the intermediate aldimine or ketimine can be carried out by heterogeneous catalytic hydrogenation over metal catalysts such as platinum, palladium, nickel or Raney nickel. The overall reaction can be regarded as an alkylation of the amino compounds, and also as a reductive amination of the aldehyde or ketone (Scheme 3).

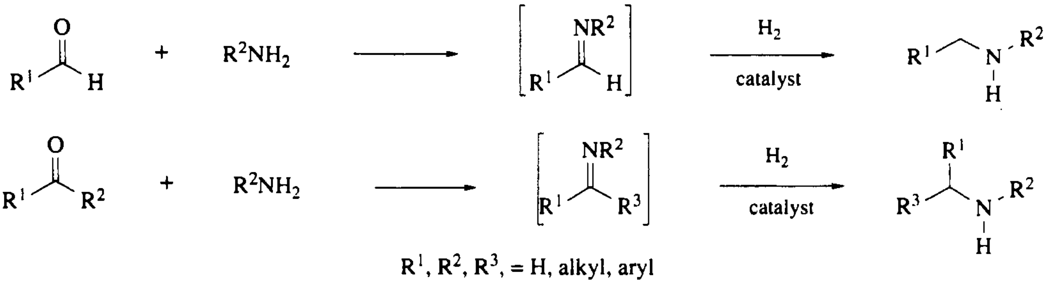

$R^1, R^2, R^3, =$ H, alkyl, aryl

**Scheme 3**

The intermediate aldimine or ketimine is prepared from the amine and the aldehyde or ketone in an organic solvent, and is usually hydrogenated without isolation. However, in some cases, the intermediate azomethine compounds are isolated and then hydrogenated. Extensive studies on this two-step hydrogenation have been carried out, and the reactions have been reviewed by Emerson.[1] Therefore, the catalytic hydrogenation of aldimines and ketimines are not included in this review.

Catalytic hydrogenation of aldehydes and ketones in the presence of ammonia is used for the preparation of primary amines. The reaction product usually contains the secondary amine and an excess of ammonia should be used to minimize its formation. On the other hand, symmetrical secondary amines can be synthesized by catalytic hydrogenation using an excess of aldehyde.[66]

The synthesis of α-amino acids has been carried out from α-keto acids by reductive amination using a platinum or palladium catalyst, mimicking their biosynthesis. Thus alanine,[67] leucine,[68] phenylalanine,[67–69] aspartic acid[67] and glutamic acid[67,70] have been synthesized by reductive amination. When an optically active primary amine is used, asymmetric induction can proceed in the course of the reductive amination.

## 1.6.4 DIASTEREOSELECTIVE ASYMMETRIC HYDROGENATION

### 1.6.4.1 Asymmetric Hydrogenation of the C═O Bond

Catalytic hydrogenation of esters of α-keto acids with optically active alcohols using metal catalysts has been carried out.[71–73] The alcohols used were (–)-menthol and (+)-borneol, and the catalysts used were $PtO_2$, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$ and Raney nickel. The optical purities of the resulting α-hydroxy acid esters were not high. When (–)-menthyl benzoylformate (**9**) and (+)-bornyl benzoylformate were hydrogenated over Raney nickel, $PtO_2$ or alkali-treated Pd/C, the major products were (–)-and (+)-mandelate, respectively.[72] However, when acid-treated catalysts were used, the hydrogenation products were (+)- and (–)-mandelate, respectively (Scheme 4). Thus the configuration of the resulting mandelic acid was not determined by the chiral source but by the manner in which the catalyst was modified.[71,72] Similar inversion of configuration was observed in the catalytic hydrogenation of (*S*)-(–)-α-phenethyl benzoylformate[73] and menthyl α-naphthylglyoxylate.[74] However, in the catalytic hydrogenation of menthyl pyruvate, the change in configuration of the product using a basic or an acidic catalyst was not observed.[75] The change was observed in the hydrogenation of aromatic α-keto acid esters, but not when aliphatic α-keto acid esters were used.[72–76] In order to explain the changeover in configuration, the substrate was presumed to prefer an *s-trans* conformation when an alkali catalyst was used, and an *s-cis* conformation with an acidic catalyst.[72–75] The interconversion was explained by the formation of a hemiketal (equation 4),[77] so that the *s-trans* conformer was converted to an *s-cis* conformer in acidic media and then hydrogenated to form the α-hydroxy acid ester that has a configuration opposite to that obtained using the basic catalyst.

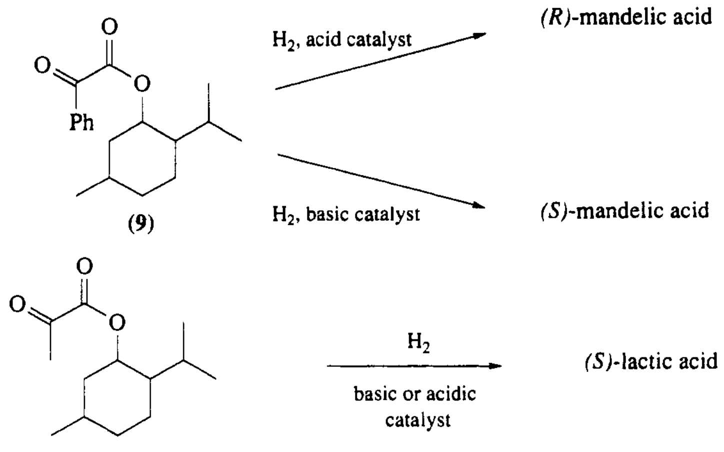

Scheme 4

The catalytic hydrogenation of the benzoylformic acid amides of optically active amino acid esters was carried out.[78] When the (*S*)-amino acid ester was used, the resulting mandelic acid had the (*R*)-configuration. When pyruvic acid amides of optically active benzylic amines were hydrogenated over palladium, optically active lactic acid was obtained in relatively high enantiomeric excess (*ee* 60%).[79] The

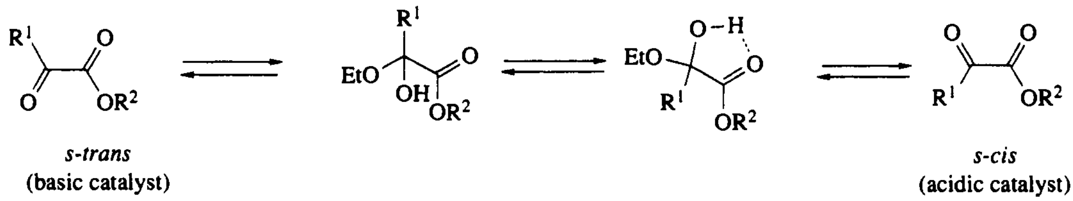

(4)

asymmetric hydrogenation shows a solvent and also a temperature effect.[80] The catalytic hydrogenation of pyruvic acid amides of optically active amino acid esters also showed a solvent effect: with a polar solvent, the configuration of the lactic acid was (*R*), but with a less polar solvent, the percentage of the (*S*)-isomer increased.[81] The solvent effect was explained by assuming competing substrate–catalyst complexes (**10**) and (**11**), as shown in Scheme 5 (chelation mechanism). In the less polar solvent, the interaction between the ester carbonyl and the catalyst was greater, and (**11**) could be the major conformation resulting in (*S*)-lactic acid. Asymmetric catalytic hydrogenation of *N*-pyruvoyl-(*S*)-proline esters was carried out under various conditions to afford *N*-[(*S*)-lactoyl]-(*S*)-proline esters with a diastereomeric excess (*de*) of up to 60%.[82] The effects of temperature and the bulkiness of the ester groups were studied, and the steric course explained by the chelation mechanism which will be described later. Catalytic hydrogenation of benzoylformic acid amide with optically active *trans* 2,5-disubstituted pyrrolidine was carried out over Pd/C, and the *de* of the product was 56%.[83]

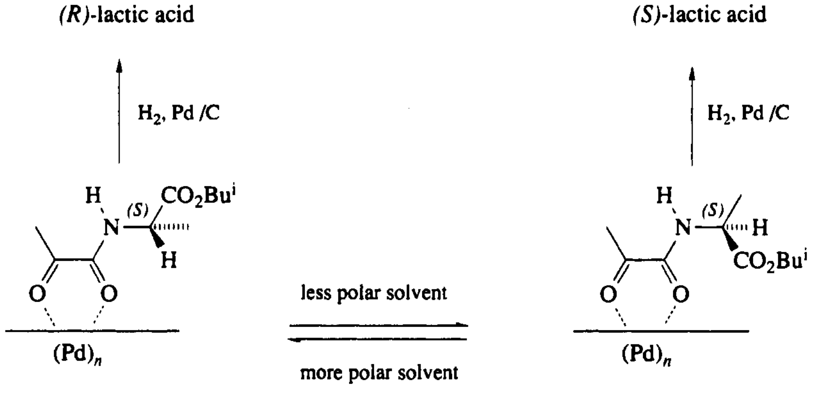

(**10**) (**11**)

**Scheme 5**

### 1.6.4.2 Asymmetric Hydrogenation of the C=N Bond

Numerous asymmetric catalytic hydrogenations of carbon–nitrogen double bonds have been carried out.[84,85] Some of the substrates used are oximes and hydrazones, but most of the reactions were carried out using Schiff's bases of ketones. α-Keto acids are precursors of α-amino acids in biosynthesis, and therefore α-keto acids have been used for the asymmetric syntheses of α-amino acids.[84,85]

An aqueous alkaline solution of a mixture of (*S*)-arginine and pyruvic acid was hydrogenated over platinum oxide to yield (+)-isooctopine (**12**),[86,87] a diastereomer of natural octopine, with 70% *de* (equation 5). Detailed syntheses and properties of the diastereomers of octopine have been reported.[88]

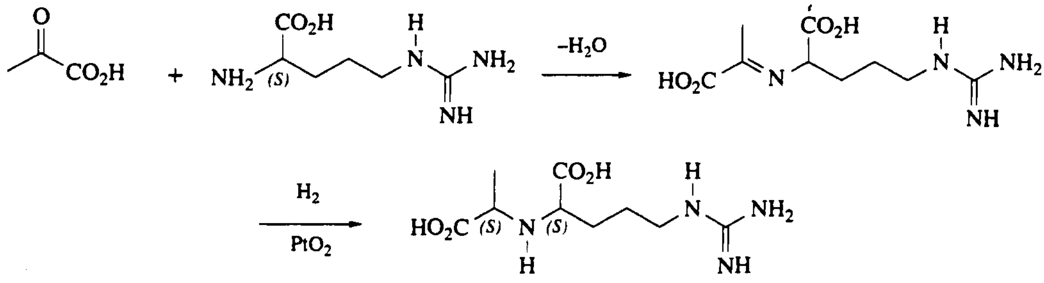

(5)

(**12**)

A systematic study of the catalytic hydrogenation of the Schiff's bases prepared from α-keto acids and optically active benzylic amines in organic solvents has been carried out, and some of the results summarized.[84,85] The resulting imino acids were hydrogenolyzed to obtain α-amino acids (equation 6). The reaction is actually a hydrogenolytic asymmetric transamination between amino compounds and α-keto acids. The chemical yields were in the range 20–80% and the enantiomeric excesses of the resulting amino acids were 12–81%. The sense of the asymmetric hydrogenation was based on the Prelog rule.[89,90] Asymmetric syntheses of alanine, α-aminobutyric acid, phenylglycine, phenylalanine and glutamic acid were carried out starting with the Schiff's bases prepared from the corresponding α-keto acids and optically active α-(*S*)-methylbenzylamine [Me(–)], α-(*S*)-ethylbenzylamine [Et(–)] and α-(*R*)-(1-naphthyl)ethylamine [Naph(+)].[91,92] The results obtained using α-methylbenzylamine were similar to those obtained earlier.[89] However, the results with the other amines were quite different from those expected from the steric course proposed.[90] The results, shown in Table 2,[91,92] suggest that the most probable conformation of the substrate in the catalytic hydrogenation could be structure (**13**). Structure (**13**) results in the formation of (*S*)-amino acid when (*S*)-amine is used, and the substituent effect of the α-keto acid can be explained by assuming conformation (**13**). The substrate initially interacts with the catalyst to form a substrate–catalyst complex, as shown in structure (**14**), which is adsorbed onto the catalyst from the less bulky face of the molecule, where the catalytic hydrogenation takes place.

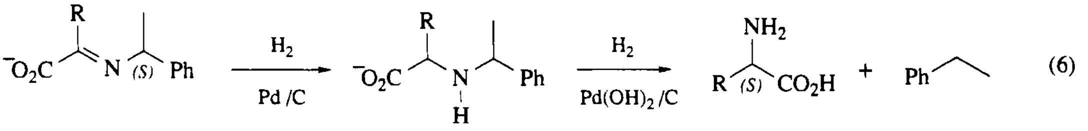

(6)

Table 2 Asymmetric Synthesis of Amino Acids by Catalytic Hydrogenation[92]

| *α-Keto acid* | *Amine* | *Amino acid* | *ee (%)* |
|---|---|---|---|
| $MeCOCO_2H$ | Me(–) | (*S*)-Alanine | 67 |
| | Et(–) | (*S*)-Alanine | 52 |
| | Naph(+) | (*R*)-Alanine | 83 |
| $EtCOCO_2H$ | Me(–) | (*S*)-Butyrine | 44 |
| | Et(–) | (*S*)-Butyrine | 33 |
| $PhCOCO_2H$ | Me(–) | (*S*)-Phenylglycine | 30 |
| | Et(–) | (*S*)-Phenylglycine | 24 |
| $PhCH_2COCO_2H$ | Me(–) | (*S*)-Phenylglycine | 14 |
| | Et(–) | (*S*)-Phenylglycine | 10 |
| $HO_2C(CH_2)_2COCO_2H$ | Me(–) | (*S*)-Glutamic acid | 12 |
| | Et(–) | (*S*)-Glutamic acid | 6 |

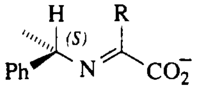

(**13**)

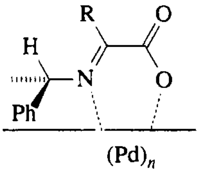

(**14**)

The 'chelation mechanism' has been tested in several hydrogenation reactions of the Schiff's bases of α-keto acids and their derivatives in organic solvents. A solvent effect in the hydrogenolytic asymmetric transamination between benzylic amines and α-keto acids[91] and their esters[93,94] was observed (Table 3). The effect is explained by the chelation mechanism as shown in Scheme 6 using the unchelated structure (**15**). Ethyl phenylglycinate can also be used as a chiral source for the asymmetric synthesis of amino acids, due to the ability of phenylglycine to be hydrogenolyzed to phenylacetic acid and ammonia in alkaline conditions.[95,96] Similarly an amino alcohol, 2-amino-2-phenylethanol,[94] amphetamine[97] and methylbenzylamine[98] have all been used as chiral sources which can also be hydrogenolyzed.

Studies on the transamination reaction between *t*-butyl esters of optically active amino acids and methyl pyruvate were carried out, as shown in Scheme 7.[99] The resulting iminodicarboxylic acid (**16**) was partially hydrolyzed and then oxidized with *t*-butyl hypochlorite to form alanine. The oxidation is a generally applicable one, and the optical purity of alanine is high (50–70%). Similar asymmetric transamination between an (*S*)-amino acid and ketones was carried out.[100] Catalytic hydrogenation of the Schiff's bases prepared from α-keto acid esters and amino acid esters was carried out, and a substituent and temperature effect observed (*de* 40–70%).[101]

**Table 3** Solvent Effect in the Asymmetric Synthesis of Alanine Using Me (–)[91]

| *Solvent* | *Yield* (%) | *Configuration* | *ee* (%) |
|---|---|---|---|
| Hexane | 75 | (*S*) | 75 |
| AcOEt | 49 | (*S*) | 60 |
| DMFA | 47 | (*S*) | 50 |
| $Pr^iOH$ | 56 | (*S*) | 46 |
| MeOH | 61 | (*S*) | 38 |
| $MeOH:H_2O$ (1:2) | 75 | (*S*) | 35 |
| $MeOH:H_2O$ (1:4) | 76 | (*S*) | 29 |

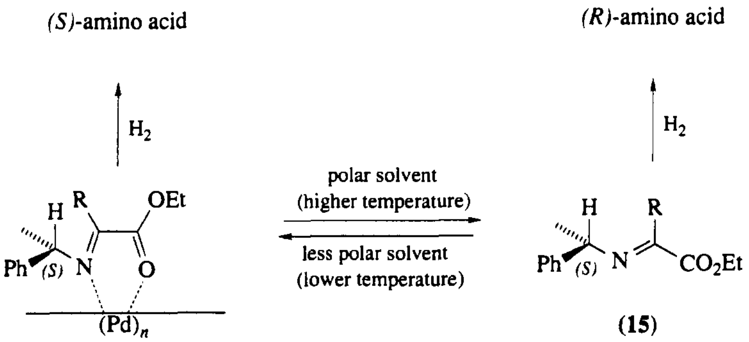
(S)-amino acid
(R)-amino acid
H2
H2
H
R
OEt
Ph
(S)
N
O
(Pd)n
polar solvent
(higher temperature)
less polar solvent
(lower temperature)
H
R
Ph
(S)
N
CO2Et
(15)

**Scheme 6**

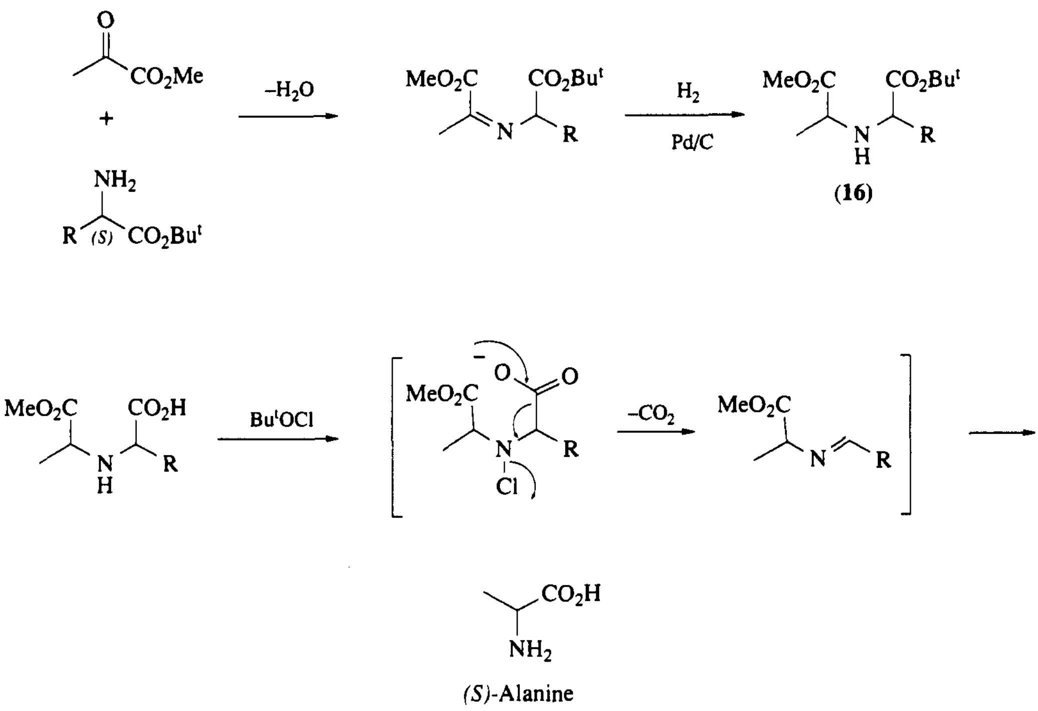
O
CO2Me
+
NH2
R
(S)
CO2But
-H2O
MeO2C
CO2But
N
R
H2
Pd/C
MeO2C
CO2But
N
H
R
(16)
MeO2C
CO2H
N
H
R
ButOCl
MeO2C
O
O
N
Cl
R
-CO2
MeO2C
N
R
CO2H
NH2
(S)-Alanine

$R = Pr^i, PhCH_2, Bu^i, Bu^tO_2CCH_2, Bu^tO_2CCH_2CH_2$

**Scheme 7**

In the hydrogenolytic asymmetric transamination between a benzylic amine and oxalacetic acid[102] the Schiff's base was hydrogenated in ethanol over palladium, but alanine rather than aspartic acid was the product (*ee* 52–69%; equation 7). A fast decarboxylation of the Schiff's base must have taken place. A study of the time course of the reaction indicated that after half an hour at room temperature, the Schiff's base of oxalacetic acid (**17**) was converted to that of pyruvic acid (**18**). Thus the reaction using oxalacetic acid is actually the same as using pyruvic acid in ethanol. The reaction is interesting in connection with aspartic acid β-decarboxylase.

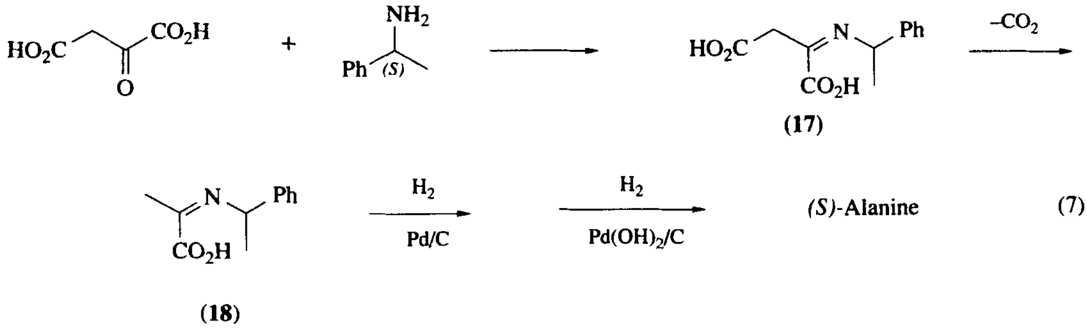

A clear temperature effect in the hydrogenolytic asymmetric transamination between optically active amines and ethyl pyruvate was observed (−20 to 65 °C).[103,104] At relatively low temperatures, when the optically active amine had the (*S*)-configuration, the resulting alanine also had the (*S*)-configuration. The *ee* of the (*S*)-alanine (80% *ee* at −20 °C) decreased as the reaction temperature increased, and at higher temperature (50 °C) the configuration of the alanine inverted to the (*R*)-configuration.

The temperature effect could be explained by the chelation mechanism.[91,92] The Schiff's base composed of α-keto acid and optically active amine interacted with the catalyst to form a substrate–catalyst complex (**14**) at lower temperature; at higher temperatures, the population of the unchelated structure (**15**) would increase as shown in Scheme 6. Asymmetric hydrogenation involving (*R*)-α-phenylglycinate and ethyl pyruvate has also been studied.[95,96]

An asymmetric catalytic hydrogenation of the Schiff's base of α-ketoacylamide derivatives $R^1C({=}NR^3)CONHR^2$ (**19**) was carried out.[105] In the synthesis of phenylglycine, when the chiral center was changed from (*S*)-α-methylbenzylamine to (*S*)-α-ethylbenzylamine, the configuration of the product was inverted.[92] In order to clarify this inversion in the sense of the induction, the Schiff's bases of pyruvylamino acid isobutyl esters were hydrogenated over palladium on charcoal.[106] When the chiral moiety was (*S*)-alanine, the configuration of the newly formed alanyl residue was predominantly (*R*) (ratio of diastereomers: 82:18). However, when (*S*)-α-aminobutyric acid was used, the configuration of the resulting alanine was inverted, and the ratio of diastereomers was now 29:71. The change of configuration in the catalytic hydrogenation was also explained by the chelation mechanism.[106]

Finally, some historical background for the 'chelation mechanism' in heterogeneous catalytic hydrogenation is given. It is known that the catalytic hydrogenation of benzil monooxime yields diphenylethanolamine. If the conformation of the substrate were planar and *anti*, as expected from steric and electronic properties, the resulting product would be the *threo* isomer as shown in equation (8). However, the resulting ethanolamine was predominantly the *erythro* isomer (equation 9).[107] Benzoin oxime also gave *erythro*-diphenylethanolamine.[108,110] Similar results have been reported in the synthesis of threonine[59,60,62,63] and phenylserine[109,111] by catalytic hydrogenation (Scheme 8). The catalytic hydrogenation is so specific that optically active *erythro*-diphenylethanolamine was converted to benzoin, and the oxime could be converted back to the original optically active *erythro*-diphenylethanolamine.[110] There-

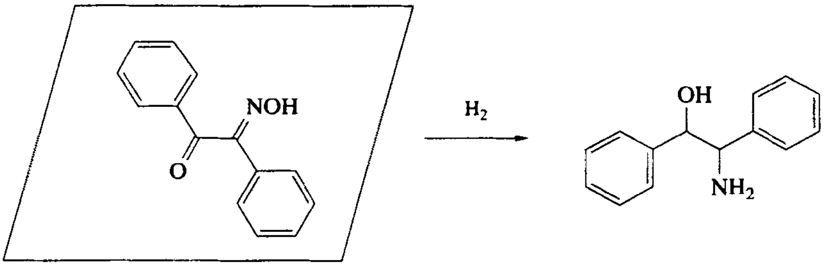

(8)

(*threo*)

fore, there must be some interaction between the substrate and the catalyst leading to an *s-cis* conformation. Chang and Hartung[111,112] proposed an interesting mechanism for the heterogeneous catalytic hydrogenation of α-oximino ketones that explains the stereoselectivity of the reaction whereby a single racemic modification is produced. This explanation can be regarded as a kind of chelation mechanism. Thus the predominant formation of the *erythro* isomer in the catalytic hydrogenation of benzil monooxime, benzoin oxime, ethyl acetoacetate oxime and ethylbenzoylacetate oxime can be explained by the formation of a substrate–catalyst complex prior to hydrogenation. Physicochemical evidence for the formation of a substrate–catalyst complex has also been obtained by IR absorption spectra of several substances on nickel or palladium surfaces.[113–115]

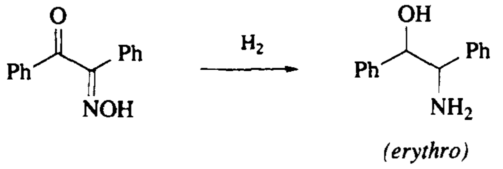

(9)

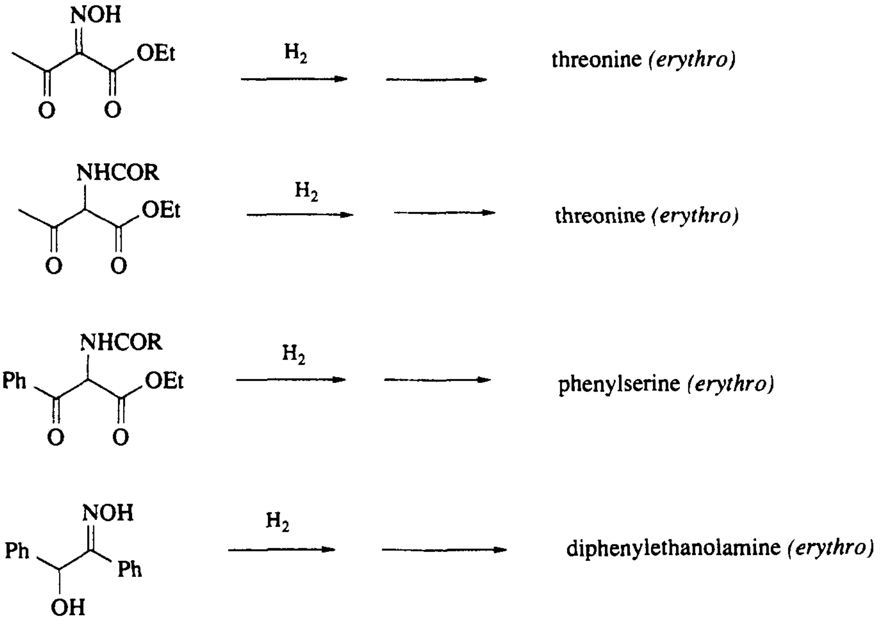

**Scheme 8**

## 1.6.5 HETEROGENEOUS CATALYTIC HYDROGENATION USING A CHIRAL CATALYST

Heterogeneous catalytic hydrogenation of a carbon–nitrogen double bond over a metal catalyst in the presence of a chiral compound was first carried out by Nakamura.[116] Acetophenone oxime was hydrogenated over platinum black with ethyl menthoxyacetate or tartaric acid to give α-methylbenzylamine with 15–18% *ee*.

Enantioselective heterogeneous catalytic hydrogenation using a chiral catalyst was pioneered by Akabori and Izumi, who prepared a palladium catalyst supported on silk fibroin. The oxime acetates of diethyl α-ketoglutarate or of ethyl phenylpyruvate were hydrogenated to form glutamic acid (7–15% *ee*) and phenylalanine (30% *ee*).[117–119] Similarly, a palladium–poly-L-leucine catalyst was used for the asymmetric synthesis of phenylalanine.[120]

### 1.6.5.1 Hydrogenation Using a Chirally Modified Catalyst

Systematic studies on the enantioselective heterogeneous catalytic hydrogenation of carbonyl compounds were carried out by Izumi using Raney nickel modified with various chiral reagents. Hydroxy acids or amino acids were used for the modification of the nickel catalyst, and (+)-tartaric acid (2*R*,3*R*) was found to be the best chiral modifying reagent. The substrates used were β-keto esters,[121,122] β-keto alcohols[123,124] and ketones.[125] Among these substrates, methyl acetoacetate is the best, and the hydrogenation of this compound has been investigated extensively using the chirally modified nickel catalyst (equation 10). The heterogeneous catalytic hydrogenation of carbonyl compounds using chirally modified nickel catalysts has been reviewed by Izumi,[126] Klabunovskii,[127] Fish[128] and Tai.[129]

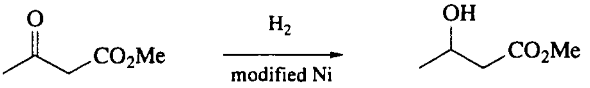

(10)

More than a hundred modifying reagents, which include amino acids and their derivatives, peptides, amino alcohols and hydroxy acids have been tested.[126] α-Amino acids or α-hydroxy acids were found to be effective modifying reagents in asymmetric hydrogenation. The order of the efficiency of the modifying reagents using Raney nickel in the hydrogenation of methyl acetoacetate is as follows: tartaric acid > malic acid > glutamic acid > aspartic acid > valine. The (*S*)-α-amino acid modified nickel gave methyl (*R*)-β-hydroxybutyrate in excess and (S)-α-hydroxy acid modified nickel gave (*S*)-β-hydroxybutyrate in excess (Scheme 9).[130] The pH and the temperature strongly affect the *ee* of the product. Sodium hydroxide is the best alkali hydroxide in the modification process, and when LiOH, KOH, RbOH and aqueous ammonia are used for the modification, the catalyst gives a low *ee* in the product.[131]

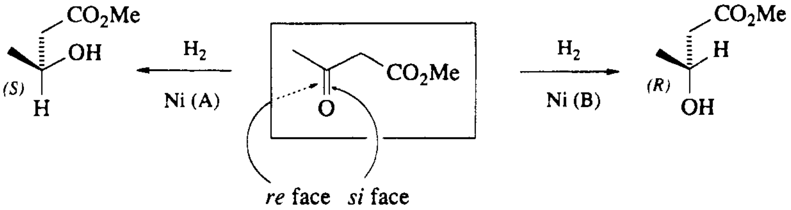

Ni (A): Modified with (*S,S*)-tartaric acid, (*S*)-malic acid, (*R*)-glutamic acid and (*R*)-valine
Ni (B): Modified with (*R,R*)-tartaric acid, (*R*)-malic acid, (*S*)-glutamic acid and (*S*)-valine

**Scheme 9**

Several other metal catalysts (Raney Co, Fe, Cu and Ru) have been investigated, but nickel catalysts show the highest activity in the asymmetric hydrogenation of ethyl acetoacetate.[132] Various nickel catalysts such as Raney nickel,[133–136] nickel acetate,[137] nickel carbonyl,[133] nickel oxide,[133,135] a nickel catalyst on Kieselguhr,[133,138] nickel on alumina[133] or on silica,[138,139] and a palladium-containing nickel catalyst on Kieselguhr[140] have been tested under various modifying and hydrogenation conditions.

The optical purity of the product is dependent not only on the preparation method of the catalyst, but also on the reaction conditions. Variables include the pressure of hydrogen, the solvent, the reaction temperature and others. The optical purity of the product is not affected by pressure at high pressure (30–120 kg $cm^{-2}$; 0.3–1.2 × $10^6$ Pa), but it is affected in a complicated way at lower pressure.[142] Similarly, a change in the reaction temperature does not affect the optical purity of the product at high pressure, but it is affected by the reaction temperature at 1 atm of hydrogen.[142]

The solvent has a large effect on the reaction. It was first thought that a polar solvent such as methanol or ethanol was best, but later studies indicated that aprotic solvents like tetrahydrofuran and ethyl acetate are better.[143] The best solvent examined to date is methyl propionate.[121]

Additives such as water, carboxylic and other organic acids, and some inorganic salts enhance the optical purity of the product.[144] Table 4[133] shows the effect of supplementary reagents in the modification

**Table 4** Hydrogenation of Methyl Acetoacetate over Raney Nickel Modified with Tartaric Acid–Inorganic Salt

| *Inorganic salt* | $[\alpha]_D^{20}$ *of product* | *ee (%)* |
|---|---|---|
| None | − 8.99 | 39 |
| NaF | −13.95 | 61 |
| NaCl | −16.55 | 72 |
| NaBr | −19.07 | 83 |
| NaI | −11.74 | 51 |
| $Na_2SO_4$ | −12.95 | 56 |
| $LiBr.H_2O$ | −14.25 | 62 |
| $NiBr_2$ | −14.36 | 63 |

of Raney nickel with tartaric acid.[145] The optical purity increased considerably with the addition of inorganic salts, especially of sodium bromide. Thus Raney nickel, modified in a solution of tartaric acid with sodium bromide, gave a higher level of optical purity without any loss of activity.[121,133,135]

In the following few paragraphs, some typical examples of the catalytic hydrogenation of alkyl acetoacetate with Raney nickel modified by (+)-tartaric acid and sodium bromide[146] will be described. The *ee* of the product is close to 88% (*R*) for all of the higher alkyl esters shown in Table 5.[146–148] Higher homologs of acetoacetate also give products of high optical purity (83–88% *ee*).[147,148]

**Table 5** Hydrogenation of Alkyl Acetoacetate over Raney Nickel Modified with (+)-Tartaric Acid and NaBr

| *β-Keto ester* $R^1COCH_2COOR^2$ | | *ee* (%) | *Configuration* |
|---|---|---|---|
| $R^1$ | $R^2$ | | |
| Me | Me | 83.0–85.0 | (*R*) |
| Me | Et | 87.9 | (*R*) |
| Me | $Pr^n$ | 87.6 | (*R*) |
| Me | $Pr^i$ | 87.7 | (*R*) |
| Me | $Bu^n$ | 88.0 | (*R*) |
| Me | $Bu^i$ | 88.1 | (*R*) |
| Me | n-$C_8H_{17}$ | 87.7 | (*R*) |
| Et | Me | 86.0 | (*R*) |
| $Pr^n$ | Me | 87.0 | (*R*) |
| $Pr^i$ | Me | 87.5 | (*R*) |
| $Bu^n$ | Me | 86.7 | (*R*) |
| $Bu^i$ | Me | 85.5 | (*R*) |
| n-$C_8H_{17}$ | Me | 87.0 | (*R*) |

Enantioselective hydrogenations of acetylacetone[149] and other β-diketones[150] were carried out using the same modified nickel catalyst. The hydrogenation of acetylacetone proceeds stepwise to form 4-hydroxy-2-pentanone, which is further hydrogenated to 2,4-pentanediol.[149] The first step of the hydrogenation is the usual enantioselective reaction yielding preferentially the (*R*)-keto alcohol (**20**; 87%). In the second step, both diastereoselective and enantioselective effects operate simultaneously. The (*R*)-keto alcohol is converted mainly to the (*R*,*R*)-diol (**21**; 78.3%), and the ratio of the minor diastereoisomers is shown in Scheme 10. The composition of the four diastereoisomers in the reaction products indicates that the stereoselective hydrogenation of the (*R*)-keto alcohol (**20**) to (*R*,*R*)-diol (**21**) is highly selective (90%). The minor product, (*S*)-keto alcohol, was converted to (*S*,*R*)- and (*S*,*S*)-diol in almost equal amounts. Thus, the enantioselective and diastereoselective effects function in the same direction to form the (*R*,*R*)-diol but oppose each other in the hydrogenation of the (*S*)-keto alcohol. When the hydrogenation of racemic keto alcohol was stopped halfway, the remaining keto alcohol was (*S*)-rich and the hydrogenated diol was (*R*,*R*)-rich, which indicates that kinetic resolution is taking place. The resulting (*R*,*R*)-diol is easily purified by recrystallization.[151]

In addition to alkyl acetoacetates and acetylacetone, several other carbonyl compounds were used for hydrogenation using the same modified nickel catalyst. The enantioselective hydrogenation of methyl alkyl ketones in the presence of pivalic acid gave the corresponding chiral secondary alcohols [(*S*)-isomer, *ee* 49–74%].[152] Similarly, the hydrogenation of 4-hydroxy-2-butanone and its methyl ether in the presence of acetic acid gave secondary alcohols [(*R*)-isomer, *ee* 68–70%].[153] The hydrogenation of β-keto sulfone proceeded smoothly to form the corresponding secondary alcohol [(*R*)-isomer, *ee* 67–71%] in the presence of acetic acid.[154]

Heterogeneous catalytic hydrogenation of the methyl esters of α-keto acids over modified metal catalysts other than nickel have been studied using a cinchonidine-modified platinum catalyst.[155–157] Methyl pyruvate and methyl benzoylformate were hydrogenated to form methyl (*R*)-lactate and (*R*)-mandelate with high *ee* (81–84%).

These studies on catalytic hydrogenation using chirally modified catalysts suggest that enantioselective hydrogenation is still an open area for the study of asymmetric synthesis, especially as a practical synthetic method for chiral nonracemic organic compounds. However, catalytic hydrogenation is affected by so many variables that it is not easy to optimize the stereoselectivity. Many physicochemical studies have been made to elucidate the reaction mechanism, and these have been reviewed by Tai.[129]

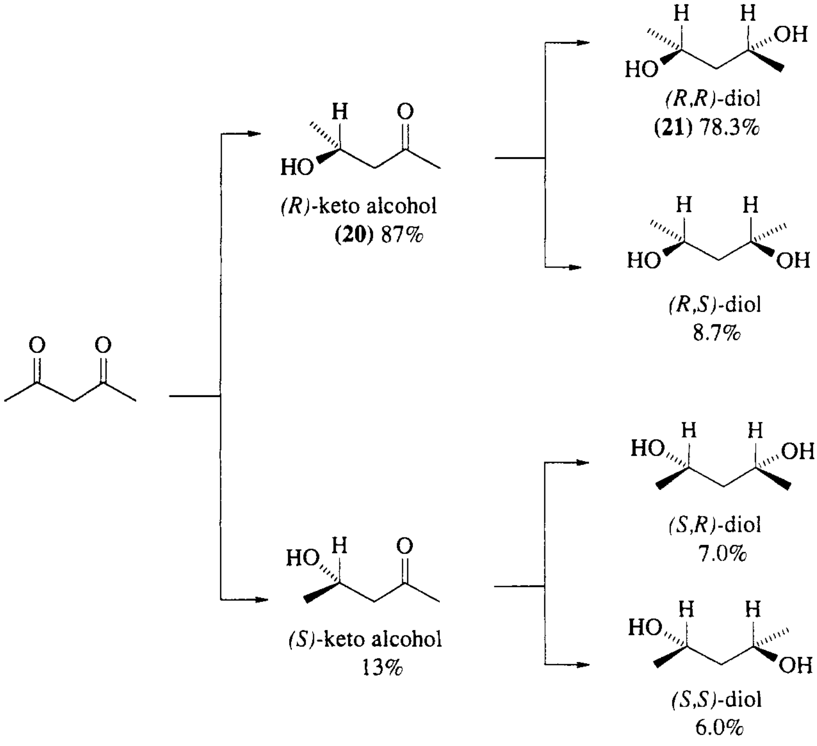

Scheme 10

## 1.6.6 HOMOGENEOUS CATALYTIC HYDROGENATION OF C=O AND C=N DOUBLE BONDS

In 1938, Calvin reported that *p*-benzoquinone could be reduced by hydrogen in the presence of copper salts [$Cu(OAc)_2$ and bis(salicylaldehydato)copper][158,159] and this is one of the first examples of a homogeneous catalytic hydrogenation. Hydrogenation of quinone in the presence of a palladium complex of ethylenediamine ([Pd(en)]$Cl_2$)[160] and of the rhodium complexes ([$Rh(NH_3)_5(OH)_2]Cl_3$, [$Rh(NH_3)_4Cl_2$])[161,162] has also been reported. In the middle 1960s, rhodium–phosphine complexes, the Wilkinson catalysts, were synthesized[163,164] and their usefulness in homogeneous catalytic hydrogenation was demonstrated.[165–167]

### 1.6.6.1 Homogeneous Hydrogenation by Rhodium or Other Complexes[2,168–172]

Early work on the hydrogenation of carbonyl compounds using Wilkinson's rhodium complex were unsuccesful, due to the low reactivity of the carbonyl group and the high susceptibility for decarbonylation.[173] The first successful reduction of a carbonyl compound was achieved for ketones using soluble rhodium complexes. Cationic rhodium complexes ($[RhH_2P_2S_2]^+ClO_4^-$ or $[RhH_2P_2S_2]^+PF_6^-$; S = solvent, P = phosphine ligand) possessing ligands ($PPh_2Me$, $PPhMe_2$, $PMe_3$) more basic than the conventional triphenylphosphine were found to be effective (equation 11).[174] The first homogeneous asymmetric catalytic hydrogenations of ketones were performed in the presence of a rhodium complex with (*R*)-(+)-benzylmethylphenylphosphine as a ligand (equation 12). Several chiral phosphine ligands have been employed for the hydrogenation of carbonyl compounds,[175–180] and a number of asymmetric hydrogenations are described below. Asymmetric hydrogenations of acetophenone and related compounds were carried out to give *ee* values of up to 95% using (aminoalkylferrocenyl)phosphine as a chiral ligand (equation 13).[179,180] A rhodium phosphine complex with a neutral phosphine ligand (BPPM) was found to be effective for the hydrogenation of α-ketocarboxylic esters[181] and ketopantolactone (86.7% *ee*; equation 14).[182] Catalysts with a phosphine ligand (BPPM or DIOP;**22**) were tested for the asymmetric hydrogenation of *N*-(α-ketoacyl)amino acid esters, but this chiral ligand was not effective.[183]

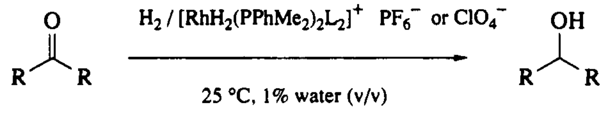
O
R
R
H2 / [RhH2(PPhMe2)2L2]+ PF6− or ClO4−
25 °C, 1% water (v/v)
OH
R
R

$R_2$ = Me, Me; Me, Et; Ph, Me

(11)

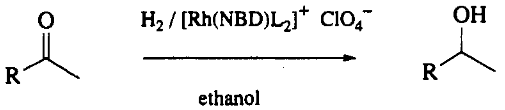
O
R
H2 / [Rh(NBD)L2]+ ClO4−
ethanol
OH
R

(12)

R = Ph, *ee* = 8.6% *(S)*; R = Et, *ee* = 1.9% *(R)*; L = *(R)*-benzylmethylphenylphosphine;
NBD = norborna-2,5-diene

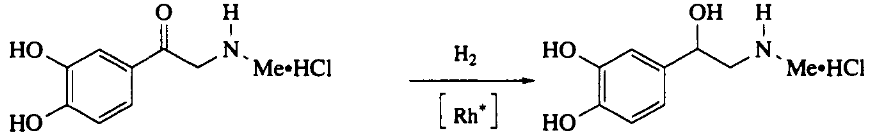
HO
HO
O
H
N
Me•HCl
H2
[Rh*]
HO
HO
OH
H
N
Me•HCl

(13)

conversion 100%; 95% *ee*

$[Rh^*]$ = $[Rh\{(R,S)\text{-BPPFOH}\}(NBD)]^+ ClO_4^-$

*(R)-(S)*-BPPFOH :

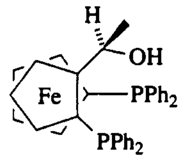
H
OH
Fe
PPh2
PPh2

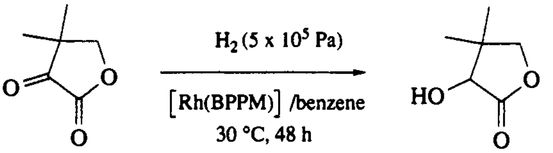
O
O
O
H2 (5 x 10^5 Pa)
[Rh(BPPM)] /benzene
30 °C, 48 h
HO
O
O

(14)

conversion 100%; *ee* 86.7%

BPPM =

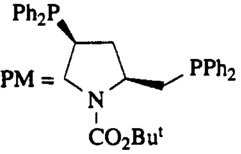
Ph2P
PPh2
N
CO2Bu^t

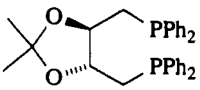
O
O
PPh2
PPh2

(–)-DIOP **(22)**

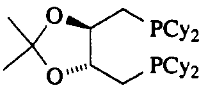
O
O
PCy2
PCy2

(–)-CyDIOP **(23)**

Cy = cyclohexyl

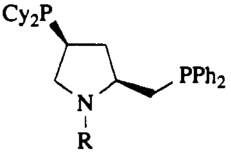
Cy2P
PPh2
N
R

**(24)**

BCPM: R = $CO_2Bu^t$
MCPM: R = $CO_2Me$
BCCPM: R = $CONHBu^t$
MCCPM: R = CONHMe

On the other hand, rhodium complexes with fully alkylated phosphine ligands[184,185] were used for the hydrogenation of carbonyl compounds,[184] α-ketoamides[184–187] and ketopantolactone (66% *ee*).[187] When a rhodium complex with CyDIOP (**23**) was used, a slightly higher asymmetric yield (71% *ee*) was observed in the hydrogenation of α-ketoamides.[188] Hydrogenation of *N*-(α-ketoacyl)amino acid esters was also performed by using a complex containing CyDIOP to give *N*-mandeloylamino acid esters with 72% *de* (equation 15).[189] Asymmetric hydrogenations of ketopantolactone (92% *ee*; equation 16),[190] α-keto esters (87% *ee*) and α-keto acetals[191] were carried out with the rhodium catalysts containing the ligands (**24**).

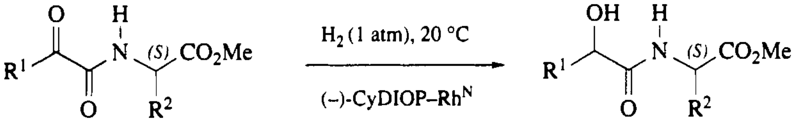
O
H
N
(S)
CO2Me
R1
O
R2
H2 (1 atm), 20 °C
(–)-CyDIOP-RhN
OH
H
N
(S)
CO2Me
R1
O
R2

(15)

$R^1$ = Ph, $R^2$ = $CH_2Ph$; conversion 100%; *de* 72%

(–)-CyDIOP–$Rh^N$ = (–)-CyDIOP + 1/2 $[Rh(C_2H_4)_2Cl]_2$

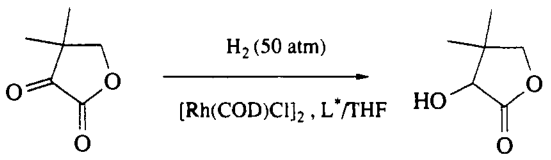
O
O
O
H2 (50 atm)
[Rh(COD)Cl]2 , L*/THF
HO
O
O

(16)

L* = BCPM: conversion 100%; *ee* 92% *(R)*

Several studies on the hydrogenation of carbonyl compounds using cobalt complexes have been reported,[192–195] including the hydrogenation of benzil in the presence of bis(dimethylglyoximato)cobalt(II)–chiral amine complexes.[193] The highest *ee* (78%) was obtained when quinine was used as the chiral base (equation 17).[194] Cyano cobalt complexes have also been reported to be effective for the hydrogenations of ketones.[196,197]

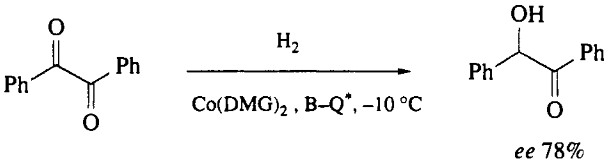
O
Ph
Ph
O
H2
Co(DMG)2 , B–Q*, –10 °C
OH
Ph
Ph
O
ee 78%

(17)

DMG = dimethylglyoxime; Q = quinine; B = benzylamine

Ruthenium complexes have been used for the hydrogenation of alkenes[2] but they had not been used for hydrogenations of carbonyl compounds until recently, when several highly selective catalytic hydrogenations of carbonyl compounds (β-keto esters, α-diketones, α-amino ketones *etc.*, *ee* > 95%) were reported using BINAP–$Ru^{II}$ complexes (equation 18).[198–202]

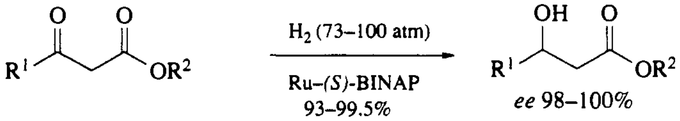
O
O
R1
OR2
H2 (73–100 atm)
Ru-(S)-BINAP
93–99.5%
OH
O
R1
OR2
ee 98–100%

(18)

$R^1$ = Me, Et, Bu, $Pr^i$; $R^2$ = Me, Et, $Pr^i$, $Bu^t$

(*S*)-BINAP =

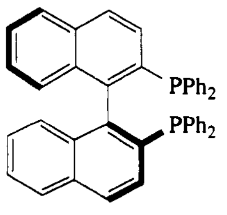

Ru–BINAP = $RuCl_2$ {(*S*)- or (*R*)-BINAP}

There are some reports on the asymmetric catalytic hydrogenation of C=N double bonds.[176,188,197] Rhodium phosphine complexes do not have high activity, and the stereoselectivity is low.[176,188] Homogeneous hydrogenation of oximes,[188] Schiff's bases[176] and cyclic imines[203] have been reported. A cyano cobalt complex has been used for the homogeneous catalytic hydrogenation of oximes and Schiff's bases[197] but the degree of asymmetric induction is unknown.

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# 1.7

# Reduction of C=X to CHXH by Chirally Modified Hydride Reagents

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## 1.7.1 INTRODUCTION

The modification of aluminum or boron hydrides with chiral protic substances, such as R*OH or RR*NH, generates useful reagents for the asymmetric reduction of prochiral ketones or imines leading to optically active secondary alcohols and amines, respectively. Some reviews have appearered in the literature.[1–11]

## 1.7.2 ASYMMETRIC REDUCTIONS OF THE CARBONYL GROUP

In 1951 Bothner-By first attempted asymmetric reductions based on the conversion of lithium aluminum hydride (LAH) into a chiral alkoxy derivative by reaction with (+)-camphor.[12] Since this pioneering work, the use of chirally modified LAH reagents has been the focus of much attention. In 1979, the first virtually complete enantiofacial recognition of prochiral carbonyl compounds was accomplished by using LAH modified with optically pure 2,2′-dihydroxy-1,1′-binaphthyl and a simple alcohol (BINAL-H).[34] Asymmetric reduction with chiral 2,5-dimethylborolane also gave alcohols in high optical yields.[108] Recently, excellent results have been obtained using a chirally modified sodium borohydride reagent (K-glucoride),[90] and chirally modified borane reagents.[100,102] The latter is particularly useful since chirality is introduced using a catalytic quantity of a chiral source.

Although *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane and related substances have also been developed as efficient asymmetric reducing agents for carbonyl compounds (Volume 8, Chapter 1.3), we discuss here only asymmetric reductions using chirally modified metal hydride reagents. The asymmetric hydrosilylation of a carbonyl group catalyzed by a chirally modified transition metal is mentioned briefly.

### 1.7.2.1 Chirally Modified Lithium Aluminum Hydride Reagents

Most reactions have been conducted using readily available, naturally occurring, chiral modifiers. The auxiliaries employed for the modification of LAH are classified into three types: (i) alcohol modifiers; (ii) dialkylamino alcohol modifiers; and (iii) primary or secondary amines and amino or monoalkylamino alcohol modifiers. Most asymmetric reductions have been investigated with acetophenone (**1**) as the substrate. Structures (**3**) to (**24**) summarize the chiral modifiers, enantiomeric excesses (*ee*) and absolute configurations of the 1-phenyl-1-ethanol (**2**) produced.

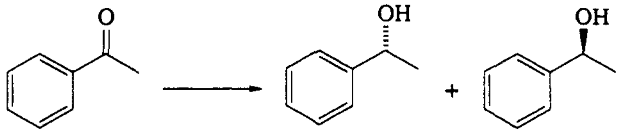

(**1**) *(R)*-(**2**) *(S)*-(**2**)

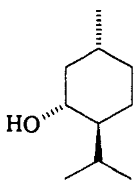

(**3**)

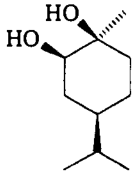

(**4**) 30% *ee*, *(R)*

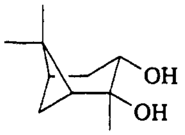

(**5**)

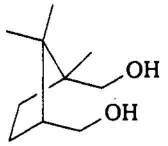

(**6**) 18% *ee*, *(R)*

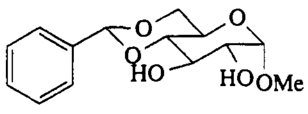

(**7**) 7.7% *ee*, *(S)*

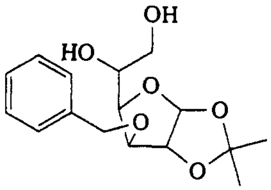

(**8**) 6% *ee* *(S)*

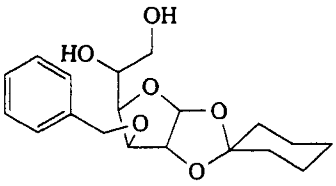

(**9**) 71% *ee*, *(R)*

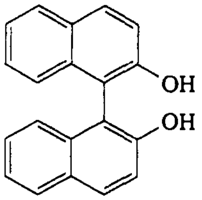

(**10**) 95% *ee*, *(R)*→*(R)* and *(S)*→*(S)*

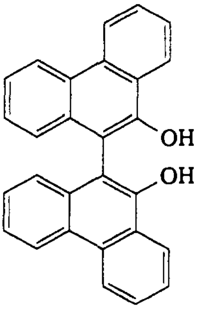

(**11**) 97% *ee*, *(R)*→*(R)* and *(S)*→*(S)*

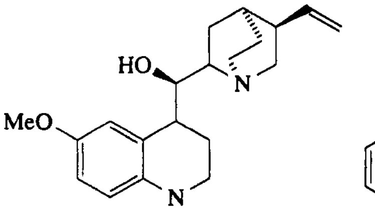

**(12)** 48% *ee*, *(R)*

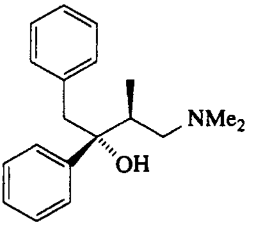

**(13)** 75% *ee*, *(R)*

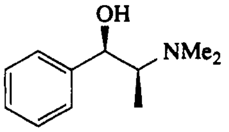

**(14)** 83% *ee*, *(R)*

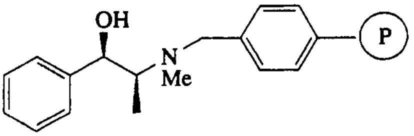

**(15)** 79% *ee*, *(R)*

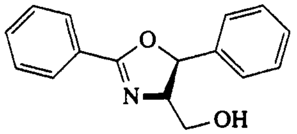

**(16)** 65% *ee*, *(R)*

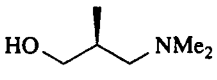

**(17)** 60% *ee*, *(S)*

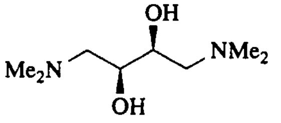

**(18)** 42% *ee*, *(S)*→*(S)* and *(R)*→*(R)*

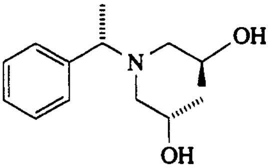

**(19)** 82% *ee*, *(R)*

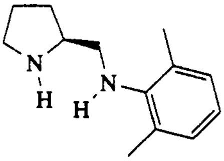

**(20)** 95% *ee*, *(S)*

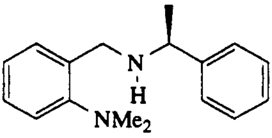

**(21)** 43% *ee*, *(R)*

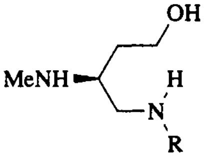

**(22)** 51% *ee*, *(S)*

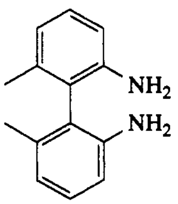

**(23)** 46% *ee*, *(R)*→*(R)* and *(S)*→*(S)*

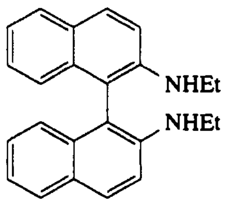

**(24)** 43% *ee*, *(R)*→*(R)* and *(S)*→*(S)*

### *1.7.2.1.1 Alcohol modifiers*

A large number of asymmetric reductions of simple prochiral ketones were carried out using LAH reagents modified with monoterpene alcohols, such as (**3**) to (**6**). However, in most cases only moderate optical yields were observed.[13-21] The failure to obtain a high level of stereoselectivity is partly due to the instability of these complex hydride reagents, which disproportionate to generate achiral reducing species. Exceptionally, a LAH–(–)-menthol reagent (**3**) reduces α- and β-amino ketones, (**25**) and (**26**), to give (*R*)-carbinols with rather good optical yields, 75% *ee* and 37% *ee*, respectively.[22,23]

When diols (**7**) to (**9**), derived from D-glucose, are employed for modification of LAH, optical yields for the reduction of acetophenone do not exceed 20% *ee*.[24] Double modification of LAH by (**9**) and etha-

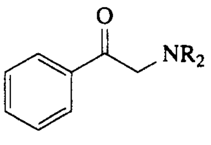

**(25)**

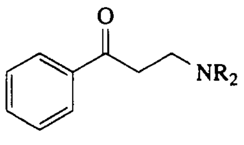

**(26)**

nol, giving empirical formula (**27**), increases the optical yields for the reduction of simple prochiral ketones, giving (*R*)-carbinols in up to 71% *ee* (Scheme 1).[25–28]

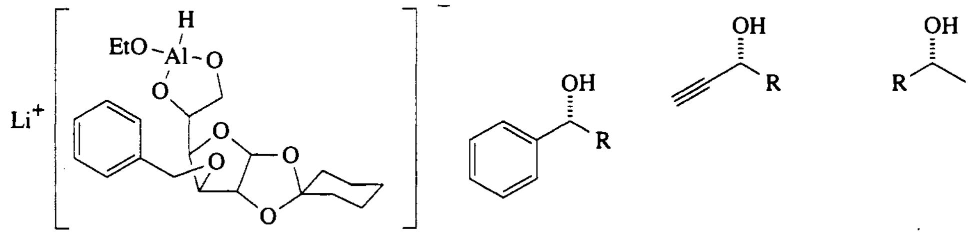

**(27)**

R = Me, 71% *ee*
R = Et, 45.8% *ee*

R = Pr$^n$, 3.5% *ee*
R = Pr$^i$, 5.9% *ee*

R = Bu$^i$, 16.6% *ee*
R = CH=CMe$_2$, 31.4% *ee*
R = C≡CBu$^n$, 7% *ee*

**Scheme 1**

Minimization of the number of reactive hydride species is crucial for obtaining a high level of enantiofacial differentiation. Noyori introduced, as a chiral auxiliary to LAH, an axially dissymmetric and bifunctional (*S*)-(–)- and (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl (**10**; binaphthol),[29] easily available *via* optical resolution[30,31] or asymmetric synthesis,[32] and achieved virtually complete enantiofacial differentiation of the carbonyl group.[33,34] This binaphthol-modified aluminum hydride reagent (hereafter referred to as BINAL-H), (*S*)- or (*R*)-(**28**), is prepared *in situ* by mixing LAH with equimolar amounts of optically pure (*S*)- or (*R*)-binaphthol (**10**) and a second alcoholic component, ethanol. The optical yield is generally enhanced by lowering the reaction temperature. For example, 95% *ee* is obtained by carrying out the reaction of acetophenone with (**28**) at –100 to –78 °C in THF. The asymmetric reduction exhibits high selectivity, and, in some cases, optically pure alcohols are prepared. Although the degree of stereoselectivity depends on the nature of the alkyl group attached to the carbonyl function, the reduction using (*R*)-(**28**) generally gives (*R*)-carbinols, while (*S*)-(**28**) produces the (*S*)-enantiomers (Scheme 2).

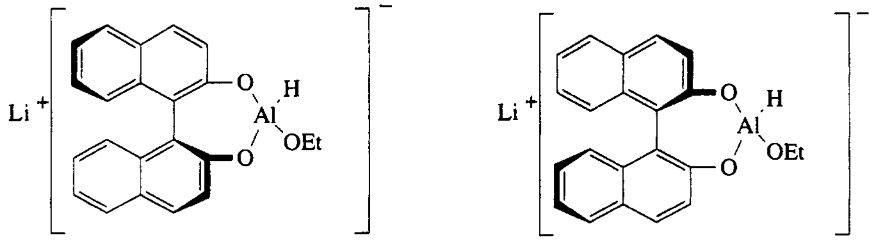

(*S*)-BINAL-H [(S)-(**28**)] (*R*)-BINAL-H [ (*R*)-(**28**)]

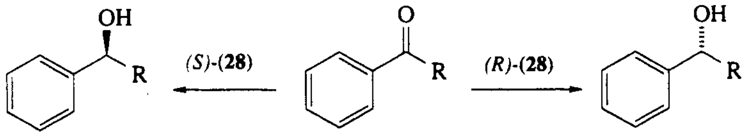

R = Me, 95% *ee*
R = Et, 98% *ee*
R = Pr$^n$, 100% *ee*

R = Bu$^n$, 100% *ee*
R = Pr$^i$, 71% *ee*
R = Bu$^t$, 44% *ee*

**Scheme 2**

The BINAL-H reduction works well with alkenic[35,36] and alkynic ketones affording alcohols with satisfactory optical purities (Scheme 3).[37,38] It is noteworthy that (*S*)-BINAL-H [(*S*)-(**28**)] reduces 1-halo-1-octen-3-one and 2-cyclopentene-1,4-dione to give the corresponding carbinols, which are important chiral building blocks for the synthesis of prostaglandins by the conjugate addition approach.[39]

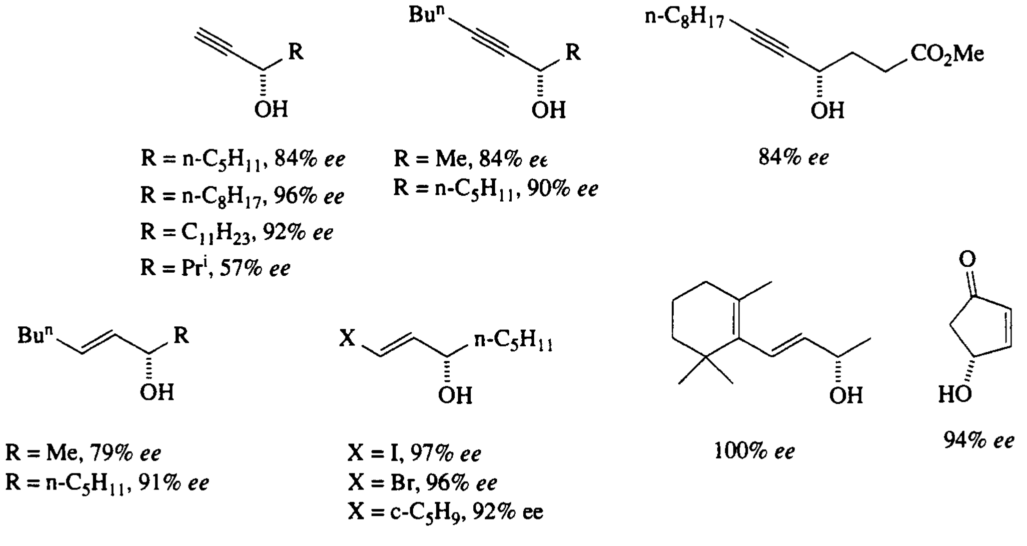

R = n-$C_5H_{11}$, 84% *ee*
R = n-$C_8H_{17}$, 96% *ee*
R = $C_{11}H_{23}$, 92% *ee*
R = Pr$^i$, 57% *ee*

R = Me, 84% *ee*
R = n-$C_5H_{11}$, 90% *ee*

84% *ee*

R = Me, 79% *ee*
R = n-$C_5H_{11}$, 91% *ee*

X = I, 97% *ee*
X = Br, 96% *ee*
X = c-$C_5H_9$, 92% ee

100% *ee*

94% *ee*

**Scheme 3**

BINAL-H reduction can also be used to control the requisite (15*S*)-configuration of prostaglandins in the Corey route.[40] When the α,β-unsaturated ketones (**37**) to (**39**) are treated with (*S*)-(**28**), the corresponding allylic alcohols possessing the (15*S*)-absolute stereochemistry are produced with >99:1 stereoselectivity.[35,37] In contrast, when (**37**) is treated with (*R*)-BINAL-H, the (15*R*)-alcohol is obtained as the major isomer but the selectivity is only 68:32 (15*R*:15*S*).[37] These results can be rationalized in terms of double stereodifferentiation. Reagent control differentiation of the hypothetical enantiofaces is calculated to be 20.6:1, and substrate control, namely the efficiency of intramolecular chirality transfer from the bicyclo[3.3.0] system to the carbonyl center attained with a hypothetical achiral agent, is evaluated to be 9.7:1 favoring the (*S*)-isomer. In a similar manner, the reduction of the monocyclic substrate (**40**) affords the prostaglandin $F_{2\alpha}$ derivative as a single stereoisomer.[35] Diastereoselective reduction of enones (**41**) with (*S*)-BINAL-H gives (15*S*)-alcohols exclusively.[41,42] A kinetic differentiation is seen in the reduction of enone (**42**) with BINAL-H. (*R*)-BINAL-H matches well with the chiral environment of (**42**) to form the (9*S*)-carbinol (9α:9β = 99:1), whereas the enantiomeric (*S*)-BINAL-H fails to react with (**42**) under identical conditions.[39]

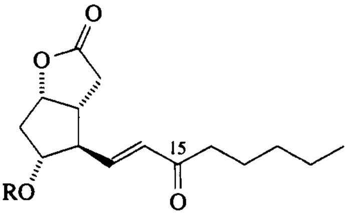

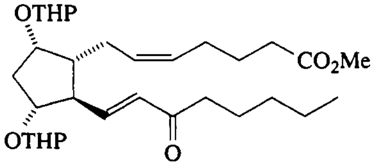

(**37**) R = COMe, (15*S*):(15*R*) = 99.4:0.6
(**38**) R = THP, 15(*S*):(15*R*) = 99.5:0.5
(**39**) R = OH, (15*S*):(15*R*) = 100:0

(**40**) (15*S*):(15*R*) = 100:0

When terpenic 1-deuterioaldehydes are subjected to the reduction with (*R*)- or (*S*)-BINAL-H, optically active, deuterium-labeled primary alcohols are produced (Scheme 4).[43]

The most important feature of the BINAL-H asymmetric reduction is the empirical rule for the orientation observed with simple prochiral carbonyl substrates of type (**43**) (Un = phenyl, alkenyl, alkynyl; R =

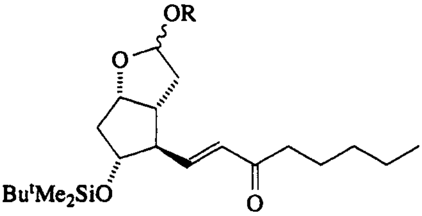

**(41)** R = Me or Et

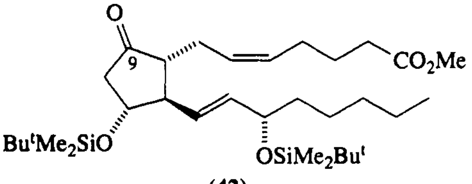

**(42)**

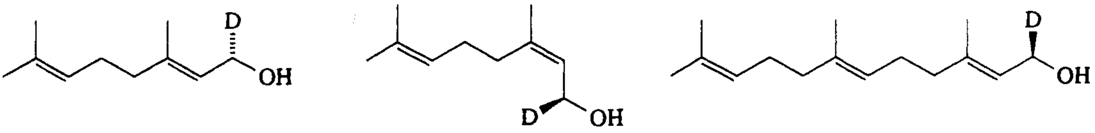

84% *ee* from (*S*)-BINAL-H 72% *ee* from (*S*)-BINAL-H 88% *ee* from (*R*)-BINAL-H

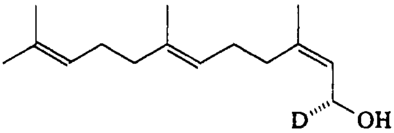

82% *ee* from (*R*)-BINAL-H

**Scheme 4**

alkyl, hydrogen). (*S*)-BINAL-H [(*S*)-(**28**)] generally affords the carbinol (**44**), in which the (*S*)-enantiomer predominates, whereas (*R*)-(**28**) forms the (*R*)-antipode. Electronically, phenyl, alkenyl and alkynyl groups exert qualitatively the same directing influence in the creation of the new asymmetric centers, but steric factors are also of some significance.[34]

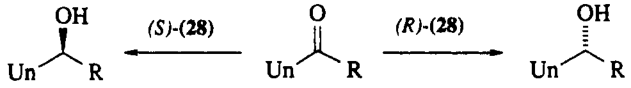

(*S*)-(**44**) (**43**) (*R*)-(**44**)

Enantioselective reduction of prochiral acylstannanes (**45**) by (*S*)-BINAL-H [(*S*)-(**28**)] gives (*R*)-α-hydroxystannanes in reasonable chemical yields and consistently good optical yields (up to 96% *ee*). The unstable α-hydroxystannanes have been isolated and characterized after protection as methoxymethyl (MOM) ethers (**46**). In contrast, (*S*)-BINAL-H reduction of *t*-butylacylstannanes and α,β-unsaturated acylstannanes affords (*S*)-α-hydroxystannanes.[44,45]

The complex (**47**), prepared from equimolar amounts of LAH, (*S*)-(–)-10,10′-dihydroxy-9,9′-biphenanthryl (**11**) and ethanol, reduces aryl alkyl ketones to give the (*S*)-alcohols in 97–98% *ee* (Scheme 5). As with (**28**), the relationship between the chirality of the reagent and the product is (*S*) to (*S*) and (*R*) to (*R*).[46]

### *1.7.2.1.2 Dialkylamino alcohol modifiers*

The reduction of acetophenone with a 1:1 complex of LAH and quinine (**12**), a β-dialkylamino alcohol, affords the (*R*)-carbinol in 48% *ee*.[47] Asymmetric induction in this chirally modified LAH system is enhanced by the presence of a suitably positioned tertiary nitrogen atom along with a chiral carbinol center in the ligand. A γ-dialkylamino alcohol (**13**), from which the analgesic Darvon is made, is an effective chiral modifier for LAH. In this system an aging effect is observed with respect to the sense and degree of asymmetric induction. A reagent freshly prepared from LAH and Darvon alcohol (**13**) in a 1:2.3 ratio reduces acetophenone to give the (*R*)-alcohol in 75% *ee*, while the reagent aged by refluxing in ether for 3 min gives rise to the (*S*)-alcohol in 75% *ee*. The structure of the fresh reagent was postulated to be (**48**). Scheme 6 illustrates the enantiomeric excesses and the absolute configurations of the

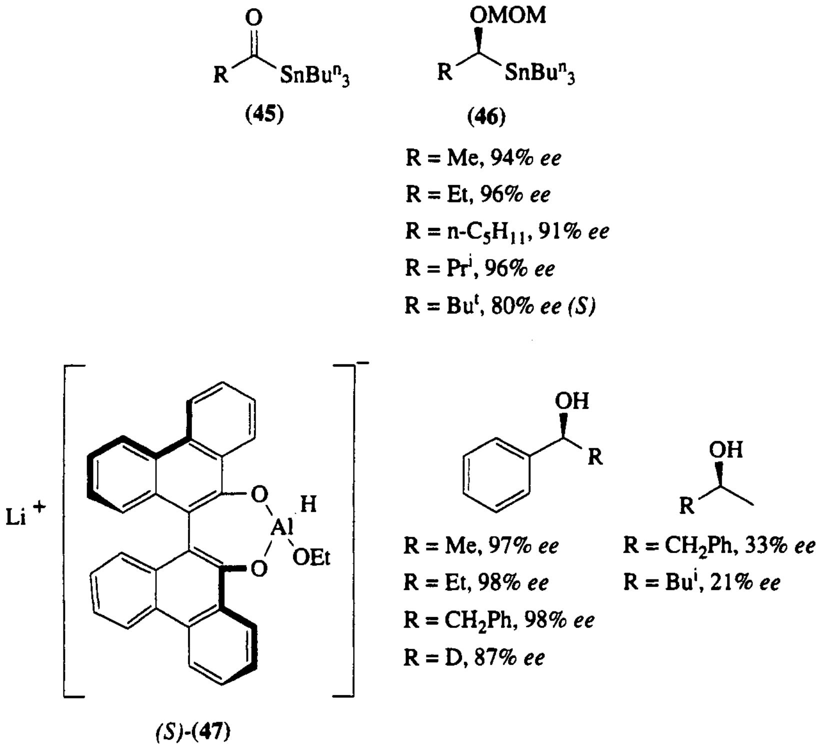

O
R
$SnBu^n_3$
OMOM
R
$SnBu^n_3$
Li$^+$
O
H
Al
O
OEt
OH
R
OH
R

**(45)**

**(46)**

R = Me, 94% *ee*
R = Et, 96% *ee*
R = n-$C_5H_{11}$, 91% *ee*
R = $Pr^i$, 96% *ee*
R = $Bu^t$, 80% *ee (S)*

*(S)*-**(47)**

R = Me, 97% *ee*
R = Et, 98% *ee*
R = $CH_2Ph$, 98% *ee*
R = D, 87% *ee*

R = $CH_2Ph$, 33% *ee*
R = $Bu^i$, 21% *ee*

**Scheme 5**

major alcohols obtained with this reagent for a series of aryl and alkynyl ketones,[48,49] and a single example of an enone.[50]

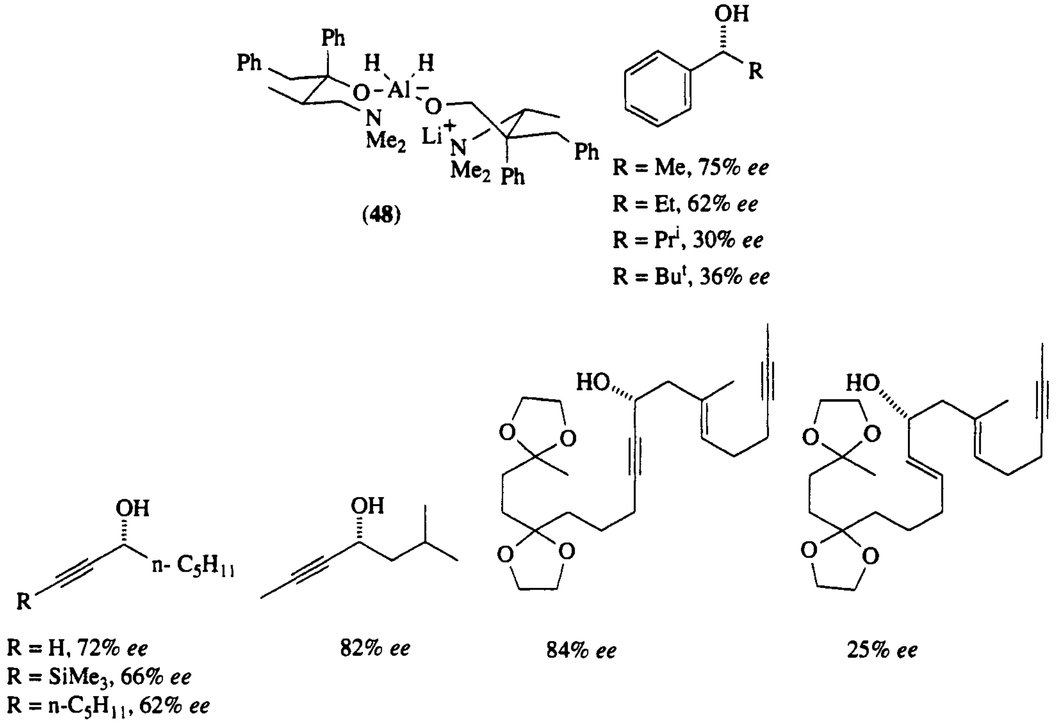

Ph
Ph
H
H
O
Al
O
N
$Me_2$
Li$^+$
N
$Me_2$
Ph
Ph
OH
R
OH
n-$C_5H_{11}$
R
OH
HO
O
O
O
O
HO
O
O
O
O

**(48)**

R = Me, 75% *ee*
R = Et, 62% *ee*
R = $Pr^i$, 30% *ee*
R = $Bu^t$, 36% *ee*

R = H, 72% *ee*
R = $SiMe_3$, 66% *ee*
R = n-$C_5H_{11}$, 62% *ee*

82% *ee*

84% *ee*

25% *ee*

**Scheme 6**

An asymmetric reducing agent (**49**), prepared from LAH, (–)-*N*-methylephedrine (**14**) and 3,5-dimethylphenol in a 1:1:2 ratio, reduces acetophenone with 83.8% *ee*.[51,52] A series of aromatic and alkynyl ketones are reduced by (**49**) to the corresponding (*R*)-alcohols (Scheme 7).[53] Some of the products are useful intermediates for the synthesis of γ-lactone insect pheromones.[54]

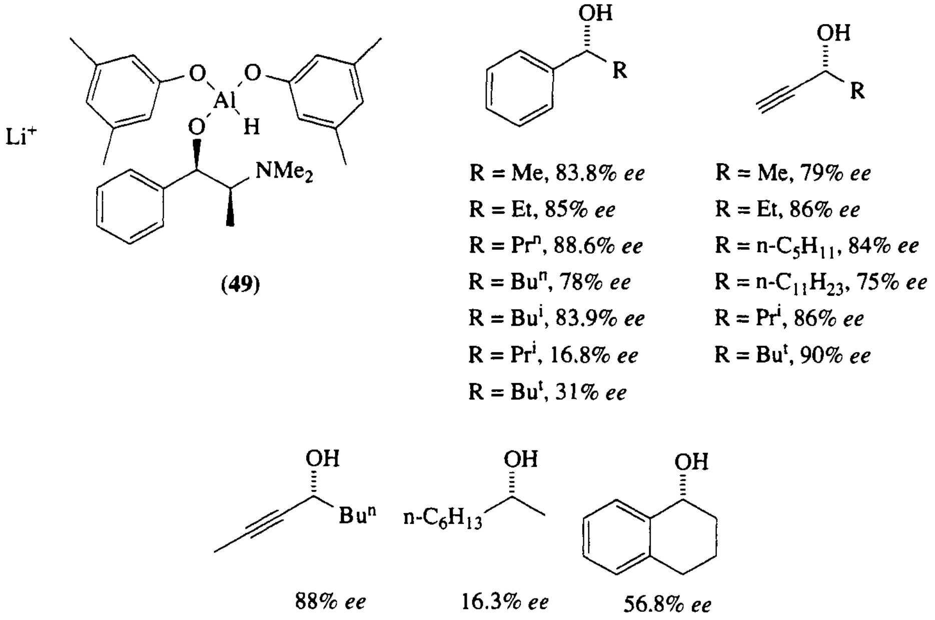

**Scheme 7**

Modification of LAH with (–)-*N*-methylephedrine (**14**) and *N*-ethylaniline affords another chiral reducing agent (**50**).[55–61] A variety of aromatic ketones are reduced by (**50**) to (*S*)-carbinols in high optical yields (Scheme 8). Acyclic α,β-unsaturated ketones are also reduced to (*S*)-carbinols with high selectivity (76–92% *ee*), but cyclic enones are reduced with only moderate selectivity.

The pyridyl analog (**51**) leads to the opposite asymmetric orientation in most cases. Asymmetric reduction of 2-cyclohexenone affords (*R*)-2-cyclohexenol with 98% *ee*. Other cyclic ketones are also converted to (*R*)-carbinols in high optical yields (Scheme 9), but the reduction of acyclic ketones is only moderately stereoselective.[56]

Generally chiral auxiliaries are liberated unchanged during or after the reaction, but attachment to an insoluble polymer facilitates recovery and reuse. This 'purification advantage', a main asset of polymer-assisted reactions, as developed by Merrifield in the early 1960s,[62] was first introduced to the chiral modification of LAH using ephedrine and following a procedure reported by Vigneron.[52] (–)-Ephedrine is immobilized on 1% cross-linked polystyrene, mixed with LAH, (**15**) and 2 equiv. of 3,5-dimethylphenol to afford the polymer-supported chiral reducing agent (**52**). The degree of functionalization is an important factor in achieving effective chiral reduction, and using 0.7 mmol $g^{-1}$ of polymer capacity 78.8% *ee* was obtained in the reduction of acetophenone at –15 °C.[63] The direction of asymmetric induction and optical yields are comparable with those of the original solution phase reaction.[52]

Asymmetric reductions with LAH modified with (**16**) and (**17**) are known, but the optical yields of the 1-phenylethyl alcohol (**2**) were only moderate. A $C_2$ dissymmetrical bis(dialkylamino) diol (DBD, **18**) and its enantiomer are available from diethyl tartrates. The (*S*)-chiral complex (**53**) of this diol reduces a variety of aryl alkyl ketones to the corresponding (*S*)-secondary alcohols in moderate optical purity in each case (Scheme 10).[64]

A LAH complex (**54**) prepared from 2.28 equiv. of the amino diol (**19**) reduces acetophenone and propiophenone to the corresponding (*R*)-alcohols with 82% *ee* and 77% *ee*, respectively.[65] The key feature of this carbinolamine-modified LAH reagent is a lithium ion chelate.

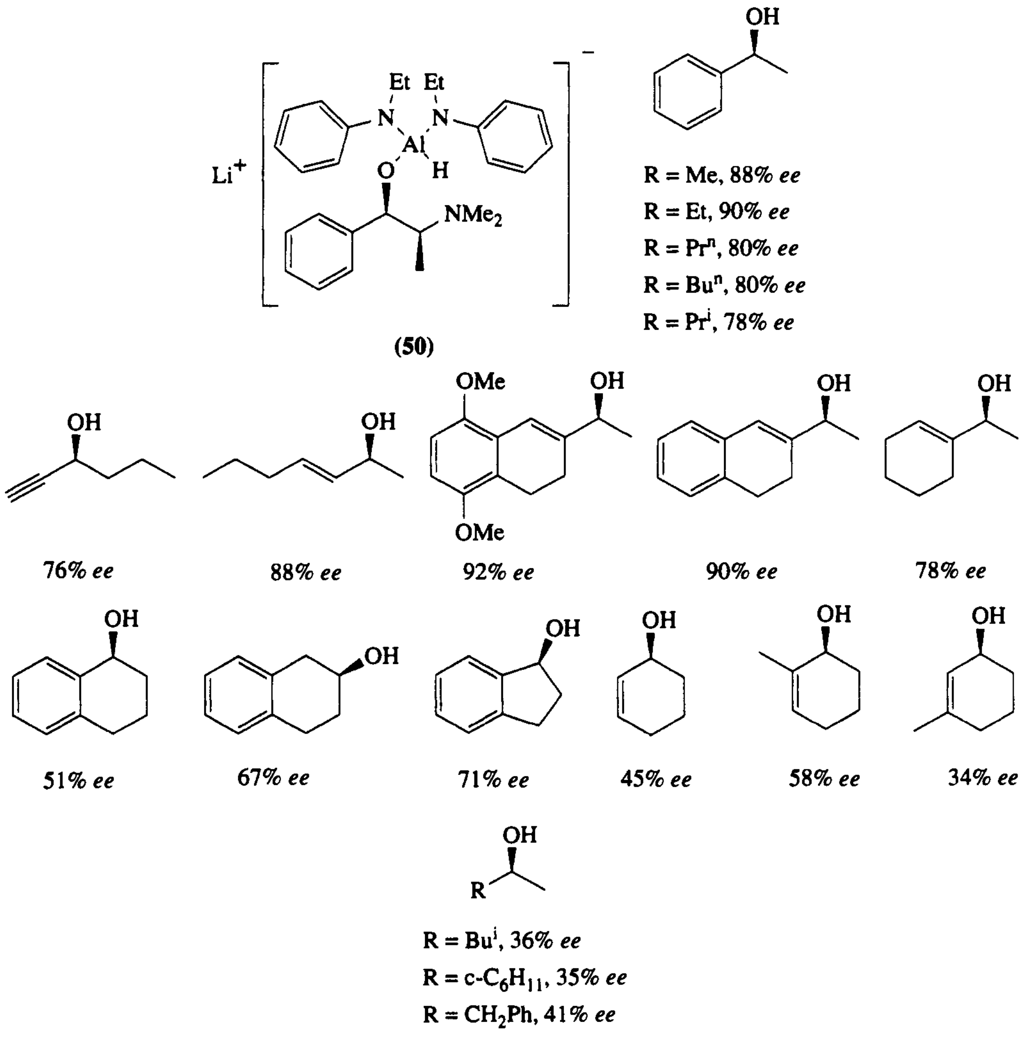
Li⁺
Et Et
N
N
Al
O
H
NMe₂
(50)
OH
R = Me, 88% ee
R = Et, 90% ee
R = Pr^n, 80% ee
R = Bu^n, 80% ee
R = Pr^i, 78% ee
OH
76% ee
OH
88% ee
OMe
OH
OMe
92% ee
OH
90% ee
OH
78% ee
OH
51% ee
OH
67% ee
OH
71% ee
OH
45% ee
OH
58% ee
OH
34% ee
OH
R
R = Bu^i, 36% ee
R = c-C₆H₁₁, 35% ee
R = CH₂Ph, 41% ee

**Scheme 8**

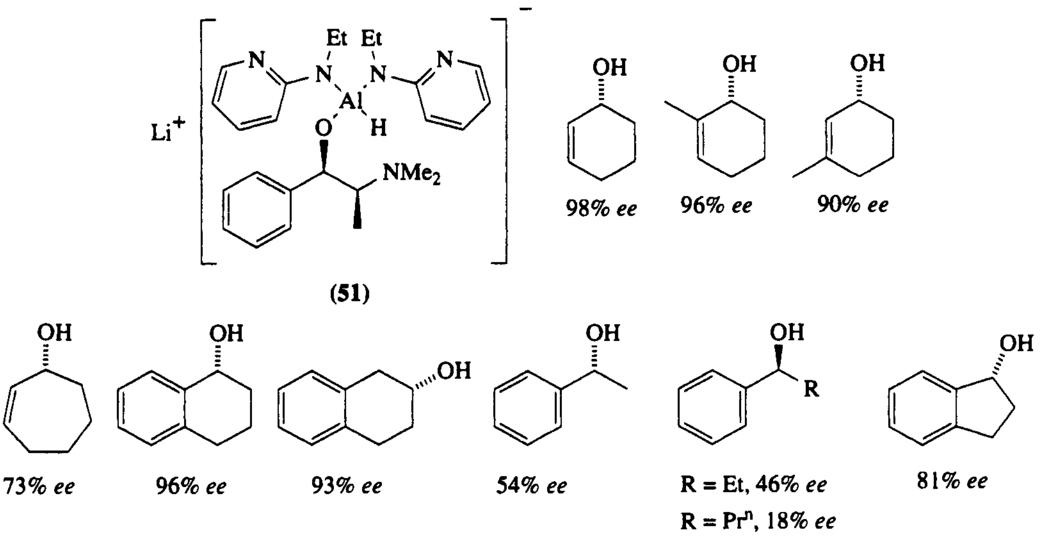
Li⁺
Et Et
N
N
N
N
Al
O
H
NMe₂
(51)
OH
98% ee
OH
96% ee
OH
90% ee
OH
73% ee
OH
96% ee
OH
93% ee
OH
54% ee
OH
R
R = Et, 46% ee
R = Pr^n, 18% ee
OH
81% ee

**Scheme 9**

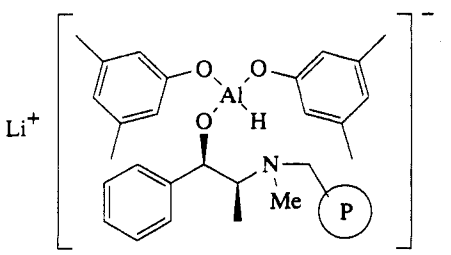

**(52)**

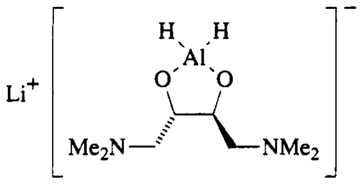

**(53)**

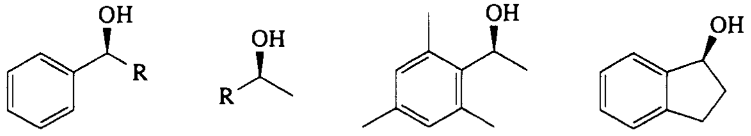

R = Me, 42% *ee*
R = Et, 44% *ee*
R = Pr$^n$, 47% *ee*
R = Pr$^i$, 27% *ee*
R = $c\text{-}C_6H_{11}$, 53% *ee*
R = Bu$^t$, 21% *ee*

R = Et, 2.4% *ee*
R = Bu$^i$, 16% *ee*

75% *ee*

15% *ee*

**Scheme 10**

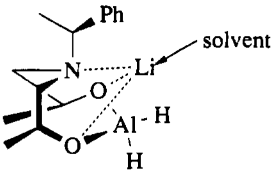

**(54)**

### *1.7.2.1.3 Primary or secondary amine and amino or monoalkylamino alcohol modifiers*

A highly efficient asymmetric reducing agent (**55**) is prepared by reaction of LAH and the β-diamine (**20**) derived from (*S*)-proline in five steps. Acetophenone is reduced by (**55**) at –100 °C to give the (*S*)-alcohol in 95% *ee*. Some other aromatic ketones also give high optical yields (Scheme 11), but this procedure is not effective for prochiral dialkyl ketones. The high stereodifferentiation has been interpreted in terms of the bicyclo[3.3.0] rigid structure of (**55**), where only one hydrogen is responsible for the reduction. The presence of additives such as tetramethylethylenediamine, DME or $MgBr_2$ reduces the optical yield, indicating that the lithium cation plays an important role.[66–68]

(*S*)-4-Anilino-3-methylamino-1-butanol (**22a**) and (*S*)-4-(2,6-xylidino)-3-methylamino-1-butanol (**22b**), tridentate chiral auxiliaries, are easily derived from (*S*)-aspartic acid. A complex (**56a**) prepared from equimolar amounts of LAH and (**22a**) in THF reduces aromatic ketones to (*S*)-carbinols in 51–88% *ee*. This complex is also effective in reducing several enones to (*S*)-allylic alcohols (Scheme 12), whereas the complex (**56b**) affords the (*R*)-enantiomers. Particularly noteworthy is the virtually complete enantiofacial differentiation of cyclohexenone giving (*S*)-2-cyclohexenol.[69,70]

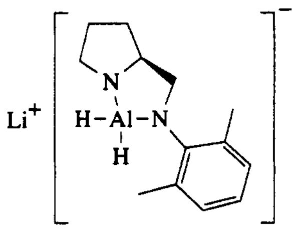

**(55)**

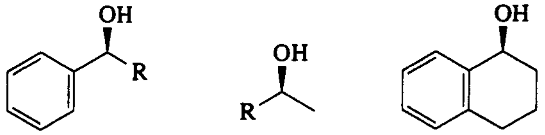

R = Me, 95% *ee*
R = Et, 96% *ee*
R = $Pr^i$, 89% *ee*

R = n-$C_6H_{13}$, 26% *ee*
R = $CH_2Ph$, 42% *ee*

86% *ee*

**Scheme 11**

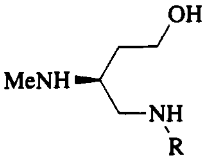

**(22a)** R = Ph
**(22b)** R = 2,6-$Me_2C_6H_3$

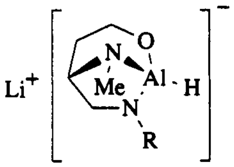
Li+
N
O
Me
Al
H
N
R

**(56a)** R = Ph
**(56b)** 2,6-$Me_2C_6H_3$

From reduction with **(56a)**

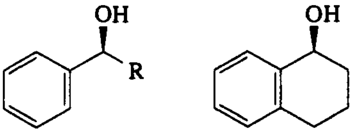

R = Me, 51% *ee*
R = Et, 68% *ee*
R = $Pr^i$, 77% *ee*
R = $Bu^t$, 86% *ee*

88% *ee*

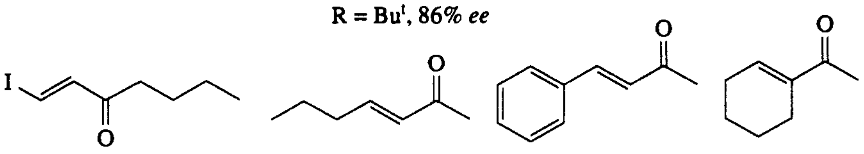

| | | | |
|---|---|---|---|
| *51% ee, (S)* | *88% ee, (S)* | *72% ee, (S)* | *5% ee, (S)* |
| *21% ee, (R)* | *84% ee, (R)* | *42% ee, (R)* | *61% ee, (R)* |

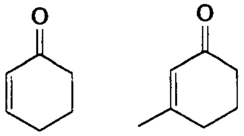

| | |
|---|---|
| *100% ee, (S)* | *28% ee, (S)* |
| *13% ee, (R)* | *2% ee, (S)* |

*(S)*-products from reduction with **(56a)**
*(R)*-products from reduction with **(56b)**

**Scheme 12**

Reduction of acetophenone with the LAH complexes of nitrogen analogs of binaphthol, (*R*)-(**23**)[71] and (*S*)-(**24**),[72] affords (*R*)-1-phenylethyl alcohol in 43% *ee* and 46% *ee*, respectively. Optical yields for the reduction of other prochiral ketones are similarly moderate.

### 1.7.2.2 Asymmetric Reduction with Borohydride Reagents

When borohydride reductions are carried out in the presence of either a chiral phase transfer catalyst or a chiral crown ether, asymmetric reduction of ketones occurs but optical yields are low. In the reduction of acetophenone with $NaBH_4$ aided with a phase transfer catalyst (**57**), 10% *ee* was obtained.[73–78] Similarly, reduction of acetophenone with $NaBH_4$ in the presence of the chiral crown ether (**58**) was ineffective (6% *ee*).[79,80] Sodium borohydride reduction of aryl alkyl ketones in the presence of a protein, bovine serum albumin, in 0.01 M borax buffer at pH 9.2 affords (*R*)-carbinols in maximum 78% *ee*.[81]

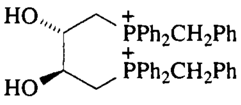

**(57)**

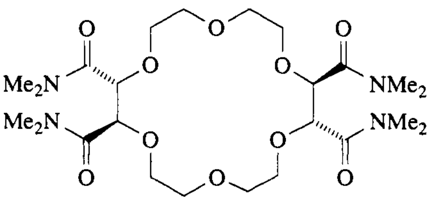

**(58)**

Partial decomposition of $NaBH_4$ or $LiBH_4$ by chiral protic substances such as R*OH or RR*NH generates modified borohydride reagents. When aromatic ketones are reduced by $NaBH_4$ modified with the sugar-derived monoalcohols (**59**) or (**60**), moderate optical yields (6–35% *ee*) result.[82,83] Modification of $NaBH_4$ with the sugar (**60**) and 2-methylpropionic acid permits the reduction of propiophenone to give the (*R*)-alcohol in 63% *ee*.[84] Racemic 2-phenylbutyric acid is also an effective comodifier affording 1-phenylpropanol in 51% *ee*.[85]

Lithium borohydride decomposed by *N*-benzoylcysteine (**61**) or *N,N'*-dibenzoylcystine (**62**), a sulfur-containing modifier, is a highly efficient chiral reducing agent. A complex prepared from (**61**), *t*-butyl alcohol and $LiBH_4$ affords carbinols in maximum 92% *ee* by the reduction of aryl alkyl ketones in THF at –78 °C (Scheme 13). A $LiBH_4$ complex with (**62**) and *t*-butyl alcohol is useful for the reduction of β-keto esters to give (*R*)-β-hydroxy esters in up to 91% *ee*. In both cases the use of *t*-butyl alcohol is essential in order to achieve efficient enantiofacial differentiation.[86–88]

A highly promising chiral reducing agent, K-glucoride (**64**), is prepared from 9-borabicyclo[3.3.1]nonane (9-BBN) and a D-glucose derivative (**59**) *via* the stable borinic ester (**63**). Reduction of aryl alkyl ketones with (**64**) in THF at –78 °C affords (*R*)-carbinols in high optical yields (78–97% *ee*). Although the enantioselectivity of the reduction of acyclic saturated dialkyl ketones is not high, prochiral cyclic ketones are converted to (*R*)-alcohols with high optical purity (Scheme 14). This procedure is also applicable to the reduction of α-keto esters to (*S*)-α-hydroxy esters.[89,90]

### 1.7.2.3 Asymmetric Reduction with Chirally Modified Boranes and Alanes

Chiral modification is not limited to boronate and aluminate complexes. Boranes or alanes are partially decomposed with protic substances such as chiral amines, alcohols or amino alcohols to form useful reagents for enantioselective reduction of carbonyl compounds. For example, reduction of acetophenone with borane modified with the amines (**65**) to (**67**) gives (*S*)-1-phenylethyl alcohol with 3.5–20% *ee*.[91–93] A 1:1 mixture of sodium L-prolinate (**68**) and borane gives rise to carbinols with as much as 62% *ee*,[94] and the complex prepared by mixing borane, *m*-nitroaniline and (*S*)-(**69**) in a 1:1:1 ratio reduces acetophenone in 84% *ee*.[95]

Itsuno's amino alcohol (**70**), prepared from L-valine, is an extremely efficient auxiliary for enantioselective reduction of aryl alkyl ketones using $BH_3$. The corresponding alcohols are obtained in up to 100% *ee* using $BH_3$ and 0.5 equiv. of (**70**) in THF at 30 °C. Reduction of dialkyl ketones affords (*R*)-carbinols in 55–73% *ee*.[96–99] Halomethyl *t*-butyl ketones are also converted to the corresponding (*S*)-carbinols in high optical purity (Scheme 15). Immobilized amino alcohol (**70**) permits reduction in a continuous flow system. 1-Phenylpentanol of 90% *ee* was prepared by this catalytic process in almost 1000% chemical yield based on the quantity of chiral auxiliary used.[100,101]

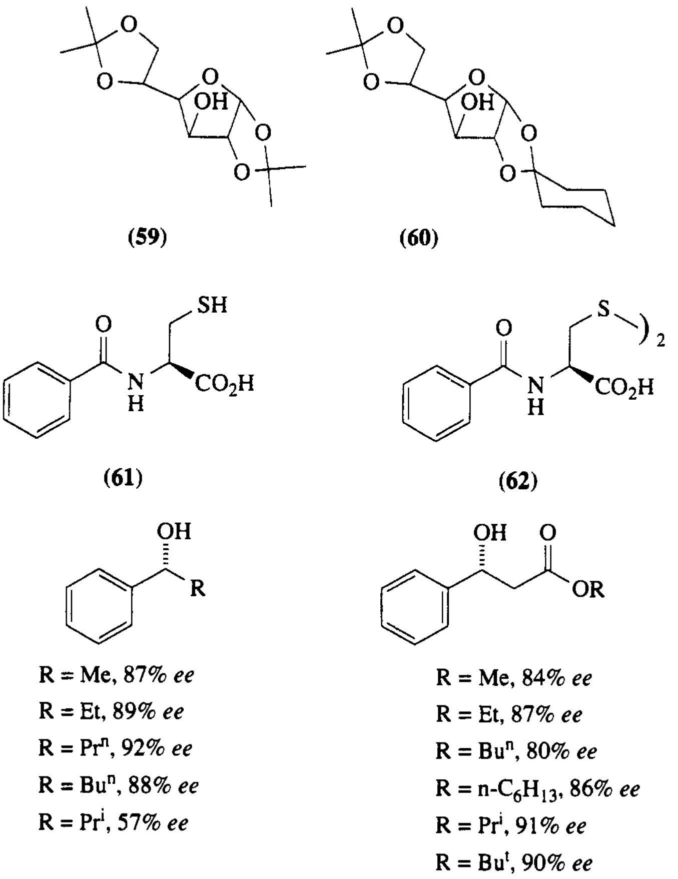

Scheme 13

Borane complex catalyzed reductions have been greatly extended by Corey and coworkers,[102] who found that oxazaborolidine (**73**) could be prepared as crystals from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine by heating with $BH_3$·THF followed by sublimation, while *B*-methylated oxazaborolidine (**74**), prepared from (**72**) and methylboronic acid, is stable enough to store in closed containers at room temperature and can be weighed or transferred in air.[104] Borane reduction of prochiral ketones in the presence of 0.05 to 0.1 equiv. of (**73**) or (**74**) generated both unsaturated and saturated carbinols with high enantioselectivity. The utility of these reagents is shown by some simple examples in Scheme 16 and by the effective chiral syntheses of compounds (**78**) to (**80**), which are intermediates in the syntheses of ginkgolide B,[106] forskolin[105] and prostaglandins,[103] respectively. Moreover, $^{11}$B NMR and IR analysis of (**73**) revealed that it is a mixture of monomer and dimer and has double bond character between the B and N atoms. A 1:1 borane/oxazaboridine (**75**) is well set up to serve as an effective reagent for carbonyl reduction. Coordination of the ketone oxygen to the electrophilic ring boron atom promotes hydride transfer from the $NBH_3^-$ unit *via* a six-membered cyclic transition state (**76**). The resulting borate (**77**) reacts with $BH_3$, regenerating the active species (**75**), thus completing a catalytic cycle.[102]

Masamune synthesized the chiral borane (**81**), possessing a chiral organic backbone, by the reaction of dihydridoborate (**82**) and methanesulfonic acid.[107] The former is obtained by reaction of (diethylamino)dichloroborane and the Grignard reagent derived from 2,5-dibromohexane, followed by resolution. Enantioselective reduction of prochiral aliphatic ketones has been accomplished using (*R,R*)-(**81**), generating (*R*)-carbinols in 79–98.4% *ee* (Scheme 17).[108,109] A borolanyl mesylate (**83**), generated *in situ* along with (**81**), plays a catalytic role by coordination with the ketone oxygen.

The sole example of a chiral alane reagent is dialkylaminoalane (**85**), prepared by the reaction of LAH and (*S*)-*N*-methyl-*N*-phenylethylamine hydrochloride (**84**). The reduction of acetophenone gives the (*S*)-alcohol in 84.5% *ee*.[110]

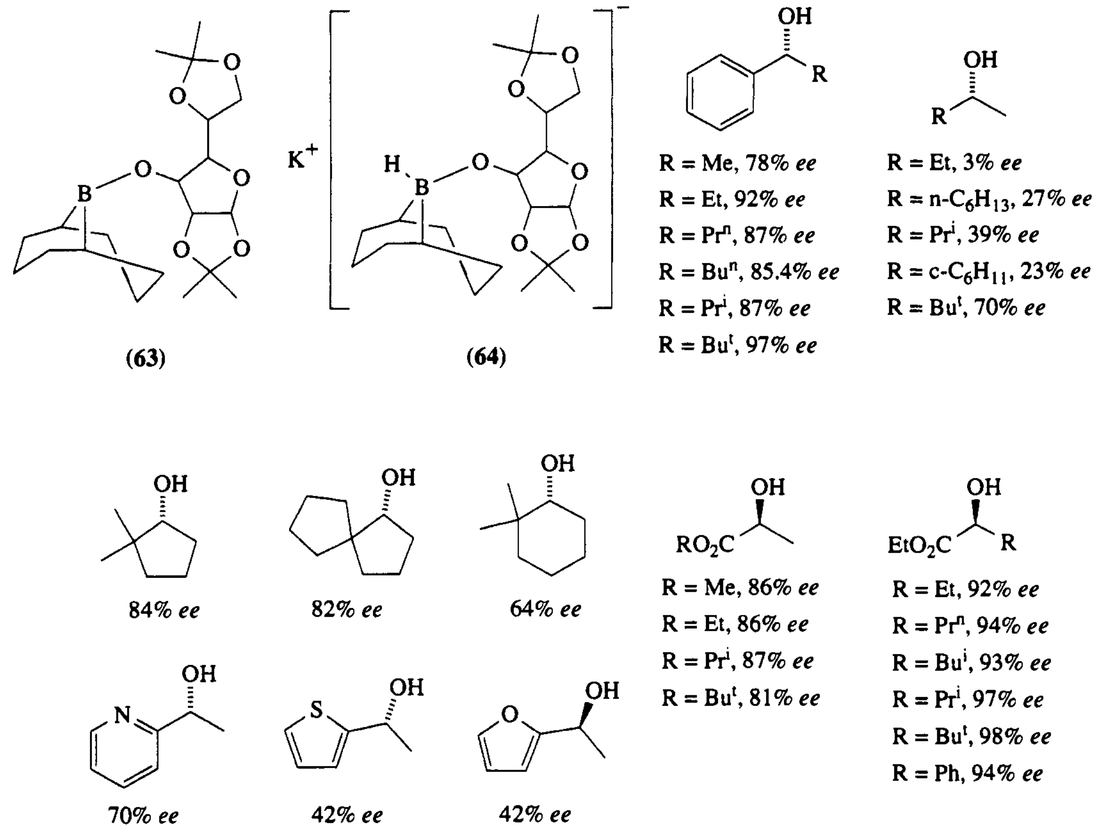
K+
H
B
O
(63)
(64)
OH
R
R = Me, 78% ee
R = Et, 92% ee
R = Pr^n, 87% ee
R = Bu^n, 85.4% ee
R = Pr^i, 87% ee
R = Bu^t, 97% ee
R = Et, 3% ee
R = n-C6H13, 27% ee
R = Pr^i, 39% ee
R = c-C6H11, 23% ee
R = Bu^t, 70% ee
84% ee
82% ee
64% ee
RO2C
R = Me, 86% ee
R = Et, 86% ee
R = Pr^i, 87% ee
R = Bu^t, 81% ee
EtO2C
R = Et, 92% ee
R = Pr^n, 94% ee
R = Bu^i, 93% ee
R = Pr^i, 97% ee
R = Bu^t, 98% ee
R = Ph, 94% ee
N
S
70% ee
42% ee
42% ee

Scheme 14

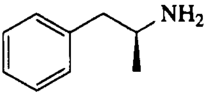

**(65)**

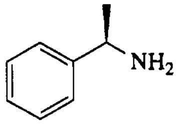

**(66)**

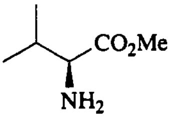

**(67)**

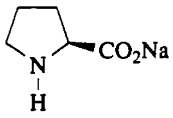

**(68)**

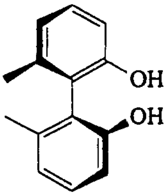

(S)-**(69)**

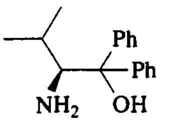

**(70)**

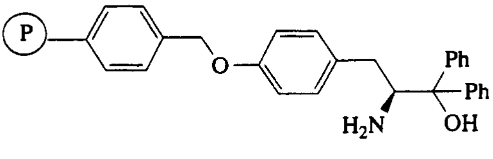
P
O
Ph
Ph
H2N
OH

**(71)**

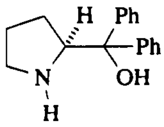

**(72)**

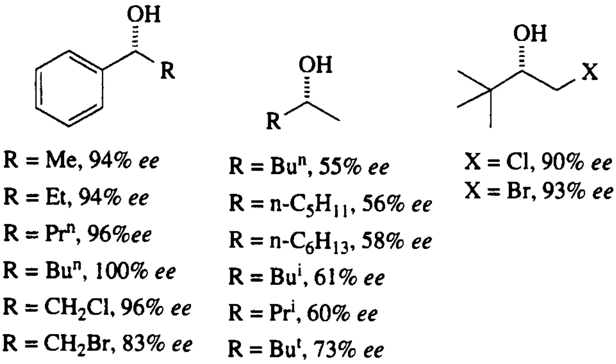
OH
R
R = Me, 94% ee
R = Et, 94% ee
R = Pr^n, 96%ee
R = Bu^n, 100% ee
R = CH2Cl, 96% ee
R = CH2Br, 83% ee
OH
R
R = Bu^n, 55% ee
R = n-C5H11, 56% ee
R = n-C6H13, 58% ee
R = Bu^i, 61% ee
R = Pr^i, 60% ee
R = Bu^t, 73% ee
OH
X
X = Cl, 90% ee
X = Br, 93% ee

Scheme 15

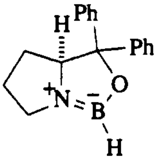

**(73)**

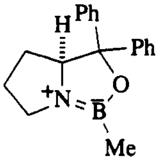
H
Ph
Ph
O
+N
B
Me

**(74)**

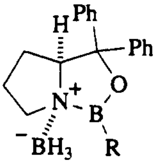
H
Ph
Ph
O
N+
B
BH3
R

**(75)**

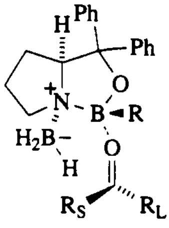
H
Ph
Ph
O
+N
B
R
H2B
H
O
RS
RL

**(76)**

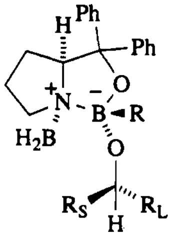
H
Ph
Ph
O
+N
B
R
H2B
O
RS
H
RL

**(77)**

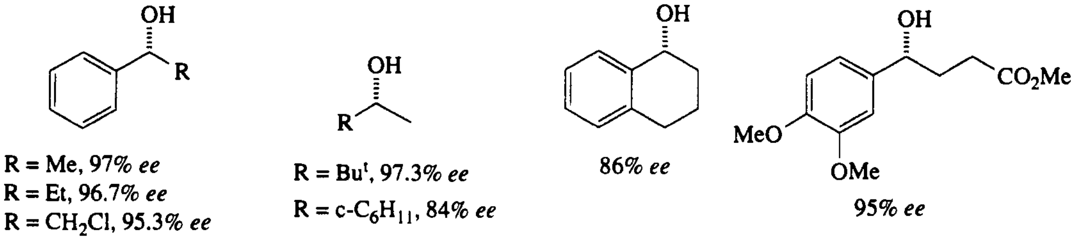
OH
R
R = Me, 97% ee
R = Et, 96.7% ee
R = CH2Cl, 95.3% ee
OH
R
R = Bu^t, 97.3% ee
R = c-C6H11, 84% ee
OH
86% ee
OH
CO2Me
MeO
OMe
95% ee

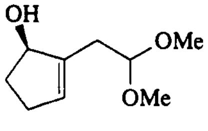

**(78)** 93% *ee*

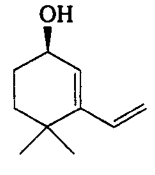

**(79)** 90% *ee*

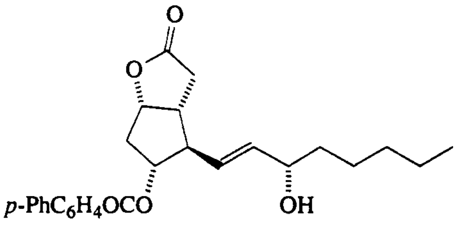
O
O
p-PhC6H4OCO
OH

**(80)** (15*S*):(15*R*) = 91:9

Scheme 16

### 1.7.2.4 Asymmetric Hydrosilylation

Addition of the elements of Si—H to a carbonyl group produces silyl ethers which are synthetically equivalent to chiral secondary alcohols since the silyl groups are easily hydrolyzed. Hydrosilylation can be catalyzed by acids or transition metal complexes. Enantioselective hydrosilylation of prochiral ketones has been extensively studied using platinum or rhodium complexes possessing chiral ligands such as BMPP (**86**), DIOP (**87**), NORPHOS (**88**), PYTHIA (**89**) and PYBOX (**90**).[111]

Hydrosilylation of aryl alkyl ketones with trimethylsilane, catalyzed by a [PtCl$_2${(*R*)-BMPP}] complex, gave (*R*)-silyl ethers (**91**) with low enantiomeric excesses,[112,113] but a combination of dimethylphenylsilane and a Rh$^0$/(*S*)-BMPP complex gave (*R*)-silyl ethers (**92**) in 44–56% *ee*.[114–117] Use of a [{Rh(COD)Cl}$_2$]/(–)-DIOP complex and α-naphthylphenylsilane[118] is effective for the reaction of α-keto esters, giving (*R*)-α-hydroxy esters (**93**).[119,120]

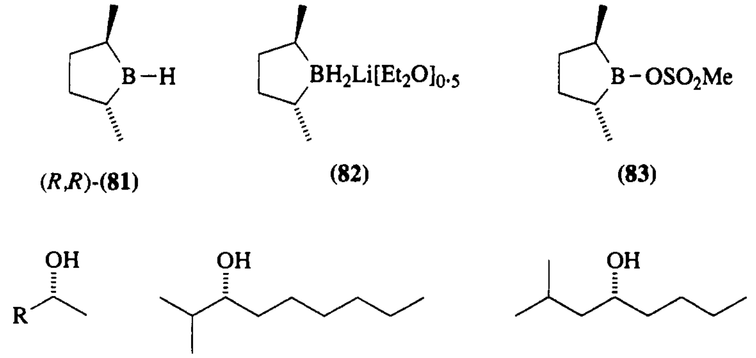

(*R*,*R*)-**(81)** **(82)** **(83)**

$R = Et$, 79% *ee*
$R = n\text{-}C_6H_{13}$, 80% *ee*
$R = CH_2Ph$, 97.3% *ee*
$R = CH_2Bu^t$, 98.4% *ee*
$R = Bu^i$, 97% *ee*
$R = Pr^i$, 98.4% *ee*
$R = c\text{-}C_6H_{11}$, 98% *ee*
$R = Bu^t$, 98.1% *ee*

91% *ee*

95.2% *ee*

**Scheme 17**

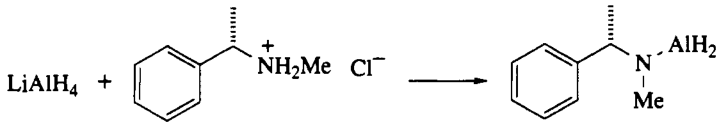

**(84)** **(85)**

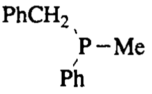

BMPP **(86)**

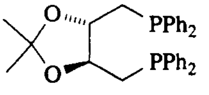

DIOP **(87)**

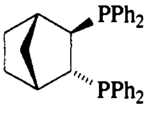

NORPHOS **(88)**

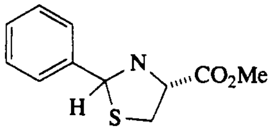

PYTHIA **(89)**

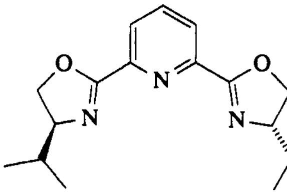

PYBOX **(90)**

Hydrosilylation of acetophenone to give silyl ether (**94**; R = Me) can also be achieved using copper(I) complexes with the chiral phosphine ligands (–)-DIOP (**87**) or (+)-NORPHOS (**88**). The enantioselectivity is rather low,[121] but a nonphosphine auxiliary, PYTHIA (**89**) with a $Rh(COD)Cl_2$ catalyst using neat diphenylsilane reduces aryl ketones to (*R*)-1-phenylethyl alcohol silyl ethers in high yield and with high enantiomeric excess (Scheme 18).[122-125]

The $C_2$ symmetrical bis(oxazolinylpyridine), PYBOX (**90**), also serves as an excellent ligand. Treatment of (**90**) with $[RhCl_3(H_2O)_3]$ in ethanol affords the complex (**95**), which has been characterized by single crystal X-ray analysis. Hydrosilylation of ketones with diphenylsilane (1.5 equiv.) in the presence of $AgBF_4$ (0.2 equiv.), (**90**) (0.06 equiv.) and (**95**) (0.01 equiv.) at 0 °C gives (*S*)-alcohols of high enantiomeric excess.[126]

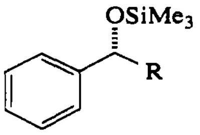

**(91)**

R = Me, 7.6% *ee*
R = Et, 10% *ee*
R = Pr$^{n}$, 8.4% *ee*
R = Pr$^{i}$, 4.5% *ee*
R = Bu$^{t}$, 18.6% *ee*

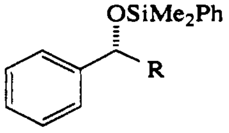

**(92)**

R = Me, 44% *ee*
R = Et, 50% *ee*
R = Pr$^{i}$, 56% *ee*

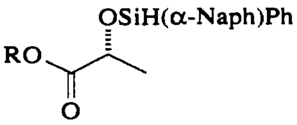

**(93)**

R = Pr$^{n}$ , 85.4% *ee*
R = Bu$^{n}$, 83.1% *ee*
R = Bu$^{i}$, 72.1% *ee*

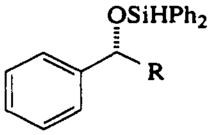

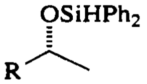

**(94)**

R = Me, 86.7% *ee*
R = Et, 76.7% *ee*
R = Pr$^{n}$, 81.3% *ee*

R = 4-MeC$_6$H$_4$, 86.2% *ee*
R = 2-ClC$_6$H$_4$, 83.1% *ee*
R = 3-MeOC$_6$H$_4$, 91.1% *ee*
R = 4-O$_2$NC$_6$H$_4$, 61.2% *ee*

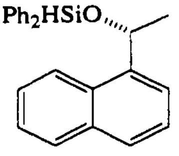

83.3% *ee*

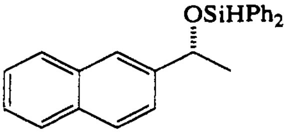

77.9% *ee*

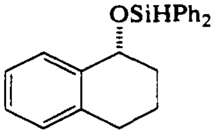

82.6% *ee*

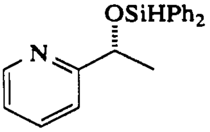

89.6% *ee*

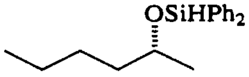

52.2% *ee*

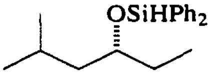

55.8% *ee*

**Scheme 18**

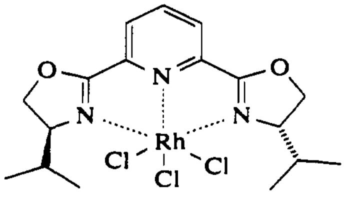

**(95)**

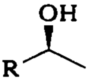

R = Ph, 94% *ee*
R = α-naphthyl, 94% *ee*
R = β-naphthyl, 92% *ee*
R = n-C$_6$H$_{13}$, 59% *ee*
R = (CH$_2$)$_2$=CMe$_2$, 70% *ee*
R = CH$_2$CO$_2$Et, 27% *ee*
R = (CH$_2$)$_2$CO$_2$Et, 95% *ee*

**Scheme 19**

### 1.7.2.5 Asymmetric Reduction of the C═N Double Bond

A general way to reduce a C═N bond to an optically active amine is still elusive. Attempted reduction, using a LAH/(–)-menthol reagent, of 2-substituted iminium salts (**96**, R = methyl, ethyl, propyl or benzyl)[127] or (**97**, R = methyl, ethyl, propyl or benzyl)[128] and imine (**98**)[129] gives the corresponding amines with low optical purities.

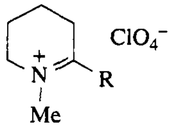

**(96)**

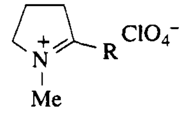

**(97)**

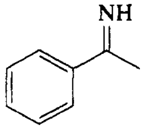

**(98)**

Reduction of oximes (**100**) and (**102**) with a LAH complex modified by a D-glucose derivative (**99**) affords (*S*)-primary amines (**101**) and (**103**) directly with 32% *ee* and 49% *ee*, respectively.[130,131]

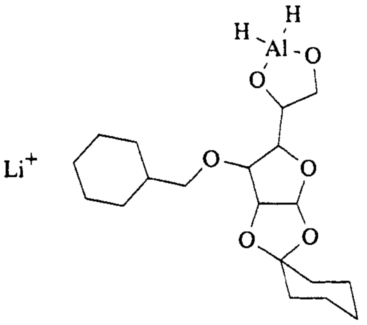

**(99)**

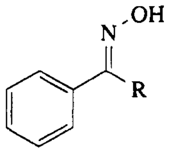

**(100)**

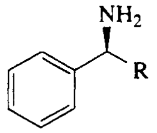

**(101)**

R = Me, 39.3% *ee*
R = Et, 45.7% *ee*

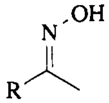

**(102)**

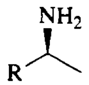

**(103)**

R = Et, 32.5% *ee*
R = n-$C_6H_{13}$, 49.3% *ee*
R = $CH_2Ph$, 43.6% *ee*
R = $Pr^i$, 44.8% *ee*

Sodium (*S*)-prolinate–borane complex (**104**) reduces cyclic imine (**105**) to give the (*S*)-tetrahydroisoquinoline derivative (**106**) in 87% *ee*. Related amines (**107**) and (**108**) are also prepared in a like manner in 86% *ee* and 71% *ee*, respectively.[132–134]

A high degree of asymmetric induction has been realized by reduction of *O*-methyloximes (**109**) to give the corresponding amines (**110**) using a borane reagent modified with (**70**). Acetophenone *O*-methyl oxime is converted to (*S*)-1-phenylethylamine in 99% *ee* after hydrolysis of the resulting methoxylamine derivative. Curiously, the asymmetric reduction of acetophenone with the same reagent induces the opposite chirality. The reduction of oxime *O*-methyl ethers derived from α-naphthyl methyl ketone occurs in only moderate optical yield.[135]

Asymmetric reduction of prochiral diphenylphosphinylimines (**111**) by (*S*)-BINAL-H (**28**), LAH–Darvon alcohol complex (**48**) or K-glucoride (**64**) affords the (*S*)-amines (**112**; Scheme 20). The protecting group of (**112**) is readily cleaved under acidic conditions to give the free amine. When the alkyl group is methyl or ethyl, (*S*)-BINAL-H shows high enantioselectivity.[136]

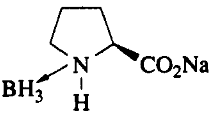

**(104)**

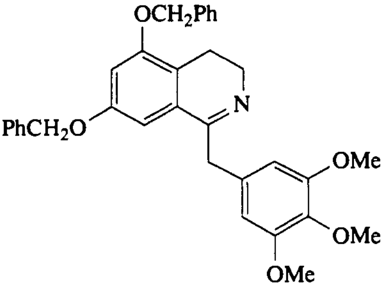

**(105)**

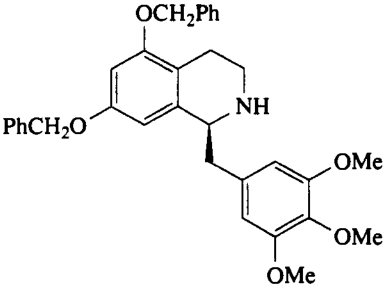

**(106)**

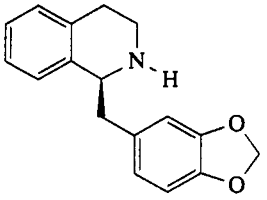

**(107)**

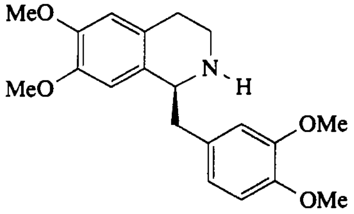

**(108)**

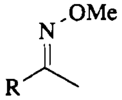

**(109)**

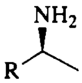

**(110)**

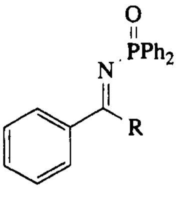

**(111)**

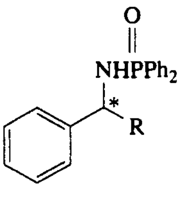

**(112)**

| | *Reducing agent* | | |
|---|---|---|---|
| *R* | *(S)*-**(28)** | **(48)** | **(64)** |
| Me | 100% *ee*, *(S)* | 41% *ee*, *(S)* | 15% *ee*, *(R)* |
| Et | 80% *ee*, *(S)* | 17% *ee*, *(S)* | 28% *ee*, *(S)* |
| $Pr^i$ | 2% *ee*, –[a] | 13% *ee*, –[a] | 57% *ee*, –[a] |

[a] Absolute configuration was not determined

**Scheme 20**

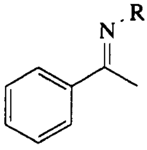

**(113)**

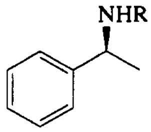

**(114)**

R = $CH_2Ph$, 65% *ee*
R = Ph, 40% *ee*

**Table 1** Optical Yields for Asymmetric Reduction of Typical C=X Compounds with Selected Chiral Hydride Reagents

*Substrate*

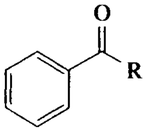

| *Reducing agent or method* | *Me* | *Et* | $Pr^n$ | $Bu^n$ | $Pr^i$ | $Bu^t$ | $CO_2Me$ | $CH_2Cl$ | 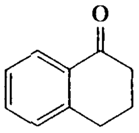 | 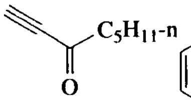 | 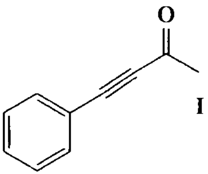 | 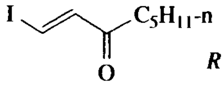 | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (**28**) | 95 | 98 | 100 | 100 | 71 | 44 | 24 | 95 | 62 | 84 | 89 | 97 | 34 |
| (**47**) | 97 | 98 | 98 | — | — | — | — | — | — | — | — | — | 46 |
| (**48**) | 75 | — | 62 | — | 48 | 36 | — | — | — | 72 | — | — | 49 |
| (**49**) | 83.8 | 85 | 88.6 | 78.1 | 16.8 | 31 | — | — | 56.8 | 84 | — | — | 52 |
| (**50**) | 88 | 90 | 80 | 80 | 78 | — | — | — | 51 | 76 | — | — | 56 |
| (**51**) | 46 | 18 | — | — | — | — | — | 96 | — | — | — | — | 60 |
| (**53**) | 42 | 44 | 47 | 27 | 21 | 21 | — | — | — | — | — | — | 64 |
| (**54**) | 82 | 77 | — | — | — | — | — | — | — | — | — | — | 65 |
| (**55**) | 95 | 96 | — | — | 89 | — | — | — | 86 | — | — | — | 68 |
| (**56a**) | 51 | 68 | — | — | 77 | 86 | — | — | 89 | — | — | 51 | 69 |
| $NaBH_4$/(**61**) or (**62**) | 87 | 89 | 92 | 88 | 57 | — | 87 | — | 48 | — | — | — | 86 |
| (**64**) | 78 | 92 | 87 | 85.4 | 87 | 97 | 92 | 77 | — | — | 61 | — | 90 |
| $BH_3$/(**70**) | 94 | 96 | 100 | — | — | 25 | 96 | — | — | 7 | — | — | 100 |
| (**75**) | 97 | 90 | — | — | — | — | — | 97 | 89 | — | — | — | 102 |
| (**81**) | — | — | — | — | — | — | — | — | — | — | — | — | 108 |
| $H_2SiPh_2$/RhCl/(**89**) | 86.7 | 76.7 | 81.3 | — | 9 | — | — | — | 82.6 | — | — | — | 125 |
| $H_2SiPh_2$/RhCl/$_3$/(**90**) | 94 | — | — | — | — | — | — | — | — | — | — | — | 126 |

Table 1 *(Continued)*

| *Reducing agent or method* | *Substrate* 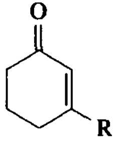 | | 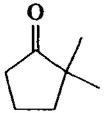 | 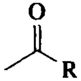 | | | | | | | 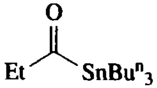 | 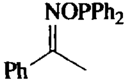 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *H* | *Me* | | *CH═CHPh* | *CH═CHBu$^n$* | *Bu$^i$* | *n-C$_6$H$_{13}$* | *CH$_2$Ph* | *Pr$^i$* | *Bu$^t$* | | | *Ref.* |
| **(28)** | — | — | 79 | 70 | 79 | — | 24 | 13 | 78 | — | 96 | 100 | 34 |
| **(47)** | — | — | — | — | — | 21 | — | 33 | — | — | — | — | 46 |
| **(48)** | — | — | — | — | — | — | — | — | — | 28 | — | 41 | 49 |
| **(49)** | — | — | — | — | — | 20.2 | 18.6 | 45.5 | 41.2 | 20.9 | — | — | 52 |
| **(50)** | 45 | 34 | 88 | 98 | 88 | 36 | 0 | 41 | — | 15 | — | — | 56 |
| **(51)** | 98 | 90 | — | 98 | 90 | — | — | — | — | — | — | — | 60 |
| **(53)** | — | — | — | — | — | 2.4 | — | 8 | 16 | 12 | — | — | 64 |
| **(53)** | — | — | — | — | — | — | — | — | — | — | — | — | 65 |
| **(55)** | — | — | — | — | — | — | 26 | 42 | — | — | 75 | — | 68 |
| **(56a)** | 100 | 28 | — | 72 | 88 | — | 33 | — | — | — | — | — | 69 |
| NaBH$_4$/**(61)** or **(62)** | — | — | — | 76 | — | — | — | — | — | — | — | — | 86 |
| **(64)** | — | — | 84 | 60 | — | — | 27 | — | 39 | 70 | — | 15 | 90 |
| BH$_3$/**(70)** | 35 | — | 96 | 6 | — | 61 | 58 | — | 60 | 79 | 68 | — | 100 |
| **(75)** | — | — | — | — | — | — | — | — | — | 92 | — | — | 102 |
| **(81)** | — | — | — | — | — | 98.6 | 81.3 | 98.9 | — | 99.3 | — | — | 108 |
| H$_2$SiPh$_2$/RhCl/**(89)** | — | — | — | 13.8 | — | 38.5 | — | — | — | 55.8 | — | — | 125 |
| H$_2$SiPh$_2$/RhCl$_3$/**(90)** | — | — | — | — | — | — | 59 | — | — | — | — | — | 126 |

Hydrosilylation by diphenylsilane, catalyzed by $[\{Rh(COD)Cl\}_2]$/(+)-DIOP, has been applied to the reduction of the C=N double bond of imines (**113**) to give amines (**114**), but only in moderate optical yield.[137]

## 1.7.3 SUMMARY

Brown and coworkers have reported a critical examination of the relative effectiveness of various reducing agents for the asymmetric reduction of different classes of ketones.[10] In Table 1 we present an expanded list of 24 typical C=X compounds and 17 selected asymmetric reducing agents or methods.

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# 1.8

# Reduction of C═X to CHXH Using Enzymes and Microorganisms

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## 1.8.1 INTRODUCTION

Applications of enzymes as specific and chiral catalysts in synthetic organic chemistry are now well established, with the utilization of oxidoreductases for C═X → CHXH conversions being one of the best documented areas of their exploitation.[1-3]

Enzymic methods of reduction take place under mild conditions, often at room temperature and at neutral pH, minimizing such problems as isomerization, racemization, epimerization and rearrangement that can plague more traditional methodology. Enzyme specificity permits the catalysis of C═X reductions to be chemospecific in the presence of other, unprotected, functional groups and with regio- and stereospecific control that is difficult, or currently impossible, to achieve nonenzymically in single-step reactions.

The following enzymes and coenzymes are abbreviated: HLADH, horse liver alcohol dehydrogenase; YADH, yeast alcohol dehydrogenase; PTADH, *Pseudomonas testosteronii* alcohol dehydrogenase; NAD(P) and NAD(P)H, oxidized and reduced forms of nicotinamide adenine diphosphate (or its phosphate) respectively; BY, baker's yeast; TBADH, *Thermoanaerobium brockii* alcohol dehydrogenase;

GDH, glycerol dehydrogenase; HSDH, hydroxysteroid dehydrogenase; MJADH, *Mucor javanicus* alcohol dehydrogenase; CFADH, *Curvularia falcata* alcohol dehydrogenase; LDH, lactate dehydrogenase; HSDH, hydroxysteroid dehydrogenase; G6PDH, glucose-6-phosphate dehydrogenase; 3HBDH, 3-hydroxybutyrate dehydrogenase; FDH, formate dehydrogenase; LeuDH, leucine dehydrogenase; and PLADH, pig liver alcohol dehydrogenase.

It is not necessary to use a different enzyme for each new substrate encountered. Some enzymes, such as HLADH have very broad specificities and can accommodate wide structural variations in their substrates. Also, a broad structural range of substrates is often accessible using a very limited number of enzymes of overlapping specificities (Scheme 1).

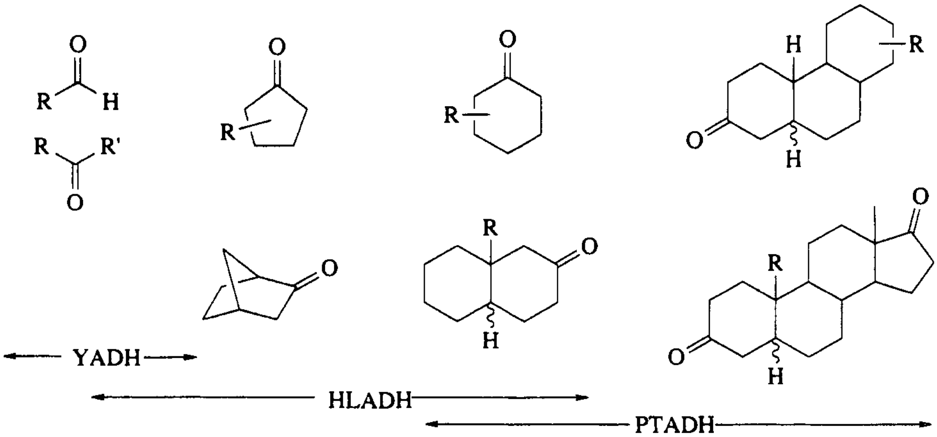

**Scheme 1**

## 1.8.2 SCOPE OF THE METHOD

In selecting the examples for this chapter, preference was given to the most recent literature. However, it must be remembered that research on this topic has been performed by many groups for over 70 years, beginning with the original, and often still definitive, work of the early 1900s.[4]

All biological C=X → CHXH reductions are dependent on the nicotinamide coenzymes NAD(P)H, as illustrated for ketone reduction in equation (1), which shows only the reactive dihydronicotinamide moiety of the NAD(P)H cofactor.

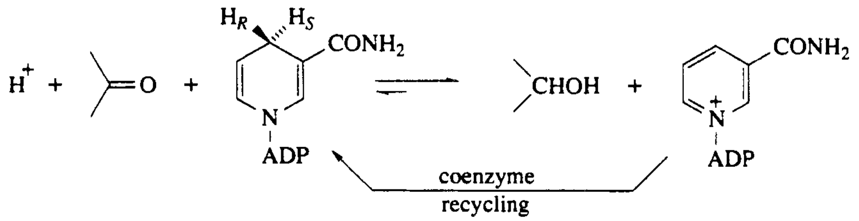

(1)

## 1.8.3 SOURCES OF ENZYMES AND MICROORGANISMS

The oxidoreductases of synthetic value can be grouped into four main supply categories. These are: (i) fully or partially purified enzymes, (ii) yeasts, (iii) other microorganisms, and (iv) mammalian sources. Mammalian enzymes usually have broader specificities than those of microorganisms, but this is compensated for by the much larger selection of microorganisms available.

Biochemical catalogs list several hundred enzymes, including most of the oxidoreductases that have been used to date in preparative-scale reductions. These catalogs also list various yeasts, but the most commonly used of these, BY, is easily obtained at the local supermarket. More specialized yeasts, and the complete range of other microorganisms available, are listed in the catalogs of the national culture collections in the USA, Japan and Europe.[5] In the future, the cloning and site-directed mutagenesis techniques of molecular biology will permit natural enzymes from any source, and mutant enzymes tailored for particular synthetic applications, to be provided in plentiful supply.

Identifying a suitable enzyme or microorganism for reduction of a new substrate is best done by perusal of reviews[1,2,6,7] and by literature search for an analogous transformation of a closely related structure. Chemical Abstracts Registry Numbers for enzymes are obtained from the Index Guide, using the enzyme commission (EC) number for the enzyme of interest. The EC numbers of all known enzymes are listed in the Enzyme Nomenclature handbook.[8] For yeasts and microorganisms, the Chemical Abstract search protocol is based on the name of the organism, again using the Index Guide for clarification, if necessary.

## 1.8.4 PRACTICAL CONSIDERATIONS

The experimental methodology for exploiting enzymes is very straightforward and can be performed with common organic equipment, and with routine experimental and work-up procedures. A range of reaction conditions can be applied, including the use of immobilized enzymes[9] and organic solvents.[10–14] For yeast, often all that is required is to suspend it, together with the substrate, in water at pH 7, and to add some glucose if a growing culture is needed. The procedures for fermentations with other microorganisms are somewhat more sophisticated, but still easily performed in the organic laboratory,[7] perhaps with some minimal initial guidance from a microbiological colleague.

The metabolisms of yeasts and microorganisms ensure a sufficient supply of the NAD(P)H coenzyme during fermentative reductions. Since the NAD(P)H needed for *in vitro* reductions catalyzed by isolated enzymes is expensive, it is used in catalytic amounts only, and continuously regenerated from the inactive pyridinium form of NAD or NADP by an economical recycling system.[15]

Unless specified otherwise, all reductions included in this chapter gave good yields of >90% enantiomeric excess (*ee*) products. Not all products of enzyme-catalyzed reactions meet the minimum % *ee* levels normally required for asymmetric synthetic applications. However, protocols exist for improving *ee*'s of imperfectly specific enzyme-mediated transformations.[14,16–19]

## 1.8.5 ORGANIZATION OF TOPICS

Preparative-scale enzyme-catalyzed reactions are conveniently considered in terms of the different aspects of specificity involved and this approach is followed here. Reactions involving a single aspect of specificity are considered first, followed by examples of different, and increasingly complex, combinations of specificity in a single-step catalysis.

Reductions that do not capitalize on the abilities of enzymes to make stereochemical distinctions are not covered (in this regard, it should be noted that the term 'stereospecificity' is used throughout in its broad, biochemical, connotation) nor are mechanistic aspects, details of which can be found in several excellent texts.[20–23] Although space limitations preclude discussion of the synthetic motivations for the reductions cited, the majority were used to prepare chiral synthons needed in total synthesis.

## 1.8.6 REDUCTION OF C=O TO CHOH

### 1.8.6.1 Enantiomeric Distinctions

Most resolutions of racemates in reductions with oxidoreductases are accompanied by stereoheterotopic face specificity and are covered in a subsequent section. Enantiomeric discrimination alone is exemplified (Scheme 2) by the partial resolutions of binaphthyls (±)-(**1**),[24] of the formyl derivatives (±)-(**2**)[25] and (±)-(**3**),[26] and of the organometallic aldehyde (±)-(**4**)[27] with BY. The racemic 1-indanone complex analog of (±)-(**4**) is also a substrate, but its BY reduction proceeds with low enantioselectivity and to give a mixture of (mainly) *endo*- and *exo*-alcohol products.[28] For the Scheme 2 reactions, the product *ee*'s can be influenced by the nature of the substituents. In the case of the binaphthyl reduction, replacement of —OMe by —Me gave the same *ee* levels, but afforded product alcohol of the opposite absolute configuration. Replacement of the 2-methyl substituent of (±)-(**2**), by —$CH_2Ph$ for example, can also result in reversals of the absolute configurations of the products.[29] Of the various thiocarbamates of (±)-(**3**) evaluated, that with R = $CH_2Bu^t$ gave the highest *ee*.[25] HLADH can also be used for resolution of racemic aldehydes, as shown in Scheme 3.[10,30]

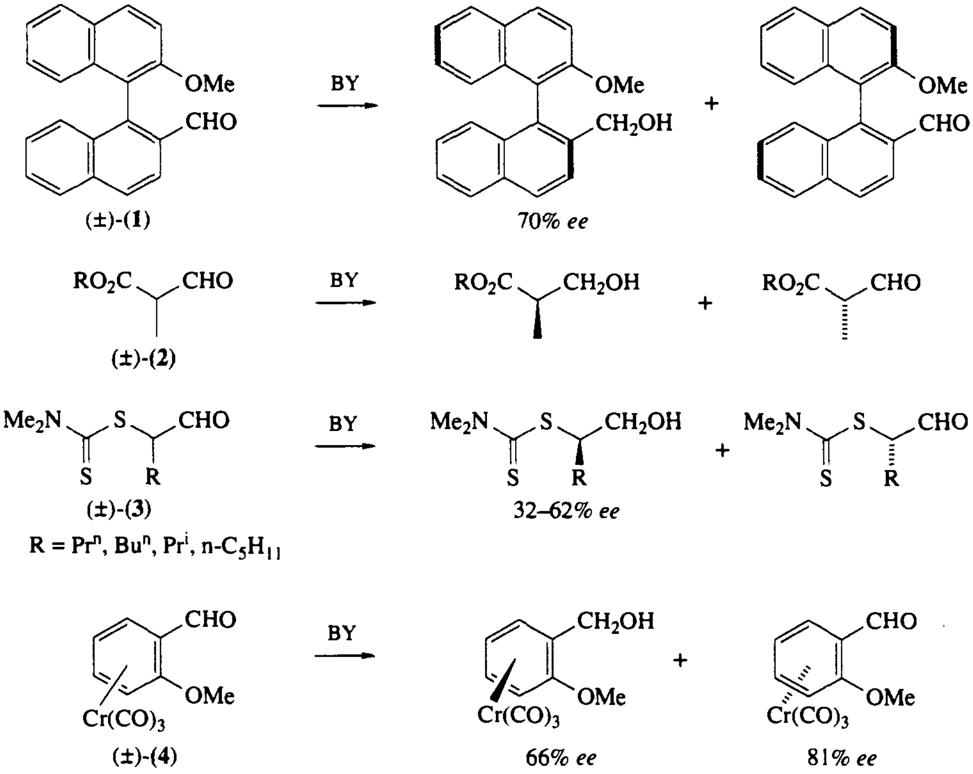
OMe
CHO
BY
CH2OH
(±)-(1)
70% ee
RO2C
(±)-(2)
Me2N
S
R
(±)-(3)
R = Prn, Bun, Pri, n-C5H11
32–62% ee
Cr(CO)3
(±)-(4)
66% ee
81% ee

**Scheme 2**

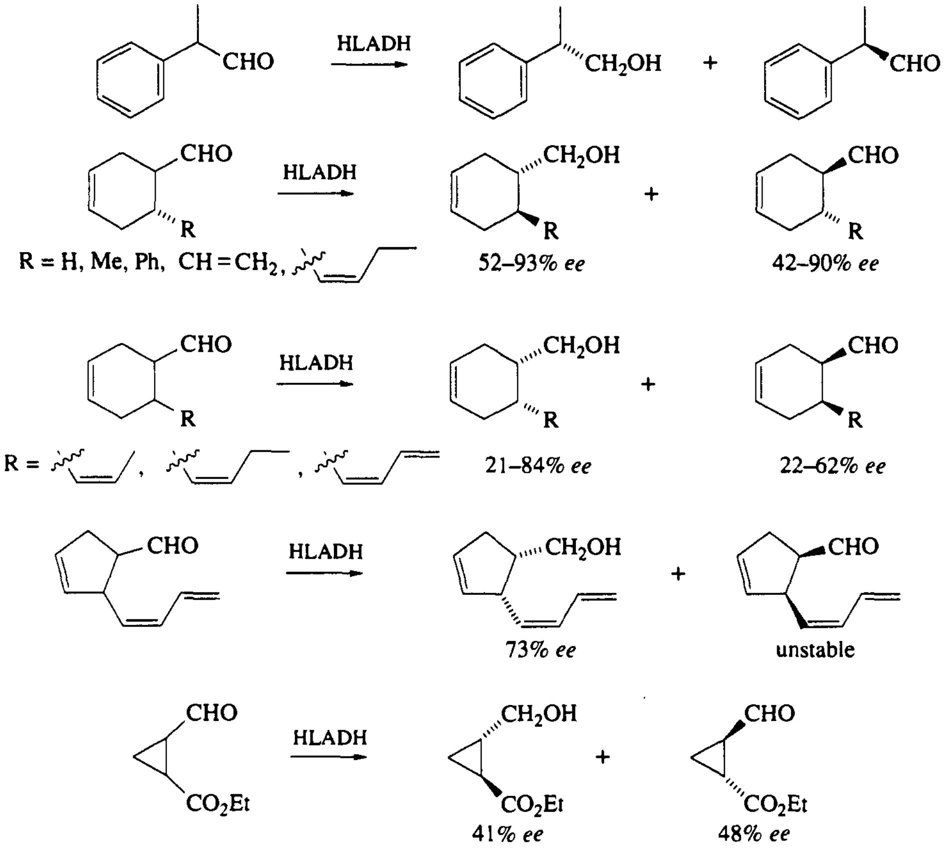
CHO
HLADH
CH2OH
R
R = H, Me, Ph, CH=CH2,
52–93% ee
42–90% ee
R =
21–84% ee
22–62% ee
73% ee
unstable
CO2Et
41% ee
48% ee

**Scheme 3**

### 1.8.6.2 Enantiotopic Face Distinctions

#### *1.8.6.2.1 Monocarbonyl substrates*

A broad spectrum of stereospecific reductions of prochiral acyclic ketones has been recorded (Scheme 4). These arise by enzyme-controlled delivery of the hydride equivalent to only one of the two enantiotopic faces of a C═O group. Such reductions are achievable with many different oxidoreductases, as illustrated for the conversions of (**5a**) → (**6a**) with GDH,[31] of (**5b–d**) → (**6b–d**) with TBADH,[32–34] of (**5e–h**) → (**6e–h**) with BY,[35–41] of (**5i**) → (**6i**) with *Kloeckera magna*[42] and of (**5j**) → (**6j**) with *Acinetobacter calcoaceticus*.[43]

The yeast-induced reduction of (**5e**) → (**6e**), (R = substituted phenyls, R′ = Me) is one of the very first preparative-scale alcohol dehydrogenase catalyzed reactions to have been reported.[35] While the transformations of (**5a–j**) demonstrate that broad structural tolerances are possible in the substrate ketones, the enzymes are sometimes very discriminating. For example, while the BY-catalyzed reductions of the 2-, 3- and 4-substituted pyridyl ketones (**5g**) proceed smoothly with high stereospecificity,[39,41] the analogous furanyl and thiophenyl ketones give virtually racemic product alcohols, and 2-acetylpyrrole is not a substrate at all.[39]

Diketones or keto aldehydes in which one carbonyl group is protected, as in (**7**) and (**10**) of Scheme 5, may also be reduced stereospecifically to the corresponding alcohols, (**8**) and (**11**). These can then be hydrolyzed chemically to give the hydroxy aldehydes (**9**) or hydroxy ketones (**12**), respectively.[44,45]

The absolute configurations of the product alcohols of acyclic ketone reductions can be reliably predicted for many oxidoreductases by using the Prelog rule (Scheme 6).[1a,46] More complex models are required for cyclic ketones, as will be seen later. For a given substrate, oxidoreductases are usually available that deliver hydride equivalents from opposite enantiotopic faces. This can be exploited to produce either alcohol enantiomer at will, as noted in Scheme 7 by the reduction of (**13**) to either (*R*)- or (*S*)-(**14**).[47] Organometallic ketones can also be reduced with enantiotopic specificity. This is demonstrated by the conversions (Scheme 8) of the ferrocenyl[48] and chromium carbonyl ketones (**15**) → (**16**) and (**17**) → (**18**), respectively.[28]

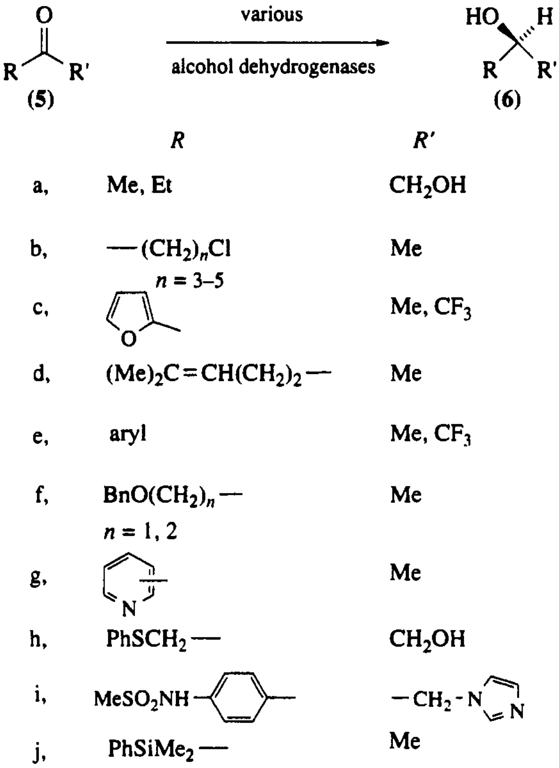

**Scheme 4**

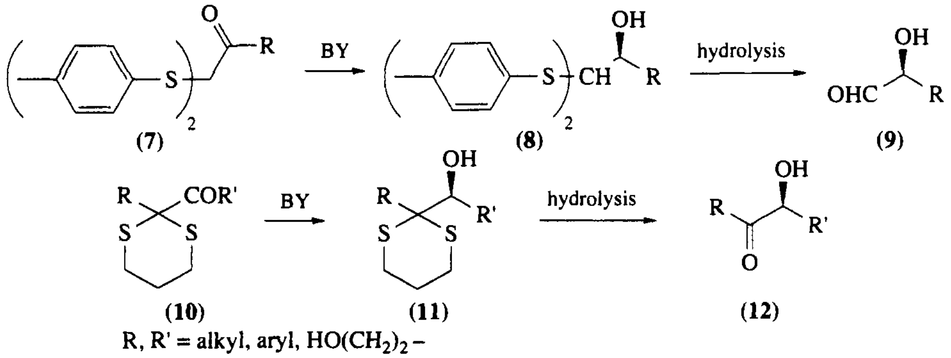
BY
hydrolysis
(7)
(8)
(9)
BY
hydrolysis
(10)
(11)
(12)
R, R' = alkyl, aryl, HO(CH2)2-

**Scheme 5**

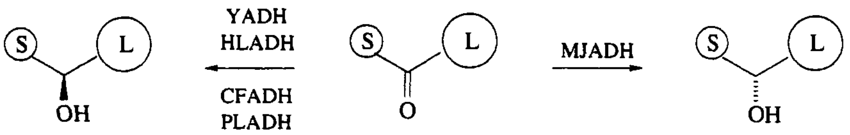
YADH
HLADH
CFADH
PLADH
MJADH

**Scheme 6**

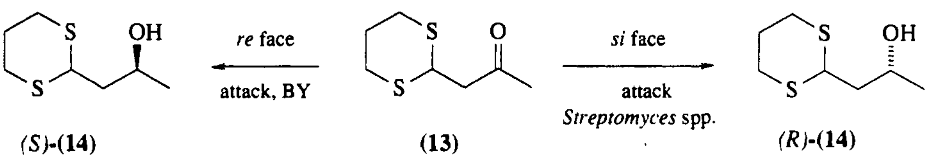
*re* face
attack, BY
*si* face
attack
*Streptomyces* spp.
(*S*)-(14)
(13)
(*R*)-(14)

**Scheme 7**

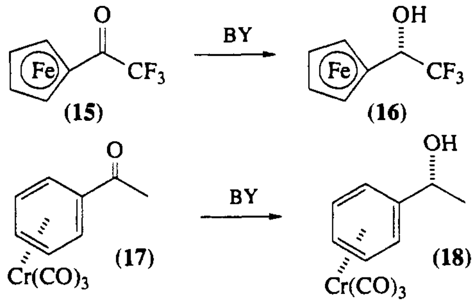
BY
(15)
(16)
BY
(17)
(18)

**Scheme 8**

### *1.8.6.2.2 Diketone substrates*

The two carbonyl groups of symmetrical diketones are distinguishable, with the carbonyl group undergoing reduction doing so with enantiotopic specificity. Some acyclic and monocyclic examples are shown in Scheme 9.[32,44,49,50] Once more, enantiomeric products can be selected by the use of organisms with opposite enantiotopic face specificities, as shown for the reduction of (**19**) to (*R*)- or (*S*)-(**20**) (Scheme 10).[51]

The (**21**) → (**22**) transformation of Scheme 11 is an interesting variation of this category in that, while reduction of both homotopic carbonyl groups of the racemic substrate (**21**) occurs with diastereotopic *re* face specificity, the product (**22**) is still racemic.[52] The (**23**) → (**24**) reduction is analogous, with only one of the two homotopic carbonyl groups reduced, again with diastereotopic face specificity.[53]

Reductions of symmetrical bicyclic diketones may also be effected selectively, as illustrated in Scheme 12. The stereospecificities of the HLADH-catalyzed transformations of the unsaturated decalindiones (**25**) and (**27**) to the corresponding hydroxy ketones (**26**) and (**28**),[54] and in fact all specificity aspects of this enzyme, are fully predictable using a simple to use, cubic-space model of the enzyme's active site.[55]

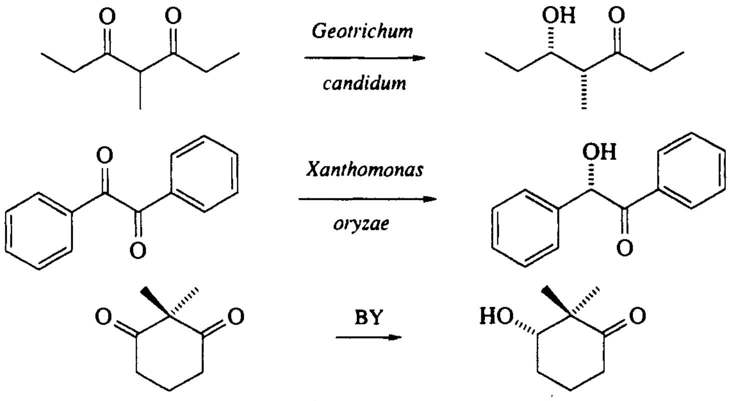
Geotrichum candidum
Xanthomonas oryzae
BY

Scheme 9

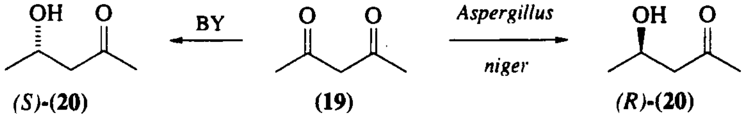
BY
Aspergillus niger
(S)-(20)
(19)
(R)-(20)

Scheme 10

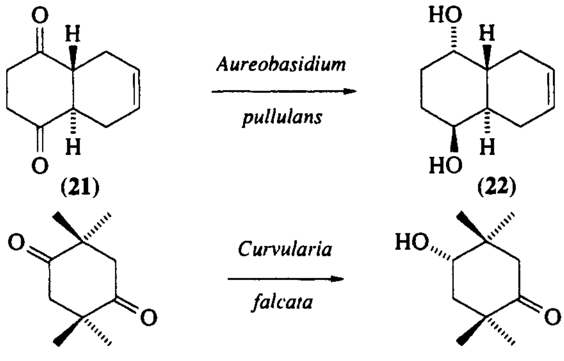
Aureobasidium pullulans
(21)
(22)
Curvularia falcata
(23)
(24)

Scheme 11

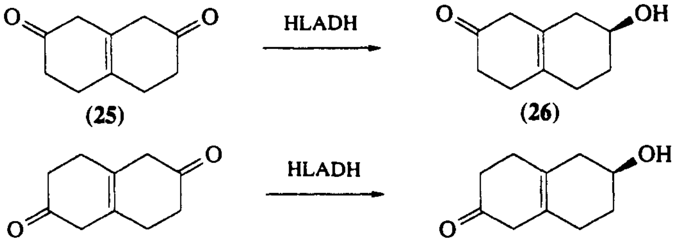
HLADH
(25)
(26)
HLADH
(27)
(28)

Scheme 12

### 1.8.6.2.3 Keto acid and ester substrates

Stereospecific reductions of α-keto acids are well documented.[56–60] L- and D-lactate dehydrogenases from common mammalian or bacterial sources are available for this purpose. By using a preselected L- or D-LDH, the preparation of a (2*S*)- or (2*R*)-hydroxy acid of >99% *ee* can be virtually assured. The structural range of α-keto acids (**29**) that has been subjected to preparative-scale reductions to hydroxy acids (**30**) is summarized in Scheme 13 for both L-[58,60,61] and D-LDH.[59,61,62] Plentiful supplies of such enzymes are guaranteed by their cloning and overexpression.[60]

Stereospecific reduction of α-keto esters is also readily achieved (Scheme 14). BY is effective for the (**31**) → (**32**) reduction,[63] but this is not always the case. Different enzyme sources are more effective for

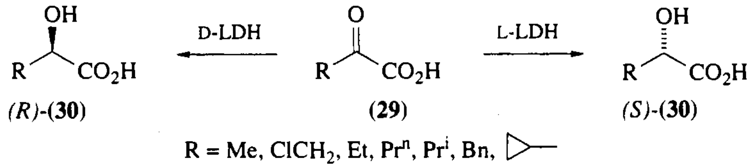

**Scheme 13**

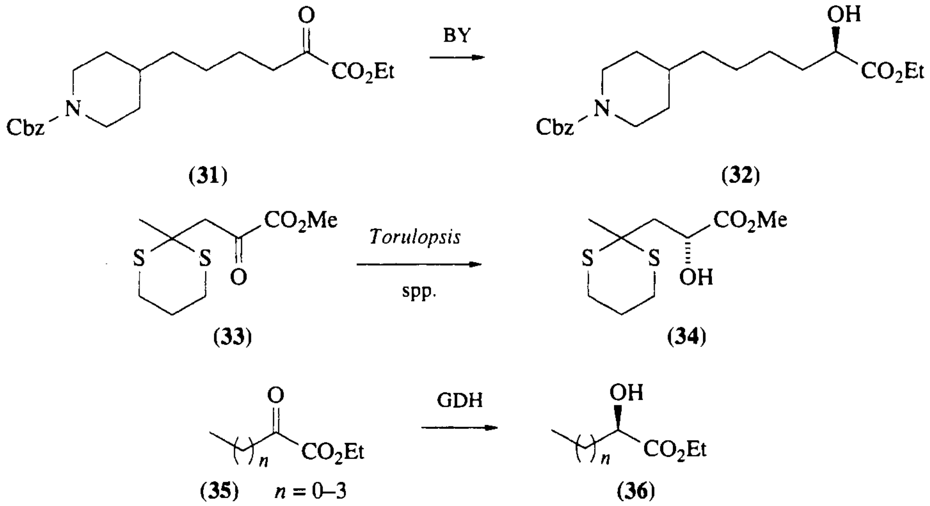

**Scheme 14**

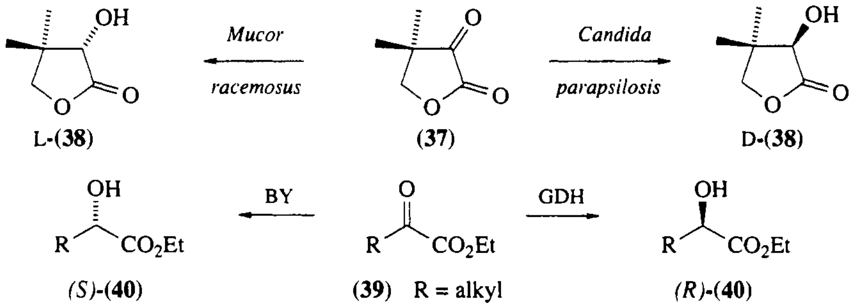

**Scheme 15**

the (33) → (34)[64] and (35) → (36)[65] conversions. Using different organisms with opposite enantiotopic face specificities permits both enantiomers of a product to be produced at will from the same substrate. This is demonstrated in Scheme 15 by the reduction of (37) to either natural[66] D- or unnatural L-pantoyllactone (38)[67] and of simple α-keto esters (39) to either the (*R*)-[65] or (*S*)-enantiomer[68] of (40).

A broad structural range of β-keto esters (41) can be reduced with enantiotopic specificity to give either the (*R*)- or (*S*)-β-hydroxy esters (42; Scheme 16).[26,69–81] Whether the configurations of the stereogenic centers of (42) will be (*R*) or (*S*) is determined by the nature of the organisms and of the substituents. However, with the appropriate combination of organisms, hydroxy esters of either (*R*)- or (*S*)-configuration can be produced from the same substrate, with either *si* or *re* face attack of the carbonyl group being selected. This is shown in Scheme 17, where the reduction of (43) to either (*R*)- or (*S*)-(44) can be achieved.[82] In this latter case, the enzymes exploited were located in different organisms. However, it is possible for 'enantiotopic' enzymes to be contained in the same organism. For example, yeast contains two fatty acid synthetases[83,84] with alcohol dehydrogenase like capabilities. These have opposite enantiotopic specificities and also distinct substrate specificities. It is possible to select between these 'L' and 'D' enzymes by varying the steric size of the β-keto ester substituents, as exemplified in Scheme 18.[19] Controlled formation of an (*R*)- or (*S*)-β-hydroxy ester from a common β-keto ester precursor can also be preordained by using enzymes with opposite enantiotopic face specificities.[85] Additional control of enantiotopic selectivity in a multiple-enzyme organism can be exerted by restricting substrate or product diffusion, as between the free and immobilized yeasts.[18] This selectivity is again controllable by vari-

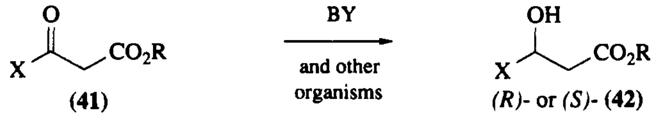
O
$CO_2R$
X
(41)
BY
and other organisms
OH
$CO_2R$
X
(R)- or (S)- (42)

$X = C_1–C_{15}$ alkyl, aryl, $CH_2O$alkyl/aryl, $CH_2Cl$, OH, S-alkyl/aryl, NHCOR, $CH_2N_3$, $CCl_3$, $CF_3$, $CO_2Me$, $CH_2CO_2H$; $R = C_1–C_8$ alkyl, aryl; $CO_2R$ = CONHR, CSSMe, $SO_2Ph$, $SCSNMe_2$

**Scheme 16**

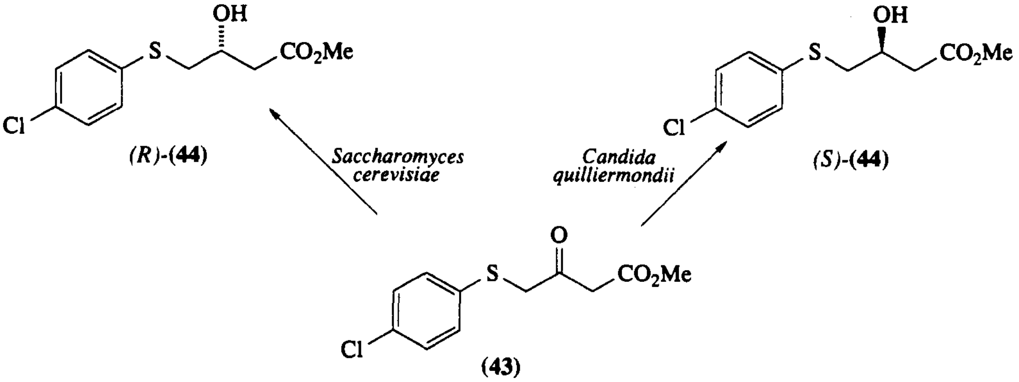
OH
S
$CO_2Me$
Cl
(R)-(44)
Saccharomyces cerevisiae
Candida quilliermondii
OH
S
$CO_2Me$
Cl
(S)-(44)
O
S
$CO_2Me$
Cl
(43)

**Scheme 17**

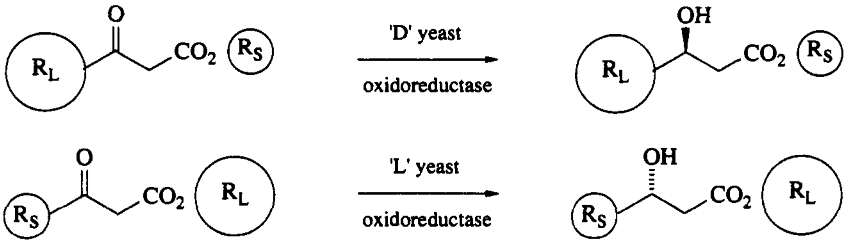
O
$R_L$
$CO_2$
$R_S$
'D' yeast
oxidoreductase
OH
$R_L$
$CO_2$
$R_S$
O
$R_S$
$CO_2$
$R_L$
'L' yeast
oxidoreductase
OH
$R_S$
$CO_2$
$R_L$

**Scheme 18**

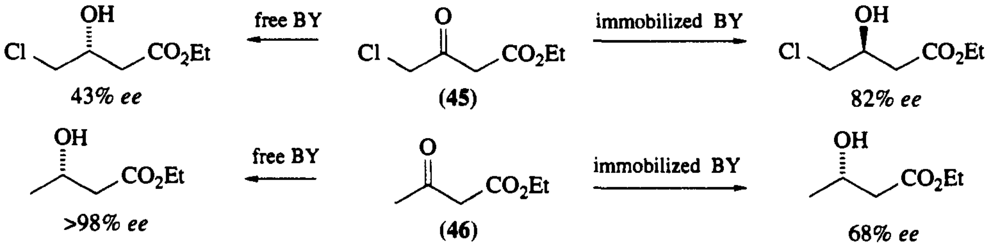
OH
Cl
$CO_2Et$
43% ee
free BY
O
Cl
$CO_2Et$
(45)
immobilized BY
OH
Cl
$CO_2Et$
82% ee
OH
$CO_2Et$
>98% ee
free BY
O
$CO_2Et$
(46)
immobilized BY
OH
$CO_2Et$
68% ee

**Scheme 19**

ations in substrate structure, as illustrated by the different stereospecificity responses towards (**45**) and (**46**; Scheme 19). Stereoselectivity can also be influenced by growth conditions[73,86] and by added solvents.[73,87]

Although reductions of β-keto esters are by far the most common, yeast-catalyzed reductions of β-keto acids are also viable.[88,89] Reductions of other keto acids and esters, where the carbonyl group is γ, or further, separated from the acid or ester function, also proceed stereoselectively, as demonstrated by the Scheme 20 conversions.[73,90–94] Reduction of an α,β-unsaturated ketone is somewhat unusual, but examples are known (Scheme 21).[95]

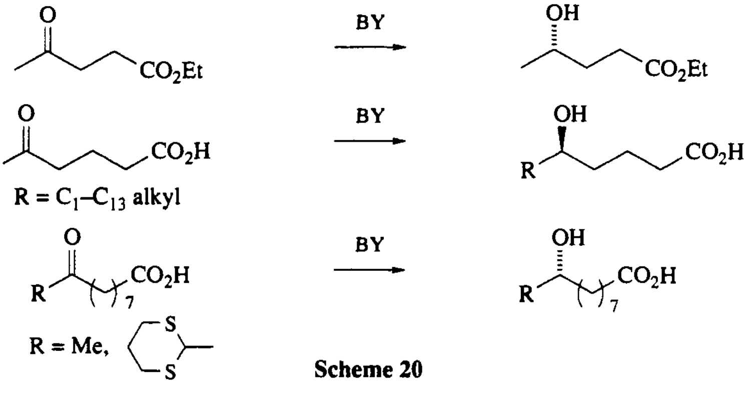
BY
BY
BY
R = C1–C13 alkyl
R = Me,

**Scheme 20**

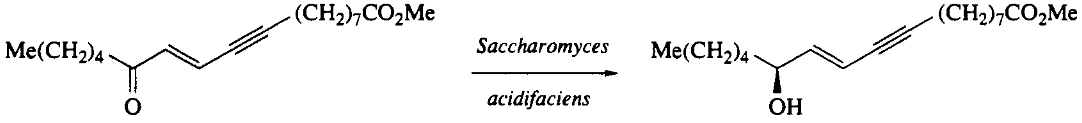
Saccharomyces
acidifaciens

**Scheme 21**

### 1.8.6.3 Diastereotopic Face Distinctions

In contrast to the multiplicity of examples of diastereotopic face discriminations in combination with other enzyme specificity discussed later, there are relatively few alcohol dehydrogenase catalyzed reductions that involve diastereotopic face selectivity alone. However, whenever a carbonyl group is present in a single chiral stereoisomer, diastereotopically face-selective reductions are possible. The reductions of the L-homocysteine derivative (**47**) → (**48**),[96] and of the (–)-oxocineole (1*S*,4*R*)-(**49**) → (**50**),[97] are two such examples (Scheme 22). A single stereoisomer can also be converted into epimeric alcohol products by employing organisms with opposite diastereotopic face specificities (equation 2 and Scheme 23).[97-99] The conversions of (1*R*,4*S*)-(**49**) to (**51**) and (**52**)[97] complement that of the reduction of its enantiomer (1*S*,4*R*)-(**49**) to (**50**) in Scheme 22. The facility with which reduction of quadrone (**53**) to either (**54**) or (**55**)[99] can be accomplished demonstrates very clearly that structural complexity is not a barrier to enzyme-catalyzed reductions.

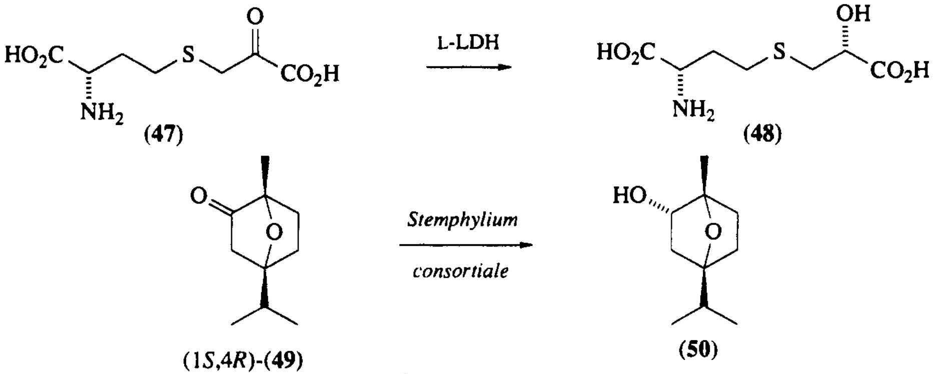
L-LDH
(47)
(48)
Stemphylium
consortiale
(1S,4R)-(49)
(50)

**Scheme 22**

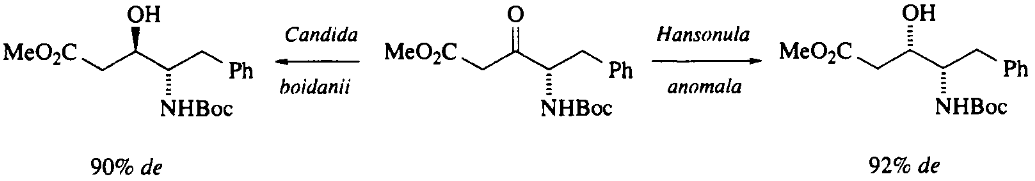
Candida
boidanii
Hansenula
anomala
90% de
92% de

(2)

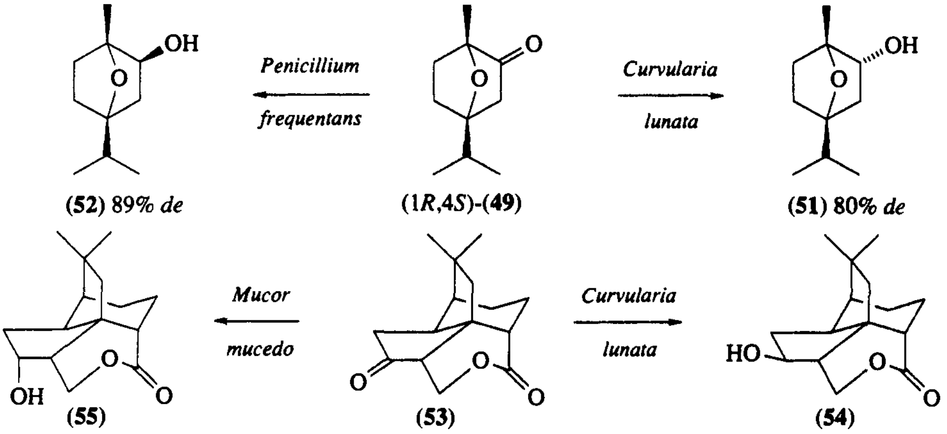
Penicillium frequentans
Curvularia lunata
(52) 89% de
(1R,4S)-(49)
(51) 80% de
Mucor mucedo
Curvularia lunata
(55)
(53)
(54)

Scheme 23

### 1.8.6.4 Combinations of Specificity

Despite the advances that have been made using nonenzymic methods in asymmetric synthesis, the degrees of control that are possible with enzymes able to combine two or more specificities in a single-step reaction remain unchallenged. Several different chemo- or regio-specific and enantiotopic face specific combinations are illustrated in Scheme 24 by the reduction of α-[100] or β-diketones[100–102] (see also Scheme 27). The control of regiospecificity that can be exerted by small structural changes is exemplified by the effect of either an *o*- or *p*-methyl group on the reductions of **(56)** and **(58)** to **(57)** and **(59)** respectively.[49] Opposite enantiotopic face specificities can be selected by using appropriate organisms (Scheme 25).

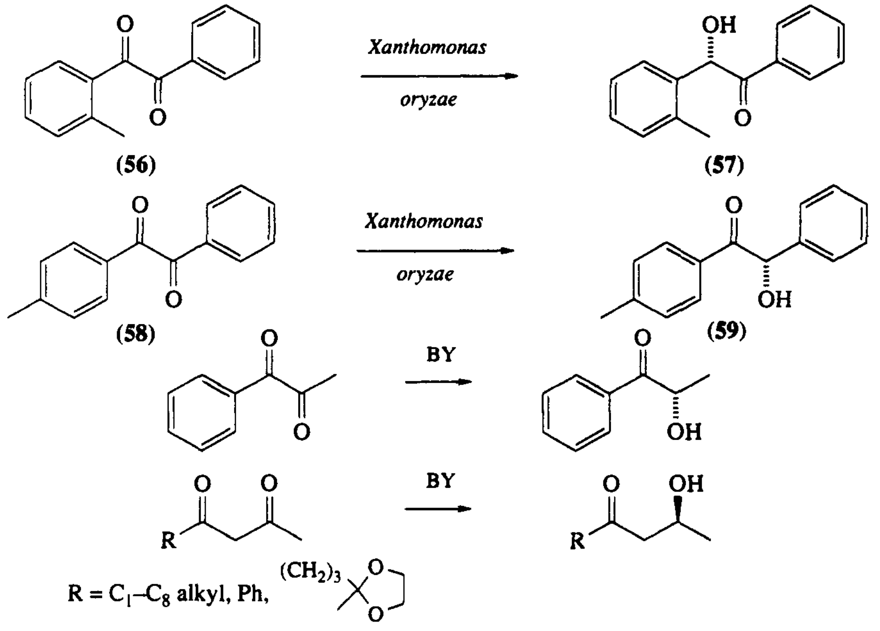
Xanthomonas oryzae
(56)
(57)
Xanthomonas oryzae
(58)
(59)
BY
BY
R = $C_1$–$C_8$ alkyl, Ph, $(CH_2)_3$

Scheme 24

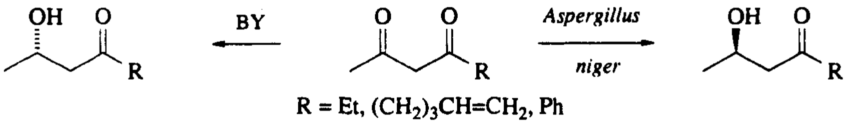
BY
Aspergillus niger
R = Et, $(CH_2)_3CH{=}CH_2$, Ph

Scheme 25

Regiospecificity combined with diastereotopic face specificity is seen in the reduction of the trione (**60**) to (**61**) (Scheme 26).[103] In Scheme 27 the reduction is quite regiospecific, but both diastereotopic faces of the exocyclic ketone function of (**62**) are attacked to give the *erythro*-(**63**) and *threo*-(**64**) hydroxy ketone products.[104a] The degree to which regio specificity and diastereotopic face specificity can be controlled with different enzymes is shown in the bile acid reductions of Scheme 28.[105]

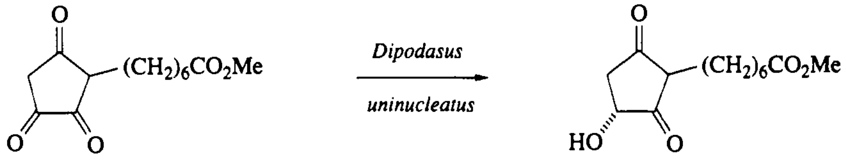
O
(CH2)6CO2Me
O
O
Dipodasus
uninucleatus
O
(CH2)6CO2Me
HO
O

(**60**) (**61**)

**Scheme 26**

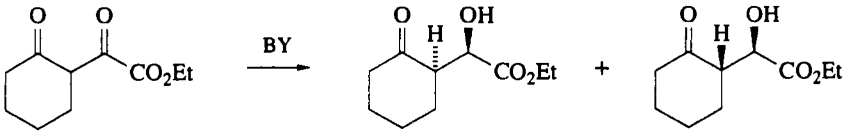
O
O
CO2Et
BY
O
OH
H
CO2Et
+
O
OH
H
CO2Et

(±)-(**62**) (**63**) (**64**)

**Scheme 27**

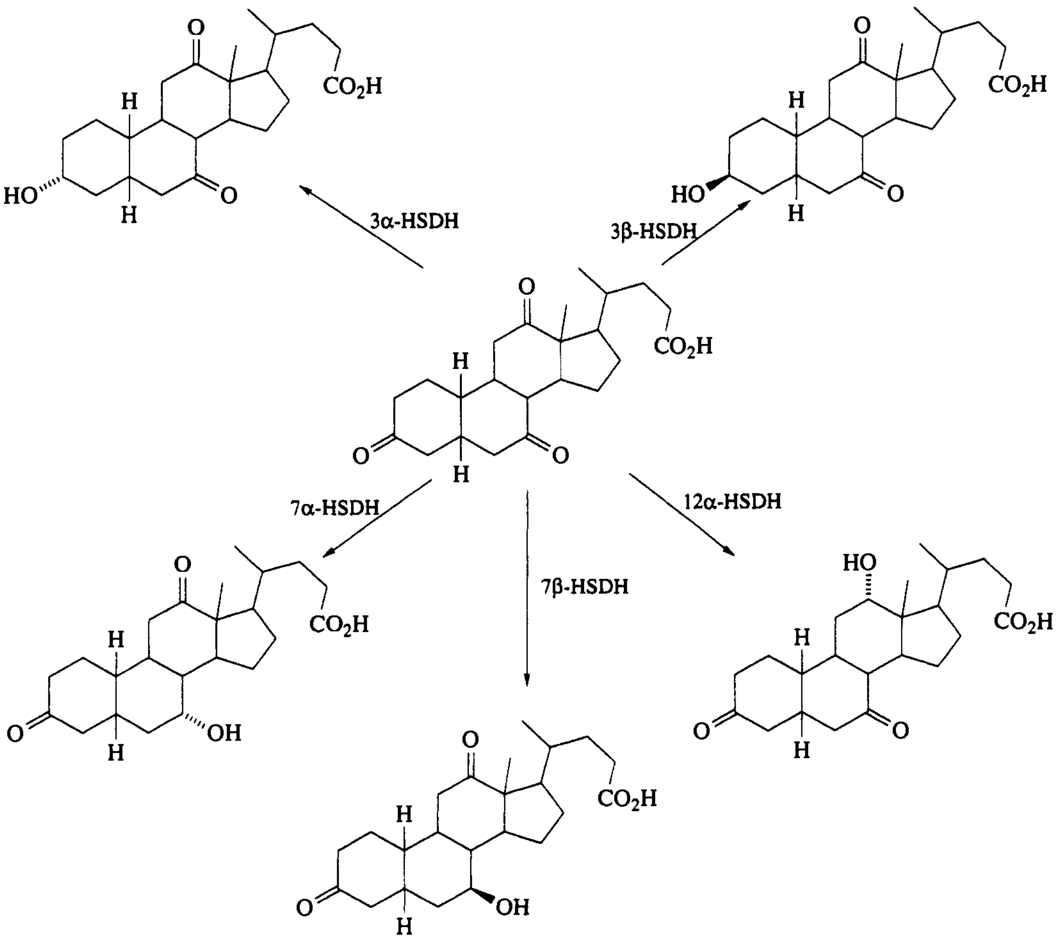
O
H
CO2H
HO
H
O
3α-HSDH
O
H
CO2H
HO
H
O
3β-HSDH
O
H
CO2H
O
H
O
7α-HSDH
7β-HSDH
12α-HSDH
O
H
CO2H
O
H
OH
O
H
CO2H
O
H
OH
HO
H
CO2H
O
H
O

**Scheme 28**

The largest group of substrates reduced with combined specificity is that involving concurrent enantiomeric and diastereotopic face discrimination. Examples for acyclic substrates are given in Schemes 29 and 30. As Scheme 29 shows, variously functionalized racemic ketones (**65**),[31] α-keto esters (**66**)[104b] and β-keto esters (**67**),[106] (**68**)[107,108] and (**69**)[109] are transformed into the corresponding *threo*- and *erythro*-hydroxy diastereomers. The transformations of Scheme 30 are of particular interest since they lead to carbohydrate chirons of unusual or unnatural configurations.[110–112] The combination of diastereomeric and diastereotopic face selectivity is also feasible. This is shown in Scheme 31, again for carbohydrate synthon production.[113] For the BY-catalyzed reduction of (±)-(**70**), the configuration at the asterisked carbon is critical. Only diastereomers that have the (*S*)-configuration at this center are substrates. This keystone selection factor, together with the yeast preferences at the other stereogenic centers, results in (**71**) being the only product.[113]

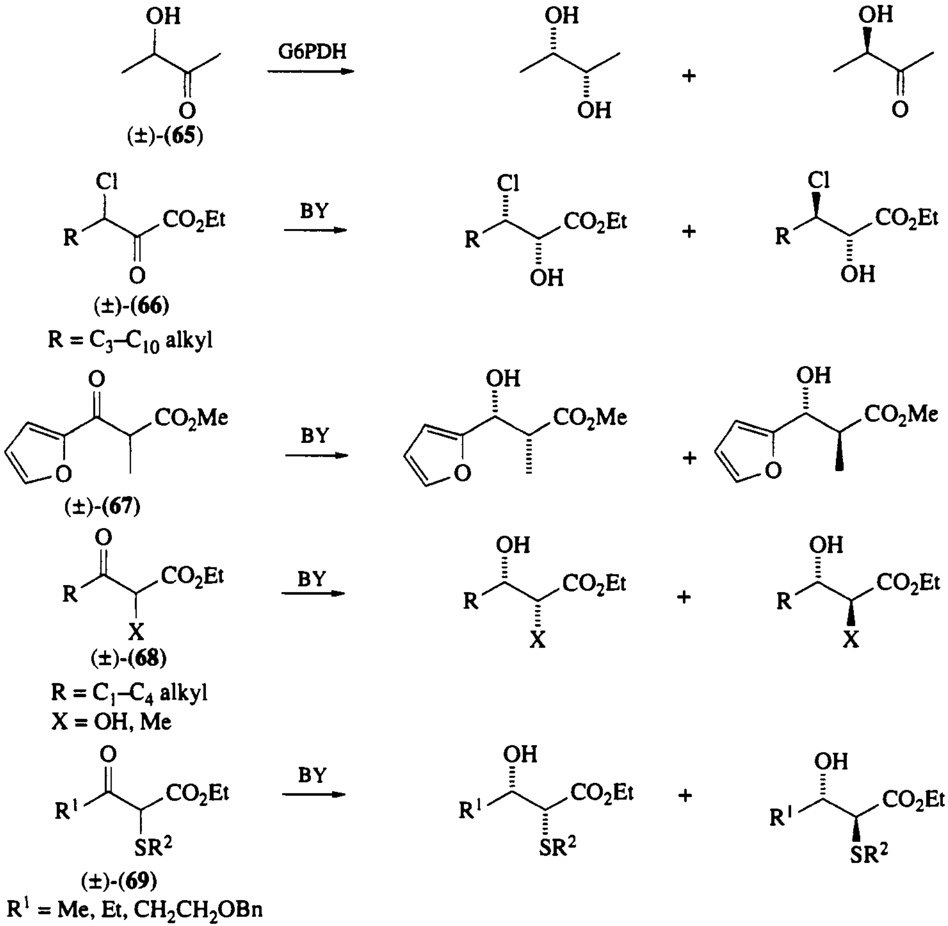

**Scheme 29**

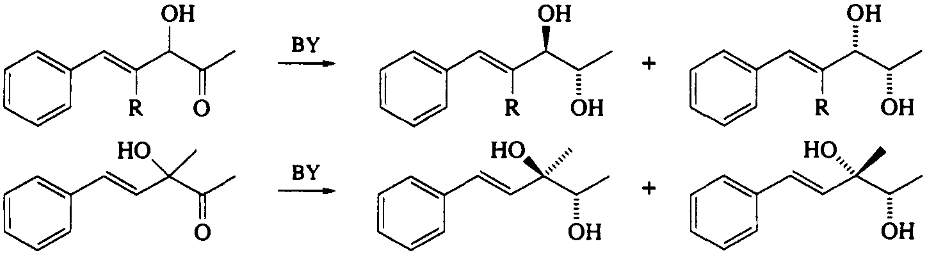

**Scheme 30**

When the stereogenic center of the racemate can undergo epimerization under the reduction conditions, the unreactive enantiomer will racemize continuously, thereby enabling complete conversion of

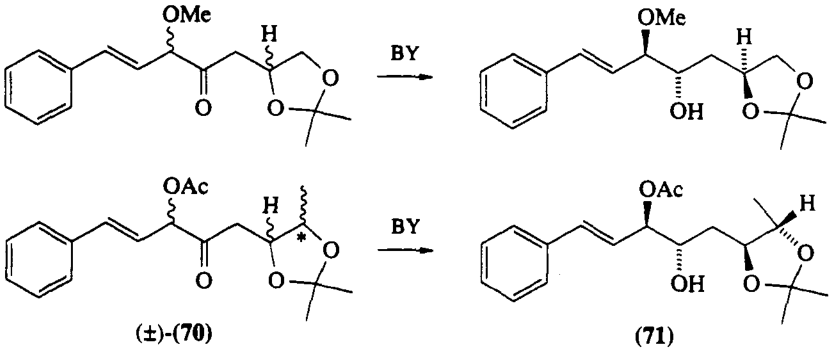

**Scheme 31**

substrate to a single product stereoisomer to be achieved. This is illustrated in Scheme 32 for the reduction of racemic β-keto esters.[77] By using the appropriate organism, different enantiomeric and diastereotopic face specificities can be preselected (Scheme 33).[114]

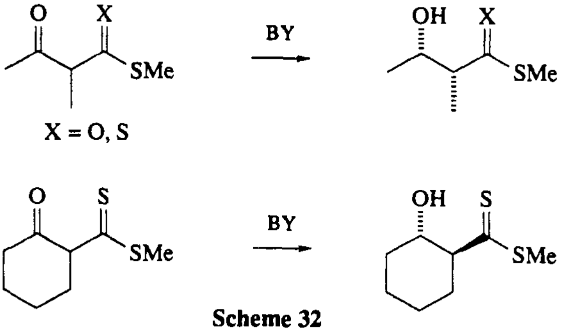

**Scheme 32**

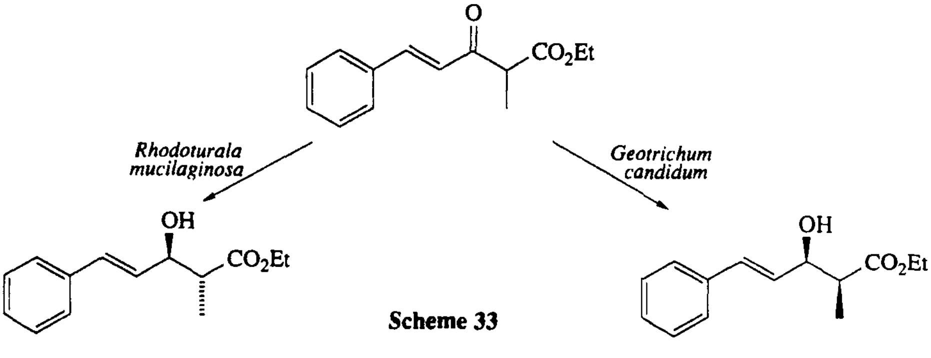

**Scheme 33**

The results with monocyclic ketones are similar. In Scheme 34, enzymic control of enantiomeric plus diastereotopic face specificity enables stereoisomerically pure product diols (**73**) and (**75**) and unreactive enantiomers (*R*)-(**72**) and (*R*)-(**74**) to be obtained from the racemates (±)-(**72**) and (±)-(**74**).[1a,31,115] In the case of the pyranones (±)-(**76**),[116] both enantiomers are reduced. When enantiomeric specificity is lacking in this way, the initial reaction is often that no resolution is possible by the enzymic procedure. However, this is not true when each enantiomer is reduced stereospecifically to a single diastereomeric product, such as (**77**) or (**78**); these are then easily separated by chromatography. In such situations, which are readily identified for HLADH using the cubic-space active-site model,[55] the reactions are allowed to proceed to completion rather than terminating at the 50% point that would apply for enantiomerically specific reductions. Using this approach, quantitative yields of each pure diastereomer may be isolated.[116] When the stereocenter is adjacent to a carbonyl group, epimerization of the unreactive enantiomer can occur under the reaction conditions. Then only the single stereoisomer product derived from the reactive enantiomer is formed. This is outlined in Scheme 35 for the BY-mediated reductions of racemic carbo- and hetero-cyclic β-keto esters and β-keto-thio esters.[117–122] By appropriate selection of the enzyme or microorganism, reductions in which the unreactive enantiomer racemizes under the reaction conditions can be directed towards either enantiomer of the starting racemate. Scheme 36 shows controlled reductions of this type, of 2-oxocyclohexanecarboxylic acid[123] or ester[117] (**79**) that give only the β-hydroxy products (**80**) of the (1*R*,2*S*) or (1*S*,2*R*) series respectively. With the right microorganisms, combinations of enantiomeric and diastereotopic face specificities can be exploited with racemic substrates to give all four possible product stereoisomers (Scheme 37).[106]

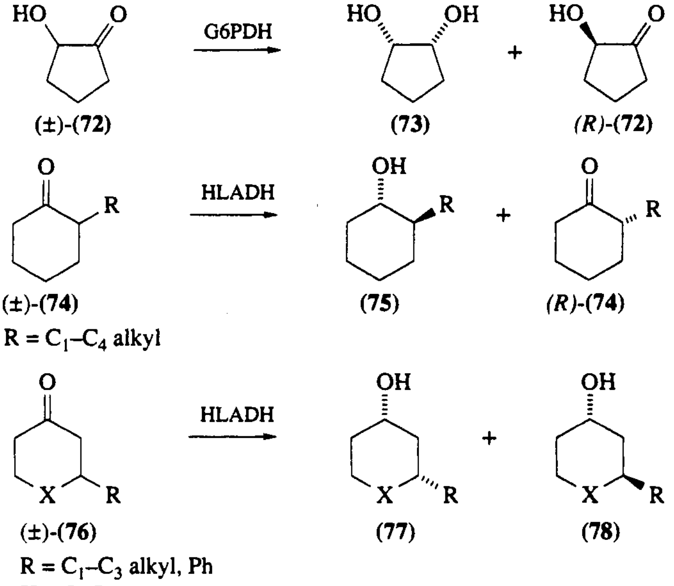
HO
O
G6PDH
HO
OH
+
HO
O
(±)-(72)
(73)
(R)-(72)
O
R
HLADH
OH
R
+
O
R
(±)-(74)
R = C1–C4 alkyl
(75)
(R)-(74)
O
X
R
HLADH
OH
X
R
+
OH
X
R
(±)-(76)
R = C1–C3 alkyl, Ph
X = O, S
(77)
(78)

**Scheme 34**

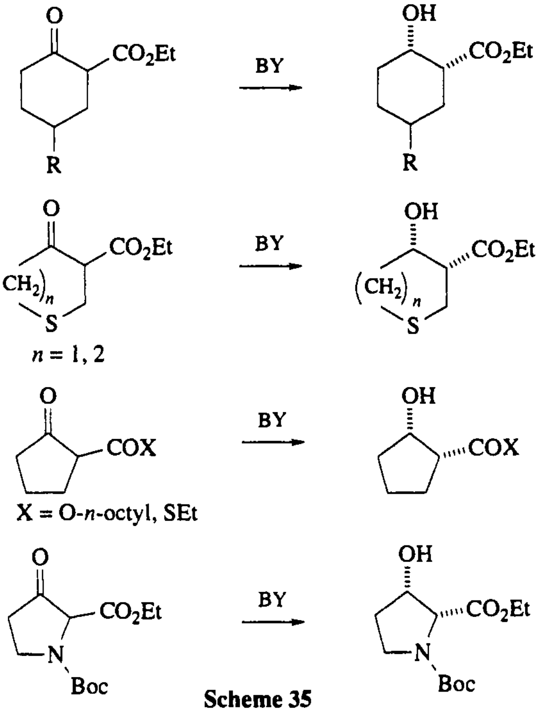
O
CO2Et
R
BY
OH
CO2Et
R
O
CO2Et
(CH2)n
S
n = 1, 2
BY
OH
CO2Et
(CH2)n
S
O
COX
X = O-n-octyl, SEt
BY
OH
COX
O
CO2Et
N
Boc
BY
OH
CO2Et
N
Boc

**Scheme 35**

Enantiomeric and diastereotopic face specific reductions are also readily effected on racemic bicyclic ketones. An illustration of the broad structural range that is amenable to enzyme-catalyzed transformation in this way is given in Scheme 38. While 2-decalones, such as (±)-(**81**)–(**83**),[124,125] and the related heterocyclic analogs (±)-(**85**)[126] are good substrates for HLADH, the 1-decalone (±)-(**84**) is not. However, by changing enzymes to MJADH, (±)-(**84**) becomes a good substrate.[127–129] Similarly, TBADH is a highly satisfactory catalyst for stereospecific reduction of (±)-(**86**), but will not accept its dimethyl

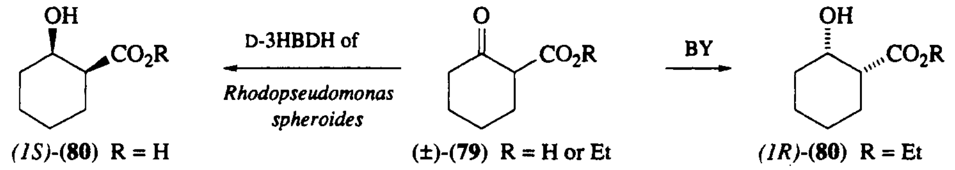
D-3HBDH of
*Rhodopseudomonas spheroides*
BY
(*1S*)-(**80**) R = H
(±)-(**79**) R = H or Et
(*1R*)-(**80**) R = Et

**Scheme 36**

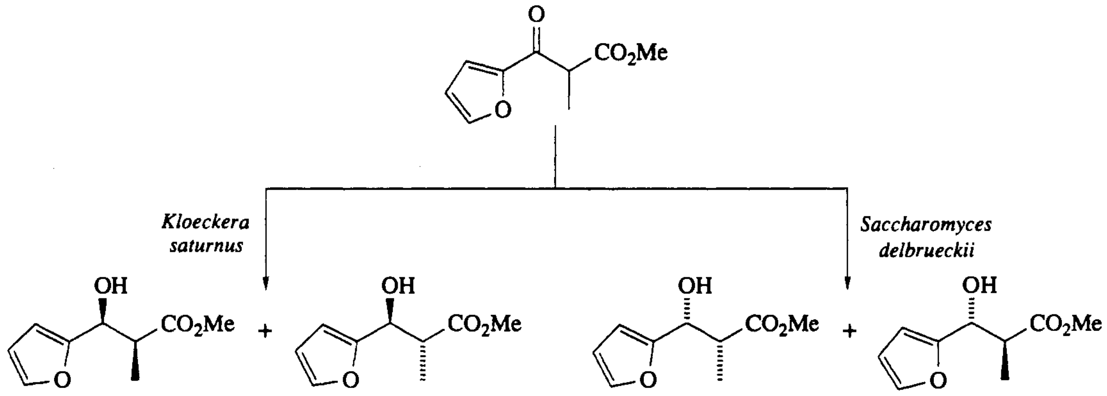
*Kloeckera saturnus*
*Saccharomyces delbrueckii*

**Scheme 37**

analog (±)-(**87**).[130] Here again, a change of enzyme to 3α,20β-HSDH solves the problem,[130] while BY is the recommended catalyst for conversions of (±)-(**88**).[131] As would be expected for similar structures, the same stereochemical pattern is followed by BY-catalyzed reductions of (±)-(**89**),[132] (±)-(**90**)[133] and (±)-(**91**).[134]

As with some of the racemic ketones discussed previously (Schemes 27, 29, 30, 31 and 37), reductions of bicyclic substrates to all possible stereoisomeric products can be achieved. The BY-mediated reduction of (±)-(**86**) to (**92**) and (**93**)[135] establishes this point (Scheme 39) and contrasts the more specific TBADH-promoted reaction of Scheme 38.[130]

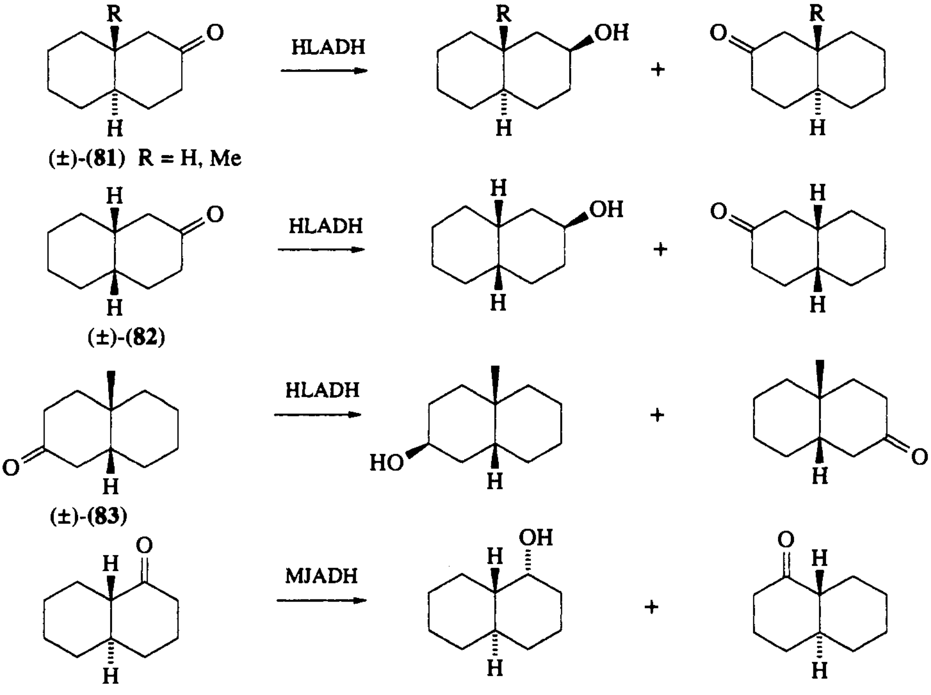
HLADH
(±)-(**81**) R = H, Me
HLADH
(±)-(**82**)
HLADH
(±)-(**83**)
MJADH
(±)-(**84**)

**Scheme 38**

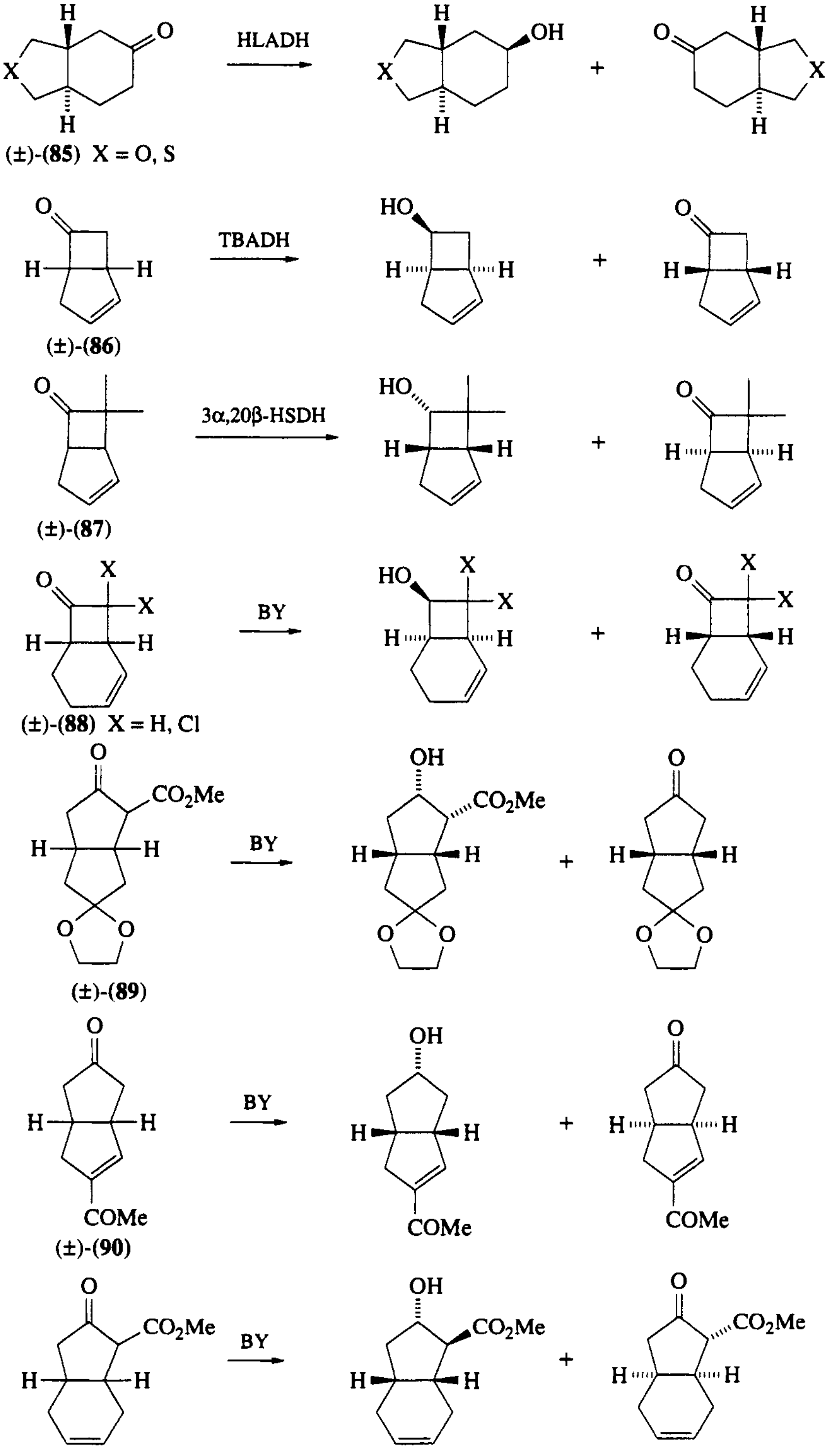

(±)-(**85**) X = O, S

(±)-(**86**)

(±)-(**87**)

(±)-(**88**) X = H, Cl

(±)-(**89**)

(±)-(**90**)

(±)-(**91**)

**Scheme 38** ***(continued)***

Exploitation of the complementary specificities of enzymes from different sources towards the same racemic substrate permits very precise control of the product stereochemistry. For example, any one of the three diastereomeric 2-decalols (**94**)–(**96**) can be obtained at will from (±)-*trans*-2-decalone (**81**; R = H) using the alcohol dehydrogenases HLADH, MJADH or CFADH, respectively (Scheme 40). The stereospecificities of these three enzymes are well documented and a simple active site model of predictive value is available for each.[1a,55] Racemic bridged bicyclic ketones are similarly discriminated, either

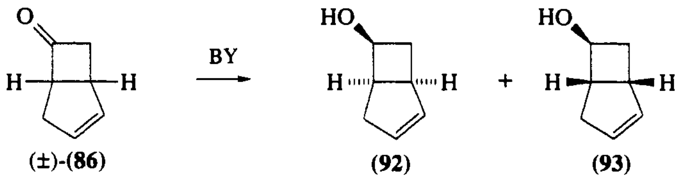

Scheme 39

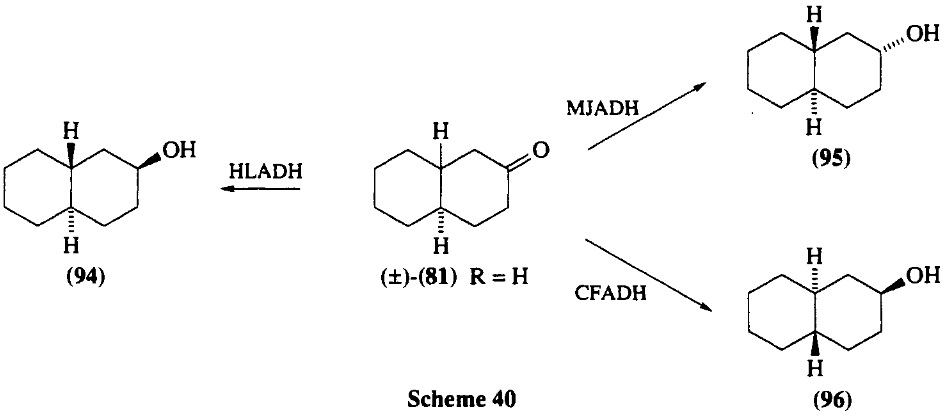
HLADH
MJADH
CFADH
(94)
(±)-(81) R = H
(95)
(96)

Scheme 40

to give the reduction products of one enantiomer, with recovery of the unreactive ketone enantiomer (Scheme 41)[136–138] or to give two diastereomerically pure alcohols from stereospecific reduction of each enantiomer (Scheme 42).[138]

The HLADH-catalyzed reduction of (±)-(**97**) is of interest since the alcohol product (**98**) is the thermodynamically less-preferred *exo* epimer. This emphasizes the fact that the geometry of an initial, kinetically controlled, product of an enzyme-catalyzed reduction reflects only the direction of attack of the hydride equivalent that is imposed by the orientation of substrate binding in the ES-complex. In this case, the reduction occurs on the *re* face of (1*S*)-(**97**),[136] in accord with the predictions of the active site

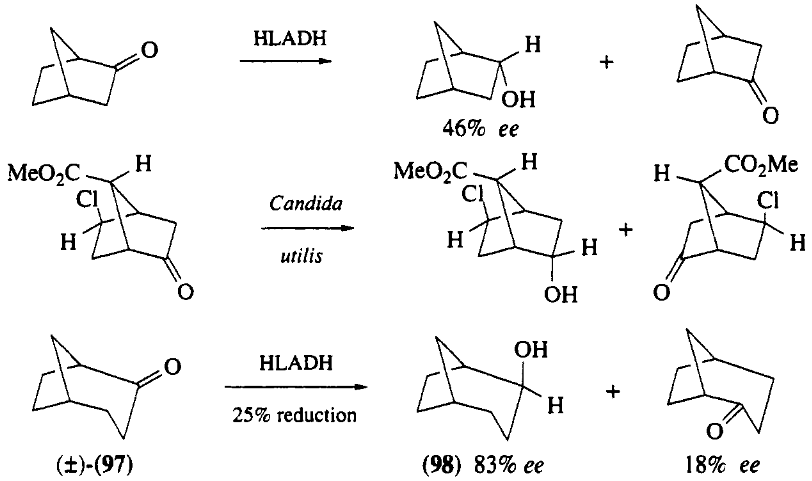
HLADH
46% ee
Candida
utilis
HLADH
25% reduction
(±)-(97)
(98) 83% ee
18% ee

Scheme 41

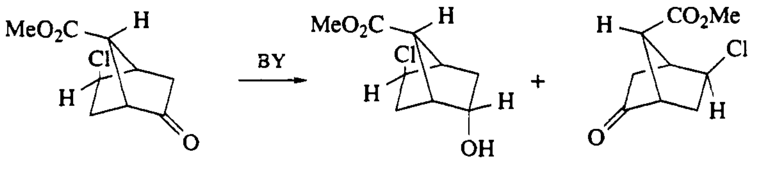

Scheme 42

model.[55] The feasibility of such discriminations for bicyclic diketones, such as (**99**), is demonstrated in Scheme 43. The hydroxy ketone (**100**) is the only alcohol product.[54] When α,β-unsaturated ketone functions are present in substrates, such as (±)-(**101**), chemospecific control can be exerted. In the example shown in Scheme 44, each enantiomer of (**101**) is reduced stereospecifically to the diastereomeric products (**102**) and (**103**), in each of which the new alcohol center has the (*S*) configuration.[139]

The examples discussed so far have been for ketones of chirality types commonly encountered. However, similar discriminations are possible with molecules of unusual chiralities, as represented in Scheme 45.

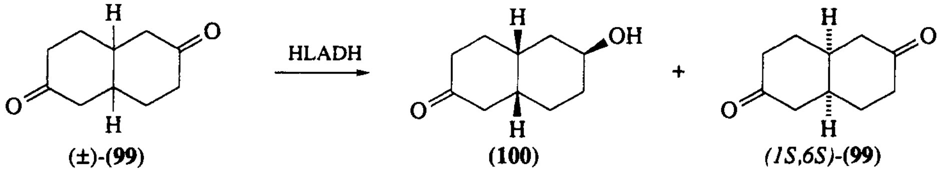

**Scheme 43**

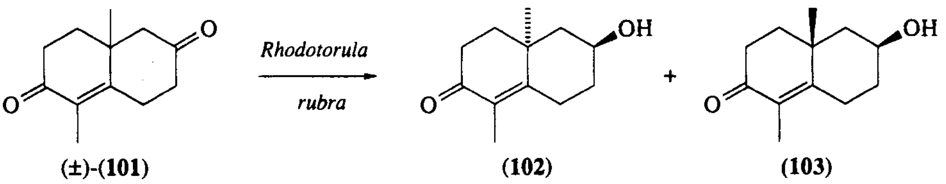

**Scheme 44**

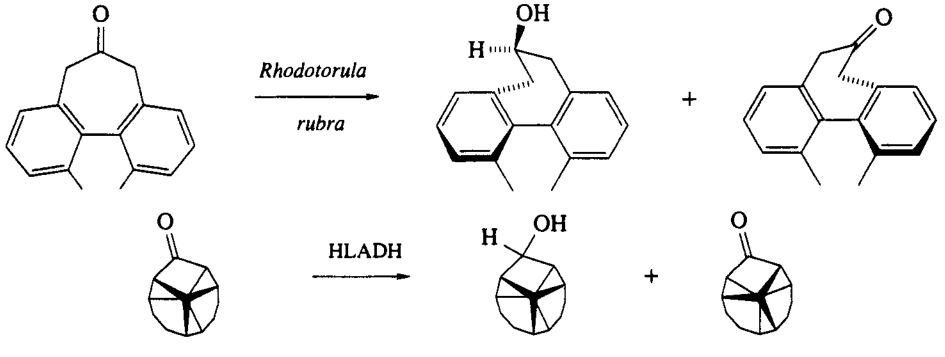

**Scheme 45**

Another important specificity combination is that of concurrent enantiotopic group and diastereotopic face selection. This is exemplified for mono-, bi- and poly-cyclic diketones in Scheme 46. Reduction of variously substituted cyclopentanediones (**104**) with BY gives products of the diastereomeric series (**105**).[140] Interestingly, *Pichia terricola* catalyzed reduction[141] of (**106**) → (**107**) proceeds in the same stereochemical senses as for the BY-mediated reductions of (**104**),[142] although (**106**) itself is not a substrate for BY.[141] For such compounds, the BY specificity selection parameters are controlled by the nature of the alkyl substituents and the ring size. The configuration of the alcohol center produced is (2*S*) in every case, but BY-mediated reduction of the 3-substituted cyclopentane- and cyclohexane-1,3-diones proceed in opposite diastereomeric senses with respect to the configuration of the 3-position.[140] The reductions of the bicyclic diketones (**108**), (**109**)[54] and (**110**),[1a,125] and the polycyclic substrate (**111**)[143] are stereospecific. Once again, different organisms can be employed to give different stereoisomers from the same substrate. The diketone (**112**) of Scheme 47 can be converted stereospecifically into the natural (**113**) or unnatural (**114**) steroid precursors.[144,145] An example of simultaneous diastereotopic group and face combination is given in Scheme 48.[54]

Even higher multiplicities of specificity combinations are possible. In Scheme 49, conversion of (**115**) to (**116**)[144] involves regiospecific reduction of an enantiotopic carbonyl group concurrently with enantiotopic face specificity. This transformation can also be achieved using *Saccharomyces* species, with the level of (**116**) produced being enhanced by the addition of unsaturated carbonyl compounds, such as acrolein.[145]

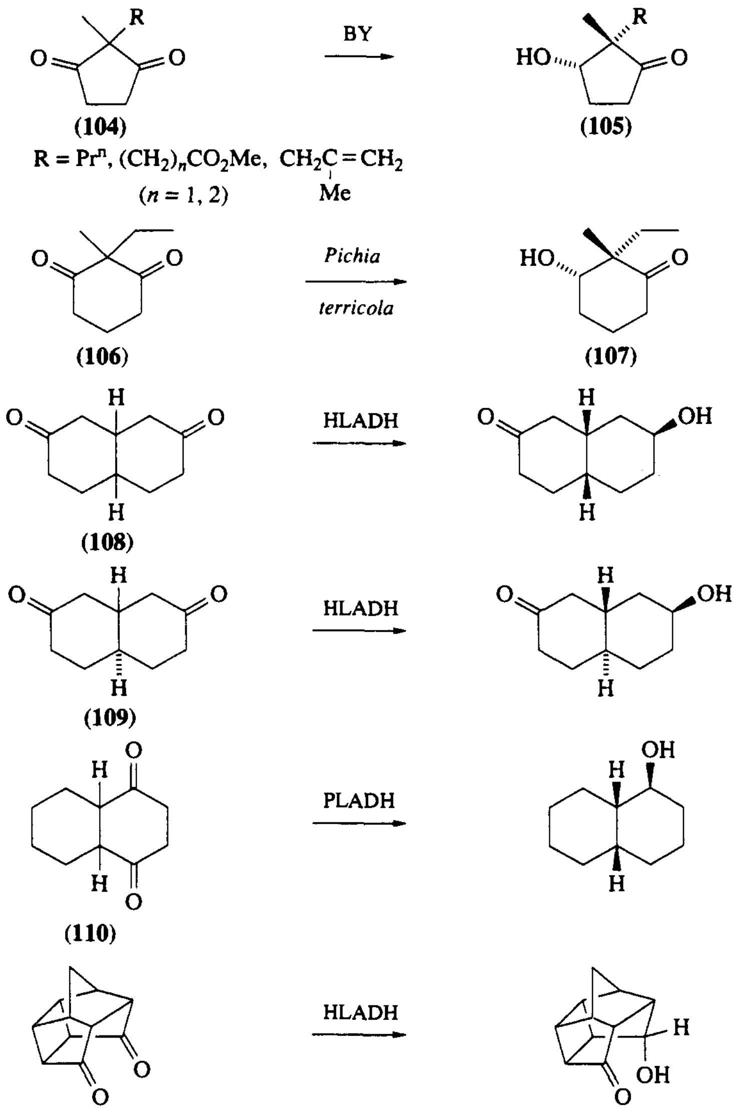
BY
(104)
(105)
R = Pr$^n$, $(CH_2)_nCO_2Me$, $CH_2C(Me)=CH_2$
($n$ = 1, 2)
*Pichia*
*terricola*
(106)
(107)
HLADH
(108)
HLADH
(109)
PLADH
(110)
HLADH
(111)

**Scheme 46**

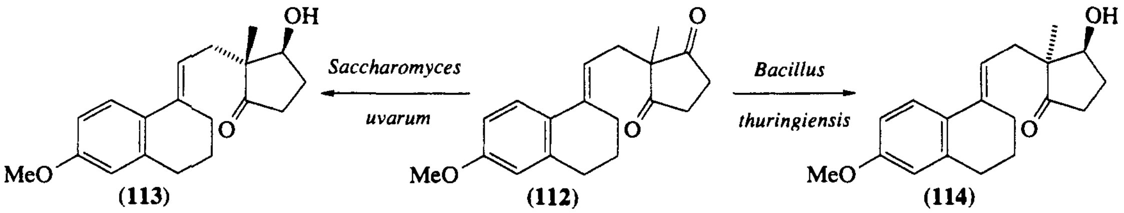
*Saccharomyces*
*uvarum*
*Bacillus*
*thuringiensis*
(113)
(112)
(114)

**Scheme 47**

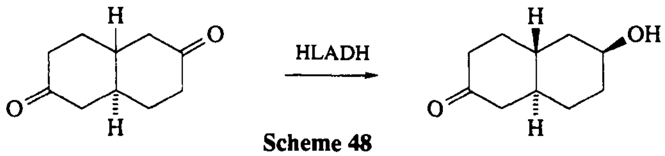

**Scheme 48**

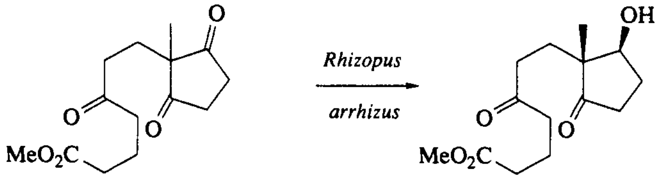
O
O
O
MeO2C
*Rhizopus*
*arrhizus*
OH
O
O
MeO2C

**(115)** **(116)**

**Scheme 49**

Sequential reductions are possible for diketones. That of Scheme 50 involves straightforward initial enantiotopic face specificity followed by diastereotopic face control.[146] In contrast, the initial alcohol (*S*)-(**118**) produced from (**117**; Scheme 51) must epimerize to (*R*)-(**118**) before the second reduction to (*R*,*R*)-(**119**) can take place.[147]

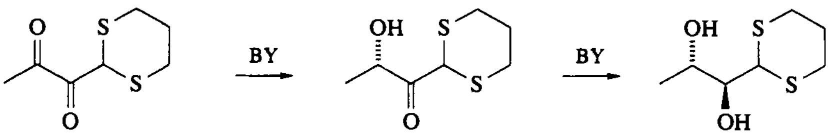
O
S
S
O
BY
OH
S
S
O
BY
OH
S
S
OH

**Scheme 50**

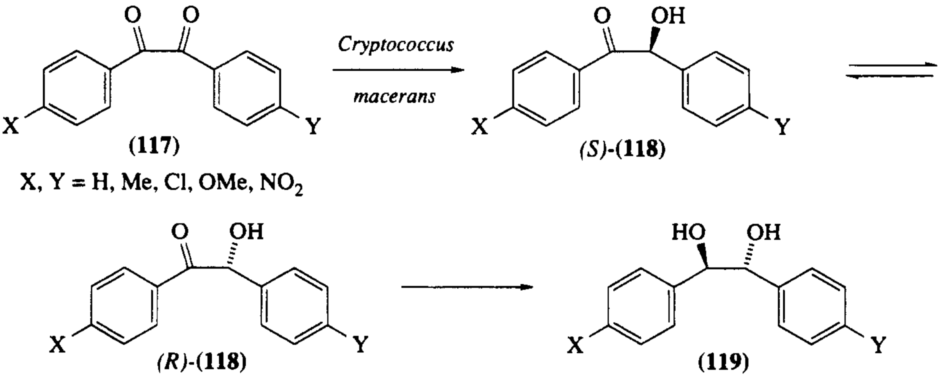
O
O
X
Y
*Cryptococcus*
*macerans*
O
OH
X
Y
O
OH
X
Y
HO
OH
X
Y

**(117)**

X, Y = H, Me, Cl, OMe, $NO_2$

*(S)*-(**118**)

*(R)*-(**118**)

**(119)**

**Scheme 51**

Yeast-mediated reductions can provide benefits in addition to their control of the stereospecificity of hydride delivery. For example, the acetaldehyde produced in the fermentation process can participate in acyloin condensations prior to the reduction steps (Scheme 52).[111,148–150]

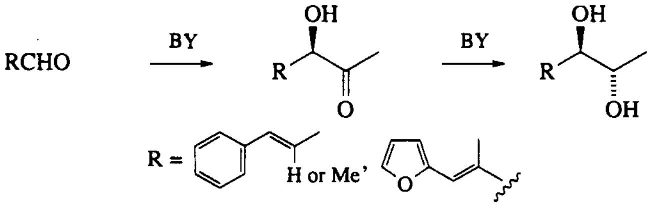
RCHO
BY
OH
R
O
BY
OH
R
OH
R =
H or Me'
O

**Scheme 52**

Enzyme-mediated carbonyl reductions are not restricted to aldehydes and ketones. With some organisms, carboxy groups can be reduced to primary alcohols. The example in Scheme 53 proceeds with enantiomeric specificity.[151]

### 1.8.6.5 Preparations of Deuterated or Tritiated Alcohols

From the broad range of stereospecific reductions listed above, it is evident that enzymes can provide attractive, and often unique, opportunities for the stereospecific introduction of isotopes. Introduction of

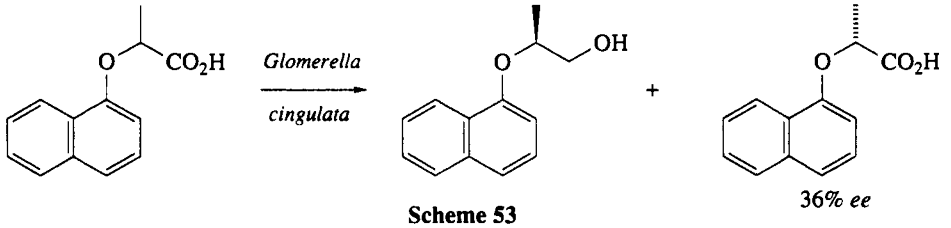

CO2H
Glomerella
cingulata
OH
+
CO2H
36% ee

**Scheme 53**

deuterium or tritium can be accomplished in several ways. The predictable stereospecificity of reductions of aldehydes can be exploited to prepare either (*R*) or (*S*) deuterated or tritiated primary alcohols. This is manifest in Scheme 54 for YADH-catalyzed reactions,[1] which occur with *re* face specificity. The opposite configurations can be produced by swapping the locations of protium and deuterium/tritium in the substrate or coenzyme respectively. If BY is employed, the label must be located in the substrate aldehyde, as represented in Scheme 55.[152] Alternatively, enzymes of opposite enantiotopic face specificities can be employed (Scheme 56).[153]

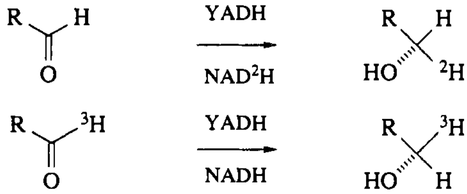

YADH
NAD²H
YADH
NADH

**Scheme 54**

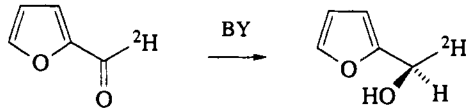

**Scheme 55**

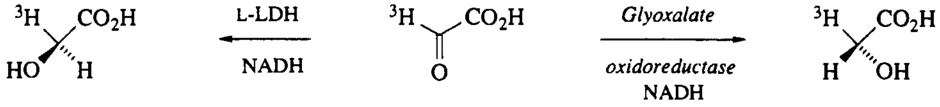

L-LDH
NADH
Glyoxalate
oxidoreductase
NADH

**Scheme 56**

The source of the label may be the solvent or a coupled substrate. It can be introduced by a single enzyme (Scheme 57)[1] or using a coupled enzyme system (Scheme 58).[31]

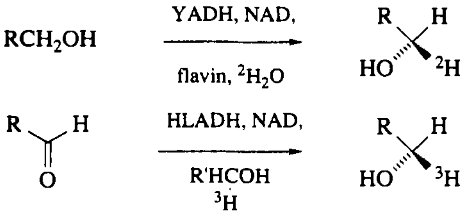

RCH2OH
YADH, NAD,
flavin, ²H2O
HLADH, NAD,
R'HCOH
³H

**Scheme 57**

## 1.8.7 REDUCTION OF C=N TO CHNH

The only preparative-scale reactions of synthetic value in this category are those catalyzed by the amino acid dehydrogenases. These enzymes catalyze the reductions of α-imino acids to α-amino acids. This can be done on a very large scale, as demonstrated by the LeuDH-catalyzed reduction of (**120**) to *t*-butyl leucine (**121**) shown in Scheme 59.[154] Another enzyme of this group with preparative promise is

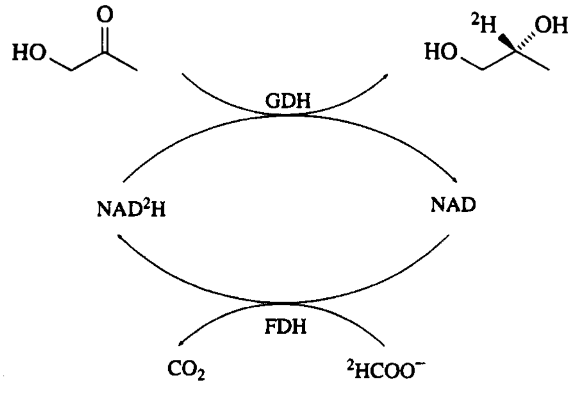

Scheme 58

pimelate dehydrogenase.[155] Enzyme-catalyzed reductions of imines have also been documented in alkaloid biosynthetic pathways,[156] but as yet are of limited synthetic practicality.

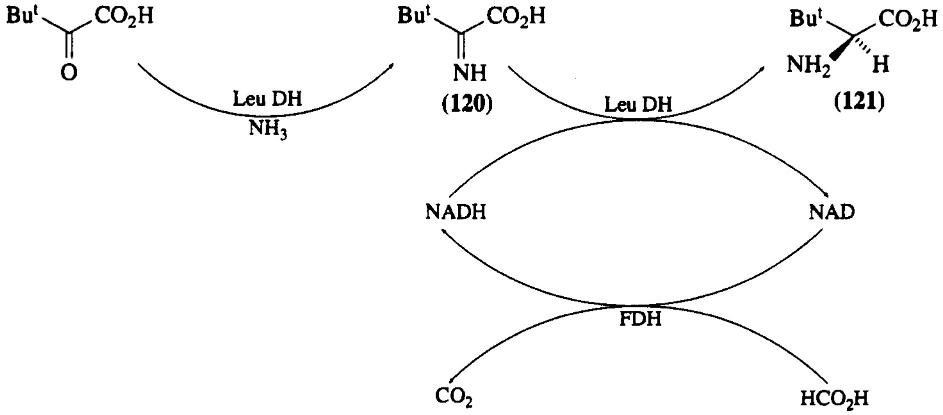

Scheme 59

## 1.8.8 REDUCTION OF C=C TO CHCH

The alkene reduction reactions most frequently observed are of α,β-unsaturated aldehydes, ketones, acids and esters. Examples of stereospecific reductions of acyclic substrates are given in Scheme 60.[148,157–159] In the formation of (**123**), the double bond of (**122**) is reduced prior to the aldehyde function.[148] The conversion of (**124**) to (**125**) involves oxidation of the intermediate alcohol to the carboxylic acid by bubbling air into the fermentation medium.[157] Stereospecific reductions of α,β-unsaturated ketones may be similarly effected (Scheme 61).[160–163] The reduction of the chloro ketone (**126**) gives (**127**) initially. This epimerizes under the reaction conditions, and each enantiomer is then reduced further to (**128**) and (**129**), with the predominance of the (**128**) stereoisomer increasing with the size of the R-group.[166] Reduction of (±)-(**130**) leads to (**131**) and (**132**).[163]

Reductions of allylic alcohols can also go stereospecifically (Scheme 62). However, they are not always substrates. For example, the allylic alcohol arising from reduction of the formyl group of the α,β-unsaturated aldehyde (**122**) is not reduced to (**123**) by *B. sulfurescens*.[148]

For the racemic allenic acid (**133**), each enantiomer is reduced stereospecifically to give the alkenoic acid diastereomers (**134**) and (**135**) (Scheme 63).[164] In contrast, the levels of enantiomeric discrimination observed in microbial reductions of allenic alcohols have so far been very low.[165]

## 1.8.9 FUTURE DEVELOPMENTS

The examples of enzyme-catalyzed C=X → CHXH transformations documented in this chapter show that the approach is already a well developed and versatile one. We may look forward to advances in the

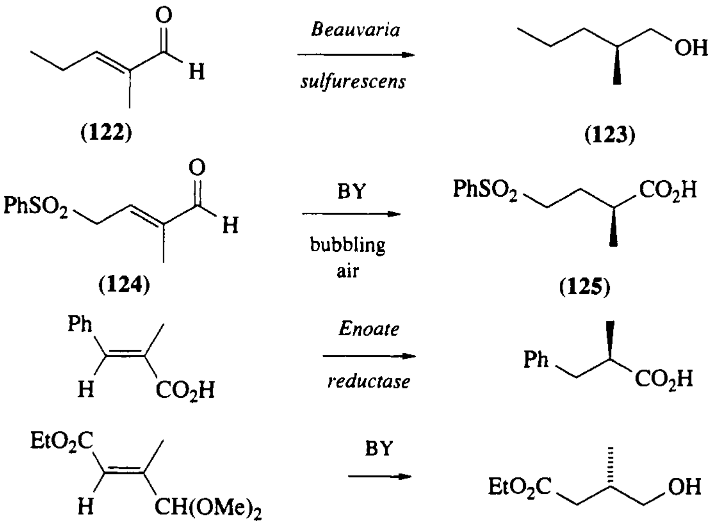
(122)
Beauvaria sulfurescens
(123)
(124)
BY
bubbling air
(125)
Enoate reductase
BY

Scheme 60

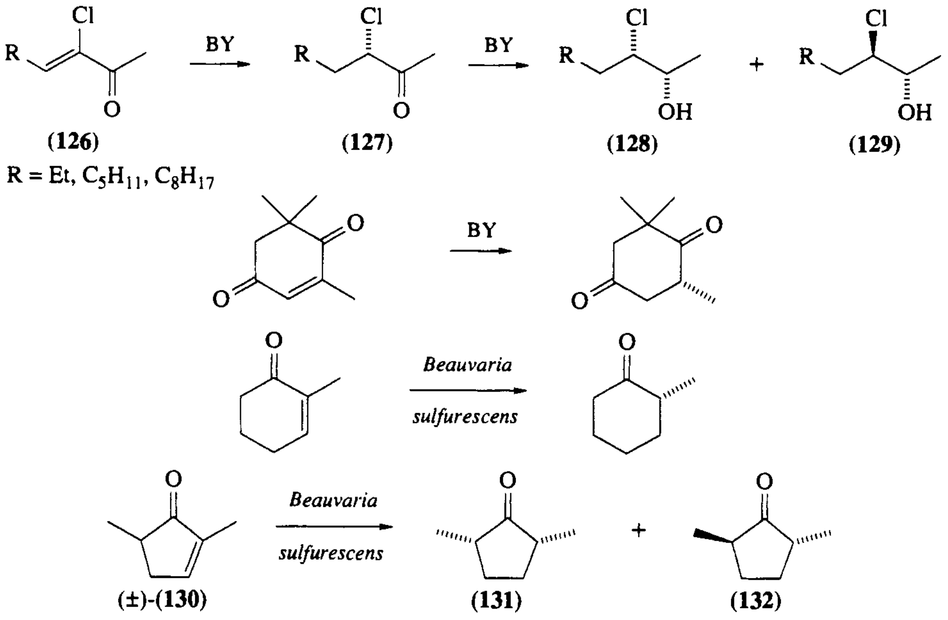
(126)
R = Et, $C_5H_{11}$, $C_8H_{17}$
BY
(127)
BY
(128)
+
(129)
BY
Beauvaria sulfurescens
(±)-(130)
Beauvaria sulfurescens
(131)
+
(132)

Scheme 61

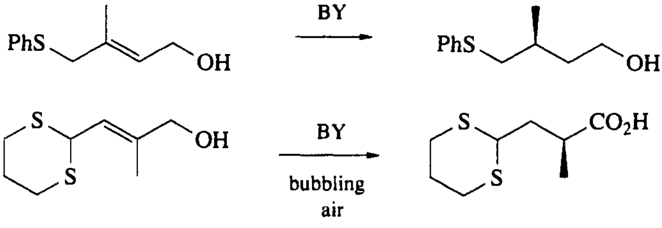
BY
BY
bubbling air

Scheme 62

use of organic solvents[13,14] and unnatural coenzymes.[166] Further ahead, there are even more exciting possibilities in the genetic manipulation of microorganisms, in the antibody-based 'abzyme' approach to the design of enzyme specificity,[167,168] and in tailoring enzyme specificities,[169,170] including those of oxidoreductases,[171–173] *via* the site-directed techniques of molecular biology.

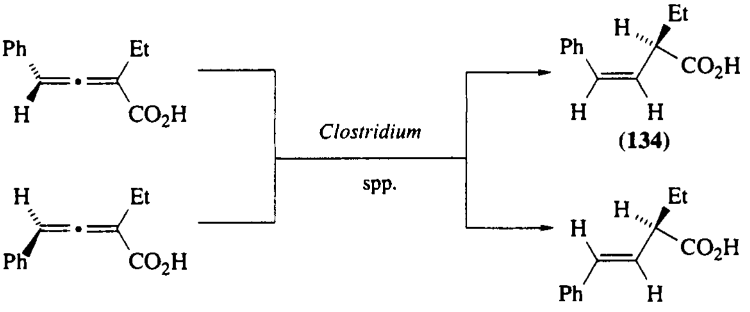

(±)-(133) (134) (135)

**Scheme 63**

## 1.8.10 REFERENCES

1. (a) J. B. Jones and J. F. Beck, *Tech. Chem. (N.Y.)*, 1976, **10**, 107; (b) J. B. Jones, *Tetrahedron*, 1986, **42**, 3351.
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6. K. Kieslich, 'Microbial Transformations of Non-steroid Cyclic Compounds', Thieme, Stuttgart, 1976; K. Kieslich, in 'Biotechnology', ed. H. J. Rehm and G. Reed, Verlag Chemie, Weinheim, 1984, vol. 6A.
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# 1.9

# Reduction of Acetals, Azaacetals and Thioacetals to Ethers

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## 1.9.1 INTRODUCTION

Acetals and ketals are passive under neutral and basic conditions; the ether groups resist alkylation and acylation, and the masked carbonyl group is protected against attack by nucleophiles and against enolization by bases,[1] although nearby unsaturation may open the system to reaction. When, however, one of the oxygen atoms acquires a Lewis or protic acid as a ligand it becomes a better leaving group, and the carbonyl carbon atom can suffer $S_N2$ and, especially, $S_N1$ reactions. These reactions can be highly regio- and stereo-selective when the two oxygen atoms are in different chemical environments. Neither the 'anomeric effect',[2] which is so important in setting the ground state conformation, nor the 'stereoelectronic effect',[3] which has come under serious attack,[4] have an overriding effect, but differences in the stability of the two possible oxocarbonium ions clearly do.

With cyclic acetals and ketals, selective reductions allow the blocked hydroxy groups of the diol to be deprotected one at a time, a matter of some importance in carbohydrate chemistry.[5] Although there have been a few studies of stereoselective reductions at the masked carbonium center of chiral ketals, more has been done with the formally related reactions in which C—C bonds are formed stereoselectively.[6]

## 1.9.2 MAJOR METHODS

### 1.9.2.1 Catalytic Hydrogenation

Aliphatic ethers are stable to ordinary catalytic hydrogenation conditions, but benzyl ethers can be cleaved in good yields and under mild conditions, making them useful as protecting groups.[1] Palladium, promoted by small amounts of acid, is the best catalyst. Thus, benzylidene acetals are cleaved to methylbenzenes in high yield,[7–9] and ketals derived from benzophenone behave similarly.[10] Allyl ethers may also be cleaved over palladium, but with other catalysts a competing hydrogenation of the double bond becomes more important.

Benzyl ethers are obtained from benzylidene acetals over nickel at 180 °C.[11] The yields are moderate, however, because the ethers are cleaved about as readily as the acetals;[12] at lower temperatures ring reduction of the hydrocarbon product is also competitive with hydrogenolysis. The best catalyst for the preparation of benzyl ethers from benzylidene acetals would appear to be cobalt carbonyl, under synthesis gas at temperatures from 128–210 °C.[13] The active reagent is probably $HCo(CO)_4$.

Better yields of ethers are obtained from aliphatic acetals;[11,14] vinyl ethers, which can be prepared from acetals over nickel (alone) at high temperatures,[15] may be intermediates. With rhodium on alumina in the presence of acid, ketals of acetone (**1**) are hydrogenolyzed to ethers (**3**) at about the same rate that the corresponding vinyl ethers (**4**) are hydrogenated,[16] indicating that the latter may be intermediates (Scheme 1). Vinyl ethers have also been suggested as intermediates in the direct formation of ethers from ketones during catalytic hydrogenation over platinum in MeOH–HCl,[17] but the oxocarbonium ion (**2**), which is a common intermediate for the formation of both the acetal and the vinyl ether, might be reduced directly.

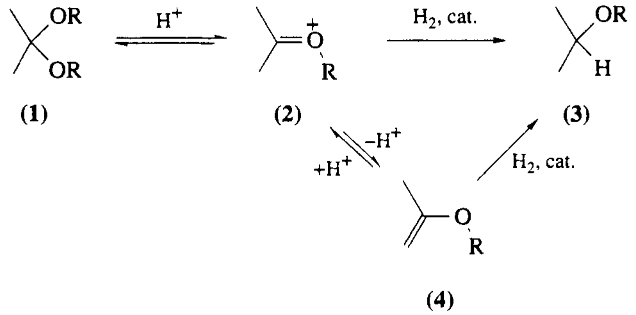

**Scheme 1**

### 1.9.2.2 Reduction with Dissolving Metals

Saturated alcohols and ethers are inert to the usual methods of reduction by dissolving metals, but benzylic alcohols, ethers, esters and acetals are completely hydrogenolyzed under the conditions of the Birch reduction.[18–20] The fission process probably occurs after two electrons have been added to the ring;[18] proton donors are not required and may, when *p*-methoxy groups are present, promote reduction of the ring instead.[21] The corresponding 1,3-dioxolanes, however, give complete hydrogenolysis.[22] The furan nucleus also promotes 'benzylic' hydrogenolysis with lithium in ammonia in the absence of proton donors.[23] The location of the side chain makes a difference. In the 3-furanyl system (equation 1)[24] single cleavage of a dioxolane predominates, but in the 2-furanyl system[25] only double cleavage, to remove both acetal oxygen atoms, occurs.

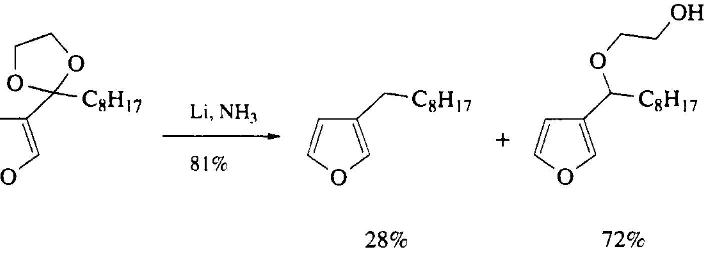

(1)

### 1.9.2.3 Reduction with Metal Hydrides

The tetrasubstituted hydrides of Group III and IV metals act only as hydride donors; for the reduction of acetals a Lewis acid partner, one that will not react faster with the hydride donor, is required and several such silicon and boron hydride systems have been developed. The trisubstituted hydrides are, of themselves, both Lewis acids and hydride donors; the halo- and alkyl-aluminum hydrides have proven to be valuable reagents of this type. In all of them modulation of reducing power can be achieved by changing the kind and numbers of substituents. Halogen atoms increase Lewis acidity in both series. Alkoxy groups enhance the reducing power of boranes but diminish that of alanes; they also permit variation in steric requirements and might allow the development of chiral reagents.

#### *1.9.2.3.1 Derivatives of alane*

Lithium aluminum hydride (LAH) does not, as a rule, react with ethers,[26,27] but does reduce ortho esters to acetals (equation 2).[28] 2-Vinyl-1,3-dioxolane (**5**) is reduced to a vinyl ether with double-bond rearrangement (equation 3), but the cinnamyl analog (**6**) is only reduced at the double bond (equation 4).

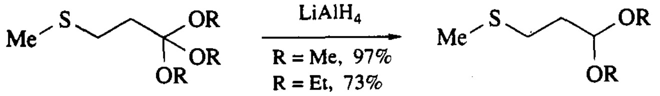

(2)

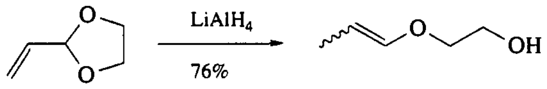

(3)

(**5**)

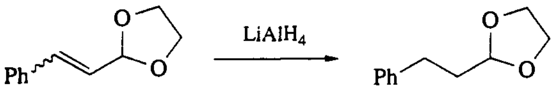

(4)

(**6**)

Although some propargylic alcohols are reduced to allenes,[29] such behavior is not seen with the simple open chain propargylic acetal (**7**).[30] Studies with LAD and $D_2O$ show that the triple bond is reduced first, and that the alumino derivative then undergoes acetal cleavage without rearrangement (Scheme 2). The resulting crotyl acetal then undergoes $S_N2$ displacement of one ethoxy group without reduction of the double bond.

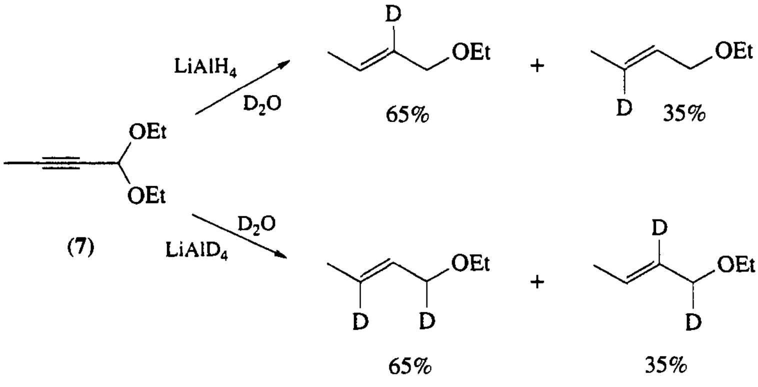

**Scheme 2**

Alane is best prepared by reaction of LAH with $H_2SO_4$; prepared so, it is stable in THF for several days and is a potentially useful selective reducing agent.[31] It can also be prepared by reaction of LAH with $AlCl_3$ (3:1); in other proportions, these reagents form the chloroalanes.[32] Alkoxyalanes and chloroalkoxyalanes can be made from these reagents by adding appropriate amounts of alcohols.[33] Of these, the haloalanes ('mixed hydride' reagents) have been most widely used, particularly where cleavage of C—O bonds is desired.[34,35] Dichloroalane, with an excess of $AlCl_3$ (1LAH:4$AlCl_3$) and used in 100% molar excess, gives good preparative cleavages of simple acetals (equation 5),[36,37] but the milder reagent $H_2AlCl$ (1LAH:1$AlCl_3$) has been used extensively in mechanistic studies.[38] Alane is a still weaker hydrogenolyzing agent.[33,38] Alkoxyalanes are even less active but offer the possibility of variation in steric requirements; dialkoxyalanes are too unreactive to be useful.

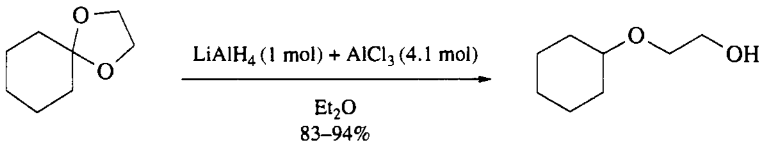

(5)

Diisobutylaluminum hydride (DIBAL-H) hydrogenolyzes simple ortho esters to acetals at room temperature and reduces acetals and ketals to ethers at 70–80 °C (equation 6); benzyl ethers are cleaved at still higher temperatures.[39] This reagent shows good selectivity and considerable versatility. It has been used to reduce acetals of formaldehyde (equation 7),[40] which few other reagents can accomplish. With catechol ketals a single reductive cleavage occurs at room temperature (equation 8).[41]

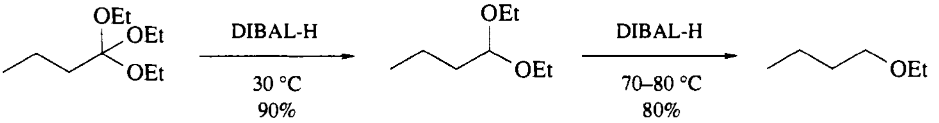

(6)

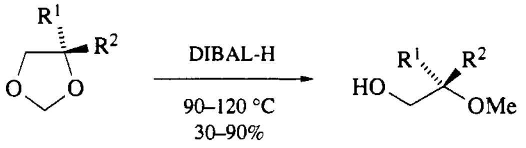

(7)

$R^1$ = H, $R^2$ = H, Ph; $R^1$ = Me, $R^2$ = Me, Ph

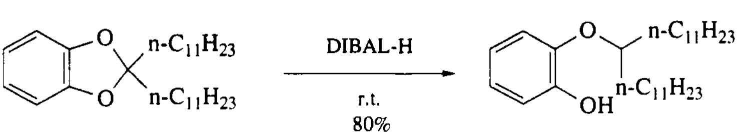

(8)

### 1.9.2.3.2 Derivatives of borane

A mixture of LAH and $BF_3$ generates diborane, but other products are formed first when $BF_3$ is added to LAH.[34] This system reduces lactones to cyclic ethers and gives some cleavage of steroidal spiroketals.[42] It gives slightly better yields of dihydroxy ethers from acetals of pentaerythritol than does chloroalane (equation 9).[43] Borane in THF gives good cleavage of acetals and ketals, usually at the less-hindered oxygen atom.[44,45] Propargylic acetals undergo reductive cleavage *via* an elimination mechanism during hydroboration (Scheme 3; *cf.* Scheme 2).[46]

Hydroboration is faster than cleavage with borane,[47] but $H_2BCl$ etherate cleaves unsaturated acetals without giving hydroboration (equation 10).[48] Lower yields are obtained with the less reactive $Me_2S$ complex, but that reagent gives good yields of dihydroxy diethers from chiral bisacetals (equation 11).[49] The diethyl acetal of benzaldehyde can be reduced to ethyl benzyl ether in moderate yield by decaborane in toluene at 120–130 °C (equation 12).[50]

The borohydride ion is a good trap for spontaneously generated carbonium ions (or ion pairs), such as those formed by secondary or tertiary benzylic or allylic halides in ionizing solvents,[51] but would be expected to be inactive when the leaving group is alkoxy unless an acidic partner were also present.

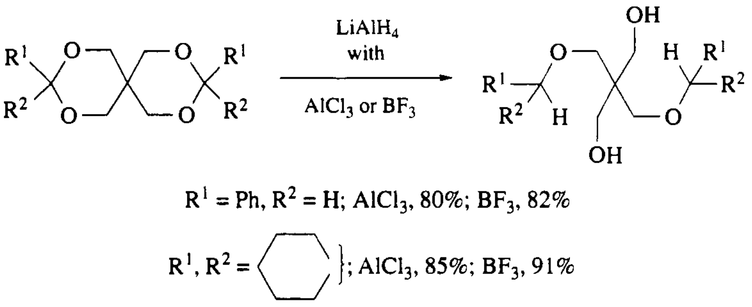
LiAlH$_4$
with
AlCl$_3$ or BF$_3$
R$^1$
R$^2$
O
OH
H
R$^1$ = Ph, R$^2$ = H; AlCl$_3$, 80%; BF$_3$, 82%
R$^1$, R$^2$ = ; AlCl$_3$, 85%; BF$_3$, 91%

(9)

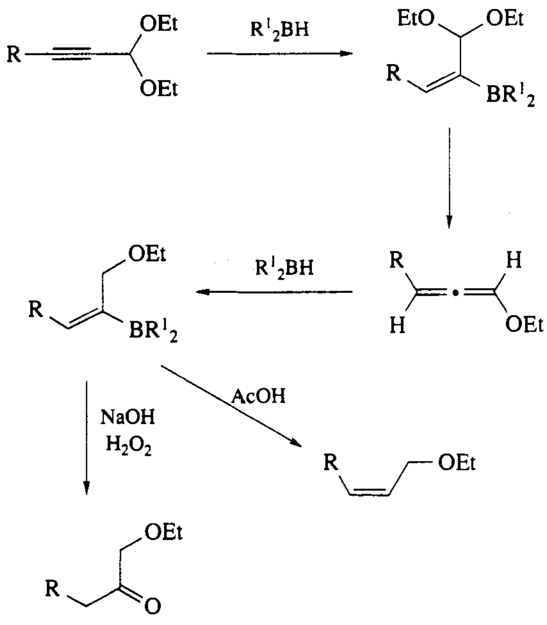
R
OEt
R$^1_2$BH
EtO
BR$^1_2$
H
NaOH
H$_2$O$_2$
AcOH
O

**Scheme 3**

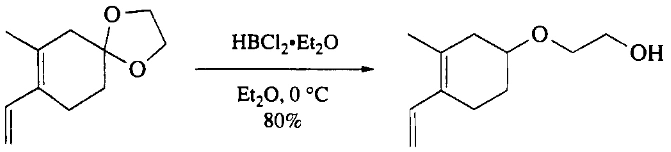
HBCl$_2$•Et$_2$O
Et$_2$O, 0 °C
80%
O
OH

(10)

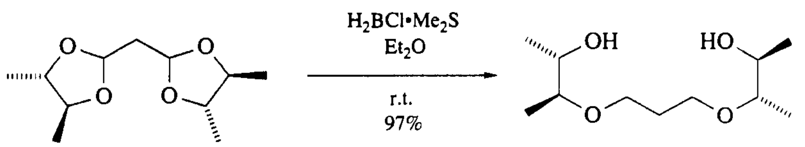
H$_2$BCl•Me$_2$S
Et$_2$O
r.t.
97%
O
OH
HO

(11)

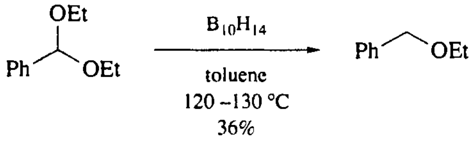
OEt
Ph
B$_{10}$H$_{14}$
toluene
120 –130 °C
36%

(12)

Sodium borohydride and trifluoroacetic acid (TFA) reduce 2-aryl-1,3-dioxolanes to hydroxy ethers.[52] Zinc borohydride, with TMS-Cl as its acidic partner, has proven to be effective in the reductive cleavage of a variety of acetals.[53] MOM ethers are reduced to methyl ethers in good yield (equation 13). Cyclohexene is hydroborated under these conditions, indicating that diborane may be present.

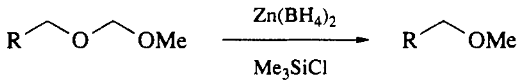

(13)

Methyl acetals and ketals are rapidly reduced to methyl ethers by sodium cyanoborohydride in methanol with dry HCl at ice temperatures.[54] A dioxolane is completely cleaved to a methyl ether, showing intervention by the solvent at some stage (equation 14), but when an inert solvent such as THF is used only single cleavage occurs; this reagent shows interesting selectivity in the reduction of benzylidene acetals in the carbohydrate series (see Section 1.9.3.4).

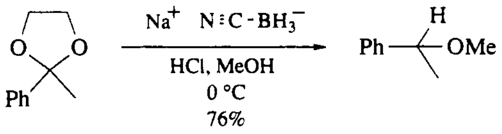

(14)

### *1.9.2.3.3 Derivatives of silane*

'Ionic hydrogenation' occurs when alkyl- or aryl-silicon hydrides reduce carbonium ions.[55–57] Thus, acetals and ketals can be reduced by trialkylsilanes in the presence of 5–10% of $ZnCl_2$.[58] Yields of 50–85% of ether are obtained from acyclic acetals (equation 15), but cyclic acetals give appreciable amounts of a by-product (**8**; equation 16), which is believed not to be the result of further reduction.

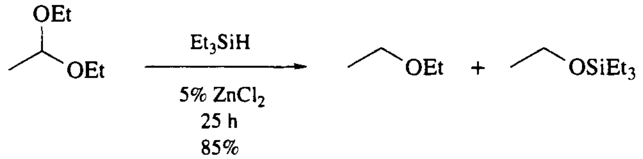

(15)

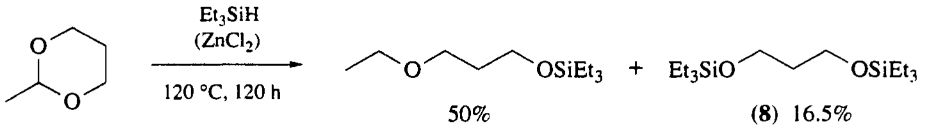

(16)

Trimethylsilyl triflate (TMS-OTf; 1%) catalyzes the reduction of acetals by TMS-H in $CH_2Cl_2$ at 0 °C,[59] with the TMS moiety acting as a chain-carrying species (equation 17).[59]

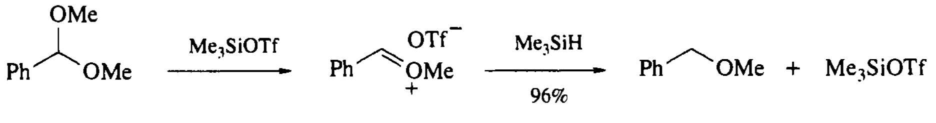

(17)

Carbonyl compounds are reduced to symmetrical ethers, probably by way of reduction of some of the starting material to a silyl ether (**9**), reaction to form the mixed ketal (**10**) and then reductive replacement of the silyloxy group. Some hydrocarbon may be obtained as a by-product by reduction of (**9**; Scheme 4). Among the acid partners that have been used are trifluoroacetic acid,[55,56] trityl perchlorate[60] (with aldehydes) and electrogenerated protons.[61] With Nafion resin[57] symmetrical ethers are obtained from aldehydes, but silyl ethers are obtained from ketones.[62,63]

Ketones in alcohol solutions give mixed ethers with triethylsilane and trifluoroacetic acid,[64] presumably *via* the hemiketal (or ketal). Similar results were obtained with ketones and silylated alcohols.[60] Studies of the acid-catalyzed reduction of alcohols with silanes provide strong support for the postulate that carbonium ions are intermediates.[65,66]

## 1.9.3 SELECTIVE REDUCTIONS

The rate-controlling step in the acid-mediated reductive cleavage of an acetal or ketal involves the breaking of one of the C—O bonds. This step is product-controlling when the two oxygen atoms are dif-

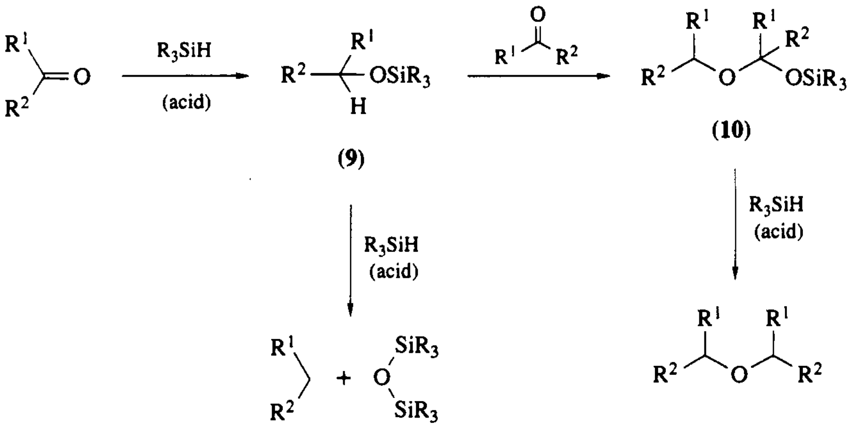

**Scheme 4**

ferent. Selectivity at this stage depends in part on the relative basicity of the two oxygen atoms and their relative accessibility to the Lewis acid. For *S*$_N$1-like reactions, the degree to which the incipient carbonium ion, which contains the other oxygen atom, can be stabilized by polar effects or destabilized by steric crowding may be more important. The ease with which the hydride donor can approach the reacting center will control the stereochemistry of the product in these reactions. In *S*$_N$2-like reactions, of course, the accessibility of the reacting center to the hydride donor determines both the structure and the stereochemistry of the product.

### 1.9.3.1 Acyclic Ketals

In hydrogenolyses with HAlCl$_2$, the dimethyl acetals of cyclobutanone and cyclohexanone are cleaved more slowly than that of 3-pentanone, while those of cyclopentanone and cycloheptanone are cleaved more rapidly (Table 1),[67] as would be expected for a carbonium ion process.[68] The differences in rate are small, suggesting that carbonium ion character is not strongly developed in the transition state. With the dimethyl acetal of 4-*t*-butylcyclohexanone, the hydride addition step occurs with strongly predominating axial addition when HAlCl$_2$ is used;[36] Zn(BH$_4$)$_2$ with TMS-Cl,[53] and TMS-H with TMSO-Tf[59] are less selective (Table 2). Equatorial attack predominates, however, in the reduction of the ketone itself with TBDMS-H and TBDMS-OTf.[63]

**Table 1** Relative Rates of Reduction of Dimethyl Ketals of Acyclic and Cyclic Ketones with HAlCl$_2$[67]

| *Ketone* | *Relative rate* |
|---|---|
| 3-Pentanone | 1.0 |
| Cyclobutanone | 0.06 |
| Cyclopentanone | 1.3 |
| Cyclohexanone | 0.5 |
| Cycloheptanone | 7.0 |

**Table 2** Diastereoselectivity in Reductions of the Dimethyl Ketal of 4-*t*-Butylcyclohexanone

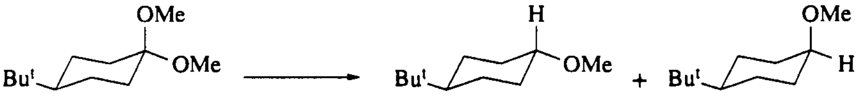

| *Reducing system* | *Yield (%)* | *Trans (%)* | *Cis (%)* | *Ref.* |
|---|---|---|---|---|
| HAlCl$_2$ | 92 | 82 | 18 | 36 |
| Zn(BH$_4$)$_2$:TMS-Cl | 95 | 59 | 41 | 53 |
| TMS-H:TMS-OTf | 89 | 56 | 44 | 59 |

In reductions with $HAlCl_2$, mixed ketals of norcamphor lose the less-branched alkoxy group preferentially, regardless of its orientation, but give only *endo*-ether as product.[69] This indicates that the oxocarbonium ion becomes essentially free and is reduced exclusively on the less-hindered *exo* face (Table 3). Some evidence for preferential cleavage of the more exposed *exo*-alkoxy group is seen in the case where the alkoxy groups differ only isotopically, but this effect is swamped in the other cases, suggesting that stabilization of the oxocarbonium ion is the main product-controlling effect.

**Table 3** Hydrogenolysis of Mixed Ketals of Norcamphor by $HAlCl_2$ in Ether at Room Temperature[69]

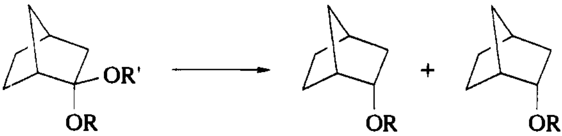

| *R* | *R'* | *Retained alkoxy groups*<br>*O—R* | <br>*O—R'* |
|---|---|---|---|
| | | *Yield (%)* | |
| Me | $CD_3$ | 67 | 33 |
| Me | Et | 20 | 80 |
| Et | Me | 86 | 14 |
| Me | Pr$^i$ | 2 | 98 |
| Pr$^i$ | Me | 99 | 1 |
| Me | Bu$^t$ | 8 | 83 |
| | | (plus 9% *endo*-norborneol) | |

### 1.9.3.2 Furanosides and Pyranosides

For synthetic purposes there is probably more interest in the reductive ring cleavage of tetrahydrofuranyl and tetrahydropyranyl ethers than in *exo* cleavage of their alkoxy side chains. With $HAlCl_2$[70] and $H_2AlCl$,[71,72] comparable furanosides react more rapidly than pyranosides and tend to give more ring cleavage (Tables 4 and 5), consistent with the greater basicity of THF.[73] Increased branching in the alkoxy group OR also promotes ring cleavage, but substituents on the other side of the acetal system ($R^1$) promote side chain cleavage. In contrast, aryloxy compounds (R = Ar)[71,74] give only side chain cleavage, while aryl substitution at $R^1$ promotes ring cleavage. These effects have been ascribed[71,72] to the electron-releasing effect of branched alkyl groups, which, located at the oxygen end of the oxocarbonium ion, would tend to stabilize it, thereby promoting cleavage at the other oxygen atom. The steric effects of branching would work in the same way. On the other hand, aryl groups can act only as electron-withdrawing groups when they are at the oxygen end of the oxocarbonium system; in such cases the polar effects would seem to outweigh the steric. A comparison of the action of different alanes on THFOBn shows that the weaker Lewis acid (stronger nucleophile) gives more ring opening (Table 6).[72] The LAH–$BF_3$ reagent resembles the less-halogenated alanes (Table 5).[70]

**Table 4** Reductive Cleavage of Tetrahydrofuranyl Ethers with $H_2AlCl$ in Ether at Room Temperature

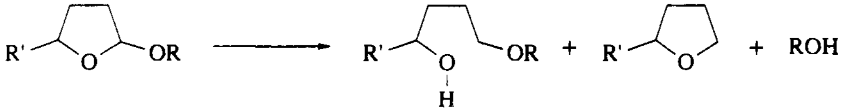

| *R'* | *R* | *Cleavage (%)*<br>*Ring* | <br>*Exo* | *Ref.* |
|---|---|---|---|---|
| H | Me, Et, Pr$^i$, Bu$^t$ | 100 | 0 | 72 |
| Me | Me | 37.5 | 62.5 | 72 |
| Pr$^i$ | Me | 14 | 86 | 72 |
| Bu$^t$ | Me | 0 | 100 | 72 |
| Ph | Me | 84.3 | 15.7 | 72 |
| H | Ph | 0 | 100 | 74 |
| H | Bn | 51.5 | 48.5 | 72 |

**Table 5** Cleavage of Tetrahydrofuranyl and Tetrahydropyranyl Ethers with $HAlCl_2$ and with $LiAlH_4:BF_3$ Reagents[70]

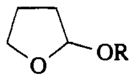

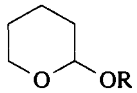

| *R* | *Cleavage (%)* *Ring* | *Exo* | *Reagent* | *Cleavage (%)* *Ring* | *Exo* |
|---|---|---|---|---|---|
| | | | $HAlCl_2$ | | |
| n-$C_6H_{13}$ | 27 | 40 | | 11 | *ca.* 90 |
| c-$C_6H_{11}$ | 63 | *ca.* 15 | | 45 | 38 |
| $Bu^t$ | 58 | — | | 72 | — |
| Bn | 4 | 83 | | — | 90 |
| | | | $LiAlH_4$–$BF_3$ | | |
| n-$C_6H_{13}$ | 66 | | | 41 | |
| c-$C_6H_{11}$ | 69 | | | 69 | |
| $Bu^t$ | 16 | | | 46 | |
| Bn | 48 | | | 25 | |

**Table 6** Cleavage of Tetrahydrofuranyl Benzyl Ether with Alanes in Ether at Room Temperature (2 h)

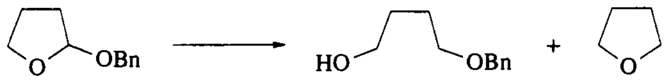

| *Reagent* | *Reacted (%)* | *Recovered (%)* | *Cleavage in recovered product* *Ring (%)* | *Exo (%)* | *Ref.* |
|---|---|---|---|---|---|
| $AlH_3$ | 67.5 | 84 | 79.5 | 20.5 | 72 |
| $H_2AlCl$ | 100 | 95 | 51.5 | 48.5 | 72 |
| $HAlCl_2$ | 100 | 90 | 9.5 | 90.5 | 72 |
| $HAlCl_2$–$AlCl_3$ | 100 | 91 | 8.7 | 91.3 | 72 |
| $LiAlH_4$–$BF_3$ | 70 | | | 48 (isolated) | 70 |

Side chain cleavage is of interest as a tool for locating links in oligosaccharides (equation 18).[75] Triethylsilane, catalyzed by $BF_3$ alone or by a 5:1 mixture of TMS-OTf and $BF_3$,[76] has proven to be useful for this purpose with both pyranosides and furanosides. In these reactions the hydride atom is delivered axially at C-1.[77]

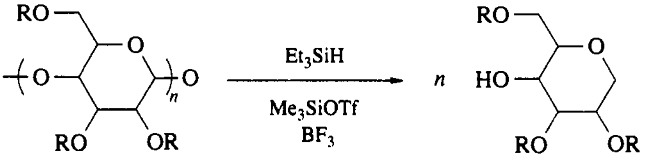

(18)

2,3-Unsaturated methylpyranosides give 3-deoxyglycals with chloride-free LAH, best in THF or dioxane.[78–81] It was shown, by use of LAD, that hydride usually enters the molecule stereospecifically on the same side as the departing oxygen (equations 19 and 20). Ease of reduction appears to be related to ease of formation of the rather tight transition state (**11**). These reactions have been used to synthesize stereospecifically 2-deuterated 2-deoxyriboses,[79] which were then used to establish the stereochemistry of nucleotide deoxygenation.[82] An axial 4-hydroxy or -alkoxy group may also serve to direct the aluminohydride to one face of the ring; in that case the oxygen atom at C-4 may be eliminated instead. This process predominates when the C-4 oxygen atom is part of a rigid ether system.

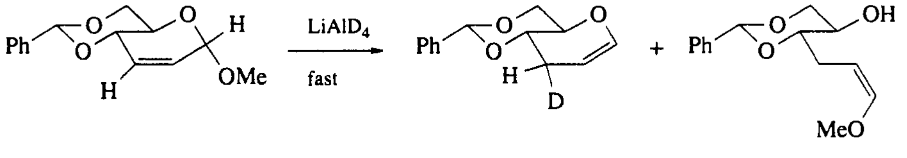

(19)

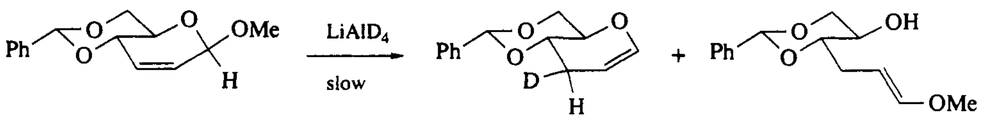

(20)

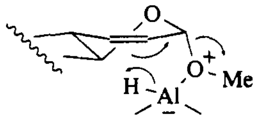

**(11)**

### 1.9.3.3 Spiroketals

The 1,6-dioxaspiro [4.5]decane nucleus (**12**; Scheme 5) might be expected, under acidic conditions, to give preferential opening of the five-membered ring (path a) in analogy with the easier opening of furanosides (see Section 1.9.3.2). On the other hand, since cyclopentyl carbonium ions form more easily (see Section 1.9.3.1), a more ready opening of the six-membered ring (path b) might be anticipated. In fact, path a is followed in $HAlCl_2$ reduction of the relatively simple ketal (**13**; equation 21),[83] while path b is followed when steroidal sapogenins are reduced (equation 22). The latter result probably reflects the higher degree of alkyl substitution in the five-membered ring.

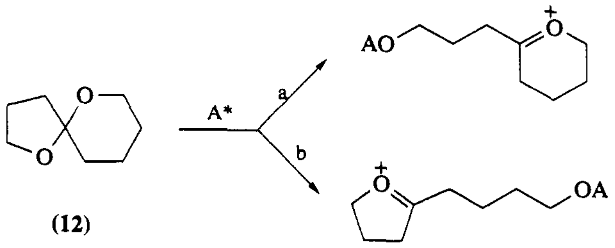

**(12)**

**Scheme 5**

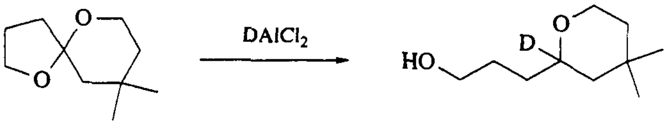

(21)

**(13)**

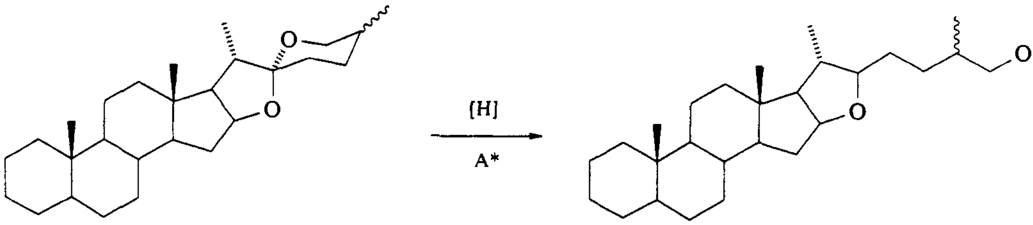

(22)

The sapogenin 'side chain' has a splendid repertoire of acid-mediated reactions[84] which could be understood only when its structure was worked out, a development not brought to fruition until it was realized that catalytic reduction in acidic medium was cleaving a spiroketal.[85] The same cleavage occurs with LAH and dry HCl,[86] and with $HAlCl_2$.[87] The LAH–$BF_3$ reagent gives some reduction of the spiroketal nucleus of several steroidal sapogenins, but hydroboration and the reduction of esters to ethers are major competing reactions.[42]

### 1.9.3.4 Dioxolanes and Dioxanes

Acetals derived from 1,2-ethanediol (1,3-dioxolanes; **14**; $R^1$ = H) are more readily hydrolyzed in acidic media than those from 1,3-propanediol (1,3-dioxanes; **15**; $R^1$ = H), but the reverse is true for the ketals (**14**, **15**; R = Me, Ph).[88] A parallel difference, suggesting a parallel mechanism for cleavage *via* an oxocarbonium ion (**18**), is seen in reductions with $H_2AlCl$ (Table 7).[89,90] These effects may be understood as arising from: (i) the greater basicity of five-membered cyclic ethers;[73] (ii) the relief of eclipsing strains in five-membered rings; and (iii) the relief of 1,3-diaxial crowding in the six-membered ring ketals. Electron-releasing substituents at C-2 (Me, Ph) would stabilize a transition state leading to (**18**), formation of which is thought to be rate controlling.[89–91] Electron-withdrawing groups would, then, retard the reaction (Tables 7 and 8).

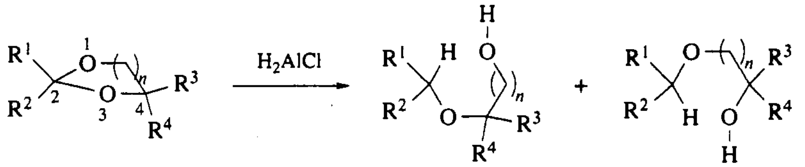

(**14**) $n = 1$
(**15**) $n = 2$
(**16**)
(**17**)
(23)

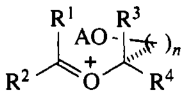

(**18**)

**Table 7** Comparative and Competitive Reductions of 1,3-Dioxolanes (**14**) and 1,3-Dioxanes (**15**) by $HAlCl_2$[89,90]

| *Substituents* *At C-2* | *At C-4* | *Time* (h) | *Total recovery* (%) | *Reduced (%)* (**14**) | (**15**) |
|---|---|---|---|---|---|
| H, H | H, H | 24 | 55 | 60[a] | |
| | | | 75 | | 28[a] |
| Me, H | H, H | 2 | 70 | 66 | 0 |
| H, H | Me, H | 2 | 80 | 40 | 0 |
| Ph, H | H, H | 0.33 | 89 | 100 | 30 |
| Me, Me | Me, H | 0.33 | 73 | 41 | 92 |

[a] Comparative reactions; all others competitive.

**Table 8** Hydrogenolysis of 2-Substituted-1,3-dioxolanes (**14**) by $H_2AlCl$ in Ether at Room Temperature[91]

| *Substituents* *$R^1$* | *$R^2$* | *Time* (h) | *Total recovery* (%) | *Reduced* (%) |
|---|---|---|---|---|
| H | H | 24 | 55 | 60 |
| Me | H | 1 | 70 | 100 |
| Me | Me | 1.5 | 71 | 100 |
| $CH_2Cl$ | H | 48 | 80 | 14 |
| $CHCl_2$ | H | 48 | 85 | 0 |
| Ph | H | 1 | 80 | 100 |

When there is no more than one substituent at C-4, cleavage tends to occur at the oxygen atom remote from the larger or more electron-releasing groups, favoring the formation of (**16**; equation 23). When the substituent is electron-withdrawing the reverse occurs and (**17**) is favored (Table 9). Steric hindrance to approach by the Lewis acid (A) and inductive electron release toward the positive (but not electron-deficient) oxygen atom of (**18**) appear to be important. Steric crowding between $R^1$ and $R^3$ in the transition state leading to (**18**) has a strong effect; thus 2,2,4,4-tetramethyl-1,3-dioxolane cleaves to give (**17**), contrary to initial expectations on steric and electronic grounds. That this is due to a steric retardation is shown by the fact that 2,2,4,4,5,5-hexamethyl-1,3-dioxolane is untouched after 1 h and only 30% reduced after 48 h.[92] Consistent with this, *cis*-2,4-dimethyl-1,3-dioxolane (**14**; $R^2$, $R^4$ = Me) cleaves more selectively at O-1 than does the *trans* isomer (**14**; $R^1$, $R^4$ = Me) or any of the other materials shown in Table 9; it reacts faster than, and during reaction isomerizes to some extent to, the *trans* isomer.[92] It hydrolyzes faster, too.[93] Borane in THF gives comparable results (Table 9).[44] Norcamphor ethylene ketal (**19**) gives almost exclusive *exo* reduction (equation 24) but camphor ketal (**20**) gives predominant *endo* reduction (equation 25),[94] consistent with the behavior of the parent ketones with $HAlCl_2$.

**Table 9** Hydrogenolysis of 2- and 4-Substituted-1,3-Dioxolanes (**14**) by $H_2AlCl^a$ and by $BH_3$–$THF^b$ (equation 23)

| *Reagent* | | *Substituents* | | | *Total recovery* | *Recovered as:* | | |
|---|---|---|---|---|---|---|---|---|
| | *R*[1] | *R*[2] | *R*[3] | *R*[4] | (%) | (**16**) (%) | (**17**) (%) | *Ref.* |
| $H_2AlCl$ | Me | Me | Me | H | 86 | 82 | 18 | 9 |
| $BH_3$–THF | | | | | 75 | 80 | 20 | 44 |
| $H_2AlCl$ | Me | Me | Ph | H | 81 | 52 | 48 | 91 |
| $BH_3$–THF | | | | | 88 | 58 | 42 | 44 |
| $H_2AlCl$ | Me | Me | $CH_2OH$ | H | 79 | 19 | 81 | 91 |
| $H_2AlCl$ | Me | Me | $CH_2Cl$ | H | 96 | 5 | 95 | 91 |
| $BH_3$–THF | | | | | 88 | 15 | 85 | 44 |
| $H_2AlCl$ | Me | Me | Me | Me | 87 | 6 | 94 | 91 |
| $H_2AlCl$ | Me | H | Me | H (*cis*) | | 96 | 4 | 92 |
| $H_2AlCl$ | Me | H | H | Me (*trans*) | | 35 | 65 | 92 |
| $H_2AlCl$ | Ph | H | Me | Me | 81 | 90 | 10 | 91 |
| $BH_3$–THF | | | | | 89 | 97 | 3 | 91 |

[a] Ether, r.t.; acetal:$AlCl_3$:LAH = 1:1:1. [b] Mix at −10 °C, let warm to r.t., 24 h, acetal:$BH_3$–THF = 1:1.5.

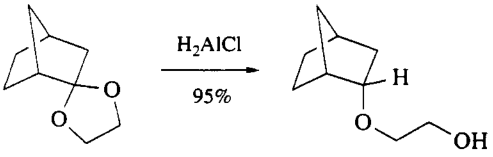

(24)

(**19**)

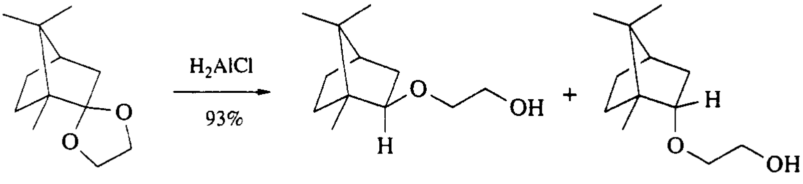

(25)

(**20**) 78% 22%

Norcamphor isobutylene ketal appears (NMR) to be a nearly equal mixture of the isomers (**21**) and (**22**) (Scheme 6),[95] but it is reduced as though it were only (**21**), reacting *via* a retention mechanism. The reduction is very slow (168 h) and it is this author's view that one cannot exclude the possibility that (**22**) is not reduced at all but is isomerized to replace (**21**) as it is consumed (a few such isomerizations have been observed).

The retention mechanism was first clearly enunciated to account for results in the steroid series,[96] where the simple ketals (**23**) and (**24**) are reduced exclusively from the less-hindered underside and where the 1,2-propylenedioxy ketal of cholest-5-en-3-one (**25**) is both opened and reduced from that side. This mechanism may be visualized by imagining that A in (**18**) carries the hydride and attacks the carbonium center as soon as it forms.[96]

With a variety of substrates, DIBAL-H in toluene at 0 °C is effective in selectively cleaving benzylidene dioxolanes and dioxanes in the same way as $H_2AlCl$.[97]

Acetals or ketals ($R^1$, $R^2$ different) of chiral 2,3-butanediol (**26**) or 2,4-pentanediol (**27**) have diastereotopic oxygen atoms which can be distinguished by Lewis acids. Stereoselective reduction will occur if the subsequent step must follow an obligatory steric course. It could also take place at the carbonium center, under the influence of the chiral ligand, but this would not be expected to be very efficient. In either case the chiral adjuvant, by remaining attached, would serve as a resolving agent and allow separation of the reduction products as diastereomers. Efficient removal of the adjuvant can be achieved by way of mild oxidation of the free hydroxy group and reduction with metals or cleavage with base.[6]

The oxygen atoms of the dioxolane (**26**) are not very different and the degree of asymmetric reduction with ketals[98] is not much by modern standards (Table 10), although some acetals do show good stereose-

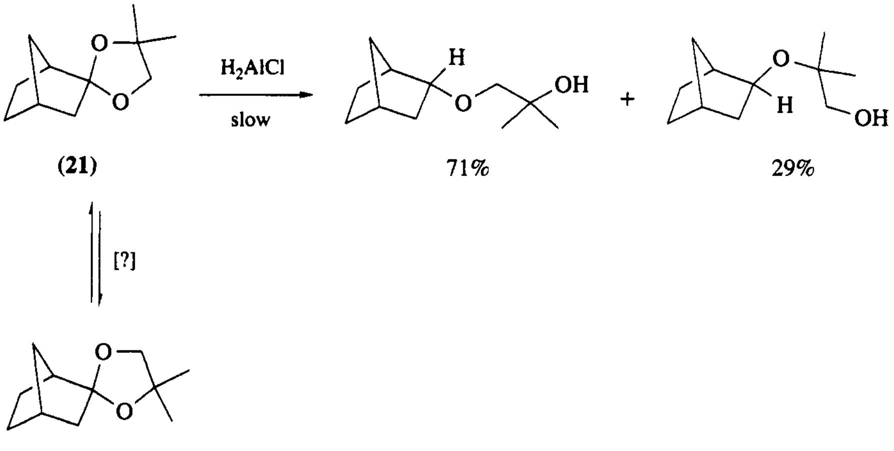

Scheme 6

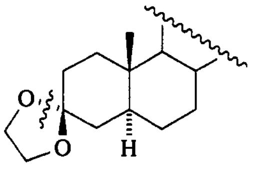

**(23)**

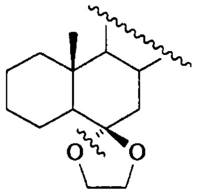

**(24)**

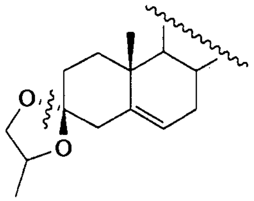

**(25)**

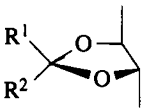

**(26)**

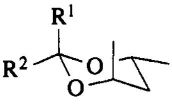

**(27)**

lectivity with $DAlCl_2$. Racemic diol was used in this work, so the sense of the asymmetric reduction is not known.

The oxygen atoms of **(27)** are, however, quite different. One is next to an axial methyl group and is quite open to attack, the other is hindered by an equatorial methyl group. Reactions of compounds of this series with various aluminum hydrides ($HAlBr_2$, $HAlCl_2$ and DIBAL-H are best) at low temperatures give good yields of the products expected from the retention mechanism (equation 26; Table 11).[99,100] Inversion (equation 27) is obtained with triethylsilane and various Lewis acid partners.

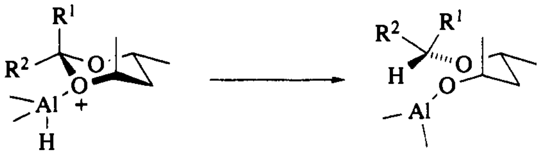

(26)

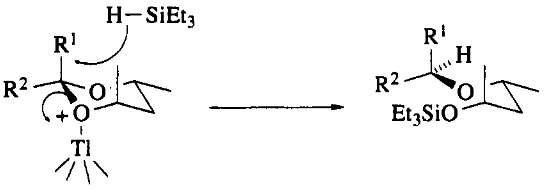

(27)

**Table 10** Reduction of 2-Substituted-2,4,5-trimethyl-1,3-dioxolanes (**26**) with $HAlCl_2$ in Ether at Room Temperature (2 h)[98]

| $R^1$ | $R^2$ | *Isomer ratio (configurations unspecified)* |
|---|---|---|
| Me | Et | 75.5:24.5 |
| | $Pr^i$ | 79:21 |
| | $Bu^t$ | 86.6:13.4 |
| | c-$C_6H_{11}$ | 75:25 |
| | 1-Adamantyl | 88.5:11.5 |
| | $Pr^n$ | 69.3:30.7 |
| | $Bu^i$ | 75.8:24.2 |
| | $CH_2Bu^t$ | 64:36 |
| | $CH{=}CH_2$ | 54.5:45.6 |
| | $C{\equiv}CH$ | 51.7:48.3 |
| | Ph | 52.5:47.5 |
| | Bn | 59.5:40.5 |
| | (with $DAlCl_2$) | |
| H | Me | 98:2 |
| | Et | 99:1 |
| | c-$C_6H_{11}$ | 90:10 |
| | $Bu^t$ | 78:22 |
| | Ph | 86:14 |
| | Bn | 90.6:9.4 |

**Table 11** Stereoselective Reductions of 2-Substituted-2,4,6-trimethyl-1,3-dioxanes (**27**)[99,100]

| *Substituents at C-2* | | *Reagent (conditions)* | *Yield (%)* | *Configuration at C-2* | *Diastereomer ratio* | *Ref.* |
|---|---|---|---|---|---|---|
| *$R^1$ (Small)* | *$R^2$ (Large)* | | | | | |
| Me | c-$C_6H_{11}$ | DIBAL-H ($CH_2Cl_2$) | 82 | (*S*) | 13:1 | 99 |
| | | $HAlCl_2$ ($Et_2O$) | 98 | (*S*) | 19:1 | 99 |
| | | $HAlBr_2$ ($Et_2O$, –20 °C) | 99 | (*S*) | 23:1 | 99 |
| | | $Et_3SiH$ ($TiCl_4$, –78 °C) | 85 | (*R*) | 49:1 | 100 |
| | n-$C_6H_{13}$ | DIBAL-H ($CH_2Cl_2$) | 58 | (*S*) | 3.5:1 | 99 |
| | | $HAlCl_2$ ($Et_2O$) | 73 | (*S*) | 2:1 | 99 |
| | | $HAlBr_2$ ($Et_2O$, –40 °C) | 87 | (*S*) | 4:1 | 99 |
| | | $Et_3SiH$ ($TiCl_4$, –78 °C) | 97 | (*R*) | 7.5:1 | 100 |
| | Ph | DIBAL-H ($CH_2Cl_2$) | 88 | (*S*) | 28:1 | 99 |
| | | $HAlBr_2$ ($Et_2O$, –78 °C) | 94 | (*S*) | 57:1 | 99 |
| | | $Et_3SiH$ ($SnCl_4$, –78 °C) | 24 | (*R*) | 4:1 | 100 |
| C≡C—Bu | Me | $HAlBr_2$ ($Et_2O$, –20 °C) | 100 | (*R*) | 17:1 | 100 |
| | | $Et_3SiH$ ($TiCl_4$, –78 °C) | 58 | (*S*) | 16:1 | 100 |

This principle has been used to convert a substance with a chirotopic, but not stereogenic, central carbon atom (**28**) to one in which that atom has, selectively, become chiral (**29**; Scheme 7).[101]

It has been stated:[102] 'It is probably true that no sugar derivative has been manipulated as successfully as methyl-4,6-*O*-benzylidene-α-D-glucopyranoside.' Reduction of derivatives of (**30**) with $H_2AlCl$ or $H_2AlBr$ in ether solvents gives increasing amounts of cleavage at O-6 to form derivatives of (**31**) as crowding by substituents at C-3 increases (Scheme 8; Table 12).[103] DIBAL-H is much less selective but gives clean cleavage at O-6 at –30 °C.[104] Borane in THF is ineffective and reacts only slowly at higher temperatures.[103] Sodium cyanoborohydride,[54] with dry HCl in THF[105] or trifluoroacetic acid in DMF,[106] reacts cleanly in the opposite sense with *p*-methoxybenzylidene acetals to form analogs of the series (**32**). It seems likely that the smaller Lewis acid can coordinate more readily at O-4 (perhaps assisted by the neighboring oxygen atom, O-3) while the hydride donor attacks from the other, less-hindered, side of the reacting carbon atom. With a more bulky reagent, $Me_3SiCl$, as acidic partner, cleavage occurs again at O-6.[106] A striking solvent effect is observed in reductions with borane:trimethylamine and $AlCl_3$;[107] with toluene as solvent cleavage occurs at O-6, but with THF it occurs at O-4. Reduction of the galactose analogs (**33**) with $H_2AlCl$ gives cleavage at O-4 (Scheme 9) when the group at C-3 is small,[108,109] but at O-6 when it is large.[109]

Acetopheneone forms a pair of 4,6-ketals with glucose.[110] The kinetic product has an equatorial phenyl group (**36**) and reacts with $H_2AlCl$ by cleavage at O-6 to give (**38**), in analogy with the conversion of (**30**) to (**31**). The more stable isomer (**37**), however, has an axial phenyl group, as found in simpler systems.[111] It reacts by cleavage at O-4. Models indicate that only an equatorial phenyl group can stabilize the incipient oxocarbonium ion by resonance; this would seem to require a boat-like transition state (**39**)

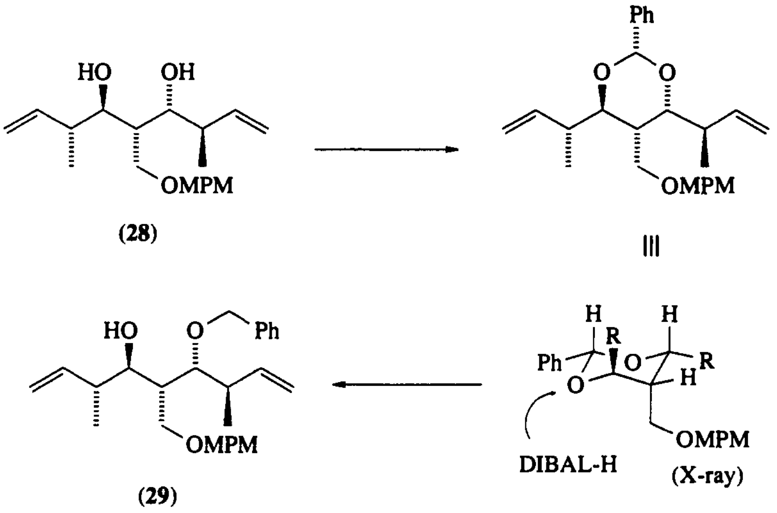
HO
OH
OMPM
(28)
Ph
O
O
OMPM
HO
O
Ph
OMPM
(29)
H
R
H
Ph
O
R
H
O
OMPM
DIBAL-H
(X-ray)

Scheme 7

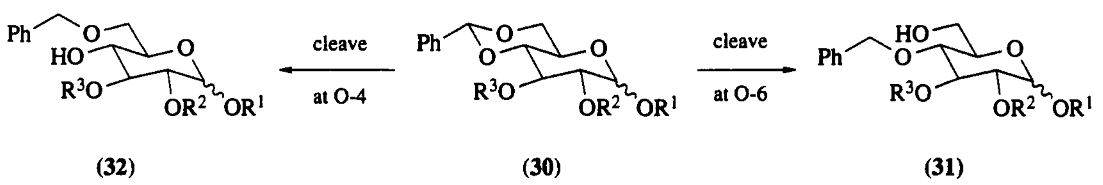
Ph
O
HO
O
$R^3O$
$OR^2$
$OR^1$
(32)
cleave
at O-4
Ph
O
O
O
$R^3O$
$OR^2$
$OR^1$
(30)
cleave
at O-6
Ph
HO
O
O
$R^3O$
$OR^2$
$OR^1$
(31)

Scheme 8

Table 12 Regioselectivity in the Reduction of 4,6-*O*-Benzylidene-D-glucopyranosides (30) with Aluminum Hydride Reagents[103]

| *Reagent (Solvent) (Temperature)* | *Substituent at C-2* | *Isolated yield (%)* (31)[a] | (32)[a] | *Product ratio* (31):(32) |
|---|---|---|---|---|
| $H_2AlCl$ | —OMe | 68 | 14 | 77:23 |
| (2:1 = $Et_2O$:$CH_2Cl_2$) | —OEt | 75 | 7 | 91:9 |
| (45 °C) | —OPr$^n$ | 91 | 3 | 94:6 |
| | —OBn | 91 | 4 | 93:7 |
| | —H ($R^2$ = Me) | 43 | 41 | 53:47 |
| $H_2AlBr$ (as above) | —OMe | 73 | 12 | 84:16 |
| DIBAL-H | —OMe | 68 | 25 | 71:29 |
| (9:1 = $Et_2O$:$CH_2Cl_2$) | | | | |
| ($C_6H_6$, 0 °C) | | 34 | 43 | 46:54 |

[a] (30); $R^1$ = Bn (β); $R^2$ = $R^3$.

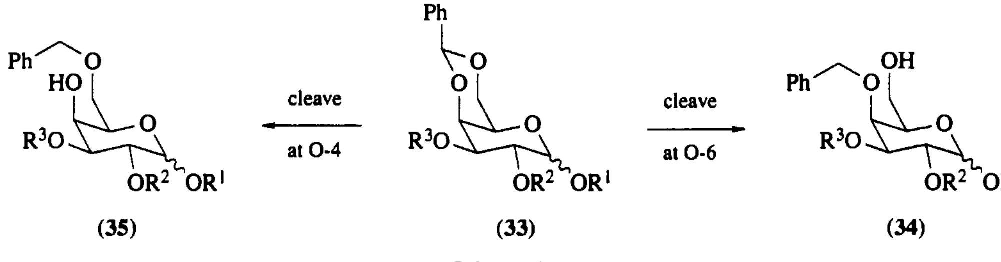
Ph
O
HO
O
$R^3O$
$OR^2$
$OR^1$
(35)
cleave
at O-4
Ph
O
O
O
$R^3O$
$OR^2$
$OR^1$
(33)
cleave
at O-6
Ph
O
OH
O
$R^3O$
$OR^2$
$OR^1$
(34)

Scheme 9

for this case (Scheme 10). This would give the observed cleavage at O-4. The corresponding galactose derivatives behave in the same way.[110]

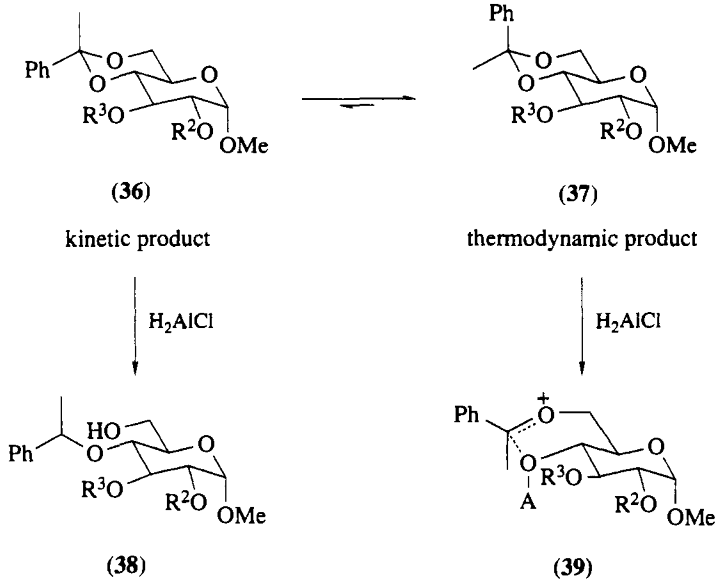

**Scheme 10**

A dioxolane fused to a six-membered ring is subject to major constraints in forming a transition state resembling (**18**), where C-4, O-3, C-2, $R^1$ and $R^2$ must all be coplanar. The oxygen atom that becomes a part of the oxocarbonium system is puckered out of the plane of the other four atoms. The substituents on the carbon atom of the developing oxocarbonium ion then adopt quasi-axial ($R^1$) or quasi-equatorial ($R^2$) orientations, the latter being required of a phenyl group if it, too, is to become coplanar and contribute to stabilization of the transition state. This now means that when the phenyl group has an *endo* orientation relative to the six-membered ring (**40**) the oxygen atom that is breaking away will be equatorial, while the one that becomes an ether oxygen is axial. The reverse is true when the phenyl group is *exo* to the six-membered ring (**41**).

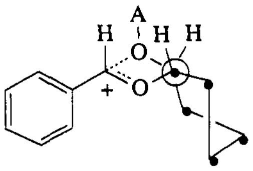

**(40)**

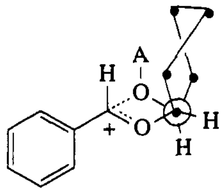

**(41)**

The *exo* and *endo* isomers of benzylidene acetals of the carbohydrate series can be obtained separately. Their behavior on reduction with $H_2AlCl$ accords with the analysis outlined above; frequently only one product is obtained. Thus, the 1,2,4,6-di-*O*-benzylidene derivatives of glucose (**42**) and (**43**; R = H or Bn) cleave rapidly with 1 equiv. of $H_2AlCl$ at 0 °C (30 min for **42** and 10 min for **43**) at the marked bonds.[112] Here, at least, it is clear that steric effects outweigh polar ones. The 2,3-*endo* and -*exo* isomers of the α-D-mannoside series (**44**) and (**45**) likewise cleave mainly equatorial (78:22) and axial (96:4), respectively, when treated with 1 equiv. of $H_2AlCl$ at room temperature.[113] The same behavior is seen with the methyl 2,3-benzylidene-α-L-rhamnosides,[114] the methyl 3,4-*O*-benzylidene-β-L-arabinosides[114] and

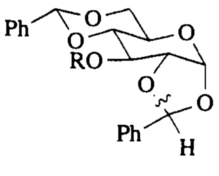

**(42)** *endo*

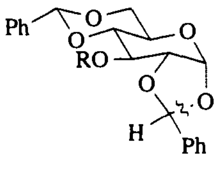

**(43)** *exo*

the methyl 3,4-*O*-benzylidene-α- and methyl-3,4-*O*-benzylidene-β-D-galactopyranosides.[115] Only with the benzylidene acetals of 1,6-anhydro-β-D-galactopyranose (**46**) and (**47**) do both acetals give the same product,[116] both cleaving at O-4. This is the normal mode of cleavage for the *endo* isomer (**46**) and it occurs readily. The normal reaction for the *exo* isomer would require puckering at O-4; this would produce a very close approach of the incipient carbonium carbon atom to C-6, perhaps producing prohibitive strain. The more difficult cleavage *via* a transition state with a quasi-axial phenyl group would then be required; consistent with this, the *exo* isomer (**47**) is distinctly more difficult to reduce.

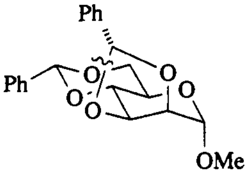

(**44**) *endo*

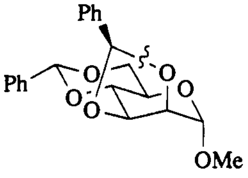

(**45**) *exo*

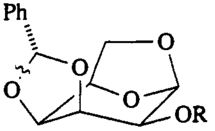

(**46**) *endo*

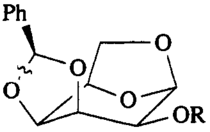

(**47**) *exo*

## 1.9.3.5 Bicyclic Acetals and Ketals

Ring strain appears to be important with bicyclic acetals—they tend to cleave under reducing conditions so as to leave six-membered rings or to avoid leaving five-membered ones. Thus, hydrogenolysis of 6,8-dioxabicyclo[3.2.1]octane (**48**; R = H)[117,118] and the 3,6,8-trioxa analog (**49**; R = H)[119] with $H_2AlCl$ occurs with cleavage of the oxygen atom that is, essentially, axial to the six-membered ring. Ketals (R = Me) give mixtures of stereoisomers,[117,119] indicating that the carbonium ion intermediate is long lived enough to be attacked from either side.

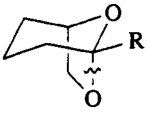

(**48**)

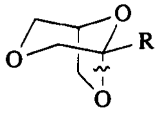

(**49**)

Good stereoselectivity has been obtained with other reagents, however. Thus, the dioxabicyclo [3.3.1]nonane (**50**) opens with retention using DIBAL-H in $CCl_4$ but with inversion using diphenylsilane and $TiCl_4$ (Scheme 11).[120] Similar stereoselectivity is shown with both reagents in reductions of dioxa[3.2.1]octanes and dioxa[2.2.1]heptanes (**51**); in the latter case cleavage occurs nearly equally at both oxygen atoms (Scheme 12).[120] In like fashion, the dioxa[3.2.1]octane (**52**) gives mainly *trans* product with DIBAL-H in $CH_2Cl_2$ at –78 °C, but *cis* product with the $Zn(BH_4)_2$:$TiCl_4$ pair or with $Et_3SiH$:$TiCl_4$, both at –78 °C, (Scheme 13).[121] These reactions are nearly quantitative and give only traces of the other isomer.

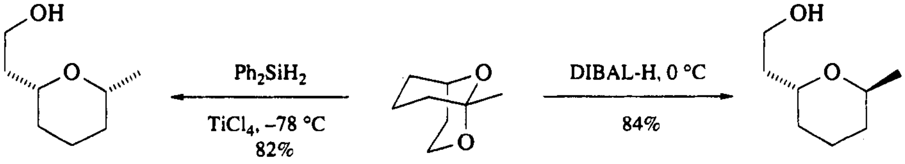

only

(**50**)

*trans*:*cis* = 92:8

Scheme 11

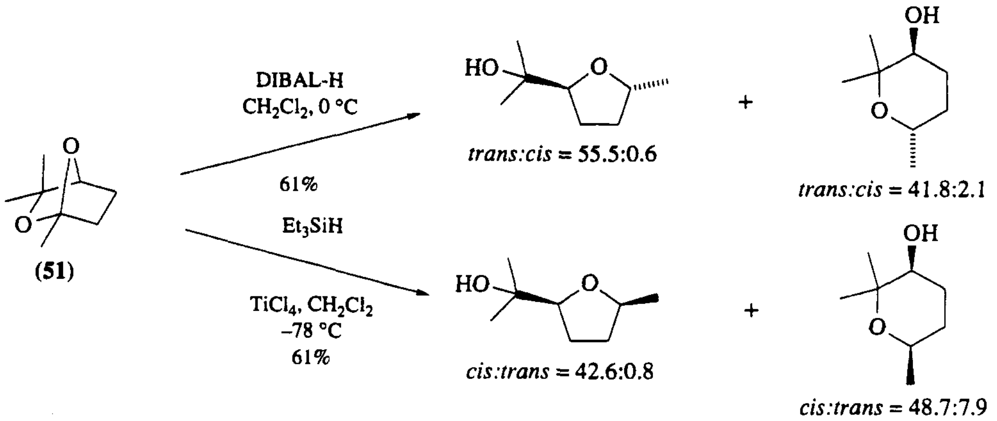
DIBAL-H
$CH_2Cl_2$, 0 °C
61%
$Et_3SiH$
$TiCl_4$, $CH_2Cl_2$
-78 °C
61%
(51)
HO
O
OH
trans:cis = 55.5:0.6
trans:cis = 41.8:2.1
cis:trans = 42.6:0.8
cis:trans = 48.7:7.9
+

**Scheme 12**

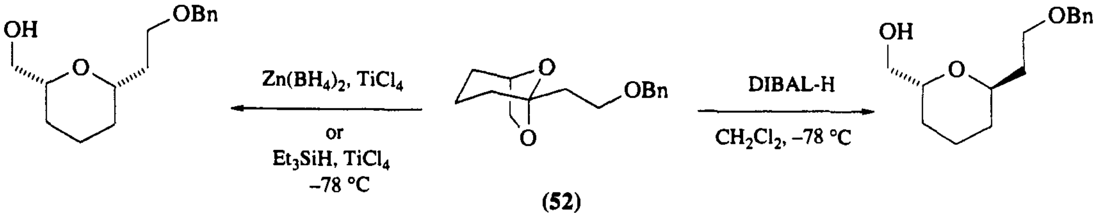
OH
OBn
O
$Zn(BH_4)_2$, $TiCl_4$
or
$Et_3SiH$, $TiCl_4$
-78 °C
(52)
DIBAL-H
$CH_2Cl_2$, -78 °C

**Scheme 13**

### 1.9.3.6 Azaacetals and Azaketals

Oxazolidines (**53**) are readily formed from aldehydes or ketones and ethanolamines; they can be hydrolyzed with ease and show reactions that might be expected of the imino alcohol intermediate (**54**). Among these are the addition of Grignard reagents[122] and catalytic hydrogenolysis of the C—O bond (equation 28).[122,123] This reaction is exothermic over Adam's catalyst in methanol but slower in acetic acid.[123] Nickel and copper chromite are also effective but at higher temperatures and pressures,[123] as is the case with palladium.[122] The same cleavage occurs with LAH (unassisted)[124,125] and with the borane–THF complex.[126]

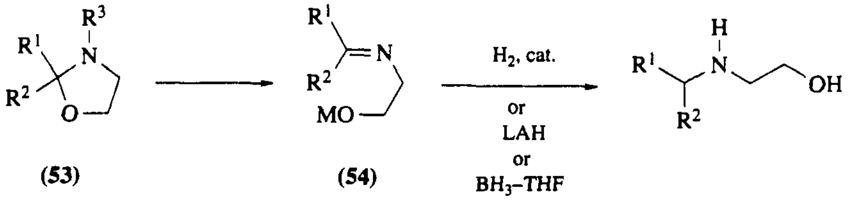
$R^3$
$R^1$
$R^2$
N
O
(53)
MO
(54)
$H_2$, cat.
or
LAH
or
$BH_3$-THF
H
OH

(28)

This pattern of cleavage is also followed when the azaacetal is acyclic (equation 29)[127] and even when the nitrogen atom is part of a three-membered ring (equation 30).[128] Tetrahydropyranylamines are reduced to ε-hydroxypentylamines by hydrogenation over Ni[129] or reduction with LAH (equation 31).[130]

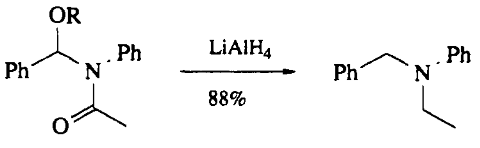
OR
Ph
N
O
$LiAlH_4$
88%

(29)

The sapogenin-like side chain of steroidal alkaloids such as solasodine[131] and tomatidine (**55**),[132,133] undergoes cleavage of the five-membered oxa ring with hydrogen over Pt[131,133] or with LAH[131,132] (equation 32; *cf.* Section 1.9.3.3). When, however, the electron-donating power of the nitrogen atom is diminished by acylation the pattern is reversed and C—N cleavage takes place (equation 33).[134]

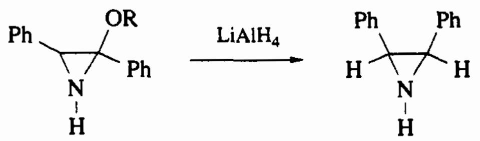

(30)

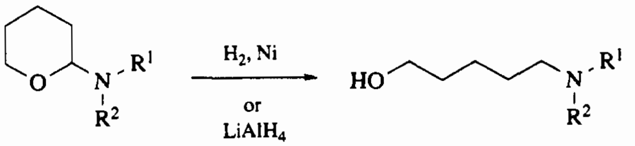

(31)

Diazaspiroalkanes (**56**) give nearly quantitative hydrogenolysis of one ring over platinum or nickel (equation 34).[135]

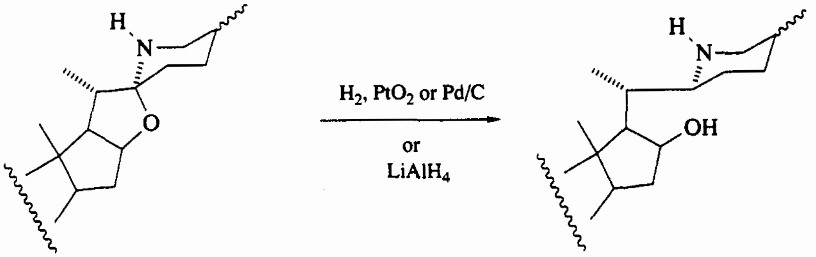

**(55)**

(32)

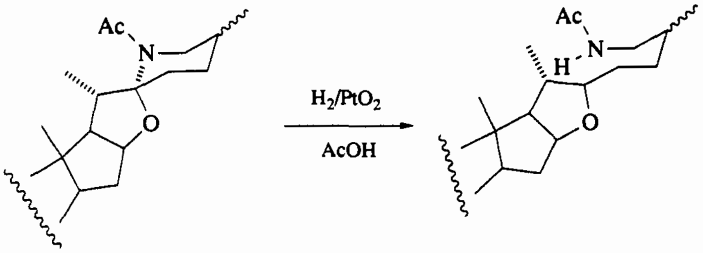

(33)

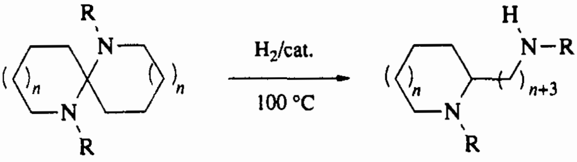

**(56)**

(34)

### 1.9.3.7 Thioacetals and Thioketals

The isomeric 1,3-oxathiolanes (**57**) and (**58**) are readily interconverted by Lewis acids such as $AlCl_3$ or $BF_3$ (Scheme 14).[136] They are reduced with previously prepared $HAlCl_2$ (but not with $BF_3$–LAH)[136] to the same mixture of products,[137] with exclusive C—O cleavage. Addition of $BF_3$ to a mixture of ketal with LAH or, better, of LAH to a mixture of ketal and $BF_3$ does, however, give reduction.[138] The latter results provided a firm basis for the accepted carbonium ion mechanism and serve to emphasize that $BF_3$–LAH mixtures can generate several reducing agents (*i.e.* $LiBH_4$ and $B_2H_6$) depending on how they are made and how quickly they are used (see Section 1.9.2.3.2). It is suggested that the Lewis acid coordinates more readily with the oxygen atom than with the sulfur atom and that this determines the direction of cleavage. With longer reaction times, the oxygen atom is removed from the product (Scheme 15); studies with deuterium-labeled reagents show that this reaction proceeds *via* the sulfonium ion (**59**).[136]

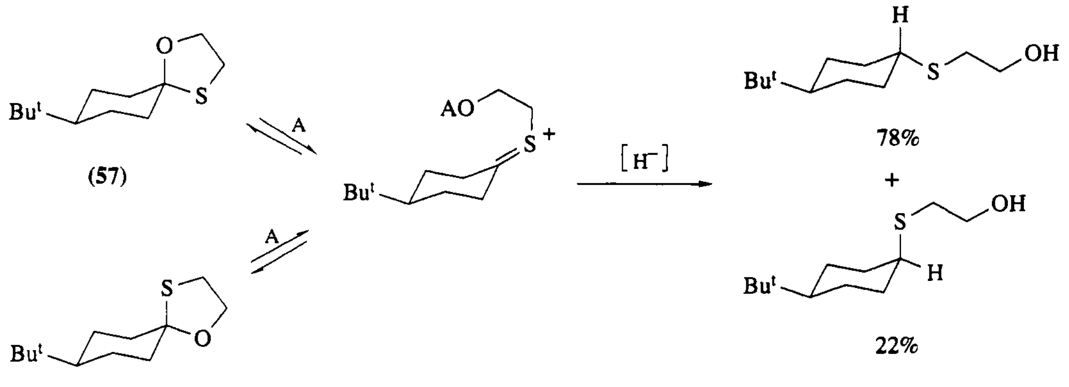

**(57)**

**(58)**

**Scheme 14**

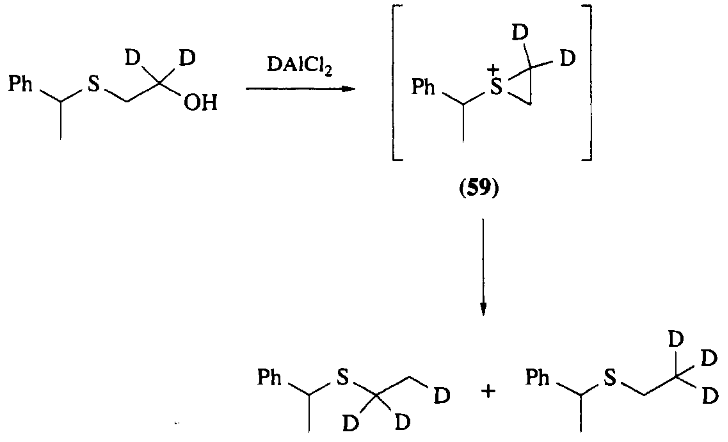

**(59)**

**Scheme 15**

1,3-Thioxanes (**60**) give similar ring-opening reactions but the subsequent reaction to lose oxygen is not observed.[137] 1,3-Dithiolanes such as the *cis* and *trans* forms of (**61**) can be isomerized by Lewis acids[138] but fail to undergo reduction with $H_2AlCl$; this may be a consequence of solubility problems.

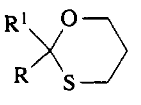

**(60)**

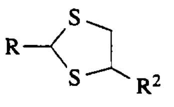

**(61)**

Tetrahydrofuranyl sulfides (equation 35; $n = 1$) and the tetrahydropyranyl analogs (equation 35; $n = 2$) give ring opening with $HAlCl_2$;[139] the subsequent removal of oxygen does not occur here.

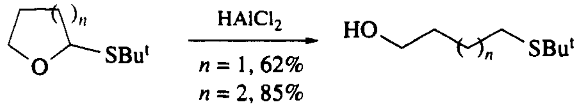

(35)

The methyl *endo-* and *exo*-benzylidenegalactopyranosides, (**62**) and (**63**), respectively, give the same product (**64**) on reduction with $H_2AlCl$, *via* the expected C—O bond cleavage (Scheme 16).[140] In conformity with the analysis presented above (Section 1.9.3.4) the *endo* isomer reacts rapidly, with its normal equatorial cleavage, while the *exo* isomer, for which equatorial cleavage is disfavored, reacts slowly at reflux.

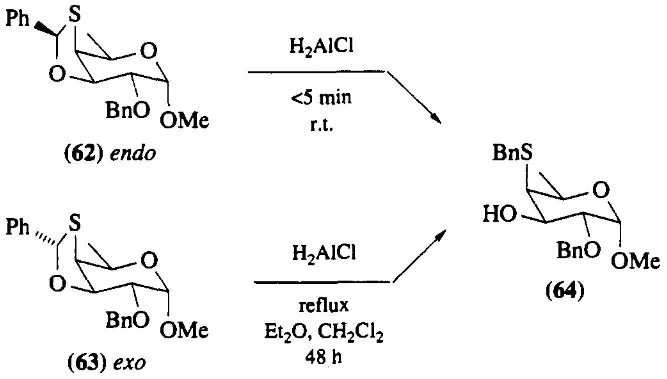
Ph
S
O
O
BnO
OMe
(62) endo
$H_2AlCl$
<5 min
r.t.
Ph
S
O
O
BnO
OMe
(63) exo
$H_2AlCl$
reflux
$Et_2O, CH_2Cl_2$
48 h
BnS
O
HO
BnO
OMe
(64)

**Scheme 16**

Thiazolidinones (**65**) can be reduced, with C—S bond cleavage, by LAH (equation 36);[141] thiazolidines (**66**; which may be intermediates) are reduced in the same way (equation 37) with LAH or $NaBH_4$.[142] An aromatic group at the reacting center promotes cleavage; thus the reduction of 5,6-dihydro-1,3-thiazines (**67**) with $NaBH_4$[143] can be stopped at the thiazane stage (**68**; equation 38), except when R is phenyl, when only the ring-opened product (**69**) is obtained. Thiazanes in general can be reduced with LAH.[144]

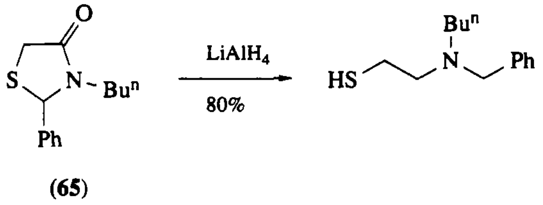
O
S
N
$Bu^n$
Ph
(65)
$LiAlH_4$
80%
$Bu^n$
HS
N
Ph

(36)

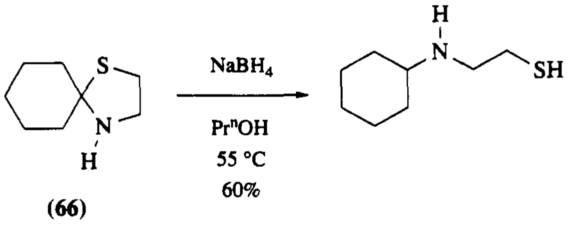
S
N
H
(66)
$NaBH_4$
$Pr^nOH$
55 °C
60%
H
N
SH

(37)

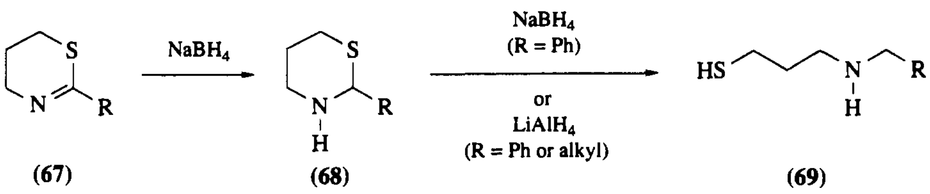
S
N
R
(67)
$NaBH_4$
S
N
R
H
(68)
$NaBH_4$
(R = Ph)
or
$LiAlH_4$
(R = Ph or alkyl)
HS
N
R
H
(69)

(38)

C—S bonds can be cleaved reductively by dissolving metals, by processes which depend on the ability of sulfur to accept electrons.[145] 1,3-Dithiolanes tend strongly to suffer cleavage of both C—S bonds with sodium in liquid ammonia when C-2 is unsubstituted or carries a phenyl group;[146] isopropylidene derivatives (**70**), however, give single cleavage (equation 39). Bond rupture requires formation of a relatively stable carbanion.

Calcium in ammonia offers some advantages[147,148] in that most cases of overreduction can be prevented by limiting the amount of active metal, although derivatives of benzaldehyde lose both C—S bonds.[147] Oxathiolanes and oxathianes give clean cleavage of the C—S bond.[146,148] In the *t*-butylcyclohexylidene series, the isomeric pairs (**71**) and (**72**) give almost convergent results, with the *trans*

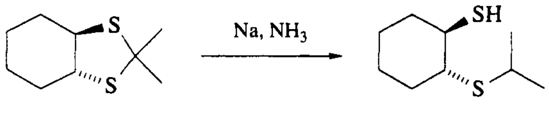

(70)

(39)

product (**74**) predominating strongly over the *cis* product (**75**; Table 13), probably *via* protonation of the carbanion (**73**), which must have an appreciable lifetime (Scheme 17).

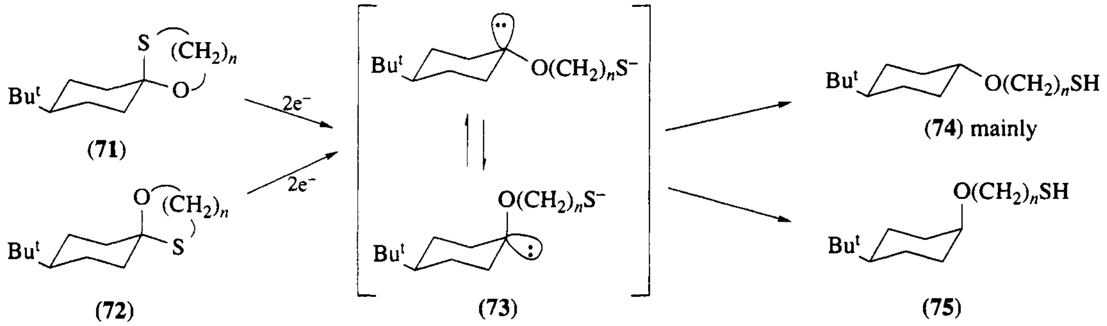

**Scheme 17**

**Table 13** Reductions of Oxathiolanes and Oxathianes with Calcium in Liquid Ammonia[148]

| *Thioketal* | *n* | *Yield (%)* | *Product (%)* (74) | (75) |
|---|---|---|---|---|
| (71) | 2 | 83–89 | 97–98 | 3–2 |
| (72) | 2 | 47–61 | 90–97 | 10–3 |
| (71) | 3 | 84–90 | 99.5 | 0.5 |
| (72) | 3 | 24–52 | 84–93 | 16–7 |

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# 1.10

# Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines

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## 1.10.1 REDUCTIONS OF CARBOXYLIC ACIDS

### 1.10.1.1 Hydrogenation Reactions

Carboxylic acids may be reduced to produce primary alcohols by hydrogenation over heterogeneous catalysts at elevated temperatures and pressures. Copper chromite, barium oxide promoted copper chromite, Raney nickel, ruthenium dioxide and rhenium oxides are the most commonly employed catalysts.[1,2] For example, glyoxalic acid was hydrogenated over ruthenium dioxide at 145–150 °C and 700–775 atm (1 atm = 101 kPa) to produce 1,2-ethanediol (83%). Such ruthenium-mediated hydrogenation reactions are frequently carried out in the presence of water to suppress ester formation. Rhenium oxides are useful for the reduction of aromatic carboxylic acids without concomitant arene hydrogenation. Representative hydrogenation reactions include the preparations of 1-decanol (100%; $Re_2O_7$, $H_2$, 137 °C, 173 atm, $H_2O$, dioxane), 2-methyl-1-propanol (90%; $ReO_3$, $H_2$, 144 °C, 205 atm, cyclohexane), 1-hexanol (93%; Cu–Ba chromite, $H_2$, 200 °C, 188 atm, $H_2O$) and 1,4-butanediol (59%, $RuO_2$, $H_2$, 150–190 °C, 720–950 atm) from the corresponding carboxylic acids or succinic acid. In general, the preparation of primary alcohols from carboxylic acids *via* such hydrogenation reactions is inconvenient. Specialist equipment and techniques are required.

There are few reports on the use of homogeneous catalysts. $H_4Ru_4(CO)_8(PBu_3)_4$ has been used to catalyze the hydrogenation of aliphatic monocarboxylic acids to produce primary alcohols at 180–200 °C and 130 atm.[3] Generally, yields of the primary alcohols were low due to poor conversions (1–44%) and concomitant formation of esters.

### 1.10.1.2 Electrochemical and Dissolving Metal Reductions

The electrochemical reduction of aromatic carboxylic acids may be used to prepare aldehydes, primary alcohols, methylarenes or dihydroarene carboxylic acids, depending on the substrate and reaction conditions employed.[2,4,5] Primary alcohol formation is observed when aromatic carboxylic acids are reduced in strongly acidic media using cathode material of high hydrogen overpotential (typically mercury or lead). These reductions proceed *via* the protonated carboxylic acid and the intermediacy of the geminal diol and the aldehyde. In general, complete reduction to the primary alcohol is observed unless the intermediate aldehyde is trapped, for example as its bisulfite adduct. Cathodic reductions of aliphatic carboxylic acids are invariably inefficient and limited. Frequently such reductions produce copious quantities of hydrogen and little primary alcohol. Applications of carboxylic acid electrochemistry in synthesis are exemplified by the transformations in Scheme 1. The dissolving metal reduction of carboxylic acids is not useful for the direct preparation of primary alcohols. Reduction of aliphatic carboxylic acids may be used to prepare aldehydes using excess Li in $MeNH_2$ or $EtNH_2$[6] at reflux, or to prepare alkanes using Mg and water at 420–450 °C and 2–5 atm pressure.[7]

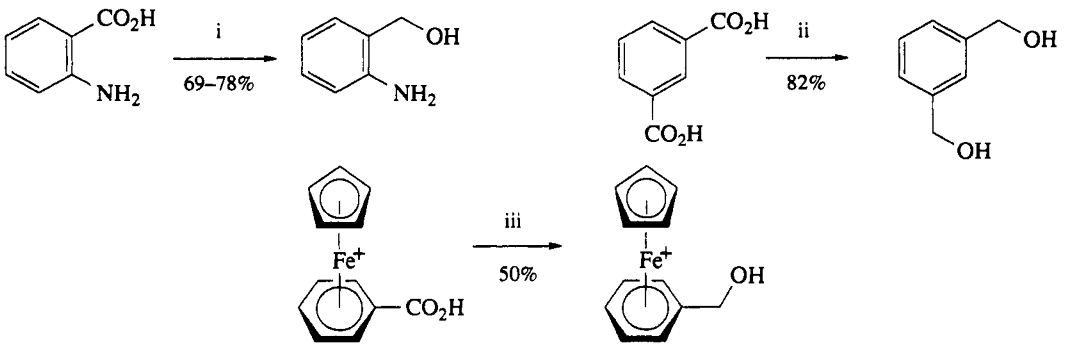

i, Pb, 1 A $dm^{-2}$, 15% $H_2SO_4$; ii, Pb, $e^-$, $H_2SO_4$, $H_2O$; iii, Hg, −1.2 V, $H_2SO_4$, $H_2O$

Scheme 1

### 1.10.1.3 Reductions using Metal Hydride Reagents

Metal hydrides are unquestionably the most useful reagents for the reduction of carboxylic acids to produce primary alcohols. A diverse variety of derivatives of $B_2H_6$ and LAH have been applied for the chemoselective reduction of polyfunctional organic molecules. $B_2H_6$ is an excellent reagent for the rapid and efficient reduction of aliphatic and aromatic carboxylic acids to produce borate esters, which are hydrolyzed on work-up to produce primary alcohols.[8] $B_2H_6$ is frequently used in THF solution, in which it exists as the complex $BH_3{\cdot}THF$. $BH_3{\cdot}SMe_2$ in THF is an alternative very soluble, more stable reagent for carboxylic acid reductions. $BH_3{\cdot}THF$ and $BH_3{\cdot}SMe_2$ rapidly reduce aldehydes, ketones, lactones, carboxylic acids and tertiary amides at 0 °C in THF. In contrast, acid chlorides, epoxides, esters, carboxylic acid salts and nitro compounds are only very slowly reduced, if at all. Alkenes may be hydroborated under the reduction conditions.[2,8] Thus $BH_3{\cdot}THF$ and $BH_3{\cdot}SMe_2$ are very useful for the selective reduction of carboxylic acids in the presence of esters *etc.* Such selective transformations are exemplified by the conversions in Scheme 2. Chemoselectivities in the reduction of carboxylic acids bearing ester, nitro, lactone, halide, amide, nitrile or (diene)tricarbonyliron functionality are noteworthy.[2,8–11] Although lactones and nitriles are reduced by $BH_3{\cdot}THF$, they do not react as rapidly as carboxylic acids. $BH_3{\cdot}THF$ is a very convenient reagent for the reduction of α-amino acids and α-acylamino acids (including peptides) to produce the corresponding β-amino (acylamino) alcohols.[2,12] $BH_3{\cdot}SMe_2$ is less reactive than $BH_3{\cdot}THF$, and thus aliphatic carboxylic acids are rapidly reduced at 25 °C in THF, while aromatic carboxylic acids react slowly. However, reduction may be accelerated by the addition of trimethyl borate.[2,8] $BH_3{\cdot}SMe_2$ is also particularly efficient for the reduction of amino acids to β-amino alcohols when used in the presence of $BF_3{\cdot}OEt_2$. Although borane in its various forms is invarably the reagent of choice for carboxylic acid reduction, occasionally problems arise. Alkenes may be hydroborated during the reaction. Additionally, deoxygenation may be observed, particularly with electron-rich heteroaromatic ring systems; one example of this is given in Scheme 2.

Various mono- ($BH_2X$) and di-substituted boranes ($BHX_2$) or borane complexes ($BH_3{\cdot}X$) have been used for the reduction of carboxylic acids to produce primary alcohols or aldehydes. Catecholborane in $CHCl_3$ at 25 °C rapidly reduces aldehydes, ketones, hydrazones, carboxylic acid salts, sulfoxides, anhydrides, epoxides, alkynes, acetals and ketals. Ketones, acid chlorides, alkenes, nitriles, carboxylic acids and tertiary amides are reduced at a much slower rate. Esters, lactones and anhydrides are not reduced.[13] $BH_3{\cdot}NHPh_2$ is a crystalline reducing agent that in THF rapidly reduces ketones, aldehydes, carboxylic acids and aliphatic esters.[14] Anhydrides and aromatic esters are inert. Both catecholborane and $BH_3{\cdot}NHPh_2$ reduce carboxylic acids to primary alcohols. 9-BBN-H in THF will slowly reduce aliphatic but not aromatic carboxylic acids.[15] Ketones, esters, lactones and tertiary amides are reduced more rapidly. The thexylborane·diethylaniline complex reduces aldehydes, ketones, carboxylic acids, anhydrides and tertiary amides. Esters, acid chlorides and nitriles are only slowly reduced. It is interesting to note that reductions of carboxylic acids with this reagent give primary alcohols. This is in contrast to thexylborane, thexylchloroborane or thexylbromoborane, which are particularly useful for the reduction of carboxylic acids to produce aldehydes.[16]

$NaBH_4$ and related reagents do not reduce carboxylic acids when used in alcohol or ether solvents. Borohydride salts in combination with powerful Lewis acids show reactivities comparable to diborane.[2,8,17] Thus, carboxylic acids may be reduced using $NaBH_4$ in the presence of $AlCl_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, $TiCl_4$ or $MeSO_3H$. $NaBH_4$ and 1,2-ethanedithiol in THF at reflux has been used to reduce esters and carboxylic acids to primary alcohols and amides to primary amines.[18] Nitriles do not react with the reagent. For example, reduction of benzoic acid gave benzyl alcohol (53%). Finally, Cho and Yoon have reported that various sodium acyloxyborohydrides slowly reduce carboxylic acids on reflux in THF. The method is useful for the selective reduction of aliphatic carboxylic acids in the presence of aromatic carboxylic acids.[19]

LAH is a powerful reducing agent that rapidly converts carboxylic acids or their salts into primary alcohols at 0 °C in $Et_2O$ or THF solution. A plethora of other groups are reduced by this reagent, including aldehydes, ketones, acid chlorides, esters, lactones, amides, nitriles, nitro compounds, aromatic halides and epoxides.[2,9,20] In consequence of its high reactivity, LAH is less useful than borane derivatives for chemoselective reduction of polyfunctional carboxylic acids. Nonetheless, unlike $B_2H_6$, it does not generally react with alkenes and is therefore useful for the selective reduction of unsaturated carboxylic acids to provide the corresponding primary alcohols. Low carboxylic acid or salt solubility in ethereal solvents may result in slow reduction and, in these cases, reduction of derived esters or acid chlorides are more convenient. A vast array of both aliphatic and aromatic carboxylic acids have been reduced using LAH, and representative examples are provided in Scheme 3. α,β-Unsaturated acids may be reduced to produce allylic or saturated alcohols, depending on the stoichiometry and temperature of reaction. Overreduction is the result of metallocycle (**1**) formation, and such intermediates may give rise to arylcyclo-

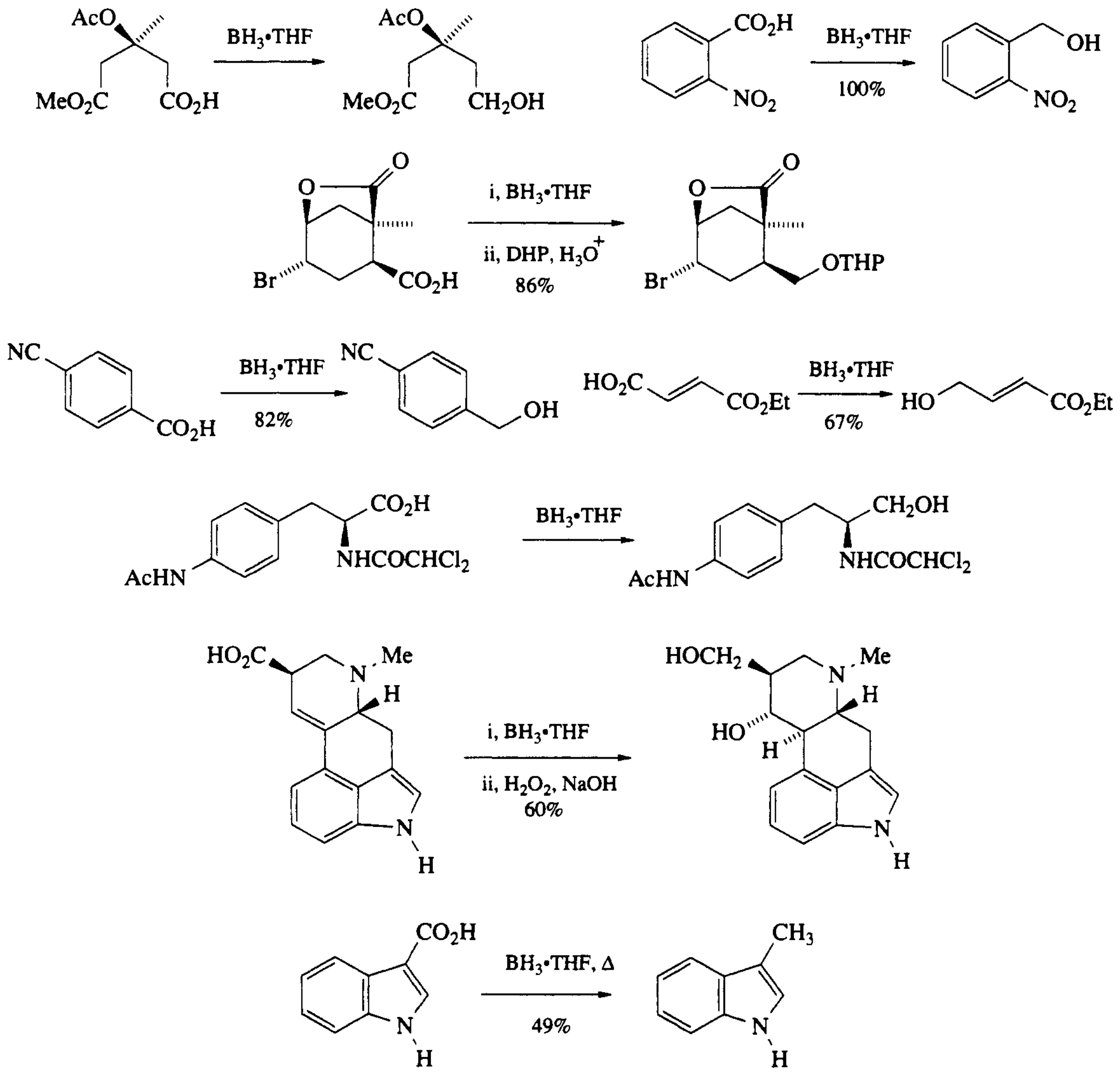
AcO
MeO2C
CO2H
BH3•THF
CH2OH
CO2H
NO2
BH3•THF
100%
OH
NO2
O
Br
CO2H
i, BH3•THF
ii, DHP, H3O+
86%
OTHP
NC
CO2H
BH3•THF
82%
OH
HO2C
CO2Et
BH3•THF
67%
HO
CO2Et
AcHN
CO2H
NHCOCHCl2
BH3•THF
CH2OH
NHCOCHCl2
HO2C
N
Me
H
i, BH3•THF
ii, H2O2, NaOH
60%
HOCH2
HO
CO2H
BH3•THF, Δ
49%
CH3

**Scheme 2**

propanes on the prolonged reduction of cinnamic acid derivatives.[20] A variety of metal alkoxyaluminum hydride reagents including $LiAlH(OMe)_3$, $NaAlH(OEt)_3$, Red-Al, $Ca(AlH_2(OCH_2CHEtBu)_2)_2{\cdot}THF$, $Ca(AlH_2(OBu^i)_2)_2{\cdot}THF$ and $Ca(AlH_2(OPr^i)_2)_2{\cdot}THF$ have been used for the reduction of carboxylic acids or their salts, to produce primary alcohols.[2,9,21] Red-Al is a particularly useful reagent that is readily soluble in aromatic hydrocarbon solvents. It is convenient for the reduction of carboxylic acids of low solubility, including α-amino acids.

Alane ($AlH_3$) and its derivatives have also been utilized in the reduction of carboxylic acids to primary alcohols.[2,9] It rapidly reduces aldehydes, ketones, acid chlorides, lactones, esters, carboxylic acids and salts, tertiary amides, nitriles and epoxides. In contrast, nitro compounds and alkenes are slow to react. $AlH_3$ is particularly useful for the chemoselective reduction of carboxylic acids containing halogen or nitro substituents, to produce the corresponding primary alcohols. DIBAL-H reduces aliphatic or aromatic carboxylic acids to produce either aldehydes (–75 °C) or primary alcohols (25 °C).[22] Aminoaluminum hydrides are less reactive reagents and are superior for aldehyde synthesis.[23]

Aromatic carboxylic acids have been reduced using $HSiCl_3$ and tertiary amines. Generally, this reaction leads to deoxygenation and the formation of (trichlorosilylmethyl)arenes. However, this reaction was found to produce ether (**3**) on the reduction of diacid (**2**; Scheme 3). Reduction by $HSiCl_3$ is selective for aromatic carboxylic acids in the presence of esters.[24] A representative reduction using $HSiCl_3$ is also given in Scheme 3.

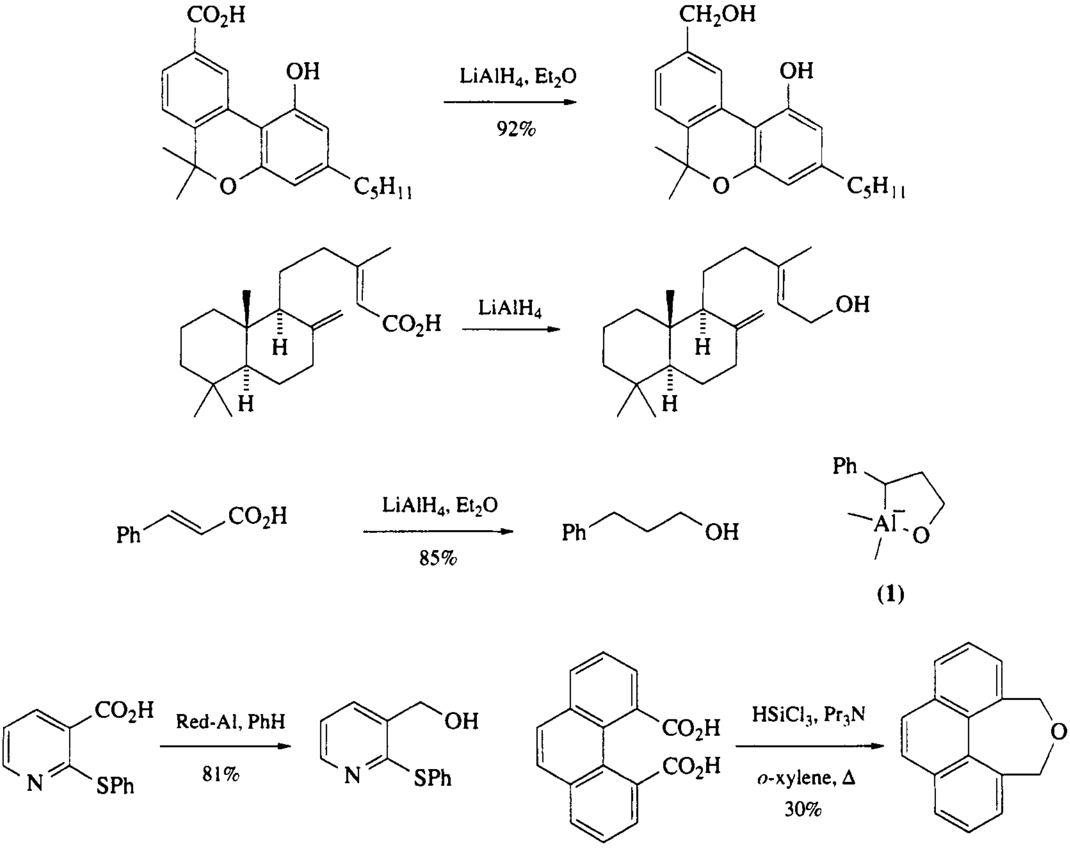

**(1)**

**(2)** **(3)**

**Scheme 3**

## 1.10.2 REDUCTIONS OF ACYL HALIDES, ANHYDRIDES AND RELATED SPECIES

### 1.10.2.1 Hydrogenation Reactions

The conversion of carboxylic acid chlorides into aldehydes *via* low temperature and low pressure hydrogenation over poisoned Pd/$BaSO_4$ is the classical Rosenmund reduction. Further hydrogenation, particularly with more active catalysts, gives rise to the corresponding primary alcohols.[25] The hydrogenation of anhydrides over heterogeneous catalysts may be used to prepare alcohols, lactones or ethers depending on the substrate and reaction conditions.[1,26] Examples of these reactions include the reduction of succinic anhydride to give $\gamma$-butyrolactone (80–94%; Pd/C, $H_2$, 35–100 °C, 16–75 atm) and of phthalic anhydride to give phthalide (90%; Raney Ni, $H_2$, 30 °C, 100 atm, dioxane). Several homogenous catalysts have been employed to reduce cyclic anhydrides to produce lactones.[3,27,28] Lyons reported that $(Ph_3P)_3RuCl_2$ efficiently catalyzed the hydrogenation of succinic anhydride at 100 °C and 5 atm to produce $\gamma$-butyrolactone (50%). Reduction of acetic anhydride using the same catalyst gave ethyl acetate (36%) and acetic acid (50%). This homogeneous hydrogenation catalyst is particularly useful for the regioselective hydrogenation of unsymmetrical anhydrides. Thus, anhydride (**4**) was converted into lactones (**5**) and (**6**) on hydrogenation at 100 °C and 10 atm in toluene solution (Scheme 4). The regioselectivity of reduction was the reverse of LAH reduction, in that the less-substituted carbonyl was preferentially reduced (see Section 1.10.2.3). Yoshikawa and coworkers have reported that cyclic anhydrides can be hydrogenated to produce optically enriched (*ee* 5–20%) $\gamma$- and $\delta$-lactones using the ruthenium complex (**7**).[28] The authors postulated that the reaction took place *via* the insertion of a ruthenium hydride into the acyl oxygen bond. The process is exemplified by conversion of anhydride (**8**) into lactone (**9**; 20% *ee*). Clearly there is considerable opportunity for optimization in this enantioselective approach to lactones.

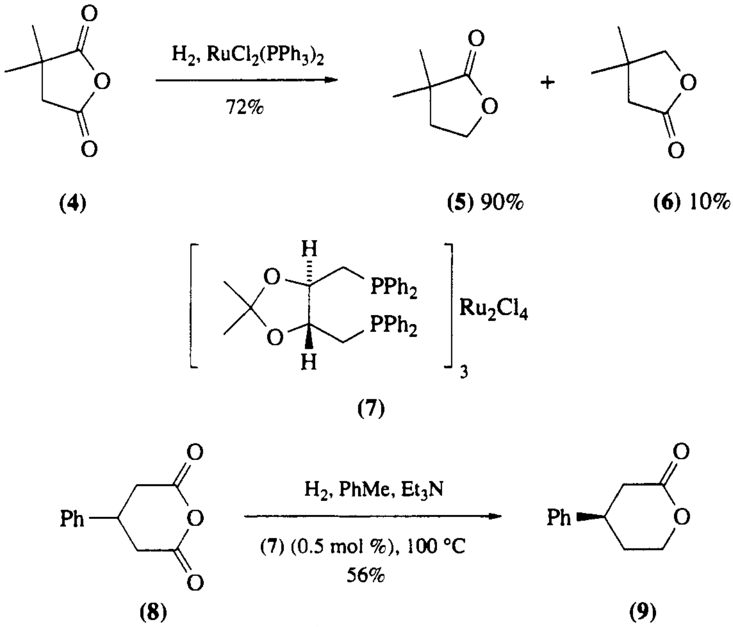

Scheme 4

### 1.10.2.2 Electrochemical and Dissolving Metal Reductions

In general, the dissolving metal or electrochemical reductions of acyl halides or acyclic anhydrides are not useful for the preparation of primary alcohols. Such reductions invariably provide acyloin esters, enediolate diesters or related species.[29] Cyclic anhydrides may be reduced to give lactones.[5,27] For example, the reduction of phthalic anhydride at a mercury cathode has been used in the synthesis of phthalide (90%). In general, however, such reduction are not widely employed in synthesis.

### 1.10.2.3 Reductions using Metal Hydride Reagents

Carboxylic acid chlorides are readily reduced to provide primary alcohols by reaction with nucleophilic hydride reagents. In contrast, electrophilic reagents including $B_2H_6$ and its derivatives react only at a very slow rate.[25] However, derivatives of $B_2H_6$ of reduced Lewis acidity will reduce acyl chlorides to produce primary alcohols. For example, 9-BBN-H in THF has been reported to reduce hexanoyl chloride to hexanol (81%).[15] Acid anhydrides, being less electrophilic than acid chlorides, are reduced by $B_2H_6$ to give diols or primary alcohols (2 mol).[2,8] Examples include the reductions of hexanoic anhydride to produce hexanol ($BH_3·THF$; 94%) and of naphthalene-1,2-dicarboxylic acid anhydride to give 1,2-naphthalenedimethanol ($NaBH_4$, $BF_3·Et_2O$, diglyme; 63%). In contrast, reduction of the 1,8-naphthoic anhydride (**10**) gave the cyclic ether (**11**; Scheme 5). Clearly in this unusual case, cyclization is favored by the proximity and activation of the *peri* substituents. Derivatives of $B_2H_6$ including $BH_3·NHPh_2$[14] and catecholborane[13] are also useful for the reduction of acyclic anhydrides.

Reductions of carboxylic acid chlorides using $NaBH_4$ in ethereal solvents (dioxane, DME, THF, poly(ethylene glycol) *etc.*)[2,9,25] rapidly provide primary alcohols. Reductions in poly(ethylene glycol)[30] are noteworthy in that esters, acyl chlorides, alkyl halides and sulfonate esters are reduced, whereas amides and nitriles are inert. Acid chlorides may alternatively be reduced using $NaBH_4$ on alumina ($Et_2O$),[31] $NaBH_4–TiCl_4$ (DME),[17] $NaBH_4–CeCl_3$ (MeCN), $NaBH(OMe)_3$ (THF), $Zn(BH_4)_2·TMEDA$ (THF),[32] $Bu_4NBH_4$ or $Bu_4NB_3H_8$ ($CH_2Cl_2$),[33] Li-9-BBN-$H_2$[34] and $KBH(OPr^i)_3·(THF)$[35] *etc.*[2,9] Since acyl chlorides are reduced very rapidly by nucleophilic borohydride reagents, chemoselectivity in the reduction of polyfunctional molecules is generally not a problem providing that temperature and stoichiometry are controlled. The choice of reagent is frequently based upon substrate solubility and ease of work-up considerations. However there is one point of note amongst this plethora of choice. Raber has reported that $Bu_4NBH_4$ in $CH_2Cl_2$ reduced benzoyl chloride to benzyl alcohol faster than benzaldehyde to benzyl alcohol.

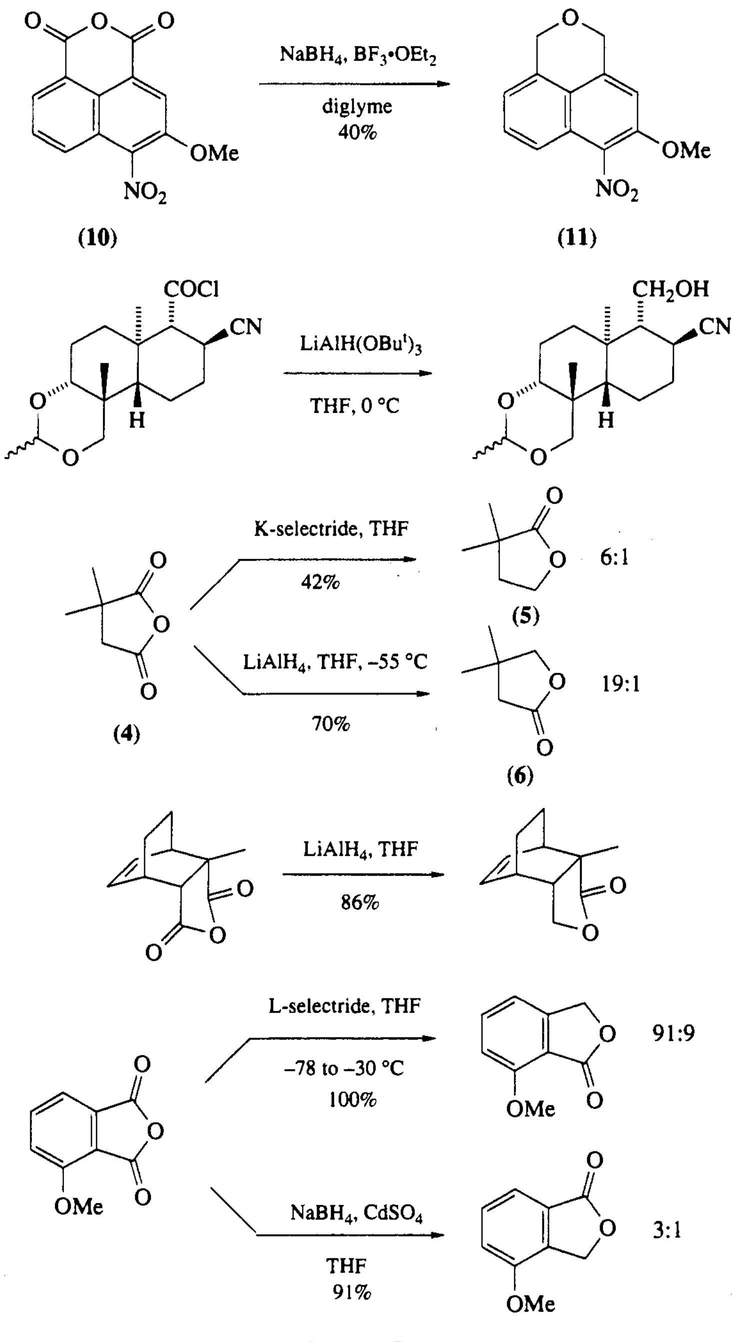
OMe
NO2
(10)
NaBH4, BF3•OEt2
diglyme
40%
OMe
NO2
(11)
COCl
CN
H
LiAlH(OBu^t)3
THF, 0 °C
CH2OH
CN
H
(4)
K-selectride, THF
42%
(5)
6:1
LiAlH4, THF, -55 °C
70%
(6)
19:1
LiAlH4, THF
86%
OMe
L-selectride, THF
-78 to -30 °C
100%
OMe
91:9
NaBH4, CdSO4
THF
91%
OMe
3:1

**Scheme 5**

Acyclic acid anhydrides are reduced to produce primary alcohols using $NaBH_4$ and its many derivatives.[2,9,36] In most cases, the reaction gives both the primary alcohol and the carboxylate salt (1:1). Whilst such monoreduction may be desirable in cyclic anhydride chemistry (*vide infra*), it is inefficient when acyclic anhydrides are reduced. Thus, $B_2H_6$ or LAH reductions are the preferred synthetic methods. The reductions of mixed anhydrides, for example carboxylic/diphenylphosphoric or carboxylic/carbonic anhydrides, produce the primary alcohol from the acyl component.[2,9,37]

LAH rapidly reduces aliphatic and aromatic acid chlorides or anhydrides to produce primary alcohols.[2,9,20,25] Activated esters, electrophilic amides and mixed anhydrides are alternative substrates for reduction to provide primary alcohols.[38] Numerous related reducing agents including $LiAlH(OMe)_3$, $NaAlH(OEt)_3$, Red-Al, $Ca(AlH_2(OCH_2CHMe_2)_2)_2$,[21] DIBAL-H,[22] DIBAL-H/Bu$^n$Li[39] and $AlH_3$[9] are also used. In general, reductions of acyl chlorides are used when the reduction of the corresponding carboxylic acid is slow for solubility reasons, or overreduction is a problem.

The reductions of cyclic anhydrides may be used to prepare hydroxylactones, lactones, lactols, cyclic ethers or diols depending on the substrate, reagents and conditions of reduction. Regioselective reductions of unsymmetrical anhydrides to produce γ- or δ-lactones have been the subject of much investigation.[27,40,41] $NaBH_4$ or LAH reductions at low temperatures are both synthetically useful for the preparation of lactones. Alternative reagents include $LiBH_4$, various lithium trialkylborohydrides, $LiAlH(OBu^t)_3$, $LiAlH(OMe)_3$, $AlH_3$ and Red-Al.[21,22] The reduction of cyclic anhydrides may alternatively be stopped at the hydroxylactone stage using $LiAlH(OBu^t)_3$ at low temperature. Alternatively, cyclic anhydrides may be completely reduced to diols using an excess of LAH or an equivalent reagent. Synthetically, the most useful reactions are reductions to produce γ- or δ-lactones. In general, unsymmetrical anhydrides are reduced using LAH or $NaBH_4$ to produce the lactone in which the more substituted carbonyl has been reduced. There are many exceptions, however. The reductions of rigid bridged ring anhydrides show the reverse selectivity. Additionally, the regiochemistry of reaction may be changed on using hindered reductants such as K-selectride. Regioselectivity is controlled by a balance between the relative electrophilicities of the two carbonyls, steric approach control (Bürgi–Dunitz vector approach), the influence of neighboring bonds coplanar with the carbonyl π-system ('the antiperiplanar effect') and the opportunity for chelation. A detailed analysis of regiocontrol is presented in the series of papers by Kayser and coworkers.[40] Representative acyl chloride and anhydride reductions are given in Scheme 5.

## 1.10.3 REDUCTIONS OF CARBOXYLIC ESTERS

### 1.10.3.1 Hydrogenation Reactions

Carboxylic esters may be hydrogenated more readily than the corresponding acids to produce primary alcohols.[1] Nonetheless, such reactions using heterogeneous catalysts require elevated temperatures and pressures. Although yields of the primary alcohols, corresponding to the acyl fragment, are frequently excellent, such reductions are synthetically inconvenient and now not widely used in small-scale synthesis.[42] Hydrogenation using copper chromite at 60–200 atm and 150–300 °C are the most frequently employed conditions. The ester is either hydrogenated alone or in a solvent such as MeOH, EtOH or dioxane. Alternatively, esters may be converted into primary alcohols by high pressure and high temperature hydrogenation over zinc chromate, copper oxide, Raney nickel, nickel/copper/aluminum/rhenium oxides or related species.[2] Hydrogenation of α-amino esters over W-6 Raney nickel is particularly useful for the preparation of amino alcohols with minimal racemization.[2,42] Specific examples include the conversions of ethyl pentanoate into 1-pentanol (94%; Cu chromite, $H_2$, 250 °C, 100 atm), diethyl tetradecanedioate into 1,14-tetradecanediol (95%; Cu chromite, $H_2$, 250 °C, 116 atm), ethyl benzoate into benzyl alcohol (65%; Cu chromite, $H_2$, 160 °C, 156 atm), *meso*-diethyl tartrate into erythritol (95%; Cu chromite, $H_2$ 165 °C, 340 atm) and ethyl alaninate into 2-amino-1-propanol (80%; W-5 Raney Ni, $H_2$, 100 °C, 156 atm). It is germane to note that esters of both aliphatic and aromatic carboxylic acids may be hydrogenated to produce primary alcohols. However, benzylic C—O hydrogenolysis is a frequent problem with esters of aromatic carboxylic acids. Additionally, aromatic ring hydrogenation takes place on phenol ester reduction. Hydrogenation may be used to prepare diols from keto acids, hydroxy acids or diesters. Esters of perfluorocarboxylic acids may be conveniently converted into the corresponding primary alcohols by hydrogenation over ruthenium catalysts. Thiol esters are readily converted into primary alcohols by reduction over W-4 Raney nickel.[43] This method is useful for the reduction of steroidal, carbohydrate and α-amino carboxylic acids. The intermediate aldehyde may be produced if deactivated Raney nickel is employed.

Grey *et al.* have reported that activated carboxylic acids may be hydrogenated under mild conditions using the homogeneous catalysts $K^+[(Ph_3P)_2Ph_2PC_6H_4RuH_2]^-\cdot C_{10}H_8\cdot Et_2O$ or $2K^+[(Ph_3P)_3(Ph_2P)Ru_2H_4]^{2-}\cdot 2$ diglyme.[44] For example, methyl trifluoroacetate was reduced with the second catalyst at 90 °C and 62 atm to produce 2,2,2-trifluoroethanol and methanol (88% conversion). These catalysts are not efficient for the hydrogenation of nonactivated esters.

### 1.10.3.2 Electrochemical and Dissolving Metal Reductions

Aromatic carboxylic esters may be reduced to produce the corresponding primary alcohol by electrolysis at a mercury, lead or cadmium cathode.[2,4,5,45] For example, methyl benzoate is readily reduced to benzyl alcohol (91%) at a mercury cathode in MeOH containing $Me_4NCl$. Ring substituents in the benzoyl group including methyl, methoxy or chloro substituents (*ortho-*, *meta-* and *para-*) are tolerated. In acidic media, benzylic alcohol formation may be suppressed and alkyl benzyl ether formation observed. The electrochemical reduction of ethyl benzoate (Pb, $H_2SO_4$, $H_2O$, EtOH) has been reported to provide benzyl ethyl ether (40%) and benzyl alcohol. Clearly the ether is formed *via* late benzylic cation formation. Aromatic 1,2-diesters may be selectively reduced to produce $\gamma$-lactones. For example diethyl phthalate has been reduced (Hg, –1.7 V, EtOH, $H_2O$, $Me_4NCl$) to provide phthalide. In contrast, diethyl 1,3- and 1,4-benzenedicarboxylates are electrochemically reduced (Hg, 10–24 F $mol^{-1}$, AcOH, EtOH, $Me_4NCl$) to produce benzene-1,3- (72%) and -1,4-dimethanol (75%), respectively. The intermediate monoesters may be isolated if the reductions are interrupted after 4.5–5 F $mol^{-1}$. Aliphatic carboxylic esters may be electrochemically reduced to produce primary alcohols. For example, reduction of methyl octanoate (Hg, 6 F $mol^{-1}$) gave 1-octanol (49%). Aliphatic esters of phenols are electrochemically reduced to produce the aliphatic primary alcohols in 30–40% yield.

The dissolving metal reduction of esters has found widespread use in synthesis. Reduction of a carboxylic ester (**12**) using an alkali metal in an alcohol solvent provides two alcohols (**13**) and (**14**; Scheme 6). This reaction is the classical Bouveault–Blanc reduction and it was the method of choice for preparing primary alcohols from aliphatic esters prior to the development of hydride reducing agents. Typically, Bouveault–Blanc reductions are carried out by adding sodium to a solution of the ester in EtOH.[46] The sodium may be replaced by other alkali or alkali earth metals or sodium amalgam and the EtOH by alternative alcohols, ethanolic ammonia or by phenol. Representative examples of Bouveault–Blanc reductions are provided in Scheme 6. The method is useful for the preparation of fatty alcohols or diols. Ketones or aldehydes may be protected from reduction *via* ketal formation. Aromatic esters undergo competitive arene reduction (Birch reduction). Esters may be reduced without concomitant carboxylic acid reduction[2,10] and such transformations are complementary to $B_2H_6$ reductions (Section 1.10.1.3). Bouveault–Blanc reductions in $EtOH/NH_3$ are frequently more efficient than reductions in EtOH alone due to the suppression of competitive ester hydrolysis or Claisen condensations at the lower temperature of reaction. The Bouveault–Blanc reduction takes place *via* two sequential one-electron transfers, protonation, aldehyde formation and further reduction.

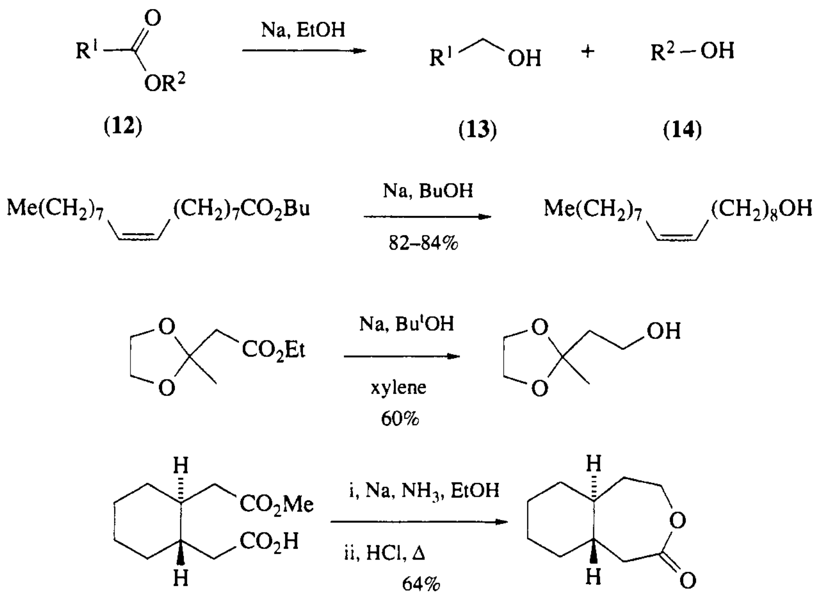

**Scheme 6**

The acyloin condensation[29] and deoxygenation[47] are two alternative dissolving metal reduction reactions of carboxylic esters. Since neither reaction results in primary alcohol formation from the acyl fragment, both are beyond the scope of this chapter. The acyloin condensation is carried out using molten Na in PhMe or in PhMe and TMS-Cl, or Na in $NH_3$. Clearly, this condensation differs from the Bouveault–Blanc reduction in that a protic solvent/cosolvent is not used, and therefore radical anion and/or dianion intermediates are not protonated and thereby undergo reactions with C—C bond formation. The author and others have reported that the reduction of alkyl carboxylates using, for example K and 18-crown-6 in $Bu^tNH_2$ or Na in HMPA, gave carboxylic acids and alkanes. These reactions again are of only indirect importance in this chapter since the ester acyl fragment is not converted to a primary alcohol. Deoxygenation *via* ester radical anion cleavage is the major reaction pathway when esters are reduced in homogeneous solution in the absence of proton sources ($pK_a < 20$) or nucleophiles.

### 1.10.3.3 Reductions using Metal Hydride Reagents

The reduction of carboxylic esters to produce primary alcohols is most conveniently carried out using metal hydride reagents. Indeed, such reductions are unquestionably the most important methods for effecting these transformations. $B_2H_6$, $NaBH_4$, LAH and legions of derivatives have found widespread use in ester reductions. $BH_3$·THF in THF solution at 0 °C only slowly reduces carboxylic esters. Thus, this reagent is frequently used to reduce aldehydes, ketones, amides or carboxylic acids chemoselectively, without accompanying ester reduction.[2,8] Prolonged reaction may lead to the reduction of aliphatic carboxylic esters to produce primary alcohols. Esters of aromatic carboxylic acids are essentially unreactive at 0 °C but may be slowly reduced at elevated temperatures. Brown and coworkers have found that $BH_3$·$SMe_2$ in THF at reflux may efficiently be used to reduce both aliphatic and aromatic carboxylic esters rapidly, by removing the $Me_2S$ liberated during the reaction.[48] For example, ethyl benzoate and hexanoate were reduced to produce benzyl alcohol (90%) and 1-hexanol (89%), respectively. Rodrigo and coworkers have observed that diester monoreduction may be used in 1-arylnaphthalide lignan synthesis.[49] Reductions in THF may be catalyzed by sodium borohydride (5 mol %).[50] Various borane derivatives have been employed in ester reduction. $BH_3$·$NHPh_2$ has been used to reduce aliphatic esters, although aromatic esters are not readily reduced.[14] Additionally, 9-BBN-H reduces aliphatic esters much more rapidly than aromatic esters, to produce primary alcohols.[15] More substituted boranes, including thexylborane,[51] thexylchloroborane·$SMe_2$,[16] catecholborane[13] and $Sia_2BH$, react only very slowly with esters.[2,9,15] A representative borane reduction is given in Scheme 7.

$NaBH_4$, in general, is slow to reduce carboxylic esters to produce primary alcohols. Borohydride salts of more Lewis acidic cations, including $LiBH_4$,[52,53] $Mg(BH_4)_2$[2] and $Ca(BH_4)_2$,[53,54] are effective reductants. $LiBH_4$ is particularly useful for the chemoselective reduction of carboxylic esters in the presence of carboxylic acids, amides or nitriles. $NaBH_4$ will slowly reduce esters when used in alcoholic solvents at room temperature. However, reductions are dramatically accelerated in $Bu^tOH$ and MeOH[55] at reflux or in poly(ethylene glycol) at 65–80 °C.[30,56] The reduction of esters may also be carried out using $Bu_4NBH_4$ in $CH_2Cl_2$ solution.[57] It is noteworthy that carboxylic esters bearing an $\alpha$-oxygen substituent are rapidly reduced by $NaBH_4$ at room temperature. Presumably, chelation and/or inductive activation accelerate the reaction. Thus, for example, glycidic esters are readily reduced to the corresponding primary alcohols.[58] Soai and Ookawa have reported that chemoselectivity in $LiBH_4$ reductions is strongly solvent dependent. In $Et_2O$ at reflux, $LiBH_4$ and MeOH (1 equiv.) selectively reduce esters, lactones and epoxides in the presence of carboxylic acids, carbamates, chlorides, nitro compounds and secondary amides. In THF or diglyme containing MeOH (4 equiv.) $LiBH_4$ is more reactive and nitroalkanes, nitriles, carboxylic acids and amides are also efficiently reduced.[59] $NaBH_4$ or $LiBH_4$ reductions of carboxylic esters may be accelerated by Lewis acids, including $AlCl_3$,[60] $(MeO)_3B$, 9-BBN-OMe,[61] Li-9-BBN-$H_2$ or $LiBHEt_3$.[62] These methods are also useful for the selective reductions of esters in the presence of amides. Under powerfully Lewis acidic conditions, ester reductions can be diverted to produce ethers. For example, esters may be converted into ethers using $NaBH_4$ and $BF_3$·$OEt_2$ at elevated temperatures.[63] Clearly this reaction involves a $BF_3$-catalyzed $B_2H_6$ reduction.

There are many substituted borohydride reagents known, and several of these have been employed in ester reductions. Such reagents include $NaBH_3(OH)$,[64] $NaBH_2(SCH_2CH_2S)$,[18,65] $NaBH(OMe)_3$,[66] $NaBH_3(NMe_2)$, $NaBH_3(NHBu^t)$ and $NaBH_3(N(Me)Ac)$.[67] In general, these offer little advantage over $LiBH_4$. However, the more-substituted reagents selectively reduce nonhindered carboxylic esters in the presence of hindered ester functionality. Alkyl-substituted borohydrides, including $LiBH_3Bu$ and $LiBHEt_3$, are potent reductants, and these readily reduce esters.[68] However, again, these reagents offer little advantage over $LiBH_4$ other than higher rates of reaction. Ireland and Thompson have reported that di-MEM esters may be selectively monoreduced using $LiBHEt_3$.[69] Finally, borohydride reductions of thiol esters and activated esters, including *N*-acyloxysuccinimide derivatives, may be used to prepare primary alcohols.[70] Representative reductions of esters using borohydride reagents are given in Scheme 7. Again, these examples are chosen to illustrate selectivities.

$AlH_3$ and alkyl derivatives are powerful Lewis acidic reducing agents that rapidly convert carboxylic esters into primary alcohols.[2,9,22,71] In many cases, the reduction may be stopped at the intermediate aldehyde stage, providing that the stoichiometry and temperature are carefully controlled. However, complete reduction is experimentally easier to carry out. DIBAL-H is the most useful and widely used alane.

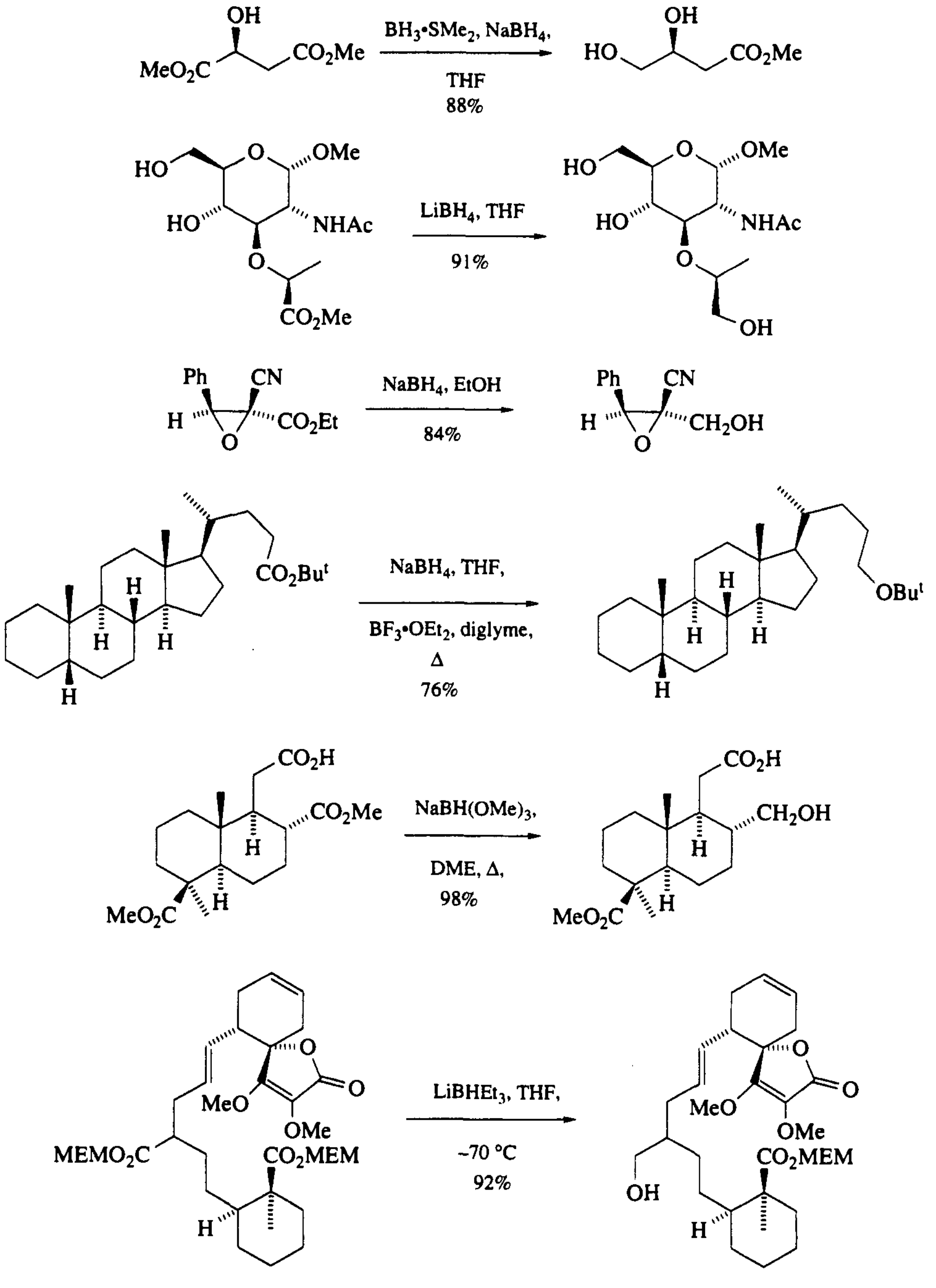

**Scheme 7**

This reagent readily reduces esters in toluene, hexanes, THF or $CH_2Cl_2$ solutions, *etc*. The reaction is especially useful for the preparation of allylic alcohols from α,β-unsaturated esters. β-Keto esters have been selectively reduced to β-hydroxy ketones *via* ketone enolate formation and $AlH_3$ reduction.[72]

LAH[2,9,20,73,74] and numerous related reagents, including LAH-silica,[75] $LiAlH(OMe)_3$, $NaAlH(OEt)_3$, Red-Al, $Ca(AlH_2(OC_6H_{11})_2)_2\cdot THF$, $Ca(AlH_2(OBu^i)_2)_2\cdot THF$, $NaAlH_2(OCH_2CH_2OPr^i)_2$, $NaAlH_2(OCH_2CH_2NMe_2)_2$, $LiAlH_2(OBu^t)_2$, $NaAlH_2Bu^i{}_2$ and $LiAlH_2Bu^i{}_2$, *etc*.,[21] readily reduce aliphatic and aromatic carboxylic esters to produce primary alcohols. More sterically hindered reagents such as $LiAlH(OBu^t)_3$ are slow to reduce esters. The most commonly used reagents are LAH or $LiAlH(OMe)_3$ in ether solvents or Red-Al in aromatic hydrocarbons or ether solvents. Dicarboxylic esters are rapidly reduced to diols although, in some cases, monoreduction of the less-hindered ester may be carried out at low temperature and with careful stoichiometric control. It should be noted that LAH also reduces aldehydes, ketones, acid chlorides, epoxides, carboxylic acids, amides, nitriles and nitro compounds. Thus it is recommended for global rather than chemoselective reduction. However, the reactivity of the alkoxy-substituted reagents decrease with increase in substitution and steric congestion. Therefore, they are easier to apply for chemo- or regio-selective control. Esters of α,β-unsaturated carboxylic acids are reduced by LAH to produce the saturated primary alcohol or the allylic alcohol depending on reaction stoichiometry and temperature. There is a myriad of ester reductions in the literature. Representative examples are given in Scheme 8. The LAH reduction of carboxylic esters may be diverted to ether formation when carried out in the presence of $BF_3 \cdot OEt_2$.[63,76] In general, yields are only modest. Alternatively, sulfides (37–80%) may be prepared from thiol esters in the same way.[77]

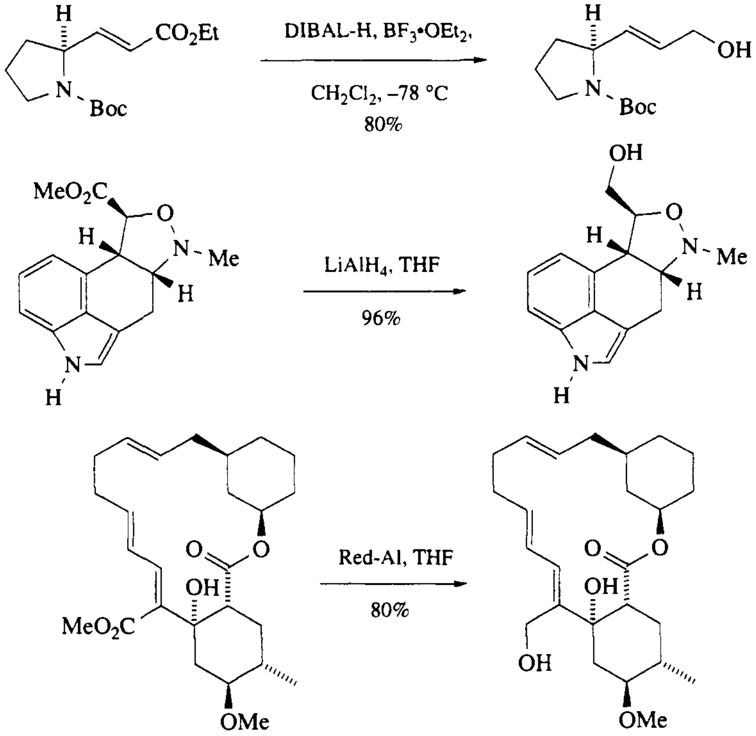

Scheme 8

Aliphatic carboxylic esters have been reduced to produce simple primary alcohols (84–92%) *via* $Cp_2TiCl_2$-catalyzed reaction with $Bu^iMgBr$.[78] Additionally, hydrosilylation of aliphatic and aromatic carboxylic esters using $Ph_2SiH_2$, $(EtO)_2Si(Me)H$, $(EtO)_3SiH$ or $MeSiO[Si(Me)H—O]_nSiMe_3$ has been used to produce simple primary alcohols (50–100%). In contrast, the photolytic reactions of esters with $HSiCl_3$ produces ethers. For example, 1-dodecyl acetate was converted into 1-dodecyl ethyl ether in this way. Competitive deoxygenation complicates ether formation particularly with secondary and tertiary alkyl esters.[79] All these exotic methods have little synthetic merit.

## 1.10.4 REDUCTIONS OF LACTONES

### 1.10.4.1 Hydrogenation Reactions

Lactones may be hydrogenated to produce diols under comparable conditions to ester hydrogenation reactions (see Section 1.10.3.1). Alternatively, the hydrogenation reaction may be used to prepare cyclic ethers. Hydrogenation (250 °C, 100 atm) of γ-butyrolactone over Cu chromite (89%) or Ni/Co/Th oxides (98%) has been used to prepare 1,4-butanediol efficiently.[1,42] Alternatively, hydrogenation (240 °C, 150 atm) of γ-butyrolactone over a Co/Re catalyst gave THF (92%). Substitution of the lactone at the γ-position may radically alter the course of reduction. For example, hydrogenation of γ,γ-dialkyl-γ-butyrolactones over Cu chromite results in C—O hydrogenolysis and formation of 4,4-dialkyl-1-butanol. Hydrogenation of γ-valerolactone over Cu chromite gave 1,4-pentanediol, 1-pentanol and/or 2-methyltetrahydrofuran. Diol formation was favored at lower temperatures (250 °C and 200–300 atm), whereas hydrogenation at 270–290°C gave mostly 1-pentanol and 2-methyltetrahydrofuran. δ-Lactones may be converted into cyclic ethers by hydrogenation (25 °C, 1 atm) over Adams' catalyst in HOAc containing $HClO_4$.[80] For example, 4-oxa-5α-cholestan-3-one was converted into 4-oxa-5α-cholestane (92%) in this way. The procedure is notable since it is particularly mild and γ-lactones are not reduced under these conditions. In general, the synthesis of diols or ethers from the catalytic hydrogenation of lactones is not widely used since it is experimentally inconvenient relative to other methods.

### 1.10.4.2 Electrochemical and Dissolving Metal Reductions

Although lactones may be reduced electrochemically or *via* Bouveault–Blanc reactions to produce diols, such reactions are more frequently used to prepare lactols.[4] Both cathodic (Hg or Pb) and Na/Hg reduction are useful in the preparation of alditols from aldonic acid γ-lactones. The reductions may be easily stopped at the intermediate aldose stage.[81]

### 1.10.4.3 Reductions using Metal Hydride Reagents

Lactones are reduced rapidly by LAH,[20] $LiAlH(OMe)_3$, $LiAlH(OEt)_3$,[21] $AlH_3$, DIBAl-H,[22] $LiBH_4$,[53] $NaBH_4–AlCl_3$, $LiBHEt_3$,[68] $LiAlHBu^i_2Bu$,[39] Li-9-BBN-$H_2$[34] and $LiBH_3Bu$ *etc.*[2,9] The reductions may also be carried out with $NaBH_4$, $BH_3·SMe_2$, $BH_3·THF$, Red-Al, $LiAlH(OBu^t)_3$, thexylborane, $Sia_2BH$ and 9-BBN-H, *etc.*, but at much slower rates.[2,8,9,21,48] These reductions may be stopped at the intermediate lactol stage in many cases with temperature and stoichiometric control, particularly with the less reactive reagents. Reductions using DIBAL-H, $Sia_2BH$ or $LiAlH(OBu^t)_3$ are especially useful in lactol synthesis.[21,71] In general, lactones are more rapidly reduced than esters and thus chemoselectivity is fre-

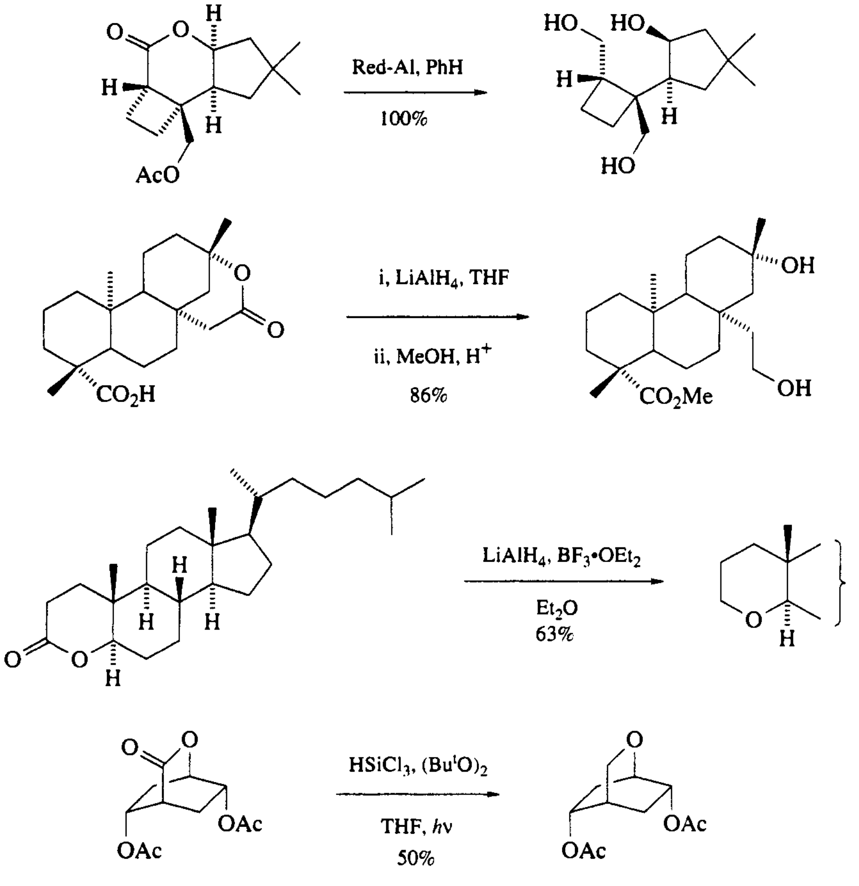

Scheme 9

quently possible in reduction. Additionally, carboxylic acids and amides are reduced more slowly using nucleophilic reagents; again, this provides opportunities for selectivity. Lactones are only slowly reduced by $NaBH_4$ in alcohol solvents at 25 °C unless the carbonyl is flanked by an α-heteroatom functionality.[58,82] Alternatively reductions of simple lactones using $NaBH_4$ may be efficiently carried out using refluxing Bu$^t$OH or THF as solvent with the slow addition of methanol.[55]

Pettit and others have reduced lactones to produce cyclic ethers using LAH/$BF_3 \cdot OEt_2$, LAH/$AlCl_3$, $BH_3 \cdot THF/BF_3 \cdot OEt_2$[63,76,83] or even with excess $B_2H_6$.[84] Under these Lewis acidic conditions, reaction takes place *via* lactol C—O fission and further 2-tetrahydrofuranyl or 2-tetrahydropyranyl cation reduction. These methods are not useful for preparing strained bicyclic ethers due to preferential ring C—O bond cleavage at the intermediate lactol stage. Additionally, the method is not satisfactory for the synthesis of hindered oxepanes, although branching α to the ring oxygen facilitates deoxygenation in these cases. Ager and Sutherland have reported that crown lactones may be reduced with LAH to produce crown ethers.[85] It is clear that lithium cation complexation prevents ring scission during these unusual reductions. γ- and δ-lactones have been reduced to provide cyclic ethers *via* reaction with DIBAL-H followed by $Et_3SiH$ and $BF_3 \cdot OEt_2$ (50–88%), or directly using $HSiCl_3$ and di-*t*-butyl peroxide under irradiation (γ or UV) (55–100%).[86,87] The $HSiCl_3$ method is useful for the chemoselective reduction of strained lactones bearing ester groups.[87] Representative examples of lactone reductions to produce diols or cyclic ethers are given in Scheme 9.

## 1.10.5 REDUCTIONS OF AMIDES AND LACTAMS

### 1.10.5.1 Hydrogenation Reactions

Primary, secondary and tertiary carboxamides may be reduced to prepare primary, secondary or tertiary amines by heterogeneous catalytic hydrogenation at elevated temperatures and pressures.[1,88] Such reactions frequently require more drastic conditions than are necessary for the hydrogenation of carboxylic acids or esters. Additionally, the preparation of amines from amides in this way requires specialist equipment and reaction conditions. It is, therefore, only recommended for the desperate. Most hydrogenation reactions have been carried out over Cu chromite or Ba/Cu chromite. Raney nickel, Raney cobalt, ruthenium on carbon and rhenium(VII) oxide[89] are alternative catalysts. The hydrogenation of primary amides frequently produces secondary amines. These are presumably formed *via* aminolysis of an intermediate imine. Primary amide hydrogenations may be directed to primary amine formation by the use of ammonia as the (co)solvent. For example, decanamide has been converted into decylamine (90%; Ba–Cu chromite, $H_2$, 350 °C, 411 atm, $NH_3$) or *N,N*-didecylamine (73%; Ba–Cu chromite, $H_2$, 350 °C, 411 atm) depending on the reaction solvent. Hydrogenation of amides in alcoholic solvents may be used to prepare primary alcohols *via* amide transacylation and ester reduction. Alternatively, *N*-alkylation may be observed when primary or secondary amides are hydrogenated in alcoholic media. Both secondary and tertiary amides may be hydrogenated to produce the corresponding amines. Tertiary amide reductions can be carried out under relatively mild conditions (260 °C and ≥15 atm). Diamides may also be reduced to produce α,ω-diamines. However, reductions of 1,4-, 1,5- and 1,6- primary or secondary dicarboxamides produce pyrrolidine, piperidine or hexahydroazepine derivatives. Such systems are most probably formed *via* aminolysis at the imine stage. Hydrogenation of amides derived from aromatic carboxylic acids generally do not provide good yields of benzylic amines. Under the drastic reaction conditions, benzylic C—N cleavage is a dominant pathway. *N*-Benzoylpiperidine has been reported to produce mostly toluene (79%) on hydrogenation (Cu chromite, 250 °C, 200–300 atm). However, rhenium(VII) oxide minimizes C—N cleavage: benzamide has been reduced to yield benzylamine (69%) using this catalyst (220 °C, 205 atm, EtOH). Lactams may also be hydrogenated to produce cyclic amines; again, drastic reaction conditions are needed. The recalcitrance of amides to undergo reduction by catalytic hydrogenation may be used to advantage in synthesis. Esters may be selectively hydrogenated in the presence of amide groups.

### 1.10.5.2 Electrochemical and Dissolving Metal Reductions

The electrochemical reduction of carboxamides ($R^1CONR^2R^3$) has been used to prepare aldehydes ($R^1CHO$), amines ($R^1CH_2NR^2R^3$) or primary alcohols ($R^1CH_2OH$) depending on the structure of the substrate and reaction conditions.[4,5] Aldehyde formation may be favored by increasing the lifetime of the carbinolamine intermediate ($R^1CH(OH)NR^2R^3$; 5- and 6-ring cyclic carbinolamines are more stable than acyclic systems) or by trapping the aldehyde ($R^1CHO$) as it is formed. Aliphatic amides have been reduced to produce primary alcohols by electrolysis under neutral or basic conditions. Typically, the primary, secondary or tertiary amide is electrolyzed in an alcohol or amine solvent using an alkali metal or tetraalkylammonium salt as the supporting electrolyte.[2,4,5,88,90] Formation of the primary alcohol is thus favored by rapid carbinolamine ($R^1CH(OH)NR^2R^3$) fragmentation and subsequent aldehyde ($R^1CHO$) reduction. Amides may be electrochemically reduced to produce amines using cathode material of high hydrogen overpotential (Pb, Hg, Cd) under strongly acidic conditions. In the presence of strong acids, the carbinolamine intermediate readily loses water to produce the iminium salt [$(R^1CH{=}NR^2R^3)^+$], which is reduced further to produce the amine. The electrolysis of amides in sulfuric acid at a lead cathode is a classical method for amine synthesis. The process is general for tertiary and secondary amines. Primary amides are reduced to amines only with considerable difficulty due to the lower stability of the intermediate iminium salt ($[R^1CH{=}NH_2]^+$). Representative electrochemical reductions include the conversion of dodecanamide into 1-dodecanol (92%; Pt, $MeNH_2$, LiCl), of *N*,*N*-dimethylhexanamide into 1-hexanol (97%; Pt, $MeNH_2$, LiCl), of *N*,*N*-dimethylbenzamide into *N*,*N*-dimethylbenzylamine (63%; Pb, $H_2O$, $H_2SO_4$) and of *N*,*N*-dibenzyl-1,4-piperazine-2,5-dione into *N*,*N*-dibenzyl-1,4-piperazine (70%; Pb, AcOH, $H_2SO_4$, $H_2O$).

The dissolving metal reduction of amides has been used to prepare aldehydes, primary alcohols or amines.[88,91] Tertiary but not primary or secondary amides have been reduced to provide aldehydes using Li in $MeNH_2$ or Na in $NH_3$ in the presence of EtOH, AcOH, or $H_2O$, *etc.* The production of aldehydes require that the carbinolamine fragmentation is slow on the reduction time scale. Reductions using excess alkali metal in $NH_3$ or HMPA containing a proton source have been used to prepare primary alcohols. Under these conditions, the excess metal is available to reduce the aldehyde formed from the carbinolamine fragmentation. Amides may be reduced by dissolving metals to produce amines when carbinolamine fragmentation to form imine intermediates is favored. For example, γ- or δ-lactams are converted in high yield into cyclic amines on dissolving alkali metal reduction in alcoholic solution. Finally, amides may be reduced indirectly to yield amines *via* dissolving metal reductions of imino chlorides, thioamides or related species.[88,92] Representative dissolving metal reductions of amides include the conversion of phenylalaninamide into 3-(2,5-dihydrophenyl)-2-amino-1-propanol (77%; Na, $NH_3$ MeOH, $NH_4Cl$, –78 °C) and of 5-phenyl-2-piperidinone into 5-phenylpiperidine (57%; Na, BuOH, Δ).

### 1.10.5.3 Reductions using Metal Hydride Reagents

Amides may be reduced using hydride reagents to produce amines, primary alcohols or aldehydes. Aliphatic and aromatic primary, secondary or tertiary amides are rapidly reduced to provide the corresponding amines using $BH_3{\cdot}THF$ or $BH_3{\cdot}SMe_2$ in ether solvents. Lactams are reduced to cyclic amines. The reaction may be chemoselective in that less reactive groups including alkyl halides, carbamates, epoxides, esters and nitro compounds may be easily tolerated.[2,8,48,93] Formamides may be selectively reduced in the presence of other amide functionality, providing that the reaction stoichiometry is carefully controlled.[94] Representative chemoselective reductions are given in Scheme 10. $B_2H_6$ is the reagent of choice for amide reductions, unless the molecule contains alkene units. In these cases, hydroboration is also observed. The $B_2H_6$ reduction of β-lactams produces β-amino alcohols and not azetidines. Clearly ring fragmentation is favored by the release of strain. Alkylboranes react more slowly with amides; both thexylborane and $Sia_2BH$ slowly reduce tertiary amides to produce aldehydes.[51,95] 9-BBN-H reduces tertiary amides to produce mostly primary alcohols.[15] For example, reduction of $PhCONEt_2$ gave $PhCH_2OH$ (80%) and $PhCH_2NEt_2$ (20%). The thexylborane·$PhNEt_2$ complex reduces aliphatic and aromatic tertiary amides to produce tertiary amines. Clearly alkyl substitution of borane alters the rate of formation and fragmentation of the intermediate carbinolamine borate esters. None of the alkylborane reagents are particularly useful for amide reductions.

Neither $NaBH_4$ in alcohol solvents nor $LiBH_4$ in ethers readily reduce amides. Under more forcing conditions, amide recalcitrance can be overwhelmed.[17,18,96] Thus, tertiary but not secondary or primary amides may be reduced using $NaBH_4$ in pyridine at reflux. Although secondary amides are recovered unchanged, primary amides are dehydrated to produce nitriles. Primary, secondary and tertiary amides are reduced to the corresponding amines with $NaBH_4$ and $MeSO_3H$ in DMSO[17] or $Bu_4NBH_4$ in $CH_2Cl_2$.[97] Primary, secondary and tertiary amides are reduced to amines (75–96%) using $NaBH_4$–$TiCl_4$ in DME or with $NaBH_4$–$CoCl_2$ or $NiCl_2$ in methanol.[17,98] $NaBH_4$–$AlCl_3$ reduces tertiary amides to amines whereas primary amides form only salts, which do not undergo reduction.[60] γ- and δ-lactams have been reduced to the corresponding cyclic amines using excess $NaBH_4$ in refluxing MeOH and $Bu^tOH$. Primary and

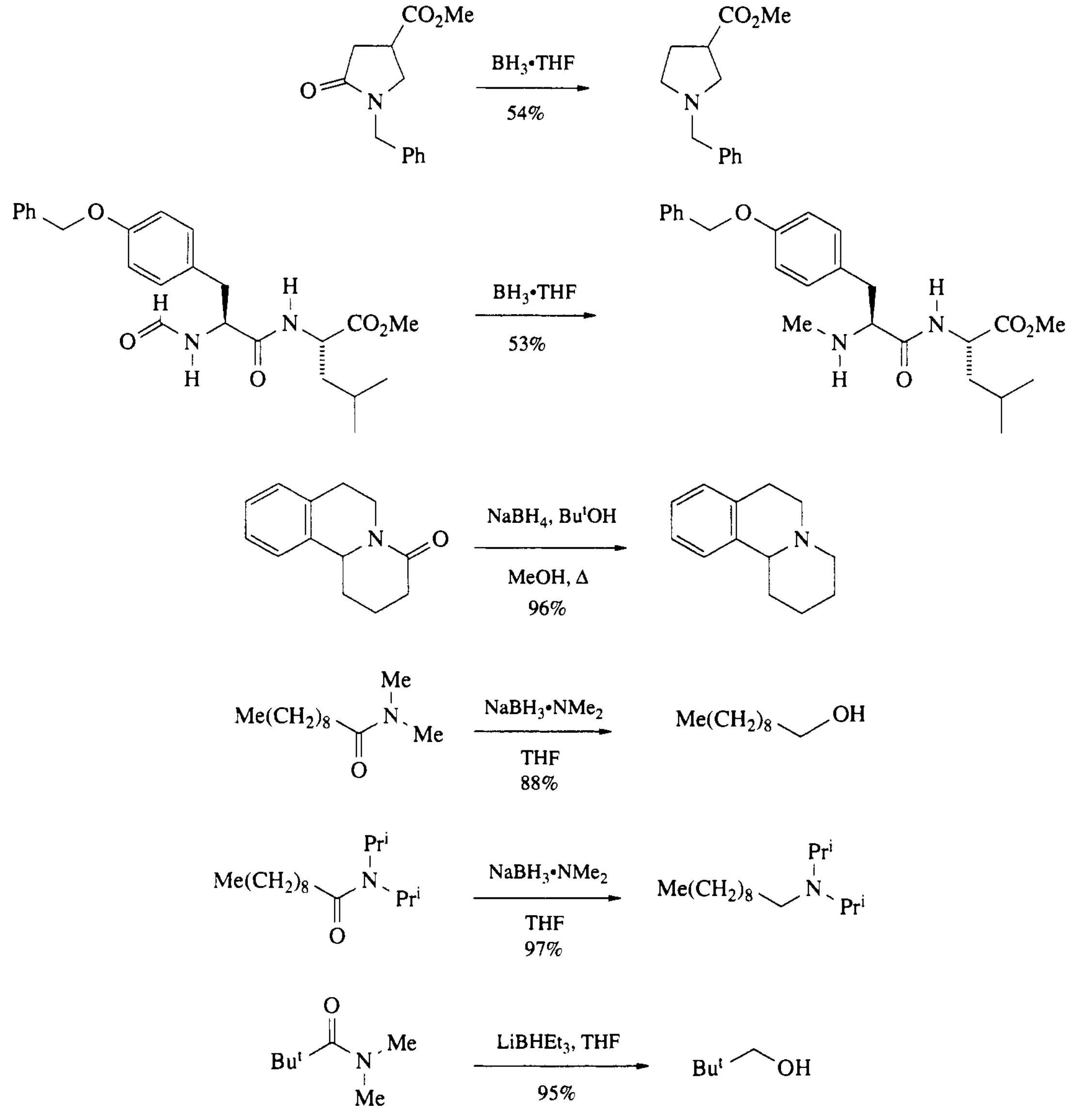

**Scheme 10**

secondary amides are reduced to the corresponding amines using $LiBH_4$ in THF and MeOH at reflux. Under these conditions, tertiary amides are reduced to primary alcohols.[59] Sulfur-, oxygen- and nitrogen-substituted borohydride reagents, which are more reactive than $NaBH_4$, have been used in amide reductions.[18,67,99-101] $NaBH_2(SCH_2CH_2S)$, $NaBH_2S_3$, $NaBH_4$/EtSH, $NaBH_4$/PhSH, $NaBH_3NMe_2$, $NaBH_3(NHBu^t)$, $NaBH_3(OAc)$, $NaBH_3(O_2CPh)$, and $NaBH_3(O_2CCl_3)$ have all been used in amide reductions to produce amines. Reductions of tertiary amides using $NaBH_3(NMe_2)$ and $NaBH_3(NHBu^t)$ are especially noteworthy in that primary alcohols are usually formed, unless the amide nitrogen is substituted by bulky groups when tertiary amines are the products. Presumably, N—C cleavage at the intermediate carbinolamine stage requires prior complexation by a boron Lewis acid and clearly this is disfavored by bulky alkyl groups. Primary amides are reduced by $NaBH_3(NMe_2)$ or $NaBH_3(NHBu^t)$ to give amines (21–77%), whereas secondary amines are recovered unchanged. Alkyl-substituted borohydride reagents reduce amides to amines or primary alcohols. $LiBHEt_3$ in THF is a powerful reducing agent that rapidly converts tertiary amides into primary alcohols[68] and it is the reagent of choice for such reductions. Li-9-BBN-$H_2$ reduces tertiary amides to amines[34] and $LiBH_3Bu$ converts tertiary amides into amine/primary alcohol mixtures.[68] None of the alkyl borohydrides are useful for the reduction of primary or secondary amides since the initially formed amide salts are insufficiently electrophilic. Amides may be rapidly reduced to produce amines by activation prior to borohydride reduction. Thus, tertiary amides are readily reduced *via* Vilsmeier salt formation or *O*-alkylation, followed by $NaBH_4$ reduction.[102] *N*-Nitrosoamides are reduced by $NaBH_4$ to produce primary alcohols (41–84%).[103] Representative examples of borohydride reductions are given in Scheme 10.

Amides and lactams are reduced by $Al_2H_3(OCH_2CH_2OMe)_3$, $AlH_3$, DIBAL-H or $AlH_2Cl$ to produce the corresponding amine. Tertiary amides are reduced more rapidly than secondary or primary amides.[22,71,104] Reductions of tertiary amides may be stopped at the intermediate carbinolamine stage, thereby providing aldehydes or enamines from lactams. In general, $AlH_3$ or DIBAL-H reductions are useful for the reduction of unsaturated amides when hydroboration or overreduction are problems. Aromatic and aliphatic amides and lactams are reduced by LAH or $NaAlH_4$ to produce the corresponding amines.[20,88,105] The reaction is general for the preparation of primary, secondary or tertiary acyclic amines and cyclic secondary or tertiary amines. The reduction of primary amides may involve the intermediacy of the nitrile, and these have been isolated in several cases. Amides and lactams have also been reduced to the corresponding amines using alkoxyaluminum hydride reagents including $LiAlH(OMe)_3$, $LiAlH(OEt)_3$, Red-Al and $Ca[AlH_2(OBu^i)_2]_2\cdot THF$ *etc.*, although they are not reduced by hindered reagents including $LiAlH(OBu^t)_3$. All these reductions may be stopped at the intermediate aldehyde stage, although reactions using a slight excess of reagents readily provide the corresponding amines.[21] As with LAH, tertiary amides are reduced more readily than primary or secondary amides. The alkoxy-substituted reagents are less reactive and therefore more selective. Representative amide reductions using $AlH_3$, LAH and derivatives are given in Scheme 11.

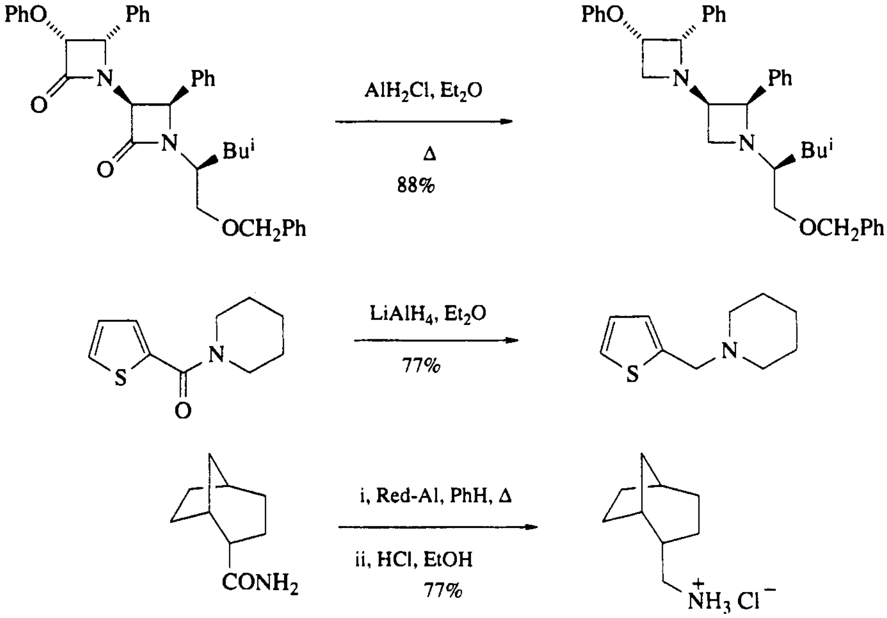

**Scheme 11**

Finally, both aliphatic and aromatic tertiary amides have been slowly reduced using $HSiCl_3$ at elevated temperatures (90–110 °C) to produce the corresponding amines (33–90%).[106] There is little reason to recommend these hydrosilylation methods for synthesis.

## 1.10.6 REDUCTIONS OF NITRILES

### 1.10.6.1 Hydrogenation Reactions

Nitriles have been hydrogenated at low temperatures and pressures over heterogeneous and homogeneous catalysts to produce amines, aldehydes, primary alcohols or alkanes.[107,108] The reduction to produce amines is by far the most widely used transformation. The most commonly used catalysts are Raney nickel, Raney cobalt, nickel boride, cobalt boride, rhodium, palladium or platinum on various supports. Products formed in the hydrogenation of a nitrile (RCN) are determined by the fate of the intermediate imine (RCH=NH). Hydrogenation may be stopped at the intermediate imine (RCH=NH) stage under carefully controlled conditions (*vide infra*). Rapid hydrolysis of the imine and further hydrogenation may be used to produce the primary alcohol. The imine may be hydrogenated further to produce the primary amine. However, unless the primary amine is removed as it is formed, transimination of RCH=NH readily takes place. Subsequent hydrogenation of $RCH=NCH_2R$ provides the secondary amine $(RCH_2)_2NH$. Transimination with RCH=NH and further hydrogenation may occasionally produce the tertiary amine $(RCH_2)_3N$. In spite of all these complications, nitrile hydrogenation reactions may be used to selectively prepare primary or secondary amines, primary alcohols or aldehydes. Complete reduction to the alkanes $(RCH_3)$ is only observed on prolonged hydrogenation with aromatic cyanides where C—N or C—O benzylic hydrogenolysis is facile. Primary amines may be easily prepared from nitriles by hydrogenation using Raney nickel in anhydrous MeOH or EtOH containing $NH_3$ (≥6 equiv.) at 100 °C and 100 atm. Lower temperatures and pressures may be used with larger quantities of highly active catalyst. Addition of ammonia favors primary amine formation by displacement of the RCH=NH and $RCH=NCH_2R$ equilibrium in favor of the former. Alternatively, nitriles may be reduced over $Rh/Al_2O_3$ or Rh/C under mild conditions. These procedures are particularly useful for minimizing C—Cl or benzylic C—N or C—O hydrogenolyses, and additionally has the advantage of experimental convenience. Secondary amine formation may also be suppressed by hydrogenation in the presence of an acid, an anhydride or $CHCl_3$ (which generates HCl *in situ*). The $CHCl_3$ method is particularly useful for acid-sensitive nitriles. Hydrogenation of nitriles in alcoholic solvents in the absence of ammonia or primary amine traps may be used to prepare symmetrical secondary amines in good yields. In general, efficient formation of tertiary amines is not observed, since the necessary intermediate $RCH=N^+(CH_2R)_2$ is not produced in appreciable quantities. Secondary amine formation is suppressed at elevated pressures and with sterically hindered substrates. Hydrogenation of nitriles in the presence of excess amines may be used to prepare unsymmetrical diamines. These are again formed *via* transimination. Transimination may also be used to prepare cyclic amines (5-, 6- and 7-membered) from the hydrogenation of amino nitriles or dinitriles. Alternatively, heterocyclic ring systems may be prepared from the hydrogenations of keto nitriles, keto amides, *etc.* Aldehydes may be produced from the transfer hydrogenation of nitriles in aqueous media using Raney nickel and formic acid or sodium hypophosphite. Alternatively, production of the aldehyde may be favored by nitrile hydrogenation in the presence of aldehyde traps such as hydrazine. Both aromatic and aliphatic nitriles have been converted into primary alcohols by hydrogenation over Raney nickel in the presence of acid resins.[109] Under these conditions, the imine (RCH=NH) and aldehyde (RCHO) equilibrium is displaced by removal of ammonia. Representative nitrile hydrogenations include the conversion of phenylacetonitrile into 2-phenylethylamine (>90%; Raney Ni, $H_2$, MeOH, $NH_3$, 100 °C, 100 atm) or (93%; $Rh/Al_2O_3$, $H_2$, EtOH, $NH_3$, 25 °C, 3 atm), of dodecanenitrile into *N*-dodecylacetamide (100%, Raney Ni, $H_2$, $Ac_2O$, NaOAc, 50 °C, 2 atm), of pentanenitrile into *N*-butylpentanamine (93%; Pd/C, $H_2$, $BuNH_2$, 25 °C, 2 atm) and of 4-methylbenzonitrile into 4-methylbenzyl alcohol (72%; Raney Ni, $H_2$, $H_2O$, Amberlyst-15, 25 °C, 1 atm).

Nitriles have been hydrogenated using homogeneous catalysts to produce primary amines.[110] For example, $(Pr^i_3P)_3RhH$ smoothly catalyzes the hydrogenation of aliphatic and aromatic nitriles to produce primary amines (44–100%) in THF solution at 20 °C and 1 atm. Alternatively, $(K^+[(Ph_3P)_2Ph_2PC_6H_4RuH_2]^-\cdot C_{10}H_8\cdot Et_2O$ and $2K^+[(Ph_3P)_3(Ph_2P)Ru_2H_4]^{2-}\cdot(diglyme)_2$ catalyze the hydrogenation of nitriles at 90 °C and 62 atm in toluene containing 18-crown-6 to produce primary amines (18–100%).[44]

In conclusion, it is germane to mention selectivity in the hydrogenation of polyfunctional molecules containing nitrile groups. Alkynes, alkenes, acid chlorides and nitro compounds are generally reduced more rapidly than nitriles. Nitriles, however, may be selectively reduced in the presence of carboxylic acids, esters, amides, aromatic ring systems, ketones and hydrogenolyzable groups.

### 1.10.6.2 Electrochemical and Dissolving Metal Reductions

The conversions of nitriles into primary amines *via* cathodic or dissolving metal reduction are treacherous procedures. Nitrile radical anions frequently undergo C—CN homolysis, thereby resulting in reductive decyanation. Electrolysis of nitriles in $EtNH_2$ containing LiCl or dissolving metal reductions using alkali metals in $Bu^tOH$ or HMPA, or on alumina, in $NH_3$, or $NH_3$ and $Bu^tOH$, K and crown ethers in PhMe or Na and $Fe(acac)_3$ result in significant decyanation.[107,111] Since the decyanation reaction takes place *via* radical anion fragmentation to produce an alkyl radical and cyanide anion, it is particularly favored with tertiary or allylic nitriles. Under certain conditions, decyanation may be observed even with acetonitrile ($Na/Fe(acac)_3$, 98%). However, the conversion of primary and secondary nitriles into the corresponding amines may be carried out in reasonable to excellent yields. Tridecanenitrile has been reduced using Na in BuOH to produce tridecanamine (90–93%).[88] Ca in $NH_3$ generally provides primary amines in better yields than Li or Na in $NH_3$ or $MeNH_2$.[112] Indeed, it is possible to prepare 1-amino-2,2-dimethylpropane (42%) from the corresponding tertiary nitrile using this reagent. Several nitriles have been reduced to provide primary amines using $Cr_2(OAc)_4$, Raney Ni alloy in alkali solution, Ni in water at reflux, and electrochemically at a lead cathode in aqueous mineral acids, *etc.*[107,113] Additionally, attention is directed to the recently described efficient reductions of nitriles to produce amines *via* electrolysis using Raney nickel[114] or *via* cobalamin-catalyzed zinc reductions.[115] These methods are exemplified by the conversions of phenylacetonitrile into 2-phenylethylamine (71%; Ni cathode, 0.75 A, NaOMe, MeOH) and of cyanocyclododecane into di(cyclododecyl)methylamine (81%; Zn, HOAc, cobalt(I) cobalamin catalyst, 25 °C).

In conclusion, nitriles may be reduced electrochemically or with dissolving metal to produce amines. Nonetheless, such reactions must be used with caution. In addition to competitive decyanation, aldehyde or 2,4,6-trialkylhexahydro-1,3,5-triazine formation and reductive dimerization are waiting to overwhelm the unwary.

### 1.10.6.3 Reductions using Metal Hydride Reagents

Aliphatic and aromatic nitriles are readily reduced by $BH_3{\cdot}THF$ to produce primary amines. Excellent yields are obtained when the intermediate borazine salts are hydrolyzed with HCl in EtOH.[2,8,48,107,116] $BH_3{\cdot}SMe_2$ in THF is an alternative reagent, that is most efficiently used at reflux with continuous removal of $Me_2S$. Nitriles may also be reduced by catecholborane and thexylborane, although rates are slow.[13,16] Nitriles are not readily reduced by more hindered dialkylboranes such as $Sia_2BH$ or 9-BBN-H nor are they rapidly reduced by $NaBH_4$, although the electrophilic polyfluoroalkyl nitriles may be converted into the corresponding primary amines.[107] Aromatic and aliphatic nitriles may be reduced to the corresponding amines (53–87%) using $Bu_4NBH_4$ in $CH_2Cl_2$.[97] Additionally, more reactive oxygen- and sulfur-substituted borohydrides are useful for converting nitriles into primary amines. $NaBH_3(OH)$,[64] $NaBH_2S_3$[100] and $NaBH_3(OCOCF_3)$[117] are all useful reagents, although thioamide formation is a complication with $NaBH_2S_3$. $NaBH_3(OCOCF_3)$ is particularly efficient for the reduction of nitriles in the presence of esters, nitroarenes or carbamates.

$NaBH_4/AlCl_3$ in diglyme, a more powerful reducing agent than $NaBH_4$, rapidly reduces aliphatic and aromatic nitriles to the corresponding primary amines (60–90%).[60,107] Alternatively, Raney nickel has been employed to catalyze the reductions of aromatic nitriles to benzylamines.[118] However, the most useful and general $NaBH_4$ reductions are those catalyzed by $CoCl_2$.[98,119] Nickel(II), osmium(IV), iridium(III), platinum(II), copper(II) and rhodium(III) salts are alternative less frequently employed catalysts. Reductions using $NaBH_4/CoCl_2$ involve the formation of cobalt boride, and this insoluble species functions as a heterogeneous catalyst for the $NaBH_4$ reduction of amides, nitriles and nitro compounds. Secondary amines have been prepared from nitriles *via* *N*-alkylation and subsequent $NaBH_4$ reduction of the resultant nitrilium salts.[120]

Nitriles may be reduced by $AlH_3$ in THF or DIBAL-H in PhMe or hexane to produce the corresponding primary amine in excellent yield.[22,71,104] However, DIBAL-H is much more frequently used to prepare aldehydes by reduction at low temperature. Under these conditions, the *N*-alumino imine is only slowly reduced further. $AlH_3$ and DIBAL-H are superior reagents to LAH in many cases. In particular α-deprotonation of acidic nitriles is less pronounced with these Lewis acidic reagents. For example, $Ph_2CHCN$ is reduced to give $Ph_2CHCH_2NH_2$ in superior yield (91%) using $AlH_3$ (46% with LAH). The basicity of LAH is underscored by the reduction of 2-aryl-1,4-butanedinitriles to produce 3-arylpropanamines.[121] Clearly, this reaction takes place *via* the cinnamonitrile and complete reduction. However, in general, simple nitriles are reduced by excess LAH in ether solvents to produce primary amines in good yields.[20,88,107] Since LAH is a very reactive species, the reduction of nitriles containing other groups generally proceeds with global rather than selective reduction. Alkoxy-substituted reagents are less reactive than LAH and may be used for selective reductions.[21] Aromatic nitriles are rapidly reduced by $LiAlH(OMe)_3$ and Red-Al to produce primary amines in high yields. Aliphatic nitriles are not efficiently reduced by Red-Al due to facile α-deprotonation and thus the starting nitrile is recovered on work-up. Nitriles are readily transformed into aldehydes on reduction with $NaAlH(OEt)_3$, $LiAlH_2(OEt)_2$, $LiAlH(OEt)_3$ or Red-Al using inverse addition techniques and/or careful temperature and stoichiometric control. Murai *et al.* have reported that $Co_2(CO)_8$ catalyzes the reduction of aromatic nitriles using $Me_3SiH$ to produce *N*,*N*-bis(trimethylsilyl)benzylamines (11–91%).[122]

In conclusion, aromatic nitriles are most conveniently and efficiently reduced by $BH_3\cdot SMe_2$, $NaBH_4$–$CoCl_2$, $AlH_3$ or LAH. Aliphatic systems should be reduced with $BH_3\cdot SMe_2$, $NaBH_4$–$CoCl_2$ or $AlH_3$. Representative nitrile reductions are given in Scheme 12.

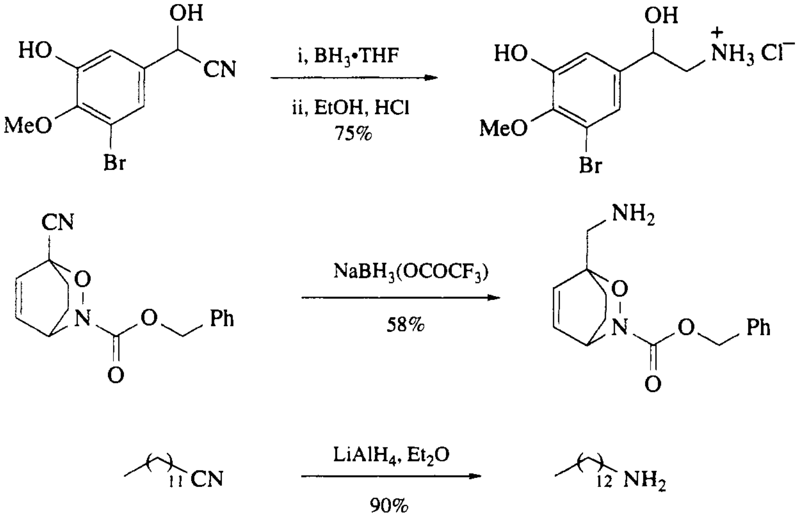

**Scheme 12**

## 1.10.7 REDUCTIONS OF IMIDES, ISOCYANATES AND CARBAMATES

Cyclic imides may be reduced to give hydroxy lactams, lactones, lactams, hydroxy amides or cyclic amines. The most useful synthetic transformations are reductions ($NaBH_4$, MeOH) to produce hydroxy lactams since these are precursors to α-acyliminium salts. However, such reductions are beyond the scope of this chapter. *N*-Alkylphthalimides may be reduced using $NaBH_4$ in 2-propanol to produce phthalide and the corresponding amine (70–97%) and this method provides a convenient procedure for releasing amines from phthalimides.[123] Phthalimide may alternatively be reduced using Zn/Cu to provide phthalide (71%).[124] Cyclic imides (5- and 6-membered) have been reduced using LAH, lithium alkoxyaluminum hydrides or $NaBH_4/BF_3\cdot OEt_2$ to provide pyrrolidine or piperidine derivatives.[21,125] For example, *N*-methylsuccinimide was reduced to produce *N*-methylpyrrolidine (92%) using Red-Al.

Aliphatic or aromatic isocyanates may be reduced to produce *N*-methylalkyl- (or *N*-methylaryl-) amines using LAH,[88] $LiAlH(OMe)_3$, Red-Al[21] or $NaBH_2S_3$.[126] Isothiocyanates show similar reactivities. Alternatively, carbamates may be reduced to yield *N*-methylalkyl- (or *N*-methylaryl-) amines using LAH or Red-Al although the rates of reduction are slow.[21,127] Representative reductions include the conversion of phenyl isocyanate into *N*-methylaniline (75–89%; LAH, $Et_2O$) and the preparation of *N*-methyl-2-(3,5-dimethoxyphenyl)ethylamine from the corresponding ethyl carbamate (83%; Red-Al, $Et_2O$, PhH). In general reduction of isocyanates or urethanes have found little use in synthesis.

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# 1.11

# Reduction of Carboxylic Acids to Aldehydes by Metal Hydrides

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## 1.11.1 INTRODUCTION

Apart from their intrinsic importance, aldehydes are useful functional groups in organic synthesis because they can be transformed readily into a wide variety of other functions. Since aldehydes are easily protected and deprotected, such transformations can be effected at various stages of a synthesis. It is unfortunate that building in an aldehyde function by 'direct' methods is generally not easy, so that methods have been sought for many years for the conversion of carboxylic acids and a variety of their derivatives into the corresponding aldehydes by direct reduction (similarly, many oxidative methods for the conversion of alcohols into aldehydes have been sought). However, aldehydes are very reactive to a large number of reagents, so much so that their synthesis by reduction of carboxylic acids or their derivatives is difficult because the aldehydes are normally more readily reduced than the carboxylic acid or its derivative, and reduction through to the alcohol stage is easy and common.

Until about 1950, reduction of carboxylic acids and their derivatives to aldehydes was not straightforward, and even one of the best methods, the Rosenmund hydrogenation of acid chlorides, required very careful control of both the reaction conditions and preparation of catalyst. The advent of aluminum and boron hydrides and their ready commercial availability transformed the situation to such an extent that the formation of aldehydes from carboxylic acids, acid chlorides, esters, amides, nitriles and similar groups in the presence of other reducible functional groups has become a relatively easy operation on both small and large scale.

Nowadays, there is a wide variety of hydride reagents but this section will concern itself mostly with those derived from boron, aluminum, tin and silicon. Even within this restricted group there is a wide range of hydride types, many of which are far too vigorous for controlled reduction of carboxylic acid derivatives to aldehydes. Accordingly, rather than select the hydrides one by one and discuss their ability to effect the desired reduction, this section will categorize carboxylic acids and their derivatives and discuss which hydrides can be used profitably for their selective reduction. Also, this review will concentrate on developments of methods rather than their application in actual synthesis in order to restrict the number of references. Suffice it to say that there are many examples of elegant, skilled use of hydride reagents to reduce carboxylic acids or their derivatives to aldehydes or their derivatives as parts of syntheses.

The ideal hydride to effect reduction of acids to aldehydes does not exist, nor is it axiomatic that the ideal reagent should react only with carboxylic acids because, in synthesis, the carboxylic acid is usually already protected in some way and it may be more convenient to reduce an amide rather than the free acid. Probably, for most organic chemists, the ideal reagent would be stable, nontoxic, cheap, easy to obtain, not reactive to air or water, would reduce only the group it was needed for and would present no difficulties on work-up: a formidable ideal.

There have been two major approaches towards achieving selective reduction of carboxylic acid derivatives to aldehydes (or derivatives) by hydrides. Firstly, hydride reagents themselves have been modified as, for example, sodium borohydride and sodium cyanoborohydride. Sometimes these modifications have led to 'finely tuned' reducing agents, as with the dimethyl sulfide adduct of thexylbromoborane (see later). Secondly, the type of carboxylic acid derivative has been modified for the optimum yield of aldehyde. For example, amides have been made from an assortment of amines in efforts to maximize yields of aldehyde. Best yields of aldehydes are obtained usually by a combination of modified hydride reagent with a modified carboxylic acid derivative.

The various functional groups will be considered in the following order: carboxylic acids, acyl chlorides, esters (including ortho esters), lactones, amides, lactams and nitriles (including imidoyl halides). Nomenclature for aluminum and boron hydrides is in a state of flux. There are the 'authorized' versions and those used by most practising organic chemists. Thus, lithium tetrahydridoaluminate is the correct name for lithium aluminum hydride ($LiAlH_4$), although the latter is more easily and widely recognized. In writing this article, the view has been taken that, for now and the near future, the more widely used nomenclature will be more readily recognized by readers and so common everyday names will be used. To avoid confusion and encourage the use of the more systematic, recommended nomenclature, this will be given in parentheses at the first mention of any one hydride; for example, tri-*n*-butyltin hydride (tri-*n*-butylstannane). Similarly, trivial but widely used names will be given, as with sodium bis(2-methoxyethoxy)aluminum hydride (sodium bis(2-methoxyethoxy)dihydridoaluminate; Red-Al).

## 1.11.2 CARBOXYLIC ACIDS

Direct reduction of carboxylic acids to aldehydes has been a long-sought transformation since acids are usually relatively easy to obtain. The number of hydride reagents which effect this transformation is limited.

Although it had been reported in 1959 that diisobutylaluminum hydride (DIBAH or DIBAL-H; diisobutylalane) reduced acids and esters to alcohols[1] at 70 °C, it was shown later that, at –75 to –70 °C, good yields of aldehydes could be obtained.[2] At higher temperatures, yields dropped dramatically. For example, caproic acid gave a 70% yield of caproaldehyde at –75 °C but, at –60 °C, the yield fell to 30%. This reaction with an alane appears to be the first reported direct reduction of acids to aldehydes. The very low temperatures required, the ease of overreduction and the possibility of reduction of other functional groups makes this reaction less attractive on a large scale. Shortly after this work, it was shown that the parent aluminum hydride itself (alane) was generally too vigorous a reducing agent, giving alcohols with acids and esters and amines with amides and nitriles; a 6% yield of caproaldehyde from caproic acid was reported.[3]

Attempts to modify the alanes led to lithium trimethoxyaluminum hydride (lithium trimethoxyhydridoaluminate)[4] and lithium tri-*t*-butoxyaluminum hydride (lithium tri-*t*-butoxyhydridoaluminate),[3] but the trimethoxy compound, with carboxylic acids, gave alcohols and the tributoxy hydride would effect no reduction at all. However, other workers[5] showed that alane could be modified with secondary amines to give compounds of the type (**1**; $HAlX_2$) and that these hydrides reduced acids directly to aldehydes in yields of 60–80% on refluxing them in tetrahydrofuran for 3–20 h. These same workers confirmed that alane itself gave almost no aldehyde and even $H_2AlX$ gave inferior yields. To prepare the reagent, an alane solution must be calibrated and reacted with exact amounts of amine; two hydride ions are lost in the preparation and the reduction requires 2–4 equiv. of reagent so that the method is neither easy nor efficient in usage of hydride. A more convenient preparation has been proposed for the modified alanes, $HAlX_2$ (**1**), starting from lithium aluminum hydride;[6] this last publication confirmed the excellent yields of aldehydes which can be obtained.

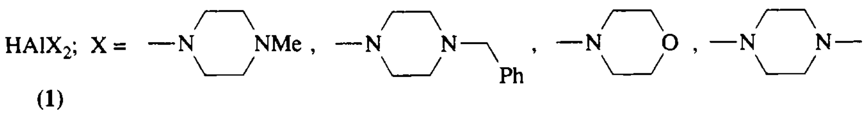

**(1)**

Analogous boranes have been investigated as suitable modified reducing agents for carboxylic acids. Diborane itself reacts vigorously with acids but does not give aldehydes.[7] In a comparative review of diborane and thexylborane (2,3-dimethyl-2-butylborane) it was pointed out that the latter reacts with acids to form hydrogen and a 1:1 complex, but with an excess of hydride reagent at −20 °C in tetrahydrofuran a sluggish reaction affords aldehydes.[8] It was emphasized later that thexylborane reacts with other functional groups so that care is needed for selective reduction of acids to aldehydes.[9] Furthermore, thexylborane adds to double or triple bonds much faster than it reduces carbonyl functional groups, thereby diminishing its usefulness for selective reduction to aldehydes.

The reducing power of diborane has been blunted by forming its adduct with dimethyl sulfide. This adduct, $Me_2S{\cdot}BH_3$, is stable and commercially available and therefore more attractive as a hydride reagent than diborane itself.[10] Nevertheless, the adduct still reduces carboxylic acids to alcohols which are isolated as cyclic boroxins (**2**; Scheme 1). In a 'one-pot' reaction, carboxylic acids can be reduced to boroxins and then oxidized with pyridinium chlorochromate to the required aldehyde (Scheme 1).[11]

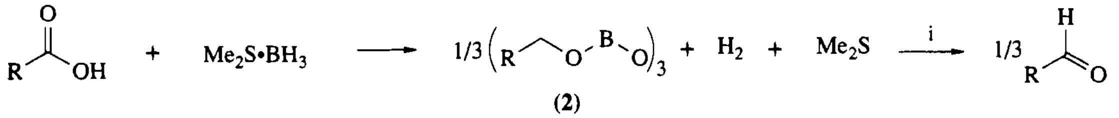

i, pyridinium chlorochromate

**Scheme 1**

In much the same way, thexylborane has been modified by reaction with HCl and dimethyl sulfide to give thexylchloroborane–dimethyl sulfide ($Me_2CHCMe_2BHCl{\cdot}SMe_2$).[12] This stable reagent is much more reactive to acids than is thexylborane itself; reduction takes place at room temperature and an excess of reagent can be tolerated. No reaction is observed with esters, epoxides, aromatic nitriles and nitro compounds. Interestingly, aliphatic acids are reduced to aldehydes in about 15 min, but aromatic acids require about 24 h so that selective reactions can be effected on aliphatic and aromatic carboxylic acids. An earlier survey of the reduction of carboxylic acids with the thexylchloroborane–dimethyl sulfide adduct showed that 46–92% yields of aldehydes could be obtained and that diacids gave high yields of dialdehydes.[13] One practical difficulty with their use lies in the removal of the resulting thexylboronic acid during work-up. Although aromatic acids require a long reaction time, it was pointed out that aromatic acid chlorides are more favorably reduced to aldehydes by lithium tri-*t*-butoxyaluminum hydride, which is therefore a complementary reagent (see Section 1.11.3).

A slight but significant development of thexylchloroborane has given a reagent which reacts equally well with carboxylic acids but does not add to double or triple bonds. Thus, the adduct thexylbromoborane–dimethyl sulfide gives approximately 95% yields of aldehydes of all types in $CS_2/CH_2Cl_2$ at room temperature;[14] the reagent is somewhat laborious to prepare but is stable and can be stored. The high molecular weight of the reagent may make it unsuitable for large scale use.

Further adaptations of the boranes has led to reagents which reduce carboxylic acids but afford thioacetals rather than the aldehyde itself.[15] Thus, with the thioborane (**3**; equation 1), aliphatic acids give 80–87% yields of thioacetals but aromatic acids respond less well in giving significant quantities of sulfides as well. Carboxylic acid esters are inert to this reagent but give sulfides if a Lewis acid is included. Similarly, the 1,3,2-dithiaborinane–dimethyl sulfide adduct (**4**; equation 2) affords cyclic dithioacetals in 70–90% isolated yields in the presence of $SnCl_2$.[16] Aliphatic acids react in about 6 h at room temperature but aromatic acids need about 20 h and yields are somewhat poorer. This area has been reviewed.[17] From a practical viewpoint, it should be noted that the dithiaborinane (**4**) requires a week for its preparation.

A completely different approach has been taken in the use of hypervalent silicon hydrides. It has been shown that pentacoordinated silanes possess enhanced reducing power. Thus, in the presence of a nucleophile, which may be external (reaction (a) in Scheme 2) or internal (reaction (b) in Scheme 2), hy-

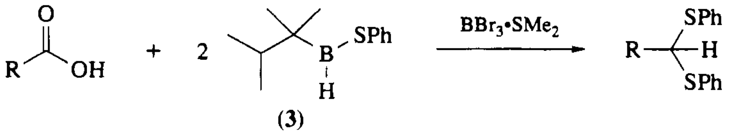

(1)

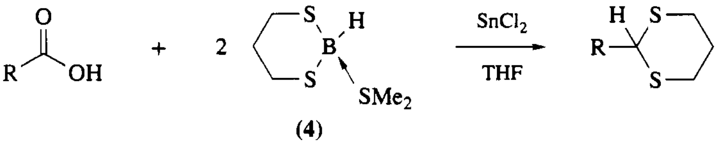

(2)

drosilanes can reduce carbonyl compounds or can react with acids because of the activation of the hydrogen in the hypervalent state.[18] In pursuing this work, it was found that the hydrosilyl ester (**5**) on heating to 110–160 °C gave aldehydes in 50–90% yields (reaction (c) in Scheme 2). It was not necessary to isolate the ester (**5**).[19] From examination of similar dihydrosilanes, the best conversion was given by compound (**6**); the importance of internal coordination of nitrogen was demonstrated by the failure of compound (**7**) to provide more than a trace of aldehyde under similar reaction conditions. α,β-Unsaturated acids can be reduced by the dihydrosilane (**6**) to the aldehyde without reduction of the double bond. The molecular weight and cost of the dihydrosilane (**6**) would appear to make it unsuitable for large scale work, whilst the need for relatively high temperatures is not suitable for relatively unstable compounds. This last drawback is obviated through the use of an acid chloride (see Section 1.11.3).

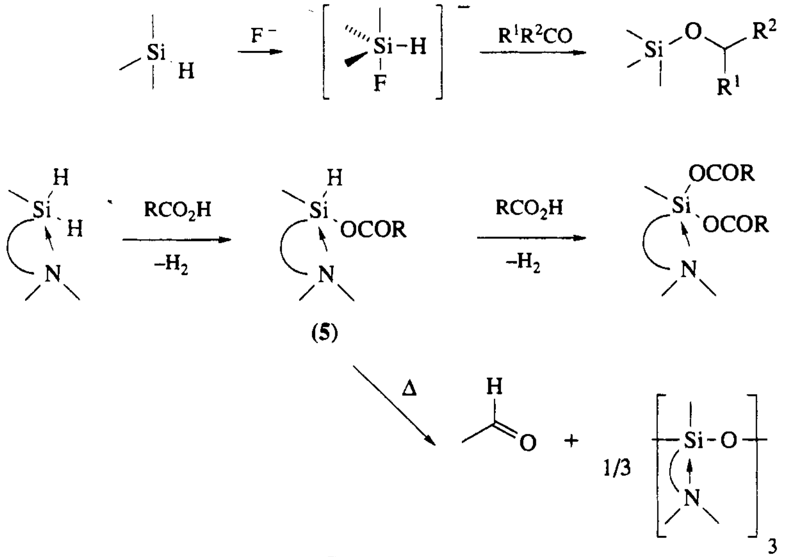

**Scheme 2**

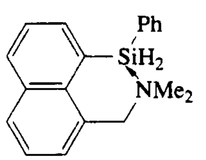

(**6**)

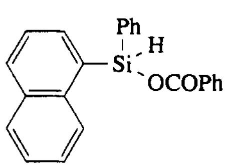

(**7**)

## 1.11.3 ACYL HALIDES

Direct displacement of chloride in acyl chlorides by hydride has been used to prepare aldehydes in 25–50% yield through the use of lithium hydride.[20] It was necessary to reflux the acid chloride in benzene or toluene with freshly prepared lithium hydride for 4–20 h. Under these conditions, there is the distinct likelihood that, when formed, aldehydes with α-hydrogen atoms would undergo aldol condensation. Sodium and calcium hydrides afforded only traces of aldehyde.

Lithium aluminum hydride is much too powerful a reducing agent to stop the reduction of acyl halides at the aldehyde stage and further reduction to alcohol is the usual result. In a preliminary communication, it was shown that even lithium trimethoxyaluminum hydride, in which the sole hydride is much less reactive than the hydrides in lithium aluminum hydride, was too powerful a reducing agent for acyl halides but lithium tri-*t*-butoxyaluminum hydride could give aldehydes.[21] This report was confirmed in two subsequent publications in which the reduction of a variety of acid chlorides in diglyme at –75 to –80 °C was described.[22,23] Aromatic acyl halides gave 60–80% yields of aldehyde but aliphatic compounds afforded only 40–60% yields. Very slow inverse addition of the hydride to the acid chloride is recommended at the very low temperatures involved. The method is convenient, particularly for aromatic aldehydes, since the reagent can be prepared *in situ* from lithium aluminum hydride and *t*-butyl alcohol, albeit with loss of three hydride equivalents. Lithium tri-*t*-amyloxyaluminum hydride gave much inferior conversions to aldehyde. The usefulness of lithium tri-*t*-butoxyaluminum hydride was confirmed in the formation of 3,5-dinitrobenzaldehyde in 60–63% yield from the acid chloride. The authors report that this hydride, with proper control, does not affect oxides, esters, acetals, nitriles and lactones.[25]

In the boron series, an analog of the alkoxyaluminum hydrides, *viz.* sodium trimethoxyborohydride (sodium trimethoxyhydroborate), has been shown to give aldehydes from acid chlorides but only in poor yield.[24] As an exception, other workers found that the same reducing agent at –80 °C afforded the aldehyde (**8**) in 85% yield from the corresponding acid chloride.[26]

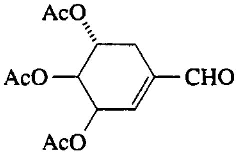

**(8)**

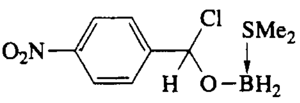

**(9)**

Diborane reduces acyl halides to alcohols as does thexylborane, but very slowly,[8,9] and disiamylborane has no effect.[27] Complexing diborane with dimethyl sulfide has a marked effect on its reactivity, but it has been found that acyl halides are still reduced to the alcohol stage, with the one exception of 4-nitrobenzoyl chloride which gave a 60% yield of 4-nitrobenzaldehyde.[28] This effect of an electron-withdrawing substituent is observed with other reducing agents described later and is probably caused by the substituent counteracting the loss of the leaving group ($Cl^-$), thereby stabilizing the intermediate (**9**) and preventing its rapid collapse to aldehyde.

Sodium borohydride and its derivatives have been examined extensively as convenient means of converting acyl halides to aldehydes. The borohydride itself or in polyethylene glycol[29] reduces the halides to alcohols, but, if care is taken to utilize only one of its hydrides, successful reduction to the aldehyde can be achieved. In one of the earliest modifications of sodium borohydride, it was mixed with cadmium chloride and dimethylformamide to give a reagent which reduced acid chlorides to aldehydes in good yield in 5 min at 0 °C.[30] The reaction is believed to involve the bidentate borohydride (**10**) and it was suggested that it proceeded through an intermediate iminium species (**11**; equation 3).[31] This suggestion was followed up by other workers who synthesized the iminium species directly from the carboxylic acid (equation 4), and, in a one-pot reaction, reduced compounds (**11**) to aldehydes in 70–90% yield using lithium tri-*t*-butoxyaluminum hydride in the presence of copper(I) iodide at –78 °C (see Section 1.11.4).[32] The reaction in equation (3) aroused the attention of other workers who demonstrated that selective reduction could be effected in dimethylformamide in the absence of the cadmium salt if the reaction was carried out at low temperatures and then quenched with acid and ethyl vinyl ether. It was surmised that liberation of diborane on quenching the reaction mixture was the cause of overreduction to the alcohol.[33] The method of quenching left difficulties with the work-up of reaction products and, in a second publication,[34] it was shown that the addition of pyridine as a diborane scavenger allowed sodium borohydride to be used at 0 °C to reduce acyl chlorides in only a few minutes. Small amounts of alcohol (5–10%) were observed with very good yields of aldehyde.

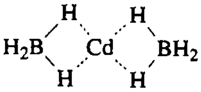

**(10)**

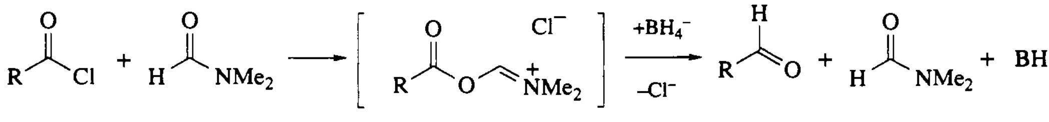

(11)

(3)

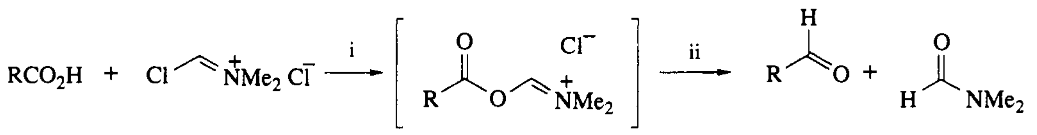

(11)

(4)

i, pyridine, –30 °C; ii, $LiAlH(OBu^t)_3$, CuI, –78 °C

Contemporary with the use of $CdCl_2$ as a moderator of borohydride reducing activity, other reports appeared on the use of copper salts. Bis(triphenylphosphine)copper borohydride (bis(triphenylphosphine)tetrahydroboratocopper) was used in acetone to reduce acid chlorides to aldehydes in 2–15 min at 25 °C (equation 5).[35] Recovery of tris(triphenylphosphine)copper chloride is relatively straightforward but extra triphenylphosphine must be added to the reaction mixture, making large scale use inconvenient. This drawback was recognized in a further publication,[36] in which was reported the same reaction, except that trimethoxyphosphine or triisopropoxyphosphine ligands were used in place of triphenylphosphine in an attempt to reduce the molecular weight of the reagent. Reduction of acid chlorides was fast, but the extra, more soluble ligand made work-up to isolate the aldehyde difficult. An advantage of this copper reagent is its stated inertness to all functional groups except acid halides and iminium salts. At the same time that this work appeared, other workers reported the same reaction with bis(triphenylphosphine)copper borohydride to give 60–85% yields of a range of aldehydes at room temperature;[37] a further publication described a simple method for recycling the copper salt.[38] Later, it was found that, whereas the moderated hydride, sodium cyanoborohydride, was still active enough to reduce acid chlorides to the alcohol stage, μ-bis(cyanotrihydroborato)-tetrakis(triphenylphosphine)dicopper reduced them to aldehydes in 50–90% yields.[39] Acidity in the reaction medium was important because, at pH 3, this same copper reagent caused overreduction to the alcohol.

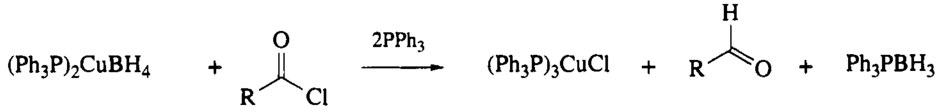

(5)

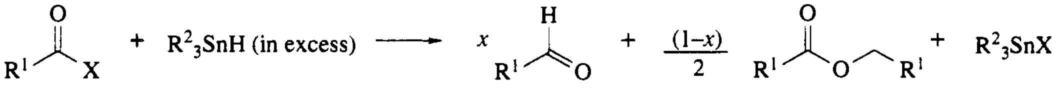

(6)

X = F, Cl, Br; $R^2$ = Ph, $Bu^n$

(12)

Tin hydrides or stannanes have been known to form aldehydes from acyl halides for many years. Acid chlorides are reduced to aldehydes in poor to modest yields by triphenyltin hydride (triphenylstannane),[40] but it has been found that tri-*n*-butyltin hydride (tri-*n*-butylstannane) was a better, more convenient reagent.[41] A second product from these reductions is the ester (**12**; equation 6), notionally formed by acylation of the alcohol produced by overreduction. In some reactions the ester forms the major product, particularly with triphenyltin hydride.[42] The ratio of aldehyde to ester appears to depend on the type of acid halide, on the experimental conditions (neat liquids or in solution) and on which stannane is used.[43–45] Thus, acid bromides with tri-*n*-butyltin hydride give good to high yields of aldehyde but acid chlorides with trimethyltin hydride afford mainly esters.[45] Acid fluorides with either hydride give esters. The yield of aldehyde is increased as the group attached to the acid chloride becomes larger or branched and solvent exerts a profound effect.[43] The reduction has been considered to be a radical process, with the initial formation of acyl radicals followed by hydrogen abstraction or coupling and hydride extraction (Scheme 3).[44] This view of the reaction has been accepted generally,[46] but more recent evidence has indicated that radicals are not involved.[47] This reassessment of the reaction revealed that the product distributions from carefully chosen acid chlorides were not those expected (from other work) if acyl radicals were important. Further, intentional addition of a radical initiator altered the product distributions so that they became in keeping with those expected for a radical reaction. It was thought that an addition compound (**13**; Scheme 4) is formed first and then undergoes further reaction, as shown.

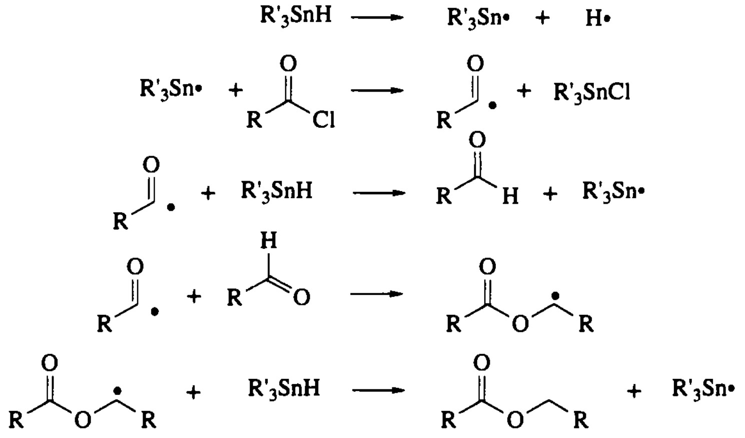

Scheme 3

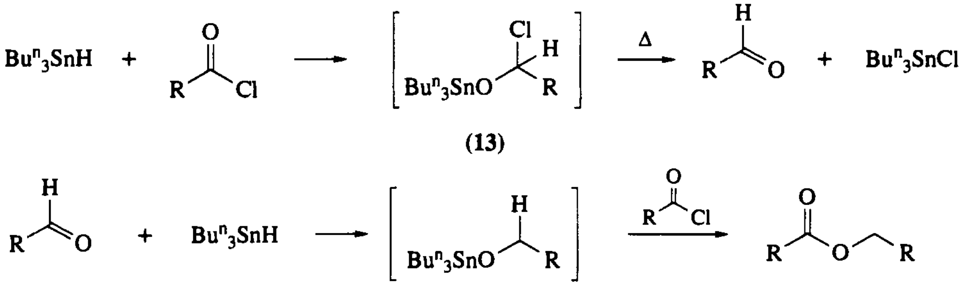

Scheme 4

A significant improvement in this reaction was the discovery that it could be catalyzed by palladium to give aldehydes in 75–95% yield; in the absence of catalyst yields of only about 10% were observed.[48,49] Tri-*n*-butyltin hydride with tetrakis(triphenylphosphine)palladium were the preferred reagents. It was noted that work-up can be troublesome with regard to removal of tri-*n*-butyltin halide. The reaction is claimed to be better than the closely analogous reaction of acyl chlorides with trialkylsilicon hydrides (see below). This metal-catalyzed reduction is also generally considered not to be a radical process.[50]

Development of a comparable reduction of acyl chlorides by silicon hydrides (silanes) began even earlier than that of the tin hydrides. It was found that acid chlorides could be reduced to aldehydes in modest yields with a variety of silanes but best results were obtained with triethylsilicon hydride (triethylsilane).[51] This reaction was much improved by use of a 10% palladium-on-charcoal catalyst which provided 30–70% yields of aldehydes.[52] Unbranched aliphatic acyl chlorides were reduced satisfactorily but, unlike the later-developed stannane reaction described above,[48,49] α-branched chlorides gave poor or no yields of aldehydes; aromatic acyl halides gave poorer results than did the aliphatic analogs. The palladium-catalyzed reduction with silanes, carried out at ambient or higher temperatures, was considered to be a better process than reduction with lithium tri-*t*-butoxyaluminum hydride[21–23] for aliphatic compounds but not for aromatics. There were difficulties in work-up of the silane reaction in that the product aldehydes could not be distilled directly from the reaction mixture because of their destruction if silanes or silyl chlorides were present. Other workers have used *cis*-$[PtCl_2(PPh_3)_2]$ and various Rh complexes as catalysts in this reaction but were able to isolate only poor quantities of aldehydes. Indeed, ketones formed significant reaction products under these conditions.[53]

In an extension of the high temperature reaction of hypervalent silanes with carboxylic acids to produce aldehydes (see Section 1.11.2),[19] it was found that acyl chlorides reacted at room temperature with compound (**14**) to give 85–95% yields of aldehydes.[54] Halogen, methoxy, nitroaryl and heteroaryl groups and carbon–carbon double bonds were unaffected; dialdehydes could be produced as readily as monoaldehydes. During work-up, it was found necessary to trap the resulting silyl chloride on wet silica, or in other ways, because its presence severely reduced yields of the aldehyde during distillation, as found with the silane and stannane reductions described above.

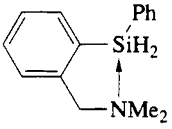

**(14)**

## 1.11.4 ESTERS OF CARBOXYLIC ACIDS (INCLUDING ORTHO ESTERS)

Hydrides based on aluminum have proved most versatile and selective for the reduction of esters ($RCO_2R^1$) to aldehydes (RCHO), but it should be noted that the nature of R and $R^1$ (aliphatic, aromatic, branched, electron-withdrawing or electron-donating, steric size) is important. Most of the reactions described here have been carried out on simple methyl or ethyl esters. It is frequently found that aliphatic esters give much better yields than do aromatic esters. Reductions are carried out at very low temperatures such that esters are still reactive to the hydride but any aldehyde produced is not. Alternatively, the intermediate formed by addition of metal hydride to the ester (**15**; Scheme 5) may be sufficiently stable that no significant amount of aldehyde is formed. Thus, if the rate constant $k_1 > k_2$ then little aldehyde will be released, and no aldehyde formed even if $k_3 > k_1$. It also seems likely that the difference in the Lewis basicity of esters and aldehydes affects the complex of rate constants shown as $k_1$, $k_2$ and $k_3$, and hence affects the relative reactivity of these two functional groups towards the different hydride reagents.

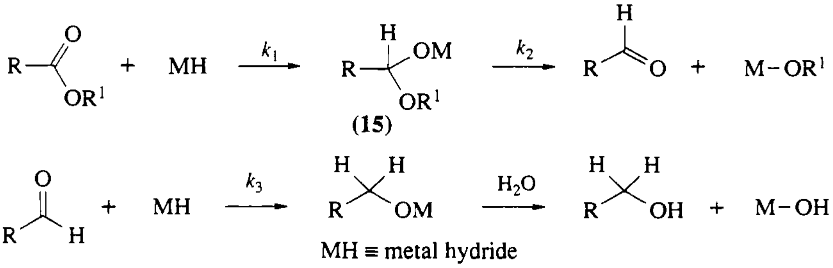

**Scheme 5**

One of the earliest reports of hydride reduction of esters involved use of diisobutylaluminum hydride (diisobutylalane; DIBAH; DIBAL-H). Methyl or ethyl esters were treated with DIBAH at –70 °C for 0.5–1 h in toluene, hexane or diethyl ether to give 60–80% yields of aldehyde.[54] This reaction afforded an 83% yield of aldehyde in a natural product synthesis, whereas attempted reduction of an amide with $LiAlH_4$ gave none, although this amide reduction is usually a good procedure (see Section 1.11.6).[55] In a detailed examination of the reduction of ethyl *n*-butyrate to butyraldehyde, it was shown that a temperature of –70 °C was essential for good yields; at –45 to –35 °C, a 'Tishchenko' oxidation/reduction led to reduced yields of aldehyde and the formation of isobutyl esters.[56] In more recent work, benzyloxycarbonyl derivatives of α-amino acid methyl or ethyl esters were reacted with DIBAH in toluene or tetrahydrofuran at –50 °C to give modest to good yields of α-amino aldehydes.[57] Importantly, these easily racemized aldehydes were isolated in high optical purity. In another useful application, DIBAH was used to reduce methyl esters to aldehydes selectively in the presence of *t*-butyl esters, an illustration of the part played by steric effects.[58] It was noted that no other hydride reducing agent could achieve the same selectivity. The use of DIBAH (and triisobutylaluminum) has been reviewed in detail.[59]

To increase the selectivity of DIBAH, it has been converted into amine derivatives, $HAlX_2$ (**1**), with X = *N*-methylpiperidino being the preferred reagent.[60] Yields of aldehydes of 60–80% from both aliphatic and aromatic esters were obtained on refluxing them with bis(*N*-methylpiperidino)aluminum hydride (bis(*N*-methylpiperidino)alane; BMPA) in tetrahydrofuran for 6–20 h; an excess of reagent can be tolerated. The higher temperatures are a distinct advantage because difficulties with the solubility of substrate, as occur at the very low temperatures required in the use of DIBAH itself, do not usually arise. It should be noted that the authors believe that the reaction proceeds through the sequence shown in Scheme 6 so that, if the reaction is stopped too early, amides and not aldehydes are isolated.

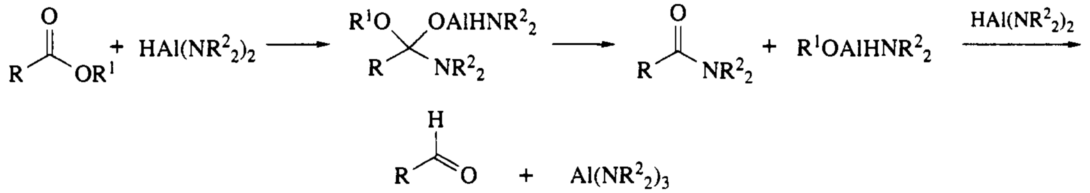

Scheme 6

At about the same time that DIBAH was developed as a selective reducing agent for the production of aldehydes from esters, the same workers[54] examined the use of sodium aluminum hydride (sodium tetrahydridoaluminate) for this purpose.[61] In tetrahydrofuran or pyridine at –65 to –45 °C, aliphatic and aromatic methyl or ethyl esters gave aldehydes in 50–80% yield. Better yields for aliphatics were found and aromatics required much longer reaction times. Control of temperature was crucial, and, if not controlled, led to sharp decreases in yields of aldehyde. A major difficulty with sodium aluminum hydride has been the low solubility of both it and the reduction intermediates at the low temperatures necessary for selective reduction to the aldehyde. In a development of this reagent, it was shown that sodium bis(2-methoxyethoxy)aluminum hydride (sodium bis(2-methoxyethoxy)dihydridoaluminate; Vitride; Red-Al) was more convenient and provided yields of about 40–90% of the aldehyde for a range of methyl esters at –50 to –70 °C; below –50 °C, aldehydes are reported to be almost unreactive towards this hydride reagent.[62] Its further modification by addition of one equivalent of *N*-methylpiperidine gives sodium bis(2-methoxyethoxy)-*N*-methylpiperidinoaluminum hydride, which is suitable for reducing aliphatic, aromatic and α,β-unsaturated esters in yields of 50–85%.[63]

Modified lithium aluminum hydride has been used successfully for the reduction of esters at temperatures of about 0 °C. Thus, lithium tri-*t*-butoxyaluminum hydride readily reduces phenyl esters of carboxylic acids to aldehydes in 33–77% yields; other esters are reported to be unreactive, as are many other functional groups (acyl chlorides react with the same reagent at –70 °C, however).[64,65] Phenylbenzoate and phenyl cyclopropanecarboxylate do not give the aldehyde. Iminium salt esters (**11**; equation 4) can be reduced with lithium tri-*t*-butoxyaluminum hydride (see Section 1.11.3).[32]

Reduction of carboxylic acid esters and ortho esters to acetals or ketals can be effected in high yield even with vigorous reducing agents. The ortho ester (**16**; Scheme 7), formed from 2-cyanoethanethiol, was reduced in refluxing benzene by using 0.25 molar equiv. of lithium aluminum hydride to give the acetal (**17**) in 97% yield, which could be converted into the aldehyde, also in excellent yield.[66] The triethyl ortho ester of benzoic acid was reduced to benzaldehyde diethylacetal with DIBAH at 30 °C over a period of 1 h. By raising the temperature to 70–80 °C, further reduction to isobutyl ethyl ether occurred.[67]

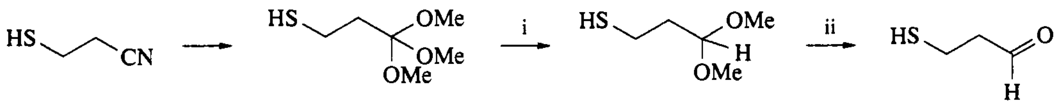

(**16**) (**17**)

i, 1/4 $LiAlH_4$; ii, Rochelle salt

Scheme 7

In a novel reaction, the ester (**18**; Scheme 8) was heated with $NaBH_4$ in pyridine to 115 °C. The reaction was stopped at the ketal stage (**19**) so that overreduction to the alcohol was not possible.[68] Overall yields of about 50% were reported but it might be noted that the other product of the reaction was the pyridine/borane adduct $C_5H_5N{\cdot}BH_3$, so that only a quarter of the available hydride was used in the reduction.

With the strongly electron-withdrawing group in ester (**20**; equation 7), reaction with sodium borohydride afforded the hemiacetal (**21**), although normally this hydride does not react with esters.[69] In some cases, electron-withdrawing groups allow isolation of the aldehydes after reaction with lithium aluminum hydride, such as with trichloropentadienoic esters[70] and chloroepoxy-α,β-unsaturated esters.[71]

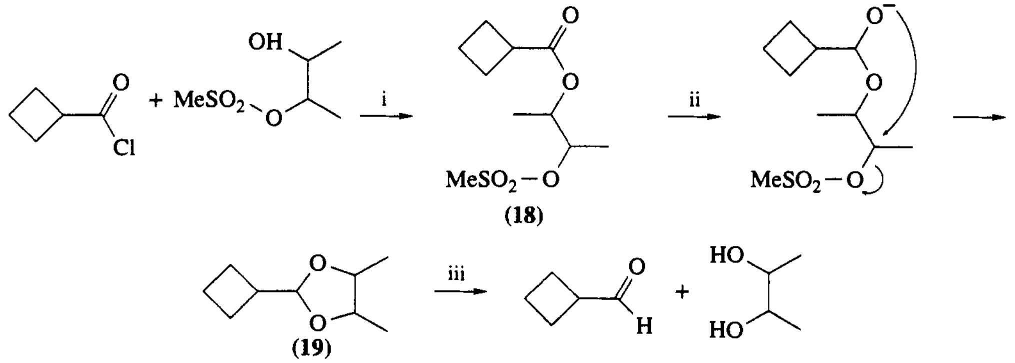

i, pyridine; ii, NaBH$_4$/pyridine/115 °C; iii, aq. acid

Scheme 8

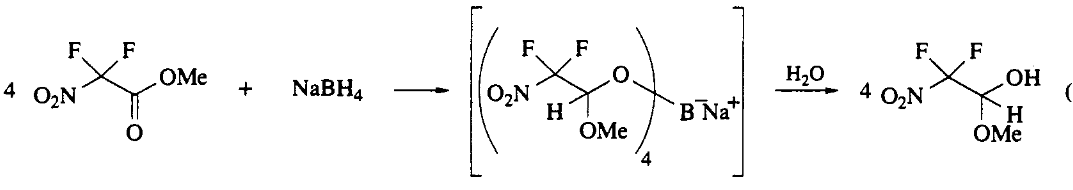

(7)

(20) (21)

Finally, thione thiolates (22) have been reduced to the dithioacetals (23) in almost quantitative yield with tri-*n*-butyltin hydride under the action of ultraviolet light.[72]

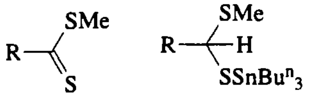

(22) (23)

## 1.11.5 LACTONES

Normally, lithium aluminum hydride is too vigorous a reagent for the reduction of lactones to the hemiacetal (hydroxyaldehyde; lactol) stage, but, in certain circumstances under carefully controlled conditions, it can be used successfully. Usually, lactones give diols with LiAlH$_4$ but, with 0.25 equiv., hemiacetals have been prepared from γ-lactones in high yield (Scheme 9).[73,74] Sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al) has been modified further by addition of one molar equivalent of ethanol to give sodium bis(2-methoxyethoxy)ethoxyaluminum hydride, a reagent which is reported to reduce γ-lactones to lactols in 84–94% yield in 25–60 min at 0 °C; one δ-lactone required a temperature of −60 °C and gave only 64% of the lactol.[63] Without the addition of ethanol, poor yields of lactol were obtained in uncontrollable reactions.

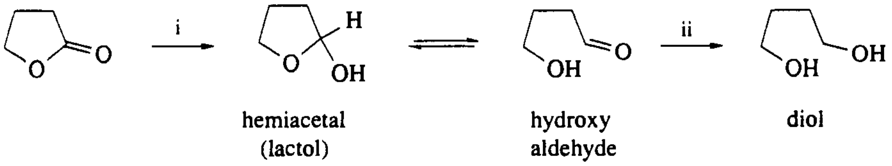

i, 1/4 LiAlH$_4$; ii, excess of LiAlH$_4$

Scheme 9

In uncontrolled reductions, lactones are reduced by lithium trialkyoxyaluminum hydrides to diols but the reduction with LiAlH(OBu$^t$)$_3$ is very slow and advantage can be taken of this to stop the reaction at the lactol stage. The first reported examples using this reagent showed that δ-lactones could be converted into lactols in high yield at about –60 °C.[75–77] A later publication suggested that even better conversions may be possible through the use of preformed, pure $LiAlH(OBu^t)_3$ rather than by its preparation first *in situ*.[78] This area has been reviewed.[79]

Reduction of lactones to lactols with diisobutylaluminum hydride has become an important, high-yielding reaction in the wake of many syntheses of prostaglandins.[59] First introduced in this role in 1969,[80] DIBAH can give 98% yields of lactols from γ-lactones by reaction at –60 °C for 20 min in toluene.[81,82]

Diborane has been used to reduce lactones to cyclic hemiacetals and, when boron trifluoride etherate was added, ethoxy compounds (**24**; Scheme 10) were isolated.[83] It was later shown that yields of hemiacetals in excess of 80% were obtainable with short reaction times.[84]

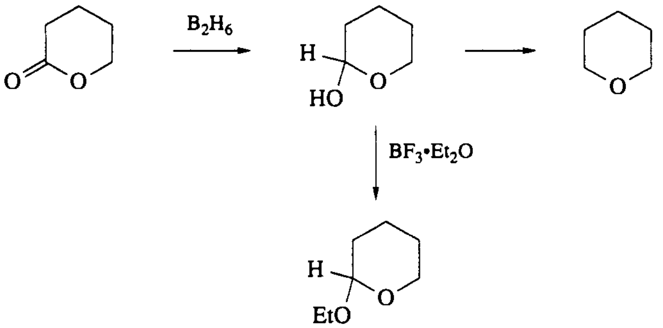

**(24)**

**Scheme 10**

Sodium borohydride in water at pH 3 has been effective in reducing aldonic lactones to aldoses in approximately 65% yield.[85] Thus, at 0 °C, D-gluco-D-guloheptano-γ-lactone gave D-gluco-D-guloheptose on simultaneous dropwise additions of aqueous $NaBH_4$ and dilute $H_2SO_4$. Similar reductions of other lactones confirmed this convenient method for the production of aldoses.[86]

Although thexylborane reduces lactones slowly,[9,87] it appears to have been little used for the purpose of synthesizing lactols; however, its close analog disiamylborane (bis(3-methyl-2-butyl)borane) has been used successfully. Simple reduction of a variety of lactones to hydroxy aldehydes or hemiacetals (Scheme 9) appears to be quite general for disiamylborane.[27] At –10 °C, this reagent was found to reduce tetraacylhexano-γ-lactones to tetraacylhexanofuranoses in 100% yield.[88] Similarly, unprotected sugars could be reduced, as with the conversion of D-erythronolactone into D-erythrose in good yield.[89] In a comparison of the rates of reduction of lactones to lactols and their yields, it has been shown that disiamylborane is superior to other analogous boranes either more or less sterically demanding. For example, disiamylborane reduces acylated aldonolactones to acylated aldoses in 100% yield at 45 °C in 6 h, but bis-2-(2,3-dimethylbutyl)borane only gives a poor yield over a long period at the same temperature.[90] Confirmation of the excellent yields afforded by disiamylborane came in the quantitative reduction of a γ-lactone to a lactol.[91] Whilst this reagent gives such good yields, it is worth bearing in mind that it is also an excellent hydroborating reagent, reacting readily with double and triple bonds. It also reacts with alcohols, phenols, thiols and amines to liberate hydrogen rapidly, and such groups would need to be protected if the use of excessive amounts of disiamylborane is to be avoided.

## 1.11.6 AMIDES OF CARBOXYLIC ACIDS

The use of lithium aluminum hydride for the reduction of carboxylic acid derivatives to aldehydes goes back to some of the earliest-reported applications of this reagent.[92] An example of this type of reduction appeared when it was reported[93] that the piperidide of cyclopropanecarboxylic acid could be reduced to cyclopropanecarbaldehyde in moderate to good yield. The following few years saw considerable interest in the reduction of amides to aldehydes and many types of amide were investigated with a view to optimizing yields. One of the difficulties with this reaction lies in there being two other possible products of reduction, *viz.* amines and alcohols (see later, Scheme 11). In an attempt to reduce the dipiperidide of phthalic acid with $LiAlH_4$, only 20% yield of the dialdehyde was obtained, but, on changing to the dimethylamide, the yield of phthalaldehyde increased to 70%.[94] However, it was later demonstrated that the piperidide of cyclohexanecarboxylic acid could be reduced to the aldehyde in good yield if the lithium aluminum hydride was added to the amide (inverse addition), instead of the usual addition of substrate to reducing agent.[95] Although inverse addition became the standard procedure in this reaction for the best yields, interest in piperidides gave way to other tertiary amides. In a preliminary communication, it was reported that *N*-methylanilides of carboxylic acids in tetrahydrofuran with inverse addition of solid $LiAlH_4$ afforded 54–75% yields of aldehydes, including dialdehydes.[96] In following up this work, a much wider range of aldehydes was synthesized, thereby demonstrating the general usefulness of the reaction in the absence of other functional groups reducible by $LiAlH_4$.[97]

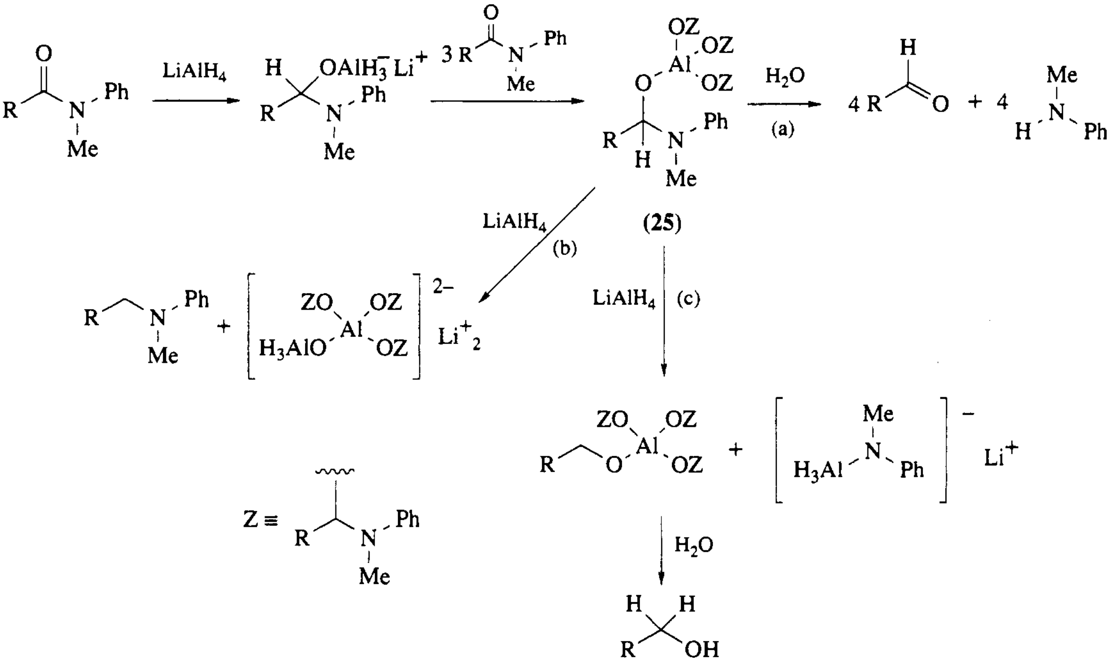

**Scheme 11**

The overall mechanism of the reaction has been discussed (Scheme 11).[97] For successful production of the aldehyde, the reaction needs to stop at the stage represented by structure (**25**; Scheme 11) and inverse addition of exactly the required amount of $LiAlH_4$ helps achieve this step; subsequent hydrolysis (step a) affords the aldehyde. If an excess of $LiAlH_4$ is used, or if the rates for steps b and c are greater than the rate of formation of structure (**25**), then alcohols and/or amines are formed (Scheme 11). The type of amine used to prepare the amide plays a considerable role in determining the stability of structure (**25**), *viz.* in determining whether steps b and c are faster or slower than the rate of formation of (**25**). The effects of the amine are apparently both steric and electronic. These factors were examined extensively when it was shown that bulky amines favored aldehyde formation (or stability in structure **25**), as did delocalization of the amide nitrogen lone pair electron density away from the amide and into an aromatic structure.[98] Especially good yields of aldehydes were obtained with acylated pyrroles, indoles or carbazoles. A fuller mechanistic study of the reduction of *N*-methylanilides with $LiAlH_4$ indicated that the reaction sequence shown in Scheme 11 is probably correct. Whereas electron-withdrawing substituents in the phenyl ring of the *N*-methylanilide decreased the rates for steps b and c, similar substituents in the phenyl ring of the benzoic acid from which the amides were made had little or no effect.[99] This reaction has been exploited as a general method for the production of aromatic aldehydes. Reaction of arenes with chloroformyl-*N*-methylanilide (**26**; Scheme 12) gave the corresponding arylcarboxy-*N*-methylanilides which were reduced to arene aldehydes with $LiAlH_4$.[100] Dialdehydes could be synthesized and some overreduction to the alcohol was observed.

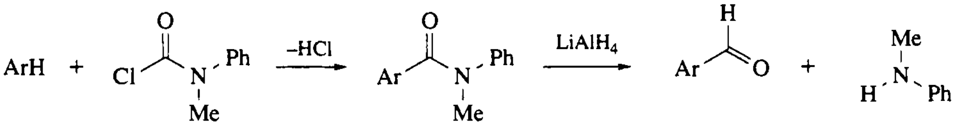

**Scheme 12**

The ideas for delocalization of nitrogen lone pair electron density into an aromatic or heteroaromatic system were pursued through reduction of acylated pyrazoles and imidazoles to aldehydes in high yield. 3,5-Dimethyl-*N*-acylpyrazoles are easy to prepare and afford 77–96% yields of aldehydes with $LiAlH_4$ in diethyl ether at 0 °C.[101] Further examples of this reaction have appeared.[102,103] Although these later publications commented unfavorably on the ability of $LiAlH_4$ to reduce acyl imidazoles to aldehydes (low yields), other workers have demonstrated that yields of 60–80% could be attained at temperatures of –20 to +20 °C in diethyl ether.[104] It was considered that the earlier failure may have been caused by the presence of impurities in the acyl imidazoles. The latter are easy to prepare from the parent carboxylic acid and *N,N'*-carbonyldiimidazole.

Unexpectedly, aziridine was found to be particularly good for the preparation of amides which could be reduced with $LiAlH_4$ in high yield to aldehydes. With butyric acid, the yields of butyraldehyde from various amides were: dimethylamide 25%, diethylamide 22%, diisopropylamide no reaction, *N*-methylphenylamide 58%, piperidide 33%, pyrrolidide 16% and aziridide 88%.[105] A later report indicated that yields of 40–80% of the aldehyde could be attained even with a 100% excess of $LiAlH_4$ if aziridides were used.[106]

With primary or secondary amides, reaction with $LiAlH_4$ is wasteful in that hydrogen gas is evolved and reduction usually proceeds through to the amine. Nevertheless, it has been shown that *t*-butylamides, refluxed with an excess of $LiAlD_4$ for 15 h in diethyl ether, give very good yields of deuteriated aldehydes, RCDO.[107]

Sodium aluminum hydride and its alkoxy derivatives have been used in place of lithium aluminum hydride.[108] In a survey of various types of amide it was found that, with $NaAlH_4$, dimethylamides were most convenient, giving 72–92% yields of aldehydes, with aromatic amides giving better results than aliphatics. Although sodium tri-*t*-butoxyaluminum hydride was more selective for the reduction of amides (being very slow acting), it was pointed out that the use of $NaAlH_4$ was more convenient and less expensive. Sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al) is readily available and has been used to reduce acyl saccharides to aldehydes (Scheme 13). Chlorosaccharin (**27**; Scheme 13) reacts with acids to give the amide (**28**).[109] Alternatively, the same amide can be prepared simply by melting together an acid chloride and sodiosaccharin (**29**).[110] The amide (**28**) has been reduced at 0–5 °C over 5–10 min using Red-Al in benzene; yields of aldehydes reached 65–80%.[110] By utilizing the melt reaction to form the amide (**28**), the conversion of acid chlorides to aldehydes *via* the amide can be made a convenient one-pot reaction.

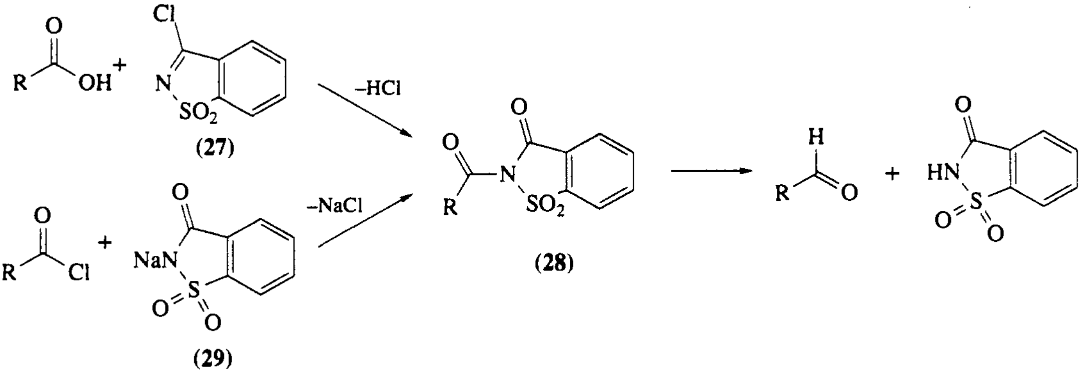

Scheme 13

In attempts to moderate $LiAlH_4$, it was reacted with ethanol or ethyl acetate to give either lithium diethoxyaluminum dihydride (lithium diethoxydihydridoaluminate) or lithium triethoxyaluminum hydride (lithium triethoxyhydridoaluminate).[111] Either of these hydrides when reacted with suitable amides afforded aldehydes in 70–90% yield.[112] It was pointed out that, whereas dimethylamides were not satisfactory with $LiAlH_4$ (see above), the ethoxyhydridoaluminates gave the best results with dimethylamides, although aziridides are better still. Since the latter are not so convenient and are more expensive than dimethylamides, it was concluded that the small increase in yields when using aziridides was not generally worth their use.[112]

It is well known that substitution of hydrogen in $LiAlH_4$ by alkoxy groups moderates its reducing activity and that substitution by alkyl groups increases its reducing capability. Thus, most emphasis on the formation of aldehydes from amides has concentrated on either the type of amide or on decreasing the reducing capacity of hydride reagents. Unusually, one high-yielding synthesis of aldehydes from amides utilizes a trialkyl-substituted $LiAlH_4$. By reacting diisobutylaluminum hydride with *n*-butyllithium (equation 8), lithium *n*-butyldiisobutylhydridoaluminate can be readily prepared.[113] At 0 °C for 2 h, or even at room temperature, this aluminate with diethylamides, pyrrolidides and piperidides gave approximately 95–98% yields of a variety of aldehydes.[113] It is probable that severe steric crowding around the aluminum effectively decreases the availability of the hydride ion so that the analog of the intermediate (**25**; Scheme 11) is not further attacked by more aluminate. It was noted that the reagent is not as selective as might be preferred in that acid chlorides, anhydrides, esters, lactones and thiol esters were all reduced to the alcohol stage; nitriles were reduced to aldehydes very slowly at room temperature.

$$\mathrm{HAlBu^i{}_2} + \mathrm{Bu^nLi} \longrightarrow \mathrm{LiAlHBu^nBu^i{}_2} \qquad (8)$$

Just as considerable effort has been exerted to utilize $LiAlH_4$ or its derivatives for the selective reduction of amides to aldehydes, so too has much exertion gone into the use of diisobutylaluminum hydride. This area has been reviewed.[79,114] With DIBAH itself in diethyl ether at 0 °C, *N*-methylanilides furnish aldehydes in yields of 25–70%, the remainder of the reaction products being mostly amines.[115] The yield of aldehyde drops severely above 0 °C. DIBAH, tempered by the addition of various amines, has been discussed in Section 1.11.2 (ref. 5) and Section 1.11.4 (ref. 60). One of these reagents, bis(4-methyl-1-piperazinyl)aluminum hydride has been recommended for the reduction of dimethylamides (and other amides) to aldehydes in 65–80% yield.[116] The hydride is mild enough for it to be necessary to reflux the amide in diethyl ether with the reagent for several hours. It should be noted that under such conditions acids and esters will be reduced also.

Almost simultaneously, two groups of workers have reported the reduction of 3-acylthiazolidine-2-ones (**30**) to aldehydes with DIBAH (equation 9).[117–120] The acylthiazolidine compounds are made easily from an acyl chloride and thiazolidine-2-thione and then reacted with DIBAH in toluene or $LiAlH(OBu^t)_3$ in tetrahydrofuran at low temperatures; the end of the reduction is indicated by the disappearance of a yellow color. Hydrolysis of the resulting complex (**31**) with acid gives the aldehyde.[117,118] An almost identical reaction used DIBAH in hexane,[119] although initially the wrong structure was assigned to the starting materials.[120] Yields of aldehyde reported by both sets of workers vary between 50% and 90%. Amides can be reduced in the presence of ester functions but low reaction temperatures are necessary to prevent overreduction to the alcohol stage. The reaction appears suitable for aliphatic, aromatic and α,β-unsaturated amides.

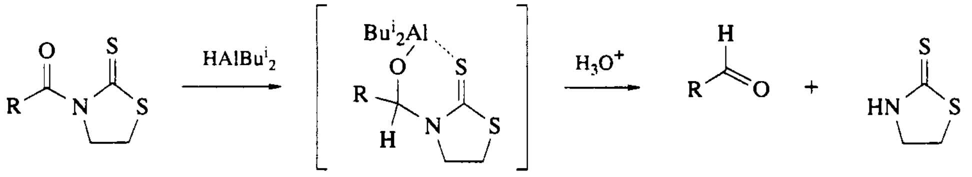

(9)

**(30)** **(31)**

Treatment of *N*,*O*-dimethylhydroxylamine with acid chlorides gives the amides (**32**; Scheme 14) which with lithium aluminum hydride at –78 °C or diisobutylaluminum hydride at 0 °C give aldehydes in about 70% yield.[121]

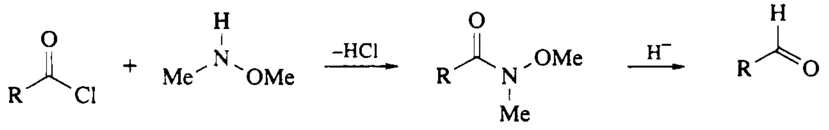

**(32)**

**Scheme 14**

Amides have been converted into imidoyl chlorides and then reduced to aldimines with $LiAlH(OBu^t)_3$, as in Scheme 15.[122] Although not claimed as a synthesis of aldehydes, the aldimines can be hydrolyzed to aldehydes quite readily. Interestingly, the authors say that an excess of the reducing agent can be used because further reduction to the amine requires 24 h, whereas the first stage to the aldimine requires only 30 min at –78 °C.

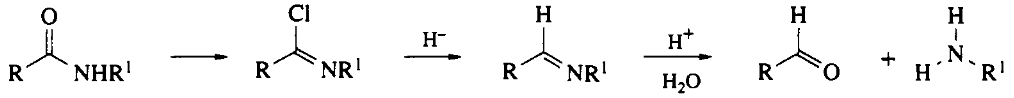

Scheme 15

In an unusual examination of the reducing capacities of several metal hydrides, the yields of aldehydes from carbazole amides were found to change markedly.[123] For one particular carbazide, *N*-9-phenylnona-2,4,6,8-tetraenoylcarbazole, yields of 9-phenylnona-2,4,6,8-tetraenaldehyde with various reducing agents were: $LiAlH_4$ 81%, $LiBH_4$ 69%, $LiBH(OBu^t)_3$ 62%, $LiZnHPh_2$ 45% and $LiBeHPh_2$ 37%. It was concluded that general use of the more readily available $LiAlH_4$ with *N*-acylcarbazoles was a convenient and simple reaction for the preparation of aldehydes, rather than the use of more esoteric hydrides.

Reference has been made already to reviews of the reactions of thexylborane[8] and disiamylborane.[27] Thexylborane reacts slowly with primary amides; tertiary amides are reduced slowly, but although some aldehyde could be isolated from the reaction mixtures there was no obvious break in the uptake of hydride at the aldehyde stage and the reaction proceeded smoothly to alcohol, viz. reduction to aldehyde and to alcohol took place simultaneously. Disiamylborane reacts with primary amides with the release of two molar equivalents of hydrogen gas but no reduction is observed. However, with dimethylamides one hydride equivalent is taken up to yield the aldehyde.

## 1.11.7 LACTAMS AND CYCLIC IMIDES

Comparatively little research has been carried out in this area. The sequence of reductions which might be expected is shown in Scheme 16. Initial reduction of the lactam should give the cyclic amino alcohol or carbinolamine (**33**), which can be expected to exist as a tautomer of the open chain amino aldehyde (**34**). Either of these tautomers can be reduced, the first to the saturated cyclic amine and the second to an open chain amino alcohol. All of these stages have been observed in hydride reductions of lactams. As might be expected, compounds (**33**) and (**34**) are easily polymerized and may not be isolable. Early in the use of $LiAlH_4$, it was found that 1-methyl-2-pyrrolidine and 1-methyl-2-piperidone could be reduced to the corresponding cyclic amino alcohols (amino aldehydes; **33** and **34**; R = Me, *n* = 1,2; Scheme 16) if stoichiometric quantities of hydride reagent were used;[124] the amino alcohols were used in syntheses of hygrine and pelletierine.[125] With an excess of $LiAlH_4$, oxygen free bases were isolated by overreduction of the intermediate amino alcohol/amino aldehyde. Other, similar reductions have been recorded.[126] The oxygenated lactam (**35**) was reduced to the corresponding cyclic amino alcohol but other structurally related amides did not give similar results.[127]

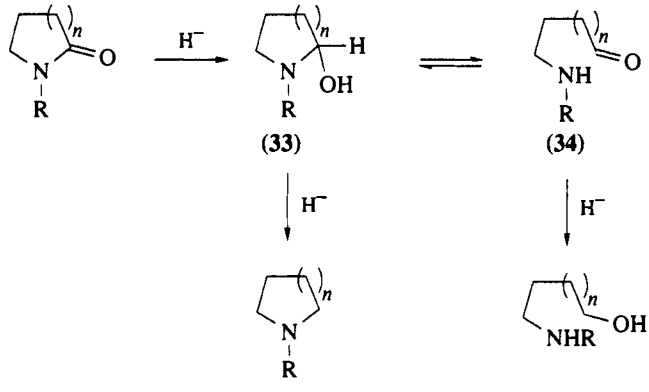

Scheme 16

Reduction of one carbonyl group to a hydroxy group in cyclic imides has been achieved to afford useful synthetic intermediates. The reaction (Scheme 17) is analogous to that shown for lactams (Scheme 16). Thus, reduction of cyclic imides (**36**) with $NaBH_4$ in acidulated water has given good yields of the hydroxy lactam (**37**).[128] Many similar examples by the same research group have appeared.[129] With so-

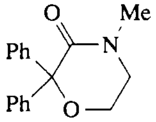

**(35)**

dium borohydride in methanol, phthalimides have been reduced in moderate to good yields to 3-hydroxyphthalimidines, with considerable overreduction to 2-hydroxymethylbenzamide.[130] This overreduction was found with diborane and 1,3,3-trisubstituted succinimides, which gave only lactams.[131] Unexpectedly, only the imide carbonyl group between the nitrogen and the 3-position (more sterically crowded) was found to be affected.

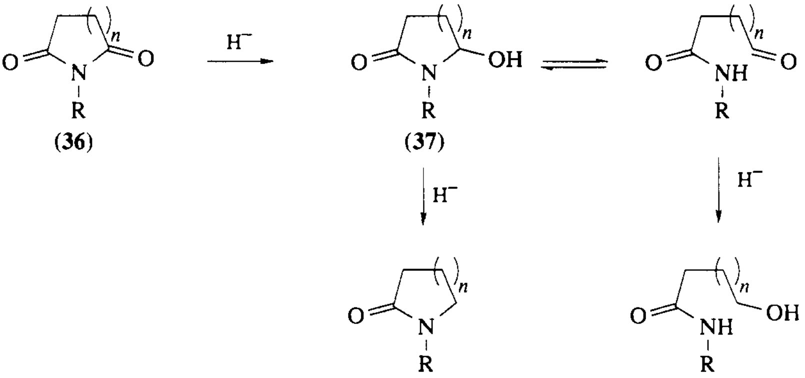

**Scheme 17**

## 1.11.8 NITRILES

Reduction of nitriles to aldehydes with $LiAlH_4$ at low temperatures has been described,[92] but the reaction does not seem to be easy to control and it does not work satisfactorily in many cases. By moderating the activity of $LiAlH_4$ through introduction of alkoxy groups, reduction of nitriles becomes more readily controllable. Reaction of $LiAlH_4$ with three equivalents of ethanol gives $LiAlH(OEt)_3$, which is found to be more reactive than the corresponding $LiAlH(OBu^t)_3$ but less so than $LiAlH_4$ itself.[132] Whereas $LiAlH_4$ reduces benzonitrile to benzaldehyde at 0 °C in 92% yield, with butyronitrile overreduction is observed. $LiAlH(OBu^t)_3$ did not react with nitriles and $LiAlH(OMe)_3$ was too reactive, giving only 15–30% yields of aldehyde. However, in tetrahydrofuran $LiAlH(OEt)_3$ afforded a 59% yield of butyraldehyde from butyronitrile. In a follow-up to this work,[132] it was found that the reaction of $LiAlH(OEt)_3$ with nitriles to give aldehydes was quite general for both aromatic and aliphatic types, but that the best solvent was diethyl ether.[133] In solvents like tetrahydrofuran or diglyme, inferior yields of aldehyde were obtained.

In other work, $NaAlH_4$ was found to be no milder than $LiAlH_4$.[134] Inverse addition of the hydride reagent at 0 °C to benzonitrile gave a 70% yield of benzaldehyde but addition of the same nitrile to the hydride reagent gave 92% of benzylamine. Similarly, it has been found that $NaAlH_4$ reduces aromatic and heterocyclic nitriles to aldehydes in 65–85% yields at 0–30 °C, but that aliphatic compounds give only 15–28% yields.[135]

Again, as with $LiAlH_4$, moderation of the activity of $NaAlH_4$ by incorporation of alkoxy groups has given hydride reagents which are less active in the reduction of nitriles to aldehydes. In view of the readier availability of $LiAlH_4$, there does not seem to be a major advantage in the use of $NaAlH_4$. Sodium triethoxyaluminum hydride has been shown to reduce aromatic nitriles at room temperature to give excellent yields of aldehydes.[136] However, phthalonitrile, 9-cyanofluorene and aliphatic nitriles do not give aldehydes; esters and acid chlorides are reduced to alcohols. Sodium bis(2-methoxyethoxy)aluminum dihydride is soluble in hydrocarbon solvents and more stable in air than many other complex hydrides but reduction of aromatic nitriles was shown to give amines.[137] Later research revealed that the solvent played a major role in this reduction and heterocyclic nitriles could be reduced to aldehydes in about 50% yield.[138] Use of sodium diisobutylaluminum dihydride at –70 °C gave only moderate yields of aldehydes.[139]

DIBAH has long been known to partially reduce nitriles. In diethyl ether, heptane or benzene, reaction of nitriles with DIBAH gives aldimines directly bonded to aluminum (**38**; Scheme 18).[140] These aldiminoaluminum compounds can be isolated by direct distillation from the reaction mixture or can be stirred with acidified water for 30 min to give typical yields of 50–90% of aldehydes. Later, it was shown that a 2:1 ratio of hydride to benzonitrile gave 82% of benzaldehyde but a 1:1 ratio gave 90%; the other major product of reduction was benzalbenzylamine.[141] In a deft adaptation of the intermediate formation of aldiminoaluminum compounds, nitriles have been reduced to this stage with DIBAH (Scheme 18) and then reacted with lithium diethylamide or *n*-butyllithium prior to reaction with an alkyl halide to give ketones (**39**).[142]

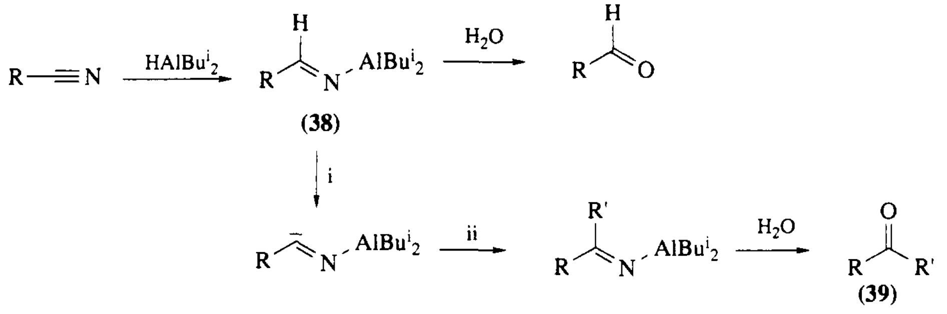

i, $LiNEt_2$ or $Bu^nLi$; ii, R'X, X = halide, sulfonate

**Scheme 18**

Nitrilium salts (**40**; equation 10) can be prepared from nitriles and triethyloxonium fluoroborate. Early workers concluded that the nitrilium salts could be reduced to amines but that the reduction could not be stopped at the aldehyde (aldimine) stage.[143] Later, it was demonstrated that reduction of the nitrilium salts with $NaBH_4$ was rapid and did give the corresponding amine, but with triethylsilane yields of 60–90% of both aliphatic and aromatic aldehydes were obtained.[144] Triethylsilane is a mild reagent which reduces carbocations but neutral compounds are generally not reduced and so overreduction is not a problem with this reagent. Formation of the nitrilium salts with triethyloxonium fluoroborate is slow but can be speeded up by the use of iron(III) chloride (Scheme 19). There were some notable exceptions to aldehyde formation with some aromatic nitriles.

$$R{-}{\equiv}N \;+\; Et_3\overset{+}{O}\,BF_4^- \longrightarrow R{-}{\equiv}NEt\;BF_4^- \;+\; Et_2O \qquad (10)$$

**(40)**

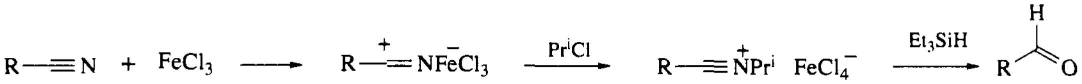
R—≡N + FeCl3
$R{-}{\equiv}\overset{+}{N}\overset{-}{Fe}Cl_3$
$Pr^iCl$
$R{-}{\equiv}\overset{+}{N}Pr^i\;FeCl_4^-$
$Et_3SiH$
H
R
O

**Scheme 19**

Disiamylborane and thexylborane react very slowly with nitriles and give only low yields of aldehydes.[27,9]

## 1.11.9 MISCELLANEOUS REDUCTIONS TO ALDEHYDES

Several related reactions involve reduction of cyclic carboxylic acid derivatives to masked aldehydes which resist further reduction but can be converted into the required aldehydes by acid hydrolysis. In a series of papers, it was established that carboxylic acids could be converted into dihydro-1,3-thiazines or dihydro-1,3-oxazines which could be reduced by $NaBH_4$ in weakly acidic ethanol. Thus, as shown in Scheme 20, dihydro-1,3-thiazines (**41**) were reduced to tetrahydro-1,3-thiazines (**42**) in yields of 66–84%. The resulting tetrahydro compounds could be hydrolyzed to aldehydes by aqueous acid.[145] In a later publication, these workers showed that there was little evidence for ring opening during reduction and that other methods of reduction (*e.g.* hydrogenation over Pt, Pd or Rh or use of dissolving metals such as Zn, Sn or Na) were totally unsuccessful.[146] In closely similar work, reduction of 5,6-dihydro-4*H*-

1,3-oxazines (**43**; Scheme 21) with $NaBH_4$ at –30 °C and pH 7 gave the corresponding tetrahydrooxazines (**44**) which could be hydrolyzed in aqueous acetic acid to provide the aldehydes:[147] overall yields were moderate to good. Without pH control or at higher temperatures ring-opened products (amino alcohols) were obtained, sometimes predominantly. Several other papers[148] describe the use of this method which was held to be useful on a large scale, unlike many other conversions of carboxylic acids into aldehydes. In a novel development of this aldehyde synthesis, the authors showed that the oxazines could be used as two-carbon synthons.[149] For example, the dihydro-1,3-oxazines (**45**; Scheme 22) were lithiated with *n*-butyllithium and reacted with an epoxide to give the oxazines (**46**). Reduction with $NaBH_4$ and hydrolysis afforded γ-hydroxy aldehydes (**47**) in good overall yields.[150]

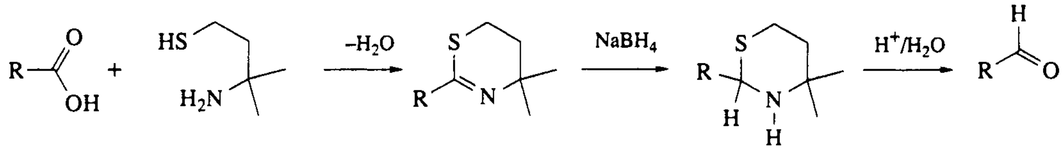

**(41)** **(42)**

**Scheme 20**

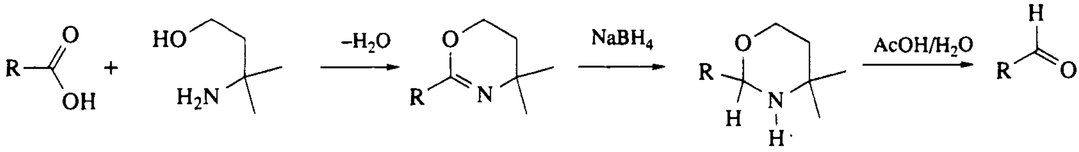

**(43)** **(44)**

**Scheme 21**

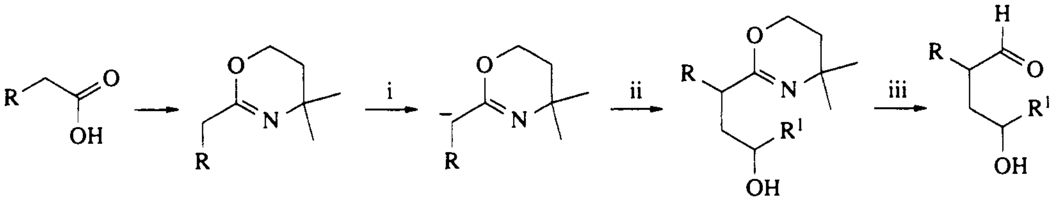

**(45)** **(46)** **(47)**

i, $Bu^nLi$; ii, $R^1$ 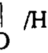 /$H^+$; iii, $NaBH_4/H_3O^+$

**Scheme 22**

(*S*)-Triazolium salts (**49**; Scheme 23), prepared from an acid chloride and the thiohydrazo compound (**48**), have been reduced to the hydro compound (**50**) and then hydrolyzed in dilute sulfuric acid to the aldehyde.[151] Overall yields of aldehyde are reported to be 46–90% and a variety of other functional groups can be supported such as alkene, halogen, nitro, ketone and ester; there can be one or two side chains on the α-carbon or it can be part of an alicyclic system.

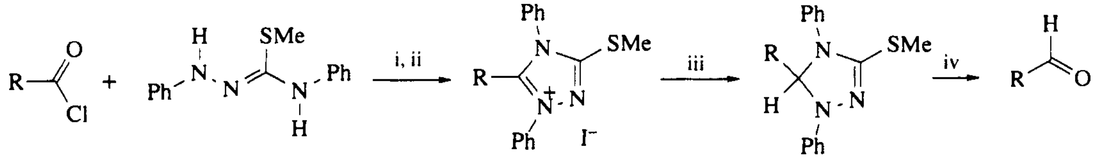

**(48)** **(49)** **(50)**

i, dioxane, reflux 20 min; ii, exchange $I^-$ for $Cl^-$; iii, $NaBH_4$; iv, aq. $H_2SO_4$

**Scheme 23**

In conceptually much the same sort of reaction, carboxylic acids have been treated with *o*-phenylenediamine and then methyl iodide to yield benzimidazolium salts (**51**; Scheme 24). Reduction of the latter with $NaBH_4$ gives the hydro compound (**52**), which can be hydrolyzed by dilute acid to give the aldehyde.[152] For the few aldehydes described, yields were about 70%.

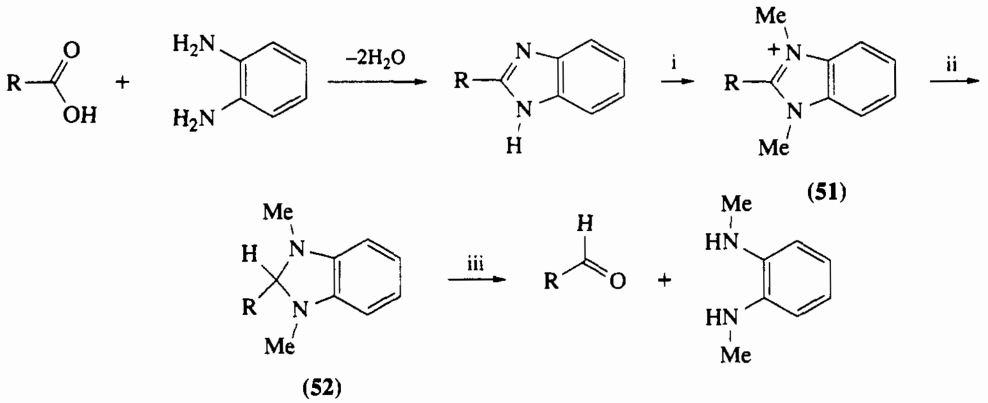

(**51**)

(**52**)

i, NaOMe/MeOH/MeI; ii, $NaBH_4$; iii, 4% aq. HCl

**Scheme 24**

2-Substituted-1,3-benzoxathiolium tetrafluoroborates (**53**; Scheme 25) can be prepared readily from acids, anhydrides, esters and trihalomethyl compounds.[153,154] The thiolium salts can be reduced easily with $NaBH_4$ in acetonitrile at 0–20 °C to give aldehydes in 71–91% overall yields.

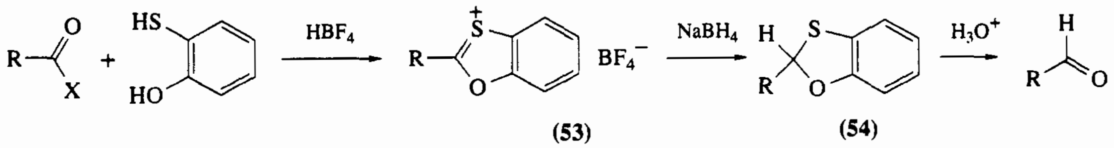

(**53**) (**54**)

X = OH, $OR^1$, $OCOR^1$, $CCl_3$

**Scheme 25**

Two methods for the formation of aldehydes embody C—C bond formation and then its cleavage by a reverse aldol reaction after reduction, and a third involves similar formation and breakage of a C—P bond. Reaction of esters with the sulfur compound (**55**; Scheme 26) affords ketones (**56**) which can be reduced with $NaBH_4$ at 0 °C to the alcohols (**57**). Simply warming this alcohol, or better, treating it with aqueous potassium carbonate, gives the aldehyde in about 95% yield for aromatic compounds but somewhat less for aliphatic; dialdehydes can be obtained from diacids.[155] Acylmalonates (**58**; Scheme 27)

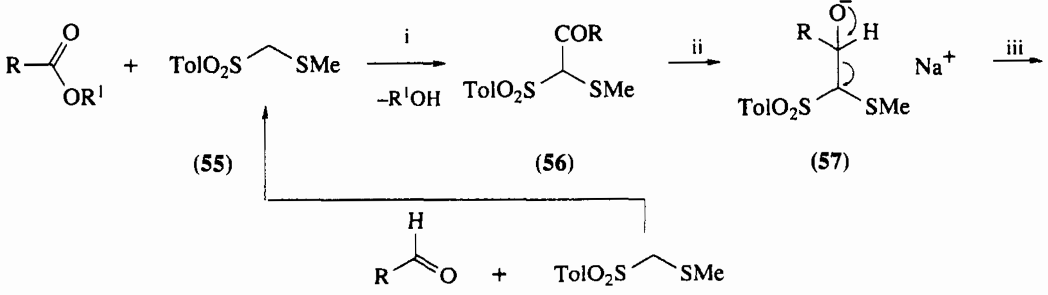

(**55**) (**56**) (**57**)

i NaH; ii, $NaBH_4$; iii, base/$H_2O$

**Scheme 26**

have been reduced with $NaBH_4$ at 0 °C to give alcohols (**59**) which, under the alkaline conditions, eliminate malonate to give aldehydes in moderate to good overall yields.[156] It is worth noting that malonates can give small yields of aldehydes directly during their reduction with $LiAlH_4$.[157] Finally, reaction of acyl halides with trialkyl phosphites (Scheme 28) gives acyl phosphites (**60**) which can be reduced with buffered $NaBH_4$ to the alcohols (**61**); under alkaline conditions, these alcohols eliminate phosphite to give aldehydes in high yields.[158]

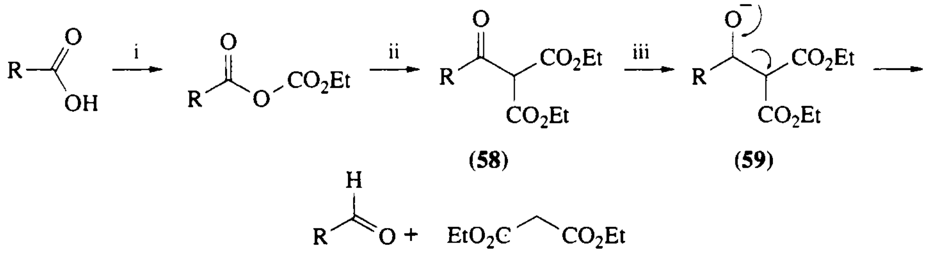

i, $ClCO_2Et$; ii, $Mg[CH(CO_2Et)_2]_2$; iii, $NaBH_4$

**Scheme 27**

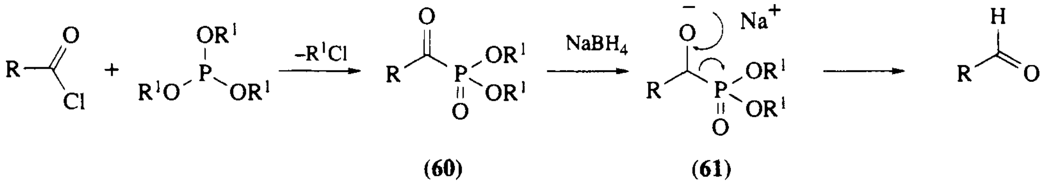

**Scheme 28**

## 1.11.10 REVIEWS AND BOOKS

The following articles are recommended because they contain specific discussions of one or more of the above sections. This list is not meant to be exhaustive and many good books and reviews which touch on reduction methods generally have been omitted simply because of their generality. The position of articles in the following list is not intended to be in order of priority or preference.

(a) E. Mosetigg, *Org. React. (N.Y.)*, 1954, **8**, 218: discusses the then-existing major methods for the conversion of carboxylic acids to aldehydes and leads up to first uses of $LiAlH_4$.

(b) N. C. Gaylord, 'Reduction with Complex Metal Hydrides', Interscience, New York, 1956: includes much of the early chemistry of hydrides including some reactions leading to aldehydes.

(c) E. R. H. Walker, *Chem. Soc. Rev.*, 1976, 23: lists all aluminum and boron hydrides used for the reduction of organic compounds. A table of functional group selectivity is given.

(d) H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567: a useful, readable review of hydride reductions with $NaBH_4$ and $LiAlH_4$ and their derivatives.

(e) M. Hudlicky, 'Reductions in Organic Chemistry', Horwood, Chichester, 1984: this gives a good account of many reduction methods with useful, practical details

(f) M. Pereyre, J. Quintard and A. Rahm, 'Tin in Organic Synthesis', Butterworths, London, 1987, pp. 76, 95: covers reductions with stannanes in organic synthesis.

(g) W. P. Neumann, *Synthesis*, 1987, 665: discusses the reduction of acyl halides to aldehydes with tri-*n*-butyltin hydride.

(h) 'Compendium of Organic Synthetic Methods', Wiley, New York, I. T. Harrison and S. Harrison, Vol. 1, 1971; vol. 2, 1974; L. S. Hegedus and L. G. Wade, vol. 3, 1977; L. G. Wade, vol. 4, 1980; L. G. Wade, vol. 5, 1984. Excellent tabulations of interconversions of functional groups, including carboxylic acids and esters to aldehydes, are contained in these volumes.

(i) Sections on oxidation and reduction by many different authors in 'Organic Reaction Mechanisms', Wiley, Chichester. This series stretching over many years includes most of the mechanistic work on hydride reductions from 1966.

(j) A. Hajos, *Methoden Org. Chem. (Houben-Weyl)*, 1981, **IV/1d**, 1. This is an excellent comprehensive review, entitled 'Metal Hydrides or Complex Hydrides as Reducing Agents', with many leading references and selected practical details (in German).

(k) A. Hajos, 'Complex Hydrides', Elsevier, Amsterdam, 1979: a comprehensive examination of the reducing properties of a whole range of mostly aluminum and boron hydrides. Functional group selectivity is considered.
(l) E. Negishi, 'Organometallics in Organic Synthesis', Wiley, New York, 1980, vol. 1, pp. 343, 377: some reductions with alanes and boranes are covered.
(m) 'Comprehensive Organometallic Chemistry', ed. G. Wilkinson, Pergamon, Oxford, 1982: contains many specific but scattered references to reduction listed under hydride types and substrate groups.
(n) E. Negishi and H. C. Brown, *Synthesis*, 1974, 77: a review of reactions of thexylborane, including reduction of carboxylic acids and derivatives.
(o) H. C. Brown, D. B. Bigley, S. K. Arora and N. M. Yoon, *J. Am. Chem. Soc.*, 1970, **92**, 7161: a useful comparison of functional group reactivity towards disiamylborane.
(p) J. Malek and M. Cerny, *Synthesis*, 1972, 217: a general review of uses of alkoxyaluminum hydrides as reducing agents for a wide range of functional groups.
(q) E. Winterfeldt, *Synthesis*, 1975, 617: a discussion of reductions in which diisobutylaluminum hydride or triisobutylaluminum are the preferred reagents in synthesis with emphasis on functional group selectivity.
(r) 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1979: reduction discussed under a wide range of headings but mostly by functional group with a variety of reagents, including hydrides.

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# 1.12
# Reduction of Carboxylic Acids to Aldehydes by Other Methods

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## 1.12.1 INTRODUCTION

Because so many of the recent developments in reduction methodology have involved metal hydride reducing agents, this chapter inevitably has an old-fashioned flavor. Most of the methods described below originated many years ago, and many of them do not figure prominently in the current literature. However, this is not to say that they have no value. In many cases they are economical and suitable for large scale use, and it is quite likely that the best way to make substantial amounts of a simple aldehyde (especially an aromatic one) will be found in this chapter. Moreover, there are some cases where recent improvements, which may not be widely appreciated, have given a classical method a new lease of life. The reader is directed particularly to the 'amine-modified Rosenmund' described in Section 1.12.3.

The question of demarcation between this and the previous chapter deserves some comment. It is not always clear whether a reduction method involves a metal hydride or not. Catalytic hydrogenation, for example, presumably involves species with metal–hydrogen bonds, although it is not normally regarded as a 'metal hydride method'. However, a clear distinction can generally be made on the basis of the source of the stoichiometric reducing equivalents, and this has been the guideline used. Thus, the methods discussed in this chapter are those in which the reducing equivalents are supplied by hydrogen gas, organic molecules, metals, low valent metal salts or (nonhydride) complexes, or an electrode. Note, however, that it has proved convenient to depart from this principle at one point. In Section 1.12.3, a number of low valent metal complex reducing agents are discussed together, in spite of the fact that some of them do behave as hydride donors.

As in the previous chapter, the material will be organized according to substrate category, starting with the carboxylic acids themselves and then moving on to the various derivatives. The methods have been placed generally in sections corresponding to the immediate precursors of the aldehydes. Thus, the hydrolysis of Reissert compounds appears under amides as opposed to acyl chlorides, and the Sonn–Müller appears under imidoyl chlorides and not amides.

## 1.12.2 CARBOXYLIC ACIDS

The central problem in the reduction of carboxylic acids and their derivatives to aldehydes is the avoidance of overreduction to primary alcohols. The difficulty is particularly acute when, as in the case of the carboxylic acids themselves, the substrates are not especially reactive towards reducing agents. Thus there are few nonhydride methods of reducing carboxylic acids to aldehydes, and none which are routinely used. Those which are available generally have some specific feature which results in the trapping or protection of the product aldehydes.

Probably the most generally useful methods are those involving: (i) $\mathrm{Bu^iMgBr}$ with $[\mathrm{Cp_2TiCl_2}]$ as a catalyst;[1] and (ii) $\mathrm{Li/MeNH_2}$.[2] The former is thought to occur by the mechanism shown in Scheme 1, in which the aldehyde product is protected as adduct (**1**), and only released on hydrolysis. As shown in Table 1, the method has been applied with reasonable success to a number of aliphatic acids and to benzoic acid (although in the latter case, some overreduction did occur). However, it failed completely with cinnamic acid.

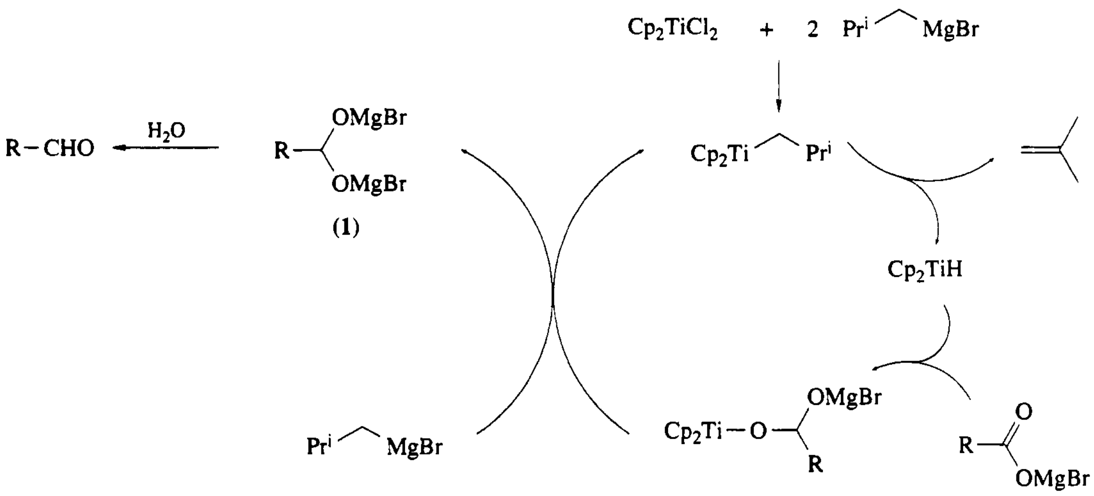

**Scheme 1**

**Table 1** Yields of Aldehydes RCHO from $\mathrm{RCO_2H}$ using $\mathrm{Bu^iMgBr/[Cp_2TiCl_2]}$[1]

| *R* | *Yield* (%) |
|---|---|
| Hexyl | 73 |
| PrCHMe | 65 |
| Cyclohexyl | 59 |
| $\mathrm{PhCH_2}$ | 48 |
| Phenyl | 55 |
| PhCH═CH | 0 |

The success of the method employing $\mathrm{Li/MeNH_2}$ again arises from the formation of the aldehyde in a protected form. In this case it is the amino alcohol salt (**2**; Scheme 2). As shown in Scheme 2, the reaction mixture is quenched with saturated aqueous ammonium chloride and may then be extracted with pentane, to yield an imine, or with ether and washed with acid to give the aldehyde. The imine is clearly not the protected form of the aldehyde, as it is reduced to the corresponding secondary amine under the conditions of the reaction. The reaction succeeds for aliphatic saturated acids, and also for one example containing an isolated C═C double bond (Table 2). However, additional reduction occurs with substrates containing aromatic rings or conjugated double bonds.

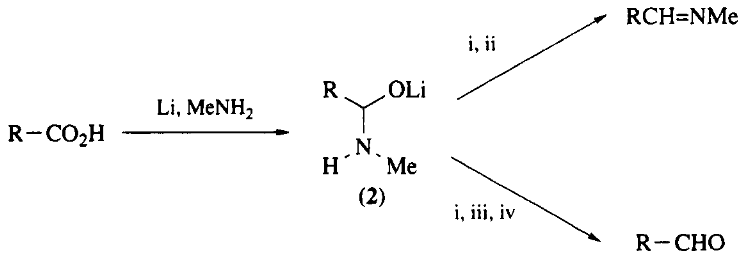

i, sat. aq. NH$_4$Cl; ii, pentane extraction; iii, ether extraction; iv, wash with aq. HCl

**Scheme 2**

**Table 2** Yields of Aldehydes RCHO from RCO$_2$H using Li/MeNH$_2$[2]

| *R* | *Yield* (%) |
|---|---|
| Butyl | 66 |
| Heptyl | 59 |
| Nonyl | 61 |
| Undecyl | 61 |
| Tridecyl | 84 |
| Bu$^t$(CH$_2$)$_2$ | 62 |
| Me(CH$_2$)$_8$CH═CH(CH$_2$)$_6$ | 60 |

There has been considerable research into the electrolytic reduction of aromatic carboxylic acids to the corresponding aldehydes. A general procedure has been described[3] in which key elements are the use of the ammonium salt of the acid, careful control of the pH and the presence of an organic phase (benzene) to extract the aldehyde and thus minimize overreduction. The method appears to work best for relatively acidic substrates; for example, salicylaldehyde was obtained in 80% yield. Danish workers have shown that, under acidic conditions, controlled electrolytic reductions are possible for certain pyridine-, imidazole- and thiazole-carboxylic acids.[4] In these cases, it is thought that the product aldehydes are protected by geminal diol formation. A chemical method which is closely related to electrolysis is the use of sodium amalgam as reductant. Although not widely used, it was successfully employed in the synthesis of a fluorinated salicylaldehyde.[5]

A classical method for preparing aldehydes from carboxylic acids is treatment with formic acid in the vapour phase over a metal oxide catalyst at temperatures of 300–400 °C. For example, aldehyde (**3**) was synthesized from the corresponding acid in 78% yield (but with only 40% conversion) using manganese(II) oxide as catalyst.[6] Closely related methods using hydrogen as reductant have been reported in patents from a number of industrial laboratories. Good selectivities and conversions are claimed, examples being the synthesis of (**4**) over ZrO$_2$ (99% selectivity, 81% conversion),[7] of benzaldehyde over MnO$_2$ (95% selectivity, 91% conversion)[8] and of pivalaldehyde (**5**) over a complex mixture of metal oxides supported on alumina (100% selectivity, 73% conversion).[9]

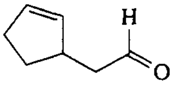

(**3**)

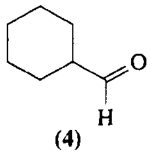

(**4**)

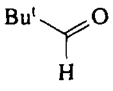

(**5**)

Finally, it may be useful to note a method which, although not actually a reduction, has the same overall effect of transforming RCO$_2$H to RCHO. As shown in Scheme 3,[10] the acid (**6**) is doubly deprotonated then treated with a formiminium salt (**7**). Carbon–carbon bond formation is followed by loss of CO$_2$ and methoxide to give enamine (**8**), which can be isolated or transformed by acid hydrolysis to the corresponding aldehyde. The scope and efficiency of the method are difficult to judge accurately, as the authors were principally interested in the synthesis of particular enamines, but it seems likely to be quite useful for acids (**6**) where $R^1$, $R^2$ = alkyl or $R^1$ = H; $R^2$ = aryl, secondary alkyl or tertiary alkyl.

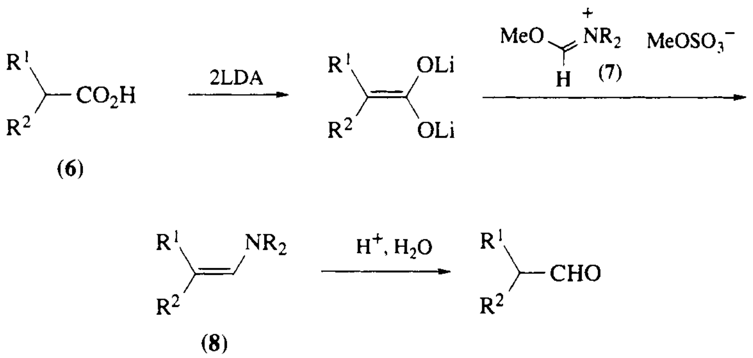

**Scheme 3**

## 1.12.3 ACYL CHLORIDES

As acyl chlorides are the most reactive of the common acid derivatives, it is not surprising that they are the easiest to reduce. All the reducing methods described in the rest of this chapter are, in a sense, methods for the reduction of acyl chlorides, as they all involve derivatives which can be made from acid chlorides. Moreover, it is possible to find reducing systems sufficiently mild to convert the acyl chlorides directly to aldehydes without then reducing the aldehydes to alcohols.

In the area of nonhydride reducing agents, the principal means of accomplishing this task is the Rosenmund reduction,[11] the catalytic hydrogenation of acyl chlorides. Before the advent of metal hydride reducing agents, this was probably the principal reductive method of aldehyde synthesis. Although it may seem outdated, modern developments have greatly improved it, so that it still merits serious consideration.

The classical Rosenmund reaction is discussed in depth in an article by Mosettig and Mozingo.[12] It was most usually accomplished by passing hydrogen gas through a refluxing solution of the substrate in toluene or xylene, in the presence of the catalyst. The hydrogen chloride formed was collected by passage through water, and was titrated occasionally in order to follow the progress of the reaction. The usual catalyst was palladium on barium sulphate, with a 'regulator' to moderate the catalytic activity and prevent overreduction (although the regulator was often omitted, especially for nonaromatic substrates). The most common regulator was quinoline-S, a crude preparation of thioquinanthrene obtained by heating together quinoline and elemental sulfur. Other sulfur-containing compounds could also be used, and later workers recommended tetramethylthiourea.[13] Table 3 shows a selection of yields and conditions, including two examples (the first two entries) which are recorded in *Organic Syntheses*.[14,15]

**Table 3** Yields and Conditions for Selected 'Classical' Rosenmund Reductions of Acyl Chlorides RCOCl with Pd–$BaSO_4$ as Catalyst

| *R* | *Solvent* | *Temperature* (°C) | *Regulator* | *Yield* (%) |
|---|---|---|---|---|
| β-Naphthyl | Xylene | 150 | Quinoline-S | 84 |
| 2,4,6-Trimethylphenyl | Xylene | Reflux | None | 70–80 |
| *p*-Nitrophenyl | Xylene | 150 | Quinoline-S | 91 |
| 3,5-Dimethoxy-4-(ethoxycarbonyl)phenyl | Toluene | 120–125 | None | 49 |
| 3-Furyl | Xylene | Reflux | None | 55 |
| $MeO_2C(CH_2)_3$ | Xylene | 140–150 | Quinoline-S | 52 |
| $Me(CH_2)_{16}$ | Xylene | 150 | None | 17–21 |
| PhCH=CH | Xylene | 122 | Thioquinanthrene, quinoline-S | 50–60 |

The classical Rosenmund reduction is quite broad in scope, and can be applied to fairly complex molecules. Not included in Table 3 are several examples giving terpenoid aldehydes which occur in yields of up to 88%.[12] Nevertheless, there are serious limitations. The yields are variable, being affected by side reactions such as overreduction and decarbonylation (Scheme 4). Moreover, the high temperatures required and the production of free hydrogen chloride are obvious disadvantages.

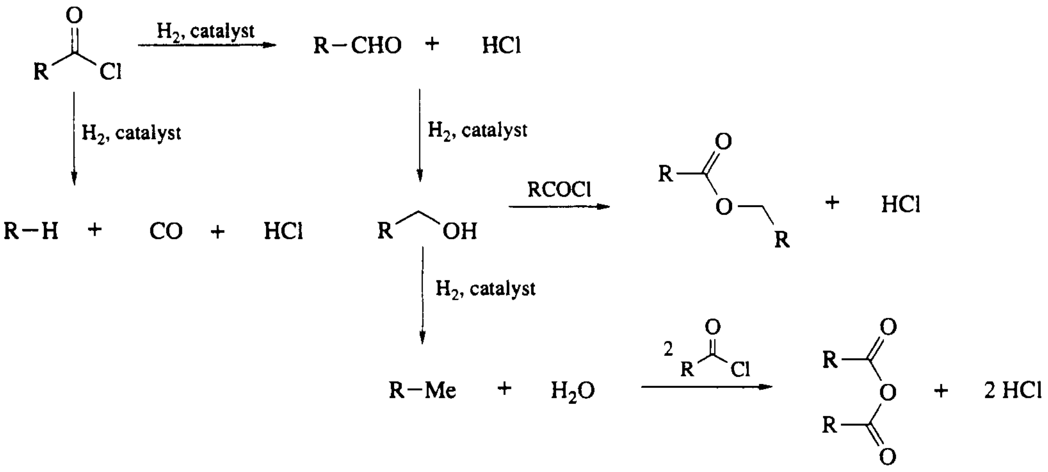

Scheme 4

However, in 1944 it was reported by Sakurai and Tanabe that with acetone or ethyl acetate as solvent, Pd–$BaSO_4$ as catalyst (no regulator) and in the presence of *N,N*-dimethylaniline as an HCl acceptor, the Rosenmund reduction occurs cleanly and rapidly at room temperature.[16] More recently, three other groups have reported mild and effective variants of the Rosenmund. In each case the key element appears to be the use of a basic additive to remove the HCl produced by the reduction and possibly also to regulate the catalyst activity. All the methods involve the use of closed hydrogenation apparatus and thus have a clear safety advantage over the classical procedure.

In the method of Rachlin *et al.*,[17] the basic additive is sodium acetate, the catalyst 10% palladium on carbon, the solvent toluene and the temperature 35–40 °C. The reaction is carried out in a medium pressure hydrogenation apparatus at 50 p.s.i. (1 p.s.i = *ca.* 6.9 kPa) of hydrogen. Several aromatic aldehydes have been produced in good yields, including examples containing nitro and benzyloxy groups.

Peters and van Bekkum[18,19] noted that the original method of Sakurai and Tanabe suffered from problems due to the competitive reduction of the *N,N*-dimethylaniline. In their modified procedure, diisopropylethylamine is used as HCl acceptor/catalyst regulator, and 10% palladium on carbon as catalyst. As for the Sukarai–Tanabe procedure, the reaction is carried out at room temperature and atmospheric pressure in acetone[18] or ethyl acetate.[19] In the latter solvent, which is said to be marginally preferable, the reduction is complete within minutes for aliphatic acyl chlorides, although aromatic substrates may take several days.

In the third procedure, due to Burgstahler *et al.*,[20] the basic additive is 2,6-dimethylpyridine. For aliphatic acyl chlorides, THF is used as solvent and 10% palladium on carbon or 5% Pd–$BaSO_4$ as catalyst. Aromatic acyl chlorides require benzene as solvent, 10% palladium on carbon/quinoline-S as catalyst and a raised temperature.

Table 4 lists most of the results reported in two papers by Peters and van Bekkum[19] and Burgstahler *et al.*[20] The reactions were carried out at room temperature except where otherwise specified, and the yields, where given, are of purified product (with the exception of entry 23). It can be seen that the 'amine-modified Rosenmund' is quite broad in scope, giving clean conversions and good to excellent yields. Ester and keto groups are tolerated. Acyl chlorides containing either C=C double bonds or aromatic nitro groups can be reduced selectively to aldehydes, provided appropriate conditions are chosen; only the method of Peters and van Bekkum (Table 4, entries 1–15) is suitable for nitroaromatics, and the conditions employing 10% palladium on carbon, 2,6-dimethylpyridine and THF (entries 16–26) were found to hydrogenate C=C double bonds. Notable are the successful syntheses of hindered aldehydes such as (**9**) (entry 26) and (**10**).[18] Tertiary acyl chlorides are particularly inclined to decarbonylation during the Rosenmund reduction, and, indeed, application of the classical conditions to the precursor of (**10**) gave only *t*-butylcyclohexane.[18]

The mechanism of the Rosenmund reduction has attracted occasional attention. The discovery of Tsuji *et al.*[21] that palladium metal can catalyze the conversion of acyl chlorides (**11**) into alkenes (**13**), carbon monoxide and HCl, presumably *via* intermediates of the form (**12**; Scheme 5), suggests that (**12**) may also be an intermediate in the Rosenmund reaction. Consistent with this suggestion is the observation that the unsaturated acyl chloride (**14**) is converted to phenol by a palladium catalyst.[22]

Affrossman and Thomson[13] used a $^{14}C$-labeling experiment to confirm that overreduction in the Rosenmund is a result of further reduction of the aldehyde product, and not a competing, direct reduction

**Table 4** Aldehydes Prepared by Modified Rosenmund Reduction

| *Entry* | *R* | *Catalyst* | *HCl acceptor* | *Solvent* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | Heptanal | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 2 | c-$\mathrm{C_6H_{12}CHO}$ | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 3 | Benzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 4 | 4-Methylbenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 5 | 4-*t*-Butylbenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 6 | 4-Methoxybenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 7 | 4-Chlorobenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 8 | 3-Chlorobenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 9 | 4-Nitrobenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 10 | 2,4,6-Trimethylbenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 11 | 3,5-Di-*t*-butylbenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 12 | 3,4,5-Trimethoxybenzaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 13 | Ferrocenylcarbaldehyde | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 14 | $\mathrm{Ph(CH_2)_2CHO}$ | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 15 | (*E*)-PhCH═CHCHO | 10% Pd–C | $\mathrm{Pr^i_2NEt}$ | EtOAc | a | 19 |
| 16 | Dodecanal | 10%Pd–C | 2,6-Dimethylpyridine | THF | 95 | 20 |
| 17 | Octadecanal | 10%Pd–C | 2,6-Dimethylpyridine | THF | 96 | 20 |
| 18 | $\mathrm{OCH(CH_2)_4CHO}$ | 10%Pd–C | 2,6-Dimethylpyridine | THF | 74 | 20 |
| 19 | $\mathrm{OCH(CH_2)_8CHO}$ | 10% Pd–C | 2,6-Dimethylpyridine | THF | 77 | 20 |
| 20 | $\mathrm{MeCO(CH_2)_6CHO}$ | 10% Pd–C | 2,6-Dimethylpyridine | THF | 85 | 20 |
| 21 | $\mathrm{Pr^iO_2C(CH_2)_2CHO}$ | 10% Pd–C | 2,6-Dimethylpyridine | THF | 89 | 20 |
| 22 | $\mathrm{Pr^iO_2C(CH_2)_3CHO}$ | 10% Pd–C | 2,6-Dimethylpyridine | THF | 89 | 20 |
| 23 | 3-Oxo-5-octanolide | 10% Pd–C | 2,6-Dimethylpyridine | THF | 94 | 20 |
| 24 | 2-Ethylhexanal | 10% Pd–C | 2,6-Dimethylpyridine | THF | 87 | 20 |
| 25 | c-$\mathrm{C_5H_9CHO}$ | 10% Pd–C | 2,6-Dimethylpyridine | THF | 78 | 20 |
| 26 | **(9)**[b] | 10% Pd–C | 2,6-Dimethylpyridine | THF | 92 | 20 |
| 27 | (*Z*)-n-$\mathrm{C_8H_{17}CH{=}CH(CH_2)_7CHO}$ | 5% Pd–$\mathrm{BaSO_4}$ | 2,6-Dimethylpyridine | THF | 96 | 20 |
| 28 | (*E*)-PhCH═CHCHO | 5% Pd–$\mathrm{BaSO_4}$ | 2,6-Dimethylpyridine | THF | 84 | 20 |
| 29 | Benzaldehyde[c] | 10% Pd–C/quinoline-S | 2,6-Dimethylpyridine | $\mathrm{C_6H_6}$ | 93 | 20 |
| 30 | 4-Chlorobenzaldehyde[c] | 10% Pd–C/quinoline-S | 2,6-Dimethylpyridine | $\mathrm{C_6H_6}$ | 77 | 20 |

[a] Reaction followed to completion by g.c. Negligible overreduction and decarbonylation.[19] [b] Carried out at 0 °C. [c] Carried out at 40–50 °C.

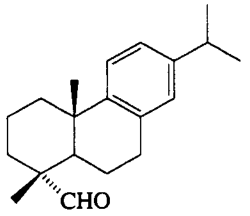

**(9)**

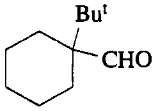

**(10)**

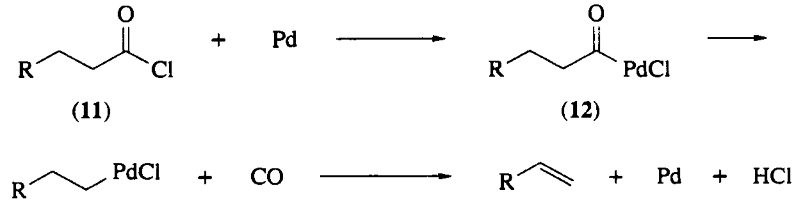

**(11)** **(12)** **(13)**

**Scheme 5**

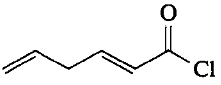

**(14)**

of the acid chloride. They also investigated the nature of the poisoning of the catalyst in the classical Rosenmund, without being able to draw any firm conclusions. More recently, McEwen *et al.*[23] argued that, considering the wide range of catalyst regulators employed in the Rosenmund, the role of the regulators might not be to form specific chemical bonds with the palladium but rather to alter its physical structure. They found that: (i) treatment of palladium on silica with indole gave an effective Rosenmund catalyst which did not, however, contain any indole; (ii) treatment of palladium black with triethylamine at 150 °C for 20 h causes rearrangement into metallic palladium with a much lower surface area; and (iii) ultrapure palladium powder is a catalyst (though somewhat inactive) for the conversion of benzoyl chloride to benzaldehyde at 0 °C.

The next group of methods to be considered represents a far more recent development than the Rosenmund: the use of the anionic metal complexes $[Fe(CO)_4]^{2-}$, $[HFe(CO)_4]^-$, $[HCr(CO)_5]^-$, $[HW(CO)_5]^-$ and $[CpV(CO)_3H]^-$. Although it is only the first of these reagents which is clearly a nonhydride reducing agent, they are all considered here because of their close structural relationship and because of possible mechanistic similarities (*vide infra*).

The method involving $[Fe(CO)_4]^{2-}$ was reported first by Watanabe *et al.*[24] The actual reagent used is the disodium salt of the anion, formed as a solution in THF by the reduction of $[Fe(CO)_5]$ by sodium amalgam. As shown in Scheme 6, the anion reacts with acyl chlorides to give acyltetracarbonylferrates (**15**), which can be decomposed with acetic acid to yield the corresponding aldehydes. This method has been applied to give simple aldehydes, typical examples and yields (by gas chromatography) being benzaldehyde 95%, *o*-chlorobenzaldehyde 65% and isobutyraldehyde 71%. Subsequently, an essentially similar procedure was reported by Siegl and Collman.[25] These authors placed more emphasis on the structural organometallic chemistry involved, and were able to isolate the intermediate anions (**15**) as salts of $[Ph_3P{=}N{=}PPh_3]^+$.

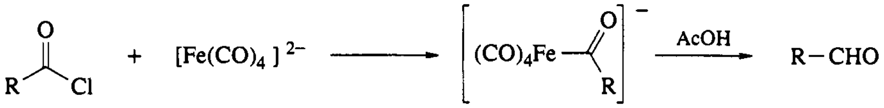

**(15)**

**Scheme 6**

The remainder of the anionic metal complexes, all of which bear a hydrogen, have been employed subsequently. The most convenient experimentally appears to be the $[HFe(CO)_4]^-$ anion, employed either as the $Me_4N^+$ salt[26] or in immobilized form on an anion exchange resin.[27] The former reagent is readily synthesized from $[Fe(CO)_5]$, $Me_4NBr$ and aqueous potassium hydroxide. In aprotic solvents such as dichloromethane, it reacts with acid chlorides giving direct formation of the corresponding aldehydes in 1–4 h at room temperature. The stoichiometry of the reaction is shown in equation (1). As some of the reagent is consumed by formation of the inert by-product (**16**), at least 1.5 equiv. are required. The method has been applied to a number of simple aldehydes, as shown in Table 5. It can be seen that it is incompatible with an aromatic nitro group, and unsatisfactory with cinnamoyl chloride. The alternative, polymer bound version of the reagent is also easy to prepare, and has the usual advantage of being easily separated from the product. It has been used to prepare several aldehydes in good isolated yields, including $OCH(CH_2)_8CHO$ (85%) and $MeO_2C(CH_2)_7CHO$ (90%).[27]

$$2\,RCOCl + 3\,[NMe_4][HFe(CO)_4] \longrightarrow 2\,RCHO + 2\,NMe_4Cl + \underset{\mathbf{(16)}}{[NMe_4][HFe_3(CO)_{11}]} + CO \quad (1)$$

The remaining complex anions, $[HCr(CO)_5]^-$,[28] $[HW(CO)_5]^-$,[28] and $[CpV(CO)_3H]^-$,[29] have been used as their salts with the bulky cation $[Ph_3P{=}N{=}PPh_3]^+$. They are capable of reducing acyl halides to aldehydes in good yield and at a much faster rate than $[HFe(CO)_4]^-$. These reagents are, however, somewhat less convenient to prepare. Although they are also capable of reducing alkyl halides, they are far more reactive towards acyl chlorides. Unlike $[HFe(CO)_4]^-$, $[HCr(CO)_5]^-$ has been shown to be fairly unreactive towards nitrobenzene. A useful feature is that it undergoes rapid H/D exchange with MeOD, giving a reagent for the conversion of RCOCl to RCDO.

The mechanism of action of these metal hydrides is somewhat uncertain. In the original report on $[HFe(CO)_4]^-$, it was suggested that, by analogy with $[Fe(CO)_4]^{2-}$, the anion displaces a chloride ion from the acyl chloride to give an intermediate (**17**) which then collapses to give the aldehyde (Scheme 7).[26] However, there are alternative possibilities, particularly that the reagents act as H-atom donors (like

**Table 5** Aldehydes RCHO from RCOCl by Treatment with $NMe_4 \cdot HFe(CO)_4$[26]

| *R* | *Yield (%)*<br>*G.c.* | <br>*Isolated* |
|---|---|---|
| Phenyl | 91 | |
| 2-Furyl | 90 | |
| Hexyl | 99 | |
| Cyclohexyl | 95 | |
| *p*-Bromophenyl | 80 | 75 |
| Isopropyl | 99 | 82[a] |
| *t*-Butyl | | 80 |
| Methyl | 100 | |
| PhCH═CH | 22 | |
| *p*-Nitrophenyl | 0 | |

[a] As 2,4-dinitrophenylhydrazone.

$Bu_3SnH$). Although the question was subjected to a detailed investigation in the case of $[CpV(CO)_3H]^-$, it did not prove possible to give a definitive answer.[29]

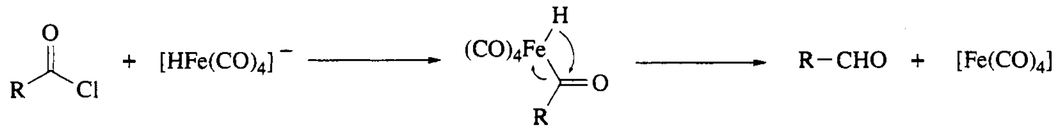

**(17)**

**Scheme 7**

Closely related to the anionic complexes described above are the neutral species $[Cp_2M(CO)H]$ (M = Nb or Ta), also capable of reducing acyl chlorides to aldehydes.[30] The reactions are reported to be virtually instantaneous, and the reagents appear to have useful selectivity. For example, *p*-nitrobenzoyl chloride and cinnamoyl chloride are reduced to their corresponding aldehydes (although yields are not recorded). However, as with the Cr, W and V anionic hydrides, these neutral complexes may prove too inaccessible to be generally useful.

A reduction method which is conceptually somewhat similar to the use of $[Fe(CO)_4]^{2-}$ is shown in Scheme 8.[31] Treatment of an aroyl chloride with phospholen (**18**) and triethylamine gives a salt (**19**) which can be decomposed with water to give the corresponding aldehyde and phospholen oxide (**20**). It appears that ring strain in (**19**) is crucial in directing attack of water to the phosphorus, as opposed to the carbonyl carbon. The method gives good yields for a number of aroyl chlorides (*e.g.* benzoyl chloride, converted to benzaldehyde in 80% yield) but is limited in scope, being inapplicable to aliphatic acyl chlorides and to aroyl chlorides containing —$NO_2$ and —OH groups.

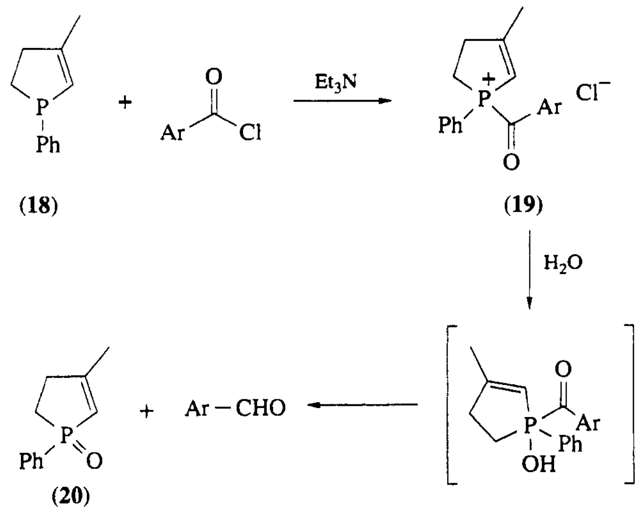

**(18)** **(19)** **(20)**

**Scheme 8**

Recently it has been shown by Chikashita *et al.* that hydride transfer is possible from the benzimidazoline (**21**) to an acyl chloride, giving the corresponding aldehyde and benzimidazolium salt (**22**; equation 2).[32] The reaction is most effective in the presence of 1 mol equiv. of acetic acid. Although it has only been used for a few aldehydes, it is successful with aromatic and aliphatic examples (*e.g.* *p*-nitrobenzaldehyde, 82% g.c. yield; cyclohexanecarbaldehyde, 80% g.c. yield) and may have substantial potential. Another new method is the treatment of aroyl chlorides with dialkylzinc reagents in the presence of catalytic palladium complexes.[33] However, the applicability would seem to be limited by the rather low yields.

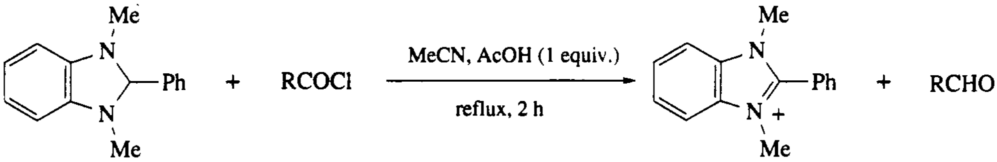

(21) (22) (2)

Finally, mention should be made of the Grundmann method which, though long winded and unlikely to be of use today, was once of some importance.[34] It is summarized in Scheme 9. In favorable cases the sequence could be carried through in over 50% overall yield, and it was valued for its ability to synthesize aldehydes inaccessible *via* the classical Rosenmund.

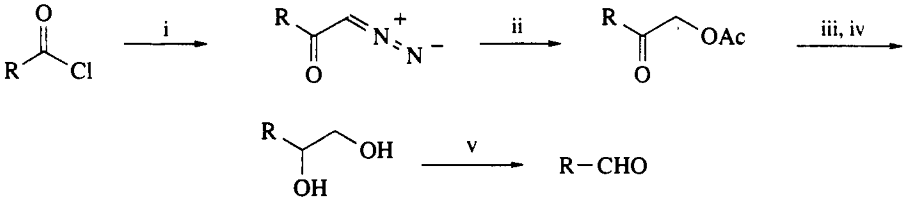

i, $CH_2N_2$; ii, AcOH; iii, $Al(OPr^i)_3$; iv, aq. HCl; v, $Pb(OAc)_4$

**Scheme 9**

## 1.12.4 CARBOXYLIC ACID ANHYDRIDES

The reduction of carboxylic acid anhydrides to aldehydes does not appear to have attracted much attention, despite the intrinsic reactivity of anhydrides. The only well-developed method is the use of $Na_2[Fe(CO)_4]$ (Scheme 10),[35,36] closely analogous to the use of the same reagent to reduce acyl chlorides (*vide supra*). Again, the reaction proceeds *via* acyltetracarbonylferrates, the formation of which can be monitored by IR. The method has been used to produce simple aldehydes from the corresponding symmetrical anhydrides in fair to good g.c. yields (*e.g.* propanal, 90%; butanal, 61%; benzaldehyde, 73%).[36] It is also successful with cyclic anhydrides, giving the corresponding aldehydic acids in quite good isolated yields, as shown in Table 6. In practical terms, this is probably the most valuable application.

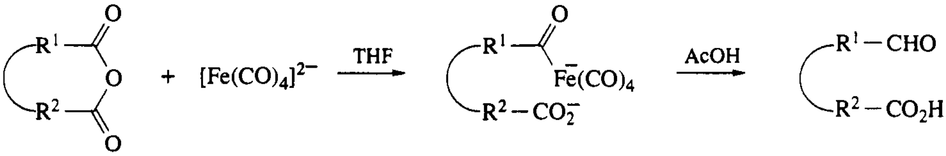

**Scheme 10**

With mixed diaryl or alkyl aryl anhydrides, the regioselectivity of attack by the tetracarbonylferrate is, not surprisingly, too poor to be synthetically useful.[36] However, the reagent can be usefully applied to the mixed carboxylic alkylcarbonic anhydrides (**23**), giving aldehydes after treatment of the intermediate acylferrates with acetic acid (equation 3).[37] The substrates (**23**) are readily available from carboxylic acids by treatment with ethylchloroformate and triethylamine. Unfortunately the quoted g.c. yields are variable (*e.g.* benzaldehyde, 41%; *p*-tolualdehyde, 76%; nonanal, 51%), suggesting that further development may be required.

**Table 6** Cyclic Carboxylic Acid Anhydrides Reduced to the Corresponding Aldehydic Acids by $Na_2[Fe(CO)_4]$[36]

| *Anhydride* | *Isolated yield of aldehydic acid (%)* |
|---|---|
| Succinic | 81[a] |
| Glutaric | 60 |
| Phthalic | 61 |
| Tetrachlorophthalic | 83 |
| 1,8-Naphthalic | 75 |

[a] As 2,4-dinitrophenylhydrazone

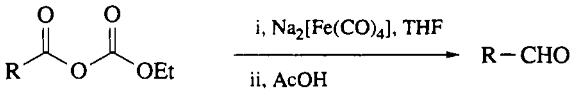

(23)

(3)

It is also possible to reduce anhydrides to aldehydes by catalytic hydrogenation, although there is no method which has been shown to be generally useful. Acetic and propionic anhydrides have been hydrogenated with Pd–$BaSO_4$ as catalyst, giving the corresponding aldehydes with reasonable selectivities (acetaldehyde, 78%; propanal, 90%) but low conversions.[38] Another method employing catalytic $[Co_2(CO)_8]$ and high pressures of $H_2$ and CO gives yields of 57% or less with simple acyclic and cyclic anhydrides.[39] High temperature hydrogenation over a metal oxide–alumina catalyst (see Section 1.12.2) has also been used with anhydrides.[9]

## 1.12.5 CARBOXYLIC ACID ESTERS

There is no generally useful nonhydride method for the direct reduction of carboxylic acid esters to aldehydes. There are, however, procedures which are valuable under particular circumstances. An important example is the one-electron reduction of aldonolactones to aldoses. Two factors presumably contribute to the success of these reactions; firstly the presence of electron-withdrawing substituents in the substrates, raising the reactivity of the carbonyl group, and secondly the ability of the products to form cyclic hemiacetals stable to further reduction.

The use of sodium amalgam originates with E. Fischer.[40] The method was a cornerstone of his aldose homologation (cyanohydrin formation, hydrolysis, lactone formation and reduction) which was so important to the development of carbohydrate chemistry. Although the yields obtained by Fischer were moderate (*ca.* 20–50%), more recent work by Sperber *et al.* has resulted in significant improvements.[41] In particular, they discovered that control of the pH of the reaction mixture was very important. At pH 3–3.5, yields in the range 52–82% were obtained with a variety of aldonolactones. As an example, the preparation of arabinose is shown in equation (4). If the pH was allowed to rise, yields were lower due to overreduction. Methyl esters of aldonic acids could also be used as substrates.

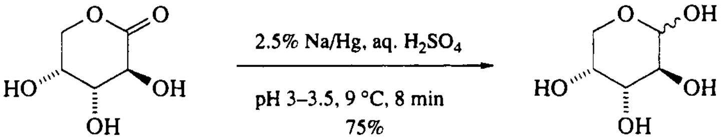

(4)

An alternative which is attractive for large scale work is the electrochemical reduction of aldonolactones.[42,43] Particular attention has been paid to the electroreductive synthesis of ribose from ribonolactone because of the importance of the former in the synthesis of riboflavin (vitamin $B_2$).[43] Processes generally involve a mercury cathode and maintenance of an acidic pH, often with the assistance of a phosphate or borate buffer. It has been reported that alkali metal ions are also necessary, suggesting that the reduction occurs *via* metal amalgam formation.[42] However, other accounts make no mention of metal ions.[44]

Early work showed that the reduction of aldonolactones to aldoses may also be carried out by catalytic hydrogenation over $PtO_2$ in aqueous solution.[45] Using this method, D-glucono-1,5-lactone was reduced to glucose in up to 80% yield, the remainder of the product being D-gluconic acid. However, careful optimization was required to achieve this result, and there appears to have been little further development of the procedure.

Whereas acyl chlorides and carboxylic acid anhydrides can be reduced to aldehydes using $Na_2[Fe(CO)_4]$ (*e.g.* Scheme 10) most esters cannot, because of their low reactivity as acylating agents. However, $Na_2[Fe(CO)_4]$ does give low yields of aldehydes (<40%) with esters of aromatic alcohols.[46]

Finally, some of the methods for carboxylic acid reduction (Section 1.12.2) have also been applied to esters. Thus, the ethyl ester of thiazole-2-carboxylic acid has been reduced electrochemically to the corresponding aldehyde,[4] and some of the high temperature metal oxide catalyzed hydrogenations have been used on esters.[8,9]

## 1.12.6 CARBOXYLIC ACID THIOL ESTERS

One of the classical reductive syntheses of aldehydes is the treatment of carboxylic acid thiol esters with Raney nickel.[34] The first report of this reaction, due to Wolfrom and Karabinos,[47] appeared around the same time as a report from Jeger *et al.* that Raney nickel under similar conditions reduced thiol esters to alcohols.[48] Later investigations by a group at the Upjohn Company[49–51] confirmed the latter result, but showed that if the Raney nickel was first deactivated by boiling in acetone (for *ca.* 1 h) it could indeed be used to convert thiol esters to aldehydes (equation 5). Some of the results obtained using the method are summarized in Table 7. It is notable that carbon–carbon double bonds in positions 5 and 11 of the steroid nucleus were unaffected. Thiol esters derived from a variety of thiols ($R^1SH$) could be used as substrates, the results being marginally better for $R^1$ = Et or $CH_2Ph$ than for Ph or $Pr^i$. The thiol esters were prepared from the corresponding acid chlorides using lead sulfides, or thiols in the presence of pyridine.

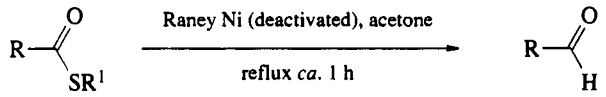

(5)

Table 7 The Reduction of Thiol Esters $RCOSR^1$ to Aldehydes RCHO by Deactivated Raney Nickel

| *RCHO* | *R*¹ | *Yield* (%) | *Ref.* |
|---|---|---|---|
| PhCHO | Et | 62[a] | 47 |
| EtCHO | Et | 73[a] | 47 |
| 3β-Acetoxy-5-cholen-24-al | Et | 63, 67[b] | 50 |
| 3β-Acetoxy-5-cholen-24-al | $PhCH_2$ | 68[b] | 50 |
| 3β-Acetoxy-5-cholen-24-al | Ph | 62[b] | 50 |
| 3β-Acetoxy-5-cholen-24-al | $Pr^i$ | 49[b] | 50 |
| 3α-Formoxy-5-cholen-24-al | Et | 78 | 51 |
| 3α-Acetoxy-11-cholen-24-al | Et | 53 | 51 |

[a] As $NaHSO_3$ adduct. [b] As 2,4-dinitrophenylhydrazone.

As thiol esters are fairly good acylating agents, they can act as substrates for the $[Fe(CO)_4]^{2-}$ procedure.[46] Thus, treatment of four simple *p*-chlorophenylthiol esters with $Na_2[Fe(CO)_4]$/THF followed by acetic acid leads to the corresponding aldehydes in low to reasonable yields (nonanal, 45%; benzaldehyde, 49%; *p*-chlorobenzaldehyde, 56%; *p*-tolualdehyde, 70%).

## 1.12.7 CARBOXYLIC ACID AMIDES

Although amides are the least reactive of the common acid derivatives under most circumstances, they are involved in several reductive syntheses of aldehydes. As described below the conversion can be accomplished by one-electron reducing agents (though relatively powerful ones), and there are specific types of amide which can be caused to decompose to aldehydes. Moreover, amides are precursors of imidoyl chlorides, Vilsmeier complexes and thioamides, which can also be reduced to aldehydes as discussed in later sections.

A number of groups have reported one-electron reductions of amides to aldehydes. Most involve the use of ammonia or methylamine as solvent, with electrons provided electrochemically or by an alkali metal. It must be said, however, that none of the methods is sufficiently effective or general to be routinely useful. In one of the earlier procedures, due to Birch *et al.*,[52] the tertiary amides (**24**) to (**26**) were reduced to the corresponding aldehydes in 80%, 53% and 47% yields, respectively, using sodium in liquid ammonia containing acetic acid. The use of acetic acid as a proton source was crucial to success; with ethanol yields were far lower, the acyl portion of the molecule being converted to nitrogen-free products. It was postulated that the reaction occurred as shown in Scheme 11. The intermediate hemiaminal (**27**) would be stable toward further reduction, and if it survived would yield the aldehyde RCHO in the work-up. However, if the proton donor BH were too weak an acid, base-catalyzed decomposition of (**27**) would occur within the reaction mixture, resulting in overreduction.

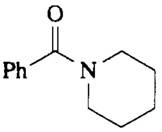

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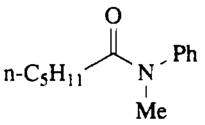

(**25**)

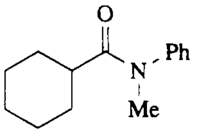

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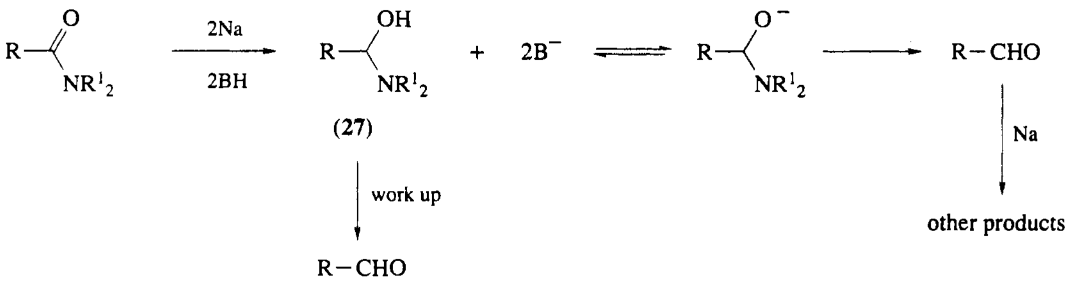

**Scheme 11**

In a later development by Bedenbaugh *et al.*,[53] methylamine was used as solvent and lithium as electron donor. No proton donor was required, suggesting that the lithium salt (**28**) of hemiaminal (**27**) is stable under the reaction conditions (both aldehydes and aldimines are reduced by the reagent; *cf.* the analogous reduction of carboxylic acids, Section 1.12.2 and Scheme 2). Yields of aldehydes produced by this method are shown in Table 8. It is notable that only tertiary amides are reduced satisfactorily. A major limitation of the reaction is the substantial formation of side products resulting from transamidation by the methylamine solvent (*i.e.* RCONHMe from RCONR$^1_2$).

**Table 8** Amides Reduced to the Corresponding Aldehydes by (A) Li/MeNH$_2$[53] or (B) e$^-$/MeNH$_2$/LiCl/EtOH[54]

| *Amide* | *Method* | *Yield of Aldehyde (%)* |
|---|---|---|
| Bu$^n$CONHMe | A | 4.4 |
| n-$C_7H_{15}$CONHMe | A[a] | 13.2 |
| n-$C_7H_{15}$CONMe$_2$ | A | 51.7 |
| n-$C_9H_{19}$CONMe$_2$ | A | |
| n-$C_9H_{19}$CONH$_2$ | B | 28 |
| n-$C_9H_{19}$CONHMe | B | 58 |
| n-$C_9H_{19}$CONMe$_2$ | B | 45 |

[a] Large excess of Li used.

Amides may be reduced to aldehydes electrochemically in methylamine, with lithium chloride as the supporting electrolyte.[54] Despite the apparent similarity between this and the foregoing method, the results are rather different. With no added proton donor, overreduction occurs leading to the corresponding alcohol. It is only in the presence of ethanol that aldehydes are obtained in reasonable yields. Another difference is that secondary amides give satisfactory yields, as shown in Table 8 where this and the foregoing method can be compared.

It has been mentioned in earlier Sections that certain electron deficient heterocyclic carboxylic acids and esters can be reduced electrochemically to aldehydes under acidic conditions, the aldehydes being protected from overreduction by geminal diol formation. This method is also applicable to the corresponding amides, allowing, for example, the conversion of amide (**29**) into aldehyde (**30**) in 93% yield.[4]

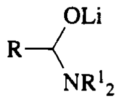

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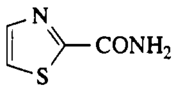

**(29)**

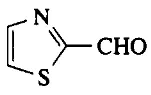

**(30)**

As mentioned above, there are two particular types of amide which can be induced to decompose to aldehydes without requiring reducing agents. They are the Reissert compounds, to be discussed first, and the sulfonylhydrazides involved in the McFadyen–Stevens method, to be discussed second.

Formally speaking, a Reissert compound[55] is an adduct of an acylium cation and cyanide anion across the C═N double bond of a heterocyclic amine. The process is illustrated in equation (6), taking quinoline as the amine. Isoquinoline and phenanthridine may also be employed as amines (giving (**32**) and (**33**), respectively) as well as a variety of more complex derivatives and analogs. The chemistry of these compounds has been investigated quite intensively over the years, and has been reviewed regularly.[34,56–58] Broadly speaking, they are of interest for two reasons. Currently, the more important is that they are valuable intermediates in heterocyclic synthesis. However, the original focus of attention was the fact that, on treatment with acid, the acyl groups RCO are cleaved from the compounds to give the corresponding aldehydes RCHO.[34,56,57]

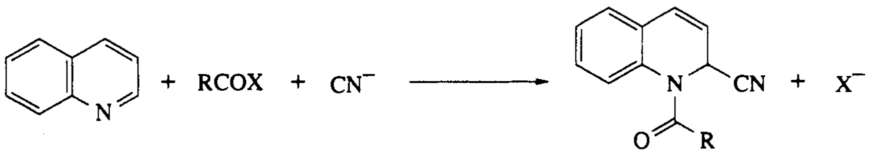

**(31)**

(6)

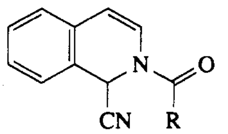

**(32)**

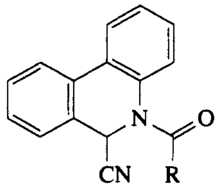

**(33)**

A mechanism for the latter transformation, suggested by Cobb and McEwan,[59] is shown in Scheme 12. This proposal was supported by the observation that the cleavage was invariably accompanied by hydrolysis of the cyano group giving amide (**34**) as well as the derived carboxylic acid (**35**). The nitrile (**36**) was never isolated. Further support for the participation of the carbonyl oxygen in the reaction was provided by the discovery that isoquinoline-derived Reissert compounds (**32**) could be treated with anhydrous acids to give salts which could be decomposed to aldehydes RCHO with aqueous acid.[60] However, although originally assigned the structure (**37**), these compounds were later reformulated as the amino

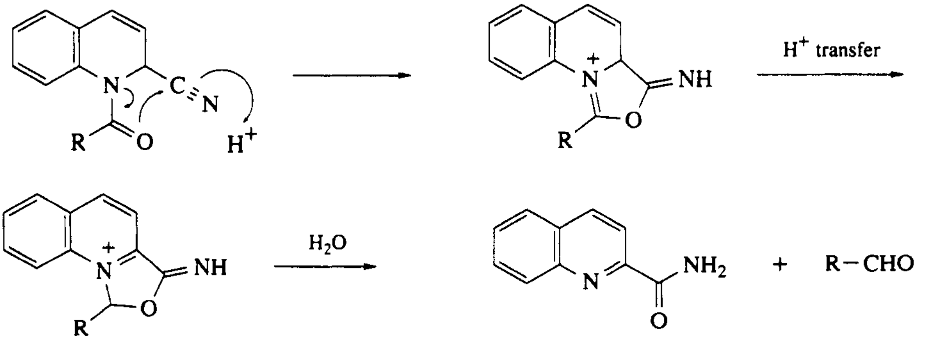

**(34)**

**Scheme 12**

tautomers (**38**).[61] This suggests that (**39**), the analogous tautomer in the quinoline series, should perhaps play a central role in Scheme 12.

The synthesis of the original Reissert's compound (**31**; R = Ph) was accomplished by mixing quinoline and benzoyl chloride in aqueous potassium cyanide.[55] A later development, which broadened the applicability of the reaction, involved the addition of dichloromethane as a solvent for the organic phase.[62] Alternatively, the synthesis can be accomplished by treating the acid chloride with the amine and anhydrous HCN in benzene.[63] The scope and limitations of these two methods are illustrated by the selection of results in Table 9. The following points may be noted: (i) although the yields listed for aldehyde formation from the Reissert compounds are generally excellent (especially for Method B, where aqueous sulfuric acid is used), most refer to the derived 2,4-dinitrophenylhydrazones. For aromatic R, the isolation of the aldehyde itself does not generally pose a problem, but it is not clear that aliphatic aldehydes can be obtained directly; and (ii) Method B, employing anhydrous HCN in benzene, is quite general for aromatic aldehydes and is also successful for unhindered aliphatic R groups. It is not, however, attractive experimentally. Method A, though more convenient, is less general, especially in that it gives lower yields with the more reactive halides. In these cases it is often more successful when isoquinoline is used as the base.

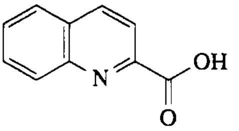

**(35)**

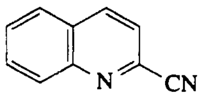

**(36)**

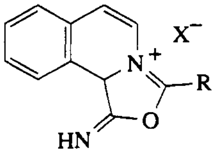

**(37)**

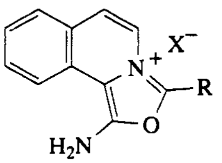

**(38)**

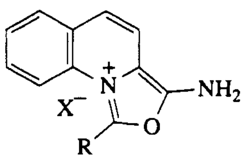

**(39)**

**Table 9** Yields of Reissert Compounds (**31**) and (**32**), and Derived Aldehydes RCHO, Prepared by RCOCl/Amine/$CH_2Cl_2$/aq.KCN (Method A)[62] or RCOCl/Amine/HCN/Benzene (Method B)[63]

| *Method* | *Reissert compound* | *R* | *Yield of Reissert compound (%)* | *Yield of aldehyde (%)*[a] |
|---|---|---|---|---|
| A | (32) | Ph | 69 | |
| A | (31) | Ph | 70 | |
| B | (31) | Ph | 96 | 98[b] |
| A | (32) | *p*-Methoxyphenyl | 72 | 90[b] |
| A | (31) | *p*-Methoxyphenyl | 80 | 96[b] |
| B | (31) | *p*-Methoxyphenyl | 88 | 98 |
| A | (32) | *p*-Chlorophenyl | 30 | 92[b] |
| A | (31) | *p*-Chlorophenyl | 20 | |
| B | (31) | *p*-Chlorophenyl | 77 | 92 |
| A | (32) | $Pr^n$ | 64 | 57[b] |
| A | (31) | $Pr^n$ | 25 | |
| B | (31) | $Pr^n$ | 64 | 97[b] |
| A | (32) | $Pr^i$ | 11 | |
| A | (31) | $Pr^i$ | 18 | 80[b] |
| B | (31) | $Pr^i$ | 28 | 98[b] |
| A | (32) | PhCH═CH | 64 | |
| A | (31) | PhCH═CH | 43 | |
| B | (31) | PhCH═CH | 91 | 82 |

[a] Method A, hydrolysis by conc. HCl or conc. HCl/$H_2O$ 6:5, in presence of 2,4-dinitrophenylhydrazine; method B, hydrolysis by 2.5–5 M aq. $H_2SO_4$. [b] As 2,4-dinitrophenylhydrazone.

In the light of the foregoing, it is perhaps not surprising that interest has lapsed in the hydrolysis of Reissert compounds as a method of aldehyde synthesis. However, the value of the compounds in heterocyclic chemistry has led to continued developments in their synthesis,[58] and it is not impossible that, for those aldehydes stable to the hydrolysis conditions, the method may at some stage regain its usefulness.

The McFadyen–Stevens aldehyde synthesis[34,64] is based on the reaction shown in Scheme 13, in which arenesulfonylhydrazides (**40**) are decomposed to aldehydes by treatment with base. It is generally presumed that the acylimides (**41**) are intermediates in the procedure. The arenesulfonylhydrazides can be synthesized either from acid hydrazides and arenesulfonyl chlorides[34] or from acyl chlorides and arenesulfonylhydrazines. The latter method is somewhat more common in recent work[65,66] and is reported to give superior yields.[65]

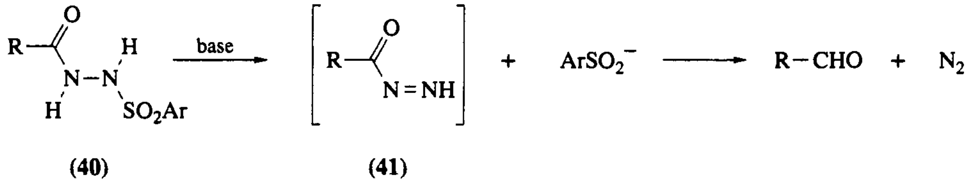

**Scheme 13**

In the classical McFadyen–Stevens method, the Ar group in (**40**) is generally phenyl or *p*-tolyl and the conditions for the decomposition are sodium or potassium carbonate in ethylene glycol at 160 °C for *ca.* 2 min.[34] This procedure is suitable for the synthesis of aromatic aldehydes, and appears to have been quite widely used. Table 10 shows a few examples; many more are tabulated elsewhere.[34] It can be seen that the best yields are obtained with electron rich aromatic nuclei.

**Table 10** Yields of Aldehydes Prepared from Arenesulfonylhydrazides (**40**; Ar = Ph or *p*-tolyl) by Treatment with Alkali Metal Carbonate in Hot Ethylene Glycol[34]

| *Aldehyde* | *Yield (%)* |
|---|---|
| Benzaldehyde | 70 |
| *p*-Methoxybenzaldehyde | 77 |
| 3,4-Methylenedioxybenzaldehyde | 87 |
| *m*-Fluorobenzaldehyde | 50 |
| *m*-Nitrobenzaldehyde | 42 |
| 3-Quinolinecarbaldehyde | 33 |

Curiously, a study of the mechanism of the reaction revealed that the presence of a finely divided solid is necessary for the decomposition.[67] A variety of solids such as sodium carbonate, charcoal, zinc powder and powdered glass were all effective, and addition of the latter to the classical reaction conditions improved the yields slightly (*e.g.* PhCHO, 81%).

Quite recently, an attempt was made to improve the method by increasing the bulk of the Ar group in (**40**), employing 2,4,6-triisopropylphenyl as opposed to phenyl or *p*-tolyl.[66] As expected, the new derivatives were found to decompose under far milder conditions ($K_2CO_3$, methanol, reflux, 15–60 min), presumably due to steric acceleration of the S—N bond cleavage. Unfortunately, for reasons which are unclear, the yields of the resulting aldehydes were poorer than those from the classical method. Nonetheless, if the reaction was carried out in the presence of hydrazine, good yields of the corresponding aldehyde hydrazones could be obtained, and the method could be useful under some circumstances.

None of the above conditions are suitable for the production of aliphatic aldehydes, and recent work has been aimed at a remedy for this deficiency. Sprecher *et al.* demonstrated that aliphatic aldehydes with no α-H could be produced in moderate yields if the reaction time was reduced to 30 s.[68] Babad *et al.* then showed that volatile aldehydes could be isolated (again in moderate yields) if they were distilled from the reaction mixture as they were formed.[65] Both results imply that the difficulty with aliphatic aldehydes is their instability in the reaction mixture.

Finally, Nair and Schechter developed a version of the McFadyen–Stevens which does appear to be genuinely useful for aliphatic aldehydes, provided that they are reasonably volatile.[69] The salts (**42**) are produced from the corresponding tosylhydrazides by treatment with NaOMe/MeOH followed by evaporation, and are then heated to 140–155 °C under a vacuum. The product aldehydes RCHO are collected in a cold trap. The method was used for butanal (68% yield), 2-methylpropanal (71% yield), 3-phenylpropanal (85% yield) and 10-undecenal (60% yield). Yields were also good for simple aromatic aldehydes.

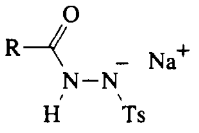

**(42)**

## 1.12.8 NITRILES

Nitriles appear to be quite useful as precursors of aldehydes, and there are a number of 'nonhydride' methods for accomplishing the conversion.[70] Classically the best known is probably the Stephen reduction.[34,70,71] It involves a reagent system prepared from anhydrous tin(II) chloride and hydrogen chloride gas in ether. The nitrile is added to this mixture, and, as shown in Scheme 14, adds HCl to give the imidoyl chloride salt (**43**), which is then reduced by the tin(II) chloride. The initial product is the complex (**44**) (often crystalline), which is then hydrolyzed to the aldehyde. Although the reaction conditions are generally thought of as anhydrous, it has in fact been found that a small amount of water is beneficial.[34]

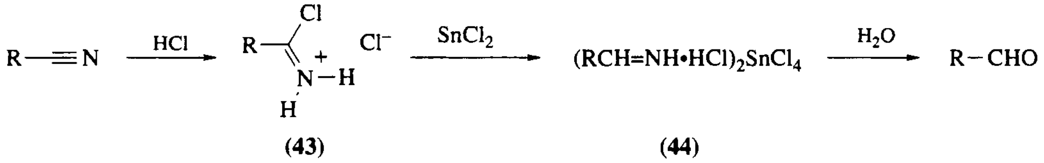

**Scheme 14**

The Stephen reduction has been applied to a variety of nitriles, but is genuinely useful only for aromatic substrates. Table 11 gives a number of representative examples, and more are available elsewhere.[34] The failure with *o*-toluonitrile is untypical, and was attributed to steric hindrance. A variant employing tin(II) bromide was successful in synthesizing cinnamaldehyde and its vinylog (**45**) in 65% and 50% yields, respectively.[72]

**Table 11** Yields of Aldehydes Prepared by the Stephen Reduction of Aromatic Nitriles[34]

| *Aldehyde* | *Yield (%)* |
|---|---|
| Benzaldehyde | 97 |
| *o*-Tolualdehyde | 9 |
| *p*-Iodobenzaldehyde | 70 |
| 4-(Methoxycarbonyl)benzaldehyde | 90 |
| β-Naphthaldehyde | 75 |
| 3-Pyridinecarbaldehyde | 83 |

With aliphatic aldehydes the yields are poor at best. In a relatively recent study, Zil'berman and Pyryalova used a modified Stephen procedure to reduce a series of aliphatic nitriles RCN.[73] As the size of R increased, the yield decreased from a maximum of 51% (R = Et). A major cause of the low yields was found to be the formation of trimeric side products (**46**).

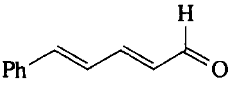

**(45)**

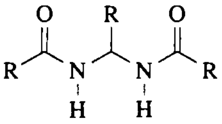

**(46)**

Aldehydes may also be synthesized by catalytic hydrogenation of the corresponding nitriles.[70] One method, applied only to aromatic aldehydes, employs Raney nickel, an atmosphere of hydrogen and a solvent system of THF/water (10:1) containing one mole equivalent of sulfuric acid.[74,75] Examples of its use are shown in Table 12.[75] Convenient and effective alternatives involve the use of phosphinic acid[76] or formic acid[77,78] as both solvent and hydrogen source. Good to excellent yields of aromatic aldehydes were obtained using these methods, although in some cases careful optimization was required. In general the best results appear to have come from using 75% aqueous formic acid as the solvent system.[78] Examples are given in Table 12, and a procedure is described in the literature.[79]

**Table 12** Aromatic Aldehydes Synthesized by the Catalytic Reduction of Nitriles using Raney Nickel in THF/$H_2O$ with 1 mol equiv. $H_2SO_4$ (Method A)[75] or 75% Aqueous $HCO_2H$ (Method B)[78]

| *Aldehyde* | *Method* | *Yield (%)* |
|---|---|---|
| 3-Formylacetophenone | A | 75 |
| Ethyl 4-formylbenzoate | A | 78 |
| 4-Formylbenzenesulfonamide | A | 76 |
| 4-Formylbenzenesulfonamide | B | 70[a] |
| Benzaldehyde | B | 97[a] |
| *p*-Chlorobenzaldehyde | B | 100[a] |
| *p*-Methoxybenzaldehyde | B | 93[a] |

[a] As 2,4-dinitrophenylhydrazone.

The catalytic hydrogenation of aliphatic nitriles to aldehydes appears to be intrinsically more difficult. The Raney nickel/formic acid method was applied to certain aliphatic aldehydes, but only with limited success (*e.g. n*-hexanal produced in 40% yield).[78] The situation can be improved by undertaking the hydrogenation in the presence of a reagent which can trap the aldehyde (or imine) as it is formed and prevent overreduction.[70] For example, hydrogenation of various aliphatic nitriles with Raney nickel in the presence of semicarbazide hydrochloride gave reasonable yields of the corresponding aldehyde semicarbazones (*e.g.* phenylacetaldehyde semicarbazone, 70%; 3-cyanopropanal semicarbazone, 60%).[80] Phenylhydrazine has also been used as a trapping agent.[81] A disadvantage of these methods is, of course, that the derivatives must be hydrolyzed in separate steps to free the aldehydes. An alternative additive which minimizes this problem is *N,N'*-diphenylethylenediamine. This forms tetrahydroimidazole derivatives which are quite easily hydrolyzed to the corresponding aldehydes.[80,82] Although not developed into a general method, this procedure proved valuable in a specific case. Thus, hydrogenation of (3,5-dimethoxyphenyl)acetonitrile gave the derivative (**47**) in 60% yield.[82] The corresponding aldehyde, obtained by acid hydrolysis of (**47**), was used for synthetic studies on yohimbane derivatives.

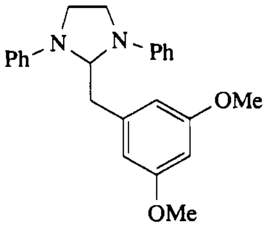

(**47**)

For the direct conversion of aliphatic nitriles to aldehydes, the best 'nonhydride' method appears to be that of Fischli.[83] The nitrile is treated with a large excess of activated zinc and a catalytic amount (0.1 equiv.) of aquocobalamine in acetic acid/water (4:1) at room temperature for several hours. Using this method, a variety of aliphatic aldehydes were obtained in yields which were generally very satisfactory. As examples, the aldehydes (**48**), (**49**) and (**50**) were produced in yields of 63%, 82% and 90%, respectively. Aldehyde (**50**) was also formed from the unsaturated nitrile (**51**) under the same conditions. The proposed mechanism is shown in Scheme 15, the key steps being the attack of cob(I)alamine on the nitrile to give intermediate (**52**) and the reductive cleavage of the latter by the zinc. It was suggested that the product aldehyde was not reduced because the adduct between itself and cob(I)alamine is, for electronic reasons, less stable than (**52**).

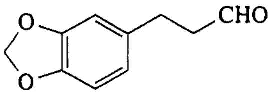

(**48**)

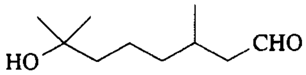

(**49**)

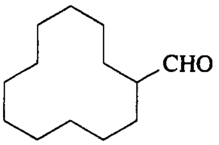

**(50)**

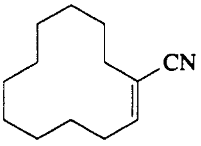

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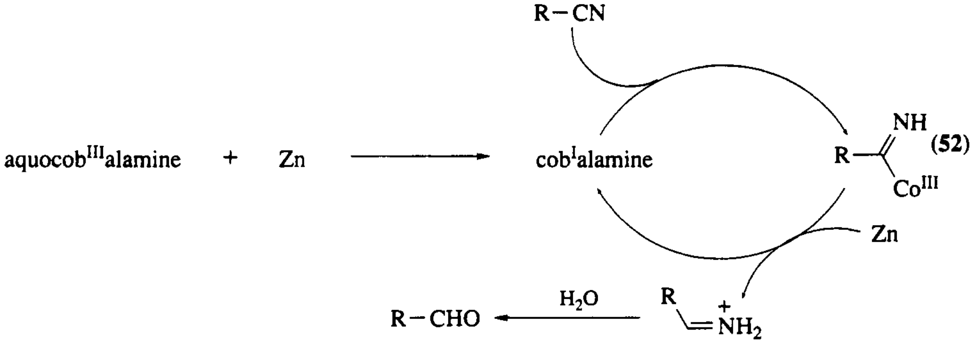

**Scheme 15**

A method which is apparently of greater theoretical than synthetic interest is the use of photochemically generated solvated electrons to reduce aromatic nitriles to aldehydes. If 3- or 4-cyanophenolate ions are irradiated at 254 nm, the corresponding aldehydes are obtained in 67% and 62% yields, respectively.[84] It appears that the absorption of a photon by the phenolate ion results in the generation of a solvated electron, which then reduces the nitrile (although the ultimate source of the reducing equivalents is not clear). The solvated electrons can also be generated from added iodide ions. Unfortunately, neither variant of the reaction gives useful yields with other substrates.

Finally, there have been several investigations into hydride transfer from Grignard reagents to nitriles, giving iminomagnesium complexes, and thus (after hydrolysis) aldehydes. Initially this type of method appeared to be of little use, being restricted to hindered tertiary nitriles and not especially successful even then.[85] However, it has been reported recently by Chinese workers that the addition of titanocene dichloride improves matters considerably, allowing the synthesis of aldehydes from nitriles and isopropylmagnesium bromide in yields of 52–68%.[86]

## 1.12.9 IMIDOYL CHLORIDES

One of the classical reductive aldehyde syntheses is the Sonn–Müller reduction of imidoyl chlorides.[34,87] The method is closely related to the Stephen reduction described in the previous section. As shown in Scheme 16, substrates (**53**) may be prepared either by the treatment of anilides with phosphorus pentachloride or sulfinyl chloride, or less usually *via* the Beckmann rearrangement.[88] They are

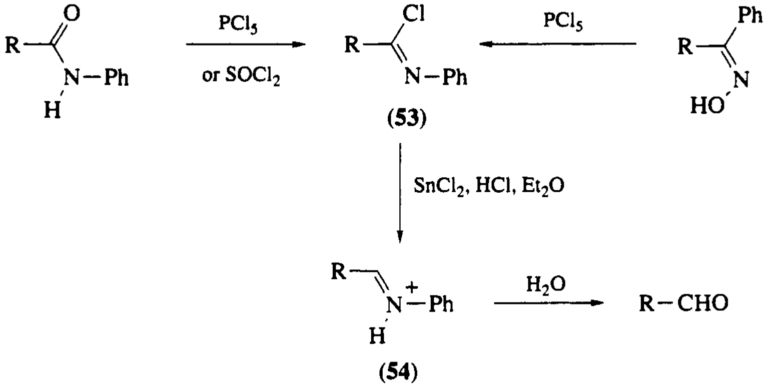

**Scheme 16**

then reduced with the same reagent as used in the Stephen reduction (*i.e.* tin(II) chloride/HCl/ether) to give iminium ions (**54**) which are hydrolyzed to aldehydes.

The method cannot be applied generally to the synthesis of aliphatic aldehydes, but for aromatic aldehydes and cinnamaldehyde the yields are good (Table 13). An example, the synthesis of *o*-tolualdehyde, is given in the literature.[89] A variant which has proved successful for α,β-unsaturated aliphatic aldehydes is the use of chromium(II) chloride.[90] However, as exemplified in Table 13, the yields are only fair. Moreover, there appears to be some question as to exactly how the reagent should be prepared.[34]

**Table 13** Aldehydes Synthesized by the Reduction of Imidoyl Chlorides using $SnCl_2$ (Sonn–Müller) or $CrCl_2$[34]

| *Aldehyde* | *Reducing agent* | *Yield (%)* |
|---|---|---|
| *o*-Tolualdehyde | $SnCl_2$ | 80 |
| 3,5-Dimethoxybenzaldehyde | $SnCl_2$ | 86 |
| *p*-(Phenylsulfonyl)benzaldehyde | $SnCl_2$ | 57 |
| Cinnamaldehyde | $SnCl_2$ | 92 |
| 2-Hexenal | $CrCl_2$ | 50 |
| 6-Methyl-1-cyclohexenal | $CrCl_2$ | 60 |
| 5,9-Dimethyl-2,4,8-decatrienal | $CrCl_2$ | 30 |

Two alternatives to the Sonn–Müller have been published in recent years. In the first, due to Alper and Tanaka, an aromatic imidoyl chloride (**55**) is reduced with the $[HFe(CO)_4]^-$ ion (equation 7) to give a mixture of imine (**56**) and amine (**57**).[91] For most of the substrates tried R was aromatic, and overreduction to (**57**) was the predominant outcome. However, in one case an aliphatic R group was used (R = Bu$^n$, Ar = Ph), and this gave a clean reduction to the corresponding imine (**56**) in 71% yield. More recently it was shown by Tanaka and Kobayashi that imidoyl chlorides could be reduced to imines using catalytic hydrogenation, with a soluble palladium complex as catalyst precursor (equation 8).[92] Although the variation of R$^1$ in their substrates (**58**) was somewhat limited, fair to good yields were obtained for R$^1$ = Ph, Bu$^t$ and 2-thiophenyl, and the method appears potentially useful.

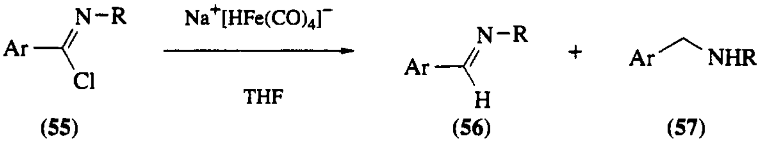

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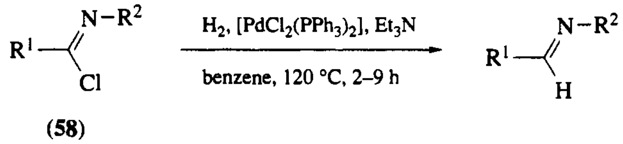

(8)

Finally, treatment of amides with phosphorus oxychloride gives Vilsmeier complexes, which are often formulated as *N*-alkylated imidoyl chlorides (**59**). Irrespective of their precise nature,[93] it has been found that they can be converted very efficiently to aldehydes by reduction with zinc followed by aqueous work-up (Scheme 17). Although the method has only been used for benzaldehyde and a number of chlorinated and brominated analogs, the yields reported are consistently high (87–97%).[94]

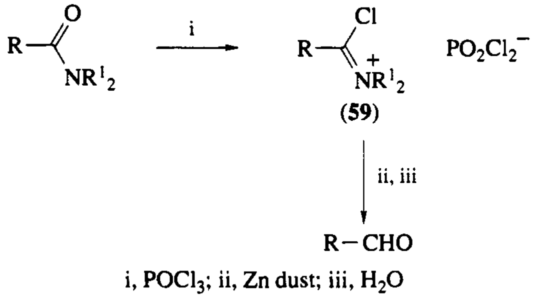

i, $POCl_3$; ii, Zn dust; iii, $H_2O$

**Scheme 17**

## 1.12.10 AMIDINES, IMIDATES AND THIOIMIDATES

Amidines are apparently rather good substrates for selective one-electron reduction to aldehydes. As early as 1908, Merling obtained good yields of some fairly complex aliphatic aldehydes by reduction of the corresponding *N*,*N*-diphenylamidines using sodium in ethanol.[95] As an example, amidine (**60**) was converted into aldehyde (**61**) in 60–70% yield.

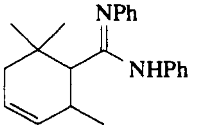

**(60)**

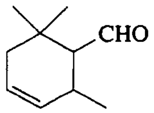

**(61)**

The method was not generalized, however, and was largely ignored until reinvestigated by Birch and coworkers,[52] who got rather better results using liquid ammonia as the solvent (retaining some ethanol as a proton source), provided the substrate was soluble therein. *N*-Unsubstituted amidines were thus preferred. As can be seen in Table 14, good yields could be obtained with both aromatic and aliphatic amidines. Presumably the geminal diamines (**62**) are intermediates (Scheme 18), and are stable under the reaction conditions, in contrast to the hemiaminal intermediates (**27**).

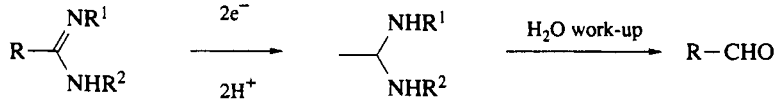

**(62)**

**Scheme 18**

**Table 14** Amidines Reduced to the Corresponding Aldehydes by Sodium and Ethanol in Liquid Ammonia[52]

| *Amidine* | *Yield of aldehyde (%)* |
|---|---|
| Benzamidine | 100 |
| Acetamidine | 53 |
| Hexanoamidine | 91 |
| Phenylacetamidine | 91 |

The selective reduction of cyclic imidates (**63**) to the aldehyde oxidation level has been demonstrated by Shono *et al.*[96] As shown in Scheme 19, the imidate is first alkylated on nitrogen and then reduced electrolytically in DMF in the presence of methanesulfonic acid. Unfortunately the scope of the method is unclear, as the main purpose of the work was to generate intermediate (**64**) in the presence of alkylating agents, leading to 2,2-disubstituted imidazolidines. Nonetheless, it was reported that decanal and dodecanal could be obtained in 82% and 70% yields, respectively.

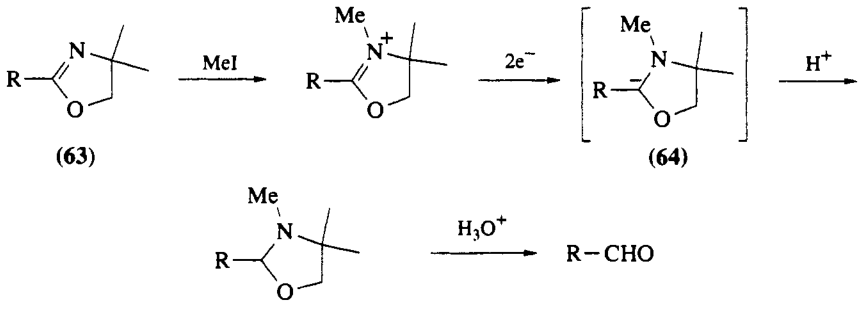

**(63)** **(64)**

**Scheme 19**

The reduction of thioimidates to the aldehyde oxidation level can be accomplished with aluminum amalgam. The reaction has not been investigated as a general method, but was developed to solve a specific problem. Thus, amide (**65**) was converted to thioimidate (**66**), which was reduced to (**67**) in 38% yield (Scheme 20).[97] Although the yield was moderate, the method succeeded in a molecule with a fairly high level of functionality.

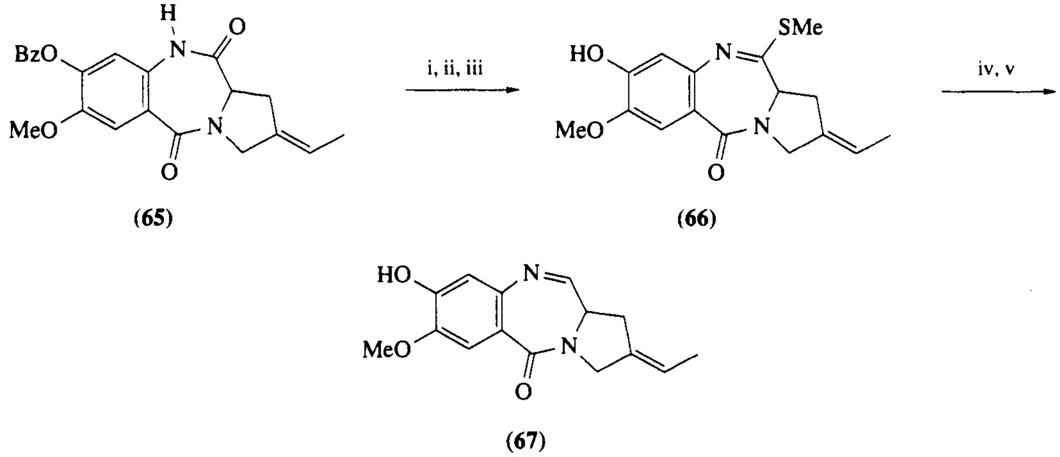

i, ($p$-$MeOC_6H_4PS_2$)$_2$, benzene; ii, MeI; iii, $K_2CO_3$, MeOH; iv, Al/Hg, aq. THF; v, $HgCl_2$, MeOH

**Scheme 20**

## 1.12.11 THIOAMIDES, THIOESTERS AND DITHIOESTERS

It has been reported from two laboratories that thioamides can be reduced to aldehydes by Raney nickel. Brovet found that thiobenzamide and thio-*p*-toluamide gave the corresponding aldehydes in yields of 77% and 42%, respectively (as 2,4-dinitrophenylhydrazones).[98] In contrast, Cronyn and Goodrich found that thiobenzamide gave poor yields, but that thiobenzanilide, *p*-methoxythiobenzanilide and *p*-hydroxythiobenzanilide gave yields in the range 78–96% (as 2,4-dinitrophenylhydrazones)[99] using Raney nickel which had previously been deactivated by boiling in acetone. Application of the method to aliphatic thioanilides was less successful, the yields being reduced to *ca.* 30%.

Recent work by Voss and coworkers has shown that tertiary thioamides,[100] thioesters[101] and dithioesters[101,102] can all be reduced electrochemically to the aldehyde level in the presence of alkylating agents. The process is summarized in equation (9). The cleanest and most efficient of the reactions appears to be that of the thioamides (**68**; X = $NR^2_2$), using anhydrous acetonitrile as solvent and simple alkyl bromides (*e.g.* EtBr, $Bu^iBr$) as alkylating agents.[100] Although the method was only demonstrated for (**68**; R = Ph and *o*-$ClC_6H_4$), the yield of α-amino sulfides was 95% in both cases.

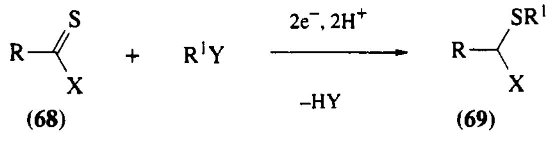

(9)

X = $NR^2_2$, $OR^2$, $SR^2$; Y = leaving group

Dithioesters can be reduced in anhydrous acetonitrile[101,102] or in methanol,[102] the best results being obtained with dimethyl sulfate as alkylating agent. The most convenient procedure involves a simple electrolysis cell with a lead cathode and methanol as solvent.[102] Eight substrates (**68**; X = SMe) were tested, with R equal to phenyl, chloro- and methoxy-substituted phenyls, and *t*-butyl. Unlike the corresponding reductions of thioamides, the reactions were not entirely clean and gave substantial amounts of side products such as (**70**). The product dithioacetals (**69**; X = SMe, $R^1$ = Me) were formed in yields of 40–60%. On two of the substrates, better yields (*ca.* 70%) could be obtained in anhydrous acetonitrile, but a more sophisticated apparatus was required.[102] One enolizable substrate (**71**) was tested, but the yield was only 30%.[101]

Finally, the thiobenzoate (**72**) was also subjected to electrochemical reduction–alkylation.[101] This reaction was still less successful, possibly because of the strongly negative reduction potential of the substrate. The expected monothioacetal product was formed, but only in 25% yield.

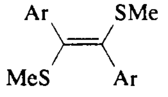

(**70**)

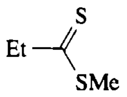

(**71**)

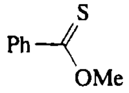

(**72**)

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# 1.13

# Reduction of C=X to $CH_2$ by Dissolving Metals and Related Methods

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## 1.13.1 INTRODUCTION

Of a variety of reduction methods,[1-3] Clemmensen reduction has long been known to convert a carbonyl function to the corresponding methylene group in strongly acidic conditions. This method cannot be utilized for an acid-labile compound, but is complemented by Wolff–Kishner reduction and related reactions which are carried out in basic media (Chapter 1.14, this volume). Electrochemical reduction is similar to Clemmensen reduction in its reaction mechanism, wherein two electrons are transferred in a stepwise manner to the substrate from the surface of a cathode instead of from the zinc metal. Both methods are able to reduce both conjugated and nonconjugated C=O functions to the corresponding methylene groups. Except for some special cases, the utility of the remaining reduction methods is limited to aromatic aldehydes and ketones, where a rather stable carbocation conjugated to the aromatic ring is presumably formed as an intermediate.

## 1.13.2 DISSOLVING METAL REDUCTION AND RELATED REACTIONS OF NONCONJUGATED AND CONJUGATED ALDEHYDES AND KETONES

### 1.13.2.1 Reduction with Alkali Metals in Liquid Ammonia

It has been known since the early part of this century that reduction of benzophenone with sodium in liquid ammonia affords diphenylmethanol *via* a ketyl intermediate,[4] and Hall *et al.* have shown more recently that aromatic aldehydes and ketones can be reduced with lithium in liquid ammonia to the corresponding methylene derivatives (equations 1–3).[5,6]

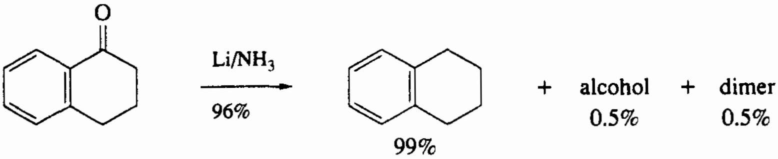
O
Li/NH$_3$
96%
99%
+ alcohol
0.5%
+ dimer
0.5%

(1)

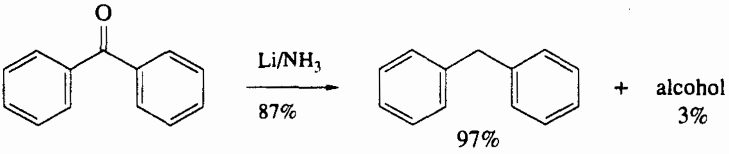
O
Li/NH$_3$
87%
97%
+ alcohol
3%

(2)

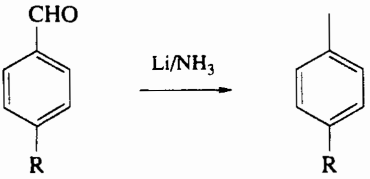
CHO
Li/NH$_3$
R
R

(3)

R = Bu$^t$; 89%, toluene:dimer = 94:2
R = Pr$^i$; 90%, toluene:dimer = 98:2

As indicated in Scheme 1, the reaction mechanism is similar to that of Birch reduction, and an alcohol intermediate has to be passed through. Therefore, while activated alcohols such as benzyl alcohols and their derivatives can be reduced under these conditions, reduction of aliphatic alcohols carrying no activating group does not take place.

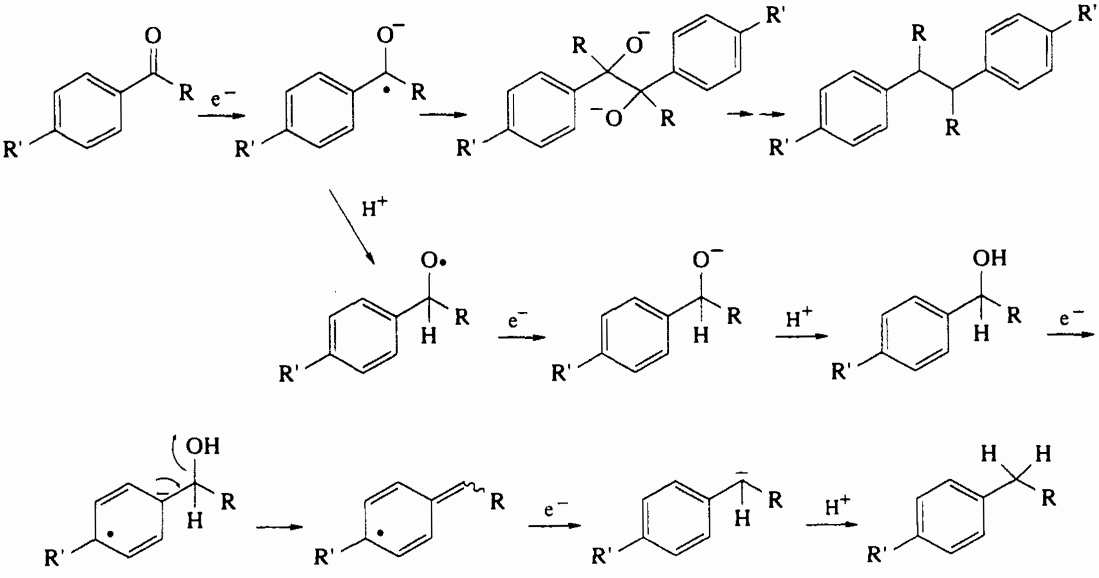
O
R
R'
e$^-$
O$^-$
R
R'
R
O$^-$
$^-$O
R
R'
R'
R
R'
R
R'
H$^+$
O•
R
H
R'
e$^-$
O$^-$
R
H
R'
H$^+$
OH
R
H
R'
e$^-$
OH
R
H
R'
R
R'
e$^-$
R
H
R'
H$^+$
H
H
R
R'

**Scheme 1**

In the case of cyclopropyl derivatives, although cyclopropyl methyl ketone gave a mixture of pentan-2-one and pentan-2-ol, cyclopropyl phenyl ketone afforded cyclopropylphenylmethane or cyclopropylphenylmethanol depending on the method of quenching (Scheme 2).[7]

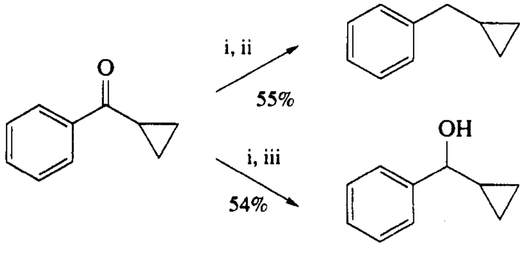

i, Li/NH$_3$; ii, NH$_4$Cl; iii, NaOBz

**Scheme 2**

In comparing aromatic aldehydes with aromatic ketones, the former are reduced faster than the latter. Thus, the presence of a trace metal such as cobalt or aluminum affected the reaction rate in the case of ketone derivatives, but this was not appreciable in the case of aldehyde derivatives, which react too fast. Also, the formation of dimeric by-products is much easier in the aldehyde case than the ketone. To prevent this dimerization, the addition of a proton source such as *t*-butyl alcohol is effective.[5,6]

### 1.13.2.2 Clemmensen Reduction

Clemmensen reduction is one of the most powerful reduction methods in organic synthesis, and many reviews have been published.[3,8–10] Generally, zinc amalgam and highly concentrated hydrochloric acid under reflux are employed to suppress the formation of by-products such as alcohols, dimerization products including pinacols, and related compounds. However, among several modifications of this synthetic procedure, the method using zinc powder in acetic anhydride or ether saturated with hydrogen chloride[11–13] is recommended for its mild conditions (0 °C, 1–2 h), and is available for reductions of aldehydes and ketones in molecules carrying such functional groups as cyano, acetoxy, phenol ether and alkoxycarbonyl, as described later.

The reaction mechanism of Clemmensen reduction has not completely been clarified, but it is well known that the alcohol is not an intermediate. As summarized in Scheme 3,[8,14] the reduction is thought to occur on the zinc metal surface, and involves protonation of the carbonyl function and a concomitant

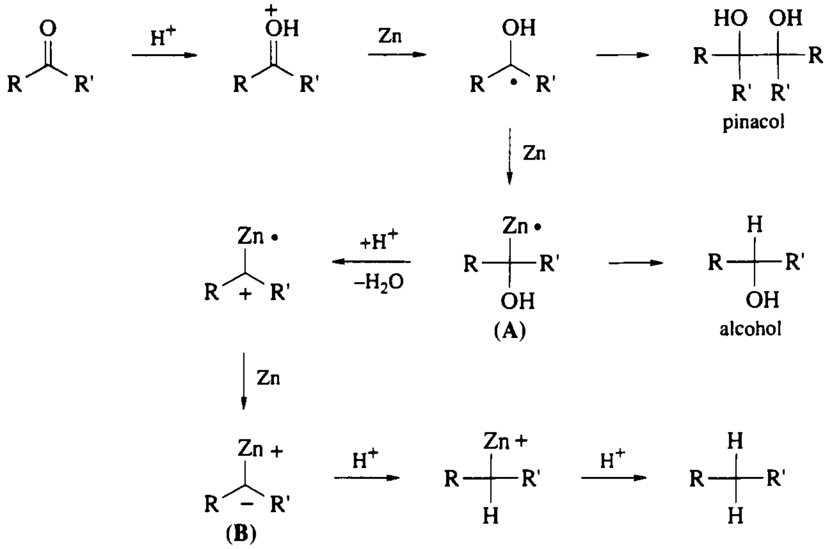

**Scheme 3**

electron transfer process to give an organozinc intermediate (**A**). Further protonation of (**A**) followed by abstraction of water and stepwise electron transfer yield a carbanion (**B**), which traps a proton, and in the final stage the corresponding methylene group is formed by exchange of the zinc with another proton.

One possibility in the case of benzaldehyde (Scheme 4) is that reduction proceeds *via* a carbene or carbenoid intermediate, which can be trapped by an alkene to give a cyclopropane (**1**) under aprotic conditions.[15]

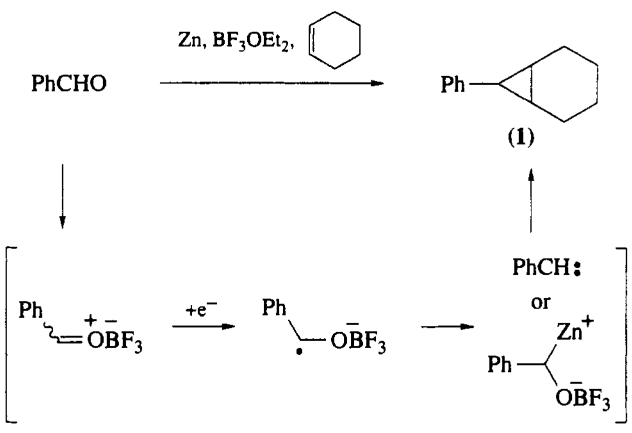

**Scheme 4**

Because of carbonium ion generation, aromatic aldehydes and ketones can usually be reduced more easily than the corresponding aliphatic compounds. However, a modified Clemmensen reduction is an effective method to reduce isolated aliphatic carbonyl groups directly to methylene groups, and typical examples are shown in equations (4)–(6).[11,13,16]

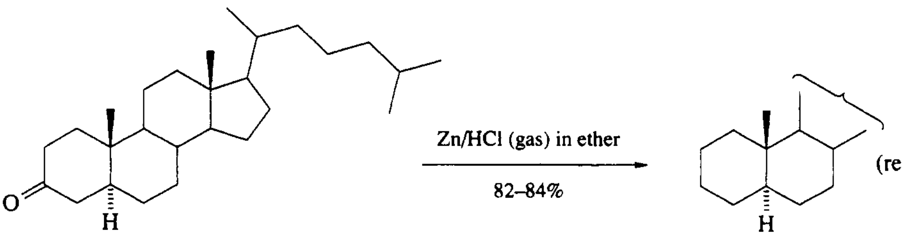

(ref. 11) (4)

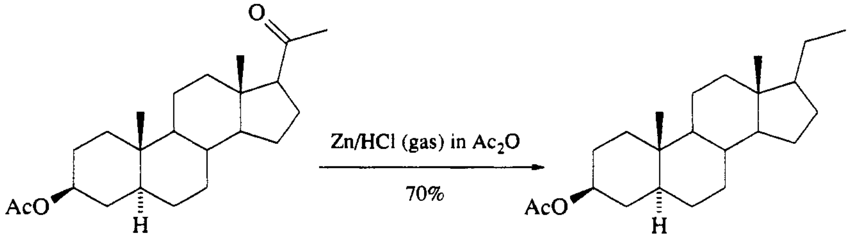

(ref. 13) (5)

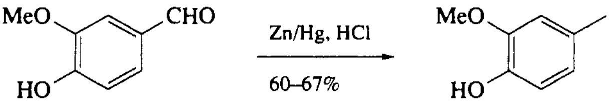

(ref 16) (6)

In deuterium-labeling experiments, 4,4-diphenylcyclohexanone (**2**) reacted with zinc dust/deuterium chloride (prepared from trimethylchlorosilane and deuterium oxide), and gave 4,4-dideuterio-1,1-diphenylcyclohexane (**3**) as the major product (isotopic purity of 81% $d_2$, 10% $d$, 6% $d_3$ and 3% $d_4$; equation 7),[8] while the ketone (**4**) was converted to (**5**) in 83% isotopic purity, along with the trideuterio compound (17%), under rather vigorous conditions (equation 8).[17]

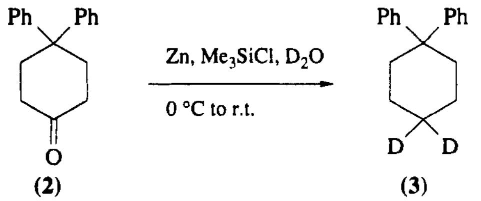
Ph
Ph
O
(2)
Zn, Me3SiCl, D2O
0 °C to r.t.
Ph
Ph
D
D
(3)

(7)

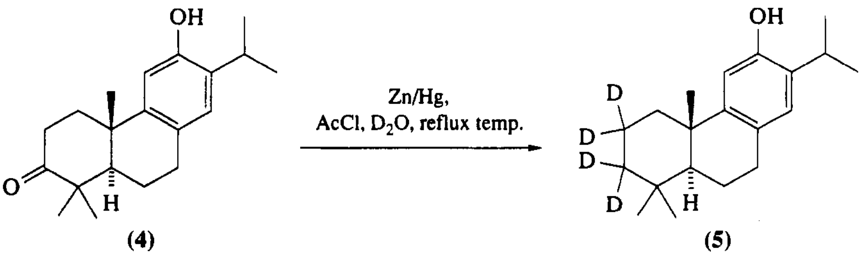
OH
O
H
(4)
Zn/Hg,
AcCl, D2O, reflux temp.
OH
D
D
D
D
H
(5)

(8)

In conjugated carbonyl systems, the usual Clemmensen conditions may give rise to reduction and isomerization of the C=C double bond. When treated with zinc powder in acetic anhydride saturated with hydrogen chloride, cholest-1-en-3-one (**6**; Scheme 5) is converted to a mixture of cholestane (**7**; 30–32%), 3-acetoxycholest-2-ene (**8**; 10–24%) and cholestan-3-one (**9**; 30–40%).[12]

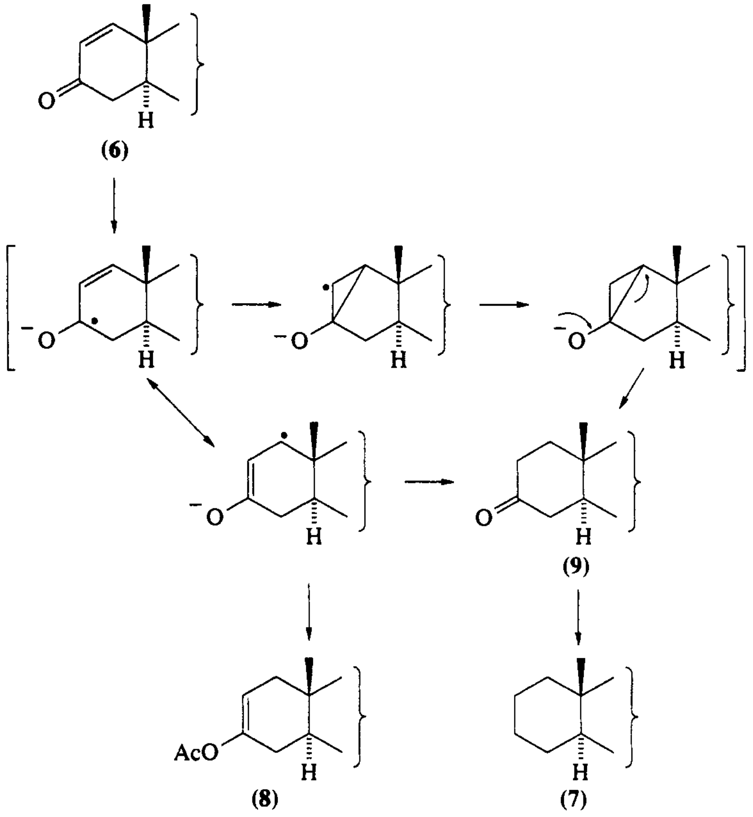
O
H
(6)
-O
H
-O
H
-O
H
-O
H
O
H
(9)
AcO
H
(8)
H
(7)

**Scheme 5**

The reaction may include a cyclopropanol intermediate derived from an anion radical, as seen in the reduction of cyclohexenones under Clemmensen conditions to afford ring-contracted cyclopentanones along with cyclohexanone derivatives.[10] Thus the diastereomeric cyclopropanol acetates (**12**) and (**13**) can be obtained in different ratios from both (**10**) and (**11**) (**12**/**13** = 3 from **10**, **12**/**13** > 100 from **11**; Scheme 6).[18]

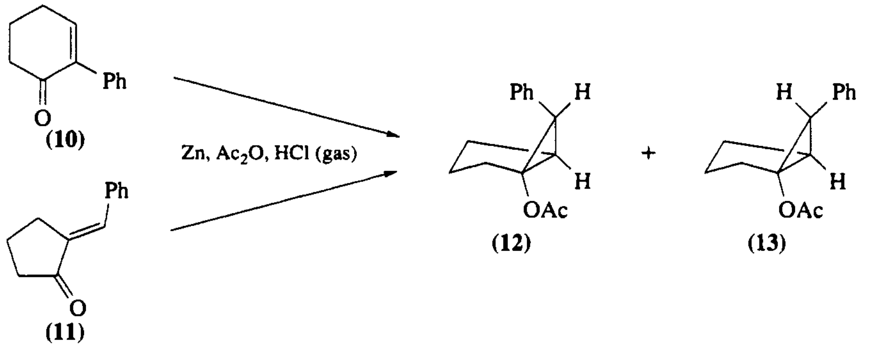

**Scheme 6**

A typical dimerization reaction in a conjugated system has been found on reduction of the octalone (**14**) with zinc amalgam in concentrated hydrochloric acid under reflux, which gave a geometrical mixture of the dehydro dimers (30–40%) along with octalin (**15**; equation 9).[19]

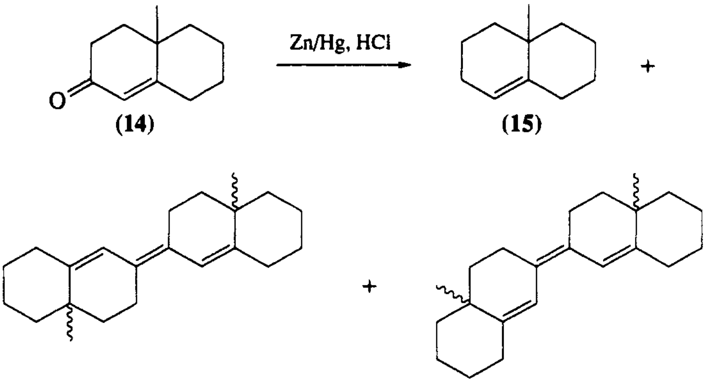

(9)

Reduction of 4,4-diphenylcyclohex-2-en-1-one with zinc dust in hydrogen chloride in aprotic solvents affords different reduction products, depending on the acid concentration. Thus, on using excess hydrogen chloride the reaction proceeds exhaustively to give 1,1-diphenylcyclohexane, while a dimeric product is obtained with only 3 equiv. of hydrogen chloride, which permits organozinc intermediates enough time to undergo the coupling reaction (Scheme 7).[9]

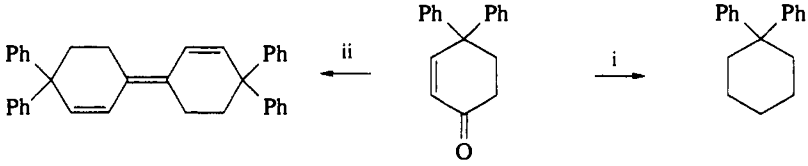

i, excess HCl (gas), Zn in Et$_2$O, ii, 3 equiv. HCl (gas), Zn in THF

**Scheme 7**

In the case of derivatives carrying two carbonyl functions stereochemically close to each other, Clemmensen reduction affords an interesting product distribution, passing through characteristic intermediates.[10] In the case of 1,3-diketones, a cyclopropanediol is involved, similar to the cyclopropanes formed from conjugated carbonyl systems.[20] For instance, 5,5-dimethylcyclohexane-1,3-dione (**16**) is converted into 2,4,4-trimethylcyclopentanone (**17**) as the major product (equation 10).[21]

Similar rearranged products can be seen in the Clemmensen reduction of many cyclic and acyclic compounds carrying the 1,3-diketone system.[9,10] The intermediacy of a cyclopropanediol derivative was established by Curphey *et al.*, who showed that the cyclopropane diacetate (**19**) can be obtained in high yield by reaction of (**18**) with zinc dust in acetic anhydride and hydrogen chloride, as well as by electrolysis.[22] The diketone (**18**) gives a mixture of rearranged products (**20** and **21**) under normal Clemmensen

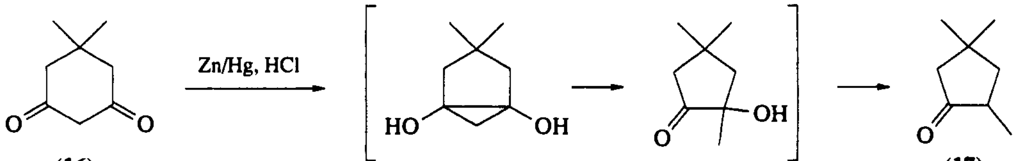

**(16)** **(17)** (10)

conditions using hydrochloric acid.[23] Reduction of cyclopentane-1,3-dione derivatives did not afford any ring contraction product because of the highly strained structure of the bicyclo[2.1.0]pentane-1,4-diol intermediate.[10]

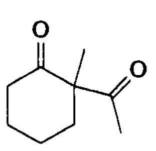

**(18)**

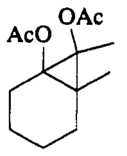

**(19)**

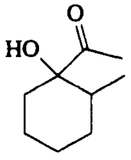

**(20)**

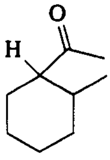

**(21)**

With 1,4-diketones the distribution of the reduction products is dependent on the stereochemical situation of the two carbonyl functions.[10] In acyclic derivatives, with no stereochemical interaction between the two carbonyl functions, the ketone groups are independently reduced to give methylene products in the usual manner. On the other hand, cyclic 1,4-diketones react differently. For example, cyclohexane-1,4-dione (**22**) suffers ring opening to give hexane-2,5-dione and hex-5-en-2-one derivatives, and products of further reduction are also detectable (equation 11). A 1,4-diketone (**23**) in which the two carbonyls are stereochemically close, gave the diketone (**24**) under relatively mild conditions (Zn/AcOH, 25 °C), formed by the same C—C bond cleavage as seen in cyclohexane-1,4-dione. Under Clemmensen conditions this derivative was then converted to cyclobutane-1,4-diol (**25**; equation 12) in 98% yield, which is closely related to the aforementioned cyclopropanediol intermediate.[24]

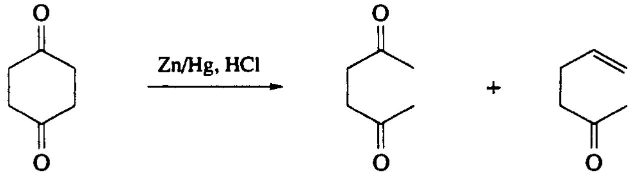

**(22)** (11)

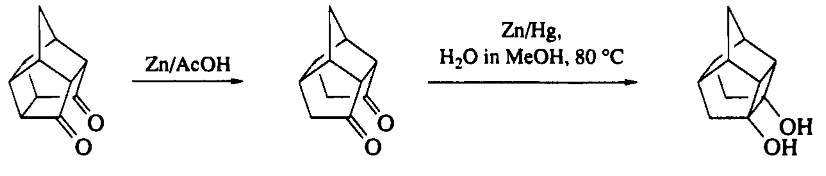

**(23)** **(24)** **(25)** (12)

## 1.13.3 METAL HYDRIDE REDUCTIONS OF AROMATIC ALDEHYDES AND KETONES

### 1.13.3.1 Reduction with $NaBH_4$, $LiAlH_4$ and Related Reagents

Generally, on using metal hydride reagents, reduction of the carbonyl group to the corresponding methylene involves two steps: at the first stage, metal hydride addition permits the formation of an alkoxide intermediate, which on quenching gives an alcohol product as shown in alkyl ketones and aldehydes. In aryl systems, however, abstraction of the oxygen can occur in a second stage to generate a carbonium ion stabilized by delocalization. Further hydride addition to the carbonium ion then gives the methylene derivative. For this reason, reduction of carbonyls with metal hydrides to the corresponding methylene compounds is limited to aryl aldehydes and ketones (Scheme 8).

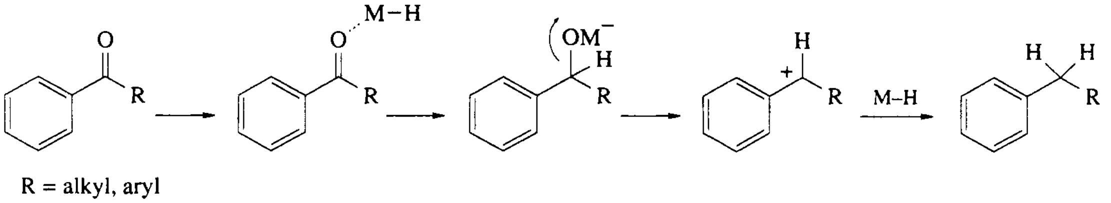

**Scheme 8**

Hydrogenolysis using lithium aluminum hydride under reflux without any additives requires the presence of strongly electron-donating groups such as alkoxy, hydroxy, and amino groups at the *ortho* or *para* position to the carbonyl substituent in the aromatic system (equation 13).[25,26]

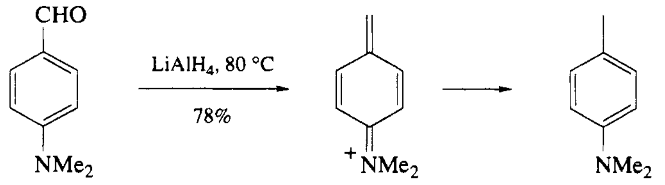

(13)

Similarly reduction of *o*- or *p*-hydroxy-substituted aryl ketones with $NaBH_4$ in refluxing aqueous NaOH solution[27] gives rise to an intermediate methylene quinone (**26**), which is further reduced to the desired methylene product (equation 14). When the hydroxy group is situated only at the *meta* position, there is no possibility to make such a methylene quinone intermediate, and the corresponding benzyl alcohol (**27**) is formed (equation 15).

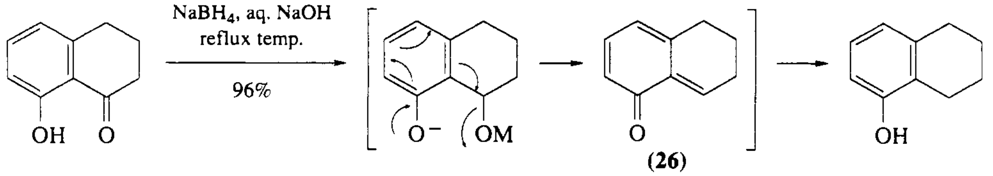

(14)

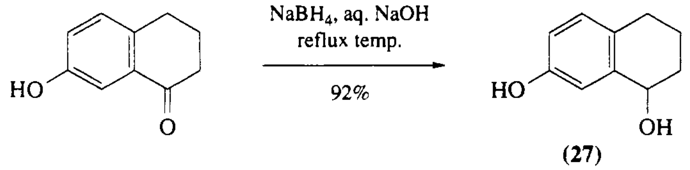

(15)

There is evidence that acyl protection of an *o*-phenolic group improves the yield of the corresponding methylene compound, and this method has been utilized for the reduction of flavanones to flavans.[28,29]

Methods using sodium cyanoborohydride in acidic solvents[30,31] are also applicable for ketone reduction. Černý and his coworkers postulated that sodium bis(methoxyethoxy)aluminum dihydride in xylene at *ca.* 140 °C[32–36] has a nearly equal effect compared with lithium aluminum hydride. The rather drastic conditions allow the cleavage of phenyl benzyl ether, and this alternative deprotection method was used in the synthesis of pentazocine (**28**; equation 16).[37]

Lithium aluminum hydride/Lewis acid reduction of aryl aldehydes carrying electron-donating groups at the *ortho* and/or *para* position proceeds even in ether under reflux within a short period, to give the corresponding methylene derivatives. Both diaryl and alkyl aryl ketones, with or without such substituents, can be reduced in the same way.[38–42] It should be noted that the active species in this system may be $AlH_3$ or $AlCl_xH_y$ generated from the 1:1–1:3 mixture of $LiAlH_4$ and $AlCl_3$. A related reduction with $NaBH_4/AlCl_3$ has also been reported.[43]

Brewster *et al.* have investigated reductions of α,β-unsaturated carbonyls with a 1:3 mixture of $LiAlH_4/AlCl_3$. The reduction is closely similar to the results mentioned above, with an allyl cation intermediate trapped by hydride attack to afford an alkenic product. As seen in equations (17) and (18),

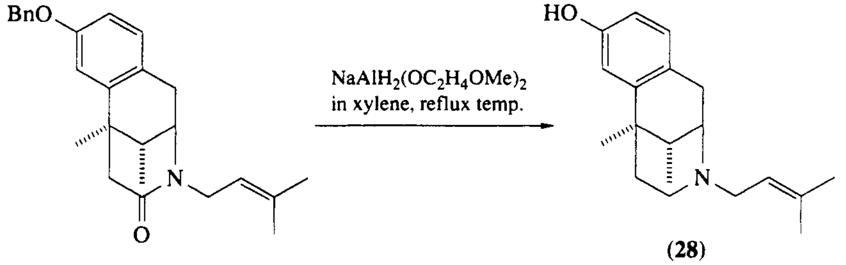

**(28)**

(16)

benzylidenecyclohexanone (**29**) gave benzylidenecyclohexane (**30**) and benzylcyclohex-1-ene (**31**) in a ratio of 7:3, and optically active carvone (**32**) afforded racemic limonene (**33**) through a symmetrical allyl cation intermediate.[41,42] This reagent was also used for reduction of steroidal unsaturated ketones, where the proportions of the various reduction products varied with the stability of the intermediate carbonium ions.[44,45]

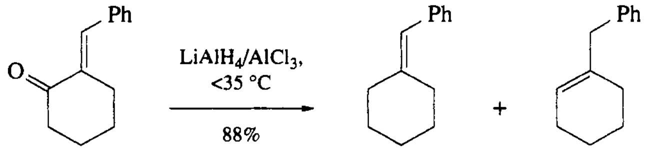

**(29)** **(30)** 70% **(31)** 30%

(17)

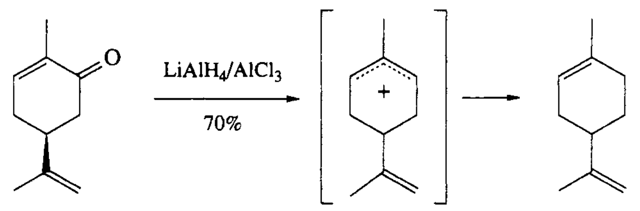

**(32)** **(33)**

(18)

Although the mechanism is still uncertain, alkyl aryl ketones with a variety of substituents can be reduced with $LiAlH_4/P_2I_4$ in refluxing benzene.[46] Similarly, under very mild and rather neutral conditions ($NaBH_4/PdCl_2$, r.t.),[47] alkyl aryl or diaryl ketones are converted to the corresponding methylene derivatives without affecting an ester function. Similarly, aryl aldehydes in indole derivatives can be reduced to a methyl group using $NaBH_4$/10% Pd–C in boiling isopropyl alcohol.[48]

Reduction of diaryl ketones carrying functional groups at the *para* position can also be performed with $NaBH_4$/TFA even in the presence of an electron-withdrawing group such as an alkoxycarbonyl, nitro, or cyano group.[49,50] A similar reagent system, $NaBH_4/BF_3{\cdot}OEt_2$, was used for the reduction of indole derivatives;[51] however, the active species might be an electrophilic borane derivative, as discussed in Section 1.13.3.2.

Sodium cyanoborohydride/zinc iodide[52] can also reduce aryl ketones, including indoles and flavanones, to the corresponding methylenes in moderate yields, which depend on the aromatic substituents. For example, electron-withdrawing groups at the *ortho* and/or *para* positions depress the yields, whereas electron-donating groups give high yields. Lau and coworkers have proposed that this reaction may proceed by single-electron transfer, as shown in Scheme 9.[53]

### 1.13.3.2 Reduction with $BH_3$, DIBAL-H and Related Reagents

Diborane has been known to be an effective reagent for reductions of aldehydes and ketones to borate esters, which give alcohols on quenching. In the case of aryl carbonyl functions, reduction with this electrophilic reagent is closely related to those mentioned in Section 1.13.3.1. For further reduction of the borate ester to the corresponding hydrocarbon, elimination of the borate anion demands acceleration by electron-donating substituents at the *ortho* or *para* positions in the aromatic system, or else $BF_3{\cdot}OEt_2$ is needed as an additive, except for highly activated cases.[54,55] For this reason, *in situ* generated diborane,

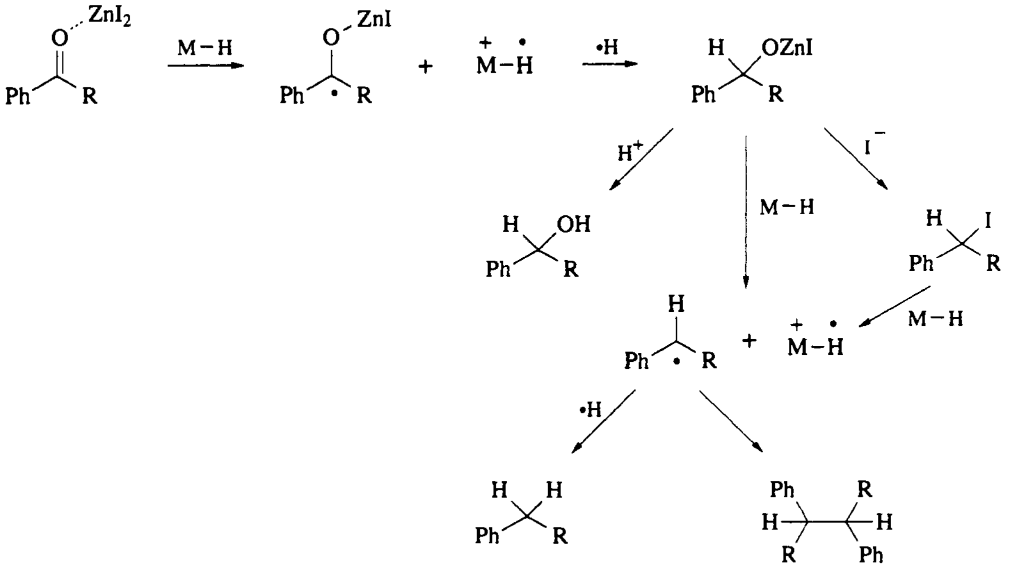

Scheme 9

still containing BF$_3$·OEt$_2$ and NaBH$_4$, may be the method of choice. Thus, substituted benzophenone derivatives were cleanly reduced to the corresponding hydrocarbons in high yields (equation 19), and 4-dimethylaminobenzaldehyde afforded 4-dimethylaminotoluene in 95% yield (equation 20).

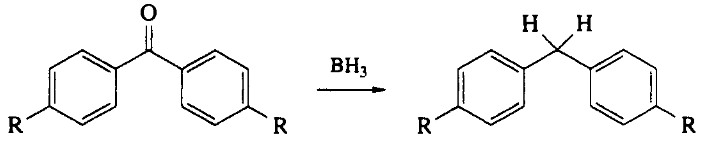

R = NMe$_2$, 90%
R = OMe, 95%

(19)

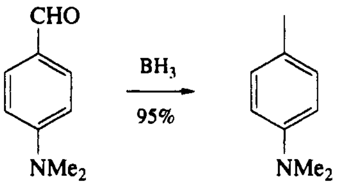

(20)

In the case of anisaldehyde, however, different results were obtained: on treatment with *in situ* generated diborane, the aldehyde gave a complex mixture including polymerized products derived from the cation (**A**), and *p*-methoxytoluene was not obtained (Scheme 10).[55]

Xanthone (**34**) and thioxanthone (**35**) are smoothly reduced with diborane in tetrahydrofuran at 0 °C to give the corresponding xanthenes (**36** and **37**). The ease of this reaction is explained by the formation of a stable xanthonium ion (**38**), generated by elimination of the borate ion (Scheme 11).[56]

The BH$_3$/BF$_3$·OEt$_2$ reagent reduces not only aryl ketones and aldehydes, but also cyclopropyl aryl or dicyclopropyl ketones to the methylene compounds without opening or rearrangement in the cyclopropyl unit (equation 21).[54]

*t*-Butylamine/borane/aluminum chloride has been reported to reduce aryl ketones and aldehydes to the corresponding methylenes without any effect on aliphatic and aromatic chloro or bromo substituents (equations 22 and 23). However, this reagent cannot be used for carbonyl compounds carrying such functional groups as acetoxy, alkoxycarbonyl and nitro groups, because of their easy reduction.[57]

During alkylation studies on 3,6-diethoxyxanthen-9-one (**39**), stepwise addition of diisobutylaluminum hydride and triisobutylaluminum in hexane yielded 3,6-diethoxyxanthene (**40**) in 75% yield, although on using these reagents separately the yield of (**40**) was much less, as shown in Scheme 12.[58]

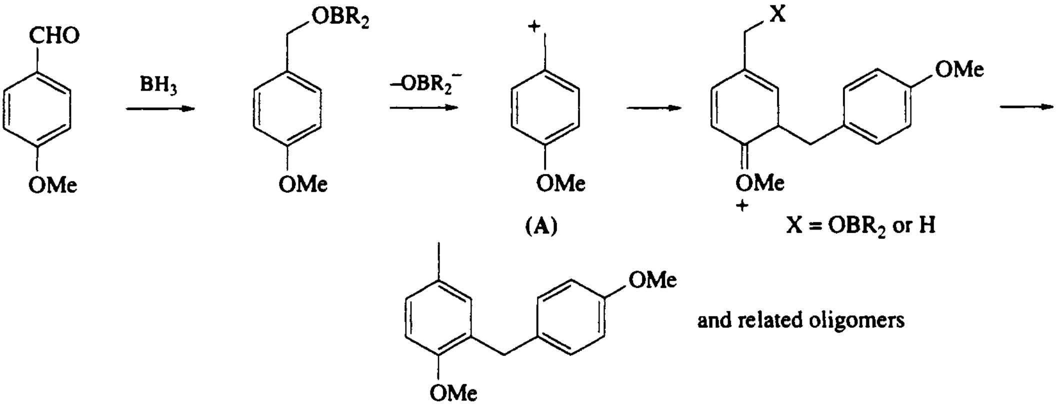
CHO
OMe
BH3
OBR2
OMe
–OBR2−
+
OMe
(A)
X
OMe
OMe
+
X = OBR2 or H
OMe
OMe
and related oligomers

Scheme 10

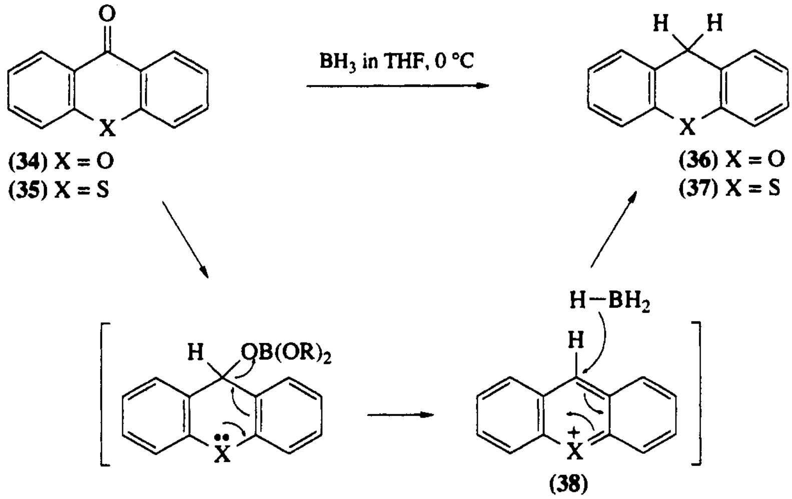
O
X
(34) X = O
(35) X = S
BH3 in THF, 0 °C
H H
X
(36) X = O
(37) X = S
H OB(OR)2
X
H–BH2
H
X
(38)

Scheme 11

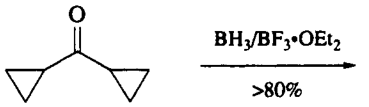
O
BH3/BF3•OEt2
>80%

(21)

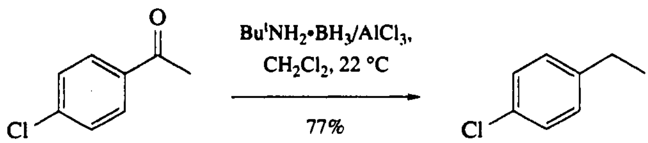
O
Cl
ButNH2•BH3/AlCl3,
CH2Cl2, 22 °C
77%
Cl

(22)

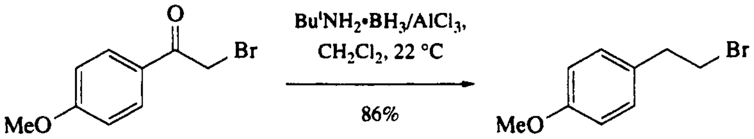
O
Br
MeO
ButNH2•BH3/AlCl3,
CH2Cl2, 22 °C
86%
Br
MeO

(23)

### 1.13.3.3 Ionic Hydrogenation

Ionic hydrogenation is the noncatalytic addition of hydrogen to carbon–carbon or carbon–heteroatom double bonds, and the hydrogenolysis of carbon–oxygen or carbon–halogen single bonds. Thus, the conversion of aldehydes and ketones to the corresponding hydrocarbon is one of its many manifesta-

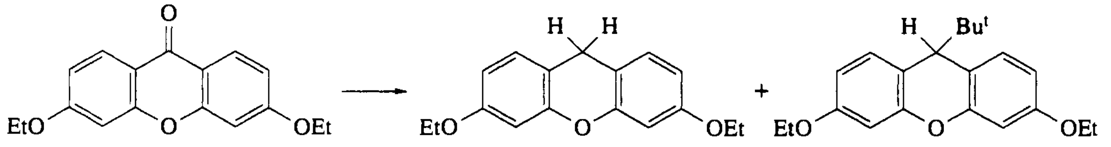

**(39)** **(40)**

| | | |
|---|---|---|
| Bu$^i_2$AlH, then Bu$^i_3$Al | 75% | - |
| Bu$^i_3$Al | 50% | 33% |
| Bu$^i_2$AlH | 52% | - |

Scheme 12

tions.[59,60] The reduction of the carbonyl system (Scheme 13) involves repeated protonation and hydride addition, and proceeds by way of an alcohol or its derivatives, which with some alkyl aldehydes and ketones can be isolated. From this viewpoint, ionic hydrogenation shows the same features as the other metal hydride methods, in which the ease of oxygen abstraction by electron-donating *ortho* or *para* substituents in the aromatic ring facilitates the reduction of aryl aldehydes and ketones. In this noncatalytic hydrogenation dimeric ether products are obtained as by-products, when the alcohol intermediate reacts with the starting material to form a hemiketal, which undergoes further protonation, dehydration, and hydride addition. Thus, benzaldehyde on ionic hydrogenation yielded dibenzyl ether in 80% yield.[61] This reduction is comparable with the conversion of ketals to ethers, which involves the formation of an alkoxy carboxonium ion followed by hydride addition.[59,60]

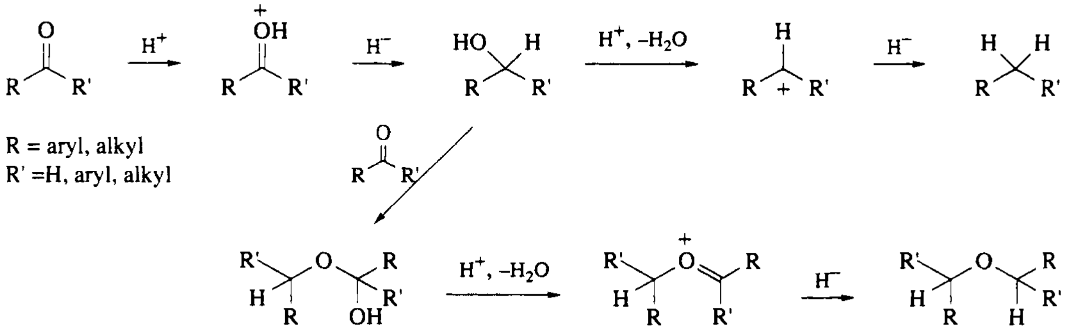

Scheme 13

Many acids, including Lewis acids, have been examined for their effect on the product distribution, whereas silanes, usually triethylsilane ($Et_3SiH$), are invariably the hydride donor, because acids do not react rapidly with silanes like $Et_3SiH$. In the original reagent combination, $Et_3SiH$/TFA,[61–64] reduction of alkyl aryl or diaryl ketones to the hydrocarbon has nearly no limitation, whereas alkyl aldehydes and ketones generally afford the corresponding alcohols or the symmetrical ethers. However, reduction of aryl aldehydes is affected by the aromatic substitution pattern: electron-withdrawing groups such as $NO_2$ and CN impede the second step, and yield the corresponding alcohols or ethers. Cyclopropyl phenyl ketone (**41**) can be reduced to cyclopropylphenylmethane (**42**) under these conditions, but ring opening also occurs, affording phenylbutane (**43**) as a by-product. Cyclobutyl phenyl ketone (**44**) gave cyclobutylphenylmethane (**45**), coupled with cyclopentane derivatives (**46** and **47**) derived from ring expansion of the carbenium ion intermediate (Scheme 14).[64]

Aryl vinyl ketones undergo reduction exhaustively to give arylpropanes in high yields.[65,66] Anthraquinone derivatives also react with $Et_3SiH$/TFA to afford the corresponding hydrocarbons, while *p*-quinone was converted to hydroquinone in 98% yield.[67]

The system consisting of gaseous $BF_3$/$Et_3SiH$ has been reported[68,69] to reduce aldehydes and ketones; thus benzaldehyde was reduced to toluene in 52% yield. In alkyl carbonyl compounds, aldehydes afford the corresponding alcohol products, whereas ketones, such as undecan-2-one and cyclohexanone, are readily converted to the hydrocarbons in high yields. On reduction with limited amounts of both reagents these alkyl ketones were reduced to the alcohols, indicating the intermediacy of the corresponding borate ester. In the case of aromatic compounds, aryl aldehydes and diaryl and alkyl aryl ketones are reduced to

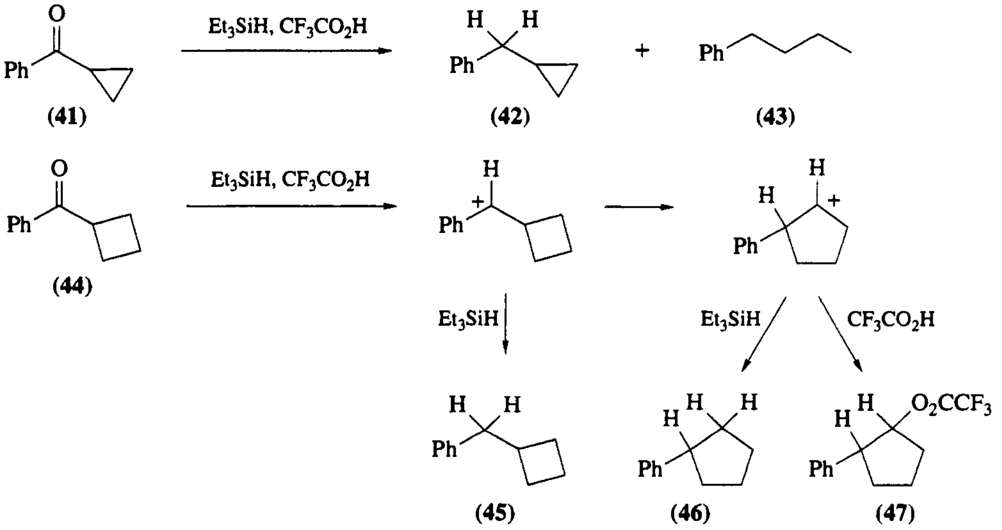

**Scheme 14**

the corresponding hydrocarbons in high yields, except for those carrying electron-withdrawing groups such as $NO_2$ and CN.

When $BF_3{\cdot}OEt_2$ was used in place of $BF_3$, the products in many cases were alcohols or symmetrical ethers. However, benzophenone and acetophenone were reduced to diphenylmethane and ethylbenzene in quantitative yields.[70] During attempts to isolate a borate ester, cyclohexene was obtained in 68% yield by direct distillation of a mixture of cyclohexanone, $Et_3SiH$ and $BF_3{\cdot}OEt_2$.[70] An analogous method using $BF_3{\cdot}OH_2$, the acidity of which is comparable to anhydrous sulfuric and hydrofluoric acids,[71] permits reductions of adamantanone, 1-tetralone and 2-acetonaphthalene to their methylene derivatives in 78, 67 and 70% yields, respectively, though the scope and limitation of this method have not yet been established.[72]

An alternative reduction method using $CF_3SO_3H$ and $Et_3SiH$ has been developed.[73] Diaryl ketones with *ortho-* or *para*-substituted groups including OH, Me, Br, F, $CF_3$ and $NO_2$, and acetophenone-type ketones undergo reduction to the corresponding methylenes. However, 4,4′-dimethoxybenzophenone did not react with this reagent, which evidently did not attack the highly stabilized protonated carbonyl group. Steric effects also interfere with the reduction. Dimesityl and mesityl xylyl ketones, for example, were not reduced, though mesityl phenyl ketone could be reduced to the hydrocarbon. The alkyl ketones, cyclohexanone and 2-adamantanone afforded the corresponding hydrocarbons in quite low yields; the major products were their alcohols.

## 1.13.4 HYDROGENOLYSIS OF AROMATIC ALDEHYDES AND KETONES

### 1.13.4.1 Catalytic Hydrogenation

Catalytic hydrogenolysis of carbonyl compounds to the hydrocarbons is a convenient method, in which the reaction proceeds *via* the corresponding alcohol. Although a variety of catalysts are known, this reduction is generally effective only with aromatic aldehydes and ketones. Platinum oxide is often used for reductions of aryl,[74] and α,β-unsaturated carbonyl compounds.[75] Depending on conditions, this catalyst can reduce even an aromatic system exhaustively; acetophenone for instance was converted to ethylcyclohexane in 84% yield.[76] A benzofluorenone derivative could be hydrogenolized to the benzofluorene (89%) using 10% Pd–C in ethanol, but on quenching after consumption of 1 mol equiv. of $H_2$, the corresponding benzyl alcohol was obtained in 93% yield.[77] Deuteriation of aryl carbonyl compounds with dideuterium in acetic *d*-acid in the presence of catalytic 10% Pd–C has been carried out. Under these conditions, the hydrocarbon products are labeled at the carbonyl carbon atom, and if present, at the benzylic methylene carbon atom.[78] Hydrogenolysis of relatively unhindered alkyl ketones at 190 °C in the presence of $Ni/Al_2O_3$ afforded the corresponding hydrocarbons;[79] however, substrates for this reduction are limited to relatively simple molecules, because other functional groups are sensitive towards this reagent.[80] As alternative catalysts, osmium on carbon,[81] molybdenum trioxide,[82] and iridium or rhodium derivatives[83] are also applicable for reduction of aromatic aldehydes and ketones.

Early work by Papa *et al.* indicated that reduction of carbonyl compounds with Raney nickel in alkaline solution gave the corresponding hydrocarbon or alcohol products,[84] and formation of the hydrocarbon was only feasible in the case of aromatic carbonyl compounds at 80–90 °C.[85] Mitchell *et al.* reported an improved method: under neutral conditions using W-7 Raney nickel in 50% aqueous ethanol, aryl aldehydes, alkyl aryl and diaryl ketones can be reduced to the methylene products in high yields.[86] Aromatic substituents such as nitro, cyano and halogen also suffer reduction under these conditions.

### 1.13.4.2 Hydrogen Transfer Reduction

Catalytic hydrogen transfer reduction is well known as a powerful method, not only for deprotection of benzyl ethers,[87] but also for the reduction of functional groups.[88] Reduction of carbonyl compounds provides either the corresponding alcohols or, particularly in the case of aromatic derivatives, the hydrocarbons. Brieger *et al.* found that reduction of aryl aldehydes and ketones to the aryl methylene products can be realized in good yields using cyclohexene or limonene as the hydrogen donor in the presence of a Pd–C catalyst, coupled with a promoter such as iron(III) chloride, aluminum chloride or even water.[89] The intermediacy of the benzyl alcohol under these conditions was proved by trapping its derivatives; for example, the reduction of anisaldehyde in the presence of acetic anhydride provided *p*-methoxybenzyl acetate in 83% yield (equation 24).[90] In the case of *o*-carboxybenzaldehyde, the benzyl alcohol intermediate had a chance to be trapped by the neighboring carboxyl group to form a γ-lactone which was stable under the reaction conditions (equation 25). Consequently, a mixture of (**48**) and (**49**) was obtained in 45 and 35% yields, respectively.[89]

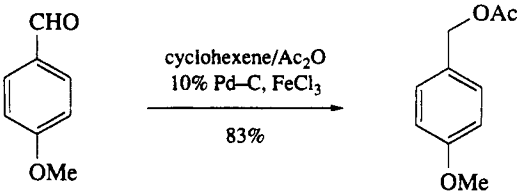

(24)

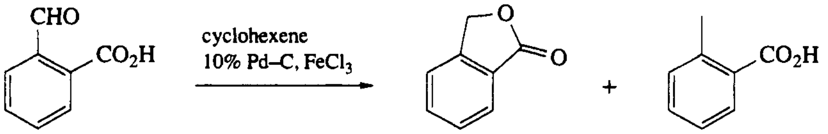

(**48**) (**49**)

(25)

Cyclopropyl phenyl ketone afforded quantitatively *n*-butylbenzene, instead of cyclopropylphenylmethane, because of the reactivity of the cyclopropyl group.[90] In the case of 6-methoxytetralone, a dehydrogenation product (**50**) was obtained in 20% yield together with the desired methylene compound (**51**) in 33% yield (equation 26). Because the tetraline structure of (**51**) can be a hydrogen donor, the newly formed product (**51**) may be consumed during the reaction; hence the formation of the naphthalene (**50**).[90]

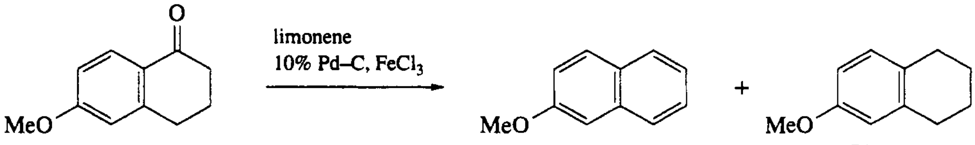

(**50**) (**51**)

(26)

The method using ammonium formate as a hydrogen donor has been reported to accelerate the reaction, but the selectivity of the reduction excludes nitro, halo or alkenic groups, which are reduced faster than the carbonyl group.[91]

## 1.13.5 ELECTROLYSIS OF NONCONJUGATED AND CONJUGATED ALDEHYDES AND KETONES

Electrolysis of carbonyl compounds provides pinacols, alcohols or hydrocarbons, depending on the conditions, such as pH, the nature of the electrode, and its potential.[92] Fundamental studies have been carried out on the mechanisms of hydrocarbon formation using acetone as a substrate.[93–95] Although several electrodes, such as Cd, Pt, Pb or Zn, are recommended, carbonyl compounds, including aryl and alkyl derivatives, require strong aqueous acidic media for reduction to the hydrocarbons. The mechanism of the electrolytic reduction is probably similar to that of Clemmensen reduction, which starts from anion radical formation by one-electron transfer, as indicated in Scheme 3. The difference is that electrolytic reduction takes place in an electric double layer, rather than on the surface of the zinc metal.

In the case of aryl aldehydes and ketones, benzaldehyde afforded benzyl alcohol as the major product, but acetophenone and its *para*-substituted derivatives carrying such groups as OMe, Cl or OH provided ethylbenzene derivatives in good yields. As with Clemmensen reduction, the alcohol produced in this reduction cannot be further reduced, and the alcohol is not therefore an intermediate. Still uncertain in the reaction mechanism of electrolytic reduction, however, is the role of adsorbed hydrogen.[96]

Electrolytic reduction of alkyl ketones, such as the conversion of menthone to menthane using a cadmium cathode in dilute sulfuric acid, can be seen in early work,[97,98] and electrolytic reduction of alkyl ketones has also been applied to such steroidal ketones as 7-oxo-,[99] 12-oxo-,[100] 3-oxo- (equation 27), 19-oxo- and 20-oxo-derivatives[101,102] using Pb,[99,102] Cd,[100] or Hg[101] electrodes in solvents containing sulfuric acid. One purpose of these deoxygenations was deuterium labeling of the carbonyl carbon atom, and products with high isotopic purity have been obtained, except with the 3-one derivative which afforded a significant amount of $d_3$ and $d_4$ isotopic impurities, because of enolizable protons α to the carbonyl group.[99,101]

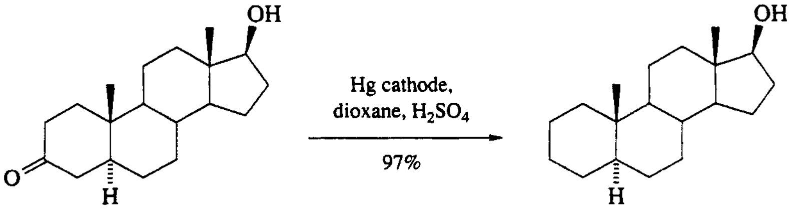

(27)

As shown in equation (28) the 17-hydroxy group at the α position to the carbonyl group at C-20 was easily removed, whereas the isolated 3-hydroxy group was unaffected. This fact supports the carbanion intermediate in the mechanism. During these studies, it was found that alkyl aldehydes can also be reduced to the corresponding methyl derivatives.[102,103]

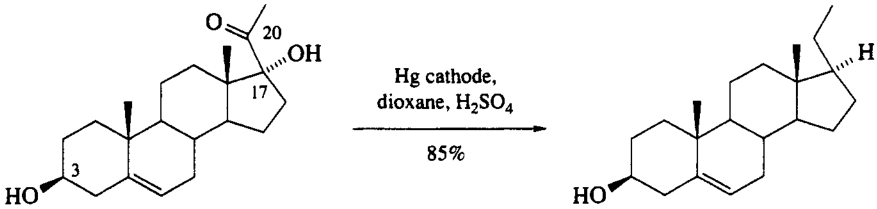

(28)

As in the electrolysis of α-ketols, the α-amino ketone (**52**) was reduced using a Pb cathode in 30% sulfuric acid to give (**53**) *via* C(α)—N bond cleavage.[104] This reduction was extended to medium-size ring formation, in which the product distribution between the ring-expanded product (**54**) and the ring-rearranged product (**55**), depends on the ring size of the starting material (Scheme 15).[105–107]

As mentioned in Section 1.13.2.2 (Clemmensen reduction), 1,3-diketone derivatives give rise to ring contraction products *via* cyclopropanediols, which can be trapped as acetates. On electrolysis using a Hg cathode in the presence of acetic anhydride, the 1,3-diketone (**18**) afforded a mixture of stereoisomers (**19**) in 33% yield, and a similar electrolysis of (**56**) gave (**57**) in 71% yield (equation 29).[22]

## 1.13.6 MISCELLANEOUS

In addition to the aforementioned methods and to those discussed in Chapter 1.14 (this volume), there are several other methods for the reduction of carbonyl functions to the corresponding methylenes.

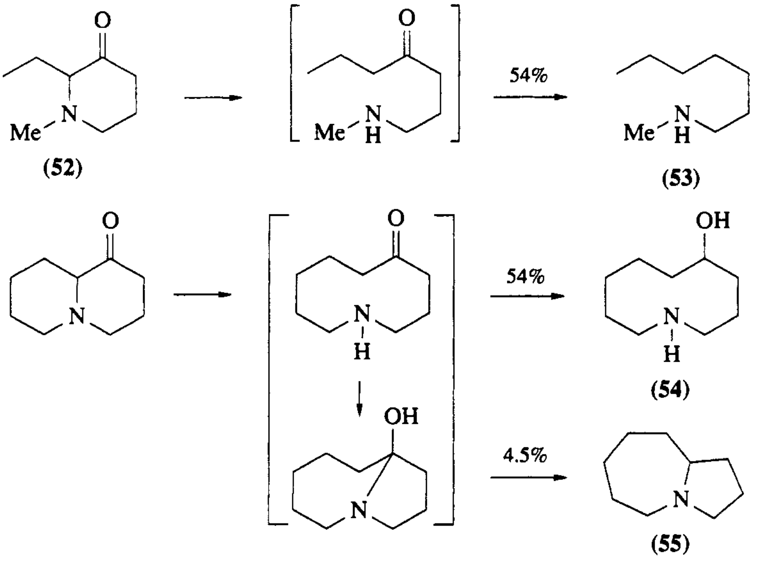

**Scheme 15**

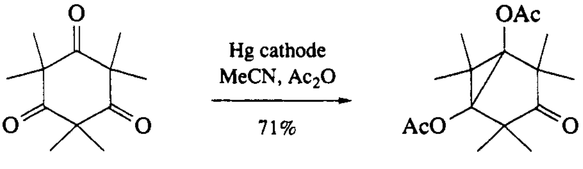

**(56)** **(57)** (29)

The reducing ability of silicon hydride has long been known, and in Section 1.13.3.3 we discussed ionic hydrogenation using the triethylsilane/acid combination. In addition, diphenylsilane at high temperature without any additives converted several diaryl ketones to the corresponding hydrocarbons. For example, 10-thiaxanthenone could be reduced with $Ph_2SiH_2$ at 260 °C to 10-thiaxanthene in 64% yield. A more detailed study has been carried out on benzophenone, which was reduced at *ca.* 260 °C to diphenylmethane in 37% yield. Benzhydryloxydiphenylsilane (**58**) was formed at 230 °C, and this compound could be converted at 270 °C to diphenylmethane, showing that (**58**; Scheme 16) is an intermediate in this reduction.[108,109]

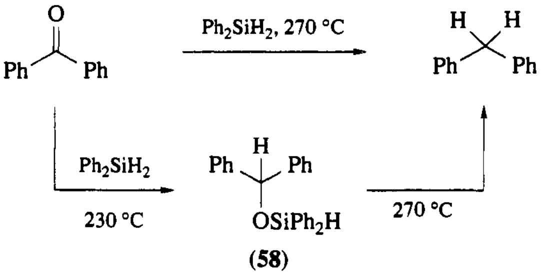

**Scheme 16**

A related reduction utilizing other silicon hydrides has been investigated by Benkeser.[59,110] Aryl aldehydes and ketones reacted with trichlorosilane–tri-*n*-propylamine to give an organosilicon derivative (**59**; Scheme 17), which on alkaline hydrolysis underwent silicon–hydrogen exchange, and consequently yielded the corresponding hydrocarbons.

Reduction of aryl ketones using $Ph_3SnH$ and acetyl chloride has been reported.[111] The stepwise process is indicated in Scheme 18. Depending on the nature of the carbonyl carbon, chloride and/or acetate intermediates are formed, of which the latter is trapped, but the former is further reduced by the tin hydride.

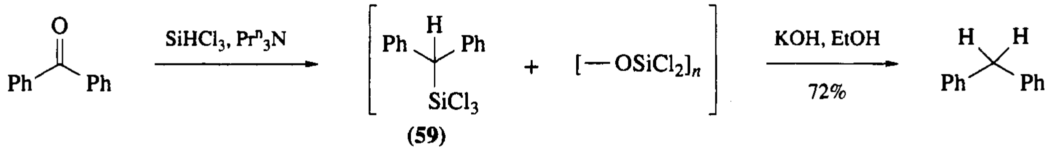

**Scheme 17**

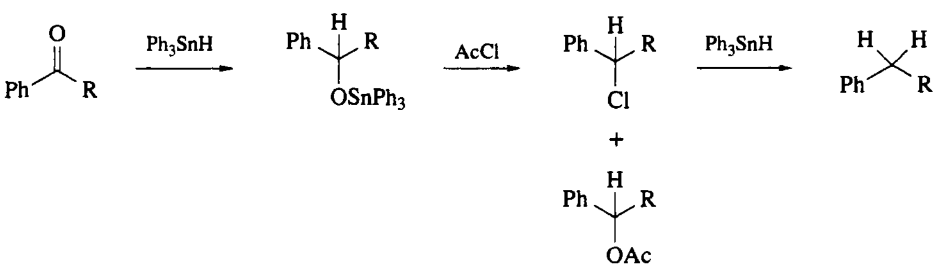

**Scheme 18**

As an application of selenium chemistry, reduction of aryl ketones with CO and $H_2O$ in the presences of selenium and DBU has been carried out. The reduction, indicated in Scheme 19, can be considered as a redox reaction by CO and $H_2O$. This reaction proceeds in high yield with only a catalytic amount of selenium. Although the reaction mechanism has not been clarified, this reaction probably involves an organoselenium hydride intermediate (**60**), which is known to give the corresponding hydrocarbon under the reaction conditions.[112]

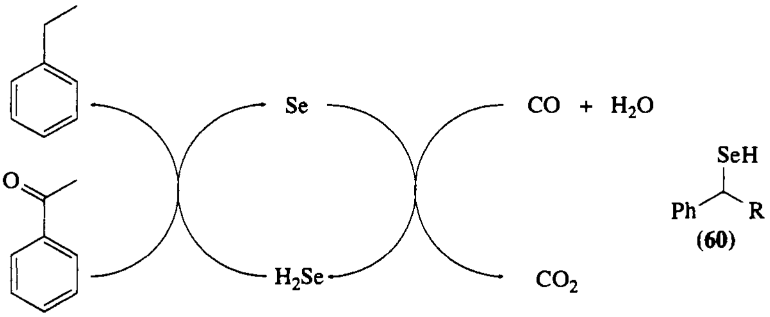

**Scheme 19**

As a variation of the hydrogen transfer method, reduction of diaryl ketones with $H_2S$ generated from hydrogen and sulfur in the presence of catalytic $MoS_3$ and *p*-TsOH afforded the corresponding diarylmethane under high pressure and at high temperature. In this case, clean reduction is limited to ketones, such as diarylketones, carrying no proton α to the carbonyl group (Scheme 20).[113]

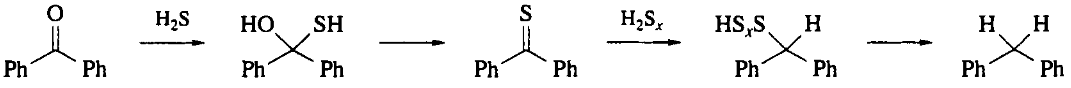

**Scheme 20**

Diaryl ketones, such as *o*-bromobenzophenone[114] and fluorenone carboxylic acids,[115,116] are reduced by HI and red phosphorus in acetic acid or propionic acid under reflux, giving *o*-bromophenylphenylmethane and fluorene carboxylic acid in high yields.

As a rather special case, alkyl aldehydes are reduced with titanocen dichloride to the hydrocarbons through a titanium-bonded alkenic intermediate as shown by a deuterium-labeling experiment. Thus, dodecanal was converted to dodecane in 71% yield, along with dodecan-1-ol in 15–20% yield; alkyl ketones such as adamantan-2-one and dodecan-6-one afforded alcohols as the major products. No reduction occurred in the case of aryl aldehydes where alkene formation is impossible.[117]

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# 1.14

# Reduction of C=X to CH2 by Wolff–Kishner and Other Hydrazone Methods

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## 1.14.1 INTRODUCTION

Since its introduction early in this century,[1,2] the deoxygenation of aldehydes and ketones to methyl or methylene derivatives, respectively, *via* base treatment of hydrazone intermediates (equation 1) has proven to be one of the most convenient and synthetically useful processes available for this important type of transformation. The reaction is termed the Wolff–Kishner reduction in recognition of the two original independent discoverers.[1,2] However, the initial recipes introduced proved tedious and unreliable with many structural, especially hindered, examples. This led to substantial efforts devoted over the years to developing more convenient and successful experimental procedures, resulting in a number of improved and more reliable modifications which are most often utilized at present. More recently, modified procedures have been provided which utilize hydride reductions of *p*-toluenesulfonylhydrazone (tosylhydrazone) derivatives and subsequent decomposition to release the hydrocarbon products under much milder and less basic conditions than those normally required for Wolff–Kishner reductions (equation 2).

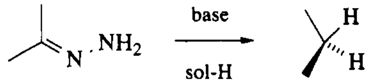

(1)

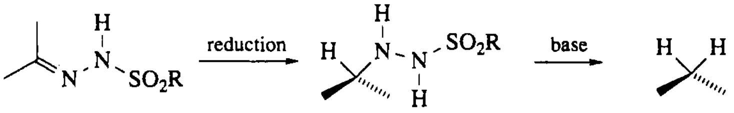

(2)

The synthetic utility of the Wolff–Kishner reduction has been the subject of several reviews.[3–6] However, the latest of these is over 20 years old[6] and fails to incorporate adequately many of the important advancements which have occurred in the past 25 years. This is particularly evident regarding the emergence over the past two decades of the above-mentioned reductions of sulfonylhydrazones with hydride donors as alternatives to standard Wolff–Kishner conditions. Consequently, this discussion will focus primarily on the period since the last major review (1968),[6] although some overlap with earlier work is essential for continuity and completeness. For further information and references to the older literature, the excellent aforementioned treatments[3–6] should be consulted. Reference 3 contains extensive tables of Wolff–Kishner reductions up to about 1947.

## 1.14.2 THE WOLFF-KISHNER REDUCTION OF ALDEHYDE AND KETONE HYDRAZONES

### 1.14.2.1 General Procedures and Mechanistic Aspects

The original protocols introduced for conversion of carbonyls to hydrocarbons by treatment with hydrazine and base involved the addition of the preformed hydrazone directly to hot potassium hydroxide (with[7] or without[1,8–10] added crushed platinized porous plate or palladium/barium sulfate[11]) at atmospheric pressure, or heating the hydrazone or semicarbazone with sodium ethoxide in a sealed tube at 160–200 °C.[2] In the ensuing years many variations of these procedures were introduced,[3] the most important of which was the use of high boiling point solvents to alleviate the inconvenience of sealed tubes or solid hydroxide and still achieve the high temperature (180–190 °C) necessary for decomposition of the hydrazones. Thus, Soffer[12,13] and, independently, Whitmore[14] (extending initial investigations by Ruzicka[15]) introduced the high boiling point solvents ethylene and triethylene glycols with which direct reductions of carbonyls were achieved *via* refluxing with hydrazine and dissolved sodium metal or sodium methoxide. These studies set the stage for the process known as the Huang-Minlon modification[16,17] and other improvements as discussed in the subsections to follow.

Mechanistic investigations[18–21] of Wolff–Kishner reductions implicate a hydrazone (**4**) as the initial intermediate generated from the carbonyl (**1**) and hydrazine or from decomposition of a preformed semicarbazone (**2**) or from an azine (**3**; Scheme 1). Subsequent rapid formation of the *trans*-hydrazone anion (**5**) by base-induced proton abstraction is followed by a rate-determining step that is viewed as an essentially concerted proton capture at the carbon coupled with a solvent-induced proton abstraction at the terminal nitrogen (*i.e.* **5**) to give a diimide anion (**6**). The process is completed by a rapid expulsion of nitrogen and protonation of the resulting carbanion (Scheme 1). An alkali metal hydroxide or alkoxide is normally employed as the basic catalyst, although with some systems (*i.e.* fluorenones[22]), excess hydrazine is also effective. Use of polar, aprotic dimethyl sulfoxide as solvent[23] or cosolvent with protic media[20] has been observed to increase the rate of, and greatly decrease the temperature required (from *ca.* 190 °C to as low as 25 °C)[23] for, Wolff–Kishner reductions, properties attributed to less efficient solvation of anions and the enhancement of the rate of proton removal by DMSO.[18,20,23,24] The greatest rate enhancement occurs with DMSO containing about 0.1–0.2 mol fraction of 2-(*t*-butoxyethoxy)ethanol[20] or *t*-butyl alcohol[24] as proton sources; greater concentrations of alcohol cause rapid decreases in the rates.[20,24]

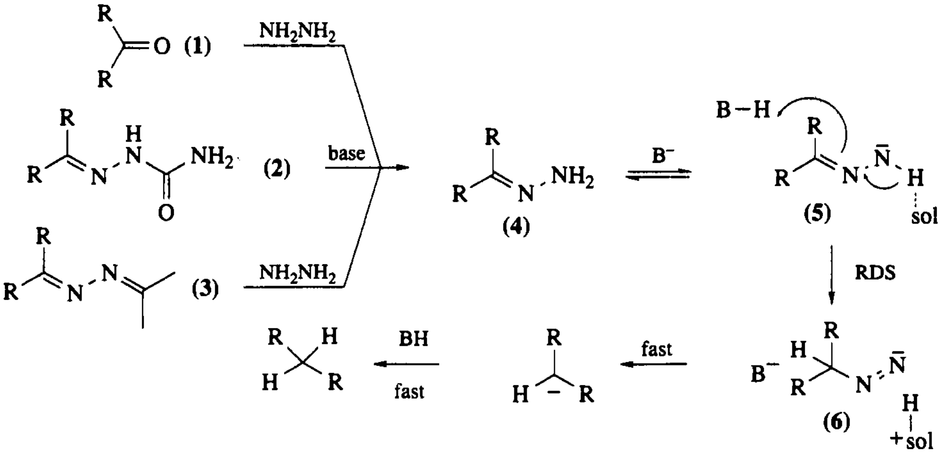

**Scheme 1**

## 1.14.2.2 Modified Procedures

The success of Wolff–Kishner reductions relies on two key processes, namely the reversible reaction of hydrazine with the carbonyl compound, which must be driven toward hydrazone formation, followed by base-induced decomposition of the hydrazone to generate a diimide anion and, subsequently, the hydrocarbon as depicted in Scheme 1. As expected, generation of the required hydrazones is highly dependent on the steric environment flanking the carbonyl and, consequently, much of the efforts devoted to improvements have focused on shifting the equilibrium toward the hydrazone by removal of water and/or the use of high concentrations of hydrazine. Coupled with this is the requirement to provide sufficient rates for the hydrazone decomposition step, which has generally meant modifications to provide increased reaction temperatures.

The most successful and synthetically useful of these modifications are discussed separately in the subsections which follow. It should be kept in mind, however, that like most synthetic methodologies, individual molecules often require further, usually slight, modifications so that within each category practitioners have utilized further variations as the need dictated. The most synthetically important of these will also be discussed.

### *1.14.2.2.1 The Huang-Minlon and related modifications*

As mentioned, in 1945, Soffer *et al.*[12,13] and Whitmore and coworkers[14] introduced the use of high boiling point solvents, such as ethylene or triethylene glycol, for Wolff–Kishner reductions in order to attain the high reaction temperatures necessary for the decomposition of the hydrazones. However, disadvantages remained, since large excesses of sodium metal and solvent were required, coupled with the need for 100% hydrazine and long reaction times (50–100 h). This was primarily due to the temperature-lowering effect of water produced in hydrazone formation, resulting in the necessity of vigorous conditions and long reaction times. In 1946, Huang-Minlon[16] provided adjusted reaction conditions (serendipitously)[25] in which excess hydrazine and water were removed by distillation subsequent to hydrazone formation. This raised the reaction temperature to the required 190–200 °C and permitted the use of the more convenient 85% hydrazine hydrate, much less solvent and sodium or potassium hydroxide as the base. Reaction times were also cut dramatically to 3–6 h. Thus, in the original disclosure,[16] the keto acid (**7**) was deoxygenated to (**8**) in 95% isolated yield (equation 3) compared to 48%[25] with the Soffer procedure and 54%[16] under Clemmensen conditions (Volume 8, Chapter 1.13).

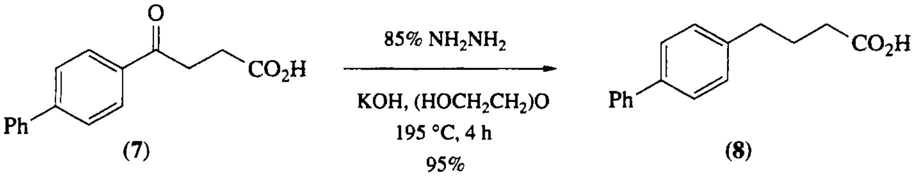

(3)

This efficient modification has become the standard general protocol for Wolff–Kishner reductions and has provided the basis for most further improvements introduced over the years. For instance, Lock[26] demonstrated that, for compounds sensitive to strong base, better results are obtained if the hydrazone is preformed by refluxing the carbonyl compound and hydrazine hydrate, while distilling out low boiling point components, followed by cooling, addition of the base and further refluxing (180–200 °C). On the other hand, the high refluxing temperatures usually associated with the Huang-Minlon procedure are not always necessary and several examples (*i.e.* veratraldehyde[27]) have been found which proceed well in the 135–160 °C range.[28,29]

The Huang-Minlon modification has been employed in an enormous number of synthetic endeavors, full coverage of which is beyond the scope of this discussion. However, Table 1 presents a collection of successful conversions, mostly from recent applications, chosen to illustrate a variety of structural types.

### *1.14.2.2.2 The Barton and related modifications*

In the course of applying his modification to steroid ketones, Huang-Minlon[17] observed that while carbonyls at positions C-3, C-7, C-12, C-17 and C-20 were smoothly deoxygenated, the highly hindered C(11)-keto site remained unaffected (see also entry 2, Table 1). To alleviate this problem, Barton and coworkers[45,46] introduced a modification, more vigorous than the Huang-Minlon process, by scrupulously avoiding moisture, and raising the temperature and time for the hydrazone decomposition. Thus, sodium was dissolved in dry diethylene glycol to generate an alkoxide base, hydrazine hydrate was replaced with anhydrous hydrazine, the apparatus was protected from outside moisture, excess hydrazine distilled until the temperature reached 210 °C, and refluxing extended for 12 h. Using this methodology, both carbonyls of 7,11-dioxolanostanyl acetate (**9**) were successfully removed[45,46] to afford (after reacetylation) lanosterol in 69% yield (equation 4). The requirement of anhydrous conditions is illustrated by the removal of only the 7-keto group of (**9**) in low yield (41%) using hydrazine hydrate and KOH.[47]

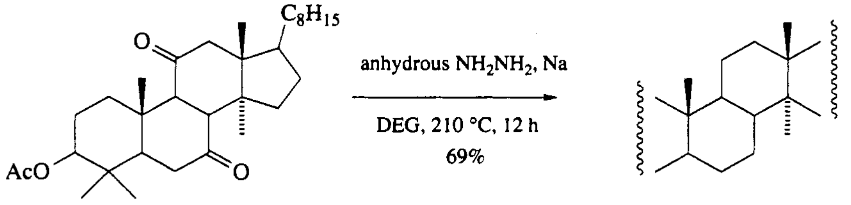

(**9**)

(4)

Since its introduction in 1954, the Barton modification[45] has enjoyed considerable utility in Wolff–Kishner reductions, especially with sterically hindered or otherwise relatively inaccessable ketones. A selection of structural examples is presented in Table 2.

Although the Barton procedure is usually successful with hindered carbonyls, failures or low yields have been noted. For example, ketone (**10**) was recovered unaltered, a result attributed to the extremely hindered environment of the carbonyl (**10** was also unaffected by $NaBH_4$ and failed to give a semicarbazone or 2,4-dinitrophenylhydrazone).[48] Likewise, Barton conditions failed to remove the highly hindered ketone in a triterpenoid (partial structure **11**).[49]

**Table 1** Wolff–Kishner Reduction of Carbonyls Using the Huang–Minlon Modification

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 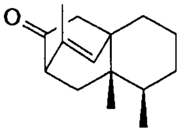 | 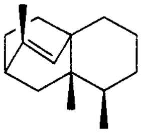 | 74 | 30 |
| 2 | 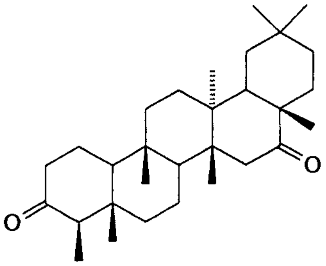 | 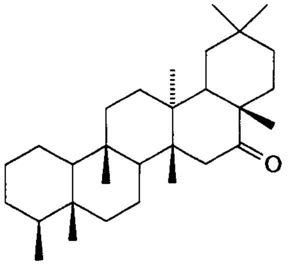 | 62 | 31 |
| 3 | 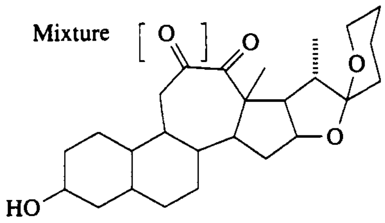 | 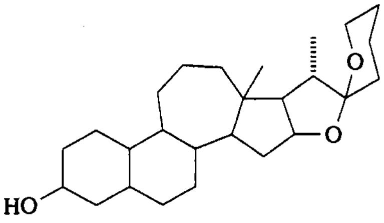 | 66 | 32 |
| 4 | 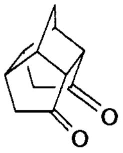 | 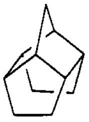 | 75 | 33 |
| 5 | 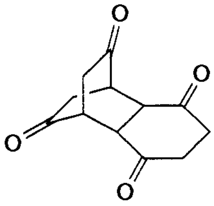 | 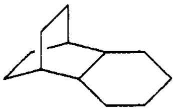 | — | 34 |
| 6 | 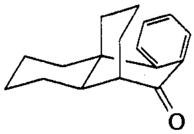 | 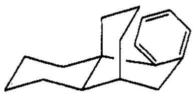 | 85 | 35 |
| 7 | 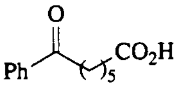 $PhC(O)(CH_2)_5CO_2H$ | 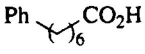 | 75 | 36 |
| 8 | 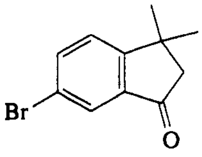 | 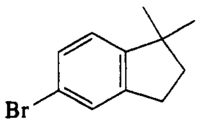 | 88 | 37 |

**Table 1** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 9 | 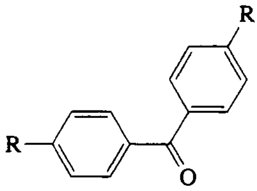 $R = F, Cl, SO_2Me, CN, NMe_2$ | 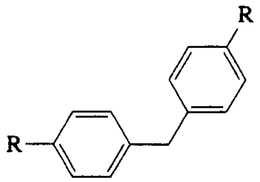 | 62–94 | 38 |
| 10 | 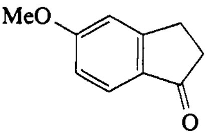 | 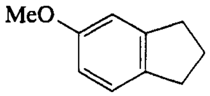 | 56 | 39 |
| 11 | 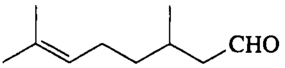 | 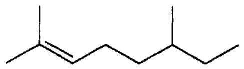 | — | 40 |
| 12 | 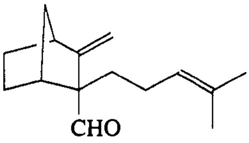 | 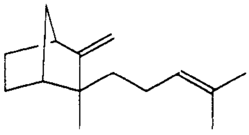 | 85 | 41 |
| 13 | 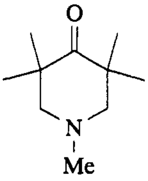 | 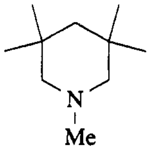 | 59[a] | 42 |
| 14 | 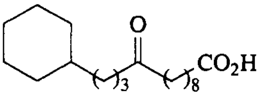 | 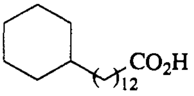 | 59 | 43 |
| 15 | 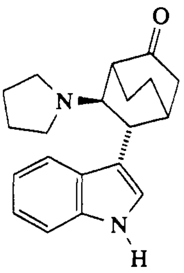 | 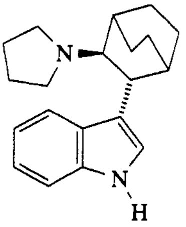 | 45 | 44 |

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[a] *Via* the preformed hydrazone.

A modification reportedly even more vigorous than the Barton procedure was introduced by Nagata and Itazaki[50] in which large excesses of hydrazine hydrate (66–400 mol %), hydrazine hydrochloride (8–30 mol %) and KOH (20–70 mol %) in triethylene glycol are heated (130 °C, 2.5–7 h) and then distilled until the temperature reaches 210–220 °C and heating continued for 3–5 h. Treatment of a hindered 11-keto steroid (partial structure **12**) under these conditions[50] afforded a 52% yield of the deoxygenated product, but only 36% using Barton conditions. However, reaction of the spiroketone (**13**) under the Nagata conditions afforded 100% recovery of starting material, while use of the Barton modification

**Table 2** Wolff–Kishner Reduction of Carbonyls Using the Barton Modification

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 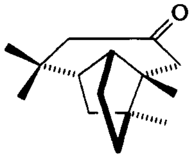 | 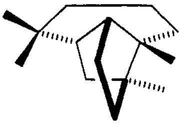 | 89 | 52 |
| 2 | 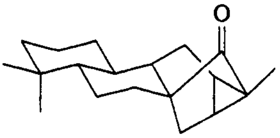 | 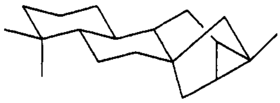 | 56 | 53 |
| 3 | 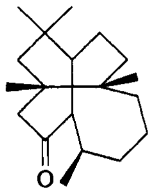 | 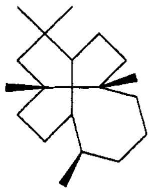 | 50 | 54 |
| 4 | 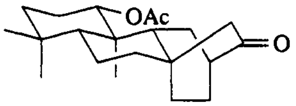 | 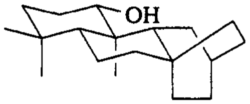 | 62 | 55 |
| 5 | 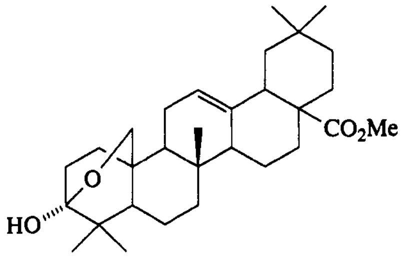 | 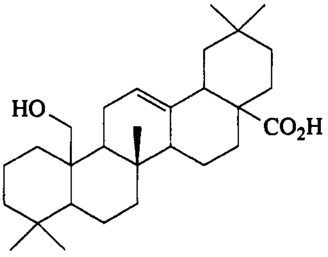 | — | 56 |
| 6 | 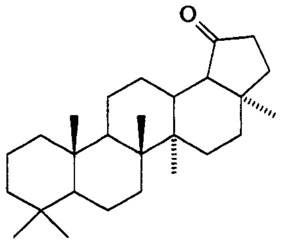 | 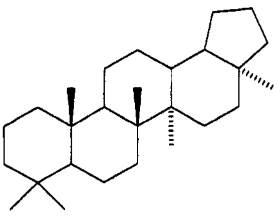 | 59 | 57 |
| 7 | 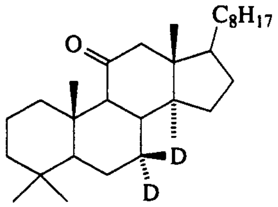 | 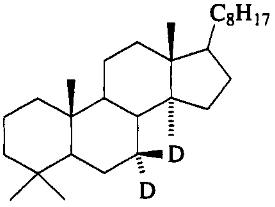 | 54 | 58 |

**Table 2** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
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| 8 | 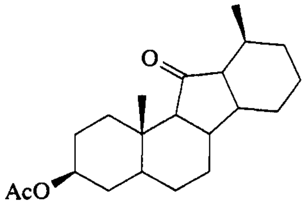 | 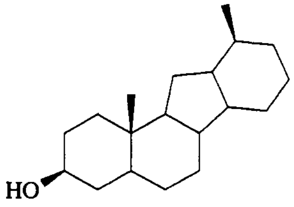 | 62 | 59 |
| 9 | 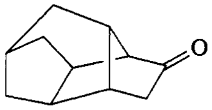 | 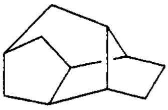 | 46 | 60 |
| 10 | 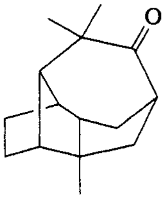 | 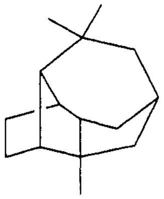 | 52 | 61 |
| 11 | 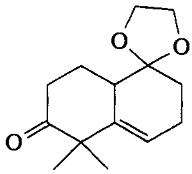 | 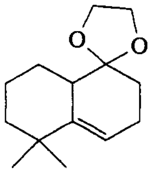 | — | 62 |
| 12 | 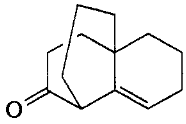 | 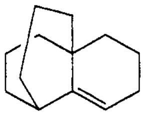 | 90 | 63 |
| 13 | 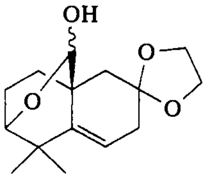 | 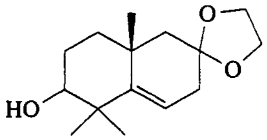 | 65 | 64 |
| 14 | 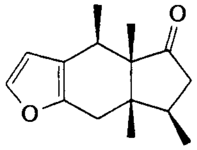 | 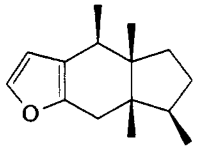 | 15 | 65 |

**Table 2** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 15 | 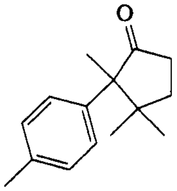 | 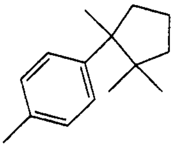 | 65 | 66 |
| 16 | 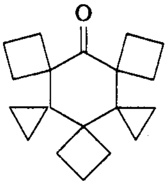 | 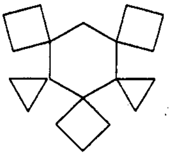 | 93 | 67 |

gave 85% of the desired hydrocarbon (**14**).[51] Thus, the efficiencies of these modifications appear to be structure dependent, and the proper choice is not always evident.

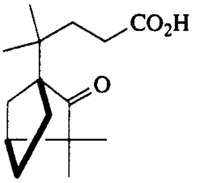

**(10)**

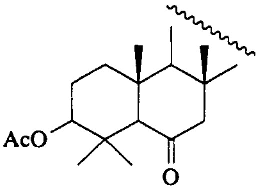

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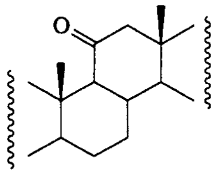

**(12)**

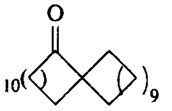

**(13)**

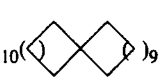

**(14)**

### 1.14.2.2.3 The Cram modification

As mentioned previously, DMSO as the reaction medium provides significant enhancement of Wolff–Kishner reaction rates and this allows the use of much lower temperatures to effect reductions. In 1962 Cram *et al.*[23] introduced the use of *t*-butoxide in dry DMSO for the successful reduction of preformed hydrazones at room temperature. Using this process, benzophenone hydrazone (**15**) afforded an 88% yield of diphenylmethane (**16**), along with 11% of benzophenone azine (**17**) as side product (equation 5). However, maximum success requires very slow addition (*i.e.* over 8 h) of the hydrazone to the reaction solution, otherwise yields of reduced products are decreased and azine formation augmented. Thus, addition of (**15**) over 0.5 h in the above reaction lowered the yield of (**16**) to 72%, while the yield of (**17**) was increased to 22%.[23] Other successful reductions reported[23] include hydrazones of benzaldehyde (67%), camphor (64%) and cyclohexanone (80%).

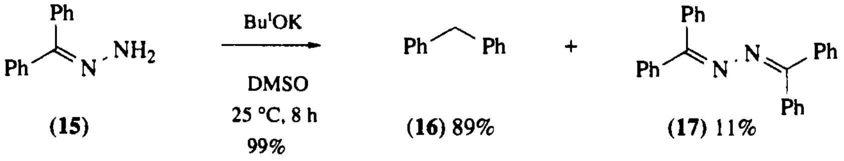

(5)

The Cram modification has not been greatly exploited in multistep synthetic endeavors, possibly because of the above-mentioned need to preform and isolate the hydrazone intermediate coupled with very slow addition of the hydrazone. This latter requirement is particularly inconvenient when milligram quantities are involved. The aldehyde in a triterpenoid (partial structure **18**) was successfully reduced to the corresponding methyl group using the Cram method, albeit in low yield (32%).[68] Notably, the hydrazone (10 mg) was not added slowly. The Cram process was not successful for the reduction of the cyclobutanone (**19**)[69] (the Huang-Minlon process succeeded), or the pyrrole aldehydes (**20**)[70] and (**21**).[71]

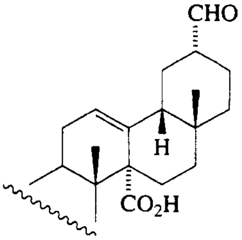

**(18)**

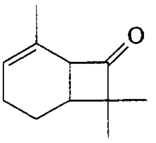

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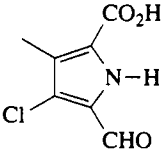

**(20)**

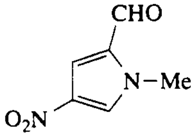

**(21)**

In view of the observations of Szmant and coworkers[20,24] that combinations of DMSO and protic solvents [*i.e.* *t*-butyl alcohol, 2-(*t*-butoxyethoxy)ethanol] provide more effective solvent systems for enhancement of Wolff–Kishner reduction rates than DMSO alone, the relative paucity of possible synthetic applications in this area is somewhat surprising. Indeed, Ramuz[72] successfully reduced the hydrazone of aldehyde (**22**) in 90% yield using the combination of potassium *t*-butoxide in DMSO containing ethylene glycol (at 100 °C). Further investigations concerning the synthetic utility of DMSO and protic solvent mixtures appears to offer significant potential.

### *1.14.2.2.4 The Henbest modification*

Another lower temperature modification of Wolff–Kishner reductions was introduced by Henbest and coworkers[73] in which carbonyl hydrazones and *t*-butoxide are refluxed in dry toluene (110 °C). Using this procedure, benzophenone hydrazone (**15**) afforded an 85% yield of diphenylmethane (**16**) in 4 h. Other conditions, including the use of DMSO at 40 and 100 °C, were explored, but with less success. The less vigorous conditions and lower temperatures appear particularly suited for carbonyl compounds prone to base-induced side reactions, primarily double bond migrations in α,β-enones[74] and functional group eliminations of certain α-substituted ketones.[75] Thus, the α-amino ketone (**23**) afforded an 83% yield of the reduced product (**24**),[73] while standard Wolff–Kishner conditions afforded (**24**) in only 44% yield, along with the elimination products 3,3-dimethylbutene and 2-methylpiperidine in 38% yield.[75] The Henbest modification has been used successfully to deoxygenate a variety of hydrazones, examples of which are illustrated in Table 3. Note that in entries 2 and 5 (Table 3), reductions were effected without concomitant migration of the α,β-double bonds and the lactam functionalities in entries 7 and 8 survived. Likewise, the dibenzocyclooctanone hydrazone (entry 4) was reduced, but elimination of the very labile α-hydroxy group was also observed.[79] Failures with the Henbest modification have been noted with the cycloheptanone (**25**)[84] and the enone (**26**).[85]

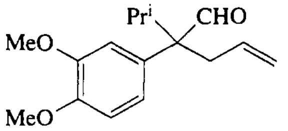

**(22)**

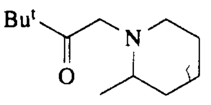

**(23)**

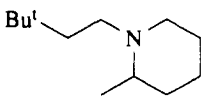

**(24)**

### *1.14.2.2.5 Reductions of semicarbazones*

Carbonyl semicarbazones often provide suitable alternative derivatives for Wolff–Kishner reductions *via* generation *in situ* of the requisite hydrazone intermediates under basic conditions (Scheme 1).[2] Although the process is successful under standard Wolff–Kishner conditions (*i.e.* sealed tube, 205 °C[86] and

**Table 3** Wolff–Kishner Reduction of Carbonyl Hydrazones Using the Henbest Modification

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 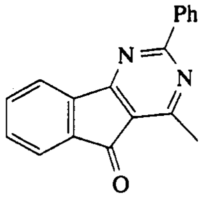 | 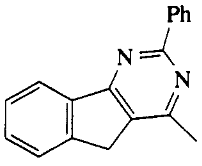 | 37 | 76 |
| 2 | 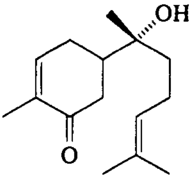 | 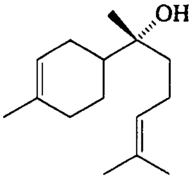 | — | 77 |
| 3 | 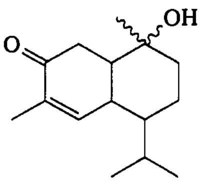 | 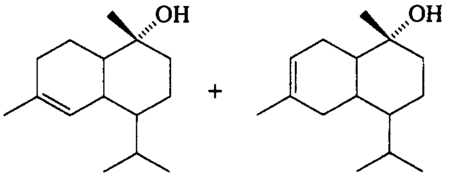 2:1 | 94 | 78 |
| 4 | 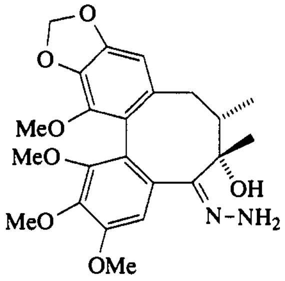 | 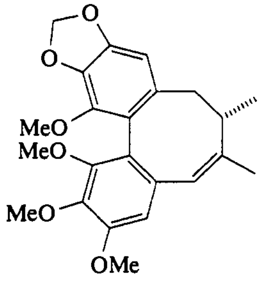 | 60 | 79 |
| 5 | Cholest-4-en-3-one | 4-Cholestene | 65 | 73 |
| 6 | 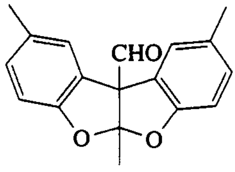 | 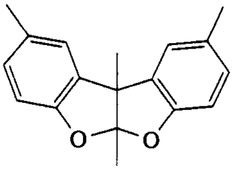 | 50 | 80 |
| 7 | 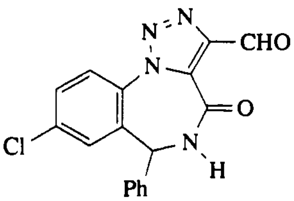 | 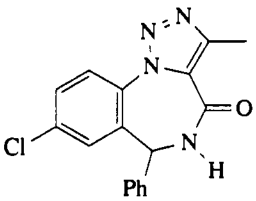 | 91 | 81 |

**Table 3** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 8 | 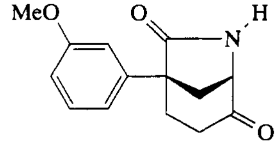 | 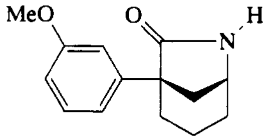 | 91 | 82 |
| 9 | 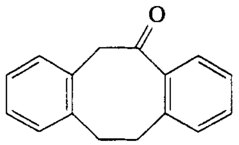 | 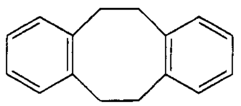 | 75 | 83 |

the Huang-Minlon modification[87,88]), utilization of the Henbest modification,[73] described in the previous section for hydrazones, appears to offer the most synthetic potential, especially for α,β-unsaturated carbonyls. Examples of successful conversions using the Henbest procedure are presented in Table 4. Entries 1–5 illustrate the absence of migration of double bonds adjacent to the carbonyl under these conditions. Noteworthy in this regard, the α,β-unsaturated enone in entry 5 afforded only the rearranged product (**27**) when reduced using Huang-Minlon conditions.[92] The Henbest procedure was unsuccessful in reducing the semicarbazone of 3-ketonorlongifolane (**28**).[94]

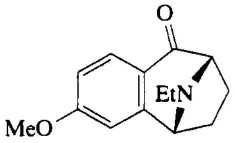

**(25)**

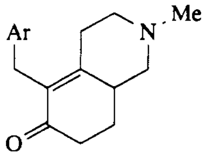

**(26)**

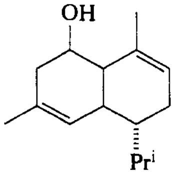

**(27)**

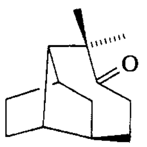

**(28)**

### *1.14.2.2.6 Other modifications*

As noted above, certain structural types of carbonyls have been observed to be reduced to the hydrocarbons by excess hydrazine without the use of strong bases such as hydroxide or alkoxide. Thus, fluorenones,[22] benzoylnaphthalenes, benzophenone, benzaldehyde and pyrene-3-carbaldehyde are reduced in good yields by heating with hydrazine hydrate.[3] In the absence of strong base, these reductions may proceed in an alternative manner to that depicted in Scheme 1 *via* isomerization of the hydrazones to the corresponding diimides (**29**), which are known to degrade with expulsion of nitrogen to give hydrocarbons (equation 6).[95]

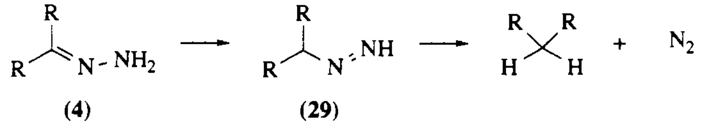

(4) (29)

(6)

## 1.14.2.3 Scope and Limitations

### *1.14.2.3.1 Chemoselectivity*

As expected, functional groups which are sensitive to the vigorous basic conditions of most Wolff–Kishner reduction conditions do not survive intact. Thus, esters and lactones are normally hydrolyzed to the corresponding acids and alcohols[6,17] (see, for examples, entries 4, 5 and 8, Table 2) and require

**Table 4** Wolff–Kishner Reductions of Carbonyl Semicarbazones Using the Henbest Modification

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 4-Cholesten-3-one | 4-Cholestene | 81 | 73 |
| 2 | 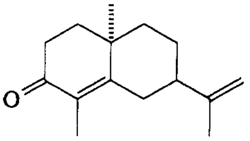 | 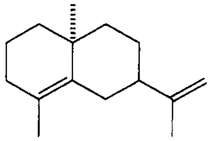 | — | 73 |
| 3 | 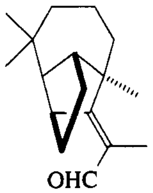 | 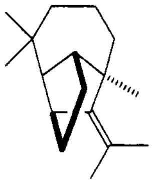 | 85 | 90 |
| 4 | 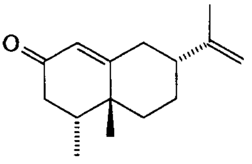 | 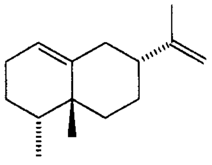 | — | 91 |
| 5 | 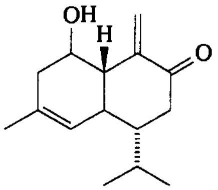 | 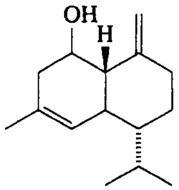 | — | 92 |
| 6 | 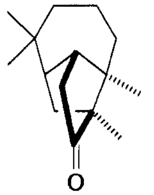 | 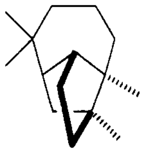 | — | 93 |

reesterification. Likewise, amides and lactam moieties are susceptible to attack. For instance, the lactam substrate of entry 8, Table 3 gave a low yield (36%) of the Wolff–Kishner product along with hydrolysis of the lactam. As indicated, this problem may be at least partly avoided by use of the Henbest modification (see also entry 7, Table 3).[82] It might be expected that nitriles would also be affected, but this does not always appear to be the case, at least with aryl derivatives (entry 9, Table 1).[38] Occasionally, reduction of ketones to alcohols is observed[3,6] if the Wolff–Kishner reduction is not successful. Thus, compound (**25**) afforded a mixture of the corresponding alcohol along with starting material under Henbest conditions,[84] and a triterpene ketone (partial structure **30**) gave only the corresponding alcohol, even under the forcing Nagata modification.[96]

Simple aliphatic halogenated compounds containing β-hydrogens are, of course, not expected to survive since Wolff–Kishner conditions simulate typical β-elimination and substitution conditions (hot hydroxide, alkoxide). An 11,20-diketo-12-bromo steroid (partial structure **31**) was debrominated along with deoxygenation of the 20-keto group to afford the 11-keto derivative (partial structure **32**) along with an unidentified isomer of (**32**).[17] The product possibly arises from attack on bromine by hydrazine to afford the corresponding enol, which survives and returns (**32**) upon protonation. Reduction of the chlorotetracyclo derivative (**33**) afforded the pentacyclo compound (**34**; 49%) resulting from internal substitution by the intermediate carbanion (Scheme 1).[97]

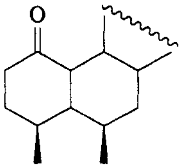

**(30)**

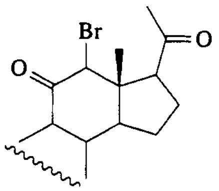

**(31)**

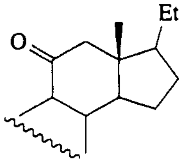

**(32)**

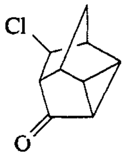

**(33)**

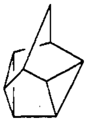

**(34)**

Although reductions of aromatic iodides and bromides have been noted,[4,6] such is not always the case, at least with bromides (see entry 8, Table 1; the corresponding 6-bromo derivative also survived Wolff–Kishner conditions[37]). Aromatic chlorides are normally not affected (entries 9, Table 1 and 7, Table 2).

Aromatic nitro compounds are reduced to amines by hydrazine in hot diethylene glycol with or without base.[98] In the presence of alkali *p*-nitrotoluene affords the dimeric *p,p′*-diaminostilbene, while *p*-toluidine is obtained without the base.[98]

### *1.14.2.3.2 Steric effects*

As previously discussed, Wolff–Kishner reductions are hampered by steric hindrance surrounding the carbonyl primarily due to difficulty in the requisite hydrazone formation. Forcing conditions such as the Barton[45] and Nagata[50] modifications have alleviated many of the problems with hindered ketones (*i.e.* 11-keto steroids, equation 4), but unyielding problems still remain (*i.e.* structures **10** and **11**) requiring alternative strategies for oxygen removal.

### *1.14.2.3.3 Isomerization of conjugated and other double bonds*

Subjection of α,β-unsaturated carbonyls to Wolff–Kishner conditions often leads to at least partial migration of the double bond to give mixtures of alkene products.[6,74] Such migrations are not unexpected since an allylic carbanion is produced, which may be protonated at two positions. Thus, isophorone affords a mixture of the alkene (**35**; 30%) along with the unrearranged isomer (**36**; 70%; equation 7).[99] This problem is at least partly alleviated by application of the Henbest modification as illustrated in Tables 3 and 4. Thus, while the enone semicarbazone in entry 2, Table 4 afforded only the unrearranged alkene using *t*-butoxide in toluene, conventional Wolff–Kishner conditions gave 50% of the rearranged isomers (**37**).[89]

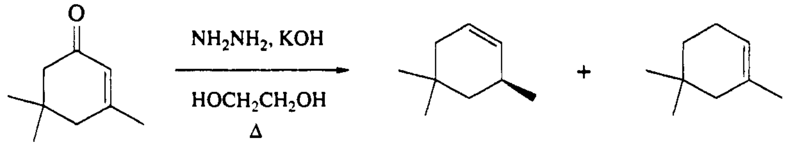

**(35)** 30% **(36)** 70% (7)

Rearrangements of nonconjugated alkenes have also been observed. Thus, a triterpenoid (partial structure **38**) afforded the alkene (**39**; 32% yield) upon reduction (Barton modification), a result attributed to initial base-induced isomerization of (**38**) to the corresponding α,β-unsaturated ketone followed by rearrangement during reduction.[100]

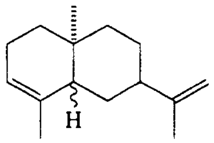

**(37)**

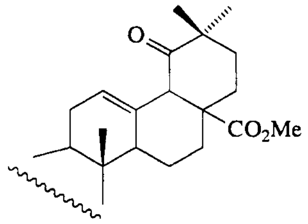

**(38)**

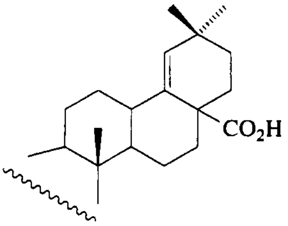

**(39)**

### 1.14.2.3.4 *Elimination of adjacent substituents (Kishner–Leonard eliminations)*

Aldehydes and ketones bearing heteroatom substituents on the carbon adjacent to the carbonyl often afford alkene side products when subjected to Wolff–Kishner conditions,[1,6,75,101] the amount depending on the leaving ability and steric environment of the substituent.[75] Thus, a series of substituted pinacolones $Bu^tCOCH_2X$ (**40**) with X = *N*-piperidinyl, trimethylacetoxy, thiophenoxy and phenoxy afforded the elimination product 3,3-dimethylbutene in 29, 52, 76 and 80% yields, respectively, in approximate order of leaving ability. The reaction (Kishner–Leonard elimination) is depicted as proceeding either through the diimide anion (**6a**), which fragments *via* elimination to an alkene (equation 8) instead of continuing to the reduction product,[75] or *via* a vinyl diimide (**29a**) as pictured in equation (9).[102] As noted previously, application of the Henbest modification (*t*-butoxide, refluxing toluene)[73] lowers the tendency for elimination, at least for amino substituents.

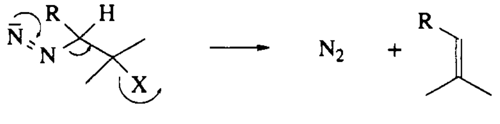

(8)

**(6a)**

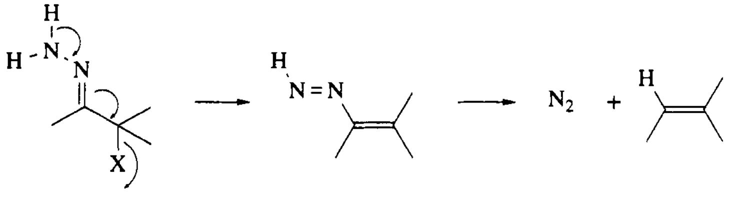

(9)

**(29a)**

Kishner–Leonard type eliminations also occur with certain α-substituted carbonyls upon treatment with hydrazine alone, the most synthetically important of which is the fragmentation of α,β-epoxy ketones to allylic alcohols (the Wharton reaction, equation 10).[6,102] The Wharton process has found application in a significant number of synthetic schemes, two of which are illustrated in equations (11)[103] and (12).[104] The latter provides the pivotal step in an efficient protocol for enone transpositions. Further reduction of the initial alkene products by diimide to afford saturated derivatives is often obtained,[6,105,106] but this can usually be prevented by exclusion of oxygen and/or adding an alkene to absorb any diimide generated.[105,106] Other side reactions,[105] including pyrazole formation, have also been noted.[107,108] Similar eliminations of α-halocyclohexanones (including α-fluoro derivatives) also appear synthetically useful, while α-sulfonyloxy and corresponding aliphatic derivatives give inferior yields.[106]

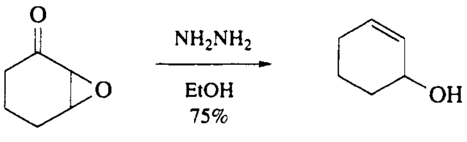

(10)

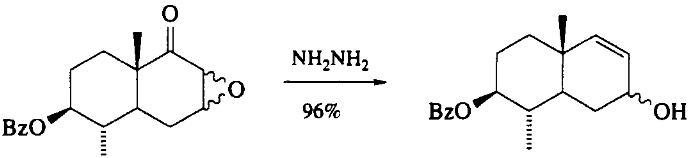

O
O
BzO
$NH_2NH_2$
96%
BzO
OH

(11)

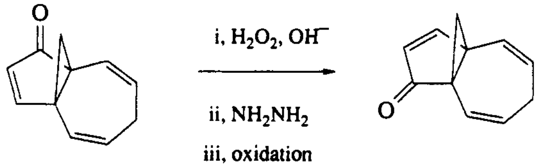

O
i, $H_2O_2$, $OH^-$
ii, $NH_2NH_2$
iii, oxidation
O

(12)

### 1.14.2.3.5 Other side and/or unusual reactions

A number of side reactions have been reported to occur during Wolff–Kishner reductions in addition to those discussed above. In particular, cleavage of strained rings located adjacent to the carbonyl may accompany reduction to afford saturated[109] and/or alkene products.[109,110] For example, the pentacyclic diketone (**41**) afforded the unsaturated tetracyclic compound (**42**) and saturated derivative (**43**) in addition to the normal Wolff–Kishner product[46] (**44**; equation 13).[109] Likewise, the cyclopropyl ring in alkaloid (**45**) suffered cleavage during reduction to give the alkene (**46**; 65%; equation 14).[110]

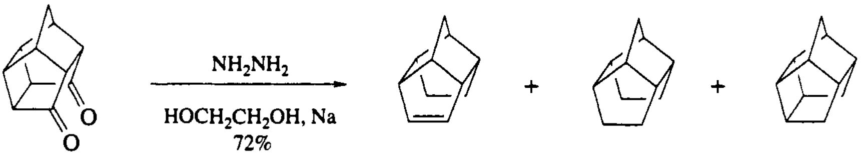

O
O
$NH_2NH_2$
$HOCH_2CH_2OH$, Na
72%
+
+

(13)

(**41**) (**42**) 4% (**43**) 32% (**44**) 63%

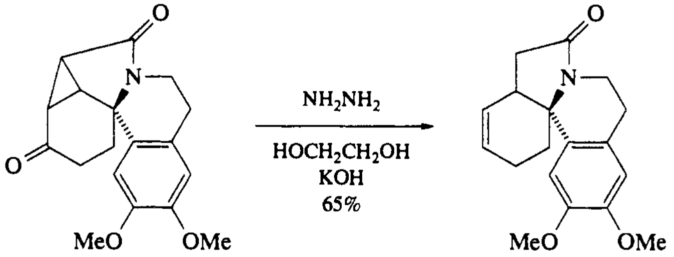

O
N
O
MeO
OMe
$NH_2NH_2$
$HOCH_2CH_2OH$
KOH
65%
O
N
MeO
OMe

(14)

(**45**) (**46**)

An unusual disproportionation reaction was observed when the amino ketone hydrazone (**47**) was reduced at temperatures above 200 °C to afford mixtures of (**48**), (**49**), and (**50**) (equation 15).[111] Lower temperature reductions gave almost entirely the expected Wolff–Kishner product (**51**; 52%), which, upon refluxing with KOH in triethylene glycol, returned a mixture of (**48**), (**49**) and (**50**).[111]

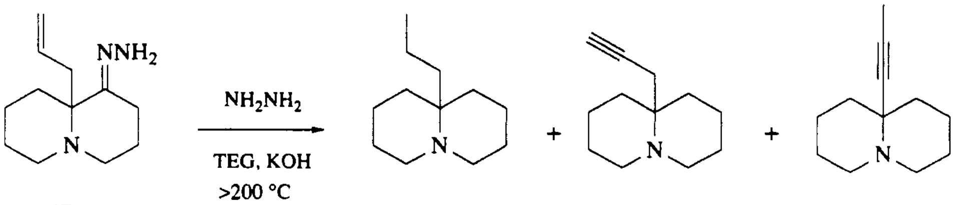

$NNH_2$
N
$NH_2NH_2$
TEG, KOH
>200 °C
N
+
N
+
N

(15)

(**47**) (**48**) (**49**) (**50**)

The presence of a second carbonyl β or γ to an aldehyde or ketone may afford cyclic derivatives upon treatment with hydrazine.[6] The intermediates from β-diketones (*e.g.* **52**) usually resist further reduction,

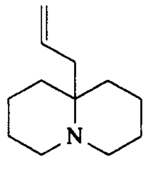

**(51)**

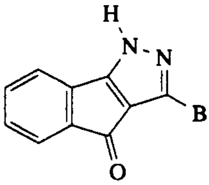

**(52)**

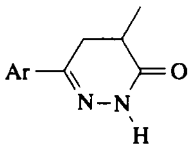

**(53)**

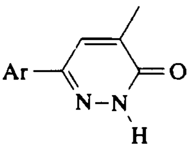

**(54)**

while (2*H*)-pyridazinones from γ-keto acids (*e.g.* **53**) are further reduced to the normal Wolff–Kishner products.[112] However, α,β-unsaturated-γ-keto acids afford cyclic derivatives (*e.g.* **54**) which do not further react,[112] while pyrazoline intermediates from α,β-unsaturated carbonyls may degrade to cyclopropyl products (equation 16).[3,6]

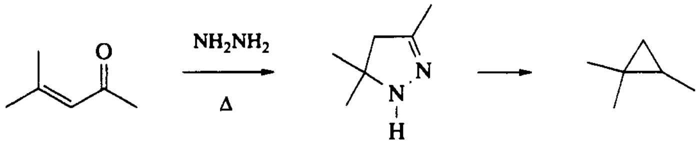

(16)

Treatment of the semicarbazone (**55**) under Wolff–Kishner conditions (KOH, NaOMe, KOBu^t, no solvent) has been utilized to synthesize the substituted cyclopentenes *cis*- and *trans*-(**56**; equation 17).[113] In DEG at 225 °C, the normal Wolff–Kishner product was obtained.[113]

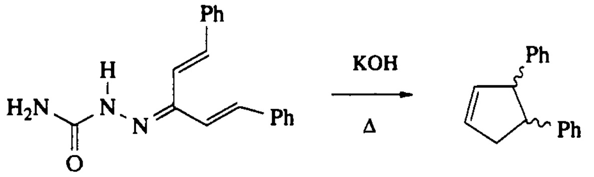

(17)

**(55)** **(56)**

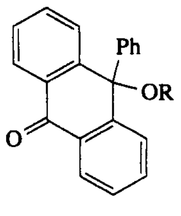

**(57)**

Tritylone ethers (**57**), used as acid-stable protecting groups for alcohols, are cleaved under Wolff–Kishner (Huang-Minlon) conditions as the unblocking step.[114]

## 1.14.3 REDUCTION OF ALDEHYDE AND KETONE ARYLSULFONYLHYDRAZONES WITH HYDRIDE REAGENTS

In the early 1960s, Caglioti and Magi[115] reported that the reduction of aldehyde and ketone *p*-toluenesulfonylhydrazones (tosylhydrazones) with $LiAlH_4$ in THF affords hydrocarbon products (equation 2). This was soon followed by the disclosure[116] that the milder reducing reagent $NaBH_4$ in refluxing methanol or dioxane was also effective for such reductions and this ushered in processes (Caglioti reactions) as alternatives to Wolff–Kishner reductions for carbonyl deoxygenations. Following these pioneering investigations, other reduction systems, particularly $NaBH_3CN$[117] and catechol borane,[118] have been introduced over the ensuing years to provide even milder and more selective methodology to effect reductions. These reduction systems have found considerable synthetic utility, especially in synthetic situations which would not tolerate the relatively harsh basic conditions of standard Wolff–Kishner reductions or the highly acidic requirements dictated in Clemmensen reductions (see Volume 8, Chapter 1.13). The availability of the reagents in isotopically labeled form (*i.e.* $LiAlD_4$, $NaBD_4$, $NaBD_3CN$, catechol borane-*d*) permits incorporation of deuterium (or tritium) into synthetic targets, which augments the utility of the methodology. Each of the major categories of reducing systems will be discussed separately in the subsections below.

Caglioti-type reductions are mechanistically related to Wolff–Kishner processes in that diimide intermediates are implicated as depicted in Scheme 2.[115,117-120] In the absence of strong base, diimide (**29a**) represents the key intermediate rather than the diimide anion (**6**) found in the Wolff–Kishner reduction (Scheme 1). Reduction with $LiAlH_4$ is probably an exception to this since this highly basic reagent should readily abstract the very acidic *N*-proton to afford (**59**), followed by hydride delivery and loss of tosyl anion to give the diimide anion (**6**).[119,120] Recent studies[121] indicate that reductions of certain structural types (*e.g.* some sugar derivatives[121] and aryl examples bearing electron deficient groups[121b]) with $NaBH_3CN$ under highly acidic conditions (HCl, pH *ca.* 3.8) in methanol proceed *via* an alternate route involving initial acid-catalyzed isomerization to the azo derivative (**60**), followed by reduction to the tosylhydrazine (**61**; equation 18). Subsequent elimination of tosylic acid leads to the hydrocarbon *via* diimide (**29**) as in Scheme 2. This process appears to be important only when tautomerization to (**60**) is facilitated by electron-withdrawing inductive effects and/or conformational restrictions.[121]

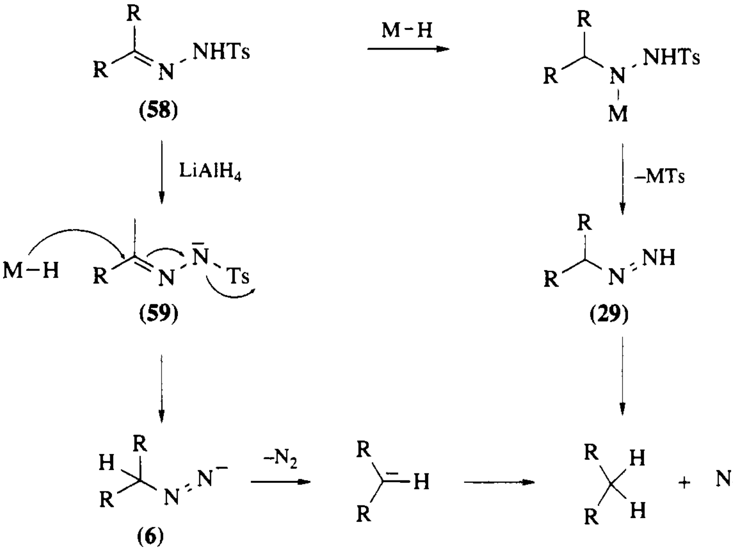

**Scheme 2**

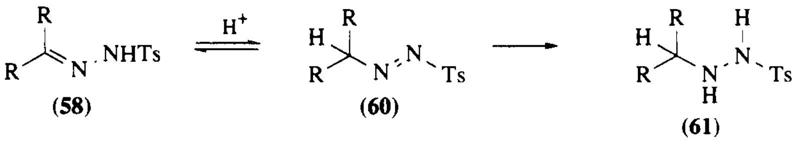

(18)

As is the case with Wolff–Kishner reactions, the application of tosylhydrazone reductions relies on the successful conversion of carbonyls to the requisite hydrazone derivatives (**58**). This usually presents no problem except with relatively hindered or deactivated ketones and, in fact, several failures of the methodology are traced to unsuccessful tosylhydrazone formation (*i.e.* for examples with **62**,[122] **63**,[123] diketone (**9**) in equation 4, and the substrate of entry 3, Table 2).

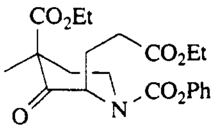

**(62)**

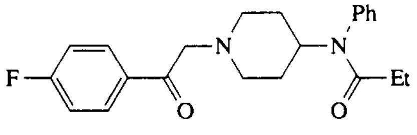

**(63)**

## 1.14.3.1 Reductions with Lithium Aluminum Hydride

### 1.14.3.1.1 Scope and limitations

As mentioned, $LiAlH_4$ in refluxing THF was the initial system introduced to reduce preformed tosylhydrazones to hydrocarbons[115] and a number of successful conversions have been reported, representative examples of which are presented in Table 5. Alkene side products often accompany the hydrocarbon products,[115,119] a result attributed to proton abstraction from the α-carbon of intermediate (**59**), leading to a vinyldiimide anion (**64**), followed by $N_2$ expulsion and protonation during work-up (Scheme 3).[119] With certain ketones, including 17-keto steroids, alkenes are the major[128] or sole product[115,127] (entries 7–9, Table 5). This side reaction mimics the elimination obtained upon treatment of tosylhydrazones with other strong bases (*i.e.* alkyllithiums, the Shapiro reaction[129]). Note that use of $LiAlD_4$ introduces one deuterium (with $H_2O$ work-up) or two deuteriums (with $D_2O$ work-up; entries 5 and 6, Table 5, respectively).

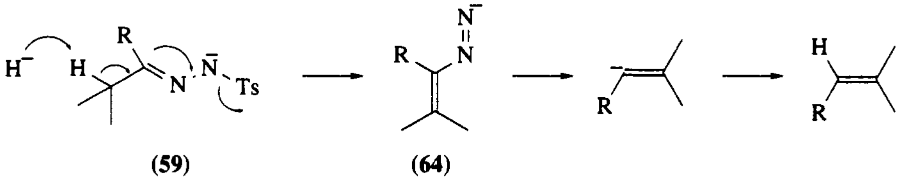

**Scheme 3**

### 1.14.3.1.2 Chemoselectivity

The powerful reducing ability of $LiAlH_4$ precludes the presence of many other functional groups, *i.e.* $CO_2H$, $CO_2R$ (entries 2 and 4, Table 5), CN, CON— (entry 6, Table 5), $NO_2$, halides, *etc.*, and this limits the synthetic applications to synthetic targets where such groups are absent or their reduction desired or unimportant.

### 1.14.3.1.3 Reduction of conjugated derivatives

Reductions of α,β-unsaturated carbonyl tosylhydrazones with $LiAlH_4$ often give mixtures of unrearranged and rearranged alkene products similar to the situation in Wolff–Kishner reductions. Thus, 3-keto-cholest-1-ene gave significant quantities of both the 1- and 2-alkene products while 3-keto-cholest-4-ene afforded 3- and 4-alkene products along with the product of elimination, 2,4-cholestadiene.[115]

## 1.14.3.2 Reductions with Sodium Borohydride

### 1.14.3.2.1 Scope and limitations

The introduction of the milder reagent sodium borohydride in refluxing methanol or dioxane for reduction of tosylhydrazones[116,120] represented an improvement over $LiAlH_4$ since many more functional groups are tolerated and the lessened basicity decreases alkene side products observed with the latter reagent. Reductions with $NaBH_4$ have found wide usage in synthesis mostly with dioxane or methanol as the solvent (where the reducing species is probably $NaBH(OMe)_3$), although other solvents, such as isopropanol and DMF, have occasionally been employed. Table 6 presents a selection of successful applications chosen to illustrate various structural types. Several features of the reductions are evident from the table. Thus, the 17-keto group in 3β-acetoxy-5α-androstane (entry 3, Table 6) was effectively removed, while reduction with $LiAlH_4$ gave only elimination (entry 7, Table 5). However, the 17-keto group in a related derivative (entry 4, Table 6) gave a mixture of the 16-alkene along with the unusual cyclopropyl derivative shown, indicating that seemingly slight structural alterations may greatly influence the course

**Table 5** Wolff–Kishner Reductions of Carbonyl Tosylhydrazones with Lithium Aluminum Hydride

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 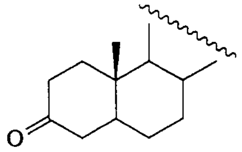 | 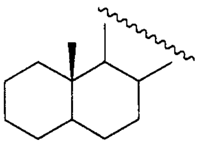 | 70 | 115 |
| 2 | 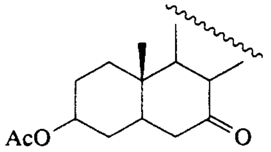 | 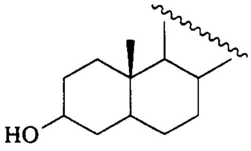 | 65–75 | 115 |
| 3 | 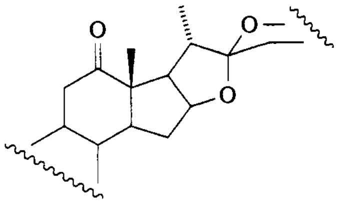 | 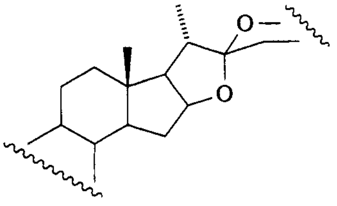 | 50 | 115 |
| 4 | 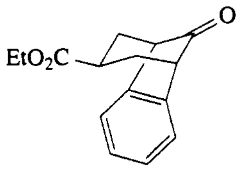 | 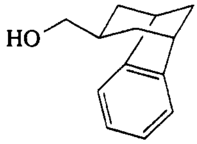 | 90 | 124 |
| 5 | 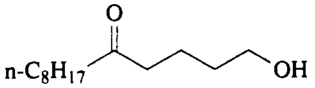 | 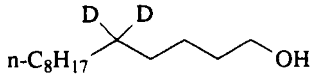 | 27[a] | 125 |
| 6 | 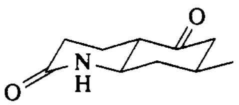 | 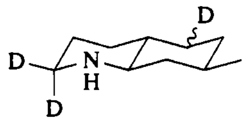 | —[b] | 126 |
| 7 | 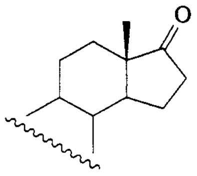 | 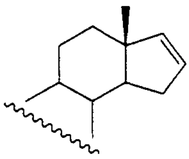 | 60–70 | 115 |
| 8 | 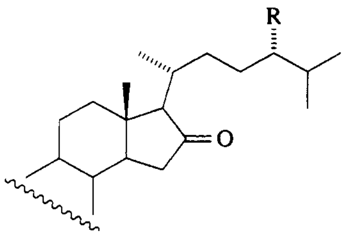 | 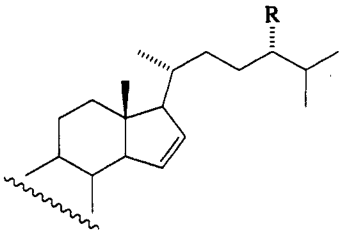 | — | 127 |

**Table 5** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 9 | 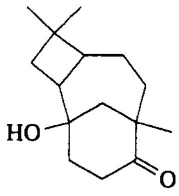 | 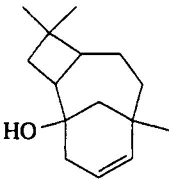 | 40 | 128 |

$^a$ LiAlD$_4$; D$_2$O. $^b$ LiAlD$_4$; H$_2$O.

of reductions. Also, configurations adjacent to carbonyls are not altered by base-catalyzed enolization as indicated in entries 5 and 6. Deuterium is incorporated *via* use of NaBD$_4$ for the reducing agent as presented in entry 7, Table 6. The introduction of only one deuterium, even though D$_2$O was used in the work-up,[133] provides evidence for the intermediacy of a diimide (**29a**) in the mechanism (Scheme 2) since (**29a**) represents the only source of hydrogen for the second incorporation.

The attempted conversion of the aldehyde in compound (**65**) to a methyl group by reduction of the tosylhydrazone with NaBH$_4$ (ethanol solvent) led instead to the furan derivative (**66**), resulting from an unusual cyclization with elimination of a MeOCH$_2$ group.[138]

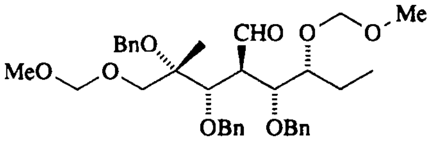

**(65)**

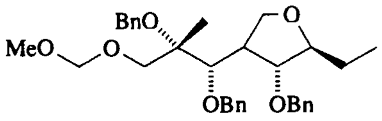

**(66)**

The combination of NaBH$_4$ in acetic acid has also proven to be a very effective system for the reduction of carbonyl tosylhydrazones.[139] The actual reducing species is probably NaBH(OAc)$_3$[140] and the acidic medium enhances the electrophilicity of the π-bonded carbon by *N*-protonation and allows the reductions to occur at mild temperatures (25–70 °C) with most aldehydes and ketones. This reducing system has been successfully employed in a number of synthetic applications, representative examples of which are displayed in Table 7. The use of NaBD$_4$ in MeCO$_2$H or MeCO$_2$D allows the regioselective introduction of one or two deuteriums, respectively (entries 6 and 7, Table 7) thus augmenting the versatility of the methodology.[139]

The transition metal complex bis(triphenylphosphine)copper(I) borohydride, (Ph$_3$P)$_2$CuBH$_4$, has also been shown to be effective for the reduction of tosylhydrazones to hydrocarbons under mild conditions (refluxing chloroform).[144] Yields from unhindered aliphatic aldehyde and ketone tosylhydrazones are generally in the range 48–84%. Reductions of hindered ketones (*e.g.* camphor) and aromatic aldehydes were less successful giving 0–20% of reduced products.[144]

### *1.14.3.2.2 Chemoselectivity*

The mild reducing ability of NaBH$_4$ (and NaBH(OMe)$_3$ or NaBH(OAc)$_3$) permits the presence of many more functional groups compared to LiAlH$_4$. Thus, CON, CO$_2$H, CN (entry 1, Table 7), and halides are expected to survive. Esters remain intact in HOAc (entries 4 and 5, Table 7) but not in MeOH (entry 2, Table 6), probably because of transesterification. Even relatively hindered or deactivated ketones (*e.g.* aryl) have been recovered untouched (entry 8, Table 6 and entry 3, Table 7, respectively). Surprisingly, the tertiary hydroxyl group in entry 3, Table 7 apparently did not give elimination, although no yield for the product was provided.[141] A complex mixture was reported[139] with *p*-nitrobenzaldehyde, indicating that the nitro group was probably attacked.

**Table 6** Reduction of Carbonyl Tosylhydrazones with Sodium Borohydride

| *Entry* | *Carbonyl* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 1 | 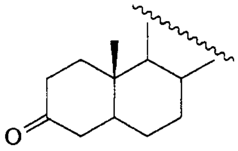 | MeOH | 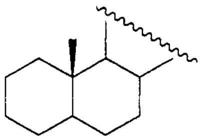 | 70–80 | 120 |
| 2 | 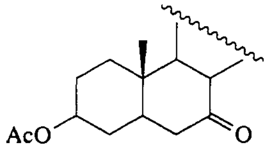 | MeOH | 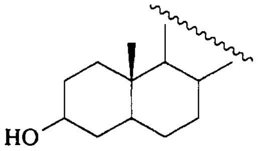 | 70–80 | 120 |
| 3 | 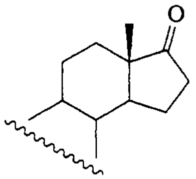 | Dioxane | 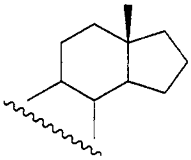 | 60–70 | 120 |
| 4 | 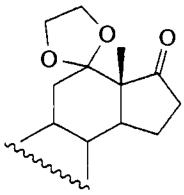 | Dioxane | 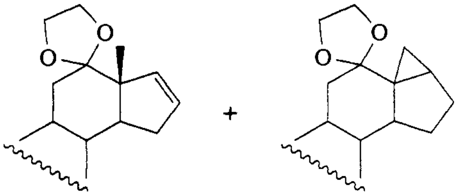 | 71 | 130 |
| 5 | 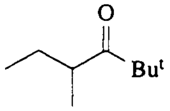<br>optically active | Dioxane | 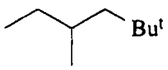<br>optically active | 37 | 131 |
| 6 | 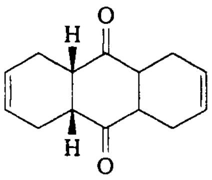 | DMF | 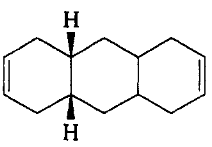 | 31 | 132 |
| 7 | 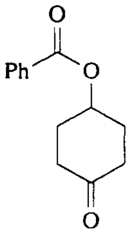 | — | 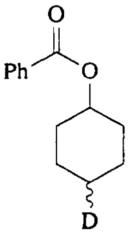 | —[a] | 133 |

**Table 6** *(continued)*

| *Entry* | *Carbonyl* | *Solvent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|---|
| 8 | 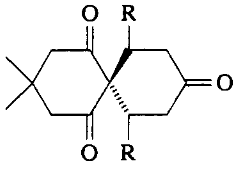 | MeOH | 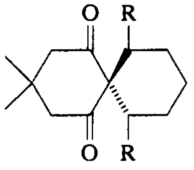 | 75 | 134 |
| 9 | 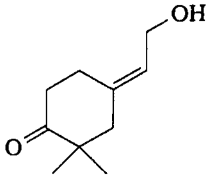 | MeOH | 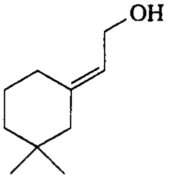 | 65 | 135 |
| 10 | 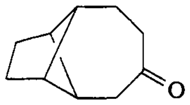 | MeOH | 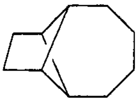 | 47 | 136 |
| 11 | 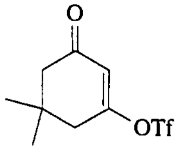 | MeOH | 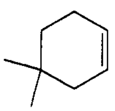 | 49 | 137 |
| 12 | 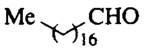 | MeOH | 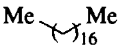 | 60–70 | 116 |

[a] Worked up with $D_2O$.

### *1.14.3.2.3 Reduction of conjugated derivatives*

Treatment of α,β-unsaturated tosylhydrazones with $NaBH_4$ in MeOH affords principally allylic ethers from cyclic derivatives[145] and pyrazoles with most noncyclic examples.[146] This divergent behavior compared to saturated tosylhydrazones has been attributed[145,146] to a lessening of the electrophilicity of conjugated imine π-bonds, which allows initial abstraction of the acidic N—H proton by $BH_4^-$ to compete with reduction, and gives alternative reactions related to the Bamford–Stevens process as depicted in Scheme 4. An exception to this may be the deoxygenation of conjugated vinyl triflates (entry 11, Table 6).[137] The cyclopropanation and elimination products produced in entry 4, Table 6 also probably arise from similar, alternative reaction paths.[130]

With acetic acid as solvent, the above paths are circumvented, since protonation of the imine nitrogen increases nucleophilic attack and prevents formation of the offending tosylhydrazone anion. The result is that deoxygenation is obtained, but with concomitant rearrangement of the double bond to the site formerly occupied by the carbonyl.[139] This unusual reaction apparently proceeds through a diimide intermediate, which deposits a hydride *via* a 1,5-sigmatropic migration as indicated in Scheme 5. The mechanistic requirement embodied in equation (20) generates the double bond migration even when the resulting alkene is thermodynamically less stable. A selection of representative reductions is presented in Table 8 and illustrates synthetically useful applications as deconjugating alkenes from double bonds (entries 1–3) or aromatic rings (entries 6, 9), producing exocyclic alkenes (entry 4) and regioselectively introducing one (entry 3) or two (entry 2) deuteriums. A limitation was noted in that isophorone tosylhydrazone afforded only an 18% yield of the rearranged alkene (entry 7, Table 8). Apparently, situating a pseudoaxial diimide group over the ring required for migration is opposed by the axial 5-methyl and other side reactions (*i.e.* Michael-type addition of hydride) compete favorably.[139]

**Table 7** Reduction of Carbonyl Tosylhydrazones with Sodium Borohydride in Acetic Acid

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 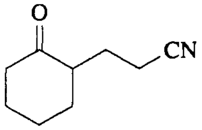 | 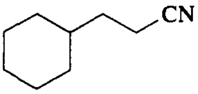 | 70 | 139 |
| 2 | 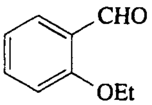 | 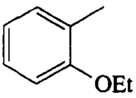 | 80 | 139 |
| 3 | 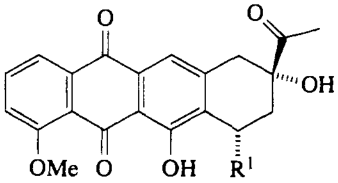 | 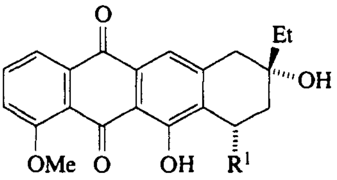 | — | 141 |
| 4 | 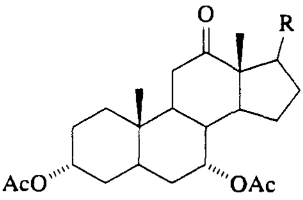 | 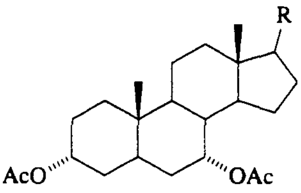 | 53 | 142 |
| 5 | 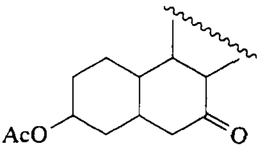 | 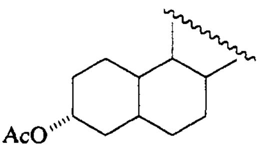 | 76 | 143 |
| 6 | 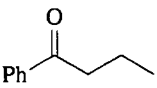 | 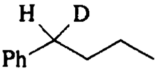 | 60[a] | 139 |
| 7 | 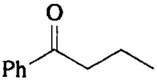 | 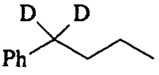 | 72[b] | 139 |

[a] $NaBD_4$, AcOH. [b] $NaBD_4$, AcOD.

## 1.14.3.3 Reductions with Sodium Cyanoborohydride

### *1.14.3.3.1 Scope and limitations*

Substitution for one of the hydrogens of borohydride with the strong electron-withdrawing cyano group greatly increases the reluctance of the resulting cyanoborohydride to deliver a hydride. The result is a moderated reducing ability (and an enhanced stability to acid) compared to borohydride. This, coupled with a high dependency of reducing capability on pH, allows remarkable, often pH controllable, selectivity among functional groups.[149]

One successful application of cyanoborohydride reductions is the reduction of tosylhydrazones to hydrocarbons which, since its introduction in 1971,[150] has been employed extensively for such conversions. The reductions are most often conducted in 1:1 DMF:sulfolane containing a small amount of acid at

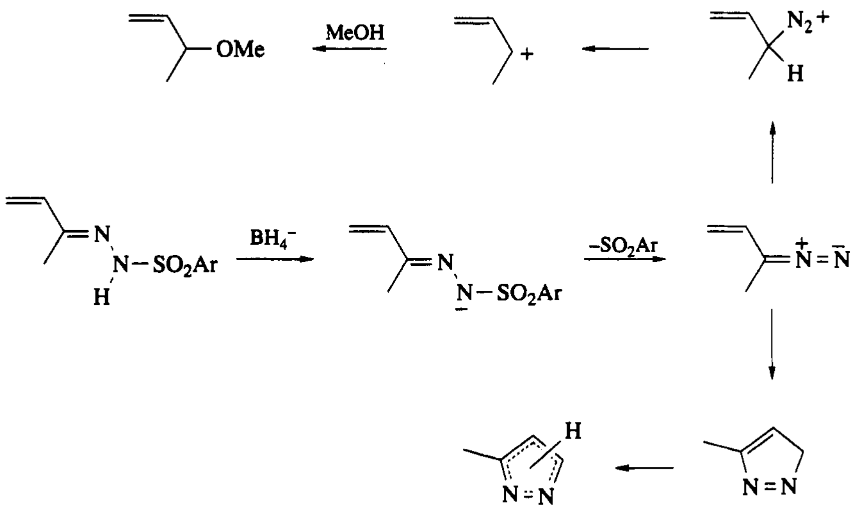

Scheme 4

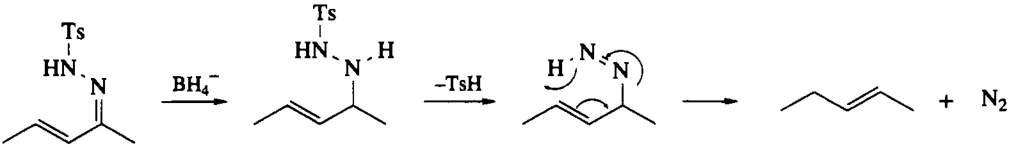

Scheme 5

about 100–110 °C.[117,149] The relatively slow rate of carbonyl attack compared to iminium ions[151] under these reaction conditions permits the *in situ* generation of tosylhydrazones and subsequent reduction of unhindered carbonyls to be conducted in one step (Scheme 6). Hindered ketones (*e.g.* α-phenyl, α-isopropyl or α-*t*-butyl or more than one alkyl group flanking the carbonyl) generally require preformation of the tosylhydrazone and fairly large excesses of cyanoborohydride.[117] Likewise, aryl ketone tosylhydrazones are not readily deoxygenated.[117]

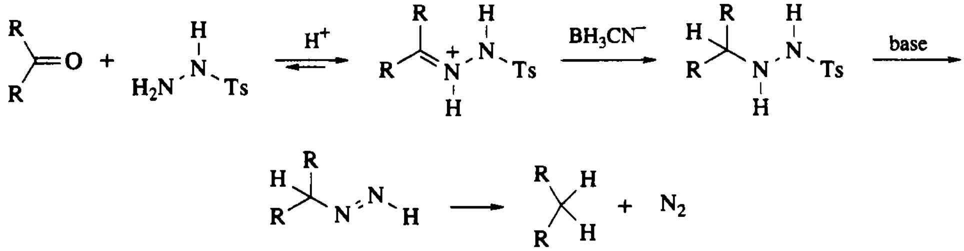

Scheme 6

Synthetic applications of the reducing methodology through 1978 have been reviewed.[149] Table 9 presents further examples chosen to illustrate the range of structural types, many of which contain other functionalities, in which carbonyls have been successfully removed with cyanoborohydride. Thus, relatively hindered types are effectively deoxygenated (entries 2, 3, 5, 13) as well as systems containing strained rings (entry 7). Deuterium (entry 12) and tritium (entry 13) may be incorporated using the appropriate isotopically labeled reagent. Sites adjacent to the carbonyl are normally not isomerized (entry 8), although exceptions have been uncovered.[165,166]

Milder modifications have been developed for systems in which the above methodology was ineffective. Thus, the tosylhydrazone of the carbohydrate (**67**) afforded mixtures of products with $NaBH_3CN$ in DMF at 110 °C, with or without acid, giving a maximum of 20% of the desired product (**68**). However, treatment of (**67**) tosylhydrazone with $NaBH_3CN$ in acidic (HCl) methanol gave the corresponding tosylhydrazine, which underwent smooth conversion to (**68**) upon treatment with NaOAc in refluxing ethanol. This procedure appears to be superior with carbohydrate[167] and other substrates,[168] although treatment

**Table 8** Reduction of Conjugated Carbonyl Tosylhydrazones with Sodium Borohydride in Acetic Acid

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 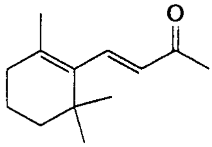 | 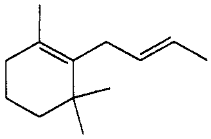 | 81–89 | 139 |
| 2 | 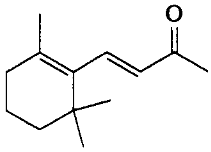 | 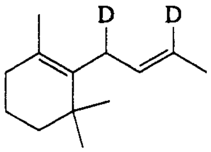 | 81[a] | 139 |
| 3 | 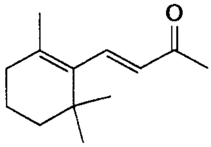 | 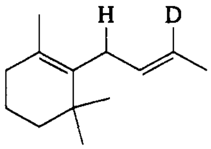 | 61–72[b] | 139 |
| 4 | 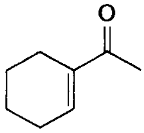 | 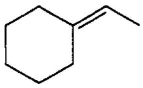 | 53 | 142 |
| 5 | 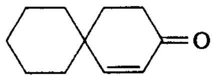 | 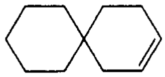 | 67 | 139 |
| 6 | 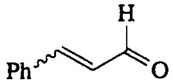 | 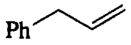 | 42–56 | 139 |
| 7 | 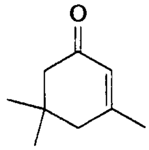 | 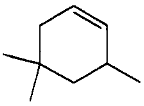 | 18 | 139 |
| 8 | 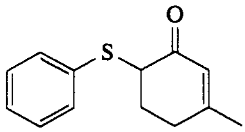 | 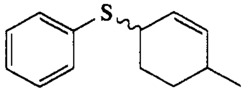 | 78 | 147 |
| 9 | 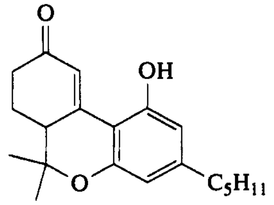 | 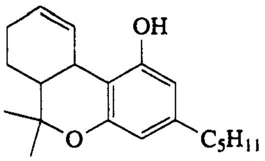 | 44 | 148 |

[a] $NaBD_4$, $MeCO_2D$. [b] $NaBD_4$, $MeCO_2H$.

**Table 9** Reduction of Carbonyl Tosylhydrazones with Sodium Cyanoborohydride in DMF–Sulfolane

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 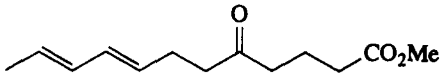 | 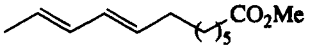 | 38 | 152 |
| 2 | 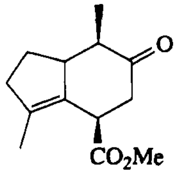 | 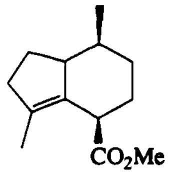 | 68 | 153 |
| 3 | 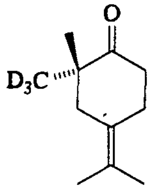 | 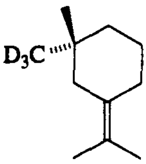 | 75 | 154 |
| 4 | 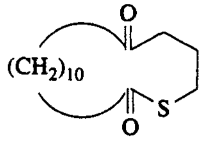 | 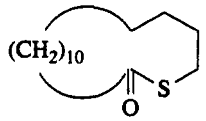 | 44 | 155 |
| 5 | 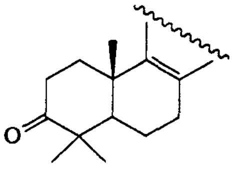 | 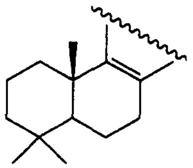 | 74 | 156 |
| 6 | 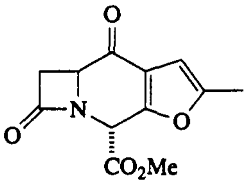 | 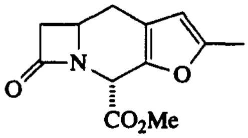 | 53 | 157 |
| 7 | 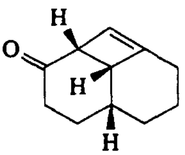 | 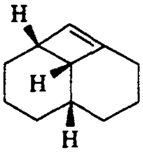 | 40 | 158 |
| 8 | 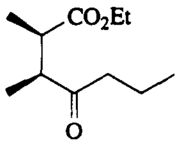 | 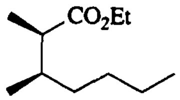 | 77 | 159 |
| 9 | 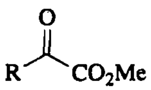 $RC(O)CO_2Me$ | 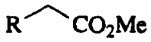 | — | 160 |

**Table 9** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
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| 10 | 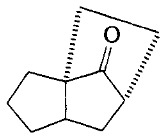 | 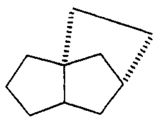 | *ca.* 100 | 161 |
| 11 | 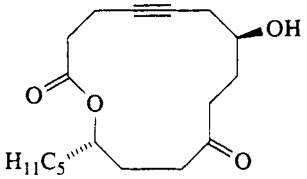 | 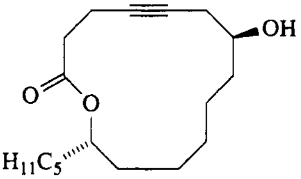 | 35 | 162 |
| 12 | 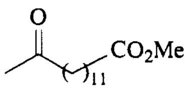 | 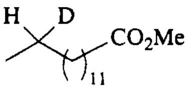 | 54[a] | 163 |
| 13 | 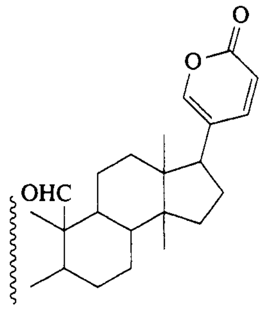 | 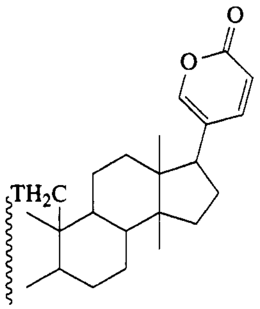 | —[b] | 164 |

[a] $NaBD_3CN$ used. [b] $NaBH_2TCN$ used.

with NaOAc is not always required, especially in refluxing methanol[169–171] or ethanol.[172] Similar mild reductions of tosylhydrazones to isolable tosylhydrazines by $NaBH_3CN$ occurs in acidic THF at room temperature,[173] and reductions in refluxing acidic THF[174] (*e.g.* with **69**) and in THF/HOAc (room temperature) have been successful.[175] Further modifications involve the combination of $NaBH_3CN$ with zinc chloride as the reducing system,[176,177] and the use of mercury complexes with tosylhydrazones as a method of activating reluctant aryl derivatives for reduction with cyanoborohydride (in acidic THF and followed by treatment with KOH/MeOH).[178]

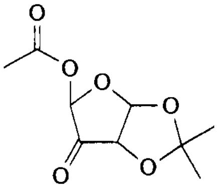

**(67)**

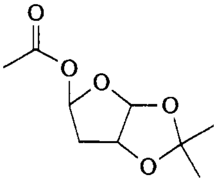

**(68)**

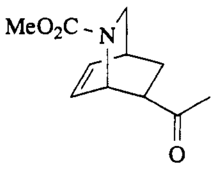

**(69)**

### *1.14.3.3.2 Chemoselectivity*

One of the major advantages of cyanoborohydride for deoxygenations is the high tolerance exhibited for other functionalities, which allows for highly discriminate carbonyl removal.[117,149] Thus, most common groups may be present, including $CO_2H$, CON— (including β-lactams; entry 6, Table 9), $CO_2R$ (entries 1, 2, 6, 8, 9, 13, Table 9), lactones (entries 11, 13, Table 9), thiolactones (entry 4, Table 9), furans (entry 6, Table 9), $NO_2$,[117] sulfoxides, aryl halides, and alkyl chlorides.[117] Indeed, the success of the one-step deoxygenation process relies on the slow reduction of even aldehydes and ketones under neutral or mildly acidic (pH > *ca.* 4.5) conditions. Alkyl bromides and iodides are reductively removed in the polar aprotic solvents DMF and sulfolane,[117] but these would probably survive with the acidic methanol methodology.[167]

### *1.14.3.3.3 Reduction of conjugated derivatives*

As with $NaBH_4$ in $MeCO_2H$, reduction of α,β-unsaturated carbonyls with $NaBH_3CN$ affords alkenes in which the double bond has migrated to the position formally occupied by the carbonyl (Scheme 5).[117,149,179,180] Compilations of successful synthetic applications are found in refs. 117 and 149. As with $NaBH_4$, isophorone tosylhydrazone affords only a low yield (36%) of the alkene product contaminated with 1,1,3-trimethylcyclohexane.[179] Other ketones which cannot readily assume a cisoid orientation for intramolecular migration (Scheme 5) also give mixtures of alkene and alkane products resulting from competing Michael-type delivery of hydride (Scheme 7).[180] This problem may be alleviated by use of $NaBH_3CN$ in $MeCO_2H$. Thus, a tetracyclic derivative (partial structure **70**) gave the single rearranged alkene (**71**; 55%).[181]

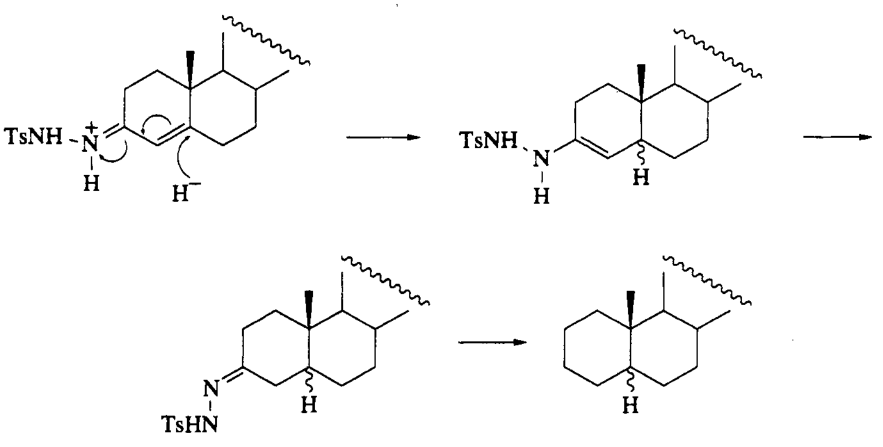

**Scheme 7**

An interesting application of the reduction–migration methodology involves the conversion of α,β-alkynic ketones to allenes.[182] Thus, reduction of the tosylhydrazone of (**72**) under slightly modified conditions (lower temperature and pH, greater excess of $NaBH_3CN$) afforded the trimethylsilylallene (**73**) in 69% yield, while the original recipe[117] gave the pyrazole (**74**; 81%).[182]

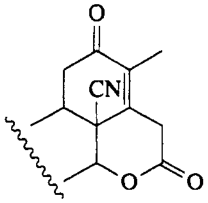

**(70)**

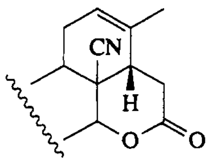

**(71)**

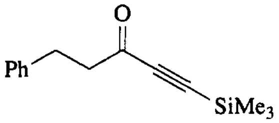

**(72)**

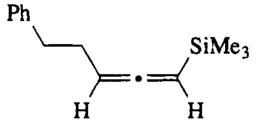

**(73)**

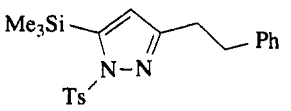

**(74)**

## 1.14.3.4 Reductions with Catechol Borane and Related Reagents

### *1.14.3.4.1 Scope and limitations*

The reduction of tosylhydrazones with catechol borane under very mild conditions ($CHCl_3$, 25 °C followed by NaOAc[118] or, preferably, $Bu_4NOAc$[183]) is also a highly effective deoxygenation process, which has been successfully utilized in a number of synthetic conversions. A 1977 review of catechol borane chemistry, including reductive deoxygenations, is available.[184] Table 10 contains a selection of successful conversions from the literature and illustrates the effectiveness of the reagent as well as the ability to incorporate a deuterium regioselectively by utilizing $NaOAc{\cdot}D_2O$ (entry 4) or two deuteriums using catechol borane-*d* and $NaOAc{\cdot}D_2O$ (entry 5, Table 10).[187] Reduction of a hindered cyclobutanone (entry 6) afforded a low yield of reduction product (20%). In this case, the Cram modification of the Wolff–Kishner reduction was more successful (56% yield).[188]

**Table 10** Reduction of Carbonyl Tosylhydrazones with Catechol Borane and Bis(benzoyloxy)borane

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 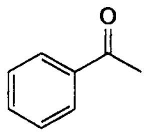 | 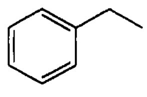 | 94 | 183 |
| 2 | 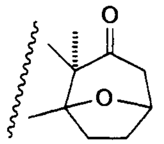 | 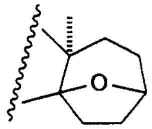 | — | 185 |
| 3 | 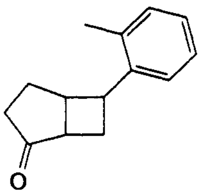 | 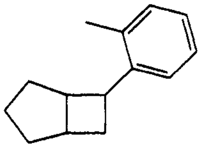 | 68 | 186 |
| 4 | 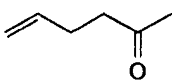 | 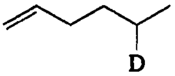 | 97[a] | 187 |
| 5 | 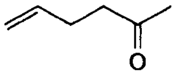 | 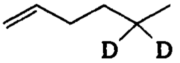 | 95[b] | 187 |
| 6 | 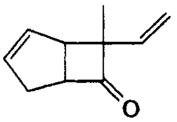 | 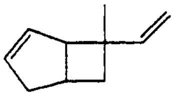 | 20 | 188 |
| 7 | 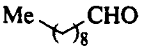 $\mathrm{Me(CH_2)_8CHO}$ | 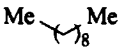 $\mathrm{Me(CH_2)_8Me}$ | 91[c] | 189 |
| 8 | 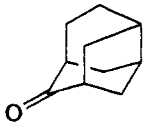 | 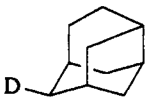 | 70–80[d] | 190 |

[a] Using $NaOAc{\bullet}3D_2O$ in workup. [b] Using catechol borane-*d* and $NaOAc{\bullet}3D_2O$ in work-up. [c] $(PhCO_2)_2BH$ as reducing agent. [d] $(PhCO_2)_2BH$ as reducing agent: NaOD, $D_2O$ used in work-up.

The related borane bis(benzoyloxy)borane[189] has also been found to be effective for tosylhydrazone reductions, examples of which are presented in Table 10 (entries 7 and 8). The latter case required the use of $NaOD/D_2O$ for efficient deuterium incorporation[190] (instead of $NaOAc/D_2O$).[189] A pyridine–borane complex likewise reduces tosylhydrazones in acidic ethanol/dioxane[191] to tosylhydrazines (91–98% yields), which may be converted to hydrocarbons by treatment with KOH/MeOH[178] or $NaOAc{\cdot}3H_2O/CHCl_3$.[191]

### *1.14.3.4.2 Chemoselectivity*

As with cyanoborohydride, very few functional groups are affected by catechol borane under the tosylhydrazone reduction conditions (25 °C), allowing highly selective conversions in the presence of most moieties, including alkenes and alkynes which are hydroborated at more elevated temperatures (70–100 °C).[192] The only exceptions to this appear to be aldehydes, carboxylates, sulfoxides, amine oxides and anhydrides, which are reduced at rates comparable to tosylhydrazones.[192]

### *1.14.3.4.3 Reduction of conjugated derivatives*

As with other hydride reagents, reductions of α,β-unsaturated carbonyl tosylhydrazones with catechol borane provides the alkene product resulting from migration of the double bond (Scheme 5).[118,193,194] Furthermore, even certain cyclic systems which afford low yields and alkane side products with $NaBH_4$ and $NaBH_3CN$ (*e.g.* isophorone, see entry 7, Table 8) normally provide only the rearranged alkene and no alkane side products.[184,193–195] Apparently, the low nucleophilicity of the reagent prevents competing Michael addition to the double bond (Scheme 5), which afflicts the reductions with anionic hydrides. Table 11 provides a collection of successful conversions of conjugated systems and illustrates the versatility (and chemoselectivity) of the method. With β-substituted rigid cyclohexenone systems, highly stereoselective introduction of hydrogen is observed. Thus, the initial attack by the reagent is apparently favored (as expected)[204] from the axial (α) direction leading to the equatorial (β) orientated diimide derivative which, in turn, leads to delivery of hydride to the top (β) face of the double bond as observed in entries 1, 4 and 7, Table 11. The geometric constraints imposed by deliverance of a hydride by an equatorial diimide to the β-position implicates a boat-type conformation (Scheme 8) or a bimolecular mechanism.[95] In one instance, (entry 4, Table 11) the principal rearranged alkene was accompanied by a small amount of the deoxygenated product in which the alkene had remained in place.[198] Other stereoselective conversions also appear to be controlled by initial approach of the reagent from the less-hindered face of the hydrazone (entry 6, Table 11). When the faces are comparable in accessibility, mixtures of isomers are obtained (*e.g.* entry 8, Table 11). The methodology is also useful for the conversion of α,β-alkynic ketones to allenes (Table 11, entry 9).[203]

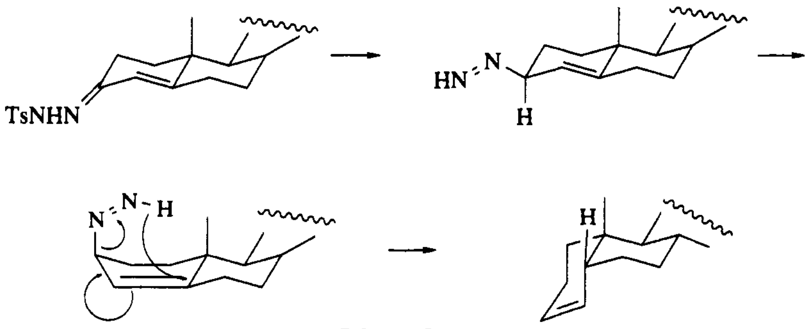

Scheme 8

An unusual reduction course is illustrated by results with the crossed dienone in Table 11, entry 7, in which reductive migration was accompanied by removal of the second double bond, the mechanism of which is not obvious.[201]

**Table 11** Reduction of Conjugated Carbonyls with Catechol Borane

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 1 | 4-Cholesten-3-one | 3-Cholestene | 83–88 | 195 |
| 2 | 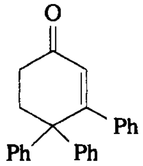 | 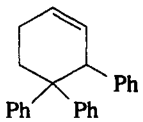 | 77 | 196 |
| 3 | 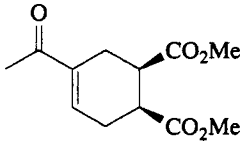 | 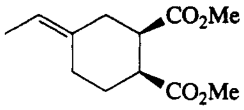 | 89 | 197 |
| 4 | 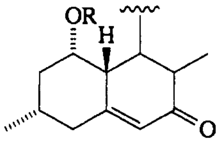 | 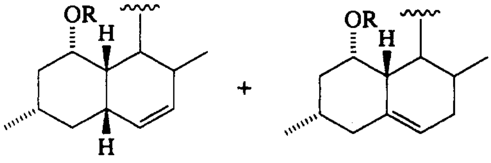<br>84:16 | 72 | 198 |
| 5 | 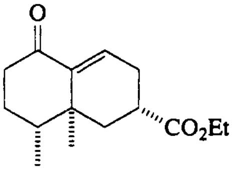 | 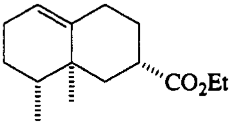 | 55 | 199 |
| 6 | 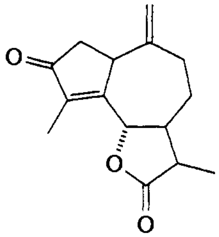 | 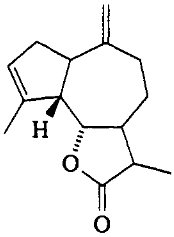 | 55 | 200 |
| 7 | 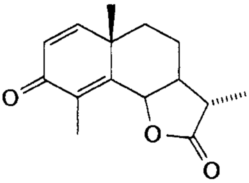 | 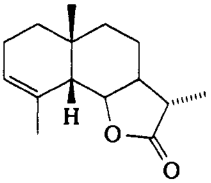 | 55 | 200,<br>201 |
| 8 | 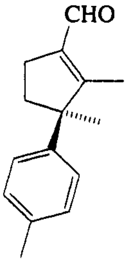 | 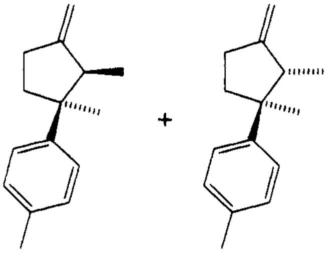<br>65:35 | 93 | 202 |

**Table 11** *(continued)*

| *Entry* | *Carbonyl* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| 9 | 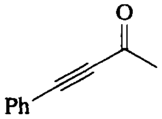 | 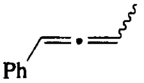 | 75 | 203 |

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# 2.1

# Reduction of Nitro and Nitroso Compounds

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## 2.1.1 INTRODUCTION

Nitro compounds are versatile synthetic intermediates which have found widespread utility in industrial applications. Aromatic nitro compounds are the usual starting materials for commercial applications, but aliphatic compounds exhibit a greater diversity of chemical behavior under reducing conditions.[1-4] Nitroso compounds, hydroxylamines, oximes, amines, nitrones, ketones and silyl nitronates are frequently encountered during the reduction of nitro compounds. Several specialized reviews have appeared which highlight the versatility of the nitro group in organic chemistry.[1-8]

### 2.1.2 REDUCTION OF AROMATIC NITRO COMPOUNDS TO NITROSO COMPOUNDS

The reduction of nitro compounds should initially produce nitroso compounds. This area has not been systematically explored because the nitroso group can be more easily introduced by alternative methods such as direct nitrosation, condensation and oxidative procedures.[9-11] In fact, there have been few instances in which nitroso compounds have been isolated as intermediates in reductions of nitro compounds. For example, it was initially believed that *m*-trifluoromethylnitrobenzene produced the corresponding nitroso compound upon reduction,[12] but subsequently the product was shown to be *m*-trifluoromethylazoxybenzene.[13] Low yields of an intramolecular dimeric, nitroso compound, benzo[*c*]cinnoline dioxide (**1**), can be obtained by reducing 2,2′-dinitrobiphenyl with zinc or sodium sulfide (equation 1).[14,15]

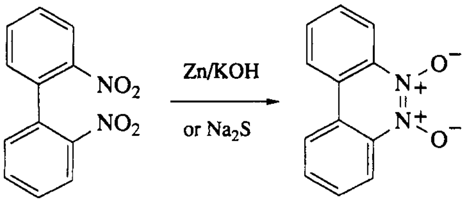

**(1)**

(1)

### 2.1.3 REDUCTION OF AROMATIC NITRO AND NITROSO COMPOUNDS TO AZO AND AZOXY COMPOUNDS

Reductions of aromatic nitro compounds often proceed to generate mixtures of nitroso and hydroxylamine products which then condense to form azoxy and, eventually, azo compounds. This bimolecular reduction is practical only for the generation of symmetrically substituted azo compounds. The situation can be further complicated if the reduction continues such that aromatic amines are formed; the amines may then condense with the intermediate nitroso compounds to generate hydrazo compounds which can then undergo a benzidine rearrangement.

A variety of reducing agents have been used to reduce nitroarenes to azo compounds. However, a mixture of zinc and sodium hydroxide is used most frequently.[16,17] Reduction under these conditions produces hydrazo compounds, which are then oxidized to azo compounds by dissolved atmospheric oxygen;[18,19] alternatively, air can be drawn through the product solution to achieve the conversion.[20,21] Occasionally, activation of the zinc dust is required prior to its use,[22] and, since metal ions form chelated complexes with azo compounds, a vigorous post-treatment with acids is recommended.[23] The zinc–sodium hydroxide reduction conditions are sufficiently mild that *p*-nitrostyrene (**2**; equation 2), can be reduced without reduction of the vinyl groups.[24]

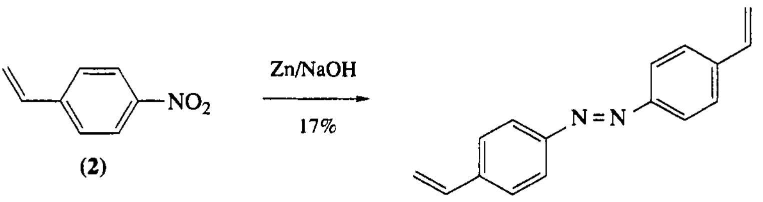

**(2)**

(2)

The reduction of (**3**) is an interesting example involving the formation of an intramolecular azo bridge (equation 3).[25]

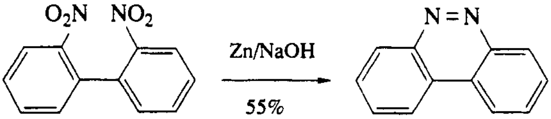

**(3)** **(4)**

(3)

As noted, the bimolecular reduction of aromatic nitro compounds may produce azoxy compounds, azo compounds, hydrazo compounds (1,2-diarylhydrazines), benzidines or amines (Scheme 1) depending on the reaction conditions. Zinc reduction under basic conditions generates azo compounds, whereas the use of acetic anhydride/acetic acid as the solvent system affords symmetrical azoxy compounds.[26] Although unsymmetrical azoxy compounds are accessible in the aliphatic series, aromatic reagents yield only symmetrical products. Azoxy compounds are of current interest because of their physiological activities and their utilization in liquid crystal systems.[27] The chemistry of aromatic azoxy compounds has been reviewed.[28,29]

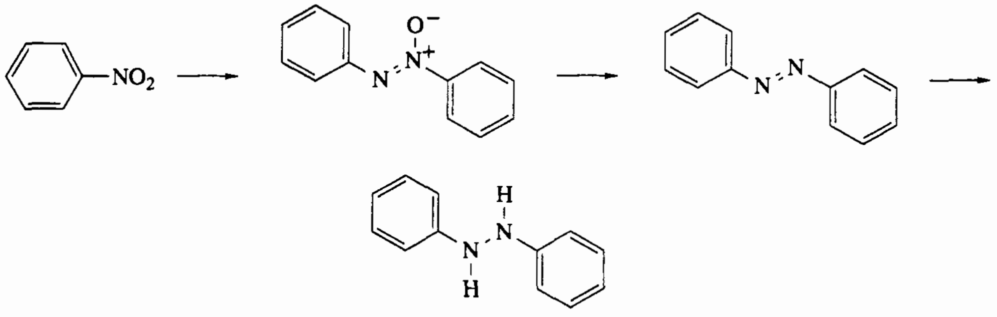

**Scheme 1**

The preparation of *o,o′*-dicyanoazoxybenzene (**6**) is representative of the reduction of aromatic nitro compounds using zinc under acidic conditions (equation 4).[26] The reduction of aromatic nitro compounds to azoxy derivatives has also been accomplished with tin(II) chloride in a basic medium.[30]

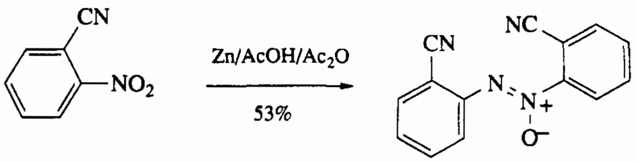

(4)

(**5**) (**6**)

Magnesium is another metallic reducing agent which produces a mixture of azoxy and azo compounds (~75%).[31] An alloy of sodium and lead (Drynap[32]) results in a similar mixture of products. A simple procedure involving the reaction of an aromatic nitro compound with thallium metal affords good yields of the corresponding azoxy compounds (equation 5).[33] Although high yields of azoxy compounds are obtainable from nitroarenes with alkyl or ether substituents, numerous other functionalities inhibit the reaction; these include CHO, COR, $CO_2H$, $CO_2R$, CN, OH and amino groups.

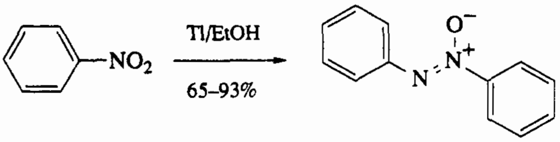

(5)

Alcoholic potassium hydroxide and sodium alcoholates have also been used as reducing agents for aromatic nitro compounds; the free alcohol or the alcoholate ion presumably acts as the reducing agent in these cases as illustrated for *m,m′*-diiodoazoxybenzene (**8**; equation 6).[17] In a few instances, where benzyl alcohol was used to prepare sodium benzylate, pure azoxy products were obtained without the formation of amino by-products.

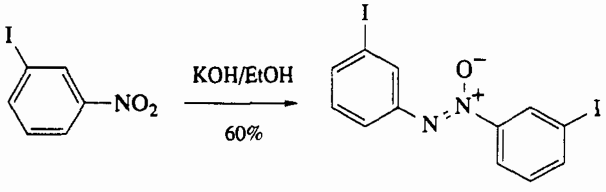

(6)

(**7**) (**8**)

An interesting reduction of aromatic nitro compounds which uses glucose in an alkaline medium (equation 7) has received little attention. The advantages of this reaction include high yields, rapid rate and ease of product isolation from oxidation by-products.[34] Other reagents which bring about the reduction of nitroarenes to azoxy compounds include potassium borohydride,[35] sodium arsenate,[36] phosphine[37] and yellow phosphorus.[38] Electrolytic methods have also been utilized.[39,40]

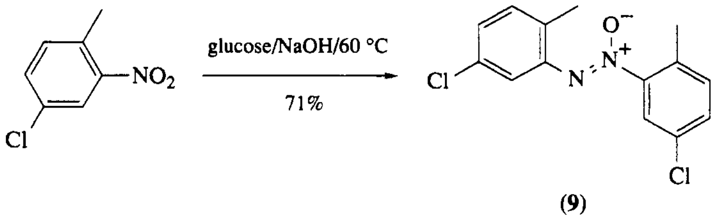

**(9)**

(7)

## 2.1.4 REDUCTION OF AROMATIC NITRO AND NITROSO COMPOUNDS TO HYDROXYLAMINES

Reduction of nitro compounds proceeds through intermediate stages involving nitroso compounds and hydroxylamines prior to amine formation (equation 8).

$$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2 \qquad (8)$$

Selective reduction to hydroxylamine can be achieved in a variety of ways; the most widely applicable systems utilize zinc and ammonium chloride in an aqueous or alcoholic medium.[41] The overreduction to amines can be prevented by using a two-phase solvent system. Hydroxylamines have also been obtained from nitro compounds using molecular hydrogen and iridium catalysts.[42] A rapid metal-catalyzed transfer reduction of aromatic nitroarenes to *N*-substituted hydroxylamines has also been developed; the method employs palladium and rhodium on charcoal as catalyst and a variety of hydrogen donors such as cyclohexene, hydrazine, formic acid and phosphinic acid.[43] The reduction of nitroarenes to arylhydroxylamines can also be achieved using hydrazine in the presence of Raney nickel[44] or iron(III) oxide.[45]

The preparation of *N*-phenylhydroxylamine in high yields from nitrobenzene under catalytic transfer hydrogenation conditions is also possible utilizing wet 5% rhodium on carbon and hydrazine hydrate.[46] Unfortunately, the transition metal catalysts tend to be expensive and the high temperatures required can be detrimental, particularly when the resulting hydroxylamines are explosive in nature.[47]

Tellurides ($H_2Te$, NaTeH, PhTeH and $Na_2Te$) are inexpensive and effective agents for reducing aromatic nitro compounds to hydroxylamines. Catalytic quantities of tellurium, in the presence of sodium borohydride, reduce *p*-substituted nitrobenzenes to *N*-arylhydroxylamines (equation 9).[48] Mild reaction conditions, absence of side reactions and experimental simplicity are the main features of this reduction sequence.

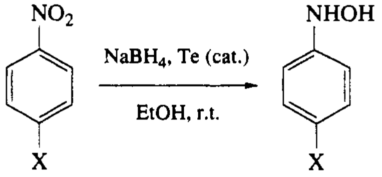

(9)

X = H, Me, Cl, CN, $NO_2$, $CO_2Et$

Selenium also catalyzes the sodium borohydride reduction of nitroarenes to the corresponding *N*-arylhydroxylamines (equation 10).[49] The active species in this selenium-catalyzed reduction was confirmed to be the hydrogen selenide anion.[50] The reaction is accelerated by electron-withdrawing groups and hindered by electron-donating substituents; nitro compounds bearing strongly electron-donating groups are completely inert under the normal reaction conditions.

The iron sulfide complex (**10**) resembles the active sites of oxidized rubredoxins: nonheme iron–sulfur proteins.[51] The complex catalyzes the reductions of aromatic nitro compounds to *N*-arylhydroxylamines by thiol (equation 11).[52] The method offers a facile, high yield approach to *N*-arylhydroxylamines. For example, *p*-dinitrobenzene was reduced to *p*-nitrophenylhydroxylamine in 92% yield.

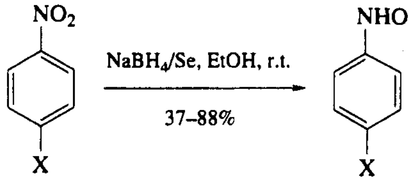

(10)

X = H, Me, Cl, CN, $NO_2$, $CO_2Et$

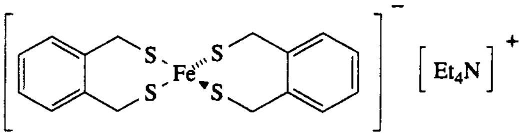

**(10)**

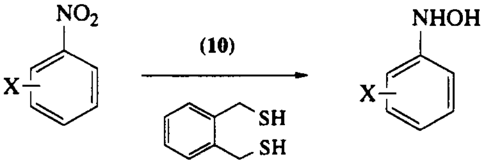

(11)

X = $NO_2$, CN, $CO_2Me$

## 2.1.5 REDUCTION OF AROMATIC NITRO AND NITROSO COMPOUNDS TO ANILINES

The synthetic, and industrially important, reduction of aromatic nitro compounds to anilines has been extensively investigated.[53–56]

### 2.1.5.1 Transfer Hydrogenation

The general area of catalytic transfer hydrogenation, as applied to nitroarenes, has also been reviewed.[57] The reduction of nitroarenes to aminoarenes using hydrazine as the hydrogen donor takes place readily in the presence of a wide variety of catalysts, including Cu, Fe, Ni, Rh, Ru and Pd.[58,59] It has been observed that controlling the reduction rates is difficult with active catalysts such as Pd but the utilization of less active catalysts results in better control, although substitution and dehalogenation reactions are quite common. In the presence of an excess of hydrazine hydrate, a number of nitrobenzenes are readily reduced to amines in high yields using iron(III) chloride on active carbon,[60] including the reduction of 5-chloro-2,4-dimethoxynitrobenzene without concomitant loss of the chlorine. The procedure is equally effective for the partial reduction of dinitrobenzene derivatives to the corresponding aminonitroarenes.[61] The superiority of catalytic transfer hydrogenation for the reduction of poly- and di-nitrobenzenes is noteworthy. Since the reduction of aminonitroarenes is considerably slower than their rate of formation, selective reduction to the half-reduced stage is the method of choice for the preparation of aminonitroarenes.

The reductive cyclization of the 2-nitrodihydrocinnamoyl group has found application for the protection of alcohols and amines using sodium phosphinate or cyclohexene as the hydrogen donor.[62] The hydrogen transfer reduction of both esters and amides regenerates the alcohols or amines under mild conditions (equation 12).

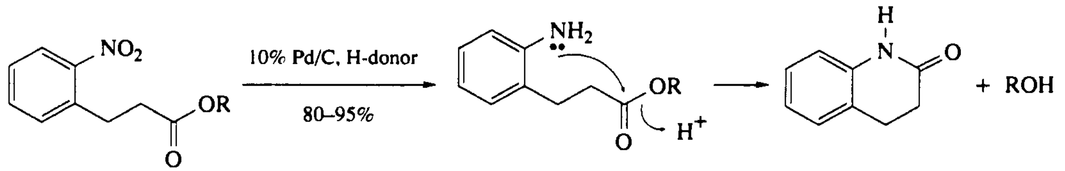

(12)

**(11)** **(12)**

The search for more active donors for transfer hydrogenation has led to the identification of economical and low cost reagents such as formic, phosphinic (hypophosphorous) and phosphorous acids.[63] Although reductions with formic acid are facile, anions of strong acids (such as $Cl^-$) quickly terminate the reduction. Thus nitroarenes containing a halogen substituent other than fluorine cannot be reduced using formic acid because of the catalyst-poisoning effect of the halide generated *in situ*. Arenes containing heterocyclic sulfur atoms are also unreactive. The use of formate salts[64] or $Pd/AlPO_4/SiO_2$ catalysts[65] obviates the difficulties encountered with termination of reductions by halogens.

The selective and rapid reduction of nitro compounds is an active area of research, particularly when other potentially reducible moieties are present in the molecules. Anhydrous ammonium formate has been developed as a catalytic hydrogen transfer agent for selectively reducing nitro groups in the presence of acid, ester, amide, halogen and nitrile groups (equation 13).[66]

$$Ar{-}NO_2 \xrightarrow{HCO_2NH_4,\ 10\%\ Pd/C,\ r.t.} Ar{-}NH_2 \qquad (13)$$

The selective reduction of nitroarenes containing benzyl-protected phenolic groups without concomitant hydrogenolysis has also been achieved using hydrazine hydrate and Raney nickel.[67] This procedure avoids strongly acidic conditions. The reaction is selective and a variety of *N*-benzyl- and chloro-substituted nitroarenes are reduced to the corresponding anilines without dehalogenation or debenzylation.

A detailed investigation of selectivity in the catalytic reduction of (nitroaryl)alkylnitriles with hydrazine and metal catalysis has been carried out.[68] On a small scale, selective reduction of (nitroaryl)alkylnitrile (**13**) to either (aminoaryl)alkylnitrile (**14**) or (aminoaryl)alkylamine (**15**) is readily achieved using a catalytic quantity of Raney nickel with hydrazine hydrate (2–5 equiv.) if adequate control of temperature is maintained. A lower temperature range (20–25 °C) affords (**14**), whereas warming (50–55 °C) with excess hydrazine hydrate (4–5 equiv.) produces (**15**) in nearly quantitative yields (Scheme 2). The advantages of the procedure include mild reaction conditions, the absence of high pressure equipment and the possibility of a simple scale-up to multikilogram quantities. Furthermore, aromatic rings are not reduced, a reaction which frequently occurs when pyridine derivatives are reduced.

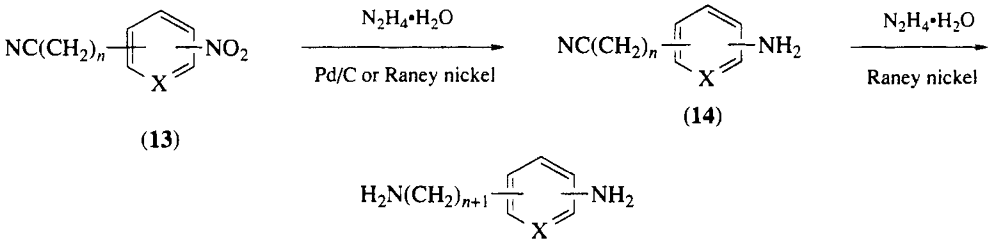

(**13**) (**14**) (**15**)

**Scheme 2**

The effect of ultrasonic irradiation on hydrazine reductions in the presence of iron powder and activated carbon in ethanol has also been evaluated.[69] The studies include graphite-catalyzed reductions of aromatic nitro compounds to the corresponding arylamines.[70] The notable features of these reactions are the low cost, high yields and the simplicity of the work-up procedure. Significantly, nitro groups can be reduced in the presence of a variety of functional groups.

Raney nickel and hydrazine hydrate have also been used to prepare 4-(benzyloxy)indoles (**16**) *via* reductive cyclization.[71] An improvement can be achieved by using nickel boride instead of Raney nickel;[72] the advantages of this method include ease of preparation of the catalyst and its nonpyrophoric nature (equation 14).

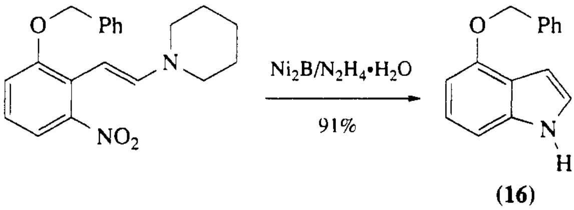

(14)

(**16**)

The observation that formic acid can be decomposed to hydrogen and carbon dioxide at room temperature using [$RuCl_2(PPh_3)_3$] in the presence of triethylamine led to the development of the [$RuCl_2(PPh_3)_3$]/$HCO_2H/Et_3N$ system as a hydrogen source. Pd/C increases the reactivity of this system, which is selective in reducing nitro groups in the presence of alkenes, esters and cyano groups.[73] Surprisingly, the hydrogenolysis of aromatic halides is slower than the reduction of the nitro group.

### 2.1.5.2 Borohydride and Borane Reductions

Sodium borohydride is an effective and widely used reducing agent. The relatively low cost and the ease with which it can be handled contribute to its popularity. However, borohydride does not generally reduce aromatic nitro compounds to the corresponding aniline derivatives in the absence of a catalyst[74] such as cobalt(II) chloride,[75] palladium,[76] titanium(IV) chloride[77] or tin(II) chloride.[78] Relatively inexpensive systems such as $NaBH_4$–iron(II) chloride[79] and $NaBH_4$–copper(I) chloride[80] also reduce nitroarenes containing electron-donating groups in the *ortho* or *para* positions.

Sodium borohydride reduces disulfides to thiols, which can then be used to reduce nitro groups. Based on the redox properties of 1,2-dithiolane, lipoamide (**17**) was used for the selective reduction of monosubstituted nitrobenzenes to the corresponding anilines.[81] Lipoamide (**17**) can also be immobilized on hydrophilic polymers such as polyvinylamine, polyethyleneimine and chitosan.[82] These polymeric reducing catalysts can be recycled and are easy to separate from the reaction mixture. The system has been used to reduce nitroarenes to anilines.[83]

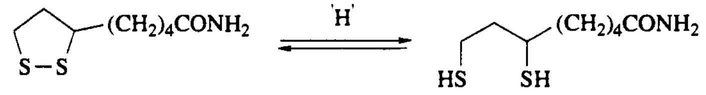

**(17)** LAm **(18)** DHLAm (15)

Sodium borohydride can also be used to couple dinitrobenzenes.[84] 1,3-Dinitrobenzene (**19**) and 1,3,5-trinitrobenzene (**21**) produce diphenylamine derivatives in reactions that are of preparative value when the nitro compound is present in excess (Scheme 3). The method involves the addition of a suspension of

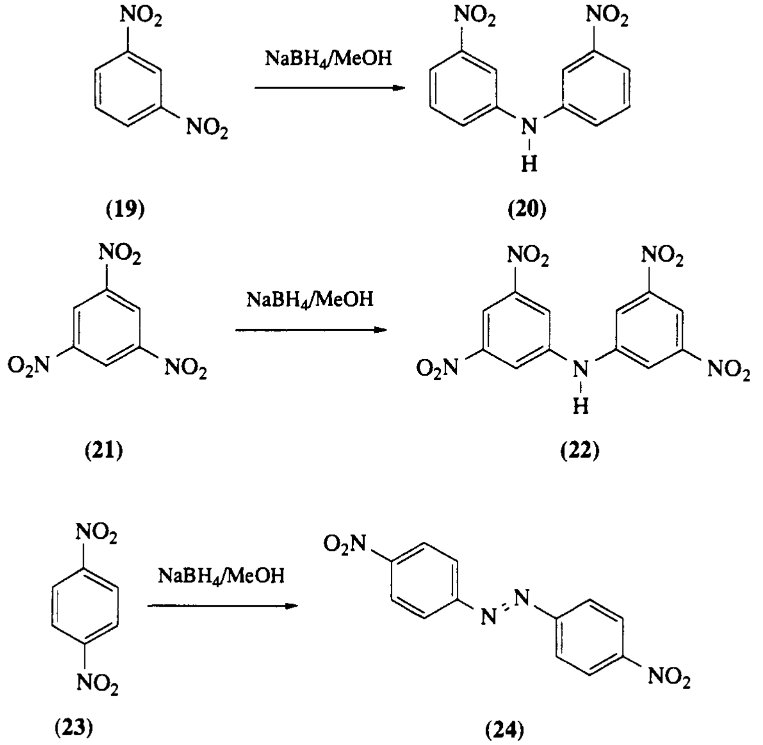

**Scheme 3**

sodium borohydride in methanolic sodium hydroxide to a solution of the nitro compound in refluxing methanol. Under these conditions, no reduction to dinitrocyclohexenes is observed.[85,86] Coupling products are not obtained from 1,2,4-trinitrobenzene, even though two of the nitro groups have a *meta* relationship. 1,4-Dinitrobenzene (**23**) undergoes reductive coupling to yield 4,4′-dinitroazobenzene (**24**).

Curiously, 1,2-dinitrobenzene (**25**) couples with the loss of one nitro group; however, the product is a diphenylhydroxylamine derivative (**26**) rather than a diphenylamine (equation 16). Nitroso compounds can also be reduced to amines in good yields using diborane (equation 17).[87]

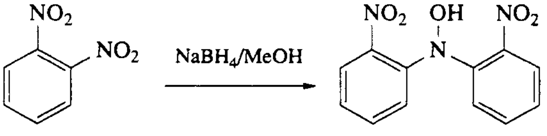

**(25)** **(26)**

(16)

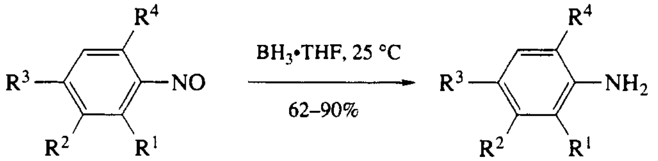

(17)

### 2.1.5.3 Reductions Involving Tellurium, Selenium and Sulfur

Selenol,[88] a very soft nucleophile, reduces nitroarenes.[89] Hydrogen telluride ($H_2Te$),[90] sodium hydrogen telluride (NaTeH)[91] and related organotellurols are also effective reducing agents. The ready autooxidation of organotellurols to ditellurides prevents their isolation; consequently these reagents are generated and used *in situ*.[92] Benzenetellurol (**27**) is prepared[93] by methanolysis of phenyl trimethylsilyl telluride or by reduction of diphenyl ditelluride with phosphinic acid or sodium borohydride and used to reduce aromatic nitro compounds to amines (Scheme 4).

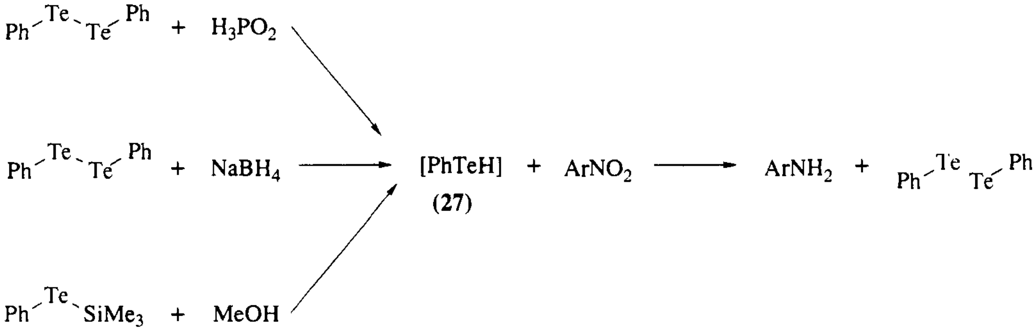

**Scheme 4**

Heating tellurium with an excess of Rongalite ($HOCH_2SO_2Na{\cdot}2H_2O$) in aqueous sodium hydroxide under an inert atmosphere affords sodium telluride ($Na_2Te$),[94] which reduces nitroarenes to anilines. The reductions are carried out using a catalytic amount of tellurium. The tellurium-mediated reduction of nitroarenes with Rongalite proceeds directly to anilines, and is the method of choice for compounds containing acid sensitive functionalities.

Interest in an old reducing agent, sodium sulfide,[95] was renewed when it was discovered that its reactivity toward nitro groups was sensitive to water.[96] In the absence of water, the aromatic nitro group in (**28**) can be reduced selectively to (**29**), without reduction of the aliphatic nitro group, but compounds such as (**30**), which contain a tertiary aliphatic nitro group eliminate the nitro moiety to yield styrene derivatives (**31**; Scheme 5). A unique application of the sulfide reduction involves the preparation of isomerically pure substituted aromatic nitro compounds and anilines.[97]

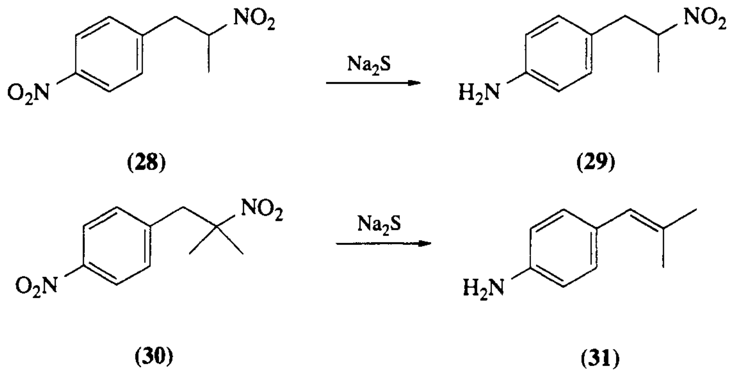

**(28)** **(29)** **(30)** **(31)**

**Scheme 5**

### 2.1.5.4 Transition Metal Reductions

Low valent species of transition metals (Groups IVB, VB and VIB) have found widespread use in the reduction of nitro compounds.[98] Chromium(II) chloride,[99] titanium(III) chloride[100] and vanadium(II) sulfate[101] readily reduce aromatic nitro compounds to arylamines. Chromium(II) chloride[102] also reduces nitrobenzene and nitroquinoline to the corresponding amines in excellent yields.[103]

Oxime deoxygenation[104] by titanium(III) chloride spurred investigation of this agent for reducing nitro aliphatics;[105] the method is applicable to other nitro compounds.[106,107] The active species are thought to be $ArNO_2H^+$ and a hydrolyzed form of titanium(II).[108] The reaction conditions have been optimized for the reduction of aromatic and even heteroaromatic nitro compounds.[109]

A combination of titanium(IV) chloride and dialkyl telluride in relatively inert solvent systems reduces nitroarenes to arylamines in moderate yields.[110] Presumably, titanium(IV) chloride is reduced to a low valent titanium species which subsequently reacts with aromatic nitro compounds to afford the corresponding amines (equation 18).

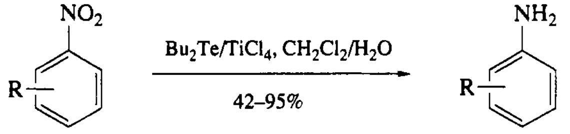

(18)

Tin(II) chloride is an effective reducing agent under acidic conditions.[111] This inexpensive reagent selectively reduces aromatic nitro compounds in nonacidic and nonaqueous media.[112] Nearly quantitative yields of arylamines are obtained using tin(II) chloride dihydrate in alcohol or ethyl acetate (equation 19). Under these conditions other reducible or acid sensitive groups such as aldehyde, ketone, ester, cyano, halogen and benzyl ethers are not affected.

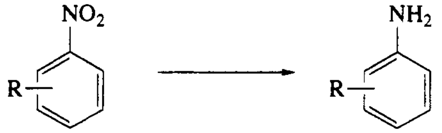

(19)

$R = H, Cl, OH, CO_2H, CHO, OMe, CO_2Me, OAc$

The iron cluster $[Fe_4S_4(SPh)_4]^{2-}$ catalyzes the reduction of nitroarenes to arylamines.[113] A less hydridic nucleophile $[HFe(CO)_4]^-$ has also found application as a selective reducing agent for nitroarenes.[114] Although $[HFe(CO)_4]^-]$ is known to reduce aldehydes, ketones and acid halides,[115] in THF solvent with trifluoroacetic acid, it selectively reduces nitrobenzenes to anilines in the presence of aldehyde and acid halide groups.

### 2.1.5.5 Hydrogenation

The catalytic reduction of aromatic nitroso compounds to amines is well documented.[116] Selective reduction of nitro aromatic compounds can be achieved at room temperature and atmospheric pressure using an interlamellar montmorillonitesilylpalladium(II) complex (equation 20).[117]

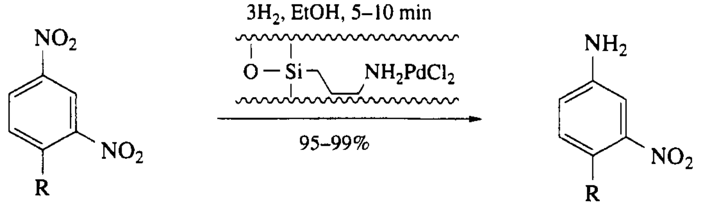

(20)

R = H, Me

There has also been continuous interest in the preparation of thermally stable polymers which can be utilized as heterogeneous catalyst supports. Polybenzimidazole (PBI) (**32**) is a thermally stable heterocyclic polymer.[118] Polybenzimidazole forms a complex with $PdCl_2$ (**33**) which can be reduced to PBI–Pd$^0$ (**34**). This catalyst is extremely stable yet it can be used to reduce a variety of nitro compounds (Scheme 6). The catalyst may be recycled simply by washing with methanol to remove the reduced substrate from the polymer; the recycled catalyst shows no loss of activity or of Pd content after more than 20 cycles.

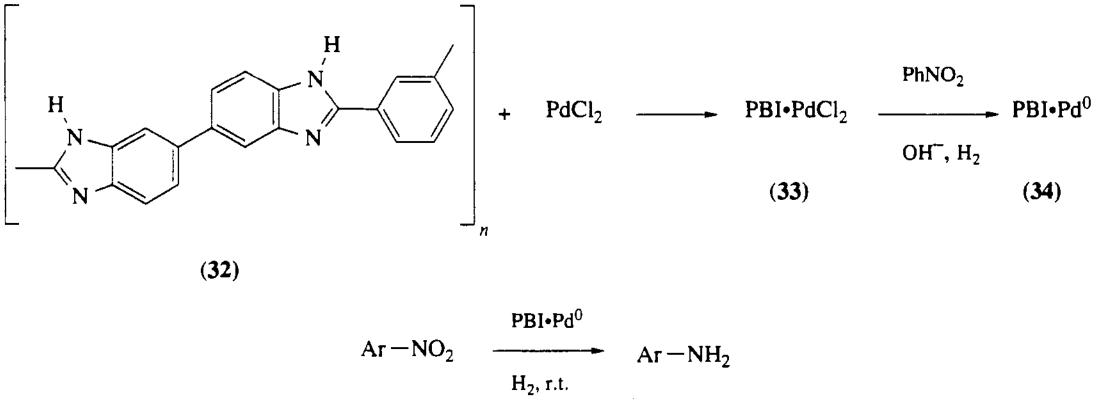

**Scheme 6**

### 2.1.5.6 Carbon Monoxide

Carbon monoxide reduces aromatic nitro compounds when iron pentacarbonyl is used as catalyst.[119] A direct homogeneous catalytic reduction of nitro derivatives with water under moderate carbon monoxide pressure also occurs when rhodium carbonyl derivatives in aqueous organic bases are used as catalysts (equation 21).[120] Presumably hydridorhodium carbonyl species[121] are the active agents whose preferred formation in aqueous organic base may be analogous to that of iron carbonyl hydrides.[122]

$$\mathrm{Ar{-}NO_2} + 3\mathrm{CO} + \mathrm{H_2O} \xrightarrow{\text{catalyst}} \mathrm{Ar{-}NH_2} + 3\mathrm{CO_2} \qquad (21)$$

Several other polynuclear metal carbonyls were tested as catalysts for the reduction of nitrobenzene to aniline using carbon monoxide and water as the reducing agent. Rhodium, iridium and osmium clusters were found to be very effective and they were far less susceptible to oxidative degradation than $[Fe(CO)_5]$.[123]

The search for a novel, low cost replacement for elemental hydrogen resulted in the discovery of a mixed gas consisting of hydrogen sulfide and carbon monoxide.[124] This gas, when used with Fe on $Al_2O_3$, reduces dinitroarenes to diamino aromatic compounds in high yield (equation 22).

$$\mathrm{Ar(NO_2)_2} \xrightarrow[\text{catalyst}]{\mathrm{H_2S/CO}} \mathrm{Ar(NH_2)_2} \qquad (22)$$

Amines are also obtained in excellent yields, at room temperature and atmospheric pressure, using carbon monoxide, ruthenium carbonyl and benzyltriethylammonium chloride in an aqueous base-organic solvent system.[125] The method is significantly milder than previously described water gas shift reaction conditions.[123]

### 2.1.5.7 Miscellaneous Reduction Methods

An atmospheric pressure hydrogenation of mononitro aromatic compounds to anilines can be achieved using hydrogen sulfide as reducing agent and titanium dioxide as catalyst.[126] The reduction of arylnitroso compounds by NADH and *N*1-(2,6-dichlorobenzyl)-1,4-dihydronicotinamide (DBDN-4H$_2$) has been investigated in model systems.[127] Arylnitroso compounds such as (**35**) are readily reduced by NADH and DBDN-4H$_2$, but the reaction conditions require the absence of oxygen, or neutral and weakly alkaline aqueous buffers (Scheme 7).

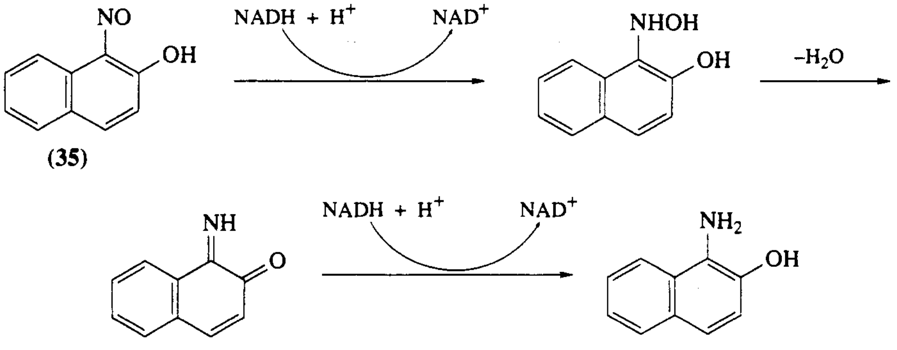

**(35)**

**Scheme 7**

Copper salt–amine complexes can also be used for the reduction of aromatic compounds to the corresponding amine.[128] A more general and convenient method for reducing nitroso compounds to amines involves the use of a nickel/aluminum alloy.[129] The low cost and ready commercial availability of nickel/aluminum alloy are important features of this reduction procedure which may find wide acceptance as a preparative method.

## 2.1.6 REDUCTION OF ALIPHATIC NITRO COMPOUNDS TO HYDROXYLAMINES

The reduction of nitroalkanes to *N*-monosubstituted hydroxylamines has not been extensively explored. The classical approach involves electrolytic reduction of primary and secondary nitroalkanes.[130–132] Catalytic hydrogenation[133] and hydride reductions[134] of nitroalkenes also yield hydroxylamine derivatives.

Diborane, which does not reduce nitro compounds,[135] readily reduces the salts of primary and secondary nitro compounds to the corresponding *N*-monosubstituted hydroxylamines (equation 23).[136]

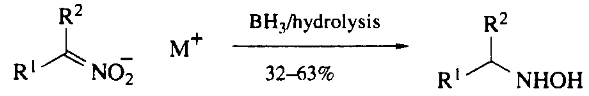

(23)

$R^1$ = H or alkyl; $R^2$ = alkyl or aryl; M = Li, K or $NH_4^+$

Trialkylboron hydrides react with conjugated nitroalkenes to yield nitronate intermediates *via* a 1,4-addition of the hydride. The corresponding nitroalkanes are easily obtained by using silica gel to protonate the nitronate salt.[137] These reactions presumably occur through a common intermediate (**36**), which is then hydrolyzed to the nitroalkane or reduced by a borane complex to yield hydroxylamine, after hydrolysis.

Even sodium borohydride catalyzes the reaction of borane complexes with conjugated nitroalkenes (equation 24).[138] This straightforward approach affords pure hydroxylamines in high yields. As an

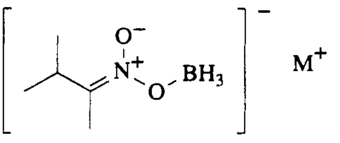

**(36)**

example, the reduction of 3-nitrochromenes (**37**) by a borane–borohydride system results in novel hydroxylaminochroman derivatives (**38**; equation 25).[139] A modification of these procedures involving the use of *in situ* generated borane (from $NaBH_4$ and $BF_3 \cdot Et_2O$) obviates the need for $BH_3 \cdot THF$, which is not universally available.[140]

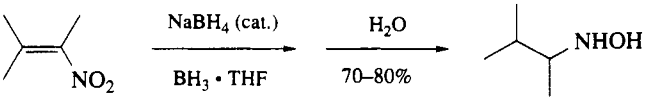

(24)

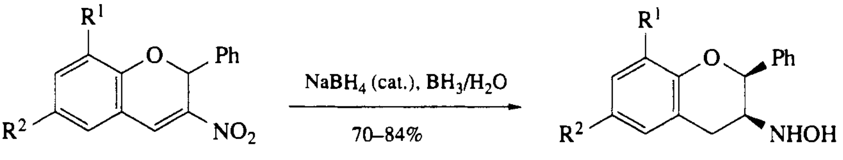

(**37**) (**38**) (25)

## 2.1.7 REDUCTION OF ALIPHATIC NITROALKANES TO AMINES

While aromatic nitro compounds are reduced to anilines by a variety of methods,[1,141] comparatively few reagents reduce aliphatic nitro compounds to the corresponding amines. Traditionally, nitro aliphatic materials have been reduced using high pressure hydrogenation,[142,143] lithium aluminum hydride[144,145] or aluminum amalgam.[146–150]

### 2.1.7.1 Nitroalkane Reductions

The value of the catalytic transfer hydrogenation route is demonstrated by the selective, high yield and rapid reduction of nitro aliphatic compounds to their corresponding amine derivatives using anhydrous ammonium formate (equation 26).[67] A wide variety of nitro compounds are reduced in the presence of other functional groups including acids, esters and nitriles. Furthermore, the method is stereospecific and proceeds with retention of configuration:[151] pure racemic *syn*-nitro alcohols (**39a**) and (**39b**) were converted to the *syn*-amino alcohols (**40a**) and (**40b**) and the axial nitrosteroid (**41a**) afforded the 6β-amine (**41b**).

$$\text{Alkyl–NO}_2 \xrightarrow[\text{r.t., MeOH; 31–98\%}]{\text{HCO}_2\text{NH}_4\text{, 10\% Pd–C}} \text{Alkyl–NH}_2 \qquad (26)$$

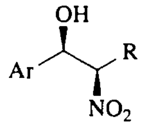

(**39a**) R = Me
(**39b**) R = $CH_2OTHP$

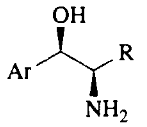

(**40a**) R = Me
(**40b**) R = $CH_2OTHP$

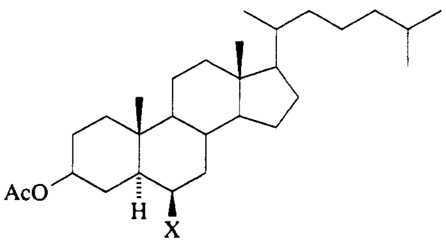

(**41a**) X = $NO_2$
(**41b**) X = $NH_2$

In view of its industrial importance, a number of homogeneous catalysts have been examined for use in selective hydrogenations of nitroalkanes to amines.[152] Tris(triphenylphosphine)ruthenium(II) chloride is particularly effective.[153] The mechanism of this hydrogenation is known to involve nitronate anion formation.[154]

Hydrazine hydrate can also be used to reduce nitroalkanes in the presence of a graphite catalyst.[70] The low cost of the catalyst serves to make this a particularly attractive reduction method. Electrochemical reduction of tertiary nitroalkanes such as the 2-substituted-1,1-dimethyl-1-nitroethanes (**42a**–**42c**) yields amines (**44a**–**44c**) as well as hydroxylamines (**43a**–**43c**; equation 27).[155]

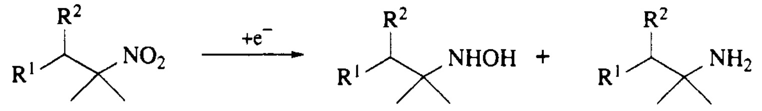

(27)

(**42a**) $R^1$ = Ar, $R^2$ = H
(**42b**) $R^1$ = Ar, $R^2$ = OH
(**42c**) $R^1$ = H, $R^2$ = OH

(**43a**–**43c**)

(**44a**–**44c**)

Titanium(II) reagents have also been used to reduce aliphatic nitro compounds to amines; halo, cyano and ester groups are not reduced.[156] Sodium borohydride, in the presence of catalytic amounts of nickel(II) chloride, reduces a variety of aliphatic nitro compounds to amines.[157] Nickel boride ($Ni_2B$) is an active catalyst for reductions of primary, secondary and tertiary nitro aliphatic compounds to amines.[158] The reduction of nitrocyclohexane (**45**) yields cyclohexylamine (**47**) as well as small amounts of dicyclohexylamine (**49**), the latter being formed *via* reaction of intermediates (**46**) and (**48**; equation 28).

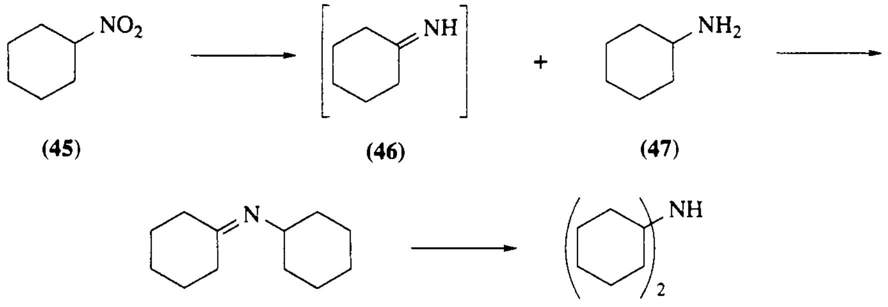

(**45**) (**46**) (**47**)

(28)

(**48**) (**49**)

1-(Indol-3-yl)-2-nitroalkanes (**50**) are reduced to the corresponding α-alkyltryptamines (**51**) using nickel boride and hydrazine hydrate (equation 29).[72]

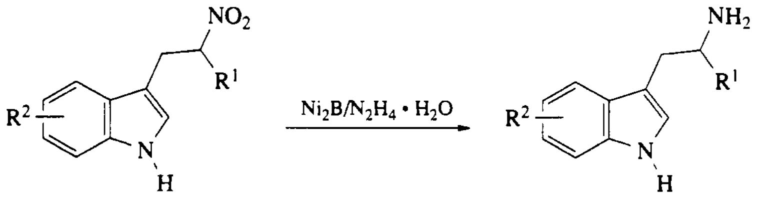

(29)

(**50**) (**51**)

### 2.1.7.2 Nitroalkene Reductions

The reduction of α,β-unsaturated nitroalkenes provides a simple access to a vast array of functionalities, including amines.[4] Early studies focused on the catalytic hydrogenation of the nitropropene derivative (**52**); 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**53**) is obtained as a minor product in a complex reaction.[133] The reverse addition of lithium aluminum hydride to β-methyl-β-nitrostyrene affords a mixture of β-phenylisopropylamine and *N*-(β-phenylisopropyl)hydroxylamine.[134]

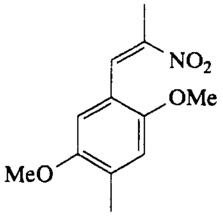

**(52)**

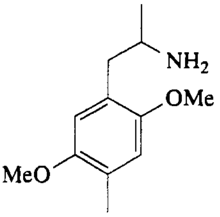

**(53)**

Alkylamines are generally accessible *via* the reduction of nitroalkenes with lithium aluminum hydride.[159–161] Substituted thienylethylamines[162] can also be obtained using this methodology (equation 30).

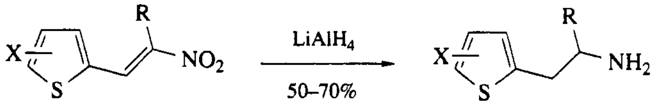

(30)

A general synthesis of β-(2- or 3-pyrrolyl)alkylamines (**55**) containing an unsubstituted nitrogen atom is available *via* the reduction of the corresponding nitroalkene (**54**; equation 31).[163]

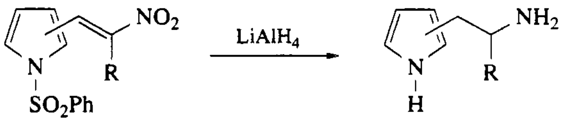

(31)

| | *Position* | *R* | | |
|---|---|---|---|---|
| **(54a)** | 3 | H | **(55a)** | 69% |
| **(54b)** | 3 | Me | **(55b)** | 68% |
| **(54c)** | 2 | H | **(55c)** | 70% |
| **(54d)** | 2 | Me | **(55d)** | 72% |

Since hydroxylamines, as well as their precursor oxime derivatives, are reduced by diborane to amines,[164] the reaction has been extended by reducing the initially formed hydroxylamine intermediates (**57**) to amines (**58**).[165] Thus excess borane reduces nitroalkenes (**56**) to amines (**58**) in the presence of a catalytic amount of sodium borohydride (equation 32).

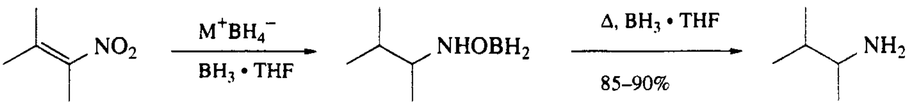

(32)

**(56)** **(57)** **(58)**

The reduction can also be achieved by utilizing *in situ* generated $BH_3$·THF (from sodium borohydride and boron trifluoride etherate).[166] The scope of this reaction includes the synthesis of novel 3-chromanamine derivatives (**60**; equation 33).[140] This stereoselective reaction proceeds *via* the hydroxylamine intermediate; only *cis*-2-aryl-3-amino derivatives are obtained.

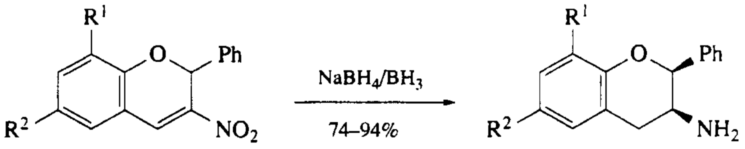

(33)

**(59)** **(60)**

In the course of investigations involving the reaction of lithium triethylhydroborate with conjugated nitroalkenes (**61**),[137,167] *N*-ethylamines (**62**) were consistently observed as by-products (equation 34).[168] The intermediacy of nitroso compounds has been confirmed in this reaction which provides a useful method for the preparation of *N*-ethylated amine derivatives. These *N*-alkylated products are not produced when sterically demanding reagents, such as potassium tri-*s*-butylborohydride, are used. Apparently, the competition between reduction and alkylation of the nitroso group is sensitive to steric effects.

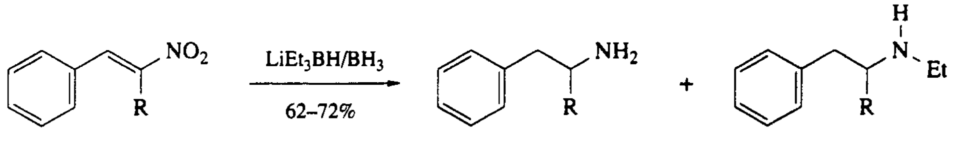

(34)

(**61**) R = H or Me

(**62**)

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# 2.2

# Reduction of N═N, N—N, N—O and O—O Bonds

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## 2.2.1 INTRODUCTION

This chapter covers methods of reduction of nitrogen–nitrogen multiple bonds and methods for the reductive cleavage of N—N, N—O and O—O bonds. Perhaps the most important use of reactions of these types is that they can allow the introduction of amino and hydroxy groups with considerable control of stereochemistry. Amino groups are often introduced by the use of azide ion and occasionally by hydroxylamines or hydrazines as nucleophiles, followed by reductive cleavage. Hydroxy groups can similarly be introduced by way of peroxides. Activated azo and nitroso compounds and singlet oxygen are excellent dienophiles in the Diels–Alder reaction and the cleavage of the heteroatom to heteroatom bonds permits two functional groups to be introduced in a controlled manner. Alkenes and alkynes can also be functionalized at both termini by the cycloaddition of 1,3-dipoles such as nitrones, nitrile imides and nitrile oxides, followed by reductive cleavage.

Inevitably there is some overlap with other chapters, particularly those dealing with reduction of C=N bonded groups (Chapters 1.2–1.8, this volume) and that on the reduction of heterocycles (Chapter 3.8, this volume). For completeness, most of the important reduction methods for the appropriate groups are also referred to here. An attempt has been made to cover the literature to late 1989; a few later references are also included.

## 2.2.2 REDUCTION OF GROUPS WITH NITROGEN-NITROGEN MULTIPLE BONDS

### 2.2.2.1 Reduction to N—N Bonded Groups

### *2.2.2.1.1 Azo and azoxy to hydrazo groups*

Standard methods which existed in the mid-1970s for the reduction of azo and azoxy compounds to hydrazo compounds have been reviewed.[1] The reduction of aliphatic azo compounds is not of much use for the synthesis of aliphatic hydrazo compounds because the azo compounds are usually prepared from them. Methods for the reduction of aliphatic azoxy compounds directly to the corresponding hydrazo compounds involve the use of tin(II) chloride in hydrochloric acid and catalytic hydrogenation over platinum oxide; electrochemical reduction can also be used.

The reduction is an important method for the preparation of aromatic hydrazo compounds. Useful reagents for the conversion of azobenzenes to hydrazobenzenes in good yield include diimide, sodium borohydride in the presence of metal catalysts, lithium aluminum hydride[2] and cobalt boride with hydrazine hydrate.[3] Catalytic hydrogenation has also been used,[4] although further reductive cleavage of the N—N bond can occur. Zinc and other metals can be used for the reduction, but strongly acidic conditions have to be avoided in order to prevent the benzidine rearrangement of the hydrazobenzenes. For the reduction of azoxybenzenes to hydrazobenzenes, commonly used reagents are zinc dust in acetic acid or in alkali and aqueous sodium disulfide.

There are several recent methods for the reduction of azobenzene to hydrazobenzene in near-quantitative yield.[5] Samarium(II) iodide reduces azobenzene to hydrazobenzene rapidly at room temperature.[6] Hydrogen telluride, generated *in situ* from aluminum telluride and water, reduces both azobenzene and azoxybenzene to hydrazobenzene;[7] a mixture of phenyllithium and tellurium powder has been used to reduce azobenzene.[8] A complex of the coenzyme dihydrolipoamide and iron(II) is also effective for the reduction of azo- and azoxy-benzene to hydrazobenzene; the reduction probably involves coordination of the azobenzene to iron(II) as shown in structure (**1**).[9] Electrochemical reduction has been used to prepare a number of hydrazobenzenes from the corresponding azobenzenes. In the presence of an acylating agent a diacylhydrazine (*e.g.* the pyridazinedione derivative **2**) can be isolated from the electrochemical reduction of azobenzene.[10]

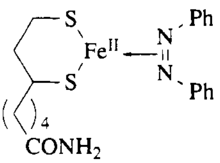

(**1**)

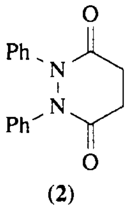

(**2**)

$ArNHNH_3^+ BF_4^-$

(**3**)

### *2.2.2.1.2 Diazo compounds and diazonium salts to hydrazines*

A few examples of the reduction of aliphatic diazo compounds to hydrazines exist,[11] but this is not a generally applicable method for the synthesis of alkylhydrazines. On the other hand, arylhydrazines can be prepared by reduction of aromatic diazonium salts.[12] The most commonly used reagents for this conversion are sulfur dioxide (or sodium sulfite) and tin(II) chloride, these being used to reduce arenediazonium chlorides in aqueous solution. Several other reagents, including sodium amalgam and triphenylphosphine, have been used for specific reductions of this type.[12] Arenediazonium tetrafluoroborates have been reduced to the corresponding hydrazinium salts (**3**) by benzeneselenol in dichloromethane solution.[13] Partial reduction of the benzenediazonium cation leads to the formation of the corresponding radical[14] or of benzenediimide, PhN=NH. Benzenediimide is an unstable (although detectable)[15] compound which readily loses nitrogen; the usual products of such partial reduction are, therefore, benzene and nitrogen.

## 2.2.2.2 Reductive Cleavage

### *2.2.2.2.1 Azo, azoxy, diazo and diazonium compounds to amines*

Standard methods for the reductive cleavage of azo and azoxy groups are described in several reviews.[1,2,4,16] Catalytic hydrogenation of azo compounds over platinum, or with Raney nickel, often leads to reductive cleavage; an example is the cleavage of the azo compound (**4**) to 2-methylindol-3-amine (85%) by catalytic reduction over platinum.[17] Catalytic transfer hydrogenation over palladium (with cyclohexene as coreagent) is also an efficient method for the reductive cleavage of azobenzenes to anilines.[18] A reagent which appears to have wide applications for reductions of this type is nickel–aluminum alloy.[19,20] When added to the substrate in aqueous methanolic potassium hydroxide at room temperature, azobenzene was reduced to aniline (79%) and the azoxy compound $MeN{=}N^{+}O^{-}Ph$ gave methylamine quantitatively. Older methods include metal and acid combinations (for example, tin(II) chloride and hydrochloric acid), hydriodic acid, sodium dithionite and diborane.

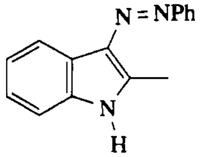

**(4)**

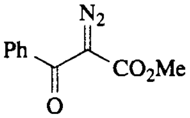

**(5)**

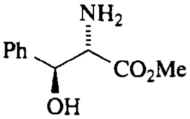

**(6)**

The reductive cleavage of diazo compounds to amines is not a reaction which has found wide use.[4,11] Catalytic hydrogenolysis of some diazo esters in acidic media can lead to the formation of amines in fair to good yield,[4,21] although other functional groups present may also be reduced; for example, reduction of the diazo compound (**5**) over palladium in 70% acetic acid gave the amine (**6**; 82%).[4] The conversion of aromatic diazonium salts to the corresponding anilines is also a reaction with little general synthetic applicability;[12] examples of the reaction have been described using zinc or tin in acidic media and ammonia (this last reagent probably forming an unstable triazene by nucleophilic attack on the diazonium ion).

### *2.2.2.2.2 Azides and triazenes to amines*

Since the azide ion is an excellent nucleophile it is often the reagent of choice for introducing a nitrogen functional group. The reduction of the azido group to a primary amino group is consequently often an important step in a reaction sequence. The attack of azide ion on a primary or secondary carbon center bearing a good leaving group proceeds with inversion of configuration and the subsequent reduction of the azido to an amino group proceeds with retention. The amino group can, therefore, be introduced with control of stereochemistry. An example of a practical application, in which these reactions are combined with enantioselective enzymic ester hydrolysis to produce optically active amino alcohols from cyclohexene oxide, is shown in Scheme 1.[22]

A wide range of reduction methods is available, including several which are claimed to permit selective reduction of the azido group in the presence of other functional groups. Many of the methods fall into one of three broad categories: (i) involving the use of hydrogen and metal catalysts, (ii) involving low-valent metals, and (iii) involving the use of nucleophiles which initially attack the terminal nitrogen of the azide with the formation of a triazene (**7**). These triazenes can sometimes be isolated, but they are usually reduced *in situ*, by the same reagent or by a different one, to the primary amine. The ease of reduction of the azido group by reagents of the third type, therefore, depends upon the susceptibility of the functional group to nucleophilic attack: aromatic azides, especially those with electron-withdrawing substituents, are generally easier to reduce than simple aliphatic azides.

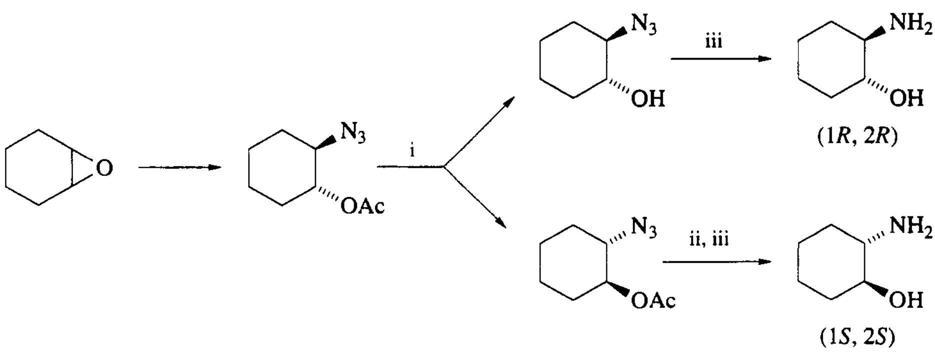

i, lipase from *Candida cyclindracea*; ii, NaOMe, MeOH; iii, $H_2$, Pd/C

**Scheme 1**

RN = NNHNu

(7) Nu = nucleophile

Reviews published in 1971 and 1988 cover the methods known at the time for the reduction of azides.[23] There are more selective reviews of catalytic methods[4] and of reduction by metal hydrides.[2]

Catalytic hydrogenation over platinum or palladium is generally an efficient method of reduction of azides when there are no other sensitive functional groups present. Nitrogen is evolved in the reaction so it is not possible, with normal hydrogenation apparatus, to follow the course of the hydrogenation by the uptake of gas. The mechanism of hydrogenation has not been established, but the triazenes $RN{=}NNH_2$ have been suggested as intermediates. Selective hydrogenolysis of azido groups in the presence of double bonds and of benzyloxy groups has been achieved using Lindlar catalyst in ethanol;[24] for example, the azide $PhCH_2O(CH_2)_3N_3$ was reduced to the corresponding amine (96%) by this method. There are also examples of the reduction of azides over palladium on carbon without affecting other sensitive functional groups, such as the benzyloxycarbonyl group.[25] Raney nickel catalyzed reduction has similarly been used for selective attack on the azido group in the presence of a double bond and a benzyloxy group.[26] Other catalytic methods include catalytic transfer hydrogenation[27] and reduction over rhodium(III) chloride in the presence of carbon monoxide.[28]

Several alkyl and aryl azides have been reduced to the corresponding amines in good yield by tin(II) chloride at room temperature; the less reactive azides require a catalytic amount of aluminum trichloride to be added.[29] Aqueous vanadium(II) chloride is a useful reducing agent for aryl azides;[30] heteroaryl and arenesulfonyl azides have been reduced with aqueous titanium(III) chloride[31] and with a molybdenum(III) catalyst generated from molybdenum(V) chloride and zinc.[32]

There are many nucleophilic reagents which can effect the conversion of azides into amines and some are very selective. Lithium aluminum hydride is a good reagent in cases where high chemoselectivity is not required. Sodium borohydride has also been used to reduce aryl and other azides, either under phase transfer conditions[33] or by adding the reagent in methanol dropwise to a solution of the azide in THF.[34] 2-Nitrophenyl azide was reduced to 2-nitroaniline (94%) by this reagent,[34] although alkoxycarbonyl groups were reduced. The complex hydride $(Ph_3P)_2CuBH_4$ has also been used to reduce 2-nitrophenyl azide; aromatic azides bearing azo and ethoxycarbonyl groups were also selectively reduced.[35]

Hydrogen sulfide has long been known as a reagent for the reduction of azides and it is selective for the azido group in the presence of many other functional groups, reaction taking place by nucleophilic attack on the terminal nitrogen of the azide. Its uses include the selective reduction of unsaturated nucleoside azides,[36] the reduction of azidothiophenes bearing formyl and cyano groups[37] and the reduction of vinyl azides to carbonyl compounds (Scheme 2).[38] A better, and highly selective, reagent is 1,3-propanedithiol (Scheme 3).[39] The dithiol can reduce aryl and alkyl azides in the presence of double and triple bonds, nitro, cyano, carbonyl and other groups. Its sensitivity to electronic and steric effects can also allow for selective reduction of different azides; for example, 4-nitrophenyl azide is reduced in 1 min at room temperature, whereas 1-azidoadamantane requires 120 h at 60 °C. Thioacetic acid has also been used for selective reduction.[40] This reagent permits reduction in the presence of nitro, *t*-butoxycarbonyl and benzyl groups at room temperature. The reduction is accompanied by acetylation so that the products are acetamides rather than free amines.

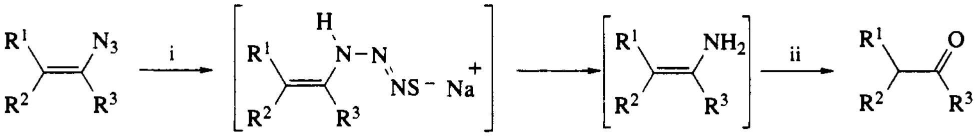

i, $Na_2S$; ii, $H_2O$

**Scheme 2**

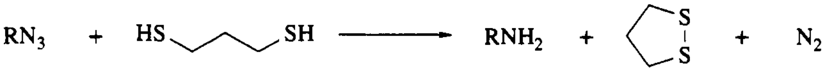

**Scheme 3**

These sulfur-based compounds are mild reducing agents. Two tin-based reagents have been described which are claimed to combine high reducing power with good selectivity.[41] The more reactive of these, $Et_3NH^+Sn(SPh)_3^-$, rapidly reduces a variety of aliphatic azides in organic solution at room temperature and without attack on a carbonyl group. The reagent $Bu_2SnH_2$ can be used to carry out the same reductions but is slower.

Phosphines are known to react with azides to give phosphine imides with elimination of nitrogen. These imides, which are often isolable, can then be converted into amines by hydrolysis (Scheme 4). The method has effectively been made into a one-pot procedure by carrying out the reaction of triphenylphosphine with azides in THF at room temperature in the presence of a slight excess of water.[42] This is a highly chemoselective method of reduction and many other functional groups, including nitro, alkoxycarbonyl and epoxide, are unaffected. The method has proved to be a useful alternative to catalytic hydrogenolysis in oligonucleotide synthesis.[43] Similar reactions have been carried out with trialkylphosphines[41] and with triethyl phosphite.[44] Diphosphorus tetraiodide has been used to reduce aryl and acyl azides directly.[45]

$$RN_3 + PPh_3 \longrightarrow RN{=}PPh_3 \xrightarrow{H_2O} RNH_2 + Ph_3PO$$

**Scheme 4**

A useful method of electrophilic amination of aromatic substrates is provided by the reaction of organomagnesium or organolithium derivatives with *p*-toluenesulfonyl azide, followed by reductive cleavage of the resulting triazene (Scheme 5).[46] The same reducing agents which cleave azides (for example, lithium aluminum hydride, sodium borohydride in phase transfer conditions and hydrogen sulfide) are used. With the increasing importance of selective lithiation of aromatic and heteroaromatic compounds, the method has become a very useful one for the regioselective introduction of an amino group. An example is provided by the selective amination of diethylamides (**8**) *ortho* to the carboxamido group (Scheme 6).[47] The same type of process has been described between vinyl azides and aryllithium reagents[48] and between (phenylthio)methyl azide and Grignard reagents.[49] In both cases the intermediate triazenes were cleaved by hydrolysis.

$$ArMgBr + TsN_3 \longrightarrow ArN{=}N\overset{-}{N}Ts\ {}^+MgBr \longrightarrow ArNH_2$$

**Scheme 5**

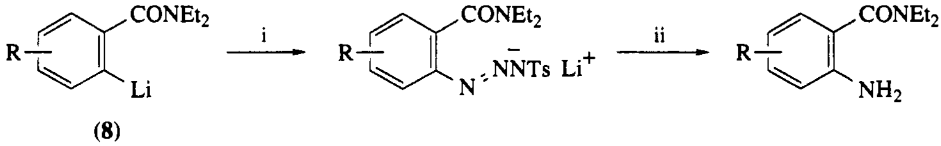

(**8**)

i, $TsN_3$; ii, $NaBH_4$, phase transfer catalyst

**Scheme 6**

All these reduction methods lead to the formation of primary amines (or to acetamides derived from them). It is also possible to convert azides reductively into secondary amines. One special case of this type is the conversion of β-iodoalkyl azides and related compounds into aziridines by reduction, usually with lithium aluminum hydride (Scheme 7).[50] A more general method, which was introduced by Brown and coworkers, is the reductive alkylation of azides by heating with trialkylboranes (Scheme 8).[51] For example, triethylborane and azidocyclohexane gave cyclohexylethylamine (73%) by heating in xylene followed by hydrolysis with methanol. (If hydrazoic acid or azidotrimethylsilane is used in this reaction the product is a primary amine.[52]) An intramolecular version of the reaction was used as the cyclization step in a synthesis of the cyclic hexapeptide echinocandin D.[53] The azide (**9**) gave the amino ester (**10**; 72%) as a single stereoisomer when treated with dicyclohexylborane at room temperature. The reaction (Scheme 9) probably involves selective migration of the methylene group of the trialkylborane by way of the cyclic intermediate shown.

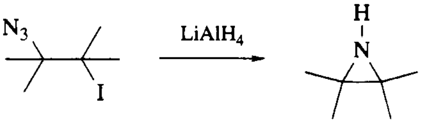

**Scheme 7**

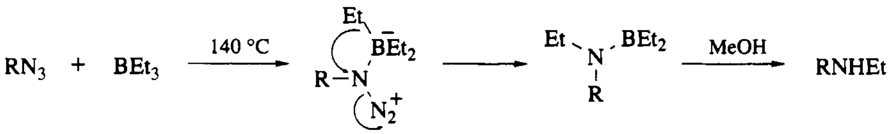

**Scheme 8**

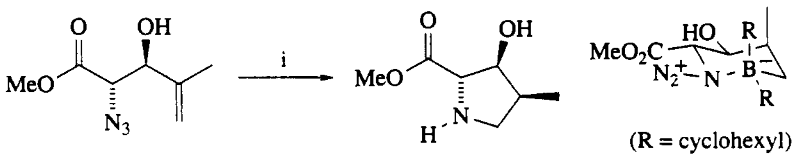

**(9)** **(10)**

i, Dicyclohexylborane, r.t.

**Scheme 9**

Intermolecular reactions of this type can be slow if either of the reaction partners has a bulky substituent. Reactions with chloroboranes $R_2BCl$ or $RBCl_2$ go under much milder conditions.[51,54] The stereochemistry of the carbon–boron bond is retained in the product; for example, the borane (**11**) gave the amine (**12**; 90%) on reaction with azidocyclohexane.

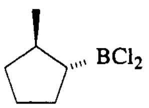

**(11)**

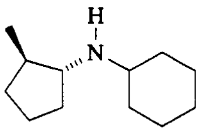

**(12)**

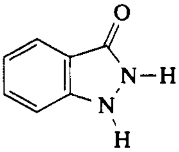

**(13)**

Reaction of aryl azides with hydrazine hydrate can result in reductive cleavage of the azido group. Azidobenzene gives a mixture of benzene and aniline when heated with an excess of hydrazine hydrate in ethanol.[55] If there is an acyl or an alkoxycarbonyl group at the *ortho* position, cyclization products are formed instead; for example, methyl 2-azidobenzoate gave indazolinone (**13**; 90%).

## 2.2.3 REDUCTION OF GROUPS WITH NITROGEN-NITROGEN SINGLE BONDS

### 2.2.3.1 Cleavage of Hydrazones

There are several examples of useful syntheses of amines which are based on the reduction and N—N bond cleavage of hydrazones. Some of these undoubtedly involve reduction of the C═N bond as the first step; in a few cases the N—N bond is probably cleaved first and in others the order in which the reactions take place has not been established. Reactions which involve reduction of the C═N bond are covered in the appropriate sections of Chapters 1.2–1.8, this volume; methods for cleavage of the resulting hydrazines are discussed in the following section (Section 2.2.3.2).

The most commonly used method for the cleavage of hydrazones is catalytic hydrogenation in the presence of acid. An example is provided by the synthesis of secondary and tertiary amines by reduction of benzophenone hydrazones (**14**), derived as shown in Scheme 10.[56] Nickel–aluminium alloy can also be used to reduce hydrazones to amines.[20]

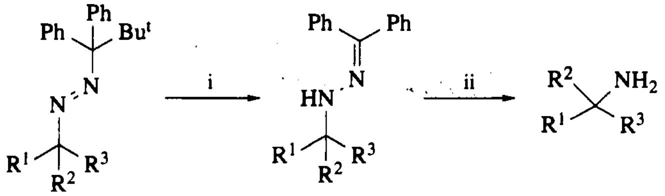

**(14)**

i, $CF_3CO_2H$; ii, $H_2$, Pd/C, HCl/EtOH, 1 atm, 50 °C

**Scheme 10**

α-Keto acids can be reduced to α-amino acids by way of their phenylhydrazones.[57] The reaction can be carried out by reduction of the hydrazone with hydrogen over palladium or platinum, or with zinc and mercury(II) chloride. As illustrated for the synthesis of alanine in Scheme 11, it is suggested that the N—N bond is cleaved first. Carbonyl compounds can be regenerated from their (2,4-dinitrophenyl)hydrazones by titanium(III) chloride; in this reaction the nitro groups are reduced and the N—N bond is then cleaved to give benzene-1,2,4-triamine, which can be isolated, and the imine of the carbonyl compound, which is hydrolyzed *in situ*.[58] Hydrazonium salts (*e.g.* **15**) derived from diaryl ketones are cleaved by Grignard reagents to give imines (Scheme 12); these reductions probably involve two successive one-electron transfers from the Grignard reagent.[59]

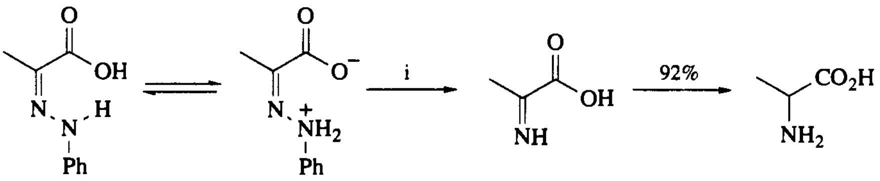

i, $H_2$, Pd/C, $H_2O$

**Scheme 11**

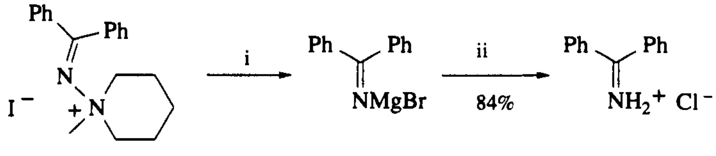

**(15)**

i, $Me(CH_2)_9MgBr$; ii, HCl

**Scheme 12**

### 2.2.3.2 Cleavage of Hydrazines, Hydrazides and *N*-Nitrosamines

There are few general methods available for the reductive cleavage of the N—N bond and the conditions required to cleave this bond can depend markedly on the substituents attached to it. The most widely used method for the cleavage of alkylhydrazines is catalytic hydrogenolysis over Raney nickel, platinum or (less commonly) palladium.[4] These reactions often require the use of hydrogen under pressure and, with platinum and palladium catalysts, an acidic medium. The cleavage reaction is a key step in a number of asymmetric syntheses of amines and amino acids. An approach which has been used by several research groups is outlined in Scheme 13; a chiral hydrazone is reduced or is converted by addition of an organometallic reagent into a hydrazine, the N—N bond of which is then cleaved catalytically.[60] A related reaction in which the choice of reduction conditions proved crucial is the synthesis of amino alcohols from aldehyde *N*,*N*-dimethylhydrazones illustrated in Scheme 14; it was important to use platinum oxide in the presence of acetic acid, rather than Raney nickel, to avoid epimerization.[61] These catalytic methods have also proved useful for the cleavage of cyclic hydrazines to diamines;[62,63] an example is provided by the reduction of the hydrazine (**16**) to the diamine (**17**) in high yield by hydrogenation over Raney nickel or platinum in the presence of hydrochloric acid.[63]

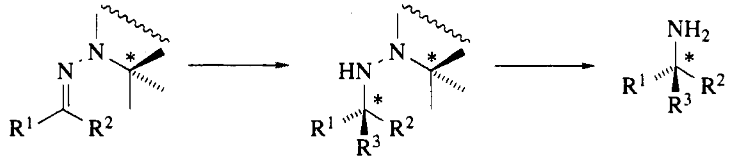

**Scheme 13**

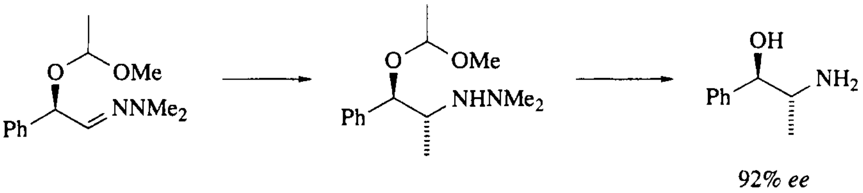

**Scheme 14**

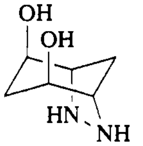

**(16)**

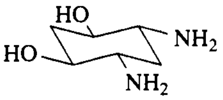

**(17)**

The structure of the substrate determines whether other reducing agents can be used. Arylhydrazines and hydrazinium salts are more easily cleaved than simple alkylhydrazines; for example, catalytic transfer hydrogenation over palladium has been used to cleave hydrazobenzene to aniline.[18] A substance in which the bond is cleaved very easily is the cyclic dication (**18**); the N—N bridge is opened with a wide range of reducing agents, including iron in aqueous acid.[64] Hydrazides can be cleaved electroreductively or by electron transfer from metals, sodium in liquid ammonia being the most widely used reagent. Two very useful surveys have been carried out, one on electroreduction[65] and the other on metal reduction,[66] which relate the ease of reduction of hydrazides to their structure. Electrochemical reduction of cyclic hydrazides is facilitated by relief of ring strain; the presence of more than one acyl substituent in a hydrazide also makes reduction easier. Mellor and Smith investigated the use of a range of metallic reagents, including zinc in acetic acid, aluminum amalgam and sodium in liquid ammonia, for the cleavage of acyclic and cyclic hydrazides.[66] The mild reducing agent aluminum amalgam efficiently cleaved 1,2-bis(*p*-toluenesulfonyl)-1,2-dimethylhydrazine and the bis(trifluoroacetyl)hydrazine (**19a**), but failed to react with the bis(ethoxycarbonyl) derivative (**19b**). On the other hand sodium in liquid ammonia proved to be a good reducing agent for compound (**19b**) but not for (**19a**). The N—N bond of a related hydrazide was selectively cleaved by sodium in liquid ammonia in the presence of an epoxide function.

Azodicarboxylic esters are excellent dienophiles and they can also add to electron-rich double bonds as heterodienes. Adducts of both types have been used as intermediates in the synthesis of amino sugars.

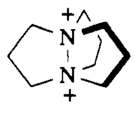

**(18)**

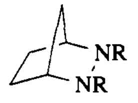

**(19)** a: R = $COCF_3$
b: R = $CO_2Et$

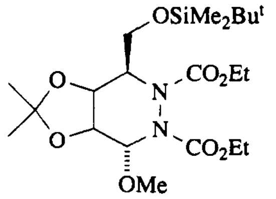

**(20)**

Schmidt and his coworkers have cleaved the N—N bond of tetrahydropyridazines (**20**) with sodium in liquid ammonia as a step in the synthesis of 4-aminolyxose derivatives.[67] Leblanc and coworkers have used carbohydrate-derived glycals as two-electron components in cycloadditions to dibenzyl azodicarboxylate; the adducts (*e.g.* **21** in Scheme 15) were subjected to methanolysis and the N—N bond was then cleaved using Raney nickel.[68]

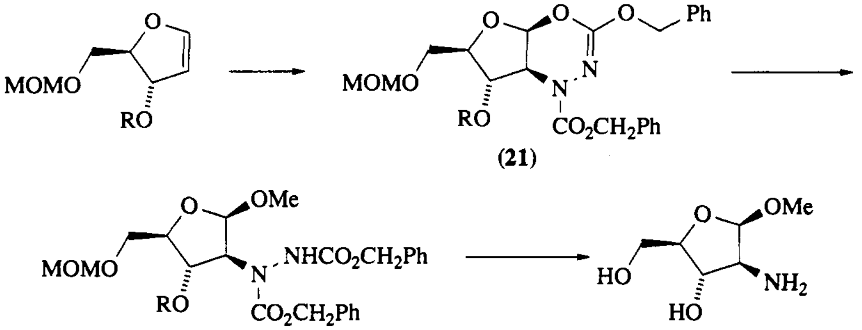

**Scheme 15**

Bicyclic hydrazides in which the nitrogen atoms are at the ring junctions have been cleaved by sodium in liquid ammonia and the reaction provides a good method of creating medium-ring amides.[69,70] The cleavage of the hydrazide (**22**) provides an example; this gave compound (**23**), which was a key intermediate in a synthesis of the spermidine alkaloid celacinnine.[70]

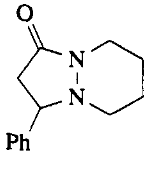

**(22)**

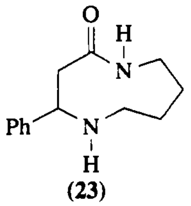

**(23)**

Other reagents which have occasionally been used to cleave hydrazides include diborane (which also reduces the carbonyl groups),[71] sodium naphthalenide,[69,72] *O,O*-diethyldithiophosphoric acid, $(EtO)_2PS_2H$,[73] and sulfur monochloride.[74] Nickel–aluminum alloy in aqueous methanolic potassium hydroxide is a good reagent for reductively cleaving a number of N—N bonded compounds, such as *N*-methyl-*N*-phenylhydrazine and *N,N*-dimethylnitrosamine.[19,20] Nitrosamines have also been cleaved with titanium(IV) chloride–sodium borohydride[75] and lithium aluminium hydride.

## 2.2.4 REDUCTION OF N—O BONDED GROUPS

### 2.2.4.1 Deoxygenation of Azoxy Compounds

This section covers the deoxygenation of compounds containing the structural units (**24**) and (**25**). Compounds of the first type include not only aliphatic and aromatic azoxy compounds, but also heterocyclic compounds, such as pyridazine *N*-oxides; those of the second type include dimers of nitroso compounds and heterocycles, such as pyridazine 1,2-dioxides.

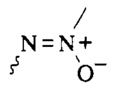

**(24)**

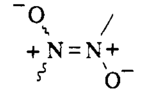

**(25)**

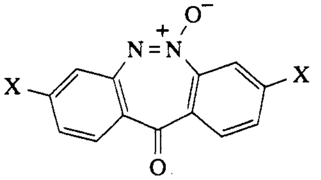

**(26)**

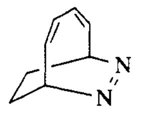

**(27)**

There are several well-established methods for the deoxygenation of azoxy compounds, the most common of which are catalytic hydrogenation, reduction with lithium aluminum hydride, and the use of zinc in an alkaline medium.[1] These methods can be rather unselective, either because they cause over-reduction of the azoxy group or because other functional groups can be reduced. Phosphorus trichloride and trialkyl phosphites are more selective;[1] phosphorus trichloride has been used to deoxygenate pyridazine *N*-oxides containing azido or nitro groups.[76] Several metal carbonyls convert azoxybenzene into azobenzene;[77,78] iron pentacarbonyl gives azobenzene in 77% yield, probably by the route shown in Scheme 16.[78] Aliphatic[1] and aromatic[79] azoxy compounds are deoxygenated with magnesium in methanol or ethanol; thus, compounds (**26**; X = Br or Cl) were cleanly deoxygenated with magnesium in ethanol. The corresponding di-*N*-oxides were also deoxygenated by this reagent. Hexachlorodisilane is a mild and selective reagent for the deoxygenation of *N*-oxides of various types;[80] it was used in a synthesis of the bicyclic azo compound (**27**) from the corresponding azoxy compound.[81]

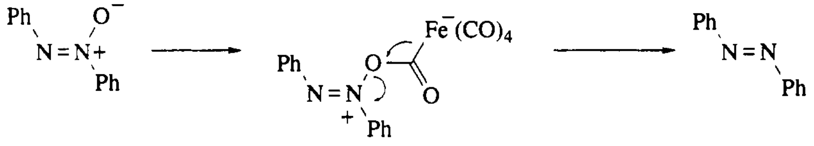

**Scheme 16**

Stepwise reduction of di-*N*-oxides has been achieved by using catalytic hydrogenation over palladium to remove one oxygen atom.[82] An electrochemical reduction method also allows controlled deoxygenation of these compounds.[83]

### 2.2.4.2 Deoxygenation of Nitrones, Nitrile Oxides and Tertiary Amine Oxides

Methods of deoxygenation of nitrones (**28**), nitrile oxides (**29**), heteroaromatic *N*-oxides (**30**) and tertiary amine oxides (**31**) are described in this section. There are some reagents, such as trialkyl phosphites, which can deoxygenate compounds of all these types as well as those in the preceding section, whereas others are more limited in scope. Oae and coworkers have outlined three distinct mechanistic types of deoxygenation process, which are illustrated in Scheme 17.[84] Clearly, a mechanism of type C will not apply to tertiary amine oxides (**31**); on the other hand, these compounds are more easily deoxygenated than heteroaromatic *N*-oxides, such as (**30**), by some reagents because the aromatic *N*-oxides are inherently more stable.

A comprehensive account of methods of deoxygenation of heteroaromatic *N*-oxides, including descriptions of experimental procedures, has been given by Ochiai.[85] The most widely used methods are catalytic reduction, reaction with phosphorus trichloride and reduction by metals or metal salts. Catalytic hydrogenation over palladium in strong acid or in a mixture of acetic acid and acetic anhydride is a good but unselective method of deoxygenation. Raney nickel in alcoholic solution can be used to deoxygenate

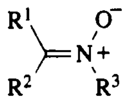

**(28)**

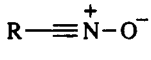

**(29)**

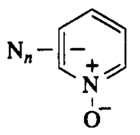

**(30)**

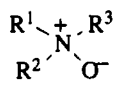

**(31)**

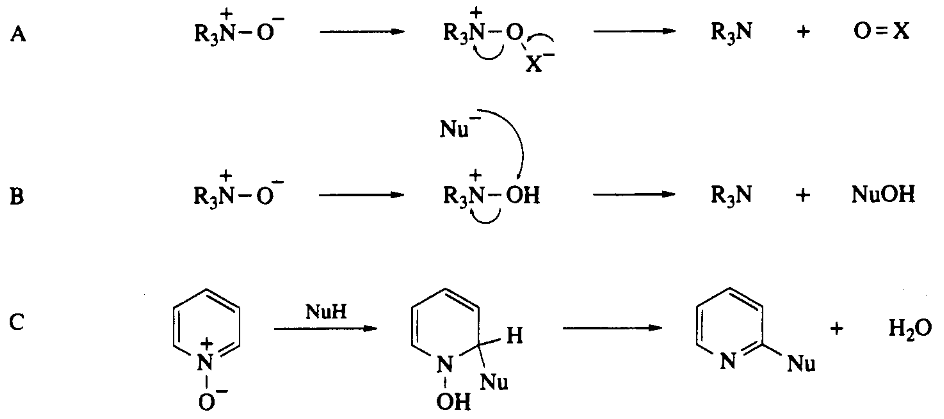

**Scheme 17**

*N*-oxides of virtually all types and it shows some selectivity; halogen substituents are unaffected and benzyloxy groups are reduced relatively slowly. Phosphorus trichloride has also been widely used; with the exception of hydroxy groups and others bearing an acidic hydrogen atom, most common functional groups are tolerated in the deoxygenation. The apparently related deoxygenation of pyridine *N*-oxides by triethyl phosphite was shown by Emerson and Rees to require the presence of oxygen and a peroxide; a radical mechanism was suggested for the deoxygenation.[86] Trimethyl phosphite has proved useful as a reagent for selective monodeoxygenation of quinoxaline 1,4-dioxides, the reaction taking place preferentially at the nitrogen atom adjacent to a carbon bearing an electron-withdrawing substituent. For example, the dioxide (**32**) gave the *N*-oxide (**33**; 81%).[87]

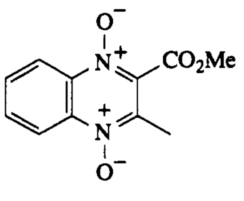

**(32)**

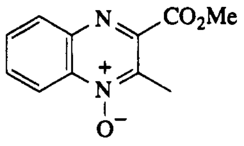

**(33)**

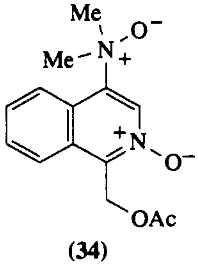

**(34)**

There are many other literature methods for the deoxygenation reaction, some of which are discussed in Ochiai's review.[85] Pyridine and quinoline *N*-oxides are deoxygenated when heated with iron powder or zinc in acetic acid and this was an early method for the one-pot synthesis of 4-aminopyridines from 4-nitropyridine *N*-oxides. Nitrogen monoxide or nitrosylsulfuric acid have also been used; it is possible to carry out a one-pot nitration and deoxygenation of pyridine *N*-oxides by carrying out the nitration with concentrated sulfuric and fuming nitric acids at elevated temperatures.[88] Sulfur dioxide can be used at room temperature for the selective deoxygenation of tertiary amine oxides of type (**31**), most heteroaromatic oxides being unaffected. Under more vigorous conditions pyridine and quinoline *N*-oxides are deoxygenated; reactions can conveniently be carried out using triethylamine–sulfur dioxide complex in dioxane[89] or by using sulfolene as a source of sulfur dioxide.[90] Another reagent which is selective for alkyl-substituted tertiary amine oxides under mild conditions is carbon disulfide (it will also reduce nitrones).[84] For example, the dioxide (**34**) was selectively reduced to its 2-oxide (70%) by carbon disulfide in methanol.[91] Isoquinoline 2-oxide is, however, deoxygenated by carbon disulfide at 110 °C.[92] Other reagents which have been reported to reduce amine oxides of type (**31**) under very mild conditions include nickel–aluminum alloy,[19] acetic formic anhydride,[93] tetraphenylporphyrinatoiron(II)[94] and sodium hydrogentelluride.[95] This last reagent reduces amine oxides but not sulfoxides; at pH 10 to 11 it can also be used to deoxygenate nitrones.

Some deoxygenation reagents are useful for particular types of aromatic *N*-oxides. Alkyl- and halo-pyridine oxides are cleanly reduced at 0 °C by a titanium(0) reagent prepared from titanium(IV) chloride and lithium aluminum hydride or magnesium.[96] Tributyltin hydride can deoxygenate *N*-oxides of pyridine and quinoline at 80 °C in the presence of AIBN: a radical mechanism is indicated.[97] Hexabutylditin and dichlorotetrabutylditin, $ClBu_2SnSnBu_2Cl$, are claimed to be superior reagents and will tolerate nitro, cyano, chloro and hydroxy groups.[98] Electrochemical reduction of pyridine *N*-oxide has also been described.[10] Simple pyridine and quinoline *N*-oxides have been deoxygenated under very mild conditions by dipropyl sulfoxylate, $(PrO)_2S$,[99] by sodium hypophosphite, $NaH_2PO_2$,[100] and by chlorotrimethylsilane in the presence of sodium iodide and zinc.[101] Hexamethyldisilane has also been used in the presence of a catalytic amount of TBAF;[102] the mechanism proposed is illustrated in Scheme 18. This is an example of type C in Scheme 17, in which deoxygenation follows nucleophilic attack at the α-carbon atom. Other reactions of this type, involving attack by organometallic reagents and by acetic anhydride, are well known and lead to the formation of a variety of 2-substituted pyridines from pyridine *N*-oxide.[103]

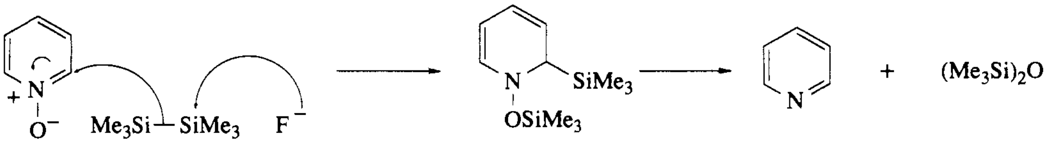

Scheme 18

The deoxygenation of nitrile oxides is rarely an important reaction, but some of the standard methods referred to above have been used, including reaction with trimethyl phosphite[104] and with iron pentacarbonyl.[105]

### 2.2.4.3 Reduction of Oximes to Imines

The reductive cleavage of the N—O bond of oximes is a reaction which has been widely used by synthetic chemists. When accompanied by reduction of the C=N bond the reaction leads to the formation of primary amines. Reactions of this type are described in Chapters 1.2–1.8, this volume. The reductive cleavage of cyclic oximes, particularly isoxazoles and 4,5-dihydroisoxazoles, has been used as a key step in several target syntheses of natural products. These cleavage reactions are covered in Chapter 3.8, this volume; however, some of the methods which clearly bring about cleavage of the N—O bond before reduction of the C=N bond are also described in this section. The products of these reactions are *N*-unsubstituted imines. Unless the imines are sterically protected or unless special precautions are employed in the work-up, the isolated products are usually carbonyl compounds formed by hydrolysis (Scheme 19). Reductive hydrolysis reactions of this type are also included here.

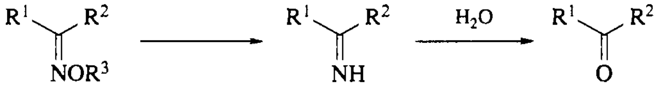

Scheme 19

A general method for the cleavage of 4,5-dihydroisoxazoles is hydrogenation over Raney nickel in the presence of an acid or a Lewis acid, such as boric acid[106] or boron trichloride.[107] The products are normally β-hydroxy ketones but in the case of compound (**35**), which was prepared as an intermediate in the construction of the AB-ring system of forskolin, reduction over Raney nickel gave an isolable imine (**36**).[108]

Barton *et al.* have described a particularly mild method for the conversion of ketoximes into ketimines (aldoximes give nitriles instead).[109] A mixture of tributylphosphine and diphenyl disulfide reacts under anhydrous conditions with ketoximes, probably by way of the phosphorane intermediates shown in Scheme 20, to give ketimines. The reagent is effectively a 'self-drying' one since it reacts irreversibly with water. Chlorodiphenylphosphine is also capable of deoxygenating ketoximes; with this reagent

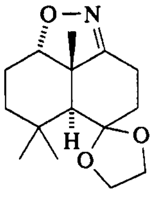

**(35)**

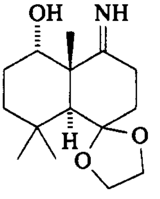

**(36)**

intermediate phosphinylimines can be isolated (Scheme 21).[110] These compounds can then be further reduced or they can be hydrolyzed to ketones.

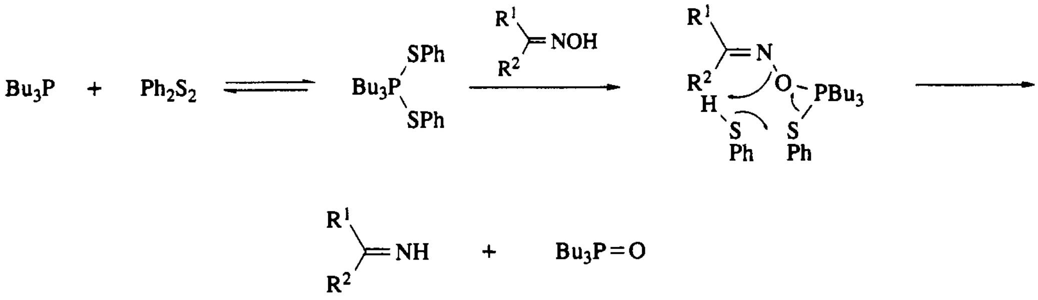
Bu3P
Ph2S2
SPh
Bu3P
SPh
R1
R2
NOH
R1
N
R2
H
O
PBu3
S
S
Ph
Ph
R1
R2
NH
Bu3P=O

**Scheme 20**

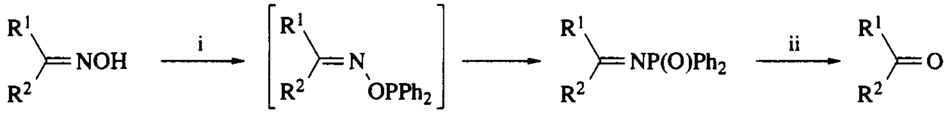
R1
R2
NOH
i
R1
R2
N
OPPh2
R1
R2
NP(O)Ph2
ii
R1
R2
O

i, $Ph_2PCl$; ii, $H_2O$

**Scheme 21**

Low-valent metal salts have been used to bring about reductive cleavage of oximes. Corey and Richman used chromium(II) acetate to convert *O*-acetyl ketoximes into imines, which were hydrolyzed to ketones.[111] Aqueous titanium(III) chloride and vanadium(II) salts also reduce oximes; again, the imines are usually hydrolyzed *in situ*, but some hindered imines, such as compound (**37**), are isolable.[112] A method of preventing hydrolysis is to carry out the reduction in anhydrous conditions in the presence of an acylating agent. The products of such reactions, when applied to oximes of enolizable ketones, are enamides. For example, these ketoximes are converted into *N*-formylenamines when heated in acetonitrile with anhydrous titanium(III) acetate and acetic formic anhydride; cyclohexanone oxime gives the enamide (**38**; 97%; Scheme 22).[113] This type of reduction has been used by Barton and coworkers to prepare enamides from steroidal oximes. They reported that the reaction could be performed by acetic

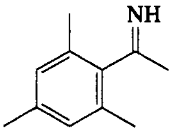

**(37)**

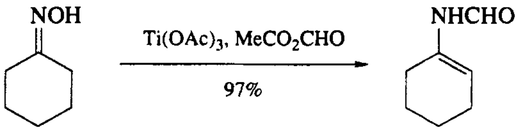
NOH
Ti(OAc)3, MeCO2CHO
97%
NHCHO

**(38)**

**Scheme 22**

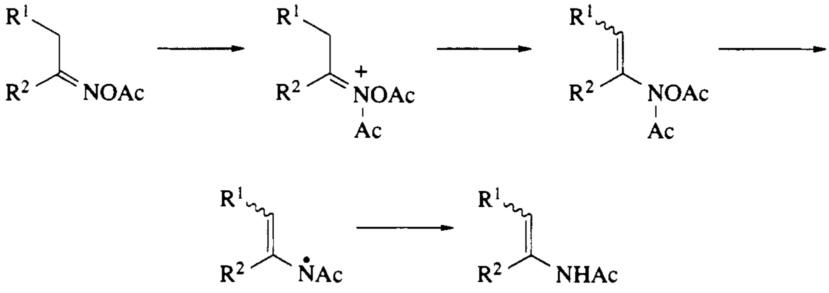

Scheme 23

anhydride alone and recommended acetic anhydride in pyridine under reflux as the reagent of choice.[114] A homolytic cleavage of the N—O bond, as shown in Scheme 23, is suggested to account for the formal reduction by acetic anhydride.

Samarium(II) iodide,[115] molybdenum hexacarbonyl[116] and iron pentacarbonyl[117] can also cleave the N—O bond of oximes. Amidines (*e.g.* **39**) can be prepared in good yield by reduction of the corresponding amidoximes with iron pentacarbonyl. The same type of reduction can be achieved electrochemically.[10] Reactions of nucleophilic reducing agents normally result in reduction of the C=N bond, but there are a few exceptions; ketoximes are reported to be cleaved to ketones, by way of the corresponding imines, with lithium aluminum hydride and HMPA.[118] Organolithium, organomagnesium and organoaluminum reagents can react with *O*-substituted oximes to give imines, which incorporate a substituent from the reagent;[119] for example, *O*-methyl oximes (**40**) of aldehydes react with organolithium reagents to give lithioketimines (**41**; Scheme 24).

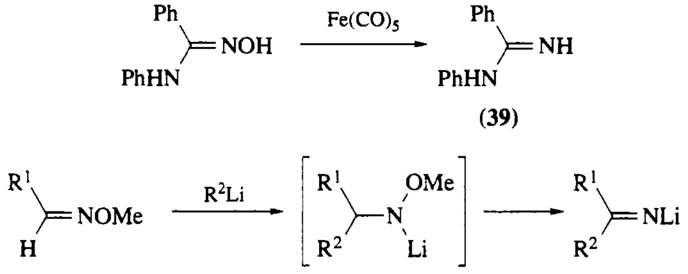

**(39)**

**(40)** **(41)**

Scheme 24

### 2.2.4.4 Reduction of Hydroxylamines to Amines

Methods for the reductive cleavage of the N—O bond in hydroxylamines have assumed increasing importance in synthesis because it is a key step in routes based on cycloaddition of nitrones and nitroso compounds. Inter- and intra-molecular cycloadditions of nitrones lead to the formation of tetrahydroisoxazoles (Scheme 25); these compounds are then converted into amino alcohols by reductive cleavage of the N—O bonds. This type of reaction sequence has been exploited in the synthesis of a number of alkaloids.[120] Nitroso compounds, particularly those activated by electron-withdrawing substituents, act as dienophiles in the Diels–Alder reaction (Scheme 26)[121] and the cycloadducts can be used as synthetic intermediates by cleaving the N—O bonds.

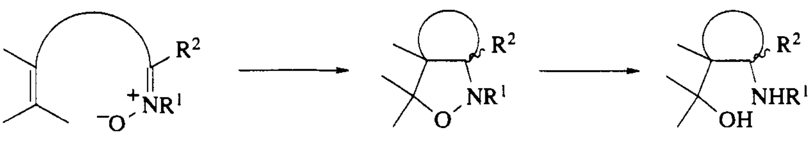

Scheme 25

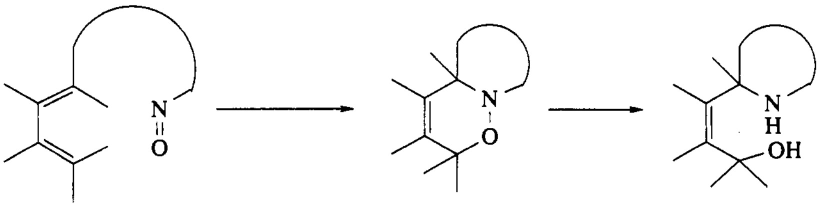

Scheme 26

*N*,*N*-Dialkylhydroxylamines can be cleaved to secondary amines by titanium(III) chloride in aqueous methanol[122] and by zinc powder in aqueous hydrochloric acid.[123] Titanium(III) chloride also reduces *N*-hydroxyimidazoles[124] and hydroxamic acids; thus the protected hydroxamic acid (**42**) was reduced to the β-lactam (**43**; 67%) with no racemization or loss of the protecting group.[125] Tetrahydro-1,2-oxazines are cleanly reduced by zinc in acetic acid. This method was used to cleave a tetrahydrooxazine (85%), generated by intramolecular Diels–Alder cycloaddition, in a synthesis of the alkaloid gephyrotoxin (Scheme 27).[126] Several tetrahydroisoxazoles have been reduced by anhydrous nickel(II) chloride and lithium aluminum hydride in THF.[127] Sodium naphthalenide proved to be the best reagent for the reduction of tri-*t*-butylhydroxylamine to di-*t*-butylamine.[128] The N—O bond of hydroxylamines can be cleaved catalytically over palladium or nickel, although any double bonds present may be preferentially reduced.[129] Diiron nonacarbonyl has also been used to cleave the bond.[130]

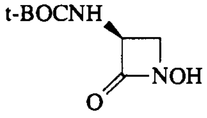

**(42)**

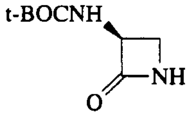

**(43)**

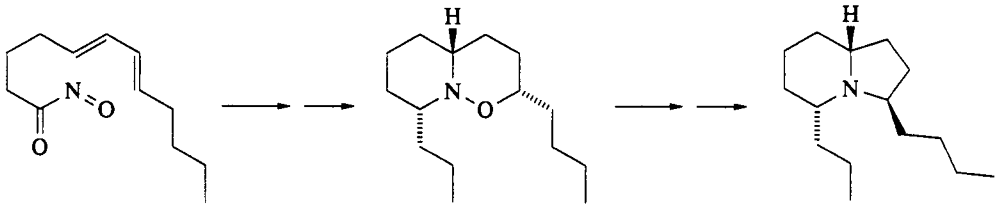

Scheme 27

When the nitrogen of a 1,2-oxazine is activated by acylation aluminum amalgam is a suitable reagent for reductive cleavage; sodium amalgam has also been used in cases where this reagent is too mild.[131] Two other very mild methods of reduction apply to hydroxylamines of specific types. Several hydroxylamines of relatively high basicity have been cleaved by dihydrolipoamide (**44**), which is formed from the coenzyme lipoamide by reduction with sodium borohydride.[132] Cyclic hydroxylammonium chlorides of the general structure (**45**) have been reduced by hydrogen in the presence of various microorganisms, the carbon–carbon double bond being unaffected.[133]

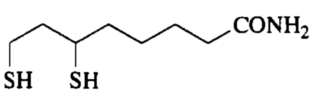

**(44)**

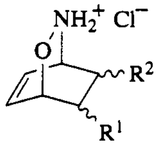

**(45)**

Oxaziridines can be regarded as a special category of cyclic hydroxylamines. Activated compounds of this type, such as the *N*-benzenesulfonyl derivative (**46**)[134] and the salt (**47**),[135] are very easily reduced. They are proving to be useful in synthesis as oxygen-transfer reagents to alkenes, thiols and other nucleophiles.

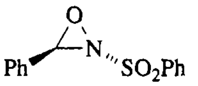

(46)

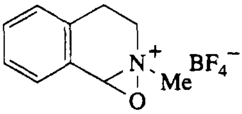

(47)

## 2.2.5 REDUCTION OF O—O BONDED GROUPS

### 2.2.5.1 Introduction

The oxygen–oxygen bond of peroxides is easily reduced and many standard reducing agents are capable of cleaving the bond efficiently. Catalytic[4] and other[136] methods have been reviewed. Whereas the reduction of hydroperoxides leads to the formation of alcohols, considerable selectivity is possible in the products derived from disubstituted peroxides. Hydroperoxides and disubstituted peroxides are, therefore, discussed separately below, even though some of the reduction methods are identical. Reductive ozonolysis of alkenes has also been included as a separate third category.

### 2.2.5.2 Reduction of Hydroperoxides to Alcohols

Alkyl hydroperoxides (**48**) are available by radical oxidation of alkanes, by nucleophilic displacement using peroxide anion, and by other methods. The reductive cleavage of the O—O bond, therefore, represents a useful method for the synthesis of alcohols. The reduction of hydroperoxides to alcohols can be brought about by many reagents. Catalytic methods have been widely used;[4] although the O—O bond is very susceptible to reduction, not all catalysts allow the bond to be cleaved selectively. It has been suggested that the best catalysts for selective reduction are the types which are used to reduce alkynes to alkenes; one such catalyst, palladium and lead(II) acetate, was used to reduce the hydroperoxide (**49**) to cyclohexenol (89%).[137] Salts of tin(II), iron(II) and other low-valent metals can cleave the bond. Many nucleophilic reducing agents have also been used, the most common being sodium hydrogensulfite, lithium aluminum hydride, sodium iodide, sodium thiosulfate, dimethyl sulfide and triphenylphosphine. The mechanism most often put forward for these reductions is nucleophilic attack on oxygen (Scheme 28).[138] These methods are usually more selective than standard catalytic reduction methods.

ROOH

**(48)**

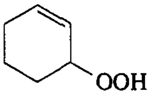

**(49)**

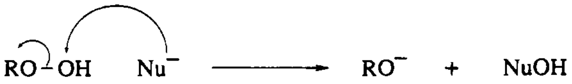

Scheme 28

### 2.2.5.3 Reduction of Disubstituted Peroxides

Disubstituted peroxides are cleaved reductively by the same reagents as are used for hydroperoxides. The usual products are alcohols derived from the two substituents, but considerable selectivity is possible with some substrates. This is illustrated by the reduction of cyclic endoperoxides of the general formula (**50**); these compounds are available from the cycloaddition of singlet oxygen to cyclic conjugated dienes.[139] The reduction of such compounds provides a good method of synthesis of *cis*-1,4-diols, which can be formed with retention of the double bond or with reduction of it (Scheme 29). It is also possible to prepare unsaturated epoxides by reduction with triphenylphosphine or other phosphorus(III) reagents.

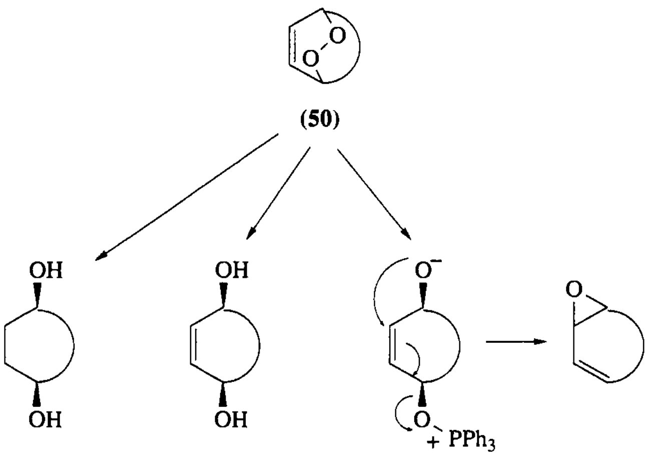

**Scheme 29**

Of the methods for reductive cleavage in the presence of a carbon–carbon double bond, reduction with lithium aluminum hydride and with thiourea have been most commonly used. Thiourea is very selective and has been used to reduce unstable cyclic endoperoxides, such as compound **(51)**, *in situ* when they are generated by dye-sensitized photooxygenation of dienes (Scheme 30).[140] Even when reduction of a double bond is also required, it may be advantageous to use a selective method of cleavage of the peroxide. For example, in the synthesis of the sesquiterpene cybullol shown in Scheme 31, the final product was most efficiently formed in two steps from the endoperoxide, by reductive cleavage (77%) with aluminum amalgam, followed by hydrogenation over platinum (100%).[141]

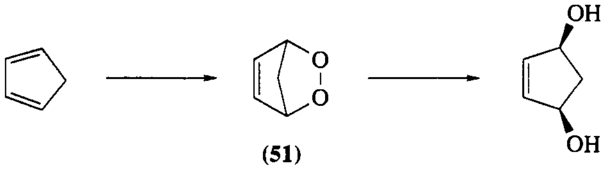

**(51)**

**Scheme 30**

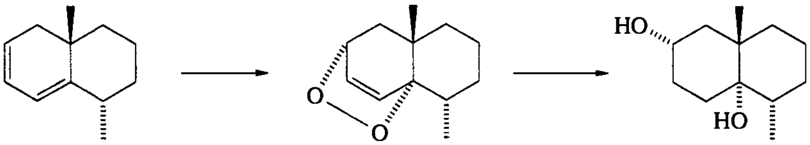

**Scheme 31**

Reactions of peroxides with triphenylphosphine usually result in monodeoxygenation.[142] Dialkyl peroxides react relatively slowly with triphenylphosphine and give ethers as the major products; for example, di-*t*-butyl peroxide gave di-*t*-butyl ether (81%) after being heated with triphenylphosphine at 110–120 °C for 30 h. The mechanism suggested for these reactions is an ionic one, triphenylphosphine acting as a nucleophile. The reaction illustrated in Scheme 29 can then be rationalized by the loss of triphenylphosphine oxide and intramolecular attack on the double bond. The reaction has found several useful applications in synthesis; an example is a preparation of naphthalene 1,2-oxide (Scheme 32).[143]

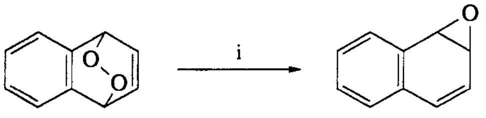

i, $PPh_3$, −78 °C

**Scheme 32**

Several thiols and sulfides (particularly dimethyl sulfide) have also been used as reducing agents. An example of this reaction which may well have biological significance is the reduction of 1,2-dioxetanes. These compounds are capable of causing damage to DNA, but they can be efficiently reduced to diols by glutathione and several other thiols. Glutathione, a tripeptide, probably protects living cells by deactivating dioxetanes and other peroxides in this way.[144] Although dimethyl sulfide can also reduce dioxetanes, the products are different, as illustrated in the example in Scheme 33. It is suggested that dimethyl sulfide acts as a reducing agent through electron transfer to the peroxide; CIDNP experiments and other evidence support this view. Ascorbic acid has been reported to cause cleavage of dilauroyl peroxide; an electron transfer mechanism has also been suggested to account for this reaction.[145]

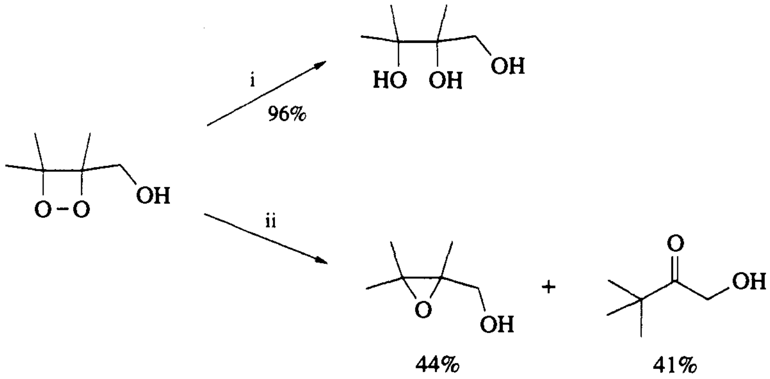

i, L-glutathione, $H_2O$, 5 °C; ii, $Me_2S$, $CHCl_3$, 5 °C

Scheme 33

Dimethyldioxirane (**52**) and other methyldioxiranes are easily generated peroxides which have proved to be very useful oxygen atom transfer agents; alkenes, sulfides and amines can all be oxidized and dimethyldioxirane is reduced to acetone.[146]

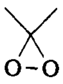

**(52)**

### 2.2.5.4 Reductive Ozonolysis of Alkenes

The cleavage of alkenes by ozone, usually to give carbonyl compounds as products, is a reaction which has been widely exploited in synthesis and on which a great deal of mechanistic work has been carried out. Reviews of this chemistry are available.[138,147] The ozonolysis usually leads to the formation of one of two distinct types of peroxidic product (Scheme 34); the cyclic peroxides (**53**), which are formed in nonnucleophilic solvents, and acyclic hydroperoxides, such as (**54**), which are formed in the

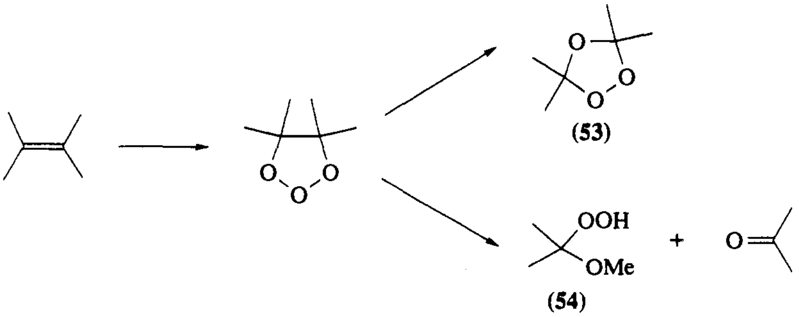

Scheme 34

presence of nucleophiles. These can then be reductively cleaved by the methods described in the preceding sections. With nucleophilic reducing agents, as shown in Scheme 28, the products can be rationalized by attack on the peroxide function. Further reduction is obviously possible with some reagents, such as lithium aluminum hydride. Dimethyl sulfide, sodium hydrogensulfite and triphenylphosphine have been commonly used when reduction to the carbonyl compounds is required. Hydrogenation over modified catalysts allows the formation of unsaturated carbonyl compounds; thus, the dialdehyde (**55**) was prepared from 1,5-cyclooctadiene by ozonolysis of one double bond followed by catalytic reduction of the ozonide. Ozonides can be reductively cleaved directly to alcohols; the best reagent for this purpose is borane–dimethyl sulfide complex.[148]

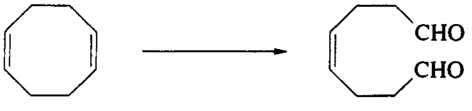

(**55**)

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# 2.3

# Reduction of S═O and SO2 to S, P═O to P, and of S—X to S—H

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## 2.3.1 INTRODUCTION

The reduction of the important sulfoxide functional group has attracted considerable attention during the past 20 years. This topic was extensively reviewed in the late 1970s,[1,2] and there have been several excellent reviews of the area very recently.[3-5] The reviews by Grossert[4] and Madesclaire[5] present a particularly thorough coverage and, in each case, include references as recent as 1987. Effective methods for the reduction of the related sulfone functionality have proved to be more elusive, in large part because of the much stronger S═O bonds present, but this topic is also given comprehensive treatment in the review by Grossert[4] and in a much earlier one by Durst.[6]

The reduction of P═O is clearly a more daunting task than the reduction of the S═O bond in a sulfone and the dearth of literature references to this topic reflects this fact. In contrast, much work has been done on the reduction of disulfides and other systems with S—X bonds,[7] including their selenium and tellurium counterparts.[8]

A number of reviews which relate to reduction in general and only in part to the types of reduction presently being considered may also be of interest to the reader. These include a review of hydride reductions in general by Brown and Krishnamurthy[9] and of metal alkoxyaluminum hydrides in particular by Malek.[10] The important role of electrophilic catalysis in achieving reductive S—O bond cleavage is summarized in a review of the applications of iodotrimethylsilane by Olah and Narang.[11]

## 2.3.2 REDUCTION OF S=O AND RELATED FUNCTIONAL GROUPS

### 2.3.2.1 Reduction (Deoxygenation) of Sulfoxides

This section will deal only with those processes which involve a straightforward reduction or deoxygenation of the sulfoxide and not, for example, with processes such as the Pummerer or sila-Pummerer reactions, which involve reduction of the sulfoxide with concomitant oxidation at one of the α-carbon atoms. Also not included will be those reactions such as desulfinylation, which involve reductive cleavage of one of the C—S bonds. As indicated in the Introduction, there have been several reviews of sulfoxide deoxygenation to the corresponding sulfide.[1-5] While many different procedures for achieving this type of reduction have been reported, it is possible to identify three major approaches, which will be discussed in turn. Although most of the literature cited is from the last 10 to 15 years, the trends already emerging in the mid 1970s have become more clearly established, in particular the need for reagents selective enough to reduce, for example, a sulfoxide in the presence of a ketone or other carbonyl functionality. Thus, while vigorous methods such as lithium aluminum hydride or dissolving metal reductions may still be used in simple cases, they have now been largely supplanted by more sophisticated procedures.

The first broad class of reagents to find general application to the reduction or deoxygenation of sulfoxides was that of the 'low valent' transition metals. These methods rely on reducing agents such as molybdenum(II),[12,13] molybdenum(III),[12,14] titanium(II),[15] vanadium(II)[14] or tungsten(III),[12] which are often generated *in situ* by zinc reduction (equation 1). These reagents give excellent yields of sulfides of all major types and can be employed in the range 25–100 °C. Other functional groups, such as ketone, ester, nitrile, (aromatic) nitro, phosphine oxide or sulfone, were shown by San Filippo and coworkers[12] to be unaffected and the reducing capabilities of such low valent metal systems have been reviewed by Ho.[16] More recently, the use of cobalt(II) in combination with $NaBH_4$,[17] and the use of titanium(III),[18] have been reported for the reduction of sulfoxides to sulfides.

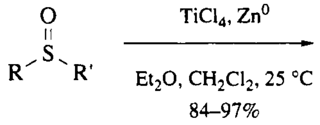

(1)

A second, single reagent procedure relies upon the use of pentavalent phosphorus compounds, in which the formation of a very strong P=O bond provides a thermodynamic driving force for the deoxygenation to proceed, often at 25 °C or lower. Thus, Still *et al.*[19] used phosphorus pentasulfide (tetraphosphorus decasulfide) for the reduction of several types of sulfoxide to sulfide, generally in yields of 60% or higher, although lower yields were recorded for sterically congested sulfoxides and for heterocyclic sulfoxides. Although $P_4S_{10}$ is well known to be capable of effecting carbonyl–thiocarbonyl exchange, the example in equation (2) illustrates that ketones (as well as ester, amide, nitro or halide compounds) are not affected under the mild conditions used. Phosphorus pentasulfide is ineffective in reducing sulfones, sulfinates or sulfites but was successfully applied in the reduction of sulfimides (sulfilimines) and selenoxides (see Sections 2.3.2.4 and 2.3.2.5). A plausible mechanistic suggestion for the $P_4S_{10}$ reduction of sulfoxides, which involves a four-center transition state and initial formation of an unisolable thiosulfoxide intermediate, has been made independently by Still *et al.*[19] and by Baechler *et al.*[20] (Scheme 1).

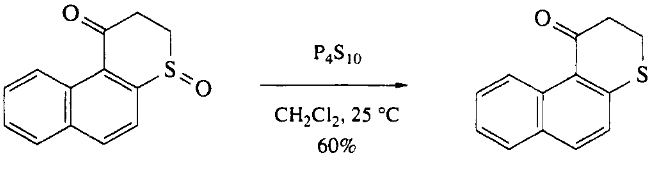

(2)

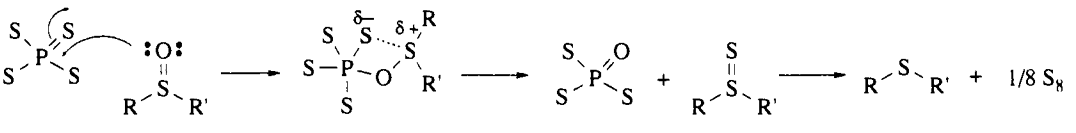

Scheme 1

Still *et al.*[21] have also developed thiophosphoryl bromide ($PSBr_3$) as an alternative to $P_4S_{10}$ which does not suffer from the drawback of insolubility in organic solvents. This reagent, readily prepared from $P_4S_{10}$, red phosphorus and bromine, gives very high yields of the sulfides in reaction times that vary from a few minutes to a few hours at 25 °C. These features make $PSBr_3$ generally superior for the sulfoxide–sulfide interconversion but the reverse was found to be true for the related conversion of sulfines (thione *S*-oxides) to thiones[22] shown in equation (3), where the requirement for aqueous work-up in the $PSBr_3$ reactions created serious difficulties in isolating water-sensitive thiones. In a promising development, Yokoyama *et al.*[23] have reported that an analog (**1**) of the organic phase soluble Lawesson reagent reduces dibenzyl sulfoxide to the sulfide in 83% yield.

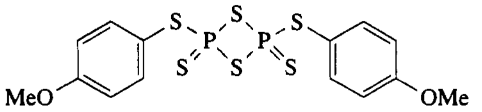

**(1)**

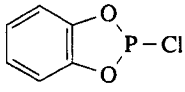

**(2)**

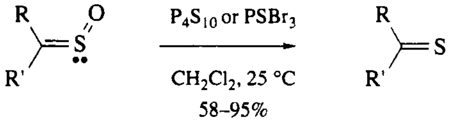

(3)

Other pentavalent phosphorus reagents which have been used for the deoxygenation of sulfoxides include phosphorus pentachloride[24] and various combinations of phosphines[25] or phosphites[26] with $I_2$ which also appear to involve pentavalent phosphorus species. In the former case, the addition of a simple enamine or tertiary aromatic amine was found to be essential to prevent formation of Pummerer-type products. $POCl_3$ or $SiCl_4$ could be used instead of $PCl_5$. Olah *et al.*[25] have suggested that a similar mechanism is operative in the reduction of sulfoxides with the reagent tris(dimethylamino)phosphine–iodine–sodium iodide (equation 4), which they find to be superior to an earlier version of this system using triphenylphosphine. The iodine appears to play a catalytic role, *via* initial formation of $(Me_2N)_3PI_2$. While not involving pentavalent phosphorus analogs, the application of other phosphorus iodides such as $P_2I_4$ or $PI_3$ to the reduction of sulfoxides and selenoxides has been reported by Denis and Krief[27,28] and, independently, by Suzuki[29] in the case of the former reagent. Finally, in an elegant application of a sulfoxide-deoxygenating agent first reported by Chasar and Pratt,[30] Ottenheijm and coworkers[31] have successfully used 1,2-phenylene phosphorochloridite (**2**) as the reducing agent in a novel reduction–oxidation sequence for the selective epimerization (at sulfur) of a series of sulfoxides, in overall yields of 26–37%.

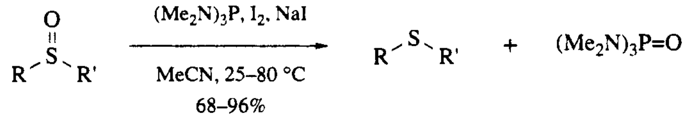

(4)

The third and final subclass of methodology in the reduction of sulfoxides to sulfides relies upon what is basically a dual reagent or 'push–pull' strategy. The nucleophilicity of the sulfoxide oxygen is utilized in an initial reaction with an electrophilic species, usually a halosilane, followed by displacement of the silanolate leaving group at the sulfonium center by various reducing species, such as $I^-$,[32] $Br^-$,[33] or PhSH.[34] The reaction is completed (Scheme 2) by a final redox step involving the generation of $I_2$, $Br_2$, or PhSSPh, respectively. In several cases, two distinct reagents for the initial two steps were employed but in other instances a single reagent could be used, such as the use by Oae and coworkers[34] of the re-

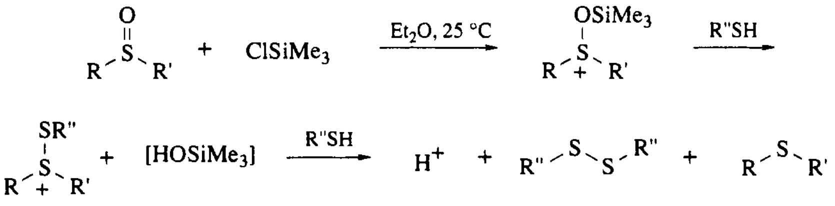

**Scheme 2**

agent PhSSiMe3 or of ISiMe3 by Olah *et al.*[32] In the former case, the advantage of a single reagent was offset by lowered yields and much longer reaction times.

Much ingenuity has been displayed in modifying the reagent system used in the above type of reduction. The basic thermodynamic driving force in all such cases is the formation of a strong Si—O bond, accompanied by the sacrifice of a relatively weak X—Si bond. Thus, reagents such as $(Me_3Si)_2S$[35] and the analogous selenides and tellurides[36] have been used to reduce sulfoxides, as well as several selenoxides and telluroxides (see Section 2.3.2.5), in high yields at 25 °C. Other variations include the use of various chlorosilanes in combination with zinc dust (equation 5).[37,38] These procedures give good to excellent yields even for heterocyclic sulfoxides, with little or no Pummerer product formation, and can be carried out in the presence of hydroxy or carboxy groups or double bonds. Olah *et al.*[39] have used trichloromethylsilane–sodium iodide as an alternative to the rather unstable iodotrimethylsilane.[32] The sulfides are produced, in yields of over 85%, in minutes at 25 °C using acetonitrile as the solvent, by this technique. While not directly relevant to the present topic, it is of interest to note that Miller *et al.*[40] have recently developed a general route to triarylsulfonium salts from diaryl sulfoxides, using similar activation by electrophilic silicon reagents, accompanied by nucleophilic displacement of silanolate by aryllithium or aryl Grignard reagents (equation 6).

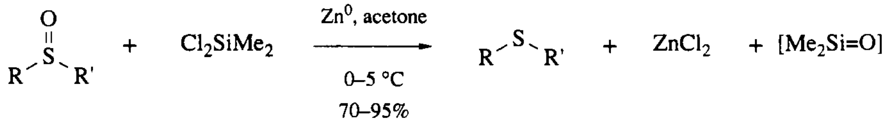

$$RS(O)R' + Cl_2SiMe_2 \xrightarrow[0\text{–}5\,^\circ C,\ 70\text{–}95\%]{Zn^0,\ \text{acetone}} RSR' + ZnCl_2 + [Me_2Si{=}O] \quad (5)$$

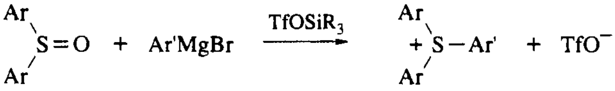

$$Ar_2S{=}O + Ar'MgBr \xrightarrow{TfOSiR_3} Ar_2\overset{+}{S}{-}Ar' + TfO^- \quad (6)$$

In addition to the above variations, the nature of the Lewis acid electrophilic activator has also been examined, from the standpoint of elements other than silicon, and several recent papers have utilized boron electrophiles in this way.[41–43] The yields of sulfide obtained are very high and the reductions can often be carried out at 0 °C or lower. The reagents used comprise either combined electrophile–nucleophile systems such as $BF_3$–NaI[41] or thexylchloroborane–dimethyl sulfide,[42] or the bromodimethylborane or bromoborane (**3**) reagents used by Guindon *et al.*[43] These workers also used $BBr_3$ but, unlike the other boron bromides, it reacted only sluggishly with diaryl sulfoxides and had the additional disadvantage of reacting with any free hydroxy groups present. Other electrophile–nucleophile combinations of a related type which have been examined include the strong Lewis acid $AlI_3$[44] and the weak Lewis acid $FeCl_3$ used in combination with $NaBH_4$ in aqueous ethanol.[45]

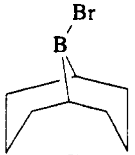

(**3**)

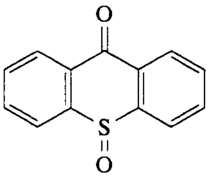

(**4**)

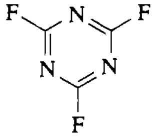

(**5**)

Other procedures which presumably operate by a very similar type of mechanism include the use of alternative electrophilic activators such as acid anhydrides[46] and acid chlorides,[47] while Olah *et al.*[48] have also used amine complexes of $SO_2$ or $SO_3$ as electrophiles, with sodium iodide in each case as the nucleophilic reductant. Among the simplest systems of this type are those reported by Chasar and Shockcor[49] using HCl–KI in chloroform, which gives excellent yields even with the keto sulfoxide (**4**), and, interestingly, even *t*-butyl bromide in refluxing chloroform, reported by Marchelli and coworkers,[50] which gives sulfides almost quantitatively. An unusual procedure reported by Olah *et al.*[51] was the use of the fluorinated triazine (**5**) or the corresponding trichloro analog (cyanuric chloride).

A number of procedures have been reported for the reduction of sulfoxides to sulfides which do not appear to fit the above broad categories but which are also versatile procedures, employing relatively low temperatures and short reaction times. For example, Drabowicz and Mikolajczyk[52] used the system thiourea *S*,*S*-dioxide–iodine in refluxing acetonitrile to reduce several sulfoxides to sulfides in yields of 89–95%. The sulfinic acid (**6**) is quite well known as a reducing agent but the catalytic role played by iodine in the present reduction is unclear. Amos[53] has successfully used the poly(styryl)diphenylphosphine–$CCl_4$ system to produce sulfides in yields of 81–99%. The method is selective for sulfoxides in the presence of aromatic nitro groups and, while very similar mechanistically to the reagent systems used by Olah *et al.*,[25] is also useful in that it avoids the separation and purification difficulties associated with the use of triphenylphosphine. Yoshihara and coworkers[54] have used the thioformamizium salt (7), readily prepared from *N*,*N*-dimethylthioformamide, in the reduction in dry chloroform of a series of sulfoxides, with yields in the range 53–82%.

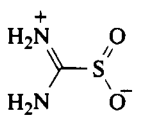
**(6)**

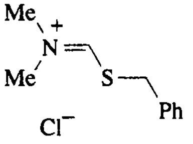
**(7)**

### 2.3.2.2 Reduction of Sulfones

The reduction of the S—O bond in sulfones is much more difficult, partly because this bond is stronger than the S—O bond in the corresponding sulfoxides.[55] In addition, powerful nucleophilic hydride reducing agents such as $LiAlH_4$[56] meet with limited success as a result of the normal steric hindrance to attack at tetracoordinate sulfur atoms and competing α- or α′-deprotonation by these strongly basic species. The use of electrophilic hydride reagents such as diisobutylaluminum hydride (DIBAL-H)[57] has been shown to be somewhat effective but only under severe conditions, presumably due to the weakly nucleophilic nature of the sulfone oxygen atoms. Grossert[4] has discussed these and related mechanistic problems in a recent comprehensive review. A further complication not found with the sulfoxide reduction is the possibility of obtaining the intermediate sulfoxide, as well as the sulfide.[58]

In spite of these obstacles, Still and Szilagyi[59] were able to achieve the so far unique reduction of sulfones to sulfoxides using a variant of the 'push–pull' strategy which has proved to be so successful in the sulfoxide reduction. After many unsuccessful attempts, it was found that electrophilic activation of one of the S—O bonds in a series of aliphatic and aromatic sulfones could be achieved using the *p*-chlorophenyl carbonium ion, derived from the corresponding diazonium tetrafluoroborate by thermal decomposition. Reduction of the aryloxysulfoxonium salt (8) was achieved by the addition of a $NaBH_4$–$Al_2O_3$ reagent to yield the corresponding sulfoxide (Scheme 3). No further reduction takes place under these conditions. The proposed mechanism, involving nucleophilic attack at the sulfoxonium center by hydride to give the *S*-protonated sulfoxide (9), was confirmed as the major pathway by deuterium-labeling experiments.[60] The yields are moderate and the nature of the electrophile restricts the reaction to simple, monofunctional sulfones, but this remains the only general method of converting sulfones into the corresponding sulfoxides.

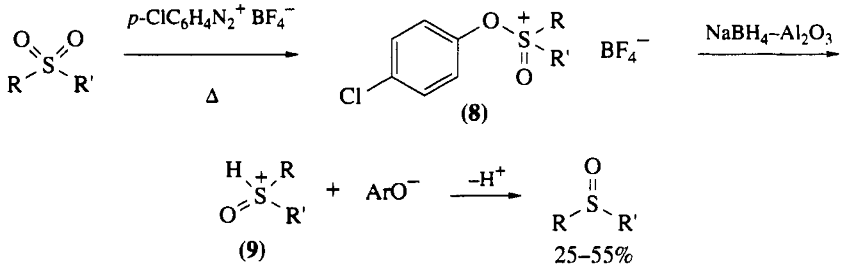

**Scheme 3**

Because of the importance of the sulfone moiety in organic synthesis as an 'activating' group and the need, therefore, for its facile subsequent removal, it is no surprise that much more attention has been paid to methods of reductively cleaving the C—S bond in sulfones. Many such methods are available and they have been thoroughly examined in the recent review by Grossert.[4] They will not be discussed further here.

### 2.3.2.3 Reduction of Sulfonic and Sulfinic Acids and Their Derivatives

The pronounced affinity of sulfur for the higher (+4, +6) oxidation states means that other subclasses of compound exist which contain S═O units. Many of these are little known but a number of successful reductions have been reported, especially of sulfonic acids and their ester, acid halide, *etc.* derivatives. These will be discussed in this section.

Although a common functional group in organic chemistry, the sulfonic acid ($RSO_3H$) unit is remarkably inert to reduction to RSH or any intermediate oxidation level. In contrast to carboxylic acids, for example, it is claimed that sulfonic acids resist refluxing with $LiAlH_4$ in dibutyl ether for three days.[61] On the other hand, it has long been known that sulfonyl chlorides can be reduced to the corresponding thiols by using amalgamated zinc–sulfuric acid[62] or tin(II) chloride–hydrochloric acid.[63] This works very well in the aromatic series where chlorosulfonyl groups can be introduced by chlorosulfonation and then reduced to the corresponding thiols. Lithium aluminum hydride can also be used to achieve this reduction but at –70 °C the intermediate sulfinic acid can be isolated in over 60% yield.[64] Brown and Rao[65] also achieved the sulfonic acid to thiol reduction using a $NaBH_4$–$AlCl_3$ system. Much more recently Nose and Kudo[66] have reported the use of $NaBH_4$ alone in THF at 0 °C for the conversion of aromatic sulfonyl chlorides to the corresponding sulfinic acids in good yields. The same reagent at higher temperatures produced mixtures of the disulfide and arenethiol.

In recent times, several groups have attempted to employ the indirect method of (electrophilic) activation of one of the S—O bonds, followed by reduction, often with a mild reducing agent. One of the earliest such attempts was reported by Chan *et al.*,[67] who found that sulfonyl chlorides and sulfonate esters, as well as the analogous sulfenyl and sulfinyl compounds, could be reduced to the corresponding disulfides (equation 7) using an $HSiCl_3$–$NPr_3$ system. Oae and coworkers[68] were the first to develop a successful reduction of arene- and alkane-sulfonic acids to thiols, using a system, $(CF_3CO)_2O$–$Bu_4N^+I^-$ at 25 °C, very similar to that used earlier[46] for the reduction of sulfoxides. Yields, however, were moderate and the thiol was present predominantly as the trifluoroacetate ester (equation 8). Oae and Togo[69] found $Ph_3P$–$I_2$ successful in reducing arenesulfonic acids quantitatively to arenethiols in refluxing benzene. While the reduction also proceeds with alkanesulfonic acids, the thiols so formed are transformed into alkyl iodides under the reaction conditions (equation 9). In the same way presumably, arenesulfonic acids are reduced to thiols with $Ph_3P$–$Ar_2S_2$ but the alkanesulfonic acids give high yields of the mixed sulfides (RSAr) in this reaction.[70] Interestingly, Oae and Togo[71] also found that both arene- and alkanesulfonic acids could be reduced to the corresponding disulfides in good yields, using $P_4O_{10}$ or other polyphosphoric acid derivatives with KI. The reaction is presumed to proceed *via* the sulfonyl iodide — it has been known for many years that sulfonyl halides are quantitatively reduced to the disulfides with HI.[72] Olah *et al.*[73] used iodotrimethylsilane in dichloromethane at 25 °C to convert sulfonyl, sulfinyl and sulfenyl halides into the analogous disulfides. Here iodotrimethylsilane can be viewed as a milder, more convenient form of the HI reagent.

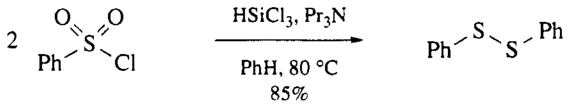

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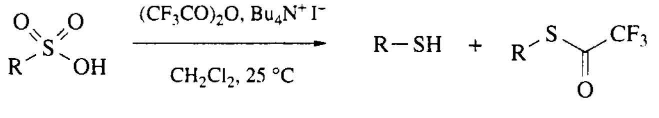

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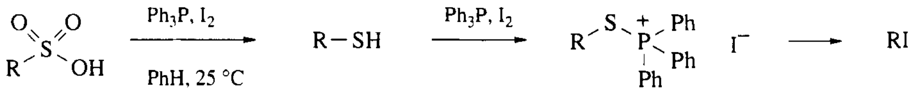

(9)

Other mild procedures for achieving the conversion of sulfonic acids to disulfides include $BBr_3$–KI in refluxing 1,2-dichloroethane[74] and $P_2I_4$ in refluxing acetonitrile.[75] Interestingly, $P_4S_{10}$ in sulfolane at 100 °C converted sulfonic acids into polysulfides ($ArS_nAr$, $n > 2$).[76] The polysulfides were subsequently converted into the thiols by $LiAlH_4$ or $NaBH_4$ reduction.[76] Cipris and Pouli[77] found that a large excess of the corresponding thiol converted aromatic sulfonyl chlorides into disulfides according to equation (10), while $AlI_3$ alone has been shown recently to convert sulfonyl chlorides into disulfides in yields of over 80%.[44] Two other reductive transformations of sulfonyl compounds of a less simple type have been noted. Arenesulfonyl azides were converted into aryl alkyl sulfides in moderate yield on treatment with trialkylboranes, followed by alkaline $H_2O_2$ (equation 11).[78] Kagabu *et al.*[79] have reported the successful conversion of a series of arenesulfonyl chlorides with trimethylsilyl cyanide into the corresponding thiocyanates. The reaction proceeds *via* the (sodium) sulfinate as intermediate and requires a reducing system ($Na_2SO_3$–$K_2CO_3$) for successful completion (equation 12).

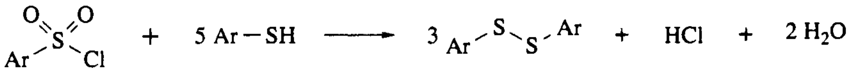
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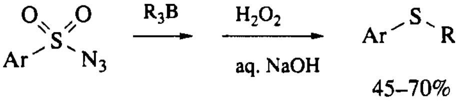
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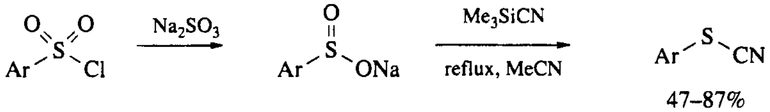
(12)

In contrast to the other types of S═O functionality already discussed, there has been very little systematic study of the reduction of sulfinic acids and their derivatives. This probably reflects nothing more than the relative paucity of such species in organic synthesis, since sulfinates have often been identified or proposed as fleeting intermediates in the reduction of sulfonic acid derivatives, as discussed above. Pinnick *et al.*[80] described an interesting reductive coupling of aromatic sulfinate salts to disulfides, using ethyl phosphinate in DMSO. Yields are moderate and the reaction is confined to aromatic sulfinates. A mechanism has been proposed *via* a sulfoxy sulfone intermediate. In a reaction reminiscent of the work of Cipris and Pouli,[77] Oae *et al.*[81] have reduced sulfinic acids to disulfides in better yields (80–100%) than those in the earlier procedure by using $ClSiMe_3$ as coreagent, along with a large excess of the thiol reducing agent (equation 13). If a mixed disulfide is required, yields are lower due to disproportionation. Two examples of reductions of sulfinyl systems in recent syntheses of natural products were noted.[82,83] One involves the reduction of allylic sulfinamides to allylic thiols with $LiAlH_4$ (equation 14), and the other the conversion of sulfinic acids into *S*-acetyl thiols by a sequence involving $SOCl_2$, thioacetic acid and triphenylphosphine (equation 15).

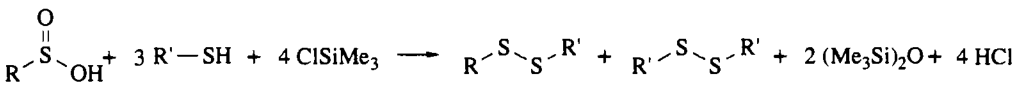
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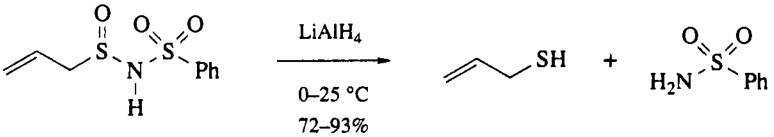
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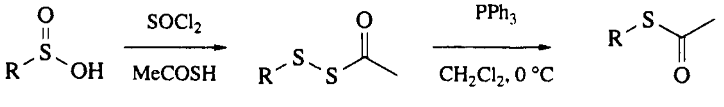
(15)

There has been recent controversy over the reduction of seleninic acids ($RSeO_2H$) to selenenic acids (RSeOH). Reich *et al.*[84] and Kice *et al.*[85] have independently concluded that earlier claims for the isolation of 'stable' selenenic acids are probably in error. While selenenic acids are stable in dilute solution, they show a pronounced tendency to form the corresponding anhydrides in the absence of water.

### 2.3.2.4 Reduction of Sulfimides (Sulfilimines) and Sulfoximides (Sulfoximines)

These nitrogen analogs of sulfoxides and sulfones are still relatively unusual types of organosulfur compound but a few methods are known for their reduction. Colonna and coworkers,[86] for example, found that *N*-tosylsulfimides could be reduced to sulfides in good yields, using formamidinesulfinic acid (thiourea *S*,*S*-dioxide) (**6**) under phase-transfer conditions at 70 °C (equation 16). This reagent was later adopted for the reduction of disulfides (see Section 2.3.4.1) and sulfoxides[52] and the latter were shown not to be intermediates in the reduction of sulfimides. Still and Turnbull[87] showed that phosphorus pentasulfide is as effective for the reduction of sulfimides as it had earlier proved to be for sulfoxides.[19] In addition to the *N*-tosyl derivatives, free diarylsulfimides were also reduced by this method. Oae and coworkers[34] showed that one of their procedures is capable of extension to *N*-tosylsulfimides (72–96% yields) and have used dichlorocarbene (generated from chloroform in a phase-transfer system) for the reduction of both sulfimides and sulfoximides to sulfides.[88] Oae and coworkers[89] have also used 1-benzyl-1,4-dihydronicotinamide (BNAH), catalyzed by various metalloporphins, for the reduction of both sulfimides and sulfoxides in benzene at 25–80 °C. Young and Reid[90] have conducted a thorough examination of the kinetics of the reduction of sulfimides to sulfides with the thiolate ion.

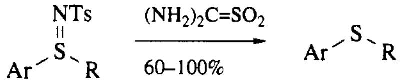

(16)

The sulfoximide system is of particular interest because stable chiral analogs are readily obtained ($R \neq R'$). A thorough examination of a series of stereochemical reaction cycles involving sulfoximides (**10**) was carried out by Cram and coworkers.[91] While the conversion of sulfoximides to sulfoxides is of course a reduction, it is perhaps more correctly viewed as a deimination reaction and Cram and coworkers reported the conversion of sulfoximides to sulfoxides in 99% yield, with 99% retention of configuration, using either $NO^+PF_6^-$ or, better, aqueous nitrous acid (equation 17). Oae *et al.*[92] have shown that other nitrosating agents such as TsNO 4-(*S*-nitrososulfonyl)toluene and *t*-butyl thionitrate may be used in dry acetonitrile and are as effective as aqueous $HNO_2$ (equation 18) for the deimination of sulfoximides (and sulfimides). Racemization of the sulfoxides obtained, however, was noted. These workers showed conclusively that $N_2O$ was evolved, as expected, from the initial *N*-nitrosation step. An interesting procedure reported by Oae *et al.*[93] for the conversion of sulfoximides to sulfoxides involves the use of elemental sulfur or diphenyl disulfide and again proceeds with essentially complete retention of stereochemical configuration.

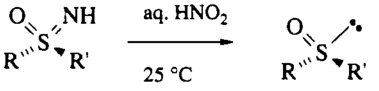

(**10**)

(17)

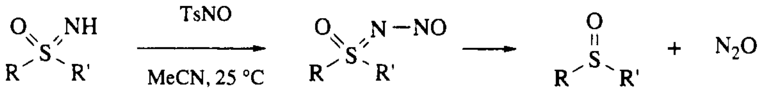

(18)

### 2.3.2.5 Reduction of Se and Te Analogs

While the literature in this area is sparse, it is useful to bear in mind that the strength of the relevant bonds is in the order S=O > Se=O > Te=O. Thus, while sulfoxides have been used as general oxidizing agents in various methods, such as the Pfitzner–Moffat or Swern procedures for the mild oxidation of primary and secondary alcohols,[94] diaryl telluroxides have been shown to be selective oxidants for the direct transformation of thiols (mercaptans) to disulfides, phosphines to phosphine oxides or hydroquinones to quinones.[95] The telluroxides could also be used in a catalytic cycle for the mild conversion of thiocarbonyl compounds to the corresponding carbonyl compounds.[95] Engman and Cava[96] have reported the first fully characterized tellurone (**11**). Not surprisingly, this is a more powerful oxidant than the telluroxide analog,[95] and will oxidize benzylic alcohols and oxidatively cleave 1,2-diols.

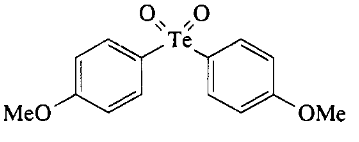

(**11**)

Likewise, diphenyl selenoxide has been shown to convert aromatic amines to the corresponding azobenzenes,[97] while, in contrast to their sulfur analogs, benzeneseleninic acid and its anhydride are well established as versatile oxidants in organic chemistry.[98]

Several of the procedures discussed in the sulfoxide section describe the successful extension of the method to the reduction of selenoxides,[19,27,28] and there is little doubt that many of the other procedures cited earlier could be used likewise. Sakaki and Oae[99] used triphenylphosphine selenide and similar selenides to reduce selenoxides to selenides in 79–93% yield (equation 19). Using a chiral phosphine selenide, these workers showed that the phosphine oxide formed had suffered predominant inversion, with a stereospecificity of over 80%. Detty[100] has reported the application of the silane PhSeSiMe$_3$ (**12**) to the reduction of selenoxides and telluroxides. The reactions are rapid and proceed essentially quantitatively, even in the presence of a hydroxy or carbonyl group.

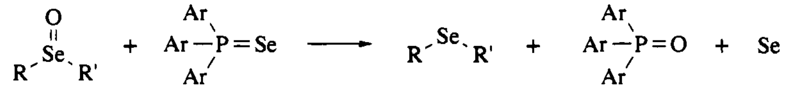

(19)

Lang and Comasseto[101] have shown that formamidinesulfinic acid, or thiourea dioxide (**6**), is an efficient and inexpensive reagent for reducing selenoxides and telluroxides, as well as various selenium(IV) halide derivatives, to the corresponding selenides and tellurides.

### 2.3.3 REDUCTION OF P=O COMPOUNDS

Little work appears to have been done with the reduction of phosphine oxides to phosphines, in sharp contrast with the voluminous literature on the reduction of sulfoxides (see Section 2.3.2.1). Two simple explanations which suggest themselves are: (i) the thermodynamic problem of a very strong P=O bond (*cf.* the sulfones); and (ii) the fact that, in contradistinction to the vast number of stable sulfone- and sulfoxide-containing intermediates encountered in organic synthesis, the supporting role of phosphorus intermediates is usually fleeting and confined very often, for example, to the single step involved in a Wittig reaction. Changes in oxidation state of the phosphorus atom, therefore, have so far been of little importance.

Nevertheless, a number of papers have appeared on this topic, including an important one by Mislow and coworkers[102] which examined the reduction of a series of chiral acyclic phosphine oxides by Si$_2$Cl$_6$ or Si$_3$Cl$_8$. These reactions proceed in high yield (70–90%), with stereochemical inversion at phosphorus and with almost complete stereospecificity. A complex mechanistic scheme is proposed to account for the observed results. The authors found that amine oxides and sulfoxides were also deoxygenated by Si$_2$Cl$_6$, although it should be noted that Pummerer-like chlorination products were observed in significant amounts for sulfoxides with α-C—H bonds. Since optically active phosphine oxides may readily be obtained from the reaction of diastereomerically pure menthyl phosphinate esters with Grignard reagents,[103] it is of interest to note that Marsi[104] has found phenylsilane (PhSiH$_3$) to be a reliable agent for the conversion of phosphine oxides to the corresponding phosphines, in quantitative yield and with complete retention of configuration (equation 20).

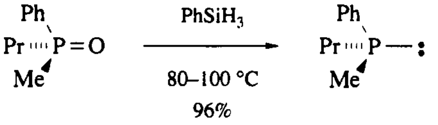

(20)

If further evidence of the difficulty of reducing the P=O bond were needed, the recent findings of Yamashita *et al.*[105] provide interesting confirmation. Many α-hydroxyalkyldiphenylphosphine oxides (**13**) were converted into the corresponding alkyldiphenylphosphine oxides (**14**) in 33–73% yield, with PCl$_3$–KI (equation 21). No competing reduction of the P=O bond was apparently observed. Majewski[106] has reported the disproportionation of dialkylphosphine oxides into dialkylphosphines and phosphinic acids (equation 22). The reaction proceeds in yields of over 90% and the phosphines are easily isolated by distillation.

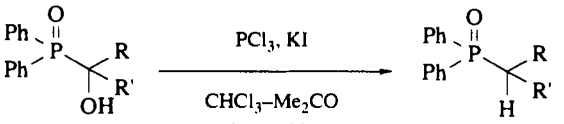

**(13)** **(14)**

(21)

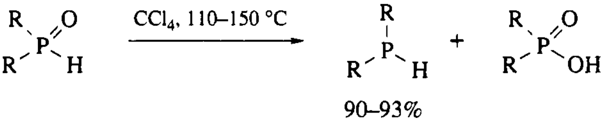

(22)

In other developments, Lecat and Devaud[107] have proposed an electrochemical reduction (Scheme 4) to recover triphenylphosphine from triphenylphosphine oxide produced, for example, in the Wittig reaction. Yields of up to 86% were obtained. Engel and Chakrabarty[108a] have reduced phosphoric and phosphonic chlorides to the corresponding monobasic phosphorous and phosphonous acid derivatives (equations 23 and 24), using $NaBH_4$ in refluxing dioxane. Triphenylphosphine oxide is reportedly[108b] reduced to triphenylphosphine in 75% yield by the electron-transfer system $SmI_2$–THF–HMPA, at 65 °C.

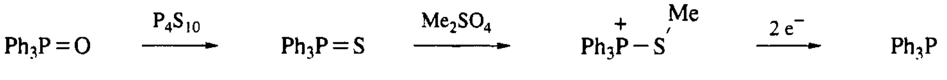

**Scheme 4**

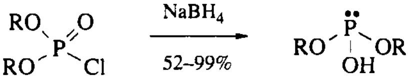

(23)

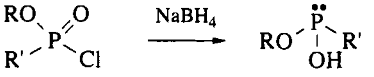

(24)

## 2.3.4 REDUCTION OF S—X TO S—H

### 2.3.4.1 Reduction of Disulfides and Diselenides

The reduction of disulfides to thiols (equation 25) is a familiar reduction process in organic chemistry, being easily effected by a variety of reducing agents. The subject has been reviewed[109] but still continues to attract attention and some recent methods will be discussed here. Various hydride reducing agents have been used, such as $NaBH_4$ (in refluxing THF–MeOH),[110] potassium triisopropoxyborohydride in THF,[111] and the mild reagents potassium triphenylborohydride[112] and lithium tri-*t*-butoxyaluminum hydride[113] in THF. In all cases, the authors noted that diaryl disulfides were reduced much faster than their dialkyl counterparts. Given the great importance of the disulfide–thiol redox relationship in living organisms, it is interesting to note that a biomimetic reducing system of 1-benzyl-1,4-dihydronicotinamide (BNAH), catalyzed by 3-methyllumiflavin, has been used by Oae and coworkers[114] for the reduction of diaryl disulfides.

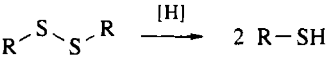

(25)

Maiti *et al.*[115] reported the reduction of a series of disulfides to thiols, using hydrazines. Other approaches to this reduction have employed thiourea *S*,*S*-dioxide (**6**),[116] a reagent known to reduce sulfoxides and sulfimides,[86] as well as selenoxides and telluroxides,[101] and an interesting Birch-type reduction using aluminum in liquid ammonia.[117] Activation of the aluminum used (by halogen or halide) appeared to be essential but the role of the activating agent was not explained. In some procedures the thiols were not isolated, but trapped by reaction of thiolate ion with alkyl halides,[116] as in Amos and Fawcett's[118] reductive cleavage using a polymer-supported phosphine reagent, or with Michael acceptors, as in an interesting procedure using CO–$H_2O$–Se[119] in an autoclave at 50–100 °C. In a similar vein, Suzuki and Sato[120] showed that $P_2I_4$ treatment of dialkyl or diaryl disulfides could be used to form mixed sulfides from benzyl alcohols (equation 26).

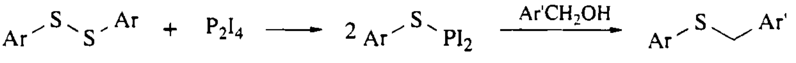

(26)

Diselenides have been cleaved reductively to the selenolate ion with CO–$H_2O$–Se,[119] $NaBH_4$ or sodium or potassium hydrides.[121] Very recently, Kong and Zhou[122] have utilized sodium hydrogen telluride to selectively reduce a variety of disulfides to thiols in yields ranging from 65–98%. Bunte salts ($RSSO_3Na$) are also efficiently reduced to the corresponding thiols using this reagent.

The desulfurization of disulfides to sulfides is also, formally, a reduction. Harpp and Gleason[123] showed that tris(dialkylamino)phosphines readily produced the corresponding sulfides, except in the case of diaryl disulfides. For example, important natural products such as α-lipoic acid and cystine could be converted to their monosulfides in excellent yield. Harpp and Gleason showed that inversion of configuration occurred at only one of the α-carbon centers, in accord with the proposed mechanism (equation 27). Later, Middleton *et al.*[124] showed that triphenylphosphine could be used to convert even diaryl disulfides into sulfides, but only under very forcing conditions (250–300 °C) in the absence of solvent. Interestingly, when diaryl disulfides are treated with triphenylphosphine in wet dioxane, the primary product obtained is not the sulfide desulfurization product, but the thiol reduction product.[125] Trapping of the arenethiolate presumed to be formed initially with a sulfenylating species (sulfur transfer agent) was shown by these workers to produce unsymmetrical disulfides in yields of 73–83%. The reactions of disulfides with trivalent phosphorus compounds have been reviewed by Mukaiyama and Takei.[126]

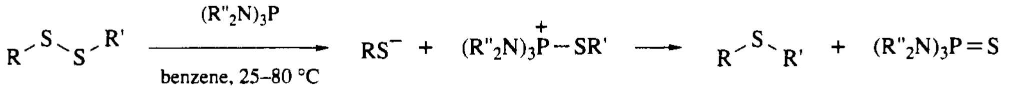

(27)

### 2.3.4.2 Reduction of Thiocyanates and their Se and Te Analogs

The reduction of thiocyanates to the corresponding thiols (equation 28) has long been known and has been extensively reviewed.[127,128] While much less well known, the reduction of seleno- and tellurocyanates has also been reviewed recently.[129,130] Among the reducing agents which have been employed in this area are sodium dithionite ($Na_2S_2O_4$), dithiothreitol (Cleland's reagent) and phosphinic acid ($H_3PO_2$). While reports of the preparation of tellurocyanates exist,[131] Engman[132] has noted that very few compounds of this type have been completely characterized, perhaps because of a facile disproportionation reaction, as shown in equation (29).

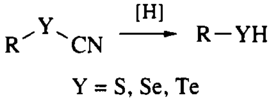

(28)

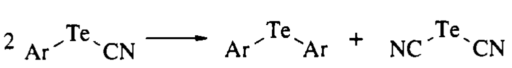

(29)

NaBH4 has been found to be an effective reducing agent for the reduction of both thiocyanates (in DMF at 25 °C)[133] and selenocyanates (in pyridine at 25 °C).[134] A procedure for the reduction of thiocyanates using tributyltin hydride (equation 30) has been reported by Ueno *et al.*[135] The mechanism of the reduction is probably homolytic and the thiostannanes (**15**) formed are stable and can be readily isolated. The thiostannanes, in addition to being more pleasant to handle than the parent thiols, can be converted into typical thiol derivatives, such as thiol esters, in excellent yields.[135]

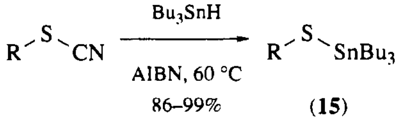

(30)

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# 3.1
# Heterogeneous Catalytic Hydrogenation of C=C and C≡C

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## 3.1.1 INTRODUCTION

### 3.1.1.1 General

Heterogeneous catalytic hydrogenation continues to be a most useful technique for the addition of $H_2$ to carbon–carbon double and triple bonds and to the aromatic nucleus, particularly if the objective involves chemo-, regio- or stereo-selectivity.[1–6] Generally, the conditions for a laboratory preparation are mild and the catalyst is easily separated from the product. A simple apparatus often can suffice, although commercial reactors add safety, convenience and the ability to conduct hydrogenations over a wide range of hydrogen pressures and temperatures. Reliable catalysts can be purchased and stored for years without significant loss of activity, and some active catalysts can be prepared conveniently when needed.

The addition of hydrogen is catalyzed by a large variety of materials, but synthetically useful procedures generally employ nickel or the platinum metals, whose surface provides the reaction centers. To increase the fraction of the metal which is exposed to the fluid phase, the metal is finely divided or distributed over the surface of an appropriate, presumedly inert, support. Although the properties of a catalyst are affected by the method of preparation, the characteristics of the metal are dominant.[3,4]

The choice of catalyst and conditions for optimal results sometimes can be critical, but often is not. A number of generalizations can aid in the selection of a suitable procedure; however, the best guide for an initial choice is based on the recorded experience of others.[1–6] However, in order to improve or adapt the procedure to a particular objective, some understanding of the dynamics and mechanism of heterogeneous catalytic hydrogenation can be helpful.

### 3.1.1.2 Catalysts

Knowledge of the source of the catalysts which are most commonly used in synthetic procedures is useful. Supported platinum metals which contain 1–10% of the metal dispersed on carbon, alumina or silica are available from commercial sources, as is Adams' platinum oxide (a catalyst much used in the past).[3] The latter is a mixture of Pt, $\alpha$-$PtO_2 \cdot xH_2O$, and $Na_xPt_3O_4$, according to Cahen and Ibers.[7] The presence of sodium is thought to be related to the promoting effect of acids on its activity.[3] If $KNO_3$ is used in place of $NaNO_3$ in its preparation, the product is a mixture of Pt and $\alpha$-$PtO_2 \cdot xH_2O$, which is reduced to Pt by $H_2$. A rhodium/platinum (7:3) oxide is prepared by a similar procedure and, when reduced by $H_2$, it exhibits the activity and selectivity of a pure rhodium catalyst.[8] Unsupported platinum metals have been prepared by the hydrogen reduction of the corresponding hydroxide (Pd, Pt, Rh, Ir) or oxide (Os) in water at atmospheric or high pressure.[9,10] High surface purity ruthenium powders have been described for use in studies of the effect of water vapor on the hydrogenation of benzene.[11] Water has an unusual promoting effect on ruthenium-catalyzed hydrogenations.[3]

Raney nickel can be purchased in a form which is ready for use (W-2), or can be prepared by published procedures which furnish catalysts with a range of activities.[3] The increase in selectivity of Raney Ni catalysts upon 'aging' apparently results from the formation of CO by the decomposition of the ethanol under which the catalyst is usually stored.[12] Highly regio- and stereo-selective catalysts are prepared as slurries by the reduction of the metal acetates, and are used *in situ* or stored for later use. P-2 nickel is prepared by reducing an aqueous alcoholic solution of $Ni(OAc)_2$ with $NaBH_4$.[13] More recently, highly selective Ni and Pd catalysts were prepared by the reduction of $Ni(OAc)_2$ or $Pd(OAc)_2$ with NaH and *t*-pentyl alcohol in THF.[14,15]

Chemically bonding metal complexes to an insoluble solid is a method of preparing catalysts whose active centers have well-defined structures, but the results have yet to be applied to synthesis.[16] Polymer-bound palladium and rhodium complexes appear to offer the combined advantages of the selectivities of soluble hydrogenation catalysts and the ease of separating heterogeneous catalysts from the products.[17]

### 3.1.2 DYNAMICS AND MECHANISM[18]

#### 3.1.2.1 Transport Phenomena[19]

The rate and selectivity of a surface-catalyzed reaction can be affected by the existence of concentration or temperature gradients in the quiescent layer of fluid which surrounds the catalyst particle or is contained within its pores upon whose surface much of the exposed active material is distributed. The reactants in the bulk phase reach the reactive sites by diffusion through these regions of the fluid, and they affect the kinetics when the rates of the surface-catalyzed reactions are fast relative to the rate of transport of reactants to the catalytic sites. In the hydrogenation of unsaturated liquids or compounds in solution, the agitation of the liquid–catalyst mixture must be adequate to assure that the solution remains saturated with hydrogen.

The transport of either the unsaturated reactant or hydrogen may limit the rate. The diffusivity of $H_2$ is much greater than any unsaturated reactant, but, in a liquid phase, the transport of hydrogen may limit the rate because of its low solubility in the commonly used solvents.[20] To minimize diffusional effects, small amounts of the metal are deposited on nonporous supports, or on supports with wide pores with the metal confined to an outer shell of the supporting particle. Colloidal particles also afford short diffusion paths. Temperature gradients are unlikely to be important if the catalyst particle is immersed in a liquid and the agitation of the mixture is vigorous. Madon *et al.* have recommended procedures to establish that neither heat nor mass transfer, either interphase or intraparticle, affect the rate.[19]

#### 3.1.2.2 Kinetics[20]

The formal kinetic expressions for the rate of surface-catalyzed reactions are like those of homogeneous catalysis, whether simplified by assuming a rapidly established equilibrium between reactants and the catalytic site, as in the Michaelis–Menten equations for enzyme catalysis, or based on less restrictive assumptions such as the steady state for the reactive intermediates. Following the simplified Langmuir–Hinshelwood method, the rate is assumed to be a function of the fraction of the active sites which are occupied by the reactants. The fraction occupied is related to the concentration of the reactant in the bulk phase through a Langmuir adsorption isotherm. One useful formulation assumes that the adsorption of the unsaturated hydrocarbon (A) is not competitive with hydrogen.[1] Under conditions in which the surface reactions are rate limiting, the expression for the rate of forming the product is equation (1) where $K_H$ and $K_A$ represent the equilibrium constants for adsorption of $H_2$ and A, respectively, and $[H_2]$ and [A] are the concentrations of the reactants in the fluid phase. If $K_A[A]$ is much greater than unity, then the rate is independent of [A]. Often this condition is met by an alkene or alkyne, giving equation (2) which holds until near the end of the reaction when the concentration of A becomes small.[21]

$$-d[A]/dt = k_A K_H K_A[H_2][A]/(1 + K_H[H_2])(1 + K_A[A]) \qquad (1)$$

$$d[A]/dt = k_A K_H[H_2] \qquad (2)$$

If the system is well represented by Langmuir–Hinshelwood kinetics, then the relative values of the adsorption equilibrium constants of various unsaturated compounds can be obtained from the relative rates determined individually and in competition.[22] The expression for the competitive reaction between two compounds A and B results from the division of the corresponding rate expressions for each compound (equation 3) to give equation (4). The ratio of the individual rates of hydrogenation, $k_A/k_B$, permits the abstraction of the ratio $K_A/K_B$ from the competitively determined ratio $k_A K_A/k_B K_B$ (equation 5). The assumption that the adsorption of the unsaturated compound is rapid and reversible relative to the rates of the surface-catalyzed reactions may not be correct. In that case, $K_A/K_B$ is an 'apparent' relative adsorption equilibrium constant (see Section 3.1.3.2.2).

$$-d[A]/dt = k_A K_H[H_2]K_A[A]/(1 + K_H[H_2])(1 + K_A[A] + K_B[B]) \qquad (3)$$

$$d[A]/d[B] = k_A K_A[A]/k_B K_B[B] \qquad (4)$$

$$\ln([A]_o/[A]_t) = (k_A K_A/k_B K_B)\ln([B]_o/[B]_t) \quad (5)$$

$$-d[A]/dt = k_A K_H[H_2]K_A[A]/(1 + K_H[H_2])(K_B[B]) \quad (6)$$

If B represents a nonreducible compound, a reversibly adsorbed inhibitor or poison, and $K_B[B]$ is greater than $(1 + K_A[A])$, then equation (3) takes the form of equation (6), which shows that a reversibly adsorbed poison causes the rate of hydrogenation of A to become proportional to its concentration, *i.e.* kinetically first order. An irreversibly adsorbed poison will slow the rate but not affect the rate expression unless particular sites are poisoned selectively or the decrease in rate moves the reaction out of a mass transport limiting regime. Although these equations are approximations, they often reproduce the form of the physical phenomena of heterogeneous catalytic hydrogenation, and provide a useful guide for the interpretation of results.

Generally, solvents exert a greater effect upon competitive reactions than upon the individual reaction rates when corrected for the solubility of hydrogen.[19–22] Solvents which are strongly nucleophilic, such as amines, compete for active sites, and benzene slows the hydrogenation of alkenes, particularly on Pd.[19,21]

### 3.1.2.3 Mechanism[1,20,23]

#### *3.1.2.3.1 Formalism of Horiuti–Polanyi*

The early use of deuterium in place of hydrogen in the study of catalytic hydrogenation led to the recognition that the process was not simply the addition of $H_2$ to the double bond. Horiuti and Polanyi proposed that both $H_2$ and alkene (**1**) are bound to the catalyst surface and transformed to products by a sequence of elementary steps, which they represented as shown in Scheme 1, where an asterisk (*) represents a vacant site on the catalyst.[24] The last step, (d), is virtually irreversible under the usual hydrogenation conditions, but can be observed in the exchange reactions of $D_2$ with alkanes. The mechanism accounts for the isomerization of an alkene if the reversal of step (c), which involves the formation of the alkyl intermediate (**3**), involves the abstraction of a hydrogen atom other than the one first added, and is coupled with the desorption of the alkene, (**2**) → (**1**). At present, the bond between the alkene and the metal often is represented as a π-complex (**4**), as in equation (7).[1–5]

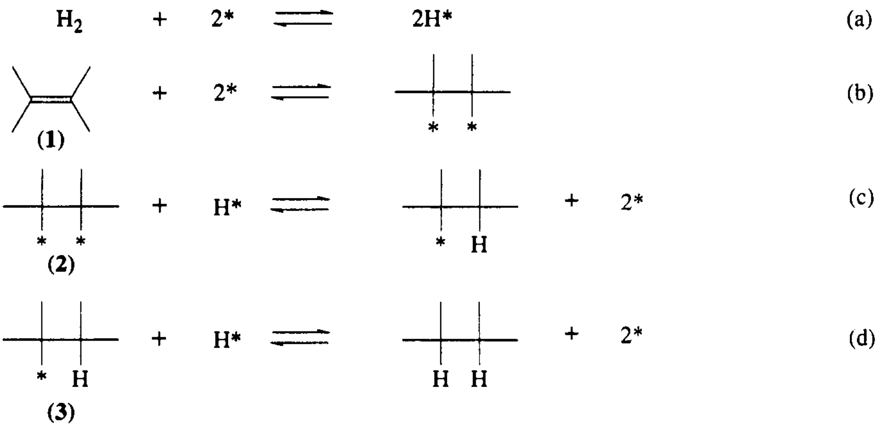

**Scheme 1** The Horiuti–Polanyi mechanism of alkene hydrogenation

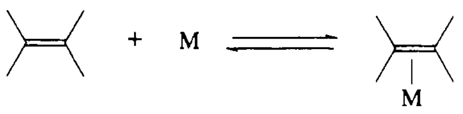

(**4**) (7)

#### *3.1.2.3.2 Organometallic analogy*

The rapid development of catalysis by soluble transition metal complexes and the results of surface science studies afford useful insights into the mechanisms of heterogeneous catalysis.[16,25,26] The surface of a metallic particle presents an array of atoms differing in coordination number which depends on the atom's location on a terrace, step or kink.[27] The spectroscopy of adsorbed reactants and intermediates have properties which suggest structural relationships to organometallic compounds and, presumably, their reactions are analogous.[27,28]

Depending upon its location, and assuming octahedral coordination as a maximum, a metal atom may have one, two or three vacant coordination sites at which a monodentate group may be bound.[29] These sites correspond approximately to a location on a terrace, step or kink.[27] A convenient symbol for the exposed atom is ${}^{x}$M where $x$ represents the number of vacant sites before exposure to the reactants. The elementary reactions which occur are assumed to be those of an organometallic complex which contains the analogous structural unit.[28] For example, the dissociation of $H_2$ on a metal surface may involve a single atom, providing it has at least two vacant coordination sites (equation 8). The migration of hydrogen atoms to other parts of the surface may be represented as in equation (9) where ${}^{x}$M may be ${}^{1}$M, ${}^{2}$M or ${}^{3}$M. Indeed $H_2$ dissociates more rapidly on the edges of a stepped platinum surface than on atoms located on the terraces or close-packed planes.[27] A single vacant site can bind an alkene, or alkyne, as a π-complex and, if it is located on an atom which also bears a hydrogen atom, its insertion into a metal–hydrogen bond may occur (equation 10). If both the alkyl group and a hydrogen atom are bound to the same metal atom then reductive elimination can proceed to the alkane (equation 11). The reactions may involve neighboring surface atoms in ways analogous to dinuclear or polynuclear metal complexes, and can be represented by an extension of the above symbolism.

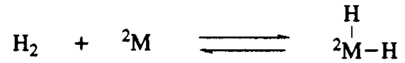

$$\mathrm{H_2} + {}^{2}\mathrm{M} \rightleftharpoons {}^{2}\overset{\mathrm{H}}{\overset{|}{\mathrm{M}}}\mathrm{-H} \qquad (8)$$

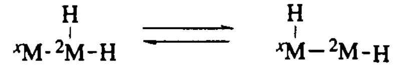

$$ {}^{x}\mathrm{M}\text{-}{}^{2}\overset{\mathrm{H}}{\overset{|}{\mathrm{M}}}\mathrm{-H} \rightleftharpoons {}^{x}\overset{\mathrm{H}}{\overset{|}{\mathrm{M}}}\mathrm{-}{}^{2}\mathrm{M\text{-}H} \qquad (9)$$

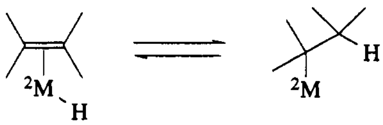

(10)

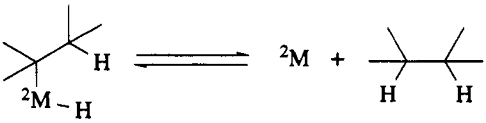

(11)

Obviously, these later representations imply more knowledge of structure than the asterisks of Horiuti and Polanyi, but they serve to emphasize possible mechanistic relationships with homogeneous catalysis. Interestingly, as in hydrogenations catalyzed by soluble transition metal complexes,[28] the spectroscopically observable structures may not include important intermediates along the main reaction paths. For example, Yates *et al.* have shown that the spectral intensity of the IR bands associated with ethylidyne, a previously postulated intermediate in the hydrogenation of ethylene,[30] is not related to the rate of the latter reaction.[31] Presumably, reaction occurs on a small fraction of the surface, most of it being occupied by unreactive groups.

### 3.1.3 HYDROGENATION OF C═C

The addition of hydrogen to simple alkenes proceeds rapidly with any of the readily available forms of palladium, platinum, rhodium or nickel catalysts. However, the structure of more complex alkenes and the presence of additional functional groups, whether or not reducible, can dictate the particular catalyst and reaction conditions which should be used to ensure that the addition of hydrogen is complete, or to promote regio- or stereo-selectivity.

### 3.1.3.1 Double Bond Migration

The isomerization of an alkene often accompanies the addition of hydrogen but goes unnoticed unless the isomer is appreciably less reactive, results in the loss of chirality in the alkene, or differs in stereoselectivity.[3,4] The relative rate of hydrogenation to isomerization depends on the structure of the alkene, the catalyst and the conditions used.[3,4,32]

Metals differ in their tendency to promote isomerization. Nishimura *et al.* found that, on unsupported platinum metals, the order of decreasing activity is Pd >> Rh, Ru, Pt > Os > Ir.[33] The more active forms of Raney Ni exhibit a greater tendency than Rh to catalyze isomerization, but aged Raney Ni (see Section 3.1.1.2) and P-2 Ni are less active in this regard.[12,13] Of the common catalysts, platinum often is used when isomerization is to be avoided, and palladium is chosen for its selectivity and reactivity when isomerization is acceptable or desired.[3,4]

#### *3.1.3.1.1 Mechanism*

The mechanisms of isomerization which have been considered fall into two categories; 'associative', first proposed by Horiuti and Polanyi,[24] and 'dissociative', advanced by Farkas *et al.*[34] The 'associative' mechanism is a consequence of the reversibility of the formation of the alkyl intermediate shown in Scheme 1 and in equation (10), while the dissociative mechanism, in its current form, involves allylic species (**5**)–(**7**) shown in Scheme 2. The Horiuti–Polanyi mechanism implies that double bond isomerization and the addition of $H_2$ proceed through a common intermediate, whereas the dissociative mechanism represents an independent path.[26]

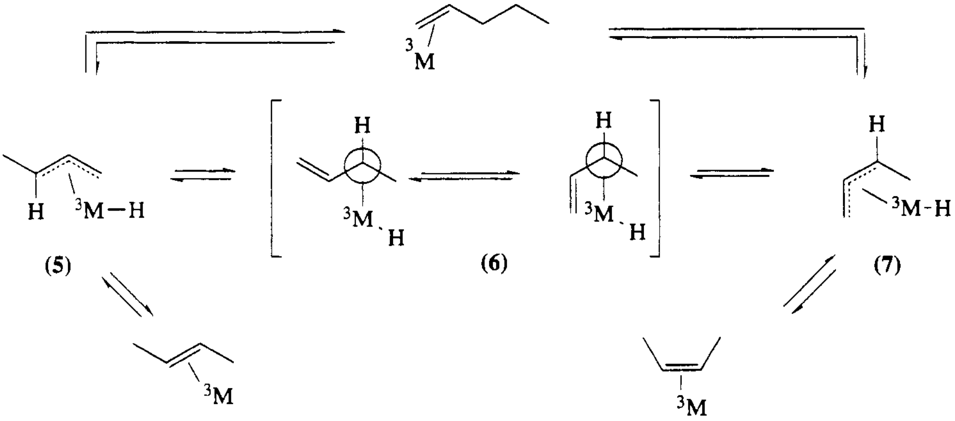

**Scheme 2** Dissociative mechanism: isomerization of 1-butene to *cis*- and *trans*-2-butene

The representations in Scheme 2 and equations (7)–(11) use a formalism which indicates important elements of structure that a surface atom requires for the respective mechanisms.[29] On a $^2$M site, the associative mechanism can take place through the reversibility of equation (9). This site provides the required hydrido group and a vacant coordination position to accept the alkene, a two-electron donor ligand.[28]

The 'dissociative' mechanism of double bond migration *via* an allylic intermediate can occur at a $^3$M site, as indicated in Scheme 2, or at a two atom site such as $^x$M—$^2$M which can provide the three vacant coordination positions which are required to bind both the π-allyl, a four-electron donor, and the hydrido group.[28,29] Because the surface of a metal provides sites which differ in structure, both mechanisms may operate on a given catalyst, the relative importance being a function of the metal, the alkene and the reaction conditions.[3,4,32]

Microwave spectroscopy identifies the location of the deuterium introduced by exchange into simple alkenes, and has been used with both homogeneous and heterogeneous catalysts to clarify the mechanisms of isomerization.[35] Using this method, Naito and Tanimoto showed that the addition and exchange reactions of propene over $Pd/SiO_2$ at 187 K take place *via* *n*-propyl and *s*-propyl adsorbed intermediates.[36] The adsorbed *s*-propyl group is not symmetric for hydrogen abstraction because of restricted rotation about the alkyl–metal bond.[26] In addition, an apparent intramolecular hydrogen migration between the 1- and 3-positions was assumed to be evidence of a suprafacial 1,3-sigmatropic shift of a hydrogen atom within the π-complexed propene. This mechanism, however, is not supported by the stereoselective exchange of $D_2$ with the 8(14)-cholestene (**10**; Scheme 3), or by the quantum mechanical calculations of

Anderson *et al.*, who concluded that a mechanism involving coadsorbed allyl and a hydrogen atom, as represented in Scheme 2, is allowed.[37]

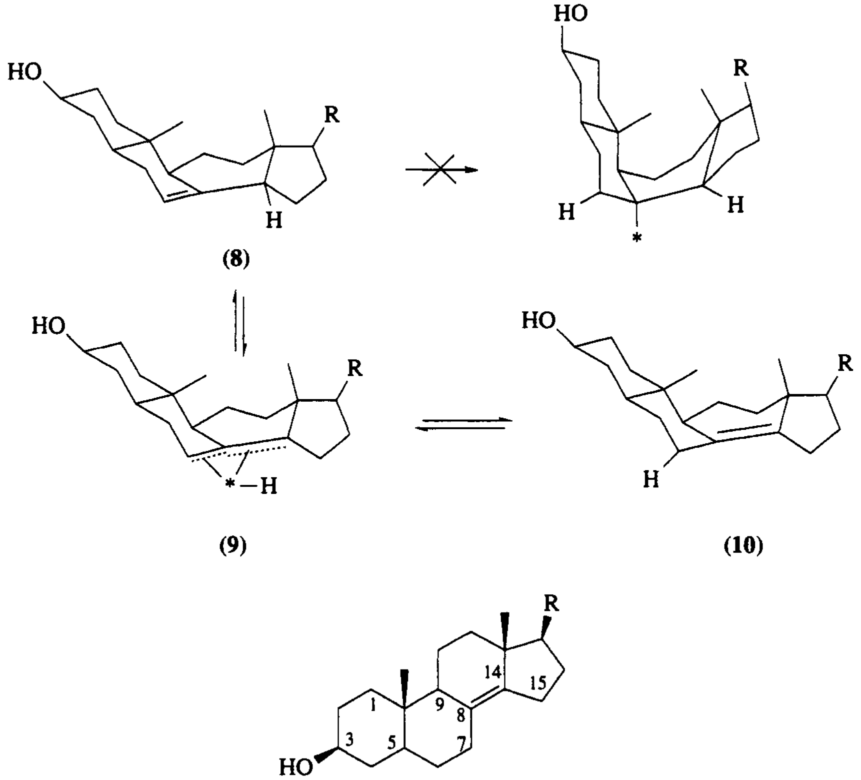

**(8)**

**(9)**

**(10)**

**(10)**

**Scheme 3**

An example of the exclusive operation of the dissociative mechanism is seen in the palladium-catalyzed isomerization of cholest-7-en-3β-ol (**8**) to cholest-8(14)-en-3β-ol (**10**) which does not add $H_2$ ($D_2$) in the absence of a strong acid (Scheme 3).[23,38] The formation of the alkyl intermediate is prevented by the increase in the internal nonbonded interactions which would have to be overcome to form a *cis* junction of the B/C rings (see Section 3.1.3.3.4). The conversion to the allylic intermediate (**9**) avoids these internal interactions. In the presence of $D_2$ and palladium, the 8(14)-ene (**10**) exchanges the α-hydrogens at carbons 7, 9 and 15 with deuterium more rapidly than at any other position, which implicates three different π-allyl complexes.[38]

### *3.1.3.1.2 Modifiers of isomerization*

A comparison of the mechanisms of isomerization and hydrogen addition shows that an increase in the availability of hydrogen at the reaction site should favor the addition of hydrogen over isomerization, and this has been demonstrated repeatedly.[1–5] The relative rate of isomerization to the addition of hydrogen can be affected also by nucleophilic reagents which include strong bases, amines, phosphines and CO.[4,39] Apparently, these nucleophiles are adsorbed reversibly and compete for vacant coordination sites with $H_2$ along with the unsaturated compound. Whether isomerization proceeds *via* the associative or the dissociative mechanism, a vacant site must be provided to accept a hydride from the adsorbed alkyl intermediate or the adsorbed alkene, respectively. The adsorption of $H_2$ not only furnishes the hydrido groups required for addition but also decreases the number of vacant sites.

The alkene itself is a nucleophile. Thus, increasing the ratio of alkene to catalyst (Pd/C) from 4:1 to 30:1 decreases the rate of isomerization of 4-*t*-butylmethylenecyclohexane (**11**) to 4-*t*-butyl-1-methylcyclohexene (**12**; equation 12), relative to the rate of hydrogen addition.[40] With the 4:1 ratio, isomerization is about 10 times as fast as addition, and the saturated product is mainly the more stable *trans* isomer (see

Section 3.1.3.3.5). Tertiary amines, triphenylphosphine and CO are much more effective inhibitors of isomerization.

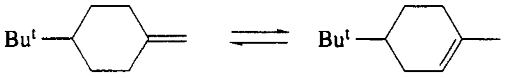

(11) (12)

(12)

Benzene appears to inhibit isomerization with Pt and Rh catalysts;[4] however, the effect may be due in part to differences in the solubility of hydrogen in the solvents. The rate of hydrogenation of cyclohexene catalyzed by $Pt/SiO_2$ is independent of the solvent, including benzene, provided that the concentration of dissolved hydrogen is used in the rate expression.[19] With Pd however, the corrected rate constants are smaller in benzene and smaller still in xylene, than in nonaromatic solvents.[21]

To compensate for the decrease in the rate of hydrogenation caused by the added nucleophile, the amount of catalyst or the hydrogen pressure may be increased.[3,4] The nucleophile shifts the kinetics from zero to first order in the alkene, which increases selectivity.

### 3.1.3.2 Structure–Reactivity

#### *3.1.3.2.1 Individual rates*

The rate of hydrogenation of a carbon–carbon double bond depends upon its structural environment, the catalyst and the reaction conditions. Attempts to find linear free energy relationships between structure and reactivity have had limited success in determining whether the substituent effects are mainly polar or steric, but the studies serve to assemble much of the available pertinent information on the subject.[41,42]

The rate of hydrogenation decreases with an increase in the number of alkyl substituents in the order $CH_2{=}CHR^1 > CH_2{=}CR^1R^2 >$ *cis*-$R^1CH{=}CHR^2 >$ *trans*-$R^1CH{=}CHR^2 > R^1CH{=}CHR^2R^3 > R^1R^2C{=}CR^3R^4$. Variation in the structure of the alkyl group has a secondary effect as does the polarity of the attached group, providing that the substituent is not conjugated with the double bond.[41] On palladium, polar effects are small or negligible.[41]

#### *3.1.3.2.2 Competitive rates*

The structure of the alkene has a greater effect on the competitive reactivities than on the individual rates. For example, Maurel and Tellier determined the individual and competitive rates in cyclohexane on a 7.5% $Pt/SiO_2$ catalyst (20 °C, 1 atm; 1 atm = 101.3 kPa) of 15 substituted alkenes (Table 1).[43] The relative values of the individual rates agree well with the rates of those compounds which are also in-

**Table 1** Individual and Competitive Rates of Hydrogenation[a] of Alkenes on Platinum[43]

| *Structural type* | *Compound* | $k_A$[b] | $k_AK_A$[c] |
|---|---|---|---|
| $RCH{=}CH_2$ | 1-Hexene | 110 | $7.4 \times 10^5$ |
| | 4-Methyl-1-pentene | 125 | $4.7 \times 10^5$ |
| $R^1R^2C{=}CH_2$ | 2-Methyl-1-pentene | 120 | $1.3 \times 10^4$ |
| | 2,3-Dimethyl-1-butene | 160 | $0.9 \times 10^4$ |
| $\overline{CH{=}CH}$<br>$(CH_2)_n$ | Cyclopentene | 100 | $1.3 \times 10^5$ |
| | Cyclohexene | (100) | $(1.0 \times 10^4)$ |
| $R^1R^2C{=}CHR^3$ | 1-Methylcyclopentene | 95 | $3.7 \times 10^3$ |
| | 3-Ethyl-2-pentene | 65 | $3.5 \times 10^2$ |
| | 1-Methylcyclohexene | 40 | $1.0 \times 10^2$ |
| $R^1R^2C{=}CR^3R^4$ | 2,3-Dimethyl-2-butene | 75 | 1.8 |
| | 1,2-Dimethylcyclohexene | 20 | 0.6 |

[a]Catalyst, 7.5% $Pt/SiO_2$. [b]Individual rate constants relative to the rate of cyclohexene scaled to 100. [c]Competitive rates scaled relative to cyclohexene, $k_cK_c = 1.0 \times 10^4$.

cluded in the study by Hussey *et al.*, who used a 0.52% $Pt/Al_2O_3$ catalyst at 25 °C in cyclohexane.[44] The rate constants cover a range of less than 10, whereas the equilibrium constants have a range of $2 \times 10^5$, and furnish a linear plot of the logarithm of the equilibrium constants against the Taft polar substituent constant $\sigma^*$. However, the polar and steric substituent constants are intercorrelated and therefore the result is ambiguous.[42]

Hussey *et al.* interpret the relative competitive rates on platinum catalysts as measures of competitive rates of alkene adsorption.[45] They note that very little isomerization accompanies hydrogenation, which suggests that desorption of the alkene is slow. A rapid interconversion of adsorbed alkene and the alkyl intermediate of the Horiuti–Polanyi mechanism is indicated by the distribution of deuterium in the deuterated alkane formed when $D_2$ is used in place of $H_2$; yet little or no deuterium appears in the recovered alkene.[32]

The appropriate interpretation may depend on the range of structures considered, the catalyst and the conditions employed. The interpretations differ in that in one, the rate of desorption is assumed to be fast relative to the conversion of adsorbed alkene to the alkyl intermediate, while in the other, desorption is assumed to be relatively slow. Catalysis by palladium may conform more closely to the reversible adsorption model than does platinum.

The relative individual rates and the relative competitive rates are determined by the difference in energy of the same transition states but different ground states; in the former the alkene is bound to the catalyst, in the latter it is free. The effect of alkene structure on relative reactivity indicates that the structural change on adsorption is greater than the changes which follow adsorption on the catalyst. Interestingly, hydrogenations over P-2 Ni are apparently first order in alkene, which probably accounts for the greater sensitivity to structure shown by this catalyst in individual hydrogenations as compared to Pt.[13]

### *3.1.3.2.3 Alkene association constants*

The relative equilibrium constants for the adsorption of alkenes on the surfaces of platinum metals are not available from static measurements. Accordingly, the kinetically derived constants have been compared with the association constants of alkenes with metal ions in solution. Of these, the measurements by Tolman are the most instructive.[46]

Tolman has shown that the equilibrium constants for the reactions of 38 substituted alkenes with $Ni[P(O\text{-}o\text{-tolyl})_3]_3$ (**13**) in benzene, to form (ENE)bis(tri-*o*-tolylphosphite)nickel complexes (**14**), are sensitive to the structure of the alkene (equation 13). Values of $K_1$ at 25 °C vary from $10^{-4}$ to $4 \times 10^8$. The stability of the complex is enhanced by electron-withdrawing substituents such as cyano and carboxy and lowered by alkyl groups. That resonance involving unshared electrons on the oxygen of an alkoxy group overpowers the inductive effect is indicated by the relative values of $K_1$ for allyl methyl ether, 1-hexene and vinyl butyl ether which diminish in that order by factors of 3:1:0.006.

$$\underset{(\mathbf{13})}{NiL_3} + ENE = \underset{(\mathbf{14})}{(ENE)NiL_2} + L \qquad \text{where } L = P(O\text{-}o\text{-tolyl})_3 \qquad (13)$$

The equilibrium constants for a series of cycloalkenes decrease in the order norbornene > *cis*-cyclooctene > cyclopentene > cycloheptene > cyclohexene, which correlates with the calculated strain energies as well as the kinetically determined relative adsorption constants on Pt (Table 2). Tolman states that electron donation from a filled metal *d*-orbital to an empty alkene $\pi^*$-orbital is extremely important in determining the stability of these complexes. Steric effects of substituents are relatively unimportant compared to electronic effects, and resonance is more important than inductive interactions. The ability of the metal to back bond is lowered progressively in the series $Ni^0 > Pt^0 > Rh^I > Pt^{II} > Ag^I$ which reduces the importance of resonance and decreases the selectivity of the metal for different substituted alkenes.

The diimide reduction of an alkene has been suggested as a model for the adsorption of an alkene on a metal, and has been used to help identify the intramolecular interactions which determine the stereochemistry of hydrogenating alkyl-substituted cycloalkenes.[47] Both processes involve *syn* addition; in one, two hydrogen atoms are transferred to the face of the double bond, in the other, a $\pi$-alkene complex is formed. Both represent changes in the direction of forming an eclipsed conformation of an alkane. Garbisch *et al.* found that the major factors that contribute to the observed reactivities in diimide reductions of unsaturated hydrocarbons are torsional strain, bond angle strain and $\alpha$-alkyl substituent effects, as indicated by the good agreement between calculated and observed relative reactivities which covered a range of 38 000.[48] This treatment was applied also to stereoselectivities. Comparisons with catalytic hydrogenations are limited but show a parallelism, and clearly, diimide reductions are more sensitive to structure than are the individual rates of hydrogenation and, possibly, the kinetically determined equilibrium constants for adsorption on Pt (Table 2).

**Table 2** Structure–Reactivity of Cycloalkenes. Comparisons of Individual and Competitive Hydrogenation Rates with Related Reactions

| *Compound* | *$H_2$, Pt*[a] | | *Ni(ENE)*[46] | *STRAIN*[46] | *Diimide*[48] |
|---|---|---|---|---|---|
| | $k_A$[44] | $K_{AB}$[45] | $K_{eq}$ | *ΔH (Kcal)* | $k_{rel}$ |
| Norbornene | 223 | — | 4.4 | 27.2 | $4.5 \times 10^2$ |
| *cis*-Cyclooctene | 10 | 25 | $6.2 \times 10^{-2}$ | 7.4 | 17 |
| Cyclopentene | 121 | 7.5 | $2.6 \times 10^{-2}$ | 6.8 | 16 |
| Cycloheptene | 78 | 6.3 | $2.3 \times 10^{-2}$ | 6.7 | 12 |
| Cyclohexene | 113 | (1.0) | $3.5 \times 10^{-4}$ | 2.5 | (1.0) |

[a] 0.52% $Pt/Al_2O_3$ at 25 °C, 1 atm.

### 3.1.3.3 Stereochemistry

#### 3.1.3.3.1 *Syn addition*

With few exceptions, the stereochemistry of the hydrogenation of a carbon–carbon double bond is the result of *syn* addition of two atoms of hydrogen from the catalyst to the proximal face of the double bond.[23] A classical demonstration is given by the hydrogenation (Pd, AcOH, 1 atm) of the (*Z*)- and (*E*)-isomers of 2,3-diphenyl-2-butene (**15**) and (**16**) which yield respectively the *meso* (98%) and (±) (98%) isomers of 2,3-diphenylbutane (equations 14 and 15).[32] Likewise the hydrogenation of dimethyl 1,2-cyclohexenedicarboxylate yields only the *cis* saturated isomer.[23] Such stereospecificity is not always found.

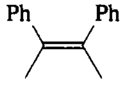

**(15)** $\xrightarrow[1\ atm]{Pd,\ H_2}$ *meso*-2,3-diphenylbutane 98% (14)

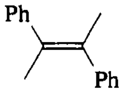

**(16)** $\xrightarrow[1\ atm]{Pd,\ H_2}$ (±)-2,3-diphenylbutane 98% (15)

The hydrogenation of 1,2-dimethylcyclohexene (**17**; $PtO_2$, HOAc, 1 atm) yields *trans*-(**19**) as well as *cis*-1,2-dimethylcyclohexane (**18**),[23,32] but Ir and Os in *t*-butyl alcohol are much more selective (equation 16).[49] The addition of hydrogen to (**17**) competes with isomerization to 1,6-dimethylcyclohexene (**20**), which not only reacts more rapidly but yields *trans* (**19**) as well as the *cis* product (**18**) *via syn* addition of the two hydrogen atoms (equation 17). In the Pt-catalyzed reaction, the intermediate (**20**) can be observed, although its steady-state concentration remains low (0.21% of the 1,2-isomer **17**) because of its

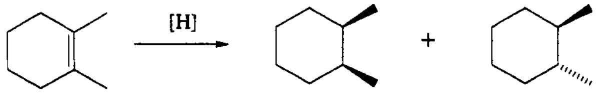

(16)

**(17)** **(18)** **(19)**

| | *Pressure* (atm) | (**18**) (%) | (**19**) (%) |
|---|---|---|---|
| Pt | 1 | 82 | 18 |
| Pt | 300 | 96 | 4 |
| Os | 1 | 98.6 | 1.4 |
| Ir | 1 | 98.9 | 1.1 |

greater competitiveness. This explanation for the apparent antarafacial addition of hydrogen is supported by the fact that the amount of the *trans* isomer (**19**) which is formed over a particular metal correlates with its ability to catalyze the migration of a double bond.[33]

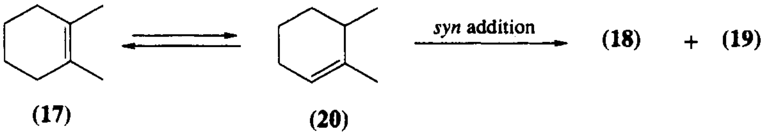

(**17**) (**20**) (17)

### *3.1.3.3.2 Apparent* anti *addition*

*Anti* addition has been observed in compounds which lack an allylic hydrogen that can participate in a 1,3-hydrogen shift as above. With heptane as solvent (25 °C, 1 atm), the hydrogenation of dimethyl bicyclo[2.2.2]oct-2-ene-2,3-dicarboxylate (**21**) yields 7.1% of the *anti* addition product (**24**) over a Pt/C catalyst, but only *syn* addition (**22**) occurs over Rh/C.[50] An acidic medium (small amounts of a strong acid in methanol) has little effect on catalysis by Rh, but greatly increases the fraction of *anti* addition catalyzed by Pd/C, as much as 60% in the presence of *p*-TsOH. Evidence for the participation of the solvent was assumed to indicate a proton transfer to the alkyl intermediate with inversion of configuration at the attached carbon atom.

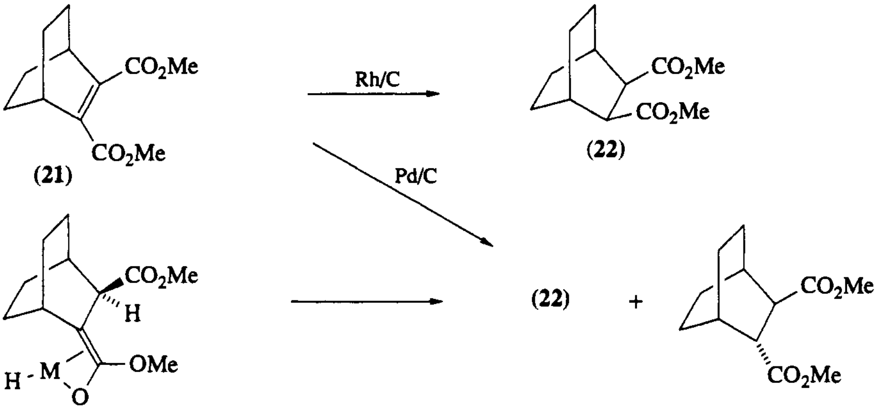

(**21**) (**22**) (**23**) (**24**)

However, the carbonyl of the methoxycarbonyl group may be involved in the formation of an oxallylic intermediate (**23**), which affords a path to both *syn* and *anti* isomers. A similar structure was proposed by Teratani *et al.* to explain the distribution of deuterium in the products of deuteration of 2-methylcyclohexanone catalyzed by palladium; such a structure was not required to explain the results of catalysis by rhodium.[51]

### *3.1.3.3.3 Catalyst hindrance*

If *syn* addition to the opposite faces of the double bond yields diastereomeric compounds, then the orientation is subject to a number of factors. Linstead *et al.* asserted that adsorption on the catalyst occurs

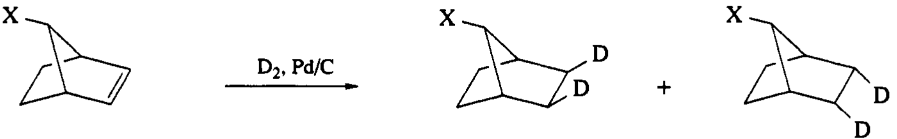

(18)

| | *exo (%)* | *endo (%)* |
|---|---|---|
| (**25**) X = OH | 100 | 0 |
| (**26**) X = $Bu^t$ | 75 | 25 |

so that steric hindrance with the catalyst is minimized, and that hydrogen is transferred to the proximal face of the double bond to yield the principal product.[52] Often, the application of this principle appears straightforward. For example, the addition of deuterium to norbornene yields the *exo*-2,3-dideuteronorbornane on Pd, Pt, or Rh.[32] Substituents at C-7 affect the orientation. An *anti* hydroxy group (**25**) has no effect, but the *t*-butyl group (**26**) exhibits an opposing influence (equation 18). A *syn* *t*-butyl group (**27**) directs 80% *endo* and 20% *exo*, while a *syn*-OH (**28**) directs 60–70% *exo* (equation 19).

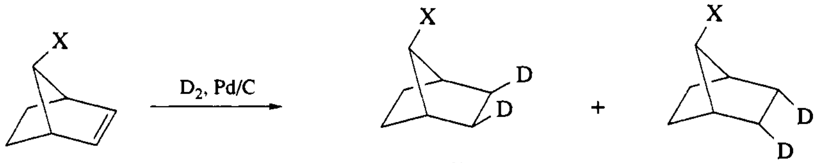

(19)

|  | *exo (%)* | *endo (%)* |
|---|---|---|
| (**27**) X = $Bu^t$ | 20 | 80 |
| (**28**) X = OH | 100 | 0 |

### *3.1.3.3.4 Intramolecular nonbonding interactions*

Adsorption alters the structure of an alkene, and the subsequent hydrogen transfers are accompanied by further changes in the organic moiety.[23] The transition state for adsorption undoubtedly has greater double bond character than the transition state for the formation of the alkyl intermediate, which implies that intramolecular nonbonding interactions will be greater in the latter.

Hydrogenation of the strained hexamethylbicyclo[2.2.0]hexa-2,5-diene (**29**) is highly stereospecific over the platinum metals at 25 °C, 1 atm.[32] Addition of hydrogen from the less-hindered *exo* direction yields the bicyclohexene (**30**) but further addition is very slow (Scheme 4). Raising the pressure (150 atm) results in the *syn, exo* addition of a second mol of $H_2$ over Ru and Rh to form (**31**; >98%). The resistance to addition can be attributed to the increase in nonbonded interactions among the four *endo* methyl groups which accompanies the formation of the alkyl intermediate. These interactions are avoided in the dissociative mechanism of isomerization to the *exo*-methylene intermediate, apparently the path taken on Pt and Ni at 50 °C, where both the *syn, exo*-(**31**) and the *anti* addition product (**32**) are formed.

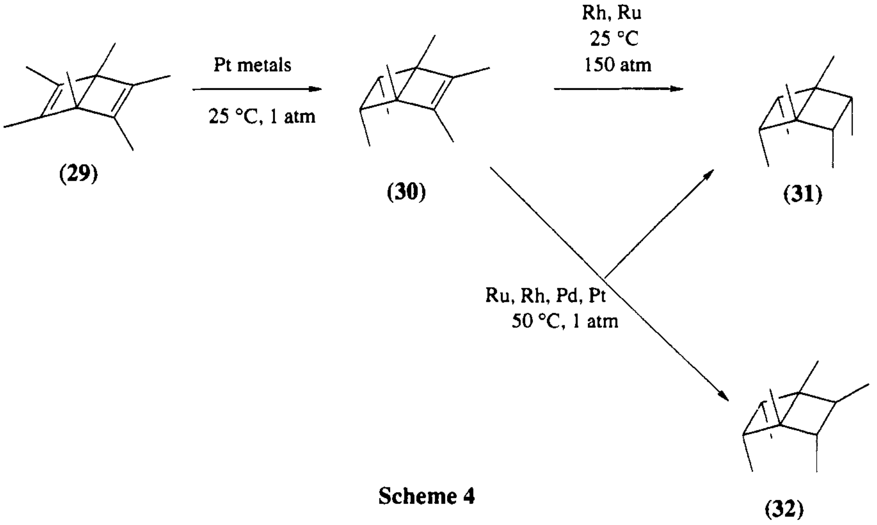

**Scheme 4**

The inability of cholest-8(14)-en-3β-ol (**10**) to be hydrogenated except in the presence of a strong acid has been explained in a similar manner (see Scheme 3).[23,38] The transfer of the first hydrogen to the less-hindered α-face of the double bond is resisted by the large increase in the repulsive nonbonding interactions involving the methyl groups at C-10 and C-13. A Δ-7 unsaturated steroid (**33**) which contains a 9β-H is hydrogenated from the β-side of the molecule to form (**34**; equation 20).[32] Other examples are found in Molnar's review which contains data on the stereochemistry of hydrogenating a large variety of steroids.[32]

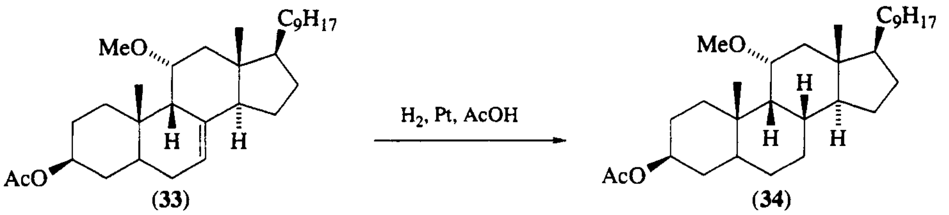

(20)

### *3.1.3.3.5 Application of conformational analysis*

The geometry of the alkene moiety at the transition state for adsorption is assumed to approximate to the most stable conformation of the alkene.[23] This model correctly explains the predominance of the axial–equatorial-disubstituted cyclohexanes in the products from alkyl-substituted methylenecyclohexanes under conditions in which alkene isomerization is a minor factor (see Section 3.1.3.1.2).[40] The effect of an increase in pressure (0.25–150 atm) on the ratio of isomers formed on hydrogenating 4-*t*-butylmethylenecyclohexane (**11**; $PtO_2$, AcOH) is explained as indicating a change in the product-controlling reaction from the formation of the alkyl intermediate to the adsorption of the alkene.[23] Similarly, the effect of increasing the hydrogen pressure on the change in stereoselectivity in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate, which is catalyzed by the chiral cationic complex [(*R*,*R*)-1,2-bis(phenyl, *o*-anisylphosphino)ethane]rhodium(I), has been demonstrated to be due to a change in the rate-limiting reaction, from the oxidative addition of hydrogen to the formation of the alkene rhodium complex.[53]

If the reductive elimination of the alkane is product-controlling, and if all the preceding reactions of the Horiuti–Polanyi mechanism are relatively rapid and reversible, including the desorption of the alkene, then the principal product should be the more stable isomer with substituents in equatorial positions. Palladium appears to conform to the expectations for this mechanism because isomerization is often rapid, and the more stable isomers predominate in the products of addition (see Section 3.1.3.1.2). However, when isomerization is inhibited by added nucleophiles, the less stable stereoisomer is the main saturated product. Gonzo and Boudart concluded from the kinetics of hydrogenation of cyclohexene catalyzed by $Pd/SiO_2$ that the rate-controlling step is the reductive elimination of alkane.[21] If their conclusions apply to the methylenecyclohexanes, then it suggests that the preceding reactions may be comparatively rapid, but not rapid enough to obtain an equilibrium distribution of the alkyl intermediates.

The principles described above may serve as a useful guide for unsaturated hydrocarbons, but substituents other than alkyl groups may involve attractive interactions with a catalytic site. A compound in which a phenyl group is attached to a double bond in a five- or six-membered cycloalkene and is also vicinal to an alkyl substituent yields a larger fraction of the *cis* stereoisomer than is formed from the related dialkylcycloalkene.[32] *Cis* isomers are formed preferentially on Pd and Rh, and are believed to involve structures in which the phenyl group is bound to the surface through its π-electrons.[32]

The Pd-catalyzed hydrogenation of alkyl-substituted 1-alkoxycyclohexenes is stereoselective. The axial/equatorial stereoisomer predominates no matter where the alkyl substituent is located on the ring.[32] Nishimura suggested that the result indicates that the product-controlling step involves the reductive elimination of the most stable alkyl intermediate which is attached to the metal at the carbon atom that bears the alkoxy group (equation 21).

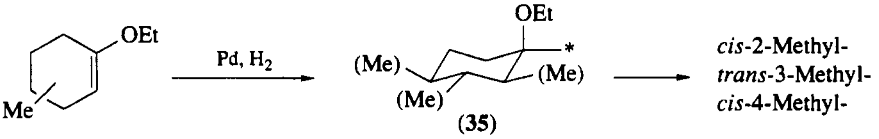

(21)

### 3.1.3.4 Haptophilicity

The location of hydroxy groups relative to the carbon–carbon double bond appears at times to direct the addition to the side of the molecule which presents the greater catalyst hindrance.[32] This has been noted by Dart and Henbest,[54] who termed it an 'anchor effect', and later by Nishimura and Mori for the hydrogenation of several steroid structures.[55]

A hydroxy group situated on an allylic carbon of a five- or a six-membered ring can exhibit an anchoring effect on a Ni catalyst (equation 22); with other metals the group's steric effect is dominant.[32] The hydrogenation of 1-methylcyclohexenes, with an amino group ($NH_2$ or NHMe) in place of the hydroxy group, exhibits stereoselectivities like the corresponding alcohols on a Ni catalyst (equation 23), but the dimethylamino group exerts only a steric effect, as do the amine hydrochlorides.[32]

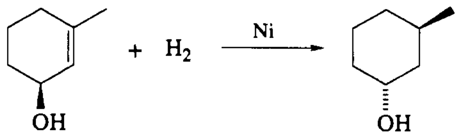

(22)

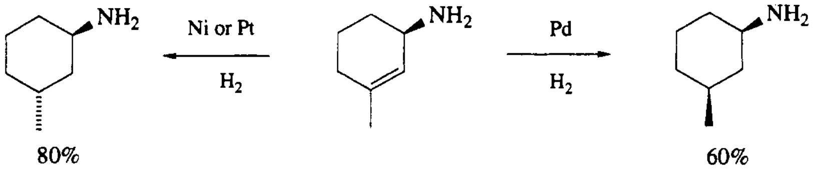

(23)

The name 'haptophilicity' was coined by Thompson to describe this effect of polar groups, which is presumed to arise through the ability of the group to coordinate to the surface of the catalyst.[56] A study of the Pd/C-catalyzed hydrogenation of a series of tetrahydrofluorenes (**36**) to the hexahydro derivatives (**37**) shows that the effect does not correlate well with the basicity of the group, *e.g.* $CH_2OH$ > $CO_2Na$ in the solvent 2-methoxyethanol (equation 24). That the groups also exert a steric effect which may be dominant is recognized, and solvent effects can be important. Other structural elements in complex molecules can influence the stereoselectivity, so it is difficult to predict the relative importance of haptophilicity.[32]

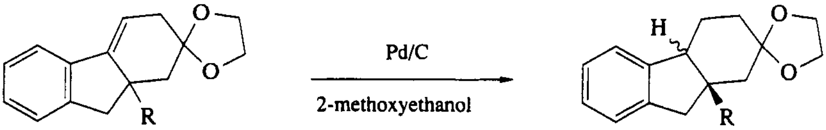

(**36**) (**37**)

(24)

| R | *cis (%)* | *trans (%)* |
|---|---|---|
| $CH_2OH$ | 95 | 5 |
| $CO_2Na$ | 55 | 45 |

## 3.1.4 HYDROGENATION OF C≡C

### 3.1.4.1 Semihydrogenation

The semihydrogenation of the carbon–carbon triple bond is a particularly valuable and frequently used application of heterogeneous catalysis to synthetic chemistry, and is the subject of several recent reviews.[4,6,57–59] Catalysts prepared from palladium and nickel are most commonly used, but the form of the catalyst and the conditions of use affect the results (see Section 3.1.1.2). A polymer-bound palladium catalyst, $PdCl_2$ with poly-4-diphenylphosphinomethylstyrene, is intended to combine the selective properties of mononuclear transition metal complexes with the ease of separating the product from a solid.[17] Whether catalysts of this type will replace the more traditional heterogeneous catalysts remains to be seen.

The hydrogenation of an alkyne can be virtually stopped at the semihydrogenated stage with various preparations of Pd and Ni catalysts by adding to the reaction mixture a nitrogen base, such as quinoline, pyridine or ethylenediamine, that is reversibly adsorbed on the catalyst in competition with the alkyne and the product alkene.[3,4,58,59] Solvents affect the adsorption equilibria. Depending upon the catalyst and the structure of the alkyne, the strength of adsorption of the amine from an alkane solvent may be so great as to slow the hydrogenation to a virtual standstill. The use of a hydrogen-bonding solvent (MeOH, EtOH) will lower the surface coverage by the amine and increase that of the hydrocarbons.[20,22]

High selectivity can be achieved because the alkyne is more strongly bound than the alkene to a metal center and either displaces or blocks the readsorption of any alkene which leaves the surface of the catalyst. Selectivity suffers unless the diffusion of the reactants to the reaction sites is faster than the catalyzed reaction (see Section 3.1.2.1). To optimize selectivity, the catalytic activity can be lowered and/or the diffusion path shortened. The latter accounts for the high selectivity for the conversion of dienes to monoenes of the recently prepared and characterized colloidal palladium catalysts.[60]

Lowering the temperature, –10 to –30 °C, has improved the selectivity of the Lindlar catalyst when used in the presence of quinoline dissolved in pentane, hexane or hexane/THF.[58] However, raising the temperature increases the rate of desorption of the alkene, which appears to account largely for the resulting increase in the selectivity of the heavier Group VIII metals for the hydrogenation of the simple alkynes.[61]

Various materials have been incorporated into the preparation of the catalysts to lower the metal's intrinsic activity.[1–4,59] Lindlar's treatment of palladium deposited on $CaCO_3$ with $Pb(OAc)_2$ lowers its activity, apparently by affecting the morphology of the metal.[62] Unfortunately, Lindlar's recommendation that quinoline be used with his catalyst is sometimes overlooked, which may account for some of the poorer selectivities reported when its use is not mentioned.

The function of quinoline is illustrated by the kinetic study of Steenhoek *et al.* who reported high stereoselectivities using quinoline with $Pd/CaCO_3$ prepared according to Lindlar but omitting the treatment with lead acetate.[1,63] Quinoline is adsorbed reversibly on the reactive sites, competing with the alkyne and the product alkene, but much more effectively with the latter. Accordingly, as the concentration of alkyne diminishes, the quinoline occupies more of the surface as does the alkene but the amount of adsorbed alkene remains too low to affect the composition of the product. Quinoline is unaffected by the usual mild experimental conditions so its concentration remains constant throughout the system, including the boundary layer and pores of the catalyst where it is most needed. Not surprisingly, the stereospecificity of the P-2 nickel catalyst for the hydrogenation of alkynes is improved markedly by the use of ethylenediamine in 2–3 times the molar amount of the catalyst.[1–4,59]

Selectivity also is increased by the use of supported catalysts in which a small amount of metal (~0.1%) is highly dispersed.[4,59] However, this strategy may fail if the reagents are not sufficiently free of adventitious catalyst poisons. A catalyst containing approximately 5% of the metal can act as a sop for such materials.[3] Very small loadings of Pd on wide pore aluminas have been shown to increase the selectivity of converting acetylene to ethylene in a large excess of the latter, an important industrial objective. Carbon monoxide is usually added to the gaseous mixture to improve selectivity, the CO functioning as a reversibly adsorbed competitor, as does quinoline when the fluid phase is a liquid.[64]

### 3.1.4.2 Mechanism

The reaction of $D_2$ with simple alkynes on Group VIII metals indicates that the reaction is more complicated than is implied by equation (25). Which of these complications should be assigned to the readsorption and subsequent reactions of the first-formed alkene or to other transformations of the adsorbed intermediates is unsettled.[57–59,61]

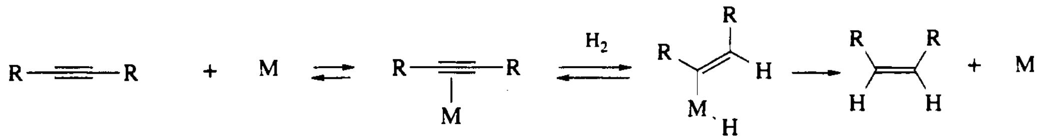

(25)

Reactions of soluble metal complexes, whose mechanisms of catalysis appear to be reasonably well known, can serve as a guide to the main reaction paths followed on heterogeneous catalysts. Mononuclear complexes catalyze *syn* addition of $H_2$ to alkynes to yield initially only *cis* isomers, as in equation (25).[65] More recently, Muetterties and coworkers showed that the dinuclear rhodium hydride complex $\{(\mu\text{-H})Rh[P(OPr^i)_3]_2\}_2$ (**38**) converts alkynes to *trans* isomers as initial products (equation 26).[66] The alkyne addition compound (**39**) was isolated; its structure shows the vinyl group bonded to one rhodium atom by a σ-bond and to the other by a π-bond, while the substituents on the vinyl group are *trans* to one another. This structure resembles ones hypothesized earlier to explain the formation of *trans* isomers and alkanes.[59,61] Hydrogenations of alkynes which are catalyzed by the dinuclear rhodium hydride are much slower than the hydrogenation of an alkene catalyzed by the dinuclear tetrahydride (**40**), which is formed rapidly from (**38**) in the presence of $H_2$ (equation 27).[66]

Additional evidence that reaction paths analogous to the reactions of mononuclear and dinuclear rhodium complexes exist on palladium is shown by the effect of triphenylphosphine on the stereoselectivity of the hydrogenation of di-*t*-butylacetylene (DTBA).[67] In the absence of $PPh_3$ but on a highly dispersed

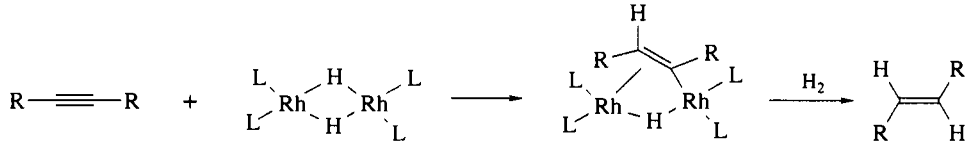

(38) (39) (26)

L = P(OPr$^i$)$_3$

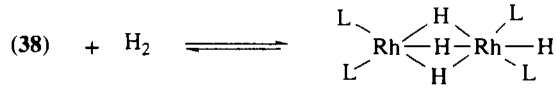

(40) (27)

catalyst, DTBA yields 84% *cis* and 16% *trans* to about 80% conversion when the isomerization of the *cis* to the *trans* isomer comes into play. With a ratio of $PPh_3$ to the exposed Pd atoms of 2.0:1 the reaction is slow but the products are the *cis* and *trans* isomers in a fixed ratio of about 1:2, which does not change during the complete semihydrogenation of the alkyne; the isomerization of *cis*-DTBA to *trans*-DTBA is rapid in the absence of $PPh_3$, but does not occur in this experiment. The result can be understood if the alkyne functions as a monodentate ligand at the site at which the more rapid hydrogenation to *cis*-alkene occurs but as a bidentate ligand at sites which yield *trans* as well as *cis* isomers as initial products. The phosphine, a monodentate ligand, is a less effective competitor at dinuclear sites. The less sterically encumbered 3-hexyne is a much more effective competitor than DTBA for the mononuclear sites and its *cis* stereoselectivity is improved by $PPh_3$, the usual consequence of adding nucleophiles.

The predominance of the *cis* isomers in the products of the Pd- or Ni-catalyzed hydrogenations of disubstituted alkynes suggests that the main reaction path involves the alkyne bound to a single metal atom as in catalysis by the mononuclear complexes $ClRhL_3$ or $HRhL_4$.[28] Surface sites which can furnish the required coordinative unsaturation correspond to the designations $^3M$ and $^2M—^2M$. The latter designation indicates a structural element which also can support a mechanism like that of the dinuclear rhodium complex (**38**).

An alternative mechanism to account for the formation of alkanes is that the alkene which is released from the catalytic site is immediately readsorbed unless the vacated site is filled by some other donor molecule. The process may be likened to the 'cage effect' in the formation of radical pairs in solution. Adsorption of the alkene is exothermic and, accordingly, is likely to have a low energy barrier. The lower selectivity of Os, Ir, and Pt has been attributed to the readsorption of alkene.[61]

### 3.1.4.3 Regio- and Stereo-selectivity

The semihydrogenation of a carbon–carbon triple bond can be accomplished in molecules containing double bonds, whether isolated or conjugated with one another.[57–59] A classical example is the final stage but one in the synthesis of β-carotene.[1] Stereospecificity is high if the triple bond is separated from the double bond by one or more methylene groups as in enyne (**41**; equation 28), but, according to Henrick, conjugated enynes such as enyne (**42**; equation 29) usually yield mixtures over Lindlar catalyst (in petroleum ether with added quinoline).[58]

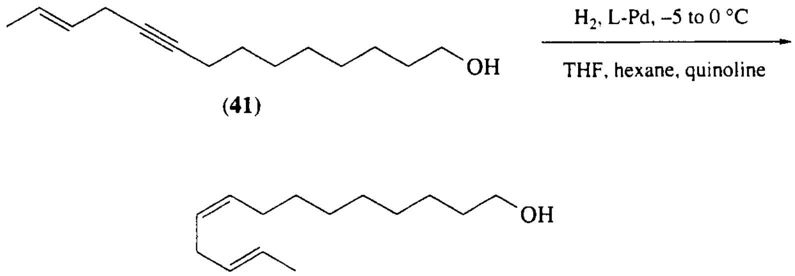

(28)

96%, 98.1% pure

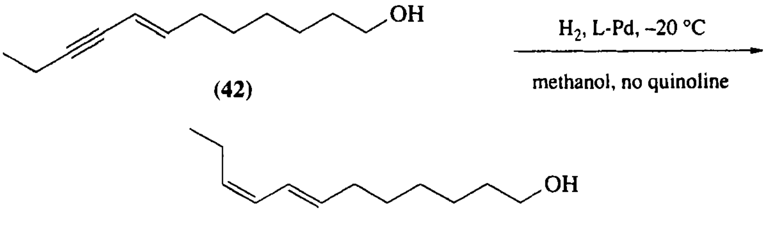

(42)

(29)

92% (7E,9Z), 8% (7E,9E)

A diyne can be semihydrogenated to the enyne if one triple bond is terminal and the other is not, the terminal bond being hydrogenated selectively.[59] If both bonds are nonterminal and unconjugated, hydrogenation to the (Z,Z)-diene is accomplished in high yield.[57–59] Interestingly, the (Z,Z)-octadeca-9,12-dienecarboxylic acid as well as the (Z)-enyne appear as initial products of the hydrogenation of octadeca-9,12-diynecarboxylic acid (Pd/$CaCO_3$, hexane, quinoline at 25 °C, 1 atm).[63]

A triple bond can be semihydrogenated in the presence of a variety of reducible or hydrogenolyzable groups, although G conjugation with the carbonyl group of aldehydes and ketones poses problems of stereoselectivity.[57,59]

## 3.1.5 DIENES AND POLYENES, REGIO- AND STEREO-SELECTIVITY

### 3.1.5.1 Isolated Dienes

Regioselectivity in hydrogenating isolated double bonds is governed mainly by the same structural effects which determine the relative competitive reactivities of monoenes. Thus terminal double bonds are reduced in preference to nonterminal and the less alkyl-substituted to the more. Strain in the double bond alters this preference, for example 5-methylenebicyclo[2.2.1]hept-2-ene is hydrogenated to 2-methylenebicyclo[2.2.1]heptane.[1,3,32] Nickel and palladium catalysts are usually most selective.

1,5-Cyclooctadiene (1,5-COD) is converted selectively to cyclooctene (97.8% on the addition of 1 mol of $H_2$ per mol of diene) over a colloidal Pd supported on poly(N-vinyl-2-pyrrolidone) in methanol.[60] The reaction is in part direct and in part proceeds through isomerization to the 1,4-COD, which is observed, and, presumably, through 1,3-COD, which is not observed. 1,3-COD is the most reactive and selective of the three dienes; at its complete conversion it yields 99.9% cyclooctene. Nishimura discovered that the reduction of 1,5-COD is highly selective over Pd/$CaCO_3$ or Pd black in the presence of phenylacetaldehyde with almost complete suppression of the reduction of cyclooctene.[68] The inhibition is probably due to the decarbonylation of the aldehyde; the adsorbed CO competes with the cyclooctene for surface sites.[69]

### 3.1.5.2 Conjugated Dienes

The hydrogenation of conjugated dienes to monoalkenes poses questions of both regio- and stereoselectivity and is a function of the metal and the conditions.[1–4,32] The distribution of products depends not only on the inherent selectivity of the initial addition process but also on the competition between the diene and the first-formed alkene(s) for the reactive sites. The latter may add hydrogen or be isomerized. If the structure of the diene allows the change, the diene itself may be isomerized. As for alkynes, palladium and nickel catalysts tend to be the most selective to the monoene.

### 3.1.5.3 Conjugated Diene Mechanisms

The monoenes formed on hydrogenating 1,3-alkadienes correspond to 1,2- and 1,4-adducts of hydrogen.[23,32] To account for the main products of the reaction of $D_2$ with 1,3-butadiene over Pd/$Al_2O_3$, 1-butene-3,4-$d_2$ and *trans*-2-butene-1,4-$d_2$, Meyer and Burwell assumed that the diene is adsorbed on the surface in the *trans* conformation.[23,32] Addition of deuterium to a terminal carbon atom forms an allylic species which is a common intermediate for the principal products. Later studies led to more detailed mechanisms designed to explain the observed regio- and stereo-selectivities.[32]

Adsorption may involve one or both double bonds. If only one double bond is involved initially the reaction would follow the sequence in equation (30). This appears to characterize additions on Cu and Au, for example.[32]

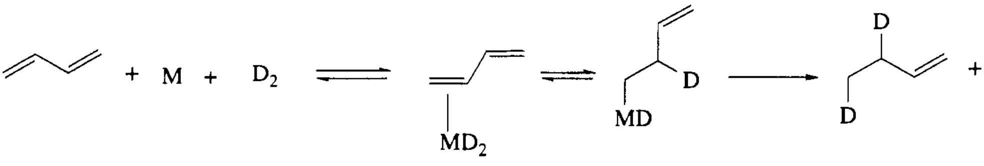

(30)

The σ-allyl intermediate may be transformed to a π-allyl structure with either the *syn* or *anti* configuration (relative to the methynyl hydrogen) as in equation (31), see also Scheme 2. The union with a second hydrogen leads to adsorbed alkenes: 1-butene and either *trans*-2-butene from the *syn*-allyl intermediate or *cis*-2-butene from the *anti* form (Scheme 2). The desorption of the alkene competes with the further addition of hydrogen to form the alkane (equation 32). The reaction of a σ-allyl structure with hydrogen can yield the unbound alkene directly. The selectivity may depend upon the relative importance of these competitive reactions, which are likely to be a function of the metal as well as the reaction conditions.[32]

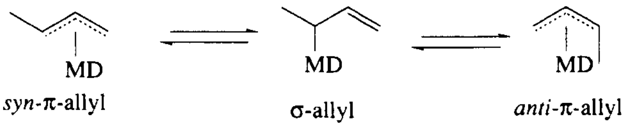

(31)

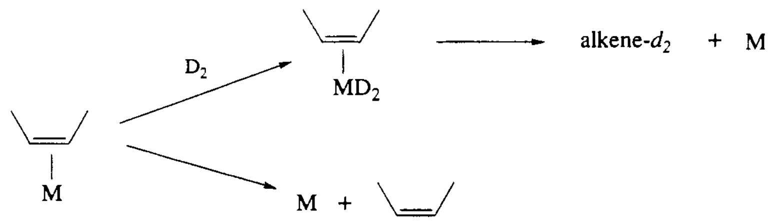

(32)

### 3.1.5.4 Allenes and Cumulenes

Acyclic allenes can be hydrogenated with high selectivities to the monoenes over palladium catalysts.[32] The less-substituted double bond tends to be the more readily reduced. Crombie *et al.* showed that, when allowed to react competitively over Pd/$BaSO_4$, a terminal alkyne is hydrogenated in preference to a terminal allenyl isomer, which in turn competes for the surface more effectively than the nonterminal alkyne, *e.g.* $HC{\equiv}CCH_2CO_2H > H_2C{=}C{=}CHCO_2H > MeC{\equiv}CCO_2H$. They also compared the regio- and stereo-selectivities of Lindlar Pd, 10% Pt/C, 10% Rh/C and a Raney Ni, all used without quinoline, to hydrogenate these compounds and found the palladium catalyst to be most selective to the enoic acid (90–99%) and stereoselective to the *cis*-2-butenoic acids, 96% from tetrolic acid and 93% from allenecarboxylic acid. The catalysts exhibit similar selectivity for the hydrogenation of both alkynes and allenes and, accordingly, one should anticipate that catalysts and conditions which lead to highly selective semihydrogenations of alkynes should be about equally effective for the semihydrogenation of allenes. Quinoline or other bases should provide self-terminating hydrogenations.

*syn*-1,2-Addition appears to be the dominant process for the addition of $H_2$ to allenes. Passing 1,2-butadiene in a stream of $H_2$ over Pd/$Al_2O_3$ produces a mixture of products consisting of 1-butene (40%), *cis*-2-butene (53%) and *trans*-2-butene (7%). The regioselectivity is only moderate; the less-substituted double bond is favored by a ratio of 3:2; however, the ratio *cis-/trans*-2-butene is 7.5:1. This difference was attributed to adsorption, which minimizes steric hindrance with the surface.[23,32] This conclusion was supported later by Crombie *et al.* from their observation of the stereochemistry of hydogenation of a group of systematically substituted allenes under ambient conditions over 5% Pd/$BaSO_4$.[32] Vinyl intermediates were invoked to explain the results (equation 33).

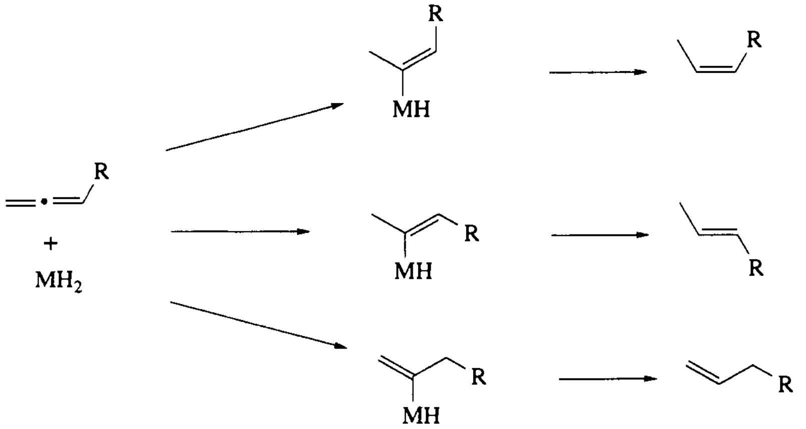

(33)

The hydrogenations of allenes may proceed through allylic intermediates.[32] The distribution of products formed during the reaction of 1,2-butadiene with $D_2$ depends on the particular nickel catalyst used. Reactions on the more selective catalysts (Ni powder, Ni/$SiO_2$) are presumed to proceed mainly *via* vinyl intermediates; reactions on the less selective catalysts (Ni/$Al_2O_3$) proceed *via* allylic intermediates (equation 34). A similar dichotomy of mechanisms is assumed to characterize reactions on Pd.

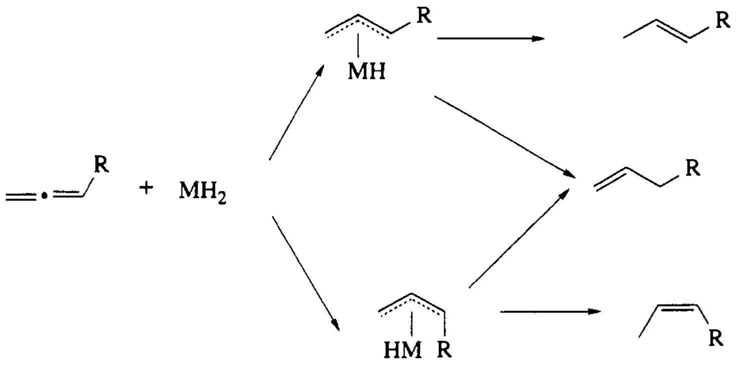

(34)

The palladium-catalyzed hydrogenations of 1,2-cyclononadiene and 1,2-cyclodecadiene form substantial amounts of *trans*- as well as the *cis*-cycloalkene.[23,32] The only unhindered approaches to either double bond of these dienes lead to a *cis* isomer. Because the *trans* is the less stable geometrical isomer in rings with fewer than 11 carbon atoms, its formation implies that an intermediate is produced which is capable of yielding both *cis*- and *trans*-cycloalkenes at comparable rates. Moore proposed that the intermediate has the *syn–anti*-π-allyl structure (**43**; equation 35).

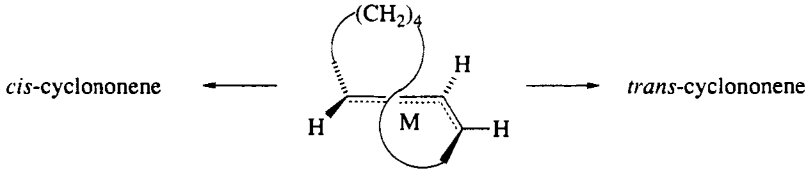

(35)

**(43)**

*syn,anti*-π-allyl

This hypothesis is supported by Lin's studies of the reactions of the $C_9$ to $C_{13}$ 1,2-cycloalkadienes with $HRh(PPh_3)_4$ and $ClRh(PPh_3)_3$,[70] complexes classified by Collman *et al.* as monohydride and dihydride hydrogenation catalysts, respectively.[28] The monohydride complex unites with allenes to form π-allyl compounds which have characteristic NMR spectra in solution. 1,2-Cyclononadiene yields almost the same proportion of *cis*- and *trans*-cyclononene with either Pd/$Al_2O_3$ or $HRh(PPh_3)_4$ as catalyst; little of the *trans* isomer is formed when $ClRh(PPh_3)_3$ is used. The X-ray crystal structure of the complex formed from the reaction of $ClRh(PPh_3)_3$ with 1,2-cyclononadiene shows that only one double bond of the diene is coordinated with rhodium.[71]

The hydrogenation of *cis*-1,4-diphenyl-1,2,3-butatriene (**44**) over Lindlar's Pd yields mainly the (*Z*,*Z*)-diene (**45**), accompanied by a little of the (*E*,*E*)-diene (equation 36).[3,32] Lower stereoselectivity accompanies the hydrogenation of 1,6-diindenylene-2,3,4-hexatriene in which the cumulene unit is conjugated with double bonds.[3] Recall that the stereoselectivity of the hydrogenation of a triple bond is lowered when it is conjugated with a double bond. Possibly the intermediate formed has a π-allylic structure which can account for the various products, just as allylic intermediates can account for the products of hydrogenating conjugated dienes on Ni and Pd catalysts.[32]

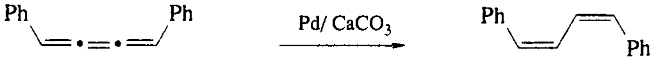

**(44)** **(45)** (36)

## 3.1.6 AROMATIC HYDROCARBONS

The hydrogenation of aromatic hydrocarbons is catalyzed by various transition metal oxides and sulfides, but for a laboratory preparation the catalyst usually is selected from Ni, Ru, Rh, Pd or Pt.[3,4] Nickel catalysts require elevated temperatures and pressures, which dictate the use of a high pressure autoclave. Rhodium, platinum and ruthenium are effective under mild conditions, rhodium being the most active. Rhodium and ruthenium are used when the hydrogenolysis of carbon–oxygen or carbon–nitrogen bonds is to be avoided. Under mild conditions, the hydrogenation of mononuclear aromatic hydrocarbons proceeds slowly over palladium, which suggests its use when the aromatic ring is to be retained.

### 3.1.6.1 Structure–Reactivity

The rate of hydrogenation of the benzene ring is lowered by alkyl substiuents, although with two or more, the arrangement of the groups affects the rate.[41] Smith *et al.* determined the individual and competitive rates of all the methyl-substituted benzenes on Pt and Rh catalysts in the solvent acetic acid, and found that not only the individual rates ($k_A$) but also the derived relative equilibrium constants ($K_{AB}$) decrease with increasing methyl substitution.[41,72] Within groups of isomers, $k_A$ and $K_{AB}$ change in opposite directions. For the xylenes, the rate constants ($k_A$) increase but the $K_{AB}$ decrease in the order 1,2- > 1,3- > 1,4-. A similar relationship applies to the trimethylbenzenes; the order of increasing rate is 1,2,3- < 1,2,4- < 1,3,5-, while $K_{AB}$ decreases in the same order. The more limited group of compounds studied on Ni at 170 °C by Wauquier and Jungers shows the same relationships.[22]

That the kinetically derived relative adsorption constants, $K_{AB}$, decrease with the numbers of alkyl substituents is surprising because alkyl substituents increase the basicity of the benzene ring and stabilize $\eta^6$-arene transition metal complexes.[28] The directly measured adsorption coefficients of benzene, toluene, *p*-xylene and mesitylene on a cobalt catalyst at 89 °C do increase with the number of methyl groups and the rates of hydrogenation decrease in that order.[41] A consensus regarding the significance of the kinetically determined adsorption constants has not been reached.[41]

Another kinetic method of determining relative adsorption constants does show that toluene is adsorbed more strongly than benzene on the platinum metals.[73] The method determines the effect of the partial pressure of toluene on the rate of hydrogenation of benzene. With the assumption that adsorption is reversible, the ratio of adsorption coefficients, $b_T/b_B$, is evaluated by the use of equation (37) where $V^o_B$ and $V_{B(T)}$ represent the rate of hydrogenation of benzene in the absence of toluene and in its presence at stated partial pressures of toluene ($P_T$) and benzene ($P_B$). This method avoids the determination of the relative individual rate constants that is required by the method of Wauquier and Jungers.[22] Xylene inhibits the hydrogenation of alkenes on Pd more effectively than does benzene, which is consistent with the effect of alkyl groups on the basicity of benzene.[21]

$$V^o_B/V_{B(T)} = 1 + (b_T/b_B)(P_T/P_B) \qquad (37)$$

The importance of steric effects on the individual rates of arene hydrogenation is not well defined, but 1,4-di-*t*-butylbenzene is more reactive than its 1,3-isomer or *t*-butylbenzene; competitive experiments show that, of the three, it has the smallest apparent adsorption constant.[74] It is not surprising that in hydrogenations of isomeric arenes, which are zero order in arene, the more strongly adsorbed arene reacts more slowly. The orientation of the substituents in the di-*t*-butylbenzenes not only affects their relative reactivity but also the proportions of the unsaturated intermediates which are formed.[74]

### 3.1.6.2 Intermediates and Mechanism

*A priori*, the mechanism of hydrogenation of benzene may be represented as a series of hydrogen transfers from the catalyst to the adsorbed benzene and the adsorbed intermediates (Scheme 5).[11,74] The often observed first order reaction in $H_2$ suggests that the addition of the second hydrogen atom is the more difficult step, indicating that the largest energy barrier lies between adsorbed arene and adsorbed diene. However, no cyclohexadienes have been detected as intermediates.

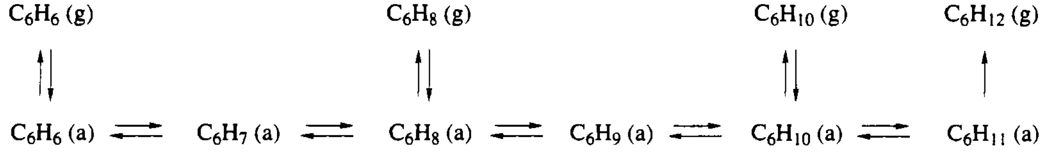

**Scheme 5**

A 1,4-cyclohexadienic structure (**46**) was proposed for the octahydroparacyclophane formed in the hydrogenation ($PtO_2$) of paracyclophane (**47**), whose unusual properties provided a degree of plausibility to the claim (equation 38).[1,75] Actually, four isomeric dienes, none of which has the first postulated structure, are formed.[76] The possible structures have one trisubstituted double bond in each six-carbon cycle, as in formula (**48**). Dienes are more reactive than the related arenes or cyclohexenes and apparently are more tightly bound to a catalytic site.[77,78]

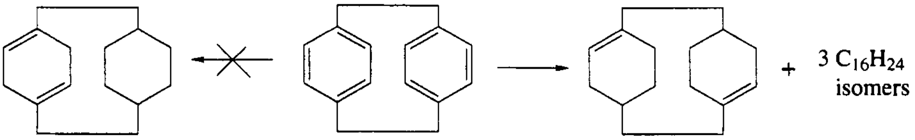

**(46)** **(47)** **(48)** (38)

Intermediate cyclohexene(s) can be detected in amounts which depend upon the structure of the aromatic compound, the catalyst and the reaction conditions, all being variables which are likely to affect the relative rates of the processes indicated in Scheme 5.[1,23,75] Strain in the arene, which is released in part upon adsorption or the addition of the first hydrogen atom, increases the competitiveness of the arene relative to the derived cyclohexene, as illustrated in the hydrogenation of paracyclophane.[76] The strained 1,2-di-*t*-butylbenzene yields 1,6-di-*t*-butylcyclohexene whose maximum concentration depends upon the catalyst and the solvent: 45% (Rh/C, AcOH), 30% (Rh/C, EtOH), and 6% (Pt/C, EtOH).[1] The reactivity of the derived cyclohexenes also are lowered by the bulky substituents, presumably a steric effect. Apparently this pathway competes with one that does not involve the desorbed cyclohexene, a path which is indicated by the stereochemistry of the reduction.[74]

Ruthenium was recognized early to be the catalyst which produced the largest amount of the intermediate cyclohexene from the xylenes, rhodium and platinum giving decreasing amounts.[23] The importance of water in maximizing the yield of cyclohexene using ruthenium as catalyst was demonstrated by Don and Scholten.[11] A recent patent application claims yields of 48% cyclohexene at 60% conversion of the benzene.[79]

### 3.1.6.3 Stereochemistry

Although *cis* isomers are the principal products of hydrogenating disubstituted benzenes under mild conditions, *trans* isomers are also formed. The reaction is kinetically controlled at near ambient conditions but *cis–trans* isomerization will occur at higher temperatures where the reversibility of the hydrogen addition becomes significant.

A comparison of the proportion of the saturated stereoisomers, formed under the same conditions ($PtO_2$, AcOH) from the isomeric xylenes and the derived dimethylcyclohexenes, leads to the proposal that the reaction proceeds through the desorbed cyclohexenes.[23] Low concentrations of the intermediate cyclohexenes were detected later. The effect of the metal on the stereoselectivity of hydrogenating *o*-xylene follows closely the effect of the metal on the hydrogenation of 1,2- and 1,6-dimethylcyclohexene.[49] The highest selectivity for the conversion of *o*-xylene to the *cis* isomer is given by iridium

(99.2%), the least by palladium (57.7%); the percent given by 1,2-dimethylcyclohexene on the two catalysts are 99.2 and 25.9%, the 1,6-isomer gives 89.0 and 25.6%, respectively.

That desorbed cyclohexenes give rise to the *trans*-disubstituted cyclohexanes is most clearly illustrated by van Bekkum and coworkers' hydrogenation of *t*-butyl-substituted benzenes.[1] For example, the hydrogenation of 2-*t*-butylbenzoic acid over Rh/C in ethanol at 22 °C and 1 atm yields *cis*-2-*t*-butylcyclohexanecarboxylic acid and 6-*t*-butylcyclohexenecarboxylic acid at a fixed ratio until about 80% conversion, at which point the hydrogenation of the cyclohexene begins and yields both *cis*- and *trans*-2-t-butylcyclohexanecarboxylic acid. 1,2-Di-*t*-butylbenzene and 1,3,5-tri-*t*-butylbenzene exhibit similar properties.[1]

The effect of pressure on the stereochemistry of hydrogenating 1,4-di-*t*-butylbenzene on rhodium also indicates a competition between the addition of six hydrogen atoms during a single period of residence on the catalyst and a path involving desorbed cycloalkenes.[74] Accessible high pressures, which are expected to increase the rate of addition of hydrogen, are unable to cause the xylenes or 1,4-di-*t*-butylbenzene to yield only the *cis* isomers. Whether an increase in pressure can improve the stereoselectivity of the iridium- and osmium-catalyzed hydrogenation of *m*- and *p*-xylene has not been tested. Small amounts of dimethylcyclohexenes are detected in the solutions (26 °C, 1 atm, Bu$^t$OH), which indicates the existence of a path through desorbed intermediates.[49]

## 3.1.7 POLYCYCLIC AROMATIC HYDROCARBONS

### 3.1.7.1 Regioselectivity

A considerable degree of control of the regioselective hydrogenation of polycyclic aromatic hydrocarbons has been achieved through the choice of catalyst and optimized conditions. The review by Nishimura and Takagi and Rylander's monographs furnish many examples and references.[3,4,6]

Of the platinum metals, palladium, which is least able to catalyze the hydrogenation of the benzene ring under mild conditions, is the most selective for converting biphenyl to phenylcyclohexane or naphthalene to tetralin. With alkyl substituents at the 2-position, the unsubstituted ring is reduced preferentially. However, the regioselectivity of reducing a 1-alkylnaphthalene depends upon the size of the alkyl group; a methyl substituent favors the unsubstituted ring, the *t*-butyl group directs to the substituted ring (equation 39).[1,75] This structural effect is attributed to the release of *peri* strain in the critical transition state, an effect which is magnified in the enhanced reactivity of the 1,8-naphthalenes.[1,4]

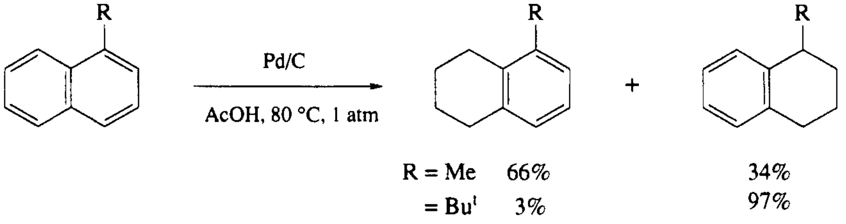

(39)

Anthracene and phenanthrene can be converted to their 9,10-dihydroderivatives in high yield over copper chromite at 100–150 °C and 150 atm. The change can be accomplished under milder conditions using platinum metal catalysts, Rh/Al$_2$O$_3$ with anthracene and Pd/C with phenanthrene.[3,4,6]

Using palladium as catalyst, the region of minimal bond delocalization is reduced preferentially, whereas platinum tends to catalyze the reduction of terminal rings (equation 40).[3,4,6]

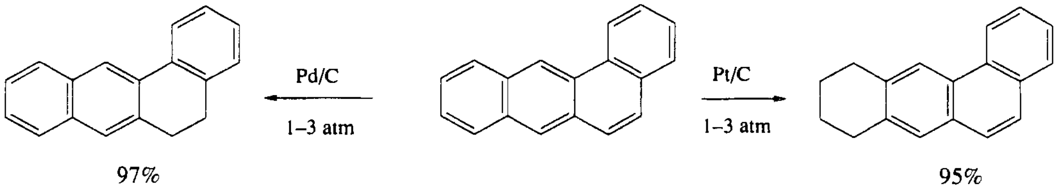

(40)

### 3.1.7.2 Stereoselectivity

The stereochemistry of hydrogenating naphthalene is described in Weitkamp's review.[80] Mainly *cis*-decalin is formed when the hydrogenation is catalyzed by platinum metals under relatively mild conditions; ruthenium is the most stereoselective (95–98% *cis*) while palladium is the least. The *trans*-decalin which is formed appears to result from the reduction of octalin intermediates *via* a mechanism similar to that which accounts for the formation of *trans*-dialkylcyclohexanes from dialkylbenzenes.

The *cis*-stereoselectivity and the rate of hydrogenation (Pd/C) of the substituted ring in 1,4-dialkylnaphthalenes increase with the bulk of the substituents; equal amounts of the *cis*- and *trans*-tetralins form from 1,4-diethylnaphthalene, while the di-*t*-butylnaphthalene yields almost exclusively the *cis* isomer (99%).[1,3,75] A similar affect of structure on rate and stereoselectivity is observed in the hydrogenations ($Rh/Al_2O_3$) of 1,4-dialkylbenzenes.[74]

The hydrogenation of phenanthrene proceeds through aromatic intermediates to the perhydrophenanthrene.[75] Under mild conditions the product has the *syn-cis-syn* configuration, but more vigorous conditions yield products of lower selectivity. Similar results can be expected for the hydrogenation of more complex polycyclic aromatic hydrocarbons.[3,6,75]

## 3.1.8 CHEMOSELECTIVITY

### 3.1.8.1 Nonconjugated Functional Groups

Carbon–carbon unsaturation can be hydrogenated selectively in compounds which also contain other reducible or hydrogenolyzeable functional groups.[1,3,4,32,59] Apparently this reflects the strong interaction of the metal with carbon–carbon double and triple bonds.

Aliphatic nonconjugated nitroalkenes can be reduced to the saturated nitro compounds without difficulty using platinum or palladium catalysts.[3,4,6] A similarly situated alkynic group too is reduced selectively using Pd.

Unconjugated unsaturated aldehydes and ketones can be reduced without affecting the carbonyl group, particularly with a Pd catalyst; Ni and Pt have been used, but the reduction must be terminated after the addition of 1 equiv. of hydrogen.[3,4,6,32] The nitrile group also can survive the reduction of carbon–carbon unsaturation in the same molecule.

The hydrogenolysis of allyl–oxygen bonds can be avoided by the use of Rh or Ru catalysts, and modified Pt catalysts have been effective.[3] Epoxides also survive conditions used to hydrogenate carbon–carbon double and triple bonds.

### 3.1.8.2 Conjugated Functional Groups

Generally, α,β-unsaturated carbonyl groups are more stable towards hydrogenation than their unconjugated isomers; however, the conjugated alkenic double bond can be hydrogenated in preference to an isolated one.[3–6] This reflects the effect of an electron-attracting substituent on stabilizing the association of an alkene with a transition metal.[46] Palladium catalysts are most useful, but selectivity is enhanced by the choice of solvent or the use of added base. Many examples are found in the reviews by Molnar and by Augustine.[32,81]

Vinyl and allyl groups can be saturated but hydrogenolysis and other undesired reactions may occur. The choice of metal as a catalyst and the solvent affects the results of hydrogenating substituted cyclohexenyl ethers.[3,32] Besides the saturated ether, the cyclohexanone and its diethyl acetal, the cyclohexanol and cyclohexane are formed in ethanol in proportions which vary with the metal. The relative rates of the competing reactions depend on both solvent and metal and yields exceeding 96% of the saturated ether are reported for catalysis by Pd in ethanol, and Ru or Rh in *t*-butyl alcohol (see Section 3.1.3.3.5).

The enamine (**49**) can be hydrogenated to the tertiary amine; Pd gives the highest yield (99%), the product having the *trans* configuration (equation 41).[4] The yield is lower with $PtO_2$ (in ethanol, 2-propanol or ethyl acetate); however, the *cis* isomer predominates (92–98%). The stereochemical result on Pd suggests that the product-controlling reaction is the union of hydrogen with the most stable alkyl intermediate, as proposed for the Pd-catalyzed hydrogenation of vinyl ethers (see Section 3.1.3.3.5).[32] The association constants measured by Tolman show that a vinyl ether is more weakly bound to a metal than is an alkene and one may infer that the vinyl amino group would affect the metal–alkene π-bond in the same way (see Section 3.1.3.2). The weakening of the π-bond facilitates the equilibration of the alkyl intermediates.

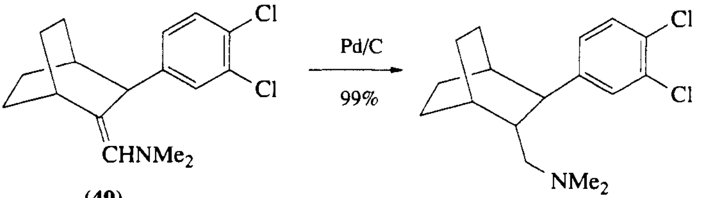

**(49)**

100% *trans*

(41)

## 3.1.9 CATALYTIC TRANSFER HYDROGENATION

The possibility that organic molecules of relatively low oxidation potential could serve as a source of hydrogen which could be transferred catalytically to unsaturated compounds under mild conditions was proposed by Braude, Linstead *et al.* in 1952, and the scope of the reaction was subsequently explored.[82] Hydrogen transfer between like molecules, as in the disproportionation of cyclohexene on Pt and Pd to form cyclohexane and benzene, had been discovered much earlier by Zelinskii *et al.* Cyclohexadienes disproportionate more rapidly on these catalysts forming equimolar amounts of cyclohexane and benzene. Indeed cyclohexene and cyclohexadiene, or their readily available alkyl derivatives, are among the most frequently cited hydrogen donors for catalytic transfer hydrogenations.[82,83] A considerable body of work has appeared since the review by Brieger and Nestrick, and the improvements in technique, including greater catalyst loadings and different hydrogen donors, have increased the utility of the process.[83]

Palladium in the form of Pd black or Pd/C is the most effective catalyst. Although Raney nickel has been used, there is doubt that it serves only as a hydrogen transfer catalyst because it contains a considerable amount of adsorbed hydrogen. Platinum and rhodium have been found to be ineffective. Both alkenes and alkynes have been hydrogenated and *syn* addition to 1,2-diphenylacetylene has been demonstrated.[59,83]

Regioselectivity in the catalytic transfer hydrogenation of dimethyl bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate is a function of the hydrogen donor.[4] Using cyclohexene or 1,3-cyclohexadiene as donor, addition to the unsubstituted double bond predominates, forming dimethyl bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate while, with 1-methylcyclohexene or α-terpinene as donor, *endo*-dimethyl[2.2.1]hepta-2-ene-5,6-dicarboxylate is the main product. Alkyl substitution in the donor slows the hydrogen transfer and allows a redistribution of the adsorbed diene species to the favored 2,3-double bond, a structure which is stabilized by the electron-withdrawing methoxycarbonyl groups (see Section 3.1.3.2.3).

Hydrogen transfer reductions are facilitated by the use of a simple column reactor containing a small amount of palladium catalyst in the form of palladium black and with formic acid as the hydrogen donor.[84] Transfer hydrogenation is accomplished by allowing a solution of the starting material, in an appropriate solvent plus 1% formic acid, to pass slowly through the column. The optimal flow rate is easily adjusted, the effluent collected and the solvent evaporated. A single pass is sufficient to complete the addition of 1 mol of hydrogen to cinnamic acid, coumarin, oleic acid, fumaric acid or cholesterol.

Discussions of the mechanisms of these reactions usually consider whether the hydrogen transfers involve a catalyst-mediated donor–acceptor complex or proceed according to mechanisms which are part of the hydrogenation–dehydrogenation reactions which are observed at low hydrogen pressures.[82,83] Both donor and acceptor molecules compete for adsorption on the catalyst and their transformations are affected by the amount of adsorbed hydrogen which is present. A recent study of the disproportionation of specifically deuterated 1,4-cyclohexadienes catalyzed by colloidal nickel shows that it is a multistep reaction.[85] The dehydrogenation of the diene is strictly *cis* selective but the hydrogen loses its molecular identity before the hydrogen addition step. The authors conclude that the direct H-transfer between two molecules of 1,4-cyclohexadiene is excluded.

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# 3.2

# Homogeneous Catalytic Hydrogenation of $C{=}C$ and $C{\equiv}C$

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## 3.2.1 HYDROGENATION OF NONCONJUGATED $C{=}C$ BONDS

Chlorotris(triphenylphosphine)rhodium(I), $[RhCl(PPh_3)_3]$, was reported independently by three groups in 1965,[2–4] and its application to catalytic homogeneous hydrogenation has been studied intensively by Wilkinson's group.[5] The Wilkinson catalyst is now the most widely used for hydrogenation of a variety of unsaturated substrates, and several extensive reviews of this catalyst have been published.[1]

With this catalyst alkenes such as 1-hexene, 2-pentene, 3-hexene, cyclohexene, 2,3-dimethyl-2-butene, styrene, allyl alcohol, allyl cyanide and acrylamide, are reduced under mild conditions. Rates of hydrogenation of some representative alkenes catalyzed by [RhCl(PPh$_3$)$_3$] are listed in Tables 1 and 2. The addition of triphenylphosphine decreases the rate of hydrogenation.[6] Small amounts of impurities such as oxygen and hydroperoxides in catalytic systems sometimes increase the rate of hydrogenation,[7,8] but large quantities of impurities cause deposition of rhodium metal.[9,10] The steric effect has been studied.[11] The less-substituted double bonds of unconjugated alkadienes are usually reduced selectively.

**Table 1** Rate Constants for the Hydrogenation of Alkenes[5b] (1.25 mM Solution of [RhCl(PPh$_3$)$_3$] in Benzene)

| *Alkene* | $k'_{298}$ ($\times 10^2$)[a] (l mol$^{-1}$ s$^{-1}$) |
|---|---|
| Cyclopentene | 34.3 |
| Cyclohexene | 31.6 |
| Cycloheptene | 21.8 |
| Hex-l-ene | 29.1 |
| Dodec-l-ene | 34.3 |
| 1-Methylcyclohexene | 0.6 |
| *cis*-Pent-2-ene | 23.2 |
| 2-Methylpent-1-ene | 26.6 |
| Styrene | 93.0 |
| *cis*-4-Methylpent-2-ene | 9.9 |
| *cis*-4-Methylpent-2-ene[b] | 12.6 |
| *trans*-4-Methylpent-2-ene | 1.8 |
| *trans*-4-Methylpent-2-ene[b] | 1.9 |

[a] Errors in the rate constants ($k'$ > *ca.* 20 x $10^{-2}$ M$^{-1}$ s$^{-1}$) do not exceed ±5%; errors on low $k'$ values are somewhat greater.
[b] Deuteriation by $D_2$.

**Table 2** Rate of Hydrogen Consumption (mmol min$^{-1}$) at 0.66 atm of Hydrogen Partial Pressure for Unsaturated Substrates under Standard Conditions; Catalyst [RhCl(PPh$_3$)$_3$], 1.25 mM in Benzene, Substrate Concentration 1.25 M[5b]

| *Substrate*[a] | *Rate* (mmol min$^{-1}$) | *Substrate* | *Rate* (mmol min$^{-1}$) |
|---|---|---|---|
| Acenaphthylene | 1.76 ± 0.11 | 3-Ethylpent-2-ene | 0.02 ± (0.002) |
| Acrylamide | 0.22 ± 0.01 | Hexa-1,5-diene | 0.21 ± 0.01 |
| Allyl alcohol | 3.02 ± 0.18 | *trans*-Hex-3-ene | 0.05 ± (0.005) |
| Allyl cyanide | 0.45 ± 0.03 | Cyclohexa-1,3-diene | 0.13 ± 0.01 |
| Octa-1,7-diene | 0.65 ± 0.04 | Penta-1,3-diene | 0.06 ± (0.004) |
| Cyclohexene | 0.80 ± 0.05 | 2,3-Dimethylbut-2-ene | 0.01 ± (0.001) |
| Styrene | 2.56 ± 0.15 | 4-Fluorostyrene | 3.70 ± 0.26 |
|  |  | 4-Methoxystyrene | 3.22 ± 0.22 |

[a] The following were either not reduced or were reduced extremely slowly (<0.01 mmol min$^{-1}$) under the standard conditions: acrylic acid, allylamine, allyl chloride, bicyclo[2.2.1]hepta-2,5-diene, cyclohexa-1,4-diene, maleic anhydride and tetrachloroethylene.

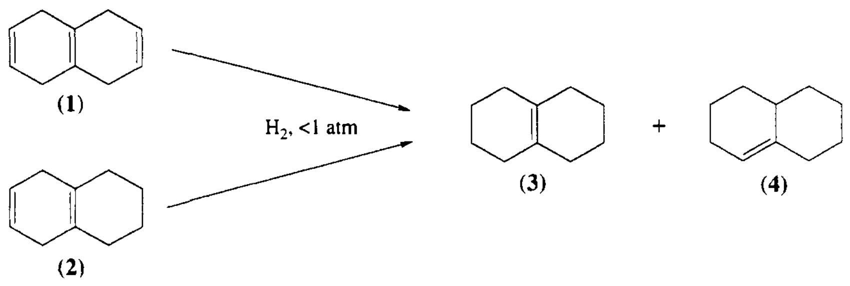

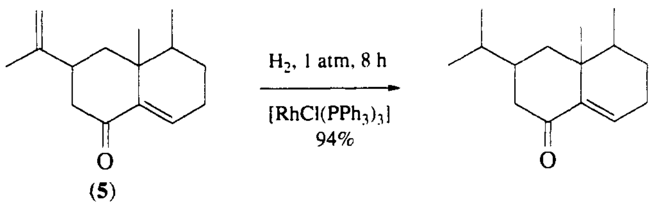

Both isotetralin (**1**) and 1,4-dihydrotetralin (**2**) are reduced in the presence of the catalyst to an 80:20 mixture of 9,10-octaline (**3**) and 1,9-octaline (**4**).[12] The sterically less-hindered double bond of eremophilone (**5**) is preferentially hydrogenated.[13]

Labeling experiments show that the addition of hydrogen to C═C bonds proceeds with *syn* stereochemistry.[5,14,15] Thus a *trans*-alkene is hydrogenated to give the *threo* product,[15] and deuteration has been shown to afford *cis* isomers.[14,16,17]

The variation of the halogen and the other ligands coordinated to rhodium exerts important effects on the activity and selectivity. $[RhBr(PPh_3)_3]$ and $[RhI(PPh_3)_3]$ show higher catalytic activities in hydrogenation of terminal alkenes than $[RhCl(PPh_3)_3]$, and lower rates of isomerization.[18] Other rhodium–phosphine complexes, such as $[Rh(NO)(PPh_3)_3]$,[19,20] $[Rh(OCOR)(PPh_3)_3]$ (R = alkyl, aryl, substituted alkyl),[21] $[RhCl(PR_3)_3]$ (R = substituted phenyl, alkyl),[22–24] and complexes having aminophosphine,[25] triphenylarsine, or triphenylstibine,[26] also catalyze hydrogenation of alkenes.

Halogen can be replaced by hydride to produce a catalyst, $[RhH(CO)(PPh_3)_3]$,[27,28] which catalyzes the selective hydrogenation of 1-alkenes. 1-Hexene gives hexane under mild conditions, while cyclohexene and *cis*-4-methyl-2-pentene are not reduced. The activity of $[RhH(CO)(PPh_3)_3]$ decreases with time,[28] but the catalyst can be reactivated by UV irradiation.[29] The hydridorhodium(I) complex [RhH(5-phenyl-5*H*-dibenzophosphole)$_4$], catalyzes rapid hydrogenation of terminal alkenes under mild conditions.[30,31] Internal alkenes, conjugated alkenes, and alkynes can be differentiated. The rhodium hydride complex derived from the reaction of $[RhCl(PPh_3)_3]$, $Cs^+$(7-butenyl-7,8-carborane)$^-$, and trimethylvinylsilane in THF, has been used for the reduction of alkenes,[32] as have $[RhCl_3(pyridine)_3]$,[33] $[Rh_2HCl_3(C_5Me_5)_2]$,[34] and $[RhHCl_2(PR_3)_2]$.[35–37] A water soluble, air stable complex, $[RhCl(TPPTS)_3]$ (TPPTS = triphenylphosphine *m*-trisulfonate), has been used for hydrogenation of linear and cyclic alkenes and polyenes with or without functional groups under very mild reaction conditions. Selective hydrogenations are achieved by controlling the volume of hydrogen absorbed. For example, (**6**) is selectively converted to (**7**) in 32 h or to (**8**) in 76 h.[38] $[Rh(1,5\text{-}COD)(MeCN)_2]BF_4$ is an efficient catalyst for the hydrogenation of 1-hexene,[39] while isomerization occurs with the analogous iridium complexes.[40]

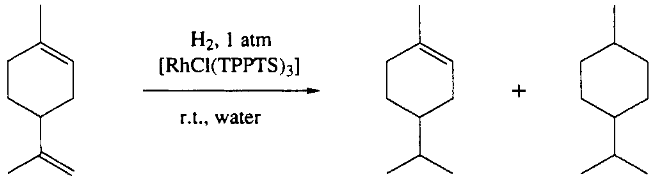

(**6**) (**7**) (**8**)

Chelating bidentate ligands affect the hydrogenation, and especially chiral ligands have been used for asymmetric hydrogenation (see Section 3.2.5). The complex $[RhCl(PPh_3)(dppcb)]$ (dppcb = 1,2-bis(diphenylphosphino)-1,2-dicarbadodecaborane) is an effective catalyst only at higher temperatures.[41]

Bis(diphenylphosphino)methane (dppm) upon coordination to rhodium forms dinuclear complexes. Some of them exhibit high activity for hydrogenation of alkenes, as has been shown with $[Rh_2(\mu\text{-}Cl)(CO)_2(dppm)_2]^+$ in methanol.[42] Tridentate phosphine ligands also form dinuclear complexes such as $[Rh_2(COD)\{CH(PPh_2)_3\}](CF_3SO_3)_2\cdot$acetone, which reacts with hydrogen in acetone to liberate cyclooctane, and on addition of 1-hexene catalytic hydrogenation proceeds (25 °C, 1 atm $H_2$).[43]

Cationic rhodium(I) complexes, such as $[RhCl(Py)_2(DMF)(BH_4)]Cl$,[44,45] $[Rh(diene)(PPh_3)_2]^+$, $[RhH_2(PPh_3)_2L_2]^+$ (L = solvent),[46–50] $[Rh(CH_2{=}CHCN)(CO)(PPh_3)_2]ClO_4$[51] and $[Rh(\eta^4\text{-}C_8H_{10})(\eta^5\text{-}C_8H_{10})]^+$,[52] also catalyze alkene hydrogenation.

Phosphine-substituted rhodium carbonyl clusters, such as $[Rh_6(CO)_{10}L_6]$ ($L_6 = (PPh_3)_6$, $[P(OMe)_3]_6$, or $[(-)\text{-DIOP}]_3$), are good catalyst precursors for cyclohexene hydrogenation.[53]

The pentamethylcyclopentadienyl (Cp*) derivatives of rhodium[54] such as $[(RhCp^*)_2(OH)_3]Cl$[54d] and the catalyst system prepared from $[(RhCp^*)_2(\mu\text{-}Cl)_2]$[54c] and pyrazole-type ligands,[55] are used for alkene hydrogenation in 2-propanol.

The complexes $[RuCl_2(PPh_3)_3]$ and $[RuHCl(PPh_3)_3]$, when used in the presence of methanol, ethanol or triethylamine, serve as efficient catalysts for the hydrogenation of 1-alkenes.[1g,56–59] At ambient temperatures rates of hydrogenation of internal alkenes and cycloalkenes and isomerization of alkenes are very low.[60] Thus, the selective reduction of terminal alkenes has been attained (equation 1).[61] When a solution of $[RuCl_2(PPh_3)_3]$ or $[RuHCl(PPh_3)_3]$ is exposed to oxygen, green complexes of triphenylphosphine oxide are formed and the activity of the catalyst is lost.[46,57] The dihydride complex $[RuH_2(PPh_3)_4]$ is also used as catalyst for selective hydrogenation of 1-alkenes.[62] The alkene-coordinated complex

[Ru(alkene)($PPh_3$)$_3$] has been isolated as a catalytically active intermediate. An analogous iron dihydride complex, [$FeH_2N_2(PEtPh_2)_3$], is usable as a catalyst for the hydrogenation of ethylene.[63] The orthometalated complex of ruthenium, [RuCl{P($OC_6H_4$)(OPh)$_2$}{P(OPh)$_3$}$_3$] is also an active catalyst, but the analog [RuHCl{P(OPh)$_3$}$_4$], which is not orthometalated, is not active.[64]

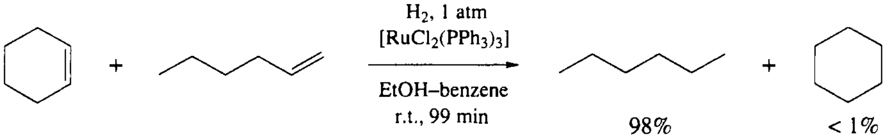

(1)

[$RuCl_2(AsPh_3)_3$],[65] [RuH(NO)($PR_3$)$_3$],[66] [RuH(OAc)($PPh_3$)$_3$],[67] [Ru(OAc)$_2$($PPh_3$)$_2$],[68] and [Ru($PPh_3$)$_3$($CF_3SO_3$)$_2$],[68] also show catalytic activities for the hydrogenation of alkenes.

The cationic complex [RuCl(DPPB)(MeCN)$_3$]$^+$$PF_6^-$ (DPPB = 1,4-bis(diphenylphosphino)butane) is a good catalyst for the hydrogenation of terminal alkenes, acetonitrile and imines.[69]

The anionic ruthenium cluster [$Ru_3$(NCO)(CO)$_{10}$]$^-$ acts as an efficient catalyst for the reduction of terminal and unactivated alkenes under mild conditions.[70] A mechanistic study using the osmium analog has been done.[71] The complexes [{Ru($\eta^4$-$Ph_4C_4CO$)(CO)$_2$}$_2$] and [{Ru($\eta^4$-$Ph_2Me_2C_4CO$)(CO)$_2$}$_2$] have been used as catalysts for the hydrogenation of alkenes, alkynes, ketones, aldehydes and anthracene under mild conditions.[72] The complex [$Ru_2$(CO)$_5$($PPh_3$)($\mu$-$PPh_2$)($\mu$-O=CPh)], obtained by pyrolysis of [$Ru_3$(CO)$_9$($PPh_3$)$_3$], is a catalyst for the hydrogenation of cyclohexene and 2-cyclohexen-1-one, giving cyclohexane and cyclohexanone with a small amount of cyclohexanol, respectively.[73]

The complex [OsHBr(CO)($PPh_3$)$_3$] is effective for the selective hydrogenation of conjugated and nonconjugated dienes to monoenes, and this complex also catalyzes the hydrogenation of linear and cyclic alkenes. (–)-Carvone (**9**) is selectively reduced to 2-methyl-5-(1-methylethyl)cyclohex-2-en-1-one (**10**) or 2-methyl-5-(1-methylethyl)cyclohexanone (**11**), depending on the reaction conditions.[74]

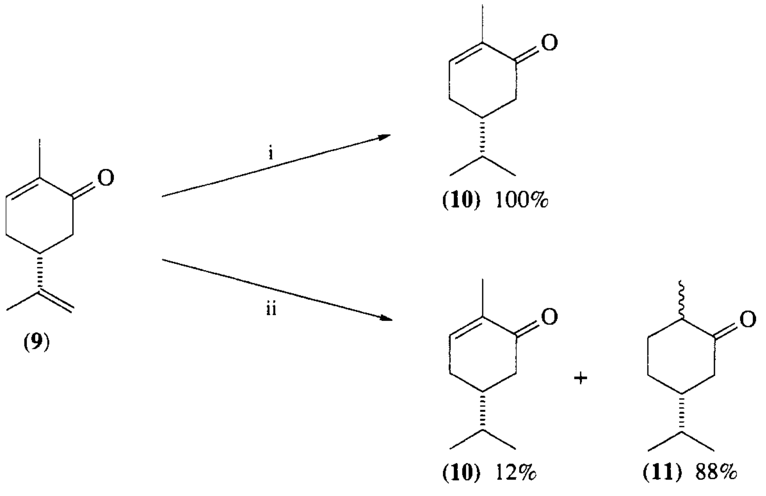

i, [OsHBr(CO)($PPh_3$)$_3$], $H_2$, 1 atm, r.t.; ii, [OsHBr(CO)($PPh_3$)$_3$], $H_2$, 5 atm, 100 °C

Vaska's complex [IrCl(CO)($PPh_3$)$_2$] and its derivatives can be used as catalysts for the hydrogenation of alkenic compounds.[75–88] The rates of hydrogenation depend on steric effects similar to those observed for [RhCl($PPh_3$)$_3$] (terminal alkene > *cis*-alkene > *trans*-alkene). Isomerization is more rapid than hydrogenation. The catalyst is activated by UV irradiation.[80] [Ir(COD)($PR_3$)$_2$]$^+$-type complexes are inactive in aromatic and hydrocarbon solvents, but active in chlorinated solvents such as chloroform and dichloromethane.[89–91] The cationic iridium complexes of the type [Ir(COD)($PR_3$)(Py)]$PF_6$ are highly efficient catalysts for hydrogenation of hindered alkenes.[92] The complex (R = $C_6H_{11}$) readily hydrogenates sterically congested steroid alkene groups without reducing carbonyl groups, carbon–halogen bonds and cyclopropane rings. For example, (**12**) is reduced to (**13**) in the presence of the above complex.[93]

In the presence of the cobalt hydride complexes, [$CoH_3(PPh_3)_3$],[94] [CoH(CO)($PPh_3$)$_3$],[94] [CoH(CO)($PBu_3$)$_3$][95] and [CoH(CO)$_2$($PBu_3$)$_2$],[95] alkenes are reduced at elevated temperatures and pressures.

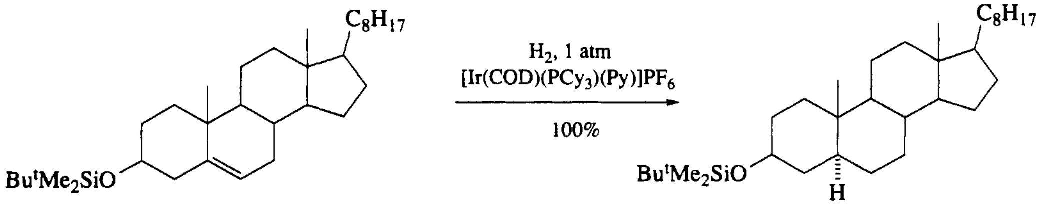

**(12)** **(13)**

The complexes $[RCo(CO)_2\{P(OMe)_3\}_2]$ (R = Me and MeCO) show a marked catalytic activity (450 turnovers $h^{-1}$) for hydrogenation of terminal alkenes under ambient conditions,[96] while more-hindered alkenes are reduced slowly. Cobalt complexes such as $[CoH_2(PR_3)_3]$[97,98] and $[CoHN_2(PPh_3)_3]$[99,100] are also active catalysts for alkene hydrogenation.

Several complexes of $Pd^0$ and $Pd^{II}$ containing $PR_3$, DMSO, *etc.* catalyze hydrogenation of monoalkenes.[101–104] Salen complexes of $Pd^{II}$ and $Ni^{II}$ are employed as catalysts for alkene hydrogenation.[105] The cluster complex of palladium $[Pd_5(PPh)_2]$, is a catalyst for the hydrogenation of alkenes, dienes, alkynes and many other kinds of unsaturated compound.[106]

The complexes derived from platinum complexes and $SnCl_2$ exhibit catalytic activity for hydrogenation under mild conditions.[107–116] These complexes have also been used for alkene hydroformylation. The above catalyst system and $[PtCl_2(PPh_3)_2]$ assist hydrogenation of polyenes to monoalkenes, but isomerization of double bonds has been observed. The anionic cluster complex $[\{Pt_3(CO)_6\}_5]^{2-}$ has been used as a catalyst for hydrogenation of cyclohexene.[117]

A number of Ziegler-type catalysts based on early transition metals exhibit catalytic activity for alkene hydrogenation.[1a,118] Hydrogenation of alkenes is also catalyzed by $d^0$-metallocene species such as $[Cp_2ZrH_2]$,[119a] $[Cp_2ZrMe_2]$,[119b] $[Cp_2MHR]$ (M = Zr, Hf; R = Me, $CHMe_2$),[120] and so on.[121] Zirconium(II) complexes catalyze the hydrogenation of 1,3- and 1,5-cyclooctadiene to give cyclooctene.[122] Titanocene derivatives[123–125] and polymer-anchored titanocenes[126] have also been used for alkene hydrogenation. $Ti^{II}$ complexes with chiral cyclopentadienyl ligands have been used for asymmetric hydrogenation of simple alkenes (see Section 3.2.5).[127–129]

Recently, both actinide and lanthanoid complexes have been used as catalysts for the hydrogenation of alkenes and alkynes. 1-Hexene is hydrogenated rapidly at atmospheric pressure in the presence of the species prepared from $UCl_4$ and *t*-butyllithium.[130] Actinide–hydride complexes are also efficient catalysts for 1-hexene.[131] Hydrogenation of propene proceeds effectively with the organoactinide complexes supported on alumina.[132] The hydride complexes, $[\{(C_5Me_5)_2LnH\}_2]$[133] and $[\{Me_2Si(C_5Me_4)_2LnH\}_2]$,[134] and the species derived from $[Cp_3Ln]$ and NaH,[135] are highly active catalysts for alkene hydrogenation. The relative ordering of activities is found to be approximately inversely proportional to metal ionic radius: Lu > Sm > Nd > La. $[\{(C_5Me_5)_2LuH\}_2]$ is the most active catalyst among the complexes shown in Table 3, exceeding 120 000 turnovers $h^{-1}$ at 25 °C and 1 atm of hydrogen.[136] Organoyttrium hydride complexes are also catalysts for alkene hydrogenation.[137]

**Table 3** Hydrogenation of 1-Hexene[136]

| *Catalyst* | *Temperature* (°C) | *Rate* ($h^{-1}$) | *Ref.* |
|---|---|---|---|
| $[RhCl(PPh_3)_3]$ | 0 | 60 | 90 |
| | 25 | 650 | 90 |
| $[RuHCl(PPh_3)_3]$ | 25 | 9000 | 90 |
| $[Rh(COD)(PPh_3)_2]PF_6$ | 25 | 4000 | 90 |
| $[Ir(COD)(PMePh_2)_2]PF_6$ | 0 | 5100 | 90 |
| $[Ir(COD)(PCy_3)(Py)]PF_6$ | 0 | 6400 | 90 |
| $[\{(C_5Me_5)_2LuH\}_2]$ | 25 | 120 000 | 136 |

Functional groups such as hydroxy, ester and amide often direct the sterochemistry of hydrogenation. Hydrogenation of allylic and homoallylic alcohols occurs with high stereoselectivity.[138] Catalysts used in the hydroxy-directed hydrogenation include: $[RhCl(PPh_3)_3]$, a cationic chelating diphosphine–rhodium complex, $[Rh(NBD)(Ph_2P(CH_2)_4PPh_2)]BF_4$ (**15**), and a cationic iridium complex, $[Ir(COD)(PCy_3)(Py)]PF_6$ (**20**).

Homogeneous hydrogenation of chiral allylic and homoallylic alcohols is accomplished with a high degree of diastereoselectivity, as shown in the hydrogenation of 3-phenylbut-3-en-2-ol (**14**) and 4-phenylpent-4-en-2-ol (**16**) in the presence of (**15**).[139]

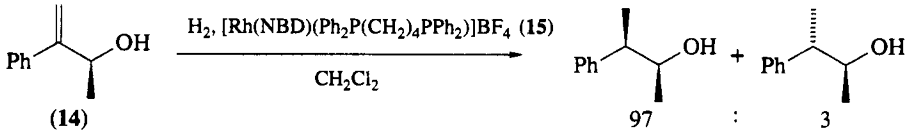
Ph
OH
(14)
H2, [Rh(NBD)(Ph2P(CH2)4PPh2)]BF4 (15)
CH2Cl2
Ph
OH
+
Ph
OH
97
:
3

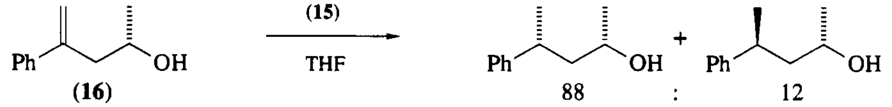
Ph
OH
(16)
(15)
THF
Ph
OH
+
Ph
OH
88
:
12

With the cationic rhodium complex (**15**) diastereoselectivity is high (>91%) at 44 atm of hydrogen,[140] but it falls off at atmospheric pressure. Hydrogenation with the cationic iridium complex (**20**) in dichloromethane (25 °C, 1 atm $H_2$) exhibits a low level of diastereoselection.[140,141] The rhodium complex (**15**) is also superior to iridium complex (**20**) in the hydrogenation of homoallyl alcohols,[142] as in the stereoselective synthesis of (**18**) from (**17**).[143]

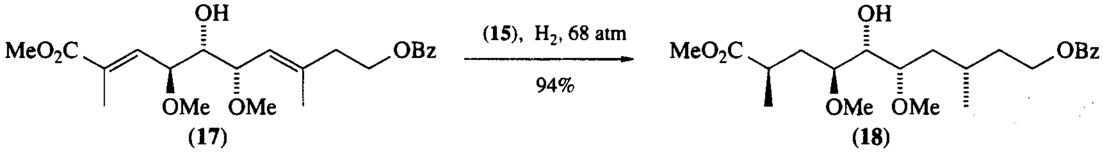
OH
MeO2C
OBz
OMe OMe
(17)
(15), H2, 68 atm
94%
OH
MeO2C
OBz
OMe OMe
(18)

Excellent diastereoselectivity has been observed in the directed hydrogenation of cyclic alkenic alcohols (**19**) and (**21**).[141,144–149] In all cases, *trans* products are formed predominantly.

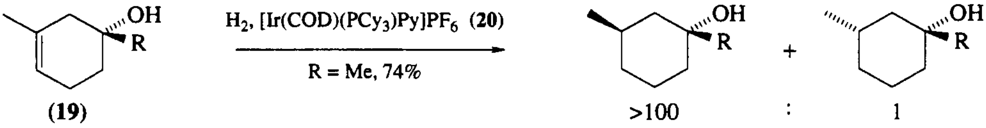
OH
R
(19)
H2, [Ir(COD)(PCy3)Py]PF6 (20)
R = Me, 74%
OH
R
+
OH
R
>100
:
1

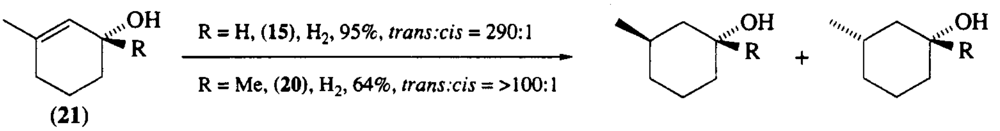
OH
R
(21)
R = H, (15), H2, 95%, trans:cis = 290:1
R = Me, (20), H2, 64%, trans:cis = >100:1
OH
R
+
OH
R

The directed hydrogenation of cyclic unsaturated ethers[145b] and carboxylic acids and their esters,[150] has been studied using the catalysts (**15**) and (**20**), but the selectivities are usually lower than those of allylic and homoallylic alcohols (equations 2a, 2b and 3).

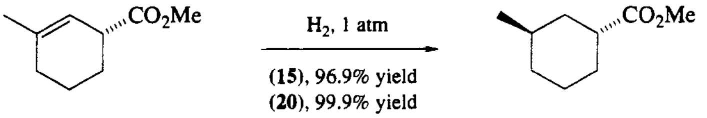
CO2Me
H2, 1 atm
(15), 96.9% yield
(20), 99.9% yield
CO2Me

(2a)

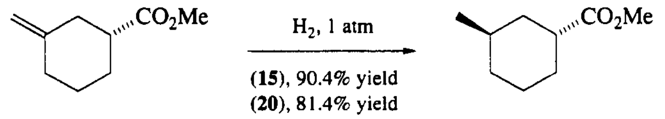
CO2Me
H2, 1 atm
(15), 90.4% yield
(20), 81.4% yield
CO2Me

(2b)

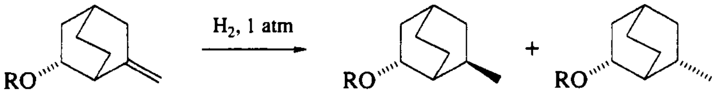
RO
H2, 1 atm
RO
+
RO

R = H, (**15**), 98:2 (**20**), 99.7:0.3

R = Me, (**15**),86:14 (**20**), 97:3

(3)

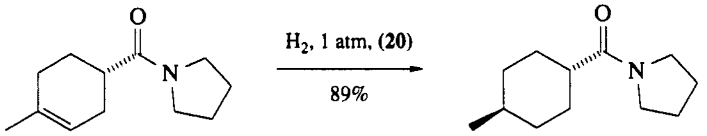

(4)

*trans*:*cis* = 130:1

The amide group is superior to the ester as a directing group (equation 4).[151,152]

The cationic rhodium complex (**15**) catalyzes the hydrogenation of 3-substituted itaconic acid esters with high diastereoselectivity. When a chiral rhodium complex is employed, effective kinetic resolution occurs.[152]

## 3.2.2 HYDROGENATION OF CONJUGATED ALKENES

### 3.2.2.1 Dienes, Trienes and Polyenes to Saturated Hydrocarbons

Sterically unhindered conjugated alkenes and chelating nonconjugated dienes (1,5-cyclooctadiene, norbornadiene) can be hydrogenated by $[RhCl(PPh_3)_3]$ under low hydrogen pressure (1 atm), though reaction proceeds slowly. At elevated hydrogen pressure (60 atm), however, the rate increases and some rather sterically hindered dienes are also rapidly hydrogenated.[5a]

Dienes and trienes are hydrogenated in aqueous–organic two-phase media using $[\{RhCl(1,5\text{-hexadiene})\}_2]$ and a phase transfer catalyst.[153]

Detailed kinetic and mechanistic studies for the homogeneous hydrogenation of polybutadiene (90% 1,2-addition; $M_n$ = 10 000) in the presence of $[RhCl(PPh_3)_3]$ as catalyst have been carried out by monitoring the amount of hydrogen consumed. Quantitative hydrogenation of carbon–carbon unsaturation present in polybutadiene proceeds at 20–50 °C under subatmospheric pressures (<1 atm).[154]

Unsaturated polymers (*cis*-1,4-polybutadiene and butadiene–styrene copolymer) are also hydrogenated by Ziegler catalysts.[155,156]

### 3.2.2.2 Dienes and Trienes to Alkenes by 1,2-Reduction

The rhodium complexes $[RhH(PPh_3)_4]$ and $[Rh(CO)_2(PPh_3)_2]\cdot 2C_6H_6$, which interact strongly with 1,3-dienes, allow selective hydrogenation of 1,3-dienes to the corresponding terminal monoalkenes (equation 5). The hydrogenation proceeds smoothly in cyclohexane at 50–100 °C under 15 atm of hydrogen.[157]

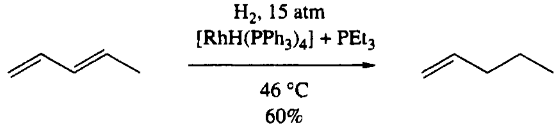

(5)

The selective hydrogenation of terminal double bonds of conjugated linear dienes can be attained using $[CpNiRu_3(\mu\text{-}H)_3(CO)_9]$ as catalyst.[158]

Potassium pentacyanocobaltate(II), derived form cobalt(II) chloride and KCN, catalyzes the hydrogenation of 1,3-dienes to monoalkenes. 1,3-Butadiene (**22**), isoprene[159] and 1-phenyl-1,3-butadiene (**23**),[160] have been converted to mixtures of the corresponding 1-butenes, *trans*-2-butenes and *cis*-2-butenes. The product distribution depends highly on reaction conditions such as the cyanide:Co ratio, the concentra-

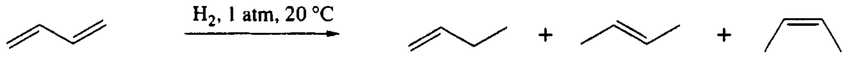

(**22**)

| | | | *Yield* | |
|---|---|---|---|---|
| *Solvent* | *CN/Co* | (%) | (%) | (%) |
| $H_2O$ | 4.8 | 16 | 81 | 2 |
| $H_2O$ | 6.0 | 95 | 4 | 1 |
| Glycerol–MeOH | 5.0 | 9 | 87 | 4 |
| Glycerol–MeOH | 5.7 | 50 | 9 | 41 |

tion of added base and the kind of solvent. Relatively high selectivity has been attained by finely tuning these factors. The reaction is usually carried out in water, aqueous alcohols, or mixed solvent systems such as methanol and ethylene glycol. Sorbic acid sodium salt (**24**) affords sodium 2-hexenoate (**25**) in high yield.[161] Tertiary aryl- or alkyl-phosphine complexes of the type $[\{Co(CO)_3(PR_3)\}_2]$ can be used as catalysts in the absence of carbon monoxide, although high substrate:catalyst ratios cause decomposition of the catalyst.[162]

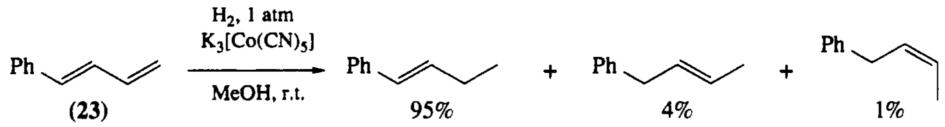
Ph
(23)
$H_2$, 1 atm
$K_3[Co(CN)_5]$
MeOH, r.t.
Ph
95%
+
Ph
4%
+
Ph
1%

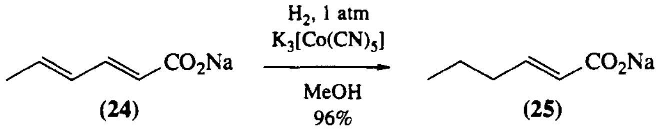
$CO_2Na$
(24)
$H_2$, 1 atm
$K_3[Co(CN)_5]$
MeOH
96%
$CO_2Na$
(25)

Several other transition metal complexes, including $[RuCl_2(PPh_3)_3]$,[163] $Pd_2(DPPM)_3$[101,102] and $PdCl_2(DMSO)$,[103,104] $[Pd(OAc)_2(PPh_3)_2]$,[106] $[Ni(acac)_2]–Al_2Et_3Cl_3–PPh_3$,[164] $[MoH_2(Cp)_2]$,[165] $[IrCl(CO)(PPh_3)_2]$,[166] $[CoH_2(bipy)(PR_3)_2]$,[167] $[Co(C_3H_5)\{P(OMe)_3\}_3]$[168] and Ziegler catalysts,[169] are used for the selective reduction of dienes to monoalkenes.

Acyclic and cyclic allenes are converted to alkenes at 60 °C under atmospheric pressure of hydrogen with $[RhCl(PPh_3)_3]$. 1,2-Nonadiene (**26**), 3-ethyl-1,2-pentadiene and 1,2-cyclotridecadiene are hydrogenated to give *cis*-2-nonene (**27**), 3-ethyl-2-pentene and cyclotridecene (*cis*:*trans* = 85:15), respectively.[170]

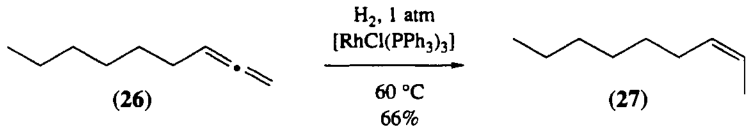
(26)
$H_2$, 1 atm
$[RhCl(PPh_3)_3]$
60 °C
66%
(27)

1,3-Cyclooctadiene (**28**) can be converted to cyclooctene (**29**) almost quantitatively by $[RhH(PPh_3)_4]$ and $[Rh(CO)_2(PPh_3)_2]·2C_6H_6$.[157] On the other hand, 1,5- and 1,4-cyclooctadiene (**30** and **31**) have been hydrogenated to cyclooctene (**29**) with $[Ir_2H_2Cl_2(1,5\text{-}COD)(PPh_3)_2]$[171] or $[Ir(1,5\text{-}COD)_2]PF_6$.[48] Zirconium(III) complexes containing the chelated bis(diphenylphosphino)methane act as catalysts for the hydrogenation of both 1,3- and 1,5-cyclooctadiene to cyclooctene in quantitative yields.[123,124]

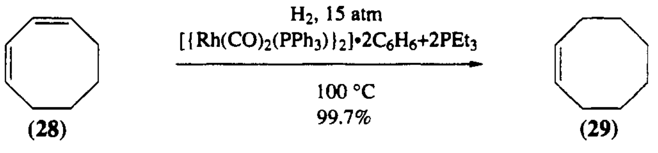
(28)
$H_2$, 15 atm
$[\{Rh(CO)_2(PPh_3)\}_2]•2C_6H_6+2PEt_3$
100 °C
99.7%
(29)

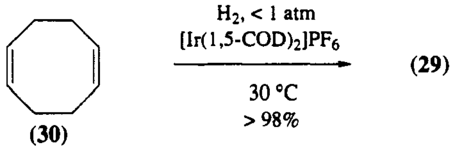
(30)
$H_2$, < 1 atm
$[Ir(1,5\text{-}COD)_2]PF_6$
30 °C
> 98%
(29)

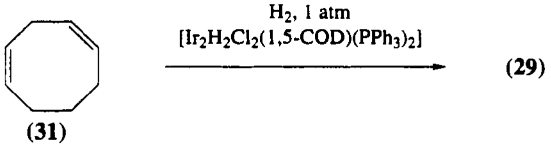
(31)
$H_2$, 1 atm
$[Ir_2H_2Cl_2(1,5\text{-}COD)(PPh_3)_2]$
(29)

In the presence of a catalytic amount of [Ru($\eta^4$-COD)($\eta^6$-COT)], cycloheptatriene is hydrogenated to cycloheptene under 1 atm of $H_2$ at room temperature.[172]

1,5,9-Cyclododecatriene (**32**) has been hydrogenated to cyclododecene (**33**) with various catalysts[173] such as [{$Co(CO)_3(PBu_3)$}$_2$],[162] [$NiI_2(PPh_3)_2$],[174] [$Pt(SnCl_3)_5$]$^{3-}$,[175] [$RuCl_2(PPh_3)_3$],[163c] [$RuCl_2(CO)_2(PPh_3)_2$][176] and [$RhCl_3(Py)_3$]/$NaBH_4$.[177]

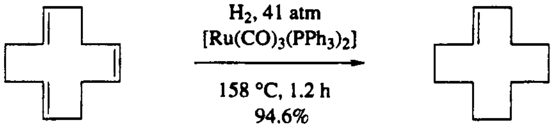

**(32)** **(33)**

Reduction of cyclic conjugated dienes such as 1,3-cyclohexadiene to cyclohexene is also attained with [$Co(CN)_2$(bipyridine)] more rapidly than with [$Co(CN)_5$]$^{3-}$.[178]

With [$Cr(PhCO_2Me)(CO)_3$], 1,3,5-cycloheptatriene gives 1,3-cycloheptadiene and cycloheptene in successive steps.[179]

### 3.2.2.3 Dienes to Alkenes by 1,4-Reduction

Several complexes having arenes, [$Cr(CO)_3$(arene)] (arene = benzene, mesitylene, methyl benzoate, *etc.*) and [$Cr(CO)_3$(cycloheptatriene)], are excellent catalysts for selective 1,4-hydrogen addition to 1,3-dienes.[179,180] 1,4-Hydrogenation of methyl sorbate (**34**), isoprene (**36**) and 1,3-pentadiene (**38**) in cyclohexane affords methyl *cis*-3-hexenoate (**35**), 2-methyl-2-butene (**37**) and *cis*-2-pentene (**39**), respectively. [$Cr(CO)_3(MeCN)_3$] is also an active catalyst under mild conditions (40 °C, $H_2$ 1.4 atm),[181] as are [$Cr(CO)_6$] or [$Cr(NBD)(CO)_4$] under UV irradiation.[182]

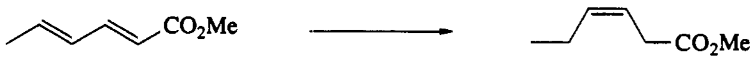

**(34)** **(35)**

| | $H_2$ (atm) | *Temperature* (°C) | *Time* (h) | *Yield* (%) |
|---|---|---|---|---|
| [$Cr(CO)_3$(benzene)] | 48 | 160 | 8 | 94 |
| [$Cr(CO)_3$(methyl benzoate)] | 48 | 150 | 2 | 99 |
| [$Cr(CO)_3$(cycloheptatriene)] | 30 | 120 | 1 | 98 |
| [$Cr(CO)_3$(chlorobenzene)] | 30 | 150 | 2 | 96 |
| [$Mo(CO)_3$(cycloheptatriene)] | 30 | 100 | 6 | 90 |
| [$Mo(CO)_3$(mesitylene)] | 30 | 150 | 0.5 | 28 (4-monoene 55) |
| [$W(CO)_3$(mesitylene)] | 30 | 165 | 6 | 13 (2-monoene 43) |

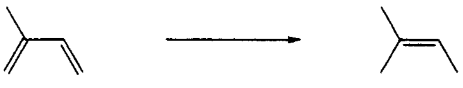

**(36)** **(37)**

[$Cr(CO)_3(MeCN)_3$], $H_2$,1.4 atm, 40 °C, 90%
[$CpCr(CO)_3$], $H_2$, 90 atm, 70 °C, 95%

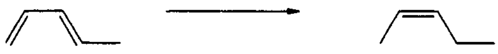

**(38)** **(39)**

[$Cr(CO)_3(MeCN)_3$], $H_2$, 1.4 atm, 40 °C, 100%
[$CpCr(CO)_3$], $H_2$, 90 atm, 70 °C, 100%

Hydrogenation of methyl β-eleostearate (methyl *trans,trans,trans*-9,11,13-octadecatrienoate) with [$Cr(CO)_3$(arene)] yields the diene products from 1,4-addition (*trans*-9-*cis*-12- and *cis*-10-*trans*-13-octadecadienoates). With α-eleostearate (methyl *cis,trans,trans*-9,11,13-octadecatrienoate), stereoselective 1,4-reduction of the *trans,trans*-diene moiety yields linoleate (*cis,cis*-9,12) accompanied by *cis,trans*-1,4-dienes which are formed from the isomerization of α- to β-eleostearate.[183]

### 3.2.2.4 Hydrogenation of C=C Bonds Conjugated with Aromatic Rings, CN, CO, $CO_2R$, *etc.*

Complex $[RhCl(PPh_3)_3]$ is a good catalyst for the hydrogenation of alkenes conjugated with aromatics, nitriles, aldehydes, ketones, carboxylic acids, esters, lactones, amides, nitro compounds, furans, thiophenes and other unsaturated heterocyclic compounds.[5b,13,145] With aldehydes, decarbonylations sometimes occur on hydrogenation by $[RhCl(PPh_3)_3]$.[184] α,β-Unsaturated ketones resist decarbonylation, but are converted into saturated dimethyl acetals during hydrogenation in benzene–methanol. Electron-withdrawing substituents increase the rate of hydrogenation; for the alkenes $H_2C{=}CHR$, the order is R = CN > $CO_2Me$ > Ph > alkyl. (–)-Dehydrogriseofulvin (**40**) gives griseofulvin (**41**), indicating that hydrogenation at the MeC=C(CO) group is faster than at the MeOC=C(CO) group.[13]

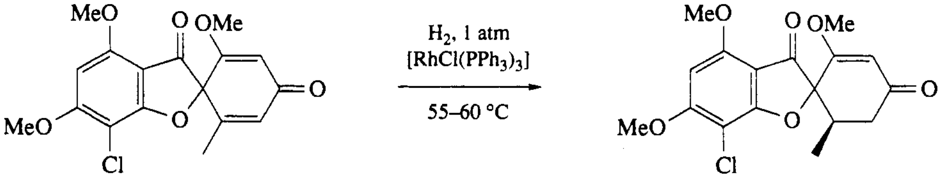

**(40)** **(41)**

$[RhCl(PPh_3)_3]$ catalyzes the hydrogenation of α,β-unsaturated nitro compounds, and the nitro group survives.[184a] A modified catalyst having a phenyldipiperidylphosphine ligand hydrogenates styrene to ethylbenzene.[25,26,185]

The air stable complex $[RhCl(Py)_2(DMF)(BH_4)]Cl$ can hydrogenate α,β-unsaturated carbonyl compounds to saturated products. Methyl 3-phenylbutenoate (**42**) is converted to methyl 3-phenylbutanoate (**43**). 4-Cholesten-3-one, testosterone, 17-methyltestosterone and progesterone are also hydrogenated in good yields.[44,185]

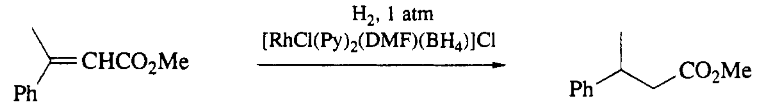

**(42)** **(43)**

Cationic $Rh^I$ complexes $[RhL(CO)(PPh_3)_2]ClO_4$ (L = unsaturated nitrile) show catalytic activities for the hydrogenation of α,β-unsaturated nitriles under mild conditions (30 °C).[186] Selective reduction of the carbon–carbon double bonds of α,β-unsaturated carbonyls also occurs in high yield with $[\{Rh(1,5\text{-hexadiene})Cl\}_2]$ and a phase transfer catalyst in aqueous media.[153]

With $[RuCl_2(PPh_3)_3]$, α,β-unsaturated ketones are reduced to saturated ketones.[57,58] Hydrogenation of 1,4-androstadiene-3,17-dione (**44**) gives the 4-ene-3,17-dione (**45**) in high yield.[187] $[OsHBr(CO)(PPh_3)_3]$ also catalyzes hydrogenation of α,β-unsaturated ketones to give saturated ketones.[74]

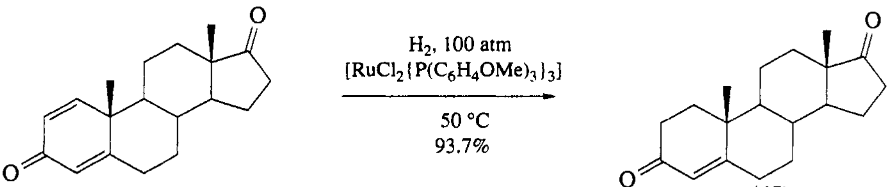

**(44)** **(45)**

Crabtree's catalyst, $[Ir(COD)(PCy_3)(Py)]PF_6$, is quite inert to other functional groups under hydrogenation conditions, as illustrated by the reduction of the enone (**46**), in which the *gem*-dibromocyclopropane survives.[93]

The complexes $[(arene)Cr(CO)_3]$ (arene = methyl benzoate, naphthalene) are highly efficient catalysts for selective hydrogenation of acyclic enones to ketones.[188] Isolated C=C bonds remain intact.

α,β-Unsaturated carbonyl compounds such as crotonaldehyde, acrolein, methyl vinyl ketone, mesityl oxide and ethyl cinnamate can be hydrogenated in fair yields by use of $[Co_2(CO)_8]$ and $[CoH(CO)_4]$ under a carbon monoxide and hydrogen atmosphere.[94,95a,95b,189a,b] Alkenes and alkynes conjugated with aromatic rings are also hydrogenated.[189c] At elevated temperatures, however, overreduction of aldehydes and ketones to alcohols and hydrocarbons occurs.[190]

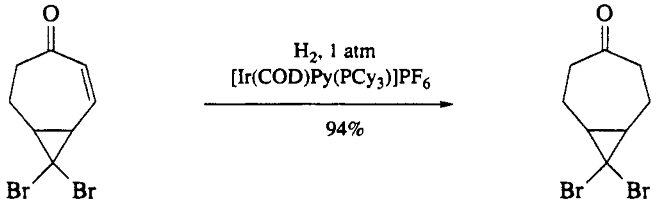

(46)

Appropriately substituted α,β-unsaturated acids or aldehydes such as α-phenylacrylic acid, α-methylacrylic acid, α-methylcrotonaldehyde, and allylic alcohols such as cinnamyl alcohol, have been reduced in the presence of $[Co(CN)_3]^{3-}$ in fair to good yields,[191] while acrylic acid and acrolein cannot be reduced. Styrene and substituted styrenes are also reduced.[192]

The complexes derived from chloroplatinic acid and tin(II) chloride can catalyze the hydrogenation of α,β-unsaturated ketones (equation 6).[111,114,115]

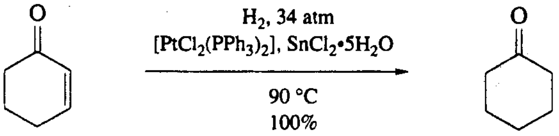

(6)

Using Vaska's complex, hydrogenation of methyl acrylate is accelerated by weak UV irradiation.[75] A related rhodium complex, $[RhH(CO)(PPh_3)_3]$, is also activated by UV irradiation in the hydrogenation of ethyl acrylate.[29]

### 3.2.2.5 Transfer Hydrogenation of Conjugated C═C Bonds

α,β-Unsaturated ketones are converted to saturated ketones in the presence of $[RuCl_2(PPh_3)_3]$ by means of transfer hydrogenation from organic compounds such as benzyl alcohol, ethylene glycol and formic acid, at relatively high temperatures.[193] For example, α,β-unsaturated ketones (**47**) and (**49**) are reduced to the corressponding ketones (**48**) and (**50**), respectively.

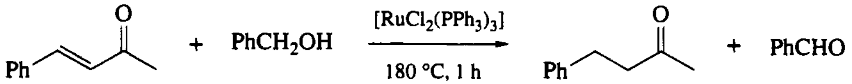

(**47**) (**48**)

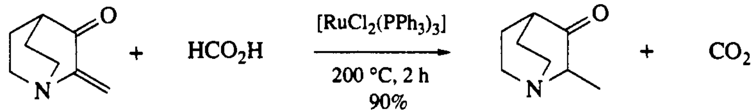

(**49**) (**50**)

## 3.2.3 HYDROGENATION OF AROMATIC AND HETEROAROMATIC RINGS

The hydrogenation of isolated aromatic rings is not an easy task with homogeneous transition metal catalysts. Several complexes, however, have been successfully used for this purpose.

Benzene and substituted benzenes are hydrogenated to cyclohexanes by several catalyst systems. With $[\{(\eta^6\text{-}C_6Me_6)RuCl_2\}_2]$ and $Na_2CO_3$, 9 000 molecules of benzene are reduced to cyclohexane per molecule of catalyst at 50 °C under 50 atm of hydrogen for 36 h.[194] Under the same conditions, styrene, anisole, methyl benzoate, acetophenone and benzophenone are completely hydrogenated to ethylcyclohexane, methoxycyclohexane, cyclohexanecarboxylic acid methyl ester, methyl cyclohexyl ketone and dicyclohexyl ketone, respectively (equation 7). Hydrogenation of benzene-$d_6$ gives $C_6D_6H_6$ in 95% yield.[194]

Other ruthenium complexes also catalyze the hydrogenation of benzenes. Under high pressure of hydrogen, benzene is hydrogenated to cyclohexane by use of $[(\eta^6\text{-}C_6Me_6)RuHCl(PPh_3)]$.[195] With

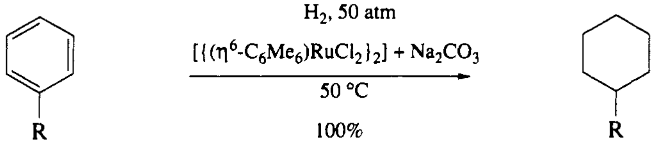

(7)

R = H, Me, OMe, $CO_2Me$, COMe

[(η$^6$-$C_6Me_6$)(η$^4$-$C_6Me_6$)Ru], *p*-xylene is hydrogenated to *cis*-1,4-dimethylcyclohexane. The rate of hydrogenation decreases with alkyl substitution.[196]

Ziegler catalysts prepared from nickel or cobalt 2-ethylhexanoate and triethylaluminum (3 or 4:1 ratio) are very efficient for the hydrogenation of aromatic compounds.[118,197,198] *o*-Xylene (**51**) gives a mixture of *cis*- (**52**) and *trans*-1,2-dimethylcyclohexane (**53**) in 65:35 ratio. Phenol (**54**), dimethyl phthalate and dimethyl terephthalate are also reduced in high yield, while nitro-substituted benzene and phenols cannot be reduced. Catalytic activity toward benzene hydrogenation decreases in the order Ni ≥ Co > Fe > Cr > Cu.[197]

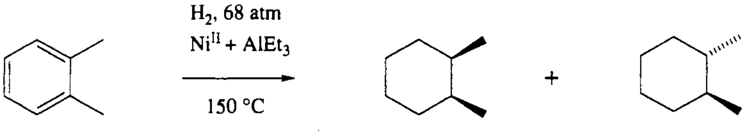

**(51)** **(52)** 65% **(53)** 35%

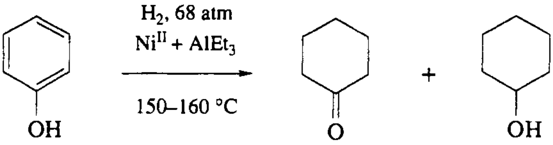

**(54)** 92% 5%

Arenes are hydrogenated under mild conditions using $Rh^I$–*N*-phenylanthranilic acid anchored to polystyrene beads. For example, benzene is reduced to cyclohexane at room temperature under 3.4 atm of hydrogen.[199]

Benzene-$d_6$ is converted to $C_6D_6H_6$ (nearly all *cis*) by hydrogenation with [{(η$^5$-$C_5Me_5$)$RhCl_2$}$_2$] in the presence of bases. Benzene is hydrogenated faster than toluene, and acetophenone is reduced to methyl cyclohexyl ketone (50 °C, 50 atm).[200]

The complex [{RhCl(1,5-COD)}$_2$] and a phase transfer catalyst (cetyltrimethylammonium bromide or tetrabutylammonium hydrogen sulfate) also reduce aromatic hydrocarbons under hydrogen.[201]

Benzene and substituted benzenes are reduced under mild conditions using [Co($C_3H_5$){P(OMe)$_3$}$_3$] as catalyst. Benzene, anisole and alkylbenzenes are converted to cyclohexanes, while alkyl benzoates give 1-alkoxycarbonylcyclohexenes.[168,202] Interesting is the fact that benzene is more easily reduced than cyclohexene because of the special affinity of the benzene ring for cobalt.

Strongly acidic systems ($TaF_5$/HF or $SbF_5$/HF) have also been used for hydrogenation of aromatic compounds at 50 °C under 50–100 atm of $H_2$.[203]

Naphthalene (**55**) and anthracene (**57**) are hydrogenated to decalin (**56**) and perhydroanthracene (**58**) catalyzed by [Co($C_3H_5$){P(OMe)$_3$}$_3$].[168,202] $Rh^I$–*N*-phenylanthranilic acid anchored to polystyrene beads can also hydrogenate naphthalene to decalin.[199]

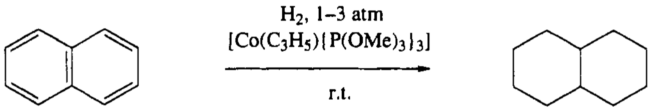

**(55)** **(56)**

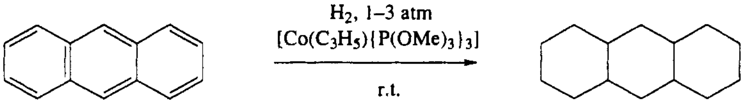

**(57)** **(58)**

With nickel(II) 2-ethylhexanoate and triethylaluminum, tetralin (**59**) is obtained by hydrogenation of naphthalene (**55**).[197] Polycyclic aromatics, such as anthracene (**57**; equation 8), 9-methylanthracene and 9-trifluoroacetylanthracene, are partially hydrogenated to 1,2,3,4-tetrahydroanthracene derivatives by use of $[Rh(DPPE)(arene)]^+$ in methanol[204] and by ruthenium hydride complexes having triphenylphosphine ligands.[91,205]

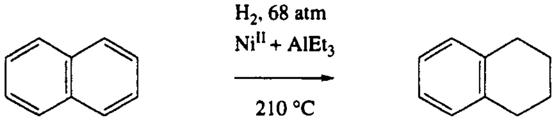
$H_2$, 68 atm
$Ni^{II}$ + $AlEt_3$
210 °C
84%

**(55)** **(59)**

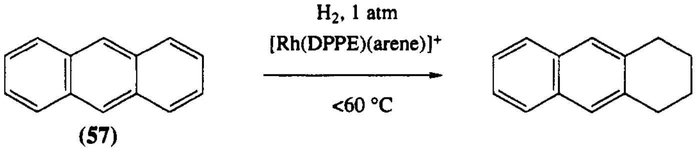
$H_2$, 1 atm
$[Rh(DPPE)(arene)]^+$
<60 °C

**(57)** (8)

Partial hydrogenation of aromatic rings can also be accomplished with catalysts such as $[Co_2(CO)_8]$ under an atmosphere of carbon monoxide and hydrogen, but the isolated benzene nucleus cannot be reduced.[206] Anthracene (**57**), naphthacene, perylene (**61**) and pyrene (**63**) are converted to 9,10-dihydroanthracene (**60**), 5,12-dihydronaphthacene, 1,2,3,10,11,12-hexahydroperylene (**62**) and 4,5-dihydropyrene (**64**), respectively.

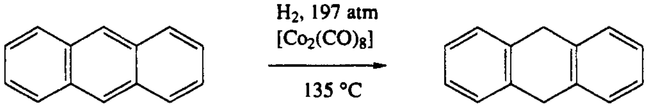
$H_2$, 197 atm
$[Co_2(CO)_8]$
135 °C
99%

**(57)** **(60)**

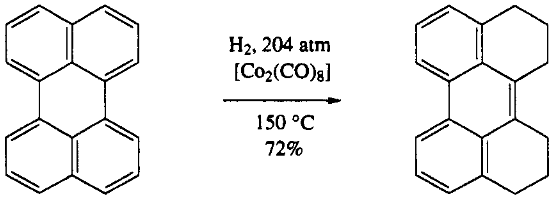
$H_2$, 204 atm
$[Co_2(CO)_8]$
150 °C
72%

**(61)** **(62)**

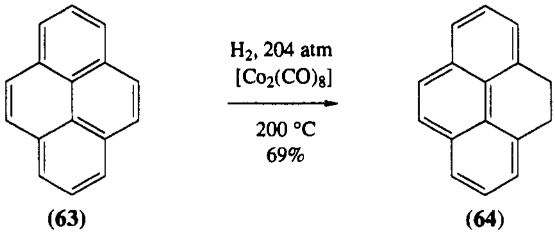
$H_2$, 204 atm
$[Co_2(CO)_8]$
200 °C
69%

**(63)** **(64)**

Pyridine (**65**) is converted to piperidine (**66**) in 98% yield with Ziegler catalyst, $Ni^{II}$ + $AlEt_3$.[118,197] The phase transfer catalyst system $[\{RhCl(1,5\text{-}COD)\}_2]$ with cetyltrimethylammonium bromide or tetrabutylammonium hydrogen sulfate can also reduce heteroaromatic compounds.[201]

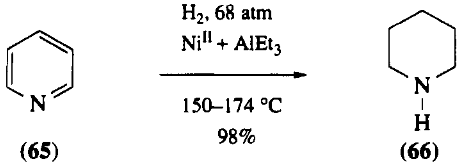
N
$H_2$, 68 atm
$Ni^{II}$ + $AlEt_3$
150–174 °C
98%
N
H

**(65)** **(66)**

Pyridine and quinoline are also reduced to piperidine and 1,2,3,4-tetrahydroquinoline by [$RhCl_3(Py)_3$] and $NaBH_4$. Isoquinoline and indole are not hydrogenated.[207]

[$RuHCl(PPh_3)_3$] and [$RuH_2(PPh_3)_2(PPh_2C_6H_4)$]$^-$ can reduce polyaromatic compounds under hydrogen. Quinoline (**67**) and phenanthridine (**69**) are converted to 1,2,3,4-tetrahydroquinoline (**68**) and 9,10-dihydrophenanthridine (**70**).[91,205a]

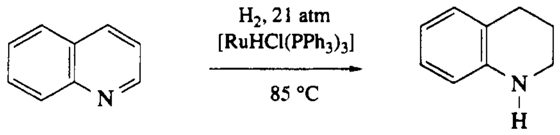

(**67**) (**68**)

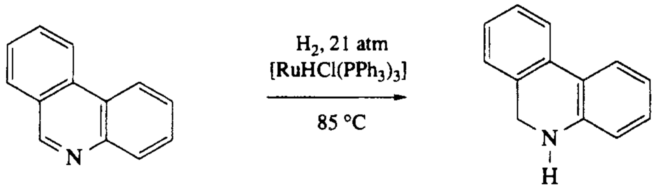

(**69**) (**70**)

Sulfur-containing heteroaromatics can be smoothly hydrogenated with [$Co_2(CO)_8$] under carbon monoxide and a hydrogen atmosphere (238–272 atm), as demonstrated by the reduction of thiophene derivatives (**71**).[208]

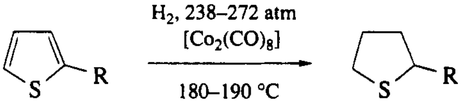

(**71**)

R = H, 66%; R = Me, 77%; R = Et, 82%

### 3.2.4 HYDROGENATION OF C≡C BONDS

### 3.2.4.1 Reduction of C≡C Bonds to Saturated Hydrocarbons

With [$RhCl(PPh_3)_3$] or [$Rh(OAc)(PPh_3)_3$], 1-hexyne (**72**) and other alkynes are hydrogenated to the saturated compounds by way of the alkenes.[5a,21]

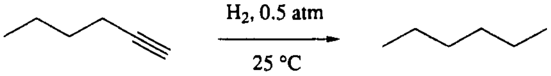

(**72**) (**73**)

| | *Relative rate* |
|---|---|
| [$RhCl(PPh_3)_3$] | 2.22 |
| [$Rh(OAc)(PPh_3)_3$] | 1 |

Under an atmosphere of hydrogen and acetylene (2:1), [$Rh_2(CO)_2(DPPM)_2$] in toluene hydrogenates acetylene at 80 °C to ethane at a rate of ~3.3 mol of ethane mol$^{-1}$ of Rh dimer h$^{-1}$. No cyclotrimerization of acetylene is observed in this reaction.[209]

[$Ti(Cp)_2(CO)_2$] is a catalyst for the hydrogenation of phenylacetylene to ethylbenzene, while alkyl-substituted terminal alkynes are reduced to alkenes.[210] Electron rich titanium(II) complexes, [$Cp_2Ti(PhC{\equiv}CPh)(PMe_3)$], [$(MeCp)_2Ti(PhC{\equiv}CPh)(PMe_3)$] and [$CpCp^*Ti(PhC{\equiv}CPh)$] are also catalyst precursors for the hydrogenation of alkynes to alkanes at 20 °C under atmospheric pressure of hydrogen.[211]

### 3.2.4.2 Reduction of Terminal C≡C Bonds to Alkenes

In benzene and with acidic alcohols such as 2,2,2-trifluoroethanol or phenol as cosolvents, the rate of hydrogenation of alkyne by Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, is accelerated, while that of C=C bonds does not change, which allows selective hydrogenation of alkynes.[212] $[Rh(COD)(PPh_3)(Py)]PF_6$ can also catalyze the selective reduction of 1-alkynes to 1-alkenes in the presence of benzoate ion. For example, phenylacetylene is slowly reduced with 1 equiv. of $D_2$ (1 atm) to *cis*-PhCD=CHD by $[Rh(COD)(PPh_3)(Py)]PF_6$ in the presence of an excess of $Et_3NH^+PhCO_2^-$. Thus compound (**74**) is converted selectively to (**75**).[213]

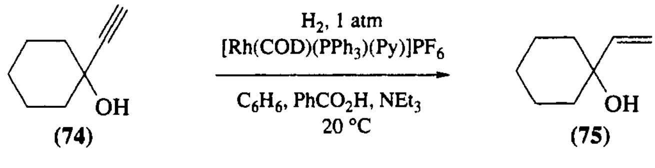

(**74**) (**75**)

Methanolic solutions of the dinuclear complexes $[Rh_2(\mu\text{-}X)(CO)_2(Ph_2ECH_2EPh_2)_2]^+$ (X = Cl, Br; E = P, As) and $[Ir_2Cl(CO)_3(Ph_2PCH_2PPh_2)_2]$ are catalysts for the hydrogenation of alkynes to alkenes.[42] The complex $[RuH(PMe_2Ph)_5]PF_5$ selectively converts terminal alkynes to alkenes without hydrogenating C=C bonds.[214] $[CoH(CO)(PBu^n_3)_3]$ catalyzes partial hydrogenation of 1-pentyne (**76**) to 1-pentene (**77**) in 95% yield without isomerization of the alkenic bond, but aldehydes are not tolerated under the reaction conditions.[95a,95b] $[CoCl\{P(OEt)_3\}_n]$ (*n*=3,4) is also active for hydrogenation of alkynes to alkenes.[215]

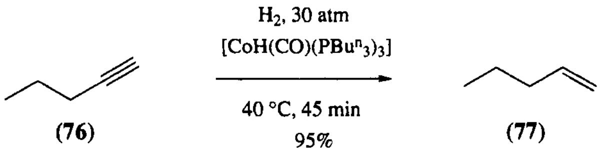

(**76**) (**77**)

$[Co_2(CO)_6(HC{\equiv}CH)]$ has catalytic activity for hydrogenation of acetylene to ethylene. On increasing the acetylene concentration, however, cyclotrimerization to benzene becomes the dominant process.[216]

1-Pentyne and 1-hexyne are hydrogenated with $[Ti(Cp)_2(CO)_2]$ to 1-pentene and 1-hexene, respectively, but phenylacetylene gives ethylbenzene.[210] Reduced compounds of $[Ti(Cp)_2Cl_2]$ with Na, Mg, Ca, sodium naphthalenide, or butyllithium catalyze the hydrogenation of a variety of alkynes to alkenes.[122,126]

The C≡C bond in phenylacetylene can be selectively reduced, giving styrene, by $[OsHBr(CO)(PPh_3)_3]$ under $H_2$ at atmospheric pressure. After *ca.* 100 catalytic cycles, the selectivity for the production of styrene is still close to 100%.[74] In the absence of the alkyne, styrene is reduced to ethylbenzene at a comparable rate, but the presence of as little as 1% phenylacetylene suppresses the reduction of the double bond almost completely.

The iron cluster $[\{(\eta^5\text{-}C_5H_5)Fe(\mu_3\text{-}CO)\}_4]$ catalyzes the selective hydrogenation of alkynes to alkenes at 100–130 °C and 6.8–68 atm of hydrogen. Terminal alkynes are selectively hydrogenated to alkenes even in the presence of alkenes or internal alkynes.[217]

### 3.2.4.3 Reduction of C≡C Bonds to *cis*-Alkenes

Highly stereo- and chemo-selective hydrogenation of internal alkynes to *cis*-alkenes has been attained with $[(arene)Cr(CO)_3]$ complexes.[188] For example, reduction of 7-tetradecyne (**78**) gives (**79**) in quantitative yield.

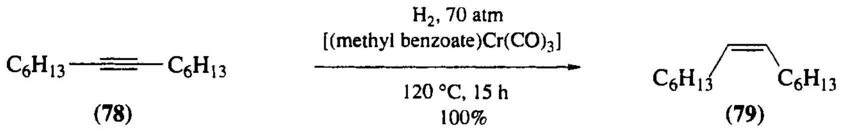

(**78**) (**79**)

The complex $[CoH(CO)(PBu^n_3)_3]$ catalyzes partial hydrogenation of 2-pentyne to *cis*-2-pentene in 85% yield.[98a,98b,215] Catalysts can also be generated from $[\{Co(CO)_2(PR_3)\}_3]$ (R = Ph, $Bu^n$) under hydrogenation conditions.[95c,218]

The complexes of the type $[Rh(diene)L_n]PF_6$ (diene = norbornadiene, 1,5-cyclooctadiene; L = tertiary phosphine; *n* =2 or 3) are also used as catalysts for the reduction of internal alkynes to *cis*-alkenes (equation 9). Selectivity is greater than 95%.[48,50] At 1 atm of $H_2$ $[(\mu\text{-H})_2H_2Rh_2(\text{triphos})_2]^{2+}$ in DMF at 22 °C catalyzes, although very slowly, the hydrogenation of dimethyl acetylenedicarboxylate (**80**) to dimethyl maleate (**81**).[219]

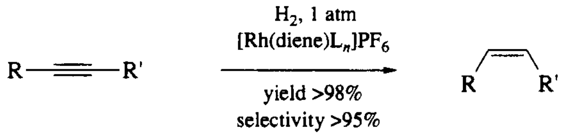

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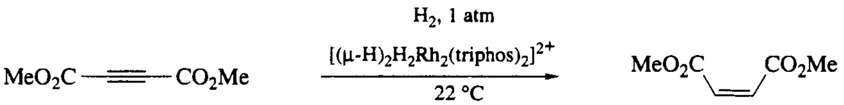

(**80**) (**81**)

Hydrogenation of alkynes to *cis*-alkenes with $[RuHCl(PPh_3)_3]$ proceeds at a rate roughly 0.1 times as fast as that of alkenes.[220] The complex $[RuH(PMe_2Ph)_5]PF_5$ selectively reduces internal and terminal alkynes without hydrogenating the corresponding alkenes. 2-Butyne is hydrogenated to *cis*-2-butene at 20 °C under 1 atm of $H_2$.[214] Disubstituted alkynes are hydrogenated stereoselectively in the presence of $[RuCl_2(PPh_3)_3]$ to give *cis*-alkenes in a 1:1 mixture of ethanol and benzene at 20 °C.[221]

$[Pd_5(PPh)_2(PPh_3)_2]$ is a catalyst for the hydrogenation of various alkynes and conjugated dienes, with alkynes selectively hydrogenated to *cis*-alkenes.[222]

In the presence of $[Cp_2Mo_2(CO)_4]$,[223b] $[Ni_2(COD)_2(\mu\text{-}\eta^2\text{-RC}{\equiv}\text{CR})]$,[223c] and $[Ni_4(RNC)_4(\mu_3\text{-}\eta^2\text{-RC}{\equiv}\text{CR})_3]$,[223d] alkynes are converted to *cis*-alkenes. The alkenes once formed no longer bind to the complex and hydrogenation does not proceed further to give alkanes or even isomerized alkenes.[223]

Cocondensation of lanthanoid metal atoms with internal alkynes generates lanthanoid complexes of alkynes, which are potential catalysts for hydrogenation. $[\{Sm(1\text{-hexyne})\}_n]$ or $[\{Er(3\text{-hexyne})\}_n]$ catalyzes hydrogenation of hex-3-yne to *cis*-hex-3-ene (97% *cis*) at room temperature and atmospheric pressure of $H_2$.[224]

Cyclopentadienyltitanium(II) complexes, $[Cp_2Ti(PhC{\equiv}CPh)(PMe_3)]$, $[CpCp^*Ti(PhC{\equiv}CPh)]$ and $[(MeCp)_2Ti(PhC{\equiv}CPh)(PMe_3)]$, are catalyst precursors for the hydrogenation of alkynes to *cis*-alkenes in the presence of an excess of $PMe_3$ under mild conditions (1 atm of $H_2$).[211]

The iron cluster $[\{(\eta^5\text{-}C_5H_5)Fe(\mu_3\text{-CO})\}_4]$, catalyzes the selective hydrogenation of alkynes to alkenes at 100–130 °C and 6.8–68 atm of $H_2$. Internal alkynes are slowly reduced to *cis*-alkenes, but nitro groups attached to aromatic rings and terminal carbon–carbon double bonds are also hydrogenated.[218]

### 3.2.4.4 Reduction of C≡C Bonds to *trans*-Alkenes

The hydrogenation of acetylenedicarboxylic acid dimethyl ester (**80**) and diphenylacetylene (**83**) with $[RhH_2(OC({=}O)OH)(PPr^i_3)_2]$ gives dimethyl fumarate (**82**) and *trans*-stilbene (**84**), respectively. This complex also catalyzes an isomerization of *cis*-stilbene to *trans*-stilbene, though hydrogenation of alkyne is about eight times faster than the isomerization.[225]

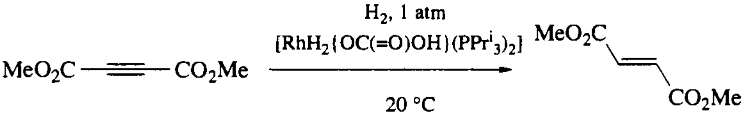

(**80**) (**82**)

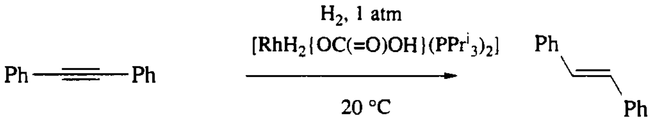

(**83**) (**84**)

The dinuclear hydridorhodium complex $[\{(\mu\text{-H})Rh\{P(O{—}Pr^i)_3\}_2\}_2]$ is a catalyst for the stereoselective hydrogenation of dialkylalkynes and diarylalkynes to the corresponding *trans*-alkenes. Although the hydrogenation rates are much lower than for terminal alkenes (approximately 1 turnover min$^{-1}$ at 20 °C), the catalytic reaction is totally stereoselective. Unfortunately, the lifetime of the catalyst is very short; after approximately 5 min under the catalytic conditions, *cis*-alkenes become significant products.[226]

With [$RhCl_3(Py)_3$], DMF and $NaBH_4$, diphenylacetylene is hydrogenated to *trans*-stilbene as the sole product, while dimethyl acetylenedicarboxylate is converted to dimethyl maleate, and butyne-1,4-diol to *cis*-but-2-ene-1,4-diol.[227]

## 3.2.5 HOMOGENEOUS ASYMMETRIC HYDROGENATION OF C=C BONDS USING CHIRAL CATALYSTS

### 3.2.5.1 Chiral Catalysts

Attempts to prepare optically active organic compounds by enantioselective hydrogenation of prochiral alkenes with the aid of homogeneous catalysts emerged in the late 1960s and now this methodology has become one of the most attractive synthetic approaches to this class of compounds.[228] Horner and Knowles independently demonstrated, for the first time, that phosphine–rhodium complexes were promising catalysts for asymmetric hydrogenation.[229,230] Early in the 1970s Kagan[231] and Knowles[232] developed the chiral chelating diphosphines (**85a**)[231] and (**85b**),[232] respectively, and had great success in the asymmetric hydrogenation of certain alkenic substrates. Since then, a great number of chiral diphosphines have been synthesized and used as chiral ligands.[233] Most of the highly efficient diphosphines are 1,2-diphosphines and 1,4-diphosphines such as (**85c**)–(**95**). The ferrocenylphosphines (**96**) are also important chiral ligands.[245]

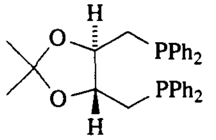

*(R,R)*-DIOP (**85a**)

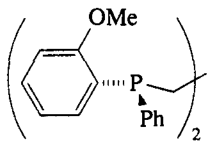

*(R,R)*-DIPAMP (**85b**)

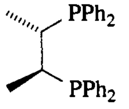

*(S,S)*-CHIRAPHOS (**85c**) (ref. 234)

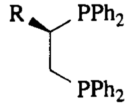

R = Me: *(R)*-PROPHOS (**86**) (ref. 235)
R = Ph: *(R)*-PHENPHOS (**87**) (ref. 236)
R = $C_6H_{11}$: *(R)*-CYCPHOS (**88**) (ref. 237)

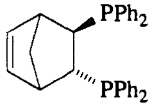

*(R,R)*-NORPHOS (**89**) (ref. 238)

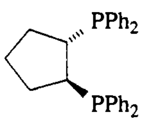

*(S,S)*-DPCP (**90**) (ref. 239)

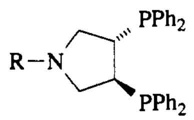

*(S,S)*-PYRPHOS (**91**) (ref. 240)

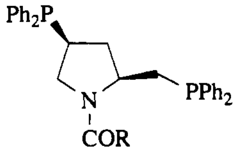

R = Bu$^t$O: *(S,S)*-BPPM (**92**) (ref. 241)
R = R$^1$NH: *(S,S)*-R'-CAPP (**93**) (ref. 242)
R' = 3,4-$Cl_2C_6H_3$, *p*-$BrC_6H_4$

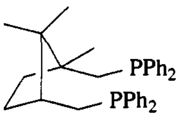

CAMPHOS (**94**) (ref. 243)

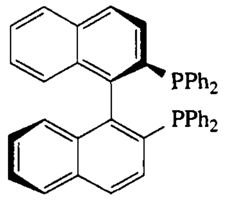

*(R)*-BINAP (**95**) (ref. 244)

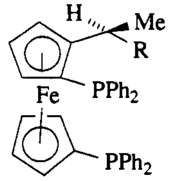

R = $NMe_2$: *(R,S)*-BPPFA (**96a**) (ref. 245)
R = OH: *(R,S)*-BPPFOH (**96b**)
R = N(Me)$CH_2CH_2$N 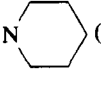 (**96c**)

Chiral bidentate ligands such as diphosphinites,[228b,246] diaminophosphines[228b,247] and aminophosphine–phosphinites,[228b,248] have also been used.[228b] Although much information has been accumulated the choice of chiral catalysts and reaction conditions still remains empirical, and one must make an effort to find the most suitable catalytic system and reaction conditions for every new substrate.

### 3.2.5.2 Asymmetric Hydrogenation of Enamides and Related Substrates

α-Acylaminoacrylic acids (**97**) were the first successful alkenic substrates used in homogeneous asymmetric hydrogenation. Kagan reported asymmetric hydrogenation of (*Z*)-α-acetylaminocinnamic acid with DIOP–Rh$^+$ complexes giving *N*-acetylphenylalanine in 72% *ee*.[231] The Monsanto group also developed chiral ligands, (*R*)-*o*-anisylcyclohexylmethylphosphine [(*R*)-CAMP][230] and (**85b**),[232] and obtained very high optical yields (>90%) in the Rh$^I$-catalyzed asymmetric hydrogenation of (**97**). Now, a number of chiral phosphine ligand–metal complexes are known to catalyze this type of asymmetric hydrogenation, some of which are listed in Table 4. In contrast to the high *ee* obtained for (*Z*)-α-acylaminoacrylic acids and esters, the hydrogenation of the (*E*)-isomers usually proceeds very slowly and in poor *ee*, though some alkyl-substituted (*E*)-α-acylaminoacrylic acids are hydrogenated in high *ee*.[249] Using Rh–PYRPHOS complexes, (**97**) can be hydrogenated with a high substrate to catalyst ratio (up to 50 000).[250] With a water soluble catalyst, [Rh(1,5-COD){3*R*,4*R*)-3,4-bis(diphenylphosphino)-1,1-dimethylpyrrolidinium-*P*,*P*′}]·2BF$_4$, the sodium salt of α-(acetylamino)cinnamic acid has been hydrogenated in aqueous media in 90% *ee*.[251]

Extensive studies on the mechanism of the reaction have been carried out by Halpern[252] and Brown.[253]

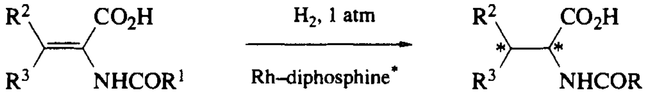

(**97**) (**98**)

**Table 4** Asymmetric Hydrogenation of α-Acylaminoacrylic Acids[a]

| *Substrate* | *DIOP (% ee)* | *DIPAMP (% ee)* | *NORPHOS (% ee)* | *BPPM (% ee)* | *BINAP (% ee)* | *BPPFA (% ee)* |
|---|---|---|---|---|---|---|
| 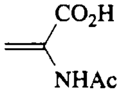 **a** | 73 | 94 | 90 | 99 | (98) | 93 |
| 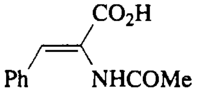 **b** | 82 | 96 | 97 | 91 | (100) | |
| 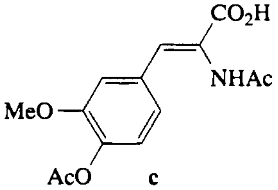 **c** | 84 | 94 | 94 | 86 | (79) | 86 |

[a] Figures in parentheses are given for the hydrogenation of *N*-benzoyl derivatives.

The carboxylic functionality in α-acylaminoacrylic acids can be replaced by other electron-withdrawing groups such as alkoxycarbonyl, carbonyl, keto and cyano groups.[228b] These substrates have been reduced in high enantioselectivity (more than 90% *ee*; equation 10). Dipeptides and oligopeptides have been obtained in high *ee* by asymmetric hydrogenation of the corresponding prochiral dehydropeptides.[254] Although enamides without any other functional groups have been reduced only with difficulty in high *ee*, BINAP–ruthenium(II) complexes bring about high enantioselectivities (99% *ee*).[255,256] Thus the hydrogenation of *N*-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines in the presence of [Ru(OCOR)$_2$(BINAP)] gives isoquinoline alkaloids generally in high optical purity (equation 11). This method finds a very wide applicability and has been successfully applied to asymmetric synthesis of morphines, benzomorphans and morphinans.[257]

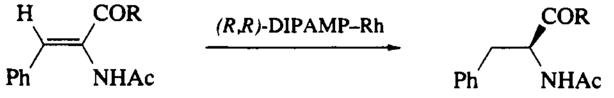

R = OMe, 95% *ee*; R = $NH_2$, 94% *ee*

(10)

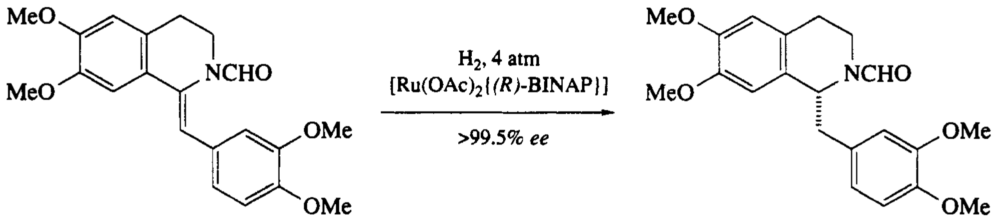

(11)

### 3.2.5.3 Asymmetric Hydrogenation of Acrylic Acids and Esters

Acrylic acids were the substrates chosen at the early stage of the asymmetric hydrogenation of alkenes. Reduction of (*E*)-3-phenyl-2-butenoic acid with a neomenthyldiphenylphosphine–rhodium complex as catalyst was achieved in 61% *ee*, which showed that asymmetric hydrogenation of acrylic acids is a promising way to produce optically active carboxylic acids.[258] However, it was soon revealed that other coordinating functionalities such as amido, carboxy, amidomethyl, alkoxycarbonylmethyl and hydroxycarbonylmethyl groups, are required for obtaining high enantioselectivity. Thus, itaconic acid (**99**) has been reduced to (*R*)-2-methylsuccinic acid (**100**) in 95% *ee* with the (*S*,*S*)-R-CAPP–Rh$^+$ complex.[259] Asymmetric reduction of itaconic acid by transfer hydrogenation with the catalyst derived from [{Rh(COD)Cl}$_2$] and BPPM, and triethylammonium formate as hydrogen source, also proceeds with high enantioselectivity.[260]

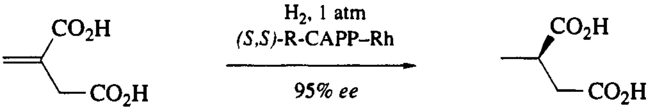

**(99)** **(100)**

Certain alkyl- or aryl-substituted acrylic acids such as tiglic acid and 2-(6-methoxy-2-naphthyl)propenoic acid (**101**) are hydrogenated in 92% and 97% *ee*, respectively, with [Ru(OAc)$_2${(*S*)-BINAP}].[261] Acrylic acids having hydroxyalkyl substituents or their esters can also be hydrogenated in high enantiomeric excesses with the same catalyst system (equation 12). The sense of stereochemistry is the same as that found for the corresponding substrates without these functional groups. Trisubstituted acrylic acids have been reduced with the modified ferrocenyldiphosphine–Rh complex in 98% *ee* (equation 13).[262]

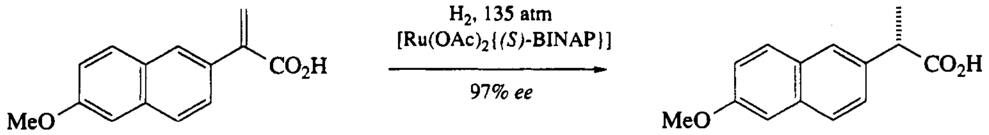

**(101)**

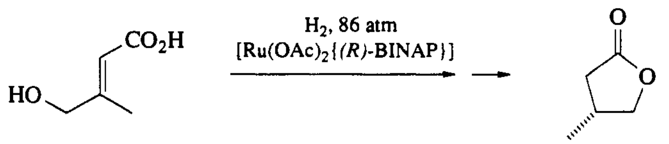

93% *ee*

(12)

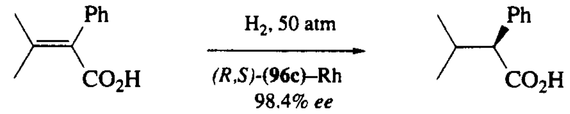

(13)

Hydrogenation of acrylic acid esters with high enantioselectivity has usually been accomplished with difficulty. The enantioselective reduction of α,β-unsaturated carboxylates with sodium borohydride in the presence of cobalt–semicorrin complexes has been achieved in up to 96% *ee* (equation 14). The (*E*)- and (*Z*)-isomers each afford products of opposite configuration, and the isolated double bonds remain untouched.[263]

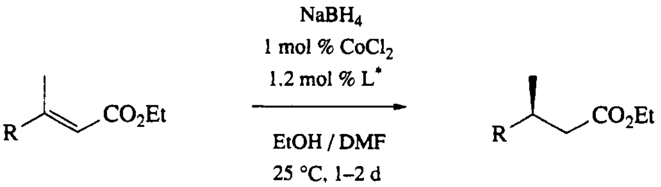

(14)

R = $PhCH_2CH_2$, 94% *ee*; R = $Me_2C{=}CH(CH_2)_2$, 94% *ee*; R = $Me_2CH$, 96% *ee*; R = Ph, 81% *ee*

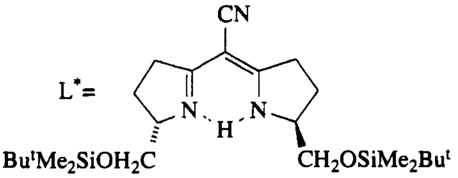

With the catalysts derived from (*S*,*S*)-1,2-bis(diphenylphosphinomethyl)cyclobutane and $[RhH(CO)(PPh_3)_3]$ or rhodium carbonyls, the α,β-unsaturated aldehydes, neral and geranial, are hydrogenated to (*R*)- and (*S*)-citronellal in 79% and 60% *ee*, respectively.[264] Cyclic α,β-unsaturated ketones such as isophorone and 2-methyl-2-cyclohexenone have been hydrogenated using ruthenium hydrides coordinated with chiral diphosphines in up to 62% *ee* to give chiral ketones, though conversions are not satisfactory.[265]

### 3.2.5.4 Asymmetric Hydrogenation of Allylic Alcohols

Some cationic Rh– and Ir–phosphine complexes have been used for diastereoselective hydrogenation of chiral allylic and homoallylic alcohols.[266] Here, the preexisting chirality of the $sp^3$-hybridized carbons induces new asymmetry on the neighboring alkenic diastereofaces through coordination of the hydroxy group to the transition metals (see Section 3.2.1).

Highly enantioselective hydrogenation of prochiral alkenic alcohols has been attained with BINAP–$Ru^{II}$ catalysts.[267] (*R*)- or (*S*)-citronellol (**102**) was obtained in nearly quantitative yield and with 96–99% enantioselectivity by hydrogenation of geraniol or nerol using $[Ru(OAc)_2(BINAP)]$. The stereochemical outcome is outlined in Scheme 1. The hydrogenation is carried out in methanol at room temperature, at an initial hydrogen pressure higher than 30 atm. The substrate to catalyst mol ratio reaches more than 20 000 without difficulty. The allylic and nonallylic double bonds in the substrates can be clearly differentiated and the product was contaminated by less than 0.5% dihydrocitronellol. This procedure has

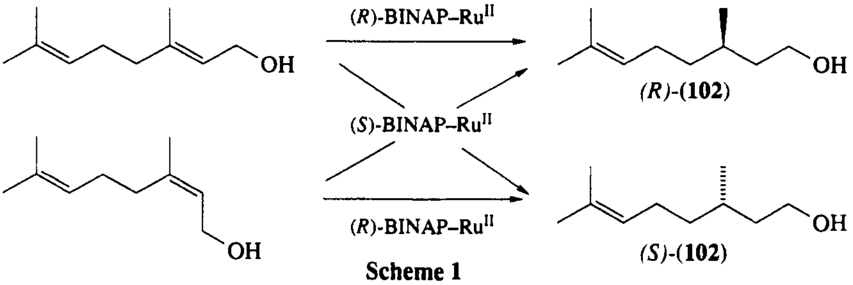

**Scheme 1**

been successfully applied to the asymmetric synthesis of (3*R*,7*R*)-3,7,11-trimethyldodecanol, a versatile intermediate for the synthesis of α-tocopherol. Homogeraniol can be hydrogenated in 92% *ee*.

In the hydrogenation of racemic allylic alcohols catalyzed by a chiral Rh catalyst, at most, 20:1 discrimination has been attained for some acyclic substrates.[268] BINAP–Ru complexes have been used for kinetic resolution of chiral acyclic and cyclic secondary alcohols with up to 74:1 differentiation between the enantiomeric alcohols (equation 15).[269]

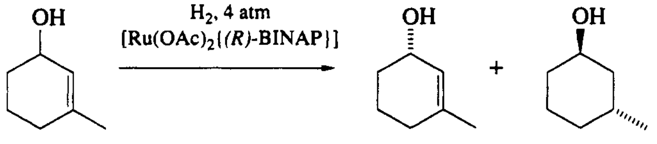

(15)

### 3.2.5.5 Asymmetric Hydrogenation of Simple Alkenes

Hydrogenation of simple alkenes in high enantiomeric excesses has not been attained with the chiral rhodium catalysts,[270] but a fused cyclopentadienyl ligand with $C_2$ symmetry has been used in enantioselective titanocene-catalyzed hydrogenation of alkenes.[127–129] Thus 2-phenyl-1-butene (**103**) was hydrogenated in 96% *ee*.

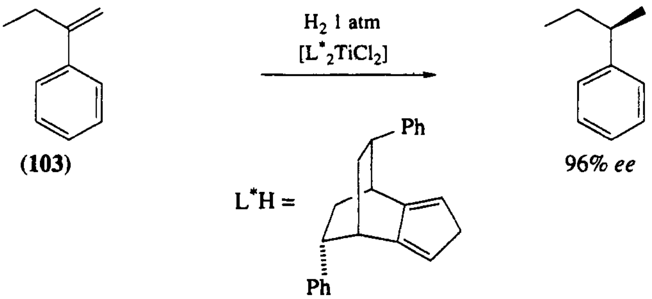

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# 3.3

# Reductions of C═C and C≡C by Noncatalytic Chemical Methods

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## 3.3.1 INTRODUCTION

This chapter is devoted to the discussion of the reduction of carbon–carbon double and triple bonds by noncatalytic methods. These methods include reductions by diimide, by dissolving metals in the presence or absence of proton donors, by low-valent metal ions, by metal hydride–metal halide combinations and by so-called 'ionic hydrogenation' procedures. Of these widely diverse methods of reduction of carbon–carbon double and triple bonds, the reduction by diimide appears to be the most versatile. The reduction of carbon–carbon double and triple bonds by diimide occurs with complete stereoselectivity and stereospecificity, and can be effected in the presence of a variety of other, very chemically reactive functional groups. The other methods of reduction of carbon–carbon double and triple bonds described in this chapter possess excellent synthetic utility in certain cases; however, their application depends critically on the structure of the unsaturated organic substrate and the reagent(s) used to effect the reduction.

## 3.3.2 REDUCTION OF C=C AND C≡C BY DIIMIDE

### 3.3.2.1 Introduction

The first observation of the reduction of a carbon–carbon double bond by 'diimide' appears to be the report of the reduction of glyceryl oleate to stearic hydrazide in the presence of hydrazine, although at the time it was not recognized that diimide was the active reducing agent.[1] (Diimide has also been referred to as diimine and diazene. As diimide is the name most commonly used in the current literature, diimide is the term used in this chapter.) Although there were several other reports of the reduction of double bonds in the presence of hydrazine, it was not until the early 1960s that the synthetic potential of the reaction was recognized when results of studies from several independent laboratories implicated diimide ($HN{=}NH$) as the actual reducing agent.[2–5] Following the proposal that diimide is the reactive intermediate in these reduction reactions, numerous experimental and theoretical studies were initiated to find other methods for the generation of diimide, and to determine the structure(s) of the reactive intermediate(s) and the mechanism of the reduction reaction.

### 3.3.2.2 Methods of Generation of Diimide

Many methods have been discovered for the generation of diimide in solution. However, not all of these methods are synthetically useful or practical. The most widely used procedures are described in the following paragraphs.

1. Diimide can be generated by the oxidation of hydrazine with oxygen (air) in the presence of a catalytic quantity of $Cu^{II}$ and/or a carboxylic acid in a wide range of protic and aprotic solvents. The organic substrate is dissolved in a suitable solvent, hydrazine is added along with a catalytic amount of $Cu^{II}$ and acetic or propionic acid. The solution is vigorously stirred, or air is bubbled through the solution.

2. Diimide can be generated by the oxidation of hydrazine with hydrogen peroxide, generally in the presence of a catalytic quantity of $Cu^{II}$ and an added carboxylic acid.[2] The organic compound is dissolved in a suitable solvent, hydrazine is added along with a catalytic amount of $Cu^{II}$ and acetic or propionic acid and 30% hydrogen peroxide is slowly added dropwise.

3. Diimide is generated by the acid-catalyzed hydrolysis of the dipotassium or disodium salt of azodiformate ($K^+\ {}^-O_2CN{=}NCO_2^-\ K^+$) in protic or aprotic solvents.[4] The azodiformate is dissolved or suspended in the organic solvent containing the compound to be reduced and acetic acid is slowly added.

4. Diimide is also formed in the thermal and base-catalyzed decomposition of benzene-, 4-methylbenzene-,[4] 4-nitrobenzene-,[6] and 2,4,6-triisopropylbenzene-sulfonyl hydrazide.[7]

The protic solvents most widely used are methanol, ethanol, ethoxyethanol and methoxyethanol in which most organic molecules are soluble. Aprotic solvents that have found extensive use are diglyme, dimethoxyethane, tetrahydrofuran, methylene chloride and chloroform.

### 3.3.2.3 Mechanism of Reduction by Diimide

There are three isomeric structures for diimide, $N_2H_2$; *cis*- and *trans*-diimide (**1** and **2**), and 1,1-diimide (aminonitrene; **3**). 'Diimide' has been generated and trapped at low temperatures from the gas-phase electric discharge of hydrazine,[8] and by the thermal decomposition of metal salts of *p*-toluenesulfonyl hydrazide.[9] A careful analysis of the available spectroscopic data has indicated the formation and presence only of (**2**).[10] 1,1-Diimide (**3**) has been recently generated by the low temperature photochemi-

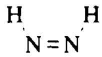

(**1**)

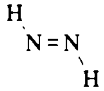

(**2**)

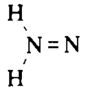

(**3**)

cal decomposition of carbamoyl azide.[11] As theoretical studies have suggested, *cis*-diimide must be formed as a reactive intermediate in the reduction systems, although it has not yet been physically characterized.

The $N_2H_2$ system has been subjected to several theoretical studies at many different levels of theory. To summarize, *trans*-diimide is calculated to be lowest in energy, with *cis*-diimide being higher in energy by 4.7–7.3 kcal $mol^{-1}$ (1 kcal $mol^{-1}$ = 4.18 kJ $mol^{-1}$) and 1,1-diimide being 24.5–27.4 kcal $mol^{-1}$ higher in energy. The results of the theoretical calculations also indicate that the *trans*-to-*cis* inversion and rotation barriers are very high (over 40 kcal $mol^{-1}$).

Stereochemical studies on the reduction of C=C and C≡C by diimide have shown that the transfer of hydrogens from 'diimide' occurs in a completely *syn* manner.[2] The reduction of (**4**) and (**5**) with dideuteriodiimide, generated by the deuterolysis of dipotassium azodiformate, resulted in the formation of the *meso*- and (±)-reduction products (**6**) and (**7**) in at least 97% stereospecificity (the lower limit of detectability with IR spectral analysis).[2] The reduction of diphenylacetylene (**8**) produces only *cis*-stilbene (**9**) as an intermediate reduction product.[2] It was considered that the reduction of multiple bonds by diimide occurred as a synchronous transport of a pair of hydrogens to a single face of the π-system *via* a transition state represented as (**10**).[2]

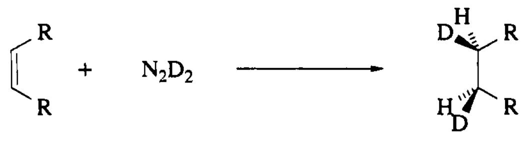

(**4**) (**6**)

(1)

R = $CO_2H$, $CH_2OH$, Ph

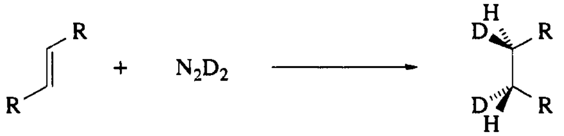

(**5**) (**7**)

(2)

R = $CO_2H$, $CH_2OH$, Ph

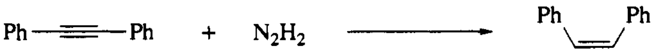

(**8**) (**9**)

(3)

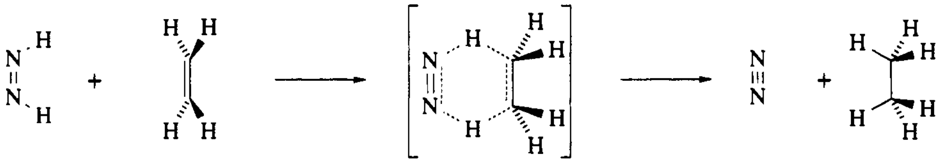

(**10**)

(4)

Theoretical calculations of the energy surfaces for the concerted transfer of hydrogen from (**1**), (**2**) and (**3**) to ethylene give calculated energy barriers of 26.7, 45.3 and 45.8 kcal $mol^{-1}$, respectively.[12] Although *cis*-diimide has not been observed, the results of the theoretical studies indicate that *cis*-diimide undergoes hydrogen atom transfer to ethylene with a considerably lower energy barrier than does *trans*- or 1,1-diimide.[12] Since most of the procedures used to generate diimide in solution probably produce *trans*-diimide, isomerization of *trans*- to *cis*-diimide must occur, most probably involving a rapid protonation–deprotonation sequence catalyzed by the added carboxylic acid. In this chapter the term 'diimide' will imply *cis*-diimide as the reducing agent.

During diimide reductions considerable nitrogen gas is formed by the disproportionation of diimide. Theoretical calculations on the energy surfaces for the transfer of hydrogen from *cis*-diimide to *cis*- and *trans*-diimide give energy barriers of 19.3 and 23.8 kcal mol$^{-1}$, respectively, considerably smaller than that for the transfer of hydrogen from (**1**) to ethylene.[13] From a practical point of view, the occurrence of the disproportionation of diimide requires the use of a considerable excess of the diimide precursor, and places a lower limit of reactivity for diimide reduction of a double or triple bond if it is to be observed.

### 3.3.2.3.1 *Relative reactivities*

Several studies have been carried out to determine the relative reactivities of substituted alkenes and dienes toward reduction by diimide. Garbisch *et al.* have determined the relative reactivities of a large number of substituted alkenes toward reduction by diimide generated by the triethylamine-induced decomposition of *p*-toluenesulfonyl hydrazide in diglyme at 80 °C.[14] Representative results appear in Table 1. Increasing alkyl substitution on the double bond results in decreased reactivity. *Trans* double bonds are, in general, more reactive than *cis* double bonds, and strained double bonds are more reactive than nonstrained double bonds. It was concluded that the major factors contributing to the observed relative reactivity differences are torsional strain, bond angle bending strain and α-alkyl substituent effects.[14] (A more detailed description of these interactions and examples will be cited in Section 3.3.2.4.) An empirical correlation was developed to calculate the relative rates of the reduction of substituted alkenes with diimide.[14]

**Table 1** Relative Reactivities of Substituted Alkenes Toward Reduction with Diimide[14]

| *Substrate* | $k_{rel}$[a] | *Substrate* | $k_{rel}$[a] |
|---|---|---|---|
| 1-Pentene | 20.2 | 1-Methylcyclohexene | 0.11 |
| *trans*-2-Pentene | 2.59 | 1,2-Dimethylcyclohexene | 0.012 |
| *cis*-2-Pentene | 2.65 | Cycloheptene | 17.0 |
| 2-Methyl-1-pentene | 2.04 | Cyclooctene | 17.0 |
| 2-Methyl-2-butene | 0.28 | Cyclononene | 5.7 |
| 2,3-Dimethyl-2-butene | 0.50 | Cyclodecene | 0.85 |
| Cyclopentene | 15.5 | Bicyclo[2.2.1]heptene | 450 |
| Cyclohexene | 1.00 | Bicyclo[2.2.2]octene | 29 |

[a] $k_{rel}$ relative to cyclohexene.

A similar trend in relative reactivities has been observed in the reductions of unsaturated acids (Table 2).[15] The presence of strongly electron-withdrawing groups, such as the carboxylic acid function, enhances reactivity toward reduction of a double or triple bond by diimide.

**Table 2** Relative Reactivities of Unsaturated Acids Toward Reduction with Diimide[15]

| *Acid* | $k_{rel}$[a] | *Acid* | $k_{rel}$[a] |
|---|---|---|---|
| Fumaric | 100 | *trans*-Cinnamic | 10 |
| Maleic | 10 | *cis*-Cinnamic | 3 |
| Methylfumaric | 3 | *trans*-Methylcinnamic | 1.4 |
| Methylmaleic | 0.7 | *cis*-Methylcinnamic | 1.4 |

[a] $k_{rel}$ relative to fumaric acid.

Conjugated dienes are more reactive than monoenes (Table 3).[16] The selectivity between double bonds of an unsymmetrically substituted diene follows the substitution trend noted for monoenes, *i.e.* the less substituted double bond preferentially undergoes reduction.

**Table 3** Relative Reactivities of Conjugated Dienes Toward Reduction with Diimide[16]

| *Diene* | $k_{rel}$[a] | *Diene* | $k_{rel}$[a] |
|---|---|---|---|
| 1,3-Cyclohexadiene | 47 | 2,3-Dimethyl-1,3-butadiene | 3.1 |
| 2-Methyl-1,3-butadiene | 13.6[b] | 2,5-Dimethyl-2,4-hexadiene | 0.5 |

[a] $k_{rel}$ relative to rate of reduction of cyclohexene. [b] Relative rate of reduction of the least substituted double bond.

### *3.3.2.3.2 Stereoselectivity of diimide reductions*

The results of many stereochemical studies have indicated that diimide approaches from the less sterically hindered side of the double bond, *i.e.* steric approach control dominates the stereoselectivity of the diimide reduction reaction. This is consistent with the rather exothermic nature of the reaction,[12] which suggests that the transition state for the reaction occurs early along the reaction coordinate, in which case ground state electronic and steric effects will control the stereoselectivity of the reaction. However, when the approach to the faces of the double bond are similar in steric hindrance, alkene conformational and torsional effects play dominant roles in determining the stereoselectivity of the reduction process.[14] Examples showing the effect of steric hindrance on the approach of diimide to the two faces of the double bond on the stereoselectivity of the reduction of a double bond are illustrated in equations (5)–(9). In equation (5), the reduction of norbornadiene occurs exclusively from the *exo* direction to produce (**12**), which undergoes further reduction exclusively from the less sterically hindered *exo* direction to produce (**13**).[17] 3,4-Dimethylcyclobutene (**14**) undergoes reduction on the face of the ring opposite the two methyl groups (equation 6).[18] Reduction of the bicyclo[2.2.0]hexadiene (**16**) occurs exclusively from the *exo* direction (equation 7).[19] The reduction of α-pinene (**18**) occurs highly stereoselectively on the face of the double bond on the same side as the bridging methylene (equation 8).[20] And finally, the steroid derivative (**21**) undergoes reduction from the less hindered α side (equation 9).[21]

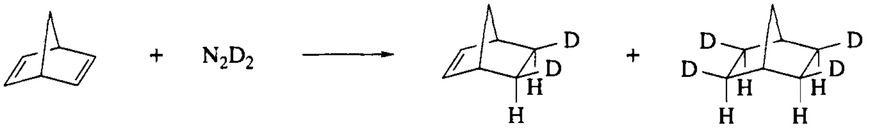

**(11)** **(12)** 44% **(13)** 26% (5)

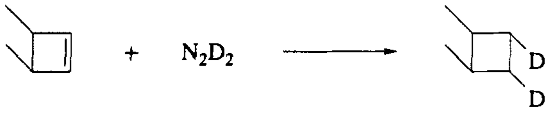

**(14)** **(15)** (6)

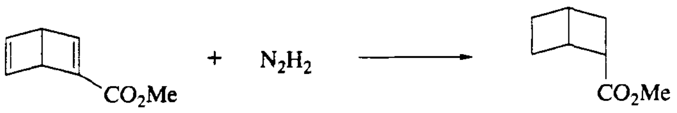

**(16)** **(17)** (7)

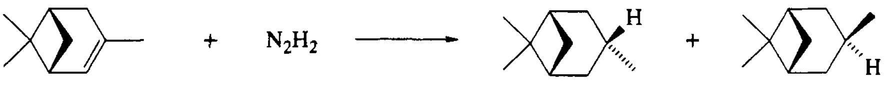

**(18)** **(19)** 99% **(20)** 1% (8)

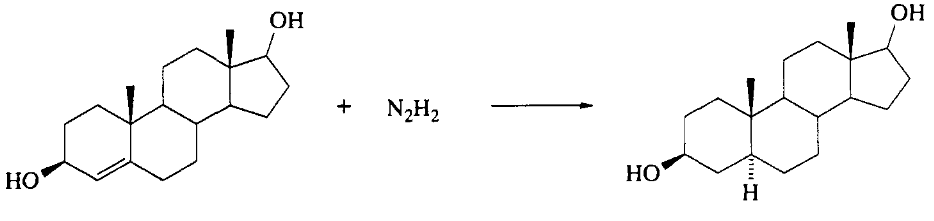

**(21)** **(22)** 85–95% (9)

Interesting exceptions have been reported in which the diimide approaches the most sterically hindered double bond. The reduction of 7-hydroxy-, 7-acetoxy- and 7-*t*-butoxy-norbornadiene (**23a–c**) occur in a highly *syn,exo* manner (equation 10).[17] Two possible explanations have been forwarded to account for these results.[17] The first involves an electronic interaction of the functional groups with the *syn* double bond, which enhances its reactivity toward reduction with diimide. The second involves hydrogen bond formation between diimide and the oxygen-containing functions, which directs the diimide reduction of the *syn* double bond.

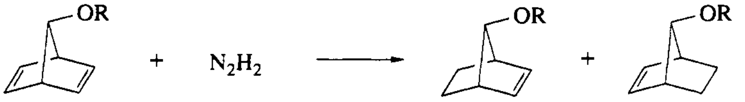

(10)

**(23)** a: R = H
b: R = COMe
c: R = OBu$^t$

**(24)** a: 8%
b: 10%
c: 0–3%

**(25)** a: 27%
b: 50%
c: 63–65%

In the reduction of alkylidenecyclohexanes the approach to the faces of the double bond are similarly sterically hindered, and roughly equal amounts of products derived from attack at the two faces of the double bond should be formed. This is the case with (**26a**). Replacement of the vinyl hydrogens with methyl groups should not greatly affect the approach of diimide to either face of the double bond. However, such substitution results in increases favoring formation of the *trans* isomer (**28**). This trend has been interpreted in terms of subtle changes in the conformations of the alkenes, which affect the ease of approach of diimide to the two faces of the double bonds.[14,23]

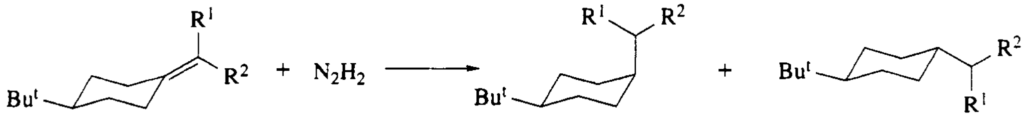

(11)

**(26)** a: R$^1$ = R$^2$ = H
b: R$^1$ = Me, R$^2$ = H
c: R$^1$ = R$^2$ = Me

**(27)** a: 49%
b: 46%
c: 30%

**(28)** a: 51%
b: 54%
c: 70%

The reduction of 1,5-dimethylcyclopentene (**29a**) and 1,6-dimethylcyclohexene (**29b**) results in the preferential formation of the *trans*-dimethyl products (**31**; equation 12).[22] In these cases the approach of the diimide occurs from the direction which will allow the methyl groups to move away from each other, *i.e.* in the transition state for hydrogen transfer from diimide the direction of the approach of diimide is dictated by torsional effects generated between the methyl groups.[23]

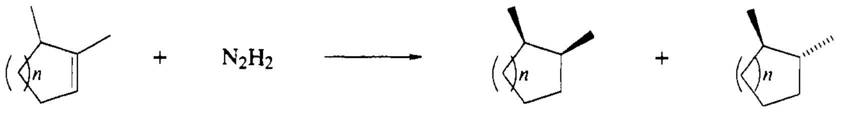

(12)

**(29)** a: *n* = 1
b: *n* = 2

**(30)** a: 31%
b: 29%

**(31)** a: 69%
b: 71%

### 3.3.2.4 Scope and Limitations

The reduction of carbon–carbon double and triple bonds with diimide can be carried out under exceptionally mild conditions, which can be selected to tolerate the presence of a number of reactive functional groups that would either be reduced or would suffer hydrogenolysis under catalytic hydrogenation conditions. Diimide reductions can be carried out in the presence of reactive functional groups including allylic halides,[23,24] esters,[23] amines[23] and disulfides.[25] Vinyl halides and ethers undergo reduction, but they react only very slowly.[23,26] Unsaturated ketones are reduced to saturated ketones by diimide generated by the hydrolysis of dipotassium azodiformate.[23,27] (The use of hydrazine as the diimide precursor results in the formation of azines with aldehydes and ketones.) Other functions that are rather sensitive toward reduction by other reducing agents, but are not reduced by diimide, are N—O[28] and O—N—N[29] containing systems. The reduction of double bonds in very thermally labile systems can be accomplished at −70 °C in methylene chloride by diimide generated by the acidolysis of dipotassium azadiformate with acetic acid.[30] The reaction shown in equation (13) illustrates the use of this procedure to reduce the highly reactive endoperoxide (**32**).[30a]

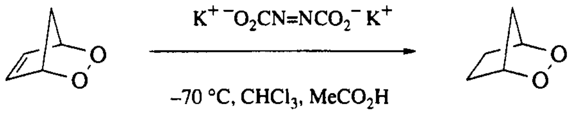

(**32**) (**33**) (13)

Substituted allenes readily undergo reduction with diimide to produce alkenes, which undergo further slower reduction to alkanes.[31,32] The diimide preferentially approaches the allene chromophore from the less hindered side of the less substituted double bond to produce the alkene having the *cis* stereochemistry as is illustrated by the reductions of allenes (**34**) and (**37**) in equations (14)[32] and (15).[33] The reactivity of the allene chromophore towards reduction by diimide appears to be only slightly greater than that of the product alkenes; however, extensive overreduction occurs in the presence of the highly electronegative carboxylic acid functional group, as illustrated in equation (15).[33] Increasing the degree of substitution on the allene chromophore increases the reactivity of the allene to reduction. This effect must be due to the long-range electronic effect of functional groups attached to the remote end of the allene chromophore on the energy of the π MOs of the bond undergoing reduction.[34] An interesting example is the reduction of allene (**41**) involving the more highly strained exocyclic double bond from the less sterically hindered direction opposite the phenyl group as illustrated in equation (16).[35]

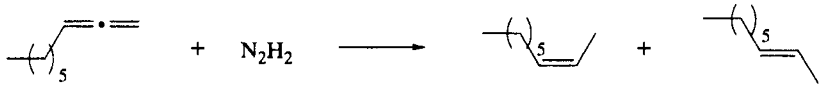

(**34**) (**35**) 32% (**36**) 1% (14)

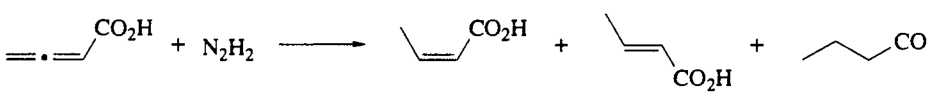

(**37**) (**38**) 20% (**39**) 6% (**40**) 31% (15)

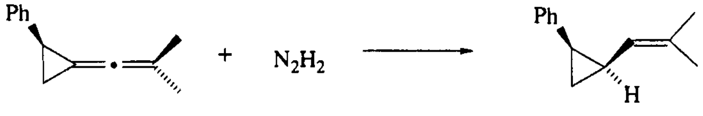

(**41**) (**42**) (16)

Alkynes undergo reduction to produce *cis*-alkenes, which in turn undergo further reduction to the alkane. With alkyl-substituted alkynes, the reactivity of the triple bond is comparable with that of the double bond of the product alkenes, and extensive overreduction occurs. With 1-iodoalkynes, however, the reduced reactivity of the product *cis*-1-iodoalkenes toward further reduction allows for the isolation of the *cis*-1-iodoalkenes in good yields. An example is the reduction of the iodoalkyne (**43**) shown in equation (17).[36]

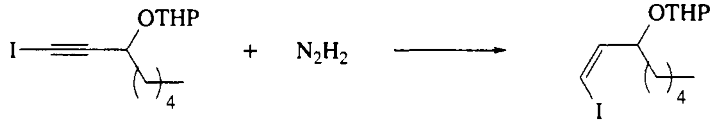

(**43**) (**44**) (17)

Highly regio- and stereo-selective deuterium and tritium labeling can be readily accomplished by diimide reduction in aprotic solvents using dipotassium azodiformate and labeled acetic acid, or by the hydrolysis of azodiformate salts in labeled protic solvents.

A limitation to the use of diimide as a reducing agent appears to be the relative rate at which diimide reacts with the unsaturated substrate. If the rate of reduction is sufficiently slower than that of the disproportionation of diimide, the latter reaction will dominate and no reduction will be accomplished. A further consideration is the reactivity of any other functional groups present in the substrate toward reaction with hydrazine, which may be used as the source of the diimide, or, if not, formed by the disproportionation of the diimide generated from other sources.

Although diimide was initially thought to be useful only for the reduction of symmetical double and triple bonds (*i.e.* C=C, C≡C, N=N, *etc.*), it was subsequently demonstrated that aromatic aldehydes can be reduced to the corresponding benzyl alcohols in excellent yield by diimide generated by the hydrolysis of dipotassium azodiformate.[37] Aromatic ketones are reduced more slowly, while aliphatic aldehydes and ketones are reduced even more slowly yet.[23] Imines of aromatic and aliphatic aldehydes and ketones undergo reduction in good yield with diimide generated from hydrazine.[38]

## 3.3.3 REDUCTION OF C=C AND C≡C BY DISSOLVING METALS

### 3.3.3.1 Introduction

The reduction of a carbon–carbon multiple bond by the use of a 'dissolving' metal was first accomplished by Campbell and Eby in 1941.[39] The reduction of disubstituted alkynes to *cis*-alkenes by catalytic hydrogenation, for example by the use of Raney nickel, provided an excellent method for the preparation of isomerically pure *cis*-alkenes. At the time, however, there were no practical synthetic methods for the preparation of pure *trans*-alkenes. All of the previously existing procedures for the formation of an alkene resulted in the formation of mixtures of the *cis*- and *trans*-alkenes, which were extremely difficult to separate with the techniques existing at that time (basically fractional distillation) into the pure components. Campbell and Eby discovered that dialkylacetylenes could be reduced to pure *trans*-alkenes with sodium in liquid ammonia in good yields and in remarkable states of isomeric purity.[39] Since that time several metal/solvent systems have been found useful for the reduction of C=C and C≡C bonds in alkenes and alkynes, including lithium/alkylamine,[40] calcium/alkylamine,[41] sodium/HMPA in the absence or presence of a proton donor,[42,43] activated zinc in the presence of a proton donor (an alcohol),[44,45] and ytterbium in liquid ammonia.[46] Although most of these reductions involve the reduction of an alkyne to an alkene, several very synthetically useful reactions involve the reduction of $\alpha,\beta$-unsaturated ketones to saturated ketones.[47]

### 3.3.3.2 Mechanisms of Dissolving Metal Reductions

The mechanism of dissolving metal reductions depends on the nature of the solvent and the nature of the substrate. The proposed mechanism for the reduction of dialkylacetylenes by sodium in HMPA in the presence of a proton donor is illustrated in equation (18).[42] The addition of an electron to the triple bond of (**45**) is proposed to produce the *trans*-sodiovinyl radical (**46**), or the corresponding radical anion (**47**), which undergoes protonation by the added alcohol to produce the radical (**48**). Further reduction of (**48**) by sodium produces the *trans*-sodiovinyl compound (**49**), which on protonation produces the *trans*-alkene (**50**). In the absence of a proton donor, the reduction of (**45**) with sodium in HMPA results in the formation of a mixture of *cis*- and *trans*-2- and 3-hexenes.[42] Control studies showed that the isomerization products 2- and 3-hexene are not formed by rearrangement of the *cis*- or *trans*-3-hexenes. It was concluded that the starting alkyne (**45**) acts as a reversible proton donor reacting with an intermediate anion or radical anion to produce the delocalized anion (**51**) which is then protonated to produce the allene (**52**). Reduction of the allene (**52**), or further rearrangement to the alkyne (**53**) followed by reduction, then leads to the formation of the mixture of the *cis*- and *trans*-2- and 3-hexenes (equation 19).[42]

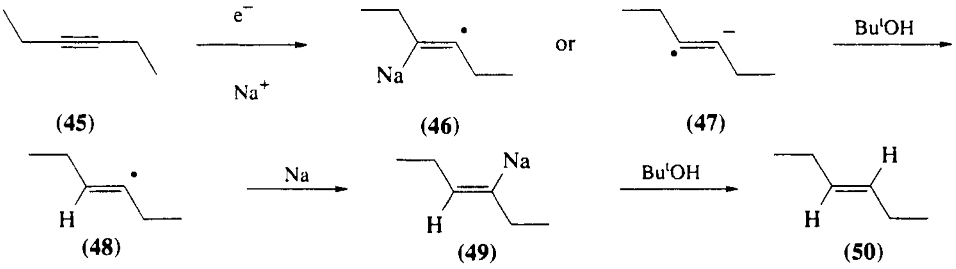

(18)

Although the mechanisms of the reductions of substituted alkynes by the other dissolving metal/solvent combinations have not been studied in such detail, it would appear that similar mechanisms are operative.

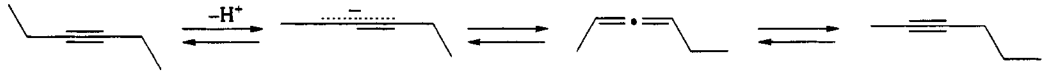

(19)

**(45)** **(51)** **(52)** **(53)**

The mechanism and stereochemistry of the lithium in ammonia reduction of α,β-unsaturated ketones has been studied by Stork and coworkers.[47] The reduction is proposed to proceed by formation of a metallated oxyallyl anion (**55**; equation 20), which undergoes protonation at the β-carbon atom.[47a] The stereochemistry of the protonation step was probed by the use of substituted octalones.[47b] The results supported the suggestion that the reduction of an octalone system with lithium in ammonia will produce the product of greatest stability (*cis* or *trans*) having the newly introduced hydrogen axial to the ketone-containing ring. This is required by the necessity of maintaining continual overlap of the π-orbital with the enolate double bond as shown in intermediate (**57**) in equation (21).[47b]

$$\mathrm{C{=}C{-}C{=}O} \xrightarrow[\mathrm{NH_3}]{\mathrm{Na}} \mathrm{C{=}C{=}C{-}OM} \qquad (20)$$

**(54)** **(55)**

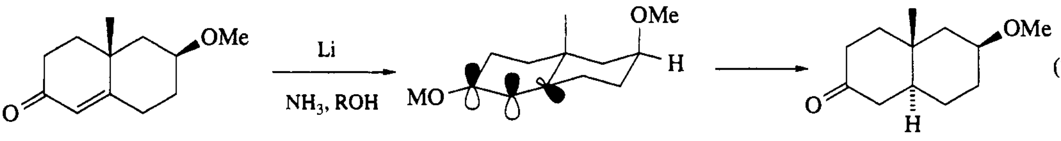

(21)

**(56)** **(57)** **(58)**

The reduction of α,β-unsaturated ketones with alkali metals in HMPA in the absence of a proton donor has been proposed to proceed *via* the mechanism shown in equation (22), in which a dianion is formed.[48] Protonation during work-up results in the formation of the final reduced product (**63**).

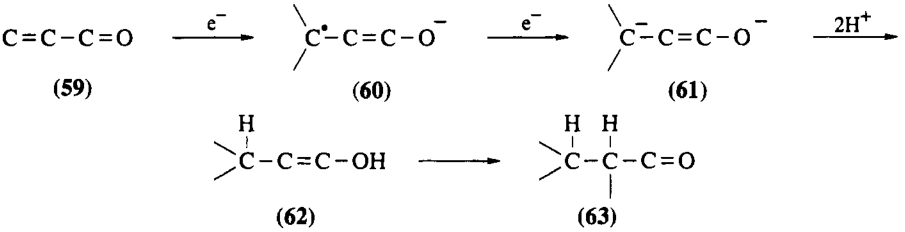

(22)

### 3.3.3.3 Scope and Limitations

In the initial studies by Campbell and Eby it was noted that 3- and 4-octyne, 3-hexyne and 5-decyne could be efficiently reduced to the corresponding *trans*-alkenes in good yields and with remarkably high stereoselectivity.[39] Shortly thereafter, Henne and Greenlee reported the quantitative reduction of 1-alkynes to 1-alkenes using sodium in ammonia in the presence of ammonium ion.[49] In the absence of ammonium ion, however, extensive metallation of the 1-alkyne occurs.[49] In the presence of ammonium ion dialkylacetylenes are inefficiently reduced (extensive hydrogen evolution occurs, in which sodium is consumed).[49]

Benkeser *et al.* have reported that the reduction of 3- and 5-octyne with lithium in ethylamine at −78 °C produces the corresponding *trans*-alkenes in good yield.[40] At 17 °C, however, overreduction of the alkene can occur if excess lithium is present.[40]

Although most of the reductions of carbon–carbon π-systems have involved the reduction of triple to double bonds, Whitesides and Ehmann have described the reduction of alkenes to alkanes using sodium

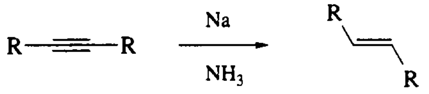

(64) R = Et, Pr$^n$, Bu$^n$ (65) (23)

in HMPA in the presence of *t*-butyl alcohol.[43] These reductions appear to be fairly stereoselective and produce the alkane probably arising from the more thermodynamically stable conformation of the intermediate anion, as illustrated in the reductions of (**66**) and (**69**) shown in equations (24) and (25).[43]

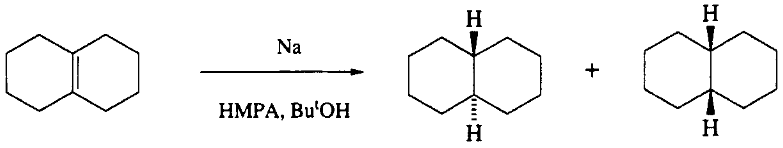

(**66**) (**67**) 91% (**68**) 3% (24)

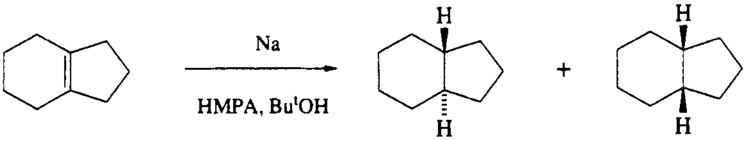

(**69**) (**70**) 73% (**71**) 27% (25)

The reduction of disubstituted acetylenes with calcium in mixed solvent systems or methylamine, ethylenediamine or amine–mixed solvent systems produces *trans*-alkenes in 70–88% yields; however, extensive migration (9–28%) of the π-bond occurs, which is attributed to isomerization of the alkyne as illustrated in equation (19).[41]

Zinc, either activated as a zinc/copper couple or by reaction with 1,2-dibromoethane, in the presence of an alcohol solvent effectively reduces alkynes to alkenes. Terminal alkynes are reduced essentially quantitatively to 1-alkenes.[44] Disubstituted acetylenes, interestingly, are reduced to the corresponding *cis*-alkenes, one example being illustrated in equation (26).[44] Zinc, activated by either LiCuBr$_2$ or dibromoethane, reduces conjugated diynes to conjugated (*Z*)-eneynes.[45] The triple bond nearest to a heteroatom functional group is preferentially reduced (equation 27).[45] The triple bonds of eneynes are also preferentially reduced (equation 28).[45] Finally, the disubstituted alkyne (**78**) is smoothly reduced to the

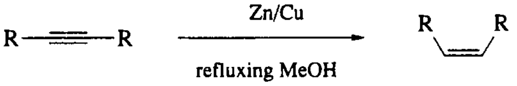

(**72**) R = Ph, CH$_2$OH (**73**) (26)

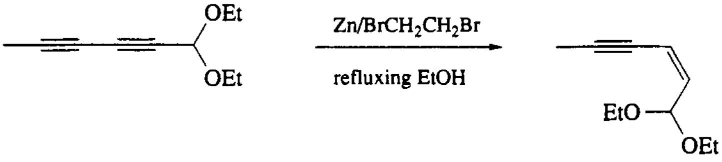

(**74**) *cis*-(**75**) (27)

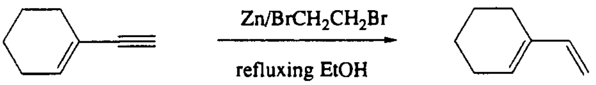

(**76**) (**77**) (28)

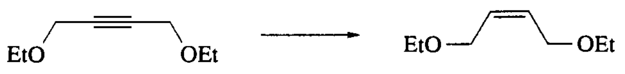

**(78)** **(79)**

(29)

($Z$)-alkene (**79**) without loss of the alkoxy functional groups (equation 29).[45] The mechanism of the zinc reduction of alkynes does not appear to have been studied in detail and the factors leading to the observed chemoselectivity and stereoselectivity are not readily apparent.

The reduction of disubstituted acetylenes with ytterbium in liquid ammonia also produces *trans*-alkenes in good yields.[46] This reducing system does reduce some double bonds, such as the strained double bond in norbornadiene; however, in general, carbon–carbon double bonds do not undergo reduction with this reducing system.[46] The expense of powdered metallic ytterbium does not make this a very practical reducing agent for synthetic purposes.

α,β-Unsaturated ketones undergo reduction with lithium in ammonia in the presence of an alcohol, as exemplified in equation (21).[47] A number of acyclic and cyclic α,β-unsaturated ketones have been reduced by alkali metals in anhydrous HMPA (*via* the dianion), or HMPA-containing nonprotic solvents, to the corresponding saturated ketones in 45–95% yields (equations 30 and 31).[48] The formation of the intermediate dianion apparently prevents further reduction of the carbonyl group.

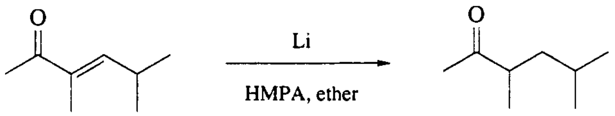

**(80)** **(81)** 55%

(30)

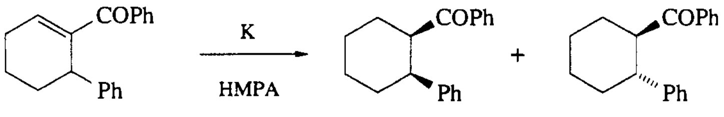

**(82)** **(83)** 72% **(84)** 18%

(31)

In summary, dissolving metal reductions are useful for the reduction of conjugated and nonconjugated alkynes, and the carbon–carbon double bonds of α,β-unsaturated ketones. The reduction of conjugated dienes appears not to have been extensively reported, and would probably give rise to mixtures of isomers. The reduction of conjugated dienes is a source of by-products in Birch reduction, when the intermediate anion is protonated at the terminus of the pentadienye system (see Chapters 3.4 and 3.5). Only one report on the reduction of nonconjugated alkenes has appeared. Although the results of studies on the attempted reductions of functionally substituted alkenes other than α,β-unsaturated ketones have not been reported, it should be obvious that this reduction procedure cannot be applied to systems that contain functional groups that will react with the dissolving metal, or the highly basic conditions that are generated during the course of the reaction.

## 3.3.4 REDUCTION OF C=C AND C≡C BY LOW-VALENT METAL SPECIES

### 3.3.4.1 Introduction

The reduction of alkynes[50] and electronegatively substituted alkenes[51] by $Cr^{II}$ in aqueous DMF was first reported by Castro and coworkers in 1964, who also carried out a detailed study of the mechanism of the reactions. It does not appear that reductions by other low-valent metal ions have been studied, or if so they are not capable of reducing carbon–carbon double and triple bonds.

### 3.3.4.2 Mechanism of the Reduction of C=C and C≡C by $Cr^{II}$

Alkynes are reduced to *trans*-alkenes in excellent yields by $Cr^{II}SO_4$ in aqueous DMF at room temperature (equation 32).[50] Terminal alkynes are reduced to terminal alkenes in excellent yield (equation 33).[50] The reduction of alkynes is second order in $Cr^{II}$. The proposed mechanism for the reduction involves rate-determining attack by $Cr^{II}$ on a 1:1 alkyne–$Cr^{II}$ complex as is illustrated in equation (34).[50] In order to account for the observed stereochemistry, the reduction is proposed to occur *via* the transition state structure (**91**).

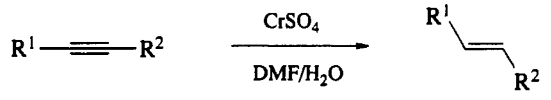

(32)

**(85)** **(86)** >85%

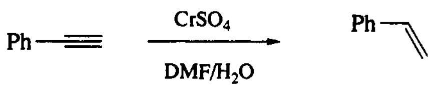

(33)

**(87)** **(88)**

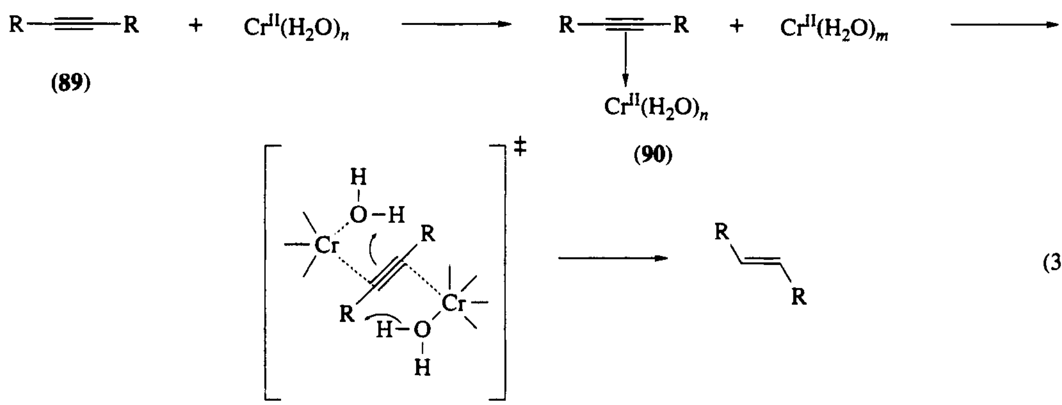

(34)

**(89)** **(90)** **(91)**

Simple alkenes do not undergo reduction by $Cr^{II}$.[51] However, electronegatively substituted alkenes, or apparently those bearing functional groups that are capable of forming a complex with $Cr^{II}$, are readily reduced by $Cr^{II}SO_4$ in good yields in aqueous DMF at room temperature.[51] As in the reduction of the substituted alkynes, this reaction has been shown to be second order in $Cr^{II}$ and first order in alkene. The reduction of alkenes, in general, shows little stereoselectivity or stereospecificity as is illustrated in equations (35) and (36), but in one case, equation (37), an unexplained high level of selectivity was observed. A mechanism was proposed for the reduction of electronegatively substituted alkenes involving com-

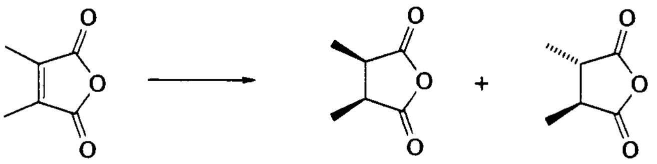

(35)

**(92)** **(93)** 85%; *meso*:(±) = 48:52

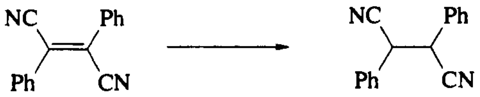

(36)

**(94)** **(95)** 84%; *meso*:(±) = 50:50

plexation of the substrate and reduction to an enol complex of general structure (**98**).[51] The presence of a carboxy, ester or nitrile function appears to be necessary to induce the reduction of carbon–carbon double bonds.

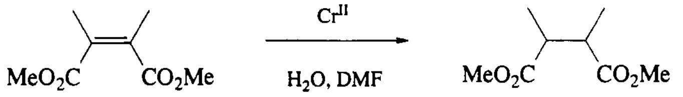

(37)

(**96**) (**97**) 100%; *meso*:(±) = 100:0

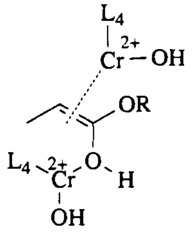

(**98**)

### 3.3.4.3 Scope and Limitations

The reduction of a carbon–carbon triple bond to a *trans*-alkene is a synthetically useful reaction. However, the synthetic utility of this reaction does not appear to have been evaluated, in particular with respect to the compatibility of other functional groups that might be present in the substrate molecule with the highly reducing capability of the Cr$^{II}$.

The reduction of carbon–carbon double bonds requires the presence of electronegative functional groups capable of forming a complex with Cr$^{II}$. Again, the problem of the compatibility of other functional groups with Cr$^{II}$ must be condsidered. The essentially total lack of stereospecificity in the reduction of such substituted alkenes also severely limits the synthetic applicability of this reduction reaction.

## 3.3.5 REDUCTION OF C=C AND C≡C BY METAL HYDRIDE–TRANSITION METAL HALIDE COMBINATIONS

### 3.3.5.1 Introduction

Alkynes and alkenes have been found to undergo reduction to alkenes and alkanes with LiAlH$_4$ in the presence of transition metal-(II) and -(III) halides from titanium to nickel.[52,53] The extent of reduction depends on the nature of the transition metal and the reaction conditions.[52] Copper and zinc halides do not effect reduction with LiAlH$_4$.[52,53] LiAlH$_4$ in the presence of Ti$^{IV}$ halides[54] and Zr$^{IV}$ halides[55] also effectively reduces alkenes to alkanes. NaBH$_4$ appears to less effective, only reducing alkynes and alkenes in the presence of Co$^{II}$.[56] NaH in the presence of Ni$^{II}$ acetate[57] and MgH$_2$ in the presence of Cu$^{I}$ iodide[58] reduce alkynes peferentially to *cis*-alkenes, and alkenes to alkanes.

### 3.3.5.2 Mechanism of Metal Hydride–Transition Metal Halide Reductions

All of the proposed mechanisms for the reduction of alkynes with metal hydride–transition metal halide combinations involve an initial hydrometallation of the π-system by the transition metal hydride, formed by the reaction of the original metal hydride with the transition metal halide, to form the vinylmetallic intermediate (**99**; equation 38). For the reduction of alkenes, similar alkylmetallic intermediates are implied to be formed. In the case of the reduction of alkenes with NaBH$_4$ in the presence of Co$^{II}$ in alcohol solution, the hydrometallation reaction appears to be reversible as evidenced by the incorporation of an excess of deuterium when NaBD$_4$ was used in the reduction.[56]

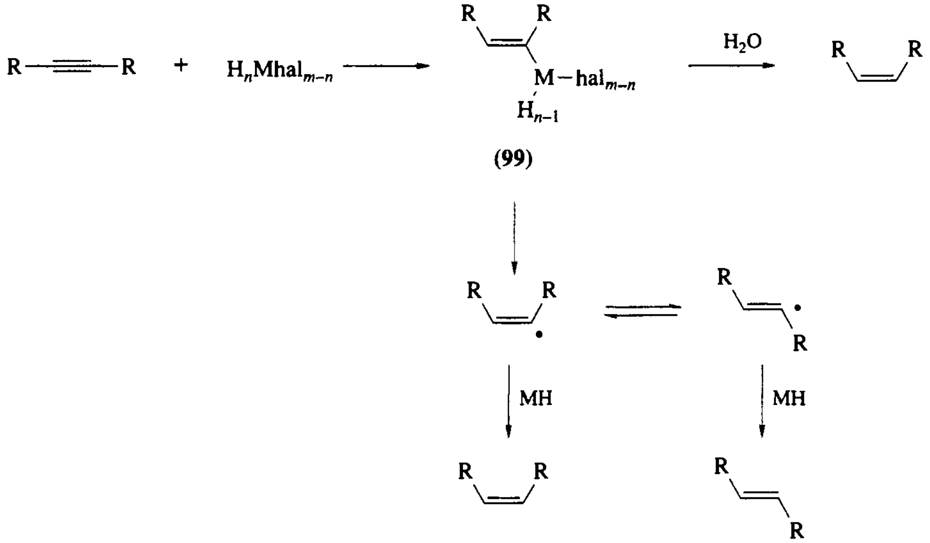

(99)

(38)

The mechanisms vary, however, in how the intermediate organotransition metallic intermediates are converted to the reduced products. In most cases, the reduction of alkynes results in the formation of predominantly the *cis*-alkenes; however, significant quantities of the *trans*-alkenes are also formed.[52,53,58] Also, in these cases there is little deuterium incorporation when the reaction mixture is worked up with deuterium oxide. In these cases a homolytic dissociation of the C—M bond is proposed to occur, the resulting vinyl radical then abstracting a hydrogen atom from a metal hydride species.[52] The stereochemistry of this process is consistent with the generally observed stereochemistry in such radical processes involving vinyl radicals. This homolytic process is very reasonable, particularly with those organotransition metal species possessing very weak C—M bonds. However, in the reduction of alkynes using $Ti^{III}$, quenching the reaction mixture with deuterium oxide results in very high incorporation of deuterium in the product, suggesting that the intermediate vinylmetallic species is stable toward homolytic cleavage under the reaction conditions. The reduction of alkynes with $MgH_2$ in the presence of $Cu^{I}$ gives the *cis*-alkene as the sole product.[58] In this case, the *cis*-alkene is proposed to be formed by the hydrolysis of the C—Cu bond during the hydrolytic work-up. This is also reasonable in view of the greater stability of C—Cu bonds and their hydrolytic reactivity.

In the case of the reduction of alkenes to alkanes, it does not appear that the stereo-selectivity or -specificity of this process has been studied. It is doubtful that the final steps in the reduction reactions differ from those proposed for the reduction of alkynes, and little stereo-selectivity or -specificity is to be anticipated. The mechanism for the reduction of alkenes with $LiAlH_4$ in the presence zirconium(IV) chloride is proposed to occur *via* a metal exchange reaction followed by hydrolysis (equation 39).[55]

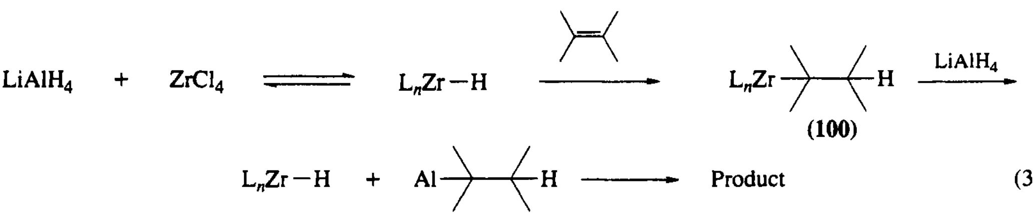

(100)

(39)

(101)

A possibility not suggested as a possible mechanism for the exclusive formation of the *cis* reduction product of a π-system is the reductive elimination of an organometallic hydride intermediate as illustrated in equation (40).

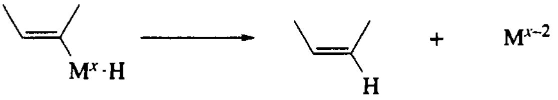

(40)

(102)

### 3.3.5.3 Scope and Limitations

The reduction of mono- and di-substituted alkenes with a 1:1 molar ratio of $\mathrm{LiAlH_4}$ and $\mathrm{Ti^{III}}$, $\mathrm{V^{III}}$, $\mathrm{Cr^{III}}$, $\mathrm{Mn^{II}}$, $\mathrm{Fe^{II}}$, $\mathrm{Fe^{III}}$, $\mathrm{Co^{II}}$ and $\mathrm{Ni^{II}}$ chlorides occurs in very high yields, with the relative efficiencies being Co > Ni > $\mathrm{Fe^{II}}$ > $\mathrm{Fe^{III}}$ > Ti > Cr > V > Mn > Cu > Zn.[52,53] Only Ti, Co and Ni were effective when present in catalytic quantities.[52,53] $\mathrm{Ti^{IV}}$ (ref. 54) and $\mathrm{Zr^{IV}}$ (ref. 55) chlorides are also effective for the reduction of alkenes to alkanes. Trisubstituted alkenes undergo reduction only slowly, and then only in the presence of $\mathrm{Co^{II}}$ and $\mathrm{Ni^{II}}$.[52,53] Tetrasubstituted alkenes apparently do not undergo reduction.

1-Alkynes undergo reduction to 1-alkenes, which in turn are further reduced to the corresponding alkanes. However, when the reduction of phenylacetylene is carried out in the presence of a stoichiometric amount of $\mathrm{FeCl_2}$, or a catalytic amount of $\mathrm{NiCl_2}$, at –40 °C for a short period of time, styrene is formed in excellent yield (very minor amounts of overreduction also occur).[52] When the reductions are carried out at room temperature for 24 h, however, excellent yields of ethylbenzene are obtained (equations 41 and 42).[52] The diarylacetylene, diphenylacetylene (**106**), is reduced to only *cis*-stilbene by $\mathrm{LiAlH_4}$ in the presence of $\mathrm{Fe^{II}}$ chloride (equation 43).[52] Dialkylacetylenes, such as (**107**), are cleanly reduced to *cis*-alkenes by $\mathrm{LiAlH_4}$ in the presence of $\mathrm{Ni^{II}}$ chloride (equation 44).[52] The use of the other transition metal chlorides in the reduction of alkynes results in the formation of small amounts of the *trans*-alkenes in addition to the predominant *cis*-alkene.[52-54]

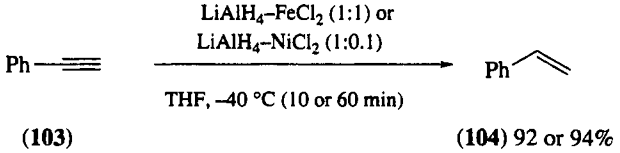

(41)

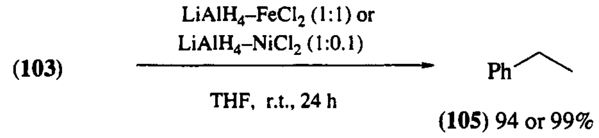

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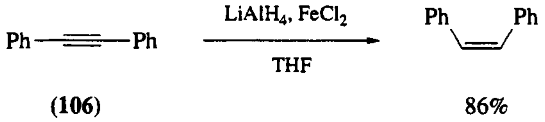

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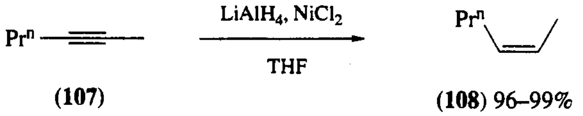

(44)

The use of $\mathrm{NaBH_4}$ as the hydride source appears to have been employed only with $\mathrm{Co^{II}}$ chloride.[56] Mono- and di-substituted alkenes readily undergo reduction, with *cis*-alkenes undergoing reduction faster than *trans*-alkenes. Trisubstituted alkenes react extremely slowly, while tetrasubstituted alkenes apparently do not undergo reduction.

NaH in the presence of *t*-butoxide and $\mathrm{Ni^{II}}$ acetate reduces mono- and di-substituted alkenes.[57] Trisubstituted alkenes do not react. 1-Alkynes are reduced to mixtures of *cis*- and *trans*-alkenes, which undergo competitive, further reduction to alkanes. $\mathrm{MgH_2}$, in the presence of $\mathrm{Cu^{I}}$ iodide or *t*-butoxide in THF at –78 °C, reduces 1-alkynes to 1-alkenes,[58] which are stable toward further reduction. Disubstituted acetylenes are cleanly reduced to *cis*-alkenes.[58]

The utility of metal hydride–transition metal halide reductions is limited only to alkenes and alkynes which do not contain functional groups which can react with the metal hydride, or with potential low-valent transition metal species. This severely limits the use of this reaction.

## 3.3.6 REDUCTION OF C═C BY IONIC HYDROGENATION REACTIONS

### 3.3.6.1 Introduction

'Ionic hydrogenation' is a term used to describe the reduction of a C═X π-system, or the hydrogenolysis of a C—X bond, by the use of a proton source and a hydride source in the same reaction.[59] Protonation of the π-system or the X functional group occurs to form a cationic intermediate, the cationic intermediate then abstracting a hydride from the hydride source. Although many proton sources have been utilized, the most common is trifluoroacetic acid. Similarly, many hydride sources have been investigated, with the most common being an organosilane.

### 3.3.6.2 Mechanism of the Ionic Hydrogenation Reaction

The rate-determining step in the ionic hydrogenation reaction of carbon–carbon double bonds involves protonation of the C═C to form a carbocation intermediate, followed by the rapid abstraction of hydride from the hydride source (equation 45).[60] There is a very sensitive balance between several factors in order for this reaction to be successful. The proton source must be sufficiently acidic to protonate the C═C to form the intermediate carbocation, yet not so acidic or electrophilic as to react with the hydride source to produce hydrogen. In addition, the carbocation must be sufficiently electrophilic to abstract the hydride from the hydride source, yet not react with any other nucleophile source present, *i.e.* the conjugate anion of the proton source. This balance is accomplished by the use of trifluoroacetic acid as the proton source, and an alkylsilane as the hydride source. The alkene must be capable of undergoing protonation by trifluoroacetic acid, which effectively limits the reaction to those alkenes capable of forming a tertiary or aryl-substituted carbocation. This essentially limits the application of this reaction to the reduction of tri- and tetra-substituted alkenes, and aryl-substituted alkenes.

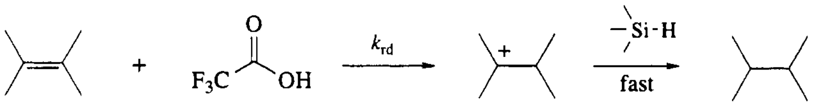

(45)

The ability of an organosilane to transfer a hydride to an intermediate carbocation is, in most cases, quite sensitive to the nature and number of the alkyl or aryl groups bonded to the silicon atom. The general sequence of reactivity decreases in the sequence: $Et_3SiH > (n\text{-}C_8H_{19})_3SiH > Et_2SiH_2 > Ph_2SiH_2 > Ph_3SiH > PhSiH_3$.[61–63]

The stereoselectivity of the ionic hydrogenation reaction appears to be controlled by the steric size of the trialkylsilane in the reduction of $\Delta^{9(10)}$-octalin (**109**; equation 46), which shows a high degree of sensitivity to the steric size of the organosilane hydride donor.[60] However, in the reduction of (**112**; equation 47) there is a considerably smaller change in the range of stereoselectivity of the reduction process.[60] The lower sensitivity in the stereoselectivity of reduction of (**112**) relative to (**109**) has been interpreted

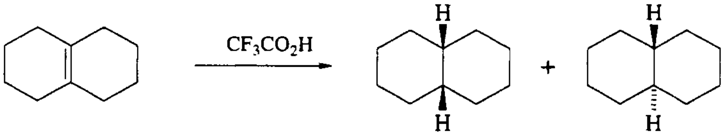

(46)

**(109)** **(110)** **(111)**

| | (110) | (111) |
|---|---|---|
| $Bu^nSiH_3$ | 22% | 78% |
| $Et_2SiH_2$ | 40% | 60% |
| $Et_3SiH$ | 42% | 58% |
| $Ph_3SiH$ | 58% | 42% |
| $Bu^s_3SiH$ | 72% | 28% |
| $Bu^t_2MeSiH$ | 83% | 17% |
| $Bu^t_3SiH$ | 93% | 7% |

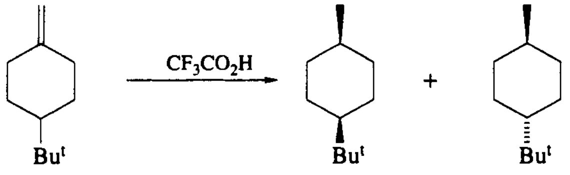

(47)

(112)

| | (113) | (114) |
|---|---|---|
| Bu$^n$SiH$_3$ | 4% | 96% |
| Et$_2$SiH$_2$ | 8% | 92% |
| Et$_3$SiH | 10% | 90% |
| Bu$^s_3$H | 16% | 84% |
| Bu$^t_2$MeSiH | 16% | 84% |

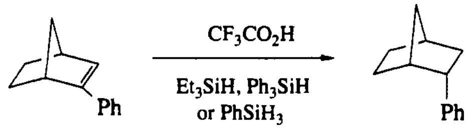

(48)

(115)

(116)

in terms that steric approach control may not be the sole factor responsible for the stereoselectivities observed in these reactions.[60] However, in the reduction of (**115**; equation 48), the delivery of hydride to the carbocation occurs exclusively from the less sterically hindered *exo* face.[64] It appears that the stereoselectivity of this reduction reaction is sensitive to the structure of the substrate, the structure of the hydride source and perhaps the solvent used for the reaction.

The 'ionic hydrogenation' reaction is not limited to the reduction of appropriately substituted alkenes, but has also been observed to occur with C=O and C=N π-systems.[59] In the case of the reduction of ketones,[67] if protonation of the resulting alcohol followed by loss of a molecule of water produces an aryl-substituted cation, reduction to the corresponding alkane occurs. Similarly alcohols can be induced to undergo 'ionic hydrogenolysis' if a reasonably stabilized carbocation can be formed on dehydration.[63,65,66] Other systems containing good leaving groups such as halides can also be induced to undergo 'ionic hydrogenolysis'.[59]

### 3.3.6.3 Scope and Limitations

The 'ionic hydrogenation' of carbon–carbon multiple bonds has been demonstrated only for the reduction of carbon–carbon double bonds which on protonation result in the formation of tertiary, or aryl-substituted, carbocations. The ability to use this reduction reaction with functionally substituted alkenes will be limited to those systems that do not contain functional groups that would otherwise react with trifluoroacetic acid or the organosilane.

There has been no report on the success, or failure, of the attempted reduction of C≡C bonds by the ionic hydrogenation type of reaction. The reason for this is not clear. Carbon–carbon triple bonds are capable of being protonated by trifluoroacetic acid to produce what appear to be vinyl cationic species, which should be capable of abstracting a hydride from an organosilane.

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# 3.4

# Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods

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## 3.4.1 INTRODUCTION

The reduction of aromatic compounds to their dihydro derivatives by dissolving metals is one of the most powerful synthetic procedures available to organic chemists. In one simple reaction it provides a bridge between aromatic and alicyclic molecules, thereby making much of the huge arsenal of aromatic chemistry readily available for the construction of alicyclic structures. It also furnishes the facility to carry through a protracted synthesis a moiety which is inert towards an extensive array of reagents, but which is readily converted by the reductive process into a range of useful functionalities.[1–6]

The most commonly used procedure is that established by Wooster[7] and extensively developed by Birch,[8] *i.e.* the reduction of a solution of the substrate in a mixture of liquid ammonia with an alcohol (usually ethanol or *t*-butyl alcohol) and an inert cosolvent (*e.g.* diethyl ether, tetrahydrofuran) with an alkali metal (lithium, sodium or potassium). Low molecular weight amines have been utilized in place of the ammonia, although the procedure then leads to more extensive reduction. Hexamethylphosphoramide may also serve in place of the ammonia,[9] but there is no apparent advantage to offset its higher cost, toxicity and carcinogenicity. Of rather more interest is the potential of electrochemical and photochemical approaches, which may give complementary outcomes.

The great majority of applications of the 'Birch reduction' have been centered on aromatic ethers, simple alkylbenzenes and bicyclic and polycyclic aromatic hydrocarbons. Over the past decade or so, however, there has been increasing attention given to other derivatives. The reductions of aromatic acids and amides have been placed on a systematic basis, while new procedures have been established for substrates which have until recently been regarded as unsuitable candidates for reduction, *e.g.* aromatic ketones and esters,[6] and even nitriles.[10]

## 3.4.2 THE BIRCH REDUCTION

Metals of Groups I and II dissolve readily in liquid ammonia. The resulting solutions of solvated electrons are powerful reducing agents that may be used to perform highly selective reactions. Our

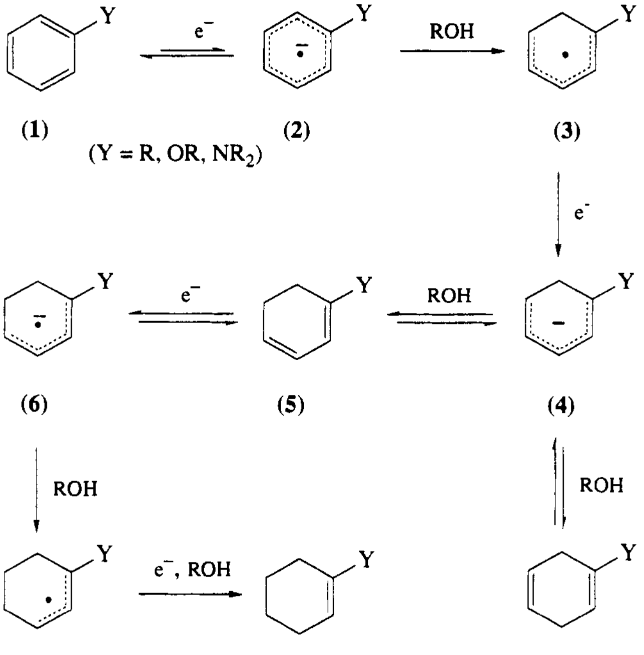

Scheme 1

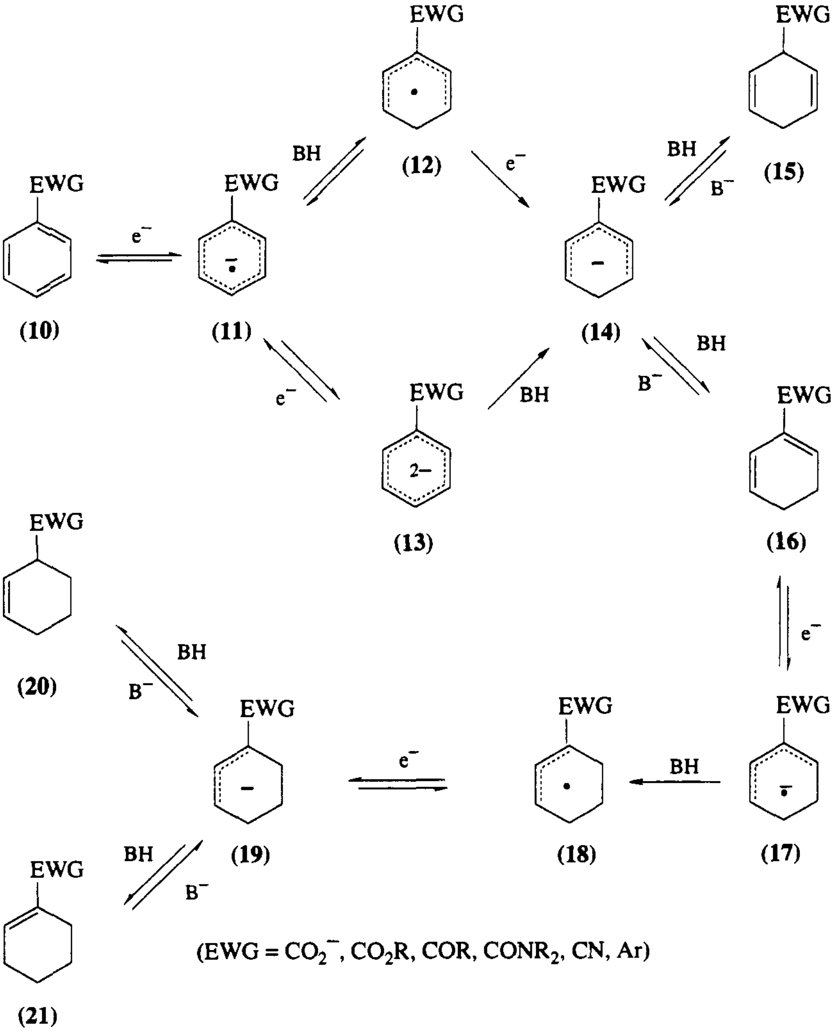

(EWG = $CO_2^-$, $CO_2R$, COR, $CONR_2$, CN, Ar)

**Scheme 2**

understanding of the details of the reduction process as applied to benzenoid substrates (**1**) and (**10**) is summarized in Schemes 1 and 2, respectively.[11] In the first case electrons are added in a reversible step to form a radical anion (**2**), which is protonated and reduced further to a pentadienyl anion (**4**).[12] For the more reactive substrate (**10**), the radical anion (**11**) may be protonated to afford the pentadienyl radical (**12**), or reduced further to a dianion (**13**)[13] which is then protonated to afford the same pentadienyl anion (**14**) that would be formed by reduction of (**12**). Protonation of anions (**4**) and (**14**) occurs predominantly at the central carbon atom[14] to form the unconjugated 1,4-dienes (**9**) and (**15**), respectively, which are resistant to further reduction.

With substrates bearing electron-withdrawing groups (EWG) the radical anions are formed in sufficiently high concentrations that protonation by ammonia proceeds rapidly. However, with hydrocarbons and aromatic ethers *etc.*, it is necessary to displace the initial equilibrium between the substrate and the radical anion through protonation by a stronger acid than ammonia ($pK_a$ *ca.* 35). Alcohols ($pK_a$ 16–20) are normally used for this purpose.

Overreduction may occur as a consequence of initial protonation at the terminal atoms of the cyclopentadienyl anions to form the conjugated 1,3-dienes (**5**) or (**16**), which are then vulnerable to further reduction, affording tetrahydro products, *e.g.* (**8**), (**20**) or (**21**). These products can also be formed when the reaction medium is sufficiently basic to catalyze conjugation of the 1,4-dienes to the 1,3-isomers. The alcohol may then serve an important additional role by functioning as a buffer (*cf.* Section 3.4.3.6, however).

### 3.4.2.1 Experimental Procedures

Procedures for metal–ammonia reductions have been described in several reviews[1–6] and are outlined for specific substrates in later parts of this section. The following comments are therefore only a summary of the more important factors. Many reductions are relatively insensitive to the choice of conditions, but the majority may be significantly improved by the appropriate choice of metal, proton source, temperature, order of mixing and quenching procedure.

Although it may not always be necessary it is advisable, at least during feasibility studies on a new reaction, that reduction be carried out in ammonia which has been thoroughly dried and then distilled. This is especially important when sodium or potassium are employed since colloidal iron, which invariably contaminates commercial sources of ammonia, catalyzes the formation of amide ion and the reaction of these metals with alcohols; lithium is not significantly affected. There are many examples, however, where reaction mixtures have been deliberately doped by iron salts to suppress overreduction.

Sodium metal is a convenient drying agent for liquid ammonia, and a small amount of an iron salt should be added to catalyze the formation of sodium amide, since sodium itself reacts progressively more slowly with water as the pH of the ammonia solution increases. Oxygen should be rigorously excluded from the reaction, and although ammonia at reflux provides quite good protection, it is advisable to employ an inert atmosphere. Nitrogen is usually satisfactory, but there is a potential for reaction with lithium, so the use of helium or argon has been recommended for reductions with this metal.[3] Temperature is often an important factor and should be monitored with an internal thermometer or sensor. Low temperatures (less than –70 °C) may be crucial for the ring reduction of aromatic esters and ketones, and help to suppress unwanted side reactions with other substrates, *e.g.* hydrogenolysis of methoxy substituents.

The choice of metal can have a profound effect on the outcome of a reduction,[15] and this has been attributed in some cases to the differences in reduction potential (Li = –2.99 V, Na = –2.59 V, K = –2.73 V, Ca = –2.39 V), but variations in outcome are probably due more to the effects of aggregation or coordination of intermediates with the metal cation. Lithium and sodium are usually the most satisfactory, but potassium may be superior, and sometimes essential for specialized applications.[16] Calcium metal has been recommended for reductions in methylamine/ethylenediamine and for the reduction of α-acetoxy ketones, while magnesium appears to offer advantages in some reductions of aromatic amides, esters and polycyclic hydrocarbons.[17] On the whole, however, there appears to be little point to the use of metals other than the common members of Group I. The solubilities of ionic substrates, *e.g.* carboxylate salts, and their products depend very much on the metal counterion, although it is common for insoluble substrates to dissolve as the reduction progresses. Alcohols aid solubility, but a cosolvent is usually necessary, and tetrahydrofuran (which must be dry and oxygen free) is most commonly utilized, although other ethers may be employed.

Tertiary alcohols (butyl and amyl) react very slowly with the metal, but methanol or ethanol protonate the intermediate radical anions more rapidly and can suppress side reactions; propan-2-ol may provide an effective compromise.[5] Water and ammonium salts have also been used for protonation, but have an undesirable effect on many reactions, and should be avoided for quenching purposes while any metal remains. Any excess of metal is best consumed by the addition of a simple diene (isoprene or penta-1,3-diene), since the metal will often react more rapidly with the (protonated) product than with the quenching agent, leading to overreduction. Inverse quenching has been advocated for especially sensitive products.[18]

It has been noted elsewhere[3] that the order of addition of reagents is the most important single variable to influence product distribution. A procedure which is convenient and normally reliable is based on the addition of small pieces of metal to a mixture of substrate, ammonia, solvent and (if appropriate) alcohol at less than –70 °C until the blue colour persists for a reasonable period (approximately 10 min). For less reactive substrates, lithium should be used and the addition of the alcohol delayed so that a higher concentration of metal is maintained during the reduction process. Quenching is best effected by 1,3-pentadiene (or similar substance), followed either by ammonium chloride or another electrophile. In reactions where *in situ* alkylations are performed these are best carried out on lithium derivatives, so in cases where other metals have been used for reduction carefully dried lithium bromide is added before the electrophile.

### 3.4.2.2 Scope and Limitations

#### *3.4.2.2.1 Substituent effects*

Electron-releasing groups direct reduction to unsubstituted 2,5-positions, and while alkyl groups retard reduction (*t*-butyl > isopropyl > ethyl > methyl), alkoxy groups slightly accelerate the rate of reaction.[19] A selection of reaction rates is provided in Table 1. Phenols are rapidly ionized and the resulting salts are resistant to electron addition, although reduction may be effected with high concentrations of lithium.[20] In sharp contrast, β-naphthols are reduced in the hydroxy-bearing ring, furnishing the corresponding β-tetralones.[21]

**Table 1** Rates of Reduction of Substituted Benzenes Relative to Benzene[19]

| *Compound* | *Relative rate* | *Compound* | *Relative rate* |
|---|---|---|---|
| *p*-Di-*t*-butylbenzene | <0.005 | *m*-Xylene | 0.28 |
| Mesitylene | 0.017 | *p*-Xylene | 0.30 |
| *t*-Butylbenzene | 0.050 | Dimethylaniline | 0.30 |
| *o*-Xylene | 0.050 | Tetralin | 0.38 |
| Isopropylbenzene | 0.10 | Indane | 0.94 |
| Aniline | 0.10 | Benzene | 1.0 |
| *n*-Butylbenzene | 0.21 | Anisole | 3.28 |
| Ethylbenzene | 0.25 | Sodium benzoate | >200 |

Groups which allow electron delocalization also accelerate reduction (sodium benzoate reduces >200 times more rapidly than benzene, for example) and afford 1,4-dihydro derivatives, irrespective of alkyl, alkoxy and amino substituents. A major limitation on the choice of electron-withdrawing groups is the ease with which they themselves undergo reduction. Carboxylic acids present no difficulties, but esters, amides, ketones and polycyclic aromatic compounds usually require specially selected conditions. In the absence of an electron-withdrawing group, however, it is often difficult to reduce benzene rings which carry bulky substituents or which are heavily substituted, although there are examples where intramolecular protonation greatly accelerates reaction (see below).

#### *3.4.2.2.2 Secondary reactions*

A variety of secondary reactions may reduce the yield of a desired product and in some cases prevent its formation altogether, *e.g.* it is possible for ether groups to be dealkylated, and for both aryl and benzylic heteroatom substituents to undergo hydrogenolysis (see Section 3.4.3.11). Rearomatization may be a problem, usually through the presence of oxygen but in some cases by loss of hydride ion. Tetrahydro products often arise as a consequence of either initial protonation at C-1 or C-5 of the intermediate pentadienyl anions, or base-catalyzed conjugation of 1,4-cyclohexadienes, or as a result of quenching procedures which do not ensure complete consumption of the metal before protonation of the product anions. Ammonia is an excellent solvent for alkylations but may prove to be too nucleophilic for very reactive electrophiles, such as benzyl iodides.

## 3.4.3 SURVEY OF BIRCH REDUCTIONS

### 3.4.3.1 Benzenoid Hydrocarbons and Ethers

The use of anisoles (**22**) as synthetic equivalents to cyclohex-2-enones (Scheme 3) has been widespread since the original observations of Birch, and the literature is replete with examples over the past five decades, *e.g.* in the syntheses of steroids,[2] terpenoids[6] and alkaloids.[22,23] The most thorough studies have been carried out within the context of the conversion of estrone derivatives to 19-norandrostane and pregnane derivatives and are instructive for the selection of reagents and reaction parameters for reductions of this general type.[5]

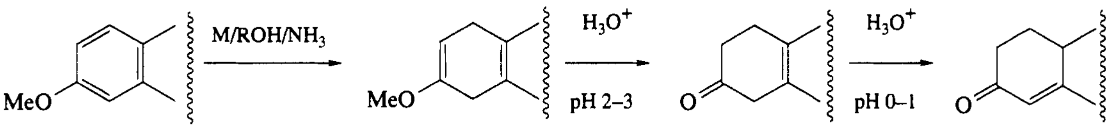

**(22)**

**Scheme 3**

The Birch reduction of aromatic hydrocarbons and ethers to the 2,5-dihydro derivatives proceeds most satisfactorily when the substitution pattern allows the addition of hydrogen to two unsubstituted positions in a *para* relationship. If this requirement is satisfied, better yields are obtained from more highly substituted aromatic rings than from (say) anisole itself, which affords a substantial amount (20%) of 1-methoxycyclohexene (*cf.* Scheme 1). Extra substitution presumably hinders protonation at the terminus of the dienyl anion (which would lead to a conjugated diene and overreduction). The utilization of anisole moieties as precursors to cyclohexenones has been of very limited value with many 1,2,3-substitution patterns and more densely substituted derivatives. Compounds (**23**) to (**26**), for example, have only been reduced by employing massive excesses (200–600 equiv.) of lithium metal,[24] while the aromatic ring in (**28**) is completely resistant to reduction.[25]

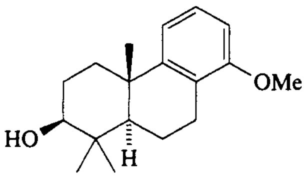

**(23)**

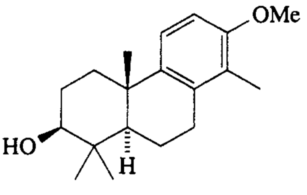

**(24)**

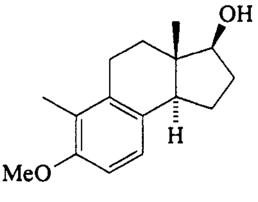

**(25)**

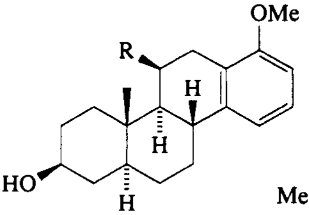

(**26**) R = H
(**27**) R = OH

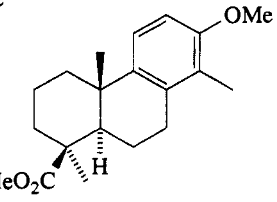

**(28)**

The reduction of silyl aryl ethers in place of the more common alkyl analogs is a useful variation,[26] which would seem to have considerable potential in view of the widespread use of silyl ethers in synthesis. Trimethylsilyl ethers are cleaved during the reaction process (presumably through attack by alkoxide ion), but both *t*-butyldimethylsilyl (**29**) and isopropyldimethylsilyl (**30**) phenyl ethers are stable in the reducing medium and afford the 1,4-dihydroaryl silyl ethers (**31**) and (**32**) in 80–97% yields. The dihydroaromatics (**33**; R = Me, OMe) were used as precursors to the relatively inaccessible β,γ-unsaturated ketones (**34**) through fluoride-mediated hydrolysis of the silyl enol ethers. Alternatively, (**33**; R = Me) could be regiospecifically *C*-acylated to give (**35**).

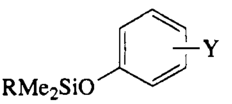

(**29**) R = $Bu^t$
(**30**) R = $Pr^i$

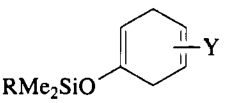

(**31**) R = $Bu^t$
(**32**) R = $Pr^i$

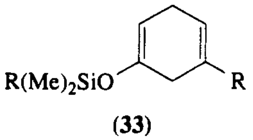

**(33)**

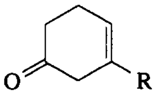

**(34)**

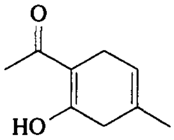

**(35)**

### *3.4.3.1.1 Intramolecular protonation of Birch intermediates*

A number of isolated reports in the literature indicate that neighboring hydroxy functions enhance the rates of reduction of substrates which would otherwise be very slow to react. It has been suggested that the rate accelerations may stem from both complexation with the metal counterion associated with the intermediate radical anion and intramolecular protonation. It was found, for example, that the yield of reduction products from the 11β-hydroxy derivative (**27**) was significantly enhanced (>69%)[27] when compared with the 33% yield obtained from the analog (**26**), although the reaction was still carried out with *ca.* 600 equiv. of lithium metal. Selective reduction of the A-ring in the tetrahydropyranyl ether (**36**) could be achieved satisfactorily, but in the alcohol (**37**) concomitant reduction of the 13-phenyl group took place, indicating participation by the 17α-hydroxy.[28]

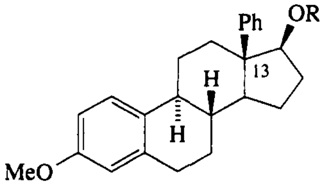

**(36)** R = THP
**(37)** R = H

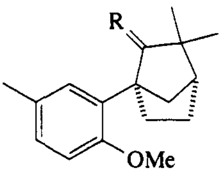

**(38)** R = O
**(39)** R = CH$_2$

Lithium–ammonia reduction of the arylnorbornanone (**38**) proceeded satisfactorily *via* the *exo*-alcohol to give the normal dihydroaromatic derivative, whereas the methylene analog (**39**) gave a 1:1 mixture of dihydro and tetrahydro products.[29] Recent studies on the reduction of dimethanoanthracenes (**40**) to (**42**) have provided some very interesting examples of the intramolecular protonation of radical anions (Scheme 4). Reduction of the parent hydrocarbon (**40**) or the methoxy derivative (**41**) proceeds very slowly to give the expected dihydro compounds (**43**) and (**44**), respectively. Alcohol (**42**), however, is

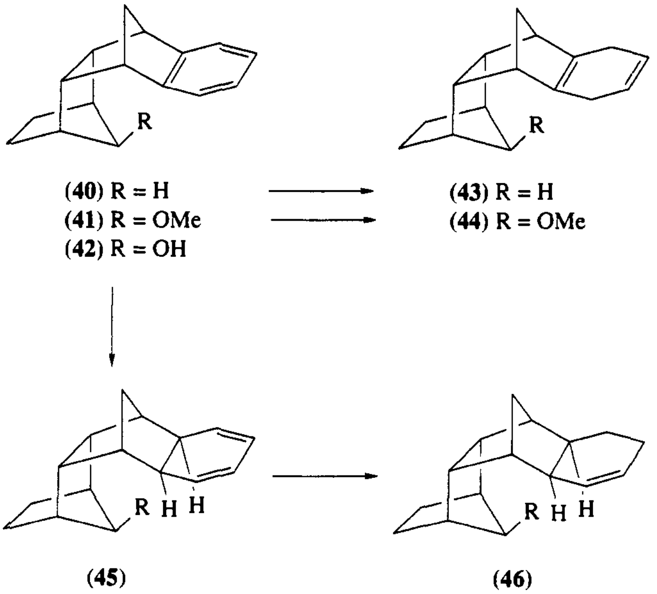

**Scheme 4**

reduced within minutes to the tetrahydro product (**46**), which arises through protonation at substituted positions on the more hindered face of the aromatic ring and is therefore clearly intramolecular in nature. It may be assumed that diene (**45**) is an intermediate, and it has been found that a sample prepared independently is reduced under the same conditions to (**46**).[30]

During a total synthesis of the diterpenoid enmein, the tricyclic alcohols (**47**) and (**48**) were converted into a range of C-ring ketones (Scheme 5). The degree of reduction and the ease with which it occurs, relative to (**23**), make it apparent that intramolecular protonation is involved here also.[31]

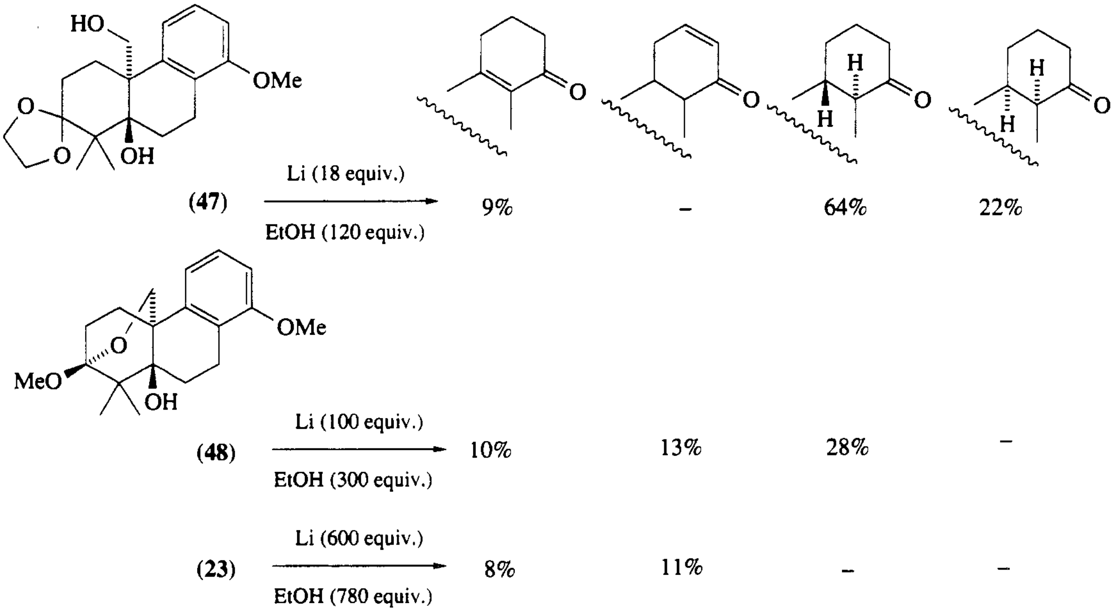

Scheme 5

### 3.4.3.2 Alkyl- and Alkoxy-naphthalenes

Naphthalene (**49**) reacts with sodium in liquid ammonia to form a red complex which is quenched by methanol to form the 1,4-dihydro derivative (**51**), and may therefore be assumed to be the dianion (**50**).[32] If alcohol is present in the reaction mixture, then the 1,4,5,8-tetrahydro derivative (**52**) is formed (Scheme 6). 1-Naphthyl derivatives are reduced in the unsubstituted ring, whereas there is a marked preference for reduction of the substituted ring in 2-methyl- and 2-methoxy-substituted isomers. This preference is not as well defined for bulkier substituents, however, and is reversed in the case of 2-*t*-butylnaphthalene; further details are in a 1970 review.[3] Because of the facile isomerization of the 1,4-dihydro isomers to conjugated derivatives, overreduction occurs readily and ether groups are fairly readily hydrogenolyzed. It is therefore important to select the reaction conditions with care.[33]

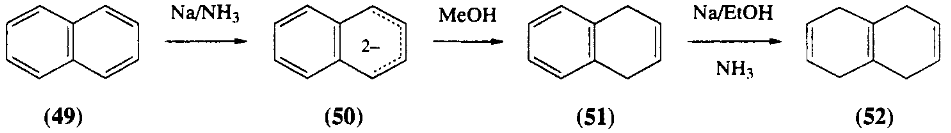

Scheme 6

### 3.4.3.3 Biphenyls, Fluorenes and Fused Polycyclic Hydrocarbons

There has been some confusion over the structure of the dihydro reduction product of biphenyl (**53**), first reported 50 years ago. However, it has been firmly established that it is the 1,4-dihydro derivative (**54**), as would be expected if the second aryl group is viewed as an EWG substituent, and from theoretical considerations.[34] The conflicting analyses have been due to the ease with which the products undergo isomerization. Biphenyls with substituents at C-2 and C-3 tend to undergo reduction in the substituted ring (*e.g.* 80% in the 3-methyl derivative). Reduction of 4-methylbiphenyl is indiscriminate, however, while the 4-methoxy analog gives only deoxygenated products.[35]

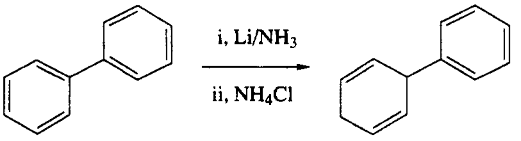

**(53)** **(54)**

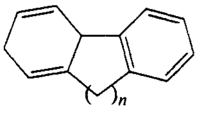

**(55)**

Fluorene has been reported to afford the 3,9a-dihydro product, but it is almost certain that this is the 2,4a-dihydro isomer (**55**; *n* = 1) by analogy with biphenyl.[3] 9,10-Dihydrophenanthrene (**56**) is reduced as expected to (**55**; *n* = 2), but spontaneously reverts to the starting material on standing. These systems do not require the presence of alcohol for reduction and it is consequently possible to alkylate the intermediate anions with alkyl halides, as (**56**) gives (**57**).[36] These products are much more stable and structural analysis is simplified accordingly; oxidation of the doubly allylic methylene occurs readily to afford the dienone (**58**; Scheme 7). Dienones of this type have potential as intermediates for the synthesis of natural products.[37] Anthracene and phenanthrene are both readily reduced in the central ring to form the 9,10-dihydro derivatives as might be expected, but to avoid further reduction it is necessary to have an iron salt present. Further examples are reviewed elsewhere.[3]

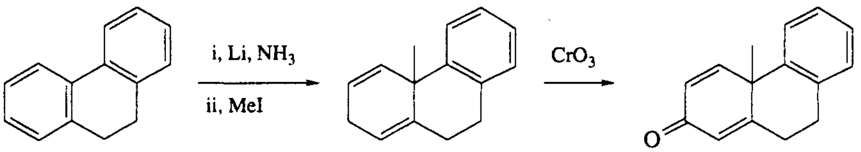

**(56)** **(57)** **(58)**

**Scheme 7**

### 3.4.3.4 Phenols

Phenols are normally resistant to reduction as a consequence of ionization. This property was put to good effect in the reduction of 7-methoxyfluoren-2-ol (**59**; Scheme 8).[38] Because the phenoxide ring does not serve as an electron sink, the 5,8-dihydro derivative is formed, while the styrenic double bond is protected from reduction. However, phenols have been reduced with concentrated solutions of lithium (Scheme 9),[20] and 4-methoxyphenol (**63**) is reduced to (**64**) under surprisingly mild conditions (Scheme 10).[39]

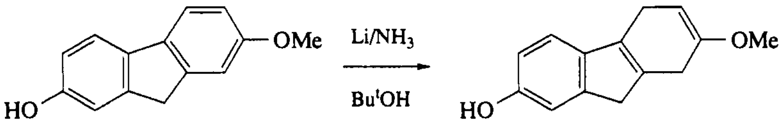

**(59)** **(60)**

**Scheme 8**

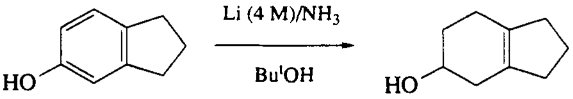

**(61)** **(62)**

**Scheme 9**

2-Naphthols are reduced to β-tetralones (which are presumably protected from further reaction as the corresponding enolate anions) even more readily and it is surprising to find that even 6-methoxy-2-naphthol (**65**) is converted into ketone (**66**; Scheme 11).[40] Reduction of the equilenin ketal (**67**) was found to be highly dependent on the choice of metal. Reduction of (**67**; Scheme 12) or its sodium salt by lithium in the absence of an alcohol afforded (after acid hydrolysis) equilin (**68**) as the major product, whereas

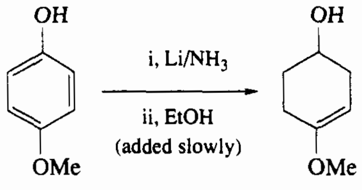
OH
i, $Li/NH_3$
ii, EtOH
(added slowly)
OMe
OH
OMe

**(63)** **(64)**

**Scheme 10**

the tetrahydro derivative (**69**) was obtained by reduction with potassium. It was shown that (**68**), the presumed intermediate in the formation of (**69**), was reduced directly and was not isomerized to the conjugated 8-ene beforehand. Similar results were obtained by reduction of 2-naphthol (**71**; Scheme 13) with sodium (again without an added proton source) which afforded a 3:2 mixture of (**72**) and (**73**). Reduction of (**67**) by calcium, however, yielded the A ring reduced derivative (**70**) as a mixture of epimers.[15]

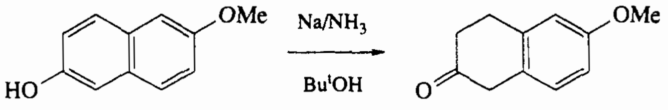
OMe
HO
$Na/NH_3$
$Bu^tOH$
OMe
O

**(65)** **(66)**

**Scheme 11**

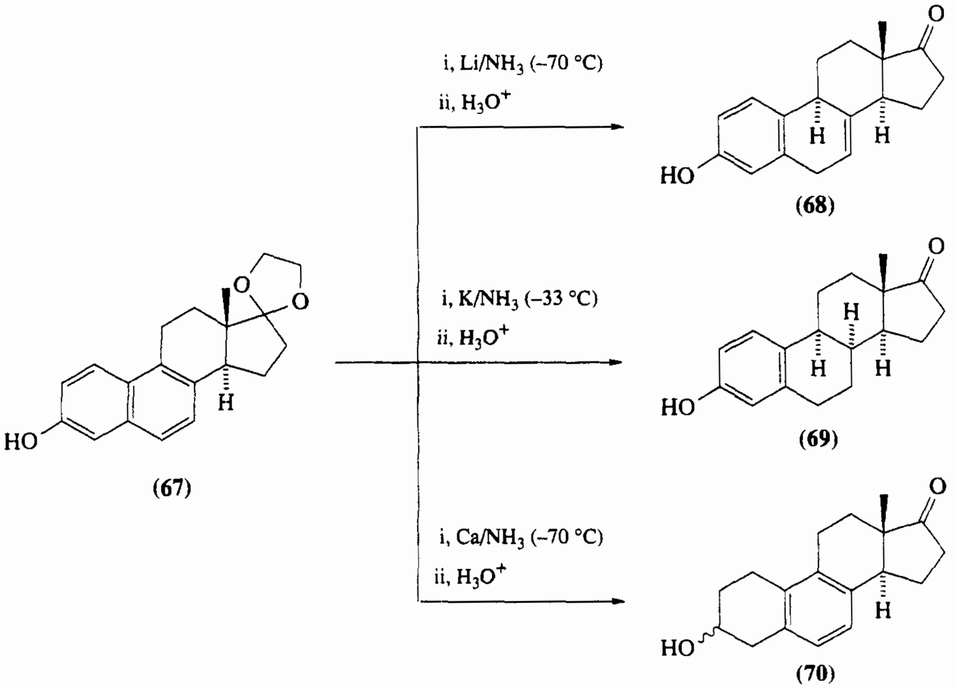
i, $Li/NH_3$ (−70 °C)
ii, $H_3O^+$
i, $K/NH_3$ (−33 °C)
ii, $H_3O^+$
i, $Ca/NH_3$ (−70 °C)
ii, $H_3O^+$
(67)
(68)
(69)
(70)
HO
O
H

**Scheme 12**

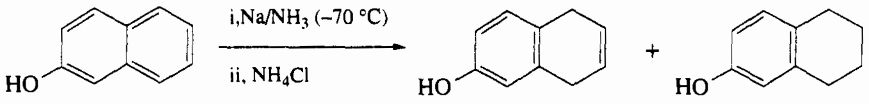
i, $Na/NH_3$ (−70 °C)
ii, $NH_4Cl$
HO
+

**(71)** **(72)** **(73)**

**Scheme 13**

### 3.4.3.5 Aromatic Amines

*N*,*N*-Dimethylaniline was one of the earliest substrates for reduction examined by Birch. This and subsequent studies have shown that a variety of aniline derivatives are reduced initially to the 2,5-dihydro derivatives (**74**), but also that these are easily isomerized to the 2,3-dihydro isomers (**75**) either *in situ* (leading to tetrahydro derivatives) or during work-up procedures.[41] The dienamines formed in this way may be hydrolyzed to cyclohexenones, treated with electrophiles, or utilized in [4 + 2] cycloadditions. The less basic morpholino dienamines (**76**) are more stable and afford the most reliable outcomes.[42]

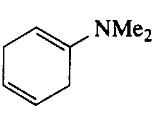

(**74**)

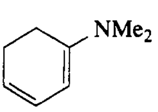

(**75**)

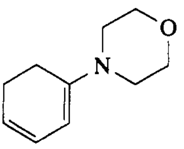

(**76**)

### 3.4.3.6 Carboxylic Acids

Aromatic acids are reduced by metal–ammonia solutions very much more readily than simple hydrocarbons and ethers. In contrast to the normal requirements for the latter derivatives, it is often possible to achieve reduction with close to stoichiometric quantities of metal. The addition of aromatic carboxylic acids to liquid ammonia (or *vice versa*) results in the immediate precipitation of the ammonium salt. As the metal is added, however, the precipitate usually dissolves as reduction proceeds, especially if lithium is used. If reduction is carried out in carefully dried, redistilled ammonia, as little as 2.2 mol of lithium are consumed in some cases, thereby demonstrating that the substrate is reduced much more readily than the ammonium ions, which instead react with the intermediates from reduction of the substrate. However, protonation by $NH_4^+$ is not essential since reduction proceeds equally well on preformed metal carboxylates (although low solubility is then often a problem). The addition of an alcohol is not necessary, but it may serve as a useful buffer and can often improve solubility. The presence of alcohol can nevertheless be deleterious, since it facilitates isomerization of the initially formed 1,4-dihydro isomer to the 3,4-isomer and in this way affords the possibility of further reduction.[43]

#### *3.4.3.6.1 Reductive alkylations*

The reduction of benzoic acids affords the dienolate (**77**) which may be alkylated *in situ* by a variety of electrophiles to afford 1-substituted derivatives. Clearly, the addition of alcohol must be avoided or limited to small quantities. It may also be necessary to remove the ammonia before adding the electrophile. The vast majority of applications have been based on reactions with alkyl halides to form (**78**), but additions of (**77**) to formaldehyde,[44] epoxides[45] and α,β-unsaturated esters[46] to form the range of adducts (**79**) to (**81**) have also been reported (Scheme 14).

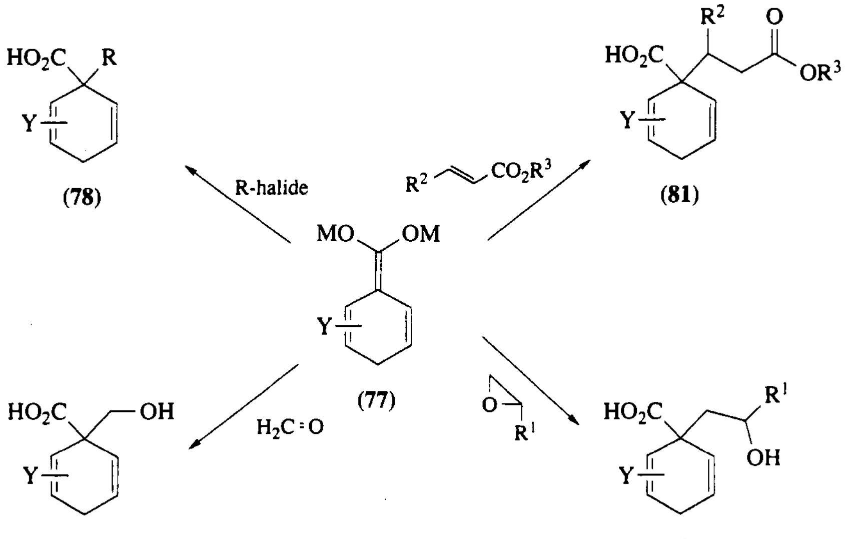

Scheme 14

The 1,4-dihydrobenzoic acids derived from reductive alkylation may undergo facile rearomatization with either loss of the carboxylic acid group or the alkyl group. The gibberellin synthesis intermediate (**82**), for example, was found to be especially labile, forming (**83**) simply on exposure to air.[47] Oxidative decarboxylation may be deliberately achieved with lead tetraacetate or electrochemically.[48] Loss of the 1-alkyl group is likely to be a problem when the alkyl moiety can form a reasonably stable free radical, since a chain reaction may then be sustained.[49]

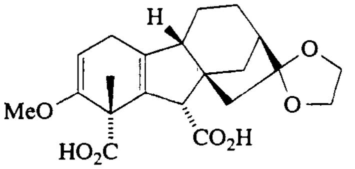

(**82**)

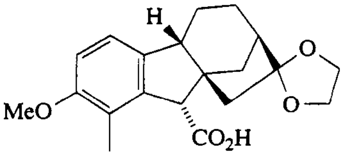

(**83**)

### 3.4.3.6.2 *Alkylbenzoic acids*

Following the early studies of Birch,[8] a comprehensive study of the reduction of alkylbenzoic acids was undertaken by Van Bekkum *et al.*[43] These authors found that 2-alkyl derivatives gave almost quantitative yields of 1,4-dihydro products irrespective of the procedures employed. With other alkyl derivatives, generally excellent yields of 1,4-dihydro compounds were again obtained from combinations of Li–NH$_3$ (NH$_4$Cl quench), Li–NH$_3$–H$_2$O, or Li–NH$_3$–EtOH (NH$_4$Cl quench). With the last combination, however, significant quantities of tetrahydro products from 4-alkyl derivatives were obtained, and if the NH$_4$Cl quench was omitted, 4,5-dihydro isomers became the major products. If an excess of NH$_4$Cl was added before the lithium metal, then extensive reduction of the carboxy group took place. *C*-Alkylation experiments were also conducted and invariably gave 1-alkyl-1,4-dihydro products when alkylation occurred. Not surprisingly, alkylation did not occur when water had been added, while variable results were obtained in the presence of ethanol. In the absence of an added proton source the yields were excellent.

### 3.4.3.6.3 *Tetrahydrobenzoic acids*

The first sets of experiments carried out on the reduction of benzoic acids gave mixtures of dihydro and tetrahydro derivatives. This is hardly surprising in the light of the Van Bekkum study. The first systematic investigation appears to have been carried out on *p*-isopropylbenzoic acid (**84**; Scheme 15),[50] for which it was found that reduction by lithium–ammonia at –70 °C followed by the addition of ethanol and then ammonium chloride at 5 min intervals furnished a 2:1 mixture of *trans*- and *cis*-1,4-dihydro derivatives (**85**). In the absence of ammonium chloride the 3,4-dihydro isomer (**86**) was obtained and this could be reduced further to a 2.5:1 mixture of the tetrahydro derivatives (**87**) (ammonium chloride quench) and (±)-phellandric acid (**88**).

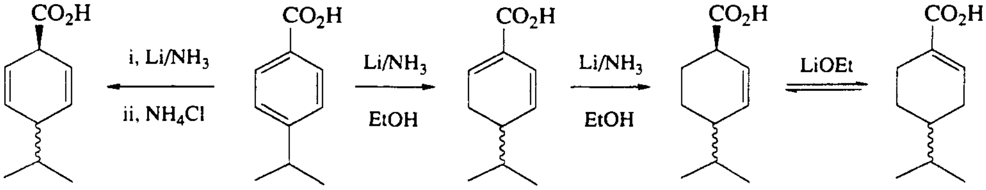

(**85**) (**84**) (**86**) (**87**) (**88**)

**Scheme 15**

Indane-2-carboxylic acid (**89**) has been converted in a similar manner (Scheme 16) to the hydrindene acid (**90**).[51] A crucial step in the conversion of (–)-abietic acid into (+)-kaurene (**93**) and (+)-phyllocladene (**94**) involved the reduction of (**91**) to the mixture of epimers (**92**) combined with other double-bond isomers (Scheme 17).[52]

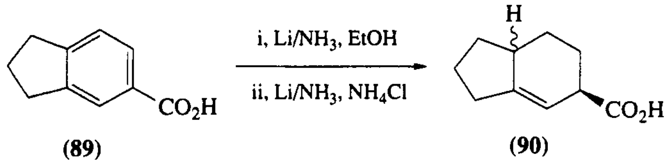

Scheme 16

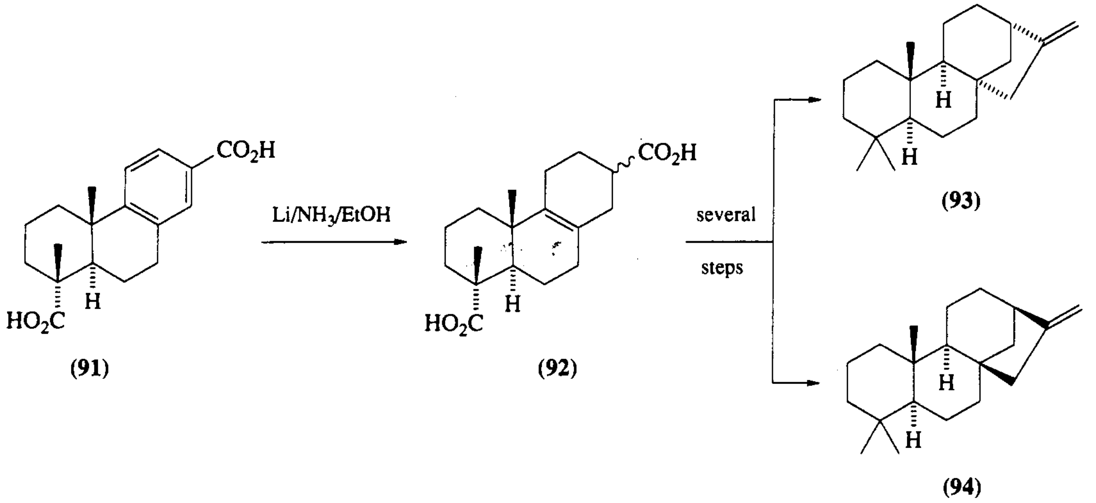

Scheme 17

### 3.4.3.6.4 *Methoxybenzoic acids*

One of the synthetically most useful groups of aromatic acids are those which also bear alkoxy functions, in that the reduced products are potential cyclohexenones, while oxidative rearomatization may afford useful aromatic substitution patterns. The electron densities of the intermediate radical anions are dominated by the carboxy group so that 1,4-dihydro products are formed initially, although the problems of subsequent isomerization and overreduction are similar to those encountered with alkylbenzoic acids. The main problem with anisoic acids is the potential for hydrogenolysis of the alkoxy function(s). Alkoxy groups in a *meta* relationship to the acyl group present no difficulties, but *para* substituents are invariably hydrogenolyzed[53] and *ortho* substituents are often vulnerable to reductive cleavage.[54] The extent of *ortho* alkoxy loss depends very much on the substrate and reaction conditions. A simple Li–$NH_3$ reduction of 2-methoxybenzoic acid under 'aprotic' conditions at –33 °C, for example, results in *ca.* 70% loss of the methoxy group,[55] whereas 2,5-dimethoxybenzoic acid under the same conditions furnishes a quantitative yield of the 1,4-dihydro derivative. Hydrogenolysis can be suppressed through the use of methanol as the proton source,[56] but one-pot reductive alkylation is then impractical.

#### *(i) Reduction of 3-methoxybenzoic acid*

Early studies on the reduction of 3-methoxybenzoic acid (**95**) led to a variety of products and a number of uncertainties in structural assignments. A careful study of the reduction was therefore undertaken and revealed that when (**95**) was reduced by sodium–ethanol–ammonia the 1,4-dihydro derivative (**96**) was formed initially, but isomerized rapidly and quantitatively to the 4,5-dihydro compound (**97**) under the reaction conditions. Further reduction could then occur to give the tetrahydro compound (**98**; Scheme 18).[57]

The method of choice for the preparation of the 1,4-dihydro compound (**99**) therefore entails reduction of (**95**) with lithium in ammonia in the absence of alcohol, followed by quenching with ammonium chloride. Acid (**99**) is also susceptible to rearrangement under acidic conditions, however, and the isomer (**100**) is formed at pH 4–5 (conditions which might readily prevail during the isolation procedure). 3-Methoxybenzoic acid (**95**) undergoes reductive alkylation at C-1 without difficulty, and has been used extensively in synthesis.

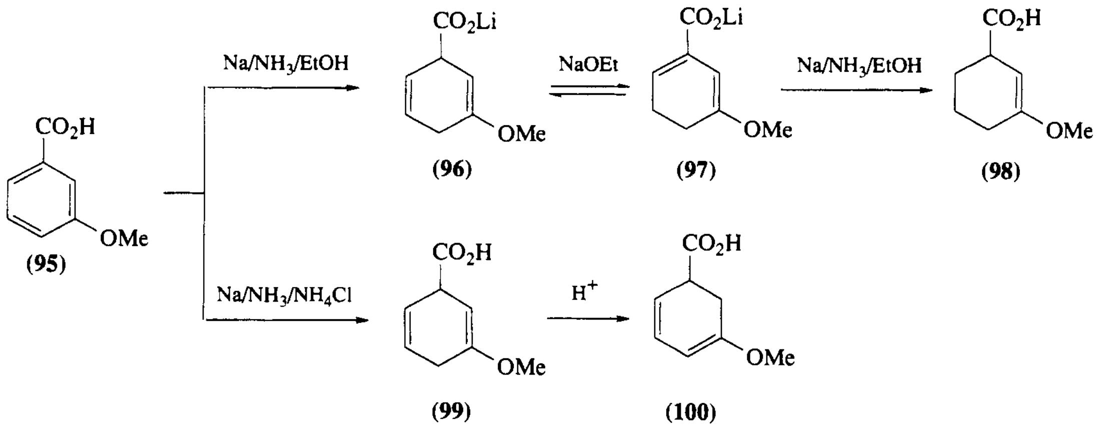

**Scheme 18**

*(ii) Reduction of 2-methoxybenzoic acid and derivatives*

Reduction of 2-methoxybenzoic acid (**101**) with lithium or sodium in ammonia with methanol as the proton source affords the 1,4-dihydrobenzoic acid (**102**; R = H) in good yields,[56] but with more weakly acidic alcohols or in the absence of methanol (conditions which are necessary for reductive alkylation), the methoxy group suffers partial hydrogenolysis; the extent to which this occurs depends on the metal used and the reaction temperature. For example, in the reductive alkylation of (**101**) to (**102**; R = Me), the major product from reduction by lithium in ammonia under reflux (–33 °C) followed by quenching with methyl iodide is (**103**) (corresponding to *ca.* 70% hydrogenolysis of the methoxy group). The use of sodium in place of lithium reduces the loss significantly (<50%),[54] while reduction with potassium completely suppresses the hydrogenolysis.[58]

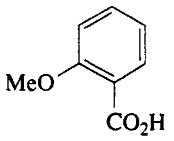

**(101)**

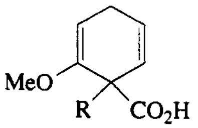

**(102)**

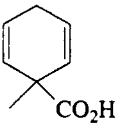

**(103)**

The variable loss of the methoxy substitutent is in fact a feature common to most 2-methoxybenzoic acid derivatives and appears to stem from the ammonium ions which are generated on mixing of the acid with ammonia. Pretreatment with one equivalent of base prevents hydrogenolysis completely in most cases,[58] although the reduced solubility of the carboxylate salt can lead to incomplete reduction. Potassium salts are reasonably soluble, but reduction of the benzoate esters may afford the best solution (see Section 3.4.3.7).

### *3.4.3.6.5 Naphthoic acids*

The metal–ammonia reduction of naphthoic acids occurs initially in the ring bearing the carboxy group, the position of which is an important factor in governing the final outcome of the reduction.

1-Naphthoic acid (**104**) gives dihydro acid (**106**), resulting from 1,4-reduction of the carboxy-bearing ring (Scheme 19).[59] The intermediacy of the enediolate (**105**) is indicated, since it may be trapped by a strong proton source such as ammonium chloride, or an alkyl halide.[60] If the simple 1,4-dihydro compound (**106**; R = H) is required, rapid quenching of the reaction mixture with ammonium chloride gives superior results[61] to carrying out the reduction in the presence of an alcohol, particularly ethanol; the latter conditions can lead to isomerization and/or overreduction.[62]

2-Methoxy-1-naphthoic acids (**107**; $R^1$ = H, OMe) have been reduced with lithium[63] or sodium[64] in ammonia, with no loss of the *ortho* methoxy substituent being reported. Thus, in the presence of ethanol the 1,4-dihydro acids (**108**; $R^2$ = H) are obtained, while reduction in the absence of a proton source and quenching with methyl iodide affords the alkylated acids (**108**; $R^1$ = H, OMe, $R^2$ = Me).[65] The conditions used for the reductive alkylation in the earlier examples (Na/NH3/–70 °C) would enhance retention of the

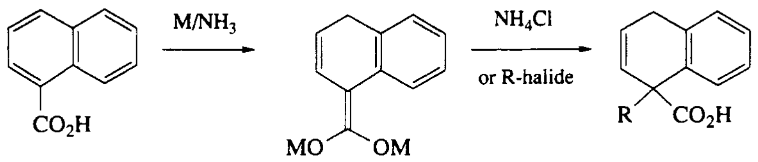

**(104)** **(105)** **(106)**

**Scheme 19**

methoxy group for reasons mentioned earlier. 4-Methoxy-1-naphthoic acid loses the methoxy group completely during reduction by metal–ammonia solutions, affording (**106**; R = H). Reductive methylation with lithium in ammonia, followed by a methyl iodide quench, gives a mixture of mono- and dialkylated acids (**106**; R = Me) and (**109**).[66] Reduction of the second ring occurs only after reduction of the first ring is complete. Dihydro acids (**108**; $R^2$ = Me, $R^1$ = H or 7-OMe) have been reduced further and the products utilized in model studies for the construction of the A-ring region of gibberellins,[65] while acid (**108**; $R^1$ = 6-OMe, $R^2$ = H) has been used as a convenient source of the corresponding β-keto ester.[67]

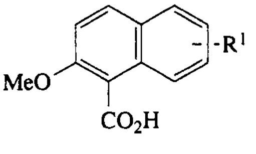

**(107)**

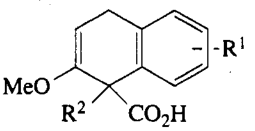

**(108)**

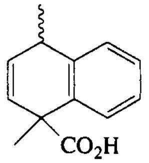

**(109)**

2-Naphthoic acids similarly undergo preferential reduction in the carboxy-bearing ring. If alcohol and limited quantities of metal (*ca.* 5 equiv.) are used, the 1,2,3,4-tetrahydro derivatives are formed in excellent yield. Reduction in the second ring also proceeds cleanly in the expected sense when additional metal is added, and acids (**110**) and (**111**) have been obtained in this way.[68]

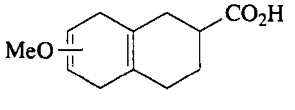

**(110)** 2,6-isomer
**(111)** 2,7-isomer

In the absence of alcohol the reduction may be halted at the dihydro stage, but with difficulty. Stoichiometric control (3 equiv. of metal) gives reasonable results, but it seems to be most effective to use 5 equiv. of lithium with added iron(III) chloride.[69] Thus, from the reduction of (**112**), quenching with ammonium chloride gives either the 1,2- or 1,4-dihydro products (**114**) and (**115**), respectively, while reaction with methyl iodide affords excellent yields of the 2-methyl-1,2-dihydro derivatives (**113**; Scheme 20).

Initial reduction of the C(1)—C(2) π-bond, in contrast to the normal 1,4-pathway encountered with most aromatic carbonyl compounds, is presumably a consequence of the energetic advantage in preserving aromaticity in the second ring. Similar results have been obtained with 2-acetylnaphthalenes and 3,4-dihydrophenanthren-1(2*H*)-ones (Section 3.4.3.9.3). Methoxy substituents in the ring bearing the carboxy group are prone to hydrogenolysis. Methoxy is invariably lost from C-1, C-3 and C-4 when reduction proceeds to the tetrahydro stage, but retention at C-3 and C-4 is possible when reduction is limited to the dihydro stage in the presence of anhydrous iron(III) chloride. Acids (**116**) to (**119**) have been prepared thus in 65–80% yields.[66]

Controlled hydrogenolysis of a methoxy substituent has been used to advantage in an expeditious synthesis of the tetrahydronaphthoic acid (**122**), an important starting material for the total synthesis of gibberellins, *i.e.* regioselective metallation of 1,6-dimethoxynaphthalene (**120**) at C-7 followed by carboxylation to afford (**121**) and then reduction furnished (**122**) in 71% overall yield (Scheme 21).[70]

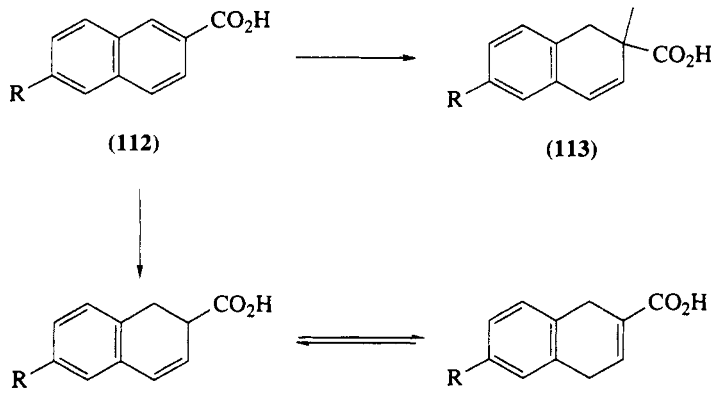
CO$_2$H
R
CO$_2$H
R
CO$_2$H
R
CO$_2$H
R

(112) (113)

(114) (115)

Scheme 20

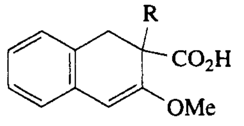

(116) R = H
(117) R = Me

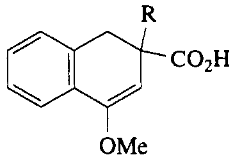

(118) R = H (isolated as keto acid)
(119) R = Me

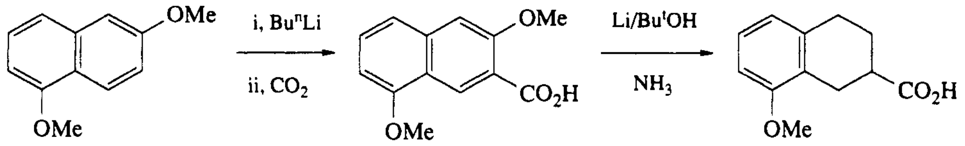
OMe
OMe
i, Bu$^n$Li
ii, CO$_2$
OMe
CO$_2$H
OMe
Li/Bu$^t$OH
NH$_3$
CO$_2$H
OMe

(120) (121) (122)

Scheme 21

### 3.4.3.6.6 *Biphenylcarboxylic acids*

While 2-phenylbenzoic acid is reduced smoothly (Li or Na, $NH_3$; $NH_4Cl$) to the dihydro derivative (**123**), the outcome from the reduction of the C-4 isomer is very sensitive to reaction conditions. It was found that in addition to the expected products (**124**) and (**125**) (the latter arising from isomerization of the 1,4-dihydro isomer), there was formed a 25% yield of a mixture of alcohol (**126**) and hydrocarbon (**127**).[71] In a subsequent investigation, in which rapid quenching procedures were employed, a 3:1 mixture of (**124**) and (**125**) was obtained, indicating that the previous overreduction had occurred during the quenching process. Greatly improved results were obtained by substituting the corresponding *t*-butyl ester as a substrate, for which reduction occurs only in the more-substituted ring.[72]

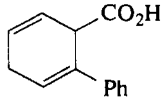

(123)

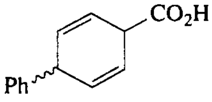

(124)

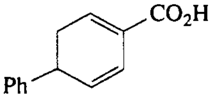

(125)

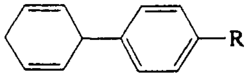

(126) R = $CH_2OH$
(127) R = Me
(128) R = $CO_2H$

### *3.4.3.6.7 Intramolecular reductive alkylation*

Reduction of acid (**129**) by lithium in ammonia furnished the spiro-fused bicyclic acid (**130**) as the major product (Scheme 22). Equally good results were obtained with calcium metal, but lower yields were obtained with sodium and potassium.[73] The bromo and iodo analogs of (**129**), and the isomeric acid (**131**) failed to give any bicyclic products, however.[74]

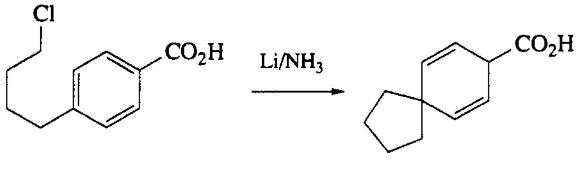

(**129**) (**130**)

**Scheme 22**

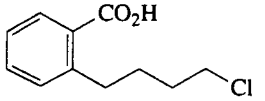

(**131**)

### 3.4.3.7 Aromatic Carboxylic Esters

Early studies on the reduction of aromatic esters by metal–ammonia systems afforded little, if any, ring-reduced compounds but rather the products of functional group reduction,[75] and this became the prevailing wisdom for four decades. Nevertheless, a completely general procedure for ring reduction appears to be the low temperature reduction by sodium[76] or potassium[58] in the presence of one equivalent of *t*-butyl alcohol. Even lithium has been shown to give excellent results and may be the preferred metal if the reduction is followed by *in situ* alkylation (see below);[77] lithium fails to give ring reduction with 2,6-disubstituted substrates, however. The role of the proton source has been examined in one systematic study,[78] the results of which are summarized in Table 2. It appears that methoxy substituents promote reduction and, in the case of methyl 2,6-dimethoxybenzoate (**132**), obviate the need for an added proton source.

Rabideau has advocated the use of water as the proton source, added prior to the addition of the metal (sodium), followed by inverse quenching with aqueous ammonium chloride. The procedure is of little generality, however, since it was found to be unsatisfactory for methyl esters and reduction was inhibited by *para* ethyl, isopropyl and *t*-butyl substituents.[79]

Quenching the ester reductions with ammonium chloride affords the 1,4-dihydrobenzoates in 90–100% yields.[80] On the other hand, reaction with alkyl bromides or iodides, *in situ*, generally affords the C-1-alkylated products, again with good to excellent efficiency. These procedures have been successfully applied to more complex substrates, *e.g.* the gibbanes (**133**) and (**134**; Scheme 23).[81] In these cases the alkylations were completely stereoselective, with the approach of the electrophile being controlled by the neighboring B-ring carboxy. However, no diastereoselectivity was observed in the reductive methylation of the (–)-menthyl ester (**135**).[82]

Alkylation of potassium enolates is not always fruitful, and so counterion exchange with lithium bromide prior to addition of the electrophile has been recommended.[58] Reduction of aromatic esters instead of acids provides a number of potential advantages. The esters tend to be more soluble than carboxylate salts, hydrogenolysis of 2-alkoxy substituents does not appear to present the same problem, and the products are more stable. This can be important when enol ether functions are generated, allowing the necessarily acidic work-up procedures for carboxylic acids to be avoided. Indeed, the hydrolysis of enol ether functions may be very slow in aqueous acid and is best achieved through catalysis by mercury(II) nitrate.[81]

It is of considerable interest to find that *t*-butyl esters may be reduced satisfactorily, in contrast to aliphatic *t*-butyl esters, which are cleaved to acids under Birch conditions.[83] Also noteworthy is the regioselective reduction of the ester (**136**; Scheme 24),[72] in marked contrast to the reduction of the corresponding acid. Hydronaphthoate esters (**137**), (**138**) and (**139**) have been prepared (Scheme 25) and are envisaged as useful intermediates for diterpene synthesis.

**Table 2** Reduction of Benzoate Esters by Metals in Liquid Ammonia[a]

| *Substrate* | *Metal* | *Proton source* | *Yield of 1,4-dihydrobenzoate (%)* |
|---|---|---|---|
| 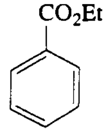 | Na | — | <5 |
| | Na | Bu$^t$OH | >95 |
| | K | — | 30–50 |
| | K | Bu$^t$OH | >95 |
| 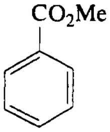 | K | — | 20–30 |
| | K | Bu$^t$OH | >95 |
| | Li | Bu$^t$OH | >95 |
| 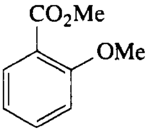 | K | — | 60–70 |
| | K | Bu$^t$OH | >95 |
| 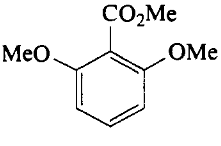 **(132)** | K | — | >95 |
| | K | Bu$^t$OH | >95 |

---

[a] Reductions carried out at −78 °C with 2.5 gram equiv. of metal and 1.5 mol equiv. of Bu$^t$OH (if added).

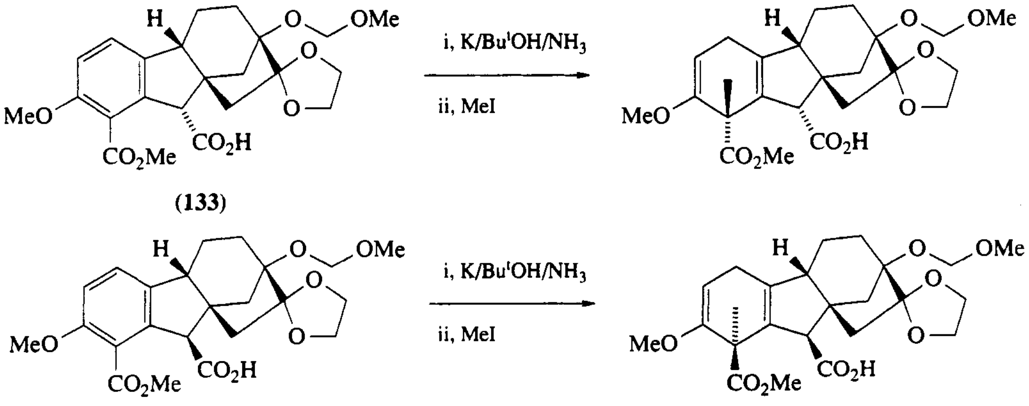

**(133)**

**(134)**

**Scheme 23**

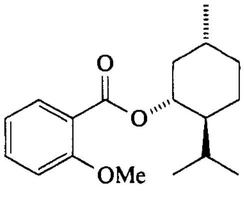

**(135)**

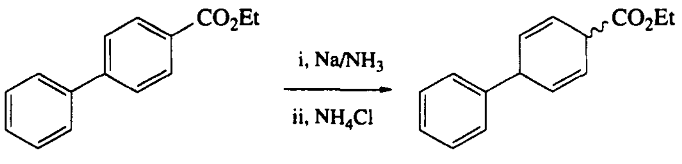

**(136)**

**Scheme 24**

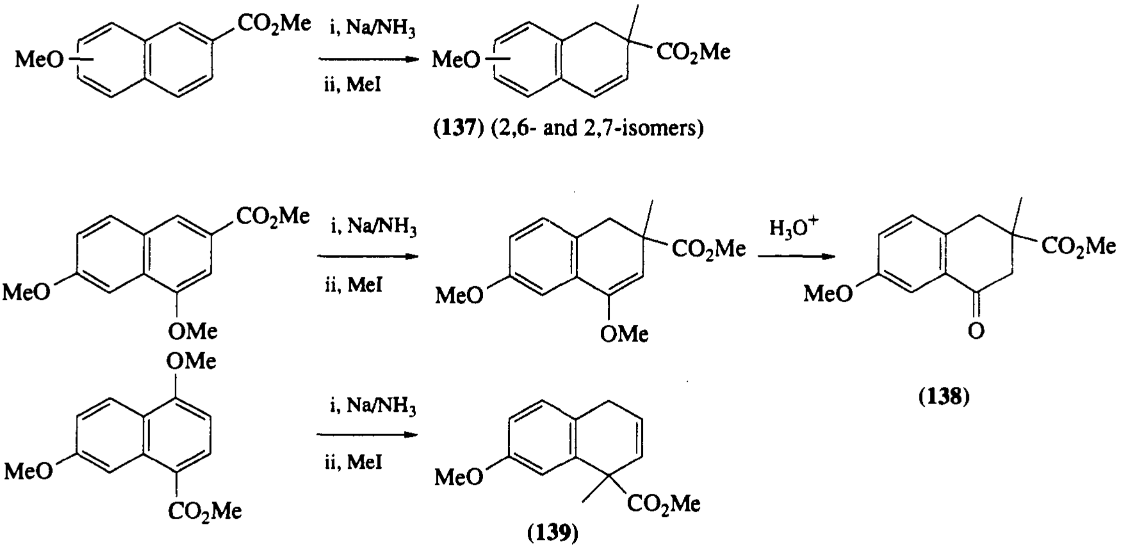

**(137)** (2,6- and 2,7-isomers)

**(138)**

**(139)**

**Scheme 25**

### 3.4.3.8 Aromatic Amides

The ring reduction of aromatic amides, and in particular benzamides, was once thought not to be possible,[84] and in fact sodium–liquid ammonia reductions of secondary amides had been recommended as a route to benzaldehydes.[85] It was found subsequently, however, that under the appropriate conditions 1,4-dihydrobenzamides could be prepared using sodium in ammonia in the presence of an alcohol. Both primary and secondary amides could be reduced, although increasing the steric bulk of the alkyl group decreased the yields of the 1,4-dihydro compound dramatically, while tertiary benzamides gave either reduction of the carbonyl group or a very low yield of the 1,4-dihydro compound.[53,86]

In a more recent study it was found that the conditions (potassium metal, ammonia, –78 °C, 1 equiv. *t*-butyl alcohol) which had proved to be so effective with esters also gave excellent results with the 2-methoxybenzamides (**140**) and (**141**; Scheme 26), although the successful outcome was tentatively attributed to the presence of the *ortho* methoxy. While both (**140**) and (**141**) gave high yields of the *C*-methylated derivatives (**142**) and (**143**), respectively, only the less-hindered (**140**) could be alkylated with 2-bromoethyl acetate, to give (**144**). Amide (**141**) was prepared by C-6 lithiation of (**140**) followed by *C*-methylation, and opens up the exciting prospect of combining two powerful methodologies.[82]

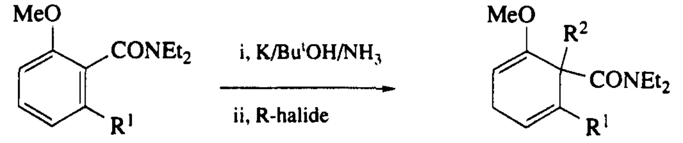

(**140**) $R^1 = H$

(**141**) $R = Me$

(**142**) $R^1 = H, R^2 = Me$

(**143**) $R^1, R^2 = Me$

(**144**) $R^1 = H, R^2 = CH_2CH_2OAc$

**Scheme 26**

Although the potential for achieving enantioselective syntheses through the reductive alkylation of esters incorporating a chiral auxiliary into the substrate appears to be poor, the potential for stereocontrol in the corresponding reactions of chiral amides is excellent. The L-prolinol derived oxazepine (**145**) afforded the *C*-methylated product (**146**) as an 85:15 mixture with its *cis* diastereomer, while higher levels of diastereoselectivity were obtained with bulkier halides (*e.g.* EtI, 99:1 and $CH_2$═$CHCH_2Br$, 98:2) (Scheme 27). A range of prolinolamides were also studied, including (**147**; R = H, Me, $CH_2OMe$), which affords even better stereoselectivity independent of R, *e.g.* (**148**) was formed as a 260:1 mixture with its C-1 epimer (Scheme 28).[87]

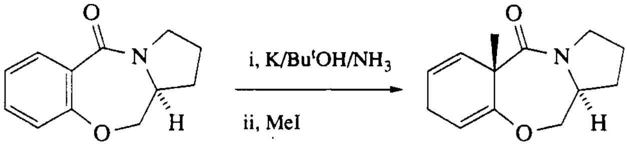

(**145**) (**146**)

Scheme 27

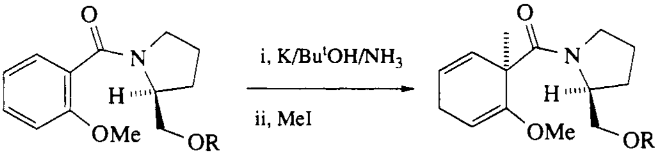

(**147**) (**148**)

Scheme 28

### 3.4.3.9 Aromatic Ketones

As with esters, the prevailing view held for many years was that ring reduction of aromatic ketones was not feasible. The first indication that this was incorrect was provided by the reduction of the hydrophenanthrenone (**149**; Scheme 29).[88] Further isolated examples of ring reduction in naphthyl ketones and molecules containing such moieties have been reported subsequently, but it is clear that these systems are much more easily reduced than simple benzenoid systems. Optimal procedures for the reduction and reductive alkylation of such systems were first established by Watanabe and Narisada for acetophenone and its methoxy derivatives.[16]

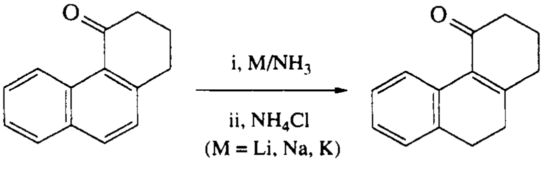

(**149**) (**150**)

Scheme 29

#### 3.4.3.9.1 Acetophenones

A systematic study of the reductive alkylation of acetophenones[16] revealed that the desired transformation (Scheme 30) required a careful selection of reagents and conditions. The best results were obtained from reduction by potassium in ammonia at −78 °C, with *t*-butyl alcohol as the proton source. Exchange of the potassium counterion of the enolate (**152**; M = K) for lithium then ensured regioselective alkylation at C-1 to give (**153**) in 80–90% yields (Scheme 30). Metals other than potassium as the reductant led to undesirable side reactions with the carbonyl group, which included simple reduction to the methylcarbinol and ethylbenzene (lithium or sodium), while the absence of a proton source or presence of a strong one ($H_2O$ or acetic acid) during the reduction encouraged formation of the pinacol (**154**). Sodium as a counterion with the enolate (**152**; M = Na) led to overalkylated and *O*-alkylated products. The successful outcomes with potassium as reductant may be due to the fact that the potassium pinacolates are unstable (addition of $KNH_2$ to benzopinacol, for example has been shown to cause dissociation to benzophenone ketyl).[89]

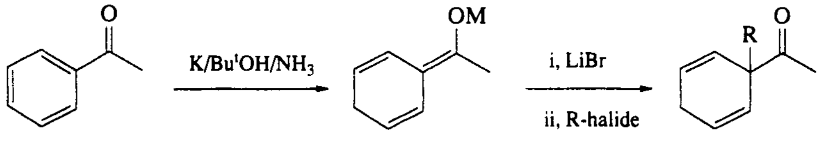

**(151)** **(152)** **(153)**

**Scheme 30**

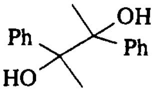

**(154)**

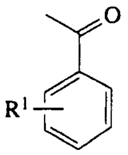

**(155)** R$^1$ = 2-OMe
**(156)** R$^1$ = 3-OMe
**(157)** R$^1$ = 4-OMe
**(158)** R$^1$ = 2,5-$(OMe)_2$

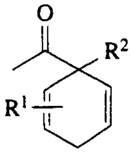

**(159)** R$^1$ = H, R$^2$ = Et
**(160)** R$^1$ = H, R$^2$ = $CH_2CH=CH_2$
**(161)** R$^1$ = H, R$^2$ = $CH_2CO_2Et$
**(162)** R$^1$ = 2-OMe, R$^2$ = Me
**(163)** R$^1$ = 3-OMe, R$^2$ = Me
**(164)** R$^1$ = 2,5-$(OMe)_2$, R$^2$ = $CH_2Ph$

Acetophenone and several derivatives, (**155**) to (**158**), were subjected to reductive alkylation using the appropriate conditions. As might be expected from results with benzoic acids, the methoxy group was lost from 4-methoxyacetophenone, but the 2- and 3-derivatives (**155**) and (**156**) gave good yields of alkylated 2,5-cyclohexadienes, as did the 2,5-dimethoxy compound (**158**). A range of products with various electrophiles was obtained in good to excellent yield, including (**159**) to (**164**).[16,90]

### *3.4.3.9.2 1-Tetralones and 1-indanones*

Early reports indicated that 1-tetralones are reduced by sodium or lithium in liquid ammonia at −33 °C to the corresponding tetralols or tetralins, although a very recent study has shown that up to seven products (four of them dimeric) may be formed when lithium is utilized.[91] Nevertheless, the reductive alkylation conditions applied successfully to the ring reduction of acetophenone also succeed with 1-tetralones. 1-Tetralone itself was transformed into (**165**) in 60% yield,[16] while modifications to the original procedure allowed the methoxylated derivatives (**166**) to (**169**) to be prepared in excellent yields.[92]

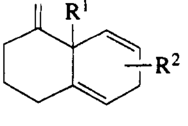

**(165)** R$^1$ = Me, R$^2$ = H
**(166)** R$^1$ = Me, R$^2$ = 5-OMe
**(167)** R$^1$ =Me, R$^2$ = 7-OMe
**(168)** R$^1$ = Me, R$^2$ = 5,7-$(OMe)_2$
**(169)** R$^1$ = $CH_2C(Br)=CH_2$, R$^2$ = 5-OMe

Keto acid (**170**) has been transformed into the diastereomeric mixture of keto acids (**171**) and (**172**), where the predominant reaction pathway involves approach of the electrophile *anti* to the carboxylate group (Scheme 31). It was found to be essential to neutralize the ammonium ions generated from addition of the substrate acid to the liquid ammonia before adding the potassium metal, however.[92]

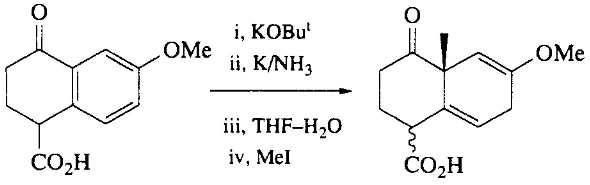

(**170**)

(**171**) 4α 64%
(**172**) 4β 19%

**Scheme 31**

1-Indanones also undergo reductive alkylation, although not as well as 1-tetralones. Good yields were obtained with methyl iodide and 1-indanone as well as its 4-, 6- or 7-methoxy derivatives to give the dihydroindanones (**173**) to (**176**).[93]

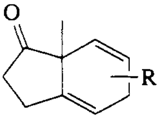

(**173**) R = H
(**174**) R = 4-OMe
(**175**) R = 6-OMe
(**176**) R = 7-OMe

### *3.4.3.9.3 Acetylnaphthalenes and hydrophenanthrenones*

The reduction and reductive alkylation of acetylnaphthalenes follows a similar course to that found for naphthoic acids, in that the ring bearing the acetyl group is preferentially reduced. Simple reduction products are stable enough to be isolated, and regiospecific alkylations of the generated enolates do not appear to be as dependent on the cation as they are with acetophenones, 1-tetralones and 1-indanones. 1-Acetylnaphthalene may be reduced by lithium, sodium or potassium in liquid ammonia at –33 °C to the dienolate (**177**),[94,95] which is alkylated regiospecifically at C-1 by methyl iodide to give (**178**; R = Me) and also protonated at C-1 to give (**178**; R = H) when the reaction mixture is subjected to an inverse quench with a large excess of aqueous ammonium chloride.[96] Traditional quenching procedures afford the 3,4-dihydro isomer (**179**) as a result of isomerization (Scheme 32). The 1-methoxy group of 1,7-dimethoxynaphthalene (**180**) directs electrophilic attack to the *para* position; sodium/ammonia solutions then readily hydrogenolyze this group, thereby giving ready access to 1-alkanoyl-6-methoxynaphthalenes (**182**; Scheme 33).[97]

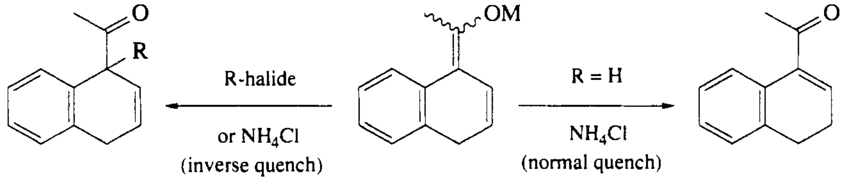

(**178**) (**177**) (**179**)

**Scheme 32**

Early studies on the reduction and reductive alkylation of 2-acetylnaphthalenes (**184**) afforded mixtures of dihydro and tetrahydro derivatives. In one case, the alcohol (**188**) was the major product.[98] A comprehensive examination of the reductive process and quenching methods has been carried out recent-

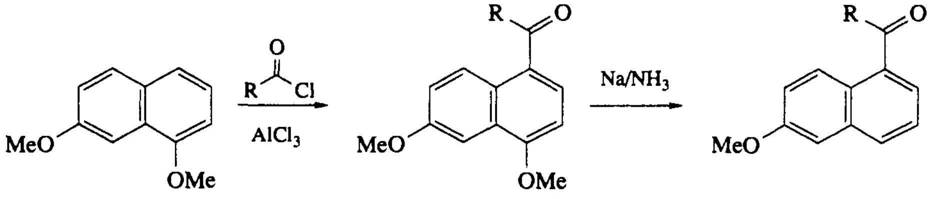

(180) (181) (182)

Scheme 33

ly, however, and the conditions required to optimize the yields of either dihydro derivatives (**186**) or tetrahydro products (**187**) defined, as summarized in Scheme 34.[95]

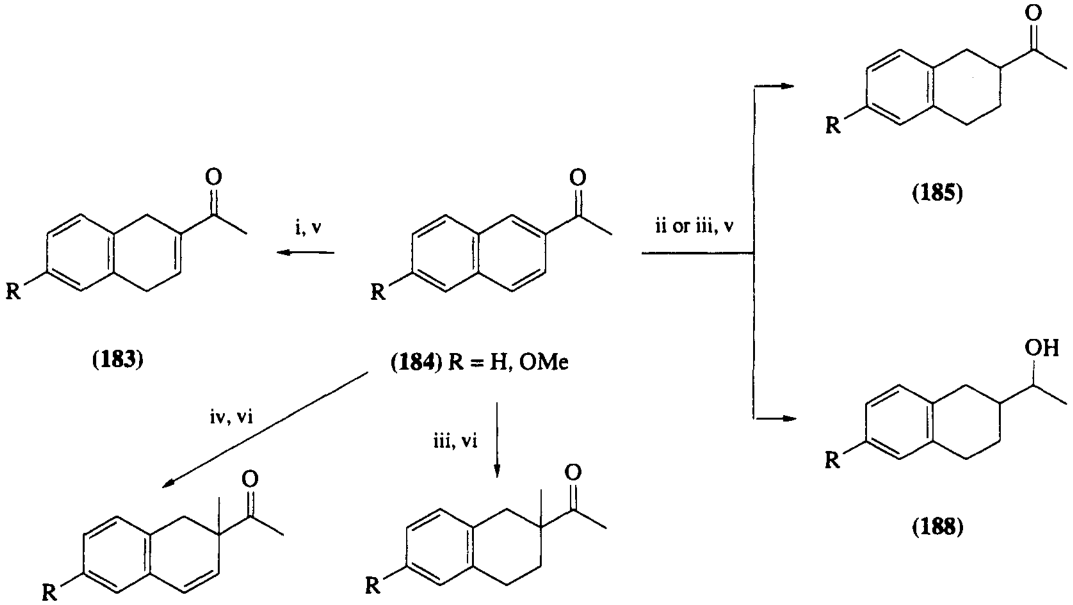

(183) (184) R = H, OMe (185) (188) (186) (187)

i, K/NH$_3$; ii, Na/NH$_3$; iii, Li/NH$_3$; iv, Li/NH$_3$/FeCl$_3$; v, NH$_4$Cl; vi, MeI

Scheme 34

Dihydrophenanthren-4(1*H*)-one (**189**) is readily reduced by lithium, sodium or potassium in ammonia at –33 °C, presumably to the dienolate (**190**), since reaction with methyl iodide affords (**191**). Quenching with ammonium chloride, however, leads to the conjugated enone (**192**; Scheme 35).

The isomeric ketone (**193**) reduces equally well with lithium, sodium or potassium in refluxing ammonia, but to the tetrahydro stage, *i.e.* to ketone (**194**); optimal yields were obtained with 4 mol equiv. of metal and catalytic amounts of iron(III) chloride.[99] The presence of the iron salts in this example did not limit the reduction to the dihydro stage, contrary to the findings with 2-acetylnaphthalenes, but gave slightly higher yields than did reductions in their absence. Reductive alkylation of (**193**) affords a variety of products depending on the metal used (Scheme 36). Potassium and sodium are effective reductants, but encourage bisalkylation, yielding mostly (**195**) with a *cis* ring fusion. Alkylation of the lithium enolate is regiospecific, affording mainly (**196**), but less stereoselective.

The B-ring in the tetracyclic compounds (**197**; R = H, OMe) has been reduced with sodium and alcohol in liquid ammonia to afford the α,β-unsaturated ketones (**198**; R = H, OMe; Scheme 37).[100]

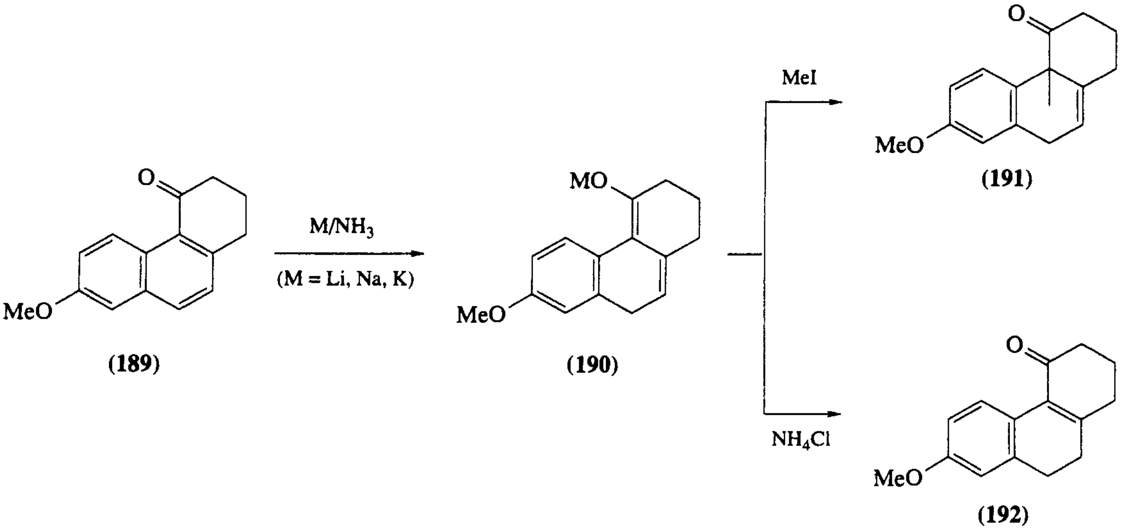
M/NH$_3$
(M = Li, Na, K)
MeI
NH$_4$Cl
MeO
MO
O
(189)
(190)
(191)
(192)

**Scheme 35**

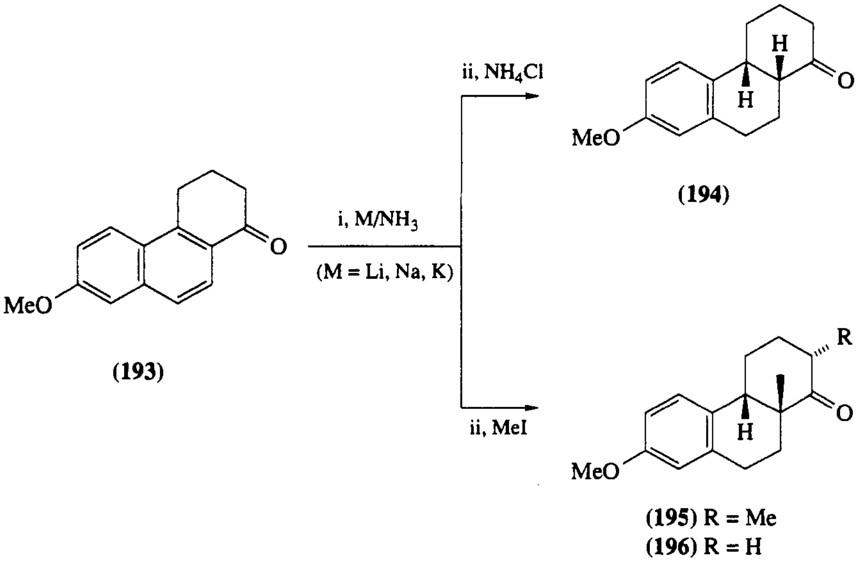
i, M/NH$_3$
(M = Li, Na, K)
ii, NH$_4$Cl
ii, MeI
MeO
O
H
R
(193)
(194)
(195) R = Me
(196) R = H

**Scheme 36**

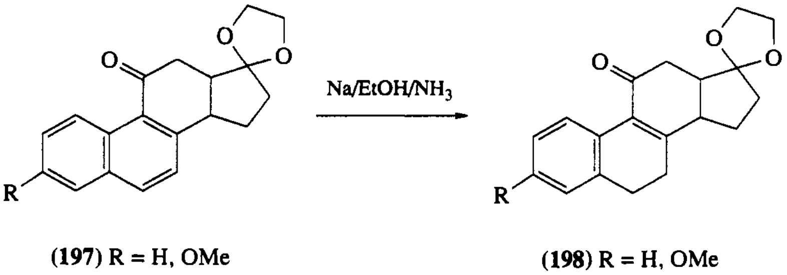
Na/EtOH/NH$_3$
O
R
(197) R = H, OMe
(198) R = H, OMe

**Scheme 37**

### 3.4.3.10 Aryl- and Benzyl-silanes

#### *3.4.3.10.1 Arylsilanes*

Birch reduction of aryltrialkylsilanes by lithium–liquid ammonia–ethanol at –70 °C has been studied systematically and a typical conversion is indicated in Scheme 38.[101] The major products are usually the 1,4-dihydro derivatives in accord with ESR evidence, which shows that a trimethylsilyl group stabilizes aromatic radical anions.[102] A significant exception is *p*-trimethylsilyltoluene (**199**), which affords the 2,5-dihydro product (**200**) in 95% yield (Scheme 39) and is probably typical of arylsilanes bearing a *para* substituent which is electron releasing. Cleavage of allylic silyl groups in the products by ethoxide ion is a significant problem, especially at higher temperatures (–30 °C). Further reduction to tetrahydro and perhydro derivatives also occurs under these conditions. Electrochemical reduction (in methylamine–lithium chloride) affords better yields of the simple dihydroarylsilanes.[103]

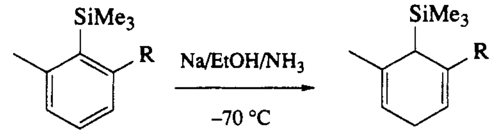

**Scheme 38**

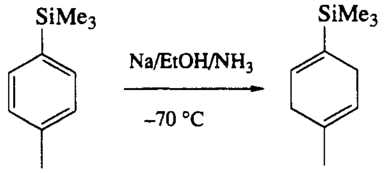

**(199)** **(200)**

**Scheme 39**

The 'activating' influence of the trimethylsilyl function is also apparent in the reduction of naphthalene derivatives (Scheme 40). The 1,4-disilyl derivative (**201**) is reduced exclusively in the substituted ring to give (**202**), while 2-trimethylsilylnaphthalene (**203**) affords a 4:1 mixture of (**204**) and (**205**), respectively.[102] As would be expected, the reduction of *C*-silylbenzoic acids and their esters is controlled by the carboxy function.[6]

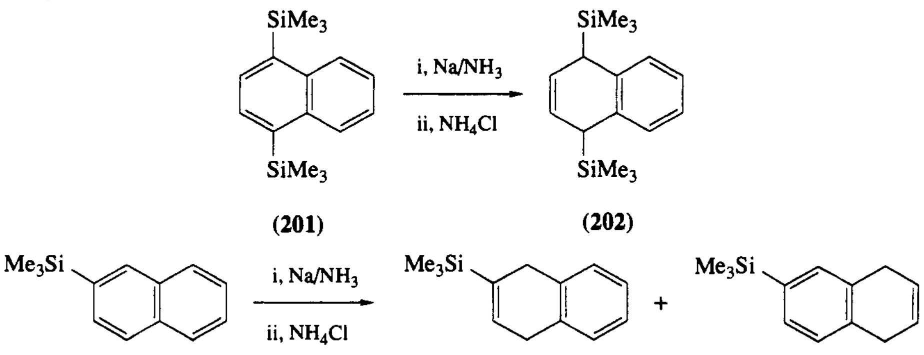

**(201)** **(202)**

**(203)** **(204)** **(205)**

**Scheme 40**

#### *3.4.3.10.2 Benzylsilanes*

The Birch reduction of benzylsilanes generally proceeds in high yield and affords the opportunity to prepare alkylidenecyclohexene structures by protodesilylation of the dihydroaromatic products, examples of which are provided in Scheme 41.[104] Reduction of the parent benzyltrimethylsilane proceeds satisfactorily with ethanol as the proton source, but fails with some substrates. The substitution of *t*-butyl alcohol for ethanol, however, avoids the generation of nucleophilic ethoxide, thereby furnishing a more satisfactory procedure. The methodology has also been used in the preparation of γ-hydroxysilanes which were subjected to oxidative fragmentations.[105]

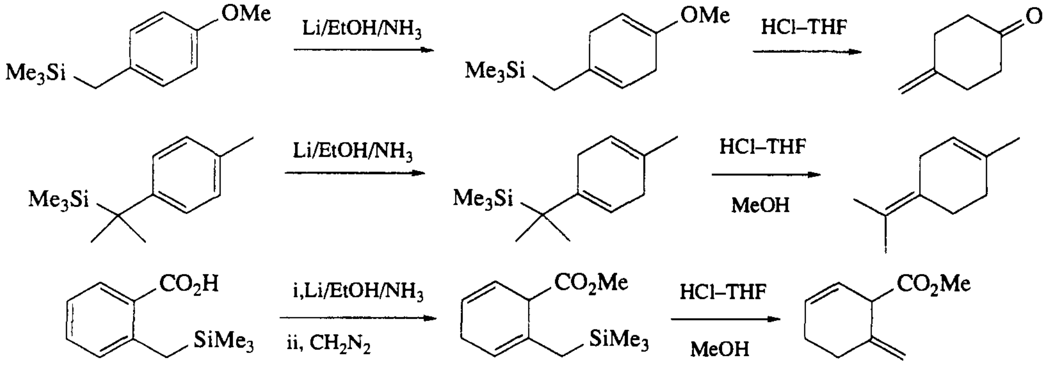

Scheme 41

### 3.4.3.11 Hydrogenolysis during Birch Reductions

#### *3.4.3.11.1 Hydrogenolysis of nuclear substituents*

Hydrogenolysis of halogen and sulfur groups is to be expected during Birch reductions, but if the substrate is sufficiently activated it is possible to preserve a fluorine substituent.[106] The thioether function has also been retained in the reduction of 3-methylthiobenzoic acid to its 1,4-dihydro derivative, but not the *ortho* isomer.[107] Hydrogenolysis of simple aryl alkyl ethers is rare, but there are a number of well-defined situations in which this is likely to occur, *e.g.* ethylenedioxybenzene is reduced to phenol.[108] It has already been noted in earlier sections (3.4.3.6 and 3.4.3.7) that alkoxy groups in a *para* relationship to a carbonyl group are invariably lost during metal–ammonia reductions. The methoxy group of 4-methoxybiphenyl is also lost during reduction,[109] but its loss may be prevented by the presence of a strategically located hydroxy group (converted to phenoxide during the reaction, *cf.* Scheme 8), as in the formation of (**207**; Scheme 42).[110] Biaryl ethers undergo reductive fission, a reaction which has been applied extensively to structure elucidation in the dibenzylisoquinoline alkaloids.[111]

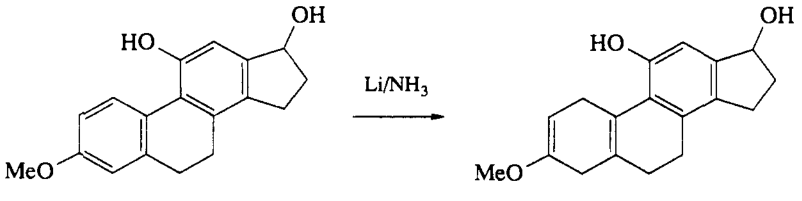

**(206)** **(207)**

Scheme 42

Deoxygenation of phenols may be achieved by reduction of aryl diethyl phosphates with lithium or sodium in liquid ammonia.[112] A recent application of the methodology is outlined in Scheme 43.[113] The reaction works well with a variety of substituted phenols, but not with dihydric phenols or naphthols. The alternative reduction of aryl sulfonates has also been examined, but the limited solubility of these derivatives can present difficulties.

#### *3.4.3.11.2 Protocols for the retention of benzylic substituents*

As a general rule, oxygen substituents are lost from benzylic positions during metal–ammonia reductions. An important set of exceptions are those compounds which possess a methoxy group in a *para* relationship to the benzylic substituent. Thus, 4-methoxybenzyl alcohol (**208**) may be reduced in high yield

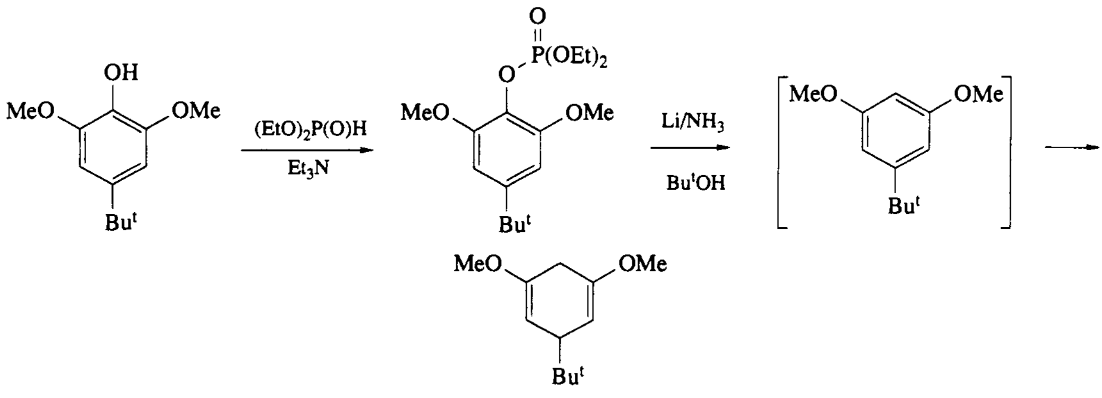

**Scheme 43**

to the 2,5-dihydro derivative (**209**; Scheme 44), whereas benzyl alcohol itself and the 2- and 3-methoxy derivatives are reduced to the dihydrotoluenes.[114]

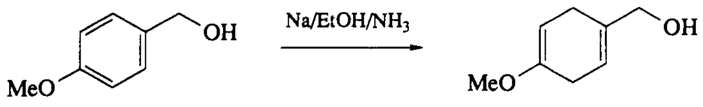

(**208**) (**209**)

**Scheme 44**

Reduction of 1-(4-methylphenyl)ethanol affords a 4:1 mixture of the 2′,5′-dihydro derivative with 4-ethyltoluene,[115] showing again the influence of an electron-releasing substituent in the *para* position. The result with 4-methoxybenzyl alcohol appears to be completely general. Benzylic hydroxy groups may also be preserved when the proximal aryl ring is hydroxylated, as in the formation of (**207**; Scheme 42) and in the reduction outlined in Scheme 45.[116]

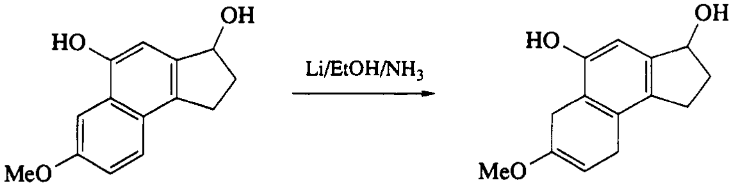

**Scheme 45**

Metal–ammonia reduction of acetal (**210**) was reported to afford the deoxygenated derivative (**211**; Scheme 46) as the major product,[117] but the choice of a dioxolane protecting group turns out to be unfortunate, since hydrogenolysis is probably a consequence of strain in the five-membered ring. It is possible to retain the acetal function during reduction of the acyclic or 1,3-dioxane analogs and 30–75% yields of the dihydro derivatives (**212**) have been reported.[118]

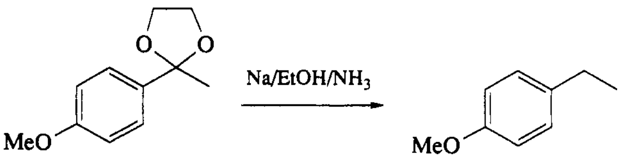

(**210**) (**211**)

**Scheme 46**

Benzylic amines are resistant to hydrogenolysis under Birch reduction conditions, unless the amine is quaternary, as in the Emde reaction. A means of preserving an aryl carbonyl group is therefore to protect it as an aminal derivative. An illustration is provided by the preparation of aldehyde (**213**), an important flavor constituent of cumin, as outlined in Scheme 47.[119]

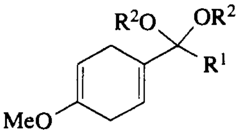

**(212)**

$R^1$ = H, Me; $R^2$ = Me, Et, $-CH_2CH_2-$

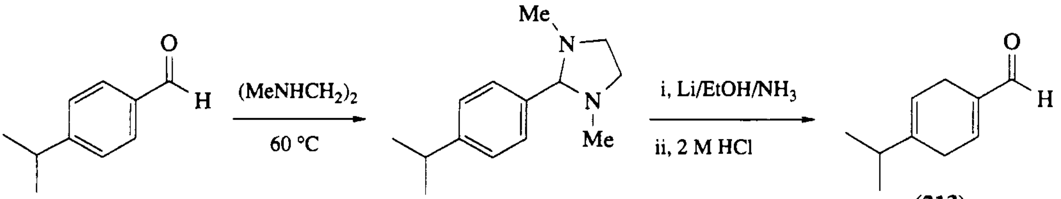

**(213)**

Scheme 47

## 3.4.4 FURTHER METHODS FOR THE REDUCTION OF AROMATIC RINGS

Extensive investigations have been made into further methods for the reduction of aromatic rings based on the use of dissolving metals in other solvents, especially the lower molecular weight amines (the Benkeser reduction), electrochemical methods (cathodic reductions), photochemical methods and the reaction of radical anions with silylating reagents rather than proton sources. The aim of much of this work has been to produce the normal Birch products more conveniently or cheaply, but very often the outcome has been quite distinct. The alternative method may then provide access to products which are not so easily obtained by the standard metal–liquid ammonia methodology.

### 3.4.4.1 The Benkeser Reduction

Solutions of Group I metals in the lower molecular weight amines are more potent reductants than those in liquid ammonia, and as a general rule substrates are more extensively reduced than by the Birch method.[120] Naphthalene (**49**; Scheme 48), for example, is reduced by a solution of lithium in ethylamine to a 1:1 mixture of $\Delta^{1(9)}$- and $\Delta^9$-octalins (**214**) and (**215**). If ethylenediamine is employed as the medium, the completely saturated decahydronaphthalene is formed, while the proportion of (**215**) may be increased to 80% by utilizing a (1:1) mixture of ethylamine with dimethylamine.[121] The formation of the more-substituted alkene appears to be a general result for such primary and secondary amine mixtures and has been used to good effect in the reduction of both toluene and cumene to their 3,4,5,6-tetrahydro derivatives (**216**) and (**217**), respectively, in *ca.* 80% yields. A comprehensive review of these kinds of reducing systems, which also draws comparisons with the Birch method, is available,[122] but more recent-

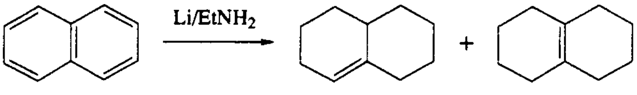

**(49)** **(214)** **(215)**

Scheme 48

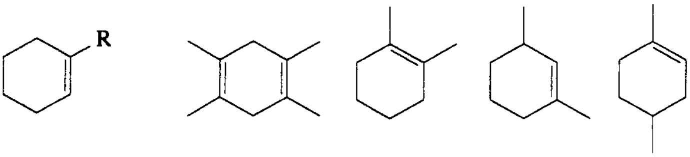

**(216)** R = Me **(219)** **(220)** **(221)** **(222)**

**(217)** R = $Pr^i$

**(218)** R = $Bu^t$

ly an improved system has been described. This is based on solutions of calcium in methylamine–ethylenediamine (1:1) and products (**218**) to (**225**), for example, have been formed in generally high yields from the parent aromatic hydrocarbons.[123]

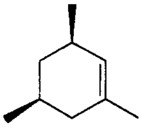

(**223**)

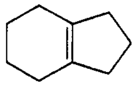

(**224**)

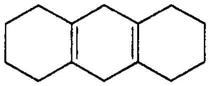

(**225**)

### 3.4.4.2 Electrochemical Methods

Electrochemical methods for the reduction of aromatic substrates utilizing ammonia and amines as solvents with lithium salts as electrolytes have been successful. Toluene was reduced to the 2,5-dihydro derivative in 95% yield in methylamine–lithium chloride if an undivided cell was used, while a 53:47 mixture of 3- and 4-methylcyclohexenes was formed in a divided cell.[124]. Of greater interest, however, are attempts to achieve these reductions in aqueous media. In one experiment utilizing a two-phase mixture of substrate in aqueous tetra-*n*-butylammonium hydroxide and a mercury cathode, anisole was reduced on a preparative scale (15 g) to its 2,5-dihydro derivative in 80% yield. The optimal temperature for most reductions appeared to be 60 °C and under these conditions, even suspensions of high molecular weight substrates could be successfully reduced, *e.g.* steroid (**226**) afforded a >90% chemical yield of (**227**). Much higher coulombic yields were obtained when a small amount of THF was added to the mixture, however.[125]

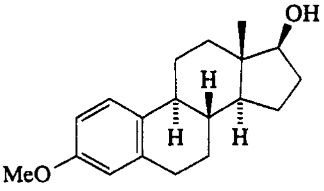

(**226**)

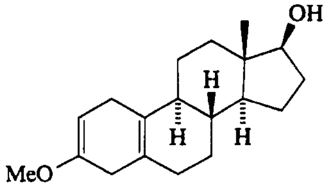

(**227**)

### 3.4.4.3 Photochemical Methods

Photochemical electron transfer reactions of electron donor–acceptor pairs in polar solvents provide a convenient and effective method for the generation of radical cations which can be trapped by complex metal hydrides. One of the most effective systems is based on irradiation of a solution of substrate, sodium borohydride and 1,4- or 1,3-dicyanobenzene. A range of bi- and poly-cyclic aromatic hydrocarbons has been converted into the dihydro derivatives in this way.[126] An especially important aspect of this route to dihydroaromatic compounds is that it may give access to products which are regioisomeric with the standard Birch reduction products. Thus, *o*-xylene is converted into the 1,4-dihydro product (**229**) rather than the 'normal' 3,6-dihydro isomer (**228**). The *m*- and *p*-xylenes are similarly reduced to (**230**) and (**231**), respectively.[127]

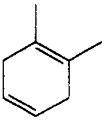

(**228**)

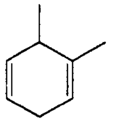

(**229**)

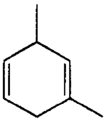

(**230**)

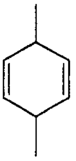

(**231**)

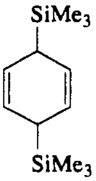

(**232**)

### 3.4.4.4 Reductive Silylations

An interesting alternative to the Birch reduction with useful synthetic potential is provided by reductive silylation. Benzene, on treatment with lithium metal and trimethylsilyl chloride in THF for a prolonged period, for example, affords a high yield of the 1,4-disilyl derivative (**232**).[128] Naphthalene is converted into a 2:1 mixture of the 1,2- and 1,4-adducts (**233**) and (**234**), respectively (Scheme 49).[129]

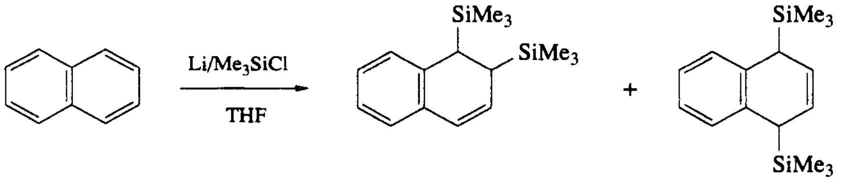
Li/Me$_3$SiCl
THF
SiMe$_3$
SiMe$_3$
+
SiMe$_3$
SiMe$_3$

**(49)** **(233)** **(234)**

**Scheme 49**

Estradiol bis(trimethylsilyl) ether (**235**; Scheme 50) has been converted into a diasteromeric mixture of adducts (**236**) which were hydrolyzed by aqueous acetic acid to a mixture of the isomeric enones (**237**; 36% yield) and (**238**; 9% yield).[130] This provides an especially direct route for the introduction of functionality at C-1, which would otherwise require a multistep sequence. Reductive silylation has also been used to convert anisole into enone (**239**)[131] which, following a kinetic resolution, has been used in an enantioselective synthesis of (+)-α-curcumene (**240**; Scheme 51).[132] The silyl substituent was employed to control the stereochemical and regiochemical aspects of subsequent steps.

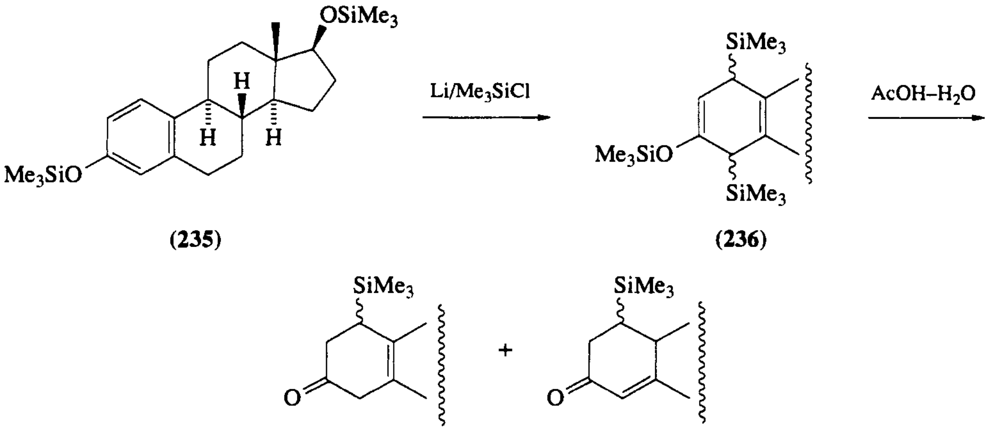
OSiMe$_3$
H
H
H
Me$_3$SiO
Li/Me$_3$SiCl
SiMe$_3$
Me$_3$SiO
SiMe$_3$
AcOH–H$_2$O
(235)
(236)
SiMe$_3$
O
+
SiMe$_3$
O

**(237)** **(238)**

**Scheme 50**

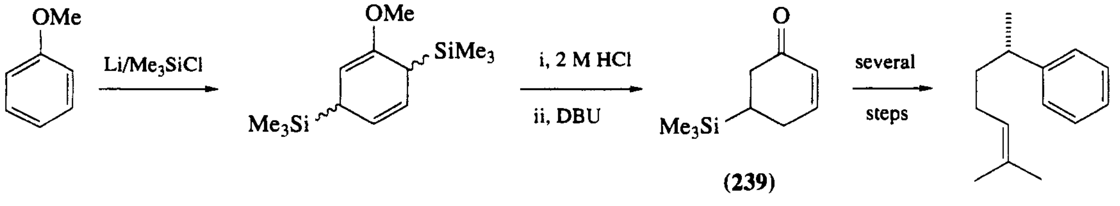
OMe
Li/Me$_3$SiCl
OMe
SiMe$_3$
Me$_3$Si
i, 2 M HCl
ii, DBU
O
Me$_3$Si
several
steps
(239)

**Scheme 51**

### 3.4.4.5 Organometallic Procedures

Unlike most $\eta^2$-coordinated complexes, those derived from osmium(II), *e.g.* [Os(NH$_3$)$_5$($\eta^2$-C$_6$H$_6$)] possess a reasonable degree of kinetic stability and are formed regioselectively. For example, on treatment with a mixture of zinc amalgam and [Os(NH$_3$)$_5$(OTf)$_3$], anisole rapidly forms the 2,3-isomer (**241**), although this rearranges to the 3,4-isomer ($k$ ~ 1 s$^{-1}$ at 20 °C). The complexes are more reactive towards catalytic hydrogenation than the parent aromatic ligand and are readily reduced to $\eta^2$-coordinated cycloalkenes which may then be demetallated by oxidation. Hydrogen is added stereoselectively *anti* to the metal centre and (**241**) affords either the tetrahydro or dihydro derivative, depending on the reaction conditions (Scheme 52).[133] The method has the potential to give reduction products in which the alkenic bond is in a complementary location to that expected from the Birch process.

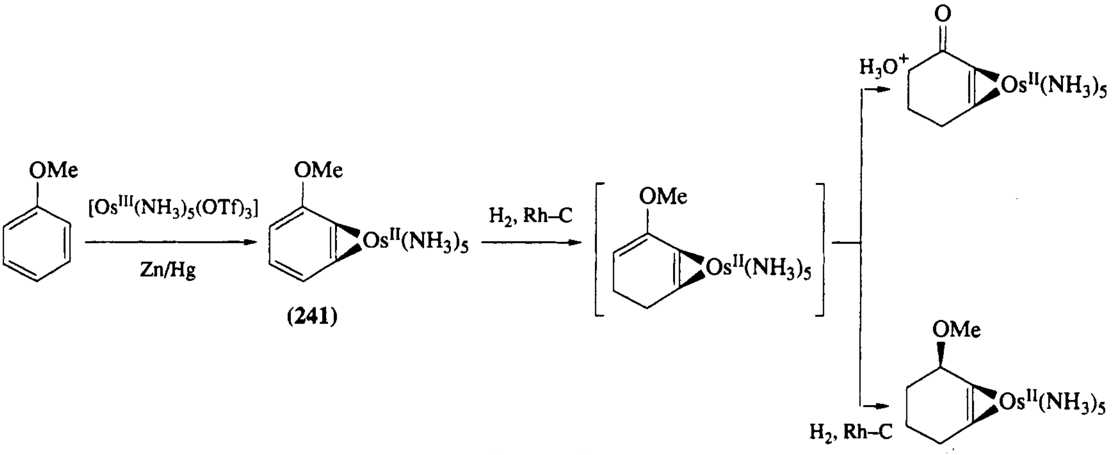

**Scheme 52**

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# 3.5

# Partial Reduction of Enones, Styrenes and Related Systems

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## 3.5.1 INTRODUCTION

Although the conjugated systems of polyenes and unsaturated carbonyl compounds are somewhat similar in terms of structure and bonding, their chemical reactivities are significantly different. The number of available methods for partial reduction of unsaturated carbonyls is overwhelmingly greater than the number of known methods for polyene reduction, and this review deals almost exclusively with unsaturated carbonyl compounds, concentrating upon the reduction of the C=C double bond. We subdivide it according to synthetic methodology rather than substrate nature, an arrangement that provides a general view clarifying the scope and limitations of a given method and saving repetition. Dienes and styrenes are discussed at the end of the review.

Methods for reduction of enones may be divided conveniently into four historically based classes. The earliest procedures employed dissolving metals; more recent developments, such as reduction with low-valent transition metal compounds and electrochemical processes, may also be included in this category as they all proceed *via* sequential addition of electrons and protons to the substrate molecule. These methods are discussed in Section 3.5.2.

Catalytic hydrogenation (Section 3.5.3) may be regarded as the second generation of reducing systems. Indeed, both heterogeneous and homogeneous catalytic hydrogenation replaced many of the earlier dissolving metal techniques.

The discovery of metal hydrides and complex metal hydrides, particularly those of boron and aluminum in the early 1940s, revolutionized the reduction of organic functional groups. These reagents may be regarded as the third generation of reducing systems. Extensive studies have led to a broad variety of hydridic reagents whose reducing power and selectivity are controlled by appropriate modification of the ligands in the metal coordination sphere.[1] Applications of these hydridic reagents as well as other main group metal hydrides, such as silicon and tin derivatives, are discussed in Section 3.5.4. A variety of transition metal hydrides, such as iron, copper, chromium and cobalt compounds are employed in stoichiometric quantities, and are presented in Section 3.5.5. Composite reducing systems consisting of a transition metal catalyst and a relatively nonreactive hydride donor represent the fourth generation. Many of the transfer hydrogenation methods may be included within this fourth category as well. Therefore, although in many respects several transfer hydrogenation techniques resemble regular catalytic hydrogenations, they are discussed in Section 3.5.6, which deals with composite reducing systems. Biocatalyzed reduction is a useful approach to enantioselective reduction of enones under very mild conditions. A number of microbiological and enzymatic transformations, as well as biomimetic reactions, are outlined in Section 3.5.7. A few other methods that were not included above are presented as miscellaneous techniques in Section 3.5.8. Finally, partial reductions of dienes and styrenes are discussed in Section 3.5.9.

## 3.5.2 ELECTRON TRANSFER REDUCTIONS

### 3.5.2.1 Dissolving Metal Reduction

A variety of organic functional groups are reduced by active metals either in the presence of a proton donor or followed by treatment with a proton donor. This approach is one of the earliest reduction procedures in organic chemistry. Although its importance has decreased with the development of catalytic hydrogenation and metal hydride reduction, there remain a substantial number of dissolving metal reductions that are still in use due to their advantageous selectivity. Dissolving metal reductions of α,β-unsaturated carbonyl compounds have been discussed in several review articles.[2-10]

Metals commonly utilized include the alkali metals, mainly lithium, sodium and potassium, and also calcium, zinc, magnesium, tin and iron. Alkali metals and calcium have been used in liquid ammonia,[10] in low molecular weight aliphatic amines,[11] in hexamethylphosphoramide,[12] in ether or in THF containing crown ethers,[13c] or in very dilute solutions in polyethers such as 1,2-dimethoxyethane (DME).[11a,13] Reactions with metal solutions in liquid ammonia often use a cosolvent, such as ether, THF or DME, to increase solubility of the organic substrate in the reaction mixture. These same metals, as well as zinc and magnesium, have been used as suspensions in various solvents including ether, toluene, xylene, *etc*.

In all procedures a proton source (frequently ethanol, 2-propanol, *t*-butyl alcohol or even water) is provided in the reaction medium, added with the substrate, or added during the work-up procedure.

Sodium amalgam, aluminum amalgam, zinc, zinc amalgam, tin and iron have been added directly to solutions of the substrate in hydroxylic solvents such as ethanol, 2-propanol, *n*-butyl alcohol, *i*-pentyl alcohol, acetic acid, water or aqueous mineral acid. With hydroxylic solvents, and especially with relatively acidic ones, metal amalgams are often used rather than free metals, to minimize the release of hydrogen gas as a side product.

The dissolving metal reductions are better classified as 'internal' electrolytic reductions in which an electron is transferred from the metal surface (or from the metal in solution) to the substrate. Reduction with low-valent metal ions may also be included in this general class (*vide infra*).

The generally accepted mechanism for dissolving metal reduction of enones (Scheme 1)[10] involves reversible addition of an electron to a vacant orbital of the substrate (S), yielding a radical anion ($S^{-}\cdot$). The latter can be protonated to give a neutral radical, which may either dimerize or accept another electron and a proton. Alternatively, stepwise or simultaneous reversible addition of two electrons to S can give a dianion capable of accepting two protons. The sequence and timing of these steps depend upon the substrate, the homogeneity and reduction potential of the medium, and the presence and nature of proton donors in the medium, among other factors.

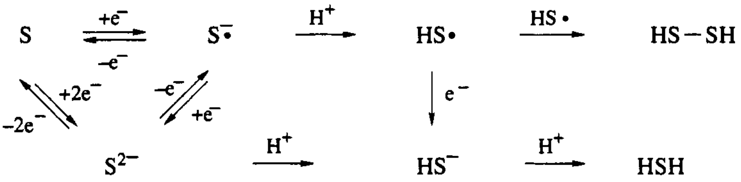

**Scheme 1**

The stereochemistry of reduction has been extensively studied. Metal–ammonia reduction of steroid and terpenoid enones with a β-carbon at the fusion of two six-membered rings leads, in general, to the thermodynamically more stable isomer at that position.[14] Stork has formulated a more general rule, namely that the product will be the more stable of the two isomers having the newly introduced β-hydrogen axial to the ketone ring.[15] This rule has correctly predicted the stereochemical outcome of many metal–ammonia reductions, with very few exceptions. The rule is rationalized in terms of stereoelectronic effects in the transition state (either the radical anion or the dianion stage). For example, in reduction of octalones of the type shown in Scheme 2, only two (**1** and **2**) of three possible anionic transition states involving a half-chair conformation of the enone-containing ring would be allowed stereochemically.[15]

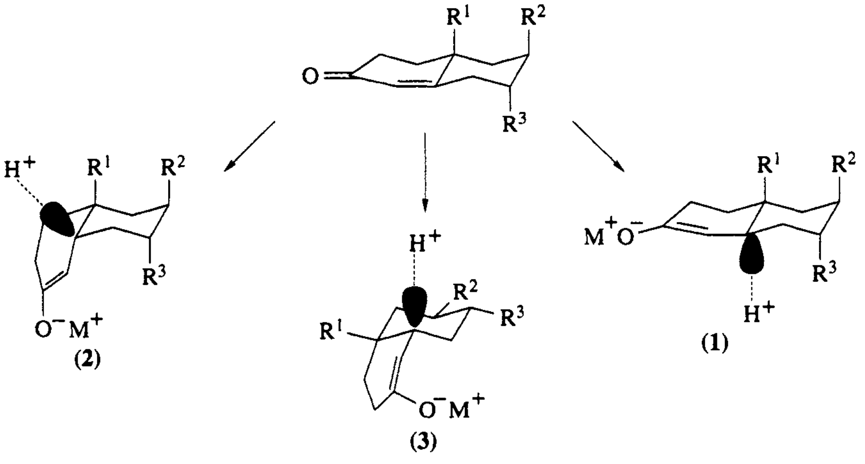

**Scheme 2**

In these two conformers the orbital of the developing C—H bond overlaps with the remainder of the π-system of the enolate. The alternative conformer (**3**) is not allowed because it does not fulfil the overlap requirement. The *trans* transition state (**1**) is generally more stable than *cis*-(**2**), and the *trans*-2-decalone reduction product would be obtained despite the fact that the *cis* isomer, having a conformation related to (3) should be more stable when $R^2$ and/or $R^3$ are larger than a hydrogen atom. This rule of 'axial protonation' has been found to be widely applicable to metal–ammonia reductions of octalones, steroids and other fused-ring systems. Representative examples are given in Scheme 3.[15–18]

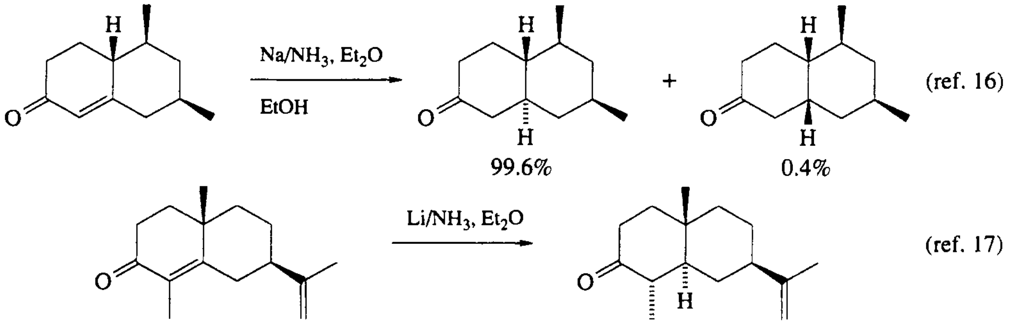

**Scheme 3**

Generally, the conditions employed in the work-up of metal–ammonia reductions leads to products having the more stable configuration at the α-carbon atom, but products having the less stable configuration at this center have been obtained by kinetic protonation of enolate intermediates.[19,20] A more detailed discussion of stereochemistry in metal–ammonia reduction of α,β-unsaturated carbonyl compounds is given in ref. 10.

### *3.5.2.1.1 Scope and limitations*

Before the introduction of metal–ammonia solutions for the reduction of α,β-unsaturated carbonyl compounds,[10] sodium, sodium amalgam, or zinc in protic media were most commonly employed for this purpose. Some early examples of their use include the conversion of carvone to dihydrocarvone with zinc in acid or alkaline medium,[21] and of cholest-4-en-3-one to cholestanone with sodium in alcohol.[22,23] These earlier methods are complicated by a variety of side reactions, such as over-reduction, dimerization, skeletal rearrangements, acid- or base-catalyzed isomerizations and aldol condensations, most of which can be significantly minimized by metal–ammonia reduction.

A wide variety of α,β-unsaturated ketones have been reduced to saturated ketones, usually in good yield, by metal solutions, mainly in liquid ammonia.[10,24–26] The reduction is applicable to compounds with any degree of substitution on the double bond. Although only 2 equiv. of these metals are required for the conversion of an enone to a saturated ketone, it is often convenient to employ the metal in excess. A suspension of lithium bronze ($Li_4NH_3$)[27] in ether allows the employment of the metal in stoichiometric amounts. Proton donors are often employed to reduce competing side reactions, such as dimerization. The presence of proton donors in the medium may lead to the conversion of an α,β-unsaturated ketone to the saturated alcohol, but at least 4 equiv. of metal must obviously be present for this type of reduction to take place.

Alcohols, such as methanol and ethanol, lead to the sole formation of saturated alcohols from unsaturated ketones when the former are present in excess during the reduction. Mixtures of ketones and alcohols are generally formed when 1 equiv. of these proton donors is employed.[28] These alcohols have an acidity comparable to that of saturated ketones, and when they are present, an equilibrium can be established between the initially formed metal enolate and the saturated ketone. The latter is then reduced to the saturated alcohol. Such reductions generally do not occur to a very significant extent when 1 equiv. of *t*-butyl alcohol[29] or some less acidic proton donor, such as triphenylcarbinol,[28] is employed. The acidity of the ketone involved, as well as the solubility of the metal enolate in the reaction medium, are important in determining whether alcohols are formed.

Even though the reaction conditions may lead to formation of the metal enolate in high yield, further reduction may occur during the quenching step of the reaction. Alcohols such as methanol and ethanol convert metal enolates to saturated ketones much faster than they react with metals in ammonia,[30,31] and quenching of reduction mixtures with these alcohols will usually lead to partial or complete conversion to alcoholic product rather than to the saturated ketone. Rapid addition of excess solid ammonium chloride is the commonly employed quench procedure if ketonic products are desired,[32] but other reagents that destroy solvated electrons before neutralization may be employed, such as sodium benzoate,[33] iron(III) nitrate,[34,35] sodium nitrite,[36] bromobenzene,[37] sodium bromate,[38] 1,2-dibromoethane[4] and acetone.[14]

### 3.5.2.1.2 Reduction–alkylation

The versatility of metal–ammonia reduction was considerably advanced by the discovery that the lithium enolates of unsymmetrical ketones generated during reduction can undergo *C*-alkylation with alkyl halides and carbonation with carbon dioxide.[39,40] These enolate-trapping reactions allow regiospecific introduction of groups at the carbon atoms of unsymmetrical ketones *via* the appropriate enone precursors. This procedure has been widely employed for ketones of a variety of structural types.[29,39–45] The procedure usually involves generation of a specific lithium enolate of an unsymmetrical ketone by reduction of the corresponding α,β-unsaturated ketone with 2 equiv. of lithium in liquid ammonia that contains no proton donor or just a single equivalent of one. This enolate is then reacted with excess alkylating agent (Scheme 4).

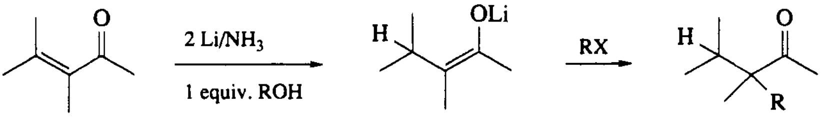

**Scheme 4**

This reduction–alkylation sequence has been extensively used in the total synthesis of natural products, such as progesterone and lupeol (Scheme 5).[46,47]

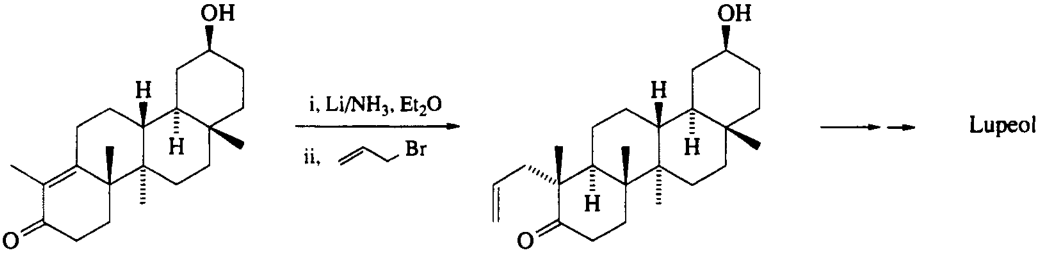

**Scheme 5**

If the ammonia is removed and replaced by anhydrous ether, the intermediate lithium enolate can be converted to a β-keto ester by carbonation, followed by acidification and treatment with diazomethane, as illustrated in Scheme 6.[48]

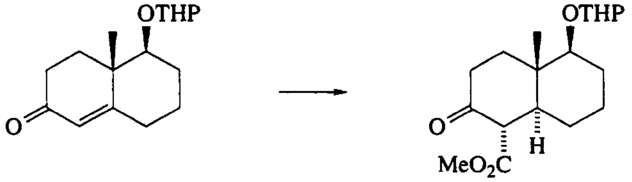

i, $Li/NH_3$; ii, $CO_2/Et_2O$; iii, $H_3O^+$; iv, $CH_2N_2$

**Scheme 6**

### 3.5.2.1.3 Dimerization processes

Because of the intermediacy of radical anions and/or hydroxyallyl free radicals in dissolving metal reductions of enones, dimerization may compete with simple reduction. Scheme 7 shows the three types of dimers that may be produced.

The dimerization products shown in Scheme 7 are generally the major ones obtained in electrochemical reductions[49–52] (*vide infra*) or reductions at metal surfaces,[49,53] in which radical anion intermediates must diffuse to a surface before further electron transfer can occur. In metal–ammonia solutions, however, simple reduction is generally favored over dimerization. These solutions provide high concentrations of available electrons, favoring the probability of the radical ion or hydroxyallyl radical accepting a second electron.

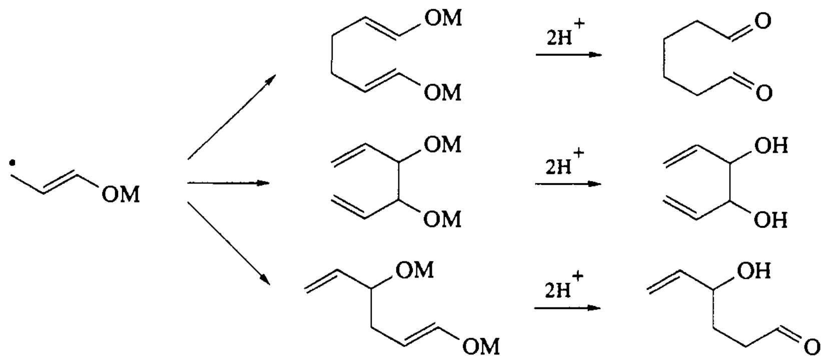

Scheme 7

### 3.5.2.1.4 Alkene synthesis

Appropriate quenching of a reductively formed lithium enolate with a carboxylic acid anhydride,[54,55] chloride,[56] methyl chloroformate[57] or diethyl phosphorochloridate yields the corresponding enol esters, enol carbonates or enol phosphates. These derivatives may be transformed into specific alkenes *via* reductive cleavage of the vinyl oxygen function,[58] as illustrated by the example in Scheme 8.

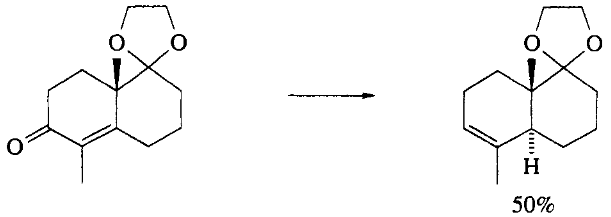

i, Li/NH$_3$, Et$_2$O; ii, (EtO)$_2$POCl, Et$_2$O; iii, Li/EtNH$_2$

Scheme 8

### 3.5.2.1.5 Intramolecular reactions

Dissolving metal reductions of unsaturated ketones involve intermediates with carbanionic character at the β-position. Therefore, intramolecular displacements, additions, and eliminations may occur during the reduction of polyfunctional enones. Many α,β-unsaturated carbonyl compounds have structural features which allow such intramolecular reactions. The examples given in Scheme 9 include intramolecular substitution of a tosylate leaving group,[59] addition to a ketone to form a cyclopropanol,[60] and elimination of an acetate group to give an unconjugated enone.[61]

This approach has been applied in the synthesis of a perhydroindanedione skeleton *via* intramolecular addition to an ester group,[62] in formation of a stable steroidal hemiacetal,[63] and in lithium–ammonia conversion of a bicyclic unsaturated triester into a tricyclic keto diester (Scheme 10).[64]

α,β-Unsaturated ketones with leaving groups at the γ-position normally undergo reductive elimination with metals in ammonia to give metal dienolates as an initial product. Quenching these enolates with ammonium chloride allows the isolation of the β,γ-unsaturated ketone. The latter can isomerize under basic conditions to the conjugated enone. Such processes have been reported with a broad variety of leaving groups, such as hydroxide,[65,66] alkoxide[67] and acetate,[61] as well as during fission of a lactone[68–70] or an epoxide ring.[71]

α,β-Unsaturated carbonyl compounds having a leaving group at the β-position react with dissolving metals to give metal enolates, which may undergo elimination to yield new α,β-unsaturated carbonyl compounds that are susceptible to further reduction.[44,72–78] For example, β-alkoxy-α,β-unsaturated esters[73,74] and acids[79] have been found to undergo double reduction. This procedure was used as a key step in the total synthesis of eremophilane sesquiterpenes (Scheme 11).[73]

Both linear and cross-conjugated dienones are reduced by solutions of metals in liquid ammonia. For example, steroidal 4,6-dien-3-ones (Scheme 12) and related compounds are reduced initially to 3,5-dienolates;[45,80–87] while addition of ammonium chloride to the latter leads to formation of the noncon-

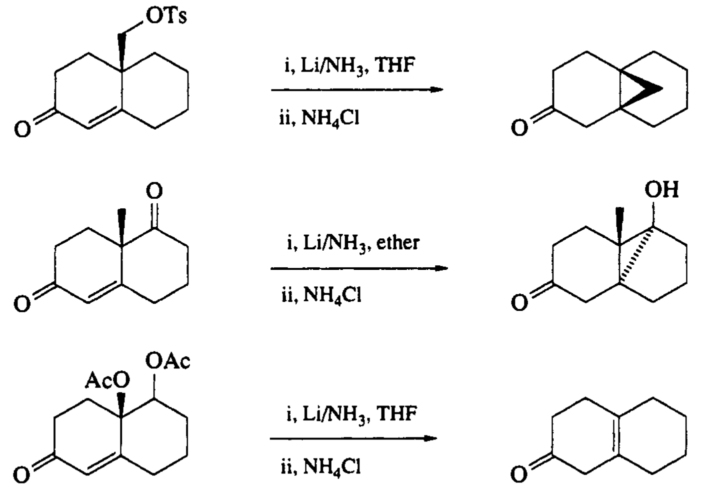
OTs
i, Li/NH3, THF
ii, NH4Cl
O
O
OH
i, Li/NH3, ether
ii, NH4Cl
AcO
OAc
i, Li/NH3, THF
ii, NH4Cl

**Scheme 9**

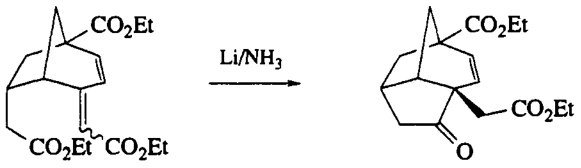
CO2Et
CO2Et
CO2Et
Li/NH3
CO2Et
CO2Et
O

**Scheme 10**

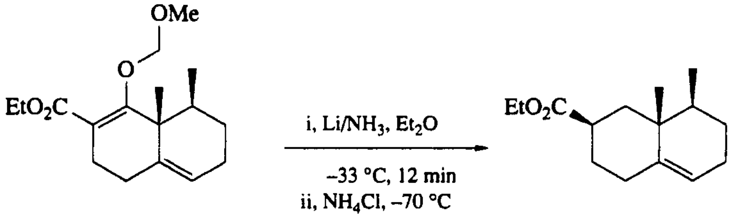
OMe
O
EtO2C
i, Li/NH3, Et2O
−33 °C, 12 min
ii, NH4Cl, −70 °C
EtO2C

**Scheme 11**

jugated 5-en-3-one system,[84] addition of proton donors such as ethanol or water initiates isomerization leading to the more stable, conjugated 4-en-3-one skeleton.[81,82] Treatment of the dienolate with excess methyl iodide rather than a proton donor gives the 4,4-dimethyl-5-en-3-one.[45,88]

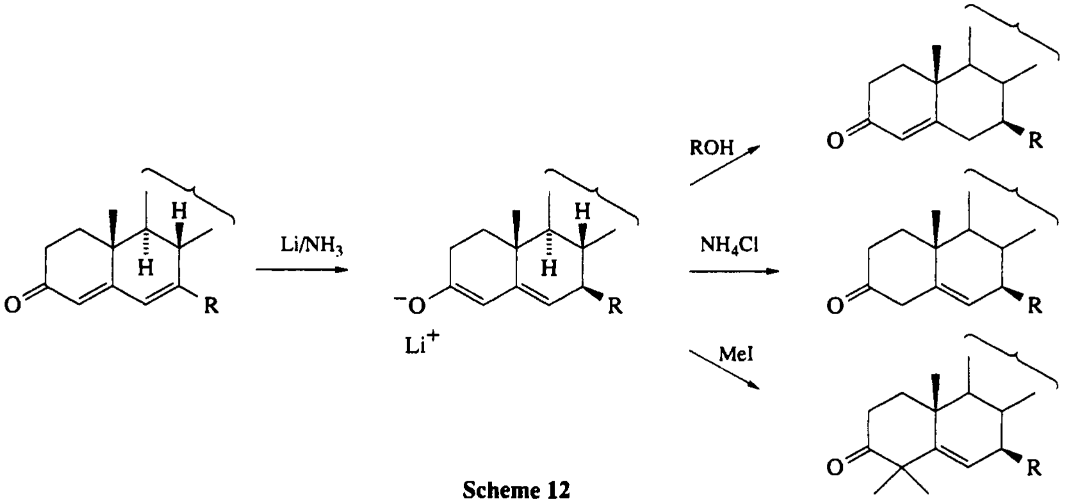
H
H
O
R
Li/NH3
H
H
−O
Li+
R
ROH
NH4Cl
MeI
O
R
O
R
O
R

**Scheme 12**

Linearly conjugated dienones may be completely reduced to saturated alcohols using excess lithium in liquid ammonia.[89] In variously substituted dienones, the less-substituted double bond is often selectively reduced under these conditions. For example, treatment of a steroidal 14,16-dien-20-one with lithium in liquid ammonia (with or without 1-propanol) leads mainly to reduction of the 16,17 double bond (Scheme 13),[90,91] and the less-substituted double bond of cross-conjugated steroidal dienones,[4,45,92,93] santonin, or related substrates is selectively reduced under these conditions (Scheme 13).[68–70,94]

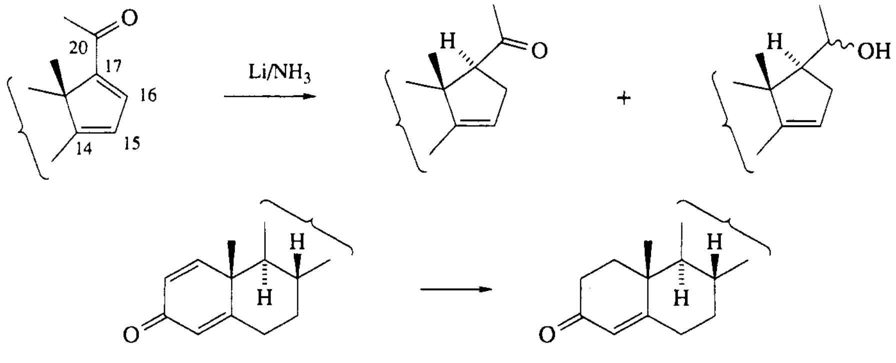

Scheme 13

### 3.5.2.1.6 Chemoselectivity

Although a host of organic functionalities are reduced by dissolving metals,[2,3,5–9] it is often possible to reduce double bonds of α,β-unsaturated carbonyl systems without affecting other reducible groups. Internal, isolated alkenes are normally stable to metal–ammonia solutions unless they have very low lying antibonding orbitals[95] or special structural features that stabilize radical anion intermediates.[96] However, terminal alkenes may be reduced by dissolving metals.[97] Mono- and poly-cyclic aromatic compounds undergo reduction with dissolving metals in liquid ammonia (Birch reduction),[2,3,5,8,98,99] but these reactions are generally slow unless proton donors are added. It is therefore possible to reduce α,β-unsaturated ketones selectively in the presence of aromatic rings.[100–103] Selective reduction preserving a reducible indole ring was performed.[104]

Ethynyl carbinols are reduced to allyl alcohols and eventually to alkenes with metal–ammonia solutions containing proton donors.[105] However, by excluding proton donors, selective reduction of conjugated enones has been carried out despite the presence of ethynyl carbinol groups.[35,106–108] Similarly, selective reduction of conjugated enones containing allylic alcohols has also been achieved.[35,106,108] Carbon–halogen bonds of alkyl and vinyl halides are readily cleaved by metals in ammonia.[5,8,9] Yet, as shown in Scheme 14, alkyl fluoride may be retained by limiting reaction times,[93] and a rather sensitive vinyl chloride functionality is preserved by using an inverse addition technique.[109]

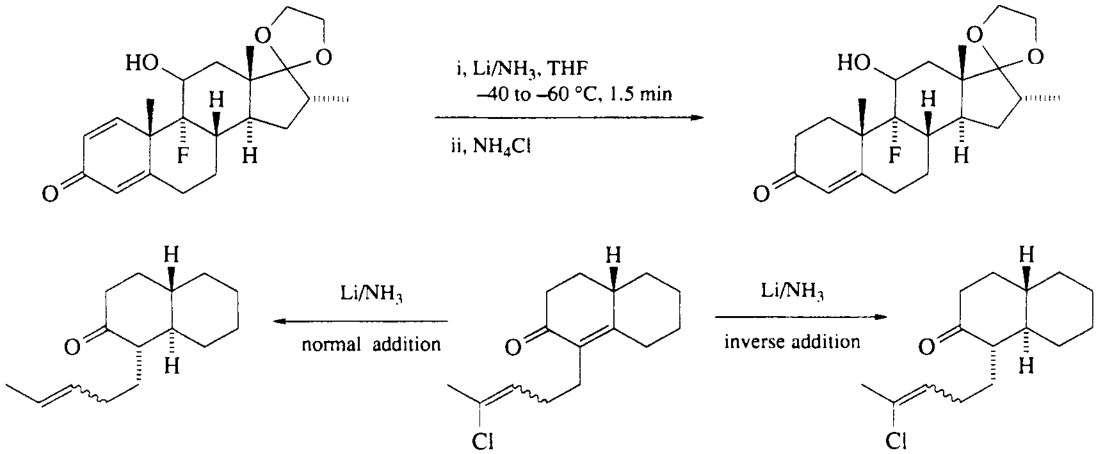

Scheme 14

Many other examples of chemoselective enone reduction in the presence of other reducible functionalities have been reported. For instance, the C—S bonds of many sulfides and thioketals are readily cleaved by dissolving metals.[5,8,9,110] Yet, there are examples of conjugate reduction of enones in the presence of a thioalkyl ether group.[110,111] Selective enone reduction in the presence of a reducible nitrile group was illustrated with another steroidal enone.[112] While carboxylic acids, because of salt formation, are not reduced by dissolving metals, esters[113] and amides[2,8] are easily reduced to saturated alcohols and aldehydes or alcohols, respectively. However, metal–ammonia reduction of enones is faster than that of either esters or amides. This allows selective enone reduction in the presence of esters[114] and amides[37,115,116] using short reaction times and limited amounts of lithium in ammonia.

### 3.5.2.2 Reduction with Low-valent Transition Metals

Low-valent species of early transition metals, such as chromium(II),[117] titanium(II), titanium(III),[118] vanadium, molybdenum and tungsten are useful reducing agents.[119] Electron-deficient alkenes and alkynes are easily reduced by chromium(II) sulfate, (*Z*)-alkenes being more rapidly reduced than the corresponding (*E*)-isomers.[120] Titanium(III) species are weaker reducing agents, exhibiting higher chemoselectivity.[121] Several steroid enediones have been reduced by chromium(II) chloride;[122] interestingly, reduction of cholest-4-ene-3,6-dione yields a different product from that obtained by titanium(III) reduction of the identical substrate (Scheme 15).[121c]

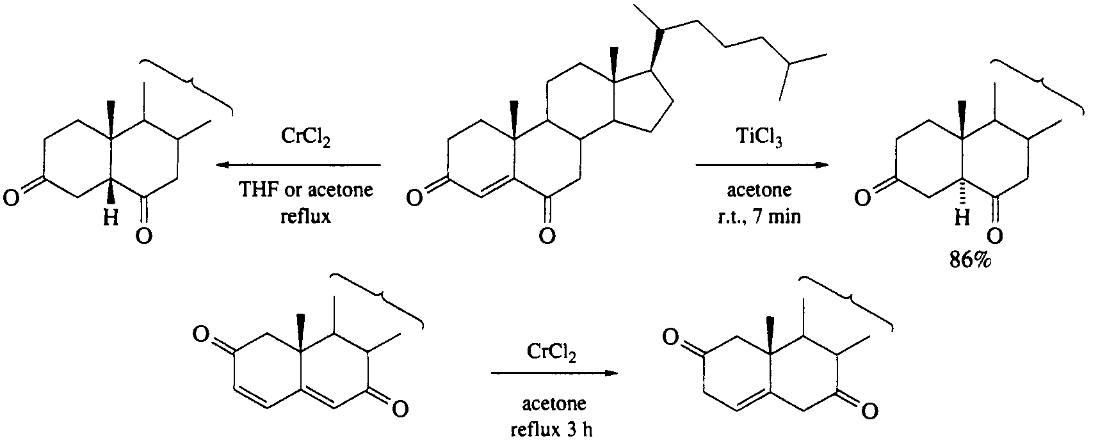

**Scheme 15**

Solutions of chromium bis(ethylenediamine)diacetate complex in methanol are capable of reducing simple α,β-unsaturated ketones to the corresponding saturated ketones. Useful yields are obtained provided a proton donor (AcOH) and a good hydrogen donor (BuSH) are present in the reaction mixture (Scheme 16).[123]

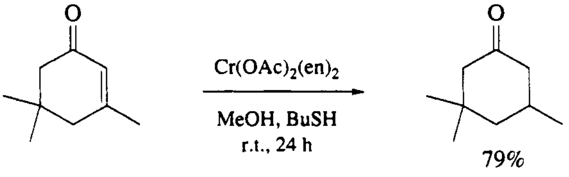

**Scheme 16**

Reductive dimerization of α,β-unsaturated ketones is effected by either Cr$^{II}$ or V$^{II}$ chloride to give 1,6-diketones, but aliphatic α,β-unsaturated aldehydes are dimerized to the allylic glycals.[124] Interestingly, nonconjugated aldehydes are stable towards these reagents. Similar pinacolic couplings of aldehydes and ketones with Ti$^{II}$ reagents were developed by Corey.[125]

Highly reactive metallic titanium, prepared from $TiCl_3$ and potassium, reduces enol phosphates to alkenes, permitting regioselective synthesis of dienes from α,β-unsaturated ketones.[126]

### 3.5.2.3 Electrochemical Reduction

The electrochemical reduction of α,β-unsaturated ketones and related compounds[5] in aprotic media in the absence of metal cations can, in some cases, lead to relatively stable anion radicals.[12c,127] However, in the presence of proton donors the latter are protonated to form hydroxyallyl radicals, which tend to dimerize more rapidly than they diffuse back to the electrode to undergo further reduction (Scheme 17).[12c] Although these allyl radicals prefer to dimerize by coupling at the β-position, if this position is sterically hindered, as in the case of cholest-4-en-3-one, coupling at the carbonyl carbon may be observed, yielding pinacols.[128]

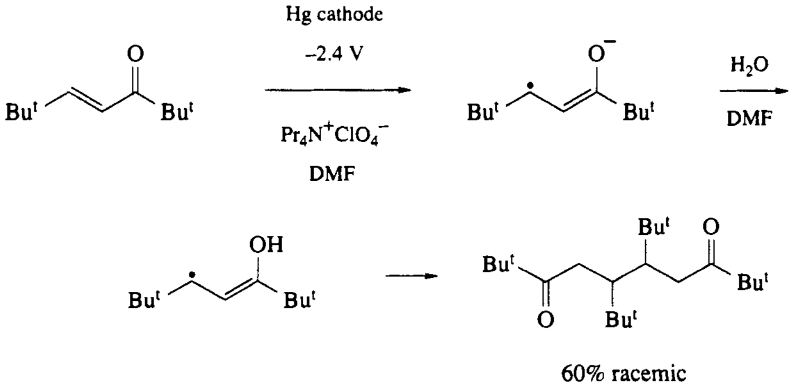

Scheme 17

Reductive dimerizations have been recorded when unsaturated carbonyl compounds are reacted with various metals, such as lithium, sodium, sodium amalgam, potassium, aluminum amalgam, zinc or magnesium.[129,130] Formation of monomeric reduction products is impeded in these reactions because the intermediate allylic radical must diffuse back to the electrode surface or metal particle for further reduction. A possible solution to this problem might be concurrent electrochemical generation of a soluble reducing agent that can intercept radical intermediates before their dimerization. For example, solutions of magnesium in liquid ammonia can be generated electrochemically.[131c] Similarly, tertiary amine salts, such as yohimbine hydrochloride, can participate in the electrochemical reduction of enones (Scheme 18),[131a,b] *via* concurrent reduction of the amine to a radical which transfers a hydrogen atom to the intermediate allyl radical.

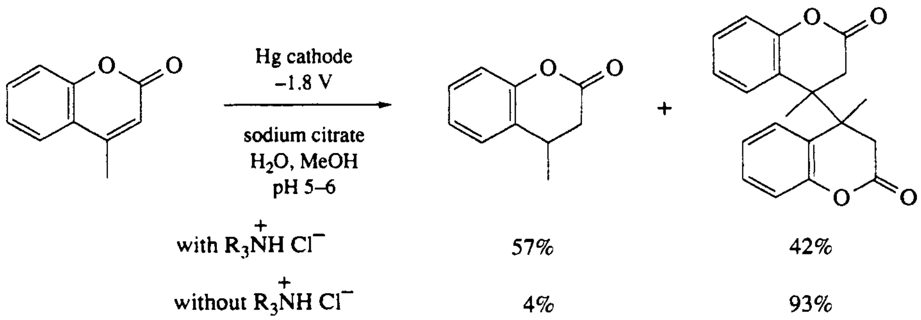
Hg cathode
-1.8 V
sodium citrate
$H_2O$, MeOH
pH 5–6
with $R_3\overset{+}{N}H\ Cl^-$
57%
42%
without $R_3\overset{+}{N}H\ Cl^-$
4%
93%
O

Scheme 18

Reductive dimerization of enones to form a new carbon–carbon bond at the β-position, known as hydrodimerization or electrohydrodimerization, has considerable synthetic utility.[132] For example, high yields of cyclic products are achieved when cyclization is kinetically favorable, leading to three- to six-membered rings from the corresponding unsaturated diesters (Scheme 19).[132d]

The product ratio in electrochemical reduction of benzalacetone is significantly altered by surfactants and various cations, which cause micellar and/or ion-pairing effects. Using these additives, it is possible to control the partitioning of the initially formed radical anion between the two main reaction pathways: either dimerization or further reduction to the saturated ketone.[133] Additionally, micellar surfactants allow the use of aqueous media without cosolvents.

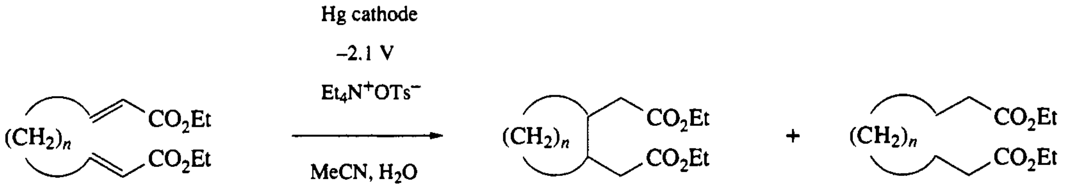

| | | |
|---|---|---|
| $n = 2$ | 41% | 48% |
| 3 | 100% | – |
| 4 | 90% | – |
| 6 | – | 43% |
| 8 | – | 50% |

**Scheme 19**

### 3.5.3 CATALYTIC HYDROGENATION

Addition of molecular hydrogen to conjugated systems has been extensively reviewed.[5,134–136] Enones can be converted to saturated ketones or to unsaturated or saturated alcohols. Usually, double bonds conjugated to the carbonyl moiety are reduced prior to nonconjugated ones. 1,2-Reduction to allylic alcohols *via* catalytic hydrogenation is quite rare, and this transformation is more conveniently performed with hydridic reducing agents, such as boron and aluminum hydrides (*vide infra*). Nevertheless, there are a number of reported cases where 1,2-reduction is preferred over 1,4-selectivity. Citronellal, for example, is reduced preferentially at the carbonyl function using nickel on silica gel as a catalyst, while hydrogenation catalyzed by Pd/$BaSO_4$ yields the corresponding saturated aldehyde.[137] Reduction to the saturated alcohol is achieved by catalytic hydrogenation over nickel,[138] copper chromite,[139] or nickel–aluminum alloy in NaOH.[140]

Enones are reduced to saturated ketones by catalytic hydrogenation provided the reaction is stopped following the absorption of 1 mol of hydrogen.[141] A number of catalysts were found useful for this, including platinum,[142] platinum oxide,[143,144] Pt/C,[141] Pd/C,[141,145] Rh/C,[141] tris(triphenylphosphine)rhodium chloride,[146,147] nickel–aluminum alloy in 10% aqueous NaOH,[148] and zinc-reduced nickel in an aqueous medium.[149] Mesityl oxide is formed from acetone and reduced in a single pot to methyl isobutyl ketone using a bifunctional catalyst which comprised palladium and zirconium phosphate (Scheme 20).[150]

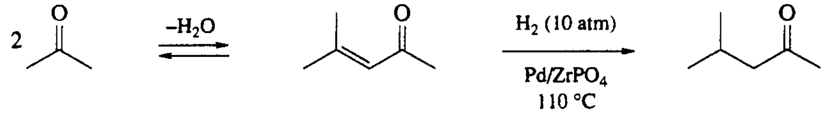

**Scheme 20**

The ease and the stereochemical course of hydrogenation of α,β-unsaturated ketones are particularly influenced by the nature of the solvent and the acidity or basicity of the reaction mixture. Some efforts have been made to rationalize the effect of the various parameters on the relative proportions of 1,2- to 1,4-addition, as well as on the stereochemistry of reduction.[151] For example, the product distribution in β-octalone hydrogenation in neutral media is related to the polarity of the solvent if the solvents are divided into aprotic and protic groups. The relative amount of *cis*-β-decalone decreases steadily with decreasing dielectric constant in aprotic solvents, and increases with dielectric constant in protic solvents, as exemplified in Scheme 21 (dielectric constants of the solvents are indicated in parentheses).[152] Similar results were observed in the hydrogenation of cholestenone and of testosterone.[153] In polar aprotic solvents 1,4-addition predominates, whereas in a nonpolar aprotic solvent hydrogenation occurs mainly in the 1,2-addition mode.

Acids and bases have a crucial effect on product stereochemistry in hydrogenation of ring-fused enone systems, as illustrated in Scheme 22.[154]

The increased amounts of *trans*-fused product obtained in basic solutions was suggested to arise from hydrogenation of the relatively flat enolate ion which adsorbs irreversibly onto the catalyst surface. Hydrogenation proceeds by hydride ion transfer from the metal catalyst, followed by protonation. Conversely, in an acidic medium protonation occurs initially, followed by irreversible adsorption on the catalyst, and then transfer of a hydride ion.[151] The stereochemistry of reduction is also related to catalyst activity, catalyst concentration, pressure and stirring rate, as they all affect hydrogen availability at the catalyst

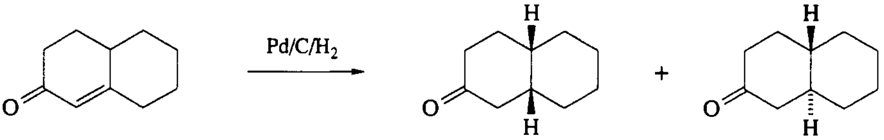

| | |
|---|---|
| DMF (38) | 79:21 |
| AcOEt (6) | 57:43 |
| diethyl ether (4.34) | 58:42 |
| hexane (1.89) | 48:52 |
| methanol (33.6) | 41:59 |
| propanol (21.8) | 68:32 |
| *t*-butyl alcohol (10.9) | 91:9 |

**Scheme 21**

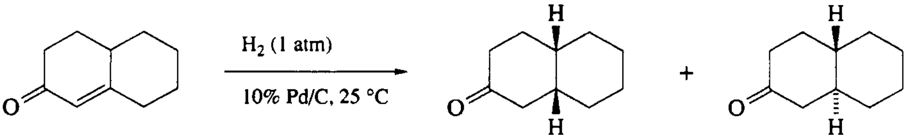

| | |
|---|---|
| EtOH | 53:47 |
| EtOH, $H_2O$, HCl | 93:7 |
| EtOH, KOH | 35–50:65–50 |

**Scheme 22**

surface. Under conditions of low hydrogen availability a reversible adsorption is favorable and therefore the product stereochemistry is determined by the relative stability of the *cis* and *trans* adsorbed species. However under conditions of high hydrogen availability, product stereochemistry is determined mainly by the nature of the initial adsorption.[151,152] Platinum catalysts, more than palladium varieties, give products determined by the initial adsorption.

Substrate structure has an important influence on the stereoselectivity of hydrogenation. For example, hydrogenation of hydrindenone having a trisubstituted double bond gives mainly the *cis* product (Scheme 23),[155] whereas similar compounds with a tetrasubstituted double bond tend to give the *trans* isomer. This phenomenon has been rationalized in terms of the preferred conformation of the adsorbed enone, which minimizes steric interactions.[155,156] A high degree of stereocontrol can be achieved in hydrogenation of substrates containing allylic or homoallylic alcohols. Results are rationalized by the coordination of the homogeneous catalyt $Ir(COD)Py(PCy_3)PF_6$ with the hydroxy groups.[157]

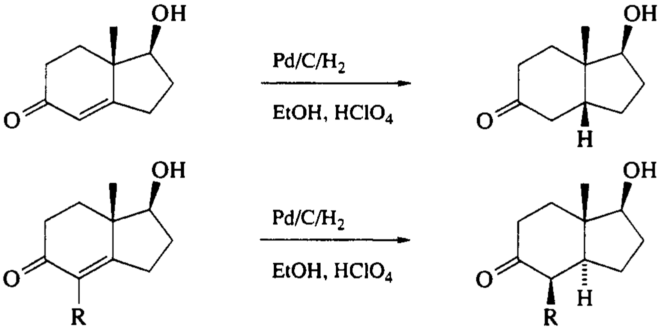

**Scheme 23**

The key step in the synthesis of 2-deoxycrustecdysone from the corresponding 20-oxo steroid is the stereoselective catalytic hydrogenation of the α,β-unsaturated lactone to afford a 2:3 mixture of δ- and γ-lactones, respectively.[158] This crude product was converted into the thermodynamically more stable γ-lactone by treatment with aqueous NaOH. α,β-Unsaturated aldehydes and ketones are hydrogenated to produce allylic alcohols in high regioselectivity using hydridoiridium phosphine complexes, such as $[Ir(PEt_2Ph)_4]_4$.[159]

In the case of multiply unsaturated carbonyl compounds, regioselectivity is also sensitive to the nature of the catalyst, to reaction conditions, and to the structure and degree of substitution of the hydrogenated double bonds. For example, hydrogenation of 3,5-heptadien-2-one over nickel on alumina or nickel on zinc oxide occurs mainly at the γ,δ-double bond. But if the catalyst is modified by the addition of lead or cadmium, reduction occurs mainly at the α,β-double bond (Scheme 24).[160]

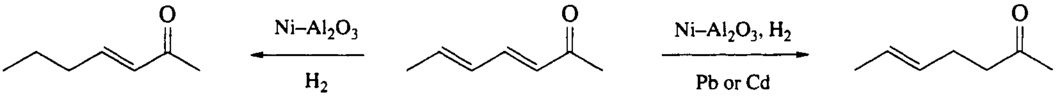

**Scheme 24**

Selective reduction of the γ,δ-double bond of the dienal shown in Scheme 25 was achieved by hydrogenation over palladium on carbon inhibited by quinoline and sulfur. Without inhibition, hydrogenation to the saturated aldehyde was observed.[161]

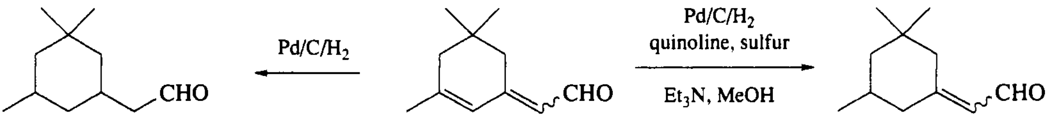

**Scheme 25**

Homogeneous catalysts, such as $RhCl(PPh_3)_3$[147] and $RuCl_2(PPh_3)_3$[162] have proved efficient in the selective hydrogenation of enones and dienones. For example, the hydrogenation selectivity of 1,4-androstadiene-3,17-dione to 4-androstene-3,17-dione is increased by elevated pressures, low temperatures and the presence of optimal amount of amines (Scheme 26).[162]

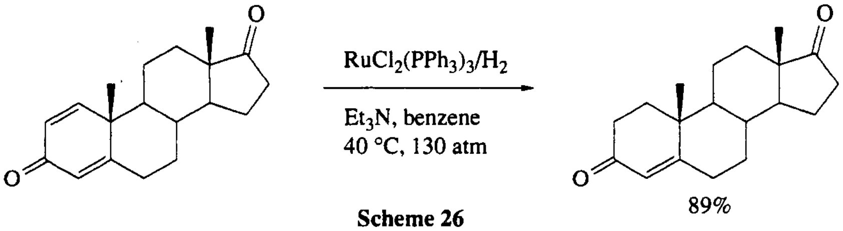

**Scheme 26**

The solvated ion pair $[(C_8H_{17})_3NMe]^+[RhCl_4]^-$, formed from aqueous rhodium trichloride and Aliquat-336 in a two-phase liquid system, hydrogenates α,β-unsaturated ketones and esters selectively at the C═C double bond.[163] The reduction of benzylideneacetone follows first-order kinetics in substrate below 0.2 M, and approaches second-order in hydrogen at partial pressures below 0.12 atm (1 atm = 101.3 kPa). The catalysis also depends on the nature of the solvent, the phase transfer catalyst and stirring rates.

The homogeneous water soluble hydrogenation catalyst $K_3(Co(CN)_5H)$ is very active for hydrogenating conjugated dienes and α,β-unsaturated ketones under phase transfer reaction conditions.[164] Thus, conjugated dienes are converted into monoenes, generally with overall 1,4-addition to yield (*E*)-alkenes, and α,β-unsaturated ketones are reduced to saturated ketones in high yields. These conditions are not useful with α,β-unsaturated aldehydes, as they lead to polymerization of the starting material.

Of special interest is the formation of new asymmetric centers by homogeneous catalytic hydrogenation using chiral ligands. This approach is particularly appealing for the synthesis of optically active amino acids *via* hydrogenation of the corresponding α,β-unsaturated *N*-acetylaminocarboxylic acid derivatives. This rather successful methodology has been extensively reviewed;[165] although most of the catalysts employed in these asymmetric hydrogenation reactions are various chiral complexes of rhodium, other metals were also examined, usually affording lower optical yields.[166]

## 3.5.4 REDUCTION WITH MAIN GROUP METAL HYDRIDES

### 3.5.4.1 Boron Hydrides

Although $NaBH_4$ does not attack isolated alkenes, C–C double bonds conjugated to strong anion-stabilizing groups may be reduced by this reagent.[167–169] Rationalization of the regioselectivity of borohydride reduction of α,β-unsaturated aldehydes and ketones has been attempted using the 'hard' and 'soft' acid and base concept[170] (*vide infra*, discussion of aluminum hydrides). It is assumed that the relatively soft hydrides add preferentially to the enone system *via* a 1,4-mode while hard reagents attack the carbonyl carbon. Borohydrides are considered softer than the corresponding aluminum hydrides. Replacement of a hydride group on boron by alkoxide makes it a harder reagent. Lithium salts are harder than sodium species. Thus, $LiAlH_4$ gives more 1,2-attack than $LiBH_4$, which, in turn, gives more than $NaBH_4$. $NaBH(OMe)_3$ yields more 1,2-reduction product than $NaBH_4$, and when production of alkoxyborates is prevented, 1,4-reduction predominates. This implies that slow addition of borohydride to a substrate solution should help to build up alkoxyborate species and increase the relative amount of 1,2-reduction. Generally, aldehydes undergo more 1,2-reduction than the corresponding ketones.

The reduction of α,β-unsaturated aldehydes and ketones by $NaBH_4$ leads, in general, to substantial amounts of fully saturated alcohols. In alcoholic solvents, saturated β-alkoxy alcohols can be formed *via* conjugate addition of the solvent.[171] This latter process becomes the main reaction path when reduction is performed in 2-propanol in the presence of sodium isopropoxide. In base, a homoallylic alcohol can become the major product of borohydride reduction of an enone.[171] Analysis of the influence of substrate structure on $NaBH_4$ reduction has shown that increasing steric hindrance on the enone increases 1,2-attack.[171]

$NaBH_4$ reduction of 3-substituted 5,5-dimethylcyclohex-2-enones in alkaline solution of water dioxane occurs exclusively at the 1,2-positions. The rate of reduction is strongly dependent on the 3-substituent. A Hammett-type correlation revealed similar reaction characteristics to those of borohydride reduction of substituted acetophenones.[172]

In order to study the factors determining the regioselectivity of sodium borohydride reduction of α,β-unsaturated ketones, reactions with 3-methylcyclohexenone, carvone and cholestenone were carried out in 2-propanol, diglyme, triglyme or pyridine.[173] Mixtures of 1,2- and 1,4-reduction products were obtained in the alcoholic and ether solvents, whereas pure 1,4-reduction was observed in pyridine. Addition of triethylamine to $NaBH_4$ in diglyme led to formation of triethylamine borine, $Et_3N·BH_3$. Similarly, with pyridine, pyridine·borine could be isolated, leading to exclusive 1,4-reductions.

The results were interpreted in terms of steric requirements of the actual reducing species. It was suggested that attack of $BH_4^-$ proceeds exclusively along the 1,4-reduction mode, whereas alkoxyborohydrides (formed as reaction products) prefer the 1,2-reduction mode. The pyridine·borine itself does not reduce enones under the reaction conditions, but it inhibits formation of alkoxyborohydrides.[173] The same trend was observed with aluminum hydride reductions. When $LiAlH_4$ was first reacted with pyridine to form lithium tetrakis(dihydro-*N*-pyridyl)aluminate, 1,4-reduction predominated.[173]

Low regioselectivity is observed in reduction of enones with a 2:1 mixture of sodium cyanoborohydride and zinc chloride in ether at room temperature.[174] A mixture containing 1,2- and 1,4-reduction products is obtained in a ratio that is greatly dependent upon substrate.

From the reduction in methanol of a series of substituted 2-aryl-(*Z*)- and 2-aryl-(*E*)-cinnamates by $NaBH_4$ at room temperature, it was concluded that the facile reduction to give dihydrocinnamates proceeds through an early transition state of considerable polarity.[167,175]

Several organoborohydrides were found to effect the selective 1,4-reduction of enones. For example, lithium and potassium tri-*s*-butylborohydrides (L- and K-selectride) and lithium triethylborohydride were found useful for conjugate reduction of α,β-unsaturated ketones and esters. In general, β-unsubstituted cyclohexenones undergo exclusive 1,4-reduction to the corresponding ketone enolates, which can be protonated or alkylated in high yields. Ketones such as 5-*t*-butylcyclohex-2-en-1-one are cleanly reduced to the saturated ketone using K-selectride at –78 °C in THF (Scheme 27).[176] This regioselectivity, however, is not general, but is a result of steric hindrance of the alkene, as well as the size of the ring. Thus alkyl substitution at the β-position completely suppresses the 1,4-reduction mode. While enones in five- and seven-membered rings are reduced preferentially in a 1,2-manner, six-membered ring enones are reduced in a 1,4-mode. Trapping the intermediate enolate by an alkylating agent (*e.g.* MeI, allyl bromide) results in an efficient reductive alkylation. Accordingly when the reduction of α,β-unsaturated esters is performed in dry ether solvents, the major reaction product arises from carbonyl condensation. However addition of a proton source such as *t*-butyl alcohol results in 1,4-reduction.

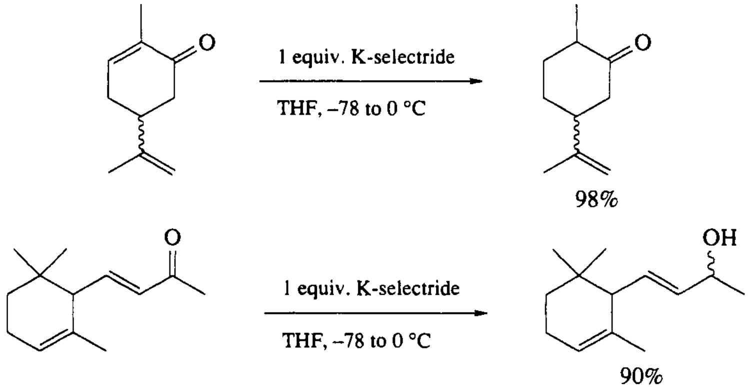

**Scheme 27**

Reduction of α,β-unsaturated aldehydes and ketones with 9-borabicyclo[3.3.1]nonane (9-BBN-H) proceeds selectively and cleanly to form the corresponding allylic alcohols.[177] The reaction tolerates a large variety of functionalities, such as nitro, carboxylic acid, amide, nitrile, sulfide, disulfide, epoxide, *etc.* Hydroboration of the double bond is a much slower reaction, which does not interfere with carbonyl reduction. For example, 1,2-reduction of cyclohexenone at room temperature with excess of 9-BBN-H in THF is completed within 10 min, while hydroboration of the double bond requires three days. Amine·borane complexes have been used for selective 1,2-reduction of α,β-unsaturated ketones and aldehydes. Thus, cyclohexen-2-one was reduced to hexenol with *t*-butylamine·borane.[178] Borohydride exchange resin, which is obtained from $NaBH_4$ and the quaternary ammonium resin Amberlite 400 IRA, reduces cinnamaldehyde and benzalacetone to the corresponding allylic alcohols.[179] 1-Pyrrolylborane·THF complex reduces α,β-unsaturated ketones and aldehydes to the corresponding allylic alcohols in high yields.[180] Borohydride reduction of α,β-unsaturated carbonyl compounds has been widely applied in natural product chemistry. A number of α,β-unsaturated ketone derivatives of gibberellins are reduced to the corresponding saturated alcohols by $NaBH_4$.[181–184] Sodium borodeuteride reduction of gibberellin $A_3$ 3-ketone affords gibberellin $A_1$ and its 3-epimer.[181,182] Attack of hydride proceeds stereospecifically from the β-face at C-1. Protonation at C-2 proceeds with limited selectivity. Thus, reduction of the above-mentioned gibberellin with either $NaBH_4$–CuCl in deuterated methanol or $NaBH_4$–LiBr followed by treatment with $D_2O$ gave 2-deuteriogibberellin $A_1$ methyl ester together with some 3-epi-$GA_4$ with approximately 2:1 ratio of the 2β:2α deuterides. Using L-selectride for the reduction of a similar gibberellin enone derivative resulted mainly in the 1,2-reduction product, affording the 3α-allylic and saturated alcohols in 47% and 30% yields, respectively.[183]

Substituted gibberellins, such as 1α- and 1β-hydroxy $GA_5$ and $GA_{20}$ were prepared from a single enone precursor by 1,2-reduction with $NaBH_4$ (Scheme 28). Conversely, catalytic hydrogenation of the same enone with 10% Pd/$CaCO_3$ in pyridine afforded the 1,4-reduction product, 1-oxo-$GA_{20}$.[184]

The stereoselective 1,2-reduction of the α,β-unsaturated ketone group was one of the key steps in Corey's prostaglandin synthesis (Scheme 29).[185] Various boron and aluminum hydride reagents gave mixtures of the corresponding (15*S*)- and (15*R*)-allylic alcohols in various ratios.[186] Best selectivity was obtained with highly hindered lithium trialkylborohydrides, and even better with R = *p*-$PhC_6H_4NHCO$ This derivative was reduced with thexyl-di-*s*-butylborohydride and tri-*s*-butylborohydride with (15*S*):(15*R*) ratios of 88:12 and 89:11, respectively.[185] 1,2-Reduction of an α,β-unsaturated aldehyde with $NaBH_4$ represents one of the steps in the total synthesis of 6,15-hydroxyperezone.[187]

Stereoselective reduction of an enone lactone was a key step in the construction of the 20-hydroxyecdysone side chain. Totally different mixtures of products were obtained when the reduction was carried out with sodium borohydride or by catalytic hydrogenation (Scheme 30).[158] In all cases, the 1,4-reduction mode is preferred. With borohydride, however, this process is followed by a subsequent reduction of the saturated ketone and base-catalyzed rearrangement of the δ-lactone into a γ-lactone.

Stereoselective conjugate reduction of α,β-unsaturated amides with L-selectride was achieved by using a chiral sultam, temporarily attached to the molecule.[188] Alkynic ketones are enantioselectively reduced to the corresponding propargylic alcohols in up to 92% *ee* using *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane.[189] The conjugate reduction of acyclic α,β-unsaturated ketones can provide selectively regio- and stereo-chemically defined enolates that are unattainable by other methods. A knowledge of enone ground-state conformational preferences allows one to predict which enolate geometrical isomer will predominate in these reactions (Scheme 31).[190]

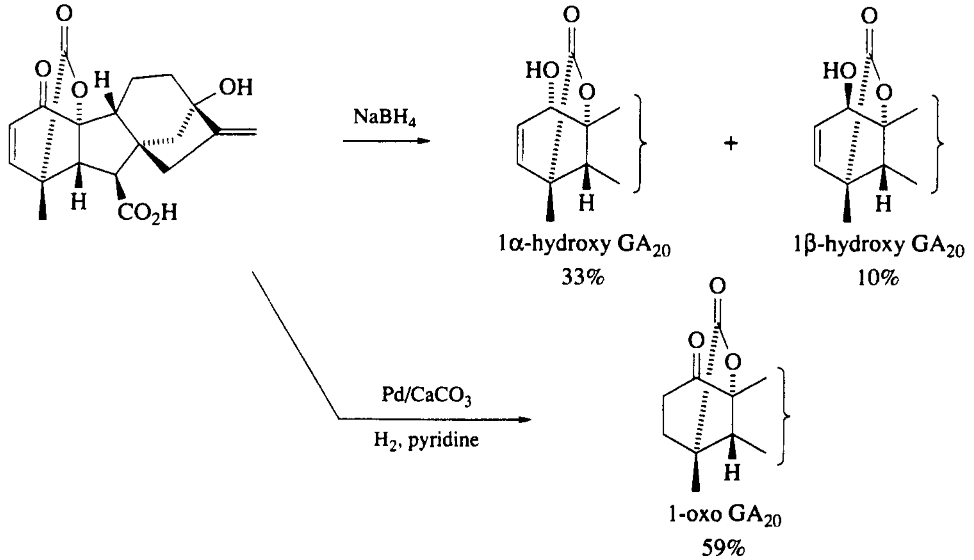

**Scheme 28**

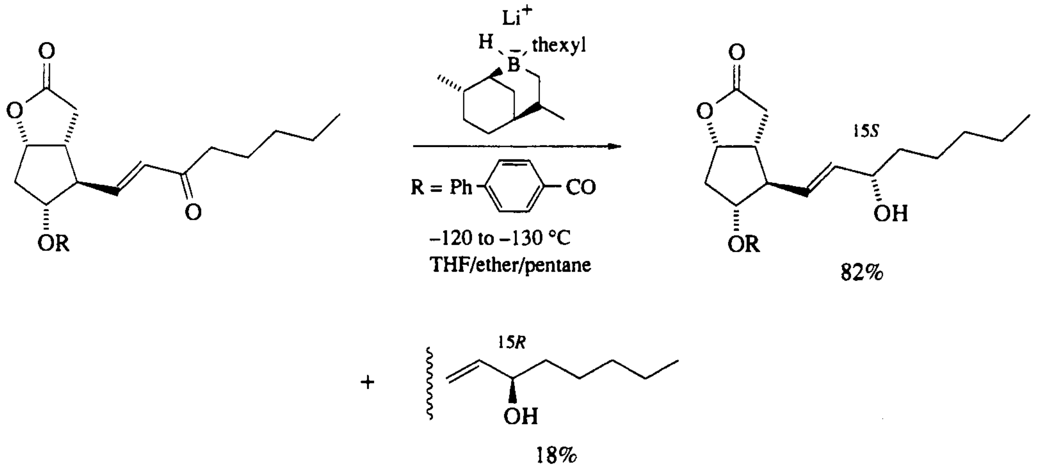

**Scheme 29**

Thus, enones that exist preferentially as *s-trans* conformers will give rise to (*E*)-enolates, whereas conjugate addition of hydride to *s-cis* enones will lead to (*Z*)-enolates. These can be trapped by trimethylsilyl chloride (TMS-Cl) to give the corresponding silyl enol ethers (Scheme 32).[190]

Sodium cyanoborohydride ($NaBH_3CN$) or tetrabutylammonium cyanoborohydride in acidic methanol or acidic HMPA reduces α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols.[191] This system is limited to enones in which the double bond is not further conjugated, in which case the allylic hydrocarbon is formed in substantial amounts. Thus, reduction of chalcone gives mainly 1,3-diphenylpropene (48%) as well as 26% of the allylic ether. Cyclic enones are also not good substrates, as competing 1,4-addition gives large fractions of saturated alcohols.[191]

Lithium *n*-butylborohydride is prepared by reacting equimolar amounts of *n*-butyl lithium and borane·dimethyl sulfide complex.[192] This reagent effectively reduces enones in toluene–hexane mixtures at −78 °C to give, in most cases, high yields of the corresponding allylic alcohols.[192] Conjugated cyclopentenones, however, give mixtures of 1,2- and 1,4-reduction products. Under identical reaction conditions, saturated ketones are reduced to alcohols. The latter process can take place in the presence of simple esters.

Regioselective 1,2-reduction of enones to the corresponding allylic alcohols is achieved with $NaBH_4$ in the presence of lanthanoid ions, such as $La^{3+}$, $Ce^{3+}$, $Sm^{3+}$, $Eu^{3+}$, $Yb^{3+}$ and $Y^{3+}$.[193] This procedure is complementary to those giving predominantly 1,4-selectivity, such as $NaBH_4$ in pyridine.[173] The general

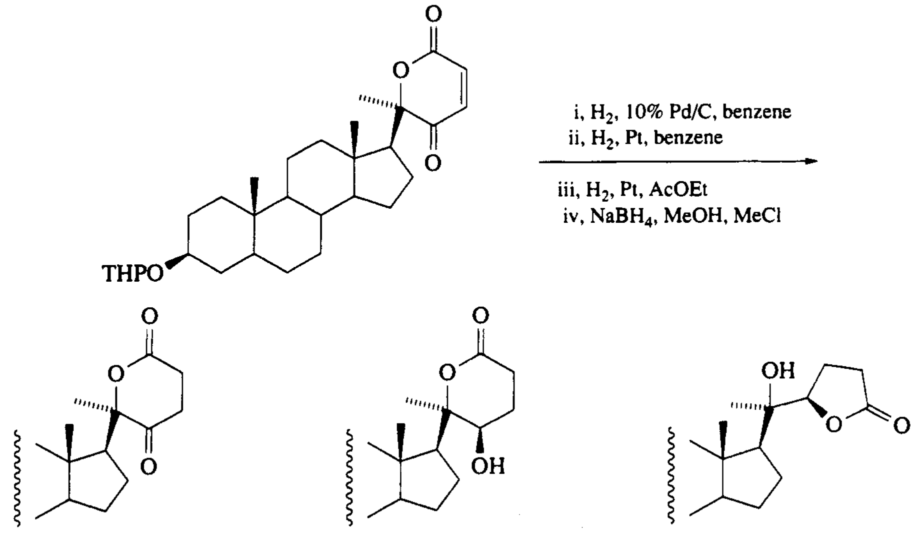
THPO
O
i, $H_2$, 10% Pd/C, benzene
ii, $H_2$, Pt, benzene
iii, $H_2$, Pt, AcOEt
iv, $NaBH_4$, MeOH, MeCl
OH

| | | | |
|---|---|---|---|
| i | 98% | – | – |
| ii | 17% | – | 81% |
| iii | – | 80% | 20% |
| iv | – | 5% | 78% |

**Scheme 30**

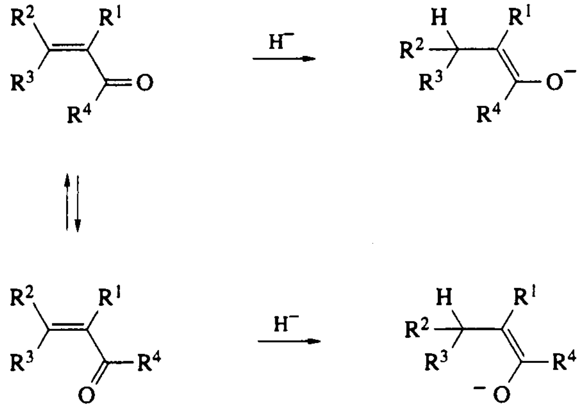
$R^2$
$R^1$
$R^3$
$R^4$
O
$H^-$
H
$O^-$
$^-O$

**Scheme 31**

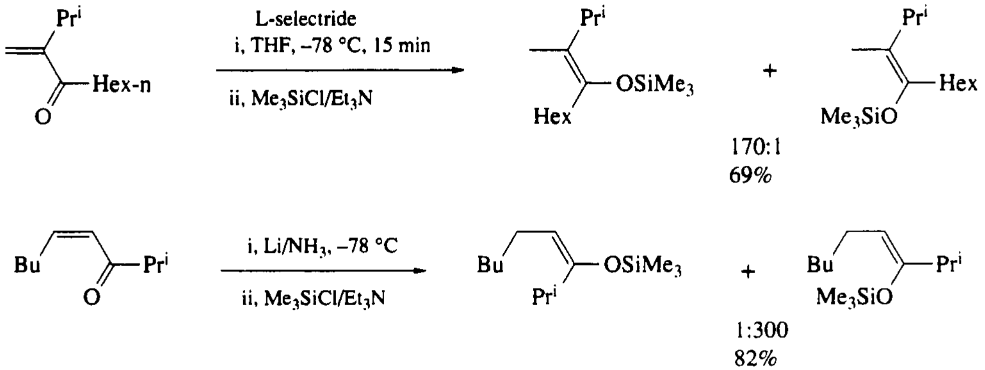
$Pr^i$
Hex-n
O
L-selectride
i, THF, –78 °C, 15 min
ii, $Me_3SiCl/Et_3N$
$OSiMe_3$
Hex
+
$Me_3SiO$
170:1
69%
Bu
i, $Li/NH_3$, –78 °C
ii, $Me_3SiCl/Et_3N$
1:300
82%

**Scheme 32**

utility of $NaBH_4$–$CeCl_3$ selective reduction is illustrated by the conversion of cyclopentenone to cyclopentenol in 97% yield and only 3% of cyclopentanol, although conjugate reduction of cyclopentenone systems by most hydride reagents is usually highly favored (Scheme 33).

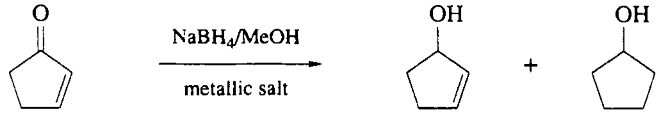

| | | |
|---|---|---|
| $La^{3+}$ | 90 | 10 |
| $Ce^{3+}$ | 97 | 3 |
| $Sm^{3+}$ | 94 | 6 |
| $Eu^{3+}$ | 93 | 7 |
| $Yb^{3+}$ | 89 | 11 |
| $Y^{3+}$ | 86 | 14 |
| $Li^{+}$ | 1 | 99 |

**Scheme 33**

Thus, reaction of equimolar amounts of α,β-unsaturated ketones and either samarium or cerium chloride hexahydrate in methanol with sodium borohydride produced high yields of the corresponding allylic alcohols.[193] This method has gained considerable success and has often been used in regio- and stereo-selective syntheses of natural products.[194,195] Trivalent lanthanoid ions were shown to promote selective 1,2-reduction of conjugated aldehydes in the presence of saturated aldehydes. For example, citral is quantitatively reduced to geraniol with $NaBH_4/ErCl_3$, while citronellal is sluggishly reduced (13%) under the same conditions.[196,197] Conversely, 1,4-reduction of γ-pyrones occurs with tritiated $NaBH_4/Ce(NO_3)_3$.[198]

A mechanistic study of the role of the lanthanide cations suggests that they catalyze decomposition of borohydride by the hydroxylic solvent to afford alkoxyborohydrides, which may be responsible for the observed regioselectivity. The stereoselectivity of the process is also modified by the presence of $Ln^{3+}$ ions, in that axial attack of cyclohexenone systems is enhanced.[193] α,β-Unsaturated aldehydes are regioselectively reduced to allylic alcohols by bis(triphenylphosphine)copper(I) tetrahydroborate in the presence of Lewis acid catalyst.[199]

β-Dialkylamino conjugated enones are reduced to the corresponding γ-amino alcohols with $NaBH_4$ in the presence of $FeCl_3$. These amino alcohols could be converted into conjugated enones by chromic acid oxidation and deamination (Scheme 34).[200] On the other hand, β-acylamino conjugated enones are reduced by $NaBH_4$ to afford β,γ-unsaturated γ-acylamino alcohols, which are regioselectively hydrolyzed to conjugated enones.

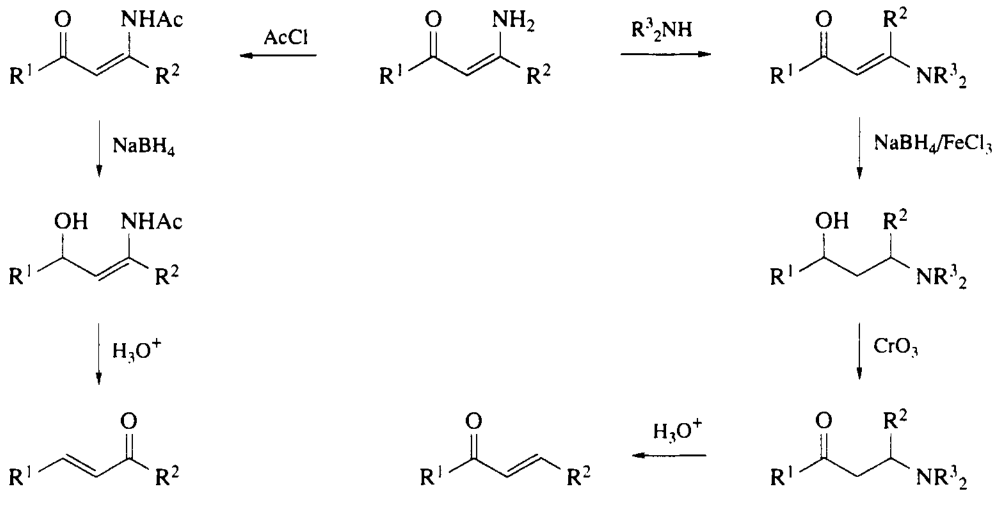

**Scheme 34**

β,β-Bis(alkylthio)-α,β-unsaturated ketones are selectively reduced in a 1,2-manner to the corresponding allylic alcohols by tritiated $NaBH_4$ in ethanol.[201] Enaminones are similarly reduced by tritiated

NaBH$_4$ to the corresponding β-amino carbonyl compounds, while reduction with LiAlH$_4$ resulted in deaminated products. This is explained on the basis of the HSAB principle, with NaBH$_4$ being considered a soft base and the vinylic β-carbon being a soft acid.[202] Reduction of β-sulfenylated α,β-unsaturated ketones with NaBH$_4$ in the presence of catalytic amounts of CoCl$_2$ or NiCl$_2$ in methanol produces the corresponding desulfenylated, saturated ketones (Scheme 35).[203] These substrates, however, were not affected by combinations of NaBH$_4$ and other metal salts, including FeCl$_2$, FeCl$_3$, CuI and CuCl$_2$. Conjugate reduction of substituted cinnamic acids was achieved with tritiated NaB[$^3$H]$_4$–NiCl$_2$ in methanol.[204]

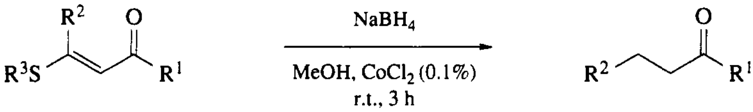

**Scheme 35**

### 3.5.4.2 Aluminum Hydrides

The properties of complex metal hydrides, particularly those of aluminum, and their use in organic synthesis have been compared in a number of papers, review articles and monographs.[205–209] Useful tables, listing the most appropriate hydride reagents for selective reduction of various polyfunctional compounds, have been published.[1,208–211] Use of chiral metal alkoxyaluminum hydride complexes in asymmetric synthesis has also been reviewed.[212]

The two modes of reduction of α,β-unsaturated aldehydes and ketones, 1,2- and 1,4-addition of metal hydride to the enone system, lead respectively to either an allylic alcohol or a saturated ketone. It has been suggested that the relative importance of these paths depends upon substrate hardness or softness, as defined in terms of the coefficients of the lowest unoccupied molecular orbital (LUMO) (*vide supra*, the discussion of borohydrides). While 1,2-addition is considered to be a mainly charge-controlled process, 1,4-addition is a frontier orbital controlled process.[213] These considerations predict, for example, that the 1,4-addition of a given metal hydride to cyclopentenone should always be faster than a similar addition to cyclohexenone.[214] Moreover, in cases where the enone system is further conjugated to a phenyl ring, as in cinnamaldehyde, increased frontier orbital control should render the enone more prone to 1,4-addition.[215] Obviously, the course of reduction of conjugated carbonyl compounds is also highly influenced by the nature of the metal hydride. According to Pearson's concept of soft and hard acids and bases,[216,217] hard metal hydrides add preferentially to the 2-position and soft metal hydrides to the 4-position of the conjugated enone system.[213–215] As shown in Table 1, these predictions agree well with representative experimental results.[214,218]

**Table 1** Ratio of 1,4- to 1,2-Reduction Products

| | 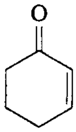 | 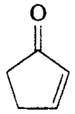 | 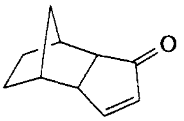 |
|---|---|---|---|
| LiAlH(OMe)$_3$ | 5:95 | 10:90 | 24:76 |
| LiAlH$_4$ | 22:78 | 86:14 | 100:0 |
| LiAlH(SMe)$_3$ | 56:44 | 95:5 | |
| LiAlH(OBu$^t$)$_3$ | 78:22 | 100:0 | 100:0 |
| LiAlH(SBu$^t$)$_3$ | 95:5 | 100:0 | |

Because of their electrophilic nature, Li$^+$ cations accelerate the reduction of carbonyl compounds by LiAlH$_4$ or NaBH$_4$. Li$^+$-complexing agents, such as cryptands, crown ethers or polyamines decrease the rate of reduction.[219] In the case of α,β-unsaturated ketones, this slow down is associated with altered regioselectivity. For example, LiAlH$_4$ reduction of cyclohexenones in the absence of the cryptand proceeds predominantly with 1,2-reduction. In the presence of the cryptand, 1,4-attack is favored. This selectivity is more pronounced with LiAlH$_4$ than with NaBH$_4$ (Scheme 36)[219] and is also dependent on solvent. For example, with diethyl ether the 1,2-attack prevails, whereas when the cation is complexed, 1,4-addition predominates.

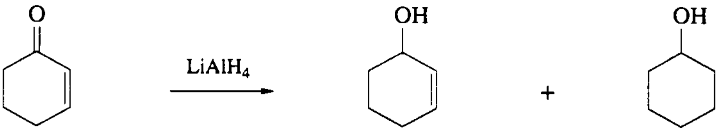

| | | |
|---|---|---|
| THF | 86:14 | 98% |
| ether | 98:2 | 98% |
| THF, 1.2 equiv. cryptand | 14:86 | 85% |
| ether, 1.2 equiv. cryptand | 23:77 | 80% |

cryptand =

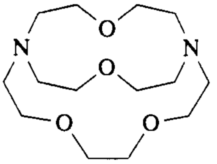

**Scheme 36**

This effect is explained in terms of frontier molecular orbitals treatment.[219] The regioselectivity of reduction depends upon the relative values of the C-1 and C-3 atomic coefficients in the LUMO. The atom with the larger coefficient corresponds to the predominant site of attack. When $Li^+$ is complexed by the α-enone, the C-1 coefficient is larger than that of C-3, and C-1 attack is favored. In the absence of such complexation, the C-3 coefficient is larger, leading to 1,4-attack. The strength of carbonyl–$Li^+$ interaction is strongly dependent upon the solvent, the nature of the complexing agent, and the interaction between the $Li^+$ ion and the reducing agent. Thus, in strongly coordinating solvents, such as pyridine,[173] 1,4-reduction predominates.

Steric and electronic factors in the enone substrate may also alter selectivity. For example, the high tendency of $LiAlH(OBu^t)_3$ to undergo 1,4-addition with simple enones is modified in the example given in Scheme 37.[220]

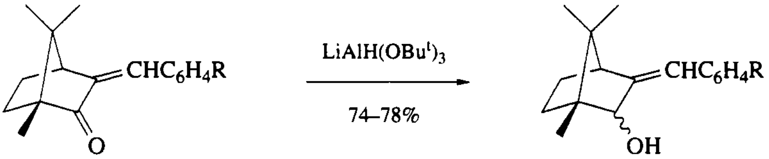

R = H, *m*-F, *p*-Me, *p*-MeO

**Scheme 37**

β,β-Bis(alkylthio)-α,β-unsaturated ketones undergo two-step reduction with $LiAlH_4$. The first step is a 1,2-addition to the carbonyl, leading to allylic alcohols, which may undergo further reduction of the alkenic bond.[221] The ratio of 1,2- to 1,4-addition of aluminum hydride to an α,β-unsaturated ketone is highly dependent on the enone structure, solvent, relative initial concentrations of reactants, temperature, and softness or hardness of the hydride reagent. These reductions can be controlled to proceed with either 1,2- or 1,4-addition, with high selectivity.[205] Scheme 38[222–225] illustrates the prominent tendency of $LiAlH_4$ and $LiAlH(OMe)_3$ to yield 1,2- rather than 1,4-adducts, as compared to $LiAlH(OBu^t)_3$.

The reagent $NaAlH_2(OCH_2CH_2OMe)_2$ favors 1,2-addition to cyclic enones[223,226–230] with greater selectivity than with either $LiAlH(OMe)_3$[214] or $AlH_3$.[218] In the reduction of 9-oxoisolongifolene to the allylic 9α- or 9β-alcohols, reversal of stereochemistry occurs when $NaAlH_2(OCH_2CH_2OMe)_2$ is used instead of $LiAlH_4$ or $NaBH_4$.[231] While the latter two reagents lead to formation of the thermodynamically more stable α-alcohol as the major product, increased steric bulk of the former seems to favor the less stable β-isomer. Chiral compounds containing enones are often reduced to the corresponding allylic alcohols with high stereoselectivity.[232] For example (–)-*cis*-carveol is obtained by $LiAlH_4$ reduction of carvone at low temperatures.[233]

Sterically unhindered enones, such as cyclohexenone, are reduced by $LiAlH(OBu^t)_3$ to give predominantly the corresponding saturated ketone,[214] but more sterically congested systems are cleanly reduced *via* the 1,2-mode to give the allylic alcohol, usually with high stereoselectivity.[234–238]

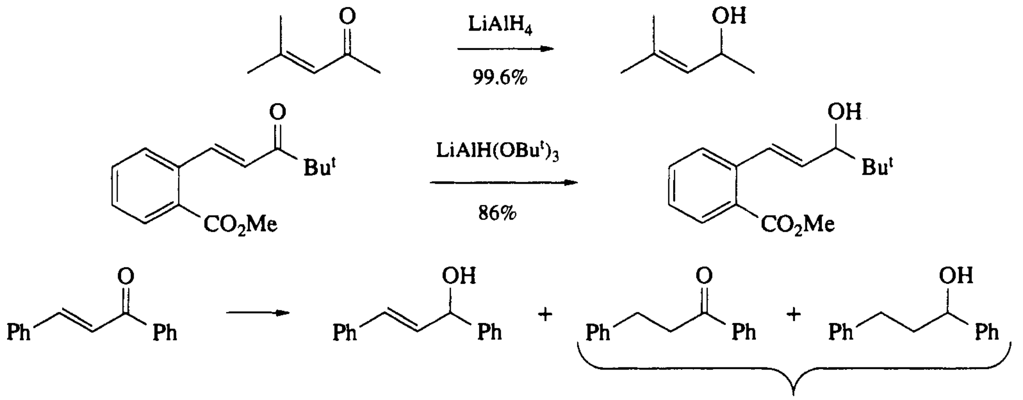
O
LiAlH4
99.6%
OH
O
Bu<sup>t</sup>
CO2Me
LiAlH(OBu<sup>t</sup>)3
86%
OH
Bu<sup>t</sup>
CO2Me
O
Ph
Ph
OH
Ph
Ph
+
O
Ph
Ph
+
OH
Ph
Ph

| | | |
|---|---|---|
| $LiAlH(OMe)_3$ | 94% | 6% |
| $LiAlH(OBu^t)_3$ | 38% | 62% |

**Scheme 38**

1,2-Reduction has been reported for other hydride reagents, such as diisobutylaluminum hydride (DIBAL-H),[213,230,239,240] aluminum hydride[218] and 9-BBN-H.[241] α,β-Unsaturated lactones are also reduced by DIBAL-H to the corresponding lactols in high yields.[242]

1,4-Reduction of enones can be effected with high selectivity with $AlH(OBu^t)_2$, $AlH(OPr^i)_2$, $AlH(NPr^i_2)_2$ forming saturated ketones in 90–100% yield. $AlH(NPr^i_2)_2$ exhibited the lowest selectivity, as no 1,4-reduction of mesityl oxide or isophorone is observed with this reagent. Reacting $AlH(NPr^i_2)_2$ with methyl vinyl ketone or cyclohexanone led to a mixture of products. *trans*-Chalcone also undergoes quantitative 1,4-reduction with the above-mentioned hydrides.[240] Similarly, reduction of 9-anthryl styryl ketone or anthracene-9,10-diyl-bis(styryl ketone) with $LiAlH(OBu^t)_3$ affords the saturated ketone as the sole product.[243] Hydrides such as $LiAlH(OBu^t)_3$ and $LiAlH(SBu^t)_3$ favor 1,4-reduction in cyclopentenones,[214,215,218,244–247] as in the example in Scheme 39.[248,249]

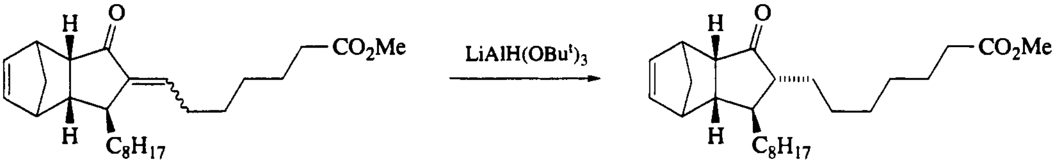
H
O
CO2Me
H
C8H17
LiAlH(OBu<sup>t</sup>)3
H
O
CO2Me
H
C8H17

**Scheme 39**

Scheme 40 illustrates an interesting two-step selective reduction of an enone system, first with sodium hydride and $NaAlH_2(OCH_2CH_2OMe)_2$ and then with the same reagent in the presence of 1,4-diazabicyclo[2.2.2]octane. Specific reduction, however is not achieved with $NaBH_4$, $LiBH_4$, $LiBHBu^s_3$ or 9-BBN-H.[250]

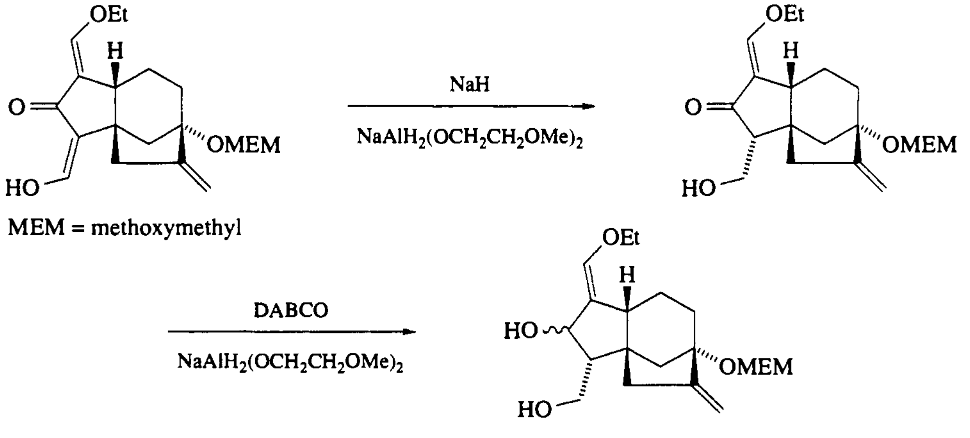
OEt
H
O
OMEM
HO
NaH
NaAlH2(OCH2CH2OMe)2
OEt
H
O
OMEM
HO
DABCO
NaAlH2(OCH2CH2OMe)2
OEt
H
HO
OMEM
HO

MEM = methoxymethyl

**Scheme 40**

Both $LiAlH(OMe)_3$ and $NaAlH_2(OCH_2CH_2OMe)_2$ are convenient reducing agents for low temperature, copper-mediated 1,4-reduction, as shown for the latter by Scheme 41.[223,251] Partial reduction of cyclopentenedione has been achieved with several of these reagents.[252–254]

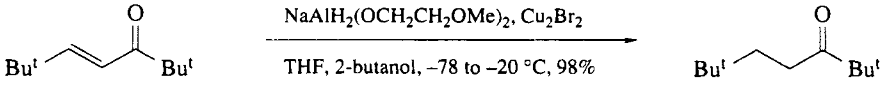
O
$Bu^t$
$Bu^t$
$NaAlH_2(OCH_2CH_2OMe)_2$, $Cu_2Br_2$
THF, 2-butanol, –78 to –20 °C, 98%
O
$Bu^t$
$Bu^t$

**Scheme 41**

There are a number of cases where a less reactive enone group remains intact while a more reactive saturated ketone present in the same substrate is selectively reduced,[255–258] but there are a number of examples of polyfunctional natural products where simultaneous reduction of both saturated and unsaturated ketones or of preferential reduction of the unsaturated one is achieved with $LiAlH(OBu^t)_3$.[259–261]

1,2-Reduction of enol ethers or enol esters of 1,3-diketones, followed by acid-catalyzed allylic rearrangement of the reduction product (see p. 85 in ref. 5) is a useful route to α,β-unsaturated ketones. Aliphatic[262,263] and alicyclic[264] enones have thus been prepared in good yields at low temperatures with $NaAlH_2(OCH_2CH_2OMe)_2$.[265,266]

Reduction of α,β-unsaturated aldehydes can afford either an unsaturated or saturated primary alcohol, or a mixture of both, depending on reaction conditions. For example, while addition of cinnamaldehyde to $NaAlH_2(OCH_2CH_2OMe)_2$ in benzene gives 97% 3-phenylpropanol, inverse addition (of the reducing agent to solution of the substrate) yields 94% cinnamyl alcohol.[267,268] Reduction with $LiAlH_4$ is similarly dependent on the addition sequence. The more sterically hindered hydride $LiAlH(OBu^t)_3$ is highly selective for 1,2-reduction of aldehydes, even under conditions of normal addition. For example, it reduces cinnamaldehyde cleanly to cinnamyl alcohol, without affecting the alkenic bond.[269–271] Similar behavior is exhibited by $NaAlH_2(OCH_2CH_2OMe)_2$, which reduces 2-butenal to 2-butenol in 97% yield.[268] On the other hand, hydrides, such as $LiAlH(OMe)_3$[206,269,270] and $NaAl_2H_4(OCH_2CH_2NMe_2)_3$,[272] usually yield the saturated primary alcohol.[273–275]

Regioselectivity of enone reduction with DIBAL-H is very susceptible to minor structural changes in the substrate. While five-membered exocyclic enones provide the allylic alcohols, which are the normal products for this reagent, reduction of chromones possessing exocyclic six-membered enones yield saturated ketones (Scheme 42).[276] This was explained by the strict coplanarity of the enone function in the five-membered structure, whereas the enones giving rise to saturated ketones are slightly twisted. Reduction of isoflavones with DIBAL-H under these conditions provides the corresponding isoflavan-4-ones in very high selectivity.[276] Reduction of a substituted dihydropyranone with DIBAL-H in benzene affords the corresponding glycal.[277]

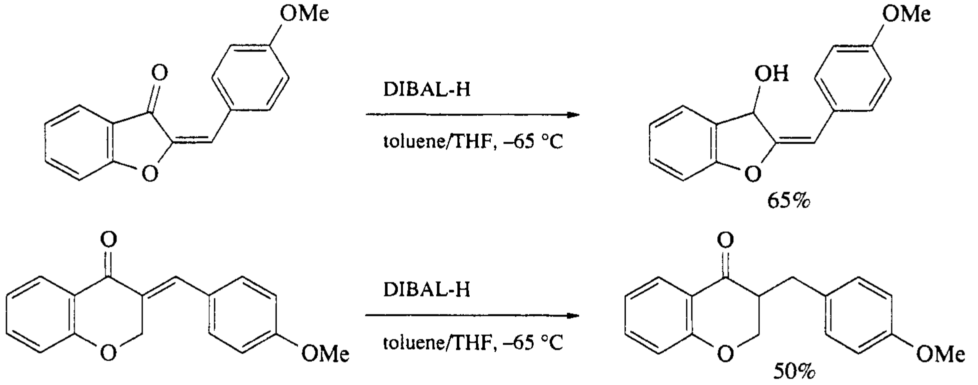

**Scheme 42**

The 'ate' complex $LiAlHBu^nBu^i_2$ is prepared from DIBAL-H and *n*-butyllithium in either THF or toluene–hexane. This reagent is more effective for selective 1,2-reduction of enones to the corresponding allylic alcohol than is DIBAL-H alone.[278] The reagent also reduces esters, lactones and acid chlorides to the corresponding alcohols, and epoxides to the respective alcohols. α,β-Unsaturated ketones derived from dehydration of aldol products from 1-(arylthio)cyclopropanecarbaldehydes and ketones were selectively reduced by this 'ate' complex or by DIBAL-H itself, yielding the allylic alcohols with minor amounts of the 1,4-reduction product.[279] Yields were typically higher with this reagent than with DIBAL-H.

Enones may be deoxygenated with $LiAlH_4/AlCl_3$ to give the corresponding alkenic hydrocarbons. The reactive species seem to be $AlHCl_2$ or $AlH_2Cl$, which act as both Lewis acids and hydride donors. The reaction involves initial 1,2-reduction to form the allylic alcohol, followed by substitution of the allylic hydroxy group by hydride (mainly *via* an $S_N2'$ mechanism) to form the corresponding mixture of alkenes.[280] This technique has been applied to the deoxygenation of natural products. By using mixtures of $LiAlH_4$ and $AlCl_3$, flavanone and chalcones were transformed into flavan and diarylpropenes, respectively.[281] In a few cases, such as with 2-bromocyclopentenone or 2-hydroxycyclohexenone, only 1,2-reduction with $LiAlH_4/AlCl_3$ is observed.[282]

Conjugate reduction is the major pathway of enone reduction with a mixture of $LiAlH_4$ and excess CuI in THF.[283] It has been shown that the active reducing agent in this mixture is an $H_2AlI$ species and not the copper hydride. Enones that have an *s-cis* geometry are reduced much more slowly than similar ketones with an *s-trans* conformation, and no reduction was observed with cyclohexenone and 3,3,5-trimethylcyclohexenone. These results suggest that the mechanism involves coordination of the metal to the carbonyl, forming a six-center transition state.[283]

Enones with two alkyl groups at the β-position are reduced very sluggishly under these conditions. Other metal salts, such as $HgI_2$, $TiCl_3$ and $HgCl_2$, premixed with $LiAlH_4$ in THF similarly give rise to 1,4-reduction. Yields and selectivities were found to be much lower than with CuI. $H_2AlI$ was found to react in the same manner as $LiAlH_4/CuI$, and the series $H_2AlI$, $HAlI_2$, $H_2AlBr$, $HAlBr_2$, $H_2AlCl$ and $HAlCl_2$ was therefore prepared. Of these, the iodo compounds exhibited the highest reactivity. $HAlI_2$ reduces enones at a slower rate than $H_2AlI$. Diisobutylaluminum-2,6-di-*t*-butyl-4-methylphenoxide was found to be an efficient and stereoselective reducing agent for 1,2-reduction of the enone at position 15 in prostaglandin synthesis,[284] and was used successfully in the synthesis of the lichen macrolide (+)-aspicilin.[285]

Chiral lithium alkoxyaluminum hydride complexes can be used to obtain optically active allylic alcohols.[286–289] These reagents are more selective than the polymer-supported $LiAlH_4$ and $LiAlH_4$–monosaccharide complexes.[290]

α,β-Alkynic ketones are selectively reduced to the corresponding propargylic alcohols with $LiAlH(OMe)_3$. Asymmetric 1,2-reduction of alkynic ketones is an effective method for preparing optically active propargylic alcohols in high yield and high enantioselectivity. Common chiral reductants for this purpose include the Mosher–Yamaguchi reagent,[291–293] the Vigneron–Jacquet complex,[294–296] and $LiAlH_4$/2,2′-dihydroxy-1,1′-binaphthyl/methanol (*R* and *S*) complexes,[297] Landor's chiral $LiAlH_4$–monosaccharide complexes,[298–300] and the $LiAlH_4$–*N*-methylephedrine–*N*-ethylaniline complex.[288]

Asymmetric reduction of $d_1$-geranial, $d_1$-neral and related linear terpenic aldehydes can be achieved with $LiAlH_4$–dihydroxybinaphthyl complex with 72–91% *ee* (Scheme 43).[301]

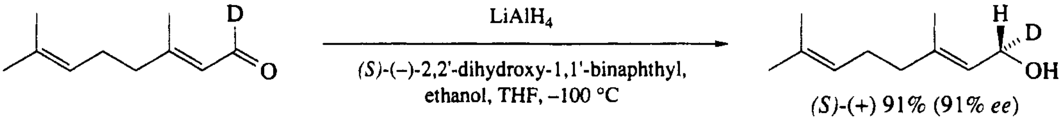

**Scheme 43**

Asymmetric reduction of prochiral α,β-unsaturated ketones with chiral hydride reagents derived from $LiAlH_4$ and (*S*)-4-anilino- and (*S*)-4-(2,6-xylidino)-3-methylamino-1-butanol gives (*S*)- and (*R*)-allylic alcohols, respectively, in high chemical and optical yields (Scheme 44).[302]

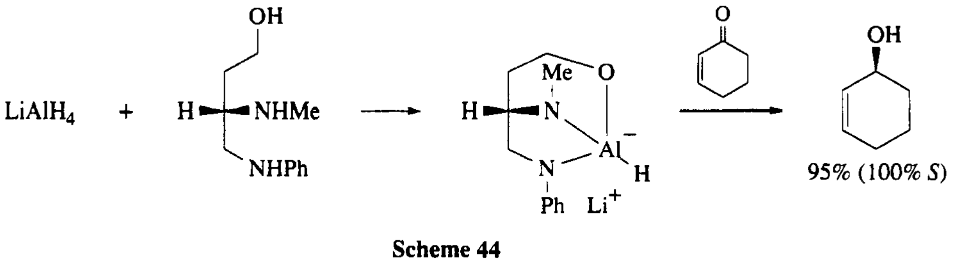

**Scheme 44**

A modified aluminum hydride prepared by treating $LiAlH_4$ in THF with equimolar amounts of ethanol and optically pure *S*-(–)-2,2′-dihydroxy-1,1′-binaphthyl, gives allylic alcohols of very high optical purity,[186,303] especially attractive in prostaglandin synthesis.[186] Considering both chemical and optical yields, these reductions compete with standard microbiological methods.[304] Asymmetric reduction of α,β-unsaturated ketones is also achieved with $LiAlH_4$, partially decomposed by (–)-*N*-methylephedrine and ethylaniline.[288] This reagent converts open chain enones into the corresponding optically active allylic alcohols in high chemical (92–100%) and optical yields (78–98% *ee*).

### 3.5.4.3 Silicon Hydrides

The hydrogen in the Si—H bond is slightly hydridic in nature, as would be expected from the relative electronegativities of silicon (1.7) and hydrogen (2.1). Therefore, silanes may function as hydride transfer agents toward highly electrophilic species such as carbonium ions. The hydridic nature of the Si—H bond may be significantly increased upon interaction with strong anionic ligands, such as fluoride and alkoxides (*vide infra*). In addition, the average bond energy of the Si—H and C—H bonds (70 and 99 kcal $mol^{-1}$, respectively; 1 kcal = 4.18 kJ) suggests that Si—H bonds should be susceptible to hydrogen atom abstraction by carbon radicals. Thus, the dehalogenation of alkyl halides with hydridosilane under homolytic conditions is explained in terms of a radical chain mechanism.[305] Alternatively, silanes readily transfer a hydride ligand to variety of transition metal complexes *via* oxidative addition, allowing for highly selective transition metal catalyzed reduction processes (*vide infra*, Section 3.5.6.2).

A useful reduction method involving hydridosilane in strongly acidic media, 'ionic hydrogenation', is useful for reduction of a number of organic functional groups.[306] The ionic hydrogenation reaction is based on the principle that the carbonium ion formed by protonation of the double bond reacts with an hydride donor to form the hydrogenated product. Reduction conditions generally involve reflux in strongly acidic media in the presence of the silane. Obviously, reduction is possible only when the substrate can produce carbonium ions under the given conditions. A hydrogenation pair most useful for many reduction processes is trifluoroacetic acid and a hydridosilane, which exhibits the following order of reactivity:[306] $Et_3SiH > (n\text{-octyl})_3SiH > Et_2SiH_2 > Ph_2SiH_2 > Ph_3SiH > PhSiH_3$.

These reducing systems tolerate carboxylic acid derivatives, nitriles, nitro groups, sulfonic esters, aromatic rings and, occasionally, alkenes, alkyl halides, ethers and alcohols as well. Reduction may be chemoselective in compounds containing many functionalities, with the functional groups most easily capable of stabilizing a carbonium ion being reduced most readily. Thus, for example, aliphatic alkenes are reduced only when they are branched at the alkene carbon atom. With α,β-unsaturated ketones, the reduction can be directed almost exclusively to the C—C double bond. Thus, using only 1 equiv. of silane, enones are reduced to saturated ketones (Scheme 45).[307]

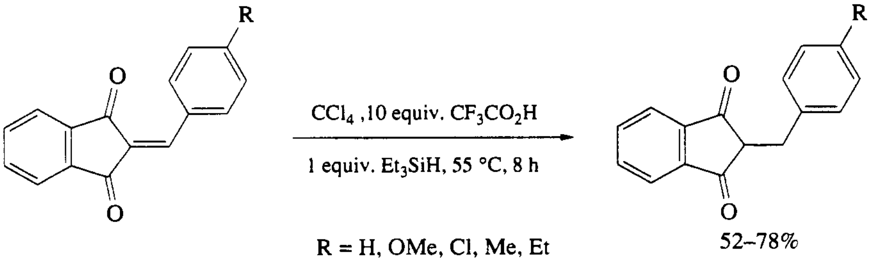
R
O
O
$CCl_4$, 10 equiv. $CF_3CO_2H$
1 equiv. $Et_3SiH$, 55 °C, 8 h
R = H, OMe, Cl, Me, Et
R
O
O
52–78%

**Scheme 45**

With excess silane, further reduction of the saturated ketone to the corresponding saturated alcohol occurs in high yield. In the case of chalcones, excess silane may effect complete reduction and deoxygenation to yield the corresponding alkane.[307,308]

The reaction of conjugated enones and dienones with trimethyl- and triethyl-silane in the presence of $TiCl_4$, followed by aqueous work-up produces the corresponding saturated ketones. This Lewis acid catalysis is particularly useful for conjugated reduction of sterically hindered systems (Scheme 46).[309] α,β-Unsaturated esters are not reduced under these conditions.

Anionic activation of Si—H bonds[310] by fluorides, such as KF or CsF, or by potassium phthalate, $KHCO_3$, KSCN, *etc.*, yields powerful hydridic reagents that reduce the carbonyl group of aldehydes, ketones and esters,[311] and 1,2-reductions of α,β-unsaturated aldehydes and ketones occur with high selectivity.[311] The analogous activation of hydridosilanes by fluoride ions is also achieved under acidic conditions with boron trifluoride etherate, in which the latter compound is consumed and fluorosilanes are formed.[312]

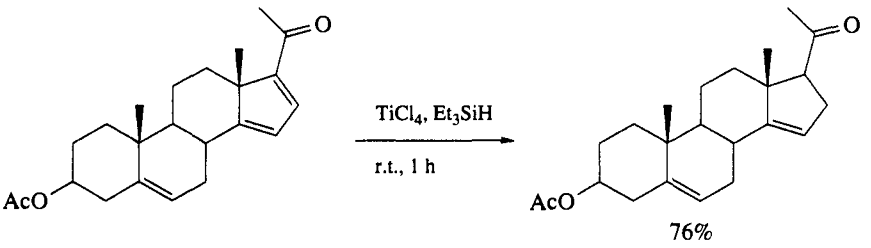

Scheme 46

Effective anionic activation of trichlorosilane can be carried out with either catechol or 2,2′-dihydroxybiphenyl in THF yielding bis(diolato)hydridosilicates.[313] Such reagents exhibit reducing power that is reminiscent of the complex aluminum hydrides. Even tertiary amines are useful activators of trichlorosilane, enhancing its hydridic character.[314]

### 3.5.4.4 Tin Hydrides

The special characteristics of organotin hydrides as reducing agents are rationalized by the fact that the tin–hydrogen bond is both weaker and less polar than the B—H or Al—H bonds.[315] These characteristics are manifested in reactions that proceed by either a free radical chain or polar mechanism, depending on the substrate, catalyst and reaction conditions.

α,β-Unsaturated aldehydes and ketones are readily reduced by organotin hydrides under rather mild conditions, but the reaction is often obscured by subsequent transformations of the adducts.[316] On heating or under UV irradiation, the organotin monohydrides add mainly at the 1,4-positions of the enone system to form the enol stannane.[315,316] The latter may be hydrolyzed (or cleaved by a second equivalent of tin hydride)[316e] resulting in overall reduction of the double bond (Scheme 47). The mechanistic pathway was demonstrated in reactions carried out with deuterated tin hydrides and/or in deuterated methanol.[317]

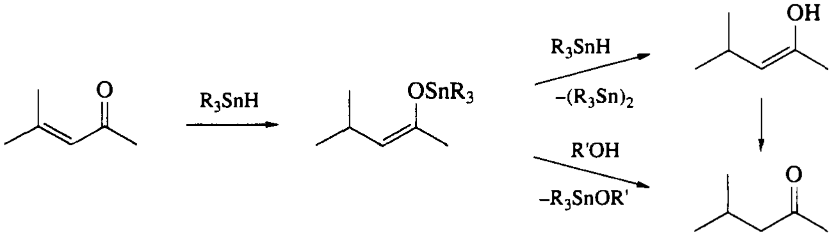

Scheme 47

Sterically unhindered enones may produce mixtures of products, including carbon stannylated species. For example, methyl vinyl ketone gives rise to significant quantities of the inverted 1,4-adduct, where tin binds at the 4-position, leading to a β-stannyl ketone. In the case of methyl propenyl ketone, addition occurs at positions 3 and 4, producing an α-stannyl ketone (Scheme 48).[316j]

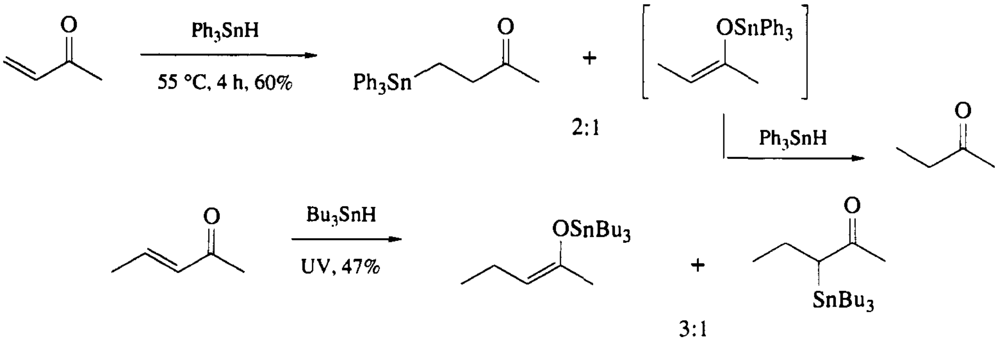

Scheme 48

In this class of reagents, diphenylstannane exhibited the highest regioselectivity, affording essentially pure 1,4-reduction. Other hydrides, such as $Bu_3SnH$ or $Ph_3SnH$, give mixtures of 1,2- and 1,4-reduction products and they usually require free radical initiation.[318]

In the case of α,β-unsaturated esters and nitriles, hydrostannation may proceed *via* either a polar or radical mechanism. Compounds containing a terminal multiple bond form the α-stannyl derivative, according to a polar mechanism, while β-adducts are formed according to the radical pathway.[319] Other conditions being equal, triarylstannanes are more active than trialkylstannanes in radical processes. In general, α,β-unsaturated nitriles undergo the polar addition more actively than do the corresponding esters. However, with acrylonitrile, the homolytic mechanism is significant as well.[320] With trialkylstannanes under the action of azobis(isobutyronitrile) or UV irradiation or with triphenylstannane on heating, β-adducts are formed exclusively. Mixtures of α- and β-adducts are produced on thermal addition of trialkylstannanes (Scheme 49).[320] The α/β ratio increases with solvent polarity.

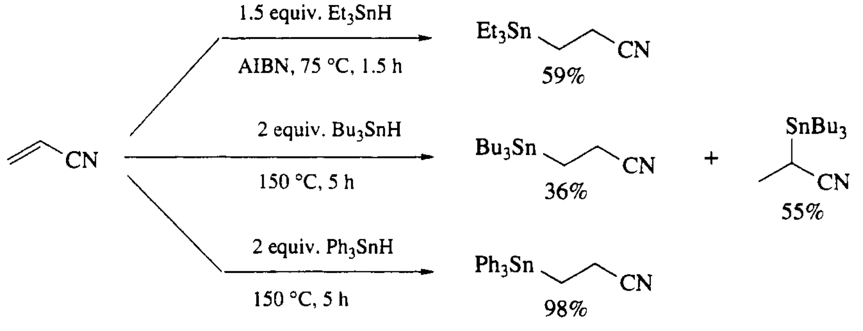

**Scheme 49**

Hydrostannation of α-alkynic esters generally produces a mixture of products.[315]

## 3.5.5 REDUCTIONS WITH STOICHIOMETRIC AMOUNTS OF TRANSITION METAL HYDRIDES

### 3.5.5.1 Copper Hydrides

The known preference of organocopper reagents to engage in 1,4-addition to α,β-unsaturated carbonyl compounds,[321] prompted an extensive search for analogous hydridocopper reagents that would undergo conjugate addition to enones. Indeed, reaction of copper(I) bromide with either 2 equiv. of lithium trimethoxyaluminum hydride or 1 equiv. of sodium bis(2-methoxyethoxy)aluminum dihydride ('Vitride' by Eastman or 'Red-Al' by Aldrich) in THF produces a heterogeneous mixture capable of 1,4-reduction of α,β-unsaturated ketones, esters[322] and nitriles.[323] The exact composition of these reagents is not yet known. Reductions usually take place between –20 and –78 °C to give moderate yields of the saturated carbonyl compound, along with varying amounts of the 1,2-reduction product (Scheme 50). The use of lithium trimethoxyaluminum deuteride with CuBr produces the saturated ketone deuterated at the β-position. Addition of $D_2O$ before the aqueous work-up leads to deuterium incorporation at the α-position. Because these reagents react with other functional groups (saturated ketones and aldehydes and alkyl bromides being reduced almost as rapidly as enones), their chemoselectivity is limited.

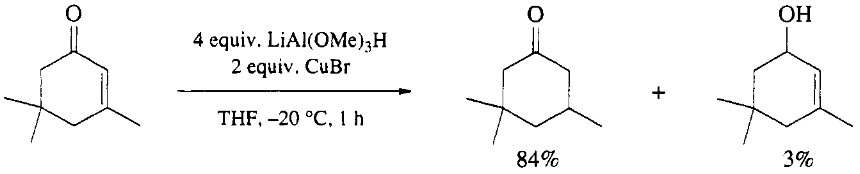

**Scheme 50**

Combination of $LiAlH_4$ and catalytic amounts of CuI in HMPA/THF (1:4) is useful for 1,4-reduction of α,β-unsaturated ketones, aldehydes and esters.[324] Reactions carried out at –78 °C for 1 h resulted predominantly in the 1,4-reduction product, but traces of the saturated and allylic alcohols were also formed.[324] It was claimed that the ratio between $LiAlH_4$ and CuI (10:1) as well as the presence of HMPA generates a hydridocuprate species which acts as the actual reducing agent. In contrast, in previously reported work using either $LiAlH_4$ or $AlH_3$ and CuI (in a 4:1 ratio) in THF, it was suggested that the active reductant is $H_2AlI$[283] (*vide supra*). An improved system based on diisobutylaluminum hydride (DIBAL-H) as the hydride donor and MeCu as the catalyst effects clean conjugate reduction of a variety of α,β-unsaturated carbonyl compounds without 1,2-reduction products. The presence of HMPA, probably acting as a ligand, was found to be of crucial importance for this reducing system, as shown in Scheme 51.[325] Other coordinating solvents including pyridine, DMF and DMSO, did not lead to comparable regioselectivity. Chemoselectivity is demonstrated by the selective 1,6-reduction of methyl sorbate in the presence of a saturated ketone, and the conjugate reduction of the enone of progesterone with only minor reduction of the saturated ketone in this molecule.

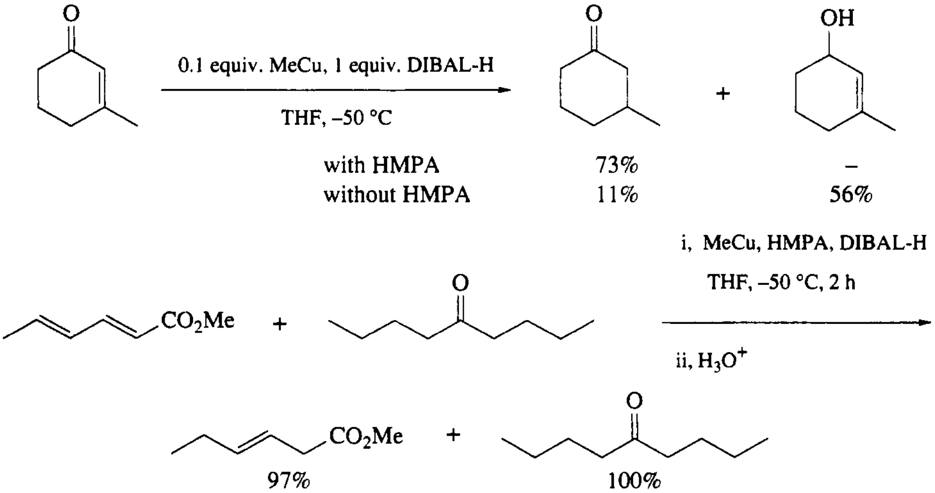

**Scheme 51**

A series of heterocuprate complexes $Li^+HRCu^-$, with R representing a nontransferable ligand such as 1-pentynyl, $Bu^tO^-$ or $PhS^-$, was generated in toluene from DIBAL-H and CuI by addition of RLi. These reagents were used for clean 1,4-reduction of α,β-unsaturated ketones, esters[326] and nitriles. Yields, however, were quite low in several cases due to the strong basicity of these reagents. Although HMPA was found to facilitate 1,4-reduction in substrates where the β-carbon is highly substituted, enone reduction in multifunctional compounds resulted in low yields (Scheme 52). In a related, independent study, the hydridocuprate complex was prepared by addition of RLi (R = alkyl or alkynyl) to a suspension of CuH in ether or in THF. These reagents were used for clean conjugate reduction of α,β-unsaturated carbonyls,[327] but with poor chemoselectivity, as saturated aldehydes and ketones were reduced under these conditions to the corresponding alcohols, and various tosylates and bromides were reductively cleaved.

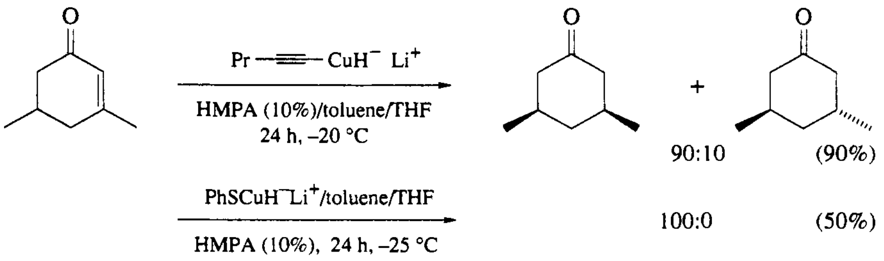

**Scheme 52**

Polyhydridocopper complexes, such as $LiCuH_2$, $Li_2CuH_3$, $Li_3CuH_4$, $Li_4CuH_5$ and $Li_5CuH_6$ were prepared[328] by $LiAlH_4$ reduction of $Li_nCuMe_{n-1}$ Reduction of α,β-unsaturated carbonyl compounds with any of these hydrides in ether or in THF produced mixtures of 1,4- and 1,2-reduction products. These reagents also reduce ketones, alkyl halides, alkyl tosylates and aryl halides.

The stable, well-characterized copper(I) hydride cluster $[(PPh_3)CuH]_6$[329] is a useful reagent for conjugate reduction of α,β-unsaturated carbonyl compounds.[330] This hydride donor is chemically compatible with chlorotrimethylsilane, allowing formation of silyl enol ethers *via* a reductive silation process (Scheme 53).

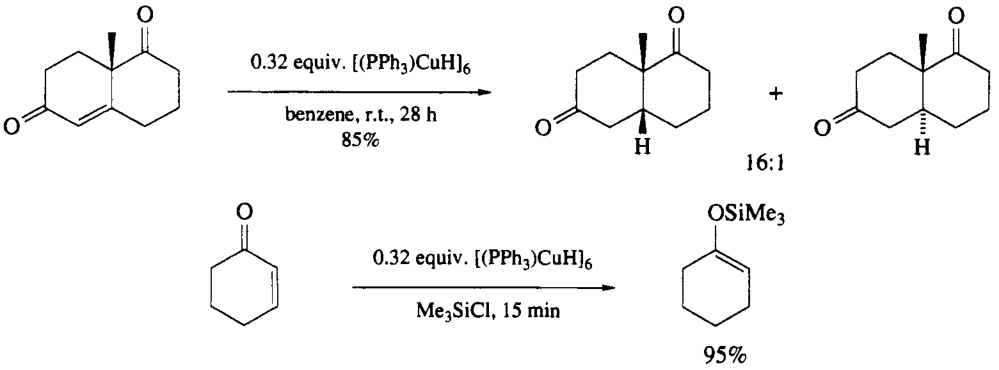
0.32 equiv. [(PPh3)CuH]6
benzene, r.t., 28 h
85%
+
16:1
0.32 equiv. [(PPh3)CuH]6
Me3SiCl, 15 min
OSiMe3
95%

**Scheme 53**

### 3.5.5.2 Iron Hydrides

Iron hydrides were also used for selective 1,4-reduction of enones.[315b] For example, tetracarbonylhydridoferrate, $NaHFe(CO)_4$, prepared in methanol, reduces benzalacetone to benzylacetone. Addition of this reagent to an ethanolic solution containing both an aldehyde and a ketone results in reductive alkylation of the ketone. The reaction probably involves base-catalyzed aldol condensation of the aldehyde and the ketone, followed by elimination of water to give the corresponding α,β-unsaturated ketone. The latter is then reduced by the tetracarbonylhydridoferrate, to afford the saturated ketone.[331] Interestingly, $NaHFe(CO)_4$ in THF reduces α,β-unsaturated carbonyl compounds to the corresponding saturated alcohols with high stereospecificity. For example, (+)- and (–)-carvones are reduced to (–)- and (+)-neodihydrocarveol, respectively.[332]

The binuclear hydride $NaHFe_2(CO)_8$,[333,334] is also useful for clean conjugate reductions. This reagent is capable of selective 1,4-reduction of α,β-unsaturated ketones, aldehydes, esters, nitriles, amides and lactones in good yields (Scheme 54). Reductions are generally performed at –50 °C in a THF solution of $NaHFe_2(CO)_8$ and HOAc. Usually, 2 or more equiv. of the reagent are required for the reduction of 1 equiv. of substrate.

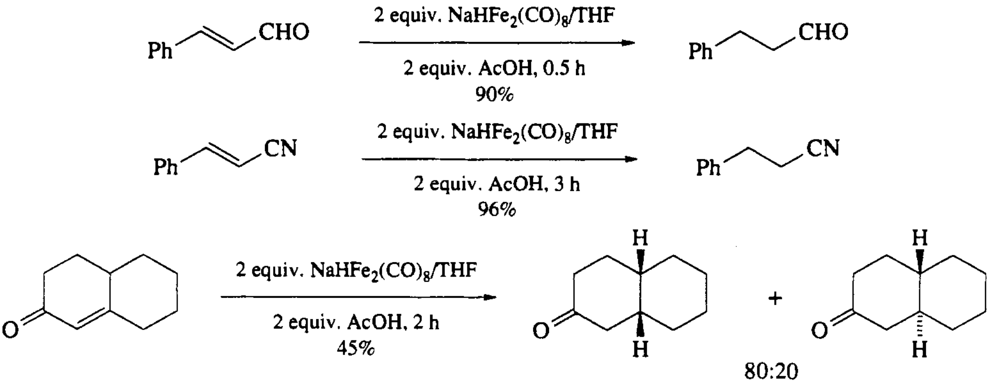
Ph
CHO
2 equiv. NaHFe2(CO)8/THF
2 equiv. AcOH, 0.5 h
90%
Ph
CHO
Ph
CN
2 equiv. NaHFe2(CO)8/THF
2 equiv. AcOH, 3 h
96%
Ph
CN
2 equiv. NaHFe2(CO)8/THF
2 equiv. AcOH, 2 h
45%
+
80:20

**Scheme 54**

According to a detailed mechanistic study,[334] the reaction involves reversible, regiospecific addition of $NaHFe_2(CO)_8$ to the C=C double bond of the enone, affording the corresponding binuclear iron enolate. Cleavage of the latter to the mononuclear iron enolate represents the rate-determining step, protonolysis of which provides the saturated ketone.

### 3.5.5.3 Other Transition Metal Hydrides

The intermetallic hydride $LaNi_5H_6$ is an effective reagent for conjugate reduction of enones. Reduction of the resulting saturated carbonyl occurs very slowly with this reagent, giving high yields of the 1,4-reduction product.[335]

α,β-Unsaturated carbonyl compounds are reduced selectively and in good yields (55–80%) to the corresponding saturated derivatives by the hydridochromium complex $NaHCr_2(CO)_{10}$ in THF at 66 °C. This latter complex is prepared by stirring chromiumhexacarbonyl with potassium graphite ($C_8K$) in dry THF with subsequent addition of water.[336]

Excess hydridocobaltcarbonyl reduces α,β-unsaturated ketones and aldehydes in moderate yield and good regioselectivity. The reaction involves complexation of the double bond to cobalt, followed by migratory insertion of hydride into the enone, forming an oxaallyl cobalt complex.[337] Poor chemoselectivity is one of the major drawbacks of this reaction, as simple alkenes are rapidly hydroformylated to the corresponding aldehyde under the reaction conditions (25 °C, 1 atm of CO).

α,β-Unsaturated ketones and esters are selectively 1,4-reduced by $Et_4N[\mu\text{-}HMo_2(CO)_{10}]$ and HOAc in refluxing THF.[338] Benzalacetone is quantitatively reduced to benzylacetone under these conditions. However, reduction of cinnamaldehyde gives a mixture of dihydrocinnamaldehyde (3%), cinnamyl alcohol (85%), and phenylpropane (12%).

## 3.5.6 COMPOSITE REDUCING SYSTEMS

Composite reducing systems comprise at least two components, namely a relatively inactive source of hydride ions and a transfer agent to deliver the hydride selectively from that donor to a target functionality. This family of reducing systems will, therefore, selectively transfer a hydride ion to various electrophilic functional groups, including α,β-unsaturated carbonyl compounds. The acceptor properties of the latter make them excellent ligands for low-valent, electron-rich transition metals and, obviously, good substrates for selective reduction with nonreactive hydride donors.

Such multiple-component reducing systems offer high flexibility because they involve a large number of independent variables that can be tailored to various synthetic tasks, especially in comparison to metal hydride reduction which utilizes a single reagent. Thus, appropriate modification of the hydride donor, judicious selection of a transition metal transfer agent, and in some cases, use of a cocatalyst, provide an opportunity for creating a wide variety of reducing systems that exhibit improved chemoselectivity, as well as regio- and stereo-control.

### 3.5.6.1 Transfer Hydrogenation using Alcohols as Hydrogen Donors

Catalytic transfer of hydrogen from an organic donor to a variety of unsaturated organic acceptors is widely documented.[339] This approach has also been applied to the reduction of α,β-unsaturated carbonyl compounds, utilizing a catalyst and an organic compound with a low enough oxidation potential to be oxidized under the reaction conditions by the unsaturated carbonyl substrate.[339] With respect to enone reduction, the most commonly used hydrogen donors are primary or secondary alcohols. Temperatures for catalytic transfer hydrogenation are usually in the range 100–200 °C, depending upon the hydride source.

When α,β-unsaturated ketones are heated with a primary or secondary alcohol in the presence of $RuCl_2(PPh_3)_3$ or $RuHCl(PPh_3)_3$ at 200 °C, hydrogen is transferred selectively to the alkenic double bond.[340–342] The competing equilibrium that reduces the saturated ketone back to the alcohol may be suppressed by use of a primary alcohol such as benzyl alcohol or, more conveniently, by the use of boiling ethylene glycol, since saturated ketones are readily separated from insoluble glyoxal polymers.[343] Polyvinyl alcohol can also be used as a convenient hydrogen donor.[344] α,β-Unsaturated ketones give higher yields than the corresponding aldehydes, which undergo self-condensation. α,β-Unsaturated esters undergo transesterification side reactions with the donor alcohol.

Studies on the role of a $Ru^{II}$ catalyst as well as the mechanism of hydrogen transfer in enone reduction with benzyl alcohol at 170–190 °C revealed that $RuCl_2(PPh_3)_3$ is converted by the primary alcohol into $RuH_2(CO)(PPh_3)_3$, which then hydrogenates benzylideneacetone.[345]

Transfer hydrogenation catalyzed by $RuCl_2(PPh_3)_3$ has been applied to the synthesis of cyclododecane-1,2-dione in 53% yield from the corresponding 1,2-diol using benzylideneacetone as the hydrogen acceptor.[346] 5,5-Dimethylcyclohexane-1,3-dione reacts *via* its enol tautomer on heating with ethylene glycol in the presence of $RuCl_2(PPh_3)_3$ to give 3,3-dimethylcyclohexanol, 3,3-dimethylcyclohexanone and its corresponding ketal.[347]

Vinyl ketones, such as methyl vinyl ketone, are not reduced in the presence of $RuCl_2(PPh_3)_3$ on heating with common primary or secondary alcohols, but they are reduced on heating with allylic alcohols, such as hex-1-en-3-ol, using hydrated $RuCl_3$, $RuCl_2(PPh_3)_3$, $RuHCl(PPh_3)_3$, $RuH(OAc)(PPh_3)_3$ or, most efficiently, $Ru_3O(OAc)_7$ (Scheme 55).[348] Surprisingly, other ketones, including acetophenone or benzylideneacetone, are not reduced under these conditions.

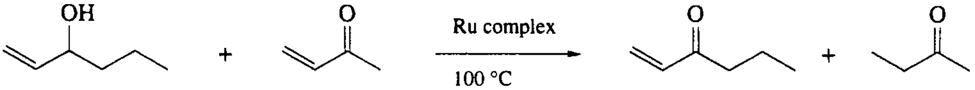

**Scheme 55**

As in hydrogen transfer between alcohols and saturated ketones, the rate-determining step in the reaction with α,β-unsaturated ketones is hydrogen abstraction from the α-carbon atom. It has been suggested that the hydrogen atom is transferred directly to the β-carbon of the enone, yielding an $\eta^3$-oxaallyl complex which following protonation yields the saturated ketone.[340]

Unsaturated esters also undergo transfer hydrogenation under $RuCl_2(PPh_3)_3$ catalysis to the saturated esters, but significant transesterification reaction with the reacting alcohol also occurs.[341] Simple alkenes are reduced, in general, very slowly under the reaction conditions, although $RuCl_2(PPh_3)_3$ is reported to catalyze hydrogen transfer from indoline to cycloheptene in refluxing toluene, to give cycloheptane and indole,[349] and other $Ru^{II}$ complexes catalyze hydrogen transfer from alcohols to diphenylacetylene to yield *cis*-stilbene.[350] α,β-Unsaturated aldehydes are selectively reduced in THF with formic acid and trialkylamine and catalytic amounts of $RuCl_2(PPh_3)_3$ to produce allylic alcohols.[351]

Transfer hydrogenation of a prochiral alkene in the presence of a chiral catalyst may lead to a chiral saturated product. For example, tiglic acid ($MeCH{=}C(Me)CO_2H$) is hydrogenated at 120 °C by either 2-propanol in the presence of $Ru_4H_4(CO)_8(-)\text{-diop})_2$[352] (diop = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) or by benzyl alcohol in the presence of $Ru_2Cl_4(diop)_3$ at 190 °C.[353] The optical purities reported for the resulting saturated acids, however, do not exceed 10–15%, a lower figure than that obtained by catalytic hydrogenation with hydrogen gas.

Prochiral α,β-unsaturated esters can also be asymmetrically hydrogenated by benzyl alcohol or 1-phenylethanol and catalytic $Ru_2Cl_4(diop)_3$,[353] but the optical purities of the resulting esters are even lower than those obtained from hydrogenating the corresponding acids. Enantioselectivity is also observed in transfer hydrogenation of α,β-unsaturated ketones, such as $PhCH{=}CHCOMe$, by racemic 1-phenylethanol in the presence of $Ru^{II}$ chloro complexes containing optically active tertiary phosphines, including diop and neomenthyldiphenylphosphine. Thus the optical purity of 1-phenylpropan-1-ol enriched in the (*S*)-(–)-isomer is 11% when reacted under these conditions with benzylideneacetone.[354]

Asymmetric hydrogen transfer from optically active monosaccharides, such as 1,2-α-D-glucofuranose, to prochiral enones is catalyzed by $RuCl_2(PPh_3)_3$ in diphenyl ether at 180 °C or by $RuH_2(PPh_3)_4$ in toluene at 100 °C (Scheme 56).[355] Catalytic hydrogen transfer from sugars with free anomeric hydroxy groups was studied with 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose and $RuH_2(PPh_3)_4$. In an excess of enone acceptor, these sugars were converted in high yields into the corresponding lactones (Scheme 56).[356]

The 1,4-reduction of styryl ketones by 1-phenylethanol using $RuH(PPh_3)_4$ catalyst can be carried out at 50 °C, a relatively low temperature for transfer hydrogenation. An electron-withdrawing group present in the enone system increases the initial rate of reduction, suggesting a transfer of hydrogen to the enone by an intermediate with hydride ion character.[357] Isotope labeling of the alcohol donors shows that hydrogen is regioselectively transferred from the carbinol carbon to the β-carbon of the enone, with the hydroxylic proton being transferred to the α-position. Cleavage of an O—H bond is the rate-determining step in this reaction.[358]

High catalytic activities, with turnovers of up to 900 cycles $min^{-1}$, is displayed in the transfer hydrogenation of α,β-unsaturated ketones, such as benzylideneacetone and chalcone, using 2-propanol and catalytic amounts of $[Ir(3,4,7,8\text{-}Me_4\text{-phen})COD]Cl$ (phen = 1,10-phenanthroline; COD = 1,5-cyclooctadiene) in a weakly alkaline medium.[359] Other Ir-chelated complexes are also active catalysts in this reaction, with over 95% selectivity for the 1,4-reduction mode. Divalent lanthanide derivatives, such as $SmI_2$ or $YbI_2$ in stoichiometric quantities, in THF and *t*-butyl alcohol or methanol reduce ethyl cinnamate and cinnamic acid to give the saturated derivatives.[360] Similarly, 3-methylcyclohexenone is reduced to 3-methylcyclohexen-1-ol in 67% yield, but α,β-unsaturated aldehydes are nonselectively reduced with these systems.

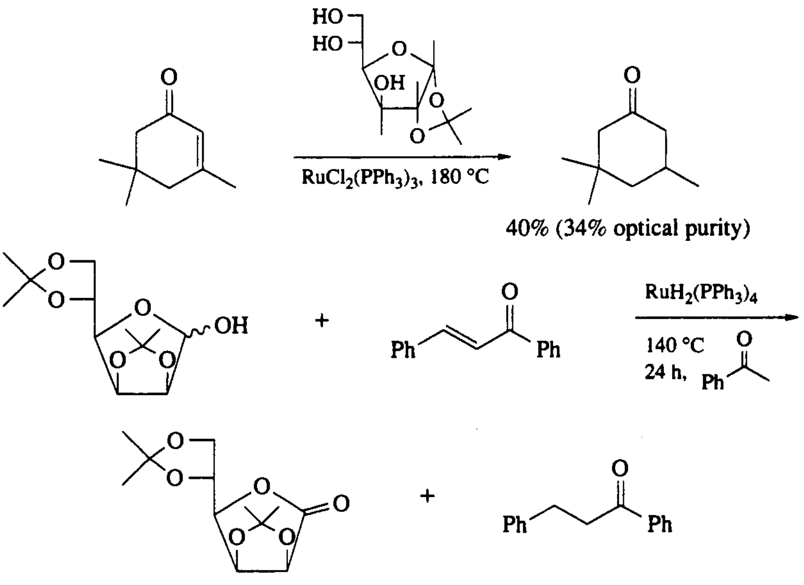

Scheme 56

### 3.5.6.2 Transition Metal Catalyzed Reductions with Group 14 Metal Hydrides

Group 14 metal hydrides, especially those of silicon and tin, are satisfactory nonreactive hydride donors, as in the absence of a catalyst they are, generally, poor reducing agents. Transition metal complexes are attractive transfer agents because they insert readily into Si—H or Sn—H bonds and they also bind specifically to various functional groups.

Indeed, a combination of tributyltin hydride, Pd$^0$ catalyst and a weak acid, such as ammonium chloride, forms an effective, yet mild tool for conjugate reduction of α,β-unsaturated aldehydes and ketones.[361] Similar results are obtained with other acidic cocatalysts, such as zinc chloride, acetic acid and tributyltin triflate.[362] With this system, reductions occur with high regioselectivity, providing a useful approach for deuterium incorporation into either the β- or α-position by using either tributyltin deuteride or $D_2O$, respectively (Scheme 57).[361]

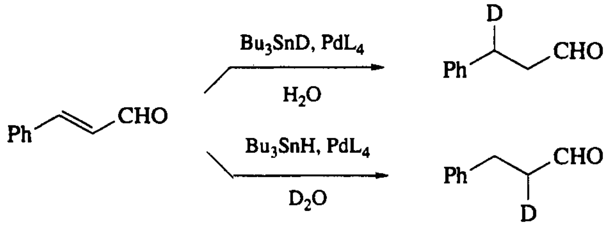

Scheme 57

Silicon hydrides offer even greater selectivity in these reductions.[363] Their superiority over tin hydrides is manifested by the greater stability of the palladium catalyst in the reaction solution, and the absence of diene side products, frequently formed *via* the competing Pd-catalyzed elimination processes.

The combination of silicon hydrides and a Pd$^0$ catalyst is essentially useless for reduction of electron-deficient alkenes. However, addition of catalytic amounts of zinc chloride creates a new three-component mixture that enables rapid conjugate reduction of α,β-unsaturated ketones and aldehydes.[364] In fact, soluble palladium complexes of various oxidation states were equally efficient catalysts, an obvious practical advantage of this approach. The generality of the method with respect to the substrate, its experimental simplicity, and its easy applicability to large-scale work make it a method of choice for conjugate reduction of unsaturated ketones and aldehydes.

The reaction was found to be both regio- and stereo-selective. In all cases where diphenyldideuteriosilane was used to reduce unsaturated ketones, deuterium was stereoselectively introduced at the less-hindered face of the substrate and regioselectively at the β-position (Scheme 58). Conversely, when reductions were carried out in the presence of traces of $D_2O$, deuterium incorporation occurred at the α-position just as with the tin hydride reductions of Scheme 57.[364]

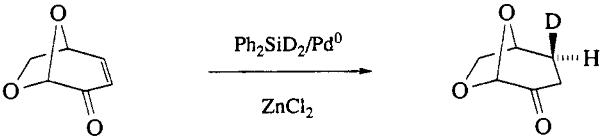

**Scheme 58**

This method is highly selective for unsaturated ketones and aldehydes, whereas reduction of α,β-unsaturated carboxylic acid derivatives, such as esters, amides and nitriles, is very sluggish. Thus, benzylideneacetone was selectively and cleanly reduced in the presence of methyl cinnamate, cinnamonitrile or cinnamamide.[364]

Combination of silicon hydrides with catalytic amounts of a ruthenium(II) complex in tetrahydrofuran, chloroform or benzene has afforded a new reducing system capable of efficient reduction of α,β-unsaturated carboxylic acids, esters, amides, *etc.*[365] Addition of a weak proton source, such as a sterically hindered phenol significantly increases reaction rates. The ruthenium mixture was found to exhibit the same regioselectivity observed with the above-described palladium systems.

The order of reactivity of this Ru/silane combination to various functional groups differs greatly from that of its Pd/silane/$ZnCl_2$ analog. While the latter is very useful for allylic reductions and essentially useless for unsaturated esters, the Ru-based system exhibits opposite reactivity. This complementary chemoselectivity is illustrated by the reduction of cinnamyl cinnamate (Scheme 59), a substrate containing both an allylic carboxylate and an α,β-unsaturated ester.[365] Each of these can be reduced separately by silicon hydride and the appropriate transition metal catalyst.

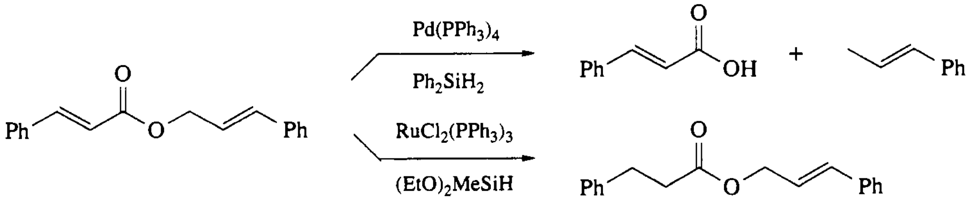

**Scheme 59**

Early transition metal complexes, including those of Group 6, have rarely been used to catalyze transfer hydrogenation[366] and hydrogenation with hydrogen gas,[367] and similarly little is known about hydrosilation with these catalysts. Under mild thermal conditions, catalytic amounts of $Mo(CO)_6$ and phenylsilane engender a powerful reducing system, suitable for conjugate reduction of α,β-unsaturated ketones, carboxylic acids, esters, amides, *etc.* The mixture is especially useful for conjugate reduction of unsaturated nitriles, usually difficult to reduce with other media (Scheme 60).[368] Although the reaction also works with mono- and di-hydridosilanes, the general order of silane reactivity is $PhSiH_3 > Ph_2SiH_2 > Me(EtO)_2SiH >$ PMHS, $PhMe_2SiH$, $Et_3SiH$.

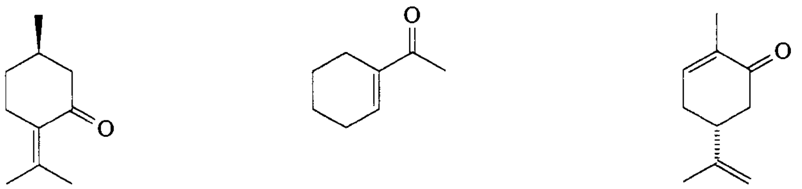

Pulegone
3 h, 100%

Acetylcyclohexene
4.5 h, 100%

Carvone
24 h, no reaction

**Scheme 60**

Of special interest are the relative rates of reduction of various cyclic enones, such as carvone, acetylcyclohexene and pulegone (Scheme 60). While the enone system in carvone is frozen in its transoid form, in acetylcyclohexene it is flexible and may adopt either transoid or cisoid conformation. Acetylcyclohexene is completely reduced, while essentially no reaction is observed with carvone, demonstrating the clear preference of the cisoid form and indicating that the molybdenum atom interacts simultaneously with both the alkenic bond and the carbonyl of the enone system. Accordingly, pulegone, which is frozen in the cisoid form, is reduced much faster than the other two compounds. A similar phenomenon was observed in enone hydrogenation catalyzed by arene-chromium tricarbonyl complex, where the cisoid conformation is also markedly preferred.[367c] With Pd$^0$ catalyst, however, enones behave as monodentate ligands and reductions of the above-mentioned substrates proceed at comparable rates.[364] These reactivity characteristics may be utilized for chemoselective differentiation between similar enones. For example, benzalacetone is quantitatively reduced to benzylacetone in the presence of carvone.[368] Allylic heterosubstituents and α-halo carbonyl compounds are also reduced very efficiently under these conditions.[369]

Highly regioselective reduction of α,β-unsaturated ketones and aldehydes to give either the corresponding saturated carbonyls or allylic alcohols as the predominant product is effected by hydrosilation catalyzed by tris(triphenylphosphine)chlororhodium (Wilkinson catalyst), followed by methanolysis of the resulting adducts.[370] Regiospecific deuteration is also achieved by using deuteriosilanes. Product distribution is mainly dependent upon the structure of the hydrosilane employed. In general, monohydridosilanes afford the 1,4-adduct (silyl enol ether), which may be hydrolyzed to the corresponding saturated carbonyl compound. Diaryl- or dialkyl-dihydridosilanes produce mainly silyl ethers (1,2-adduct), which may be hydrolyzed to the corresponding allylic alcohol. Other factors controlling the regioselectivity of this method include the enone structure, the hydridosilane/substrate ratio, the solvent and temperature. Although regioselectivity here is generally satisfactory (Scheme 61),[370] in some cases mixtures of 1,2- and 1,4-reduction products are obtained, even under maximally optimized conditions. The reaction is usually completed within 30–120 min at 0–80 °C in benzene, or in the absence of solvent, using 1.1 equiv. of the hydridosilane and 0.1 mol % of the Rh$^I$ catalyst.

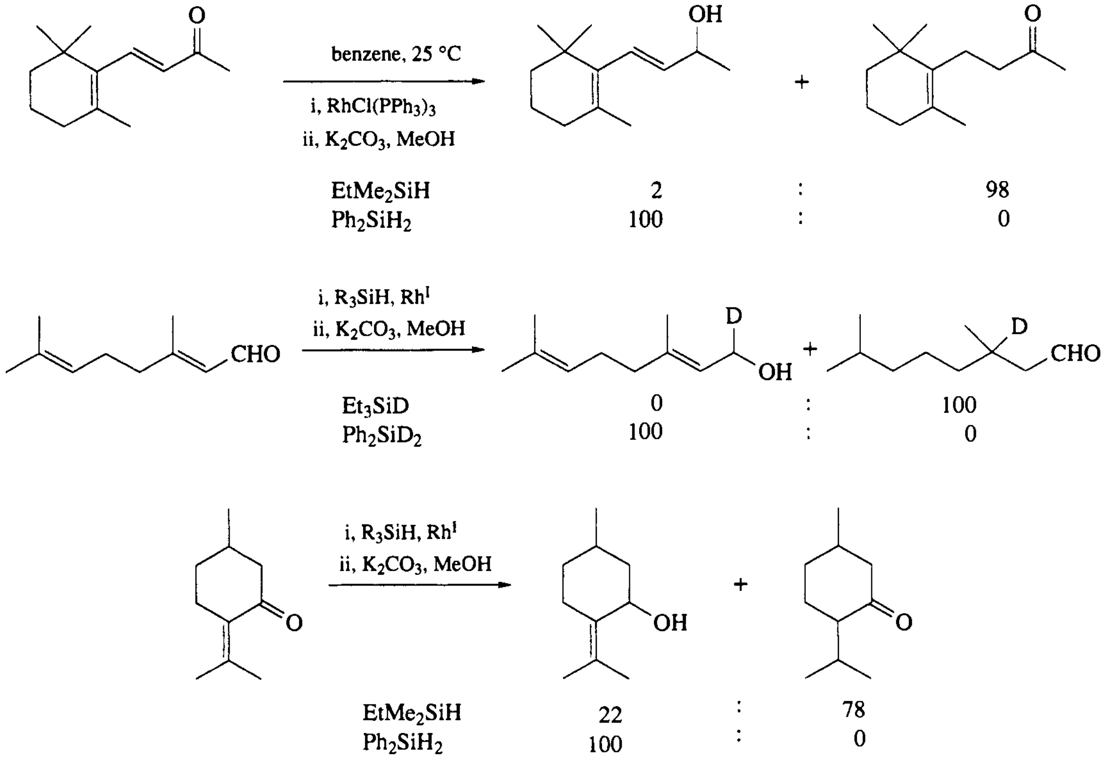

**Scheme 61**

Treatment of α,β-unsaturated esters with triethylsilane in benzene in the presence of catalytic amounts of RhCl(PPh$_3$)$_3$ at room temperature yields the corresponding saturated esters. Conjugated diene esters are reduced to the β,γ- or γ,δ-unsaturated esters, depending upon their substitution pattern (Scheme 62).[371]

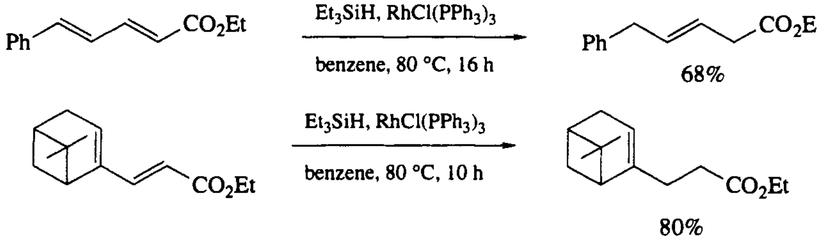
Ph
CO2Et
Et3SiH, RhCl(PPh3)3
benzene, 80 °C, 16 h
Ph
CO2Et
68%
CO2Et
Et3SiH, RhCl(PPh3)3
benzene, 80 °C, 10 h
CO2Et
80%

**Scheme 62**

Other Rh catalysts were also employed for hydrosilation of α,β-unsaturated carbonyl compounds and unsaturated nitriles. Thus, Rh(acac)2 and a tetrakis(μ-acetato)dirhodium cluster were used as catalysts in the hydrosilation[372] of α,β-unsaturated aldehydes. These reactions, however, are not chemoselective, as alkynes, conjugated dienes and alkenes are also hydrosilylated, and allylic heterosubstituents are reductively cleaved.

Optically active, saturated carbonyl compounds and allylic alcohols were prepared *via* 1,4- and 1,2-asymmetric hydrosilation of enones using $Rh^I$ catalysts bearing chiral ligands. For example, 1,4-hydrosilation of α,β-unsaturated ketones afforded the corresponding optically active ketones in 1.4–15.6% *ee* (Scheme 63).[373]

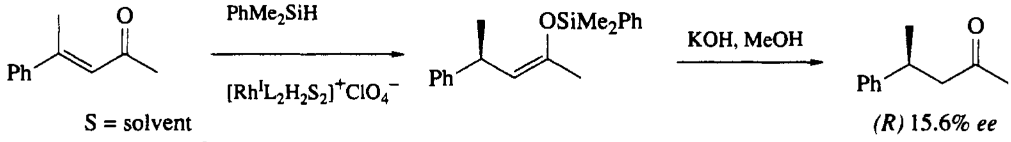
O
Ph
PhMe2SiH
[RhIL2H2S2]+ClO4−
S = solvent
L = (R)-(PhCH2)MePhP
OSiMe2Ph
Ph
KOH, MeOH
O
Ph
(R) 15.6% ee

**Scheme 63**

Asymmetric 1,2-hydrosilation in benzene of α,β-unsaturated ketones with dihydridosilanes and a chiral $Rh^I$ catalyst produced allylic alcohols with up to 69% *ee*.[374] Highly stereoselective hydrosilation of an α,β-unsaturated aldehyde was achieved with triethylsilane and nonchiral Wilkinson catalyst.[375] Dehydrofaranal was thus stereoselectively reduced to the insect pheromone (3*S*,4*R*)-faranal with 85% *de* (Scheme 64).

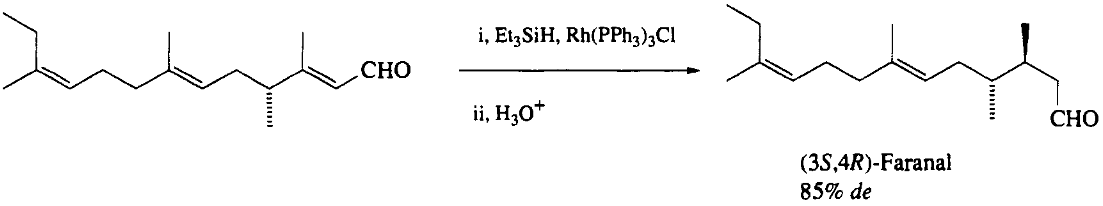
CHO
i, Et3SiH, Rh(PPh3)3Cl
ii, H3O+
CHO
(3S,4R)-Faranal
85% de

**Scheme 64**

The main product in hydrosilation of α,β-unsaturated ketones and aldehydes catalyzed by chloroplatinic acid, platinum on alumina, or metallic nickel is the corresponding silyl enol ether.[376] With nickel catalyst, product distribution is highly dependent on the enone structure.[377] Hydridosilanes add to α,β-unsaturated esters, producing the corresponding silyl enolate as well as carbon silylated products. The course of addition depends on substrate structure and the hydridosilane utilized. Thus, triethylsilane undergoes 1,4-addition to methyl acrylate in the presence of chloroplatinic acid, while trichlorosilane with either chloroplatinic acid or Pt/C gives the β-silyl ester (Scheme 65).[378]

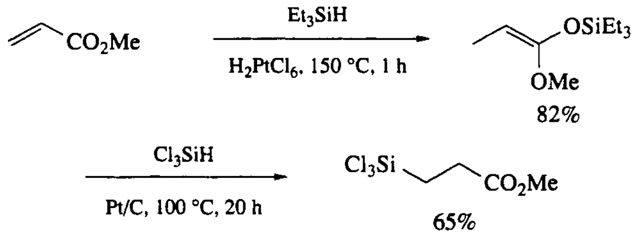
CO2Me
Et3SiH
H2PtCl6, 150 °C, 1 h
OSiEt3
OMe
82%
Cl3SiH
Pt/C, 100 °C, 20 h
Cl3Si
CO2Me
65%

**Scheme 65**

This approach was successfully applied to the total synthesis of (±)-muscone.[379] Treatment of the α,β- and β,γ-enone mixture (Scheme 66) with triethylsilane in refluxing glyme containing catalytic amounts of chloroplatinic acid afforded 1-triethylsilyloxycyclotetradecene. The two isomeric enones rapidly equilibrate under these conditions.

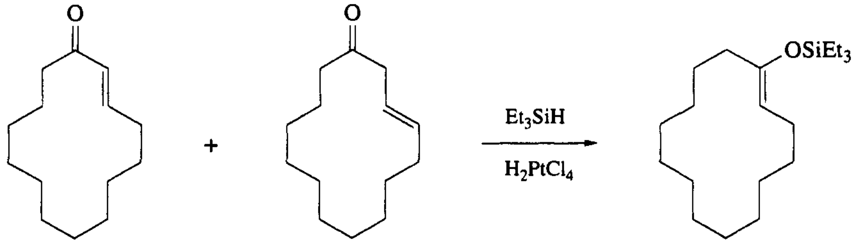

**Scheme 66**

Selective reduction of pregna-14,16-dien-20-ones to pregn-14-en-20-ones is achieved *via* hydrosilation with tetramethyldisiloxane and catalytic amounts of chloroplatinic acid (Scheme 67).[380] α,β-Unsaturated esters are also reduced to the corresponding saturated esters under these conditions.[381]

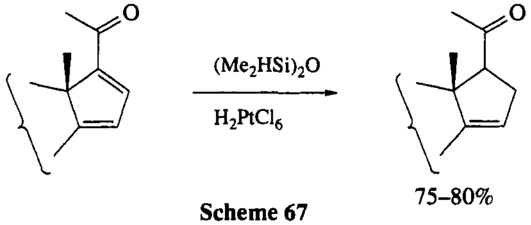

**Scheme 67**

The platinum dimer $(Pt(\mu\text{-}H)(SiR_3)(PR'_3))_2$ also catalyzes the hydrosilation of α,β-unsaturated aldehydes and ketones. Several aldehydes and ketones were hydrosilated in high yield in the presence of this dimer[382] at 60–100 °C and trialkylsilanes, including $MePh_2SiH$, $EtMe_2SiH$ and $Et_3SiH$. Triethoxysilane was inert under these reaction conditions. Excellent regioselectivity was generally observed except in cases of highly sterically hindered enones such as tetraphenylcyclopentadienone, where the 1,2-reduction mode was observed. Saturated aldehydes and ketones were not reduced under these reaction conditions, and unsaturated carboxylic acids and esters were only sluggishly reduced. Unfortunately, terminal alkenes and alkynes were efficiently hydrosilated. A suggested mechanism involves cleavage of the platinum dimer to a platinum hydride species, its coordination to the alkene, and subsequent transfer of the $R_3Si$ group to the carbonyl oxygen, affording a π-allyl platinum complex. Hydride migration from Pt to the allylic ligand produces the corresponding silyl enol ether.

### 3.5.6.3 Transition Metal Catalyzed Reductions with other Hydrogen Donors

Aromatic aldehydes and DMF can serve as hydrogen donors and transfer their formyl hydrogen to α,β-unsaturated ketones in the presence of $RuCl_2(PPh_3)_3$. However, in some cases, decarbonylation of the aldehyde is so severe that no transfer hydrogenation is observed.[383]

A particularly convenient hydrogen donor is formic acid, which not only hydrogenates α,β-unsaturated ketones,[384] but also terminal alkenes in the presence of a variety of ruthenium complexes under mild conditions.[385] Trialkylammonium formate and catalytic amounts of palladium on carbon form a convenient reducing system for reduction of a number of organic functional groups, including α,β-unsaturated aldehydes, ketones and esters.[386] Conjugated dienes reduce to monoenes with 1 equiv. of reagent fairly selectively. Typical reductions are carried out at 100 °C with 10% excess formic acid, 30% excess triethyl- or tributyl-amine, and 1 mol % of palladium in the form of 10% Pd/C. Progress of the reduction is conveniently monitored by measuring the amount of $CO_2$ evolved. Two examples are given in Scheme 68.[386] The chemoselectivity of this system is somewhat limited, as it affects many other functionalities, such as halo- and nitro-aromatic compounds,[387] allylic heterosubstituents,[388] and terminal alkynes and alkenes.[386]

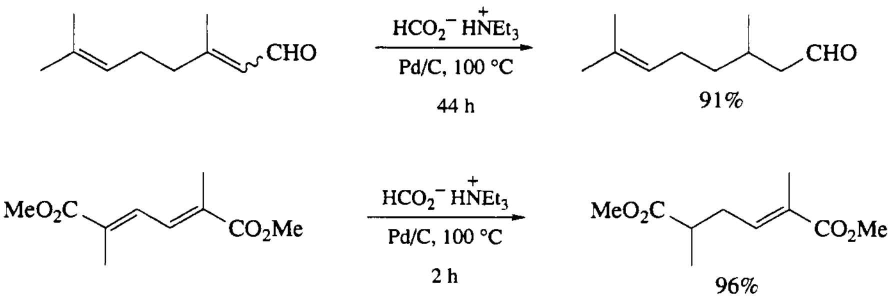

**Scheme 68**

Triisobutylaluminum reduces α,β-unsaturated ketones to allylic alcohols in pentane at room temperature. These products however are accompanied by substantial amounts of tertiary alcohols arising from 1,2-addition of the isobutyl group. The extent of these reactions depends both on the structure of the enone and on the ratio between reagent and substrate. Under similar experimental conditions, bis(*N*-methylsalicylaldimine)nickel catalyzes conjugate reduction of α,β-unsaturated ketones by triisobutylaluminum.[389] In all cases, 1,2-reduction products were also obtained (probably *via* noncatalyzed reduction) and in some cases, side products containing isobutyl group were also formed. The reaction is interpreted in terms of a catalytic cycle involving a hydridonickel intermediate formed by reaction of $Bu^i_3Al$ with the nickel complex. Addition of the hydridonickel to the alkene affords a nickel enolate that undergoes transmetallation to give an aluminum enolate. The latter is finally hydrolyzed to the saturated ketone.

A number of composite reducing systems consisting of heterogeneous mixtures of transition metal salts, sodium alkoxides and sodium hydride were developed, which are useful for reduction of various organic functional groups.[390] In organic chemistry, sodium hydride is generally used as a base for proton abstraction. Although some substrates can be reduced by NaH, it is by itself a poor reducing agent. Typical reducing systems (known as complex reducing agents, CRA)[390] are prepared from a transition metal chloride or acetate, sodium *t*-pentoxide and sodium hydride (in 1:1:4 ratio) in either THF or DME. Obviously, neither the exact structure of the actual reducing entity nor their reduction mechanism is fully understood.

The CRA reagents involving nickel salts exhibit reducing properties that are significantly different from those of the corresponding CRA prepared from zinc or magnesium salts. It was demonstrated that the three-component mixture, $NaH/RONa/Ni(OAc)_2$ (NiCRA) reduces carbon–carbon double bonds.[391] Conversely, the mixture $NaH/RONa/ZnCl_2$ (ZnCRA) reduces alkenes poorly but effectively reduces saturated carbonyl functionalities, particularly when mixed with alkaline or alkaline earth metal salts.[392] These observations led to the expected complementary regioselectivity when reducing α,β-unsaturated carbonyl compounds with these reagents. Indeed NiCRA exhibits very high regioselectivity for 1,4-reduction of a number of α,β-unsaturated ketones, while under the same conditions ZnCRA exhibits high regioselectivity for 1,2-reduction.[393] Addition of magnesium bromide enhances the activity of both reagent mixtures. The general applicability of CRA reagents is somewhat limited due to their high basicity as well as to their tendency to undergo side reactions *via* one-electron transfer processes.

## 3.5.7 BIOCHEMICAL REDUCTIONS

### 3.5.7.1 Enzymatic Reductions

Much work has been published on the microbiological reduction of α,β-unsaturated ketones. Under anaerobic conditions the reduction of $\Delta^4$-3-keto steroids by *Clostridium paraputrificum* led to the 3-keto 5β-derivatives (Scheme 69).[394] Similar transformations were observed previously with *Bacillus putrificus*,[395] *Penicillium decumbens*,[396] *Rhizopus nigricans*[397] or *Aspergillus niger*.[398] In most cases further reduction led to the corresponding 3α-hydroxy 5β-derivatives.

Highly enantioselective conjugate reductions of substituted cyclopentenones and cyclohexenones were reported by Kergomard using *Beauveria sulfurescens* (ATCC 7159) under anaerobic conditions.[399] The reaction takes place only with substrates containing a small substituent in the α-position and hydrogen in the β-position. The saturated ketones obtained were, in some cases, accompanied by saturated alcohols.

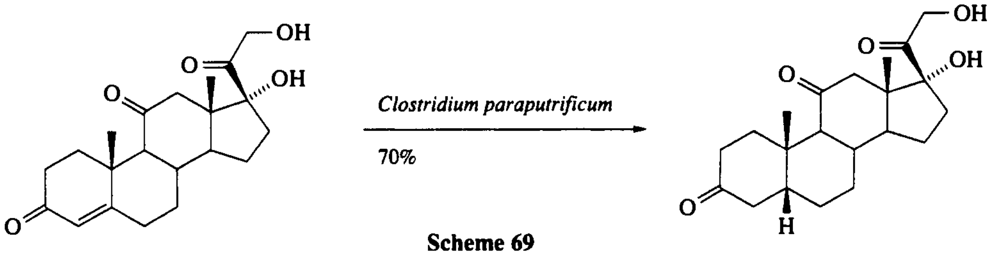

*Clostridium paraputrificum*
70%

**Scheme 69**

A number of useful transformations, including enantioselective reductions of acyclic substrates, are illustrated in Scheme 70.

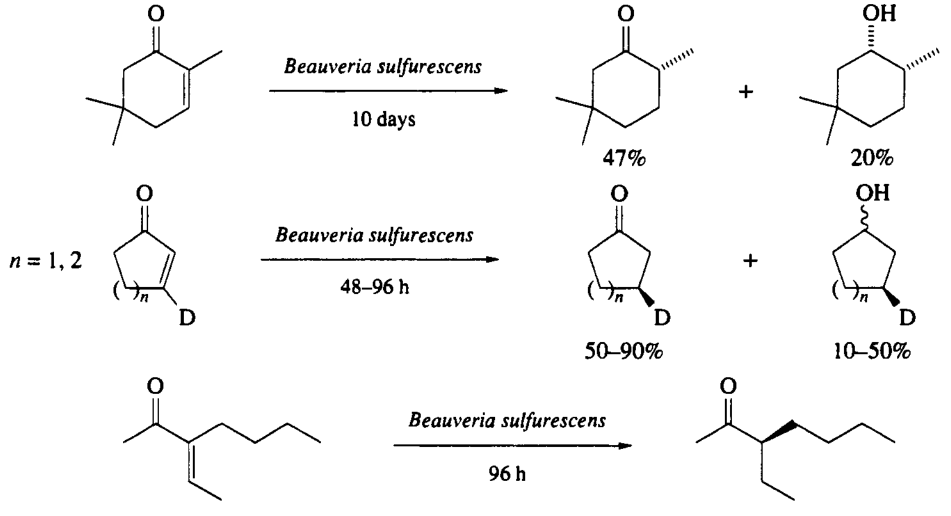

*Beauveria sulfurescens*
10 days
47%
20%
*n* = 1, 2
*Beauveria sulfurescens*
48–96 h
50–90%
10–50%
*Beauveria sulfurescens*
96 h
95%

**Scheme 70**

Both naturally occurring enantiomers of carvone were selectively reduced by *B. sulfurescens* (Scheme 71). (–)-Carvone was reduced to (+)-dihydrocarvone (*trans*) and further to (+)-neodihydrocarveol, whereas (+)-carvone was reduced to (–)-isodihydrocarvone (*cis*), which was then converted to (–)-neoisodihydrocarveol.[400] Similar reductions with identical stereoselectivities were observed earlier with *Pseudomonas ovalis* (strain 6-1) and with a strain of *Aspergillus niger*.[400]

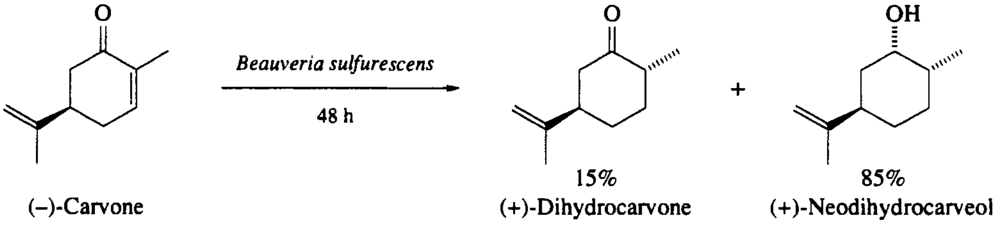

*Beauveria sulfurescens*
48 h
15%
85%
(–)-Carvone
(+)-Dihydrocarvone
(+)-Neodihydrocarveol

**Scheme 71**

The reduction of α,β-unsaturated aldehydes by *Beauveria sulfurescens* proceeds along two mechanistic pathways; (i) reversible formation of the corresponding allylic alcohols, and (ii) irreversible formation of the saturated alcohol (Scheme 72).[401] The latter involves initial, slow 1,4-reduction, followed by fast reduction of the resultant saturated aldehyde. A similar sequence was proposed for the reduction of geranial and geraniol to (*R*)-citronellol with *Saccharomyces cerevisiae*.

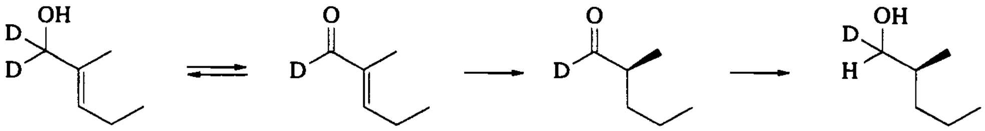

**Scheme 72**

The above-described reducing characteristics of *B. sulfurescens* were found to be a general phenomenon exhibited by many types of eukaryotic organisms (six fungi) and prokaryotes (more than 20 *Actinomycetes* and *Clostridium* species).[402] For example, in conjugate reduction of cyclohexenone derivatives the addition of two hydrogen atoms across the alkene occurs with *trans* stereochemistry, as shown in Scheme 73 where X represents a small alkyl group and Y, a hydrogen atom. In all cases, the 1,4-reduction mode was completed within 48 h. As these characteristics are shared by many organisms, it was suggested that they all contain very similar reducing enzymes.[402]

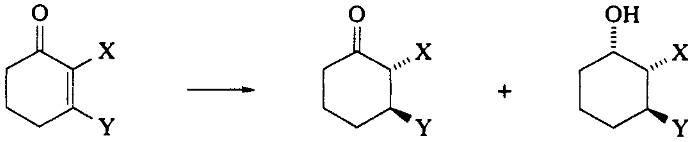

**Scheme 73**

α,β-Unsaturated ketones bearing perfluoroalkyl groups are reduced by baker's yeast (Scheme 74).[403] Perfluoroalkyl alkenyl ketones give mainly the saturated ketone, along with a small amount of optically active saturated alcohol. Substrates having perfluoroalkyl groups attached to the alkene moiety give mixtures of optically active allylic as well as saturated alcohols, whose relative concentration is time-dependent.

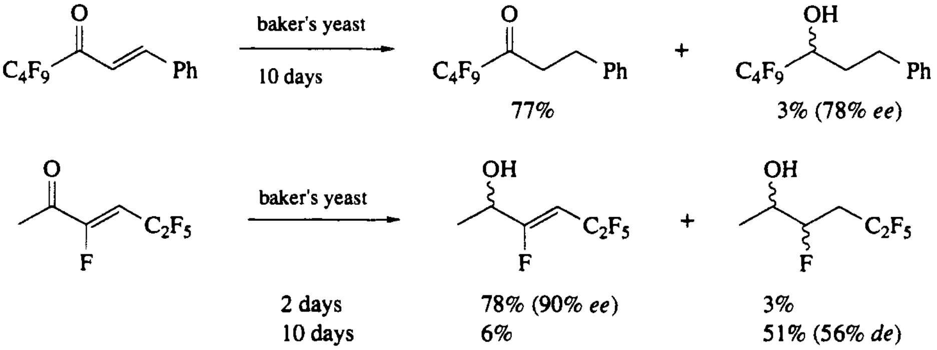

**Scheme 74**

Unsaturated aldehydes derived from citronellol and geraniol are also reduced by baker's yeast to the corresponding saturated primary alcohols with very high enantioselectivity (Scheme 75).[404]

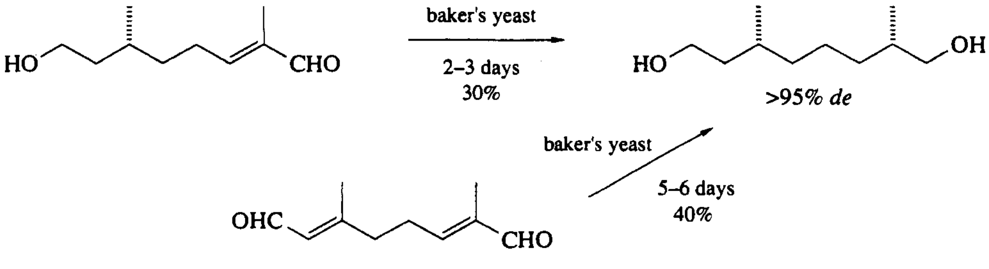

**Scheme 75**

Two key chiral building blocks used in the total synthesis of α-tocopherol were prepared *via* microbial reduction of unsaturated carbonyl compounds with baker's yeast and with *Geotrichum candidum*.[405]

Similarly, a key intermediate in the total synthesis of optically active natural carotenoids was prepared by microbial reduction of oxoisophorone with baker's yeast.[406] An alternative approach to the synthesis of α-tocopherol employs a chiral building block that was obtained by baker's yeast reduction of 2-methyl-5-phenylpentadienal.[407]

Microbial reduction of enones has been applied to prostaglandin synthesis. For example, enantioselective reduction of the enone system in $\Delta^{8(12)}$-15-dehydro-PGE$_1$ with *Flavobacterium sp.* (NRRL B-3874) provided optically pure (–)-15-epi-$\Delta^{8(12)}$-PGE$_1$.[408] NADH-dependent enoate reductase isolated from clostridia is a catalyst for conjugate reduction of α,β-unsaturated carboxylic acids and aldehydes.[409] Enoyl CoA hydratase in $D_2O$ converts crotonyl CoA to (2*R*,3*S*)-2-deuterio-3-hydroxybutyrylCoA.[410] Substituted chalcones are selectively reduced in a 1,4-manner by incubation with *Corynebatesium equi* IFO 3730 to give saturated ketones.[411]

As a general rule in enzymatic reductions, the 1,4-reduction of enones is preferred over the 1,2-reduction mode. However, when an electronegative substituent, such as halogen, is introduced that stabilizes the double bond, enzymatic reduction to allylic alcohols may be achieved.[304]

### 3.5.7.2 Biomimetic Reductions with NAD(P)H Models

A number of pyridine nucleotide linked dehydrogenases catalyze the reversible hydrogenation–dehydrogenation of the double bond in α,β-unsaturated ketones.[412] Similar biomimetic conjugate reductions of α,β-unsaturated aldehydes and ketones occur with NAD(P)H models, such as 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester). With highly electron-deficient alkenes, such as maleic acid, maleic anhydride, diethyl maleate, diethyl fumarate, *etc.*, reductions proceed well.[413] Similarly, the alkenic bond of 1-phenyl-4,4,4-trifluorobut-2-en-1-one is reduced by dihydropyridines under mild conditions (Scheme 76).[414] Tracer experiments showed that hydrogen is transferred directly from the 4-position of the pyridine ring to the β-position of the enone system. The reaction thus parallels the enzymatic reduction of androstenedione.[415]

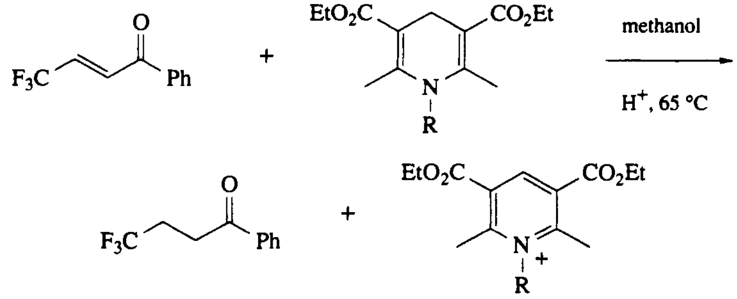

**Scheme 76**

However, these reaction conditions (refluxing methanol or photoactivation at room temperature) are useful only for the reduction of highly activated double bonds.[416] Nevertheless, it was found that the reaction is promoted by silica gel,[417] broadening the scope of reducible enone substrates. The method is highly chemoselective as no alcoholic products are observed, and saturated carbonyls, nitro, cyano, sulfinyl and sulfonyl groups remain intact under the reaction conditions (Scheme 77).

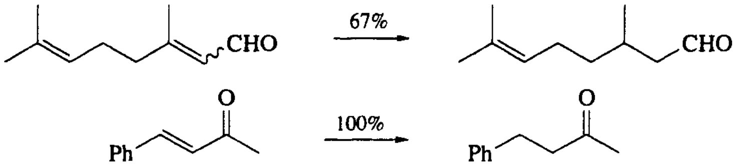

**Scheme 77**

Pandit has provided evidence for the Lewis acid catalysis postulated to operate in these reduction reactions.[418] The reduction of various cinnamoylpyridines by 1,4-dihydropyridine derivatives to the corresponding saturated ketones is catalyzed by zinc or magnesium cations. The reduction rate was fastest in the case of 2-cinnamoylpyridine, in which the metal ion can complex simultaneously to both the nitrogen and oxygen sites (Scheme 78). This example is regarded as a model of Lewis acid catalysis of the NADH-dependent enzymatic reduction of $\Delta^4$-3-keto steroids.

In a similar manner, iminium salts derived from α,β-unsaturated aldehydes and ketones are reduced by Hantzsch ester (Scheme 79).[419] The ratio between the 1,4- and 1,2-reduction products depends upon the p$K_a$ of the amine component. α-Keto-β,γ-unsaturated esters are reduced by NAD(P)H models in the presence of $Mg(ClO_4)_2$. At room temperature 1 equiv. of the reducing agent effects 1,4-reduction of the

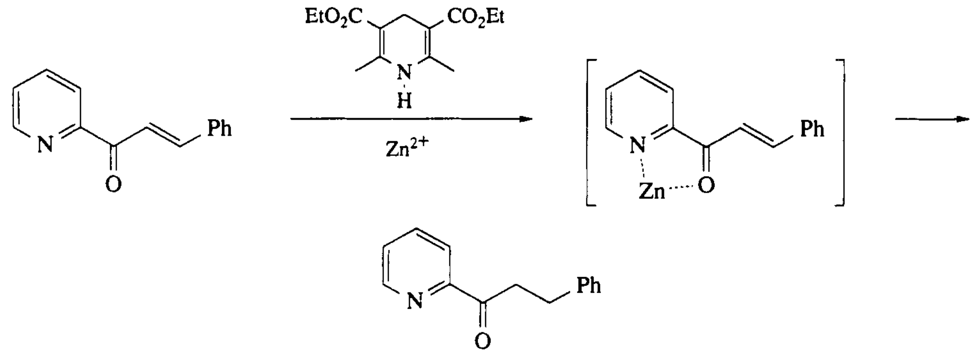

**Scheme 78**

substrate. At a higher temperature, excess reagent reduces the product to the corresponding $\alpha$-hydroxy esters.[420] Several $\alpha,\beta$-unsaturated esters, ketones and nitriles can be reduced by 1-benzyl-1,4-dihydronicotinamide upon selective photoexcitation in the presence of Ru(2,2′-bipyridine)$_3$.[421]

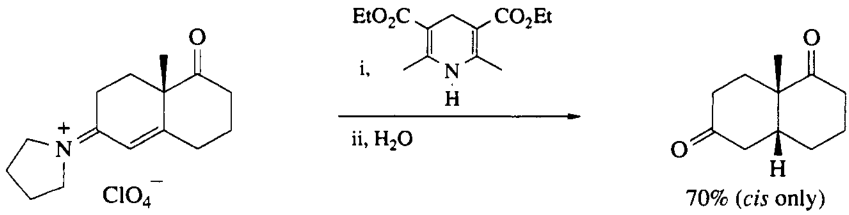

**Scheme 79**

An autorecycling system for the specific 1,4-reduction of $\alpha,\beta$-unsaturated ketones and aldehydes was based on 1,5-dihydro-5-deazaflavin, which can be regarded as an NADH model.[422] The reaction occurs on heating the substrate with catalytic amounts of 5-deazaflavin in 98% formic acid, typically at 120 °C for 24 h (Scheme 80).

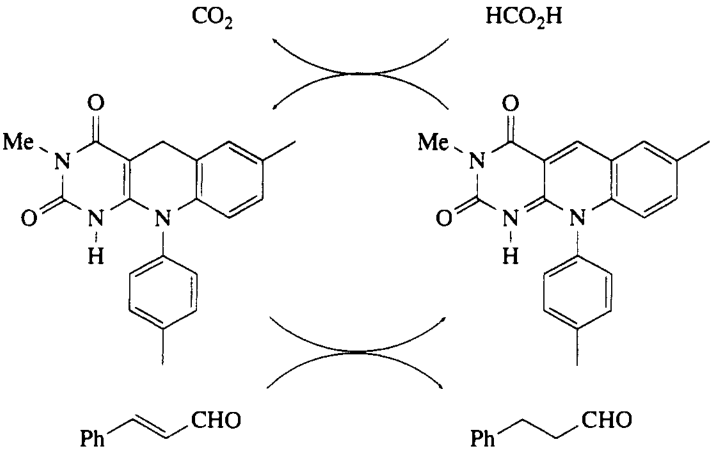

**Scheme 80**

The iminium salts of 3,3,5-trimethylcyclohex-2-en-1-one were reduced with 1,4-dihydronicotinamide sugar pyranosides to give the corresponding optically active saturated ketone in enantiomeric excess ranging over 3–31%. The product stereochemistry changed sensitively with structural variations in the sugar residues.[423]

The cobalt(I) cobalamin catalyzed reduction of $\alpha$-methyl-$\alpha,\beta$-unsaturated carbonyl compounds produces the corresponding saturated derivatives having an (*S*)-configuration at the $\alpha$-carbon (Scheme 81).[424] The highest enantiomeric excess (33%) is exhibited by the (*Z*)-configurated methyl ketone. The

(*E*)-configurated enone is reduced by this system to the corresponding (*R*)-product with poor enantiomeric excess.

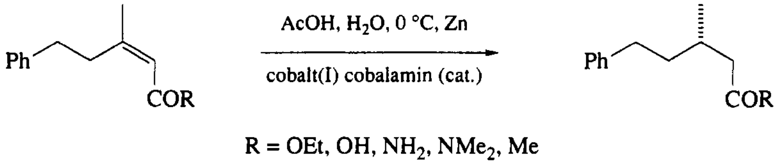

**Scheme 81**

### 3.5.8 MISCELLANEOUS REDUCING AGENTS

Several techniques utilizing miscellaneous reagents, that were not mentioned in the preceding sections, have been reported to effect the 1,4-reduction of α,β-unsaturated aldehydes and ketones.

Sodium dithionite under nitrogen at 80 °C in a water/benzene mixture and in the presence of a phase transfer catalyst reduces dienoic carboxylic acids and esters in a 1,6-mode.[425] Enones such as isophorone, pulegone and carvone are similarly reduced to the saturated ketones. Citral and dimethyl maleate are also reduced in a 1,4-manner in moderate yield.[426]

2-Phenylbenzothiazoline reduced α,β-unsaturated carbonyl compounds in a 1,4-fashion in the presence of stoichiometric amounts of aluminum chloride.[427] No 1,2-reduction products or saturated alcohols were detected. The reagent reduces unsaturated esters and aldehydes much less effectively.

Condensation of an α,β-unsaturated ketone with benzylamine gives the corresponding Schiff base. Treatment with a base such as potassium *t*-butoxide affects rearrangement to a benzaldehyde derivative, as shown in Scheme 82.[428] Hydrolysis of the latter with dilute acetic acid furnishes the corresponding saturated ketone with concomitant formation of benzaldehyde.

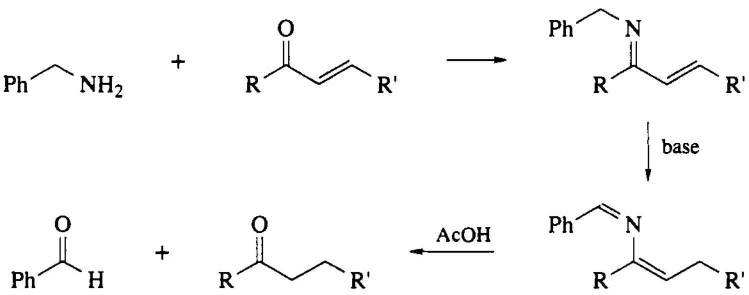

**Scheme 82**

A reagent prepared from tellurium powder and sodium borohydride in ethanol engenders 1,4-reduction of α,β-unsaturated aldehydes, ketones and esters in high yield and with good regio- and chemo-selectivity (no 1,2-reduction and no reduction of isolated double bonds).[429] Enedicarbonyl compounds are reduced to their saturated analogs by treatment with NaI and HCl in acetone.[430] Activated alkenes of the type $Ph_2C{=}CXY$ where X and Y are $CO_2Et$, COPh, $CO_2Et$ and CN react in THF at low temperature with lithium amides having hydrogen at the α-position to give the corresponding saturated derivatives.[431] Carvone is reduced in a 1,4-manner by stereospecific addition of thiophenol to the conjugated double bond followed by desulfurization.[432] Pyridazin-3-ones[433] and allene-1,3-dicarboxylic acids[434] are reduced at the C—C double bond with Zn dust in acetic acid. α,β-Unsaturated esters and amides are reduced to the corresponding saturated compounds with magnesium in methanol.[435]

Anthracene hydride (the anion derived from 9,10-dihydroanthracene) reacts rapidly with chalcone to form an anionic Michael adduct along with a chalcone dimerization product (Scheme 83).[436] Prolonged reaction in the presence of anthracene hydride cleaves the Michael adduct into anthracene and the enolate of the saturated ketone. The partial structure RCCCO is essential for this fragmentation, as mesityl oxide, for example, gave only the Michael adduct.

Photolysis of 4a-methyl-4,4a,9,10-tetrahydro-2-(3*H*)-phenanthrone in 2-propanol gave rearranged and 1,4-reduction products, along with traces of 1,2-reduction and small amounts of coupling products.[437]

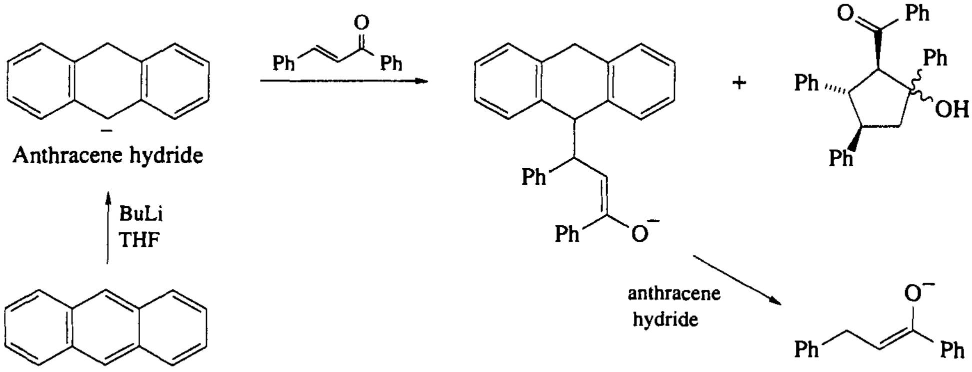

Scheme 83

2-Propanol doped on dehydrated alumina reduces various aldehydes and ketones at room temperature to the corresponding alcohols.[438] α,β-Unsaturated aldehydes are selectively reduced under these conditions to the corresponding allylic alcohols. For example, citral is converted to geraniol in 88% yield.

α,β-Unsaturated nitriles are reduced to saturated nitriles with triethylamine–formic acid azeotrope in DMF.[439]

α,β-Unsaturated ketones are reduced to allylic alcohols with β-branched trialkylaluminum compounds, such as $Bu^i_3Al$ and tris-[(*S*)-2-methylbutyl]aluminum. The latter reagent reduces prochiral enones to optically active allylic alcohols with 7%–15% enantiomeric excess.[440,441]

## 3.5.9 PARTIAL REDUCTION OF CONJUGATED DIENES AND STYRENES

### 3.5.9.1 Dissolving Metal Reduction

Alkenes conjugated to aromatic rings can be selectively reduced to the corresponding alkylarenes using dissolving metal techniques.[442] These reductions are generally stereoselective, with *trans* addition of a hydrogen molecule across the double bond.[443] As is usually observed in dissolving metal reduction of enones, here also, in the absence of a proton donor, dimerization of the initially formed anion radical is the major reaction product (Scheme 84).[444]

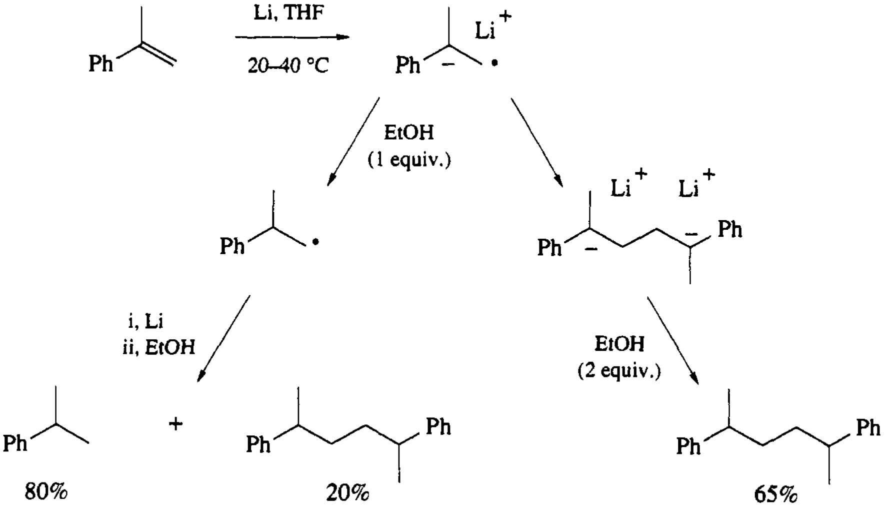

Scheme 84

Carbon–carbon double bonds conjugated to multiple bonds other than aromatic systems may also be reduced with metals. Again the nature of the reduction product is dependent on the availability of a proton donor in the reaction medium. In the absence of an excess of proton donors, dimerization of the initially formed anion radical is observed.[445] Both the reduction of 1,3-dienes[446] and trapping experiments with trimethylsilyl chloride[447] (Scheme 85) have suggested that the initial anion radical formed from these acyclic dienes possesses *cis* configuration, when formed at low temperatures and/or in nonpolar media. This configuration of the tight ion pair intermediate is presumably favored for electrostatic reasons.

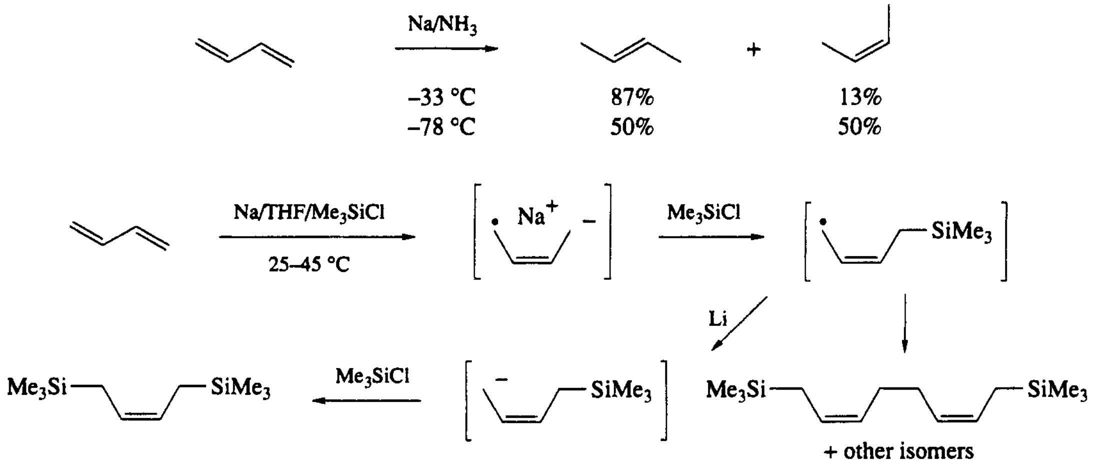

**Scheme 85**

Selective reduction of ergosterol and its derivatives has been carried out using electron transfer reduction. Product distribution depends on the hydroxy substituent as well as on the solvent and the metal used (Scheme 86).[448]

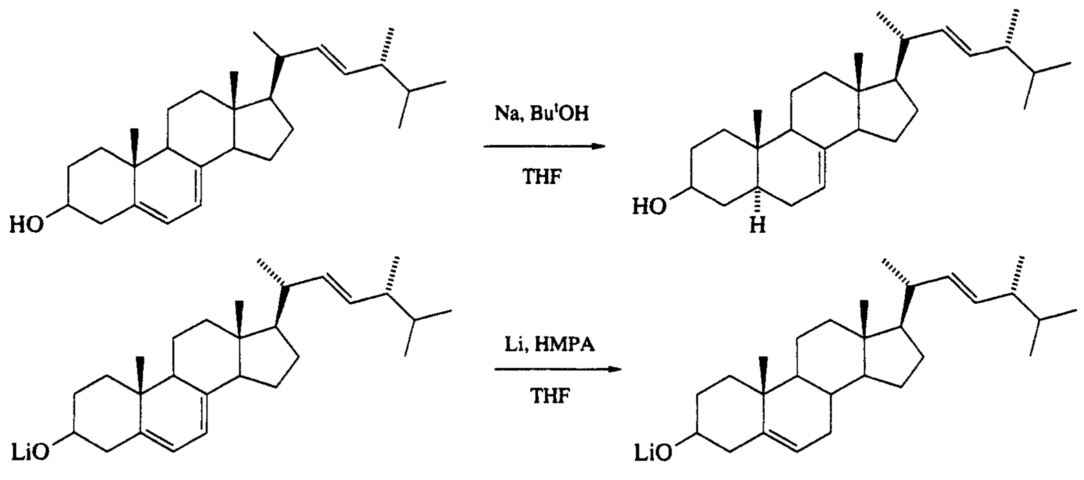

**Scheme 86**

Various diphenylethylenes are reduced in high yield by magnesium in methanol.[449] Expectedly, reductions of conjugated double bonds *via* one-electron transfer processes can also be carried out electrochemically. Scheme 87 illustrates both the reduction of a conjugated alkene and partial trapping of the intermediate anion radical to yield a mixed hydrodimerization product.

### 3.5.9.2 Catalytic Hydrogenation

Partial hydrogenation of conjugated dienes or polyenes is a nontrivial synthetic transformation. This reaction commonly yields a mixture of products arising from 1,2- and 1,4-addition of hydrogen to the butadiene moiety, as well as complete hydrogenation of both double bonds. Unless there is a substantial difference between the two double bonds in terms of substitution pattern and electronic density, selectiv-

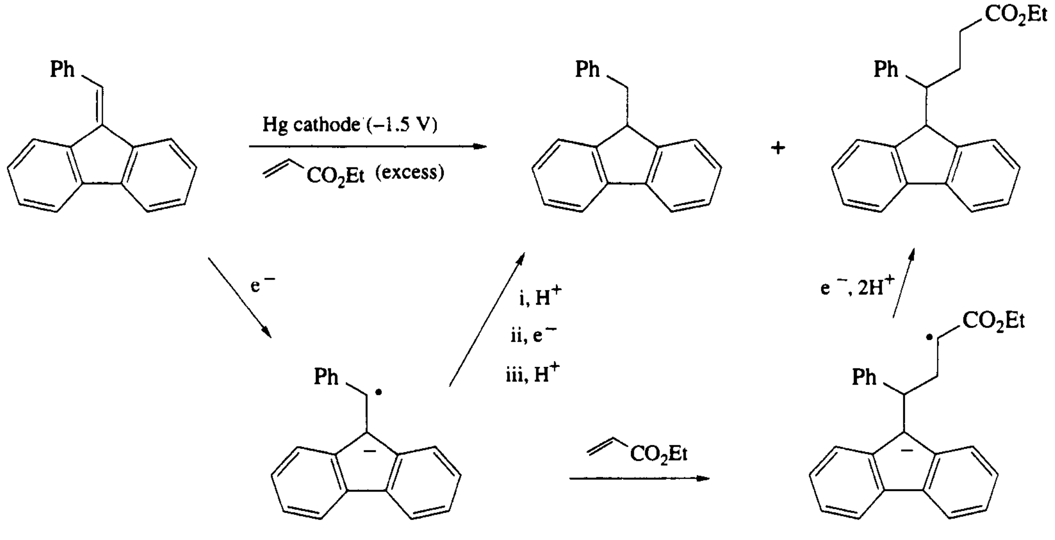
Ph
Hg cathode (−1.5 V)
CO2Et (excess)
Ph
+
CO2Et
Ph
e−
i, H+
ii, e−
iii, H+
Ph
e−, 2H+
CO2Et
Ph
CO2Et

Scheme 87

ity of these reactions is rather poor. Chemists often meet this challenge by a trial and error approach, using heterogeneous hydrogenation catalysts.

Alkene hydrogenation rates usually decrease with increasing degree of substitution on the double bond. This general tendency may also be influenced by the steric bulk and position of the substituents. For instance, in ring systems, exocyclic double bonds are reduced much faster than endocyclic ones.

A number of steroidal dienes have been selectively hydrogenated at the sterically less-hindered position using various catalysts. Raney nickel and $PtO_2$ are the most commonly used heterogeneous catalysts for this purpose.[450] Several examples of selectivity in heterogeneous catalytic hydrogenation of dienes are illustrated in Scheme 88.[451–457]

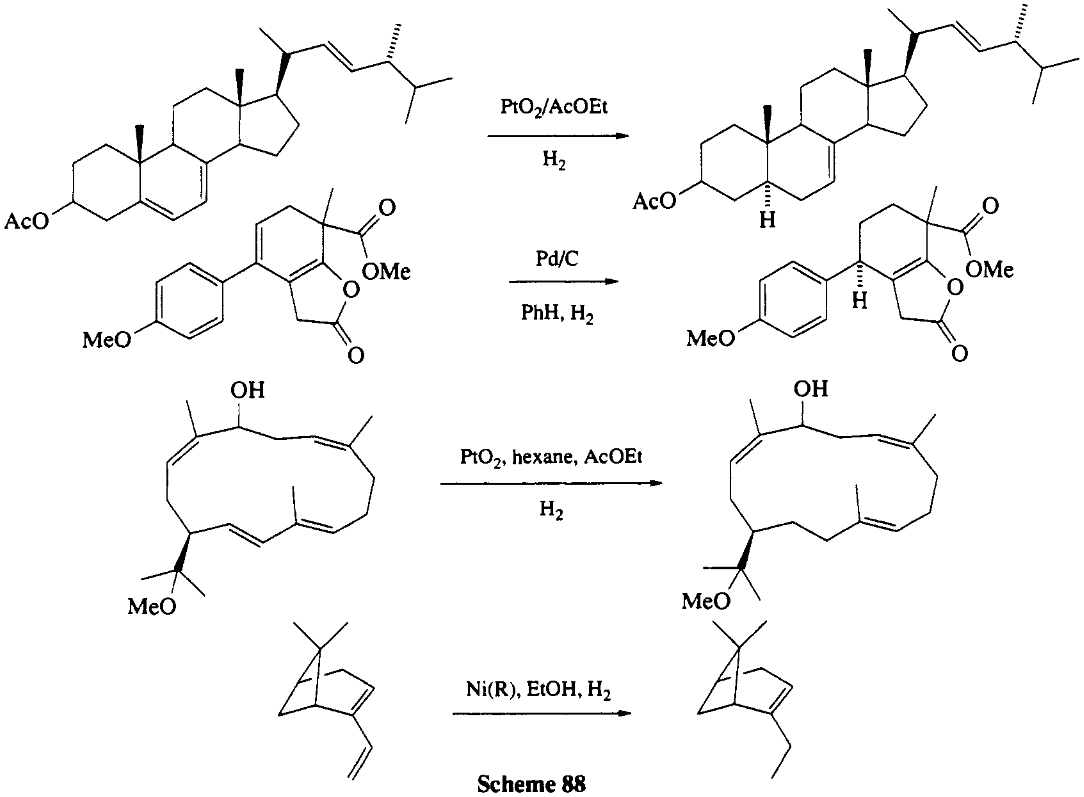
AcO
PtO2/AcOEt
H2
AcO
H
O
OMe
O
O
MeO
Pd/C
PhH, H2
MeO
H
O
OMe
O
O
OH
MeO
PtO2, hexane, AcOEt
H2
OH
MeO
Ni(R), EtOH, H2

Scheme 88

Utilization of homogeneous catalysts for selective hydrogenation of steroidal dienes proved to be beneficial, although the reason for selectivity in these reactions has not been extensively explored. Partial reduction of conjugated dienes may be carried out with soluble chromium complexes. For example, 1,4-hydrogenation of conjugated dienes is selectively achieved with (methylbenzoate)$Cr(CO)_3$[367b] to afford the *cis*-monoalkene. The reaction is highly stereospecific for *cis*-dienes or for cyclic 1,3-dienes held in the required *cisoid* configuration, and affords a product with a *cis* double bond. This catalyst has been successfully employed in partial hydrogenation of several diene intermediates in prostaglandin synthesis. In all cases, the less-substituted double bond was selectively hydrogenated (Scheme 89)[458]

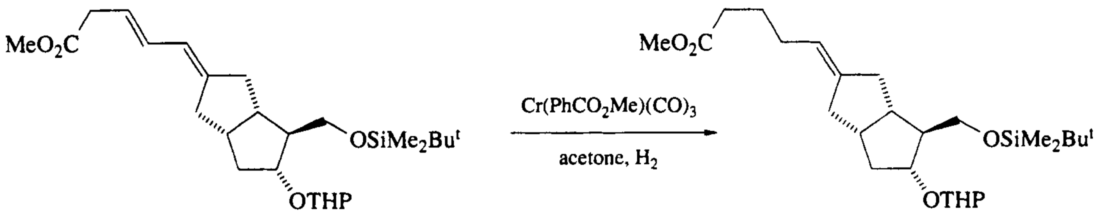

**Scheme 89**

However, the reaction conditions required for catalytic hydrogenation with Cr(arene)$(CO)_3$ are relatively forcing (160 °C/30 atm). A closely related complex $Cr(CO)_3(MeCN)_3$, with relatively labile acetonitrile ligands, operates under far milder conditions (40 °C/1.5 atm).[459] Similarly, the photoactivated complex $Cr(CO)_6$, catalyzes 1,4-hydrogen addition to dienes under 1 atm of hydrogen at room temperature.[460] Nonconjugated 1,4-dienes are also hydrogenated with (arene)$Cr(CO)_3$ at high temperatures, probably *via* isomerization to the conjugated system prior to reduction. No reaction occurs with either 1,5- or 1,6-dienes, owing to the inability of the chromium complex to affect conjugation of the double bonds.

The pentacyano cobalt anion $Co(CN)_5{}^{3-}$ has found synthetic application in the reduction of conjugated dienes to monoenes.[461] This catalyst is prepared by reaction of cobalt(II) chloride with potassium cyanide under a nitrogen atmosphere in either aqueous (more common) or nonaqueous (*e.g.* methanol) solvents. The preference for aqueous solutions has limited the applications of this reaction due to poor water solubility of most organic substrates. This solution requires preactivation by addition of hydrogen (1 atm) for 1–2 h at 20 °C to generate the active species $(Co(CN)_5H)^{3-}$. This solution is then used immediately, as the actual catalyst tends to loose activity upon standing. A number of simple dienes, including butadiene, isoprene, 1-phenylbutadiene, cyclohexa-1,3-diene, and cyclopentadiene, were successfully hydrogenated under these mild conditions. However, the catalyst is rather sensitive to steric hindrance, which inhibits hydrogenation. For example, 2,5-dimethylhexa-2,4-diene is not reduced by this system. Generally, monoenes are not reduced by $[Co(CN)_5]^{3-}$, but activated monoalkenes, such as styrenes and α,β-unsaturated carbonyl compounds, can be hydrogenated (Scheme 90). Acrylic acid and acrolein do not react under these conditions.

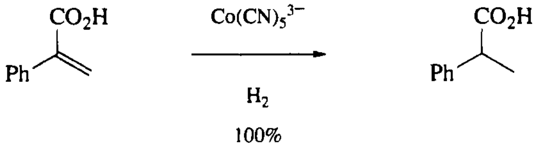

**Scheme 90**

With terminal 1,3-dienes and either $RhH(PPh_3)_4$ or $(Rh(CO)_2(PPh_3))_2$ in the presence of excess phosphine at 50–100 °C and 15 atm, selective hydrogenation of the terminal double bond is achieved (Scheme 91). Hydrogen uptake must be monitored in these reactions in order to prevent further hydrogenation of the partially reduced product. As is the case for the cobalt cyanide system, here also, substitution at the double bond inhibits the rate of hydrogenation and limits its general applicability.

While most catalysts reduce the least-substituted double bond preferentially, the novel catalyst system $CoBr(PPh_3)_3{\cdot}BF_3OEt_2$ can selectively hydrogenate conjugated dienes to monoenes *via* 1,2-hydrogen addition to the more substituted double bond (Scheme 92). Unfortunately, hydrogenation of functionalized alkenes, such as methyl vinyl ketone, methyl acrylate and *n*-butyl vinyl ether, does not occur even under forcing conditions.

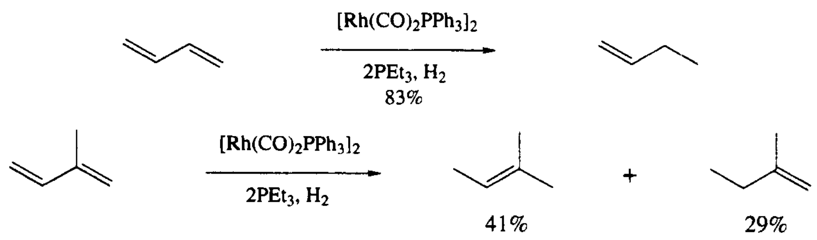

**Scheme 91**

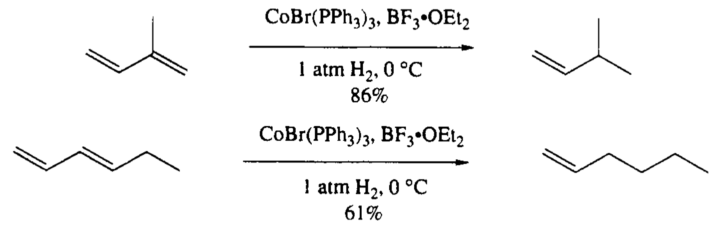

**Scheme 92**

Hydrogenation of penta-1,3-dienes to pent-2-ene is selectively achieved with $RuH(PPh_3)_3Cl$.[462] Butadiene and isoprene are hydrogenated in 62% yield using $Cp_2VCl_2$·BuLi, affording *trans*-but-2-ene (84%), *cis*-but-2-ene (14%) and but-1-ene (2%).[463] Homogeneous hydrogenation of penta-1,3-diene using $LiAlH_4$ as a catalyst affords *trans*-pent-2-ene (57%), *cis*-pent-2-ene (10%) and pent-1-ene (8%).[464] Tricarbonylcyclopentadienylhydrido-molybdenum and -tungsten were used for hydrogenation of hexa-2,4-diene, 4-methylpentadiene, and octa-2,4,6-triene, producing in all cases a mixture of monoalkene products.[465]

The hydrogenation of alkenes conjugated to aromatic systems is usually much less difficult than partial reduction of polyenes, as the aromatic ring is less susceptible to reduction. Many catalysts of Group 10 metals have been used for this transformation, including Raney nickel,[466] Pd adsorbed on carbon,[467] Pd adsorbed on calcium carbonate,[468] Pd on barium sulfate,[469] metallic palladium,[470] $PtO_2$,[471] chloroplatinic acid[472] or platinum metal.[473] Normally, the stereochemistry of the reduced product arises from *syn* addition of a hydrogen molecule to the less-hindered face of the double bond, as exemplified in the catalytic hydrogenation of a steroidal styrene over metallic palladium (Scheme 93).[474]

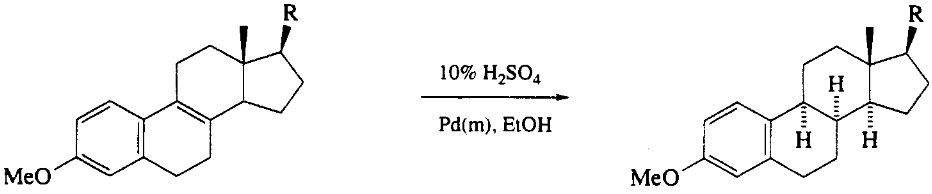

**Scheme 93**

A number of other soluble transition metal complexes may catalyze hydrogenation of styrene. These include $HCo(CO)_4$,[475] $SnCl/H_2PtCl_2$,[476] $KNi_2(CN)_2$,[477] $RhCl(PPh_3)_3$,[478] $RhH(CO)(PPh_3)_3$,[479] $K_3Co(CN)_5$,[480] $Cr(acac)_3$, $Co(acac)_3$, $Fe(acac)_3$, $Ti(OPr^i)_4$, $VO(OEt)_3$, which in the presence of trialkylaluminum catalyze hydrogenation of *trans*-stilbene.[481]

### 3.5.9.3 Miscellaneous Reducing Agents

Reactive styrenes, such as acenaphthylene[482] and compounds in which the double bond is part of an allylic alcohol are reduced with $LiAlH_4$.[483] The double bond of benzalquinaldine is reduced by heating with thiocresol in HCl, affording the corresponding hydrogenated product, as well as the disulfide as a by-product.[484] Benzyl alcohol in KOH may act as a reducing agent for several fluorenyl styrenes.[485] Hydrazine can reduce the double bond of various stilbenes.[486]

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# 3.6

# Partial and Complete Reduction of Pyridines and their Benzo Analogs

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## 3.6.1 INTRODUCTION

This review deals with the formation of reduced pyridines and their benzo analogs from the parent heteroaromatic bases. Included are acridines, isoquinolines, pyridines and quinolines and their quaternary ammonium salts and *N*-oxides. The formation of the reduced species by other methods, *e.g.* Hantzsch dihydropyridine synthesis, is not addressed.

## 3.6.2 CHEMICAL REDUCTION

This encompasses all reduction methods other than hydrogenation and includes hydride equivalents and one-electron reductions. Catalytic hydrogen transfer is included under hydrogenation (see Section 3.6.3).

### 3.6.2.1 Metal Hydride Reductions

Hydride reagents formally add hydrogen to polarized carbon–heteroatom double bonds, the most widely used being based on aluminum (*e.g.* lithium aluminum hydride, LAH) and boron (*e.g.* sodium borohydride, NBH). Complex metal hydrides are generally sufficiently nucleophilic to react with π-electron-deficient heteroaromatics such as pyridines. The modification of these reagents with, for example, alcohols, alkyl groups, amines and Lewis acids greatly affects both their reactivity and selectivity. Solvents have a profound effect on the activity of these reagents, particularly so in the case of borohydrides. LAH and its derivatives are generally used in ethers, whereas borohydride reductions are frequently carried out in alcohols. These reagents can also be used to generate other active species *in situ* (*e.g.* hydrides of Si, Sn and Cu). During the reaction each hydrogen is sequentially replaced by the reduced substrate (Scheme 1). The electronic and steric character of the reductant therefore changes as the reaction proceeds, *e.g.* (**1**) → (**2**) → (**3**), and changes in regio- and enantio-selectivity may occur. The operation of both direct hydride transfer and single-electron transfer (SET) processes has been proposed as mechanisms.[1] Stable radical intermediates have been detected in the reductions of 1,10-phenanthroline, 2,2-bipyridine and isoquinoline with lithium di- and tri-*t*-butoxyaluminum hydrides. The initial radical pair formed (**4**; Scheme 2) can undergo further reduction to (**5**) or to the dissociated free radical anion (**6**) prior to reaction.

$$\underset{(1)}{\mathrm{LiAlH_4}} \xrightarrow{\mathrm{R}} \underset{(2)}{\mathrm{LiAl(RH)H_3}} \xrightarrow{\mathrm{R}} \underset{(3)}{\mathrm{LiAl(RH)_2H_2}} \longrightarrow\!\!\longrightarrow \mathrm{LiAl(RH)_4} \xrightarrow{\mathrm{H_2O}} \mathrm{LiOH} + \mathrm{Al(OH)_3} + 4\mathrm{RH_2}$$

**Scheme 1**

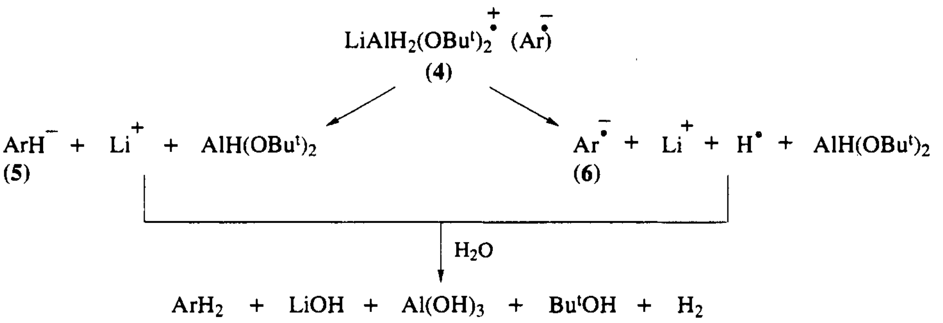

LiAlH2(OBut)2• (Ar•)
(4)
ArH− + Li+ + AlH(OBut)2
(5)
Ar•− + Li+ + H• + AlH(OBut)2
(6)
H2O
ArH2 + LiOH + Al(OH)3 + ButOH + H2

**Scheme 2**

Alanes and boranes are initially electrophilic rather than nucleophilic, and coordinate onto free electron pairs in the molecule prior to hydride delivery. The chemistry of metal hydrides has been extensively reviewed,[2] as has the reduction of nitrogen heterocycles with complex metal hydrides.[3] Generally, NBH reductions, carried out in alcohols, produce tetrahydropyridines, whilst LAH generates mainly dihydropyridines.

### *3.6.2.1.1 Pyridines with borohydrides*

Pyridine itself is not reduced by NBH under normal conditions and ring reduction occurs only if electron-withdrawing groups are attached. 3-Cyanopyridine (**7**) when reduced with NBH in ethanol gives 3-cyano-1,4,5,6-tetrahydropyridine (**8**; Scheme 3) as the major product. In aprotic solvents such as pyridine or diglyme, the 1,4-dihydropyridine (**9**) is produced.[4] Reactions of pyridines substituted with electron-withdrawing groups at the 2- and 4-position generally occur at the substituent.[5] Although generally not reactive towards NBH, carboxylic acid esters at the 2- and 6-position of the pyridine ring are reduced to the alcohol.

Sodium cyanoborohydride (**10**) produces mainly 1,4-dihydropyridines (**11**) in the reduction of 3,5-dicyano- and 3,5-diethoxycarbonyl-pyridines, diborane produces more of the 1,2-isomer.[6] With NBH, mixtures of 1,2- and 1,4-dihydro adducts are produced, the latter predominating when carried out in pyridine solution.[6] Nicotinamide (**13**) in ethanol can be reduced to (**8**) in moderate yield; at 140 °C in diglyme the tetrahydropyridine (**8**) was isolated in admixture with the piperidine (**14**), presumably *via* dehydration of the amide.[7] 3-Nitropyridine affords 3-nitropiperidine in moderate yield when reduced in ethanol.[5] The carboxylic acid and halo derivatives of pyridine are generally not reactive toward NBH.

Quinolines, like pyridines, are susceptible to attack at both the 2- and 4-position; however, they are more reactive, quinoline (**15**; R = H) forming a mixture of 1,2-dihydroquinoline (**16**; R = H) and 1,2,3,4-tetrahydroquinoline (**17**; R = H) when reacted in hot ethanol or diglyme.[5] Electron-withdrawing groups

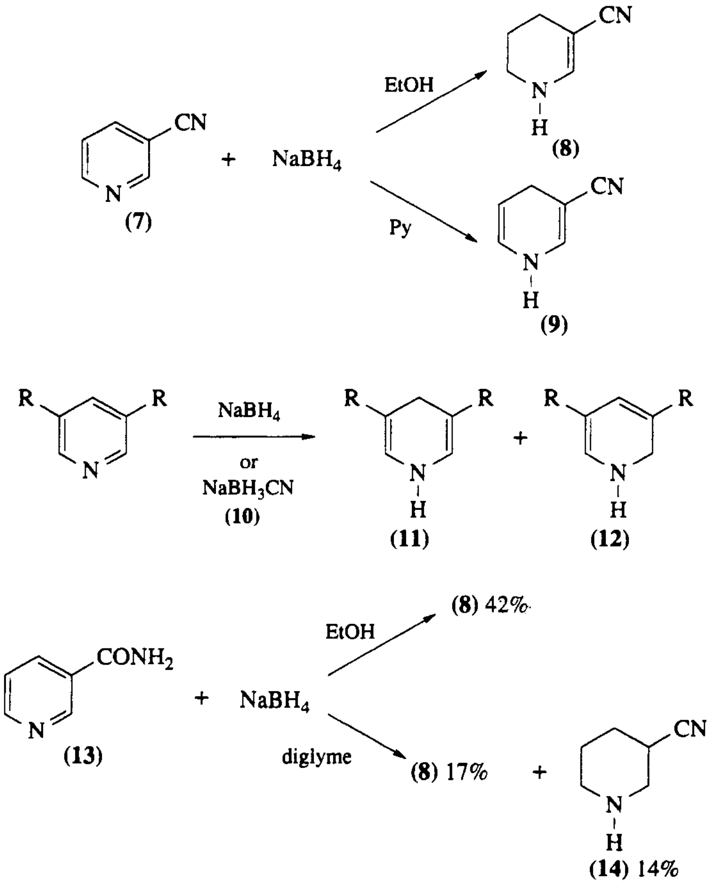

**Scheme 3**

in the 3-position (**15**; R = CN, $CONH_2$, $CO_2Et$) gave high yields of 1,4-dihydroquinolines (**18**), whereas halogentated quinolines (**15**; R = Br, F) produced 1,2-dihydroquinolines (**16**) in only moderate yield.[5] 3-Dimethylaminoquinoline (**15**; R = $NMe_2$) was unreactive under the conditions employed. 2- and 4-cyanoquinolines undergo reduction to give substituent- and/or ring-reduced products, depending upon the solvent employed.[5] Reduction in the presence of carboxylic acids has been used to facilitate reduction with and without alkylation. Quinoline and NBH in carboxylic acids produce *N*-alkyl-1,2,3,4-tetrahydroquinolines (**19**; Scheme 4), whereas sodium cyanoborohydride produces 1,2,3,4-tetrahydroquinolines (**20**).[8] The reduction of quinolines substituted in the benzene ring with nitro groups produces the 1,2-dihydroquinolines (**21**) in high yield when reduced with NBH in acetic acid at low temperature.[9] At higher temperatures the 1,2-dihydroquinoline (**22**) was produced in moderate yield.[8]

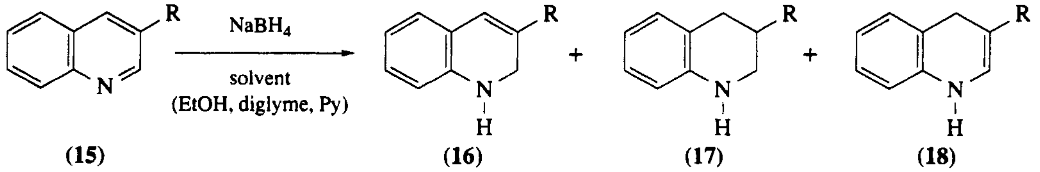

Isoquinoline (**23**; R = H; Scheme 5) undergoes reduction to 1,2,3,4-tetrahydroisoquinoline (**24**; R = H) when treated with NBH in aqueous solvents.[5] Isoquinolines bearing an electron-withdrawing group in the 4-position undergo reduction with NBH to give 1,2-dihydroisoquinolines (**25**) or 1,2,3,4-tetrahydroisoquinolines (**24**), depending upon the solvent.[5] Substituent reduction may also occur. 1,2-Dihydroisoquinolines (**25**) are the expected products in aprotic solvents. With 1- and 3-cyanoisoquinolines both ring and substituent reduction are known to occur. Ring reduction is favored with the former and substituent reduction predominates with the latter producing both amides and amidines.[5] Like quinoline, isoquinoline undergoes reductive alkylation to *N*-alkyl-1,2,3,4-tetrahydroisoquinolines (**26**; Scheme 5) with

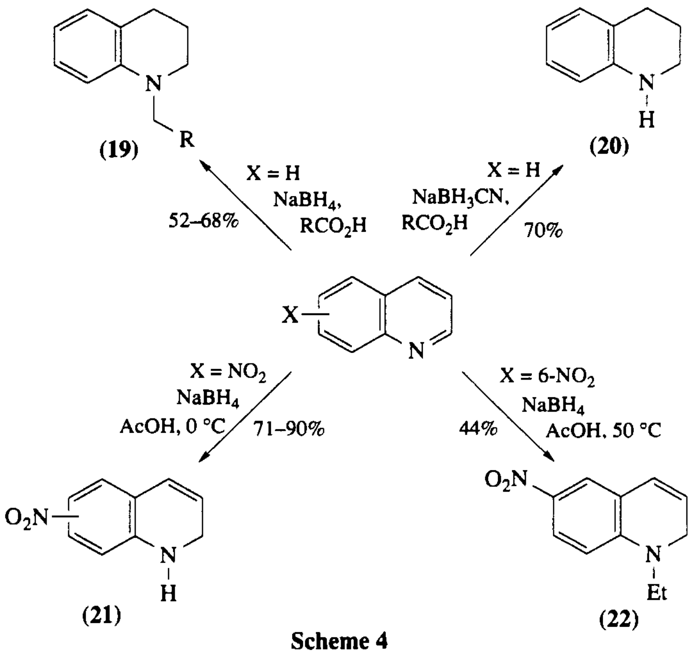
(19)
R
N
X = H
NaBH4,
RCO2H
52–68%
(20)
N
H
X = H
NaBH3CN,
RCO2H
70%
X
N
X = NO2
NaBH4
AcOH, 0 °C
71–90%
X = 6-NO2
NaBH4
AcOH, 50 °C
44%
O2N
N
H
(21)
O2N
N
Et
(22)

**Scheme 4**

NBH, in the presence of carboxylic acids. Reduction with sodium cyanoborohydride gives reduction but no alkylation under similar conditions.[8] The reduction of 5-nitroisoquinoline produced dihydroisoquinoline (**27**) or tetrahydroisoquinoline (**28**) with NBH in acetic acid, depending on the solvent and temperatures employed.

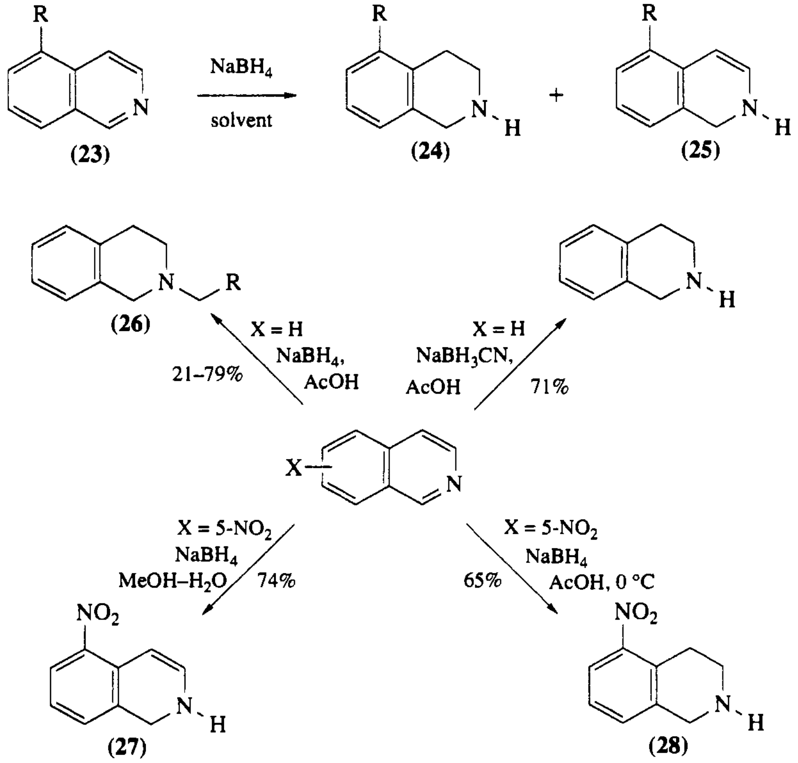
R
N
(23)
NaBH4
solvent
R
N
H
(24)
+
R
N
H
(25)
N
R
(26)
X = H
NaBH4,
AcOH
21–79%
N
H
X = H
NaBH3CN,
AcOH
71%
X
N
X = 5-NO2
NaBH4
MeOH–H2O
74%
NO2
N
H
(27)
X = 5-NO2
NaBH4
AcOH, 0 °C
65%
NO2
N
H
(28)

**Scheme 5**

Sodium triethylborohydride (**29**) reacts with isoquinoline to yield the boron-activated enamine (**30**) which undergoes attack by electrophiles to produce 4-substitued isoquinolines (**31**; Scheme 6) in a convenient 'one-pot' synthesis.[10]

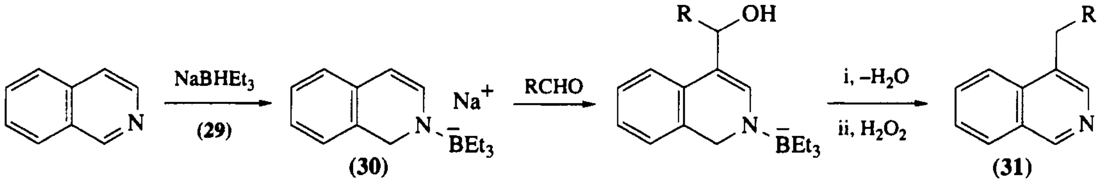
NaBHEt3
(29)
Na+
N
BEt3
(30)
RCHO
R
OH
BEt3
i, -H2O
ii, H2O2
R
N
(31)

R = H, alkyl, aryl; 25–65%

**Scheme 6**

### *3.6.2.1.2 Pyridines with aluminum hydrides*

Lithium aluminum hydride (LAH) reacts with pyridines and their analogs in aprotic solvents to give dihydro- and tetrahydro-pyridines. In the absence of proton sources dihydropyridines normally predominate, solutions of pyridine and LAH form lithium complexes (**32**; Scheme 7), which likely consist of both 1,2- and 1,4-dihydropyridines.[11] This intermediate has been used as a reducing agent for ketones, and reaction with alkyl halides generates 3-substituted pyridines (**33**) in good yield.[12]

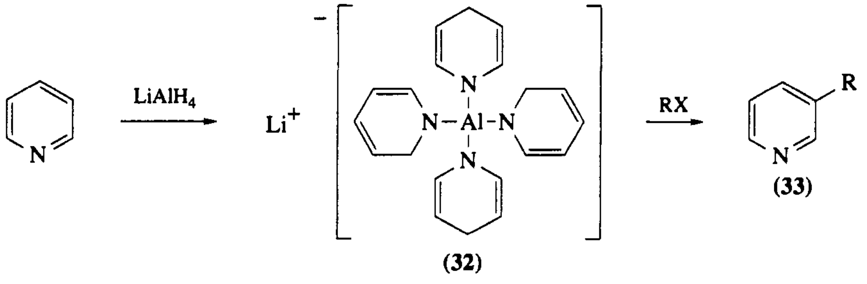
N
LiAlH4
Li+
N-Al-N
N
RX
R
(33)
(32)

**Scheme 7**

3,5-Dicyanopyridine produces mixtures of 1,2-dihydropyridines (**35**) and 1,4-dihydropyridines (**36**; Scheme 8)) with LAH. The more hindered alkoxyaluminates favor 1,4-dihydropyridine formation.[13] 1-Alkyl-2-pyridones (**37**) are reduced when aluminum chloride is used in conjunction with LAH. Tetrahydropyridines (**38**) are the major products produced, minor amounts of the piperidines (**39**) are also formed.[14]

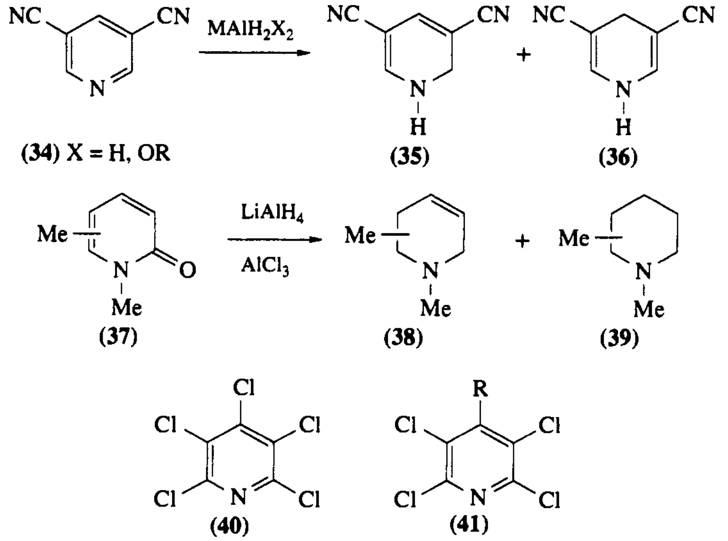
NC
CN
N
MAlH2X2
(34) X = H, OR
NC
CN
N
H
(35)
+
NC
CN
N
H
(36)
Me
N
O
Me
(37)
LiAlH4
AlCl3
Me
N
Me
(38)
+
Me
N
Me
(39)
Cl
Cl
Cl
Cl
N
Cl
(40)
R
Cl
Cl
Cl
N
Cl
(41)

**Scheme 8**

Pentachloropyridines (**40**) and 4-substituted tetrachloropyridines (**41**) undergo dehalogenation on treatment with LAH. Minor amounts of ring-reduced products are observed.[15]

Quinolines generally produce 1,2-dihydroquinolines with aluminum hydrides. Diisobutylaluminum hydride and Red-Al have been used to reduce quinolines and quinoline-*N*-boranes (**42**; Scheme 9). The reactions are believed to proceed *via* aminoalanes or boranes and the dihydroquinolines produced are quenched and trapped as the carbamates by the addition of chloroformate esters.[16] Minor amounts of 1,4-dihydro- and 1,2,3,4-tetrahydro-quinolines are also formed. The possession of a 2-substituent hinders reaction. At low temperatures the kinetic product, *i.e.* (**43**), is favored, but at higher temperatures reduction at the 4-position predominates which subsequently produces the tetrahydro derivative (**44**). A similar approach has been employed with isoquinoline, generating 1,2-disubstituted tetrahydroisoquinolines (**45**; Scheme 9).[17]

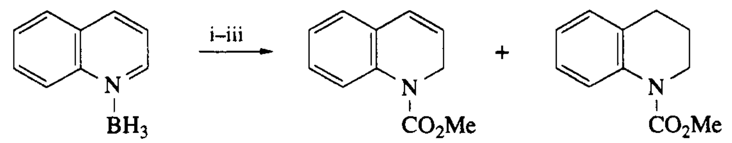

**(42)**

| *Temperature* (°C) | *Time* (h) | *Yield* (%) | (**43**) (%) | (**44**) (%) |
|---|---|---|---|---|
| –78 | 0.33 | 90 | 100 | – |
| 25 | 18 | 85 | 44 | 56 |

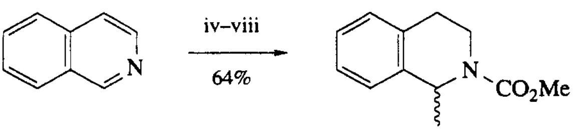

**(45)**

i, 2 equiv. $NaAl(OR)_2H_2$; ii, $ClCO_2Me$; iii, $H_3O^+$; iv, $BH_3{\bullet}THF$, –78 °C; v, MeLi, –78 °C; vi, DIBAL-H, –78 to 25 °C; vii, $ClCO_2Me$, –25 to 0 °C; viii, HCl

**Scheme 9**

### *3.6.2.1.3 Pyridinium salts with borohydrides*

Coenzyme $NAD(P)^+$ involves a nicotinamide derivative and the transfer of a hydrogen species in a stereoselective manner *via* a 1,4-dihydropyridine (**47**; Scheme 10) and has led to much work on the reduction of NAD and its simpler derivatives (**46**; R = $PhCH_2$, $C_{12}H_{25}$). Most work has been done on the stereoselective reduction of ketones,[18] but heteroaromatic cations have also been reduced (see Section 3.6.2.3).[19] Both single-electron transfer (SET) and direct hydride transfer mechanisms have been proposed.[20]

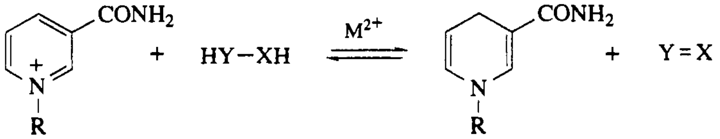

(**46**) M = Mg, Zn

(**47**)

**Scheme 10**

Pyridinium salts (**48**; Scheme 11) with borohydride can give three different products, 1,2-, 1,4- and 1,6-dihydropyridines. 1,4-Dihydropyridines (**49**) are thermodynamically favored, being *ca.* 2 kcal $mol^{-1}$ (1 cal = 4.18 J) more stable than the 1,2(6)-dihydropyridines (**50**). The chemistry of dihydropyridines has been extensively reviewed.[3,21–23] The dihydropyridine systems produced, being enamines, normally undergo protonation in protic solvents to give the iminium salts and hence further reduction. Mixtures of piperidines (**51**) and tetrahydropyridines (**52**) often result, with the former produced by initial hydride attack at the 4-position.[3] Bulky *N*-substituents are known to favor 4-attack.[24] Electron donors in the 3-position direct hydride attack predominantly to the 2-position when reduced as the *N*-alkoxycarbonylpyridinium salts (**53**; Scheme 12) with a variety of boron- and aluminum-based reducing agents.[25] 3-Methoxy and 3-methylthio derivatives gave exclusively 1,2-dihydropyridines (**54**) with NBH,

$K(Pr^iO)_3BH$ and $Li(Bu^tO)_3AlH$. 3-Trimethylsilyl and 3-trialkylstannyl groups gave very high regiospecificity (80–100%) to the 1,6-dihydropyridines (**55**). 3-Alkylpyridines produced predominantly the 1,2-adducts (**54**) and electron-withdrawing groups in the 3-position produced mixtures of all three isomers. Dihydropyridines containing electron-withdrawing groups at the 3-position are often resistant to further reduction, particularly in the case of the 1,6- and 1,4-dihydro (**56**) derivatives. 1,2-Dihydropyridines are converted to the tetrahydropyridines.[3,26]

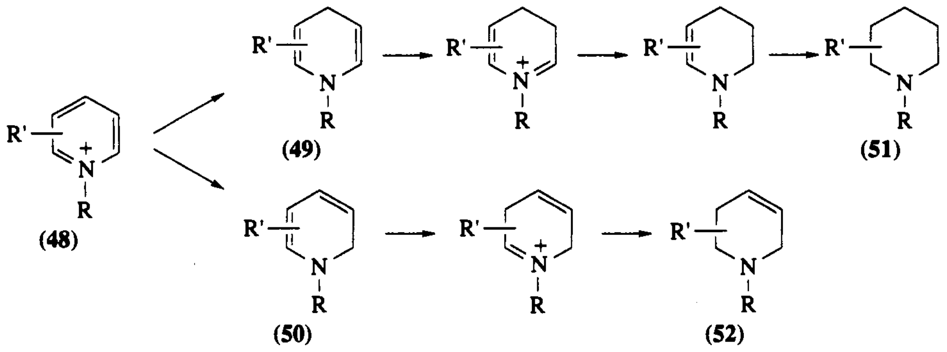

Scheme 11

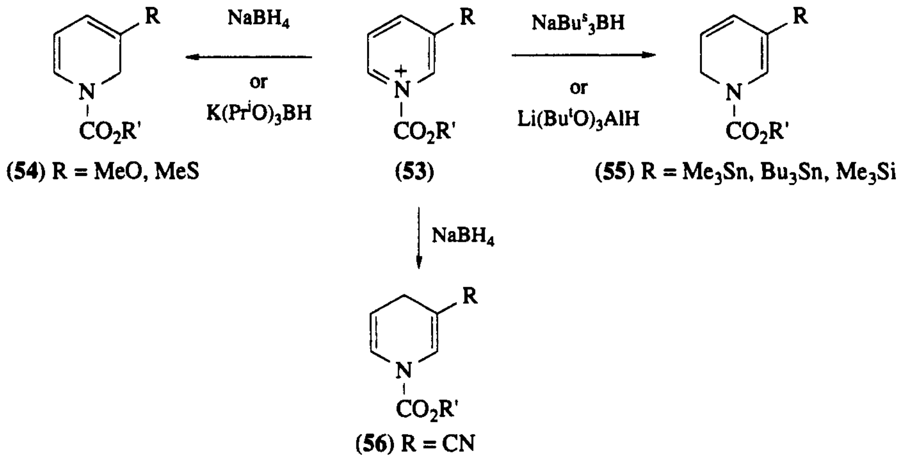

Scheme 12

Dihydropyridines may be prevented from undergoing further reduction by carrying out reductions in aprotic solvents or in protic systems at high pH. Phase transfer methods have also been used to remove the dihydro adducts from the reactive medium prior to further reduction. An elegant solution to the problem of overreduction was developed by Fry; reduction is carried out in the presence of cyanide ion, which traps the dihydropyridine system as 2-cyano-1,2,3,6-tetrahydropyridine (**57**; Scheme 13).[27] The addition of alkoxide re-forms the dihydropyridine (**58**). Separation of 1,4-dihydropyridines from mix-

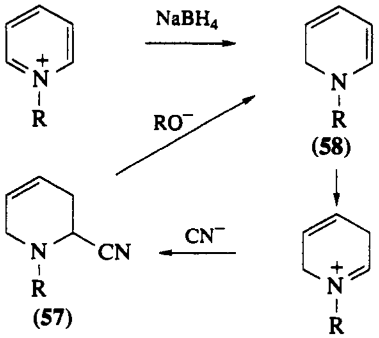

Scheme 13

tures with the 1,2-dihydropyridines can be achieved because 1,2-dihydropyridines undergo Diels–Alder reactions with maleic anhydride to produce isoquinuclidines (Scheme 13).[28] The regiospecific delivery of hydride to the 4-position has been achieved in high selectivity (**59**) → (**60**) (>90%) by the *in situ* generation of a 'copper hydride' reagent from lithium tri-*t*-butoxyaluminum hydride and copper(I) bromide.[29]

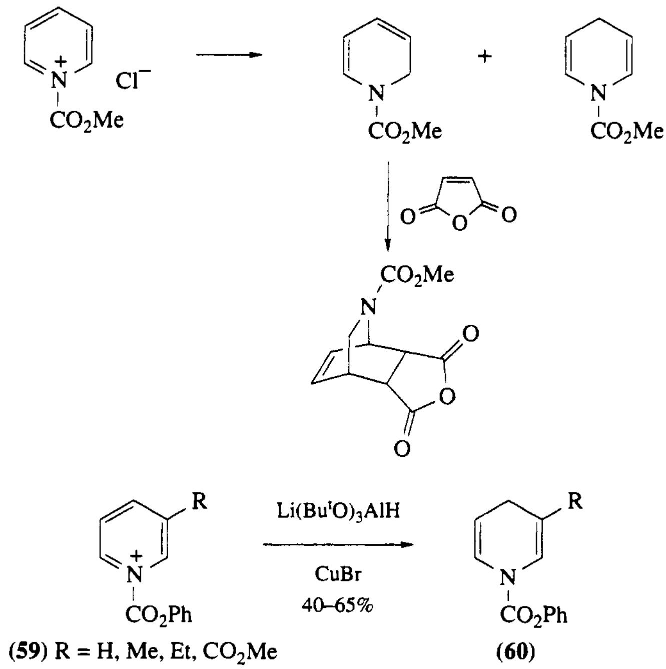
Cl⁻
N
CO2Me
+
O
R
Li(ButO)3AlH
CuBr
40–65%
CO2Ph
(59) R = H, Me, Et, CO2Me
(60)

**Scheme 13** ***(continued)***

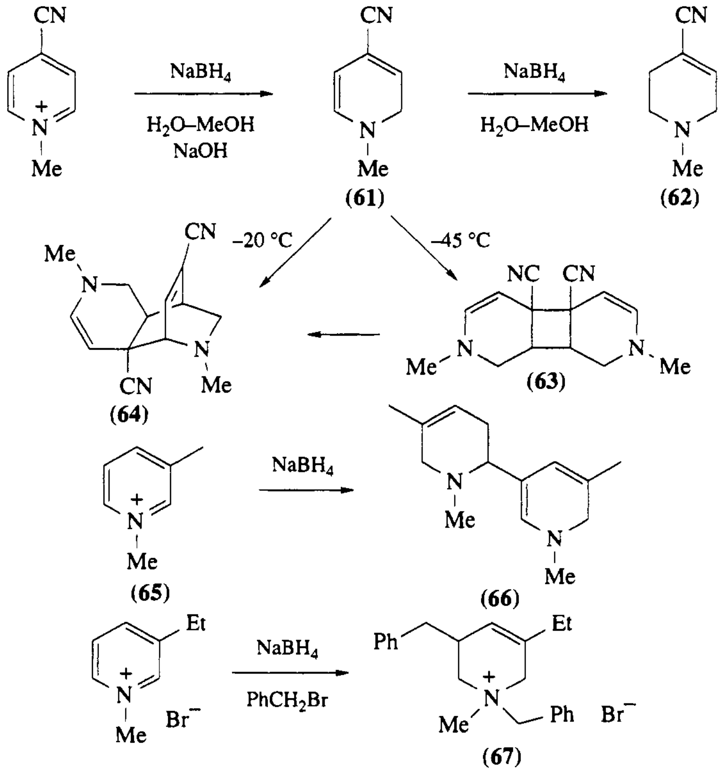
CN
N
Me
NaBH4
H2O–MeOH
NaOH
NaBH4
H2O–MeOH
(61)
(62)
–20 °C
–45 °C
NC
(63)
(64)
(65)
(66)
Et
Br⁻
PhCH2Br
Ph
(67)

**Scheme 14**

When reduced in aqueous methanol, 1-methyl-4-cyanopyridinium iodide gave the tetrahydropyridine derivative (**62**; Scheme 14). In the presence of sodium hydroxide two different products could be isolated at different temperatures, resulting from [2 + 2] (**63**) and [4 + 2] (**64**) cycloadditions, with the latter formed at higher temperatures or by thermal rearrangements of (**63**).[30] Similar behavior has been observed with other pyridinium salts.[31] Other dimerization processes involving dihydropyridines also occur, as with the C(2)–C(3) dimer (**66**) formed *via* enamine–iminium reactivity during the reduction of 1,3-dimethylpyridinium salts (**65**).[32] Conducting reductions in the presence of external electrophiles enables substituted pyridines, *e.g.* (**67**), to be prepared by reaction of the enamine system produced.[33] Benzomorphans and indole alkaloids can be conveniently prepared from reduced pyridines.[34,35] Pyridine *N*-oxides tend to undergo deoxygenation on reduction. *N*-Aminopyridinium salts undergo ring reduction to di- and tetra-hydropyridines, similar to their carbon analogs.[36]

Quinolinium salts (**68**; Scheme 15) can undergo attack at either the 2- or 4-position. The former normally predominates and the latter leads to 1,2,3,4-tetrahydroquinolines (**69**). 3-Substituents generally produce mixtures of the 1,2- and 1,4-dihydro adducts.[5] Isoquinolinium salts (**70**; Scheme 15) produce both 1,2-dihydroisoquinolines (**71**) and 1,2,3,4-tetrahydroisoquinolines (**72**). Reduction in protic solvents normally produces the tetrahydro adducts, in anhydrous pyridine or dimethylformamide the reduction generally stops at the 1,2-dihydroisoquinoline. Reaction of the enamine system of 1,2-dihydroisoquinolines with electrophiles has been used as a method for generation of 4-substituted isoquinolines.[10,37,38] With some 4-substituents reduction with borohydride does not proceed past the dihydro adduct even in protic solvents.[39] Certain 1-(2-nitrophenylmethyl)isoquinolinium salts, *e.g.* (**73**), have been found to undergo substituent cleavage on reduction with borohydride.[40]

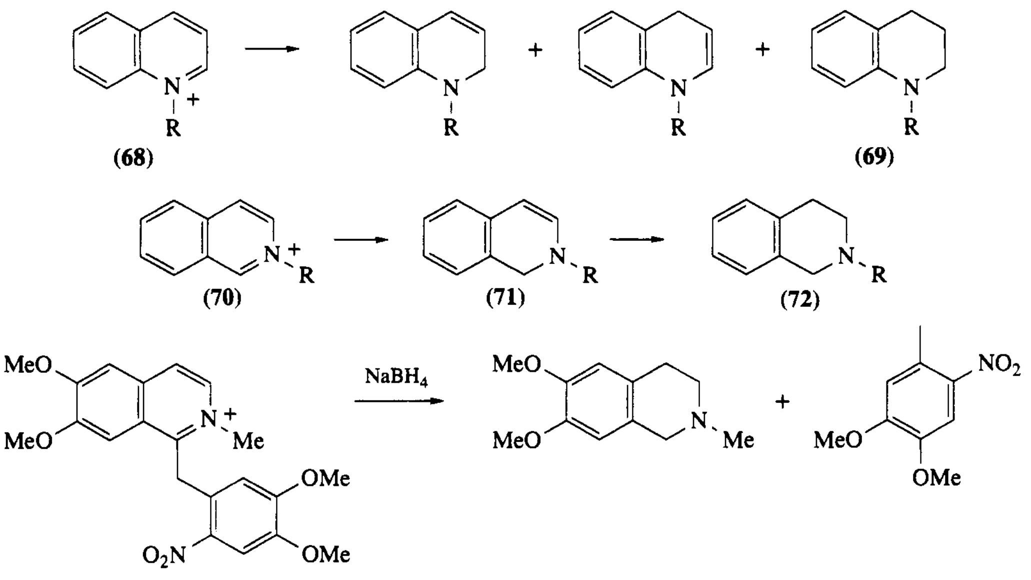

**Scheme 15**

### 3.6.2.1.4 *Pyridinium salts with aluminum hydrides*

Aluminum hydrides react readily with pyridinium species producing both di- and tetra-hydropyridines. Prolonged heating with an excess of the hydride reagent produces 1,3-pentadiene derivatives (**74**; Scheme 16) from C—N bond cleavage as the major product. The preference is for initial 1,2-dihydropyridine formation, as illustrated by the only minor amounts of piperidines (**75**) produced.[41] *N*-Oxides and alkoxypyridinium salts (**76**; Scheme 16) undergo deoxygenation prior to ring reduction, giving tetrahydropyridine (**77**) and piperidine (**78**) along with the parent pyridine. Ring-oxygenated analogs also undergo reduction, the 3-hydroxy-1-phenylpyridinium salt (**79**) produced the tetrahydropyridine (**80**) when treated with LAH in refluxing THF. The 3,2-dimer (**81**) was isolated when the 1-methyl analog was employed.[42]

Quinolinium[43] and isoquinolinium salts form predominantly 1,2-dihydro products with LAH reductions in aprotic solvents. With the latter the enamine system revealed is amenable to functionalization

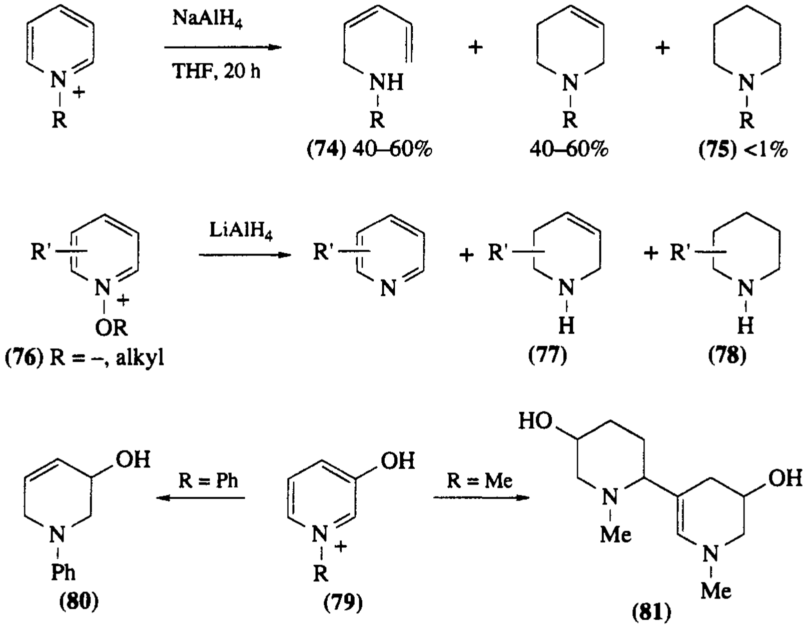
NaAlH$_4$
THF, 20 h
(74) 40–60%
40–60%
(75) <1%
LiAlH$_4$
(76) R = –, alkyl
(77)
(78)
R = Ph
R = Me
(80)
(79)
(81)

Scheme 16

with electrophiles and offers synthetic routes to alkaloids.[38] A variety of useful synthetic transformations have been performed on 1,2-dihydroisoquinolines.[44]

### 3.6.2.1.5 *Other hydrides*

Sodium hydride reduction of quinoline in HMPA leads to a 2:3 mixture of 1,2-dihydroquinoline (**82**) and 1,4-dihydroquinoline (**83**) isolated as the *N*-methoxycarbonyl derivatives.[45] *In situ* produced copper hydride reagents react with pyridinium species with high regioselectivity generating 1,4-dihydropyridine

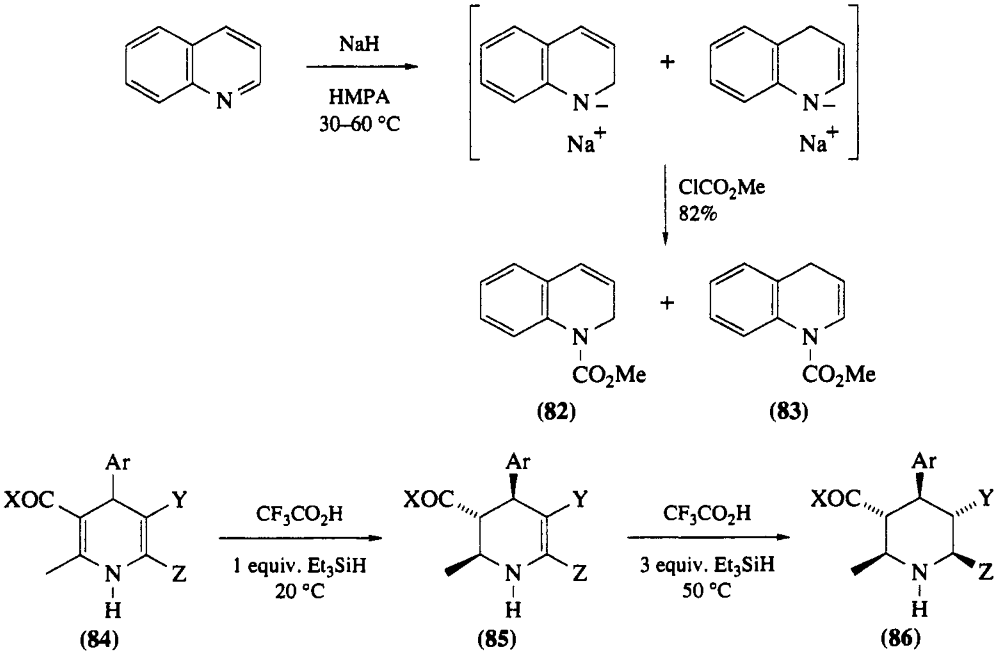
NaH
HMPA
30–60 °C
ClCO$_2$Me
82%
(82)
(83)
CF$_3$CO$_2$H
1 equiv. Et$_3$SiH
20 °C
CF$_3$CO$_2$H
3 equiv. Et$_3$SiH
50 °C
(84)
(85)
(86)

X = Me, OMe; Y = CO$_2$R, COMe, CN; Z = Me, CO$_2$Et

Scheme 17

(see **59** → **60**; Scheme 13; Section 3.6.2.1.3).[29] Magnesium and zinc hydrides produce dihydropyridinyl species, which subsequently reduce ketones, nitriles and heterocycles.[46] Triethylsilane in trifluoroacetic acid conveniently reduces Hantzsch type 1,4-dihydropyridines (**84**; Scheme 17) to all-*trans* isomers of 1,2,3,4-tetrahydropyridines (**85**) and piperidines (**86**). Reduction is controlled by temperature and the number of equivalents of silane employed. Good to moderate yields of products are obtained.[47]

### 3.6.2.2 Reduction of Pyridinium Salts with Dihydropyridines

Heteroaromatic cations undergo reduction when treated with 1,4-dihydronicotinamide.[48] An early study showed that the 10-methylacridinium ion (**87**) was rapidly reduced in a redox reaction to the 9,10-dihydro adduct by 1,4-dihydronicotinamides (**88**; Scheme 18).[49] A variety of systems including pyridines, isoquinolines, quinolines and phenanthridines have been studied using this and related procedures.[48] The selective reduction of pyridinium and quinolinium salts with 1-benzyl-1,2-dihydroisonicotinamide (**89**) has been achieved.[50] The selective conversion to the thermodynamically more stable 1,4-dihydro species (**90**; Scheme 18) is rationalized by the reversibility in the formation of the kinetic products (*i.e.* the 1,2-adducts) in the presence of pyridinium ions. In the pyridinium case 1,6-dihydro adducts were also observed in some cases. Reactivity in such systems is sometimes hindered due to hydration of the dihydropyridine system. This is particularly so in aqueous systems designed to replicate biological activity. Dihydroazines derived from isoquinolines and 3,5-disubstituted pyridines have been reported to overcome some of these difficulties.[51]

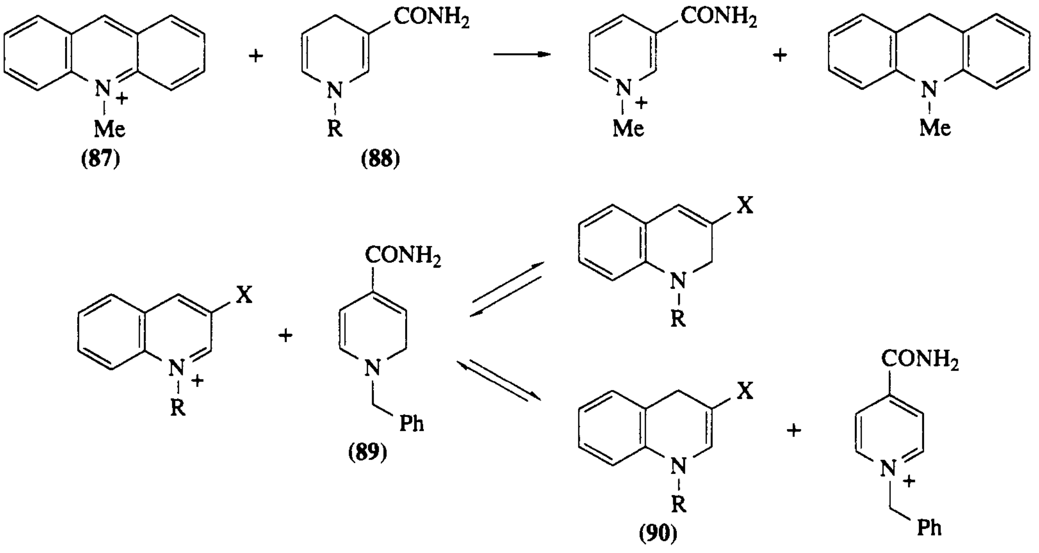

Scheme 18

### 3.6.2.3 Reduction with Sodium Dithionite

Pyridinium salts can be reduced with the mildly nucleophilic dithionite ion to produce mixtures of dihydropyridines. Much work has been carried out since the early observation that NADPH could be obtained from NADP with this reagent.[52] Reduction produces mainly the 1,4-dihydro isomer with minor amounts of the 1,2- or 1,6-dihydro adducts.[53] The reduction is believed to proceed *via* a stable and sometimes isolable sulfinate intermediate (**91**). In acid solution this decomposes with loss of sulfur dioxide to form the dihydropyridine (**92**; Scheme 19). Various substituted pyridinium species undergo this reaction and the isomer ratio obtained is dependent upon the nature of the solvent, temperature and pH.[22,53] With 1-methyl-4-carbamoylpyridinium bromide (**93**) and dithionite in aqueous sodium carbonate at 0–5 °C for 10 min the only isolated product was the 1,2,5,6-tetrahydropyridine (**94**) obtained in 16% yield, but the 3-carbamoyl salt gave the 1,4-dihydronicotinamide (**95**) in 90% yield, free of the 1,6-isomer.[53] The 3-chloropyridinium ion (**96**) gave a moderate yield of the 1,4-dihydropyridine (**97**).

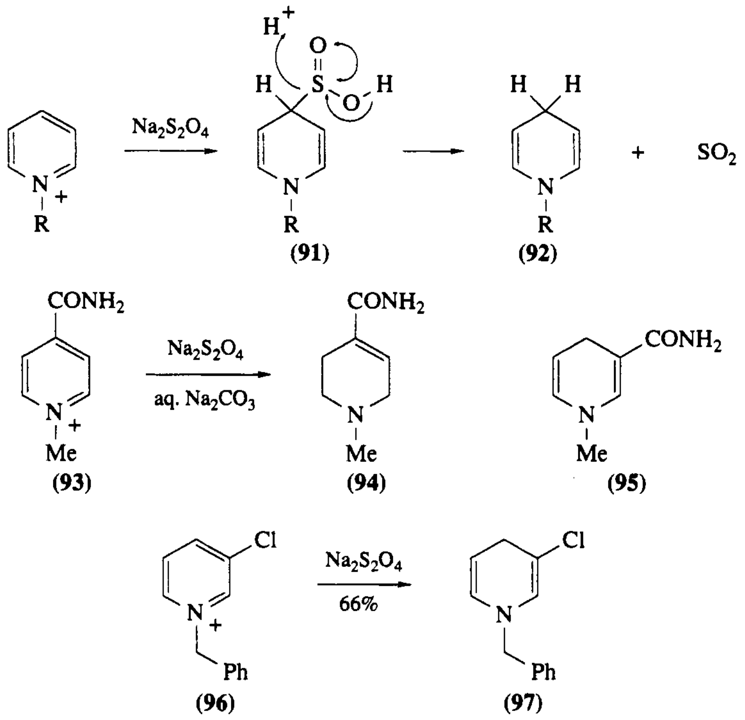
$Na_2S_2O_4$
(91)
(92)
+ $SO_2$
(93)
$Na_2S_2O_4$
aq. $Na_2CO_3$
(94)
(95)
(96)
$Na_2S_2O_4$
66%
(97)

Scheme 19

### 3.6.2.4 Reduction with Formic Acid

The reduction of pyridinium species with formic acid in the presence of its salts at elevated temperatures is often referred to as Lukes reduction and has been reviewed.[54] Mixtures of tetrahydropyridines (**98**) and piperidines (**99**; Scheme 20) commonly result. The isolated double bond is resistant to further reduction under these conditions. Reductive cleavage and subsequent cyclization have also been observed, producing ketones as by-products.[55]

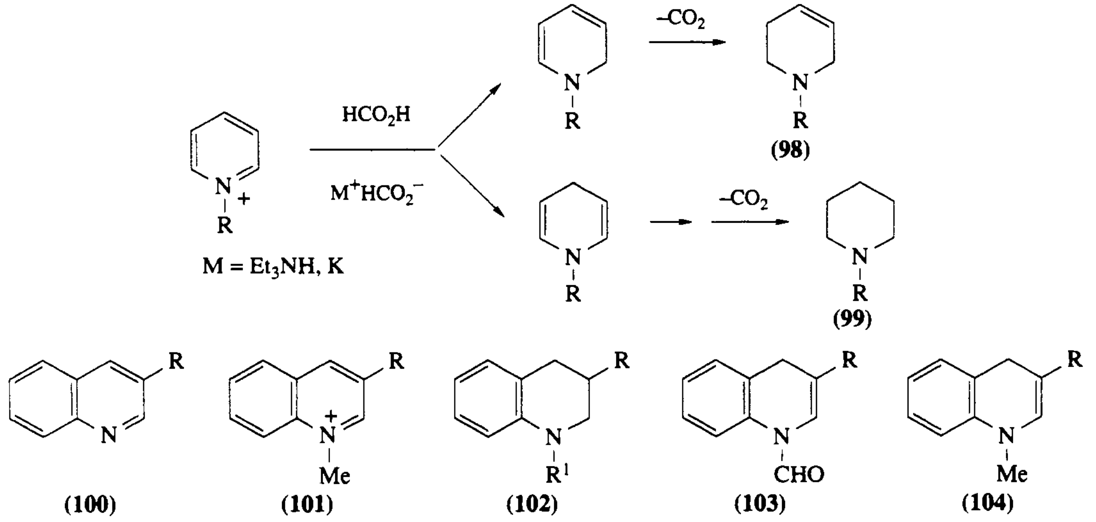
$HCO_2H$
$M^+HCO_2^-$
M = $Et_3NH$, K
$-CO_2$
(98)
$-CO_2$
(99)
(100)
(101)
(102)
(103)
(104)

R = OH, OMe, MeCO, $CONH_2$; $R^1$ = Me, CHO

Scheme 20

On reduction with triethylammonium formate, quinolines (**100**) and their 1-methylquinolinium salts (**101**) possessing an electron-donating group in the 3-position gave the *N*-formyl- and the *N*-methyl-1,2,3,4-tetrahydroquinolines (**102**) as the major products. With electron-withdrawing groups present the quinolines produced mixtures of (**102**; $R^1 = CHO$) and the 1,4-dihydroquinolines (**103**), (**101**) gave only (**104**) under the same conditions.[56] The 2-, 3- and 4-methylquinolines, hydroxymethylquinolines, carbaldehyde- and cyano-quinolines and their quaternary salts produce a variety of ring-reduced and substituent-modified products on reaction with triethylammonium formate.[57] Formates have also been used to reduce NADP mimics to 1,4-dihydropyridines.[58] Catalytic hydrogen transfer has also been achieved with ruthenium complexes in the presence of formic acid. 2-Methyltetrahydroquinoline is produced on heating 2-methylquinoline and the ruthenium–phosphine complex $RuCl_2(PPh_3)_2$ in the presence of formic acid.[59]

### 3.6.2.5 One-electron Reduction

Dissolving metal and electrochemical reduction are some of the oldest reactions known. Both occur with initial electron transfer to give, in the case of pyridines (**105**), the radical anion (**106**; Scheme 21), which can then react with a proton or with another radical leading to dimerization (**107**). Dimerization is therefore expected to be the major product in aprotic solvents. Reductions are more successful when labile hydrogens are available, generating dihydropyridines (**108**) and (**109**), tetrahydropyridine (**110**) and piperidine (**111**). Dissolving metal reductions have to a large extent been superseded by metal hydride reductions or catalytic hydrogenation. However, in certain applications, *i.e.* Birch reductions, they are still widely used. Electrochemical reductions proceed by similar mechanisms and are prone to the same dimer formation reactions mentioned above.

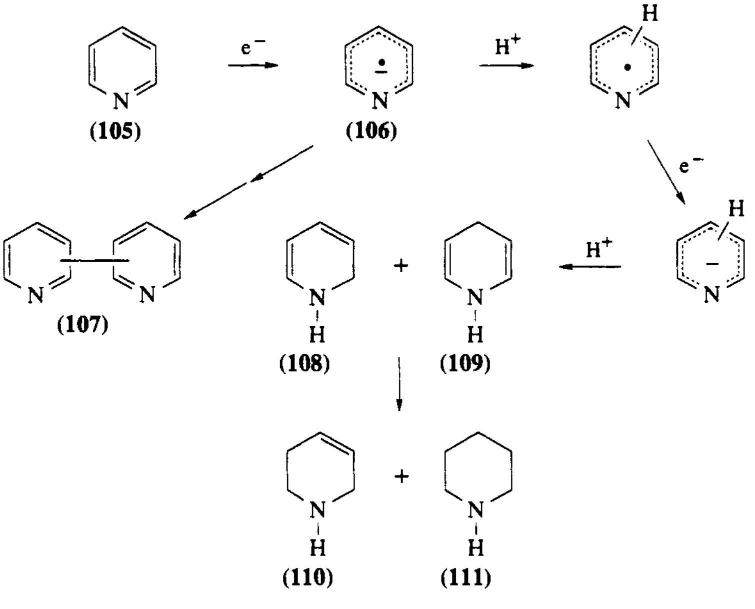

**Scheme 21**

#### *3.6.2.5.1 Electrochemical reduction of pyridines*

The electrochemical behavior of pyridines has been reviewed.[60–62] As usual, electron-withdrawing groups facilitate reduction, which occurs at the cathode and is most often carried out in aqueous sulfuric acid. However, polar aprotic solvents (*e.g.* MeCN, DMF) and liquid ammonia have been used for the polarographic reduction of pyridine.[60] Pyridine, itself, was first reduced to piperidine (**111**) at a lead cathode in 10% sulfuric acid nearly 100 years ago,[63] with dimeric piperidines also formed. Among partially reduced pyridines only 1,2,5,6-tetrahydropyridine (**110**) has been reported, the unpolarizable double bond being incapable of further reduction. Alkylpyridines similarly generate mixtures of alkylpiperidines and alkyl-1,2,5,6-tetrahydropyridines.[61] In some cases the tetrahydropyridine predominates, as do the all-*cis* products. In the presence of aldehydes and ketones the reductive alkylation of both pyridine and alkylpyridines to alkylpiperidines and tetrahydropyridines is achieved. Both carbon and nitrogen alkylation have been reported but 2-piperidinecarbinols (**112**; Scheme 22) and 4-piperidinecarbinols (**113**) predominate, along with minor amounts of the di- and tri-alkylated products. This reaction is related to the Emmert reaction. Dihydropyridines also undergo electroreduction, the 1,4-dihydropyridine (**115**) was further reduced to the tetrahydropyridine (**116**) in moderate yield at a mercury cathode in tetraethylammonium tetrafluoroborate solution.[64]

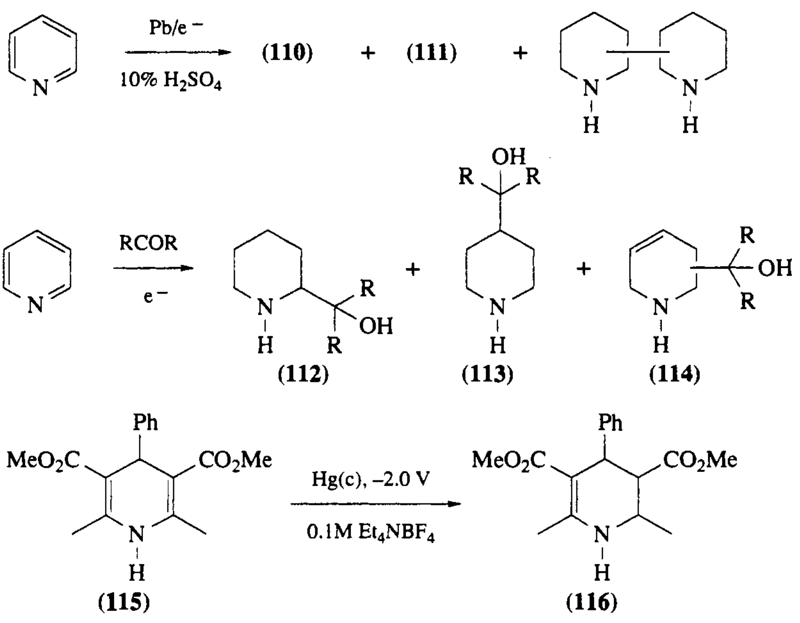

Scheme 22

Electroreduction of pyridine derivatives bearing carboxylic acid derivatives (**117**; Scheme 23) leads to a variety of products from substituent transformation through ring reduction to ring cleavage.[61]

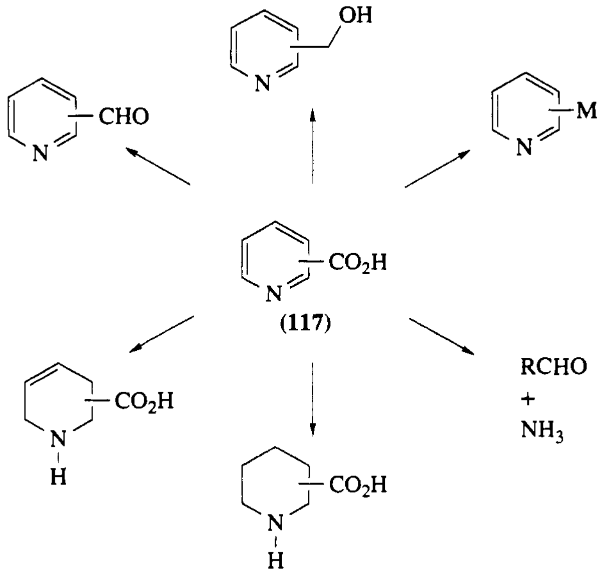

Scheme 23

Nicotinamide (**118**) forms the 1,6-dihydropyridine (**119**) and the 6,6′-dimer (**120**) upon polarography in aqueous solution.[65] The 4-isomer (**121**; Scheme 24) generates the aldehyde (**122**) when reduced in 0.8 M hydrochloric acid and the alcohol (**123**) in an alcoholic citric acid buffer solution. The thioamides produce the 4-aminomethyl- or 4-cyano-pyridines under related conditions.[66] The isomeric cyanopyridines

(**124**) can undergo a variety of reactions including pyridine formation, dimerization with and without nitrile cleavage as well as reduction of the cyano group to the aminomethylpyridines (**125**).[67]

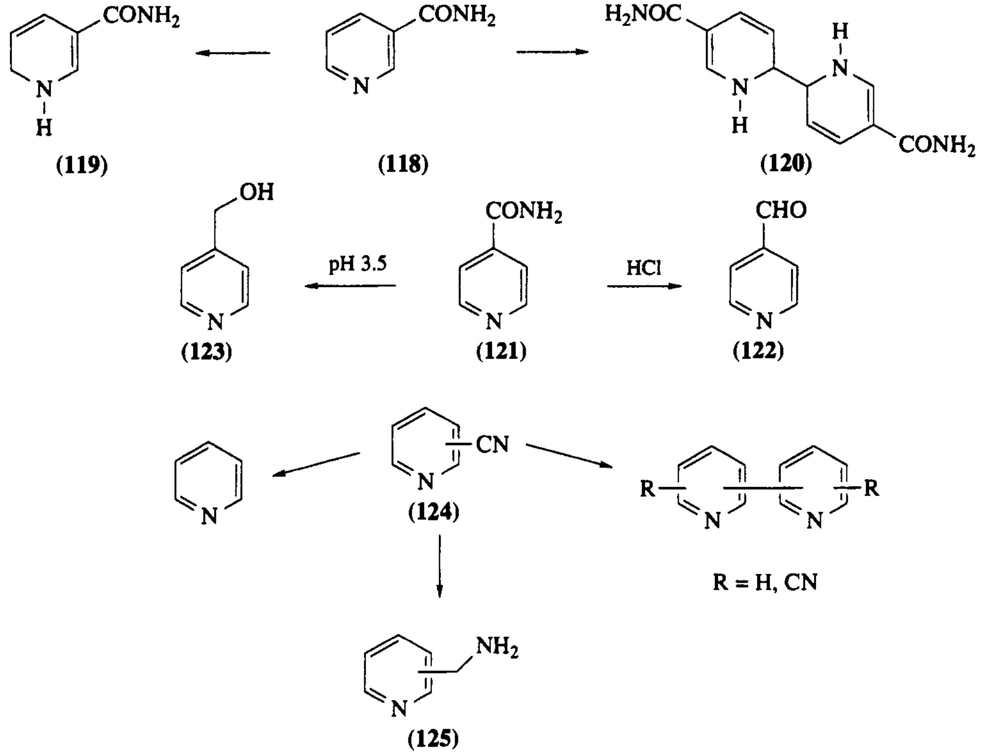
CONH2
CONH2
H2NOC
CONH2
(119)
(118)
(120)
OH
CONH2
CHO
pH 3.5
HCl
(123)
(121)
(122)
CN
(124)
R = H, CN
NH2
(125)

**Scheme 24**

Nitropyridines exhibit substituent reductions including through-nitrogen (azo/azoxy) coupling. Aminopyridines have been found to be unreducible when using voltammetry.[68] Hydroxypyridines and pyridones generally yield mixtures of piperidines and 1,2,5,6-tetrahydropyridines. Halogenated derivatives

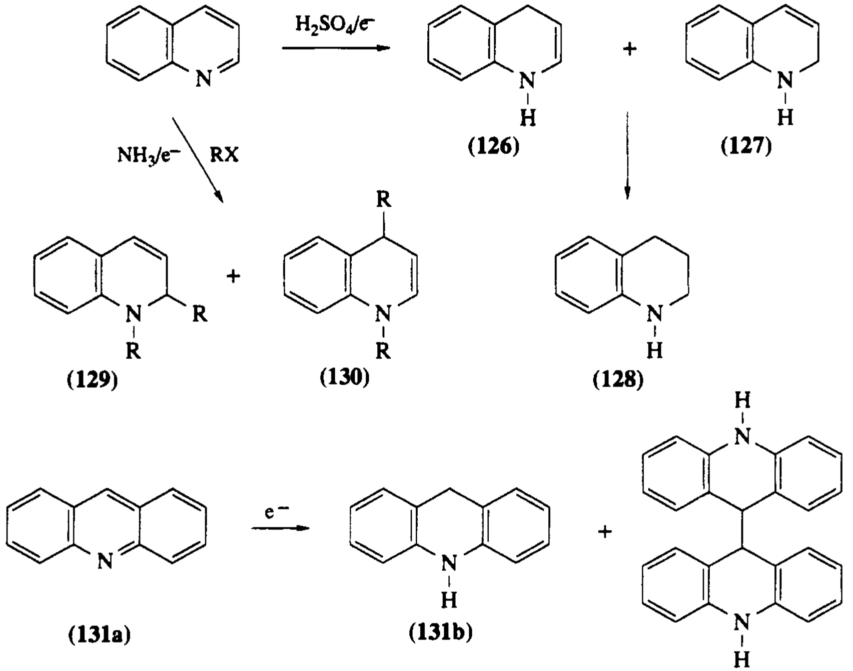
H2SO4/e⁻
(126)
(127)
NH3/e⁻
RX
(129)
(130)
(128)
e⁻
(131a)
(131b)

**Scheme 25**

tend to undergo dehalogenation on electroreduction.[69] *N*-Oxides undergo preferential deoxygenation i most cases, some overreduction or substituent reaction may occur.[70]

Quinoline and isoquinoline undergo reduction more readily than does pyridine. In aqueous sulfuri acid quinoline forms both dihydroquinolines (**126** and **127**) and tetrahydroquinolines (**128**). In nonaqueous media (DMF, liquid ammonia) the anion radical may be quenched by alkyl halides to generat both 1,2-dialkyldihydroquinolines (**129**) and 1,4-dialkyldihydroquinolines (**130**).[71] The product distribution is dependent on the nature of the alkylating agent. With isoquinoline preferential alkylation in th benzene ring has been found to occur in some cases.[72] Acridine (**131a**) is reduced to 9,10-dihydro derivative (**131b**) both in acidic and alkaline aqueous solution; 9,9′-dimerization also occurs.

### *3.6.2.5.2 Electrochemical reduction of pyridinium salts*

In deference to their biological significance much work has been done on this class of compound a model studies to analyze or mimic the behavior of pyridine nucleotides and bipyridinium herbicides, pyridinium ions (**132**; Scheme 26) being more susceptible to reduction. Dimerization is a common fate o the neutral radical formed. The most thermodynamically stable product, the 4,4′-bipyridyl species predominate, and other dimers can sometimes rearrange to the 4,4′-bipyridyl isomer.[73] Radicals with merc

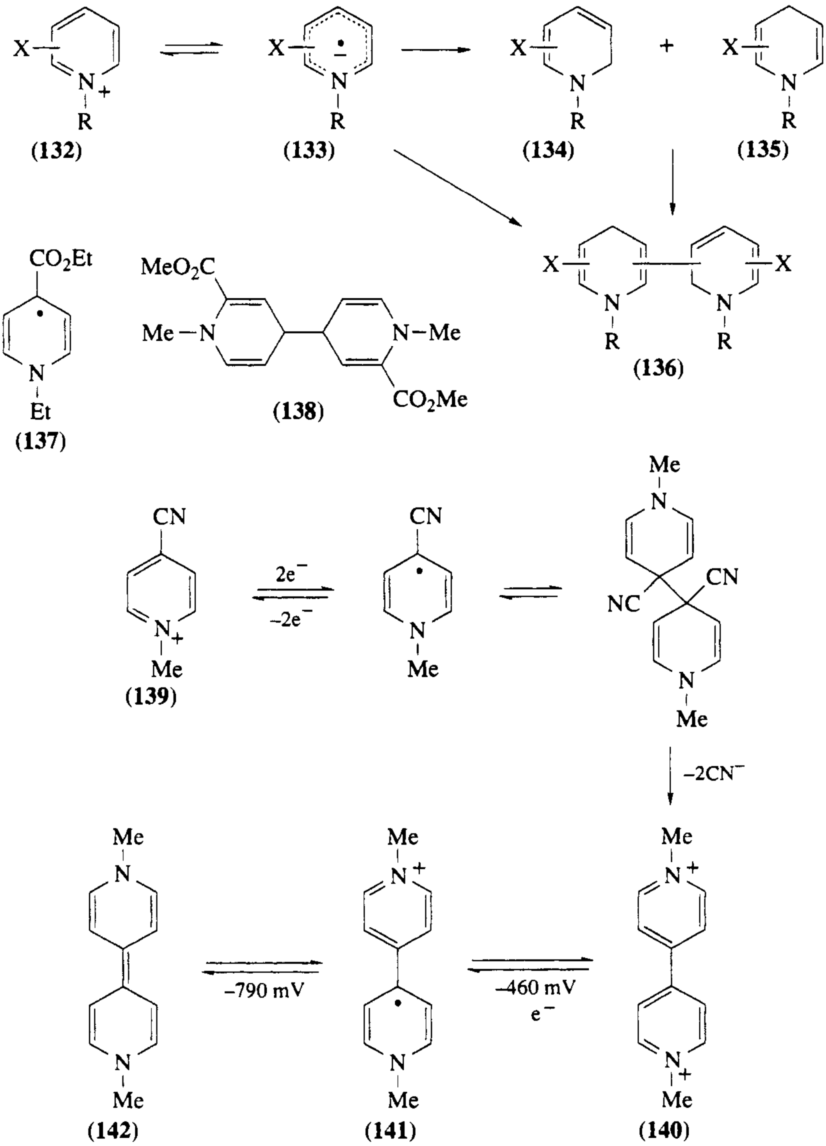

**Scheme 26**

stabilization by an α- or δ-substituent are surprisingly stable, the radical (**137**) even surviving distillation. Methyl *N*-methyl-2-pyridiniumcarboxylate, methyl *N*-methyl-3-pyridiniumcarboxylate, and methyl *N*-methyl-4-pyridiniumcarboxylate radicals are stabilized in the order 4 > 2 > 3. The 4-ester forms a stable radical, the 3-isomer dimerizes irreversibly, and the 2-isomer dimerizes reversibly to the bipyridine (**138**). Dimerization can occur with both ionic or radical species. Polarographic reduction of 4-cyano-1-methylpyridinium salts (**139**; Scheme 26) suggested that reversible radical formation was followed by irreversible anion generation and dimerization.[74] Loss of cyanide generates the potent herbicidal bipyridinium species (**140**).[75] The ion radical, *e.g.* (**141**), has been proposed as one of the reactive intermediates responsible for the biological effects exhibited by these molecules. The intermediacy of pyridinyl radicals has also been proposed in NADP/NADH(H) interconversion. Pyridinium species have been used as coatings or additives in attempts at the surface modification of electrodes and subsequently to increase selectivity on reduction.[76]

When the pyridinium ring bears reducible substituents reduction in acidic media favors substituent reductions. At high pH, dimers and dihydropyridine are the primary products. Thus, methyl *N*-methyl-2-pyridinecarboxylate (**143**) generates either the alcohol (**144**) or the dimer (**145**), depending on the pH of the electrolyte.[73,75] In the case of 4-nitroarylpyridinium salts (**146**; Scheme 27) preferential ring rather than substituent reduction occurred. Under the conditions employed (graphite or platinum electrodes in MeCN) no ring reduction was observed in the absence of the nitro group. The specific orientation of the nitro group was also found to be important, the wave potential being 50–160 mV more negative when *meta* than for the *ortho* and *para* isomers.[77] Cathodic reduction of *N*-amino- and *N*-acylamino-pyridinium ions (**147**) cleaves the N—N bond, forming the pyridine and the amine or amide species, respectively.[78]

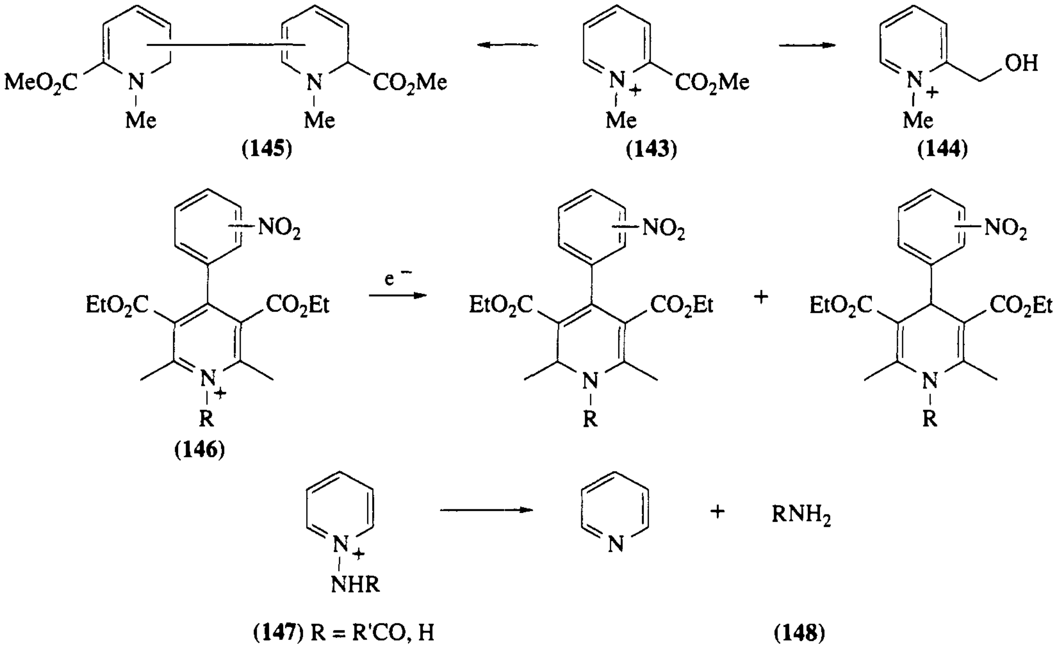

Scheme 27

### 3.6.2.5.3 *Dissolving metal reductions*

The reduction of organic compounds with metals has been known for a long time. The relative reducing powers of the metals are in accordance with their electrode potentials and the alkali and some alkaline earth metals are capable of reducing a large number of functionalities, including the pyridine ring.[79] When carried out in the presence of a proton source dimerization of the initial radical ions formed is supressed. Thus, sodium in alcohols (Ladenburg reduction)[80] will reduce pyridines to mixtures of tetrahydropyridines (**110**) and piperidines (**111**) as with electroreduction (Section 3.6.2.5.1) and reaction with metal hydrides (Section 3.6.2.1.5). The position of initial attack will dictate which product is finally

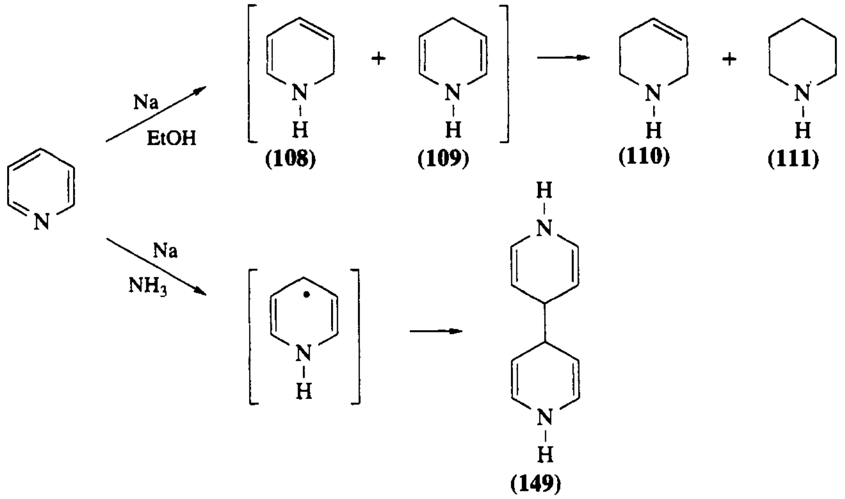

Na
EtOH
(108)
(109)
(110)
(111)
Na
$NH_3$
(149)

**Scheme 28**

formed. In aprotic solvents sodium produces tetrahydrobipyridyls (**149**) *via* dimerization of the radical ion formed. Alkylpyridines behave similarly. Ferles has studied reductions of this type with a variety of carbonyl and carboxylic acid derivatives.[54,81] Bipyridines are found as by-products in the Chichibabin reaction.[82]

Sodium in liquid ammonia and ethanol reduces quinoline to 1,2-dihydroquinoline (**150**; Scheme 29)[83] and isoquinoline to tetrahydroisoquinoline (**151**).[84] Zinc and formic acid can also be used. Using higher

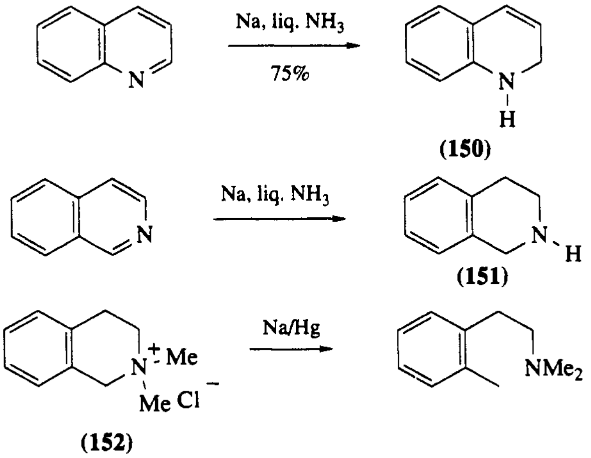

Na, liq. $NH_3$
75%
(150)
Na, liq. $NH_3$
(151)
Me
Me Cl
Na/Hg
$NMe_2$
(152)

**Scheme 29**

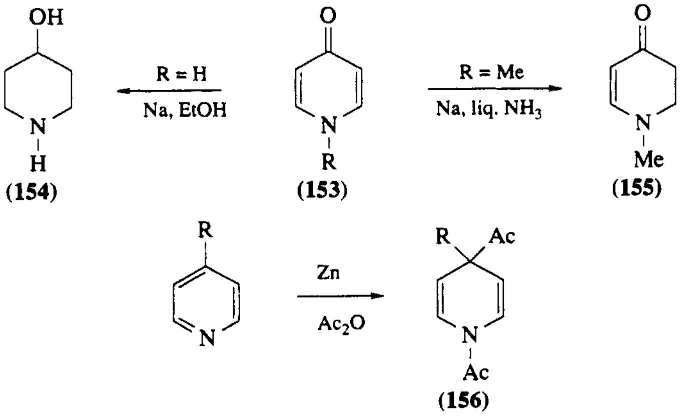

OH
R = H
Na, EtOH
O
R = Me
Na, liq. $NH_3$
O
(154)
R
(153)
Me
(155)
R
Zn
$Ac_2O$
R
Ac
Ac
(156)

**Scheme 30**

boiling alcohols (*n*-butyl or *t*-butyl alcohols; Birch reduction) can lead to further reduction. Sodium amalgam reductions generally proceed only on pyridinium ions. However, a variant of the Hofmann degradation, the Emde degradation, will cause reductive cleavage of quaternary nitrogen species (*e.g.* **152**).[85]

4-Pyridone (**153**) is converted to 4-hydroxypiperidine (**154**; Scheme 30) by sodium in ethanol. However, with sodium or lithium in liquid ammonia *N*-methyl-4-pyridone (**153**; R = Me) produced the dihydropyridone (**155**) in moderate yield.[86] Higher conversions were achieved with sodium tetraalkoxyaluminates. Pyridines are generally not reducible by zinc and carboxylic or hydrochloric acids. However, zinc and acetic anhydride converts 4-substituted pyridines to their 1,4-diacyldihydropyridine derivatives (**156**).[87] Tetrahydrobipyridyls have also been found in this reaction.[88] Pyridinium ions are reduced more easily and give mixtures of tetrahydropyridines and piperidine. Substitutents may also be reduced. Zinc and hydrochloric acid along with tin and hydrochloric acid effect complete reduction of the pyridinium ring.

## 3.6.3 HYDROGENATION

Catalytic hydrogenation is the most frequently employed method of saturating the pyridine ring. Complete reduction to the piperidine normally occurs, the intermediates formed being reactive under the conditions employed. Heterogeneous catalysts continue to be the most popular method for a variety of uses ranging from the synthesis of intermediates to the denitrogenation of fossil fuels. Extensive reviews on the reduction of pyridines have been published.[79,89–93]

For low pressure hydrogenation both supported and unsupported platinium (as its oxide) are effective, however, rhodium is the more effective under mild conditions. Nickel is used at higher pressures and temperatures and *N*-alkylation may occur when alcohols are present. Palladium and ruthenium have likewise been used for a variety of pyridine derivatives. Reductions of pyridine compounds are often carried out in acidic media, as the strongly coordinating amines formed on hydrogenation frequently cause catalyst inhibition. At elevated temperatures hydrogenolysis of the carbon–nitrogen bond can also occur. Generally, the rate of this cleavage is only significant above 120 °C but will obviously depend on the nature of the substituents. Alkylamines, ammonia and alkanes are generally produced. Pyridine and its derivatives may also be reduced by Raney nickel with 2-propanol as the hydrogen source *via* its dehydrogenation to acetone and catalytic hydrogen transfer.[94] Similarly, nickel–aluminium alloy in potassium hydroxide reduces pyridines (*e.g.* **157**; Scheme 31), quinolines and isoquinolines in moderate to high yields,[95] but much higher metal/substrate ratios are required. The accelerating effects of 2-substituents has been observed both in traditional high pressure hydrogenation with nickel or ruthenium and in catalytic transfer hydrogenation.[95] 2-Methylpyridine (**157**) is hydrogenated at a faster rate than pyridine itself. Indeed, 2-methylpyridine can be hydrogenated in the presence of 3- and 4-methylpyridine, this is most likely due to a reduced propensity toward catalyst poisoning due to steric effects, and with 2,6-di-

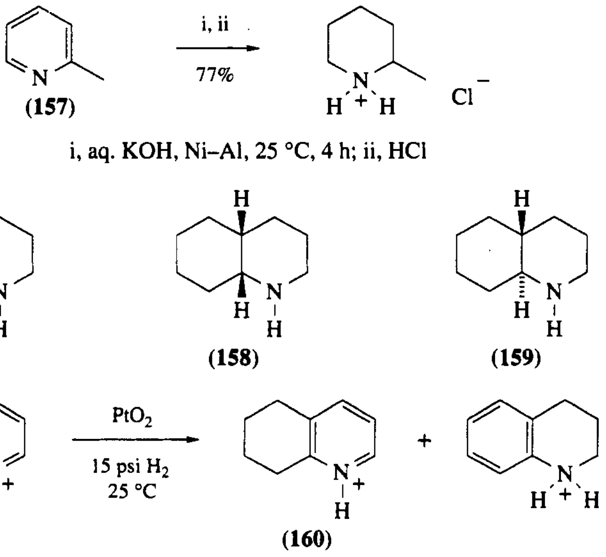

i, aq. KOH, Ni–Al, 25 °C, 4 h; ii, HCl

**Scheme 31**

methylpyridine an additional rate enhancement is observed. However, nonplanar 2-phenylpyridine is hydrogenated more slowly due to the impedance of nickel adsorption to the catalyst surface. In the case of quinoline, hydrogenation with nickel occurs rapidly and preferentially in the pyridine ring, generating 1,2,3,4-Tetrahydroquinoline (**128**). Extended hydrogenation times or more forcing conditions generate *cis*-decahydroquinolines (**158**) and *trans*-decahydroquinolines (**159**). 1,2,3,4-Tetrahydroquinolines can be generated exclusively on hydrogenation with a variety of catalysts.[96] Selective reduction of the benzene ring, however, is more difficult, generating mixtures of tetrahydroquinolines. Some selectivity can be achieved by reduction of quinolines in strong acid over platinum.[97] The major product is the 5,6,7,8-tetrahydroquinoline derivative (**160**; Scheme 31). This effect is more pronounced in the isoquinoline series.

Isoquinoline itself hydrogenates less readily than does quinoline. Studies of the catalytic hydrogenation of isoquinoline over Raney nickel have shown that the reaction proceeds consecutively *via* 1,2,3,4-tetrahydroisoquinoline (**161**), 5,6,7,8-tetrahydroisoquinoline (**162**) and *cis*-decahydroisoquinoline (**163**) to *trans*-decahydroisoquinoline (**164**).[98] Acridine undergoes similar hydrogenative isomerizations with supported Pd.[99] Both *cis*- and *trans*-1,2,3,4,4a,9,9a,10-octahydroacridines were formed at 150 °C and only three (**165**, **166** and **167**) of the six possible stereoisomers of perhydroacridine were found, with (**165**) and (**166**) predominant. Alumina was preferred to carbon as a support.[100]

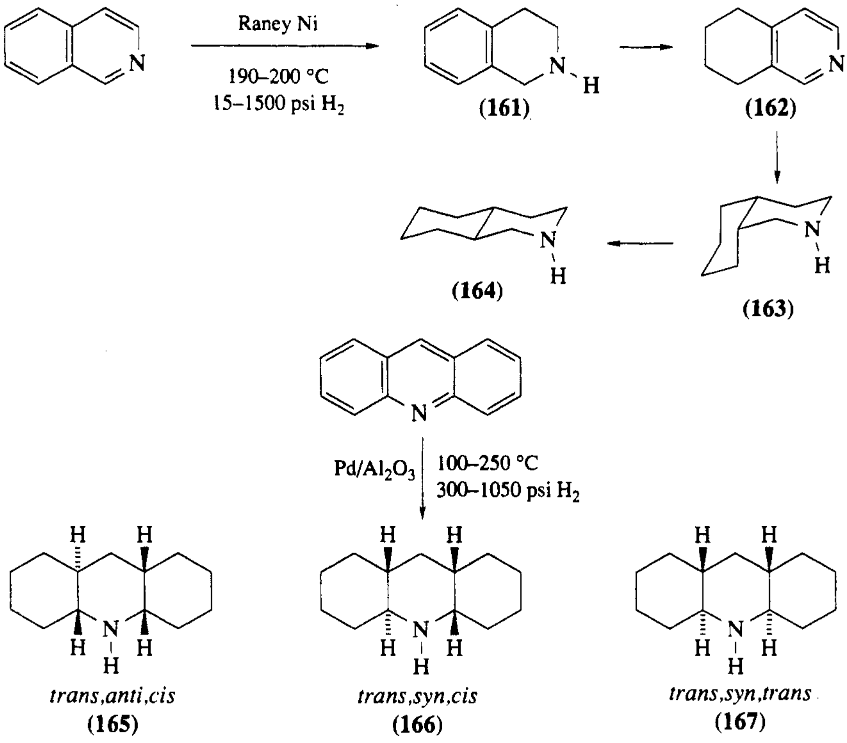

**Scheme 32**

The hydrogenation of amino- and hydroxy-pyridines is controlled to a large extent by the tautomeric forms in which they prefentially exist. 2-Aminopyridines (Scheme 33) are reduced to the amidine (**168**) by Pt, Rh or Ru, which is resistant to further hydrogenation but will undergo hydrogenolysis to piperidine (**169**) and the amine (**170**). 3-Aminopiperidine (**171**) forms readily when the parent heterocycle is hydrogenated over $PtO_2$ in hydrochloric acid. However, 4-aminopyridine requires much higher pressures for reduction to 4-aminopiperidine (**172**). 2- and 4-pyridones (Scheme 33) generate 2-piperidone (**173**) and 4-hydroxypiperidine (**174**), respectively, when hydrogenated in acetic acid. 2-Pyridone is hydrogenated more readily using Pt.[90] Equal rates of hydrogen uptake were observed, however, when Pd on carbon was used. Varying degrees of hydrogenolysis are observed on reduction of 3-hydroxypyridine to 3-hydroxypiperidine.

Pyridines containing electron-withdrawing groups may undergo only partial ring reduction. Functional groups which readily undergo hydrogenation, *e.g.* nitro and cyano, will be reduced prior to the heteroaromatic ring, whereas those groups strongly resistant to reduction, *e.g.* carboxylic acids and esters, will survive ring reduction unchanged. In addition, when a product can be a vinylogous amide (*e.g.* **175**; Scheme

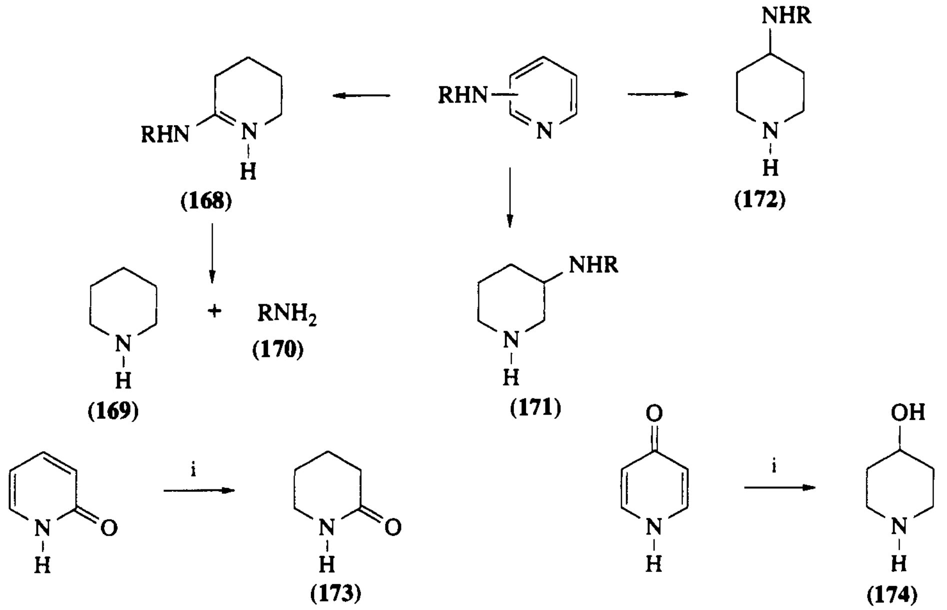
RHN
N
H
(168)
RHN
N
NHR
N
H
(172)
N
H
(169)
+ RNH2
(170)
NHR
N
H
(171)
N
O
H
i
N
O
H
(173)
O
N
H
i
OH
N
H
(174)

i, PtO$_2$, 20 °C, 15 psi H$_2$

**Scheme 33**

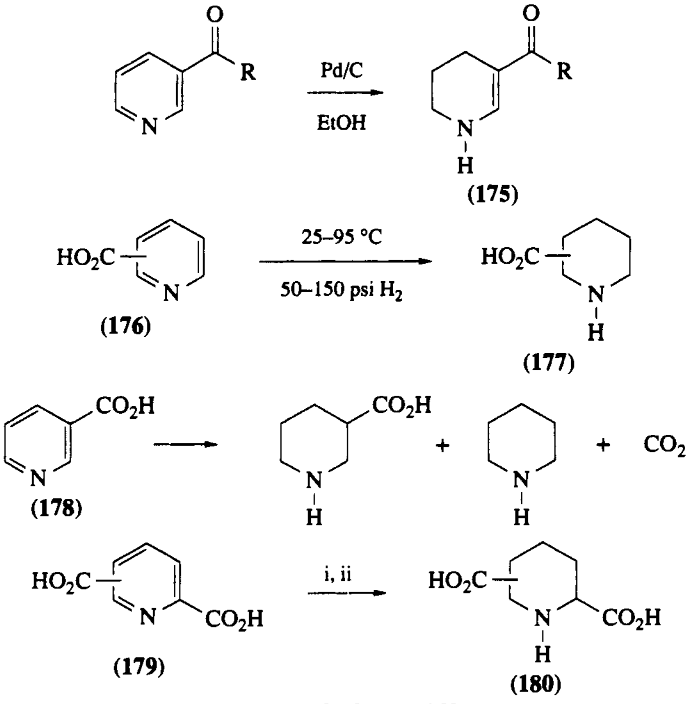
O
R
N
Pd/C
EtOH
O
R
N
H
(175)
HO2C
N
(176)
25–95 °C
50–150 psi H2
HO2C
N
H
(177)
CO2H
N
(178)
CO2H
N
H
+
N
H
+ CO2
HO2C
N
CO2H
(179)
i, ii
HO2C
N
CO2H
H
(180)

i, HCl; ii, Pt, 20 °C, 15 psi H$_2$

**Scheme 34**

34), it generally resists further hydrogenation. The pyridine monocarboxylic acids (**176**) are reduced readily to their piperidine derivatives (**177**) over Rh, Pd or Ru under increasingly forcing conditions. Platinum may also be used for this conversion. In the case of nicotinic acid (**178**), piperidine, the product of decarboxylation, is also formed. This can be prevented by the addition of an equivalent of inorganic base when using Pt or Rh. Hydrogenation of pyridinedicarboxylic acids (**179**) over platinum in hydrochloric acid gives the *cis*-piperidinedicarboxylic acids (**180**).[101] Pyridinium salts are reduced more readily than pyridines, the tertiary amines formed do not inhibit catalyst activity. Partial hydrogenation as in the free pyridines may also occur. In the case of pyridine *N*-oxides deoxygenation generally occurs first.

Hydrogenation with homogeneous catalysis has received increasing attention over the last few decades.[93] Hexarhodium hexadecacarbonyl (**181**; Scheme 35) under water gas shift conditions forms 1,2,3,4-tetrahydroquinoline (**128**) or *N*-formyl-1,2,3,4-tetrahydroisoquinoline (**182**) with the parent heteroaromatic.[102] When hydrogen is substituted for carbon monoxide, 4-methylquinoline is reduced to 4-methyl-5,6,7,8-tetrahydroquinoline (**183**) exclusively.[102] Isoquinoline behaves similarly generating *N*-formyl-1,2,3,4-tetrahydroisoquinoline (**184**). Similar reductions under water gas shift or synthesis gas conditions using transition metal carbonyls derived from Mn, Co and Fe, have been recorded.[103,104] Promotion by phase transfer agents is observed in some cases.

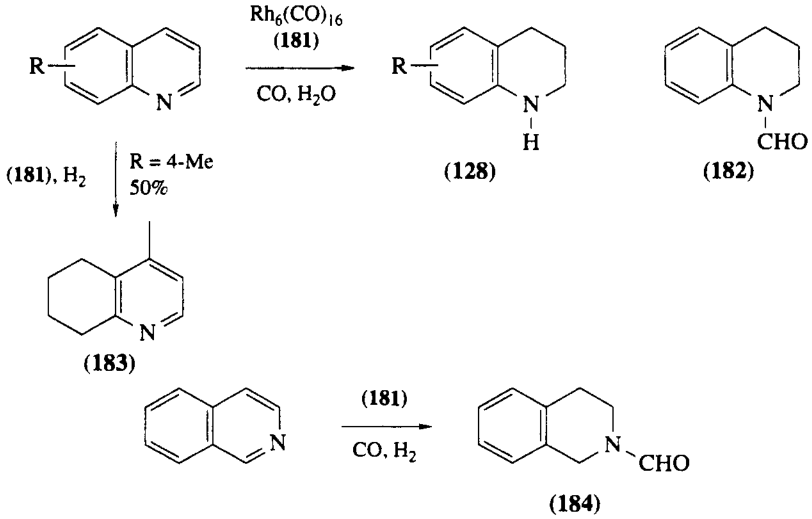

**Scheme 35**

Styrene–divinylbenzene copolymer supported chlorotris(triphenylphosphine)rhodium was also found effective for the regioselective reduction of quinoline and acridines.[105] The supported catalyst was more active than its homogeneous analog. Rhodium supported on soluble organic polymers as macroligands, showed sufficient activity so as to allow the hydrogenation of pyridine to piperidine under mild conditions.[106] The partial reduction of *N*-alkyl-3-carbamoylpyridinium salts (**185**) proceeded selectively when bis(dimethylglyoximate)chloro(pyridine)cobalt (**186**; $CoCl(DMG)_2Py$) was employed as catalyst. When sodium hydrogencarbonate was present no overreduction was observed. An increased preference for 1,4-dihydropyridines (**187**) over 1,2-dihydropyridines (**188**) and 1,6-dihydropyridines (**189**) was observed.[107]

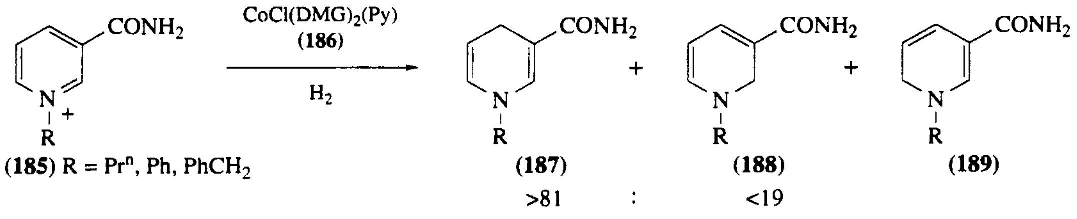

**Scheme 36**

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# 3.7

# Partial and Complete Reduction of Pyrroles, Furans, Thiophenes and their Benzo Analogs

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## 3.7.1 INTRODUCTION

A fundamental chemical tactic in the synthetic manipulation of heterocycles by organic chemists is the reduction of the heterocyclic ring. This chapter will review advances in the partial and complete reduction of pyrroles, furans, thiophenes and their benzo analogs, indoles, benzo[*b*]furans and benzo[*b*]thiophenes. As appropriate, coverage will include the reduction of those benzo analogs of lesser interest: isoindole, carbazole, benzo[*c*]furan (isobenzofuran), dibenzofuran and dibenzothiophene.

Unlike alkenes and π-deficient heterocycles, such as pyridine, quinoline and isoquinoline, the π-excessive heterocycles that are the subject of the present chapter are inherently more difficult to reduce. Nonetheless, many new and extremely useful reduction technologies for these classes of heterocycles have been developed over the past decade. It is these advances that will be the main focus of this chapter.

## 3.7.2 REDUCTION OF PYRROLES

### 3.7.2.1 Catalytic Hydrogenation

The catalytic hydrogenation of pyrroles to pyrrolidines (2,3,4,5-tetrahydropyrroles), although an old transformation (equation 1),[1,2] has not been heavily exploited as a preparative route to pyrrolidines. Nevertheless, sufficient examples exist so as to illustrate the importance of this method. As would be expected, the hydrogenation of 2,5-disubstituted pyrroles proceeds with *cis* stereoselectivity (equation 2).[3,4]

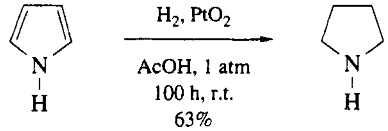

(1)

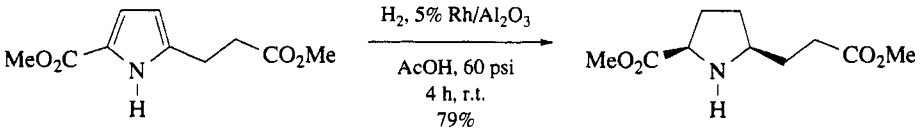

(2)

From the several examples that have been reported (equations 1 and 2, and *vide infra*), it seems evident that rhodium is superior to platinum and palladium as the hydrogenation catalyst for the reduction of pyrroles. For example, the hydrogenation of fused pyrrole (**1**) affords pyrrolizidine (**2**) in excellent yield (equation 3),[5] and, in a synthesis of anatoxin *a*, Bates and Rapoport found that pyrrole ester (**3**) gives (**4**) upon rhodium-catalyzed hydrogenation (equation 4).[6] The latter transformation does not proceed with a platinum catalyst. In a synthesis of 2-acetyl-1-pyrroline, an important aroma component of cooked rice, Buttery and coworkers hydrogenated 2-acetylpyrrole to 2-(1-hydroxyethyl)pyrrolidine using $Rh/Al_2O_3$.[7] Whereas Labouta *et al.* found that $Rh/Al_2O_3$ effects the hydrogenation of the pyrrole ring and the propenoic acid unsaturation in (**5**), leading to the γ-aminobutanoic acid (GABA) analog (**6**; equation 5),[8] Paine and Dolphin were able to remove selectively the benzyl group in (**7**) using Pd/C without

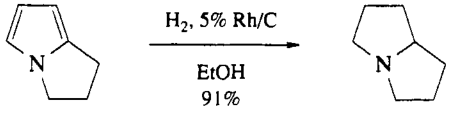

(3)

**(1)** **(2)**

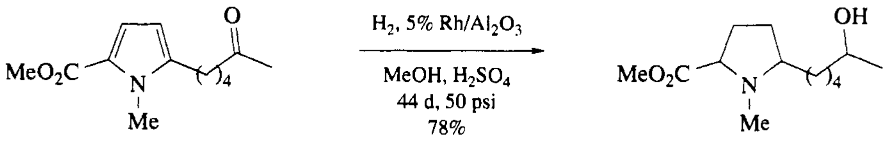

(4)

**(3)** **(4)**

hydrogenating the pyrrole ring (equation 6).[9] The pyrrole ring in carbamate (**8**) can be cleanly hydrogenated using rhodium as the catalyst (equation 7).[8]

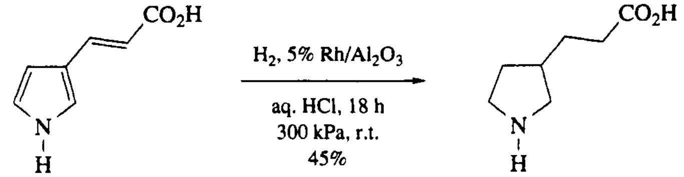
$CO_2H$
$H_2$, 5% $Rh/Al_2O_3$
aq. HCl, 18 h
300 kPa, r.t.
45%
$CO_2H$
N
H
N
H

(**5**) (**6**)

(5)

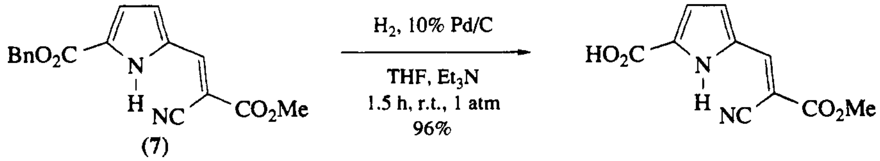
$BnO_2C$
N
H
NC
$CO_2Me$
$H_2$, 10% Pd/C
THF, $Et_3N$
1.5 h, r.t., 1 atm
96%
$HO_2C$
N
H
NC
$CO_2Me$

(**7**)

(6)

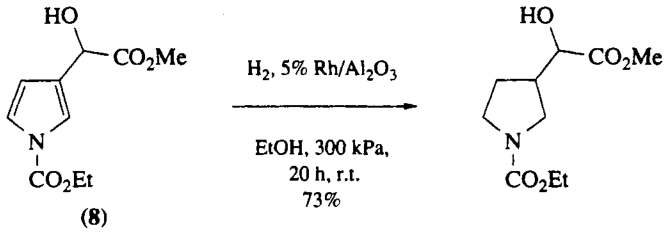
HO
$CO_2Me$
N
$CO_2Et$
$H_2$, 5% $Rh/Al_2O_3$
EtOH, 300 kPa,
20 h, r.t.
73%
HO
$CO_2Me$
N
$CO_2Et$

(**8**)

(7)

The use of rhodium–amino acid complexes in catalytic hydrogenation has been reported by Rajca to be capable of reducing a wide variety of aromatic and heteroaromatic compounds under mild conditions (1 atm, 22 °C, DMF; 1 atm ≈ 101 kPa).[10] Thus, the rhodium–anthranilic acid catalyzed hydrogenation of pyrrole under these mild conditions yields a 2:1 mixture of pyrrolidine and 2,5-dihydropyrrole (53% conversion after 8 h).[10] Recently, Lunn found that the hydrogenation of pyrrole can be carried out with a nickel–aluminum alloy, as generated with aqueous KOH, to give pyrrolidine in 58% yield, albeit relatively slowly (4 d, r.t.).[11]

### 3.7.2.2 Dissolving Metals and Metals in Acid

Although the Birch reduction (alkali metals in liquid $NH_3$) of the pyrrole ring is apparently unknown[12] (*cf.* equation 8),[13] the partial reduction of pyrroles to 2,5-dihydropyrroles using Zn/HCl has been of considerable utility.[2,14] For example, pyrrole gives 2,5-dihydropyrrole as the major product upon treatment with Zn dust/20% aq. HCl (equation 9),[2,15] and Lemal and McGregor observed that 2,5-dimethylpyrrole gives a mixture of *trans*- (78%) and *cis*-2,5-dimethyl-2,5-dihydropyrrole (22%) under similar conditions (47% yield).[14,16] In one of these studies, Hudson and Robertson demonstrated that 2,5-dihydropyrrole is not reduced to pyrrolidine under these reaction conditions.[15] Using these same conditions, Schumacher and Hall reported the reduction of 2-benzylpyrrole to the 2,5-dihydro derivative (67%) in a synthesis of the antibiotic anisomycin.[17]

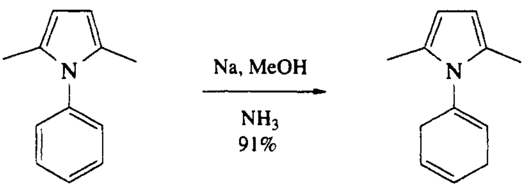
N
Na, MeOH
$NH_3$
91%
N

(8)

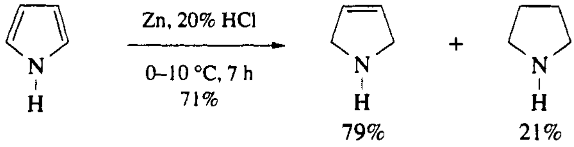
N
H
Zn, 20% HCl
0–10 °C, 7 h
71%
N
H
79%
+
N
H
21%

(9)

### 3.7.2.3 Miscellaneous Methods

Apart from catalytic hydrogenation and dissolving metal methods, very few other techniques exist for the reduction of the pyrrole ring. However, one example is the improved use of hypophosphorus acid that has been described by Scott and coworkers in a reduction of pyrrole-2-carboxylic acid to the prolyl hydroxylase inhibitor (*S*)-3,4-dehydroproline (after resolution) (equation 10).[18]

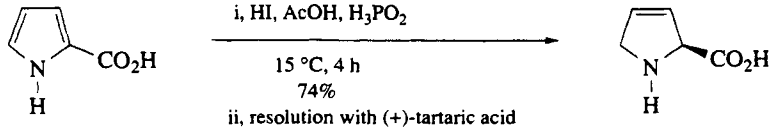

$CO_2H$
N
H
i, HI, AcOH, $H_3PO_2$
15 °C, 4 h
74%
ii, resolution with (+)-tartaric acid
N
H
$CO_2H$

(10)

## 3.7.3 REDUCTION OF FURANS

### 3.7.3.1 Catalytic Hydrogenation

The catalytic hydrogenation of furans to tetrahydrofurans, which is an important industrial process, has a long history and can be accomplished with a variety of catalysts.[19-24] Nevertheless, new studies of these reductions continue to be reported.[10,25] For example, as shown in Scheme 1, Karakhanov *et al.* have reported that polymer-containing catalysts are particularly efficient in the hydrogenation of furan[25] and le Noble and coworkers have discovered that the combination of isopropyl alcohol and Raney nickel provides for a convenient reduction of furan in a transfer hydrogenation process.[26] The same Russian group has also reported the selective hydrogenation of alkenic double bonds in unsaturated furan ketones using a Raney Pd–Al catalyst (Scheme 1).[27]

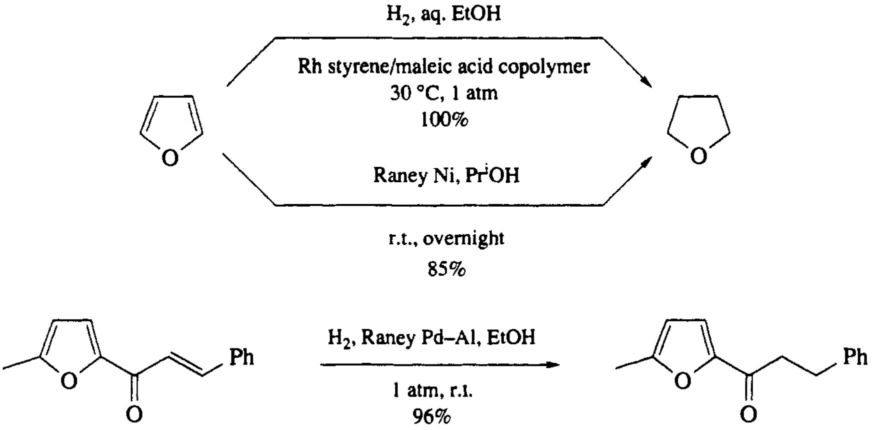

$H_2$, aq. EtOH
Rh styrene/maleic acid copolymer
30 °C, 1 atm
100%
O
O
Raney Ni, Pr$^i$OH
r.t., overnight
85%
O
O
Ph
$H_2$, Raney Pd–Al, EtOH
1 atm, r.t.
96%
O
O
Ph

**Scheme 1**

A study by Soós has demonstrated that the formation of 5-hydroxy-2-pentanone in the hydrogenation of 2-methylfuran in aqueous alkaline media does not involve 2-methyl-4,5-dihydrofuran as an intermediate,[28] as was earlier believed. Soós proposes that 2-methylfuran is hydrated on the catalyst surface (Pd/C) to give 2-hydroxy-2-methyl-2,5-dihydrofuran, which is hydrogenated to afford eventually 5-hydroxy-2-pentanone (Scheme 2).[28]

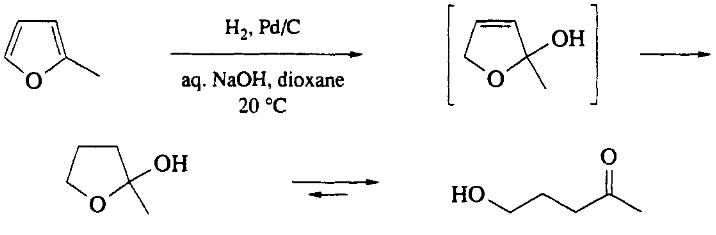

O
$H_2$, Pd/C
aq. NaOH, dioxane
20 °C
O
OH
O
OH
HO
O

**Scheme 2**

Although normally very difficult,[24] the reduction of furans to 4,5-dihydrofurans can be accomplished by trapping, and later regenerating, the dihydro product (equation 11) as the trifluoroacetate (**9**).[29]

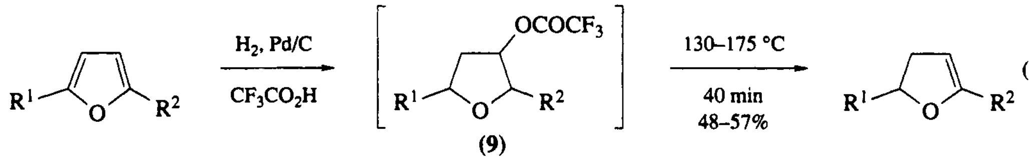
R1
O
R2
H2, Pd/C
CF3CO2H
OCOCF3
R1
O
R2
(9)
130–175 °C
40 min
48–57%
R1
O
R2

(11)

$R^1 = R^2 = H$; $R^1 = Me, R^2 = H$; $R^1 = H, R^2 = CO_2Me$

### 3.7.3.2 Dissolving Metals

Although furan itself is reduced by Li/MeNH2 only under forcing conditions to give a complex mixture,[30] the Birch reduction of furoic acids proceeds easily, is synthetically useful, and has been scrutinized by several groups, as summarized in equations (12)–(14).[31–33] The reduction of 5-alkyl-2-furoic acids is stereorandom, leading to equal amounts of *cis-* and *trans-*dihydro products (equation 13).[31,32] Attempts thus far to effect an asymmetric Birch reduction of furoic acids by chiral protonation have been disappointing (equation 14).[34]

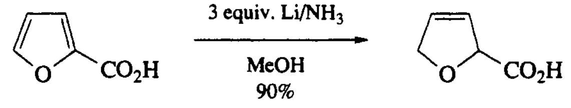
O
CO2H
3 equiv. Li/NH3
MeOH
90%
O
CO2H

(12)

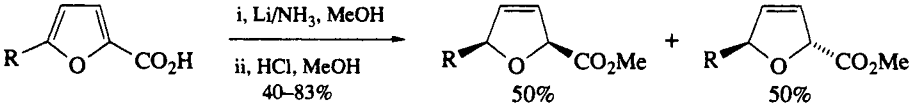
R
O
CO2H
i, Li/NH3, MeOH
ii, HCl, MeOH
40–83%
R
O
CO2Me
50%
+
R
O
CO2Me
50%

(13)

R = Me, Et, $Pr^i$, $Pr^n$, $Bu^t$, Bn

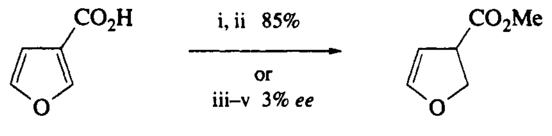
CO2H
O
i, ii 85%
or
iii–v 3% ee
CO2Me
O

(14)

i, Na/NH3, $Pr^iOH$; ii, $CH_2N_2$; iii, Na/NH3, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose; iv, $H^+$; v, $CH_2N_2$

Kinoshita and coworkers have found that, in contrast to the result obtained using $Pr^iOH$ (equation 14), in the presence of nucleophilic alcohols (MeOH, EtOH) the Birch reduction of 3-furoic acid leads to the corresponding acetal (equation 15).[33]

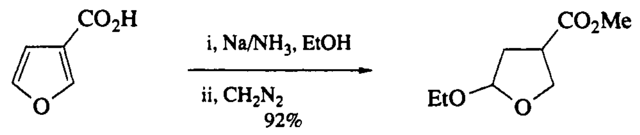
CO2H
O
i, Na/NH3, EtOH
ii, CH2N2
92%
CO2Me
EtO
O

(15)

The reduction of 5-phenyl-2-furoic acid takes a completely different course, reflecting the benzylic nature of the intermediate dihydrofuran ring (equation 16).[32]

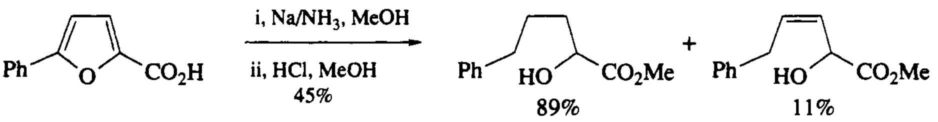
Ph
O
CO2H
i, Na/NH3, MeOH
ii, HCl, MeOH
45%
Ph
HO
CO2Me
89%
+
Ph
HO
CO2Me
11%

(16)

Birch and Slobbe have found that the intermediate anion from the reduction of 2-furoic acid can be alkylated *in situ* (equation 17).[35] These dihydrofuroic acids can be oxidatively decarboxylated with LTA to afford the corresponding 2-alkylfurans[36] in what clearly represents an attractive alternative to the standard two-step metallation–alkylation of the furan ring.

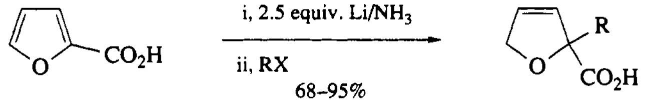

(17)

R = Me, Et, Pr$^i$, Bn, allyl; X = I, Br, Cl, OMs

### 3.7.3.3 Ionic Hydrogenation

A very convenient and versatile new reduction method, which has been intensively studied for the reduction of thiophenes (*vide infra*), makes use of the combination of a trialkylsilane and an acid, usually trifluoroacetic acid (TFA). This so-called 'ionic hydrogenation' provides a novel reduction of furans to tetrahydrofurans (Scheme 3).[37] Although Bolestova *et al.* find that the conditions are critical in order to avoid polymerization, the yields of tetrahydrofurans can be quite good. The reduction is accelerated by the presence of boron trifluoride etherate but fails with carbonyl-substituted furans, such as methyl pyromucate.[37]

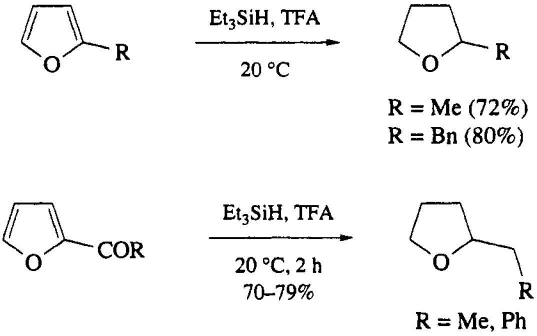

**Scheme 3**

## 3.7.4 REDUCTION OF THIOPHENES

Several excellent reviews of the early work on thiophene reduction are available.[38–40] The present discussion will not cover the important industrial topic of catalytic hydrodesulfurization of thiophenes in petroleum.[41–43]

### 3.7.4.1 Catalytic Hydrogenation

The catalytic hydrogenation of the thiophene ring is inherently difficult because of its high degree of aromaticity and the tendency of the sulfur atom to poison the catalyst. Nevertheless, a number of successful hydrogenation conditions have been developed. For example, Greenfield *et al.* have observed that thiophene and several 2-substituted derivatives can be hydrogenated to the tetrahydro derivatives (equation 18) using synthesis gas and a cobalt catalyst under relatively harsh conditions.[44]

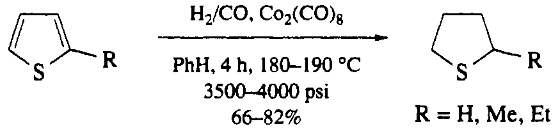

(18)

More recently, several milder reducing conditions have been described (equations 19–21).[10,45–48] Noteworthy is the *cis* hydrogenation of thiophene (**10**) performed by Confalone and coworkers in a synthesis of the vitamin biotin (equation 20).[46]

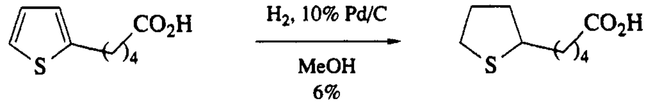
$CO_2H$
$H_2$, 10% Pd/C
MeOH
6%
$CO_2H$

(19)

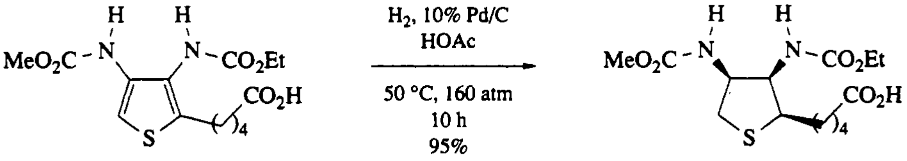
$MeO_2C$
$CO_2Et$
$CO_2H$
$H_2$, 10% Pd/C
HOAc
50 °C, 160 atm
10 h
95%

**(10)**

(20)

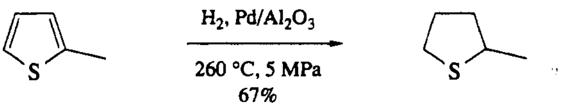
$H_2$, $Pd/Al_2O_3$
260 °C, 5 MPa
67%

(21)

### 3.7.4.2 Dissolving Metals

Although the Birch reduction of thiophenes leads to ring cleavage (equation 22),[12,49] the corresponding reaction of thiophene-2-carboxylic acids and 2-acylthiophenes takes a different course. For example, thiophene-2-carboxylic acid gives either the 2,5-dihydro derivative or the cleavage product as the major product, depending on the reaction conditions (equation 23),[50,51] although, in the former case, the reaction mixture is contaminated with the three overreduction products (**11**)–(**13**).[50] However, a modification in the procedure that employs the dry lithium carboxylate prevents overreduction.[52]

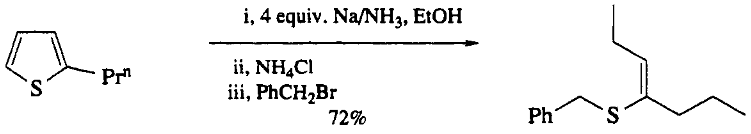
$Pr^n$
i, 4 equiv. $Na/NH_3$, EtOH
ii, $NH_4Cl$
iii, $PhCH_2Br$
72%
Ph

(22)

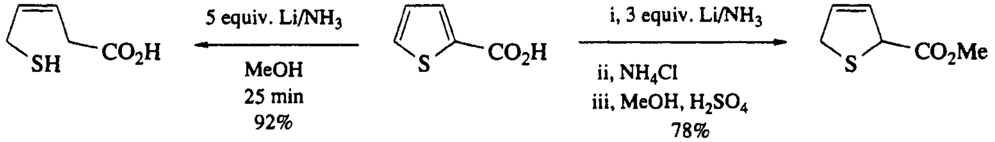
$CO_2H$
5 equiv. $Li/NH_3$
MeOH
25 min
92%
$CO_2H$
i, 3 equiv. $Li/NH_3$
ii, $NH_4Cl$
iii, MeOH, $H_2SO_4$
78%
$CO_2Me$

(23)

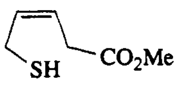

(**11**) 9.5%

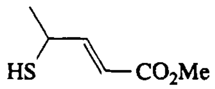

(**12**) 7%

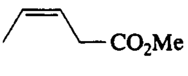

(**13**) 5%

Nishino *et al.* found that 2-acylthiophenes are also reduced to the corresponding 2,5-dihydro derivatives (equation 24)[53] and the intermediate anions can be intercepted with alkylating agents (equation 25).[54] The resulting compounds can be easily converted into the corresponding 1,3-dienyl ketones (equation 25). Dmitrienko and coworkers have found that the Birch reduction of thiophene-3-carboxylic acid leads to the 2,3-dihydro derivative.[55]

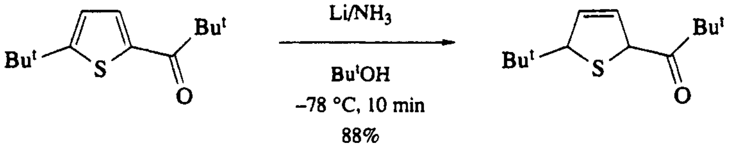
$Bu^t$
$Bu^t$
O
$Li/NH_3$
$Bu^tOH$
-78 °C, 10 min
88%
$Bu^t$
$Bu^t$
O

(24)

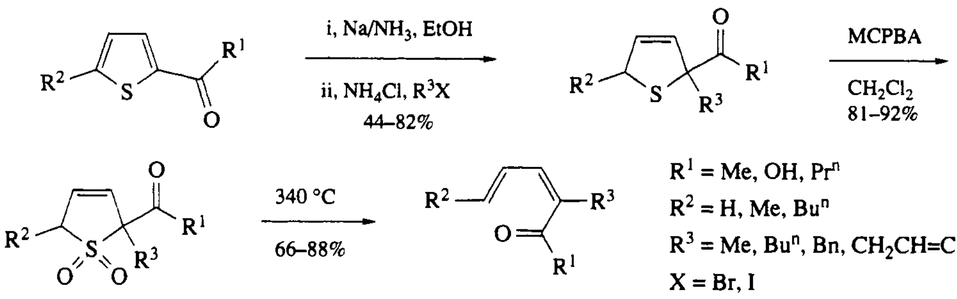

$R^1$ = Me, OH, $Pr^n$
$R^2$ = H, Me, $Bu^n$
$R^3$ = Me, $Bu^n$, Bn, $CH_2CH{=}CH_2$
X = Br, I

(25)

### 3.7.4.3 Ionic Hydrogenation

An extremely powerful and efficient new reduction of thiophenes to tetrahydrothiophenes involves ionic hydrogenation with a trialkylsilane and an acid. Typically, a mixture of triethylsilane and trifluoroacetic acid is employed (equations 26 and 27).[56] This reduction is reasonably general, although thiophene itself is poorly reduced (equation 26) and 2,5-diphenylthiophene is inert to these conditions. Not surprisingly, 2-benzoylthiophene is converted to 2-benzyltetrahydrothiophene (75%).[56]

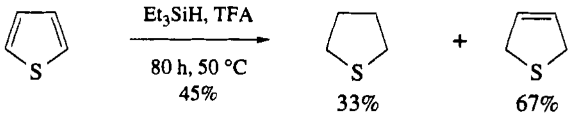

(26)

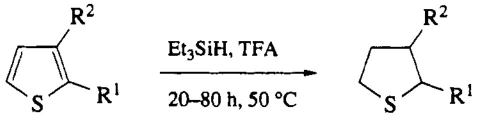

(27)

$R^1$ = Me, $R^2$ = H (80%)
$R^1$ = H, $R^2$ = Me (60%)

For this ionic hydrogenation of thiophenes, Kursanov and coworkers have proposed the pathway shown in Scheme 4, based on the labeling results obtained for the reduction of 2,5-dimethylthiophene.[56]

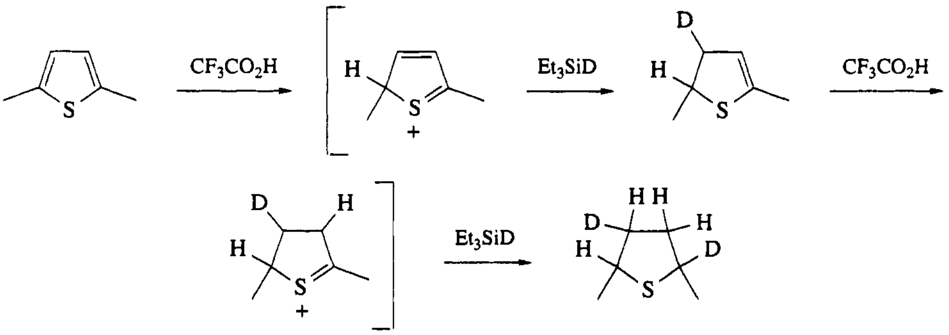

Scheme 4

Zav'yalov and Dorofeeva have utilized this reduction to synthesize the biotin analogs shown in Scheme 5.[57]

This ionic hydrogenation can be improved by the addition of either boron trifluoride etherate[58] or certain salts and acids.[59] Furthermore, a more powerful set of conditions involving $Et_3SiH$ and HCl–$AlCl_3$ has been used to reduce thiophenes that are recalcitrant under the usual $Et_3SiH$/TFA conditions (equations 28 and 29).[60] In fact, the intermediate salt (**14**) can be isolated.

In what might be viewed as a variation on the ionic hydrogenation theme, this same Russian group has found that the combination of zinc/aluminum halide/*p*-toluenesulfonic acid reduces 2-alkylthiophenes mainly to the tetrahydro derivatives (equation 30).[61] The minor product, 2-alkyl-2,5-dihydrothiophene, is

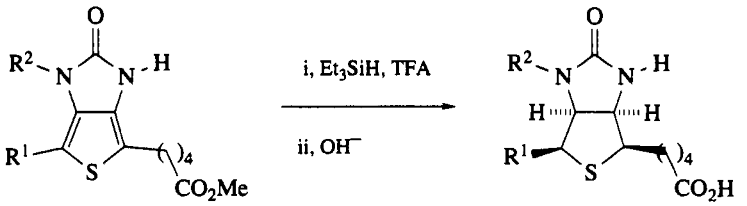
i, Et$_3$SiH, TFA
ii, OH$^-$
CO$_2$Me
CO$_2$H

$R^1$ = H, $R^2$ = Me (82%)
$R^1$ = Me, $R^2$ = H (72%)

**Scheme 5**

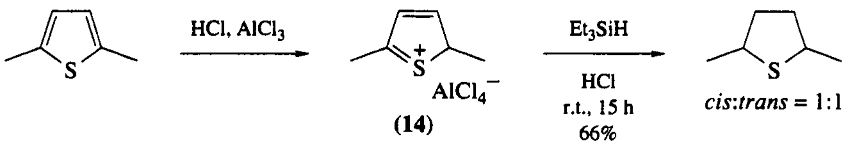
HCl, AlCl$_3$
AlCl$_4^-$
(14)
Et$_3$SiH
HCl
r.t., 15 h
66%
*cis*:*trans* = 1:1

(28)

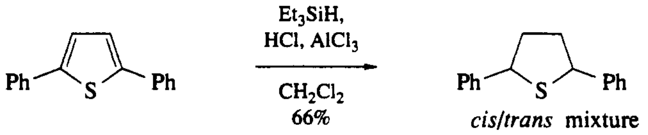
Et$_3$SiH,
HCl, AlCl$_3$
CH$_2$Cl$_2$
66%
*cis*/*trans* mixture

(29)

not converted to the 2-alkyltetrahydrothiophene under the reaction conditions, suggesting that the reduction proceeds *via* a 4,5-dihydrothiophene intermediate, as shown in Scheme 4.

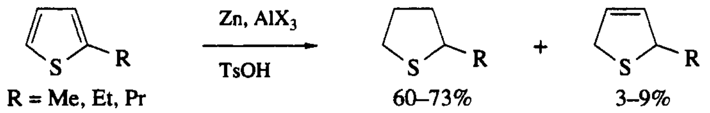
Zn, AlX$_3$
TsOH
R = Me, Et, Pr
60–73%
3–9%

(30)

Perhaps surprisingly, Yamanochi and Yamane describe the reduction of 2-thiopheneacetonitrile with NaBH$_4$/MeSO$_3$H (DMSO, 70 °C, 2 h) to give 2-(2-thienyl)ethylamine (64% yield) in which the thiophene ring is not reduced.[62]

### 3.7.4.4 Electrochemical

The electrochemical reduction of thiophene[63] and 5-methyl-2-thiophenecarboxylic acid[64] has been reported but would appear not to be of preparative interest. Thus, thiophene affords a mixture of 2,5-dihydrothiophene (56%) and tetrahydrothiophene (44%) in 55% yield upon electrolysis in aqueous DMF.[63]

### 3.7.4.5 Miscellaneous Methods

In a process that is related to the ionic hydrogenation method discussed above, Wristers has discovered that the unusual combination of H$_2$/isopentane/HF/TaF$_5$ reduces thiophene to tetrahydrothiophene in 80% yield.[65] These conditions also reduce dibenzothiophene to hexahydrodibenzothiophene. It has also been reported that Zn/TFA reduces thiophenes to 2,5-dihydrothiophenes (equations 31 and 32).[66] However, both acetic acid and HCl/benzene are ineffective with zinc in this regard.[66]

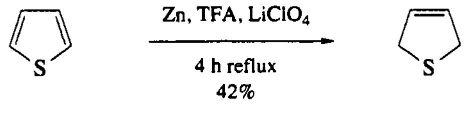
Zn, TFA, LiClO$_4$
4 h reflux
42%

(31)

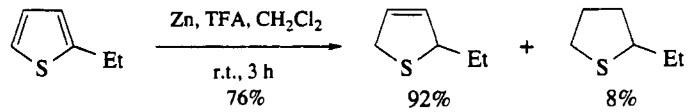
Zn, TFA, CH$_2$Cl$_2$
r.t., 3 h
76%
92%
8%

(32)

## 3.7.5 REDUCTION OF INDOLES

The reduction of indoles to indolines (2,3-dihydroindoles) has been intensively studied since the turn of the century and several reviews to the early literature are available.[67–71] Nevertheless, over the past decade, a number of new and exciting methods for effecting this important reduction have been discovered.

### 3.7.5.1 Catalytic Hydrogenation

The catalytic hydrogenation of indoles has a long history and a number of catalysts have been investigated in this context.[67–71] Although indoles are readily hydrogenated, it has not always been possible to control the site and degree of reduction. Moreover, rarely was it possible in these early works to establish a set of conditions that was generally applicable to a variety of different indoles. For example, although Noland and Hammer were able to hydrogenate indole to indoline in 92% yield with Raney nickel (EtOH, 100 atm, 100 °C), the same conditions with 2-methylindole give mostly overreduction (equation 33).[72] Another example is seen in the recent work of Shaw and Stapp, who examined several catalysts in the hydrogenation of indoles.[73] The highest conversions were observed with 5% platinum/alumina, but with erratic results (equation 34). The reduction of carbazole was also accomplished using this same catalyst and the products were 1,2,3,4-tetrahydrocarbazole (36%), *cis*-1,2,3,4,4a,9a-hexahydrocarbazole (5%) and a mixture of dodecahydrocarbazoles (6%).[73]

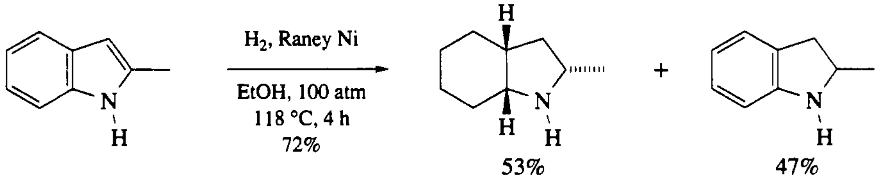

(33)

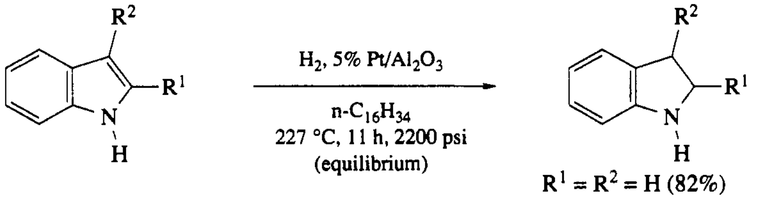

(34)

$R^1 = R^2 = H$ (82%)
$R^1 = Me$, $R^2 = H$ (65%)
$R^1 = R^2 = Me$ (28%)

Interestingly, platinum/silica gel effects the hydrogenolysis of the C—N bond (equation 35).[74]

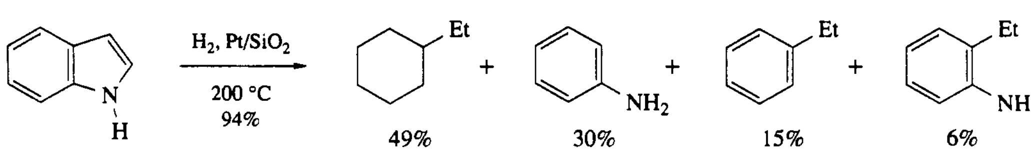

(35)

In accord with the propensity for indoles to protonate at the C-3 position,[75,76] Smith and Utley found that the catalytic hydrogenation of indoles in the presence of fluoboric acid proceeds smoothly to the indoline stage (equation 36).[77] It seems that these acidic conditions are strong enough to protonate the in-

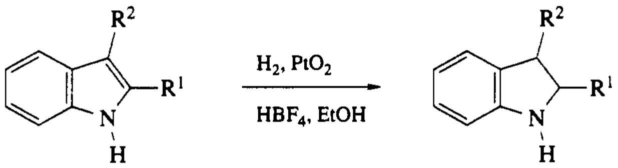

(36)

$R^1 = R^2 = H$ (>85%)
$R^1 = H$, $R^2 = Me$ (>95%)
$R^1, R^2 = -(CH_2)_4-$ (100%)

dole ring, but do not facilitate the polymerization of indole, which is frequently encountered with mineral acid. These hydrogenation conditions have been used to prepare a series of psychotropic hexahydro-γ-carbolines (**15**; equation 37).[78]

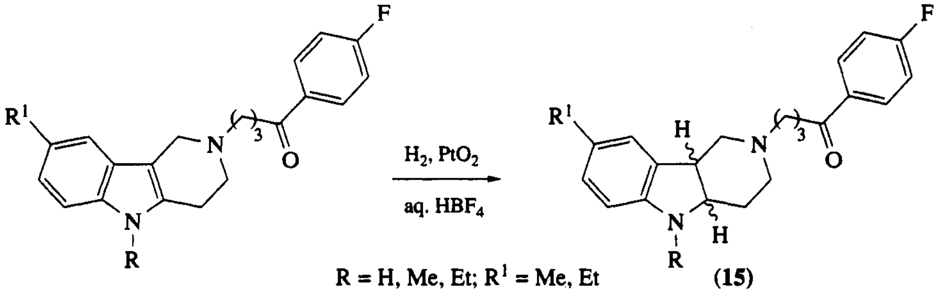
F
R1
N
3
O
N
R
H2, PtO2
aq. HBF4
F
R1
H
N
3
O
N
H
R

R = H, Me, Et; $R^1$ = Me, Et **(15)** (37)

Ames *et al.* have reported that indoles can be cleanly reduced to indolines under very mild conditions with palladium in the presence of acid (perchloric, acetic, sulfuric, phosphoric) (equation 38).[79]

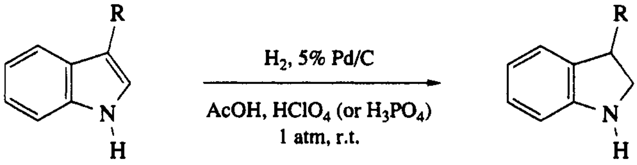
R
N
H
H2, 5% Pd/C
AcOH, HClO4 (or H3PO4)
1 atm, r.t.
R
N
H

R = H (74%); R = Me (69%) (38)

Raney nickel (RaNi) also accomplishes the hydrogenation of indoles to indolines (equations 39 and 40)[70] but the danger of overreduction can be a problem (equation 40). Under slightly different conditions ($H_2$, RaNi, MeOH/$H_2SO_4$, 3 h, 60 °C), the yield of indoline from indole is 95%.[80] These latter conditions have been reported to reduce a variety of substituted indoles (*i.e.* 4-OH, 5-OMe, 5-Cl, 5-Bu$^t$, 2-Ph, 2-Et-5-Pr) to the corresponding indolines.[80] The use of RaNi is particularly valuable in the reduction of *N*-acetylindoles to *N*-acetylindolines (**16**; equation 41).[70] Lunn's conditions (Ni/Al, aq. KOH) also serve to reduce indole to indoline in 73% yield.[11] A ruthenium catalyst ($RuCl_2(PPh_3)_3$, $H_2$, 310 psi, 85 °C; 1 psi = 6895 Pa) has been used to reduce indole to indoline but the yield was not reported, and this was the only example investigated.[81]

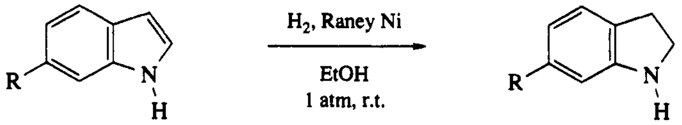
R
N
H
H2, Raney Ni
EtOH
1 atm, r.t.
R
N
H

R = H (75%); R = OMe (76%) (39)

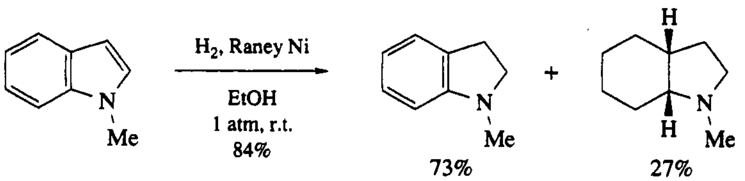
N
Me
H2, Raney Ni
EtOH
1 atm, r.t.
84%
N
Me
73%
+
H
N
H
Me
27%

(40)

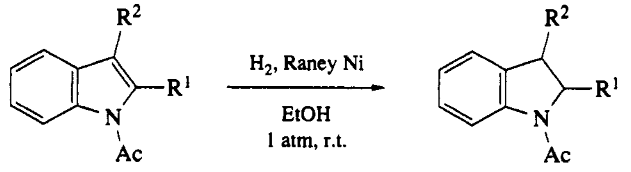
R2
R1
N
Ac
H2, Raney Ni
EtOH
1 atm, r.t.
R2
R1
N
Ac

**(16)** (41)

$R^1 = R^2$ = H (99%); $R^1$ = H, $R^2$ = Me (98%); $R^1 = R^2$ = Me (97%)

An interesting variation on conventional catalytic hydrogenation is catalytic transfer hydrogenation, in which formic acid or formate serves as the hydrogen source. Thus, indoles are smoothly reduced (and formylated) to the corresponding *N*-formylindoles (equations 42 and 43).[82] Since it is difficult to avoid formylation of the indoline, it is best to employ triethylammonium formate to maximize yields of the reduction product (equation 43).

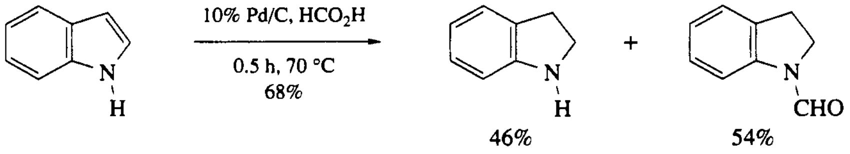
N
H
10% Pd/C, HCO$_2$H
0.5 h, 70 °C
68%
N
H
46%
+
N
CHO
54%

(42)

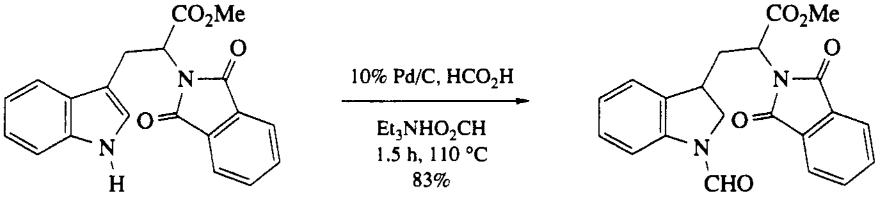
CO$_2$Me
O
N
O
N
H
10% Pd/C, HCO$_2$H
Et$_3$NHO$_2$CH
1.5 h, 110 °C
83%
CO$_2$Me
O
N
O
N
CHO

(43)

Watanabe and coworkers have reported that the ruthenium-catalyzed reduction of indoles using formic acid as the hydrogen source leads to indolines (equation 44).[83] It seems likely that acid is required in these reductions (equation 42–44) in order to protonate the indole C-3 position, since, in at least one report using only ammonium formate and palladium, the indole ring is not reduced (equation 45).[84] Admittedly, these conditions are much milder than those that use formic acid.

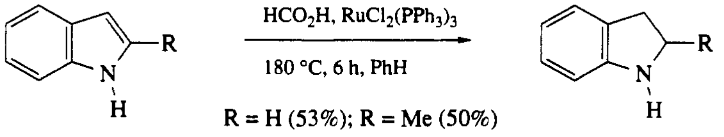
R
N
H
HCO$_2$H, RuCl$_2$(PPh$_3$)$_3$
180 °C, 6 h, PhH
R = H (53%); R = Me (50%)
R
N
H

(44)

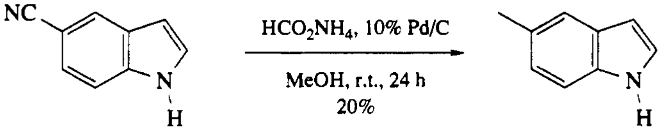
NC
N
H
HCO$_2$NH$_4$, 10% Pd/C
MeOH, r.t., 24 h
20%
N
H

(45)

### 3.7.5.2 Dissolving Metals and Metals in Acid

In addition to the general reviews on indole reduction that were cited above, several reviews and key papers on the dissolving metal reduction of indoles should be consulted for reference to the early work.[12,85,86]

Whereas *N*-phenylindoles are reduced to the corresponding dihydroindoles with Na/NH$_3$ (equations 46 and 47)[87–89] and indole-2-carboxylic acid is reduced to the indoline with Li/NH$_3$/PhNH$_2$ (equation 48),[90] indole itself is reduced to 4,7-dihydroindole (Li/NH$_3$, MeOH) in 51% yield.[91] These latter conditions also reduce carbazole to 1,4-dihydrocarbazole in 73% yield.[91]

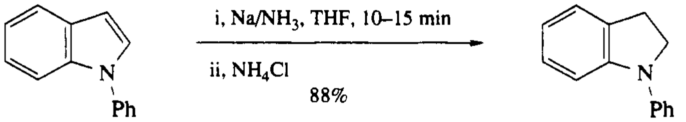
N
Ph
i, Na/NH$_3$, THF, 10–15 min
ii, NH$_4$Cl
88%
N
Ph

(46)

In some cases, very high chemoselectivity can be achieved depending on the reaction conditions. Thus, Remers and coworkers demonstrated that 5-methoxy-1-methylindole can be reduced either in the pyrrole ring or in the benzene ring, depending upon the availability of a good proton source (MeOH) (equation 49).[86]

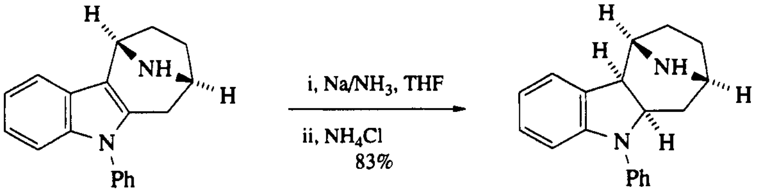
i, Na/NH$_3$, THF
ii, NH$_4$Cl
83%

(47)

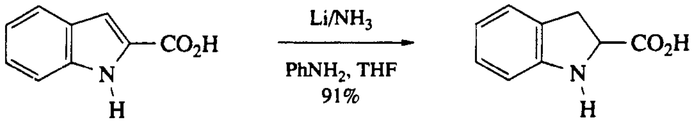
Li/NH$_3$
PhNH$_2$, THF
91%

(48)

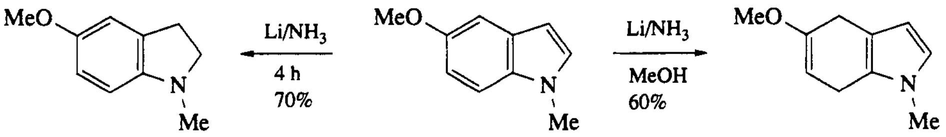
Li/NH$_3$
4 h
70%
Li/NH$_3$
MeOH
60%

(49)

However, Sauer and coworkers have been able to reduce selectively the styrene double bond in ergoline derivative (**17**) without affecting the indole double bond (equation 50).[92]

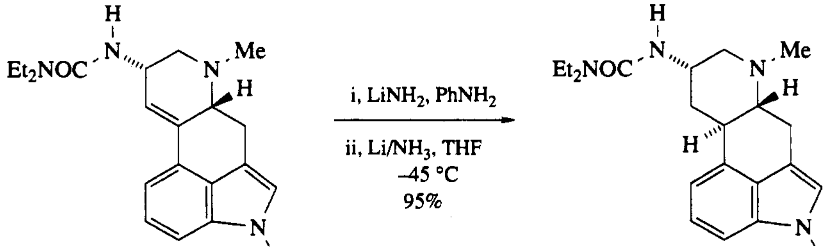
i, LiNH$_2$, PhNH$_2$
ii, Li/NH$_3$, THF
–45 °C
95%

(**17**)

(50)

Independently, Youn and Pak, and Fagan *et al.* found that Mg/MeOH reduces indoles to indolines that have a carbonyl group at the 2-position (equation 51).[93,94] This research supplements a reduction reported by Corey and coworkers that uses Sn/HCl (equation 52).[95] However, ethyl indole-3-carboxylate is not reduced with Mg/MeOH.[93]

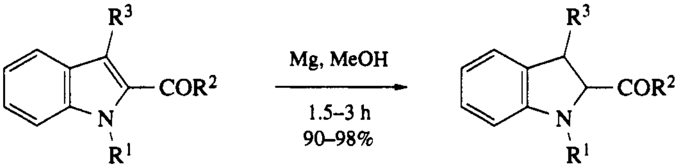
Mg, MeOH
1.5–3 h
90–98%

(51)

$R^1$ = H, Ac; $R^2$ = OMe, NH$_2$, NHMe; $R^3$ = H, Me

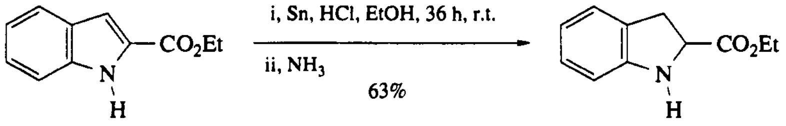
i, Sn, HCl, EtOH, 36 h, r.t.
ii, NH$_3$
63%

(52)

Although the early attempts to reduce indole to indoline with metals (Sn and Zn) and mineral acid (*e.g.* hydrochloric acid) invariably led to polymerization, Dolby and Gribble found that 85% phosphoric acid is a suitable medium in combination with Zn for a successful indole to indoline reduction (69%).[96] However, the reactions of 2,3-dimethylindole and 1,2,3,4-tetrahydrocarbazole with Zn/H$_3$PO$_4$ give much lower yields of reduction product.[96]

A related procedure utilizes zinc dust amalgam and HCl. Thus, several indoles are reduced to indolines in excellent yield (equation 53).[97,98] Somewhat similarly, the facile reduction of the indole double bond in pyridylindole (**18**) with zinc and acetic acid has been described (equation 54).[99] In this example, presumably, protonation of the pyridine nitrogen facilitates the reduction of the indole ring. Interestingly, Birch conditions (Na, EtOH, reflux) with (**18**) result in reduction of only the pyridine ring (93% yield).[100]

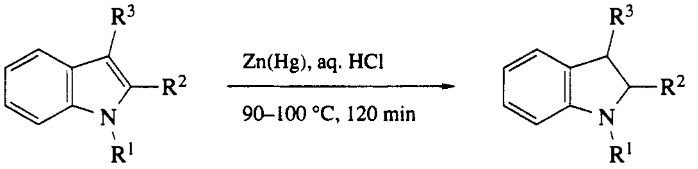

(53)

$R^1 = R^2 = R^3 = H$ (97%)
$R^1 = R^3 = H$, $R^2$ = cyclohexyl (92%)
$R^1 = H$, $R^2 = R^3 = Me$ (90%)
$R^1 = R^3 = H$, $R^2 = Ph$ (95%)
$R^1 = R^2 = Me$, $R^3 = H$ (97%)
$R^1 = R^2 = H$, $R^3 = Et$ (95%)
$R^1 = Me$, $R^2 = R^3 = H$ (100%)
$R^1 = R^3 = H$, $R^2 = Me$ (100%)

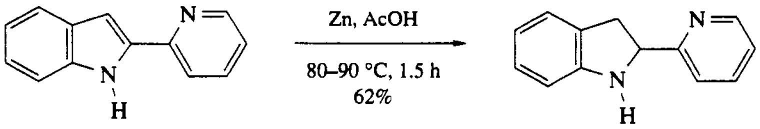

(**18**)

(54)

### 3.7.5.3 Boron Hydrides and Related Methods

As will be seen in this section, mixed boron hydrides and complexes of boron probably represent the most general and efficient reagents for the reduction of the indole double bond.

Although a few examples were known previously, Monti and Schmidt, in a careful study, found that diborane is able to reduce *N*-unsubstituted indoles to indolines (equation 55).[101] *N*-Alkylindoles are not reduced under these conditions.

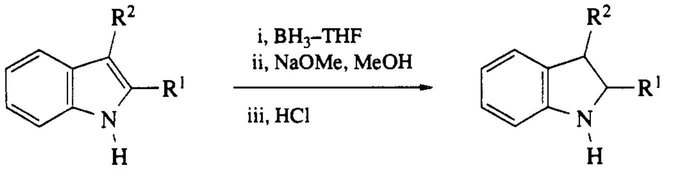

(55)

$R^1 = R^2 = H$ (44%)
$R^1 = Me$, $R^2 = H$ (50%)
$R^1 = H$, $R^2 = Me$ (66%)
$R^1 = R^2 = Me$ (93%)
$R^1, R^2 = -(CH_2)_4-$ (98%)

The mechanism proposed to account for this somewhat remarkable result is shown in Scheme 6, involving as the key intermediate the indolylborane (**19**). Methoxide addition to (**19**) serves to activate the indole C-3 position towards protonation and the resulting indolenium ion (**20**) is reduced by a boron hydride species to give indoline.

Although indoles are not normally reduced by either sodium borohydride or lithium aluminum hydride,[68] Gribble and coworkers have found that $NaBH_4$ in carboxylic acid media reduces indoles to *N*-alkylindolines in excellent yield (equations 56 and 57).[102] This unusual reaction involves C-3 protonation of the indole, borohydride reduction to give an intermediate indoline and subsequent *N*-alkylation under the reaction conditions to give the *N*-alkylindoline. The reduction of *N*-alkylindoles with $NaBH_4$/HOAc gives the corresponding *N*-alkylindolines. Indeed, the combination of $NaBH_4$/$RCO_2H$ is an excellent one for amine alkylation.[102,103]

Although most common carboxylic acids can be used successfully in this context (equation 57),[102] formic acid gives the indole dimer derived side product (**21**; equation 58)[104] and trifluoroacetic acid gives the condensation product (**22**; equation 59),[105] in addition to the expected products. The particular prob-

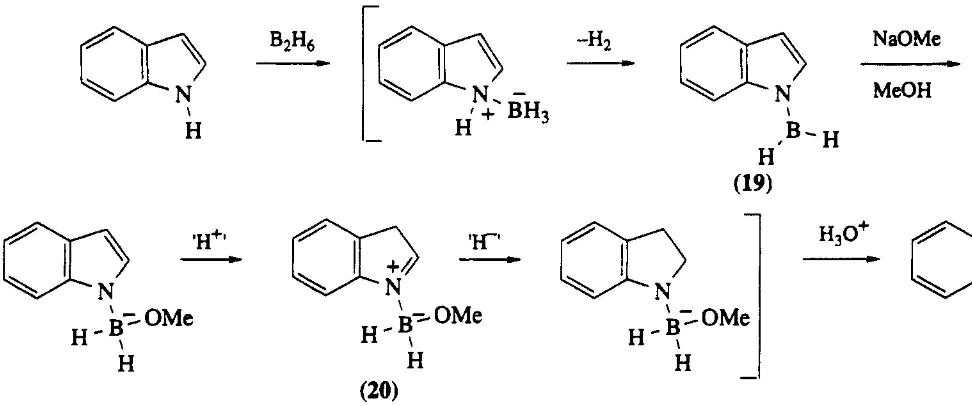
B$_2$H$_6$
−H$_2$
NaOMe
MeOH
'H$^+$'
'H$^-$'
H$_3$O$^+$
(19)
(20)

Scheme 6

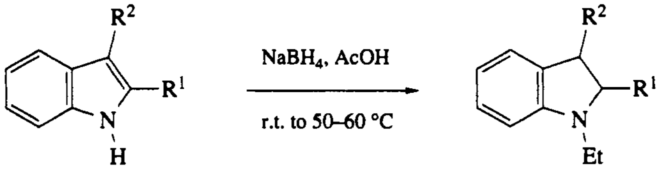
NaBH$_4$, AcOH
r.t. to 50–60 °C

(56)

$R^1 = R^2 = H$ (86%)
$R^1 = Me, R^2 = H$ (84%)
$R^1 = H, R^2 = Me$ (45%)

$R^1 = R^2 = Me$ (60%)
$R^1, R^2 = -(CH_2)_4-$ (77%)

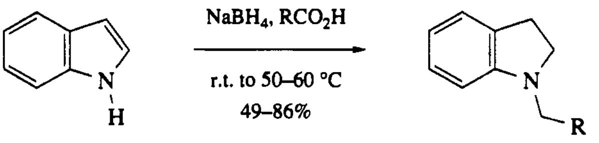
NaBH$_4$, RCO$_2$H
r.t. to 50–60 °C
49–86%

(57)

R = H, Me, Et, Pr$^i$

lem encountered with formic acid in this indole reductive *N*-methylation sequence can be circumvented by using a combination of paraformaldehyde/$NaBH_3CN/HOAc$.[106]

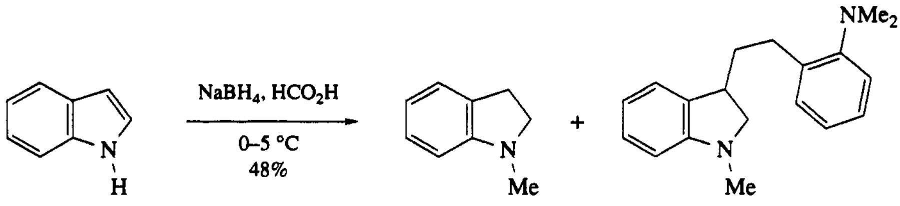
NaBH$_4$, HCO$_2$H
0–5 °C
48%

(58)

33% (21) 67%

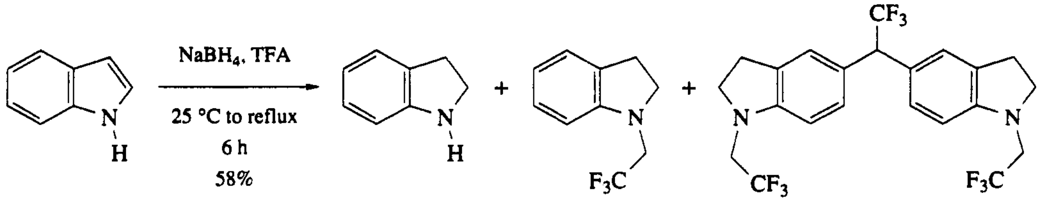
NaBH$_4$, TFA
25 °C to reflux
6 h
58%

(59)

69% 9% (22) 22%

In a companion study, Gribble and coworkers found that the combination $NaBH_3CN/HOAc$ is superlative for reducing indoles to indolines rapidly and under mild conditions (equation 60).[102,107] With this reagent combination, *N*-alkylation occurs only at higher temperatures.[108]

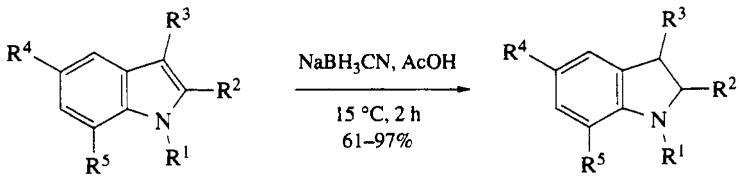

(60)

$R^1$ = H, Me, Et, Pr$^n$, Bn, Ph; $R^2$ = H, Me; $R^3$ = H, Me; $R^2$, $R^3$ = $-(CH_2)_4-$; $R^4$ = H, Br; $R^5$ = H, Me

Only those indoles that are sufficiently basic to be protonated by acetic acid are reduced under these conditions. Thus, 5-nitroindole and 2,3-diphenylindole are recovered unchanged,[107] whereas 5,6-dimethoxyindole is cleanly reduced to 5,6-dimethoxyindoline in 86% yield with $NaBH_3CN/HOAc$.[109,110] This differential reactivity has been exploited by Cava and Rawal in their synthesis of CC-1065 analogs in which only the more basic double bond in (**23**) is reduced (equation 61).[111–113] Indeed, this same tactic has since been utilized by Boger,[114] Moody[115,116] and Sundberg,[117] and their coworkers, in their respective synthetic efforts towards CC-1065 and the related phosphodiesterase inhibitors PDE-I and PDE-II. Likewise, Joule and coworkers have utilized $NaBH_3CN/HOAc$ in a chemoselective reduction of the more basic indole double bond in benzodipyrrole (**24**; equation 62).[118]

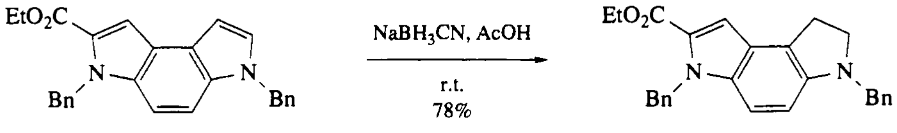

(**23**)

(61)

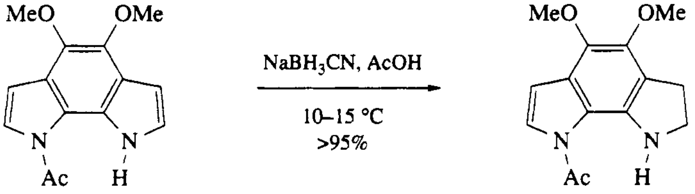

(**24**)

(62)

Although the reduction of indoles that contain a basic nitrogen atom fails with $NaBH_4$ (or $NaBH_3CN$) in acetic acid, this reaction is successful using the stronger trifluoroacetic acid, and many examples are known (equations 63–66).[102,119–126] Not surprisingly, the bromine is removed in the reduction of 2-bromoergolines (equation 65).[123] The reduction of β- and γ-carbolines invariably gives the *cis* product (equations 63 and 66),[119,121,124] the result of hydride transfer to the iminium ion from the least hindered face and leading to the more stable *cis* ring fusion. As would be expected, $NaBH_3CN/TFA$ is also capable of reducing these basic indoles to indolines (equations 67 and 68).[127–129] This combination has also been used to reduce methyl and ethyl *N*-alkylindole-2-carboxylates to the corresponding indolines in excellent yield.[94]

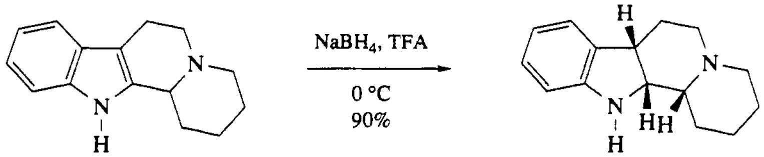

(63)

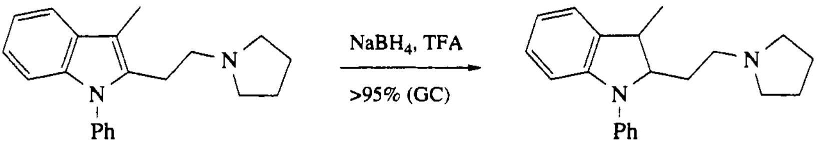

*cis*:*trans* = 40:60

(64)

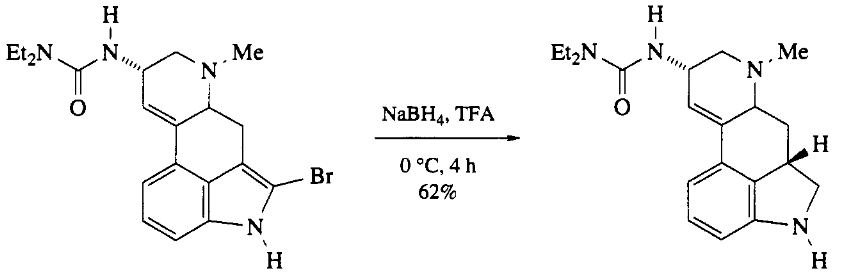

(65)

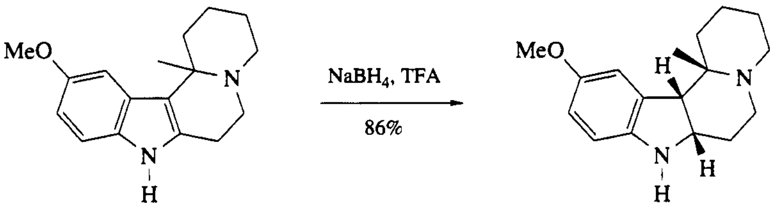

(66)

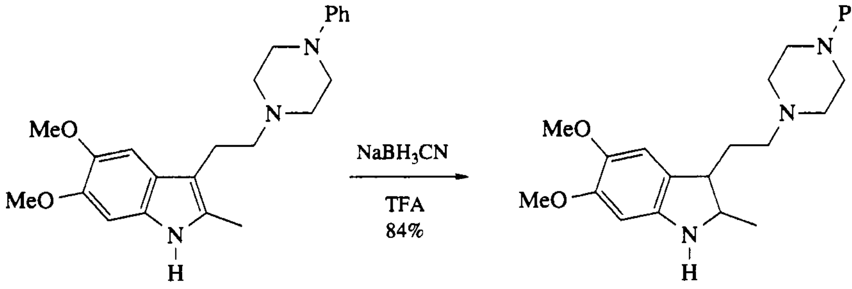

*cis*:*trans* = 44:56

(67)

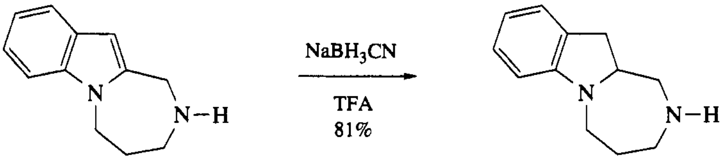

(68)

In some instances, it is essential to use NaBH$_3$CN/TFA rather than NaBH$_4$/TFA, in order to preclude W-trifluoroethylation, which can occur using the latter conditions (equations 69 and 70).[105,121,129]

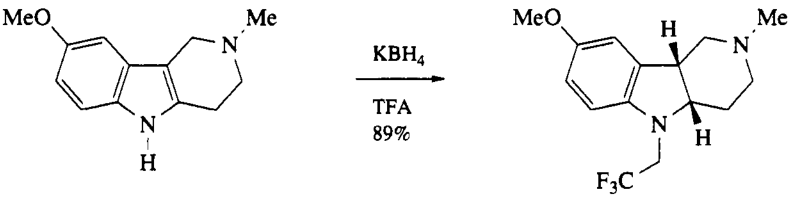

(69)

Whereas indoles that contain a basic nitrogen are smoothly reduced to the corresponding indolines with NaBH$_4$/TFA (*vide supra*), this reagent combination with simple indoles can lead to complications (*i.e.* **22**; equation 59).

The utility of sodium borohydride (and related metal hydrides) in carboxylic acid media in the reduction of indoles has been reviewed recently and several additional examples can be found cited in this review.[103] There is increasing evidence to suggest that acyloxyborohydride species are the actual reducing agents that form under these conditions.[130]

Sodium borohydride in concert with AlCl$_3$–pyridine also reduces indoles to indolines (equation 71),[131] but this reagent combination is less effective than those reported above using carboxylic acids.

Somewhat surprisingly, it has been reported that both tetra-*n*-butylammonium borohydride and zinc borohydride, in the absence of acid, are capable of reducing indoles to indolines (equations 72 and

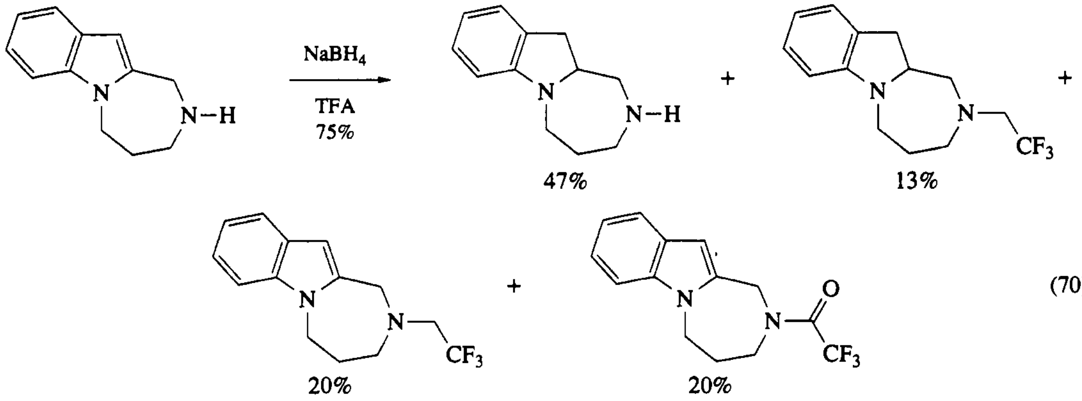

(70)

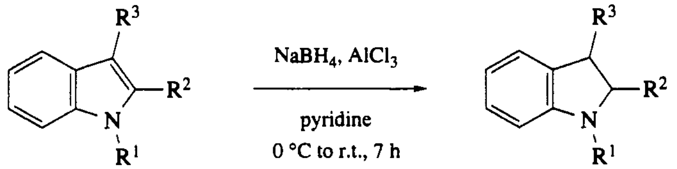

(71)

$R^1 = R^2 = R^3 = H$ (76%)
$R^1 = R^2 = H, R^3 = Me$ (75%)
$R^1 = R^3 = H, R^2 = Me$ (80%)
$R^1 = Me, R^2 = R^3 = H$ (56%)
$R^1 = R^3 = H, R^2 = Ph$ (15%)
$R^1 = R^2 = H, R^3 = (CH_2)_2NHBz$ (56%)

73),[132,133] although only the latter method would appear to be comparable in terms of yield and versatility to those methods described above. The mechanisms of these reductions are unclear, but it may be that reduction is occurring during work-up, as has been found by Maryanoff and coworkers during their studies,[129] and/or that diborane is involved.

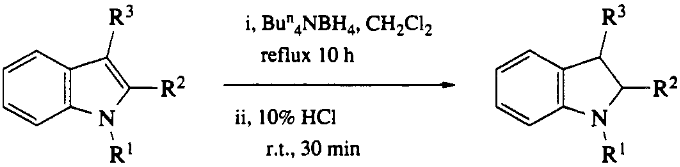

(72)

$R^1 = R^2 = R^3 = H$ (48%)
$R^1 = R^3 = H, R^2 = Me$ (66%)
$R^1 = R^2 = Me, R^3 = H$ (44%)
$R^1 = R^2 = H, R^3 = Me$ (6%)
$R^1 = H, R^2, R^3 = -(CH_2)_4-$ (57%)

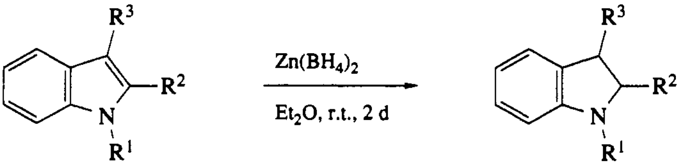

(73)

$R^1 = R^2 = R^3 = H$ (92%)
$R^1 = R^3 = H, R^2 = Me$ (94%)
$R^1 = R^2 = H, R^3 = Me$ (38%)
$R^1 = H, R^2 = R^3 = Me$ (39%)
$R^1 = H, R^2, R^3 = -(CH_2)_4-$ (30%)
$R^1 = Me, R^2 = R^3 = H$ (0%)

Pioneered by Berger, Kikugawa and Maryanoff, and their coworkers, it has been found that borane and amine–boranes in conjunction with acid are capable of reducing indoles to indolines (equations 74–77).[89,128,129,134–138] Depending on the exact system, these methods may or may not be more efficient than the use of the chemically related $NaBH_4(NaBH_3CN)/RCO_2H$ reagent combination. Okamoto and coworkers have employed 2-amino-4-methylpyridine–borane in HOAc to reduce indole to indoline in 86% yield.[139]

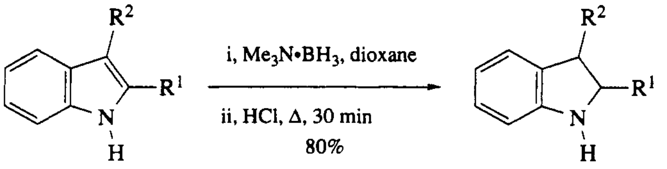

R2
R1
N
H
i, Me3N•BH3, dioxane
ii, HCl, Δ, 30 min
80%
R2
R1
N
H

(74)

$R^1 = R^2 = H$ (80%); $R^1, R^2 = -(CH_2)_4-$ (87%) *(cis)*

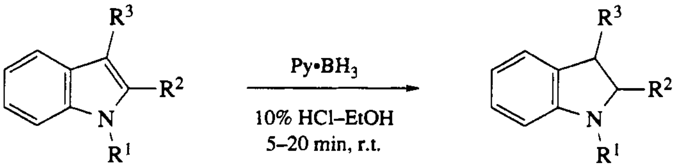

R3
R2
N
R1
Py•BH3
10% HCl–EtOH
5–20 min, r.t.
R3
R2
N
R1

(75)

| | |
|---|---|
| $R^1 = R^2 = R^3 = H$ (82%) | $R^1 = R^2 = H, R^3 = Me$ (82%) |
| $R^1 = R^3 = H, R^2 = Me$ (98%) | $R^1 = Me, R^2 = R^3 = H$ (54%) |
| $R^1 = R^3 = H, R^2 = Ph$ (56%) | |

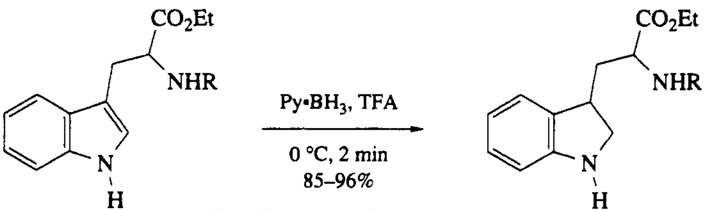

CO2Et
NHR
N
H
Py•BH3, TFA
0 °C, 2 min
85–96%
CO2Et
NHR
N
H

(76)

R = H, Ac, Bn, CHO, $CO_2Bn$

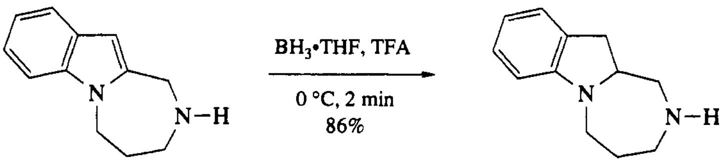

N
N–H
BH3•THF, TFA
0 °C, 2 min
86%
N
N–H

(77)

Berger and coworkers have found that the reaction can be manipulated so as to give the *trans*-fused carboline product (equation 78).[88] This stereoselective reduction was later extended to secondary amines in the γ-carboline series by Elliott and Guzik.[140,141]

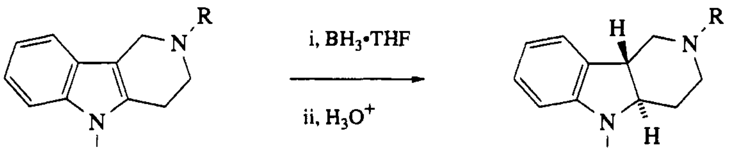

R
N
N
Ph
i, BH3•THF
ii, H3O+
H
R
N
N
H
Ph

(78)

R = Me (65–75%); R = H (>80%)

This stereoselective reduction is thought to involve the pathway shown in Scheme 7, wherein the key step is intramolecular hydride delivery from an amine–borane complex (**25**). This mechanism is supported by the appropriate deuterium labeling experiments.[88]

Zagorevskii *et al.* have observed the same stereoselective *trans* reduction with several tetrahydro-γ-carbolines by generating the diborane from $NaBH_4$ *in situ* (equation 79).[142] As expected, treatment of these carbolines with pyridine–borane and acid gives the *cis*-fused isomers (equation 80).[142] Bosch and coworkers have also utilized an *in situ* generation of diborane to effect the chemoselective reduction of the indole double bond during the synthesis of a new indolomorphan.[143]

Chu and coworkers observed that the indole ester (**26**) can be reduced selectively using pyridine–borane/HCl (equation 81),[144] but Fritz and coworkers found that the same conditions reduce both the indole double bond and the carbonyl group in ketone (**27**; equation 82) but only the indole double bond in amide (**28**; equation 83).[145]

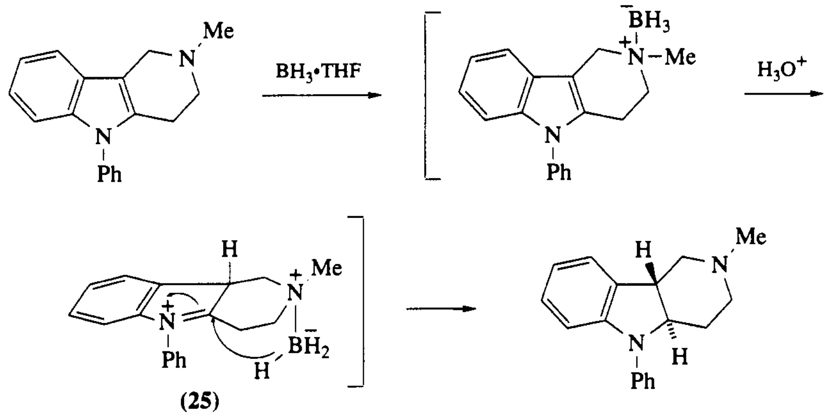
Me
N
N
Ph
BH₃•THF
BH₃
N–Me
N
Ph
H₃O⁺
H
Me
N
N
Ph
BH₂
H
(25)
H
Me
N
N
Ph
H

**Scheme 7**

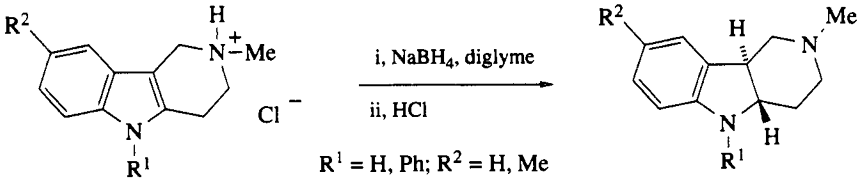
R²
H
N–Me
N
R¹
Cl⁻
i, NaBH₄, diglyme
ii, HCl
R¹ = H, Ph; R² = H, Me
R²
H
Me
N
N
R¹
H

(79)

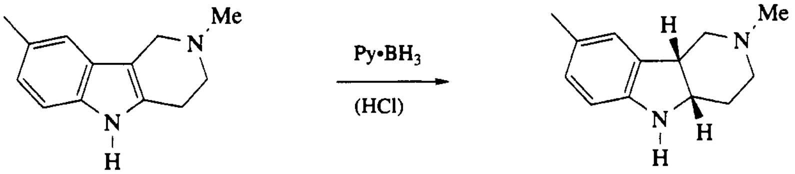
Me
N
N
H
Py•BH₃
(HCl)
H
Me
N
N
H
H

(80)

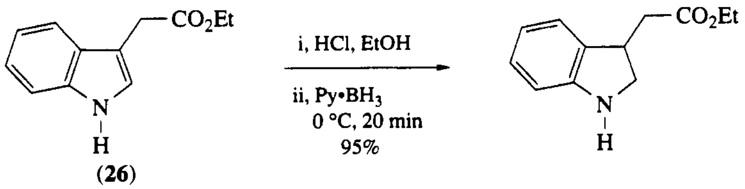
CO₂Et
N
H
(26)
i, HCl, EtOH
ii, Py•BH₃
0 °C, 20 min
95%
CO₂Et
N
H

(81)

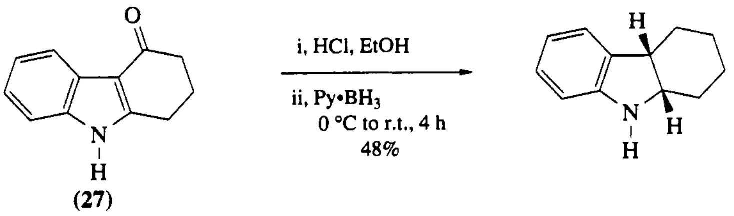
O
N
H
(27)
i, HCl, EtOH
ii, Py•BH₃
0 °C to r.t., 4 h
48%
H
N
H
H

(82)

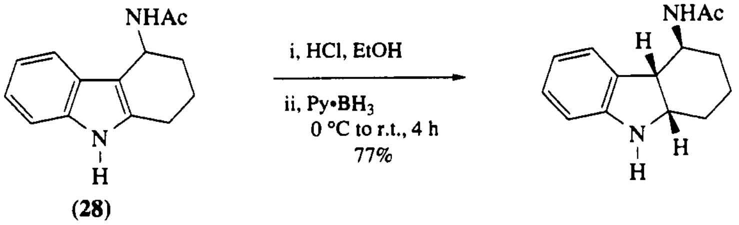
NHAc
N
H
(28)
i, HCl, EtOH
ii, Py•BH₃
0 °C to r.t., 4 h
77%
NHAc
H
N
H
H

(83)

Interestingly, whereas NaBH3CN/HOAc fails to reduce the indole ring in the PDE thiophene analog (**29**), this double bond is reduced using borane–TFA (equation 84).[146] These conditions are also reported by Cava and coworkers to reduce a furan analog of (**29**).[113]

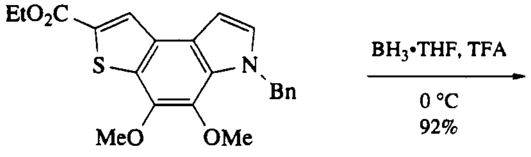
EtO$_2$C
S
N
Bn
MeO
OMe
BH$_3$•THF, TFA
0 °C
92%
EtO$_2$C
S
N
Bn
MeO
OMe

(**29**)

(84)

The ionic hydrogenation of indoles to indolines using Et3SiH/TFA has been described by Parnes *et al.*[147] and utilized by McKenzie,[127] Magnus,[148,149] Hlasta[150] and Ward,[151] and their coworkers in several different situations (equations 85–89). For the most part, the chemoselectivity and stereoselectivity that are observed with this reagent combination parallel that which was observed with NaBH4/TFA (*vide supra*).

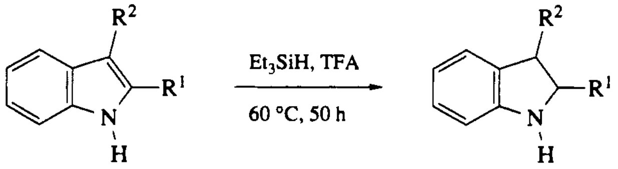
R$^2$
R$^1$
N
H
Et$_3$SiH, TFA
60 °C, 50 h
R$^2$
R$^1$
N
H

(85)

R$^1$ = Me, R$^2$ = H (83%); R$^1$ = R$^2$ = Me (80%) (*cis*:*trans* = 42:58)

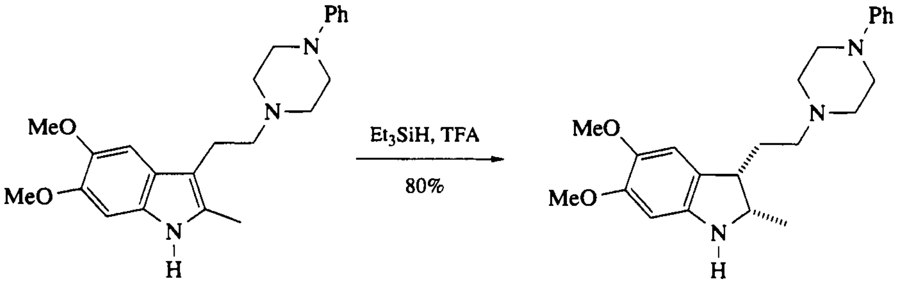
Ph
N
N
MeO
MeO
N
H
Et$_3$SiH, TFA
80%
Ph
N
N
MeO
MeO
N
H

(86)

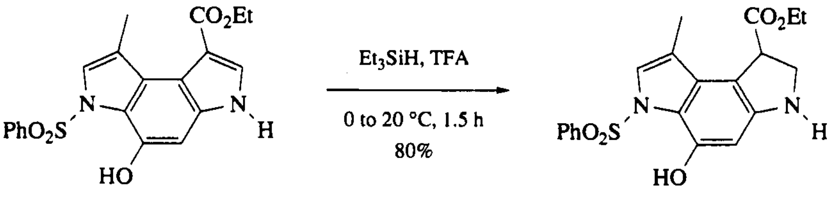
CO$_2$Et
N
PhO$_2$S
N
H
HO
Et$_3$SiH, TFA
0 to 20 °C, 1.5 h
80%
CO$_2$Et
N
PhO$_2$S
N
H
HO

(87)

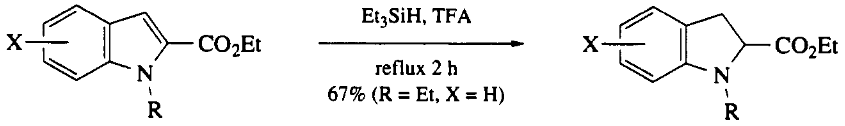
X
CO$_2$Et
N
R
Et$_3$SiH, TFA
reflux 2 h
67% (R = Et, X = H)
X
CO$_2$Et
N
R

(88)

R = Me, Et, Pr, Bn, allyl; X = H, 5-F, 7-Cl, 5,7-diCl$_2$

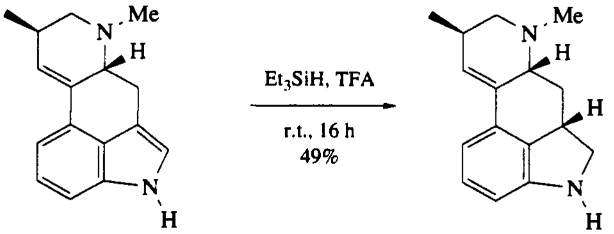
Me
N
H
N
H
Et$_3$SiH, TFA
r.t., 16 h
49%
Me
N
H
H
N
H

(89)

In summary, myriad boron hydride and silicon hydride reduction methods are available for the reduction of indoles to indolines. It is interesting to compare the various methods for the stereoselective reduction of 2,3-dimethylindole to *cis*- and *trans*-2,3-dimethylindoline (Table 1). While most methods show a preference for the more stable *trans* isomer, only with $Zn(BH_4)_2$ is this preference pronounced.

**Table 1** Stereochemistry of the Reduction of 2,3-Dimethylindole

| *Conditions* | *Cis(%)* | *Trans(%)* | *Yield(%)* | *Ref.* |
|---|---|---|---|---|
| $Zn(BH_4)_2$, r.t. | 6 | 94 | 39 | 133 |
| $Zn(BH_4)_2$, 40 °C | 18 | 82 | 61 | 133 |
| $H_2$, $Pt/Al_2O_3$ | 18 | 82 | 28 | 73 |
| $NaBH_3CN$, HOAc | 25 | 75 | 90 | 107 |
| $BH_3$–TFA | 33 | 67 | 82 | 129 |
| $Et_3SiH$, TFA | 42 | 58 | 80 | 147 |
| $B_2H_6$, NaOMe, HCl | 47 | 53 | 93 | 101 |
| $BH_3$–$Me_3N$, HCl | 57 | 43 | 72 | 134 |
| Zn, TFA | 63 | 37 | — | 147 |
| Zn, $H_3PO_4$ | 65 | 35 | 19 | 96 |
| Zn, HCl | 70 | 30 | — | 147 |

### 3.7.5.4 Miscellaneous Methods

Two indole reduction methods that have not been studied in detail are the use of phosphonium hydriodide (equation 90)[152] and electrolysis (equations 91–93).[153–155]

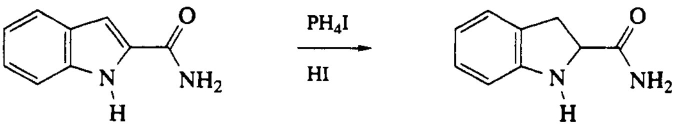

(90)

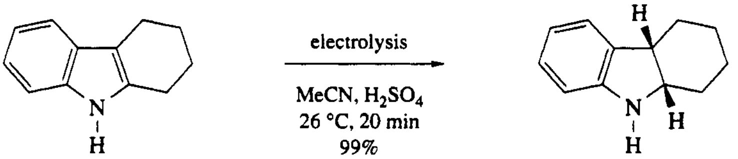

(91)

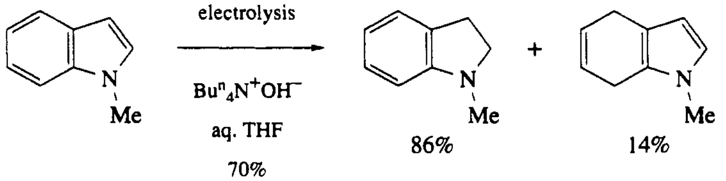

(92)

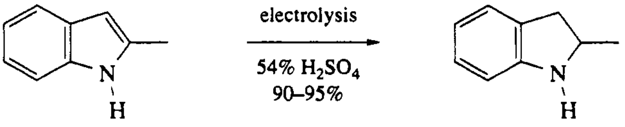

(93)

The isomeric isoindoles are very susceptible to reduction. But because no new methods to accomplish this reduction have been reported in the years since an excellent review[156] was published over 20 years ago, nothing further on this topic will be presented here.

## 3.7.6 REDUCTION OF BENZO[*b*]FURANS

Unlike the enamine double bond of indoles, the corresponding double bond of benzo[*b*]furans is less basic and, therefore, is much less susceptible to the protonation–reduction tactic exploited so successfully with indoles (*vide supra*). Nevertheless, several reduction methods are possible and reviews of early work are available.[157,158]

### 3.7.6.1 Catalytic Hydrogenation

Studies of the hydrogenation of benzo[*b*]furans with several Pt, Pd and Rh catalysts (equations 94–97) revealed that Pd gives the highest yields of dihydrobenzo[*b*]furans (equations 94 and 96).[159–163] A Pd/styrene–maleic acid copolymer catalyst reduces benzofuran to dihydrobenzo[*b*]furan in quantitative yield.[25] Platinum gives significant amounts of the cleavage product 2-ethylphenol and rhodium gives overreduction (equation 95).[161] A nickel catalyst results in the deoxygenation of a benzylic acetate (equation 97).[163]

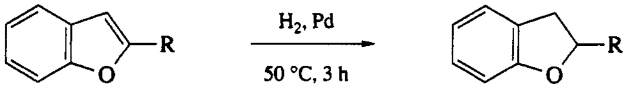
R
O
$H_2$, Pd
50 °C, 3 h
R
O

(94)

R = H (97%); R = Me (22%); R = Et (33%); R = Pr$^n$ (5%)

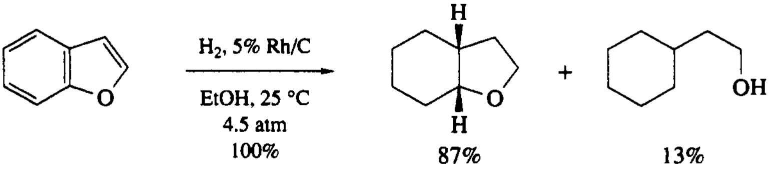
O
$H_2$, 5% Rh/C
EtOH, 25 °C
4.5 atm
100%
H
O
H
87%
+
OH
13%

(95)

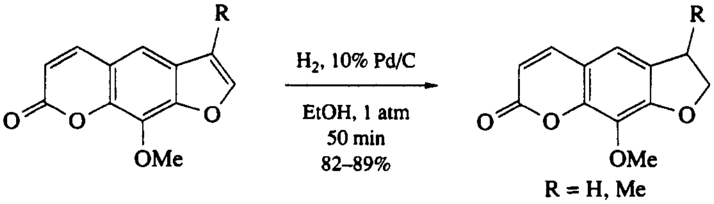
R
O
O
O
OMe
$H_2$, 10% Pd/C
EtOH, 1 atm
50 min
82–89%
R
O
O
O
OMe
R = H, Me

(96)

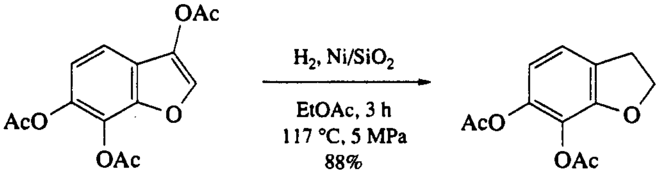
OAc
AcO
O
OAc
$H_2$, Ni/SiO$_2$
EtOAc, 3 h
117 °C, 5 MPa
88%
AcO
O
OAc

(97)

A careful study by Matsumoto and coworkers on the hydrogenation of the diterpene precursor (**30**) reveals that the less active catalyst palladium gives a higher percentage of the (*S*)-isomer than does the more active catalyst platinum (equation 98).[164]

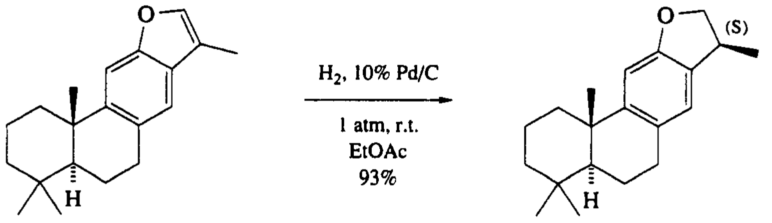
O
H
$H_2$, 10% Pd/C
1 atm, r.t.
EtOAc
93%
O
(S)
H

(**30**)

(*S*):(*R*) = 5:1
($PtO_2$/AcOH gives (*S*):(*R*) = 2:1)

(98)

Interestingly, Venugopalan and Balasubramanian found that only the pyran ring is hydrogenated in furopyran (**31**) using Pd/C (equation 99).[165] Somewhat similarly, Horaguchi and coworkers noted that the furan double bond in 7-methoxycyclohepta[*cd*]benzofuran (**32**) is unaffected during the hydrogenation of the cycloheptadiene portion of the molecule (equation 100).[166]

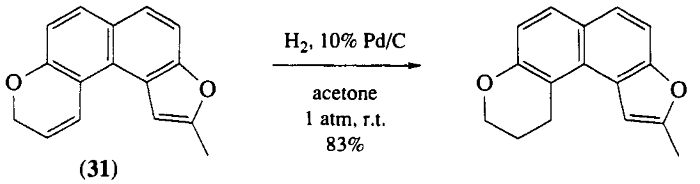
O
O
H2, 10% Pd/C
acetone
1 atm, r.t.
83%
O
O

**(31)**

(99)

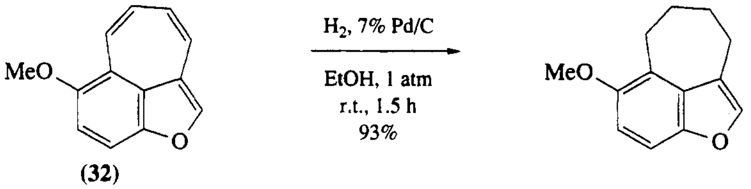
MeO
O
H2, 7% Pd/C
EtOH, 1 atm
r.t., 1.5 h
93%
MeO
O

**(32)**

(100)

Rapoport and coworkers have used a hydrogenation–dehydrogenation protocol to introduce tritium into psoralen derivatives (equation 101).[167] For the same class of compounds, Heindel and coworkers have discovered a very simple catalytic transfer hydrogenation of the furan double bond (equation 102).[168,169]

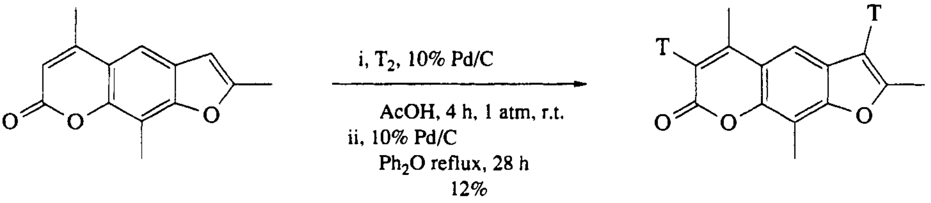
O
O
O
i, T2, 10% Pd/C
AcOH, 4 h, 1 atm, r.t.
ii, 10% Pd/C
Ph2O reflux, 28 h
12%
T
T
O
O
O

(101)

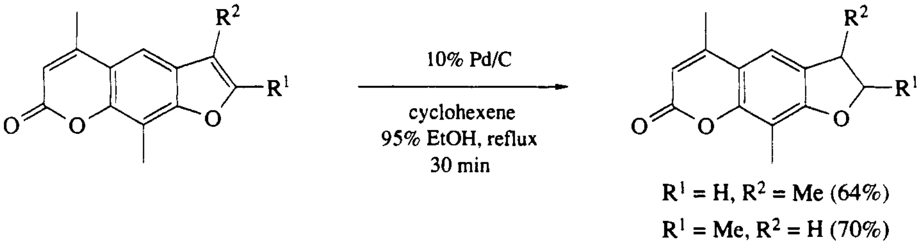
R2
R1
O
O
O
10% Pd/C
cyclohexene
95% EtOH, reflux
30 min
R2
R1
O
O
O
R1 = H, R2 = Me (64%)
R1 = Me, R2 = H (70%)

(102)

Although reduction of the isomeric benzo[*c*]furans (isobenzofurans) has been much less studied than the reduction of benzo[*b*]furans, some examples of their reduction are known.[170] Thus, 1,3-diphenylbenzo[*c*]furan can be hydrogenated to afford the two products shown in equation (103).[171]

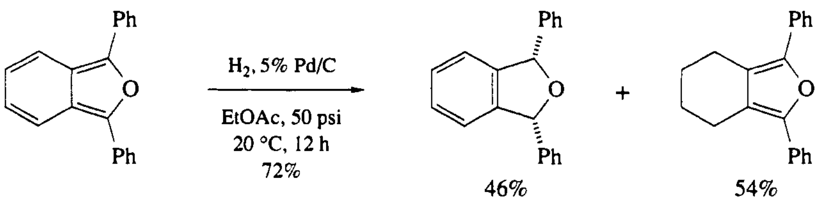
Ph
O
Ph
H2, 5% Pd/C
EtOAc, 50 psi
20 °C, 12 h
72%
Ph
O
Ph
+
Ph
O
Ph
46%
54%

(103)

### 3.7.6.2 Dissolving Metals

The dissolving metal reduction of benzo[*b*]furans and dibenzofurans is a classical technique and, depending on the conditions, can give rise to a variety of products.[157,158] Several examples are summarized in equations (104–108).[172–175] The cleavage of dibenzofurans to afford 2-hydroxybiphenyls (equation 107) is a particularly valuable route to these compounds.[174] The reduction of 3-carbomethoxybenzofurans with Mg/MeOH (equation 108)[175] is reminiscent of the indole reduction reported earlier (equation 51).

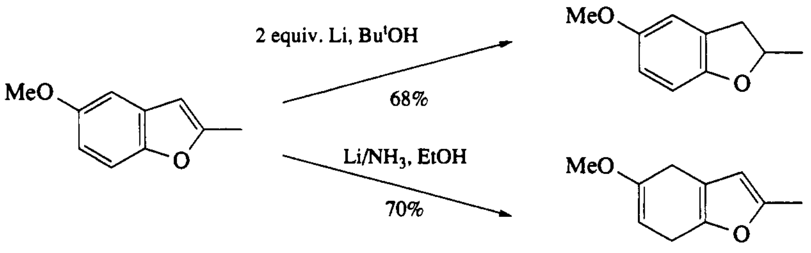
MeO
2 equiv. Li, Bu$^t$OH
68%
Li/NH$_3$, EtOH
70%
MeO
MeO
O
O
O

(104)

(105)

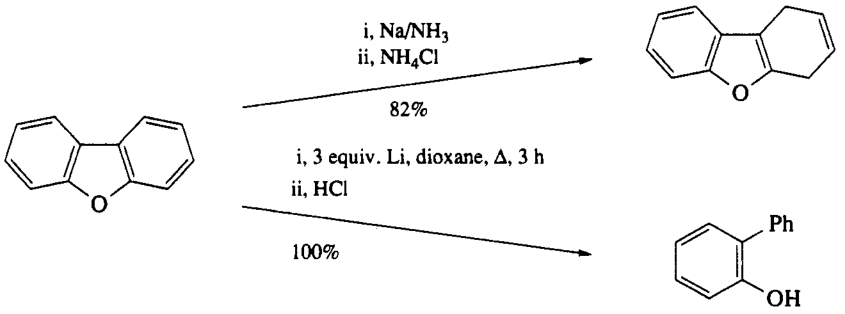
i, Na/NH$_3$
ii, NH$_4$Cl
82%
i, 3 equiv. Li, dioxane, Δ, 3 h
ii, HCl
100%
O
O
Ph
OH

(106)

(107)

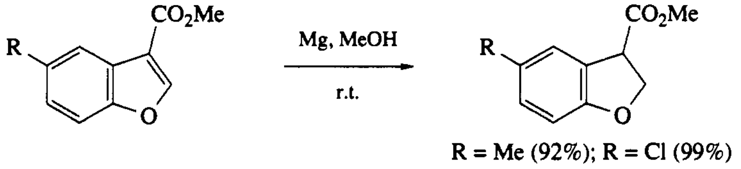
CO$_2$Me
R
O
Mg, MeOH
r.t.
CO$_2$Me
R
O
R = Me (92%); R = Cl (99%)

(108)

In contrast to their observations noted earlier, Horaguchi and coworkers were able to reduce (**32**) using Na/EtOH (equation 109).[166]

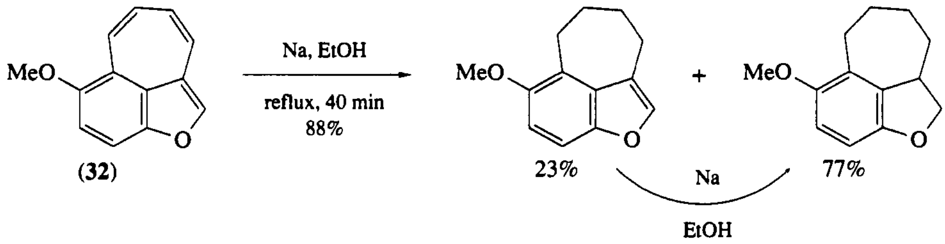
MeO
O
Na, EtOH
reflux, 40 min
88%
MeO
O
23%
+
MeO
O
77%
Na
EtOH

(**32**)

(109)

The Birch-type reduction of 1,3-diphenylbenzo[*c*]furan (**33**) has been studied in detail by Smith and McCall (equation 110).[171]

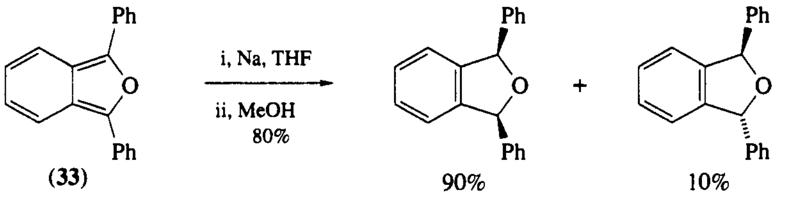
Ph
O
Ph
i, Na, THF
ii, MeOH
80%
Ph
O
Ph
90%
+
Ph
O
Ph
10%

(**33**)

(110)

### 3.7.6.3 Boron Hydrides and Related Methods

Although much less explored than the analogous reductions of indoles (*vide supra*), the reduction of benzofurans with mixed metal hydrides is showing promise as a useful and versatile methodology.

Borisova *et al.* have found that benzofurans are reduced to dihydrobenzofurans using $NaBH_4$ (or $KBH_4$)/TFA (equation 111).[176] In the case of 2-ethyl-3-methylbenzofuran, the ratio of *cis*:*trans* products is 40:60. In contrast to this result, Cava and coworkers did not observe reduction of the benzofuran double bond in (**34**) using $BH_3$/TFA (equation 112).[113]

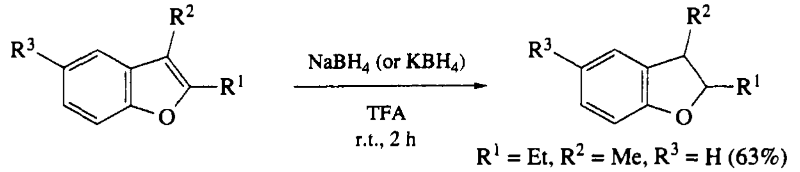

$R^1$ = Et, $R^2$ = Me, $R^3$ = H (63%)
$R^1$, $R^2$ = $-(CH_2)_4-$, $R^3$ = H (67%)
$R^1$, $R^2$ = $-(CH_2)_4-$, $R^3$ = OH (52%)

(111)

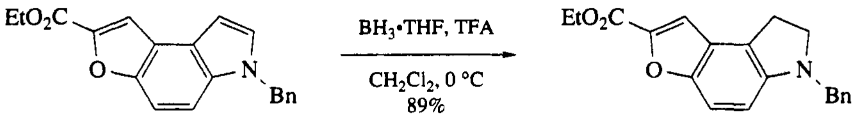

(**34**)

(112)

Karakhanov and coworkers successfully applied the ionic hydrogenation tactic, using $Et_3SiH$/TFA, to the reduction of several benzofurans (equation 113).[177] In the case of 2,3-dimethylbenzofuran, the ratio of *cis*:*trans* products is 19:81. It is interesting to note the deuterium-labeling results reported by these Russian scientists. Thus, whereas treatment of benzofuran (or 2-methylbenzofuran) with $Et_3SiD$/TFA gives rise to the 2-deuterio derivative, indicating the expected C-3 protonation, the same treatment of 3-methylbenzofuran gives rise to the 3-deuterio derivative, indicating C-2 protonation (Scheme 8).

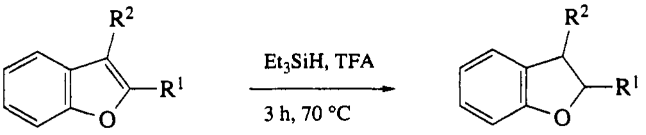

$R^1$ = $R^2$ = H (81%)
$R^1$= H, $R^2$ = Me (96%)
$R^1$ = Me, $R^2$= H (96%)
$R^1$ = Et, $R^2$ = H (96%)
$R^1$ = $R^2$ =Me (94%)

(113)

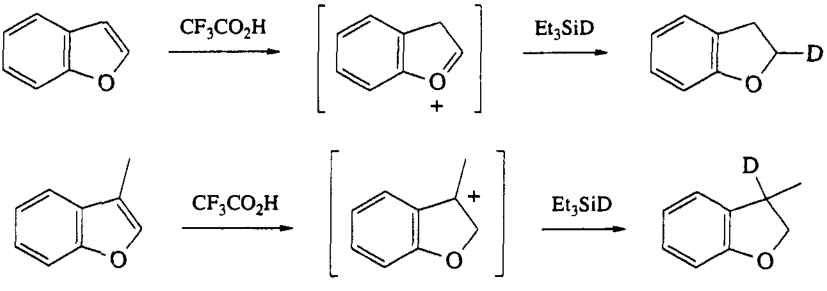

Scheme 8

### 3.7.6.4 Miscellaneous Methods

A photoreduction of 3-phenylbenzofurans has been reported by Parkanyi and coworkers (equation 114)[178] and benzo[*b*]furans can be electrochemically reduced (equation 115).[154] Further electrolysis of 2,3-dihydrobenzofuran gives 2,3,4,7-tetrahydrobenzofuran. Similarly, electrolysis of 5-methoxybenzofuran gives 69% of the dihydro product. In the absence of water, only 2-ethylphenol is observed.[154]

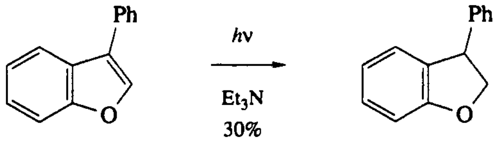
Ph
hν
Et₃N
30%
O
Ph
O

(114)

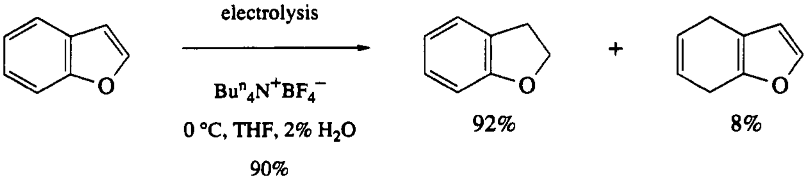
O
electrolysis
Buⁿ₄N⁺BF₄⁻
0 °C, THF, 2% H₂O
90%
O
92%
+
O
8%

(115)

## 3.7.7 REDUCTION OF BENZO[*b*]THIOPHENES

The early reductions of benzo[*b*]thiophenes, including hydrosulfurization reactions, have been reviewed.[42,43,179–181]

### 3.7.7.1 Catalytic Hydrogenation

The catalytic hydrogenation of benzo[*b*]thiophene to 2,3-dihydrobenzo[*b*]thiophene using both a PdS catalyst and a rhodium catalyst have been reported (equation 116).[182–184] Fish and coworkers have also accomplished this reduction using a ruthenium catalyst.[81]

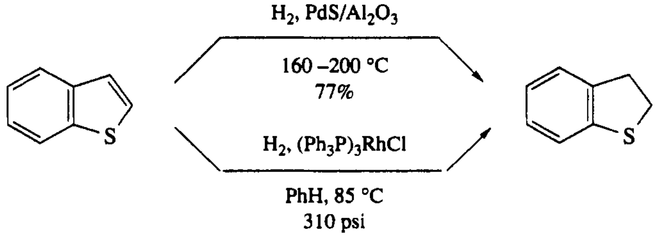
S
H₂, PdS/Al₂O₃
160 -200 °C
77%
H₂, (Ph₃P)₃RhCl
PhH, 85 °C
310 psi
S

(116)

### 3.7.7.2 Dissolving Metals

The Birch reductions of benzothiophene and dibenzothiophene have been studied for a number of years.[12] The major pathway in the former reaction is cleavage to 2-ethylthiophenol, under several conditions with $Na/NH_3$,[185] while the major mode of reaction for dibenzothiophene depends on the order of mixing, but is mainly ring cleavage.[12] A recent report by Wood and coworkers describes the use of calcium in this regard (equations 117 and 118).[186] In contrast to this ring cleavage, the conjugated benzothiophene (**35**) is cleanly reduced to the 2,3-dihydro derivative by the action of Mg/MeOH (equation 119).[175]

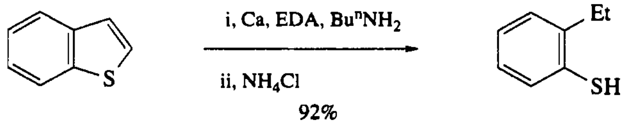
S
i, Ca, EDA, BuⁿNH₂
ii, NH₄Cl
92%
Et
SH

(117)

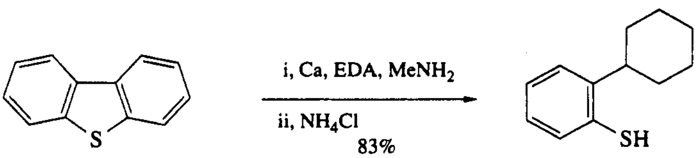
S
i, Ca, EDA, MeNH₂
ii, NH₄Cl
83%
SH

(118)

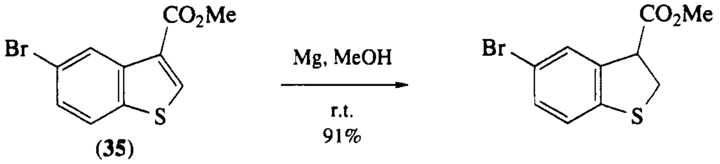

(119)

### 3.7.7.3 Ionic Hydrogenation

The only reduction of benzothiophenes involving metal hydrides is ionic hydrogenation utilizing $Et_3SiH/TFA$ (equation 120).[56,187] The rate of reduction of benzothiophene itself is very sluggish and much slower than that of benzofuran (equation 113).

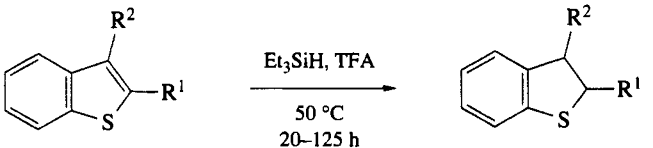

(120)

$R^1$ = Me, $R^2$ = H (80%)
$R^1$ = H, $R^2$ = Me (90%)
$R^1$ = $R^2$ =H (55%)

The deuterium-labeling studies parallel those which were observed with benzofurans (Scheme 8). Thus, 2-methylbenzothiophene is protonated at C-3 and 3-methylbenzothiophene is protonated at C-2 to give the products (**36**) and (**37**), respectively, after deuteride transfer to the respective intermediate carbocations.[187]

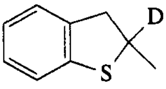

(**36**)

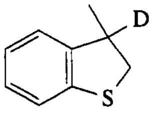

(**37**)

### 3.7.7.4 Electrochemical

The electrolytic reduction of benzo[*b*]thiophene has been described by Pacut and Kariv-Miller (equation 121).[188] Because the two products can be easily separated, this electrochemical Birch reduction is a very good preparation of 2,3-dihydrobenzo[*b*]thiophene.

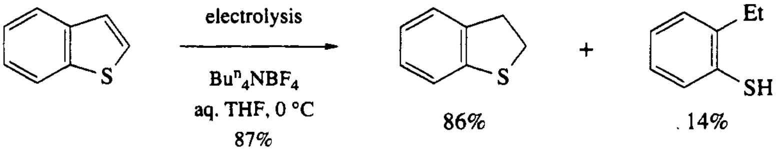

(121)

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# 3.8

# Partial and Complete Reduction of Heterocycles Containing More Than One Heteroatom

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## 3.8.1 INTRODUCTION

To cover the reductive behavior of all types of heterocycles bearing more than one heteroatom within the confines of one brief chapter is impossible, thus the content of this chapter has been edited to reflect those topics and systems in which there is most interest. Many polycyclic and less common heterocyclic molecules are not included. Similarly the weighting of the subject matter is not uniform, and greater emphasis is placed on those areas where the reduction of heterocycles gives access to useful synthons or provides templates which exert stereochemical control in target-orientated syntheses.

## 3.8.2 REDUCTION OF HETEROCYCLES CONTAINING TWO NITROGEN ATOMS

### 3.8.2.1 Five-membered Ring Systems

### *3.8.2.1.1 Pyrazoles, indazoles, pyrazolines and pyrazolidines*

The pyrazole ring is resistant to most reducing agents and survives intact when other heterocycles are cleaved. An illustration is provided by the reaction of the pyrazoloimidazolidinone (**1**) with LAH.[1] Here the imidazolidine unit is sensitized to nucleophilic attack by the presence of a lactam carbonyl group, and the product formed is the monocyclic pyrazole (**2**). The stability of pyrazoles to reduction has been exploited in a synthesis of aldehydes from acyl halides. Thus *N*-acylpyrazoles (**3**) on reduction with LAH produce complexes of the type (**4**); these when hydrolyzed yield aldehydes and the parent pyrazoles (**5**).[2]

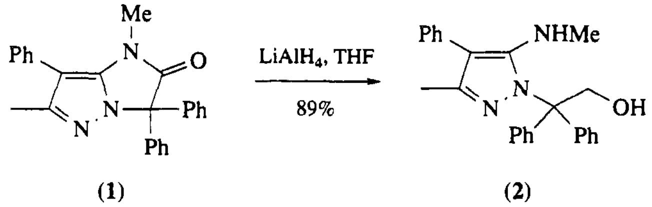

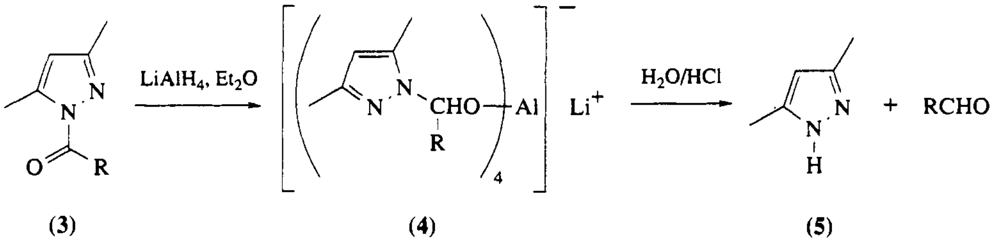

Unsaturated groups bonded to the carbon atoms of pyrazoles are also reduced, either by chemical reagents such as sodium and ethanol,[3] or through hydrogenation over nickel or palladium catalysts.[4] Nitropyrazoles can be converted into the corresponding amino compounds by exposure to dissolving metals in aqueous acids, but pyrazoles (**6**) are not stable to catalytic hydrogenation in the presence of acids and pyrazolines (**7**) are formed. Now the reaction can proceed further to yield pyrazolidines (**8**), and ultimately acyclic 1,3-diaminopropanes (**9**).[5] Over-reduction is not a problem if neutral media are employed and the hydrogenation of 2-pyrazolidines (**10**) in organic solvents over palladium or Adams' catalyst only serves to reduce the azo group attached to C-5 giving the de-azo derivatives (**11**).[6] LAH reduces both pyrazolines and pyrazolinium salts (**12**) to pyrazolidines (**13**).[7]

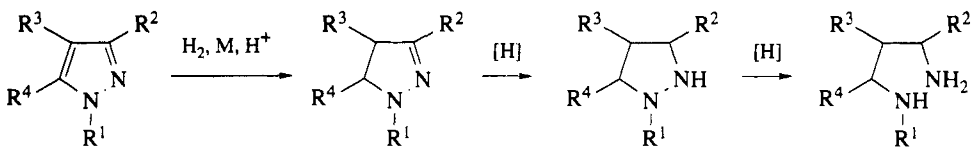

(6) (7) (8) (9)

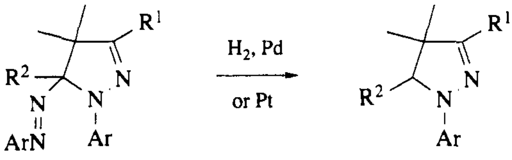

(10) (11)

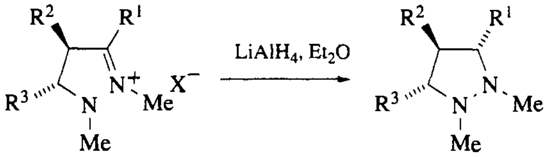

(12) (13)

Catalytic hydrogenation of pyrazolin-5-ones (**14**) under mild conditions affords the corresponding pyrazolidinones (**15**), the lactam units of which may be reduced to give the pyrazolidines (**16**) by treatment with LAH.[8] *N*-Sulfonylpyrazolin-4-ones (**17**) can be reduced with L-selectride to afford pyrazolinols (**18**), without affecting the alkenic bond of the heterocycle.[9] The N—N bond of pyrazolidines is cleaved by hydrogenation over Raney nickel as catalyst and, for example, hydrogenolysis of the 1,5-diazabicyclooctane (**19**) yields the 1,5-diazaoctane (**20**).[10] Similar reactions do not occur with *N*-acyl derivatives, although ring opening can now be achieved through the action of sodium in liquid ammonia. In this way the dicarbamate (**21**) is transformed into the 1,3-diaminocyclopentane (**22**).[11]

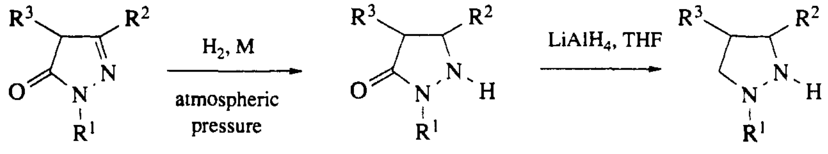

(14) (15) (16)

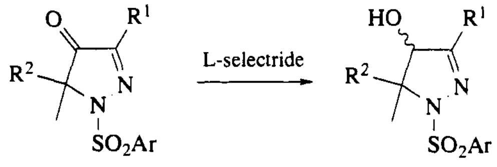

(17) (18)

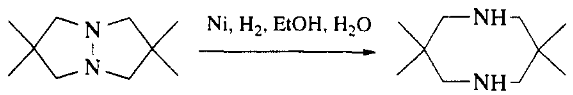

(19) (20)

The nucleus of indazole, like that of pyrazole, is stable to reduction, so that treatment of the amido derivative (**23**) with LAH leads only to the amine (**24**).[12] Indazolium salts (**25**) are more reactive and undergo reduction with potassium borohydride to give indazolines (**26**).[13]

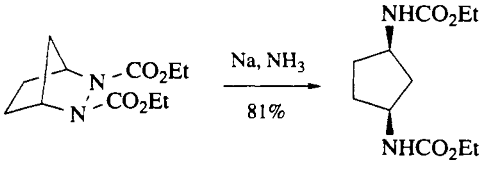

**(21)** **(22)**

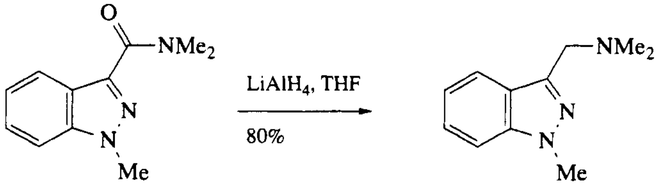

**(23)** **(24)**

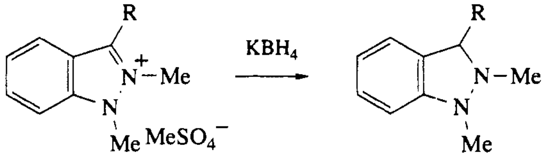

**(25)** **(26)**

### *3.8.2.1.2 Imidazoles, benzimidazoles, imidazolines and imidazolium salts*

The aromaticity of the imidazole nucleus ensures stability towards reduction, and when benzimidazole (**27**) is hydrogenated over Adams' catalyst in acetic acid the carbocyclic ring is reduced first to give the tetrahydrobenzimidazole (**28**). However, if the solvent is changed to acetic anhydride, *N*-acylation promotes the reduction of the heterocycle and the 1,3-diacetylbenzimidazoline (**29**) is then formed (Scheme 1).[14] Imidazole (**30**) under these conditions gives 1,3-diacetylimidazoline (**31**). Imidazolium salts (**32**) are easily reduced and treatment with excess sodium borohydride in 95% aqueous ethanol culminates in the formation of 1,2-diamines, (**33**) or (**34**). Either N—C bond may cleave, although if the substituent $R^1$ is benzyl the major products are benzylamines (**33**; $R^1$ = Bn).[15]

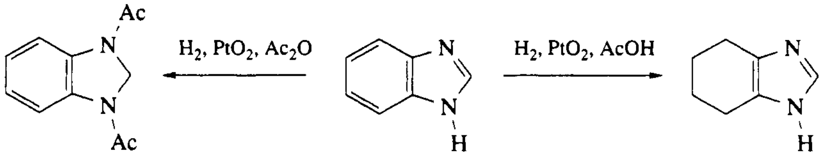

**(29)** **(27)** **(28)**

**Scheme 1**

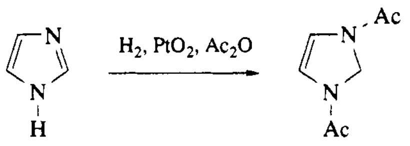

**(30)** **(31)**

2-Imidazolines (**35**) also undergo reductive decyclization to diamines (**36**) with metal hydrides, but here LAH is a superior reagent to sodium borohydride, and other hydrides such as sodium cyanoborohydride fail to react.[16] In the case of benzimidazolium salts (**37**) LAH in diethyl ether or THF, or sodium borohydride in water, gives benzimidazolines (**38**). Ring scission does not occur.[17]

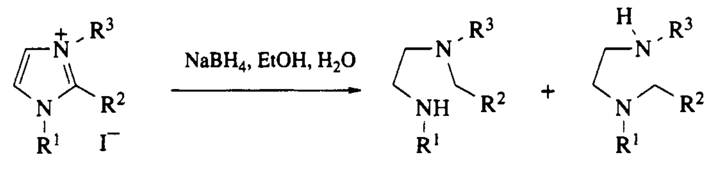

**(32)** **(33)** **(34)**

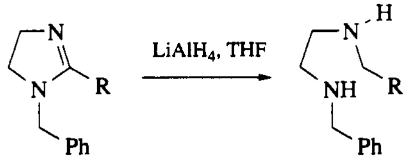

**(35)** **(36)**

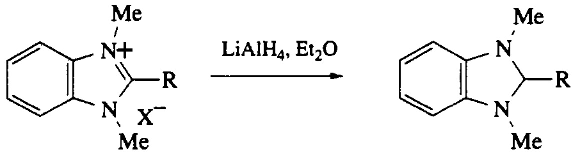

**(37)** **(38)**

Imidazolidin-2-ones (**39**) are inert to reduction with sodium borohydride, but LAH converts them into the corresponding imidazolidines (**40**), the rate of the reaction being determined by the size of the *N*-substituents.[18] *N*-Substituted guanidines are similarly unaffected by treatment with sodium borohydride or lithium borohydride, but if an acetoxymethyl substituent is present, as in the derivative (**41**), selective *O*-deacetylation occurs to give the corresponding alcohol (**42**).[19] The carbonyl groups of hydantoins (**43**) survive treatment with sodium amalgam, or Raney nickel in sodium hydroxide, although side chain double bonds are reduced giving dihydro derivatives (**44**).[20] On the other hand, 2,4-dithiohydantoins (**45**) are desulfurized by exposure to Raney nickel in boiling ethanol, and yield the parent imidazoles (**46**).[21]

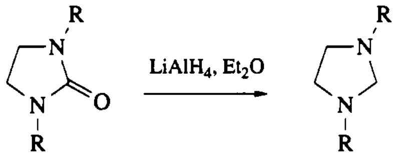

**(39)** **(40)**

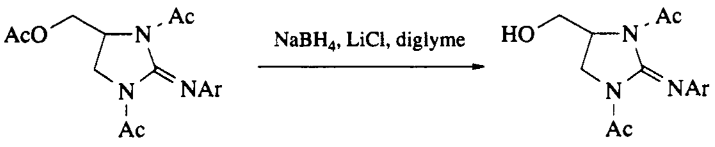

**(41)** **(42)**

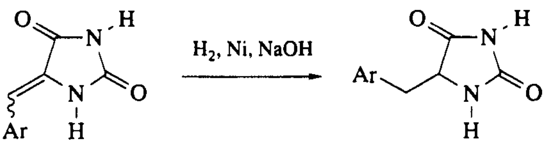

**(43)** **(44)**

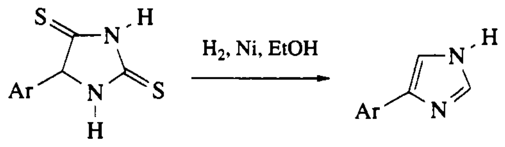

**(45)** **(46)**

### 3.8.2.2 Six-membered Ring Systems

#### 3.8.2.2.1 *Pyridazines, pyridazinium salts, dihydropyridazines, tetrahydropyridazines, cinnolines and phthalazines*

Pyridazine *N*-oxides (**47**) are partially deoxygenated by hydrogenation at atmospheric pressure over palladium on carbon affording a mixture of the corresponding mono-*N*-oxides (**48**) and (**49**).[22] By contrast, electrochemical methods cause ring opening, provided that the solvent contains acetic anhydride, and under these conditions pyridazine (**50**) itself is converted into 1,4-diacetamidobutane (**51**).[23] A similar ring scission is achieved if *N*,*N*-diacylhexahydropyridazines are treated with sodium in liquid ammonia; thus the dicarbamate (**52**) affords the lyxose derivative (**53**),[24] and treatment of the bicyclic amide (**54**) with sodium amalgam effects ring opening to give the pyrrolidinone (**55**).[25]

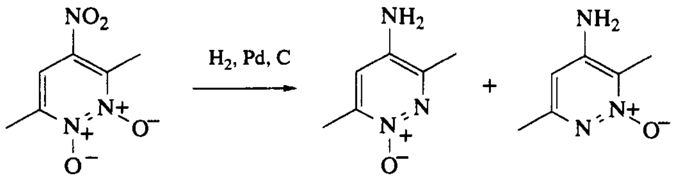

**(47)** **(48)** 55% **(49)** 42%

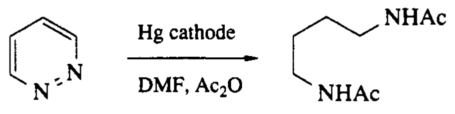

**(50)** **(51)**

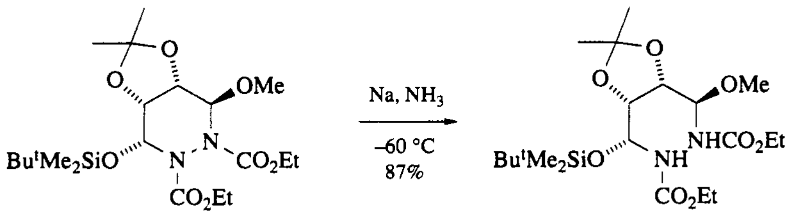

**(52)** **(53)**

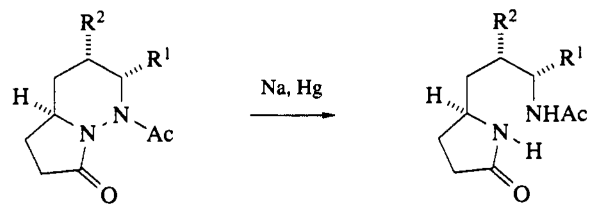

**(54)** **(55)**

Pyridazines (**56**) are reduced by treatment with a mixture of dimethyl sulfate (which forms the corresponding salts *in situ*) and sodium borohydride to yield 1,6-dihydropyridazines (**57**; $R^1$ = Me), together with minor amounts of 1,4,5,6-tetrahydropyridazines (**58**; $R^1$ = Me). Normally 1,6-dihydropyrazines are unstable and decompose in air, but *N*-acylated derivatives are more stable. Thus if methyl chloroformate replaces dimethyl sulfate in the reaction mixture both 1,4-dihydro- (**59**; $R^1$ = $CO_2Me$) and 1,6-dihydropyridazines (**57**; $R^1$ = $CO_2Me$) can be isolated, the latter predominating if there is an electron-withdrawing group at C-6 in the starting material (Scheme 2).[26]

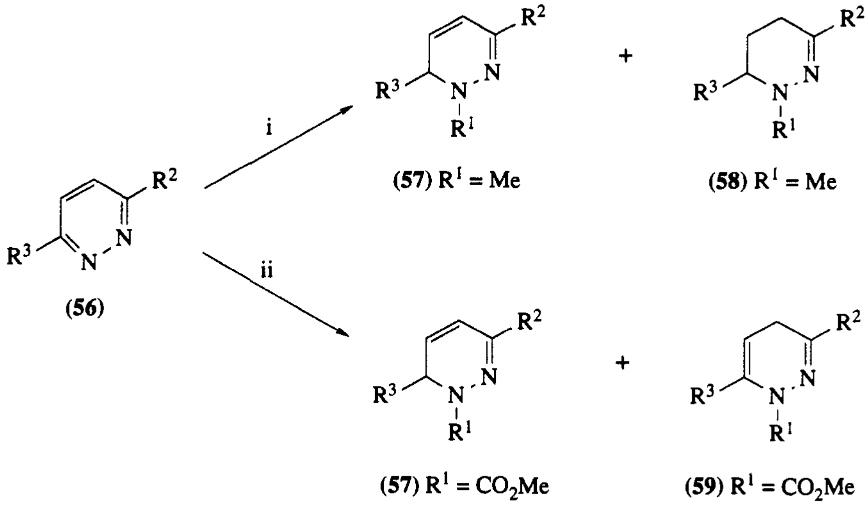

i, $Me_2SO_4$, $NaBH_4$; ii, $ClCO_2Me$, $NaBH_4$

**Scheme 2**

LAH converts 1-alkylpyridazin-6-ones (**60**) into the corresponding 1,6-dihydropyridazines (**57**; $R^1$ = Me, $R^3$ = H), whereas excess reagent reduces 4,5-dihydropyridazin-6-ones (**61**) to a mixture of 1,4,5,6-tetrahydro- (**62**) and hexahydro-pyrazines (**63**).[27] Cinnolines (**64**) and phthalazines (**66**) both undergo ring opening during cathodic reduction, giving diamines (**65**) and (**67**), respectively.[28]

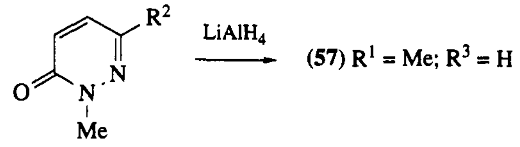

**(60)**

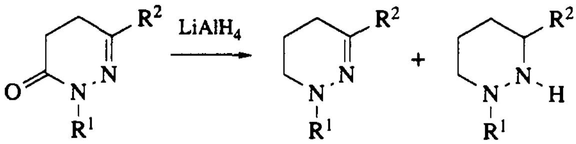

**(61)** **(62)** **(63)**

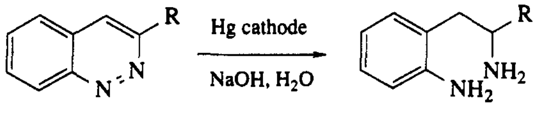

**(64)** **(65)**

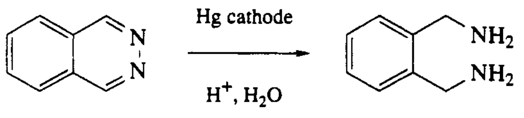
Hg cathode
H+, H2O
N
N
NH2
NH2

(66) (67)

### 3.8.2.2.2 Pyrimidines and quinazolines

Metal hydrides react with pyrimidines (**68**) to give 3,4-dihydropyrimidines (**69**),[29] but electrochemical reduction of the analogs (**70**) gives radical anions (**71**) which may dimerize or, in the presence of a proton source, yield dihydro derivatives (**72**). The latter exist in equilibrium with acyclic tautomers (**73**),[30] and at high potentials further reduction produces anions (**74**) and (**75**) which may then be protonated to give pyrroles (**76**).[31] *N*-Benzyldihydropyrimidines (**77**; R = Bn) are reduced by sodium borohydride in ethanol to give hexahydro derivatives (**78**), but if the *N*-substituent is a phenyl group excess reagent leads to diamines (**79**; Scheme 3).[32] Similar products form when dihydropyrimidinium salts (**80**) are treated with this reagent, although reduction with LAH yields amino imines (**81**). Cathodic reduction of quinazoline (**82**) in aqueous alkali gives first dihydro- (**83**) and then tetrahydro-quinazoline (**84**).[33]

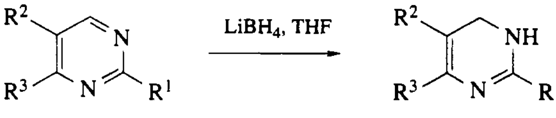
R2
N
R3
N
R1
LiBH4, THF
R2
NH
R3
N
R1

(68) (69)

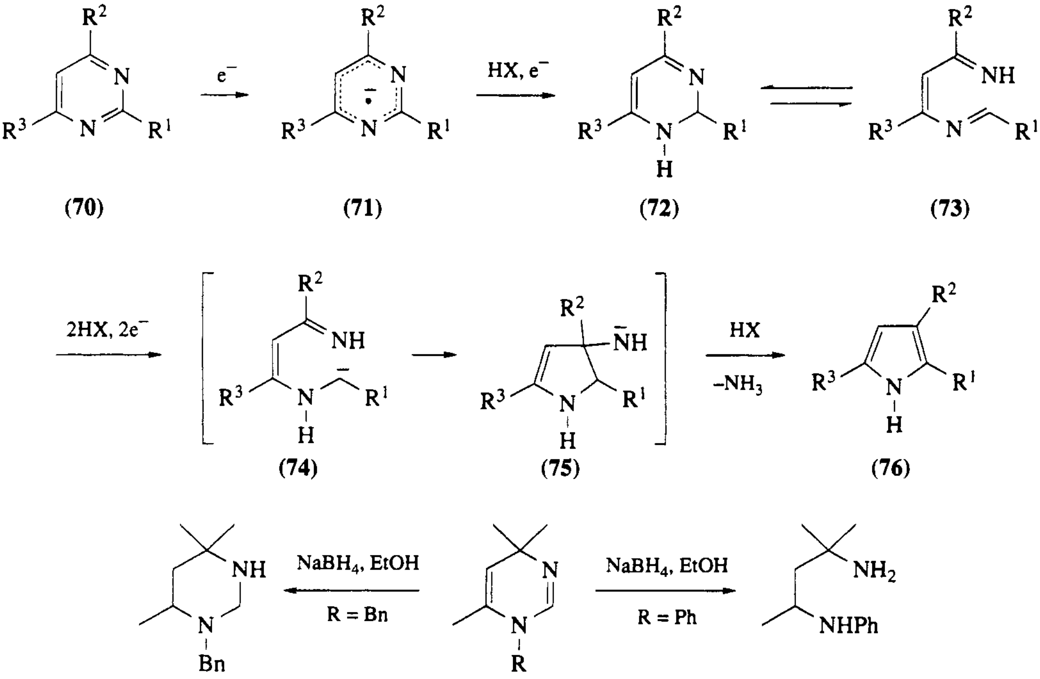
R2
N
R3
N
R1
e−
R2
N
R3
N
R1
HX, e−
R2
N
R3
N
R1
H
R2
NH
R3
N
R1
2HX, 2e−
R2
NH
R3
N
R1
H
R2
NH
R3
N
R1
H
HX
-NH3
R2
R3
N
R1
H
NH
N
Bn
NaBH4, EtOH
R = Bn
N
N
R
NaBH4, EtOH
R = Ph
NH2
NHPh

(70) (71) (72) (73)

(74) (75) (76)

(78) (77) (79)

Scheme 3

Pyrimidin-2(1*H*)-ones (**85**; X = O) and -thiones (**85**; X = S) on reduction with sodium borohydride afford mixtures of 1*H*-3,4- (**86**) and 1*H*-3,6-dihydropyrimidinones (**87**), the product ratios depending on the acidity of the medium, and some further reduction to the fully reduced pyrimidinones may also occur. Similar results are obtained with LAH as the reductant, although 1-arylpyrimidine-2-thiones mainly form the corresponding 3,6-dihydropyridine-2-thiones (**88**), especially if a hydroxy or methoxy group occupies an *ortho* position in the aryl substituent. This suggests that the group may complex with the reagent and facilitate an intramolecular hydride transfer reaction.[34] L-Selectride reduces *N*-benzyl-

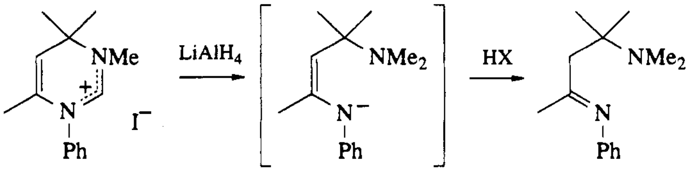
NMe
I$^-$
Ph
LiAlH$_4$
NMe$_2$
N$^-$
Ph
HX
NMe$_2$
N
Ph

**(80)** **(81)**

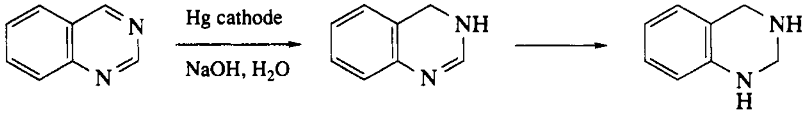
N
N
Hg cathode
NaOH, H$_2$O
NH
N
NH
N
H

**(82)** **(83)** **(84)**

uracils (**89**) to dihydrouracils (**91**; R = H), and the intermediate anions (**90**) can be quenched by alkyl halides, rather than by water, to give 5-alkyl derivatives (**91**; R = Alkyl).[35]

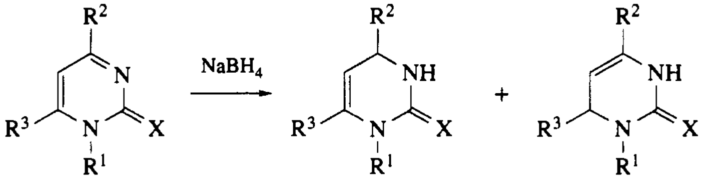
R$^2$
N
R$^3$
N
X
R$^1$
NaBH$_4$
R$^2$
NH
R$^3$
N
X
R$^1$
+
R$^2$
NH
R$^3$
N
X
R$^1$

**(85)** **(86)** **(87)**

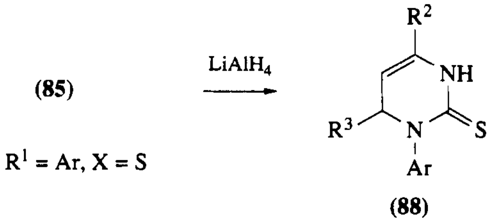
LiAlH$_4$
R$^2$
NH
R$^3$
N
S
Ar

**(85)**

R$^1$ = Ar, X = S

**(88)**

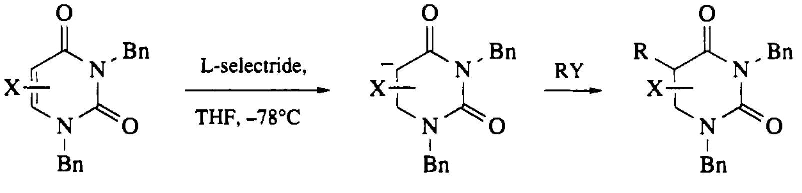
O
Bn
N
X
N
O
Bn
L-selectride,
THF, -78°C
O
Bn
N
X
N
O
Bn
RY
R
O
Bn
N
X
N
O
Bn

**(89)** **(90)** **(91)**

X = H, 5-F, 5-C≡CSiMe$_3$ or 6-CO$_2$Et

### *3.8.2.2.3 Pyrazines and quinoxalines*

Dissolving metals and amalgams all reduce pyrazines to hexahydropyrazines (piperazines). The same products are formed by the hydrogenation of pyrazines over Adams' catalyst at high pressure, and in the case of 2,5-dibenzylpyrazine (**92**) hydrogenation affords both the *cis*- and *trans*-piperazines (**93**) and (**94**) respectively.[36] For the tetracarbonyl derivative (**95**), reduction is easier and a tetrahydro compound (**96**) is formed by hydrogenation at atmospheric pressure. This product, however, undergoes spontaneous oxidation back to the dihydropyrazine (**97**), which is also produced by direct reduction of the parent pyrazine with sodium dithionate.[37] The stability of the 1,4-tetrapyrazine system is utilized in a synthesis of chiral alcohols (**99**) *via* the reduction of the corresponding bis-diamides (**98**) with lithium triethylborohydride.[38] Benzopyrazine (quinoxaline) (**100**; R = H) on electrochemical reduction yields the 1,4-dihydro derivative (**101**; R = H), but if an alkyl group is present at C-2 the 3,4-dihydro formulation (**102**) is preferred.[33]

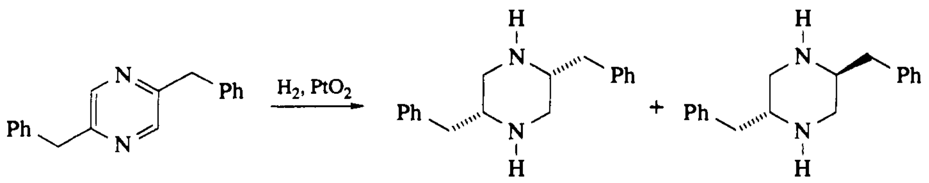
Ph
N
N
Ph
$H_2$, $PtO_2$
H
N
N
H
Ph
Ph
+
H
N
N
H
Ph
Ph

**(92)** **(93)** 26% **(94)** 51%

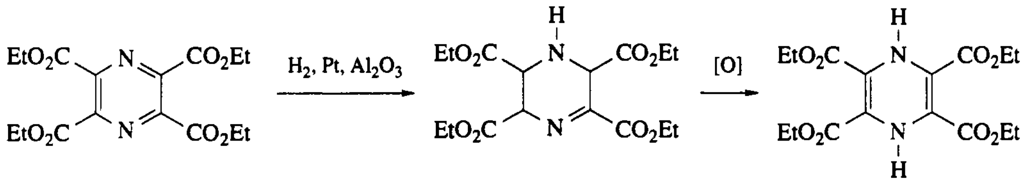
$EtO_2C$
$CO_2Et$
$EtO_2C$
$CO_2Et$
N
N
$H_2$, Pt, $Al_2O_3$
H
N
N
$EtO_2C$
$CO_2Et$
$EtO_2C$
$CO_2Et$
[O]
H
N
N
H
$EtO_2C$
$CO_2Et$
$EtO_2C$
$CO_2Et$

**(95)** **(96)** **(97)**

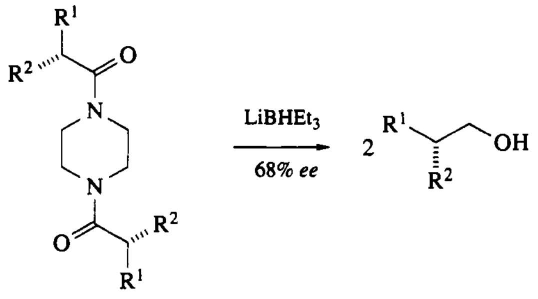
$R^1$
$R^2$
O
N
N
O
$R^2$
$R^1$
$LiBHEt_3$
68% *ee*
2
$R^1$
OH
$R^2$

**(98)** **(99)**

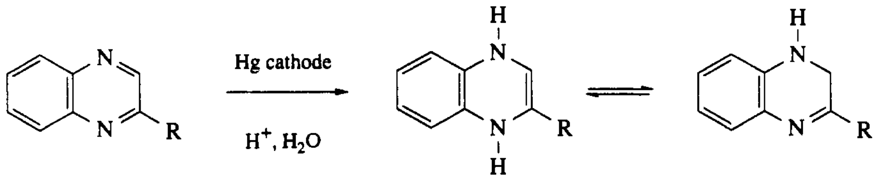
N
N
R
Hg cathode
$H^+$, $H_2O$
H
N
N
H
R
H
N
N
R

**(100)** **(101)** **(102)**

## 3.8.3 REDUCTION OF HETEROCYCLES CONTAINING ONE NITROGEN ATOM AND ONE OXYGEN ATOM

### 3.8.3.1 Five-membered Ring Systems

#### *3.8.3.1.1 Isoxazoles, isoxazolium salts, isoxazolines and isoxazolidines*

*(i) Isoxazoles*

As early as 1891 Claisen noted that isoxazoles, when treated with sodium and either pentyl alcohol or moist diethyl ether, undergo reductive ring opening to give 1,3-enaminoketones.[39] These products may then be hydrolyzed to 1,3-dicarbonyl compounds. In more recent times the use of readily available isoxazoles as masked 1,3-dicarbonyl compounds has found wide application in synthesis, although dissolving metal reductants are not now in favor.[40] Instead hydrogenation over Raney nickel as catalyst is frequently employed as, for example, in the synthesis of hentriacontane-14,16-dione (**104**), a component of natural waxes, from the isoxazole (**103**).[41] The reductive ring scission of the diisoxazole (**105**) occurs in a similar manner, but here hydrolysis of the bis-1,3-enaminoketone (**106**) in the presence of acids is assumed to afford a 'polyketide intermediate' (**107**) which undergoes spontaneous cyclodehydration to the acylrescorcinol (**108**),[42] thereby mimicing the last stages of the biosynthesis of similar compounds through the 'acetate pathway'.

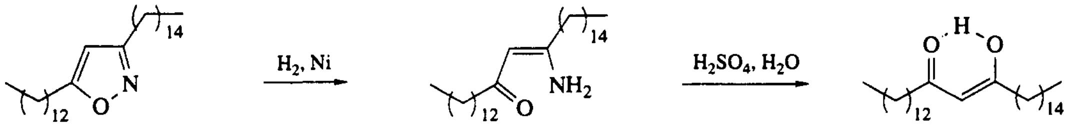

**(103)** **(104)** 75% yield overall

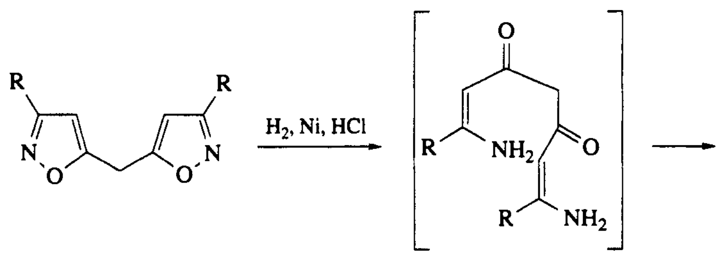

**(105)** **(106)**

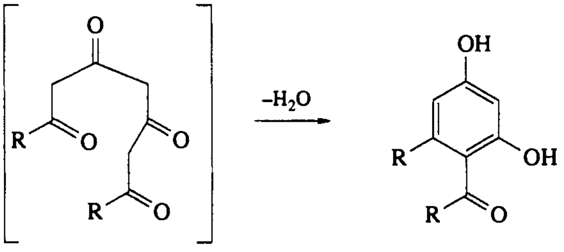

**(107)** **(108)**

Hydrogenation of isoxazolylsulfonamides (**109**) over Raney nickel catalyst also gives enaminoketones, but these products undergo cyclodehydration without the need of acid treatment, affording 1,2,6-thiadiazine-1,1-diones (**110**) in good yields.[43] Stork *et al.* have developed this type of reaction into a general synthesis of pyridines (**112**), using 4-(oxoalkyl)isoxazoles (**111**) as starting materials. In this instance the hydrogenation step is achieved using palladium on carbon as catalyst and the cyclization step is promoted by the addition of triethylamine to the reaction mixture. Intermediate dihydropyridines are formed which are easily oxidized to the corresponding pyridines, often simply by exposure to air.[44]

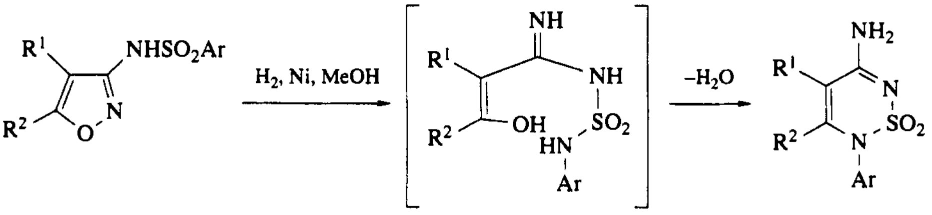

**(109)** **(110)**

Other reagents recommended for the reduction of isoxazoles to 1,3-enaminoketones include samarium diiodide, molybdenum hexacarbonyl in aqueous acetonitrile, and diiron nonacarbonyl in water.[45] Electrochemical methods have also been employed.[46] A particularly mild method involves reaction with the reduced form of the coenzyme lipoamide ($LA_2$) complexed with iron(II).[47] Birch reduction (sodium and

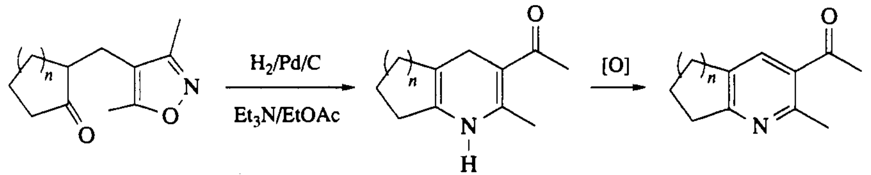

(**111**) $n$ = 1 or 2 (**112**) $n$ = 1 or 2

liquid ammonia) of isoxazoles gives 1,3-aminoketones rather than 1,3-enaminoketones, and exposure of these compounds to acids tends to cause elimination of ammonia and the production of enones. Treatment of isoxazoles with metal hydride reductants gives variable results and the products formed seem to depend on the nature and substitution pattern of the groups attached to the heterocycle. Thus, unless an electron-withdrawing group is present at C-4 of the isoxazole ring, sodium borohydride or lithium diisobutylaluminum hydride fail to react at the nucleus, although vulnerable substituents (such as carbonyl groups) are reduced in the expected manner, and 5-chloroisoxazoles may be partially dechlorinated if they are reacted with sodium borohydride in dimethylsulfoxide as solvent.[48] When reduced with lithium aluminum hydride isoxazoles (**113**) afford aziridine alcohols (**114**), together with smaller amounts of aziridines (**115**) and 3-aminoalcohols (**116**).[49] However, for 4-cyanoisoxazoles (**117**) the reduction takes a different course and acyclic intermediates are assumed to form, which on acidification recyclize to give 5-aminoisoxazoles (**118**).[50]

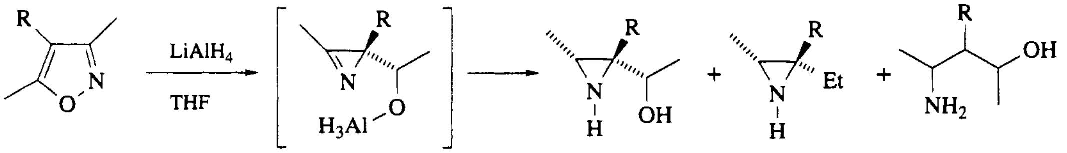

(**113**) (**114**) (**115**) (**116**)

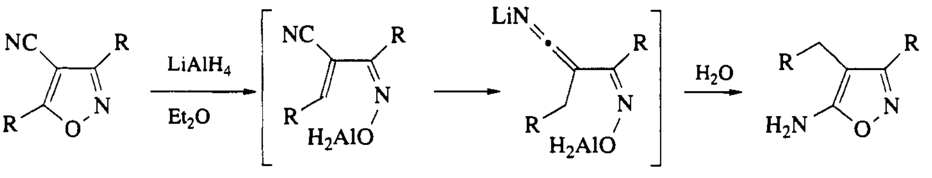

(**117**) (**118**)

*(ii) Isoxazolium salts*

The reduction of isoxazolium salts with metal hydrides is also not entirely predictable, and here the progress of the reaction depends on (i) the reagent, (ii) the solvent, and (iii) the ring substituents.[51] Generally, isoxazolium salts (**119**) on reduction with sodium borohydride in aqueous acetonitrile give 4-isoxazolines (**120**), their borane complexes, 3-isoxazolines (**121**), isoxazolidines (**122**), and minor amounts of 3-hydroxypropylamines (**123**). In some cases, however, particularly if the substituent group at C-3 is aryl and the reaction is carried out in ethanol rather than acetonitrile, the major products are

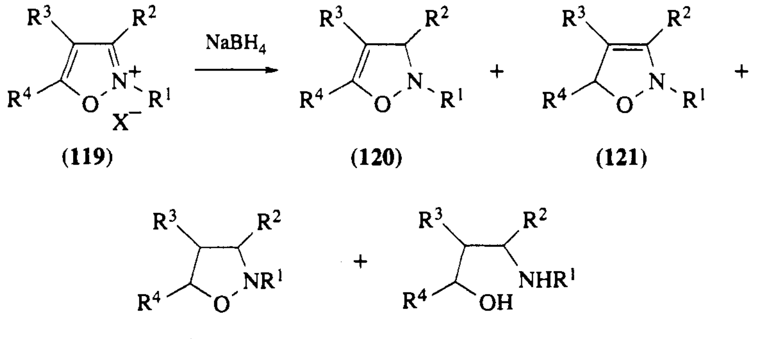

(**119**) (**120**) (**121**)

(**122**) (**123**)

isoxazolines. Best yields (*ca.* 60%) of isoxazolidines are obtained if LAH in tetrahydrofuran is used as the reductant.

### *(iii) Isoxazolines*

2-Isoxazolines, easily formed by the [3 + 2] cycloaddition of nitrile oxides and alkenes, are extremely versatile synthons for 1,3-aminoalcohols and 1,3-hydroxycarbonyl compounds, and through them to enones and 1,3-dienes. The conditions required to obtain this array of products have been known for many years, but their application to target-orientated syntheses is of much more recent origin.[52]

LAH is commonly used to cleave 2-isoxazolines to 1,3-aminoalcohols, often with a high degree of diastereoselectivity. In the case of 3,5-diphenyl-2-isoxazoline (**124**), for example, the two isomeric alcohols (**125**) and (**126**) are formed in the ratio 19:1.[53] In other cases the nature, position and number of the substituent groups on the ring influence the isomer preferences.[54] Thus, although most groups at C-4 and C-5 are *anti* directing, a hydroxy group at C-4 induces *syn* addition of hydride ion. This stereoselectivity has found application in the syntheses of amino sugars, amino acids and amino polyols. An illustration is the reduction of the two acetals (**127**) and (**129**) which give products conforming to the xylo- (**128**) and arabino- (**130**) series, respectively. In each case the yield of the reduction is high and the diastereoselectivity exceeds 95%.[55]

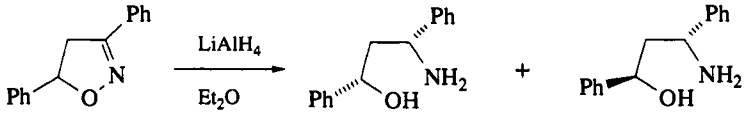

**(124)** **(125)** 95% **(126)** 5%

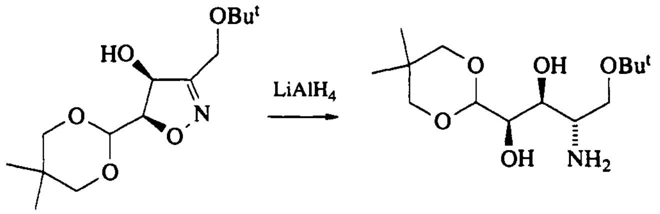

**(127)** **(128)** 95%

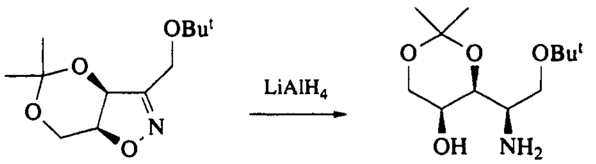

**(129)** **(130)** 73%

In this last case there are no problems with the choice of the reductant, but where the substrate bears groups themselves liable to reduction then catalytic hydrogenation can sometimes be used. This has been adopted by Kametani *et al.* in the formation of the β-lactams (**132**), related to thienamycin, from isoxazoline-4-carboxylic esters (**131**; Scheme 4).[56] DIBAL has also been employed as reductant, and this reagent was selected by Burri *et al.* in their synthesis of the antibiotic vermiculine (**134**) from the 2-methyl-2-isoxazoline (**133**; Scheme 5).[57]

Hydrogenation of 2-isoxazolines over Raney nickel as catalyst and in the presence of acids often leads first to 1,3-hydroxyimines, and then, through hydrolysis, to 1,3-hydroxycarbonyl compounds. In some cases the stereochemical integrity of the starting material is maintained, but in others hydrolysis of the intermediate imines may cause scrambling of stereochemistry at the α-carbon atom. Rapid protonation of the imine function minimizes this possibility and the use of Lewis acids, such as boron trichloride or aluminum trichloride which release hydrochloric acid on contact with moist methanol, is frequently recommended. Boric acid serves a similar purpose and is effective in, for example, the stereocontrolled reductive ring opening of the 2-isoxazoline (**135**) *en route* to crispatic acid (**136**; Scheme 6).[58]

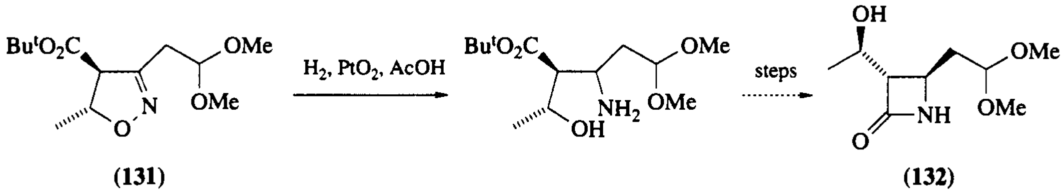
H$_2$, PtO$_2$, AcOH
steps

(131) (132)

Scheme 4

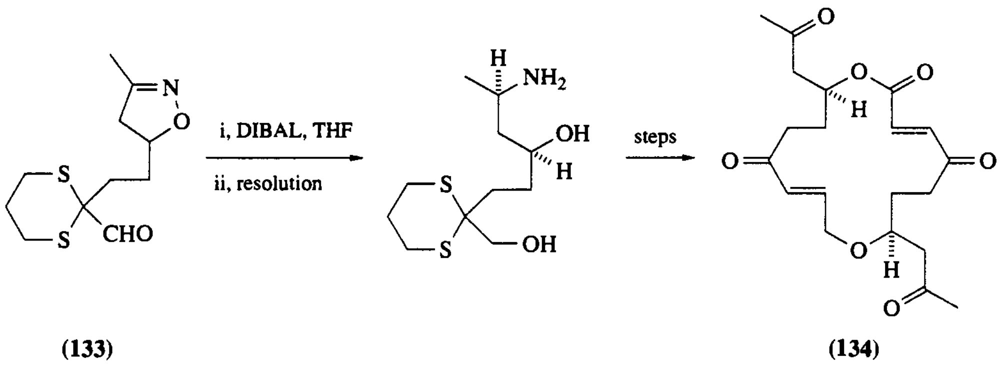
i, DIBAL, THF
ii, resolution
steps

(133) (134)

Scheme 5

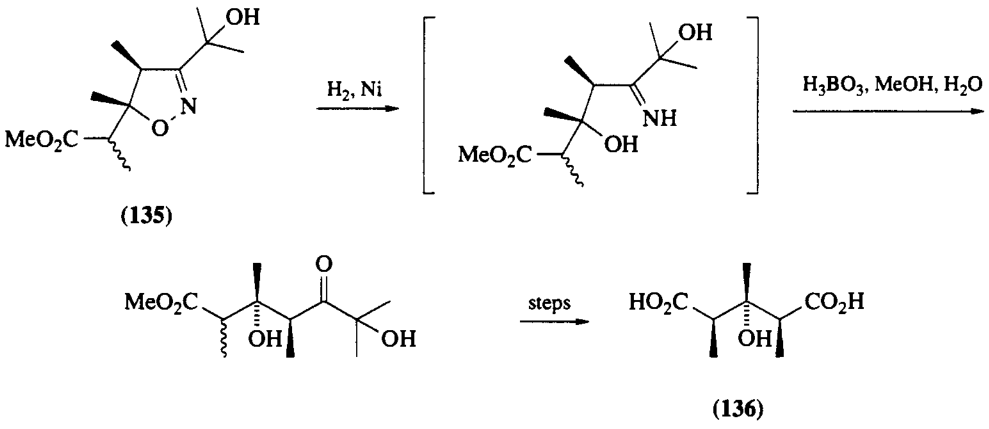
H$_2$, Ni
H$_3$BO$_3$, MeOH, H$_2$O
steps

(135) (136)

Scheme 6

*(iv) Isoxazolidines*

1,3-Hydroxyamines are formed by the reductive ring opening of isoxazolidines. Thus treatment of the derivative (**137**) with sodium in liquid ammonia, followed by hydrolysis of the carbamate unit, affords *N*-benzyl-*threo*-β-hydroxyornithine (**138**; R = Bn). A wide variety of reductants can be used to accomplish this type of reaction, providing account is taken of the reactions of the substituent groups about the heterocycle. So, for example, if the same substrate (**137**) is hydrogenated over Pearlman's catalyst [(Pd(OH)$_2$/C] not only is the ring cleaved, but the 2-*N*-benzyl group is also removed to afford *threo*-β-hydroxyornithine (**138**; R = H) directly.[59] Perhaps the mildest method for the formation of 1,3-hydroxy-

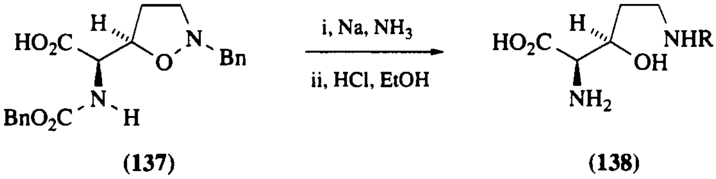
i, Na, NH$_3$
ii, HCl, EtOH

(137) (138)

amines involves the reaction of isoxazolidines with the reduced form of the lipoamide $A_2$–iron complex (previously described in Section 3.8.3.1.1i). Hydrogenation of isoxazolin-5-ones over palladium on carbon as catalyst gives the corresponding isoxazolidinones. Despite some confusion in the literature,[60] in the case of benzylidene derivatives (**139**) it is possible to control the reduction so that only the exocyclic double bond is reduced, giving first benzylisoxazolinones (**140**), and then isoxazolidinones (**141**). When the benzylisoxazolinones (**140**) are treated with hydrogen chloride in acetic acid they undergo ring fragmentation with loss of carbon dioxide, possibly as shown, to afford intermediate iminium salts, which on hydrolysis yield α,β-unsaturated ketones (**142**).[60]

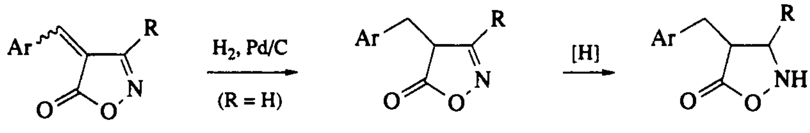

**(139)** **(140)** **(141)**

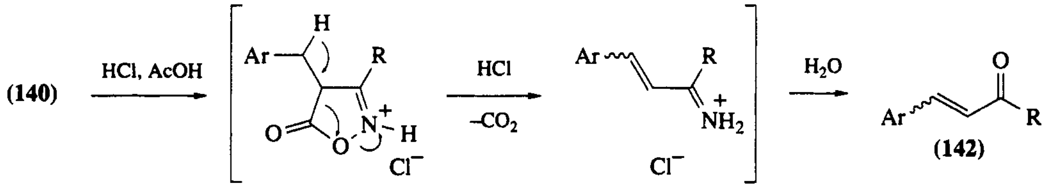

*(v) Benzisoxazoles*

1,2-Benzisoxazoles (**143**) behave similarly to monocyclic isoxazoles and are reductively cleaved to 2-hydroxyarylalkylimines (**144**) by catalytic hydrogenation over palladium on barium sulfate, although if the catalyst is Raney nickel deamination occurs, and under severe conditions the aromatic ring may be reduced to yield the appropriate cyclohexanol (**145**). Deamination also results from the chemical reduction of benzisoxazoles with hydrazine, but now the reaction terminates with the formation of phenols (**146**). Sodium and various alcohols normally convert benzisoxazoles into 2-hydroxyarylalkylamines (**147**; Scheme 7).[61] 2,1-Benzisoxazoles (**148**) are rather more stable and are normally prepared by the reductive cyclization of 2-nitroarylcarbonyl compounds. Hydrogenation at high pressure over Raney nickel catalyst will, however, cause degradation to toluidines (**149**).[62]

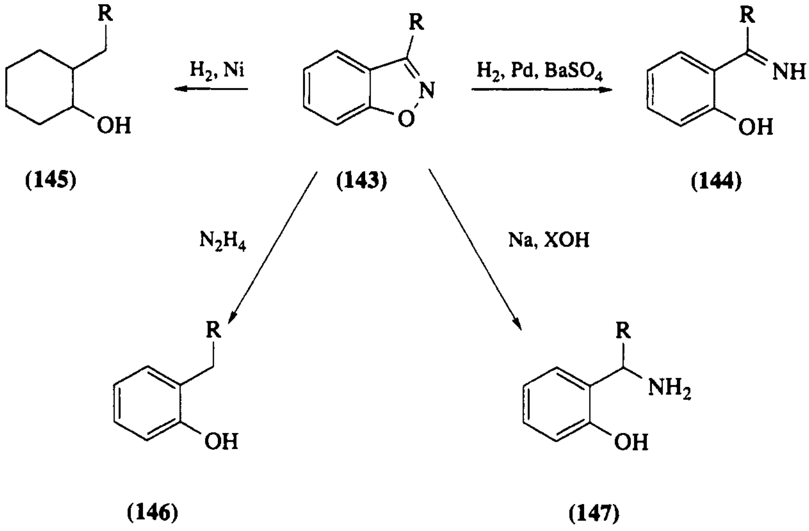

**Scheme 7**

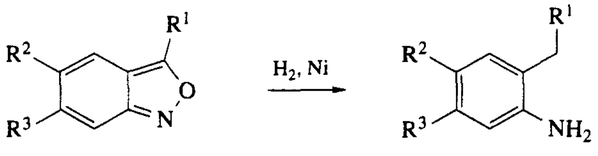

**(148)** **(149)**

### *3.8.3.1.2 Oxazoles, benzoxazoles, oxazolium salts, oxazolines and oxazolinones*

Oxazoles (**150**) are reduced to oxazolines (**151**) by treatment with sodium and ethanol, and these products may then undergo further reduction to oxazolidines (**152**) and eventually to amino alcohols (**153**). Reduction with LAH follows the same course,[63] as does electrochemical reduction.[64] In the same way 2,2-bis(oxazoles) (**154**) when reacted with LAH afford diaminodiols (**155**).[65]

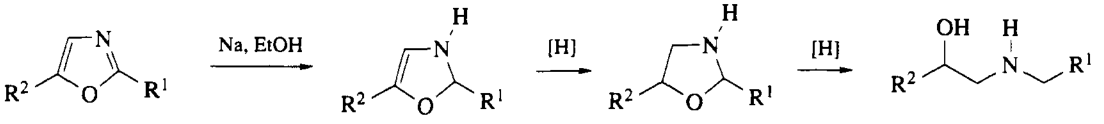

**(150)** **(151)** **(152)** **(153)**

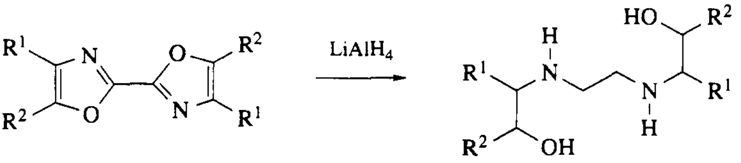

**(154)** **(155)**

The heterocyclic ring of benzoxazoles (**156**) can be cleaved by exposure to diborane giving borazoles (**157**; possibly as shown in Scheme 8). Treatment of these products with hydrochloric acid leads to the formation of 2-aminophenols (**158**).[66] Catalytic hydrogenation of the parent compound (**156**; R = H) over molybdenum sulfide has a similar end result although, since the conditions of the reaction are quite severe, phenol and 2-toluidine can form as by-products.[67]

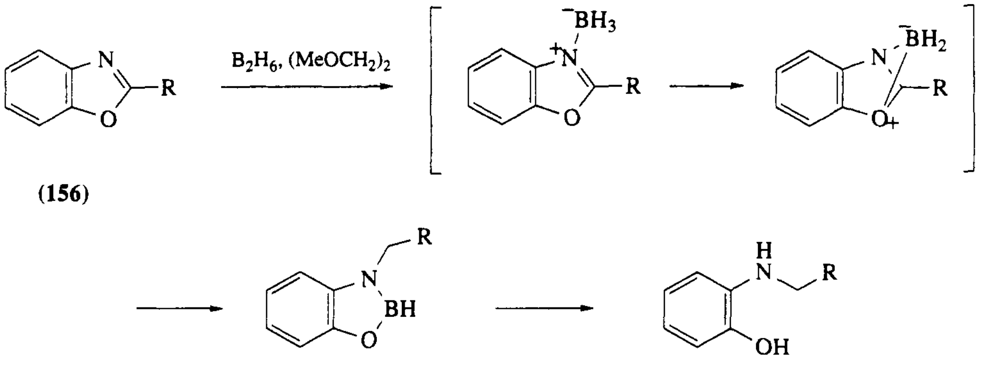

**(156)** **(157)** **(158)**

**Scheme 8**

The oxazolium salt (**160**), formed from the oxazole (**159**) by reaction with methyl triflate in acetonitrile, may be reductively ring opened by treatment with phenylsilane in the presence of cesium fluoride to give the azomethine ylide (**161**) (presumably this species is in tautomeric equilibrium with the corresponding oxazoline). The azomethine ylide can be trapped as an adduct with a suitable dipolarophile, such as dimethyl acetylenedicarboxylate (DMAD). In the case of this reagent the adduct (**162**) can be oxidized to the corresponding pyrrole (**163**) through reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 9).[68]

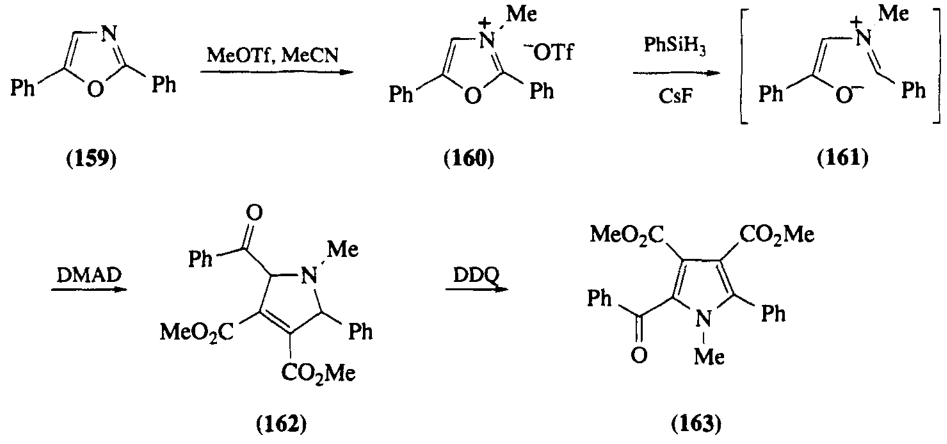
MeOTf, MeCN
PhSiH₃
CsF
DMAD
DDQ
(159)
(160)
(161)
(162)
(163)

Scheme 9

2-Oxazolines are inert to reduction by LAH, but they are readily hydrolyzed to acids, C-2 providing the carbon atom of the carboxylic acid group. This is a valuable property since carbonyl groups in side chains are reduced normally. An example is shown in Scheme 10, where the 2-oxazolines (**164**) are used as starting materials for the synthesis of ω-hydroxyalkanoic acids (**165**).[69]

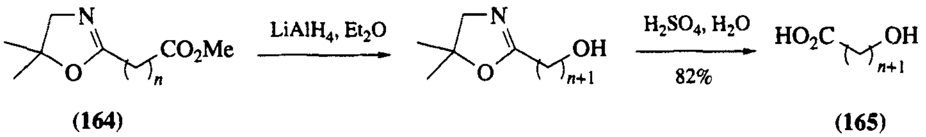
LiAlH₄, Et₂O
H₂SO₄, H₂O
82%
(164)
(165)

Scheme 10

Oxazolinones are not so stable and 2-oxazolin-5-ones (**166**), for example, react with sodium borohydride to yield 2-hydroxyamides (**167**),[70] and their alkylidene derivatives (**168**) are converted into the corresponding alkyloxazolinones (**169**) by hydrogenation over palladium on carbon as catalyst. These

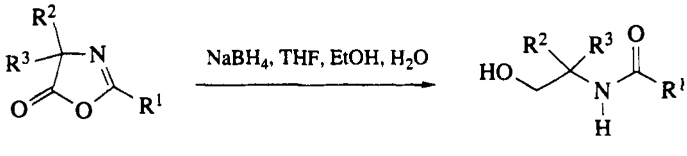
NaBH₄, THF, EtOH, H₂O

(**166**) (**167**)

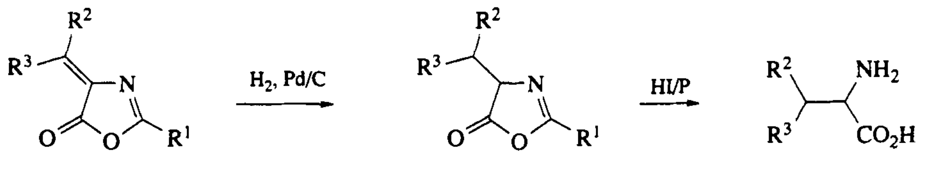

(**168**) (**169**) (**170**)

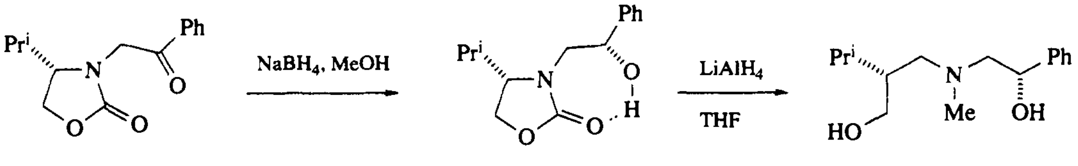
NaBH₄, MeOH
LiAlH₄
THF

(**171**) (**172**) (**173**)

compounds may then be cleaved to α-amino acids (**170**) by treatment with hydriodic acid and phosphorus. 3-Oxazolin-2-ones are reduced by LAH firstly to oxazolidin-2-ones[71] and, if *N*-alkylated, then on to 2-hydroxyalcohols.[72] For example, if (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**171**) is reduced first with sodium borohydride in methanol, or with lithium butoxyaluminum hydride in THF, the alcohol (**172**) is formed as the major product (71–83%). When this compound is isolated and reduced further with LAH ring scission occurs to produce the acyclic diol (**173**). Should the oxazolidinone (**171**) be reduced directly with LAH there is again a preference for the production of the diol (**173**).[73]

## 3.8.3.2 Six-membered Ring Systems

### *3.8.3.2.1 Oxazines, benzoxazines and phenoxazines*

*(i) 1,2-Oxazines*

Dissolving metal reduction of 2*H*-3,6-dihydrooxazines (**174**) effects ring opening and the formation of aminoenols (**175**),[74] whereas hydrogenation of these heterocycles, or of the isomeric 4*H*-5,6-dihydrooxazines (**177**), over a variety of catalysts gives tetrahydrooxazines (**176**).[75] The imine bond of 4*H*-5,6-dihydrooxazines is also reduced by reaction with LAH, but here, as with hydrogenation under high pressure (1500 psi, over Pt or Pd; 1 psi = 6895 Pa),[76] the process continues a further step to afford acyclic 4-aminobutanols (**178**; Scheme 11).[77] Aluminum amalgam in aqueous THF, or hydrogenation over palladium in dry ethanol containing triethyl borate, may be also used to reduce dihydrooxazines to 1,4-amino alcohols. However, in the case of the esters (**179**) the reaction mechanisms for the two types of reduction differ. For the first the final products are pyrroles (**180**) and for the second both pyrroles and pyrrolidines (**181**) are produced (Scheme 12).[78]

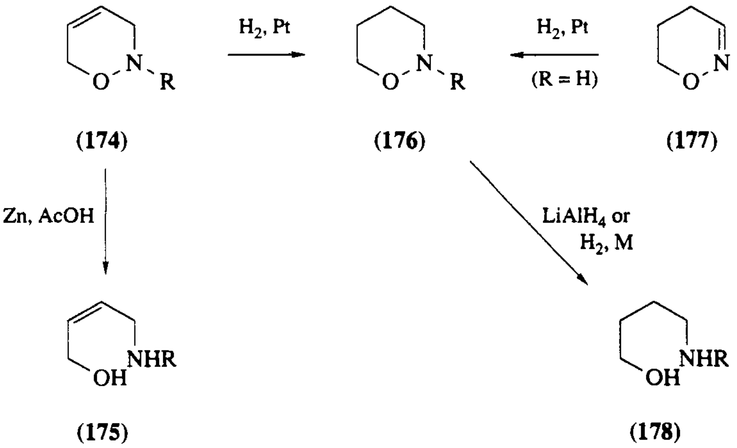

**Scheme 11**

As indicated above, dihydrooxazines, and through them tetrahydrooxazines, can act as masked 4-aminobutanols and advantage is often made of the fact that dihydrooxazines are synthesized by the cycloaddition of nitroso compounds and 1,3-dienes. In this way the relative stereochemistry of the substituents at C-4 and C-6 in the heterocycle is set and this then determines the regioselectivity of addition reactions to the double bond. A good example is provided by the synthesis of the tetraacetylaminoallose (**183**; Scheme 13), which proceeds through a double hydrogenolysis of the *N*-carbamoyltetrahydrooxazine (**182**).[79]

The comparative stability of the 1,2-oxazine ring towards various reductants is well illustrated by the construction of the neurotoxin gephyrotoxin (**189**), in the form of its racemate (Scheme 14).[80] This synthesis begins with the intramolecular cycloaddition of the acylnitroso species (**184**), to give the adduct (**185**). This product may be reduced to the tetrahydrooxazine (**186**), without ring opening, by hydrogenation over 5% palladium on carbon as catalyst in methanol solution. After reaction with propylmagnesium bromide, the derived enamine (**187**) may be further reduced, again without ring opening, to the tetrahydrooxazine (**188**) by treatment with sodium cyanoborohydride in methanol at pH 3.8–5.4. The exclusive formation of this product is possibly due to the fact that only in the least stable of the two possible chair

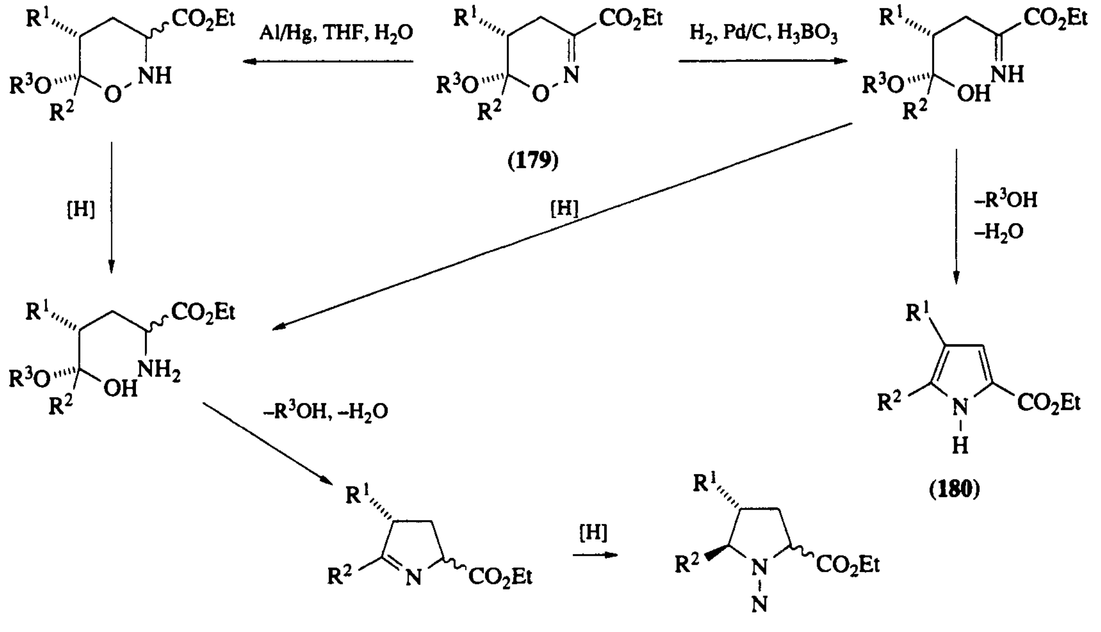

Scheme 12

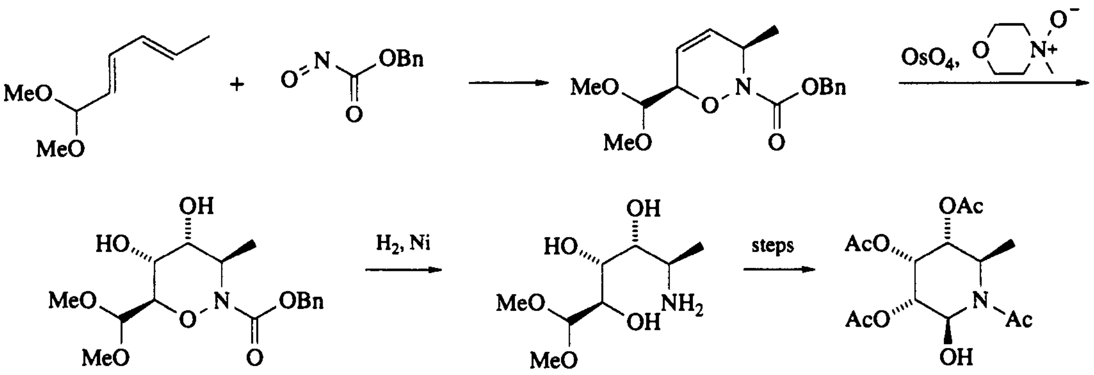

Scheme 13

transition states for the reaction can the incoming reagent avoid severe steric interaction with the bulky butyl substituent of the substrate. Finally the tetrahydrooxazine (**188**) is cleaved by reduction with zinc and acetic acid and the product then undergoes spontaneous recyclization to (±)-gephyrotoxin.

### *(ii) 1,3-Oxazines*

Much interest lies in the use of dihydro-1,3-oxazines (**190**) as enolate equivalents, since, if an alkyl group is carried at C-2, these compounds may be deprotonated and the anions formed reacted with numerous types of electrophiles. Reduction of the imine bond of the products (**191**), is then conveniently effected by treatment with sodium borohydride. The tetrahydrooxazines (**192**) which are formed may then be ring opened by hydrolysis with aqueous acid (Scheme 15). This topic and its utility in synthesis has been well reviewed.[81,82]

### *(iii) 1,4-Oxazines, 1,4-benzoxazines, phenoxazines and tetrahydro-1,4-oxazines*

As with tetrahydro-1,3-oxazines the tetrahydro-1,4-oxazine ring system is stable to reduction by complex metal hydrides, and, for example, LAH can be used to reduce the lactam carbonyl function of mor-

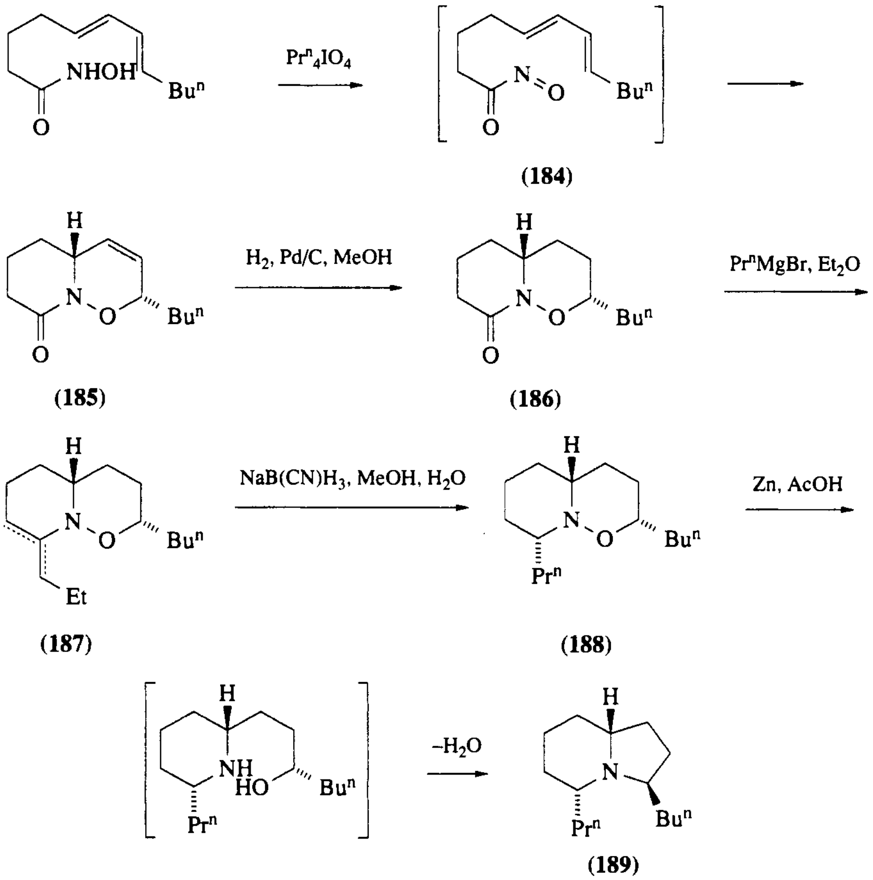
NHOH
Bun
O
Prn4IO4
N
O
(184)
H
H2, Pd/C, MeOH
PrnMgBr, Et2O
(185)
(186)
NaB(CN)H3, MeOH, H2O
Zn, AcOH
Et
Prn
(187)
(188)
NH
HO
-H2O
(189)

Scheme 14

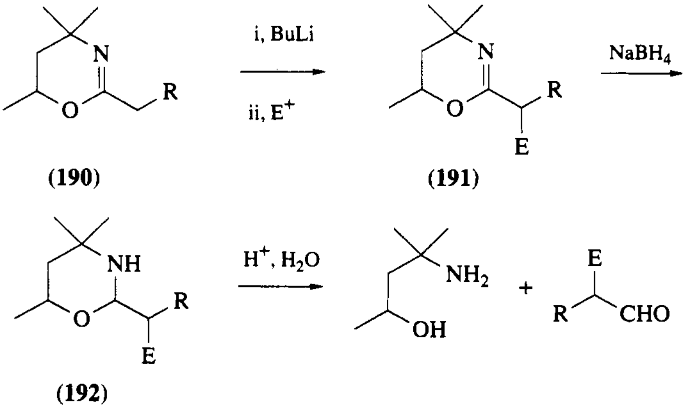
N
R
O
i, BuLi
ii, E+
E
NaBH4
(190)
(191)
NH
H+, H2O
NH2
OH
CHO
+
(192)

Scheme 15

pholinones (**193**) to give the corresponding morpholines (**194**).[83] Likewise *N*-alkyldihydro-1,4-benzoxazin-3-ones (**195**) react with this reagent to form benzomorpholines (**196**). The same products can be obtained by the reduction of 2*H*-1,4-benzoxazines (**197**), and indeed a synthesis of benzomorpholines requires the hydrogenation of 2-nitrophenyloxymethyl ketones (**198**) over Raney nickel as catalyst (Scheme 16).[84] Since the aromatic nuclei of benzoxazines and phenoxazines are inert to most reductants, substituent groups can be reduced in the expected manner. Similarly the restoration of aromaticity in the products ensures that the reduction of phenoxazin-3(3*H*)-ones (**199**) to 3-hydroxyphenoxazines (**200**) is easily achieved as, for example, by reaction with sodium dithionate in aqueous acetone.[85]

Oxazinones (**201**) and (**204**), which are available in high states of optical purity, can be reacted with *N*-bromosuccinimide and then treated with metal alkyls (RM) to form the corresponding 3-alkyl derivatives

(**202**) and (**205**). In the case of the former, cleavage to the zwitterionic L-amino acids (**203**) can be achieved in *ca.* 98% *ee* by hydrogenolysis in ethanol solution over palladium as catalyst; the chiral auxiliary is lost in the form of bibenzyl. For the second class of compounds ring opening and deprotection to give D-amino acids (**206**) is best carried out through reduction with lithium and liquid ammonia in tetrahydrofuran containing ethanol. The optical and product yields in this second procedure are also excellent and between them these two reaction sequences provide access to a wide range of natural and unnatural amino acids in a predictable manner.[86] (Scheme 17).

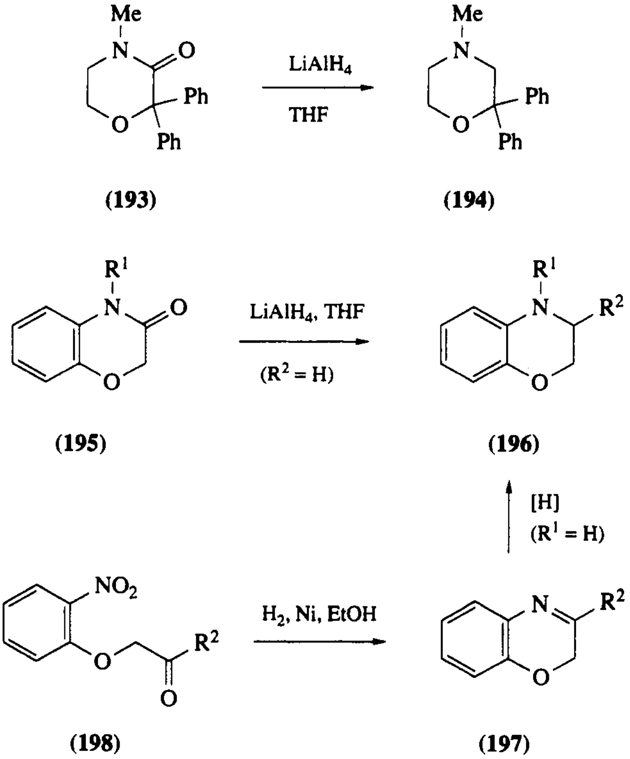
Me
N
O
Ph
Ph
LiAlH4
THF
(193)
(194)
R1
R2
LiAlH4, THF
(R2 = H)
(195)
(196)
[H]
(R1 = H)
NO2
H2, Ni, EtOH
(198)
(197)

**Scheme 16**

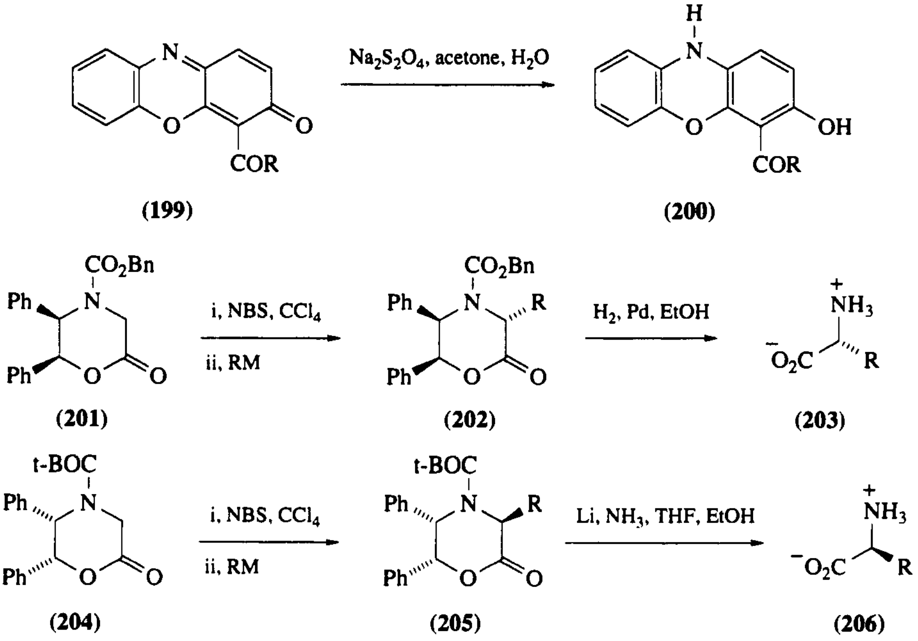
H
N
O
COR
OH
Na2S2O4, acetone, H2O
(199)
(200)
CO2Bn
Ph
i, NBS, CCl4
ii, RM
R
H2, Pd, EtOH
NH3
O2C
(201)
(202)
(203)
t-BOC
Li, NH3, THF, EtOH
(204)
(205)
(206)

**Scheme 17**

## 3.8.4 REDUCTION OF HETEROCYCLES CONTAINING ONE NITROGEN ATOM AND ONE SULFUR OR SELENIUM ATOM

### 3.8.4.1 Five-membered Ring Systems

### *3.8.4.1.1 Isothiazoles*

The ring system of isothiazoles (**207**) is stable to treatment with sodium borohydride and LAH, and these reagents are employed to reduce ring substituents such as nitro or carbonyl groups to the corresponding amines or alcohols, respectively. Similarly, catalytic hydrogenation of 4-nitroisothiazoles affords the corresponding amines. In this case, however, the reaction should be carried out below 10 °C, otherwise ring scission occurs, probably to form enaminothiones (**208**).[87]

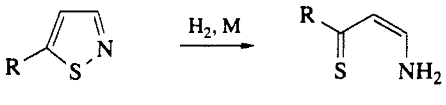

**(207)** **(208)**

### *3.8.4.1.2 Thiazoles and thiazolines*

Thiazoles are deactivated towards electrophilic substitution, and thus direct reaction with hydride reductants to give thiazolines should be facilitated. There are indeed some examples of this type of reaction,[88] but it is more common to reduce *N*-alkylated thiazolium salts (**209**). These compounds are converted first by reaction with sodium borohydride into 4-thiazolines (**210**), which in protic solvents become protonated and undergo further reduction to yield thiazolidines (**211**).[89] Similarly the isoquinolinium salt (**213**), formed by the acid-promoted cyclization of the isoquinoline (**212**), is converted into the tetrahydroisoquinoline (**214**) (presumably *via* an intermediate 1,2-dihydroisoquinoline) by reaction with sodium borohydride.[90]

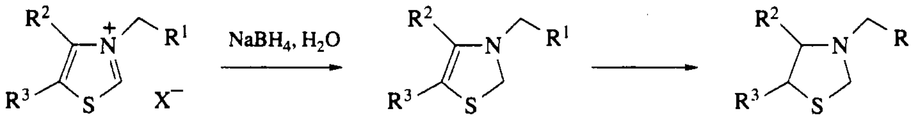

**(209)** **(210)** **(211)**

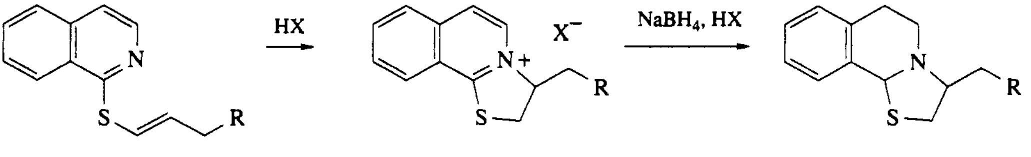

**(212)** **(213)** **(214)**

4-Alkylidene-1,3-thiazolin-5-ones (**215**) are also reduced by the action of sodium borohydride, but in this case only the exocyclic double bond reacts.[91] Similarly, this reagent may be used to reduce carbonyl groups in the side chains of thiazoles without any effect on the heterocycle itself. The thiazole ring also survives hydrogenation over Raney nickel catalyst at atmospheric pressure,[92] but the fully reduced thiazole ring system is vulnerable to desulfurization. This occurs under quite mild conditions, and thus when

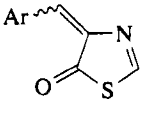

**(215)**

the tricyclic thiazolidine (**216**) is treated with silver nitrate and the product, without isolation, is reacted with sodium borohydride the pyrrolidine (**217**) is formed.[93] Sodium in liquid ammonia also causes ring opening, and reaction of the thiazoline-2-thiones (**218**) with this reagent system affords azadienyldithiolates (**219**). The products recyclize to thiazoles (**220**) when acidified with hydrochloric acid.[94]

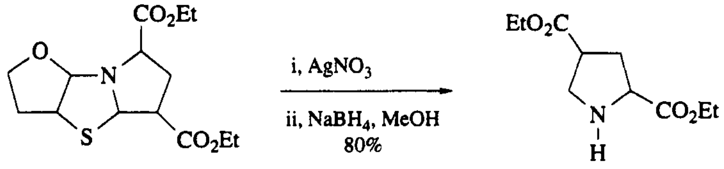
CO2Et
O
N
S
CO2Et
i, AgNO3
ii, NaBH4, MeOH
80%
EtO2C
N
H
CO2Et

**(216)** **(217)**

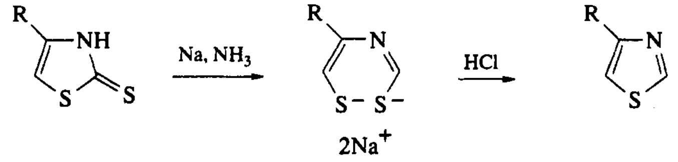
R
NH
S
S
Na, NH3
R
N
S- S-
2Na+
HCl
R
N
S

**(218)** **(219)** **(220)**

The carbonyl group and the thiocarbonyl function of the thiazolidine derivative (**221**) are not changed by electrochemical reduction in an acidic medium, but the oximino unit at C-5 is transformed into an amino group and salts (**222**) are produced.[95]

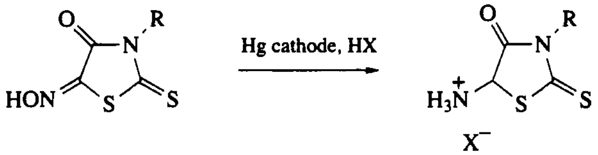
O
R
N
HON
S
S
Hg cathode, HX
O
R
N
H3N+
S
S
X−

**(221)** **(222)**

### *3.8.4.1.3 Benzothiazoles and benzothiazolium salts*

Benzothiazoles are rather more prone to reductive decyclization than are thiazoles, although it is possible to form benzothiazolines (**224**) through the sodium borohydride reduction of benzothiazolium salts (**223**).[96] On hydrolysis these products yield 2-aminothiophenols (**225**). Prolonged exposure of benzothiazolines to excess sodium borohydride also causes ring opening to aminothiophenols,[97] as does reaction with LAH. In this last case the substrates for reduction may be benzothiazoles (**226**), which presumably initially form benzothiazolines with the reagent (Scheme 18).[98]

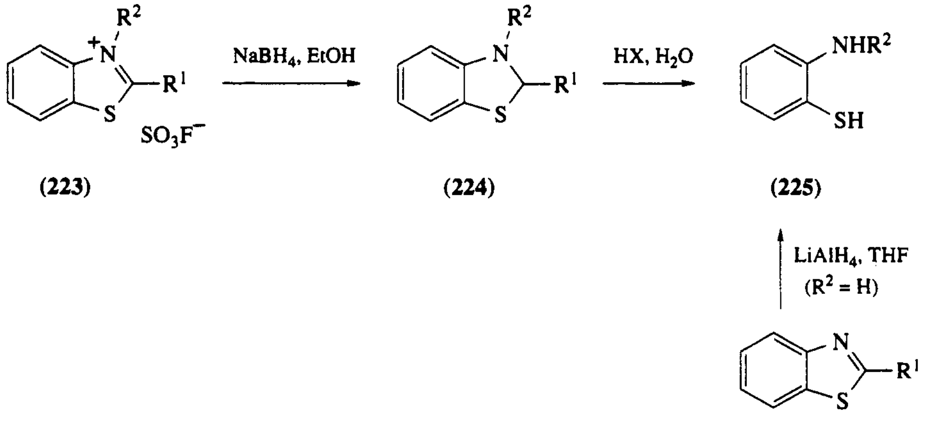
R2
+N
R1
S
SO3F−
NaBH4, EtOH
R2
N
R1
S
HX, H2O
NHR2
SH
LiAlH4, THF
(R2 = H)
N
R1
S

**(223)** **(224)** **(225)**

**(226)**

**Scheme 18**

#### *3.8.4.1.4 Isoselenazoles*

Isoselenazoles are very easily cleaved by fragmentation of the C—Se bond. Reagents such as sodium borohydride are effective and, for example, treatment of the pyrimidoisoselenazole (**227**) with this reagent affords the aminopyrimidinone (**228**).[99]

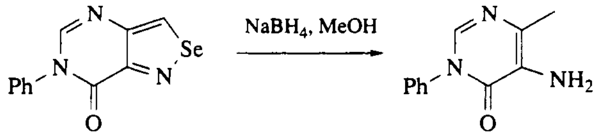

**(227)** **(228)**

### 3.8.4.2 Six-membered Ring Systems

#### *3.8.4.2.1 Thiazines, benzothiazines and phenothiazines*

*(i) 1,3-Thiazines*

Reduction of 5-acyl-1,3-thiazines (**229**) with sodium cyanoborohydride in acid media, or with triethylsilane, gives 3,6-dihydro-2*H*-1,3-thiazines (**230**),[100] whereas sodium borohydride has no effect upon the unsaturation of the ring and only reduces the carbonyl group of the side chain. Some other reagents cause ring opening under very mild conditions; thus treatment of 1,3-thiazinium salts (**231**) with hydrogen sulfide is sufficient to yield thioenethioamides (**232**).[101] LAH also cleaves the 1,3-thiazine ring; the 1,3-benzothiazin-4-one (**233**), for example, forms 2-mercaptobenzylamine (**234**), plus a small amount of benzoisothiazole (**235**).[102]

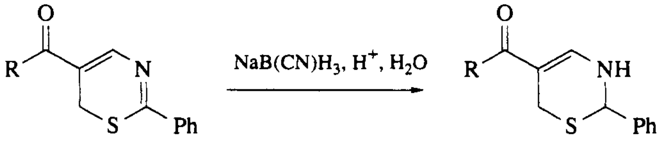

**(229)** **(230)**

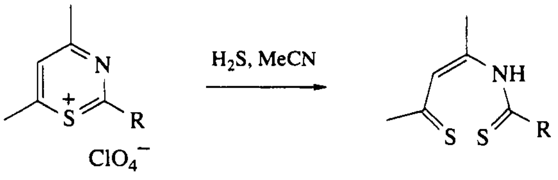

**(231)** **(232)**

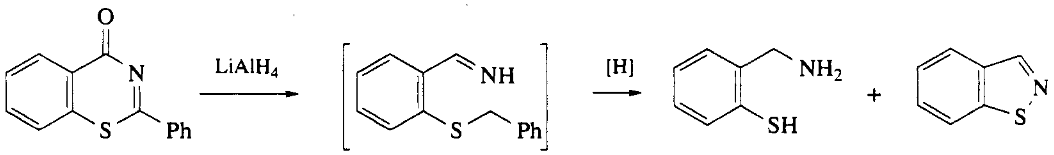

**(233)** **(234)** **(235)**

*(ii) Benzo-1,4-thiazines*

2*H*-Benzo-1,4-thiazines (**236**) undergo ring opening and ring contraction when hydrogenated over Raney nickel, or palladium on carbon, as catalyst. Here the initial step in the reaction is reductive fragmentation of a C—S bond. Imino intermediates (**237**) may then form, which recyclize to benzothiazoles (**238**).[103]

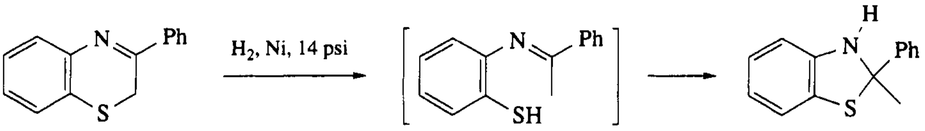

**(236)** **(237)** **(238)**

*(iii) Phenothiazines*

Phenothiazines, like phenoxazines (Section 3.8.3.2.2i), are relatively stable compounds and unsaturated substituents attached to the carbocycles can be reduced by the usual reagents, leaving the nuclei intact. There is one important difference, however, namely that phenothiazines may be desulfurized. An early example is provided by the degradation of phenothiazines (**239**) to diphenylamines (**240**) by hydrogenolysis over Raney nickel catalyst.[104]

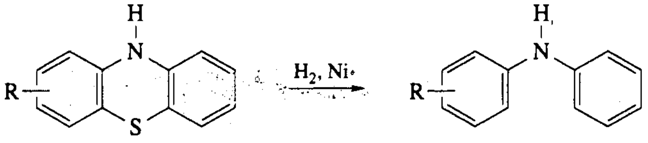

**(239)** **(240)**

## 3.8.5 REDUCTION OF HETEROCYCLES CONTAINING TWO OXYGEN ATOMS OR TWO SULFUR ATOMS

### 3.8.5.1 Dioxolanes, Dioxanes, Dithioles and Benzodithioles

### *3.8.5.1.1 1,3-Dioxolanes and 1,3-dioxanes*

Reductive cleavage of a C—O bond of 1,3-dioxolanes may be achieved by a variety of methods; commonly chemical reductants are employed and, although LAH alone is ineffective, the mixed reductants LAH/AlCl$_3$ or LAH/AlBr$_3$ cleave 2-substituted dioxolanes (**241**) to hydroxy ethers (**242**), sometimes with a high degree of diastereotopic selectivity.[105] This is usually explained in terms of the selective complexation of the reagent with one of the oxygen atoms of the ring, which then allows the delivery of hydride ion to one face of the heterocycle, rather than to the other.

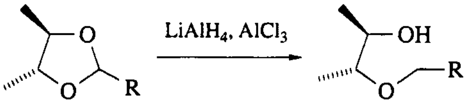

**(241)** **(242)**

The same methodology can be applied to the ring opening of 1,3-dioxanes and this has been used in effecting the chiral reduction of ketones to alcohols. As an illustration, cyclohexyl methyl ketone (**243**) can be converted into the dioxane (**244**) by reaction with (2*R*,4*S*)-pentanediol and cleaved with LAH/AlBr$_3$ to afford (2*R*)-cyclohexylethanol (**245**) in good yield and in high enantiomeric excess. Interestingly, the stereoselectivity of the ring-opening reaction can be reversed if the reagent is changed to triethylsilane and a Lewis acid (preferably TiCl$_4$). Now the 1,3-dioxane (**244**) is opened to give the alternative enantiomer (**246**; Scheme 19).[106]

Stereoselective monodeprotection of one hydroxy group in a polyhydroxylated system is a common requirement in synthesis, and in the case of cyclic orthoesters this can be accomplished through reactions

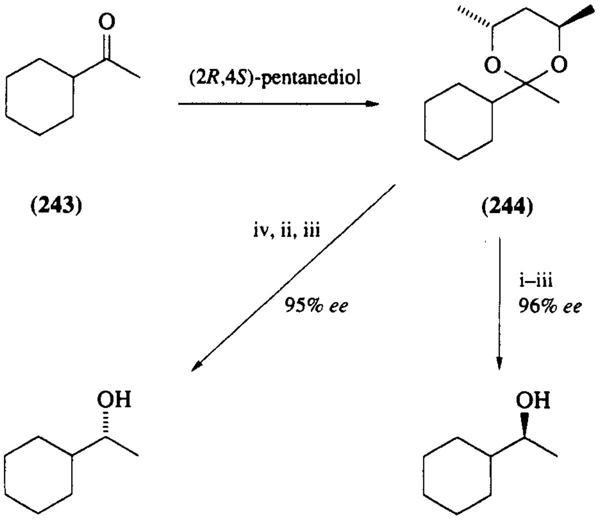
(2*R*,4*S*)-pentanediol
iv, ii, iii
95% *ee*
i–iii
96% *ee*
O
O
O
OH
OH

**(243)** **(244)** **(246)** **(245)**

i, $AlH_3$, $AlBr_3$; ii, $(COCl)_2$, DMSO, $Et_3N$; iii, $Na_2CO_3$, $H_2O$; iv, $Et_3SiH$, $TiCl_4$

**Scheme 19**

with DIBAL in nonpolar media. The ring-opening process is highly regioselective, and for the unsymmetrical substrate (**247**) only the hydroxy ether (**248**) is formed (Scheme 20). Ring size is important in this type of reaction, however, and only 1,3-dioxolanes and -dioxanes give satisfactory results.[107]

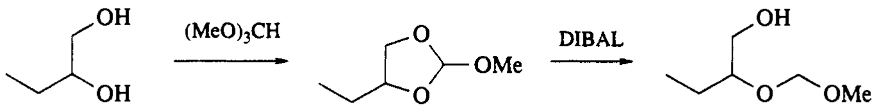
OH
OH
$(MeO)_3CH$
O
O
OMe
DIBAL
OH
O
OMe

**(247)** **(248)**

**Scheme 20**

### *3.8.5.1.2 Dithioles and benzodithioles*

The S—S bond of 1,2-dithioles is easily cleaved by reduction and, for example, dithioles (**249**) can be converted into acyclic methyl dithiolates (**251**) by electrochemical reduction, followed by alkylation of the intermediate dianions (**250**).[108] Benzodithioles (**252**) are more stable and the heterocycle survives reduction with zinc and trifluoroacetic acid, although the exocyclic double bond is saturated to give 2-alkyldithiolanes (**253**).[109]

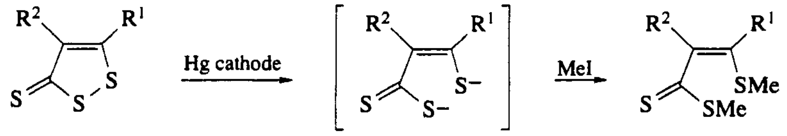
R2
R1
S
S
S
Hg cathode
R2
R1
S–
S
S–
MeI
R2
R1
SMe
S
SMe

**(249)** **(250)** **(251)**

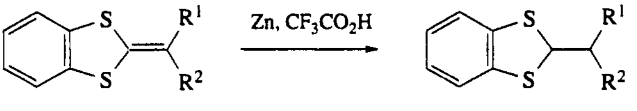
S
S
R1
R2
Zn, $CF_3CO_2H$
S
S
R1
R2

**(252)** **(253)**

Benzo-1,3-dithiole-2-thiones (**254**) are cleaved to thiocatechols (**256**) by treatment with DIBAL-H, or diborane·dimethyl sulfide. Sodium borohydride, LAH or Red-Al are much less efficient reagents for this purpose. Under more controlled conditions it is possible to obtain good yields of the intermediate benzodithiolanes (**255**).[110]

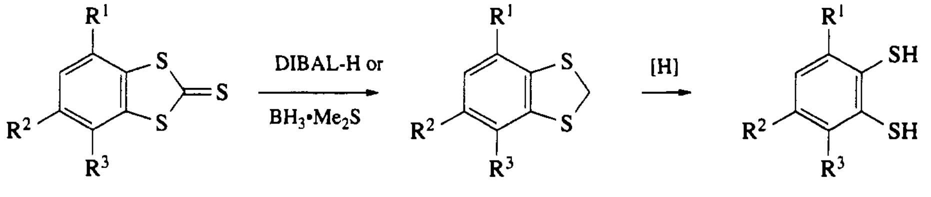

**(254)** **(255)** **(256)**

## 3.8.6 REDUCTION OF HETEROCYCLES CONTAINING THREE NITROGEN ATOMS

### 3.8.6.1 Triazoles, Triazolium Salts and Benzotriazoles

#### *3.8.6.1.1 1,2,3-Triazoles and 1,2,3-benzotriazoles*

The ring system of 1,2,3-triazoles (**257**) is stable to dissolving metals in acids,[111] and 1,2,3-triazolium salts are resistant to reduction unless they are substituted at both positions N-1 and N-2. Thus whereas salts of the type (**258**) are not reduced, analogs of the form (**259**) are converted into triazolines (**260**) by reaction with sodium borohydride.[112]

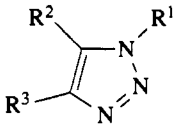

**(257)**

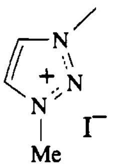

**(258)**

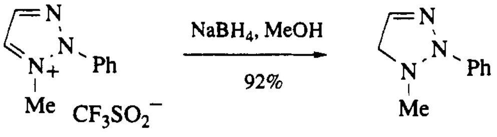

**(259)** **(260)**

Benzotriazoles, like their monocyclic counterparts, are often synthesized by reductive cyclizations and it is only when they are activated as salts that reductions with metal hydrides occur. Potassium borohydride, for example, reacts with aqueous solutions of the salt (**261**) to give 2-methylaminoaniline (**262**). Some *N*-demethylation leading to the triazole (**263**) also takes place, and this may be caused by the prevailing alkaline reaction conditions. LAH in diethyl ether is a more effective reagent for the reductive ring opening of benzotriazoles, and this reagent also cleaves 1,3-dimethylbenzotriazolium methylsulfate (**264**) to 1,2-di(methylamino)benzene (**265**).[113]

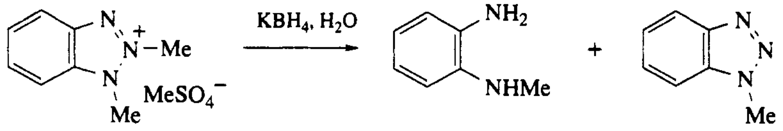

**(261)** **(262)** **(263)**

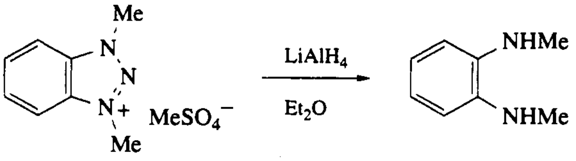
Me
N
N
N+
MeSO4−
Me
LiAlH4
Et2O
NHMe
NHMe

**(264)** **(265)**

### *3.8.6.1.2 1,2,4-Triazolium salts*

1,2,4-Triazolium salts are readily reduced by treatment with sodium borohydride to give the corresponding triazolines. However, these products are unstable to conditions of acid work-up and fragment to give aldehydes. This property has been exploited to homologate aldehydes using 3-methylthio-1,4-diphenyl-1,2,4-triazolium chloride (**266**) as a masked carboxylate equivalent, as illustrated in Scheme 21.[114]

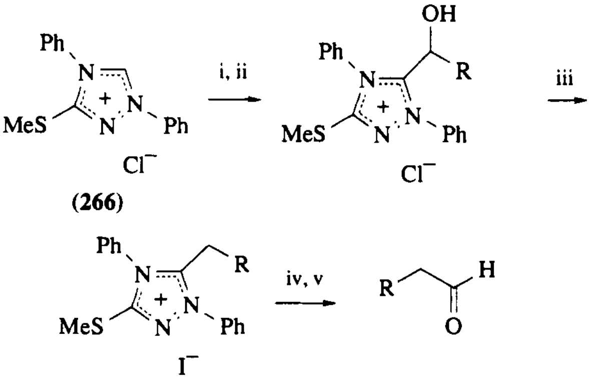
Ph
N
+
N
MeS
N
Ph
Cl−
(266)
i, ii
OH
R
iii
iv, v
I−
H
O

i, $Et_3N$; ii, RCHO; iii, $SOCl_2$, KI, $NaHSO_3$; iv, $NaBH_4$; v, HX, HCHO

Scheme 21

LAH reduces 1,2,4-triazol-5-ones (**267**) to both triazoles (**268**) and triazolines (**270**). The course of the reaction depends on the nature of the *N*-substituent; thus when R = H triazoles are formed in modest yield (15–30%), but when R = alkyl triazolium salts (**269**) are produced as intermediates and these are then reduced to triazolines (**270**; Scheme 22).[115]

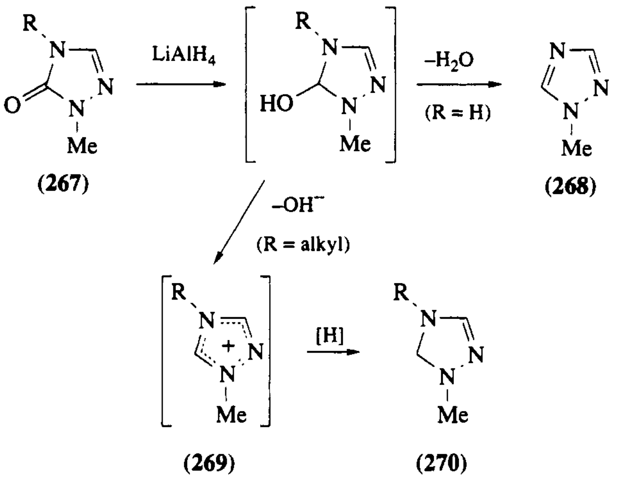
R
N
N
O
N
Me
(267)
LiAlH4
HO
−H2O
(R = H)
(268)
−OH−
(R = alkyl)
+
[H]
(269)
(270)

Scheme 22

## 3.8.7 REDUCTION OF HETEROCYCLES CONTAINING TWO NITROGEN ATOMS AND ONE OXYGEN ATOM

### 3.8.7.1 Oxadiazoles and Benzoxadiazoles

### *3.8.7.1.1 1,2,4-Oxadiazoles*

1,2,4-Oxazadiazoles (**271**) undergo ring opening either by catalytic hydrogenation over platinum, palladium or nickel, or by treatment with LAH. In the first case O–N bond cleavage occurs to give imino-amides (**272**), whereas during chemical reduction the products are amino oximes (**273**) (Scheme 23). In some instances the first-formed reduction products may undergo rearrangement; thus hydrogenation of azo derivatives (**274**) eventually affords 1,2,4-triazoles (**275**),[116] and vinylogous amides (**276**) give rise to pyrimidines (**277**).[117] Amino oximes (**279**) are also obtained when oxadiazolin-5-ones (**278**) are reacted with LAH, indicating that oxadiazoles are intermediates in the reaction.[118] 3-Phenyl-1,2,4-oxadiazolines (**280**) yield anions (**281**) when reacted with sodium in liquid ammonia; these products combine with alkyl halides, and where R = Me equal amounts of the two *N*-alkyl isomers (**282**) and (**283**) are formed.[119]

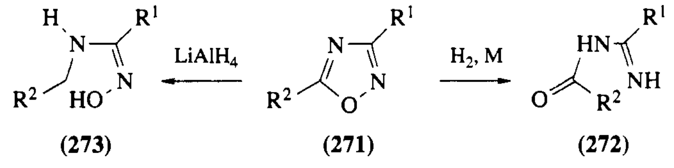

**Scheme 23**

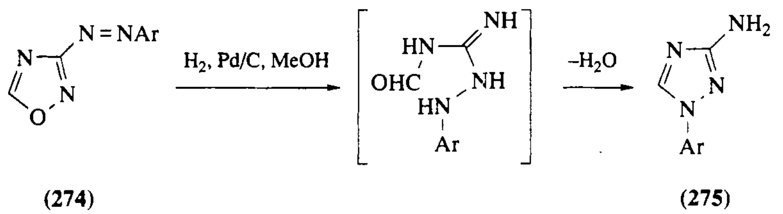

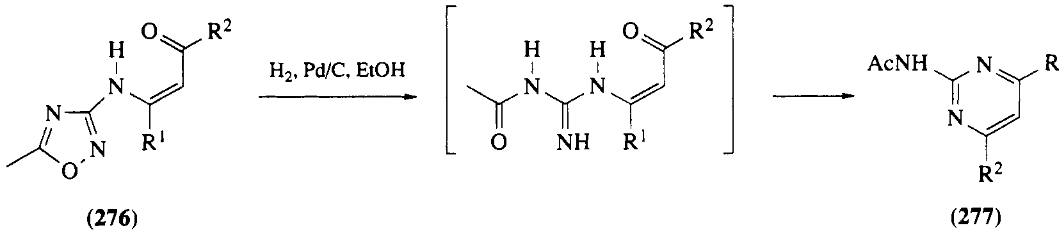

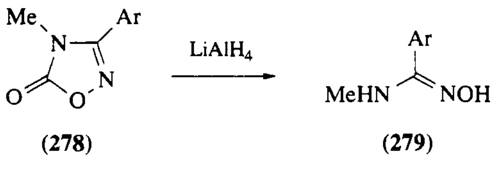

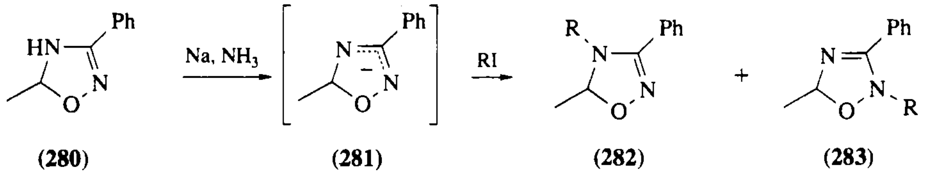

### *3.8.7.1.2 1,2,5-Oxadiazoles and 1,2,5-benzoxadiazoles*

1,2,5-Oxadiazole-2-oxides (furoxans; **284**) undergo ring opening and reduction to 1,2-diketones (**285**) when treated with zinc and acetic acid, but with tin and hydrochloric acid, or with hydriodic acid alone, only deoxygenation to the parent heterocycles (**286**) is observed (Scheme 24).[120] Hydrogenation over palladium on carbon as catalyst converts benz-1,2,5-oxadiazole (**287**) into its tetrahydro derivative (**288**), and causes some ring opening to give 1,2-phenylenediamine (**289**; Scheme 25).[121] If electron-donating groups are present at C-4 the proportion of the corresponding ring-opened product is increased. Chemical reduction with tin and hydrochloric acid only gives 1,2-phenylenediamines.

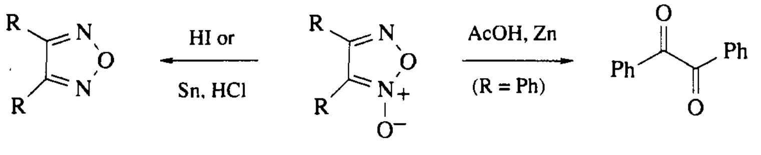

**(286)** **(284)** **(285)**

**Scheme 24**

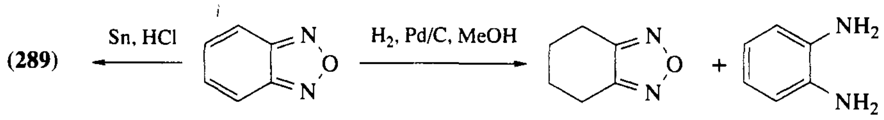

**(289)** **(287)** **(288)** 80% **(289)** 9%

**Scheme 25**

### *3.8.7.1.3 1,3,4-Oxadiazoles*

1,3,4-Oxazdiazoles are much more stable to reduction and it is possible to reduce substituent groups without affecting the nucleus; however, salts (**290**) are susceptible to reductive decyclization and treatment with sodium sulfide, for example, leads to acylthioacylhydrazines (**291**).[122] LAH reacts in a similar manner, and converts the 1,3,4-oxadiazolidine (**292**) into the *N*-methylaminotetrahydroisoquinoline (**293**).[123]

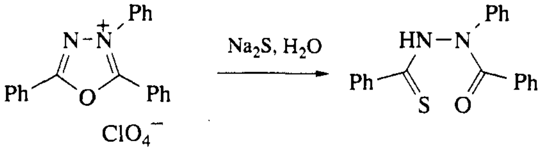

**(290)** **(291)**

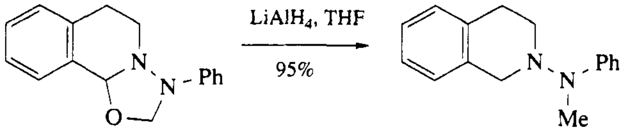

**(292)** **(293)**

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# 3.9

# Hydrozirconation of C=C and C≡C and Hydrometallation by Other Metals

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## 3.9.1 INTRODUCTION

Hydrometallation, as represented by equation (1), is the addition of a metal–hydrogen bond across an unsaturated group to yield an alkyl metal intermediate or product. From the point of view of organic synthesis, the latter is of interest as a nonstabilized carbanion equivalent, suitable for addition to C=X (see Volume 1, Part 1) or C=C (Volume 4, Chapter 1.6) π-bonds, coupling reactions (Volume 3, Part 2), oxidation (Volume 7, Chapter 4.2) and other transformations; and hydrometallation is just an alternative route to these reagents. Although hydrometallation virtually always participates as a key step in the overall mechanism of catalytic hydrogenation (as well as related catalytic processes, such as hydroformylation), its major applications are not found in the realm of reductions, except for special cases such as stereo- and regio-specific isotopic labelling.

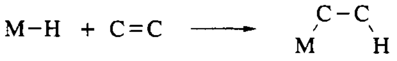

$$\mathrm{M{-}H} + \mathrm{C{=}C} \longrightarrow \underset{\mathrm{M}\qquad\mathrm{H}}{\mathrm{C{-}C}} \tag{1}$$

There are basically two reasons for making hydrometallation the route of choice: if an alkene or alkyne is the most convenient (accessible, cheap) starting material, or if alternative methods for generating the organometallic reagent are incompatible with other functional groups and/or the key synthetic goals. The classical preparation of lithium or Grignard reagents from organic halides and the corresponding metals will generally not be viable when there are other readily reducible groups present, or when stereochemistry at the reacting center is crucial.

The ideal system for hydrometallation would have the following attributes: a conveniently prepared starting reagent (the metal hydride); favorable kinetics and thermodynamics and high selectivity (in all its aspects) with all alkenes and alkynes that might be used as substrates; and a resulting organometallic reagent that is stable and highly versatile for subsequent transformation, exhibiting the full spectrum of organometallic reactivity. Obviously, there is no single system which is going to satisfy all of these criteria. However, two tactics may overcome the limitations of a single metal: transmetallation and catalyzed hydrometallation. These are represented in Scheme 1. In the first, $M_1H$ readily undergoes hydrometallation, but $M_1R$ cannot be used for the desired transformation. Hence the organic group is transferred to $M_2$, which can undergo the reaction but which has no suitable direct hydrometallation route. In the second, $M_2$ has both a suitable hydrometallation precursor and the desired organometallic reagent versatility, but direct hydrometallation does not proceed readily. In such cases addition of a catalytic amount of an $M_1$ compound may achieve the target organometallic reagent synthesis. Hydroalumination is a prime representative. These cases are discussed in Sections 3.9.3.4.2 and 3.9.4.2, respectively.

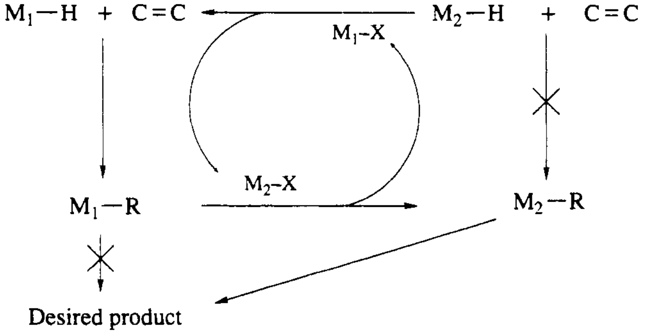

**Scheme 1**

Until around 15 years ago, hydrometallation was essentially limited to main group examples; for transition metals, the existence of appropriate hydrides, the stability of the organometallic reagents derived therefrom, and their utility for organic transformations were all considered questionable at best. This situation changed completely in the mid 1970s, when Schwartz and coworkers developed hydrozirconation. Here, for the first time, a stable and (moderately) well-characterized transition metal hydride could be added to unsaturated hydrocarbons to produce stable and well-characterized organometallic compounds, which have subsequently been demonstrated to effect a wide variety of synthetic transformations, either directly or following transfer to a second metal center.[1] In fact, many transition metal hydrides are better hydrometallation reagents: $M_1$ in Scheme 1 is nearly always a transition metal.

Throughout this chapter we will use the abbreviation zr = $Cp_2ZrCl$—; thus zrR = $Cp_2ZrRCl$.

## 3.9.2 MECHANISTIC ASPECTS

Generally the detailed mechanism will include steps such as precoordination of the alkene, dissociation of an auxiliary ligand, *etc*. Bercaw has noted that most commonly the actual hydrometallation step is not rate determining.[2] Since the most important hydrometallation reagent is an insoluble polymer, it is easy to see why mechanistic understanding has not kept pace with applications in this field.

### 3.9.2.1 Thermodynamic Considerations

Scheme 2 represents the key equilibria in hydrometallation. Note that: (i) association of the alkene (or alkyne) with the metal hydride (**1**) requires a vacant coordination site in the latter, whether (**2**) is an actual intermediate or merely a transition state. Since coordinatively unsaturated species such as (**1**) are rarely stable, a preliminary dissociation of an oligomer, or of an extra ligand, will be required. The latter may well be the limiting step in a given system; (ii) if metal–alkene bonding is strong, (**2**) can be such a stable intermediate that hydrometallation does not take place; on the other hand, if the metal–alkene interaction is very weak (**2**) may never form at all. In either case the organometallic reagent (**3**) will not be obtained. A delicate balance may thus be essential.

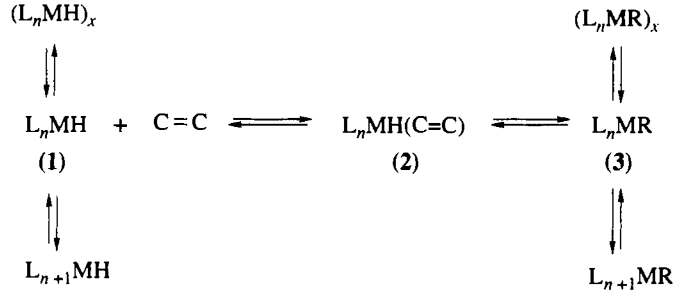

**Scheme 2**

Schwartz's reasoning for optimizing these thermodynamic considerations led to the development of hydrozirconation.[1] Hydride complexes of the late transition metals do not in general exhibit the hydrometallation reaction, probably because the alkene complexes are too stable. This may be understood from the Dewar–Chatt–Duncanson model for alkene bonding, wherein back donation of metal *d*-electrons to the alkene $\pi^*$-orbital is a major contributor. For metal centers with $d^0$-electron configurations, there should be substantial stabilization of (**3**) with respect to (**2**). Such metals are only found towards the left end of the Periodic Table, particularly Groups IIIA to VA.

Compare equations (2) and (3). Niobium complex (**4**) is a $d^2$-metal center: back bonding is important, and hydrometallation does not proceed, even when an additional ligand $PR_3$ is provided. Only when another good $\pi$-acceptor ligand (CO) is added does the alkenyl product (**5**) form.[3] In contrast, zirconium complex (**6**) is $d^0$, and here hydrometallation proceeds directly; no intermediate alkyne complex can be detected.[4] This qualitative picture is reinforced by theoretical studies on the 'bent metallocene' structure.[5] As shown in Figure 1, for a $d^0$-complex the two highest-filled orbitals are essentially unchanged or stabilized during hydrometallation. However, for a $d^2$-complex the next orbital, labelled ($1a_1 + \pi^*$), is also occupied, and it is strongly destabilized by hydrometallation; Hoffmann estimates that the thermodynamics are about 50 kcal mol$^{-1}$ worse for $d^2$ than for $d^0$ (1 cal = 4.2 J). Note that inclusion of a good $\pi$-acceptor ligand such as CO would restabilize the $1a_1$ orbital and cancel most or all of this unfavorable factor.

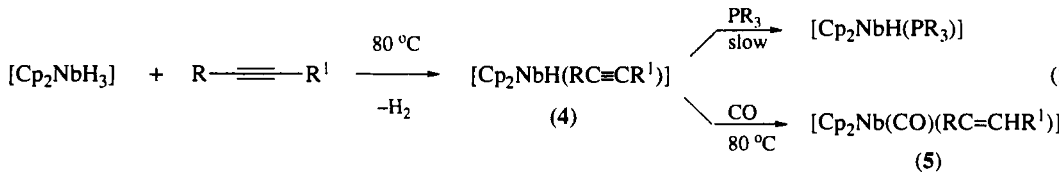

$[Cp_2NbH_3]$ + R—≡—$R^1$
80 °C
$-H_2$
$[Cp_2NbH(RC{\equiv}CR^1)]$
(4)
$PR_3$
slow
$[Cp_2NbH(PR_3)]$
CO
80 °C
$[Cp_2Nb(CO)(RC{=}CHR^1)]$
(5)

(2)

$$[Cp_2ZrHCl] + R{-}{\equiv}{-}R^1 \xrightarrow{25\ ^\circ C} [Cp_2ZrCl(RC{=}CHR^1)] \qquad (3)$$

(**6**)

Thermodynamic analysis of the overall hydrometallation process is straightforward: using the cycle of Scheme 3 we get the following expression for equation (4): $\Delta H^0 \approx D(M{-}H) - D(M{-}R) - X$, where $X \approx$ 36–38 kcal mol$^{-1}$.[6,7] Further estimating $\Delta S^0$ at −27 to −30 eu, it may be concluded that equation (4) is thermodynamically favored as long as the metal–hydride bond is no more than 27–30 kcal mol$^{-1}$ stronger than the metal–alkyl bond.

A survey of available thermochemical data suggests that this requirement is nearly always satisfied, although there are some cases that are close. The difference between $[CpMo(CO)_3H]$ and $[CpMo(CO)_3Et]$ has been estimated to be around 29 kcal mol$^{-1}$;[8] clean hydrometallation with this system has not been

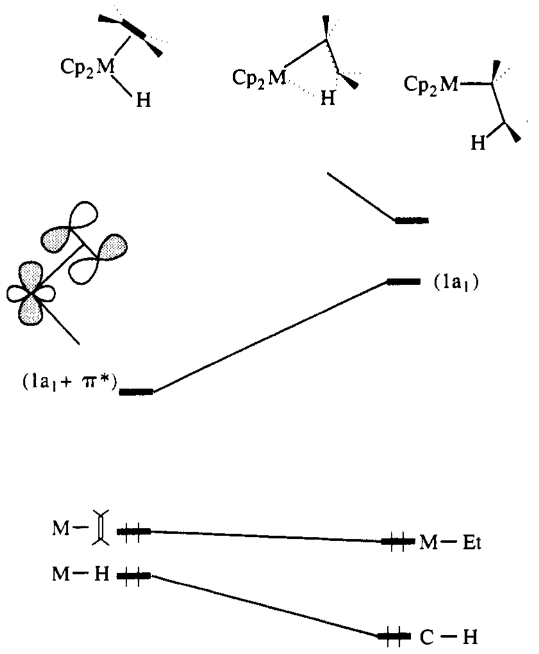

**Figure 1** Orbital correlation diagram for hydrometallation in bent metallocene complexes (reproduced from ref. 5 by permission of the American Chemical Society)

$$\begin{array}{rcl} L_nM{-}H & \longrightarrow & L_nM\bullet + H\bullet \\ H\bullet + C_2H_4 & \longrightarrow & Et\bullet \\ Et\bullet + L_nM\bullet & \longrightarrow & L_nM{-}Et \\ \hline L_nM{-}H + C_2H_4 & \longrightarrow & L_nM{-}Et \end{array} \qquad (4)$$

**Scheme 3**

demonstrated. Actinides[9] and early transition metals[10] exhibit smaller differences between M—H and M—R bond strengths than do the middle and late transition metals. This important trend has been attributed to bond polarity[9,11] or to repulsions between filled metal *d*-orbitals and alkyl group orbitals in the latter group.[10] We thus have a second thermodynamic reason for expecting early transition metals to provide superior hydrometallation reagents.

For hydrometallation of alkynes, similar analysis shows that *D*(M—H) − D(M—vinyl) need only be less than *ca.* 37 kcal mol$^{-1}$; metal–vinyl bonds are generally stronger than metal–alkyl bonds,[6,9] so this should be easy to achieve. Wayland has concluded that on thermodynamic grounds '...virtually any transition metal should be capable of accomplishing this reaction'.[7]

As for competing formation of (**2**), we calculate that (**2**) will be more stable than (**3**) when the strength of the metal–alkene interaction is greater than the quantity {36 kcal mol$^{-1}$ − [*D*(M—H) − *D*(M—R)]}. Unfortunately, data for absolute metal–alkene bond energies are virtually nonexistent. Some estimates can be made from thermochemical data and (possibly questionable) approximations: $D(L_2Pt{-}C_2H_4) \approx$ 73 kcal mol$^{-1}$,[12] $D(Fe(CO)_4{-}C_2H_4) \approx$ 28 kcal mol$^{-1}$;[13] or from theoretical calculations $D(Cl_3Pt^-{-}C_2H_4)$ ≈ 28 kcal mol$^{-1}$.[14] In general (especially for later transition metals) *D*(M—H) is considerably greater than *D*(M—C); hence stability of (**2**) will present a problem unless the metal–alkene bond is considerably weaker than in these typical cases. Again we see the important advantage for $d^0$-metals.

For main group metals, which exhibit relatively small differences between M—H and M—C bond strengths and no strong metal–alkene interactions, the thermodynamics of hydrometallation should be even more favorable than for early transition metals. This does not appear to be the case, especially for hydroalumination (Volume 8, Chapter 3.11). The reason is almost certainly the additional stability of the metal hydride reagent conferred by aggregation: organoaluminum hydrides exist as rather tight dimers, and the bridging bond energy is enough to shift the equilibrium away from the hydrometallation side in many cases.[15]

Similar arguments apply to selectivity issues. Hydrometallation should be preferred for an alkyne over an alkene; for a terminal over an internal double bond; and for anti-Markovnikov addition. Equation (5) is never thermodynamically preferred over hydrometallation of an alkene;[7] however, hydrometallation in the opposite sense to give an alkoxide (equation 6) will be preferred if the metal–oxygen bond is at least 24 kcal mol$^{-1}$ stronger than the metal-carbon bond. The latter condition is probably not generally satisfied for later transition metals,[16] but surely is for the more oxophilic early transition metals[10,17] as well as main group metals (with the latter, even saturated C—O functional groups may not be tolerated). For terminal alkynes, elimination of $H_2$ to form an alkynyl complex (equation 7) will be favored over hydrometallation if the metal–alkynyl bond is at least 35 kcal mol$^{-1}$ stronger than the metal–vinyl bond, a situation which could arise:[12,18] a difference as large as 38 kcal mol$^{-1}$ was reported for a uranium system.[9] For all these issues it must be kept in mind, of course, that kinetic factors can and usually do have more impact on selectivity than thermodynamic factors. We turn to that aspect next.

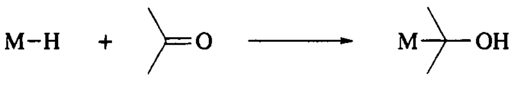

(5)

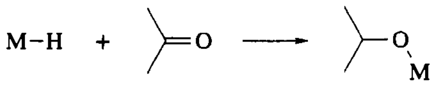

(6)

$$M{-}H \;+\; R{-}{\equiv} \longrightarrow M{-}{\equiv}{-}R \;+\; H_2 \qquad (7)$$

### 3.9.2.2 Detailed Mechanism of Hydrometallation

A general picture for the mechanism is shown in Scheme 4, which is based upon a theoretical analysis by Thorn and Hoffmann.[19] Here distinction between (**2**) and (**2a**) reflects the general assumption, supported by calculations, that the insertion step requires the M—H and C═C groups to be *cis* and coplanar, which need not be the case for the first-formed and/or thermodynamically most stable alkene complex (**2**). Thorn and Hoffmann conclude that most or all metal hydrides will have some pathway that leads to hydrometallation without a large kinetic barrier, so long as none of the key intermediates along the way is too stable. The same inference was drawn for the bent metallocene systems discussed earlier (Figure 1): a kinetic barrier to insertion, found only for the $d^2$-cases, is a consequence of the thermodynamic stabilization of alkene complex (**2**).[5]

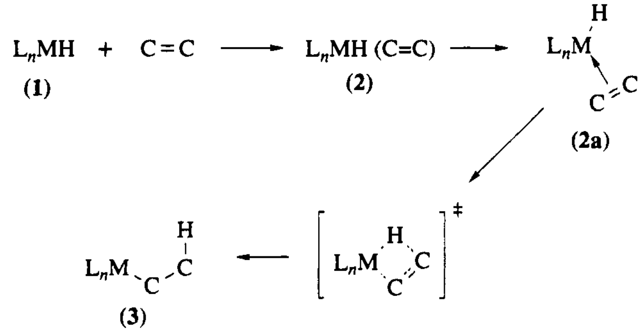

**Scheme 4**

When the barrier to hydrometallation is solely a consequence of the strength of the metal–alkene interaction, the implication is unfavorable for selectivity. Suppose the kinetic scheme of equation (8) operates; then the rate for formation of (**3**) from a given alkene will be related to the product of the constants $k$ and $K$ for that alkene. However, factors which tend to make $K$ larger (more stable alkene complex) will make $k$ smaller and thus tend to cancel out, resulting in little kinetic differentiation between substrates.

$$\underset{(\mathbf{1})}{L_nMH + C{=}C} \;\overset{K}{\rightleftharpoons}\; \underset{(\mathbf{2})}{L_nMH(C{=}C)} \;\xrightarrow{k}\; \underset{(\mathbf{3})}{L_nMR} \qquad (8)$$

This is in fact the result found for hydrometallation of substituted styrenes by $[RhH_2Cl(PR_3)_3]$ (equation 9).[20] $K$ and $k$ vary inversely as the substituent X is changed, so the overall rates are fairly constant.

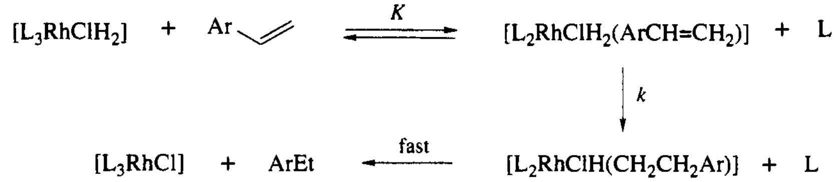

(9)

A quite different case is presented by the bent metallocene systems, $[Cp_2MH(alkene)]$ where M = Nb or Ta.[2,21] Here the metal–alkene complex is relatively quite stable, so much so that the kinetics of formation of a stable alkyl metal complex cannot be easily studied. Nonetheless it is possible to get a handle on the hydrometallation kinetics by means of dynamic NMR methods (Table 1). The increased rate for propene *versus* ethylene results from both steric destabilization of the ground state and electronic stabilization of the transition state for the former. The first is typical of alkene complexes; the second implies that some partial positive charge develops at the β-carbon during the hydrometallation process, also seen in the trend for substituted styrenes.

**Table 1** Kinetic Parameters (at 50 °C) for Hydrometallation in Complexes $[Cp^*_2NbH(CH_2CHR)]^2$

| $R$ | $k$ ($s^{-1}$) | $\Delta G^{\ddagger}$ (kcal $mol^{-1}$) |
|---|---|---|
| H | 2.62 | 18.3 |
| Me | 890 | 14.6 |
| Ph | 3.18 | 18.2 |
| $p$-$Me_2NC_6H_4$ | 6.80 | 17.7 |
| $p$-$MeOC_6H_4$ | 4.81 | 17.9 |
| $p$-$MeC_6H_4$ | 3.47 | 18.1 |
| $p$-$CF_3C_6H_4$ | 0.91 | 19.4 |

Two conclusions follow from the apparent positive charge build-up. First, anti-Markovnikov addition is favored kinetically as well as thermodynamically, which means that the opposite regiochemistry will be hard to achieve; second, the hydrogen atom behaves more as hydride, $H^-$, during its migration to the carbon atom. If this accurately represents the chemical nature of the metal–hydrogen bond in the ground state as well, it has clear implications for functional group tolerance. It is not clear to what extent these results can be applied to any other system.

For the ordinary Cp analogs of both Nb and Ta, two isomers of the (substituted alkene) hydride complex are accessible, labelled *endo* and *exo* (Figure 2).[21] These undergo reversible hydrometallation without interconverting, showing that the barrier to alkene rotation is very high and that the hydrogen can move only to the adjacent carbon atom. Such a situation offers potential for regioselectivity modification, as hydrometallation from the *exo* isomer generates the more-substituted metal alkyl (Markovnikov addition). Unfortunately, it has not proven possible in this system to trap that product with added ligand: alkene displacement dominates instead.[21]

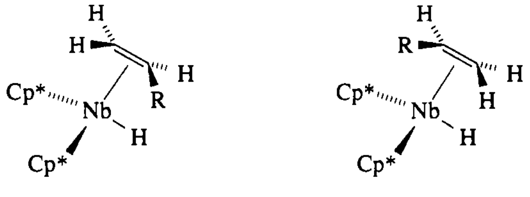

*endo* *exo*

**Figure 2**

The other questions raised above—about the relative roles of alkene complexation and hydrometallation, and the possible requirement for structural rearrangement before insertion—cannot be answered in this system, as the alkene binding and geometry are essentially immutable. Roe has shown for a rhodium complex with *trans* alkene and hydride ligands, that rearrangement does not contribute to the hydrometallation barrier: the first step in equation (10) is fast, and $k_2$ is rate determining.[22] It is notable that for this reaction $\Delta G^\ddagger \approx 12$ kcal mol$^{-1}$, substantially less than that found for the bent niobocene complexes above, and presumably reflecting stronger alkene binding in the latter.

$$\textit{trans}\text{-}[L_2RhH(C_2H_4)] \underset{}{\overset{K}{\rightleftharpoons}} \textit{cis}\text{-}[L_2RhH(C_2H_4)] \xrightarrow{k_2} [L_2RhEt] \qquad (10)$$

Summing up to this point: we have concluded that $d^0$ complexes are preferred for hydrometallation on thermodynamic grounds, and that in the expected absence of strong metal–alkene binding no great kinetic barriers should be anticipated. What mechanistic factors will operate, then, especially as regards selectivity issues?

Unfortunately we have very little information to draw upon. The main hydrometallation reagent, [$Cp_2ZrHCl$] (**6**), is an insoluble polymer; its reactions are either heterogeneous or limited by the very small extent of dissolution, and detailed kinetics of hydrometallation are essentially unattainable. Several soluble complexes ($Cp^*_2MH_2$, M = Zr,[23] Hf;[24] $Cp^*_2ScH$[25]) hydrometallate alkenes very rapidly at low temperatures, which at least confirms the prediction that there should be no high barrier. [$Cp^*_2ZrHCl$] has been prepared[26] but not examined as a hydrometallation reagent. The phenomenology of hydrometallation by [$Cp_2ZrHCl$]—relative reactivities, observed selectivities and the like—is presented in the following sections.

For $d^0$ metals, does the alkene complex (**2**) have any stable existence as an intermediate? It has commonly been thought that an alkene complex of a $d^0$ transition metal or main group metal (with no π back bonding component) could not have any lifetime, but would correspond only to a transition state (or at best a negligibly shallow minimum) in the energy surface. For example, gas phase studies on hydroboration were interpreted in terms of a 3-center transition state (structurally equivalent to a boron–alkene complex) as the highest point on the energy surface.[27]

While direct evidence for a somewhat stable intermediate alkene complex has never been obtained, it is possible to infer stability from rearrangement studies. One of the most striking characteristics of hydrozirconation is the facile rearrangement of products obtained from internal alkenes (Scheme 5).[28] The obvious mechanism is a sequence of reversible β-hydrogen additions and eliminations; but does this proceed *via* intermediate alkene complexes (path a) or free alkenes (path b)? Only the starting alkene oct-4-ene and the final *n*-octylzirconium product can be detected,[28] which implies that path (a) is followed: the organic group must always remain associated with the zirconium complex (unless the hydrozirconation rates for oct-3-ene and oct-2-ene are much faster than that for oct-4-ene, and there is nothing that would support this argument). Likewise, ethylene does not displace octene from complexes such as (**7**),[1] which would be anticipated if they are in equilibrium with the free alkene. (Formation of isomerized alkene was found in hydrozirconation of very long chain alkenes, but these reactions required prolonged times and somewhat elevated temperatures.[29])

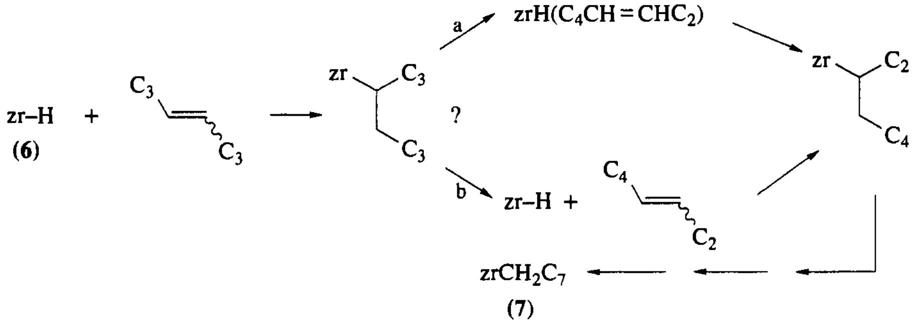

**Scheme 5**

A related result suggests that even boron–alkene complexes have some stability: the rearrangement shown in equation (11) leads mainly to the *cis* isomer (**8**), whereas hydroboration of 2-methylmethylenecyclohexane under the same conditions gives mostly the *trans* isomer.[30] This shows that the B—H group adds most often to the same face of the double bond from which it is eliminated, and boron thus must remain associated with the methylenecyclohexane. We may conclude that alkene complexes of $d^0$ metals are in fact viable.

Before leaving this section we briefly examine hydrometallation mechanisms completely different from the 'classic' one depicted in Scheme 2. One class involves metal hydrides which do not have a readily available vacant site and requires conjugated alkenes — 1,3-dienes, styrenes; these proceed *via* a

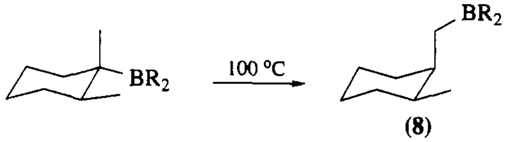

(8)

(11)

free radical pathway, as in Scheme 6.[31,32] More frequently this leads to alkene hydrogenation rather than to a stable hydrometallation product, as indicated by the left hand pathway in Scheme 6; many of the systems do not meet the criteria for favorable hydrometallation thermodynamics discussed earlier. The requirement for conjugation reflects the need to generate a relatively stable alkyl radical; it has been suggested that the regioselectivity of styrene hydrometallation might allow differentiation between the classical (equation 12) and radical (equation 13) mechanisms.[32] The most unequivocal demonstration of the Scheme 6 mechanism is the observation of CIDNP effects in the NMR.[31,32]

Scheme 7 depicts a different radical mechanism; this is a chain path, unlike Scheme 6, that has been observed for main group metals such as tin but apparently not for transition metals.[32] Note that it gives the regiochemistry of equation (12), not equation (13). Still another nonclassical possibility is the transfer of hydrogen as a proton instead of a hydrogen atom; this is primarily observed in some cobalt chemistry[33] [for example equation 14, where (Co) = bis(dimethylglyoximato)cobalt and py = pyridine]. Some of these reactions may involve radical pathways as well.[34]

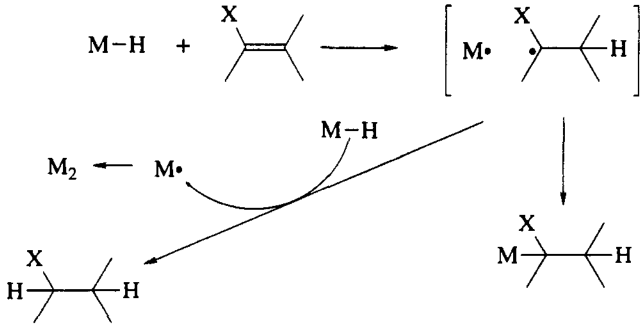

Scheme 6

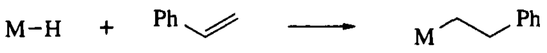

(12)

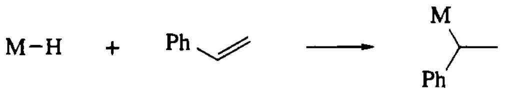

(13)

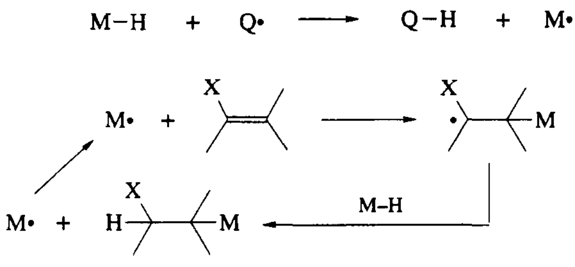

Scheme 7

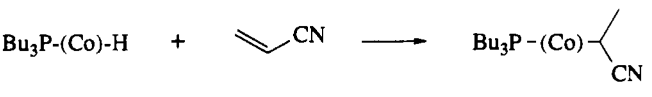

(14)

## 3.9.3 HYDROZIRCONATION WITH [$Cp_2ZrHCl$] AND RELATED COMPOUNDS

### 3.9.3.1 Synthesis, Structure and Properties of Reagents

The synthesis of [$Cp_2ZrHCl$] (**6**), along with several other zirconocene hydrides, was first reported by Wailes and Weigold in 1970.[35] Treatment of [$Cp_2ZrCl_2$] with one equivalent (on a hydrogen basis) of either $LiAlH_4$ or $LiAl(OBu^t)_3H$ in THF afforded high (>90%) yields of [$Cp_2ZrHCl$] as an insoluble white solid. Shortly afterwards, Wailes and coworkers showed that [$Cp_2ZrHCl$] reacts with alkenes[36] and alkynes,[37] although few of the products were completely characterized, and there was no indication of any particular synthetic value.

In 1974 Schwartz and coworkers, following the rationale sketched out above, demonstrated the potential power of hydrozirconation.[28] Preparation of the [$Cp_2ZrHCl$] reagent (a commercial preparation is now available) utilized a different reductant—$Na[AlH_2(OCH_2CH_2OMe)_2]$, known commercially as 'Red-Al' or 'Vitride'—from those employed by Wailes. The Red-Al procedure affords the reagent contaminated with small amounts of [$Cp_2ZrH_2$] and much larger amounts (as much as 30%) of NaCl.[38] Formation of [$Cp_2ZrHCl$] by direct hydrogenation of the dichloride has been disclosed in a patent.[39]

Purity may be important: attempts to hydrozirconate long chain alkenes failed for certain preparations, especially when $LiAlH_4$ was employed; it was suggested that aluminum-containing impurities might be responsible.[40] An improved preparation uses a filtered ether solution of $LiAlH_4$ as reductant and a wash with $CH_2Cl_2$ to convert over-reduced [$Cp_2ZrH_2$] back to [$Cp_2ZrHCl$]. This gives 77–92% yields and around 95% purity, with the dihydride the only significant contaminant.[41] The absence of salt impurities means that the hydrozirconation reaction mixture will contain no insolubles upon completion, which makes work-up more convenient. One other point is notable: both the absolute and relative rates of hydrozirconation for several unsaturated compounds were found to be quite different for this preparation. Some of the generalizations about mechanism and selectivity in the following sections might not prove to be universally valid, depending instead on the exact nature of the reagent used.

Yet another alternative is *in situ* preparation of [$Cp_2ZrHCl$], by adding reductant to a solution of [$Cp_2ZrCl_2$] already containing the unsaturated substrate. The reductant may be a standard hydridic reagent such as Red-Al,[29,42] or a precursor such as a *t*-butyl Grignard reagent, which presumably generates a transient *t*-butylzirconium complex that readily undergoes β-hydrogen elimination.[42] The main advantages are the elimination of the need for inert atmosphere filtration and (possibly) improved reactivity by avoiding insoluble reagents. However, in the latter case hydrozirconation of styrene or butadiene gave some (or mostly) *t*-butylated products as well.[42]

Variants include changing auxiliary ligand X in [$Cp_2ZrHX$], or substituting cyclopentadienyl rings. The dihydride [$Cp_2ZrH_2$] hydrozirconates unsaturated molecules, but the products are generally not useful reagents. Instead they undergo secondary reactions, frequently leading to overall hydrogenation. Such reactions are mechanistically complex, involving prior complexation of additional ligand[43–45] or interaction with Cp ring substituents.[46] Often reaction with additional substrate leads to products such as metallocycles; equation (15) shows one such example.[47] Similarly, although a divinylzirconium complex (from double hydrozirconation) was proposed for equation (16),[37] the correct product is (**9**).[48] This problem of instability may effectively preclude the use of [$Cp_2ZrH_2$] or [$Cp_2ZrHR$] species as synthetic reagents.

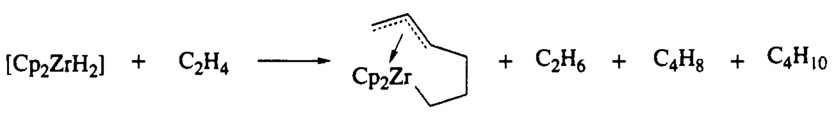

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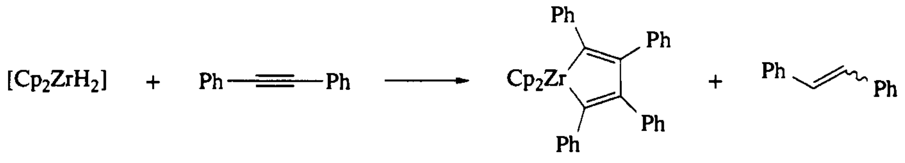

(**9**)

(16)

A number of (substituted Cp) derivatives have been made, but the vast majority are the dihydrides, [$Cp'_2ZrH_2$]. This alleviates the problem of insolubility: [$(\eta\text{-}C_5H_4Me)_2ZrH_2$][49] and [$CpCp^*ZrH_2$][50] are both dimeric, whereas [$(\eta\text{-}1,2,4\text{-}C_5H_2Me_3)Cp^*ZrH_2$][50] and [$Cp^*_2ZrH_2$][23] are monomers. ([$Cp_2ZrHCl$]

appears to be dimeric in solution;[48] whether its extremely low solubility is due to higher aggregation in the solid state is not known.) Again, dihydrides may not be useful hydrozirconation reagents. Even where clean hydrometallation can be achieved (see Table 7), the presence of excess alkene induces reductive elimination; one would have to worry about reagents used for synthetic transformations doing the same.

Complexes of type [$Cp^*_2MHX$] (M = Zr, Hf; X = F, Cl, Br,[24,26] OR,[24,51,52] $NR_2$[52,53]) should exhibit hydrozirconation, and might offer some intriguing advantages such as mechanistic studies uncomplicated by insolubility, and selectivity modulation by steric control. On the other hand, their preparation is likely to be considerably more inconvenient and/or expensive than [$Cp_2ZrHCl$]. Note that reagents which lead to the precipitation of [$Cp_2ZrHCl$] ($LiAlH_4$, $LiAlH(OR)_3$) afford instead the dihydrides with substituted Cp.[49] [$Cp^*_2ZrHCl$] was not made directly, but by comproportionation of the dihydride plus dichloride[26] or the reaction of [$Cp^*_2ZrH_2$] with one equivalent of MeCl.[51] A polymer-supported reagent was obtained by chloromethylating polystyrene, displacing chloride with $Cp^-$, deprotonating and attaching to Zr and reducing with Red-Al, in hopes of a recyclable hydrozirconation agent. While *n*-alkenes could be hydrozirconated, the presence of uncomplexed Cp groups in the polymer complicated the stoichiometry, and recycling was not achieved.[54]

Reactions of the hafnium analog of (**6**), [$Cp_2HfHCl$], differ little from those of the zirconium complex.[55] It was suggested that the hafnium reagent is somewhat more sensitive to steric inhibition, as cyclohexene and related cyclic alkenes failed to react; but this might well be due to the specific preparation of the solid (see above), rather than to any inherent molecular differences. There are some changes in the stereochemical outcome of hydrometallation of bicyclic alkenes (see Section 3.9.3.3.3), but it is far from clear that hafnium will provide any features sufficient to overcome the availability and cost advantages of zirconium.

### 3.9.3.2 Hydrozirconation of Alkenes and Alkynes

Standard conditions for the hydrozirconation of unsaturated hydrocarbons are those originally employed:[28] the hydrocarbon is added to a suspension of a roughly equimolar amount of [$Cp_2ZrHCl$] in benzene or toluene, and the mixture stirred at ambient or slightly elevated temperatures for 1–3 h. Formation of the hydrozirconation product, [$Cp_2ZrRCl$], is signalled by dissolution of the white Zr reagent to give a yellow to orange solution. Attempted isolation of the product usually gives an oil, although some crystalline products have been obtained; more frequently characterization is limited to NMR of the solution. Even more frequently the product is not characterized at all, but used directly for subsequent transformation (see Section 3.9.3.4).

Examples of reported hydrozirconations of alkenes and alkynes are summarized in Tables 2–6. Simple alkenes appear always to react as long as they are no more than trisubstituted. The only reported failure is that of a long chain internal alkene, triacont-15-ene,[79] but such alkenes have subsequently been successfully hydrozirconated, albeit at slightly elevated temperature.[40] The order of reactivity, based primarily on qualitative observations, is: terminal alkene > internal alkene (*cis* ≈ *trans*) > exocyclic alkene > cyclic alkene ≈ trisubstituted alkene.[1] Trisubstituted cyclic olefins and tetrasubstituted olefins do not react. Representative examples are shown in Table 2.

Migration of the metal group along the carbon chain is facile; in all cases, the least substituted possible alkylzirconium product (*e.g.* **7**) is the only one obtained. Contrast hydroboration, which takes place under comparably mild conditions; but the migration of boron to the terminal position requires prolonged heating and is seldom a clean transformation (Volume 8, Chapter 3.10). Rearrangement of hydroalumination products is also slow (Volume 8, Chapter 3.11), but for zirconium it is not possible to arrest migration to the terminal position (save for special cases—aromatic or functionalized alkenes—which will be considered in Section 3.9.3.3.2).

Alkynes are universally hydrozirconated as well; the only failure in the literature is that of a perfluorinated compound, $C_7F_{15}C{\equiv}CH$.[69] Alkynes appear to be more reactive than alkenes, both by qualitative comparison and from the results on enynes (Table 6; also see Section 3.9.3.3.1). Furthermore, hydrozirconation of alkynes can compete with reduction of unsaturated functional groups such as nitriles and esters (Table 5), which is generally not true for alkenes. Dienes can be cleanly monohydrozirconated if one of the double bonds is terminal; other cases are considered in Section 3.9.3.3.1.

Hydrozirconation of unsaturated organometallics gives bimetallic compounds, such as substituted analogs of the so-called Tebbe reagent, [$Cp_2Ti(\mu\text{-}CH_2)(\mu\text{-}Cl)AlMe_2$]. (The latter has proven a versatile precursor of a 'methylene equivalent' for Wittig-type reactivity or for alkene metathesis,[80] but is only available as the simple $CH_2$ version.) Equation (17) gives the desired isomer (**10**) cleanly only for the bulkiest R; analogs were also prepared from alkenyl-boron and -zinc precursors. None of these, however,

**Table 2** Hydrozirconation of Simple Alkenes

| *Alkene* | *Product* | *Conditions*[a] | *Characterization*[b] | *Yield (%)*[c] | *Use* | *Comments* | *Ref.* |
|---|---|---|---|---|---|---|---|
| Oct-1-ene (also *cis*- and *trans*-oct-4-ene) | $zr(CH_2)_7Me$ | S | N | 96 | Transfer to Al | | 38 |
| Oct-1-ene | | | | 86 | | *In situ* preparation | 42 |
| Dec-1-ene | $zr(CH_2)_9Me$ | S | | | Hydrocyanation | | 56 |
| $RCH{=}CHR$ ($R = C_nH_{2n+1}$; $n = 11, 12, 13, 14, 16, 20$) | $zr(CH_2)_{2n+1}Me$ | 40 °C/THF/50–170 h | | (30–80 as RI) | | *In situ* preparation | 40 |
| Cyclohexene | $zrC_6H_{11}$ | S | N | 90 | Transfer to Al | | 38 |
| Norbornene (and other bicyclic alkenes) | 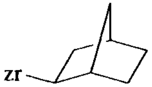 | 60 °C | | (95 as ROH) | | See Section 3.9.3.3.3 for stereochemistry | 57 |
| $H_2C{=}CHBu^t$ | $zr(CH_2)_2Bu^t$ | S | N, A | 88 | Transfer to Al | | 38 |
| $H_2C{=}CHSiMe_3$ | $zr(CH_2)_2SiMe_3$ | S | | | Hydrocyanation | | 56 |
| 2-Methyloct-1-ene | $zrCH_2CHMe(CH_2)_5Me$ | S | | | | Deuteration | 58 |
| $H_2C{=}CMeCH_2Bu^t$ | $zrCH_2CHMeCH_2Bu^t$ | | | | | | 59 |
| 2-Methylbut-2-ene | $zr(CH_2)_2Pr^i$ | S | | (100 as RBr) | | | 28 |
| Methylenecyclohexane | $zrCH_2C_6H_{11}$ | S | N, A | 95 | Transfer to Al | | 38, 60 |
| Styrene | $zr(CH_2)_2Ph$ | S | N | | | | 59, 61 |
| | + $zrCHPhMe$ | | | (60 as RH) | | | 42 |
| | | | | | Oxidation | | 29 |
| $H_2C{=}CMePh$ (and other aromatic alkenes) | $zrCH_2CHMePh$ | | | (100 as ROH) | | *In situ* preparation | 29 |

[a] Reaction conditions; S = standard conditions (see text). [b] Method of characterization for $[Cp_2ZrRCl]$: N = $^1H$ NMR; C = $^{13}C$ NMR; A = elemental analysis; I = infrared; X = X-ray crystallographic structure. [c] Yield of isolated $[Cp_2ZrRCl]$ except for numbers in parentheses which are yields of indicated simple derivative.

**Table 3** Hydrozirconation of Alkenes with Oxygen-containing Functional Groups

| *Alkene* | *Product* | *Conditions*[a] | *Characterization*[b] | *Yield (%)*[c] | *Use* | *Comments* | *Ref.* |
|---|---|---|---|---|---|---|---|
| $CH_2{=}CH(CH_2)_3OH$ | $zr(CH_2)_5Ozr$ | | | (56 as RI) | | *In situ* preparation | 42 |
| $CH_2{=}CH(CH_2)_2O^-K^+$<br>(and related alkenoxides) | See equation (36) | THF | X | 10–40 | | Dimer with oxygen bridges | 62 |
| 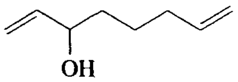 (and related dienols) | 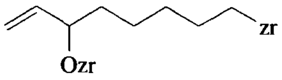 | 2 equiv. Zr<br>10 °C | N | (54–70 as RH) | | See Section 3.9.3.3.2 for regiochemistry | 63 |
| 2-Vinylfuran | 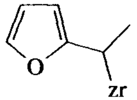 | S | | | Hydrocyanation | | 56 |
| 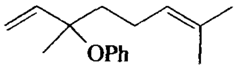 | 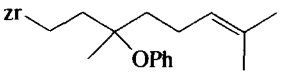 | S | | | Hydrocyanation | | 56 |
| Oleic acid oxazoline (and other long chain acid oxazolines) | See Scheme 8 | | | (62–82 as RH) | | Solvent effect, see Section 3.9.3.3.2 for regiochemistry | 58, 64<br>65 |

[a–c]See footnotes to Table 2.

**Table 4** Hydrozirconation of Simple Alkynes

| *Alkyne* | *Product* | *Conditions*[a] | *Characterization*[b] | *Yield (%)*[c] | *Use* | *Comments* | *Ref.* |
|---|---|---|---|---|---|---|---|
| $C_2H_2$ | zrCH=CH$_2$ | 50 °C | N, A, C | 86 | | | 61 |
| | | S | | | Pd/coupling | | 66 |
| Prop-1-yne | zrCH=CHMe | 50 °C | N, A, I | | | | 61 |
| But-1-yne | zrCH=CHEt | 78 °C | | | | | 37 |
| Hex-1-yne | zrCH=CH$(CH_2)_3$Me | 0 °C/$CH_2Cl_2$ | | '100' | | | 41 |
| | | S | | | Pd/coupling | | 66 |
| | | S | | | ($\eta^2$-hexyne)Zr | | 67 |
| Oct-1-yne | zrCH=CH$(CH_2)_5$Me | S | N | | Ni/conjugate addition | | 68 |
| Dec-1-yne | zrCH=CH$(CH_2)_7$Me | S | | | Hydrocyanation | | 56 |
| | | S | | | Pd/coupling | | 66 |
| HC≡CBu$^t$ | zrCH=CHBu$^t$ | S | N, A | 89 | Transfer to Al | | 38 |
| | | | | | Ni/conjugate addition | | 68 |
| | | 50 °C | N, A, I | | | | 61 |
| HC≡CPh | zrCH=CHPh | 78 °C | N | | | | 37 |
| | | 50 °C | N, A, I | | | | 61 |
| | | S | | | Pd/coupling | | 66 |
| HC≡C$C_6H_4$-*p*-OMe | zrCH=CHAr | S | | | Pd/coupling | | 66 |
| HC≡C$CH_2C_6H_4$-*p*-OMe | zrCH=CHCH$_2$Ar | | | | Pd/coupling | | 69 |
| Hex-3-yne | *cis*-zrC(Et)=CHEt | S | N | 93 | Transfer to Al | | 38 |
| | | | | | Ni/conjugate addition | | 68 |
| | | 0 °C/$CH_2Cl_2$ | | '100' | | | 41 |
| | | | | | Pd/coupling | | 66 |
| EtC≡CMe | | S | | | | | 4 |
| Pr$^n$C≡CMe | See equation (39) | S | | | | | 4 |
| Pr$^i$C≡CMe | and | S | N | 80 | | See Section 3.9.3.3.2 | 4, 38 |
| Bu$^i$C≡CMe | Table 8 | S | | | | for regiochemistry | 4 |
| Bu$^t$C≡CMe | | S | | | | | 4 |
| PhC≡CPh | *cis*-zrC(Ph)=CHPh | 78 °C | N | | | | 37 |

[a–c] See footnotes to Table 2.

**Table 5** Hydrozirconation of Alkynes with Functional Groups

| *Alkyne* | *Product* | *Conditions*[a] | *Characterization*[b] | *Yield (%)*[c] | *Use* | *Comments* | *Ref.* |
|---|---|---|---|---|---|---|---|
| $BuCC{\equiv}CCH_2OH$ (and related) | Direction of addition unknown | 2 equiv. Zr | | (85 as RH) | | | 70 |
| $HC{\equiv}CCH_2CMe_2OH$ | $zrCH{=}CHCH_2CMe_2Ozr$ | 2 equiv. Zr | | | Couple to Pd(allyl) | | 71 |
| $HC{\equiv}COEt$ | $zrCH{=}CHOEt$ | S | | | Pd/coupling | | 66, 72 |
| $HC{\equiv}CCH_2OTHP$ | $zrCH{=}CHCH_2OTHP$ | S | | | Ni, Pd/coupling | | 72 |
| $HC{\equiv}CCH_2OSiMe_2Bu^t$ | $zrCH{=}CHCH_2OSiMe_2Bu^t$ | S | | | Hydrocyanation | | 56 |
| $HC{\equiv}C(CH_2)_4OSiMe_2Bu^t$ | $zrCH{=}CH(CH_2)_4OSiMe_2Bu^t$ | S | N | | Ni/conjugate addition | | 68 |
| 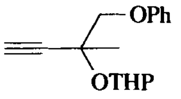 | 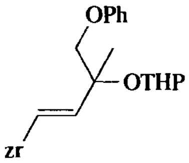 | | | (10 as RI) | | | 73 |
| 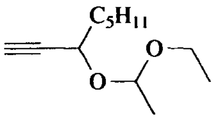 (and related) | 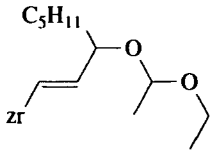 | S | N | | Ni/conjugate addition | | 68 |
| $HC{\equiv}C(CH_2)_3CO_2Bu^t$ | $zrCH{=}CH(CH_2)_3CO_2Bu^t$ | S | N | 81 | | Yield 41% with methyl ester | 68 |
| $HC{\equiv}C(CH_2)_8CO_2Me$ (and other esters) | $zrCH{=}CH(CH_2)_8CO_2Me$ | S | | | Pd/coupling | | 66 |
| $HC{\equiv}C(CH_2)_3CN$ | $zrCH{=}CH(CH_2)_3CN$ | S | | | Pd/coupling | | 66 |
| $HC{\equiv}C(CH_2)_3Cl$ | $zrCH{=}CH(CH_2)_3Cl$ | S | | | Pd/coupling | | 66 |

[a–c] See footnotes to Table 2.

Table 6 Hydrozirconation of Dienes, Diynes and Enynes

| *Substrate* | *Product* | *Conditions*[a] | *Characterization*[b] | *Yield (%)*[c] | *Use* | *Comments* | *Ref.* |
|---|---|---|---|---|---|---|---|
| 1,3-Butadiene (and substituted) | $zrCH_2CH_2CH{=}CH_2$ | S | | (59–98 as RCHO) | | | 74 |
| 1,3-Pentadiene | $zrCH_2CH_2CH{=}CHMe$ | S | N | 73 | Transfer to Al | | 38 |
| | | S | | | hydrocyanation | See Section 3.9.3.3.2 for regiochemistry | 56 |
| 1,5-Hexadiene | $zr(CH_2)_4CH{=}CH_2$ | S | N | 92 | Transfer to Al | | 38 |
| 1,7-Octadiene | $zr(CH_2)_6CH{=}CH_2$ | S | N | 98 | Transfer to Al | | 38 |
| 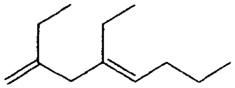 | 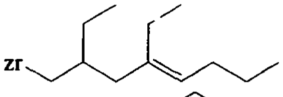 | | | (34 as RCHO) | Bacteriocide | | 75 |
| 4-Vinylcyclohexene | 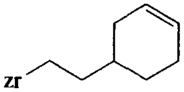 | | | (81 as RI) | | *In situ* preparation | 42 |
| Vitamin $D_3$ | See equation (41) | | | (84 as RH) | | See Section 3.9.3.4.3 | 76 |
| $HC{\equiv}C(CH_2)_2C{\equiv}CH$ | $zrCH{=}CH(CH_2)_2C{\equiv}CH$ | S | | | Pd/coupling | | 66 |
| $HC{\equiv}C(CH_2)_nC{\equiv}CTMS$ | $zrCH{=}CH(CH_2)_nC{\equiv}CTMS$ | | | | Pd/coupling | Protect for mono product | 77 |
| $HC{\equiv}CCH{=}CH_2$ | $zrCH{=}CHCH{=}CH_2$ | | | 75–90 | | | 78 |
| $HC{\equiv}CCMe{=}CH_2$ | $zrCH{=}CHCMe{=}CH_2$ | S | | | | Relatively low yield | 66 |
| $HC{\equiv}CCH{=}CHOMe$ | $zrCH{=}CHCH{=}CHOMe$ | | | | | See Section 3.9.3.3.3 | 78 |
| $HC{\equiv}CCH{=}CH(CH_2)_4Me$ | $zrCH{=}CHCH{=}CH(CH_2)_4Me$ | | | | Pd/coupling | | 77 |
| 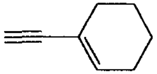 | 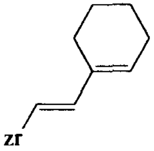 | | | | | | 78 |

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[a–c] See footnotes to Table 2.

performed well in alkenation reactions. The same compounds may be alternatively generated by hydroalumination of alkenylzirconium.[81,82]

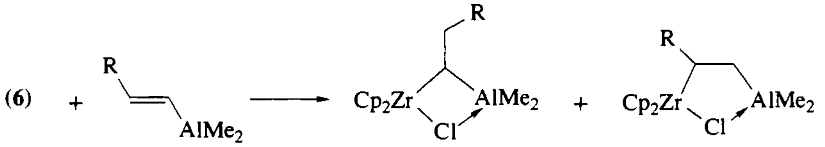

**(10)** **(11)** (17)

| | (10) | (11) |
|---|---|---|
| R = Bu$^t$ | >95% | <5% |
| R = Bu$^n$ | 60% | 40% |
| R = Me | 33% | 67% |

Hydrozirconation of vinylzirconium (**12**), itself obtained by hydrozirconating acetylene, gives the μ-ethylene product (**13**; equation 18) and thus amounts to an overall double hydrozirconation of an alkyne. However, this reaction is not general: attempted hydrozirconation of (substituted vinyl)zirconium does not lead to analogs of (**13**).[61] This may be relevant to the proposed mechanism for isomerization of alkenylzirconium complexes (Section 3.9.3.3.2). Finally, hydrozirconation of an alkynylzirconium species (**14**; equation 19) proceeds 'normally' to give the (μ-alkenediyl)dizirconium complex (**15**).[83] While no attempts to exploit such bimetallic structures synthetically have been reported, it seems quite possible that they might prove useful with sufficient imagination.

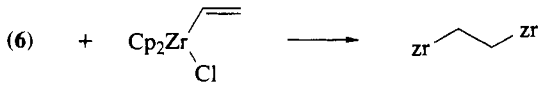

**(12)** **(13)** (18)

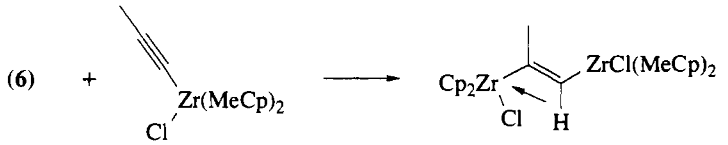

**(14)** **(15)** (19)

Hydrometallations with variants of the [Cp$_2$ZrHCl] reagent are collected in Table 7. As discussed in Section 3.9.3.1, most of these are dihydrides, which cause problems for subsequent synthetic application. Related reactions involving different metals may be found in Section 3.9.4.1.

**Table 7** Hydrometallations with Other [Cp$_2$MHX] Systems

| *Compound* | *Substrate* | *Comments* | *Ref.* |
|---|---|---|---|
| [Cp$_2$HfHCl] | Hept-1-ene<br>*trans*-Pent-2-ene<br>Isoprene<br>β-Pinene<br>Dodec-1-yne | All very similar to Zr analogs | 55 |
| [Cp*$_2$ZrH$_2$] | Ethylene | Products stable if no excess ethylene | 84 |
| [Cp*$_2$HfH$_2$] | | | 24 |
| [Cp*$_2$ZrH$_2$] | Propene | Product unstable | 84 |
| [Cp*$_2$HfH$_2$] | Styrene | | 24 |
| [Cp*$_2$ZrH$_2$] | Isobutene | Stable to 75 °C | 46 |
| [Cp*$_2$HfH$_2$] | | | 24 |
| [Cp*$_2$HfH$_2$] | Bu$^t$C≡CH | Stable to 125 °C | 24 |
| [Cp*$_2$(Zr,Hf)H$_2$] | MeC≡CH<br>EtC≡CH<br>PhC≡CH<br>MeC≡CMe | Dialkenyl product<br>Dialkenyl<br>Mono/di mixture<br>Mono, unstable | 85 |
| [Cp*$_2$HfH(CH=CHBu$^t$)] | Ethylene | Stable to 80 °C | 24 |

### 3.9.3.3 Selectivity Issues

#### *3.9.3.3.1 Chemoselectivity*

Early transition metals are strongly electropositive and form strong M—O and M—N bonds, and their hydrides exhibit strong hydridic or $H^-$ character.[86] Hence reactions of $[Cp_2ZrHCl]$ (**6**) with proton donors such as alcohols and acids, and with polar multiple bonds such as ketones and nitriles, are strongly favored on both thermodynamic and kinetic grounds. Complex (**6**) readily deprotonates or reduces all the above,[87] as well as esters,[87] isonitriles,[88] thioketones,[89] epoxides,[87] CO, $CO_2$, RNCO and RNCNR;[90] even so weak an acid as CpH.[87] The only hetero multiple bond found not to undergo hydrometallation is the C=N bond in PhCH=NMe. (Imines with neighboring C—H bonds do react, but not by hydrozirconation.[91]) Also several ketones (cyclohexanone, menthone, camphor, *etc.*) reacted readily with (**6**) to give the corresponding alcohol after hydrolysis, but acetophenone was recovered unchanged from the same conditions.[92]

Of course, these findings do not automatically mean that such functional groups cannot be tolerated; that depends upon relative rates. For instance, hydrozirconation of nitriles can be relatively slow: complete reaction of RCN under standard conditions required 72 h, 14 h and 1.5 h, respectively for R = Me, Ph, Bn.[93] Consistent with previous indications that alkynes are more reactive than alkenes towards (**6**), hydrozirconation of an alkyne can be carried out in the presence of a nitrile group (see Table 5),[66] whereas methacrylonitrile gives only C≡N hydrozirconation (equation 20).[78]

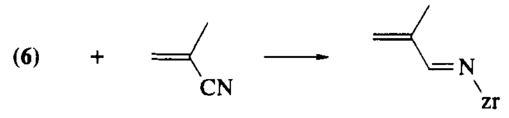

(20)

Similarly, alkynic esters have been successfully hydrozirconated (Table 5). $HC{\equiv}C(CH_2)_3CO_2Bu^t$ gave the alkenylzirconium product in much higher yield than the corresponding methyl ester, which exhibited carboxy reduction.[68] Clearly the reactivities of the C≡C and ester groups are in close balance here, with steric factors sufficient to tip it towards the former. Hydrozirconation of an alkenic ester would not be expected to work well; no example is reported. In the reaction of an enone with (**6**; equation 21) little if any hydrozirconation of the C=C bond occurs.[94]

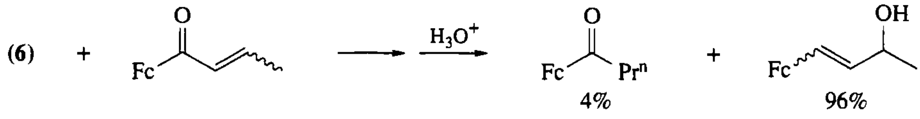

(21)

Ether linkages seem to be tolerated well (examples in Tables 3 and 5); this stands in contrast to hydroalumination where the Al—O bond strength generally makes the products unstable. Only for an actual vinyl ether were problems encountered: alkoxide migration appears to be facile in the presumed β-alkoxyalkylzirconium intermediate (**16**; equation 22).[95] The β-alkoxyalkenylzirconium complex obtained from HC≡COEt, though, is stable.[66,72]

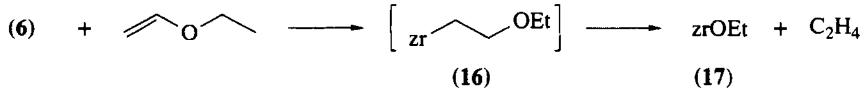

(22)

Functional groups can be protected: carboxylic acids as oxazolines[58,64,65] or silyl esters;[66] and alcohols as THP derivatives[66,72,73] or potassium alkoxides.[62] In fact, it may not be necessary to protect alcohols at all: just use two equivalents of reagent! The first will deprotonate the alcohol to give an alkoxyzirconium complex, and the second can then hydrozirconate the C=C or C≡C bond (equation 23). Several examples are shown in Tables 3 and 5. The presence of such functional groups does frequently have regiochemical consequences, as will be shown in the following section.

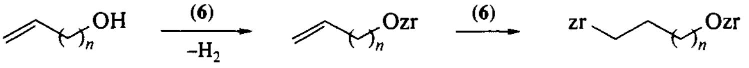

(23)

Metal hydrides often give reductive dehalogenation of organic halides, usually via a free radical pathway. [$Cp_2ZrHCl$] reacts readily with polyhalogen compounds, such as $CH_2Cl_2$ and $CHCl_3$,[35,41] that are most susceptible to radical attack; less is known about its tolerance for simple alkyl halides. The hydrozirconation of chloroalkenes can lead to some cyclization, as in equation (24); simple reduction of both C=C and C—Cl competes (with the analogous bromide there is much more reduction).[96] Reduction of chlorocyclohexane by (**6**) requires 24 h at 85 °C;[96] hydrozirconation of alkenes containing C—Cl bonds might be achieved cleanly at room temperature. Success with a chloroalkyne has been reported (Table 5), but hydrozirconation of a (*p*-chlorophenyl)alkene is accompanied by some reduction.[29]

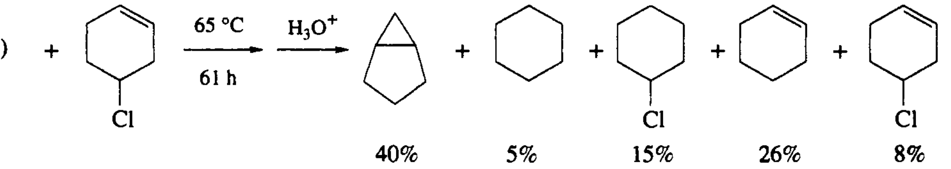

(24)

Selecting for C≡C over C=C should be easy, based on comparative reactivities cited earlier. Several examples of hydrozirconation of terminal alkynes in the presence of terminal or internal alkenes were shown in Table 6. Selective hydrozirconation of an internal alkyne in the presence of a terminal alkene might be more difficult; no attempt has been published. A variety of both conjugated and nonconjugated dienes can be cleanly monohydrozirconated; examples may be found in Table 6. Even if both double bonds are in terminal positions, as in 1,3-butadiene, there is no competing double addition or 1,4-addition[74]—a significant and useful contrast to many reactions of main group hydrides. The presence of a double bond in a conjugating position can alter regiochemistry (Section 3.9.3.3.2) or the outcome of subsequent transformation (Section 3.9.4.3.1). In contrast, some α,ω-diynes could not be cleanly monohydrozirconated; it was necessary instead to half protect with EtMgBr/TMSCl to get single addition.[77]

Complications are found for 2,4-dienes, with which three equivalents of [$Cp_2ZrHCl$] react to give saturated alkylzirconium products; details of these reactions are not understood.[1] It is not known whether similar problems will arise for nonconjugated, diinternal alkenes; no examples have been studied. The hydrozirconation of 1,3-dienes was initially reported to be much slower than that of simple alkenes;[74] but later work suggests this is dependent upon the mode of reagent preparation.[41]

### *3.9.3.3.2 Regioselectivity*

With simple alkenes terminal alkylzirconium compounds are formed, even if the original alkene is not terminal! Presumably this reflects steric disfavoring of a secondary alkylzirconium; the only examples of the latter are found with cyclic alkenes such as cyclohexene or norbornene. The postulated mechanism for the relocation of Zr to a terminal position was shown in Scheme 5, but in truth very little detailed information on this process is available. The intermediate secondary alkyl and internal alkene complexes must be in close energetic balance, so that the rearrangement is rapid on the time scale of the overall hydrozirconation; but is the final stable product still in moderately rapid equilibrium with these less stable intermediates? This question is highly relevant to targets such as regio- or stereo-specifically deuterium-labelled alkanes. Exchange in alkyl(hydrido)zirconium complex (**19**) suggests equilibration (equation 25),[43] but alkyl(chloro)zirconium complexes (such as **18**) may differ. Experiments to probe this issue, such as migration of deuterium labels or magnetization transfer in NMR, would be of interest here.

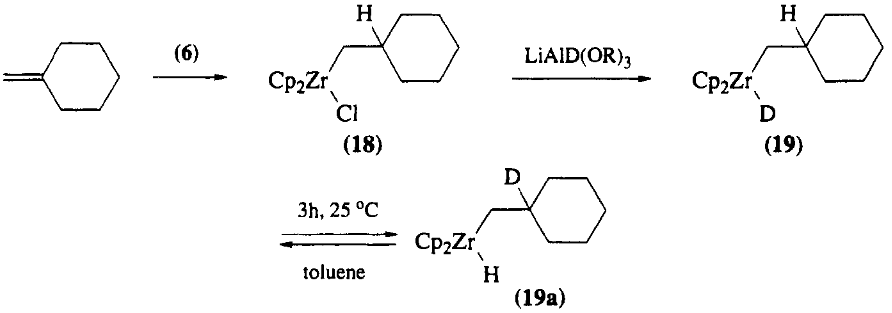

(25)

Tertiary alkylzirconium compounds appear to be generally inaccessible even as intermediates. Tetrasubstituted alkenes are not hydrozirconated at all;[1] also, zirconium is unable to migrate past a tertiary position in a carbon chain. Attempted hydrozirconation of an internal alkene which is 'blocked' at both ends (**20**; equation 26) gives only isomerized alkene (**21**).[97] The only exception, which appears to involve a tertiary intermediate, is found in the hydrozirconation of dienol (**22**) in equation (27).[63]

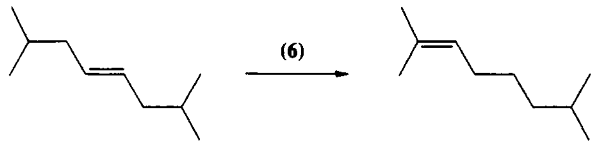

**(20)** **(21)**

(26)

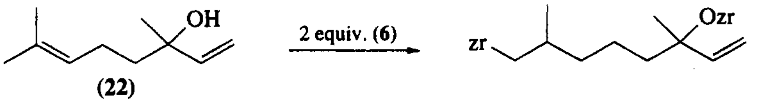

**(22)**

(27)

The exclusively terminal regioselectivity can be altered, however, for alkenes containing groups such as aromatic rings, additional double bonds, or oxygen centers. A number of workers have noted that styrene hydrozirconation is not completely regioselective: after subsequent transformation/cleavage steps, the relative amounts of the 'normal' and 'reversed' products, $PhCH_2CH_2X$ and PhCHXMe, respectively, range from 67:33 to 90:10.[29,42,56,59] Unfortunately, such results are not unequivocal: do they represent the static population of organozirconium isomers; competitive reaction of rapidly equilibrating isomers; or even isomerization brought about during the cleavage reaction? Ratios of the isomeric alcohols (equation 28) depend upon oxidant.[29] Only one published study reports NMR of the initial hydrozirconation product (**23**) itself: there is no evidence for the reversed isomer (**24**),[61] but it is not clear how carefully they looked. Recent work suggests a ratio for normal and reversed products of around 85:15 (equation 29). There is no fast equilibrium between (**23**) and (**24**), since complete scrambling of a deuterium label among all alkyl positions was not observed.[98]

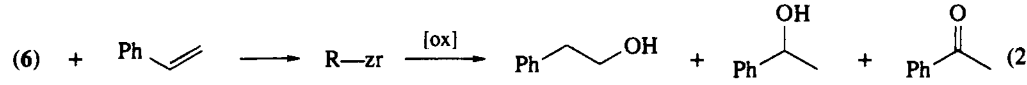

(28)

| | | | |
|---|---|---|---|
| [ox] = $O_2$ | 67% | 20% | 13% |
| [ox] = TBHP | 93% | 7% | – |

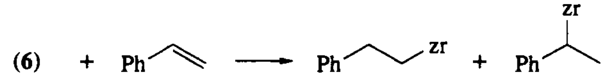

**(23)** 85% **(24)** 15%

(29)

Why is the prohibition against secondary alkylzirconium relaxed for phenyl substituents? Buchwald *et al.* suggest that the flat phenyl group is less sterically demanding than an alkyl,[56] while others have proposed an electronic effect favoring benzylic zirconium compounds.[59] Evidence supports the latter: for internal aromatic alkenes hydrozirconation initially gives mostly the benzylic isomer (**25**) (based on the alcohol products of oxidation), which slowly (48–96 h at 40 °C) converts to the terminal isomer (**26**; equation 30).[29]

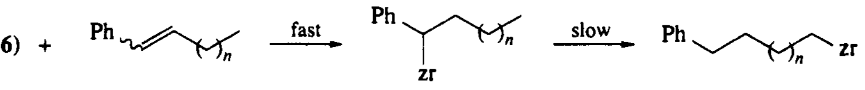

**(25)** **(26)**

(30)

Similarly, with 1,3-dienes there is some tendency towards Markovnikov addition, yielding an allylic product, although again there are conflicting results. Buchwald *et al.* conclude that hydrozirconation of 1,3-pentadiene proceeds as in equation (31),[56] whereas Schwartz finds only terminal isomer (**27**), but sees isomerism with a more-substituted diene (equation 32).[1] Again, this may be attributable to electronic stabilization of an allylic zirconium compound. No indication of $\eta^3$-allyl formation has ever been observed, even though [$Cp_2ZrRCl$] is formally coordinatively unsaturated.

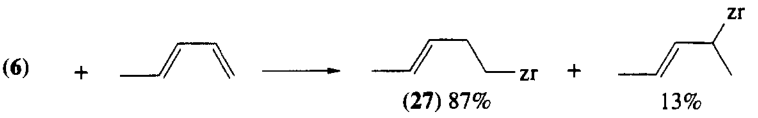

(31)

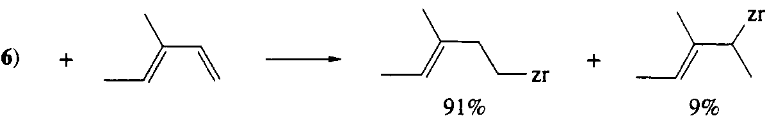

(32)

Oxygen- and nitrogen-containing functional groups may significantly perturb regiochemistry; here it does appear that additional coordination is involved. Stability of the five-membered chelate ring in intermediate (**28**) was proposed to account for the 3-hydroxystearate obtained in Scheme 8.[64] Hydrozirconation of unsaturated acid oxazolines with the double bond in the 2,3- or 3,4-position, followed by deuterolysis, gives mixtures of 2-, 3- and ω-deuteroacids, depending upon the exact structure, while if the double bond is initially in the terminal position, only ω-deuteration is found.[58,65] These reactions may be accompanied by positional and *cis–trans* isomerization in 'unreacted' alkene; clearly one must proceed with caution in applying hydrozirconation to synthetic transformations of such compounds. Hydrozirconation of 2-vinylfuran gives only the internal product (Table 3),[56] which may be due to *O*-coordination, aromatic stabilization or reduced steric effect of the flat furan ring (see above), or a combination of these.

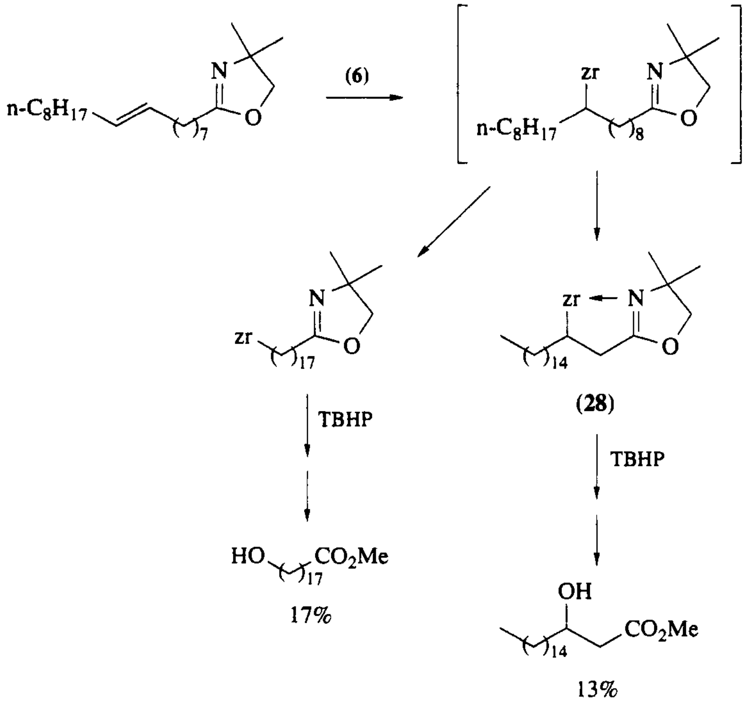

**Scheme 8**

Definitive evidence for the role of heteroatom coordination may be seen in the hydrozirconation of alkenoxide (**29**; equation 33) where the five-membered ring favors (**30**) (confirmed by the X-ray crystal structure).[62] A related structure was obtained in equation (34); the *O*-coordinated product (**31**) does not isomerize to the terminal alkylzirconium product (**16**) below 140 °C.[95] (At 140 °C it slowly decomposes to **17**, presumably *via* **16**; *cf.* equation 22 above.) In contrast, hydrozirconation of dienols shows preferred reactivity of the double bond remote from the —OH group; an example is shown in Table 3.[63] Probably the first equivalent of (**6**) reacts with the —OH group both to increase steric bulk and prevent the oxygen from coordinating to the second Zr, which does the actual hydrozirconation. After protolysis, oct-1-en-3-ol is the sole product obtained.

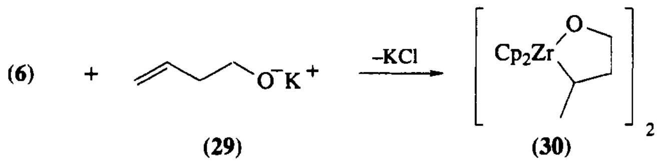

(33)

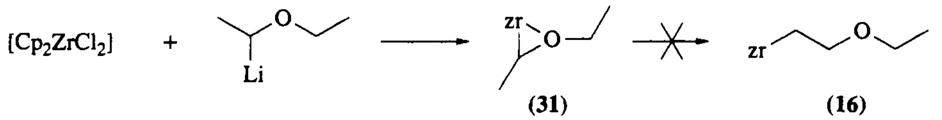

(34)

Terminal alkynes are always hydrozirconated to the terminal alkenylzirconium product,[1] even in the presence of functional groups (Table 5). Internal alkynes give internal alkenyls, without the migrations found for alkenes. With asymmetric internal alkynes $RC\equiv CR^1$, the zirconium goes preferentially to the carbon atom bearing the sterically smaller R group, subject to both kinetic and thermodynamic control. For the example shown in equation (35), reaction of **(6)** with a slight excess of **(32)** gives only a slight preference for the favored isomer **(33a)**; the composition is stable to prolonged standing at room temperature. Addition of a small amount of **(6)** effects slow isomerization to virtually all **(33a)**. Further such results are shown in Table 8.[4] Note that very high regioselectivity can be attained, even where the steric differentiation between the ends is relatively modest (*e.g.* Me *versus* Et). A doubly hydrozirconated intermediate is proposed for the isomerization (equation 36), to account for the requirement for excess $[Cp_2ZrHCl]$.[4] As noted earlier, such a species **(13)** has been isolated for $C_2H_2$ (equation 18), although not for any substituted alkynes.[61]

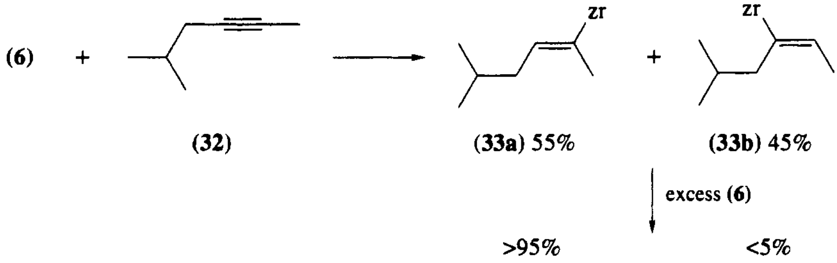

(35)

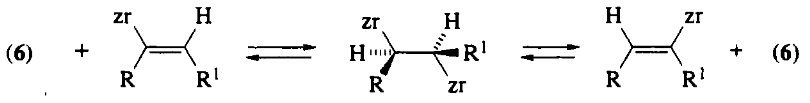

(36)

**Table 8** Regiochemistry of Internal Alkyne Hydrozirconation

| *R* | *R*$^1$ | *zrCR*=*CHR*$^1$:*zrCR*$^1$=*CHR* *Initial* | *Final* |
|---|---|---|---|
| H | $Bu^n$ | >98:2 | Same |
| Me | Et | 55:45 | 89:11 |
| Me | $Pr^n$ | 69:31 | 91:9 |
| Me | $Pr^i$ | 84:16 | >98:2 |
| Me | $Bu^i$ | 55:45 | >95:5 |
| Me | $Bu^t$ | >98:2 | Same |

Since most of the regioselectivity patterns appear to be sterically driven, one would expect that Cp* analogs would show even more pronounced preferences. Terminal alkenes show exclusive selectivity for terminal products, as do terminal alkynes (Table 7). It would be of interest to see whether rearrangement occurs with internal alkenes. A rearrangement has been observed in the alkenylzirconium **(34)**, obtained from an internal alkyne (equation 37).[85] This differs from the simple Cp analogs, both in the rearrangement of an alkyne-derived product and the formation of an $\eta^3$-allyl complex. The mechanism is not known with certainty, and may depend upon the presence of the hydride ligand in (**34**).

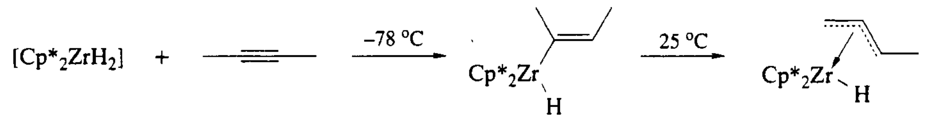

(**34**)

(37)

### 3.9.3.3.3 *Diastereoselectivity*

The mechanism for hydrometallation would appear to require *cis* addition to C═C and C≡C bonds, and this result is essentially always obtained.[1] Apparent exceptions can probably be ascribed to subsequent chemistry. For example, hydrozirconation/oxygenation of 2-methylindene gives a *cis–trans* mixture of alcohols, but the loss of specificity occurs at the oxygenation step, not during hydrozirconation (see Section 3.9.3.4.1).[29] Overall hydrocyanation of terminal alkynes, starting with hydrozirconation, also gives a mixture of isomers; it is not known how this occurs.[56] Reaction of [$Cp_2ZrHCl$] with diphenylacetylene at 100 °C for prolonged periods gives mostly *trans*-stilbene,[99] but this obviously involves more than simple hydrozirconation.

For acyclic alkenes, the facile rearrangement process obviates most possibilities of stereoselective transformation. The one exception is that of stereospecific isotopic labelling, for which hydrozirconation is a potentially powerful technique: compounds of type $Bu^tCHDCHDX$ (**36**), useful for NMR-based mechanistic studies, are conveniently obtained as in Scheme 9.[100] This requires that four separate processes — hydrozirconation of alkyne, cleavage of alkenylzirconium, hydrozirconation of alkene and cleavage of alkylzirconium — all be completely stereospecific.

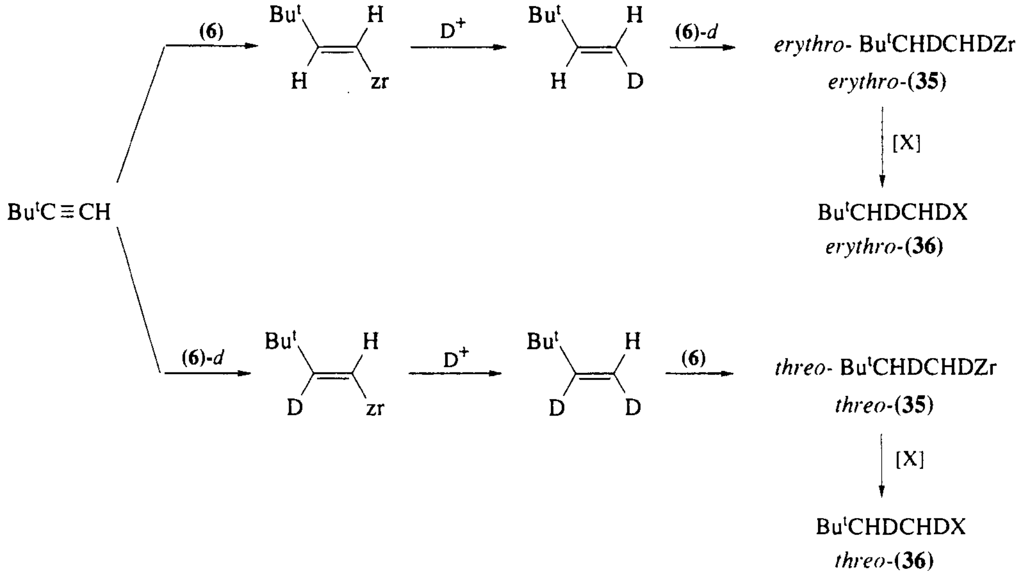

**Scheme 9**

With the possible exception of the third, these can all be easily satisfied. Labinger *et al.* report that either isomer of (**35**) prepared as in Scheme 9 is contaminated with about 10% of the opposite diastereomer; the composition does not change on standing.[100] How does this small amount of net *trans*-hydrozirconation occur? One possibility is that the initial hydrozirconation occasionally takes place with the wrong regiochemistry; this could scramble stereochemistry, as shown in equation (38). Of course, this mechanism also scrambles isotope locations: isomers such as [$Bu^tCH_2CD_2ZrClCp_2$] should be present as well. None were observed, but it must be noted that the state of NMR equipment at the time of this study was not what it is today; a reinvestigation might be rewarding.

Stereospecific preparation of PhCHDCHDX compounds by this route has not been successful: application of both the top and bottom sequences in Scheme 9 to phenylacetylene results in the same product mixture, although $^2$H NMR results do not show the complete scrambling required by the mechanism of equation (38).[98] Further study appears warranted to determine whether this approach is limited in scope.

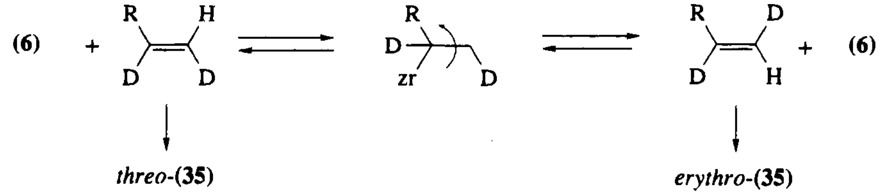
(6)
+
R
H
D
D
R
D
zr
D
R
D
D
H
+
(6)
threo-(35)
erythro-(35)

(38)

With cyclic alkenes, fairly high diastereoselectivity can be achieved. Hydrozirconation of norbornene, followed by TBHP oxidation, gives the *exo*-alcohol in 95% yield, while the more complex bicyclics camphene (**37**) and β-pinene (**38**) give the mixtures shown in equations (39) and (40), respectively.[57] The hafnium analog shows the opposite preference with β-pinene and does not react with camphene at all, attributed to significantly greater steric demand.[55] Diastereoselectivity in cyclohexanols obtained by hydrozirconation of ketones has also been examined.[92]

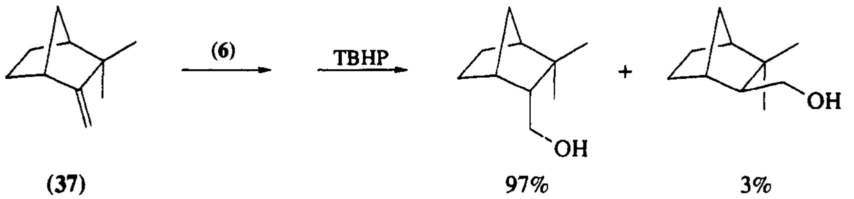
(6)
TBHP
+
OH
OH
(37)
97%
3%

(39)

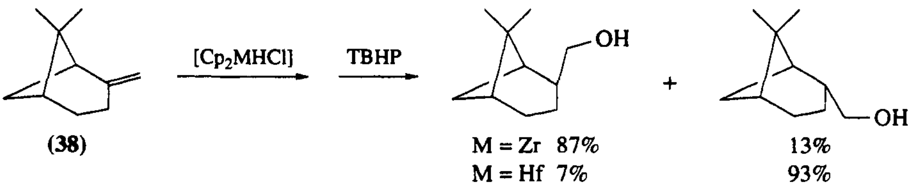
[Cp$_2$MHCl]
TBHP
OH
+
OH
(38)
M = Zr 87%
M = Hf 7%
13%
93%

(40)

Hydrozirconation of vitamin D$_3$ (**39**) gives a mixture of four diastereomers resulting not only from addition to either face of the reacting exocyclic double bond, but also isomerization of the 'nonreacting' 5,6-double bond (equation 41), even though no isomerization of unreacted (**39**) was detected.[76] No explanation was offered. Partial isomerization of a double bond during hydrozirconation of a triple bond has also been observed.[78]

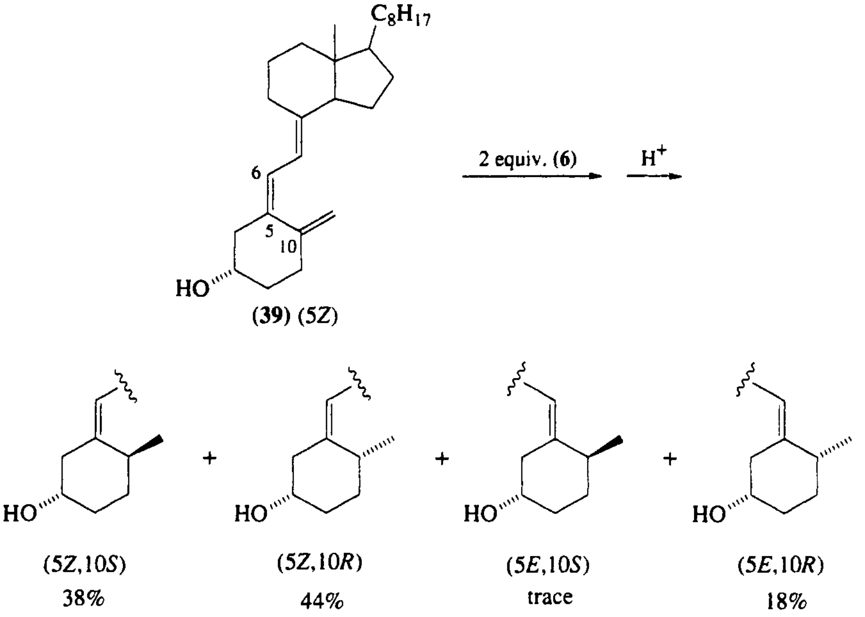
C$_8$H$_{17}$
6
5
10
HO
(39) (5Z)
2 equiv. (6)
H$^+$
HO
+
HO
+
HO
+
HO
(5Z,10S)
38%
(5Z,10R)
44%
(5E,10S)
trace
(5E,10R)
18%

(41)

Addition of [$Cp^*_2MH_2$] (M = Zr, Hf) to alkynes is, not surprisingly, also strictly *cis*; although two isomers are obtained from the Hf compound and but-2-yne, they appear to be conformational and not configurational.[85]

### 3.9.3.3.4 Enantioselectivity

Virtually nothing has been done in this arena. The sole study involves the use of complexes of the type [$Cp'_2ZrH_2$], where Cp′ bears a chiral substituent, as catalysts for the hydrogenation of prochiral alkenes; a maximum of 2% *ee* was obtained.[101] It is known that chiral zirconium complexes of the so-called *ansa* type, developed by Brintzinger and coworkers,[102] effect very high stereoregularity in propene oligomerization and polymerization.[103] It seems extremely likely that the corresponding —ZrHCl complexes would afford excellent asymmetric induction in the hydrozirconation of prochiral alkenes.

## 3.9.3.4 Synthetic Utilization of Hydrozirconation

The synthetic utility of organozirconium complexes has been reviewed,[104] and many aspects are considered in greater depth in Volume 1, Chapter 1.5. One general issue which should be mentioned is the stability of organozirconium reagents and effects thereof on yields. Thermal stability appears rarely to be a problem; the most common mode of decomposition for organometallics, β-hydrogen elimination, does not operate here for reasons discussed earlier. Compounds are quite sensitive to proton sources, and reduction (R—Zr to R—H) can compete even without any obvious proton source; examples are presented in the following section. Still, it is usually possible to achieve overall synthetic transformations based upon hydrozirconation in quite high yields; causes of reduced yields are rarely examined.

### 3.9.3.4.1 Reactions of alkyl- and alkenyl-zirconium complexes

Since zirconium is strongly electropositive, these complexes exhibit considerable carbanion character ($Zr^+$—$R^-$) and are subject to electrophilic cleavage just as are main group organometallics. Typical reaction patterns are shown in Scheme 10. The simplest such reaction is protonolysis: all hydrozirconation products react readily with aqueous acid. The net result of this overall sequence is hydrogenation. Protodezirconation of both alkyl- and alkenyl-zirconium complexes appears always to proceed with retention of both regio- and stereo-chemistry, so this provides a method for clean *cis* hydrogenation, with high selectivity for triple bonds or terminal double bonds in multiply unsaturated substrates. It is, of course, a stoichiometric hydrogenation, so it will rarely be the method of choice for large scale applications. Catalytic hydrogenation based on hydrozirconation can be accomplished, especially by starting

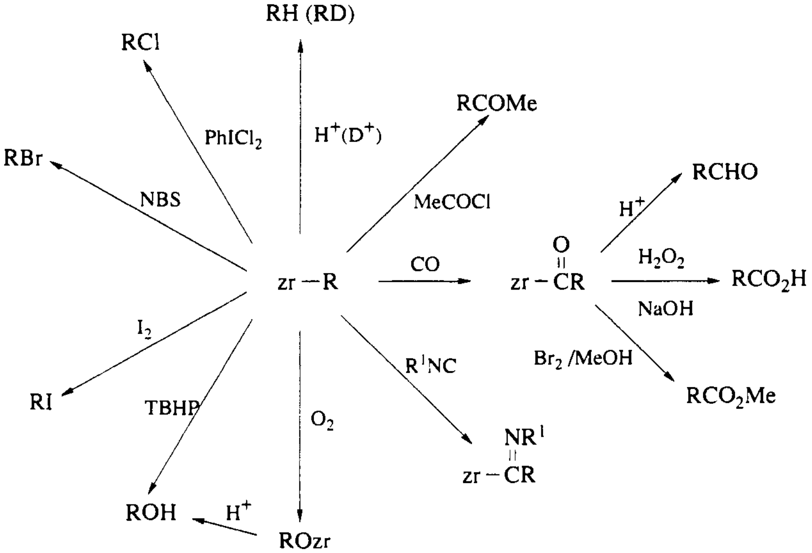

**Scheme 10**

with [$Cp_2ZrH_2$] or [$Cp_2ZrR_2$] complexes, but these do not appear to be very good catalytic systems. Generally high temperatures are required, around 100 °C,[36,99] and clean selective reductions are hard to achieve: hydrogenation of diphenylacetylene gives a mixture of *cis*- and *trans*-stilbenes.[99]

Perhaps the most useful application of the hydrozirconation/protodezirconation sequence is for specific introduction of deuterium label; some examples were presented in the previous section. Although most such work indicates that deuterium incorporation is essentially complete, Svenson and coworkers have found that around 20% of the alkane thus obtained from simple alkenes is undeuterated. The amount of alkane-$d_0$ depends upon the mode of preparation of (**6**) and increases with longer hydrozirconation reaction times, so transfer of hydrogen to give alkane prior to hydrolysis is probably responsible. This '*in situ*' hydrogenation was found to be even more pronounced for α,β-unsaturated carboxylic acid oxazolines, giving 70% of the undeuterated saturated product.[58]

Protonolysis can also be effected with weaker acids; in some cases this may be essential. For example, hydrozirconation of alkynic alcohols $Me(CH_2)_nC{\equiv}C(CH_2)_mOH$ with 2 equiv. of (**6**), followed by hydrolysis with 2% aqueous $NH_4Cl$, affords the corresponding *cis*-alkenol in high yield and selectivity, whereas use of aqueous HCl causes both *cis–trans* isomerization and allylic rearrangement.[70] Protonolysis by weak acid may be slow enough for other reactions to compete: TBHP can be used as an oxidant (see below).

Hydrozirconation is not sufficiently reversible to liberate the organic group as an alkene by displacement; but that can be achieved *via* hydride abstraction with trityl ion. This generates a sequence for net alkene isomerization in the counterthermodynamic direction (equation 42).[1]

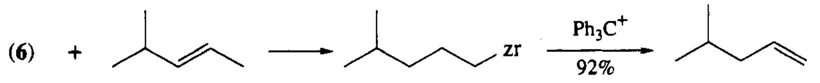

(42)

Halogenative cleavage likewise appears completely general for both alkyl- and alkenyl-zirconium complexes (Scheme 10),[1] and proceeds with complete retention of configuration at carbon.[100] For the hydrozirconation products of 3-methyl-1,3-dienes, such as (**40**), cyclization competes (equation 43).[1,74] Analogs without the 3-methyl subsitutent, or with more remote double bonds, give only the uncyclized products in good yields.[74]

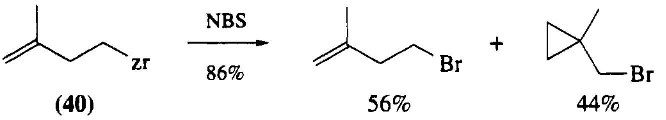

**(40)**

(43)

Conversion of R—Zr to R—OH can be effected by a variety of oxidants, including (dry) $O_2$, TBHP, MCPBA, $CrO_2Cl_2$[1,105] and $MoO_5{\cdot}2HMPA$.[55] The mechanism of autoxidation with $O_2$ appears to be closely similar to that established for main group organometallics (Scheme 11).[100,105] Most telling is the stereochemical outcome: from either primary alkyl (**35**)[100] or the secondary alkyl obtained by hydrozirconation of 2-methylindene,[29] the mixture of alcohols shows 50% racemization and 50% retention of configuration at the reacting carbon center. This requires that oxidation by ROO— proceeds with retention, which was separately established.[105] Hydrozirconation/autoxidation of hexa-1,5-diene gives 4% of cyclopentylmethanol, attributed to cyclization of the free radical intermediate.[105] Oxidation of alkenylzirconium complexes does not proceed well, with either $O_2$ or TBHP.[1]

$$\text{R—zr} + O_2 \longrightarrow [\text{R}\bullet\ \text{zrOO}\bullet] \longrightarrow \text{zr—OOR}$$

$$\text{zr—OOR} + \text{R—zr} \longrightarrow 2\ \text{zr—OR}$$

**Scheme 11**

CO insertion works well for both alkyl and alkenyl derivatives.[1,106] The resulting acyls may subsequently be converted to aldehydes, acids or esters as shown in Scheme 10; yields (based on zrR) typically range from 50–99%.[106] Two such applications have appeared in the patent literature.[75,107] CO insertion proceeds with stereochemical retention,[100] as in all metal systems studied. The Cp* analogs show quite different CO chemistry. Although insertion to form an acyl (*e.g.* **41**) is the first step, facile rearrangement to alkenoxides (**42**) ensues (equations 44[23] and 45[85]).

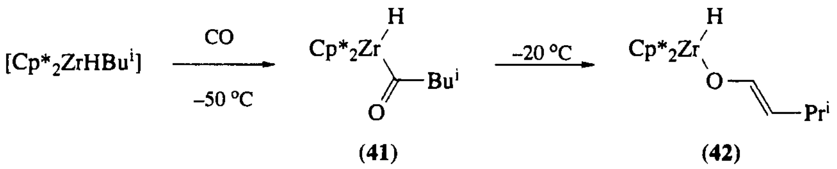

(44)

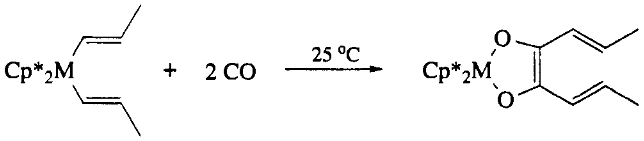

(45)

Insertion of isocyanides $R^1NC$ ($R^1 = Me_3C$ or $Me_3Si$), which are isoelectronic to CO, appears to be quite similar (Scheme 10); this step has been used to achieve overall hydrocyanation (see Section 3.9.3.4.3).[56] C—S and C—N bonds may also be generated. $SO_2$ inserts with retention of configuration to yield $[Cp_2ClZrO_2SR]$,[100] while NO leads to *N*-nitrosohydroxylamine derivatives $[Cp_2ClZr\{ON(NO)R\}]$.[1] Neither of the last two has been exploited synthetically.

### *3.9.3.4.2 Transmetallations*

Hydrozirconation products can be used directly as carbanion equivalents, but such reactions are generally not highly successful. Alkylzirconium complexes react with acetyl chloride to give methyl ketones (Scheme 10),[28] but yields are not always good and alkenyls do not react.[38] Addition to ethylene oxide takes place slowly, while carboxylation with $CO_2$ does not take place at all.[1] This reduced reactivity (compared to main group organometallics) may be largely overcome by first transferring the alkyl or alkenyl group to a more reactive metal center, such as aluminum. (**43**) and (**44**) react with acetyl chloride to give the methyl ketones in near quantitative yields (equation 46).[38] Complications were found only for cyclohexene, which gave virtually none of the desired methyl cyclohexyl ketone (acyclic secondary alkylaluminum reagents are, of course, not accessible by this route, since they cannot be prepared by hydrozirconation), and for certain dienes where cyclization can apparently occur during the transmetallation step (equation 47). Transfer of both alkyl and alkenyl from Zr to Al proceeds with retention of configuration.[38]

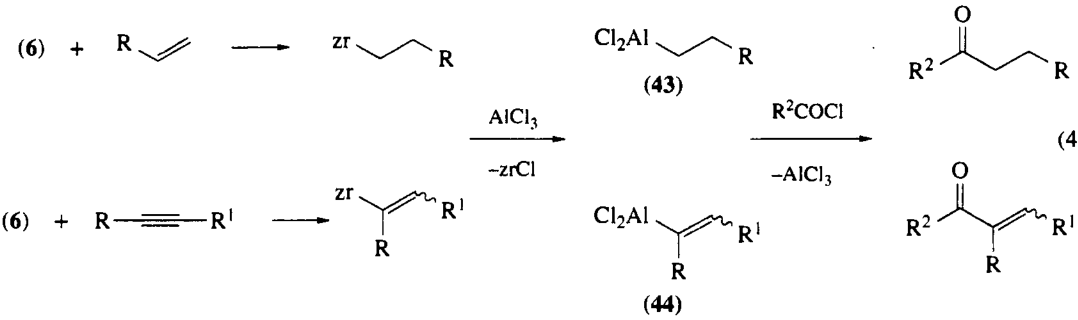

(46)

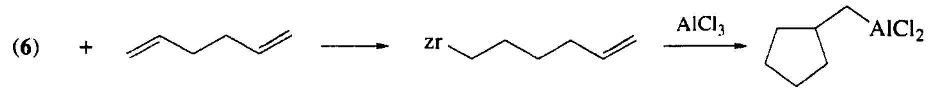

(47)

This hydrozirconation/transmetallation sequence provides a route to net hydroalumination of alkenes and alkynes; the direct reaction is often difficult to achieve. The use of catalytic amounts of Zr will be discussed in Section 3.9.4.2

Even acyl groups may be transferred from Zr to Al, as in equation (48); this generates an acylaluminum or 'acyl anion equivalent' (**45**). Its acyl anion chemistry appears limited, however: only protonolysis to the aldehyde was achieved in good yield, and that could have been done directly with the acylzirconium precursor.[38]

The thermodynamics of the transmetallation reaction should depend largely upon electronegativity considerations: the reaction should proceed to give the more metal–organic product. However, this may

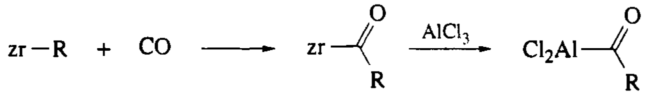

**(45)**

(48)

be modulated by other ligands: $R_3Al$ will alkylate $[Cp_2ZrCl_2]$, whereas $[Cp_2ZrRCl]$ alkylates $AlCl_3$. Similarly, $[Cp_2ZrCl(alkenyl)]$ transfers the alkenyl group to $R_2AlCl$,[38] but the direction of transmetallation can be reversed by addition to BuLi to form an ate complex.[108] Transmetallation from Zr to Li has been reportedly achieved by decomposition of a zirconium ate complex, but no details are available;[109] this would be rather surprising on thermodynamic grounds.

Transfer of alkenyl from Zr to other metals appears more general than alkyl transfer.[38] With CuCl, while the alkenylcopper product was not characterized, it exhibits characteristic decomposition and conjugate addition reactions as shown in equations (49) and (50).[110] In contrast, $[Cp_2ZrCl(octyl)]$(**7**) does not react with CuI.[111] Similarly, transfer of dienyl groups to $Bu_3SnCl$ gives the corresponding dienyltin compounds in 60–90% yields, sought for study in Diels–Alder reactions.[78] Transfer of the octyl group from (**7**) to $SnCl_4$ gave up to 81% yield of $(octyl)SnCl_3$, but further transfers were more difficult.[111]

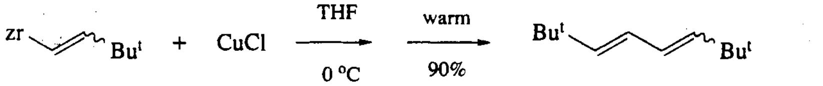

(49)

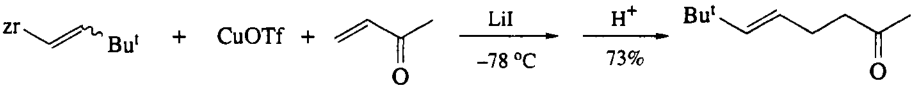

(50)

Although the transmetallation sequence of equation (**46**) failed with catalytic amounts of $AlCl_3$, other applications can be done catalytically. For example, (alkenyl)zirconium groups (**46**) may be coupled with organic halides, as in Scheme 12.[72,104,112,113] Catalysts are zerovalent Ni or Pd complexes and yields are typically 70% or better, with sterically crowded alkenyl groups causing problems which may be overcome by an additional cocatalyst such as $ZnCl_2$.[114] The mechanisms of both Ni-[114] and Pd-catalyzed[72] alkenyl–aryl coupling have been investigated, and both appear to proceed *via* reductive elimination from a diorgano-nickel or -palladium intermediate formed by successive transmetallation and oxidative addition, although the oxidation state couples involved for the two metals are different. In a variant, (**46**) can be added to a preformed allylpalladium complex with similar results;[71,115] an application is presented in the following section.

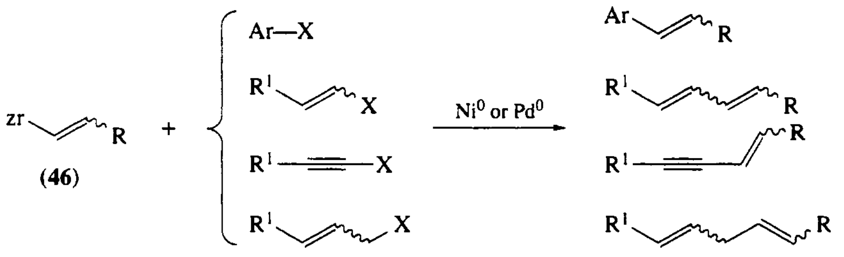

**Scheme 12**

Lastly, (**46**) undergoes conjugate addition to enones, catalyzed by Ni complexes (equation 51).[68] Yields vary depending upon structures, but may be significantly improved by reducing the precatalyst $[Ni(acac)_2]$ with DIBAL-H.[68] The reaction appears to be mechanistically similar to conjugate addition with copper reagents, involving electron transfer.[114] This system has potential advantages over copper-based routes, both in reagent preparation and in avoiding the need for an additional ligand in the copper ate reagents. The initial product of conjugate addition is a zirconium enolate;[116] instead of simply hydrolyzing to the $\gamma,\delta$-enone as in equation (51), it may be used directly for additional transformations such as generation of selenium reagents.[117] A more elaborate example is shown below.

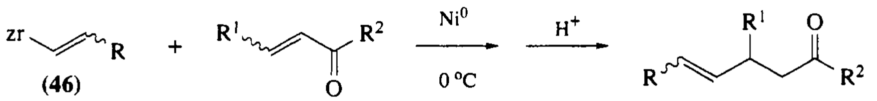

(51)

### *3.9.3.4.3 Practical examples*

We will attempt only to give an indication of the scope and flavor of hydrozirconation-based synthetic routes. Terminally functionalized long chain alkanes, which have a variety of important industrial uses, may be obtained from shorter chain terminal alkenes *via* metathesis, hydrozirconation and cleavage (equation 52).[40]

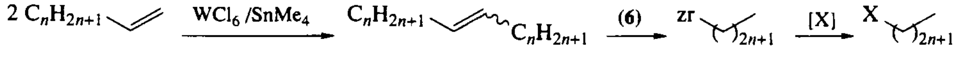
2 $C_nH_{2n+1}$
$WCl_6$ /$SnMe_4$
$C_nH_{2n+1}$
$C_nH_{2n+1}$
(6)
zr
2n+1
[X]
X
2n+1

(52)

A method for the hydrocyanation of alkenes and alkynes is based upon hydrozirconation followed by isonitrile insertion (Scheme 13); overall yields range from 45–90%.[56] Certain examples do not exhibit the clean regiochemistry represented here, and these were discussed in Section 3.9.3.3.2. The hydrozirconation/protonolysis of equation (53) results in high yield, stereoselective formation of *C*-methyldeoxysugars, an alternative to free radical deoxygenation.[118]

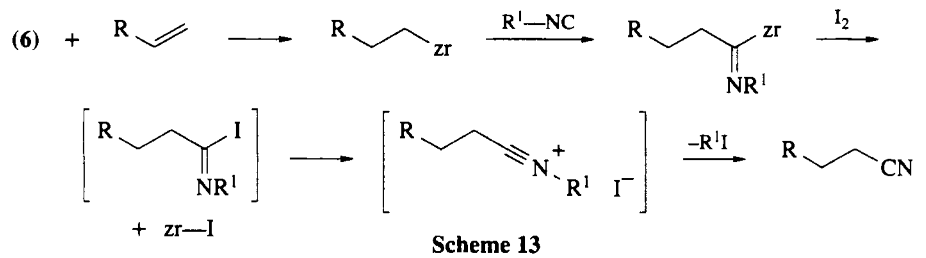
(6)
+
R
R
zr
R¹—NC
R
zr
NR¹
$I_2$
R
I
NR¹
+ zr—I
R
N
+
R¹
I⁻
-R¹I
R
CN

**Scheme 13**

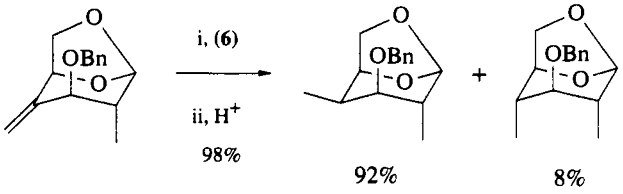
O
OBn
O
i, (6)
ii, H⁺
98%
O
OBn
O
92%
+
O
OBn
O
8%

(53)

ω-Alkynic isobutyl amides such as (**48**), of interest as insecticides, can be made by Pd-catalyzed coupling, as shown in Scheme 14.[77] Similarly, hydrozirconation of a wide variety of alkynes, followed by Pd-catalyzed coupling to an iododeoxyuridine (**49**; dR = 2′-deoxyribose), gives alkenyldeoxyuridines (**50**) which have antitumor and antiviral properties.[66]

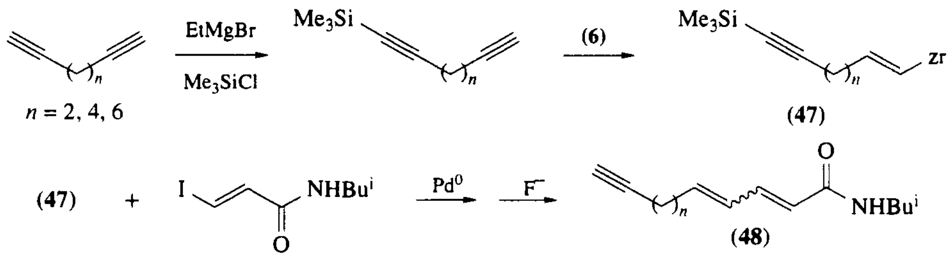
n
n = 2, 4, 6
EtMgBr
$Me_3SiCl$
$Me_3Si$
n
(6)
$Me_3Si$
n
zr
(47)
(47)
+
I
NHBuⁱ
O
Pd⁰
F⁻
n
O
NHBuⁱ
(48)

**Scheme 14**

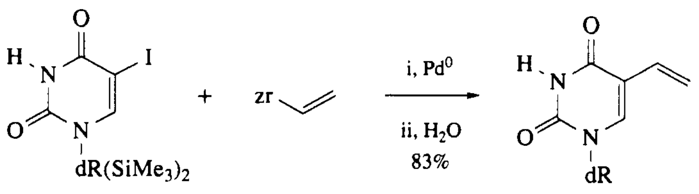
O
H
N
I
O
N
$dR(SiMe_3)_2$
+
zr
i, Pd⁰
ii, $H_2O$
83%
O
H
N
O
N
dR

(**49**) (**50**)

Addition of alkenylzirconium (**51**) to steroid-derived allylpalladium (**52**), followed by hydrogenation and hydrolysis, gives 25-hydroxycholesterol in 66% overall yield from (**52**; Scheme 15).[71] Finally, several approaches to prostaglandins or their precursors have been based upon Ni-catalyzed conjugate addition of alkenylzirconium to enones;[68] one example is depicted in Scheme 16. A prostaglandin synthesis utilizing hydrozirconation has been patented.[119]

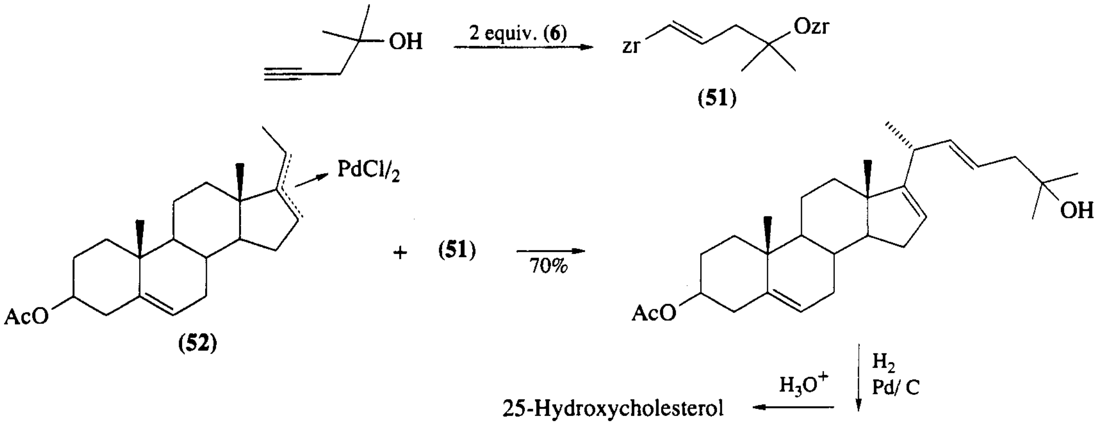
OH
2 equiv. (6)
zr
Ozr
(51)
PdCl/2
AcO
(52)
+ (51)
70%
OH
AcO
H2
Pd/ C
H3O+
25-Hydroxycholesterol

**Scheme 15**

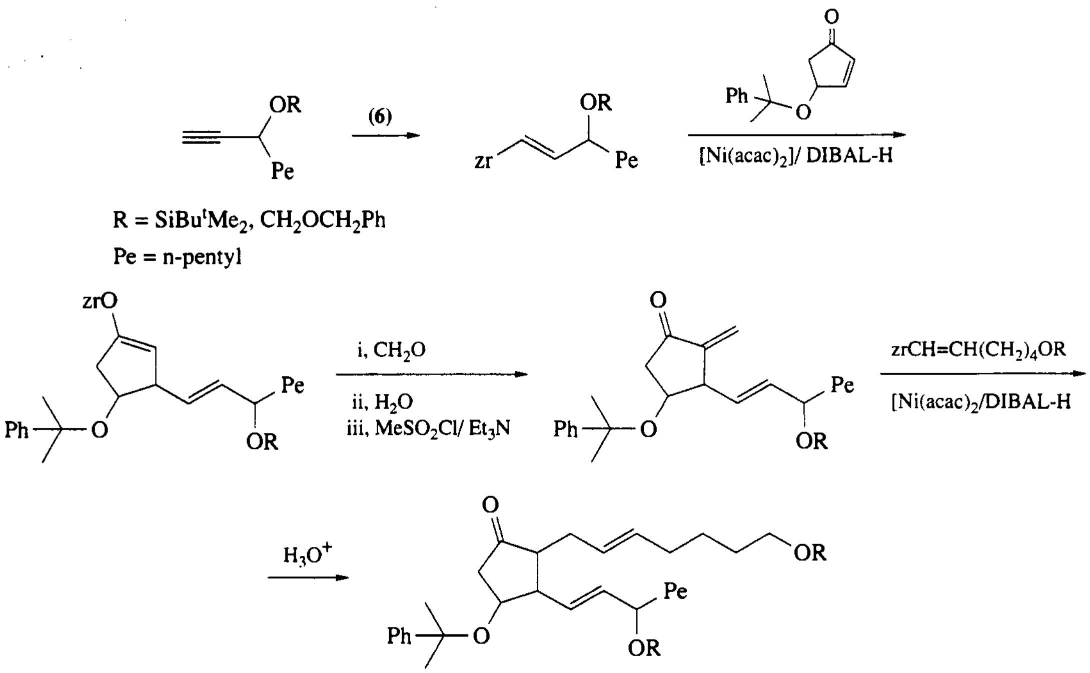
OR
Pe
(6)
OR
zr
Pe
O
Ph
O
[Ni(acac)2]/ DIBAL-H
R = SiBu^tMe2, CH2OCH2Ph
Pe = n-pentyl
zrO
Pe
Ph
O
OR
i, CH2O
ii, H2O
iii, MeSO2Cl/ Et3N
O
Pe
Ph
O
OR
zrCH=CH(CH2)4OR
[Ni(acac)2/DIBAL-H
H3O+
O
OR
Pe
Ph
O
OR

**Scheme 16**

## 3.9.4 OTHER HYDROMETALLATIONS

### 3.9.4.1 Hydrometallation with Other Transition Metals

Although zirconium is only one out of over 50 potentially usable metals in this class (including the lanthanides and actinides), virtually all synthetic applications of hydrometallation with transition metals involve zirconium! Why is this so? The primary reason derives from the near requirement of a $d^0$-metal center for hydrometallation of a general alkene or alkyne. For later transition metals, hydrometallation to give a stable organometallic product can usually be achieved only for special cases—conjugated dienes, alkenes with electronegative substituents, *etc.* This is due to the relative stability of the $\eta^2$-complex, as discussed previously.

One exception to this exclusion of late transition metals may be copper. CuH—$MgX_2$ complexes, prepared *in situ* from $MgH_2/CuX$[120] or from NaH/CuX/$MgX_2$,[121] react with terminal alkynes to give alkenylcopper species. So far, these have only been used as sources for dialkenyl-coupling products, as in equation (54),[121] but there is no obvious reason why other copper-based procedures should not be accessible, as was found for alkenylcopper obtained by transmetallation from Zr (Section 3.9.3.4.2). Alkylcopper cannot be made by hydrometallation (nor by transmetallation), as CuH does not add to alkenes,[120] except for special ones such as enones.[122]

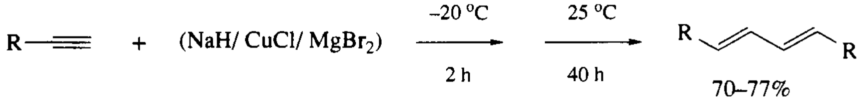

(54)

What about other early transition metals? Stable titanium hydrides with $d^0$-configurations are uncommon, owing to ready reduction to titanium(III) species. Hydrotitanation has been found only for conjugated dienes[123] and trienes[124] where stable $\eta^3$-allyls result; such reactivity is found throughout the Periodic Table.[125] With [$Cp^*_2ScH$] (obtained either as a THF adduct, which is monomeric, or an unsolvated polymer),[126] hydrometallation of alkenes and alkynes does take place rapidly even at –80 °C, but complications set in. Ethylene readily undergoes additional insertion into the Sc—C bond to give a polymer, while substituted alkenes such as propene and isobutene react to form vinyl complexes, such as (**53**), by the so-called σ-bond metathesis mechanism (Scheme 17).[25,126] The predominance of σ-bond metathesis reactions is probably related to the lower coordination here than in the hydrozirconation reagents. It is faster for C—H bonds with higher *s*-character; thus terminal alkynes are not hydrometallated at all, but instead undergo the reaction in equation (55),[126] even though the expected hydrometallation product (**53**) is stable.

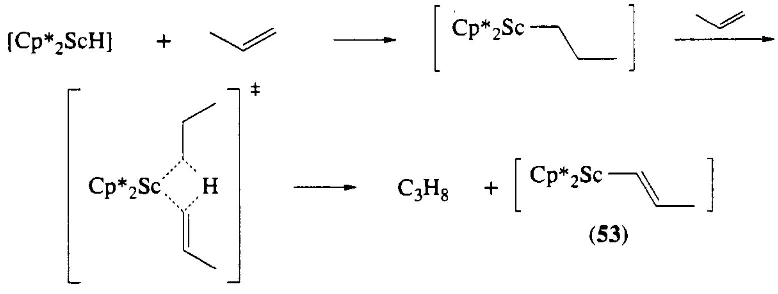

**Scheme 17**

$$(\mathbf{53}) \;\not\leftarrow\; [\mathrm{Cp^*_2ScH}] + \equiv\!\!-\mathrm{Me} \longrightarrow [\mathrm{Cp^*_2ScC{\equiv}CMe}] + \mathrm{H_2} \qquad (55)$$

The situation for lanthanides and actinides is similar. A number of [$(Cp^*_2LnH)_2$] complexes have been prepared and found to be very active hydrogenation catalysts. The mechanism in Scheme 18 appears to operate, with alkyl complex (**54**) the dominant species present in solution and its hydrogenolysis the rate-determining step.[127] In the absence of added $H_2$, polymerization and/or σ-bond metathesis sets in (although in contrast to Sc, the result of the latter is an $\eta^3$-allyl).[128] No reactions with one equivalent of alkene or alkyne apparently were performed, though, and it is possible that stable alkyllanthanides might be isolable under the right conditions, as with Sc above. The related actinide complexes [{$Cp^*_2M$(μ-

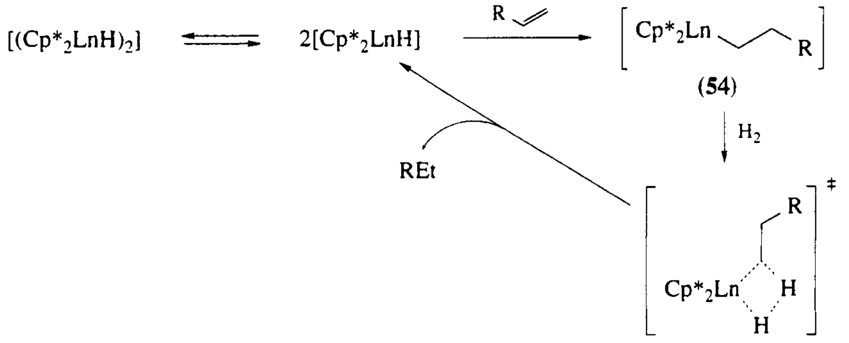

**Scheme 18**

H)H}2] (M = Th, U) are also hydrogenation catalysts, albeit much less active; for Th the reaction with ethylene afforded thermally stable but light sensitive [$Cp^*_2ThEt_2$].[129]

For all these cases — Sc, lanthanides, actinides — it is probable that conditions for clean hydrometallation could be worked out, but it is questionable whether subsequent transformations would also be clean, and the starting hydrides are all much more expensive and difficult to synthesize than [$Cp_2ZrHCl$].

Moving the other way to Group VA, the system depicted in equation (2) presents opportunities for highly regioselective additions to alkynes, although subsequent reactions may be complex (equation 56).[3] This, coupled with the difficulty of effecting hydrometallation, makes it unlikely that such systems will find much use in synthesis.

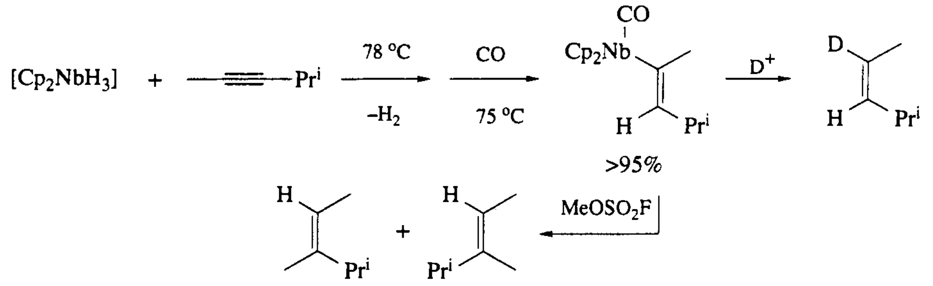

(56)

### 3.9.4.2 Catalytic Hydrometallation with Main Group Metals

Although main group organometallics are frequently more powerful synthetic reagents (or at least better understood!) than their transition metal counterparts, their preparation by direct hydrometallation is often difficult or impossible. The most probable cause is the greater tendency for aggregation of the main group hydrides, as other factors should be no less favorable (Section 3.9.2). Both alkali and alkaline earth hydrides are polymeric and do not hydrometallate at all. Group IIIA hydrides are generally dimeric, and hydroalumination works reasonably well for alkynes but not alkenes; hydroboration of course is quite general. As for Group IVB hydrides, these are monomeric, but they have no low-lying orbital available for interaction with the unsaturated substrate and hence are even less reactive.

This problem may be generally solved by catalyzed hydrometallation, which proceeds as shown in Scheme 1. Here the actual hydrometallating species is a transition metal hydride, but only catalytic amounts are needed. The following survey of such methods is brief; more details on the two most important systems, hydroalumination and hydrosilylation, may be found in Volume 8, Chapters 3.11 and 3.12 respectively.

#### *3.9.4.2.1 Groups IA, IIA and IIB*

Only one report involving Li has appeared: 'active' LiH, prepared by hydrogenolysis of BuLi, adds to terminal alkenes in the presence of transition metal halides to give (after hydrolysis) the corresponding alkane. $VCl_3$ was found to give the best alkane yield, but only a small amount of deuterium was incorporated when $D_2O$ was used for cleavage, indicating a stable alkyllithium compound was not obtained. [$Cp_2TiCl_2$] gave better D incorporation but lower yields.[130] It is not known whether this is a viable general route to alkyllithium reagents for other uses. The selectivity is unusual, though: with $VCl_3$ as catalyst internal alkenes and alkynes are unreactive. We thus have a method for hydrogenation of C=C in the presence of C≡C, which is otherwise difficult.[130]

Much more has been done on the preparation of Grignard reagents by catalyzed hydromagnesation. This topic has been recently reviewed;[131] only highlights will be summarized here. The basic reaction is essentially a 'transalkenation', the mechanism of which is shown in Scheme 19. The best catalysts are titanium complexes, $TiCl_4$ and [$Cp_2TiCl_2$], although there is good evidence that the actual catalytic species $MY_n$ is a titanium(III) species, at least for the latter.[132] Only terminal alkenes are hydrometallated,[131] so isomerization can be a major complication.[132] The usual anti-Markovnikov regioselectivity is observed, except for styrene.[131] In some cases carbometallation may be a complication, as in equation (57),[42] although this example utilizes a stoichiometric amount of Zr.

As an alternative, an isolable magnesium hydride can be used directly: successful examples include RMgH;[132,133] $Et_2NMgH$;[134] and $MgH_2$. For the last, reaction with terminal alkenes using $ZrX_4$ as catalyst affords dialkylmagnesium compounds in 80–85% yield.[135] A special preparation of $MgH_2$ (by direct hy-

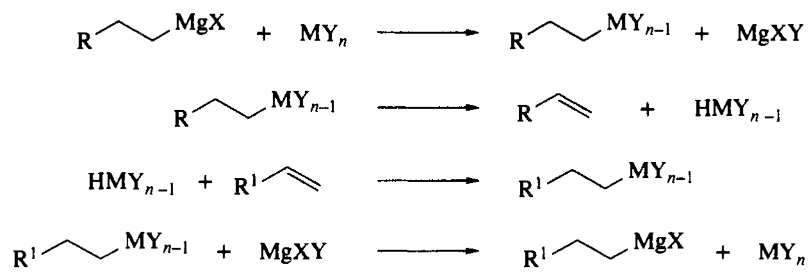

**Scheme 19**

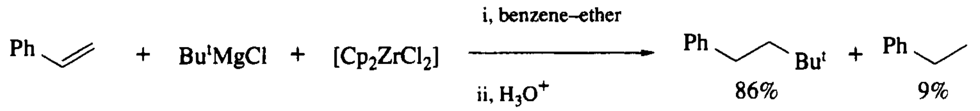

(57)

drogenation of Mg metal in the presence of $CrCl_3$) undergoes Ti-catalyzed 1,4-addition to isoprene.[136] This hydromagnesation route to allylic Grignards, which can also be achieved with other starting Mg reagents, avoids the complication of coupling frequently found in the direct preparation from the halide,[131] and has been applied to complex syntheses such as that of polyisoprene polyols.[137] Other transition metal catalysts for hydromagnesation include $[Cp_2ZrCl_2]$[133] and $NiCl_2$.[133,138]

Internal and TMS-protected terminal alkynes are hydromagnesated with high stereoselectivity and (for the latter) excellent regioselectivity, providing a source of vinyl Grignard reagents;[131] Scheme 20 shows a typical use.[139] Note that the Grignard can be thus obtained directly from an alcohol simply by using two equivalents of the Mg reagent, which would not be possible for preparation from a halide and Mg metal; also note the *cis–trans* isomerization which takes place under the reaction conditions.

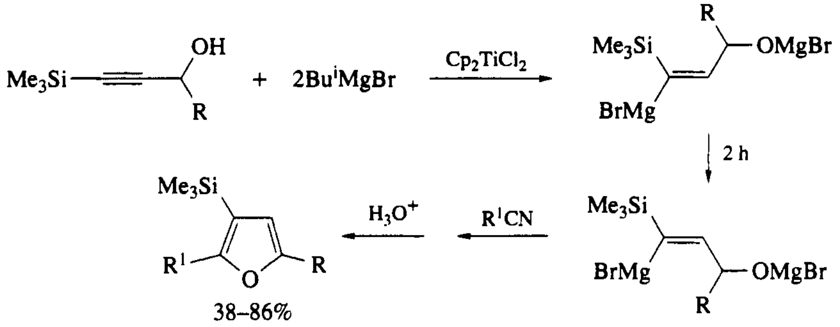

**Scheme 20**

Organozinc compounds are obtained analogously from $ZnH_2$ with Zr or Ni catalysts,[133,140] but little has been done to demonstrate the generality or utility of this method.

### *3.9.4.2.2 Group IIIB*

The vast majority of work here is on hydroalumination of alkenes. Hydroboration (Volume 8, Chapter 3.10) generally proceeds perfectly well without any requirement for catalyst. One reason for employing a catalyst might be to allow the use of boron hydrides such as $LiBH_4$[141] or $NaBH_4$,[142] which are somewhat more convenient to handle than the classic hydroboration reagents, and catalyzed hydroboration has been used to control the regio- and stereo-chemistry in 1,3-diol synthesis from allylic alcohol derivatives.[143]

Hydroalumination of alkenes by LAH, catalyzed by Ti and Zr chloride complexes, was demonstrated by two Japanese groups (equation 58).[144,145] Subsequently this reaction has been extended to other sources of Al—H and other catalysts. Further information on catalyzed hydroalumination may be found in Chapter 3.11 of this volume as well as in an earlier review.[146] Hydrogallation by $NaGaH_4/[Cp_2MCl_2]$ (M = Ti, Zr) has been briefly examined and appears quite similar;[147] little if anything is known about the synthetic utility of organogallium reagents.

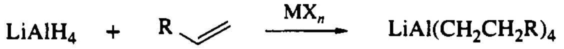

(58)

### 3.9.4.2.3 Group IVB

This group is mechanistically distinct from all those discussed above, in two ways. First, as already noted, no hydride compound with a vacant orbital is readily accessible, precluding coordination of the unsaturated substrate and direct hydrometallation. Uncatalyzed hydrosilylation therefore follows a radical mechanism, such as the one in Scheme 7, and requires high temperatures for 'unactivated' alkenes. Second, the (catalytic metal)–hydride complex is generated by oxidative addition of the (Group IVB metal)–H bond (Scheme 21); hence late transition metal catalysts are required, such as $H_2PtCl_6$, $[Co_2(CO)_8]$, $[(Ph_3P)_3RhCl]$, *etc.* Hydrosilylation has been extensively studied, and several reviews are available;[148] see also Chapter 3.12 of this volume. More recently hydrogermylation and hydrostannylation have been examined.[149,150]

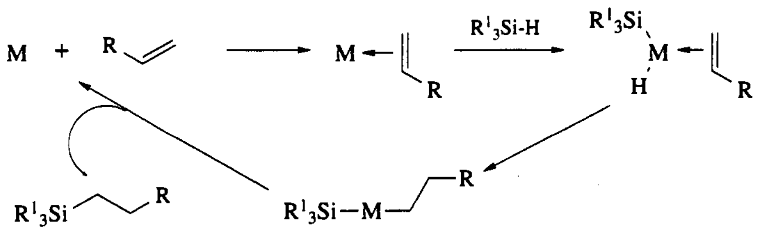

**Scheme 21**

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# 3.10

# Hydroboration of C═C and C≡C

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## 3.10.1 GENERAL CONSIDERATIONS

### 3.10.1.1 Introduction

Net hydrogenation of carbon–carbon double and triple bonds is readily achieved by a two-stage process involving initial addition of BH across the multiple bond, and subsequent protonolysis of the B—C bond (Scheme 1).

The method is particularly attractive since the first stage, known as hydroboration, can be applied to almost any nonaromatic carbon–carbon multiple bond and exhibits very useful selectivity features. Hydroboration is also the most attractive means of synthesizing organoboranes, which are arguably the most versatile organometallic reagents available to the organic chemist.[1] The reaction has received extensive

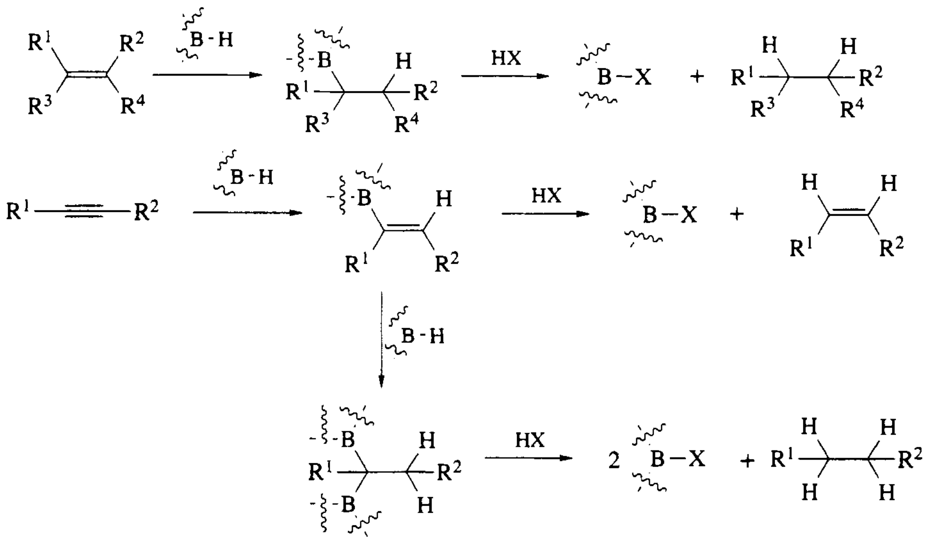

Scheme 1

study and is consequently fairly well understood. Furthermore, a whole range of hydroborating agents has been developed. This provides considerable flexibility with which to control the selectivity of the reaction and the nature of the organoboranes produced. For these reasons the bulk of this review is devoted to the various aspects of the hydroboration reaction. Treatment is necessarily brief, but a recent monograph[1] deals with the topic more fully.

A number of types of organoboranes, including aryl, benzyl, *t*-butyl and methyl derivatives, cannot be obtained *via* hydroboration. Their preparation can be achieved by a number of approaches, the most general of which involves the reaction of a reactive organometallic reagent with a boron halide or alkoxide;[1,2] the organometallic reagent may sometimes be prepared *in situ*.

The reactions of organoboranes are in general not discussed here, but are distributed throughout 'Comprehensive Organic Synthesis' wherever appropriate reaction types are under consideration. However, protonolysis of organoboranes is treated in Section 3.10.7 because of its necessary role in the reduction of carbon–carbon multiple bonds *via* hydroboration (Scheme 1). Reviews of other synthetically useful organoborane reactions appear elsewhere.[1,3–6]

### 3.10.1.2 Fundamentals of the Hydroboration Reaction

Although different hydroborating agents show considerable differences in ease of reaction and in degree of selectivity (see below), several features are common to all hydroborations.[1,3–6] Thus, the addition across a double bond occurs cleanly in a *cis* fashion. When the two faces of the double bond are sterically differentiated, addition generally occurs preferentially from the less-hindered face, and the regioselectivity is such as to place the boron atom at the less-substituted end of the double bond. Thus, in the hydroboration of α-pinene the organoborane produced consists almost entirely of a single diastereoisomer (equation 1).[1,6] Substantial stereofacial selectivities are also sometimes achieved in acyclic cases.[7]

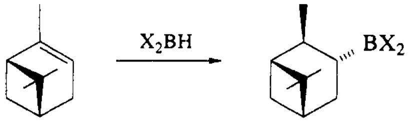

(1)

Substituents which withdraw electron density from a double bond tend to cause alkenes to react more slowly and to produce greater proportions of products having boron on the side bearing the electron-withdrawing substituent. Electron-donating substituents have exactly the opposite effect. For example, hydroboration of *para*-substituted styrenes with borane–THF produces the 'internal' isomers in proportions which increase as the electron-withdrawing capabilities of the substituents increase (equation 2).[1,8]

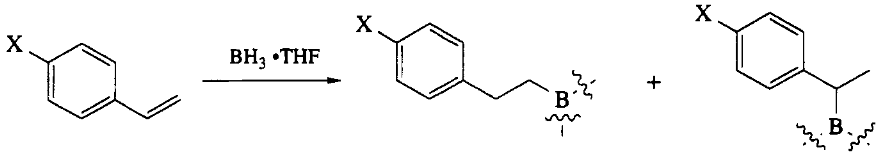

(2)

| | |
|---|---|
| X = OMe | 93:7 |
| X = H | 81:19 |
| X = $CF_3$ | 66:34 |

If hydroboration proceeds to place boron at a position proximate to a substituent then complications may arise. For example, β-chloroalkylboranes readily eliminate a chloroborane species to give an alkene. If this occurs during the course of the hydroboration reaction then further hydroboration may result, as is observed in the hydroboration of 3-chlorocyclopentene with borane–THF (Scheme 2).[1,9] The ease of elimination of groups other than halide may be crudely correlated with the leaving group capabilities of the substituents. Thus, β-alkoxyalkylboranes are more stable than β-haloalkyl compounds, though they may still undergo elimination reactions relatively easily under acid or base catalysis.[4] β-Aminoalkylboranes generally require addition of propanoic acid and heat in order to effect clean elimination.[4,10,11] The geometry of the intermediates may also affect their stability, and compounds in which substituents are in a fixed orientation about a ring may be more stable than acyclic analogs.[4]

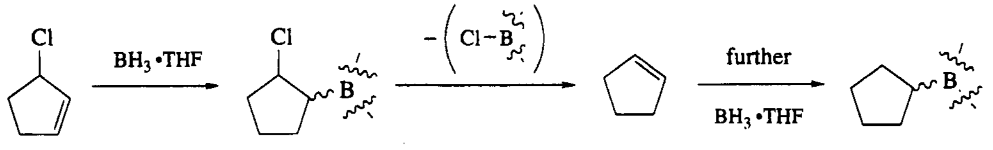

Scheme 2

Haloalkylboron compounds in which the halogen atom is more distant than the β-position are more stable than β-haloalkylboranes,[4] while α-haloalkylboranes undergo ready rearrangement.[12] β,γ-Unsaturated organoboranes may show a tendency to undergo metallotropic rearrangement (Scheme 3).[1,4]

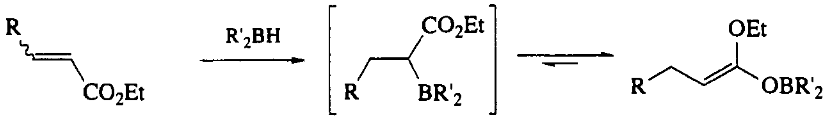

Scheme 3

Dienes and trienes provide opportunities for selective hydroboration of particular double bonds, independent hydroboration of all double bonds, or production of cyclic or oligomeric organoboron structures. However, the products obtained are highly dependent on the nature of the hydroborating agent used and are therefore not discussed further here. Similarly, alkynes give vinylboranes or diborylalkanes in proportions which depend on the reagent and conditions used. As a general rule, however, greater selectivity is available with substituted boranes, such as $R_2BH$ or $X_2BH$, than with borane itself.[1,4] Because of the differences in selectivity observed with different reagents it is necessary to consider the various types of reagent separately, and this is done in the following subsections. A brief review of trends with different reagents has appeared elsewhere.[13]

## 3.10.2 HYDROBORATION WITH DIBORANE AND BORANE COMPLEXES

### 3.10.2.1 Hydroboration with Borane–Tetrahydrofuran

Alkenes react with gaseous diborane only under forcing conditions.[1,3–6,14] However, in the presence of an ether solvent the reaction is much more rapid, and simple alkenes react readily and quantitatively to produce trialkylboranes (equation 3). Diborane has significantly greater solubility in THF than in most other ethers, and forms relatively stable solutions at moderate concentrations. In such solutions the reagent exists substantially in the form of a complex between monomeric borane and THF. This reagent forms the basis against which the properties of other reagents may be compared.

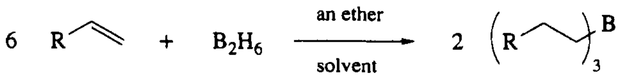

(3)

The reactions of alkenes with borane–THF occur sequentially to give first monoalkylboranes, then dialkylboranes, and finally trialkylboranes (Scheme 4).[1] Mono- and di-alkylboranes, like borane itself, exist as hydrogen-bridged dimers in the free state, although they may be complexed as the monomers by suitable Lewis bases. In most cases they will be referred to in this section as though they were monomeric, on the grounds of simplicity and clarity, unless there is a particular reason for consideration of the dimers. It is, however, important for understanding the mechanism of hydroboration that equilibria involving dimers should be recognized (see Section 3.10.6).

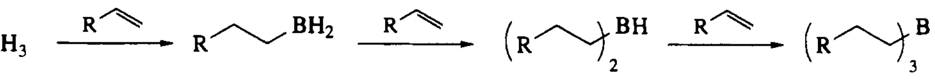

**Scheme 4**

Unhindered alkenes react rapidly as far as the trialkylborane stage, and it is not possible to obtain pure mono- or di-alkylboranes by control of the stoichiometry in such cases. However, alkenes which are somewhat hindered, such as trialkylethylenes, react readily only as far as the dialkylborane stage. Even with some 1,2-dialkylethylenes the rate of the third hydroboration step is sufficiently slower than the first two to allow clean production of dialkylboranes. This is the case with cyclohexene, for example (equation 4).[1]

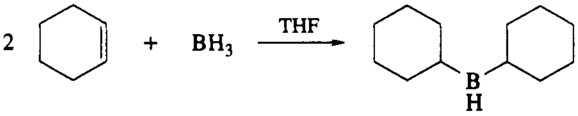

(4)

Dicyclohexylborane, $Chx_2BH$

Tetrasubstituted ethylenes and other very hindered alkenes, such as 1,2-di-*t*-butylethylene and 1,3-dimethylcyclohexene, react readily only as far as the monoalkylborane stage. The production of 1,1,2-trimethylpropylborane (thexylborane) in this way is particularly important (equation 5).[1,15]

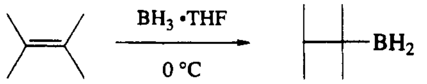

(5)

Thexylborane

Although it is general that hydroboration of simple alkenes places boron predominantly at the less-hindered end of the original double bond (see Section 3.10.1.2), the degree of selectivity varies significantly with the nature of the alkene. Figure 1 (see also equation 2) indicates the site of boron placement for a number of representative alkenes.[6,16] It should also be recognized that the regioselectivity increases for the second and particularly for the third hydroboration step (see later). Thus, even though only 6% of the boron atoms are placed at internal positions on hydroboration of unsubstituted 1-alkenes, the trialkylboranes produced contain *ca.* 82% of tri-*n*-alkylborane and *ca.* 18% of di-*n*-alkylmono-*s*-alkylborane.[1,4,5] Less selective hydroborations produce even greater proportions of isomeric organoboranes.

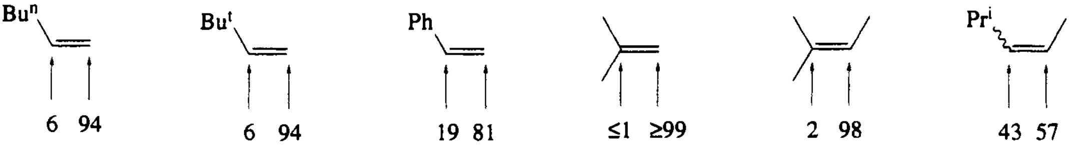

**Figure 1** Sites of attack on alkenes by the boron atom of borane–THF (%)

Although considerable selectivity for the less-hindered face is shown in the hydroboration of α-pinene (see equation 1) borane–THF shows only moderate selectivity for the different faces of most simple substituted cyclohexenes and methylenecyclohexanes (*e.g.* Figure 2).[1,17–20]

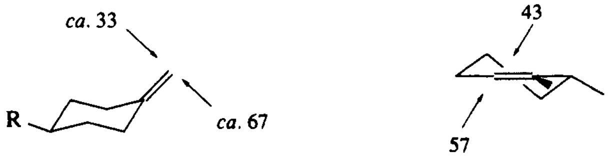
*ca.* 33
R
*ca.* 67
43
57

**Figure 2** Facial selectivities for attack on alkenes by the boron atom of borane–THF (%)

Functional groups can substantially modify the regioselectivity (see Section 3.10.1.2, in particular equation 2 and Scheme 2). Some typical regioselectivities for functionally substituted alkenes are shown in Figure 3.[1,4,9,21–23] More extensive accounts of the hydroboration of functional alkenes appear elsewhere.[4,14]

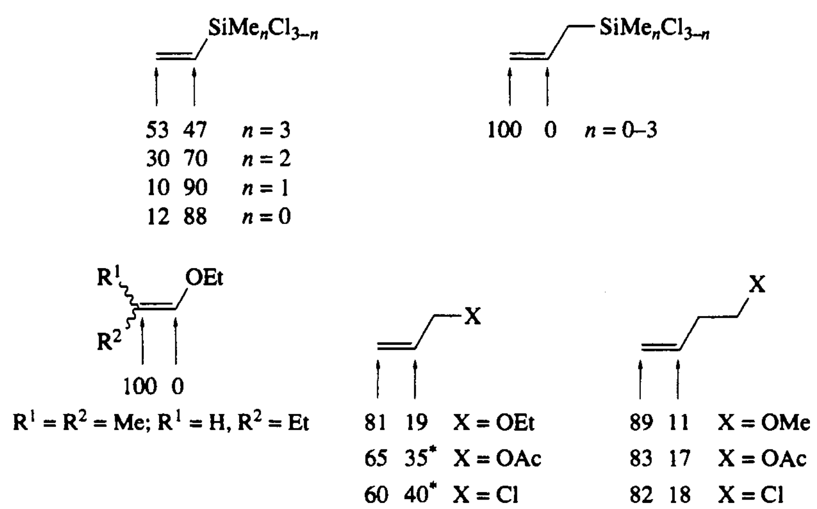
$SiMe_nCl_{3-n}$
53 47 $n = 3$
30 70 $n = 2$
10 90 $n = 1$
12 88 $n = 0$
$SiMe_nCl_{3-n}$
100 0 $n = 0–3$
$R^1$
OEt
$R^2$
100 0
$R^1 = R^2 = Me$; $R^1 = H$, $R^2 = Et$
X
81 19 X = OEt
65 35* X = OAc
60 40* X = Cl
X
89 11 X = OMe
83 17 X = OAc
82 18 X = Cl

**Figure 3** Sites of attack by the boron atom of borane–THF on functionalised alkenes (%). *The products of attack at this point are unstable under the reaction conditions

The hydroboration of simple, open-chain dienes can be somewhat complicated, leading to mixtures of regioisomers, cyclic and open-chain structures, and oligomeric structures of different sizes, all depending on reaction conditions and/or reactant proportions.[1,24] However, by control of stoichiometry, thermal isomerization of product mixtures, control of temperature during the hydroboration stage, subsequent treatment of a trialkylborane with further borane, or similar 'tricks', it is often possible to arrive at an unique product. Several important cyclic dialkylboranes can be made in this way, as shown in equations (6),[25] (7)[26–28] and (8).[29] Similar treatment of trienes can lead to bicyclic systems (*e.g.* equation 9).[1,24,30]

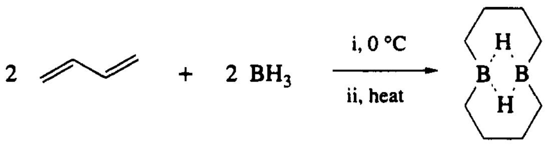
2
+ 2 $BH_3$
i, 0 °C
ii, heat
H
B B
H

(6)

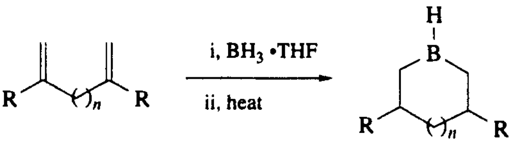
R
n
R
i, $BH_3$ •THF
ii, heat
H
B
R
n
R

(7)

R = H; $n = 1$; heat at 170 °C for borinane; for details see Section 3.10.4.3
R = Me; $n = 1$; heat at 70 °C for 3,5-dimethylborinane
R = Me; $n = 2$; heat at 70 °C for 3,6-dimethylborepane

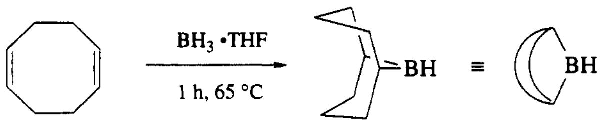

(8)

9-Borabicyclo[3.3.1]nonane, 9-BBN-H

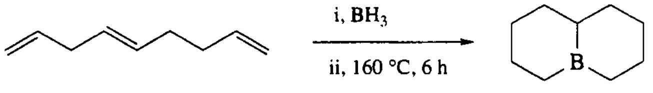

(9)

The reactions of simple, acyclic allenes with borane–THF are usually complicated. However, cyclic allenes give cleaner reactions, which can be controlled to give monohydroboration products, involving predominant attack of boron on the central carbon atom, though the intermediate vinylboranes have not generally been isolated.[1,31,32]

Terminal alkynes also generally give complicated mixtures of products in reactions with borane–THF.[1,33–35] However, internal alkynes react in a more controlled manner and it is possible to obtain reasonable yields of the corresponding (*Z*)-trialkenylboranes from such reactions (equation 10).[33]

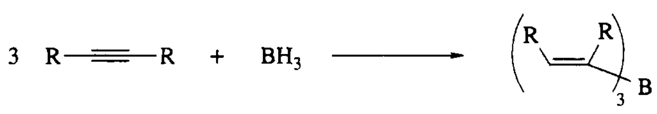

(10)

In the case of unsymmetrical alkynes the regioselectivity is only modest.[34] Use of excess borane–THF results in dihydroboration. Many of the problems encountered in hydroboration reactions of borane–THF can be overcome by the use of more selective reagents such as dialkylboranes or dihaloboranes.

### 3.10.2.2 Hydroboration with other Sources of Borane

Early reports of hydroboration reactions often recommended *in situ* generation of diborane from sodium tetrahydroborate (borohydride) and trifluoroborane etherate or some similar mixture.[3] Indeed, it is still reasonable to use this method for simple hydroborations, provided that nothing more complicated than oxidation of the resultant organoborane is intended. Otherwise, the approach should be avoided, particularly since borane is now commercially available in the form of several Lewis base complexes.

In principle, all borane–Lewis base complexes are potential hydroborating agents. To a first approximation, however, the stronger the complex, the less reactive it is as a hydroborating agent, because free borane may be required for hydroboration (see Section 3.10.6).[36]

Borane–dimethyl sulfide is a particularly useful reagent.[37,38] The complex is more stable than borane–THF and can be prepared in neat form. It is soluble in a range of organic solvents and retains sufficient 'looseness' to allow it to react readily with alkenes. It carries out most of the reactions of borane–THF, perhaps somewhat more slowly, and gives the same selectivity almost irrespective of solvent. It has been used to hydroborate alkynylsilanes at the α-position.[39] Borane–thioxane is an alternative to borane-dimethyl sulfide.[40]

Similar claims are also made for diphenylamine–borane, which is a solid and relatively stable reagent.[41] Aliphatic amine–borane complexes, however, require elevated temperatures in order to effect hydroboration.[1,3,42] Although this is in general a serious drawback, on occasions it may be advantageous by allowing slow liberation of borane, which leads to cyclization products rather than polymers. An example of the use of triethylamine–borane in this way is shown in equation (11).[30] Alternatively, methyl iodide or a Lewis acid may be added to complex the amine and thus liberate the reactive, free borane[1,42]

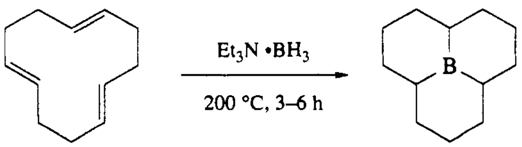

(11)

Hydroborates in the presence of an ester or of methyl iodide have also been used for hydroborations.[43] For example, the system lithium tetrahydroborate–ethyl acetate provides a simple route to dialkylboryl compounds (equation 12).[43a] Alkynes provide alkenylboron compounds.

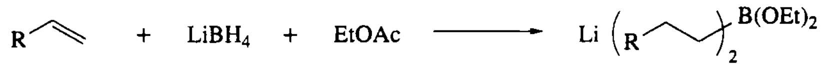

(12)

Sodium acetoxytrihydroborate is also effective,[44] while certain titanium, rhodium and cobalt complexes catalyze hydroborations with sodium tetrahydroborate.[45] In the latter case the facial selectivities can be quite different from, even opposite to, those observed with borane–THF.[45a]

## 3.10.3 HYDROBORATION WITH MONOSUBSTITUTED BORANES

### 3.10.3.1 Hydroboration with Thexylborane and other Alkyl- and Aryl-boranes

Thexylborane is the most easily prepared (see equation 5) and widely studied monoalkylborane.[15] However, it may be expected that the hydroboration characteristics of most other monoalkylboranes will be broadly comparable.[1]

Thexylborane slowly isomerizes to a *primary* alkylborane at ambient temperature, so it is usual to prepare it freshly and to use it, at 0 °C, when it is required. However, addition of an equimolar quantity of *N*,*N*-diethylaniline produces a reagent which appears significantly more stable yet retains the hydroborating and reducing capabilities.[46]

The reactions of hindered alkenes with thexylborane are generally accompanied by a significant amount of dehydroboration to give 2,3-dimethyl-2-butene. Thus, a very large excess of the latter is needed in order to produce (monomeric) dithexylborane.[47] Hydroboration of α-pinene (1:1 ratio) with thexylborane results in *ca.* 75% dehydroboration.[15a] However, alkenes of somewhat lower steric requirements, such as simple 1,2-disubstituted ethylenes, can be converted fairly cleanly into the corresponding thexylmonoalkylboranes (*e.g.* equation 13).[15] These are mixed dialkylboranes and behave like other fairly hindered dialkylboranes (Section 3.10.4.3). They can hydroborate alkenes of lower steric requirements to give totally mixed trialkylboranes.

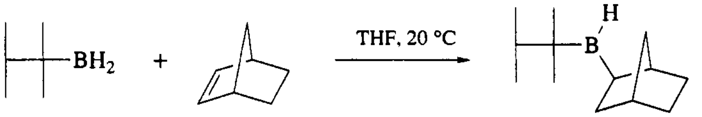

(13)

Unhindered alkenes react with thexylborane to give thexyldialkylboranes. Thus, if mixed thexyldi-*n*-alkylboranes are required, an alternative procedure involving thexylchloroborane must be adopted (Section 3.10.4.5).

Thexylborane is somewhat more regioselective than borane–THF in hydroborations of simple alkenes (Figure 4; compare Figure 1). The differences can be almost wholly attributed to the greater relative importance of the final hydroboration step, which involves a highly regioselective dialkylborane.[1]

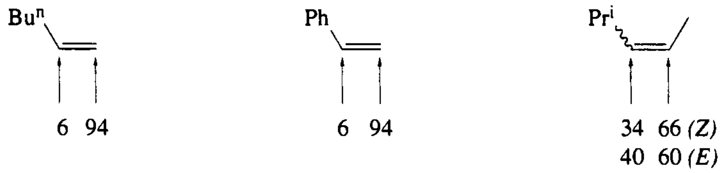

**Figure 4** Regioselectivity of attack by the boron atom of thexylborane on alkenes (%)

Thexylborane is more reliable than borane for permitting clean formation of ring compounds from dienes. Under kinetic control there is a preference for formation of five- or seven-membered rather than six-membered rings (equations 14 and 15).[1,15,48] This regioselectivity can be altered by modification of the substitution pattern or by thermal isomerization after the initial hydroboration.

A number of other monoalkylborane derivatives can be prepared by treating an amine adduct of thexylborane with an alkene (*e.g.* equation 16);[49–51] by displacement of 2,3-dimethyl-2-butene or another

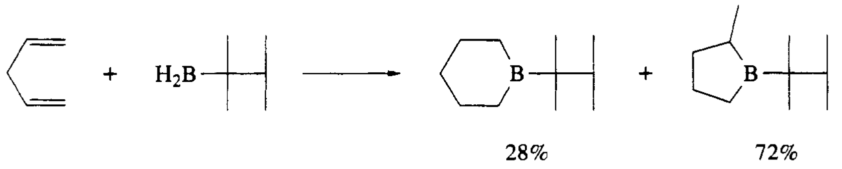

(14)

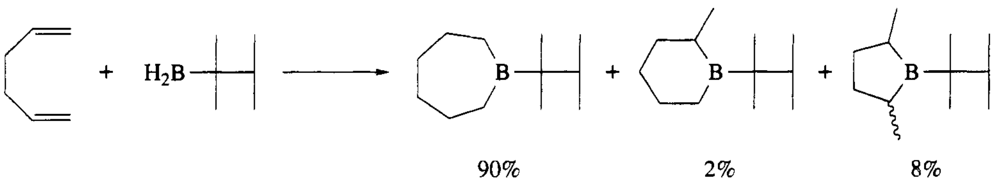

(15)

hindered alkene from a dialkylborane by addition of TMEDA or triethylamine;[52,53] by redistribution of a dialkylborane with further borane (*e.g.* equation 17);[54] or by reduction of a compound of the general type $RBX_2$ with a hydride reagent (*e.g.* equation 18).[55] *t*-Butylborane and several arylboranes have been produced by reduction of boroxin derivatives.[56]

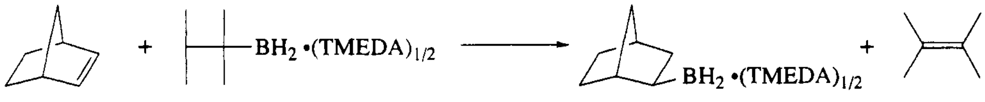

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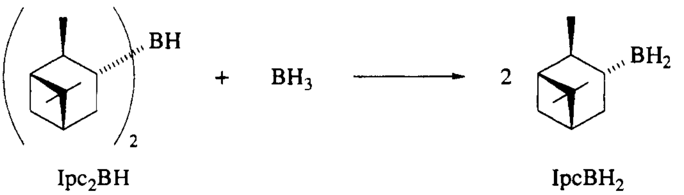

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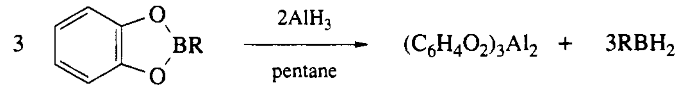

(18)

Recently, methylborane has been prepared from lithium methyltrihydroborate (equation 19).[57] Other alkylboranes have been obtained by similar methods.[58]

$$LiMeBH_3 + HCl_{(g)} \longrightarrow LiCl + H_2 + MeBH_2 \quad (19)$$

Most monoalkylboranes are not stable for prolonged periods. They tend to redistribute to give mixtures containing dialkylborane, trialkylborane and borane itself. Methylborane appears to be more stable than many,[57] but the others can be stabilized and stored as TMEDA or other trialkylamine complexes.[49,59–61] The free borane is liberated when required by addition of trifluoroborane.

Although systematic comparisons have not been made, it appears that regioselectivities and reactivities of monoalkyl- and monoaryl-boranes are broadly comparable to those of thexylborane. Strangely, however, methylborane appears to be *more* regioselective.[57]

Monoisopinocampheylborane can be prepared in high enantiomeric purity and is an important reagent for asymmetric hydroboration (see Section 3.10.5).

### 3.10.3.2 Hydroboration with Monohaloboranes

The early literature associated with monochloroborane hydroborations contains errors and it is probably appropriate to ignore publications prior to about 1970.[4] Monochloroborane complexes THF more strongly than does borane and this slows down its reactions with alkenes in this solvent. Thus, other reactions may compete and mixtures may result. The diethyl ether complex is weaker and hydroborations occur readily in this solvent. Dialkylchloroboranes, monoalkylchloroboranes (equation 20), and divinylchloroboranes (equation 21) can be prepared under appropriate conditions.[62]

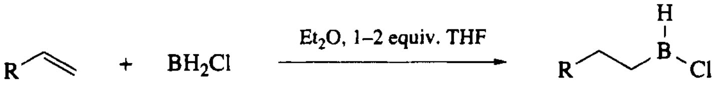

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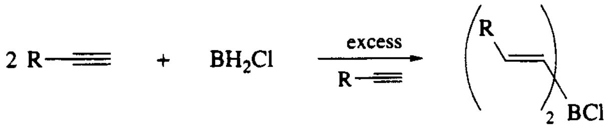

(21)

The reactions of monochloroborane in diethyl ether with α,ω-dienes lead initially to mixtures which are partially polymeric and possibly composed of different ring sizes. However, careful distillation can lead to both depolymerization and isomerization, so that in several cases a single cyclic product can be obtained (*e.g.* Scheme 5).[63]

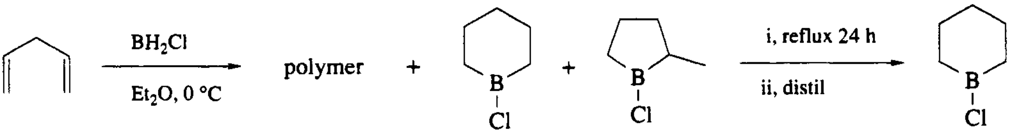

**Scheme 5**

The preparation of monochloroborane in ether is capricious and the product is not stable.[62] A more convenient source of monochloroborane is its dimethyl sulfide complex, which is readily prepared by reaction of borane–dimethyl sulfide with either tetrachloromethane (equation 22)[64] or trichloroborane–dimethyl sulfide (equation 23).[65] The latter reaction has also been modified for synthesis of the bromoborane[65] and iodoborane[66] complexes.

$$\mathrm{BH_3{\bullet}SMe_2 \;+\; CCl_4 \;\xrightarrow{heat}\; BH_2Cl{\bullet}SMe_2 \;+\; CHCl_3} \qquad (22)$$

$$\mathrm{2\,BH_3{\bullet}SMe_2 \;+\; BX_3{\bullet}SMe_2 \;\xrightarrow{heat}\; 3\,BH_2X{\bullet}SMe_2} \qquad (23)$$

Monochloborane–dimethyl sulfide coexists with small amounts of the borane and dichloroborane complexes, but the bromoborane–dimethyl sulfide complex appears to be almost pure.[65,66] These complexes react readily with alkenes at 25 °C and can be used for hydroborations in a variety of solvents. Dialkylhaloboranes are obtained in high yield as their dimethyl sulfide complexes (equation 24), but dimethyl sulfide is readily removed under reduced pressure if required.[64,67] The reagents are also useful for cyclic hydroborations of dienes such as cyclooctadiene (equation 25).[68] An alternative approach to dialkylbromoboranes involves the reaction of dialkyl(methylthio)boranes with bromine.[69]

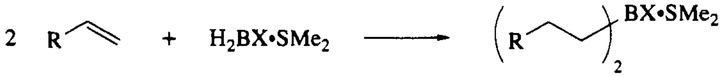

(24)

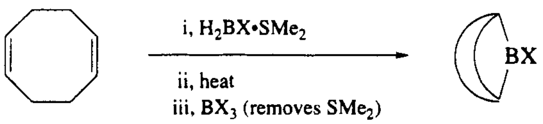

(25)

Monohaloboranes generally exhibit significantly greater regioselectivities than borane–THF in hydroboration reactions (Figure 5),[67] though there may be some exceptions to the rule.

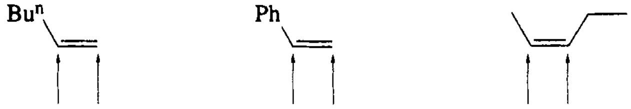

| | | | | | | |
|---|---|---|---|---|---|---|
| $BH_3$•THF | 6 | 94 | 19 | 81 | 55 | 45 |
| $BH_2Cl$•$OEt_2$ | <0.5 | >99.5 | 4 | 96 | 58 | 42 |
| $BH_2Cl$•$SMe_2$ | 0.8 | 99.2 | 7 | 93 | – | – |
| $BH_2Br$•$SMe_2$ | 0.4 | 99.6 | 4 | 96 | 63 | 37 |

**Figure 5** Regioselectivities of hydroborations with haloboranes (%)

## 3.10.4 HYDROBORATION WITH DISUBSTITUTED BORANES

### 3.10.4.1 General Considerations

The structures of some of the more common examples from a whole range of disubstituted hydroborating agents are given in Figure 6.[1]

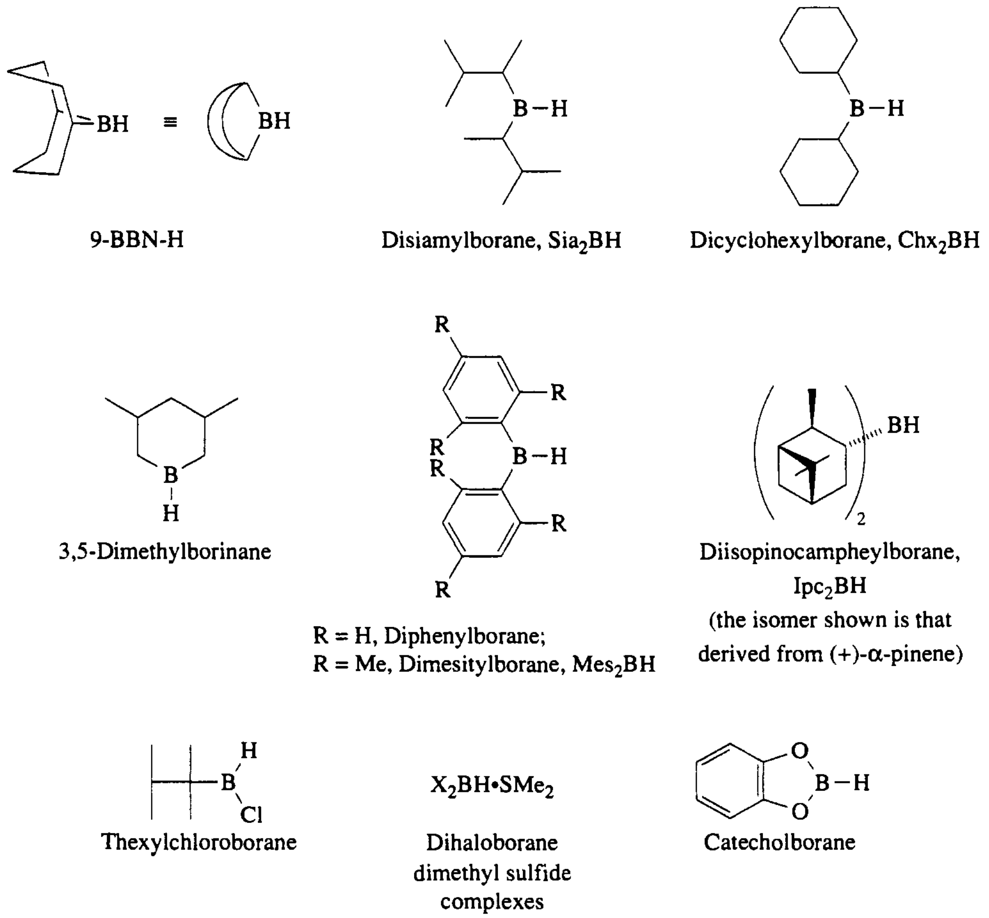

9-BBN-H

Disiamylborane, $Sia_2BH$

Dicyclohexylborane, $Chx_2BH$

3,5-Dimethylborinane

R = H, Diphenylborane;
R = Me, Dimesitylborane, $Mes_2BH$

Diisopinocampheylborane, $Ipc_2BH$
(the isomer shown is that derived from (+)-α-pinene)

Thexylchloroborane

$X_2BH$•$SMe_2$
Dihaloborane dimethyl sulfide complexes

Catecholborane

**Figure 6** Some common disubstituted borane hydroborating agents

9-Borabicyclo[3.3.1]nonane (9-BBN-H) has received greater study than the others and a separate section is devoted to its reactions, with the other dialkyl- and diaryl-boranes considered as a group. Separate sections are also devoted to dihaloboranes, alkylchloroboranes and catecholborane and its analogs.

### 3.10.4.2 Hydroboration with 9-BBN-H

9-BBN-H is readily prepared (Section 3.10.2.1, equation 8) and is commercially available. It shows considerable stability, even in air for limited periods,[70] and is therefore a very convenient hydroborating agent.[1,71,72] Unlike di-primary-alkylboranes it is not prone to disproportionation, but it is substantially less hindered than other di-*s*-alkylboranes such as dicyclohexylborane and disiamylborane. Thus, it hydroborates hindered alkenes such as 2,3-dimethyl-2-butene slowly.[72] It is less sensitive to steric factors and more sensitive to electronic factors than disiamylborane. Thus, it shows relatively little ability to discriminate between (*E*)/(*Z*) pairs[73] but readily discriminates between 4-methoxystyrene and 4-(trifluoromethyl)styrene.[72]

All dialkylboranes are highly regioselective, but 9-BBN-H is often the most regioselective of all, frequently giving almost total regioselectivity. Figure 7 shows some typical regioselectivities;[72,74–76] values for borane–THF and for disiamylborane are given for comparison.

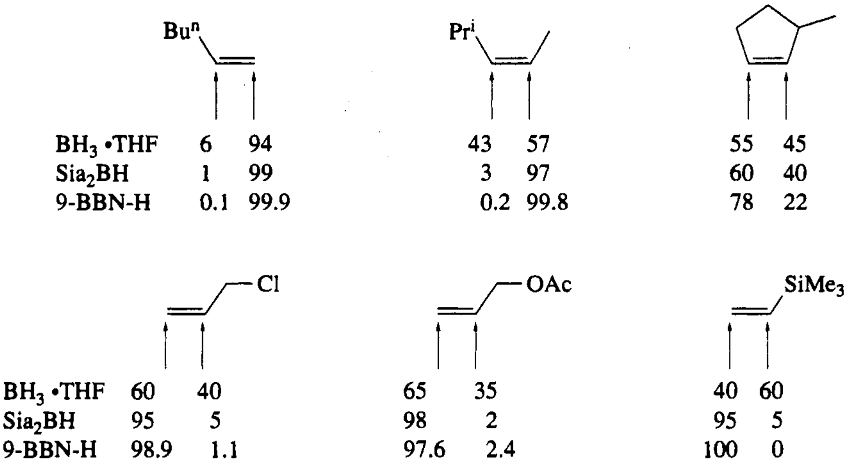

| | | | | | | |
|---|---|---|---|---|---|---|
| $BH_3$•THF | 6 | 94 | 43 | 57 | 55 | 45 |
| $Sia_2BH$ | 1 | 99 | 3 | 97 | 60 | 40 |
| 9-BBN-H | 0.1 | 99.9 | 0.2 | 99.8 | 78 | 22 |

| | | | | | | |
|---|---|---|---|---|---|---|
| $BH_3$•THF | 60 | 40 | 65 | 35 | 40 | 60 |
| $Sia_2BH$ | 95 | 5 | 98 | 2 | 95 | 5 |
| 9-BBN-H | 98.9 | 1.1 | 97.6 | 2.4 | 100 | 0 |

**Figure 7** Regioselectivities of attack by the boron atom of dialkylboranes on alkenes (%)

9-BBN-H tolerates many functional groups, and this, coupled with its high regioselectivity, allows the clean synthesis of a number of functionalized organoboranes (*e.g.* equation 26),[74] including many derived from unsaturated heterocyclic compounds.[77] It also shows impressive stereofacial selectivity in the hydroboration of cyclic alkenes (*e.g.* equations 27–29),[75,78] and sometimes in the cases of acyclic alkenes.[7]

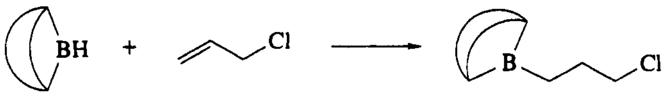

(26)

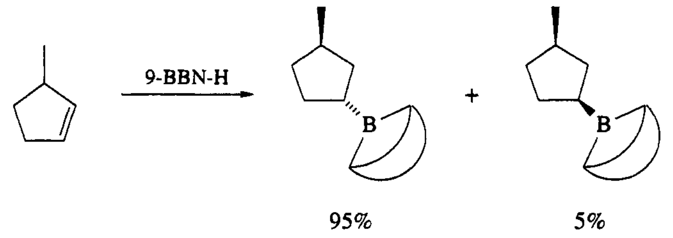

(27)

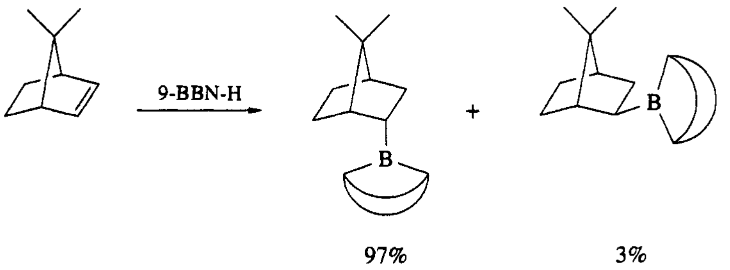

(28)

Furthermore, the products of reactions with 9-BBN-H seem to be less prone to isomerization than those derived using borane–THF. For example, 1-methylcyclooctene is readily converted into 9-(*trans*-2-methylcyclooctyl)-9-BBN (equation 30),[75] whereas its reaction with borane–THF produces a complex mixture.

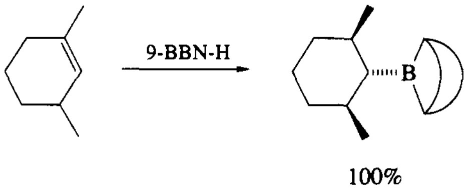

(29)

Hydroboration of acyclic, symmetrical, nonconjugated dienes with one equiv. of 9-BBN-H produces almost statistical mixtures of mono- and di-hydroborated species,[74] but cyclic analogs may show substantial deviations from the statistical mixture. For example, monohydroboration of 1,5-cyclooctadiene occurs to the extent of 85% using 1:1 stoichiometry (equation 31),[79,80] whereas disiamylborane gives predominantly dihydroboration product under such conditions.

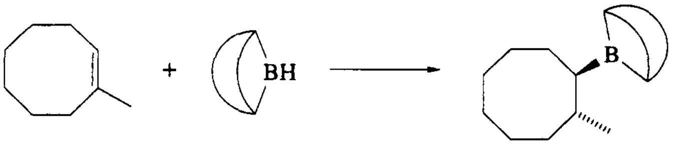

(30)

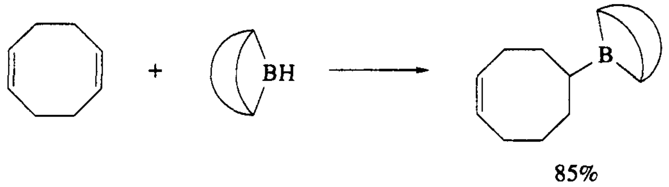

(31)

Unsymmetrical, nonconjugated dienes are generally easier to monohydroborate because of intrinsic differences between the two double bonds. Both 9-BBN-H and disiamylborane favor attachment to a terminal double bond rather than an internal double bond (*e.g.* equation 32).[79] On the other hand, 2-methyl-1,5-hexadiene reacts predominantly at the 1-position with 9-BBN-H and almost exclusively at the 6-position with disiamylborane.[79] The products of dihydroboration of α,ω-dienes with 9-BBN-H can be redistributed with borane–dimethyl sulfide to give boracyclanes.[81] In this way, some of the problems sometimes associated with direct hydroboration of dienes with borane (see Section 3.10.2.1) may be overcome.

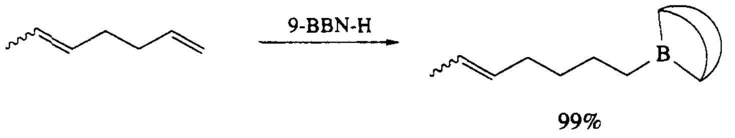

(32)

Conjugated dienes are deactivated relative to isolated double bonds towards 9-BBN-H, so monohydroboration is difficult to achieve unless the second hydroboration stage is slowed by intrinsic lack of reactivity of the system or by steric crowding, when it is possible to produce allylic organoboranes (*e.g.* equation 33).[82]

Allylic-9-BBN derivatives are also available by hydroboration of allenes with 9-BBN-H. Unlike disiamylborane, 9-BBN-H shows a marked preference for attachment of boron to one of the termini of the allene system rather than to the central carbon atom. Allene itself is dihydroborated by 9-BBN-H, but substituted allenes give rise predominantly to allylboranes (*e.g.* equation 34).[83]

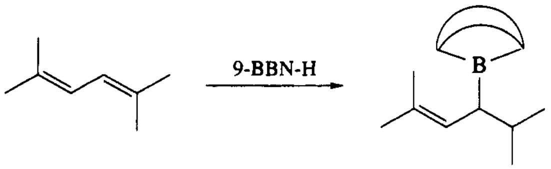

(33)

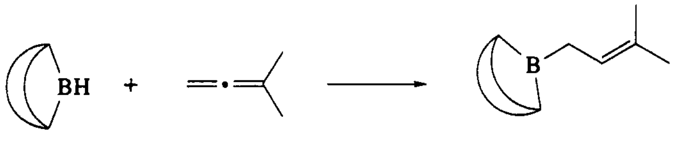

(34)

Hydroboration of internal alkynes with 9-BBN-H in stoichiometric amounts is a useful way of synthesizing vinylboranes (Scheme 6).[84,85] Further hydroboration of the product is slow, but can be used to produce *gem*-diboryl compounds (Scheme 6).[84]

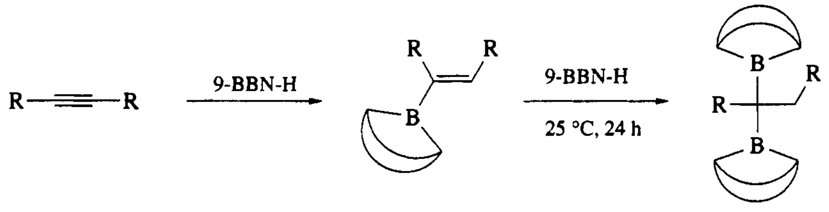

**Scheme 6**

The regioselectivity of monohydroboration is governed both by steric and electronic effects, as illustrated in Figure 8. Once again, 9-BBN-H is more susceptible to electronic factors and less to steric factors than is disiamylborane.[84]

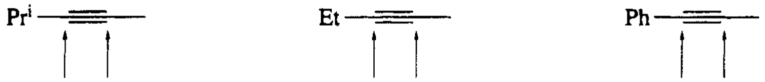

| | Pr$^i$ | | Et | | Ph | |
|---|---|---|---|---|---|---|
| $BH_3$•THF | 25 | 75 | 40 | 60 | 74 | 26 |
| $Sia_2BH$ | 7 | 93 | 39 | 61 | 19 | 81 |
| 9-BBN-H | 4 | 96 | 22 | 78 | 65 | 35 |

**Figure 8** Regioselectivities in hydroborations of alkynes (%)

1-Alkynes give mainly 1,1-diborylalkanes with 9-BBN-H and the reaction becomes essentially quantitative with a 1:2 ratio of reactants.[1,4,42] The alkenylborane can be made to predominate by use of excess alkyne, but more hindered reagents, such as disiamylborane, give the alkenylborane readily with 1:1 stoichiometry.[85a] 9-BBN-H reacts with alkenes more readily than with alkynes, thereby permitting the synthesis of organoboranes containing an alkyne unit (*e.g.* equation 35),[85b] in contrast to the preferential hydroboration of the alkyne group by other dialkylboranes.

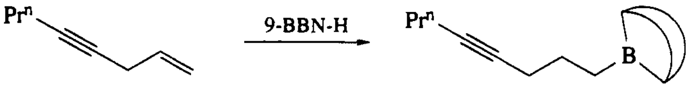

(35)

### 3.10.4.3 Hydroboration with other Dialkyl- and Diaryl-boranes

Few publications[77,85a] have explored the different properties of a range of hydroborating agents with a single substrate. More commonly, the properties of a particular reagent have been compared only with those of borane–THF or 9-BBN-H. Nevertheless, it appears from these reports that there are essentially two other types of diorganylboranes; (i) those which are very hindered, *i.e.* more hindered than 9-BBN-H; and (ii) those which are less hindered than 9-BBN-H, *i.e.* di-primary-alkylboranes.

Possibly the most hindered reagent of all — dimesitylborane, an air-stable white solid with poor solubility in ether solvents — reacts only slowly with alkenes.[86] Reaction with a simple 1-alkene requires 8 h at 25 °C to go to completion, and that with cyclohexene proceeds only to the extent of 20% after 24 h at 65 °C. Other heterogeneous hydroborations have been helped by sonication[87] and perhaps this might help with dimesitylborane. However, even in the absence of such treatment dimesitylborane readily monohydroborates both terminal and internal alkynes,[86] and it seems therefore to be a very discriminating reagent, though no enynes have yet been hydroborated with it.

The regioselectivity of hydroboration of unsymmetrical alkynes is greater with dimesitylborane than with any other known hydroborating agent (Figure 9).[86] The reagent is dominated by steric rather than electronic effects and there are therefore no problems with dihydroboration. It appears likely that the reagent will also tolerate functional groups.[86] Thus, it is a very useful reagent for production of alkenylboranes. Unfortunately, it is not available *via* hydroboration, though it is now commercially available.

| | $Pr^n$—≡— ↑ | ↑ | Ph—≡— ↑ | ↑ |
|---|---|---|---|---|
| $BH_3$•THF | 40 | 60 | 74 | 26 |
| $Sia_2BH$ | 39 | 61 | 19 | 81 |
| Catecholborane | 40 | 60 | 27 | 73 |
| 9-BBN-H | 22 | 78 | 65 | 35 |
| $Br_2BH$•$SMe_2$ | 25 | 75 | 64 | 36 |
| $Mes_2BH$ | 10 | 90 | 2 | 98 |

**Figure 9** Regioselectivities of disubstituted boranes in hydroborations of alkynes (%)

Highly hindered dialkylboranes, such as diisopinocampheylborane and disiamylborane, are more easily prepared. However, they may undergo a significant amount of retrohydroboration in reactions with relatively hindered alkenes.[1,88] Dicyclohexylborane is less prone to this problem and is also less prone to isomerization than disiamylborane,[89] yet is still highly regioselective. It is a solid which can be stored for considerable periods under dry nitrogen.[4] Its hydroboration properties have been less well studied, for historical reasons, than those of disiamylborane, but the two reagents appear to be very comparable. Its reactions may benefit from sonication.[87] Section 3.10.4.2 provides much comparative information on disiamylborane and 9-BBN-H and coverage here is therefore brief. From what little is known about diphenylborane, it appears comparable to dicyclohexylborane or disiamylborane in its ability to hydroborate alkenes.[90]

The rates of reaction of alkenes with disiamylborane vary over a much wider range than those with borane–THF, and alkynes react more rapidly than comparable alkenes. The great selectivity shown allows ready distinction between different alkenes, or between two different double bonds in a nonconjugated diene (*e.g.* equation 36).[91] Selective monohydroboration of conjugated dienes is more troublesome. However, selective monohydroboration of some conjugated dienes, such as 1,3-cyclohexadiene, can be achieved with disiamylborane,[92] as is also the case with 9-BBN-H.

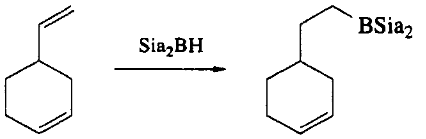

(36)

In general, the regioselectivities and stereoselectivities of reactions with disiamylborane are more susceptible to steric effects and less to electronic effects, but are otherwise similar to those of 9-BBN-H (Section 3.10.4.2).[1]

Both terminal and internal alkynes react readily to produce vinylboranes with disiamylborane or dicyclohexylborane (*e.g.* equation 37), and dihydroboration is often incomplete even with excess reagent.[33–35,85] This is in contrast to the situation with 9-BBN-H.

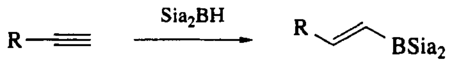

(37)

Conjugated diynes may be monohydroborated with disiamylborane, while with dicyclohexylborane dihydroboration is easier (Scheme 7).[93]

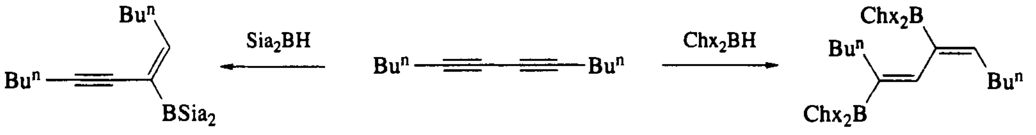

**Scheme 7**

Disiamylborane and dicyclohexylborane, in contrast to 9-BBN-H, reduce the triple bond of enynes in preference to the double bond.[93,94] Hydroboration of functional alkynes is also possible (*e.g.* equations 38[95] and 39[96]; see also ref. 97).

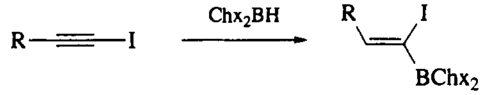

(38)

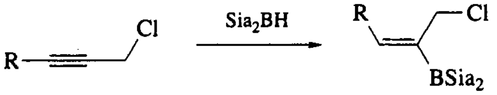

(39)

Less hindered dialkylboranes cannot generally be prepared by direct stoichiometric hydroboration of 2 equiv. of an alkene with borane (Section 3.10.2.1), although 3,5-dimethylborinane and 3,6-dimethylborepane are exceptions.[27,28] Borinane itself is obtained by a sequence involving hydroboration (diene:$BH_3$ = 3:2), thermal isomerization, and then redistribution with further borane–THF,[98,99] but there is as yet no similar direct route to the parent borepane.[100]

The simplest approach to pure acyclic di-primary-alkylboranes involves reduction of a species of the type $R_2BX$ with a hydride reagent such as sodium or potassium hydride (equation 40),[101] aluminum hydride,[102] or lithium aluminum hydride.[103,104]

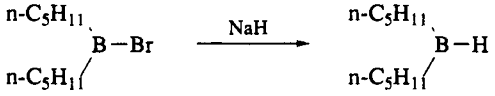

$$(n\text{-}C_5H_{11})_2B\text{-}Br \xrightarrow{NaH} (n\text{-}C_5H_{11})_2B\text{-}H \qquad (40)$$

The dialkylboranes must either be used immediately or converted into more stable products; otherwise redistribution takes place. Such redistribution reactions (*e.g.* equation 41) can be used in reverse to generate dialkylboranes,[105] but this method does not generally give rise to a single component.

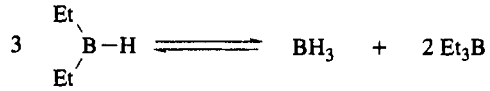

$$3\ Et_2B\text{-}H \rightleftharpoons BH_3 + 2\ Et_3B \qquad (41)$$

Pure dialkylboranes can be stored as amine complexes or as dialkyldihydroborates, in a manner analogous to that used to stabilize monoalkylboranes (Section 3.10.3.1). They are then reliberated by reactions with appropriate electrophiles.[1,4,42] Dimethylborane has recently been obtained from its hydroborate in this way.[57]

Di-primary-alkylboranes react readily at 25 °C with most alkenes. Nevertheless, even mixtures of mono-, di- and tri-alkylboranes with compositions which correspond overall to that of a simple dialkylborane distinguish impressively between alkenes of different steric requirements.[106] Of course, mixtures of different trialkylboranes, $R^1_nBR^2_{n-3}$ result in such cases. Di-primary-alkylboranes also exhibit regioselectivity which is often only marginally worse than that of disiamylborane.[106] For example, 3,5-dimethylborinane hydroborates 1-hexene to give 99% of the 1-hexyl isomer (equation 42).[28] Dimethylborane is generally somewhat less regioselective than other dialkylboranes.[57]

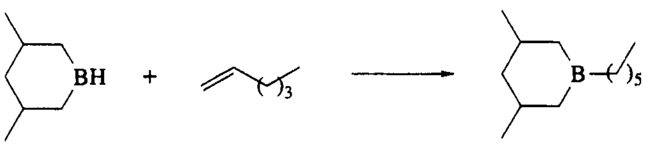

(42)

Di-primary-alkylboranes monohydroborate internal alkynes, but readily dihydroborate 1-alkynes.[85a] Thus, it is difficult by this approach to make 1-alkenyldi-*n*-alkylboranes.

Lithium tri-*n*-alkylhydroborates add B—H across the double bonds of substituted styrenes.[107] The reaction places boron at the α-position, unlike hydroboration with dialkylboranes which places boron at the β-position. It is therefore useful for preparation of unusual organoboranes,[107] but the mechanism is presumably quite different from that occurring in normal hydroborations. The reaction is also very restricted in scope.

### 3.10.4.4 Hydroboration with Dihaloboranes

The most convenient dihaloborane reagent is the dibromoborane–dimethyl sulfide complex. It is commercially available as a neat liquid or is readily prepared by a redistribution reaction, of a type which is also applicable to chloro and iodo analogs (equation 43).[65,66] Unlike the chloro analog, however, it reacts readily with alkenes[108–110] and alkynes[111] in dichloromethane without need for a decomplexing agent such as trichloroborane.

$$BH_3{\bullet}SMe_2 \quad + \quad 2\ BX_3{\bullet}SMe_2 \quad \rightleftharpoons \quad 3\ BHX_2{\bullet}SMe_2 \qquad (43)$$

The selectivities exhibited by dibromoborane–dimethyl sulfide are also interesting. In contrast to the situation with 9-BBN-H, internal alkynes are hydroborated faster than either terminal alkynes or terminal alkenes. Unlike reactions with disiamylborane, 1,1-disubstituted ethylenes are hydroborated in preference to simple 1-alkenes. These properties can lead to interesting possibilities for selective hydroboration of polyunsaturated molecules (*e.g.* Schemes 8 and 9).[112]

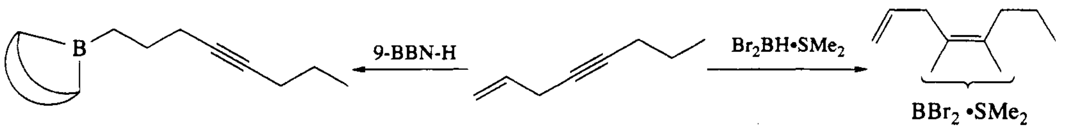

Scheme 8

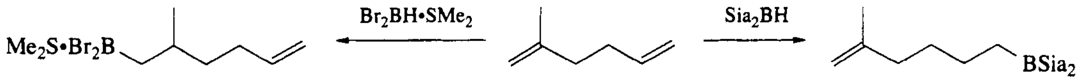

Scheme 9

Dibromoborane–dimethyl sulfide exhibits regioselectivity in hydroboration of alkenes which is comparable to that exhibited by dialkylboranes. Excess alkene should be avoided in reactions of trisubstituted ethylenes, otherwise hydrogen bromide liberated during work-up may add to the excess ethylene and cause problems.[110]

Alkyldibromoboranes isomerize only slowly and dibromoborane–dimethyl sulfide may have advantages over borane–THF for hydroboration of problematical alkenes such as 1-methylcyclooctene[113] (compare equation 30, Section 3.10.4.2).

If alkyldichloroboranes are specifically required, dichloroborane–dimethyl sulfide is the reagent of choice.[114] It is more stable and more convenient than the dichloroborane–diethyl ether complex, but its hydroborating properties are very similar.[115] Dichloroborane complexes ethers even more strongly than monochloroborane, and its reactions with alkenes in this solvent are slow and lead to mixtures. Therefore, it is generally used in pentane and trichloroborane is added to liberate uncomplexed dichloroborane. Under these conditions it readily gives alkyldichloroboranes on reaction with alkenes or alkenyldichloroboranes on reaction with alkynes.[114,115] The latter reaction has been applied to alkynylsilanes (equation 44).[116]

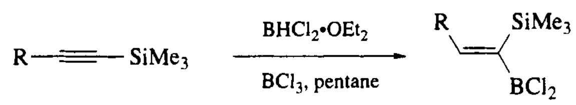

(44)

### 3.10.4.5 Hydroboration with Alkylhaloboranes

Although several monoalkylchloroboranes have been prepared by the 1:1 reaction of an alkene with monochloroborane–diethyl ether (see Section 3.10.3.2),[62] almost the only one to receive detailed investigation is thexylchloroborane. This reagent is most useful as its dimethyl sulfide complex, prepared according to equation (45)[117,118] or equation (46).[119]

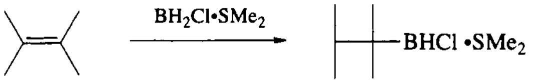

(45)

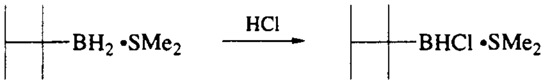

(46)

Alkylbromoborane–dimethyl sulfide complexes are available by controlled reduction of alkyldibromoborane complexes (equation 47).[120]

$$\mathrm{RBBr_2 \cdot SMe_2} \xrightarrow[\mathrm{Et_2O}]{0.25\ \mathrm{LiAlH_4}} \mathrm{RBHBr \cdot SMe_2} \qquad (47)$$

Thexylchloroborane–dimethyl sulfide is very sensitive to steric factors, reacting, for example, 1000 times faster with 1-hexene than with cyclohexene.[121] In this respect it resembles the dialkylboranes, but it appears to be more sensitive to electronic factors than the latter, and its ability to discriminate between (*E*)- and (*Z*)-isomers is exceptional. For example, it reacts with (*Z*)-3-hexene 100 times more rapidly than with (*E*)-3-hexene.[121]

Reactions of thexylchloroborane with 1-alkenes and unhindered 1,2-disubstituted ethylenes give thexylmonoalkylchloroboranes cleanly (equation 48).[122] Regioselectivities in hydroboration of such alkenes are comparable to those with 9-BBN-H. For the less reactive alkenes, however, the overall yield of thexylmonoalkylchloroborane and the regioselectivity observed in the hydroboration are often lower due to the *in situ* production of thexylborane, formed by slow redistribution of thexylchloroborane during the long reaction times.[117,122]

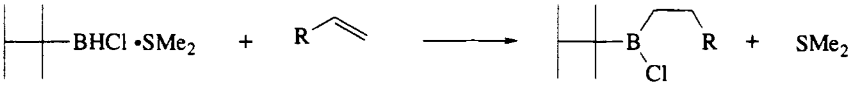

(48)

The hydroborating characteristics of alkylbromoborane complexes have not been so extensively investigated, but a range of alkenes appears to be accommodated.[120]

From a synthetic point of view the advantage of alkylhaloborane reagents is that they provide access to mixed dialkylhaloboranes and thereby ultimately to totally mixed trialkylboranes which would be difficult or impossible to obtain by simple stepwise hydroborations. Thus, reactions of simple, unhindered alkenes are of greatest significance, and these work well.

Conversion of mixed dialkylhaloboranes into totally mixed trialkylboranes can be achieved *via* reaction with organometallic reagents[119] or *via* reduction–hydroboration.[120,123] The application of the latter approach for synthesis of totally mixed organoboranes is shown in Scheme 10.

$$\mathrm{R^1BBr_2 \cdot SMe_2} \xrightarrow{0.25\ \mathrm{LiAlH_4}} \mathrm{R^1BHBr \cdot SMe_2} \xrightarrow{\text{alkene 2}}$$

$$\mathrm{R^1R^2BBr \cdot SMe_2} \xrightarrow{\mathrm{MeO^-,\ MeOH}} \mathrm{R^1R^2BOMe} \xrightarrow[\text{alkene 3}]{0.33\ \mathrm{LiAlH_4}} \mathrm{R^1R^2R^3B}$$

**Scheme 10**

### 3.10.4.6 Hydroboration with Catecholborane and Related Compounds

Acyclic dialkoxyboranes, $(RO)_2BH$, readily disproportionate,[124] but a number of heterocyclic analogs, such as the trimethyldioxaborinane (**1**), catecholborane (**2**; 1,3,2-benzodioxaborole) and 1,3,2-dithiaborolane (3) are more stable.[1] Unfortunately, because of the low Lewis acidity of (1) hydroboration occurs only at elevated temperatures. Nevertheless, it has been employed in the hydroboration of alkenes,[125] 1,3-dienes and allenes.[126]

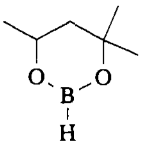

**(1)**

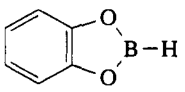

**(2)**

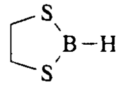

**(3)**

Catecholborane is somewhat more reactive than (1), though still far less reactive than dialkylboranes.[127,128] It is readily prepared by the reaction of catechol with borane–THF, is stable at 0 °C, and hydroborates alkenes slowly and alkynes (equation 49) more rapidly in refluxing THF.[128,129] The rate of reaction can be considerably enhanced by use of Wilkinson's catalyst, *N*,*N*-dimethylaniline–borane or lithium borohydride.[130]

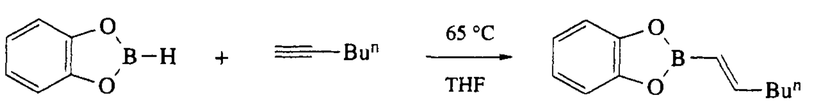

(49)

Regioselectivities appear to approach those achieved with disiamylborane (*e.g.* see Figure 9, Section 3.10.4.3).[129] The *cis* additions to alkynes[131] give alkenylborane derivatives which are useful synthetic intermediates.[132]

1,3,2-Dithiaborolane (3) is potentially as useful as catecholborane, but has not been so fully investigated. It is quite stable, and more electrophilic and more reactive towards alkenes than catecholborane.[133]

## 3.10.5 CHIRAL HYDROBORATION

### 3.10.5.1 General Considerations

Asymmetric induction during the course of a hydroboration reaction is a well-established phenomenon.[1,134,135] The induction may result from the presence of an asymmetric center in the alkene undergoing hydroboration, or by the incorporation of asymmetric groups into the hydroborating agent. A dramatic example of the former type of induction occurs in the hydroboration of α-pinene; each of the newly generated asymmetric centers is almost exclusively the stereochemistry shown in equation (1) (Section 3.10.1.2). In less rigid systems the degree of control may be less, but even so some impressive inductions have been noted (*e.g.* equation 50).[136] The hydroborating agent chosen may dramatically influence the degree of induction achieved in such asymmetric hydroborations.[137]

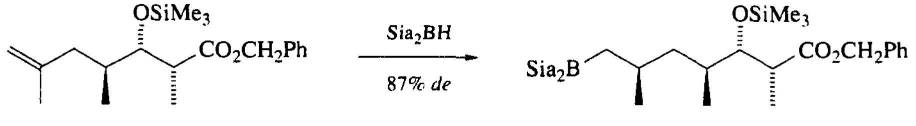

(50)

The alternative approach, in which a chiral hydroborating agent is utilized, is more flexible in that there is no requirement for asymmetry in the alkene. However, if such asymmetry should be present of necessity, then there is the possibility of utilizing the principles of 'double asymmetric induction' by correct choice of chiral reagent.[138] Little work has been done in this field as yet and it will not be discussed further.

Chiral hydroborating agents can be generated by two approaches: (i) by hydroboration of a readily available chiral alkene, the classic example of which is α-pinene; or (ii) by a designed synthesis, followed by resolution of the product. The former method has the advantages that it is quick and easy to generate a reagent, and is inexpensive if the chiral alkene is cheap, as is the case with a number of naturally occurring terpenes. The disadvantage is that the molecule does not necessarily incorporate the appropriate structural design features for the specific purpose required. Nevertheless, a number of terpene-derived hydroborating agents have been prepared and can be very useful for asymmetric hydroboration of certain classes of alkene.[1,134] Most notable among them are diisopinocampheylborane

($Ipc_2BH$), monoisopinocampheylborane ($IpcBH_2$) and dilongifolylborane ($Lgf_2BH$) (Figure 10)[1,134,139] but a number of others, such as dicaranylborane[140] have also been used.

The second approach is more tedious and more expensive, but may provide a reagent with ideal structural features. To date the approach has been used only for generation of chiral *trans*-2,5-dimethylborolane (Figure 10), the synthesis of which involves initial production of the ring system as a mixture of *cis* and *trans* isomers, separation and resolution of the pure *trans* compound, and then manipulation of the boron-bound group to obtain the free borane.[138]

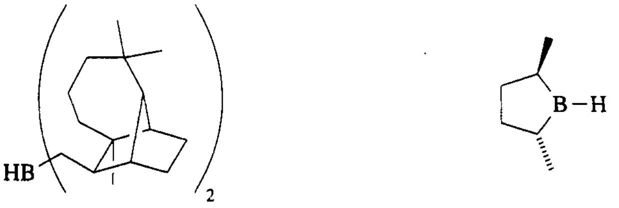

Dilongifolylborane, $Lgf_2BH$
(available cheaply only from
(+)-longifolene)

*trans*-2,5-Dimethylborolane
(available in both enantiomeric forms)

**Figure 10** Structures of some chiral hydroborating agents; see also equation (17), Section 3.10.3.1, for structures of $IpcBH_2$ and $Ipc_2BH$, each of which is cheaply available in either enantiomeric form

Dilongifolylborane is simply prepared by admixture of borane–dimethyl sulfide and 2 equiv. (+)-longifolene in THF, whereupon the product crystallizes out of solution as the dimer, and can readily be separated from the solvent. It is used as a suspension for hydroboration reactions.[141]

Diisopinocampheylborane can be prepared in a similar way from (+)- or (–)-α-pinene, and early work was carried out with reagent so prepared. However, α-pinene is often available only in purities up to *ca.* 95%, so that $Ipc_2BH$ produced by direct hydroboration can also be somewhat impure. Fortunately, equilibration of the reagent (dimethyl sulfide must first be removed if borane–dimethyl sulfide is used for the hydroboration) with α-pinene, at 0 °C over several days, results in preferential incorporation of the major enantiomer of α-pinene into the $Ipc_2BH$. This then becomes available in 98–99% enantiomeric purity.[142]

Monoisopinocampheylborane cannot be directly obtained by controlled hydroboration of α-pinene. However, treatment of $Ipc_2BH$ with one-half equivalent of TMEDA liberates α-pinene and gives a bis-complex of $IpcBH_2$ with TMEDA. Monoisopinocampheylborane of high optical purity is readily obtained from the complex by treatment with trifluoroborane etherate (equation 51).[134] Alternatively, redistribution of $Ipc_2BH$ with further borane can be used to give $IpcBH_2$ (equation 17, Section 3.10.3.1).[53,54,60,143] Again, the reagent is available in essentially 100% enantiomeric purity.[1,134]

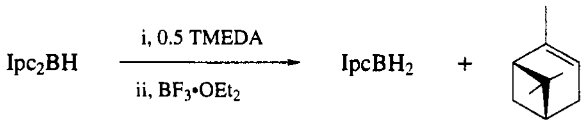

(51)

### 3.10.5.2 Survey of Reactions

Four basic types of simple alkene are susceptible to asymmetric hydroboration, as indicated in Figure 11.

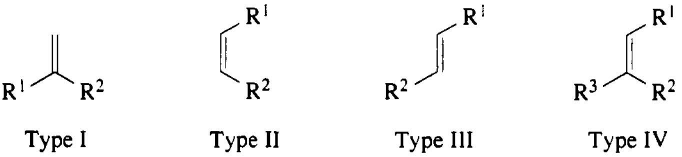

Type I Type II Type III Type IV

**Figure 11** General types of alkenes which undergo asymmetric hydroboration

Types I and IV are easily controlled from a *regioselectivity* viewpoint, but types II and III ($R^1 \neq R^2$) generally require highly regioselective reagents in order to provide a single regioisomer. Type I has the disadvantage that the incipient asymmetric center is at a site relatively remote from the chiral groups on boron and so this type of alkene is the most difficult to influence stereochemically.

No single reagent has the appropriate properties to give high asymmetric induction with all four alkene types. Table 1 gives some results for selected examples of the four types with the four major chiral hydroborating agents.[134,138,142,144]

**Table 1** Asymmetric Induction During Hydroboration[a]

| *Alkene* | *Type* | *Ipc$_2$BH* | *IpcBH$_2$* | *Lgf$_2$BH* | *Dimethylborolane* |
|---|---|---|---|---|---|
| 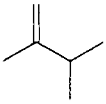 | I | 30 | (1.5)[b] | - | 1.4 |
| 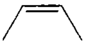 | II | 98.4 | 24 | 78 | 95.2 |
| 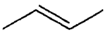 | III | 13 | 73 | - | 97.0 |
| 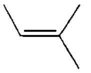 | IV | 14 | 53 | 70 | 94.2 |
| 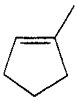 | IV | 22 | 66 | 62 | 97.0 |

[a] Figures are enantiomeric excess (%) for the chiral alcohol obtained following hydroboration–oxidation. [b] Figure refers to 2-methyl-1-butene, not 2,3-dimethyl-1-butene.

As can be seen from Table 1, there is no really successful system for asymmetric hydroboration of type I alkenes. The best available appears to be diisopinocampheylborane. Type II alkenes are the most easily hydroborated in a chiral fashion and diisopinocampheylborane is again the reagent of choice. *trans*-2,5-Dimethylborolane gives comparable results, but is much less convenient to obtain. This reagent is, however, significantly better than other reagents for chiral hydroboration of type III or type IV alkenes. Diisopinocampheylborane is of minimal use in these cases because of competitive retrohydroboration.[1] However, Lgf$_2$BH and IpcBH$_2$ both provide respectable levels of induction for type IV, and IpcBH$_2$ likewise for type III. (Lgf$_2$BH has yet to be tested for type III.)

The monoalkylborane derived from a modified terpene, 2-ethylapopinene, may give somewhat better results than IpcBH$_2$, but at a heavy price in convenience.[145] The reactions of 1-phenylcycloalkenes with IpcBH$_2$ appear to be particularly favorable, 1-phenylcyclopentene giving 85% *ee* and 1-phenylcyclohexene giving 97% *ee* on hydroboration with this reagent.[146] For less favorable alkenes IpcBH$_2$ can be used in a modified manner which allows the product to be upgraded to essentially 100% optical purity.[147] The process consists of reacting the alkene with IpcBH$_2$ (1:1 ratio) in diethyl ether and then crystallizing the dialkylborane dimer, sometimes after 'aging' the mixture, from the solution. A specific diastereoisomer (that produced in predominance during the hydroboration step) crystallizes in reasonable yield (generally around 70%) and almost 100% optical purity (*e.g.* Scheme 11).[147] After washing, the product is available for further transformation.

One particular transformation of IpcBHR$^*$ involves the reaction with acetaldehyde, which results in displacement of α-pinene and production of a chirally pure alkyldiethoxyborane (equation 52).[147] These derivatives can be subjected to a whole range of organoborane reactions, which result in attachment of the chiral unit to other groups, thereby providing a plethora of synthetic possibilities.[148] They can also be reduced to the corresponding chiral alkylboranes (R$^*$BH$_2$), which offer interesting possibilities as alternative chiral hydroborating agents.

Asymmetric hydroborations of several heterocyclic alkenes with diisopinocampheylborane appear to be particularly favorable, resulting in products of almost 100% enantiomeric purity (*e.g.* equation 53).[149] The reagent has also been used in asymmetric syntheses of a number of complex molecules. Discussion is beyond the present scope but a single example is given as an illustration (equation 54).[150]

A number of models have been proposed in order to account for the favored enantiomers produced during asymmetric hydroboration reactions.[4,134] None of the early models were without criticism and were based on scanty theoretical background. Recently, however, much more has become known about the mechanism of the hydroboration reaction (see Section 3.10.6). From these studies it appears that monomeric dialkylboranes (and alkylboranes, *etc.*) are the active intermediates in hydroboration re-

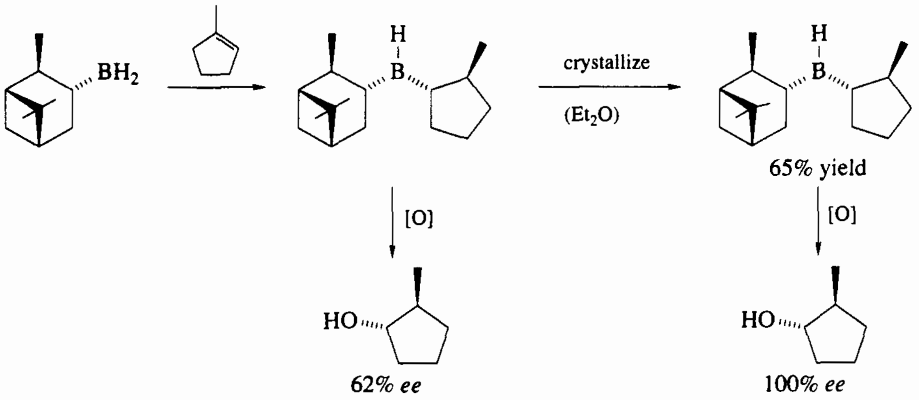
BH₂
H
B
crystallize
(Et₂O)
65% yield
[O]
[O]
HO
HO
62% ee
100% ee

**Scheme 11**

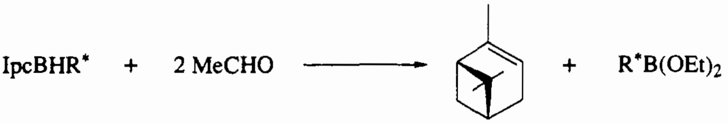
IpcBHR*
+
2 MeCHO
+
R*B(OEt)₂

(52)

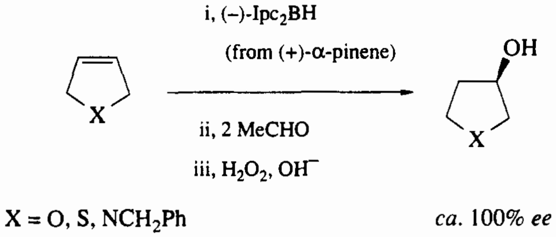
i, (–)-Ipc₂BH
(from (+)-α-pinene)
ii, 2 MeCHO
iii, H₂O₂, OH⁻
X
OH
X
X = O, S, NCH₂Ph
ca. 100% ee

(53)

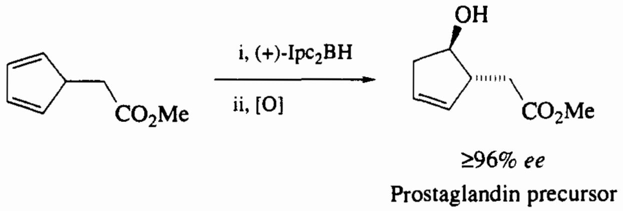
CO₂Me
i, (+)-Ipc₂BH
ii, [O]
OH
CO₂Me
≥96% ee
Prostaglandin precursor

(54)

actions. Calculations which assume gas phase monomeric structures are not, therefore, entirely unreasonable. Using modified MM2 calculations, optimal geometries of transition states have been calculated,[151] and these predict the correct stereochemistries for various asymmetric hydroboration reactions. Figure 12 shows the calculated preferred conformations for the reactions of (*E*)-2-butene with $IpcBH_2$ and of (*Z*)-2-butene with $Ipc_2BH$.

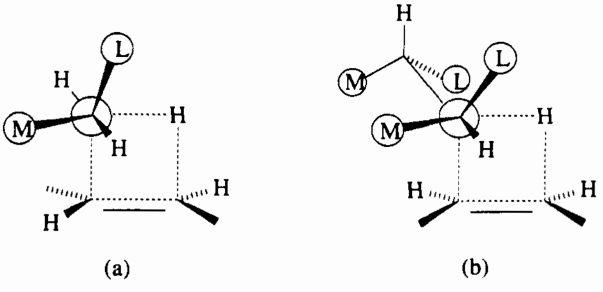
L
H
M
H
H
H
H
H
L
M
L
M
H
H
H
H

(a) (b)

**Figure 12** Calculated (ref. 151) transition state geometries for reactions of: (a) $IpcBH_2$ + (*E*)-2-butene; (b) $Ipc_2BH$ + (*Z*)-2-butene; M represents the $CH_2$ unit and L the CHMe unit adjacent to the boron-bonded carbon atom of each Ipc group

## 3.10.6 MECHANISM OF THE HYDROBORATION REACTION

The early literature concerning the mechanism of the hydroboration reaction is confused and confusing. Only in relatively recent times, through the careful, systematic and painstaking work of Brown and coworkers, has the mechanism become clear.[1,152] The complexity of hydroboration of simple alkenes with borane–THF requires that the problem be simplified if useful kinetic data are to be obtained. Thus, much of this kind of work has utilized either 2,3-dimethyl-2-butene, which reacts readily only as far as the monoalkylborane stage,[153,154] or a monofunctional hydroborating agent such as 9-BBN-H.[155–162] The information provided by such studies has then led to more appropriate determinations of kinetic data for reactions of other hydroborating agents.[163–167] As a result, it is now clear that *all* hydroborations follow a similar mechanistic course involving the reaction of a free, monomeric borane with the appropriate alkene, although the manifestations in terms of kinetics may vary from case to case.

In view of this conclusion it is intriguing that *ab initio* calculations for the reaction of $BH_3 \cdot OH_2$ (a model for a borane–ether complex) with ethylene suggest a direct, $S_N2$-like displacement of water by ethylene, rather than prior dissociation.[168] Previous calculations[169] could be criticized for not taking solvent into account, but the experimental evidence now suggests that the actual hydroborating agent does not involve solvent. This does not imply that solvent or added coordinating agent is unimportant. There is ample evidence that coordinating solvents play a major catalytic role in the reactions.[1,152] However, that role must be in facilitating the *production* of monomer, either by providing a species (the complex) with a lower dissociation energy than the dimer or by reacting directly with the dimer to produce uncomplexed monomer together with complexed monomer.

Most calculations[169a–e] have considered the interaction of unsubstituted borane and ethylene. They suggest the likely formation of a loose three-center complex, which then reorganizes to a four-center transition state[169e] with little or no activation energy. The experimental evidence shows, however, that there may be significant activation energies in reactions of some hindered alkenes with substituted boranes.[155,156]

A few calculations have considered reactions of substituted boranes or ethylenes,[151,169c,f,g,170] and reasonable qualitative accounts of observed selectivities can sometimes be produced.

## 3.10.7 PROTONOLYSIS OF ORGANOBORANES

### 3.10.7.1 General Considerations

The overall process of reduction of an alkene to an alkane, or of reduction of an alkyne to either an alkene or an alkane, *via* hydroboration requires that the intermediate organoborane be protonolyzed (Section 3.10.1.1). However, simple trialkylboranes are remarkably resistant to hydrolysis. For example, trimethylborane gives only 69% of hydroxydimethylborane after 7 h at 180 °C with 1 equiv. of water.[171] Similar resistance is shown to alcohols, phenols and amines, and even mineral acids do not completely protonolyze trialkylboranes with any ease.[4] Thus, aqueous or anhydrous hydrogen bromide removes only one alkyl group from tributylborane after reflux for 1 h.[172]

Anhydrous hydrogen fluoride is much more effective and cleaves all three groups at room temperature in an autoclave.[173] Alternatively, trialkylboranes are readily protonolyzed by carboxylic acids.[174] Two alkyl groups are removed from many trialkylboranes by treatment with excess of an anhydrous carboxylic acid at room temperature, and the third is removed on heating. Typically, the trialkylborane is refluxed for 2–3 h with propanoic acid in diglyme to effect complete conversion (equation 55). The method is considered in greater detail in Section 3.10.7.2. Alternatively, 2,2-dimethylpropanoic acid can be used to catalyze the reaction with water or other protic species.[175,176]

$$R_3B \xrightarrow[\text{diglyme, 165 °C}]{\text{excess EtCO}_2\text{H}} 3\,RH \qquad (55)$$

All three alkenyl groups of a trialkenylborane can be removed at 0 °C with a carboxylic acid,[33,177] and alkenyldialkylboranes undergo preferential protonolysis of the alkenyl group.[178] Stereochemistry is retained during protonolysis, so the sequence hydroboration–protonolysis, applied to internal alkynes, provides a useful, general method for synthesis of (*Z*)-alkenes (Scheme 12).[178]

If acidic conditions are undesirable, alkenyldialkylboranes can be converted into alkenyltrialkylborates by addition of butyllithium; this allows hydrolysis under alkaline conditions.[179] Alternatively, alkenylbo-

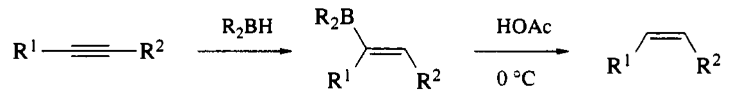

**Scheme 12**

ron compounds have been cleaved by ammoniacal silver oxide,[180] or under the influence of palladium acetate catalysis.[181] Methanolysis can also be used for cleavage of many alkenylboron compounds.[178]

Arylboron compounds appear to be comparable in reactivity to alkenylboron compounds, but comparative data are not available. Alkynylboranes are fairly readily hydrolyzed,[182] as are benzylboranes, particularly when substituted by electron-withdrawing groups on the benzene ring.[8a] However, none of these groups are available *via* hydroboration and so further discussion here is inappropriate.

Allylboron compounds can sometimes be obtained *via* hydroboration of allenes or 1,3-dienes with dialkylboranes (*e.g.* see Section 3.10.4.2). Allylboron compounds are particularly readily hydrolyzed, and hydrolysis is accompanied by transposition of the double bond.[183] For example, tricrotylborane reacts with water at room temperature to give 2 mol of 1-butene and 1 mol of crotyldihydroxyborane (Scheme 13).

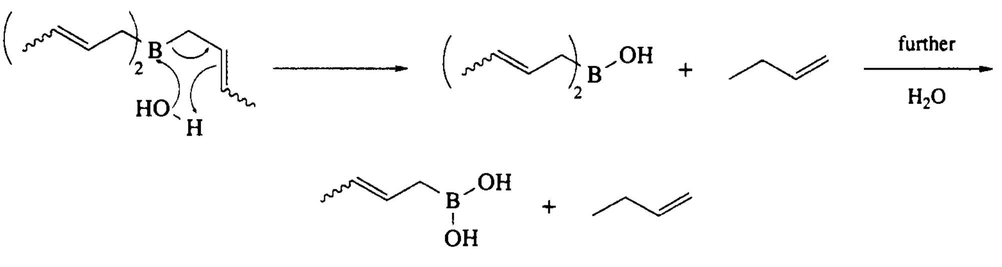

**Scheme 13**

Allyl groups are selectively cleaved from allyldialkylboranes and all three allyl groups can be readily hydrolyzed from a triallylborane.[183]

A number of other reagents, including alkanethiols and β-dicarbonyl compounds, protonolyze organoboranes. However, they are not generally employed in synthetic procedures and are not discussed here. More exhaustive treatment of protonolyses with other reagents is given elsewhere.[4,14] The remaining sections of this chapter deal with the synthetically useful protonolyses of alkylboron compounds with carboxylic acids and of alkenylboron compounds utilizing carboxylic acids or methanol.

### 3.10.7.2 Protonolysis of Alkylboranes with Carboxylic Acids: Synthesis of Alkanes

Carboxylic acids readily cleave the first alkyl group from a trialkylborane at 20 °C. The second group is cleaved somewhat more slowly, and the third requires the use of elevated temperatures.[4,14,174] For practical purposes it is usual to employ around 4 equiv. of propanoic or butanoic acid in refluxing diglyme at 165 °C, though use of other solvents is not precluded. The reaction is quite sensitive to steric factors, and tri-*s*-alkylboranes react substantially more slowly than tri-primary-alkylboranes. Nevertheless, some 'mixed' di-*s*-alkylmono-primary-alkylboranes show only a relatively modest preference for cleavage of the primary-alkyl group upon partial protonolysis, though *t*-alkyl groups are substantially less readily cleaved than primary-alkyl groups.[174,184]

Protonolysis with carboxylic acids differs from that with mineral acids in that it appears to involve coordination of the carbonyl oxygen atom of the carboxylic acid to the boron atom of the organoborane, followed by intramolecular proton transfer (Scheme 14).[174,185] This is presumably the reason for the relative ease of protonolysis with carboxylic acids.

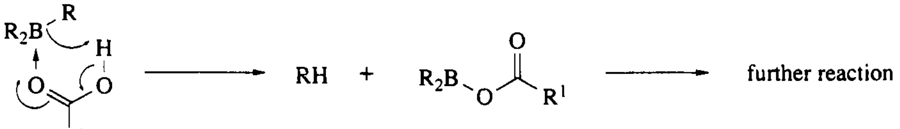

**Scheme 14**

Replacement of alkyl groups by substituents bearing nonbonding electrons renders the boron atom less electrophilic, and this, together with internal coordination from its own acyloxy groups, explains why the acyloxyboron intermediates become progressively less reactive towards protonolysis.[174]

Protonolysis occurs with retention of stereochemistry at the carbon atom originally attached to boron.[174,186] Thus, by use of a deuteriated hydroborating agent (*e.g.* 9-BBN-D) or of a deuteriated carboxylic acid, or both, deuterium atoms can be introduced at specific and predictable locations in a molecule. An example is the conversion of 2-norbornene into *exo,exo*-2,3-dideuterionorbornane (equation 56).[174]

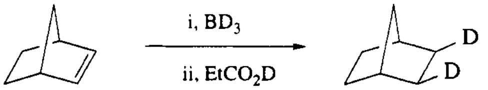

(56)

The protonolysis reaction tolerates functionalities such as halide or ether groups in the alkylborane.[174] However, β-dialkylaminoalkylboron compounds undergo elimination to give alkenes under these conditions (see Section 3.10.1.2).[4,10,11] Also, systems which are intrinsically labile to either acid or heat, such as some terpenoids, may give problems. For example, enantiomerically pure limonene produces 1-menthene which is substantially racemized on hydroboration–protonolysis (Scheme 15).[174]

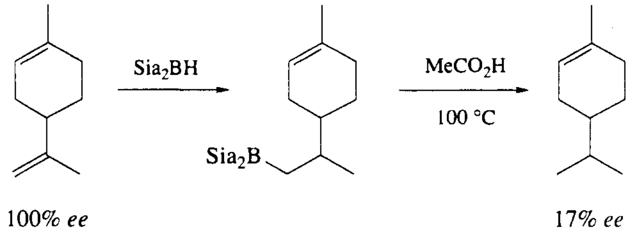

**Scheme 15**

### 3.10.7.3 Protonolysis of Alkenylboranes: Synthesis of Alkenes and Dienes

1-Alkenyldialkylboranes undergo simple protonolysis of the alkenyl group on treatment with hydrochloric acid, but other alkenyldialkylboranes rearrange under these conditions.[187] This problem does not arise on protonolysis with a carboxylic acid, and hydroboration with a dialkylborane followed by protonolysis with a carboxylic acid is therefore of general utility for conversion of alkynes into alkenes.[178] Internal alkynes cleanly give (*Z*)-alkenes (Scheme 12, Section 3.10.7.1).[33,177,178] The process can also be used for stereospecific production of (*E*)-1-deuterio-1-alkenes from terminal alkynes (equation 57).[34,188] Tritiated alkenes have been prepared similarly.[189]

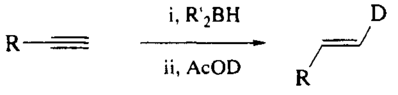

(57)

The combination of deuterioboration and then deuterolysis allows the synthesis of (*Z*)-1,2-dideuterioalkenes and such a process has been used for preparation of dideuteriocycloalkenes (e.g. equation 58).[190–193]

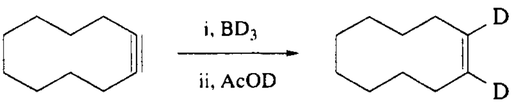

(58)

The protonolysis of alkenylboranes occurs under sufficiently mild conditions that a number of functional groups, including halo, ether and some ester groups, may be tolerated.[14,178b] For example, 1-haloalkynes can be converted into (*Z*)-haloalkenes (*e.g.* equation 59).[95,194]

α,β-Alkynoic esters in most cases undergo the reaction satisfactorily, although a mixture of (*Z*)- and (*E*)-isomers may sometimes occur (*e.g.* equation 60),[195] probably as a result of tautomerism of the intermediate organoborane (see Section 3.10.1.2).

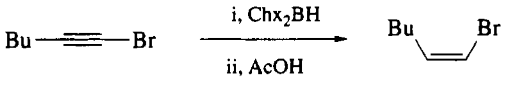
Bu
Br
i, Chx₂BH
ii, AcOH
Bu
Br

(59)

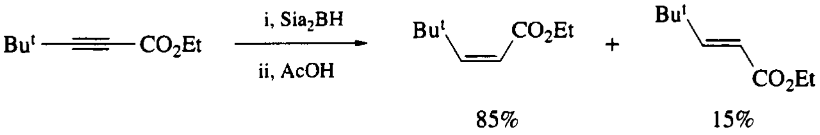
Buᵗ
CO₂Et
i, Sia₂BH
ii, AcOH
Buᵗ
CO₂Et
+
Buᵗ
CO₂Et
85%
15%

(60)

For some functionalized alkenylboranes, cleavage with methanol may be preferable to cleavage with a carboxylic acid. Relatively unhindered alkenyldialkylboranes, such as 9-alkenyl-9-BBNs, are readily cleaved by 1 equiv. of methanol under gentle heating.[178] More hindered derivatives may require catalysis by 2,2-dimethylpropanoic acid, but these mild, almost neutral conditions may be beneficial for acid-labile functionalities. For example, methanolysis has been used for production of enol ethers (*e.g.* equation 61).[196]

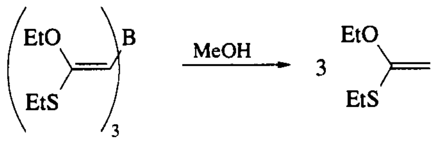
EtO
B
EtS
3
MeOH
3
EtO
EtS

(61)

Advantage may be taken of the selective hydroboration of alkynes as compared to alkenes by dicyclohexylborane or disiamylborane (Section 3.10.4.3) to provide syntheses of dienes and their deuteriated derivatives (*e.g.* equation 62).[34,93,197] Dibromoborane–dimethyl sulfide may be used similarly (Section 3.10.4.4).[112] The approach has been used for the stereospecific synthesis of an allylic hydroxydiene (equation 63).[198]

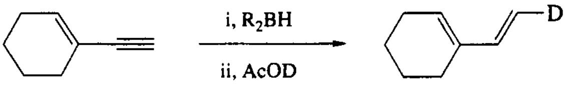
i, R₂BH
ii, AcOD
D

(62)

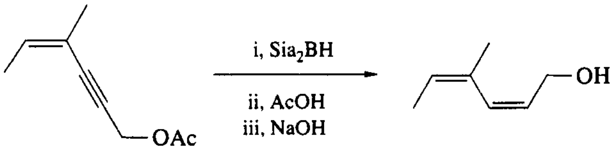
OAc
i, Sia₂BH
ii, AcOH
iii, NaOH
OH

(63)

Diynes can lead to enynes or to dienes depending on the dialkylborane chosen as the hydroborating agent, the stoichiometry and the substitution pattern of the diyne (*e.g.* equations 64 and 65).[93,199]

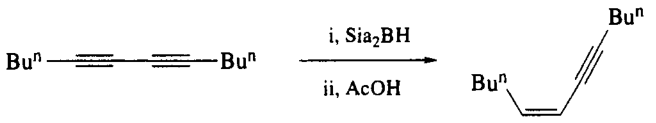
Buⁿ
Buⁿ
i, Sia₂BH
ii, AcOH
Buⁿ
Buⁿ

(64)

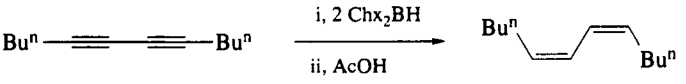
Buⁿ
Buⁿ
i, 2 Chx₂BH
ii, AcOH
Buⁿ
Buⁿ

(65)

Hydroboration–protonolysis is thus a general, stereospecific and versatile route from alkynes to alkenes, enynes and dienes.

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# 3.11

# Hydroalumination of C=C and C≡C

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## 3.11.1 INTRODUCTION

### 3.11.1.1 Nature of the Overall Reaction

The addition of aluminum hydrides to alkenic and alkynic carbon–carbon unsaturation, namely the hydroalumination reaction, is the most versatile route to organoaluminum compounds.[1-3] With unsymmetrically substituted C=C and C≡C linkages, the regiochemistry of such hydroaluminations is governed by the interplay of steric and electronic factors, so that these additions can occur in a highly regioselective manner. The addition of dialkylaluminum hydrides to β-substituted styrenes (**2**), for example, can lead regiospecifically to only one of the possible adducts: for steric reasons, a β-*t*-butyl group produces only isomer (**1**); for polar reasons, a β-phenylsulfonyl group yields exclusively isomer (**3**; equation 1).

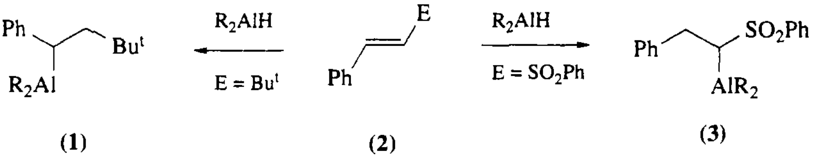

(1)

In addition to the regiochemical course, the stereochemistry of these additions can be highly selective. Illustrative of this characteristic is the behavior of 1-alkynylsilanes (**5**) toward diisobutylaluminum hydride.[4] In the presence of a Lewis base, such as *N*-methylpyrrolidine, the hydroalumination gives >95% of the *syn* adduct (**4**); in the absence of a donor, the adduct has >95% of the *anti* configuration (**6**; equation 2).

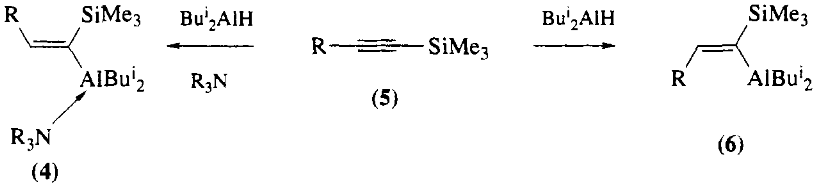

(2)

Finally, the high locoselectivity[5] or chemoselectivity of hydroalumination toward substrates having both C=C and C≡C bonds is exemplified by the reaction of diisobutylaluminum hydride with 1-octen-7-yne (**7**).[6] The only organoaluminum product detected (**8**) was that of a regioselective *syn* stereospecific addition to the C≡C bond (equation 3).

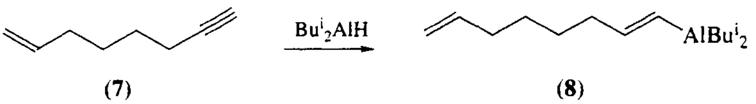

(3)

### 3.11.1.2 Historical Context and Development

The discovery of the hydroalumination reaction by Ziegler and Gellert in 1949 was the culmination of a series of experiments on the thermal stability of metal alkyls begun by Karl Ziegler in the early 1930s.[7] During an attempt to distill ethyllithium, Ziegler found that the compound decomposed over 100 °C into ethylene and lithium hydride; the ethylene reacted, in steps, with the ethyllithium to give higher *n*-alkyllithiums and these, in turn, eliminated lithium hydride to produce a mixture of higher α-alkenes (Scheme 1).[8]

If lithium hydride would add to ethylene, *in situ*, Ziegler speculated, then the various other steps given in Scheme 1 would become accessible and lithium hydride could thereby catalyze the conversion of ethylene into a mixture of higher alkenes. Indeed, at over 200 °C lithium hydride did begin to effect the oligomerization of ethylene into higher alkenes. However, because of allylic lithiation (**9**) and subsequent elimination of LiH, conjugated dienes (**9a**) were formed and they polymerized to resins that coated the LiH catalyst and thereby retarded the ethylene oligomerization (equation 4).

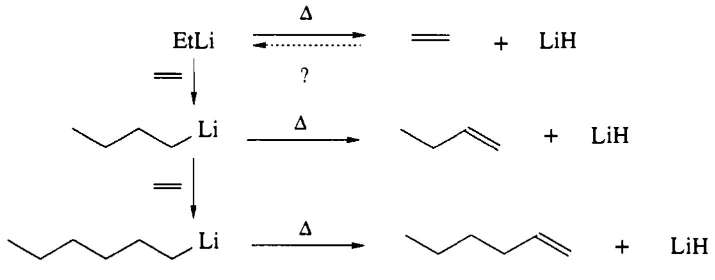

**Scheme 1**

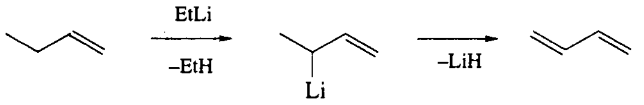

(9) (9a) (4)

With the purpose of employing a more soluble form of complexed lithium hydride in such a process, Ziegler and Gellert heated ethylene in ether under pressure at 120–140 °C with LAH, which had been prepared for the first time by Schlesinger and coworkers.[9] To Ziegler's gratification LAH was smoothly converted into lithium tetraethylaluminate (**10**), which could be isolated in high yield as a crystalline adduct. As proof of structure, the same adduct was also synthesized by the admixture of the lithium and aluminum ethyl derivatives in a 1:1 ratio (Scheme 2). This study represents the first authenticated instance of hydroalumination.

$$4 = \quad + \quad LiAlH_4 \xrightarrow{120\text{–}140\ ^\circ C} \underset{(\mathbf{10})}{LiAlEt_4} \longleftarrow EtLi \quad + \quad Et_3Al$$

**Scheme 2**

As part of the same comprehensive study Ziegler and Gellert also showed that at 180–200 °C complex (**10**) did catalyze the oligomerization of ethylene into higher α-alkenes. Subsequently, the unstable $AlH_3$ was found to add even more readily to ethylene and other α-alkenes (**11**) regioselectively to provide quantitative yields of the tri-*n*-alkylaluminum (**12b**). This reaction is thus the prototype for the hydroalumination of unsaturated hydrocarbons (equation 5).

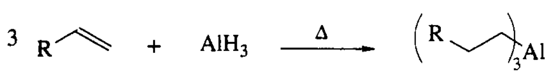

(11) (12a) (12b) (5)

Since the hydroalumination of an alkene is a readily reversible process, especially at high temperatures, with β,β-disubstituted alkenes or in the presence of nickel,[10] one need not employ the unstable $AlH_3$ (**12a**) as such but can instead use the commercially available triisobutylaluminum (**13a**).[11] This interesting alkyl can be synthesized directly from activated aluminum metal, hydrogen and isobutylene, and when it is heated at 100–110 °C, it in turn dissociates into the dialkylaluminum hydride and isobutylene. Therefore, $AlH_3$ can be transferred from (**13a**) to a less volatile α-alkene (**11**) simply by heating (**13a**) and (**11**) and permitting the isobutylene to escape. This hydroalumination by $AlH_3$ transfer is a widely applicable synthetic method for trialkylaluminums (**12**; Scheme 3).

The hydroalumination of alkynes was first observed by Wilke and Müller in 1955, when they demonstrated that dialkylaluminum hydrides added to disubstituted alkynes stereospecifically in a *syn* fashion (**13b**).[12,13] Subsequently, Zakharkin and coworkers were able to add $NaAlH_4$ to phenylacetylene by employing 5% of $Bu^i{}_2AlH$ and diglyme as a solvent, but did not ascertain the stereochemistry of reaction.[14] Some 10 years later, in 1966, Slaugh found that LAH in refluxing THF–diglyme mixtures, hydroaluminates such alkynes exclusively in an *anti* manner (**14**; equation 6).[15,16]

During the succeeding decade the regiochemistry and stereochemistry for the hydroalumination of various heteroatom-substituted 1-alkynes was extensively studied and established by the laboratories of Eisch and of Zweifel.[17]

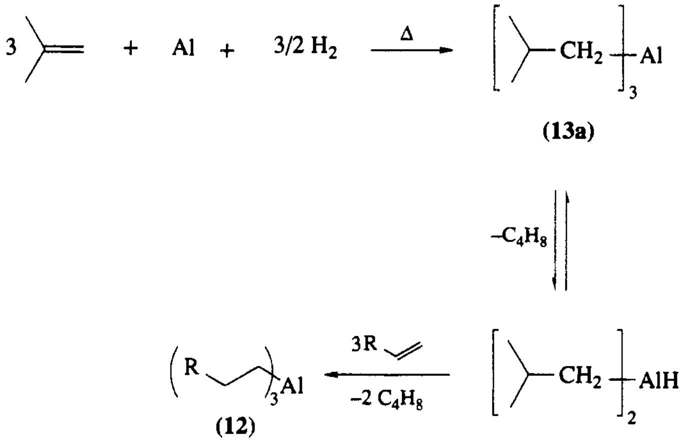

(13a)

(12)

Scheme 3

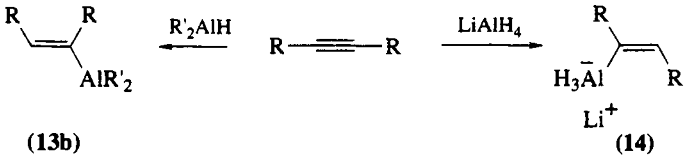

(13b) (14)

(6)

### 3.11.1.3 Sources of the Aluminum Hydrides

The most commonly employed hydroaluminating agents, DIBAL-H and LAH, are commercially available in a wide variety of ether and hydrocarbon solvents or as the pure reagents.[18] For reactions where a different $R_2AlH$ may be deemed advisable or where the deuterioaluminating agent $R_2AlD$ is required, the corresponding $R_2AlCl$ can be treated with MH or MD (M = Li, Na; equation 7).[19,20]

$$\mathrm{Bu^i_2AlD} \xleftarrow[\mathrm{R\,=\,Bu^i}]{\mathrm{LiD/Et_2O}} \mathrm{R_2AlCl} \xrightarrow[\mathrm{R\,=\,Et}]{\mathrm{NaH}} \mathrm{Et_2AlH} \qquad (7)$$

Aluminum hydride, $AlH_3$, and dichloroaluminum hydride, $Cl_2AlH$, can be obtained as etherates by the original method of Schlesinger and coworkers[9] and can be employed for hydroalumination (equation 8).[21]

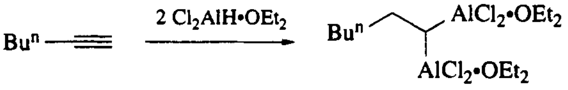

(8)

Lithium trialkylaluminum hydrides, such as lithium diisobutyl(methyl)aluminum hydride (**15**), which can be readily prepared by the interaction of diisobutylaluminum hydride with methyllithium in DME, are useful for the *anti* hydroalumination of internal alkynes (equation 9).[22]

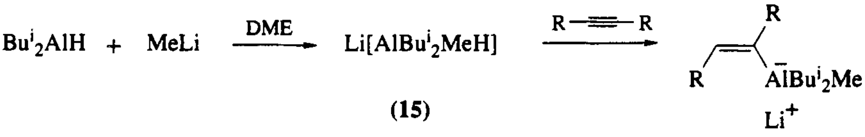

(9)

In addition to simple and complex aluminum hydrides, aluminum alkyls with β-branched chains often serve as hydroaluminating agents themselves, because of their tendency to form Al—H bonds during reaction by the thermal or nickel-catalyzed loss of alkene (*cf.* Scheme 3; equation 10).[23]

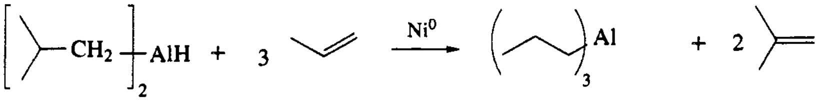

(10)

### 3.11.1.4 Uncatalyzed and Catalyzed Hydroalumination

Typically, hydroaluminations are carried out by heating the substrate with $R_2AlH$ in hydrocarbon media or with $MAlR_3H$ in higher boiling, strongly donating ethers.[17] Metal salts of zirconium,[23] nickel,[24] titanium,[25] and uranium[26] have been found to increase the rate of hydroaluminations. It should be noted, however, that such catalyzed reactions may exhibit a regioselectivity and stereoselectivity different from those of the uncatalyzed hydroalumination.[24] Thus, the hydroalumination of 1-phenylpropyne by $Bu^i_2AlH$ gives an 82:18 ratio of regioisomers (**16**) and (**17**) in the thermal reaction, while the nickel-catalyzed reaction yields a 56:44 ratio of (**16**) and (**17**; equation 11). Furthermore, the uncatalyzed reaction yields only *cis*-1-phenylpropene upon hydrolysis, while the nickel-catalyzed process produces 1-phenylpropene having 6% of the *trans* isomer.

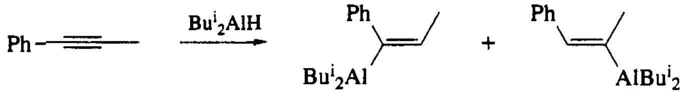

(**16**) (**17**)

thermal: 82 : 18

Ni catalyzed: 56 : 44

(11)

It is noteworthy that the transition metals that serve as hydroaluminating catalysts are also active in establishing the equilibrium between aluminum alkyls and their decomposition products, aluminum, hydrogen and alkene (equation 12). Accordingly, these metals, in addition to hafnium, niobium, vanadium, scandium and lanthanum, have found use as activators for the direct synthesis of aluminum alkyls (equation 12, to the left).[2] Probably most of these metal salts will also be capable of accelerating the hydroalumination reaction.

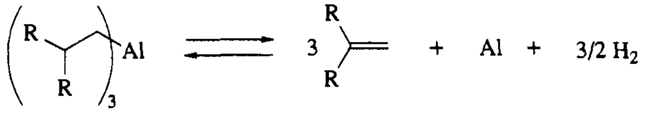

(12)

### 3.11.1.5 Potential of Resulting Organoaluminum Reagents in Organic Synthesis

Depending upon the nature of the hydroaluminating agent ($R_2AlH$, $MAlR_3H$ or LAH), the organoaluminum product will have one to four new carbon–aluminum bonds at which cleavage or insertion reactions can be conducted. Two such reactions are protodealumination (equation 13) and carbonation (equation 14).[27]

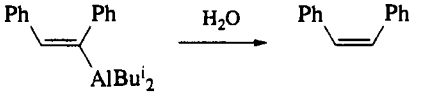

(**18**) (**19**)

(13)

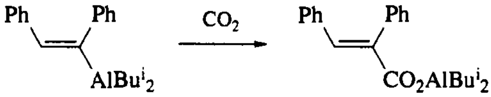

(**18**) (**20**)

(14)

Important aspects of such reactions are: (i) the configuration at the original carbon–aluminum bond is usually retained in such cleavages or insertions; (ii) not all three carbon–aluminum bonds undergo reaction with some reagents ($CO_2$, $R_2CO$, RX, *etc.*), but vinylic or alkynic carbon–aluminum bonds are generally more reactive than alkyl carbon–aluminum bonds. Thus, in (**18**) carbonation leads to a 96% yield of *cis*-α-phenylcinnamic acid [as salt (**20**)]; any organic products resulting from the R-group in the hydroaluminating reagent itself (*e.g.* isobutyl) should not interfere with isolating the pure desired product. In equations (13) and (14) the isobutane formed by hydrolysis or any isovaleric acid resulting from carbonation can readily be separated from the *cis*-stilbene (**19**) or from the *cis*-α-phenylcinnamic acid [from salt (**20**)] by volatility; and (iii) if the vinyl carbon–aluminum bond of the hydroalumination adduct itself is insufficiently reactive toward certain cleavage agents, it may be activated by first forming the tetrasubstituted aluminate complex with methyllithium (Scheme 4).[28]

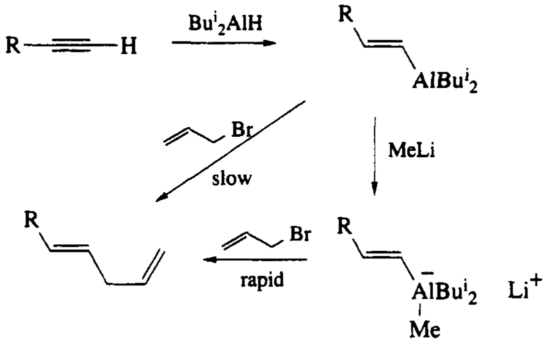
R—≡—H
$Bu^i_2AlH$
R
$AlBu^i_2$
MeLi
Br
slow
R
Br
rapid
R
$AlBu^i_2$
Li+
Me

Scheme 4

In light of the foregoing, the utility of hydroalumination in selective organic synthesis will be more applicable to alkynic substrates, where the greater chemical reactivity of the resulting vinyl–aluminum bond will permit the formation of derivatives even with those reagents ($CO_2$, $R_2CO$, RX) not cleaving all available carbon–aluminum bonds. Alkenic substrates generally will be less suitable in hydroalumination reactions where the adduct is then required to react with a selective reagent (*e.g.* $CO_2$) that attacks at most one carbon–aluminum bond. Thus the similar reactivity of two competing alkyl–aluminum bonds will inevitably give a mixture of products and low yields of the desired derivative (Scheme 5). Both (**21**) and (**22**) are unreactive toward further insertion of $CO_2$ under mild conditions.[29]

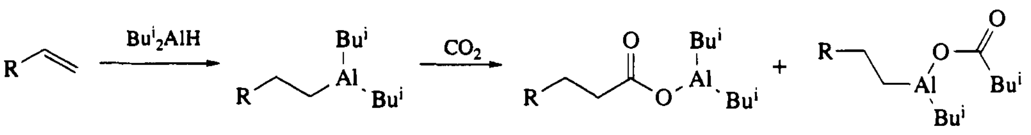
R
$Bu^i_2AlH$
R
Al
$Bu^i$
$Bu^i$
$CO_2$
R
O
O
Al
$Bu^i$
$Bu^i$
+
R
O
O
Al
$Bu^i$
$Bu^i$

(**22**) (**21**)

Scheme 5

Only with reagents that attack all available carbon–aluminum bonds ($H_2O$, $D_2O$, $O_2$, $X_2$, $SO_2$, *etc.*) will the hydroalumination of alkenic substrates and the derivatization of such adducts prove useful. That two of three C—Al bonds of adduct (**23**) are expended in the formation of side products, which have to be separated, may be an acceptable price to pay for the convenient, high-yielding generation of a desired specifically deuteriated reduction product, (**24**) or (**25**),[30] primary alcohol (**26**),[31] primary halide (**27**)[32] or sulfinic acid.[29] Of course the isobutylated side products should, in each case, be easily separable (Scheme 6).

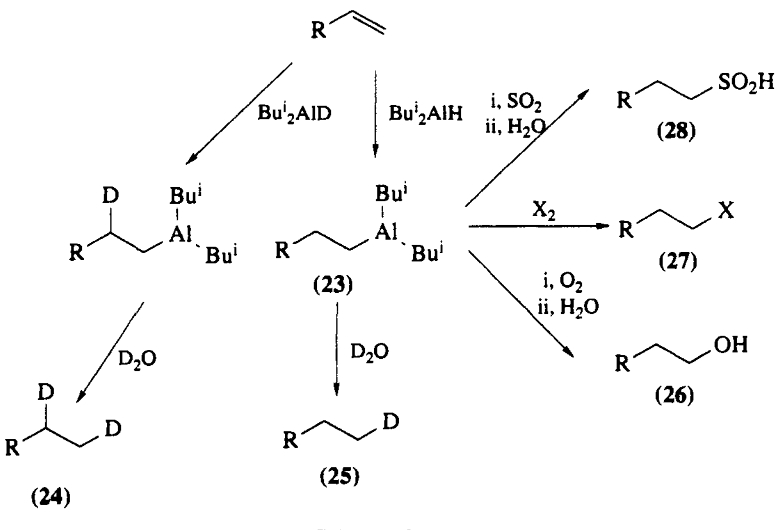
R
$Bu^i_2AlD$
$Bu^i_2AlH$
i, $SO_2$
ii, $H_2O$
R
$SO_2H$
(28)
D
$Bu^i$
Al
$Bu^i$
R
$Bu^i$
Al
$Bu^i$
R
(23)
$X_2$
R
X
(27)
i, $O_2$
ii, $H_2O$
$D_2O$
$D_2O$
R
OH
(26)
D
R
D
R
D
(25)
(24)

Scheme 6

## 3.11.2 SCOPE OF HYDROALUMINATION

### 3.11.2.1 Suitable Alkenic Substrates

The hydroalumination of alkenes, either by direct addition of $R_2AlH$ or by aluminum hydride transfer from triisobutylaluminum (Scheme 3), proceeds readily and without catalysis with terminal alkenes, whether or not there is a chain branch in the β-position (Table 1).

**Table 1** Scope of Suitable Alkenic Substrates for Hydroalumination with Dialkylaluminum Hydrides[11,19]

| *Substrate* | *Ease of addition* |
|---|---|
| $RCH{=}CH_2$ (R = *n*-alkyl) | Very fast |
| Cycloalkenes ($C_4$–$C_{11}$) | Fast ($C_4$, $C_8$)<br>Slow ($C_5$, $C_7$, $C_9$)<br>Very slow ($C_6$, $C_{10}$, $C_{11}$) |
| $RR'C{=}CH_2$ (R, R′ = alkyl, aryl) | Fast |
| $RR'C{=}CH_2$ (R, R′ = alkyl, cycloalkyl) | Less fast |
| β-Pinene | Less fast |
| Camphene | Less fast |
| Limonene | Less fast |
| $RCH{=}CHR$ | Very slow |

Thus, all α-alkenes can be readily converted into the tri-*n*-alkylaluminum (>95%) by heating with about 0.33 mol equiv. of $Bu^i_2AlH$ or $Bu^i_3Al$, until isobutylene ceases to be evolved. With β-pinene hydroalumination can also be achieved in this manner but the result is the formation of $R'_2AlH$, rather than $R'_3Al$. At the temperature of reaction, such branched $R'_3Al$ tend to eliminate 1 mol of alkene (equation 15).[33]

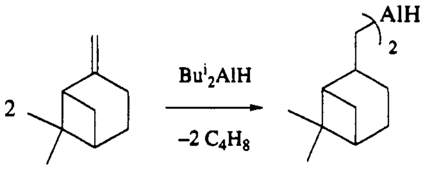

(15)

With alkenes having internal C═C bonds, hydroalumination is disfavored by both kinetic and thermodynamic factors, and the uncatalyzed reaction is generally unfeasible. The hydroalumination of internal alkenes can be catalyzed by the addition of titanium(IV) alkoxides but the same catalysts also promote the isomerization of the secondary aluminum alkyls generated into their primary isomers (equation 16).[34]

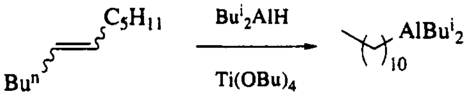

(16)

The hydroalumination of cycloalkenes exhibits two interesting minima in relative rates toward diethylaluminum hydride. The half-life (in min) of a 3:1 ratio of $Et_2AlH$ and cycloalkene at 78 °C varied thus with ring size:[19] $C_4$, 40; $C_5$, 200; $C_6$, 1880; $C_7$, 110; $C_8$, 86; $C_9$, 280; $C_{10}$, 2500; $C_{11}$, 1350. The reactivity of cycloundecene is approximately that of an open-chain internal alkene. The low reactivity of cyclohexene can be ascribed to the eclipsing repulsions generated in the transition state by the *syn* attack of $Et_2AlH$ on the C═C bond (equation 17).[35]

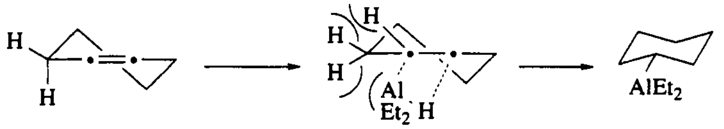

(17)

Such repulsions would be distinctly less with the more planar $C_4$ and $C_5$ rings, as well as with the less rigid $C_7$ and $C_8$ rings. The minimum in reactivity encountered with the $C_{10}$ ring is indicative that transannular repulsions may be restricting access to one face of the C═C bond, while also generating further transannular repulsions as the vinylic hydrogens bend away from the attacking $Et_2AlH$ molecule (**29**).

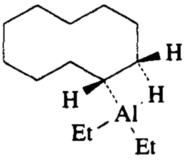

**(29)**

In contrast with the impracticality of hydroaluminating open-chain internal alkenes, all the unsubstituted cycloalkenes can be usefully hydroaluminated, with titanium catalysis if need be, since isomerization of the C═C bond is of no significance.

### 3.11.2.2 Suitable Alkynic Substrates

As a class alkynes are much more reactive in hydroalumination than are alkenes. Hence, both terminal and internal alkynes react at feasible rates with both dialkylaluminum hydrides in alkanes and lithium aluminum hydrides ($LiAlR_nH_{4-n}$) in ethers. Selected examples of such additions are presented in Table 2. With alkyl or aryl substituents, it should be noted that $R_2AlH$ adds in a kinetically *syn* manner, (**5**; equation 2) and (**7**; equation 3), and LAH yields the *anti* adduct (**14**; equation 6).

**Table 2** Scope of Suitable Alkynic Substrates for Hydroalumination with $R'_2AlH$ or $MAlR'_3H$ Reagents

| *Substrate* | *Reagent* | *Product(s)* | *Ref.* |
|---|---|---|---|
| $RC\equiv CH$ | $R'_2AlH$ | 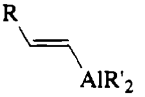 | 30 |
| $RC\equiv CE$ (E = $SiMe_3$, $GeMe_3$) | $R'_2AlH$ | 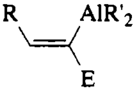 | 4 |
| $RC\equiv CE$ | $R'_2AlH{\bullet}NR'_3$ | 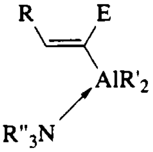 | 4 |
| $RC\equiv CR$ (R = alkyl, aryl) | $R'_2AlH$ | 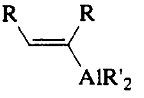 | 12, 13, 30 |
| $RC\equiv CR$ | $LiAlMeBu^i_2H$ | 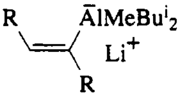 | 22 |
| $RC\equiv CR''$ | $R'_2AlH$ | 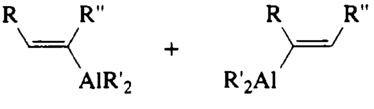 <br>mixture of regioisomers | 39, 40 |
| $H_2C{=}CH(CH_2)_4C\equiv CH$ | $R'_2AlH$ | 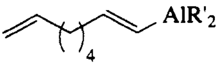 | 6 |

Although reactivity is not a problem with alkynes, the occurrence of side reactions can raise serious difficulties in preparative applications. In addition to the general aspects of reagent selectivity, which are discussed in Section 3.11.2.6, alkynes present the possibility of specific reactions competing with hydroalumination. First, terminal alkynes may undergo alumination (proton–aluminum exchange), which becomes especially prominent with $LiAlR_nH_{4-n}$ (equation 18)[36] and $R_2AlH–R'_3N$ complexes (equation 19).[37]

$$MAlH_4 + 4\ {\equiv}{-}R \longrightarrow M\left({-}{\equiv}{-}R\right)_4 + 4\,H_2 \qquad (18)$$

M = Li, Na, K; R = alkyl, aryl

$$2\,Et_2AlH{\bullet}NEt_3 + {\equiv} \xrightarrow{-2H_2} Et_2Al{-}{\equiv}{-}AlEt_2{\bullet}2Et_3N \qquad (19)$$

Secondly, alkynes can add 2 equiv. of $R_2AlH$ with a regioselectivity strongly favoring the geminal dialuminum derivative (equations 8 and 20).[13]

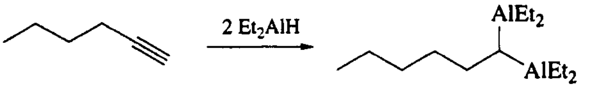

(20)

Thirdly, although proton–aluminum exchange may not occur with the starting $R_2AlH$ (equation 19), it may be significant between the hydroalumination adduct and the unconsumed terminal alkyne (equation 21).[38]

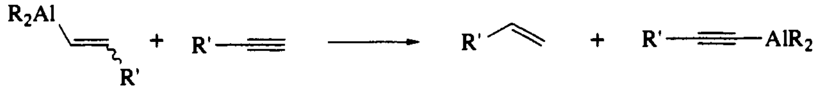

(21)

Fourthly, the vinylic hydroaluminum adduct (**30**) can either insert a second mole of (**30**) into the vinyl–aluminum bond and thereby dimerize (equation 22),[13] or it can insert a second mole of alkyne (equation 23).[13,39]

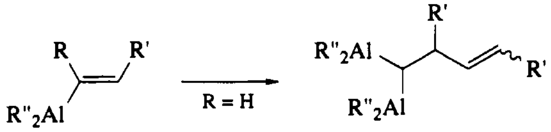

**(30)**

(22)

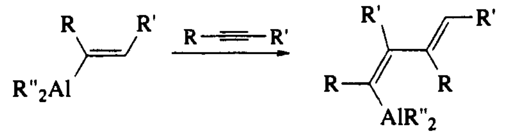

**(30)**

(23)

Finally, in uncatalyzed hydroaluminations with organosubstituted alkynes, the initially formed *syn* adduct can isomerize to the more stable *anti* adduct by way of the dialuminoalkane (equation 24).[40]

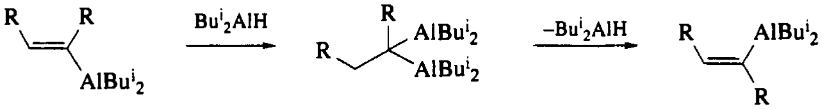

(24)

Despite this gamut of competing reactions, reaction conditions can usually be found for preparing either the *syn* or the *anti* adduct of many terminal alkynes with high regio- and stereo-selectivity (Table 2). Failing this the 1-alkynylsilanes can be employed as masked forms of 1-alkynes. In hydroalumination reactions, such silanes have little or no tendency to undergo the side reactions (equations 19–24) to which terminal alkynes are prone. After the silyl-masked alkyne has been hydroaluminated and thereupon derivatized, the silyl group can be removed from the product (Scheme 7).[41]

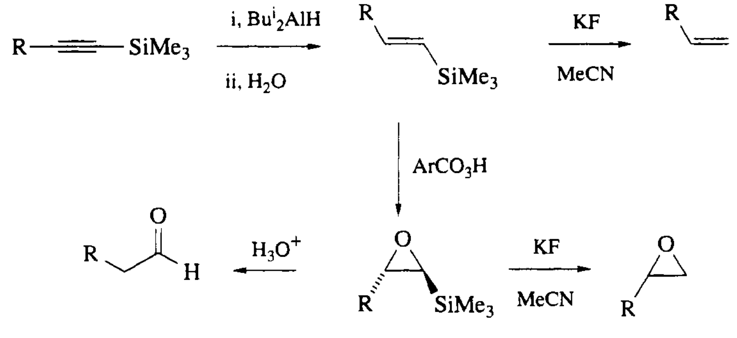

**Scheme 7**

Although most internal alkynes can be readily hydroaluminated by $R_2AlH$ or LAH (equation 6), the reaction is generally preparatively useful only with symmetrically substituted alkynes. The addition of $R_2AlH$ is stereoselectively *syn* and that of LAH stereoselectively *anti*, but the reaction has a low regioselectivity and thus gives a mixture of regioisomers (equation 11). This problem may be alleviated by enhancing steric factors through the use of a bulky substituent on the C≡C bond (equation 25)[42] but cannot be solved for every internal alkyne.

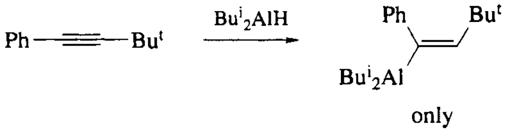 (25)

### 3.11.2.3 Selective Hydroalumination with Multiunsaturated Substrates

As will become clear in Section 3.11.2.4 many polar and unsaturated functional groups interfere with the hydroalumination of carbon–carbon unsaturation. Hence, the selectivity considered here is the locoselectivity between two different C=C bonds, between a C=C and a C≡C bond or between two C≡C bonds in the same molecule. If such competing groups are not in conjugation, locoselective monohydroalumination of just one such groups can often be easily achieved in the following situations: (i) in dienes, where a terminal C=C bond reacts preferentially;[43] (ii) in alkenynes, where the greater reactivity of the C≡C group leads to selective attack;[6] and (iii) in 1,*n*-alkadiynes, where a terminal C≡C group undergoes addition (Table 3).[44]

With conjugated or cumulated C=C bonds,[45] one bond may respond locoselectively but with the formation of regioisomers as well (**31** and **32**; equation 26). Since one of the regioisomers (**32**) is an allylic aluminum compound, it can generate its allylic isomer (**33**) as well.

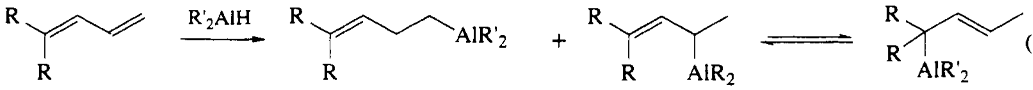 (26)

**(31)** **(32)** **(33)**

### 3.11.2.4 Interfering Functional Groups

Many functional groups commonly encountered in organic molecules can readily react with the hydroaluminating agent before the carbon–carbon unsaturation does. These groups include: (i) proton sources that cleave the Al—H bond, such as OH, SH, certain NH, $CO_2H$ and even alkynic C—H (*cf.* equation 18); (ii) oxidants that attack the Al—H linkages, such as $RO_2R$, $RS_2R$, $NO_2$, RX, $RSO_2X$ and $R_3PO$; (iii) electrophiles which add Al—H bonds, such as C=O, C=S, C=N and C≡N derivatives, epoxides, aziridines and episulfides; and (iv) other organometallic compounds, such as RLi[46] or subval-

**Table 3** Selective Hydroalumination of Multiunsaturated Substrates with Dialkylaluminum Hydrides

| *Substrate* | *Product(s)* | *Ref.* |
|---|---|---|
| $Ph_2C{=}CH_2$ | $Ph_2CHCH_2AlR'_2$ | 45 |
| $Ph_2C{=}C{=}CH_2$ | 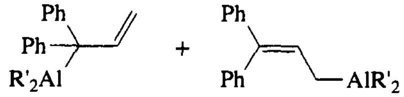 | 45 |
| $Ph_2C{=}CHCH{=}CH_2$ | 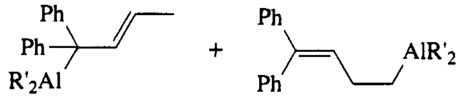 | 45 |
| $RCH{=}CH(CH_2)_nCH{=}CH_2$ | $RCH{=}CH(CH_2)_nCH_2CH_2AlR'_2$ | 166 |
| $MeCH{=}CHC{\equiv}CEt$ | 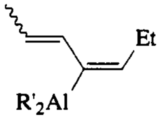 | 163 |
| $RC{\equiv}CCH_2C{\equiv}CSiMe_3$ | 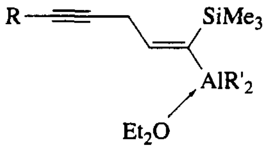 | 164 |
| $RC{\equiv}CC{\equiv}CSiMe_3$ | 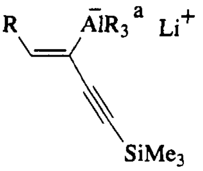 | 164 |

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[a] Hydroaluminating agent : $LiAlBu^nBu^i{}_2H$

ent transition metal complexes (alkene–nickel(0) reagents),[47] which can alter (equation 9) or even destroy (equation 27) the hydroaluminating agent.

$$LiAlH_4 + bipyNiCOD \xrightarrow{THF} LiAlH_2{\bullet}Ni{\bullet}bipy + H_2 \qquad (27)$$

In certain cases, by working with special solvents at low temperatures, one may be able to hydroaluminate a C≡C rather than a competing C≡N group (equation 28)[48] or a C≡C group in addition to a reactive OH group (equation 29).[49]

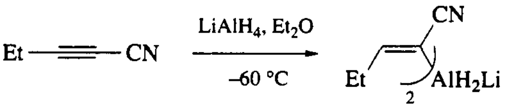

(28)

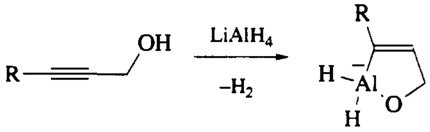

(29)

### 3.11.2.5 Side Reactions

The extent and types of interfering reactions during hydroalumination of alkynes were examined in Section 3.11.2.2 (equations 18–24). To a lesser degree two of these reactions are also encountered in Al—H additions to alkenes and cycloalkenes. Analogous to the reductive dimerization of alkynes (equation 23) is the dimerization of α-alkenes by $Bu^i_2AlH$, which can be conducted catalytically in hydride to give high yields of dimer (equation 30).[50]

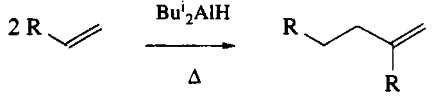

(30)

The second side reaction with alkenes is the configurational change at the $sp^3$-hybridized carbon–aluminum bond in the hydroalumination adduct (equation 31).[51]

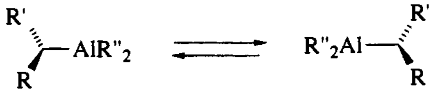

(31)

Thus, 1,1-dimethylindene (**34**) was subjected to hydroalumination with $Bu^i_2AlD$ in diethyl ether solution. The initially formed adduct was shown to have the *syn* configuration (**35**) by cleaving it with $D_2O$ and demonstrating that only *cis*-dimethylindan-2,3-$d_2$ (**36**) was formed (Scheme 8). In the absence of donor solvents during the hydroalumination, a 1:1 mixture of (**35**) and its epimer were formed, and deuteriolytic work-up gave both the *cis*- and *trans*-1,1-dimethylindanes-2,3-$d_2$. This study demonstrates that the hydroalumination of C=C bonds occurs in a kinetically controlled *syn* fashion and $sp^3$-hybridized carbon centers bonded to tricoordinate aluminum undergo rapid inversion of configuration.[52] If one hopes to attain stereoselective cleavages of such C—Al bonds with retention of configuration, the aluminum center must be kept tetracoordinate. However, even this precaution does not always assure a stereoselective reaction (*cf.* Section 3.11.4).

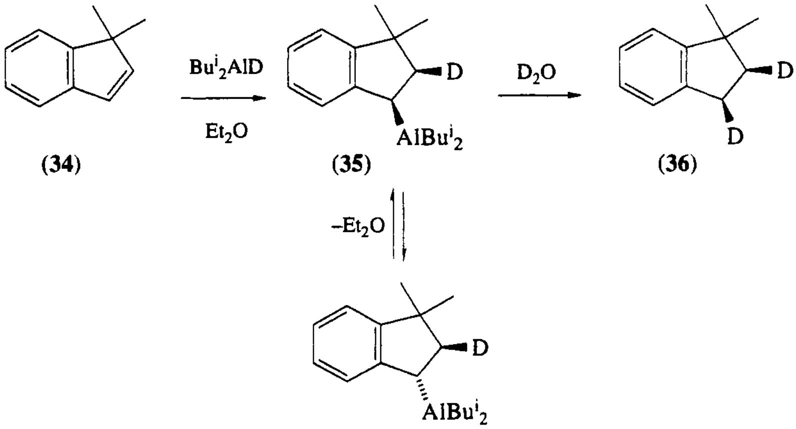

(**34**) (**35**) (**36**)

**Scheme 8**

### 3.11.2.6 Selectivity

#### *3.11.2.6.1 Locoselectivity*

The main locoselective features of hydroalumination, which are discussed in some detail in Section 3.11.2.3 are: (i) C≡C bonds are attacked in preference to C=C bonds; (ii) terminal HC≡C and $H_2C$=CH groups are hydroaluminated much more rapidly than internal C≡C and CH=CH linkages; and (iii) electron-releasing substituents on the carbon–carbon unsaturated group increase the rate of hydroalumination (Table 4).[53] Illustrative are the relative initial rates for PhC≡CE: with E = Ph, Me, H, SEt, Bu$^t$, TMS and NMe$_2$, the rates increase in the same order: 1.0 < 1.1 < 12 < 25 < 28 < 185 < 431 < 19000. By contrast, steric factors appear to have little effect on rate; di-*t*-butylacetylene reacts with Bu$^i_2$AlH some 20 times faster at 30 °C than does di-*n*-butylacetylene.

**Table 4** Relative Reactivity of Alkynes towards Hydroalumination with Diisobutylaluminum Hydride

| *Alkyne* | *Relative reactivity*[a] | *Reactivity ratio*[b] |
|---|---|---|
| $PhC\equiv CH$ | 11.8 | 10.2 |
| $PhC\equiv CMe$ | 1.16 | |
| $n\text{-}C_6H_{13}C\equiv CH$ | 115 | 18.3 |
| $Pr^nC\equiv CPr^n$ | 6.26 | |
| $n\text{-}C_8H_{17}C\equiv CH$ | 117 | 16.8 |
| $Bu^nC\equiv CBu^n$ | 6.92 | |
| $Bu^n\equiv CBu^n$ | 6.92 | 1.11 |
| $Pr^nC\equiv CPr^n$ | 6.26 | |
| $n\text{-}C_8H_{17}C\equiv CH$ | 117 | 1.01 |
| $n\text{-}C_6H_{13}C\equiv CH$ | 115 | |
| $Bu^tC\equiv CBu^t$ | 151 | 21.8 |
| $Bu^nC\equiv CBu^n$ | 6.92 | |
| $PhC\equiv CBu^t$ | 27.8 | 24.0 |
| $PhC\equiv CMe$ | 1.16 | |
| $CyC\equiv CMe$ | 8.22 | 7.10 |
| $PhC\equiv CMe$ | 1.16 | |
| $p\text{-}MeC_6H_4C\equiv CC_6H_4Me\text{-}p$ | 9.84 | 1.52 |
| $PhC\equiv CPh$ | 6.47 | |
| $PhC\equiv CPh$ | 1.00 ($k_0$) | 1.00 |
| $PhC\equiv CMe$ | 1.16 | 1.16 |
| $PhC\equiv CH$ | 11.8 | 11.8 |
| $PhC\equiv CSEt$ | 24.6 | 24.6 |
| $PhC\equiv CBu^t$ | 27.8 | 27.8 |
| $PhC\equiv CAlPh_2$ | 185 | 185 |
| $PhC\equiv CTMS$ | 431 | 431 |
| $PhC\equiv CNMe_2$ | 19 000 | 19 000 |

[a] Relative reactivities were determined by the method of initial rates and normalized to 35 °C. [b] For pairs of compounds as indicated; for the last eight entries, relative to PhC≡CPh = 1.

### *3.11.2.6.2 Regioselectivity*

The highest regioselectivity in hydroaluminating unsymmetrically substituted C═C and C≡C bonds with R$_2$AlH occurred in the following structures: (i) with terminal carbon–carbon unsaturation, generally >95% of the adduct has the R$_2$Al group attached to the terminal carbon (Scheme 3); (ii) with alumino-, sulfonyl-, silyl- or germyl-masked 1-alkynes, R-C≡C-E, where E = Ph$_2$Al, TMS, Me$_3$Ge and PhSO$_2$, >98% of the adduct has the R$_2$Al group attached to the carbon bearing Me$_3$M (equation 32);[4] (iii) with C≡C bonds bearing amino (R'$_2$N) or alkoxyl (R'O) groups, the R$_2$Al group of the R$_2$AlH becomes attached exclusively to the carbon β to the R'$_2$N or R'O substituent (equation 33).

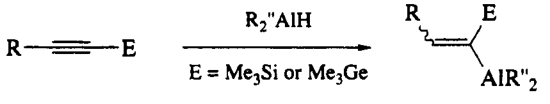

(32)

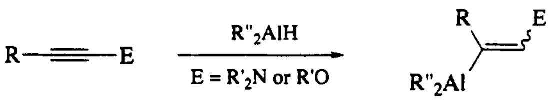

(33)

Other steric or polar influences on the regiochemistry tend to be less selective:[4,54] (i) a *t*-butyl group on the C≡C bond tends to place the R$_2$Al group on the distal carbon (equations 25 and 34; 85–100%); and (ii) a R'S or R'$_2$P group on the C≡C bond tends to place the R$_2$Al group on the proximal carbon (equation 35; 83–85%).

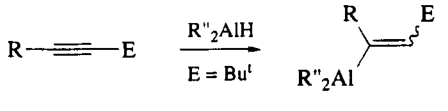

(34)

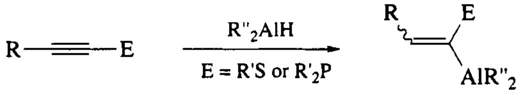

(35)

### 3.11.2.6.3 *Stereoselectivity*

From all available evidence it is reasonable to conclude that the hydroalumination of both alkenes and alkynes by $R_2AlH$ occurs in a kinetically controlled *syn* manner and that any *anti* adduct formed results from a subsequent isomerization to the more stable configuration. In many situations the *syn* adduct can be isolated or detected prior to isomerization and its conversion to the *anti* adduct monitored.[4,52-54] In Table 5 are summarized the stereoselectivities observed in the hydroaluminations of a spectrum of substituted alkynes under various conditions. It is noteworthy that the thermal isomerization of the *syn* adduct can proceed with remarkable facility (at 0 °C) when a TMS or $Me_3Ge$ group is attached to the C≡C linkage.

**Table 5** Stereoselectivities Observed in the Hydroalumination of Heterosubstituted Alkynes by Diisobutylaluminum Hydride

| *Substrate* | *Product(s)* | *Ratio* | *Ref.* |
|---|---|---|---|
| $PhC\equiv CBu^t$ | *syn* | ∞ | 42 |
| $PhC\equiv CTMS$ | *syn* > *anti* ($R_3N$) | 96/4 | 4 |
| | *anti* > *syn* | 96/4 | 4 |
| $PhC\equiv CGeMe_3$ | *syn* > *anti* ($R_3N$) | 98/2 | 4 |
| | *anti* > *syn* | 94/6 | 4 |
| $PhC\equiv CPMe_2$ | *syn* | ∞ | 4 |
| $PhC\equiv CNMe_2$ | *anti* | ∞ | 54 |
| $PhC\equiv CSEt$ | *syn* | ∞ | 54 |
| $Bu^nC\equiv COEt$ | *syn* > *anti* ($R_3N$) | 97/3 | 54 |
| $PhC\equiv CSO_2Ph$ | *anti* | ∞ | 62 |
| $PhC\equiv CM$ (M = Li, $AlR_2$) | *syn* | a | 54 |

[a] The stereochemistry of addition could not be ascertained in these cases, but by analogy to phenylethynylmetallics, $PhC\equiv CE$, where E = Si or Ge, such additions most likely are *syn*.

Distinctly less is known about the *anti* hydroalumination adducts obtained from alkynes with $MAlH_4$ or $MAlR_3H$ reagents (equation 9). These adducts could be the direct result of a *trans* addition but, pending further information, they might also arise from initial *syn* addition and subsequent isomerization.

Regardless of mechanistic conclusions, much useful experimental detail has been reported on how various stereochemical outcomes in hydroaluminations can be achieved and maintained.[17,52-54]

## 3.11.2.7 Modifications in the Hydroalumination Process

### 3.11.2.7.1 *Nature of the aluminum hydride*

In general, tricoordinate hydrides such as $AlH_3$, $R_2AlH$ or $Cl_2AlH$ (even though they may contain some coordinated ether or amine) react toward unsaturated hydrocarbons as electrophilic agents, while alkali aluminum hydrides of the types, $MAlH_4$, $MAlR_2H_2$ or $MAlR_3H$, behave as nucleophilic sources of hydrides. It follows that the electrophilic character of a hydroaluminating agent should be enhanced by adding $AlCl_3$ to $R_2AlH$ or by utilizing $Cl_2AlH$ directly. Such increased electrophilic character may not always be advantageous; sensitive, oxygen-containing masking groups such as acetals and ketals may thereby be more readily attacked (equation 36).[55]

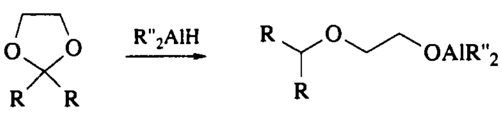
(36)

Augmenting the nucleophilic nature of $MAlH_4$ increases the hydroaluminating reactivity towards alkynes and this can be achieved experimentally by replacing the lithium salt (M) with the sodium or potassium salt.[14] However, this nucleophilic activation has its drawbacks, for the $AlH_4$ thereby becomes a strong Brønsted base and can cause competitive metallations of terminal alkynes (equation 18) and other acidic C—H groups ($CH_2C{\equiv}C$, $ArCH_2$, and $C{=}CCH_2C{=}C$).

### *3.11.2.7.2 Solvent effects*

The presence of donor solvents (ethers or amines) or of Lewis bases ($R_3N$, $R_3P$, $R_2O$ or $R_2S$) markedly retards the rate of hydroalumination with neutral $R_2AlH$ reagents because the tricoordinate monomer $R_2AlH$ must function as an electrophile toward the C—C π-bond in the rate-determining step.[3] Despite this retardation donors are often useful adjuvants in hydroaluminations with $R_2AlH$, because they stabilize the initially formed *syn* configuration (equation 2; Scheme 8).

Donor solvents appear to promote hydroaluminations with $MAlR_3H$ reagents, both through their solubilizing action on such salts and probably by solvating the metal cation and freeing thereby the aluminate anion for attack. Crown ethers would seem to be ideal for this role.

### *3.11.2.7.3 Transition metals*

In Section 3.11.1.4 it was pointed out that salts of certain transition metals, lanthanides and actinides promote the hydroalumination reaction. Since such metal salts are introduced into the reaction in their high oxidation states it can be assumed that the metal ions are rapidly reduced to a lower oxidation state and that this state is the active catalyst. For nickel(II) salts, Wilke has shown conclusively that the active agent is a nickel(0)–alkene complex.[56] Analogously, for titanium(IV) salts, such as $TiCl_4$, $Ti(OR)_4$ and $Cp_2TiCl_2$, it is most likely that a titanium(III) state is involved.[57] The possible role of such metal centers in accelerating hydroalumination will be considered in the next section.

## 3.11.3 MECHANISMS OF HYDROALUMINATION

### 3.11.3.1 Reaction Rates and Kinetic Rate Expressions

Careful and extensive kinetic studies have been carried out only for hydroaluminations with dialkylaluminum hydrides. Adequate kinetic information is still lacking on transition metal catalyzed hydroalumination and on the hydroaluminating action of complex metal hydrides, $MAlR_nH_{4-n}$. Preliminary studies on the nickel-catalyzed process have revealed an unstable rate behavior brought about by the deactivation of the catalyst with time.[58]

With $MAlR_nH_{4-n}$ reagents, knowing the kinetic order of the reaction would prove most helpful in discerning whether the Al—H addition occurs initially in an *anti* manner, or whether a *syn* addition is followed by an isomerization to the *anti* adduct. A direct *anti* hydroalumination would likely require the synergistic action of 2 mol of $MAlR_3H$ in the rate-determining step and thus would be second-order in complex hydride (equation 37).

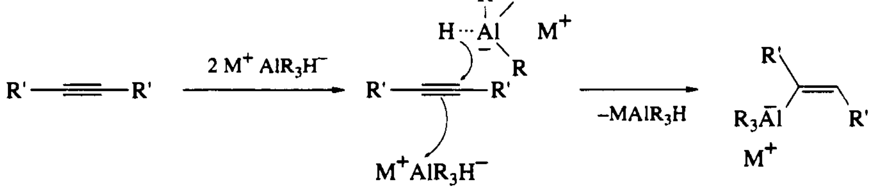
(37)

However, there are published reports that can be interpreted as favoring the pathway of *syn* addition and subsequent isomerization.[14] As already noted in equation (18), $NaAlH_4$ in bis(2-methoxyethyl) ether at 120–140 °C converts phenylacetylene into sodium tetrakis(phenylethynyl)aluminate. But if the reaction is conducted in the presence of 5% of $Bu^i_2AlH$, 95% of the phenylacetylene undergoes hydroalumination instead. This dramatic change in reaction course can be ascribed[14] to a rapid addition of $Bu^i_2AlH$ to phenylacetylene and the aluminum exchange of the vinylaluminum adduct (**37**) with $NaAlH_4$ to regenerate $Bu^i_2AlH$ and continue the catalytic hydroalumination cycle (Scheme 9).

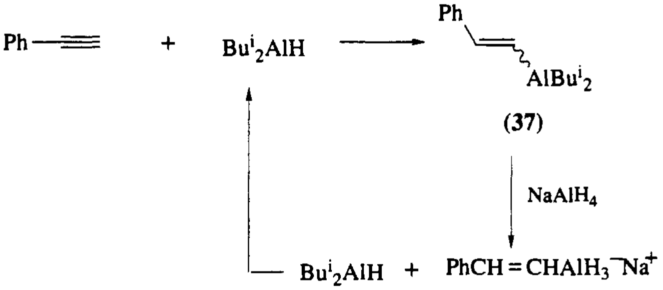

**Scheme 9**

This study opens up the possibility that hydroaluminations by LAH or $LiAlBu^i_2MeH$ actually occur by the dissociation of such complex hydrides into $AlH_3$ and $R_2AlH$ at higher temperatures. Steps of conventional *syn* hydroalumination, aluminum exchange and vinylic lithium isomerization could then lead to the *anti* adduct (Scheme 10).

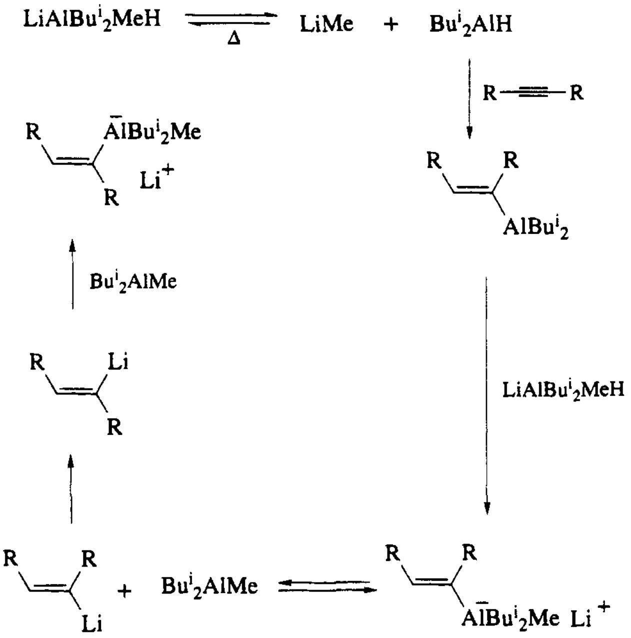

**Scheme 10**

Kinetic information on the addition of $Bu^i_2AlH$ itself to alkynes has permitted the formulation of a very clear reaction pathway. For additions to masked terminal alkynes, such as the ethynylsilane (**38**)[59] and internal alkynes like 4-octyne (**39**),[60] the reaction is first order in the alkyne and essentially one third order in the hydride (0.37 ± 0.01). The respective Arrhenius relationships for (**38**) and (**39**) were found to be: $k = (1.1 \pm 0.4) \times 10^{10}\ e^{-17\,330 \pm 220/RT}\ l^{1/3}\ mol^{-1/3}\ s^{-1}$; and $k = (4.5 \pm 0.6) \times 10^{10}\ e^{-20\,840 - 50/RT}\ l^{1/3}\ mol^{-1/3}\ s^{-1}$; with activation entropies of –13.4 ± 0.1 eu at –5.2 °C for (**38**) and –11.0 ± 0.3 eu at 30 °C for (**39**). Both reactions exhibit rate retardation as a function of conversion, but such retardation was much less with the alkynylsilane. In addition, the alkynes both underwent *syn* hydroalumination but the alkynylsilane adduct isomerized to the *anti* adduct during the reaction. In fact, equilibration between the *syn* and *anti* adducts of (**38**) proved to be so facile that an equilibrium constant of 120 at −5.2 °C, favoring the *anti* adduct, could be conveniently determined.

$Ph{-}C{\equiv}C{-}SiMe_3$ (**38**)    $Pr^n{-}C{\equiv}C{-}Pr^n$ (**39**)

These kinetic data support a reaction mechanism in which the normally trimeric hydride $(R_2AlH)_3$, must dissociate into its monomer (**40**), which attacks the alkyne in a *syn* fashion in the rate-determining step (Scheme 11). The importance of tricoordinate (**40**) in initiating the electrophilic attack on the alkyne is seen in the effect of donor solvents; the rate of reaction in hexane is $10^3$ times faster than that in THF. The latter solvent is known to form a strong 1:1 complex with (**40**).

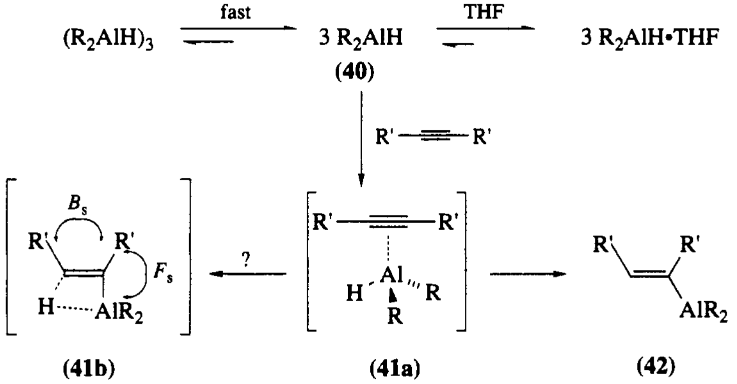

**Scheme 11**

The rate retardation observed in hydroaluminating 4-octyne (**39**) was traced back to the formation of a stable 1:1 complex (**44**) between the *syn* adduct (**43**) and the monomeric hydride (**40**) (equation 38). In effect, adduct (**43**) behaves like a donor molecule, such as THF or an amine.

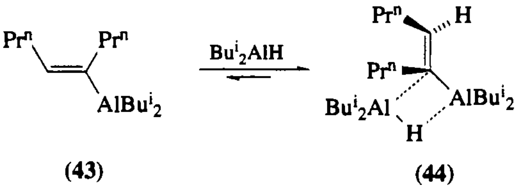

(38)

A decision can also be made on whether the transition state for *syn* addition of the Al—H bond resembles a π-complex (**41a**; Scheme 11), where little geometrical change in the starting alkyne has occurred, or whether a change in hybridization at carbon and some Al—H bond stretching are significant (**41b**). The observed kinetic deuterium isotope effect for $Bu^i_2AlH$ *versus* $Bu^i_2AlD$ is about 1.7. Such a value cannot represent a primary isotope effect and thus would not be consistent with the considerable stretching of the Al—H bond implicit in transition state (**41b**). This isotope effect is more likely connected with the preequilibrium between monomer (**40**) and its trimer.

A further kinetic datum arguing against (**41b**) and for (**41a**) is the effect of bulky substituents. If the transition state resembled (**41b**) large substituents on the alkyne should encounter both back-strain ($B_s$) and front-strain ($F_s$) in (**41b**). But, in fact, di-*t*-butylacetylene is some 20 times more reactive than di-*n*-butylacetylene toward $Bu^i_2AlH$. By passing through an earlier π-complex-like transition state (**41a**), such steric strains could be minimized, and yet the greater electron release of the *t*-butyl group ($\sigma^* = -0.300$) over that of the *n*-butyl groups ($\sigma^* = -0.130$) could still serve to enhance the observed reactivity.[61]

### 3.11.3.2 Substituent Effects on Relative Rates of Alkynes

The most extensive compilation of initial relative rates for the hydroalumination of alkynes by $Bu^i_2AlH$ is presented in Table 4.[53] Normalized for 35 °C, such initial rates avoid complications setting in at extensive conversions, such as autoretardation through complexation (equation 38), isomerization (equation 24) and bishydroalumination (equation 20). As previously noted, steric properties of the substituents appear not to exert any retarding effect; *t*-butyl-substituted alkynes react faster than their methyl- or *n*-alkyl-substituted counterparts (~20×); and trimethylsilylalkynes are again more reactive than *t*-butylalkynes (~15×).

The principal activating influence seems to be polar, and to be related to the electron-donating character of the substituent as assessed by $\sigma^*$ values (*cf.* the last eight entries in Table 4).[53] $\sigma^*$ values that are not directly measurable can generally be calculated from the relation, $\sigma_X^* \approx \sigma^*CH_2X$, for cases where $\sigma^*CH_2X$ can be observed. The calculated value of $\sigma^*$ for TMS can thus be estimated as –0.73 and it is thereby evident why this group should activate an alkyne more than the $Me_3C$ group ($\sigma^* = -0.30$). Appropriate $\sigma^*$ values for SEt, $AlPh_2$ and $NMe_2$ are neither available nor derivable, but from its very negative Hammett $\sigma_p$ value (–0.83) the $NMe_2$ is known to be strongly electron donating. The Allred–Rochow electronegativities of sulfur (2.44) and especially aluminum (1.87) are distinctly less than carbon (2.50), so that both SEt and $AlPh_2$ should release electron density to an adjacent *sp*-hybridized carbon.

Since in every instance the reactivity of an alkyne, RC≡CR, toward $Bu^i{}_2AlH$ can be related to electron release by R and R′, substituent effects are perfectly consistent with the mechanism depicted in Scheme 11, where $R_2AlH$ attacks the π-cloud of the alkyne electrophilically in the slow step.

### 3.11.3.3 Substituent Control of Regiochemistry with Alkynes

The variegated regiochemistry with which alkynes, RC≡CR′, respond to $Bu^i{}_2AlH$ (equations 32–35) can be understood by considering the π-complex-like transition state (**41a**) as unsymmetrical in the sense (**45**) or (**46**), where one carbon is electron deficient.

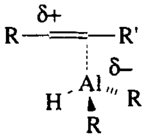

**(45)**

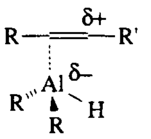

**(46)**

The regioisomer derived from (**45**) will be favored when the R-group can sustain partial positive character better than the R′-group, as when R is a π-donor such as $R_2N$, RO, $Me_2P$ and EtS, since the unshared electrons on the heteroatom can stabilize the positive charge. If R = $PhSO_2$, structure (**45**) would be destabilized, because positive charge would be borne by the carbon attached to a strong electron-withdrawing group, and the regiosisomer derived from (**46**) will be preferred.[62] When R = TMS or $Me_3Ge$, the alternative transition state (**46**) is favored, even though these groups are σ-electron releasing. The electronic effect operative here would appear to be σ-bond hyperconjugation,[63] wherein such groups stabilize an electron deficiency β to their M—C bond.

### 3.11.3.4 Stereochemical Effects of Lewis Acids and Bases

Since hydroalumination by neutral aluminum hydrides is an electrophilic attack on a C=C or C≡C linkage, the reaction can be accelerated by Lewis acids such as aluminum halides, and be retarded by Lewis bases like $R_3N$, $R_2O$ or even unsaturated $R_3Al$ (*cf.* equation 38). Such reagents also exert an effect on the *syn* or *anti* character of the Al—H adduct. Evidence suggests that Lewis acids or bases principally affect the rate of isomerization of the initial *syn* adduct into the generally more stable *anti* adduct; Lewis bases retard such isomerizations, while Lewis acids promote them. The presence of ethers or tertiary amines stabilize the *syn* adducts of alkynyl-silanes and -germanes (**47**) and permit such adducts to be formed in >95% geometrical purity (Scheme 12).[4]

If the donor-free syn adduct (**48**) is generated by adding a Lewis acid, then it can rapidly isomerize to the *anti* adduct (**50**) at 25 °C. Available evidence indicates that the rotational barrier about the C=C bond in (**48**) and (**50**) is very small. A possible explanation is that $p_\pi$–$p_\pi$ bonding with the 3*p*-orbital on aluminum lowers the C=C double bond character. Furthermore, σ-bond hyperconjugation in the transition state for rotation (**49**) reduces its energy and hence the barrier to rotation. That the facile isomeriza-

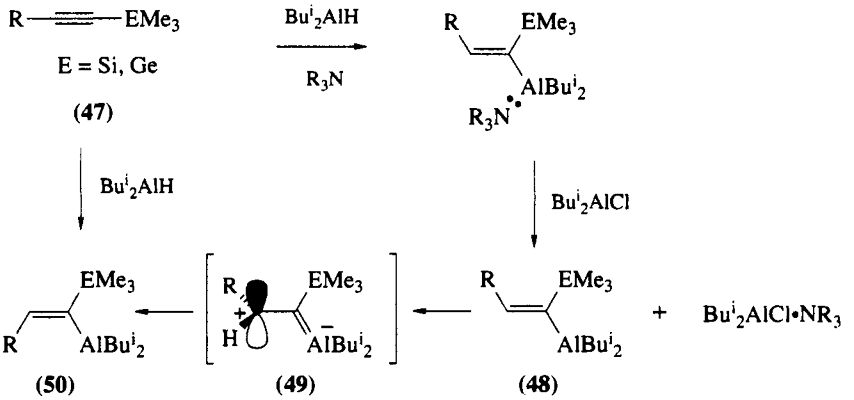

Scheme 12

tion of *syn*-(**48**) into *anti*-(**50**) requires the presence of tricoordinate aluminum speaks for the involvement of the 3*p*-orbital on aluminum in the isomerization process.

An analogous situation arises in the hydroalumination of prochiral alkenes, as already explained in Section 3.11.2.5 and exemplified in the behavior of 1,1-dimethylindene (Scheme 8). The inversion of configuration at the $sp^3$-hybridized C—Al bond (**51** → **52**) is so facile that the addition of $\mathrm{Bu^i_2AlH}$ must be conducted in the presence of a donor ($\mathrm{R_2O}$) to preserve the syn configuration of the initial adduct (**53**; Scheme 13). Again, addition of a stronger Lewis acid liberates (**51**), which, having a tricoordinate Al center, rapidly equilibrates with (**52**). This observation again shows that an available 3*p*-orbital on Al is necessary for configurational inversion.[52]

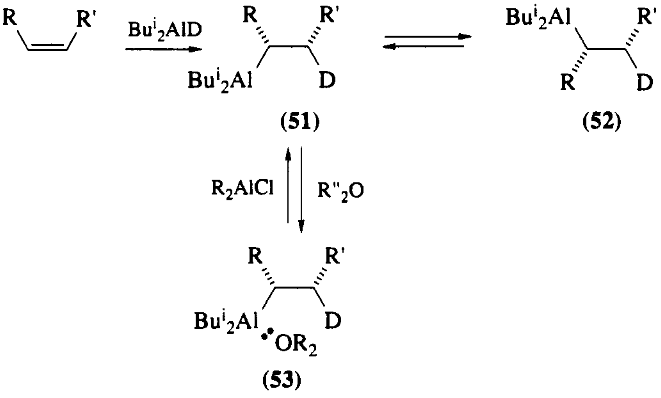

Scheme 13

*Syn* adducts of purely diorganosubstituted alkynes, such as MeC≡CMe or PhC≡CPh, do not isomerize readily, and the pathway for the formation of *anti* adducts from them involves the addition and elimination of a second hydride (equation 20).

### 3.11.3.5 Kinetic Effects of Transition Metals

Of the various metal promoters of hydroalumination, only for nickel and possibly for titanium is the mechanistic basis for their catalysis at all clear. In the case of titanocene dichloride, $\mathrm{Cp_2TiCl_2}$, not only does this reagent catalyze hydroalumination but also hydromagnesiation of C═C and C≡C bonds by Grignard reagents.[64] In both instances it is known that $\mathrm{R_2AlH}$ or RMgX leads to a reduction and alkylation of the titanium to $\mathrm{Cp_2TiR}$.[65] Such titanium(III) alkyls readily eliminate alkene and form hydrides of the type, $\mathrm{Cp_2TiH}$ or $\mathrm{Cp_2TiH{\cdot}HAlR_2}$.[57] These hydrides appear to hydrotitanate the unsaturated hydrocarbon and the adduct (**54**) undergoes metal–titanium exchange with $\mathrm{R_2AlH}$ or RMgX to regenerate the catalytic agent, $\mathrm{Cp_2TiR}$ or $\mathrm{Cp_2TiH}$ (Scheme 14).

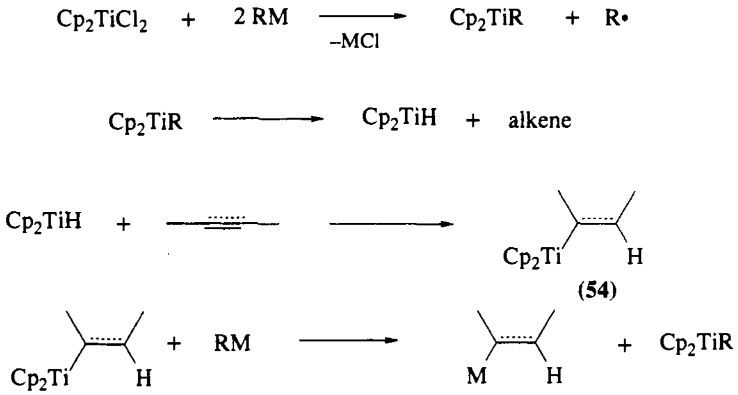
Cp2TiCl2 + 2 RM → Cp2TiR + R•
-MCl
Cp2TiR → Cp2TiH + alkene
Cp2TiH
Cp2Ti
H
(54)
RM
M
H
Cp2TiR

**Scheme 14**

For nickel catalysis by nickel(II) salts, it is now well established that $R_3Al$ or $R_2AlH$ causes reduction to nickel(0), which is held in hydrocarbon solution as a nickel(0)–alkene complex.[56] Wilke's proposal for the nickel-catalyzed, aluminum hydride transfer from $R_3Al$ to another alkene invokes a complex of the $R_3Al$ and the alkene substrate with the nickel(0) center, and the Al—H is transferred in a pericyclic reorganization. Recent evidence in this laboratory, however, assigns a more involved role to nickel(0) in this catalysis.[58] The essence of our proposal is that the actual catalytic carrier is $R_2Al$–Ni—H (**55**), formed from either $R_3Al$ or $R_2AlH$, and the catalytic cycle is that depicted in Scheme 15.

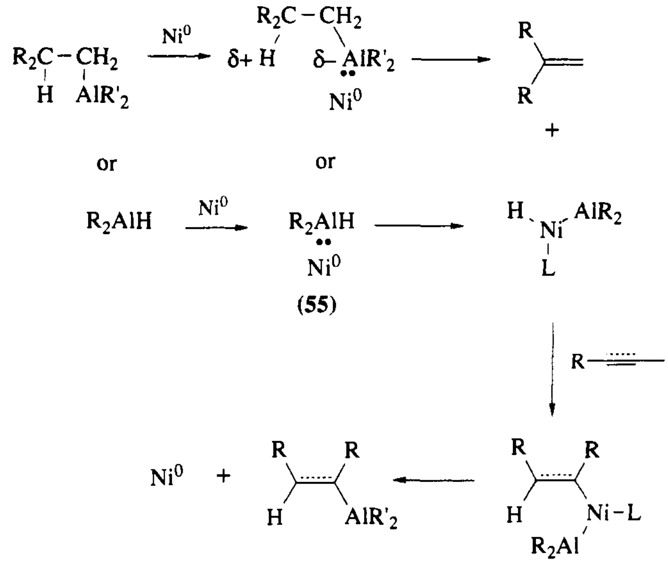
R2C-CH2
H AlR'2
Ni0
R2C-CH2
δ+ H δ- AlR'2
Ni0
R
R
+
or
or
R2AlH
Ni0
R2AlH
Ni0
(55)
H Ni AlR2
L
R
Ni0
+
R R
H AlR'2
R R
H Ni-L
R2Al

**Scheme 15**

The experimental observations favoring this proposal are the following: (i) the regioselectivities for nickel-catalyzed hydroaluminations differ significantly from those obtained from the uncatalyzed process (*e.g.* equation 11); (ii) certain hindered alkenes do not undergo uncatalyzed hydroalumination under conditions where the nickel-catalyzed reaction is essentially complete (*e.g.* equation 39); (iii) nickel(0) complexes have been shown to insert into Al—H bonds to yield $R_2Al$–Ni—H intermediates (equation 40);[66] and (iv) such Al–Ni—H intermediates react with Al—H bonds, with the rate depending upon sub-

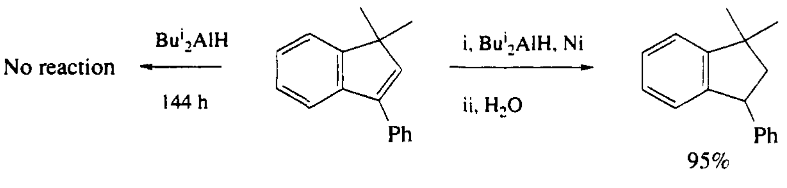
No reaction
Bu^i2AlH
144 h
Ph
i, Bu^i2AlH, Ni
ii, H2O
Ph
95%

(39)

stituents, to evolve dihydrogen and yield aluminum nickelides, causing deactivation of the catalyst (*cf.* equation 27).

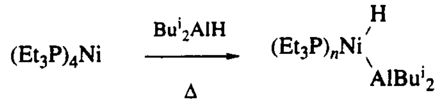

$$(Et_3P)_4Ni \xrightarrow[\Delta]{Bu^i_2AlH} (Et_3P)_nNi(H)(AlBu^i_2) \qquad (40)$$

## 3.11.4 CHEMICAL DERIVATIVES OF HYDROALUMINATION ADDUCTS

### 3.11.4.1 Experimental Conditions: Protolysis and Oxidation

Because organoaluminum compounds react readily with all types of Brønsted acids and with atmospheric oxygen or peroxides, hydroalumination reactions must be conducted anhydrous in an atmosphere of pure nitrogen, and in deoxygenated solvents. Detailed experimental directions for the manipulation and transfer of aluminum alkyls and hydrides are available.[2,3,17,20]

Once the hydroalumination adducts of C=C and C≡C bonds have been cleanly formed, protolysis or oxidation can produce useful derivatives. With $H_2O$ or $O_2$, generally all available C—Al bonds are destroyed. Protolysis or deuteriolysis of such adducts constitutes an overall reduction or deuteriating reduction of the original C—C unsaturation (equations 13, 39 and 41; Schemes 6–8).[30,52,54,55] Any stereoselectivity or regioselectivity of the original hydroalumination is preserved.

When the adducts are allylic, propargylic or benzylic, varying amounts of rearranged protolytic products can result, depending upon the kind of proton source (equation 42).[67]

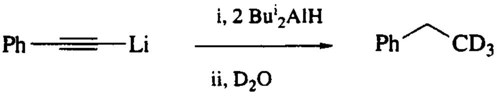

(41)

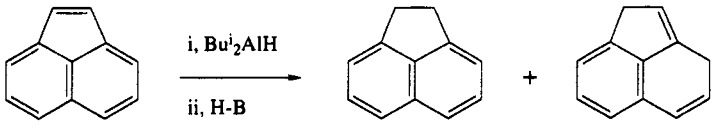

(42)

| | | |
|---|---|---|
| $H_2O$•Py: | 95% | 5% |
| Bu$^t$OH: | 60% | 40% |

Oxidation of $R_3Al$ compounds with dioxygen proceeds most efficiently with trialkylaluminum compounds (Scheme 6) and, in cases where the resulting isobutyl alcohol can be tolerated, is an efficient route to primary alcohols (equation 43).[31]

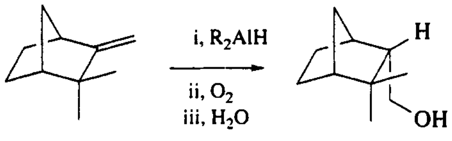

(43)

The substitution of aluminum by oxygen can be effected by various peroxide derivatives, such as di-*t*-butyl peroxide,[68] benzoyl peroxide[69,70] and *t*-butyl perbenzoate.[71] The main reaction is accompanied by telltale free-radical side reactions, such as the formation of RR from $R_3Al$, which become major pathways with aryl and vinyl compounds.[71-74] Oxidation of alkenyl derivative (**56**) with *t*-butyl perbenzoate yields 45% of a mixture of *cis* and *trans* ethers (**57**; equation 44).[71] As of yet there is no generally applicable, highly efficient method for oxidizing vinylaluminum compounds.

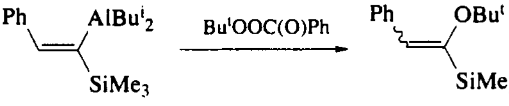

(**56**) (**57**) (44)

### 3.11.4.2 Nonmetallodealumination

The cleavage of C—Al bonds can be achieved by nonmetal sources with varying degrees of ease and efficiency. For such reagents not containing carbon (*cf.* Section 3.11.4.4), the following have found some utility: (i) halodealumination by $Br_2$, BrCN or $I_2$ with retention of vinylic configuration (equation 45);[22,75–79] (ii) sulfur or selenium insertion to form thiols or selenols in good yields with the consumption of one C—Al bond (equation 46);[80,81] (iii) $SO_2$ and $SO_3$ can be inserted into two or even three of the C—Al bonds in $R_3Al$, and good yields of the sulfinic and sulfonic acids obtained upon hydrolysis (equation 47);[29,82–84] (iv) both thionyl chloride and sulfuryl chloride can react with all three C—Al bonds in $R_3Al$ to give high yields of sulfoxides (equation 48)[85] and sulfonyl chlorides (equation 49)[86] respectively; (v) halides of the elements of Group V (P, As, Sb and Bi) react with aluminum alkyls to yield fully alkylated derivatives, $R_3E$ or partially alkylated halides, $R_nEX_{3-n}$, depending upon the ratio of reactants and reaction conditions (equation 50).[87–95]

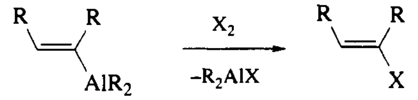

(45)

$$R_3Al \ + \ S \longrightarrow R_2AlSR \xrightarrow{H_2O} RSH \qquad (46)$$

$$R_3Al \ + \ SO_n \longrightarrow R_2Al(SO_nR)_2 \xrightarrow{H_2O} RSO_nH \qquad (47)$$

$$2\,R_3Al \ + \ 3\,SOCl_2 \longrightarrow 3\,R_2SO \ + \ 2\,AlCl_3 \qquad (48)$$

$$R_3Al \ + \ 3\,SO_2Cl_2 \longrightarrow 3\,RSO_2Cl \ + \ AlCl_3 \qquad (49)$$

$$R_3Al \ + \ EX_3 \longrightarrow R_3E \ + \ R_{3-n}AlX_n \qquad (50)$$

### 3.11.4.3 Metallodealumination

The conversion of C—Al bonds into carbon–metal bonds by the interaction of $R_3Al$ with the appropriate metal salt is widely applicable to most metals and metalloids (*cf.* Section 3.11.4.2) except those of Groups I and II (equation 51). The utility of this reaction depends upon several factors: (i) the tendency of $R_3Al$ to undergo exchange of one, two or three R-groups with $MZ_n$ (*i.e.* the successive reactivity of $R_2AlZ$ and $RAlZ_2$ toward $R_mMZ_{n-m}$; (ii) the kinetic stability of the metal alkyl produced (especially of concern with labile transition metal alkyls); and (iii) the ease of separating the desired metal alkyl from the Lewis acidic $R_nAl_{3-n}$ by-products.

$$n\,R_3Al \ + \ MX_n \longrightarrow R_nM \ + \ n\,R_2AlX \qquad (51)$$

The driving force for this aluminum–metal exchange is chiefly the high strength of the resulting Al—Z bond; the same factor underlies the failure of aluminum alkyls to exchange with the very stable salts of the alkali and alkaline earth metals. Instead, these salts form stable complexes (equation 52).[96–100]

$$R_3Al \ + \ MZ \longrightarrow M[AlR_3Z] \qquad (52)$$

$$M = L, Na, K, Rb, Cs; \ Z = X, H, R', OR', NR'_2$$

Beryllium is an understandable exception, but then its salts are more covalent.[101] However, by the use of less stable salts such as alkoxides, $R_3Al$ can produce aluminates with these metals (equation 53).[102]

$$2\,R_3Al \ + \ KOR' \longrightarrow K[AlR_4] \ + \ R_2AlOR' \qquad (53)$$

The method has been successful for producing the alkyls of beryllium,[103] zinc,[104] cadmium,[105] mercury,[106] boron,[107] gallium,[108] indium,[109,110] germanium,[111] tin,[112] lead[113] and many transition metals.[114]

With transition metals the lability of their carbon–metal bonds often does not permit the isolation of the metal alkyl. Feasible preparation then requires the presence of stabilized ligands on the metal, such as phosphines, 2,2-bipyridyl and cyclopentadienyl. The preparation of dimethyltitanocene from titanocene dichloride and $Me_3Al$ is illustrative.[115] A compilation of typical preparations is provided in Table 6.

**Table 6** Preparation of Metal Alkyls by the Aluminum–Metal Exchange Between Aluminum Alkyls and Metal Salts

| *Metal salt* | *Aluminum reagent* | *Product* | *Yield (%)* | *Ref.* |
|---|---|---|---|---|
| $SnCl_4$ | $Et_3Al$ (+KCl) | $Et_4Sn$ | 80 | 112 |
| $Et_3SnCl$ | $Et_2AlH$ | $Et_3SnH$ | 89 | 112 |
| $GeCl_4$ | $Me_3Al$ (+NaCl) | $Me_4Ge$ | 73 | 111 |
| $PbCl_2$ | $Et_3Al{\bullet}OEt_2$ | $Et_4Pb$ | 70 | 113 |
| $ZnCl_2$ | $Bu^i_3Al$ | $Bu^i_2Zn$ | 95 | 104 |
| $GaCl_3$ | $Et_3Al$ (+KCl) | $Et_3Ga$ | 84 | 108,109 |
| $HgCl_2$ | $NaAlEtCl_3$ | EtHgCl | 91 | 106 |

### 3.11.4.4 Carbodealumination

The most important substitution occurring at the C—Al bond is an aluminum–carbon exchange (equation 54).

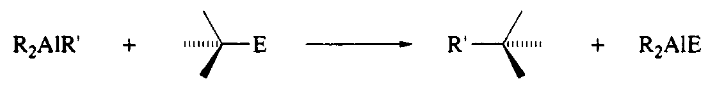

(54)

Often, only one C—Al bond can be made to react and even then the C—Al bond might require promotion by transition metals like Ni,[116] Pd[117] or Cu[118] or might benefit by activation through aluminate salt formation ($LiAlR_3R'$).[28,119,120] Fortunately, in the vinylic aluminum compounds resulting from the hydroalumination of alkynes (equations 2, 3 and 14) or in the vinylic aluminate complexes arising from Al—H additions to alkynes (equations 6 and 9; Scheme 4), the vinylic carbon–aluminum bond is generally much more reactive than the alkyl C—Al linkages and is thus cleaved preferentially.

Suitable cleaving agents include organic halides such as: primary alkyl bromides, iodides or sulfonates;[28,119,120] allylic,[118,121,122] allenic[123] and propargylic bromides;[120] vinylic or aryl halides with nickel or palladium promoters;[124–127] alkyl chloroformates;[128,129] epoxides;[130,131] and even cyanogen[132] or cyanogen bromide.[133,134] Typical examples of such couplings are depicted in equations (55)–(57).

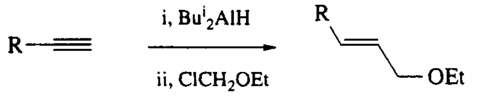

(55)

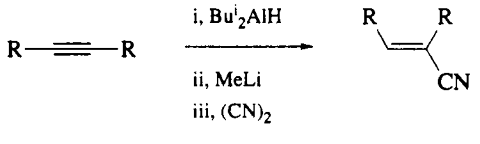

(56)

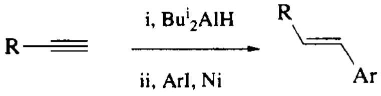

(57)

The reactions often proceed in high yield and predominantly with retention of configuration at the vinyl—aluminum bond. Many experimental variations of this substitution reaction remain to be studied systematically and the method appears to have great promise for the synthesis of unsaturated carbon chains. Because only one C—Al bond in $R_2AlR'$ responds to cleavage the method has little appeal for application to the $R_2AlH$ adducts of alkenes (Scheme 3). Little preference for cleavage of the three C—Al bonds would be expected, so conversion to the R′E would be low.

### 3.11.4.5 Carbalumination

The addition of organoaluminum reagents to unsaturated carbon-containing substrates is probably the most versatile and widely applicable method for forming carbon–carbon bonds from $R_3Al$ compounds. Besides the stepwise insertion of ethylene into the C—Al bonds of triethylaluminum, the so-called Aufbau-Reaktion originally discovered by Ziegler (*cf.* Section 3.11.1.2), most primary alkenes and alkynes are able to undergo a single or several insertions into a carbon–aluminum bond (*cf.* equations 23 and 30). Such reactions can form the basis for the catalytic oligomerizations of alkenes (equation 30)[50] and alkynes (equation 58).[13,39]

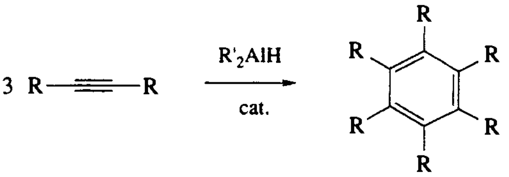

(58)

But a wide spectrum of other unsaturated carbon centers can insert cleanly in the C—Al bond as well. Possibly the most interesting and most closely akin to Ziegler's ethylene insertion is the preferential methylene insertion brought about by diazomethane into vinylic aluminum bonds (equation 59).[135-139]

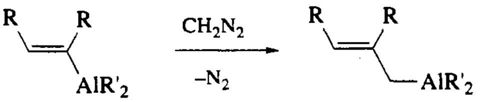

(59)

For reasons not yet understood, the Simmons–Smith methylenating agent [$CH_2Br_2$, Zn(Cu)][140] brings about cyclopropanation, instead, to provide cyclopropylaluminum derivatives in good yield (equation 60).[141]

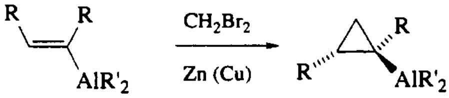

(60)

Other addends that generally cleave only one C—Al bond, and that usually being the more reactive vinylic aluminum bond, include: (i) $CO_2$,[142-144] COS[145] and $CS_2$;[146] (ii) aldehydes, such as $H_2CO$[147,148] and MeCHO,[149] and ketones;[150] (iii) esters,[151] lactones,[152] anhydrides[153] and isocyanates;[154] (iv) substrates having C=N,[155] C≡N[156] and C=S[157] linkages; and (v) α,β-unsaturated carbonyl compounds, where 1,4-addition is often attainable.[158,159] Illustrative reactions are given in equations (14), (61) and (62).

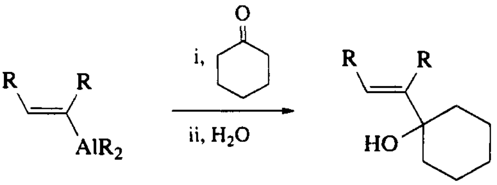

(61)

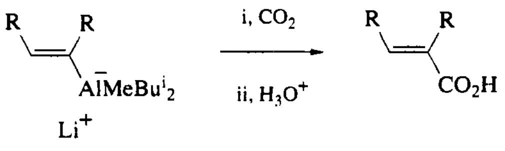

(62)

Several influences on the course of inserting C=E units (E = O, N, S) into C—Al bonds merit brief mention: (i) although dialkyl(vinylic)aluminums are often sufficiently reactive to undergo insertion of C=E with retention of configuration, in some cases it may be advantageous to preform the tetraorganoaluminate for better reaction (equation 62);[160] (ii) although saturated $R_2AlR'$ will generally not insert C=E into a given R—Al or R'—Al bond preferentially, such preferential reaction will occur if R' is benzylic or allylic, but then with loss of configuration (equation 63);[161] (iii) for slow insertions of C=E into diisobutyl(vinylic)aluminum adducts the isobutyl groups may cause competitive reduction of C=E linkages by Al—H transfer (Scheme 3).[162] Such Al—H reductions will be especially serious at higher temperatures or in the presence of transition metals.

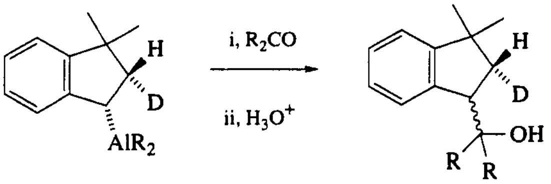

(63)

## 3.11.5 APPLICATIONS IN ORGANIC SYNTHESIS

The stereocontrolled synthesis of alkenes and the use of vinyl- and alkyl-aluminum and -aluminate reagents as nucleophiles has been described above. In addition, the aluminum reagents are also useful in diene synthesis, in reactions with enones and epoxides, and in cyclizations.

### 3.11.5.1 Dienes, Polyenes and Enynes

A variety of conjugated dienes can be synthesized stereospecifically *via* the hydroalumination of alkynes. For example, the first-formed adduct from an alkyne can insert a second mole of alkyne and upon hydrolysis yield the (*E*,*E*)-1,3-alkadiene (equation 23).[13,39] Alternatively, the first-formed adduct can directly oxidatively dimerize to the (*E*,*E*)-1,3-diene (equation 64).[124]

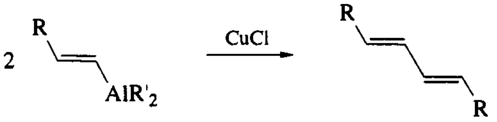

(64)

Besides such homocoupling of alkynes, adduct (**58**) may be heterocoupled, under palladium catalysis, with a vinylic bromide that itself may have been formed by the hydroalumination of a different alkyne (equations 65 and 66).[125]

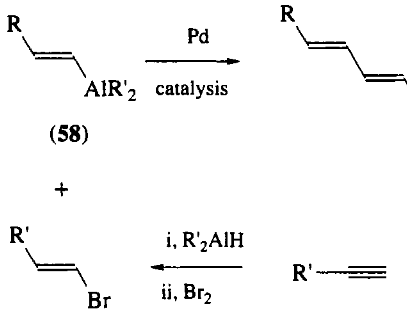

(65)

(66)

R = alkyl; R' = H

Conjugated enynes and diynes can be hydroaluminated to produce (*E*,*Z*)- and (*Z*,*Z*)-1,3-alkadienes, respectively (equations 67 and 68).[6,79,163,164]

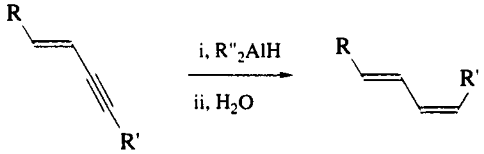

(67)

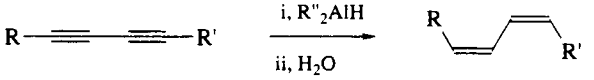

(68)

Finally, unconjugated dienes and even polyenes can be produced (R = alkyl, aryl; R′ = H) by the transition metal promoted coupling (Cu, Ni, Pd) with an allylic[121,122] or other unsaturated halide (equations 65 and 66; Scheme 4).[124–127]

The preparation of enynes by the locoselective monohydroalumination of diynes can be exemplified by equation (69).[164] In addition, a heterocoupling of adduct (**58**) with 1-halo-1-alkynes can produce conjugated enynes in high yield.[117]

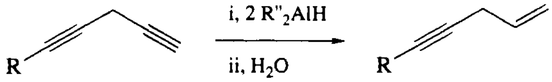

(69)

### 3.11.5.2 Additions to Epoxides and Conjugated Enones

Other promising methods for the stereoselective introduction of the vinyl moiety into functionalized organic substrates are the reactions of such adducts with epoxides to produce homoallylic alcohols (equation 70)[130,131] and with conjugated enones to yield ketones (equation 71).[158,159] Both reactions have major limitations, and their application in a special instance may require a study of the effect of Lewis acids or transition metals as promoters or selectivity agents.

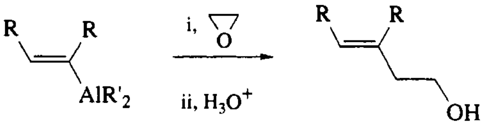

(70)

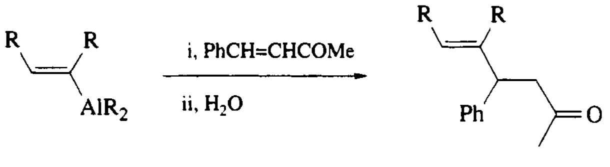

(71)

### 3.11.5.3 Carbocyclizations

A scattered but tantalizing array of reactions have been observed, in which hydroalumination brings about the closure of open-chain compounds to carbon rings. Perhaps the most typical of such reactions is the monohydroalumination of 1,5-hexadiene at –40 °C, which is followed by an intramolecular carbalumination (equation 72).[165,166]

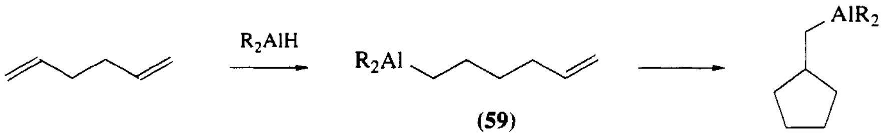

(72)

In the presence of diethyl ether the reaction does not proceed beyond the formation of (**59**). Similar treatment of 1,6-heptadiene with $Et_2AlH$ gives the monoadduct, which requires prolonged heating at 100 °C to cyclize to the cyclohexylmethylaluminum derivatives.[167] In contrast, 1,4-pentadiene,[168] 1,7-octadiene, 1,8-nonadiene or 1,9-decadiene, show little tendency to cyclize.[169,170]

Similar cyclizations to substituted cyclopenta rings have also been reported (equations 73 and 74).[43,171] The method holds considerable promise for the synthesis of *cis*-fused $C_5$ and $C_6$ ring systems.[172]

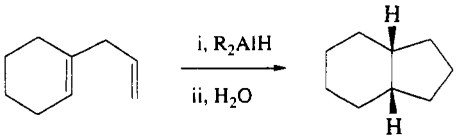

(73)

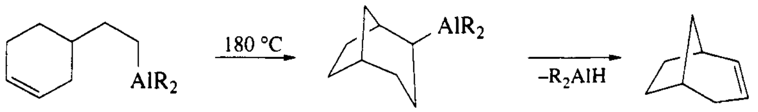

(74)

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# 3.12

# Hydrosilylation of C=C and C≡C

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## 3.12.1 INTRODUCTION

The addition reaction of hydrosilanes to alkenes and alkynes is called hydrosilylation, a reaction which was discovered when a mixture of 1-octene and trichlorosilane was heated in the presence of diacetyl peroxide. This reaction is particularly useful for the synthesis of organosilicon compounds. Since then, a variety of catalysts and conditions have been reported.[1] Characteristic features of the reaction are discussed in this chapter.

### 3.12.1.1 Catalysts

Various reagents and conditions which generate silyl radicals from hydrosilanes induce hydrosilylation of alkenes and alkynes. Peroxides like diacetyl peroxide, dibenzoyl peroxide, di-*t*-butyl peroxide and AIBN along with its derivatives are reagents of choice. UV irradiation or $\gamma$-irradiation are also applicable. Sometimes, simple heating of a mixture of a substrate and a hydrosilane affords a hydrosilylated product. Since the addition of the silyl radical is reversible, the silyl group attaches itself to the terminal carbon of the substrate to give the thermally more favorable, substituted carbon radical, and hydrosilylation of terminal alkynes gives rise to *trans*-vinylsilanes.[2]

Transition metal complexes, particularly those of Group VIII, are popular catalysts. Of these, Pt and Rh are employed most frequently. A Cr catalyst is a unique catalyst for stereoselective hydrosilylation of 1,3-dienes. Catalysts based on Fe, Os and Ir are rarely used.

Hexachloroplatinic(IV) acid ($H_2PtCl_6$, **1**) is the catalyst of choice for hydrosilylation with a wide variety of silanes and substrates. This catalyst is commercially available as a hexahydrate; dissolved in isopropyl alcohol, the catalyst is activated.[3] With the platinum catalyst, hydrosilylation proceeds under mild conditions with stereospecificity, namely, *syn* addition to C≡C. The modification of the structure into $[A^+]_2[PtCl_6]^{2-}$ (**2**), wherein A = K, Na, $R_4N$, $R_4P$ and $R_4As$, has been studied. In comparison with $H_2PtCl_6$, the complex (**2**; A = K, Na) is less reactive, but the $R_4N$ analog exhibits similar reactivity.[4a] Platinum–carbon, though inactive by itself, is activated when exposed to air to achieve triple hydrosilylation with $RSiH_3$, giving fully alkylated silanes.[4b] Ultrasonic waves also activate the catalyst.[4c] The platinum phosphine complexes $[PtCl_2(PPh_3)_2]$ and $[Pt(PPh_3)_4]$ also catalyze hydrosilylation, but the reactivity decreases in the order $H_2PtCl_6$ > $[PtCl_2(PPh_3)_2]$ > $[Pt(PPh_3)_4]$. By choosing an appropriate catalyst, selective hydrosilylation is attainable, as shown in equation (1).[5]

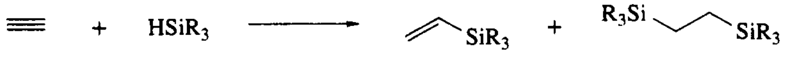

(1)

| | Catalyst | Yield (%) | |
|---|---|---|---|
| $HSiCl_3$ | $H_2PtCl_6$ | 90 | 0 |
| | $[PtCl_2(PPh_3)_2]$ | 54 | 15 |
| | $[Pt(PPh_3)_4]$ | 0 | 0 |
| $HSiCl_2(n\text{-}C_6H_{13})$ | $H_2PtCl_6$ | trace | 82 |
| | $[PtCl_2(PPh_3)_2]$ | 5 | 53 |
| | $[Pt(PPh_3)_4]$ | 87 | 3 |

Iridium complexes other than $[\{IrCl(cyclooctene)_2\}_2]$[6] are much less reactive and scarcely used for synthetic reactions.

Palladium complexes $[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$ and $[PdCl_2(PhCN)_2]$ are not as reactive as $H_2PtCl_6$ toward hydrosilylation but they are more selective: selective 1,4-addition to 1,3-dienes occurs to give allylsilanes, and for asymmetric hydrosilylation with (*R*)-(*S*)-PPFA-Pd see Section 3.12.7.

Rhodium complexes of various types, *e.g.* $[RhCl(PPh_3)_3]$, $[RhCl(CO)(PPh_3)_2]$, $[\{RhCl(CO)_2\}_2]$, $[RhH(CO)(PPh_3)_3]$, $[\{RhCl(C_8H_{14})_2\}_2]$ and $[\{RhCl(C_2H_4)_2\}_2]$, are available for the hydrosilylation of alkenes and alkynes as well as enones and ketones. Under strictly deoxygenated conditions with the pure rhodium complex, the reaction is extremely slow, and a trace amount of oxygen or peroxide is necessary to activate the catalyst.[7]

Ruthenium complexes are not much employed for hydrosilylation, since they are not in general reactive enough. $[RuCl_2(PPh_3)_3]$ and $[RuHCl(PPh_3)_3]$ are examples,[8] and [(1,4-diaza-1,3-diene)RuHCl(COD)] specifically catalyzes the hydrosilylation of isoprene to give an allylsilane.[9]

Typical examples of nickel catalysts for hydrosilylation are nickel(II) complexes like $[NiCl_2(PPh_3)_2]$, $[NiCl_2(PEt_3)_2]$, $[NiCl_2(dppe)]$ and $[NiCl_2(dmpe)]$ and nickel(0) complexes like $[Ni(PPh_3)_2(CH_2{=}CH_2)]$ and $[Ni(diphos)(CH_2{=}CH_2)]$ as well as the Ziegler-type catalyst $[Ni(acac)_2]$–$AlEt_3$. However, unexpected reaction paths are sometimes observed, such as the disproportionation of chlorohydrosilane (equation 2) and disilylation of alkynes (*cf.* Section 3.12.2.3).[10]

$$2HSiMeCl_2 \xrightarrow{[NiCl_2P_2],\ >120\ °C} MeSiH_2Cl + MeSiCl_3 \qquad (2)$$

$P_2 = Me_2PCH_2CH_2PMe_2$, 1,1'-bis(dimethylphosphino)ferrocene

Bis(tetracarbonylcobalt) is the most effective among Co catalysts. The reactive species are $[HCo(CO)_4]$ and $[R_3SiCo(CO)_4]$, both of which are produced by the initial reaction between $[Co_2(CO)_8]$

and $HSiR_3$. Quite a few examples of iron catalysts are recorded, the most useful for organic synthesis being $[Fe(CO)_5]$.

Polynuclear metal carbonyls, for example $[Rh_4(CO)_{12}]$, $[Rh_6(CO)_{16}]$, $[Co_4(CO)_{12}]$, $[Co_6(CO)_{16}]$, $[Co(CO)_4]_4Sn$, $[Ru_3(CO)_{12}]$, $Et_4N[HRu_3(CO)_{11}]$, $[Ir_4(CO)_{12}]$, $[Re_2(CO)_{12}]$, $[Mn_2(CO)_{10}]$ and $[Cr(CO)_6]$, are also active for hydrosilylation.[11]

Aluminum chloride facilitates hydrosilyation of the more-substituted alkenes (see Section 3.12.4.3).[12]

The metal catalysts mentioned above may be supported on polymers to facilitate the recovery of the catalyst from reaction mixtures. Rh and Pt can be complexed with a polymer phosphine such as $[—COC_6H_4CONH(CH_2)_mN(PPh_2)—]_n$ or $SiO_2(\equiv SiCH_2CH_2PPh_2)$.[13] Cobalt carbonyl adsorbed on silica gel or alumina is also reported.[14]

### 3.12.1.2 Hydrosilanes Available

The basic industrial process for hydrosilane synthesis is the reaction of metallic silicon with hydrogen chloride, giving trichlorosilane. The Si—X (X = Cl, Br, OR, H) bond is converted into an Si—C bond by the reaction with organo-lithium or -magnesium reagents, and the Si—Cl bond is also readily transformed to Si—H with lithium aluminum hydride as the reagent of choice. Various kinds of hydrosilanes are available commercially, such as the chlorosilanes $HSiCl_3$, $HSiMeCl_2$, $HSiMe_2Cl$, $HSiEtCl_2$, $HSiPh_2Cl$; the alkoxysilanes $HSi(OMe)_3$, $HSiMe(OMe)_2$, $HSi(OEt)_3$; the hydrosilanes containing only organic groups $HSiMe_3$, $HSiEt_3$, $HSiMe_2Ph$, $HSiEt_2Me$, $HSiPh_3$, $H_2SiEt_2$, $H_2SiPh_2$, $H_3SiPh$, $H_2SiMePh$, $HSiMe_2CH_2CH{=}CH_2$, $HSiMePhCH{=}CH_2$; the polysilyl compounds $HSiMe_2—O—SiMe_2H$, $HSiMe_2—O—SiMe_3$, $HSiMe_2—C_6H_4—SiMe_2H$, $HSiMe_2—O—SiMe_2—O—SiMe_2H$, $HSiMe(OSiMe_3)_2$, $HSi(OSiMe_3)_3$, $(SiHMeO)_5$; the polymethylhydrosiloxane $Me_3Si—O—(SiHMeO)_n—SiMe_3$ ($n$ = 3–35); and the copolymers which contain the —(SiHMeO)— unit.

### 3.12.1.3 Solvents

As most hydrosilanes are oils, hydrosilylation is usually carried out without solvent using an equimolar amount or an excess of the hydrosilane. In cases where a substrate is solid or extremely volatile, solvents are employed. Both nonpolar solvents (hexane, benzene, toluene, xylene) and polar solvents (THF, diglyme, nitrobenzene, acetone) are applicable, although some polar solvents may affect the yield and selectivity of hydrosilylation,[15] as in equation (3).

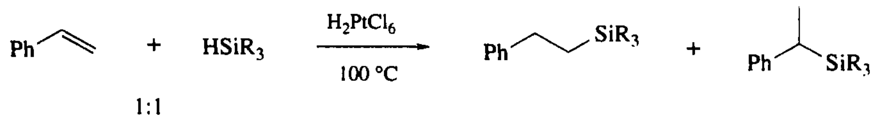

(3)

| | | |
|---|---|---|
| $HSiCl_3$ | No solvent | 57 : 43 |
| | THF | 100 : 0 |
| $HSiMe_2Cl$ | No solvent | 85 : 15 |
| | THF | 86 : 14 |

### 3.12.1.4 Mechanism

The mechanism of the hydrosilylation reaction varies depending on the kind of catalyst and other factors discussed above, and is classified roughly into three types: (i) radical-initiated hydrosilylation; (ii) transition metal catalyzed hydrosilylation; and (iii) ionic hydrosilylation.

In the presence of a radical initiator like peroxide or AIBN, or under UV or γ-ray irradiation, the Si—H bond is cleaved homolytically to afford a silyl radical (**3**; Scheme 1), which adds across a C=C or C≡C bond. The regioselectivity of the addition is governed mainly by the stability of the newly generated radical center. The resulting radical (**4**) picks up hydrogen from another molecule of hydrosilane to complete the catalytic cycle and regenerate the active silyl radical (**3**).[16]

Most of the transition metal catalyzed reactions are explained in terms of the hydrometallation mechanism (Harrod–Chalk mechanism) summarized in Scheme 2.[17] The alkene coordinates to the metal (M) to give an alkene complex (**5**), which oxidatively adds to the Si—H bond of the hydrosilane to give (**6**).

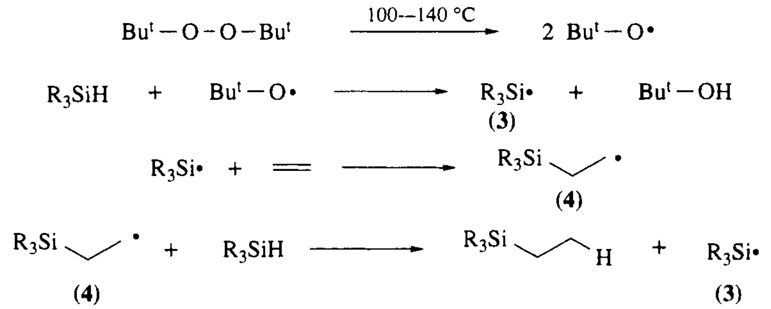
Bu$^t$—O—O—Bu$^t$
100–140 °C
2 Bu$^t$—O•
R$_3$SiH
Bu$^t$—O•
R$_3$Si•
Bu$^t$—OH
(3)
R$_3$Si
(4)
R$_3$SiH
H
R$_3$Si•
(4)
(3)

**Scheme 1**

The *cis* ligand alkene then inserts into the M—H bond (hydrometallation) of (**6**) to afford an alkyl metal complex (**7**), which interacts with another molecule of alkene to induce the coupling of the alkyl and silyl ligands and to regenerate the active catalyst (**5**). This last reaction is the rate-determining step of the catalytic cycle.

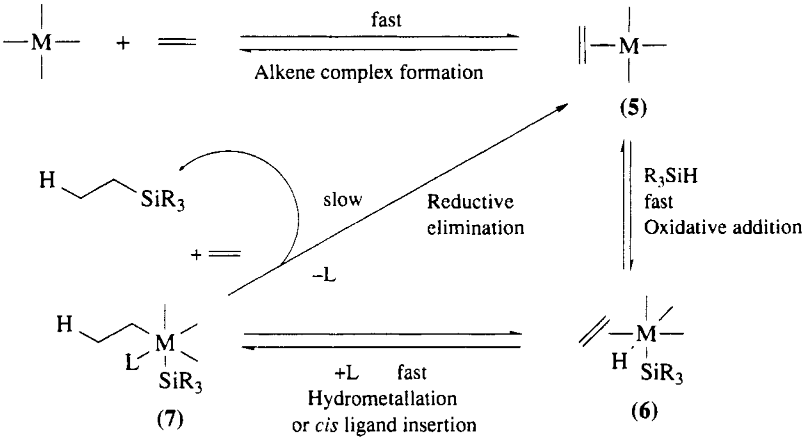
M
fast
Alkene complex formation
(5)
H
SiR$_3$
slow
Reductive elimination
-L
R$_3$SiH
fast
Oxidative addition
H
M
L
SiR$_3$
(7)
+L fast
Hydrometallation
or *cis* ligand insertion
M
H
SiR$_3$
(6)

L = neutral ligand or solvent

**Scheme 2**

As a model of the oxidative addition product, a platinum(0) complex (**8**) has been found to afford an isolable platinum(II) compex (**9**), which has a Si—Pt—H bond.[18]

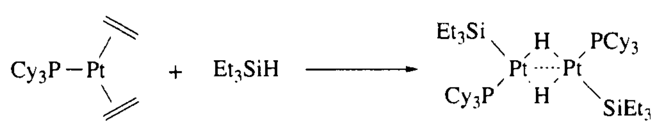
Cy$_3$P—Pt
Et$_3$SiH
Et$_3$Si
H
PCy$_3$
Pt
Pt
Cy$_3$P
H
SiEt$_3$

(4)

(**8**) Cy = cyclohexyl (**9**)

The stereochemistry of the oxidative addition has been studied using optically active 1-naphthyl(methyl)phenylsilane (**11**) and its deuterium derivative (**10**). The H/D exchange reaction of the hydrosilane proceeds with 100% retention of configuration (equation 5). Addition of the hydrosilane (**11**) to 1-octene gives 1-naphthyl(methyl)octyl(phenyl)silane (**12**) with retention of the configuration of the silicon (equation 6).[19]

Reaction of the Pt complex (**13**) with (**11**) gives a silylplatinum complex (**14**), the silyl group of which has the same configuration as that of (**11**). The oxidative addition is thus assumed to take place from the front side of the Si—H bond (equation 7). The hydrosilane (**11**) reacts with a manganese complex (**15**) to give rise to a complex (**16**; equation 8), which has a structure similar to the intermediate of the oxidative addition step.[20]

Photocatalyzed hydrosilylation of alkenes using $[Fe(CO)_5]$, $[Ru_3(CO)_{12}]$, $[(CO)_4CoSiR_3]$ and $[RhCl(PPh_3)_3]$ often produces 1-alkenylsilanes, in addition to normal hydrosilylated products. This is attributed to a different mechanism from that discussed above. Using a low temperature UV irradiation

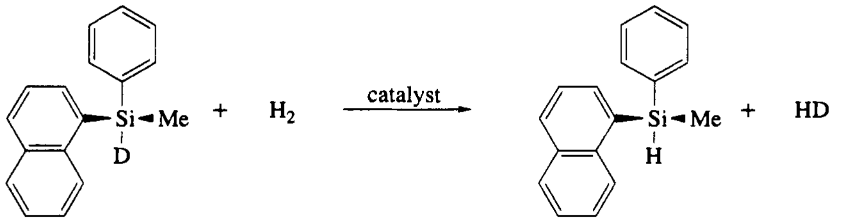
Si
Me
D
H$_2$
catalyst
Si
Me
H
HD

(5)

(+)-(**10**)

(+)-(**11**)
100% exchange
100% retention

*Catalyst*

[IrClCO(PPh$_3$)$_2$]
[Co$_2$(CO)$_8$]
[R$_3$Si*Co(CO)$_4$]
H$_2$PtCl$_6$
[PtCl$_2$(C$_2$H$_4$)$_2$]

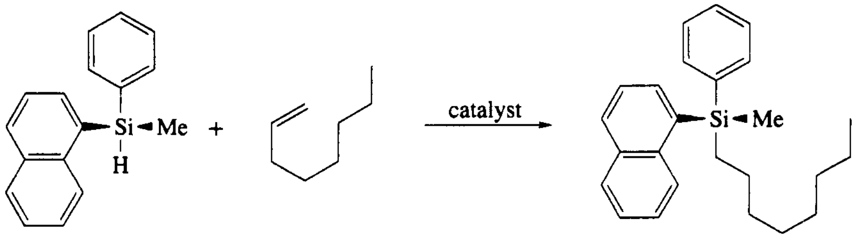
Si
Me
H
catalyst
Si
Me

(6)

(**11**) (**12**)

| *Catalyst* | *Yield* (%) | *Retention* (%) |
|---|---|---|
| Pt/C | 85 | 100 |
| H$_2$PtCl$_6$ | 75 | 100 |
| PtCl$_2$(C$_2$H$_4$)$_2$ | 56 | 92 |

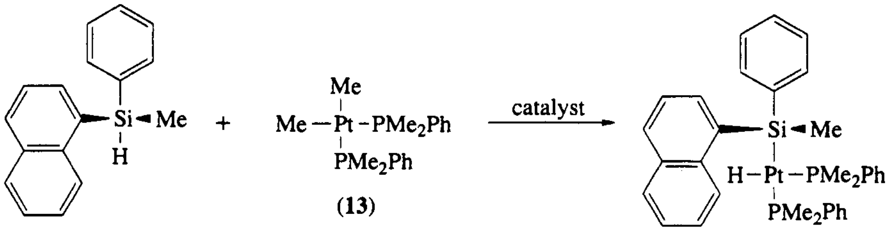
Si
Me
H
Me
Me—Pt—PMe$_2$Ph
PMe$_2$Ph
catalyst
Si
Me
H—Pt—PMe$_2$Ph
PMe$_2$Ph

(7)

(**11**) (**13**) (**14**)

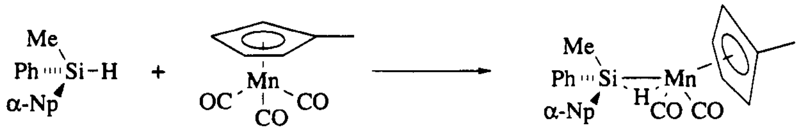
Me
Ph
Si
H
α-Np
Mn
OC
CO
CO
Me
Ph
Si
Mn
α-Np
H
CO
CO

(8)

(**11**) (**15**) (**16**)

technique in a matrix and FTIR spectrometry, hydrosilylation of ethene with a [(CO)$_4$CoSiR$_3$][21] or [Cp*(CO)$_2$FeSiR$_3$] catalyst[22] has been studied, and a mechanism, which involves insertion of an alkene into the M—Si bond (silylmetallation), is proposed. The catalytic cycle is demonstrated in Scheme 3 for the cobalt-catalyzed hydrosilylation.[21]

Tertiary amines catalyze the addition of trichlorosilane with electron deficient alkenes, *e.g.* acrylonitrile, and such alkynes as phenylethyne (Scheme 4). The reaction is understood in terms of the nucleophilic addition of a trichlorosilyl anion (**17**), which is generated by proton abstraction from a zwitterion (**18**) by tertiary amines.[23]

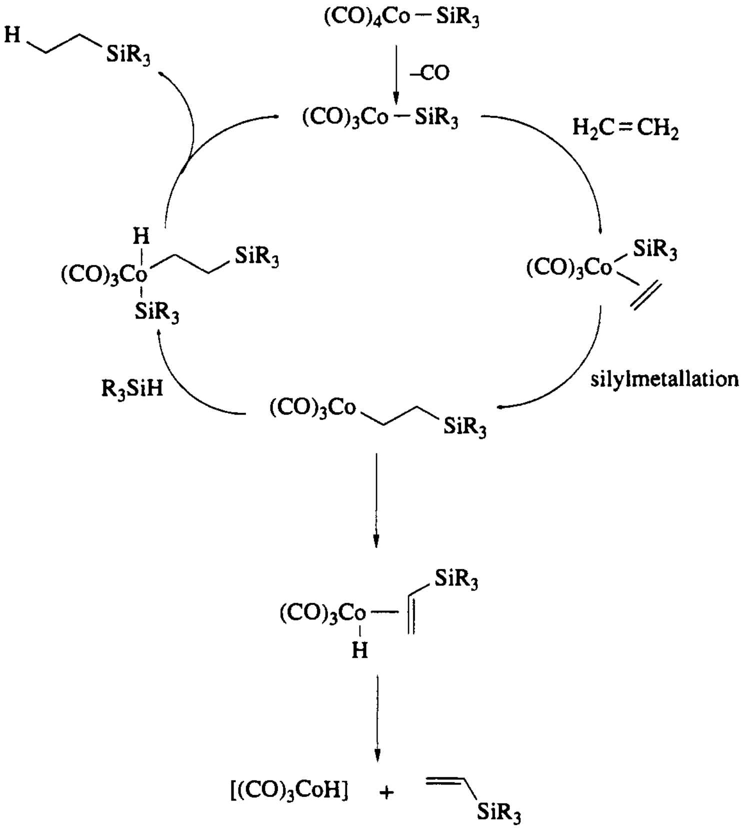
$(CO)_4Co-SiR_3$
-CO
$(CO)_3Co-SiR_3$
$H_2C=CH_2$
$H\!\!\diagup\!\!\!\diagdown SiR_3$
$(CO)_3Co(H)(SiR_3)CH_2CH_2SiR_3$
$(CO)_3Co$ $SiR_3$
$R_3SiH$
silylmetallation
$(CO)_3Co\!\!\diagup\!\!\!\diagdown SiR_3$
$(CO)_3Co(H)$ $SiR_3$
$[(CO)_3CoH]$ + $SiR_3$

**Scheme 3**

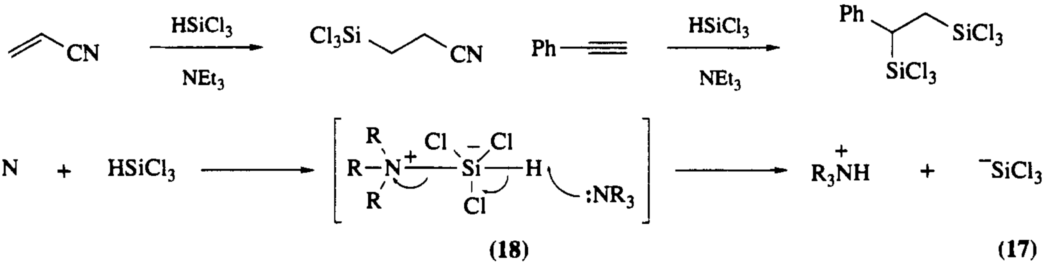
CN
$HSiCl_3$
$NEt_3$
$Cl_3Si$ CN
Ph
$HSiCl_3$
$NEt_3$
Ph $SiCl_3$
$SiCl_3$
$R_3N$ + $HSiCl_3$
R Cl Cl
R–N–Si–H
R Cl :$NR_3$
$R_3\overset{+}{N}H$ + $^{-}SiCl_3$
(18)
(17)

**Scheme 4**

Reactions of silylcuprates provide additional examples of a silyl anion based mechanism (Scheme 5). The reagent (**19**), prepared from silyllithium and copper(I) cyanide, reacts with a C≡C bond to give, after aqueous work-up, *cis*-hydrosilylated products (**20**). Conjugate addition of (**21**) to α,β-unsaturated

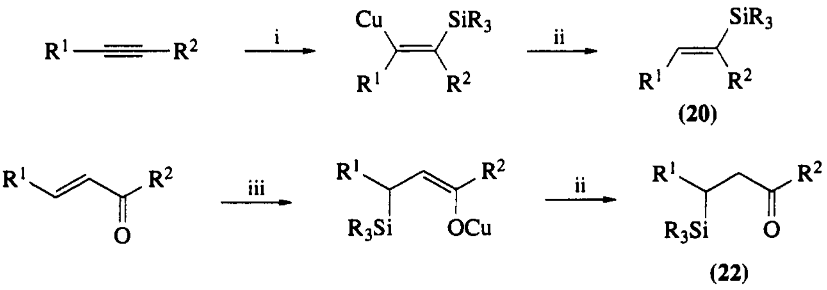
$R^1$ $R^2$
i
Cu $SiR_3$
$R^1$ $R^2$
ii
$SiR_3$
$R^1$ $R^2$
(20)
$R^1$ $R^2$
O
iii
$R^1$ $R^2$
$R_3Si$ OCu
ii
$R^1$ $R^2$
$R_3Si$ O
(22)

i, $(R_3Si)_2CuLi_2CN$ (**19**); ii, $H_2O$; iii, $(R_3Si)_2CuLi$ (**21**)

**Scheme 5**

ketones and esters is an alternative way for hydrosilylating such electron deficient alkenes. Thus, β-silyl ketones or esters (**22**) are easily accessible and are known to be versatile synthetic intermediates.[24]

## 3.12.2 HYDROSILYLATION OF CARBON–CARBON TRIPLE BONDS

### 3.12.2.1 Hydrosilylation of Acetylene

Acetylene is converted into vinylsilane (**23**) under appropriate hydrosilylation conditions with a Pt, Rh, Ru or Al catalyst.[25] However, depending on the catalyst and conditions, the initial 1:1 product (**23**) undergoes further reaction to afford 1,2-disilylethane (**24**; equation 9).[1b] Formation of 1,1-disilylethane is scarcely recorded.

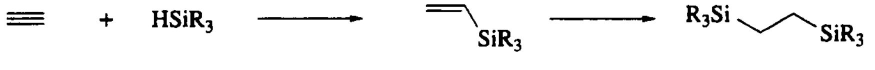

+ HSiR₃
SiR₃
R₃Si
SiR₃

(9)

**(23)** **(24)**

To obtain vinylsilanes from alkynes, transition metal complexes of Group VIII combined with a main group metal chloride are particularly effective.[1b] In the presence of a heterogeneous catalyst like Pd/γ-alumina, Rh/carbon and polymer bound Pt, trichlorosilane gives trichlorovinylsilane with atmospheric pressure of acetylene.[1b] Platinum supported on sulfur-containing silica gel is a practical catalyst for 1,2-dihydrosilylation, as exemplified in equation (10).[26]

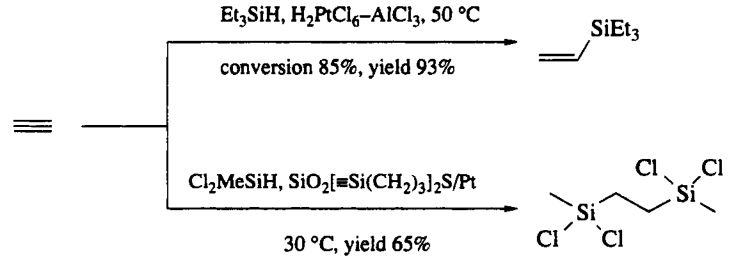

Et₃SiH, H₂PtCl₆–AlCl₃, 50 °C
conversion 85%, yield 93%
SiEt₃
Cl₂MeSiH, SiO₂[≡Si(CH₂)₃]₂S/Pt
30 °C, yield 65%
Cl
Cl
Si
Si
Cl
Cl

(10)

Thermal hydrosilylation of acetylene is feasible, but requires a high reaction temperature. A rather unusual example is shown in equation (11).[27]

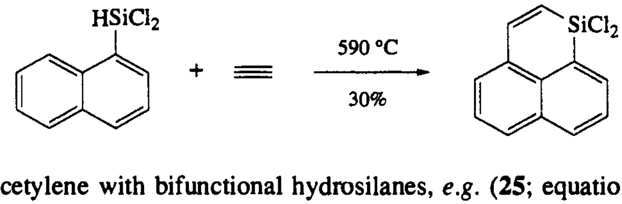

HSiCl₂
+
590 °C
30%
SiCl₂

(11)

Hydrosilylation of acetylene with bifunctional hydrosilanes, *e.g.* (**25**; equation 12) and (**27**; equation 13), leads to polymers, *e.g.* (**26**) and (**28**) respectively, which contain silicon in the polymer main chain.[28–30]

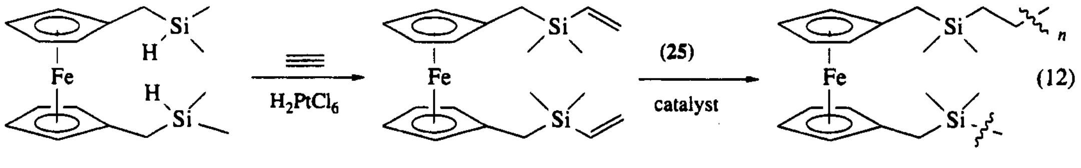

Si
H
Fe
H
Si
H₂PtCl₆
Si
Fe
Si
(25)
catalyst
Si
Fe
Si
n

(12)

**(25)** **(26)**

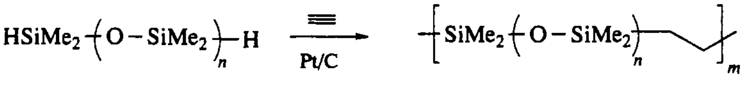

HSiMe₂(O–SiMe₂)ₙH
Pt/C
SiMe₂(O–SiMe₂)ₙ
m

(13)

**(27)** **(28)**

### 3.12.2.2 Hydrosilylation of Monosubstituted Alkynes

Hydrosilylation of monosubstituted alkynes (**29**) should give, *a priori*, three isomeric products: (**30**; β-*Z*), (**31**; β-*E*) and (**32**; α), as illustrated in equation (14). Though the product distribution changes depending on the kind of substituent R, the silane, the solvent and the reaction temperature, it is well accepted that (**30**) is derived from radical-initiated hydrosilylation, whereas (**31**) is derived from transition metal catalyzed hydrosilylation. Table 1 summarizes typical examples. For instance, 1-hexyne (**29**; R = $Bu^n$) is converted into (**30**; R = $Bu^n$, $SiR^1_3$ = $SiCl_3$) with $(PhCOO)_2$, but into (**31**; R = $Bu^n$, $SiR^1_3$ = $SiCl_3$) with $H_2PtCl_6$ at low temperature.[2b] When a large excess of $HSiCl_3$ was employed and the reaction time was prolonged, the yield of the 1:1 adducts decreased to 62% and 1:2 adducts were produced in fair amounts ($Cl_3Si(CH_2)_6SiCl_3$, 20% and $Bu^nCH(SiCl_3)CH_2SiCl_3$, 18%). Platinum catalyst (**1**) is more effective in giving (**31**), particularly at low temperature.[31,32] Hydrosilylation of 1-hexyne (**29**; R = $Bu^n$) with $Et_3SiH$ and the Pt catalyst (**1**) again gave (**31**; R = $Bu^n$, $SiR^1_3$ = $SiEt_3$) at ambient temperature,[33] but at 100 °C the formation of (**32**; R = $Bu^n$, $SiR^1_3$ = $SiEt_3$) increased.[34] The reactivity of 1-alkynes in hydrosilylation with $Et_3SiH$ and $[\{(Cy_3P)(Me_3Ge)(\mu\text{-}H)Pt\}_2]$ catalyst has been studied,[35] and the following relative order was disclosed: $Pr^nC{\equiv}CH$ (1.0), $Bu^nC{\equiv}CH$ (1.4), n-$C_5H_{11}C{\equiv}CH$ (1.5), $MeEtC(OH)C{\equiv}CH$ (6.8), c-$C_5H_9C{\equiv}CH$ (7.4), $Me_2C(OH)C{\equiv}CH$ (9.5) and $PhCH(OH)C{\equiv}CH$ (12.9). The factors controlling the reactivity and regioselectivity of hydrosilylation are correlated to the $^{13}C$ NMR chemical shifts of C-1 and C-2 of 1-alkynes. The chemical shifts of C-2 generally appear at lower field than C-1 and show a linear dependence on reactivity: those 1-alkynes with C-2 absorption at low magnetic field are the more reactive.[36]

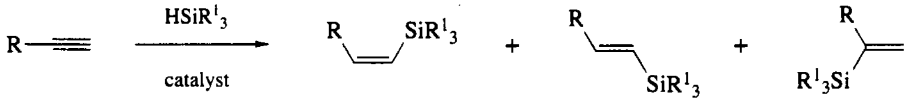

(14)

(**29**) (**30**) β-(*Z*) (**31**) β-(*E*) (**32**) α

**Table 1** Hydrosilylation of Monosubstituted Ethynes (**29**)

| *R in (**29**)* | *$HSiR^1_3$* | *Catalyst* | *Yield (%)* | *Products ratio*<br>*β-(Z) (**30**)* | <br>*β-(E) (**31**)* | <br>*α (**32**)* | *Ref.* |
|---|---|---|---|---|---|---|---|
| $Bu^n$ | $HSiCl_3$ | $(PhCOO)_2$ | 36 | 77 | 23 | — | 2b |
| $Bu^n$ | $HSiCl_3$ | Pd/C | 93 | ~0 | ~100 | — | 2b |
| $Bu^n$ | $HSiCl_3$ | $H_2PtCl_6$ (71 °C) | 92 | — | 78 | 22 | 31 |
| $Bu^n$ | $HSiCl_3$ | $H_2PtCl_6$ (5 °C) | — | — | 95 | 5 | 32 |
| $Bu^n$ | $HSiEt_3$ | $H_2PtCl_6$ (20 °C) | 100 | — | 82 | 18 | 33 |
| $Bu^n$ | $HSiEt_3$ | $H_2PtCl_6$ (100 °C) | 78 | — | 42 | 58 | 34 |
| $Bu^n$ | $HSiEt_3$ | $[RhCl(PPh_3)_3]$ | 95 | 65 | 35 | — | 37 |
| $Bu^n$ | $HSiMe_2Ph_3$ | $[RhCl(PPh_3)_3]$ | 98 | 72 | 28 | — | 37 |
| $Bu^n$ | $HSiMe_2Et$ | $[RhCl(PPh_3)_3]$ | 95 | 81 | 19 | — | 37 |
| Ph | $HSiCl_3$ | $H_2PtCl_6$ | 96 | — | 69 | 31 | 38 |
| Ph | $HSiCl_2Me$ | $H_2PtCl_6$ | 97 | — | 82 | 18 | 38 |
| Ph | $HSiEt_3$ | $H_2PtCl_6$ | 93 | — | 81 | 19 | 38 |
| Ph | $HSiCl_3$ | $[RhCl(PPh_3)_3]$ | 60 | 15 | 57 | 28 | 38 |
| Ph | $HSiCl_2Me$ | $[RhCl(PPh_3)_3]$ | 98 | 11 | 71 | 18 | 38 |
| Ph | $HSiEt_3$ | $[RhCl(PPh_3)_3]$ | 35 | 45 | 36 | 19 | 38 |
| $MeCl_2Si$ | $HSiClMe_2$ | $H_2PtCl_6$ | 94 | — | only | — | 39 |
| $MeCl_2Si$ | $HSiClMe_2$ | $[RhCl(PPh_3)_3]$ | 85 | — | 60 | 40 | 39 |
| $MeCl_2Si$ | $HSiClMe_2$ | $[Pt(PPh_3)_4]$ | 95 | — | 4 | 96 | 39 |
| $Me_3Si$ | $HSiClMe_2$ | $[Pt(PPh_3)_4]$ | — | — | 80 | 20 | 39 |

In contrast to Pt catalysts, Rh catalysts like $[RhCl(PPh_3)_3]$ afford the β-(*Z*) product (**30**) mainly. The product ratio depends on the donor capability of the phosphine ligand: (**30**) is preferred in the order of $P(o\text{-}MeOC_6H_4)_3 \gg PPh_3 \approx P(o\text{-tolyl})_3 \approx P(p\text{-}MeOC_6H_4)_3 \gg P(OMe)_3 \approx P(OEt)_3 \approx P(OPh)_3$. In other words, acceptor ligands favor *syn* addition leading to the β-(*E*) adduct (**31**).[40] It is also claimed that $[RhCl(PPh_3)_3]$ strictly purified under a completely deoxygenated atmosphere exhibits low activity, but the reactivity is much enhanced by a trace of oxygen or *t*-butyl peroxide.[7] The catalyst prepared *in situ* from $[\{RhCl(C_8H_{14})_2\}_2]$ and 2 mol of $PPh_3$ is the most reactive rhodium system.[41]

Phenylacetylene (**29**; R = Ph) shows similar reactivity to other 1-alkynes. $H_2PtCl_6$ catalyst (**1**) affords (**31**; R = Ph) preferentially along with a small amount of (**32**; R = Ph), irrespective of the substituents on the silanes used. The catalyst system, which consists of $H_2PtCl_6$ and an additive of $AlCl_3$, $SiCl_4$, $GeCl_4$ or $CeCl_3$, increases the yield of the 1:1 adducts and enhances the selectivity in favor of the β-(*E*) product

(**31**).[25] In contrast, the regioselectivity using Rh catalysts such as $[RhCl(PPh_3)_3]$, $[RhCl(CO)(PPh_3)_2]$ and $[Rh(acac)(CO)_2]$ depends on the electronic nature of the hydrosilane: chlorosilanes give (**31**) and (**32**), and trialkylsilanes give (**30**) as the major products, respectively. The ligand effect in the series $[RhCl(CO)P_2]$ has been studied: *syn* addition leading to (**31**) is preferred in the order $P = PPh_3 > PPh_2Bu^n > PPhEt_2 > PPh_2Pr^i > PPhBu^n{}_2 > PEt_2Pr^i > PPhPr^i{}_2 > PBu^n{}_3$.[42]

Hydrosilylation of silylalkynes (**29**; $R = SiR^2{}_3$) gives (**31**; $R = SiR^2{}_3$) as the major product.[1b] The steric repulsion overrides the electronic effect which should encourage the formation of (**32**; $R = SiR^2{}_3$). This trend applies also to the $[Pt(PPh_3)_4]$ catalyst, but unusual selectivity is reported in the platinum(0)-catalyzed reaction of $MeCl_2SiC{\equiv}CH$ with $Me_2ClSiH$, whereby (**32**; $R = SiCl_2Me$) is obtained with exceptionally high selectivity (96%). An additional example of α-adduct (**32**) formation is the $H_2PtCl_6$-catalyzed hydrosilylation using a trisilacyclohexane, $CH_2(SiMe_2CH_2)_2Si(Me)H$.[43]

The nickel(0) catalyst prepared by reduction of $[Ni(acac)_2]$ with $Et_3Al$ induces the reaction of 1-pentyne with $(EtO)_3SiH$ to give a 2:1 adduct (**33**) in 80% yield instead of the normal 1:1 adduct (equation 15).[44]

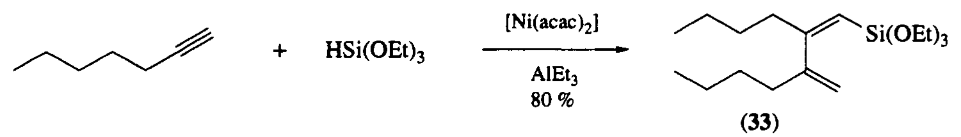

(**33**)

(15)

Many other examples are recorded of monosubstituted alkynes with substituents $ClCH_2$,[45] $BrCH_2$,[46] $CF_3$,[47] $HOCR^2{}_2$,[48] $R^2{}_2NCH_2$,[48] $R^2OCH_2$,[48] 2-thienyl[48] and others.[1b] In all cases the corresponding vinylsilanes are produced in high yields.

An alternative route to the hydrosilylation product of monosubstituted alkynes (**29**) is that which involves silylmetallation of the alkynes (equation 16).[24] A cuprate reagent (**34**) prepared from CuCN and 2 mol of $Me_2PhSiLi$ adds in a *syn* manner to the C≡C bond with the $Me_2PhSi$ group at the terminal carbon. Quenching with water affords a product of type (**31**).

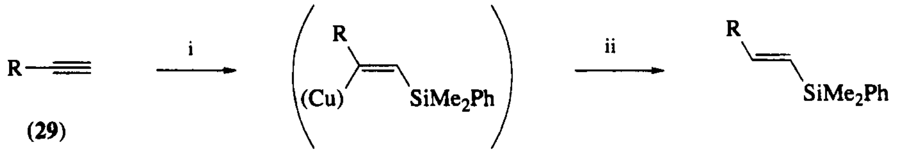

(16)

i, $(Me_2PhSi)_2CuLi_2CN$ (**34**); ii, $H_2O$ R = H, 78%; R = Me, 94%; R = Ph, 67%

### 3.12.2.3 Hydrosilylation of Disubstituted Alkynes

The hydrosilylation of disubstituted alkynes using platinum catalysts is slower than the hydrosilylation of monosubstituted alkynes but exhibits similar selectivities.[35] Examples are shown for 2-butyne and 2-pentyne in equations (17) and (18), respectively.[49] In both cases *syn* addition takes place exclusively. The regioselectivity (65:35) for 2-pentyne is attributed to the general trend that the silyl group prefers the alkyne carbon which has the less bulky substituent (compare the regioselectivity of 1-propyne, where silicon adds to the terminal carbon with a selectivity of 96:4[36]). As a trimethylsilyl group is larger than an alkyl group, hydrosilylation of 1-trimethylsilyl-1-alkynes takes place highly selectively, as shown in equation (19).[50]

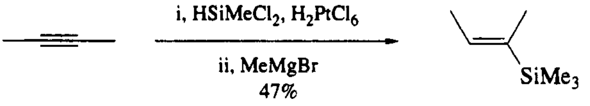

(17)

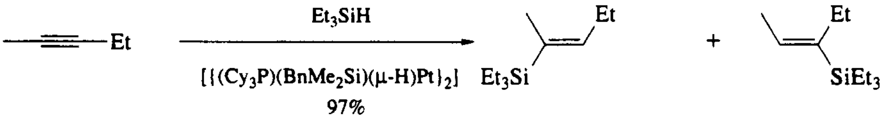

65:35

(18)

In contrast to platinum catalysts, rhodium catalysts often effect *anti* addition (equation 20).[51]

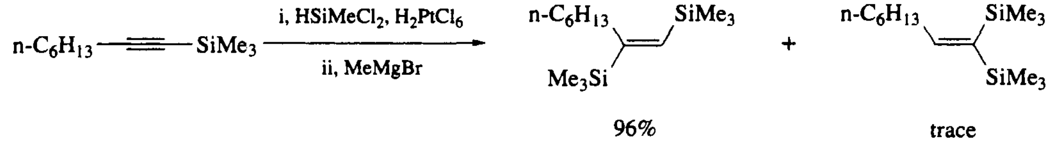
n-C6H13—≡—SiMe3
i, HSiMeCl2, H2PtCl6
ii, MeMgBr
n-C6H13
SiMe3
Me3Si
96%
+
n-C6H13
SiMe3
SiMe3
trace

(19)

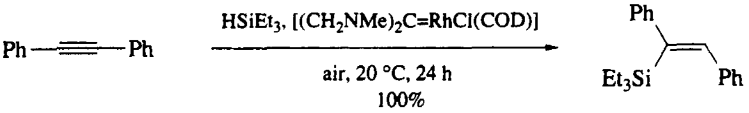
Ph—≡—Ph
HSiEt3, [(CH2NMe)2C=RhCl(COD)]
air, 20 °C, 24 h
100%
Ph
Et3Si
Ph

(20)

A nickel catalyst induces, in addition to normal hydrosilylation, double silylation (equation 21)[52] and silacyclopentadiene formation (equation 22).[53]

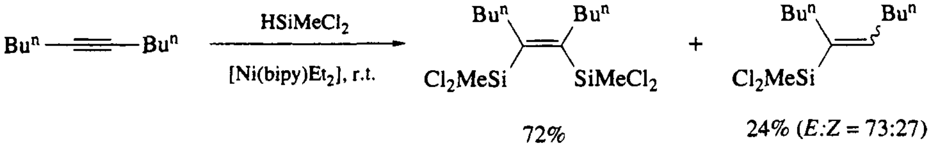
Bun—≡—Bun
HSiMeCl2
[Ni(bipy)Et2], r.t.
Bun
Bun
Cl2MeSi
SiMeCl2
72%
+
Bun
Bun
Cl2MeSi
24% (E:Z = 73:27)

(21)

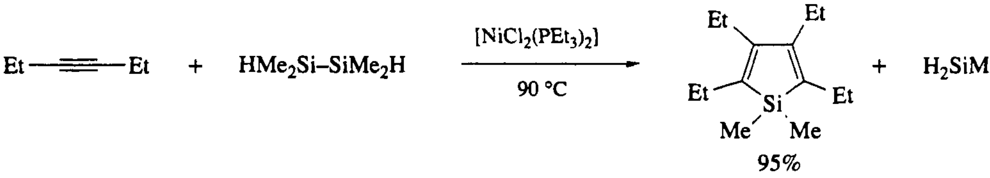
Et—≡—Et
+
HMe2Si–SiMe2H
[NiCl2(PEt3)2]
90 °C
Et
Et
Et
Et
Si
Me
Me
95%
+
H2SiMe2

(22)

### 3.12.3 HYDROSILYLATION OF CONJUGATED CARBON-CARBON TRIPLE BONDS

Three reaction pathways are possible for vinylalkyne (**34**): 1,2-addition to the C≡C moiety to give (**35**) and/or (**36**); 1,2-addition to the C=C moiety; and 1,4-addition leading to *e.g.* (**37**; equation 23). The reaction favoring the second path remains to be found, but conjugate addition to give allenes (**37**) is sometimes observed as a minor reaction. In most cases, only the alkyne moiety undergoes hydrosilylation, the regioselectivity of which depends on the substituent R connected to the alkynic carbon.[54–60] When R is H or $CH_2OMe$, (**36**) is produced exclusively, whereas (**35**) predominates when R is bulky, like trialkylsilyl or trisubstituted alkyl. A typical example is illustrated in equation (24).

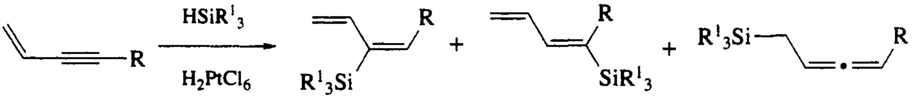
R
HSiR'3
H2PtCl6
R
R'3Si
+
R
SiR'3
+
R'3Si
R

(23)

**(34)** **(35)** **(36)** **(37)**

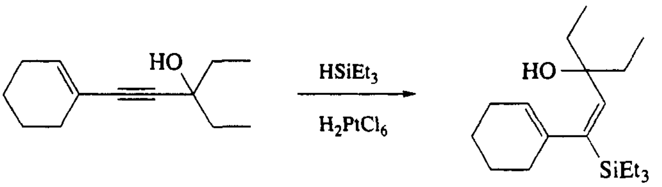
HO
HSiEt3
H2PtCl6
HO
SiEt3

(24)

In some cases, consecutive 1,2-addition and 1,4-addition take place (equation 25).[61]

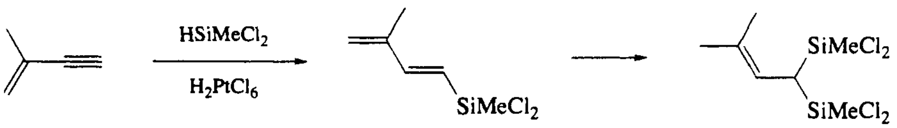
HSiMeCl2
H2PtCl6
SiMeCl2
SiMeCl2
SiMeCl2

(25)

Only a few examples are reported of hydrosilylation of conjugated diynes. 1,4-Bis(trimethylsilyl)butadiyne (**38**) gives at first trisilyl-substituted butenyne (**39**), wherein the hydrosilane-derived silyl group has added to an inner alkyne carbon. The butenyne (**39**) undergoes further hydrosilylation in various ways depending on the electronic nature of the hydrosilanes (Scheme 6). Dichloromethylsilane reacts with the remaining alkynic bond of (**39**) to give (**40**).[62] Trialkylsilane reacts with the intermediate (**41**) in a conjugate manner to give the allene (**42**).[63] This type of reaction is sensitive to the steric bulk of the substituents. The substrate whose C≡C is sterically less crowded undergoes 1,2-addition (equation 26).

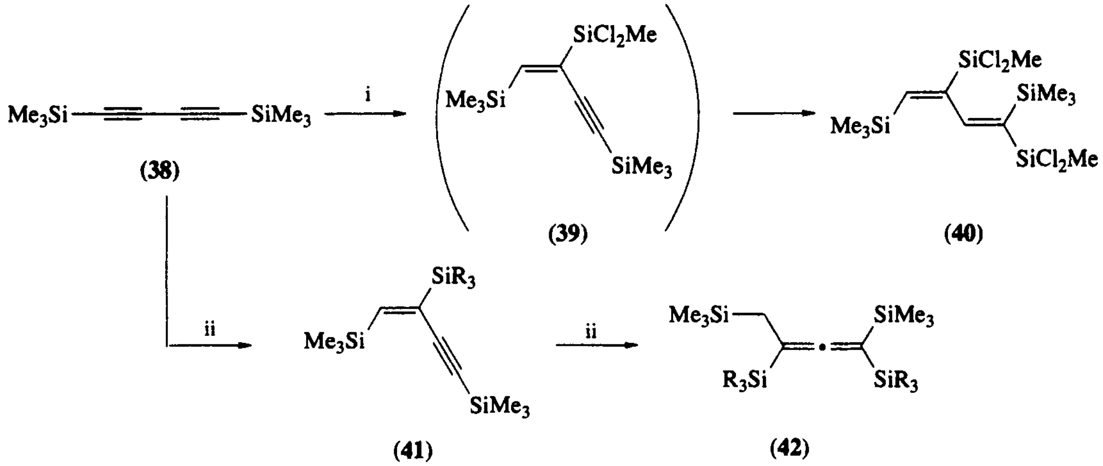

i, $HSiCl_2Me$, $H_2PtCl_6$; ii, $HSiR_3$ (R = Me, Et, Ph), $H_2PtCl_6$ or $[RhCl(PPh_3)_3]$

**Scheme 6**

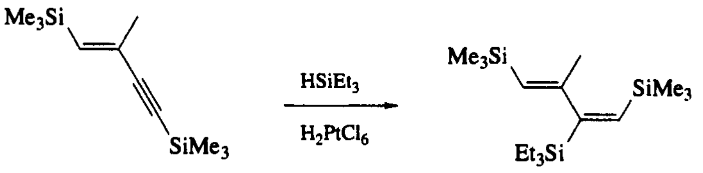

(26)

## 3.12.4 HYDROSILYLATION OF CARBON–CARBON DOUBLE BONDS

### 3.12.4.1 Hydrosilylation of Ethylene

Hydrosilylation of ethylene (equation 27) is the prototype for the addition of hydrosilanes across carbon–carbon double bonds, and is achieved by means of such metal complex catalysts as $H_2PtCl_6$,[64] $[RhCl(PPh_3)_3]$,[65] $[\{RhCl(CO)_2\}_2]$ (equation 28),[15] $[Co_2(CO)_8]$,[65] $[HCo(CO)_4]$,[66] $[NiCl_2(dmpf)]$,[10,67] $[Pd(PPh_3)_4]$[68] and also with the aid of γ-rays, which initiate radical reactions.[69]

$$H_2C=CH_2 \quad + \quad HSiR_3 \quad \xrightarrow{\text{catalyst}} \quad EtSiR_3 \qquad (27)$$

R = Cl, OEt, Me, Et, Ph *etc.*

$$H_2C=CH_2 \; + \; HSiCl_3 \quad \xrightarrow[\substack{\text{60 atm ethylene} \\ 95\%}]{[\{RhCl(CO_2\}_2],\ 20\ ^\circ C,\ 65\ h} \quad EtSiCl_3 \qquad (28)$$

When trialkylsilanes are employed, vinylsilane is often produced as the main product. This oxidative hydrosilylation can be carried out with $[Me_3SiCo(CO)_4]$,[21] $[Cp^*{}_2Rh_2Cl_4]$ (equation 29),[70] $[\{Ir(OMe)(COD)\}_2]$,[6b] $[Cp^*Fe(CO)_2SiMe_3]$,[22] or $Na[HRu_3(CO)_{11}]$[11d,11e] catalysts. This unusual reaction is understood in terms of silylmetallation rather than the ordinary hydrometallation mechanism.[7]

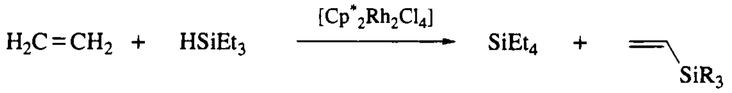

(29)

| | | |
|---|---|---|
| 1 atm | 74% | 26% |
| 7 atm | 40% | 60% |

### 3.12.4.2 Hydrosilylation of Monosubstituted Alkenes

In principle, two regioisomers are produced by the reaction of terminal alkenes and hydrosilanes: one where the terminal carbon forms a bond to the silyl group (normal product) and the other which has the silyl group at the inner carbon (branched product). Platinum and rhodium catalysts yield in general the normal products, whereas palladium catalysts sometimes prefer the reaction pathway leading to the branched products. Ruthenium and rhodium afford additional by-products such as alkenylsilanes and alkanes. A typical example is the hydrosilylation of 1-octene (equation 30).[71]

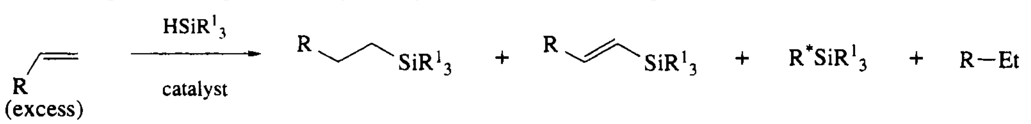

(30)

$R = n\text{-}C_6H_{13}$, $HSiR^1_3 = HSiMe_2(n\text{-}C_{10}H_{21})$, $R^* = n\text{-}C_5H_{11}CH{=}CHCH_2$

| | | | | | |
|---|---|---|---|---|---|
| *Catalyst* | $H_2PtCl_6$ | 96% | – | – | – |
| | $[Ru_3(CO)_{12}]$ | 11% | 47% | 43% | 87% |
| | $[RhCl(PPh_3)_3]$ | 60% | 32% | 8% | 38% |
| $R = Ph$, $HSiR^1_3 = HSiEt_3$ | | | | | |
| | $[Ru_3(CO)_{12}]$ | ~0 | 93% | - | 96% |
| $R = Bu^n$, $HSiR^1_3 = HSiEt_3$, $R^* = Pr^nCH{=}CHCH_2$ | | | | | |
| | $[Ru_3(CO)_{12}]$ | ~0 | 83% | 16% | not determined |

The product distribution depends on the mole ratio of the substrate alkene to hydrosilane. In the presence of a large excess of alkene, dehydrogenative hydrosilylation is apt to become the major process, as illustrated in equation (31).[70]

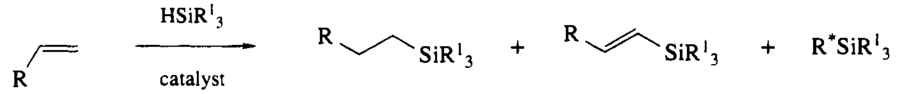

(31)

$R = n\text{-}C_5H_{11}$, $HSiR^1_3 = HSiEt_3$, catalyst = $[Cp^*_2Rh_2Cl_4]$, $R^* = Bu^nCH{=}CHCH_2$

| *Substrate:hydrosilane* | | | |
|---|---|---|---|
| 1:1 | 94% | 0% | 3% |
| 5:1 | 34% | 52% | 8% |
| $R = MeOCO$, $HSiR^1_3 = HSiMeEt_2$, catalyst = $[Co_2(CO)_8]$ | | | |
| 1:3 | 58% | 0% | - |
| 1:1 | 10% | 30% | - |
| 2.5:1 | 5% | 94% | - |

Vinylsilanes give 1,1-disilylethane and/or 1,2-disilylethane depending on the substituent of the hydrosilane (equation 32) and the metal catalyst (equation 33). Thus by choosing these variables properly, both types of disilylethane are readily accessible.[72,73]

Under radical conditions, hydrosilanes add across terminal alkenes to give 1-silylalkanes. Di-*t*-butyl peroxide is the catalyst of choice (equation 34). Benzoyl peroxide or AIBN is much less effective.[74]

Intramolecular hydrosilylation affords silacycles. Diphenyl(4-pentenyl)silane (**43**) undergoes ring closure upon treatment with a transition metal catalyst, with or without a solvent, to give the five-membered ring compound (**44**) preferentially, rather than the silacyclohexane (**45**; equation 35).[75] The mode of ring closure has been studied by changing *n* in (**46**), as summarized in equation (36).[76] The silylalkene (**46**) with *n* = 0 or 1 gave polymers by intermolecular hydrosilylation and no monomeric cyclic products.

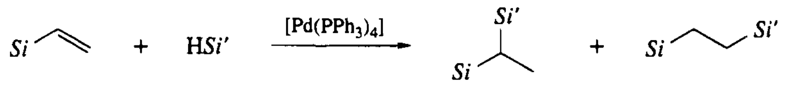
Si
HSi′
[Pd(PPh3)4]
Si′
Si
Si
Si′

(32)

| | | |
|---|---|---|
| *Si* = $Cl_3Si$, *Si′* = $SiCl_3$ | 90% | 2% |
| *Si* = $Cl_3Si$, *Si′* = $SiMeCl_2$ | 3% | 90% |
| *Si* = $Cl_2MeSi$, *Si′* = $SiCl_3$ | 1% | 89% |
| *Si* = $ClMe_2Si$, *Si′* = $SiCl_3$ | 0% | 80% |

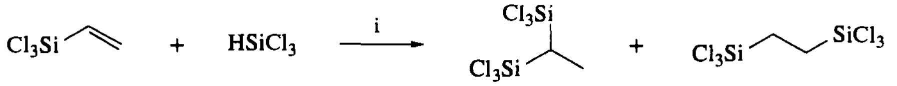
Cl3Si
HSiCl3
i
Cl3Si
Cl3Si
Cl3Si
SiCl3

(33)

| *Catalyst* | | |
|---|---|---|
| $H_2PtCl_6$–cyclohexanone | 0% | 92% |
| $[RhCl(PPh_3)_3]$ | 6% | 90% |
| $[NiCl_2(PPh_3)_2]$ | 30% | 50% |
| $[Pd(PPh_3)_4]$ | 81% | 4% |

i, vinylsilane:hydrosilane:catalyst = 1:1:2x$10^{-4}$ at 120 °C

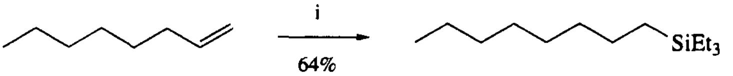

(34)

i, $HSiEt_3$ (6 mol), $Bu^tOOBu^t$ (0.2 mol), 170 °C, 0.5 h

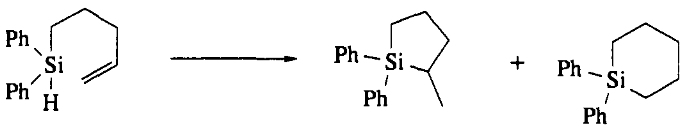
Ph
Si
Ph
H
Ph
Si
Ph
Ph
Si
Ph

(43) (44) (45)

(35)

| | | |
|---|---|---|
| $H_2PtCl_6 \cdot 6H_2O$, neat, 20 °C | 93% | 20–22:1 |
| Phenylalanine•Pt•$C_2H_4$•$Cl_2$, toluene, 80 °C | 89% | 100:0 |
| $[RhCl(PPh_3)_4]$, neat, 80 °C | 89% | 6.6:1 |

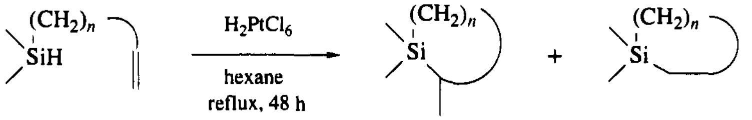
(CH2)n
SiH
H2PtCl6
hexane
reflux, 48 h
(CH2)n
Si
(CH2)n
Si

(46)

(36)

| *n* | *Yield* (%) | *Ratio* |
|---|---|---|
| 2 | 46 | 0:100 |
| 3 | 58 | 90:10 |
| 4 | 70 | 53:47 |
| 5 | 16 | 54:46 |
| 6 | 2 | 100:0 |

Allyl halides (equation 37), vinyl halides (equation 38) and vinyl ethers are good substrates for the preparation of organosilanes having functional groups at the β- or γ-position. Reduction of these substrates sometimes takes place to give the parent alkenes (equation 37), which are derived from β-elimination of the regioisomeric hydrosilylation intermediates.[77]

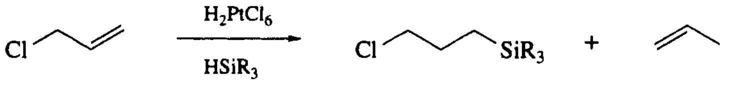
Cl
H2PtCl6
HSiR3
Cl
SiR3
+
(37)

| | | |
|---|---|---|
| $HSiEt_3$ | 5% | 70% |
| $HSiPh_2Me$ | 70% | 10% |

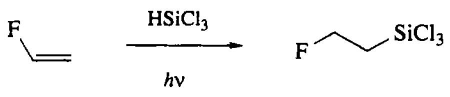
F
HSiCl3
hν
F
SiCl3
(38)

### 3.12.4.3 Hydrosilylation of Disubstituted and More Highly Substituted Alkenes

With $H_2PtCl_6$ as the catalyst, highly substituted alkenes undergo double-bond migration before hydrosilylation to give rise to the products which have silyl groups at the least-substituted, commonly terminal, carbons. These substrates generally require longer reaction times.[1c,3,78] Three examples are given in equation (39).

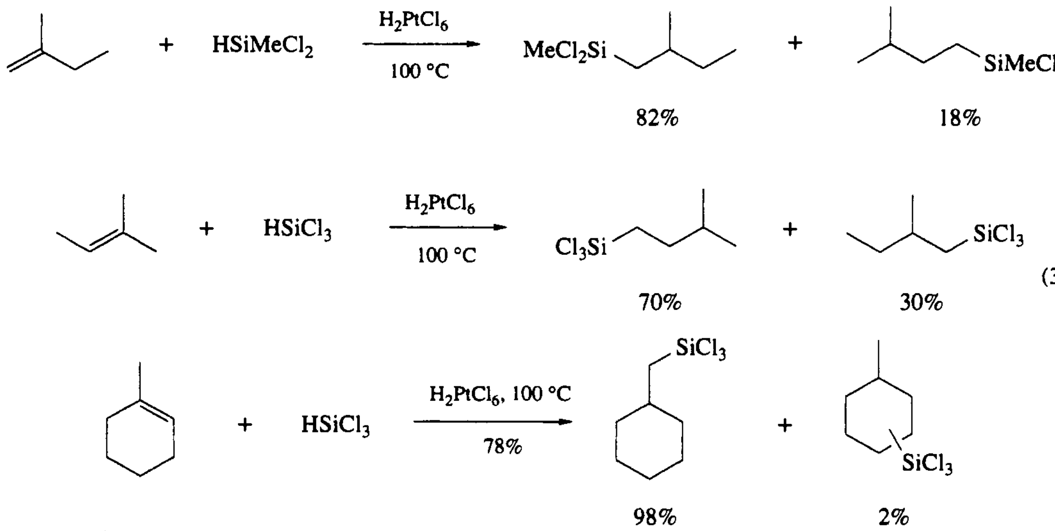
+ HSiMeCl2
H2PtCl6
100 °C
MeCl2Si
+
SiMeCl2
82%
18%
+ HSiCl3
H2PtCl6
100 °C
Cl3Si
+
SiCl3
70%
30%
+ HSiCl3
H2PtCl6, 100 °C
78%
SiCl3
+
SiCl3
98%
2%
(39)

Disubstituted alkenes which have an allylic quaternary carbon center (**47**) undergo skeletal rearrangement as shown in equation (40).[79]

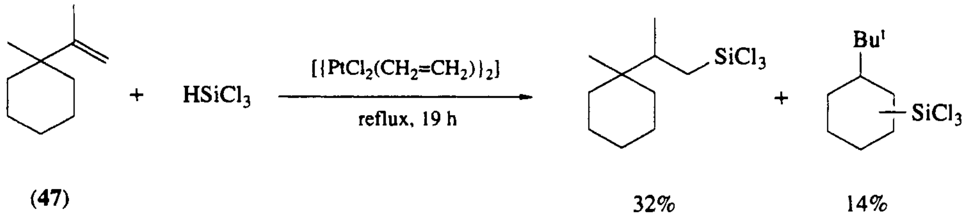
+ HSiCl3
[{PtCl2(CH2=CH2)}2]
reflux, 19 h
SiCl3
+
Bu<sup>t</sup>
SiCl3
32%
14%
(40)

(**47**)

Wilkinson's catalyst is less reactive towards 1,1- and 1,2-disubstituted alkenes, and low yields and side reactions are often observed. However, the catalyst (**48**) is reactive enough to afford straightforward products in fair yields without double-bond migration (equation 41).[80]

Fully substituted alkenes are hydrosilylated with aluminum chloride without double-bond migration.[81a] The products have tertiary alkyl groups and thus may be utilized as silyl protecting groups for alcohols and related functional groups.[81b] For example, chlorodimethylthexylsilane (**49**) is readily prepared from 2,3-dimethyl-2-butene (equation 42).

In contrast to the $H_2PtCl_6$-catalyzed hydrosilylation, the formation of positional isomers is negligible under radical conditions, although the stereochemical results are random. Thus 1-methylcyclohexene

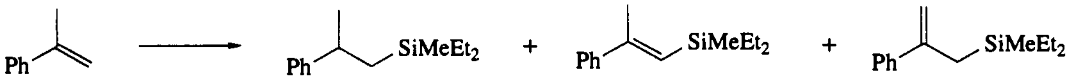

| | | | | | |
|---|---|---|---|---|---|
| i, 20% | 76.3 | : | 15.1 | : | 8.6 |
| ii, 61.2% | 100 | : | 0 | : | 0 |

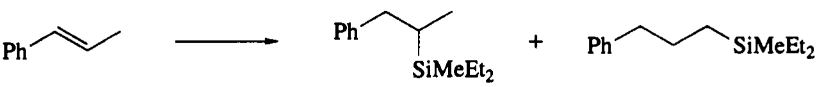

(41)

| | | | |
|---|---|---|---|
| i, 16.2% | 64.6 | : | 26.1 |
| ii, 52.1% | 95.2 | : | 4.8 |

i, $HSiMeEt_2$, $[RhCl(PPh_3)_3]$, 60 °C, 6 h; ii, $HSiMeEt_2$, $[\{RhCl(CH_2{=}CH_2)_2\}_2]$ (**48**), 60 °C, 6 h

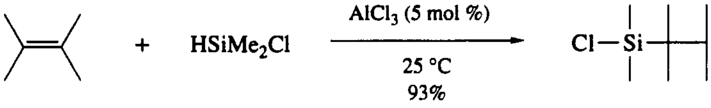

**(49)**

(42)

The following can be prepared similarly:

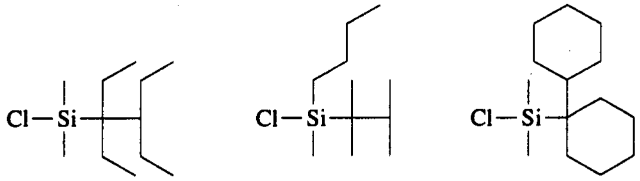

80% 80% 67%

gives a 5.5–9:1 mixture of (**50**) and (**51**).[2a] In contrast, thermal reaction induces some double-bond isomerization, and a third product (**52**) is produced (equation 43).

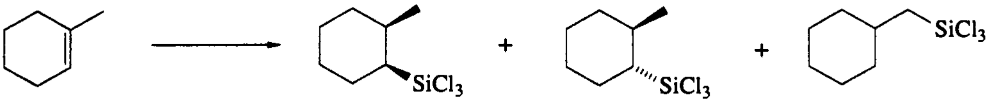

(43)

| | (**50**) | | (**51**) | | (**52**) |
|---|---|---|---|---|---|
| i, 100% | 85 | : | 15 | : | 0 |
| ii, 44% | 89 | : | 11 | : | 0 |
| iii, 100% | 58 | : | 23 | : | 19 |

i, $HSiCl_3$, $(AcO)_2$, reflux (45 °C), 9 h; ii, $HSiCl_3$, UV, reflux, 44 h; iii, $HSiCl_3$, 300 °C, 24 h

Hydrosilylation of (-)-β-pinene (**54**) under radical conditions results in opening of the strained cyclobutane ring to give only (**53**; equation 44).[82a] However, Pt-catalyzed hydrosilylation gives the expected product, which, after conversion of Si—Cl to Si—H, is used for the asymmetric reduction of ketones.[82b]

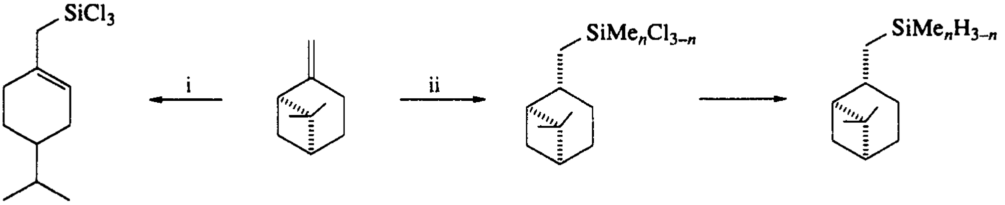

(44)

(**53**) (**54**) $n = 1, 2$

i, $HSiCl_3$, $(AcO)_2$ or Hg lamp; ii, $HSiCl_2Me$ or $HSiClMe_2$, $H_2PtCl_6$

An enamine (**55**) reacts with trichlorosilane in acetonitrile in the absence of catalyst to give a hydrosilylated product (**56**; equation 45). The regiochemistry is opposite to the standard pattern, the silyl group attaching itself to the more-hindered carbon.[83]

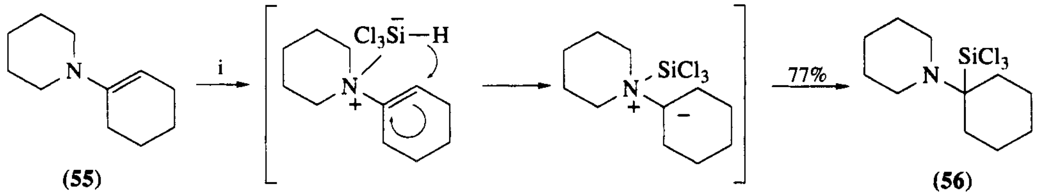

(**55**) (**56**) (45)

i, $HSiCl_3$, MeCN, reflux, 2.5 h

Alkenes are reduced with hydrosilanes in an acidic solvent like trifluoroacetic acid. The reaction is called 'ionic hydrogenation' and is useful particularly for reduction of highly substituted alkenes. The reaction is assumed to proceed through a carbocationic intermediate, to which hydride is delivered from the hydrosilane.[84] An example is given in equation (46), but see also Chapters 1.1 and 3.3, this volume.

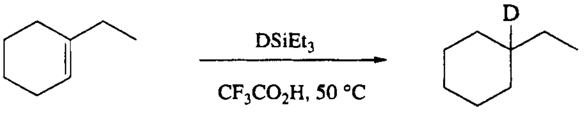

(46)

## 3.12.5 HYDROSILYLATION OF POLYENES

### 3.12.5.1 Hydrosilylation of Acyclic Polyenes

Polyenes whose C=C bonds are not conjugated behave as the substituted alkenes described above, and thus the hydrosilylation products are those in which the silyl group attaches itself to the less-hindered alkenic carbons.[85] When dihydrosilanes are employed, both silacarbocycles and polymers are produced (Scheme 7).[86]

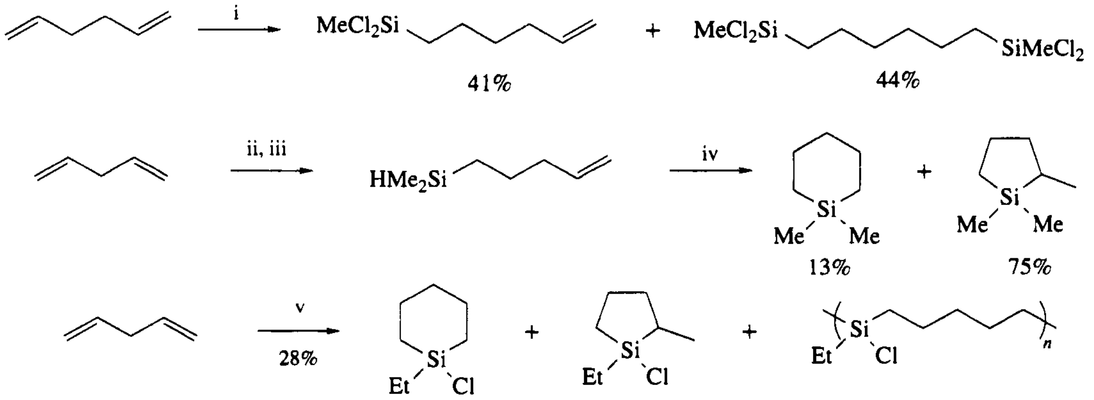

70:30

i, $HSiMeCl_2$, $H_2PtCl_6$, 140–150 °C, 13 h; ii, $HSiMe_2Cl$, $H_2PtCl_6$; iii, $LiAlH_4$; iv, $H_2PtCl_6$; v, $H_2SiClEt$, $H_2PtCl_6$

**Scheme 7**

Conjugated dienes like 1,3-dienes give 1:1 adducts of various types: usually 1,2- and 1,4-addition products, and the regio- and stereo-isomers of each type, but also 1:2 adducts, and dimerization and reduction products. The product distribution depends on the kinds of dienes, silanes and particularly on the kind of catalyst.[87,88] Of these, chromium hexacarbonyl is specific for the formation of (*Z*)-crotylsilanes from butadienes.[11g] Similar (*Z*)-selective hydrosilylation is observed with $HSiCl_3$ and $[Pd(PPh_3)_4]$ catalyst.[68] The reaction pattern of 1,3-butadiene is summarized in Scheme 8.

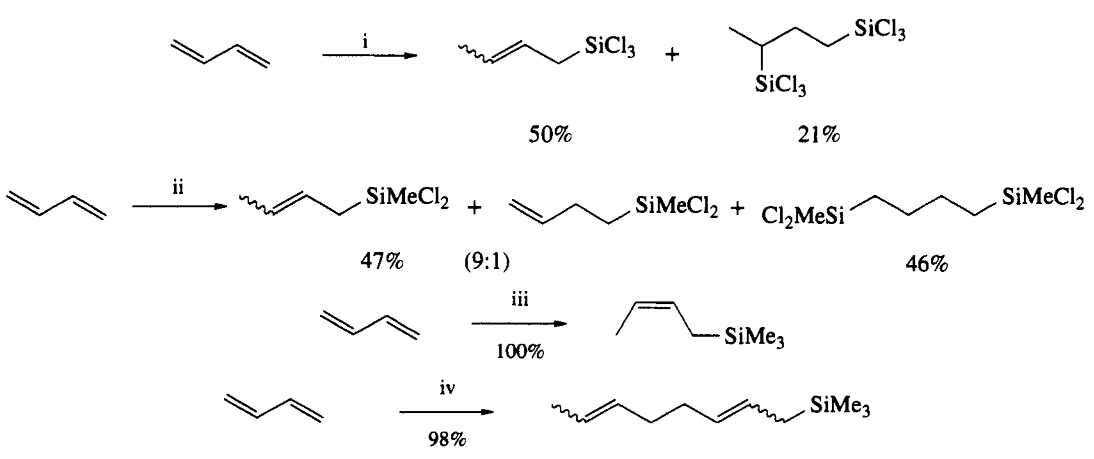
i
SiCl₃
SiCl₃
SiCl₃
50%
21%
ii
SiMeCl₂
SiMeCl₂
Cl₂MeSi
SiMeCl₂
47%
(9:1)
46%
iii
100%
SiMe₃
iv
98%
SiMe₃

i, Pt–C, $HSiCl_3$, 160 °C, 1.3 h; ii, $HSiMeCl_2$, $H_2PtCl_6$, 200 °C, 4 h; iii, $HSiMe_3$, $[Cr(CO)_6]$, *hv*;
iv, $HSiMe_3$, $[Pd(PPh_3)_2]$ (fumaric anhydride), 85 °C, 4.5 h

**Scheme 8**

Hydrosilylation of isoprene (**57**) has been well studied and the results are summarized in Table 2.[1d,89] Since 1,3-dienes are relatively reactive, metal complexes which do not catalyze hydrosilylation of common alkenes may be employed. Pd, Rh, Ni and Cr catalysts prefer 1,4-addition products with the (*Z*)-configuration. No catalyst is available which prefers 1,2-addition with high selectivity.

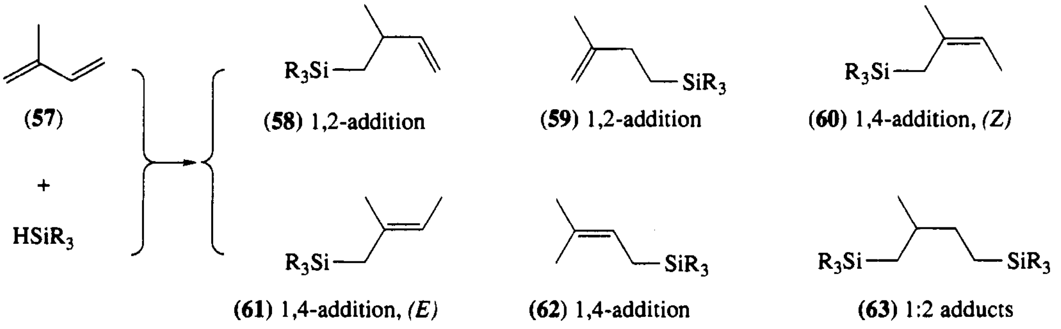
(57)
+
HSiR₃
R₃Si
(58) 1,2-addition
SiR₃
(59) 1,2-addition
R₃Si
(60) 1,4-addition, (Z)
R₃Si
(61) 1,4-addition, (E)
SiR₃
(62) 1,4-addition
R₃Si
SiR₃
(63) 1:2 adducts

**Scheme 9**

**Table 2** Hydrosilylation of Isoprene (**57**)

| *Catalyst* | *Hydrosilane* | *Conditions* | *Yield (%)* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *(**58**)* | *(**59**)* | *(**60**)* | *(**61**)* | *(**62**)* | *(**63**)* |
| $H_2PtCl_6$ | $HSiCl_3$ | 165 °C, 17 h | | | | | 72 | 6 |
| | $HSiCl_2Me$ | 165 °C, 17 h | | 31 | | | 57 | 9 |
| | $HSiMe_3$ | 165 °C, 17 h | | 27 | 20$^{a}$ | | <2 | 24 |
| $[Pt(PPh_3)_4]$ | $HSiCl_2Me$ | 48–82 °C, 25 h | | 38 | | | | 38 |
| $[PdCl_2(PhCN)_2]/PPh_3$ | $HSiCl_2Me$ | 70 °C, 6 h | | | 95 | — | | |
| $[PdCl_2(PPh_3)_2]$ | $HSiCl_3$ | 80 °C, 4 h | | | 100 | — | | |
| $[Pd(PPh_3)_4]$ | $HSiCl_3$ | 110 °C, 6 h | | | 83 | | 4 | |
| $[RhCl(PPh_3)_3]$ | $HSiClMe_2$ | 130 °C, 15 h | | | 19 | — | 41 | |
| | $HSiMe_2Ph$ | 80 °C, 2 h | | | 27 | | 71 | |
| $[Rh(acac)_3]$ | $HSiEt_3$ | 60 °C, 15 h | | 5$^{b}$ | | 94$^{c}$ | | |
| Ni (vapor) | $HSi(OEt)_3$ | −196 to −5 °C | | | 100 | — | — | |
| $[Ni(acac)_3]/AlEt_3$ | $HSiEt_3$ | 20 °C, 4 h | | | 96$^{d}$ | | | |
| $[Cr(CO)_6]$. *hν* | $HSiMe_3$ | 30 °C | | | 60 | — | 40 | |
| [HRu(COD){(−)-menthyl—N═CH—}$_2$]Cl | $HSi(OEt)_3$ | 25 °C, 150 h | 38 | 7 | — | — | 25 | — |

[a] Yield for (**60**) and (**61**). [b] Yield for (**58**) and (**59**). [c] Yield for (**60**), (**61**) and (**62**). [d] Yield for (**60**) and (**61**).

Myrcene (**64**) undergoes hydrosilylation preferentially at the terminal vinyl moiety to give a homoallylsilane (**65**), as shown in equation (47).[90]

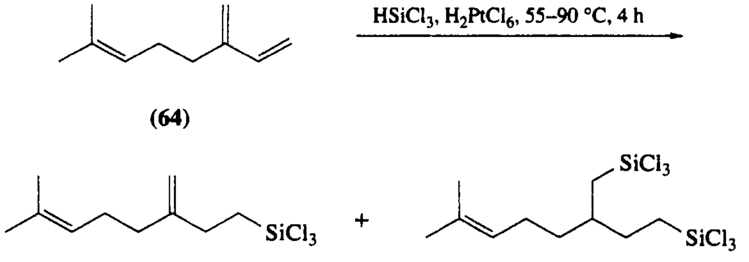

**(64)**

**(65)** 41% 19% (47)

The 1,2-dihydrodisilane (**66**) reacts with 2,3-dimethylbutadiene, in the presence of a Ni catalyst, to give both the normal hydrosilylation product and (*Z*)-1,4-disilyl-2-butene (Scheme 10). The nickel catalyst is assumed to be reduced to nickel(0), which oxidatively adds to the Si—Si bond of (**66**) in competition with addition to the Si—H bond.[53]

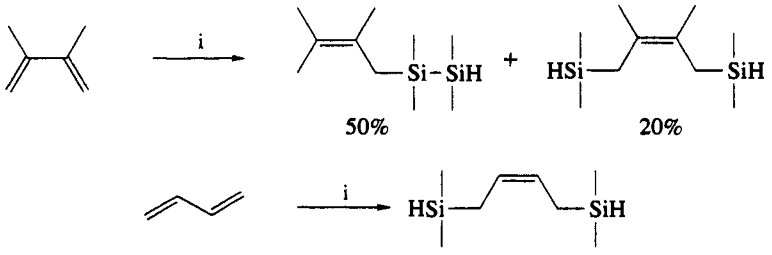

69%

i, $HSiMe_2–SiMe_2H$ (**66**), $[NiCl_2(PEt_3)_2]$, 90 °C

**Scheme 10**

### 3.12.5.2 Hydrosilylation of Cyclic Polyenes

Cyclic conjugated dienes intrinsically have a fixed cisoid diene system and therefore readily undergo 1,4-addition to give allylsilanes regardless of the kind of catalyst and substituents on the hydrosilanes (equations 48 and 49). Nonconjugated dienes like (**67**) and (**68**) give the same allylic silane as the conjugated isomers. The results are ascribed to alkene isomerization into conjugated dienes followed by hydrosilylation (equations 50 and 51).[91–95]

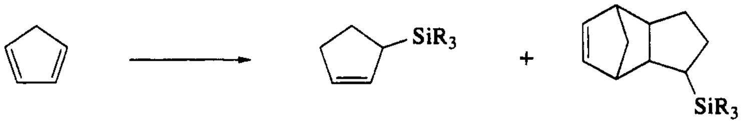

(48)

| | | |
|---|---|---|
| i | 52% | 40% |
| ii | 80–90% | – |

i, $HSiCl_3$, $H_2PtCl_6$, 250 °C; ii, $HSiCl_xMe_{3-x}$, $[PdCl_2(PhCN)_2]/PPh_3$, 80–90 °C

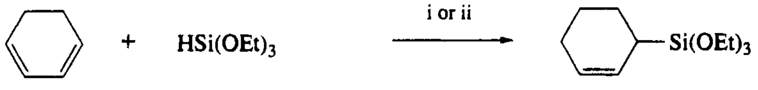

(49)

i, $[Ni(acac)_2]/Al(OEt)Et_2$, 20 °C, 97%; ii, $[Co_2(CO)_8]$, 20 °C, 88%

In contrast, a large ring polyene undergoes normal hydrosilylation. For example, (*Z*,*E*,*E*)-1,5,9-cyclododecatriene (**69**) gives the monoadducts (**70**) and (**71**), in which the two C═C bonds remain intact

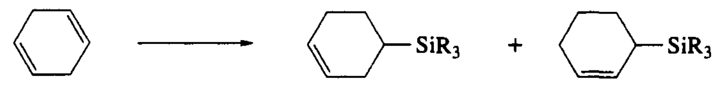

(50)

| (67) | | | |
|---|---|---|---|
| | i | 41% | 55% |
| | ii | – | 52% |

i, $HSiMeCl_2$, $[NiCl_2(PPh_3)_2]$, 120 °C; ii, $HSi(OEt)_3$, $[Ni(acac)_2]/Al(OEt)Et_2$, 20 °C

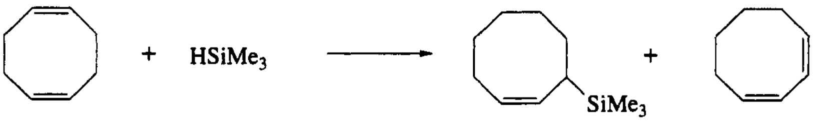

(51)

| (68) | | | |
|---|---|---|---|
| | i | 35% | – |
| | ii | 53% | 42% |
| | iii | 32% | 68% |

i, $H_2PtCl_6$, 45 °C; ii, $[H_2Pt(C_2H_4)(Py)]$; iii, Pt–C, 200 °C

(equation 52). As in many electrophilic reactions of (**69**), the (*E*)-C═C bonds are more reactive than (*Z*)-C═C bonds.[96]

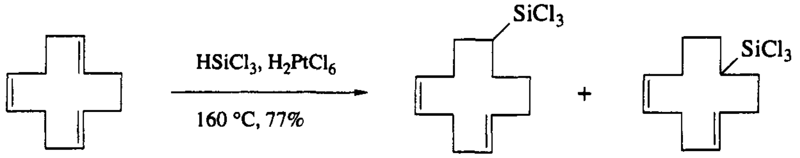

(52)

(**69**) (**70**) (**71**)

Norbornadiene (**72**) gives a tricyclic product (**73a**) in addition to the normal *endo*- and *exo*-hydrosilylated products (**73b**) and (**73c**) (equation 53). The tricyclic product is preferred under radical conditions.[97]

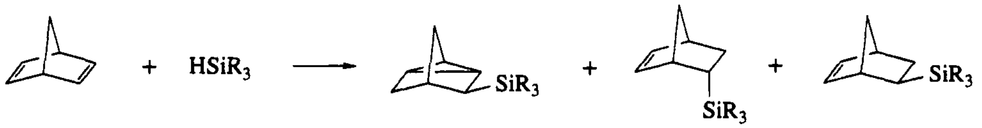

(53)

| (72) | | | (73a) | | (73b) | | (73c) |
|---|---|---|---|---|---|---|---|
| | i | 80% | 30 | : | 64 | : | 6 |
| | ii | 77% | 94 | : | 6 | : | 0 |
| | iii | 25% | 100 | : | 0 | : | 0 |
| | iv | 80% | 53 | : | 7 | : | 28 |

i, $HSiMeCl_2$, $H_2PtCl_6$, 50–60 °C; ii, $HSiMeCl_2$, Pt–C, 50–60 °C; iii, $HSiCl_3$, Pt–C, 35–50 °C;
iv, $HSiCl_3$, AIBN, 80–100 °C

Dicyclopentadiene (**74**) produces 1:1 adduct(s) (**75**) by reaction with $HSiClMe_2$ and various metal catalysts (Scheme 11). A second addition is achieved only with γ-rays. The resulting 1:2 adducts (**76**) are converted into thermally fairly stable polymers (**77**).[98]

## 3.12.6 HYDROSILYLATION OF CONJUGATED ENONES

Transition metal catalyzed hydrosilylation of α,β-unsaturated ketones and aldehydes (**78**) proceeds in a 1,4- and/or 1,2-fashion to give enol silyl ethers (**79**) (or the saturated carbonyl compounds **80** after acidic work-up) and/or allyl silyl ethers (**81**) (or allyl alcohols **82**), respectively (equation 54). Monohydrosilanes combined with a Pt or Rh catalyst prefer 1,4-addition. This reaction is an alternative method for the preparation of enol silyl ethers (**79**). Diphenylsilane with $[RhCl(PPh_3)_3]$ catalyst reduces the car-

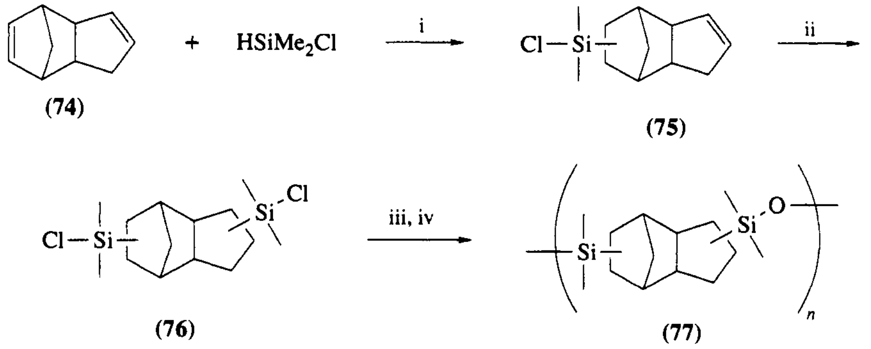

i, $H_2PtCl_6$; ii, $HSiMe_2Cl$, γ-ray; iii, $H_2O/NaHCO_3$; iv, tetramethylguanidine, $CF_3CO_2H$

**Scheme 11**

bonyl group preferentially to afford allyl alcohols (**82**) after aqueous work-up, whereas the phenylsilane/$[Mo(CO)_6]$ catalyst combination leads to the formation of the saturated ketone (**80**).[99-101]

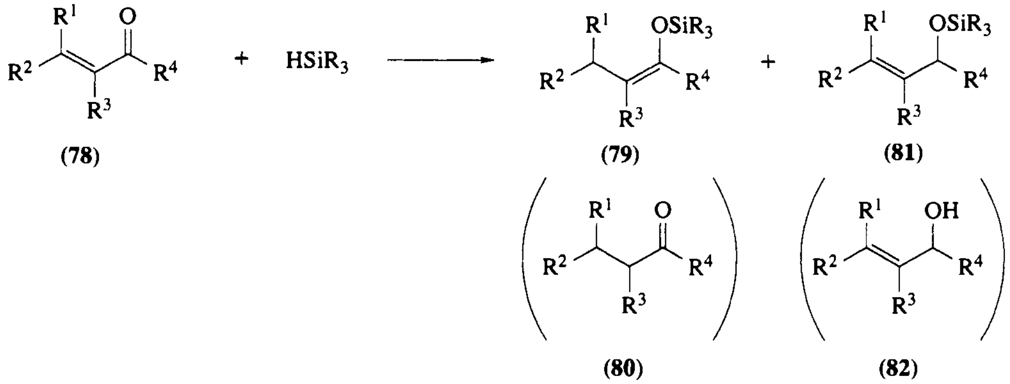

(54)

| | *HSiR₃* | *Catalyst* | *Yields (%)* | |
|---|---|---|---|---|
| $R^1 = R^2 = R^3 = H, R^4 = Me$ | $HSiEt_3$ | $H_2PtCl_6$ | 100 | 0 |
| $R^1 = R^3 = H, R^2 = R^4 = Me$ | $HSiPhMe_2$ | $[PtCl_2(2,4,6\text{-collidine})_2]$ | 100 | 0 |
| $R^1 = R^3 = R^4 = H, R^2 = Ph$ | $HSiEt_3$ | $[RhCl(PPh_3)_3]$ | 100 | 0 |
| $R^1 = R^3 = R^4 = H, R^2 = Ph$ | $H_2SiPh_2$ | $[RhCl(PPh_3)_3]$ | 0 | 100 |
| $R^1 = R^3 = H, R^2 = Ph, R^4 = Me$ | $H_3SiPh$ | $[Mo(CO)_6]$ | 100 | 0 |

Two modes of reaction are possible for α,β-unsaturated esters (**83**): hydrosilylation of the alkenic moiety to give (**84**) and/or (**85**) and 1,4-reduction to give ketene silyl acetals (**86**) (or saturated esters **87** after aqueous work-up), as illustrated in equation (55). The parent acrylates undergo hydrosilylation, whereas substituted acrylates favor the formation of (**86**) (or **87**).[102,103]

Alkynyl ketones (**88**) behave like substituted alkynes (**29**). Thus, the triple bond reacts first to give vinylsilanes (**89**) and/or (**90**) (equation 56), which are sometimes reduced further to allyl silyl ethers (**91**) and/or (**92**).[104]

As an alternative route to the reduction of α,β-unsaturated ketones accompanied by introduction of a silyl group at the β-position, a silylcuprate reagent is applicable (equation 57).[24b]

## 3.12.7 ASYMMETRIC HYDROSILYLATION OF CARBON–CARBON DOUBLE BONDS

Hydrosilylation of monosubstituted alkenes with palladium catalysts and trichlorosilane follows a course which favors branched products. By using a chiral phosphine ligand, asymmetric reaction is feasible. Initially, menthyldiphenylphosphine (MDPP, **93**) and neomenthyldiphenylphosphine (NMDPP, **94**) were employed with little success.[105] Later, (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-diphenylphosphinoferrocenyl]ethylamine [(*R*)-(*S*)-PPFA] (**95**) and its enantiomer were prepared, and these have proved to be the

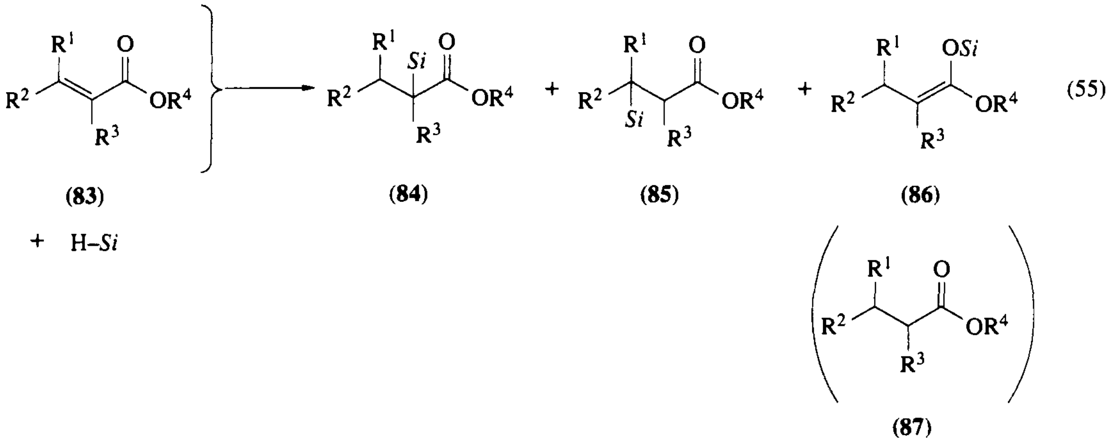

| *(83)* | *H–Si* | *Catalyst* | *Yields (%)* | | | |
|---|---|---|---|---|---|---|
| | | | **(84)** | **(85)** | **(86)** | **(87)** |
| $CH_2$=$CHCO_2Me$ | $HSiMe_3$ | $H_2PtCl_6$ | 33 | 4 | – | 22 |
| $CH_2$=$C(Me)CO_2Me$ | $HSiMe_3$ | $H_2PtCl_6$ | – | 69 | – | – |
| MeCH=$CHCO_2Me$ | $HSiMe_3$ | $H_2PtCl_6$ | 17 | – | – | 28(54)* |
| $CH_2$=$CHCO_2Et$ | $HSiMe_2Ph$ | $[RhCl(PPh_3)_3]$ | – | 85 | – | |
| $CH_2$=$CHCO_2Et$ | $HSiMe_2Cl$ | $[RhCl(PPh_3)_3]$ | 65 | – | – | |
| MeCH=$CHCO_2Me$ | $HSiMe_2Ph$ | $[RhCl(PPh_3)_3]$ | – | – | 70 | |

*$MeCH_2CH(CO_2Me)CHMeCH_2CO_2Me$

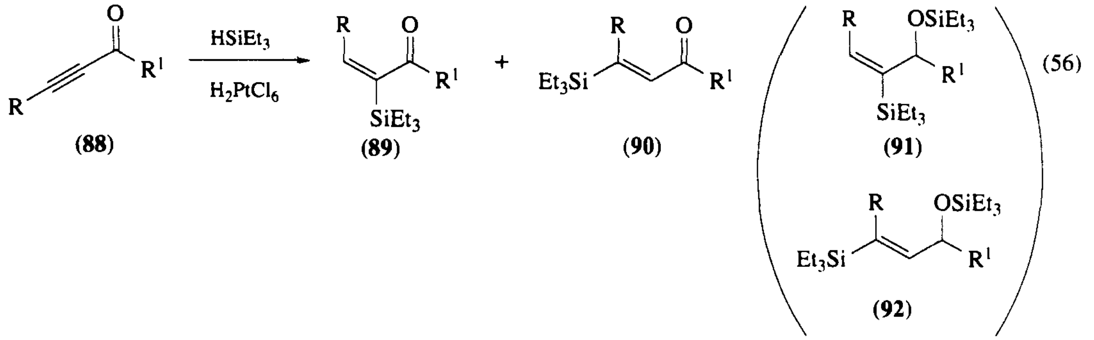

| | | | | | |
|---|---|---|---|---|---|
| HC≡CCOMe | 70% | 0.9 | : | 1 | (<15%) |
| $Me_3SiC$≡CCOMe | 39% | 5 | : | 1 | (<15%) |

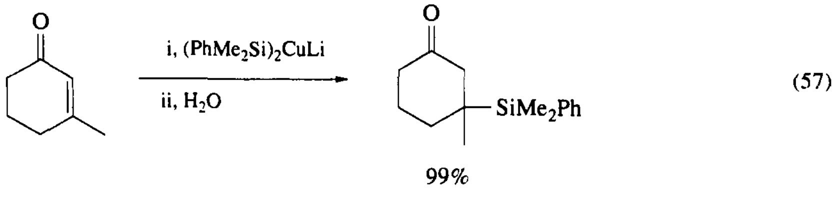

99%

best ligands so far for asymmetric hydrosilylation.[106] Thus, styrene is hydrosilylated with trichlorosilane and the palladium catalyst (**96**) to give trichloro-1-phenylethylsilane with moderately good asymmetric induction (Scheme 12). The absolute configuration and the optical purity of the product was determined by conversion into 1-phenylethanol.[107]

The transformation of conjugated dienes to allylsilanes can also be carried out with asymmetric induction. The efficiency of the asymmetric synthesis for acyclic dienes is moderate, but for cyclic dienes it remains to be improved.[108,109] Nevertheless, these reactions provide us with a method for the preparation

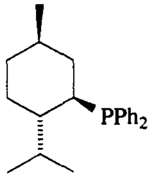

MDPP (**93**)

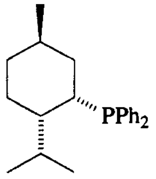

NMDPP (**94**)

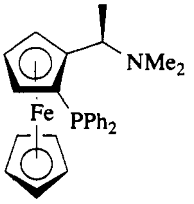
NMe2
Fe
PPh2

*(R)-(S)*-PPFA (**95**)

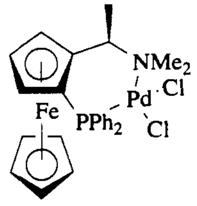
NMe2
Pd
Cl
Cl
Fe
PPh2

*(R)-(S)*-PPFA-Pd (**96**)

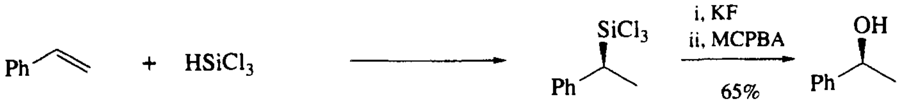
Ph
+ HSiCl3
SiCl3
Ph
i, KF
ii, MCPBA
65%
OH
Ph

| | | |
|---|---|---|
| $[PdCl_2(MDPP)_2]$ | 87% | 34% *ee (S)* |
| $[PdCl_2(NMDPP)_2]$ | 87% | 22% *ee (R)* |
| *(R)-(S)*-PPFA-Pd (**96**) | >95% | 52% *ee (S)* |

**Scheme 12**

of a chiral allylsilane (**97**; Scheme 13), which has been useful in the study of stereochemical aspects of the reactions of organosilicon compounds.

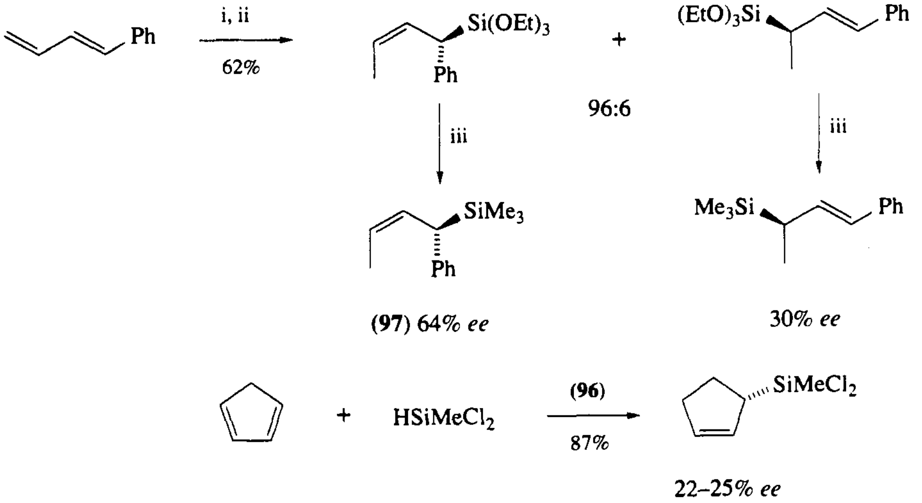
Ph
i, ii
62%
Si(OEt)3
Ph
+
(EtO)3Si
Ph
96:6
iii
iii
SiMe3
Ph
Me3Si
Ph
(97) 64% ee
30% ee
+
HSiMeCl2
(96)
87%
SiMeCl2
22–25% ee

i, (**96**), $HSi(OEt)_3$; ii, $NEt_3$, EtOH; iii, MeMgBr

**Scheme 13**

Although asymmetric 1,4-reduction of conjugated enones is recorded,[110] the enantiomeric excess is not high (equation 58).[111]

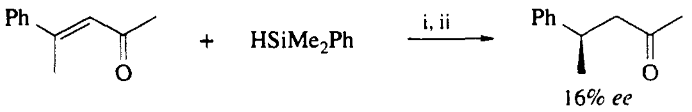
Ph
O
+ HSiMe2Ph
i, ii
Ph
O
16% ee

(58)

i, $[Rh\{(R)\text{-}PMePh(CH_2Ph)\}_2H_2S_2]^+ClO_4^-$; ii, $H_2O$

Conjugate addition of a silylcuprate reagent (**34**) to the α,β-unsaturated acid amide or ester of a pertinent chiral amine or alcohol, respectively, is an alternative route to β-silyl amides and esters. Conjugate addition of a cuprate reagent to a β-silyl acrylamide also gives a chiral β-silyl amide. The diastereomeric excess of the newly produced chiral center is fairly high, as summarized in Scheme 14.[112]

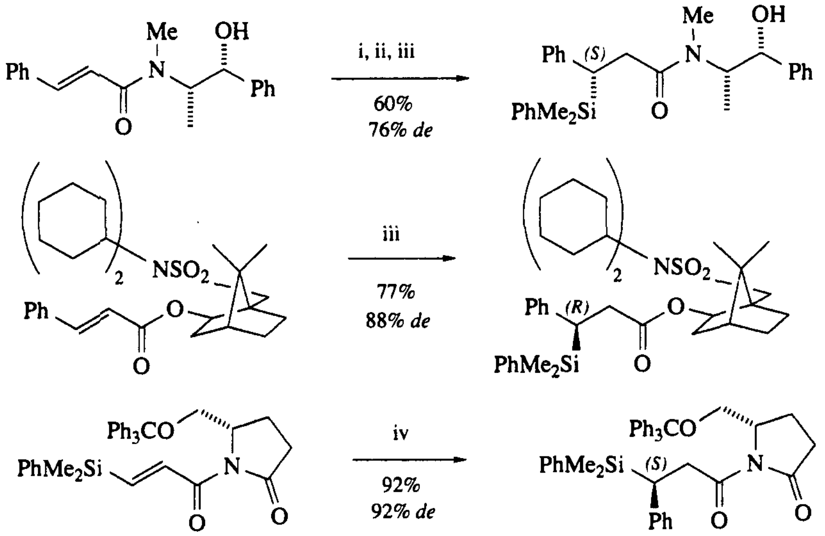

i, $Bu^nLi$; ii, $TiCl_4$; iii, $(PhMe_2Si)_2CuLi_2CN$ (**34**); iv, PhMgBr, $CuBr{\bullet}Me_2S$

Scheme 14

## 3.12.8 SYNTHETIC EXTENSION AND APPLICATION

The addition of Si and H across a π-bond is formally a reduction, since Si is more electropositive than carbon. However, unambiguous reduction is only complete when the silicon is replaced by hydrogen. This is easily possible by the protodesilylation of allylsilanes and vinylsilanes.

### 3.12.8.1 Reaction of Vinylsilanes with Electrophiles

The C—Si bond of vinylsilanes is transformed to C—H by hydrogen iodide with retention of configuration (Scheme 15).[1] The proton attaches itself to the carbon which has the silyl group, because the resulting carbonium ion is stabilized by the silyl group (β-effect). The silyl group is then attacked by a nucleophile to give the alkene. A silicon-bridged carbonium ion (**98**) is sometimes assumed to explain the stereochemical outcome (equation 59).[113] The overall reaction is thus unambiguously reduction of the triple bond to a double bond, but the reaction scheme is applicable to various other electrophiles.[114]

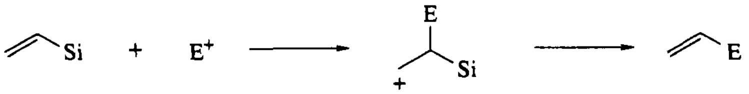

Scheme 15

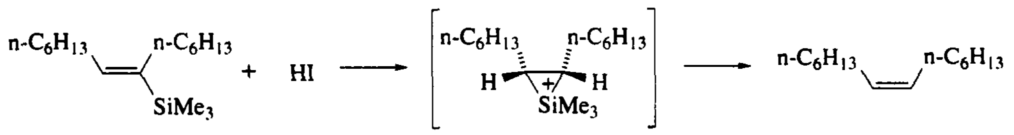
(59)

(**98**)

Bromine and chlorine react with vinylsilanes to afford vinyl bromide and chloride with net inversion of configuration. Addition of these halogens proceeds with *anti* stereochemistry. Elimination of halosilane in the presence of a nucleophile like $F^-$ or $RO^-$ also is assumed to take place in an *anti* manner (Scheme 16). The same transformation using iodine is applicable only to 1,2-dialkylvinylsilanes.[115] The process is a reliable method for the preparation of vinyl halides of defined configuration. The reactions are not, overall, reductions, and they are included here only to emphasize the usefulness of the products of hydrosilylation.

The reactions of vinylsilanes with carbon electrophiles is discussed in Volumes 2–4.

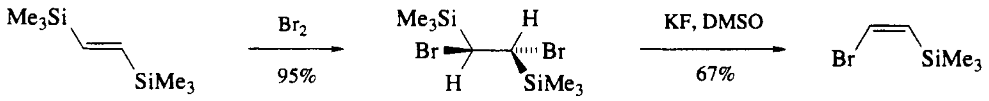

**Scheme 16**

### 3.12.8.2 Coupling Reactions of Vinylsilanes with Organic Halides

In the presence of a fluoride ion generating reagent such as tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF, **99**) and a palladium catalyst, vinyltrimethylsilane couples with vinyl and aryl iodides.[116] For substituted vinylsilanes, the fluorodimethylsilyl group is particularly effective in the coupling reaction, which takes place with retention of configuration of both substrates (Scheme 17). Silicon-based C—C bond formation is as useful as that which employs organoborons[117] for the synthesis of stereo-defined conjugated dienes.

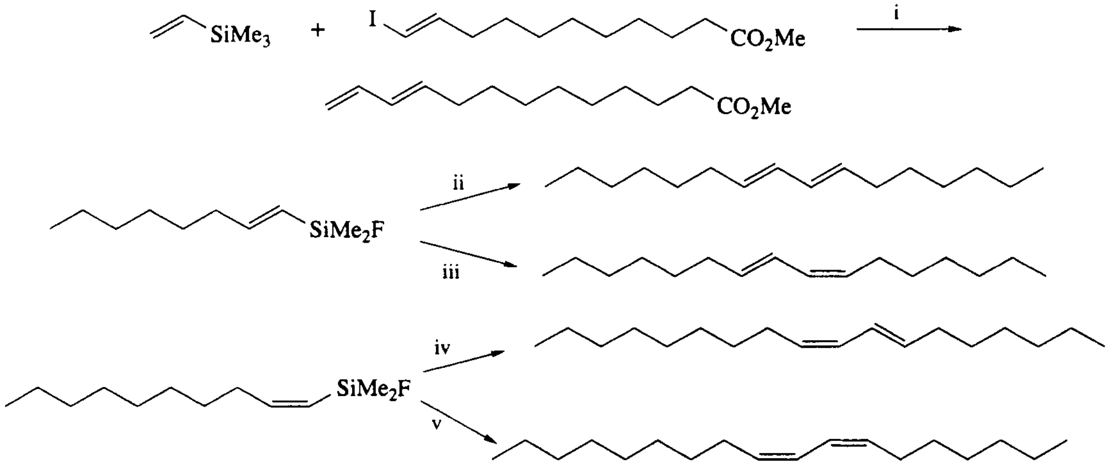

i, [{(allyl)PdCl}$_2$], P(OEt)$_3$, THF, (**99**); ii, [{(allyl)PdCl}$_2$], THF, (**99**), (*E*)-1-iodo-1-octene;
iii, [{(allyl)PdCl}$_2$], THF, (**99**), (*Z*)-1-iodo-1-octene; iv, [Pd(PPh$_3$)$_4$], DMF, (**99**), (*E*)-1-iodo-1-octene;
v, [Pd(PPh$_3$)$_4$], DMF, (**99**), (*Z*)-1-iodo-1-octene

**Scheme 17**

### 3.12.8.3 Reaction of Allylsilanes with Electrophiles

Allylsilanes are easily protodesilylated, completing the reduction process. In the presence of Lewis acids, allylsilanes also react with electrophiles like aldehydes, ketones and acid halides through an $S_E2'$ mechanism involving *anti* stereochemistry. These reactions are extensively discussed in Volumes 2–4.

### 3.12.8.4 Aldol Reactions

Enol silyl ethers undergo aldol reactions with aldehydes, acetals and their equivalents with the aid of a Lewis acid catalyst. These reactions are discussed in Volumes 2–4. Enol silyl ethers prepared by hydrosilylation of α,β-unsaturated ketones with a rhodium catalyst can be used for aldol reactions with aldehydes or ketones *in situ* under neutral conditions (equation 60).[118]

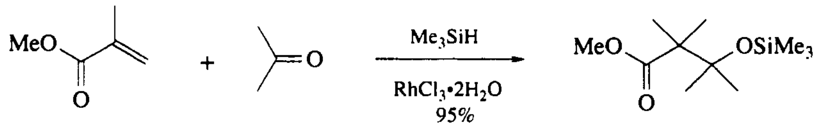

(60)

### 3.12.8.5 Synthetic Reactions of Pentafluorosilicates

Trichlorosilanes are readily transformed to the pentafluorosilicate compounds (**100**) and (**101**) by reaction with excess potassium fluoride. The C—Si bond of the hexavalent organosilicon species is converted into a C—X (X = halogen or heteroatom like hydroxy and alkoxy) or a C—C bond. Thus, through the hydrosilylation reaction net transformations of alkenes and alkynes to halides, ethers and alcohols, as well as the construction of carbon frameworks, is easily achieved (Scheme 18).[119]

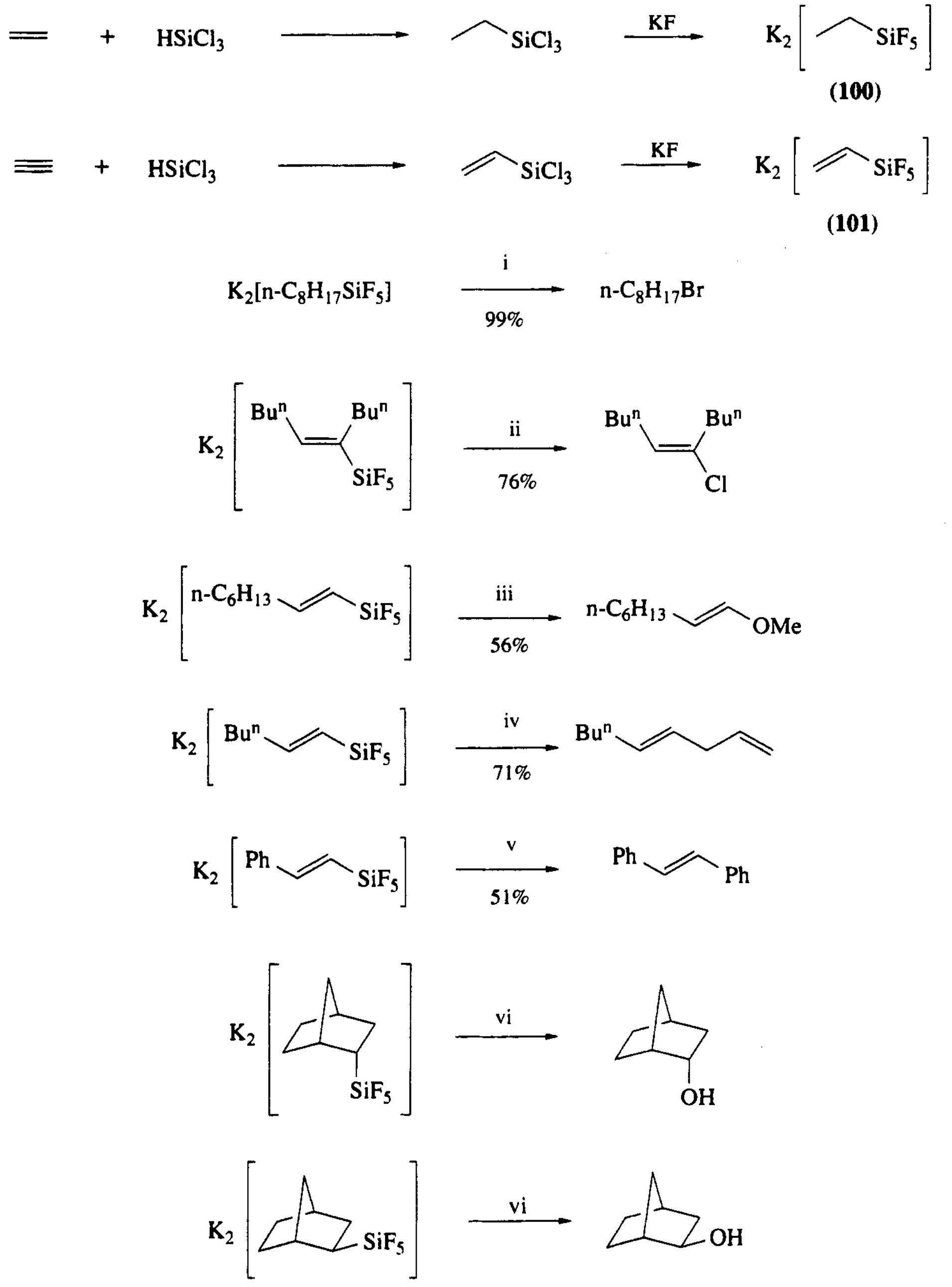
HSiCl3
SiCl3
KF
K2
SiF5
(100)
(101)
i
K2[n-C8H17SiF5]
n-C8H17Br
99%
Bun
ii
76%
Cl
n-C6H13
iii
56%
OMe
iv
71%
Ph
v
51%
vi
OH

i, NBS; ii, $CuCl_2$; iii, MeOH, $Cu(OAc)_2$; iv, $CH_2{=}CHCH_2Cl$, $Pd(OAc)_2$; v, PhI, $Pd(OAc)_2$, $PPh_3$, $NEt_3$; vi, MCPBA

Scheme 18

### 3.12.8.6 Oxidative Transformation of C—Si Bonds

Modification of the last reaction in the previous section has led to a new version of the C—Si to C—O transformation that is highly versatile in organic synthesis. Hydrosilylation of alkenes or alkynes with a hydrosilane of type $HSiR_nX_{3-n}$ (R = organic group, X = H, F, Cl, $R^1O$, $R^1_2N$), followed by oxidation with 30% hydrogen peroxide in the presence of a base such as KF, potassium hydroxide or potassium hydrogencarbonate, leads to alcohols, ketones and acetals.[120] Typical examples are summarized in Scheme 19. This transformation is applicable to intramolecular hydrosilylation, which allows us to introduce contiguous chiral centers in a predictable manner, starting with a properly substituted alkenol, *e.g.* (**102**) and (**103**), as shown in Scheme 20.[121]

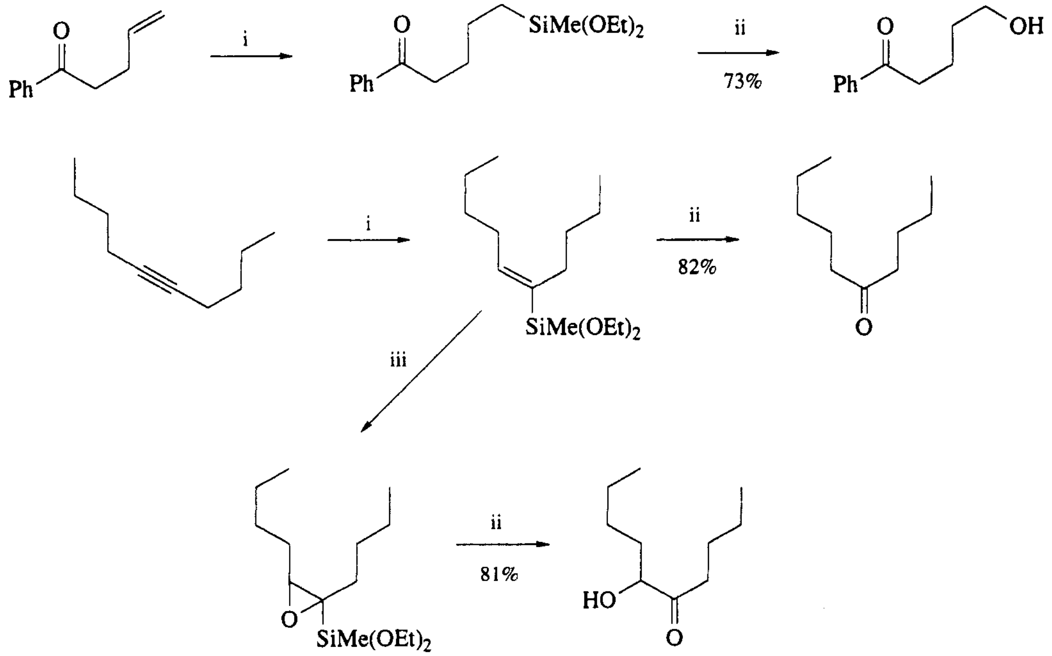
O
Ph
i
O
SiMe(OEt)2
Ph
ii
73%
O
OH
Ph
i
SiMe(OEt)2
ii
82%
O
iii
O
SiMe(OEt)2
ii
81%
HO
O

i, $HSiMe(OEt)_2$, $H_2PtCl_6$; ii, 30% $H_2O_2$, $KHCO_3$; iii, MCPBA

**Scheme 19**

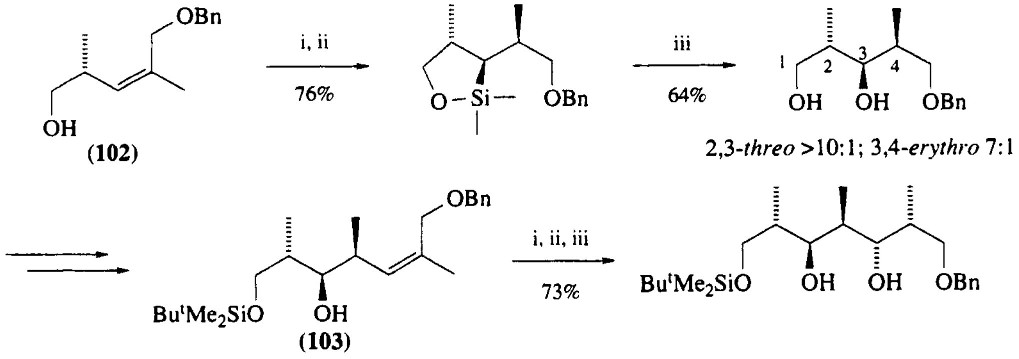
OBn
OH
(102)
i, ii
76%
O–Si–
OBn
iii
64%
1
2
3
4
OH
OH
OBn
OBn
Bu$^t$Me$_2$SiO
OH
(103)
i, ii, iii
73%
Bu$^t$Me$_2$SiO
OH
OH
OBn

2,3-*threo* >10:1; 3,4-*erythro* 7:1

i, $(HMe_2Si)_2NH$, r.t. to 60 °C; ii, $H_2PtCl_6{\bullet}6H_2O$ (0.1 mol %), 60 °C; iii, $H_2O_2$, KF, $KHCO_3$, MeOH–THF, r.t.

**Scheme 20**

### 3.12.8.7 Hydrosilylation in the Presence of CO

The mechanism of hydrosilylation on a transition metal catalyst involves an intermediate with a carbon–transition metal bond. Carbon monoxide, if present, inserts into the carbon–metal bond to give an acyl metal complex, which can undergo enolization and silylation. A one-carbon extended aldehyde enol silyl ether is produced, useful for further synthetic transformations. Dicobalt octacarbonyl is the best-studied catalyst (Scheme 21).[122] A ruthenium cluster catalyst exhibits similar reactivity (equation 61),[11d] but rhodium carbonyl catalyzes the reaction only of alkynes to afford α,β-unsaturated aldehydes containing a β-silyl group (equation 62).[123]

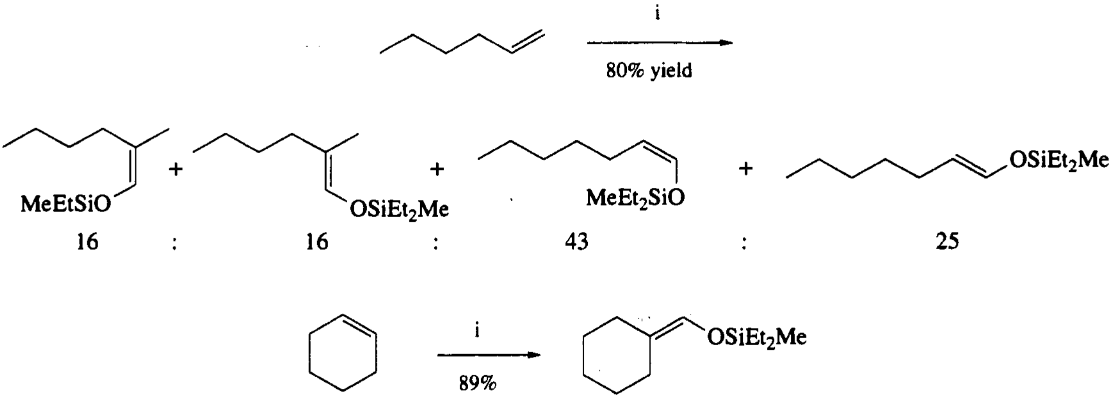

i, $HSiEt_2Me$, CO, $[Co_2(CO)_8]$, 140 °C

**Scheme 21**

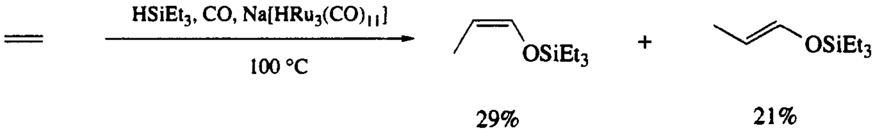

(61)

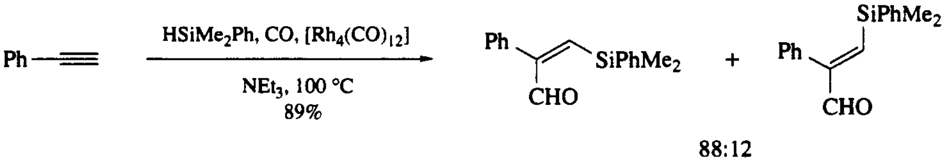

(62)

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# 4.1

# Reduction of Saturated Alkyl Halides to Alkanes

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## 4.1.1 INTRODUCTION AND SCOPE OF THE REVIEW

The reduction of saturated alkyl halides to alkanes, as represented in equation (1), is the most fundamental reaction of reductive dehalogenations of organic halides. The importance of these reductions has stimulated considerable investigation, and a number of successful approaches have been reported hitherto. Numerous reducing agents or reagent systems are available and many of them have been applied to practical organic synthesis with notable success.

$$R{-}X \xrightarrow{\text{reducing agent}} R{-}H \qquad (1)$$

R = alkyl group; X = F, Cl, Br, I

In 1980, Pinder presented an excellent review dealing with the hydrogenolysis of organic halides.[1] Many other reviews[2-12] are also available, although they are not devoted to reductive dehalogenation but deal with it as part of the broader topic of reduction.

This chapter surveys the reduction of saturated alkyl halides to alkanes. Reductive β-eliminations of vicinal dihalides to alkenes are also described briefly. Reduction of vinyl and aryl halides is covered in this volume, Chapter 4.5; hydrogenolysis of allyl and benzyl halides is covered in this volume, Chapter 4.7, and reduction of α-halo-substituted carbonyl compounds CX—CO to carbonyl compounds CH—CO is covered in this volume, Chapter 4.8.

This subject matter will be treated from the aspect of the type of reagent. Emphasis is made on chemoselective dehalogenation, since the replacement of a halogen atom by hydrogen must often be accomplished in complex molecules containing other functional groups. Reagents and reducing conditions capable of effecting reductive dehalogenations are illustrated by many examples, including practical applications. The mechanisms of the reductions are also discussed briefly in some sections.

## 4.1.2 GENERAL OBSERVATIONS

The order of ease of reductive dehalogenation of organic halides in the same type of structural environment is: I > Br > Cl >> F. This order is parallel with the dissociation energy of carbon–halogen bonds ($H_3C$—I: 234 kJ $mol^{-1}$; $H_3C$—Br: 293 kJ $mol^{-1}$; $H_3C$—Cl: 351 kJ $mol^{-1}$; $H_3C$—F: 452 kJ $mol^{-1}$) and is generally observed in the reduction of alkyl halides.[3] Consequently, selective reduction of di- or polyhalides containing different halogen atoms is possible. Fluorides are often removed only with difficulty and examples of such reductions are comparatively limited.

The reactivities of primary, secondary and tertiary halides are largely dependent on the reagents employed. The ring size of halogenated cycloalkanes and the steric environment also influence the rate of reduction. In general, when the reduction proceeds through an $S_N2$ type of reaction, primary halides are most easily reduced. On the other hand, when the reduction proceeds through an $S_N1$ process or involves free radicals as intermediates, the order of reduction falls in the expected sequence: tertiary > secondary > primary.

## 4.1.3 CATALYTIC HYDROGENOLYSIS

Organic halides are known to be subject to hydrogenolysis in the presence of a catalyst, such as Pd/C or Raney nickel. This catalytic hydrogenolysis is one of the more convenient ways of removing halogens under mild conditions and numerous examples have been reported. Several reviews dealing with this subject have been published.[1,5,6]

Catalytic hydrogenolysis is often inhibited by the release of hydrogen halide produced during the reaction, since both hydrogen ions and halide ions are known to deactivate the catalysts. Hydrogen ions exhibit a particularly strong inhibiting effect, and, therefore, the hydrogenolysis of organic halides is usually carried out in the presence of 1 mol or more of a base. The added base is to neutralize the acid and to maintain the catalytic metal in a low valency or nucleophilic state. Sodium, potassium, calcium and barium hydroxides are generally employed, while sodium acetate, an amine or ammonia are often used for base-labile compounds.

The rate of catalytic hydrogenolysis depends significantly on the structure and halogen involved. Among the types of halides, alkyl halides are much less readily hydrogenolyzed than aryl, vinyl, benzyl and allyl halides (see this volume, Chapters 4.5 and 4.7). Generally, the order of ease of dehalogenation of alkyl halides is I > Br ~ Cl >> F and tertiary > secondary > primary halides. Alkyl fluorides are very difficult to reduce to the corresponding hydrocarbons by conventional catalytic hydrogenation procedures.

Among many catalysts, Pd/C is less susceptible to the poisoning effect of halide ions; hence, this catalyst is preferred by most investigators. Platinum and rhodium are not effective for catalytic dehalogenations. Schemes 1 and 2 illustrate representative Pd/C catalyzed hydrogenolyses of an alkyl iodide and an alkyl bromide.[13,14]

Raney nickel possesses remarkable hydrogenolysis ability, but the catalyst is readily deactivated by the halide ion released. Therefore, massive amounts of the catalyst are usually required to obtain satisfactory results. An example showing the reduction of a primary and a secondary alkyl chloride is shown in Scheme 3.[15]

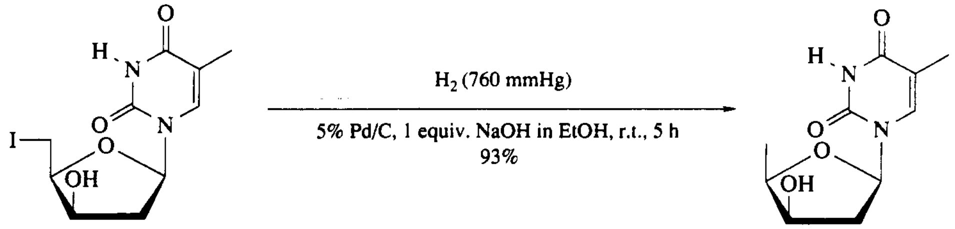

Scheme 1

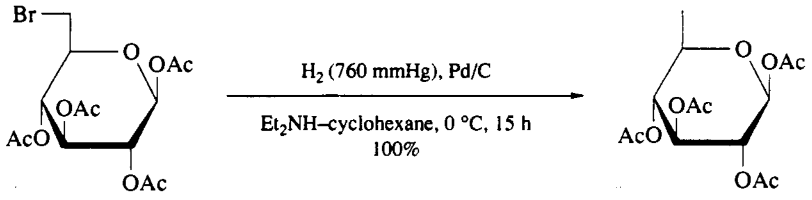

Scheme 2

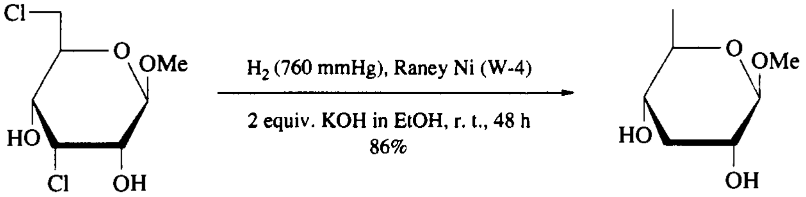
H₂ (760 mmHg), Raney Ni (W-4)
2 equiv. KOH in EtOH, r. t., 48 h
86%

Scheme 3

## 4.1.4 REDUCTION WITH METALS OR LOW-VALENT METAL SALTS

### 4.1.4.1 Reductions with Metals (Dissolving Metal Method)

Organic halides are reduced by reaction with a metal in the presence or absence of a proton donor. The metals commonly used are the alkali metals (Li, Na, K, Na–K alloy), alkaline earths (Mg, Ca, Ba) and other metals (Zn, Fe, *etc.*).[2]

A classical method using Na– or Li–liquid ammonia (Birch reduction conditions) is effective for reductive dehalogenations of aryl and vinylic halides, but it is not always successfully applied to alkyl halides, although cyclopropyl halides and bridgehead halogens are exceptions.[16,17] Under such conditions, the reactions are often accompanied by side reactions, such as elimination, the Wurtz coupling reaction, cyclization and reduction of carbonyl compounds. An example, a synthesis of pentaprismane (**1**), is shown in Scheme 4.[17]

A currently employed method for dehalogenation of alkyl halides is to use a Li– or Na–alcohol reagent system.[18-20] This method is effective not only for simple alkyl halides but also for the reduction of a halogen atom attached to a bridgehead. Carbon–carbon unsaturated bonds are not affected under the conditions, as shown in Scheme 5.[18]

Alkyl halides are reduced with zinc powder in alcoholic potassium hydroxide[21] or in the presence of a catalytic amount of nickel chloride.[22,23] The former method is employed for the monoreduction of geminal dihalocyclopropyl methyl ketones.[21]

Reduction of alkyl fluorides, which is difficult using conventional dissolving metal methods, can be accomplished using a potassium–crown ether reagent system.[24] Potassium metal dissolves in toluene or diethylene glycol dimethyl ether (diglyme) in the presence of dicyclohexyl-18-crown-6 to form a blue-black solution. The resultant reagent exhibits powerful reducing ability, higher than sodium naphthalene;[25] unactivated primary, secondary and tertiary alkyl fluorides are reduced at room temperature by this reagent to the corresponding alkanes in high yields, as exemplified in Scheme 6.[24]

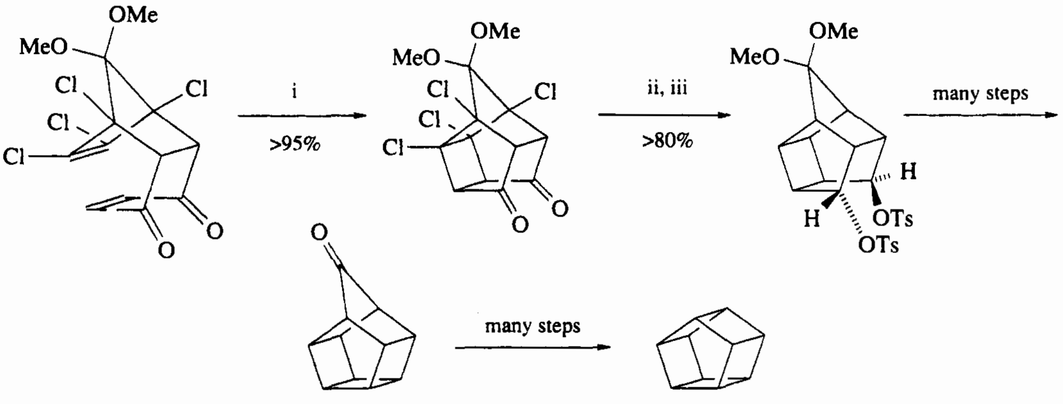
OMe
MeO
Cl
Cl
Cl
Cl
O
O
i
>95%
ii, iii
>80%
H
OTs
OTs
many steps
many steps

(1)

i, *h*ν /acetone; ii, Li/liq.$NH_3$/THF/$Bu^tOH$–$H_2O$; iii, TsCl, pyridine

**Scheme 4**

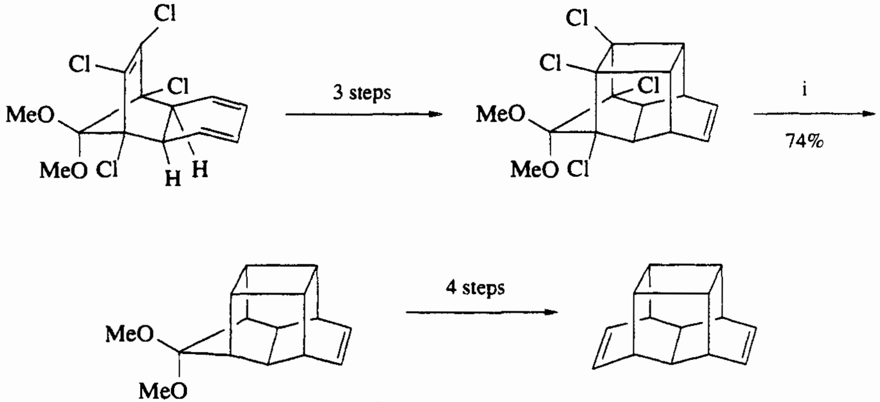
Cl
Cl
Cl
MeO
MeO
Cl
H
H
3 steps
i
74%
4 steps

i, Na, $Bu^tOH$, THF, reflux, 36 h

**Scheme 5**

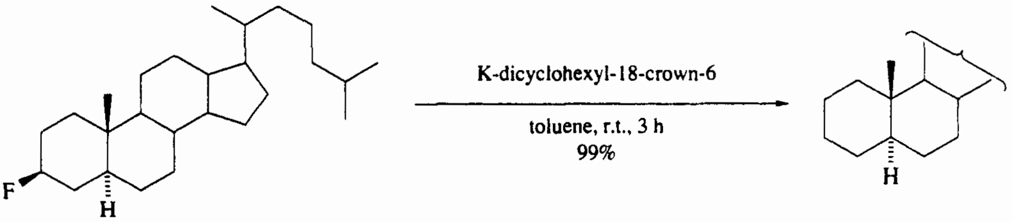
F
H
K-dicyclohexyl-18-crown-6
toluene, r.t., 3 h
99%
H

**Scheme 6**

### 4.1.4.2 Reduction with Low-valent Metal Salts

#### *4.1.4.2.1 Chromium(II) salts*

Chromium(II) salts, such as $Cr(OAc)_2$, $CrCl_2$, $Cr(ClO_4)_2$ and $CrSO_4$ are used for reductive dehalogenation. The reactions are usually carried out in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). Addition of ethylenediamine or ethanolamine as a chelating agent enhances remarkably the reducing ability.[26,27] Generally, the ease of hydrogenolysis is I > Br > Cl and tertiary > secondary > primary halides. Reduction with $Cr^{II}$ involves a radical process, which in some cases is accompanied by side reactions, such as rearrangement and dimerization. Use of a hydrogen atom donor, such as a thiol, is effective for suppressing such side reactions.[28,29] Chemoselective dehalogenation with $Cr^{II}$ is possible, as exemplified in Scheme 7.[28]

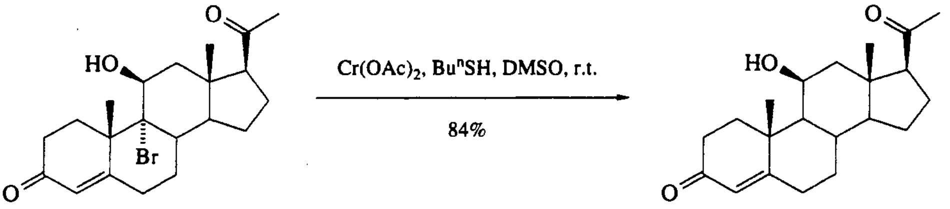

Scheme 7

An electrochemical reduction procedure using a chromium(II) salt as the catalyst is effective for the dehalogenation of β-hydroxy halides.[30] This procedure is a convenient entry to deoxynucleosides, as shown in Scheme 8.

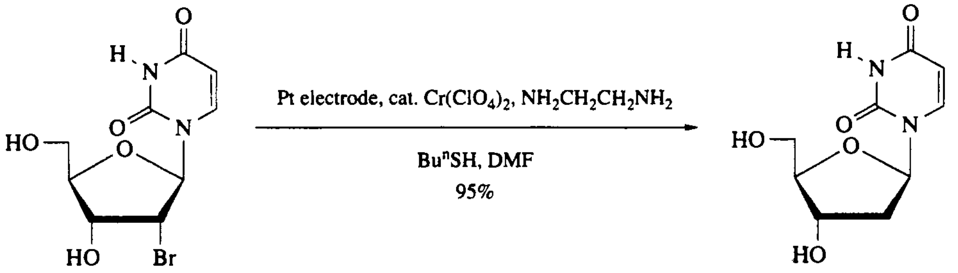

Scheme 8

### 4.1.4.2.2 Samarium(II) iodide

Divalent samarium is known to reduce alkyl halides.[31,32] However, reductions of iodides and bromides in tetrahydrofuran (THF) require a long reaction time and chlorides are not reduced even at refluxing temperature.

Addition of hexamethylphosphoramide (HMPA) to $SmI_2$ in THF results in the formation of a purple solution of an HMPA complex. The complex exhibits remarkably enhanced reducing power, as shown in equation (2).[33] Thus, bromides and iodides are very rapidly reduced at room temperature to the corresponding alkanes in essentially quantitative yields; ester functions remain intact under these conditions. Chlorides are reduced at refluxing temperature, while fluorides are inert under the conditions.

$$\text{R–X} \xrightarrow[\text{THF/HMPA, r.t. to 65 °C, 100\%}]{2\ \text{SmI}_2} \text{R–H} \qquad (2)$$

X = Cl, Br, I

### 4.1.4.2.3 Other low-valent metal salts

Some other low-valent metal species have proved effective in hydrogenolysis of alkyl halides. Nickel tetracarbonyl in THF reductively converts polyhalomethyl groups into di- or mono-halomethyls in good yields.[34] An ionic vanadium carbonyl hydride, $[(\eta^5\text{-}C_5H_5)V(CO)_3H]^-$, is capable of reducing alkyl bromides, but not chlorides.[35] Monoreduction of geminal dibromocyclopropanes proceeds in essentially quantitative yields under these conditions. The titanium(III) chloride/magnesium,[36] titanocene dichloride $[(\eta^5\text{-}C_5H_5)_2TiCl_2]$/magnesium[37] and titanocene dichloride/isopropylmagnesium bromide[38] reagent systems exhibit relatively high activity toward alkyl halides, but the reaction with halocycloalkanes tends to provide significant amounts of alkenes.

Reductions of vicinal dibromides have been extensively studied, using new reagents or reagent systems which involve low-valent metal species, such as $[(\eta^5\text{-}C_5H_5)Cr(NO)_2]_2$,[39] iron–graphite,[40] $TiCl_3$–$LiAlH_4$ or $TiCl_4$–$LiAlH_4$,[41] $VCl_3$–$LiAlH_4$,[42] Zn–$TiCl_4$,[43] Zn–$[(\eta^5\text{-}C_5H_5)_2TiCl_2]$[44] and $CrCl_3$/$LiAlH_4$.[45] These reagents promote reductive β-elimination to afford the corresponding alkenes in good to excellent yields. In most cases, the reactions proceed through predominant *anti* elimination and the corresponding (*Z*)- and (*E*)-alkenes are obtained with high isomeric purity. A representative example is shown in Scheme 9.[43]

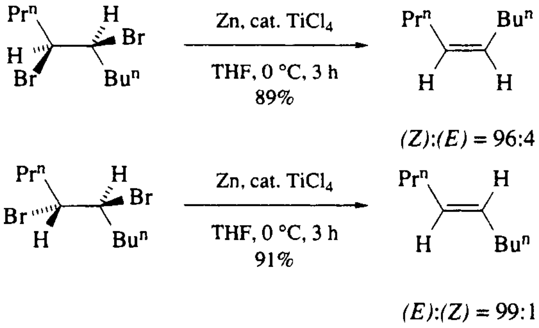

Scheme 9

## 4.1.5 REDUCTION WITH METAL HYDRIDES

### 4.1.5.1 Tributyltin Hydride

Tributyltin hydride ($Bu^n_3SnH$) is an extremely versatile reagent for replacing halogen atoms in organic molecules by hydrogen atoms.[8,9] Iodides and bromides tend to react spontaneously with this reagent in the absence of a solvent, but usually radical initiators, such as 2,2′-azobisisobutyronitrile (AIBN) or UV irradiation, are used as well as thermal initiation. Chlorides require heating or catalysis by a free radical source. Alkyl fluorides are practically unreactive. Recently, it has been reported that the use of triethylborane as a catalyst significantly accelerates the reduction; alkyl iodides and bromides are reduced even at −78 °C.[46]

As free radicals are involved as intermediates in tin hydride reductions, the nature of the organic group strongly influences the rate of reductions. The order of facility of dehalogenation is tertiary > secondary > primary. Bridgehead halides are also reduced by $Bu^n_3SnH$.[47–50] Stepwise reductions of trihalomethyl groups and geminal dihalides, including geminal dihalocyclopropanes, are possible,[51–54] as exemplified in Scheme 10.[51]

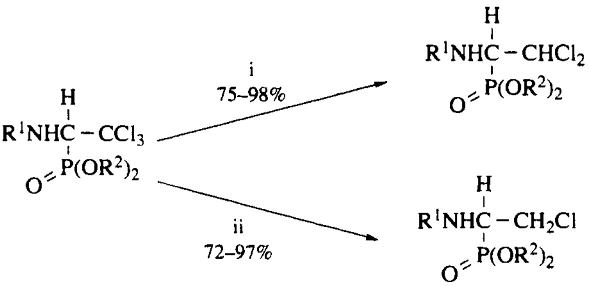

$R^1 = PhSO_2, PhCH_2CO_2, EtCO_2, HCO$; $R^2$ = Me or Et

i, $Bu^n_3SnH$, $C_6H_6$, 80 °C, 6–8 h; ii, 2 $Bu^n_3SnH$, AIBN, $C_6H_6$, 8–10 h

Scheme 10

Vicinal dichlorides react with 2 equiv. of $Bu^n_3SnH$ to give the corresponding saturated hydrocarbons in essentially quantitative yields, whereas vicinal dibromides lead to alkenes in high yields.[55]

A major side reaction encountered in these dehalogenations is intramolecular radical cyclization in systems having unsaturated moieties; cyclization to form five- or six-membered ring systems is frequently observed (see Volume 4, Chapter 4.2).

It is emphasized that the $Bu^n_3SnH$ reductions are highly chemoselective. Thus, a variety of other functional groups, such as alcohol, alkene, alkyne, ketone, nitrile, nitro groups, ester, epoxide, and even peroxide[56] and nitrate ester[57] are tolerated. The method using $Bu^n_3SnH$ is, therefore, extremely useful for dehalohydrogenolysis in complex molecules having other sensitive functionalities. Several representative examples employed in the synthesis of natural products are illustrated in Schemes 11–15.[57–61]

The method can be applied to the synthesis of deuterium-[62–65] or tritium-labeled[65] compounds by using $Bu^n_3SnD$ or $Bu^n_3SnT$. The former reagent ($Bu^n_3SnD$) is commercially available (Aldrich) and the latter

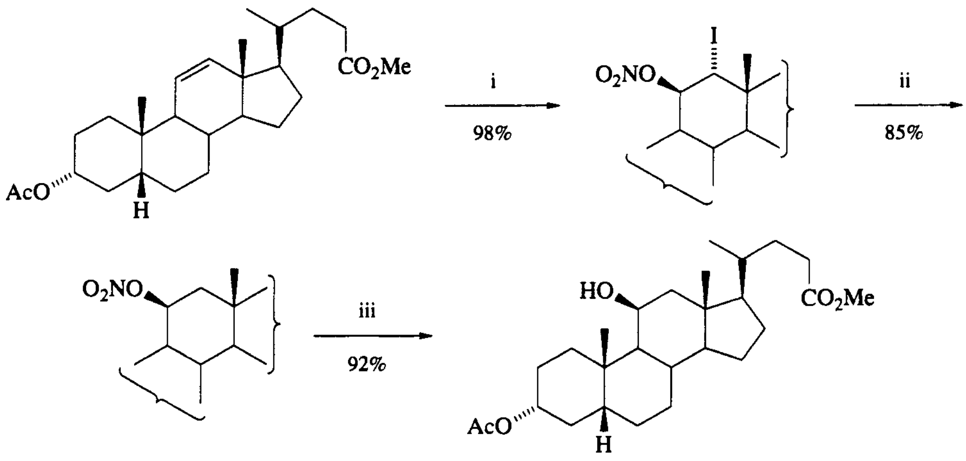
CO2Me
AcO
H
i
98%
O2NO
I
ii
85%
O2NO
iii
92%
HO
CO2Me
AcO
H

i, $I_2$, $N_2O_4$, $CHCl_3$, 0 °C to r.t., 16 h; ii, $Bu^n{}_3SnH$, $C_6H_6$, reflux, 48 h; iii, Zn, AcOH, r.t.,16 h

**Scheme 11**

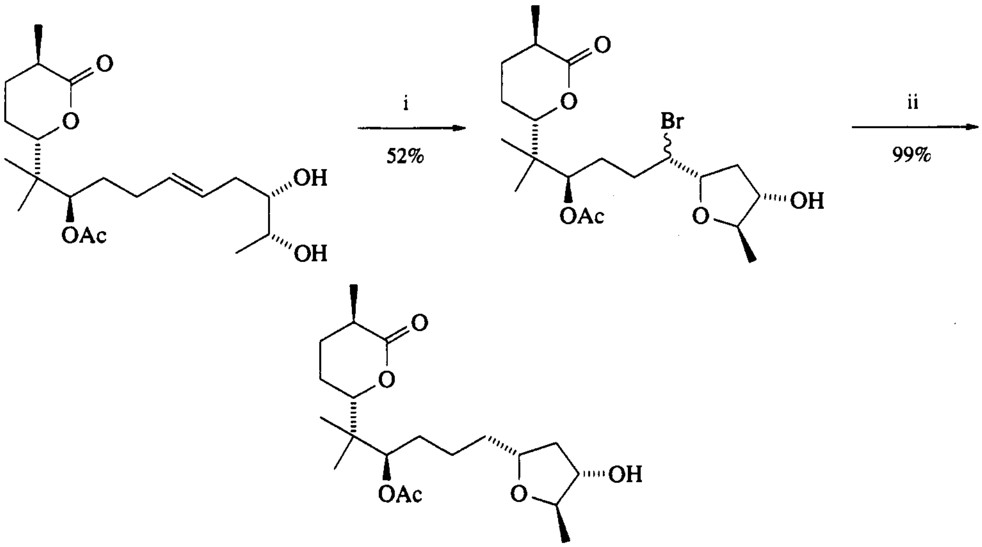
O
O
OAc
OH
OH
i
52%
O
O
Br
OAc
O
OH
ii
99%
O
O
OAc
O
OH

i, NBS, $Et_2O$–MeCN (5:1), –110 °C, 4 h; ii, $Bu^n{}_3SnH$, AIBN, $C_6H_6$, reflux, 2 h

**Scheme 12**

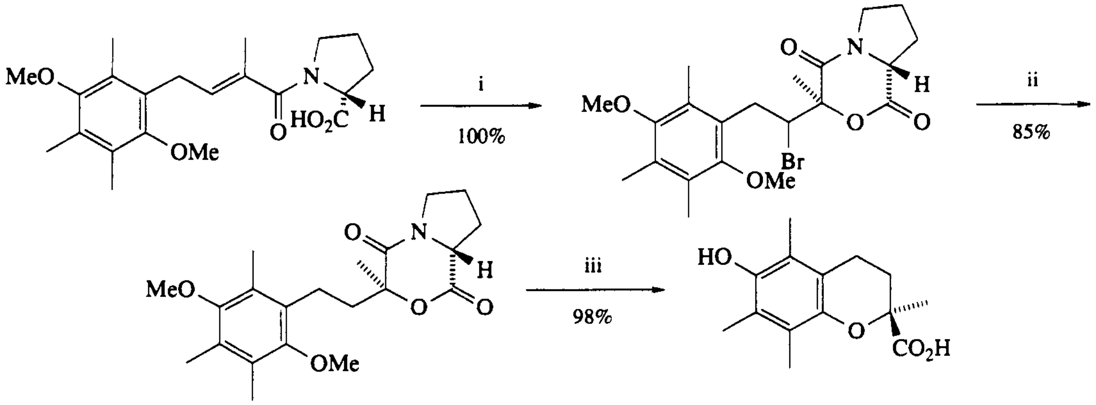
MeO
OMe
N
HO2C
H
O
i
100%
MeO
OMe
Br
O
N
H
O
O
ii
85%
MeO
OMe
O
N
H
O
O
iii
98%
HO
O
CO2H

i, NBS, $Bu^tOK$, –20 °C, 2 h, then r.t., 48 h; ii, $Bu^n{}_3SnH$, $C_6H_6$, 90 °C, 10 h; iii, conc. HCl, reflux, 10 h

**Scheme 13**

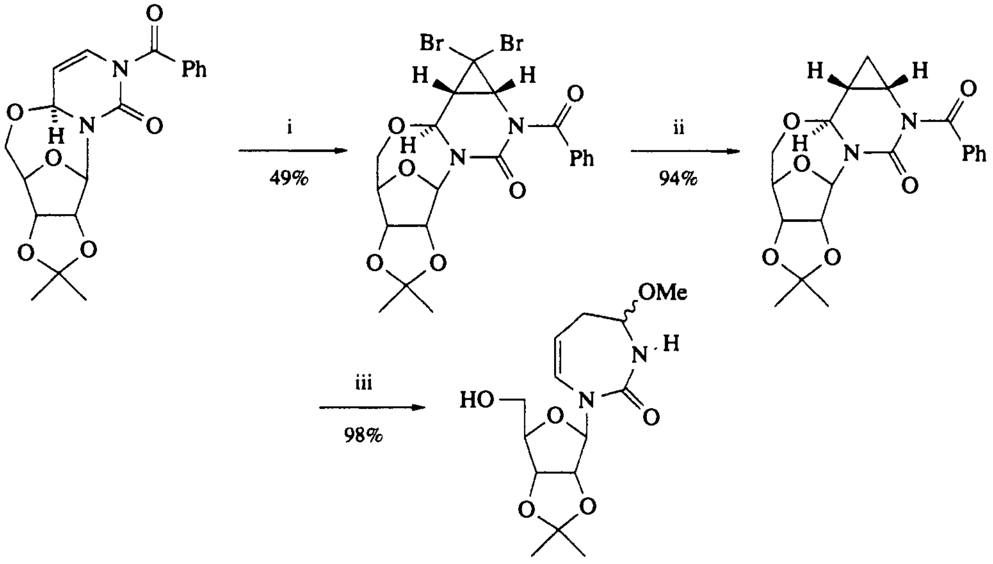

i, $PhHgCBr_3$, $C_6H_6$, reflux, 52 h; ii, $Bu^n_3SnH$, 25 °C, 41 h; iii, MeONa/MeOH, r.t., 1 min

**Scheme 14**

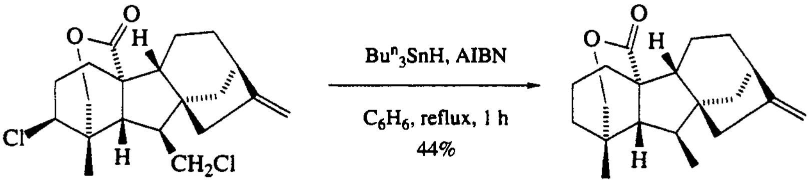

**Scheme 15**

($Bu^n_3SnT$) is prepared by the reaction of $Bu^n_3SnLi$ with tritiated water or by the reaction of $Bu^n_3SnCl$ with tritiated sodium borohydride.[65] Representative preparations of labeled compounds with a high degree of stereoselectivity are shown in Schemes 16 and 17.[62,65]

Because organotin hydrides are in general highly toxic, some modifications of the reagents have been devised. The $NaBH_4$–$Bu^n_3SnCl$ system, where $Bu^n_3SnCl$ is used as the catalyst, is effective,[66,67] and immobilization of organotin hydrides or dihydrides on reticulated polystyrene,[68] alumina or silica gel[69] is another approach. The organic products are not contaminated with organotin residues and the reagents are regenerated with $NaBH_4$ or $LiAlH_4$.

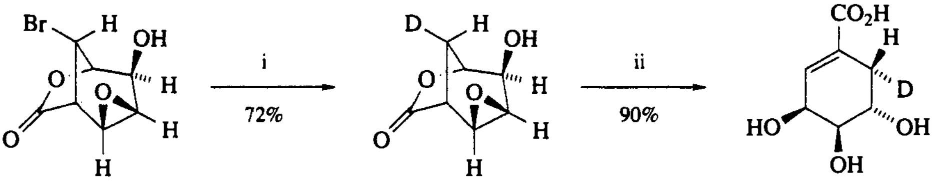

i, $Bu^n_3SnH$, AIBN, toluene, reflux, 2 h; ii, KOH, MeOH–$H_2O$, r.t., 24 h

**Scheme 16**

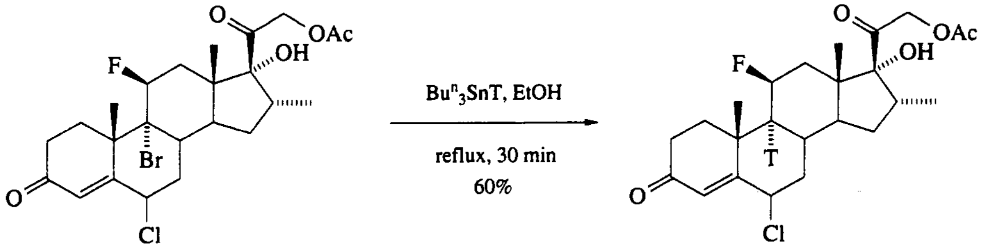

**Scheme 17**

### 4.1.5.2 Copper Hydrides

Various copper hydrides, such as $2LiAlH(OMe)_3{\cdot}CuI$,[70] $LiCuH(n\text{-}C_4H_9)$,[71] $(KCuH_2)_n$,[72] $Li_nCuH_{n+1}$ ($n$ = 1–5)[73] are known to reduce alkyl halides under mild conditions. Among these, the reagent prepared from $LiAlH(OMe)_3$ and CuI reveals unique reactivity. It reduces bromides and chlorides at room temperature in THF in excellent yields. It is interesting to note that the reduction of both *exo*- and *endo*-2-bromonorbornane proceeds with 100% retention, whereas the corresponding phenyl methanesulfonates undergo complete inversion of stereochemistry, as shown in Scheme 18.[70] The results suggest that the copper hydride reagent may attack the bromides from the front side to form copper complexes which, in turn, undergo ligand reorganization and finally release the deuterated products.

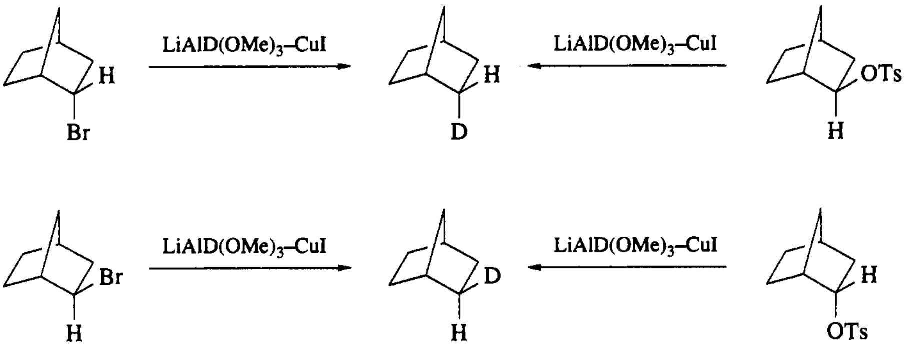

**Scheme 18**

### 4.1.5.3 Other Metal Hydride Reagents

#### *4.1.5.3.1 Organosilane hydrides*

Organosilane hydrides are generally inert toward alkyl halides, while they exhibit potential reducing ability when mixed with a catalytic amount (5 mol %) of aluminum chloride.[74] For instance, bromocyclohexane is reduced to cyclohexane in 90% yield by treatment with $Et_3SiH/AlCl_3$ at 0–40 °C; however, bromocycloheptane under similar conditions is converted to a 60:40 mixture of cycloheptane and methylcyclohexane in 65% combined yield.[74]

Recently, Chatgilialoglu *et al.* have reported that tris(trimethylsilyl)silane is like organotin hydrides in being capable of reducing organic halides (equation 3).[75] The data available so far are still limited, but it seems that this reagent rivals tributyltin hydride and is more acceptable from an ecological and toxicological perspective.

$$\mathrm{R{-}X} \xrightarrow[h\nu \text{ or } (PhCO_2)_2]{(Me_3Si)_3SiH} \mathrm{R{-}H} \qquad (3)$$

$$X = Cl, Br, I$$

#### *4.1.5.3.2 Complex reducing agents (CRA)*

Sodium hydride itself exhibits only weak reducing ability, but it becomes highly reactive when coupled with sodium alkoxide and transition metal salts. The reagent system designated by Caubère *et al.* as 'complex reducing agents (CRA)' can be used for reductive dehalogenation of organic halides.[10]

Among various CRAs, NaH–*t*-pentyl-ONa–$Ni(OAc)_2$ (NiCRA) and NaH–*t*-pentyl-ONa–$ZnCl_2$ (ZnCRA) possess particularly notable reducing ability toward alkyl halides.[76] With NiCRA, the general reactivity follows the trend RI > RBr > RCl and primary > secondary > tertiary. ZnCRA reduces only primary halides, following the trend RI > RBr >> RCl. Elimination is not observed in the reduction of β-halo ethers and α-halo acetals.

## 4.1.6 REDUCTION WITH COMPLEX METAL HYDRIDES

### 4.1.6.1 Reduction with $LiAlH_4$

Alkyl halides are reduced with $LiAlH_4$ (LAH) to the corresponding saturated hydrocarbons in good to high yields. In view of its ready availability, convenient handling, and ease of removal after completion of reaction, LAH is attractive for the reduction of organic halides. The reduction is usually carried out in ethereal solvents. The classical method using slurries of LAH in ether is not always effective for the reduction, because of its low solubility. Use of THF, dimethoxyethane (DME) or diglyme as the solvent is more effective; for instance, the reduction of *n*-octyl iodide is essentially complete in 0.25 h in these solvents, while the reduction in ether is sluggish, requiring 24 h for 90% completion.[77]

For efficiency and reasons of economy THF is recommended. Representative dehalogenations in THF are shown in Table 1.[78] Most alkyl halides are reduced at 25 °C to alkanes, except for bicyclic halides, such as *exo*-2-bromonorbornane. In most cases, the reaction exhibits the typical characteristics of an $S_N2$ substitution reaction in the reactivity order I > Br > Cl; primary > secondary > tertiary. In all cases, no alkene, or only traces of it, is formed as a side product as a result of elimination. This method provides a convenient synthetic procedure for hydrodehalogenation of alkyl halides.

**Table 1** Reduction of Alkyl Halides with LAH in THF[78]

| *Alkyl halide*[a] | *Temperature* (°C) | *Time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|---|
| 1-Iodooctane | 25 | 0.25 | *n*-Octane | 94 |
| 1-Bromooctane | 25 | 0.5 | *n*-Octane | 96 |
| 1-Chlorooctane | 25 | 24 | *n*-Octane | 73 |
| 1-Chlorooctane | 65 | 4 | *n*-Octane | 94 |
| 2-Bromooctane | 25 | 24 | *n*-Octane | 70 |
| 2-Bromooctane | 65 | 24 | *n*-Octane | 97 |
| 1-Bromo-2-methylpentane | 25 | 6 | 2-Methylpentane | 92 |
| Bromocyclopentane | 25 | 24 | Cyclopentane | 91 |
| Iodocyclohexane | 65 | 6 | Cyclohexane | 93 |
| Bromocyclohexane | 25 | 24 | Cyclohexane | 5 |
| Bromocyclohexane[b] | 65 | 12 | Cyclohexane | 96 |
| Chlorocyclohexane | 25 | 24 | Cyclohexane | Trace |
| Bromocycloheptane[c] | 25 | 24 | Cycloheptane | 94 |
| *exo*-2-Bromonorbornane | 25 | 24 | Norbornane | 3 |

[a]Unless otherwise stated, the concentrations of the alkyl halide and LAH are 0.25 M. [b]1.0 M LAH. [c]0.5 M LAH.

The mechanism of LAH reduction of alkyl halides has been investigated by several research groups. Ashby and his coworkers have extensively studied the mechanism using cyclizable probes, hydrogen donor trapping agents and optically active alkyl halides.[79–83] Their exhaustive investigations have led to the following conclusion: alkyl chlorides are reduced entirely by an $S_N2$ pathway. In the case of bromides, it appears that $S_N2$ and a single electron transer (SET) are in competition, with the $S_N2$ process being strongly favored. For alkyl iodides it appears that SET is the major reaction pathway. On the other hand, Newcomb *et al.* have recently claimed that SET is not an important process for LAH reduction of unhindered primary halides, including iodides.[84,85] The mechanism of LAH reduction of cyclopropyl bromides has also been studied. These reductions are believed to proceed predominantly through an SET process.[86,87]

### 4.1.6.2 Lithium Aluminum Hydride–Metal Salt Systems

Ashby *et al.* have studied reductive dehalogenation by the combined use of LAH and first row transition metal halides (Co$^{II}$, Ni$^{II}$, Fe$^{II}$, Fe$^{III}$, Mn$^{II}$, Ti$^{III}$ and V$^{III}$).[88,89] Table 2 shows that $CoCl_2$, $NiCl_2$ and $TiCl_3$ notably elevate the reducing ability of LAH, and the added salts need only be present in catalytic amounts (10 mol %). Among them, the reagent system LAH–$NiCl_2$ shows the highest reactivity; that is, primary, secondary and cyclic halides (I, Br, Cl) are reduced in essentially quantitative yield at room temperature.

**Table 2** Reduction of Alkyl Halides by LAH–Transition Metal Chlorides at Room Temperature in THF[89]

| *Alkyl halide* | *Transition metal chloride*[a] | *Time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|---|
| 1-Chlorodecane | None | 24 | *n*-Decane | 68 |
| | $FeCl_3$ | | *n*-Decane | 100 |
| | $CoCl_2$ (10 mol %) | | *n*-Decane | 100 |
| | $NiCl_2$ (10 mol %) | | *n*-Decane | 100 |
| | $TiCl_3$ (10 mol %) | | *n*-Decane | 100 |
| 1-Fluorodecane | None | 24 | *n*-Decane | 0 |
| | $FeCl_2$ | | *n*-Decane | 16 |
| | $CoCl_2$ (10 mol %) | | *n*-Decane | 10 |
| | $NiCl_2$ (10 mol %) | | *n*-Decane | 7 |
| | $TiCl_3$ (10 mol %) | | *n*-Decane | 9 |
| Bromocyclohexane | None | 24 | Cyclohexane | 0 |
| | $FeCl_2$ | | Cyclohexane | 97 |
| | $CoCl_2$ | | Cyclohexane | 99 |
| | $NiCl_2$ | | Cyclohexane | 99 |
| | $TiCl_3$ | | Cyclohexane | 100 |
| Chlorocyclohexane | None | 24 | Cyclohexane | 0 |
| | $CoCl_2$ | | Cyclohexane | 92 |
| | $CoCl_2$ (10 mol %) | | Cyclohexane | 3 |
| | $NiCl_2$ | | Cyclohexane | 95 |
| | $NiCl_2$ (10 mol %) | | Cyclohexane | 5 |
| | $TiCl_3$ | | Cyclohexane | 95 |
| | $TiCl_3$ (10 mol %) | | Cyclohexane | 95 |

[a] Molar ratio of LAH to transition metal chloride is 1:1, except when noted.

It has been reported that the LAH–$AgClO_4$ (1%) system also exhibits enhanced reactivity toward halides.[90] The reagent system is effective for such substrates as geminal dihalocyclopropanes, which exhibit poor $S_N2$ reactivity.

The combination of LAH with Lewis acid has a powerful reducing ability. The use of aluminum chloride[91] or cerium chloride[92] under more drastic conditions enables primary alkyl fluorides to be converted to the corresponding saturated hydrocarbons in good to excellent yields.

### 4.1.6.3 Sodium Borohydride

Sodium borohydride, a representative borohydride reagent, behaves as an effective source of nucleophilic hydride in an aprotic polar solvent, such as DMSO, sulfolane, HMPA, DMF or diglyme, and is used for the reduction of alkyl halides.[93,94] As shown in Table 3, primary and secondary iodides, bromides and chlorides are converted to hydrocarbons at temperatures between 25 and 100 °C using sodium borohydride. Vicinal dihalides, such as 1,2-dibromooctane, are smoothly converted to the corresponding saturated hydrocarbons, in contrast to the reductions using $LiAlH_4$ or low-valent metal salts, which predominantly afford alkenes.

Sodium borohydride reduction offers a significant advantage in synthetic applications. The method allows the reductive removal of halides selectively without affecting other functional groups, such as ester, carboxylic acid, nitrile and sulfone. A typical chemoselective dehalogenation is illustrated in Scheme 19.[95]

Some alkyl halides (primary I, Br, Cl and secondary Br) are reduced by $NaBH_4$ under phase-transfer conditions, as shown in equation (4).[96] This reaction is carried out by the addition of a concentrated aqueous solution of $NaBH_4$ to a stirred solution of substrate and catalyst in a suitable solvent, such as toluene. Yields are nearly quantitative in most cases, although an excess of sodium borohydride is required.

**Table 3** Reduction of Alkyl Halides with $NaBH_4$ in Polar Aprotic Solvents[93]

| *Alkyl halide* | *Molar ratio (NaBH₄/halide)* | *Solvent* | *Temperature* (°C) | *Time* (h) | *Product* | *Yield* (%) |
|---|---|---|---|---|---|---|
| 1-Iododecane | 2 | DMSO | 85 | 0.25 | Decane | 93 |
| 1-Iododecane | 2 | Sulfolane | 100 | 0.25 | Decane | 93 |
| 1-Iodododecane | 1 | HMPA | 25 | 0.025 | Dodecane | 87 |
| 1-Iodooctane | 5.3 | Diglyme | 45 | 1 | Octane | 91 |
| 1-Bromodecane | 2 | DMSO | 85 | 1.5 | Decane | 94 |
| 1-Bromododecane | 1 | HMPA | 25 | 0.022 | Docecane | 73 |
| 1-Bromododecane | 2 | DMSO | 85 | 1.5 | Dodecane | 95 |
| 1-Bromododecane | 2 | Sulfolane | 100 | 1.5 | Dodecane | 96 |
| ω-Bromoundecanoic acid | 2 | DMSO | 25 | 2.5 | Undecanoic acid | 98 |
| 1-Chlorododecane | 2 | DMSO | 85 | 4 | Dodecane | 91 |
| 1-Chlorododecane | 2 | Sulfolane | 100 | 6 | Dodecane | 85 |
| 2-Iodooctane | 3 | DMSO | 85 | 1 | Octane | 82 |
| 2-Iodooctane | 3 | Sulfolane | 100 | 1 | Octane | 81 |
| 2-Bromododecane | 3 | DMSO | 85 | 18 | Dodecane | 86 |
| 2-Bromododecane | 3 | Sulfolane | 100 | 18 | Dodecane | 69 |
| 2-Chlorodecane | 3 | DMSO | 85 | 18 | Decane | 68 |
| Ethyl 5-bromovalerate | 4 | HMPA | 25 | 0.5 | Ethyl valerate | 85 |
| Styrene dibromide | 4 | DMSO | 85 | 1.5 | Ethylbenzene | 65 |
| Styrene dibromide | 4 | Sulfolane | 100 | 1.5 | Ethylbenzene | 64 |
| 1,2-Dibromooctane | 4 | HMPA | 70 | 2 | Octane | 84 |

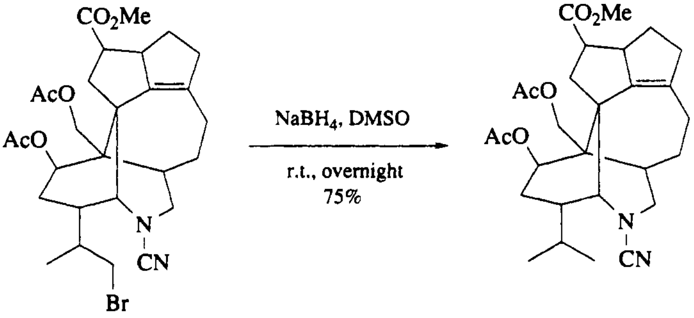

**Scheme 19**

$$R{-}X \xrightarrow[\text{cat. } Q^+\text{Halo}^-\text{, heat, solvent}]{\text{aq. NaBH}_4} R{-}H \qquad (4)$$

R = alkyl group; X = Cl, Br, I; Q = $(alkyl)_4N$, $(alkyl)_4P$

### 4.1.6.4 Lithium Triethylborohydride

Triethylborohydride ($LiEt_3BH$) is the most powerful nucleophilic reducing agent for the reduction of alkyl halides.[97,98] This reagent is far more powerful and cleaner than lithium aluminum hydride and lithium borohydride, as indicated in Figure 1.[98] The replacement of three of the four hydrogen atoms in $LiBH_4$ by ethyl groups enhances the nucleophilicity by a factor of 10 000. This enhanced nucleophilicity arises from the electron-donating effect of the three ethyl groups.

Representative reductions of alkyl halides with $LiBEt_3H$ are shown in Table 4. Most alkyl halides, including chlorides, are reduced under mild conditions in essentially quantitative yields. Even hindered alkyl halides, such as neopentyl bromide and *exo*-norbornyl bromide, undergo facile reduction to the corresponding alkanes in more than 96% yield with this reagent.

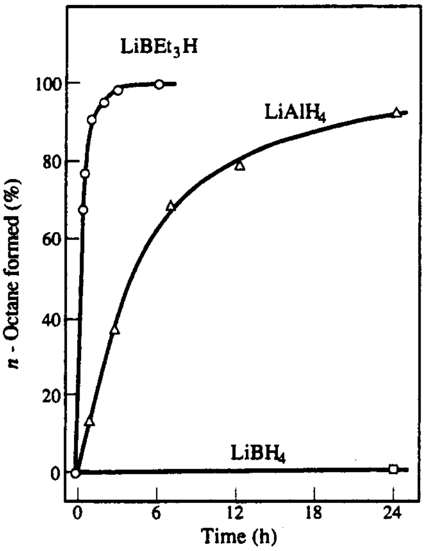

**Figure 1** Rates of reduction of *n*-octyl chloride (0.25 M) with representative complex metal hydrides (0.5 M) in THF at 25 °C (reproduced from ref. 98 by permission from S. Krishnamurthy and H. C. Brown)

**Table 4** Reduction of Alkyl Halides with Lithium Triethylborohydride in THF[98]

| *Alkyl halide*[a] | *Temperature* (°C) | *Time* (h) | *Products* (%)<br>*RX* | <br>*RH* | *Other* |
|---|---|---|---|---|---|
| 1-Iodooctane | 25 | 0.02 |  | 100 |  |
| 1-Bromooctane | 25 | 0.03 |  | 100 |  |
| 1-Chlorooctane | 25 | 1 | 9 | 91 |  |
| 1-Chlorooctane | 25 | 3 |  | 100 |  |
| 1-Bromo-2-methylpentane | 25 | 0.08 |  | 98 |  |
| Neopentyl bromide | 25 | 24 | 14 | 86 |  |
| Neopentyl bromide | 65 | 3 | 5 | 96 |  |
| 2-Bromooctane | 25 | 3 |  | 98 |  |
| 2-Bromo-2-methylpentane | 25 | 24 | 8 | <2 | 84, alkenes |
| Iodocyclohexane | 25 | 12 |  | 92 | 2, alkene |
| Bromocyclohexane | 25 | 24 | 34 | 64 |  |
| Bromocyclohexane | 65 | 6 | 4 | 88 | 2, alkene |
| Chlorocyclohexane | 25 | 24 | 99 | 1 |  |
| Chlorocyclohexane | 65 | 48 | 58 | 34 |  |
| Bromocyclopentane | 25 | 1 |  | 99 |  |
| Bromocycloheptane | 25 | 3 |  | 99 |  |
| Bromocyclooctane | 25 | 24 |  | 95 |  |
| *exo*-Norbornyl bromide | 25 | 24 | 84 | 12 |  |
| *exo*-Norbornyl bromide | 65 | 12 | 40 | 59 |  |
| *exo*-Norbornyl bromide | 65 | 72 | 4 | 96 |  |

[a] In all cases solutions are 0.25 M in alkyl halide and 0.5 M in $LiEt_3BH$.

This reagent is conveniently prepared by the reaction of triethylborane with lithium hydride in THF.[98] The THF solution (1.0 M) is commercially available from Aldrich under the name of 'Super-Hydride'.

A corresponding deuterated derivative is conveniently prepared from lithium deuteride in quantitative yield; the reagent 'Super-Deuteride' is also commercially available from Aldrich. The ready availability of this reagent offers a simple means of introducing deuterium into the system with stereochemical inversion at the center undergoing substitution. An example is shown in Scheme 20.

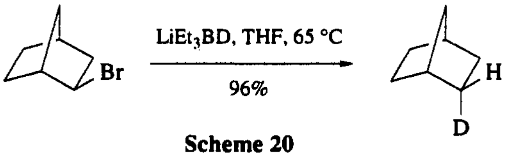

**Scheme 20**

The reduction of alkyl halides by $LiEt_3BH$ exhibits typical $S_N2$ characteristics, but it has been suggested by Ashby *et al.* that the reductions of secondary alkyl iodides and bromides proceed in part by an SET pathway.[99]

### 4.1.6.5 Other Borohydrides and Related Reagents

Cyanoborohydride and its modified reagents have been used for reductive dehalogenations. Thus, the combination of sodium or tetrabutylammonium cyanoborohydride, sodium or potassium 9-cyano-9-hydro-9-borabicyclo[3.3.1]nonanate [9-BBNCN] (**2**) or polymeric cyanoborane (**3**) in HMPA furnishes an efficient and mild system for the reduction of alkyl halides.[100] The reagents are selective in that other functional groups, including ester, carboxylic acid, amide, cyano, alkene, nitro, sulfone, ketone, aldehyde and epoxide, are essentially inert under the reduction conditions; thus, the reduction procedure is attractive for synthetic schemes which demand minimum damage to sensitive portions of the molecule.

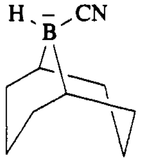

**(2)**

$$-\!\left(\bar{B}H_2CN^{+}-\bar{B}H_2CN^{+}\right)_n\!-$$

**(3)**

A zinc-modified cyanoborohydride reagent, prepared *in situ* by the reaction of sodium borohydride with zinc chloride in ether, reduces tertiary halides in high yields, whereas primary and secondary halides remain intact.[101] Similar reactivity is observed with lithium 9,9-di-*n*-butyl-9-borabicyclo[3.3.1]-nonanate (**4**), as shown in equation (5).[102]

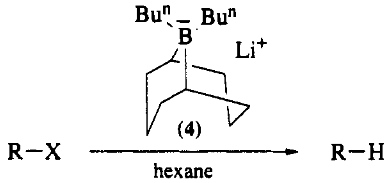

(5)

Yoon and Kim have prepared potassium triphenylborohydride ($KPh_3BH$) and examined the reducing ability toward alkyl halides.[103] *n*-Octyl iodide is reduced within 1 h at 0 °C, whereas *n*-octyl bromide takes 24 h for complete reduction. Secondary bromides are inert under these conditions.

## 4.1.7 MISCELLANEOUS REDUCTION PROCEDURES

Some anionic species have been examined for the reduction of organic halides. Among these are $(MeO)_2PK$,[104] $Ph_2PK$,[105] $K(EtO)_2P(O)H$,[106,107] NaTeH,[108] $Bu^n{}_3SnLi$[109] and $MeSOCH_2Na$,[110] which have been examined for selective reduction of alkyl halides. These reagents possess a strong nucleophilic characteristic and are not always suitable for the reduction of simple alkyl halides, but they are suited to selective monoreduction of geminal dihalocyclopropanes (equation 6). Table 5 summarizes various methods of monoreduction, including the representative ones mentioned in the previous sections.

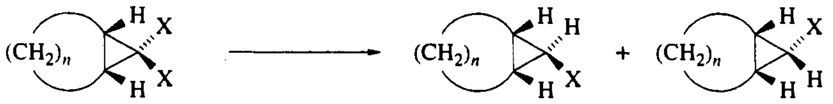

(6)

Phosphorus reagents, particularly $(MeO)_2PK$ and $Ph_2PK$, provide a high yield of monoreduction with excellent stereoselectivity, which is in contrast to other methods, such as LAH reduction.

Reductive elimination of 1,2-dibromoalkanes has been studied by many investigators using sodium disulfide,[121–123] poly(styrylmethylthiol),[124] methyl- or phenyl-selenolate,[125] bis(2-thienyl)ditelluride/$NaBH_4$,[126] sodium telluride/rongalite[127] and trimethylstannylsodium.[128] Among these, sodium sul-

**Table 5** Monoreduction of Cyclopropyl Geminal Dihalides

| | *Reagent or method* | *Solvent* | *Yield (%)* | *exo:endo* | *Ref.* |
|---|---|---|---|---|---|
| $n = 4$, X = Br | $(MeO)_2PK$ | Liquid $NH_3$ | 100 | 100:0 | 104 |
| | $(MeO)_2PK$ | DMSO | 97 | 99:1 | 104 |
| | $HP(O)(OEt)_2/Et_3N$ | | 83 | 17:83 | 106 |
| | NaHTe | EtOH | 55 | 24:76 | 108 |
| | $MeSOCH_2Na$ | DMSO | 72 | 99–90:1–10 | 110 |
| | MeMgBR | THF | 72 | 27:73 | 111 |
| | LAH | $Et_2O$ | 73 | 25:75 | 112 |
| | $LAH/AgClO_4$ | $Et_2O$ | 67 | 7:93 | 90 |
| | $NaAlH_2(OCH_2CH_2OMe)_2$ | $C_6H_6$ | 65 | 74:26 | 113 |
| | $NaBH_4$ | DMF | 79 | 36:64 | 114 |
| | $CrSO_4$ | DMF | 25 | 0:100 | 115 |
| | $Cr(OAc)_2$ | DMSO | 82 | 9:91 | 116 |
| | $n$-$Bu_3SnH$ | | 82 | 29:71 | 117 |
| | Hg cathode | $MeOH/H_2O$ | 80–90 | 16:84 | 118 |
| $n = 6$, X = Br | $(MeO)_2PK$ | Liquid $NH_3$ | 82 | 100:0 | 104 |
| | $HP(O)(OEt)_2/NEt_3$ | | 74 | 22:78 | 106 |
| | NaHTe | EtOH | 59 | 33:67 | 108 |
| | $MeSOCH_2Na$ | DMSO | 71 | 95:5 | 110 |
| | $LAH/AgClO_4$ | THF | 75 | 17:83 | 90 |
| | $NaBH_4$ | DMSO | 90 | 36:64 | 114 |
| | $Bu^n{}_3SnH$ | | 84 | 0:100 | 117 |
| | $Bu^n{}_3SnH/Et_3B$ | PhMe | 84 | 18:82 | 46 |
| | $CrSO_4$ | DMF | 32 | 0:100 | 115 |
| | Zn | AcOH | 95 | 10:90 | 119 |
| | Hg cathode | MeOH | 80–90 | 0:100 | 118 |
| $n = 4$, X = Cl | $Ph_2PK$ | DMSO | 88 | 94:6 | 105 |
| | LAH/$h\nu$ | THF | 93 | 28:72 | 120 |
| | $Bu^n{}_3SnH$ | | 83 | 36:64 | 117 |
| | Hg cathode | MeOH/HCl | 80–90 | 0:100 | 118 |

fide provides high yields of the corresponding alkenes. The reductions are simply carried out in DMF or phase-transfer conditions. This method compares favorably with the methods using Zn–$TiCl_4$[43] and electrochemical reduction.[129]

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# 4.2

# Reduction of Saturated Alcohols and Amines to Alkanes

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## 4.2.1 INTRODUCTION

This chapter will deal with reductive processes which, either directly or following appropriate derivatization, replace hydroxy and amino groups attached to saturated carbon with hydrogen, as indicated in equation (1). Such processes are usually referred to as deoxygenations and reductive deaminations. In general, we will not deal with functional group removal from allylic or benzylic carbon, except where the behavior of these systems is of particular relevance to the fully saturated case; the same remarks apply to processes which proceed through carbonyl compounds or imines, since the reduction of C═X to $CH_2$ is covered in detail in Chapters 1.13 and 1.14 of this volume.

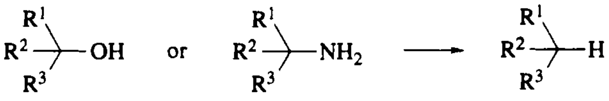

(1)

In the context of total synthesis, the reduction in the level of functionalization implicit in these processes is not always at variance with synthetic objectives, a simple example being the aldol condensation–deoxygenation sequence of Scheme 1, which could replace a (frequently more difficult) direct enolate alkylation. The conversion of readily available, polyfunctionalized materials such as carbohydrates into specifically deoxygenated or deaminated derivatives provides a variety of chiral synthons for the assembly of more complex substances.

The second, major use for deoxygenations and reductive deaminations is the modification of complex natural products, and the need to achieve regio- and chemo-selectivity in such processes has provided significant impetus to the search for novel methods which carry out these transformations under mild

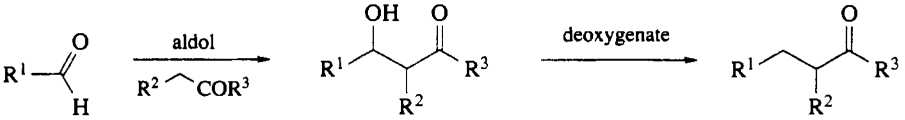

Scheme 1

conditions. Such alteration of natural products is important both for structure elucidations and correlations, and for the exploration of biological structure–activity relationships. For example, therapeutic advantage may be gained by removing a functional group which is not essential to intrinsic activity, but which is a site for metabolic inactivation.

Chemically, methods for deoxygenation and reductive deamination have seen additions in the last two decades which depart from those traditional approaches using hydride reduction of activated alcohols and diazene generation from aliphatic amines. New methods for amine activation, new complex hydrides and, in particular, methods using electron transfer and free radical processes have greatly expanded the range of substrate molecules which can be subject to efficient functional group removal.

In the following sections, the advantages and disadvantages of each method will be illustrated by pertinent examples. The various techniques for removing hydroxy or amino are arranged according to the basic mechanistic process involved in the key step.

## 4.2.2 DEOXYGENATION OF ALCOHOLS AND THEIR DERIVATIVES

### 4.2.2.1 Hydride Reduction Methods

The LAH reduction of tosylates[1] is generally useful for primary and some unhindered secondary alcohols. The relatively indiscriminate reactivity of LAH towards many other functional groups means that these must be protected, as exemplified by the synthesis of the 6-deoxygalactose derivative (**2**) shown in equation (2). Primary tosylates are also reduced by $NaBH_4$ in dipolar, aprotic solvents,[2,3] and cyclododecyl tosylate was reduced slowly.[4] Mesylates were also reduced: $NaBH_4$ in DMSO converted (**3**) to (**4**) without significant reduction or cleavage of the secondary sulfonates.[5] The reduction of $RCH_2OTs$ also took place with $NaBH_3CN$ in HMPA; although the reactions were slow, these conditions did permit the survival of nitriles, esters and aryl ketones.[6] More activated sulfonates such as triflates would presumably react more rapidly with $NaBH_3CN$. For primary alcohols, conversion to the bromo or iodo compound should also be considered, since this affords a number of choices (hydride, electron transfer or stannane) for the subsequent reduction step (see Chapter 4.1, this volume).

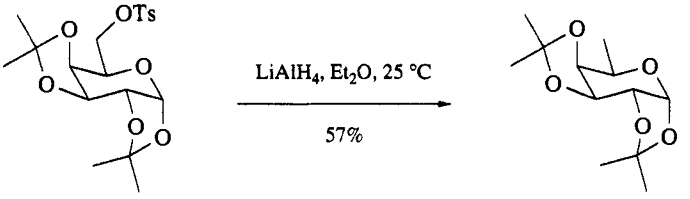

(**1**) (**2**) (2)

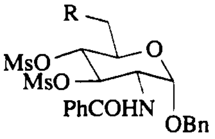

(**3**) R = OMs
(**4**) R = H

When secondary sulfonates are treated with LAH, competing reactions frequently occur. For polyoxygenated, carbohydrate-derived substrates, complexation of the reagent, inductive deactivation and lone pair–nucleophile repulsion all can cause severe retardation of the desired $S_N2$ process, and S—O scission to the parent alcohol is the usual result.[2,7] In cyclohexanes, elimination may be the dominant process when the tosylate is axial and/or the β-H is activated, an extreme case being that shown in equation (3).

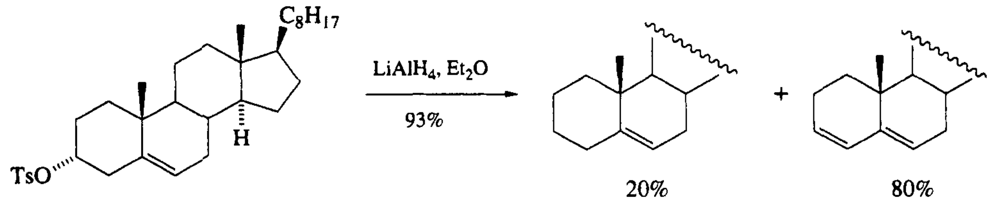

(3)

In a study of the reduction of primary neopentyl and cycloalkyl mesylates and tosylates, two groups[8] showed that $LiBEt_3H$ in THF is superior to LAH and L-selectride in both rate and selectivity for reduction *versus* elimination. While cyclohexyl tosylate still gave 20% alkene, elimination was not seen for the cyclo-pentyl, -heptyl and -octyl esters. The lower rate for neopentyl systems was used to advantage in the selective reduction of (**5**) to (**6**) at 25 °C. In a more complex system,[9] $LiBEt_3H$ reduction of (**7**; $R^2$ = OMs, OTs) regenerated the alcohol (**7**; $R^2$ = OH), whereas the more hindered 2-propanesulfonate (**8**) afforded the deoxy compound (**9**). Methods for preparing other hindered sulfonates ($ROSO_2Bu^t$ and $ROSO_2CPh_2CF_3$) have been described,[10] but their behavior towards LAH and other hydrides remains to be systematically explored.

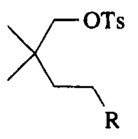

(**5**) R = OTs
(**6**) R = H

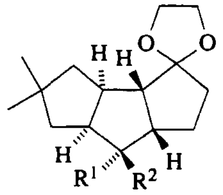

(**7**) $R^1$ = H, $R^2$ = OH
(**8**) $R^1$ = H, $R^2$ = $OSO_2Pr^i$
(**9**) $R^1$ = $R^2$ = H

Chemoselective reagents of the general type Li(CuHR) were developed by Masamune *et al.*[11] for reducing halides and sulfonates. A reagent prepared from CuI and $2LiAlH(OMe)_3$ in THF reduced several mesylates efficiently in a net $S_N2$ process, and the related reagent $LiCuHBu^n$ converted mesylate (**10**) to (**11**) without reducing the ester. Under the same conditions, these reagents reduced ketones and substrates susceptible to conjugate addition.

As might be anticipated, attempts to apply sulfonate–hydride processes to tertiary alcohols lead to elimination and rearrangement reactions. However, the relative ease of carbonium ion formation from these systems permits the use of 'ionic hydrogenations'[12] in which an alcohol (or ether, alkene or ester) is reacted with a protic or Lewis acid (usually $CF_3CO_2H$) in the presence of a mild, acid-stable hydride donor such as $Et_3SiH$. Although most frequently used for benzylic alcohols, some aliphatic cases have been studied and examples are the efficient conversion of (**12**) to (**13**) and of (**14**) to (**15**) in $Et_3SiH$–$CF_3CO_2H$. 2-Octanol was reduced to octane with $BF_3$–$Et_3SiH$.[13] The stereochemical course of these reactions is known for some alkene reductions, and would presumably follow a similar course for tertiary alcohol or ether precursors. The methylcholestene (**16**) gave mostly the equatorial product (**17**),[14] but mixtures were obtained from 1,2-dimethylcycloalkenes. These reactions are subject to rearrangement of the carbonium ion prior to hydride capture: 5-cholestene gave an isomer mixture derived by prior back-

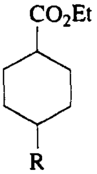

(**10**) R = OMs
(**11**) R = H

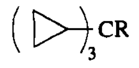

(**12**) R = OH
(**13**) R = H

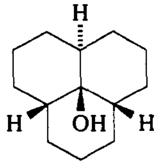

(**14**)

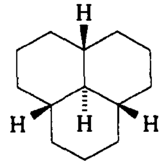

(**15**)

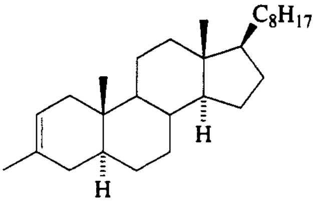

**(16)**

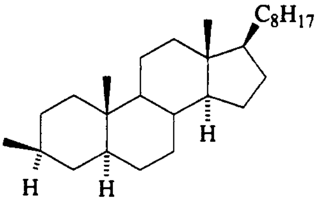

**(17)**

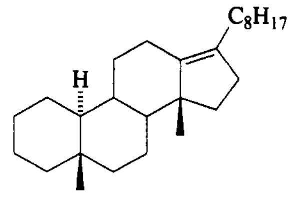

**(18)**

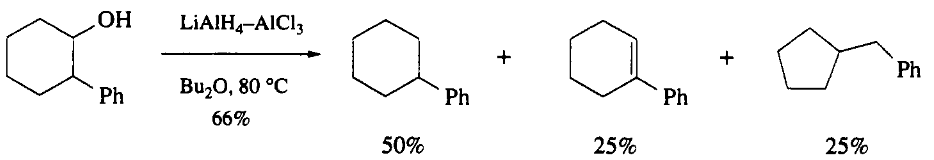

(4)

bone rearrangement to (**18**), and the obtention of the all-*trans* product (**15**) from *cis-cis-trans* (**14**) was a consequence of complete 1,2-hydride shift before reduction.[14] For the same reason, reduction of saturated secondary and tertiary alcohols by LAH–$AlCl_3$ mixtures corresponding to '$Cl_2AlH$' frequently produced alkenes and rearranged materials in addition to the simple deoxy compound, as shown in equation (4).[15]

The reduction of 1,2-diols and their derivatives by hydride or other methods often constitutes a special case. The following guidelines may be useful, and will be exemplified in later sections. For 1,2-diols with a primary center as the target for reduction, selective activation (a bulky reagent such as mesitylenesulfonyl chloride[16] may be advantageous) can be followed by hydride reduction, which may proceed *via* the epoxide if the second hydroxy is not blocked. In carbohydrates, reduction of bis-secondary 1,2-disulfonates frequently occurs *via* S—O cleavage, epoxide formation and 1,2-diaxial opening (see Chapter 4.4, this volume). Removal of both hydroxy groups is commonly carried out through the corresponding alkene, but can also be done directly with certain photoreduction and free radical methods; the latter provide the methods of choice for monodeoxygenation of diols at the more substituted center.

### 4.2.2.2 Catalytic Hydrogenolysis

Despite the haptophilic behavior of the hydroxy group towards both heterogeneous and homogeneous noble metal catalyst systems,[17] a C—OH bond unactivated by adjacent alkenic or aromatic groups (see Chapter 4.7) is quite resistant to hydrogenolysis, and forcing conditions are usually required.

In a series of papers,[18] Adkins and coworkers reported hydrogenolysis of alcohols over $CuCrO_2$, BaO–$CuCrO_2$ and Ni catalysts. At the elevated temperatures and pressures needed to induce reduction, cleavage of C—C bonds also took place *via* dehydrogenation–decarbonylation and retroaldol processes. For simple systems, primary alcohols were converted to the next lower hydrocarbon (equation 5), whereas 2-octanol and cyclohexanol were simply deoxygenated. Similar results were obtained with NiO–$Al_2O_3$ catalysts.[19] Rearrangement of branched compounds was avoided using Co–$Al_2O_3$, but only partial conversion was seen under very forcing conditions.[20]

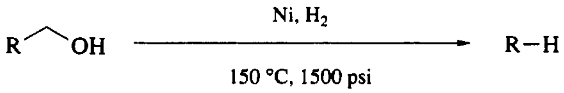

(5)

Some selectivity for monodeoxygenation of glycols was obtained over Ni or $CuCrO_2$, and depended upon the separation of the hydroxy groups: under conditions which did not affect the 1,4-diol, cyclohexane-1,3-diol gave cyclohexanol. The examples of equations (6) and (7) show that there was some selectivity for removing primary hydroxy groups.

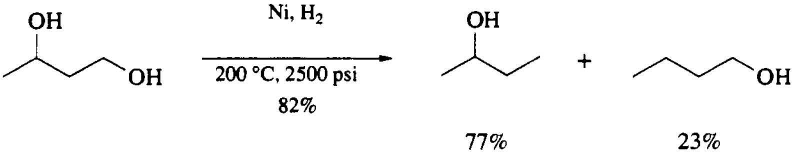

(6)

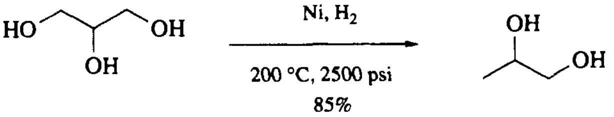

(7)

The more facile reduction[21] of tertiary alcohols and esters and of secondary tosylates over Pt in HOAc or $CF_3CO_2H$ was ascribed to alkene formation prior to reduction. The deoxygenation of tertiary alcohols with Raney nickel in refluxing toluene[22] also proceeds through the alkenes; these conditions also effected the transformation shown in equation (5).

The two-step sequence shown in Scheme 2 has been used to deoxygenate a variety of monohydric, acyclic alcohols.[23] Reaction of the alcohol with DCC (other carbodiimides gave less satisfactory results in the reductive step) catalyzed by CuCl gave the *O*-alkyl-*N*,*N*′-dicyclohexylisourea, which was hydrogenated over Pd–C in EtOAc to the deoxy compound. Excellent yields were obtained (Table 1) for primary, secondary and tertiary acyclic systems with reduction times of 2–30 h, the tertiary case being the most reactive. However, this method was not useful for most cycloalkanols, the reductive step being extremely slow. The *O*-isobornyl derivative (**19**) was reduced readily, but with rearrangement, giving *endo*-isocamphane (**20**).

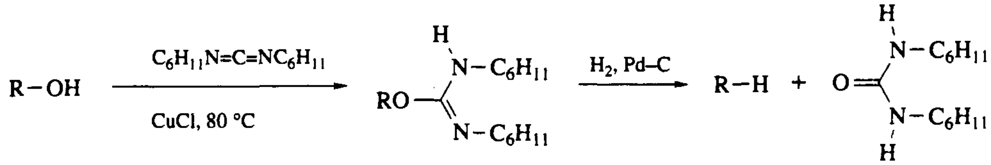

**Scheme 2**

**Table 1** Formation and Hydrogenation of *O*-Alkyl-*N*,*N*′-dicyclohexylisoureas[23]

| *Alcohol* | *Isourea, yield* (%)[a] | *Hydrocarbon, yield* (%)[b] |
|---|---|---|
| Octan-1-ol | 93 | 97 (81) |
| Octan-2-ol | 94 | 98 |
| Octan-4-ol | 93 | 97 |
| Tetradecanol | 93 | 96 (76) |
| 2-Phenylethanol | 94 | 91 |
| 2-Methylheptan-2-ol | c | 94 |

[a] Isolated yield, 0.10 mol scale. [b] Determined by GLC; overall yields in parentheses represent examples in which the intermediate isourea was not isolated. [c] Not cited.

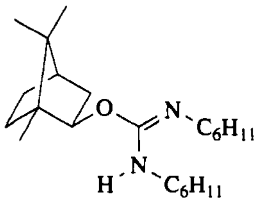

(**19**)

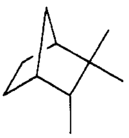

(**20**)

### 4.2.2.3 Electron Transfer Reductions

When a carboxylic, phosphoric or sulfonic ester (or thioester) of an aliphatic alcohol is made to accept electrons, several reaction pathways are available to the resulting radical anion, as shown in Scheme 3.

The desirable fragmentation (A) to give the alkyl radical represents a viable method for overall deoxygenation, providing that alternative processes involving O—X fission (B), or H-abstraction (C) or net two-electron reduction (D; the Bouveault–Blanc reduction of esters, for example) followed by O—X fission, can be minimized. Conditions have been established which cause (A) to be the dominant process for X = C, P and S; this section will compare the merits of these processes for alcohol deoxygenation.

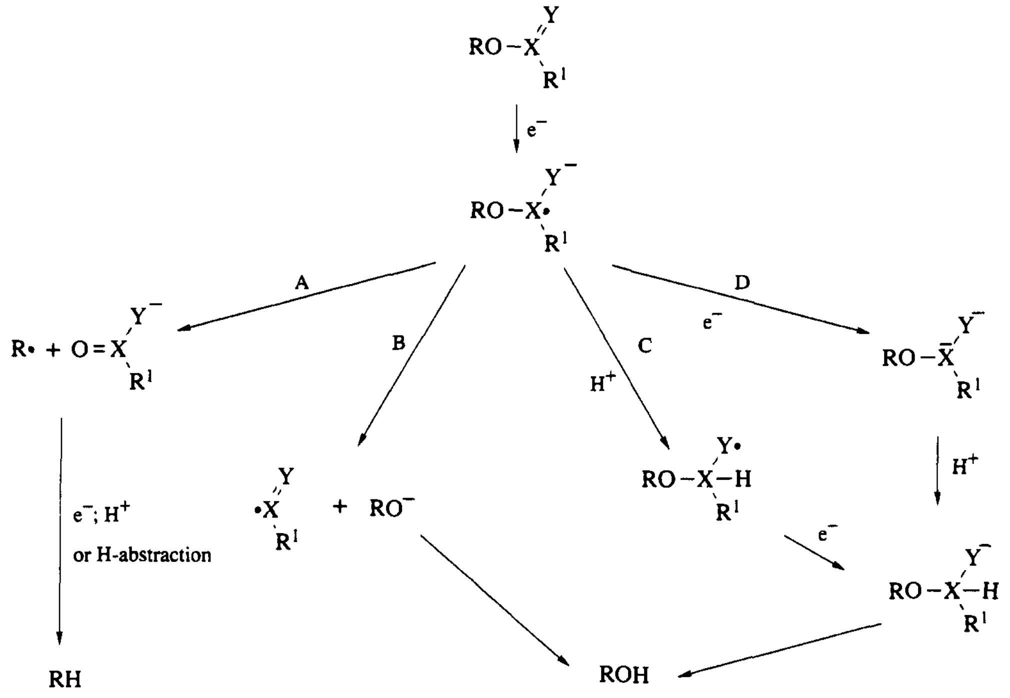
RO−X(=Y)R¹
e⁻
RO−X•(Y⁻)R¹
A
B
C
D
R• + O=X(Y⁻)R¹
e⁻; H⁺
or H-abstraction
RH
•X(=Y)R¹ + RO⁻
H⁺
e⁻
RO−X(Y•)(H)R¹
RO−X(Y⁻)R¹
H⁺
e⁻
RO−X(Y⁻)(H)R¹
ROH

**Scheme 3**

From the viewpoint of experimental conditions, three methods have been used to supply the solvated electrons required: dissolving metals, electrochemistry and photochemistry. Several groups have explored the reduction of esters by dissolving metals, and this proves to be a general method for deoxygenating tertiary and hindered secondary alcohols. For primary and unhindered secondary systems, substantial amounts of alcohol tend to be regenerated, although this can be minimized by using esters of bulky carboxylic acids. Reductions of the esters of 3$\beta$,6$\beta$,5$\alpha$-cholestanediol illustrate salient points.[24] The diacetate (**21**) with Li–EtNH$_2$ or Li–NH$_2$CH$_2$CH$_2$NH$_2$ gave the 6-deoxy compound (**22**) and diol (**23**) in 1.3:1 ratio, improved to 2:1 by using K–Bu$^t$NH$_2$ and 18-crown-6. When the pivalate (**24**) was similarly reduced, the RH:ROH ratio was 8.8:1. Compelling evidence for a carbon radical intermediate was provided by the cyclosteroid example shown in equation (8), and is consistent with the very efficient

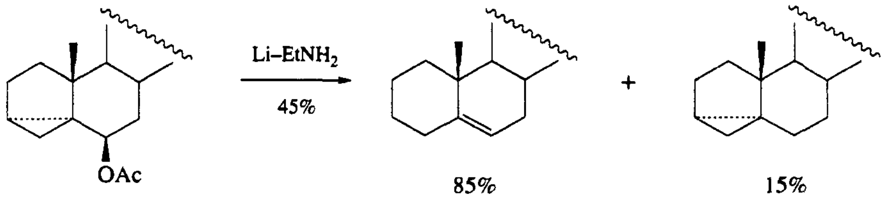
OAc
Li-EtNH₂
45%
+
85%
15%

(8)

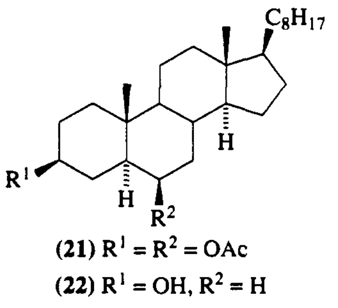
C₈H₁₇
H
R¹
H
R²

(**21**) R$^1$ = R$^2$ = OAc

(**22**) R$^1$ = OH, R$^2$ = H

(**23**) R$^1$ = R$^2$ = OH

(**24**) R$^1$ = R$^2$ = O$_2$CBu$^t$

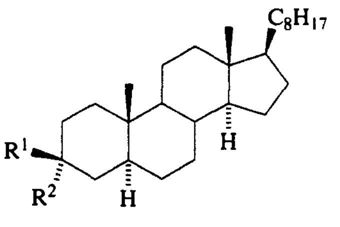
C₈H₁₇
H
R¹
R²
H

(**25**) R$^1$ = OAc, R$^2$ = Me

(**26**) R$^1$ = Me, R$^2$ = OAc

deoxygenation[25] of tertiary acetates (**25**) and (**26**) by Na–HMPA–$Bu^tOH$. Similar reductions have been effected with Na–K alloy in THF in the presence of $(MeOCH_2CH_2OCH_2CH_2O)_3N$,[26] avoiding side reactions associated with cleavage of 18-crown-6.

Several methods are available which minimize the O—X cleavage process,[27] of which the most general was developed by Ireland and coworkers.[28] A wide variety of alkyl and cycloalkyl *N,N,N′,N′*-tetramethylphosphorodiamidates were cleanly deoxygenated (Scheme 4) with essentially no regeneration of the starting alcohol. Examples are the conversion of (**27**) to (**28**) and of cholesterol to cholest-5-ene, with near-quantitative yields in the reduction step. For tertiary alcohols, the *O,O*-diethylphosphates were satisfactory, as in the conversion of (**29**) to adamantane. Metal–amine reductions of *N,N*-dimethylthiocarbamates,[29] *N,N*-dimethylsulfamates[30] and triflates[31] have also been reported; in some carbohydrate examples, equatorially disposed β-hydroxy groups survived without alkene formation, but this was not generally the case for these reactions proceeding *via* carbanionic intermediates.

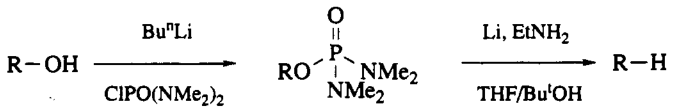

**Scheme 4**

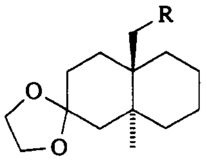

(**27**) R = OH
(**28**) R = H

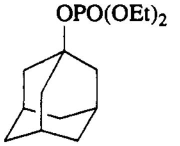

(**29**)

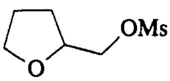

(**30**)

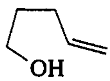

(**31**)

Mesylates, which tend to undergo O—S scission with dissolving metals, were reduced electrochemically in DMF. Yields of 70–85% were reported[32] under conditions which left esters, nitriles and epoxides unchanged. The conversion of (**30**) to (**31**) again indicated a carbanionic intermediate.

Photochemical methods have been used for deoxygenation under milder conditions. Photolysis of acetates at 254 nm in 95:5 HMPA–$H_2O$ was generally useful for molecules which did not contain chromophoric groups, and removed primary, secondary and tertiary oxygens.[33] Pivalates were generally superior to acetates, as exemplified by the formation of deoxy compound (**32**) in 65% yield from (**33**) and in 75% yield from (**34**). Homolytic scission from the radical anion followed by H-atom abstraction is clearly involved; metal–amine reduction of (**35**) did not give (**32**), but led to complete ring scission *via* elimination from C-2. In appropriate cases, interfering chromophores could be modified by protection: deoxygenation of testosterone acetate was achieved by photoreduction of ketal (**36**) to (**37**) in HMPA–$H_2O$, followed by acid hydrolysis to (**38**) in 60% overall yield. In all of these direct photoreductions of acetates, pivalates or triflates, the use of HMPA–$H_2O$ was essential for deoxygenation.

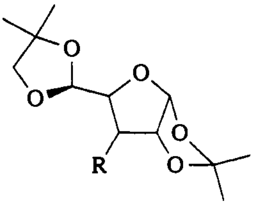

(**32**) R = H
(**33**) R = OAc
(**34**) R = $O_2CBu^t$
(**35**) R = $OPO(NMe_2)_2$

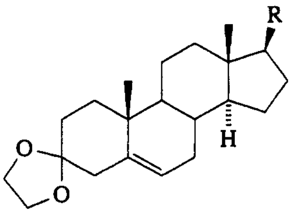

(**36**) R = OAc
(**37**) R = H

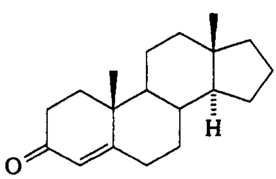

(**38**)

For substrates with UV-absorbing functional groups, an interesting photosensitized ester deoxygenation has been described.[34] Irradiation (Pyrex) of an EtOH–$H_2O$ solution of the *m*-trifluorobenzoyl derivative (**39**) containing *N*-methylcarbazole (MCZ) as the sensitizer gave 91% of (**40**) with recovery of MCZ and *m*-$CF_3C_6H_4CO_2H$. This process was specific for secondary alcohols and did not proceed through carbanionic intermediates: the adenosine triester (**41**; A = adenine) was converted cleanly to the 2′,3′-dideoxy compound (**42**) with no 2′,3′-alkene. A radical process was confirmed by incorporation of deuterium from $CD_3CD_2OH$, but not from $D_2O$. This method would seem to be particularly useful for vicinal dideoxygenation, the more so since thiocarbonyl–stannane methods are not satisfactory for this transformation. In a further simplification the unsubstituted benzoate (**43**; U = uracil), which was a poor substrate when irradiated with MCZ alone, was efficiently converted to (**44**) in the presence of $Mg(ClO_4)_2$.

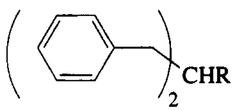

(**39**) R = $O_2CC_6H_4$-*m*-$CF_3$
(**40**) R = H

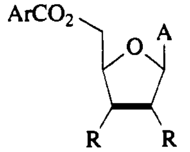

(**41**) R = $O_2CAr$
(**42**) R = H
[Ar = $C_6H_4$-*m*-$CF_3$]

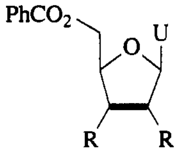

(**43**) R = $O_2CPh$
(**44**) R = H

### 4.2.2.4 Stannane Reduction of *O*-Thiocarbonyl Derivatives

The free radical deoxygenation of secondary alcohols[35] by the reaction of various *O*-thiocarbonyl derivatives with tri-*n*-butylstannane ($Bu_3SnH$) shown in equation (9) was the prototype for several modifications and related processes which, taken as a whole, permit the deoxygenation of most types of alcohols and the monodeoxygenation of 1,2 and 1,3-diols. In these two-step processes, the initial derivatization involves either basic or near-neutral conditions and the reductive step occurs in neutral, aprotic solvents at 80–160 °C. These processes are limited only by those side-reactions (intramolecular cyclizations or fragmentations) of carbon radicals which can successfully compete with H-abstraction from an efficient donor ($R_3SnH$), and frequently provide the method of choice for deoxygenation in polyfunctionalized systems bearing groups sensitive to hydride or dissolving metal reagents. These methods have been reviewed in brief[36] and in detail,[27] and are included in general reviews of carbon radical chemistry[37] and synthetic uses of $Bu_3SnH$.[38]

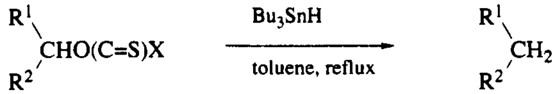

$$R^1R^2CHO(C{=}S)X \xrightarrow[\text{toluene, reflux}]{Bu_3SnH} R^1R^2CH_2 \qquad (9)$$

Scheme 5 shows the reactions that occur when a thioester or similar substrate (**45**) interacts with $Bu_3SnH$ under free-radical conditions. After initial addition (which may be reversible) to afford the stabilized intermediate radical (**46**), the desired fragmentation (A) will take place with an ease which depends to some extent on the nature of X (in ROCSX), but is more determined by the temperature, and by the nature of R. Steric compression about the C—O region encourages the fragmentation without seriously affecting the addition step, making these methods very useful for hindered systems. After fragmentation, the major fate of the alkyl radical is H-abstraction (C) to give the deoxy compound (**49**) and the chain carrier ($Bu_3Sn\cdot$); a less common occurrence is (D), where capture of R by the substrate rather than $Bu_3SnH$ results in overall conversion to the isomeric *S*-thioester. More frequent (but usually quite minor) side-reactions arise from abstraction prior to fragmentation (B) and ultimately produce the starting alcohol (**52**) or the ether (**53**), depending upon the particular substrate. An alternative possibility involving $S_H2$ attack on the singly bonded sulfur exists for dithiocarbonates (xanthates) and was proposed on the basis of ESR (electron spin resonance) measurements, which indicated some production of ROCS· from $ROCS_2Me$ at low temperatures.[39] Under typical deoxygenation conditions, however, experiments using dithiocarbonates with *S*-substituents with different steric and electronic characteristics indicated that the addition of $Bu_3Sn\cdot$ to C═S is the important initial step.[40] The presence of $Et_3B$ allowed some deoxygenations to proceed at ambient temperature,[41] but the mechanistic processes involved were not established.

For a given secondary alcohol, the choice of thiocarbonyl derivative is predicated more by structural features (steric hindrance, other functional groups) present in the alcohol than by the actual reductive step. Barton and McCombie[35] reported comparable results for *S*-methyldithiocarbonyl (MDC), thiobenzoyl (TB) and imidazole-1-thiocarbonyl (ITC) derivatives, and typical preparations of these are shown in

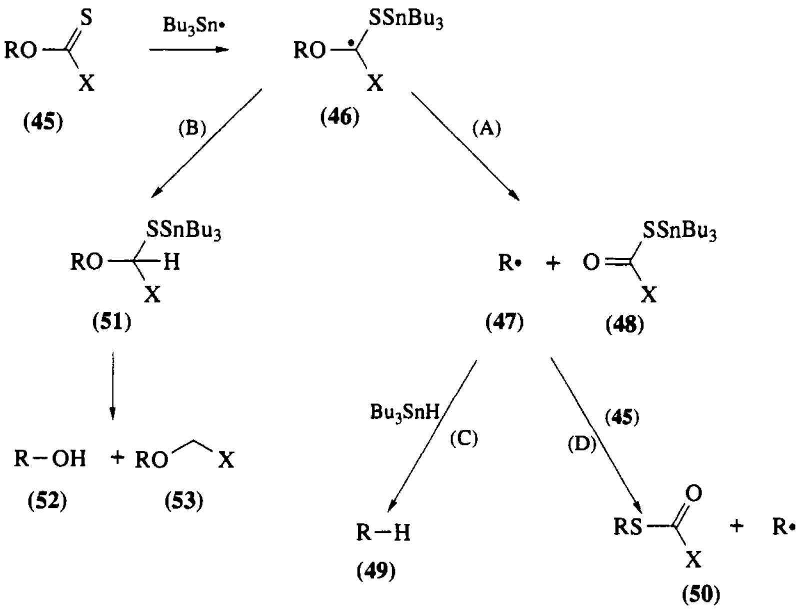

Bu$_3$Sn•
(45)
(46)
(B)
(A)
(51)
(47)
(48)
R−OH
(52)
(53)
Bu$_3$SnH
(C)
(D)
(45)
R−H
(49)
(50)
R•

Scheme 5

equations (10)–(12). The ITC derivatives were recommended by Rasmussen *et al.*[42] for carbohydrates, and phenoxythiocarbonyl (PTC) derivatives prepared as shown in equation (13) were introduced by Robins *et al.*[43] for nucleoside deoxygenation.

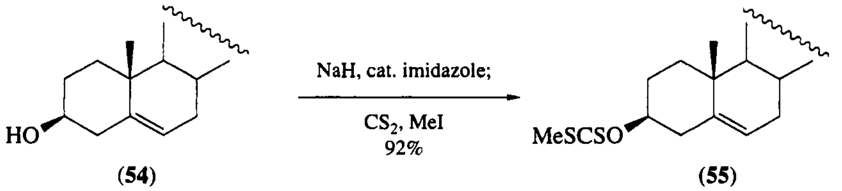

NaH, cat. imidazole;
CS$_2$, MeI
92%
HO
MeSCSO
(54)
(55)

(10)

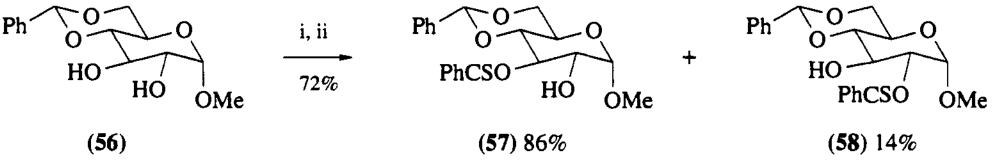

i, ii
72%
(56)
(57) 86%
(58) 14%

(11)

i, PhCCl=NMe$_2^+$Cl$^-$, Py; ii, H$_2$S, Py, 25 °C

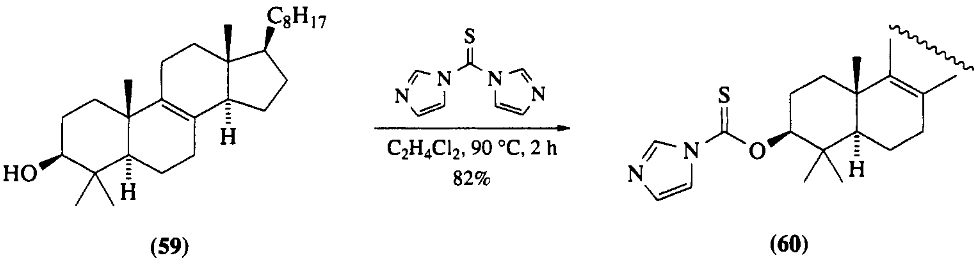

C$_2$H$_4$Cl$_2$, 90 °C, 2 h
82%
(59)
(60)

(12)

Table 2, which compares syntheses of the protected 3-deoxyglucose (**32**) and of cholest-5-ene (**63**), shows that all of the thiocarbonyl derivatives gave good to excellent yields. In general, the MDC and PTC derivatives gave rise to the smallest amounts of by-product, which in the case of the TB and ITC derivatives was mostly the starting alcohol. Although TB derivatives required gradual addition to Bu$_3$SnH solution, and occasionally gave rise to significant amounts of the benzyl ether,[44] the preparative route shown in equation (11) does have one special characteristic: since the prethiolysis intermediate

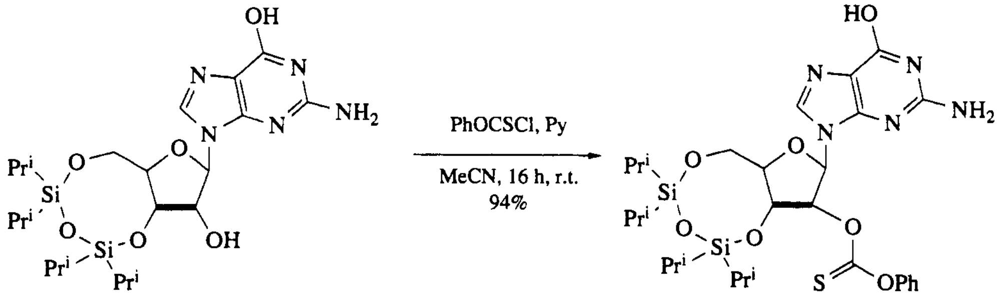

**(61)** **(62)** (13)

(like the reagent, $PhCCl{=}NMe_2^+Cl^-$) is charged, only a single hydroxy in a polyol is functionalized under mild conditions.[35] For example, (**64**) gave only monoester (**65**); to obtain the bis-TB derivative (**66**), it was necessary to subject isolated (**65**) to a second sequence.

**Table 2** Tri-*n*-butylstannane Reduction of *O*-Thiocarbonyl Derivatives of Cholesterol (A) and 1,2,5,6-Di-*O*-ispropylidene D-glucofuranose (B) in Toluene

| *Alcohol* | *Derivative* | *Temperature* (°C) | *Time* (h) | *Yield* (%)[e] | *Ref.* |
|---|---|---|---|---|---|
| A | PhCS[a,b] | 110 | 2 | 73 | 35 |
| A | MeSCS[b] | 110 | 7 | 78 | 35 |
| A | ImCS[b] | 110 | 6 | 74 | 35, 42 |
| A | PhOCS[c] | 110 | 7 | 85 | 43 |
| B | MeSCS[b] | 110 | 18 | 85 | 35 |
| B | ImCS[b] | 110 | 6 | 74 | 42 |
| B | PhOCS[c] | 80 | 3 | 85 | 43 |

[a]Thioester added over 0.5–1 h. [b]No initiator added. [c]0.2 equiv. $Bu^t_2O_2$ added. [d]0.2 equiv. AIBN added. [e]Isolated yield.

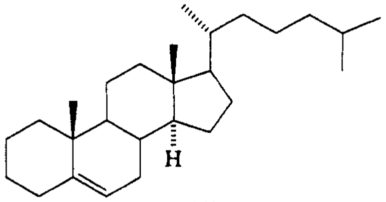

**(63)**

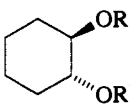

(**64**) $R^1 = R^2 = H$
(**65**) $R^1 = H, R^2 = CSPh$
(**66**) $R^1 = R^2 = CSPh$

Secondary hydroxy groups have been removed from a wide range of polyfunctionalized molecules[27] using these processes, which tolerate the presence of esters, ketones, alcohols, C—F bonds, protected amines and alkenes, providing the latter are not situated so as to encourage cyclization of the intermediate radical. The aminoglycoside antibiotics provide some elaborate examples: the protected kanamycin (**67**) was converted to MDC derivative (**68**) and thence to deoxy compound (**69**) in 59% overall yield, and other secondary positions in related systems were deoxygenated *via* *S*-phenyldithiocarbonyl derivatives prepared from the alcohol and PhSCSCl–pyridine.[45] The reductions of lanosterol thioesters[35] and of the hirsutene intermediate (**70**) to (**71**)[46] exemplify deoxygenations at neopentyl centers. As previously noted,[41] inclusion of $Et_3B$ in these reactions permits secondary deoxygenations to be run at ambient temperature, which may be advantageous for thermally labile materials.

Monodeoxygenation of 1,2- and 1,3-diols was achieved[47] *via* their cyclic thiocarbonates, prepared from the diol and *N*,*N*′-thiocarbonyldiimidazole, by reaction with $Bu_3SnH$–AIBN followed by alkaline hydrolysis (presumably, $F^-$ would also be effective for the cleavage step). Equation (14) shows this process applied to synthesis of a derivative (**73**) of 5-deoxyglucose. Exclusive secondary deoxygenation is expected on the basis of radical stability; in contrast, the derivative (**72**) was readily converted by an ionic process to an intermediate suitable for 6-deoxygenation, since treatment with KI gave (**74**) quantitatively.

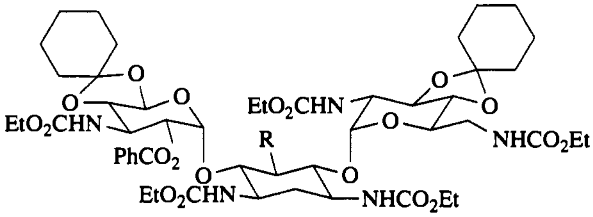
O
O
O
EtO2CHN
PhCO2
O
EtO2CHN
EtO2CHN
O
O
R
O
O
NHCO2Et
NHCO2Et

(67) R = OH
(68) R = OCSSMe
(69) R = H

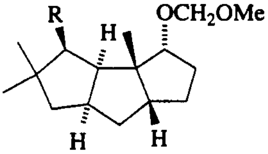
R
H
OCH2OMe
H
H

(70) R = OCSSMe
(71) R = H

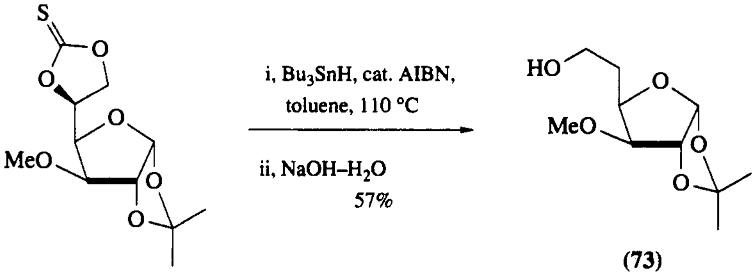
S
O
O
O
MeO
O
O
i, Bu3SnH, cat. AIBN,
toluene, 110 °C
ii, NaOH-H2O
57%
HO
O
MeO
O
O

(72) (73)

(14)

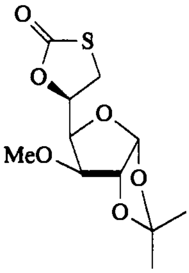

(74)

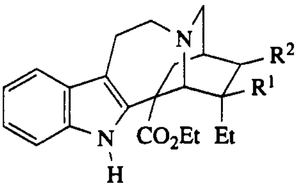
O
S
O
O
MeO
O
O
N
R2
R1
N
H
CO2Et
Et

(75) $R^1, R^2$ = –OCSO–
(76) $R^1$ = H, $R^2$ = OH

Radical stability also accounts for efficient deoxygenation at the tertiary center in the conversion of (**75**) to (**76**) in a synthesis of vinblastine,[48] although a concentration dependent competition between tertiary *versus* secondary reduction was reported for some branched carbohydrate derivatives.[49] When the starting diol contains two secondary centers, mixtures frequently result, as shown in equation (15).

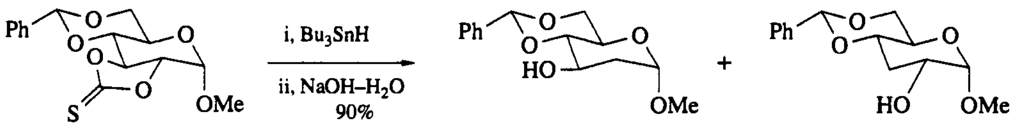
Ph
O
O
O
O
O
S
OMe
i, Bu3SnH
ii, NaOH-H2O
90%
Ph
O
O
O
HO
OMe
+
Ph
O
O
O
HO
OMe

(15)

67% 33%

Because the lower degree of stabilization of primary radicals retards the fragmentation (process (A) in Scheme 5), the standard procedure was inefficient for *O*-thiocarbonyl derivatives of primary alcohols, but was rendered acceptable by running the reductive step at 150 °C.[50] Conversion of methylhederagenin (**77**) to monoxanthate (**78**) followed by heating with $Bu_3SnH$ in *p*-cymene gave methyl oleanolate (**79**) in 51% overall yield.

Radical deoxygenation of an isolated tertiary hydroxy, desirable if involvement of adjacent stereocenters (in alkene formation or rearrangements) has to be avoided, presented problems in derivatization. Scheme 6 shows an inventive solution[51] in which the alcohol (**80**) was converted to imidate (**81**). Choice of this electron-rich aromatic system secured smooth thiolysis to (**82**), which was efficiently deoxyge-

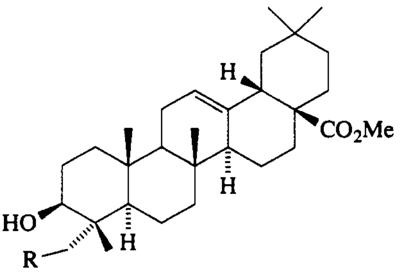
H
$CO_2Me$
H
HO
R
H

**(77)** R = OH
**(78)** R = OCSSMe
**(79)** R = H

nated by $Bu_3SnH$ (secondary thioformates, although easily prepared, are not satisfactory deoxygenation substrates in most systems).

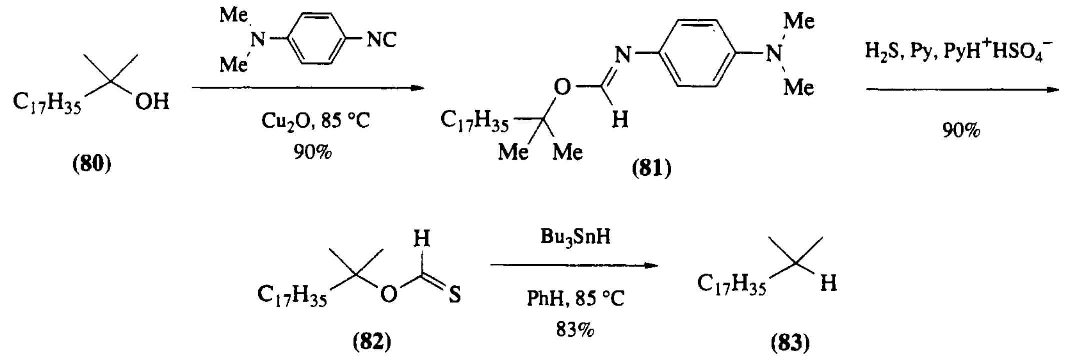
$C_{17}H_{35}$
OH
(80)
Me
N
Me
NC
$Cu_2O$, 85 °C
90%
N
Me
N
Me
O
H
$C_{17}H_{35}$
Me
Me
(81)
$H_2S$, Py, $PyH^+HSO_4^-$
90%
H
$C_{17}H_{35}$
O
S
(82)
$Bu_3SnH$
PhH, 85 °C
83%
$C_{17}H_{35}$
H
(83)

**Scheme 6**

All of the foregoing reactions, together with those described in Sections 4.2.2.5 and 4.2.3.3, which proceed *via* homolytic C—O or C—N scission, are subject to side reactions (which may become the dominant process) characteristic of carbon-centered free radicals. If the β-carbon bears a group which can yield a relatively stable radical, then alkene formation is the result (Scheme 7).

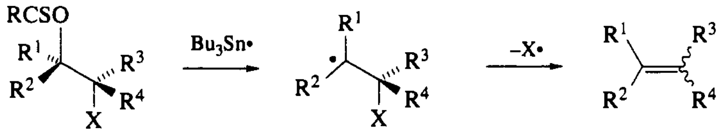
RCSO
$R^1$
$R^2$
$R^3$
$R^4$
X
$Bu_3Sn\bullet$
$R^1$
$R^2$
$R^3$
$R^4$
X
$-X\bullet$
$R^1$
$R^2$
$R^3$
$R^4$

X = $NO_2$, SPh, $SO_2Ph$, Cl

**Scheme 7**

This process occurs for X = O only in two special cases, which have been developed into synthetic methods for alkenes and allylic alcohols. Reaction of $Bu_3SnH$ with 1,2-bis-MDC derivatives gave alkenes from diols[52] in a process which was independent of the geometry of the starting diol. Examples are the conversions of (**84**) to (**85**) and of (**86**) to (**87**).

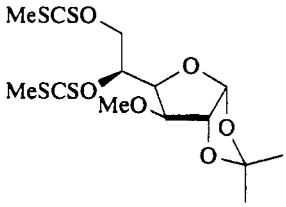
MeSCSO
MeSCSO
MeO
O
O
O

**(84)**

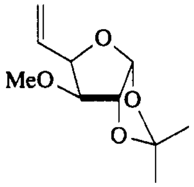

**(85)**

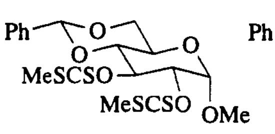
Ph
O
O
O
MeSCSO
MeSCSO
OMe

**(86)**

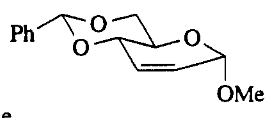

**(87)**

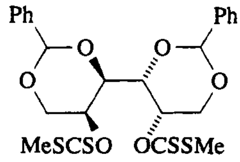

**(88)**

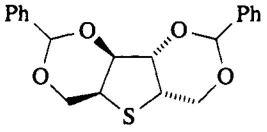

**(89)**

The formation of alkenes from TB or MDC derivatives of β-hydroxy sulfides and sulfones[53] is also a useful procedure. When the 1,4-bis-MDC derivative (**88**) was reacted with $Bu_3SnH$, the tetrahydrothiophene (**89**) was produced,[54] presumably by the process shown in Scheme 8. The first intramolecular step is related to the attack on C=S by a carbon radical in the reactions of 1,2-bis-TB derivatives with $Bu_3SnH$ (equation 16).[35]

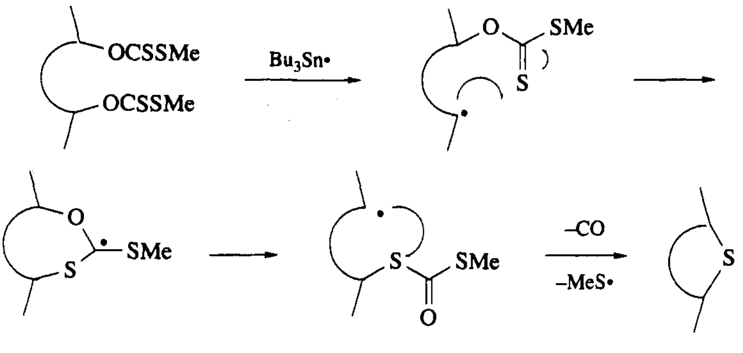

**Scheme 8**

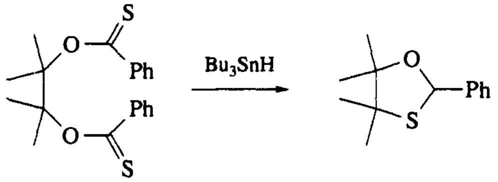

(16)

Alkene formation also took place upon attempted deoxygenation of ITC derivatives of 2,3-epoxy alcohols.[55] This radical-based alternative to the Wharton rearrangement is shown in equation (17), and is analogous to the rearrangement of cyclopropylcarbinyl radicals.

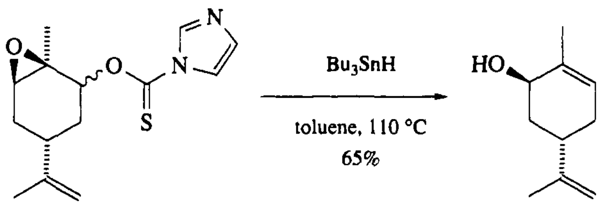

(17)

Finally, we note that interception of the carbon radical by a proximate C=C or C≡C system, which has received much attention in recent years as a useful synthetic tool,[37,56] can be a problem when simple deoxygenation is desired at a center five or six atoms removed from the multiple bond. The efficient, planned cyclization[57] of (**90**) to (**91**) also represents an unsuccessful deoxygenation of a secondary alcohol! The initial adduct radicals (to C=S) have also been trapped in intramolecular reactions.[58]

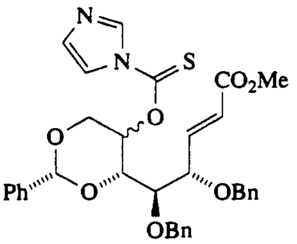

**(90)**

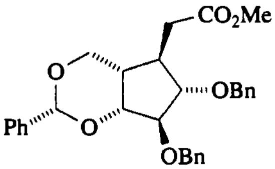

**(91)**

### 4.2.2.5 Stannane and Silane Reduction of Esters and Carbonates

From a study of various substrates, Khoo and Lee[59] concluded that direct reduction of *O*-benzoates by $Bu_3SnH$ is satisfactory for benzylic or allylic alcohols, but is not preparatively useful for saturated systems, as shown by the examples of equations (18) and (19). The mechanism probably involves direct attack of $Bu_3Sn\cdot$ on the ethereal oxygen, and is facilitated by electron-withdrawing groups; reduction of $PhCH_2OCOCF_3$ was some four times faster than reduction of $PhCH_2OCOPh$.

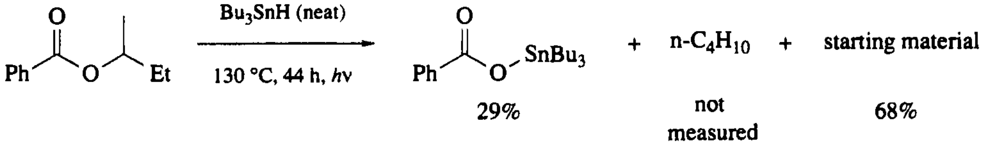

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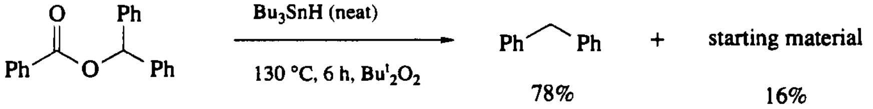

(19)

A more useful process was found in the reduction of methyloxalates of secondary and tertiary alcohols.[60] One advantage of this method is the high reactivity of the derivatizing reagents [MeOCOCOCl or $(COCl)_2$], which react easily with hindered alcohols. In the gibberellin series, (**92**) could not be converted to a phenoxythiocarbonyl derivative but was deoxygenated in 65% yield to (**93**) *via* (**94**). The final step in the synthesis[61] of bilabolide acetate (**95**) involved a similar reduction of (**96**) at high dilution in toluene, and gave a 2:1 mixture of deoxy compound and starting alcohol.

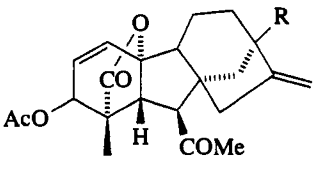

**(92)** R = OH
**(93)** R = H
**(94)** R = $O_2CCO_2Me$

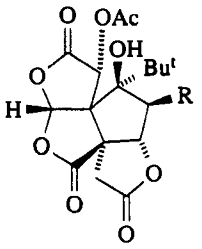

**(95)** R = H
**(96)** R = $O_2CCO_2Me$

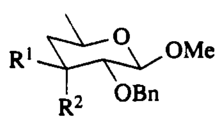

**(97)** $R^1$ = Ac, $R^2$ = $O_2CPh$
**(98)** $R^1$ = $O_2CPh$, $R^2$ = Ac
**(99)** $R^1$ = Ac, $R^2$ = H
**(100)** $R^1$ = H, $R^2$ = Ac

The reduction of α-ketobenzoates by $Bu_3SnH$[62] constitutes a special case, probably involving addition of the stannyl radical to the ester carbonyl. Reductions of isomerically pure (**97**) and (**98**) gave the same 4:1 ratio of the epimeric products (**99**) and (**100**).

Simple acetates were reduced at 140 °C with an excess of either $Ph_3SiH$ or *p*-$HPh_2SiC_6H_4SiPh_2H$ and substantial amounts of free radical initiator, necessary to offset dimerization of the chain-carrying silyl radicals. Good yields were obtained (Table 3) for a number of nonfunctionalized primary, secondary and tertiary acetates.[63] Esters lacking any strongly absorbing chromophore, when photolyzed with $HSiCl_3$, gave a mixture of ether and deoxy compound.[64]

Table 3 Reduction of Acetates to Alkanes with $Ar_3SiH$ and $Bu^t_2O_2$[63]

| *Ester* | *Method*[a] | *Yield* (%)[b] |
|---|---|---|
| $c$-$C_{12}H_{23}OAc$ | A | 89 |
| | B | 82 |
| $PhCH_2CMe_2OAc$ | A | 71 |
| $n$-$C_{12}H_{25}OAc$ | A | 95 |
| | B | 67 |
| Cholesteryl-OAc | A | 59 |

[a] Method A: 1.3 mmol of ester, 2 mmol of $p$-$C_6H_4(SiPh_2H)_2$ and 1.3 mmol of $Bu^t_2O_2$ were reacted for 15 h at 140 °C. Method B: as in A, but 5.2 mmol of $Ph_3SiH$ were used in place of the disilane. [b] Isolated yield of hydrocarbon.

Finally, there are several methods for alcohol deoxygenation which depend upon generating the corresponding alkoxycarbonyl radical, as shown in Scheme 9. Decarboxylation (A) must frequently compete with direct quenching (B), but the decarbonylation (C) is not significant.

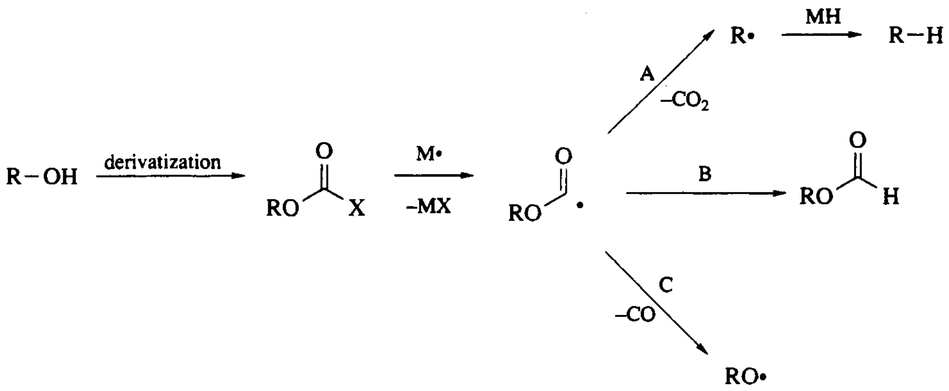

**Scheme 9**

Early studies[65] of the ROCOCl–$Bu_3SnH$ reaction at 30–80 °C indicated that the decarboxylation step was dominant only for stabilized educt radicals such as $PhCH_2\cdot$. By using higher temperatures and a less efficient H-donor ($Pr^n_3SiH$), good yields of RH were obtained from simple primary and secondary chloroformates, but cholesterol was deoxygenated in only 25% yield.[66] The high affinity of tin-centered radicals for $Se^{II}$ was used to good advantage in reduction of steroidal *Se*-phenylselenocarbonates, as shown in Scheme 10. The corresponding formate and small amounts of the alcohol were side products; as indicated for the reduction of (**101**) shown in equation (20), lower reaction temperatures gave increasing amounts of the formate.[67]

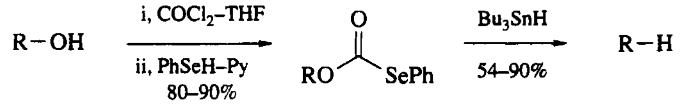

**Scheme 10**

Since tertiary chloroformates are difficult to prepare and are unstable above 0 °C, they are not suitable substrates for the foregoing processes. Tertiary alcohols were deoxygenated efficiently[68] *via* the chloroglyoxylates through *in situ* generation of the corresponding thiohydroxamate in the presence of a hindered thiol (Scheme 11). Using $Me_3CSH$ in place of $Et_3CSH$ gave slightly lower yields with corresponding formation of the oxalate thioester, as exemplified by the reduction of (**102**) *via* chloroglyoxylate (**103**): with $Me_3CSH$, a 2.5:1 mixture of (**104**) and (**105**) was obtained, whereas $Et_3CSH$ gave a high yield of deoxy compound (**104**). To avoid acid-catalyzed skeletal rearrangement when the process was applied to (**106**), the chloroglyoxylate was prepared from the TMS ether (**107**). The product (**108**) was the result of radical quenching from the less hindered side. Applied to a typical secondary alcohol, this reaction gave comparable amounts of deoxy compound and formate even at 178 °C, indicating stepwise loss of $CO_2$ from the initial radical.

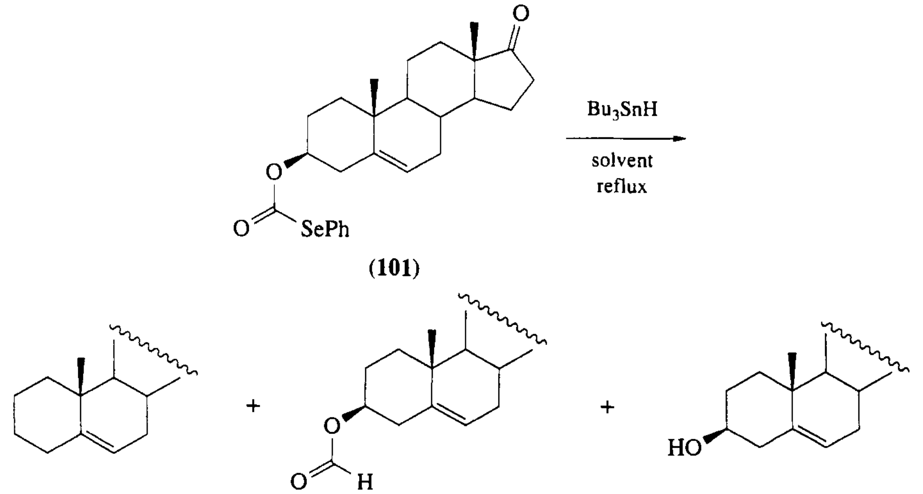

(101)

| | | | |
|---|---|---|---|
| 144 °C (xylene) : | 73% | 16% | 11% |
| 110 °C (toluene) : | 39% | 42% | 14% |
| 80 °C (benzene) : | 5% | 76% | 9% |

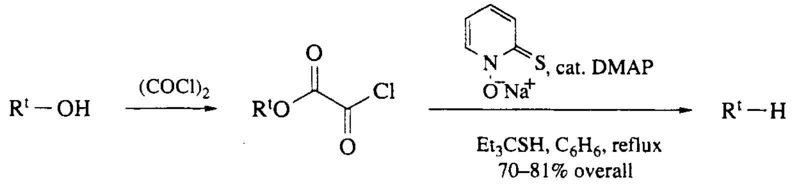

**Scheme 11**

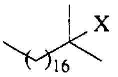

**(102)** X = OH
**(103)** X = $O_2CCOCl$
**(104)** X = H
**(105)** X = $O_2CCOSBu^t$

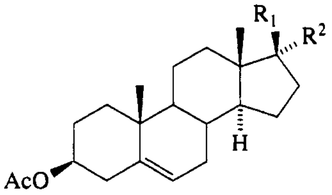

**(106)** $R^1$ = OH, $R^2$ = Me
**(107)** $R^1$ = OSiMe$_3$, $R^2$ = Me
**(108)** $R^1$ = Me, $R^2$ = H

## 4.2.3 REDUCTIVE DEAMINATION OF AMINES AND THEIR DERIVATIVES

### 4.2.3.1 Hydride and Hydrogenolysis Methods

Because of the lower electronegativity of nitrogen relative to oxygen, and the lower acidity of, for example, $PhSO_2NH_2$ compared with $PhSO_2OH$, activation of an amine to an extent sufficient to allow an $S_N2$ displacement which breaks the C—N bond is more difficult than the analogous process for an alcohol. In fact, this process is possible only for primary amines, where double activation or conversion to a heterocyclic quaternary system is possible. Simple quaternary salts are susceptible to $S_N2$ reactions with strong nucleophiles, but this is not generally a useful deamination method since attack on the least hindered center will take place (equation 21).[69] Systems with additional activation are exceptions: Mannich bases were reduced, in some cases with $NaBH_4$, and more generally by quaternization followed by treatment with $NaBH_3CN$, as shown in equation (22).[70]

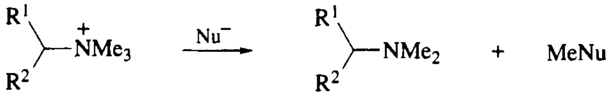

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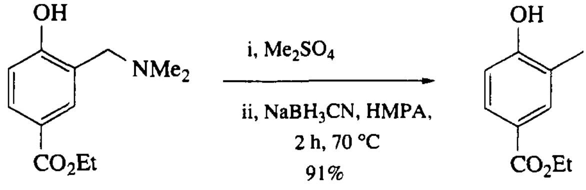

(22)

*N*,*N*-Disulfonimides, $RN(SO_2R')_2$, have been advanced as amine derivatives suitable for $S_N2$ processes, at least in those cases where R is a primary radical. *N*-(1-Decyl)-*N*,*N*-di(*p*-toluene)sulfonimide (**109**) was reduced efficiently to decane by $NaBH_4$ in HMPA at 175 °C but the cyclododecyl analog (**110**) gave desulfonylation to (**111**). *N*,*N*-Di(trifluoromethane)sulfonimides (triflimides) such as (**112**), prepared from the trifluoromethanesulfonamide with NaH–$(CF_3SO_2)_2O$, are more susceptible to $S_N2$ reactions with soft nucleophiles, but also eliminate readily: attempted preparation of $Bu^tN(SO_2CF_3)_2$ gave isobutene even at −78 °C. The reactions of triflimides with nucleophiles including $NaBH_4$ have been reviewed.[71]

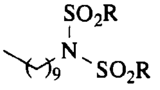

(**109**) R = *p*-$MeC_6H_4$
(**112**) R = $CF_3$

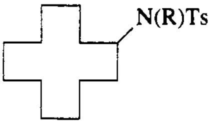

(**110**) R = Ts
(**111**) R = H

Katritzky and coworkers have extensively developed the activation of amines by reaction with pyrylium salts to provide *N*-alkyl (or *N*-aryl) pyridinium compounds.[72] When buttressing substituents were present to discourage attack on the pyridine ring, the *N*-alkyl substituent was subject to displacement and elimination processes. In general, primary alkyl substituents reacted with most nucleophiles in a normal $S_N2$ process as shown in Scheme 12, whereas competition between substitution and elimination took place with the secondary analogs, with elimination dominating the reactions starting from cycloalkylamines.

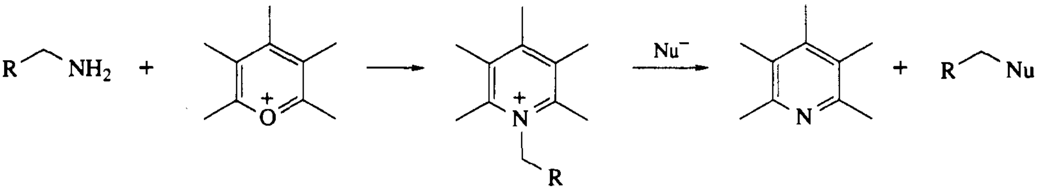

**Scheme 12**

Direct reductive cleavage of these pyridinium salts was not possible since hydride reagents attacked the ring to give 1,2- or 1,4-dihydropyridines; with suitable substitution patterns, however, these species could be used to achieve overall reductive deamination of $RCH_2NH_2$ to $RCH_3$. In the first process,[73] shown in Scheme 13, amines were converted to 2,3,5,6-tetraphenylpyridinium salts (**113**), which were reduced to the 1,4-dihydro compounds (**114**). Pyrolysis of these materials at 180–200 °C then liberated the hydrocarbon: *n*-octane was obtained in 61% overall yield from 1-aminooctane. For aliphatic amines, less satisfactory results were obtained upon heating the 1,2-dihydropyridines derived from 2,4,6-triphenylpyridinium salts, although this was an efficient process for allylic and benzylic amines.[74] The second method also relies upon the formation of 1,4-dihydropyridines such as (**115**), prepared from the amine by treatment with the salt (**116**) followed by $NaBH_4$. On heating at 100–140 °C with DBN, the corresponding alkane was formed in good yield.[75] Cyclohexylamine reacted with (**116**) to give cyclohexene at room temperature.

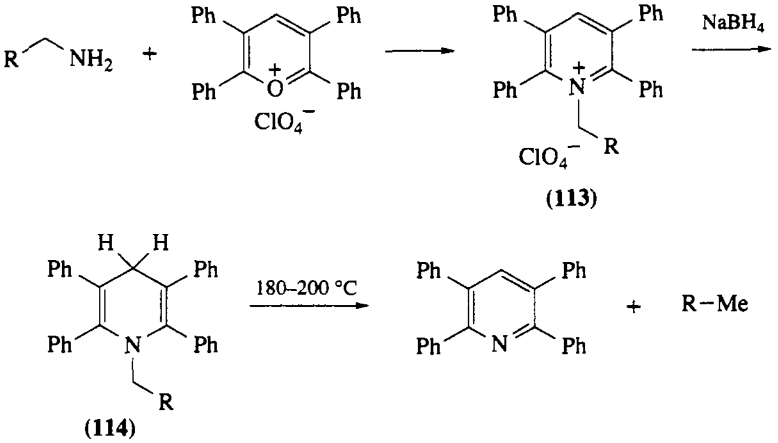

Scheme 13

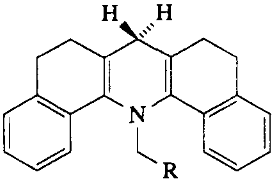

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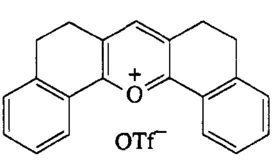

(116)

Completely saturated quaternary ammonium salts, in contrast with those derived from allylic or benzylic amines, are unaffected by catalytic reduction and by mild reducing agents including Na–Hg in protic solvents. More vigorous reduction with Na in hot dioxane or $NH_3$ (liq.) led to cleavage and elimination to mixtures of alkane and alkene, but little discrimination was seen for cleavage of N—R *versus* N—Me in $RNMe_3^+$, except when the alkyl group was tertiary.[76] Amines of general structure $RNMe_2$ or RNHMe, in which the group R bears a β-hydrogen, are most simply converted to RH *via* the corresponding alkene, prepared by elimination from the quaternary salt or *N*-oxide, as described in Chapters 5.1 and 5.4, Volume 6.

### 4.2.3.2 Deamination *via* Diazenes and Related Species

Given the high bond energy of molecular $N_2$, monoalkyl diazenes (diimides) are potentially attractive intermediates for reductive deamination of primary amines. Although RN═NH species are moderately stable in dilute, neutral solutions, they decompose quite readily to give predominantly the alkane by one of two mechanisms, shown in Scheme 14: in neutral solution, a bimolecular process believed to involve triplet pairs and caged radical species occurs, whereas in base the diazene anion loses $N_2$ to give the corresponding carbanion. These processes have been discussed in some detail,[77] and the stereochemical consequences of having a chiral center at the C—N bond have been examined for a tertiary, benzylic case.[78]

The success of the Wolff–Kishner and related C═O to $CH_2$ transformations (see Chapter 1.14, this volume) attests to the efficiency of the diazene decomposition route; applied to the reductive deamination of primary amines, this requires methods which transform $RNH_2$ into RN═NH, which corresponds to an amination–oxidation sequence. Several one- or two-step processes have been described which carry out this transformation. Treatment of amino acids in alkaline solution with excess hydroxylamine-*O*-sulfonic acid (HOS) gave moderate yields of deamination product,[79] as exemplified by the dipeptide case shown in equation (23).

In a related process, HOS in large excess reacted with sulfonamides in hot aqueous alkali to give alkanes,[80] presumably by the process shown in Scheme 15. Yields were generally high when corrected for unchanged sulfonamide, but conversions were quite low even when a large excess of HOS was added in several portions: with 20–25 equiv. of reagent, *N*-cyclohexylbenzenesulfonamide gave 70% cyclohexane at 20% conversion. Although not reported, the use of more recently developed aminating agents such as

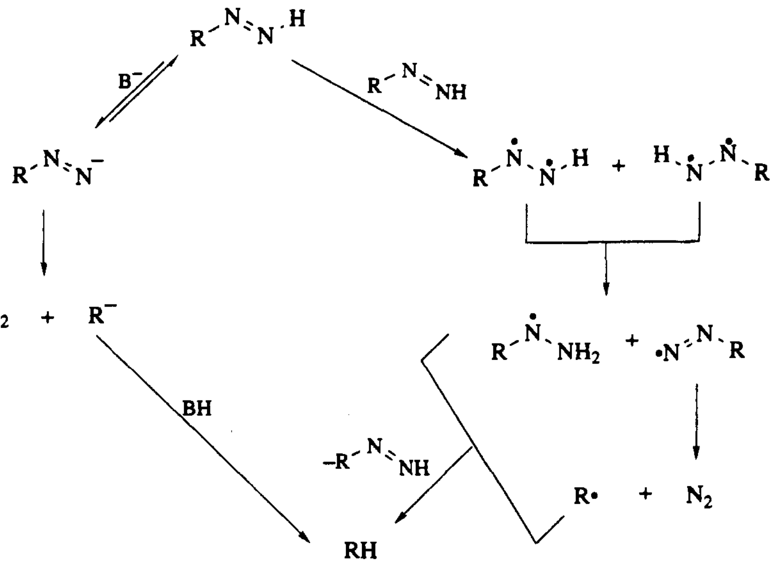

Scheme 14

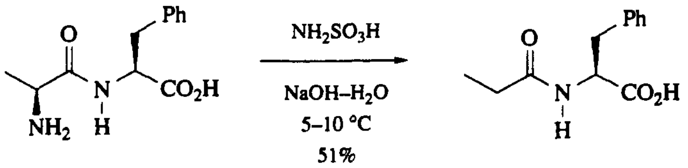

(23)

*O*-mesitylenesulfonylhydroxylamine[81] or *O*-diphenylphosphinylhydroxylamine[82] might permit these processes to be carried out under nonaqueous conditions.

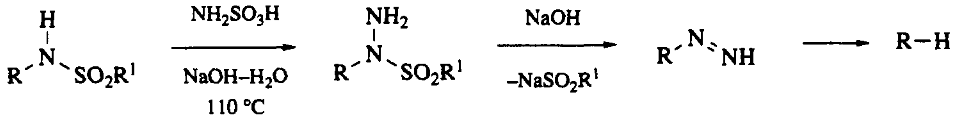

Scheme 15

Difluoramine ($HNF_2$) has also been used to convert amines to hydrocarbons,[83] according to the process shown in equation (24). No additional base was included, so an excess of the amine was necessary. Yields of 40–77% based on $HNF_2$ were obtained for simple aliphatic amines. Under these conditions, free radical decomposition of the diazene was probably involved, since a cyclopropylcarbinylamine gave a rearranged product. This ring opening was not detected in the Wolff–Kishner reduction of the corresponding ketone (equations 25 and 26). When an allylic amine was treated with $HNF_2$, deamination with clean double bond transposition occurred by intramolecular H-transfer in the diazene intermediate (equation 27).

$$3\ RNH_2 + HNF_2 \longrightarrow RH + 2\ RNH_3{}^+F^- \qquad (24)$$

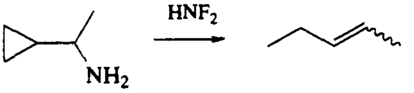

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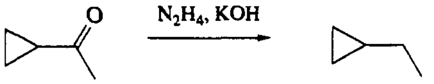

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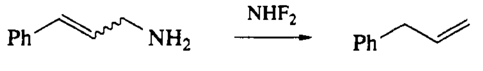

(27)

Finally, we note that deamination could in principle be achieved by generating an aliphatic diazonium ion in the presence of a hydride source; this could lead to an alkane either *via* the diazene, or by $S_N2$ attack with loss of $N_2$. Protonating an aliphatic diazo compound, or treating an $N^1$-alkyl, $N^3$-aryltriazene with protic or Lewis acid in the presence of a suitable reducing agent ($NaBH_3CN$, $NaBH(OAc)_3$ or $R_3SiH$) might achieve this transformation.

### 4.2.3.3 Reduction of Isonitriles and Related Compounds

To an even greater extent than was the case for deoxygenation, the introduction of dissolving metal and free radical reduction processes for suitable amine derivatives has greatly expanded the range of substrates which can be subjected to efficient reactions, and primary amino groups can now be reductively removed from molecules containing a variety of other functional groups. For amines, in contrast to alcohols, the choice of derivative is much more limited since the driving force obtained in going from C—N to C═N (or from N—X to N═X) is not generally sufficient to induce fragmentation from radical or anion radical intermediates; however, highly stable RCN or $CN^-$ fragments are readily ejected upon suitable reduction of isonitriles, which (as such, or generated *in situ*) are now the substrates of choice for reductive deaminations. Isonitriles are readily prepared from primary amines in excellent yield by formylation (with EtOCHO or HCOOAc), followed by dehydration with TsCl–py, $COCl_2$–$R_3N$ or similar reagents.[84]

**Table 4** Metal–Ammonia Reduction of Isonitriles to Hydrocarbons[85]

| *R in RNC* | *Metal*[a] | *Yield of RH (%)* |
|---|---|---|
| $Me_3C$ | Na | 93[b] |
| *c*-$C_6H_{11}$ | Li | 96[b] |
| *c*-$C_6H_{11}$ | Na | 93[b] |
| *c*-$C_6H_{11}$ | Ca | 95[b] |
| *n*-$C_{12}H_{25}$ | Na | 88[c] |

[a]2 g equiv of metal were used. [b]Determined by quantitative IR. [c]Isolated yield.

Ugi and Bodesheim[85] first reported the efficient reduction of isonitriles to hydrocarbons by Na, Li or Ca in liquid ammonia: some results are shown in Table 4. Reduction of *c*-$C_6H_{11}NC$ was also reported in a study of the metal–amine reduction of nitriles,[86] and the mechanism of isonitrile reduction was examined by Niznik and Walborsky[87] who showed that acyclic, chiral isonitriles gave racemic products. In the reduction of 1,1-diphenyl-2-isocyano-2-methylcyclopropane, those rearrangement and coupling processes which dominated the reduction with Na–$NH_3$ or metals dispersed in DME were largely suppressed in favor of normal deamination when the reductant was Na–naphthalenide in DME. It seems likely that, depending upon the particular isonitrile and the conditions, these reductions may proceed either by fragmentation of the radical anion (to R· + $CN^-$), or by addition of a second electron to this species with explusion of the carbanion. Whichever is the case, a carbanion is the ultimate source of RH in the reduction of RNC, and hence fragmentation by β-elimination of a leaving group may occur, as in the related cases of dissolving metal deoxygenation.

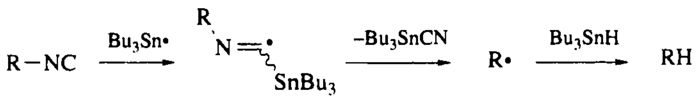

**Scheme 16**

The $Bu_3SnH$ decyanation of isonitriles (Scheme 16) was first reported by Saegusa,[88] and was developed as a general, mild method for reductive deamination by Barton and coworkers who initially showed that a variety of isonitriles, isothiocyanates and isoselenocyanates reacted with $Bu_3SnH$ under the usual free radical conditions (reflux in benzene, toluene or xylene with catalytic AIBN) to give good yields of the corresponding hydrocarbon.[89] In concert with the normal order of radical stability, primary alkaneisonitriles required higher reaction temperatures, whereas a tertiary example was reduced at 50 °C (Table 5).

**Table 5** Reduction of Isonitriles and Isothiocyanates with $Bu_3SnH$[89]

| *RNCX* | *Solvent*[a] | *Temperature* (°C) | *Yield of RH* (%) |
|---|---|---|---|
| *n*-$C_{18}H_{37}NC$ | Xylene | 145 | 81[c] |
| $EtO_2CCH_2NHCOCH_2NC$ | Benzene | 80 | 71 |
| 3-Isocyanocholestane | Toluene | 110 | 56 |
| 3-Isothiocyanatocholestane | Toluene | 110 | 83 |
| n-$C_{17}H_{35}CMe_2NC$ | Benzene | 50 | 91 |
| *meso*-PhCH(NC)CH(NC)Ph | Benzene | 80 | 56[d] |
| (±)-PhCH(NC)CH(NC)Ph | Benzene | 80 | 53[d] |

[a] RNCX in the solvent containing AIBN (0.05–0.2 equiv.) was added to $Bu_3SnH$ (1.7–5.0 equiv. in solvent) at the indicated temperature. [b] Isolated yield. [c] Obtained in 73% yield with $Bu_3GeH$ in place of $Bu_3SnH$. [d] Yield of $PhCH_2CH_2Ph$; stilbene was not produced.

The isonitrile (**117**), isothiocyanate (**118**) and isoselenocyanate (**119**) gave equally high yields of the deamino compound (**120**), and IR monitoring showed that (**117**) was the intermediate in both of the heterocumulene reductions; potential advantages for RNCS over RNC lie in the somewhat better stability (*e.g.* to acids) and the fact that isothiocyanates may be obtained by one-step processes ($CSCl_2$–NaOH, *N,N'*-thiocarbonyldiimidazole or $CS_2$–DCC) from the amine. The lack of stilbene formation in the reductions of the isomeric 1,2-diisocyano-1,2-diphenylethanes indicates that β-isocyanoalkyl radicals are not prone to fragmentation. Alkene formation was observed from the altrose derivative (**121**), presumably through initial attack at the isonitrile residue. As usual, other β-oxy substituents which did not give stabilized radical fragments were not eliminated: reduction of (**122**) and (**123**) proceeded without alkene formation.

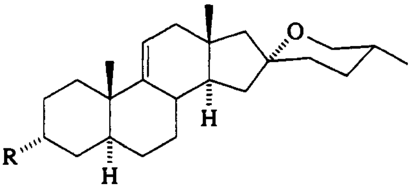

(**117**) R = NC
(**118**) R = NCS
(**119**) R = NCSe
(**120**) R = H

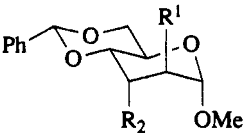

(**121**) R¹ = NC, R² = OCSSMe
(**122**) R¹ = NC, R² = OH
(**123**) R¹ = NC, R² = OMs

In addition to the foregoing steroidal and carbohydrate-derived examples, reductive decyanation has been applied to other areas of natural product chemistry, including the controlled deamination of the aminoglycoside antibiotic fragment neamine (**124**).[90] In addition to the glycylglycine example in Table 5, other amino acids were deaminated: tryptophan ester (**125**) was converted through (**126**) and (**127**) to the indolepropanoate (**128**) in 53% overall yield.[91] The deamination was also used in a synthesis of 6β-substituted penicillanic acid derivatives, as shown in Scheme 17.[92]

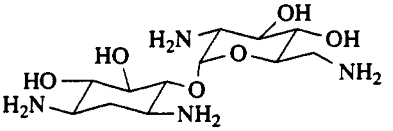

(**124**)

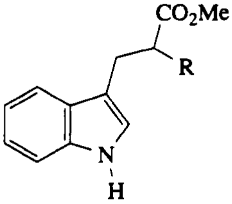

(**125**) R = $NH_2$
(**126**) R = NHCHO
(**127**) R = NC
(**128**) R = H

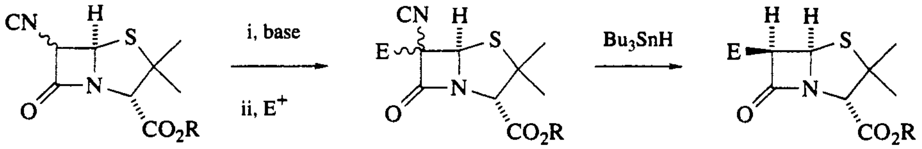

Scheme 17

## 4.2.4 REFERENCES

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# 4.3

# Reduction of Sulfur–Carbon Bonds and of Other Heteroatoms Bonded to Tetrahedral Carbon

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## 4.3.1 REDUCTION OF SULFUR–CARBON BONDS

### 4.3.1.1 Introduction

Organic sulfur chemistry is a powerful tool in organic synthesis because of the unique properties of sulfur, derivatives of which are reactive and versatile synthons. However, these useful properties would be of no use if it were not possible to remove sulfur from the final product. Fortunately reductive cleavage of a C—S bond is often easy and constitutes the 'last step' of many syntheses. This formal hydrogenolysis, called desulfurization (but spelled in several different ways), may be performed by numerous reagents and procedures. As usual if different systems are proposed, it means that no one is a panacea, and that they all have their drawbacks. This situation must be accepted. Indeed the diversity of molecules is such that it is impossible to find a unique reagent having all the virtues (inexpensive, catalytic, easily handled, chemo- and stereo-selective...) that an organic chemist wants. So the best we can hope is that reagents will be complementary.

### 4.3.1.2 Raney Nickel and Nickel(0) Complexes

Desulfurization of organic compounds with Raney nickel is an old reaction[1] with widespread application.[1,2] Raney Ni exists in several forms, called W-1 to W-8,[1b,1c] and differing in the procedures for their preparation. The properties (reactivity, stability, *etc.*) vary from one form to another and with aging. Thus when no information is given about a Raney Ni used, it may be hard to reproduce the reaction. Although sometimes called a catalyst, it is always used in large or very large excess. Raney Ni is sometimes symbolized as Ni(H) or erroneously Ni($H_2$). These misleading formulae do not mean that hydrogen is used during the reaction but that hydrogen is included in reagents which have not been degassed. A large number of the properties and drawbacks of Raney Ni have been established for a long time.[1,2] These reagents are well known to desulfurize every substrate containing carbon–sulfur bonds, and yields may vary from low to excellent. The main drawbacks are related to their handling and chemical reactivities. Thus the disadvantages of Raney Ni lie in its preparation, the unpredictable deactivation on aging and the difficulty in determining accurately the weight of Ni used because of the necessity of keeping the pyrophoric solid wet. On the other hand, the main limitations of Raney Ni are the lack of stereoselectivity and the reduction or hydrogenolysis of other functional groups, such as unsaturated C=C groups, nitro and carbonyl groups. Oxidations (*e.g.* alcohol dehydrogenations) as well as rearrangements or condensations may also be observed. A number of side reactions may be diminished and sometimes suppressed by using deactivated Raney Ni. Concerning the mechanism of desulfurization with Raney Ni it appears that the hydrogen atom replacing the sulfur generally comes from hydrogen included in the reagent, although the solvent may also play a part in the reductions. Radical mechanisms intervene during reductive desulfurizations, and racemizations are observed with chiral substrates. However, reductive cleavage of optically active sulfones was found to take place without racemization.

More recent publications confirm or complete the above picture of the scope and limitations. Thus, hindered glycols were obtained by reductive desulfurization of tetrahydrothiophenes (equation 1).[3]

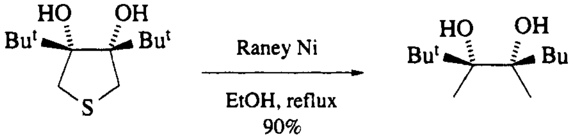

(1)

Interesting chemoselectivity of Raney Ni is illustrated by the desulfurization in good yield (with few exceptions) of the functional sulfides (**1**),[4] (**2**),[5] (**3**),[6] (**4**)[7] and (**5**).[8]

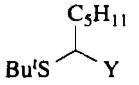

Y = $CO_2Me$, CN, COMe

**(1)**

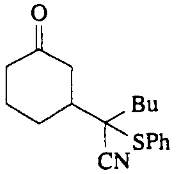

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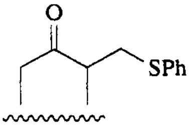

**(3)**

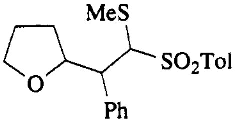

**(4)**

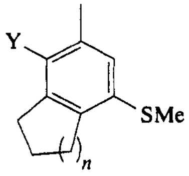

Y = H, COMe

**(5)**

The lower reactivity of Raney Ni towards sulfones allows the chemoselective desulfurization of (**4**) with Raney W-2, but an appreciable amount of reduction of keto groups was observed.[8] Raney Ni W-2 also tolerates sulfonamides;[9] in this work an ionic mechanism was suggested in order to explain the substitution reaction observed. Lactones,[10a,10b] keto lactones,[10c] and unsaturated lactones[10a,10d] were tolerated during the desulfurization of sulfide or dithioketal[10c] groups, but deactivated (*e.g.* by acetone) Raney Ni was generally used. In contrast, carbon–halide bonds are cleaved where the desulfurization is stereoselective only because the product is the thermodynamically more stable *cis*-lactone (equation 2).[10e,10f]

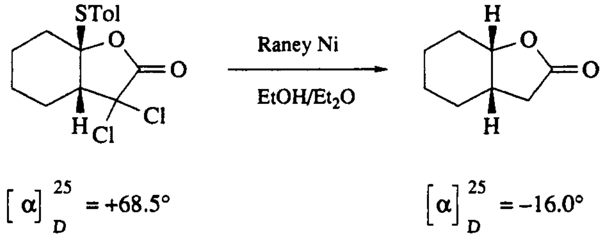

(2)

From comparative studies, it appears that a number of C=C double bonds are tolerated only when Raney Ni has been deactivated.[10a,10d] It has been claimed[11] that desulfurization of thiophenes could lead to acceptable yields of unsaturated products, but this result seems to be due to steric hindrance in the unsaturation formed. Curiously it has been found that Raney Ni desulfurization of unsaturated lithium thiolates resulting from Li–EtNH2 desulfurization (*vide infra*) takes place easily, while direct reduction of the starting heterocycles is unsatisfactory (Scheme 1).[12]

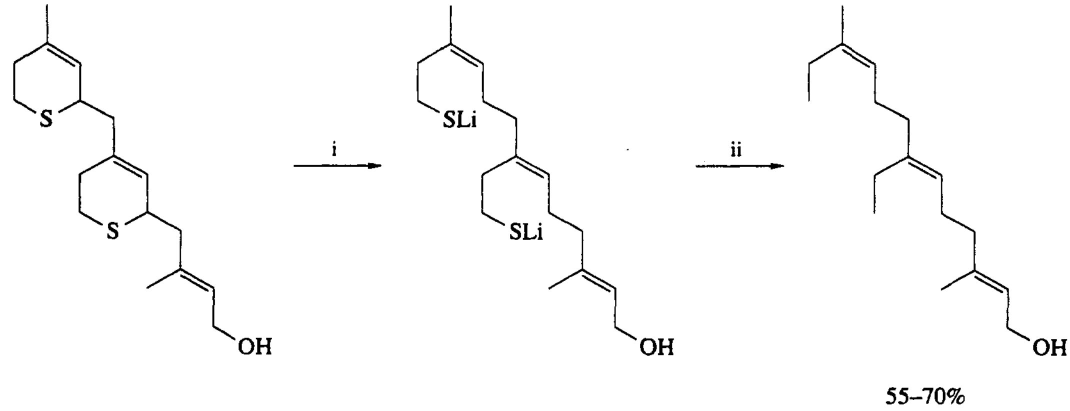

i, Li–EtNH$_2$, −78 °C; ii, deactivated Raney Ni, EtOH reflux

**Scheme 1**

Finally, it has been possible to preserve C=C double bonds during desulfurization of vinyl sulfides (50 to >99%),[13a–13c] and alkenes can be reduced simultaneously with desulfurization, causing the saturation of vinyl sulfides.[14]

Although less commonly used, Raney Ni cleavage of the C—S bond of sulfoxides and sulfones is also of interest. For example, the removal of sulfoxides is one of the steps in the synthesis of spiroketals[15a] and of tetrahydrofuran derivatives (Scheme 2).[15b] Exceptionally, the desulfurization is not accompanied by the hydrogenolysis of a benzyl ether group.

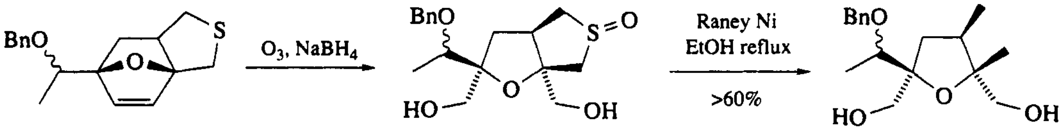

**Scheme 2**

In contrast, the unexpected hydrogenolysis of a tertiary alcohol was observed during the desulfurization either of 1,3-dithiane derivatives or of their monosulfoxides, as exemplified in Scheme 3.[16] It is intriguing that even deactivated W-2 Raney Ni did not improve the result, but a low temperature did allow convenient desulfurization with a minimum amount of side product.

The removal of sulfoxide[17] or sulfone[18] groups from molecules containing chiral alcohols is not always accompanied by racemization, indicating that oxidation of alcohols by Raney Ni[1] may be avoided.

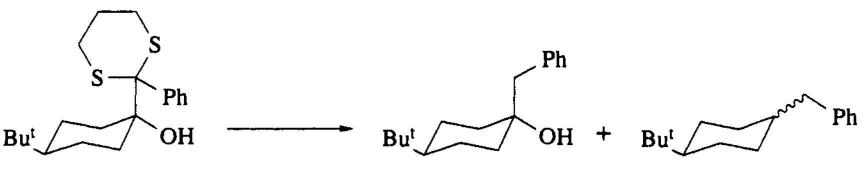

| | | |
|---|---|---|
| Raney Ni W-2 deactivated or not, 25 °C, EtOH | 80% | 20% |
| Raney Ni W-2 freshly prepared, 0 °C, EtOH | 96.7% | 3.1% |

**Scheme 3**

Desulfurization of thioesters can be used in the synthesis of ethers[19] and particularly of crown ethers,[19b] although yields are rather low (equation 3).

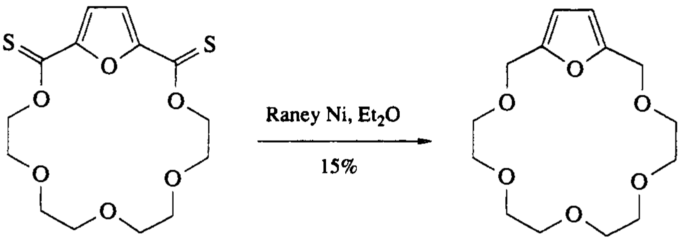

(3)

We can conclude that Raney Ni continues to be useful in synthesis, but it must be kept in mind that, besides the side reactions it gives, the main drawback is the need to use a large excess of a hazardous reagent.

Desulfurization with Raney Ni is always performed under heterogeneous conditions using Ni metal as reagent. It was guessed that a soluble nickel(0) species might be more efficient. Moreover, such studies were expected to give information about the mechanism of desulfurization. That nickel(0) species can insert into C—S bonds by oxidative addition has been established by isolation of the corresponding complexes.[20] On the other hand, [(bipy)Ni(COD)] in small excess (2 mol equiv.) efficiently desulfurizes sulfur-containing heterocycles.[21] The mechanism proposed is given in Scheme 4.

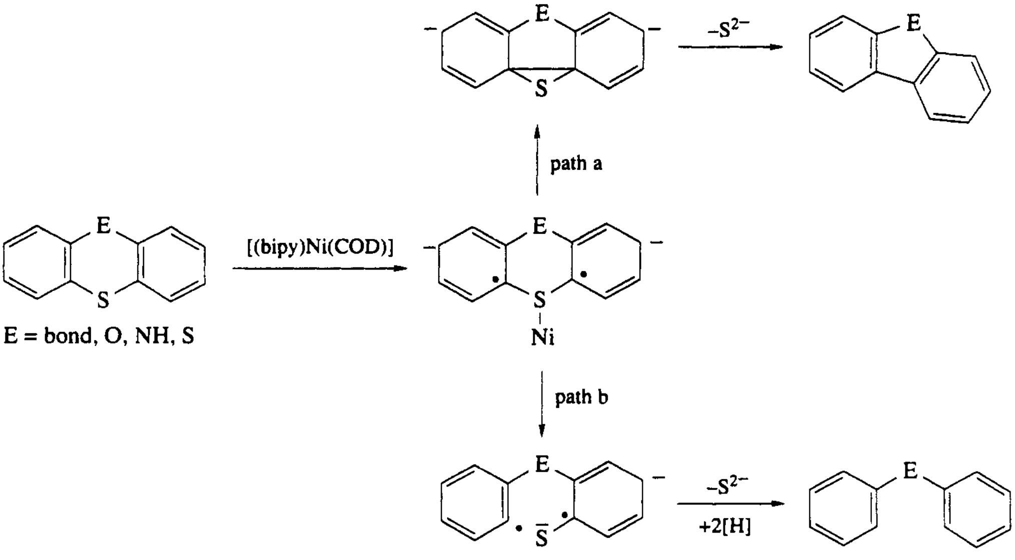

**Scheme 4**

In Scheme 4, path (a) is dominant. In path (b), the hydrogen comes from the solvent (THF). We shall see later that path (b) may be favored by the presence of a complex hydride.[21a,21c] Synthetic application of this desulfurization remains to be demonstrated. It may be that the drawbacks in the preparation of the very sensitive starting complex could be avoided by using one of the better known procedures for the generation of nickel(0) species *in situ*.[22] Finally, nickel(0) species have been proposed as intermediates in the eliminative desulfurization of 1,2-disulfones.[23]

### 4.3.1.3 Hydrides or Organometallics Combined with Transition Metal Salts or their Complexes

Among the drawbacks of Raney Ni are its highly pyrophoric nature, the loss of activity on storage and the difficulty of knowing the amount of Ni used. One way to avoid these disadvantages would be to generate Ni *in situ* from a known amount of one of its salts. This is possible by reacting a Ni salt with $NaBH_4$; the black reagent thus obtained looks like a metal, often behaves like a metal, but is not a metal: it is a Ni boride.[24] Use of different metal salts has led to the preparation of a number of metal borides,[24] and the reaction has been extended by using lithium aluminum hydride, thus allowing the preparation of metal aluminides.[24] Metal borides and aluminides are well known as desulfurizing reagents.[2c,2d,24]

Among metal borides, Ni boride is the one most often used in desulfurizations. Always used in large (and often very large) excess, it may be prepared before use or preferably generated *in situ* in the presence of the substrate to be desulfurized. The solvent may be water, and EtOH alone, or added to ethers such as THF. In a number of cases $NaBH_4$ is used in even larger excess than the Ni salt. Generation *in situ* allows for more efficient desulfurizations.[11] However, hydrogen is generated in the presence both of the substrate and of Ni boride, which is a hydrogenation catalyst.[24] Finally Ni boride is less reactive than Raney Ni,[13a,25] and does not desulfurize sulfones.[25a] Due to its lower reactivity, Ni boride is more apt to give chemoselective desulfurizations, but is not devoid of side reductions. For example, during the desulfurization of thioalkyl, aryl or heteroaryl ethers, a benzylamino group was not hydrogenolyzed but a carbonyl group was reduced.[26a]

The desulfurizations illustrated in Scheme 5 show that Ni boride may tolerate hindered alkenes,[13a,26b] alcohols[27a] (without oxidoreduction), ketones[26b,28] and esters.[27] However, under certain conditions,

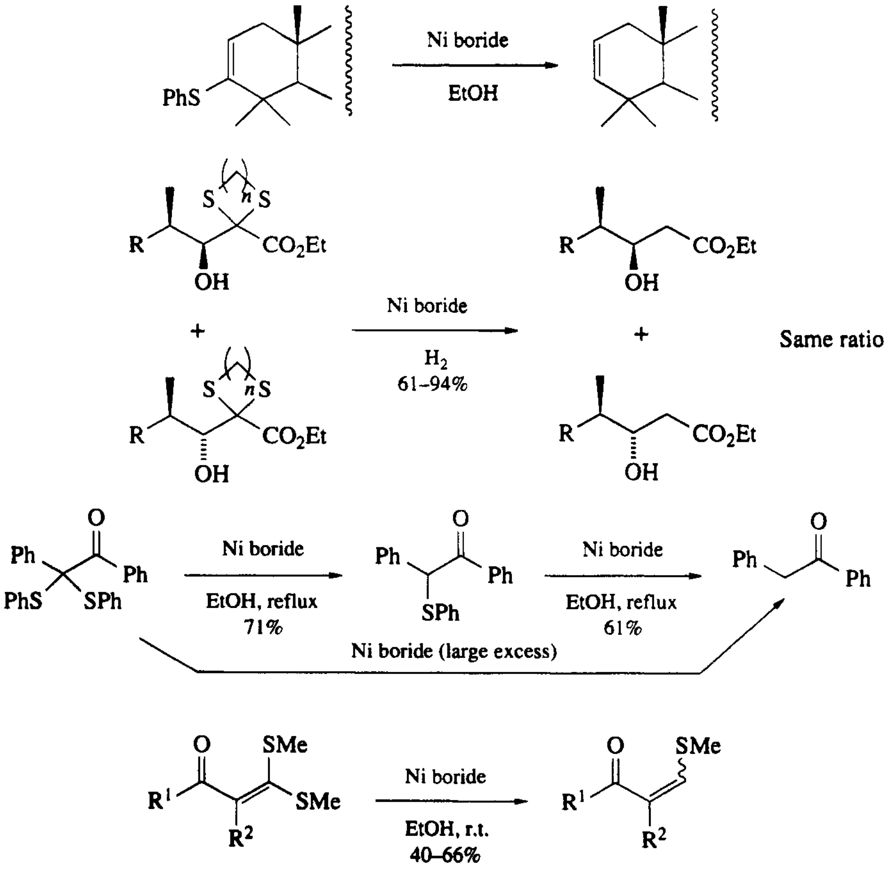

Scheme 5

reduction of alkenes may take place along with the desulfurizations.[13a,29] The use of a hydrogen atmosphere improved the procedure.

A number of metal salts or complexes have been combined with NaBH$_4$. Although some results are obtained with Co boride, none of the systems used are as efficient as Ni boride.[26,29] An interesting exception is [Pd(PPh$_3$)$_4$] or, better, [PdCl$_2$(DPPP)] combined with NaBH$_4$, which allows the reductive desulfurization of allyl sulfones.[30] Based on the concept that allyl sulfones undergo substitution by nucleophiles in the presence of palladium(0) complexes this procedure can use the Pd reagents in catalytic amounts, and replacement of NaBH$_4$ by LiHBEt$_3$ seems to improve the procedure (Scheme 6).[30b]

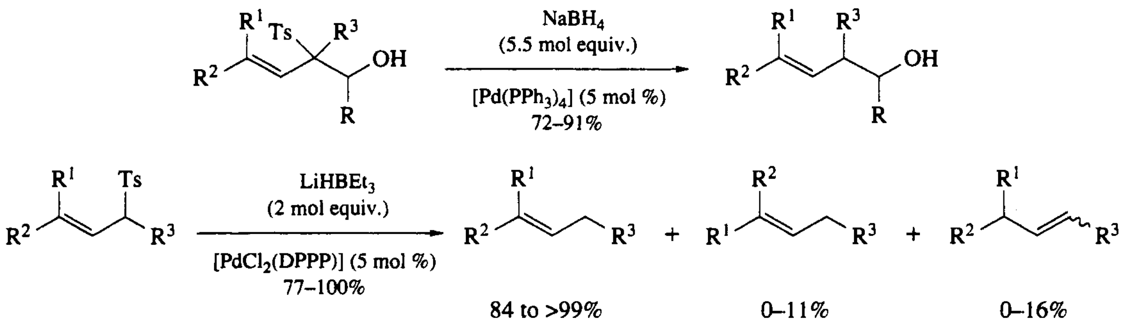

Scheme 6

Note that, while the palladium(0)-containing reagent was of limited application but did not cause isomerization, the palladium(II)-containing reagent, although more versatile, did cause isomerization. LiHBEt$_3$–[Pd(PPh$_3$)$_4$] desulfurized allyl thiophenyl ethers, but migrations and (*E*)/(*Z*)-isomerizations were also observed.[31] LiHBEt$_3$ or NaHBEt$_3$ have also been used to generate Fe- or Co-containing reagents which desulfurize thiols.[32]

Reagents of potential interest were also obtained from LAH. The most often used contain Ni or Cu. Thus homogeneous desulfurizations are performed with [(Cp$_2$NiAlH$_2$)$^-$Li$^+$]$_2$ prepared from [Cp$_2$Ni] and LAH in THF.[33] The ratio of reagent to substrate varies from 1:1 with thiols to 2:1 with sulfides, sulfoxides or sulfones and to 8:1 with thioketals. Yields, although often moderate, may reach 80%. α-Acyl-substituted, benzyl and aryl C—S bonds are rather easily cleaved, while isolated tetrahedral carbon C—S bonds require more vigorous conditions. It seems that alkenes, methoxy and carbonyl groups as well as esters are tolerated. It is claimed that C–halogen bonds were tolerated, but the examples given are insufficient for a firm conclusion. Nitro groups, conjugated alkenes and terminal alkynes are reduced. A few examples are given in Scheme 7.

The reaction of [(bipy)Ni(COD)] in THF with LAH led to [(bipy)NiAlH$_2$]Li·$n$THF, a rather efficient desulfurization agent.[21a,21c,34] During reactions such as the ones given in Scheme 4, the presence of the hydride favored path b. Some of the other reagents prepared in the same way and containing different metal species[34] deserve to be studied further.

LAH–CuCl$_2$ used in moderate to large excess desulfurizes sulfides and dithioketals in good to very good yields (55–87%),[35] but with allyl sulfides, migration of the double bond occurs. Finally vinyl phenyl sulfones are reductively cleaved in good yields (65%) without reduction of C═C bonds even by an excess of reagent.[36]

Completely different in nature are those curious but efficient reducing agents called 'Metal Complex Reducing Agents' (MCRA),[37] very easily prepared from NaH, a sodium alkoxide and a metal salt. NiCRA–bipy and NiCRA (prepared from NaH, t-C$_5$H$_{11}$OH and Ni(OAc)$_2$ with or without bipy, respectively), are not very sensitive and are easily handled. Used in moderate to large excess, they desulfurize alkyl and aryl sulfides, sulfur-containing heterocycles, sulfoxides, sulfones and dithioketals. Under appropriate conditions, dithioketals are selectively transformed into sulfides.[38] So far it has been established that these reagents tolerate ketones, esters, and, to some extent, alkenes. The reactivity of MCRAs is illustrated in Scheme 8.

Desulfurizations of unsaturated sulfur-containing substrates are often accompanied by reductions, migrations or isomerizations, and reagents devoid of these drawbacks are in keen demand. One candidate is a suitable Grignard reagent in the presence of Ni complexes. Thus, Pr$^i$MgBr (in excess) in the presence of a catalytic amount of [(Ph$_3$P)$_2$NiCl$_2$] stereospecifically desulfurized phenyl thiovinyl substrates in acceptable to good yields,[39] and acetals, ethers, aromatic systems and isolated alkenes appear to be tolerated. The same kind of reductions were performed with aryl thiomethyl and ethyl thiovinyl ethers

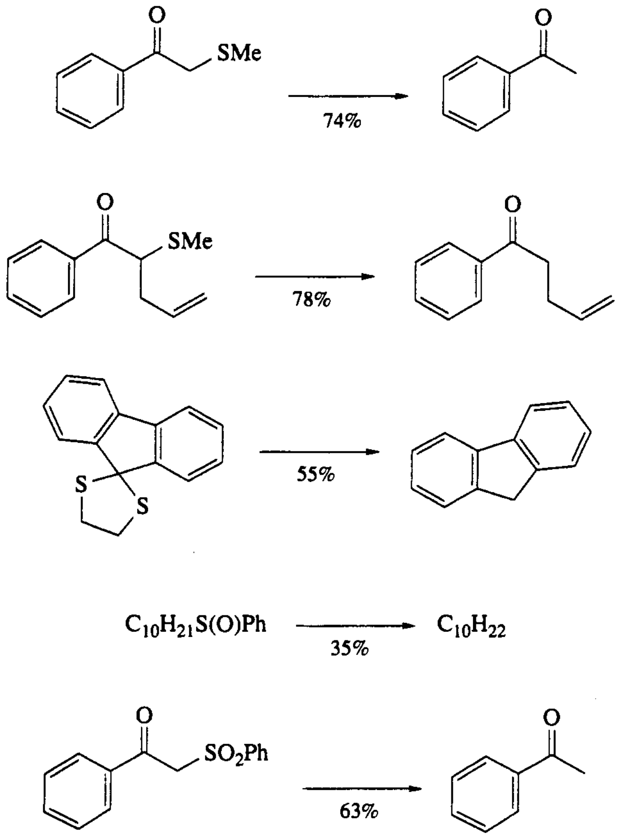
SMe
74%
SMe
78%
S
S
55%
$C_{10}H_{21}S(O)Ph$
35%
$C_{10}H_{22}$
$SO_2Ph$
63%

Desulfurization with $[(Cp_2NiAlH_2)^-Li^+]_2$

**Scheme 7**

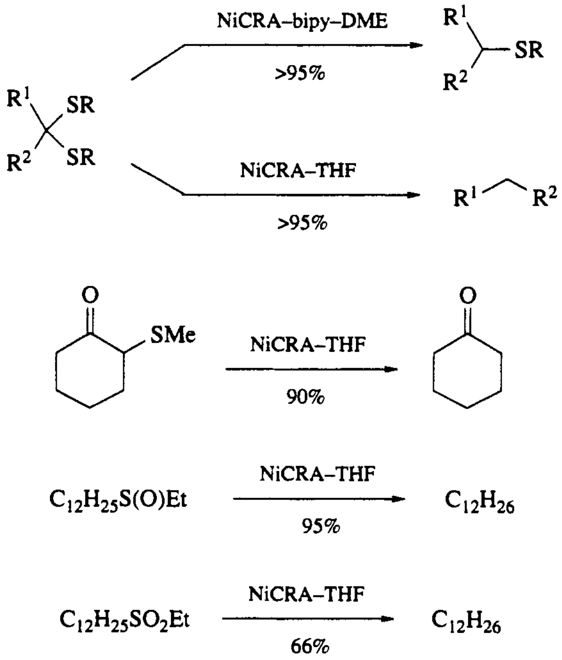
NiCRA–bipy–DME
>95%
$R^1$
SR
$R^2$
SR
SR
NiCRA–THF
>95%
SMe
NiCRA–THF
90%
$C_{12}H_{25}S(O)Et$
NiCRA–THF
95%
$C_{12}H_{26}$
$C_{12}H_{25}SO_2Et$
NiCRA–THF
66%
$C_{12}H_{26}$

**Scheme 8**

using Pr$^i$MgBr or c-$C_6H_{11}$MgBr and $NiCl_2$–$PPh_3$ in $C_6H_6$–$Et_2O$.[40] However, a change in the nature of the ligand may lead to substitution instead of desulfurization, since substitution of thioalkyl groups by Grignard reagents in the presence of Ni complexes is a well-known synthetic reaction.[8,41] Vinyl sulfones are also desulfurized by BuMgCl in the presence of transition metal complexes either as such or in the presence of DABCO, $Bu_3P$ or $Ph_3P$.[42a–42d] The most efficient systems contain Ni or Pd and the reagents tolerate isolated alkenes.[42b] The behavior of polyenyl substrates may be more complicated.[42c]

### 4.3.1.4 Metals and Amalgams

Electropositive metals have been widely used to cleave C—S bonds. Alkali metals are the most commonly used, but Mg, Ca and Zn are also included in a number of procedures. Alkali metals (Li holds the prominent place) are the most widely used to desulfurize sulfides, sulfoxides, sulfones, dithioketals *etc.*, and a large amount of information may be obtained from reviews devoted either to reduction by alkali metals[43] or to sulfur chemistry.[2a–2e,44] Before briefly commenting on the scope and limitations of these reductions, it must be emphasized that single electron transfer (SET) takes place during these desulfurizations, which are generally performed in the presence of an excess of a reducing agent. Thus functional groups sensitive to SET may be reduced. However, advantage may be taken of this side reaction, to perform selective desulfurization of α-sulfurated carbonyl substrates (Scheme 9).

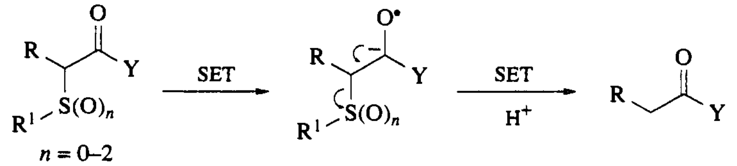

Scheme 9

SET cleavage of C—S bonds is accompanied by eliminations (which are often the only reactions observed) when a good leaving group is present at the vicinal position (Scheme 10).

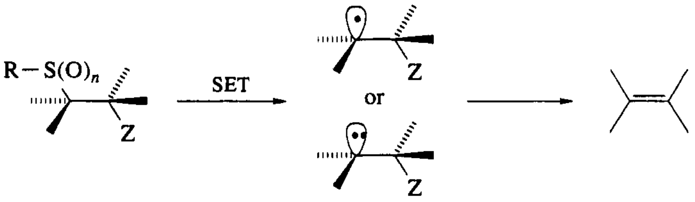

Scheme 10

Li, Na and K in hydrocarbons, ethereal solvents, HMPA or DMA have been used to desulfurize sulfides,[43b,43c,45] but applications are limited to simple sulfides, and particularly to aryl alkyl sulfides. Since these desulfurizations were performed without protic solvent, the organometallics formed may react further and particularly with the solvent. Thus low temperatures were recommended. Potassium graphite ($C_8K$) in excess in ether was also proposed for the desulfurization of allyl or vinyl sulfones, but this reagent is not free of disadvantages.[46]

The SET ability of alkali metals may be improved by the presence of aromatic compounds such as naphthalene or its derivatives. Thus a number of desulfurizations of sulfides[4,44a,44b,45] or dithioketals[44a,44b,47] have been performed (generally at low temperature in order to diminish side reactions) with Li in the presence of a catalytic amount of naphthalene, or with an excess of lithium naphthalenide or lithium 1-(dimethylamino)naphthalenide (LDMAN; Scheme 11).[47] Note that 1-dimethylaminonaphthalene may be easily removed from the reaction product during the work-up. These desulfurizations tolerate ethers[45] and nitriles[4] but do not respect halides,[45] ketones, esters and a few other structures.[4]

Use of excess alkali metal in liquid ammonia or an amine (generally $EtNH_2$ or ethylenediamine, EDA) is also a widespread procedure used to desulfurize sulfides, dithioketals and sulfones.[2a–2e,43b,43c] From the numerous works published, a number of interesting features emerge. Thus desulfurization of sulfides in liquid $NH_3$–THF tolerates esters and ketones,[4] while Li–$EtNH_2$ cleaves the C—S bonds of unsaturated substrates without side reactions (Scheme 1).[12] Sodium in liquid ammonia was found to be a better

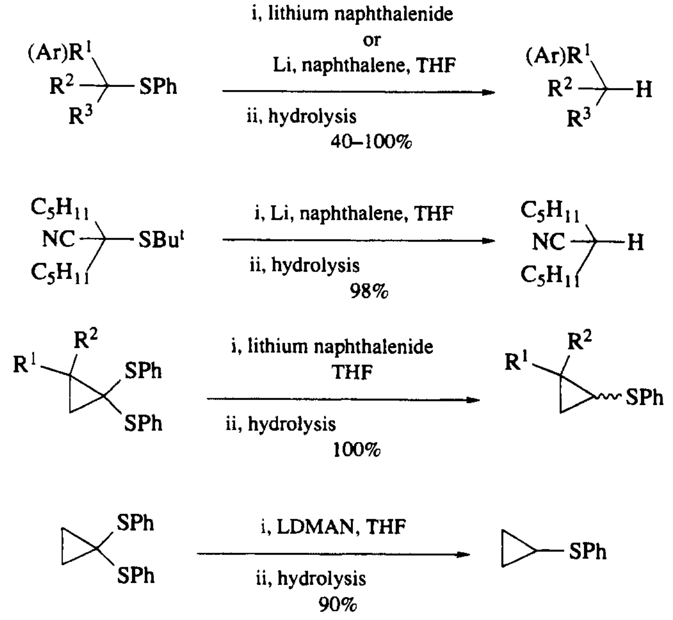
i, lithium naphthalenide
or
Li, naphthalene, THF
ii, hydrolysis
40–100%
i, Li, naphthalene, THF
ii, hydrolysis
98%
i, lithium naphthalenide
THF
ii, hydrolysis
100%
i, LDMAN, THF
ii, hydrolysis
90%

Scheme 11

reagent than Raney Ni, Ni boride or $Bu_3SnH$ (*vide infra*) to desulfurize sulfides in the deoxysugar series.[48] Recently, a careful study of the desulfurization of diaryl sulfides has shown that the reductions depend upon the structure (polycondensed or not) of the substrate.[49]

Unsaturated sulfones were desulfurized by $Li–EtNH_2$ without isomerization (Scheme 12),[50,51] while other procedures were unsuccessful.[50] Isomerization was observed with the same reagent during the desulfurization of allyl and vinyl sulfones.[46]

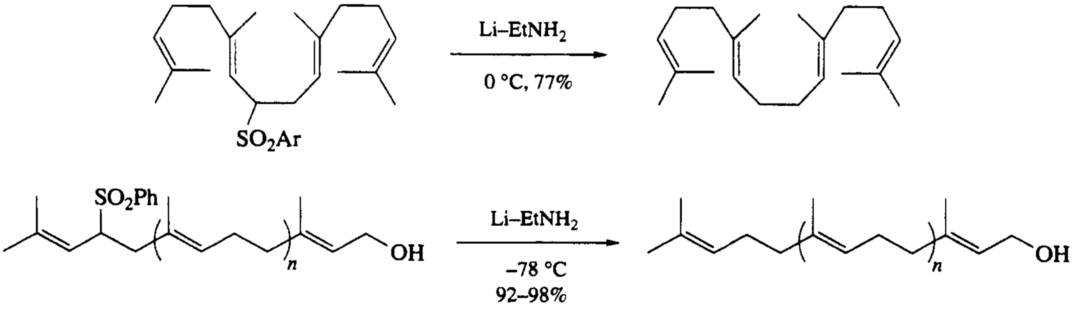
Li–EtNH2
0 °C, 77%
SO2Ar
SO2Ph
OH
n
Li–EtNH2
–78 °C
92–98%
OH
n

Scheme 12

Further examples are the ready reductive desulfurizations of α-keto sulfones by Li in liquid $NH_3$–THF,[52] of hydroxy α-keto sulfones by Li–EDA–THF,[53] of α,β-unsaturated-γ-sulfonyl ketones by Li in liquid $NH_3$, and of chiral hydroxy sulfones by Li–EDA.[55]

Although little used, Mg in MeOH easily desulfurizes sulfones and 1,1-disulfonylated substrates.[56] Desulfurization by Ca in liquid $NH_3$ has also been used to reduce mono- and di-thioketals[57] and α-ethoxycarbonyl sulfones.[51] Zn–AcOH desulfurizes α-thioalkyl, sulfoxy or sulfonyl ketones,[2b,2c,58] as well as γ-sulfonyl-α,β-unsaturated ketones, in good yields,[54] but this procedure does not tolerate acid labile functional groups. This disadvantage has been circumvented by using Zn in excess in the presence of $Me_3SiCl$,[59a] and still more efficiently using $NH_4Cl$ in THF–$H_2O$ (Scheme 13).[59b,59c]

Zn–$NH_4Cl$ desulfurizes sulfides more slowly than sulfoxides, and α-phenyl sulfides of purely aliphatic esters are hardly desulfurized. Lactones and esters are not hydrolyzed, and α,β-unsaturated ketones are tolerated as well as alkenes, with which no migrations are observed.

Sodium amalgam [Na(Hg)] used in excess in alcohols, is well known to desulfurize sulfides, sulfoxides, and, above all, sulfones,[2a–2c,2e,2f,60,61] but a number of side reactions can occur. It was found[62] that

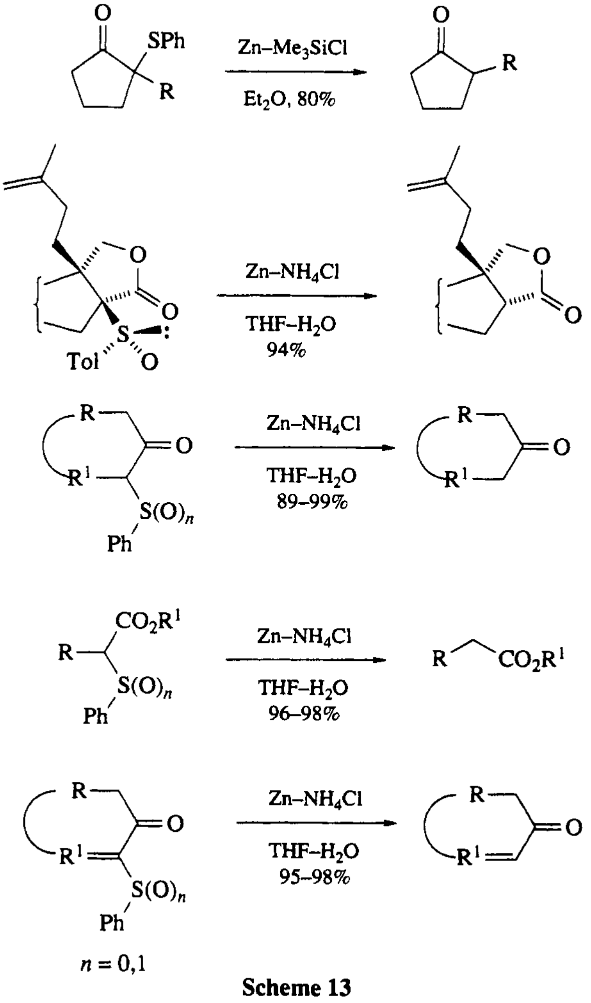

**Scheme 13**

6% Na(Hg) used in excess with $Na_2HPO_4$ in MeOH was particularly efficient, and presented fewer drawbacks. It was possible to perform reductive desulfonylations of sulfones in the presence of alkyl phenyl sulfides.[63] This procedure tolerates ethers, a trimethylsilyl group,[63] esters,[51,63] ketones,[51,64] isolated double[51,63,64a,65] and triple[65] bonds, ketals,[63,66] amides[67] and lactones.[68] A few examples are given in Scheme 14.

However, this procedure also has a number of drawbacks. A large quantity of Hg must be used. Moreover, alkenic bonds are reduced during the desulfurization of conjugated dienyl vinyl sulfones,[42c] and β-eliminations take place in the presence of good vicinal leaving groups.[69]

Since the pioneering work,[70] where Al(Hg) in large excess was shown to desulfurize sulfoxides, sulfones and sulfonamides under mild conditions, this reagent has been widely used.[2a–2c,2e,44b] It is prepared by immersing aluminum foil in 2% aqueous $HgCl_2$, and is often used in THF–$H_2O$. Efficient in the desulfurization of α-keto[71] and alkoxycarbonyl[72] sulfoxides, it has been used for removing chiral sulfoxides used in asymmetric synthesis. Al(Hg) also desulfurizes α-phenylthio[73] or sulfonyl ketones,[53,74] and allows the monodesulfonylation of 1,1-disulfonyl substrates.[42c] A few examples are given in Scheme 15.

Al(Hg) reduces the carbon–halogen bond[10f] but tolerates a trifluoromethyl group[72a] and isolated alkenes,[72c,73,74] thus allowing the desulfonylation of vinyl sulfones,[36,75] in a reaction which seems to be stereoselective.[36] However, the procedure is not free of drawbacks, since epimerization is observed in the desulfurization of α-thiophenyl ketones.[73] During the desulfurization of functional α-sulfonyl ketones, reduction of nitro groups and, surprisingly, of the keto group, was observed.[76] Desulfurizations of conjugated dienyl vinyl sulfones are accompanied, as with Na(Hg), by the complete reduction of the alkene unit bearing the sulfonyl group.[42c]

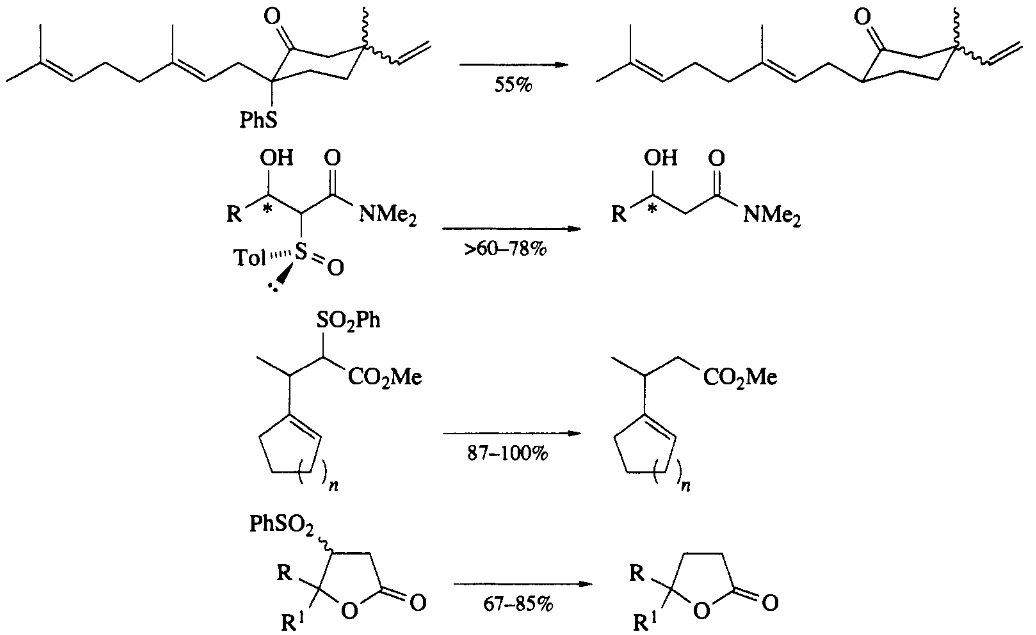

PhS
55%
OH O
NMe$_2$
Tol S O
>60–78%
SO$_2$Ph
CO$_2$Me
87–100%
PhSO$_2$
R
R$^1$
O
67–85%

Desulfurization with 6% Na(Hg)–MeOH–$Na_2HPO_4$ or $NaH_2PO_4$

**Scheme 14**

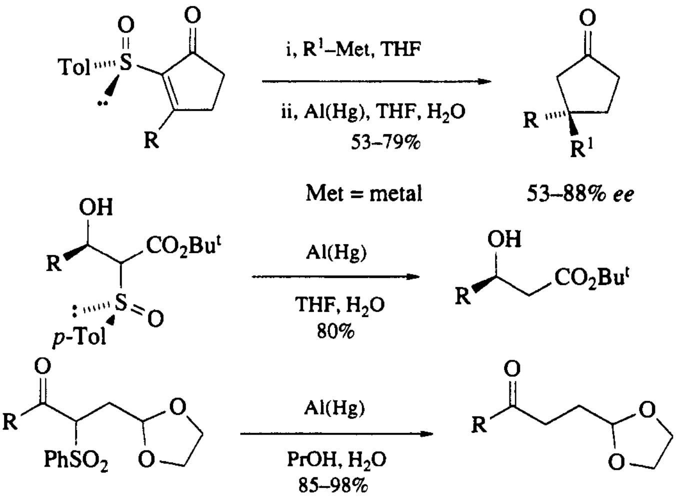

Tol S O
R
i, R$^1$–Met, THF
ii, Al(Hg), THF, H$_2$O
53–79%
R$^1$
Met = metal
53–88% *ee*
OH
CO$_2$Bu$^t$
*p*-Tol
Al(Hg)
THF, H$_2$O
80%
PhSO$_2$
Al(Hg)
PrOH, H$_2$O
85–98%

R = Pr, hexyl, heptyl, allyl, $C_7H_{15}CO_2Bu^t$

**Scheme 15**

#### 4.3.1.5 Tin Hydrides

Tin hydrides, generally $Bu_3SnH$ (TBTH) or $Ph_3SnH$ (TPTH) (which may be more efficient), usually used in hot toluene or benzene in the presence of AIBN, cleave C—S bonds by a radical mechanism. Because the C—S bond is not very reactive, reactions performed without AIBN are ineffective. Extensive reviews on tin hydride properties[77] have been published. Information about their use in desulfurizations may also be obtained from other reviews.[44a,44b,78] Evaluation of TBTH in the desulfurization of sulfides has led to a number of important conclusions.[79] Thus, the mechanism of desulfurization is that shown in Scheme 16.

The reaction is of interest only when one of the alkyl groups of the starting sulfide gives stabilized radicals. Moreover, the C—S bond of the thioalkyltin intermediate is much more reactive, and, as a con-

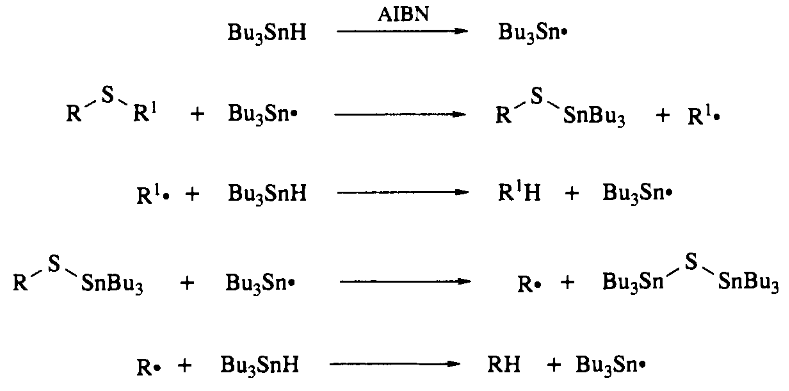

Scheme 16

sequence, selectivity in desulfurization of unsymmetrical sulfides is not possible. Finally, allyl sulfides may react in an *S*H or *S*H′ sense, leading to reduced or stannylated derivatives. Note that *S*H′ reductive stannylation of allyl- or propargyl-sulfurated substrates is a well-known reaction.[80]

Desulfurization of sulfides (or thiols) by TBTH–AIBN tolerates nitriles, esters, ketones,[79] ethers,[48,81] lactones,[10f,82] β-lactams[83] and isolated alkenes.[79,83] In contrast, halides are reduced and the stereochemistry of the starting sulfides is not conserved. Yields of these desulfurizations vary considerably, and β-eliminations may occur with vicinally substituted compounds. Some examples of TBTH desulfurizations are given in Scheme 17.

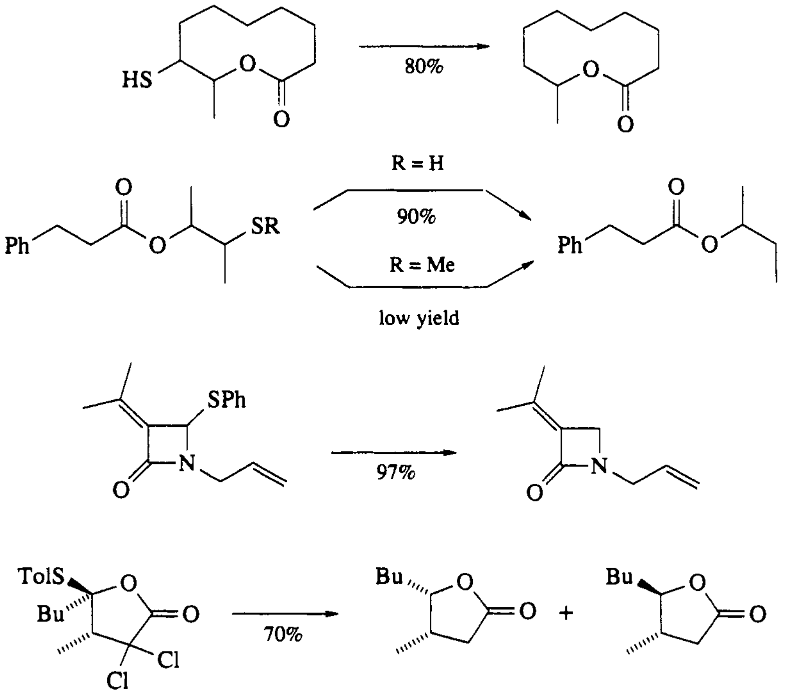

Desulfurization with $Bu_3SnH$–AIBN in $C_6H_6$ or PhMe

Scheme 17

Benzothiazolyl alkyl sulfides, prepared from the corresponding alcohols, are easily desulfurized (87–99%) by TBTH–AIBN.[84] This reaction constitutes a good indirect deoxygenation of alcohols. Desulfurization of dithioketals may be controlled. Thus 1,3-dithiolanes with 1 mol equiv. of TBTH lead to β-alkyl (or β-aryl) thiols (64–82%), while 4 mol equiv. of TBTH leads to the completely desulfurized derivative.[85] Desulfurization of heterocyclic thiones is also performed with this reagent.[86] In passing, it should be noted that generation of radicals from C—S bonds and tin hydrides in the presence of radical initiators is of large synthetic interest.[44b,87]

### 4.3.1.6 Miscellaneous Desulfurizations

The lack of stereoselectivity of the above reagents in a number of reductions of vinyl sulfurated substrates led to a search for new procedures. Thus the problem of stereoselective reduction of vinyl sulfones was solved in many cases by using sodium dithionite.[42c,88] This mild desulfurization proceeds by anionic addition–elimination,[88d] is highly stereoselective, but not devoid of side reactions.[42c,88b]

In the special case of aryl alkyl sulfides, desulfurization may be performed by $S_N2$ reactions with nucleophiles such as $RS^-$, $RSe^-$, and sometimes $RO^-$ or $R^1R^2N^-$.[43b,43c,89] 1,2-Eliminations, where the thioaryl group is the leaving group, have also been used.[43c]

Nucleophilic attack on the sulfur atom of sulfides by $RS^-$ in aprotic or protic solvents may constitute a mild procedure.[2b] BuLi is also a good reagent for attacking one of the sulfur atoms of 2,2-diaryl-1,3-dithiolanes and -dithianes, leading to the corresponding thioalkyl sulfides.[90] In the same way, $Bu_3SnLi$ easily desulfurizes sulfides and dithioketals.[44b,91] Desulfurization of allenyl sulfoxides occurs by attack on sulfur with MeLi.[92] Mild desulfurizations of α-keto sulfoxides and α,β-unsaturated-γ-sulfonyl ketones are obtained with $Me_2CuLi$.[54,71] Recently SET from $SmI_2$ was successfully used to desulfurize α-phenylthio and phenylsulfoxy ketones.[93]

Although of little synthetic interest at the present time, mention must be made of desulfurizations by transition metal carbonyls. Thus thiols and/or sulfides are desulfurized by complexes such as $[Mo(CO)_6]$, $[Fe_3(CO)_{12}]$, $[Co_2(CO)_8]$ and $[Os_3(CO)_{12}]$.[94] Coupling desulfurizations of dithioketals have been performed with $[W(CO)_6]$ or $[Mo(CO)_6]$,[95] and a recent review[96] gives further information about the hydrodesulfurization of thiophenes.

## 4.3.2 REDUCTION OF SELENIUM–CARBON BONDS

### 4.3.2.1 Introduction

In many respects selenium is like sulfur. Its derivatives are malodorous and they are often considered to be more toxic. The organic chemistry of selenium is younger than the chemistry of sulfur, and reports where reductive cleavage of C—Se is used as a 'last step' always deal with substrates containing nonoxygenated selenium.

With selenium, there are only a few hundred references to reductive deselenation compared with several thousands for the reductive cleavage of the C—S bond. Since the chemistries of selenium and sulfur are so similar, it is not surprising that the main deselenation procedures were borrowed from the desulfurization procedures. However, from the practical point of view, appreciable differences will be encountered due to the weaker C—Se bond and to the greater sensitivity of Se towards nucleophilic attack.

### 4.3.2.2 Raney Nickel

Reviews devoted to Se chemistry[97] or Raney nickel[1b] show that these are efficient reagents in reductive deselenations. Of course the advantages and drawbacks encountered with desulfurizations (see Section 4.3.1.2) must also be taken into consideration with deselenations. Raney Ni, often freshly prepared, is generally used in excess in solvents such as EtOH, ether, THF or DME, and under conditions milder than those for desulfurizations. From the numerous works published, it appears that the procedure tolerates alkyl and aryl ethers,[98,99,102] ketals,[100a,100b] ketones,[100b,101] esters,[101] lactones[10b,102] and sulfonamides.[9] A few representative examples are given in Scheme 18.

Among the drawbacks of using Raney Ni are the handling of large amounts of a hazardous reagent, and the lack of chemoselectivity against reducible functions such as unsaturation, allylic and benzylic oxygens, 1,3-dithianes, *etc.* Moreover, depending upon the chemical grade of Raney Ni or of the details of its preparation, yields may vary from excellent to very poor. Note, for example, that lactones, which are expected to be tolerated by Raney Ni, may be damaged by basic impurities remaining from the preparation of the reagent.[10b] Finally it appears that deselenations can proceed, at least in part, *via* an alkene, due to the formal elimination of RSeH.[97d] If the carbon atom adjacent to the carbon carrying the Se is a chiral center, the stereochemistry is lost. Note that some of these drawbacks may sometimes be used in synthesis: Raney Ni and $H_2$ (under pressure) can simultaneously perform deselenation, saturation of an alkene, and debenzylation of a benzyl ester.[98]

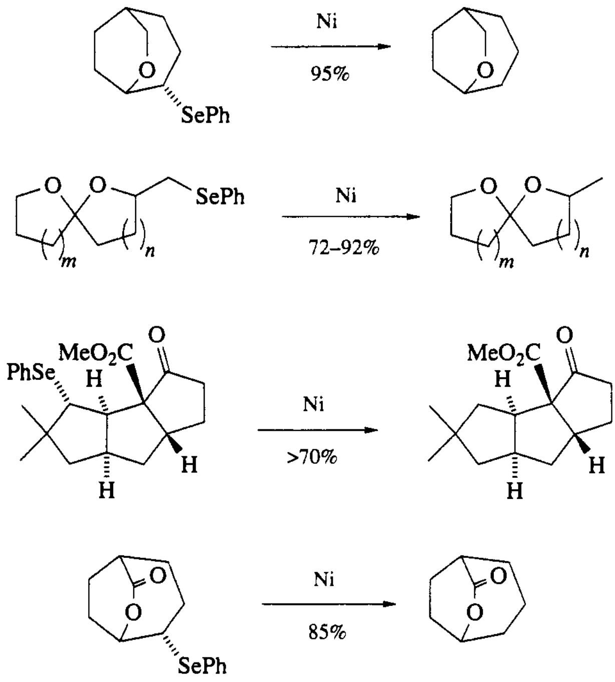

Scheme 18

### 4.3.2.3 Metal Borides

While numerous systems containing hydrides, or organometallics combined with transition metal derivatives, have been used in desulfurizations (see Section 4.4.1.3), deselenations have been performed only with Ni boride.[97f] From a recent careful study,[103] the following main features emerge: (i) the reaction is best performed in THF–MeOH; (ii) $NaBH_4$ must be taken in excess relative to the substrate (the ratio substrate:reagent depends on the structure of the substrate); (iii) to be efficient, $NaBH_4$ must be added to a mixture of the substrate and the Ni salt (no deselenation took place by addition of the substrate to a preformed Ni boride); (iv) hydrogen incorporated into the substrate originated from the MeOH and the $NaBH_4$, but not from THF (this result ruled out a radical mechanism); and (v) the deselenation applies to saturated or vinyl selenides, as well as to diselenoketals, and yields vary, with few exceptions, from good to very good. This procedure tolerates alkyl chlorides (but not alkyl iodides), nitriles, esters,[103] amides,[104] sulfonamides,[9] sulfides and sulfones (an interesting property for selective deselenations) but not sulfinate esters.[103] Moderately hindered alkenes were tolerated,[103,105] but less-hindered systems were reduced. Ketones were more or less tolerated, but the easily reduced ones may lead to the formation of appreciable amounts of alcohols.[103] Moreover, β-selenoketones can give β-elimination, and the usual complications were observed when the selenide group was vicinal to a good leaving group.[103] Allyl selenides were deselenated by $LiHBEt_3$–$[Pd(PPh_3)_4]$ (cat.) in excellent yield (82%) but with migration and (*E*)/(*Z*)-isomerization of the double bonds.[31]

### 4.3.2.4 Alkali Metals

The two main systems of this kind used in the deselenation of selenides and diselenoketals are Li–$EtNH_2$[97b,97c,97e,97f] and Na in liquid $NH_3$.[10b,99] Na in HMPA or DMA has also been used with some special aryl alkyl selenides.[43c] This procedure does not deserve special comment since, broadly speaking, the behavior of the reagents towards selenated substrates was very similar to that observed with sulfur-containing substrates (see Section 4.3.1.4). As expected from the difference of bond energies, C—Se bonds are more easily cleaved than C—S bonds. However, few selective deselenations have been performed in the presence of sulfur groups. C—O bonds vicinal to C—Se bonds are, of course, removed with alkene formation, and this property has found interesting applications.[10b,99]

### 4.3.2.5 Tin Hydrides

The reductive cleavage of the C—Se bonds of selenides and diselenoketals by TBTH or TPTH is a widespread deselenation method mentioned in numerous reviews.[44a,77c,97a,97c–97f,106] A radical mechanism is involved with both hydrides, which are used in refluxing benzene or toluene. TPTH is generally more suitable than TBTH, and freshly distilled TPTH allows shorter reaction times. AIBN is used as a radical initiator with both hydrides, but an interesting point is that deselenation with TPTH can be performed in refluxing toluene *without* AIBN,[97d,107] making this already mild deselenation still more chemoselective, particularly with sulfur-containing substrates. Using appropriate conditions, deselenations may be performed without the reduction or hydrogenolysis of isolated alkenes (even unhindered),[97d,98,102,108,109] alcohols[97d,102] (even allylic[108]), ethers (even benzyl[111]), sulfides,[99,110] dithioketals,[97d] ketones,[113] esters,[97d,98,102,113] lactones,[10b,97d,102,110,112] amides,[104,114] β-lactams[109] and carbamates.[97d,115] A few examples are given in Scheme 19.

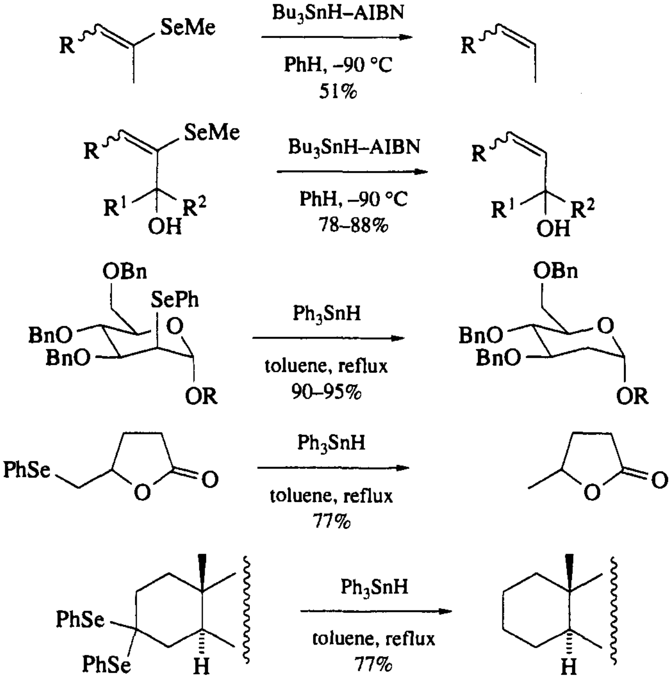

Scheme 19

These deselenations do not tolerate halides, which are generally reduced. Among the drawbacks in addition to side reactions inevitable with radical intermediates, the use of an excess of an expensive reagent and a high reaction temperature may make the procedure less useful, especially with sensitive substrates. Note that the generation of radicals using deselenation by tin hydrides is also very useful in organic synthesis.[87]

### 4.3.2.6 Miscellaneous Deselenations

Only one kind of deselenation deserves to be mentioned in the present section and deals with the use of nucleophiles. Since selenium is much more sensitive to nucleophilic attack than sulfur, it reacts easily with strong nucleophiles/bases. This property may be a drawback, but is also a useful tool with which to generate organometallics. The main reagents encountered in these deselenations are BuLi[43c,97a,97c,97e,116] and PhSeLi,[43c,97b,117] although others have been used.

Deselenations with organolithium reagents have been successfully performed on mono-, 1,1-di- or 1,1,1-tri-selenides, generally in ethereal solvents such as THF, at more or less low temperature. Of course the deselenated products are obtained after hydrolysis, and yields vary from moderate to very good. One of the main drawbacks with organolithiums is their reactivity towards several functional groups.

Note that the relative insensitivity of sulfur toward nucleophilic attack allows the selective deselenation of thioselenoketals.[118] On the other hand, ketones are tolerated by PhSeLi, a useful property for chemoselective deselenations of α-phenylseleno ketones (Scheme 20).[119]

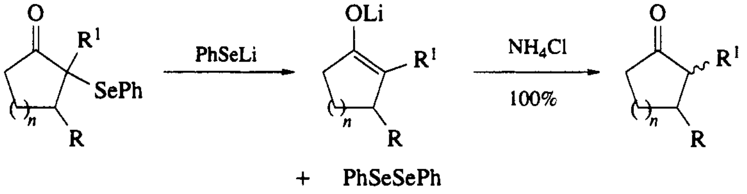

**Scheme 20**

## 4.3.3 REDUCTION OF MERCURY-CARBON BONDS

Methods which realize mercury–hydrogen exchange in organomercurials include homolytic decomposition in solvents capable of hydrogen atom transfer, protonolysis by protonic acids and reduction.

The former cannot be considered a good synthetic method because a mixture of reaction products is usually obtained. The protonolysis of organomercury compounds has been extensively studied from a mechanistic standpoint but has found little synthetic utility except for isotopic labelling of organic molecules. Reduction is the most useful method for the demercuration of organomercury compounds, particularly of solvomercurials in the solvomercuration–demercuration reaction, and a lot of reductants are used for this purpose.

The present review considers recent advances in mercury–hydrogen interchange by protonolysis and reducing agents, and especially metal hydride demercuration.

### 4.3.3.1 Protonolysis

The protic cleavage of the carbon–metal σ-bond ranks among the simplest of all electrophilic substitution processes. As organomercurials are readily prepared in high purity, can be manipulated with ease and are monomeric in solution, most mechanistic studies of the protonolysis of carbon–metal σ-bonds have focused on the protic cleavage of organomercurials. Reviews[120] and a book[121] have been published on this subject.

The cleavage of diphenylmercury in acetic acid with perchloric acid, and the reaction of dialkylmercury with mercury nitrate, may be considered as exhibiting the pure $S_E2$ mechanism, where an attack of the electrophile at the metal-bonded C-atom is the rate-determining step.[120a]

The coordination of the nucleophilic part Nu of the acid NuH with the mercury atom can occur and may be responsible for a four-center transition state (Scheme 21).

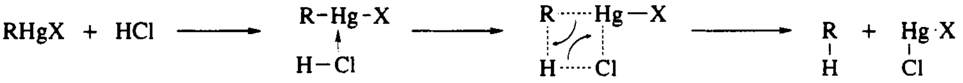

**Scheme 21**

However, intramolecular nucleophilic participation by the conjugate base during protonolysis of a C—Hg bond is questionable. A study of the acidolysis of the carbon–mercury bond in unsymmetrical dialkylmercurials rather suggests that the reaction proceeds *via* a three-center transition state.[122] In any case, substantial kinetic and stereochemical evidence has led to the idea that reaction occurs by a concerted, front side attack with a transition state that involves a pentacoordinate carbon center.[121] In some cases unimolecular mechanisms, $S_E1$, also have been observed.[120a,122]

The importance of organomercurials in organic synthesis is due in large part to the valuable solvomercuration–demercuration reaction. As the reaction of proton acids with solvomercurated products derived from alkenes leads back to the alkene,[123] protonolysis has in this procedure little synthetic utility.

However, the protonolysis of alkenylmercurials derived from the solvomercuration of alkynes is known as a method for preparing stereoisomerically pure alkenes. Acidic deuterolysis provides also a convenient route to labelled organic substrates. For instance, in a study on the regio- and stereo-selectivity of the acetoxymercuration of alkynes, protodemercuration with acetic acid of a 3:1 mixture of the vinylmercury compounds (**6**) and (**7**) occurred almost quantitatively to give a 3:1 mixture of the corresponding esters (**8**) and (**9**) (equation 4),[124] and other examples of protodemercuration occurring with retention of configuration are known.[125]

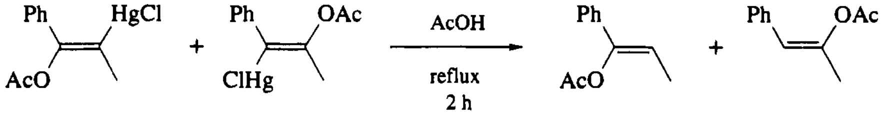
Ph
HgCl
AcO
Ph
OAc
ClHg
AcOH
reflux
2 h
Ph
AcO
Ph
OAc

(**6**) (**7**) (**8**) (**9**)

(**6**):(**7**) = 3:1 (**8**):(**9**) = 3:1

(4)

However, the alkenylmercury acetate (**10**) undergoes mercury–hydrogen exchange with HCl with inversion. A mercurinium ion intermediate has been proposed, where the vicinal phenyl groups provide the driving force for isomerization (Scheme 22).[126]

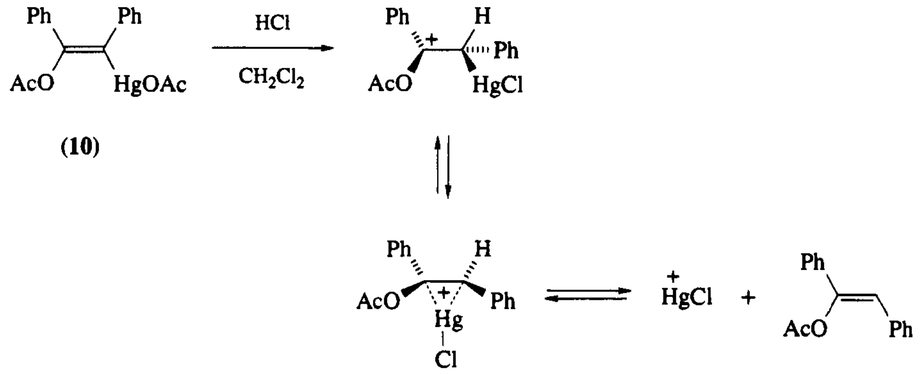
Ph
Ph
AcO
HgOAc
HCl
CH2Cl2
Ph
H
Ph
AcO
HgCl
Ph
H
AcO
Ph
Hg
Cl
HgCl
Ph
AcO
Ph

(**10**)

**Scheme 22**

Acidic deuterolysis and protonolysis have also been used for clarification of the placement of the mercury atoms[127] after the mercuration step, in particular for porphyrin derivatives.[128]

Protodemercuration as the second step of intramolecular *C*-vinylation induced by mercury(II) salts has been recently described: examples are in equations (5)[129] and (6).[130] A large enhancement of the hydrolysis rate was observed when NaI was added to the acid solution.[129b] This effect can be attributed to halide-catalyzed protodemercuration, an established method for cleavage of arylmercurials.[131]

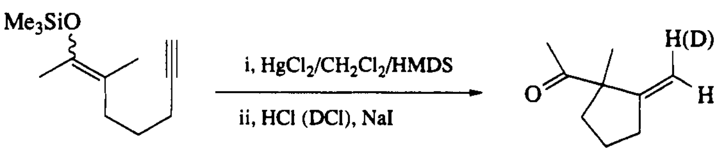
Me3SiO
i, HgCl2/CH2Cl2/HMDS
ii, HCl (DCl), NaI
O
H(D)
H

(5)

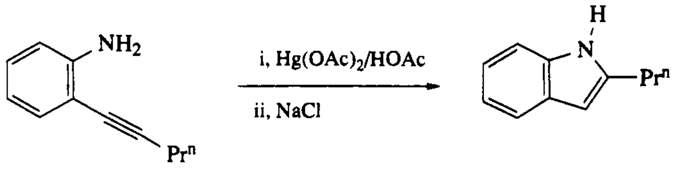
NH2
Prn
i, Hg(OAc)2/HOAc
ii, NaCl
H
N
Prn

(6)

### 4.3.3.2 Metal Hydride Demercuration

The reduction of organomercurials by sodium borohydride has been widely studied and the noncage free radical chain mechanism indicated in Scheme 23 is generally accepted.[132,133]

However, recent findings of Singh and Khanna on the LAH reduction of organomercury(II) halides suggested an electron transfer mechanism of the $S_{RN}1$ type, involving attack of R· on the metal hydride (Scheme 24).[134] In other respects, LAH has been relatively little used as a reducing reagent for demercuration in the last decade.[135]

$$\mathrm{RHgX} \xrightarrow{\mathrm{NaBH_4}} \mathrm{RHgH} + \mathrm{NaBH_3X}$$

$$\mathrm{R}\bullet + \mathrm{RHgH} \longrightarrow \mathrm{RH} + \mathrm{RHg}\bullet$$

$$\mathrm{RHg}\bullet \longrightarrow \mathrm{R}\bullet + \mathrm{Hg}$$

**Scheme 23**

$$\mathrm{R}\bullet + \mathrm{AlH_4^-} \longrightarrow \mathrm{RH} + \mathrm{AlH_3}\bullet^-$$

$$\mathrm{AlH_3}\bullet^- + \mathrm{RHgX} \longrightarrow \mathrm{AlH_3} + \mathrm{R}\bullet + \mathrm{Hg} + \mathrm{X^-}$$

**Scheme 24**

A similar process was questioned by Russell and Guo for the reduction of organomercury(II) halides with $NaBH_4$. Although alkyl radicals can abstract a hydrogen atom from $NaBH_4$, hydrogen abstraction from $BH_4^-$ occurs more slowly than abstraction from MeOH/NaOH, or from RHgH, and much less readily than attack upon $AlH_4^-$. These results confirm that the reduction of alkylmercury(II) halides with $NaBH_4$ in MeOH/NaOH proceeds *via* hydrogen abstraction by the alkyl radical from RHgH and not from $NaBH_4$.[136]

Rearrangements of the initially formed radicals frequently occur. For instance, the reduction of 5-hexenylmercury(II) bromide with $NaBH_4$ or $NaBD_4$ affords 1-hexene and methylcyclopentane, the two expected products of the 5-hexenyl radical.[133a] The intermediate radicals derived from 2,2,2-triphenylethylmercury(II) chloride[137] and 2,2-dimethyl-2-phenylethylmercury(II) chloride have been trapped by oxygen to give the expected products, accompanied by side products arising from radical rearrangements.[138] Trapping of the radicals generated in the metal hydride reduction has also been achieved with alkenes to give coupled products. Some examples of this strategy are given in Scheme 25.[139]

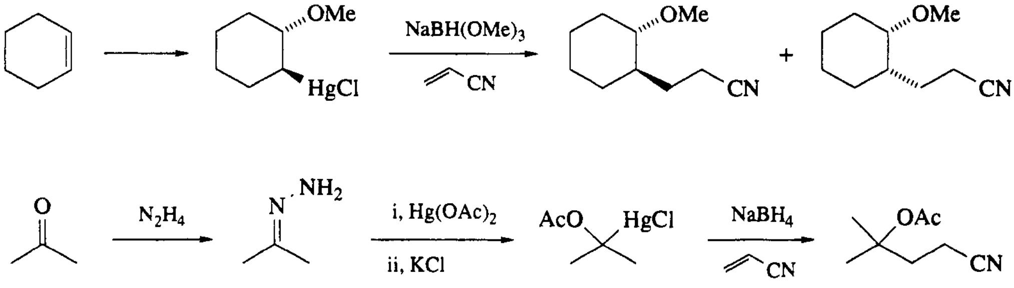

**Scheme 25**

Stereochemical studies have brought an important contribution to the radical mechanism of the borohydride reduction of organomercurials.[133b] A recent $^2$H NMR study of the reduction of norbornyl-type mercurials with $NaBD_4$ confirmed the previous finding of Gray and Jackson[140] about the composition of the product mixture. The major components were clearly nortricyclanol and *anti*-7-norborneol. $^2$H NMR data provided accurate measures of the preferred directions of deuterium abstraction by the radical intermediate.[141]

Reduction with $NaBD_4$ of *exo*- and *endo*-norbornylmercury(II) bromide provides mostly *exo*-[2-$^2H_1$]norbornane.[133b] The loss of stereochemistry could also be observed in the sodium borohydride reduction of *cis*- and *trans*-4-methylcyclohexylmercury(II) bromide, which yielded essentially the same mixture of *cis*- and *trans*-4-methyl[1-$^2H_1$]cyclohexane (Scheme 26).[141] These reductions are thus stereoselective, but not stereospecific.

The stereoselectivities in the cleavage of the C—Hg bond with $NaBH_4$ depend upon the nature of the radical intermediates and the reaction conditions. Recent attempts to find optimal conditions for this stereoselective cleavage have been published.[142] The principle is given in Scheme 27 for the oxymercuration–demercuration of α,β-unsaturated esters, generating two asymmetric centers in the 3-alkoxy-2-alkyl ester.

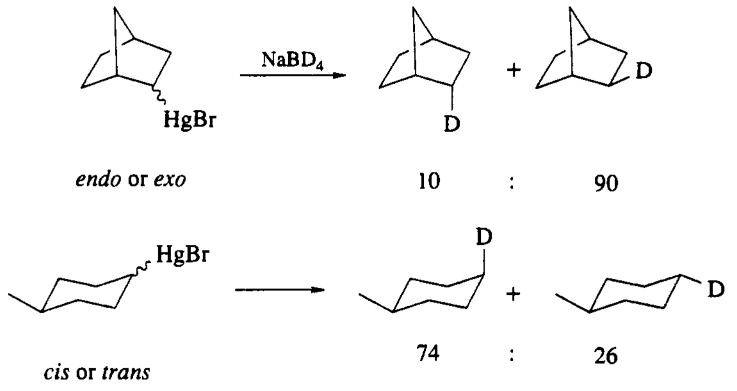

Scheme 26

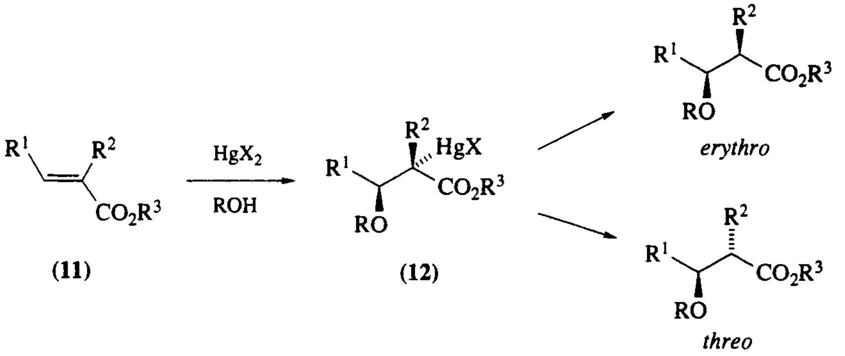

Scheme 27

It has been suggested that radical intermediates such as (**14**) are involved in the NaBH$_4$ cleavage, and that they produce the *threo* isomers selectively from the cyclic ethers (**13**), whereas no stereoselectivity occurs with the radicals derived from the tiglic acid adducts (**12**).[143]

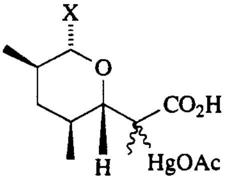

(**13**)

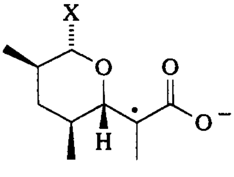

(**14**)

Other factors affecting the diastereoselectivity in the metal hydride demercuration of α-mercury(II) carbonyl compounds have also been identified, which include the nature of the solvent, the amount of hydride used, the mode of addition, the nature of the hydride source and the ligand on mercury. The rationalization of these results is difficult.[142b]

A frequent problem associated with oxymercuration–demercuration is reverse deoxymercuration, which can occur during the reduction step.[144] Brown's method of using a basic homogeneous medium is often used to minimize deoxymercuration.[145] The structure of the organomercurial is also important and affects the choice of hydride, sodium trimethoxyborohydride being preferred to NaBH$_4$ for β-alkoxy-substituted organomercury(II) compounds.[146]

Another example is mercurilactonization, which proceeds with good stereocontrol in the formation of both γ- and δ-lactones, but suffers from elimination during the reductive demercuration. An exploration of a number of reagents and conditions, including NaBH$_4$ and various pHs, hydrogen over Wilkinson's catalyst, Bu$_3$SnH and Na$_2$S, indicates that reductive elimination is minimized in alkali borohydride, although it cannot be avoided entirely (Scheme 28).[147]

In contrast, NaBH$_4$/NaOH must be avoided in the demercuration of organomercurials obtained by alkoxymercuration of vinyl ethers bearing conjugated electron-withdrawing groups, because of substantial

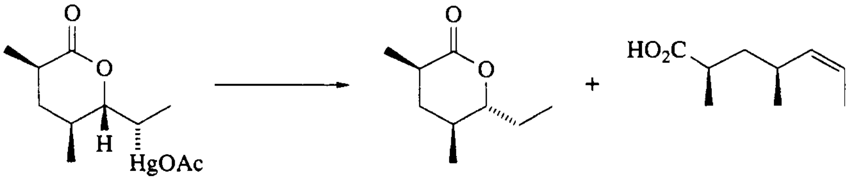
O
O
H
HgOAc
O
O
+
HO2C

**(15)** **(16)** **(17)**

| *Reagent/Conditions* | *Yield (%)* | |
|---|---|---|
| $NaBH_4$, MeOH, –78 °C | 90 | 10 |
| $H_2/[(Ph_3P)_3RhCl]/MeOH$ | 0 | 100 |
| $Bu_3SnH$ | 66 | 30 |
| $Na_2S$ | 0 | 100 |

**Scheme 28**

reductive elimination. However, demercuration in simple vinyl ethers can be accomplished with this reagent (Scheme 29).[148]

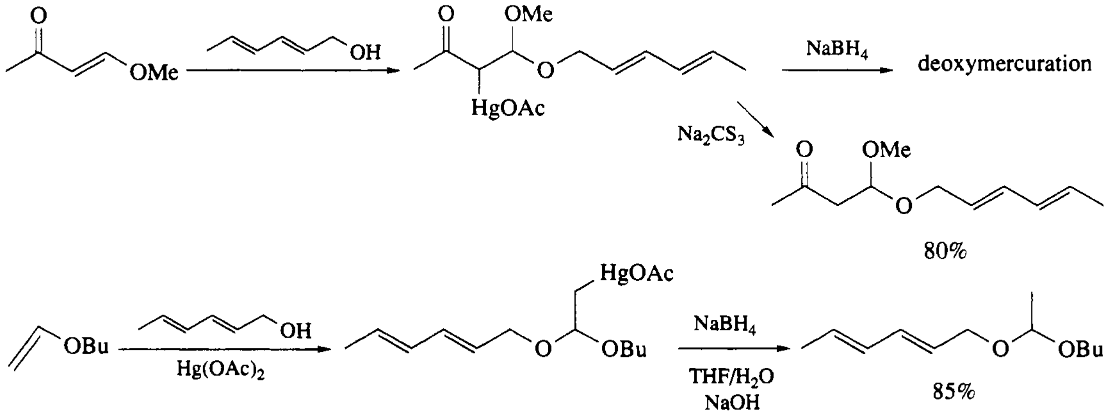
O
OMe
OH
O
OMe
O
HgOAc
NaBH4
deoxymercuration
Na2CS3
O
OMe
O
80%
HgOAc
OBu
OH
Hg(OAc)2
O
OBu
NaBH4
THF/H2O
NaOH
O
OBu
85%

**Scheme 29**

The products obtained from the oxymercuration–demercuration of alkenylacetates under standard conditions ($NaBH_4/NaOH$ 3 M) are diols. However, the yields are significantly lower than with methoxy- and hydroxy-alkenes because of competitive deoxymercuration.[149] Increasing the amount of base results in major increases in the yield of hydrated products. A less basic procedure has been developed, which allows for the survival of the acetate group.

Phase transfer reagents sometimes avoid deoxymercuration during the reduction step, as with the products (**18**) to (**20**) from hydroxymercuration,[150] amidomercuration[151] and from spiroacetals.[152]

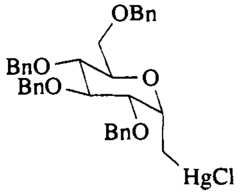
OBn
BnO
BnO
O
BnO
HgCl

**(18)** 73%

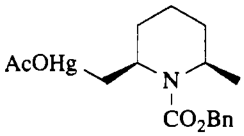
AcOHg
N
CO2Bn

**(19)** 93%

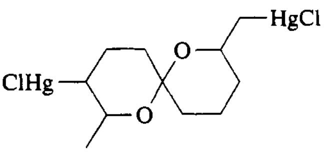
HgCl
O
ClHg
O

**(20)** >90%

Phase transfer catalysis often avoids other side reactions. For instance, the reaction of organomercurials (**21**) with $NaBH_4$ in the standard conditions leads to symmetrical organomercurials (**22**) whereas Lattes's phase transfer conditions give 2-alkenyl-pyrrolidines (**23**) and -piperidines (**24**) in 35–90% yields.[153,154]

In the reaction between peroxymercurials and sodium borohydride,[155] epoxide formation and deoxymercuration compete with hydrogenodemercuration (Scheme 30). Except for the synthesis of *t*-butyl

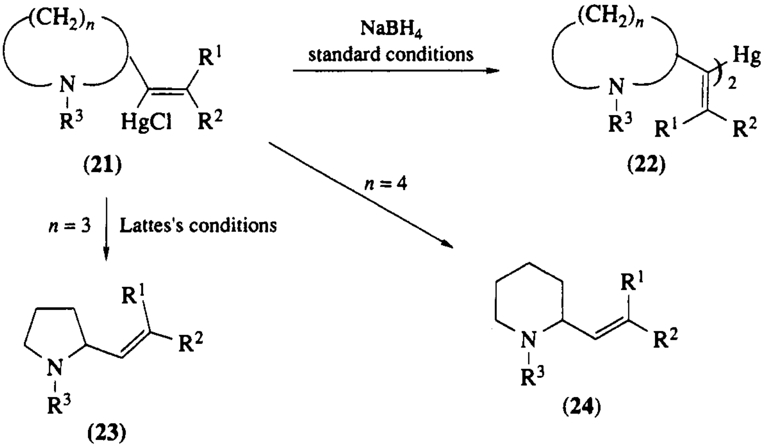

*exo*-2-norbornyl peroxide and the *t*-butyl peroxy derivative of styrene, the peroxymercuration and borohydride reduction of nonterminal alkenes is not an attractive method.[155]

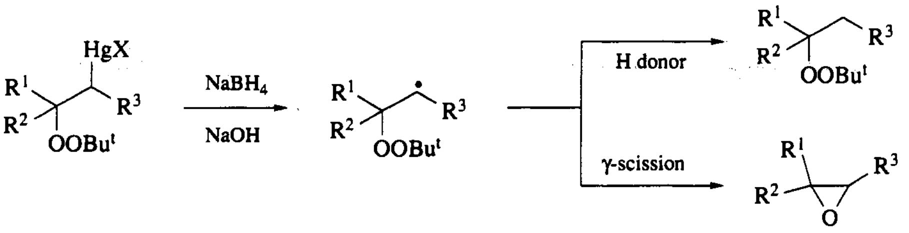

Scheme 30

It has also been reported that cycloperoxymercurials[156–160] give by-products when submitted to hydrogenodemercuration with $NaBH_4$. The amount of by-product is dependent on the structure of the peroxymercurials. Cycloperoxymercurials containing endocyclic mercurio substituents have a strong tendency to deoxymercuriate and poor yields of peroxides are obtained, the major products being unsaturated alcohols (Scheme 31).[156]

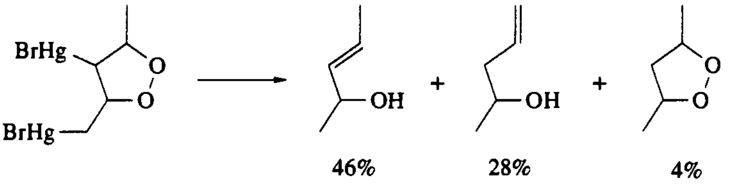

Scheme 31

On the other hand, cycloperoxymercurials which contain exocyclic mercurio substituents are reduced, *via* an exocyclic β-peroxy radical, and give a mixture of the cyclic peroxide resulting from H-atom abstraction and the epoxy alcohol resulting from $S_H{}^i$ radical attack on the peroxide bond (Scheme 32).[157]

The relative amounts of peroxide and epoxy alcohol are dependent on the structure of the intermediate radical. It has been suggested that the critical steric condition for the $S_H{}^i$ reaction is the dihedral angle about the O—C bond between the attacking radical and the leaving oxygen. When the peroxide bond and the radical center are colinear, which can be realized for a six-membered ring, maximum $S_H{}^i$ reaction occurs. For the analogous radical derived from a five-membered ring the O—C dihedral angle has a maximum of approximately 165° in the most favourable conformation for $S_H{}^i$ attack, and the amount of epoxy alcohol ($S_H{}^i$ product) is substantially less than for the six-membered radical. No $S_H{}^i$ reaction is possible from endocyclic radicals because they cannot assume the required conformation to give internal radical attack. These conclusions are consistent with the observation that reduction of peroxymercurials derived from methyl oleate gives no epoxy alcohols, but peroxymercurials derived from methyl linoleate give mixtures of unsaturated epoxides and epoxy alcohols as major reaction products.[158]

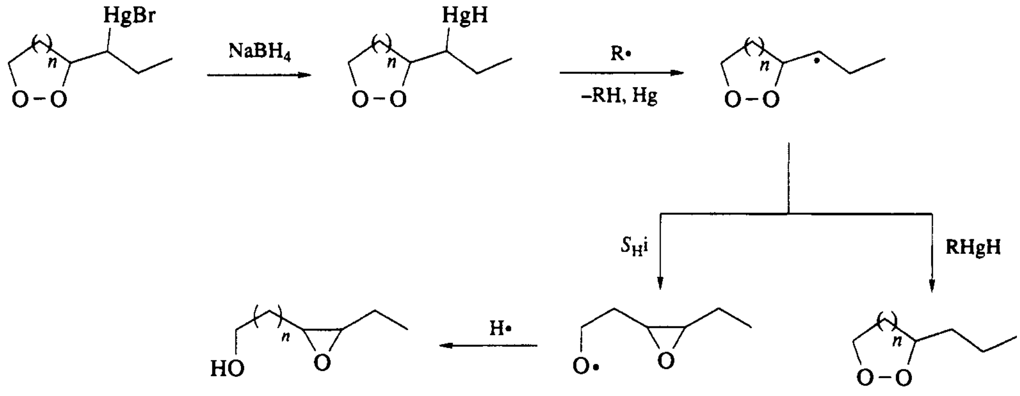

| *n* | *Yield (%)* *Peroxide* | *Epoxy alcohol* |
|---|---|---|
| 1 | 75 | 25 |
| 2 | <10 | 90 |
| 3 | 100 | 0 |

**Scheme 32**

A number of demercurations of RHgX or RHgOR′ use tributyltin,[147,135b] or triphenyltin hydride,[161] but complete removal of tin residues can sometimes be difficult; $NaBH_4$ reduction is then preferred.[152] Deoxymercuration has also been observed during demercuration.[147] The presence of anhydrous sodium acetate avoided this side reaction with $Ph_3SnH$,[161] and the use of tributyltin hydride instead of $NaBH_4$/NaOH in the demercuration of peroxymercurials led to much improved yields of peroxides (Scheme 33).[155]

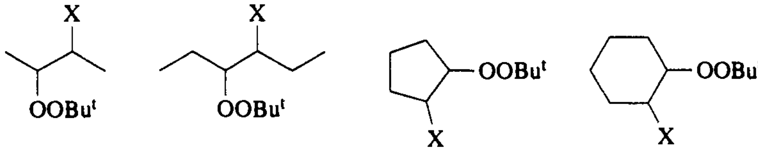

| Peroxymercurial (X = HgBr) | | | | |
|---|---|---|---|---|
| Peroxide yields (X = H) (%) | | | | |
| $Bu_3SnH$ | 63 | 24 | 59 | 61 |
| $NaBH_4$/NaOH | 0 | 0 | 2 | 13 |

**Scheme 33**

That epoxides are formed as by-products supports the assumption of β-peroxyalkyl radicals as intermediates, and tributyltin hydride itself will be the principal hydrogen donor. A mechanism has been suggested[155] which involves a hitherto unreported $S_H2$ displacement of alkylmercury by tributyltin, but another radical mechanism has also been proposed.[162]

Although β-elimination of the mercury group and formation of side products can occur during the reduction of organomercurials, sodium borohydride remains the most important reducing reagent for this purpose. Numerous papers over the past 10 years mention slight modifications in the experimental sections. These include: (i) the hydroxymercuration–demercuration, without internal cyclization, of iridoid glucosides,[163] alkyl-substituted cycloalkenes,[164] methylenecycloalkanes,[165] bicyclooctene, trimethylenenorbornene and related alkenes,[166] cyclopropane[167] and vinylcyclopropanes,[168] alkenylsilanes,[169] and, with internal cyclization, of alkenylphenols[170] and alkenyl alcohols;[171] (ii) the alkoxymercuration–demercuration, without internal cyclization, of 1-octene in aqueous sodium dodecylsulfate,[172] of the dihydropyran group in a total synthesis of (–)-specionin,[173] and, with internal cyclization, of a cyclobutene double bond in a synthesis of (±)-lineatin;[174] (iii) the aminomercuration–demercuration, without internal cyclization, of alkenes,[175] α,β-unsaturated esters,[176] terminal alkynes,[177] and enynes,[178] and, with internal cyclization, of allylamines, dialkylamines, 1,4- and 1,5-hexadiene,[179] 1,5-cyclooctadiene,[180] a butenyl-substituted β-lactam,[181] and a butenyl-substituted aminodioxolane;[182] (iv) the amidomercuration–demercuration, without internal cyclization, of alkenes,[183] and, with internal cyclization, of alkenylcarbamates,[184] (hydroxyalkenyl)carbamates,[185] and substituted acrylanilides;[186] (v) the sulfonamidomercuration of alkenes or dienes,[187] and the phosphoramidomercuration of alkenes;[188] and (vi) the mercury(II)-induced cyclization–demercuration as a chemical mimic of terpenoid biosynthesis of polyenes,[189] for transannular cyclization of cycladienes[190] or cyclatrienes,[191] and for [3,3] sigmatropic rearrangements of dienes.[192]

### 4.3.3.3 Miscellaneous Methods

In the past 10 years other reductants of the C—Hg bond have been used, mainly thiols and sodium amalgam. Reduction with hydrogen sulfide,[193] sodium dithionite,[194] metals,[143,195] alcohols,[196] alkaline aqueous bases,[197] aromatic amines,[198] Wilkinson's catalyst[143] and electrochemical reductions[199] have also been described. Organomercurials react with thiols by free radical substitutions with an $S_H2$ mechanism (Scheme 34).[200] The reaction between PhSH and $\Delta^5$-hexenylmercury chloride initiated by light or AIBN gives a mixture of 1-hexene and methylcyclopentane.[201]

$$\mathrm{PhS}^{\bullet} + \mathrm{RHgCl} \longrightarrow \mathrm{R\dot{H}g(PhS)Cl}$$

$$\mathrm{R\dot{H}g(PhS)Cl} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{PhSHgCl}$$

$$\mathrm{R}^{\bullet} + \mathrm{PhSH} \longrightarrow \mathrm{RH} + \mathrm{PhS}^{\bullet}$$

**Scheme 34**

Hydrogenolytic cleavages using $H_2S$–pyridine, $Na_2S$–aqueous NaOH, $Na_2S$–pH3 buffer, $Na_2S$–MeCN, $Na_2CS_3$, sodium amalgam (and $NaBH_4$)[143] have also been studied with the mercurial precursors (**13**) of the Prelog–Djerassi lactone and with the mercurials (**12**) derived from α,β-unsaturated acids.[142b] Excellent yields are obtained in reduced products but with variable stereoselectivities. On the basis of the stereochemical results the same radical intermediate (**14**) is suggested in the hydrogen sulfide–pyridine cleavage as in the $NaBH_4$ reduction of cyclic mercurial ethers which produce the *threo* isomer selectively.

In the case of mercurated tiglic acid adducts (**12**), the *erythro* product is obtained with aqueous $Na_2S$, and an ionic mechanism has been proposed with an intermediate carboxylate enolate (**25**).[143] Sodium trithiocarbonate[143] and, especially, 1,3-propanedithiol[142b] exhibit a preference for retention of configuration leading to the *erythro* isomer. Such sulfur-containing reagents are probably capable of intramolecular hydrogen atom delivery as illustrated schematically in (**26**), and they also promote demercuration by an ionic mechanism.

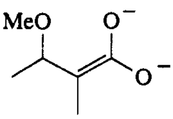

(**25**)

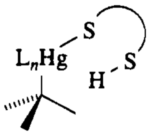

(**26**)

However, a limitation in the use of certain thiol reagents, as for most reagents used for demercuration, can be their propensity to undergo elimination with reversion to the starting material. Sodium sulfide, for example, cannot be used in the reduction step of the mercurilactonization (Scheme 28),[147] and the presence of a base ($NaHCO_3$ or $Et_3N$) is necessary in the 1,3-propanedithiol reduction of mercurials.[142b] In other cases, thiol reagents ($Na_2CS_3$) succeed where $NaBH_4$ induces substantial elimination (Scheme 29).[148]

The sodium amalgam cleavage of alkylmercurials involves an ionic mechanism.[202] The stereochemical course of the replacement of mercury by deuterium in a range of organomercury halides or acetates employing 1–2% sodium amalgam/$D_2O$/NaOH has been investigated by $^2H$ NMR spectroscopy. The results confirm that sodium amalgam reductions are completely stereospecific with retention at carbon. No rearrangement was observed in the rearrangement prone nortricyclyl–norbornenyl pair (equation 7),[141] although inversion of configuration in the demercuration of the vinylmercurial derived from the acetoxymercuration of diphenylacetylene has been described.[126] Sodium amalgam has also been used for reducing the amidomercurial derived from methyl undecylenate.[203]

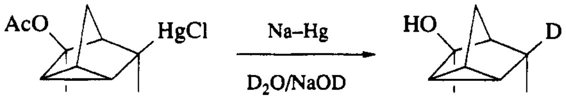

(7)

The overall replacement of mercury by hydrogen can be achieved by metal/mercury exchange, *e.g.* Li/Hg in an aprotic medium[195] and then hydrolysis, or Zn/Hg in acetic acid.[126] The dilithioalkene (**30**) prepared by Li/Hg exchange[195] can be obtained free of lithium amalgam if the bromomercury compound (**29**) is used, and not allowed to react with lithium powder but with *t*-butyllithium in cyclopentane (Scheme 35).

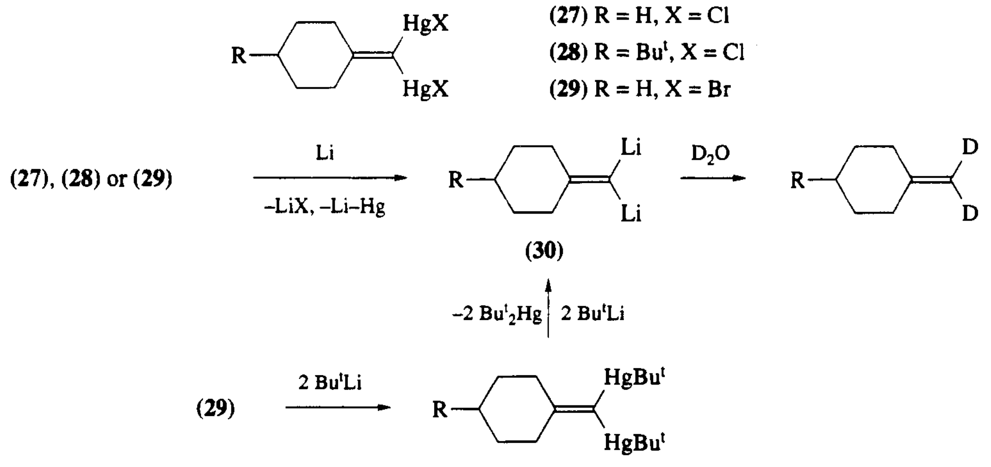

**Scheme 35**

A novel electron transfer free radical mechanism has been elucidated for sodium naphthalenide induced demercuration.[204] A new reductant for the cleavage of the C—Hg bond, *N*-benzyl-1,4-dihydronicotinamide (BNAH), has also been proposed; it reduces alkylmercury(II) acetates *via* an electron transfer chain substitution mechanism.[205]

## 4.3.4 REDUCTION OF PHOSPHORUS–CARBON BONDS

Reduction of the phosphorus–carbon bond is generally achieved with the aim of preparing new phosphorus compounds, and not with the object of preparing reduced carbon compounds. It is a striking difference from mercury–carbon bond cleavage, which is usually carried out in order to prepare carbon compounds.

### 4.3.4.1 Reduction of Tervalent Organophosphorus Compounds

The cleavage of the C—$P^{III}$ bond can be achieved by alkali metals (Li, Na, K), transition metal complexes, organometallics (RLi, Na/naphthalene) and by photolysis.[206]

For instance, it is well established that the P—C bond of tertiary phosphines, having at least one aromatic group, can be cleaved by an alkali metal (Li/THF or $NH_3$, Na or K/dioxan, $NH_3$ or diglyme) to the corresponding phosphide anion, which can then be alkylated with electrophiles to give substituted tertiary phosphines. It can also give the secondary phosphine upon treatment with water or an alcohol.[207] On the basis of reaction rates of various aromatic tertiary phosphines with potassium in dioxan the following cleavage series has been proposed:[208] α-naphthyl > phenyl > *p*-tolyl > 2,5-dimethylphenyl > ethyl > cyclohexyl.

The selective reductive cleavage of the P—C bond between phosphorus and a phenyl group is a slow reaction especially for large scale preparations.[209] Recent findings report that ultrasonic irradiation accelerates the reduction of phenylphosphines with metallic lithium, and provides a clean source of phosphide anions.[210]

Whereas diphosphines $RPhP(CH_2)_nPPhR$ ($n$ = 2–6) have been prepared from the reduction of the corresponding tertiary diphosphines $Ph_2P(CH_2)_nPPh_2$, $CH_2$—P cleavage is observed for $n$ = 1.[211] Sodium naphthalenide has also been used as a selective reagent for the reductive cleavage of one aryl–phosphorus bond in these tertiary diphosphines.[212] Similarly, the synthesis of compounds derived from phospholyl anions relies upon a phosphorus-phenylphosphole bond cleavage by alkali metals or sodium naphthalenide (Scheme 36).[213]

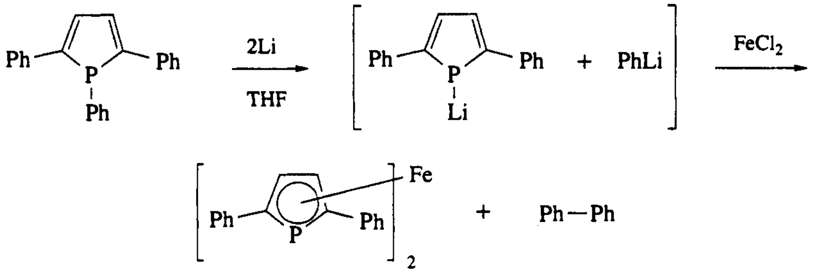

**Scheme 36**

Recently it has become clear that tertiary phosphine–metal complexes are reactive and liable to undergo carbon–phosphorus bond scission. The reaction between the C—$P^{III}$ bond and the transition metal to which the tertiary phosphine is bound has profound implications on homogeneous catalysis, particularly on the mode of homogeneous catalyst deactivation in hydroformylation (Rh- and Co-catalyzed) and various other hydrogenation/dehydrogenation reactions, including asymmetric hydrogenation.[214]

An interesting example, observed by Nishiguchi and coworkers, is the extensive hydrogenolysis of $PPh_3$ coordinated to various transition metals. When $[RuH_2(PPh_3)_4]$, $[RhH(PPh_3)_4]$, $[RuCl_2(PPh_3)_3]$ and $[RhCl(PPh_3)_3]$ were heated at 140 °C for 1 h in pyrrolidine, a solvent which shows the highest hydrogen-donating ability in this reaction, the triphenylphosphine ligands were hydrogenolyzed almost completely to benzene. Radical inhibitors did not retard the reaction and radical initiators did not speed up the reaction, indicating that the hydrogenolysis did not proceed by a radical process.[215]

A plausible mechanism was reported for the catalytic formation of benzene resulting from phosphorus–carbon bond cleavage which occurs during propylene hydroformylation catalyzed by triphenylphosphine-substituted rhodium carbonyls under higher $H_2$ partial pressures (Scheme 37).[216]

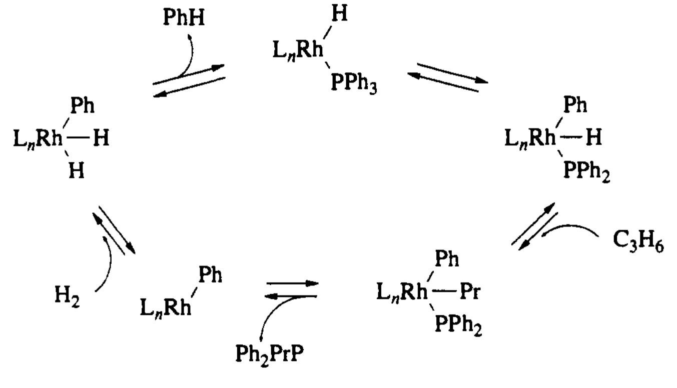

**Scheme 37**

Alkyllithiums also induce C—$P^{III}$ cleavage. In the reaction of (**31**) with MeLi, P—C cleavage occurs to give $Ph_2PMe$ and the corresponding allenyllithium, which is converted into tris(diphenylphosphine)-allene (**32**) upon hydrolysis.[217]

Reactions of the paramagnetic pentacoordinate $[TaBr_3(PhPMe_2)_2]$ adduct with methyl- or butyllithium (or with the proton sponge 1,8-bis(dimethylamino)naphthalene) lead to methyltantalum(IV) derivatives as a result of P—Me bond cleavage. The cleavage of the P—Me bond rather than the phosphorus–aryl bond is unprecedented.[218]

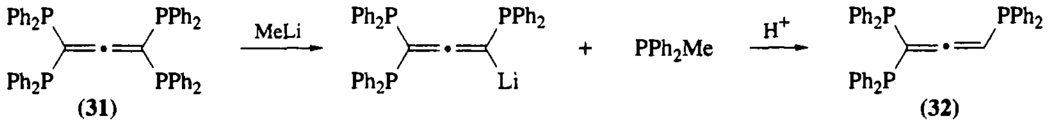

(31) (32)

### 4.3.4.2 Reduction of Tetravalent Organophosphorus Compounds

The procedures to break the C—$P^{IV}$ bond are rather limited. The main methods are alkaline hydrolysis and LAH reduction of phosphonium salts. Electrochemical reductions can also be used for this purpose.

The alkaline cleavage of quaternary phosphonium salts is a well-documented reaction, which represents one of the most important methods for preparing phosphine oxides. Hydrocarbons are the other products of this reaction (equation 8).[219]

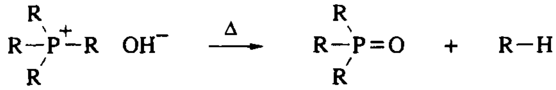

$$R_4P^+\ OH^- \xrightarrow{\Delta} R_3P{=}O + R{-}H \qquad (8)$$

Numerous data[219,220] illustrate a third order rate dependence for this type of reaction, first order with respect to the phosphonium ion concentration and second order with respect to hydroxide ion concentration. The influence of the solvent has been studied.[221] Optically active benzylethylmethylphenylphosphonium hydroxide was shown to decompose stereospecifically with inversion to produce optically active ethylmethylphenylphosphine oxide.[222] On the basis of these findings, the mechanism generally admitted is indicated in Scheme 38.

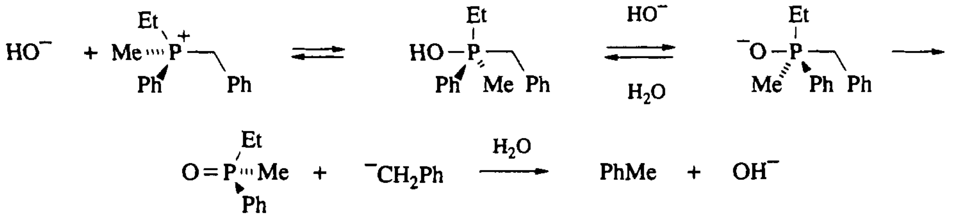

**Scheme 38**

The order of ease of displacement of groups from the phosphonium salts is allyl, benzyl > phenyl > methyl > 2-phenylethyl > ethyl, higher alkyls.[219] The usefulness of this method for the preparation of various alkyldiphenylphosphine oxides from the available triphenylphosphine is particularly noteworthy. In contrast, the preparative value of this method is diminished in cases where the carbanions corresponding to the leaving groups on the phosphorus have approximately the same stability. In some cases the reaction is used to prepare the carbon compound (equations 9 to 14).[223]

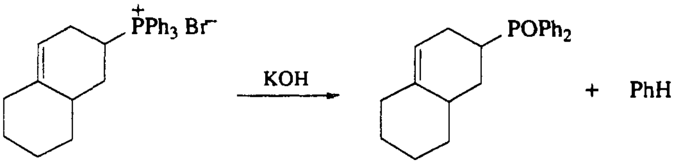

(ref. 223a) (9)

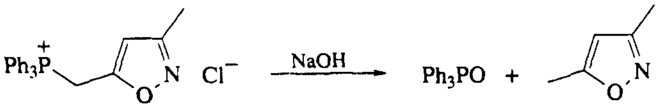

(ref. 223b) (10)

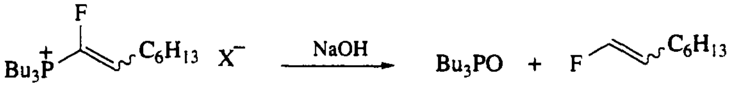

(ref. 223c) (11)

(Z):(E) = 6:94 (Z):(E) = 100:1

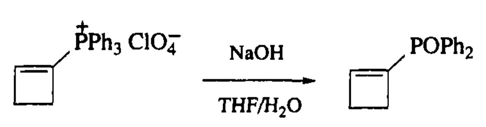
$\overset{+}{P}Ph_3$ $ClO_4^-$
NaOH
THF/$H_2O$
$POPh_2$
+ PhH

(ref. 223d) (12)

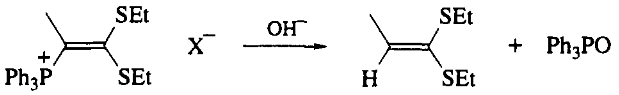
SEt
$Ph_3\overset{+}{P}$
SEt
$X^-$
$OH^-$
SEt
H
SEt
+ $Ph_3PO$

(ref. 223e) (13)

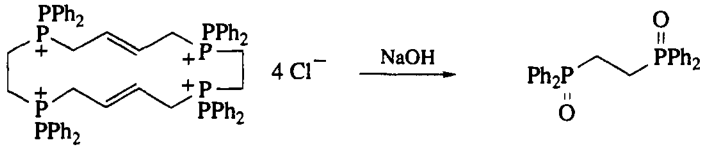
$PPh_2$
$PPh_2$
$PPh_2$
$PPh_2$
4 $Cl^-$
NaOH
$Ph_2P$
O
O
$PPh_2$

(ref. 223f) (14)

For cyclic derivatives, ring size is an important factor in reaction rate and stereospecificity.[224] Alkali hydroxide induced decompositions of chiral $[R^1R^2R^3R^4P]^+OH^-$ have also been found to occur with retention, inversion or racemization, depending both on the nature of $R^n$ and on the reaction conditions.[225]

Interesting effects on the rate and the regioselectivity of the alkaline cleavage of quaternary phosphonium salts are observed when an *o*- or *p*-methoxy- or *o*- or *p*-dimethylamino-phenyl group is present in the molecule. For example, phosphonium bromide (**33**) undergoes alkaline cleavage in 1:1 dioxane–water to give *N*,*N*-dimethylaniline (96.5 %), benzene (3.5 %) and benzyldiphenylphosphine oxide (96 %) $10^3$ times more rapidly at 38 °C than phosphonium bromide (**34**), which gives only toluene as the hydrocarbon product (Scheme 39).[226]

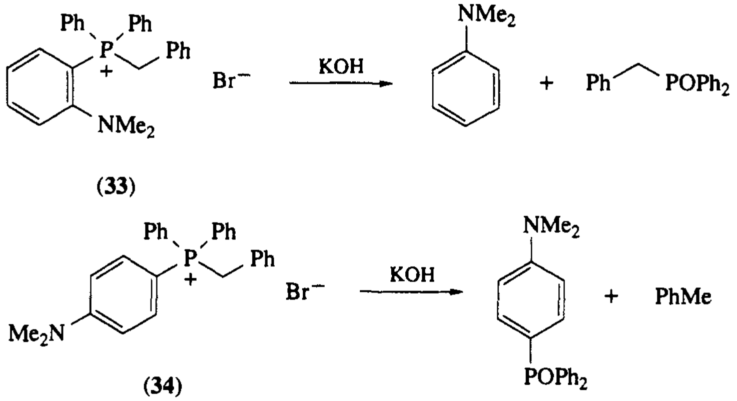
Ph
Ph
P
Ph
$Br^-$
$NMe_2$
KOH
$NMe_2$
+
Ph
$POPh_2$
(33)
Ph
Ph
P
Ph
$Me_2N$
$Br^-$
KOH
$NMe_2$
+ PhMe
$POPh_2$
(34)

**Scheme 39**

In the base hydrolysis of the unsymmetrical fluoromethylene bisphosphonium salt (**35**) the regioselectivity of C—P bond cleavage can be accounted for by the susceptibility of the phosphonium center to nucleophilic attack by hydroxide ion and not by the relative stability of the newly formed fluoromethylene ylide (Scheme 40).[227]

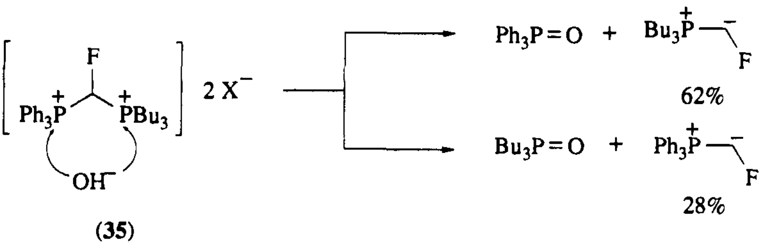
F
$Ph_3\overset{+}{P}$
$\overset{+}{P}Bu_3$
$OH^-$
2 $X^-$
(35)
$Ph_3P{=}O$ + $Bu_3\overset{+}{P}$
F
62%
$Bu_3P{=}O$ + $Ph_3\overset{+}{P}$
F
28%

**Scheme 40**

In some cases, decomposition of phosphonium salts which have a phenyl group or a negative substituent Z in a β-position to the phosphorus atom can occur *via* elimination reactions. According to the nature of Z, tertiary phosphines (Z = Ph, CN; equation 15)[219] or vinylphosphonium salts (Z = OPh, OAc, OH, Br; equation 16) are obtained. In the latter case, the vinylphosphonium salts cannot be isolated from the aqueous medium because they add water very easily, but trapping with methanol reveals their presence.[228]

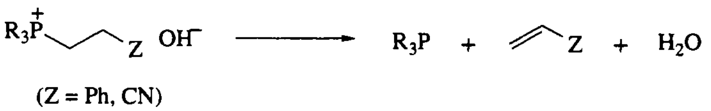

(15)

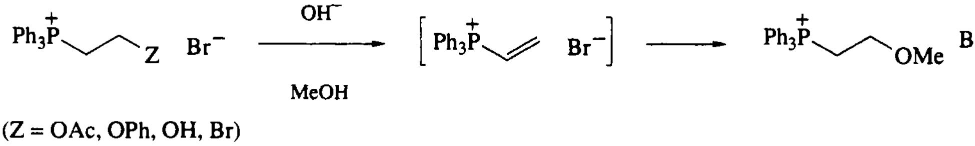

(16)

Ureidomethylphosphonium salts, which contain a hydrogen substituent on N-1, follow a β-elimination pathway similar to the one indicated in equation (15) giving the tertiary phosphine, but if the N-1 position is blocked by a methyl group the reaction follows the *S*NP pathway giving the tertiary phosphine oxide (Scheme 41).[229]

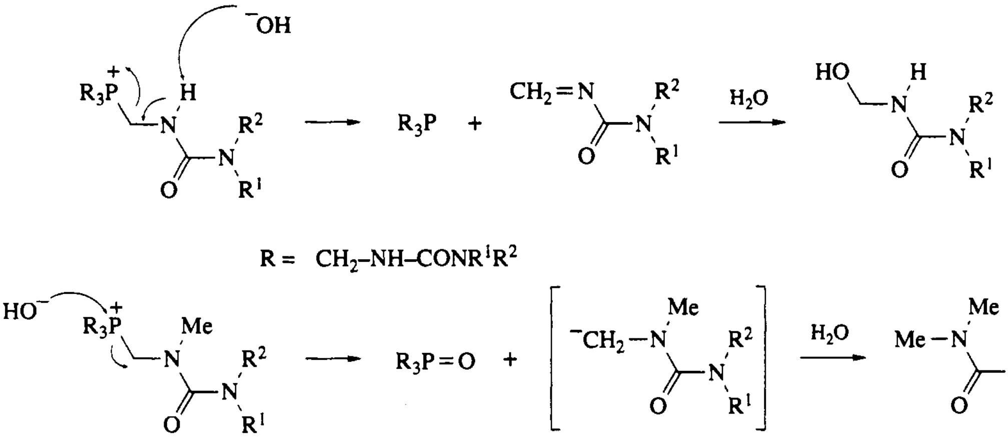

**Scheme 41**

Certain vinylphosphonium salts substituted by an electron-withdrawing group ($Z = CH{=}CH_2$, Ph, PhCO, RCO) react with aqueous bases to give phosphine oxides resulting from an anionotropic migration of a phenyl group from phosphorus to the α-carbon (*S*NPmig) (Scheme 42).[230]

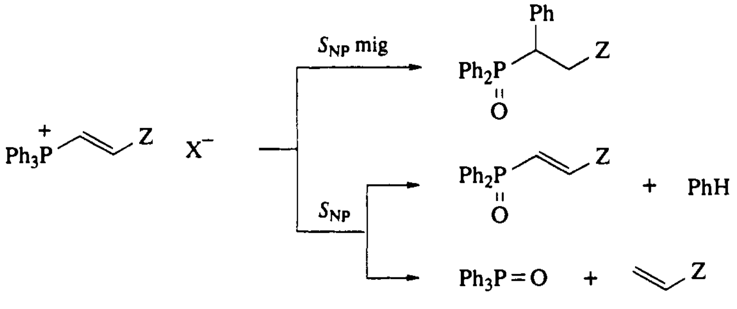

**Scheme 42**

Basic hydrolysis of phosphonium salts has been studied in phase transfer conditions. The results indicate that a heterogeneous medium ($H_2O/CH_2Cl_2$) speeds up the hydrolysis (up to 83 % yield after 15 h at 20 °C in $CH_2Cl_2/H_2O$, 2% yield without $CH_2Cl_2$). As a consequence the degradation of phosphonium salts in basic heterogeneous media has to be taken into account when using these reagents as phase transfer catalysts.[231] Micellar effects on competitive hydrolysis and hydration of vinylphosphonium salts also have been observed.[232]

Lithium aluminum hydride is the second method which is used to cleave the C—$P^{IV}$ bond. The mechanism of attack at phosphorus by hydride is similar to the attack of hydroxide ion, with subsequent or simultaneous expulsion of the group which gives the most stable anion. Thus the preferential removal of benzyl groups, one at a time, is observed. 1,2-Vinylene- and 1,4-butadienylene-bis(phosphonium) salts react with LAH to give selective cleavage of the unsaturated bridge between the two phosphorus atoms.[233] Cyclic phosphonium salts with a benzyl group attached to the phosphorus are cleaved in good yield to the corresponding cyclic phosphines by use of LAH.[234] Cleavage with total $S_N2'$ attack occurs with allylic phosphonium salts. Of particular interest is the fact that a triphenylphosphonium salt with a γ-position extremely crowded gives exclusively the γ-hydrogenolysis product (Scheme 43).[235]

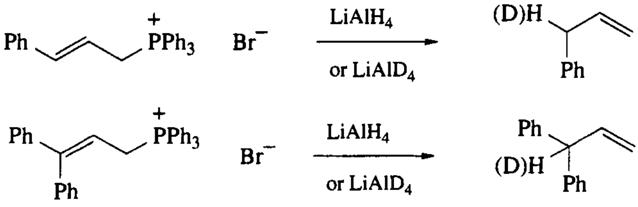

**Scheme 43**

Metals such as Na or alkali metal amalgams can also be used in the cleavage of the C—$P^{IV}$ bond.[236] In the latter case, reductive cleavage of achiral and optically active quaternary phosphonium salts succeeds in high yields with retention of configuration.[237]

### 4.3.4.3 Reduction of Pentavalent Organophosphorus Compounds

This short review is limited to the reduction of pentavalent organophosphorus compounds with coordination number four.

Various methods or reagents have been used in the last decade to reduce a C—$P^V$ bond into a C—H bond and the following methods are reported: alkaline hydrolysis, nucleophile-induced cleavage by alcoholates, metal hydrides and metal naphthalenides, metals, thermolysis and photolysis.

Alkaline hydrolysis of ylides is a general method which achieves the C—P/C—H exchange. Protonation of ylides affords a phosphonium hydroxide, which can react with a second $OH^-$ ion and then decompose into hydrocarbon and phosphine oxide. Among the four ligands of the ylide, the ligand that is the most electronegative or the best stabilized as an anion is the best leaving group (equation 17).[238]

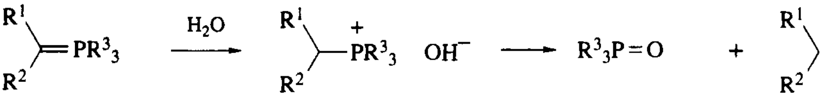

(17)

Reductions of certain (acylalkylidene)phosphoranes with Zn–HOAc and conversion of (acylalkoxycarbonylmethylene)phosphoranes to β-keto esters by a thermolysis route have been reported, but gave poor results with (acylethoxycarbonylmethylene)phosphoranes. The desired reductive removal of triphenylphosphine may be achieved in this case with excess Al–Hg in wet THF, with periodic addition of acids (equation 18).[239]

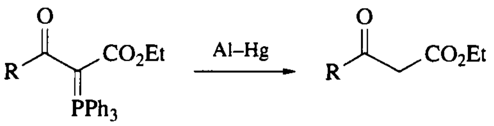

(18)

Hydrolysis of alkyl-substituted phosphine oxides is generally difficult, heating with solid sodium or potassium hydroxide is needed in order to break the P—C bond. Hydrolysis of phosphonates and phosphinates occurs with P—O cleavage in preference to P—C cleavage. Exceptions have been reported with several aromatic phosphine oxides containing *p*- and *o*-nitrobenzyl groups and other stabilized systems.[240] Perfluorinated phosphine oxides can also be hydrolyzed to the phosphinic and phosphonic acids.[241]

In a dibenzophosphepin, the degree of exocyclic *versus* endocyclic C—P bond rupture of (**36**) can be correlated with the relative apicophilicity of the nucleophile. Assuming a trigonal bipyramidal intermediate or transition state in these reactions, relatively highly apicophilic nucleophiles (such as H$^-$) give ring cleavage, whereas poorly apicophilic nucleophiles (such as OH$^-$) lead to exocyclic C—P bond rupture (Scheme 44).[242]

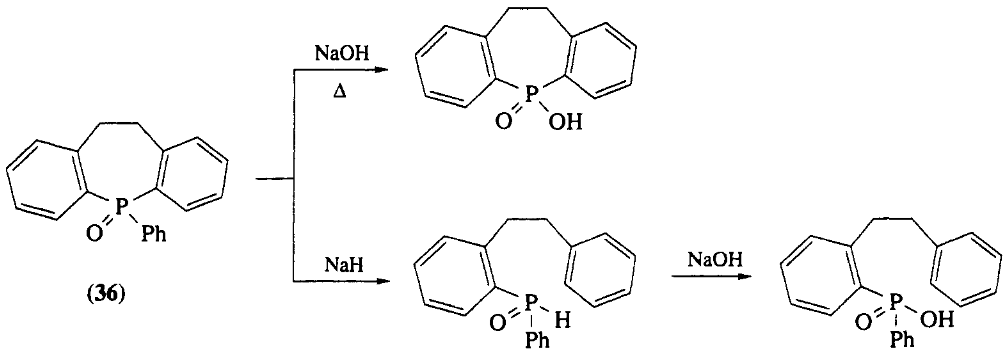

**Scheme 44**

Rearrangement can occur during this type of reaction: the *N*-*t*-butyl-α-chlorophosphonoamidates (**37a**) and (**37b**) react with methanolic benzyltrimethylammonium methoxide to give, respectively, the products (**38**; R = Me) and (**39**; R = Ph) (Scheme 45).[243]

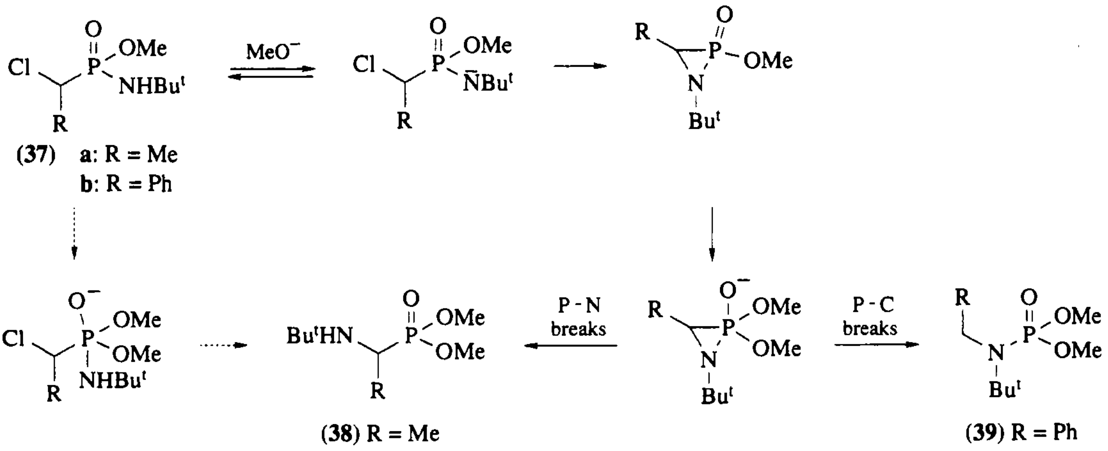

**Scheme 45**

Allylphosphine oxides may be used to make allyl alcohols by the reductive removal of the $Ph_2PO$ group with LAH. The reaction involves transposition of the double bond (equation 19).[235,244] Li(Bu$^t$O)$_3$AlH breaks selectively the C—P phosphonate bond, and this reagent is chemoselective and can

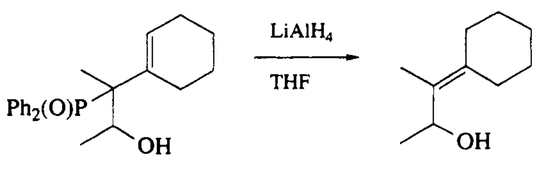

(19)

be used in the presence of keto or ester carbonyl groups. Reduction of the same types of compounds with $NaBH_4$/EtOH gives the β-hydroxyphosphonates and does not cleave the C—P bond (equation 20).[245]

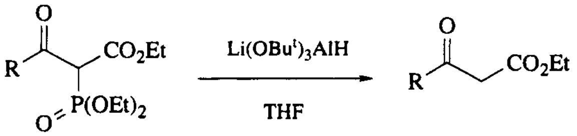

(20)

The use of the 1-naphthylmethyl moiety as a P—H protecting group in the synthesis of a phosphino macrocycle has been described; the protecting group is removed from the phosphine sulfide by treatment with excess potassium naphthalenide (equation 21).[246]

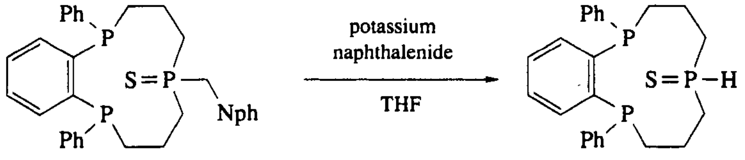

(21)

Nph = naphthyl

Thermolysis is a method that can sometimes be used to cleave the C—$P^V$ bond, particularly in phosphole chemistry. For instance, an optimized phosphole–phosphorin conversion procedure has been described for preparing the first known 2-(2′-pyridyl)phosphorin from 1-phenyl-3,4-dimethylphosphole.[247] The nickel is not only used as a desulfurizing reagent but also as a catalyst for the cleavage of the phosphorus–phenyl bond.[248] Photolysis has also been reported for C—$P^V$ bond cleavage. Thus *p*-nitrophenylmethylphosphonic acid undergoes easy photochemical P—C bond cleavage in alkaline ethanol solution resulting in *p*-nitrotoluene, orthophosphate and ethyl phosphate.[249]

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231. H. J. Cristau, A. Long and H. Christol, *Tetrahedron Lett.*, 1979, 349.
232. D. A. Jaeger and D. Bolikal, *J. Org. Chem.*, 1986, **51**, 1350.
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235. T. Hirabe, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, 1984, **49**, 4084.
236. H. J. Meeuwissen, Th. A. Van der Knaap and F. Bickelhaupt, *Tetrahedron*, 1983, **39**, 4225.
237. L. Horner and K. Dickerhof, *Phosphorus Sulfur*, 1983, **15**, 213.
238. H. J. Bestmann and R. Zimmermann, in 'Carbon–Carbon Bond Formation', ed. R. L. Augustine, Dekker, New York, 1979, vol. 1, chap. 3.
239. M. P. Cooke, Jr., *J. Org. Chem.*, 1982, **47**, 4963.
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244. R. R. Arndt and S. Warren, *Tetrahedron Lett.*, 1978, 4089.
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# 4.4
# Reduction of Epoxides

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## 4.4.1 INTRODUCTION

Two types of reductions of epoxides, reduction giving alcohols and deoxygenation to alkenes, are dealt with in this chapter, because of their wide applicability in organic synthesis.[1] These reactions provide access to alcohols and to alkenes when combined with appropriate methods for the synthesis of the starting epoxides, but the two-step conversion of alkenes to alcohols *via* epoxides is the more important.

## 4.4.2 REDUCTION OF EPOXIDES TO ALCOHOLS

Three major types of reagents, metal hydrides, dissolving metals and hydrogen, have been used to reduce epoxides to alcohols. To be useful as a synthetic transformation the reductive ring opening of epoxides should be regioselective and compatible with other functional groups existing in the same molecule. In this section the emphasis will be on illustrating such selectivity.

### 4.4.2.1 Metal Hydrides

For more than 40 years LAH (lithium aluminum hydride, $LiAlH_4$)[2,3] has been the most widely employed reagent for reducing epoxides to the corresponding alcohols. Although only 0.25 equiv. of LAH is stoichiometrically necessary, a slight excess of LAH is generally used. Both the reactivity and regioselectivity are highly dependent on the substitution pattern of the epoxides. The reduction of the more-substituted epoxides[4] and of cycloalkene oxides in medium-sized rings (from eight to eleven membered)[5] requires higher temperatures and longer reaction times. The yields and product ratio of the reduction of some representative alkyl- and aryl-substituted epoxides with LAH are shown in Table 1. The opening of the epoxy ring generally takes place at the less-substituted carbon.[4] For β-methylstyrene oxide, only the *trans* isomer is reduced primarily by benzylic attack.[7] The *cis* isomer and other aryl-substituted epoxides undergo ring opening predominantly at the carbon away from the phenyl group. The vinyl group in a 1-methyl-1-vinyl-substituted epoxide[8] does not affect the normal regioselectivity that gives the more-substituted alcohol. However, a steroidal diene monoepoxide undergoes conjugate reduction with lithium aluminum deuteride (equation 1).[9]

**Table 1** Reduction of Epoxides with $LiAlH_4$

| *Epoxide* | *Yield (%)* | *Products ratio* | *Ref.* |
|---|---|---|---|
| 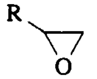 | | 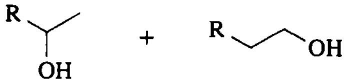 | |
| R = Me | 60 | 100:0 | 6 |
| R = $PhCH_2$ | 84 | 100:0 | 4 |
| R = Ph | 82 | 95:5 | 6 |
| 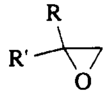 | | 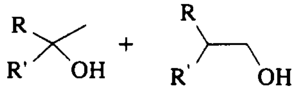 | |
| R = R' = Me | 26 | 95:5 | 6 |
| R = R' = Ph | 97 | 96:4 | 4 |
| R = $CH_2$=CH, R' = Me | 48 | 100:0 | 8 |
| 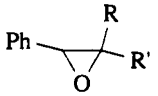 | | 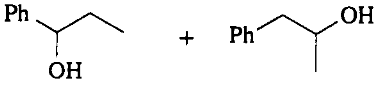 | |
| R = H, R' = Me | | 10:90 | 7 |
| R = Me, R' = H | | 96:4 | 7 |
| 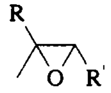 | | 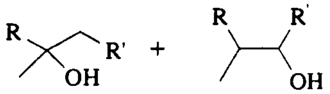 | |
| R = R' = Me | 25 | 100:0 | 4 |
| R = Me, R' = $Bu^t$ | 21 | 0:100 | 10 |
| R = Ph, R' = Me | | 99:1 | 7 |
| 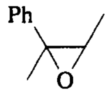 | | 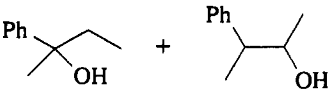 | |
| | | 100:0 | 7 |

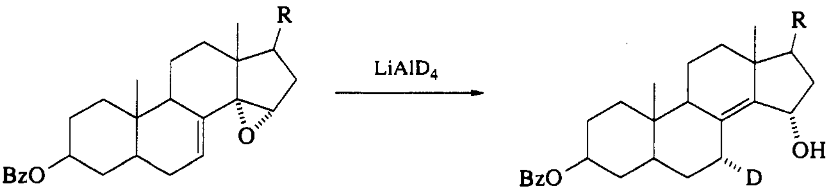

(1)

The reduction of cyclohexene oxides having substituents at various positions has been studied both because of synthetic and mechanistic interest.[11–18] As for alkyl-substituted epoxides, the regioselectivity of ring opening of cyclohexene oxides depends on the substitution pattern. In some cases[9–12] inversion of configuration of the hydroxy group appears to have taken place in the minor products. Some results with rather good regioselectivity are shown in equations (2)–(4).

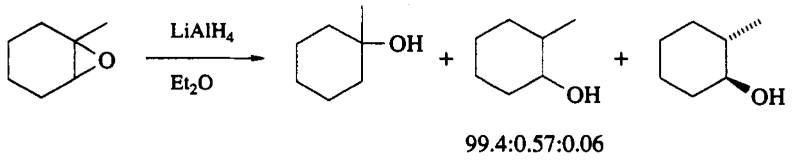
LiAlH4
Et2O
O
OH
99.4:0.57:0.06

(2)

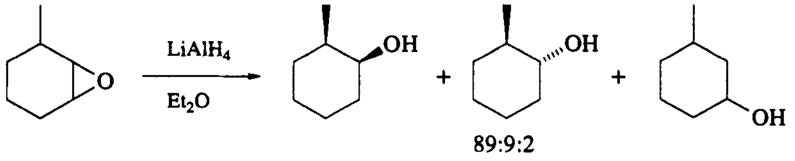
LiAlH4
Et2O
O
OH
89:9:2

(3)

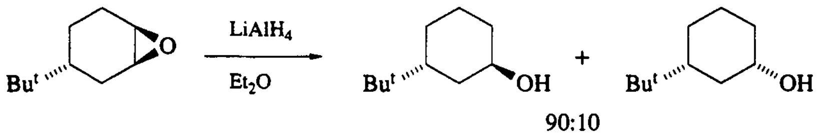
LiAlH4
Et2O
O
Bu^t
OH
90:10

(4)

In contrast to the low selectivity for a simple β-hydroxycyclohexene oxide (equation 5),[15] high regioselectivities are observed for similar steroidal epoxides (equations 6 and 7).[16,17]

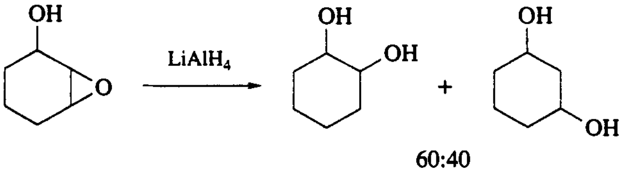
OH
O
LiAlH4
60:40

(5)

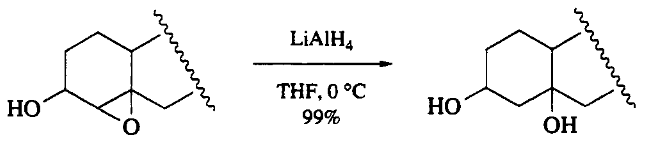
HO
O
LiAlH4
THF, 0 °C
99%
OH

(6)

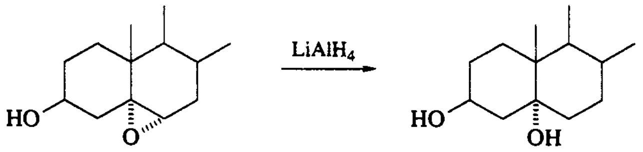
HO
O
LiAlH4
OH

(7)

A dramatic reverse in selectivity was observed for 2-substituted cyclohexene oxide by simply changing the *t*-butyl group to a TMS or trimethylgermyl group,[14] as depicted in equation (8). Regiocontrol by the TMS group is further demonstrated in the corresponding cyclopentene and cycloheptene oxides.[19]

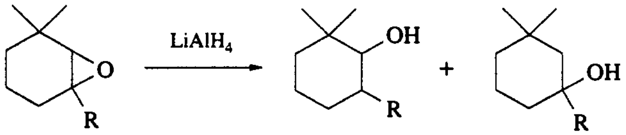
O
R
LiAlH4
OH

(8)

| | |
|---|---|
| R = $CMe_3$ | 0:100 |
| R = $SiMe_3$ | 99:1 |
| R = $GeMe_3$ | 96:4 |

However, this substituent effect does not apply to 3-substituted cyclohexene oxides,[15] where a mixture of isomers is obtained both for the *t*-butyl- and TMS-substituted epoxides (equation 9).[20]

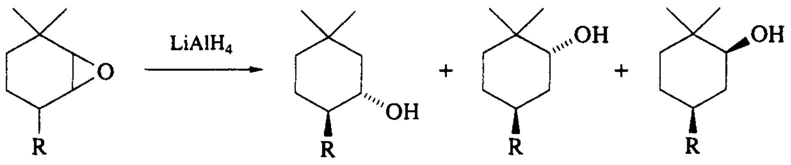
LiAlH4
O
OH
OH
OH
R
R
R
R

(9)

R = CMe$_3$ 1:82:17
R = SiMe$_3$ 0:83:17

For epoxy-protected ketones, highly regioselective ring opening leading to β-keto alcohols was attained (equation 10).[21] In the reduction of a diepoxide, 1,4-diol derivatives were predominantly obtained (equation 11).[22]

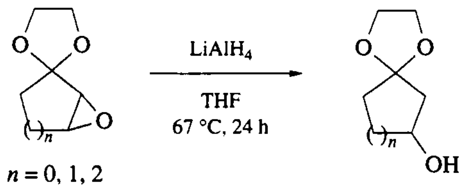
O
O
O
n
n = 0, 1, 2
LiAlH4
THF
67 °C, 24 h
O
O
n
OH

(10)

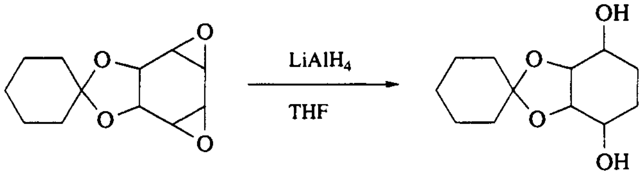
O
O
O
O
LiAlH4
THF
OH
O
O
OH

(11)

Reductions with LAH are frequently applied to natural product synthesis to yield the more-substituted alcohols. Some recent examples are given in equations (12) and (13).[23,24] In the nucleoside synthesis,[23] the adenosine group can tolerate the reduction conditions.

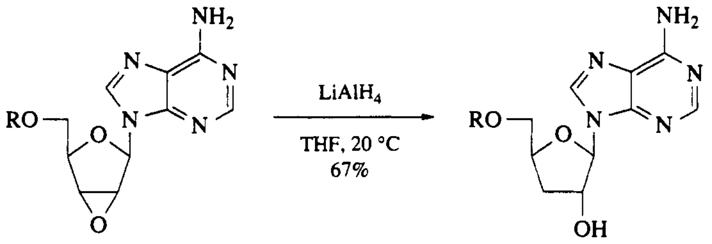
NH2
N
N
N
N
RO
O
O
LiAlH4
THF, 20 °C
67%
NH2
N
N
N
N
RO
O
OH

(12)

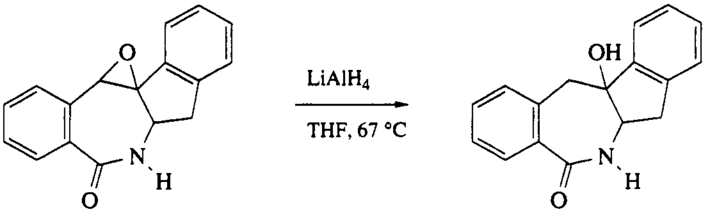
O
N
H
O
LiAlH4
THF, 67 °C
OH
N
H
O

(13)

Sodium borohydride (NaBH$_4$), a relatively mild reducing agent, reduces epoxides only sluggishly[25,26] except for nitro epoxides.[27] In the mixed solvent *t*-butyl alcohol and methanol, sodium borohydride can reduce aryl-substituted epoxides, terminal epoxides and cyclohexene oxide, to the corresponding alcohols.[25,28] The regiochemistry of this reaction is nearly the same as that with LAH. For example the reduction of styrene oxide with potassium borohydride gives only the α-phenethyl alcohol, although the yield is low (equation 14).

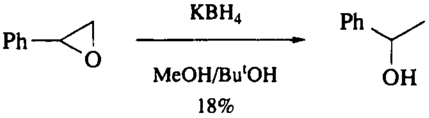

(14)

Because of the low reactivity of sodium borohydride, functional groups such as carbamonyl, carbonyl, nitro and cyano groups, which are generally reduced with LAH, can tolerate the reaction conditions.[28] For example, it has been used for the selective reduction of an epoxy group in an ω-cyano epoxide (equation 15).[29]

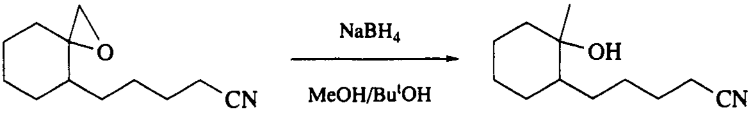

(15)

2-Phenylpropene oxide is selectively reduced in the presence of *trans*-stilbene oxide even with an excess amount of sodium borohydride (equation 16),[28] and a similar system using lithium borohydride ($LiBH_4$) also shows selective reduction of a styrene oxide in the presence of a benzamide.[30]

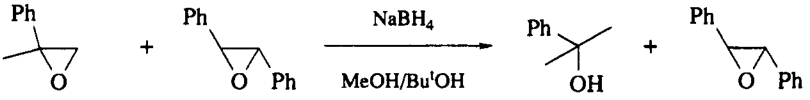

(16)

The effect of additives and of modified aluminum and borohydrides has been extensively examined in efforts to enhance reactivity and improve selectivity. The system of LAH and aluminum chloride was early applied to achieving opposite regioselectivity.[5] For example, the reduction of styrene oxide with this system takes place at the benzylic position to give β-phenethyl alcohol as the major product,[5] and the same effect is observed with 1,4-dialkylcyclohexene oxide (equation 17).[14]

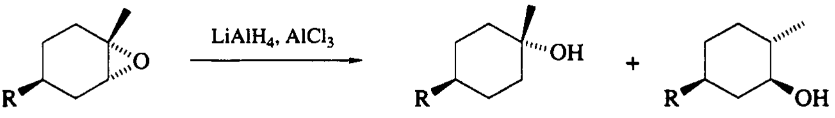

(17)

| | |
|---|---|
| R = Me | 6.5:93.5 |
| R = Bu$^t$ | 2.3:97.7 |

In addition to reversing the regiocontrol, the addition of aluminum chloride also enhances the reactivity of LAH towards tetrasubstituted epoxides, as shown in Table 2. The regioselectivity in the case of unsymmetrically substituted epoxides is not always high.[31,32] Moreover, this enhanced reactivity enables cycloalkene oxides in medium-sized rings to be reduced to the corresponding alcohols smoothly,[33] although a 3:1 ratio of LAH to aluminum chloride is essential for this reaction. Higher proportions of the latter give rise to by-products, whereas lower proportions decrease the reactivity. This system appears to be economically advantageous compared with the reductions using lithium triethylborohydride ($LiBHEt_3$) to be described later.

Another modified metal hydride, lithium triethylborohydride,[34] the so-called 'superhydride', has been introduced as a powerful reducing agent especially suitable for trisubstituted, tetrasubstituted and bicyclic epoxides (Table 3). With trisubstituted epoxides the regiochemistry is completely controlled to give only tertiary alcohols. No skeletal rearrangement is observed for benzonorbornadiene oxide.

Furthermore, 'superhydride' is used as an alternative to LAH in the reduction of carbohydrate epoxides (equation 18).[35] In this example, the C—O bond away from the hydroxy group is selectively cleaved, but a tosyloxy group is also reduced in epoxides having a hydroxy group protected with tosyl. A kinetic study of reductions with 'superhydride' has been reported.[36]

Although diborane $(BH_3)_2$ reduces epoxides, it usually gives a mixture of products in addition to the usual alcohols.[38,39] The reduction of styrene oxide derivatives with diborane has been studied in order to develop a new route to 1,3-diols from epoxides (equation 19).[40] α,β-Unsaturated epoxides[41] undergo

**Table 2** Reduction of Tetrasubstituted Epoxides with $LiAlH_4/AlCl_3$[a]

| *Substrate* | *Reaction time* (h) | *Yield* (%) | *Product(s) ratio* |
|---|---|---|---|
| 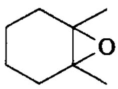 | 4 | 94 | 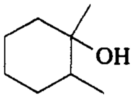 |
| 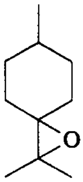 | 8 | 93 | 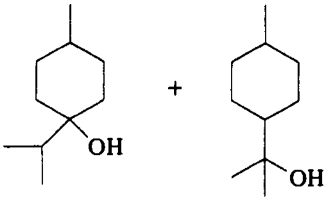<br>75:25 |
| 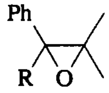 | | | 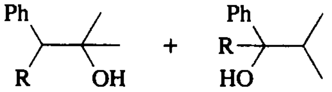 |
| R = Me | 4 | 97 | 8:92 |
| R = Ph | 6 | 96 | 17:83 |

[a] Ref. 32.

**Table 3** Reduction of Epoxides with $LiEt_3BH$[a]

| *Epoxide* | *Time* | *Temperature* (°C) | *Yield* (%) | *Product* |
|---|---|---|---|---|
| 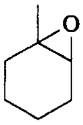 | 5 min | 25 | 99 | 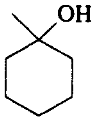 |
| 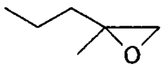 | 5 min | 25 | 100 | 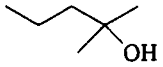 |
| 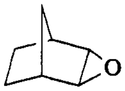 | 3–6 h | 65 | 100 | 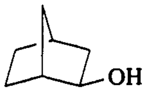 |
| 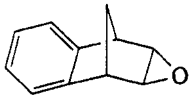 | 24 h | 65 | 100 | 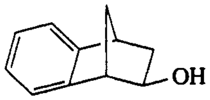 |

[a] Ref. 34.

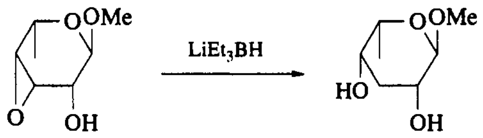

(18)

conjugate reduction with diborane to give (*Z*)-allylic alcohols selectively (equation 20), and the selectivity of this reaction does not appear to depend on the substitution pattern of the epoxides.

The reverse selectivity has been described with diborane/boron trifluoride,[38] sodium borohydride/diborane,[42] sodium borohydride/trichlorotrispyridine–rhodium,[43] lithium 9,9-di-*n*-butyl-9-borabicyclo[3.3.1]nonanate (for structure, see Table 4),[44] sodium cyanoborohydride/boron trifluoride,[45] and

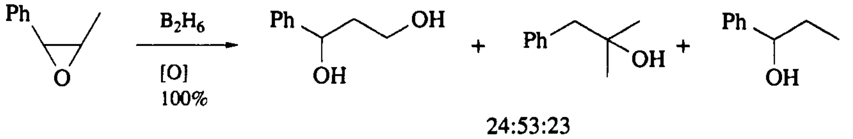

(19)

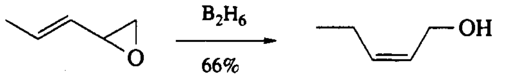

(20)

diborane/morpholine.[46] Representative results are summarized in Table 4. Although the regioselective ring opening of aryl-substituted epoxides leading to the less-substituted alcohol can be achieved by some reagents, only the sodium cyanoborohydride/boron trifluoride system is highly efficient for the conversion of monosubstituted epoxides to primary alcohols.

**Table 4** Regiochemistry of Ring Opening of Epoxides with Borohydride Derivatives

| *Epoxide* | *Reagent* [a] | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|
| 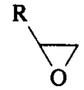 | | | 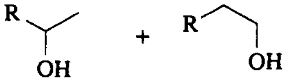 | |
| R = Et | A | 95 | 100:0 | 42 |
| R = n-$C_8H_{17}$ | B | 100 | 93:7 | 44 |
| R = $C_{10}H_{21}$ | C | 83 | 11:89 | 45 |
| R = Ph | D | 98 | 100:0 | 37 |
| | B | 100 | 1:99 | 44 |
| | C | 79 | 3:97 | 45 |
| | E | 100 | 100:0 | 46 |
| 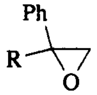 | | | 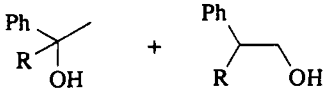 | |
| R = Me | D | 100 | 0:100 | 37 |
| | B | 86 | 2:98 | 44 |
| | C | 94 | 1:99 | 45 |
| R = Ph | D | 95 | 0:100 | 37 |
| | B | 94 | 17:83 | 44 |
| 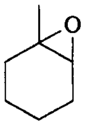 | | | 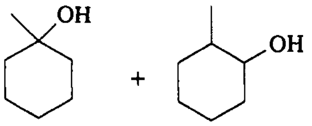 | |
| | A | 100 | 26:74 | 42 |
| | C | 87 | 3:97 | 45 |
| | E | 94 | 11:89 | 46 |

[a] A, $NaBH_4/B_2H_6$; B, lithium 9,9-di-*n*-butyl-9-nonabicyclo[3.3.1]nonane, see below; C, $NaBH_3CN/BF_3$; D, $NaBH_4/BF_3$; E, $NaBH_4$/morpholine, (BuNO)/$BF_3$.

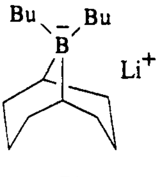

(B)

The reduction of carbohydrate epoxides has also been examined with the sodium borohydride/diborane system.[47] As shown in Table 5, the corresponding alcohols are obtained in good yields, although the regiochemistry of ring opening appears to be much affected by steric and polar factors. It should be noted that arylsulfonyloxy and ketal groups remain intact, whereas they are reduced by LAH.

**Table 5** Reduction of Carbohydrate Epoxides with $NaBH_4/BH_3$[a]

| *Epoxide* | *Yield (%)* | *Product ratio* |
|---|---|---|
| 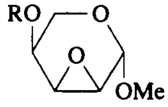 | 80[b] | 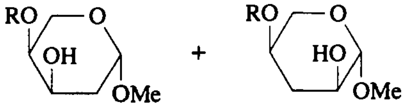<br>94:6 |
| 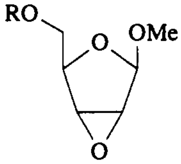 | 40 | 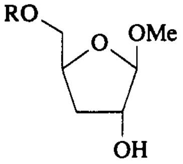 |
| 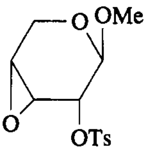 | 90 | 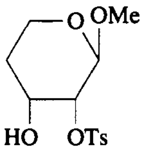 |

[a] Ref. 47. [b] $p$-$ClC_6H_4SO_2$, $p$-$MeC_6H_4SO_2$.

The system of sodium hydride, sodium alkoxide and metal salts developed by Caubère and his coworkers can selectively reduce epoxides to alcohols (Table 6).[48] The regiochemistry of ring opening is con-

**Table 6** Reduction of Epoxides with $NaH/C_5H_{11}ONa/MX_n$[a]

| *Epoxide* | *M in $MX_n$* | *Yield (%)* | *Product ratio* |
|---|---|---|---|
| 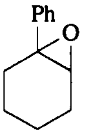 | | | 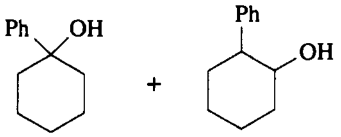 |
| | Zn | 87 | 100:0 |
| | Ni | 95 | 10:90 |
| 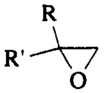 | | | 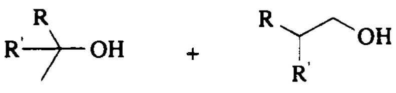 |
| R = $C_6H_{13}$, R' = H | Zn | 99 | 100:0 |
| | Ni | 99 | 30:70 |
| R = Ph, R' = H | Zn | 96 | 100:0 |
| | Ni | 96 | 0:100 |
| R = Ph, R' = Me | Zn | 95 | 100:0 |
| | Ni | 93 | 0:100 |
| 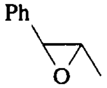 | | | 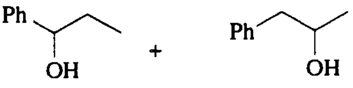 |
| | Zn | 95 | 100:0 |
| | Ni | 95 | 35:65 |

[a] Ref. 48.

trolled using either the Zn or the Ni salt. Thus, with zinc chloride, styrene oxide is converted to α-phenethyl alcohol, whereas the use of nickel chloride results in the selective formation of β-phenethyl alcohol.

The selective conversion of epoxy alcohols to 1,3-diols has been studied using Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride, $[(MeOCH_2CH_2O)_2AlH_2]Na$) because of the recent dramatic progress in the asymmetric synthesis of epoxy alcohols. Although Red-Al has been used as a reducing agent for epoxides since 1971,[49] attention had not been paid until three groups independently reported the reduction of epoxy alcohols to 1,3-diol derivatives in 1982 (Table 7).[50–52] According to Kishi and his co-worker,[52] the selectivity of the reduction with Red-Al was improved by lowering the temperature to –20 °C. In some cases the use of THF as a solvent is also critical in enhancing the regioselectivity.[53] For phenyl-substituted epoxy alcohols, DME is superior to THF.[54] As an exceptional case a 1,2-dialkyl-1-hydroxymethyl-substituted epoxide undergoes ring opening at the carbon away from the hydroxy group to give a 1,2-diol (equation 21).

**Table 7** Reduction of Epoxy Alcohols

| *Epoxide* | *Reagent* [a] | *Yield (%)* | *Ratio of 1,3- and 1,2-diols* | *Ref.* |
|---|---|---|---|---|
| 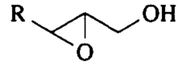 | | | | |
| R = Bu$^n$ | A | 97 | 1:150 | 49 |
| R = *n*-heptyl | B | 90 | 100:1 | 53 |
| | C | 94 | 4:1 | 53 |
| R = *n*-decyl | A | 93 | 1:145 | 54 |
| | B | 95 | 100:1 | 53 |
| | C | 77 | 5:1 | 53 |
| R = $BnOCH_2CH_2$ | B | | 150:1 | 52 |
| | D | | 1:13 | 52 |
| 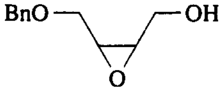 | C | 95 | 100:1 | 51 |
| 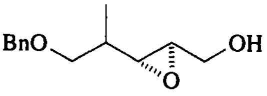 | C | | >20:1 | 52 |
| | D | | 1:8 | 52 |
| 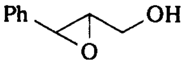 | A | 76 | 1:54 | 53 |
| 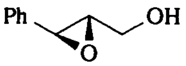 | C | | 22:1 | 54 |
| 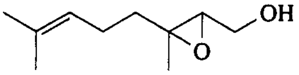 | B | 95 | 100:1 | 53 |
| | C | 96 | 1:6.8 | 55 |
| 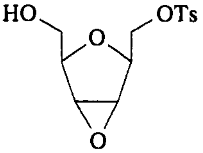 | B | | 12:1 | 50 |

[a] A, $Ti(OPr^i)_4/LiBH_4$; B, Red-Al; C, $LiAlH_4$; D, DIBAL-H.

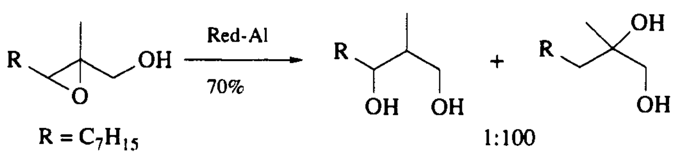

(21)

The reverse regiocontrol, giving 1,2-diols, is observed with DIBAL-H (diisobutylaluminum hydride).[51] The remarkable effect of titanium tetraisopropoxide as an additive to lithium borohydride has also been reported.[55] In this reaction benzene is a better solvent than THF, probably because a Ti complex using both oxygens in epoxy alcohols is formed in benzene before the hydride attack. Other metal hydrides used include sodium hydrogen telluride (NaHTe)[56] and an ate complex derived from DIBAL-H and butyllithium,[57] both of which reduce epoxides to alcohols, although they have been tested with only a small number of examples.[56] In the former case the reaction may proceed *via* a 2-hydroxyalkyltellurol intermediate.

### 4.4.2.2 Dissolving Metals

Lithium and sodium in amine solvents are well known as dissolving metals capable of reducing epoxides to alcohols, but they have not been used as frequently as metal hydrides. In contrast to LAH, lithium in ethylenediamine,[58] and sodium in liquid ammonia[59] reduce bicyclic epoxides within 2 h to give alcohols without rearrangement, as indicated in Table 8. However, the reaction conditions must be rigorously controlled, otherwise the reaction is accompanied by rearrangement, as observed for tricyclic epoxides.[60,61] The reduction of norbornene oxide using lithium and lithium chloride in THF followed by a hydrolytic work-up gives the *exo*-alcohol.[62] Functional groups such as acetyl,[63] carbonyl,[64,65] ethoxycarbonyl[59] and vinyl[63] remain intact under these conditions. The ring opening of epoxides predominantly takes place at the less-substituted carbon[57,58] to give the more-substituted alcohols, except for aryl-substituted epoxides.[58] The epoxy ring in an alkynic epoxide can be reduced selectively upon successive treatment with methyllithium and lithium in ammonia (equation 22).[66]

**Table 8** Reduction of Epoxides with a Dissolving Metal[a]

| *Epoxide* | *Metal* | *Yield (%)* | *Product* | *Ref.* |
|---|---|---|---|---|
| 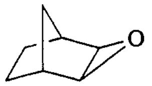 | Li<br>Na<br>Ca | 86<br>82<br>99 | 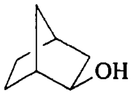 | 58<br>59<br>71 |
| 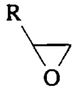 R = Et<br>R = Bu | Li<br>Ca | 82<br>100 | 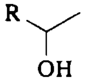 | 58<br>71 |
| 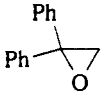 | Na | 89 | 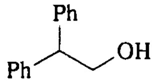 | 59 |
| 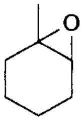 | Li<br>Ca | 93<br>97 | 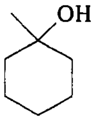 | 58<br>71 |
| 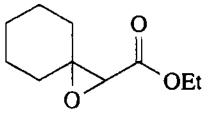 | Na | 46 | 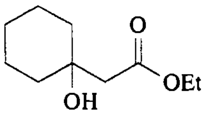 | 59 |
| 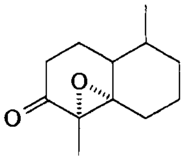 | Li | 53 | 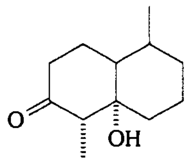 | 64 |

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[a] Ethylenediamine or liquid ammonia was used as a solvent.

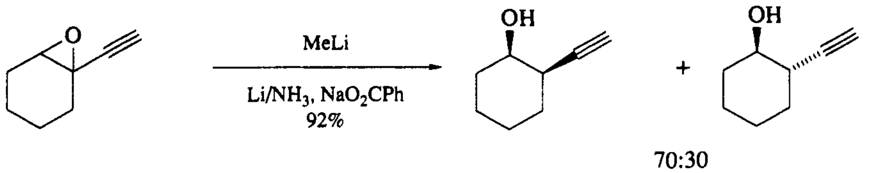

(22)

As dissolving metals, aluminum,[67–70] calcium,[71] and zinc[21,72,73] have also been used. In the case of aluminum, water can be used as a solvent.[68,70] Calcium[71] can reduce epoxides in ethylenediamine in the presence of white sand to give similar results to those for lithium. This reagent is particularly suitable from the economical and safety point of view for large-scale reduction. Noteworthy is the regioselectivity using the zinc/trimethylchlorosilane system followed by a hydrolytic work-up,[21,73] as shown in Table 9. Alkyl-substituted epoxides[73] undergo ring opening predominantly at the more-substituted carbon to yield primary alcohols.

**Table 9** Reduction of Epoxides with Zn/Me$_3$SiCl[a]

| *Epoxide* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|
| 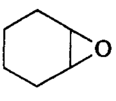 | 98 | 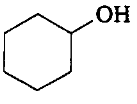 | 73 |
| 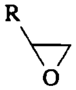<br>R = n-C$_9$H$_{19}$ | 96 | 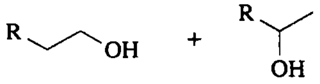<br>69:31 | 73 |
| 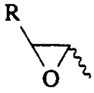<br>R = C$_5$H$_{11}$ | 97 | 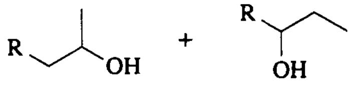<br>66:34 | 73 |
| 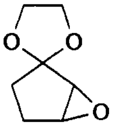 | 97 | 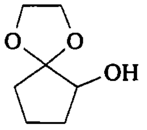 | 21 |
| 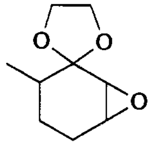 | 93 | 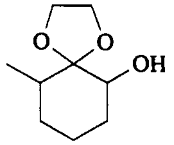 | 21 |

[a] The alcohols were obtained after the hydrolytic work-up.

For epoxy acetals, a complete reverse in regioselectivity is attained with the zinc/trimethylchlorosilane system as compared with LAH (equation 10).[21]

### 4.4.2.3 Hydrogenolysis

Hydrogenolysis of epoxides to yield alcohols has been much reported in the patent literature, because of its importance as an industrial process, but studies on reactivity and selectivity have not been done systematically. The selectivity is highly dependent on the substituents, as in the case of reduction using metal hydrides. As a metal catalyst, Raney Ni was intensively examined in the early stage.[74–83] It usually requires high pressures (*ca.* 100 atm) and temperatures (100 °C), as shown in Table 10. Alcohols, benzene, THF and even water have been used as solvents. Accordingly, a hydroxy group in the epoxides remains intact, and hydrocarbons are formed only as by-products. In some cases by-product formation can be suppressed by adding sodium hydroxide or triethylamine. Ring opening of epoxides takes place exclusively at the more-substituted carbon atoms. Other nickel catalysts include nickel borate[80] and nickel–phosphine,[81] which convert terminal epoxides into primary and secondary alcohols in a ratio of more than 85 to 15 (equation 23).

**Table 10** Raney-Nickel Catalyzed Hydrogenolysis of Epoxides

| *Epoxide* | *Conditions* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|
| 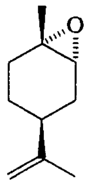 | 80 °C, 120 atm | 100 | 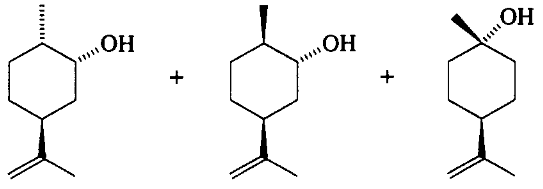<br>16:81:3 | 72 |
| 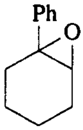 | | | 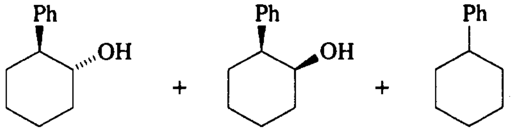 | |
| | 25 °C, 1 atm | 100 | 30:11:59 | 73 |
| | 25 °C, 1 atm, NaOH | 100 | 5:93:2 | 73 |
| 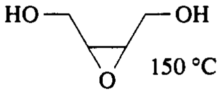 | 150 °C, 200 atm | 88 | 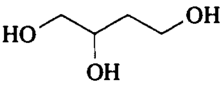 | 76 |
| 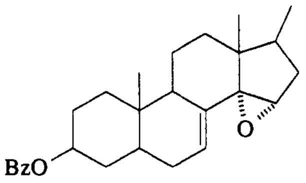<br>R = $C_8H_{17}$ | 24 atm | 85 | 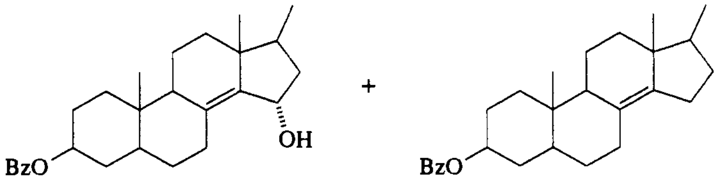<br>46:54 | 78 |
| | 24 atm, $Et_3N$ | 89 | 100:0 | 78 |

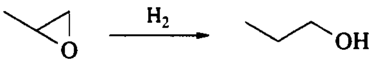
(23)

| | |
|---|---|
| Ni borate, 150 °C, 2 h | 98% |
| Ni–P, 150–190 °C, 3 h | 91% |

Catalysts based on palladium, such as 10% palladium on charcoal,[84,85] have also been used frequently. In these cases ketones derived from isomerization of the epoxides are often obtained as by-products. As shown in Table 11, both product- and regio-selectivities are highly dependent on the configuration of the starting epoxides. Geneste *et al.*[84] suggested that the selectivity may be controlled at the stage of the approach of epoxides to catalyst.

It is noteworthy that the epoxy ring is selectively reduced to a hydroxy group in the nitrosugar epoxides, with regioselectivity controlled by the nitro group (equation 24).[86]

Palladium on barium sulfate has been used in the hydrogenolysis of epoxides in natural product synthesis.[87] The reaction in equation (25) illustrates its high level of functional group compatibility.

A platinum-based catalyst, such as Adams' catalyst, is an alternative to nickel and palladium, and is more active.[88] For example, when the reaction in equation (24) is carried out in the presence of a platinium catalyst, the nitro group is also reduced.[86] The hydrogenolysis of 2-butene oxide and propylene oxide proceeds at a slightly lower temperature than when using nickel,[84] and for propylene oxide the

**Table 11** Pd/C-Catalyzed Hydrogenolysis of Epoxides[a]

| *Epoxide* | *Yield (%)* | *Product ratio* |
|---|---|---|
| 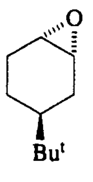 | 100 | 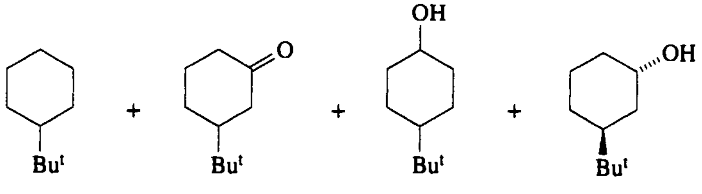<br>2:20:2.5:75.5 |
| 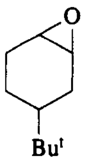 | 98 | 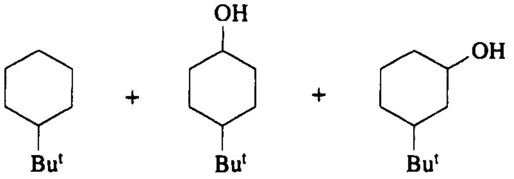<br>18:6:76 |
| 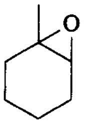 | 100 | 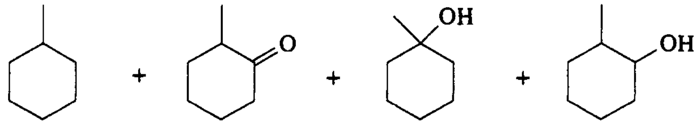<br>5:32.5:19:43.5 |

[a] Ref. 84.

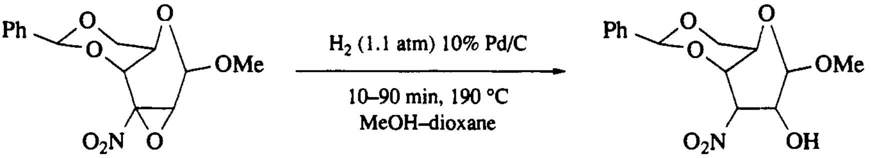

(24)

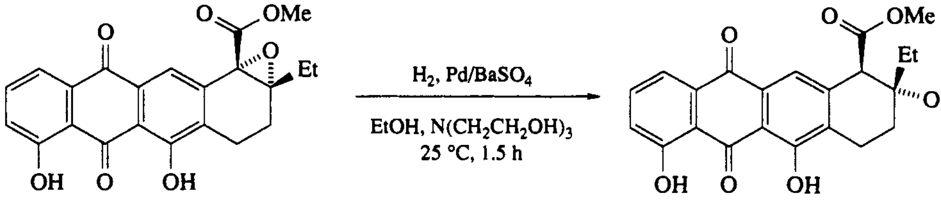

(25)

regioselectivity is reversed with platinium, giving 2-propanol predominantly.[89] Only a few studies on the mechanism of hydrogenolysis have been reported.[90]

### 4.4.2.4 Miscellaneous

Low-valent metal salts, such as chromium(II) acetate[91,92] and samarium iodide,[93–95] have been reported to be useful. With chromium(II) acetate, a steroid epoxy ketone is efficiently converted to a β-hydroxy ketone (equation 26).

Samarium iodide is a reagent capable of highly selective reduction of epoxy ketones and esters to the corresponding alcohols (Table 12). Diene monoepoxides are converted with high regio- and stereo-selectivity to the (*E*)-allylic alcohols, and the reaction can be carried out at –90 °C under neutral conditions. As a result functional groups such as alkoxycarbonyl, carbonyl and cyano survive.

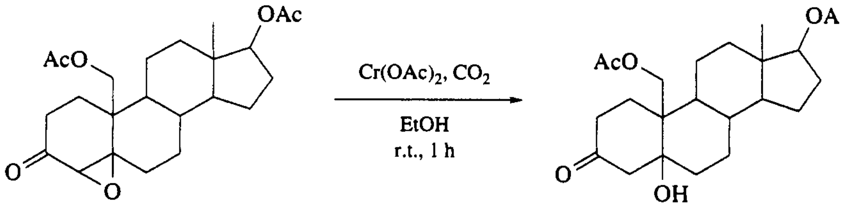

(26)

**Table 12** Reduction of Epoxy Ketones, Esters and Vinyl Epoxides with SmI$_2$

| *Epoxide* | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|
| 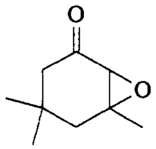 | 82 | 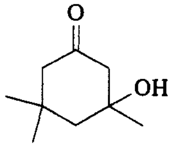 | 93 |
| 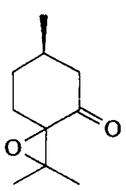 | 79 | 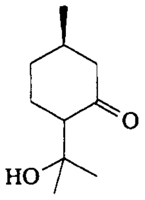 | 93 |
| 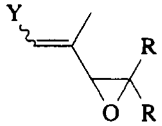<br>Y = CO$_2$Et, R = H<br>Y = CO$_2$Et, R = Me | <br>77<br>75 | 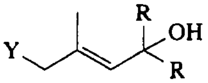 | 94 |
| 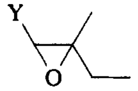<br>Y = CO$_2$Et | 68 | 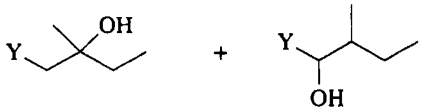<br>>200:1 | 95 |
| 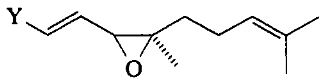<br>Y = COSEt<br>Y = SO$_2$Ph<br>Y = PO(OEt)$_2$<br>Y = H<br>Y = Me<br>Y = SPh | <br>80<br>82<br>84<br>69<br>42<br>54 | 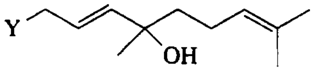 | 94 |

Although electrochemical reduction[96] and enzymic reduction[97] of epoxides to alcohols have been reported, little information is available about their characteristic features.

## 4.4.3 DEOXYGENATION OF EPOXIDES

Deoxygenation of epoxides to alkenes[1,98,99] is occasionally an important process in the synthesis of complex molecules, and a number of reagents for this transformation have been developed. Conventionally, multistep deoxygenation using hydrogen bromide and zinc in acetic acid has been used.[100,101] However, this system is not highly selective. As a result much effort has been devoted to improving the yield and the stereoselectivity of the reaction. In this section various kinds of reagents capable of one-step deoxygenation will be dealt with in the following order: (i) phosphorus reagents; (ii) silicon reagents; (iii) selenium and tellurium reagents; (iv) low-valent metals; (v) metal carbonyls; and (vi) miscellaneous. Two- or multi-step deoxygenation of epoxides to alkenes[98] will be mentioned only briefly in this section since the one-step process is generally superior. Deoxygenation giving a saturated carbon–carbon bond will not be included, because the process is synthetically less important.

### 4.4.3.1 Phosphorus Reagents

In 1955 Wittig *et al.* found that triphenylphosphine could induce the deoxygenation of epoxides at 200 °C.[102] Mechanistically, this process probably involves *anti* opening of the epoxide followed by *syn* elimination of triphenylphosphine oxide from a betaine intermediate. Accordingly, the reaction proceeds with inversion of stereochemistry, which means that *trans*-epoxides give *cis*-alkenes. The systems of bis(dimethylamino)phosphorous acid/butyllithium,[103] and lithium diphenylphosphide[104] have been examined

**Table 13** Deoxygenation of Epoxides with Phosphorus Reagents

| *Epoxide* | *Reagent* [a] | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|
| 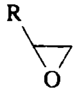 | | | 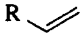 | |
| R = n-$C_{10}H_{21}$ | A | 60 | | 105 |
| R = n-$C_7H_{15}$ | B | 95 | | 106 |
| R = n-$C_{18}H_{37}$ | C | 95 | | 108 |
| R = PhCH=CH | C | 42 | | 106 |
| 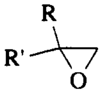 | | | 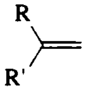 | |
| R =Ph, R' = cyclopropyl | B | 54 | | 106 |
| 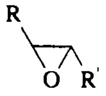 | | | 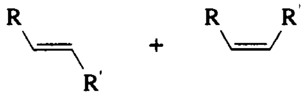 | |
| R = $MeOCO(CH_2)_7$, R' = n-$C_8H_{17}$ | A | 99 | 100:0 | 105 |
| R = $MeCO(CH_2)_3$, R' = n-$C_8H_{17}$ | C | 94 | >98:2 | 108 |
| 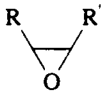 | | | 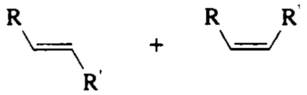 | |
| R = $MeOCO(CH_2)_7$, R' = n-$C_8H_{17}$ | A | 95 | 0:100 | 105 |
| R = $HCO_2(CH_2)_8$, R' = $Bu^n$ | C | 93 | 0:100 | 108 |
| 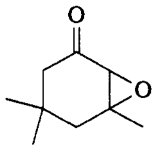 | B | 95 | 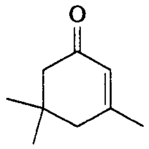 | 106 |
| 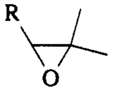 | | | 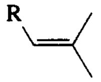 | |
| R = $CH_2CH_2CH(Me)CH_2CH_2OMe$ | A | 99 | | 105 |
| R = $CH_2CH_2CH(Me)CH_2CH_2OCOH$ | C | 98 | | 108 |

[a] A, $(PhO)_3P^+Me\ I^-$; B, $P_2I_4$; C, $Ph_3PHI/Ph_3PI_2$.

at lower temperature. The reaction with both systems proceeds with more than 96% inversion at room temperature, although the yield of the product with $Me_2NP(O)H$/butyllithium is not so high. With $Ph_2PLi$ the alkenes were obtained quantitatively from the corresponding epoxides. However, the reaction is highly affected by the steric circumstance around the epoxides. Furthermore, because $Ph_2PLi$ is a strong base, functional groups sensitive to base have to be protected.

For deoxygenation of epoxides with retention of stereochemistry (*trans*-epoxides giving *trans*-alkenes) methyltriphenoxyphosphonium iodide/boron trifluoride etherate,[106] diphosphorous tetraiodide,[106,107] and triphenylphosphine hydriodide/triphenylphosphine diiodide[108] have been introduced. The reaction with these systems generally proceeds below room temperature in high yield (Table 13). For terminal epoxides a slightly higher temperature (gentle reflux of dichloromethane) is needed. Because of the mild reaction conditions functional groups, such as alkoxycarbonyl and carbonyl groups, remain intact. In all cases the reaction begins with *anti* opening of the epoxides, followed by *anti* elimination, leading overall to retention of configuration. Both *trans*- and *cis*-alkenes have been made from a *trans*-epoxide by using either $Ph_2PLi$ or $Ph_3PI_2$ (equation 27).[109] Trisubstituted steroidal epoxides are converted to the corresponding alkenes with the triphenylphosphine/iodine system.[110]

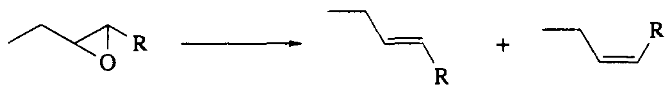

(27)

| | | |
|---|---|---|
| $P_2I_4$ | 80% | >99:<1 |
| $Ph_3PI/MeI$ | 77% | <1:>99 |

### 4.4.3.2 Silicon and Tin Reagents

Trialkylsilyl metals, such as trimethylsilylpotassium,[111] dimethylphenylsilyllithium,[112] and dimethylphenylsilyldiethylaluminum,[113] have been known to induce deoxygenation of epoxides. The reaction with TMSK and $PhMe_2SiLi$ proceeds with inversion of stereochemistry (Table 14) whereas $PhMe_2SiAlEt_2$ shows complete retention in the case of *trans*-stilbene oxide and cinnamyl alcohol epoxide.

**Table 14** Deoxygenation of Epoxides with Silicon and Tin Reagents

| *Epoxide* | *Reagent*[a] | *Yield (%)* | *Product ratio* | *Ref.* |
|---|---|---|---|---|
| 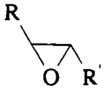 R O R' | | | 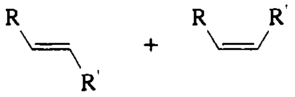 R R' + R R' | |
| $R = R' = Pr^i$ | A | 93 | <1:99 | 111 |
| $R = R' = Ph$ | B | 83 | <1:99 | 112 |
| $R = R' = Bu^n$ | C | 80 | 99:1 | 113 |
| $R = Ph$, $R' = CH_2OPh$ | C | 88 | 99:1 | 113 |
| 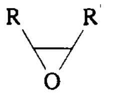 R R' O | | | 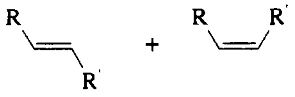 R R' + R R' | |
| $R = R' = Pr^i$ | A | 75 | >92:8 | 111 |
| $R = R' = Ph$ | B | 83 | >99:1 | 112 |
| $R = R' = Bu^n$ | C | 67 | 1:99 | 113 |
| $R = n\text{-}C_6H_{13}$, $R' = CH_2OH$ | C | 65 | 1:99 | 113 |

[a] A, $Me_3SiK$; B, $Me_2PhSiLi$; C, $(Bu^n{}_3SnAlMe_3)^-$ $Li^+$

It should be noted that the ate complex $(PhMe_2SiAlMe_3)Li$ shows selectivity opposite to that of $PhMe_2SiAlEt_2$, deoxygenation proceeding with inversion, as in equation (28). The reaction with a similar ate complex $(Bu^n{}_3SnAlMe_3)Li$, however, proceeds with retention of stereochemistry (Table 14). It is noteworthy that the hydroxy group in allylic alcohol epoxides does not affect the reaction using $(Bu^n{}_3SnAlMe_3)Li$, which probably involves a β-oxytin intermediate.[113]

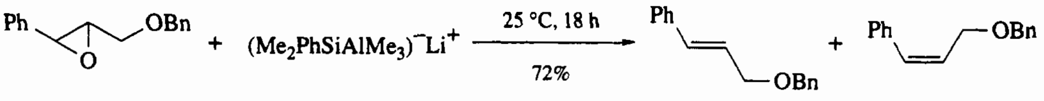

0:100 (28)

### 4.4.3.3 Selenium and Tellurium Reagents

Triphenylphosphine selenide,[114] potassium selenocyanate,[115] 3-methyl-2-selenoxobenzothiazole (**1**),[116] sodium *O,O*-diethyl phosphorotelluronate,[117] *O,O*-dialkylphosphoroselenoic acid salts[118] and benzeneselenocarboxamide,[119] have all been reported as reagents capable of one-step deoxygenation of epoxides.

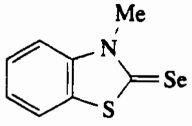

(**1**)

The reaction with (**1**) and $(EtO)_2P(O)TeNa$ proceeds at below room temperatures under acidic condtions, whereas the reaction with $Ph_3PSe$ is carried out using a slightly alkaline solution. For cycloalkene oxides, except for cyclohexene oxide, the reaction is sluggish. In all cases the stereochemistry of the product is retained. The reactions proceed *via* episelenium or epitellurium intermediates followed by extrusion of selenium or tellurium, although the reaction pathways to these intermediates are not the same. For example, the reaction with KSeCN may form a cyclic intermediate after nucleophilic *anti* opening of the epoxide (equation 29), followed by *anti* attack of selenium, forming an episelenium intermediate (equation 30).

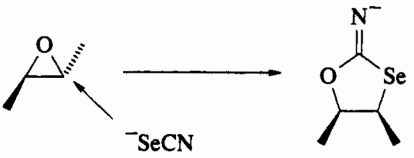

(29)

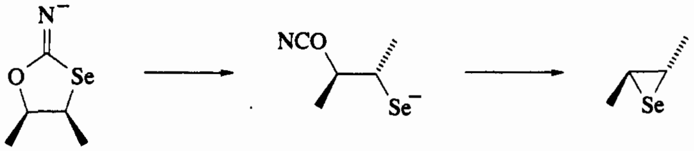

(30)

With sodium *O,O*-dialkyl phosphorotelluronate, terminal epoxides are converted to alkenes very quickly, and *cis*-epoxides are reduced more easily than *trans*-epoxides (equation 31). The corresponding selenoate reagent has been applied to sugar epoxide deoxygenation (equation 32).

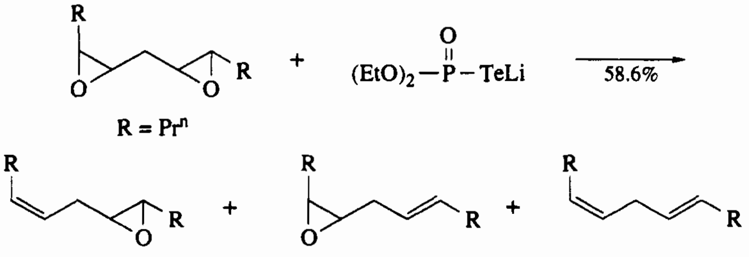

80:9:11

(31)

β-Hydroxy selenides prepared by the reaction of epoxides with selenophenol and methanol are converted to alkenes upon treatment with thionyl chloride/triethylamine in methylene chloride (equations 33 and 34).[120] The overall transformation is formally a deoxygenation of an epoxide. This method is particularly suitable for the formation of tri- and tetra-substituted alkenes.

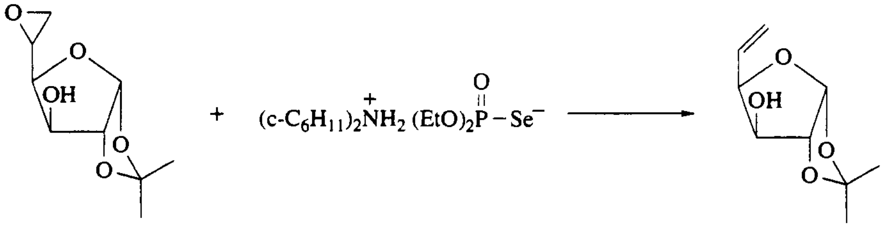
OH
O
+ $(c\text{-}C_6H_{11})_2\overset{+}{N}H_2\ (EtO)_2\overset{O}{\overset{\|}{P}}-Se^-$
OH
O

(32)

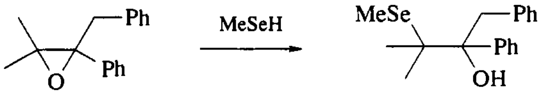
Ph
Ph
O
MeSeH
MeSe
Ph
Ph
OH

(33)

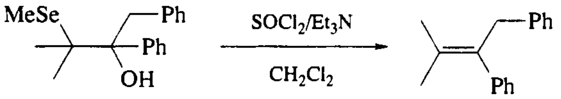
MeSe
Ph
Ph
OH
$SOCl_2/Et_3N$
$CH_2Cl_2$
Ph
Ph

(34)

### 4.4.3.4 Low-valent Metals

The study of lower valent tungsten halides by Sharpless *et al.* in 1972[121] was the first systematic study of low-valent metals as deoxygenating reagents, although some studies on low-valent chromium[122] and the zinc–copper couple[123] had appeared in the earlier literature. The tungsten reagents were prepared from tungsten hexachloride in three ways: (i) with butyllithium; (ii) with a lithium dispersion; and (iii) with lithium iodide (equations 35–37). In each case the ratio of $WCl_6$ to lithium reagent is important.

$$WCl_6 + Bu^nLi \xrightarrow{THF} WCl_6/Bu^nLi \tag{35}$$

$$WCl_6 + \text{Li dispersion} \xrightarrow{THF} WCl_6/Li \tag{36}$$

$$WCl_6 + LiI \xrightarrow[\text{in vacuo, no solvent}]{130\ ^\circ C} WCl_6/LiI \tag{37}$$

For isomeric cyclododecene oxides[124] all these tungsten reagents show high reactivity and selectivity (greater than 95% yield, with more than 95% retention), but only the reagent prepared by reaction of $WCl_6$ with three equimolar amounts of lithium iodide could convert *cis*-4-octene oxide to the *cis*-alkene with high stereoselectivity (equation 38). The reagent of equation (35) has been used for deoxygenation in natural product synthesis (equation 39).[125]

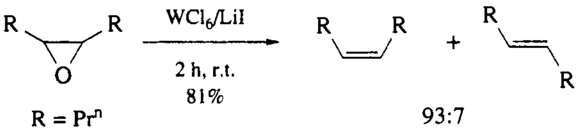
R
R
O
R = Pr$^n$
$WCl_6/LiI$
2 h, r.t.
81%
R
R
+
R
R
93:7

(38)

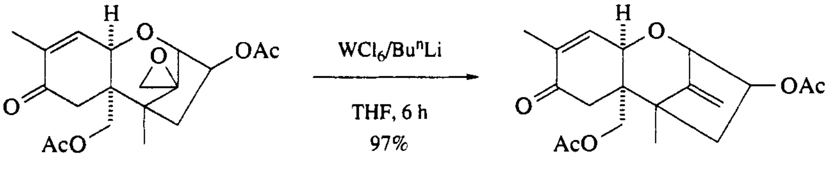
H
O
O
OAc
O
AcO
$WCl_6/Bu^nLi$
THF, 6 h
97%
H
O
OAc
O
AcO

(39)

Iron trichloride/tungsten hexachloride,[126] titanium trichloride/LAH[127] and $WCl_6$/LAH[128] have also been examined, and show similar results to the Sharpless systems mentioned above. In these cases the stereochemical course is not determined by the kind of reagent; instead, *trans*-alkenes are predominantly formed from both *cis*- and *trans*-epoxides (equations 40 and 41).

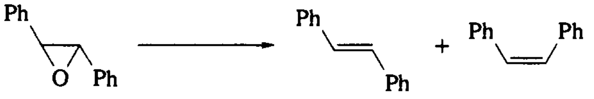

(40)

| | | |
|---|---|---|
| $FeCl_3/Bu^nLi$ | 81% | 94:6 |
| $WCl_6/LiAlH_4$ | 84% | 99:1 |

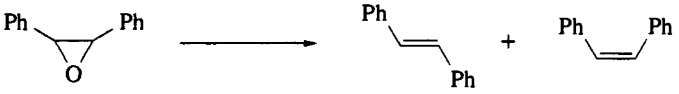

(41)

| | | |
|---|---|---|
| $WCl_6/Bu^nLi$ | 86% | 89:11 |
| $WCl_6/LiAlH_4$ | 84% | 96:4 |

Metallocene dichlorides catalyze the deoxygenation of epoxides with sodium amalgam,[129] but the stereoselectivity is not high. However, when magnesium is employed as a reductant in combination with titanocene dichloride,[130] even trisubstituted epoxides are efficiently converted to alkenes (equation 42). With this reagent, *trans*-epoxides are deoxygenated to *trans*-alkenes with 100% selectivity, whereas *cis*-epoxides give *cis*-alkenes with *ca.* 80% selectivity. Furthermore, functional groups such as carbonyl groups, alkenes, ethers and acetals remain intact under these conditions.

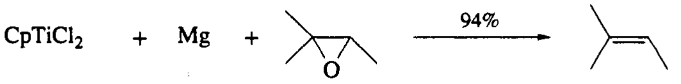

(42)

Epoxides undergo deoxygenation upon treatment with vanadium or molybdenum acetylacetonate complexes, although their stereoselectivity is low.[131] When the molybdenum(VI) oxo complex $MoO(S_2CNEt_2)_2$ is employed, the deoxygenation proceeds with retention of configuration. For example, *cis*-2-butene oxide is converted to *cis*-2-butene at 130 °C in 83% yield.[132]

An alkylmanganese complex[133] has been examined; reduction of aryl-substituted epoxides and cycloalkene oxides gives the corresponding alkenes in good yield with retention of stereochemistry (equation 43).

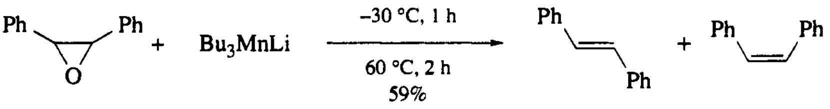

(43)

10:90

Samarium iodide has also been used for reducing epoxides to alkenes. Compared with other low-valent metal systems this reagent requires prolonged reaction time at room temperature, but the stereoselectivity, with *cis*-epoxides giving *cis*-alkenes, is high.[134]

Metal atoms such as lithium,[135] and first row transition metal atoms,[136] have been studied for deoxygenation of epoxides. Limonene oxide is converted in high yield to the corresponding alkene upon treatment with lithium and biphenyl in DME (equation 44).[137]

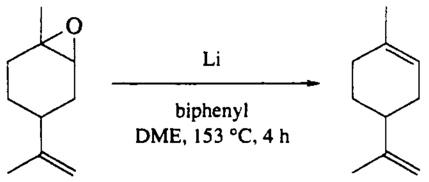

(44)

### 4.4.3.5 Metal Carbonyls

Sodium (cyclopentadienyl)dicarbonylferrate,[138] dicobaltoctacarbonyl,[139] and iron pentacarbonyl[140] have been reported to deoxygenate epoxides efficiently to the corresponding alkenes. The reaction with (cyclopentadienyl)dicarbonylferrate proceeds with inversion of stereochemistry, whereas $Fe(CO)_5$ shows low stereoselectivity. Both $Co_2(CO)_8$ and $Fe(CO)_5$ are applicable to epoxides having carbonyl groups (equations 45 and 46).

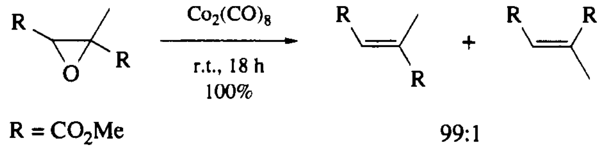

(45)

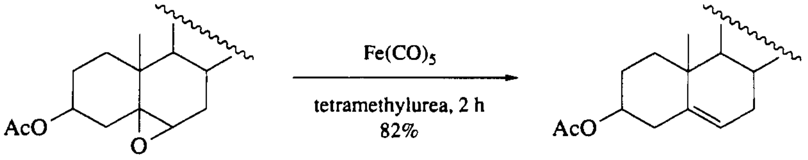

(46)

The reaction with (cyclopentadienyl)dicarbonylferrate can be directed to give either *trans*- or *cis*-alkenes simply by changing the reaction conditions. Thus, reaction with *cis*-stilbene oxide followed by treatment with sodium iodide in acetone gives *cis*-stilbene, whereas only *trans*-stilbene is obtained when the reaction is prepared at room temperature and is heated under reflux in THF (equation 47). Although deoxygenation of terminal epoxides proceeds very rapidly, internal epoxides require longer times. Consequently, as in equation (48), selective reduction of diepoxides can be carried out.

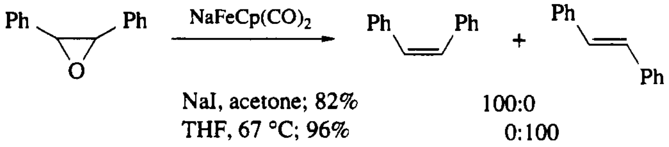

(47)

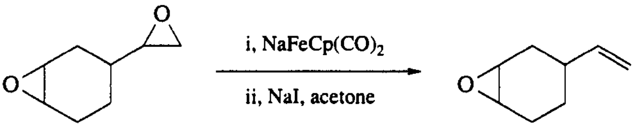

(48)

### 4.4.3.6 Miscellaneous

Vapor-deposited carbon atoms have been known to reduce epoxides to alkenes but with low stereoselectivity,[141] whereas chemically generated carbon atoms, by thermal decomposition of 5-tetrazolediazonium chloride (**2**), deoxygenate *cis*- and *trans*-2-butene oxide with a high degree of retention of stereochemistry.[142]

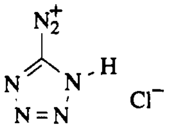

(**2**)

Carbenes or carbenoids have also been reported to deoxygenate epoxides. To generate these species, dimethyl diazomalonate/rhodium(II) acetate[143] and 9-diazofluorene[144] have been employed; both reagents show high stereoselectivity. For example, *cis*-2-butene oxide is converted to *cis*-alkene with more than 93% retention under irradiation (350 nm) using 9-diazofluorene, and functional groups, such as carbonyl, can survive using diazomalonate and rhodium(II) acetate (equation 49).

Trifluoroacetyl iodide, generated *in situ* from trifluoroacetic anhydride and sodium iodide, deoxygenates epoxides.[145] The reaction begins by *anti* opening of the epoxide, followed by the formation of an

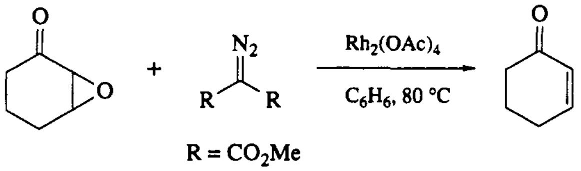

(49)

iodonium ion intermediate and subsequent deiodonation to give alkenes. Because of the mild reaction conditions, this reagent has been used for the reduction of compounds having various functional groups (equation 50).[146]

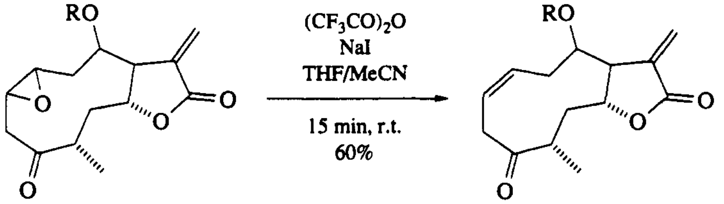

(50)

Deoxygenation *via* iodohydrin intermediates using chlorosilane/sodium iodide[147] and *p*-toluenesulfonic acid/sodium iodide[148] has also been reported. In a natural product synthesis,[149] an epoxide has been deoxygenated with a large excess of triethylsilane at 300 °C for 30 h (equation 51).

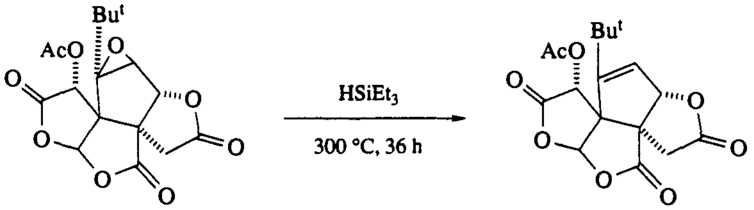

(51)

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# 4.5

# Reduction of Vinyl Halides to Alkenes, and of Aryl Halides and Related Compounds to Arenes

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## 4.5.1 HYDROGENOLYSIS OF THE CARBON–HALOGEN BOND IN VINYL HALIDES

Unlike most reductions of organic compounds, hydrogenolysis of the bond between trigonal carbon and a halogen does not possess many synthetic applications. Who would be interested in converting, for example, laboriously prepared iodobenzene to benzene by replacing iodine by hydrogen? However, the knowledge of reaction conditions for hydrogenolysis of halogen compounds is frequently useful for preventing such a reaction during reductions of other functions in an organic molecule.

Compared with alkyl halides, of which the fluorides practically do not undergo hydrogenolysis,[1] vinyl halides are hydrogenolyzed more readily, sometimes even in preference to reduction of double bonds[2,3,4] and aldehyde groups.[5] The ease of replacement of halogens by hydrogen parallels the strength of the carbon–halogen bonds, although halogens with a higher bond dissociation energy may, on occasion, be hydrogenolyzed preferentially.[6,7]

### 4.5.1.1 Hydrogenolysis of Vinylic Fluorides

Hydrogenolysis of vinylic fluorides is hardly ever done with the aim of removing fluorine from a molecule. Rather, it occurs as a usually undesirable side reaction, accompanying reductions of other functions in fluorinated compounds.[8-11] It frequently takes place during catalytic hydrogenation of fluorinated alkenes. A clear-cut saturation of the double bonds in polyfluorinated alkenes is rare and usually requires mild reaction conditions,[12-14] and hydrogenolysis of fluorine without reduction of the double bond in catalytic hydrogenation is unknown. Numerous examples are quoted in the review literature,[10,11] and a few samples are shown in Table 1.

**Table 1** Hydrogenation and Hydrogenolysis of Polyfluoroalkenes

| *Starting fluoroalkene* | *Reaction conditions* | *Product of hydrogenation (yield %)* | | *Product of hydrogenolysis (yield %)* | | *Ref.* |
|---|---|---|---|---|---|---|
| $CF_2{=}CF_2$ | $H_2$/Pd, 20 °C | $CHF_2CHF_2$ | (96) | $CHF_2CH_2F$ | (—) | 12,13 |
| | $H_2$/Ni, 90–100 °C | | (66) | | (14) | |
| $(CF_3)_2C{=}CF_2$ | $H_2$/Pd, 20 °C | $(CF_3)_2CHCHF_2$ | (95) | $(CF_3)_2CHMe$ | (—) | 12,13 |
| | $H_2$/Ni, 100°C | | (10) | | (75) | |
| 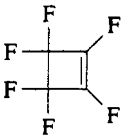 | $H_2/Pd/Al_2O_3$, 40 °C, 1 atm | 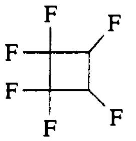 | (100) | 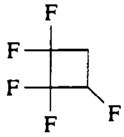 | (—) | 15 |
| | $H_2$/Pd (pumice), 45 °C, 1 atm | | (70) | | (26)[a] | |
| | $H_2$/Ni (pumice), 25 °C, 1 atm | | (67) | | (22) | |
| | Ni (Raney), 60 °C, autoclave | | (21) | | (41)[b] | |

[a]The balance (4%) is *trans*-1,2,3,3,4,4-hexafluorocyclobutane. [b]The balance (36%) is 1,1,2,2-tetrafluorocyclobutane.

Catalytic hydrogenation of fluoro- and difluoro-*cis*- and *trans*-butenedioic acids and their esters frequently affords products only of hydrogenolysis, especially when platinum oxide (Adams' catalyst) is used. Hydrogenolysis is favored in polar solvents, and is found to be more effective when rhodium or nickel rather than palladium are used as the catalysts (Table 2). Hydrogenolysis takes place prior to the saturation of the double bonds: fluoro- and 2,3-difluoro-succinic acids do not suffer any loss of fluorine under the same reaction conditions.[8]

**Table 2** Catalytic Hydrogenation of Difluoromaleic Acid

| *Catalyst* | *Solvent* | *Temperature (°C)* | *Yield of $HO_2CCHFCHFCO_2H$ (%)* | *Yield of $HO_2CCHFCH_2CO_2H$ (%)* | *Yield of $HO_2CCH_2CH_2CO_2H$ (%)* |
|---|---|---|---|---|---|
| 10% Pd (C) | $Et_2O$ | -70 | 37 | 41 | 3[a] |
| 10% Pd (C) | $Et_2O$ | 25 | 19 | 70 | 11 |
| 10% Pd (C) | $H_2O$ | 25 | | 67 | 33 |
| 5% Rh (C) | $H_2O$ | 25 | | 11 | 89 |

[a]19% remained unreacted.

Complete hydrogenolysis of fluorine is observed in unsaturated fluorinated amino acids[9] and their derivatives.[16] γ-Amino-α-fluorocrotonic acid and 5-amino-2-fluoro-2-hexenedioic acid afford, on hydrogenation over platinum oxide, γ-aminobutyric and α-aminoadipic acid, respectively. The same compounds are obtained on treatment of the above fluoroamino acids with hydriodic acid and red phosphorus.[9] Fluorine is also replaced by hydrogen in *trans*-α-fluorostilbene, which on catalytic hydrogenation over palladium gives bibenzyl (equation 1),[17] and in difluorostilbene, which on heating with sodium affords the same product.[18]

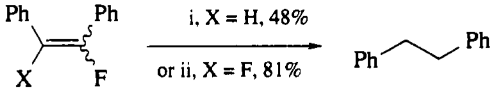

(1)

i, $H_2$/10% Pd(C), $CaCO_3$, EtOH, r.t., 2.5 atm, 5 h; ii, Na, MeOH, heat, 5 min

Vinylic fluorine in heavily fluorinated alkenes is readily replaced by hydrogen in reductions with lithium aluminum hydride and sodium borohydride. The isomeric 1-phenylpentafluoropropenes are reduced by lithium aluminum hydride regio- and stereo-specifically to tri- and tetra-fluoropropenes. (equations 2 and 3).[19]

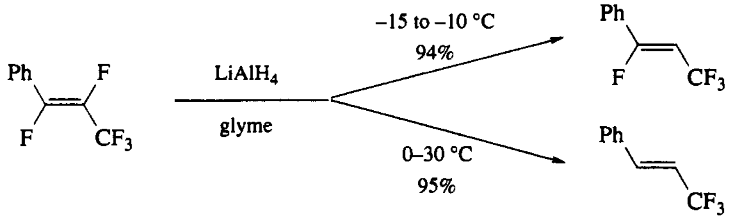
Ph
F
F
CF3
LiAlH4
glyme
-15 to -10 °C
94%
0–30 °C
95%
Ph
F
CF3
Ph
CF3

(2)

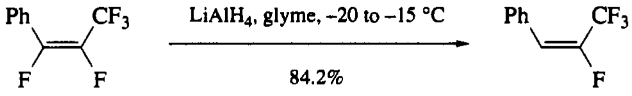
Ph
CF3
F
F
LiAlH4, glyme, -20 to -15 °C
84.2%
Ph
CF3
F

(3)

Hexafluorocyclobutene is reduced with lithium aluminum hydride in ether at −78 °C to 3,3,4,4-tetrafluorocyclobutene in 37% yield.[20] 1,3,3,4,4-Pentafluorocyclobutene and 1,3,3,4,4,5,5-heptafluorocyclopentene on treatment with lithium aluminum hydride or sodium borohydride afford 3,3,4,4-tetrafluorocyclobutene and 3,3,4,4,5,5-hexafluorocyclopentene, respectively (equation 4).[7]

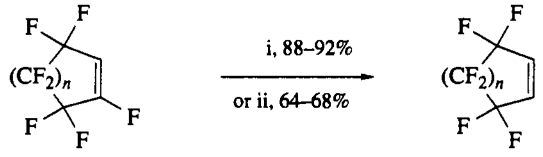
F
F
$(CF_2)_n$
F
F
F
i, 88–92%
or ii, 64–68%
F
F
$(CF_2)_n$
F
F

(4)

i, $LiAlH_4$, $Et_2O$, 0 °C; ii, $NaBH_4$, diglyme, 0 °C

In 1-chloroperfluorocyclopentene, fluorine is replaced by hydrogen in preference to chlorine in reductions with complex hydrides (equation 5).[6]

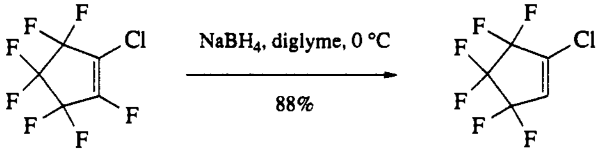
F
F
F
Cl
F
F
F
F
NaBH4, diglyme, 0 °C
88%
F
F
F
Cl
F
F
F

(5)

In 1-chloro-2-hydroperfluorocycloalkenes, a direct nucleophilic attack by hydrides substitutes hydrogen for chlorine giving (**1**), whereas allylic displacement ($S_N2'$) replaces fluorine and forms (**2**) (equation 6 and Table 3).[7]

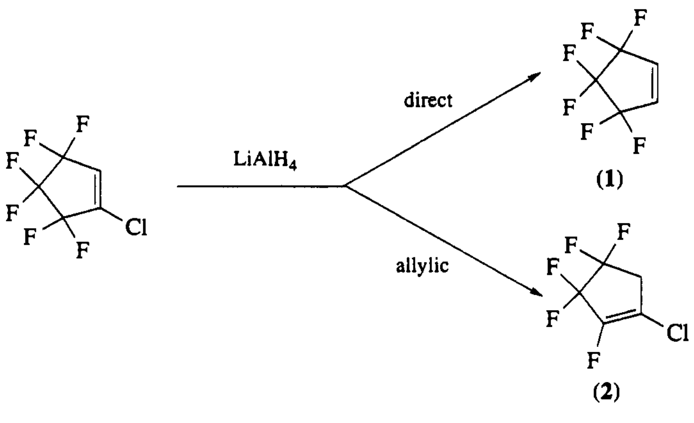
F
F
F
F
F
F
Cl
LiAlH4
direct
allylic
F
F
F
F
F
F
(1)
F
F
F
F
Cl
F
(2)

(6)

### 4.5.1.2 Hydrogenolysis of Vinylic Chlorides

Like vinyl fluorides, vinyl chlorides suffer hydrogenolysis during catalytic hydrogenation. Rhodium is claimed to effect addition of hydrogen rather than hydrogenolysis of vinylic chlorides. However, hy-

**Table 3** Reduction of 1-Chloro-2-hydroperfluorocycloalkenes with Complex Hydrides (equation 6)[7]

| | *Products in equation (6)* | *Yield of (**1**) (%)* | *Yield of (**2**) (%)* |
|---|---|---|---|
| $n = 2$ | $LiAlH_4$, $Et_2O$, 0 °C | 24 | 40 |
| | $NaBH_4$, diglyme, 0 °C | 60 | 12 |
| $n = 3$ | $LiAlH_4$, $Et_2O$, 0 °C | 8 | 88 |
| | $NaBH_4$, diglyme, 0 °C | 8 | 40 |

drogenation of both *cis*- and *trans*-1,3-dichloropropene over 5% rhodium on alumina in cyclohexane at 100 °C and 48–49 atm (1 atm = 101 325 Pa) gives only 43–47% of 1,3-dichloropropane, and 31–34% of 1-chloropropane, resulting from replacement of vinylic chlorine by hydrogen prior to the saturation of the double bond.[21] Hydrogenation of 2-chloroheptene over Raney nickel in methanol in the presence of 1 equiv. of potassium hydroxide at room temperature and atmospheric pressure affords heptane in 85% yield.[22] Under similar conditions, but in the presence of 3 equiv. of potassium hydroxide, 1,1,5-trichloro-1-pentene yields 72% of pentane, resulting from hydrogenolysis of both vinylic chlorine and that bonded to tetrahedral carbon.[22] Alkynic chlorine is hydrogenolyzed in the presence of 1 equiv. of potassium hydroxide, 1-chloro-1-hexyne giving hexane in 85% yield.[22]

Selective replacement of the vinylic chlorines takes place in the hydrogenation of chlorinated norbornenes (equations 7 and 8), which suffer saturation of the double bonds as well as hydrogenolysis of the chlorines.[23–25]

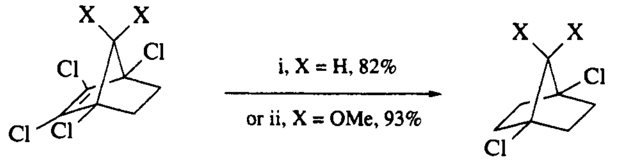

(7)

i, $H_2$/Raney Ni, KOH, r.t.; ii, $H_2$/5% Pd(C), EtOH, $Et_3N$

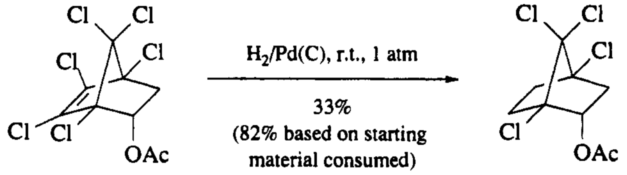

(8)

In hexachlorocyclopentadiene, all the chlorines are hydrogenolyzed and both double bonds saturated in vapor phase hydrogenation over palladium on silica at 330 °C, giving cyclopentane in 82% yield.[1]

Vinylic chlorine is replaced by hydrogen in 1-chloro-3,4-dihydro-2-naphthaldehyde during catalytic hydrogenation, which saturates the double bond, but leaves the aldehyde group intact (equation 9).[5]

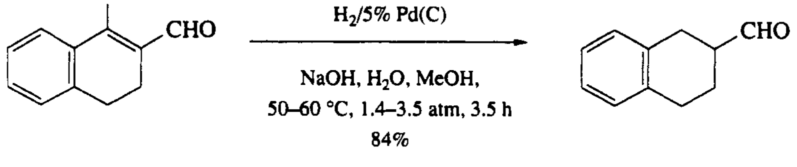

(9)

Selective hydrogenolysis of chlorine in preference to fluorine occurs during catalytic hydrogenation of chlorotrifluoroethylene. In addition to trifluoroethylene, trifluoroethane is formed by reduction of the double bond (equation 10).[3,13]

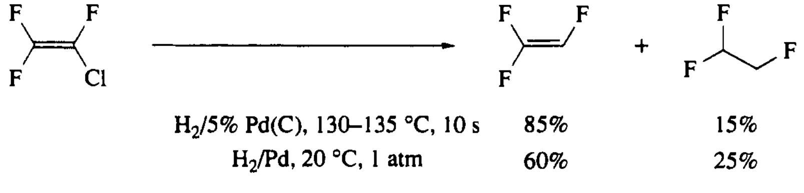

(10)

Replacement by hydrogen of vinylic chlorine without reduction of the double bond can be accomplished by complex hydrides. The efficacy of lithium aluminum hydride is increased by titanium tetrachloride. Thus α-chloro-*trans*-stilbene (**3**) gives 98% of *trans*-stilbene (**4**) with only 1% of bibenzyl (equation 11).[26]

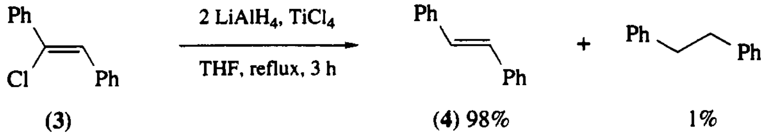
Ph
Cl
Ph
2 LiAlH$_4$, TiCl$_4$
THF, reflux, 3 h
Ph
Ph
+
Ph
Ph
(3)
(4) 98%
1%

(11)

In 1-chloro-2-hydroperfluorocyclobutene and cyclopentene, direct reaction of hydride substitutes hydrogen for chlorine (**1**), while allylic reduction leads to replacement of fluorine (**2**) (equation 6, Table 3).[7]

Reduction with metals such as sodium, lithium and zinc leaves the double bonds intact, with rare exceptions.[27] In (**5**), both allylic and vinylic chlorine atoms are replaced by hydrogen using sodium or lithium in *t*-butyl alcohol.[27] While sodium does not reduce the double bond, lithium affords a mixture of (**6**) and (**7**) (equation 12).[27]

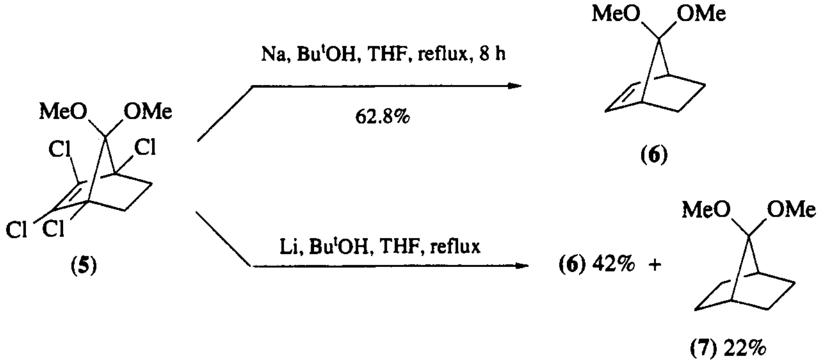
MeO
OMe
Cl
Cl
Cl
Cl
(5)
Na, Bu$^t$OH, THF, reflux, 8 h
62.8%
MeO
OMe
(6)
Li, Bu$^t$OH, THF, reflux
(6) 42% +
MeO
OMe
(7) 22%

(12)

In contrast, zinc in acetic acid replaces only one of the bridge chlorines in (**8**) leaving vinylic and allylic chlorines as well as the double bond intact.[23,25] Similar results are obtained using chromium(II) acetate (equation 13).[25]

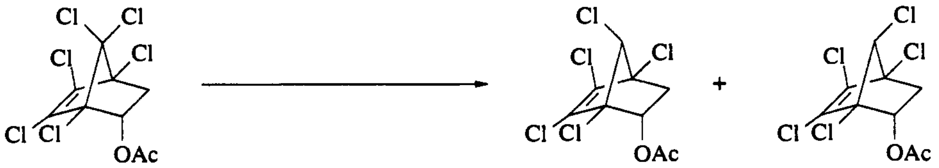
Cl
Cl
Cl
Cl
Cl
Cl
OAc
Cl
Cl
Cl
Cl
Cl
OAc
+
Cl
Cl
Cl
Cl
Cl
OAc

(13)

| | | | |
|---|---|---|---|
| (**8**) | Zn, AcOH, reflux, 4.5 h | 70% | 9% |
| | Cr(OAc)$_2$, AcOH, reflux, 16 h | 78% | 18% |

Zinc in acetic acid hydrogenolyzes vinylic chlorine in phenyl (*Z*)-β-chlorostyryl sulfone (equation 14).[28]

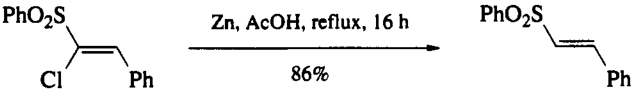
PhO$_2$S
Cl
Ph
Zn, AcOH, reflux, 16 h
86%
PhO$_2$S
Ph

(14)

### 4.5.1.3 Hydrogenolysis of Vinylic Bromides

Vinylic bromine can be replaced fairly easily without reduction of the double bond. This is a characteristic difference from hydrogenolysis of vinylic chlorine and especially fluorine. Catalytic hydrogenation of ethyl α-methyl-β-bromocrotonate resulted in replacement of bromine and formation of ethyl α-methylcrotonate (equation 15).[2] In 14-bromocodeinone (**9**), replacement of bromine occurs with a double bond shift to give neopinone (**10**; equation 16).[4]

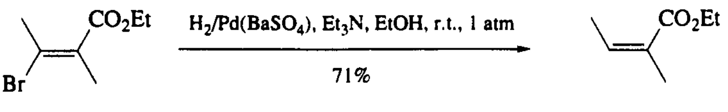
CO$_2$Et
Br
H$_2$/Pd(BaSO$_4$), Et$_3$N, EtOH, r.t., 1 atm
71%
CO$_2$Et

(15)

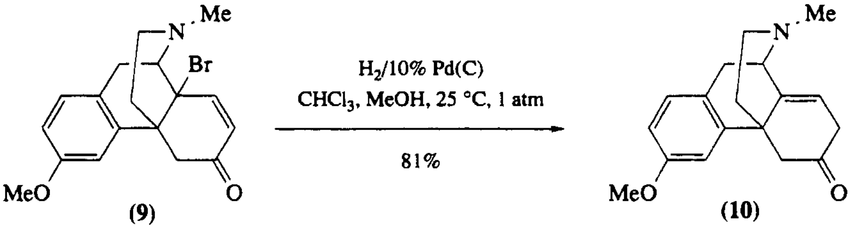
Me
N
Br
MeO
O
H2/10% Pd(C)
CHCl3, MeOH, 25 °C, 1 atm
81%
Me
N
MeO
O

**(9)** **(10)** (16)

Homogeneous catalytic hydrogenation over tetrakis(triphenylphosphine)palladium using hydrogen or sodium formate as hydrogen donors converts β-bromostyrene to styrene in 37% and 35% yields respectively (the other products being polymers).[29]

Electrolytic replacement of vinylic bromine by hydrogen in (*E*)-bromostilbene is complicated by the formation of diphenylacetylene in addition to *trans*- and a small amount of *cis*-stilbene.[30]

An interesting hydrogenolysis of bromine is observed when 2-bromocycloalken-2-ones are treated with diethyl phosphite and triethylamine. The predominant products are 3-cycloalkenones with only minor amounts of 2-cycloalkenones (equation 17).[31]

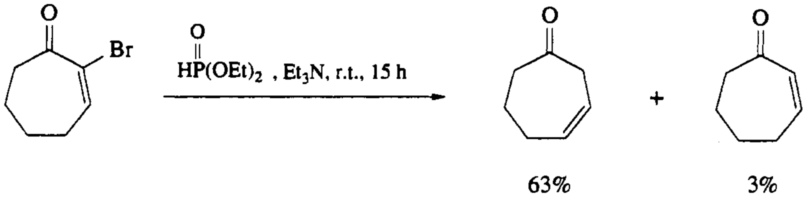
O
Br
O
HP(OEt)2 , Et3N, r.t., 15 h
O
+
O
63%
3%

(17)

### 4.5.1.4 Hydrogenolysis of Vinylic Iodides

Very scanty documentation is available on replacement of vinylic iodine by hydrogen. Treatment of iodotrifluoroethylene with sodium borohydride in diethylene glycol and water or alcohol affords trifluoroethylene in 73% yield. In the case of chlorotrifluoroethylene and bromotrifluoroethylene no hydrogenolysis, but saturation of the double bond results under identical conditions (equation 18).[32]

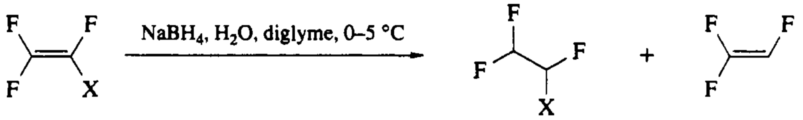
F
F
F
X
NaBH4, H2O, diglyme, 0–5 °C
F
F
F
X
+
F
F
F

(18)

| | | |
|---|---|---|
| X = Cl | 86% | 6% |
| X = Br | 94% | 3% |
| X = I | – | 73% |

1-Chloro-2-iodotetrafluorocyclobutene and 1-chloro-2-iodohexafluorocyclopentene treated with sodium aluminum hydride in diglyme by addition of the compounds to the reagent give, after decomposition of the intermediate complex with deuterium oxide, 1-chloro-2-deuteriotetrafluorocyclobutene in 38% yield, and 1-chloro-2-deuteriohexafluorocyclopentene in 43% yield, respectively (equation 19).[33] The iodine in iodoalkene (**11**) is replaced by hydrogen on refluxing with zinc and hydrochloric acid to give iodine-free alkene (**12**; equation 20).[34]

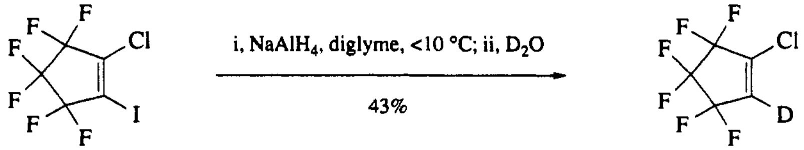
F
F
F
Cl
F
F
F
I
F
i, NaAlH4, diglyme, <10 °C; ii, D2O
43%
F
F
F
Cl
F
F
D
F

(19)

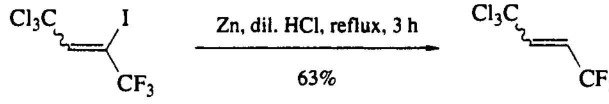
Cl3C
I
CF3
Zn, dil. HCl, reflux, 3 h
63%
Cl3C
CF3

**(11)** **(12)** (20)

## 4.5.2 HYDROGENOLYSIS OF THE TRIGONAL CARBON–HALOGEN BOND IN ARYL HALIDES

Replacement of aromatic halogens by hydrogen can be accomplished by catalytic hydrogenation and by reduction with complex hydrides, with sodium, with zinc, and with inorganic and organic reducing agents.

### 4.5.2.1 General

Hydrogenolysis of aromatic halides using catalytic hydrogenation takes place easily with rates of replacement of halogen decreasing in the order I > Br > Cl > F. For example, replacement of chlorine in preference to fluorine takes place in chlorofluoropyridines (equation 21).[35]

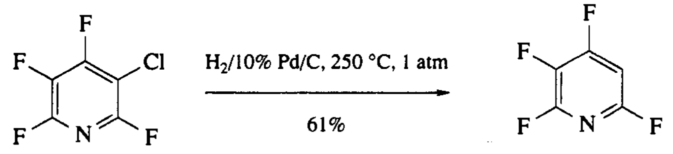
F
F
Cl
F
N
F
$H_2$/10% Pd/C, 250 °C, 1 atm
61%
F
F
F
N
F

(21)

The same order of ease of replacement applies to reduction of aryl halides with lithium aluminum hydride[36,37] and with zinc (equations 22 and 23).[38]

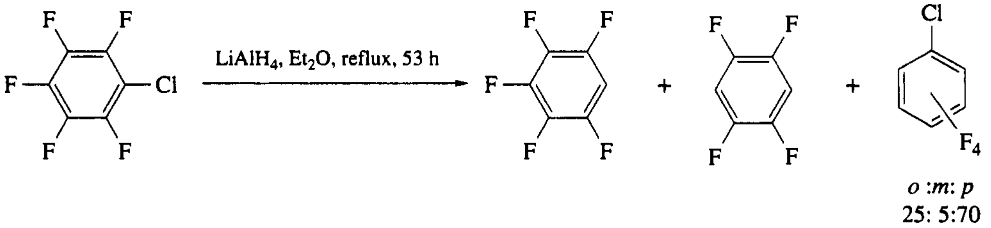
F
F
F
Cl
F
F
$LiAlH_4$, $Et_2O$, reflux, 53 h
F
F
F
F
F
+
F
F
F
F
+
Cl
$F_4$
o :m: p
25: 5:70

(22)

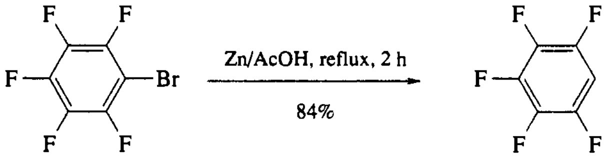
F
F
F
Br
F
F
Zn/AcOH, reflux, 2 h
84%
F
F
F
F
F

(23)

Replacement of fluorine in preference to chlorine is observed in chlorofluoropyridines, where lithium aluminum hydride replaces the fluorines in the $\alpha$- and $\gamma$-positions of lower electron density faster than the chlorine in the $\beta$-position (equation 24).[39]

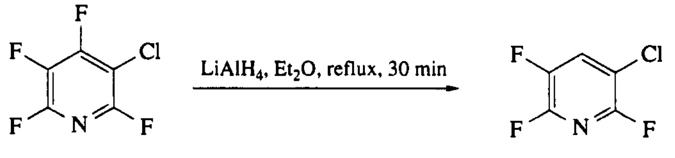
F
F
Cl
F
N
F
$LiAlH_4$, $Et_2O$, reflux, 30 min
F
Cl
F
N
F

(24)

Another regioselective hydrogenolysis of fluorine with hydrides takes place in perfluorotoluene,[40] and electrolytically in pentafluorobenzoic acid (equations 25 and 26).[41]

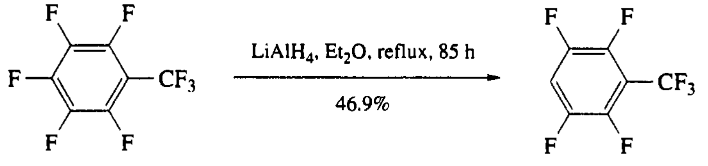
F
F
F
$CF_3$
F
F
$LiAlH_4$, $Et_2O$, reflux, 85 h
46.9%
F
F
$CF_3$
F
F

(25)

Because of the different rates of hydrogenolysis, aryl halides containing different halogens can be reduced selectively. 1-Bromo-2-chlorobenzene is reduced to chlorobenzene in 96% yield on treatment for 2 h at room temperature with 'a complex reducing agent' prepared from nickel(II) chloride, sodium hydride and *t*-pentyl alcohol.[42] 1-Bromo-4-chlorobenzene is converted to chlorobenzene on treatment with

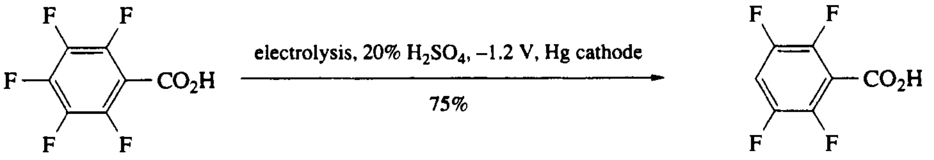
electrolysis, 20% $H_2SO_4$, –1.2 V, Hg cathode
75%

(26)

triphenyltin hydride,[43] and 4-bromo-2-chlorophenol to 2-chlorophenol on treatment with ethanethiol and aluminum chloride (equation 27).[44]

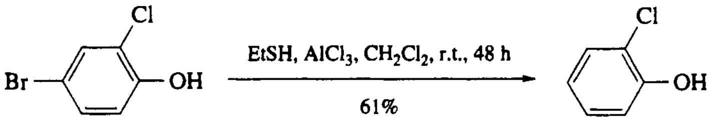
EtSH, $AlCl_3$, $CH_2Cl_2$, r.t., 48 h
61%

(27)

The reverse order of replacement of halogens, *i.e.* preferential substitution of chlorine rather than of bromine by hydrogen in bromochloro compounds, is possible if chlorine is activated by its position in the molecule. For example, 5-bromo-6-chloro-2,4-dimethylpyrimidine, in which chlorine is rendered labile by its α-position to one of the ring nitrogens, is reduced to 5-bromo-2,4-dimethylpyrimidine by refluxing with *p*-toluenesulfonylhydrazine in chloroform (equation 28).[45]

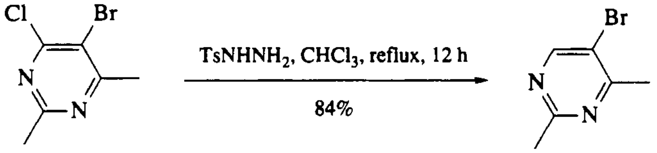
TsNHN$H_2$, $CHCl_3$, reflux, 12 h
84%

(28)

Substitution of halogen by hydrogen in aryl halides can take place without, or with only partial, reduction of carbon–carbon double bonds,[46] aldehydes,[46] nitriles,[46] and even readily reducible nitro groups[46,47] present in the molecule (equations 29–32).

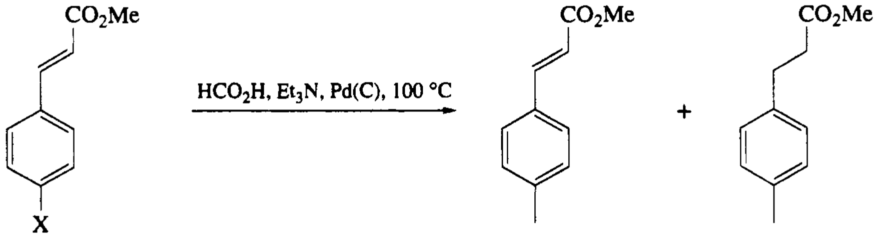
$HCO_2H$, $Et_3N$, Pd(C), 100 °C
+

(29)

| | | | |
|---|---|---|---|
| X = Cl | 1.5 h | 22% | 55% |
| X = Br | 7.0 h | 93% | – |

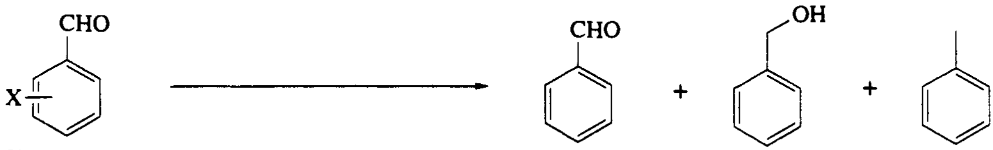

(30)

| X | | | | |
|---|---|---|---|---|
| 4-Br | $H_2$/Pd($PPh_3$)$_4$, AcOK, DMF, 100 °C, 3 h | 76% | – | – |
| 2-Br | $HCO_2H$, $Et_3N$/5% Pd(C), 50 °C, 2 h | 44% | 8% | – |
| 2-Br | $HCO_2H$, $Et_3N$/Pd(OAc)$_2$, 2P(*o*-Tol)$_3$, 50 °C, 2 h | 43% | 10% | 10% |

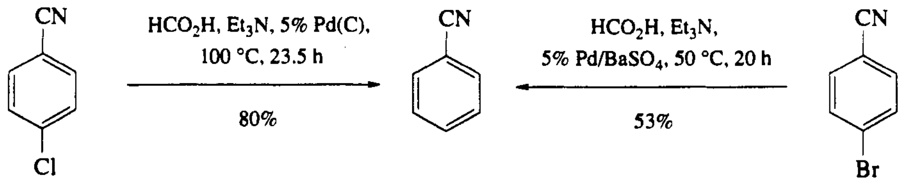
$HCO_2H$, $Et_3N$, 5% Pd(C), 100 °C, 23.5 h
80%
$HCO_2H$, $Et_3N$, 5% Pd/$BaSO_4$, 50 °C, 20 h
53%

(31)

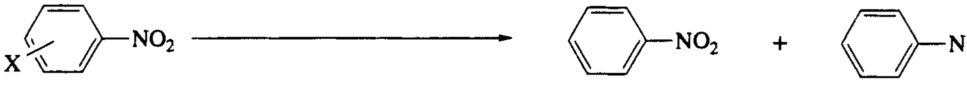
X
$NO_2$
$NO_2$
+
$NH_2$

(32)

| X | | | |
|---|---|---|---|
| 2-Cl | $H_2/Pd(PPh_3)_4$, AcOK, DMF, 100 °C, 6 h | 67% | - |
| 2-Br | $H_2/Pd(PPh_3)_4$, AcOK, DMF, 100 °C, 6 h | 80% | - |
| 2-Br | $HCO_2H$, $Et_3N$, 5% Pd(C), 50 °C, 48 h | 78% | 8% |
| 4-Cl | $HCO_2H$, $Et_3N$, 5% Pd(C), 100 °C, 1 h | 90% | - |

### 4.5.2.2 Hydrogenolysis of Aryl Fluorides

Substitution of hydrogen for fluorine in compounds containing single fluorine atoms linked to aromatic rings occurs during catalytic hydrogenation of *p*-fluorobenzoic acid, which gives benzoic acid and cyclohexanecarboxylic acid on treatment with hydrogen over platinum black,[48] and in hydrogenation of *p*-fluorophenylacetic acid, which affords ethyl cyclohexylacetate on heating with hydrogen, ethanol and Raney nickel (yields of these experiments were not quoted) (equation 33).[49]

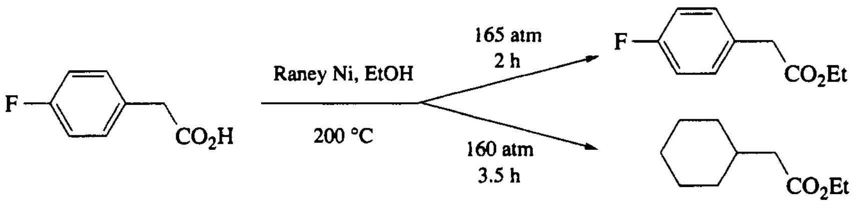
F
$CO_2H$
Raney Ni, EtOH
200 °C
165 atm
2 h
160 atm
3.5 h
F
$CO_2Et$
$CO_2Et$

(33)

Hydrogenation of (**13**) over palladium black yields mainly (**14**) with only partial hydrogenolysis of fluorine to give (**15**; equation 34).[50]

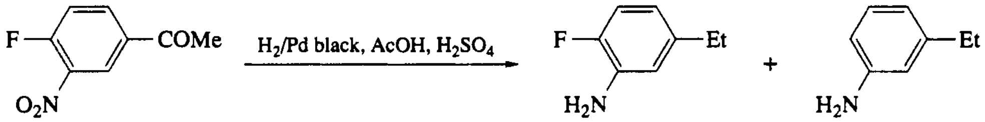
F
COMe
$O_2N$
$H_2/Pd$ black, AcOH, $H_2SO_4$
F
Et
$H_2N$
+
Et
$H_2N$

(34)

(**13**) (**14**) 80% (**15**) 20%

Reduction of *p*-fluoroacetophenone with Raney alloys in 5% sodium hydroxide gives 1-phenylethanol in high yields (equation 35).[51]

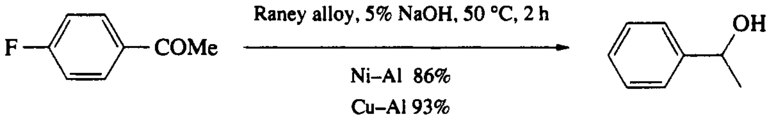
F
COMe
Raney alloy, 5% NaOH, 50 °C, 2 h
Ni–Al 86%
Cu–Al 93%
OH

(35)

Catalytic hydrogenation of pentafluoropyridine (**16**) gives a mixture of the tetrafluoropyridines (**17**)–(**19**), with reduction taking place most easily at the 4-position and to only a trace extent at the 3-position (equation 36).[35]

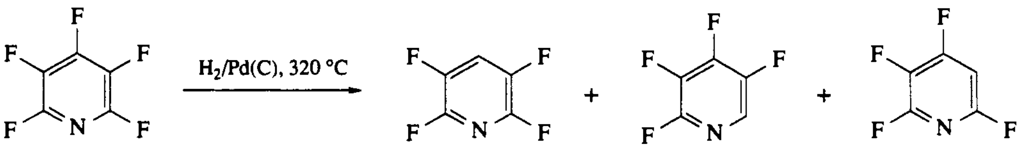
F
F
F
F
F
N
$H_2/Pd(C)$, 320 °C
F
F
F
F
N
+
F
F
F
F
N
+
F
F
F
F
N

(36)

(**16**) (**17**) 30% (**18**) 5% (**19**) trace

Single fluorine atoms in aromatic fluoro compounds such as *p*-fluorotoluene and *p*-fluoroanisole are replaced by hydrogen using lithium aluminum hydride in the presence of di-*t*-butyl peroxide under irradiation (equation 37).[52]

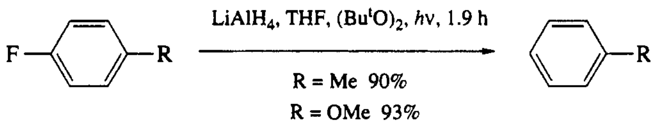

(37)

Hydrogenolysis of polyfluoro and perfluoro aromatics by lithium aluminum hydride has already been shown in equations (24) and (25). Additional examples are replacement of fluorine by hydrogen in pentafluorobenzene, where the predominant product is 1,2,4,5-tetrafluorobenzene (**20**), resulting from the reduction by lithium aluminum hydride *para* to the hydrogen (equation 38),[53] and replacement of fluorine in the $\beta$-position in 1,2,3,4-tetrafluoronaphthalene (equation 39).[54]

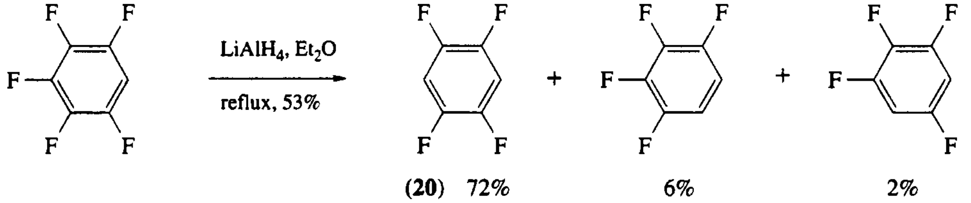

(38)

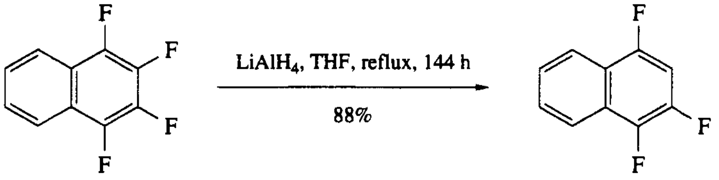

(39)

Removal of fluorine from 1-fluoronaphthalene is accomplished by treatment with ethanethiol and aluminum chloride at room temperature (equation 40).[55]

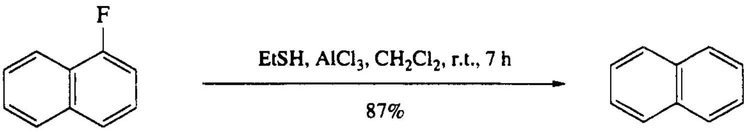

(40)

Further examples of hydrogenolysis of aryl fluorides can be found in the review literature.[10,11]

### 4.5.2.3 Hydrogenolysis of Aryl Chlorides

A general method for replacement of aromatic chlorine by hydrogen is catalytic hydrogenation over palladium on carbon,[56] calcium carbonate[57a] or silica gel,[57b] over platinum oxide (Adams' catalyst),[56] and over Raney nickel.[58,59] Platinized charcoal is inhibited by some halogen compounds.[56] Reductions, especially those using Raney nickel, have to be carried out in the presence of alcoholic potassium hydroxide to neutralize hydrogen chloride resulting from the hydrogenolysis.[58,59] In dichlorides with equivalent chlorine atoms, partial or total hydrogenolysis can be accomplished, depending upon whether 1 or 2 equiv. of the base are used.[59]

In catalytic hydrogenation, chlorine is replaced by hydrogen in chlorinated aromatic hydrocarbons (equations 41 and 42),[57] phenols (equation 43),[60] amines (equation 44),[56] carboxylic acids (equation 45),[56,59] and nitro compounds (equation 46).[46,47] Hydrogenolysis of chlorine in chloronitro compounds takes precedence over reduction of nitro groups,[46,47] provided that contact with the halogen-free product is not too long.[46] The reaction is achieved using palladium on carbon[46] or tetrakis(triphenylphos-

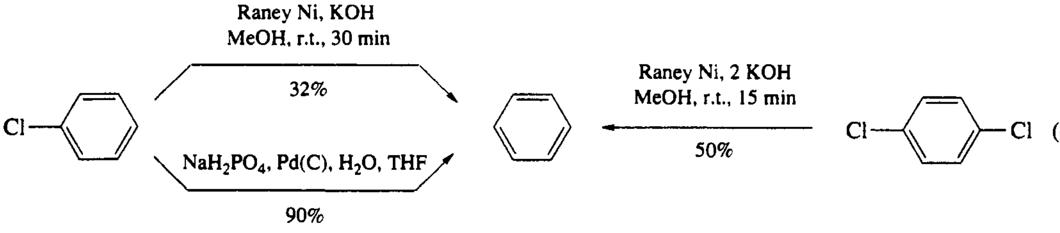

(41)

phine)palladium.[47] Hydrogen donors such as sodium hypophosphite,[61] ethanol[62] or ammonium formate[60] can be employed in catalytic hydrogen transfer.

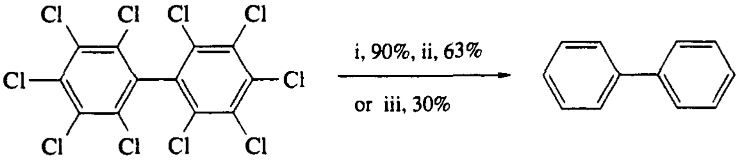
Cl
i, 90%, ii, 63%
or iii, 30%

(42)

i, $H_2$/Pd($SiO_2$), 330 °C, 6 h; ii, $H_2$/Ni($Al_2O_3$); iii, $H_2$/Fe($SiO_2$)

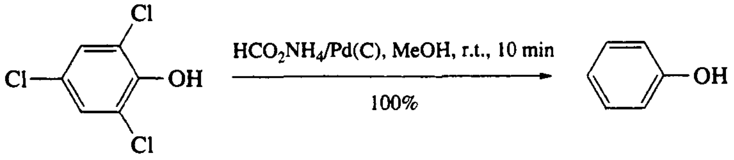
Cl
OH
$HCO_2NH_4$/Pd(C), MeOH, r.t., 10 min
100%

(43)

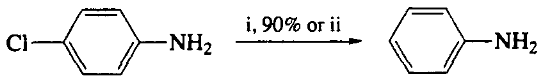
Cl
$NH_2$
i, 90% or ii

(44)

i, Raney Ni, KOH, MeOH, r.t., 70 min; ii, $H_2$/Pd(C), KOH, MeOH, r.t., 11 min

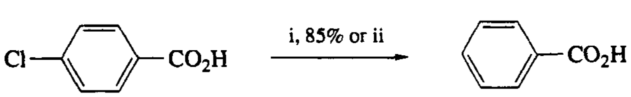
Cl
$CO_2H$
i, 85% or ii

(45)

i, Raney Ni, 2 KOH, MeOH, r.t., 5 h; ii, $H_2$/Pd(C), 95% EtOH

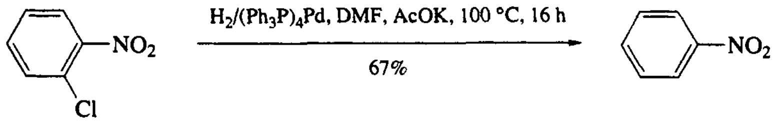
$NO_2$
Cl
$H_2/(Ph_3P)_4Pd$, DMF, AcOK, 100 °C, 16 h
67%

(46)

In the reduction of *p*-chlorocinnamic acid with an excess of sodium hypophosphite and palladium (equation 47), the double bond is saturated and the hydrogenolysis of chlorine occurs. With one equivalent of the hypophosphite, only saturation of the double bond takes place, and *p*-chlorohydrocinnamic acid is obtained after 1.5 h.[61]

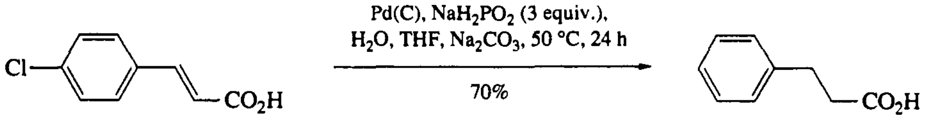
Cl
$CO_2H$
Pd(C), $NaH_2PO_2$ (3 equiv.),
$H_2O$, THF, $Na_2CO_3$, 50 °C, 24 h
70%

(47)

In aromatic heterocycles, chlorine is replaced by hydrogen in catalytic vapor phase hydrogenation over palladium on charcoal at 280 °C. 3,5-Dichlorotrifluoropyridine affords 2,4,6-trifluoropyridine in 75% yield.[35]

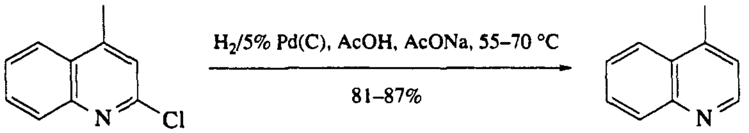
N
Cl
$H_2$/5% Pd(C), AcOH, AcONa, 55–70 °C
81–87%

**(21)** **(22)**

(48)

Chlorine in 2-chlorolepidine (**21**) is very reactive, since the compound can be considered an imide chloride. It is readily replaced by hydrogen to form lepidine (**22**; equation 48).[63] Similarly (**23**) is converted to (**24**) on catalytic hydrogenation (equation 49).[62] The above reductions may be applied to many six-membered aromatic heterocycles containing chlorine on the carbon next to nitrogen; thus pyridones, quinolones and related compounds can be converted to their parent heterocycles by way of their α-chloro compounds.

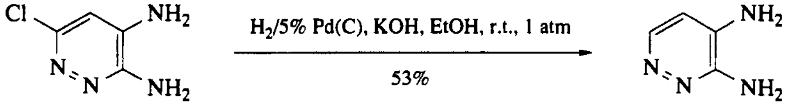

**(23)** **(24)** (49)

High yields of 1-phenylethanol are obtained on heating chlorinated acetophenones at 50 °C with Raney nickel or Raney copper alloys in 5% sodium hydroxide (equation 50). Copper alloy is somewhat less efficient, as in some cases the hydrogenolysis of chlorine is incomplete.[51]

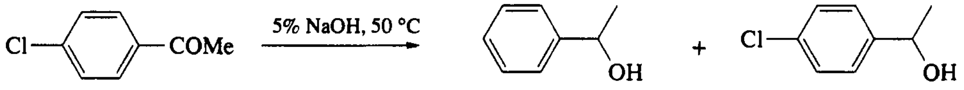

(50)

| | | |
|---|---|---|
| Ni–Al alloy | 88% | – |
| Cu–Al alloy | 44% | 56% |

Examples of hydrogenolysis of aryl chlorides by lithium aluminum hydride are rare. Chlorobenzene is reduced to benzene only in a low yield,[36] but chloronaphthalene gives a good yield of naphthalene with lithium aluminum hydride in the presence of either di-*t*-butyl peroxide[52] or titanium tetrachloride (equation 51).[26]

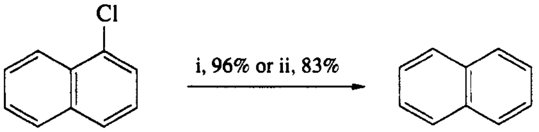

(51)

i, $LiAlH_4$, $(Bu^tO)_2$, *hν*, r.t., 2 h; ii, 2 $LiAlH_4$, $TiCl_4$, THF, reflux, 3 h

Zinc dust in the presence of nickel chloride, triphenylphosphine and sodium iodide as a catalyst reduces chlorobenzene in methanol after 20 h at 60 °C to benzene in 99% yield, and *p*-chloroanisole to anisole in dimethylformamide/water in 88–97% yields.[64] The yields are considerably lower without sodium iodide (equation 52).[64]

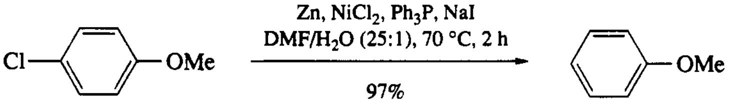

(52)

A similar effect on aryl halides is produced by using a suspension of zinc dust, nickel chloride and sodium iodide in moist hexamethylphosphoramide at 60 °C under ultrasound sonication.[65] Chlorobenzene is thus converted to benzene in 64–93% yields.[65]

Chlorine in position 2 in 2-chloro-4,6-dimethylpyrimidine is replaced by hydrogen on heating for 10 min at 100–110 °C with azeotropic (57%) hydriodic acid, giving a 78% yield of 4,6-dimethylpyrimidine.[66]

Hydrogenolysis of aryl chlorides can also be achieved by treatment with triethylsilane in the presence of palladium,[67] and by reduction with isopropyl alcohol under UV irradiation (equation 53).[68]

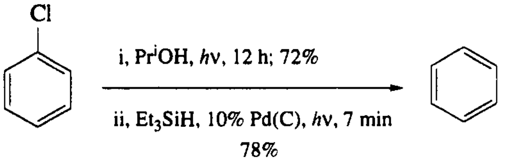

(53)

### 4.5.2.4 Hydrogenolysis of Aryl Bromides

Substitution of hydrogen for bromine is easier and faster than for chlorine. In catalytic hydrogenation, 10% palladium on carbon is a more active catalyst than platinum oxide, and this in turn is better than

10% platinum on carbon.[56,69] A palladium complex with triphenylphosphine and Raney nickel in the presence of potassium hydroxide is equally suitable for the hydrogenolysis (Table 4).[59,70] Instead of hydrogen, hydrogen donors such as formic acid (equation 54)[71] and triethylammonium formate[46] are employed in the presence of 10% palladium on carbon[46,71] or palladium diacetate complexed with phosphines.[46]

**Table 4** Examples of Reduction of Bromobenzene to Benzene

| *Reaction conditions* | *Yield (%)* | *Ref.* |
|---|---|---|
| $H_2$/Pd ($CaCO_3$), 10% KOH, EtOH, r.t. | 99 | 38 |
| $H_2$/10% Pd (C), MeOH, r.t., 5 h | | 56 |
| $HCO_2H$/10% Pd (C), DMF, reflux, 3 h | 85–90 | 71 |
| $HCO_2H$, $Et_3N$/Pd$(OAc)_2$ + [P$(OC_7H_7)_3$]$_2$, 50 °C, 4.5 h | 92 | 46 |
| $LiAlH_4$, THF, 25 °C, 24 h | 95 | 36 |
| $LiAlH_4$, THF, 65 °C, 6 h | 100 | 36 |
| $NaAlH_2(OCH_2CH_2OMe)_2$, xylene, 100–115 °C, 1 h | 53 | 72 |
| Zn, $NiCl_2$, NaI, $H_2O$, HMPA, 60 °C, ultrasound | 81 | 65 |
| $ZnBr_2$, K, THF, reflux 4 h; diglyme, reflux 8 h | 83 | 73 |
| $Ph_3SnH$, reflux | 60–75 | 43 |
| $Et_3SiH$/10% Pd (C), 4 min | 79 | 67 |
| $Me_2CHOH$, *hν*, r.t. | 72 | 68 |

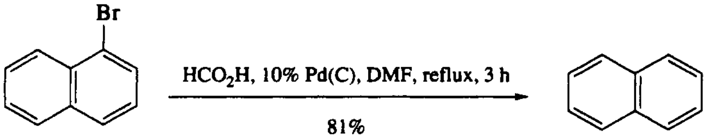

(54)

Bromoanilines are reduced to anilines by hydrogenation over Raney nickel (equation 55),[59] and *p*-bromoacetophenone is converted to 1-phenylethanol on heating at 50 °C with Raney alloys in 5% sodium hydroxide. The best yields are obtained using copper–aluminum alloy (89–91%).[51]

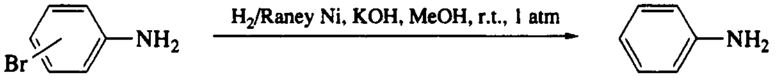

(55)

| | *Time* (min) | *Yield* (%) |
|---|---|---|
| *o*-Br | 45 | 90 |
| *m*-Br | 50 | 91 |
| *p*-Br | 60 | 85 |

Reduction of aryl bromides with lithium aluminum hydride takes place in tetrahydrofuran solutions at room temperature.[36] It has also been performed with better results in the presence of di-*t*-butyl peroxide under UV irradiation[52] or in the presence of titanium tetrachloride (equations 56 and 57).[26] Reduction of bromobenzene with sodium bis(methoxyethoxy)aluminum hydride (Red-Al, Vitride) at 100–115 °C gives benzene in 53% yield (Table 4).[72]

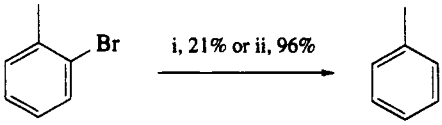

(56)

i, $LiAlH_4$, THF, 25 °C, 24 h; ii, $LiAlH_4$, THF, $(Bu^tO)_2$, *hν*, r.t.

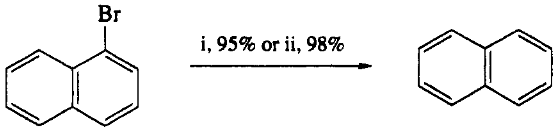

(57)

i, $LiAlH_4$, $(Bu^tO)_2$, THF, *hν*, r.t., 2.3 h; ii, $LiAlH_4$, $TiCl_4$, THF, reflux, 3 h

Replacement of bromine in aryl bromides by hydrogen using zinc takes place at higher temperatures. Bromobenzene gives benzene by refluxing in diglyme with zinc, generated *in situ* from anhydrous zinc bromide and potassium in tetrahydrofuran (Table 4).[73] Zinc powder in boiling acetic acid reduces pentafluorobromobenzene to pentafluorobenzene in 84% yield after refluxing for 2 h. Iron filings and aluminum flake do not react.[38]

Under rather complex conditions, bromobenzene is reduced to benzene by heating with zinc powder and nickel chloride in dimethylformamide or hexamethylphosphoramide containing small amounts of water (Table 4).[65]

A regioselective substitution by hydrogen of the more reactive bromine atoms in the α-positions on the thiophene ring converts 2,3,5-tribromothiophene to 3-bromothiophene by refluxing with zinc powder in acetic acid (equation 58).[74]

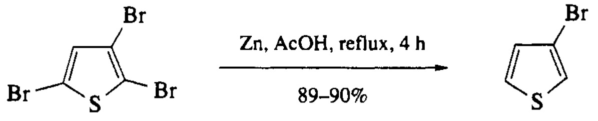

(58)

Metal salts such as chromium(II) chloride ($CrCl_2$) complexed with ethylenediamine reduce α-bromonaphthalene in dimethylformamide at room temperature in 93–98% yield.[75]

A selective reducing agent for replacement of halogens by hydrogen, triphenylstannane (triphenyltin hydride), reduces aryl bromides to arenes in high yields (Table 4).[43] Triethylsilane (triethylsilicon hydride) converts bromobenzene to benzene in the presence of 10% palladium on carbon in 79% yield (Table 4).[67]

A strongly reducing mixture is prepared by treatment of nickel(II) chloride and *t*-pentyl alcohol with sodium hydride. In dimethoxyethane, *o*-bromochlorobenzene is selectively reduced to chlorobenzene in 96% yield after 2 h at 20 °C.[42]

Isopropyl alcohol under UV irradiation converts bromobenzene to benzene in 72% yield (Table 4).[68] Similar replacement of bromine by hydrogen is accomplished by treatment of aryl bromides dissolved in dichloromethane with a mixture of ethanethiol and anhydrous aluminum chloride.[44,55] This hard acid–soft base combination reacts with polycyclic aromatic halides[55] and halogenated phenols[44] by an addition–elimination mechanism, leading to an aryl ethyl sulfide through a radical anion intermediate. This is converted by another molecule of ethanethiol to the debrominated arene and diethyl disulfide.[55] 1-Bromonaphthalene is thus transformed into naphthalene (equation 59), 2,4,6-tribromophenol into phenol (equation 60), and bromochlorophenols into chlorophenols in 61–91% yields.[44]

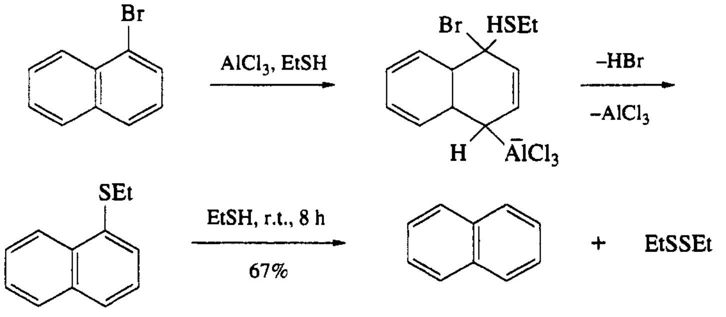

(59)

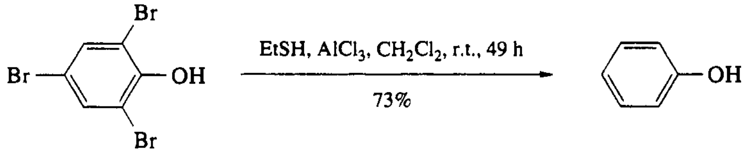

(60)

In 5-bromouracil having no substituents on N-1, bromine is replaced by hydrogen on heating at 180 °C with 1-benzyl-1,4-dihydronicotinamide. Thus (**25**) yields (**26**), (**27**) and (**28**) (equation 61).[76]

### 4.5.2.5 Hydrogenolysis of Aryl Iodides

As might be expected, substitution of iodine by hydrogen in aryl iodides is easier than in aryl bromides. This is evident in selective reduction of chloroiodo aromatics (equation 62),[36,52] and especially bromoiodo aromatics (equation 63),[77] and also in the selective reduction of iodonitro aromatics to nitro aromatics (equations 64 and 65).[78]

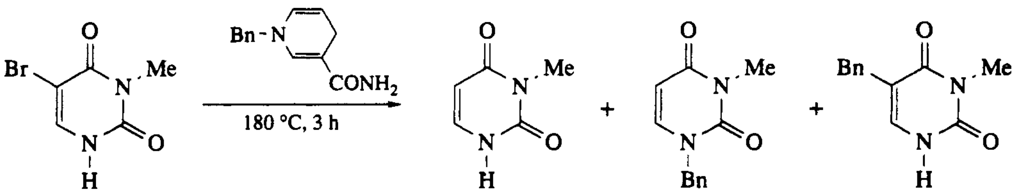
Br
O
N
Me
N
H
O
Bn-N
CONH2
180 °C, 3 h
+
Bn

**(25)** **(26)** 54% **(27)** 10% **(28)** 19% (61)

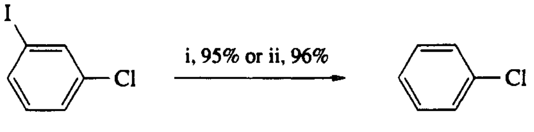
I
Cl
i, 95% or ii, 96%

(62)

i, $LiAlH_4$, THF, 25 °C; ii, $LiAlH_4$, $(Bu^tO)_2$, THF, *h*v, 42 min

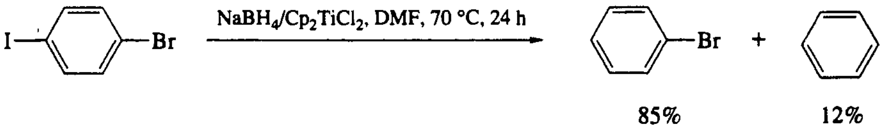
I
Br
NaBH4/Cp2TiCl2, DMF, 70 °C, 24 h
+
85%
12%

(63)

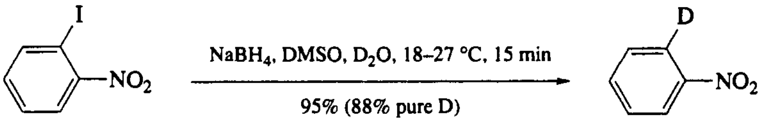
I
NO2
NaBH4, DMSO, D2O, 18–27 °C, 15 min
95% (88% pure D)
D

(64)

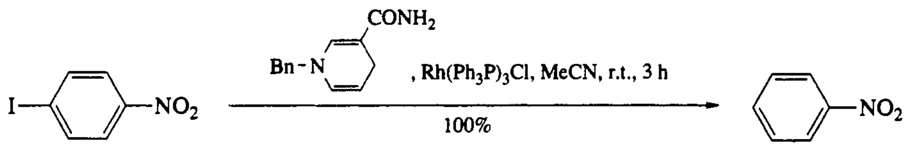
I
NO2
CONH2
Bn-N
, Rh(Ph3P)3Cl, MeCN, r.t., 3 h
100%

(65)

Reduction of aryl iodides has been accomplished by catalytic hydrogenation using hydrogen or hydrogen donors over palladium[71] or Raney nickel catalysts (equation 66),[59] by reduction with complex hydrides (equations 62–64),[36,52,77,78] with metals[65] and their compounds,[79] with hydrogen iodide,[66] and with organic compounds (equations 65 and 67).[44,79,80] Table 5 shows reaction conditions for reduction of iodobenzene to benzene.

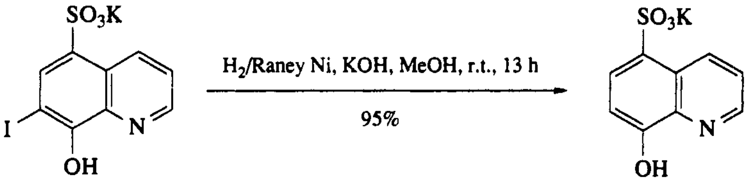
SO3K
I
N
OH
H2/Raney Ni, KOH, MeOH, r.t., 13 h
95%

(66)

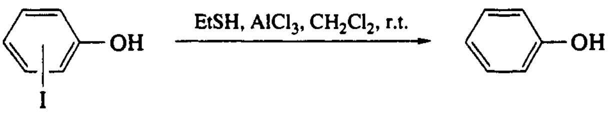
OH
I
EtSH, AlCl3, CH2Cl2, r.t.

(67)

| | *Time* (min) | *Yield* (%) |
|---|---|---|
| *o*- | 9 | 87 |
| *p*- | 10 | 82 |

**Table 5** Examples of Reduction of Iodobenzene to Benzene

| *Reaction conditions* | *Yield (%)* | *Ref.* |
|---|---|---|
| $H_2$/Pd ($CaCO_3$), KOH, EtOH, r.t. | 100 | 57 |
| $HCO_2H$/10% Pd (C), DMF, reflux 3 h | 90–95 | 71 |
| $LiAlH_4$, THF, 25 °C, 24 h | 83 | 36 |
| $NaBH_4$/$Cp_2TiCl_2$, DMF, 70 °C, 9 h | 98 | 77 |
| Zn, $NiCl_2$, NaI, $H_2O$, HMPA, 60 °C, ultrasound, 4 h | 92 | 65 |
| $Fe(CO)_5$, $K_2CO_3$, CO, MeOH, 60 °C, 48 h | 88 | 79 |

## 4.5.3 HYDROGENOLYSIS OF TRIGONAL CARBON-OXYGEN BONDS

Hydrogenolysis of the carbon–oxygen bond in alcohols, enols and phenols is relatively difficult, regardless of type.

### 4.5.3.1 Hydrogenolysis of Enols

In derivatives of enols, cleavage of the trigonal carbon to oxygen bond has been accomplished by catalytic hydrogenation and by sodium. Examples are substitution of the trifluoromethanesulfonyloxy (triflyloxy) group by hydrogen in steroidal enol triflates by catalytic hydrogenation (equation 68),[81] and by catalytic transfer of hydrogen using tributylammonium formate and palladium (equation 69),[82] and formation of cyclohexene in the Birch reduction of 1-methoxy-1,4-cyclohexadiene with sodium in liquid ammonia.[83]

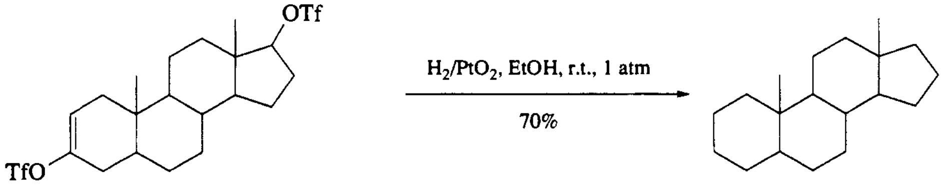

(68)

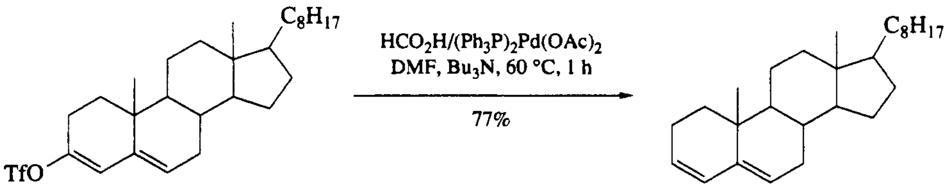

(69)

A more comprehensive discussion of the reduction of enol derivatives can be found in Chapter 4.6, this volume.

### 4.5.3.2 Hydrogenolysis of Phenols and Their Derivatives

Replacement of a free hydroxy group in phenols by hydrogen is impractical. It takes place only under very energetic conditions, for example on distillation with zinc dust, or by heating with dry lithium aluminum hydride at 350 °C.[84] Such drastic procedures are certainly not suited for compounds carrying sensitive functional groups. Substitution of hydroxy by hydrogen in polycyclic aromatic hydroxy compounds is achieved by extended refluxing with azeotropic (57%) hydriodic acid in acetic acid (equation 70).[85] The same limitation to polycyclic phenols is valid for a very gentle method of hydrogenolysis using an excess of a mixture of ethanethiol with anhydrous aluminum chloride (equation 70).[55]

Though direct hydrogenolysis of free phenols seems hardly feasible, this does not apply to derivatives of phenols such as their ethers, esters, sulfonyl esters, arylisoureas and aryloxytetrazoles. Some phenol ethers are hydrogenolyzed by heating with sodium in ethanol. Pyrogallol trimethyl ether (1,2,3-trimethoxybenzene) loses the central methoxy group, yielding the dimethyl ether of resorcinol (equation 71).[86]

The two reducing agents used for hydrogenolysis of polycyclic phenols, *i.e.* hydriodic acid and ethanethiol with aluminum chloride, are also applicable to polycyclic phenol ethers. Thus 7-methoxybenz[*a*]an-

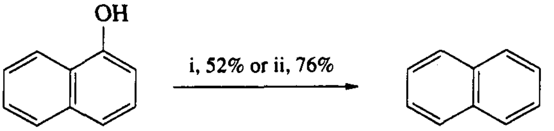

(70)

i, 57% HI, P, AcOH, reflux, 15 h; ii, 2.5 equiv. $AlCl_3$, 5 equiv. EtSH, $CH_2Cl_2$, r.t., 5 h

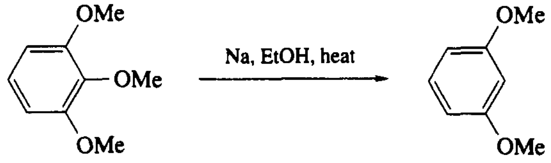

(71)

thracene is transformed in 95% yield into benz[*a*]anthracene on refluxing for 15 h with 57% hydriodic acid and acetic acid,[85] and 9-methoxy- and 9-ethoxy-phenanthrene are converted to phenanthrene on treatment with ethanethiol and aluminum chloride (equation 72).[55]

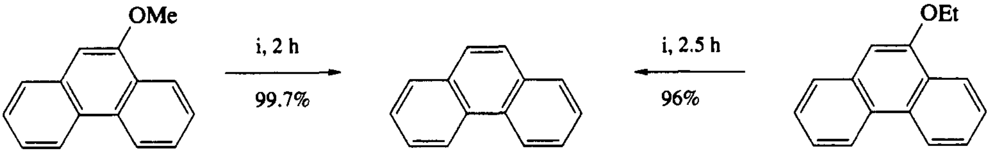

(72)

i, 2.5 equiv. $AlCl_3$, 5 equiv. EtSH, $CH_2Cl_2$, r.t.

Hydriodic acid reduces some esters of polycyclic phenols. 7-Acetoxybenz[*a*]anthracene and 7,12-diacetoxybenz[*a*]anthracene are converted to benz[*a*]anthracene on refluxing with hydriodic acid and acetic acid (equation 73).[85] On the other hand, 9-acetoxyphenanthrene is not reduced, but hydrolyzed to 9-hydroxyphenanthrene.[85]

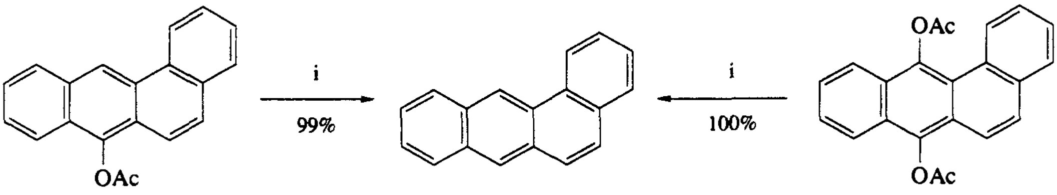

(73)

i, 57% HI, AcOH, reflux, 15 h

A more general method for hydrogenolysis of aryl–oxygen bonds is reduction of aryl trifluoromethanesulfonates (triflates). The cleavage can be effected by catalytic hydrogen transfer using triethylammonium formate[87,88] or sodium borohydride[88] as hydrogen donors, and palladium complexes as catalysts. This method is applicable not only to triflates of condensed aromatic phenols, but also to phenyl triflates. The hydrogenolysis of the triflate group occurs in preference to reduction of reducible groups present in the molecule such as nitro[87] and cyano (equations 74–76).[88]

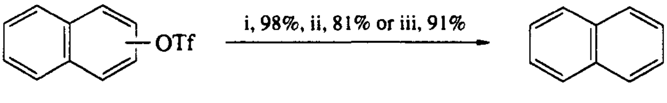

(74)

i, (TfO-α) $HCO_2H$, $Et_3N$, DMF, $Pd(OAc)_2$, $Ph_3P$, 65 °C, 12 h; ii, (TfO-α) $NaBH_4$, $(Ph_3P)_4Pd$, $Ph_3P$, THF, 62 °C, 15 h; iii, (TfO-β) $HCO_2H$, $Et_3N$, DMF, $Pd(OAc)_2$, $Ph_3P$, 60 °C, 1 h

Other aryl fluoroalkanesulfonates besides trifluoromethanesulfonyl esters of phenols can be reduced to arenes. Moreover, the preparation of such esters and their reduction may be carried out 'in one pot'. A mixture of *m*-methoxyphenol, perfluorooctanesulfonyl fluoride, triethylamine, dimethylformamide, for-

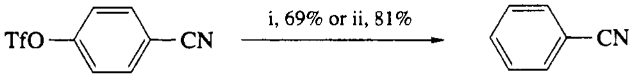

(75)

i, $HCO_2H$, $Et_3N$, DMF, $Pd(OAc)_2$, $Ph_3P$, 65 °C, 12 h; ii, $NaBH_4$, $(Ph_3P)_4Pd$, $Ph_3P$, THF, 62 °C, 2 h

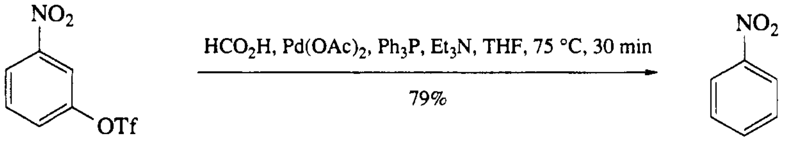

(76)

mic acid and bis(triphenylphosphine)palladium dichloride heated at 80 °C for 8 h affords a 70% yield of anisole.[89]

Several derivatives of phenols have been found to be especially suited for hydrogenolysis by catalytic hydrogenation. Phenol ethers prepared by the reaction of phenols with 1-phenyl-5-chlorotetrazole or with 2-chlorobenzoxazole are hydrogenolyzed over 5% palladium on carbon or over platinum oxide, but not over Raney nickel. The hydrogenations are run at 35 °C in benzene, ethanol or tetrahydrofuran, and give 35–89% yields of the corresponding hydrocarbons.[90] The reaction sequence is exemplified by conversion of phenylphenols to biphenyls (equation 77).

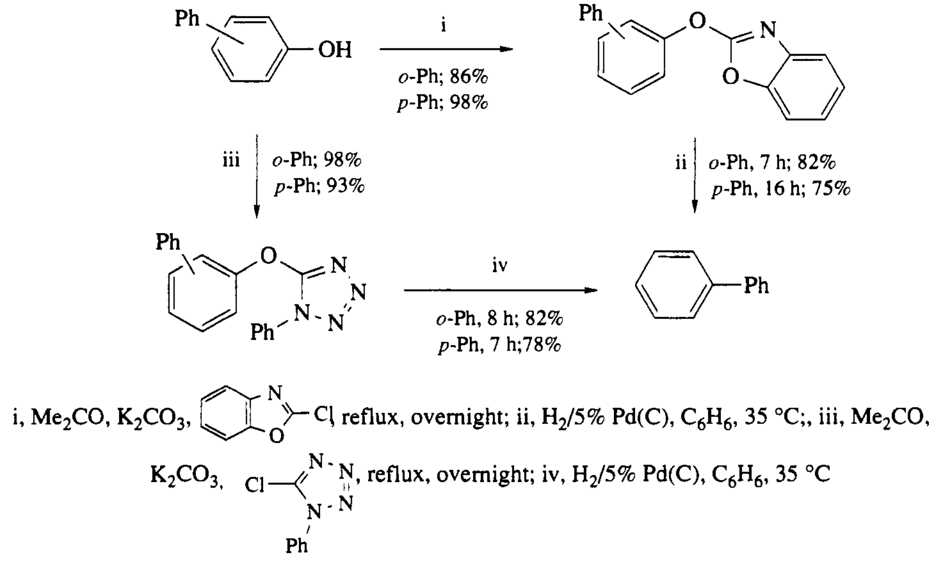

(77)

i, $Me_2CO$, $K_2CO_3$, reflux, overnight; ii, $H_2$/5% Pd(C), $C_6H_6$, 35 °C;, iii, $Me_2CO$, $K_2CO_3$, reflux, overnight; iv, $H_2$/5% Pd(C), $C_6H_6$, 35 °C

In this way, guaiacol affords an 86% yield of anisole, thymol a 72% yield of *p*-cymene, 1- and 2-naphthol 50% and 65% yields of naphthalene respectively, and *p*-chlorophenol a 70% yield of benzene with simultaneous hydrogenolysis of chlorine.[90]

Other derivatives of phenols liable to hydrogenolysis are alkylated arylisoureas: *O*-aryl-*N*,*N*-dialkylisoureas[91] and *O*-aryl-*N*,*N'*-dialkylisoureas.[92] Both derivatives suffer easy hydrogenolysis by catalytic hydrogenation under very mild reaction conditions (equation 78).[91,92]

Conversion of phenols to aryl cyanates is carried out by adding equivalent amounts of the phenol and triethylamine dissolved in ether to a stirred solution of cyanogen bromide in the same solvent at −10 °C, filtering triethylamine hydrobromide after 50 min, and evaporating the solvent *in vacuo* at room temperature.[91] Aryl cyanates are transformed to *O*-aryl-*N*,*N*-diethylisoureas by adding to their suspensions in dry ether with stirring at 0–20 °C a solution of diethylamine in ether, and by evaporating the ether after 15–60 min at room temperature *in vacuo*. Hydrogenolysis is then best effected in ethanol over 5% palladium on carbon at 20 or 45 °C at atmospheric pressure. Yields of hydrogenations are usually 95–100% (78–97% overall based on phenols). *ortho*-Substituted derivatives are hydrogenolyzed more slowly than *para* and *meta* analogs. *p*-Chlorophenol and *p*-nitrophenol are in this way converted into benzene and aniline in 88% and 52% overall yields, respectively. Under the conditions used, chlorine is hydrogenolyzed, and the nitro group is reduced to the amino group.[91]

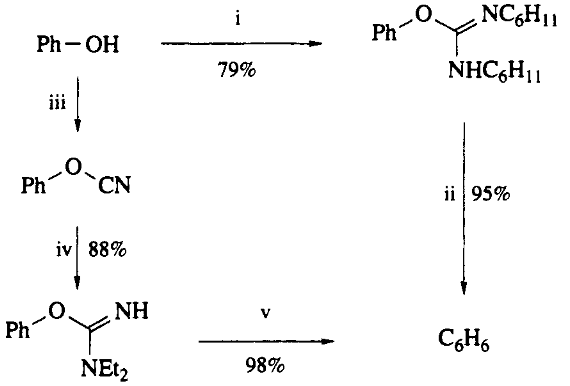

(78)

i, $C_6H_{11}N{=}C{=}NC_6H_{11}$, 70 °C, 24 h; ii, $H_2$/5% Pd(C), EtOAc, 20 °C, 1 h; iii, BrCN, $Et_3N$, $Et_2O$, –10 °C, 1 h; iv, $Et_2NH$; v, $H_2$/5% Pd(C), EtOH, 20 °C, 8 h

*O*-Aryl-*N*,*N*′-dicyclohexylisoureas are synthesized by stirring mixtures of phenols with 2–3 mol equiv. of dicyclohexylcarbodiimide at 45–100 °C for 1–3 d. Hydrogenations are accomplished in isopropyl alcohol or ethyl acetate at 20 °C and atmospheric pressure using 200–300 mg of 5% palladium on carbon or on calcium carbonate per 0.02 mol of the phenol. The hydrogenolysis can also be effected with the crude mixture of the *O*-arylisoureas and the unreacted carbodiimide using as much hydrogen as needed for hydrogenation of the excess carbodiimide.

Table 6 shows results of hydrogenolysis of phenols by all four methods described above.

**Table 6** Comparison of Results of Hydrogenolysis of Phenols after their Conversion to 5-Aryloxy-1-phenyltetrazoles (A), 2-Aryloxybenzoxazoles (B), *O*-Aryl-*N*,*N*-'diethylisoureas (C), and *O*-Aryl-*N*,*N*′-dicyclohexylisoureas (D) [90–92]

| *Phenol* | *Product* | *Method A*[a] *yield (%)* | *Method B*[b] *yield (%)* | *Method C*[c] *yield (%)* | *Method D*[d] *yield (%)* |
|---|---|---|---|---|---|
| 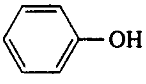 | 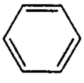 | | | 86 | 85 |
| 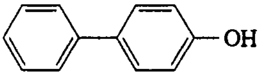 | 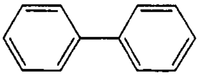 | 73 | 75 | 96 | 78 |
| 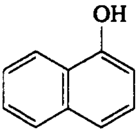 | 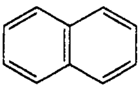 | 44 | | 92 | 44 |
| 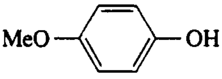 | 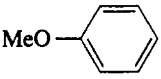 | 81 | | 90 | 70 |
| 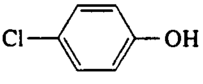 | 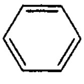 | 64 | | 88 | 76 |

[a] $H_2$/cat./tetrazole. [b] $H_2$/cat./benzoxazole. [c] $H_2$/cat./diethylisourea. [d] $H_2$/cat./dicyclohexylisourea.

## 4.5.4 HYDROGENOLYSIS OF TRIGONAL CARBON–SULFUR BONDS

Hydrogenolysis of vinyl sulfides,[26] vinyl sulfoxides[93] and vinyl sulfones[94] is rare, and may be accompanied by saturation of the double bond.[26] Thus vinylic sulfide (**29**) gives only 5% of 1,5-diphenyl-2-

pentene, and 80% of 1,5-diphenylpentane on reduction with lithium aluminum hydride in the presence of titanium tetrachloride (equation 79).[26]

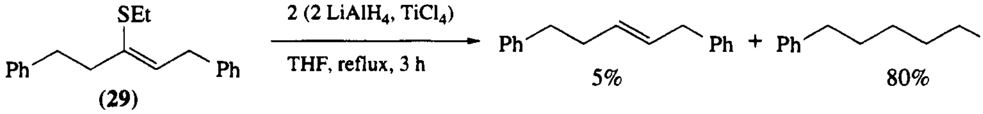

**(29)**

(79)

Vinylic sulfoxide (**30**) is desulfurized to (**31**) with *t*-butyllithium (equation 80),[93] and sulfone (**32**) affords triphenylethylene on reduction with aluminum amalgam or lithium aluminum hydride (equation 81).[94]

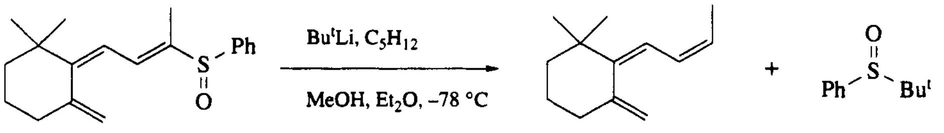

**(30)** **(31)** 72% 92–95%

(80)

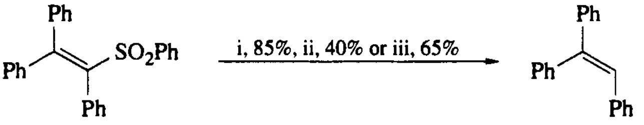

**(32)**

(81)

i, $AlHg_x$, 10% $H_2O$ in THF, reflux, 3 h; ii, $LiAlH_4$, $Et_2O$, reflux; iii, $LiAlH_4$–$CuCl_2$ (1:2)

Hydrogenolysis of compounds with sulfur atoms attached to aromatic rings such as benzenethiols, and aryl sulfides, disulfides, sulfoxides and sulfones takes place on refluxing with Raney nickel or nickel boride. Sulfur combines with nickel, and hydrogen replaces the sulfur-containing group.

Raney nickel is a stronger desulfurizing agent than nickel boride. On the other hand nickel boride, prepared from nickel(II) chloride and sodium borohydride, is more selective since it does not desulfurize aromatic sulfones. An example of such selectivity is desulfurization of *p*-phenylsulfonylphenyl *p*-tolyl sulfide (**33**), which affords diphenyl sulfone in 91% yield and toluene in 84% yield. In contrast, Raney nickel desulfurizes both the sulfide and the sulfone giving a mixture of benzene and toluene (equation 82).[95]

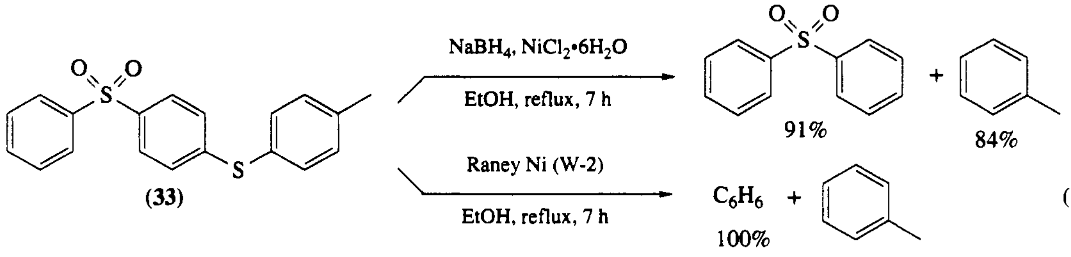

**(33)**

(82)

As is evident from Table 7, nickel boride does not give as high yields as Raney nickel. However, it offers certain advantages over the latter. In addition to higher selectivity, its preparation is faster and more simple than that of Raney nickel, it allows for better dosage, and is not pyrophoric.[95]

1-Naphthyl phenyl sulfide is desulfurized to naphthalene on refluxing with lithium aluminum hydride and titanium tetrachloride,[26] and 1-naphthyl ethyl sulfide and 1-naphthyl isopropyl sulfide are converted to naphthalene on treatment with ethanethiol and anhydrous aluminum chloride (equation 83).[55]

**Table 7** Desulfurization of Aromatic Sulfur Compounds by Nickel Boride and Raney Nickel[95]

| *Compound* | *% Yield of toluene with*<br>*Nickel boride* | <br>*Raney nickel* |
|---|---|---|
| 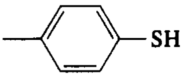 | 60 | 91 |
| 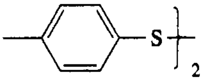 | 37 | 85 |
| 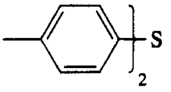 | 72 | 86 |
| 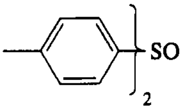 | 80 | 100 |
| 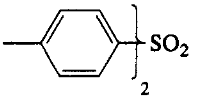 | 0 | 88 |

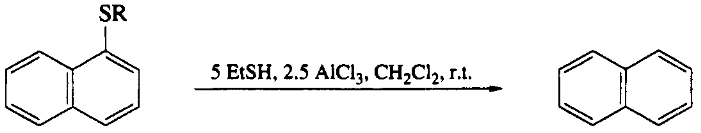

(83)

| | *Time* (h) | *Yield* (%) |
|---|---|---|
| R = Et | 5.5 | 89 |
| R = Pr | 10 | 91 |
| R = Ph (8 LiAlH$_4$, 4 TiCl$_4$, THF, reflux) | 3 | 56 |

## 4.5.5 HYDROGENOLYSIS OF TRIGONAL CARBON-NITROGEN BONDS

### 4.5.5.1 Hydrogenolysis of Enamines

Substitution of hydrogen for amino or alkylated amino groups is very rare. One example is hydrogenolysis of enamines. Reduction of enamines with complex hydrides, particularly with sodium cyanoborohydride, results in saturation of the double bond and conversion to amines. On the other hand, treatment of enamines with chloroalanes and especially alanes results in the cleavage of the carbon–nitrogen bond and formation of the corresponding alkene and amine; some examples are shown in Table 8.[96] The cleavage proper takes place by an addition–elimination mechanism in which the first step is addition of the alane across the double bond, yielding an aminoalkylalane. Whereas hydrolysis of the addition product with water would give the saturated amine, heating it in refluxing solvents results in elimination of aminoalane to afford an alkene (equation 84).[96]

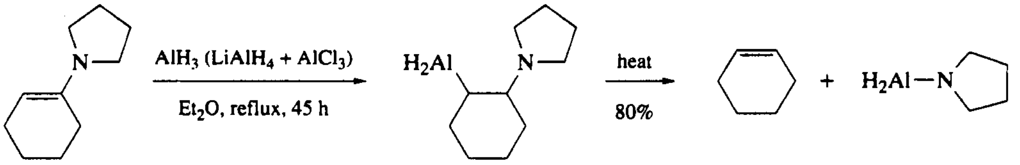

(84)

**Table 8** Examples of Reduction of Pyrrolidine Enamines[96]

| *Enamine* | *Alane* | *Alkene* | *Yield (%)* | *Amine* | *Yield (%)* |
|---|---|---|---|---|---|
| 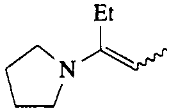 | $AlHCl_2$<br>$AlH_2Cl$<br>$AlH_3$ | MeCH=CHEt | 27<br>35<br>81 | 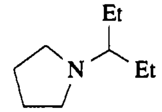 | 66<br>56<br>13 |
| 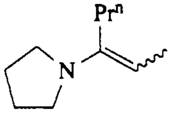 | $AlHCl_2$<br>$AlH_2Cl$<br>$AlH_3$ | EtCH=CHPr$^n$ | 19<br>30<br>85 | 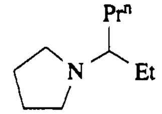 | 78<br>56<br>9 |
| 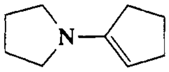 | $AlH_3$ | 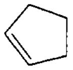 | 92 | 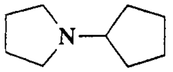 | 5 |
| 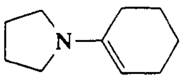 | $AlHCl_2$<br>$AlH_2Cl$<br>$AlH_3$ | 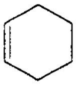 | 75<br>75<br>80 | 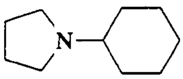 | 22<br>15<br>13 |
| 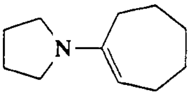 | $AlH_3$ | 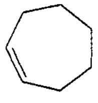 | 85 | 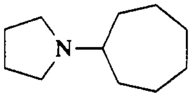 | 14 |
| 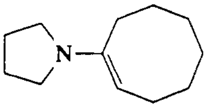 | $AlH_3$ | 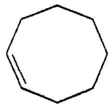 | 85 | 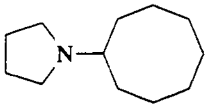 | 10 |

### 4.5.5.2 Hydrogenolysis of Aromatic Amines

One-step replacement of an aromatic amino group by hydrogen is impractical. Exceptionally, hydrogenolysis took place when *p*-toluidine was treated with solid lithium aluminum hydride at approximately 350 °C. Toluene was obtained in 17% yield.[84]

Equally unusual is hydrogenolysis of a bond between an aromatic ring and a quaternary amino group. Phenyltrialkylammonium iodides are reductively cleaved to benzene and trialkylamines by electrolysis (equation 85).[97]

$$\begin{array}{llll} \mathrm{Ph{-}\overset{+}{N}Me_3\,\overset{-}{I}} \xrightarrow{\mathrm{Na_2CO_3,\ H_2O,\ Pb\ cathode,\ 30\ A,\ 2.5\ h}} & \mathrm{C_6H_6} & + & \mathrm{Me_3N{\bullet}HCl} \\ & 75\% & & 77\% \end{array} \qquad (85)$$

### 4.5.5.3 Hydrogenolysis of Arenediazonium Salts

A general method of replacement of the primary aromatic amino group by hydrogen is reduction of aromatic diazonium salts, prepared by diazotization, typically by treatment of the primary amine or its salts with sodium or potassium nitrite in strongly acidic aqueous media. Conversion to the diazonium salts may also be accomplished in nonaqueous media using acetic acid,[98] or using alkyl nitrites (equation 86).[99] Most diazonium salts decompose at temperatures above 0–5 °C. Only certain salts such as naphthalene-1,5-sulfonates,[100] tetrafluoroborates[101–103] and hexafluorophosphates[104,105] are stable at room temperature.

Reduction of diazonium salts resulting in replacement of the diazonium group by hydrogen has been known for 125 years, and has been carried out using alcohols,[106–109] sodium stannite,[110] hypophosphorous acid,[111,112] formaldehyde,[113] zinc,[100] and other reagents.[114] In addition to these classical reagents, reviewed in an article in *Organic Reactions*,[114] several new reducing agents have been developed:

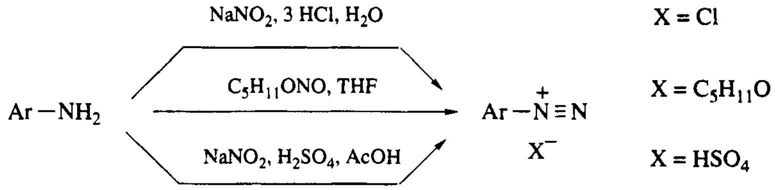

(86)

potassium ferrocyanide,[115] tin in hydrochloric acid,[116,117] sodium borohydride,[102] triethylsilane,[103] tributylstannane (tributyltin hydride),[103] and a roster of organic compounds which provide hydrogen for combinations with the aryl cations[104] or radicals[99,103,108,118] formed by decomposition of the diazonium salts.

The mechanism of displacement of the diazonium group by hydrogen depends on the chemical nature of the diazonium compound, the reducing agents and the reaction conditions. Electron-withdrawing groups in the aromatic ring generally facilitate the replacement.[115]

In appropriately polar solvents, diazonium salts decompose to nitrogen and aryl cations, and formation of arenes may take place by transfer of hydrogen from the reducing agent or from the solvent. Depending on reaction conditions, an ionic mechanism (equation 87),[119] or a radical mechanism (equation 88)[107] may be operating, and experimental evidence is claimed for both. However, the radical mechanism seems to have more support.

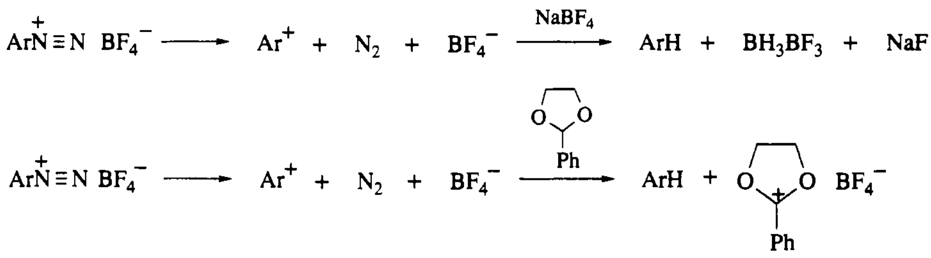

(87)

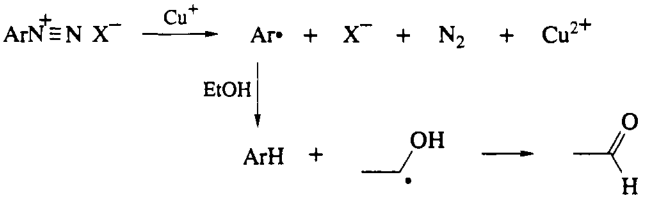

(88)

In reduction of arenediazonium fluoroborate with tributylstannane, formation of the arene takes place not only by hydrogen atom abstraction from the stannane, but also by reaction of the radical intermediate with the solvent. Reduction of 4-methoxybenzenediazonium fluoroborate with tributyltin deuteride in tetrahydrofuran or acetonitrile affords not only deuterated but also deuterium-free arenes (equation 89). There are also small amounts of biphenyl by-products.[103]

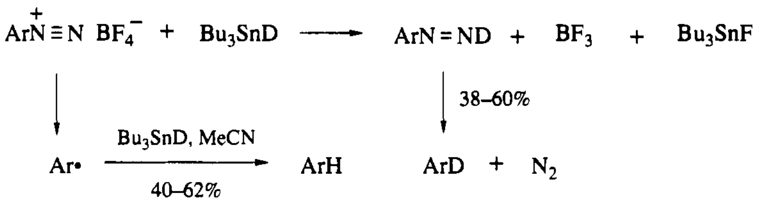

(89)

Finally, hydrogen transfer can occur intramolecularly, as in the reduction of arenediazonium fluoroborates with formamide. The intramolecular transfer has been proven by reaction with *C*-deuterated formamide, which introduced deuterium in place of the diazonium group (equation 90).[101]

Sodium stannite converts (**34**) to (**35**). Both the diazonium salt and the sodium stannite are prepared *in situ* (equation 91).[110]

Tin metal in the presence of aqueous hydrochloric acid in a mixture of dichloromethane and polyethylene glycol replaces the diazonium group with hydrogen in 38–76% isolated yields (equation 92).[116,117]

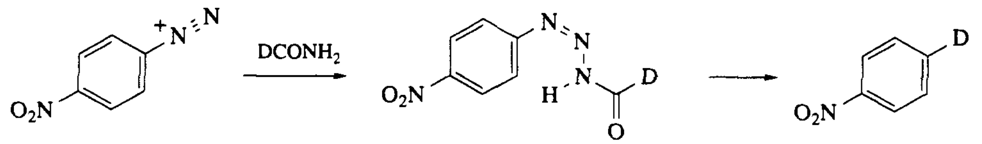

(90)

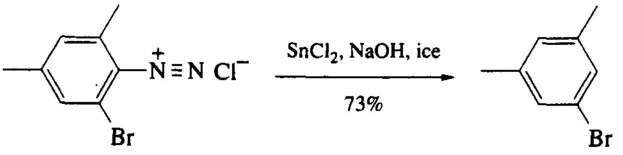

**(34)** **(35)**

(91)

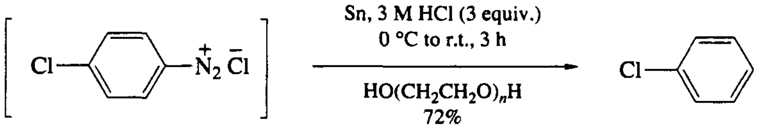

(92)

The most specific reagent for replacement of a diazonium group by hydrogen is hypophosphorous acid.[111,112] It is commercially available, it works at room temperature, and it is especially selective: it does not reduce any of the common functional groups present in diazonium salts. The reductive removal of the amino group can be carried out in one pot using a large excess (5–15 mol) of aqueous hypophosphorous acid after diazotization (equation 93).[114] Both diazotization and reduction may be carried out in hypophosphorous acid. Under such conditions, an amino group linked to the aromatic ring is replaced by hydrogen, while aliphatic amino groups are left intact (equation 94).[111]

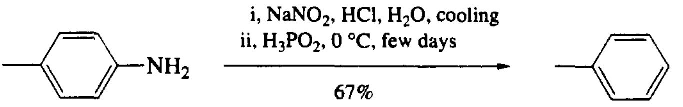
i, NaNO$_2$, HCl, H$_2$O, cooling
ii, H$_3$PO$_2$, 0 °C, few days
67%

(93)

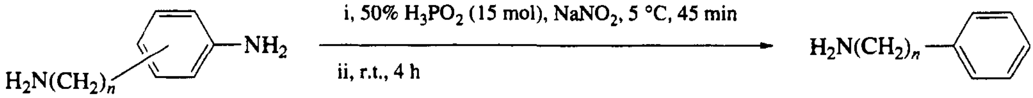

(94)

| | *Yield*(%) |
|---|---|
| *m*-, *n* = 1 | 87 |
| *m*-, *n* = 2 | 70 |
| *p*-, *n* = 1 | 84 |
| *p*-, *n* = 2 | 71 |

Historically, the first replacement of a diazonium group by hydrogen was accomplished with alcohols.[109] Of these, ethanol is the best, while methanol tends to convert diazonium compounds to aryl methyl ethers.[114] The hydrogen atom replacing the diazonium group comes from the alcohol, which is converted to the corresponding aldehyde. The reaction is catalyzed by UV irradiation[108] and by copper(I) oxide.[106,107] Copper(I) oxide alone reduces the diazonium compounds, but in poor yields.[107] The reaction can be carried out in aqueous media[108] or in organic solvents.[106,107]

Hydrogen donors other than alcohols have been used for replacement of the diazonium group by hydrogen; these include acetone,[108] tetrahydrofuran,[99,120] dioxane,[120] dioxolane,[120] ethylene glycol dimethyl ether,[120] hexamethylphosphoramide (HMPA)[121] and other compounds.[120]

Very often, the replacement of a diazonium group by hydrogen is carried out using stable crystalline diazonium salts, such as the 1,5-naphthalenedisulfonates,[100] 2-naphthol-1-sulfonates,[100] tetrafluoroborates,[101–103,115,118] hexafluorophosphates[104] and mercury bromides.[72]

Diazonium tetrafluoroborates are reduced with potassium ferrocyanide at rates depending strongly on substituents in the benzene rings. Relative rates of reduction of *p*-nitrobenzenediazonium, benzenediazonium and *p*-methoxybenzenediazonium fluoroborates have been found to be 3062:1:0.0031, showing a span of six orders of magnitude, electron-withdrawing substituents increasing, and electron-releasing groups decreasing the rates.[115]

A useful addition to the roster of reducing agents capable of replacement of diazonium groups by hydrogen in good yields is sodium borohydride. It is applied to dry diazonium fluoroborates in suspension in methanol or in solution in dimethylformamide (equation 95).[102]

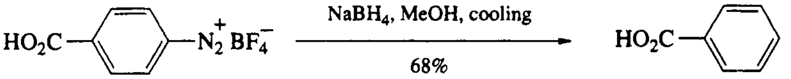

(95)

Another hydride used successfully for the same purpose is tributylstannane (tributyltin hydride) in ether, tetrahydrofuran or acetonitrile.[103] Triethylsilane acts similarly, but more slowly and more selectively: it does not reduce nitro groups (equation 96).[103]

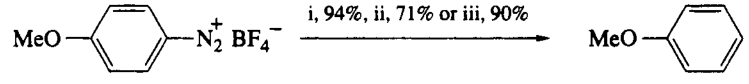

(96)

i, $Bu_3SnH$, THF, r.t., 50 min; ii, $Bu_3SnH$, MeCN, r.t., 1.5 h; iii, $Et_3SiH$, MeCN, r.t., overnight

Other hydrogen donors which have been applied to the reduction of diazonium fluoroborates are formamide[101] and *N*-benzyl-1,4-dihydronicotinamide (equation 97).[118]

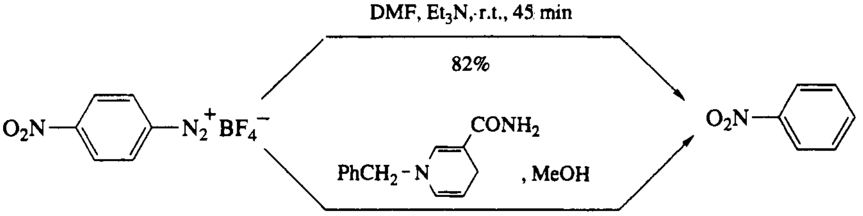

(97)

Like diazonium fluoroborates, diazonium fluorophosphates decompose under anhydrous conditions in tetramethylurea to give the parent compounds. The reaction is carried out by adding dry diazonium salts to tetramethylurea at room temperature. The reaction is exothermic, but in some cases warming to 65 °C is desirable (equation 98).[104]

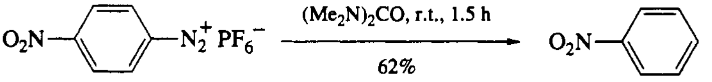

(98)

An unexpected displacement of a diazonium group in diazotized aminonaphthalenes by hydrogen was discovered when diazonium mercury(II) bromides, prepared by treatment of diazonium bromides with mercury(II) bromide, were stirred at room temperature for 10–20 min in hexamethylphosphoramide (HMPA) (equation 99).[121]

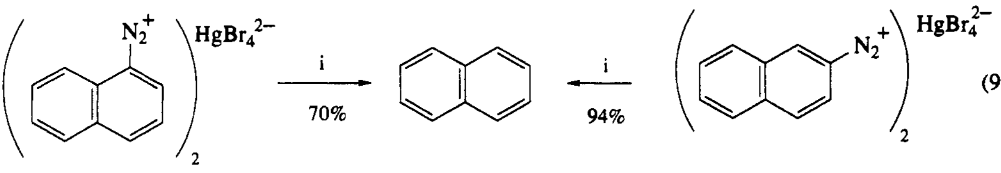

(99)

i, HMPA, r.t., 10–20 min

Examples of replacement of diazonium groups by hydrogen by means of various reducing agents are shown in Table 9.

**Table 9** Comparison of Various Methods of Replacement of Diazonium Group by Hydrogen

| | *% Yield of product with* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Sn/HCl* | *$H_3PO_2$* | *EtOH/hv* | *EtOH/$Cu_2O$* | *$NaBH_4$* | *$Et_3SiH$* | *$Bu_3Sn$* | *$HCONH_2$* | *$(Me_2N)_2CO$* |
| 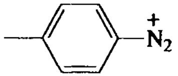 | | 77–83[104] | | 45[106] | | 25[103] | 87[103] | | 25–30[104] |
| 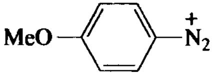 | 74–87[117]<br>(48–76)[a] | | | | | 90[103] | 94[103] | | |
| 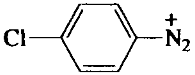 | 64–100[116]<br>(50–72)[a] | | | | | 70[103] | 89[103] | | 70[104] |
| 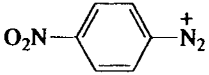 | | 55–60[104] | | 97[106] | | 72[103] | 52[103b] | 82[101] | 62[104] |
| 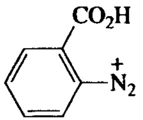 | | | 92.5[108] | | 77[102] | | | | |

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[a] Yield of pure compound. [b] Partial reduction to aniline lowered the yield.

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# 4.6

# Reduction of Ketones to Alkenes

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## 4.6.1 INTRODUCTION

The carbon–carbon π-bond plays a central role in synthesis, not only in its own right as a functional group present in many target molecules, but also as a synthetic intermediate through which an extraordinary number of important transformations are accomplished. In fact, nearly two complete volumes of 'Comprehensive Organic Synthesis' are devoted to alkene reactions, many of which require stereo- or regio-isomerically homogeneous starting materials if they are to be useful. This chapter examines one of the more important general routes to this fundamentally important functional group, the transformation of ketones into alkenes.

Although there are a few methods for carrying out this reductive process in a single step, it is rarely conducted by such direct methods. In the vast majority of cases, two-step procedures are employed. The ketone can be first converted into a vinyl–heteroatom derivative (*e.g.* a vinyl phosphate) or a substituted hydrazone, followed by reductive cleavage or elimination, respectively. Alternatively, the transformation can be accomplished by reduction of the ketone followed by elimination; however, since both ketone reductions and elimination reactions are covered elsewhere in this series, this chapter will focus on the former methods.

## 4.6.2 DIRECT METHODS

There are few reports of the direct conversion of ketones into alkenes. Phiel has reported the conversion of pentan-2-one into pent-1-ene in the vapor phase over a supported $MnO_2$ catalyst (Scheme 1).[1] No other examples were reported, so that that the generality of the selectivity in favor of the less substituted double bond is uncertain.

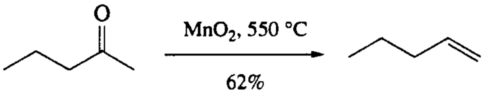

Scheme 1

2-Phenylacetophenone has been reduced to (*E*)-stilbene using elemental sulfur in HMPA at elevated temperatures (Scheme 2).[2] Since (*Z*)-stilbene is rapidly converted into the (*E*)-isomer under the reaction conditions, it is unclear whether (*Z*)-stilbene forms first and then isomerizes to the more stable (*E*)-isomer or whether (*E*)-stilbene forms directly. These conditions were also found to convert 2-hydroxy-2-phenylacetophenone into (*E*)-stilbene.

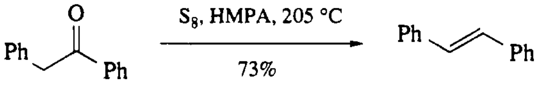

Scheme 2

Finally, functionalized cyclohexanone derivatives have been converted into the corresponding cyclohexene products by zinc and trimethylsilyl chloride (Scheme 3).[3] The reaction, which proceeds through an ylide-stabilized organozinc carbenoid intermediate rather than a silyl enol ether, shows a slight preference for the formation of the more substituted double bond, and is compatible with acetoxy and halogen functional groups. Similar conditions have been employed to convert 3-keto steroids into the corresponding $\Delta^2$-derivatives regioselectively, as well as selectively reducing the 3-keto group of 3,6-, 3,7-, 3,17-, 3,20-diketo steroids to the $\Delta^2$-products, leaving the other ketone group intact.[4]

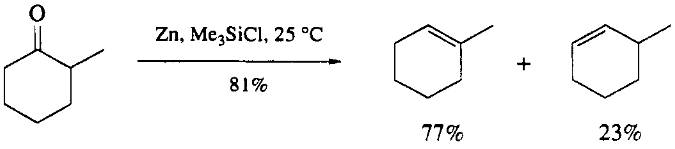

Scheme 3

## 4.6.3 REDUCTION AND SUBSEQUENT DEHYDRATION

One of the most general reaction sequences for the transformation of ketones into alkenes is reduction of the ketone to the corresponding alcohol followed by dehydration. While this method has been widely used, it often suffers from a lack of both stereo- and regio-chemical control in the formation of the double bond. Since the reduction of ketones and the subsequent dehydration of the resultant alcohols are covered in depth in other sections (this volume, Chapter 1.1 and Volume 6, Chapter 5.1), we present here only a few representative examples and divert the reader to these other sections for a detailed analysis of this area. In the total synthesis of (+)-occidentalol (Scheme 4), 1,2-reduction of the enone moiety gave the corresponding allylic alcohol, which was selectively dehydrated in the presence of a tertiary alcohol to give the diene system.[5] Reduction of an enone and subsequent dehydration of the resulting allylic alcohol was also employed in preparing the unsaturated decalin fragment of compactin (Scheme 4).[6] In this instance, the resulting 1,3-diene arose from carbon–carbon double bond migration during the dehydration. Finally, Murae *et al.* have reduced and dehydrated a highly functionalized pyrone to the corresponding dihydropyran in the course of the formal total synthesis of bruceantin.[7] These representative examples illustrate that this methodology can be useful in complex molecules and that it is compatible with an array of functional groups, including amines, aryl and silyl ethers, tertiary alcohols, dithianes, esters and lactones.

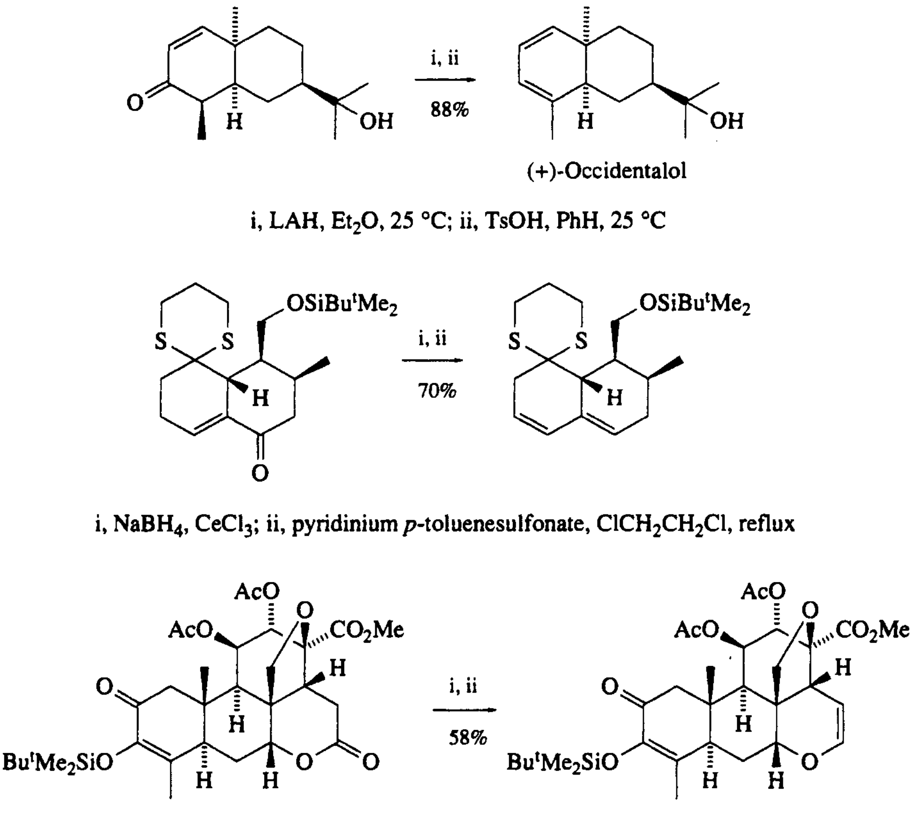

(+)-Occidentalol

i, LAH, $Et_2O$, 25 °C; ii, TsOH, PhH, 25 °C

i, $NaBH_4$, $CeCl_3$; ii, pyridinium *p*-toluenesulfonate, $ClCH_2CH_2Cl$, reflux

i, $NaBH_4$, EtOH–$CH_2Cl_2$, 0 °C; ii, $POCl_3$, pyridine, 100 °C

**Scheme 4**

Not surprisingly, if the ketone in the starting material is flanked by an unsaturated functional group (*i.e.* $CO_2Me$[8] or $NO_2$[9,10]), dehydration gives exclusively the α,β-unsaturated product (the β,γ-unsaturated regioisomer is available *via* other methods, discussed below). While the methods described above involve direct dehydration of the alcohol, a number of reduction–dehydration sequences have been conducted by initial reduction of the ketone and subsequent derivatization of the resultant alcohol (as the phenyl methanesulfonate, methyl *p*-toluenesulfonate, xanthate, acetate, methyl ether, *etc.*). This type of reduction–dehydration sequence is discussed in detail in Volume 6, Chapter 5.1.

## 4.6.4 REDUCTIVE ELIMINATION OF α-SUBSTITUTED KETONES

A variety of α-substituted ketones (α-halo, -hydroxy, -methoxy and -amino) have been converted into alkenes by reductive elimination. Obviously, this approach, depends not only on the feasibility of α-functionalization but also on the ability to introduce the α-substituent regioselectively. α-Halo ketones, which are readily prepared from the starting ketone,[11] have been subjected to reductive elimination conditions to afford the desired alkenic products. For example, in the preparation of (±)-eriolanin (Scheme 5),[12] the protected dihydroxy keto ester is treated sequentially with LDA and $Br_2$ to afford the α-bromo ketone. Selective ketone reduction to the halohydrin followed by zinc-induced elimination of HOBr affords the partially deprotected alkenic ester. Similar conditions have been employed in steroidal systems (Scheme 6).[13]

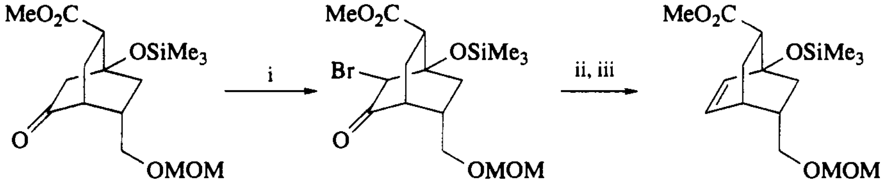

(74% overall)

i, LDA, $Br_2$, $NaHCO_3$; ii, $NaBH_4$, EtOH; iii, Zn, EtOH

Scheme 5

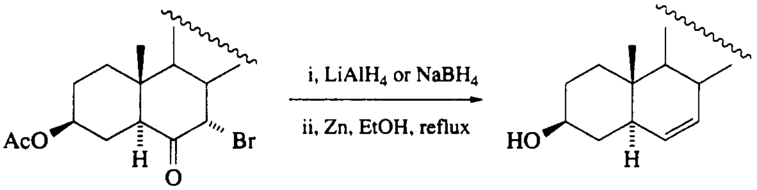

Scheme 6

In 1913, Kishner observed in one instance that under standard Wolff–Kishner reduction conditions, 2-hydroxy-2,6-dimethyloctan-3-one underwent eliminative reduction upon treatment with hydrazine hydrate and base at elevated temperatures to afford 2,6-dimethyloctan-2-ene (Scheme 7).[14] This same reaction was later found to occur in the case of α-methoxy ketones[15] and has since been referred to as the Kishner eliminative reduction. The reaction entails initial formation of the hydrazone and elimination of the α-substituent to afford the intermediate alkenyldiazene, which subsequently collapses to the desired alkene. Given the facile transformation of ketones into α-halo ketones,[11] these conditions have been used to introduce alkenes regioselectively in the 2α-halocholestan-3-one series[16] as shown in Scheme 8. Yields of 2-cholestene parallel the resistance of the α-halogen to undergo competitive elimination reactions.

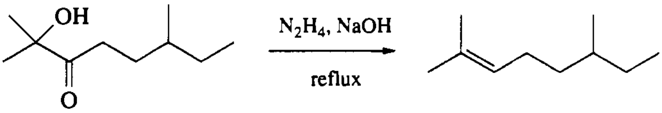

Scheme 7

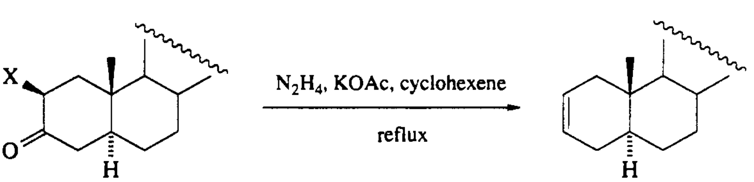

| | | | |
|---|---|---|---|
| X = F | 71% | X = Br | 62% |
| X = Cl | 68% | X = I | 54% |

Scheme 8

Similar conditions have also been employed in the reduction of α-tosyl ketones, but only low yields were realized.[17] On the other hand, a wide variety of other α-substituents have been shown to undergo reductive elimination to afford good yields of the alkenic product (Scheme 9).[17] The temperature at which the reaction occurs in these examples depends on the nature of the substituent and its ease of elimination. Kishner eliminative reduction conditions have also been applied to 2-azacycloalkanones, for which ring size determines the course of reaction.[18] While 1-azacyclohexan-3-ones give only the Wolff–

Kishner reduction product (azacyclohexanes), the seven-membered ring analogs afford the acyclic eliminative reduction products (Scheme 10). This difference is presumably due to the greater ease with which the leaving group in the larger ring can follow an energetically favorable trajectory (*i.e.* perpendicular to the incipient $\pi$-bond) during elimination. A wide variety of acyclic $\alpha$-amino ketones have also been studied as substrates for the eliminative reduction pathway. The yield of alkene (*versus* the normal Wolff–Kishner reduction product) parallels the size of the $\alpha$-amino substituent and hence the steric bulk around the C—N bond.[18]

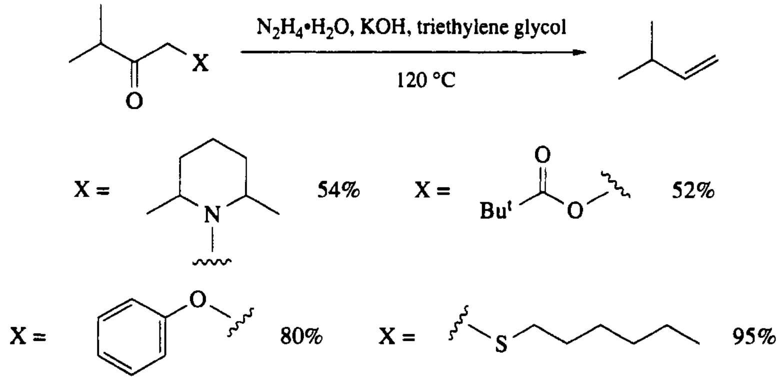

**Scheme 9**

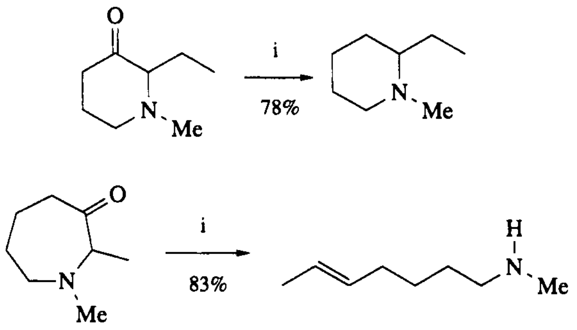

i, $N_2H_4{\bullet}H_2O$, KOH, triethylene glycol, 120 °C

**Scheme 10**

The most widely applied extension of the Kishner eliminative reduction methodology is the Wharton reaction,[19] in which the hydrazone derivative of an $\alpha,\beta$-epoxy ketone undergoes elimination to generate an allylic alcohol (Scheme 11). Since the starting epoxy ketone is derived directly from the corresponding enone, this reaction sequence represents an overall transformation of enone into allylic alcohol in which oxygen undergoes a 1,3-transposition within a concomitant migration of the carbon–carbon double bond.

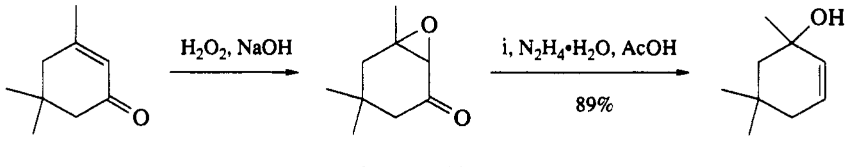

**Scheme 11**

This transformation has found extensive use in converting cyclopentenone and cyclohexenone ring systems to the rearranged allylic alcohols during the course of the total syntheses of natural products. In the preparation of (±)-quadrone (Scheme 12),[20] the tricyclic enone was epoxidized and the resulting $\alpha,\beta$-epoxy ketone treated with hydrazine to afford the allylic alcohol. The cyclopropane-directed epoxidation shown in Scheme 13 gives an allylic alcohol that is taken on to (–)- and (+)-carenones.[21] In the total synthesis of (±)-α-costal (Scheme 14),[22] Liu and Wynn selectively epoxidized an enone carbon–carbon double bond in the presence of an isolated alkene in order to obtain a diene alcohol. Finally, the Wharton reaction has been employed, although with only modest success, in the preparation of 2,6-epoxy-1(2*H*)-benzoxocin sugars (Scheme 15).[23]

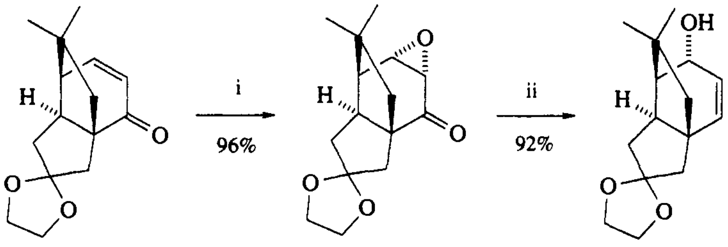

i, Bu$^t$OOH, NaOH, MeOH, 25 °C; ii, $N_2H_4$•$H_2O$, MeOH, AcOH

**Scheme 12**

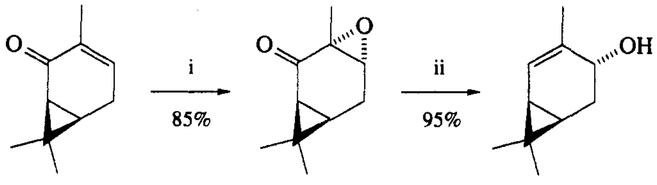

(–)-Carvone

i, 30% $H_2O_2$, NaOH; ii, $Me_3SiCl$, $N_2H_4$•$H_2O$, DMF

**Scheme 13**

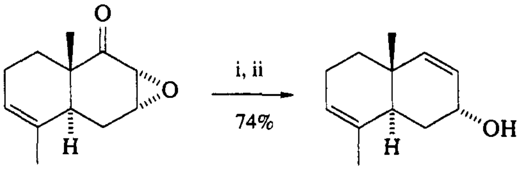

i, $N_2H_4$, AcOH; ii, $CuCl_2$, THF, $H_2O$, pH 7

**Scheme 14**

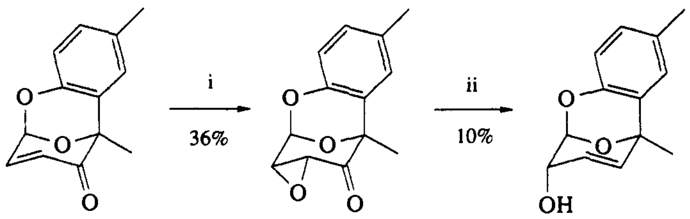

i, NaOCl, dioxane; ii, $N_2H_4$, AcOH

**Scheme 15**

While it is not clear from these applications whether the Wharton reaction necessarily proceeds *via trans* diaxial epoxide opening, Ziegler *et al.*[24] in synthetic studies towards quassinoids, have found that there is no such stereoelectronic requirement in a rigid *trans*-decalin ring system (Scheme 16).

The Wharton reaction has also been applied to the conversion of exocyclic α,β-epoxy ketones to the corresponding exocyclic hydroxy methylene products (Scheme 17).[25] Similar conditions transform exocyclic methyl ketones into the exocyclic ethylidene derivative (Scheme 18).[26] Not unexpectedly, the (*Z*)-alkene is isolated in only slightly higher yields than the (*E*)-isomer.

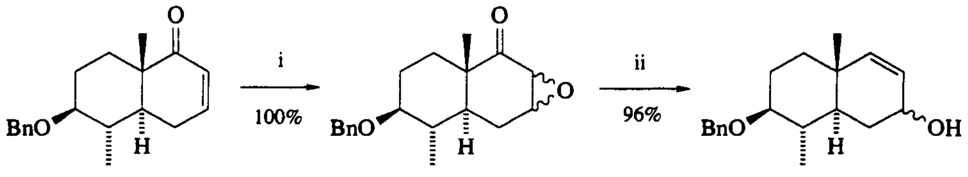

i, 30% $H_2O_2$; 6 M NaOH, 15 °C; ii, 95% $N_2H_4$, AcOH, MeOH

Scheme 16

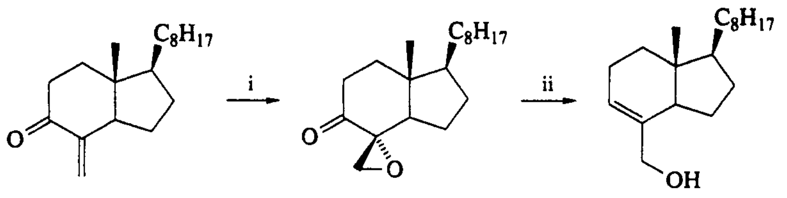

i, 30% $H_2O_2$, 20% NaOH, MeOH; ii, $N_2H_4$, MeOH, 0 °C

Scheme 17

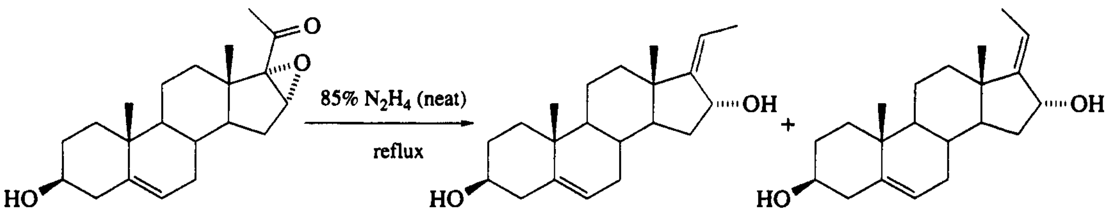

Scheme 18

There are a few applications of the Wharton reaction in acyclic systems. For example, treating an acyclic α,β-epoxy ketone (Scheme 19) with hydrazine hydrate at 0 °C affords the expected product, but as a 1:1-(*E*):(*Z*) mixture.[27] However, the major product (60%) in this particular case is the bicyclic alcohol that arises *via* cyclization of the intermediate vinyl radical (or anion) on the endocyclic carbon–carbon double bond.

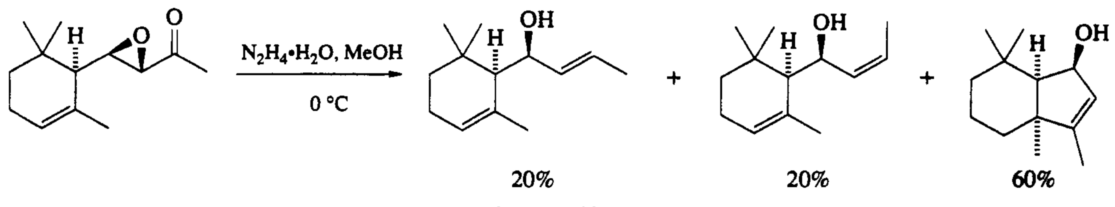

Scheme 19

In isolated cases in which the Wharton reaction has failed, alternative strategies have been developed. For example, in a total synthesis of confertin,[28] the starting enone (Scheme 20) was reduced to an allylic alcohol and subsequently epoxidized to afford the epoxy alcohol. Conversion to the phenyl methanesulfonate followed by reduction gave the sought-after rearranged allylic alcohol. An attempted Wharton reaction in the total synthesis of β-2,7,11-cembratriene-4,6-diol (β-CBT; Scheme 21)[29] also failed to give the desired allylic alcohol. In this case, initial epoxide formation was followed by reduction of the ketone (rather than treatment with hydrazine) and the resultant secondary alcohol was converted into the phenyl methanesulfonate. Reduction of the epoxy phenyl methanesulfonate then afforded the formal Wharton product in good yields. This adaptation also gives high yields in acyclic systems.[30]

A final method of alkene formation from α-derivatized ketones entails formation of unsaturated tosylhydrazones from α,β-unsaturated ketones followed by conjugate reduction with sodium cyanoborohydride in acid media.[31] This transformation, which proceeds with regioselective migration of the original double bond, has been applied to the synthesis of quassinoids by Ganem *et al.* (Scheme 22).[32] A similar

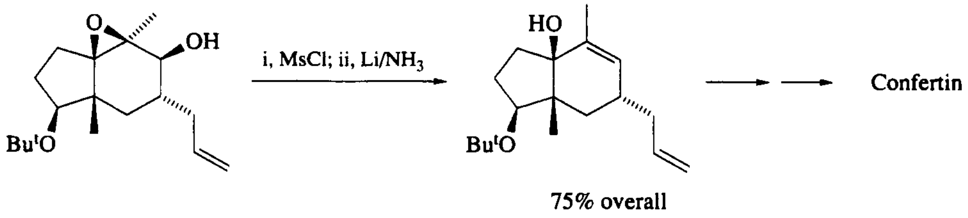

Scheme 20

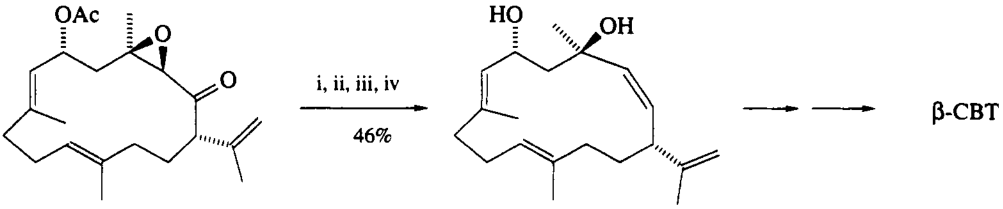

i, NaBH$_4$, 0 °C; ii, MsCl, Et$_3$N, 0 °C; iii, K$_2$CO$_3$, 0 °C; iv, Na/NH$_3$, –40 °C

Scheme 21

reaction, with diborane as the reducing agent, has been employed in the conversion of $\Delta^4$-cholesten-3-one into 5α-cholest-3-ene and of cholestenone into cholesta-3,5-diene.[33]

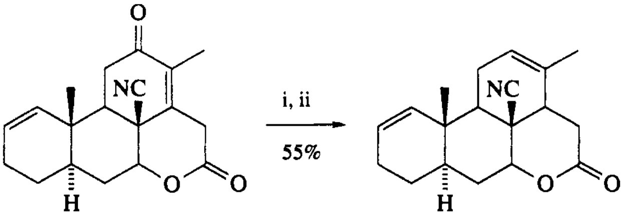

i, $p$-MeC$_6$H$_4$SO$_2$NHNH$_2$; ii, NaCNBH$_3$, HOAc, 68 °C

Scheme 22

## 4.6.5 REDUCTION OF VINYL–HETEROATOM DERIVATIVES

### 4.6.5.1 Vinyl Esters

One of the most useful methods for the transformation of ketones into alkenes is conversion of the ketone, *via* enolate formation, into a vinyl–OR derivative and subsequent reductive cleavage of the $sp^2$-oxygen bond. Because there are a number of ways to generate either the kinetic or thermodynamic enolate selectively, this route offers one of the most important ways of introducing the alkenic double bond with excellent control of regioselectivity.

#### *4.6.5.1.1 Vinyl phosphates*

Within the general category of vinyl esters, the most widely used method for ketone to alkene transformation involves the sequence ketone → vinyl phosphate → alkene, which was originally developed independently by Fetizon[34] and by Ireland.[35] Fetizon's procedure requires α-halogenation of the starting ketone and subsequent vinyl phosphate formation *via* a Perkow reaction with triethyl phosphite (Scheme 23). In contrast, Ireland's method (Scheme 24)[35] offers a direct route to vinyl phosphates *via* controlled enolate formation and trapping. More recently, Ireland has also employed vinyl *N,N,N′,N′*-tetramethylphosphorodiamidate derivatives,[36] rather than the original diethyl phosphates (Scheme 25), although it is not clear if this modification is superior to the original procedure. Besides reduction with Li or Na in an amine solvent, vinyl phosphates have also been reduced to the alkene under aprotic conditions with activated Ti.[37] These reduction conditions afford better yields of the alkene, and enones can be reduced to the corresponding diene without overreduction of the diene products.

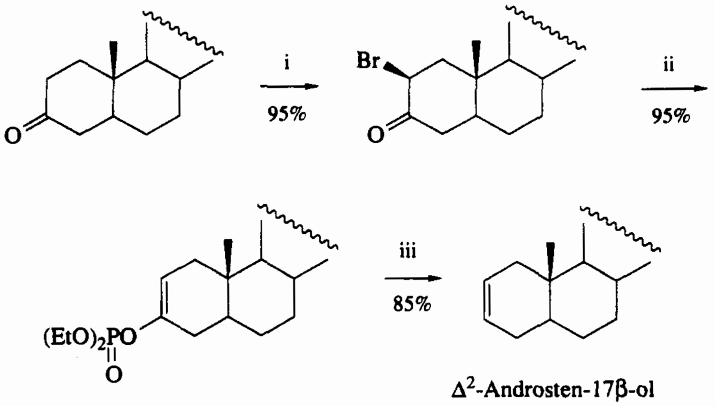

$\Delta^2$-Androsten-17β-ol

i, $Me_3PhN^+Br^-$; ii, $(EtO)_3P$ (neat), Δ; iii, Li/$NH_3$, Bu$^t$OH

**Scheme 23**

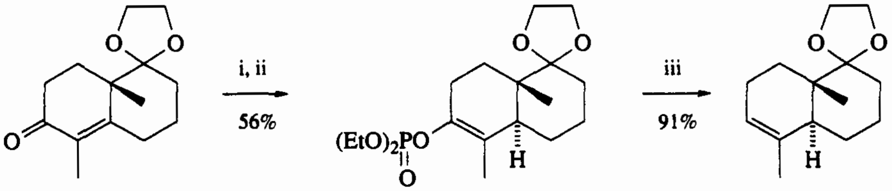

i, Li/$NH_3$; ii, $(EtO)_2POCl$; iii, Li, $EtNH_2$, Bu$^t$OH

**Scheme 24**

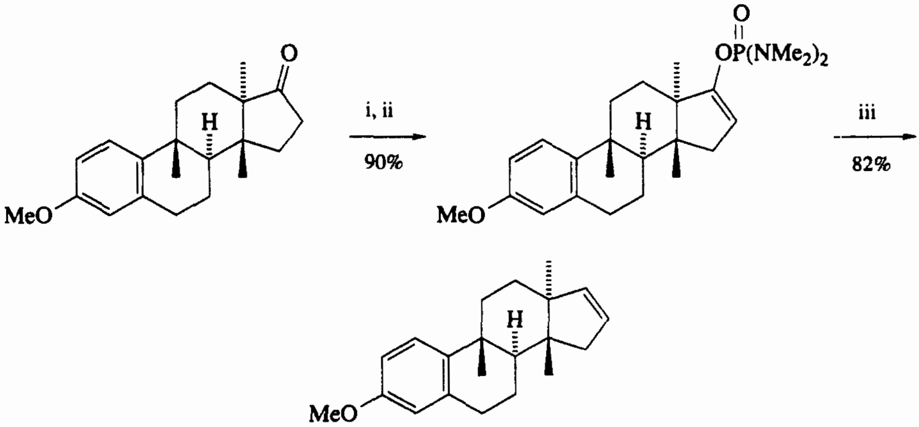

i, LDA; ii, $(Me_2N)_2POCl$, TMEDA; iii, Li/$NH_3$

**Scheme 25**

Despite these modifications, Ireland's original method of both vinyl phosphate formation and reduction remains the most popular. In studies on the cationic rearrangements of [4.3.2]propellanes, Smith *et al.*[38] converted a tricyclic ketone, *via* the diethyl vinylphosphate derivative, into the corresponding alkene (Scheme 26). In a similar manner, Kamata *et al.*[39] prepared $\Delta^{11}$- and $\Delta^6$-steroids (Scheme 27) with excellent control of regiochemistry. As shown in this example, esters are susceptible to cleavage under the standard reduction conditions (Li, $NH_3$, Bu$^t$OH, −35 °C), while acetals survive.

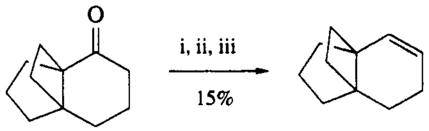

i, LDA; ii, $(EtO)_2POCl$; iii, Li, $EtNH_2$

**Scheme 26**

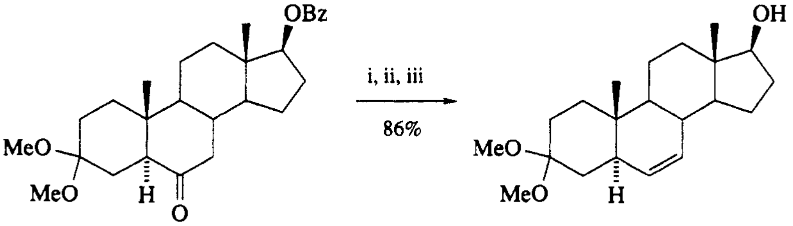

i, LDA, −78 °C; ii, $(EtO)_2POCl$, −78 °C; iii, $Li/NH_3$, $Bu^tOH$, −35 °C

**Scheme 27**

Vinyl *N,N,N′,N′*-tetramethylphosphorodiamidates have also been of value in the total syntheses of natural products, such as (±)-castelanolide (Scheme 28)[40] and (±)-albene (Scheme 29).[41] Acetals survive the reduction, but benzyl ethers are cleaved.

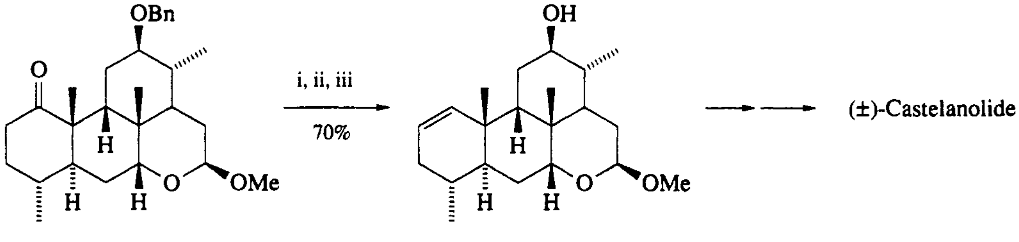

i, $LiNPr^i_2$, TMEDA, −78 °C; ii, $(Me_2N)_2POCl$, 0 °C; iii, $EtNH_2$, $Bu^tOH$

**Scheme 28**

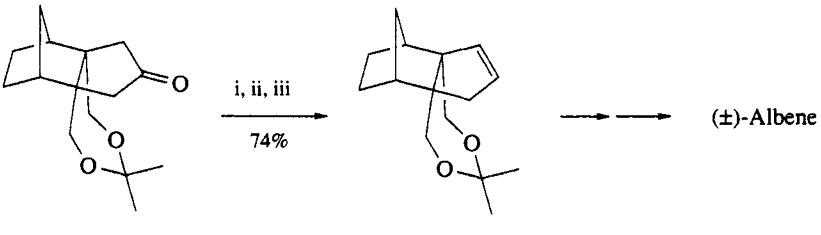

i, $LiNPr^i_2$, −78 °C; ii, $(Me_2N)_2POCl$, HMPA, 0 °C; iii, Li, $EtNH_2$, $Bu^tOH$, 5 °C

**Scheme 29**

This methodology has also been applied to the conversion of alkyl esters into vinyl ethers[42] with high stereoselectivity favoring the (*Z*)-isomer (Scheme 30). While standard Li/amine reduction conditions were not applicable, the enol phosphates could be reduced using triethylaluminum and tetrakis(triphenylphosphine)palladium.

In a related reaction, aryl phosphates (prepared from the corresponding phenols) have been reduced to the parent hydrocarbon with Li or Na in $NH_3$.[43] Yields are increased if electron-donating groups are present on the aromatic ring. While reduction of the aromatic ring itself can be avoided under these conditions, addition of an alcohol to the reducing medium results in isolation of the fully saturated cyclohexane analog. Ireland *et al.*[44] have reported a similar reduction of a phenol to the arene with $Li/NH_3$ and ethanol.

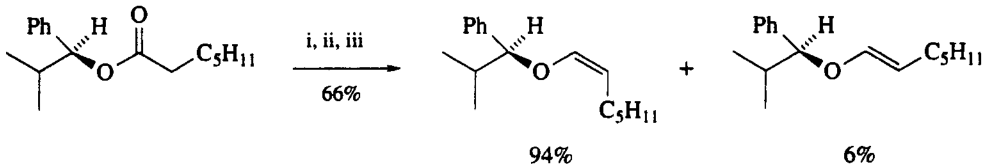

i, $LiNPr^i_2$; ii, $(EtO)_2POCl$, HMPA; iii, $Et_3Al$, $Pd(PPh_3)_4$

**Scheme 30**

### 4.6.5.1.2 *Vinyl triflates*

While not receiving as much attention as vinyl phosphates, vinyl triflates have been successfully employed as intermediates in the transformation of ketones into alkenes (Scheme 31). As in the case of vinyl phosphates, regioselective alkene formation ultimately results from kinetic or thermodynamic enolate generation (Scheme 32).[45]

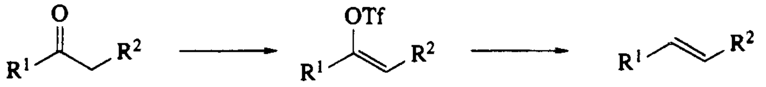

**Scheme 31**

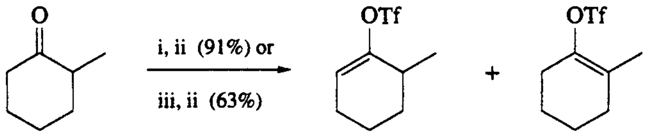

| | |
|---|---|
| reagents i, ii | 95: 5 |
| reagents iii, ii | 3:97 |

i, LDA; ii, $Tf_2NPh$; iii, $Pr^i_2NMgBr$

**Scheme 32**

Vinyl triflates have been prepared from the starting ketones using 2,6-di-*t*-butyl-4-methylpyridine/triflic anhydride,[46] sodium bicarbonate/triflic anhydride[47] in the case of activated systems and lithium hexamethyldisilazide/HMPA/*N*-phenyltriflimide.[45,48] Once formed, vinyl triflates are readily reduced to the corresponding alkene with tributyltin hydride/tetrakis(triphenylphosphine)palladium(0) in the presence[47] or absence of lithium chloride,[45] triethylsilicon hydride/tetrakis(triphenylphosphine)palladium(0)/lithium chloride,[47] or tri-*n*-butylamine/bis(triphenylphosphine)palladium acetate/formic acid.[49] The latter conditions, in which the reducing species is proposed to be tri-*n*-butylammonium formate, are compatible with a wide range of functional groups, including ketones, esters, ethers and alcohols. Dolle *et al.* have utilized this methodology under conditions of thermodynamic control of enolization to convert an enone into a steroidal diene in the preparation of ergosterol β-isomers (Scheme 33).[50]

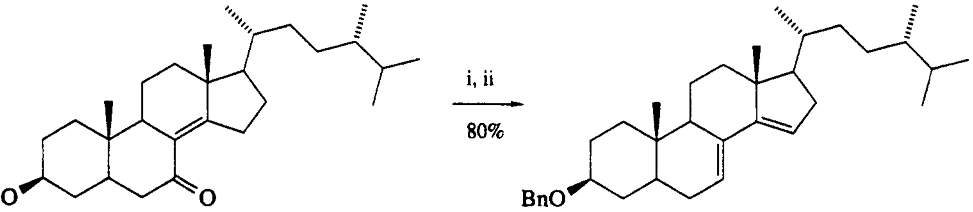

i, $Tf_2O$, 2,6-di-*t*-butyl-4-methylpyridine; ii, $Bu_3N$, $HCO_2H$, cat. $Pd(OAc)_2(Ph_3P)_2$, DMF

**Scheme 33**

Similar to the reduction of aryl phosphates, phenols can be reduced to arenes *via* the corresponding aryl triflates.[51,52] The reducing systems employed are compatible with a wide array of functional groups, including ketones, ethers, sulfides, aryl ethers, nitro compounds, esters, amides, lactones and cyano groups. Finally, Subramanian *et al.*[53] have employed the nonafluoro-*n*-butyl triflate derivative to effect the conversion of phenols into arenes.

### *4.6.5.1.3 Vinyl acetates*

While not extensively explored, vinyl acetates have also been reduced to the corresponding alkenes with iron pentacarbonyl at elevated temperatures (Scheme 34).[54] In addition, vinyl acetates have been subjected to hydroboration,[55] but elimination of the boronate ester in the intermediate and subsequent hydroboration of the resulting alkene are so rapid that this method is not synthetically useful for ketone to alkene conversion.

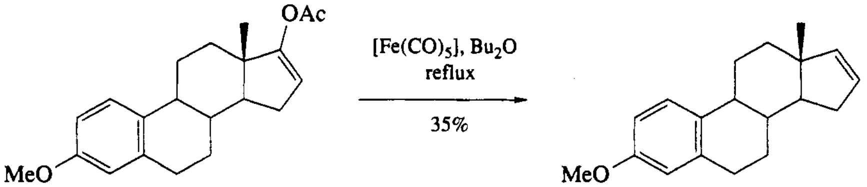

Scheme 34

## 4.6.5.2 Vinyl Ethers

Although not as extensively employed as vinyl esters, vinyl ethers find occasional use as intermediates in the conversion of ketones into alkenes. Once again, vinyl ethers can be generated regioselectively by kinetic or thermodynamic enolate generation and, therefore, offer another route by which ketones can be regioselectively replaced by alkenic double bonds.

### *4.6.5.2.1 Vinyl sulfides, selenides and sulfoxides*

Within the general class of vinyl ethers, vinyl sulfides are the most frequent choice for carrying out the transformation of ketones into alkenes, according to the synthetic sequence shown in Scheme 35. Vinyl sulfides are generally prepared from the corresponding ketones by either of two strategies. The first involves introduction of an α-alkylthiol group followed by formal dehydration (route A; Scheme 35). As indicated, regioselective introduction of the α-alkylthiol group is accomplished by kinetic or thermodynamic enolate generation and, therefore, allows for regioselective alkene formation. The second process (route B; Scheme 35) entails direct conversion of the ketone into a vinyl sulfide, in which the carbonyl oxygen is replaced by sulfur.

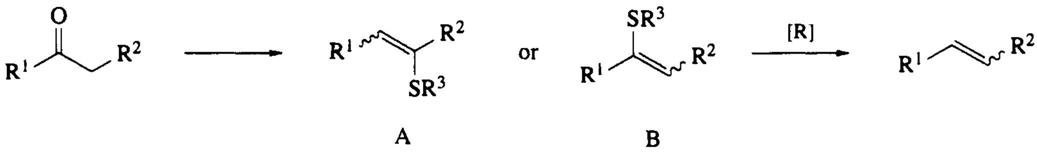

Scheme 35

As an example of the former method (route A; Scheme 35), enolate formation in spirocyclobutanone systems followed by treatment with diphenyl disulfide affords the α-thiophenyl ketone; subsequent hydride reduction provides the α-hydroxythiane, which upon mesylation and base-induced elimination gives the vinyl sulfide in good yields.[56] Alternatively, α-alkylthiol ketones, such as 2-*S*-methyl-1-tetralone can be converted into the corresponding tosylhydrazones, which undergo the Shapiro reaction (Section 4.6.5.4) to afford the target vinyl sulfide.[57] In a related procedure, 4-methylcyclohexanone has been converted into 1-*S*-methyl-5-methylcyclohexene in a one-pot sequence by initial tosylhydrazone formation and subsequent sulfenylation of the dianion generated with Bu$^n$Li. *In situ* Shapiro reaction of this intermediate then affords the desired vinyl sulfide.[58] Although this latter procedure provides an interesting method for 1,2-carbonyl transposition, it is obviously of little value for the ketone to alkene conversion because the same alkene would be formed in the direct Shapiro reaction of the starting ketone.

Employing the second general method (route B; Scheme 35), vinyl sulfide formation in acyclic systems has been accomplished from ketones by initial thioacetal formation under acidic conditions with benzenethiol, followed by thiol elimination employing copper(I) triflate.[59] If acid sensitive products are generated, the elimination step can be conducted in the presence of 2,6-lutidine or Hünig's base. Finally, vinyl sulfides have been prepared from the starting ketone in a single step by treatment with benzenethiol and *p*-toluenesulfonic acid[60] or with benzenethiol and $P_2O_5$ in methylene chloride.[60]

Vinyl sulfides have been reduced to the corresponding alkene with isopropylmagnesium bromide/nickel chloride/tri-*n*-octylphosphine[61] or isopropylmagnesium bromide/tris(triphenylphosphine)-nickel chloride at elevated temperatures,[62] in which the reducing agent is postulated as 'NiH'. Raney nickel[63,64] and $NiCl_2/NaBH_4$ ('NiB')[63] have also been found to reduce vinyl sulfides to alkenes; however, 'NiH' and 'NiB' are usually the method of choice because of their functional group compatibility and their unreactivity towards isolated carbon–carbon double bonds. As an example of this methodology, Boar *et al.*[63] have employed a vinyl sulfide intermediate in the conversion of 5α-lanost-8-en-3-one to 5α-lanosta-2,8-diene (Scheme 36). Since it is necessary to maintain an acidic reaction medium in order to avoid overreduction of the isolated alkenic double bond, boric acid is added.

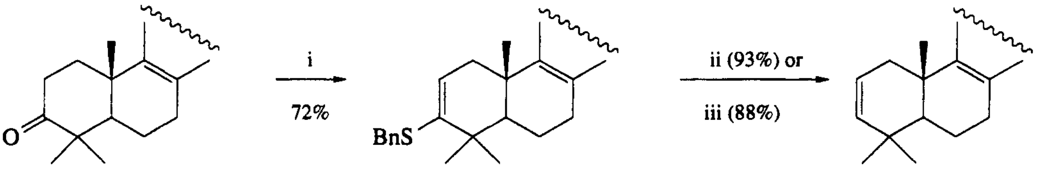

i, BnSH, $BF_3{\bullet}Et_2O$, AcOH; ii, $NiCl_2$, $NaBH_4$, $H_3BO_3$, EtOH; iii, Raney Ni

**Scheme 36**

Thioacetals, prepared from the corresponding ketones, have also been reduced to alkenes using 'moderately active' Raney nickel as the desulfurization agent (Scheme 37).[65] This form of Raney nickel does not reduce the newly formed alkene or react with other isolated carbon–carbon double bonds. Note that under these conditions the saturated hydrocarbon often observed in Raney nickel desulfurizations[66] is not formed. Similar conditions have been used for the conversion of cyclodecanone to cyclodecene.[67] While thioacetals have also served as intermediates in the analogous conversion of enones into dienes, a mixture of diene products is obtained. For instance, dithiane generation from 17β-hydroxy-$\Delta^4$-androsten-3-one, followed by desulfurization affords a 4:1 mixture of 17β-hydroxy-$\Delta^{2,4}$-androstadiene and 17β-hydroxy-$\Delta^{3,5}$-androstadiene, respectively.[65]

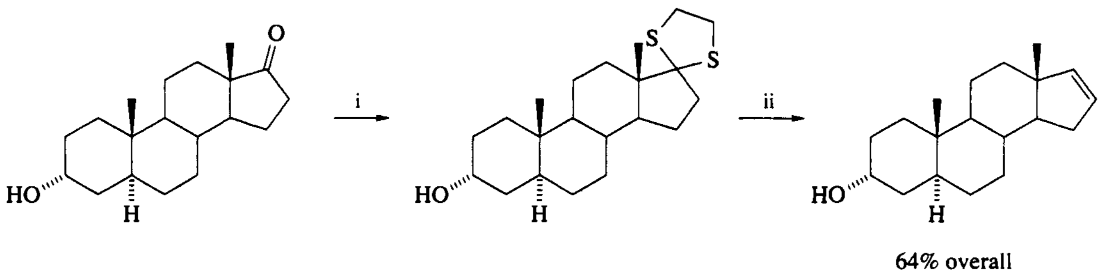

64% overall

i, $HSCH_2CH_2SH$, $BF_3{\bullet}Et_2O$; ii, Raney Ni (moderately active)

**Scheme 37**

α-Acetoxy ketones have also been converted to alkenes through the intermediacy of a 1,2-dithiane derivative. In the transformation of pulchellin to pulchellon (Scheme 38), Inayama *et al.*[64] treated the starting α-acetoxy ketone with 1,2-ethanedithiol to generate the diacetoxydithiane intermediate, which upon desulfurization with deactivated Raney nickel afforded the desired alkenic product. The lactam moiety of indanone undergoes a related reductive process, *via* the amide ketene thioacetal, to give indole (Scheme 39).[68]

Vinyl selenides, which behave similarly to vinyl sulfides, have also been prepared from ketones and reduced to the alkenic product. By this route, 3β-hydroxypregn-5-en-20-one was converted into the exocyclic 17-ethylidene derivative (Scheme 40).[69] Vinyl selenides have also been reduced with 'NiB' during

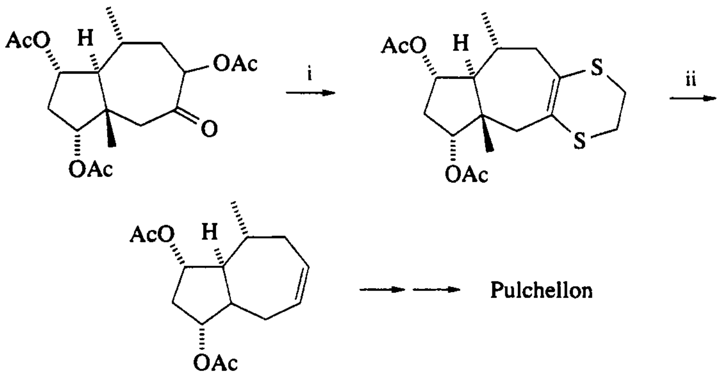

i, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$; ii, Raney Ni (deactivated), acetone, reflux

Scheme 38

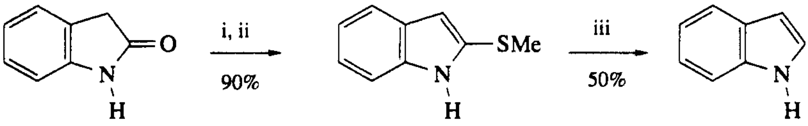

i, Lawesson's reagent; ii, MeI, $K_2CO_3$; iii, $Pr^iMgBr$, $[(Ph_3P)_2NiCl_2]$

Scheme 39

the course of synthetic studies on the ergot alkaloids[70] and in acyclic systems.[71] In the latter case, the reduction proved to be nonstereospecific (Scheme 41).

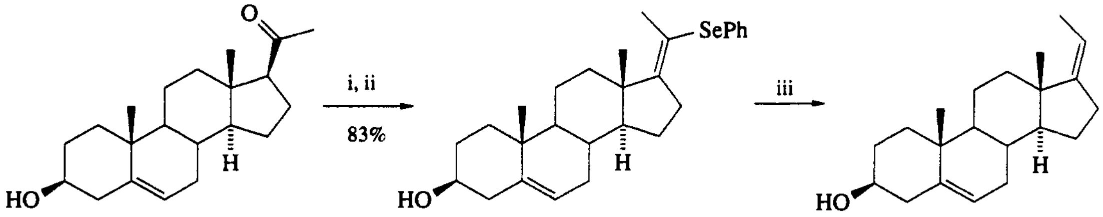

i, $N_2H_4$; ii, PhSeBr, *t*-butyltetramethylguanidine; iii, Na, EtOH

Scheme 40

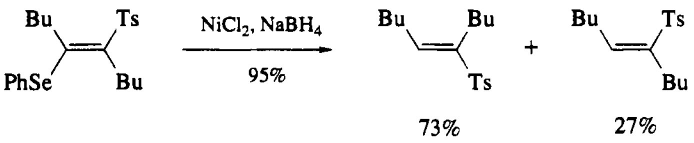

Scheme 41

In addition to vinyl sulfides and selenides, vinyl sulfoxides have been reduced to the corresponding alkenes using *t*-butyllithium.[72]

### *4.6.5.2.2 Silyl enol ethers*

Silyl enol ethers, which are readily generated regiospecifically from ketones, can also be reduced to alkenes, particularly by hydroboration.[73–76] Hydroboration of silyl enol ethers results in the addition of boron to the β-carbon of the double bond to afford *trans*-β-trimethylsilyloxy organoboranes, which in cyclic systems undergo *anti* elimination in the presence of acid to give the alkenic product (Scheme 42).[74] A number of acids have been tested successfully, including carboxylic acids, $BF_3 \cdot Et_2O$ and aqueous HCl. Since enolate formation can be conducted under kinetic or thermodynamic control, either alkene regioisomer is obtainable. In acyclic systems, the initially formed *trans*-β-trimethylsilyloxyorganoborane undergoes rapid *syn* elimination, even in the absence of acid, to afford the alkene product.[76] As a result, the (*E*):(*Z*) ratio of the product follows directly from the stereochemistry of the starting enol ether (Scheme 43).

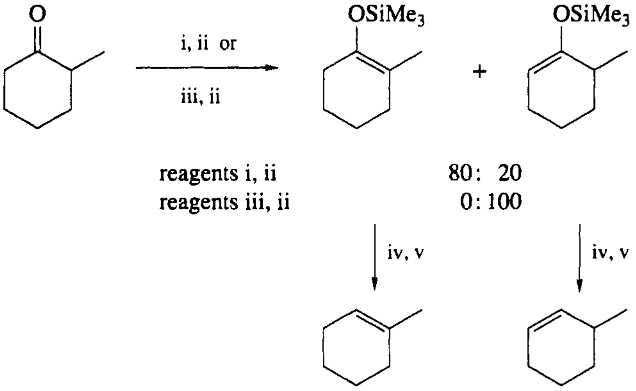

i, $Et_3N$, DMF; ii, $Me_3SiCl$; iii, LDA; iv, $B_2H_6$, 0 °C; v, $H^+$

Scheme 42

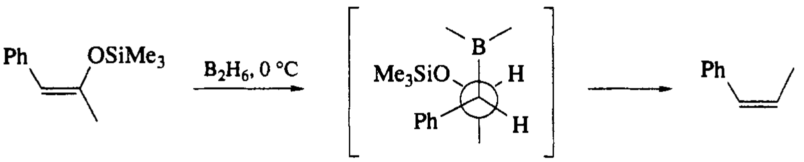

Scheme 43

#### *4.6.5.2.3 Alkyl enol ethers*

Only a few cases of the reduction of alkyl enol ethers to the corresponding alkene have been reported. α-Ethoxystyrene and related derivatives are reduced to alkenes by treatment with Grignard reagents.[77] In addition, enol ethers of cyclohexanone derivatives have been cleaved to the cyclohexene products using either DIBAL at elevated temperatures[78] or diborane/boron trifluoride etherate.[79] By analogy to the hydroboration of silyl enol ethers, this latter method involves formation of an intermediate β-ethoxy organoborane which undergoes acid-catalyzed elimination to afford the alkene.

### 4.6.5.3 Vinyl Halides

Vinyl halides represent yet another important class of intermediates in the conversion of ketones to alkenes. The most widely applied conditions for the conversion of ketones into vinyl halides are those developed by Barton *et al.*[80] for the conversion of 3β-acetoxyandrost-5-ene-17-one into 3β-hydroxyandrosta-5,16-diene (Scheme 44). These conditions of vinyl halide formation and subsequent reduction have been useful in a number of steroid systems for the introduction of a $\Delta^{16}$-carbon–carbon double bond[81,82] and have been shown to be compatible with such functional groups as alcohols, isolated double bonds and acetals. The scope of vinyl iodide formation from hydrazones has been studied by Pross and Sternhell,[83] and recently the original reaction conditions were improved by using sterically hindered guanidine bases rather than triethylamine.[84,85] Haloalkenes have also been prepared from the corresponding ketones by treatment with iodoform and chromium chloride[86] or with phosphorous pentahalides.[87]

The reduction of vinyl halides most often is carried out *via* a metallation–protonation reaction. For instance, sodium in ethanol was employed by Barton *et al.*[80] for the reduction of a steroidal vinyl iodide (Scheme 44). A number of conditions for vinyl halide reduction to alkenes have been reported, representative examples of which include: vinyl chloride and bromide reduction in acyclic systems with

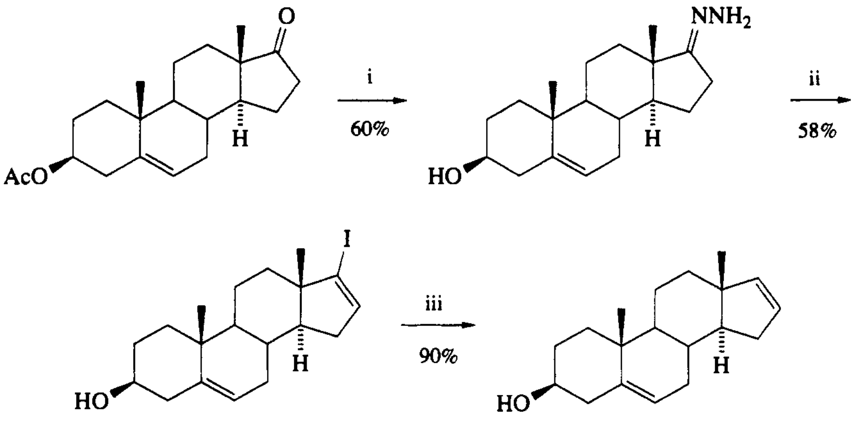

i, 64% $N_2H_4$, $Et_3N$, Δ; ii, $I_2$, $Et_3N$; iii, Na, EtOH

**Scheme 44**

DIBAL-H/*n*-butyllithium,[88] in cyclic and acyclic systems with iron pentacarbonyl,[54] in cyclodecanes with lithium dihydrodimethoxyaluminate(III)/copper(I) iodide,[89] and in cyclohexane and cyclopentane systems with NaH/sodium *t*-butylpentyl/$Ni(OAc)_2$.[90] The monoreduction of 1,3-diketones can be carried out under similar conditions, as illustrated by the reaction of a substituted cyclohexane-1,3-dione with oxalyl chloride[91] to give the corresponding 1-chlorocyclohexenone, which was subsequently reduced to the enone with zinc–silver couple (Scheme 45).[92] Kropp *et al.*[93] have reported the photolytic reduction of vinyl iodides in acyclic systems; however, when an α-hydrogen is present, formation of the diene product is a limiting side reaction (Scheme 46). For a more extensive discussion of vinyl halide reductions, see the preceding chapter in this volume.

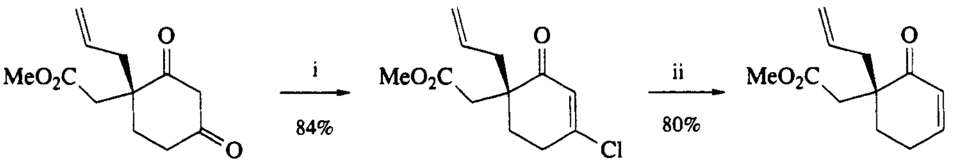

i, $(COCl)_2$, $CHCl_3$, Δ; ii, Zn–Ag, MeOH, 25 °C

**Scheme 45**

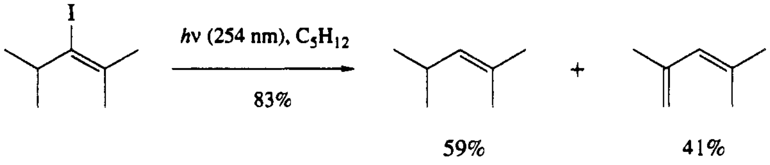

**Scheme 46**

## 4.6.5.4 Enamines

Enamines represent a final class of vinyl–heteroatom derivatives that can be prepared from ketones and subsequently reduced to alkenes (Scheme 47). Since enamine formation is covered in depth elsewhere, this section will deal only with the reduction of enamines to alkenes.

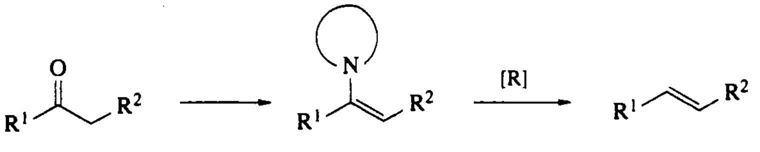

**Scheme 47**

Cyclic enamines have been reduced to alkenes with lithium aluminum hydride/aluminum chloride.[94] The reducing efficiency of simple aluminum hydrides as well as chlorinated aluminum hydrides has been studied in detail, and $AlH_3$ has been found to be the most effective for the conversion of cyclohexenamines into cyclohexene (Scheme 48).[95]

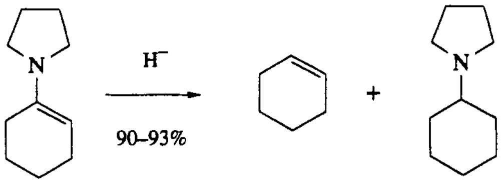

| | | |
|---|---|---|
| $AlHCl_2$ | 77% | 23% |
| $AlH_2Cl$ | 83% | 17% |
| $AlH_3$ | 84% | 16% |

**Scheme 48**

As with silyl and alkyl enol ethers, enamines react with boron hydrides to afford the corresponding simple alkenic products. In the case of cyclohexyl enamine, hydroboration gives the β-amino organoborane, which upon acid-induced *anti* elimination affords cyclohexene as the product.[96] Similar conditions were employed by Friary *et al.*[97] in the regioselective preparation of unsaturated proline derivatives (Scheme 49). Brown *et al.*[98] have shown that a single acyclic enamine geometric isomer can be reduced to either the (*E*)- or (*Z*)-alkene depending on the reducing species (Scheme 50): treatment of (*E*)-1-morpholino-1-phenyl-1-propene with borane methyl sulfide followed by methanolysis gives the β-aminoboronate ester, which upon peroxide oxidation undergoes *syn* elimination to afford (*E*)-1-phenyl-1-propene, while hydroboration with 9-BBN gives the trialkyl boronate, which on methanolysis undergoes *anti* elimination to give (*Z*)-1-phenyl-1-propene.

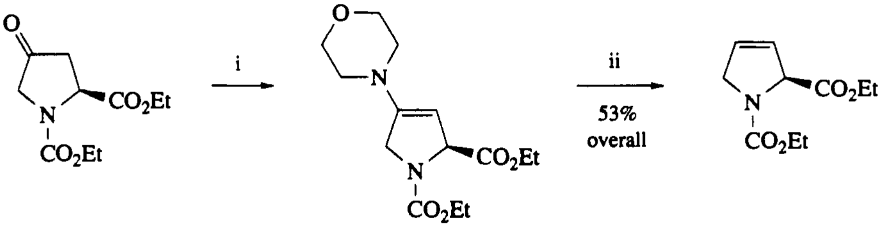

i, morpholine, TsOH; ii, $B_2H_6$, THF, reflux

**Scheme 49**

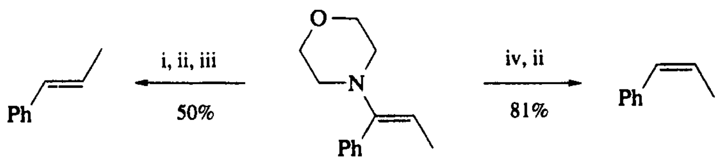

i, $BH_3 \cdot Me_2S$; ii, MeOH; iii, $H_2O_2$, NaOH; iv, 9-BBN

**Scheme 50**

## 4.6.6 REDUCTIVE ELIMINATION OF HYDRAZONE DERIVATIVES

In the early 1950s Bamford and Stevens reported a thermally induced reaction of ketone tosylhydrazone monosodium salts that gives products derived either from carbene intermediates (aprotic conditions) or carbocations (protic conditions). Both reactions, which are illustrated in Scheme 51, can give alkenes as the major product, although the protic reaction is of marginal synthetic value because mixtures of alkene regioisomers and rearrangement products are normally obtained. On the other hand, the aprotic reaction does on occasion offer excellent regiochemical control in the preparation of alkenes, although it has found more widespread use in the synthesis of multicyclic, strained hydrocarbons. Both reactions have been covered in previous reviews.[99] Treating tosylhydrazones with alkyllithium bases results in a mechanistically different reaction that also provides alkenes, but *via* an alkenyllithium intermediate (Scheme 51). This process, commonly known as the Shapiro reaction, has been applied to the preparation of a large number of structurally diverse alkenes and is also the subject of earlier reviews.[99,100] The Shapiro reaction has itself been modified to allow trapping of the intermediate vinyllithium with electrophiles; however, this aspect of arenesulfonylhydrazone chemistry, which is the subject of a recent comprehensive survey,[101] is not within the scope of this section and is therefore excluded. Related eliminations of α-heteroatom hydrazones are discussed above in Section 4.6.4.

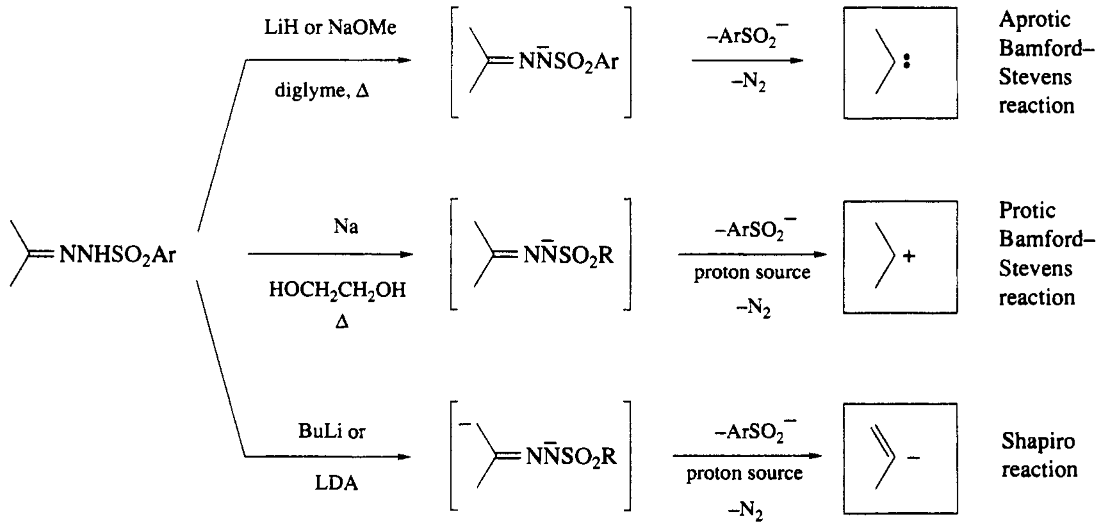

Scheme 51

### 4.6.6.1 Formation of Arenesulfonylhydrazones

By far the most common sulfonylhydrazone derivatives reported to undergo the Bamford–Stevens or Shapiro reaction have been ketone tosyl- or trisyl-hydrazones (trisyl = triisopropylbenzenesulfonyl), although there are a few reports of the use of benzenesulfonylhydrazones or *N*-aminoaziridine-derived hydrazones. In terms of availability and cost of precursors, tosylhydrazones, which are prepared from ketones and commercially available tosylhydrazine, are preferred. Equimolar amounts of the reactants are generally dissolved in methanol, ethanol or acetic acid, usually in the presence of an acidic catalyst, such as concentrated hydrochloric acid, and allowed to react at room temperature or somewhat above, and then stored in the cold, after which the crystalline tosylhydrazone can be isolated in good yield by filtration. Even hindered ketones, such as camphor, react smoothly at somewhat higher temperatures. Diethyl ether can also serve as the reaction solvent and reportedly is superior to alcohols.[102] Although trisylhydrazones are prepared in an analogous manner (commonly in methanol, ethanol, acetonitrile or diethyl ether), the starting trisylhydrazine is not currently commercially available; it must be prepared from the sulfonyl chloride and hydrazine hydrate.[103] Even hindered ketones, such as camphor and diisopropyl ketone, undergo the reaction in good yield,[103] although extraordinarily crowded ketones can be totally resistant to trisylhydrazone formation (Scheme 52).[104] Arenesulfonylhydrazones of aldehydes are prepared by the same general method, with minor modifications.[15] The formation of β-keto ester tosylhydrazones has also been reported,[105] as has a procedure for converting orthoesters into ester tosylhydrazones[106] and acyl halides into amide trisylhydrazones ('trisylamidrazones').[107]

Arenesulfonylhydrazones exist as mixtures of (*E*)- and (*Z*)-isomers, which usually cannot be physically separated at ambient temperatures[108,109] because the inversion barrier of the azomethine bond is too low, although spectroscopic methods can distinguish between the two isomers.[110] As expected, the (*E*):(*Z*) ratio for any given hydrazone is dependent upon the sizes of the groups attached to the azomethine carbon, with the less sterically crowded (*E*)-isomer usually predominating.

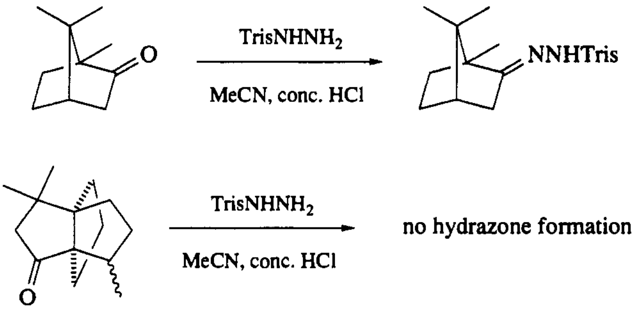
O
TrisNHNH$_2$
MeCN, conc. HCl
NNHTris
O
TrisNHNH$_2$
MeCN, conc. HCl
no hydrazone formation

**Scheme 52**

### 4.6.6.2 The Aprotic Bamford–Stevens Reaction

The aprotic reaction is generally conducted on a preformed lithium, potassium or sodium salt. Since the N—H proton of arenesulfonylhydrazones is relatively acidic, deprotonation is readily achieved with relatively weak bases, such as LiH, KH or sodium methoxide. The salt is then heated (and sometimes irradiated, presumably encouraging more rapid breakdown of the diazoalkane intermediate to the carbene) to give the product. For aldehyde hydrazone salts, mixtures of alkenes and β-insertion products are usually observed (Scheme 53).[111] On the other hand, the salts of most five- and six-membered ring hydrazones give predominantly alkene products under these conditions (Scheme 54),[112] while medium ring derivatives usually form bicyclic products *via* transannular carbene insertion.[113] Likewise, bridged bicyclic hydrazone salts give alkene products[114] only if an appropriately positioned C—H bond is not present across the ring in the rigidly held boat (Scheme 55).[103]

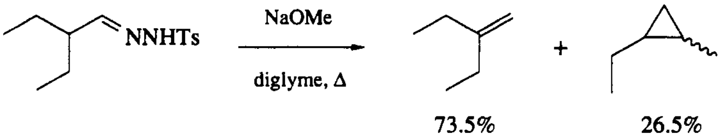
NNHTs
NaOMe
diglyme, Δ
+
73.5%
26.5%

**Scheme 53**

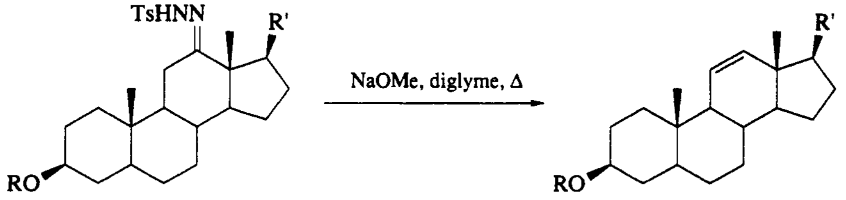
TsHNN
R'
RO
NaOMe, diglyme, Δ
R'
RO

**Scheme 54**

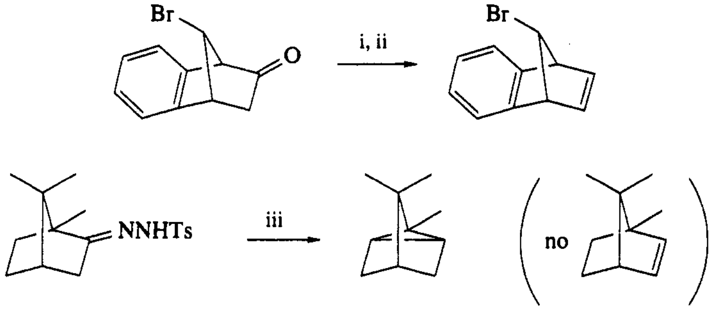
Br
O
i, ii
Br
NNHTs
iii
no

i, TsNHNH$_2$; ii, *hν* on Li salt; iii, NaOMe, diglyme

**Scheme 55**

Within the constraints imposed by the intermediacy of a carbene, the aprotic Bamford–Stevens reaction can provide good yields of alkene with occasional examples of excellent regiochemical control in specific cases. In general, the more highly substituted regioisomer predominates. For instance, thermal decomposition of the sodium salt of 2-methylcyclohexanone tosylhydrazone affords a 2:1 mixture of methylcyclohexenes, favoring the 1-methyl isomer (Scheme 56).[115] A slight preference (2:1) for the formation of the less substituted alkene regioisomer was observed in Paquette's synthesis of precapnelladiene,[116] an example that also illustrates that transannular insertion is not always the preferred pathway in medium rings. Although these marginal selectivities are typical, there are exceptions. Some steroidal tosylhydrazones, for example, have been shown to afford exclusively the $\Delta^2$ double bond isomer if the A/B ring juncture is *trans*, while the $\Delta^3$ isomer is formed from the A/B *cis* starting material (Scheme 57).[117] Sugar tosylhydrazone salts have been converted into unsaturated sugars in high yield (Scheme 58),[118] with no competitive formation of the alternative bicyclic vinyl ether regioisomer.

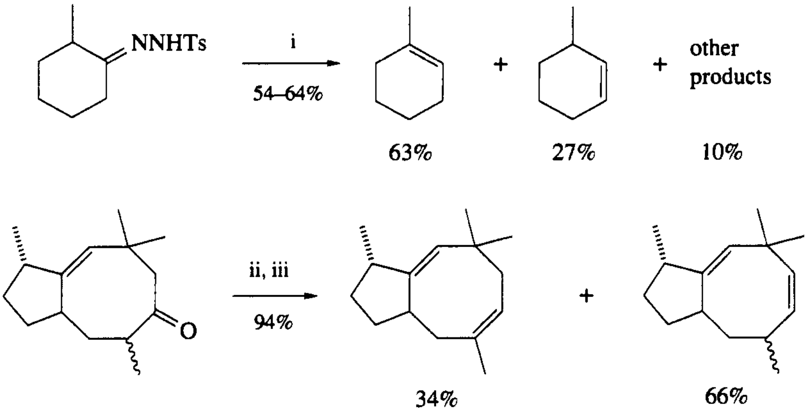

i, NaOMe, NMP, Δ; ii, $TsNHNH_2$; iii, $Bu^nLi$, diglyme, reflux

**Scheme 56**

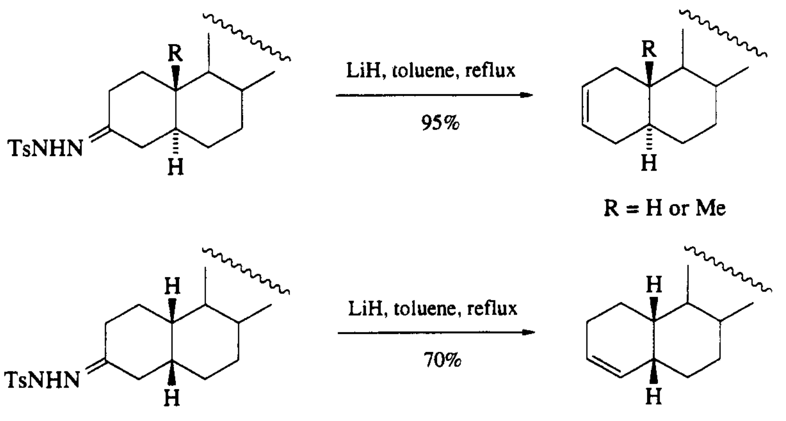

**Scheme 57**

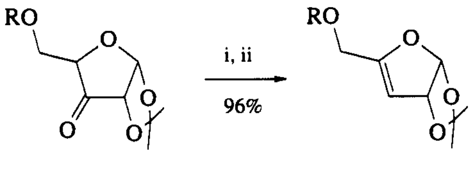

i, $TsNHNH_2$, EtOH; ii, NaOAc, DMF, 100 °C

**Scheme 58**

The issue of stereoselectivity in acyclic systems has not been studied systematically, but a high degree of control is not expected. There is one report of the formation of an ethylideneazacyclohexane with excellent control of stereoselectivity (Scheme 59).[119] No explanation for this dramatic selectivity was offered, nor is one readily apparent. Note also the strong preference for the formation of the more highly substituted regioisomer.

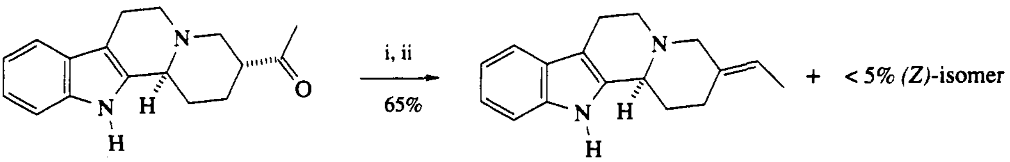

(±)-Deplancheine

i, $TsNHNH_2$, AcOH; ii, NaOMe, diglyme, 150 °C

**Scheme 59**

### 4.6.6.3 The Protic Bamford–Stevens Reaction

The protic reaction on occasion is a useful method of alkene formation, but is far from general because the cation intermediate tends to undergo rearrangements.[120] Further, even for cases in which elimination to an alkene is the predominant pathway, the regioselectivity of the process is often mediocre. A key step in the synthesis of (+)-α-eudesmol and (–)-α-selinene exemplifies this point (Scheme 60).[121] There are, however, isolated examples of excellent selectivity, such as the reaction of a 3-ketotetrahydrofuran tosylhydrazone salt to give the corresponding cyclic enol ether as the major product (Scheme 61),[122] the intro-

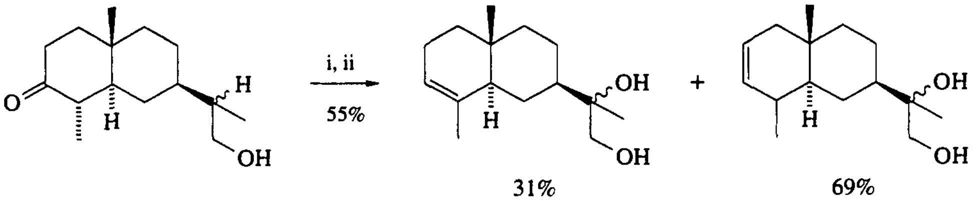

i, $TsNHNH_2$, $BF_3•Et_2O$; ii, Na, $HO(CH_2)_2OH$, Δ

**Scheme 60**

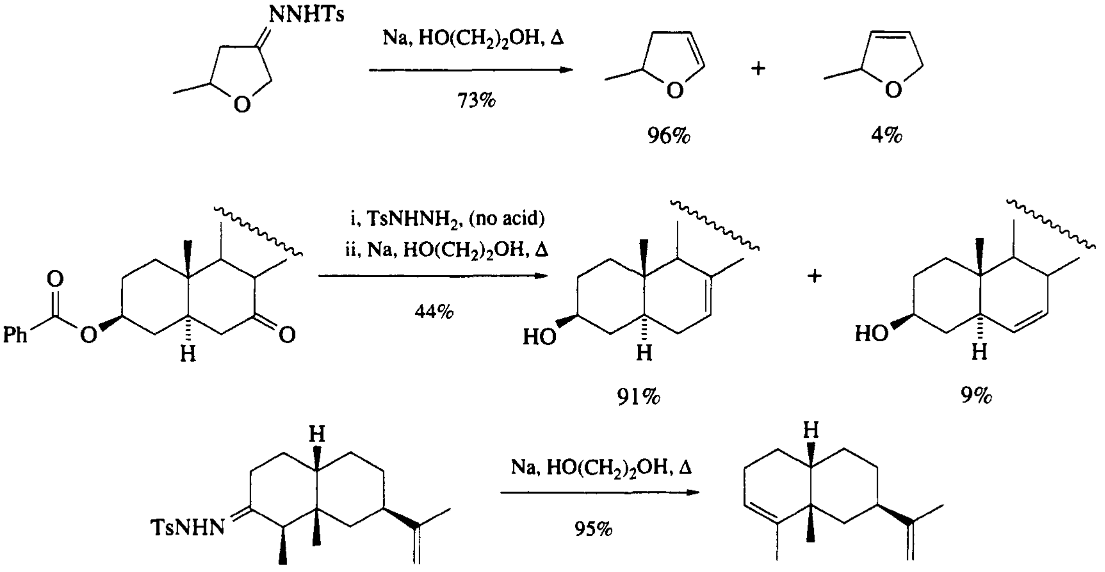

**Scheme 61**

duction of a $\Delta^7$ double bond in a steroid skeleton,[123] and the exclusive formation of the more highly substituted alkene regioisomer in a terpenoid decalin ring system (Scheme 61).[124] In some cases, it is the less substituted regioisomer that predominates, as illustrated by one step in the synthesis of azaprostaglandin analogs (Scheme 62).[125] These examples clearly illustrate that predicting regioselectivities in the aprotic Bamford–Stevens reaction without extremely close precedent is treacherous.

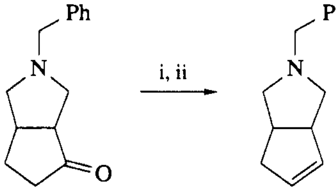

i, $TsNHNH_2$, TFA; ii, $NaO(CH_2)_2ONa$, $HO(CH_2)_2OH$, HMPA

Scheme 62

### 4.6.6.4 The Shapiro Reaction

The Shapiro reaction is the most generally applicable of the three variations discussed in this section. In contrast to the Bamford–Stevens reaction, the Shapiro modification reliably affords alkenes without skeletal rearrangements or competing insertion reactions. Scheme 63 shows several representative examples of typical Shapiro reactions that would give different results under Bamford–Stevens conditions. Most ketone tosyl- or trisyl-hydrazones with at least one α-proton undergo deprotonation with strong bases to give a dianion that decomposes *in situ* ultimately to the alkene product. A major advantage of the reaction of arenesulfonylhydrazones derived from unsymmetrical ketones is that the regiochemistry of the resultant alkene is highly predictable, almost always favoring the less substituted isomer, although arenesulfonylhydrazones of α,β-unsaturated ketones are an occasional exception to this generalization.

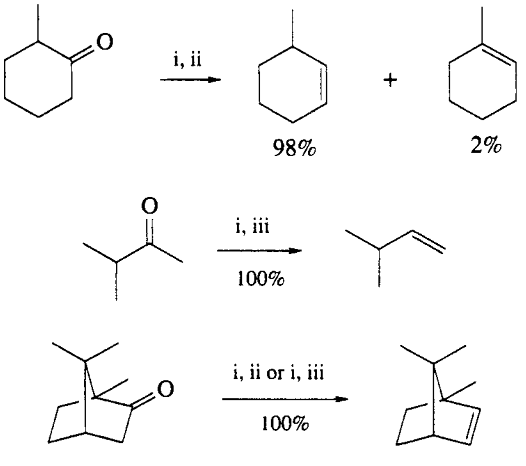

i, $TsNHNH_2$; ii, MeLi, $Et_2O$; iii, $Bu^nLi$, hexane

Scheme 63

#### 4.6.6.4.1 *Regioselectivity*

One of the most valuable attributes of arenesulfonylhydrazones as a source of vinyllithiums is that the reaction exhibits a strong preference for the formation of one of the two possible vinyllithium regioisomers. In general, one may be confident that for unsymmetrically substituted ketone tosyl- or trisyl-hydrazones, deprotonation of the monoanion will occur predominantly at the less substituted α-position, *i.e.* Me > $CH_2$ > CH, to give, after elimination, the corresponding less substituted alkene product, which is generally favored over the more highly substituted regioisomer by ratios of 50:1 or more (Scheme 63). There are very few exceptions to this generalization. In one bicyclic derivative the bridgehead methine undergoes significant deprotonation to give the more highly substituted lithioalkene as a major by-product.[126] Similarly, the trisylhydrazone of a β-keto acetal undergoes deprotonation at the more highly substituted α-position, which in this case results in elimination of ethoxide followed by conjugate addition–elimination of the resultant monoanion to give a 1,2-pyrazole heterocycle.[127] Other than such rare exceptions, the Shapiro reaction consistently gives good yields of the less substituted alkene regioisomer and has been applied extensively in the synthesis of natural products, including approaches to aconitium alkaloids,[128] luciduline,[129] β-elemol,[130] costunolide[131] and compactin,[132] as well as a dodecahedrane intermediate (Scheme 64).[133]

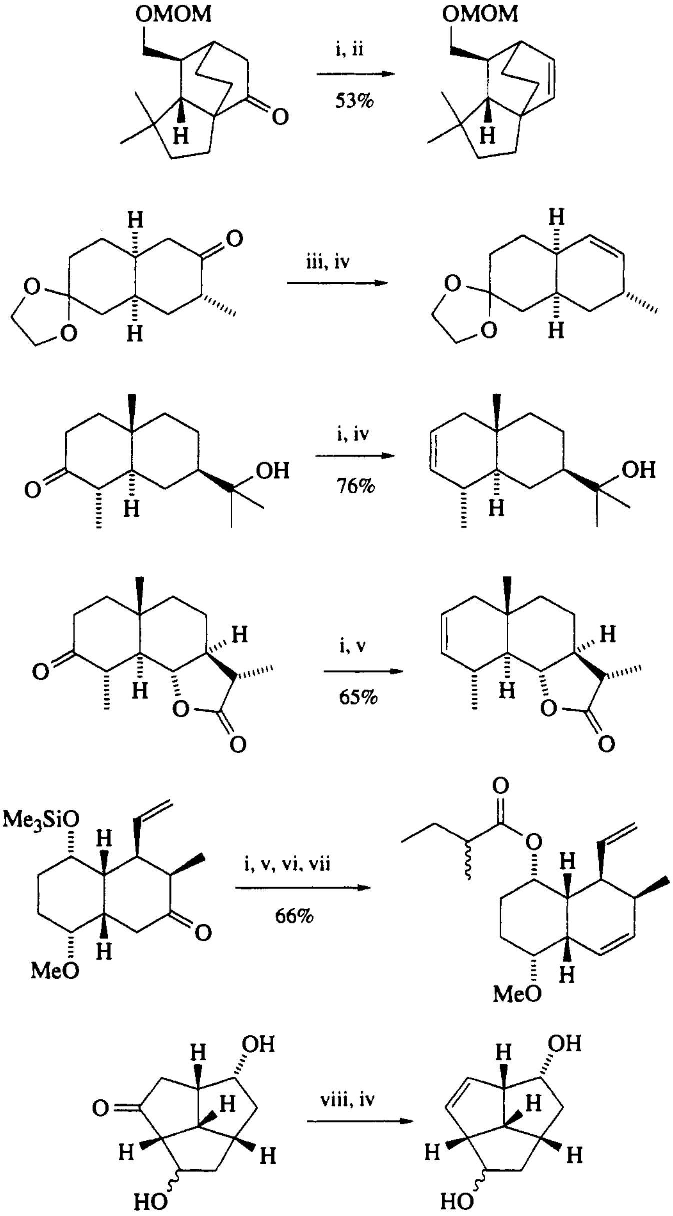

i, TsNHNH$_2$, BF$_3$•Et$_2$O; ii, Bu$^n$Li, TMEDA; iii, TsNHNH$_2$, 25 °C; iv, MeLi; v, LDA, –78 to 0 °C; vi, 2% aq. HCl, 25 °C; vii, (BuCO)$_2$O, pyridine, DMAP; viii, TrisNHNH$_2$, MgSO$_4$

**Scheme 64**

Generalizing about regioselectivity in α,β-unsaturated systems is much less straightforward. There can be as many as three acidic sites that could undergo deprotonation and predicting *a priori* which might be preferred is difficult. There are instances of deprotonation at the least highly substituted of several positions and just as many counter examples.[103,134] Nonetheless, high levels of selectivity are often observed. For example, (+)-pulegone trisylhydrazone gives an excellent yield of the diene derived from deprotonation of the endocyclic α-methylene group in preference to either γ-methyl substituent (Scheme 65).[135] Heathcock's compactin synthesis (Scheme 65)[136] and van Tamelen's aphidicolin approach (Scheme 65)[137] both illustrate applications of this reaction in the terpene area.

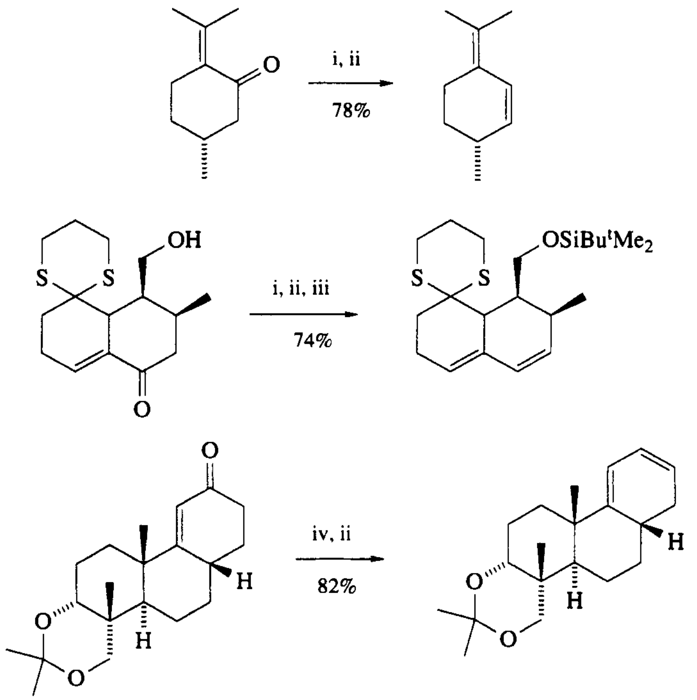

i, TrisNHNH$_2$, HCl; ii, Bu$^n$Li, TMEDA; iii, Bu$^t$Me$_2$SiCl; iv, TsNHNH$_2$, TsOH

**Scheme 65**

In contrast to the high regioselectivity observed for most saturated ketone arenesulfonylhydrazones, differential substitution adjacent to equivalently substituted α-positions does not appear to afford good regiochemical control. For instance, 3-alkyl-,[103] 3,4-dialkyl-[138] and 3,5-dialkyl-cyclohexanone derivatives[139] exhibit virtually no regioselectivity. One 3-ketosteroid reportedly gives the $\Delta^2$ regioisomer,[140] but the yield is only 50% and no mention is made of the $\Delta^3$ isomer. Finally, only meagre selectivity is observed in the reaction of 2-*n*-butyl-6-methylcyclohexanone tosylhydrazone.[141] These examples are summarized in Scheme 66.

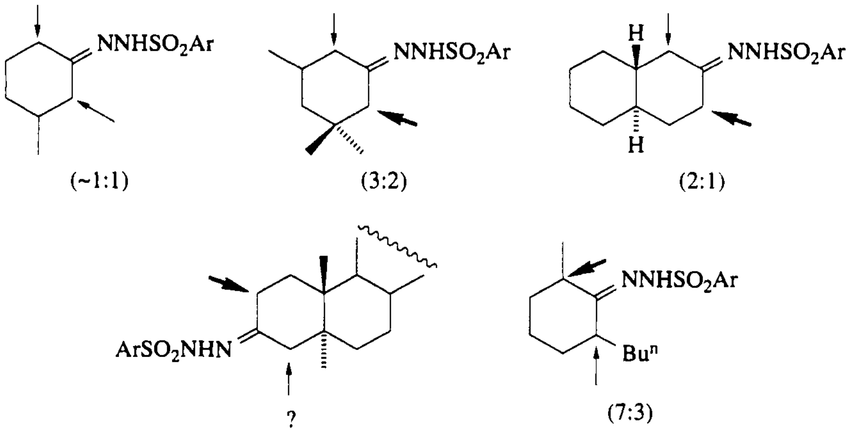

**Scheme 66**

Although the observed regiochemical preferences in dianion formation bear a strong resemblance to those of kinetic enolate formation, there are a few examples that dramatize the fact that the regioselectivity cannot be understood exclusively on the basis of kinetically controlled deprotonation in the less substituted position. Specifically, the stereochemistry of the azomethine bond can come in to play as a '*syn*-directing effect', known to occur in the deprotonation of other imine derivatives.[142] Of course, these two factors themselves are not independent, since the (*E*)-hydrazone isomer is usually present in large excess under most conditions (see examples above), so that deprotonation in the less sterically encumbered position is predicted by either rationale, rendering the point immaterial in most cases. However, there are circumstances under which substantial deprotonation occurs at the more substituted position or, in α,β-unsaturated ketone arenesulfonylhydrazones, at a position otherwise not consistent with simple kinetically controlled deprotonation. For example, deprotonation regioselectivity for pulegone tosylhydrazone is a function of the hydrazone stereochemistry, but this effect is observed only in TMEDA and not in benzene.[109]

Similarly, for alkenes derived from saturated methyl ketones the regioselectivity is determined by starting hydrazone (*E*):(*Z*) ratios in some solvents but not in others. Thus 2-octanone trisylhydrazone, which is an inseparable 85:15 mixture of (*E*)- and (*Z*)-isomers, gives an 85:15 ratio of 1-octene:2-octene if vinyllithium formation is carried out in THF, but a 98:2 ratio of the same products when 10% TMEDA–hexane is the solvent.[103] The implication of this observation is that in THF the regioselectivity is determined by azomethine stereochemistry but that in TMEDA–hexane it is not. Note, however, that in this case a *syn*-directing effect does not occur in TMEDA, whereas in the previous example it does. Thus more than 10 years after it was asserted that a 'detailed explanation of the observed solvent dependencies...await further studies owing to the complexities of the reaction system....',[109] little headway has been made.

In the case of β-dicarbonyl compounds, either regioisomer can be obtained, depending upon reaction conditions. Monotosylhydrazones of cyclic β-diketones give the α,β-unsaturated ketone by treatment with potassium carbonate,[143] while the reaction of β-keto esters with stronger base (LDA) gives β,γ-unsaturated esters (Scheme 67).[144] In the former example, only the more acidic α-proton is removed (in ad-

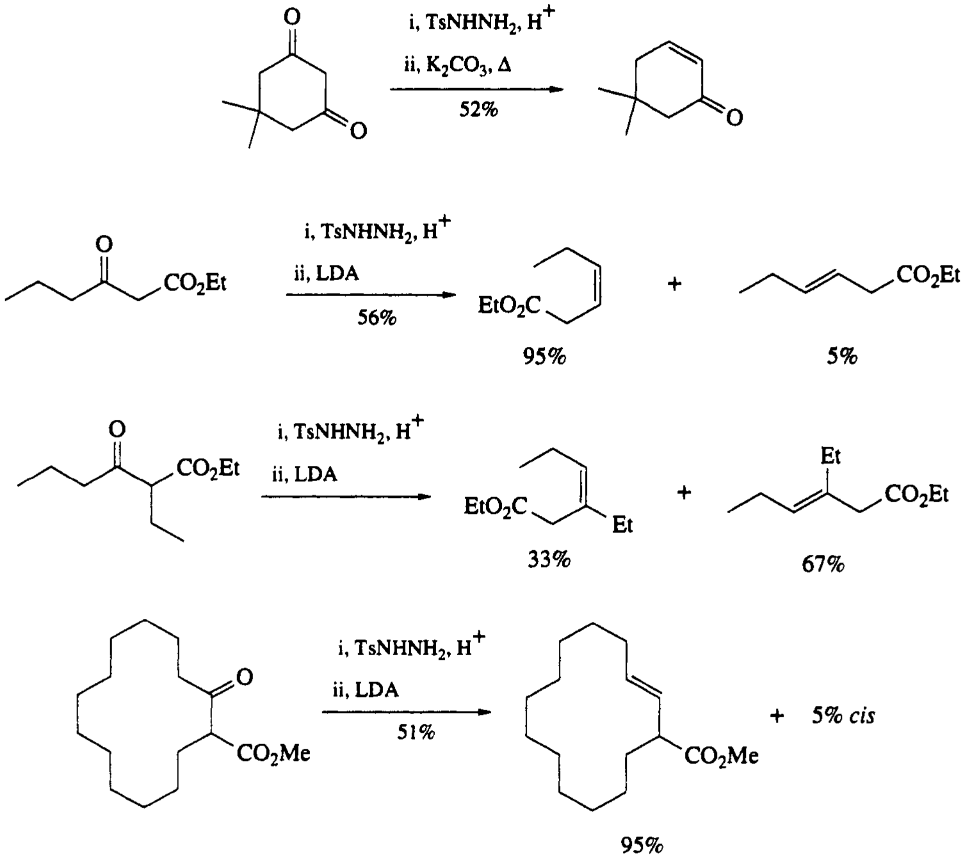

**Scheme 67**

dition to the N—H), while LDA forms a trianion which preferentially eliminates in the opposite direction. A similar result was reported by Evans *et al.*, in a synthesis of juvabione (Scheme 68),[145] which made use of an *N*-aminoaziridine-derived hydrazone in place of the usual arenesulfonylhydrazone. The authors noted that such *N*-aminoaziridine derivatives are generally applicable to the Shapiro reaction, but no published study on the subject has appeared.

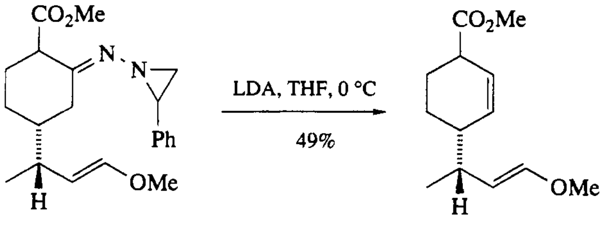

Scheme 68

### 4.6.6.4.2 Stereoselectivity

The issue of stereoselectivity of alkene formation from acyclic tosyl- or trisyl-hydrazones has been addressed in only a few cases. For straight chain ketones, there is a preference for *cis*-alkene formation (see Scheme 67). A few other examples appear to give lower ratios, which is surprising in view of several reports of highly *cis* selective reactions in which the vinyllithium intermediate was trapped with electrophiles.[101] Hydrocarbon branching in the $\alpha'$-position degrades the stereoselectivity considerably (Scheme 67).

### 4.6.6.4.3 Limitations

There are some notable limitations of the Shapiro reaction. Most prominently, aldehyde arenesulfonylhydrazones do not form alkenes, but instead suffer addition of the alkyllithium 'base' to the azomethine bond.[146] Several other specific types of hydrazone derivatives also fail to undergo alkene formation, proceeding instead through well-documented alternative pathways. For example, arenesulfonylhydrazones with a leaving group in the $\alpha$-position can suffer elimination at the monoanion stage, giving a tosylazoalkene as the major product.[147] When the elimination step is the opening of an $\alpha,\beta$-oxirane ring, this process initiates the Eschenmoser fragmentation.[148,149] A related elimination has been observed in attempts to form a cyclic enol ether from the tosylhydrazone of a 3-ketotetrahydropyran (Scheme 69),[150] and some cyclic ether derivatives give allenes *via* a related elimination pathway.[151] On the other hand, a polycyclic $\alpha$-amino ketone was found not to undergo elimination of the amino group (presumably because the conjugate base of the amine is a poorer leaving group), giving instead the expected allylic amine (Scheme 70).[152]

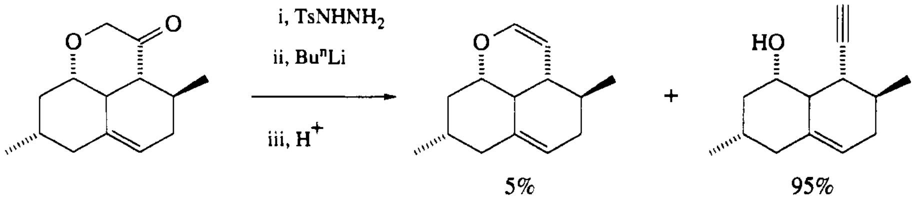

Scheme 69

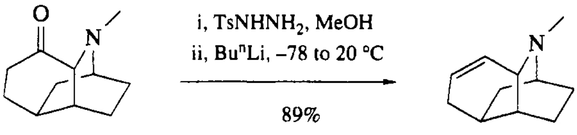

Scheme 70

In contrast to these results, it has been demonstrated that α-(methylthio)tosylhydrazone monoanions, formed by reaction of an initially formed dianion with dimethyl disulfide, undergo *in situ* dianion formation rather than elimination, to give vinyl sulfides (Scheme 71).[58] Since vinyl sulfides can be hydrolyzed to ketones, this sequence constitutes a very effective 1,2-carbonyl transposition.

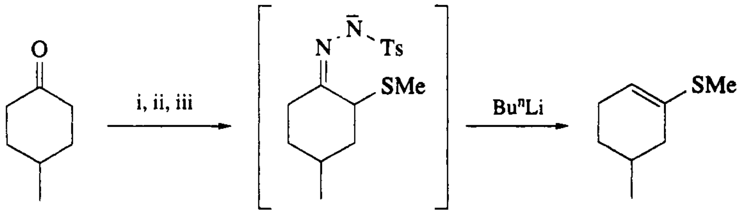

i, $TsNHNH_2$; ii, $Bu^nLi$, TMEDA, –50 °C; iii, $Me_2S$

**Scheme 71**

Finally, hindered arenesulfonylhydrazones can undergo addition of the alkyllithium rather than deprotonation, and, in fact, the normal Shapiro conditions generally do not give any alkene if an α-methine proton must be removed in the initial deprotonation step. Shapiro reported that the use of LDA overcomes the problem,[153] but there are later examples in which this modification is ineffective. In one such case, lithium *t*-butylamide proved to be superior (Scheme 72)[154] and in another it proved necessary to resort to the aforementioned *N*-aminoaziridine derivative in an aprotic Bamford–Stevens reaction, when the normal Shapiro and Bamford–Stevens conditions failed (Scheme 73).[155]

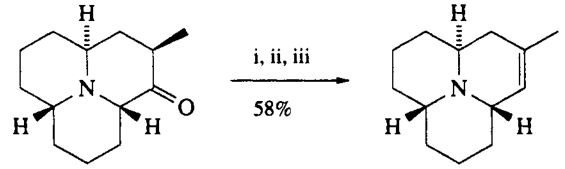

i, $N_2H_4$, EtOH, Δ; ii, TsCl; iii, $Bu^tNHLi$

**Scheme 72**

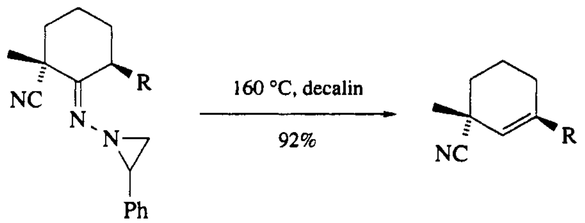

**Scheme 73**

## 4.6.7 MISCELLANEOUS RELATED TRANSFORMATIONS

### 4.6.7.1 Quinones to Arenes

A variation of the ketone to alkene transformation is conversion of quinones into arenes, for which a number of reagent systems have been employed. Over a century ago, the reduction of polycyclic quinones to aromatic systems with phosphorous and hydroiodic acid at elevated temperatures was reported.[156] These conditions, however, resulted in complex reaction mixtures consisting of phenols and polyhydrogenated products. More recently, Konieczny and Harvey[157] have reported the reduction of quinones in the absence of phosphorous using hydroiodic acid in acetic acid, which alleviates the need for high temperatures and results in cleaner reactions and higher yields of the arene products (Scheme 74).

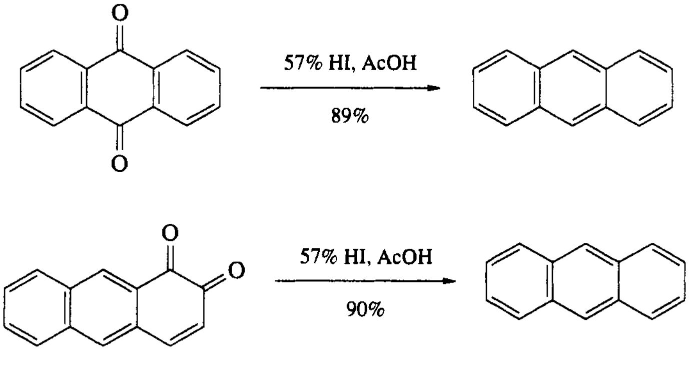

Scheme 74

Other methods to reduce polycyclic quinones to arenes that have met with some success include $SnCl_4/HCl$,[158] $Zn/NH_3$,[159] $Zn/pyridine/MeCO_2H$,[160] $NaBH_4/BF_3{\cdot}Et_2O$,[161] and $NaBH_4$ in MeOH.[162] All of these methods are compatible with aryl halides and the latter two are also compatible with aryl ethers, anilines and phenols. 10-Arylmethylene-9-anthrones have also been reduced to anthracenes with diborane (Scheme 75).[163]

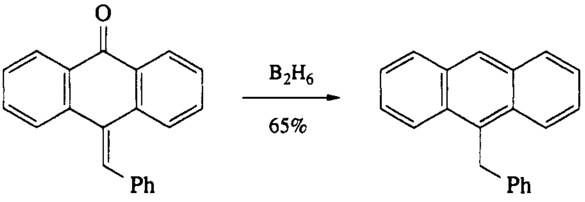

Scheme 75

The conversion of quinones to phenols and subsequently to arenes is an indirect alternative to this process and is covered in this volume, Chapter 4.5.

### 4.6.7.2 Ketones and 1,2-Diketones to Alkynes

Ketones and 1,2-diketones are readily converted into alkynes, which can subsequently be reduced to alkenes. Since there are a number of methods to reduce alkynes stereoselectively, this route offers a method of controlling the stereochemistry of acyclic alkenes derived from ketone starting materials. The most common approach for the ketone to alkyne transformation has been conversion of the starting ketone into a vicinal dichloride and subsequent bis elimination induced by strong base.[164]

Acetophenone derivatives have been converted into the corresponding alkynes employing $NaNH_2$ in $NH_3$[165] or sodium *t*-butoxide[166] as the base in the elimination step. Ferrocenylalkynes[167] have been prepared in a similar manner: treating acetylferrocene with $POCl_3$ in DMF[168] results in the formation of the β-chloro aldehyde, which upon treatment with KOH in dioxane affords the ferrocenylalkyne in high yield. Alkynes have also been prepared from benzyl alkyl ketones by initial hydrazone formation and subsequent oxidation with mercury(I) trifluoroacetate.[169] Ketones have also been converted into the corresponding vinyl halide[170] or vinyl phosphate[171] derivatives, according to the methods described in Section 4.6.5 of this chapter, and then subjected to elimination conditions to afford the target alkynes.

Cyclooctanone has been converted into cyclooctyne by treatment with semicarbazide acetate, resulting in the formation of the semicarbazone, which was oxidized to the 1,2,3-selenadiazole, and then pyrolyzed over glass powder to give cyclooctyne.[172]

1,2-Diketones have also been converted into alkynes, most commonly through the bishydrazone derivatives. Originally, cyclodeca-1,2-dione was converted into cyclodecyne by initial bishydrazone formation and subsequent oxidation with mercury(II) oxide (Scheme 76).[173] More recently, cyclic

1,2-bishydrazones have been converted to the corresponding alkynes with $Pb(OAc)_4$[174] or by irradiating an aqueous methanolic NaOH solution of the bishydrazone.[175] In acyclic systems 1,2-bishydrazones have been oxidized with $Cu_2Cl_2$ in pyridine or $Cu(OAc)_2$ in the presence of $O_2$.[176] Finally, substituted diphenyl diketones (benzils) have been converted into 1,2-diphenylalkynes (tolanes) upon heating in triethyl phosphite.[177]

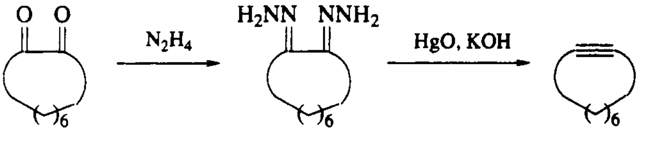

36% overall

**Scheme 76**

## 4.6.8 REFERENCES

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# 4.7

# Hydrogenolysis of Allyl and Benzyl Halides and Related Compounds

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## 4.7.1 INTRODUCTION

Hydrogenolysis to effect replacement of a group —XR attached to a benzylic or allylic center by its heteroatom (X), is widely used in organic synthesis, especially in protecting group strategies, most frequently involving replacement of one group XR, where X is O, N or S (Scheme 1). In reviewing this area of chemistry we have dealt with the material in a functional, rather than an historical, approach, covering first the catalytic methods, then the hydride reducing reagents, followed by dissolving metal reductions. These three sections form the bulk of the review, with other methods, which are less widely employed, examined in less detail at the end.

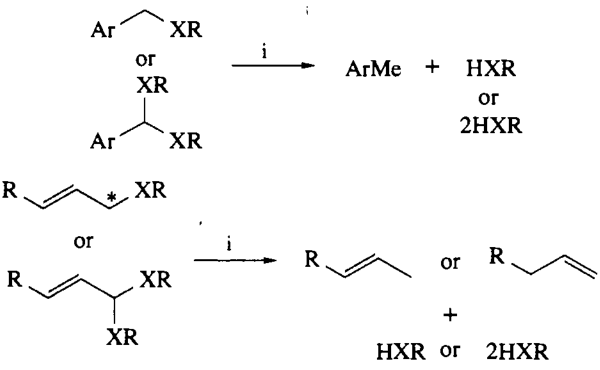

i, hydrogenolysis

**Scheme 1**

## 4.7.2 HYDROGENOLYSIS WITH PALLADIUM AND ITS DERIVATIVES AND WITH OTHER TRANSITION METAL CATALYSTS

### 4.7.2.1 Hydrogenolysis over Palladium with Molecular Hydrogen

Debenzylation by reductive cleavage over palladium metal catalysts with molecular hydrogen has been widely utilized for many decades. A comprehensive review[1] of the early literature on hydrogenolysis of benzyl groups emphasized the main applications and described a number of preparative procedures which are still frequently used, along with a wider range of newer chemical and catalytic methods.

The main interest in hydrogenolysis of benzyl derivatives stems from the use of the benzyl group as a protecting group for hydroxy, amino and carboxylic acids.[1] Recovery of the transformed substrate rather than the toluene formed is usually more important. The disadvantages of the general method using supported palladium metal and molecular hydrogen are mainly lack of regioselectivity, and overreductions, effects more frequently experienced with cleavage of allyl derivatives. For many conversions these deficiencies have been resolved by variations in the use of the catalyst (see later sections) and source of hydrogen donor for both allyl and benzyl derivatives. Where regioselectivity, or stereospecificity, is not an important requirement, hydrogenolysis over palladium on charcoal (Pd/C, $H_2$) remains a widely useful method.

Primary,[2] secondary[3] and tertiary[4] benzyl alcohols (equation 1) can be reduced to the corresponding toluene with Pd/$H_2$ on a wide range of supports such as charcoal, $BaSO_4$, $SrSO_4$ and $CaCO_3$. Similar cleavages[5,6] of C—OH bonds in aromatic methanols are commonly achieved (equation 2). Concomitant reduction of ring substituents such as halogen, and nitrile can often be a problem. Allylic alcohols[7] are more susceptible to saturation of the double bond. Indeed allylic unsaturation can be reduced without hydrogenolysis in some cases. In many hydrogenolysis reactions the presence of an acid (<1%) enhances the reaction rate.[12]

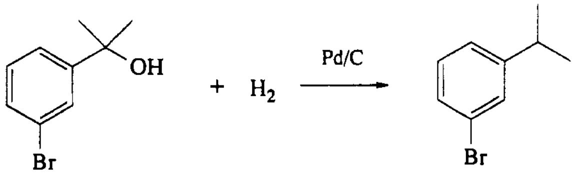

(1)

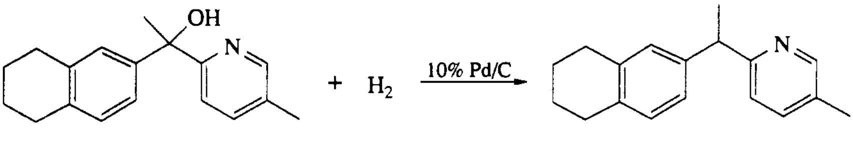

(2)

The ether and ester derivatives of benzyl alcohols are widely utilized as protecting groups.[1,8] In the case of protected peptides hydrogenolysis often has advantages over hydrolysis. This conversion is useful especially for ring opening of oxygen heterocycles (equation 3)[9] where inversion of configuration can be achieved, but deprotection of benzyl ethers is the principal application. Other arylalkyl ethers are cleaved (equation 4), and acetals[1] derived from benzaldehyde are debenzylated.

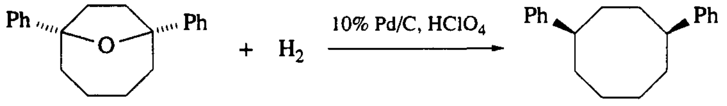
Ph
Ph
O
+ H₂
10% Pd/C, HClO₄
Ph
Ph

(3)

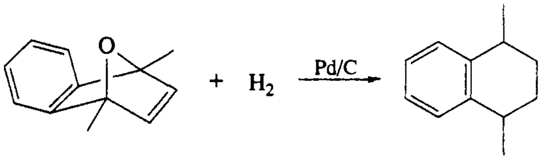

(4)

Many practical procedures have been described.[1] Primarily these are of use in peptide chemistry when deprotection of benzyloxycarbonyl (Z) derivatives is readily achieved with Pd/C and molecular hydrogen (equation 5). A great variety of other types of transformation has been reported, *e.g.* equations (6)–(8).[10–12]

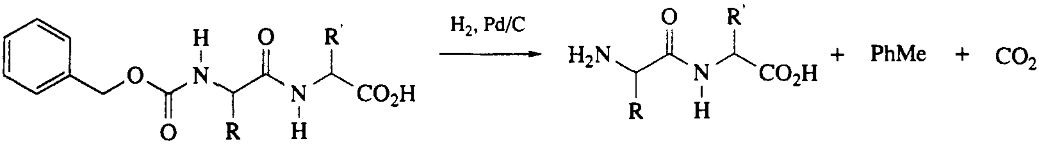
H
O
R'
O
N
N
CO₂H
O
R
H
H₂, Pd/C
O
R'
H₂N
N
CO₂H
R
H
+ PhMe + CO₂

(5)

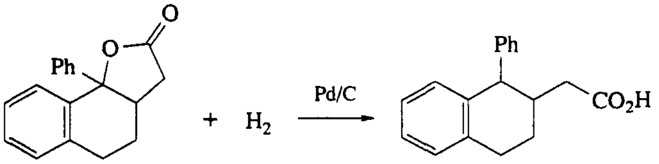
O
Ph
O
+ H₂
Pd/C
Ph
CO₂H

(6)

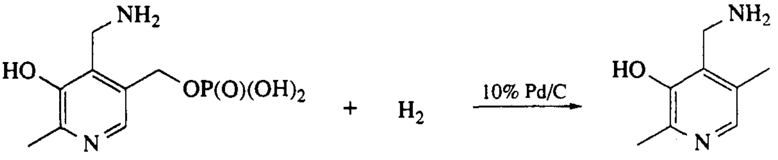
NH₂
HO
OP(O)(OH)₂
N
+ H₂
10% Pd/C
NH₂
HO
N

(7)

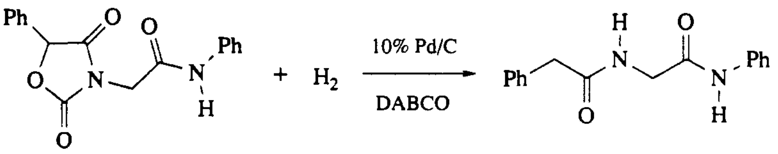
Ph
O
O
Ph
O
N
N
H
O
+ H₂
10% Pd/C
DABCO
H
O
Ph
N
Ph
N
O
H

(8)

Simple primary and secondary benzylamines are generally resistant to hydrogenolysis over Pd/C, but helpful substituents (equation 9) or a different aromatic system (equation 10) do undergo cleavage.[13,14] Related dibenzylamine cleavages have been studied,[15] and where one of the aryl groups is substituted cleavage occurs readily. Tertiary benzylamines are cleaved in high yield. A useful *C*-methylation of aromatic rings *via* amino methylation exemplifies this usage (Scheme 2).[16] Cleavage of allylamines under similar conditions has not found much usage.

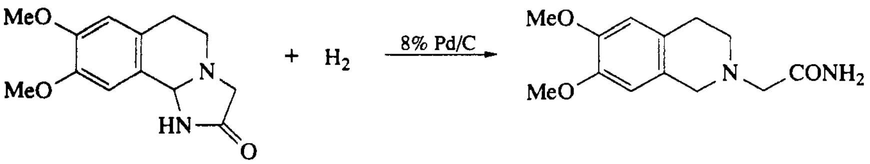
MeO
MeO
N
HN
O
+ H₂
8% Pd/C
MeO
MeO
N
CONH₂

(9)

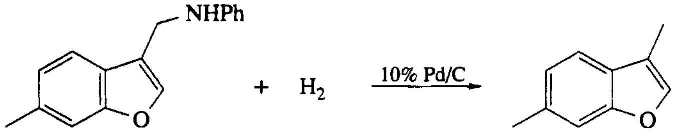

(10)

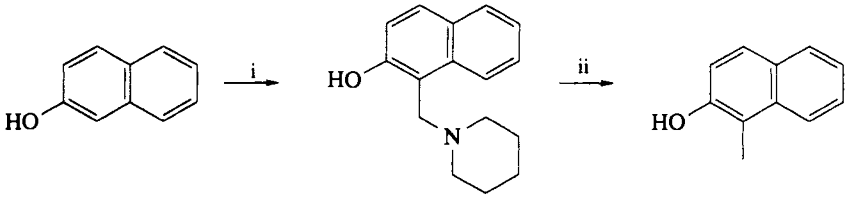

i, HCHO, piperidine; ii, $H_2$, 1% Pd/$SrCO_3$

Scheme 2

Arylalkyl quaternary ammonium groups are generally cleaved more readily by chemical methods. Reduction over Pd/C is used to advantage in obtaining a sample of desacetimido colchiceine (equation 11) from the natural product.[17]

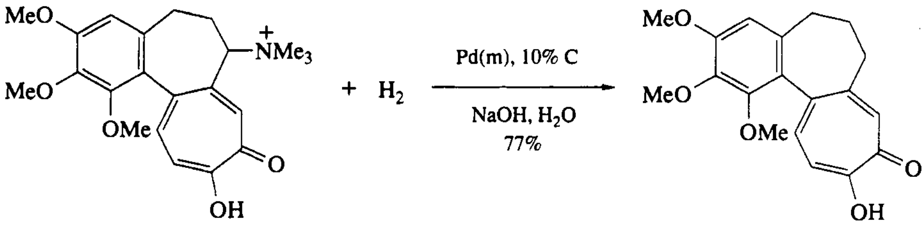

(11)

Catalyst poisoning by sulfur has discouraged development of procedures for cleavage of sulfides. Desulfurization of highly activated allylic methyl sulfides can be effected by addition of lead to the palladium(0) catalyst.[18] In the presence of various tertiary amines satisfactory cleavage of several related allyl sulfides has been utilized (equation 12) using a modified Pd/$CaCO_3$ catalyst.

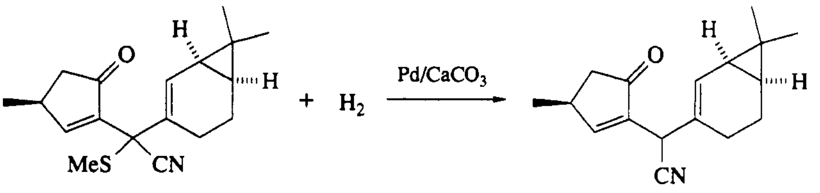

(12)

Both benzyl and allyl halides are rapidly hydrogenolyzed. Cleavage can be achieved selectively in the presence of aryl and alkyl halides. Double bond isomerization can often prevent any stereoselectivity in allylic cleavages.

### 4.7.2.2 Hydrogenolysis over Palladium with Other Hydride Sources

Many of the difficulties experienced with heterogeneous Pd-catalyzed hydrogenolysis of benzyl groups have been overcome by deploying such alternatives to molecular hydrogen as cyclohexene and formate anion. A recent review of catalytic transfer hydrogenation describes the application to hydrogenolysis of benzyl and allyl derivatives.[19]

In particular the use of both cyclohexene and formates has gained wide acceptance for cleavage of benzyl, benzyloxycarbonyl (Z) or 4-methoxybenzyloxycarbonyl (PMZ) protected amino acids and peptides (Scheme 3).[20] An extensive table listing conditions for debenzylation of over 70 protected amino acids or peptides has been prepared.[19] Generally nonracemized products are obtained since transfer hydrogenolysis with cyclohexene occurs usually under mild conditions of refluxing methanol or ethanol.

Cleavage is effected at lower temperatures using cyclohexadienes,[21] or more usually formic acid or formates when reaction times are often as low as 0.15 h.[22]

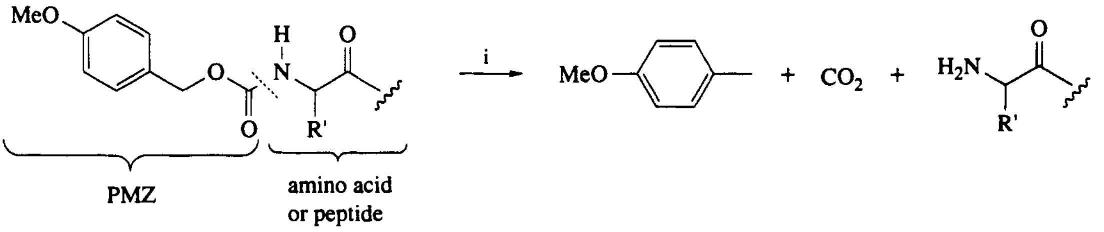

i, cyclohexene, ROH, 10% Pd/C, Δ

**Scheme 3**

Cleavage of *N*-(benzyloxycarbonyl) groups from methionine has been achieved. Using liquid ammonia solution also allowed deprotection of (*S*)-benzylcysteine and other methionine-containing peptides.[23] Simultaneous removal of *t*-butoxycarbonyl protection occurs to advantage when formic acid as donor is used to remove Z-groups.

Similar utilization for cleavage of benzyl alcohols, ethers and esters has made this method the preferred one where regioselectivity is required, but for allylic cleavage double bond isomerization becomes a problem.[24] A number of benzylic ethers and alcohols (equation 13), and benzhydric ethers and acetals (equation 14) have been cleaved in relatively high yield using cyclohexene in the presence of $AlCl_3$.[25] Mild conditions of cleavage are frequently required for debenzylation of carbohydrates and a number of protected carbohydrates have been cleaved with formic acid as donor (equation 15).[26]

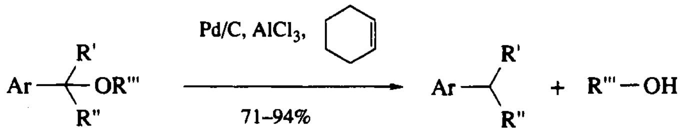

(13)

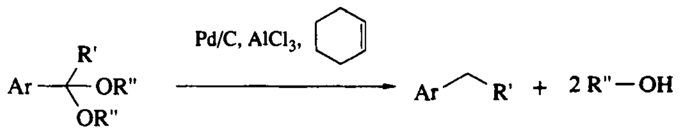

(14)

$$\text{2,3,4,6-Tetra-}O\text{-benzyl-}\alpha\text{-D-glucopyranose} \xrightarrow[\text{Pd/C}]{\text{HCO}_2\text{H}} \text{D-Glucose} \qquad (15)$$

Alcohols or phenols[27] protected by benzyloxycarbonyl groups are very smoothly reduced over Pd/C using phosphinic acid or sodium phosphinate as hydrogen donor. Effective cleavage of an allylic *t*-amine has been demonstrated (equation 16) utilizing ammonium formate as donor.[28] The lack of regiospecificity could possibly be overcome by selective use of catalysts. For example, double bond migration can be influenced by Pd/Hg or Pd/Pb catalysts.[29]

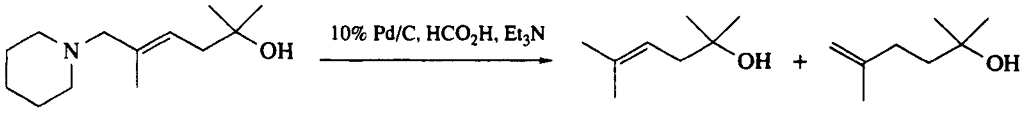

(16)

The successful application of catalytic hydrogen transfer reduction to benzylic reductions has not been mirrored for allylic cleavage. Use of homogeneous or ligated palladium catalysts has however extended hydrogenolysis by transfer hydrogenation to allyl transformations. The extensive use of the electrophilic properties of π-allyl complexes in many synthetic strategies is widely documented.[30] Reduction of such (π-allyl)palladium intermediates with hydride from decarboxylated formate was shown to yield 1-alkenes (equation 17), where the hydride attack was preferentially on the more-substituted side of the π-allylic system. The conversion (equation 18) indicates the regioselectivity and use of allyl as a protecting group. Isomeric allyl acetates or phenyl ethers were also selectively reduced (equation 17). Later work refined this method and showed that greater selectivity for 1-alkenes could be achieved using $PBu^n_3$ as ligand.[31]

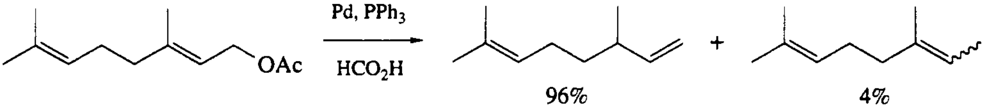

(17)

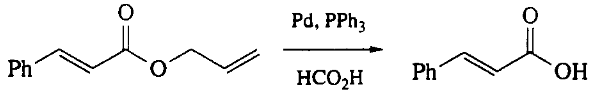

(18)

A greater selectivity toward formation of (*E*)-2-alkenes from allylic acetates is achieved using 2-propanol as a hydrogen donor and $Pd^0/SmI_2$ as catalyst generated from $PdCl_2/PPh_3$ (Scheme 4). In the formation of (±)-limonene from (–)-carvyl acetate, optical activity is lost by this method.[32] Although very high yields are attainable, control of the regiochemistry and stereochemistry is variable.[32] Conversion of allyl propionate, phenyl ether and other substituted allyl acetates to 1-alkenes with $Pd(PPh_3)_4$ and formic acid, occurs in only modest yield. Triallylamine yielded a mixture of products containing diallylamine and allylamine.[33]

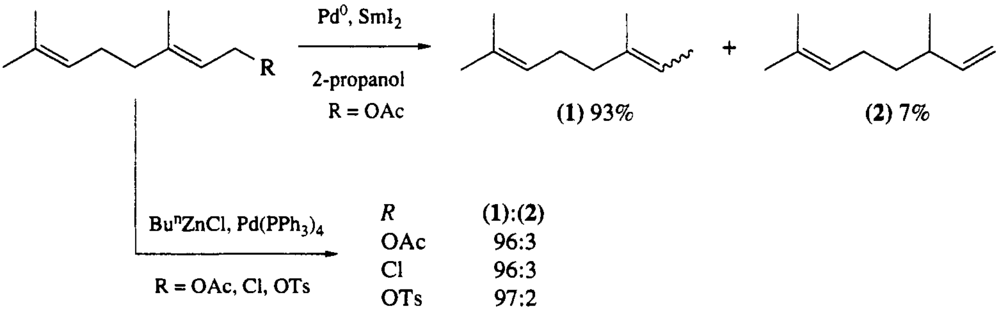

| *R* | (1):(2) |
|---|---|
| OAc | 96:3 |
| Cl | 96:3 |
| OTs | 97:2 |

**Scheme 4**

A study of the cross coupling of allylic electrophiles with organometallics provides a useful regio- and stereo-selective hydrogenolysis of allylic acetates, halides and tosylates.[34] The reaction of geranyl acetate with *n*-butylzinc chloride (Scheme 4) in the presence of $Pd(PPh_3)_4$ yielded a mixture of (*E*)/(*Z*)-isomers of 2,6-dimethyl-2,6-octadiene (96% yield). The presence of β-hydrogens on the alkylzinc and the size of the alkyl group, appear to be critical for regio- and stereo-selectivity.

As a useful alternative source of $H^-$ various metal hydrides have been studied. Allylic acetates such as geranyl and cinnamyl are efficiently hydrogenolyzed with $Pd(PPh_3)_4$ and $NaBH_3CN$.[35] For many other examples of allylic acetate cleavage better regioselectivity was observed when $NaBH_4$ was used, but very variable *cis/trans* isomer ratios were found. Conjugation of the allylic unsaturation to aromatic rings produces conjugated alkenes exclusively. Overall control of the 1-ene/2-ene ratio was variable.

Greater regioselectivity and control over (*E*)/(*Z*) ratios of the alkene products can be obtained by utilizing less labile leaving groups such as —OPh, —SPh, —$SO_2Ph$, —SePh, —Cl and —$OSiMe_2Bu^t$, in conjunction with more powerful hydride donors. Of these the most effective appears to be the hindered hydride $LiBHEt_3$.[36] This achieves selectivity for 2-enes and retention of (*E*)-geometry, and appears to attack rapidly at the less-hindered side of the π-allyl complex. $NaBH_3CN$ and ammonium formate control the product geometry less effectively. A useful alternative catalyst $[PdCl_2(DPPP)]$ for regiospecific cleavage of allylic *p*-tolyl sulfones with $LiBHEt_3$ (equation 19) illustrates the importance of the π-allyl complex in controlling the specificity.[37]

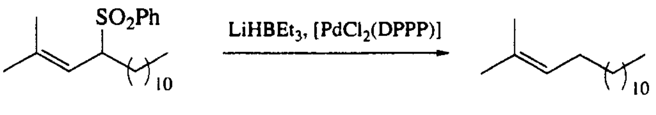

(19)

Steric control of the mechanism has been clearly demonstrated by the reduction of 3-tosyl-1-cyclohexane derivatives (Scheme 5). This control has been deployed in the synthesis of coenzyme $Q_{10}$. The wider use of these reductions has been studied and very high stereoselectivity is observed for hydrogenolysis of farnesyl derivatives, —Cl, —OPh, —$OSiMe_2Bu^t$, —SPh, —SOMe, —$SO_2Me$ and $^+N(=CH_2)Me$.

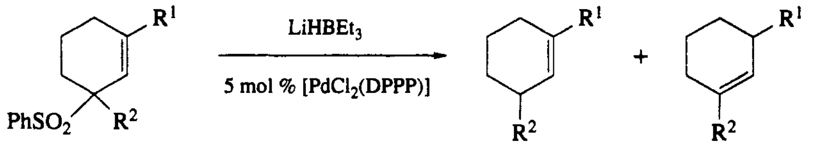

| | | |
|---|---|---|
| $R^1 = H, R^2 = Bn$ | 0 | >99 |
| $R^1 = Bn, R^2 = H$ | >99 | 0 |

**Scheme 5**

Increased chemoselectivity has been achieved by using $Pd^0$ and $Pd^{II}$ activation of the allylic centers, but many reagents such as the strong hydride donors are often incompatible with electrophilic groups such as ketones and aldehydes. Stereospecific reduction of the model compounds (**3**) and (**4**) in Scheme 6 suggested that the hydride could be delivered by an internal transfer and thus need not have high nucleophilicity. Hydrogenolysis with such a hydride source as tributyltin hydride with free radical scavenging fulfils this requirement. Its chemoselectivity is effectively demonstrated by the high yield transformations (equations 20 and 21). Some allylic amines can also be cleaved in moderate yields (equation 22).[38] Substrates which possess a relatively acidic hydrogen α to the allylic unit are incompatible with the low basicity of $Bu_3SnH$ and undergo β-hydride elimination to yield the corresponding diene.[39] Reduction of these allylic systems can be effected with polymethylhydrosiloxane (PMHS) as donor (equation 23),[40] which has advantages such as stability, nontoxicity and lower cost compared to metal hydrides. In cleavages where the formation of the π-allyl intermediate is slow, for example when the allyl unit is sterically crowded and competing reactions cause yield loss, PMHS is a more effective donor (Scheme 7). Both $Pd^0$ and $Pd^{II}$ catalyst complexes can be used with PMHS. Michael acceptors are readily reduced by $Bu_3SnH$ but are unaffected by PMHS. The greater chemoselectivity of PMHS as a hydride donor is also demonstrated by the failure to reduce allylic acid chlorides which are sensitive to $Bu_3SnH$. While greater chemoselectivity is an advantage of the use of either $Bu_3SnH$ or PMHS, less regioselectivity is observed than for the other hydrides described.

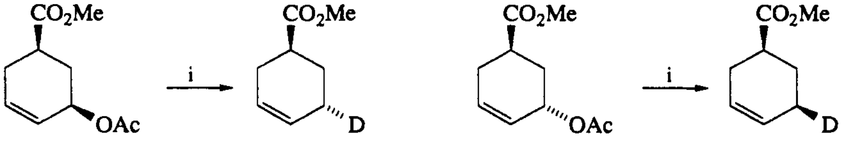

(**3**) (**4**)

i, $NaBD_4$, $Pd(PPh_3)_4$

**Scheme 6**

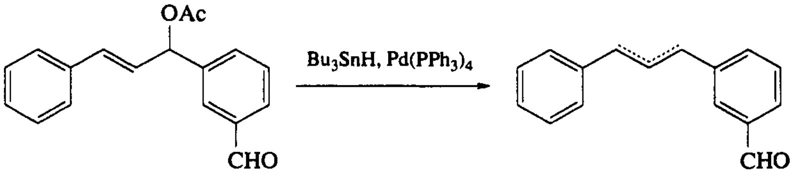

(20)

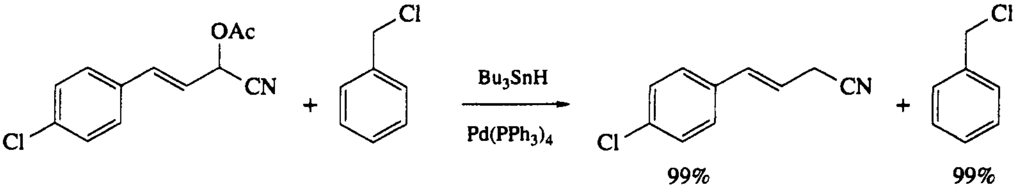

(21)

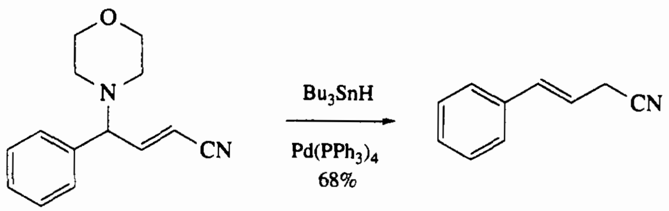
N
O
CN
Bu3SnH
Pd(PPh3)4
68%
CN

(22)

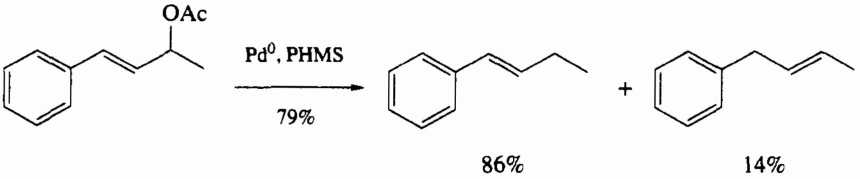
OAc
Pd0, PHMS
79%
+
86%
14%

(23)

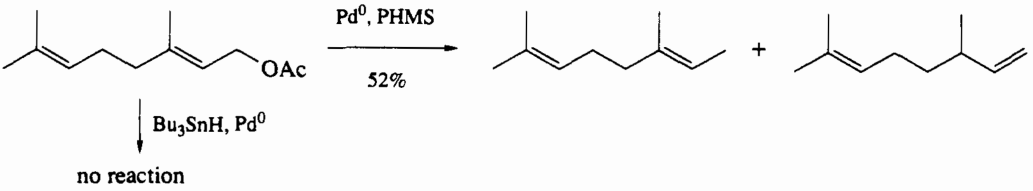
OAc
Pd0, PHMS
52%
+
Bu3SnH, Pd0
no reaction

**Scheme 7**

Cleavage of the allylic C—N bond over Pd$^0$ with hydrides has been reported only rarely. The unusual hydrogenolysis of allylic nitro compounds[41] by Pd$^0$-catalyzed hydride transfer (Scheme 8) could have more extensive use than the reported synthesis of homoallylic alcohols. Regioselectivity is dependent on the nature of the π-allyl unit and on substitution as well as the nature of the hydride (equations 24–26). Good nucleophilic hydride sources such as NaBH$_4$ with small ligands are utilized to obtain 2-alkenes regioselectively. High regioselectivity is also evident with α,β-unsaturated ester reductions.

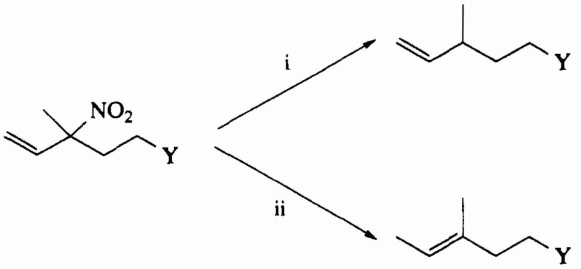

Y = $CO_2Me$, CN, $SO_2Ph$

i, $HCO_2NH_4$, Pd$^0$; ii, $NaBH_4$, Pd$^0$

**Scheme 8**

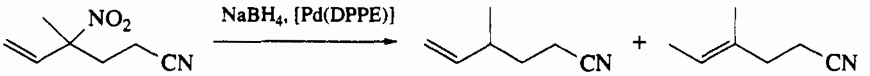
NO2
CN
NaBH4, [Pd(DPPE)]
CN
+
CN

(24)

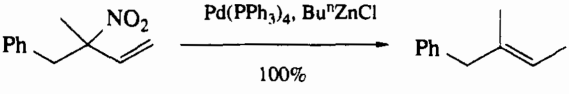
NO2
Ph
Pd(PPh3)4, BunZnCl
100%
Ph

(25)

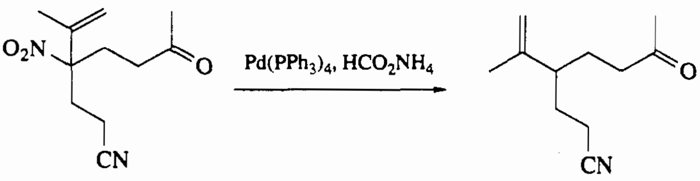
O2N
O
CN
Pd(PPh3)4, HCO2NH4
O
CN

(26)

### 4.7.2.3 Hydrogenolysis over Other Transition Metal Catalysts

Both palladium and platinum metals are widely used as hydrogenation catalysts. Although only palladium has found significant usage for benzylic and allylic cleavage of C–heteroatom bonds, catalyst poisoning has discouraged its use for the cleavage of C—S bonds. Where deactivated catalysts have been required, both rhodium and rhenium metals or their ligated complexes have, however, been utilized as well as doped palladium. Desulfurization of benzylic and allylic compounds is readily achieved with $Rh^0$ complexes.[42] Regioselectivity is affected markedly by alkyl substituents on the alkenic bond of the substrate (equations 27 and 28). Terminal alkenes are often isomerized to inner alkenes and the stereochemistry is uncontrolled. Benzylic thiols, sulfides and disulfides are cleaved in high yield to the hydrocarbon with molecular hydrogen over $Rh(PPh_3)_3Cl$ or $Rh(PPh_3)_2(CO)Cl$.[43] Chemoselectivity is achieved more readily with these catalysts.

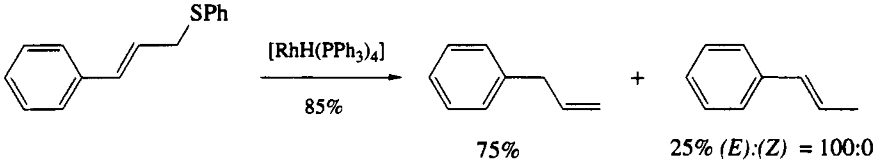

(27)

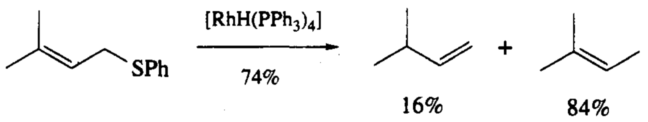

(28)

Copper chromite ($CuCr_2O_4$) has historically been widely used as a hydrogenation catalyst. Generally because of its low catalytic activity its chemoselectivity is useful, although it does require high temperature and autoclave pressure conditions. It is effective for cleavage of benzylic alcohols,[44] primary and secondary benzylic esters[45] and ethers.[46] Efficient cleavage of benzylamines has also been utilized (equation 29).[47] Other copper salts and copper alloys have found infrequent use.

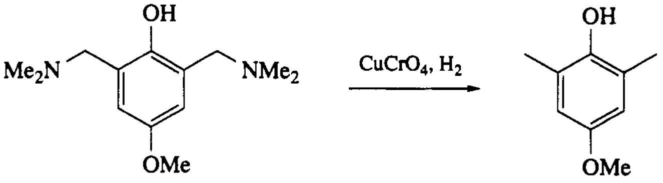

(29)

The wider utility of palladium metal catalysts and hydride cleavage of allylic systems has more or less replaced interest in using platinum-based catalysts such as Adams' catalyst. Where this has been used for conjugation-stabilized allylic centers good yields have been achieved.[47] The use of platinum for debenzylation at low $H_2$ pressure is effective.[48]

### 4.7.2.4 Hydrogenolysis over Raney Nickel

Reduction of benzylic oxygen functional groups with Raney nickel has occasionally been reported, but there are very few examples in the recent literature. Hydrogenolysis over W-2 Raney nickel has been used to selectively remove benzyl ether protection in the presence of a 4-methoxybenzyl protecting group (equation 30).[49]

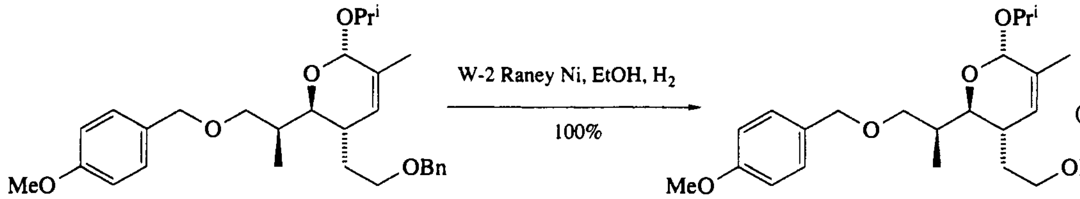

(30)

Benzylic halides have also been reduced to hydrocarbons by hydrogenolysis over Raney nickel (equation 31).[50] Benzylic amines have been cleaved by hydrogenolysis over Raney nickel (equation 32)[51] or by treatment of a methiodide salt with basic Raney nickel (equation 33).[52]

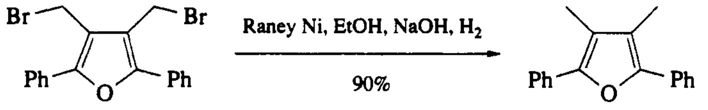
Br
Br
Ph
O
Ph
Raney Ni, EtOH, NaOH, H2
90%
Ph
O
Ph

(31)

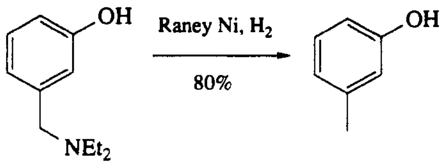
OH
NEt2
Raney Ni, H2
80%
OH

(32)

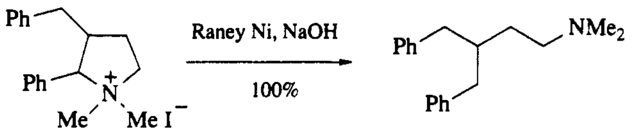
Ph
Ph
N
+
Me
Me I
−
Raney Ni, NaOH
100%
Ph
NMe2
Ph

(33)

Raney nickel is most frequently used to reduce organic sulfur compounds, usually to hydrocarbons.[53] Many different types of organosulfur derivatives can be reduced in this way using various grades of Raney nickel, usually in alcoholic solvents. Thiols in general are readily reduced, but benzylic thiols with α-hydroxy groups form products from alternative reactions (equation 34).[54] Benzylic alkyl and aryl sulfides are readily reduced to alkanes with Raney nickel in the presence of a variety of other functional groups (equations 35–39).[55–59] When a sulfide is removed from an asymmetric center with Raney nickel stereochemical integrity is lost. However, in this instance, oxidation to the sulfone, followed by desulfurization, retained optical activity (equations 40 and 41).[60]

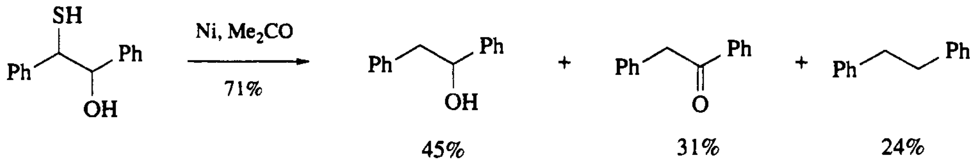
SH
Ph
Ph
OH
Ni, Me2CO
71%
Ph
Ph
OH
+
Ph
Ph
O
+
Ph
Ph
45%
31%
24%

(34)

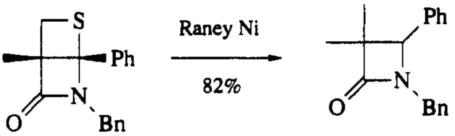
S
Ph
O
N
Bn
Raney Ni
82%
Ph
O
N
Bn

(35)

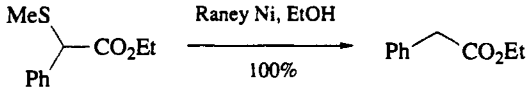
MeS
CO2Et
Ph
Raney Ni, EtOH
100%
Ph
CO2Et

(36)

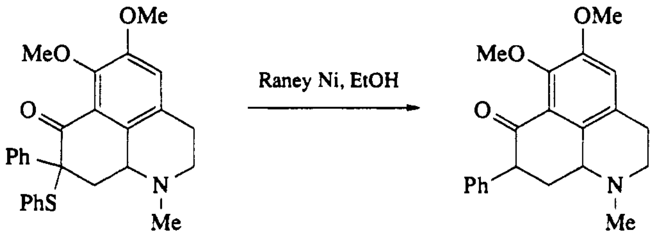
OMe
MeO
O
Ph
PhS
N
Me
Raney Ni, EtOH
OMe
MeO
O
Ph
N
Me

(37)

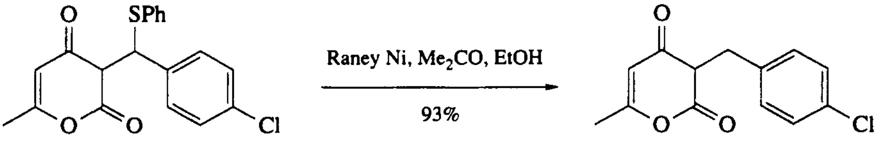

(38)

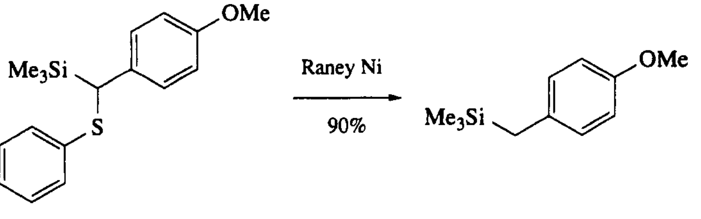

(39)

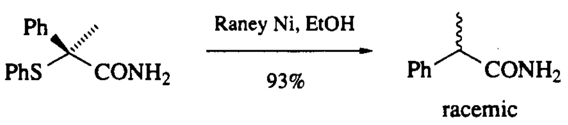

(40)

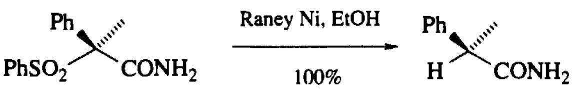

(41)

## 4.7.3 HYDROGENOLYSIS WITH HYDRIDE REDUCING AGENTS

### 4.7.3.1 Lithium Aluminum Hydride

On treatment with LAH, benzylic halides and related compounds are reduced to the corresponding hydrocarbon (equations 42 and 43),[61,62] although in some cases coupled, dimeric products can also be obtained. Selectivity between halides is possible,[63] and in some examples LiH has been added to the reaction mixture.[64]

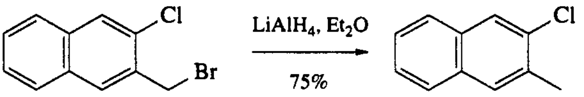

(42)

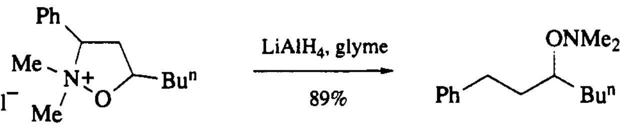

(43)

Reduction of allylically placed functional groups with LAH normally occurs *via* one of two mechanisms: $S_N2$ or $S_N2'$.[65] In acyclic systems the mechanism followed depends on the nature of the leaving group. It has been shown (Table 1) that good leaving groups generally give unrearranged products ($S_N2$), while poor leaving groups give rearranged products ($S_N2'$).[66] The evidence suggests that reduction of triphenylphosphonium salts is a suitable method for the specific formation of $S_N2'$ products, even when the structural features of the substrate favor an $S_N2$ mechanism.

The regio- and stereo-chemical outcome of reductions of cyclic allylic systems is controlled by more complex factors.[65] Reduction of the allyl bromides (**6**) and (**7**) occurs exclusively by *syn* γ-attack (Scheme 9),[67] but other structural features influence the reaction. For example, where the allylic double bond is in a thermodynamically stable position, rearrangement does not normally occur.[68] The reaction has also been studied in complex carbohydrate alkenes.[69]

Reduction of allylic carbonyl derivatives usually leads to the corresponding allylic alcohol; however, in some cases, intermediate oxidation states can be obtained. Reduction of amide derivatives such as *N*-acylpyrazoles results in the formation of an aldehyde in good yield.[70]

Table 1 Reduction of Allylic Functional Groups with LAH

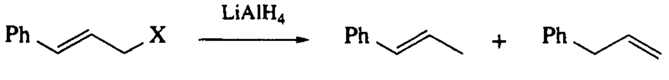
Ph
X
LiAlH4
Ph
+
Ph

**(5)** **(5a)** **(5b)**

| *X* | *Reaction time* (h) | *Yield* (%) | *Ratio* (**5a**):(**5b**) |
|---|---|---|---|
| Br | 0.5 | 100 | 100:0 |
| Cl | 0.5 | 78 | 100:0 |
| Ts | 1.0 | 50 | 100:0 |
| $^+SMe_2Br^-$ | 0.5 | 90 | 90:10 |
| $^+NEt_3Br^-$ | 0.5 | 62 | 76:24 |
| $^+NBu_3Br^-$ | 6.0 | 2 | 76:24 |
| $P(O)(OEt)_2$ | 0.5 | 46 | 2:98 |
| $^+PBu_3Br^-$ | 0.5 | 90 | 7:93 |
| $^+PPh_3Br^-$ | 0.5 | 95 | 0:100 |

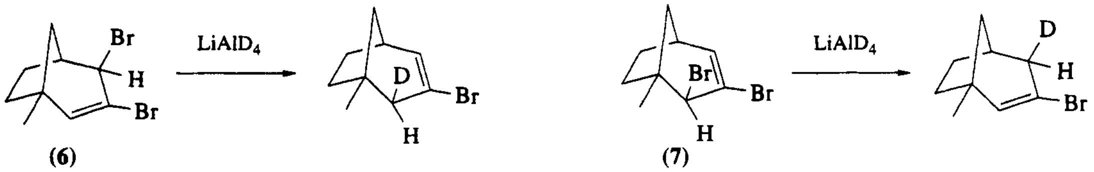
Br
H
Br
LiAlD4
D
Br
H
Br
Br
H
LiAlD4
D
H
Br

**(6)** **(7)**

**Scheme 9**

Certain benzylic alcohols, ethers, acetals and thiols, which are normally resistant to reduction by LAH, can be reduced to the hydrocarbon when the substrate is activated with a Lewis acid. $AlCl_3$ has been most widely used in this role. Various acetals can also be reduced to ethers using the same reagent (equation 44).[71] A related procedure has been used to convert aldehydes into sulfides (equation 45).[72]

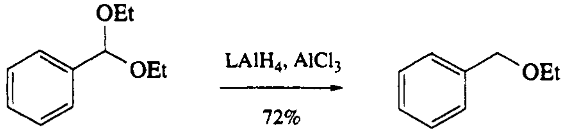
OEt
OEt
LAlH4, AlCl3
72%
OEt

(44)

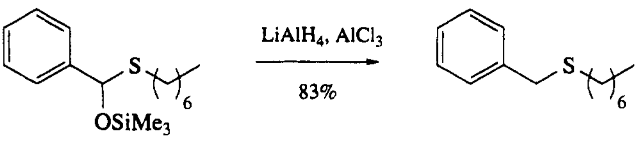
S
6
OSiMe3
LiAlH4, AlCl3
83%
S
6

(45)

A variety of other Lewis acids have been used in conjunction with LAH, including nickel, copper and titanium salts, the resulting reagents being used to reduce sulfides and benzyl ethers to hydrocarbons (equations 46–48).[73–75] Addition of nickelocene to LAH produces a specific desulfurization reagent which does not reduce ketones and esters.[76]

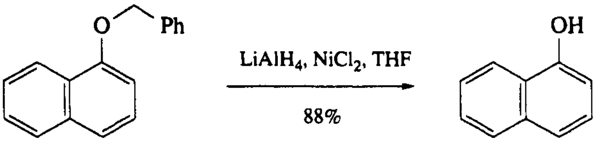
O
Ph
LiAlH4, NiCl2, THF
88%
OH

(46)

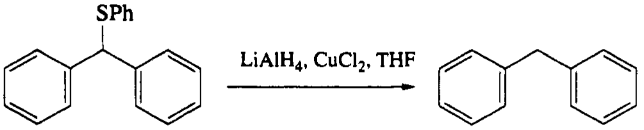
SPh
LiAlH4, CuCl2, THF

(47)

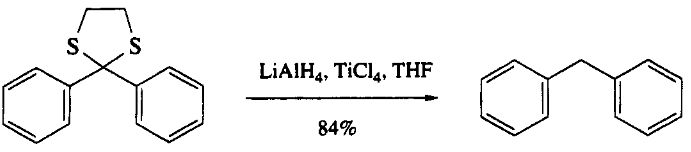

(48)

The enhanced reductive power of Lewis acid/LAH mixtures observed with benzyl substituents is reflected in allyl compounds. Thus allyl methyl ethers are readily demethoxylated with LAH/$TiCl_4$ (equation 49),[77] with complete rearrangement of the double bond and some (*Z*)-selectivity. Allyl alcohols are reduced to alkenes with the same reagent or with LAH/$AlCl_3$ (equation 50).[78] With both these reagents double bond migration was observed to varying degrees as well as diene formation. Primary allyl alcohols have been reduced to alkenes with titanocene and LAH (equation 51).[79]

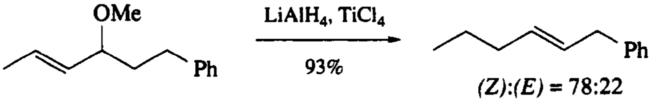

(49)

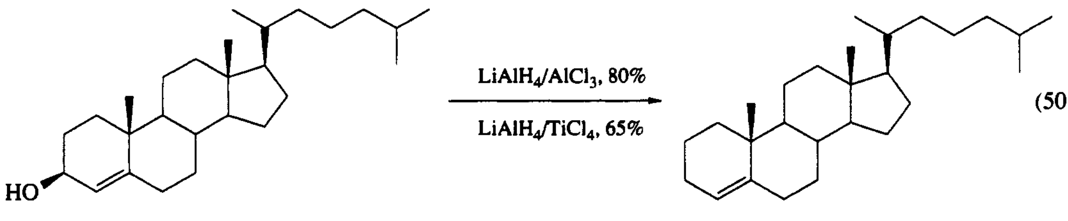

(50)

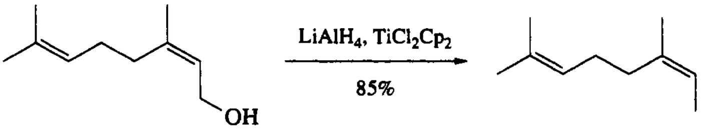

(51)

### 4.7.3.2 Derivatives of Lithium Aluminum Hydride

Reduction of organic compounds in general with alkoxyaluminum hydrides has been reviewed.[80] Benzylic aldehydes, ketones and carboxylic acids are reduced to benzylic alcohols with $NaAlH_2(OC_2H_4OMe)_2$. However this reagent can also be used to reduce the benzylic alcohol so formed to a hydrocarbon, particularly when there are electron-donating groups on the aromatic ring (equation 52). It should be noted however that aromatic halides are unstable towards reduction under these conditions.[81] DIBAL-H has also been used to reductively detosylate at the benzylic position (equation 53).[82]

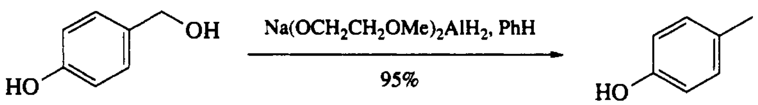

(52)

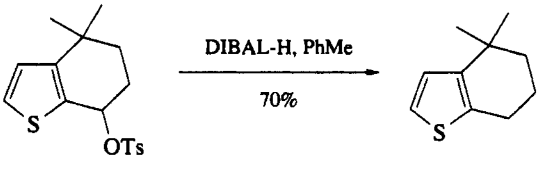

(53)

### 4.7.3.3 Sodium Borohydride

Some unusual benzylic functional groups can be reduced to hydrocarbons using $NaBH_4$ alone in alcohols (equation 54).[83] Choice of solvent can be used to enhance (or reduce) the reductive power of $NaBH_4$. Thus in DMSO (or sulfolane), $NaBH_4$ effectively reduces primary, secondary and tertiary benzylic halides to alkanes, leaving nitro, ester and carboxylic acids untouched (equation 55).[84] There has also been one report of the reductive cleavage of a benzylic trichloromethyl group with $NaBH_4$ in another rate-enhancing aprotic solvent, DMF (equation 56).[85]

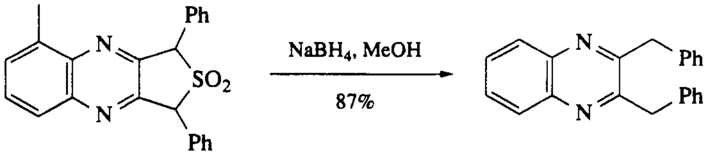
Ph
N
SO2
N
Ph
NaBH4, MeOH
87%
N
Ph
Ph
N

(54)

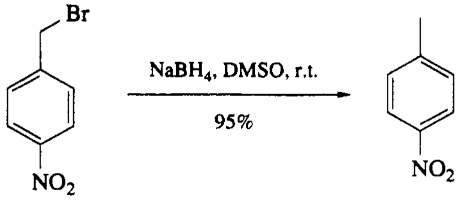
Br
NO2
NaBH4, DMSO, r.t.
95%
NO2

(55)

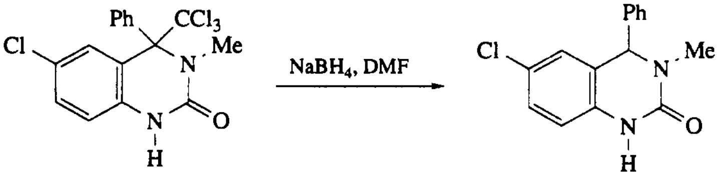
Ph
CCl3
Cl
N
Me
N
H
O
NaBH4, DMF
Ph
Cl
N
Me
N
H
O

(56)

Benzylic alcohols can be reduced with $NaBH_4$ under acidic conditions using either mineral acid (equation 57)[86] or trifluoroacetic acid.[87] These reactions involve formation and reduction of a benzylic carbonium ion. Similarly the Lewis acid $AlCl_3$ can be used in place of a Brønsted acid, reducing diaryl and aryl alkyl ketones and carbinols to hydrocarbons in excellent yield.[88] Benzylic carbonium ions can also be trapped with $NaBH_4$ after generation under solvolytic conditions. Thus a variety of aryl-, diaryl- and triaryl-methyl chlorides can be reduced in aqueous diglyme containing sodium hydroxide (equation 58).[89]

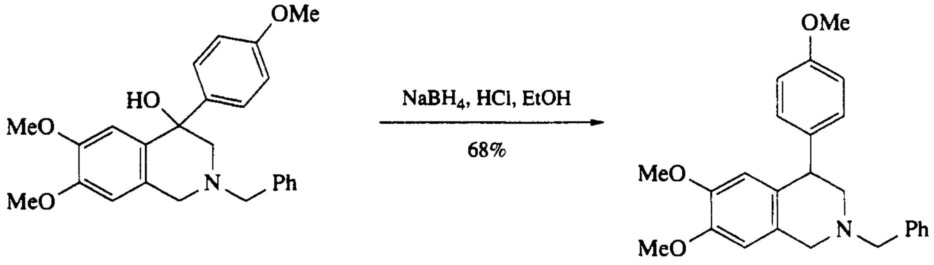
OMe
HO
MeO
MeO
N
Ph
NaBH4, HCl, EtOH
68%
OMe
MeO
MeO
N
Ph

(57)

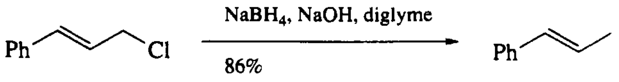
Ph
Cl
NaBH4, NaOH, diglyme
86%
Ph

(58)

Nickel boride has been used to reduce benzylic dithioacetals to sulfides or hydrocarbons (equation 59).[90] More recently the reagent has been applied to the reduction of allylic functional groups. The reagent effectively reduces allyl alcohols, acetates, trifluoroacetates and benzoates, but leaves methyl and benzyl ethers untouched and appears to lead to the thermodynamically more stable alkene (equation 60).[91,92]

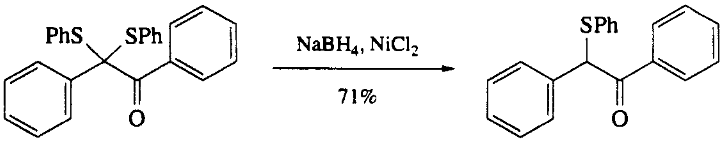
PhS
SPh
O
NaBH4, NiCl2
71%
SPh
O

(59)

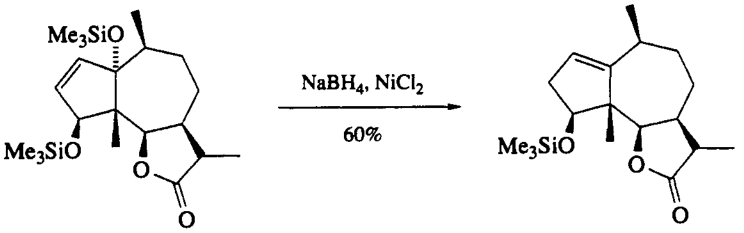

(60)

### 4.7.3.4 Derivatives of Sodium Borohydride

The reductive power of NaCNBH$_3$ can be modified by the addition of Lewis acids in a similar manner to NaBH$_4$ itself. Thus addition of ZnCl$_2$ to NaCNBH$_3$ produces a reagent which is stable in aqueous media and is capable of reducing a variety of benzylic and allylic functional groups to the corresponding hydrocarbon (equations 61–63).[93]

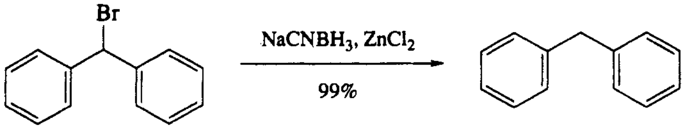

(61)

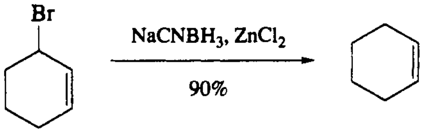

(62)

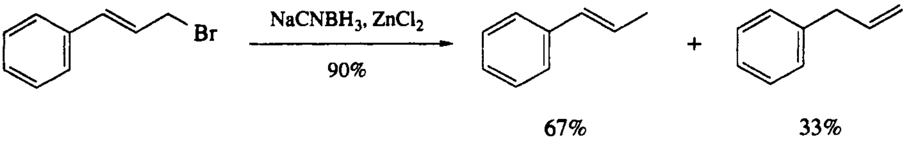

(63)

Zinc iodide can be used in a similar manner to the chloride in this type of reaction, but the reagent so formed has been examined in more detail and has been shown to reduce benzylic and allylic aldehydes, ketones and alcohols to hydrocarbons (equation 64).[94] The reagent is much more reactive than that formed between ZnI$_2$ and NaBH$_4$. The ZnI$_2$/NaCNBH$_3$ reagent is, however, relatively unselective, attacking esters and nitro groups to some extent. Unactivated carbonyls are reduced to alcohols.

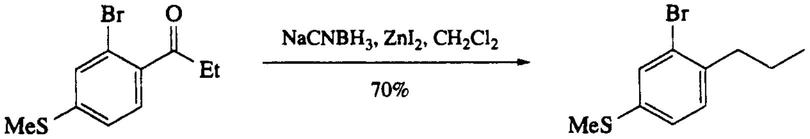

(64)

NaCNBH$_3$ can also be used in an important protecting group strategy to reductively cleave 4-methoxybenzylidene acetals. As shown in Scheme 10, either 6-*O*- or 4-*O*-4-methoxy benzyl ethers can be obtained, depending on additive and solvent.[95,96]

### 4.7.3.5 Other Hydride Reducing Agents

The reducing system produced from an organosilane and BF$_3$ has been applied to both benzylic and allylic systems. Among the many different types of alcohol reduced to hydrocarbons by the reagent, the reduction of benzylic alcohols can be effected with various organosilanes as hydride donors (equation 65).[97]

Radical reduction of allylic and benzylic functional groups with Bu$_3$SnH and AIBN has been applied to benzylic nitro groups and benzylic and allylic sulfides, the former technique providing a high yielding chemoselective method of reducing secondary and tertiary benzylic nitro groups (equation 66).[98] Unsym-

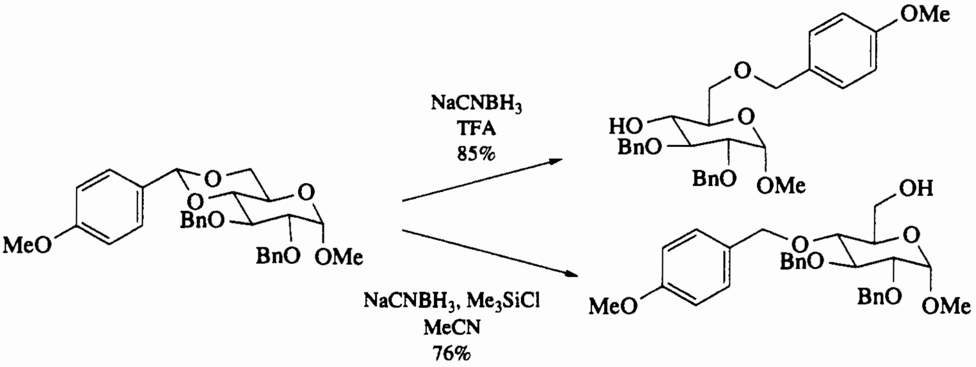
NaCNBH3
TFA
85%
NaCNBH3, Me3SiCl
MeCN
76%
MeO
BnO
OMe
HO
OH

**Scheme 10**

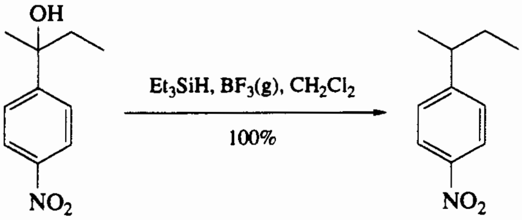
OH
Et3SiH, BF3(g), CH2Cl2
100%
NO2

(65)

metrical benzyl and allyl sulfides have also been reduced with $Bu_3SnH$.[99] In the former case the enhanced stability of benzylic radicals results in the formation of toluenes and tin sulfides (equation 67). In the latter case cleavage of the allyl—S bond predominated over other reactions (equation 68) (with the exception of methylallyl sulfides). Some preference for reduction without rearrangement of the allyl system was detected. An allylic analog of the Barton–McCombie reaction has also been reported (equation 69).[100]

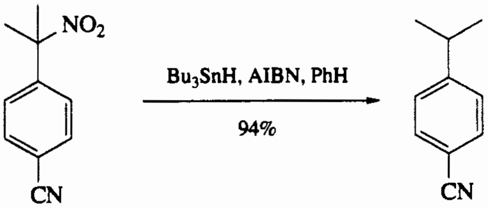
NO2
Bu3SnH, AIBN, PhH
94%
CN

(66)

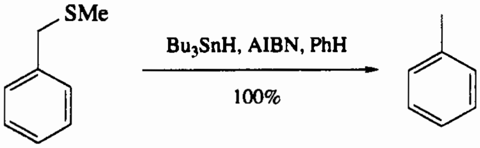
SMe
Bu3SnH, AIBN, PhH
100%

(67)

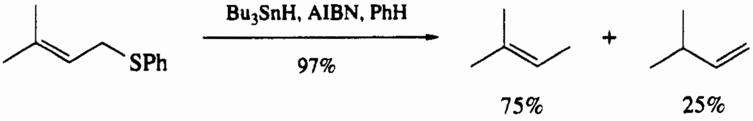
SPh
Bu3SnH, AIBN, PhH
97%
+
75%
25%

(68)

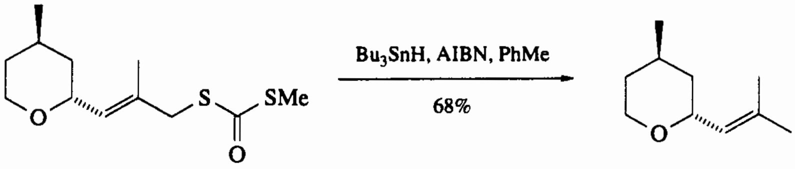
O
S
SMe
Bu3SnH, AIBN, PhMe
68%

(69)

## 4.7.4 DISSOLVING METAL REDUCTIONS

### 4.7.4.1 Lithium and Sodium in Liquid Ammonia

Lithium and sodium dissolved in liquid ammonia have been extensively employed in the reduction of benzylic hydroxyls, carbonyl compounds and acetals. These reductions have been reviewed.[101] Overreduction of benzyl alcohols by Li/$NH_3$ to 1,4-dihydro derivatives can be avoided using an ammonium chloride quench.[102] Aryl halides are unstable under these conditions.

Sodium in liquid ammonia, often with alcohols as cosolvents, provides a less vigorous reducing system for benzylic alcohols. Terminal and disubstituted alkenes are reduced by the Li/$NH_3$ system, while only terminal alkenes usually succumb to Na/$NH_3$, allowing benzylic alcohols containing unsaturation to be effectively reduced with the latter reagent.[101] Benzylic ketals are readily reduced to hydrocarbons without overreduction using Na/$NH_3$/alcohol (equation 70).[103] Lithium in ammonia can lead to overreduction.

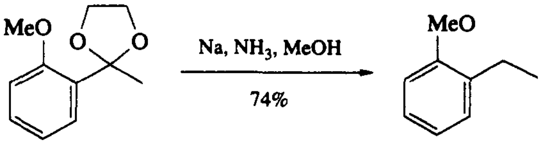

(70)

Allylic alcohols are reduced with lithium or sodium in ammonia, or low molecular weight amines either with or without alcohols.[101] The thermodynamically more stable product is often formed, leading to rearrangement in some cases (equation 71).[104] Methyl and cyclic ethers are similarly reduced (equations 72 and 73),[105,106] as are allylic acetates, halides and epoxides (equation 74 and 75).[107,108]

Benzylic and allylic sulfides and sulfones are readily reduced to hydrocarbons using lithium or sodium in alcoholic solvents or in amines.[109,110] Allylic sulfones are reduced in a similar manner (Scheme 11),[111] either with or without migration of the double bond, depending on the reaction conditions used.

Benzylic and allylic tertiary amines may be reduced to hydrocarbons using one of two methods. Oxidation to an amine oxide followed by reduction with lithium in liquid ammonia provides one of these

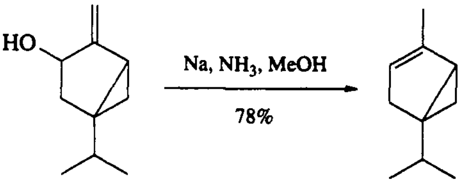

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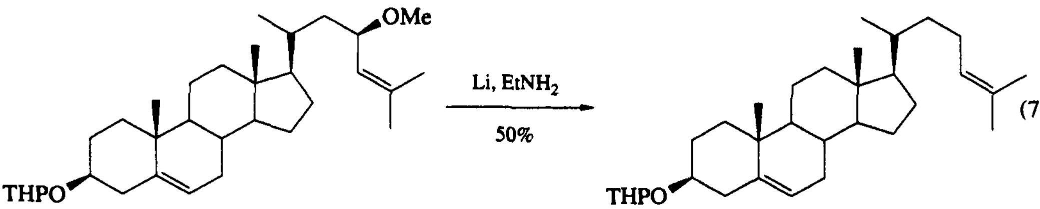

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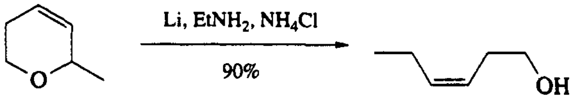

(73)

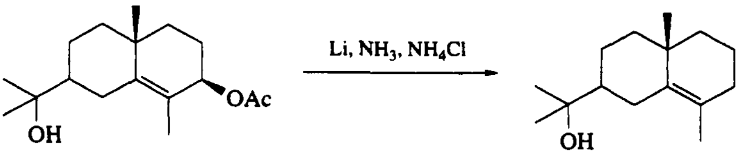

(74)

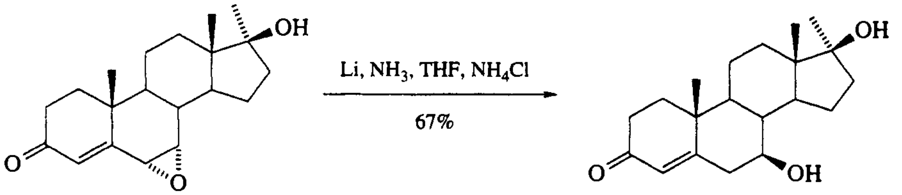

(75)

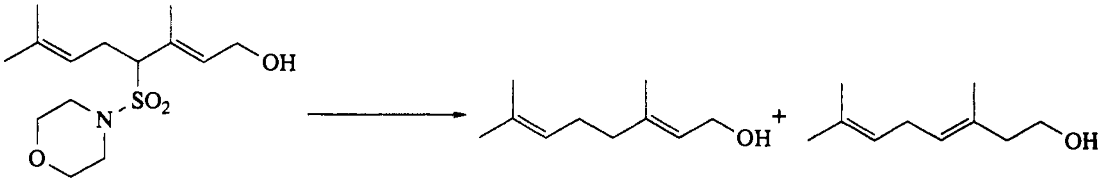

| | | |
|---|---|---|
| Li/$NH_3$, $Bu^tOH$; 70% | 7% | 93% |
| Na/$NH_3$, dibenzo-18-crown-6; 75% | 95% | 5% |

**Scheme 11**

(equation 76).[112] Alternatively, formation of a labile quaternary salt, followed by reduction and hydrolysis, leads to secondary amine products (Scheme 12).[113]

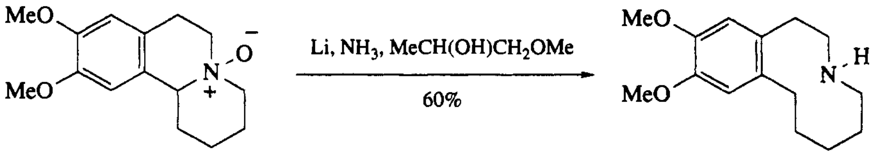

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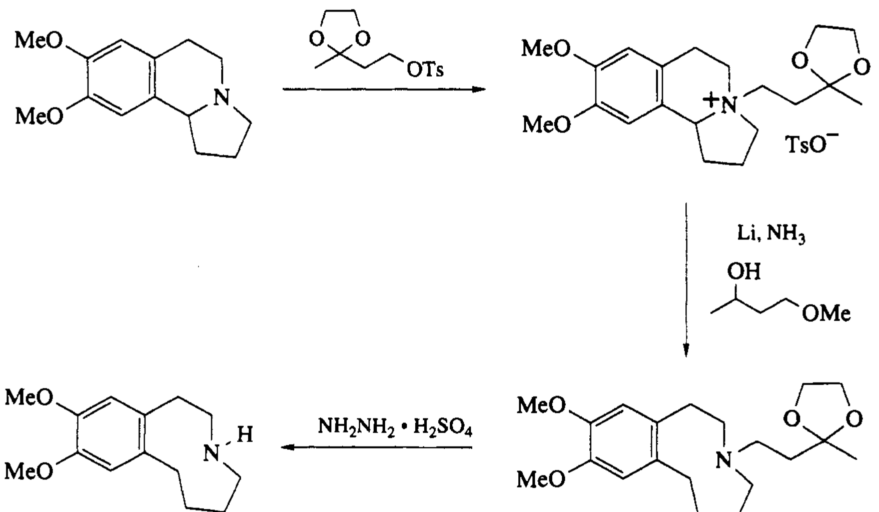

**Scheme 12**

## 4.7.4.2 Other Metals

Zinc metal and zinc amalgam have been widely used for the reduction of benzylic and allylic functional groups. Primary, secondary and tertiary benzylic alcohols are readily reduced by zinc amalgam or zinc dust under acidic conditions (equation 77).[114] Other acid-stable functional groups are unaffected (*e.g.* aryl—Cl, aryl—OH, $CO_2H$). The reaction can also be carried out under basic conditions (equation 78).[115] Esters of benzyl alcohols are similarly cleaved under acidic or basic conditions without reduction of the resulting carboxylic acid (equation 79).[116]

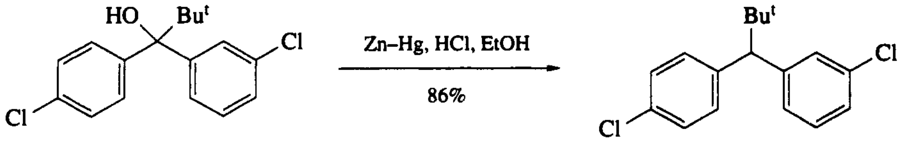
HO
Bu$^t$
Cl
Cl
Zn–Hg, HCl, EtOH
86%
Bu$^t$
Cl
Cl

(77)

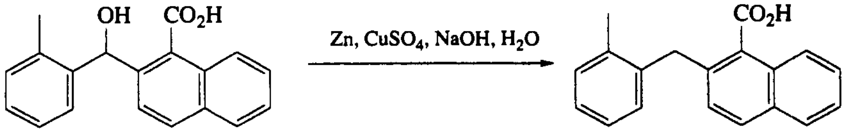
OH
CO$_2$H
Zn, CuSO$_4$, NaOH, H$_2$O
CO$_2$H

(78)

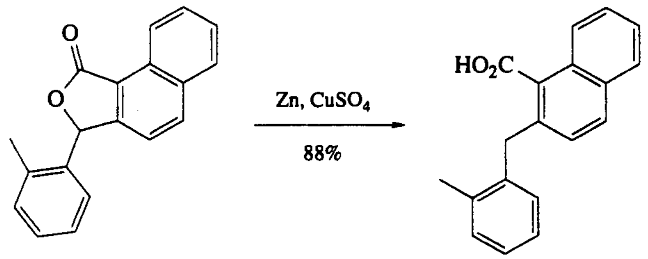
O
O
Zn, CuSO$_4$
88%
HO$_2$C

(79)

Primary, secondary and tertiary benzylic halides are cleaved with zinc dust in acetic acid or under basic conditions (equations 80 and 81).[117,118] Benzylic C—N bonds can also be cleaved (equation 82),[119] with particular ease when quaternary ammonium salts are reduced (equation 83).[120] There has also been a recent report of cyclopropane cleavage with zinc metal and zinc chloride (equation 84).[121]

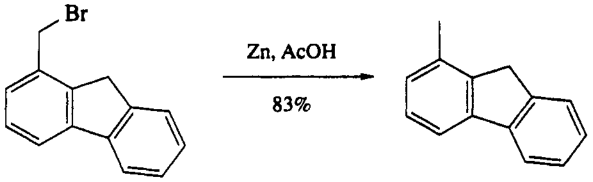
Br
Zn, AcOH
83%

(80)

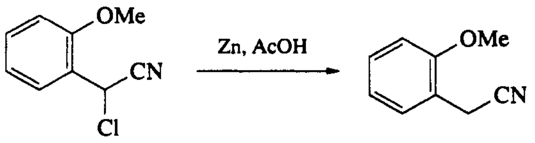
OMe
CN
Cl
Zn, AcOH
OMe
CN

(81)

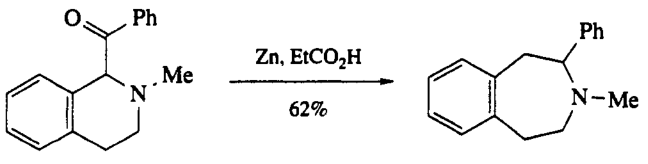
O
Ph
N
Me
Zn, EtCO$_2$H
62%
Ph
N–Me

(82)

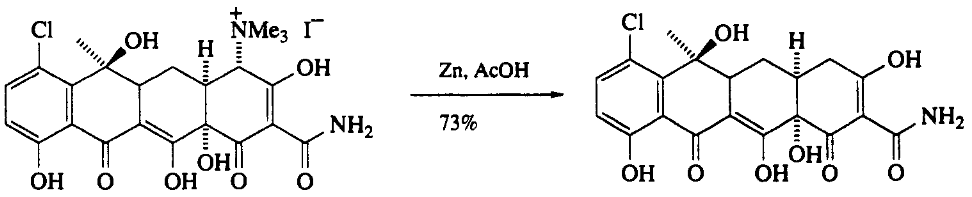
Cl
OH
H
$\overset{+}{N}$Me$_3$ I$^-$
OH
NH$_2$
OH
O
OH
OH
O
O
Zn, AcOH
73%
Cl
OH
H
OH
NH$_2$
OH
O
OH
OH
O
O

(83)

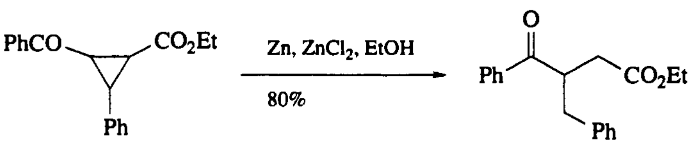
PhCO
CO$_2$Et
Ph
Zn, ZnCl$_2$, EtOH
80%
O
Ph
CO$_2$Et
Ph

(84)

Allylic functional groups can be reduced with zinc metal (*cf.* equation 83). Alcohols, esters and strained rings are all cleaved under the usual conditions in good yield and with similar chemoselectivity to the benzylic situation (equations 85–87).[122–124] Allylic sulfonate esters are similarly reduced (equation 88).[125]

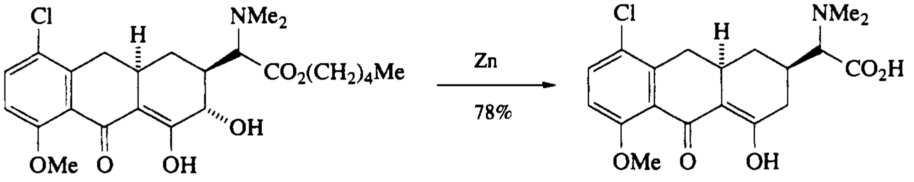

(85)

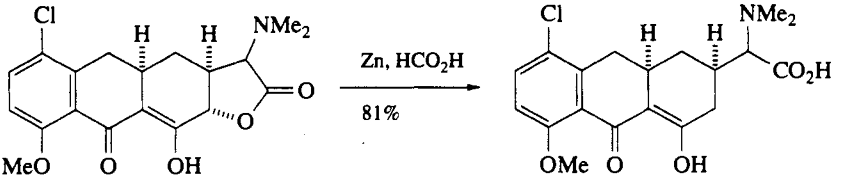

(86)

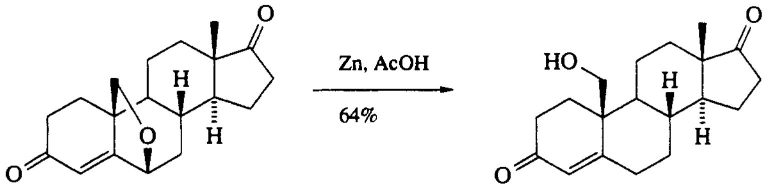

(87)

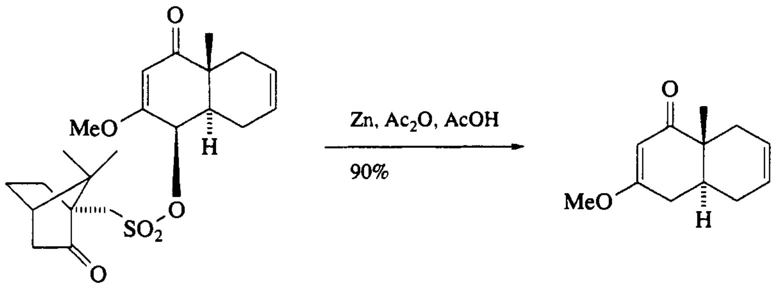

(88)

## 4.7.5 ELECTROLYTIC REDUCTION PROCESSES

Electrochemical hydrogenolysis of allylic and benzylic centers can be achieved, but application of this reduction has not been either widely used or acclaimed. It is less convenient experimentally than the comparable method using dissolving metals and control of selectivity is more difficult to achieve than with other methods. Only limited applications are found. Generally electroreduction is carried out using cathodes of metals of high overvoltage such as copper, cadmium, lead and mercury, with anodes of platinum.

Selective reduction of aromatic acids and their derivatives to aldehydes can be achieved electrochemically.[126] Reduction of the carbinolamines is observed, as in the formation of anilinomethylpyridine (Scheme 13) and 4-methylpyridine.[127] Reductive cleavage of benzyl methyl ethers can be achieved leading to hydrocarbons when the ring substituents are electron attracting.[128]

A more useful application of the electron-attracting effect of aryl subtituents is found in the cleavage of 4-picolyl derivatives of protected cysteine and tyrosine in peptide synthesis (Scheme 14).[129] Catalytic cleavage of these derivatives is usually unattractive for S-containing acids. Protecting groups removable also include 3- and 4-picolyl esters.[130]

Esters of secondary benzyl alcohols can also be electrohydrogenolyzed (equation 89).[131] Electrolysis of resolved methyl *O*-benzoylatrolactate gave racemized 2-phenylpropionic acid. This result is in sharp contrast with the 77–92% inversion of configuration claimed for the electrochemical dechlorination in equation (90).[132]

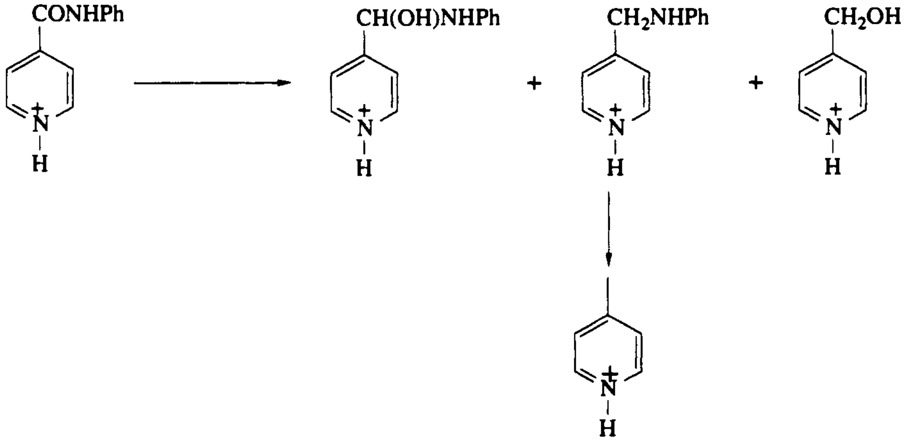

**Scheme 13**

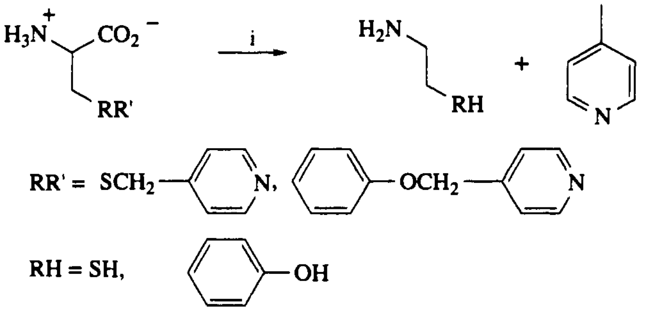

i, Hg, cathode, 0.25 M $H_2SO_4$

**Scheme 14**

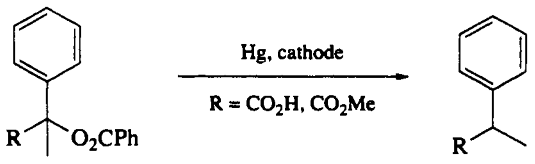

(89)

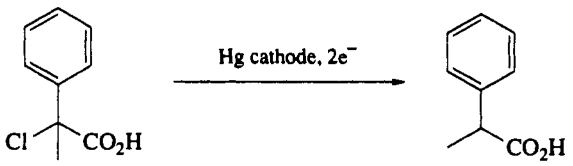

(90)

In contrast with other methods only infrequent use of electrohydrogenolysis of benzylic or allylic esters has been made in synthetic strategies. Control of the electrode potentials and electrolyte pH have been shown to be important and essential for chemoselectivity, and would need to be studied in many instances before a particular application was made. The instability of the product towards further electrolysis often causes problems (however see equation (91) for a successful application).[133]

Greater control over the product selectivity is observed when more precise control of the cell conditions and process is used. Since in general the current distribution at the working electrode is not uniform and the effective potential is therefore not the same over the whole electrode, it is difficult to reduce selectively one of two electroactive groups when potentials differ by less than 0.15 V.

One useful approach involves indirect electrochemical reduction using an electron transfer catalyst which is selected for inertness to any anion radicals or dianions present.[134] Thus allylic sulfones (Scheme

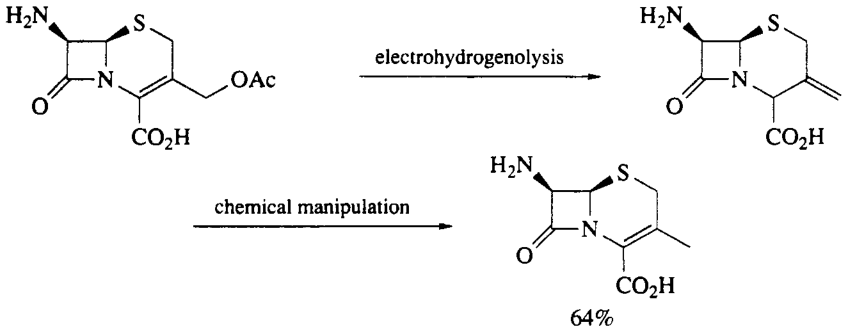
H2N
S
N
O
OAc
CO2H
electrohydrogenolysis
chemical manipulation
64%

(91)

15) are preparatively converted to the hydrocarbon without loss of the alkylsulfonyl group. Both sulfonyl groups are lost by direct electroreduction.

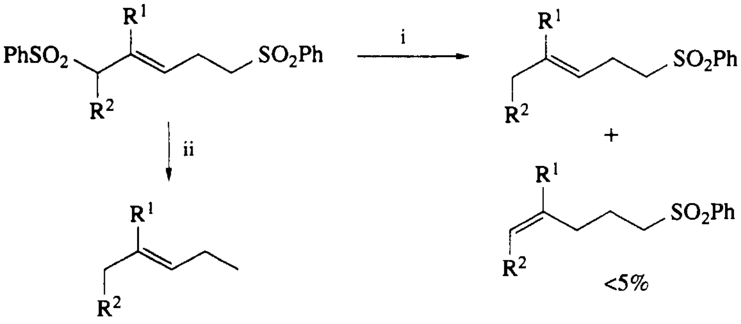
PhSO2
SO2Ph
R1
R2
i
ii
+
<5%

$R^1 = Me, R^2 = H$

$R^1 = Me, R^2 = CH_2CH{=}CMe_2$

i, electrolysis with anthracene; ii, electrolysis without anthracene

**Scheme 15**

An alternative approach to the commonly utilized cleavage of allylic isoprenoid compounds (Scheme 16) using attack of $+2e^-$ in place of $H^-$ at a $Pd^0$ π-allyl complex also requires a catalyst addition.[135] Electrolysis of allylic acetates with Pb cathode and Pt anode in the presence of $Pd(PPh_3)_4$ in MeCN, gave moderate yields of the inner alkenes from both terminal and inner acetates (equations 92 and 93). Control of the regioselectivity was clearly dictated by the attack of $H^+$ from the less-hindered side of the allylic carbanions.

Electrolytic desulfurization of *o*-aminobenzyl sulfide, sulfoxide or sulfone illustrates carbon–sulfur bond cleavage. Careful control of the reaction conditions is important to achieve chemoselectivity (Scheme 17).[136] Trifluoromethyl substituents are not reduced under the conditions used (Cd sheet ca-

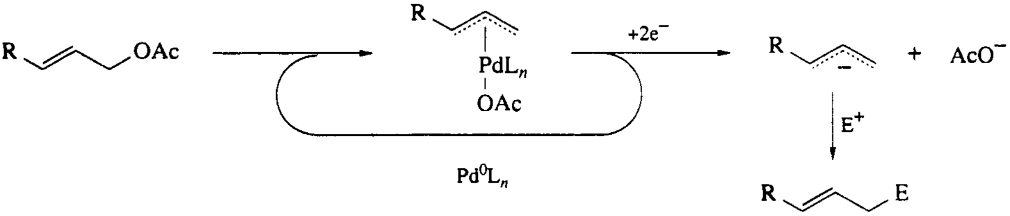
R
OAc
PdLn
OAc
+2e−
AcO−
+
E+
E
Pd0Ln

**Scheme 16**

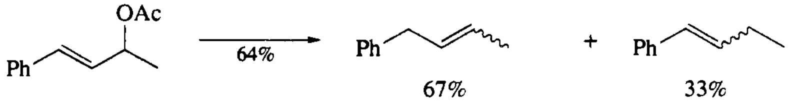
OAc
Ph
64%
+
67%
33%

(92)

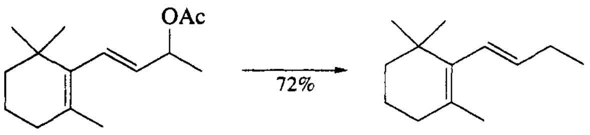

(93)

thode and Pt-coated Ti anode), and surprisingly the 2-amino substituent did not interfere with cathodic discharge. An alternative cleavage of the chloroacetanilide of the sulfalimine salt obtained *via* Scheme 17 by electrolysis over a Hg cathode in phosphate-buffered electrolyte, gave good yields of the corresponding toluene.[137] Some dehalogenation of the chloroacetyl group does occur, illustrating the difficulty of controlling chemoselectivity.

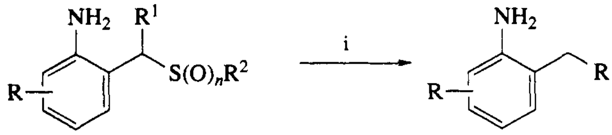

$R^1$ = alkyl; $R^2$ = alkyl, aryl; R = $CF_3$; $n$ = 0–2

i, electrolysis, Cd cathode, Pt anode

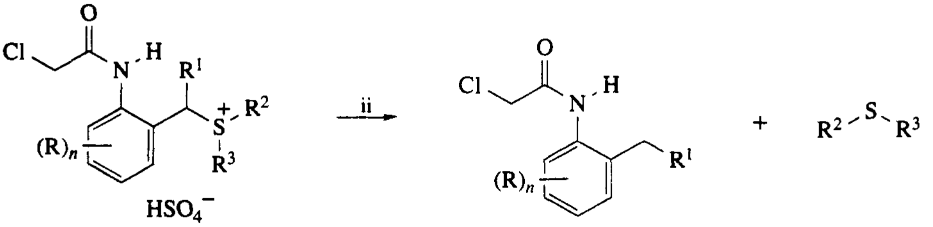

ii, Hg cathode, Pt anode

Scheme 17

## 4.7.6 BIOMIMETIC REDUCING AGENTS

Attempts to mimic enzymatic reduction processes have been reported.[138] Of major interest has been the involvement of NAD(P)H in redox reactions.[139] The most investigated model compounds employed as donors are analogs or derivatives of 1,4-dihydronicotinamide. In the presence of a catalyst the hydrogenolysis of cinnamyl acetate (Scheme 18) is readily effected with *N*-propyl-1,4-dihydronicotinamide. $RhCl(PPh_3)_2$ appears to be more effective than $PdCl_2(PPh_3)_2$ or $RuCl_2(PPh_3)_3$.[140] This reduction appears to have a complex mechanism as it is very sensitive to added salts such as $LiClO_4$, which is essential for a high conversion. $Mg(ClO_4)_2$ effectively prevents cleavage. The high yields are also dependent on the use of acetonitrile in the solvent. Although the chemoselectivity is high, ketones and esters being inert, the type of allylic structure that can be reduced appears to be restricted to compounds with allylic unsaturation conjugated to aryl rings. This requirement assists the formation of mainly 2-alkenes from acetates, chlorides and phenylsulfonyl derivatives. *N*-Phenyl-1,4-dihydronicotinamide (BNAH) has also been utilized in a visible light catalyzed reduction of sulfonate esters of methyl mandelate (Scheme 19).[141] A number of functional groups, including keto, nitro and ester groups, were unaffected. These conversions are accelerated by addition of photosensitizers such as tris(bipy)ruthenium(II) dichloride or tetraphenylporphine.

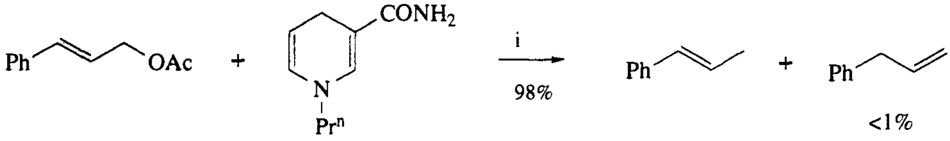

i, $RhCl(PPh_3)_3$, $LiClO_4$, MeCN, dark

Scheme 18

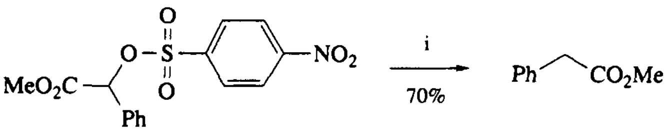

i, *h*ν, BNAH, Py, tris(bipy)ruthenium(II) dichloride

**Scheme 19**

## 4.7.7 PHOTOLYTIC REDUCTION PROCESSES

Photochemically aided hydrogenolysis of allylic C–heteroatom bonds has attracted little interest. A few methods for debenzylation of ethers, amines and thiols, catalyzed by irradiation, have been utilized (see previous section also). An unusual desulfurization of benzyl thiol with triethyl phosphite (equation 94) in high yield, catalyzed by UV irradiation, is a useful alternative to other methods described in other parts of this chapter.[142]

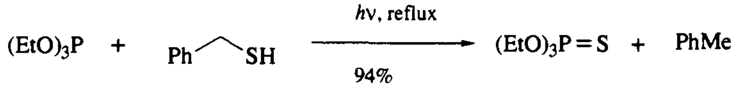

(94)

## 4.7.8 MISCELLANEOUS REDUCING AGENTS

Historically, hydrogen derived from dissociation of hydrogen iodide has been utilized widely for reduction. Acceleration of the hydrogenolysis rate is achieved by addition of phosphorus to remove the iodine formed.[143] In general reduction with HI is efficient for acid-tolerant substrates and is a useful alternative to catalytic methods, especially to achieve chemoselectivity (equations 95 and 96).[144,145] Application of HI to cleavage of allylic centers has not been useful as allylic and other unsaturated centers are more susceptible to HI addition and elimination effects.

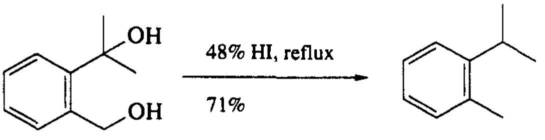

(95)

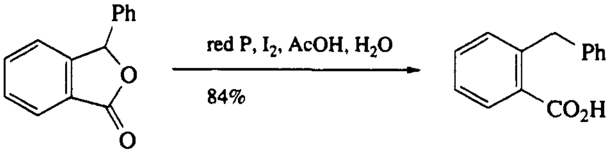

(96)

The use under neutral conditions of this reagent has more recently been effective for the cleavage of primary, secondary and tertiary benzyl alcohols in refluxing benzene.[146] The hydrocarbons from a range of variously substituted alcohols were obtained in 60–98% yields (Scheme 20).

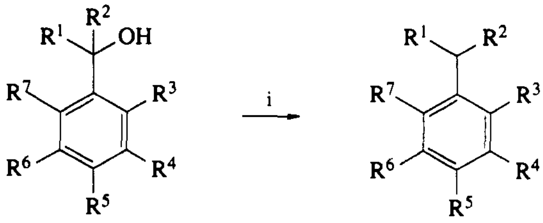

i, $P_2I_4$, PhH, $N_2$, Δ

$R^1, R^2$ = H, Me, Ph, $Bu^t$

$R^3$-$R^7$ = H, Me, Ph, $NO_2$, $CO_2Et$, CN, Br

**Scheme 20**

As an alternative mild application of HI, diiododimethylsilane ($Me_2SiI_2$) has merit for reduction of secondary and tertiary benzylic alcohols to hydrocarbons at room temperature in near quantitative yields.[147] Side chain carbonyl groups were unaffected, but benzyl alcohol itself was converted to the iodide. TMS-Cl–NaI–MeCN is recognized as an equivalent to TMS-I and is a less costly alternative to $Me_2SiI_2$. Applications of these milder reagents have not been reported for allylic cleavages.

As an alternative to the use of tin metal, tin(II) chloride has been widely utilized. Less acidic conditions can be employed than is normal for tin metal dissolution and examples of allylic systems (equation 97)[148] have been cleaved as well as secondary and tertiary benzylic centers. Primary benzyl centers can be cleaved *via* the iodide (equation 98).[149]

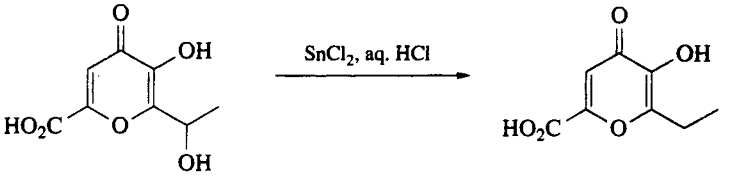

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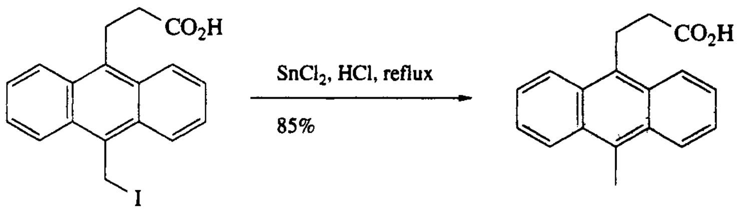

(98)

## 4.7.9 REFERENCES

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# 4.8

# Reduction of α-Substituted Carbonyl Compounds —CX—CO— to Carbonyl Compounds —CH—CO—

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## 4.8.1 GENERAL CONSIDERATIONS

### 4.8.1.1 Scope of the Review

This review addresses in particular the reductive cleavage of groups X from α-substituted carbonyl compounds (equation 1). Since such studies have almost always involved ketones, the carbonyl group is understood herein to be that of a ketone unless stated otherwise. X is usually a heteroatom (most often halogen, but also oxygen, sulfur or nitrogen, and occasionally other atoms such as selenium or tellurium), but can be carbon in special cases. Since many reductive cleavages of compounds of type (**1**) involve production of enol and enolate ion intermediates, alternative reaction paths involving other components of the medium are sometimes observed. Where these involve carbon–carbon bond formation, they are more properly treated elsewhere in this series. A few such reactions are however referred to herein where appropriate from a mechanistic point of view, and the review also covers reductive conversions of (**1**) to enol derivatives.

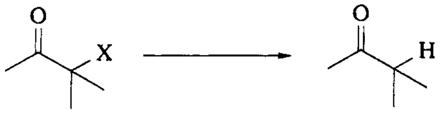

(**1**) (1)

### 4.8.1.2 Mechanisms of Bond Cleavage

Reductive cleavages of the type with which we are concerned here exhibit some common features. The strength of the bond being cleaved is an important determinant of the ease of cleavage. Thus, the ease of reduction of α-halocarbonyl compounds follows the order: I > Br > Cl > F. By the same token, cleavage of α-ketols (**1**; X = OH) is more facile if the hydroxy group is first converted to a sulfonate or other ester.[1] In principle the dependence upon bond strength can be taken advantage of in order to remove one of several α-substituents selectively. Reports of this type of selective reduction are uncommon, but a few examples will be noted herein. Enolate ions and/or enols are frequently generated in the cleavage process, and ease of reduction is therefore also usually correlated with the stability of the incipient enolate or enol. For example, 2-substituted 1,3-dicarbonyl compounds are reduced more readily than α-substituted ketones, which in turn are more easily reduced than α-substituted esters and amides.

Many reagents have been introduced for the reductive cleavage of compounds (**1**), especially where X is a halogen atom.[2–4] The various methods fall into several quite different mechanistic categories. Conversions corresponding to equation (1) can be effected by: (i) electron transfer, (ii) strong nucleophiles, (iii) metal hydrides, (iv) metal carbonyls, and (v) heterogeneous hydrogenation catalysts. We describe here the general features of each type of reduction; specific reducing agents and α-substituents are taken up in subsequent sections. It is sometimes unclear which route is involved in a given case; for example, it may be difficult to distinguish between mechanisms (i) and (ii) with some combinations of reagents. In such cases the assignment of a particular procedure to a specific mechanistic category may be arbitrary.

Electron transfer agents were among the first to be used to effect the conversion shown in equation (1). The cleavage may be effected with active metals, by low-valent transition metal ions, or electrochemically, at a cathode. The nature of the electron transfer step in such reactions is not well understood. It is tempting to postulate that the initial step is injection of an electron into the LUMO of the carbonyl compound to afford intermediate (**2**), followed by loss of $X^-$ from (**2**) to afford a radical (**3**), which is then reduced further (Scheme 1). However, the strong dependence of the reduction rate on the strength of the C—X bond[5] and the fact that axial α-halocyclohexanones are much easier to reduce by electron transfer than their equatorial epimers[6] imply that the LUMO energy is lowered by overlap of the C—X bond with the C=O group.

Another common method for cleavage of substituents α to a carbonyl group involves reaction of the substituted carbonyl compound with an appropriate nucleophile. Such reactions are believed to occur by nucleophilic attack upon the α-substituent to afford an enolate (equation 2). Nucleophiles which can accomplish this conversion encompass a wide variety of structural types. Some of the best methods for reduction of halocarbonyl compounds fall into this category.

Most methods in the literature for reductive removal of α-substituents involve either electron transfer or nucleophilic cleavage, but other mechanistic pathways have been encountered with certain reagents or

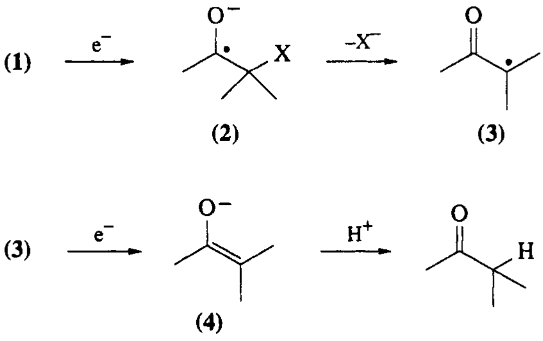

**Scheme 1**

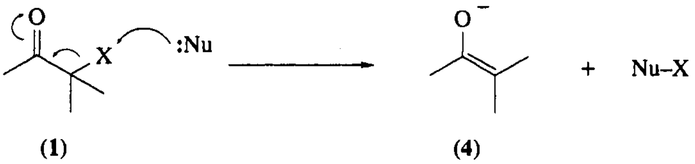

(2)

combinations of reagents. Metal hydrides have been used for the reductive cleavage process; the most frequently employed hydrides have been those of tin. In general the reactions of tin hydrides with α-substituted carbonyl compounds appear to be of free radical type, generating (**3**) in the key cleavage step (equation 3). Transition metal carbonyls have also been used to effect equation (1), especially with α-halo ketones. Such reactions appear to proceed either by metal enolates or by π-complexes (**5**). Most activity in this area has involved attempts to build up carbocyclic systems through cycloaddition of such complexes with added dienes, and is not relevant in the present context. Some studies, however, have afforded reduced ketones, and will be discussed here. Finally, hydrogenolysis of α-substituents can frequently be effected at noble metal hydrogenation catalysts.

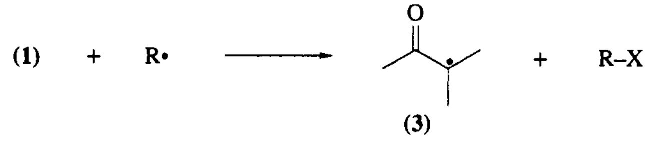

(3)

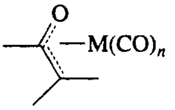

**(5)**

## 4.8.2 THE CARBON–HALOGEN BOND

### 4.8.2.1 Reduction By Electron Transfer

α-Halocarbonyl compounds are very easily reduced by electron transfer agents. The remarkable ease of reduction of such compounds can be seen from inspection of a few representative electrochemical reduction potentials: −0.34 V for bromoacetone and −1.15 V for chloroacetone, compared with −2.23 and <−2.6 V for typical alkyl bromides and chlorides, respectively, or even −1.27 V for benzyl bromide (potentials reported relative to the saturated calomel electrode, or SCE).[7] As these data demonstrate, α-halo- (especially bromo- and iodo- ) carbonyl compounds are among the easiest of all organic compounds to reduce by electron transfer. The reductive dehalogenation of such compounds can be carried out by a wide variety of metals and low-valent metal ions. In particular, the great ease with which bromo ketones are reduced has led to a profusion of reagents for reductive cleavage of such compounds.

#### *4.8.2.1.1 Reductive cleavages by metals*

Reduction of chloro, bromo and iodo ketones can be effected readily by active metals. Zinc in acetic acid has generally been used for this purpose,[8] but many other metals would presumably serve as well, in view of the extreme ease with which this type of compound is reduced. Fry and Herr showed that the reduction of bromo ketones can be carried out even by a metal as low in the electromotive series as metallic mercury, and they provided an approximate thermodynamic analysis of the factors to be considered in addition to the reduction potential of the metal itself.[9] The initial intermediate in the reduction of halo ketones by zinc is presumably a zinc enolate (**6**), but this is immediately cleaved by the protic solvent to afford the corresponding enol, which then tautomerizes to afford the corresponding carbonyl compound. Reduction in the presence of a deuterated or tritiated solvent should therefore permit introduction of a deuterium (or tritium) atom into the α-position (equation 4). Indeed, reduction of mono-, di- and tri-halo esters and amides in $D_2O$ does afford products containing one, two and three α-deuteriums, respectively, in synthetically useful yields and isotopic abundances.[10] However, reduction of halo ketones in this solvent is accompanied by base-promoted loss (exchange) of the isotope from the product α-deuterio ketone. Reduction in DOAc (or HOAc containing TOAc when the tritiated ketone is desired), where exchange is slower, eliminates this problem, however. The direction of approach of the proton donor upon the intermediate enol is governed by stereoelectronic considerations,[8] and reduction in this solvent can therefore be used to introduce the isotope stereoselectively, as formation of (**7–9**; equations 5–7)[11-12] illustrates. Reduction of α-chloro esters and ketones is facilitated by addition of sodium iodide to the medium, probably by formation of the iodocarbonyl compound.[13]

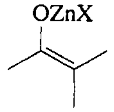

(**6**)

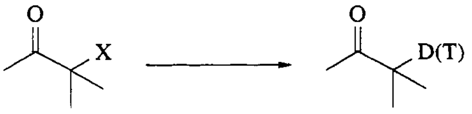

(4)

(**1**)

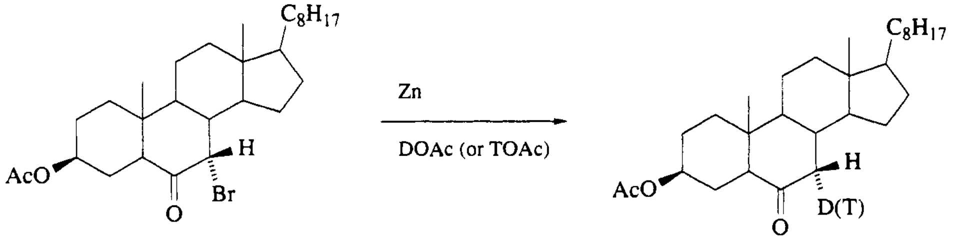

(5)

(**7**)

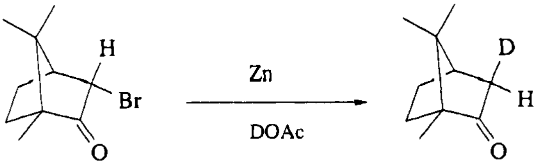

(6)

(**8**)

If the reaction between an α-halo ketone and zinc is carried out in an aprotic solvent in the presence of an electrophilic reagent, the zinc enolate (**6**) can be trapped. Products corresponding to reaction at carbon are observed with carbon electrophiles (alkyl halides or aldehydes; equation 8),[14] but reaction occurs at oxygen with halosilanes and acid anhydrides (equation 9).[15-17]

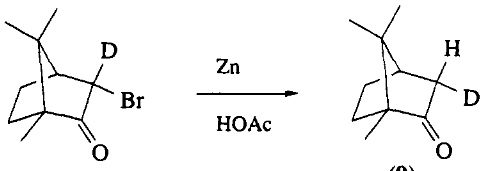

**(9)**

(7)

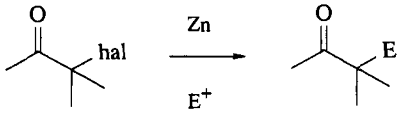

(8)

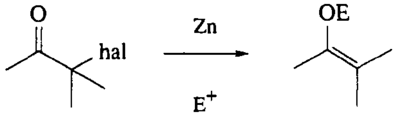

(9)

#### *4.8.2.1.2 Reductive cleavages by low-valent metal ions*

A number of low-valent metal ions have been shown to reduce α-halocarbonyl compounds.[18] The most commonly used species for this purpose have been chromium(II)[19] and low-valent titanium[20] salts, although vanadium(II), samarium(II), iron(II) and tin(II) salts have also been used.[17,21,22] Chloro, bromo and iodo ketones can all be reduced by chromium(II) and titanium(III) salts. Selective reductions are possible: axial halides are reduced in preference to equatorial,[23] and α,α-dihalo ketones can be selectively reduced to the corresponding monohalides (equation 10).[17] The use of samarium(II) iodide has recently been advocated for such α-cleavages.[22] α-Halo esters and ketones are reduced instantaneously at –78 °C in excellent yields. α-Acetoxy esters are stable to this reagent.

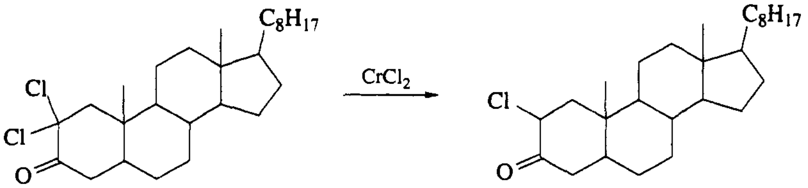

(10)

#### *4.8.2.1.3 Electrochemical reductive cleavages*

α-Halocarbonyl compounds are readily reduced electrochemically.[5] In principle, the ease with which this can be effected should readily permit selective removal of α-halogen atoms in the presence of most other organic functional groups, but this point seems not to have been investigated. Reduction is best carried out under conditions which ensure that the initially formed enolate is quickly protonated, thus preventing undesired side reactions. Typically, this means conducting the electrolysis in an acidic protic solvent such as acetic acid or an aprotic solvent containing a proton donor such as phenol or malonic ester.[24] Curious behavior is observed during the electrochemical reduction of α,α,α-trifluoroacetophenone (**10**). When the solution is monitored during electrolysis, it is possible to observe the build-up and eventual decay of the corresponding monofluoride (**12**), but not of the difluoride (**11**).[5] It appears that the ease of reduction of these substances follows the order (**11**) > (**10**) > (**12**) > (**13**). In other words, (**11**) appears to fall out of its expected place in the sequence. It is not obvious why this should be so.

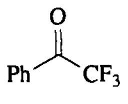

**(10)**

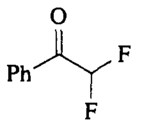

**(11)**

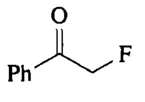

**(12)**

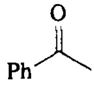

**(13)**

In order to inquire into the stereochemical course of electrochemical reduction of α-halocarbonyl compounds, it is first necessary to appreciate that the problem should not even be posed in these terms. Two separate questions have to be addressed: (i) is there a preferred geometry for reduction of the halo ketone to an enolate? and (ii) is there a preferred geometry for ketonization of the intermediate enolate or enol? The answer to the first of these questions is a most definite yes. Equatorial α-halocyclohexanones and *exo*-α-halo ketones in the camphor series are reduced at potentials which are considerably more negative than those required for their axial and *endo* epimers, respectively.[5,6] These facts are consistent with a transition state for electron transfer in which the halogen atom of the C—X bond is nearer the electrode surface at the point of electron transfer. Electron transfer then generates the enolate, whose ketonization path is no different than when it is produced by other processes.[8]

A possibly special stereochemical situation is presented by α-halocarbonyl compounds in the cyclopropane series.[25] Electrochemical reduction of the α-halo acid (**14**) proceeds predominantly with stereochemical inversion, whereas reduction of the corresponding carboxylate proceeds predominantly with retention of configuration.

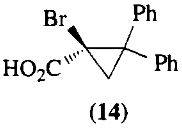

**(14)**

### 4.8.2.2 Reduction By Strong Nucleophiles

As mentioned in Section 4.8.1.2, reductive dehalogenation of halocarbonyl compounds can be carried out by a large number of nucleophilic reagents according to equation (2). Such dehalogenations occur more cleanly and rapidly, and under milder conditions, if carried out in such a way that nucleophilic attack on the halogen atom is assisted by electrophilic attack upon the carbonyl group. In particular, considerations based upon hard and soft acid–base (HSAB) theory[26] suggest that the combination of a hard acid (to coordinate with the carbonyl oxygen) and a soft base to attack the α-substituent ought to be especially efficient at such cleavages (equation 11). This principle works remarkably well, and a number of dehalogenation methods have been based upon it.

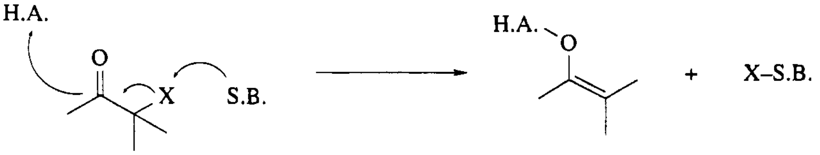

(11)

Although many nucleophiles dehalogenate α-halocarbonyl compounds, the most generally used have been halides, especially iodide ion, thiols and other nucleophilic sulfur species, and phosphines. All of these are effective by themselves, but all benefit by addition of an electrophile to the medium to assist cleavage by coordination to the carbonyl (equation 11).

#### *4.8.2.2.1 Reductive cleavages by halide salts*

Historically, sodium and potassium iodides were the first halide salts found to dehalogenate halo ketones. The reductions are carried out in acidic media, in order to protonate the ketone.[27] The acyclic bromine atom in (**15**) could be removed in this manner without affecting either the acetoxy group at the same site or the sterically hindered bromine atom at C-12.[28] By using metal ions[29] or other Lewis acids[30] to assist the dehalogenation process, even bromide and chloride salts can be used to effect dehalogenation. Among the best reagents of this type is a combination of $SnCl_2$ and NaCl in aqueous THF.[29] Rather than using a mixture of two salts, the two functions can be combined into one by using an iodide salt of which the cation is a good Lewis acid. Cerium(III) iodide is particularly effective in this respect because of the high 'oxaphilicity' of lanthanide ions. This substance readily dehalogenates many halo ketones at room temperature.[31] Cerium enolates (**16**) are produced initially; these can be trapped by carbonyl compounds in the medium to form aldols or by $D_2O$ to afford the deuterated ketone.[32]

Trimethylsilyl iodide (TMS—I), as such or generated *in situ*, is especially effective as a mild dehalogenation agent for halo ketones.[33] The reaction appears to generate the enol silyl ether initially, and this is converted to the carbonyl compound during work-up (equation 12). Both cyclic and acyclic α-bromo and α-chloro ketones are dehalogenated, generally in excellent yields. Methyltrichlorosilane, on the other

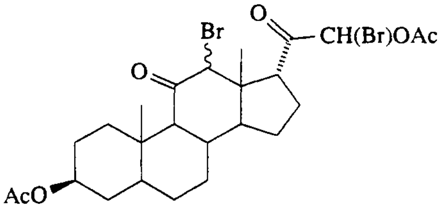

**(15)** either diastereomer

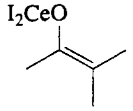

**(16)**

hand, reacts only slowly with chloro ketones and cyclic bromo ketones,[34] and might be useful for selective dehalogenation of an acyclic α-bromo ketone in the presence of one of the latter functionalities.

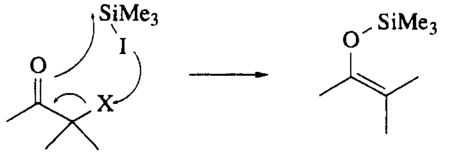

(12)

### 4.8.2.2.2 *Reductive cleavages by sulfur species*

Thiols efficiently dehalogenate α-halo and α,α-dihalo ketones.[35] Reduction is typically carried out in ethanol containing a weak base. Although this system will also reduce α-thio ketones, it is believed that the halo ketone is reduced, and that reaction proceeds as in equation (11), with a proton from the solvent serving as Lewis acid to assist dehalogenation by thiol (or thiolate). The reactions are of course accelerated by inclusion of a metal salt in the medium.[36]

An especially interesting application of HSAB theory was reported by Fuji and coworkers.[37] They found that chloro and fluoro ketones (**17**) are converted to the reduced dithioacetals (**20**) by the combination of ethanethiol (EtSH) and $AlCl_3$ (Scheme 2). Diethyl disulfide (EtSSEt) is ineffective at promoting this transformation, whereas either EtSH or EtSSEt could be used in concert with $AlCl_3$ to convert a bromo or iodo ketone (**18**) to (**20**). It was suggested that ketones (**17**) are first converted to the corresponding halodithioacetals (**19**), which are then dehalogenated in a sense (equation 13) which is inverse to that shown in equation (11). Apparently chlorine and fluorine are too hard to permit attack by the thiol, even when assisted by $AlCl_3$. Substrates (**18**) presumably react as in equation (11), with either EtSH or EtSSEt serving as soft base, to afford the dehalogenated ketone (**21**), which is then converted to (**20**).

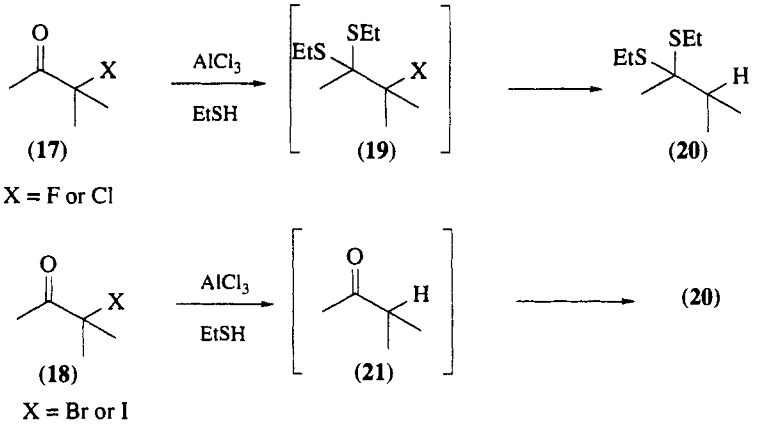

**Scheme 2**

Other sulfur species which can be used in this way include $SH^-$, $S^{2-}$, $HSO_3^-$, $SO_3^{2-}$, $S_2O_3^{2-}$ and $S_2O_4^{2-}$.[38] In general, these offer no particular synthetic advantage, although $NaHSO_3$ has been found to remove the tertiary iodine atom of (**22**) selectively to afford (**23**) in 71% yield (equation 14).[39] The remaining iodine atom of (**23**) could be removed by further reaction with $NaHSO_3$.

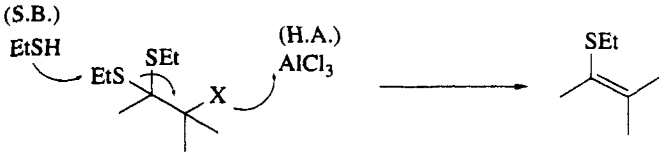

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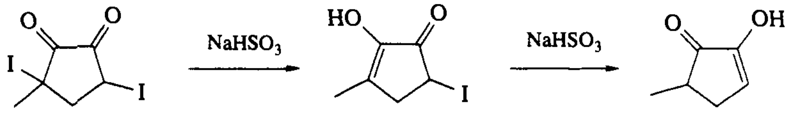

(22) (23)

(14)

### 4.8.2.2.3 Reductive cleavages by other nucleophiles

While a number of other nucleophilic agents besides those already mentioned have been found to effect reductive dehalogenation of α-halocarbonyl compounds, the only ones of synthetic interest are organic phosphines ($R_3P$) and organotelluride ions ($RTe^-$). Tertiary phosphines react with halo ketones to form enol phosphonium salts, which can be either isolated or immediately hydrolyzed to afford the carbonyl compound (equation 15).[40] A competing reaction involves direct displacement of halogen by phosphorus to form an α-ketophosphonium salt; this is especially a problem with primary halo ketones. The α,α-dichloro ketone (**24**) could be converted *via* the enol phosphonium salt (**25**) to the corresponding monohalide (**26**) or to the mixed bromo chloro ketone (**27**; Scheme 3).[40] $PI_3$ and $P_2I_4$[41] and diphenylphosphine[42] are also useful dehalogenation agents. The latter is believed to occur according to the general path described in equation (11), with phosphorus acting as a soft base and hydrogen as a hard acid.

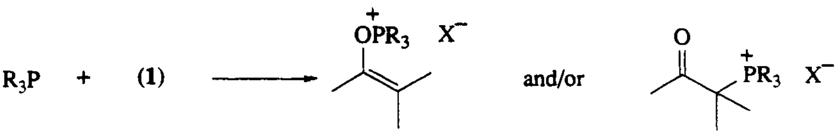

(15)

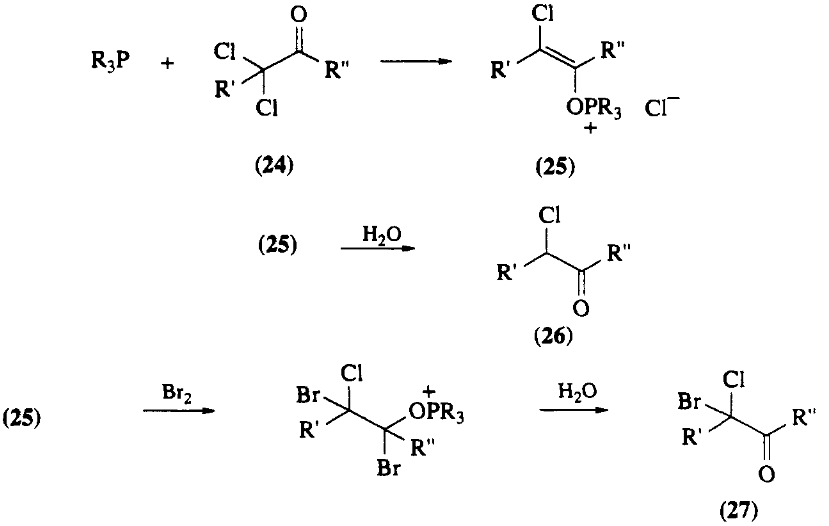

**Scheme 3**

The organotelluride salt (**28**) readily dehalogenates a variety of α-halocarbonyl compounds, including ketones, acids and esters.[43] It is not clear whether the first step is displacement of halide to afford an α-tellurocarbonyl compound, followed by attack upon the latter by (**28**), or whether (**28**) attacks the α-substituent directly. Reduction can be effected by $NaBH_4$ containing a catalytic quantity of (**28**).[43]

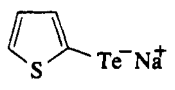

**(28)**

#### 4.8.2.3 Other Reduction Methods

Transition metal carbonyls, including $Fe(CO)_5$, $Fe_2(CO)_9$, $[HFe(CO)_4]^-$, $Co_2(CO)_8$ and $Mo(CO)_6$, together with related reagents such as nickel and palladium salts, all effect dehalogenation of α-halocarbonyl compounds.[3,4,18] Yields in general are not high, and a number of competing reactions, including dimerization of the halocarbonyl compound, are sometimes observed. The reactions have sometimes been used for obtaining α-deuteriocarbonyl compounds by inclusion of $D_2O$ in the medium.[44]

A number of tin hydrides have been shown to dehalogenate α-halocarbonyl compounds. Species which have been used include trialkyltin hydrides ($R_3SnH$) and dialkyltin hydrides ($R_2SnH_2$).[45] Dehalogenation of α-bromo ketones can be carried out under very mild conditions (–78 °C, 10 min) by a mixture of $SnCl_2$ and DIBAL-H in the presence of TMEDA.[46] The reaction probably involves $SnH_2$ as an intermediate. It has been reported that reduction of (**29**) by $NaBH_4$ affords (**30**), except in the presence of a trace of $Pb(OAc)_2$, $Ni(OAc)_2$ or $Hg(OAc)_2$, in which case the α-bromine is removed selectively to afford (**31**).[47] The latter reductions may involve intermediate metal hydrides.

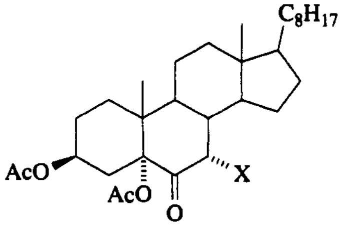

(**29**) X = Br
(**31**) X = H

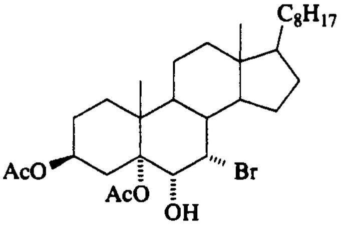

(**30**)

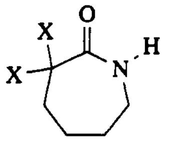

(**32**) X = Br or Cl

Finally, hydrogenolysis of the halogen atom of α-halocarbonyl compounds can be carried out at noble metal catalysts.[48] Palladium is frequently used for this purpose. Selective removal of just one of the halogen atoms in the dihalides (**32**) can be effected in NaOAc/HOAc over a palladium catalyst.[49]

### 4.8.3 THE CARBON–OXYGEN BOND

Carbon–oxygen bonds are generally stronger and hence harder to break than structurally related carbon–halogen bonds. Since bond cleavage involves ejection of the α-oxygen as an anion, the ease of bond cleavage is correlated with the leaving group ability of the oxygenated function; thus, the ease of reducibility decreases in the sequence: sulfonate > acyloxy > hydroxy or alkoxy.[5] Reductive cleavage is also faster in acidic media, where the neutral leaving group can be ejected.

#### 4.8.3.1 Reduction By Electron Transfer

##### *4.8.3.1.1 Reductive cleavages by metals*

Active metals readily cleave α-ketols and α-ketol acetates. Reductions can be carried out with the aid of lithium, barium or calcium in ammonia,[50] or with zinc or tin, which are usually used in acidic media.[51]

Zinc is a relatively mild reducing agent and is therefore somewhat selective. Axial steroidal ketol acetates are reduced more readily than equatorial (equations 16 and 17).[51] On the other hand, metal–ammonia systems are powerful reductants; thus, calcium and barium reduce axial and equatorial isomeric ketol acetates with equal ease.[50] Lithium is a more powerful reductant and frequently overreduces α-ketols

(Section 4.8.3.1.3).[5] The phenacyl group has been suggested as a protecting group for acids and phenols.[52] It is readily removed by zinc in acetic acid at room temperature.

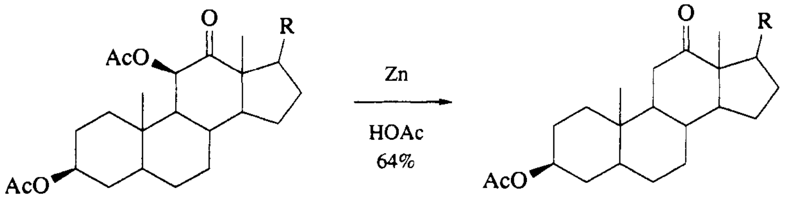

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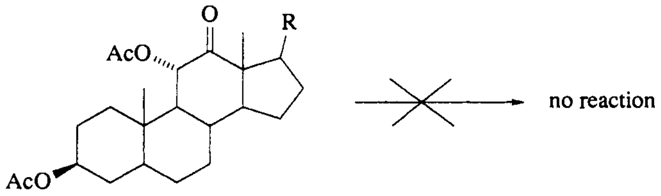

(17)

### *4.8.3.1.2 Reductive cleavages by low-valent metal ions*

The more negative potentials characteristic of α-oxygenated substrates compared to their halogenated counterparts call for relatively powerful reductants such as chromium(II), titanium(II) and samarium(II) to effect α-cleavage, although reduction can be facilitated in a series of related substances by increasing the leaving group ability of the oxygenated function (Section 4.8.3).

α-Ketols are not reduced efficiently by low-valent metal ions. One of the few reports of this conversion was made by McMurry and coworkers, who found that 1-acetyl-1-cyclohexanols are converted to the corresponding ketones by a mixture of $TiCl_4$ and zinc (in which the active reagent is probably $Ti^{II}$).[53] Unfortunately, the reaction is not general; other α-ketols afford rearranged products under the same conditions. Deoxygenation of ketols generally requires that the hydroxy group be converted to a derivative such as an ester or sulfonate before reduction. Even so, chromium(II) requires relatively vigorous conditions to effect reduction.[54] The major exception to this generalization is the reduction of α,β-epoxy ketones, which can be carried out to produce the corresponding β-ketols (aldols; equation 18) by chromium(II) under mild conditions, driven in this case by relief of strain in the three-membered ring.[50] Reduction affords the corresponding α,β-unsaturated carbonyl compound if reduction is carried out under more highly acidic conditions. Samarium(II) reduces a variety of α-oxygenated ketones very readily at –78 °C in THF/MeOH in excellent yields, again except for α-ketols.[22a] These, however, could be reduced cleanly by adding a solution of the ketol and $Ac_2O$ to $SmI_2$, in order to form and reduce the ketol acetate *in situ*. α-Oxygenated esters, including even α-hydroxy esters, can be reduced by $SmI_2$ in THF/HMPA at room temperature.[22b]

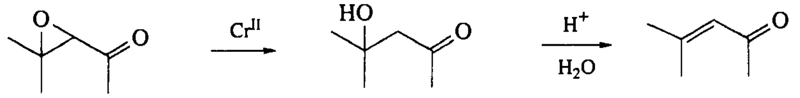

(18)

### *4.8.3.1.3 Electrochemical reductive cleavages*

The electrochemical reduction of α-oxygenated carbonyl compounds has been reviewed.[5] In a series of phenacyl derivatives, $PhCOCH_2OR$, where R is acetyl, benzoyl, phenyl and hydrogen, the first two are about 0.1 V (or in energy terms a few kcal $mol^{-1}$; 1 cal = 4.18 J) easier to reduce than the latter two. Ring strain (**33**), use of an acidic solvent and buttressing by a second activating group (**34**) all favor the cleavage process. Electrochemical reduction of α-ketols and ketol acetates (R = H or Ac) cannot be stopped at the ketone stage (**35**), because the latter are reduced at about the same potential as the starting ketol. An overall four-electron process takes place, and the saturated alcohol (**36**) is formed (equation 19). Reduction is stereoselective: reduction of a series of steroidal ketol acetates afforded the equatorial alcohol in 90–100% yield.[5] Vinylogous α-cleavage with bond migration has been observed with cephalosporanic acid derivatives (**37**; equation 20).[55]

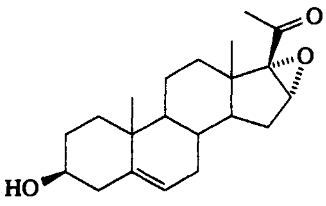

**(33)**

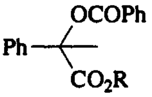

**(34)**

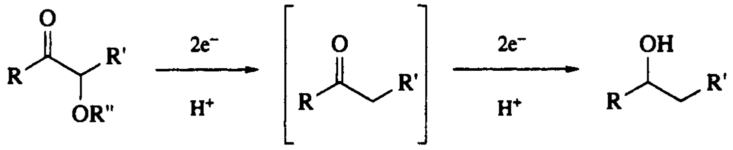

**(35)** **(36)**

(19)

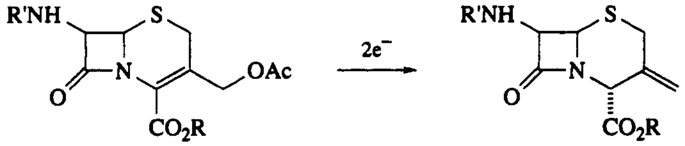

**(37)**

(20)

### 4.8.3.2 Other Reduction Methods

Although very common with α-halocarbonyl compounds, cleavage of α-oxygenated substances by nucleophiles is almost unknown. A mixture of phenyl trimethylsilyl selenide (**38**) and $MgBr_2$ dehalogenates substituted benzoin acetates under mild conditions.[56] The reaction probably proceeds by the HSAB path (equation 11); the precise function of $MgBr_2$ is unclear.

$PhSeSiMe_3$

**(38)**

Reductive cleavage of α-ketol acetates can also be effected in moderate yield by $Fe(CO)_5$.[57] Ketones, esters and alkenes are unreactive toward this reagent.

## 4.8.4 THE CARBON–SULFUR BOND

The following discussion includes removal of a variety of sulfur substituents, including not just alkyl- and aryl-thio (RS), but also sulfinyl (RSO), and sulfonyl ($RSO_2$) groups α to carbonyl groups.

### 4.8.4.1 Reduction By Electron Transfer

#### *4.8.4.1.1 Reductive cleavages by metals*

Alkylthio groups can be removed (equation 21) by reaction of the α-alkylthio ketone with either zinc in wet ether in the presence of TMS–Cl,[58] lithium in amine solvents or in THF containing an electron mediator such as naphthalene or trimesitylborane,[59] or $Na(Hg)_x$ in methanol buffered with $Na_2HPO_4$.[60] The enolate formed by Li reduction in $NH_3$ can be alkylated (equation 22).[61]

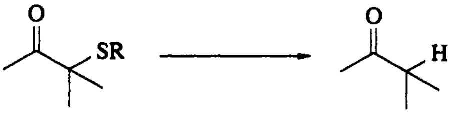

(21)

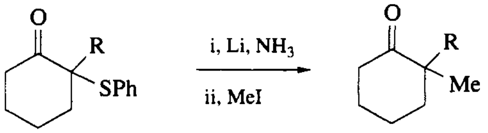

(22)

Sulfinyl and sulfonyl groups are easier to reduce than α-(alkylthio)carbonyl compounds. Aluminum amalgam has frequently been used for removal of sulfinyl and sulfonyl groups.[62] This reagent is typically used in refluxing (wet) THF; reduction of β-keto sulfones can be carried out at room temperature by $Na(Hg)_x$, if the solution is buffered with $Na_2HPO_4$.[60]

Phenacylsulfonamides (**39**) are readily reduced by zinc in acetic acid. The phenacylsulfonamido group has therefore been suggested as a protecting group for primary and secondary amines (equation 23), as well as a temporary acidifying group to facilitate conversion of primary to secondary amines.[63]

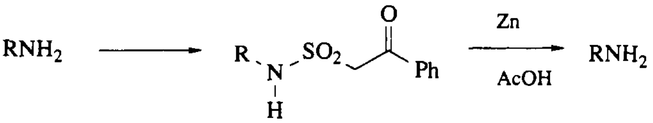

**(39)**

(23)

### 4.8.4.1.2 *Reductive cleavages by low-valent metal ions*

The potent reductant $SmI_2$ readily reduces α-alkylthio, α-sulfinyl and α-sulfonyl ketones at −78 °C.[22] A mixture of iron(II) polyphthalocyanine and thiophenol has been used to reduce α-halo, α-alkylthio, and α,α-bis(alkylthio) ketones.[64] The iron compound apparently reacts as an electron transfer mediator; the actual source of electrons is the thiophenol, which is converted to diphenyl disulfide in the course of the reaction.

### 4.8.4.1.3 *Electrochemical reductive cleavages*

α-Alkylthio groups are most readily removed electrochemically when sulfur carries a positive charge, as in phenacylsulfonium ions (**40**), or when a second activating group is present (**41**).[5] Torii reported a synthetic route to 2,2-disubstituted acetates (**42**) using the 2-benzothiazolylthio moiety as a blocking group to prevent overalkylation. The group is easily removed electrochemically after alkylation (equation 24).[65] A similar sequence has been employed using the phenylsulfonyl group as prosthetic group (equation 25).[66]

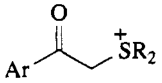

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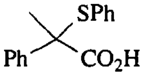

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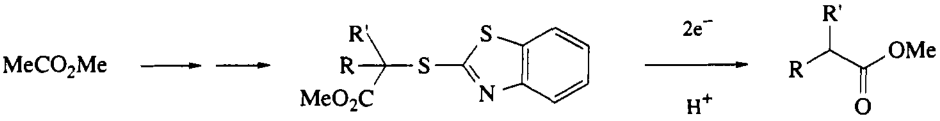

**(42)**

(24)

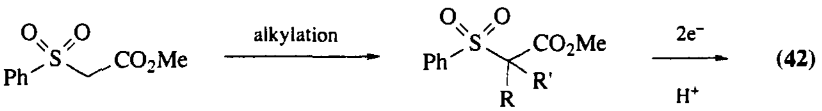

(25)

#### 4.8.4.2 Other Reduction Methods

Thiolate ions react with α-(alkylthio)carbonyl compounds to afford disulfides and the corresponding reduced ketone (equation 26).[67] The reaction apparently involves direct nucleophilic attack by thiolate on the sulfur atom of the alkylthio group. Other soft bases, such as cyanide ion, thiourea and tertiary phosphines, also effect this conversion.[67] Raney nickel of course readily desulfurizes α-alkylthiocarbonyl compounds. The reaction is quite selective; for example, the ester, ketone and alkenic moieties of (**43**) are unaffected by the Raney nickel treatment (equation 27).[68] Raney nickel reduction of (**44**) is reported to proceed with retention of configuration in ethanol and with inversion in acetone.[69] Telluride salts also desulfurize α-alkylthio ketones.[43]

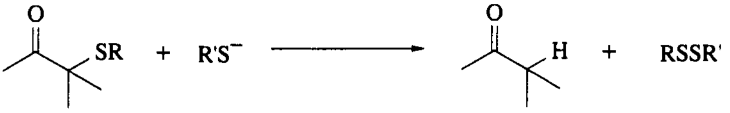

(26)

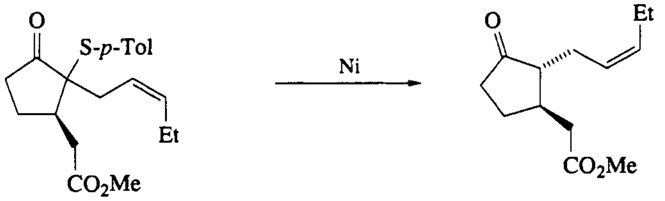

(**43**)

(27)

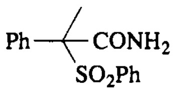

(**44**)

### 4.8.5 THE CARBON–NITROGEN BOND

Carbon–nitrogen bonds are harder to cleave than carbon–oxygen bonds. Cleavage generally requires a powerful reductant. The nitrogen atom should carry a positive charge, or the leaving group should be highly stabilized, preferably both of these.[5] Reduction of quaternary ammonium ions, the Emde reduction for example, is generally most efficient where one of the four groups is benzylic.

#### 4.8.5.1 Electrochemical Reduction

Electrochemical reductive cleavage of α-amino ketones becomes easier as the acidity of the medium is increased, indicating that they are reduced as their conjugate acids.[5] As with α-ketols (Section 4.8.3.1.3), reductive cleavage of the carbon–heteroatom bond is frequently accompanied by reduction of the carbonyl group (equation 28).[5]

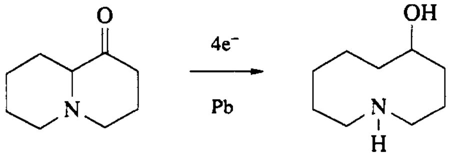

(28)

### 4.8.6 THE CARBON–CARBON BOND

Indanedione dehydro dimers (**45**) undergo facile carbon–carbon bond cleavage (equation 29), either electrochemically,[5] or by a variety of chemical reductants such as $Pt/H_2$, $Na/NH_3$ or $Zn/HCl$.[70] Presumably the process is markedly assisted here by the production of two β-diketonate anions. By the same token, acyclic 1,1,2,2-tetracarboxylates (**46**) and the related cyclic derivatives (**47**) are readily reduced to the corresponding malonates and linear tetraesters in 95–100% yield (equations 30–31).[5]

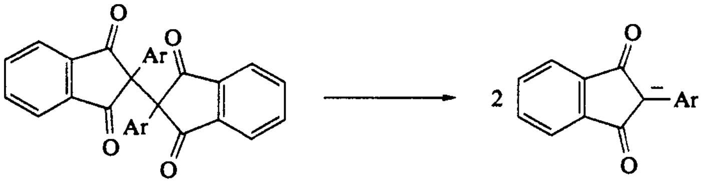

(**45**)

(29)

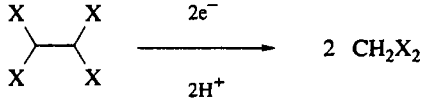

(**46**)

(30)

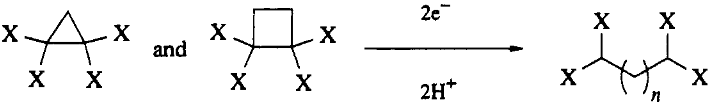

(**47**) $X = CO_2Me$ ($n$ = 1 or 2)

(31)

## 4.8.7 THE CARBON–SELENIUM BOND

Cleavage of carbon–selenium bonds α to carbonyl groups follows similar principles to those obeyed by the corresponding carbon–sulfur bonds, except that milder conditions are required, as befits the lower bond strength of the carbon–selenium bond. Thus cleavage is very facile if selenium carries a positive charge (**48** → **49**; equation 32)[71] or if the acidity of the leaving group is enhanced, as in the aryl selenide (**50**).[72] Nickel boride, used in the latter reaction, has been shown to reductively remove selenium in the presence of sulfur.[72]

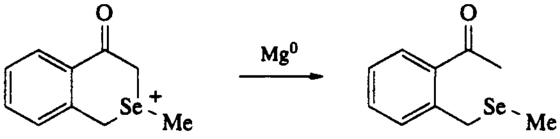

(**48**) (**49**)

(32)

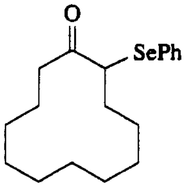

(**50**)

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This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

Abbott, D. E., 6[12,12c], 10[40], 573[53,54]

The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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# Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C $\pi$-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

BARRY M. TROST
*Palo Alto, California*

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# Cumulative Author Index

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Each entry consists of the author's name, bold numbers, and other numbers which are associated with superscripts. For example

Abbott, D. E., **2**, 6[12,12c], 10[40], 573[53,54]

The bold number indicates the volume number, and the other numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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Amrani, Y., **8**, 535$^{166}$
Amrein, W., **5**, 219$^{37}$
Amri, H., **3**, 246$^{34}$; **4**, 34$^{97}$, 35$^{97}$
Amriev, R. A., **4**, 288$^{187}$
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Amstutz, E. D., **2**, 747$^{121}$; **3**, 564$^{12}$
Amstutz, R., **1**, 1$^{1}$, 3$^{1}$, 26$^{1}$, 28$^{142}$, 30$^{151}$, 37$^{238,240,241}$, 38$^{261}$, 41$^{151}$, 43$^{1}$, 299$^{61}$, 316$^{61}$; **2**, 100$^{2}$, 280$^{25}$; **5**, 841$^{104}$; **6**, 112$^{65}$
Amtmann, R., **8**, 742$^{42}$, 746$^{42}$
Amupitan, J. A., **2**, 546$^{90}$; **3**, 348$^{29}$, 355$^{53}$, 357$^{53}$
Amvam-Zollo, P.-H., **6**, 51$^{105}$
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Ananchenko, S. N., **2**, 382$^{313}$
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Anand, R. C., **5**, 944$^{241}$
Ananda, G. D. S., **7**, 96$^{199}$, 112$^{198}$, 820$^{26}$
Anandrut, J., **1**, 303$^{79}$
Anani, A., **7**, 662$^{55}$
Ananthanarayan, T. P., **3**, 816$^{80}$; **8**, 623$^{148}$
Anantharamaiah, G. M., **6**, 635$^{15}$, 636$^{15}$, 651$^{136,136c}$, 668$^{250}$; **8**, 959$^{22}$
Anantha Reday, P., **3**, 462$^{149}$
Anastasia, M., **7**, 674$^{42}$; **8**, 565$^{448}$
Anastassiou, A. G., **5**, 634$^{77}$, 716$^{85}$; **7**, 21$^{13}$, 25$^{46}$, 26$^{46,60}$, 479$^{95}$, 507$^{307}$; **8**, 407$^{58}$, 625$^{161}$
Anciaux, A. J., **1**, 631$^{47}$, 656$^{154}$, 658$^{154}$; **3**, 87$^{92}$, 1047$^{8}$, 1051$^{8}$; **4**, 318$^{560}$, 1033$^{16,16d,e}$, 1035$^{16e}$, 1051$^{125}$, 1052$^{16d}$
Ancillotti, F., **4**, 307$^{396}$
Andal, R. K., **8**, 446$^{65}$
Andermann, G., **8**, 370$^{96}$, 639$^{19}$
Anders, E., **6**, 172$^{11}$
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Andersen, K. S., **5**, 552$^{14}$
Andersen, L., **4**, 436$^{140}$; **5**, 686$^{53}$
Andersen, N. H., **1**, 506$^{10}$, 582$^{7}$; **2**, 90$^{41}$, 381$^{310}$, 544$^{85}$, 547$^{85,96,110-112}$, 551$^{96,110-112}$, 552$^{85}$, 572$^{42}$, 710$^{28}$; **3**, 132$^{334}$, 133$^{334}$, 136$^{334}$, 354$^{62}$, 356$^{56}$; **4**, 373$^{72}$; **6**, 134$^{29}$
Andersen, P., **1**, 33$^{163}$
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Anderson, A. G., **1**, 846$^{16}$, 851$^{16}$
Anderson, A. G., Jr., **2**, 169$^{164}$, 323$^{27}$; **6**, 204$^{23}$; **8**, 568$^{472}$
Anderson, A. L., **8**, 900$^{32}$
Anderson, B. A., **5**, 1070$^{29}$, 1074$^{29}$, 1076$^{44}$, 1080$^{52}$
Anderson, B. C., **3**, 380$^{5}$
Anderson, B. F., **8**, 500$^{51}$
Anderson, C., **4**, 857$^{103}$
Anderson, C. B., **7**, 92$^{50}$
Anderson, C. E., **6**, 660$^{199}$
Anderson, C. L., **7**, 597$^{48}$, 641$^{5}$
Anderson, D., **6**, 508$^{286}$, 537$^{286}$
Anderson, D. F., **3**, 749$^{81}$
Anderson, D. G., **1**, 618$^{56}$; **4**, 120$^{197}$
Anderson, D. J., **2**, 787$^{53}$, 792$^{53}$; **7**, 743$^{60}$
Anderson, D. K., **2**, 763$^{59}$; **4**, 14$^{46}$; **5**, 1022$^{76}$
Anderson, D. M. W., **2**, 367$^{225}$; **3**, 826$^{40}$
Anderson, D. R., **5**, 684$^{36b}$, 834$^{53}$
Anderson, F. E., III, **4**, 18$^{59}$
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Anderson, G. K., **4**, 915$^{15}$; **8**, 447$^{116}$
Anderson, G. W., **6**, 614$^{90}$, 636$^{26}$, 637$^{26}$, 664$^{222}$
Anderson, H. J., **1**, 474$^{84}$; **2**, 743$^{84,87}$, 780$^{9}$; **5**, 581$^{176}$
Anderson, J., **5**, 413$^{48}$
Anderson, J. D., **8**, 532$^{132,132d}$
Anderson, K., **7**, 160$^{49}$
Anderson, K. D., **1**, 471$^{67}$
Anderson, K. W., **3**, 736$^{27}$
Anderson, L. G., **4**, 85$^{75}$
Anderson, M. B., **1**, 238$^{37}$, 529$^{123}$, 735$^{28}$, 736$^{28}$
Anderson, M. W., **1**, 366$^{52}$; **2**, 494$^{56,57}$; **4**, 76$^{47}$; **6**, 516$^{321}$, 552$^{692}$; **8**, 638$^{16}$
Anderson, N. H., **4**, 120$^{201}$; **7**, 228$^{93}$, 258$^{44}$; **8**, 278$^{157}$, 374$^{147,148}$
Anderson, O. P., **1**, 827$^{67}$; **4**, 161$^{87,87b}$, 560$^{26}$; **5**, 1107$^{168}$; **7**, 399$^{33}$; **8**, 333$^{57}$, 345$^{127}$
Anderson, P. C., **3**, 227$^{208}$, 421$^{61}$, 422$^{61}$, 589$^{161,162}$, 610$^{161,162}$; **4**, 18$^{59}$, 121$^{208}$, 373$^{82}$, 386$^{148b}$, 387$^{148}$, 993$^{161}$
Anderson, P. H., **3**, 927$^{48}$; **6**, 134$^{37}$
Anderson, P. S., **3**, 380$^{11}$; **5**, 382$^{121}$, 410$^{41}$; **8**, 580$^{3}$, 584$^{3}$, 585$^{3}$
Anderson, R., **1**, 731$^{4}$, 815$^{4}$
Anderson, R. A., **3**, 663$^{26}$, 665$^{26}$
Anderson, R. C., **2**, 827$^{126}$; **5**, 350$^{80}$, 841$^{86}$; **6**, 859$^{164}$, 978$^{21}$; **7**, 261$^{67}$; **8**, 566$^{450}$
Anderson, R. J., **1**, 116$^{45}$, 128$^{45}$, 433$^{139}$, 434$^{139}$; **2**, 159$^{127}$; **3**, 220$^{121}$, 224$^{163}$, 226$^{192}$, 257$^{120}$, 265$^{187}$, 365$^{94}$, 419$^{43}$; **6**, 4$^{20}$, 9$^{40}$
Anderson, R. L., **4**, 104$^{135c}$; **5**, 1076$^{35,38,46}$, 1079$^{49}$
Anderson, R. S., **8**, 73$^{248}$, 74$^{248}$, 373$^{136}$
Anderson, S. M., **8**, 802$^{86}$
Anderson, S. W., **4**, 1007$^{112}$
Anderson, T., **6**, 175$^{75}$
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Anderson, V. E., **6**, 455$^{149}$
Anderson, W. K., **5**, 581$^{172}$

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Ando, K., **2**, 8$^{37}$, 13$^{37}$, 20$^{37a}$, 35$^{37}$, 43$^{147}$, 44$^{147}$; **3**, 137$^{376}$; **4**, 21$^{69}$, 222$^{173,176}$; **6**, 864$^{197}$; **7**, 764$^{116}$; **8**, 847$^{91}$
Ando, M., **1**, 98$^{84}$, 99$^{84}$, 387$^{136}$; **2**, 443$^{15}$, 445$^{24}$, 451$^{15}$, 576$^{79}$, 718$^{77}$, 995$^{45}$; **3**, 1041$^{113}$; **4**, 24$^{75}$, 25$^{75a}$, 857$^{104}$, 970$^{72}$, 972$^{81}$; **5**, 841$^{88}$; **6**, 542$^{601}$, 767$^{28}$, 768$^{28}$, 769$^{28}$, 984$^{59}$; **7**, 155$^{25}$, 163$^{73}$, 641$^{6}$, 696$^{43}$, 697$^{43}$; **8**, 43$^{108}$, 47$^{108}$, 64$^{220}$, 66$^{108}$, 67$^{220}$, 394$^{119}$
Ando, N., **8**, 170$^{79}$
Ando, R., **1**, 670$^{186}$; **7**, 761$^{63}$, 771$^{279}$, 773$^{279}$
Ando, T., **2**, 115$^{124}$; **3**, 218$^{98}$; **4**, 354$^{130}$, 1006$^{96}$, 1017$^{211}$, 1021$^{211,242}$; **6**, 66$^{5}$, 498$^{167}$, 968$^{106}$; **7**, 255$^{38}$; **8**, 86$^{26}$, 798$^{54}$
Ando, W., **3**, 887$^{6}$, 889$^{6}$, 893$^{6}$, 894$^{6}$, 896$^{6}$, 897$^{6}$, 900$^{6}$, 903$^{6,123}$, 919$^{28,32}$, 923$^{43,44}$, 934$^{44,63}$, 954$^{44}$, 1008$^{70,71}$; **6**, 114$^{76}$, 440$^{77}$, 846$^{101}$; **7**, 763$^{102}$, 769$^{222}$, 778$^{403}$, 851$^{24}$; **8**, 979$^{147}$
Andrac, M., **2**, 81$^{5}$
Andrade, J. G., **3**, 499$^{124}$, 507$^{124}$, 670$^{58}$, 673$^{58}$, 693$^{141}$; **7**, 336$^{34}$; **8**, 459$^{240}$, 460$^{250}$
Andre, C., **1**, 419$^{79}$, 797$^{292}$, 802$^{292}$; **6**, 995$^{104}$, 996$^{104}$; **7**, 400$^{46}$
André, E., **4**, 47$^{133}$
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Andreani, A., **2**, 787$^{52}$
Andree, H., **7**, 760$^{40}$
Andree, R., **6**, 111$^{64}$
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Andreetti, G. D., **3**, 386$^{57}$; **6**, 195$^{224}$
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Andreeva, L. N., **4**, 992$^{154}$
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Andrews, D. R., **1**, 883$^{124}$; **5**, 806$^{104}$, 1029$^{91}$; **7**, 90$^{32}$
Andrews, D. W., **6**, 707$^{42}$
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Andrews, L., **5**, 704$^{21}$
Andrews, L. H., **8**, 604$^{2}$, 605$^{2}$
Andrews, L. J., **5**, 71$^{144}$; **6**, 980$^{39}$; **8**, 796$^{27}$, 888$^{122}$
Andrews, M. A., **7**, 107$^{163}$
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Andrews, R. C., **3**, 100$^{202}$, 168$^{202}$, 170$^{202}$, 172$^{202}$; **5**, 173$^{123}$; **6**, 7$^{34}$, 158$^{183}$; **7**, 89$^{27}$
Andrews, S. B., **1**, 213$^{18}$
Andrews, S. L., **6**, 936$^{105}$; **7**, 205$^{61}$
Andrews, S. M., **4**, 439$^{159}$
Andrews, S. W., **1**, 612$^{49}$; **3**, 752$^{93}$; **5**, 247$^{24}$
Andriamialisoa, R. Z., **1**, 838$^{169}$; **4**, 598$^{206}$; **5**, 409$^{37}$; **6**, 487$^{75}$, 921$^{49}$; **7**, 164$^{80}$; **8**, 58$^{174}$, 66$^{174}$
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Andrianova, G. M., **1**, 555$^{112}$
Andrieux, C. P., **3**, 574$^{77}$; **8**, 135$^{49}$
Andriollo, A., **8**, 446$^{74}$, 452$^{74}$, 457$^{74}$
Andrisano, R., **8**, 161$^{22}$
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Andrus, A., **3**, 1025$^{36}$; **5**, 854$^{181}$
Andrus, W. A., **4**, 107$^{142}$; **6**, 676$^{307}$
Andruzzi, R., **8**, 132$^{14}$
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Aneja, R., **7**, 544$^{34}$; **8**, 568$^{467}$
Anet, F. A. L., **1**, 174$^{3}$, 528$^{113}$; **2**, 811$^{67}$; **3**, 164$^{475}$, 382$^{36}$; **5**, 552$^{21}$; **7**, 483$^{125}$
Añez, M., **8**, 16$^{101}$, 537$^{180}$
Angeletti, E., **2**, 345$^{20}$
Angeli, A., **3**, 890$^{35}$; **8**, 664$^{120}$
Angelici, R. J., **8**, 608$^{42}$, 629$^{42}$, 847$^{96}$
Angelini, G., **3**, 300$^{40}$; **4**, 445$^{206}$; **8**, 336$^{70}$
Angelino, N., **7**, 749$^{123}$
Angell, E. C., **7**, 221$^{31}$, 227$^{31}$
Angelo, M. M., **2**, 710$^{23}$
Angeloni, A. S., **8**, 161$^{22}$
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Angelova, O., **1**, 36$^{175}$
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Angermann, A., **1**, 54$^{20}$, 338$^{83}$; **2**, 31$^{114,114a}$; **7**, 253$^{18}$
Angermund, K., **1**, 14$^{77}$, 37$^{251}$, 180$^{30}$, 531$^{132}$; **5**, 497$^{224}$; **8**, 682$^{83}$
Angibeaud, P., **7**, 247$^{104}$
Angibeaund, P., **8**, 479$^{48}$, 481$^{48}$, 528$^{56}$
Angier, R. B., **7**, 30$^{80}$
Angiolini, L., **1**, 59$^{35}$; **2**, 948$^{184}$
Angle, S. R., **1**, 889$^{143}$, 890$^{143}$; **5**, 311$^{104}$, 563$^{89}$, 843$^{121}$, 934$^{188}$
Angoh, A. G., **1**, 882$^{123}$, 885$^{133c}$; **3**, 219$^{110}$; **4**, 10$^{32}$, 733$^{79}$, 791$^{54}$, 824$^{235}$
Angrick, A., **6**, 33$^{6}$, 34$^{6}$, 40$^{6}$, 46$^{6}$
Angst, C., **1**, 343$^{107}$; **2**, 1074$^{149}$, 1075$^{149}$; **4**, 382$^{134}$; **5**, 836$^{63}$
Angus, H. J. F., **5**, 646$^{4}$
Angus, R. H., **6**, 436$^{10,11}$
Angus, R. O., Jr., **4**, 1010$^{161}$; **6**, 977$^{18}$
Angustine, R. L., **7**, 564$^{86}$
Angyal, S. J., **1**, 2$^{15}$; **4**, 187$^{96}$; **6**, 648$^{117a}$; **7**, 231$^{139}$, 666$^{72,73,76}$, 803$^{52}$
Anh, N. T., **1**, 49$^{7,8}$, 50$^{7}$, 110$^{20}$, 153$^{55}$, 182$^{47}$, 185$^{47}$, 198$^{47}$, 222$^{69}$, 310$^{102}$; **2**, 24$^{96}$, 217$^{137}$, 666$^{38}$, 677$^{38}$; **4**, 70$^{11}$, 71$^{16a}$, 139$^{2,3}$; **5**, 64$^{27}$, 260$^{72}$, 263$^{72}$, 417$^{63}$, 453$^{67}$, 683$^{219}$; **6**, 873$^{2}$; **8**, 3$^{23}$, 7$^{37}$, 16$^{104}$, 536$^{170}$, 541$^{213,214,215}$, 542$^{214}$, 543$^{213,214,215}$, 930$^{34}$
Anhoury, M.-L., **8**, 237$^{12}$
Anikina, E. V., **3**, 303$^{57}$
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Anisimov, K. N., **4**, 701$^{28,29}$, 702$^{28,29}$
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Anjaneyulu, B., **5**, 92$^{68}$, 95$^{68}$, 96$^{68}$
Anjik, T., **7**, 335$^{32}$
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Anklekar, T. V., **1**, 477$^{131}$; **3**, 75$^{43}$, 76$^{43}$, 77$^{57}$, 80$^{43}$; **7**, 227$^{80}$
Ankner, K., **8**, 994$^{66}$
Anliker, R., **8**, 108$^{2}$, 118$^{2}$, 530$^{91}$
An-naka, M., **3**, 461$^{148}$, 541$^{113}$, 543$^{113}$; **6**, 46$^{59}$
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Anner, G., **3**, 816$^{79}$; **6**, 1015$^{23}$, 1059$^{64}$; **7**, 41$^{20}$; **8**, 974$^{124}$
Annino, R., **8**, 988$^{25}$
Annis, G. D., **1**, 849$^{28}$; **2**, 546$^{89}$; **6**, 979$^{26}$, 1004$^{140}$
Annis, M. C., **6**, 279$^{136}$; **7**, 699$^{54}$
Anno, K., **8**, 269$^{86}$
Annoura, H., **1**, 63$^{43,44}$, 64$^{46}$; **4**, 304$^{356}$; **5**, 736$^{145}$, 737$^{145}$, 838$^{74}$
Annunziata, R., **1**, 519$^{65,66}$, 520$^{67}$, 523$^{80}$, 524$^{86\text{-}88}$, 765$^{151}$; **2**, 31$^{108}$, 228$^{166,167}$, 374$^{276}$, 435$^{62,65}$, 486$^{42}$, 492$^{52}$, 515$^{55\text{-}57}$, 516$^{58}$; **6**, 149$^{97,99,102}$, 840$^{71}$; **7**, 442$^{47}$, 767$^{193}$, 778$^{411}$; **8**, 72$^{239}$, 74$^{239}$, 844$^{67}$
Anoshina, G. M., **6**, 530$^{421}$, 538$^{555}$, 550$^{421}$
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Ansari, J. A., **7**, 92$^{43}$, 481$^{112}$
Anschütz, R., **3**, 828$^{45}$
Anschütz, W., **3**, 909$^{152}$
Ansell, M. F., **1**, 739$^{37}$; **3**, 326$^{164,165}$; **4**, 313$^{462}$, 951$^{1}$, 968$^{1}$, 979$^{1}$; **5**, 433$^{136a,b}$, 605$^{56}$, 612$^{77}$, 819$^{152}$; **6**, 104$^{1,9}$
Anselme, J.-P., **1**, 845$^{10}$; **2**, 830$^{137}$; **6**, 249$^{140}$, 809$^{67}$; **7**, 663$^{59}$, 749$^{120}$
Anson, F. C., **3**, 213$^{51}$; **8**, 595$^{76}$
Anstad, T., **6**, 242$^{94}$
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Antel, J., **2**, 345$^{34}$, 351$^{34}$, 357$^{34}$, 371$^{34}$, 373$^{273,274}$; **5**, 14$^{99}$, 17$^{121}$, 468$^{125}$
Anteunis, M., **5**, 1130$^{7}$; **6**, 80$^{66}$, 237$^{69}$; **8**, 212$^{17}$, 348$^{132}$
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Anthon, N. J., **4**, 381$^{126b}$, 382$^{126}$, 383$^{126}$
Anthonsen, T., **1**, 823$^{41,42}$, 832$^{41}$; **8**, 528$^{66}$
Anthony, D. R., Jr., **6**, 515$^{235}$
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Anthony, N. J., **1**, 801$^{303}$
Antipin, I. S., **5**, 76$^{248}$
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Antonakis, K., **2**, 555$^{141}$; **7**, 265$^{97,98}$, 272$^{98}$; **8**, 64$^{212}$, 66$^{212}$, 67$^{212}$, 68$^{212}$
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Antonini, I., **5**, 92$^{63}$
Antonioletti, R., **3**, 512$^{213}$, 515$^{213}$; **4**, 391$^{176}$; **5**, 771$^{151}$, 772$^{151}$; **7**, 265$^{102}$, 266$^{107}$, 267$^{102,107}$, 530$^{15}$
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Antonova, N. D., **2**, 534$^{32}$, 535$^{38}$
Antonsson, T., **7**, 453$^{77}$
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Anwer, M. K., **8**, 904$^{60}$, 905$^{60}$
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Aoe, K., **2**, 1066$^{122}$; **4**, 398$^{217}$, 399$^{217b}$, 401$^{217b}$, 403$^{217b}$, 404$^{217b}$, 803$^{132}$; **7**, 353$^{35}$, 355$^{35}$
Aoki, H., **5**, 504$^{276}$
Aoki, K., **5**, 1142$^{87,89}$; **7**, 802$^{49}$
Aoki, O., **1**, 279$^{86}$, 280$^{86}$; **3**, 567$^{190}$, 595$^{190}$, 607$^{190}$
Aoki, S., **1**, 212$^{12}$, 213$^{12}$, 215$^{12b}$, 217$^{12}$, 448$^{207}$; **2**, 443$^{19}$, 447$^{19}$, 448$^{19}$, 449$^{19}$, 450$^{52,53}$, 451$^{56}$, 578$^{88}$, 587$^{88}$; **3**, 169$^{509}$, 221$^{131,132}$, 455$^{125}$, 460$^{125}$; **4**, 163$^{96}$, 164$^{96}$; **5**, 74$^{205}$; **6**, 848$^{110}$; **8**, 846$^{80}$
Aoki, T., **2**, 784$^{38}$, 1052$^{51}$; **7**, 707$^{29}$, 708$^{29}$, 803$^{51}$; **8**, 151$^{147}$, 881$^{82}$
Aoki, Y., **1**, 373$^{88}$, 374$^{88}$; **5**, 844$^{131}$
Aono, M., **4**, 1095$^{152}$
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Aoyagi, T., **3**, 623$^{39}$
Aoyama, H., **3**, 1057$^{38}$; **4**, 614$^{372,373}$, 840$^{37}$, 905$^{207}$; **5**, 181$^{150}$; **8**, 964$^{55}$
Aoyama, M., **4**, 147$^{42}$
Aoyama, T., **1**, 844$^{6,7}$, 851$^{40,47}$, 852$^{40}$, 853$^{47}$; **3**, 900$^{90}$; **4**, 507$^{151}$; **6**, 121$^{127,\text{-}128}$, 127$^{159}$, 129$^{166}$, 507$^{240}$, 515$^{240}$
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Apeloig, Y., **4**, 986$^{132}$, 987$^{132}$
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Apparao, S., **5**, 464$^{112}$, 466$^{112}$
Apparu, M., **4**, 789$^{31}$; **6**, 2$^{3}$, 25$^{3}$
Appel, R., **2**, 520$^{66}$; **4**, 21$^{69}$, 104$^{137}$, 222$^{168}$, 224$^{168}$; **5**, 829$^{23,26}$; **6**, 74$^{37}$, 172$^{12,28}$, 190$^{197,198}$, 196$^{198}$, 205$^{29,31}$, 525$^{385}$; **7**, 474$^{49}$, 476$^{49}$
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Appelman, E. H., **4**, 347$^{97}$
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Apple, D. C., **8**, 764$^{6}$
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Applegate, H. E., **6**, 644$^{93}$
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Barfknecht, C. F., **8**, 146[97]
Bargar, T. M., **3**, 492[73], 497[73]; **4**, 455[44,45], 457[45], 463[44,45], 464[45], 465[45], 466[44,45], 467[45], 469[45], 472[45], 476[44,45], 532[83], 543[83], 545[83]
Bargas, L. M., **7**, 228[96]
Barger, P. T., **8**, 673[26], 676[26]
Bargiotti, A., **6**, 984[55]
Bari, S. S., **5**, 96[105,116,119]
Barieux, J.-J., **8**, 705[10], 726[10]
Barili, P., **5**, 456[87]
Barili, P. L., **2**, 291[71]; **3**, 725[19], 734[9], 743[58]
Barillier, X., **5**, 829[22]
Barinelli, L. S., **4**, 695[4]
Barker, A. J., **6**, 1045[24]
Barker, J. M., **2**, 963[54]
Barker, M. W., **5**, 113[228,232], 117[277]
Barker, P. J., **8**, 818[39]
Barker, R., **2**, 456[42], 466[42], 467[42]
Barker, W., **2**, 159[128]
Barker, W. D., **3**, 903[126]
Barkley, L. B., **1**, 446[195]
Barkley, R. M., **3**, 4[22]
Barkovich, A. J., **5**, 1151[132,136]
Barl, M., **4**, 924[33]
Barlet, R., **4**, 1000[7]; **8**, 795[21]
Barlett, P. A., **2**, 555[143]; **4**, 377[104,104a], 378[104a], 381[104a]
Barlin, G. B., **7**, 768[202]
Barlos, K., **8**, 245[73]
Barlow, A. P., **8**, 557[382]
Barlow, L., **3**, 585[137], 587[148]
Barltrop, J. A., **5**, 165[85]; **7**, 884[182]; **8**, 143[58], 493[21], 526[25]
Barluenga, J., **1**, 361[32a,b], 782[234], 830[94]; **2**, 790[57], 980[21], 981[21]; **3**, 282[48], 788[50]; **4**, 290[196,200], 291[211,212,213,214,215,216,217,218,219,220], 292[224,225,228], 295[248,249,254], 302[338], 303[341], 311[446,453], 315[511,513], 347[93], 349[110], 351[93c,124], 354[93d,110], 405[251], 735[82], 741[82], 799[111]; **5**, 161[63,64], 410[42], 411[42], 433[136b], 480[178], 484[179], 848[141], 850[162]; **6**, 184[150], 494[135], 555[810,811,812], 757[134]; **7**, 93[54], 486[141,142], 490[176], 501[255], 505[285], 533[35,36], 534[35], 536[52-55], 632[60]; **8**, 13[72], 124[87,88], 851[132], 854[150], 856[176,177,178,179,180,183], 857[187,196,198]
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Barnela, S. B., **2**, 787[52], 789[55,56]
Barner, B. A., **1**, 263[41], 359[22], 383[22], 384[22]; **4**, 77[50], 206[45,47,49], 893[155]; **6**, 25[100], 842[78]; **7**, 300[54]
Barner, R., **5**, 834[50,53], 850[146], 877[5]; **8**, 205[159], 560[405]
Barnes, D. G., **3**, 331[200a]
Barnes, G. H., **8**, 764[3], 776[3]
Barnes, J. C., **7**, 440[39,39b]
Barnes, J. H., **8**, 135[48]
Barnes, J. R., **7**, 845[77]
Barnes, K. K., **7**, 854[55], 855[55]
Barnes, R. A., **2**, 740[58]; **7**, 16[159]; **8**, 568[467]
Barnes, R. P., **8**, 286[15]
Barnett, G. H., **2**, 780[9]
Barnett, J. E. G., **7**, 239[46]
Barnett, P. G., **2**, 782[22]
Barnette, W. E., **4**, 255[192], 260[192], 368[18], 369[18b,20,24], 370[31], 371[60], 372[31,60], 374[20], 397[31], 413[271a,b,272,273]; **5**, 386[135]; **6**, 540[583], 650[132], 1031[113]; **7**, 522[41], 523[41,46], 524[54]; **8**, 343[114], 847[99], 848[99], 849[99]
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Barnick, J. W. F. K., **2**, 801[36]; **5**, 986[38]
Barnier, J.-P., **3**, 727[32]; **5**, 910[89], 956[305]
Barnikow, G., **6**, 422[34], 429[34], 449[113], 453[113]
Barnum, C., **4**, 245[89]; **6**, 1030[107]; **7**, 131[83-85]; **8**, 850[119]
Barnum, C. S., **1**, 642[111], 644[111], 669[111,183], 670[183], 671[111,183], 699[183]
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Baron, W. J., **6**, 776[55]
Barone, A. D., **6**, 619[118]
Barone, G., **4**, 347[95]; **7**, 438[17-19], 445[17-19]
Baroni, A., **7**, 774[320]
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Barr, P. J., **3**, 219[109], 530[72], 534[72], 547[124]
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Barreiro, E., **4**, 229[212]; **8**, 881[69]
Barrero, A. F., **7**, 634[68]

Barret, R., **7**, 764$^{114}$

Barrett, A. G. M., **1**, 511$^{28}$, 569$^{253}$, 797$^{293}$; **2**, 321$^{15}$, 325$^{15}$, 332$^{57}$, 338$^{75}$, 635$^{50}$, 640$^{50}$, 645$^{81}$, 742$^{77}$, 784$^{39a}$, 968$^{78}$, 1059$^{74}$; **3**, 251$^{79}$, 254$^{79}$, 613$^{2}$, 615$^{2}$; **4**, 35$^{98f}$, 380$^{121}$, 384$^{142}$; **5**, 85$^{9}$, 116$^{269,270}$, 407$^{28}$, 1068$^{12,13}$, 1075$^{30}$; **6**, 107$^{24}$, 473$^{73}$, 687$^{380}$, 779$^{68}$, 783$^{86,87}$, 784$^{88-90}$, 961$^{68}$, 987$^{72}$, 996$^{107}$, 1017$^{37}$; **7**, 529$^{11}$; **8**, 84$^{15}$, 117$^{74}$, 243$^{47}$, 248$^{82}$, 363$^{2}$, 374$^{151}$, 505$^{83}$, 816$^{24}$, 817$^{29}$, 822$^{52}$, 940$^{100,108}$

Barrett, G. C., **1**, 820$^{12}$; **3**, 86$^{21,22}$, 104$^{21}$, 121$^{21,22}$; **4**, 316$^{535}$; **6**, 423$^{47}$, 424$^{55}$, 437$^{32}$, 450$^{118}$; **8**, 403$^{7}$

Barrett, J., **4**, 37$^{107}$

Barrett, J. H., **5**, 634$^{68,69}$, 687$^{62}$, 688$^{62}$; **7**, 507$^{306}$

Barrett, J. W., **8**, 328$^{9}$

Barrette, E.-P., **7**, 278$^{165}$, 279$^{165}$

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Barrière, J. C., **1**, 561$^{166}$

Barrio, J. R., **8**, 48$^{109}$, 66$^{109}$

Barrio, M. G., **1**, 858$^{62}$

Barrios, H., **1**, 544$^{35}$, 552$^{80}$

Barrish, J. C., **2**, 547$^{100}$, 548$^{100}$; **4**, 370$^{29}$, 390$^{171}$; **5**, 433$^{137b}$; **8**, 704$^{7}$, 713$^{7}$

Barron, C. A., **5**, 731$^{130b}$

Barron, H. E., **7**, 765$^{153}$

Barros, M. T., **7**, 298$^{36}$

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Barry, C. N., **6**, 24$^{97}$

Barry, J., **6**, 2$^{5}$, 18$^{5}$

Barry, J. E., **2**, 971$^{93}$

Barsoum, S., **8**, 435$^{71}$

Barstow, D. A., **8**, 206$^{172}$

Barstow, J. F., **4**, 370$^{25}$; **5**, 841$^{91}$, 877$^{7}$; **6**, 859$^{174}$

Barta, M. A., **6**, 182$^{139}$; **7**, 100$^{129}$, 104$^{129}$, 260$^{43}$, 779$^{421}$

Barta, T. E., **5**, 524$^{49}$, 539$^{49}$

Bartak, D. E., **4**, 453$^{27}$, 471$^{27}$, 872$^{37}$

Bartel, K., **6**, 295$^{250}$

Bartels, A. P., **8**, 114$^{58}$, 308$^{5,6}$, 309$^{5,6}$

Bartels, H. M., **4**, 729$^{61}$, 730$^{61}$, 765$^{61}$

Bartes, O., **7**, 235$^{1}$

Bartetzko, R., **3**, 614$^{6}$, 623$^{6}$, 627$^{6}$

Barth, G., **7**, 676$^{62}$; **8**, 353$^{154}$

Barth, J., **2**, 96$^{56}$; **6**, 554$^{783}$

Barth, M., **6**, 7$^{34}$

Barth, V., **5**, 829$^{23}$

Barthels, R., **6**, 639$^{53,54}$

Bartholomew, D., **1**, 751$^{92}$; **7**, 237$^{36}$

Bartkowiak, F., **8**, 535$^{166}$

Bartlett, N., **7**, 882$^{168}$

Bartlett, P. A., **1**, 49$^{10}$, 109$^{14}$, 286$^{9}$, 348$^{142}$, 608$^{38}$, 749$^{80}$, 766$^{154}$, 804$^{313}$, 805$^{313}$; **2**, 1$^{1}$, 123$^{200}$, 125$^{200}$, 193$^{64}$, 202$^{96}$, 280$^{24}$, 281$^{24}$, 555$^{142}$, 580$^{100}$, 649$^{106}$, 657$^{163}$, 904$^{50}$; **3**, 341$^{5}$, 365$^{5}$, 366$^{99}$, 374$^{5}$; **4**, 142$^{16}$, 311$^{442}$, 364$^{1,1m}$, 366$^{8}$, 367$^{15}$, 370$^{25,25a}$, 373$^{1m,78}$, 377$^{104}$, 378$^{104b,111}$, 380$^{120,120b,122,125}$, 381$^{8a,120b,122a,125a,b}$, 382$^{120b,134,134a}$, 383$^{15,134a,137}$, 384$^{15}$, 386$^{8b,125a,148a,151}$, 387$^{125a,148,148a}$, 390$^{104b,175c}$, 815$^{189}$; **5**, 308$^{95}$, 827$^{2}$, 829$^{2}$, 836$^{65}$, 837$^{68}$, 841$^{91}$, 855$^{187,192}$, 859$^{236}$, 877$^{7,8}$; **6**, 26$^{105-107}$, 855$^{148}$, 856$^{154}$, 859$^{174}$, 897$^{95}$, 938$^{126}$, 968$^{107}$, 998$^{120,121}$, 1021$^{50}$; **8**, 7$^{39}$, 541$^{207}$, 542$^{226}$, 853$^{143,147}$, 856$^{147}$, 857$^{143,147}$

Bartlett, P. D., **3**, 705$^{4}$, 725$^{18}$; **4**, 5$^{17}$, 868$^{11}$, 1089$^{133}$, 1099$^{176}$; **5**, 63$^{5,6}$, 64$^{32,51}$, 65$^{61}$, 69$^{5,6,105,106}$, 70$^{5,107-110}$, 71$^{5,122,143}$, 72$^{6}$, 74$^{5,208}$, 77$^{6}$, 211$^{67}$, 1188$^{15}$; **7**, 98$^{100}$, 480$^{102}$; **8**, 91$^{51}$

Bartlett, R. A., **1**, 11$^{57}$, 23$^{118}$

Bartlett, R. K., **6**, 961$^{70}$

Bartlett, R. S., **8**, 60$^{181}$, 66$^{181}$, 73$^{248}$, 74$^{248}$, 373$^{136}$

Bartlett, W. R., **3**, 362$^{89}$, 369$^{117}$, 371$^{114}$, 372$^{117}$; **5**, 828$^{7}$, 839$^{7}$, 882$^{13}$, 888$^{13}$, 892$^{13}$, 893$^{13}$

Bartley, W. J., **8**, 140$^{14}$, 248$^{89}$

Bartmann, D., **4**, 386$^{147}$

Bartmann, W., **1**, 78$^{12}$; **2**, 240$^{5}$, 369$^{253}$, 370$^{253}$, 371$^{253}$, 372$^{253}$, 455$^{1}$; **4**, 91$^{89}$, 792$^{66}$, 876$^{64}$; **5**, 461$^{95}$, 464$^{95}$, 468$^{95}$, 645$^{1}$, 648$^{1j}$, 651$^{1}$; **6**, 33$^{2}$, 34$^{2}$, 40$^{2}$, 50$^{2}$, 51$^{2}$, 53$^{2}$, 54$^{2}$, 57$^{2}$, 538$^{569}$, 655$^{166}$, 746$^{93}$, 765$^{17}$, 767$^{25}$; **7**, 694$^{32}$, 695$^{35}$; **8**, 5$^{25}$

Bartmess, J. E., **1**, 632$^{66}$; **5**, 788$^{15}$

Bartnik, R., **1**, 387$^{132}$, 836$^{142}$; **4**, 1086$^{117}$

Bartocha, B., **1**, 214$^{25}$

Bartók, M., **1**, 819$^{3}$; **3**, 726$^{23}$; **6**, 2$^{2,3}$, 23$^{2}$, 25$^{3,99}$; **7**, 358$^{6}$, 372$^{6}$; **8**, 418$^{5}$, 420$^{5}$, 423$^{5}$, 439$^{5}$, 441$^{5}$, 442$^{5}$, 883$^{89,90}$

Bartok, W., **7**, 759$^{5}$

Bartoletti, I., **3**, 1028$^{47}$

Bartoli, D., **1**, 670$^{187}$, 678$^{187}$; **4**, 437$^{148}$, 438$^{148}$; **7**, 340$^{45}$, 770$^{256b}$, 771$^{256}$, 773$^{306}$, 779$^{427}$

Bartoli, G., **1**, 569$^{262}$; **4**, 85$^{78a}$, 86$^{78b,c,e,79a,b}$, 424$^{11}$, 426$^{37}$, 428$^{11,77-79}$, 429$^{80-82}$; **6**, 115$^{83}$; **7**, 331$^{16}$

Bartoli, J. F., **7**, 108$^{176}$, 383$^{109}$

Bartolini, G., **4**, 98$^{114}$, 113$^{114}$

Bartolini, O., **7**, 762$^{84}$, 777$^{380}$

Bartolotti, L. J., **1**, 476$^{127}$, 477$^{129}$; **3**, 66$^{16}$, 67$^{16}$, 74$^{16,42}$, 75$^{42}$, 77$^{42}$; **7**, 227$^{78}$, 230$^{78}$

Barton, D. H. R., **1**, 2$^{6}$, 174$^{8}$, 175$^{8}$, 391$^{150}$, 489$^{18}$, 499$^{18}$, 542$^{5}$, 543$^{5}$, 544$^{5}$, 546$^{5}$, 561$^{166}$, 580$^{1}$, 630$^{10}$, 698$^{242}$, 699$^{242}$, 820$^{7,12}$, 822$^{7}$, 833$^{117}$; **2**, 240$^{12}$, 321$^{11}$, 323$^{32}$, 329$^{11}$, 784$^{39a}$, 791$^{60}$, 866$^{4}$; **3**, 86$^{21,22,32,33,37,38,48,62}$, 104$^{21}$, 121$^{21,22}$, 147$^{32,33}$, 154$^{32}$, 158$^{37,38}$, 159$^{37}$, 163$^{38}$,164$^{37}$, 173$^{37,38,62}$, 386$^{66}$, 419$^{35}$, 422$^{68}$, 505$^{158,159}$, 613$^{2}$, 615$^{2}$, 660$^{8}$, 664$^{30}$, 681$^{97}$, 689$^{123}$, 733$^{2}$, 780$^{10}$, 831$^{63}$; **4**, 3$^{8}$, 6$^{8}$, 24$^{72,72c}$, 27$^{83}$, 99$^{118d}$, 259$^{276}$, 316$^{535}$, 344$^{77}$, 347$^{104}$, 483$^{4}$, 484$^{4}$, 495$^{4}$, 605$^{293}$, 646$^{293}$, 674$^{35}$, 688$^{35}$, 725$^{43}$, 747$^{149,151,152,153}$, 748$^{155,156,157,158,159}$, 753$^{159}$, 765$^{223,226}$, 768$^{239}$, 790$^{35}$, 800$^{120}$, 820$^{221}$, 824$^{234}$, 953$^{8}$, 968$^{57}$, 987$^{133}$, 1002$^{51}$, 1004$^{76,77}$, 1021$^{76,77}$, 1093$^{149}$; **5**, 223$^{77}$; **6**, 2$^{1}$, 28$^{1}$, 70$^{20}$, 104$^{1,9}$, 111$^{64}$, 116$^{90}$, 133$^{5}$, 134$^{11}$, 171$^{4}$, 177$^{4}$, 198$^{4}$, 211$^{78}$, 225$^{5}$, 226$^{5}$, 258$^{5}$, 293$^{229}$, 419$^{1}$, 421$^{1}$, 436$^{15}$, 437$^{15}$, 442$^{87}$, 447$^{104}$, 448$^{15}$, 450$^{15}$, 451$^{104}$, 453$^{15}$, 455$^{15}$, 473$^{72,73}$, 474$^{72,84-86}$, 475$^{72,93}$, 659$^{195}$, 687$^{380}$, 690$^{394,399}$, 691$^{399}$, 692$^{399}$, 837$^{59}$, 938$^{130}$, 942$^{130}$, 954$^{14}$, 980$^{45}$, 981$^{47}$, 987$^{72}$, 1017$^{37,38}$, 1024$^{38}$; **7**, 13$^{115-117,119}$, 14$^{142}$, 15$^{145}$, 27$^{62}$, 40$^{11}$, 41$^{18,22}$, 84$^{1}$, 85$^{1}$, 90$^{32}$, 92$^{41,41a,49}$, 94$^{41}$, 108$^{1,180}$, 110$^{187,188}$, 123$^{35}$, 129$^{72}$, 132$^{72,91,92,95,97-100}$, 133$^{72,92}$, 134$^{92}$, 144$^{35}$, 146$^{100}$, 159$^{45}$, 170$^{122}$, 171$^{122}$, 223$^{42}$, 227$^{87}$, 231$^{141}$, 244$^{69,70}$, 299$^{50,51}$, 307$^{16}$, 310$^{16}$, 318$^{16}$, 319$^{16}$, 322$^{16}$, 329$^{4}$, 343$^{4}$, 345$^{1}$, 356$^{48}$, 470$^{2}$, 529$^{11}$, 594$^{4}$, 598$^{4}$, 671$^{10}$, 673$^{10}$, 687$^{10}$, 704$^{12-14}$, 705$^{14}$, 719$^{6,7}$, 720$^{6}$, 721$^{7}$, 722$^{20}$, 723$^{24}$, 724$^{24}$, 725$^{7,31,33}$, 726$^{6,7,20,35-37}$, 727$^{38}$, 728$^{7,41,42}$, 730$^{45-47,49,51}$, 731$^{45,52,53,55}$, 732$^{59}$, 741$^{49}$, 747$^{94,106}$, 761$^{59}$, 776$^{59,357,362}$ ; **8**, 26$^{12}$, 27$^{12}$, 108$^{3}$, 110$^{3}$, 116$^{3}$, 117$^{74}$, 121$^{77}$, 141$^{37}$, 243$^{47}$, 247$^{81}$, 279, 301$^{93}$, 330$^{45,46}$, 340$^{45}$, 342$^{46}$, 370$^{91}$, 392$^{95,109}$, 393$^{113}$, 394$^{114}$, 403$^{2,6-8}$, 404$^{2}$, 505$^{83}$, 525$^{14}$, 526$^{14}$, 565$^{448}$, 699$^{148}$, 704$^{4}$, 705$^{4}$, 706$^{4}$, 707$^{4}$, 710$^{4}$, 715$^{4}$, 716$^{4}$, 717$^{4}$, 722$^{4}$, 724$^{4}$, 725$^{4}$, 726$^{4}$, 728$^{4}$, 794$^{3}$, 796$^{28}$, 816$^{24}$, 818$^{35,36,40}$, 820$^{35,47}$, 821$^{50,51}$, 822$^{52}$, 823$^{35,55}$, 825$^{68}$, 830$^{89}$,

831[89-91], 836[9], 837[13a], 839[13a], 840[13a], 847[9], 848[9,105], 880[56], 935[63,69], 936[70], 937[80,84,85], 984[2]
Barton, D. L., **6**, 960[58]
Barton, F. E., **8**, 795[25]
Barton, H. D., **6**, 65[1]
Barton, J. C., **1**, 107[6], 110[6]; **3**, 223[160]
Barton, T. J., **5**, 65[73], 199[27], 587[206,208], 588[208]
Bartos, J., **2**, 354[106,107]
Bartra, M., **8**, 385[41]
Bartroli, J., **1**, 400[11]; **2**, 25[99], 250[38], 251[38,39], 260[38], 274[38], 436[67]; **7**, 300[53]; **8**, 720[136]
Bartrop, J., **5**, 153[24]
Bartsch, R. A., **6**, 220[126], 953[7], 954[19], 955[24], 959[32]; **7**, 543[13]
Bartulin, J., **5**, 478[162]
Bartz, W., **3**, 909[152]
Bartz, W. J., **6**, 535[529]
Barua, A. K., **8**, 333[56]
Barua, N. C., **3**, 380[10]; **6**, 987[70]
Baruah, J. N., **8**, 891[148]
Baruah, P. D., **6**, 539[578]
Baruah, R. N., **8**, 891[148]
Barylett, P. A., **6**, 22[84]
Baryshnikova, T. K., **7**, 596[40]
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Basato, M., **2**, 369[245]
Basavaiah, D., **3**, 795[83,84]; **4**, 34[97], 35[97]; **7**, 596[36]; **8**, 715[85,85a], 716[85], 718[85a], 719[120]
Bascetta, E., **4**, 390[173a]; **8**, 855[158]
Basche, R. W., **4**, 170[20]
Basendregt, T. J., **8**, 144[70]
Basha, A., **1**, 92[68], 93[68], 376[94], 385[116,117,120], 386[120], 400[10]; **2**, 746[112]; **8**, 27[32], 66[32], 249[92], 301[94]
Basha, F. Z., **4**, 10[34], 113[164]; **5**, 406[23,23b]; **6**, 83[82], 814[88]; **8**, 34[62], 66[62]
Bashe, R. W., **1**, 431[134]; **3**, 248[55], 251[55], 269[55], 419[47], 494[87], 502[87]
Bashe, R. W., II, **7**, 123[33]
Bashiardes, G., **8**, 935[69], 937[84,85]
Bashir-Hashemi, A., **4**, 161[87]; **5**, 383[125]
Bashkin, J., **8**, 459[239]
Basile, T., **2**, 925[111], 926[111]; **5**, 102[174]
Baskakov, Yu. A., **2**, 854[236]
Baskar, A. J., **1**, 300[69]
Baskaran, S., **7**, 266[106], 267[106], 276[106]
Basok, S. S., **6**, 94[139]
Bass, J. D., **5**, 124[6], 125[6], 128[6]
Bass, L., **2**, 88[29]
Bass, L. S., **1**, 889[142], 890[142]; **7**, 441[42]
Bass, R. G., **4**, 48[138]
Bassani, A., **4**, 426[63]
Bassedas, M., **1**, 543[24,26]
Basselier, J.-J., **2**, 289[70], 291[70], 917[88]
Basset, J.-M., **5**, 1115[1], 1116[1,9], 1118[9]; **8**, 445[53]
Bassetti, M., **4**, 300[306]
Bassi, I. W., **1**, 303[77]
Bassignani, L., **7**, 439[25]
Bassindale, A. R., **1**, 580[2], 581[2], 582[2], 610[2a], 611[2a], 616[2a], 618[58], 621[67], 784[239,240], 815[239]; **2**, 601[35]; **3**, 419[31]
Bassler, G. C., **8**, 754[83]
Bassner, S. L., **2**, 127[236]
Basso-Bert, M., **8**, 447[122], 457[122]
Bassova, G. I., **8**, 318[63], 486[61]
Bast, H., **7**, 92[46], 154[14]
Bast, K., **4**, 1079[58]
Bast, P., **1**, 2[10]
Bastiaansen, L. A. M., **8**, 94[81], 95[82]
Bastian, J.-M., **2**, 765[71]
Bastiani, B., **1**, 34[167], 70[63], 141[22]
Bastide, J., **4**, 1073[26]; **5**, 247[26]
Bastos, C., **7**, 443[51b]; **8**, 459[228]
Bastos, H., **1**, 837[154]
Basu, A., **8**, 446[73]
Basu, B., **1**, 534[143]; **8**, 505[80]
Basu, N. K., **1**, 174[8], 175[8]; **7**, 41[22]; **8**, 796[28]
Basu, P. K., **5**, 452[55], 453[55]
Basu, S. K., **7**, 71[95]
Basyouni, M. N., **4**, 50[142]
Batchelor, M. J., **5**, 531[74]
Batcho, A. D., **2**, 530[23], 547[100], 548[100]; **4**, 390[171]; **5**, 4[39], 5[39,42,44], 8[44], 256[58], 257[58b]; **6**, 960[56]; **7**, 268[122], 564[92], 567[92]; **8**, 368[71]
Bate, N. J., **5**, 1125[54]
Bateman, L., **7**, 762[73], 763[85], 766[85]
Bates, D. J., **4**, 48[137]
Bates, G., **1**, 95[72]
Bates, G. S., **4**, 113[173]; **6**, 134[25], 438[42,57], 440[76], 463[27]; **8**, 549[327], 681[78], 683[78], 689[78], 693[78], 696[122], 801[70,71], 813[11], 938[89]
Bates, H. A., **2**, 1012[14]; **6**, 736[30]; **7**, 208[85]; **8**, 604[6], 639[18]
Bates, R. B., **4**, 495[86]
Bateson, J. H., **5**, 105[194]
Bath, S. S., **8**, 964[50]
Bather, P. A., **6**, 734[15], 923[57]
Batis, F., **7**, 43[43]
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Batra, R., **7**, 49[65]
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Batres, E., **7**, 92[42], 93[42]; **8**, 566[450]
Batroff, V., **3**, 623[35]
Bats, H., **6**, 563[895]
Bats, J. W., **2**, 547[113], 551[113]; **3**, 56[285]; **4**, 229[235,236], 1055[138]; **8**, 545[285]
Batsanov, A. S., **4**, 218[147]
Batt, D. G., **4**, 373[74]; **5**, 335[49]; **8**, 355[181], 929[32]
Batta, A. K., **3**, 644[149]
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Battegay, M., **6**, 423[43]
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Battioni, J.-P., **4**, 240[45]
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Battista, R. A., **4**, 573[9], 614[378]
Battiste, M., **3**, 896[67]
Battiste, M. A., **1**, 789[262b], 790[262]; **4**, 587[48,49]; **5**, 531[73], 947[267], 948[267,271]
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Batu, G., **2**, 332[61]; **3**, 219[112]
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Baudisch, O., **3**, 890[35]
Baudouy, R., **1**, 853[50], 876[50]; **3**, 256[113]; **5**, 772[162], 774[171], 780[162]; **7**, 298[34]; **8**, 945[127]
Baudrowski, E., **4**, 289[192]
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Bauer, K., **3**, 828[44]
Bauer, L., **6**, 119[117], 795[15], 798[15], 821[15], 822[118]
Bauer, M., **1**, 846[12], 851[12], 852[12]
Bauer, P., **3**, 723[10]; **8**, 552[357,358]
Bauer, P. E., **8**, 333[57], 345[127]
Bauer, T., **1**, 54[19], 109[14], 183[57], 185[57], 339[84]; **2**, 31[116], 671[51], 694[77], 995[43]; **5**, 432[124], 433[139,139f], 434[139i]; **7**, 397[29], 713[73]
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Bauer, W., **1**, 19[103], 20[107], 23[123-125], 32[156], 34[170], 35[172]; **2**, 100[4], 508[30]; **4**, 872[40]; **6**, 419[7], 420[7], 423[7], 437[33], 440[33], 441[33], 443[33], 444[33], 445[33], 446[33], 519[338]
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Baukov, Yu. I., **1**, 608[39]; **2**, 597[96], 607[76], 609[76,79], 610[96], 616[135], 726[122]; **8**, 547[315], 548[315]
Bauld, N. L., **3**, 423[79], 649[202], 650[202c], 652[202c]; **5**, 63[11], 453[65], 520[39], 522[43], 704[20,22], 1020[68,69], 1023[69,78]; **7**, 860[74], 879[148,149], 880[148,149,154], 882[166]; **8**, 564[446]
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Baum, G., **1**, 18[94], 37[242]
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Baum, M., **4**, 379[116], 380[116c]
Baum, T., **5**, 196[12]
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Baumeister, U., **6**, 190[198], 196[198]
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Baumgarten, R. J., **3**, 567[37], 606[37], 857[91]; **6**, 1042[6]; **7**, 229[108]; **8**, 827[71]
Baumgartner, M. T., **3**, 505[156]; **4**, 460[98], 463[109], 470[137], 471[109], 477[98]
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Baures, P. W., **1**, 41[195]
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Bauta, W. E., **5**, 1070[20], 1071[20], 1072[20], 1074[20], 1089[84], 1098[117], 1099[117], 1100[117], 1101[117], 1110[20], 1111[20], 1112[117]
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Baxter, A. J. G., **5**, 105[194], 403[9]
Baxter, E. W., **4**, 1040[73], 1043[73]; **5**, 829[21]; **6**, 122[135]
Baxter, G. J., **2**, 355[125]; **5**, 732[133,133b]
Baxter, S. L., **8**, 838[19,19b]
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Bayard, P., **5**, 416[56], 480[168,169], 483[169]
Baydar, A. E., **5**, 478[163]
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Bayer, E., **2**, 1099[110]; **6**, 670[273]
Bayer, H. O., **4**, 1097[166]; **8**, 314[41], 315[41], 814[15]
Bayer, J., **3**, 835[80]
Bayer, M., **6**, 692[408]
Bayer, O., **6**, 233[44]
Bayer, R., **6**, 535[535], 538[535]
Bayer, R. P., **8**, 364[13]
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Bayerlein, F., **3**, 814[70]; **6**, 911[18], 912[18]
Bayet, P., **1**, 630[40], 631[40], 648[132], 649[40], 651[132], 652[132], 655[132], 656[40], 659[40], 672[40,132], 673[132], 675[132], 679[132], 684[132], 708[40], 709[40], 710[40]; **3**, 87[66,116]
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Bayless, J., **1**, 377[97]; **6**, 727[206]; **8**, 943[120]
Bayless, P. L., **2**, 283[43], 296[43]
Bayley, H., **7**, 21[18]; **8**, 384[39]
Baylis, A. B., **4**, 34[97], 35[97]
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Bayner, C. M., **7**, 451[24]
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Baynham, M. K., **3**, 380[13]
Bayod, M., **4**, 311[453]; **5**, 848[141], 850[162]; **8**, 857[196]
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Bayomi, S. M., **4**, 350[116,118]
Bayón, A. M., **1**, 361[32a,b]; **2**, 980[21], 981[21]; **4**, 290[196], 399[224]; **8**, 856[180]
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Baysdon, S. L., **5**, 1202[56]
Bažant, V., **8**, 907[72], 918[72]
Bazant, V., **8**, 544[267]
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Baze, M. E., **3**, 1050[18], 1060[18]
Bazhulina, V. I., **3**, 644[140,141]
Beaber, N. J., **6**, 149[92]
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Beal, C., **5**, 939[223], 951[223], 962[223], 964[223]
Beal, D. A., **7**, 235[3]
Beal, P. F., **3**, 888[17], 891[39], 892[39], 898[39]
Beal, R. B., **1**, 885[132]; **2**, 547[105], 550[105]; **5**, 796[56], 835[61], 1029[92]
Beale, J. M., Jr., **7**, 58[53a], 62[53,53a], 63[53a,58]; **8**, 192[99]
Beale, M. H., **3**, 222[140]; **8**, 537[183]
Beam, C. F., **2**, 190[55,56], 512[46], 522[72], 523[73,74]
Beamer, R. L., **8**, 149[120]
Beames, D. J., **1**, 430[128]; **4**, 1040[82], 1043[82]; **8**, 503[68]
Bean, F., **7**, 602[94]

Beanland, J., **5**, 180[147]
Beard, C. C., **8**, 201[145]
Beard, C. D., **7**, 747[98]
Beard, L., **4**, 746[146]
Beard, R. D., **3**, 159[467], 166[467]
Beard, R. L., **4**, 372[62]
Beard, R. M., **3**, 877[86]
Beard, W. Q., **3**, 914[12]
Bearse, A. E., **4**, 307[394], 312[456], 313[456]
Beasley, G. H., **2**, 477[12]; **3**, 431[95,96]; **5**, 856[196]
Beattie, T. R., **2**, 212[118]; **8**, 384[25]
Beatty, K. M., **4**, 315[519]
Beau, J.-M., **3**, 174[525], 196[26], 231[253]; **4**, 339[45], 792[62]; **6**, 60[147], 632[4], 978[24]; **8**, 849[111]
Beaucage, S. L., **6**, 618[108], 650[131]
Beaucaire, V. D., **2**, 348[55]
Beauchamp, J. L., **1**, 287[16]; **4**, 980[109]
Beauchamp, P. D., **5**, 805[100]
Beaucourt, J.-P., **3**, 416[17], 417[17], 462[152], 513[207]; **6**, 690[401], 692[401]; **8**, 679[66], 680[66], 681[66], 683[66], 694[66]
Beaudegnies, R., **5**, 416[56], 480[168]
Beaudoin, S., **1**, 773[202]
Beaujean, M., **1**, 700[245], 705[245], 709[245]; **4**, 758[190]
Beaulieu, F., **8**, 136[51]
Beaulieu, N., **6**, 937[117], 939[117], 940[117]
Beaulieu, P., **1**, 419[79]; **7**, 153[7]
Beaulieu, P. L., **3**, 213[44]; **4**, 183[80], 340[54], 342[63], 784[17], 789[30], 791[30], 815[190]; **7**, 520[28], 521[36]
Beaumont, A. G., **3**, 564[15]
Beaupere, D., **8**, 552[357,358]
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Bebb, R. L., **1**, 630[39], 631[39], 701[39], 702[39]
Bebernitz, G. E., **3**, 25[152]
Bebernitz, G. R., **2**, 189[46], 209[46]
Bebikh, G. F., **3**, 864[21]
Becalski, A., **4**, 1039[62]
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Becher, J., **2**, 150[97]; **5**, 531[74], 532[74a]
Becherer, J., **5**, 65[63]
Bechgaard, K., **7**, 801[39]
Bechstein, U., **2**, 779[5], 782[25]
Bechtolsheimer, H.-H., **6**, 659[193]
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Beck, A. K., **1**, 34[167], 166[113], 314[128], 323[128], 341[98], 631[48,49], 636[49], 656[49], 658[48,49], 659[48,49], 672[48,49], 708[48,49], 710[48,49], 721[49]; **2**, 323[22,26], 332[55], 335[26], 336[26], 830[138]; **3**, 87[68,69], 89[68], 128[322], 130[322], 134[322,338], 135[338], 137[338], 144[384], 145[384], 147[384]; **5**, 79[291]; **6**, 147[84]; **7**, 774[316]
Beck, A. L., **7**, 32[91]
Beck, F., **3**, 634[25b,28], 635[25b,43], 639[25b], 640[97], 655[43], 656[43]; **7**, 248[108]
Beck, G., **6**, 538[569], 765[17]; **7**, 694[32]
Beck, H., **8**, 904[59], 907[59], 909[59]
Beck, J. F., **2**, 456[29]; **8**, 183[1], 185[1], 187[1a], 196[1a], 199[1a], 201[1a], 204[1], 207[1a], 209[1a]
Beck, J. R., **4**, 425[28], 441[172,174,175,176,178]
Beck, K. R., **2**, 5[20], 6[20], 21[20]
Beck, W., **6**, 554[772,777]
Becker, D., **4**, 45[128]; **5**, 139[85], 142[93], 143[85]
Becker, D. A., **1**, 604[33], 605[34]; **2**, 85[17]; **5**, 277[17]
Becker, D. P., **5**, 1060[57]
Becker, E. I., **3**, 262[159], 264[159]; **7**, 92[40], 94[55]; **8**, 74[250], 850[120], 902[43], 907[43], 908[43]
Becker, H., **3**, 691[135], 829[54]
Becker, H.-D., **5**, 229[117,118]; **7**, 135[106], 835[85], 877[131]
Becker, H. G. O., **2**, 896[11,12]
Becker, J., **6**, 175[77], 1058[58], 1067[101]
Becker, J. L., **7**, 801[37]
Becker, J. Y., **6**, 282[153,155,156]; **7**, 107[168], 799[25], 800[32], 801[41]
Becker, K. B., **1**, 755[115], 812[115], 813[115]; **3**, 497[102], 873[65], 874[65]; **4**, 252[159], 273[44]; **5**, 65[74]; **6**, 1036[141], 1041[1], 1042[1]; **8**, 537[185]
Becker, K. M., **7**, 724[30]
Becker, M., **3**, 348[31], 358[31]
Becker, P., **2**, 1016[25]
Becker, P. D., **1**, 835[132]; **3**, 88[131], 90[131], 105[131]
Becker, P. N., **2**, 127[233], 314[39]; **7**, 484[136]
Becker, R. S., **5**, 729[125], 741[156]
Becker, S., **4**, 155[74]; **8**, 840[38]
Becker, S. B., **8**, 754[88]
Becker, W., **6**, 476[96]
Becker, W. G., **7**, 854[61]
Becker, Y., **1**, 442[178]; **4**, 926[40], 930[50]; **8**, 395[130]
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Beckert, W. F., **3**, 319[130]
Beckett, A. H., **6**, 116[88]; **8**, 64[202], 66[202]
Beckett, B. A., **3**, 20[105]; **8**, 331[30]
Beckh, H. J., **5**, 635[86]
Beckham, L. J., **7**, 15[154]
Beckham, M. E., **5**, 676[3]
Beckhaus, H., **1**, 846[19b], 847[19b], 850[19b]
Beckhaus, H.-D., **3**, 382[36]; **4**, 717[12], 758[191]
Becking, L., **3**, 647[197,198], 649[200]; **4**, 805[142]; **7**, 806[72]
Beckley, R. S., **7**, 4[16]; **8**, 857[202]
Beckman, J. C., **2**, 356[129]
Beckmann, E., **6**, 763[1]; **7**, 689[1]
Beckmann, P., **8**, 918[120]
Beckmann, W., **3**, 628[47]
Beckwith, A. L. J., **1**, 269[59], 699[255], 894[155]; **3**, 107[227], 600[212]; **4**, 453[37], 736[88], 753[165], 780[2,3], 781[6], 784[13,14], 785[2,22], 786[6,24], 787[6,27], 790[3], 795[83], 796[91,100], 797[102], 805[139,140,141], 812[183], 815[191,197], 816[197,200], 820[219], 822[224], 827[6]; **5**, 4[32], 133[52], 918[126]; **6**, 261[13], 763[4], 802[42], 803[42]; **7**, 40[3], 96[82], 689[6], 842[29,30,32], 883[176]; **8**, 807[120], 818[39], 903[52], 906[52], 907[52], 908[52], 909[52]
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Beddoes, R. L., **3**, 810[43]; **6**, 523[347]
Bedell, A., **5**, 639[122]
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Bedenbaugh, J. H., **8**, 236[6], 249[91], 284[2], 285[2], 607[30]
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Bederke, K., **5**, 422[88], 423[88]
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Bedoukian, R., **5**, 17[117]
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Beereboom, J. J., **3**, $707^{11}$; **5**, $595^{15}$, $596^{15}$; **6**, $265^{38}$
Beermann, C., **1**, $140^{8}$, $141^{15}$
Beers, S., **3**, $197^{33}$
Beerstecher, W., **8**, $528^{71}$, $971^{108}$
Beetz, I., **3**, $1028^{48}$
Beetz, T., **6**, $38^{37}$, $658^{186b}$
Beger, J., **4**, $294^{243}$; **6**, $283^{168}$, $287^{183}$, $288^{186,187,188,189,190}$, $526^{400,401}$; **7**, $490^{179}$
Begland, R. W., **5**, $486^{196}$, $687^{63}$, $688^{63}$
Begley, M. J., **2**, $494^{57}$, $534^{34}$, $535^{34}$; **3**, $407^{147}$, $586^{153}$, $604^{153}$, $610^{153}$; **4**, $76^{47}$; **5**, $136^{67}$, $181^{151}$, $432^{129}$, $841^{87}$; **6**, $859^{171}$, $1062^{76}$, $1063^{81}$; **7**, $338^{42}$
Begley, T., **5**, $41^{29}$
Begley, W. J., **3**, $623^{32}$, $677^{84}$; **4**, $373^{67}$
Bégué, J. P., **1**, $530^{128}$; **2**, $546^{91}$; **3**, $842^{16}$
Behaghel, O., **7**, $769^{234}$, $770^{234}$
Behan, J. M., **8**, $887^{115}$
Behforouz, M., **2**, $121^{189}$; **4**, $185^{86}$; **7**, $355^{42}$
Behling, J. R., **3**, $209^{17}$, $216^{68}$, $224^{168}$; **4**, $175^{43}$; **6**, $831^{9}$
Behnam, E., **6**, $481^{121}$
Behner, O., **8**, $649^{62}$
Behnke, M., **1**, $114^{35,36}$; **2**, $120^{177}$; **4**, $98^{114,114b}$, $113^{114}$
Behrens, C. H., **3**, $225^{185}$, $264^{181}$; **6**, $2^{3}$, $25^{3}$, $88^{105}$, $89^{105,112,113}$, $253^{157,159}$; **7**, $390^{10}$, $403^{10,65}$, $406^{77}$, $409^{77}$, $414^{77}$, $415^{77}$, $421^{77}$, $423^{77}$
Behrens, O. K., **6**, $644^{90}$
Behrens, U., **1**, $21^{110}$
Behrman, E. J., **7**, $863^{85}$
Behrooz, M., **2**, $109^{70}$; **3**, $164^{478}$, $167^{478}$, $168^{478}$; **8**, $746^{62}$, $750^{62}$
Beier, B. F., **8**, $458^{223,223c}$
Beifuss, U., **2**, $345^{33}$, $350^{71}$, $354^{71,103}$, $357^{71,103}$, $369^{255a}$, $372^{271}$, $373^{71,103,272,273,274}$; **5**, $14^{99}$, $17^{118\text{-}121}$, $466^{120}$
Beigelman, L. N., **6**, $618^{114}$
Beijer, B., **6**, $604^{29}$
Beilefeld, M. A., **7**, $720^{10}$
Beiler, F., **1**, $34^{228}$
Beilinson, E. Yu., **8**, $623^{147}$, $624^{147}$
Beirich, C., **1**, $202^{102}$, $203^{102}$, $234^{26}$, $331^{47}$
Beiser, W., **6**, $566^{922}$
Beisler, J. A., **1**, $856^{54}$
Beissner, C., **5**, $1148^{123}$
Beissner, G., **3**, $482^{3}$
Beisswenger, H., **8**, $873^{19}$
Beisswenger, T., **4**, $331^{7}$; **6**, $142^{65}$
Beke, D., **1**, $370^{70}$, $371^{70}$; **8**, $957^{14}$
Bekhazi, M., **4**, $1089^{132}$
Bekker, R. A., **2**, $726^{122}$
Belan, A., **8**, $187^{32}$, $188^{32}$
Belanger, A., **2**, $169^{167}$; **4**, $1040^{83}$, $1043^{83}$
Belanger, D., **5**, $578^{156}$
Bélanger, G., **3**, $635^{38}$
Bélanger, J., **2**, $662^{20}$, $663^{20}$, $664^{20}$; **5**, $432^{130}$
Bélanger, P. C., **7**, $693^{26}$; **8**, $315^{52}$, $969^{94}$
Belaud, C., **1**, $214^{21}$; **2**, $980^{22}$, $981^{22}$
Belavin, I. Y., **2**, $597^{96}$, $607^{76}$, $609^{76,79}$, $610^{96}$
Beldid, B., **6**, $514^{306}$, $543^{306}$
Belen'kii, L. I., **3**, $615^{7}$; **4**, $468^{132}$, $469^{132}$; **8**, $608^{40}$, $610^{56,60}$, $630^{56}$
Beletskaya, I. P., **1**, $3^{23}$, $276^{78}$, $277^{78}$, $437^{157}$, $438^{159}$, $441^{175}$, $445^{175}$; **3**, $219^{111}$, $436^{14}$, $503^{152}$, $524^{29}$, $529^{29,48}$, $530^{73}$, $531^{88}$, $534^{73}$, $537^{88}$; **4**, $423^{8}$, $426^{8}$, $444^{8}$, $452^{7}$, $519^{12}$, $610^{340,341}$; **8**, $2^{9}$
Belew, J. S., **7**, $54^{3}$, $56^{3}$, $66^{3}$, $77^{3}$, $78^{3}$, $542^{6}$, $543^{6}$
Belfoure, E. L., **7**, $738^{20}$
Belgaonkar, V. H., **2**, $792^{66}$
Belik, M. Yu., **3**, $306^{77}$
Belikov, V. M., **4**, $218^{147,148}$
Belikova, N. A., **8**, $124^{92}$, $125^{92}$
Belikova, Z. V., **8**, $775^{77}$
Belin, B., **6**, $85^{87}$
Belinka, B. A., Jr., **1**, $570^{264}$; **8**, $384^{38}$, $385^{48}$
Bell, A., **3**, $201^{76}$, $721^{4}$; **5**, $71^{153}$; **6**, $960^{49}$
Bell, A. J., **6**, $819^{109}$
Bell, A. P., **8**, $447^{119a,b}$, $675^{36,37}$, $679^{37}$, $691^{36}$
Bell, A. S., **3**, $510^{184}$
Bell, C. L., **6**, $822^{118}$
Bell, E. V., **7**, $763^{98}$
Bell, F., **2**, $367^{225}$; **3**, $826^{40}$
Bell, F. A., **5**, $63^{9}$; **7**, $879^{146}$
Bell, H. C., **3**, $505^{160}$; **7**, $649^{45}$
Bell, H. M., **8**, $214^{51}$, $709^{43}$, $812^{3}$, $908^{78}$, $909^{78}$, $968^{89}$
Bell, K. H., **2**, $809^{58}$, $811^{58}$; **3**, $806^{17}$; **8**, $60^{185}$, $66^{185}$, $314^{27}$
Bell, K. L., **1**, $593^{25}$, $595^{25}$; **2**, $1030^{83,84}$; **8**, $537^{189}$, $755^{131}$, $758^{131}$
Bell, L. A., **4**, $85^{77c}$
Bell, L. T., **2**, $1049^{19}$; **8**, $542^{221}$
Bell, N. A., **1**, $2^{8}$, $21^{111}$; **8**, $754^{101}$
Bell, R., **6**, $1024^{77}$
Bell, R. A., **8**, $244^{66}$
Bell, R. P., **7**, $709^{46}$
Bell, S. H., **2**, $606^{69}$
Bell, S. I., **5**, $423^{91}$, $424^{92}$
Bell, T. W., **1**, $343^{110}$; **3**, $219^{106}$, $224^{165}$, $512^{201}$; **6**, $743^{71}$
Bell, V. L., **2**, $149^{86}$, $355^{124}$
Bellamy, A., **4**, $239^{35}$
Bellamy, A. J., **4**, $30^{87}$; **8**, $114^{54}$
Bellamy, F., **4**, $390^{174}$; **5**, $948^{291}$
Bellamy, F. D., **8**, $371^{112}$
Bellamy, L. J., **6**, $724^{151}$, $727^{201}$
Bellard, S., **1**, $2^{3}$, $37^{3}$
Bellasoued, M., **1**, $214^{22}$, $218^{22}$, $220^{22}$; **2**, $283^{49}$, $286^{65}$, $287^{65}$, $486^{38}$, $614^{117}$, $634^{37}$, $640^{37}$; **4**, $95^{102g}$, $880^{91}$, $883^{91,101}$, $884^{101,106}$
Belleau, B., **1**, $123^{78}$; **2**, $213^{126}$, $554^{133}$, $1056^{67}$; **4**, $398^{216}$, $399^{216d}$; **5**, $94^{85}$, $96^{111}$, $418^{69}$; **6**, $561^{871}$; **7**, $797^{18,19}$, $799^{28}$, $800^{28a}$
Bellegarde, B., **2**, $607^{75}$, $608^{75}$
Bellemin, A.-R., **4**, $1009^{141}$
Bellenbaum, M., **5**, $30^{2,2f}$
Belleney, J., **4**, $519^{27}$
Beller, H., **2**, $770^{10}$, $771^{10}$
Bellesia, F., **3**, $395^{98}$; **4**, $337^{32}$; **8**, $389^{74}$
Bellet, P., **8**, $201^{144}$
Belletire, J. L., **4**, $598^{205}$, $638^{205}$; **5**, $373^{106,106b}$
Belley, M. J., **4**, $316^{540}$, $1040^{101}$, $1045^{101a}$
Belli, A., **3**, $789^{56}$
Bellido, I. S., **3**, $396^{115}$
Bellmann, P., **2**, $850^{218}$
Belloli, R. C., **7**, $26^{59}$
Bellora, E., **6**, $550^{678}$
Belloto, D., **4**, $809^{163}$
Bellucci, C. G., **4**, $330^{3}$, $345^{3,79}$
Bellucci, G., **3**, $733^{1}$, $734^{9}$
Bellus, D., **1**, $830^{96}$, $843^{2b}$; **3**, $848^{50}$; **4**, $754^{174,175}$, $819^{209}$; **5**, $4^{31}$, $68^{98}$, $90^{58}$, $829^{14,15}$; **7**, $205^{65}$
Bellut, H., **8**, $724^{175}$
Bellville, D. J., **5**, $453^{65}$, $520^{39}$, $704^{22}$, $1020^{68,69}$, $1023^{69}$; **7**, $879^{148}$, $880^{148,154}$, $882^{166}$
Belmonte, F. G., **8**, $478^{41}$, $480^{41}$, $517^{123}$

Belniak, K., **2**, 538$^{64}$, 663$^{28}$, 664$^{28}$
Belokon', Y. N., **4**, 218$^{147,148}$
Belot, G., **8**, 135$^{39}$, 137$^{53}$, 390$^{83}$
Belotti, D., **1**, 268$^{55}$, 269$^{55}$; **3**, 599$^{209,210}$, 602$^{223}$, 603$^{228}$; **5**, 310$^{100}$
Belov, P. N., **1**, 837$^{147}$
Belov, V. N., **5**, 432$^{129}$
Belovsky, O., **8**, 164$^{47}$
Below, P., **2**, 163$^{146}$
Bel'skij, I. F., **8**, 956$^{5}$
Belsner, K., **6**, 215$^{102}$
Belter, R. K., **7**, 453$^{71}$
Beltrami, H., **4**, 425$^{24,25}$, 428$^{24}$, 430$^{24}$
Belyaeva, O. Ya., **6**, 502$^{209}$, 531$^{453}$, 554$^{763}$
Belyakova, Z. V., **8**, 763$^{1}$, 769$^{1b}$, 771$^{1b}$, 775$^{77}$, 778$^{88}$, 785$^{1}$
Belzecki, C., **1**, 838$^{163,165,166}$; **5**, 99$^{137}$, 100$^{137}$, 108$^{207}$, 111$^{224,225}$, 260$^{63a}$, 264$^{73}$
Belzner, J., **4**, 1009$^{145}$
Bemiller, J. N., **7**, 235$^{1}$
Bemis, A., **6**, 280$^{143}$
Ben, I., **3**, 591$^{171}$
Benage, B., **2**, 1067$^{127}$, 1068$^{127}$; **5**, 467$^{116,117}$, 531$^{80}$, 539$^{109}$; **7**, 297$^{33}$
Benaim, J., **2**, 504$^{2}$, 506$^{2}$, 509$^{2}$, 524$^{2}$; **3**, 23$^{140}$, 30$^{140}$, 33$^{140}$, 34$^{140}$, 35$^{140}$; **6**, 722$^{140}$, 727$^{192}$
Benary, E., **4**, 123$^{210a}$
Benassi, R., **5**, 439$^{166}$
Benati, L., **4**, 336$^{29,30}$; **7**, 493$^{197}$
Ben-Bassat, J. M., **5**, 706$^{26}$
Benbow, J. W., **4**, 404$^{244}$; **7**, 410$^{97b}$
Bencini, E., **3**, 1033$^{72}$
Bencivengo, D. J., **8**, 850$^{121}$
Bencze, W. L., **3**, 566$^{33}$
Ben-David, D., **8**, 35$^{66}$, 66$^{66}$
Bender, C. O., **5**, 207$^{50}$
Bender, D., **4**, 852$^{90}$
Bender, D. R., **2**, 943$^{171}$, 945$^{171}$
Bender, H., **6**, 440$^{74}$; **7**, 658$^{26}$
Bender, H.-J., **4**, 13$^{45}$, 14$^{45b}$
Bender, H. S., **5**, 949$^{277}$
Bender, M. L., **7**, 659$^{36}$, 660$^{40}$
Bender, S. L., **1**, 130$^{97}$, 401$^{12,15}$, 402$^{12}$; **2**, 263$^{55}$; **4**, 366$^{7}$, 384$^{7,143}$; **7**, 245$^{79}$, 408$^{90}$, 418$^{90}$, 545$^{25}$
Benderly, A., **1**, 92$^{70}$; **2**, 111$^{84}$; **4**, 293$^{235}$
Benders, P. H., **4**, 45$^{126}$; **5**, 676$^{4}$, 686$^{48,49}$, 687$^{48,49}$
Bendich, A., **7**, 657$^{25}$
Bendig, J., **5**, 724$^{110}$
Bénéchie, M., **6**, 7$^{30}$
Benecke, B., **4**, 222$^{181}$, 224$^{181}$
Benecke, H. P., **3**, 926$^{46}$, 928$^{46}$
Benedetti, F., **3**, 174$^{534,535}$, 176$^{534,535}$, 178$^{534,535}$; **4**, 20$^{63}$, 21$^{63}$, 442$^{184}$
Ben-Efraim, D. A., **8**, 935$^{67}$
Benesova, V., **8**, 334$^{65}$
Ben-Et, G., **2**, 1074$^{143}$
Benetti, S., **2**, 803$^{32}$; **3**, 738$^{37}$; **5**, 403$^{8}$; **7**, 143$^{140,141}$; **8**, 392$^{108}$, 394$^{116}$, 645$^{45}$
Benezra, C., **1**, 219$^{56,58}$; **7**, 550$^{52}$
Benfaremo, N., **4**, 27$^{83}$
Benfield, F. W. S., **7**, 3$^{11}$
Benhamou, M. C., **4**, 290$^{204}$, 291$^{204,210}$, 292$^{204}$, 311$^{439,440}$; **7**, 632$^{61}$; **8**, 854$^{154}$
Benington, F., **4**, 504$^{131}$; **8**, 146$^{97}$, 568$^{466}$
Ben-Ishai, D., **2**, 1074$^{143,144,145,146,148}$, 1079$^{157}$; **5**, 406$^{22}$, 407$^{25}$, 501$^{264}$; **6**, 96$^{150}$, 636$^{17}$; **7**, 555$^{66}$
Benjamin, B. M., **3**, 328$^{179}$, 726$^{22}$, 782$^{20}$
Benjamin, L., **7**, 602$^{102}$
Benkeser, R. A., **1**, 180$^{28}$; **2**, 5$^{20}$, 6$^{20}$, 21$^{20}$, 588$^{152}$; **6**, 1034$^{134}$, 1035$^{135}$; **8**, 238$^{24}$, 249$^{91}$, 251$^{106}$, 294$^{54}$, 322$^{110}$, 478$^{40,41}$, 479$^{40}$, 480$^{41}$, 516$^{120,121}$, 517$^{123,124}$, 547$^{314}$, 629$^{186}$, 764$^{2}$, 767$^{23}$, 770$^{2b,31}$, 776$^{79}$, 880$^{71}$, 881$^{71}$
Benkó, P., **6**, 553$^{702,703}$
Benko, Z., **4**, 753$^{165}$
Benkovic, P. A., **2**, 956$^{10}$
Benkovic, S. J., **2**, 956$^{10}$; **8**, 31$^{46}$, 66$^{46}$, 93$^{69}$, 94$^{69}$, 206$^{168}$
Benkser, R. A., **5**, 1003$^{20}$
Benn, F. R., **5**, 2$^{20}$
Benn, M., **7**, 31$^{87}$
Benn, R., **1**, 2$^{10}$, 180$^{30}$; **4**, 608$^{318,319}$; **5**, 442$^{182}$; **6**, 179$^{124}$
Benn, W. R., **8**, 928$^{26}$
Bennani, Y. L., **4**, 110$^{151}$
Bennasar, M.-L., **2**, 765$^{77}$; **8**, 587$^{34}$
Benneche, T., **5**, 1012$^{52}$; **6**, 11$^{46}$, 842$^{82}$
Bennek, J. A., **8**, 219$^{77}$
Benner, C. W., **5**, 821$^{163}$, 857$^{225}$
Benner, J. P., **2**, 534$^{33-35}$, 535$^{34,35}$; **5**, 432$^{129}$
Benner, S., **8**, 82$^{6}$, 84$^{6}$, 197$^{123}$
Benner, S. A., **6**, 432$^{120}$; **7**, 672$^{17}$
Bennet, A. J., **8**, 388$^{64}$
Bennet, W., **1**, 205$^{105}$
Bennetau, B., **2**, 713$^{44}$, 726$^{124}$
Bennett, C. F., **7**, 769$^{209,217}$
Bennett, D. A., **2**, 74$^{70}$; **3**, 103$^{205}$, 108$^{205}$; **7**, 207$^{83}$, 208$^{83}$, 209$^{83}$, 210$^{83}$
Bennett, D. W., **3**, 380$^{7}$; **7**, 544$^{39}$, 553$^{39}$, 556$^{39}$
Bennett, F., **1**, 760$^{135}$; **4**, 382$^{135,135b}$, 383$^{135a}$; **5**, 736$^{145}$, 737$^{145}$; **7**, 440$^{38}$
Bennett, G. B., **5**, 829$^{26}$, 853$^{172}$, 877$^{8}$; **6**, 488$^{33}$, 834$^{35}$, 855$^{35}$
Bennett, G. M., **7**, 763$^{98}$
Bennett, J. N., **5**, 451$^{30}$, 453$^{30}$, 464$^{30}$, 513$^{5}$, 514$^{5}$, 527$^{5}$
Bennett, M. A., **8**, 152$^{164}$, 443$^{3}$, 453$^{194,195}$
Bennett, M. J., **8**, 14$^{80}$
Bennett, R. D., **1**, 293$^{33}$
Bennett, R. H., **7**, 208$^{80}$
Bennett, S. M., **3**, 219$^{110}$
Bennett, W. D., **6**, 65$^{2}$; **7**, 229$^{119}$
Bennua, B., **6**, 49$^{97}$, 193$^{215}$
Benny, D., **3**, 619$^{27}$
Bennyarto, F., **3**, 909$^{152}$
Beno, M. A., **1**, 23$^{119}$
Benoiton, N. L., **2**, 403$^{36}$
Bensadat, A., **7**, 498$^{220}$
Bension, R. M., **4**, 868$^{17}$, 869$^{17}$, 877$^{67}$; **5**, 30$^{3}$
Benson, A. A., **8**, 143$^{65}$
Benson, B. W., **7**, 31$^{86}$
Benson, F. R., **4**, 296$^{265}$, 1099$^{180}$; **6**, 262$^{15}$, 264$^{15}$, 268$^{15}$
Benson, R. E., **4**, 1090$^{139}$; **5**, 1141$^{82}$
Benson, S. W., **4**, 1072$^{17}$; **5**, 64$^{36}$, 856$^{193}$, 900$^{8}$; **7**, 8$^{54,57}$; **8**, 407$^{55}$
Benson, W., **6**, 501$^{204}$
Benson, W. R., **5**, 723$^{108a}$
Bentham, S., **4**, 301$^{322}$, 302$^{322}$
Bentlage, A., **2**, 385$^{321}$
Bentley, K. W., **3**, 836$^{81}$; **6**, 212$^{83}$
Bentley, P. H., **6**, 669$^{265}$; **7**, 671$^{6}$
Bentley, R., **6**, 653$^{150}$
Bentley, R. K., **7**, 306$^{4}$
Bentley, T. W., **3**, 799$^{99}$
Benton, J. L., **7**, 10$^{79}$

Bentor, Y., **2**, 766[83]
Bentrude, W. G., **7**, 7[42]
Bentz, P., **5**, 290[41], 1189[21,22], 1190[22], 1192[22]; **8**, 773[70], 774[70]
Ben-Yakov, H., **6**, 217[111]
Benzaid, A., **4**, 313[471]
Benzing, M., **2**, 368[233]
Benzinger, E., **3**, 660[6]
Benzing-Nguyen, L., **7**, 255[32]
Benzon, M. S., **5**, 826[158], 857[224]
Beppu, K., **1**, 410[39], 568[231]; **3**, 124[280], 125[280], 126[280]; **6**, 49[96]
Beranek, I., **4**, 730[66]
Berardi, F., **6**, 787[99,100]
Bercaw, J. E., **5**, 1145[105], 1174[37], 1178[44]; **8**, 668[2], 670[11], 671[16,18], 672[2,21], 673[23-26], 675[23,46,50], 676[24,26,51-53], 682[24,46,85], 685[98], 687[85], 689[98], 690[85], 691[23,85], 696[25,126]
Berchet, G. J., **4**, 315[517]
Berchier, F., **7**, 257[49]
Berchtold, G. A., **2**, 904[49]; **4**, 5[19,19e], 7[24], 45[126,126a]; **5**, 322[12], 855[186,189]; **7**, 78[125], 365[46,47], 429[151]; **8**, 726[190]
Bercovici, T., **5**, 729[125]
Bercz, P. J., **6**, 965[90]
Berenblit, V. V., **3**, 639[82], 644[82,137]
Berenblyum, A. S., **8**, 447[106], 450[106], 963[43]
Berenbom, M., **3**, 888[17]
Berends, W., **8**, 643[37]
Berenjian, N., **5**, 126[22], 127[22], 128[22]
Berenschot, D. R., **7**, 179[153]
Béres, J., **7**, 723[25]
Beretta, M. G., **2**, 267[64], 630[21], 631[21], 632[21], 634[21], 640[21], 641[21], 642[21], 644[21], 645[21]
Berezin, I. V., **3**, 499[125]
Bereznitskii, G. K., **3**, 305[70]
Berg, H., **3**, 482[3]
Berg, H. A. J., **5**, 799[73]
Bergami, B., **5**, 73[204]
Bergan, J. J., **6**, 22[83]; **7**, 752[154]
Bergbreiter, D. E., **1**, 357[1]; **2**, 102[24], 476[4], 489[48], 490[48], 505[11], 510[11,37,38,40-42], 917[89], 919[89], 920[89], 924[89], 935[89]; **3**, 30[181], 31[185], 32[185], 34[192,193], 39[192], 418[26]; **4**, 5[17], 221[157], 738[98]; **5**, 100[147]; **6**, 531[448], 719[125], 720[125,130], 722[139], 723[146], 725[125]; **7**, 604[138]; **8**, 113[38], 720[131], 800[67], 947[142]
Bergdahl, M., **1**, 112[27]; **4**, 152[56], 255[204]
Berge, D. D., **7**, 143[147]
Berge, J. M., **5**, 689[73]
Bergen, E. J., **7**, 76[117]
Bergens, S., **7**, 416[123]
Bergenthal, M. D., **6**, 966[96]
Berger, A., **6**, 636[17]
Berger, B., **5**, 468[123]; **7**, 131[87]
Berger, C. R. A., **8**, 314[40]
Berger, D. E., **2**, 530[23]; **5**, 4[39], 5[39,44], 8[44]
Berger, G., **8**, 35[64], 52[145], 53[128], 66[64,128,145]
Berger, H., **7**, 759[14]
Berger, J., **1**, 130[96]; **7**, 54[7]
Berger, J. G., **2**, 965[68]; **8**, 59[178], 66[178], 614[88,89], 620[89,134,135], 621[88], 624[134]
Berger, K. R., **2**, 709[6]
Berger, M. H., **4**, 10[33], 23[33d], 107[144], 262[306]
Berger, S., **1**, 191[77], 272[68], 300[67], 322[67], 335[63]; **2**, 6[35], 247[35], 630[7], 631[7]; **6**, 217[114]
Bergeron, R., **6**, 83[78]
Bergeron, R. J., **7**, 668[82,83]; **8**, 62[195], 66[195], 994[63]
Bergin, W. A., **8**, 236[6], 284[2], 285[2], 607[30]
Bergius, M., **3**, 822[5], 834[5]
Bergman, A., **5**, 715[81]
Bergman, J., **3**, 511[191]; **4**, 342[64], 343[64,72], 386[155]; **5**, 721[102]; **6**, 463[24], 824[123]; **7**, 534[43]
Bergman, P. M., **8**, 364[13]
Bergman, R., **3**, 767[165]
Bergman, R. G., **2**, 125[212,213], 127[212,213,233], 310[30], 311[30], 313[36,37], 314[39], 655[143]; **5**, 588[209], 736[144], 790[21], 797[63], 820[21], 1134[38], 1145[105], 1149[38,126]; **7**, 3[12], 4[15], 8[12], 484[136]; **8**, 289[29], 290[29], 669[6], 670[6], 797[35]
Bergmann, A., **2**, 356[132]
Bergmann, E., **3**, 724[14]
Bergmann, E. D., **2**, 352[85]; **3**, 124[264], 867[35]; **4**, 3[7], 4[7], 63[7b], 65[7b], 70[2], 258[231]; **6**, 219[124]; **7**, 107[168]; **8**, 228[125]
Bergmann, H.-J., **2**, 212[121]
Bergmann, K., **8**, 319[79]
Bergmann, M., **6**, 632[3], 635[3]
Bergmann, W., **3**, 892[51]
Bergmark, W., **3**, 580[107]
Bergmeyer, H. U., **2**, 456[45,47]
Bergmeyer, J., **2**, 456[45,47]
Bergson, G., **6**, 489[96]
Bergstein, W., **4**, 874[54]; **5**, 30[2]; **8**, 460[254]
Bergstorm, F. W., **4**, 491[67]
BergStresser, G. L., **1**, 15[80]
Bergstrom, D. E., **3**, 459[135], 462[149,151], 470[218], 476[218], 513[207]
Bergstrom, F. W., **8**, 143[65]
Bergstrom, R. G., **6**, 556[26], 563[26]
Beringer, F. M., **4**, 42[122a]; **8**, 995[70]
Berk, H. C., **3**, 623[33]; **5**, 347[73a]
Berk, S. C., **1**, 212[5,8,11], 213[5,8,11], 214[5b,19], 432[138], 433[138]; **2**, 450[50]; **3**, 209[18]; **4**, 175[42]
Berka, A., **7**, 704[8]
Berkessel, A., **5**, 200[30], 201[31]
Berkowitz, L. M., **7**, 236[12], 572[114]
Berkowitz, W. F., **5**, 143[97,98], 636[88], 945[250]; **6**, 786[96]; **7**, 242[61]
Berks, A. H., **1**, 262[35], 739[41]; **2**, 441[1], 443[1]
Berkvich, E. G., **4**, 485[29]
Berlan, J., **1**, 112[27], 124[81]; **2**, 448[43]; **3**, 155[430]; **4**, 152[58], 210[70-76], 229[223], 240[45]; **5**, 557[53]; **8**, 111[21], 123[21]
Berlin, A. J., **4**, 1023[260]; **5**, 1006[35]
Berlin, A. Y., **5**, 453[59]
Berlin, K. D., **4**, 273[46], 280[46]
Berlin, Y. A., **6**, 603[21]
Berlo, R. G., **8**, 367[58]
Berman, D. A., **6**, 809[69]
Berman, E., **7**, 438[22]
Berman, E. M., **4**, 403[241]
Berman, R. J., **7**, 545[26]
Berman, Z., **7**, 79[135]
Bernady, K. F., **4**, 141[15], 142[15]; **6**, 648[124]
Bernal, I., **1**, 310[107]; **8**, 459[238]
Bernard, D., **1**, 331[50]; **3**, 482[5], 499[5], 505[5], 509[5]
Bernard, G., **1**, 631[54], 658[54], 659[54], 660[54], 661[54], 662[54], 663[54], 664[54], 672[54]; **3**, 87[72], 95[72]
Bernard-Henriet, C., **5**, 109[219]; **6**, 578[980]; **7**, 502[262]
Bernardi, A., **2**, 103[28], 221[146], 267[63], 488[43], 605[57], 614[57], 630[21], 631[21], 632[21], 634[21], 636[56], 637[56,59], 640[21,56,59], 641[21,71], 642[21,71,73,74], 643[73,74], 644[21,73], 645[21,59], 652[59], 920[98], 930[131], 931[131]; **4**, 152[58], 207[57,58]

Bernardi, F., **1**, 506[8,11]; **4**, 330[5]; **5**, 75[220,223], 114[244]; **6**, 133[4]
Bernardi, R., **1**, 55[23], 153[57], 543[28]; **8**, 187[47]
Bernardinelli, G., **1**, 307[111], 312[111], 770[187]; **2**, 631[17], 632[17], 634[17], 924[108a]; **4**, 21[69], 85[72], 111[153], 201[16], 202[16], 204[33], 218[137], 231[282], 249[120], 520[28]; **5**, 45[36], 157[38], 260[70], 263[70], 362[93], 363[93a,d], 364[93d], 365[93a,e], 543[117], 545[120]
Bernardini, A., **3**, 251[75]
Bernardon, C., **1**, 226[94], 227[99]; **4**, 98[110]
Bernardon, J.-M., **3**, 262[167]; **7**, 359[16]
Bernardou, F., **4**, 883[96,97], 884[96,97,105]
Bernasconi, C. F., **2**, 349[67-69]
Bernasconi, S., **1**, 566[216]; **2**, 833[148]; **4**, 261[285,288,290]
Bernassau, J.-M., **8**, 111[20], 118[20]
Bernath, G., **5**, 583[186], 584[194]; **6**, 525[382], 534[519]
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Binns, M. R., **1**, 520[69,70,72,73], 635[90], 636[90], 678[90], 681[90], 691[90]; **2**, 66[33], 75[33,82a]; **3**, 87[94]; **4**, 12[37,37a-d], 119[192a,b,193], 159[85], 226[190,191,192,194], 258[245], 260[245]; **6**, 150[114], 154[145], 864[192]
Binns, R. N., **1**, 635[83], 678[83], 681[83], 691[83]
Binns, T. D., **3**, 638[94]; **7**, 805[67]
Binsch, G., **3**, 896[71]; **5**, 714[74]; **8**, 335[67]
Biougne, J., **4**, 48[137,137c], 51[143]
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Birbaum, J.-L., **4**, 770[248]
Birch, A. J., **2**, 170[171,173], 598[17], 619[149], 723[98], 761[51], 838[165]; **3**, 17[91], 831[63]; **4**, 6[21], 27[79,79c], 181[74], 665[8,10,11], 666[11], 667[10,11], 668[14], 669[11], 670[8,10,14-17,19,21,28], 674[8,10,17], 677[14], 683[59,60], 687[59,60,63,64], 688[65,66], 695[2], 698[22], 1018[221]; **5**, 841[100]; **6**, 690[402], 692[402]; **7**, 884[183]; **8**, 139[2], 152[2,173], 154[2], 212[18], 249[91], 293[52], 302[52], 443[1], 445[13,14], 447[1a], 452[13,184,184a], 490[4,8], 491[12], 492[4], 493[21], 499[42], 500[8,48], 501[53,55], 502[59], 507[53,84,85], 514[108-110], 515[114,115,119], 524[2], 526[19,36], 530[2,98], 531[2], 533[147], 535[147], 605[12,13], 608[35,36], 609[12], 614[12], 629[12], 910[83], 971[104]
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Birch, D. J., **4**, 745[140]
Birch, S. F., **3**, 331[198]
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Birchall, G. R., **2**, 739[43a]
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Bird, T. G. C., **3**, 159$^{457}$, 173$^{457}$; **5**, 137$^{80}$, 386$^{135}$; **6**, 217$^{112}$; **7**, 69$^{92}$, 73$^{92}$
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Birkhahn, M., **3**, 851$^{67}$
Birkhofer, H., **4**, 758$^{191}$
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Birkofer, L., **1**, 583$^{8,8b}$; **2**, 725$^{111}$, 726$^{111}$, 935$^{147}$; **5**, 99$^{138}$, 100$^{138}$; **6**, 91$^{124}$, 653$^{149,150}$
Birks, J. B., **5**, 650$^{23}$, 653$^{23}$; **7**, 852$^{42}$
Birktoft, J. J., **8**, 206$^{172}$
Birladeanu, L., **2**, 744$^{99}$, 745$^{99}$; **4**, 972$^{78}$; **5**, 478$^{162}$; **6**, 291$^{222}$, 707$^{42}$; **7**, 236$^{22,25}$
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Birnbaum, G. I., **2**, 538$^{64}$
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Birse, E. F., **1**, 774$^{209}$
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Birum, G. H., **1**, 562$^{170}$; **7**, 206$^{69}$
Bisacchi, G. S., **5**, 692$^{91}$, 696$^{91}$
Bisagni, E., **1**, 471$^{70}$, 474$^{109}$, 475$^{109}$; **2**, 379$^{294}$; **7**, 350$^{21}$
Bisaha, J., **4**, 524$^{59}$; **5**, 186$^{170}$, 361$^{92}$, 543$^{116,116b}$
Bischofberger, K., **6**, 902$^{125}$
Bischofberger, N., **2**, 456$^{33}$, 457$^{33}$, 458$^{33}$, 459$^{33}$, 460$^{33}$, 461$^{33}$, 462$^{33}$, 466$^{33}$; **5**, 929$^{169}$, 930$^{169}$
Bischoff, C., **3**, 848$^{52}$
Bishop, J. L., **2**, 969$^{83,83b}$
Bishop, K. C., III, **5**, 1185$^{1}$
Bishop, P. M., **2**, 303$^{6}$; **3**, 371$^{115}$; **5**, 37$^{22a}$
Bishop, R., **3**, 383$^{46}$; **4**, 293$^{238,239}$; **6**, 266$^{54}$, 278$^{131}$
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Bisling, M., **2**, 127$^{239}$; **8**, 889$^{133}$
Biss, J. W., **8**, 275$^{141}$
Bissell, R. L., **2**, 190$^{55,56}$
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Biswas, S., **3**, 783$^{28}$
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Bitter, I., **6**, 499$^{177}$, 514$^{307}$, 520$^{340}$
Bitter, J., **2**, 371$^{261}$; **5**, 76$^{239}$
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Björkling, F., **6**, 811$^{76}$; **8**, 163$^{36}$
Bjorklund, C., **3**, 499$^{120}$; **8**, 252$^{111}$
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Blackadder, D. A., **8**, 364$^{18}$
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Blackburn, G. M., **3**, 202$^{85}$, 919$^{30}$, 933$^{30,62}$, 946$^{30}$; **4**, 507$^{154}$; **6**, 893$^{79}$
Blackburn, T. F., **1**, 143$^{33}$; **4**, 153$^{62c}$; **7**, 453$^{80}$; **8**, 669$^{4}$, 679$^{4}$, 687$^{4}$, 691$^{105}$
Blackett, B. N., **3**, 742$^{57}$, 743$^{57,60}$
Blacklock, T. J., **1**, 447$^{198}$; **4**, 573$^{8}$, 614$^{376}$, 905$^{208}$; **5**, 67$^{84,86,88,89}$, 795$^{52}$, 914$^{114}$, 948$^{270}$; **6**, 789$^{106}$
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Blade-Font, A., **8**, 860$^{222}$
Bladon, C. M., **2**, 555$^{146}$; **5**, 437$^{159}$
Bladon, P., **4**, 703$^{32}$, 704$^{32}$; **5**, 1039$^{18}$, 1046$^{18}$, 1051$^{36a}$, 1062$^{59}$; **7**, 582$^{149}$; **8**, 532$^{128}$
Blagg, J., **1**, 307$^{111}$, 312$^{111}$; **2**, 252$^{41}$, 253$^{41}$; **3**, 197$^{37}$; **5**, 362$^{93}$, 365$^{93e}$
Blagg, M., **8**, 927$^{21}$
Blagg Cox, M., **1**, 767$^{180}$
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Blanchard, J. M., **8**, 545$^{296}$
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Blanchard, M., **5**, 341$^{60}$
Blanchette, M. A., **1**, 434$^{140}$, 769$^{182}$; **2**, 264$^{58}$
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Blankespoor, C. L., **3**, 325[161]
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Blanton, C. D., Jr., **3**, 629[53,54]
Blanton, J. R., **4**, 738[98]; **8**, 800[67]
Blaqevic, N., **6**, 85[87]
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Blaser, G., **6**, 174[57]
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Blaskó, G., **2**, 812[72]; **3**, 682[165]
Blass, H., **8**, 70[225], 71[225]
Blass, J., **2**, 968[81]
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Blaszczyk, K., 7, 255[34]
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Blatchford, T. P., **3**, 583[119]
Blatt, A. H., **2**, 933[137]; **7**, 689[2]
Blatt, H., **3**, 575[83]
Blatt, K., **2**, 819[98]; **5**, 501[268]; **6**, 672[285]
Blatt, R. S., **8**, 643[35]
Blattner, R., **6**, 978[25]
Blazejewski, J.-C., **3**, 664[30]
Bleasdale, D. A., **2**, 809[51], 823[51]
Blechert, S., **1**, 664[169], 665[169], 669[169], 670[169]; **4**, 56[158]; **5**, 827[2], 829[2], 847[135], 867[2a], 1004[30]; **6**, 834[36], 855[36]
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Bleicher, W., **8**, 319[79]
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Blezard, M., **1**, 524[91]; **3**, 748[77]
Blicke, F. F., **2**, 420[24], 894[1], 897[1], 953[1], 1090[61]; **3**, 781[12]; **8**, 608[38]
Blidner, B. B., **8**, 96[94]
Blizzard, T. A., **4**, 893[156]; **7**, 410[94]
Bloch, I., **6**, 435[5a]
Bloch, R., **1**, 59[34]; **2**, 194[66]; **3**, 173[518]; **4**, 38[108]; **5**, 15[105], 17[116], 21[142], 553[45,47], 555[45], 567[102,103]; **8**, 9[55]
Block, E., **1**, 630[33], 675[33], 722[33], 786[252]; **2**, 74[76], 866[5]; **3**, 86[8], 121[8], 147[8], 154[8], 173[8], 878[92-95], 879[92-94,96,97], 880[94,98], 881[94]; **4**, 331[16,17], 335[25], 345[83], 346[85], 348[108], 349[108c], 359[159], 771[251], 987[133]; **5**, 440[174], 441[174,179], 829[26]; **6**, 161[180,181,182], 686[371], 687[371], 829[3], 934[101], 982[48], 984[48]; **7**, 516[5], 517[13], 768[203]; **8**, 842[44,44b], 844[44b], 845[44b], 846[44b], 847[44b]
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Blodgett, J. K., **6**, 803[47], 804[47]
Blohm, M., **2**, 464[94]
Blohm, M. L., **8**, 374[146], 446[70]
Blok, A. P., **8**, 657[94]
Blom, J. E., **4**, 588[58]
Blom, J. H., **5**, 426[106], 451[3]
Blomberg, C., **1**, 13[69], 16[86], 219[55]
Blommerde, W. W. J. M., **6**, 249[142]
Blomquist, A. T., **1**, 630[32], 675[32], 722[32]; **2**, 529[20], 530[21]; **3**, 905[139]; **5**, 752[39]; **6**, 968[110]; **7**, 660[37]; **8**, 142[52], 568[467], 950[173]
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Blondet, D., **5**, 412[47]
Bloodworth, A. J., **3**, 380[9]; **4**, 306[374,375,376,377,378,379,380,381,382,383,384,385], 307[385,390,391], 309[420,421], 310[428], 311[444], 314[480], 390[174,174a,c], 800[121]; **7**, 534[37], 632[57], 728[40]; **8**, 798[56], 854[155], 855[155,156,159], 856[155]
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Bloom, B. M., **8**, 530[101]
Bloom, J. D., **1**, 129[93], 779[224]; **6**, 509[253]; **8**, 37[99], 42[99], 66[99]
Bloom, M. S., **2**, 296[87]
Bloom, S. H., **3**, 215[63], 251[80], 254[80]; **4**, 403[240], 872[38]; **6**, 783[84]; **7**, 503[270]
Bloomfield, J. J., **2**, 602[40,41], 797[6], 806[6], 808[6], 813[6], 814[6], 848[6], 849[6]; **3**, 597[200], 613[1], 614[1,5], 615[1,10], 616[1], 617[5a,14], 619[1], 620[1,14], 621[1], 622[1], 623[1], 625[1], 626[1,42], 627[1], 628[1], 629[1], 630[1]; **5**, 571[116]; **8**, 240[29], 242[41], 243[29]
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Blough, B. E., **1**, 418[72], 767[164], 768[167]; **3**, 226[199]; **7**, 418[127]
Blount, J. F., **2**, 384[319], 877[36]; **3**, 390[85], 392[85], 407[148], 623[32], 626[32b], 675[72], 872[57], 873[57]; **4**, 249[125], 258[125], 370[32], 371[32], 629[416]; **6**, 531[430], 1031[115]; 7, 524[49]; **8**, 645[43], 836[10b], 847[10b], 848[10b], 849[10b], 861[225]
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Bloy, V., **4**, 956[17]; **8**, 166[53,54], 545[294,295]
Bludsuss, W., **7**, 483[130,131]
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Blues, E. T., **3**, 415[6]
Blum, D. M., **1**, 738[39]; **2**, 814[77]
Blum, J., **6**, 93[132]; 7, 107[168], 475[50], 476[50]; **8**, 453[193], 535[163], 551[340,341,343,347], 552[340,341], 557[383]
Blum, L., **3**, 505[163]
Blum, M. S., 7, 528[9]; **8**, 51[123], 66[123]
Blum, R. B., **2**, 600[31]; **3**, 20[120], 194[6]
Blum, S., **4**, 292[234]; **6**, 264[32,33], 268[33]
Blum, Y., **8**, 446[72]
Blumbach, J., **5**, 85[1]; 7, 131[88]
Blumbergs, J. H., 7, 674[43]
Blume, G., **4**, 1001[37,39], 1015[37]
Blumel, J., **1**, 476[115]; **5**, 568[110]
Blumenfeld, J., **2**, 232[175]
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Blumenkopf, T. A., **1**, 583[8,8a], 589[8a,19,20a,b], 591[19,20b], 592[8a,20a], 595[8a]; **2**, 555[136], 570[36], 580[96], 1030[81]; **3**, 867[34]; **4**, 155[68c]; **6**, 742[67], 752[111,113]; **7**, 256[25]
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Blunt, J. W., **3**, 741[50,52]; **8**, 213[29]
Bluthe, N., **1**, 892[149]; **5**, 800[79], 802[82]; **8**, 857[192]
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Blye, R. P., **7**, 372[71]
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Bokanov, A. I., **6**, $487^{74}$, $489^{74}$
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Boland, W., **3**, $220^{120}$; **5**, $563^{91}$, $973^{15}$, $975^{15}$; **8**, $185^{30}$, $798^{52}$
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Boldrini, G. P., **1**, $188^{73}$, $189^{73}$, $192^{82}$; **2**, $35^{130}$, $36^{130}$, $566^{23}$; 7, $549^{42}$; **8**, $36^{80}$, $54^{80}$, $66^{80}$, $550^{333}$, $551^{336}$
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Bond, F. T., **1**, $377^{97}$; **2**, $588^{150}$; **3**, $251^{79}$, $254^{79}$; **4**, $273^{51}$; **6**, $781^{78,79}$; **8**, $940^{103}$, $941^{103}$, $946^{103,141}$, $947^{103}$
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Bongini, A., **2**, $925^{111}$, $926^{111}$; **4**, $344^{78a}$, $375^{94}$, $377^{104}$, $386^{94a,153,153a,157}$, $387^{94a,153a,157}$, $388^{164}$, $393^{164c}$, $401^{226}$, $407^{104c,153a,157b,254}$; **5**, $102^{174}$; **6**, $26^{106}$, $648^{124}$; 7, $493^{184}$, $503^{269}$
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Bordas, X., **6**, 77[54]
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Borel, D., **5**, 938[207]
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Borer, R., **6**, 560[868]; **8**, 544[257,258]
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Borkent, G., **4**, 278[95], 286[95], 289[95]
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Bos, M. E., **2**, 588[151], 589[151]; **5**, 1070[29], 1074[29]
Bos, M. G. J., **7**, 12[101]
Bos, T. J. T., **4**, 897[171], 898[171], 899[171]
Bos, W., **5**, 561[84,85]
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Boschelli, D. H., **7**, 243$^{64}$, 477$^{71}$
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Bose, J. A., **4**, 390$^{175c}$
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Boshar, M., **4**, 1075$^{33}$
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Bosman, W. P., **8**, 96$^{92}$
Bosnich, B., **4**, 564$^{40,43}$, 567$^{40}$, 590$^{90}$, 599$^{221}$, 624$^{221}$, 641$^{221}$, 653$^{443,444,445}$, 927$^{44}$, 945$^{44}$; **6**, 450$^{117}$, 843$^{88}$; **7**, 416$^{123}$; **8**, 459$^{234,235}$, 535$^{166}$
Bosnjak, J., **7**, 831$^{68}$
Bosold, F., **6**, 114$^{78}$, 119$^{114,115}$
Bosone, E., **2**, 922$^{101}$, 923$^{101}$
Boss, R., **6**, 652$^{146}$
Bossert, F., **2**, 377$^{281}$, 384$^{281}$
Bosshard, C., **7**, 3$^{5}$
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Bosshard, H. H., **2**, 748$^{127}$; **6**, 204$^{20}$
Bosshard, P., **2**, 964$^{57}$; **5**, 947$^{288}$; **8**, 606$^{21}$
Bosshardt, H., **7**, 99$^{107}$
Bost, H. W., **2**, 283$^{51}$
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Bostock, S. B., **2**, 379$^{293}$
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Bos Vanderzalm, C. H., **3**, 575$^{83}$
Boswell, G. A., Jr., **7**, 751$^{140}$
Bosworth, N., **7**, 833$^{72}$
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Botta, M., **4**, 113$^{171,171g}$; **6**, 490$^{109}$; **7**, 713$^{71}$
Bottaccio, G., **5**, 1133$^{23}$
Bottari, F., **3**, 741$^{51}$
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Bottaro, J. C., **1**, 477$^{144,145}$, 545$^{46-48}$; **2**, 523$^{75}$, 588$^{152}$; **6**, 109$^{44}$, 783$^{85}$; **7**, 231$^{153,154}$, 471$^{19}$, 746$^{87}$; **8**, 940$^{107}$
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Botteghi, C., **3**, 124$^{286}$, 125$^{286}$, 127$^{286}$, 228$^{222}$, 487$^{45}$; **4**, 915$^{9,15}$, 919$^{18,19}$, 920$^{20}$, 930$^{50}$; **5**, 1152$^{143}$, 1153$^{145}$; **8**, 236$^{3}$, 239$^{3}$, 552$^{352}$
Botteron, D. G., **3**, 564$^{8}$, 727$^{28}$
Böttger, R. C., **3**, 208$^{6}$
Bottin, J., **8**, 536$^{170}$, 541$^{215}$, 543$^{215}$
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Bouchoule, C., **1**, 219$^{63}$; **2**, 988$^{32}$, 989$^{32}$
Bouda, H., **1**, 821$^{20}$
Boudart, M., **8**, 419$^{19-21}$, 420$^{19-21}$, 424$^{19,21}$, 429$^{21}$, 430$^{20}$, 436$^{21}$, 454$^{198}$
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Boudet, R., **8**, 658$^{102}$
Boudjouk, P., **1**, 308$^{96}$; **2**, 279$^{19}$; **3**, 466$^{189}$, 565$^{16}$, 578$^{16}$; **5**, 386$^{132}$, 387$^{132a}$, 638$^{118}$, 639$^{119}$; **6**, 977$^{15}$; **8**, 764$^{4c}$
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Boudrow, C., **4**, 557$^{13}$
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Bouffard, F. A., **2**, 213$^{122}$; **5**, 107$^{199}$; **6**, 125$^{148}$, 127$^{148}$
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Boujlel, K., **4**, 478$^{167}$
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Boukouvalas, J., **1**, 52$^{16}$, 134$^{114}$, 135$^{114}$; **2**, 625$^{162}$, 631$^{17}$, 632$^{17}$, 634$^{17}$; **5**, 157$^{38,39}$
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Bourelle-Wargnier, F., **5**, 829$^{25}$, 930$^{175}$, 931$^{175}$, 932$^{175}$
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Bourgain-Commercon, M., **1**, 107$^{3}$, 113$^{34}$, 428$^{119}$, 436$^{145}$; **2**, 584$^{125}$; **3**, 246$^{35}$, 470$^{223,226}$, 473$^{226}$, 482$^{4}$, 485$^{4}$; **4**, 183$^{81}$, 898$^{178}$
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Bowers, K. G., **5**, 605[55], 612[76]
Bowers, K. W., **3**, 577[87]; **4**, 537[99,100], 538[99,100]; **8**, 524[12], 527[49], 532[12c]
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Bowman, R. G., **8**, 447[132]
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Boyd, D. R., **1**, 837[152]; **4**, 356[135]; **7**, 6[34], 78[125], 750[131]; **8**, 187[36], 541[212]
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Boyd, G. V., **5**, 478[163], 491[206]; **6**, 438[60], 493[127], 504[220]; **7**, 772[296]; **8**, 664[122]
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Boyd, S. D., **6**, 1000[125]
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Boyer, J. H., **4**, 1099[181]; **6**, 76[43], 104[1], 110[47], 525[380], 799[26]; **7**, 736[4], 737[4], 747[100], 748[100], 749[119], 750[4], 752[4]
Boyer, P. D., **2**, 456[43,48], 464[99], 466[43,117], 467[43], 468[117]
Boyer, R., **6**, 208[63]
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Boyle, L. W., **5**, 255[50]
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Bradbury, R. H., **4**, 382[134,134b]; **5**, 707[34], 725[34], 803[92], 979[26]
Bradbury, S., **7**, 743[65]
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Bradley, J. S., **1**, 443[179]
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Bradshaw, J. B., **6**, 436[28], 437[28], 447[28], 448[28], 449[28], 450[28], 452[28]
Bradshaw, J. S., **4**, 489[59,60]; **5**, 163[70]; **6**, 71[21], 283[158], 449[116]; **7**, 415[113]; **8**, 828[78], 838[19,19b]
Bradshaw, R. W., **6**, 79[65], 81[65]
Bradsher, C. K., **1**, 412[54]; **3**, 251[77], 254[77], 324[149]; **5**, 499[253,255], 501[253]; **8**, 323[114], 587[38], 588[38]
Brady, D. G., **4**, 48[138,138d], 66[138d], 597[179]
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Brady, K. A., **8**, 764[6], 770[40]
Brady, L. E., **6**, 277[128], 288[128]
Brady, S. F., **3**, 362[90]
Brady, T. E., **8**, 967[83]
Brady, W. T., **3**, 848[49], 905[141]; **4**, 53[151]; **5**, 86[26], 87[38,39,43,44], 90[26,55,59], 94[59], 99[133,134,135,139], 100[133,135]
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Braekman, J. C., **5**, 456[86]; **6**, 914[27]
Braendin, H. P., **5**, 513[4]
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Brahma, R., **5**, 243[13], 244[13]
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Branca, M., **4**, 930[50]
Branca, Q., **3**, 167[485], 168[485]; **6**, 1058[59]; **7**, 57[27]

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Branch, G. E. K., **7**, 602$^{100}$
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Branchaud, B. P., **2**, 940$^{163}$; **4**, 761$^{202,205}$, 768$^{237}$; **8**, 72$^{238}$, 74$^{238}$
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Brandänge, S., **2**, 233$^{188}$, 827$^{128}$; **6**, 85$^{87}$
Brandenburg, C. F., **5**, 830$^{36}$
Brandes, E., **5**, 349$^{76}$, 854$^{179,180}$, 855$^{179}$; **7**, 569$^{107}$
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Brandi, A., **5**, 922$^{135}$; **8**, 851$^{127}$
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Brandt, J., **2**, 1099$^{107}$; **4**, 874$^{48}$
Brandt, P., **8**, 262$^{20}$
Brandt, S., **3**, 500$^{132}$, 505$^{132}$; **4**, 980$^{110}$, 982$^{110}$
Brandvold, T. A., **5**, 1089$^{87}$, 1090$^{87,90}$, 1091$^{90}$, 1094$^{87}$, 1098$^{87}$, 1099$^{87,90}$, 1100$^{87}$, 1101$^{87,90}$, 1102$^{147}$, 1112$^{87}$, 1113$^{87}$; **7**, 487$^{149}$
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Brannigan, L. H., **1**, 532$^{136}$
Brannock, K. C., **3**, 21$^{122}$; **4**, 45$^{126,126b,e}$; **5**, 71$^{153,158}$, 686$^{50}$, 847$^{132}$, 850$^{151}$, 862$^{247}$; **6**, 426$^{70}$; **8**, 140$^{19}$
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Braun, H., **5**, 418$^{71}$; **6**, 104$^{5}$; **7**, 505$^{283,284}$; **8**, 395$^{131}$
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Bremholt, T., **7**, 835$^{85}$
Bremmer, M. L., **5**, 414$^{52}$, 415$^{55}$, 539$^{108}$
Bremner, J., **8**, 847$^{88}$
Bremner, J. B., **2**, 421$^{26}$
Breña, L. J., **2**, 514$^{51}$
Brena-Valle, L. J., **6**, 119$^{110}$
Brendel, J., **4**, 152$^{55}$
Breneman, C. M., **1**, 428$^{121}$, 429$^{121}$, 457$^{121}$; **3**, 209$^{15}$, 211$^{34a}$, 213$^{34a}$; **4**, 184$^{82}$
Brener, L., **8**, 713$^{75,78}$, 714$^{75}$
Brennan, J., **1**, 755$^{115}$, 812$^{115}$, 813$^{115}$; **6**, 193$^{215}$
Brennan, M. P. J., **3**, 635$^{36}$
Brennan, M. R., **7**, 154$^{16}$, 174$^{137}$
Brenner, A., **7**, 154$^{15}$
Brenner, D. G., **1**, 389$^{141}$; **6**, 278$^{130}$

Brenner, W., **3**, 390$^{84}$, 392$^{84}$; **5**, 800$^{76}$, 809$^{113}$; **6**, 685$^{354}$, 959$^{46}$
Breque, A., **3**, 201$^{82}$; **8**, 865$^{247}$
Bresadola, S., **7**, 500$^{239}$
Bresinsky, E., **4**, 52$^{147,147f}$
Breslauer, H., **7**, 92$^{46}$
Breslow, D. S., **3**, 1029$^{54}$; **7**, 21$^{14}$, 24$^{29,30,36,38}$, 25$^{36,43}$, 26$^{43,47}$, 219$^{14}$; **8**, 447$^{118}$, 454$^{118}$, 455$^{118}$, 568$^{481}$
Breslow, R., **1**, 543$^{18}$; **3**, 896$^{67}$, 1058$^{40}$; **4**, 1005$^{92}$; **5**, 344$^{66}$, 345$^{66}$, 346$^{66}$, 453$^{66}$, 493$^{212}$, 789$^{18}$, 854$^{175}$, 1133$^{28}$; **6**, 564$^{908}$; **7**, 24$^{39}$, 25$^{39}$, 40$^{8,13}$, 42$^{32,34}$, 43$^{8,35,36,38,46,47}$, 46$^{48\text{-}50}$, 47$^{50\text{-}52,54}$, 48$^{58\text{-}61}$, 49$^{62\text{-}68}$, 50$^{74}$, 805$^{66}$, 854$^{49}$, 855$^{49}$
Bressan, M., **7**, 238$^{43}$
Bresse, M., **1**, 462$^{16}$
Bressel, U., **5**, 75$^{217}$, 78$^{217}$
Brestensky, D. M., **4**, 254$^{184}$; **8**, 550$^{330}$
Breswich, M., **1**, 310$^{107}$
Breton, P., **6**, 690$^{401}$, 692$^{401}$
Bretsch, W., **4**, 1046$^{115}$
Bretschneider, H., **2**, 740$^{62}$; **7**, 678$^{69}$; **8**, 496$^{32}$
Bretschneider, T., **1**, 122$^{72}$
Brett, D., **6**, 228$^{18}$
Bretting, C., **4**, 149$^{52}$, 181$^{72,73}$
Brettle, R., **3**, 583$^{126}$, 635$^{36}$, 638$^{94}$, 643$^{122}$; **7**, 794$^{7b,d}$, 805$^{67}$; **8**, 563$^{435}$
Breu, V. A., **6**, 543$^{616}$
Breuckmann, R. B., **5**, 64$^{29}$
Breuer, A., **8**, 352$^{148}$
Breuer, E., **1**, 836$^{141}$; **5**, 959$^{319}$; **7**, 606$^{153}$; **8**, 315$^{54}$, 316$^{54}$, 707$^{25}$
Breuer, S. W., **3**, 418$^{27}$; **7**, 595$^{28,31}$
Breuer, W., **2**, 1099$^{110}$
Breuilles, P., **5**, 305$^{84,86}$
Breulet, J., **5**, 703$^{15}$
Brevilles, P., **4**, 593$^{136}$, 763$^{212}$
Brew, S. A., **8**, 70$^{228}$
Brewer, D., **5**, 167$^{94}$
Brewer, E. N., **2**, 838$^{176}$
Brewer, P. D., **3**, 251$^{77}$, 254$^{77}$
Brewster, A. G., **7**, 110$^{188}$
Brewster, J. H., **3**, 927$^{51,57}$; **4**, 3$^{9}$; **8**, 314$^{41,42}$, 315$^{41,42}$, 541$^{207}$, 814$^{15}$
Brewster, P., **6**, 3$^{13}$, 4$^{13}$
Brewster, R. Q., **8**, 916$^{113}$
Brewster, W. D., **8**, 409$^{80}$
Brey, W. S., Jr., **3**, 898$^{80}$
Brezhnev, L. Yu., **8**, 606$^{24}$, 607$^{24}$
Brice, M. D., **1**, 2$^{3}$, 37$^{3}$
Brich, Z., **4**, 257$^{219}$; **6**, 71$^{22}$, 726$^{176}$
Brickner, S. J., **3**, 423$^{79}$, 1031$^{65,65b}$
Brickner, W., **3**, 705$^{1}$
Bridges, A. J., **2**, 90$^{40}$, 616$^{138}$; **3**, 139$^{378}$, 154$^{378}$, 155$^{378}$; **4**, 336$^{28}$, 342$^{28}$, 346$^{28}$, 347$^{28}$, 395$^{205}$; **5**, 333$^{45}$, 683$^{36a}$; **6**, 146$^{89}$, 1016$^{33}$, 1022$^{33}$; **7**, 316$^{47}$, 317$^{47}$, 521$^{35}$; **8**, 844$^{64,64a}$
Bridon, D., **4**, 747$^{153}$, 765$^{223}$; **7**, 726$^{35,37}$, 727$^{38}$, 728$^{41}$, 730$^{49}$
Bridson, J. N., **2**, 111$^{83}$, 242$^{15}$, 909$^{64}$, 911$^{64}$; **4**, 145$^{31,32}$
Brieger, G., **5**, 451$^{30}$, 453$^{30}$, 464$^{30}$, 513$^{5}$, 514$^{5}$, 527$^{5}$; **8**, 320$^{88\text{-}90}$, 440$^{82}$, 551$^{339}$
Brien, D. J., **5**, 1154$^{159}$
Briggs, L. H., **3**, 759$^{126}$; **7**, 92$^{40}$; **8**, 228$^{131}$
Briggs, P. C., **3**, 347$^{25}$; **8**, 530$^{109}$
Brijoux, W., **5**, 1152$^{140,141}$, 1154$^{140,149}$
Brikhahn, M., **4**, 1041$^{105}$
Brill, G., **2**, 356$^{132}$
Brimacombe, J. S., **1**, 760$^{135}$; **4**, 297$^{272,273,274}$; **7**, 262$^{79}$, 440$^{38,39a,b}$
Brimble, M. A., **6**, 750$^{105}$; **7**, 350$^{19}$; **8**, 844$^{66}$
Brindell, G. D., **8**, 755$^{133}$
Brindle, I. D., **4**, 391$^{178c}$
Brindle, J. R., **8**, 64$^{206}$, 66$^{206}$, 250$^{100}$, 253$^{100}$, 254$^{126}$
Brindley, P. B., **7**, 599$^{66}$
Brine, G. A., **3**, 677$^{85}$
Briner, K., **6**, 54$^{128}$, 128$^{162}$
Briner, P. H., **2**, 69$^{48}$; **3**, 196$^{32}$
Bringhen, A. O., **5**, 635$^{87}$
Bringmann, G., **2**, 173$^{181}$; **3**, 505$^{169}$, 677$^{82}$; **6**, 489$^{100}$, 734$^{8}$, 736$^{8,29}$, 738$^{52\text{-}56}$, 751$^{53}$; **8**, 830$^{89}$, 831$^{89\text{-}91}$
Brini, M., **8**, 568$^{469}$
Brinich, J. M., **1**, 488$^{12}$
Brink, M., **7**, 306$^{5}$
Brinker, U. H., **3**, 466$^{183}$; **4**, 1009$^{146}$, 1012$^{173,176}$, 1022$^{252}$; **7**, 800$^{30}$
Brinkman, G. A., **7**, 535$^{47}$
Brinkman, K., **2**, 125$^{223}$
Brinkman, M. R., **7**, 26$^{50}$
Brinkmann, A., **5**, 293$^{46}$, 1188$^{19}$, 1190$^{25}$, 1191$^{25,30}$, 1193$^{30}$, 1197$^{42,43}$
Brinkmann, R., **5**, 37$^{22b}$, 1152$^{141}$, 1153$^{146,147}$, 1154$^{149}$
Brinkmeyer, R. S., **1**, 608$^{41}$; **3**, 125$^{291}$, 126$^{291}$, 223$^{152,153}$, 363$^{88}$, 373$^{127}$; **4**, 402$^{235}$, 404$^{235}$, 408$^{235}$; **6**, 488$^{31}$, 571$^{31}$; **7**, 503$^{273}$; **8**, 165$^{50}$, 545$^{292,293}$
Brintzinger, A., **6**, 226$^{9}$
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Brion, J.-D., **2**, 141$^{39}$; **6**, 436$^{8}$, 515$^{314}$, 522$^{314}$
Brisdon, B. J., **4**, 837$^{19}$
Brisse, F., **2**, 605$^{61}$, 625$^{61}$
Bristol, D., **7**, 41$^{16}$
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Britt, R. W., **2**, 74$^{73}$
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Britton, D., **1**, 33$^{164}$
Britton, R. W., **2**, 843$^{196}$; **3**, 20$^{108}$; **8**, 121$^{79}$, 986$^{14}$
Britton, T. C., **1**, 400$^{9}$
Britton, Th. C., **6**, 118$^{103}$, 248$^{137}$, 256$^{171}$
Britton, W. E., **8**, 389$^{72}$
Brizzolara, A., **3**, 28$^{170}$, 30$^{170}$; **4**, 6$^{21,21a}$, 7$^{21a}$; **6**, 703$^{3}$, 714$^{3}$
Brlik, J., **6**, 917$^{36}$
Broach, V., **8**, 357$^{195}$, 358$^{195}$
Broadbent, H. S., **3**, 124$^{282}$, 125$^{282}$, 128$^{282}$, 129$^{282}$; **8**, 140$^{14}$, 248$^{89}$
Broadbent, T. A., **4**, 24$^{74}$
Broadhurst, M. D., **2**, 477$^{12}$; **3**, 431$^{95,96}$
Broadhurst, M. J., **3**, 380$^{10}$; **4**, 709$^{45}$, 710$^{45,52}$; **5**, 395$^{148}$; **7**, 351$^{28}$, 355$^{28}$
Broadley, K., **2**, 910$^{67}$, 933$^{140}$
Brobst, S. W., **4**, 497$^{97}$
Brocard, J., **3**, 990$^{34,34a}$
Brock, C. P., **5**, 1068$^{12}$
Brock, D. J. H., **3**, 699$^{162}$

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Brockman, H. L., **2**, 456[28]
Brockmann, C. J., **3**, 634[18]
Brockmann, H., **3**, 699[160]
Brockmann, M., **8**, 764[9]
Brocksom, T. J., **1**, 641[107], 672[107], 677[107]; **3**, 222[141]; **5**, 828[7], 839[7], 882[13], 888[13], 891[37], 892[13,37], 893[13]; **7**, 239[54], 355[39]
Brocksom, U., **7**, 355[39]
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Brode, W. R., **2**, 960[34]
Brodie, B. B., **7**, 11[89]
Brodie, T. D., **5**, 718[95]
Brodowski, W., **2**, 598[13]; **5**, 388[137]
Brodskaya, T. G., **8**, 99[107]
Brodt, W., **6**, 650[128]
Broeckx, W., **7**, 475[52]
Broekema, R. J., **6**, 559[860]
Broekhof, N. L. J. M., **1**, 563[172,174]; **6**, 134[32], 705[32-34]; **7**, 235[1]
Broekhuis, A. A., **2**, 662[22], 663[22], 664[22]; **5**, 76[241], 431[121], 434[121b]
Broess, A. I. A., **3**, 367[100]
Broger, E. A., **3**, 431[101]; **5**, 835[59]
Brogli, F., **7**, 867[90]
Brohi, M. I., **3**, 530[74], 534[74]
Brois, S. L., **7**, 474[37]
Broka, C. A., **1**, 104[98]; **2**, 622[155]; **3**, 125[294], 126[294], 167[294], 168[294]; **4**, 378[110], 384[110], 812[181]; **6**, 851[128], 879[43]; **7**, 246[88], 519[21], 633[66]
Brokaw, F. C., **1**, 742[46]; **3**, 766[158]
Brokke, M. E., **3**, 790[59]
Broline, B. M., **5**, 229[121]; **7**, 616[11]
Bromidge, S. M., **4**, 1089[128], 1092[128], 1093[128]
Bromley, D., **7**, 718[3], 724[3]
Broms, M., **4**, 313[461]
Bronberger, F., **5**, 430[116,116b]
Bronneke, A., **1**, 162[91]
Bronson, J. J., **5**, 847[136], 913[105], 1012[49]
Brook, A. G., **1**, 436[147], 608[39], 618[56]; **2**, 601[35]; **3**, 125[314]; **4**, 98[112], 115[182], 120[197]; **5**, 843[126]; **6**, 140[54]; **7**, 163[77], 164[77]
Brook, M. A., **1**, 180[50], 182[50], 366[49], 391[49,149]; **2**, 336[72], 616[132], 619[132], 620[151], 621[132], 630[5], 913[74], 978[10]; **4**, 161[89c]; **6**, 677[309]
Brook, P. R., **3**, 767[162], 901[109]; **7**, 676[63]
Brooke, G. M., **8**, 901[37], 904[53]
Brooke, P. K., **4**, 435[136]
Brooker, A. C., **5**, 949[278]
Brooker, L. G. S., **6**, 477[100]
Brookes, A., **3**, 380[10]
Brookes, C. J., **3**, 648[187]
Brookhart, M., **1**, 116[43]; **4**, 115[180c], 688[67], 696[5,7], 703[32-35], 704[32-34], 705[34b], 712[34,35], 976[100], 980[100j], 983[117,119], 984[120,123,124], 985[130]; **5**, 715[78], 904[49], 905[49], 1084[58], 1086[70,74], 1089[80]
Brookhart, T., **5**, 5[43,45], 8[43,45]
Brooks, D. J., **8**, 584[17]
Brooks, D. W., **1**, 385[116,120], 386[120]; **2**, 112[98], 195[71], 244[30], 246[34], 247[34], 801[31]; **6**, 446[102]; **7**, 579[132]; **8**, 190[75], 198[132], 201[140,142]
Brooks, G., **6**, 471[64]
Brooks, H. G., **1**, 619[60]; **4**, 120[197]
Brooks, J. J., **1**, 12[59]
Brooks, L. A., **2**, 838[174], 839[174]
Brooks, P., **8**, 859[211]
Brookshire, K. W., **5**, 736[145], 737[145]
Broom, A. D., **6**, 635[12], 643[12], 660[210], 662[210]; **8**, 533[154]
Broom, D. M. P., **1**, 130[95]
Broom, N. J. P., **4**, 14[47], 111[154f]
Broome, J., **8**, 315[44], 545[281]
Brophy, B. V., **3**, 901[109]; **7**, 676[63]
Brophy, G. C., **5**, 468[135]
Broschard, R. B., **8**, 973[120]
Broser, E., **5**, 394[146], 395[146]
Bross, H., **5**, 734[137]
Brossi, A., **2**, 1048[7], 1049[7]; **4**, 505[149]; **6**, 736[28], 738[53], 751[53]; **8**, 968[86]
Brossmer, R., **2**, 464[97]; **7**, 306[6]
Broster, F. A., **3**, 418[27]; **7**, 595[28]
Brot, F. E., **3**, 358[66]
Brothers, D., **7**, 130[77]
Brotherton, C. E., **4**, 433[119]; **5**, 65[57], 78[270], 266[76], 267[76], 268[76], 573[127], 594[7], 599[7], 604[7,54]; **6**, 559[864], 751[107]
Brotherton-Pleiss, C. E., **5**, 266[76], 267[76], 268[76]
Brougham, P., **7**, 194[4], 374[78], 674[41]
Broughton, H. B., **4**, 27[81], 35[98f], 380[121]; **5**, 524[55]
Brouin, J., **4**, 905[210]
Brounts, R. H. A. M., **8**, 95[82]
Brouwer, A. C., **3**, 750[82]; **5**, 116[255]
Brouwer, A. M., **5**, 707[40]
Brouwer, D. M., **2**, 727[135]; **3**, 330[191]
Brouwer, W. M., **7**, 759[10]
Brovarets, V. S., **6**, 524[365]
Brovet, D., **8**, 303[98]
Brovko, V. S., **8**, 765[13]
Brower, K. R., **4**, 433[122]
Brown, A., **5**, 857[228]
Brown, A. C., **3**, 633[4]; **6**, 999[124]; **8**, 843[56]
Brown, A. L., **2**, 771[12]
Brown, B. B., **5**, 524[50,52], 539[50], 548[50c]
Brown, B. R., **8**, 314[38], 315[44], 545[281]
Brown, B. S., **3**, 438[35]
Brown, C. A., **1**, 511[29], 566[213]; **2**, 709[12], 710[17], 799[13]; **4**, 10[34], 113[163]; **8**, 14[82,84], 18[120], 240[35], 375[158], 418[13], 422[13], 425[13], 715[85,85b], 716[85]
Brown, C. H., **8**, 756[159], 758[159]
Brown, C. J., **3**, 688[115]
Brown, C. K., **8**, 445[28]
Brown, D., **6**, 487[70], 836[58]; **7**, 131[86], 273[134]
Brown, D. J., **3**, 568[45], 636[59]; **6**, 533[489], 554[732]; **8**, 906[66], 909[66]
Brown, D. L., **4**, 404[244]; **7**, 410[97b]
Brown, D. M., **6**, 614[85]; **8**, 879[50]
Brown, D. S., **2**, 657[162]; **5**, 21[161], 23[161]
Brown, D. W., **2**, 198[85], 632[27], 640[27]; **4**, 1011[166]
Brown, E., **3**, 501[139], 509[139], 512[139]; **4**, 258[255]
Brown, E. A., **6**, 680[331]
Brown, E. D., **3**, 390[71,72], 396[111,114], 398[111,114]; **8**, 231[146]
Brown, E. G., **4**, 380[123], 386[148a], 387[148,148a]; **6**, 26[107]
Brown, E. J., **5**, 829[20]
Brown, E. V., **3**, 564[8]; **7**, 829[57]
Brown, F., **3**, 898[74]; **4**, 976[100]
Brown, F., Jr., **8**, 389[71]
Brown, F. J., **5**, 1065[2], 1066[2], 1074[2], 1083[2], 1084[2], 1093[2]
Brown, F. K., **5**, 79[292], 257[61], 347[72,72c], 516[19,22], 517[22], 518[22]
Brown, F. R., Jr., **2**, 868[20], 869[20], 871[20], 872[20], 876[20], 890[20]
Brown, G. G., Jr., **4**, 665[10], 667[10], 670[10], 674[10]

Brown, G. M., **2**, 466[125]
Brown, G. R., **8**, 563[433], 614[84]
Brown, G. W., **6**, 204[8], 209[8], 213[8]
Brown, H. C., **1**, 192[81], 223[84], 225[84c], 292[23], 343[104], 489[14,16], 563[183]; **2**, 5[22], 6[23,23c], 10[22,23], 13[56], 33[23c,123], 42[146], 43[146,146b], 44[146b,c], 45[146b,c], 52[23a], 111[83,85,86], 112[88], 241[14], 242[14b,16], 247[82], 735[11], 977[3]; **3**, 231[245], 242[6], 249[66], 257[6], 259[6], 260[143], 274[21], 299[33], 300[35,36], 421[53], 483[10,11], 522[20], 523[24], 554[24], 706[6], 779[8], 793[8,69,71-75], 794[76-78], 795[8,75,82-84], 797[75,91-95], 798[95], 799[98]; **4**, 145[23,24,29a], 146[37a,b], 147[38a,39,40], 164[99,99a], 272[32,34], 273[34,47,49,52], 294[244], 300[312,313], 301[312,313,314,315,318,328,329,330], 302[328], 303[339], 309[416,417], 314[478], 756[181,183]; **6**, 78[59,60], 283[167], 284[167,169], 724[160], 865[201], 954[16], 955[25], 958[30]; **7**, 14[134], 16[166], 253[13], 264[90], 474[40,48], 476[48], 594[3], 595[3,11-13,17,19,24,30,127], 596[35-37], 597[49], 598[3,19], 599[62,63,69-71], 600[77], 601[3,77,80,89,90], 602[92,93,103], 603[123,126], 604[127,132,135,137], 605[141,142,144,145], 606[146,147,149,152,153,154,159], 607[162,163,164,165,169], 608[169]; **8**, 1[1], 2[4,14], 14[78,79,84], 15[90], 16[105], 17[109], 18[119,120], 26[2,8,11,13,18,23,25], 27[8,11,13,18], 36[8,11,18], 37[8,11], 43[23], 64[201], 66[23,25,201], 67[25], 74[25,251], 101[123], 159[10], 170[89], 180[10], 214[31,51], 217[68], 237[8,9,15,16], 238[9], 240[8,9,15,34,35], 241[9], 244[8,9,15,16,48,53,60-62], 245[9], 247[8,9,34,48,53], 249[8,15,48,60,93,95], 250[34], 251[104], 253[8,16,48,60,104,116], 260[3,4], 261[7,11-13], 263[21-24,27], 265[21-23], 267[64,65], 269[27,87], 271[105,106,111,112], 273[27], 274[132,133], 275[27], 278, 279, 373[135], 386[51], 403[9], 408[65], 412[111], 524[1], 537[177], 541[1,206,207,211,218], 542[218], 543[218,241], 544[206,269,270,271], 703[1], 704[1-3,5,6,8], 705[1,3,5,6,9,11-13], 706[1,5,6,15,16], 707[1,9,19,21,23-30], 708[1,3,30,33,36,37,40,42], 709[1,15,15a,43,43a,47-51], 710[49,52-55,57-60], 711[62,63,65,67,68], 712[1], 713[1,70-75,77,78], 714[74,75,79-83], 715[1,42,77,84,85a], 716[1,33,85-88,91,92], 717[1,27,28,42,57,98-100,102-104], 718[65,85a,107-115], 719[62,117,118,120-123], 720[1,128,129,134], 721[1,53,54,60,134,139,140,141,142,143], 722[1,134,142,144,145,146,147,148,149], 724[1,33,152,155-167,174,177,178], 725[8a,174,178], 726[11,33,174,177,178,178b,187], 727[112,178], 728[42], 802[78], 803[94], 804[97,98], 805[98], 853[145], 854[149], 856[164,166], 875[34,36,38,39], 876[34,38,42], 877[42], 880[58], 901[36], 906[36], 907[36], 908[36], 909[36], 910[36], 934[55], 939[98], 968[89]
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Brown, J. H., Jr., **8**, 212[16]
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Brown, K. A., **7**, 862[81], 880[155], 888[81]
Brown, K. C., **7**, 564[83], 584[158]; **8**, 383[14], 917[115], 918[115]
Brown, K. H., **5**, 586[205]
Brown, K. L., **6**, 708[50]
Brown, L., **1**, 824[45]; **2**, 205[104], 206[104]; **3**, 225[187]; **5**, 835[59]; **6**, 174[54]
Brown, L. A., **5**, 8[56]
Brown, L. E., Jr., **2**, 175[184]
Brown, L. R., **6**, 801[35]
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Brown, M. J., **1**, 891[147]; **2**, 554[135]; **3**, 792[68]
Brown, N. M. D., **1**, 488[6,10]
Brown, P., **3**, 1056[34], 1062[34]; **5**, 76[243], 385[130]; **6**, 930[85]; **8**, 220[83]
Brown, P. B., **5**, 125[15], 153[25]
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Buchanan, J. G., **3**, 733[1]; **6**, 614[89]; **8**, 309[10], 311[10], 312[10], 313[10]
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Buchholz, M., **6**, 667[243]
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Calo, V., **3**, 222[145], 246[40], 257[40]; **4**, 34[97], 35[97]; **7**, 120[14], 760[49], 764[49], 854[57], 855[57]; **8**, 887[116]

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Calundann, G. W., **7**, 738$^{31}$
Calverley, M. J., **1**, 656$^{148}$, 699$^{148}$; **3**, 89$^{144}$, 107$^{144}$, 109$^{144}$, 116$^{144}$
Calvert, B. J., **8**, 90$^{46}$
Calvin, M., **8**, 152$^{159}$, 285$^{5}$
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Camacho, F., **3**, 327$^{171}$
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Cambie, R. C., **1**, 753$^{102}$; **3**, 675$^{74}$, 753$^{105}$, 759$^{126}$; **4**, 347$^{96}$, 350$^{121}$, 351$^{126}$, 354$^{126-128}$, 369$^{21,22}$, 370$^{21,22}$, 371$^{21}$, 377$^{21,22,101}$, 545$^{126}$; **6**, 668$^{254}$, 669$^{254}$; **7**, 92$^{40}$, 121$^{24}$, 331$^{14}$, 438$^{15,16}$, 445$^{15,16}$, 447$^{16}$, 502$^{261}$, 530$^{20}$, 531$^{20}$, 706$^{25}$; **8**, 944$^{123}$
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Cameron, A. F. B., **6**, 675$^{299}$
Cameron, A. G., **1**, 570$^{263}$; **2**, 800$^{17}$; **5**, 841$^{87,94}$, 863$^{255}$; **6**, 176$^{95,97,98}$, 859$^{171}$
Cameron, D. D., **2**, 148$^{78}$
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Cameron, I. R., **2**, 1048$^{11}$
Cameron, S., **1**, 822$^{38}$; **7**, 177$^{147}$, 550$^{48}$; **8**, 888$^{125}$
Cameron, T. S., **1**, 528$^{122}$, 804$^{308}$, 805$^{308}$; **5**, 645$^{1}$, 650$^{1q,25}$, 651$^{1}$; **7**, 258$^{55}$
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Campbell, A., **3**, 914$^{6}$, 927$^{6}$; **6**, 799$^{22}$
Campbell, A. L., **3**, 209$^{17}$, 216$^{68}$, 224$^{168}$; **4**, 175$^{43}$; **8**, 497$^{37}$
Campbell, B. K., **3**, 273$^{6}$
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Campbell, C., **5**, 515$^{12}$, 516$^{12b}$
Campbell, C. B., **4**, 375$^{93}$, 386$^{93}$
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Campbell, C. L., **6**, 722$^{138}$; **7**, 228$^{91}$
Campbell, D. H., **7**, 485$^{140}$
Campbell, E. A., **8**, 114$^{54}$
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Campbell, J. B., **7**, 597$^{49}$
Campbell, J. B., Jr., **3**, 249$^{66}$, 483$^{10,11}$; **6**, 901$^{123}$, 1066$^{94}$; **8**, 718$^{111}$
Campbell, J. R., **6**, 207$^{47}$; **7**, 571$^{115}$
Campbell, K. N., **3**, 273$^{6}$; **8**, 478$^{39}$, 479$^{39}$
Campbell, M. M., **2**, 632$^{27}$, 640$^{27}$, 1048$^{11}$; **7**, 373$^{72b}$, 473$^{29}$
Campbell, M. W., **2**, 198$^{85}$
Campbell, P., **6**, 423$^{49}$; **7**, 49$^{66,67}$
Campbell, P. G. C., **4**, 314$^{481,482}$, 603$^{274}$; **7**, 92$^{47}$, 94$^{56}$
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Campbell, S., **1**, 694$^{238}$, 697$^{238}$, 698$^{238}$, 801$^{302}$; **6**, 1006$^{145}$
Campbell, S. A., **4**, 38$^{108,108c}$
Campbell, S. F., **6**, 533$^{490}$, 550$^{490}$, 994$^{98}$
Campbell, S. J., **3**, 969$^{136}$
Campbell, T. W., **7**, 84$^{1}$, 85$^{1}$, 108$^{1}$; **8**, 568$^{470}$
Campelo, J. M., **2**, 345$^{18}$, 359$^{18}$, 360$^{18}$
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Campopiano, O., **5**, 242$^{8}$, 243$^{13}$, 244$^{13,14}$
Campos, M. P. A., **4**, 347$^{89}$
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Campos, P. J., **3**, 282$^{48}$; **4**, 347$^{93}$, 351$^{93c}$, 354$^{93d}$; **6**, 494$^{135}$; **7**, 536$^{52-55}$; **8**, 854$^{150}$
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Camps, M., **4**, 312$^{457}$, 313$^{471}$, 315$^{516}$
Camps, P., **6**, 563$^{901}$, 984$^{54}$
Campus, P. J., **2**, 790$^{57}$; **7**, 501$^{255}$
Camus, A., **4**, 170$^{11}$; **8**, 450$^{167}$, 552$^{359}$
Can, N.-T. H., **8**, 540$^{194}$
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Canceill, J., **2**, 289$^{70}$, 291$^{70}$, 292$^{78}$
Candlin, J. P., **8**, 445$^{61}$, 457$^{212}$
Cane, D. E., **2**, 839$^{172}$; **3**, 249$^{64}$, 1059$^{43}$, 1060$^{43}$; **8**, 885$^{103}$
Canepa, C., **2**, 345$^{20}$
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Cannic, G., **3**, 896$^{69}$
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Cannizzo, L., **1**, 743$^{51,68}$, 745$^{68}$, 746$^{51}$, 748$^{68,72}$, 749$^{78}$, 811$^{51}$, 816$^{78}$; **2**, 1062$^{98}$; **4**, 979$^{101}$; **5**, 1115$^{3}$, 1121$^{27}$, 1122$^{3}$, 1123$^{3}$, 1124$^{3,44,49}$
Cannon, J. G., **2**, 760$^{43}$; **8**, 53$^{130}$, 66$^{130}$
Cannon, R. D., **7**, 852$^{33}$
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Cano, F. H., **5**, 410$^{42}$, 411$^{42}$
Canonica, L., **3**, 752$^{97}$; **7**, 153$^{9}$
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Cantacuzene, D., **2**, 209$^{108}$
Cantello, B. C. C., **5**, 985$^{36}$
Cantin, D., **8**, 594$^{70}$
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Cantow, H.-J., **3**, 557$^{48}$
Cantrall, E. W., **7**, 27$^{71}$; **8**, 319$^{74}$
Cantrell, G. L., **5**, 909$^{97}$
Cantrell, T. S., **3**, 381$^{32}$; **5**, 161$^{61,65,66}$, 163$^{65,66}$, 176$^{130}$, 637$^{106}$
Cantuniari, I. P., **3**, 295$^{10}$; **7**, 5$^{25}$
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Caplar, V., **2**, 406$^{47}$; **8**, 459$^{228}$, 535$^{165}$
Caple, G., **5**, 702$^{9,9b}$, 710$^{51}$, 713$^{51}$
Caple, R., **2**, 725$^{108,109}$; **4**, 273$^{50}$, 282$^{141,142}$, 868$^{17}$, 869$^{17}$; **5**, 345$^{70}$, 346$^{70}$, 453$^{66}$, 775$^{176}$, 1055$^{46}$, 1056$^{48}$
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Caporusso, A. M., **3**, 217$^{80,80b}$, 246$^{41}$, 247$^{41}$, 257$^{41}$, 439$^{40,41}$, 483$^{12}$, 491$^{70}$; **8**, 99$^{108}$, 100$^{118}$, 348$^{131}$, 558$^{389}$, 564$^{440}$
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Capparella, G., **8**, 449$^{157}$, 450$^{157}$
Capperucci, A., **4**, 247$^{97}$, 256$^{97}$; **5**, 438$^{162}$
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Capuano, L., **1**, 377$^{97}$; **2**, 1087$^{35}$; **6**, 189$^{187}$, 526$^{396}$, 575$^{967}$
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Cardani, S., **1**, 524$^{88}$; **2**, 103$^{28}$, 266$^{61}$, 267$^{63}$, 515$^{57}$, 516$^{58}$, 605$^{57}$, 614$^{57}$, 630$^{21}$, 631$^{21}$, 632$^{21}$, 634$^{21}$, 640$^{21}$, 641$^{21}$, 642$^{21,73,74,78}$, 643$^{73,74,78}$, 644$^{21,73}$, 645$^{21}$, 920$^{98}$; **4**, 152$^{58}$, 207$^{57,58}$
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Cardellicchio, C., **1**, 416$^{67}$, 452$^{220}$; **3**, 463$^{155,166}$; **4**, 93$^{93d}$; **6**, 446$^{101}$
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Cardillo, G., **2**, 66$^{32}$, 187$^{43}$; **3**, 45$^{250}$; **4**, 375$^{94}$, 377$^{104}$, 386$^{94a,153,153a,157}$, 387$^{94a,153a,157}$, 388$^{164}$, 389$^{166,166a}$, 393$^{164a,c}$, 401$^{226}$, 407$^{104c,153a,157b,254}$, 408$^{254a,b,259c}$; **6**, 26$^{106}$, 533$^{497}$, 648$^{124}$; **7**, 137$^{124}$, 252$^{1}$, 280$^{177}$, 493$^{184}$, 503$^{269}$, 530$^{13}$, 663$^{62}$, 664$^{63}$, 816$^{8}$, 817$^{8}$, 821$^{8}$, 824$^{8}$, 825$^{8}$
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Carey, F. A., **1**, 622$^{71}$, 732$^{17}$, 786$^{251}$; **3**, 135$^{368}$, 136$^{368}$, 137$^{368}$; **4**, 349$^{109}$, 717$^{8}$; **6**, 686$^{372}$, 982$^{49}$; **8**, 216$^{65}$, 486$^{63}$, 487$^{63-66}$, 813$^{14}$, 814$^{14}$
Carey, F. H., **6**, 134$^{12}$
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Carey, S. C., **2**, 878$^{40}$
Cargill, R. L., **3**, 19$^{103}$, 23$^{134}$; **5**, 130$^{42}$, 133$^{57}$, 676$^{3}$, 900$^{11}$, 901$^{11}$, 906$^{11}$, 907$^{11}$, 910$^{11}$; **6**, 689$^{387}$
Caringi, J. J., **3**, 590$^{163}$
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Carless, H. A. J., **2**, 599$^{19}$; **5**, 151$^{5}$, 153$^{24}$, 159$^{53}$, 164$^{77}$, 165$^{84,85,88}$, 167$^{5}$, 168$^{5}$, 178$^{5}$, 180$^{145,146,147,148}$
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Carlson, A. A., **6**, 236$^{57}$, 709$^{54}$
Carlson, B. A., **3**, 794$^{76}$; **5**, 430$^{116}$
Carlson, C. G., **3**, 327$^{168}$
Carlson, C. L., **2**, 744$^{93}$
Carlson, E. H., **2**, 141$^{37}$
Carlson, G. R., **2**, 711$^{35}$; **5**, 768$^{125}$, 779$^{125}$
Carlson, J. A., **5**, 129$^{33}$
Carlson, J. G., **3**, 717$^{45}$, 752$^{94}$; **8**, 946$^{137}$
Carlson, J. L., **3**, 369$^{120}$
Carlson, P. G., **7**, 167$^{100}$
Carlson, P. H. J., **7**, 710$^{52}$
Carlson, R., **2**, 1099$^{114}$; **6**, 705$^{24}$
Carlson, R. D., **6**, 208$^{59}$
Carlson, R. G., **3**, 103$^{207}$, 874$^{71}$; **5**, 218$^{35}$, 219$^{40}$, 221$^{35,59}$, 451$^{32}$, 453$^{32}$, 464$^{32}$, 513$^{5}$, 514$^{5}$, 527$^{5}$; **8**, 528$^{62}$, 880$^{66}$
Carlson, R. K., **4**, 904$^{204}$
Carlson, R. M., **2**, 481$^{20}$; **3**, 106$^{223,224}$, 113$^{223,224}$, 125$^{299}$, 135$^{367}$, 137$^{377}$, 278$^{34}$; **4**, 120$^{201}$, 262$^{307}$, 308$^{405}$; **6**, 677$^{316,316a}$; **7**, 228$^{93}$; **8**, 374$^{147}$
Carlsson, A., **7**, 331$^{15}$, 831$^{64}$
Carlsson, R., **5**, 721$^{102}$
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Carman, R. M., **6**, 204$^{24}$; **7**, 352$^{30}$, 356$^{30}$
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Carmichael, C. S., **5**, 435$^{149}$, 524$^{53}$
Carmody, M. A., **5**, 165$^{86}$
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Caron, H., **5**, 578[155]
Caron, M., **2**, 303[6]; **6**, 89[115], 91[115], 237[62]; **7**, 405[69]
Caronna, S., **6**, 551[682]
Caroon, J. M., **4**, 500[107]
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Carpanelli, C., **5**, 423[89]
Carpenter, A. J., **1**, 471[66], 472[73,74,76], 474[74]
Carpenter, B. K., **1**, 747[63]; **4**, 537[95], 538[102], 539[102], 1036[48]; **5**, 552[27], 595[8], 596[8b], 604[8b], 608[8b], 710[54], 788[16], 854[176], 855[176], 856[176,212,213], 905[62], 908[62], 1000[9,10], 1001[9], 1002[10], 1009[10], 1031[9]
Carpenter, C. W., **5**, 199[25]
Carpenter, F. H., **6**, 635[18], 636[18]
Carpenter, G. B., **1**, 19[105], 26[135,136], 43[136]; **2**, 100[6,7]
Carpenter, J. F., **5**, 424[96]; **6**, 838[65], 900[113]
Carpenter, N. E., **5**, 1075[30]
Carpenter, P. D., **2**, 764[64]
Carpenter, R. A., **2**, 740[59]
Carpenter, T. C., **6**, 213[84]
Carpino, L. A., **3**, 883[109]; **6**, 636[26], 637[26], 638[37,39], 639[47], 671[37], 999[124]; **7**, 480[105], 482[105], 662[50], 763[100], 766[100], 767[196]; **8**, 843[56]
Carpino, P., **2**, 373[273]
Carpino, P. A., **1**, 635[88,89], 806[315]; **3**, 104[208,209], 117[208,209]; **6**, 846[103], 905[145]
Carpio, H., **8**, 526[24]
Carpita, A., **3**, 217[91], 221[128], 439[37], 489[58], 495[58], 511[58], 515[58], 525[38-40], 527[45], 539[45,103,104], 541[45,105], 554[27]; **7**, 453[81]; **8**, 743[49]
Carr, C. S., **7**, 169[116], 171[116]
Carr, D., **8**, 65[211], 66[211]
Carr, D. B., **4**, 143[19]; **8**, 675[38], 677[38], 679[38], 681[38], 692[38], 693[38]
Carr, K., **7**, 630[52]; **8**, 344[123]
Carr, M. D., **3**, 724[15,16], 761[143]; **7**, 445[59]
Carr, P. W., **8**, 52[140], 66[140]
Carr, R. A. E., **1**, 797[293]; **6**, 996[107]
Carr, R. C., **5**, 514[9], 527[9]
Carr, R. V. C., **4**, 390[174]; **5**, 324[18a]; **6**, 1003[134]; **7**, 96[87]; **8**, 844[63]
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Carrasco, M. C., **8**, 312[19]
Carraway, K. L., **6**, 36[30]
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Carre, M. C., **1**, 563[184]; **4**, 250[138], 496[95]; **5**, 692[100]; **6**, 91[121]
Carrea, G., **8**, 194[105]
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Carreira, L. A., **5**, 901[24]
Carrell, C. J., **1**, 8[38]
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Carrick, W. L., **3**, 664[33], 723[9], 731[9]; **7**, 571[120,121], 575[120,121], 576[120,121]
Carrie, R., **4**, 38[109b], 955[11], 964[48], 990[146]; **5**, 254[48], 944[244]; **6**, 76[45], 690[401], 692[401]; **7**, 476[63]; **8**, 385[42], 386[54]
Carrol, J. T., **4**, 386[152a]
Carroll, G. L., **1**, 328[21,23], 846[17]; **3**, 781[13]; **5**, 241[4], 243[10]; **6**, 682[338,340]
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Carroll, P., **2**, 1097[101]
Carroll, P. J., **1**, 838[162]; **3**, 618[21]; **6**, 448[106,107]; **7**, 778[399]
Carroll, S., **7**, 723[23], 724[28]
Carrupt, P.-A., **7**, 257[49]
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Carruthers, W., **1**, 428[121], 429[121], 457[121]; **3**, 1[6], 53[6], 54[6]; **4**, 405[248]; **5**, 451[45]; **7**, 543[11]; **8**, 269[78], 856[184]
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Carson, J. R., **2**, 745[104]; **8**, 28[37], 66[37]
Carson, K. G., **8**, 54[160], 66[160]
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Carter, C. G., **4**, 350[119], 1039[63]; **6**, 531[441]
Carter, D., **7**, 58[56], 62[56], 63[56]
Carter, H. E., **2**, 396[6], 402[6], 403[6]; **4**, 279[108], 310[430]
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Cole, E. R., **7**, 13[110], 338[38], 765[153]
Cole, L. L., **6**, 204[12]
Cole, P., **2**, 911[71]; **4**, 121[209]
Cole, T. E., **3**, 797[93]; **6**, 78[59]; **7**, 595[13], 606[159]; **8**, 289[26],
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Cole, T. W., Jr., **5**, 123[5]
Cole, W., **2**, 838[175]; **6**, 959[43]
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Coleman, D. T., III, **3**, 824[19]; **8**, 86[23]
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Coleman, H. A., **5**, 797[60]
Coleman, J. P., **3**, 634[24], 639[24], 649[24]; **7**, 8[56]; **8**, 133[23,25],
  236[5], 240[5], 242[5], 248[5], 249[5], 292[43]
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Coleman, R. S., **4**, 797[105]; **5**, 492[238,242,243,244], 498[238],
  736[145], 737[145]; **7**, 34[100], 543[23], 544[23]; **8**, 618[114]
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Colens, A., **6**, 493[129]
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Coll, J., **5**, 36[18], 57[54]; **6**, 172[18]; **7**, 123[35], 144[35]; **8**, 500[50],
  515[119], 563[425]
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Collard, J. N., **1**, 219[58]
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Collie, J. N., **2**, 170[170]
Collienne, R., **6**, 472[70]
Collier, T. L., **3**, 35[206]; **4**, 200[2]; **6**, 719[126], 725[126];
  **8**, 159[9], 720[135]
Collignon, N., **1**, 788[257]; **2**, 482[27], 483[27]; **3**, 201[83];
  **4**, 459[77], 473[77], 474[77]
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  273[70], 274[75]; **8**, 552[360]
Collington, E. W., **1**, 366[51], 570[269], 741[45], 779[225]; **2**,
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Collins, C. H., **4**, 272[41], 280[41]; **6**, 1033[129]
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Collins, J. C., **2**, 758[25]; **7**, 100[131], 256[42]

Collins, J. J., **5**, 735[139]; **6**, 866[205]
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Colombo, L., **1**, 72[72], 524[86,87], 526[100], 527[101,102,107], 528[108]; **2**, 103[28], 221[146], 266[61,62], 267[62], 488[43], 514[54], 515[55,56], 605[57], 614[57], 630[19], 631[19], 636[19,56], 637[19,56], 640[56], 642[73], 643[73], 644[73], 930[131], 931[131]; **4**, 113[166], 159[82], 218[145], 226[187,188]; **6**, 118[105], 149[96,108]; **7**, 128[63], 441[45]
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Conn, R. E., **1**, 400[11]; **2**, 113[107], 254[43]
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Conover, L. H., **7**, 157[33]; **8**, 314[25], 974[122]
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Conrad, N. D., **5**, 856[201,203]
Conrad, P., **3**, 960[116]; **5**, 894[48]; **6**, 898[107b]
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Cook, N. C., **4**, 272[38,39], 273[38,39], 287[38,39]
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Cook, S. J., **3**, 1022[19]; **6**, 51[106]
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Cooper, C. S., **6**, 517[328,329]; **8**, 190[75]
Cooper, D., **5**, 847[135]; **8**, 775[77]
Cooper, D. K., **5**, 514[9], 527[9]
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Cooper, M. S., **2**, 962[45], 964[45]; **7**, 194[4], 374[78], 674[41]
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Cox, J. H., **2**, 388$^{341}$
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Cox, P., **2**, 655$^{140}$
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Cox, R. A., **8**, 52$^{146}$, 66$^{146}$
Cox, R. H., **3**, 629$^{53}$; **6**, 23$^{94}$
Cox, S. D., **8**, 446$^{93}$, 452$^{93}$, 534$^{157}$
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Coyle, T. D., **1**, 292$^{24}$
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Coyner, E. C., **5**, 63$^{16}$
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Davis, N. R., **3**, 125$^{314}$
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Doughty, D. H., **3**, $1041^{110}$
Doughty, M., **7**, $772^{296}$
Douglas, A. J., **6**, $455^{155}$
Douglas, A. W., **7**, $877^{135}$; **8**, $54^{159}$, $66^{159}$
Douglas, B., **8**, $568^{471}$
Douglas, E. C., **3**, $328^{179}$
Douglas, J. L., **2**, $170^{174}$
Douglass, C. H., Jr., **6**, $708^{48}$
Douglass, J. E., **3**, $327^{170}$
Douglass, J. G., III, **4**, $1089^{129}$
Douglass, M. L., **4**, $310^{434}$; **8**, $853^{144}$
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Doukas, P. H., **6**, $498^{168}$
Doumaux, A. R., Jr., **5**, $513^{4}$; **7**, $230^{135,136}$, $766^{174}$; **8**, $253^{112}$
Doutheau, A., **4**, $308^{406}$, $311^{452}$, $395^{205,205c,d,206}$, $396^{209}$, $397^{209,211}$; **5**, $773^{166,167}$, $774^{167,169}$, $797^{66}$
Dove, M. F. A., **3**, $299^{33}$
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Dow, R. L., **1**, $400^{11}$; **4**, $384^{145b}$; **6**, $116^{94}$; **7**, $315^{43}$; **8**, $448^{142}$
Dowbenko, R., **3**, $380^{9}$
Dowd, P., **1**, $259^{28}$, $265^{28}$, $894^{154,156}$; **2**, $448^{39}$; **4**, $54^{153b}$, $822^{225}$, $1007^{110}$, $1041^{104}$; **5**, $165^{79}$, $240^{2}$, $244^{2c}$; **6**, $117^{95}$, $677^{318,318a}$, $686^{366}$; **8**, $413^{121}$, $890^{139}$
Dowd, S. R., **1**, $361^{34}$; **3**, $30^{179}$; **4**, $1000^{15}$; **6**, $703^{4}$, $719^{129}$
Dowdall, J. F., **2**, $529^{19}$
Dowell, D. S., **8**, $584^{17}$
Doweyko, A. M., **3**, $158^{447}$, $159^{447}$; **8**, $87^{33}$
Dowle, M. D., **2**, $963^{55}$; **4**, $364^{1,1a}$, $368^{1a}$, $373^{1a}$
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Downe, I. M., **6**, $228^{18}$
Downs, A. J., **8**, $460^{253}$
Doxsee, K. M., **3**, $503^{149}$, $512^{149}$; **4**, $427^{66}$
Doyama, K., **5**, $1137^{56}$
Doyle, I. R., **5**, $561^{86}$; **8**, $806^{104}$, $807^{104}$
Doyle, K. M., **2**, $867^{17}$; **6**, $424^{52}$
Doyle, M. J., **5**, $1185^{1}$
Doyle, M. P., **2**, $710^{27}$; **3**, $919^{29}$, $920^{34}$, $923^{34b}$, $925^{34a}$, $934^{34}$, $1008^{69}$, $1056^{35}$, $1062^{35}$; **4**, $953^{8}$, $954^{8n}$, $964^{45}$, $965^{51}$, $996^{8n}$, $1031^{2,3}$, $1032^{2}$, $1033^{17,20,22,22a}$, $1034^{2}$, $1035^{2,37,41}$, $1036^{47,49,50,53}$, $1037^{17,37}$, $1038^{59}$, $1049^{2}$, $1057^{22a\text{-}c}$; **5**, $904^{47,48}$, $905^{47,48}$, $917^{123}$, $1084^{60}$; **6**, $126^{154}$, $127^{161}$, $208^{56}$, $212^{80}$, $873^{9}$, $874^{9c,13}$, $883^{13}$, $897^{9b}$; **7**, $315^{43}$, $740^{44}$; **8**, $88^{41}$, $89^{41}$, $105^{41}$, $216^{64}$, $319^{70}$, $383^{14}$, $486^{60}$, $487^{60,67}$, $546^{312}$, $801^{74}$, $917^{115}$, $918^{115}$
Doyle, P., **3**, $386^{68}$
Doyle, T. D., **5**, $723^{108a}$
Doyle, T. W., **5**, $92^{70}$, $94^{83\text{-}85}$, $736^{145}$, $737^{145}$; **6**, $538^{573}$, $569^{937}$; **8**, $231^{148}$, $232^{148}$, $303^{97}$, $843^{57}$
Dozorova, E. N., **6**, $554^{773}$
Drabowicz, J., **6**, $149^{98,101}$; **7**, $760^{45}$, $762^{69,74,81}$, $764^{108}$, $777^{69a}$, $778^{69,407}$; **8**, $403^{1,3}$, $404^{1,3,15}$, $406^{46,52}$, $408^{46}$, $410^{52}$
Drach, B. S., **6**, $524^{360,364,365}$, $528^{413}$, $532^{364}$, $539^{577}$
Dradi, E., **4**, $106^{138e}$; **5**, $36^{16}$
Draggett, P. T., **8**, $445^{52}$
Dragisich, V., **5**, $1076^{45}$, $1101^{143}$, $1102^{147}$
Drago, R. S., **4**, $306^{371}$
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Dragu, E., **6**, $489^{85}$
Draguet, C., **6**, $462^{6}$
Drahnak, T. J., **5**, $199^{28}$
Drake, B. V., **5**, $618^{1}$
Drake, C. A., **6**, $284^{177}$
Drake, J., **3**, $380^{8}$
Drake, J. E., **3**, $46^{255}$, $47^{255}$
Drake, R., **1**, $493^{42,42b}$, $495^{42}$
Drake, S. D., **7**, $347^{17}$, $355^{17}$
Drakesmith, F. G., **8**, $901^{35,41}$, $903^{35}$, $905^{35}$
Dralle, G., **3**, $647^{199}$
Dran, R., **2**, $816^{85}$
Draney, D., **2**, $345^{32}$
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Draper, R. W., **7**, $488^{154}$, $504^{154}$, $508^{154}$
Dra$\check{\text{s}}$ar, P., **2**, $382^{313}$
Drauz, K., **8**, $459^{228}$
Drebowicz, J., **7**, $778^{407}$
Drechsel-Grau, E., **4**, $729^{61}$, $730^{61}$, $765^{61}$
Drechsler, H. J., **6**, $524^{355}$, $525^{355}$, $527^{410}$, $532^{355}$
Drechsler, K., **6**, $834^{40}$
Drees, F., **6**, $644^{87}$
Drefahl, G., **4**, $280^{130}$, $281^{130}$, $282^{130}$, $286^{130}$
Dreger, L. H., **5**, $857^{229}$
Dreiding, A. S., **1**, $876^{102}$; **2**, $158^{123}$, $711^{30}$, $725^{115}$; **3**, $804^{3}$, $807^{22}$, $810^{48}$, $1049^{14,15}$, $1058^{42}$; **4**, $148^{50}$; **5**, $18^{128}$, $689^{73}$, $710^{47}$, $770^{137,138,139}$, $806^{106}$, $829^{25}$, $1025^{83}$, $1026^{83}$; **6**, $778^{63}$, $1058^{60}$; **7**, $483^{120}$, $487^{147}$, $493^{147}$, $495^{147}$
Dreikorn, B. A., **6**, $526^{392}$
Drenth, W., **4**, $278^{95}$, $286^{95}$, $289^{95}$; **6**, $489^{89,94}$, $533^{508}$; **7**, $95^{70,70a}$
Dresely, K., **1**, $149^{50}$
Dresely, S., **2**, $39^{137,137b,139}$, $44^{151,151a}$, $45^{151}$; **7**, $597^{52}$
Dress, F., **6**, $644^{94}$
Dressaire, G., **1**, $115^{40}$; **2**, $784^{39a}$
Dressel, J., **3**, $874^{70}$
Dressler, H., **2**, $362^{186}$, $363^{186}$
Dressler, V., **4**, $6^{23}$
Dreux, J., **4**, $4^{14}$, $191^{114}$; **7**, $124^{41}$
Dreux, M., **3**, $257^{117}$
Drevs, H., **4**, $841^{46}$
Drew, H. D. K., **7**, $774^{328,329}$
Drew, J., **7**, $821^{31}$
Drew, M. G. B., **2**, $823^{115}$; **5**, $648^{20}$
Drew, R., **4**, $303^{342}$, $390^{175b}$
Drew, R. A. I., **7**, $635^{70}$; **8**, $854^{152}$, $856^{152}$
Drewer, R. J., **4**, $953^{8}$
Drewes, M. W., **1**, $56^{29}$, $460^{3}$; **2**, $646^{84}$; **6**, $644^{88}$
Drewes, S. E., **1**, $188^{72}$, $189^{72}$; **2**, $20^{81}$, $51^{81}$; **3**, $421^{52}$; **4**, $34^{97}$, $35^{97}$; **5**, $834^{56}$
Drewniak, M., **6**, $84^{86}$
Drexler, S. A., **4**, $213^{106}$, $215^{106}$
Dreyer, G. B., **5**, $656^{30}$, $660^{30}$, $667^{43}$, $924^{148}$
Driessen, P. B. J., **6**, $294^{245}$
Driessen-Engels, J. M. G., **3**, $367^{101}$
Driggs, R. J., **3**, $470^{204}$, $473^{204}$
Driguez, H., **6**, $648^{123}$; **7**, $499^{231}$
Drizina, I. A., **6**, $554^{730}$
Droghini, R., **2**, $648^{97,97c}$, $649^{97c}$
Dromzee, Y., **8**, $847^{88,88d}$
Dronkina, M. I., **6**, $496^{154}$, $543^{622,623}$, $552^{622}$
Dronov, V. I., **7**, $767^{190}$
Drosten, G., **8**, $303^{102}$

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Drozd, V. N., **4**, 50[142], 452[7]; **7**, 606[161]
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Druckrey, E., **5**, 708[41]
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Dua, S. S., **3**, 457[128]
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Dubac, J., **5**, 2[19], 3[19]; **6**, 832[15]
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Dube, S., **1**, 508[20]; **3**, 96[164], 98[164], 99[164]; **8**, 531[115]
Dubeck, M., **7**, 587[168]
Düber, E. O., **2**, 510[44]; **6**, 722[141], 724[141]
Dubey, S. K., **5**, 420[75]; **6**, 958[35]; **7**, 489[170]
Dubina, V. L., **6**, 428[83]
Dubini, R., **3**, 996[45]; **5**, 851[166]
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Dubois, J. C., **2**, 286[62]; **4**, 106[138d]
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Dubois, M., **2**, 153[110,111], 268[69]
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Dudek, V., **8**, 161[17], 176[129]
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Dudley, C., **7**, 107[168]
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Duffaut, N., **3**, 577[90]; **8**, 518[131]
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Dufour, R., **1**, 644[123], 646[123], 668[123], 669[123], 695[123]
Dufresne, C., **8**, 315[52], 316[57], 969[94]
Dufresne, Y., **6**, 210[74], 214[74]
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Duggan, A. J., **5**, 459[91], 612[73]; **8**, 795[16]
Duggan, M. E., **3**, 224[174], 618[20,21]; **5**, 687[67]; **7**, 407[84b], 408[88c]
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Duggleby, P. McC., **3**, 888[15]; **6**, 129[165]
Duguay, G., **6**, 554[751,752]; **8**, 658[100]
Dugue, B., **2**, 1004[60], 1005[60]
Dugundji, J., **2**, 1090[75]
Duh, H.-Y., **5**, 260[68], 261[68], 262[68]
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Duhamel, P., **1**, 56[30], 366[47], 566[210]; **2**, 899[25], 900[25]; **4**, 159[81]; **6**, 509[256], 713[80b], 717[109]
Duhl-Emswiler, B. A., **1**, 514[52], 755[116], 756[116], 758[116,116a], 761[116]
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Duke, A. J., **3**, 767[162]
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Duke, R. E., Jr., **5**, 216[14], 219[14], 626[34]
Duke, R. K., **7**, 373[74], 375[74]
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Dumas, P., **7**, 282[178]; **8**, 113[37]
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Dumont, C., **5**, 677[9,10]
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Florent'ev, V. L., **5**, $491^{206}$
Flores, M. C. L., **7**, $745^{74}$
Flores R, H., **3**, $901^{112}$
Florian, W., **2**, $368^{234}$
Floriani, C., **1**, $29^{150}$; **2**, $127^{229}$; **5**, $1174^{36}$; **8**, $447^{125}$, $683^{90}$
Florio, E., **8**, $517^{127}$
Florio, S., **1**, $113^{29}$; **2**, $87^{26,27}$, $211^{117}$, $213^{127}$, $495^{64,65}$, $496^{64,65}$; **3**, $461^{145}$; **7**, $737^{15}$
Floris, B., **4**, $300^{306}$
Florvall, L., **8**, $617^{108}$
Flowers, H. M., **6**, $41^{44}$
Flowers, L. I., **4**, $931^{57}$
Flowers, M. C., **5**, $910^{79}$
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Floyd, A. J., **4**, $811^{172}$; **5**, $723^{106}$
Floyd, C. D., **3**, $200^{69}$; **5**, $536^{96}$
Floyd, D., **1**, $430^{130}$
Floyd, D. M., **1**, $112^{25}$, $118^{58}$, $129^{58}$; **3**, $217^{87}$, $250^{70,73}$; **4**, $176^{47}$, $183^{79}$; **5**, $553^{43}$; **6**, $9^{42}$, $21^{78}$
Floyd, J. C., **1**, $412^{52}$
Floyd, M. B., **4**, $141^{15}$, $142^{15}$; **6**, $648^{124}$
Fluckiger, E., **2**, $875^{30}$
Fludzinski, P., **3**, $284^{54}$; **4**, $42^{121}$, $129^{224}$; **6**, $967^{104}$; **8**, $237^{11}$
Fluharty, A. L., **8**, $269^{89}$
Flynn, A. P., **5**, $461^{101}$, $463^{101}$
Flynn, D. L., **1**, $134^{113}$; **2**, $824^{121}$
Flynn, G. A., **2**, $911^{68}$
Flynn, J. H., **8**, $447^{107}$
Flynn, J. R., **2**, $760^{43}$; **8**, $53^{130}$, $66^{130}$
Flynn, K. E., **7**, $413^{116}$, $416^{121a}$
Flynn, R. M., **6**, $172^{10}$
Flynn, R. R., **4**, $490^{66}$, $499^{66}$
Flynn, S. T., **5**, $1156^{164}$
Foa, M., **3**, $1018^{11}$, $1026^{37}$, $1033^{72}$, $1039^{100}$; **5**, $1138^{62}$
Fobare, W. F., **2**, $1002^{56}$, $1027^{76}$, $1034^{89,90}$; **4**, $735^{85}$; **5**, $408^{34}$, $409^{34}$, $411^{34,43}$, $552^{39}$; **6**, $212^{80}$, $859^{174}$
Fobker, R., **1**, $831^{100}$
Focella, A., **8**, $606^{18}$
Foces-Foces, C., **5**, $410^{42}$, $411^{42}$
Fochi, R., **2**, $737^{39}$; **3**, $125^{307}$; **6**, $134^{13}$; **8**, $277^{153,154}$, $660^{109}$
Fodor, C. H., **7**, $224^{54}$
Fodor, G., **2**, $735^{17}$; **6**, $213^{84}$, $291^{206,218,219,220}$, $525^{375,378}$, $529^{467}$
Fodor, P., **6**, $430^{95}$
Foerst, D. L., **6**, $437^{35}$
Foerst, W., **2**, $477^{7}$, $478^{7}$; **5**, $451^{7}$; **6**, $242^{86}$, $243^{86,100}$; **8**, $536^{169}$
Fogagnolo, M., **3**, $232^{267}$, $511^{186,187}$, $514^{186}$
Foglia, T. A., **7**, $498^{229}$
Föhles, J., **6**, $668^{253}$, $669^{253}$
Föhlisch, B., **5**, $595^{18,20}$, $596^{18,20}$, $605^{62}$, $609^{69}$; **8**, $91^{63}$
Föhr, M., **7**, $770^{251}$, $773^{303}$
Fok, C. C. M., **8**, $884^{98}$, $885^{98}$
Fokin, A. V., **7**, $493^{196}$
Fokken, B., **6**, $509^{244}$
Fokkens, R., **6**, $494^{131}$
Foland, L. D., **5**, $689^{76,77}$, $690^{80,80c}$, $733^{136,136c,f,g}$, $734^{136f,g}$
Folcher, G., **8**, $737^{26}$
Foley, H. C., **5**, $1090^{89}$
Foley, K. M., **8**, $767^{23}$
Foley, L., **5**, $75^{214}$
Folkers, E. A., **3**, $14^{74,75}$, $15^{74,75}$
Folkers, K., **2**, $284^{56}$; **7**, $778^{414}$
Folli, U., **3**, $95^{154}$, $119^{154}$; **5**, $439^{166}$; **7**, $777^{371,372,373,384}$
Folliard, J. T., **6**, $937^{114}$
Folsom, T. K., **8**, $502^{62}$
Folting, K., **3**, $583^{119}$; **8**, $550^{329}$
Foltz, R. L., **5**, $455^{80}$
Fomum, Z. T., **4**, $55^{157}$, $57^{157c}$, $251^{145}$
Foner, S. F., **8**, $472^{8}$
Fones, W. S., **3**, $888^{17}$
Fong, L. K., **8**, $671^{16}$
Fong, W. C., **3**, $854^{75}$
Fonken, G. J., **3**, $329^{189}$; **4**, $241^{57}$; **5**, $702^{12}$
Fonken, G. S., **2**, $169^{166}$; **7**, $54^{3}$, $56^{3}$, $58^{35,36}$, $66^{3}$, $77^{3}$, $78^{3}$, $429^{152}$
Font, J., **2**, $381^{300}$; **6**, $4^{19}$, $173^{42}$, $563^{901}$, $984^{54}$
Fontain, E., **2**, $1093^{84,85}$
Fontaine, T. D., **8**, $220^{86}$, $228^{132}$
Font-Altaba, M., **1**, $34^{223}$; **3**, $380^{7}$
Fontan, R., **4**, $478^{168}$
Fontana, F., **4**, $768^{235,240,243}$, $770^{244}$; **7**, $778^{411}$
Fontanella, L., **8**, $641^{27}$
Fontanille, M., **4**, $980^{115}$, $982^{115}$; **5**, $1103^{150}$, $1104^{150,158}$
Fontecave, M., **7**, $95^{72}$, $108^{176}$, $383^{109}$
Fooks, A. G., **3**, $829^{55}$
Foos, J. S., **2**, $710^{26}$; **6**, $986^{68}$
Foote, C. S., **5**, $72^{182}$, $428^{107}$, $429^{107}$; **7**, $98^{99}$, $765^{166}$, $769^{220}$, $881^{158,159}$, $884^{187}$
Foote, R. S., **2**, $512^{46}$, $522^{72}$, $523^{73}$
Forbes, C. P., **7**, $299^{51}$
Forbes, E. J., **8**, $963^{45}$
Forbes, J. E., **8**, $393^{113}$
Forbes, W. F., **5**, $757^{77}$, $758^{83}$, $759^{77}$
Forbus, T. R., **3**, $328^{179}$
Forbus, T. R., Jr., **2**, $740^{54}$
Forcellese, M. L., **7**, $832^{69}$
Forche, E., **4**, $270^{5}$, $271^{5,23}$, $272^{23}$; **6**, $204^{4}$
Forchiassin, M., **4**, $20^{63}$, $21^{63}$
Ford, G. P., **4**, $484^{11}$; **5**, $856^{197}$
Ford, J. A., Jr., **7**, $706^{21}$
Ford, M. E., **6**, $725^{170}$, $728^{170}$; **7**, $665^{67}$, $829^{59}$
Ford, P. W., **5**, $804^{96}$
Ford, T. A., **5**, $1138^{65}$; **8**, $814^{20}$
Ford, T. M., **1**, $859^{65}$; **4**, $1089^{136}$
Fordham, W. D., **8**, $542^{231}$
Ford-Moore, A. H., **7**, $764^{113}$
Fordyce, W. A., **8**, $455^{205}$
Foreman, G. M., **8**, $425^{47}$, $476^{22}$
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Forenza, S., **5**, $736^{145}$, $737^{145}$; **8**, $347^{141}$, $350^{141}$
Foresti, E., **4**, $426^{55}$; **5**, $829^{15}$
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Forlani, L., **4**, $426^{55}$
Fornasier, R., **1**, $828^{70}$; **2**, $435^{60}$; **5**, $211^{61}$; **8**, $170^{73,75,76}$, $409^{86}$, $412^{86}$
Forni, A., **1**, $837^{155}$, $838^{160}$; **7**, $747^{96}$, $778^{402}$; **8**, $187^{37}$
Forni, L., **7**, $8^{59}$
Forrest, A. K., **5**, $404^{17}$, $428^{109}$; **8**, $389^{67}$
Forrest, D., **5**, $901^{28}$
Forrester, A. R., **3**, $689^{122}$
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Fowler, J. S., **2**, 959[30]; **4**, 445[204]; **8**, 344[123]
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Fowler, R., **2**, 901[35], 908[35], 909[35], 910[35]
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Francis, R. F., **2**, 912[72]; **8**, 583[12]
Francisco, C. G., **4**, 814[187], 817[203]; **7**, 157[34], 495[210], 722[19], 723[19], 725[19]
Francisco, M. A., **8**, 843[49]
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Franck, R. W., **2**, 720[85]; **4**, 239[18], 249[18], 257[18], 261[18]; **5**, 348[74a], 414[54], 499[252], 500[252], 531[82]; **6**, 705[25]; **7**, 258[53]; **8**, 939[97]
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Francois, D., **1**, 543[19]
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Franich, R. A., **3**, 753[105]
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Frank, F. J., **7**, 100[131], 256[42]
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Frank, R., **2**, 424[35]; **6**, 526[391]; **7**, 206[68], 212[68], 765[152]

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Frank, R. L., **4**, 6[20]
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Frank, W. C., **4**, 401[228c]
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Franke, F. P., **2**, 456[58,63], 458[58,63]
Franke, K., **6**, 579[983]
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Frankel, E. N., **8**, 451[179,180,183], 554[367], 567[367b]
Frankel, J. J., **3**, 757[124]; **6**, 271[86]
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Franko, J. B., **8**, 51[123], 66[123]
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Frantzen, V., **3**, 888[20], 889[20], 894[20]
Franz, J. A., **4**, 736[89], 738[89], 797[101]
Franz, J. E., **4**, 35[98c]; **6**, 419[12]; **7**, 506[298]
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Franzen, V., **3**, 553[13]; **5**, 913[107]; **6**, 122[136]; **7**, 663[56,57], 833[75]; **8**, 87[31]
Franzmann, K. W., **8**, 964[57]
Franzus, B., **5**, 856[210], 1003[22]; **6**, 205[30]; **8**, 475[17]
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Galindo, J., **1**, 417[70], 418[74]; **5**, 456[85]
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Gallagher, T., **2**, 73[67], 655[140]; **3**, 673[70], 674[70b]; **4**, 308[410], 397[210], 412[268b-e,269,270,270b], 413[268c,269b], 562[34]; **5**, 385[130]; **6**, 930[85]; **7**, 199[37]; **8**, 623[148]
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Gallmeier, H. J., **5**, 436$^{157}$
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Gallos, J. K., **3**, 282$^{47}$
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Gallucci, J. C., **1**, 240$^{43}$; **2**, 926$^{115}$, 937$^{115}$; **4**, 374$^{91}$, 790$^{41}$, 791$^{41,48}$, 1010$^{157}$; **5**, 100$^{152}$, 857$^{230}$; **7**, 163$^{76}$, 164$^{76}$, 647$^{31}$; **8**, 447$^{129}$, 463$^{129}$, 514$^{107}$, 861$^{224}$
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Galton, S. A., **4**, 42$^{122a}$; **8**, 995$^{70}$
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Gambaro, A., **2**, 6$^{29,31,32}$, 18$^{31}$, 564$^{12}$, 566$^{20}$, 726$^{127}$; **4**, 527$^{67}$
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Gambaryan, N. P., **5**, 113$^{227,234}$; **6**, 498$^{169}$, 527$^{409}$, 547$^{667}$, 552$^{667}$; **7**, 800$^{35}$
Gamboni, R., **7**, 162$^{56}$, 180$^{160}$
Gammill, R. B., **3**, 24$^{146}$, 969$^{133}$; **5**, 683$^{35}$; **6**, 501$^{205}$, 893$^{88}$; **7**, 452$^{57}$, 462$^{123}$, 571$^{119}$, 577$^{119}$; **8**, 542$^{221,238}$
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Gander-Coquoz, M., **3**, 40$^{221}$, 41$^{227}$
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Gandhi, S. S., **4**, 505$^{132,133}$; **6**, 819$^{110}$
Gandillon, G., **5**, 913$^{108}$
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Gandolfi, R., **4**, 1093$^{147}$; **5**, 78$^{281}$, 257$^{60}$, 625$^{31}$, 626$^{33}$
Gandolfi, V., **2**, 369$^{245}$
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Ganellin, C. R., **4**, 33$^{95,95a}$
Ganem, B., **1**, 329$^{36}$, 343$^{105,118}$, 619$^{63}$; **2**, 904$^{51}$; **3**, 22$^{132}$, 224$^{169}$, 262$^{169}$, 1055$^{32}$; **4**, 8$^{27}$, 240$^{53}$, 254$^{183}$, 260$^{183}$, 367$^{13}$, 369$^{19,23}$, 373$^{74}$, 374$^{19}$, 398$^{213}$, 404$^{247}$, 405$^{247a,b}$, 1036$^{48}$; **5**, 335$^{49}$, 854$^{176}$, 855$^{176}$, 856$^{176}$; **6**, 5$^{23,27}$, 95$^{147}$, 116$^{84}$, 685$^{364}$, 807$^{60}$; **7**, 299$^{42}$, 367$^{58}$, 403$^{64}$, 406$^{72}$, 503$^{272}$, 545$^{27}$, 636$^{72}$, 656$^{13}$, 745$^{79}$, 763$^{89}$; **8**, 29$^{40,41}$, 36$^{78}$, 37$^{78}$, 39$^{78}$, 44$^{78}$, 46$^{78}$, 54$^{78}$, 56$^{170}$, 64$^{199}$, 66$^{40,41,78,170,199}$, 253$^{119}$, 254$^{123}$, 355$^{181}$, 375$^{157}$, 499$^{44}$, 536$^{176}$, 794$^{11}$, 798$^{62}$, 800$^{62}$, 839$^{24}$, 890$^{143}$, 929$^{32}$
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Ganguly, S. N., **6**, 546$^{655}$, 552$^{655}$
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Ganis, P., **2**, 564$^{9}$, 566$^{20}$; **4**, 744$^{131}$
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Gano, J. E., **5**, 65$^{66}$
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Gänshirt, K. H., **8**, 494$^{24}$
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Garbarino, G., **4**, 426$^{58}$, 457$^{63,64}$, 460$^{64}$, 475$^{148}$, 476$^{64,158,159,160,161}$; **6**, 240$^{80}$
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Garbesi, A., **3**, 179$^{547}$, 181$^{547}$
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Garburg, K.-H., **6**, 943$^{156}$
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Garcia, B., **3**, 87$^{99}$, 104$^{99}$; **4**, 768$^{239}$; **7**, 732$^{59}$
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Garcia, G. A., **1**, 552$^{81,83}$; **2**, 183$^{18}$; **3**, 198$^{49}$; **8**, 544$^{262}$
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García, J. I., **2**, 406$^{45}$
Garcia, J. L., **4**, 517$^{5}$, 518$^{5}$, 535$^{93}$, 537$^{95}$, 538$^{93}$, 539$^{93}$
Garcia, J. M., **2**, 649$^{102}$, 1059$^{75}$; **8**, 125$^{94}$
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Garcia, T., **6**, 490$^{101,103}$
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Garcia Mendosa, P., **2**, 348$^{60}$, 357$^{60}$
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Garcia-Raso, A., **3**, 825$^{24,24b}$, 835$^{24}$; **7**, 346$^{8}$

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Garcia Segura, R., **2**, 386$^{329}$
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Gardein, T., **1**, 34$^{224}$, 36$^{174}$
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Gardner, D. V., **4**, 674$^{36}$
Gardner, H. C., **7**, 874$^{102}$
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Gardner, J. H., **8**, 254$^{124}$
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Gardner, J. O., **3**, 48$^{260}$; **4**, 83$^{65c}$
Gardner, P. D., **2**, 149$^{84}$, 736$^{28}$; **4**, 276$^{80}$, 303$^{346}$, 304$^{346}$, 310$^{425}$, 1014$^{191}$; **6**, 970$^{127}$; **7**, 167$^{99}$; **8**, 530$^{95}$, 708$^{31}$, 806$^{110}$, 807$^{110,119}$
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Gardner, T. S., **7**, 666$^{77}$
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Gardrat, C., **4**, 753$^{166}$
Garegg, J., **8**, 969$^{96}$
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Garner, P., **1**, 759$^{133}$; **2**, 699$^{83}$; **4**, 1041$^{104}$; **5**, 344$^{67a,b}$, 349$^{76}$, 854$^{175}$; **7**, 407$^{80}$, 569$^{107}$
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Garti, N., **8**, 421$^{29}$, 422$^{29}$, 436$^{74}$, 437$^{76,77}$
Gartiser, T., **8**, 384$^{27}$
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Garver, L., **4**, 311$^{451}$
Garvey, B. S., **8**, 140$^{20}$, 150$^{20}$
Garvey, D. S., **1**, 410$^{43,44}$, 436$^{153}$; **2**, 2$^{7}$, 100$^{13}$, 113$^{102}$, 224$^{153}$, 240$^{13}$, 242$^{18}$, 245$^{18b}$, 246$^{18b}$, 253$^{42}$, 256$^{13}$, 303$^{5}$, 630$^{9}$, 926$^{117}$; **5**, 832$^{41}$; **7**, 257$^{52}$
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Gasc, J. C., **3**, 21$^{131}$
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Gasdaska, J., **1**, 821$^{27}$; **4**, 1081$^{79}$; **6**, 542$^{602}$
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Gaset, A., **1**, 821$^{20\text{-}22}$; **2**, 354$^{108}$, 404$^{40}$, 772$^{17}$, 775$^{29}$; **6**, 173$^{46}$, 175$^{46,71,73}$
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Gasiorek, M., **8**, 606$^{22}$
Gaskell, A. J., **8**, 587$^{34}$
Gaspar, P. P., **5**, 950$^{285}$; **8**, 765$^{16}$
Gasparrini, F., **6**, 727$^{190}$
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Gassman, P. G., **1**, 118$^{61}$, 648$^{137}$, 654$^{137}$, 655$^{137}$, 846$^{17}$; **3**, 334$^{218}$, 614$^{5}$, 649$^{206}$, 876$^{78\text{-}80}$, 890$^{31}$, 901$^{112}$, 903$^{99}$, 905$^{138}$, 969$^{131,132}$; **4**, 285$^{161}$, 430$^{94,95,97}$; **5**, 341$^{58}$, 520$^{37,38,40,41}$, 521$^{42}$, 522$^{41}$, 585$^{203}$, 856$^{216}$, 936$^{200}$, 1186$^{4}$; **6**, 237$^{64}$, 243$^{64}$, 657$^{181}$, 672$^{181}$, 736$^{24}$; **7**, 125$^{55}$, 126$^{55}$, 208$^{81}$, 476$^{62}$, 794$^{5}$, 874$^{104}$, 878$^{145}$; **8**, 899$^{27}$, 994$^{62}$
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Gaston, R. D., **5**, 527$^{63}$, 534$^{90}$, 535$^{90}$
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Gatenbeck, S., **6**, 811$^{76}$
Gates, B. C., **7**, 840$^{7}$
Gates, J. W., Jr., **3**, 747$^{72}$; **8**, 912$^{90}$
Gates, M., **8**, 330$^{28,29}$
Gatilov, Y. V., **3**, 386$^{68}$
Gatterman, L., **3**, 582$^{112}$
Gatti, A., **2**, 737$^{39}$; **8**, 277$^{153}$
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Gattow, G., **6**, 233$^{49}$, 552$^{694}$
Gattuso, M., **4**, 387$^{160}$
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Gaudemar, F., **4**, 55$^{156}$
Gaudemar, M., **1**, 214$^{22,22a}$, 218$^{22,49}$, 220$^{22,49,65}$, 223$^{49}$; **2**, 81$^{2,4,5}$, 122$^{193}$, 183$^{19}$, 277$^{5}$, 279$^{5,15}$, 280$^{28}$, 281$^{5}$, 283$^{49}$, 284$^{55}$, 286$^{65,66}$, 287$^{65}$, 291$^{75}$, 292$^{76}$, 294$^{84}$, 296$^{84}$, 486$^{38}$, 630$^{22}$, 631$^{22}$, 632$^{22}$, 634$^{22}$, 635$^{51}$, 640$^{51}$, 983$^{28}$, 989$^{34,35}$, 990$^{34}$, 992$^{36}$, 993$^{36}$; **4**, 89$^{84f}$, 95$^{102b,e,g}$, 880$^{91}$, 883$^{91,101}$, 884$^{101,105}$; **5**, 100$^{145}$; **6**, 425$^{69}$
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Gaudemer, F., **7**, 451[35], 462[35]
Gaudenzi, M. L., **3**, 217[91], 539[103]
Gaudin, J.-M., **1**, 767[179]; **5**, 46[38], 47[41], 48[38,41], 49[38], 50[38,41,43], 51[45,45a], 53[45a], 55[49], 56[49]; **7**, 229[120]
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Gaudry, R., **8**, 527[43,45], 528[45], 529[45], 530[45]
Gaugler, R. W., **6**, 263[21]
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Gaul, M. D., **3**, 1061[46], 1062[46]; **4**, 501[114]; **5**, 854[175]
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Gault, H., **2**, 147[73]
Gault, R., **6**, 288[185,191]
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Gaur, J. N., **7**, 705[15]
Gaus, P. L., **8**, 22[146], 289[28], 371[114]
Gautheron, B., **6**, 464[31,32]; **8**, 447[120,129], 463[129], 683[87,94], 688[99], 690[101], 691[99]
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Graythwaite, W. R., **7**, 779$^{423}$
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Greaves, A. M., **2**, 1057$^{71}$, 1058$^{71}$; **5**, 407$^{29}$
Greaves, E. O., **2**, 722$^{91,92}$; **4**, 697$^{12}$, 698$^{14}$
Greaves, P. M., **4**, 55$^{157}$; **6**, 235$^{53}$, 265$^{40}$
Greaves, W. S., **3**, 643$^{125}$
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Greck, C., **1**, 513$^{49}$, 833$^{118}$; **3**, 174$^{527}$, 175$^{527c}$, 258$^{127}$; **4**, 381$^{126b}$, 382$^{126}$, 383$^{126}$; **6**, 93$^{132}$, 155$^{155}$, 156$^{155,156,157}$, 994$^{98}$; **7**, 487$^{146}$, 495$^{146}$; **8**, 12$^{66}$, 837$^{17}$
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Greeley, R. H., **5**, 716$^{88}$
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Green, B., **2**, 355$^{119}$, 382$^{314}$; **8**, 248$^{83}$
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Green, B. S., **3**, 382$^{36}$; **5**, 183$^{157}$; **8**, 977$^{138}$
Green, D. L. C., **1**, 350$^{155}$
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Green, F. R., III, **1**, 804$^{313}$, 805$^{313}$; **4**, 142$^{16}$; **5**, 308$^{95}$; **6**, 938$^{126}$, 968$^{107}$, 998$^{120,121}$
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Green, G. E., **3**, 735$^{18}$
Green, I. R., **2**, 746$^{109}$
Green, J., **6**, 644$^{83}$; **8**, 528$^{81}$, 529$^{81}$
Green, J. A., II, **6**, 294$^{231}$
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Green, M. J., **6**, 563$^{903}$, 1019$^{44}$
Green, M. L. H., **1**, 139$^{4}$; **4**, 980$^{108}$; **6**, 686$^{370}$; **7**, 3$^{11}$, 4$^{17,18}$; **8**, 99$^{107}$, 459$^{439}$, 889$^{129}$
Green, M. M., **7**, 777$^{369}$
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Greenberg, S. G., **5**, 492$^{246}$
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Greene, R. N., **5**, 908$^{72}$
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Grimm, E. L., **4**, 27[79], 1048[119]; **5**, 539[105]
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Grimm, K. G., **6**, 147[87]
Grimm, R. A., **8**, 836[1,1c], 837[1], 995[69]
Grimme, W., **5**, 10[78], 552[29,37], 702[10], 716[10], 794[47], 806[47], 824[47], 847[136]
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Grimova, J., **6**, 524[368]
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Grinberg, V. A., **3**, 647[177,196], 648[177,178], 649[177]
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Grisdale, P. J., **1**, 580[4]; **8**, 496[34]
Grisebach, H., **6**, 294[235]
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Grisso, B. A., **2**, 655[149]
Grissom, J. W., **4**, 1086[111]; **8**, 651[68]
Griswold, P. H., Jr., **6**, 678[324]
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Grivet, C., **4**, 532[88], 534[88], 537[88], 538[88], 539[88]
Grizik, S. I., **6**, 554[773]
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Grobe, J., **5**, 442[183], 444[188], 577[147]
Grobe, K. H., **7**, 10[80]
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Gröbel, B. T., **1**, 542[3], 544[3], 563[3], 564[3], 566[3], 568[3], 569[3], 636[95], 642[95], 665[95], 672[95]; **3**, 86[20], 87[82,88],

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Groen, M. B., **3**, 361$^{76}$, 367$^{76,100,103}$
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Groliere, C. A., **8**, 560$^{402}$
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Gross, B., **1**, 219$^{62}$; **2**, 977$^{4}$; **6**, 74$^{36}$, 790$^{111}$
Gross, E., **2**, 1094$^{86}$; **6**, 635$^{11}$, 645$^{11}$, 664$^{224}$, 665$^{227}$, 668$^{227}$, 669$^{227}$, 670$^{270}$, 698$^{270}$
Gross, G., **4**, 484$^{15}$; **6**, 440$^{74}$
Gross, G. W., **4**, 1000$^{13}$
Gross, H., **2**, 60$^{18}$, 900$^{26}$, 960$^{35}$, 962$^{35}$, 1088$^{44}$; **6**, 134$^{36}$, 488$^{30}$, 533$^{513}$, 566$^{30}$; **7**, 235$^{1}$
Gross, N., **2**, 933$^{137}$
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Grossa, M., **3**, 817$^{90,92}$
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Grossel, M. C., **8**, 504$^{71}$
Grosser, J., **1**, 873$^{92,95a}$
Grossert, J. S., **1**, 528$^{122}$, 804$^{308}$, 805$^{308}$; **3**, 865$^{28}$; **8**, 403$^{4}$, 404$^{4}$, 407$^{4}$
Grossi, L., **1**, 569$^{262}$; **4**, 424$^{11}$, 428$^{11,77}$
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Grover, E. R., **6**, 581$^{989}$; **7**, 800$^{30}$; **8**, 85$^{19}$
Grover, S. K., **7**, 143$^{150}$, 144$^{150}$
Groves, J. K., **2**, 708$^{3}$, 710$^{3}$; **4**, 238$^{4}$; **5**, 581$^{176}$, 777$^{183}$
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Groweiss, A., **3**, 380$^{13}$, 395$^{102}$, 396$^{102}$, 407$^{146}$
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Grubb, P. W., **5**, 714$^{65}$
Grubb, S. D., **8**, 880$^{59}$
Grubbs, E. J., **1**, 846$^{11}$
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Grueter, H.-W., **5**, 636$^{98}$
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Grummitt, O., **2**, 142$^{48}$; **6**, 204$^{18}$
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Grünbaum, W. T., **5**, 209$^{55}$
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Grundmann, C., **4**, 1078$^{54}$; **5**, 379$^{112}$, 383$^{112}$, 384$^{112}$; **6**, 225$^{3}$, 226$^{3}$, 227$^{3}$, 228$^{3}$, 229$^{3}$, 231$^{3}$, 232$^{3}$, 233$^{3}$, 234$^{3}$, 235$^{3}$, 236$^{3}$, 237$^{3}$, 238$^{3}$, 240$^{3}$, 241$^{3}$, 242$^{92}$, 243$^{92}$, 245$^{118}$, 246$^{118}$, 247$^{118}$, 248$^{118}$, 249$^{118}$, 252$^{118}$, 253$^{118}$, 254$^{118}$, 255$^{118}$, 258$^{3}$, 259$^{3}$, 817$^{104}$; **8**, 392$^{104}$
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Gschwend, H. W., **1**, 23[120], 460[4], 463[4], 464[34], 471[4], 472[4], 473[4], 480[155]; **2**, 74[80]; **3**, 67[19], 193[2], 194[2], 261[146], 264[146]; **5**, 527[64,65], 530[64,65]; **6**, 554[766]
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Guitart, J., **8**, 563[425]
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Guo, M., **2**, 146[70]; **4**, 107[141]; **5**, 356[90], 358[90b]
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Gupta, D. N., **5**, 124[11], 129[11]; **7**, 709[36], 747[101], 765[136], 843[49]
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Gupta, K., **2**, 296[85]; **5**, 100[141]
Gupta, P., **2**, 283[46]; **3**, 661[25]
Gupta, P. K., **5**, 92[79], 95[101]
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Hamilton, G. S., **8**, 618$^{117}$
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Hamilton, J. G., **5**, 1120$^{22}$
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Hamilton, R., **3**, 334$^{220}$, 677$^{83}$; **5**, 801$^{80}$
Hamilton, R. J., **8**, 505$^{77,78}$
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Hammell, M., **2**, 182$^{4}$
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Hammer, C. F., **8**, 612$^{72}$
Hammer, G. N., **2**, 968$^{82}$
Hammer, H., **5**, 945$^{247}$
Hammer, J., **7**, 530$^{24}$, 531$^{24}$
Hammerer, S., **2**, 478$^{13}$
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Hammond, D. A., **7**, 131$^{88}$
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Hammond, G. B., **2**, 103$^{33-35}$
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Hammond, S. M., **2**, 465$^{107}$
Hammond, W. B., **3**, 892$^{52}$; **5**, 596$^{28}$, 597$^{28}$
Hammoud, A., **3**, 487$^{47}$, 530$^{68}$, 533$^{68}$
Hamoaka, T., **7**, 606$^{152}$
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Hamon, L., **1**, 107$^{4}$; **3**, 216$^{69}$, 419$^{45}$, 420$^{45}$; **4**, 176$^{48}$
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Hamuro, J., **7**, 16$^{167}$
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Han, G., **8**, 404$^{17}$
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Han, K. I., **5**, 1135$^{49}$; **8**, 743$^{47}$, 838$^{21,21c}$, 840$^{21c}$
Han, L. P.-B., **3**, 829$^{56}$
Han, N. F., **8**, 783$^{107}$
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Han, Y. K., **2**, 546$^{88}$, 548$^{88}$
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Hanack, M., **1**, 416$^{68}$; **3**, 381$^{18}$, 396$^{103,104}$ ; **4**, 270$^{11,12}$, 271$^{21,22}$, 272$^{21}$; **6**, 19$^{68}$, 72$^{24}$, 172$^{20}$, 500$^{183}$, 1012$^{4}$, 1013$^{4}$, 1033$^{125}$; **8**, 349$^{137}$, 873$^{19}$, 933$^{47}$
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Hanafusa, T., **1**, 116$^{50}$, 118$^{50}$, 555$^{115}$ ; **4**, 972$^{78}$; **5**, 79$^{286}$; **6**, 233$^{41}$
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Hancock, J. E. H., **2**, 742$^{71}$; **4**, 4$^{16}$
Hancock, K. G., **2**, 6$^{24,26}$; **5**, 220$^{43-45}$ ; **8**, 717$^{94}$
Hancock, W. S., **6**, 668$^{251}$, 669$^{251}$
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Handa, Y., **1**, 271$^{63}$; **3**, 566$^{28}$, 571$^{28}$, 578$^{28}$; **8**, 412$^{108b}$
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Hangauer, D. G., Jr., **7**, 313$^{38}$
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Hankinson, B., **2**, 744$^{95}$
Hanko, R., **1**, 180$^{31}$; **2**, 10$^{43}$, 21$^{43}$, 22$^{43}$
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Hanna, J., **2**, 613$^{110}$; **3**, 565$^{23}$, 570$^{23}$, 583$^{23}$; **8**, 168$^{66}$
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Hanna, M. T., **8**, 860$^{221}$
Hanna, R., **1**, 760$^{135}$; **7**, 440$^{38,39a}$
Hanna, Z. S., **4**, 598$^{208}$, 622$^{208}$; **8**, 882$^{86}$
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Hannebaum, H., **3**, 634$^{28}$; **8**, 624$^{153}$
Hannessian, S., **6**, 210$^{74}$, 214$^{74}$
Hannick, S. M., **2**, 297$^{92}$, 298$^{92}$
Hannon, F. J., **1**, 223$^{82}$, 224$^{82}$, 313$^{119,120}$, 314$^{119,120}$, 317$^{151,152}$, 319$^{151,152}$; **2**, 120$^{182}$; **3**, 212$^{37,38}$; **4**, 172$^{30}$, 229$^{231}$; **5**, 134$^{66}$, 137$^{66}$
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Hansen, D. W., Jr., **6**, 71$^{23}$; **7**, 35$^{105}$, 352$^{29}$
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Hansen, F., **2**, 150$^{97}$
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Hansen, H., **6**, 668$^{254}$, 669$^{254}$
Hansen, H.-J., **3**, 809$^{39,40}$, 874$^{69}$; **4**, 1033$^{21}$, 1037$^{21}$, 1040$^{21}$, 1081$^{73,74,78}$, 1084$^{95}$; **5**, 681$^{27}$, 707$^{32}$, 709$^{45}$, 712$^{45d}$, 713$^{32}$, 799$^{72}$, 822$^{164}$, 829$^{20}$, 834$^{50,52}$, 837$^{67}$, 850$^{146}$, 856$^{67,199}$, 857$^{67,199,226,227}$, 858$^{199}$, 877$^{5}$, 1130$^{8}$; **6**, 185$^{166}$, 535$^{542}$, 538$^{542}$
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Hansen, J., **1**, 34$^{170}$, 35$^{171}$, 341$^{96}$, 345$^{124}$, 477$^{132}$, 482$^{132}$; **2**, 150$^{97}$
Hansen, J. F., **3**, 507$^{174}$, 677$^{85}$
Hansen, J. H., **4**, 30$^{91,91a}$
Hansen, M. M., **2**, 123$^{200}$, 125$^{200}$, 280$^{24}$, 281$^{24}$, 1024$^{63}$; **4**, 239$^{25}$, 247$^{25}$, 258$^{25}$, 260$^{25}$; **5**, 249$^{32}$; **6**, 1063$^{87}$
Hansen, M. R., **7**, 608$^{172}$
Hansen, P.-E., **6**, 173$^{40}$, 473$^{72}$, 474$^{72}$, 475$^{72,87}$
Hansen, R., **8**, 285$^{8}$, 293$^{8}$
Hansen, R. T., **4**, 143$^{19}$; **7**, 247$^{100}$
Hansen, S. C., **8**, 140$^{16}$
Hansen, S. W., **5**, 680$^{24,24a}$
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Hansske, F., **7**, 259[60]; **8**, 819[43], 820[43]
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Hansson, S., **4**, 631[420,421]; **7**, 453[77]
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Happer, D. A. R., **2**, 350[72], 363[72]
Haque, F., **4**, 541[111], 689[69]
Haque, M. S., **1**, 86[42-44], 874[103,104]; **2**, 109[66-68]; **5**, 524[54,54f], 526[57], 534[54] ; **7**, 163[69]
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Hara, H., **3**, 672[65]; **4**, 1017[213], 1019[213] ; **7**, 339[43]
Hara, K., **3**, 135[345], 174[345]; **4**, 964[46]
Hara, M., **8**, 773[68], 778[68]
Hara, N., **6**, 989[78], 993[78]
Hara, R., **4**, 159[82]
Hara, S., **1**, 851[39], 852[39]; **2**, 819[97], 823[97]; **3**, 231[248], 251[78], 254[78], 262[158], 443[56], 490[66], 511[66], 515[66], 523[25]; **4**, 147[38b,41,42], 148[45b], 250[137], 286[174], 287[174], 290[174], 358[153,154,155,156,157,158], 886[118]; **7**, 169[114], 248[112]
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Harada, F., **7**, 761[56]; **8**, 450[164]
Harada, K., **1**, 360[26], 364[26]; **2**, 894[7], 916[7], 933[7]; **4**, 494[84], 878[76]; **6**, 704[5]; **7**, 124[46], 474[46,47]; **8**, 26[5,22], 27[5], 36[5], 37[22], 66[22], 123[84], 124[84], 144[78,79], 145[80-82,85], 146[85,91-96,101], 147[91,102], 148[91,92,95,96,103,104,106,110], 149[115], 535[166], 642[34]
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Harada, N., **4**, 227[204]; **7**, 761[56]
Harada, S., **3**, 469[216], 470[216], 476[216] ; **6**, 516[319]
Harada, T., **1**, 215[36]; **2**, 18[72], 31[112], 82[10], 211[115], 215[115], 216[135], 572[46,48], 610[89], 651[113,114], 657[164], 867[15]; **3**, 1047[6]; **4**, 76[44c], 100[122], 249[117], 257[117], 958[26], 960[26], 1014[185]; **5**, 791[26], 889[32]; **6**, 425[65], 509[248,250] ; **8**, 150[121-125,129,133,135], 151[121,129,133,135,145,146,148,149,150,151,152,153,154]
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Harangi, J., **6**, 660[207]; **8**, 226[112-114]
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Harano, Y., **4**, 1024[264]
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Harbert, C. A., **2**, 1026[73]; **3**, 363[85], 369[117], 372[117]
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Hardegger, E., **8**, 141[33], 794[14]
Hardenbergh, E., **2**, 366[220]
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Harder, U., **6**, 277[129], 288[129]
Harding, C. E., **3**, 396[103]
Harding, D. R. K., **6**, 668[251], 669[251]
Harding, K., **8**, 374[148]
Harding, K. E., **2**, 710[18], 728[137], 1077[155] ; **3**, 341[4], 343[17], 348[27], 349[40], 351[40], 353[46,48,50], 354[4c,50], 355[17,48], 357[17,48], 358[68], 369[40], 788[53]; **4**, 295[250,252], 404[242,242a,b,246], 405[246], 407[256a-d], 408[257b,258]; **5**, 758[86], 759[86]; **6**, 1066[95]; **7**, 254[29], 490[178]; **8**, 854[151]
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Hardy, A. D. U., **4**, 697[13]
Hardy, A. T., **5**, 223[81]
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Hardy, P. M., **2**, 1096[96]; **6**, 639[51], 666[51], 667[51]
Hardy, R., **3**, 242[6], 257[6], 259[6]
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Hargrove, R. J., **3**, 380[4]; **6**, 966[91]
Harirchian, B., **3**, 105[215]; **5**, 63[11], 522[43], 704[22], 1020[69], 1023[69,78]; **6**, 1023[71]; **7**, 771[266], 772[266]
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Harkins, J., **7**, 247[100]
Harland, P. A., **5**, 374[107,107a]; **6**, 83[79]
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Harling, J., **5**, 736[145], 737[145]
Harling, J. D., **4**, 823[227]
Harlow, R. L., **5**, 1171[27], 1172[27], 1178[27]
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Harman, R. E., **2**, 757[16]
Harman, W. D., **1**, 310[108]; **8**, 519[133]
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Harmon, C., **5**, 65[60]
Harmon, C. A., **3**, 380[10]; **8**, 390[77]
Harmon, J., **7**, 138[126]
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Harris, S. H., **3**, 1040[105]
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Harrison, C. H., **7**, 709[38]
Harrison, C. R., **2**, 310[29], 630[6]; **3**, 274[23], 799[99]; **6**, 489[99], 525[99], 545[635], 767[24]; **7**, 763[103]
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Hassall, C. H., **3**, 660[15], 690[124], 818[94] ; **5**, 395[148]; **7**, 351[28], 355[28], 671[1], 672[1], 674[1], 684[1]
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Heinzer, J., **3**, 75$^{46}$
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Heisler, R. Y., **6**, 253$^{158}$
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Heissler, D., **2**, 816$^{86}$; **7**, 517$^{14}$, 564$^{88}$, 568$^{88}$
Heiszwolf, G. J., **2**, 101$^{18}$, 597$^{11}$
Heitkämpfer, P., **5**, 157$^{42}$
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Heitmann, P., **1**, 546$^{58}$; **2**, 249$^{84}$, 654$^{129}$
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Heitz, W., **4**, 461$^{99}$, 475$^{99}$
Heitzmann, M., **5**, 386$^{133,133a}$
Helbert, M., **6**, 489$^{82}$
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Helbig, W., **2**, 33$^{121}$; **8**, 196$^{121}$
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Helder, R., **4**, 230$^{241}$
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Helfer, A. P., **5**, 950$^{285}$
Helfer, D. L., II, **6**, 553$^{723}$, 554$^{723}$
Helferich, B., **6**, 39$^{38}$, 42$^{45}$, 49$^{90}$
Helfrich, O. B., **7**, 768$^{197}$
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Helgée, B., **2**, 1051$^{35}$, 1052$^{35}$; **4**, 455$^{42}$; **7**, 801$^{36}$
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Helle, M. A., **1**, 768$^{171}$; **4**, 408$^{257a}$
Heller, H. G., **5**, 721$^{103}$, 722$^{104,105}$, 729$^{124}$
Heller, M., **6**, 959$^{36}$
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Hellring, S., **1**, 482$^{164,165}$; **3**, 71$^{34}$, 72$^{38}$; **6**, 545$^{629}$, 551$^{681}$; **7**, 224$^{48}$
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Helmkamp, G. K., **6**, 277$^{125,126}$; **8**, 614$^{91}$
Helmlinger, D., **3**, 383$^{44}$
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Hembre, R. T., **3**, 1026$^{39}$
Hemetsberger, H., **3**, 804$^{10}$; **5**, 198$^{23}$, 209$^{54}$, 210$^{57}$, 413$^{49}$; **7**, 32$^{92}$
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Hemo, J. H., **8**, 27$^{31}$, 66$^{31}$
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Henbest, H. B., **2**, 156$^{114}$; **3**, 734$^{4}$, 741$^{53}$; **4**, 301$^{325}$, 302$^{336}$, 315$^{508}$ ; **5**, 767$^{119}$; **6**, 1042$^{10}$; **7**, 152$^{4}$, 153$^{4}$, 221$^{33-35}$, 236$^{17}$, 390$^{1}$, 582$^{149}$, 768$^{205}$, 769$^{205,211}$; **8**, 336$^{73}$, 337$^{73}$, 338$^{73}$, 339$^{73}$, 341$^{73}$, 429$^{54}$, 533$^{154}$

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Henderson, M. J., **1**, 17$^{218}$
Henderson, R., **8**, 883$^{91}$
Henderson, W. A., Jr., **5**, 712$^{60}$
Henderson, W. W., **6**, 244$^{106}$
Hendi, M. S., **4**, 464$^{118}$, 465$^{118}$
Hendi, S. B., **7**, 29$^{79}$
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Hendric, R., **7**, 365$^{49}$
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Hendrick, M. E., **4**, 1011$^{166}$; **6**, 776$^{55}$
Hendricks, R. T., **5**, 797$^{65}$
Hendrickson, J. B., **1**, 894$^{158}$; **3**, 158$^{436}$, 159$^{436}$, 174$^{538,539}$, 177$^{538,539}$, 831$^{63}$, 868$^{42-44}$, 869$^{43,44}$, 876$^{44}$, 1048$^{10}$; **4**, 6$^{23,23b}$, 52$^{147,147a}$, 1033$^{33}$, 1089$^{127}$, 1092$^{127}$; **5**, 700$^{7}$; **6**, 83$^{78}$, 125$^{147}$ ; **7**, 299$^{41}$, 668$^{82,84}$; **8**, 916$^{102}$, 917$^{102}$, 918$^{102}$, 919$^{102}$, 920$^{102}$, 992$^{52}$, 994$^{63}$
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Heng, K. K., **2**, 185$^{31}$; **4**, 243$^{67}$, 244$^{67}$, 260$^{67}$, 261$^{67}$
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Henke, B. R., **1**, 294$^{38}$, 304$^{38}$; **2**, 6$^{35}$, 568$^{32}$
Henke, K., **1**, 66$^{53}$; **2**, 536$^{41}$
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Hennessy, M. J., **3**, 1055$^{31}$, 1062$^{31,47}$; **4**, 1033$^{32}$; **6**, 123$^{141}$, 125$^{141}$
Hennige, H., **6**, 502$^{215}$, 531$^{215}$
Henning, R., **2**, 63$^{23}$, 337$^{73}$; **3**, 851$^{68}$ ; **4**, 12$^{43}$, 13$^{43b}$, 104$^{136a,c}$; **5**, 596$^{36}$, 598$^{36}$, 609$^{70}$; **6**, 16$^{61}$, 284$^{171}$ ; **7**, 360$^{22}$, 646$^{26}$; **8**, 788$^{120}$
Henninger, M., **2**, 523$^{90}$; **8**, 384$^{30}$
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Henrot, S., **3**, 41$^{225}$, 263$^{175}$; **6**, 3$^{17}$ ; **8**, 196$^{114}$
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Henry-Basch, E., **1**, 86$^{33,41}$, 215$^{40}$, 216$^{40}$, 218$^{49}$, 220$^{49}$, 223$^{49}$, 226$^{49a,90-92,94,96}$, 326$^{6,7}$, 327$^{8}$, 349$^{143,144}$; **4**, 95$^{97}$, 98$^{108d,109d-f}$
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Hensel, M. J., **1**, 765$^{174}$
Henshall, A., **7**, 506$^{298}$
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Herges, R., **2**, 1090$^{72}$; **5**, 77$^{251}$
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Hergrueter, C. A., **3**, 251$^{77}$, 254$^{77}$
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Herman, D. F., **1**, 139$^{2}$, 140$^{8}$
Herman, F., **7**, 24$^{39}$, 25$^{39}$
Herman, G., **4**, 987$^{147}$; **8**, 935$^{59}$
Herman, J. J., **4**, 609$^{330}$; **5**, 86$^{35}$
Herman, L. W., **2**, 323$^{21}$
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Hermann, C. K. F., **4**, 463$^{110}$, 468$^{110}$, 469$^{110}$
Hermann, C. W., **2**, 1066$^{122}$
Hermann, E. C., **6**, 270$^{77}$
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Hermes, M. E., **7**, 474[39], 480[98]
Hermolin, J., **8**, 594[73], 595[73,74]
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Hernandez, A., **1**, 790[262]; **8**, 707[22], 936[75,76], 937[76]
Hernandez, D., **2**, 111[79]; **8**, 707[22], 936[75]
Hernandez, E., **5**, 1140[77]; **8**, 936[74]
Hernandez, H., **6**, 554[735]
Hernandez, J. E., **7**, 706[22]
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Hernandez, O., **3**, 135[368], 136[368], 137[368] ; **6**, 23[94], 650[128]
Hernandez, R., **2**, 1049[16]; **4**, 342[61], 814[187]; **7**, 41[15], 722[19], 723[19], 725[19]
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Herold, T., **1**, 192[81]; **2**, 33[121]; **4**, 130[226b]
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Herr, R., **6**, 4[19,20], 11[47], 176[91], 196[227,234]
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Herrera, F. J. L., **4**, 379[115]
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Herrmann, J., **7**, 763[96]
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Hertenstein, U., **1**, 547[63], 548[63]; **2**, 69[45]; **3**, 197[40]; **6**, 681[333], 682[340]
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Hess, B. A., Jr., **3**, 901[105]; **5**, 702[14], 703[14], 740[14]
Hess, H. M., **8**, 541[218], 542[218], 543[218]
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Hess, T. C., **3**, 891[43], 892[43]
Hess, W. W., **7**, 100[131], 256[42]
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Hesse, K.-D., **5**, 500[258]
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Hesse, R. H., **1**, 174[8], 175[8]; **4**, 344[77], 347[104,105]; **7**, 15[145], 41[21,22], 90[32], 741[49], 747[94]; **8**, 796[28]
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Heusler, K., **2**, 156[117], 358[153]; **4**, 410[262]; **6**, 667[242], 685[361]; **7**, 41[19,20] ; **8**, 974[124]
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Ho, S., **1**, 748[72], 749[78], 816[78]; **4**, 979[101]; **5**, 1115[3], 1122[3], 1123[3], 1124[3]
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Hoffmann, H. M. R., **1**, 761[138], 773[204]; **2**, 527[3], 528[3], 708[4]; **4**, 34[97], 35[97], 797[104]; **5**, 1[1], 2[1], 6[1], 7[55], 9[73], 15[1], 341[58], 594[4], 595[8-11,15], 596[8b,9,15,24,25,32,34,36], 597[24,25,32], 598[34,36], 602[4], 603[9,32,49], 604[8b], 608[4,8b,24a,66], 609[49,70], 612[75]; **6**, 204[22], 215[102], 233[47], 569[935]; **7**, 262[78], 362[25], 429[157a]
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Hofmann, K., **2**, 605$^{63}$, 681$^{58}$, 683$^{58}$ ; **6**, 560$^{870}$; **7**, 650$^{51}$
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Hoke, D., **8**, 812$^{4}$, 967$^{84}$
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Holdren, R. F., **2**, 964$^{56}$; **8**, 140$^{27}$
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Holm, R. H., **8**, 366$^{51}$
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Holman, R. J., **3**, 647$^{195}$; **8**, 133$^{23,24}$
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Holme, K. B., **7**, 550$^{50}$
Holmes, A., **6**, 541$^{595}$
Holmes, A. B., **1**, 744$^{55}$; **2**, 355$^{124}$, 370$^{258}$, 725$^{114}$; **3**, 39$^{214}$, 281$^{46}$, 284$^{52}$, 555$^{30}$; **5**, 403$^{9}$, 1123$^{36}$; **7**, 679$^{75}$, 683$^{90}$
Holmes, C. P., **2**, 202$^{96}$, 657$^{163}$; **4**, 380$^{125}$, 381$^{125a}$, 386$^{125a}$, 387$^{125a}$
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Holmes, R. H., **8**, 861$^{224}$
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Holy, N. L., **1**, 366[44]; **2**, 901[35], 908[35], 909[35,63], 910[35]; **4**, 262[310]; **7**, 453[79], 861[76], 882[171]; **8**, 454[199]
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Honan, M. C., **2**, 1072[140]; **6**, 1056[54] ; **7**, 318[60]
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Honda, M., **5**, 308[96]; **6**, 527, 217[117], 221[117]; **7**, 400[44], 408[44], 415[115a]
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Honda, T., **2**, 547[121], 551[121], 552[121], 1049[13]; **4**, 500[110], 510[176], 795[84] ; **5**, 92[74], 410[38], 524[54], 534[54], 536[97], 541[110], 693[109,110], 694[110]; **7**, 243[68], 423[142], 476[59]; **8**, 340[100], 534[158], 537[158], 821[48]
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Imai, H., **1**, 544[44], 551[77]; **4**, 162[93,94a]; **6**, 238[72]; **8**, 552[349], 557[384]

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Imai, K., **1**, 387[133]; **3**, 159[455], 161[455]; **4**, 300[305]

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Jephcote, V. J., **1**, 832[114]; **2**, 39[135], 566[19], 574[59], 575[19], 587[142]; **6**, 863[190]
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Jernow, J. L., **7**, 728[42]
Jernstedt, K. K., **4**, 366[8], 386[8b,148a,151], 387[148,148a]; **6**, 26[105,107]
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Jesce, M. R., **6**, 558[858]
Jeschke, R., **5**, 480[176], 829[15]
Jeschkeit, H., **6**, 635[11], 645[11], 665[11c], 667[11c], 668[11c], 669[11c]
Jeske, G., **8**, 447[133,134,136], 696[127,-128]
Jesser, F., **4**, 229[225,226,228]
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Jewell, C. F., Jr., **5**, 689[77], 690[77a], 733[136,136b], 734[136b], 1202[56]; **8**, 41[95], 66[95]
Jewers, K., **6**, 719[127]
Jewett-Bronson, J., **8**, 20[136]
Jeyaraman, R., **1**, 834[125,127]; **3**, 736[24]; **7**, 13[124], 750[129]
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Jiang, Y.-Y., **8**, 769[26]
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Jie, C., **5**, 856[205]
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Jinbo, T., **8**, 246[78], 284[1]
Jinbo, Y., **4**, 650[425]
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Jitsukawa, K., **4**, 603[275], 626[275], 645[275]; **7**, 321[66], 587[171], 823[36]
Jizba, J., **8**, 590[55]
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Jochum, P., **2**, 1099[107]
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Joern, W. A., **7**, 219[13]
Joffe, M. L., **5**, 850[146]
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Jogun, K. H., **4**, 429[87]
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Johannes, J., **1**, 551[71]
Johannesen, R. B., **8**, 217[68]
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Johansen, N. L., **6**, 637[31]
Johansen, Ø. H., **2**, 365[209]
Johansen, T., **2**, 150[97]
Johanson, E., **2**, 1099[115]
Johansson, J.-A., **5**, 2[18]
Johansson, R., **6**, 205[32], 652[139], 660[139]; **7**, 237[33]; **8**, 224[106], 969[95]
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John, D. I., **1**, 656[152], 658[152], 832[114]; **3**, 934[64], 953[64]; **8**, 831[92], 849[109]
John, G. R., **4**, 670[15,20]
John, J. A., **2**, 6[33], 35[33]
John, J. P., **4**, 4[14]; **8**, 530[108]
John, L. S., **7**, 155[29]
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John, T. K., **1**, 822[39]
John, T. V., **7**, 172[126], 258[53]
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Johns, A., **4**, 820$^{222}$; **5**, 830$^{35}$
Johns, I. B., **8**, 140$^{27}$
Johns, N., **6**, 441$^{83}$
Johns, R. B., **6**, 618$^{109}$
Johns, W. F., **2**, 158$^{124}$; **8**, 495$^{27}$, 530$^{92,102}$
Johnson, A. L., **2**, 357$^{135}$; **5**, 634$^{70}$; **7**, 138$^{126}$
Johnson, A. P., **2**, 1050$^{27}$; **7**, 654$^{10}$
Johnson, A. T., **1**, 822$^{31}$
Johnson, A. W., **1**, 630$^{25}$, 675$^{25}$, 722$^{25}$, 820$^{8}$, 825$^{8}$; **3**, 86$^{40}$, 665$^{36}$, 921$^{36}$; **4**, 707$^{42}$; **5**, 687$^{62}$, 688$^{62}$; **6**, 171$^{2}$, 198$^{2}$, 200$^{2}$
Johnson, B. F., **3**, 125$^{294}$, 126$^{294}$, 167$^{294}$, 168$^{294}$; **7**, 246$^{88}$
Johnson, B. F. G., **4**, 115$^{180a}$, 665$^{9}$, 673$^{31}$, 688$^{9}$, 691$^{76}$, 706$^{36-40}$, 707$^{40,41}$; **6**, 690$^{399,403}$, 691$^{399}$, 692$^{399,403}$
Johnson, C. A., **7**, 673$^{30}$
Johnson, C. D., **2**, 965$^{65}$; **4**, 37$^{107}$
Johnson, C. K., **3**, 749$^{81}$
Johnson, C. R., **1**, 112$^{27}$, 233$^{17}$, 238$^{17}$, 248$^{65}$, 433$^{226}$, 531$^{129}$, 532$^{134,135,137}$, 533$^{138}$, 534$^{139,140,141,142}$, 535$^{146}$, 621$^{70}$, 722$^{278}$, 734$^{24}$, 735$^{24}$, 736$^{24}$, 737$^{32,33}$, 738$^{33}$, 739$^{42}$, 740$^{43}$; **2**, 418$^{22}$, 425$^{38}$, 448$^{46}$, 726$^{126}$; **3**, 9$^{48}$, 11$^{48}$, 86$^{62}$, 88$^{136}$, 91$^{136}$, 173$^{62,521}$, 179$^{136,548}$, 181$^{136}$, 212$^{40}$, 223$^{158}$, 224$^{176}$, 226$^{192}$, 248$^{57}$, 249$^{57}$, 250$^{70}$, 251$^{57}$, 263$^{57,177}$, 265$^{187}$, 786$^{40}$, 871$^{51}$, 942$^{81b}$, 1008$^{67}$; **4**, 115$^{184d}$, 152$^{56}$, 170$^{18,19}$, 177$^{57}$, 226$^{189}$, 245$^{85}$, 987$^{133,135,136}$, 989$^{136}$; **5**, 439$^{166}$, 765$^{112}$, 855$^{187}$, 905$^{58}$; **6**, 4$^{19,20}$, 9$^{41}$, 11$^{47}$, 139$^{50}$, 874$^{15}$, 998$^{116}$, 1066$^{97}$; **7**, 194$^{5,7}$, 204$^{7}$, 205$^{7}$, 292$^{7}$, 363$^{39}$, 440$^{41}$, 441$^{41}$, 621$^{33}$, 764$^{119,127,130}$, 767$^{119}$, 778$^{394}$
Johnson, D., **5**, 687$^{64}$; **7**, 723$^{23}$, 724$^{28}$; **8**, 425$^{47}$, 476$^{22}$
Johnson, D. A., **1**, 474$^{86,87}$; **3**, 262$^{170}$
Johnson, D. C., **7**, 705$^{16}$
Johnson, D. K., **7**, 829$^{59}$; **8**, 51$^{121}$, 66$^{121}$
Johnson, D. M., **6**, 237$^{65}$, 243$^{65}$
Johnson, D. W., **5**, 794$^{48}$, 809$^{48}$; **6**, 1055$^{52a}$
Johnson, E. F., **6**, 707$^{43}$
Johnson, F., **2**, 1011$^{12}$, 1031$^{12}$; **3**, 13$^{69}$, 14$^{69}$; **4**, 48$^{139}$, 292$^{231}$; **5**, 1096$^{111}$, 1098$^{111}$; **6**, 236$^{56,57}$, 261$^{10}$, 273$^{10}$, 280$^{10}$, 685$^{357}$, 709$^{52-54}$, 711$^{69}$, 751$^{109}$, 876$^{25}$; **7**, 160$^{49}$; **8**, 43$^{106}$, 66$^{106}$, 524$^{6}$, 528$^{82}$, 529$^{82}$, 530$^{6}$, 563$^{428}$, 566$^{457}$, 568$^{468}$
Johnson, F. H., **3**, 743$^{59}$
Johnson, F. M., **2**, 735$^{13}$
Johnson, G., **2**, 1048$^{11}$; **7**, 90$^{32}$
Johnson, G. B., **8**, 254$^{127}$
Johnson, G. M., **1**, 733$^{11}$
Johnson, H. E., **1**, 851$^{36}$; **8**, 568$^{466}$
Johnson, J. A., **7**, 602$^{94}$
Johnson, J. E., **6**, 291$^{223}$
Johnson, J. H., **8**, 140$^{14}$
Johnson, J. L., **5**, 478$^{161}$; **6**, 533$^{505}$, 554$^{709}$; **7**, 548$^{62}$, 553$^{62}$; **8**, 36$^{48}$, 66$^{48}$, 347$^{140}$, 616$^{102}$, 617$^{102}$, 618$^{102,119}$
Johnson, J. R., **2**, 142$^{48}$, 395$^{1}$, 396$^{1,8}$, 399$^{1,20}$, 400$^{1}$, 406$^{1}$, 1090$^{61}$; **3**, 273$^{11}$; **4**, 311$^{447}$; **7**, 595$^{8}$, 599$^{8a}$; **8**, 364$^{22}$, 724$^{172}$
Johnson, J. W., **8**, 454$^{196}$
Johnson, L. F., **5**, 128$^{27}$
Johnson, M., **4**, 856$^{102}$; **5**, 553$^{44}$
Johnson, M. A., **5**, 854$^{181}$
Johnson, M. D., **1**, 206$^{110}$; **4**, 746$^{147}$; **8**, 674$^{34}$, 850$^{122}$
Johnson, M. G., **3**, 807$^{18}$
Johnson, M. I., **5**, 1021$^{71}$
Johnson, M. R., **4**, 301$^{326,327}$, 314$^{485}$; **6**, 5$^{24}$; **7**, 57$^{26}$, 369$^{64}$; **8**, 267$^{68}$, 536$^{171}$
Johnson, M. W., **7**, 166$^{87}$
Johnson, N. A., **5**, 829$^{22}$; **7**, 750$^{134}$
Johnson, P. C., **2**, 547$^{110}$, 551$^{110}$
Johnson, P. D., **7**, 415$^{111}$
Johnson, P. R., **2**, 287$^{67}$
Johnson, P. Y., **2**, 279$^{18}$; **3**, 380$^{9}$, 625$^{40}$, 629$^{51,52}$
Johnson, R. A., **4**, 231$^{273}$, 384$^{143}$, 398$^{219}$; **6**, 2$^{8}$, 22$^{8}$; **7**, 54$^{3,4}$, 56$^{3,4}$, 57$^{34}$, 64$^{4}$, 66$^{3,4}$, 71$^{4}$, 72$^{4}$, 75$^{4}$, 77$^{3,4}$, 78$^{3,4}$, 80$^{4}$, 340$^{46}$, 393$^{16}$, 394$^{18}$, 395$^{18}$, 398$^{16,18}$, 399$^{18}$, 424$^{18}$, 429$^{152}$, 633$^{65}$
Johnson, R. E., **2**, 739$^{43a}$; **7**, 14$^{131}$
Johnson, R. G., **7**, 718$^{1}$, 731$^{1}$
Johnson, R. L., **8**, 895$^{6,7}$, 897$^{6,7}$, 898$^{7}$, 899$^{7}$
Johnson, R. N., **4**, 276$^{73}$, 277$^{73}$, 303$^{344}$
Johnson, R. P., **4**, 1010$^{159,161}$; **5**, 212$^{69}$; **6**, 961$^{70}$, 977$^{18}$
Johnson, R. T., **4**, 922$^{25}$
Johnson, R. W., **7**, 800$^{30}$
Johnson, S., **1**, 753$^{100}$
Johnson, S. E., **8**, 474$^{16}$
Johnson, S. J., **3**, 325$^{157}$, 353$^{49}$
Johnson, T. A., **5**, 834$^{53}$; **8**, 366$^{47}$
Johnson, T. B., **2**, 916$^{82}$; **3**, 890$^{35}$
Johnson, T. H., **8**, 161$^{21}$
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Johnson, W. L., **6**, 205$^{33}$, 834$^{40}$
Johnson, W. M. P., **2**, 741$^{66}$
Johnson, W. S., **1**, 347$^{136,137,138}$, 348$^{138,139,142}$, 546$^{59}$, 601$^{40}$, 608$^{36,37,40}$; **2**, 148$^{78}$, 158$^{125}$, 162$^{142}$, 555$^{142,143}$, 556$^{154}$, 578$^{85}$, 580$^{97}$, 650$^{110,111}$, 651$^{110,111a,b}$, 753$^{1}$, 838$^{166}$, 1026$^{73}$; **3**, 11$^{52}$, 17$^{52}$, 126$^{320}$, 133$^{335}$, 136$^{335}$, 226$^{206}$, 281$^{45}$, 341$^{3}$, 349$^{40}$, 351$^{40}$, 353$^{3,46,47}$, 358$^{66,67}$, 360$^{72}$, 361$^{75}$, 362$^{89,90}$, 363$^{83,85}$, 364$^{91,93}$, 366$^{99}$, 369$^{40,107,108,117-125}$, 370$^{109-113}$, 371$^{114,116}$, 372$^{117-119,121,122,124,125}$, 373$^{126,-128,129}$; **4**, 4$^{15}$, 24$^{72,72b}$, 31$^{92,92e}$, 83$^{65a}$, 312$^{459}$, 386$^{149}$, 387$^{149}$; **5**, 828$^{7}$, 839$^{7}$, 857$^{229}$, 882$^{13}$, 888$^{13}$, 891$^{37}$, 892$^{13,37,38a,40}$, 893$^{13}$; **6**, 237$^{68}$; **7**, 111$^{190}$, 167$^{100}$, 169$^{113}$, 564$^{93}$, 565$^{93}$, 568$^{93}$, 711$^{57}$; **8**, 58$^{175}$, 66$^{175}$, 353$^{156}$, 494$^{24}$, 495$^{27}$, 530$^{101,103}$, 542$^{226,228}$, 545$^{293}$, 564$^{442}$, 566$^{451}$
Johnston, A. D., **8**, 514$^{113}$
Johnston, B. D., **7**, 238$^{41}$, 401$^{54}$
Johnston, B. H., **1**, 409$^{38}$
Johnston, D. B. R., **5**, 107$^{199}$; **6**, 219$^{123}$, 659$^{197a}$
Johnston, D. E., **3**, 334$^{220}$
Johnston, F., **4**, 272$^{36}$, 273$^{36}$
Johnston, G. A. R., **6**, 81$^{76}$, 82$^{76}$, 818$^{106,107}$
Johnston, J. D., **7**, 157$^{33}$; **8**, 974$^{122}$
Johnston, L. J., **5**, 164$^{76}$; **6**, 960$^{57}$
Johnston, M. D., Jr., **1**, 294$^{44}$
Johnston, M. I., **2**, 547$^{105}$, 550$^{105}$; **4**, 377$^{104}$
Johnstone, R. A. W., **3**, 229$^{232}$; **6**, 119$^{109}$, 635$^{14a}$, 636$^{14}$, 834$^{32}$, 1022$^{62}$; **7**, 772$^{288}$; **8**, 18$^{123}$, 81$^{4}$, 91$^{4}$, 104$^{4}$, 263$^{30,31}$, 366$^{43}$, 367$^{57}$, 368$^{63}$, 440$^{83}$, 551$^{339}$, 887$^{115}$, 958$^{19,20}$, 959$^{29}$
Johri, K. K., **7**, 723$^{27}$
Jokic, A., **7**, 92$^{41,41a}$, 94$^{41}$
Jokubaityte, S. P., **6**, 570$^{944}$
Jolidon, S., **5**, 829$^{20}$
Joliveau, C., **6**, 509$^{274}$
Jolly, B. S., **1**, 13$^{73}$, 37$^{177}$
Jolly, P. W., **3**, 228$^{214}$, 436$^{9}$; **4**, 596$^{161}$, 601$^{245}$, 608$^{318,319}$, 939$^{73}$, 980$^{107}$; **5**, 641$^{131}$, 1142$^{86}$
Jolly, R. S., **4**, 803$^{131}$
Jolly, W. L., **8**, 244$^{64}$, 253$^{64}$, 526$^{32}$
Jommi, G., **1**, 566$^{216}$; **2**, 833$^{148}$; **4**, 261$^{285,288,290}$
Jonas, D. A., **3**, 383$^{46,50}$
Jonas, J., **5**, 453$^{63}$, 454$^{63}$, 458$^{63}$; **7**, 235$^{1}$; **8**, 214$^{35}$

Jonas, K., **8**, 747[56], 752[56]

Jonassen, H. B., **5**, 800[75]; **8**, 452[190]

Jonczyk, A., **2**, 76[83a], 429[49,50], 430[52a], 431[52a], 432[56]; **3**, 158[448], 159[448], 168[448], 174[529]

Jondahl, T. P., **5**, 710[50]

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Jones, A. J., **5**, 536[96]; **7**, 31[87]

Jones, A. S., **1**, 569[252]

Jones, B., **7**, 689[3]

Jones, B. A., **6**, 436[28], 437[28], 447[28], 448[28], 449[28,116], 450[28], 452[28]; **8**, 838[19]

Jones, C. M., **6**, 478[106]

Jones, C. R., **4**, 190[107], 980[105], 981[105]; **5**, 1085[65]

Jones, D. H., **3**, 383[46]; **8**, 340[97]

Jones, D. M., **2**, 800[15]

Jones, D. N., **3**, 114[234], 354[61]; **4**, 102[129], 258[243], 317[556,557], 587[29], 603[271], 605[292], 626[292], 646[292]; **5**, 7[52]; **6**, 1017[38], 1019[44,45], 1024[38,75-77], 1025[79], 1026[82], 1029[82]; **7**, 152[4], 153[4], 302[63], 629[49], 766[178], 771[284], 772[284]

Jones, D. S., **6**, 94[140]

Jones, D. W., **2**, 809[51], 823[51]; **3**, 690[124]; **5**, 618[6], 1003[25]; **6**, 1007[151]

Jones, E. M., **2**, 958[23]

Jones, E. R. H., **2**, 143[51], 156[114]; **3**, 554[18,19]; **4**, 55[156]; **5**, 767[119]; **6**, 217[112]; **7**, 68[82,84], 69[92], 71[82,99], 72[84], 73[92], 120[15], 158[42], 253[17], 254[30], 306[4], 582[149]

Jones, F. N., **1**, 463[23]; **3**, 484[22]

Jones, G., **1**, 243[55]; **2**, 342[3], 343[3], 352[3], 354[3], 356[3], 357[3], 358[3], 359[3], 360[3], 361[3], 362[3], 765[75]; **6**, 759[135]; **7**, 877[132]; **8**, 587[43]

Jones, G., Jr., **5**, 151[4], 158[4], 161[4], 165[86], 166[90], 168[4], 176[132], 178[4], 190[4], 687[64], 815[142]; **7**, 120[12], 123[12], 851[12], 854[61],

Jones, G. A., **7**, 247[96]

Jones, G. B., **7**, 32[97], 33[97]

Jones, G. C., **3**, 914[12]; **7**, 800[30,30b]

Jones, G. E., **2**, 725[114]; **3**, 284[52], 555[30]

Jones, G. H., **2**, 139[29]; **4**, 38[108,108a]

Jones, G. R., **6**, 116[88]

Jones, G. R. N., **2**, 385[323]

Jones, G. W., **4**, 1103[203]

Jones, J. B., **2**, 455[21], 456[21,25,29]; **3**, 125[295,296], 126[295,296], 128[296], 783[24]; **6**, 134[22], 560[868]; **7**, 79[133], 145[166], 158[41], 316[46-48], 317[46-48], 318[48]; **8**, 183[1], 185[1,11,16], 187[1a], 188[54,55], 189[60], 196[1a,55,116], 197[126], 199[1a,55], 200[136], 201[1a,54,55], 204[1], 206[173], 207[1a], 209[1a]

Jones, J. H., **2**, 756[8]; **6**, 81[74], 644[92]

Jones, J. K. N., **2**, 456[53-56,60-62,69,75], 457[55,60,61,69], 458[53,62], 460[69]; **6**, 207[47]; **8**, 794[15]

Jones, J. R., **2**, 365[213]

Jones, K., **5**, 528[67]; **6**, 538[571]

Jones, L. A., **8**, 568[472]

Jones, L. B., **3**, 242[4], 244[4]

Jones, L. D., **3**, 499[128], 500[128,132], 505[132], 509[128]; **4**, 476[163], 502[124], 766[229]; **5**, 692[101]

Jones, M., **1**, 885[134]; **4**, 33[95,95a], 976[100], 1089[136], 1101[195]

Jones, M., Jr., **2**, 838[176]; **3**, 897[92], 900[92], 903[123]; **4**, 483[4], 484[4], 495[4], 953[8,8f], 954[8f,m], 961[8f,m], 1001[45], 1002[45,48], 1011[166], 1012[174], 1014[184]; **5**, 677[8], 681[25], 716[87], 786[3], 787[3], 1065[1], 1066[1], 1074[1], 1083[1], 1084[1], 1093[1], 1094[1d]; **6**, 776[55], 1036[143]

Jones, M. D., **5**, 300[74], 307[93]

Jones, M. E., **3**, 4[22]

Jones, M. F., **2**, 822[111]; **4**, 791[46]

Jones, M. H., **4**, 287[180]

Jones, M. J., Jr., **5**, 65[71]

Jones, M. M., **8**, 152[158]

Jones, M. W., **4**, 407[256d]

Jones, N., **5**, 766[114]

Jones, N. D., **4**, 128[221], 389[167]

Jones, N. R., **1**, 568[226]; **3**, 124[278], 125[278], 128[278], 129[278], 132[278]

Jones, P. A., **2**, 958[23]

Jones, P. F., **3**, 124[289], 125[289,314]; **6**, 134[12]

Jones, P. G., **2**, 68[40]; **8**, 446[73], 987[23]

Jones, P. R., **1**, 221[67], 223[72a,b], 225[88], 226[88], 326[3]; **3**, 135[359], 136[359], 137[359], 139[359], 142[359], 260[144]; **4**, 72[23], 95[23], 98[108a,110], 434[131]; **7**, 762[79]; **8**, 707[22], 770[31]

Jones, R., **6**, 213[86]

Jones, R. A., **1**, 41[270], 432[137], 456[137]; **3**, 211[28], 215[28]; **6**, 175[75]

Jones, R. B., **2**, 801[30]

Jones, R. C. F., **1**, 300[70], 366[52]; **2**, 494[56,57], 742[69]; **4**, 76[47]; **6**, 516[321], 552[692]; **8**, 638[16]

Jones, R. E., **6**, 219[122]

Jones, R. G., **1**, 107[7]; **3**, 208[9], 244[19]; **4**, 72[23], 95[23], 148[47b]

Jones, R. H., **2**, 125[217], 127[232], 315[42], 316[42]; **4**, 217[132], 231[132]; **5**, 260[62]; **6**, 1031[109]; **7**, 630[54]

Jones, R. J., **8**, 618[113], 623[113,146], 628[113]

Jones, R. L., **4**, 1021[245]

Jones, R. R., **5**, 736[144]

Jones, R. S., Jr., **3**, 927[57]

Jones, R. V. H., **3**, 390[70]; **5**, 809[116]

Jones, R. W., **3**, 106[224], 113[224]; **4**, 308[405]

Jones, S. B., **8**, 675[49], 676[49]

Jones, S. O., **4**, 316[541]

Jones, S. R., **4**, 588[60]; **7**, 14[136]

Jones, S. S., **6**, 656[168]

Jones, T. H., **7**, 528[9]; **8**, 51[123], 66[123]

Jones, T. K., **1**, 401[14], 402[17], 585[13], 799[296]; **5**, 762[95,98-100,106], 763[95,98,109], 764[109]; **7**, 397[27]; **8**, 879[49], 946[138]

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Kawashima, M., **3**, 218[100], 220[125], 227[210], 245[30-32], 446[78], 470[212,213], 476[212,213]
Kawashima, S., **3**, 380[13]
Kawashima, T., **1**, 781[230]; **2**, 805[43]; **5**, 829[23]; **6**, 535[524]
Kawashima, Y., **5**, 297[57,59], 1196[37,38], 1197[38]
Kawata, K., **7**, 476[61]
Kawauchi, H., **5**, 1186[3], 1187[8]
Kawazoe, K., **6**, 538[562]
Kawazoe, T., **3**, 470[215], 473[215], 476[215]
Kawazoe, Y., **1**, 387[133]; **8**, 405[23]
Kawazura, H., **1**, 441[173]
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Kay, D. J., **8**, 650[63]
Kay, G., **6**, 420[24], 451[127]
Kay, I. T., **1**, 560[154], 566[218], 751[92]; **2**, 553[130], 554[130]; **4**, 55[157], 57[157f], 249[127], 258[127]; **7**, 237[35,36]
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Kaydos, J. A., **7**, 208[84]
Kaye, A. D., **3**, 985[27]; **6**, 876[27], 880[27]
Kaye, H., **7**, 586[166]
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Kaye, P., **5**, 403[9]
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Kaye, R. L., **3**, 896[68]; **5**, 64[37]
Kaye, S., **4**, 274[62], 275[62], 280[62]
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Kazama, H., **5**, 1157[169]
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Kazda, S., **8**, 592[64]
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Kazlauskas, R., **4**, 816[200]; **6**, 81[76], 82[76], 818[106]; **8**, 205[166], 206[166], 544[261]
Kazmaier, P. M., **6**, 924[62], 926[66]; **7**, 196[11], 199[11]
Kazubski, A., **1**, 405[25]; **7**, 603[115,125]; **8**, 102[126,128]
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Keats, G. H., **8**, 321[97]
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Keda, T., **6**, 563$^{900}$

Kedrinskii, M. A., **8**, 373$^{132}$

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Keely, S. L., **8**, 28$^{37}$, 66$^{37}$

Keely, S. L., Jr., **3**, 396$^{109}$, 397$^{109}$; **5**, 959$^{318}$

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Keene, B. R. T., **7**, 750$^{124}$

Kees, K., **1**, 824$^{45}$; **2**, 205$^{104}$, 206$^{104}$; **3**, 225$^{187}$, 579$^{125}$, 582$^{125}$, 583$^{125}$, 584$^{125}$, 585$^{125}$, 588$^{125,159}$, 591$^{165}$, 595$^{125}$, 596$^{125}$, 610$^{125,165}$; **4**, 595$^{157}$

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Keiko, V. V., **4**, 291$^{208}$

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Keinan, E., **2**, 608$^{78}$; **3**, 12$^{59}$, 229$^{231}$; **4**, 591$^{106}$, 594$^{137}$, 596$^{160}$, 598$^{200,202}$, 604$^{286,287}$, 605$^{287}$, 606$^{300}$, 615$^{385}$, 616$^{106,385}$, 619$^{137,385}$, 620$^{385}$, 621$^{160,385}$, 623$^{200,398}$, 626$^{286,287,385}$, 628$^{399}$, 633$^{106,399}$, 634$^{137,399}$, 636$^{160}$, 637$^{385}$, 638$^{200,202}$, 647$^{287}$; **6**, 85$^{90}$, 86$^{95}$, 848$^{111}$, 937$^{120}$, 939$^{120}$, 942$^{120}$; **7**, 14$^{127,-128}$, 40$^{2,5}$, 218$^{5}$, 465$^{131}$, 737$^{9}$, 842$^{24,25,31,35-37}$, 843$^{41,42}$; **8**, 187$^{33}$, 553$^{361,363,364}$, 554$^{364,368}$, 555$^{364,368,369}$, 782$^{101}$, 961$^{38,40}$, 984$^{4}$, 991$^{4}$

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Keitel, I., **2**, 1088$^{44}$

Keith, D. D., **6**, 543$^{621}$; **8**, 460$^{249}$

Keitzer, G., **2**, 900$^{22}$, 961$^{37}$

Kelarev, V. I., **6**, 530$^{418,422}$, 534$^{517}$

Kelbar, G. R., **6**, 687$^{381}$

Keldsen, G. L., **8**, 861$^{226}$

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Kelleher, R. G., **2**, 146$^{71}$

Keller, J., **7**, 236$^{24}$

Keller, K., **4**, 443$^{190}$, 500$^{109}$; **5**, 10$^{79}$, 19$^{79}$, 26$^{79}$, 27$^{79}$, 264$^{74}$, 385$^{131}$, 527$^{66}$, 529$^{66b}$, 681$^{29}$, 691$^{88}$

Keller, L., **3**, 500$^{132}$, 505$^{132}$; **4**, 82$^{61}$, 115$^{179b}$, 257$^{224}$, 519$^{17}$, 520$^{17}$, 540$^{17}$, 541$^{17}$, 546$^{128}$; **5**, 1094$^{98}$, 1096$^{98}$, 1098$^{98}$, 1112$^{98}$

Keller, L. S., **5**, 692$^{92}$

Keller, O., **6**, 637$^{28}$

Keller, P. C., **8**, 650$^{66}$

Keller, R. T., **7**, 92$^{42}$, 93$^{42}$

Keller, T. H., **5**, 51$^{45,45b}$, 57$^{50,50b}$, 59$^{50b}$

Keller, U., **5**, 686$^{41}$

Keller, W., **4**, 1039$^{64}$

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Kellett, R. E., **7**, 774$^{327}$

Kelley, D. F., **5**, 240$^{3}$

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Kelley, E. A., **5**, 1135$^{47}$, 1147$^{112}$

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Kelley, M. D., **6**, 751$^{107}$

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Kellner, J., **3**, 531$^{86}$

Kellog, M. S., **3**, 369$^{107}$

Kellogg, M. S., **2**, 212$^{119}$; **5**, 220$^{47}$, 707$^{39}$, 709$^{39,44}$, 737$^{44a}$, 739$^{44,44a}$

Kellogg, R. M., **1**, 299$^{62}$; **3**, 229$^{223,224,224a,b}$, 512$^{199}$, 865$^{28}$; **4**, 1074$^{28}$, 1093$^{28,150}$; **6**, 2$^{7}$, 21$^{79}$, 70$^{18}$, 980$^{46}$; **7**, 169$^{110}$; **8**, 82$^{5,6}$, 84$^{6,12}$, 93$^{74,77}$, 94$^{77}$, 95$^{91}$, 96$^{92}$, 97$^{98}$, 98$^{101}$

Kellogg, R. P., **2**, 195$^{71}$; **8**, 190$^{75}$

Kellom, D. B., **6**, 825$^{127}$, 1033$^{128}$

Kelly, B. J., **7**, 480$^{100,103}$, 481$^{100,103,106,107}$, 482$^{100,116}$, 744$^{66}$

Kelly, C. A., **5**, 71$^{153}$

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Kelly, D. R., **3**, 290$^{70}$; **4**, 375$^{97}$, 746$^{142}$

Kelly, F. W., **5**, 552$^{11}$; **6**, 1033$^{124}$, 1034$^{124}$, 1035$^{124}$

Kelly, J. A., **4**, 682$^{56}$

Kelly, J. D., **2**, 544$^{85}$, 547$^{85}$, 552$^{85}$

Kelly, J. F., **5**, 107$^{201}$

Kelly, J. T., **3**, 330$^{190}$

Kelly, J. W., **6**, 24$^{97}$, 74$^{39}$

Kelly, K. P., **7**, 452$^{49}$

Kelly, L. F., **4**, 670$^{16,17,26}$, 674$^{17}$, 683$^{59,60}$, 687$^{59,60,64}$, 688$^{65}$

Kelly, M. J., **2**, 88$^{30,31}$; **5**, 1014$^{55}$

Kelly, P. B., **2**, 958$^{27}$

Kelly, R. B., **2**, 456$^{62}$, 458$^{62}$; **3**, 20$^{105}$; **8**, 331$^{30}$, 333$^{53}$

Kelly, R. C., **3**, 651$^{219}$; **6**, 116$^{94}$; **7**, 439$^{26}$

Kelly, R. E., **4**, 41$^{118}$

Kelly, S. E., **1**, 420$^{83}$, 568$^{230}$; **4**, 53$^{150}$; **5**, 167$^{95}$

Kelly, T. A., **5**, 836$^{62}$, 841$^{100}$

Kelly, T. R., **1**, 474$^{95}$, 564$^{202}$; **2**, 521$^{71}$; **4**, 164$^{100}$, 261$^{291}$; **5**, 12$^{87}$, 376$^{109}$; **7**, 355$^{38,42}$

Kelly, W., **6**, 429$^{91}$

Kelly, W. J., **4**, 766$^{230}$; **5**, 382$^{119b}$; **7**, 219$^{16}$; **8**, 315$^{50}$

Kelly, W. L., **1**, 3$^{18,21}$

Kelm, H., **5**, 77$^{252,255,259}$, 453$^{63}$, 454$^{63}$, 458$^{63}$

Kelman, R. D., **3**, 597$^{200}$

Kelner, M. J., **2**, 725$^{108}$

Kelsey, D. R., **3**, 500$^{130}$, 509$^{130}$; **8**, 839$^{22}$

Kelsey, R., **7**, 710$^{51}$

Kelso, P. A., **7**, 41$^{26}$

Kelso, R. G., **4**, 283$^{151}$

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Kemball, C., **4**, 914[4], 924[4]; **8**, 431[64]
Kemin, M. D., **6**, 526[402]
Kemmitt, R. D. W., **5**, 300[74], 307[93]; **8**, 674[33]
Kemp, D. S., **6**, 531[450], 639[49,50]; **8**, 389[69,71]
Kemp, J. E. G., **7**, 479[96], 750[135]
Kemp, K. C., **2**, 711[32]
Kemp, T. J., **5**, 212[70]
Kempe, T., **3**, 872[56]
Kempe, U. M., **5**, 501[268]; **6**, 672[285]
Kemper, B., **2**, 13[53,55], 14[53,55]
Kempf, D. J., **1**, 477[133], 480[156,158]; **3**, 67[17]
Kemppainen, A. E., **7**, 41[26]
Kendall, E. C., **8**, 988[28]
Kendall, M. C. R., **4**, 611[349]
Kendall, P. E., **3**, 418[26]; **4**, 170[20]
Kendall, P. M., **1**, 451[217]
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Kenion, G. B., **7**, 488[158]
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Kenne, L., **6**, 23[89]
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Kennedy, J. H., **3**, 762[148], 769[148]
Kennedy, J. P., **3**, 331[199]
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Kennedy, P., **8**, 413[121]
Kennedy, R. A., **5**, 597[23], 603[23], 606[23]
Kennedy, R. M., **1**, 191[77]; **2**, 258[50]; **4**, 17[54], 63[54], 215[121]; **6**, 144[76], 1044[17], 1053[17]; **8**, 159[108], 171[108,109], 178[108], 179[108], 843[59b,c]
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Kenny, C., **1**, 264[44], 269[44,58], 270[58], 271[44,64], 273[44]; **3**, 574[73], 575[73], 599[73,208], 610[73]; **4**, 809[161]
Kenny, M. J., **4**, 27[80]
Kent, G. J., **7**, 502[263]; **8**, 342[109]
Kent, S. B. H., **6**, 670[274]
Kentgen, G., **5**, 348[73b]
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Keramat, A., **3**, 759[128]
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Kern, D. H., **3**, 568[38,39]
Kern, J. M., **7**, 805[66]
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Kernebeck, K., **6**, 664[221]
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Kerr, J. B., **7**, 801[37]
Kerr, K. M., **7**, 65[70]
Kerr, R. G., **6**, 467[48], 469[55,56]; **7**, 742[59]; **8**, 410[98]
Kerr, W. J., **5**, 1043[25], 1046[25b], 1048[25b,32], 1051[32]
Kerschen, J. A., **3**, 750[86]
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Kessel, S., **2**, 1051[40]
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Kessler, H., **2**, 547[113], 551[113]; **3**, 56[285]; **4**, 229[236]; **6**, 667[246]
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Ketcha, D. M., **2**, 744[94]
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Keumi, T., **2**, 736[24,25]; **8**, 626[174]
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Kevan, L., **4**, 537[99], 538[99]; **7**, 850[1]
Kevelam, H. J., **3**, 552[10]
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Khalikov, S. S., **3**, 306[79]
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Khalil, A. H., **2**, 287[68]
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Khalil, M. H., **2**, 422[30], 423[30], 432[54]
Khalil, Z. H., **5**, 166[90]
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Khan, A. U., **7**, 98[102]
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Khan, H. A., **7**, 208[77,82]
Khan, I. A., **7**, 675[60]
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Khan, Z. U., **6**, 535[540], 538[540]
Khanapure, S. P., **4**, 483[5], 484[5], 485[26], 486[38], 495[5], 497[5b,98], 499[5b,102]; **5**, 439[171], 440[171]; **8**, 515[116]
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Kieper, G., **5**, 1126$^{66}$
Kierstead, R. W., **2**, 1022$^{53}$; **3**, 643$^{117}$; **4**, 373$^{68}$; **5**, 341$^{61a}$; **7**, 54$^{7}$
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Kieslich, K., **4**, 182$^{76}$; **7**, 54$^{5}$, 55$^{5}$, 58$^{5}$, 59$^{5}$, 62$^{5,50b,52b}$, 63$^{5}$, 69$^{91}$, 70$^{91}$, 78$^{5}$, 429$^{157a}$; **8**, 185$^{6}$
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Kiffen, A. A., **2**, 727$^{135}$
Kigasawa, K., **4**, 495$^{85}$, 505$^{136}$, 510$^{173}$; **7**, 453$^{76}$
Kigawa, Y., **2**, 888$^{54}$; **6**, 74$^{37}$
Kigma, A. J., **4**, 249$^{120}$
Kigoshi, H., **1**, 738$^{40}$; **4**, 391$^{179}$; **6**, 998$^{117}$; **7**, 162$^{58}$, 243$^{65,66}$
Kiguchi, T., **8**, 936$^{70}$
Kihara, M., **3**, 677$^{87}$; **7**, 423$^{145}$
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Kihlberg, J., **5**, 433$^{139}$
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Kiji, J., **3**, 555$^{29}$, 1027$^{46}$; **4**, 600$^{230,232,238}$, 601$^{251}$, 602$^{251}$, 606$^{303}$, 643$^{238,251}$, 646$^{303}$; **5**, 35$^{12}$, 56$^{51}$
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Kijima, S., **8**, 241$^{37}$
Kijima, Y., **1**, 277$^{80}$
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Kikkawa, I., **1**, 417$^{69}$
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Kikuchi, M., **6**, 438$^{48}$
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Kikuchi, R., **5**, 71$^{120}$, 1139$^{75}$
Kikuchi, T., **1**, 755$^{113}$; **8**, 331$^{31}$
Kikugawa, Y., **6**, 548$^{669}$; **8**, 55$^{179}$, 60$^{182}$, 61$^{182}$, 62$^{182}$, 64$^{182}$, 66$^{179,182}$, 70$^{230}$, 71$^{230}$, 244$^{67}$, 249$^{96}$, 250$^{67}$, 357$^{191}$, 580$^{4,5,7}$, 581$^{5}$, 587$^{5}$, 614$^{82}$, 619$^{131}$, 620$^{136,137,138}$
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Kikui, T., **6**, 71$^{21}$,
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Kiladze, T. K., **8**, 214$^{40}$
Kilbourn, M. R., **6**, 219$^{118}$
Kilburn, J. D., **2**, 186$^{33}$, 200$^{90}$, 201$^{91}$; **7**, 646$^{29}$, 647$^{30}$
Kilger, R., **3**, 53$^{274}$; **5**, 225$^{96}$; **6**, 531$^{436}$
Kilian, R. J., **3**, 391$^{88}$; **6**, 1054$^{48}$
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Kiltz, H. H., **2**, 961$^{40}$; **7**, 223$^{45}$
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Kim, B. H., **4**, 1079$^{67}$; **5**, 260$^{70}$, 263$^{70}$, 841$^{89}$, 872$^{89b}$; **6**, 448$^{108}$; **8**, 856$^{173}$
Kim, B. M., **2**, 35$^{124a}$, 42$^{124}$, 112$^{101}$, 244$^{25,26}$, 258$^{48,49,51}$, 261$^{48}$; **6**, 19$^{70}$, 79$^{63}$; **7**, 431$^{161}$, 442$^{46c}$; **8**, 171$^{107}$, 720$^{138}$, 721$^{138}$, 722$^{138}$
Kim, C., **1**, 411$^{47}$, 894$^{160}$; **7**, 625$^{38}$
Kim, C.-K., **3**, 673$^{68}$, 681$^{68,98}$, 686$^{68,110}$, 807$^{32,33}$, 815$^{77}$, 816$^{81}$
Kim, C.-M., **3**, 509$^{176}$
Kim, C. R., **4**, 384$^{144,144b}$
Kim, C. S., **4**, 1000$^{11}$, **6**, 754$^{119}$
Kim, C. U., **2**, 648$^{98}$, 649$^{98}$, 1059$^{76}$; **7**, 204$^{57}$, 292$^{10}$, 297$^{29}$, 298$^{38}$
Kim, C.-W., **2**, 445$^{23}$; **6**, 1064$^{88}$; **7**, 182$^{164}$, 824$^{42}$; **8**, 514$^{105}$
Kim, D., **3**, 49$^{261}$; **4**, 731$^{68}$, 754$^{178,179}$, 755$^{178}$, 803$^{133,136}$, 820$^{133,223}$; **5**, 406$^{23,23b}$, 1056$^{49}$; **6**, 814$^{88}$
Kim, E. K., **7**, 856$^{65}$, 862$^{80}$
Kim, G., **2**, 597$^{9}$; **5**, 1124$^{49}$
Kim, H., **3**, 380$^{13}$; **6**, 108$^{34}$
Kim, H.-B., **4**, 215$^{121}$; **6**, 152$^{139}$, 153$^{139}$, 1053$^{46}$; **8**, 843$^{59b}$
Kim, H.-D., **4**, 357$^{150}$
Kim, H.-J., **7**, 530$^{16}$, 587$^{170}$, 823$^{37}$
Kim, H. K., **3**, 727$^{33}$; **7**, 372$^{71}$
Kim, H. L., **2**, 1011$^{10}$
Kim, H.-O., **6**, 446$^{103}$
Kim, H. S., **3**, 49$^{261}$; **4**, 1048$^{120}$
Kim, I. B., **8**, 452$^{186}$
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Kim, J. C., **7**, 692$^{21}$
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Kim, J. H., **4**, 505$^{137}$; **5**, 699$^{6}$
Kim, J. K., **1**, 586$^{18}$; **4**, 332$^{20}$, 337$^{20,33}$, 452$^{1}$, 453$^{1}$, 457$^{1}$, 470$^{1}$, 471$^{1}$, 472$^{1}$, 493$^{76}$, 494$^{76}$
Kim, K., **1**, 97$^{81}$; **6**, 727$^{191}$; **7**, 744$^{71}$, 752$^{143}$, 874$^{106}$, 881$^{164}$
Kim, K. E., **4**, 254$^{178}$; **8**, 18$^{121}$, 412$^{112}$, 806$^{103}$
Kim, K. H., **4**, 510$^{163}$; **5**, 413$^{49}$
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Kim, K.-W., **6**, 78$^{59}$; **7**, 606$^{159}$; **8**, 710$^{57}$, 717$^{57}$
Kim, M., **2**, 406$^{46}$; **4**, 793$^{69}$
Kim, M.-J., **2**, 456$^{22,30,33}$, 457$^{33}$, 458$^{33}$, 459$^{33}$, 460$^{33}$, 461$^{33}$, 462$^{33}$, 463$^{79,91}$, 464$^{91}$, 466$^{33}$; **8**, 189$^{58}$
Kim, M. Y., **1**, 377$^{95}$; **2**, 1049$^{23}$, 1050$^{23}$; **7**, 183$^{166}$
Kim, N.-J., **4**, 24$^{75}$
Kim, S., **1**, 408$^{35}$, 430$^{35,132}$, 435$^{142,143}$, 563$^{182}$, 846$^{20}$, 847$^{20}$, 853$^{49}$, 865$^{88}$, 876$^{49}$; **2**, 406$^{46}$; **3**, 288$^{63}$; **4**, 163$^{98}$, 372$^{64a}$; **6**, 660$^{202}$, 682$^{341}$; **7**, 278$^{157}$, 678$^{73}$; **8**, 14$^{77,81}$, 16$^{100}$, 17$^{111}$, 18$^{122}$, 54$^{152}$, 66$^{152}$, 241$^{39}$, 244$^{68}$, 247$^{39,68}$, 250$^{68}$, 261$^{15-17}$, 272$^{113}$, 354$^{176}$, 536$^{174}$, 538$^{192}$, 544$^{278}$, 806$^{101}$, 880$^{57}$, 881$^{68}$, 938$^{88}$, 969$^{93}$
Kim, S.-C., **8**, 18$^{119,120}$, 26$^{25}$, 66$^{25}$, 67$^{25}$, 74$^{25}$, 240$^{35}$, 244$^{68}$, 247$^{68}$, 250$^{68}$, 541$^{207}$, 718$^{107}$
Kim, S.-G., **6**, 799$^{20}$; **8**, 95$^{85}$
Kim, S. J., **5**, 773$^{168}$, 774$^{168}$; **7**, 318$^{54}$, 319$^{54}$
Kim, S. O., **8**, 541$^{207}$
Kim, S. S., **1**, 563$^{182}$; **2**, 47$^{154}$, 249$^{84}$; **6**, 864$^{198}$; **8**, 261$^{15,16}$
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Kim, T. H., **1**, 822$^{36}$; **4**, 35$^{98i}$; **7**, 73$^{102}$
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Kim, W. J., **1**, 798$^{286}$, 804$^{309}$; **4**, 1040$^{68}$
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Kim, Y. H., **6**, 208$^{57}$, 212$^{57}$, 727$^{191}$; **7**, 744$^{71}$, 752$^{143}$, 759$^{15}$, 761$^{57,58}$, 765$^{160}$, 766$^{189}$, 769$^{214}$

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Kim, Y. K., **8**, $781^{98}$
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Kimball, S. D., **5**, $1096^{111}$, $1098^{111}$; **7**, $160^{49}$
Kimbrough, D. R., **4**, $1036^{48}$; **5**, $854^{176}$, $855^{176}$, $856^{176}$
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Kimling, H., **6**, $968^{114}$
Kimmel, T., **2**, $651^{115,115a}$; **6**, $164^{195}$
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Kimura, B. Y., **1**, $9^{43}$
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Kimura, J., **6**, $22^{86}$
Kimura, K., **1**, $177^{19}$, $179^{19,27}$, $180^{27}$, $181^{27}$, $182^{27}$, $193^{84}$, $198^{84}$, $287^{18}$; **2**, $3^{9}$, $5^{9b,c}$, $6^{9}$, $19^{9,9b,c}$, $20^{9b,c}$, $29^{9c}$, $641^{72}$; **3**, $638^{94}$; **4**, $969^{68}$; **5**, $817^{146}$; **8**, $33^{56}$, $66^{56}$, $87^{33}$
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Kimura, R., **1**, $336^{72}$; **5**, $524^{54}$, $534^{54}$, $553^{42}$, $564^{94}$
Kimura, S., **4**, $120^{201}$
Kimura, T., **1**, $563^{178}$; **4**, $354^{130}$, $611^{367}$, $636^{367}$; **7**, $761^{65}$; **8**, $86^{26}$, $93^{72}$, $94^{80}$, $95^{85}$
Kimura, Y., **1**, $242^{47,48}$; **3**, $977^{10}$, $985^{26a}$, $992^{38}$, $993^{38}$, $999^{51}$; **4**, $1001^{43}$; **5**, $851^{165}$, $889^{31}$; **6**, $851^{130}$, $877^{36}$, $879^{36}$, $882^{47}$, $883^{36}$, $885^{47}$, $886^{36}$, $958^{28}$
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Kinast, G., **2**, $900^{29}$, $901^{29}$, $902^{29}$
Kinastowski, S., **2**, $348^{61,62}$, $354^{62}$, $399^{13}$
Kinberger, K., **8**, $711^{66}$, $718^{66}$
Kindaichi, Y., **4**, $601^{244}$, $643^{244}$
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Kindon, N. D., **2**, $569^{34}$; **4**, $231^{258}$; **7**, $646^{28}$; **8**, $784^{112}$
King, A. O., **1**, $214^{27}$; **3**, $266^{195}$, $450^{103}$, $453^{103}$, $486^{44}$, $495^{44}$, $503^{150,151}$, $524^{35-37}$, $529^{53}$; **4**, $767^{234}$, $892^{141}$, $893^{153}$; **5**, $1166^{19}$; **6**, $966^{95}$; **8**, $693^{112}$, $755^{117}$, $756^{147}$, $758^{117}$, $950^{171}$
King, F. D., **2**, $1010^{9}$; **3**, $500^{126}$, $512^{126}$
King, F. E., **2**, $837^{163b}$, $838^{163}$; **3**, $831^{59}$; **6**, $643^{76}$; **8**, $143^{58}$
King, H. F., **5**, $72^{172}$
King, J. A., **8**, $143^{60}$, $148^{60}$
King, J. A., Jr., **5**, $1143^{91}$
King, J. C., **2**, $384^{317}$; **6**, $716^{95}$
King, J. F., **3**, $707^{10}$, $867^{36}$; **5**, $571^{118}$, $904^{53}$
King, J. L., **6**, $687^{375}$
King, J. R., **3**, $330^{190}$
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King, L. G., **4**, $437^{146}$
King, M. V., **8**, $366^{39}$
King, R. B., **2**, $81^{4}$; **3**, $208^{3}$, $380^{10}$; **5**, $1134^{44}$; **8**, $390^{77}$, $459^{236}$, $736^{20}$, $753^{20}$
King, R. R., **7**, $204^{60}$; **8**, $884^{101}$
King, R. W., **6**, $1012^{4}$, $1013^{4}$, $1033^{126}$
King, S. A., **4**, $593^{131,133}$; **5**, $300^{76}$, $307^{90}$
King, S. M., **8**, $675^{41}$, $679^{41}$, $684^{41}$
King, S. W., **4**, $957^{22}$
King, T. J., **1**, $305^{86}$; **2**, $837^{163b}$, $838^{163}$; **3**, $665^{36}$
Kingma, A. J., **4**, $85^{72}$, $204^{33,35}$
Kingma, R. F., **5**, $78^{275}$
Kingsbury, C. A., **1**, $506^{18}$; **2**, $345^{32}$; **3**, $114^{233}$, $154^{233}$; **6**, $154^{149}$, $1017^{36}$; **7**, $341^{50}$; **8**, $5^{26}$
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Kingston, J. F., **2**, $839^{181}$, $840^{181}$
Kinishi, R., **8**, $170^{77,78}$
Kinloch, E. F., **8**, $478^{42}$, $531^{123}$
Kinloch, S. A., **1**, $554^{102}$
Kinnard, R. D., **4**, $441^{183}$
Kinney, C. R., **1**, $383^{111}$
Kinney, R. J., **8**, $289^{29}$, $290^{29}$, $797^{35}$
Kinney, W. A., **1**, $744^{60}$, $745^{60}$; **3**, $168^{505}$; **5**, $324^{18b}$, $831^{38}$, $1123^{37}$; **8**, $942^{116}$
Kinnick, M. D., **4**, $13^{45}$, $14^{45a}$; **6**, $1022^{63}$
Kino, T., **1**, $101^{90}$
Kinomura, K., **6**, $658^{184}$
Kinoshita, H., **3**, $159^{451}$, $160^{451}$, $161^{451}$; **4**, $127^{220b}$, $359^{161}$, $595^{151}$, $604^{288,289}$, $646^{289}$, $647^{288}$, $753^{164}$; **6**, $641^{62}$; **8**, $840^{30,30b}$, $960^{37}$
Kinoshita, K., **4**, $148^{51}$, $149^{51}$, $179^{65}$; **7**, $26^{54}$
Kinoshita, M., **1**, $513^{48}$, $564^{201}$, $569^{254}$; **2**, $263^{54}$, $350^{75}$; **6**, $27^{119}$, $46^{59}$, $60^{145}$, $1022^{65}$; **7**, $350^{23}$, $778^{391,392,393}$; **8**, $820^{46}$
Kinoshita, S., **7**, $743^{64}$
Kinoshita, T., **8**, $607^{33,34}$, $620^{139}$
Kinowski, A. K., **4**, $432^{107,108}$
Kinsel, E., **2**, $187^{43}$
Kinsley, S. A., **6**, $546^{652}$
Kinsman, D. V., **3**, $735^{14}$
Kinson, P. L., **3**, $891^{42}$, $903^{122}$
Kinstle, T. H., **4**, $273^{48}$, $279^{48}$, $280^{48}$; **7**, $548^{76}$, $558^{76}$
Kinter, C. M., **5**, $839^{83}$; **6**, $150^{131}$, $151^{131}$
Kinter, M. R., **7**, $92^{42}$, $93^{42}$
Kinugawa, N., **1**, $215^{37}$; **2**, $23^{90,90a}$; **4**, $607^{314}$
Kinzebach, W., **8**, $568^{466}$
Kinzel, E., **8**, $459^{240}$, $460^{250,251}$, $535^{166}$
Kinzer, G. W., **5**, $455^{80}$
Kinzig, C. M., **3**, $273^{15}$, $274^{15}$
Kinzy, W., **6**, $53^{117}$
Kiovsky, T. E., **6**, $291^{209}$
Kiplinger, J. P., **5**, $788^{15}$
Kipnis, F., **4**, $317^{547}$
Kipphardt, H., **2**, $455^{14}$, $514^{51}$; **6**, $119^{110,111}$, $728^{210}$
Kira, M., **1**, $180^{43}$, $181^{43}$; **2**, $6^{28}$, $17^{28,28b,d}$, $572^{44}$, $790^{58,59}$, $792^{65}$; **6**, $487^{45}$, $489^{45}$, $500^{178}$, $573^{45}$, $832^{12}$, $865^{12}$; **7**, $641^{7}$; **8**, $20^{141}$, $478^{38}$, $547^{313}$
Kirby, A. J., **8**, $211^{2}$
Kirby, G. W., **2**, $555^{146,149}$; **3**, $681^{97}$, $689^{123}$; **5**, $419^{72,74}$, $420^{76}$, $421^{79}$, $437^{159}$, $441^{176,176f}$, $442^{184}$, $575^{133}$, $576^{146}$; **6**, $104^{4}$, $212^{83}$, $609^{57}$, $614^{78}$; **7**, $748^{111}$
Kirby, J. E., **1**, $383^{111}$
Kirby, K. C., Jr., **8**, $990^{42}$
Kirby, R., **4**, $70^{6}$, $98^{6}$, $140^{7a}$
Kirby, S., **5**, $461^{101}$, $463^{101}$
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Kruse, C. W., **2**, $355^{121}$, $356^{130}$
Kruse, L. I., **2**, $807^{46}$; **3**, $18^{98}$, $1029^{55}$; **4**, $37^{107,107b,e}$, $38^{107e}$, $39^{107e}$; **7**, $554^{67}$; **8**, $542^{224}$, $933^{50}$
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Kubo, M., **1**, $477^{138}$; **6**, $20^{75}$
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Kurihara, T., **1**, $544^{32,37}$, $548^{66}$, $560^{37,155}$, $561^{37,156}$; **2**, $357^{149}$, $801^{25}$; **3**, $530^{63}$, $532^{63}$; **6**, $227^{20}$, $236^{20}$, $609^{51}$, $626^{168}$, $1045^{21,22}$
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Lindsay, J. K., **2**, 182$^{1}$
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Linn, W. S., **4**, 315$^{515}$
Linnell, S. M., **7**, 883$^{178}$
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Lion, C., **1**, 427$^{112}$; **3**, 124$^{262}$, 257$^{121}$; **4**, 350$^{117}$, 877$^{66}$
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Liotta, C. L., **3**, 3$^{17}$, 7$^{17}$; **5**, 333$^{45}$
Liotta, D., **1**, 571$^{279}$, 630$^{5,17,34}$, 631$^{17}$, 632$^{17}$, 633$^{17}$, 634$^{17}$, 635$^{76}$, 636$^{17}$, 641$^{17}$, 642$^{111}$, 644$^{17,111}$, 656$^{17}$, 658$^{17}$, 669$^{111,183}$, 670$^{17,183}$, 671$^{111,183}$, 672$^{5,17}$, 699$^{183}$, 828$^{72}$; **3**, 86$^{54}$, 87$^{54}$, 94$^{54}$, 95$^{54}$, 117$^{54}$; **4**, 38$^{108,108c}$, 245$^{89}$, 317$^{558}$, 339$^{39}$, 340$^{49}$, 342$^{39}$, 376$^{102}$, 377$^{102,124b}$, 379$^{115}$, 380$^{115h,124,124b}$, 383$^{115h}$, 438$^{152}$; **5**, 1203$^{58}$; **6**, 836$^{58}$, 1030$^{107}$; **7**, 97$^{92}$, 130$^{77}$, 131$^{83-86}$, 132$^{89,94}$, 273$^{134}$, 515$^{1}$, 520$^{24,26}$, 521$^{34}$, 523$^{1,45}$, 741$^{51}$, 819$^{20}$, 822$^{32}$, 826$^{20}$; **8**, 849$^{117}$, 850$^{119}$
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Lipton, M. S., **5**, 686$^{44}$
Liptrot, R. E., **1**, 308$^{95}$, 314$^{95}$
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Lis, L. G., **3**, 24$^{145}$
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Lynch, G. J., **4**, 301[315,318], 303[339]; **8**, 675[39], 691[107], 854[149], 856[164]
Lynch, J., **1**, 805[312]; **5**, 245[21], 308[94,97]; **6**, 990[84]
Lynch, J. E., **1**, 62[38,40], 63[42]; **2**, 227[160], 821[104], 852[104]; **5**, 99[130]; **6**, 759[139]
Lynch, L. E., **1**, 551[72], 665[172], 668[172]; **2**, 283[44], 298[44]
Lynch, P. P., **8**, 915[96], 939[94,95]
Lynch, T. J., **6**, 723[146]; **8**, 86[21], 600[103]
Lynch, V., **2**, 655[131]; **5**, 841[104]
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Lysenko, Z., **2**, 1090[70], 1100[70]; **4**, 371[60], 372[57,60]; **6**, 1031[113,115]; **7**, 517[16], 523[46]; **8**, 847[99], 848[99], 849[99]
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McCullough, J. J., **5**, 125[17], 128[29], 385[130], 650[25]; **7**, 854[54], 855[54], 876[122]
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McDade, C., **5**, 1178[44]; **8**, 682[85], 687[85], 690[85], 691[85]
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McDaniel, R. L., **1**, 884[129]
McDaniel, R. L., Jr., **5**, 806[107], 808[107b], 809[107b], 1027[88], 1028[88]
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MacDonald, A. A., **8**, 568[472]
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MacDonald, D. L., **2**, 456[73], 458[73]
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Macdonald, J. E., **1**, 462[18]; **4**, 483[8]; **5**, 839[77]
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McDonald, J. H., III, **1**, 51[13], 52[13], 108[10], 153[57], 336[68,70], 427[113], 460[2]; **2**, 9[39], 31[39], 194[67]; **4**, 380[120]
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McDonald, R. T., Jr., **8**, 409[80]
MacDonald, S. F., **2**, 376[280]
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MacDonald, T., **1**, 55[22]
Macdonald, T. L., **1**, 108[11], 109[11], 117[51,52], 134[11,51], 283[2], 315[2], 328[28], 333[58], 338[82], 339[82], 879[111a,b]; **2**, 55[2], 62[22a], 66[2,36], 68[36], 78[92], 601[37]; **3**, 196[23,30], 223[152,153]; **4**, 45[128], 158[77], 816[201], 1005[81,83], 1018[81,83]; **5**, 687[55], 798[68]; **6**, 1067[105]; **7**, 226[71]; **8**, 557[379]
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McDonnell, P. D., **2**, 965[65]
McDonnell Bushnell, L. P., **5**, 1134[38], 1149[38]
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McGarvey, G., **3**, 254[98], 257[98]; **4**, 344[78b]
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McGillivray, G., **2**, 780[11]; **6**, 487[58,59], 489[59]; **7**, 185[173]; **8**, 41[93], 66[93]
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Manwaring, R., **6**, 860$^{176}$
Manyik, R. M., **2**, 834$^{155}$; **4**, 589$^{77}$, 590$^{77}$, 591$^{77}$, 597$^{181}$, 598$^{181}$, 638$^{181}$
Manz, F., **4**, 1081$^{83}$
Manzano, C., **1**, 117$^{56}$
Manzini, G., **4**, 20$^{63}$, 21$^{63}$
Manzocchi, A., **6**, 227$^{19}$, 228$^{19}$; **7**, 279$^{171}$, 709$^{37}$, 765$^{134}$, 844$^{60}$; **8**, 187$^{38}$, 190$^{71,73}$, 191$^{73}$, 240$^{30,31}$, 244$^{30,56}$, 263$^{29}$
Mao, C.-L., **2**, 834$^{155}$
Mao, D. T., **5**, 523$^{48}$, 526$^{57}$, 788$^{12}$, 954$^{298}$, 1003$^{21}$, 1016$^{63}$; **6**, 723$^{146}$
Mao, M. K. T., **2**, 186$^{36}$; **5**, 922$^{136}$; **6**, 888$^{65}$
Mapelli, C., **4**, 988$^{137}$
Maples, P. K., **8**, 447$^{101,102}$, 450$^{101,102}$
Maquestiau, A., **2**, 351$^{80}$, 364$^{80}$
Mar, E. K., **3**, 225$^{186}$
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Marakowski, J., **5**, 403$^{7}$, 404$^{7,18}$; **6**, 744$^{77}$
Maran, F., **6**, 575$^{966}$
Maraschin, N. J., **7**, 15$^{144}$
Maravigna, P., **1**, 294$^{43}$
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Marburg, S., **3**, 262$^{166}$
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Marcaccioli, S., **7**, 778$^{402}$
Marcantoni, E., **4**, 86$^{78e}$; **6**, 115$^{83}$, 938$^{128}$, 942$^{128}$, 944$^{128}$
Marcantonio, A. F., **7**, 24$^{36}$, 25$^{36}$
Marcelli, M., **3**, 1046$^{1}$
March, J., **3**, 777$^{1}$, 908$^{147}$, 909$^{147}$; **5**, 721$^{99}$; **6**, 226$^{10,14}$, 240$^{81}$, 256$^{10}$, 257$^{10}$; **7**, 119$^{1}$; **8**, 410$^{94}$
Marchalin, S., **6**, 533$^{480}$, 550$^{480}$
Marchand, A. P., **4**, 238$^{3}$, 1073$^{23}$; **5**, 71$^{129}$, 87$^{41}$, 92$^{41}$, 109$^{41}$, 703$^{15,19}$, 705$^{19,23}$, 754$^{59}$, 1130$^{7}$; **6**, 107$^{23}$, 744$^{72}$; **8**, 36$^{88}$, 52$^{149}$, 66$^{88,149}$
Marchand, E., **5**, 488$^{195}$; **6**, 540$^{585,586}$
Marchand-Brynaert, J., **5**, 108$^{209,210,211}$, 109$^{209,210,211,216,218,222}$, 110$^{210,222,223}$, 111$^{210,222}$, 112$^{222,223}$, 113$^{236}$, 410$^{40}$; **6**, 430$^{96}$, 520$^{341,342}$, 543$^{341}$, 544$^{342}$
Marchart, G., **8**, 212$^{11}$
Marchelli, R., **6**, 936$^{109}$; **7**, 197$^{21}$; **8**, 406$^{50}$
Marchenko, A. P., **6**, 500$^{180}$
Marchenko, N. B., **6**, 507$^{228,229}$, 554$^{755,764,784,786,792}$
Marchese, G., **1**, 413$^{57}$, 416$^{67}$, 452$^{220}$; **3**, 208$^{2}$, 217$^{2}$, 230$^{235,236}$, 283$^{49}$, 436$^{11}$, 441$^{48}$, 446$^{87}$, 449$^{48,101}$, 463$^{153,154,155,166}$, 485$^{29}$, 492$^{79}$, 493$^{29}$, 503$^{29,79}$, 513$^{29,79}$; **4**, 93$^{93d}$; **6**, 446$^{101}$
Marchese, J. S., **6**, 705$^{18}$
Marchesini, A., **8**, 349$^{145}$
Marchetti, F., **5**, 1174$^{36}$
Marchetti, M., **4**, 939$^{76}$; **5**, 1152$^{144}$
Marchi, M., **4**, 600$^{243}$, 601$^{243}$
Marchington, A. P., **4**, 159$^{82}$
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Marchiori, M. L. P. F. C., **1**, 411$^{45}$
Marchioro, C., **4**, 50$^{142}$; **5**, 370$^{102}$, 371$^{102}$
Marchioro, G., **1**, 480$^{153}$; **6**, 150$^{114}$, 936$^{108}$; **7**, 205$^{64}$
Marchon, J.-C., **7**, 384$^{114b}$
Marciniec, B., **8**, 764$^{8}$, 765$^{13}$, 774$^{72,73}$
Marcinow, Z., **8**, 114$^{59}$, 509$^{91}$, 510$^{94}$
Marco, J. A., **6**, 172$^{19}$, 780$^{71}$
Marco, J. L., **1**, 555$^{119}$, 559$^{147,148}$
Marco-Contelles, J., **2**, 636$^{55}$, 637$^{55}$, 640$^{55}$
Marconi, W., **8**, 171$^{110}$
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Marcotullio, M. C., **4**, 1040$^{77}$
Marcus, R. A., **7**, 852$^{36}$
Marcuzzi, F., **4**, 277$^{89,90}$, 285$^{90}$, 298$^{280}$
Marczak, S., **8**, 163$^{42}$
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Mardis, W. S., **3**, 103$^{207}$
Marecek, J. F., **6**, 70$^{18}$, 620$^{121-127}$, 625$^{121,163}$
Maréchal, E., **3**, 331$^{199}$
Mareda, J., **5**, 257$^{61,61c}$, 560$^{70}$, 628$^{45}$, 913$^{108}$
Marei, A., **6**, 421$^{25}$
Marek, I., **3**, 223$^{154}$, 226$^{207}$; **4**, 209$^{69}$, 895$^{164}$, 900$^{164,179}$; **6**, 849$^{122}$
Mares, F., **7**, 452$^{46}$, 674$^{51}$
Maresca, L. M., **7**, 43$^{46}$
Marfat, A., **1**, 415$^{64}$, 428$^{115,116}$; **3**, 243$^{17}$, 249$^{17}$, 263$^{17,172}$, 500$^{132}$, 505$^{132}$; **4**, 91$^{88f}$, 250$^{135}$, 255$^{135}$, 898$^{174}$, 899$^{174}$
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Margaretha, P., **2**, 346$^{48}$, 347$^{48}$, 349$^{66}$, 353$^{48,94}$, 355$^{48,126}$, 356$^{48,66}$, 357$^{141,142}$, 358$^{48}$, 365$^{48}$, 367$^{48}$, 369$^{48}$, 374$^{48}$; **3**, 579$^{95}$; **4**, 251$^{144}$, 257$^{144}$; **5**, 123$^{1}$, 126$^{1}$, 128$^{28}$, 164$^{75}$, 176$^{75}$, 225$^{96}$; **7**, 876$^{126}$; **8**, 134$^{36}$
Margaryan, A. Kh., **5**, 128$^{31}$
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Margot, C., **4**, 869$^{22}$; **6**, 174$^{57}$
Margraf, B., **5**, 257$^{60}$
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Margulies, H., **3**, 804$^{7}$, 809$^{38}$, 815$^{75}$
Margulis, M. A., **4**, 969$^{66}$
Marhold, H., **2**, 362$^{184}$
Mariano, P. S., **2**, 1035$^{93}$, 1037$^{96-100}$, 1038$^{101-103}$, 1039$^{104}$, 1040$^{105}$; **4**, 753$^{165}$; **5**, 194$^{1}$, 196$^{1}$, 197$^{1}$, 198$^{1}$, 210$^{1}$, 480$^{178}$, 531$^{79}$, 829$^{21}$; **6**, 756$^{122}$, 760$^{122}$; **7**, 854$^{52}$, 855$^{52}$, 876$^{121,123,124}$, 887$^{52}$
Maricich, T. J., **7**, 24$^{33}$, 25$^{33}$
Marikawa, T., **5**, 847$^{136}$
Marinas, J. M., **2**, 345$^{18}$, 359$^{18}$, 360$^{18}$; **3**, 825$^{24,24b}$, 835$^{24}$; **8**, 368$^{65}$
Marinelli, E. R., **1**, 473$^{79}$; **3**, 262$^{158}$
Marinelli, F., **3**, 539$^{96}$; **4**, 411$^{266b}$
Maring, C., **1**, 314$^{131}$; **8**, 540$^{195}$
Maring, C. J., **2**, 455$^{16}$, 665$^{33}$, 667$^{40}$, 673$^{33,40}$, 674$^{40}$, 675$^{33,40}$, 681$^{57}$, 682$^{33,64}$, 683$^{64}$, 686$^{64}$, 689$^{33}$, 694$^{76}$; **4**, 373$^{80}$, 374$^{80}$; **5**, 434$^{145}$
Maringgele, W., **6**, 526$^{394}$
Marini-Bettòlo, G., **5**, 130$^{39}$
Marinier, A., **1**, 766$^{157}$; **3**, 380$^{10}$; **5**, 532$^{86}$
Marino, G., **2**, 735$^{12}$, 964$^{58}$
Marino, J. P., **1**, 118$^{58}$, 129$^{58}$, 431$^{133}$; **2**, 833$^{150}$; **3**, 217$^{87}$, 226$^{193,194,194a,196}$, 263$^{176}$, 264$^{183}$, 265$^{190,191}$, 667$^{48}$, 687$^{48}$, 807$^{34}$; **4**, 27$^{79}$, 120$^{196}$, 121$^{205b}$, 125$^{216,216d}$, 148$^{48}$, 164$^{48}$, 173$^{32}$, 183$^{79}$, 248$^{108,113}$, 256$^{113}$, 260$^{108}$, 261$^{113}$, 795$^{89}$, 1035$^{38}$, 1046$^{117}$, 1048$^{38}$; **5**, 268$^{78}$, 468$^{137}$, 553$^{43}$, 757$^{79}$, 766$^{79}$, 803$^{90,92}$, 921$^{143}$, 943$^{238}$, 976$^{21}$, 979$^{24,25}$; **6**, 9$^{42}$, 152$^{134,135}$, 910$^{11}$, 924$^{11}$, 934$^{100}$, 1006$^{148}$; **7**, 205$^{65}$, 227$^{86}$, 358$^{12}$, 376$^{82}$, 564$^{94}$, 566$^{94}$; **8**, 836$^{10e,f}$, 844$^{10f}$, 846$^{10f}$
Marinoni, G., **1**, 543$^{28}$
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Marioka, S., **6**, 626$^{167}$

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Marita, M., **5**, 581$^{174}$
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Märki, H.-P., **1**, 824$^{45}$; **2**, 205$^{102,104}$, 206$^{102b,104}$; **3**, 225$^{187}$
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Markies, P. R., **1**, 26$^{132,133,134}$
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Märkl, G., **2**, 369$^{248}$; **3**, 531$^{86}$, 593$^{178}$; **6**, 178$^{121}$; **8**, 865$^{248}$
Märkl, R., **5**, 1094$^{100,100a}$, 1098$^{100a}$
Markó, I., **3**, 979$^{12}$; **7**, 429$^{158}$, 430$^{158,159}$, 442$^{46a,b}$, 489$^{165}$
Markó, L., **5**, 1138$^{66}$; **8**, 152$^{177}$, 447$^{99}$, 452$^{190}$, 459$^{236}$, 551$^{345}$, 554$^{367}$
Markov, P., **8**, 492$^{17}$
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Marks, J., **2**, 102$^{22}$
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Marks, M. W., **1**, 41$^{266}$
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Marktscheffel, F., **7**, 709$^{45}$
Markus, G. A., **8**, 616$^{98}$
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Markwalder, J. A., **8**, 844$^{65}$
Markwell, R. E., **7**, 15$^{145}$; **8**, 626$^{175}$, 629$^{175}$
Marky, M., **4**, 1084$^{95}$
Marletta, M. A., **7**, 79$^{134}$
Marlewski, T. A., **2**, 348$^{55}$
Marlin, J. E., **5**, 829$^{18}$, 847$^{138}$, 1004$^{27,27c}$; **6**, 856$^{160}$, 858$^{160}$
Marlowe, C. K., **6**, 533$^{496}$
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Maroni, S., **3**, 752$^{97}$; **7**, 153$^{9}$
Maroni, Y., **8**, 873$^{18}$, 874$^{20}$
Maroni-Barnaud, Y., **2**, 428$^{44}$; **8**, 7$^{37}$
Marotta, E., **2**, 338$^{76}$
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Marples, B. A., **3**, 741$^{53}$; **5**, 21$^{161,162,163}$, 23$^{161,162,163}$; **7**, 62$^{50a}$, 429$^{151}$
Marquarding, D., **2**, 1090$^{69,71,75}$, 1091$^{69}$, 1092$^{71}$, 1093$^{71,83}$, 1094$^{71,87,89}$, 1095$^{89,93}$, 1096$^{71}$, 1098$^{71,105}$, 1099$^{106,108}$, 1100$^{71}$; **6**, 242$^{87,88}$, 243$^{87,88}$; **8**, 830$^{84}$
Marquardt, D. J., **4**, 811$^{173}$
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Marquet, A., **1**, 513$^{45,46}$, 531$^{130}$; **2**, 902$^{47}$, 903$^{47}$; **3**, 147$^{390,398}$, 149$^{390,398,407,408,409,410,411,412}$, 150$^{407,410,411}$, 151$^{390,407,408,409,410,411}$, 152$^{390,407}$, 153$^{407}$, 155$^{408,409,410}$; **6**, 641$^{58}$, 644$^{91}$; **7**, 777$^{388}$
Marquet, B., **2**, 283$^{48}$; **7**, 538$^{63}$
Marquez, C., **7**, 693$^{24}$
Marquez, E., **1**, 552$^{80}$
Marquez, V. E., **8**, 798$^{60}$
Marquis, E. T., **6**, 970$^{127}$
Marr, D. H., **7**, 801$^{36}$
Marr, G., **3**, 160$^{465}$, 164$^{465}$, 166$^{465}$
Marra, A., **7**, 245$^{76}$
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Marren, T. J., **1**, 112$^{27}$; **2**, 448$^{46}$; **4**, 152$^{56}$
Marrero, J. J., **2**, 1049$^{16}$; **4**, 817$^{203}$
Marrero, R., **7**, 182$^{162,164}$, 185$^{176}$, 186$^{179}$
Marron, B. E., **3**, 618$^{20}$; **6**, 448$^{107}$
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Marsais, F., **1**, 474$^{88,94,96,97,99,101,102}$; **3**, 261$^{146}$, 264$^{146}$; **4**, 465$^{115}$, 474$^{115}$, 478$^{115}$
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Marschall, H., **6**, 1042$^{5,7}$
Marschall-Weyerstahl, H., **3**, 752$^{92}$; **4**, 1002$^{58}$
Marschner, F., **4**, 1005$^{95}$
Marschoff, C. M., **6**, 278$^{132}$
Marsden, E., **8**, 916$^{100}$, 918$^{100}$
Marsden, R., **2**, 946$^{174,175}$
Marsh, B. K., **5**, 704$^{22}$, 1020$^{69}$, 1023$^{69}$
Marsh, C. R., **3**, 522$^{11}$
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Marsh, F. D., **7**, 21$^{13}$, 474$^{39}$, 479$^{95}$, 480$^{98}$
Marsh, G., **5**, 216$^{15}$, 219$^{15}$
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Marshalkin, M. F., **8**, 388$^{62}$
Marshall, C. W., **7**, 100$^{120}$
Marshall, D. J., **8**, 492$^{15}$, 498$^{15}$, 530$^{96}$
Marshall, D. R., **2**, 547$^{101}$, 548$^{101}$; **4**, 442$^{184}$; **7**, 123$^{31}$
Marshall, D. W., **8**, 755$^{133}$
Marshall, G. R., **6**, 644$^{83}$, 671$^{277}$
Marshall, J. A., **1**, 188$^{68}$, 767$^{164,175,178}$, 768$^{167,169}$, 772$^{200}$, 851$^{37}$; **2**, 18$^{71}$, 39$^{136}$, 160$^{132}$, 162$^{143}$, 541$^{80}$, 547$^{110,111}$, 551$^{110,111}$, 574$^{57}$, 710$^{28}$, 837$^{164}$, 838$^{164}$, 911$^{68}$; **3**, 11$^{53}$, 100$^{202}$, 135$^{365,366}$, 136$^{365,366}$, 139$^{365,366}$, 142$^{365,366}$, 168$^{202}$, 170$^{202}$, 172$^{202}$, 223$^{149}$, 226$^{197,199}$, 356$^{55}$, 380$^{8,10}$, 394$^{96}$, 592$^{172}$, 627$^{44}$, 750$^{86}$, 783$^{23}$, 943$^{89}$, 983$^{21}$, 984$^{21,21a}$, 985$^{26b}$, 994$^{39}$, 999$^{51}$, 1000$^{51b}$, 1008$^{73}$, 1009$^{74}$, 1010$^{74,76,77}$, 1011$^{78}$, 1012$^{79,80}$; **4**, 18$^{62}$, 20$^{62a-c}$, 181$^{75}$, 186$^{92}$, 243$^{65}$, 253$^{65}$, 307$^{397}$, 380$^{122}$, 868$^{17}$, 869$^{17}$; **5**, 20$^{137}$, 173$^{123}$, 517$^{29}$, 519$^{29}$, 534$^{29}$, 538$^{29e}$, 539$^{29e}$, 830$^{29}$, 931$^{185}$, 934$^{185,187}$; **6**, 10$^{44}$, 11$^{44}$, 12$^{44}$, 158$^{183}$, 174$^{60}$, 187$^{175}$, 687$^{376}$, 831$^{8}$, 834$^{29}$, 837$^{61}$, 848$^{8}$, 850$^{29}$, 874$^{11,12}$, 985$^{60,61}$, 1055$^{50,51}$; **7**, 89$^{27,28}$, 152$^{5}$, 174$^{135}$, 273$^{135}$, 364$^{41a}$, 410$^{99}$, 413$^{116}$, 416$^{121a,b}$, 421$^{99}$; **8**, 58$^{175}$, 66$^{175}$, 164$^{45}$, 252$^{111}$, 278$^{157}$, 528$^{75,83}$, 537$^{186}$, 542$^{220}$, 546$^{186}$, 844$^{65}$, 929$^{28,29}$, 971$^{107}$
Marshall, J. L., **2**, 345$^{30}$; **3**, 19$^{102}$; **8**, 502$^{62}$
Marshall, J. M., **6**, 7$^{34}$
Marshall, J. P., **7**, 86$^{16a}$
Marshall, P. A., **8**, 875$^{40}$
Marshall, R., **8**, 398$^{145}$
Marsham, P., **3**, 753$^{99}$
Marsheck, W. J., **8**, 561$^{408}$
Marsheck, W. J., Jr., **7**, 66$^{75a}$, 69$^{90}$, 74$^{90}$
Marsi, K. L., **8**, 411$^{104}$
Marsi, M., **3**, 218$^{101}$; **4**, 576$^{17}$
Marsich, N., **4**, 170$^{11}$

Marsico, J. W., **6**, $554^{710}$, $614^{90}$
Marsili, A., **3**, $741^{51}$, $745^{65}$
Marson, C. M., **2**, $786^{47,48}$; **8**, $827^{72}$
Marson, S., **3**, $99^{186}$, $107^{186}$
Marson, S. A., **8**, $389^{71}$
Marston, C. R., **6**, $507^{232}$
Martel, A., **1**, $123^{78}$; **2**, $212^{120}$, $213^{126}$, $656^{158,159}$, $1059^{77}$; **5**, $92^{70}$, $94^{84}$
Martel, B., **5**, $1012^{50}$
Martell, A. E., **7**, $851^{23}$
Martelli, G., **1**, $391^{148}$; **2**, $613^{114}$, $656^{157}$, $807^{48}$, $925^{111}$, $926^{111}$, $927^{120}$, $935^{151}$, $936^{151}$, $937^{157}$; **4**, $452^{20}$; **5**, $100^{148,155,156}$, $102^{174}$; **6**, $21^{80}$, $22^{80}$, $759^{140}$
Martelli, J., **4**, $957^{23}$, $990^{146}$
Martelli, P., **7**, $65^{68}$
Marten, D. F., **2**, $934^{143}$; **4**, $189^{104}$, $190^{107}$, $579^{23}$; **5**, $272^{5}$, $274^{7}$, $275^{7}$, $277^{7}$, $279^{7}$
Marten, K., **4**, $14^{46}$, $18^{57}$
Martens, D., **5**, $716^{85}$
Martens, F. M., **8**, $96^{93}$
Martens, H., **2**, $723^{100}$; **3**, $332^{203}$; **5**, $637^{109}$
Martens, J., **6**, $462^{9,15}$; **8**, $459^{228}$, $460^{254}$
Marth, C. F., **1**, $755^{116}$, $756^{116,116d,e}$, $758^{116,124}$, $761^{116}$
Marti, F., **4**, $31^{92,92k}$
Marti, M. J., **6**, $245^{127}$
Martigny, P., **7**, $797^{19}$, $808^{76}$; **8**, $642^{31}$
Martin, A. A., **6**, $422^{34}$, $429^{34}$, $449^{113}$, $453^{113}$
Martin, A. R., **2**, $902^{46}$; **4**, $317^{546}$; **7**, $202^{47}$
Martin, B. D., **7**, $746^{83}$
Martin, C., **7**, $452^{51}$, $453^{51}$
Martin, C. A., **7**, $395^{20b}$
Martin, D., **6**, $243^{105}$, $244^{110}$, $612^{69}$; **8**, $445^{31}$
Martin, D. F., **2**, $357^{148}$
Martin, D. J., **4**, $1011^{163}$; **5**, $797^{67}$; **6**, $970^{126}$
Martin, D. T., **8**, $797^{39}$
Martin, E. L., **8**, $309^{8}$, $310^{8}$
Martin, G., **4**, $125^{216,216b}$
Martin, G. J., **2**, $725^{102\text{-}104}$; **5**, $777^{185,186,187,188}$
Martin, H., **2**, $1090^{73}$, $1102^{73}$, $1103^{73}$; **8**, $735^{11}$, $736^{19}$, $739^{11,19}$
Martin, H. A., **1**, $139^{6}$, $159^{76,77}$; **2**, $5^{19}$, $6^{19}$; **8**, $447^{124}$, $450^{124}$, $696^{123}$
Martin, H.-D., **3**, $382^{36}$, $872^{60}$; **5**, $257^{60}$, $571^{115}$; **6**, $1015^{22}$
Martin, J., **3**, $380^{13}$, $386^{67,68}$, $595^{191}$, $600^{213}$; **7**, $452^{51,53}$, $453^{51}$; **8**, $269^{77}$
Martin, J. A., **3**, $680^{93}$, $807^{28,30}$
Martin, J. A. F., **5**, $201^{32}$, $220^{50,51}$, $221^{53}$
Martin, J. C., **1**, $468^{50}$, $471^{63}$; **2**, $740^{54}$; **6**, $448^{110}$, $814^{86}$, $960^{56}$; **7**, $311^{32}$, $324^{32}$; **8**, $141^{30}$
Martin, J. D., **4**, $373^{87}$; **5**, $830^{32}$; **6**, $959^{38}$; **7**, $413^{118}$, $820^{25}$
Martin, J. G., **5**, $451^{13}$, $470^{13}$, $513^{2}$, $518^{2}$
Martin, J. R., **8**, $27^{30}$, $66^{30}$
Martin, K., **5**, $345^{68}$, $346^{68b}$
Martin, K. J., **8**, $829^{83}$
Martin, L. D., **3**, $466^{190}$, $1032^{66}$
Martin, M., **2**, $280^{28}$; **6**, $67^{13}$
Martin, M. G., **6**, $685^{364}$; **8**, $254^{123}$, $890^{143}$
Martin, M. L., **6**, $489^{82}$
Martin, M. M., **3**, $379^{3}$, $382^{3b}$
Martin, M. R., **4**, $425^{26}$; **6**, $67^{13}$
Martín, M. V., **6**, $67^{13}$
Martin, N., **2**, $380^{299}$
Martin, O. R., **2**, $642^{78}$, $643^{78}$; **7**, $258^{55}$; **8**, $91^{50}$
Martin, P., **3**, $848^{50}$; **4**, $754^{175}$
Martin, R. A., **2**, $602^{41}$; **3**, $614^{5}$, $617^{5a}$
Martin, R. H., **6**, $707^{45}$
Martin, R. M., **1**, $480^{153}$
Martin, R. S., **7**, $96^{87}$
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Martin, S. F., **1**, $41^{270}$, $275^{77}$, $383^{110}$, $432^{137}$, $456^{137}$, $542^{1}$, $884^{130}$; **2**, $55^{1}$, $410^{4}$, $475^{3}$, $479^{17,18}$, $480^{18}$, $496^{69}$, $498^{69}$, $1067^{127}$, $1068^{127}$, $1079^{158}$; **3**, $211^{28}$, $215^{28}$; **4**, $15^{50}$, $314^{497}$, $795^{79}$; **5**, $467^{116,117}$, $528^{68}$, $529^{70}$, $530^{71}$, $531^{68,80}$, $539^{109}$, $796^{57}$, $815^{57}$, $841^{101}$; **6**, $690^{396}$, $705^{28\text{-}30}$, $722^{137,138}$, $755^{121}$; **7**, $228^{90,91}$, $297^{33}$
Martin, S. J., **3**, $283^{50}$; **4**, $337^{36}$; **6**, $239^{76}$
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Martin, T., **2**, $821^{105}$; **7**, $32^{96}$
Martin, T. R., **1**, $16^{89}$
Martin, V. S., **3**, $225^{185}$, $264^{181}$; **6**, $2^{3}$, $8^{39}$, $25^{3}$, $88^{105}$, $89^{105}$, $927^{76}$; **7**, $198^{26}$, $238^{42}$, $239^{42}$, $240^{42}$, $390^{12}$, $391^{13}$, $401^{59,60}$, $403^{59}$, $406^{59,77}$, $409^{77}$, $411^{13}$, $412^{13}$, $413^{13}$, $414^{77}$, $415^{77}$, $421^{77}$, $423^{77}$, $571^{113}$, $572^{113}$, $587^{113}$, $710^{52}$; **8**, $879^{51}$, $880^{51}$
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Martin, W. B., **1**, $371^{75}$; **2**, $971^{91}$
Martina, D., **1**, $115^{42}$; **4**, $707^{43}$; **5**, $622^{24}$, $632^{24}$; **6**, $691^{404}$, $692^{404}$
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Martinelli, J. E., **6**, $812^{79,80}$
Martinelli, L. C., **3**, $629^{53,54}$
Martinelli, M. J., **6**, $516^{318}$; **7**, $364^{41b}$
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Martinetti, G., **2**, $345^{20}$
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Martínez, A. G., **6**, $835^{44}$
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Martinez, G. R., **1**, $410^{41}$, $473^{78}$; **2**, $737^{32}$; **3**, $918^{26}$; **4**, $1086^{111,119}$, $1087^{119}$; **6**, $175^{82}$, $893^{81}$
Martinez, M., **2**, $849^{213}$
Martinez, R. A., **3**, $727^{33}$
Martinez, V. C., **7**, $462^{119}$
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Martinez-Davila, C., **1**, $887^{138}$, $888^{138}$; **5**, $856^{210}$, $913^{100}$, $1007^{38}$, $1008^{43}$, $1017^{64}$, $1018^{64}$, $1020^{64}$, $1021^{64}$
Martinez-Gallo, J. M., **4**, $302^{338}$, $349^{110}$, $351^{124}$, $354^{110}$; **7**, $533^{35,36}$, $534^{35}$
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Martin-Lomas, M., **1**, $759^{132}$; **4**, $108^{146h}$, $230^{247}$; **8**, $227^{116}$
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Martius, C., **8**, $145^{86}$
Marton, D., **2**, $6^{29,32}$, $564^{9,11,12}$, $566^{20}$, $572^{47}$, $726^{127}$
Marton, M. T., **5**, $165^{86}$
Martos-Bartsai, M., **1**, $370^{70}$, $371^{70}$
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Maruoka, H., **7**, $672^{18}$
Maruoka, K., **1**, $78^{10,12,13,18}$, $79^{21}$, $80^{21}$, $81^{21}$, $82^{21}$, $83^{27}$, $88^{51,52,54,55}$, $92^{60,61}$, $98^{84}$, $99^{84,85}$, $100^{18}$, $165^{111}$, $266^{48}$, $283^{3}$, $316^{3}$, $333^{60,61}$, $335^{60,61}$, $348^{141}$, $387^{136}$; **2**,

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Marx, E., **8**, 35[65], 47[65], 66[65]

Marx, J. N., **2**, 388[341]; **3**, 804[5,9]; **4**, 162[92]; **7**, 128[66]

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Masamune, H., **3**, 223[156]; **7**, 390[4], 393[4,17], 394[4], 395[4], 396[4], 397[4], 398[4], 399[4], 400[4], 401[4], 406[4], 407[4], 410[4], 411[4], 413[4]

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Masamune, T., **1**, 161[88,89], 566[209], 823[43]; **2**, 159[131]; **3**, 125[306], 126[306], 735[22]; **4**, 238[11], 245[11], 255[11], 260[11]; **6**, 1049[36]; **7**, 253[23], 680[80]; **8**, 334[59], 528[67], 607[32]

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Mashima, K., **1**, 162[93,95,100], 163[106], 180[32]; **2**, 5[18], 6[18], 24[18,18a]; **5**, 1172[28], 1182[28]; **8**, 459[244], 678[62], 683[62], 686[62]

Mashimo, K., **7**, 137[123], 139[123]

Mashkina, A. V., **8**, 608[47,48], 629[182,183]

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Mason, K. G., **5**, 21[161], 23[161]

Mason, N. R., **8**, 618[110], 623[151]

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Massoli, A., **4**, 437[148], 438[148]; **7**, 340[45]
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Masson, S., **3**, 124[260]; **4**, 85[74]; **5**, 575[135]; **6**, 455[151,152,153]
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Masuda, H., **1**, 317[141]; **6**, 614[86]; **8**, 160[100], 170[100], 176[135], 178[100]
Masuda, K., **2**, 810[66], 851[66]; **5**, 768[131], 779[131]
Masuda, R., **1**, 563[178]; **4**, 435[135]; **6**, 510[292]; **7**, 764[124], 843[50], 844[51,52]; **8**, 18[128], 245[75], 315[46]
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Masuda, T., **1**, 187[64]; **5**, 1148[114]; **6**, 867[209]
Masuda, Y., **3**, 470[196,197], 473[196,197], 522[21]; **5**, 829[24]; **7**, 602[99], 604[130], 608[170,171]; **8**, 720[130]
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Masui, M., **6**, 439[69]; **7**, 158[35], 248[112], 752[153], 809[84]; **8**, 375[155]
Masui, Y., **6**, 637[36]; **7**, 745[78]
Masumi, F., **2**, 558[160]; **4**, 211[87], 252[163]
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Masunaga, T., **4**, 1020[239]; **8**, 806[106], 807[106], 900[31]
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Mathew, C. T., **8**, 338[88]
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Mathew, L., **5**, 901[27]
Mathey, F., **3**, 201[82]; **4**, 688[67]; **5**, 444[186]; **8**, 859[213], 865[247]
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Mathur, N. K., **7**, 446[61]; **8**, 271[110]
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Matl, V. G., **6**, 669[263]
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Nakahara, Y., **1**, 410$^{39}$, 568$^{231}$; **3**, 124$^{280}$, 125$^{280}$, 126$^{280}$; **4**, 18$^{62}$, 20$^{62i}$; **5**, 351$^{82}$; **6**, 51$^{108}$, 53$^{108}$, 468$^{53}$
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Nakahata, M., **8**, 150$^{122}$, 151$^{148}$
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Nakahira, T., **5**, 219$^{38}$
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Nakai, M., **7**, 451$^{20}$, 452$^{20}$, 454$^{20}$; **8**, 187$^{40}$
Nakai, S., **1**, 88$^{55}$; **4**, 140$^{11}$, 209$^{66}$; **6**, 850$^{125}$
Nakai, T., **1**, 584$^{11}$; **2**, 116$^{141}$, 119$^{161}$, 455$^{18}$, 538$^{68}$, 539$^{68}$, 556$^{156,157}$, 558$^{158,159}$, 569$^{35}$, 635$^{40}$, 640$^{40}$, 648$^{96}$, 649$^{96}$, 653$^{128}$, 656$^{153}$, 657$^{166}$, 715$^{56}$, 937$^{152,153,154,155}$, 1059$^{76}$; **3**, 97$^{174,175,176}$, 103$^{175,176}$, 108$^{174}$, 109$^{175,176}$, 117$^{174}$, 136$^{372}$, 942$^{80}$, 976$^{7}$, 977$^{10}$, 984$^{22,23}$, 985$^{22,25a,26a}$, 986$^{28}$, 987$^{24,31\text{-}33}$, 988$^{33a}$, 989$^{25a}$, 992$^{37,38}$, 993$^{25a,38}$, 994$^{41}$, 999$^{51}$, 1000$^{52}$, 1002$^{57}$, 1004$^{59}$, 1005$^{61\text{-}63}$, 1008$^{65}$; **4**, 128$^{221}$; **5**, 16$^{112}$, 24$^{166,167}$, 102$^{168}$, 821$^{162}$, 833$^{49}$, 839$^{85}$, 841$^{95}$, 850$^{147,159}$, 851$^{164,165}$, 888$^{28,29}$, 889$^{31}$, 1001$^{16}$; **6**, 14$^{51}$, 172$^{15}$, 780$^{73,75}$, 834$^{30}$, 846$^{100}$, 850$^{30}$, 851$^{129,130}$, 852$^{30,136,138}$, 853$^{30}$, 854$^{144}$, 856$^{151}$, 860$^{179}$, 873$^{7}$, 874$^{14}$, 875$^{7}$, 876$^{26,31,32,34}$, 877$^{14,31,36,37}$, 879$^{36,41}$, 882$^{26,31,47,48}$, 883$^{14,36,52,54,55,58}$, 885$^{26,31,34,47,48}$, 886$^{36}$, 887$^{32,58,61,64}$, 888$^{7}$, 890$^{48,52,69}$, 891$^{54,69,70}$, 892$^{74}$, 896$^{74}$; **7**, 263$^{88}$; **8**, 352$^{147}$, 934$^{58}$, 949$^{58}$
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Nakajima, K., **6**, 96$^{149}$; **7**, 62$^{51}$, 778$^{404}$
Nakajima, M., **1**, 72$^{69,70}$, 342$^{99}$, 563$^{171}$, 845$^{10}$; **2**, 65$^{29}$, 830$^{145}$; **3**, 197$^{41}$, 199$^{41}$; **6**, 989$^{78}$, 993$^{78}$; **7**, 307$^{11}$, 438$^{13}$, 442$^{50}$, 443$^{13}$, 749$^{120}$; **8**, 285$^{7}$
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Nakajima, T., **3**, 135$^{345}$, 174$^{345}$, 300$^{46}$, 302$^{46}$, 313$^{105}$, 314$^{108}$, 315$^{113}$, 318$^{129}$, 769$^{169}$; **5**, 438$^{161}$, 442$^{185,185a}$, 532$^{84}$; **6**, 17$^{63}$, 18$^{63,65}$; **7**, 645$^{19,20}$; **8**, 788$^{121}$
Nakajima, Y., **1**, 349$^{147}$; **5**, 473$^{153}$, 477$^{153}$; **8**, 170$^{77}$
Nakajo, E., **1**, 113$^{30}$, 624$^{85}$; **2**, 23$^{90,90b}$, 29$^{90b}$, 59$^{16}$; **3**, 225$^{184}$, 262$^{165}$; **5**, 473$^{151}$, 479$^{151}$; **7**, 643$^{14}$
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Nakamura, H., **2**, 73[63]; **4**, 27[79,79a]; **6**, 8[38]; **7**, 761[56]; **8**, 903[51], 906[51], 907[51]
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Nakamura, T., **1**, 212[9], 213[9,15], 215[41], 216[41], 448[207]; **2**, 442[13,14], 449[13,14], 450[13,14,51], 816[83], 819[102]; **3**, 231[242], 420[48], 443[61], 445[61], 463[159]; **4**, 810[167]; **5**, 809[120]; **6**, 509[258], 538[556]; **7**, 239[49], 710[56]; **8**, 174[126], 178[126], 179[126]
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Nakayama, T., **6**, 507[240], 515[240]
Nakayama, Y., **2**, 74[74]; **3**, 135[348], 136[348], 139[348], 141[348], 144[348]; **7**, 564[95], 568[95], 709[37]
Nakazaki, M., **1**, 860[68-70]; **3**, 592[173], 628[49]; **8**, 164[46], 178[46], 179[46]
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Nakazawa, T., **3**, 483[9]; **6**, 753[115], 754[115]; **7**, 743[64]
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Ollis, W. D., **1**, 2$^{6}$, 391$^{150}$, 489$^{18}$, 499$^{18}$, 542$^{5}$, 543$^{5}$, 544$^{5}$, 546$^{5}$, 580$^{1}$, 630$^{10}$, 820$^{7,12}$, 822$^{7}$, 833$^{117}$; **2**, 240$^{12}$, 321$^{11}$, 323$^{32}$, 329$^{11}$; **3**, 86$^{21,22,32,33,37,38,48,62}$, 104$^{21}$, 121$^{21,22}$, 147$^{32,33}$, 154$^{32}$, 158$^{37,38}$, 159$^{37}$, 163$^{38}$, 164$^{37}$, 173$^{37,38,62}$, 419$^{35}$, 422$^{68}$, 660$^{15}$, 688$^{115}$, 780$^{10}$, 862$^{2}$, 914$^{10}$, 916$^{16,19,20}$, 919$^{30}$, 923$^{45}$, 926$^{47}$, 928$^{47}$, 930$^{10,59}$, 931$^{10}$, 932$^{60}$, 933$^{30,62}$, 946$^{30}$, 949$^{94-96,98,99}$, 954$^{98}$, 963$^{121}$; **4**, 3$^{8}$, 6$^{8}$, 99$^{118d}$, 316$^{535}$, 483$^{4}$, 484$^{4}$, 495$^{4}$, 507$^{154}$, 725$^{43}$, 953$^{8}$, 968$^{57}$, 987$^{133}$, 1002$^{51}$, 1004$^{76,77}$, 1021$^{76,77}$, 1096$^{160}$, 1097$^{160}$, 1098$^{160}$; **5**, 847$^{135}$; **6**, 2$^{1}$, 28$^{1}$, 104$^{1,9}$, 111$^{64}$, 116$^{90}$, 133$^{5}$, 134$^{11}$, 171$^{4}$, 177$^{4}$, 198$^{4}$, 225$^{5}$, 226$^{5}$, 258$^{5}$, 293$^{229}$, 419$^{1}$, 421$^{1}$, 436$^{15}$, 437$^{15}$, 440$^{73}$, 448$^{15}$, 450$^{15}$, 453$^{15}$, 455$^{15}$, 893$^{79}$, 897$^{95,96,98}$; **7**, 41$^{18}$, 84$^{1}$, 85$^{1}$, 108$^{1,180}$, 329$^{4}$, 343$^{4}$, 345$^{1}$, 470$^{2}$, 594$^{4}$, 598$^{4}$, 671$^{10}$, 673$^{10}$, 687$^{10}$; **8**, 26$^{12}$, 27$^{12}$, 247$^{81}$, 279, 301$^{93}$, 403$^{2,6-8}$, 404$^{2}$, 699$^{148}$, 704$^{4}$, 705$^{4}$, 706$^{4}$, 707$^{4}$, 710$^{4}$, 715$^{4}$, 716$^{4}$, 717$^{4}$, 722$^{4}$, 724$^{4}$, 725$^{4}$, 726$^{4}$, 728$^{4}$, 794$^{3}$, 984$^{2}$
Ollivier, J., **4**, 1046$^{118}$; **5**, 911$^{90}$, 923$^{137}$, 954$^{90}$, 956$^{307}$; **7**, 14$^{135}$
Ollmann, G., **2**, 900$^{26}$, 960$^{35}$, 962$^{35}$

Olmstead, H. D., **1**, $3^{18,19}$; **2**, $124^{201}$, $183^{17}$, $184^{24,25}$, $235^{190}$, $268^{66}$, $280^{23}$, $289^{23}$, $311^{34}$, $599^{23}$; **3**, $4^{18}$, $7^{18}$, $8^{18}$, $11^{18}$, $14^{70}$; **7**, $130^{76}$
Olmstead, M. M., **1**, $11^{58}$, $23^{119}$, $34^{220,221,222}$, $41^{265,271}$, $488^{13}$; **3**, $213^{43}$, $1025^{34}$; **4**, $372^{62}$; **5**, $1039^{17}$, $1041^{19}$, $1043^{22}$, $1046^{19}$, $1049^{22}$, $1050^{17}$, $1052^{17,19}$
Olmstead, T. A., **3**, $58^{292}$; **5**, $843^{122}$
Olmsted, A. W., **6**, $204^{9}$
Olofson, R. A., **1**, $755^{116}$, $756^{116}$, $758^{116}$, $761^{116}$; **2**, $182^{10}$; **4**, $486^{39}$, $966^{53}$; **5**, $1008^{44}$
Olofson, R. S., **6**, $501^{186}$, $502^{186}$
Olofsson, B., **3**, $634^{7}$, $636^{7,7b}$, $637^{7}$
Olsen, B. A., **3**, $854^{76}$
Olsen, D. J., **3**, $1038^{91}$; **4**, $561^{30}$
Olsen, D. K., **6**, $498^{163}$
Olsen, D. O., **6**, $835^{48}$
Olsen, E. G., **5**, $709^{44}$, $716^{84}$, $739^{44}$
Olsen, H., **5**, $78^{282}$; **6**, $691^{404}$, $692^{404}$; **8**, $365^{27}$, $390^{81}$
Olsen, R. J., **1**, $418^{72}$
Olsen, R. K., **4**, $190^{107}$; **6**, $446^{103}$, $814^{96}$
Olsen, R. S., **2**, $842^{192,193}$
Olson, A., **6**, $824^{124}$
Olson, D. H., **3**, $296^{14}$, $330^{194}$
Olson, E. S., **7**, $673^{23}$
Olson, G. L., **3**, $168^{493}$, $169^{493}$, $171^{493}$, $362^{90}$; **4**, $305^{363}$; **7**, $347^{15}$
Olson, K. D., **7**, $878^{145}$
Olson, R. E., **1**, $636^{93}$, $638^{93}$, $640^{93}$, $646^{93}$, $647^{93}$; **2**, $88^{31}$, $601^{36}$, $602^{38}$; **3**, $87^{103}$, $104^{103}$, $106^{103}$, $111^{103}$, $117^{103}$; **5**, $1014^{55}$; **7**, $826^{47}$, $827^{47}$
Olsson, L., **4**, $395^{203}$
Olsson, L. F., **4**, $560^{22}$
Olsson, L. I., **3**, $217^{82}$; **4**, $308^{407}$, $395^{202}$, $872^{42}$; **6**, $652^{147}$, $653^{147}$, $654^{147}$, $655^{147}$, $681^{147}$, $866^{203}$
Olsson, T., **1**, $112^{27}$; **2**, $120^{170}$; **4**, $18^{56}$, $152^{56}$, $171^{26,27}$, $202^{24}$, $255^{204}$, $256^{207}$, $262^{207}$; **6**, $632^{6}$
Olszanowski, A., **3**, $619^{23}$
Oltay, E., **4**, $915^{11}$
Oltmann, K., **1**, $661^{167}$
Oltvoort, J. J., **2**, $599^{20}$; **6**, $57^{139}$, $652^{145}$
Omae, I., **8**, $548^{319}$
O'Mahoney, R., **1**, $419^{80}$
O'Mahony, M. J., **1**, $130^{94}$, $801^{301}$; **6**, $994^{98}$
O'Mahony, R., **4**, $794^{75}$
O'Malley, G. J., **4**, $27^{83}$, $370^{35}$, $385^{35}$
O'Malley, R. F., **7**, $800^{35}$
O'Malley, S., **7**, $427^{148f}$
Omar, M. E., **6**, $423^{46}$
Omar, M. T., **4**, $50^{142}$
Omata, T., **7**, $470^{11}$
O'Meara, D., **3**, $822^{2}$, $831^{2}$
Omi, T., **1**, $223^{74}$
Omietanski, G. M., **2**, $524^{76}$
Omizu, H., **3**, $602^{221}$; **8**, $173^{113}$
Omkaram, N., **5**, $211^{62}$
Omori, K., **2**, $97^{59}$
Omori, Y., **6**, $227^{20}$, $236^{20}$
Omote, Y., **1**, $373^{88}$, $374^{88}$; **3**, $1057^{38}$; **5**, $181^{150}$; **6**, $67^{14}$, $69^{14}$; **8**, $541^{203}$, $642^{32,34}$, $840^{29}$, $964^{55}$
Omoto, H., **7**, $806^{75}$
Omoto, S., **7**, $341^{51,52}$
Omura, H., **2**, $451^{55}$; **7**, $25^{43}$, $26^{43}$
Omura, K., **6**, $501^{185}$, $531^{185}$; **7**, $297^{27}$, $298^{27}$, $302^{64}$
Omura, S., **2**, $1^{2}$, $240^{5}$; **5**, $151^{9}$; **6**, $918^{37}$; **7**, $406^{87}$
Omura, T., **7**, $11^{88}$
Onak, T., **7**, $594^{6}$, $598^{6}$
Onak, T. P., **1**, $292^{27}$
Onaka, M., **1**, $453^{221,222}$; **2**, $576^{75}$, $615^{130}$, $631^{14}$, $635^{14}$, $655^{139}$; **3**, $426^{82}$, $429^{82}$; **4**, $161^{88}$, $1002^{46}$; **6**, $66^{4}$, $89^{108}$, $93^{130}$, $237^{66}$, $254^{160}$
Onaka, S., **8**, $150^{133}$, $151^{133,145}$
Onami, T., **3**, $224^{180}$; **7**, $393^{16}$, $398^{16,16a}$
Onan, K. D., **2**, $217^{139}$; **5**, $348^{74a}$, $499^{252}$, $500^{252}$; **8**, $614^{89}$, $620^{89}$
Onda, H., **8**, $709^{45}$
Ondik, H., **1**, $8^{35}$
O'Neal, H. E., **5**, $856^{193}$
O'Neil, I. A., **2**, $742^{77}$, $968^{78}$; **4**, $744^{134}$
O'Neill, B. T., **6**, $960^{57}$
O'Neill, H. J., **7**, $95^{74}$
O'Neill, M. E., **1**, $2^{8}$; **3**, $208^{1}$
O'Neill, P., **2**, $107^{61}$
Ong, B. S., **5**, $596^{31}$, $597^{31}$, $608^{31}$, $780^{205}$; **6**, $1005^{142,143}$
Ong, C. C., **2**, $710^{27}$
Ong, C. W., **4**, $667^{12}$, $668^{14}$, $670^{14}$, $675^{39}$, $677^{14}$, $678^{42}$, $682^{12}$
Ong, J., **5**, $834^{53}$
Ongania, K. H., **5**, $92^{62}$; **6**, $543^{614}$
Ongoka, P., **2**, $77^{91}$; **4**, $987^{162}$, $993^{162}$
O'Niel, B., **4**, $405^{252}$
Onishchenko, A. S., **5**, $451^{10}$, $513^{2}$, $518^{2}$
Onishi, A., **3**, $168^{501}$, $169^{501}$, $170^{501}$
Onishi, H., **6**, $237^{61}$
Onishi, T., **1**, $803^{306}$; **5**, $15^{105}$, $787^{8}$, $797^{61}$, $799^{74}$, $882^{14}$; **6**, $157^{172}$, $991^{89}$; **7**, $660^{43}$
Onishi, Y., **7**, $764^{107}$
Onisko, B. C., **4**, $390^{168}$
Onistschenko, A., **6**, $95^{146}$; **7**, $470^{9}$, $487^{9}$; **8**, $563^{436}$
Onitsuka, K., **5**, $1137^{56}$
Onken, D. W., **4**, $48^{140}$
Ono, A., **8**, $314^{43}$, $369^{79,80}$, $968^{88}$, $988^{29}$, $989^{36,38}$
Ono, H., **8**, $528^{67}$
Ono, M., **1**, $255^{17}$, $566^{209}$; **3**, $541^{106}$, $735^{22}$; **4**, $238^{1}$, $371^{47}$; **5**, $753^{58}$; **6**, $552^{690}$; **7**, $98^{104}$, $537^{61}$, $770^{256c}$, $771^{256}$, $819^{22}$; **8**, $97^{95}$, $115^{65}$, $607^{32}$
Ono, N., **2**, $321^{17}$, $323^{17}$, $330^{17}$, $332^{63,64}$, $333^{64\text{-}66}$, $334^{68}$, $360^{168}$; **4**, $13^{44,44b}$, $31^{92,92i}$, $37^{105}$, $64^{92i}$, $591^{108}$, $599^{219}$, $633^{108}$, $641^{219}$, $790^{36}$; **5**, $320^{10,11}$; **6**, $161^{178}$, $926^{69}$, $1000^{128,129,130}$; **7**, $197^{19}$, $883^{174}$; **8**, $962^{41}$, $969^{98}$
Ono, S., **5**, $79^{286}$
Ono, T., **1**, $176^{17}$, $520^{71,75}$; **2**, $363^{193}$, $374^{275}$; **4**, $258^{248}$, $261^{248}$; **6**, $780^{72}$; **8**, $934^{57}$
Onoda, Y., **1**, $328^{29}$
Onodera, A., **8**, $29^{38}$, $66^{38}$
Onodera, K., **7**, $299^{44}$
Onoe, A., **3**, $381^{29}$, $382^{29}$; **7**, $530^{25}$; **8**, $476^{24}$
Onomura, O., **2**, $1067^{123}$; **7**, $227^{75}$, $248^{109}$, $803^{55}$, $804^{62}$
Onopchenko, A., **8**, $764^{4b}$, $774^{71}$
Onoue, H., **1**, $123^{75}$, $373^{82}$; **4**, $590^{99}$
Onozuka, J., **1**, $561^{165}$
Onrust, R., **5**, $714^{75b}$, $847^{136}$
Onuma, K., **3**, $243^{18}$, $244^{18}$, $247^{18}$, $464^{169}$; **8**, $460^{254}$
Onuma, K.-i., **8**, $535^{166}$
Onyestyak, G., **4**, $298^{287}$
Onyido, I., **4**, $425^{23}$
Onyiriuka, O. S., **4**, $1060^{159}$
Oohara, T., **1**, $524^{93}$, $526^{93,95}$; **2**, $429^{48}$; **6**, $93^{134}$, $156^{152}$; **7**, $425^{149c}$
Ooi, H. C., **6**, $570^{951}$
Ooi, N. S., **7**, $846^{83}$
Ooi, T., **3**, $750^{86}$
Ooi, Y., **8**, $369^{78}$

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Ookita, M., **4**, 903[202], 904[202]
Oommen, P. K., **8**, 502[64], 503[67], 568[467]
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Ootake, K., **3**, 159[455], 161[455]
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Oparina, L. A., **6**, 509[282]
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Opitz, K., **5**, 391[143], 721[101]
Opitz, R. J., **6**, 281[147,149]
Oplinger, J. A., **2**, 714[53]; **3**, 363[86]; **4**, 1049[121b]; **5**, 516[28], 814[140], 994[53], 997[53]; **8**, 927[20]
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Oppenheim, E., **6**, 441[85]
Oppenländer, T., **5**, 195[9], 209[9]; **6**, 530[419]; **8**, 95[90]
Opperman, M., **8**, 708[37]
Oppolzer, W., **1**, 87[49], 214[25], 223[25b], 225[25b], 289[110], 307[111], 311[110], 312[111], 313[117,118], 317[154], 320[154], 404[24], 767[179], 770[187]; **2**, 69[48], 106[54], 231[172], 252[41], 253[41], 358[153], 455[11], 527[5], 528[5], 540[5], 544[5], 636[55], 637[55], 640[55], 681[60], 924[108a,b], 1015[22]; **3**, 17[89], 46[252], 159[457], 173[457], 178[541], 196[32], 728[35]; **4**, 21[69], 85[72], 107[141], 111[153], 152[54], 184[85], 189[85a], 201[12-16], 202[13-16,21,22], 204[21,32-36], 218[137,138], 231[282,283], 249[120,121], 257[121], 500[108,109], 501[115], 602[262], 644[262], 876[64], 1076[39], 1077[52], 1078[52], 1079[68], 1095[155], 1096[156]; **5**, 1[3], 2[3], 9[3], 10[79], 11[80-83], 13[90,91,93-95], 14[96,97], 15[3], 19[3,79], 26[79], 27[3,79], 37[20,21,22a], 38[22c], 40[26,27], 41[28-30], 42[31], 43[32], 44[34], 45[35,36], 46[38], 47[41], 48[38,41], 49[38], 50[38,38c,41-44], 51[42,45,45a,b], 52[46], 53[45a], 55[42,49], 56[42,49,50a], 57[50,50a,b], 59[50b], 71[124], 123[1], 126[1], 137[73,80], 139[84], 141[89], 186[170], 247[25], 253[46,46c], 260[25,70], 263[70], 264[74], 331[42,42b], 333[42c], 351[83], 354[84a], 356[84,90], 358[90b], 362[93,94], 363[93a,b,d,g,94b], 364[93c,d], 365[93a,e], 376[84a], 385[130,131], 386[130c,135], 390[130a], 391[141], 414[53], 435[151], 451[31,35], 453[31], 464[31], 513[5], 514[5], 515[17], 518[17], 524[5c], 527[5,62,66], 528[66a], 529[66a-c], 543[113,115,117,117b], 545[120], 547[17], 681[29], 682[30], 691[83,83b,84,87,88], 692[83,84], 693[83], 742[162], 779[198], 829[25], 1031[95]; **6**, 77[55], 94[143], 118[106], 248[137], 667[242], 756[125], 757[131], 879[42], 1018[41], 1050[40], 1063[85,86]; **7**, 174[135], 182[165], 646[27]; **8**, 61[189], 66[189], 537[188], 784[112]
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Or, Y. S., **7**, 683[89]; **8**, 623[148], 795[17]
Orahovats, A. S., **3**, 1038[93]; **6**, 74[37]
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Orange, C., **6**, 2[5], 18[5]
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Organ, H. M., **1**, 780[228]
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Orlando, C. H., **5**, 158[16], 159[16], 170[16]
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Orlinkov, A. V., **2**, 727[136]; **7**, 7[51]
Orlinski, R., **4**, 12[41], 764[222], 765[222], 808[155]; **6**, 551[683]
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Ornaf, R. M., **5**, 552[31], 564[31]
Ornfelt, J., **4**, 317[547]
Ornstein, P. L., **3**, 446[83]; **6**, 214[91], 676[307]; **8**, 840[39], 935[62]
Oro, L. A., **8**, 445[55], 764[6], 773[6b]
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Orozio, A. A., **5**, 945[250]
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Orr, D. E., **7**, 486[145]
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Orr, R., **4**, 345[81]
Orrom, W. J., **5**, 129[35]
Ors, J. A., **5**, 196[12,13], 647[14], 649[14,21], 658[21], 670[48]
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Ortar, G., **1**, 195[90]; **3**, 1035[79]; **4**, 860[112], 861[112]; **7**, 92[41,41b], 93[41b], 94[41], 143[148], 144[148]; **8**, 17[118], 84[13], 910[82], 911[87], 933[49,51]
Ortega, J. P., **5**, 70[115], 79[115]
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Ortez, B., **1**, 552[80]
Ortiz, B., **1**, 544[35]
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Osaka, M., **4**, 89[85]
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Peevey, R. M., **1**, 635[88]; **6**, 846[103], 905[145]
Peevey Pratt, D. V., **3**, 104[209], 117[209]
Pegg, N., **2**, 124[202]
Pegg, N. A., **1**, 240[43]
Pegg, N. J., **5**, 796[53]
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Pegram, J. J., **6**, 648[121], 1006[147]; **8**, 62[195], 66[195]
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Peiseler, B., **6**, 852[134], 879[45]
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Pelizza, F., **3**, 1017[7]
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Peltier, D., **8**, 134[32], 137[32,60]
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Pennetreau, P., **1**, 571[277]; **3**, 142[379]; **6**, 111[62,63]; **7**, 846[99]
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Penney, M. R., **5**, 485[184]
Penning, T. D., **1**, 534[142]; **3**, 9[48], 11[48]; **4**, 245[85]
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Pennings, M. L. M., **3**, 367[101]; **8**, 60[194], 62[194], 64[194], 66[194]
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Peppler, H. J., **7**, 55[12], 56[12]
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Pereillo, J.-M., **2**, 765[74]
Pereira, M., **6**, 487[76], 489[76]
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Perera, S. A. R., **1**, $223^{77}$, $224^{77}$, $317^{150}$
Peresleni, E. M., **6**, $531^{453}$
Pereyre, M., **1**, $437^{156}$, $445^{192}$, $479^{150}$, $480^{150}$; **2**, $3^{8}$, $6^{8,8a}$, $18^{8a}$, $71^{53}$, $564^{6}$, $574^{58}$, $607^{74,75}$, $608^{75,77}$, $609^{81,83}$; **3**, $3^{14}$, $7^{33}$, $8^{14}$, $20^{119}$, $195^{16}$, $196^{25}$, $453^{115}$, $524^{30}$, $529^{30}$; **4**, $735^{83}$, $743^{128}$, $770^{83}$, $971^{75}$; **5**, $901^{30}$; **7**, $614^{4}$, $616^{15}$, $621^{4}$; **8**, 278, $547^{316,316j,317}$, $548^{319}$, $794^{8}$, $798^{8}$, $845^{77}$
Perez, A. D., **6**, $152^{134}$, $934^{100}$; **8**, $836^{10e}$
Perez, C., **6**, $959^{38}$
Pérez, C., **7**, $691^{15}$
Perez, D., **8**, $554^{368}$, $555^{368,369}$, $782^{101}$, $984^{4}$, $991^{4}$
Perez, F., **4**, $1059^{154}$; **5**, $579^{160,161}$
Perez, J. J., **5**, $689^{78,78b}$, $732^{135}$, $733^{135b}$
Perez, M., **4**, $339^{45}$
Perez, M. A., **6**, $512^{301}$, $517^{301}$
Perez, M. G., **6**, $273^{94}$
Pérez, M. S. A., **8**, $2^{10}$
Perez, S., **1**, $117^{56}$
Pérez-Blanco, D., **2**, $411^{8}$
Perez-Dolz, R., **1**, $543^{26}$
Pérez-Juárez, M., **8**, $54^{156}$, $66^{156}$
Perez Machirant, M. M., **7**, $95^{68}$
Pérez-Ossorio, R., **5**, $201^{32}$, $202^{33,34,36}$, $220^{50,51}$, $221^{52,53}$; **8**, $2^{10}$, $36^{74}$, $38^{74}$, $66^{74}$
Perez-Prieto, J., **4**, $290^{196}12291^{220}$, $311^{446}$, $399^{224}$; **8**, $856^{180}$
Perfetti, R. B., **7**, $320^{63}$, $841^{10}$; **8**, $241^{38}$
Pergreffi, P., **5**, $1137^{55}$
Periasamy, M., **1**, $149^{49b}$; **3**, $1017^{5}$; **4**, $898^{173}$; **6**, $242^{91}$, $243^{91}$; **7**, $800^{30}$; **8**, $696^{121}$, $709^{44,45}$, $720^{130}$
Pericàs, M. A., **4**, $1005^{94}$; **5**, $1047^{31}$, $1052^{31}$, $1054^{43}$, $1059^{54}$, $1062^{59}$, $1133^{33}$
Perich, J. W., **6**, $618^{109}$
Perie, J. J., **4**, $290^{198,199,202,203,207}$, $292^{221}$, $401^{230}$; **7**, $470^{1}$, $488^{1}$, $490^{1}$; **8**, $252^{109}$, $856^{175}$
Perinello, G., **5**, $176^{126}$
Perisamy, M., **4**, $254^{186}$
Perizzolo, C., **6**, $262^{18}$
Perkin, A. G., **7**, $768^{198}$
Perkin, W. H., **4**, $285^{165}$, $289^{165}$; **5**, $899^{2}$
Perkin, W. H., Jr., **2**, $149^{91}$, $395^{2}$, $399^{23}$
Perkins, M., **2**, $523^{74}$
Perkins, M. J., **3**, $505^{162}$, $507^{162}$, $512^{162}$, $803^{1}$; **4**, $37^{107}$, $766^{231}$; **8**, $383^{13}$
Perkins, M. V., **4**, $390^{175b}$
Perkinson, N. A., **6**, $554^{758}$
Perl, C., **2**, $757^{17}$
Perlberger, J.-C., **5**, $972^{8}$, $989^{8}$
Perlier, S., **6**, $456^{157}$
Perlin, A., **7**, $293^{11}$
Perlin, A. S., **6**, $36^{23}$, $49^{99}$, $603^{13}$; **7**, $703^{1}$, $709^{1,41}$, $710^{1}$; **8**, $959^{26}$
Perlman, D., **2**, $456^{29}$; **5**, $752^{46}$; **7**, $55^{12}$, $56^{12}$; **8**, $185^{7}$
Perlman, K., **5**, $1096^{110}$, $1098^{110}$
Perlmutter, H. D., **5**, $2^{13}$, $3^{13}$
Perlmutter, P., **1**, $390^{142}$; **4**, $34^{97}$, $35^{97,97d}$
Perlova, T. G., **4**, $992^{154}$
Pernet, A. G., **2**, $555^{140}$; **3**, $216^{76}$; **4**, $27^{80}$, $249^{128}$; **7**, $299^{39}$
Perni, R. B., **1**, $765^{166}$; **2**, $828^{131}$; **6**, $487^{61}$, $489^{61}$
Pero, F., **4**, $426^{52}$
Peron, U., **7**, $760^{44}$
Perot, G., **6**, $563^{897}$
Perregaard, J., **8**, $924^{2}$
Perret, A., **2**, $138^{23}$
Perret, C., **4**, $520^{28}$; **5**, $37^{22a}$, $632^{60}$
Perret, R., **1**, $417^{70}$
Perreten, J., **5**, $947^{267}$, $948^{267}$
Perri, S. T., **5**, $689^{76,77}$, $690^{80,80c}$, $733^{136,136c,d,f}$, $734^{136f}$
Perrier, M., **5**, $553^{48}$
Perrier, S., **7**, $877^{135}$
Perrin, C., **8**, $383^{17}$
Perrin, C. L., **5**, $821^{161}$; **7**, $800^{33}$; **8**, $527^{50}$
Perrin, M., **8**, $133^{17}$
Perrin, P., **3**, $416^{17}$, $417^{17}$
Perrin, R., **3**, $306^{83}$
Perrio, S., **5**, $829^{22}$
Perrior, T. R., **4**, $675^{39,40}$, $679^{40,44}$
Perriot, P., **2**, $427^{42}$; **3**, $202^{92,93,95}$, $788^{49}$; **6**, $965^{87,89}$
Perron, Y. G., **4**, $398^{216}$, $399^{216d}$
Perrone, E., **8**, $409^{83}$
Perrone, M. H., **8**, $623^{150}$
Perrone, R., **6**, $787^{99,100}$
Perrot, A., **2**, $534^{32}$
Perrot, M., **8**, $262^{19}$, $265^{19}$
Perrotta, A., **7**, $243^{63}$
Perry, C. W., **3**, $350^{37}$; **5**, $20^{138}$
Perry, D. A., **4**, $248^{107}$; **5**, $436^{158,158b,g}$, $442^{158}$; **6**, $1019^{43}$
Perry, F. M., **8**, $839^{25,25a}$, $914^{95}$
Perry, G., **2**, $749^{132}$; **4**, $305^{369}$
Perry, J. J., **7**, $56^{15}$
Perry, M. B., **6**, $939^{147}$, $940^{147}$
Perry, M. W. D., **1**, $477^{144}$, $545^{46\text{-}48}$; **2**, $523^{75}$; **4**, $113^{170}$; 7, $231^{153}$
Perry, R., **3**, $289^{66}$; **4**, $1059^{156}$
Perry, R. J., **4**, $115^{181b}$
Perry, W. L., **4**, $315^{504}$
Pershin, D. G., **8**, $102^{129}$
Pershin, G. N., **6**, $543^{609}$, $554^{791}$
Persia, F., **7**, $479^{90}$
Persianova, I. V., **6**, $507^{228}$, $554^{729,773}$
Persico, F. J., **6**, $531^{445}$, $538^{445}$
Person, W. B., **7**, $863^{83}$, $865^{83}$, $868^{83}$
Persons, P. E., **1**, $768^{173}$; **7**, $409^{91}$
Perst, H., **5**, $730^{128}$, $731^{131}$; **6**, $749^{102}$
Perthuis, J., **8**, $858^{203}$
Perumal, P. T., **2**, $33^{123}$; **8**, $722^{145}$
Perumattam, J., **5**, $143^{97,98}$, $636^{88}$
Perumattam, J. J., **7**, $242^{61}$
Peruzzo, V., **2**, $6^{31,32}$, $18^{31}$, $564^{12}$, $566^{20}$, $572^{47}$, $726^{127}$
Peruzzotti, G. P., **8**, $194^{103}$, $544^{253,264,265}$, $546^{304}$, $561^{304}$
Perveen, N., **6**, $725^{167}$
Perz, R., **4**, $100^{126}$; **8**, $246^{79}$, $546^{311}$
Pesaro, M., **5**, $714^{75a}$
Pescarollo, E., **4**, $307^{396}$
Pesce, G., **3**, $222^{145}$, $246^{40}$, $257^{40}$, $283^{49}$; **4**, $34^{97}$, $35^{97}$; **7**, $120^{14}$; **8**, $887^{116}$
Pesce, M., **8**, $534^{159}$
Peseckis, S. M., **1**, $800^{300}$; **2**, $13^{57}$; **5**, $515^{12}$, $516^{12a}$, $534^{91}$, $538^{12a}$; **6**, $7^{30}$, $995^{100}$
Peseke, K., **2**, $345^{42}$; **6**, $509^{244}$
Pesez, M., **2**, $354^{106,107}$
Pesnelle, P., **2**, $477^{12}$; **3**, $431^{95,96}$
Pesotskaya, G. V., **6**, $499^{172}$
Pessolano, A. A., **6**, $487^{57}$, $489^{57}$
Pestit, Y., **6**, $3^{15}$
Petasis, N. A., **1**, $630^{1}$, $672^{1}$, $746^{71}$; **2**, $388^{345}$; **3**, $86^{56}$, $94^{56}$, $117^{56}$, $558^{51,52}$; **4**, $317^{559}$, $339^{40}$; **5**, $743^{164}$, $744^{164}$; **6**, $466^{45}$, $469^{45}$; **7**, $515^{1}$, $523^{1}$
Pete, B., **5**, $444^{187}$; **6**, $499^{177}$, $520^{340}$

Pete, J. P., **1**, 268[55], 269[55]; **3**, 281[42], 602[223], 603[228], 613[3]; **4**, 48[139], 603[276,277], 610[334-336], 645[276,277], 809[163], 857[105]; **5**, 176[129], 310[100]; **6**, 644[81], 961[71]; **7**, 107[157,158,159]; **8**, 817[25,33]
Pete, J. R., **3**, 599[209]
Peter, D., **5**, 498[237]
Peter, R., **1**, 83[26], 141[21], 145[21,41,42], 146[21,42], 148[42], 149[21,42], 150[41], 151[21,41,53,53a], 152[21,53,53a], 153[41], 154[41], 155[42], 157[53a], 158[53,53a], 170[42,122], 333[57], 335[57], 337[57]; **2**, 22[86], 117[151], 306[13], 307[14], 345[35], 351[35], 363[35], 512[47]; **3**, 421[58]; **5**, 735[138b], 740[138], 1005[32]; **6**, 903[139]
Petermann, J., **6**, 428[80]
Peters, D. G., **8**, 857[199]
Peters, E. M., **1**, 168[116a]; **2**, 35[127]; **4**, 1022[253]; **5**, 155[36], 156[36], 157[36], 200[30], 206[45,46], 224[101]; **6**, 121[130], 863[191]; **8**, 354[170]
Peters, F. N., **8**, 606[20]
Peters, J. A., **1**, 294[46]; **8**, 287[18,19], 288[19]
Peters, J. A. M., **3**, 371[116]
Peters, J. W., **7**, 765[166]
Peters, K., **1**, 168[116a]; **2**, 35[127]; **4**, 121[207], 758[191], 1022[253]; **5**, 154[29,30], 155[36], 156[29,36], 157[36], 206[45,46], 224[101]; **6**, 121[130], 863[191]; **8**, 354[170]
Peters, K. S., **7**, 851[16]
Peters, M. A., **2**, 763[61]
Peters, N. K., **8**, 491[13], 496[35]
Peterse, A. J. G. M., **2**, 817[91]
Petersen, J. L., **4**, 194[121]; **5**, 242[8], 243[10,11]; **8**, 675[49], 676[49]
Petersen, J. S., **1**, 191[77]; **2**, 2[5], 25[5], 33[5], 40[5], 134[3], 190[57], 232[180], 240[5], 248[5b], 258[49,50], 455[8], 652[124], 686[68], 867[19], 870[19], 871[19], 879[19], 979[17], 1012[15]; **6**, 8[39]; **7**, 399[40a], 442[48]; **8**, 171[107,109], 535[165], 720[138], 721[138], 722[138]
Petersen, M. R., **5**, 828[7], 839[7], 862[249], 882[13], 888[13], 891[36], 892[13,38b], 893[13]
Petersen, R. C., **7**, 804[61], 805[64]
Petersen, U., **5**, 457[90]
Peterson, B., **2**, 622[155]
Peterson, C. J., **3**, 579[97]
Peterson, D., **3**, 224[182], 760[135]
Peterson, D. H., **8**, 558[397,398]
Peterson, D. J., **1**, 345[124], 436[150], 476[112,116], 479[116], 506[4], 618[55], 620[55,66], 630[19], 731[2], 732[2], 783[238], 784[242,243,244], 815[2]; **3**, 65[4], 86[57,58], 88[58]; **4**, 120[197,198]; **5**, 1126[67]; **8**, 860[219], 862[219]
Peterson, E. R., **8**, 50[117], 66[117]
Peterson, G. A., **5**, 1089[87], 1090[87], 1094[87,102], 1098[87,130], 1099[87], 1100[87], 1101[87], 1102[102,147], 1112[87,130], 1113[87]; **8**, 911[88], 933[52]
Peterson, G. E., **1**, 300[70]
Peterson, J., **5**, 692[103]
Peterson, J. C., **3**, 380[8], 627[44]
Peterson, J. O., **8**, 583[11]
Peterson, J. R., **1**, 683[226], 684[226], 685[226], 705[226], 714[226], 717[226], 718[226], 719[226], 720[226], 722[226], 868[82], 869[82]; **3**, 786[41]; **4**, 262[307], 763[213], 764[215]; **7**, 92[43], 447[72], 487[149], 532[31]
Peterson, M. L., **3**, 648[171], 796[88]; **6**, 77[58], 98[58]
Peterson, M. W., **7**, 95[71], 108[177]
Peterson, P. E., **3**, 281[44], 380[5,16], 381[16a], 735[17]; **4**, 312[458]; **5**, 1123[34]; **7**, 268[123]; **8**, 726[190], 815[21]
Peterson, R., **4**, 1005[92]
Peterson, R. T., **4**, 21[69], 108[146g], 218[139]
Peterson, W. D., **4**, 239[31]
Peterson, W. R., Jr., **6**, 809[68,69]
Peticolas, W. L., **6**, 450[118]
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Petisi, J. P., **8**, 973[120]
Petit, A., **6**, 2[5], 18[5]
Petit, F., **3**, 583[121]; **4**, 930[49]; **8**, 460[248]
Petit, J., **7**, 59[42]
Petit, M., **3**, 583[121]; **4**, 930[49]
Petit, T., **4**, 596[158], 620[158], 621[158], 636[158]
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Reed, J. W., **5**, 239[1], 903[41], 904[42], 905[41], 907[41], 909[41], 916[41], 918[41], 937[41], 939[41], 940[41], 947[42], 951[41]; **8**, 244[64], 253[64]
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Reid, R. G., **2**, 422$^{28}$; **7**, 372$^{72a}$
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Reimann, E., **6**, 651$^{136,136b}$
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Reimer, K., **2**, 769$^{2}$, 770$^{2}$
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Rein, K., **1**, 477$^{131}$; **3**, 75$^{43}$, 76$^{43,53}$, 80$^{43}$
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Reinbach, H., **2**, 352$^{87}$, 357$^{87}$
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Reiner, L. M., **2**, 466$^{110}$
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Reissig, H.-U., **1**, 110[21]; **2**, 448[34,35], 486[40], 901[33,34], 911[33]; **4**, 27[79], 980[102], 981[111], 1007[130], 1031[8], 1035[39], 1043[8,106], 1045[8a], 1046[8a,39,106,112-115], 1048[119], 1092[144], 1093[144], 1102[199]; **5**, 211[64], 901[16,21], 904[16,21], 905[16,21], 921[16,21], 925[16], 927[16], 943[16,21], 952[16,21], 972[4], 977[22], 1006[33], 1086[75,76], 1200[53]; **6**, 456[161]; **8**, 652[76]
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Reitz, A. B., **1**, 755[114,116], 756[116,116b,118], 757[114], 758[116,116a], 759[114], 760[114], 761[114,116], 790[114], 812[114], 813[114]; **4**, 38[108,108c], 379[115], 380[115h], 383[115h]; **6**, 174[55]; **7**, 523[45]
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Sawada, M., **4**, 1089[138], 1091[138]
Sawada, S., **3**, 381[26], 382[26]; **4**, 347[87], 379[115,115b], 380[115b]
Sawada, T., **2**, 810[63], 824[63]
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Sawamura, H., **3**, 300[42]
Sawamura, M., **2**, 233[186], 317[48,49], 318[48,49], 455[19]; **3**, 54[279]; **4**, 221[160]; **6**, 717[108]
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Saxena, R. K., **8**, 405[26]
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Saxton, J. E., **4**, 6[21], 680[50]; **8**, 493[21]
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Sayer, T. S. B., **3**, 18[99], 19[100]
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Scala, A., **7**, 674[42]; **8**, 565[448]
Scalone, M., **3**, 1023[22]; **4**, 930[48], 931[48]
Scamehorn, R. G., **4**, 453[26], 456[26,46], 457[46], 467[129], 472[46]
Scandström, J., **2**, 365[210]
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Scanio, C. J. V., **4**, 18[62], 20[62g]
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Scanlon, T. S., **1**, 827[64b]
Scanlon, W. B., **6**, 936[105]; **7**, 205[61]
Scarborough, R. M., Jr., **3**, 24[149], 25[149]; **5**, 944[242]; **7**, 238[39], 243[64]
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Scarpa, N. M., **1**, 345[123]; **2**, 6[30]
Scarpati, R., **4**, 1036[45]; **6**, 558[857,858]
Scarpone, S., **5**, 453[69], 455[69]
Scatturin, A., **7**, 777[386]
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Schaad, L. J., **5**, 702[14], 703[14], 740[14]
Schaad, R. E., **4**, 295[259]; **7**, 15[148]
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Schaaf, T. K., **1**, 739[35]; **3**, 364[91]; **4**, 370[26]; **5**, 339[56], 347[56]; **6**, 998[118]; **7**, 686[100]; **8**, 163[40], 269[80,81]
Schaal, V., **8**, 267[70]
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Schaart, F. J., **1**, 571[282]; **6**, 489[91]
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Schade, G., **4**, 31[94,94d]; **5**, 809[114]; **6**, 193[207,208,210,211,213]; **7**, 97[94]; **8**, 566[457], 965[68]
Schade, U., **6**, 33[7], 40[7], 57[7]
Schädel, A., **5**, 595[18], 596[18]

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Schaefer, H. F., III, **5**, 703[15]
Schaefer, J. P., **2**, 797[6], 806[6], 808[6], 813[6], 814[6], 848[6], 849[6]; **3**, 615[10]; **6**, 209[71], 210[72]; **7**, 85[7]
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Schaeffer, R., **7**, 604[128]
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Schaer, B. H., **3**, 1038[92]
Schaer, H. P., **7**, 77[120b]
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Schäfer, B., **5**, 294[52], 296[53], 1191[30], 1192[32], 1193[30,32]
Schäfer, F., **8**, 270[97]
Schäfer, H., **2**, 748[120], 758[26]; **3**, 975[4], 979[4]; **5**, 63[14], 1197[41]; **8**, 391[88]
Schäfer, H. J., **3**, 564[9], 567[9], 598[9c], 634[12,14,15], 640[105,109], 642[115], 643[12], 644[135,142,157,158,159,160,162,165], 646[135], 647[109,170,197,198], 648[170,186], 649[200], 651[217], 653[15,227], 654[227], 904[131], 975[4], 979[4]; **4**, 345[80], 759[192], 763[192], 805[142], 1023[261]; **6**, 685[347,356]; **7**, 42[33], 236[26], 795[9], 796[14,15], 797[17], 806[69,70,72]; **8**, 54[163], 66[163], 136[50]
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Schafer, W. M., **4**, 91[90], 92[90d]
Schafer, W. R., **7**, 231[143]
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Schaffhauser, T., **1**, 286[11]
Schaffner, K., **3**, 216[75], 815[73]; **5**, 200[29], 215[2,5,8], 216[12,13,15-17], 217[2,17,19,20,24,25], 218[30], 219[5,8,12,13,15-17,37,39], 221[12,13,16,30], 222[24,25,63], 223[24,66,72], 224[2], 225[5,8,114], 226[5,8,107,109], 227[114,115], 228[5,8,114,115], 229[5,8,122,123], 230[5,8,39,114,115,127,-128,129], 231[5], 232[127,129], 233[114,115], 760[92]
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Schallner, O., **3**, 623[32]; **4**, 373[67]; **6**, 116[90], 1063[81]
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Schambach, R. A., **7**, 720[8]
Schamp, N., **2**, 343[15], 353[102], 357[102], 380[102], 423[32-34], 424[32,35]; **3**, 857[90]; **6**, 500[182], 547[663]; **8**, 36[73], 38[73], 66[73]
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Schardt, R., **6**, 421[26,27]
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Scharver, J. D., **3**, 380[11]
Schat, G., **1**, 13[69], 16[86], 746[70]; **5**, 1125[57]
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Schaub, F., **3**, 530[62], 532[62]
Schaub, R. E., **4**, 91[88g]; **8**, 527[41,45], 528[45], 529[45], 530[45], 531[111]
Schauble, J. H., **4**, 347[93], 367[14], 368[14], 369[14]; **7**, 535[49], 536[50]; **8**, 17[114], 21[114], 115[66], 536[167]
Schauder, J. R., **1**, 677[222], 678[215,216], 681[215,216], 683[222], 700[222], 705[222], 708[222], 712[215,216,222], 722[222], 723[222]; **6**, 980[44]
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Schaus, J. M., **1**, 383[109]; **2**, 479[19], 481[19]; **3**, 31[182]; **5**, 814[139]; **6**, 721[135]
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Schechter, H., **1**, 377[97]; **4**, 12[42], 279[111], 1103[203]; **7**, 500[240]
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Scheeren, H. W., **5**, 71[161], 77[261], 434[142], 677[6], 684[37]; **6**, 558[846,848,849,854]
Scheeren, J. W., **2**, 662[22], 663[22], 664[22,29], 867[11]; **5**, 71[159,160,162], 76[241], 77[260,264], 151[13], 431[121], 434[121b], 459[91]; **6**, 518[330], 556[828,831], 558[847,850,855,856], 561[872], 563[895]
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Scheffel, D. J., **4**, 299[300]
Scheffer, A., **4**, 35[99]
Scheffer, J. R., **5**, 211[62,63]; **7**, 98[103]
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Scheffold, R., **1**, 142[23]; **2**, 630[4], 681[59]; **3**, 40[223], 41[223], 42[223], 209[21], 213[49], 215[21a], 217[21], 219[21a]; **4**, 12[41], 130[226a,b], 200[5], 209[67], 764[221,222], 765[222], 808[155]; **5**, 200[29], 215[8,9], 219[8,9], 225[8], 226[8,9], 228[8], 229[8], 230[8,9], 234[9], 353[85], 543[113]; **6**, 25[102], 214[97], 652[146]; **8**, 459[228]
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Scheibye, S., **2**, 867[12,13]; **6**, 436[19], 437[19]
Scheidt, F., **5**, 683[38], 684[38], 856[210]
Scheigetz, J., **7**, 693[26]; **8**, 315[52], 316[57], 969[94]
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Scheithauer, S., **6**, $421^{29}$, $423^{41,45}$, $436^{14,25,26}$, $437^{25,26}$, $448^{14,25}$, $449^{14,25}$, $450^{14,25}$, $452^{25}$, $453^{14,25,26}$, $454^{14}$, $455^{14,26}$, $456^{14,26}$, $462^{8}$, $472^{71}$
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Schell, H. G., **5**, $689^{76}$
Schellenbaum, M., **4**, $6^{21}$
Schellenberger, H., **7**, $709^{45}$
Scheller, D., **6**, $526^{400}$
Schellhamer, D. F., **7**, $530^{28}$, $531^{28}$
Schenach, T. A., **4**, $604^{284}$
Schenck, G. O., **2**, $169^{164}$; **4**, $1058^{148}$; **7**, $96^{87}$, $97^{94}$, $769^{219}$
Schenck, T. G., **4**, $564^{40}$, $567^{40}$, $590^{90}$; **6**, $843^{88}$
Schengrund, C.-L., **2**, $463^{87}$
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Schenk, H. P., **3**, $857^{91}$
Schenk, W. N., **3**, $969^{132}$; **6**, $657^{181}$, $672^{181}$
Schenker, E., **8**, $536^{169}$
Schenker, G., **4**, $608^{319}$
Schenker, K., **2**, $889^{55}$; **3**, $379^{2}$, $849^{57}$; **5**, $732^{132,132a}$; **6**, $968^{111}$
Schenkluhn, H., **5**, $1153^{147}$
Schenone, P., **6**, $776^{57}$
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Scherer, H., **6**, $245^{123}$
Scherer, K. V., **3**, $854^{75}$
Scherer, K. V., Jr., **8**, $898^{24}$
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Scherer, P., **1**, $610^{43}$
Scherkenbeck, J., **6**, $7^{34}$
Scherm, H. P., **6**, $183^{148}$
Scherrer, R. A., **3**, $427^{88}$
Schertler, P., **5**, $1185^{2}$
Scheuer, P. J., **6**, $294^{236}$; **7**, $406^{75}$
Scheuermann, H.-J., **1**, $672^{190,191}$, $674^{190,191}$, $714^{190,191}$, $715^{190}$, $718^{190,191}$, $722^{190,191}$, $867^{80}$
Scheunemann, K. H., **5**, $85^{1}$
Scheurs, P. H. M., **5**, $949^{282}$
Scheutzow, D., **5**, $986^{37}$; **8**, $267^{70}$, $657^{98}$
Scheweizer, W. B., **1**, $299^{61}$, $316^{61}$
Schexnayder, M. A., **5**, $178^{137}$, $217^{18}$, $220^{46}$, $221^{46}$, $223^{70}$, $224^{99}$
Schiavelli, M. D., **4**, $299^{300}$; **6**, $836^{55}$
Schick, H., **3**, $55^{280}$; **6**, $654^{154}$; **7**, $586^{167}$
Schick, K. P., **4**, $608^{319}$
Schick, L. E., **5**, $787^{10}$
Schicke, H. G., **6**, $428^{85}$, $432^{118}$
Schickedantz, P. D., **6**, $431^{111}$
Schieb, T., **7**, $725^{33}$
Schiedl, G., **1**, $773^{203,203b}$
Schield, J. A., **8**, $366^{41}$
Schiemenz, G. P., **2**, $735^{18,19}$, $760^{44}$; **6**, $175^{77}$
Schier, A., **1**, $10^{46}$; **6**, $173^{50}$
Schierling, P., **6**, $193^{218}$, $558^{840,841,842,843,844}$
Schierloh, C., **2**, $547^{113}$, $551^{113}$; **3**, $56^{285}$; **4**, $229^{236}$
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Schiess, P., **4**, $123^{210b}$, $125^{210b}$; **5**, $386^{133,133a,b}$, $388^{133b}$, $394^{146}$, $395^{146}$, $681^{26}$, $692^{104}$, $710^{49}$, $741^{153}$, $742^{158}$, $809^{111}$
Schiess, P. W., **1**, $894^{158}$; **6**, $1041^{2}$, $1042^{2}$
Schiesser, C. H., **4**, $781^{6}$, $786^{6}$, $787^{6}$, $820^{219}$, $827^{6}$
Schiessler, R. W., **8**, $328^{14}$, $329^{14}$
Schiffer, R., **4**, $1102^{201}$
Schiffmann, D., **8**, $398^{144}$
Schifman, A. L., **6**, $655^{167}$
Schigeko, E. J., **3**, $530^{66}$, $533^{66}$
Schiketanz, A., **3**, $331^{196}$
Schildcrout, S. M., **8**, $425^{48}$, $474^{14}$, $475^{14}$, $476^{14}$
Schildknecht, H., **7**, $576^{124}$
Schill, G., **1**, $15^{81}$, $656^{150}$, $658^{150}$; **3**, $87^{85}$, $123^{250}$, $124^{250}$, $125^{250}$, $135^{359}$, $136^{359}$, $137^{359}$, $139^{359}$, $142^{359}$, $247^{45}$, $248^{45}$, $628^{47}$; **4**, $565^{44}$; **5**, $731^{130a}$; **6**, $734^{5}$; **7**, $762^{79}$; **8**, $214^{41}$
Schiller, A. M., **8**, $532^{130}$
Schilling, G., **3**, $872^{59}$
Schilling, L. M., **7**, $875^{113}$
Schilling, P., **3**, $322^{142a}$; **7**, $17^{174}$
Schilling, S. L., **1**, $41^{203}$
Schilling, W., **1**, $95^{72}$; **5**, $611^{72}$; **6**, $440^{75}$
Schillinger, E., **2**, $902^{40}$
Schillinger, W. J., **7**, $682^{83}$
Schilt, W., **4**, $283^{149}$
Schimdt, G., **1**, $551^{68}$
Schimperna, G., **2**, $103^{28}$, $605^{57}$, $614^{57}$, $637^{58}$, $639^{58,62}$, $640^{58,62}$, $642^{73}$, $643^{73}$, $644^{73}$, $930^{132,133}$, $932^{132,133}$; **4**, $159^{82}$, $218^{145}$; **5**, $102^{176,178}$
Schimpf, R., **4**, $887^{126}$; **8**, $758^{167}$
Schimpff, G. W., **8**, $292^{45}$
Schindewolf, U., **8**, $114^{57}$, $524^{11}$
Schindler, H., **5**, $555^{49}$
Schink, K., **6**, $525^{387}$
Schinski, W. L., **5**, $904^{54}$
Schinz, H., **3**, $345^{20}$, $351^{39}$, $358^{65}$; **5**, $833^{45}$; **7**, $154^{15}$; **8**, $141^{44}$
Schinzel, E., **3**, $807^{24}$, $813^{66}$
Schinzer, D., **2**, $89^{35}$; **3**, $348^{30,31}$, $358^{31}$; **4**, $98^{116}$, $115^{182}$, $121^{207}$, $155^{73,74}$; **6**, $734^{2}$
Schipchandler, M. T., **2**, $332^{62}$
Schipper, E., **7**, $656^{17}$
Schipper, P., **1**, $661^{165,166}$, $663^{165,166}$, $672^{166}$, $700^{166}$, $704^{166}$; **8**, $967^{82}$
Schirch, P. F. T., **5**, $618^{5}$
Schirlin, D., **2**, $71^{54}$
Schisla, R. M., **4**, $93^{93c}$
Schjånberg, E., **4**, $274^{56}$
Schlachter, S. T., **1**, $759^{134}$
Schlademan, J., **2**, $753^{2,2c}$
Schlaf, H., **8**, $657^{98}$
Schläfer, L., **8**, $898^{22}$
Schlageter, M. G., **6**, $1059^{70}$, $1066^{70}$; **7**, $376^{83}$
Schlamann, B., **2**, $371^{261}$; **5**, $76^{239}$
Schlapbach, A., **6**, $859^{175}$
Schlapkohl, K., **6**, $444^{98}$
Schlatmann, J. L. M. A., **5**, $700^{8}$, $737^{8}$
Schlecht, M. F., **2**, $611^{101}$; **3**, $226^{194}$, $265^{189}$, $380^{13}$; **4**, $161^{86b}$; **7**, $158^{37}$, $530^{16}$, $587^{170}$, $823^{37}$; **8**, $332^{44}$
Schlecker, R., **1**, $474^{107}$; **3**, $194^{9}$
Schlegel, H. B., **1**, $506^{8}$; **4**, $1070^{14}$; **6**, $133^{4}$; **8**, $2^{7}$
Schleich, K., **5**, $1154^{155}$
Schleifer, L., **5**, $223^{85}$, $224^{85}$, $740^{151}$
Schleitzer-Rust, E., **1**, $231^{3}$
Schlesener, C. J., **7**, $850^{10}$, $852^{37}$
Schlesinger, A. H., **7**, $764^{104}$
Schlesinger, H. I., **8**, $1^{1}$, $26^{1,2}$, $735^{9}$, $736^{9}$
Schlessinger, R. H., **1**, $3^{24}$, $32^{157,158}$, $527^{105,106}$, $564^{191}$, $567^{224}$, $791^{268}$; **2**, $106^{47}$, $187^{41}$, $189^{46,47}$, $209^{46}$, $221^{46a}$, $482^{36}$, $484^{36}$, $805^{45}$, $811^{71}$, $824^{71}$; **3**, $33^{190}$, $34^{197}$, $43^{238}$, $135^{358}$, $136^{358}$, $137^{358}$, $139^{358}$, $142^{358}$, $143^{358}$, $675^{72}$; **4**, $10^{32,32a\text{-}g,33,33a,34}$, $11^{32e}$, $23^{33d}$, $30^{88,88g}$, $48^{139,139f}$, $107^{144}$, $109^{148}$, $113^{166,171,171e}$,

125$^{216,216f}$, 249$^{125}$, 258$^{125}$, 262$^{306}$, 611$^{357}$; **5**, 338$^{54}$, 541$^{111}$; **6**, 134$^{26}$, 186$^{170}$, 647$^{113}$, 717$^{113}$, 1013$^{16}$, 1020$^{48}$; **7**, 105$^{151}$; **8**, 925$^{12}$
Schletter, I., **6**, 116$^{94}$
Schleyer, P. von R., **1**, 2$^{11}$, 8$^{11}$, 12$^{61}$, 13$^{65}$, 17$^{211}$, 19$^{11,100,102-104}$, 20$^{108}$, 22$^{11}$, 23$^{123-125}$, 25$^{128}$, 29$^{147}$, 35$^{172}$, 41$^{196}$, 287$^{17}$, 476$^{125}$, 477$^{125}$, 487$^{1,2}$, 488$^{1,2}$, 859$^{64,66}$; **3**, 66$^{12}$, 74$^{12}$, 194$^{4,11}$, 334$^{219,220}$; **4**, 872$^{40,41}$, 1016$^{208,209}$; **5**, 65$^{71}$, 794$^{45}$, 850$^{152}$, 984$^{33}$; **6**, 172$^{11}$, 749$^{102}$; **7**, 26$^{47}$; **8**, 91$^{53,61,64}$, 318$^{59}$, 319$^{79}$, 320$^{80}$, 322$^{59}$, 331$^{33}$, 334$^{60}$, 342$^{109}$, 724$^{168,169,169b}$, 904$^{57,57b}$, 910$^{57}$
Schlicher, J. W., **2**, 547$^{111}$, 551$^{111}$, 710$^{28}$
Schlieper, A., **3**, 822$^{5}$, 834$^{5}$
Schlimgen Davis, K., **5**, 212$^{69}$
Schlingloff, G., **3**, 667$^{46}$
Schlitt, R., **5**, 856$^{217}$
Schloemer, G., **5**, 758$^{82}$
Schlögl, K., **2**, 365$^{215}$
Schlosberg, R. H., **3**, 299$^{34b}$, 330$^{192,193}$, 333$^{34,208,211b}$, 334$^{213}$; **6**, 749$^{101}$; **7**, 6$^{28}$
Schlosser, M., **1**, 2$^{5}$, 10$^{51}$, 180$^{28}$, 755$^{115}$, 757$^{119}$, 758$^{123}$, 812$^{115}$, 813$^{115}$; **2**, 5$^{20,20a,21}$, 6$^{20}$, 13$^{21,21c,58}$, 14$^{21c,58}$, 21$^{20}$, 66$^{37}$, 977$^{6}$; **3**, 99$^{182}$, 101$^{182}$, 194$^{7}$, 215$^{62}$, 244$^{20}$, 261$^{149}$, 466$^{184}$; **4**, 70$^{9}$, 139$^{1}$, 869$^{22}$, 1001$^{38}$, 1020$^{237}$, 1035$^{42}$; **6**, 173$^{39}$, 174$^{57}$, 175$^{39,67}$, 685$^{349}$, 958$^{31}$, 959$^{31}$, 976$^{1}$; **7**, 99$^{106,107}$, 596$^{39}$, 856$^{68}$
Schlosser, W., **6**, 190$^{193}$
Schlubach, H. H., **3**, 553$^{13}$
Schlude, H., **2**, 760$^{45}$
Schlund, R., **8**, 682$^{83}$, 683$^{95}$, 686$^{95}$
Schlunke, H.-P., **3**, 822$^{12}$, 831$^{12}$, 835$^{12b}$
Schluter, G., **7**, 221$^{30}$
Schlüter, K., **6**, 970$^{122}$
Schmack, L. G., **4**, 1016$^{206}$
Schmakel, C. O., **8**, 592$^{65}$
Schmalstieg, L., **4**, 1007$^{129}$
Schmalz, D., **1**, 2$^{10}$
Schmalz, H.-G., **2**, 547$^{113}$, 551$^{113}$; **3**, 56$^{285}$; **4**, 229$^{235,236}$, 1055$^{138}$
Schmalzl, K. J., **2**, 294$^{80}$; **3**, 20$^{109}$
Schmelzer, H.-G., **3**, 890$^{31}$, 901$^{111}$, 904$^{135}$
Schmerling, L., **3**, 320$^{133}$, 331$^{201}$; **4**, 276$^{71}$, 283$^{71}$, 313$^{464}$; **7**, 7$^{46,49}$, 15$^{152}$
Schmersahl, P., **8**, 903$^{50}$
Schmetzer, J., **6**, 518$^{331}$
Schmickler, H., **3**, 593$^{179}$; **7**, 725$^{33}$
Schmid, A., **3**, 223$^{155}$
Schmid, B., **3**, 105$^{220}$, 113$^{220}$, 155$^{432}$
Schmid, C. R., **7**, 308$^{20}$
Schmid, G., **5**, 96$^{104}$, 97$^{104}$, 98$^{104}$; **6**, 5$^{24}$, 186$^{169}$, 193$^{207,208}$, 195$^{223,224,225}$, 197$^{169}$, 449$^{115}$
Schmid, G. H., **4**, 329$^{1}$, 330$^{1c,d,5}$, 339$^{41}$, 342$^{62,65,69,71}$, 344$^{1}$, 350$^{1}$, 351$^{1}$; **7**, 769$^{230}$
Schmid, H., **2**, 138$^{22}$; **3**, 809$^{39,40}$, 957$^{109}$; **4**, 14$^{46}$, 587$^{23}$, 1081$^{73,78}$, 1084$^{95}$; **5**, 596$^{26}$, 597$^{26}$, 608$^{26a}$, 638$^{117}$, 681$^{27}$, 707$^{32}$, 709$^{45}$, 712$^{45d}$, 713$^{32}$, 799$^{72}$, 812$^{131}$, 822$^{164}$, 834$^{50,53}$, 837$^{67}$, 850$^{146}$, 856$^{67,199}$, 857$^{67,199,226,227}$, 858$^{199}$, 876$^{3}$, 877$^{5}$, 894$^{43,45}$, 1130$^{8}$; **6**, 898$^{104}$; **8**, 812$^{2}$, 813$^{2}$
Schmid, J., **4**, 985$^{128}$
Schmid, K., **5**, 876$^{3}$
Schmid, M., **5**, 799$^{72}$; **6**, 204$^{20}$; **8**, 205$^{159}$, 560$^{405}$
Schmid, P., **1**, 699$^{252}$
Schmid, R., **3**, 369$^{123,124}$, 372$^{124}$, 957$^{109}$; **5**, 596$^{26}$, 597$^{26}$, 608$^{26a}$, 894$^{45}$; **6**, 898$^{104}$
Schmidbaur, H., **1**, 10$^{46}$; **6**, 173$^{50}$, 175$^{67}$, 176$^{91}$, 177$^{119}$, 178$^{119,123}$, 179$^{125}$, 180$^{128,129}$, 182$^{141}$, 183$^{148}$, 188$^{180}$, 190$^{199,200,202}$, 196$^{199,202,227,228,230,231,232,233,234}$; **8**, 859$^{217}$
Schmidhauser, J. C., **5**, 721$^{100}$
Schmidle, C. J., **2**, 782$^{22}$
Schmidlin, C., **5**, 419$^{74}$, 420$^{75}$
Schmidlin, J., **8**, 268$^{74}$
Schmidpeter, A., **6**, 196$^{229}$, 509$^{265}$
Schmidt, A., **4**, 1007$^{128}$; **6**, 531$^{437}$, 566$^{922}$
Schmidt, A. H., **8**, 405$^{33}$, 406$^{37}$
Schmidt, B., **3**, 580$^{104}$
Schmidt, C., **8**, 15$^{89}$
Schmidt, D., **2**, 68$^{40}$, 94$^{51}$; **3**, 891$^{36}$, 909$^{153}$
Schmidt, D. L., **4**, 337$^{34}$
Schmidt, E., **6**, 420$^{22}$
Schmidt, E. A., **6**, 569$^{935}$
Schmidt, F., **3**, 557$^{39}$
Schmidt, G., **1**, 762$^{141}$; **7**, 272$^{131}$, 273$^{131}$, 503$^{277}$; **8**, 837$^{13b}$
Schmidt, G. M. J., **3**, 382$^{36}$
Schmidt, H., **4**, 45$^{130,130c}$; **7**, 99$^{113}$, 221$^{32}$
Schmidt, H.-J., **2**, 476$^{5}$; **4**, 872$^{43}$; **6**, 269$^{74}$; **7**, 236$^{26}$
Schmidt, H. L., **7**, 778$^{419}$
Schmidt, H.-W., **4**, 440$^{171}$; **6**, 554$^{726}$
Schmidt, J., **3**, 828$^{44}$
Schmidt, J. G., **2**, 134$^{6}$
Schmidt, K., **2**, 399$^{15}$; **7**, 725$^{33}$
Schmidt, M., **1**, 70$^{63}$, 141$^{22}$; **2**, 902$^{45}$; **3**, 134$^{339}$, 135$^{339}$; **6**, 177$^{113}$, 182$^{113}$, 188$^{113}$, 194$^{219,220}$
Schmidt, O., **4**, 5$^{19}$
Schmidt, O. Th., **6**, 36$^{18}$
Schmidt, P., **6**, 519$^{338}$; **8**, 659$^{103}$
Schmidt, R., **4**, 1007$^{112}$; **6**, 501$^{203}$, 531$^{203}$; **8**, 802$^{86}$
Schmidt, R. R., **2**, 662$^{3}$, 1054$^{58}$, 1070$^{58}$; **3**, 105$^{220}$, 113$^{220}$, 155$^{432}$, 253$^{93}$; **4**, 121$^{205a}$, 740$^{115}$; **5**, 428$^{109}$, 430$^{118}$, 431$^{123,123a,b}$, 432$^{125,133}$, 433$^{135,135b}$, 451$^{29}$, 461$^{110}$, 464$^{110-113}$, 466$^{110-113}$, 485$^{180}$, 492$^{29}$, 501$^{29,262,265,266,271}$, 502$^{272,273}$; **6**, 33$^{1,2}$, 34$^{1,2}$, 37$^{1,34}$, 40$^{1,2}$, 43$^{51}$, 46$^{1}$, 48$^{1}$, 49$^{1}$, 50$^{1,2,101,102}$, 51$^{1,2,101,102,111-114}$, 52$^{115}$, 53$^{2,117,119,121,122}$, 54$^{1,2,123-127}$, 56$^{133,134}$, 57$^{1,2,133,134,137,138,142}$, 59$^{143}$, 60$^{149}$, 62$^{127}$, 73$^{25}$, 533$^{495}$, 534$^{520}$, 655$^{166}$, 846$^{102}$; **7**, 418$^{130a}$; **8**, 389$^{67}$, 616$^{101}$, 624$^{101}$, 640$^{24}$
Schmidt, S. J., **3**, 1029$^{55}$; **8**, 933$^{50}$
Schmidt, T., **1**, 405$^{27}$; **5**, 307$^{90}$
Schmidt, U., **1**, 188$^{73}$, 189$^{73}$, 219$^{56}$; **2**, 219$^{142}$, 735$^{18,19}$, 760$^{44}$; **6**, 430$^{101}$, 443$^{90}$, 562$^{885,886}$, 637$^{32,32c}$; **8**, 535$^{166}$
Schmidt, V., **3**, 903$^{126}$
Schmidt, W., **4**, 682$^{58}$; **5**, 705$^{25}$; **7**, 248$^{113}$, 808$^{76}$
Schmidtberger, S., **1**, 153$^{59}$, 154$^{59}$, 295$^{51,52}$, 336$^{74}$, 340$^{74}$; **2**, 307$^{15}$, 310$^{15}$, 640$^{68}$, 641$^{68}$
Schmiegel, K. K., **4**, 83$^{65a}$; **7**, 111$^{190}$; **8**, 528$^{61}$
Schmiegel, W. W., **8**, 528$^{57,61}$
Schmierer, R., **3**, 45$^{251}$
Schmiesing, R. J., **1**, 794$^{279}$; **4**, 38$^{108}$, 339$^{44}$; **5**, 814$^{136}$; **7**, 520$^{30}$; **8**, 44$^{105}$, 66$^{105}$
Schmit, C., **1**, 683$^{227}$, 714$^{227}$, 715$^{227}$, 717$^{227}$, 718$^{227}$; **3**, 786$^{42}$
Schmitt, E., **2**, 424$^{35}$; **6**, 526$^{391}$
Schmitt, G., **8**, 755$^{130}$, 758$^{130}$
Schmitt, H., **6**, 51$^{113}$
Schmitt, H.-G., **3**, 174$^{526}$
Schmitt, J., **8**, 383$^{17}$
Schmitt, J. L., **3**, 95$^{155}$
Schmitt, M., **8**, 476$^{29}$
Schmitt, R. J., **6**, 109$^{44}$, 110$^{56}$; **7**, 746$^{87}$; **8**, 91$^{60}$

Schmitt, R. K., **8**, 13$^{74}$
Schmitt, S. M., **5**, 107$^{199}$
Schmitthenner, H. F., **5**, 567$^{104}$; **6**, 756$^{128}$
Schmitz, A., **1**, 56$^{29}$; **2**, 646$^{84}$; **5**, 29$^{1}$; **6**, 561$^{873}$, 644$^{88}$
Schmitz, E., **2**, 364$^{203}$; **4**, 307$^{389}$; **5**, 15$^{101}$; **6**, 494$^{130}$, 562$^{883}$; **7**, 470$^{15,16}$, 471$^{23}$, 474$^{23}$, 746$^{89,93}$
Schmitz, H., **4**, 1104$^{211}$
Schmitz, R., **8**, 370$^{85}$
Schmolka, I. R., **8**, 231$^{141}$
Schmook, F. P., **2**, 355$^{126}$
Schmuff, N. R., **2**, 74$^{77}$; **3**, 168$^{489}$, 169$^{489}$; **4**, 589$^{86}$, 599$^{216}$, 624$^{216}$
Schmuff, R. N., **4**, 681$^{52}$, 682$^{52}$
Schmunes, E., **2**, 385$^{324}$
Schmüser, W., **6**, 444$^{98}$
Schnaithmann, M., **5**, 933$^{184}$
Schnatter, W. F. K., **5**, 1102$^{148}$, 1103$^{148}$, 1105$^{164}$
Schneebeli, J., **1**, 373$^{91}$, 375$^{91}$, 376$^{91}$; **2**, 996$^{47}$, 1077$^{154}$; **7**, 230$^{133}$
Schneider, A., **5**, 1141$^{84}$; **7**, 363$^{37}$
Schneider, C. S., 4, 54$^{152}$; **6**, 506$^{227}$, 519$^{337}$
Schneider, D. F., **1**, 760$^{136}$; **3**, 623$^{32}$; **4**, 710$^{52}$; **6**, 184$^{152}$, 189$^{185}$
Schneider, F., **1**, 524$^{85}$; **2**, 229$^{169}$, 652$^{127}$
Schneider, G., **2**, 838$^{171}$; **6**, 276$^{122}$, 612$^{72}$; **8**, 192$^{98}$
Schneider, H.-J., **4**, 274$^{60}$; **7**, 13$^{121,122}$, 50$^{70}$, 247$^{106}$; **8**, 161$^{19}$, 541$^{212}$
Schneider, H.-P., **3**, 666$^{42}$
Schneider, J., **1**, 424$^{101}$; **2**, 329$^{47}$; **5**, 66$^{77}$; **8**, 260$^{1}$, 736$^{19}$, 739$^{19}$, 744$^{50}$, 756$^{50}$
Schneider, J. A., **1**, 52$^{14}$, 108$^{9}$, 109$^{12}$, 110$^{9,12}$, 126$^{9}$, 134$^{9,12}$, 153$^{56}$, 336$^{69}$, 460$^{2}$
Schneider, K., **8**, 260$^{1}$
Schneider, L., **6**, 980$^{36}$; **8**, 880$^{62}$
Schneider, M., **3**, 587$^{141}$; **4**, 955$^{13}$; **6**, 463$^{25}$
Schneider, M. J., **4**, 370$^{37}$
Schneider, M. P., **2**, 456$^{27}$; **5**, 804$^{97}$, 933$^{184}$, 971$^{3}$, 972$^{9}$, 973$^{3,9,12,13}$, 974$^{9}$, 991$^{47}$, 992$^{47}$; **7**, 397$^{30}$
Schneider, M. R., **2**, 740$^{57}$
Schneider, P., **2**, 785$^{46}$; **4**, 204$^{36}$, 869$^{22}$; **5**, 38$^{22c}$, 45$^{35}$
Schneider, R., **3**, 530$^{62}$, 532$^{62}$; **5**, 734$^{137}$; **6**, 535$^{536}$, 538$^{536}$; **7**, 741$^{47}$
Schneider, R. A., **4**, 23$^{70}$
Schneider, R. S., **2**, 157$^{120}$; **5**, 853$^{171}$; **8**, 544$^{275}$
Schneider, S., **5**, 307$^{89}$; **6**, 489$^{100}$, 736$^{29}$
Schneider, U., **3**, 495$^{93b}$
Schneider, W. P., **2**, 148$^{78}$
Schneiders, G. E., **3**, 219$^{112}$, 676$^{76}$
Schnell, H., **4**, 293$^{236}$
Schnelle, G., **2**, 33$^{121}$
Schneller, J., **6**, 273$^{96}$
Schneller, S. W., **2**, 359$^{158}$, 361$^{158}$, 376$^{158}$, 388$^{158}$
Schnering, H. G. V., **1**, 168$^{116a}$; **4**, 758$^{191}$
Schnieder, M., **2**, 465$^{106}$
Schnoes, H. K., **2**, 879$^{41}$
Schnoes, H. N., **6**, 989$^{79}$
Schober, P. A., **1**, 520$^{72}$; **2**, 66$^{33}$, 75$^{33,82a}$; **4**, 119$^{192b,193}$, 159$^{85}$, 226$^{190,191,194}$, 249$^{129}$, 258$^{129,244}$; **6**, 154$^{145}$, 864$^{192}$
Schöberl, A., **6**, 540$^{588}$
Schöberl, V., **2**, 369$^{248}$
Schobert, R., **3**, 286$^{59}$; **6**, 193$^{209}$, 194$^{219}$; **8**, 889$^{130}$
Schoch, W., **3**, 915$^{13}$, 965$^{13}$
Schoch-Grübler, U., **2**, 482$^{23}$, 483$^{23}$
Schock, L. E., **8**, 447$^{134}$, 670$^{9}$, 671$^{9}$
Schöde, D., **6**, 288$^{187}$
Schoeller, W., **5**, 857$^{228}$
Schoemaker, H. E., **2**, 1049$^{20,25}$, 1050$^{20}$, 1054$^{57}$, 1062$^{57,100}$, 1064$^{25}$, 1072$^{57}$; **6**, 658$^{183}$, 745$^{82}$
Schoenberg, A., **3**, 1021$^{13}$, 1028$^{47}$, 1034$^{78}$
Schoeneck, W., **8**, 568$^{486}$
Schoenen, F. J., **1**, 126$^{87,90}$, 757$^{122}$; **5**, 736$^{143,145}$, 737$^{145}$, 843$^{117}$
Schoenenberger, H., **1**, 360$^{27}$
Schoenewaldt, E. F., **3**, 822$^{13}$, 829$^{13}$; **8**, 54$^{159}$, 66$^{159}$
Schoenheimer, R., **6**, 685$^{352}$
Schoening, C. E., **3**, 804$^{12}$
Schoenthaler, A. C., **4**, 274$^{57}$, 282$^{57}$
Schöffer, A., **3**, 625$^{41}$
Schoffstall, A. M., **5**, 252$^{45}$
Schofield, C. J., **4**, 744$^{134}$
Schofield, J. A., **3**, 818$^{94}$
Schofield, K., **3**, 689$^{118}$; **6**, 110$^{45}$, 291$^{216}$
Schofield, R. A., **4**, 1040$^{73}$, 1043$^{73}$
Schohe, R., **4**, 379$^{117}$, 1079$^{65}$; **5**, 260$^{65,66}$, 261$^{65,66}$; **7**, 439$^{36}$; **8**, 70$^{223}$, 647$^{54}$
Scholes, G., **4**, 115$^{180c}$, 688$^{67}$; **5**, 715$^{78}$, 985$^{36}$
Scholl, B., **4**, 1033$^{21}$, 1037$^{21}$, 1040$^{21}$
Scholl, H.-J., **4**, 1002$^{47}$
Scholl, P. C., **7**, 43$^{42}$, 802$^{50}$
Scholl, T., **3**, 737$^{30}$; **5**, 15$^{109}$
Schollenberger, C. S., **2**, 529$^{20}$
Scholler, D., **8**, 817$^{33}$
Schöllkopf, U., **1**, 55$^{26}$, 630$^{22,29}$, 641$^{105}$, 722$^{275}$, 846$^{19a,b}$, 847$^{19b}$, 850$^{19b}$; **2**, 361$^{175}$, 498$^{70\text{-}78}$, 499$^{71\text{-}76}$, 501$^{78}$, 1084$^{11}$; **3**, 53$^{274}$, 194$^{13}$, 195$^{17}$, 197$^{34}$, 303$^{53}$, 419$^{36}$, 921$^{35}$, 922$^{35a,38}$, 924$^{35a}$, 927$^{52}$, 975$^{4}$, 976$^{5,7,8}$, 979$^{4}$; **4**, 89$^{84g}$, 111$^{152d}$, 116$^{189}$, 222$^{179,180,181}$, 224$^{181}$, 966$^{54}$, 1016$^{209}$, 1038$^{60}$; **5**, 116$^{267,268}$, 117$^{272}$, 187$^{174}$, 1003$^{20}$, 1007$^{39}$, 1008$^{39}$; **6**, 531$^{431,432,433,434,435,436,443}$, 535$^{532}$, 876$^{29}$; **7**, 232$^{155}$
Scholmann, N., **4**, 784$^{15}$
Scholten, H. P. H., **7**, 230$^{134}$
Scholten, J. J. F., **8**, 418$^{11}$, 437$^{11}$
Scholz, A., **6**, 226$^{9}$
Scholz, D., **1**, 424$^{101}$; **3**, 862$^{9\text{-}11}$, 863$^{11\text{-}13}$; **6**, 438$^{41}$, 508$^{287}$; **7**, 768$^{206}$
Scholz, K.-H., **5**, 160$^{56}$
Scholz, M., **7**, 355$^{43}$
Scholz, S., **2**, 648$^{90}$, 1058$^{72}$; **5**, 407$^{28,28b}$
Schomaker, J. H., **4**, 1099$^{185}$
Schomaker, V., **4**, 275$^{67}$, 279$^{67}$, 287$^{67}$
Schomburg, D., **2**, 651$^{121}$; **6**, 509$^{265}$
Schomburg, G., **4**, 868$^{12}$, 874$^{50,51,54,55}$, 887$^{12}$; **5**, 30$^{2}$
Schön, N., **2**, 368$^{234}$
Schonber, A., **7**, 230$^{127}$
Schönberg, A., **3**, 563$^{117}$, 564$^{11}$, 567$^{11}$, 582$^{111,112,117}$; **4**, 1093$^{148}$; **5**, 433$^{135,135a}$; **6**, 519$^{339}$; **7**, 144$^{155}$
Schönberg, H., **5**, 1157$^{168}$
Schönberger, N., **6**, 846$^{102}$
Schone, R., **4**, 1079$^{64}$
Schönfelder, M., **3**, 482$^{3}$
Schönfelder, W., **5**, 1146$^{108}$
Schönhammer, B., **8**, 459$^{238}$
Schoolenberg, J., **8**, 533$^{146}$
Schoon, D., **5**, 90$^{57}$, 95$^{57}$
Schöpf, C., **2**, 943$^{168,169}$, 970$^{88}$
Schor, J. M., **2**, 741$^{67}$
Schore, N. E., **2**, 597$^{7}$; **3**, 1025$^{34}$; **4**, 72$^{29}$; **5**, 153$^{24}$, 166$^{91}$, 561$^{79}$, 1037$^{2}$, 1039$^{11,17}$, 1041$^{19}$, 1043$^{22}$, 1046$^{19,30}$, 1049$^{22}$, 1050$^{17,34}$, 1051$^{34}$, 1052$^{17,19,37}$, 1053$^{39}$, 1057$^{51\text{-}53}$, 1062$^{51\text{-}53,59}$, 1133$^{26}$, 1146$^{26}$

Schormann, N., **8**, 335$^{67}$
Schors, A., **7**, 706$^{23}$
Schorta, R., **5**, 229$^{122}$
Schortt, A. B., **6**, 495$^{151}$
Schossig, J., **3**, 921$^{35}$, 922$^{35a,38}$, 924$^{35a}$
Schostarez, H., **5**, 21$^{149}$, 22$^{149}$, 779$^{197}$
Schott, A., **3**, 482$^{3}$
Schotten, T., **5**, 973$^{15}$, 975$^{15}$
Schouten, A., **2**, 124$^{204}$, 125$^{204}$
Schouten, H. G., **8**, 614$^{90}$
Schow, S., **6**, 1059$^{70}$, 1066$^{70}$; **7**, 376$^{83}$
Schow, S. R., **1**, 129$^{93}$, 779$^{224}$; **2**, 651$^{122}$; **3**, 26$^{165}$; **7**, 73$^{103}$
Schowen, R. J., **8**, 89$^{43}$
Schowen, R. L., **1**, 314$^{137}$, 315$^{137}$
Schrader, G., **6**, 432$^{118}$
Schrader, L., **5**, 646$^{5,6}$
Schrader, T., **1**, 373$^{86}$, 374$^{86}$
Schrall, R., **3**, 691$^{135}$
Schramm, J., **2**, 935$^{147}$
Schramm, S., **7**, 471$^{23}$, 474$^{23}$
Schramm, S. B., **3**, 325$^{161,161a}$
Schrauzer, G. N., **4**, 761$^{199}$; **5**, 1141$^{83}$
Schreck, J. O., **6**, 556$^{820}$
Schreck, M., **4**, 1010$^{160}$
Schrecken, H., **3**, 482$^{3}$
Schreiber, E. C., **8**, 566$^{450}$
Schreiber, F. G., **3**, 693$^{142}$
Schreiber, J., **2**, 899$^{27}$, 901$^{27}$; **5**, 714$^{75a}$; **6**, 831$^{7}$, 1059$^{62,64,66}$; **7**, 482$^{118}$
Schreiber, R. S., **6**, 288$^{184}$
Schreiber, S. L., **1**, 8$^{39}$, 200$^{96}$, 297$^{58}$, 329$^{40}$, 420$^{83}$, 568$^{230,233}$, 768$^{172}$, 798$^{290}$, 800$^{298}$, 883$^{126}$, 898$^{126}$; **2**, 42$^{148}$, 45$^{148}$, 505$^{9}$; **3**, 217$^{95}$, 227$^{209}$, 545$^{120}$, 979$^{14}$; **4**, 53$^{150}$, 817$^{206}$; **5**, 130$^{41}$, 152$^{20}$, 167$^{95}$, 169$^{109}$, 170$^{112,121}$, 171$^{114,116,121}$, 172$^{119\text{-}122}$, 174$^{124}$, 176$^{112,116,125}$, 184$^{121}$, 185$^{124}$, 461$^{99}$, 462$^{99}$, 466$^{119}$, 467$^{118,119}$, 514$^{9}$, 527$^{9}$, 545$^{122}$, 736$^{143,145}$, 737$^{145}$, 809$^{121,123}$, 843$^{119}$, 1055$^{47}$, 1062$^{59}$; **6**, 8$^{39}$, 14$^{56}$, 16$^{56}$, 692$^{409}$, 717$^{115,116}$, 903$^{135}$, 1067$^{102,103}$; **7**, 361$^{23}$, 396$^{26}$, 416$^{26,124}$, 549$^{47}$, 676$^{61}$; **8**, 224$^{101}$, 933$^{48}$
Schreiber, T. S., **7**, 396$^{26}$, 416$^{26}$
Schreibmann, A. A. P., **3**, 564$^{13}$
Schrempf, G., **6**, 495$^{145}$
Schreuder, A. H., **8**, 33$^{58}$, 66$^{58}$
Schreurs, P. H. M., **4**, 309$^{412}$
Schrier, J. A., **7**, 66$^{72}$
Schriesheim, A., **7**, 759$^{5,13,16}$, 760$^{36}$, 761$^{36}$
Schrinner, E., **6**, 33$^{7}$, 40$^{7}$, 57$^{7}$
Schriver, G. W., **1**, 41$^{203}$
Schrock, R. R., **1**, 140$^{7}$, 174$^{15}$, 743$^{50}$, 749$^{78}$, 812$^{50}$, 816$^{78}$; **4**, 485$^{31}$; **5**, 1115$^{2}$, 1116$^{2,11,12}$, 1117$^{11,16}$, 1118$^{11}$, 1121$^{16}$, 1122$^{2d}$, 1125$^{2d,61,65}$; **8**, 152$^{174}$, 445$^{46\text{-}50}$, 450$^{48}$, 458$^{48,50}$
Schrödel, R., **8**, 274$^{136}$
Schroder, C., **5**, 164$^{75}$, 176$^{75}$
Schröder, E., **3**, 848$^{52}$
Schröder, G., **5**, 709$^{46}$, 717$^{90a\text{-}c}$; **7**, 412$^{104}$, 413$^{104}$, 429$^{158}$, 430$^{158}$, 442$^{46a}$, 446$^{62}$
Schröder, J., **6**, 421$^{27}$
Schröder, M., **7**, 166$^{88}$, 437$^{6}$, 438$^{6}$, 439$^{6,24}$, 866$^{88}$, 867$^{88}$
Schröder, S., **6**, 119$^{115}$
Schröder, W., **1**, 310$^{106}$
Schroeck, C. W., **1**, 532$^{134}$, 535$^{146}$, 825$^{49}$; **4**, 987$^{136}$, 989$^{136}$
Schroeder, B., **4**, 760$^{196}$
Schroeder, D. C., **6**, 423$^{39}$, 424$^{39}$, 428$^{39}$, 432$^{39}$
Schroeder, D. R., **4**, 1033$^{36}$; **6**, 124$^{144}$
Schroeder, F., **3**, 174$^{526}$
Schroeder, M. A., **8**, 451$^{181,182}$, 567$^{459,460}$, 765$^{11}$, 778$^{11g}$
Schroeder, M. C., **1**, 635$^{84}$, 636$^{84}$, 637$^{84}$, 640$^{84}$, 672$^{84}$; **3**, 87$^{96}$, 104$^{96}$
Schroeder, T., **8**, 446$^{73}$
Schroeder, W., **8**, 881$^{79}$
Schroedter, G., **5**, 752$^{49}$
Schroek, C. W., **1**, 722$^{278}$
Schroepfer, G. J., Jr., **7**, 264$^{91}$; **8**, 872$^{9}$, 873$^{9}$, 881$^{81}$, 882$^{81}$
Schröer, U., **2**, 587$^{141}$
Schroeter, S. H., **5**, 158$^{16}$, 159$^{16}$, 170$^{16}$; **7**, 97$^{94}$; **8**, 14$^{87}$, 141$^{45}$
Schroetter, H. W., **8**, 100$^{116}$
Schroll, G., **8**, 478$^{40}$, 479$^{40}$
Schröppel, F., **7**, 482$^{114}$
Schroter, D., **5**, 260$^{66}$, 261$^{66}$; **7**, 416$^{122}$; **8**, 70$^{223}$
Schröter, G., **3**, 887$^{1b}$, 890$^{1}$, 891$^{1,1b}$, 894$^{1}$, 897$^{1b}$, 905$^{1b}$
Schröter, R., **2**, 953$^{1}$; **8**, 367$^{53}$
Schroth, G., **4**, 608$^{319}$, 874$^{48,50,51,55}$; **5**, 30$^{2}$, 297$^{55}$, 641$^{134}$, 1192$^{31}$, 1197$^{31,41}$; **6**, 179$^{124}$
Schroth, W., **2**, 712$^{40}$; **6**, 508$^{287,288}$, 518$^{334}$, 551$^{685}$
Schrott, U., **2**, 33$^{121}$
Schubert, B., **1**, 20$^{106,108,109}$, 21$^{110}$, 39$^{190}$; **7**, 253$^{18}$
Schubert, H., **1**, 359$^{17}$, 380$^{17}$, 381$^{17}$; **2**, 514$^{50}$, 524$^{50}$; **3**, 39$^{213}$; **6**, 728$^{208,209}$; **8**, 388$^{60}$
Schubert, H.-J., **2**, 744$^{98}$
Schubert, H. W., **2**, 1088$^{51}$
Schubert, K., **6**, 564$^{907}$
Schubert, M., **3**, 687$^{112}$
Schubert, P. R., **4**, 95$^{98}$
Schubert, R., **2**, 662$^{6}$; **4**, 1073$^{21}$, 1076$^{21}$, 1090$^{21}$, 1092$^{21}$, 1098$^{21}$, 1102$^{21}$
Schubert, R. M., **8**, 875$^{34}$, 876$^{34}$
Schubert, U., **1**, 10$^{46}$, 25$^{128}$; **3**, 369$^{108}$; **4**, 976$^{100}$; **5**, 689$^{73}$, 1065$^{1}$, 1066$^{1,1a}$, 1074$^{1}$, 1083$^{1}$, 1084$^{1}$, 1090$^{88}$, 1093$^{1,96}$, 1098$^{96b}$, 1112$^{96b}$; **6**, 196$^{232}$, 500$^{179}$
Schubert, W., **4**, 1072$^{16}$
Schubert, W. M., **1**, 292$^{26}$; **2**, 753$^{2}$; **6**, 959$^{40}$
Schuchardt, J. L., **2**, 801$^{24}$; **3**, 1060$^{45}$
Schuchardt, U., **5**, 289$^{37,38}$, 290$^{39}$, 293$^{45}$, 1185$^{1}$, 1188$^{20}$, 1190$^{27}$, 1191$^{27b}$, 1195$^{35}$, 1197$^{40,44}$
Schuchardt, W., **3**, 724$^{14}$
Schuck, J. M., **8**, 497$^{40}$
Schücking, G., **2**, 143$^{53}$
Schuda, A. D., **6**, 810$^{72}$
Schuda, A. D. C., **3**, 224$^{172}$
Schuda, P., **5**, 330$^{34}$; **7**, 241$^{59}$, 438$^{22}$
Schuda, P. F., **2**, 905$^{55}$, 907$^{55}$, 908$^{55}$, 910$^{55}$, 911$^{55}$; **5**, 410$^{40}$; **6**, 189$^{190}$, 651$^{137}$; **7**, 241$^{59}$
Schudde, E. P., **4**, 1036$^{54}$
Schudel, P., **2**, 612$^{104}$; **3**, 698$^{159}$; **5**, 714$^{75a}$
Schueller, K., **5**, 69$^{106}$
Schüep, W., **8**, 794$^{14}$
Schuerch, C., **6**, 36$^{20}$, 47$^{78}$, 49$^{90}$
Schuett, W. R., **8**, 454$^{197}$, 455$^{197}$
Schuette, H., **8**, 189$^{56,57}$
Schug, R., **5**, 76$^{242}$, 78$^{276,277,278}$
Schuh, K., **6**, 531$^{456}$
Schul, W., **2**, 372$^{269}$, 373$^{269}$
Schulbach, H., **8**, 308$^{4}$
Schule, G., **7**, 416$^{124}$
Schulenberg, J. W., **2**, 758$^{25}$; **7**, 690$^{14}$

Schuler, F. W., **5**, 856[194]
Schüler, H., **6**, 558[841]
Schuler, R. H., **4**, 719[22]
Schüll, V., **4**, 181[71], 1040[69]
Schüller, M., **6**, 57[140]
Schulman, S., **4**, 24[72,72b]
Schulte, G., **2**, 675[52]; **5**, 736[143,145], 737[145]; **6**, 900[114], 1067[103]; **7**, 237[37], 245[74], 361[23]; **8**, 224[101]
Schülte, K. E., **4**, 317[555], 883[100], 884[100]
Schulte-Elte, K. H., **2**, 169[164], 540[69]; **5**, 10[76], 757[80], 761[80]; **6**, 1058[58], 1059[64], 1067[108]; **7**, 818[17]
Schulte-Frohlinde, D., **3**, 665[41]
Schulten, W., **2**, 377[283]
Schultess, A. H., **6**, 535[542], 538[542]
Schultheiss-Reimann, P., **6**, 657[178]
Schulthess, W., **4**, 70[1]
Schultz, A. G., **1**, 506[12], 769[195]; **3**, 23[135], 51[270]; **4**, 8[28], 10[34], 14[46,46b], 106[140a], 159[80], 370[38], 372[38], 390[38], 957[21], 1093[151], 1095[151], 1101[192,194]; **5**, 225[97,98], 558[63], 571[119], 572[124], 582[177], 938[217,218]; **6**, 835[46]; **7**, 120[5], 261[70], 276[151]; **8**, 449[151], 490[10], 505[82], 507[82], 508[87]
Schultz, E. M., **2**, 971[92]
Schultz, H., **7**, 248[108]
Schultz, H. P., **8**, 236[4], 242[4], 247[4], 248[4], 249[4]
Schultz, H. S., **7**, 766[173]
Schultz, J., **3**, 673[70], 674[70b]; **8**, 623[148]
Schultz, J. A., **5**, 338[54]
Schultz, M., **6**, 646[99,99b]
Schultz, P. G., **5**, 855[190,192]; **8**, 206[167]
Schultz, R. G., **4**, 587[40]
Schultze, H., **2**, 759[32]
Schultze, K. M. L., **6**, 435[5b]
Schultze, L. M., **5**, 1076[34], 1107[168,169], 1111[34]
Schulz, A., **8**, 853[144]
Schulz, B., **6**, 436[13]
Schulz, C. R., **8**, 40[89], 66[89]
Schulz, D., **5**, 1131[15]
Schulz, G., **2**, 782[30]; **7**, 498[223]
Schulz, H., **1**, 669[181,182], 670[181,182]; **6**, 182[134]
Schulz, H.-J., **3**, 509[178]
Schulz, J., **7**, 506[303]
Schulz, M., **4**, 611[345]; **7**, 140[130], 141[130]
Schulz, W., **6**, 554[802], 576[802], 581[802]
Schulz, W. H., **7**, 725[33]
Schulze, A., **2**, 153[106]
Schulze, B., **2**, 360[167]
Schulze, E., **4**, 222[181], 224[181]
Schulze, K., **3**, 382[38]; **6**, 1044[20]
Schulze, P.-E., **7**, 47[55]
Schulze, T., **1**, 185[56]; **2**, 29[106]; **7**, 549[45]
Schulze, U., **6**, 462[9], 472[67]
Schulz-Popitz, C., **4**, 1006[104]
Schumacher, D. P., **8**, 605[17]
Schumacher, J., **5**, 497[227]
Schumacher, J. N., **3**, 407[150]
Schumacher, M., **5**, 451[5,9], 513[3], 514[3]
Schumaker, R. R., **3**, 135[340], 137[340], 139[340], 141[340]
Schuman, S. C., **8**, 608[41]
Schumann, D., **4**, 5[19]; **5**, 409[36]
Schumann, H., **1**, 231[9], 251[2], 253[12]; **4**, 738[98]; **8**, 447[133,134,136], 696[127,-128], 800[69]
Schumann, I., **3**, 1028[48]
Schumann, K., **4**, 587[44]
Schumann, R. C., **2**, 249[84]
Schumann, U., **1**, 18[93], 22[116], 34[224], 36[174], 39[186]
Schumm, J. S., **2**, 835[159]
Schunck, K., **8**, 321[94,95]
Schunn, R. A., **5**, 57[53]
Schunselaar, W., **2**, 902[46]
Schupp, W., **4**, 45[130,130e]
Schurig, V., **4**, 390[175b]; **6**, 677[323]
Schuster, D. I., **3**, 815[73]; **4**, 75[43b], 100[43]; **5**, 125[13,15], 128[13], 153[25], 215[4], 221[60], 224[4]; **8**, 563[437]
Schuster, F., **5**, 344[65]
Schuster, G. B., **5**, 162[69]; **7**, 169[109], 854[61]; **8**, 890[144]
Schuster, H. F., **2**, 81[1], 82[1], 96[1]; **3**, 223[146]; **4**, 53[151], 1010[150]; **5**, 581[171]; **6**, 830[4], 873[10]
Schuster, I., **2**, 346[46]
Schuster, K. H., **6**, 227[21], 228[21], 229[21], 230[21], 231[21], 234[21]
Schuster, P., **1**, 286[10]; **2**, 346[46], 349[66], 352[91,92], 355[122], 356[66], 357[141], 358[91]
Schuster, R. E., **1**, 292[27,31], 293[33]; **6**, 294[239]
Schuster, T., **1**, 142[25]
Schut, J., **8**, 837[11], 839[11]
Schütte, H. R., **6**, 746[92]
Schutz, A., **2**, 1103[129,131]
Schütz, G., **7**, 144[155]
Schütz, J., **6**, 535[536], 538[536]
Schütz, O., **3**, 582[112]
Schwab, G. M., **8**, 451[178]
Schwab, H., **5**, 478[162]
Schwab, J. M., **4**, 285[158]; **7**, 413[107b,c]
Schwab, P. A., **3**, 739[39]
Schwab, W., **4**, 1076[46]; **8**, 69[221], 70[221,222], 647[53,54]
Schwabe, R., **5**, 690[80,80c], 733[136,136f], 734[136f]
Schwager, H., **3**, 587[150]
Schwager, I., **4**, 915[7]
Schwall, H., **1**, 844[8]; **3**, 887[8], 888[8], 893[8], 897[8], 900[8], 903[8,126]; **4**, 953[8,8b], 954[8b]; **8**, 382[11], 383[11]
Schwan, A., **6**, 829[3]
Schwartz, A., **2**, 169[164]; **3**, 667[48], 687[48]; **5**, 822[165]; **7**, 445[60]
Schwartz, C. E., **6**, 898[106]
Schwartz, E., **5**, 436[158,158g], 442[158]
Schwartz, H. M., **8**, 185[11], 192[98]
Schwartz, J., **1**, 143[33], 155[67,68], 156[68,69], 749[75], 807[316], 808[320]; **3**, 469[202], 470[202], 473[202], 483[14], 1027[42], 1030[42], 1031[63]; **4**, 10[34], 113[176], 143[19], 153[62c,63a], 154[64a,b], 155[63b], 249[124], 257[222,223], 258[124], 262[222], 309[413], 312[455], 393[197,197a], 394[197a], 594[139], 595[155,156], 619[139], 620[155,156,395,396,397], 634[139,155], 635[155,156,395], 636[396,397]; **5**, 181[152], 1124[46], 1125[62,64], 1173[31], 1178[31]; **7**, 17[179], 453[80]; **8**, 447[121], 668[1], 669[1,3,4], 673[1,28], 675[28,38,43-45], 676[1,28], 677[28,38,60], 679[4,38,68], 680[68,71], 681[38,74], 682[81,82], 683[68], 684[1,43,74], 685[1,97], 686[1], 687[1,4], 688[1,100], 691[1,74,100,105,106], 692[1,28,38,100], 693[38,68,71,109,110,113-117], 694[71], 695[68], 697[3], 889[131]
Schwartz, J. A., **2**, 204[98]
Schwartz, J. L., **5**, 829[22]
Schwartz, L. H., **3**, 735[20]
Schwartz, M., **7**, 17[175]
Schwartz, M. A., **2**, 541[78], 841[186]; **3**, 55[283], 679[88,90], 680[92], 682[164], 683[90]; **7**, 336[33]; **8**, 527[48]
Schwartz, N. N., **7**, 674[43]
Schwartz, N. V., **1**, 608[39]; **7**, 516[3]
Schwartz, R. D., **7**, 78[127], 429[153]
Schwartz, R. H., **1**, 116[44]; **2**, 602[39]; **3**, 244[27]; **8**, 771[50]
Schwartz, S. B., **5**, 165[86]
Schwartz, T., **4**, 374[91]

Schwartz, T. R., **1**, 287[20], 288[20], 289[20]; **4**, 202[20]
Schwartz, V., **7**, 67[79]
Schwartzentrinber, K. M., **7**, 13[119]
Schwartzman, L. H., **8**, 275[141]
Schwartzman, S., **4**, 305[363]
Schwartzmann, S. M., **7**, 299[41]
Schwarz, G.-U., **3**, 872[59]
Schwarz, H., **1**, 162[104]; **3**, 55[280], 623[36]; **6**, 462[9], 668[251], 669[251]
Schwarz, J., **7**, 42[34], 805[66]
Schwarz, M., **2**, 345[40], 350[40]; **6**, 269[76]
Schwarz, R., **2**, 736[27], 1090[72]; **4**, 53[149], 129[223b]; **8**, 310[16]
Schwarz, R. A., **3**, 159[467], 166[467]
Schwarz, S., **3**, 55[280]; **7**, 586[167]
Schwarz, U., **6**, 33[7], 40[7], 57[7]
Schwarz, V., **6**, 495[147]
Schwarzenbach, K., **1**, 215[34]; **4**, 962[38]
Schwarzenberg, K., **4**, 98[110]
Schwarzenbrunner, U., **6**, 543[614]
Schwechten, H. W., **7**, 850[1]
Schweckendieck, W. J., **5**, 1141[80], 1145[80]
Schweiger, E. J., **3**, 883[106]; **5**, 736[145], 737[145]
Schweiter, M. J., **7**, 399[38], 400[38], 406[38], 409[38], 415[38]
Schweitzer, H., **3**, 640[104]
Schweitzer, R., **7**, 92[41,41a], 94[41], 152[1]
Schweizer, B., **1**, 37[240]
Schweizer, E. E., **1**, 878[105]; **4**, 1000[6], 1005[6,79], 1006[103], 1016[6]; **5**, 938[215]; **6**, 173[43], 175[68], 182[143], 185[143], 209[70], 1014[20]; **8**, 604[5], 636[1]
Schweizer, W. B., **1**, 1[1], 3[1], 26[1], 28[142], 30[151], 34[170], 37[238], 38[261], 41[151], 43[1]; **2**, 100[2], 107[55], 193[65], 197[77], 280[25], 897[19], 910[66]; **4**, 21[69], 72[25], 202[19], 224[182]; **5**, 841[104]; **6**, 716[101]; **8**, 190[78]
Schwellnus, K., **4**, 162[94c]
Schwengers, D., **4**, 887[129]
Schwenk, E., **2**, 734[6]; **3**, 812[55]; **8**, 320[84]
Schwenk, R., **2**, 762[55]
Schwentner, J., **6**, 60[146]
Schwepler, D., **7**, 350[25], 355[25]
Schwetlick, K., **5**, 102[182]
Schwickardi, M., **1**, 14[77]; **8**, 697[135]
Schwickerath, W., **6**, 549[672], 550[675], 552[675,691]
Schwier, J. R., **8**, 709[49], 710[49,53], 721[53,143]
Schwille, D., **8**, 658[101]
Schwindeman, J., **2**, 713[46]; **5**, 777[190,191]
Schwindemann, J. A., **6**, 239[77]
Schwob, J. M., **2**, 969[86]
Schwobel, A., **5**, 422[86]
Schwotzer, W., **6**, 708[47]
Schwyzer, R., **6**, 637[27], 668[251], 669[251]
Sciacovelli, O., **7**, 374[77a]
Sciaky, R., **2**, 783[35]
Scialdone, M. A., **6**, 1066[97]
Sciano, J. C., **7**, 605[140]
Scilingo, A., **2**, 547[114], 551[114]
Scola, P. M., **2**, 1054[59,61], 1070[59], 1071[61]; **5**, 485[181], 531[79]
Scolastico, C., **1**, 72[72], 524[86,87], 527[101,102,107], 528[108]; **2**, 103[28], 221[146], 266[61,62], 267[62-64], 515[55,56], 516[58], 605[57], 614[57], 630[21], 631[21], 632[21], 634[21], 636[56], 637[56,59], 640[21,56,59], 641[21,71], 642[21,71,73,74,78], 643[73,74,78], 644[21,73], 645[21,59], 652[59], 920[98], 922[101], 923[101], 930[131], 931[131]; **4**, 113[166], 152[58], 207[57,58], 226[187,188]; **6**, 149[100,108]; **7**, 170[121], 441[45]
Scollar, M. P., **8**, 185[10]
Scopes, D. I. C., **5**, 92[69]; **6**, 535[541], 538[541]
Scorrano, G., **4**, 425[33], 426[60,63], 438[156]; **5**, 408[33]; **8**, 152[175,176], 155[176]
Scott, A., **6**, 668[256], 669[256]
Scott, A. D., **7**, 264[92,93]
Scott, A. E., **3**, 660[15]
Scott, A. I., **2**, 170[174]; **3**, 660[14], 679[91], 681[96], 689[119,121], 813[60]; **4**, 24[72,72c]; **6**, 920[46]; **7**, 97[96]
Scott, A. S., **1**, 786[251]
Scott, B. S., **8**, 583[12]
Scott, C., **5**, 1136[54]
Scott, C. J., **3**, 635[33], 640[107,107a], 647[33,107]
Scott, E. J. Y., **3**, 328[179]
Scott, F., **3**, 216[73], 243[14], 249[14], 263[14], 423[72], 464[172], 4 66[182]; **4**, 1009[139], 1040[75]
Scott, F. L., **2**, 291[73]; **4**, 290[197]; **7**, 696[40]
Scott, J. W., **1**, 825[48], 837[148], 838[148]; **8**, 152[168], 159[2], 459[228], 460[249], 541[212], 606[18]
Scott, K. U., **5**, 1116[8]
Scott, L. T., **1**, 116[48], 118[48]; **2**, 744[91]; **4**, 1055[137]; **5**, 716[87]; **7**, 8[60]; **8**, 341[104]
Scott, M. D., **8**, 336[73], 337[73], 338[73], 339[73], 341[73]
Scott, P. W., **2**, 856[249]
Scott, R., **5**, 1149[125]
Scott, R. B., **7**, 5[21]
Scott, R. D., **2**, 1010[8]; **5**, 141[92]
Scott, R. M., **1**, 512[36]; **4**, 753[173]
Scott, S. W., **3**, 679[88,90], 683[90]
Scott, T. W., **4**, 30[89]
Scott, W., **4**, 861[113]; **8**, 390[79]
Scott, W. E., **1**, 130[96]
Scott, W. J., **1**, 193[89], 836[145]; **2**, 110[72]; **3**, 218[99], 219[99], 232[256,258,270], 239[99], 250[71], 436[17], 446[75], 454[116], 487[48-50], 489[48], 492[48], 495[48-50]; **4**, 258[242]; **5**, 712[57d], 763[107], 779[107]; **6**, 766[22]; **8**, 933[45]
Scott, W. L., **5**, 814[137,138]; **8**, 945[129]
Scotton, M., **4**, 956[18]
Scotton, M. J., **7**, 599[66]
Scouten, C. G., **8**, 713[72,73], 715[84], 724[155,157]
Scovell, E. G., **2**, 546[90]; **3**, 348[29], 355[53], 357[53], 382[35], 769[170], 770[175], 771[170]
Scozzafava, M., **5**, 1131[17]
Screttas, C. G., **3**, 88[126], 95[126], 96[126], 107[126], 109[126], 123[126], 125[126], 194[12], 824[20,21], 825[21]; **4**, 316[539]; **8**, 842[45]
Scriabine, A., **2**, 971[92]
Scribner, R. M., **8**, 40[90], 66[90]
Scrimin, P., **6**, 67[10]; **7**, 95[69]
Scripko, J., **6**, 284[170]; **8**, 392[107]
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Sinclair, J. A., **3**, 274[21], 554[24], 799[98]; **4**, 147[40]

Sinclair, P. J., **1**, 123[74], 373[92], 375[92], 376[92]; **2**, 649[104], 1052[48], 1075[48], 1076[48,152]; **8**, 655[86]

Sindona, G., **8**, 965[62]

Singaram, B., **1**, 488[5], 492[5,37,39], 494[37], 498[51], 499[51], 501[37], 502[39]; **2**, 57[4]; **3**, 199[66], 793[75], 795[75], 797[75,91,92]; **6**, 78[59]; **7**, 595[13], 606[159]; **8**, 14[78], 705[11], 709[49], 710[49,53,58], 716[86], 721[53,143], 722[147,148], 726[11], 939[98]

Singaram, B. J., **2**, 247[82]

Singer, E., **4**, 1093[148]; **5**, 433[135,135a]; **6**, 519[339]

Singer, L. A., **4**, 719[23]; **5**, 167[100]

Singer, M. S., **3**, 164[476]

Singer, S. P., **1**, 712[264], 714[264]; **3**, 87[63], 114[63], 117[63], 865[25], 957[110,111]; **5**, 894[46]; **6**, 897[101], 906[147], 1026[81], 1027[81], 1029[81], 1030[81], 1031[81], 1033[81]; **7**, 87[22], 120[19], 121[19], 123[19], 124[38], 128[38], 129[38], 486[144], 775[353]

Singer, S. S., **6**, 140[60,61]

Singh, A., **1**, 17[212], 37[178], 699[247]; **2**, 404[41]; **3**, 421[61], 422[61]; **4**, 284[156], 365[4], 370[4], 380[4], 381[4], 398[216], 399[216a], 401[216a], 405[216a], 410[216a], 1001[42]; **6**, 470[58]; **7**, 495[211], 524[53]; **8**, 847[97,97d], 849[97d,107,112,115]

Singh, A. K., **4**, 798[110], 1040[71,72], 1043[71], 1044[72]; **5**, 85[6], 86[12]; **6**, 124[144], 777[59], 837[60]; **7**, 376[85]; **8**, 943[121], 945[130]

Singh, B. B., **6**, 727[189], 806[54]

Singh, B. P., **7**, 674[39]; **8**, 406[39], 989[34]

Singh, G., **2**, 505[7]; **3**, 125[313]; **4**, 505[142]; **6**, 456[162], 457[162]

Singh, H., **4**, 443[194]; **6**, 527[406], 579[985], 734[13]; **8**, 656[90]

Singh, H. S., **7**, 437[7], 439[7], 851[18]

Singh, J., **1**, 619[63]; **3**, 8[37], 602[220]; **4**, 8[27,27a], 24[72,72e], 74[41], 100[41]; **7**, 271[129]; **8**, 48[110], 66[110]

Singh, K., **6**, 734[13]

Singh, L. W., **8**, 839[26b], 840[26]

Singh, M., **2**, 541[75]; **4**, 497[100], 505[141,142,146]; **5**, 164[76]; **7**, 745[75], 775[346]; **8**, 752[66]

Singh, M. D., **5**, 1133[30]

Singh, M. P., **6**, 76[50]; **8**, 384[29], 412[115]

Singh, N. N., **7**, 79[128b]

Singh, N. P., **6**, 54[124]

Singh, P., **4**, 443[194], 460[94], 464[94], 477[94], 503[126], 505[144,145]; **5**, 383[123]; **6**, 579[985]

Singh, P. K., **3**, 304[67]

Singh, P. R., **6**, 215[103]; **7**, 884[190]; **8**, 851[134], 858[204]

Singh, R., **1**, 820[15]; **3**, 380[10], 541[115]; **6**, 538[565]

Singh, R. K., **2**, 161[139], 547[97]; **4**, 7[24,24c], 1040[95], 1041[95a], 1045[95a]; **5**, 683[35]; **6**, 1023[72]

Singh, R. P., **7**, 279[170], 844[61], 845[61]

Singh, S., **1**, 367[55]; **7**, 747[95]

Singh, S. B., **3**, 1048$^{12}$; **4**, 1036$^{46}$
Singh, S. K., **3**, 242$^{8}$, 257$^{8}$; **5**, 664$^{39}$, 665$^{40}$
Singh, S. M., **1**, 135$^{115}$, 343$^{104}$
Singh, S. P., **3**, 739$^{38}$, 747$^{70}$; **8**, 405$^{26}$
Singh, T., **3**, 810$^{44}$, 1057$^{39}$; **4**, 44$^{124}$
Singh, U. P., **4**, 1097$^{167}$
Singh, V. K., **1**, 317$^{144}$, 319$^{144}$; **5**, 233$^{139}$; **8**, 171$^{103}$
Singleton, A., **5**, 475$^{143}$
Singleton, D. A., **4**, 439$^{162}$, 443$^{162}$; **5**, 266$^{75}$, 268$^{75}$, 341$^{58}$, 520$^{38,40,41}$, 521$^{42}$, 522$^{41}$
Singleton, D. M., **5**, 1142$^{86}$; **6**, 980$^{39}$, 993$^{93}$; **8**, 796$^{27}$, 888$^{122}$
Singleton, E., **3**, 896$^{67}$; **8**, 457$^{214}$, 458$^{214}$
Singleton, T., **3**, 464$^{174}$
Singleton, V. D., **6**, 959$^{41}$
Sinha, A., **7**, 107$^{169}$
Sinha, A. K., **6**, 524$^{370}$, 532$^{370}$
Sinha, A. M., **5**, 736$^{145}$, 737$^{145}$
Sinha, G., **3**, 898$^{86}$
Sinha, N. D., **3**, 219$^{114}$, 499$^{140}$, 501$^{140}$, 502$^{140}$; **6**, 624$^{147}$
Sinha, S. C., **3**, 956$^{107}$
Sinhababa, A., **1**, 463$^{32}$
Sinhababu, A. K., **7**, 333$^{23}$; **8**, 70$^{231}$, 351$^{167}$, 355$^{167}$, 942$^{118}$
Sinigalia, R., **7**, 426$^{148d}$
Sinisterra, J. V., **1**, 821$^{22}$; **3**, 825$^{24,24b}$, 835$^{24}$; **8**, 86$^{26}$
Sinitsa, A. D., **6**, 524$^{366,372}$
Sink, C. W., **7**, 774$^{321}$
Sinnema, Y. A., **4**, 297$^{266}$
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Sinnreich, D., **4**, 292$^{234}$; **6**, 264$^{32}$; **7**, 765$^{167}$
Sinott, M. L., **6**, 49$^{92}$
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Sinoway, L., **2**, 121$^{188}$; **3**, 250$^{70}$
Sinsky, M. S., **4**, 48$^{138}$
Sioda, R. E., **3**, 577$^{89}$
Sipilina, N. M., **8**, 618$^{121}$, 619$^{121}$, 621$^{142}$
Sipio, W. J., **4**, 370$^{32}$, 371$^{32,60}$, 372$^{60}$; **6**, 1031$^{113,115}$; **7**, 131$^{78}$, 523$^{46}$, 524$^{49}$; **8**, 499$^{45}$, 836$^{10b}$, 847$^{10b,99}$, 848$^{10b,99}$, 849$^{10b,99}$
Sipos, F., **2**, 841$^{185}$
Sipos, W., **3**, 872$^{61,62}$; **4**, 799$^{113}$
Siragusa, J. A., **3**, 564$^{10}$, 595$^{188}$
Sirala-Hansen, K., **1**, 189$^{74}$
Sirazova, M. M., **4**, 599$^{213}$, 640$^{213}$
Sircar, J. C., **6**, 261$^{14}$, 263$^{14}$, 272$^{14}$, 275$^{14}$, 280$^{14}$
Sirear, J. C., **4**, 294$^{240}$
Siret, P., **2**, 156$^{118}$; **3**, 572$^{69}$, 573$^{69}$, 602$^{69}$, 607$^{69}$, 610$^{69}$; **4**, 373$^{70}$; **6**, 713$^{80b}$; **7**, 566$^{100}$, 711$^{60}$
Siriwardane, U., **4**, 499$^{102}$
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Siro, M., **1**, 767$^{176}$
Siroi, T., **7**, 537$^{60}$
Sironi, A., **8**, 460$^{248}$
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Sirrimanne, S. R., **7**, 99$^{110}$
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Sisani, E., **1**, 846$^{18b,c}$, 847$^{18}$
Sisbarro, M. J., **8**, 533$^{154}$
Sisido, K., **6**, 261$^{11}$; **7**, 595$^{21}$; **8**, 661$^{112}$
Sisk, S. A., **5**, 350$^{78}$
Siskin, M., **3**, 333$^{211a,b}$; **8**, 454$^{203}$
Siskind, M., **7**, 851$^{25}$
Sisko, J., **5**, 403$^{10}$
Sisler, H., **7**, 100$^{130}$, 769$^{232}$
Sisler, H. H., **2**, 524$^{76}$; **8**, 754$^{82}$
Sisti, A. J., **1**, 873$^{93}$; **3**, 756$^{115}$, 757$^{116-120}$; **8**, 956$^{4}$
Sisti, J., **2**, 662$^{13}$, 664$^{13}$
Sisti, M., **1**, 566$^{216}$; **2**, 833$^{148}$; **4**, 261$^{285,288,290}$
Sit, S.-Y., **1**, 205$^{105}$, 820$^{13}$, 823$^{13}$
Sita, G. E., **7**, 92$^{48}$
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Sitzman, M. E., **4**, 426$^{54}$
Siu, T.-W., **3**, 877$^{89}$
Sivakumar, R., **8**, 26$^{28}$, 30$^{28}$, 36$^{28}$, 37$^{28}$, 40$^{28}$, 43$^{28}$, 44$^{28}$, 46$^{28}$, 55$^{28}$, 66$^{28}$, 357$^{204}$
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Sivaram, S., **6**, 283$^{159}$
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Sjogren, E. B., **1**, 400$^{11}$; **2**, 30$^{110}$, 31$^{110}$, 113$^{106,107}$, 254$^{43}$; **5**, 98$^{126}$; **6**, 759$^{137,138}$
Sjoholm, R., **4**, 89$^{84c}$
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Skalarz, B., **7**, 703$^{4}$
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Skameikina, T. I., **3**, 306$^{84}$
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Skattebøl, L., **3**, 864$^{24}$, 865$^{24}$, 872$^{24}$; **4**, 1001$^{30}$, 1009$^{143}$, 1010$^{149,153,154,158}$, 1012$^{168,169,170}$, 1013$^{180}$, 1020$^{231,232}$, 1021$^{251}$; **5**, 19$^{130}$, 113$^{235}$, 797$^{67}$, 949$^{275}$, 950$^{293}$; **6**, 971$^{128}$; **7**, 764$^{128}$; **8**, 807$^{113}$
Skeean, R. W., **3**, 351$^{43a}$; **5**, 712$^{57e}$
Skell, P. S., **3**, 390$^{82}$, 392$^{82}$; **4**, 280$^{128}$, 281$^{128}$, 959$^{30}$, 1002$^{49}$, 1018$^{220}$; **8**, 890$^{141}$
Skelly, R. K., **5**, 679$^{19}$
Skelton, B. W., **1**, 13$^{73}$, 16$^{89}$, 17$^{217,219}$, 36$^{234}$, 37$^{177}$; **2**, 606$^{69}$
Skerlj, R. T., **3**, 215$^{60}$, 253$^{94,95}$, 489$^{55}$, 495$^{55}$; **4**, 249$^{123}$; **8**, 95$^{90}$
Skerrett, E. J., **8**, 963$^{44}$, 972$^{114}$
Sket, B., **5**, 829$^{19}$
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Skibo, E. R., **5**, 422$^{82}$
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Skinner, H. A., **7**, 593$^{1}$; **8**, 670$^{13}$
Skinner, J. F., **8**, 459$^{239}$
Skipka, G., **5**, 69$^{100}$
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Skjold, A. C., **4**, 445$^{210}$
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Skolnick, P., **7**, 340$^{46}$
Skorcz, J. A., **4**, 490$^{66}$, 499$^{66}$, 500$^{104}$; **5**, 390$^{140}$
Skorna, G., **2**, 1084$^{9}$, 1089$^{58}$

Skorova, A. E., **4**, 330$^{5}$; **6**, 153$^{143}$
Skotnicki, J., **8**, 36$^{48}$, 66$^{48}$, 347$^{140}$, 395$^{129}$, 616$^{102}$, 617$^{102}$, 618$^{102}$
Skovlin, D. O., **2**, 183$^{12}$
Skowroñska-Ptasiñska, M., **1**, 461$^{15}$, 464$^{15}$; **7**, 333$^{25}$
Skramstad, J., **4**, 1063$^{173}$
Skrydstrup, T., **6**, 7$^{30}$
Skuballa, W., **2**, 381$^{308}$; **4**, 964$^{50}$, 965$^{50}$
Skulnick, H. I., **2**, 801$^{35}$
Skundin, A. M., **3**, 648$^{181}$
Skupsch, J., **1**, 773$^{203,203a}$
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Sky, A. F., **5**, 856$^{216}$
Slabaugh, M. R., **2**, 159$^{128}$
Slack, S. C., **2**, 240$^{8}$
Slade, C. J., **7**, 332$^{18,19}$
Slade, J., **1**, 66$^{57}$, 359$^{21}$, 383$^{21}$, 384$^{21}$; **8**, 35$^{66}$, 66$^{66}$
Slade, M. J., **1**, 37$^{178}$
Sladkov, A. M., **3**, 209$^{20}$
Slagle, J. D., **6**, 205$^{30}$
Slama, J. T., **4**, 310$^{432}$
Slanian, R. A., **4**, 598$^{197}$, 623$^{197}$, 639$^{197}$
Slater, G. P., **7**, 152$^{4}$, 153$^{4}$
Slater, M., **3**, 1027$^{44}$
Slater, M. J., **5**, 1060$^{56}$
Slater, S., **8**, 458$^{223,223b}$
Slates, H. L., **2**, 160$^{135}$, 746$^{110}$; **3**, 689$^{119}$; **7**, 675$^{59}$
Slaugh, L. H., **1**, 174$^{6}$, 175$^{6}$; **8**, 568$^{464}$, 735$^{15,16}$
Slavinskaya, R. A., **6**, 432$^{116}$
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Slawin, A. M. Z., **4**, 381$^{126b}$, 382$^{126}$, 383$^{126}$; **5**, 374$^{107}$, 376$^{107b}$; **7**, 112$^{198}$, 820$^{26}$
Slayden, S. W., **7**, 597$^{50}$
Slaytor, M., **4**, 27$^{83}$; **5**, 468$^{135}$; **8**, 249$^{91}$, 293$^{52}$, 302$^{52}$, 507$^{85}$
Slebocka-Tilk, H., **4**, 330$^{3}$, 345$^{3}$; **7**, 770$^{250}$; **8**, 409$^{85}$
Sleddon, G. J., **8**, 754$^{100}$
Sleevi, M. C., **4**, 455$^{43}$, 457$^{49,50}$, 463$^{43}$, 477$^{49,50}$, 503$^{125}$
Sleezer, P. D., **7**, 92$^{50}$, 94$^{56}$
Slegeir, W., **8**, 372$^{123}$, 373$^{123}$
Sleiter, G., **2**, 965$^{69}$; **8**, 336$^{70}$
Slepushkina, A. A., **7**, 500$^{236}$
Slessor, K. N., **7**, 238$^{41}$; **8**, 341$^{105}$
Sletter, H., **7**, 7$^{48}$
Sletzinger, M., **2**, 803$^{33}$; **8**, 54$^{159}$, 66$^{159}$, 272$^{122}$
Sliede, J., **3**, 831$^{62}$
Slinckx, G., **4**, 314$^{489}$
Slinger, C. J., **8**, 819$^{42}$, 820$^{42}$
Sliskovic, D. R., **6**, 538$^{559}$, 554$^{775}$
Sliwa, E., **8**, 757$^{162}$
Sliwa, H., **2**, 962$^{48}$; **5**, 790$^{35}$; **7**, 661$^{49}$
Sliwinski, W. F., **4**, 1016$^{209}$
Sliwka, H.-R., **3**, 874$^{69}$
Slizhov, Yu. G., **8**, 629$^{182,183}$
Sloan, A. B. S., **2**, 765$^{78}$
Sloan, A. D. B., **2**, 866$^{3}$
Sloan, C. P., **4**, 797$^{104}$
Sloan, M. F., **7**, 24$^{38}$; **8**, 447$^{118}$, 454$^{118}$, 455$^{118}$, 568$^{481}$
Sloan, R. B., **5**, 929$^{173}$
Slob, C., **1**, 10$^{55}$, 11$^{55b}$
Slobbe, J., **3**, 651$^{215}$; **5**, 841$^{100}$; **8**, 500$^{48}$, 501$^{55}$, 502$^{60}$, 605$^{12}$, 608$^{35,36}$, 609$^{12}$, 614$^{12}$, 629$^{12}$
Sloboda, A. E., **6**, 554$^{724}$
Slobodin, Ya. M., **4**, 1010$^{155}$; **6**, 970$^{120}$
Slomp, G., **5**, 637$^{110,113}$
Slomp, G., Jr., **7**, 548$^{62}$, 553$^{62}$
Sloneker, J., **3**, 691$^{129}$, 693$^{129}$
Slonka, E., **4**, 432$^{106}$
Slopianka, M., **2**, 875$^{29}$; **4**, 51$^{144b}$, 1001$^{35}$
Slosse, P., **4**, 91$^{89}$
Slotin, L. A., **6**, 601$^{1}$
Slough, G. A., **2**, 310$^{30}$, 311$^{30}$, 655$^{143}$; **4**, 905$^{213}$
Slougui, N., **1**, 879$^{111e}$; **2**, 444$^{20}$
Slowey, P. D., **4**, 1009$^{143}$
Sluboski, B. C., **6**, 490$^{104}$, 534$^{515}$
Slusarchyk, W. A., **3**, 680$^{93}$, 807$^{29}$; **6**, 644$^{93}$
Slusarska, B., **2**, 378$^{290}$
Slusarska, E., **6**, 83$^{77}$
Sluski, R. J., **6**, 529$^{463}$
Slutsky, J., **1**, 859$^{66}$; **2**, 6$^{27}$, 565$^{15}$, 575$^{15}$, 582$^{15}$; **6**, 1036$^{143}$
Smaardijk, A. A., **1**, 223$^{78}$, 224$^{78}$, 317$^{148}$
Smadja, W., **4**, 276$^{75}$, 284$^{75}$, 308$^{401}$, 395$^{202}$; **5**, 772$^{155}$, 774$^{155}$
Smal, E., **2**, 780$^{11}$; **8**, 41$^{93}$, 66$^{93}$
Smal, M. A., **1**, 508$^{21}$, 519$^{63,64}$; **2**, 72$^{60}$
Smale, T. C., **3**, 1056$^{33}$, 1062$^{33}$; **5**, 105$^{194}$
Small, G. H., **8**, 971$^{102}$
Small, L. F., **8**, 568$^{468}$
Smalla, H., **5**, 422$^{88}$, 423$^{88}$
Smalley, R. K., **4**, 439$^{167}$; **6**, 530$^{416}$, 535$^{540,541}$, 538$^{540,541}$; **8**, 386$^{55}$
Smallheer, J., **7**, 243$^{63}$
Smallridge, M. J., **2**, 494$^{56}$; **4**, 76$^{47}$
Smart, B. E., **5**, 441$^{179,179b}$; **6**, 172$^{10}$
Smart, C. J., **5**, 434$^{148}$
Smart, J., **6**, 618$^{114}$, 649$^{126}$
Smart, J. B., **1**, 215$^{33}$
Smart, L. E., **5**, 1146$^{107}$
Smart, W. D., **8**, 143$^{55}$
Smeets, F., **2**, 740$^{55}$
Smeets, F. L. M., **3**, 750$^{83}$
Smeets, W. J. J., **1**, 25$^{127}$, 26$^{132,133,134}$
Smegal, J. A., **7**, 8$^{65,66}$
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Smeley, V., **3**, 896$^{72}$
Smentowski, F. J., **7**, 761$^{53}$
Smetanin, A. V., **3**, 1039$^{97}$
Smetankina, N. P., **8**, 771$^{47}$
Smets, G., **4**, 314$^{489}$; **7**, 475$^{52}$
Smetskaya, N. I., **6**, 554$^{734}$
Smidt, J., **4**, 588$^{64}$; **7**, 449$^{1,2}$, 450$^{1,2}$
Smiles, S., **3**, 689$^{117}$
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Smillie, R. D., **2**, 843$^{196}$
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Smirnov, Yu. I., **6**, 516$^{320}$
Smirnova, T. S., **5**, 948$^{273}$
Smirnova, V. V., **3**, 644$^{140,141}$
Smirnow, V. N., **4**, 885$^{115}$, 886$^{115}$
Smissman, E. E., **3**, 750$^{85}$, 788$^{51}$, 845$^{36,37}$
Smit, C. J., **3**, 568$^{46,47}$, 569$^{50}$; **4**, 459$^{87}$; **8**, 131$^{4,5}$, 132$^{4}$, 134$^{4}$
Smit, R., **5**, 77$^{264}$
Smit, V. A., **3**, 342$^{7,8,14}$, 345$^{21}$, 346$^{24}$, 349$^{35}$, 351$^{41}$, 361$^{73,80}$
Smit, W. A., **2**, 710$^{16}$, 723$^{101}$, 725$^{107\text{-}109}$; **4**, 330$^{5}$, 356$^{140}$; **5**, 345$^{70}$, 346$^{70}$, 453$^{66}$, 775$^{175,176}$, 850$^{148}$, 1055$^{46}$, 1056$^{48,49}$, 1057$^{50,51}$, 1062$^{51}$
Smith, A., **8**, 568$^{471}$, 612$^{77}$

Smith, A. B., III, **1**, 129[93], 779[224]; **2**, 189[45], 388[340], 541[77], 651[120,122], 657[165], 725[106]; **3**, 22[133], 24[149], 25[149], 26[165], 709[17,18], 906[144]; **4**, 212[97,98], 1040[102]; **5**, 145[105], 178[139], 342[63], 362[93], 363[93i], 944[242]; **6**, 174[63]; **7**, 7[47], 162[67], 176[67], 238[39], 239[44], 243[64], 298[37]; **8**, 248[83], 353[158], 931[38], 940[104]
Smith, A. E., **6**, 737[33]
Smith, A. G., **2**, 124[202]
Smith, A. H., **2**, 814[78], 818[78], 823[78]
Smith, A. J., **4**, 6[21], 680[50]; **6**, 1014[19]
Smith, A. K., **4**, 976[100]; **8**, 445[53], 453[195]
Smith, A. L., **3**, 75[51], 77[57], 78[51]; **5**, 736[145], 737[145]; **7**, 227[79,80]
Smith, A. S., **1**, 423[96]
Smith, B. C., **2**, 183[12]; **7**, 203[54]
Smith, B. F., **2**, 897[17]; **7**, 763[99], 766[99]
Smith, B. H., **3**, 628[48]; **7**, 660[37]
Smith, B. V., **8**, 383[13]
Smith, C., **3**, 919[30], 933[30,62], 946[30], 949[95]; **4**, 507[154]; **5**, 829[21]; **6**, 893[79], 897[95]
Smith, C. A., **3**, 217[95], 681[100]; **4**, 810[166]; **5**, 736[143]
Smith, C. D., **5**, 1187[9]
Smith, C. F. C., **8**, 615[94], 618[94]
Smith, C. J., **8**, 206[172]
Smith, C. V., **5**, 1199[47]
Smith, C. W., **6**, 637[30]; **7**, 446[66]
Smith, C. W., Jr., **3**, 265[187]
Smith, C. Z., **8**, 132[9]
Smith, D., **1**, 8[35]
Smith, D. A., **5**, 515[15], 518[15], 519[15,33]; **7**, 530[28], 531[28]
Smith, D. B., **1**, 41[201]; **5**, 342[62b], 843[119]; **7**, 396[26], 416[26]
Smith, D. C. C., **8**, 614[85]
Smith, D. G., **8**, 290[31]
Smith, D. J. H., **3**, 159[459], 163[459], 1028[50], 1036[84]; **4**, 553[8], 939[79], 941[79]; **5**, 904[53]; **6**, 171[4], 177[4,112], 181[112], 198[4], 200[112], 624[146], 625[146]; **7**, 451[17], 462[17]; **8**, 290[31]
Smith, D. K., **4**, 425[35], 445[35]
Smith, D. L., **4**, 50[142]; **7**, 43[44], 208[84], 774[315]
Smith, D. M., **6**, 208[55], 212[55]
Smith, D. R., **3**, 825[30]; **8**, 64[203], 66[203]
Smith, E. H., **5**, 160[55]; **6**, 245[128]
Smith, E. M., **1**, 366[50]
Smith, F. A., **7**, 666[77]
Smith, F. X., **2**, 356[128]; **4**, 89[84i]
Smith, G., **3**, 816[79]; **6**, 659[195]; **7**, 244[69]
Smith, G. A., **1**, 477[131]; **3**, 75[43], 76[43], 80[43,65], 81[65], 685[108]
Smith, G. B. L., **8**, 373[131]
Smith, G. D., **5**, 855[184]
Smith, G. F., **2**, 954[5]
Smith, G. G., **3**, 828[46]; **5**, 552[11]; **6**, 1033[124], 1034[124], 1035[124]
Smith, G. M., **2**, 743[84]
Smith, G. P., **3**, 328[177]
Smith, G. V., **3**, 864[16], 866[16], 883[16]; **8**, 150[136], 883[90]
Smith, G. W., **5**, 195[7]
Smith, H., **8**, 212[22], 490[1,8], 492[1], 500[8], 515[117], 524[2], 526[19,28,29,36], 527[29], 530[2], 531[2], 842[43], 971[103], 972[113]
Smith, H. A., **3**, 15[79]; **8**, 436[72]
Smith, H. D., **4**, 1033[27,31], 1049[27]; **5**, 804[94], 986[39]
Smith, H. E., **2**, 969[85]; **6**, 105[12]
Smith, H. L., **6**, 802[43], 803[43]
Smith, H. W., **4**, 310[432]
Smith, I. R., **4**, 33[95,95a]
Smith, J., **3**, 54[277]
Smith, J. C., **4**, 282[138,139], 285[166], 288[182]
Smith, J. D., **1**, 16[90], 17[91,208], 39[191], 41[264], 214[28]; **4**, 170[15]
Smith, J. G., **2**, 583[111]; **3**, 223[157], 262[159], 264[159], 500[132], 505[132], 579[98]; **6**, 2[3], 25[3]; **7**, 263[83], 677[66]; **8**, 123[86], 244[49], 331[37], 340[37], 626[171], 627[171], 871[1], 884[1]
Smith, J. K., **1**, 292[25], 357[1]; **2**, 476[4]; **3**, 31[185], 32[185]; **6**, 531[448], 720[130], 722[139]
Smith, J. L., **7**, 878[145]
Smith, J. N., **7**, 530[28], 531[28]
Smith, J. R. L., **6**, 923[57]; **8**, 336[85]
Smith, J. W., **8**, 880[59]
Smith, K., **1**, 489[14,18], 499[18,54], 501[54], 569[258]; **2**, 193[63], 240[12]; **3**, 124[261], 126[261], 554[22,23], 780[10], 797[95], 798[95-97]; **7**, 594[3,4], 595[3,22], 598[3,4], 600[75], 601[3], 604[134], 607[167]; **8**, 26[11,12], 27[11,12], 36[11], 37[11], 703[1], 704[1,2,4,5], 705[1,4,5], 706[1,4,5], 707[1,4], 708[1,38], 709[1], 710[4], 711[64,69], 712[1], 713[1], 715[1,4], 716[1,4], 717[1,4,101], 720[1], 721[1], 722[1,4], 724[1,4], 725[4], 726[4], 728[4]
Smith, K. D., **1**, 19[101]
Smith, K. M., **2**, 770[10], 771[10], 780[14], 1079[158]; **5**, 528[68], 531[68]; **7**, 256[25]; **8**, 851[128]
Smith, K. R., **2**, 477[11]; **5**, 906[70], 908[70]
Smith, L., **5**, 87[43,44]
Smith, L. B., **8**, 895[3], 898[3]
Smith, L. H., **6**, 209[68]
Smith, L. I., **4**, 41[118]; **8**, 269[93]
Smith, L. L., **7**, 96[87]
Smith, L. R., **3**, 901[106]; **6**, 429[88]; **8**, 119[76]
Smith, M., **3**, 734[4]; **4**, 181[74]; **6**, 603[12], 1042[10]; **8**, 212[19], 340[89], 524[9], 530[9], 531[9]
Smith, M. A., **7**, 750[136]; **8**, 35[63], 66[63]
Smith, M. B., **5**, 500[256]
Smith, M. G., **1**, 829[88]; **5**, 841[90], 859[90]; **6**, 750[103]
Smith, M. J., **4**, 887[130,130b]
Smith, M. R., **7**, 765[146], 851[23]; **8**, 383[15]
Smith, N. M., **8**, 388[66], 637[11]
Smith, N. P., **6**, 566[928]
Smith, N. R., **7**, 720[8]
Smith, P., **6**, 737[34,35]; **8**, 315[51]
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Smith, P. A. S., **1**, 360[26], 364[26], 846[15], 847[15], 848[15], 850[15]; **2**, 748[128], 759[28]; **3**, 781[11], 823[14], 835[14]; **6**, 116[90], 245[125], 249[125], 763[3], 795[2,8], 797[8], 798[8], 799[2], 806[8], 807[8]; **7**, 21[5,7], 35[5,7,105], 475[54], 671[4], 689[8]; **8**, 363[8], 372[116], 385[46], 387[59]
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Smith, P. J., **3**, 794[79]; **4**, 1089[132]; **6**, 662[216]; **7**, 614[5]
Smith, P. W., **6**, 273[98]
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Smith, R. A. J., **1**, 114[38], 511[31]; **2**, 185[31]; **4**, 11[36], 113[171], 243[67], 244[67], 260[67], 261[67], 279[117]; **6**, 134[20], 140[56], 831[9]; **8**, 526[26]
Smith, R. C., **6**, 487[70]
Smith, R. D., **4**, 969[63]; **8**, 756[140]
Smith, R. F., **6**, 516[318]; **7**, 744[69]
Smith, R. G., **3**, 124[277]; **4**, 429[83], 438[83], 441[83]; **6**, 1000[125]; **8**, 32[54], 66[54]
Smith, R. H., **6**, 530[416]
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Smith, R. L., **2**, 971[92]; **8**, 803[91]
Smith, R. S., **1**, 223[85], 224[85]; **3**, 437[20], 438[20], 439[20], 441[20], 442[20]; **4**, 240[41], 897[172]
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Smith, S. E., **2**, $547^{96}$, $551^{96}$
Smith, S. F., **1**, $287^{15}$
Smith, S. G., **1**, $477^{133,134}$; **3**, $67^{17,20}$; **4**, $171^{28}$; **7**, $225^{63}$; **8**, $2^{12}$
Smith, S. J., **2**, $85^{23}$
Smith, S. W., **6**, $677^{315}$
Smith, T. A. K., **4**, $799^{118}$
Smith, T. H., **8**, $354^{171}$
Smith, T. K., **4**, $1033^{27}$, $1049^{27}$, $1060^{27b}$; **5**, $599^{40}$; **6**, $126^{149}$
Smith, T. L., **2**, $464^{97}$
Smith, W. A., **6**, $141^{64}$
Smith, W. B., **3**, $647^{179,191,192,193}$, $648^{179}$, $724^{12}$; **8**, $877^{46}$
Smith, W. E., **2**, $772^{17}$; **3**, $723^{10}$; **8**, $767^{23}$
Smith, W. H., **8**, $594^{71}$
Smithen, C. E., **4**, $1021^{247}$
Smithers, R., **2**, $1030^{80}$; **6**, $832^{12}$, $865^{12}$
Smithers, R. H., **2**, $564^{3}$, $712^{43}$; **5**, $595^{10}$; **6**, $89^{107}$, $569^{935}$
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Smith-Strickland, S. M., **1**, $584^{9}$; **2**, $714^{50}$
Smithwick, E. L., Jr., **4**, $496^{88}$
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Smoot, J., **8**, $413^{125}$
Smurny, G. N., **6**, $245^{124}$
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Smyrniogtis, P. Z., **2**, $456^{65,71}$, $458^{65,71}$
Smyser, T. E., **2**, $355^{119}$
Smyth, M. S., **7**, $463^{128}$
Smythe, G. A., **6**, $737^{32}$
Smythe, J. A., **7**, $194^{2}$, $202^{2}$
Snader, K. M., **8**, $92^{68}$
Snaith, R., **1**, $6^{33}$, $33^{165}$, $38^{258}$, $39^{187}$; **3**, $763^{151}$
Snapper, M. L., **5**, $640^{129}$
Snatzke, G., **2**, $553^{128}$; **5**, $1146^{108}$; **7**, $252^{11}$, $649^{44}$
Snead, T. E., **5**, $225^{98}$
Sneed, R., **5**, $95^{91}$
Sneeden, R. P. A., **1**, $173^{1}$, $174^{14}$, $175^{16}$, $179^{14}$
Sneen, R. A., **3**, $12^{64}$; **8**, $340^{99}$
Sneen, R. H., **7**, $101^{133}$
Snell, J. M., **3**, $619^{22}$
Snider, B. B., **1**, $885^{132}$; **2**, $527^{8,9}$, $528^{8,9,13}$, $531^{24,25,27,28}$, $533^{24,29,30}$, $534^{25}$, $535^{40}$, $537^{24}$, $538^{27,51,52}$, $541^{76}$, $542^{40,52}$, $544^{76}$, $546^{76}$, $547^{52,76,98,99,105,118\text{-}120}$, $548^{98,99}$, $550^{98,105}$, $551^{118\text{-}120}$, $552^{120}$, $555^{139,144,145}$, $709^{8}$, $910^{65}$; **3**, $244^{26}$, $485^{28}$, $978^{11}$, $994^{44}$; **4**, $181^{69}$, $377^{104}$, $764^{216}$, $807^{148,153,154}$, $820^{217}$, $879^{84}$, $892^{144}$, $904^{206}$; **5**, $2^{6,7,11}$, $4^{7,30,35\text{-}38}$, $5^{30,35,36,40,41,44,46,47}$, $6^{46\text{-}48}$, $7^{53,54}$, $8^{44,54,56\text{-}59,61,62}$, $9^{72,74}$, $10^{78}$, $12^{88}$, $13^{89}$, $15^{48,103}$, $16^{111}$, $18^{111}$, $19^{74}$, $20^{48}$, $63^{12}$, $429^{113a}$, $433^{137c}$, $435^{137c}$, $461^{100,104}$, $463^{100}$, $519^{35}$, $527^{59,60}$, $796^{56}$, $835^{61}$, $1018^{67}$, $1021^{71}$, $1022^{67}$, $1029^{92}$; **6**, $154^{147}$; **7**, $46^{48\text{-}50}$, $47^{50,52}$, $552^{59}$; **8**, $61^{188}$, $66^{188}$
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Snitman, D. L., **1**, $410^{43}$; **2**, $2^{7}$, $100^{13}$, $224^{153}$, $630^{9}$; **8**, $334^{62}$
Sno, M. H. A. M., **2**, $1064^{108}$
Snoble, K. A. J., **8**, $885^{104}$
Snoddy, H. D., **8**, $623^{151}$
Snook, M. E., **7**, $13^{123}$
Snow, A. I., **1**, $13^{66}$
Snow, A. W., **6**, $244^{107}$
Snow, D. H., **7**, $882^{171}$
Snow, J. T., **4**, $889^{137}$; **8**, $717^{96}$, $726^{195}$, $755^{132}$
Snow, R. A., **5**, $203^{39,39a\text{-}d}$, $209^{39}$, $210^{39}$; **7**, $667^{80}$
Snowden, R. L., **1**, $754^{106}$; **2**, $69^{48}$, $553^{123}$; **3**, $196^{32}$, $264^{184}$, $345^{22}$; **5**, $253^{46,46c}$, $331^{40}$, $456^{83}$, $515^{17}$, $518^{17}$, $547^{17}$; **6**, $1067^{108,109}$; **8**, $61^{189}$, $66^{189}$
Snyder, D. C., **8**, $778^{83}$
Snyder, E. I., **6**, $205^{35}$
Snyder, E. S., **2**, $489^{48}$, $490^{48}$
Snyder, H. R., **2**, $355^{121}$, $356^{130}$, $753^{4}$, $838^{174}$, $839^{174}$, $933^{138}$, $970^{87}$, $1090^{61}$; **4**, $438^{153}$; **5**, $473^{149}$; **6**, $825^{127}$; **7**, $595^{8}$; **8**, $637^{12}$
Snyder, J. K., **5**, $343^{64}$; **7**, $166^{89}$, $441^{43}$, $442^{43}$
Snyder, J. P., **5**, $736^{145}$, $737^{145}$, $741^{153}$; **6**, $448^{106,107}$, $691^{404}$, $692^{404}$; **7**, $747^{105}$, $751^{137}$; **8**, $50^{117}$, $66^{117}$, $365^{27}$, $390^{81}$
Snyder, R., **8**, $705^{10}$, $726^{10}$
Snyder, R. G., **5**, $900^{7}$
So, J.-H., **3**, $565^{16}$, $578^{16}$
So, Y. H., **3**, $683^{101}$; **6**, $282^{153,156}$; **7**, $799^{25}$, $800^{25a,32}$
Soai, K., **1**, $62^{40}$, $63^{42}$, $70^{64}$, $71^{65}$, $72^{66\text{-}68}$, $86^{34\text{-}36}$, $141^{22}$, $223^{75,79\text{-}81,83}$, $224^{79\text{-}81,83}$, $317^{146,147}$, $319^{147}$; **4**, $85^{71}$, $158^{78}$, $203^{27\text{-}30}$, $230^{254,255}$; **6**, $76^{44}$; **8**, $13^{70}$, $170^{86\text{-}88}$, $178^{86}$, $179^{86}$, $241^{36}$, $244^{55,59}$, $248^{55}$, $250^{59}$, $384^{34}$, $412^{110}$, $643^{38}$, $874^{25,26,28}$, $875^{28,30}$
Soares, C. J., **5**, $829^{20}$, $864^{261}$
Sobała, M. C., **7**, $779^{421}$
Sobata, T., **4**, $587^{30}$
Sobczak, A., **5**, $365^{96a}$
Sobieray, D. M., **8**, $542^{221}$
Sobolov, S. B., **2**, $547^{107}$, $550^{107}$
Sobota, P., **1**, $303^{81}$; **3**, $563^{1}$
Sobotka, W., **4**, $310^{429}$
Sobotta, R., **6**, $518^{333}$, $519^{333}$
Sobti, R., **3**, $715^{37}$; **7**, $676^{64}$
Sobukawa, M., **6**, $501^{193}$
Soccolini, F., **2**, $435^{59}$; **5**, $1153^{145}$; **8**, $91^{54}$, $589^{53}$
Sochacka, R., **7**, $775^{350}$
Sochneva, E. O., **6**, $553^{728}$, $554^{728,729,785,792}$
Sodano, C. S., **8**, $533^{154}$
Sodeoka, M., **2**, $547^{94}$; **7**, $399^{40b}$, $410^{96}$; **8**, $452^{188}$, $457^{188}$, $554^{367}$, $555^{367c}$, $567^{458}$
Soderberg, B. C., **4**, $600^{239}$, $625^{239}$, $643^{239}$
Soderquist, J. A., **1**, $438^{160}$, $544^{41,42}$, $563^{181}$; **3**, $252^{83}$; **7**, $597^{48}$, $598^{55}$, $641^{5}$; **8**, $707^{21}$, $713^{70,76}$, $717^{101}$, $718^{116}$, $856^{169}$
Sodeyama, T., **7**, $6^{31}$
Sodhi, K. S., **2**, $742^{73,74}$
Sodola, F. H., **4**, $279^{113}$, $282^{113}$
Soeda, M., **8**, $598^{98,99}$
Soeder, R. W., **1**, $878^{107}$
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Soelch, R. R., **6**, $516^{318}$
Soeldner, J. S., **6**, $790^{117}$
Soerens, D., **2**, $1017^{31,34}$; **6**, $737^{31}$, $746^{89}$

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Soll, R. M., 1, 343$^{109}$, 568$^{232}$
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Stacey, N. A., **1**, 568[228]; **6**, 1028[98]
Stach, H., **1**, 843[2a], 898[2a]
Stache, U., **7**, 124[42]
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Stackebrandt, J., **2**, 1090[72]
Stacy, G. W., **1**, 226[95]; **7**, 760[39]
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Stadler, P. A., **3**, 126[311,312], 346[23], 351[39]; **6**, 494[136], 919[39]
Stadlwieser, J., **5**, 329[31]; **6**, 119[113]; **7**, 746[92], 752[92]
Staeglich, H., **1**, 38[256]
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Stahl, G. L., **6**, 637[30]
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Stajer, G., **5**, 583[186], 584[194]
Stakem, F. G., **4**, 598[186], 638[186], 839[25], 850[84], 855[96], 856[98], 904[205]
Staklis, A., **6**, 802[43], 803[43]
Staley, R. H., **1**, 287[16]
Staley, S. W., **5**, 901[22]; **6**, 953[11], 969[119]
Stalke, D., **1**, 38[183]
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Stallman, B., **4**, 850[85]
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Stam, C. H., **1**, 25[126], 28[140], 41[269]; **3**, 210[25], 211[32]; **4**, 170[12]
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Stamm, H., **2**, 283[47]; **6**, 94[145], 95[146], 96[148]; **7**, 470[9], 487[9], 495[205]; **8**, 563[436]
Stamm, W., **8**, 754[95]
Stammer, C. H., **4**, 345[84], 611[358], 988[137]; **6**, 804[48]
Stamos, I. K., **6**, 930[86]; **7**, 200[38]
Stamouli, P., **4**, 764[222], 765[222], 808[155]
Stamper, J. G., **1**, 17[91]
Stämpfli, U., **4**, 1007[120], 1008[134], 1009[135]
Stanaback, R. J., **7**, 664[65]
Stanaszek, R. S., **8**, 27[30], 66[30]
Stancino, J.-P., **1**, 804[308], 805[308]
Standnichuk, M. D., **8**, 772[54]
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Stanford, R. H., Jr., **4**, 665$^{10}$, 667$^{10}$, 670$^{10}$, 674$^{10}$
Stang, A. F., **8**, 754$^{83}$
Stang, P. J., **1**, 665$^{172}$, 668$^{172}$, 786$^{250}$; **2**, 725$^{113,117}$; **3**, 219$^{105}$, 380$^{4}$, 522$^{22}$; **4**, 250$^{134}$, 255$^{134}$, 260$^{134}$, 903$^{195}$; **6**, 19$^{68}$, 72$^{24}$, 504$^{221}$, 966$^{91\text{-}93}$; **8**, 933$^{46}$
Stange, A., **6**, 447$^{104}$, 451$^{104}$; **8**, 821$^{50,51}$
Stangeland, L. J., **6**, 242$^{94}$
Stangl, H., **3**, 893$^{53b}$; **7**, 451$^{34}$, 477$^{73}$
Stangle, H., **4**, 1081$^{75}$
Stanhop, B., **1**, 779$^{226}$
Stanier, A., **3**, 786$^{38}$
Staninets, V. I., **4**, 342$^{66,67}$, 364$^{1,1a\text{-}d,g}$, 367$^{1g}$, 368$^{1a}$, 373$^{1a,b}$, 386$^{153}$, 387$^{158}$, 391$^{177,178a,b}$, 395$^{1d}$, 397$^{1c}$, 399$^{1c}$, 400$^{228b}$, 407$^{255}$, 408$^{1c,259b}$, 409$^{259b}$, 410$^{1c}$, 413$^{1d,278c}$, 421$^{1c}$
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Stanley, D. R., **8**, 447$^{130}$
Stanley, G., **8**, 542$^{227}$
Stanley, K., **4**, 588$^{61}$
Stanley, P., **6**, 836$^{55}$
Stanley, W., **7**, 774$^{310}$
Stannard, A.-M., **5**, 500$^{260}$
Stanonis, D., **2**, 1085$^{22}$
Stanovnik, B., **3**, 904$^{133}$; **6**, 480$^{114}$, 514$^{306}$, 543$^{306}$, 554$^{712,713,714,715,716,725,739,740,742,743,744,746,747,782}$; **7**, 475$^{53}$, 476$^{53}$; **8**, 384$^{31,32}$
Stansfield, F., **4**, 1018$^{221}$; **6**, 509$^{260}$, 523$^{347}$
Stanton, J., **3**, 933$^{61}$; **8**, 93$^{76}$, 618$^{120}$
Stanton, J. L., **4**, 159$^{85}$; **8**, 35$^{66}$, 66$^{66}$
Stanton, S. A., **4**, 597$^{180}$, 622$^{180}$
Stapleford, K. S. J., **8**, 212$^{21}$, 515$^{118}$, 605$^{13}$
Stapleton, A., **7**, 338$^{42}$
Stapp, P. R., **2**, 528$^{14,15}$, 553$^{15}$; **7**, 828$^{53}$; **8**, 598$^{96}$, 612$^{73}$, 624$^{73}$
Staral, J. S., **3**, 322$^{142a}$
Staring, E. G. J., **5**, 86$^{30}$, 88$^{30,46,47}$
Stark, C. J., Jr., **1**, 532$^{135}$, 740$^{43}$, 741$^{43}$; **3**, 173$^{521}$
Stark, H., **5**, 385$^{130}$
Stark, J. C., **4**, 476$^{155}$
Stark, S. R., **7**, 500$^{243}$
Stárka, L., **7**, 96$^{82,83}$
Starke, H. M., **1**, 561$^{157}$
Starkemann, C., **4**, 85$^{72}$, 204$^{33}$, 231$^{282}$, 249$^{120}$; **5**, 260$^{70}$, 263$^{70}$
Starkovsky, N. A., **6**, 643$^{79}$, 658$^{184}$, 709$^{54}$
Starks, C. M., **4**, 1001$^{27}$
Starling, W. W., **7**, 86$^{16a}$
Starner, W. E., **1**, 390$^{143}$; **2**, 994$^{40}$, 999$^{40}$
Staros, J. V., **7**, 21$^{18}$
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Starr, L. D., **1**, 226$^{95}$
Starratt, A. N., **7**, 27$^{62}$, 41$^{22}$
Starrett, J. E., **7**, 183$^{166}$
Starrett, J. E., Jr., **1**, 377$^{95}$; **2**, 1049$^{23}$, 1050$^{23}$
Starrett, R. M., **4**, 18$^{62}$, 20$^{62g}$
Stasi, F., **2**, 87$^{26}$, 213$^{127}$
Staskun, B., **3**, 369$^{117}$, 372$^{117}$; **8**, 298$^{76\text{-}78}$, 299$^{78,79}$
Stass, W. H., **7**, 823$^{38}$
Stassinopoulou, C. F., **3**, 565$^{20}$
Staticu, S., **4**, 600$^{234}$, 643$^{234}$
Staub, A., **2**, 399$^{18}$; **3**, 734$^{6}$; **6**, 650$^{128}$
Staudacher, W., **5**, 1096$^{127}$
Staudinger, H., **4**, 283$^{149}$; **5**, 90$^{52}$; **6**, 646$^{101}$
Staudinger, J. J. P., **4**, 292$^{227}$
Stauffacher, D., **3**, 345$^{20}$
Stauffer, R. D., **3**, 500$^{132}$, 505$^{132}$; **4**, 254$^{185}$, 476$^{162,163}$, 502$^{124}$, 766$^{229}$; **8**, 542$^{223}$, 544$^{223,251}$, 548$^{322}$
Staum, M. M., **3**, 782$^{20}$
Staunton, J., **4**, 14$^{47}$
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Stavinoha, J. L., **2**, 1037$^{96,99,100}$; **7**, 876$^{121}$
Stavrovskaya, V. I., **2**, 957$^{17}$
Stawinski, J., **6**, 603$^{23}$, 614$^{95}$, 620$^{133}$
Steadman, T. R., **2**, 662$^{12}$
Steblina, E. I., **8**, 624$^{155}$
Stec, W. J., **4**, 231$^{274}$; **6**, 604$^{27}$, 606$^{40}$; **8**, 72$^{242}$, 74$^{242,244}$, 393$^{110}$
Steckbeck, S. R., **8**, 884$^{97}$
Steckhan, E., **2**, 1051$^{39}$, 1075$^{39}$; **4**, 371$^{61}$; **6**, 561$^{874}$; **7**, 248$^{113}$, 795$^{9}$, 796$^{15}$, 797$^{17}$, 808$^{76}$; **8**, 85$^{17}$, 797$^{30}$
Stedronsky, E. R., **8**, 986$^{10}$
Steege, S., **3**, 322$^{142b}$; **7**, 7$^{50}$
Steel, P., **7**, 543$^{22}$
Steel, P. G., **1**, 568$^{228}$
Steel, P. J., **2**, 19$^{77,77b}$, 31$^{77b}$, 573$^{52}$
Steele, B. R., **3**, 194$^{12}$; **4**, 274$^{64}$, 275$^{64}$
Steele, D. R., **8**, 140$^{15}$
Steele, J., **2**, 650$^{111}$, 651$^{111a}$; **3**, 373$^{128}$
Steele, J. A., **3**, 406$^{143}$
Steele, R. B., **8**, 736$^{22}$, 740$^{22}$, 754$^{22}$, 756$^{142}$
Steele, R. W., **2**, 1050$^{27}$
Steen, K., **5**, 828$^{6}$, 836$^{6}$, 888$^{26}$, 893$^{26}$
Steenhoek, A., **8**, 431$^{63}$
Steenson, B. E., **2**, 350$^{72}$, 363$^{72}$
Stefanelli, S., **1**, 519$^{66}$, 520$^{67}$; **2**, 31$^{108}$; **7**, 442$^{47}$
Stefani, A., **4**, 887$^{131}$, 919$^{18,19}$; **5**, 31$^{5}$
Stefanovic, M., **3**, 313$^{103}$, 905$^{136}$; **7**, 92$^{41,41a}$, 94$^{41}$
Stefanovsky, Y. N., **4**, 21$^{68}$
Stefanska, B., **6**, 554$^{749}$, 789$^{110}$
Steffek, R. P., **7**, 62$^{53,53b,c}$; **8**, 192$^{97}$
Steffen, J., **3**, 348$^{30}$; **4**, 155$^{74}$
Steffens, J. J., **7**, 58$^{53a}$, 62$^{53,53a,c}$, 63$^{53a}$; **8**, 94$^{79}$, 192$^{97}$
Steffgen, F. W., **7**, 576$^{123}$
Stegelmeier, H., **2**, 371$^{264}$
Stegenga, S., **2**, 1050$^{30}$, 1072$^{30}$
Steglich, W., **1**, 122$^{72}$, 373$^{83,85\text{-}87,89}$, 374$^{85\text{-}87}$, 375$^{89}$; **2**, 1052$^{46}$, 1077$^{153}$; **4**, 12$^{40}$, 42$^{120}$; **5**, 480$^{176}$, 485$^{182}$, 877$^{6}$; **6**, 437$^{37}$, 523$^{352}$, 524$^{352}$, 642$^{74}$, 657$^{176}$, 716$^{104}$, 745$^{79}$
Stegmann, H. B., **3**, 661$^{22}$
Steigel, A., **5**, 257$^{60}$, 498$^{228,229,234,235}$, 714$^{74}$
Steigerwald, M. L., **1**, 880$^{116}$; **5**, 788$^{14}$, 849$^{142}$, 1000$^{8}$
Steiman, R., **7**, 79$^{131}$
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Stein, A. R., **6**, 295$^{246}$, 529$^{465}$
Stein, C. A., **7**, 762$^{77}$
Stein, G., **5**, 451$^{4,6}$
Stein, H., **2**, 223$^{148}$
Stein, J., **6**, 487$^{66}$, 489$^{66}$
Stein, J.-L., **7**, 499$^{233}$; **8**, 798$^{47}$
Stein, N. L., **8**, 639$^{18}$
Stein, P. D., **2**, 465$^{106}$
Stein, P. M., **8**, 320$^{80}$
Stein, U., **7**, 874$^{105}$
Steinacker, K. H., **6**, 673$^{288}$
Steinbach, G., **6**, 839$^{70}$
Steinbach, K., **2**, 33$^{121}$
Steinbach, R., **1**, 83$^{26}$, 141$^{21}$, 145$^{21,41,42}$, 146$^{21,42}$, 148$^{42,46}$, 149$^{21,42}$, 150$^{41,46}$, 151$^{21,41,53,53a}$, 152$^{21,53,53a}$, 153$^{41,59}$, 154$^{41,59}$, 155$^{42}$, 157$^{53a}$, 158$^{53,53a}$, 165$^{46}$,

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Steinberg, H., **1**, $528^{114}$; **3**, $727^{27}$; **5**, $77^{263}$; **7**, $602^{105}$; **8**, $719^{124}$
Steinberg, I. V., **3**, $643^{127}$
Steinberg, M., **8**, $530^{93}$
Steinberg, N. G., **3**, $890^{32}$
Steinborn, D., **1**, $215^{33}$
Steinbrückner, C., **2**, $1087^{36,37}$, $1088^{37,50}$, $1089^{50,55}$, $1090^{36,55}$, $1100^{55}$
Steindl, F., **6**, $443^{90}$
Steindl, H., **3**, $380^{7}$
Steiner, E., **4**, $754^{175}$
Steiner, G., **5**, $76^{238}$, $77^{245}$, $78^{276,278}$
Steiner, H., **5**, $703^{16a}$, $709^{16a}$
Steiner, R. P., **5**, $804^{93}$
Steiner, U., **5**, $1130^{8}$
Steinlein, E., **5**, $1066^{8}$
Steinman, D. H., **1**, $805^{312}$; **5**, $245^{21}$, $308^{97}$
Steinman, D. M., **6**, $990^{84}$
Steinmetz, A., **7**, $842^{38}$
Steinmetz, M. G., **5**, $204^{40}$, $209^{55}$
Steinmetz, R., **4**, $1058^{148}$; **5**, $167^{98}$
Steinmüller, D., **3**, $124^{283,284}$, $125^{283,284}$, $127^{283}$, $132^{283}$
Steinwand, P. J., **4**, $947^{94}$
Steinweg, E., **6**, $1035^{139,140}$
Stelakatos, G. C., **6**, $666^{232}$, $667^{232}$, $668^{252}$, $669^{252}$
Steliou, K., **3**, $693^{141}$; **6**, $938^{124}$; **7**, $336^{34}$
Stella, L., **1**, $557^{130}$; **4**, $758^{189}$, $812^{180}$, $820^{220}$; **5**, $70^{111,112}$; **6**, $495^{142,143}$, $496^{143}$, $497^{143}$; **7**, $499^{233}$; **8**, $798^{47}$
Stelling, G. D., **3**, $358^{66}$
Steltenkamp, R. J., **7**, $816^{11}$
Stelzel, P., **6**, $665^{226}$, $667^{226}$, $668^{226}$, $669^{226}$
Stemke, J. E., **1**, $377^{97}$; **2**, $588^{150}$; **3**, $251^{79}$, $254^{79}$; **6**, $781^{78}$
Stemniski, M. A., **7**, $698^{52}$
Stenberg, J. F., **8**, $251^{105}$
Stener, A., **3**, $503^{149}$, $512^{149}$
Stenger, R. J., **2**, $741^{64}$
Stenhagen, E., **3**, $643^{129}$
Stenkamp, R. E., **8**, $89^{45}$
Stensiö, K.-E., **7**, $820^{24}$
Stenstrøm, Y., **5**, $19^{130}$
Stenvall, K., **5**, $686^{53}$
Stenzel, T. T., **4**, $475^{151}$
Stenzel, W., **6**, $41^{44}$
Step, G., **5**, $65^{67}$
Stepanov, B. I., **6**, $438^{50}$
Stepanov, D. E., **4**, $314^{487}$
Stepanov, F. N., **3**, $383^{47}$; **6**, $266^{53}$
Stepanov, R. G., **8**, $636^{5}$
Stepanova, E. E., **6**, $546^{645}$
Stepanova, I. P., **8**, $600^{106}$, $606^{25}$, $625^{25}$
Stepanyan, A. A., **6**, $712^{78}$
Stepanyan, G. M., **6**, $507^{237}$, $515^{237}$
Stephan, D., **5**, $386^{132,132d}$, $387^{132d}$; **6**, $977^{16}$; **8**, $28^{36}$, $66^{36}$
Stephan, E., **4**, $210^{74}$
Stephan, W., **6**, $519^{339}$; **7**, $144^{153,154}$
Stephanatou, J. S., **6**, $440^{73}$
Stephanian, M., **5**, $1123^{34}$
Stephanidou-Stephanatou, J., **8**, $636^{6}$
Stephen, E., **8**, $271^{109}$
Stephen, H., **8**, $271^{109}$, $298^{71}$
Stephens, C. J., **3**, $649^{190}$
Stephens, C. R., **6**, $265^{38}$
Stephens, F. A., **8**, $446^{67}$
Stephens, J. A., **8**, $974^{125}$
Stephens, J. C., **8**, $978^{143}$
Stephens, J. R., **4**, $310^{437,438}$
Stephens, R., **4**, $407^{256a}$; **7**, $760^{28}$
Stephens, R. D., **3**, $521^{4}$, $522^{4}$; **8**, $481^{50,51}$, $482^{50,51}$, $483^{51}$, $531^{120}$
Stephens, T. B., **6**, $147^{82}$; **7**, $210^{96}$, $211^{96}$, $212^{96}$
Stephenson, B., **6**, $206^{43}$, $210^{43}$, $214^{43}$
Stephenson, D. S., **8**, $335^{67}$
Stephenson, G. R., **4**, $665^{9}$, $670^{15,16}$, $675^{41}$, $688^{9,65,66}$, $691^{75}$; **6**, $690^{403}$, $692^{403}$
Stephenson, L., **3**, $804^{13}$; **8**, $987^{23}$
Stephenson, L. M., **2**, $528^{11}$; **5**, $2^{9}$, $64^{38}$, $640^{127}$; **7**, $86^{14}$, $816^{10}$, $818^{10}$, $819^{19}$
Stephenson, M., **3**, $334^{221,221a}$
Stephenson, M. A., **5**, $942^{235}$
Stephenson, R. A., **3**, $279^{39}$, $770^{172}$; **6**, $247^{131}$
Stephenson, R. W., **4**, $190^{107}$
Stepovik, L. P., **8**, $753^{68}$
Steppan, H., **3**, $887^{12}$, $904^{132}$
Steppan, W., **2**, $681^{58}$, $683^{58}$; **6**, $502^{217}$, $560^{870}$; **7**, $650^{51}$
Steppel, R. N., **3**, $739^{41}$
Stepuk, E. S., **4**, $314^{487}$
Stercho, Y. P., **8**, $26^{28}$, $30^{28}$, $36^{28}$, $37^{28}$, $40^{28}$, $43^{28}$, $44^{28}$, $46^{28}$, $55^{28}$, $66^{28}$, $74^{245}$, $176^{136}$, $244^{67}$, $250^{67}$, $357^{204}$, $393^{110}$
Sterk, H., **4**, $4^{16,16b}$
Sterling, J. J., **1**, $432^{135}$; **2**, $121^{187}$; **3**, $8^{41}$, $9^{41}$, $15^{41}$, $20^{41}$, $212^{39}$, $226^{39a}$, $250^{70}$; **4**, $176^{49}$, $178^{49,61}$, $245^{87}$, $256^{206,211}$; **5**, $595^{13}$
Stermitz, F. R., **3**, $461^{144}$, $683^{101}$, $685^{106,107}$; **4**, $505^{147,148}$; **7**, $801^{41}$, $873^{99}$
Stermitz, T. A., **4**, $505^{148}$
Stern, A., **2**, $770^{10}$, $771^{10}$
Stern, A. G., **1**, $856^{55}$
Stern, A. J., **4**, $143^{21}$
Stern, E. W., **8**, $447^{101,102}$, $450^{101,102}$
Stern, M., **3**, $302^{51}$; **6**, $246^{130}$
Stern, P., **5**, $724^{111}$
Stern, R., **3**, $262^{166}$; **8**, $445^{25,26}$, $452^{25,26}$
Sternbach, D., **6**, $83^{78}$, $1056^{56}$; **7**, $668^{82,84}$
Sternbach, D. D., **5**, $534^{95}$; **8**, $63^{198}$, $64^{198}$, $66^{198}$, $67^{198}$, $69^{198}$
Sternbach, L. H., **1**, $130^{96}$; **6**, $922^{52}$
Sternberg, E., **5**, $291^{43}$, $1144^{96,97}$, $1190^{29}$, $1192^{29}$
Sternberg, E. D., **4**, $691^{77}$, $898^{176}$
Sternberg, H. W., **5**, $1138^{67}$
Sternberg, J. A., **1**, $768^{170}$; **4**, $253^{168}$
Sternerup, H., **2**, $1051^{35}$, $1052^{35}$
Sternfeld, E., **8**, $505^{75}$
Sternfeld, F., **3**, $174^{527,527a}$, $175^{527a}$; **7**, $363^{34}$
Sternhell, S., **2**, $345^{29}$; **3**, $505^{160}$; **5**, $468^{135}$; **7**, $352^{31}$, $356^{31}$, $649^{45}$; **8**, $501^{53}$, $507^{53}$, $937^{80,83}$
Sterzycki, R., **4**, $310^{429}$
Stetin, C., **4**, $221^{159}$; **6**, $726^{180}$
Stetter, H., **1**, $542^{7}$, $543^{7}$, $546^{7}$, $547^{7}$, $548^{7}$, $556^{7}$; **2**, $342^{6}$, $354^{104}$, $363^{188}$; **3**, $383^{44}$, $890^{34}$, $903^{126}$; **4**, $8^{29,29e}$, $12^{39}$, $13^{45}$, $14^{45b,46}$, $18^{57}$; **6**, $267^{58,59}$, $269^{76}$, $563^{893,894,904}$, $567^{931}$, $673^{288}$, $681^{335}$, $682^{336}$; **7**, $17^{175,176}$; **8**, $388^{62}$
Steudle, H., **2**, $283^{47}$
Steudle, O. W., **8**, $100^{116}$, $739^{33}$
Steven, D. R., **4**, $307^{392}$
Stevenaert, N., **3**, $963^{124}$
Stevenart-De Mesmaeker, N., **4**, $795^{82}$

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Stevens, C. L., **3**, 740$^{45}$, 790$^{58,60}$, 842$^{21}$, 843$^{23}$; **4**, 274$^{59}$, 282$^{59}$; **6**, 622$^{135}$, 959$^{48}$; **7**, 168$^{104,106}$, 170$^{106}$, 272$^{142}$, 276$^{148}$, 656$^{16}$
Stevens, C. M., **6**, 640$^{56}$, 641$^{56}$
Stevens, D. R., **7**, 7$^{38}$
Stevens, H. C., **6**, 204$^{18}$
Stevens, I. D. R., **5**, 428$^{108}$, 429$^{112}$, 679$^{20}$; **6**, 566$^{928}$
Stevens, J. A., **5**, 486$^{185}$, 487$^{185}$
Stevens, K. D., **4**, 272$^{37}$, 273$^{37}$
Stevens, K. E., **2**, 728$^{146}$; **5**, 225$^{87,88}$, 231$^{87,88,132}$
Stevens, M. F. G., **6**, 554$^{803}$
Stevens, R. E., **7**, 760$^{43}$
Stevens, R. V., **2**, 1011$^{10,11}$, 1013$^{18}$, 1015$^{20}$, 1016$^{29}$; **3**, 287$^{61}$; **4**, 510$^{168,169}$; **5**, 249$^{33}$, 692$^{91}$, 696$^{91}$, 945$^{254,255}$, 946$^{254,255,256}$, 947$^{255,256,258,260,261}$, 952$^{255,256}$, 959$^{313,314,315,316,317}$, 960$^{258,260,320}$, 961$^{261,317,322}$, 962$^{322}$; **6**, 284$^{175}$, 937$^{117}$, 939$^{117}$, 940$^{117}$, 1059$^{70}$, 1066$^{70,92}$; **7**, 318$^{61}$, 376$^{83}$; **8**, 34$^{59}$, 56$^{166}$, 66$^{59,166}$
Stevens, R. W., **2**, 116$^{127,130,137}$, 117$^{144}$, 436$^{68}$, 437$^{68}$, 610$^{90,92}$, 611$^{92}$; **4**, 100$^{125}$
Stevens, T. B., **7**, 207$^{75}$, 208$^{75}$
Stevens, T. E., **6**, 803$^{45}$; **7**, 229$^{114}$, 502$^{265}$
Stevens, T. S., **3**, 822$^{8}$, 836$^{8}$, 913$^{1,2}$, 914$^{3-5}$, 921$^{35}$, 927$^{53}$; **6**, 283$^{161}$, 786$^{95}$, 961$^{69,70}$; **8**, 297$^{64}$
Stevenson, B. K., **8**, 340$^{97}$
Stevenson, D., **8**, 974$^{129}$
Stevenson, D. P., **3**, 332$^{207}$
Stevenson, J. R., **3**, 386$^{67}$
Stevenson, J. W. S., **1**, 749$^{80}$; **5**, 850$^{149}$, 1123$^{37}$
Stevenson, P., **3**, 484$^{21}$; **4**, 753$^{173}$, 848$^{78}$, 854$^{93}$; **5**, 1149$^{125}$
Stevenson, P. J., **3**, 955$^{106}$; **6**, 897$^{99}$
Stevenson, R., **3**, 219$^{112}$, 676$^{75,76}$, 692$^{138}$, 693$^{142}$; **8**, 566$^{450}$
Stevenson, R. W., **8**, 828$^{76}$
Stevenson, T., **1**, 313$^{118}$; **2**, 924$^{108b}$; **3**, 46$^{252}$; **4**, 152$^{54}$, 201$^{14,15}$, 202$^{14,15}$, 204$^{34}$, 850$^{85}$; **6**, 879$^{42}$; **7**, 646$^{27}$; **8**, 784$^{112}$
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Stewart, O. J., **3**, 499$^{112}$
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Stewart, R., **4**, 274$^{58}$; **7**, 12$^{105,106}$, 578$^{150}$, 851$^{19}$
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Stilbs, P., **1**, 293$^{35,36}$
Stiles, A. B., **7**, 247$^{96}$
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Stille, C., **6**, 455$^{149}$
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Takeuchi, Y., **1**, 619$^{62}$; **2**, 635$^{46}$, 640$^{46}$, 836$^{160}$; **4**, 341$^{55}$, 1093$^{145}$; **5**, 480$^{177}$, 483$^{174}$; **6**, 20$^{75}$, 91$^{128}$, 109$^{39-41}$, 150$^{128}$, 466$^{46}$, 564$^{916}$, 624$^{144}$; **7**, 475$^{57}$, 496$^{217}$, 497$^{218}$, 522$^{39}$; **8**, 395$^{129}$
Takeue, S., **4**, 507$^{153}$
Takeya, T., **3**, 676$^{77}$, 695$^{153}$, 696$^{154}$
Takeyama, T., **1**, 259$^{29}$, 260$^{32,32a}$, 261$^{32a}$, 829$^{87}$, 831$^{104}$; **8**, 803$^{92}$
Takezawa, K., **4**, 239$^{26}$, 251$^{26}$, 257$^{26}$; **5**, 583$^{183}$
Taki, H., **7**, 227$^{88}$, 314$^{40}$, 315$^{40}$
Taki, K., **3**, 295$^{8}$
Takido, T., **6**, 443$^{89}$, 493$^{139}$, 508$^{285}$; **8**, 323$^{113}$
Takigawa, H., **7**, 57$^{22}$
Takigawa, T., **3**, 17$^{87}$, 124$^{263}$, 126$^{263}$; **4**, 1005$^{88}$, 1020$^{235}$; **6**, 657$^{177}$, 836$^{50}$; **7**, 682$^{83,84}$
Takikawa, Y., **5**, 442$^{185}$
Takinami, S., **3**, 251$^{78}$, 254$^{78}$, 490$^{66}$, 511$^{66}$, 515$^{66}$; **4**, 286$^{174}$, 287$^{174}$, 290$^{174}$, 358$^{158}$
Takino, T., **5**, 915$^{113}$
Takino, Y., **4**, 231$^{277}$
Takita, S., **7**, 132$^{96}$, 158$^{36a}$

Takita, T., **2**, 917$^{85}$; **7**, 489$^{173}$
Takita, Y., **8**, 132$^{7}$
Takiura, K., **4**, 309$^{418}$, 314$^{494}$
Takiyama, N., **1**, 232$^{12}$, 234$^{12,21}$, 248$^{61,62}$, 260$^{32}$, 261$^{32c}$, 332$^{53}$, 735$^{25}$; **4**, 973$^{86}$
Takizawa, T., **5**, 1130$^{3}$; **8**, 797$^{34}$
Takken, H. J., **2**, 782$^{17,21}$; **3**, 251$^{79}$, 254$^{79}$; **8**, 535$^{161}$, 542$^{229}$, 946$^{139}$
Takle, A., **6**, 989$^{76}$
Takuma, K., **6**, 1066$^{97}$
Takundwa, C., **3**, 531$^{87}$, 538$^{87}$
Takusagawa, F., **1**, 838$^{161,167}$; **5**, 417$^{62}$, 420$^{62}$
Takyu, M., **6**, 87$^{102}$
Tal, D., **7**, 842$^{31}$, 843$^{42}$
Talakvadze, T. G., **8**, 772$^{60}$
Talamas, F. X., **6**, 677$^{314}$
Talanov, V. N., **6**, 546$^{645}$
Talanov, Yu. M., **8**, 150$^{132}$
Talapatra, B., **3**, 396$^{112}$, 398$^{112}$
Talapatra, S. K., **3**, 396$^{112}$, 398$^{112}$
Talaty, E. R., **1**, 420$^{85}$
Talbert, J., **1**, 212$^{8}$, 213$^{8}$, 432$^{138}$, 433$^{138}$; **2**, 450$^{50}$; **4**, 175$^{42}$
Talbiersky, J., **4**, 121$^{205a}$
Talbot, H. P., **4**, 282$^{140}$, 288$^{140}$
Tallec, A., **8**, 135$^{47}$, 136$^{47}$, 137$^{59}$
Talley, J. J., **1**, 846$^{17}$; **4**, 48$^{139}$; **5**, 468$^{136}$, 534$^{95}$, 585$^{203}$
Tallman, E. A., **4**, 14$^{48}$
Talma, A. G., **8**, 95$^{91}$, 96$^{92}$
Talwalker, P. K., **6**, 543$^{618}$
Talwar, K. K., **8**, 338$^{92}$, 339$^{92}$
Tam, C. C., **2**, 72$^{79}$; **3**, 131$^{325}$; **4**, 113$^{164}$, 259$^{256}$; **5**, 885$^{19}$
Tam, J. P., **6**, 637$^{32,32d}$
Tam, K.-F., **5**, 63$^{15}$, 123$^{1}$, 126$^{1}$; **7**, 815$^{4}$, 824$^{4}$, 833$^{4}$
Tam, S. W., **6**, 765$^{18}$
Tam, S. Y.-K., **6**, 553$^{795}$, 554$^{795}$, 987$^{69}$; **7**, 318$^{53}$, 319$^{53}$; **8**, 219$^{80}$, 965$^{69}$
Tam, T.-F., **2**, 827$^{127}$; **3**, 217$^{92}$; **4**, 394$^{189,189c}$
Tam, W., **3**, 457$^{127}$, 458$^{134}$; **8**, 671$^{16}$, 684$^{96}$
Tamada, Y., **7**, 828$^{54}$
Tamagnan, G., **4**, 89$^{84j}$
Tamai, K., **3**, 245$^{32}$, 470$^{213}$, 476$^{213}$
Tamai, S., **2**, 116$^{140}$, 610$^{94}$, 611$^{94}$, 1059$^{78}$
Tamaki, K., **3**, 789$^{70}$; **7**, 773$^{309}$, 776$^{309}$
Tamano, H., **1**, 559$^{150}$; **2**, 1049$^{18}$
Tamano, T., **8**, 916$^{108}$, 917$^{108}$, 918$^{108}$, 920$^{108}$
Tamao, K., **1**, 113$^{30,32}$, 619$^{61}$, 624$^{85}$; **2**, 23$^{90,90b}$, 29$^{90b}$, 59$^{16}$, 584$^{118}$; **3**, 200$^{68}$, 225$^{184}$, 228$^{216,217,218,222}$, 229$^{225}$, 262$^{165}$, 436$^{3,10}$, 437$^{21,25,26}$, 438$^{31}$, 440$^{25}$, 448$^{25,96}$, 449$^{25,99,100}$, 450$^{25,26}$, 451$^{25,106}$, 452$^{25,106,107,111}$, 453$^{31}$, 457$^{129,130}$, 459$^{31,137,139}$, 460$^{107,130,137}$, 461$^{137}$, 464$^{171}$, 469$^{203}$, 470$^{203}$, 473$^{203}$, 483$^{16}$, 487$^{45}$, 492$^{74}$, 497$^{104}$, 503$^{145}$, 510$^{183,206}$, 513$^{205,206}$, 524$^{27}$; **4**, 116$^{188a}$, 120$^{202}$, 682$^{57}$, 840$^{34}$; **5**, 1132$^{19}$, 1183$^{55}$; **6**, 16$^{59,60}$, 17$^{59,63}$, 18$^{59,63}$; **7**, 172$^{129}$, 453$^{93}$, 455$^{93}$, 641$^{3}$, 642$^{8\text{-}12}$, 643$^{13\text{-}15}$, 644$^{16}$, 645$^{17\text{-}21}$, 647$^{34,36,38}$, 816$^{13}$; **8**, 764$^{10}$, 770$^{32}$, 772$^{52}$, 773$^{10,67}$, 782$^{105}$, 783$^{106,107,109}$, 787$^{119}$, 788$^{120,121}$
Tamaoka, T., **2**, 82$^{9}$, 374$^{275}$, 575$^{64}$
Tamara, K., **4**, 611$^{359}$
Tamara, Y., **4**, 948$^{95}$; **7**, 314$^{39}$
Tamariz, J., **1**, 552$^{83}$; **3**, 198$^{49}$
Tamarkin, D., **3**, 619$^{26,27}$
Tamaru, R., **4**, 599$^{218}$, 640$^{218}$
Tamaru, Y., **1**, 212$^{9}$, 213$^{9,15}$, 215$^{41}$, 216$^{41}$, 217$^{47}$, 327$^{12}$, 449$^{210}$; **2**, 185$^{30}$, 211$^{115}$, 215$^{115,133}$, 216$^{133,135}$, 217$^{30,136}$, 442$^{13,14}$, 449$^{13,14,49}$, 450$^{13,14,51}$, 867$^{15}$; **3**, 221$^{131}$, 231$^{242}$, 420$^{48,49}$, 443$^{61}$, 445$^{61}$, 463$^{157,159}$, 1023$^{23}$, 1032$^{70}$, 1033$^{71}$, 1040$^{103}$; **4**, 75$^{44a}$, 76$^{44c}$, 85$^{73}$, 100$^{122}$, 249$^{117,118}$, 257$^{117,118}$, 377$^{104}$, 379$^{104j,114,114b,115,115b}$, 380$^{104j,115b}$, 382$^{114b}$, 383$^{114b}$, 402$^{236}$, 403$^{237}$, 404$^{237}$, 408$^{259d}$, 413$^{114b}$, 557$^{14}$, 558$^{19}$, 564$^{41,42}$, 599$^{214,220}$, 606$^{308}$, 607$^{308}$, 642$^{220}$, 841$^{45}$, 858$^{109}$; **5**, 347$^{72,72a}$, 353$^{72a}$, 438$^{164}$, 791$^{26}$, 889$^{32}$; **6**, 425$^{65}$, 509$^{248,250}$, 538$^{567}$; **7**, 125$^{54}$, 503$^{273}$; **8**, 856$^{185}$
Tamary, T., **7**, 7$^{36}$
Tamás, J., **2**, 817$^{90}$, 851$^{223}$; **7**, 746$^{93}$
Tamasi, M., **2**, 1094$^{89}$, 1095$^{89}$
Tamasik, W., **7**, 166$^{87}$
Tamblyn, W. B., **8**, 240$^{33}$
Tamblyn, W. H., **3**, 920$^{34}$, 925$^{34a}$, 934$^{34}$; **4**, 1033$^{17,20}$, 1035$^{37,41}$, 1036$^{47,49}$, 1037$^{17,37}$; **6**, 873$^{9}$, 897$^{9b}$
Tamborski, C., **3**, 450$^{104}$, 457$^{128}$
Tamburasev, Z., **6**, 766$^{23}$; **7**, 698$^{51}$
Tamburini, H. J., **1**, 294$^{47}$
Tambute, A., **4**, 869$^{27}$, 870$^{27}$, 871$^{27}$, 877$^{27d}$
Tamm, C., **2**, 100$^{9}$; **3**, 736$^{25}$; **6**, 1062$^{80}$; **7**, 120$^{13}$, 123$^{13}$, 162$^{56}$, 180$^{160}$, 429$^{151}$; **8**, 315$^{45}$
Tammer, T., **2**, 1087$^{35}$
Tamnefors, I., **4**, 55$^{157}$, 56$^{157a}$
Tamori, S., **2**, 372$^{270}$, 373$^{270}$; **5**, 468$^{130}$
Tamoto, K., **2**, 810$^{59}$; **7**, 881$^{160}$
Tamres, M., **8**, 218$^{73}$, 221$^{73}$
Tamura, C., **6**, 566$^{927}$
Tamura, H., **2**, 547$^{108}$, 550$^{108}$; **3**, 635$^{44}$; **4**, 159$^{81}$; **5**, 79$^{288}$
Tamura, M., **2**, 633$^{31}$, 640$^{31}$; **3**, 210$^{23}$, 243$^{13}$, 244$^{19}$, 415$^{10}$, 418$^{10,25}$, 436$^{1,2,6}$, 437$^{24}$, 438$^{2}$, 464$^{24}$, 482$^{7}$, 494$^{84}$, 499$^{7}$; **4**, 158$^{79}$, 159$^{83}$, 161$^{90}$, 923$^{31}$, 924$^{31}$, 925$^{31}$; **5**, 1012$^{51}$; **6**, 658$^{184}$, 804$^{48}$; **7**, 595$^{21}$; **8**, 146$^{94}$, 535$^{166}$
Tamura, N., **2**, 157$^{122}$; **7**, 132$^{96}$, 158$^{36a}$
Tamura, O., **1**, 391$^{152}$; **2**, 611$^{102}$, 643$^{79}$, 644$^{79a}$, 647$^{88a,b}$; **4**, 161$^{91}$; **6**, 935$^{104}$; **7**, 202$^{46}$
Tamura, R., **1**, 759$^{128,129}$; **2**, 333$^{65}$, 334$^{68}$; **4**, 589$^{81,87,88}$, 598$^{81,191}$, 600$^{226}$, 638$^{81,191}$, 790$^{36}$; **5**, 1088$^{78}$, 1102$^{148}$, 1103$^{148}$; **6**, 1000$^{128,129}$; **7**, 883$^{174}$; **8**, 598$^{98}$, 969$^{98}$
Tamura, S., **6**, 552$^{690}$
Tamura, T., **2**, 249$^{84}$, 258$^{50}$, 348$^{56}$, 350$^{74}$, 362$^{56}$, 363$^{56}$; **8**, 159$^{108}$, 171$^{108}$, 178$^{108}$, 179$^{108}$, 350$^{143}$, 797$^{34}$
Tamura, Y., **1**, 63$^{43,44}$, 64$^{46}$, 242$^{49\text{-}51}$, 243$^{52}$, 391$^{152}$, 448$^{207}$, 474$^{100}$; **2**, 215$^{134}$, 556$^{152}$, 611$^{102}$, 643$^{79}$, 644$^{79a}$, 647$^{88a,b}$; **3**, 386$^{57}$, 904$^{134}$, 939$^{79}$; **4**, 14$^{46}$, 55$^{157}$, 57$^{157h}$, 75$^{44b}$, 125$^{216,216c}$, 155$^{75}$, 160$^{86a}$, 161$^{91}$, 163$^{97}$, 249$^{114}$, 257$^{114}$, 261$^{286}$, 304$^{356}$, 350$^{116,118}$, 562$^{33}$; **5**, 133$^{53,54}$, 439$^{170}$, 451$^{18}$, 470$^{18}$, 473$^{153}$, 477$^{153}$, 504$^{274}$, 838$^{74}$; **6**, 764$^{13}$, 846$^{105}$, 910$^{3}$, 930$^{87}$, 931$^{88,89}$, 935$^{104}$, 936$^{112}$; **7**, 199$^{34}$, 200$^{41}$, 202$^{46}$, 208$^{86}$, 209$^{89}$, 211$^{86}$, 382$^{108}$, 606$^{156}$, 746$^{90}$, 829$^{56,56c}$; **8**, 274$^{130}$, 568$^{466}$, 829$^{81}$, 837$^{14}$, 964$^{56}$
Tamura, Z., **1**, 34$^{168}$
Tamuru, R., **4**, 599$^{219}$, 641$^{219}$
Tan, C., **4**, 740$^{118}$
Tan, C. C., **4**, 487$^{43}$
Tan, E. W., **4**, 744$^{134}$
Tan, J. L., **8**, 455$^{205}$, 456$^{205a}$, 613$^{81}$, 629$^{81,184}$
Tan, S.-H., **6**, 529$^{465}$
Tan, S. L., **5**, 132$^{48}$
Tan, S. Y., **6**, 66$^{6}$
Tan, T. S., **7**, 412$^{106}$
Tanabe, K., **3**, 300$^{43}$
Tanabe, M., **2**, 505$^{8}$; **3**, 34$^{195}$; **5**, 835$^{59}$; **6**, 1043$^{15}$, 1059$^{15,63}$; **8**, 528$^{63}$, 531$^{116}$, 934$^{54}$, 938$^{54}$, 948$^{149}$, 993$^{57}$

Tanabe, T., **8**, $150^{131}$
Tanabe, Y., **2**, $802^{38}$; **3**, $470^{207}$, $473^{207}$; **8**, $287^{16}$
Tanác, B., **7**, $764^{120}$
Tanaguchi, M., **7**, $335^{32}$
Tanahashi, Y., **3**, $741^{50}$
Tanaka, A., **7**, $415^{115b}$
Tanaka, C., **4**, $792^{65}$
Tanaka, H., **1**, $101^{90}$, $471^{71}$; **2**, $73^{61}$, $976^{2}$, $981^{2}$, $982^{2}$; **3**, $99^{181}$, $101^{181}$, $501^{137}$, $509^{137}$, $579^{101}$, $650^{211}$, $652^{220}$; **4**, $254^{189}$, $257^{189}$, $606^{307}$, $607^{307,315}$, $647^{307}$; **5**, $73^{201}$, $473^{153}$, $477^{153}$, $1200^{49}$; **6**, $552^{690}$, $563^{900}$, $656^{171}$, $836^{50}$; **7**, $356^{50}$, $537^{58,60,61}$, $761^{60}$, $765^{60}$; **8**, $976^{135}$, $994^{65}$
Tanaka, I., **2**, $292^{79}$
Tanaka, J., **2**, $482^{21}$; **4**, $120^{197}$
Tanaka, K., **1**, $223^{84}$, $225^{84d}$, $546^{60}$; **2**, $73^{64}$, $74^{64}$, $357^{143}$, $736^{26}$, $743^{81}$, $876^{34}$; **3**, $99^{180}$, $100^{180}$, $159^{455}$, $161^{455}$, $174^{526}$; **4**, $40^{114}$, $78^{54}$, $86^{54b}$, $128^{221}$, $251^{147}$, $402^{236}$; **5**, $839^{85}$; **6**, $528^{411,412}$, $1022^{63}$; **7**, $59^{38}$, $503^{273}$, $761^{65}$, $766^{172}$; **8**, $162^{30}$, $427^{51}$, $562^{422}$, $859^{215}$
Tanaka, K.-I., **8**, $421^{26}$, $422^{26}$
Tanaka, M., **1**, $823^{44a}$, $881^{118}$; **2**, $105^{39}$, $348^{58}$, $357^{58,145}$, $358^{145}$, $726^{123}$; **3**, $226^{200}$, $507^{175}$, $529^{51}$, $1016^{3}$, $1024^{26}$, $1039^{101,102}$; **4**, $159^{81}$, $930^{46,47,52}$, $945^{91}$, $1095^{152}$; **5**, $134^{61}$, $256^{56}$, $596^{21}$, $597^{21}$, $601^{21}$, $603^{21}$, $606^{21}$, $608^{21}$, $810^{126}$, $812^{126}$; **6**, $4^{19}$, $527^{405}$, $1052^{42a}$; **7**, $6^{31}$, $142^{138}$, $324^{71}$, $417^{130c}$; **8**, $36^{81}$, $54^{81}$, $55^{180}$, $66^{81,180}$, $152^{178}$, $289^{24}$, $291^{35}$, $301^{91,92}$, $463^{270}$
Tanaka, N., **1**, $14^{74}$; **3**, $159^{455}$, $161^{455}$; **4**, $378^{107}$; **5**, $196^{15}$
Tanaka, O., **4**, $378^{107}$; **7**, $43^{40,41}$
Tanaka, R., **4**, $3^{10}$, $41^{10}$, $47^{10}$, $65^{10a}$, $66^{10,10a}$, $278^{100}$, $286^{100}$, $370^{44}$
Tanaka, S., **1**, $65^{51}$, $187^{62,63}$, $188^{62}$, $779^{222}$; **3**, $575^{82}$, $740^{46}$; **4**, $21^{66,66a,c}$, $62^{66c}$, $107^{146b,c}$, $218^{143}$, $315^{526}$; **5**, $24^{169}$, $790^{22}$, $820^{22}$; **6**, $960^{64}$; **7**, $760^{32}$; **8**, $397^{140}$
Tanaka, T., **1**, $183^{51}$, $658^{158}$, $659^{158}$, $664^{158}$, $665^{158}$, $672^{158}$, $763^{145}$; **2**, $10^{40}$, $232^{177}$, $567^{30}$, $649^{103}$, $833^{147}$, $1059^{76}$, $1066^{122}$; **3**, $222^{144}$; **4**, $13^{44,44c}$, $159^{85}$, $253^{169}$, $256^{208,212}$, $261^{208,284}$, $262^{212,308}$, $278^{100}$, $286^{100}$, $682^{57}$, $1089^{138}$, $1091^{138}$; **5**, $105^{195}$, $833^{46}$; **6**, $96^{149}$, $614^{96}$, $625^{162}$, $652^{140}$, $837^{60}$, $942^{154}$, $944^{154}$; **7**, $137^{123}$, $139^{123}$, $155^{25}$, $245^{73}$, $246^{81,83,84,86}$, $643^{15}$, $645^{19}$, $693^{28}$, $806^{71}$, $883^{180}$; **8**, $7^{41}$, $11^{59}$, $95^{86}$, $152^{183}$, $460^{254}$, $500^{52}$, $535^{166}$, $788^{120}$, $963^{49}$
Tanaka, Y., **1**, $820^{16}$; **2**, $4^{12}$, $6^{12}$, $10^{41}$, $368^{235}$, $446^{31}$, $573^{50}$, $575^{50}$; **3**, $244^{27,28}$, $464^{177}$; **4**, $359^{161}$; **5**, $822^{165}$; **6**, $554^{727}$; **7**, $458^{111}$, $675^{54}$; **8**, $64^{207a}$, $65^{207a}$, $66^{207}$, $237^{17}$, $240^{17}$, $244^{54}$, $249^{17}$, $369^{77}$, $389^{75}$
Tancrede, J., **5**, $272^{4}$, $273^{4}$, $275^{4}$; **8**, $890^{138}$
Tancrede, T., **6**, $686^{365}$
Tandon, S. K., **6**, $487^{65}$
Tane, J. P., **5**, $1134^{37,41}$
Taneja, H. R., **3**, $125^{299}$
Taneja, K. L., **3**, $325^{159}$
Tanemura, K., **8**, $625^{166}$, $627^{166}$
Tang, C.-P., **7**, $40^{7}$, $367^{56}$
Tang, F. Y. N., **5**, $929^{173}$
Tang, H., **3**, $638^{93}$
Tang, J.-Y., **6**, $619^{118}$
Tang, P. C., **2**, $547^{100}$, $548^{100}$; **4**, $390^{171}$; **5**, $1070^{25}$, $1072^{25}$, $1074^{25}$, $1089^{86}$, $1090^{86}$, $1093^{96}$, $1094^{102}$, $1096^{106,108,108c}$, $1098^{96a,106,108a,c}$, $1099^{106,108c}$, $1100^{116}$, $1102^{102}$, $1112^{96a,106,108a,c,116}$, $1183^{57}$
Tang, P.-F. L., **2**, $632^{26}$, $640^{26}$
Tang, P.-W., **2**, $74^{80}$; **3**, $155^{433}$, $157^{433}$, $230^{238}$; **6**, $150^{116}$, $151^{116}$
Tang, Q., **3**, $505^{157}$; **4**, $464^{114}$, $470^{138}$, $477^{114}$, $478^{114}$
Tang, R., **7**, $13^{108}$
Tang, R. T., **7**, $872^{98}$
Tang, W., **7**, $586^{163}$
Tang, X., **2**, $772^{16}$
Tanguy, G., **3**, $1026^{39}$
Tani, F., **7**, $427^{148e}$
Tani, H., **1**, $214^{27}$; **8**, $385^{45}$, $408^{75}$, $978^{146}$
Tani, K., **6**, $866^{208}$; **7**, $426^{148a}$; **8**, $153^{184,185,186,187}$, $154^{189}$
Tani, M., **2**, $736^{26}$, $743^{81}$
Tani, S., **3**, $286^{56a}$
Tanida, H., **5**, $210^{56}$, $585^{201}$, $619^{11}$, $620^{11}$, $621^{18}$, $631^{57,58}$; **6**, $421^{31}$
Tanielian, C., **5**, $154^{31}$
Tanigawa, E., **8**, $153^{184,185}$, $154^{189}$
Tanigawa, H., **4**, $163^{97}$
Tanigawa, S., **4**, $159^{82}$
Tanigawa, Y., **2**, $587^{139,146}$; **4**, $589^{76}$, $598^{189,198}$, $640^{423}$; **3**, $222^{143}$, $223^{150}$, $259^{130}$, $437^{23}$; 6, $74^{36}$, $76^{53}$, $85^{92}$, $86^{97}$, $253^{156}$; **7**, $92^{41,41a}$, $94^{41}$, $173^{133}$
Taniguchi, H., **1**, $162^{104}$, $254^{14,14b}$, $277^{80,82,83}$, $278^{14a,84}$, $279^{86}$, $280^{86}$; **3**, $295^{11}$, $302^{11}$, $567^{36,190}$, $595^{190}$, $607^{190}$, $610^{36}$; **4**, $837^{10}$, $856^{100}$; **6**, $283^{163,164}$; **8**, $113^{36}$
Taniguchi, K., **2**, $573^{56}$
Taniguchi, M., **1**, $198^{91}$, $564^{201}$; **2**, $116^{125}$, $139^{29}$, $323^{23}$, $331^{23}$, $332^{23}$; **4**, $285^{164}$, $289^{164}$; **6**, $8^{38}$, $27^{119}$
Taniguchi, R., **2**, $736^{24,25}$
Taniguchi, T., **2**, $1089^{57}$; **6**, $86^{97}$
Taniguchi, Y., **2**, $357^{136}$; **3**, $45^{248}$; **4**, $598^{198}$, $640^{423}$; **6**, $76^{53}$, $113^{69}$, $176^{89,90}$, $253^{156}$; **7**, $693^{27}$; **8**, $145^{83}$, $395^{123}$
Tanikaga, R., **2**, $348^{56}$, $350^{73,74}$, $362^{56}$, $363^{56,73}$; **3**, $153^{415}$, $224^{170}$; **4**, $13^{44}$, $251^{147}$; **6**, $87^{102}$, $839^{69}$, $926^{68,69}$, $927^{68}$, $1022^{63}$; **7**, $197^{17,19}$, $667^{79}$
Tanimoto, M., **8**, $422^{36}$
Tanimoto, N., **2**, $159^{131}$; **4**, $238^{11}$, $245^{11}$, $255^{11}$, $260^{11}$; **7**, $680^{80}$
Tanimoto, S., **2**, $555^{138}$, $792^{68}$; **3**, $95^{152}$; **4**, $310^{435}$, $510^{170}$, $610^{342}$; **6**, $104^{7}$, $109^{7}$, $134^{31}$; **7**, $443^{51a}$, $747^{97}$, $778^{409}$; **8**, $170^{81}$, $847^{90}$, $856^{170}$
Tanimoto, Y., **8**, $159^{34}$, $162^{33,34}$, $164^{34}$, $178^{34}$, $179^{34}$
Tanimura, H., **6**, $563^{899}$, $626^{164}$
Tanino, H., **2**, $384^{319}$, $879^{42}$; **6**, $266^{50}$; **8**, $563^{425}$
Tanis, S. P., **1**, $733^{11}$, $826^{61}$; **3**, $220^{122}$, $224^{172,172b,175}$, $325^{162}$, $416^{11-13,19}$, $417^{13}$, $751^{87}$, $752^{95}$; **5**, $320^{8}$, $851^{170}$; **7**, $362^{30}$
Taniyama, E., **4**, $295^{251}$, $561^{31}$, $741^{125}$; **8**, $856^{186}$
Tanji, K., **6**, $530^{423}$
Tanke, R. S., **8**, $64^{207b}$, $66^{207}$
Tanko, J., **5**, $221^{58}$, $226^{58,112}$, $900^{12}$, $901^{12}$, $903^{12}$, $905^{12}$, $907^{12}$, $913^{12}$, $921^{12}$, $926^{12}$, $943^{12}$, $1006^{33}$; **7**, $815^{3}$, $824^{3}$, $833^{3}$
Tanner, D., **1**, $779^{226}$, $798^{291}$; **3**, $593^{180,183}$, $594^{184}$; **4**, $202^{24}$, $399^{225,225a,b}$; **6**, $93^{132}$, $990^{83}$; **7**, $7^{44,45}$, $17^{170}$, $399^{35}$, $473^{26}$
Tanner, D. D., **3**, $1046^{2}$; **7**, $883^{175}$; **8**, $20^{140}$, $584^{20}$
Tannert, A., **1**, $202^{101}$, $234^{22}$, $253^{8}$, $331^{48}$, $734^{22}$
Tanno, N., **8**, $166^{55-60}$, $178^{56,60}$, $179^{56,60}$, $545^{288,289}$, $546^{288}$
Tanny, S. R., **4**, $1061^{162}$
Tanoguchi, M., **7**, $340^{45}$
Tanol, M., **1**, $838^{167}$
Tanoury, G. J., **1**, $750^{108}$; **5**, $1125^{55}$, $1143^{91}$
Tanoury, G. L., **5**, $1183^{53}$
Tanouti, M., **7**, $595^{21}$
Tansey, L. W., **8**, $376^{161}$

Tantillo, A. W., **5**, 195$^{10}$
Tanzella, D. J., **5**, 841$^{91}$; **6**, 859$^{174}$
Tao, E. V. P., **4**, 312$^{458}$
Tao, F., **4**, 1011$^{164}$; **7**, 446$^{64}$
Tao, K., **4**, 695$^{4}$
Tao, N. S., **6**, 423$^{45}$
Tao, T., **5**, 796$^{55}$
Tao, X., **4**, 590$^{89}$, 613$^{89}$
Tao, Y.-T., **3**, 172$^{514}$; **6**, 954$^{18}$
Taoka, A., **7**, 429$^{155}$
Tapia, R., **6**, 155$^{152}$; **7**, 355$^{43}$
Tapiolas, D., **4**, 1039$^{62}$
Tapolczay, D. J., **6**, 1031$^{109}$
Tapp, W. J., **5**, 473$^{149}$
Taqui Khan, M. M., **8**, 446$^{65}$
Tarakanova, A. V., **5**, 900$^{10}$, 901$^{10}$, 906$^{10}$, 907$^{10}$, 972$^{6}$, 982$^{6}$, 984$^{6}$, 989$^{6}$
Tarama, K., **8**, 449$^{159,160}$, 453$^{191}$, 567$^{461}$
Taran, M., **3**, 741$^{50}$
Tarantello, M., **6**, 508$^{289}$, 509$^{271}$
Tarara, G., **2**, 68$^{40}$, 94$^{53}$
Tarasco, C., **1**, 192$^{82}$; **2**, 35$^{130}$, 36$^{130}$, 566$^{23}$; **7**, 549$^{42}$
Tarasov, V. A., **5**, 1056$^{48,49}$, 1057$^{50}$
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Tarlin, H. I., **8**, 896$^{17}$
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Taschner, E., **6**, 665$^{230}$, 667$^{230}$, 668$^{259}$
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Taya, S., **3**, 992$^{37}$, 994$^{41}$, 999$^{51}$; **5**, 821$^{162}$, 851$^{165}$, 888$^{29}$, 889$^{31}$; **6**, 851$^{130}$, 852$^{138}$, 876$^{26}$, 877$^{36}$, 879$^{36}$, 882$^{26}$, 883$^{36}$, 885$^{26}$, 886$^{36}$
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Wahl, G. H., Jr., **3**, $736^{23}$, $906^{143}$
Wahren, M., **4**, $485^{29}$
Wahren, R., **8**, $550^{334}$
Wai, J. S. M., **1**, $763^{146}$; **4**, $255^{202}$; **7**, $430^{159}$, $442^{46b,c}$, $489^{165}$
Waid, K., **6**, $190^{197}$
Waigh, R. D., **8**, $839^{26a}$, $840^{26}$
Wailes, P. C., **1**, $139^{4}$; **3**, $824^{18}$; **4**, $153^{62a}$; **8**, $447^{119a,b}$, $675^{35\text{-}37}$, $679^{37}$, $684^{35}$, $691^{36}$, $754^{114}$
Waiss, A. C., Jr., **3**, $666^{45}$
Waite, A. C., **8**, $860^{221}$
Waite, H., **4**, $310^{436}$
Waitkins, G. R., **7**, $84^{1}$, $85^{1}$, $108^{1}$
Waits, H. P., **4**, $725^{46}$
Wajirum, N., **5**, $578^{149}$; **6**, $690^{388}$
Wakabayashi, H., **4**, $107^{140d}$
Wakabayashi, N., **5**, $835^{59}$, $862^{250}$
Wakabayashi, S., **1**, $520^{71,75}$; **2**, $374^{275,277}$; **4**, $258^{248}$, $261^{248}$; **6**, $149^{104}$, $603^{15}$, $619^{120}$, $624^{15,120}$, $902^{130,131}$, $939^{137}$; **7**, $454^{96}$; **8**, $353^{152}$
Wakabayashi, T., **2**, $885^{50}$; **8**, $493^{22}$
Wakabayashi, Y., **1**, $347^{132,134}$; **4**, $23^{71}$, $162^{92}$, $567^{49}$; **6**, $237^{67}$, $564^{913,914}$; **8**, $168^{70}$, $545^{302}$
Wakamatsu, H., **3**, $1027^{44}$; **5**, $1138^{70}$; **8**, $292^{39}$
Wakamatsu, K., **1**, $95^{78}$, $450^{213}$, $738^{40}$; **2**, $19^{76}$, $59^{15}$; **4**, $391^{179}$, $607^{310}$, $626^{310}$, $647^{310}$, $770^{248}$, $886^{117}$; **6**, $998^{117}$; **7**, $162^{58}$, $243^{65,66}$
Wakamatsu, T., **5**, $808^{109}$; **6**, $8^{38}$; **8**, $244^{57}$, $249^{97}$, $253^{97}$, $527^{47}$, $620^{132}$
Wakamiya, T., **4**, $958^{27}$
Wakamoto, K., **4**, $878^{83}$
Wakasa, N., **3**, $229^{230}$, $246^{33}$, $257^{33}$

Wakasa, T., **7**, 414[108]
Wakasugi, T., **8**, 18[126]
Wakatsuka, H., **7**, 693[30], 694[30]
Wakatsuki, Y., **5**, 1139[74], 1140[74], 1141[81], 1142[74,87-89], 1145[103], 1146[74], 1152[137,138,142], 1153[103,148], 1154[150], 1158[137]
Wakefield, B. J., **1**, 2[6,7], 125[84], 412[50], 631[51], 672[51]; **3**, 86[4], 419[34,35]; **4**, 257[218], 426[53], 867[6], 968[57]; **5**, 829[25]; **6**, 546[654], 557[834]; **7**, 329[2]; **8**, 198[130]
Waki, M., **2**, 1094[88]
Wakimasu, M., **6**, 644[82]
Wakisaka, K., **5**, 724[111]
Wakisaka, M., **8**, 405[24]
Wakita, Y., **5**, 634[78]
Wakselman, C., **2**, 209[108], 749[129]; **3**, 257[121]; **4**, 1020[236]; **6**, 526[397,398], 527[408]
Wakselman, M., **6**, 639[48]
Walach, P., **8**, 863[234]
Walba, D. M., **1**, 429[125]; **2**, 547[101], 548[101]; **7**, 257[50], 268[124], 553[60]; **8**, 544[260]
Walborsky, H. M., **3**, 255[111], 439[38], 482[3], 587[146], 610[146], 1040[107]; **4**, 39[112], 200[7], 1007[107]; **5**, 30[3], 355[87a], 901[26]; **6**, 242[91], 243[91], 295[247,248], 727[194], 790[119], 985[66]; **7**, 712[65]; **8**, 74[249], 830[87]
Wald, L., **5**, 423[89]
Walde, A., **7**, 99[107]
Walder, L., **4**, 130[226a,b], 764[222], 765[222], 808[155]
Walding, M., **6**, 46[67], 47[67]
Waldmann, H., **2**, 1102[123]; **5**, 366[97], 411[43,43c]; **6**, 46[63], 641[63], 643[80], 666[245,248], 667[245], 670[63,266,267], 671[266]
Waldmann, H. J., **2**, 456[22,33,52], 457[33], 458[33,52], 459[33,52], 460[33], 461[33], 462[33], 466[33]
Waldner, A., **6**, 937[117], 939[117], 940[117]
Waldron, J. J., **4**, 91[90], 92[90c], 261[294]
Waldvogel, G., **7**, 86[16a]
Walenta, R., **4**, 211[88]
Walinsky, S. W., **3**, 936[73]; **5**, 439[169], 910[88]
Walker, A., **5**, 116[269]; **6**, 783[87]
Walker, A. M., **8**, 83[7]
Walker, B., **6**, 455[155]
Walker, B. H., **7**, 252[10]
Walker, B. J., **1**, 755[115], 758[127], 761[137], 812[115], 813[115]; **7**, 396[22]
Walker, C., **5**, 531[75], 549[75]; **7**, 105[149]
Walker, C. B., Jr., **5**, 765[111]
Walker, D. G., **1**, 791[269]; **2**, 486[30], 488[30], 821[106]; **5**, 494[215,216], 579[162,163]
Walker, D. L., **7**, 318[53], 319[53]
Walker, D. M., **2**, 855[243]; **5**, 143[103]
Walker, E., **8**, 244[52]
Walker, E. F., **2**, 916[84]
Walker, E. R. H., **3**, 715[43]; **8**, 2[3], 37[102], 66[102], 237[9], 238[9], 240[9], 241[9], 244[9], 245[9], 247[9], 278, 541[209]
Walker, F. J., **3**, 225[185], 264[181]; **6**, 2[3], 8[39], 25[3], 88[105], 89[105,112], 927[71,76]; **7**, 198[26], 401[59], 402[63], 403[59,65], 406[59,77], 409[77], 414[77], 415[77], 421[77], 423[77]
Walker, G. N., **7**, 543[15]; **8**, 70[227], 71[227]
Walker, H. G., **7**, 84[1], 85[1], 108[1]
Walker, H. G., Jr., **2**, 735[16]
Walker, H. M., **6**, 280[142]
Walker, J., **3**, 633[4]; **8**, 916[98]
Walker, J. A., **3**, 528[46], 799[102], 939[77]; **5**, 829[12], 948[272], 1001[13]
Walker, J. C., **2**, 125[215,216], 127[232], 272[79], 564[9]; **3**, 47[257]; **4**, 82[62b,e], 217[129,130,131,132], 231[130,132], 243[74,75], 257[74,75], 260[75]; **5**, 367[100]
Walker, K. A. M., **8**, 152[173], 277[152], 445[13,14], 452[13,184,184a], 533[147], 535[147]
Walker, K. E., **8**, 376[161]
Walker, L. E., **5**, 70[109,110]
Walker, M. A., **1**, 835[133]
Walker, O. J., **3**, 636[45,57]
Walker, P., **7**, 135[105], 136[105], 137[105], 145[105]
Walker, P. J. C., **4**, 518[9], 542[9], 689[71]; **8**, 444[10]
Walker, R. A., **8**, 937[77]
Walker, R. T., **1**, 569[252]
Walker, S. M., **5**, 639[123]
Walker, T., **8**, 987[23]
Walker, W. E., **4**, 589[77], 590[77], 591[77], 597[181], 598[181], 638[181]
Walker, W. E., Jr., **3**, 407[150]
Walkowicz, C., **7**, 675[56]
Walkup, R. D., **2**, 214[132], 603[49]; **4**, 395[207a], 396[207a,b], 558[16]
Walkup, R. E., **2**, 780[10]
Wall, A., **3**, 878[93,94], 879[93,94], 880[94], 881[94]; **4**, 335[25], 359[159], 771[251]; **5**, 440[174], 441[174]; **6**, 161[182]
Wall, D. K., **3**, 888[18], 893[55]
Wall, M. E., **6**, 685[360]
Wall, R. G., **5**, 2[13], 3[13]
Wall, R. T., **2**, 897[14]
Wall, W. F., **8**, 198[130]
Wallace, B., **2**, 534[33-35], 535[34,35]
Wallace, D. J., **5**, 129[35]
Wallace, E., **8**, 103[130]
Wallace, G. M., **6**, 551[688]
Wallace, I. H., **5**, 862[251]
Wallace, I. H. M., **2**, 606[67], 619[67]
Wallace, M. A., **5**, 765[111]
Wallace, P., **1**, 782[232]
Wallace, P. M., **5**, 419[74]; **8**, 253[117], 395[129]
Wallace, R. G., **4**, 502[119]; **6**, 119[112], 765[16]
Wallace, R. H., **1**, 272[65]; **3**, 42[233], 572[64]; **8**, 109[7,13], 110[7], 112[7], 113[35]
Wallace, R. W., **6**, 1016[27]
Wallace, T. J., **7**, 759[5,13,16], 760[17,21,34-36], 761[36]
Wallace, T. W., **3**, 502[141]; **4**, 215[118], 497[96]; **5**, 683[39,115], 684[39], 692[94], 693[113,115], 694[115]; **6**, 152[140], 153[140]; **8**, 540[194]
Wallach, O., **2**, 141[38], 142[45], 152[104]; **3**, 822[4], 831[4], 832[4]; **4**, 239[33]; **8**, 526[21,22]
Wallbaum, F., **3**, 809[42]
Wallbillich, G., **4**, 1083[92], 1085[100,101]
Wallenberger, F. T., **3**, 574[80]
Wallenfels, K., **2**, 359[159]; **6**, 225[4], 226[4], 228[4], 230[4], 231[4], 232[4], 233[4], 234[4], 235[4], 236[4], 238[4,73], 239[4], 240[4], 241[4], 258[4], 489[87]
Waller, B., **6**, 646[99,99b]
Waller, C. W., **8**, 973[120]
Waller, F. J., **4**, 945[89]
Walley, R. J., **8**, 143[58]
Wallfahrer, U., **5**, 491[209]
Wallin, A. P., **1**, 480[159]
Wallin, S., **6**, 660[206]; **8**, 224[105], 969[96]
Walling, C., **3**, 154[417], 649[202]; **4**, 279[102,109], 282[109], 316[537], 716[1], 717[7,10], 725[10], 751[1], 752[162], 765[162]; **6**, 1022[62]; **7**, 11[86], 13[111], 17[169], 41[16], 95[81], 860[70]
Wallingford, V. H., **2**, 800[15]
Wallis, A. F. A., **3**, 690[126], 691[130], 693[130]

Wallis, C. J., **1**, 774$^{209}$, 779$^{225}$; **2**, 596$^{4}$
Wallis, E. S., **3**, 892$^{50}$; **6**, 795$^{6}$, 796$^{6}$, 801$^{6}$
Wallis, J. D., **1**, 823$^{40}$; **4**, 55$^{157}$, 57$^{157j}$
Wallis, J. M., **7**, 863$^{82}$, 864$^{86}$, 874$^{108}$
Wallis, T. G., **3**, 872$^{56}$
Walliser, F. M., **5**, 21$^{145}$, 572$^{123}$
Wallner, A., **4**, 820$^{219}$
Wallo, A., **8**, 242$^{44}$, 252$^{44}$, 455$^{205}$
Walls, F., **1**, 552$^{80}$; **8**, 368$^{67}$, 374$^{67}$
Walpole, A. L., **3**, 351$^{38}$
Walsgrove, T. C., **4**, 14$^{47,47h}$; **7**, 362$^{27}$
Walsh, A. D., **5**, 900$^{4}$; **7**, 10$^{78}$
Walsh, C., **8**, 87$^{31}$, 185$^{23}$
Walsh, C. T., **2**, 904$^{49}$
Walsh, E. B., **5**, 473$^{153}$, 477$^{153}$, 484$^{179}$
Walsh, E. J., **1**, 885$^{134}$; **2**, 759$^{29}$; **4**, 1060$^{161}$, 1063$^{161a}$
Walsh, E. J., Jr., **5**, 787$^{6,9}$, 794$^{49}$, 856$^{209}$; **8**, 264$^{43-45}$, 825$^{65}$
Walsh, E. N., **5**, 949$^{276}$
Walsh, R., **3**, 382$^{36}$; **5**, 160$^{55}$, 571$^{115}$, 585$^{199}$, 905$^{61}$, 906$^{61}$
Walsh, T. F., **5**, 154$^{33}$
Walsh, W. L., **8**, 736$^{23}$, 737$^{23}$
Walshaw, K. B., **8**, 530$^{97}$
Walshe, N. D. A., **1**, 797$^{293}$; **6**, 996$^{107}$
Walt, D. R., **5**, 1096$^{111}$, 1098$^{111}$
Walter, D., **3**, 423$^{81}$, 975$^{4}$, 979$^{4}$
Walter, D. S., **4**, 161$^{91}$
Walter, G. J., **8**, 536$^{167}$
Walter, H. A., **7**, 657$^{24}$
Walter, L., **7**, 878$^{145}$
Walter, P., **4**, 48$^{139}$
Walter, R., **6**, 637$^{30}$; **7**, 771$^{268}$, 772$^{268}$
Walter, S., **1**, 38$^{183}$
Walter, W., **2**, 867$^{16}$; **3**, 105$^{218}$; **6**, 419$^{4,5}$, 420$^{4,5,17-19}$, 421$^{18,19,30}$, 422$^{30}$, 423$^{38}$, 424$^{18,19,30,38}$, 425$^{5}$, 432$^{123}$, 482$^{124}$, 488$^{12}$, 508$^{12}$, 509$^{12,251}$, 512$^{12}$, 539$^{580}$, 540$^{589}$, 541$^{597}$, 545$^{12}$, 722$^{144}$
Walter, W. F., **8**, 836$^{1,1b}$, 837$^{1}$, 847$^{1b}$, 964$^{53}$
Walters, C. P., **6**, 509$^{253}$; **8**, 37$^{99}$, 42$^{99}$, 66$^{99}$
Walters, M. E., **3**, 616$^{13}$; **8**, 531$^{126}$, 931$^{37}$
Walters, R. L., **8**, 121$^{78}$
Walters, T. R., **7**, 737$^{17}$
Walther, D., **1**, 320$^{160}$; **5**, 1157$^{168}$
Walther, S., **4**, 1008$^{134}$
Walther, W., **7**, 709$^{43}$, 710$^{43}$
Walthew, J. M., **4**, 496$^{87}$
Walton, D. R. M., **2**, 725$^{112}$, 743$^{78}$; **3**, 219$^{104}$, 419$^{31}$, 500$^{126}$, 512$^{126}$, 522$^{17}$, 555$^{31}$; **4**, 115$^{182}$; **6**, 426$^{77}$; **8**, 766$^{20}$
Walton, E., **2**, 284$^{56}$
Walton, E. S., **5**, 787$^{10}$
Walton, J. C., **3**, 380$^{9}$; **4**, 717$^{8}$, 729$^{63}$, 791$^{51}$; **7**, 860$^{71}$
Walton, R., **4**, 815$^{194}$, 817$^{194}$
Walts, A. E., **2**, 6$^{25}$, 12$^{25}$, 13$^{25,57}$, 26$^{25}$, 27$^{25}$, 30$^{25}$, 31$^{25}$, 35$^{125}$, 41$^{25,125}$, 42$^{25}$; **5**, 534$^{91}$; **7**, 401$^{62}$
Walz, P., **2**, 614$^{119}$
Walzer, E., **2**, 547$^{113}$, 551$^{113}$; **3**, 56$^{285}$; **4**, 229$^{235,236}$, 1055$^{138}$
Wambsgans, A., **8**, 74$^{245}$, 176$^{136}$, 393$^{110}$
Wamhoff, H., **4**, 45$^{130,130c-e}$; **5**, 484$^{179}$; **6**, 428$^{86}$; **7**, 739$^{38}$, 748$^{108}$
Wamprecht, C., **6**, 526$^{396}$, 575$^{967}$
Wamsley, E. J., **4**, 24$^{72,72a}$
Wan, P., **4**, 298$^{293}$, 300$^{293}$; **7**, 247$^{97}$
Wanagat, U., **7**, 598$^{59}$
Wanat, R. A., **1**, 28$^{143}$, 29$^{144}$, 34$^{169}$; **2**, 507$^{26,27}$, 508$^{27,32}$; **3**, 33$^{189}$, 34$^{198,199}$, 39$^{198,199}$; **6**, 727$^{195,196,197}$
Wand, M. D., **1**, 429$^{125}$
Wander, J. D., **7**, 703$^{1}$, 709$^{1}$, 710$^{1}$
Wandrey, C., **8**, 204$^{154}$
Wang, A., **6**, 707$^{44}$
Wang, B. S. L., **8**, 840$^{33}$
Wang, C. H., **7**, 883$^{178}$
Wang, C. J., **5**, 257$^{59,59a}$
Wang, C.-L. J., **2**, 160$^{133}$, 369$^{249}$; **3**, 212$^{39}$, 253$^{92}$; **4**, 75$^{42b}$, 377$^{145a}$, 384$^{145a}$; **6**, 76$^{45}$, 182$^{139}$; **7**, 358$^{10}$, 371$^{10}$, 377$^{90}$, 674$^{45}$
Wang, D., **2**, 553$^{132}$, 554$^{132}$, 567$^{26}$; **7**, 423$^{144}$; **8**, 777$^{82b}$
Wang, D. G., **3**, 888$^{16}$
Wang, E. J., **4**, 966$^{55}$
Wang, H. H., **4**, 95$^{98}$
Wang, I. C., **8**, 295$^{60}$
Wang, J. L., **7**, 367$^{56}$
Wang, J.-T., **1**, 165$^{112b}$
Wang, J.-X., **5**, 1138$^{60}$
Wang, K. K., **2**, 84$^{12}$, 88$^{28}$; **3**, 215$^{60}$; **4**, 395$^{204}$; **8**, 2$^{14}$, 724$^{152,155-157,160-162,178}$, 725$^{178}$, 726$^{178,178b}$, 727$^{178}$
Wang, L. C., **4**, 964$^{45}$
Wang, M. O., **5**, 151$^{18}$
Wang, N., **4**, 73$^{32}$, 111$^{158a}$; **6**, 116$^{93}$, 938$^{125}$, 940$^{125}$
Wang, N.-Y., **8**, 188$^{52}$
Wang, P. C., **2**, 1090$^{70}$, 1100$^{70}$; **6**, 247$^{131}$
Wang, P. J., **5**, 799$^{73}$
Wang, R. H. S., **2**, 387$^{337}$
Wang, S., **1**, 339$^{89}$; **4**, 815$^{191}$
Wang, S.-S., **6**, 666$^{234}$, 667$^{234}$, 671$^{275}$; **8**, 64$^{215}$, 394$^{118}$
Wang, S. Y., **8**, 566$^{457}$, 568$^{468}$
Wang, T., **3**, 163$^{472}$; **5**, 636$^{99}$
Wang, T.-F., **2**, 547$^{102,103}$, 548$^{102}$, 549$^{103}$; **3**, 368$^{105}$; **5**, 789$^{30}$; **8**, 341$^{103}$, 928$^{24}$
Wang, W., **4**, 871$^{34}$; **7**, 883$^{178}$
Wang, W.-L., **1**, 273$^{69}$
Wang, X., **3**, 999$^{51}$, 1000$^{51b}$; **7**, 374$^{77b}$
Wang, Y., **1**, 188$^{95}$, 198$^{95}$, 838$^{167}$; **2**, 579$^{94}$, 772$^{16}$; **5**, 680$^{21}$, 1031$^{97}$; **7**, 313$^{35}$
Wang, Y. F., **2**, 909$^{63}$; **4**, 262$^{310}$; **8**, 191$^{94}$
Wang, Z., **1**, 768$^{172}$; **2**, 505$^{9}$, 786$^{48}$; **5**, 841$^{87}$; **7**, 583$^{156}$; **8**, 224$^{101}$
Wang-Griffin, L., **8**, 97$^{98}$
Waninge, J. K., **8**, 95$^{91}$
Wanless, G. G., **4**, 276$^{77}$, 284$^{77}$, 288$^{77}$, 289$^{77}$
Wann, S. R., **8**, 237$^{17}$, 240$^{17}$, 249$^{17}$
Wannagat, U., **2**, 183$^{13}$
Wanner, K. T., **2**, 657$^{160}$, 1052$^{50}$, 1053$^{50}$, 1067$^{50,125}$; **3**, 42$^{232}$
Wanner, M. J., **2**, 718$^{81}$; **6**, 181$^{132}$, 182$^{132}$
Wanzke, W., **6**, 456$^{159}$
Wanzlick, H.-W., **4**, 126$^{217d}$
Warawa, E. J., **7**, 253$^{19}$, 254$^{19}$
Warburg, O., **6**, 642$^{64}$; **8**, 589$^{52}$
Warburton, W. K., **8**, 663$^{116}$
Ward, A. D., **2**, 809$^{55}$; **4**, 340$^{50}$; **7**, 534$^{42}$, 772$^{298}$; **8**, 56$^{167}$, 66$^{167}$
Ward, B., **5**, 736$^{145}$, 737$^{145}$
Ward, D. D., **5**, 350$^{79}$
Ward, D. E., **8**, 16$^{106}$, 17$^{106}$, 18$^{124}$
Ward, D. G., **1**, 180$^{42}$, 181$^{42}$
Ward, G., **8**, 140$^{26}$
Ward, H. P., **6**, 120$^{125}$
Ward, H. R., **4**, 1010$^{148}$, 1013$^{178}$; **5**, 802$^{85}$; **6**, 970$^{125}$
Ward, J., **5**, 1116$^{8}$

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Ward, J. G., **7**, 27[66], 32[94]
Ward, J. S., **8**, 623[151]
Ward, M. D., **7**, 17[179]
Ward, N. D., **8**, 478[37]
Ward, P., **3**, 160[471], 161[471], 163[471], 803[1]
Ward, R. S., **1**, 566[217,218]; **3**, 692[137], 816[84]; **4**, 113[176], 239[20], 249[127], 258[20,127]
Ward, R. W., **8**, 626[175], 629[175]
Ward, S. E., **4**, 811[172]; **5**, 723[106]
Ward, S. J., **8**, 623[150]
Ward, T. J., **8**, 28[34], 66[34]
Wardell, J. L., **1**, 2[8]; **4**, 72[24], 867[7]; **8**, 412[109], 413[127], 851[132]
Wardle, R. B., **5**, 1123[39]; **6**, 814[96]
Wardleworth, J. M., **3**, 511[189]
Ware, A. C., **7**, 646[25]
Ware, D. W., **4**, 386[153,153b]
Ware, J. C., **7**, 595[14], 597[14], 600[78], 601[78]
Ware, R. S., **3**, 681[95]; **7**, 801[41]
Wariishi, K., **2**, 629[1], 635[1], 804[42]
Warin, R., **4**, 1033[16,16d], 1052[16d]
Waring, A. J., **3**, 803[1], 804[6]; **4**, 3[8], 6[8], 99[118d]; **5**, 223[74,80]; **7**, 108[180], 671[10], 673[10], 687[10]; **8**, 984[2]
Waring, C., **7**, 732[56]
Waring, P., **8**, 906[66], 909[66]
Warita, Y., **3**, 871[54]
Warkentin, J., **3**, 896[67]; **4**, 284[152], 815[191], 1089[132]; **5**, 901[27]; **6**, 1059[68]
Warman, D., **2**, 740[63a]
Warmus, J. S., **5**, 516[24], 517[24], 518[24], 524[50,51], 539[50], 548[50c]
Warne, T. M., Jr., **4**, 18[62], 20[62a,c]
Warner, A. M., **7**, 474[36]
Warner, C. R., **8**, 781[97]
Warner, D. T., **2**, 156[115]; **4**, 239[36,37], 243[37]
Warner, J. C., **5**, 492[249]
Warner, P., **1**, 343[114]; **2**, 125[216,217,221,222,224], 127[228], 271[77], 272[77,79,80], 315[42,44], 316[42,44], 317[44]; **4**, 217[131], 1012[175], 1021[241]; **6**, 1036[144]
Warner, R. W., **3**, 174[532], 176[532], 177[532], 178[532]; **4**, 629[412,413]; **6**, 849[118]
Warnet, R. J., **2**, 823[112]; **3**, 571[58], 596[193], 728[37], 1051[22], 1052[22]
Warnhoff, E. W., **1**, 853[48]; **3**, 380[7], 784[30], 854[73]; **4**, 1031[6], 1043[6], 1052[6], 1063[6]; **5**, 905[56]; **7**, 123[31], 673[25]; **8**, 90[48]
Warning, K., **2**, 1051[37]
Warnock, J., **7**, 281[174], 282[174]
Warnock, W. J., **5**, 257[59]
Warpehoski, M. A., **3**, 969[134]; **7**, 91[35]
Warr, J. C., **3**, 888[16]
Warrellow, G. J., **7**, 35[102]; **8**, 28[34], 66[34]
Warren, C. B., **5**, 571[116]
Warren, C. D., **3**, 273[7]; **6**, 652[143]
Warren, J. D., **6**, 554[710], 809[70]
Warren, K. S., **3**, 822[10], 829[10]
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Wilkinson, J., **4**, 588[53]
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Wilkinson, S. P., **5**, 1130[6]
Wilks, H. M., **8**, 206[172]
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Willard, P. G., **4**, 313[473]
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Willi, M. R., **8**, 388[62]
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Williams, A. D., **3**, 600[216]; **4**, 17[54], 63[54]; **6**, 1053[46]; **8**, 843[59c]
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Williams, B. J., **6**, 671[276]
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Williams, C. N., **2**, 963[55]
Williams, D., **7**, 444[55]
Williams, D. H., **2**, 346[44]; **6**, 690[395]; **8**, 344[119], 345[119]
Williams, D. J., **1**, 832[114]; **2**, 204[99], 742[77]; **3**, 902[119], 934[64], 953[64]; **4**, 379[115], 380[115g], 381[126b], 382[126], 383[126], 390[175a], 391[115g]; **5**, 374[107], 376[107b], 528[67], 534[92]; **6**, 842[79], 995[103]; **7**, 112[198], 132[92], 133[92], 134[92], 352[33], 523[48], 820[26]; **8**, 847[100b]
Williams, D. L., **3**, 125[305], 126[305], 127[305]; **8**, 566[457], 568[468]
Williams, D. L. H., **4**, 366[5]; **7**, 493[194], 500[194], 746[84]
Williams, D. R., **1**, 109[15], 205[105], 514[53-55], 795[282], 820[13], 823[13]; **3**, 31[185], 32[185], 36[209], 37[212]; **4**, 380[119], 403[238], 404[238,244], 405[238], 406[238], 893[155]; **5**, 527[63], 534[90], 535[90], 769[136]; **6**, 25[100], 723[147], 725[171,173], 726[175], 728[171], 842[78], 997[113], 1030[108]; **7**, 131[79], 160[54], 274[136], 300[54], 410[97b], 503[276], 544[38], 551[38]; **8**, 846[86]
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Williams, E. G., **2**, 553[130], 554[130]; **7**, 237[35]
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Williams, G. H., **3**, 505[162], 507[162], 512[162]
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Williams, H. J., **4**, 189[103]; **8**, 543[243], 545[280]
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Williams, J. F., **2**, 456[58,63], 458[58,63], 465[103]
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Williams, J. H., **3**, 572[66]; **8**, 312[22], 321[22], 566[450]
Williams, J. K., **5**, 76[232]
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Williams, J. M., **1**, 109[14], 127[92], 427[114]; **2**, 1[1], 225[155]; **3**, 18[97], 42[97], 43[97]; **5**, 96[122], 98[122]; **7**, 390[9], 401[61b], 407[61b]; **8**, 431[66], 459[226]
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Williams, N. R., **3**, 734[12]; **8**, 514[112], 932[43]
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Williams, P. D., **5**, 249[36], 531[76]
Williams, P. H., **2**, 139[31]; **5**, 432[130], 433[130b]; **7**, 446[70]
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Williams, R. E., **4**, 571[1], 572[1]
Williams, R. G., **5**, 715[82], 739[82]

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Wilson, J. M., **4**, 426[42], 427[42]; **6**, 799[24]
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Wilson, T. M., **2**, 564[9], 568[32], 630[8], 655[145]
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Wingard, R. E., Jr., **3**, 867[33], 873[33]; **5**, 609[67]; **6**, 247[131]
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Winken, T., **5**, $161^{62}$
Winkhaus, G., **4**, $689^{71}$
Winkler, H. J. S., **4**, $519^{13}$, $520^{13}$
Winkler, J., **5**, $418^{71}$; **7**, $505^{284}$
Winkler, J. D., **2**, $1010^{8}$; **3**, $24^{144}$, $58^{291}$, $218^{97}$, $380^{9}$; **4**, $24^{73,73a,b}$, $791^{50}$, $801^{125}$, $820^{50}$; **5**, $134^{64,66}$, $137^{66,82,83}$, $141^{92}$
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Winkler, P., **6**, $531^{428}$
Winkler, R. R., **2**, $153^{109}$
Winkler, T., **1**, $830^{96}$; **2**, $534^{36}$; **3**, $381^{32}$; **4**, $754^{175}$; **5**, $439^{166}$, $837^{67}$, $856^{67}$, $857^{67}$; **6**, $487^{73}$, $489^{73}$
Winn, L. S., **3**, $539^{100}$
Winnick, F. M., **5**, $21^{148}$
Winnik, M., **7**, $42^{32}$
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Winter, B., **5**, $217^{25}$, $222^{25}$
Winter, C. A., **6**, $219^{123}$
Winter, M., **6**, $612^{70}$, $1059^{64}$
Winter, M. J., **1**, $310^{109}$; **4**, $976^{100}$; **5**, $1144^{101}$, $1145^{104}$
Winter, R., **3**, $896^{67}$
Winter, R. A. E., **4**, $349^{109}$; **6**, $686^{372}$, $982^{49}$
Winter, R. E. K., **3**, $620^{29}$; **5**, $678^{17}$, $680^{24}$, $683^{24c}$; **7**, $228^{93}$; **8**, $374^{147}$
Winter, S. R., **3**, $1024^{27}$, $1028^{51}$
Winter, W., **7**, $777^{364}$
Winter, W. J., **5**, $74^{208}$
Winterfeldt, E., **1**, $753^{101}$; **2**, $381^{308}$, $651^{121}$, $1026^{67}$, $1028^{67}$; **4**, $3^{10}$, $41^{10}$, $47^{10}$, $48^{137,137a}$, $52^{147,147e}$, $55^{156,156n}$, $65^{10e}$, $66^{10,10e}$, $200^{4}$, $211^{88,89,91}$, $222^{177,178}$; **5**, $945^{247}$; **6**, $501^{204}$, $740^{63}$, $745^{81}$, $746^{93}$, $834^{36}$, $855^{36}$; **7**, $679^{74,74b}$; **8**, $58^{176}$, $66^{176}$, $100^{115}$, $244^{71}$, $247^{71}$, $251^{71}$, $253^{71}$, $266^{58,59}$, $269^{59}$, 279, $543^{239}$
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Winton, P. M., **3**, $416^{22}$
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Winzenberg, K., **1**, $129^{93}$, $779^{224}$; **2**, $651^{120}$; **5**, $342^{63}$; **6**, $807^{58}$
Wipf, D. O., **7**, $854^{45}$
Wipf, P., **3**, $994^{43}$, $996^{43}$, $1000^{43}$; **5**, $482^{172}$, $842^{108}$, $843^{108}$, $844^{130}$, $859^{238}$, $863^{238}$; **6**, $540^{582}$, $834^{35}$, $855^{35}$, $858^{162}$
Wipff, G., **1**, $49^{8}$, $631^{59}$, $632^{59}$; **4**, $538^{104}$, $539^{104}$; **5**, $468^{127}$; **6**, $133^{4}$; **8**, $3^{21}$, $89^{43}$
Wippel, H. G., **1**, $761^{138}$, $773^{204}$
Wireko, F., **5**, $211^{62,63}$
Wiriyachitra, P., **7**, $330^{11}$, $774^{334}$
Wirkus, M., **6**, $531^{430}$
Wirth, D. D., **5**, $520^{39}$, $704^{22}$, $1020^{69}$, $1023^{69}$; **7**, $879^{148}$, $880^{148}$
Wirth, E., **3**, $829^{54}$
Wirth, M. M., **7**, $10^{79}$
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Wirth, R. P., **6**, $667^{239}$
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Wirth, W., **1**, $466^{45}$
Wirth, W.-D., **3**, $414^{1}$
Wirth-Peitz, F., **2**, $464^{93}$
Wirthwein, R., **4**, $491^{68}$, $492^{72}$
Wirtz, K. R., **5**, $689^{75}$
Wirz, B., **8**, $185^{10}$
Wirz, J., **4**, $300^{307}$
Wischhöfer, E., **2**, $1102^{127}$
Wise, D. S., **2**, $555^{140}$
Wise, S., **5**, $67^{93}$, $70^{116}$, $514^{9,10}$, $527^{9}$
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Wishka, D. G., **1**, $343^{108}$
Wisloff Nilssen, E., **1**, $488^{8}$
Wismontski-Knittel, T., **5**, $729^{123}$
Wisnieff, T. J., **4**, $1060^{161}$, $1063^{161a}$
Wisotsky, M. J., **6**, $263^{21}$
Wisowaty, J. C., **2**, $759^{31}$
Wissinger, J. E., **1**, $881^{119}$; **5**, $806^{103}$, $1026^{86}$; **7**, $673^{20}$
Wissocq, F., **4**, $95^{102f}$
Wistrand, L.-G., **2**, $1051^{34}$, $1066^{121}$
Wiszniewski, V., **1**, $564^{190}$
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Witt, K. E., **3**, $588^{158}$
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Witte, J. F., **3**, $201^{81}$
Witte, K., **8**, $364^{16}$
Witte, L., **2**, $354^{114}$, $357^{114}$
Wittek, P. J., **2**, $171^{178,179}$, $173^{180}$, $832^{153}$
Witten, C. H., **8**, $301^{89}$
Wittenberg, D., **3**, $381^{23}$, $382^{23}$, $565^{17}$
Wittenberger, S., **3**, $960^{118}$; **5**, $436^{158,158g}$, $442^{158}$; **6**, $898^{105}$, $905^{144}$
Wittenbrink, C., **3**, $644^{164}$
Wittenbrook, L. S., **7**, $212^{100}$
Wittereen, J. G., **4**, $18^{62}$, $20^{62h}$
Witteveen, J. G., **5**, $768^{132}$; **6**, $714^{87}$
Witthake, P., **2**, $780^{9}$
Wittig, G., **1**, $213^{17}$, $215^{34}$; **2**, $124^{205}$, $182^{5}$, $476^{5}$, $477^{6,7}$, $478^{7}$, $482^{23}$, $483^{23}$; **3**, $914^{7}$, $915^{13}$, $924^{7,41}$, $965^{13}$, $975^{1}$; **4**, $70^{10}$, $96^{103a}$, $98^{103a}$, $140^{6,7b}$, $483^{2}$, $484^{2}$, $488^{55}$, $492^{69}$, $500^{103}$, $869^{21}$, $872^{43}$, $962^{38}$; **5**, $69^{99,100}$, $379^{113b}$, $380^{113b,d,114,115}$, $381^{115}$; **6**, $685^{362}$, $719^{128}$, $720^{128}$, $961^{66}$, $967^{103}$, $968^{115,116}$; **8**, $273^{123}$, $298^{72}$, $885^{102}$
Wittig, U., **5**, $291^{43}$, $1190^{29}$, $1192^{29}$
Wittle, E. L., **2**, $759^{33}$
Wittman, G., **8**, $418^{5}$, $420^{5}$, $423^{5}$, $439^{5}$, $441^{5}$, $442^{5}$
Wittman, M. D., **1**, $131^{99}$, $777^{219}$; **3**, $1007^{64}$; **5**, $827^{2}$, $829^{2}$, $867^{2b}$; **7**, $546^{30}$, $580^{30}$, $737^{12}$
Wittmann, M. D., **6**, $859^{174}$, $878^{40}$, $883^{40}$
Wittmann, R., **6**, $608^{49}$, $610^{61}$
Wityak, J., **8**, $648^{59}$
Witz, M., **7**, $747^{95}$
Witzel, B., **6**, $487^{57}$, $489^{57}$
Witzel, D., **6**, $233^{43}$
Witzel, T., **5**, $159^{51}$, $189^{51}$
Witzeman, J. S., **5**, $805^{100}$
Witzgall, K., **4**, $115^{182,182e}$; **6**, $172^{11}$, $179^{127}$
Wix, G., **7**, $70^{93}$
Wladislaw, B., **3**, $644^{148,148a}$
Wladkowski, B. D., **6**, $245^{124}$

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Wogan, G. N., **3**, 499[121]
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Wohl, R. A., **2**, 1023[56], 1026[56]; **6**, 271[90]; **7**, 506[299]
Wöhler, F., **3**, 822[5], 834[5]; **6**, 233[42]
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Wojciechowski, M., **6**, 558[859]
Wojcik, B., **8**, 814[18]
Wojnarowski, T., **8**, 756[146]
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Wolcke, U., **2**, 740[62]; 7, 678[69]
Wolcott, R. G., **6**, 277[126]
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Wold, S., **2**, 1099[115]; **3**, 721[5]
Wolf, A., **3**, 382[38]; **6**, 602[2]
Wolf, A. P., **3**, 1040[109]; **4**, 445[203,204,206]; **5**, 1148[119,120]; **8**, 344[123]
Wolf, D. E., **2**, 284[56]; 7, 778[414]
Wolf, F. J., **7**, 710[49]
Wolf, G., **2**, 64[24]; **8**, 568[471]
Wolf, G. C., **4**, 771[250]
Wolf, H., **3**, 348[28], 373[130]; **6**, 500[179]
Wolf, H. J., **7**, 67[78], 68[81]
Wolf, H. R., **5**, 221[62]
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Wolf, K., **6**, 518[332]
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Wolf, U., **4**, 54[152]
Wolf, W., **3**, 505[164], 507[164,173], 512[164], 515[164]; **6**, 182[141]
Wolf, W. A., **4**, 1033[33]
Wolfarth, E. F., **5**, 854[174]
Wolfbeis, O. S., **2**, 362[184]; **6**, 553[704]
Wolfe, J. F., **2**, 166[152], 189[54]; **4**, 426[59], 452[16], 455[43], 456[47], 457[49], 458[65], 462[65,104], 463[43,110], 464[118], 465[65,104,116,118-120], 466[65,104,119], 467[119,130,131], 468[104,110], 469[104,110,116,134], 472[134], 473[134], 475[134], 477[49], 503[125]; **6**, 2[4], 110[56], 438[61]
Wolfe, J. R., **5**, 637[108]
Wolfe, J. W., **4**, 457[50], 477[50]
Wolfe, S., **1**, 506[8,11], 512[42,43], 528[116,117]; **2**, 414[14]; **3**, 147[399], 154[418], 155[418]; **4**, 314[481,482], 603[274]; **6**, 133[4], 207[47], 924[62], 926[66]; **7**, 92[47], 94[56], 196[11], 199[11], 236[28], 237[28], 571[115], 768[204], 844[57]
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Wölfel, G., **2**, 1004[58], 1005[58]; **6**, 83[81]
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Wolff, H., **6**, 795[10], 798[10], 817[10], 820[10]; 7, 666[71], 690[13]
Wolff, J. J., **2**, 1072[140]; **7**, 318[60]
Wolff, L., **3**, 887[1a], 890[1], 891[1], 893[1a], 894[1], 900[1a]; **8**, 328[2], 336[2]
Wolff, M. A., **8**, 704[8]
Wolff, M. E., **4**, 814[188]; **7**, 16[161], 236[14-16]
Wolff, O., **5**, 451[5]
Wolff, R. E., **3**, 30[175]
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Wolfrom, M. L., **1**, 55[26], 153[57]; **6**, 660[202]; **8**, 269[85,86], 293[47]
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Wolin, R. L., **4**, 809[164]
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Wollenberg, R. H., **2**, 588[152]; **3**, 247[49], 250[49]; **4**, 143[18]; **7**, 26[59], 620[27]
Wollheim, R., **3**, 890[35], 903[127]
Wollmann, T. A., **2**, 112[101], 258[48,50], 261[48]; **8**, 159[108], 171[108], 178[108], 179[108]
Wollowitz, S., **5**, 948[290]; **6**, 154[148], 903[136], 904[141], 1026[88], 1027[88]; **7**, 770[249]; **8**, 409[84]
Wollthan, H., **4**, 868[13]
Wollweber, H., **5**, 316[2], 318[2], 426[105], 428[105], 429[105], 451[11], 513[2], 518[2], 594[1], 601[1], 604[1]
Wolman, Y., **2**, 1094[88,89], 1095[89]
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Wolterson, J. A., **5**, 603[51], 612[74]
Wong, A. C., **5**, 581[173]
Wong, C. F., **6**, 914[26]; **7**, 222[40]
Wong, C. H., **2**, 455[20], 456[20,24,27,34,49-51], 459[50], 460[49,51], 461[49,50], 462[50,51], 463[34,79,91], 464[91]; **6**, 49[94], 665[228]; **7**, 79[132], 80[132], 312[33], 316[45]; **8**, 183[2,3], 185[2,12], 187[34]
Wong, C. K., **1**, 699[247,254]; **3**, 107[225,226], 109[226], 386[60]; **4**, 372[55], 398[216], 399[216a], 401[216a], 405[216a], 410[216a]; **6**, 470[58]; **7**, 495[211]; **8**, 847[97,97d], 849[97d,107,110,115]
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Wong, C. M., **1**, 563[186]; **2**, 762[55]; **3**, 854[73]; **4**, 12[42]; **6**, 134[17]; **7**, 760[48], 765[150]; **8**, 371[107], 987[20]
Wong, C. S., **8**, 447[116], 847[94,95]
Wong, F., **8**, 337[81]
Wong, G. S. K., **4**, 792[60], 795[86]
Wong, H., **3**, 168[491], 169[491], 171[491]; **4**, 398[216], 399[216d]; **6**, 538[573], 923[58]; **8**, 303[97]
Wong, H. M. C., **5**, 63[15]
Wong, H. N. C., **5**, 123[1], 126[1], 221[58], 226[58,112], 900[12], 901[12], 903[12], 905[12], 907[12], 913[12], 921[12], 926[12], 943[12], 1006[33]; **7**, 815[3,4], 824[3,4], 833[3,4]; **8**, 884[98], 885[98]
Wong, H. S., **4**, 629[416]
Wong, J., **2**, 353[100]; **4**, 262[311]; **7**, 31[87]
Wong, J.-W., **5**, 541[111]
Wong, J. Y., **4**, 738[98]; **8**, 800[68]
Wong, K. C. K., **4**, 955[12]
Wong, L. C. H., **2**, 780[10]
Wong, M. G., **4**, 538[103]

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Wong, P. K., **1**, 442[178]; **2**, 934[143]; **4**, 614[381]
Wong, R. Y., **3**, 672[66]
Wong, S. S., **1**, 37[239]
Wong, T., **8**, 884[98], 885[98]
Wong, W., **8**, 858[206]
Wong, W. C., **8**, 36[97], 42[97], 66[97]
Wong, W. S. D., **8**, 54[158], 66[158]
Wonnacott, A., **1**, 166[113], 314[128], 323[128], 341[98], 780[228]; **3**, 174[527,527a,b], 175[527a-c]
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Woo, J. C., **8**, 445[51]
Woo, P. W. K., **8**, 843[48], 846[48]
Woo, S. H., **2**, 846[202]; **6**, 680[330]
Woo, S. L., **3**, 280[40]
Woo, S.-O., **3**, 689[122]
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Wood, A. E., **7**, 767[192]
Wood, A. F., **3**, 688[116]
Wood, A. M., **3**, 383[49]
Wood, C. Y., **2**, 1049[16]; **8**, 187[34]
Wood, D. C., **4**, 709[44,47], 710[44,47], 712[70]
Wood, G., **3**, 564[8], 727[28]
Wood, G. P., **6**, 463[23]
Wood, G. W., **3**, 380[5], 381[17]; **7**, 582[149]
Wood, H. B., **8**, 269[85]
Wood, H. C. S., **2**, 456[26]; **3**, 246[35]; **8**, 369[76]
Wood, J., **6**, 219[122]
Wood, J. L., **4**, 348[108,108a], 349[108a]; **7**, 105[151]
Wood, K. V., **8**, 629[186]
Wood, L. L., **3**, 814[71]
Wood, M. L., **2**, 963[54]
Wood, R. D., **4**, 398[213]; **6**, 5[27]; **7**, 406[72], 503[272]
Wood, S. E., **8**, 673[30]
Wood, S. G., **6**, 474[83]
Wood, T. R., **6**, 270[77]
Wood, W. A., **2**, 466[117], 468[117]; **8**, 36[68], 66[68]
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Woodard, S. S., **3**, 225[185], 264[181]; **6**, 2[3], 25[3], 88[105], 89[105]; **7**, 391[13], 406[77], 409[77], 411[13], 412[13], 413[13], 414[77], 415[77], 420[135,136], 421[77,136], 423[77]
Woodbridge, D. T., **7**, 765[157], 769[242,243], 771[242], 773[242]
Woodburn, H. M., **6**, 546[651]
Woodbury, R. P., **2**, 279[12], 605[60]; **7**, 144[152]
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Woodgate, P. D., **1**, 753[102]; **3**, 325[157], 675[74]; **4**, 347[96], 350[121], 351[126], 354[126-128], 369[21,22], 370[21,22], 371[21], 377[21,22], 545[126], 1058[149]; **7**, 121[24], 502[261], 530[20], 531[20], 706[25]; **8**, 309[10], 311[10], 312[10], 313[10], 944[123]
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Woodin, R. L., **1**, 287[16]
Woodman, D. J., **6**, 547[666]
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Woods, J. C., **6**, 802[39]
Woods, J. M., **7**, 737[17]
Woods, L. A., **1**, 107[7]; **3**, 208[9], 244[19]; **4**, 148[47b]
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Woods, S. G., **4**, 443[185]
Woods, T. L., **5**, 639[120]
Woods, W. G., **8**, 720[125]
Woodward, B., **8**, 650[64]
Woodward, P., **3**, 380[10]; **4**, 712[70]; **5**, 1136[54], 1146[107]
Woodward, P. R., **6**, 443[93]
Woodward, R. A., **8**, 851[126], 858[126]
Woodward, R. B., **2**, 149[92], 156[117], 214[129], 358[153], 542[83], 773[24], 1022[53]; **3**, 781[14], 810[44], 914[9]; **4**, 44[124], 50[142], 120[202], 373[68], 1016[204], 1070[10], 1075[10], 1093[10]; **5**, 64[25], 66[25], 318[4], 341[61a], 451[50,51], 552[20], 618[3,4], 619[3], 620[15], 621[15], 622[15], 632[63], 635[3], 678[13], 699[1], 732[132,132a], 743[1], 754[61,69], 758[69], 760[61], 794[51], 819[155], 830[27], 857[223], 1002[19], 1009[19], 1186[6]; **6**, 46[74], 667[242], 672[284], 680[332], 681[332], 736[23], 1011[1]; **7**, 157[33], 438[14], 444[14]; **8**, 80[3], 844[76], 974[122]
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Woolsey, N. F., **2**, 422[30], 423[30]; **4**, 872[37]; **7**, 723[24], 724[24]
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Wooster, C. B., **8**, 308[4], 490[7], 509[89]
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Worster, P. M., **6**, 726[181]
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Wren, D., **6**, 941[152]
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Wriede, U., **6**, 426[74]
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Wright, B. T., **4**, 785[21], 790[40], 791[21,40]
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Wright, D. B., **5**, 9[67,69]
Wright, D. R., **6**, 1013[10]
Wright, D. S., **1**, 6[33]; **3**, 763[151]
Wright, G. A., **5**, 1135[47]
Wright, G. C., **6**, 515[235]
Wright, G. F., **4**, 272[35], 273[35], 294[246], 310[433], 311[443]; **6**, 208[63], 283[165]; **7**, 92[42], 93[42], 746[86]
Wright, I. G., **2**, 170[174]
Wright, J., **4**, 85[75]; **6**, 883[60], 884[60]; **7**, 552[57]
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Wright, J. L., **4**, 379[115], 380[115g], 391[115g]; **7**, 523[48]
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Wright, J. S., **5**, 72[170]

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Wright, S. H. B., **4**, 85[77c]
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Wright, S. W., **6**, 452[136]; **8**, 616[104]
Wright, W. D., **5**, 1007[42]
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Wu, C., **4**, 82[62g], 218[133]; **5**, 71[143], 277[12]
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Wu, J. P., **7**, 246[87]
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